# The Synthesis of Enantiomerically Pure Aryltetralin Lignans

by

David E. Bogucki

A thesis

submitted to the Faculty of Graduate Studies

in partial fulfillment of the requirements

for the degree of

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Department of Chemistry

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# THE SYNTHESIS OF ENANTIOMERICALLY PURE ARYLTETRALIN LIGNANS

BY

DAVID E. BOGUCKI

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

DOCTOR OF PHILOSOPHY

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*Dedicated to the memory of*

*Stanley Bogucki*

# Abstract

The preparation of enantiomerically pure aryltetralin lignans has been accomplished using both a Diels-Alder approach and a newer oxidative free radical coupling/cyclization.

Past research established that aryltetralins could be asymmetrically prepared by a Diels-Alder reaction of $\alpha$-hydroxy-$\alpha$-phenyl-*ortho*-quinodimethane with a chiral dienophile. In this thesis, the previous preliminary work was extended to the preparation of a cycloadduct that was further elaborated to the natural lignan (-)-deoxy-podophyllotoxin. In the latter steps, an unprecedented stereoselective ionic reduction was developed.

In the pursuit of an even more efficient method for the synthesis of aryltetralin lignans, new stereoselective Diels-Alder reactions of *ortho*-quinodimethanes were investigated. Substituted chiral crotonate esters were successfully reacted with $\alpha$-hydroxy-*ortho*-quinodimethane and found to diastereoselectively give only one cycloadduct in high yield.

A new approach to the synthesis of aryltetralin lignans involving the oxidative coupling of substituted chiral cinnamic acid esters was studied. It was discovered that the chiral methyl (*R*)-mandelyl group would induce diastereoselectivity in the oxidative coupling/cyclization of its sinapic acid ester, forming the diester of the naturally occurring lignan thomasidioic acid. This unprecedented stereoselective reaction was used to prepare (+)-rabdosiin and its (-)-(1*R*,2*S*)-isomer, the enantiomers of which are natural anti-viral lignans.

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# List of Abbreviations

| | |
|---|---|
| $[\alpha]$ | specific rotation |
| Ac | acetyl |
| anal. | analysis |
| aq | aqueous |
| Ar | aryl |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| br | broad |
| *c* | concentration |
| cal | calorie(s) |
| calcd | calculated |
| cAMP | cyclic adenosine-3',5'-monophosphate |
| CI | chemical ionization |
| CNS | central nervous system |
| conc. | concentrated |
| $\delta$ | chemical shift in parts per million downfield from tetramethylsilane |
| D | dalton |
| d | doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| de | diastereomeric excess |

| | |
|---|---|
| ° | degrees |
| °C | degrees Celsius |
| DHBF | dihydrobenzofuran |
| DHN | dihydronaphthalene |
| diphos-4 | 1,4-bis(diphenylphosphino)butane |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| DOPA | 3-(3',4'-dihydroxyphenyl)alanine |
| $EC_{50}$ | effective concentration 50% |
| EDG | electron donating group |
| ee | enantiomeric excess |
| EI | electron impact |
| eq | equivalent(s) |
| Et | ethyl |
| EWG | electron withdrawing group |
| FAB | fast atom bombardment |
| FMO | frontier molecular orbital |
| g | gram(s) |
| GC | gas chromatography |
| h | hour(s) |
| HDL | high-density lipoprotein |

| | |
|---|---|
| HIV | human immunodeficiency virus |
| HMPA | hexamethylphosphoric triamide |
| HOMO | highest occupied molecular orbital |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrum |
| Hz | hertz |
| *i* | *iso* |
| I.A. | inverse addition |
| $IC_{50}$ | inhibitory concentration 50% |
| $ID_{50}$ | inhibitory dose 50% |
| *i*-Pr | isopropyl |
| IR | infrared |
| *J* | coupling constant |
| J | joule(s) |
| k | kilo |
| L | litre(s) |
| $LD_{50}$ | lethal dose 50% |
| LDA | lithium diisopropylamide |
| LDL | low-density lipoprotein |
| lit. | literature |
| LUMO | lowest unoccupied molecular orbital |
| *m* | *meta* |
| m | metre(s), milli, multiplet |

| | |
|---|---|
| μ | micro |
| M | moles per litre |
| MCMV | murine cytomegalovirus |
| *m*-CPBA | *m*-chloroperoxybenzoic acid |
| Me | methyl |
| min | minute(s) |
| MOD-DIOP | 4,5-bis[bis(4'-methoxy-3',5'-dimethylphenyl)phosphinomethyl]-2,2-dimethyl-1,3-dioxolane |
| mol | mole(s) |
| mp | melting point |
| *m/z* | mass to charge ratio |
| n | nano |
| N.A. | not available |
| nbd | norbornadiene |
| NBS | *N*-bromosuccinimide |
| *n*-Bu | *n*-butyl |
| NDGA | nordihydroguaiaretic acid |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser effect spectroscopy |
| NSAID | non-steroidal anti-inflammatory drug |
| *o* | *ortho* |
| *o*-QDM | *o*-quinodimethane |
| *p* | *para* |

| | |
|---|---|
| P | podophyllotoxin |
| PAF | platelet activating factor |
| Ph | phenyl |
| ppm | parts per million |
| PSMO | polysubstrate monooxygenase |
| q | quartet |
| RAS | rosmarinic acid synthase |
| $R_f$ | retention factor |
| RT | reverse transcriptase |
| rt | room temperature |
| s | singlet, solid |
| sat. | saturated |
| S.M. | starting material |
| $S_N2$ | bimolecular nucleophilic substitution |
| *t* | *tert* |
| t | triplet |
| TBDMS | *tert*-butyldimethylsilyl |
| TBTU | *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate |
| *t*-Bu | *tert*-butyl |
| temp. | temperature |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| T.I. | therapeutic index |

| | |
|---|---|
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl, tosyl |
| UV | ultraviolet |
| VIS | visible |

# Chapter 1

# Introduction

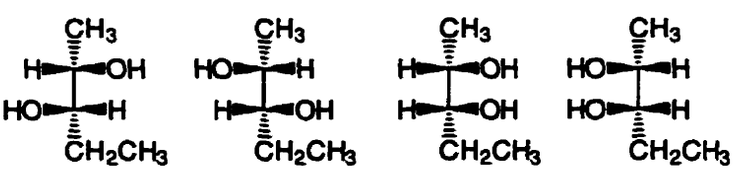
The present day synthetic organic chemist is faced with more challenges to overcome than ever before. One of these challenges is to synthesize compounds that consist of only single enantiomers. The work presented in this thesis is directed at this general problem with a focus on the stereoselective synthesis of aryltetralin lignans, a group of natural chiral compounds with a long history of medicinal usage. Some of the key steps in the syntheses described in this thesis involve the well-known Diels-Alder reaction, along with the oxidative coupling/cyclization of cinnamate esters. In the introduction to the thesis, a review of the biological activity of lignans will be presented. The Diels-Alder reaction will be discussed in terms of its stereoselectivity with special attention to reactions of a group of compounds known as *ortho*-quinodimethanes. There will also be a review of the selectivity of oxidative coupling reactions as they pertain to lignan synthesis, and a discussion of previous lignan syntheses will be provided.

## 1.1 Enantiomerically Pure Compounds

Chemical substances that have the same number and kinds of atoms but differ in their physical and/or chemical properties due to some difference in structure are referred to as isomers. All organic compounds exist as three-dimensional structures and are often

viewed from this perspective. Considering compounds as three-dimensional objects, or stereochemically, has introduced additional terminology to the chemical world. Isomers that are identical in every respect except for the arrangement of their atoms in space are termed stereoisomers. A pair of enantiomers, more specifically, are two stereoisomers whose structures are mirror images of each other but are not superimposable, as shown by the example of (2*S*,3*S*)- and (2*R*,3*R*)-dihydroxypentane in Figure 1.1. The (2*S*,3*R*)- and (2*R*,3*S*)-dihydroxypentane molecules are also a pair of enantiomers. In Figure 1.1 we see that (2*S*,3*S*)-dihydroxypentane, although a stereoisomer of the (2*R*,3*S*) structure, is not a mirror image of this compound and can not be superimposed upon it. Such compounds are known as diastereomers.

**Figure 1.1**



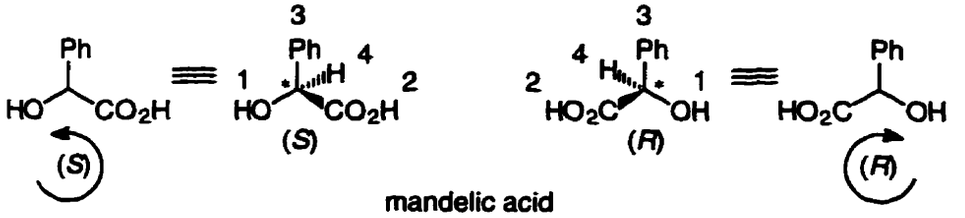

four stereoisomers of 2,3-dihydroxypentane

Chirality is another important concept in stereochemistry, and it can be used to describe various stereochemical situations. The word "chiral" is derived from the Greek word "cheir" or hand.[1] Like one's left and right hands, a chiral molecule can not be superimposed upon its mirror image. Another definition of chirality as it applies to individual molecules is that a molecule is chiral if it does not contain certain elements of symmetry, such as a plane ($\sigma$), center ($i$), or alternating axis ($S_n$) of symmetry. The only symmetry element that a chiral molecule may contain is an axis of rotation ($C_n$).

Enantiomeric compounds, although not always diastereomeric compounds (see Section 1.1.2.4), are therefore chiral.

Chiral compounds usually, but not always, contain at least one chiral center. A chiral center is the atom (X), most often carbon, in a tetrahedral (Xabcd) or trigonal pyramidal (Xabc) structure to which four or three respectively different ligands (abc(d)) are attached. There are only two possible ways in which the ligands can be oriented in space relative to each other, and each configuration is identified by using the Cahn-Ingold-Prelog system of assigning the stereodescriptor *S* or *R* to a particular chiral center. Descriptions of this naming system can be found in standard textbooks on stereochemistry. An example is given in Figure 1.2.

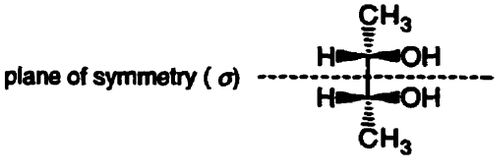
**Figure 1.2**




mandelic acid

It is quite possible that a molecule that is not chiral can contain chiral features. For example, a molecule with two chiral centers may not be a chiral entity as a whole due to a molecular plane of symmetry (see Figure 1.3). Such a molecule is referred to as a meso

**Figure 1.3**

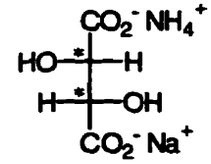



(2*S*,3*R*)-dihydroxybutane

compound. It should also be noted that a molecule can still be chiral despite not having any tetravalent-atom-based chiral centers as will be seen later in this chapter.

The fact that molecules are known to be able to exist as enantiomers dates back to 1809 when E. L. Malus, a French physicist, reported[2] the phenomenon of linearly (also known as plane) polarized light. In 1815, J. B. Biot observed[3] that if plane polarized light was passed through certain organic liquids like turpentine or organic solids (sucrose, camphor, or tartaric acid) in solution, the plane of the polarized light was either rotated in a clockwise or counterclockwise direction. However, it was not until many years later that L. Pasteur would correctly postulate the cause of this optical rotation.[4,5] Pasteur, in 1848, had an aqueous solution of tartaric acid in the form of its sodium ammonium salt (see Figure 1.4) that would not rotate that plane of polarized light. The water was slowly

**Figure 1.4**




sodium ammonium salt of tartaric acid

evaporated to give large enantiomorphous crystals. That is, the facets of the crystals were arranged in such a manner that some of the crystals were non-superimposable mirror images of the other crystals. The crystals were large enough to allow Pasteur to manually separate the two types of crystals using a microscope and tweezers. Making separate aqueous solutions of each type of crystal, it was observed that one solution would rotate the plane of polarized light clockwise ((+)-tartaric acid) and the other counterclockwise ((-)-tartaric acid). Thus, it was realized that, like a crystal, organic compounds could exist

as non-superimposable mirror images, and the dissymmetry of these types of compounds (enantiomers) was the cause of optical rotation.

Despite the length of time that chemists have been aware of enantiomers, the synthesis of single enantiomers has only attracted significant attention in the last 25 years. Now, when challenged with synthesizing a particular chiral organic compound, a chemist must first decide if a racemic (1:1 mixture of enantiomers) or enantiomerically pure product is desired. This decision must be made first as it will greatly affect the synthetic route that will be taken. Single enantiomers are often chosen to be synthesized because of the advantages that they possess over racemic mixtures.

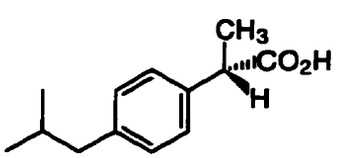
### 1.1.1 Reasons for Developing Enantiomerically Pure Compounds

There are numerous reasons for the interest in synthesis of single enantiomers. In academia, the intellectual challenge of designing efficient routes to pure enantiomers has stimulated a flurry of research in recent years. New reagents, reactions, syntheses, separation/purification techniques, analytical equipment, and even computer software are constantly being investigated specifically in conjunction with single enantiomers. While single enantiomers offer more challenging research opportunities, the advantages of obtaining single enantiomers versus racemic samples are more apparent when considering their differences in biological activity and other concerns in the pharmaceutical industry. These advantages will be the focus of the discussion in this section.

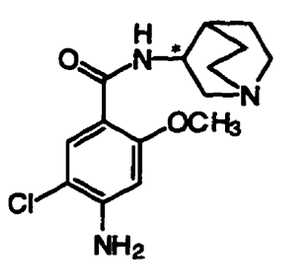
The industrial importance[6,7] of single enantiomers is particularly noticeable in the United States due to the regulations set forth by the FDA (Food and Drug Administration). It was only in June of 1992 that the FDA supplied its guidelines for the marketing of chiral drugs (an $18 billion industry in 1990[6] and $45.2 billion in 1994[7] for single enantiomers alone), and it has had a profound effect. The FDA guidelines require strict justification for the development of a racemic drug before the drug is allowed to be marketed. It is therefore understandable that producing a single enantiomer would be preferred if it could meet marketing approval easier and faster than a racemate. There are necessary tests that a product must undergo before it is FDA approved, and this translates into enantiomerically pure products being more cost effective. For a pure enantiomer, purification usually only requires simple chromatography. Purification of a racemate on the other hand involves simple chromatography followed by chromatography on an asymmetric solid support in order to isolate both enantiomers of the mixture. Each enantiomer must then be tested, which doubles the cost of testing racemic mixtures relative to pure enantiomers. The interest in the synthesis of enantiomerically pure drugs is also being driven by the fact that the patents of many racemic drugs have expired or are about to expire. Drug manufacturers can place patents on the single enantiomers of these brand name racemates (racemic switching). Less testing is needed for the enantiomer since the racemate already has FDA approval. The enantiomer can be approved approximately three times faster and eighty times more cheaply than a newly developed compound. The company would also obtain an extension of the exclusive marketing of the brand name drug. Generic drug companies would not be able to profit from the benefits of the already established brand name by performing their own racemic switching.

The fact that a single pure enantiomer can have different pharmacological activities than its mirror image isomer is also a major influence that often favours enantiopure drug production. It is often observed that only one enantiomer of a racemate is biologically active. For ibuprofen (see Figure 1.5), a pain reliever found in Motrin®, Nuprin®, and Advil®, only the (*S*)-(+)-isomer is active. Similarly, only one enantiomer is active for zacopride (see Figure 1.5), an anti-psychotic drug that works by blocking type-three receptors of the neurotransmitter 5-hydroxytryptamine (serotonin). It would be more

**Figure 1.5**




(*S*)-(+)-ibuprofen




zacopride

advantageous to omit the inactive enantiomer from a drug formulation since it makes no pharmacological contribution. Eliminating the inactive enantiomer from the drug preparation means that a given weight of the drug has an increased biological effect. A more potent drug can be administered less frequently meaning more convenience to the user. A more potent drug can also be administered in smaller doses which lessens the load on metabolism. The FDA is more likely to approve over-the-counter versus prescription distribution of a drug that requires a smaller dose. Thus, the drug would be more accessible and profitable.

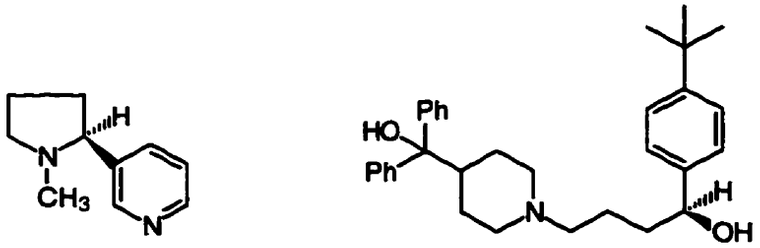
Single enantiomers, not necessarily as a result of increased potency, can be faster acting. Many non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, are

undergoing racemic switches due to the speed at which the single isomers become effective.

One enantiomer of a racemate may also interact better with primary detoxification pathways. This enantiomer will have reduced interactions with other common drugs present in the body.

One enantiomer may produce unwanted physiological effects. For example, the transdermal delivery of (*S*)-(-)-nicotine (see Figure 1.6) using a skin patch is much less irritating than a skin patch containing the racemate. Racemic terfenadine, an anti-histamine better known as Seldane®, causes dizziness and dry mouth, but the (*S*)-isomer

**Figure 1.6**



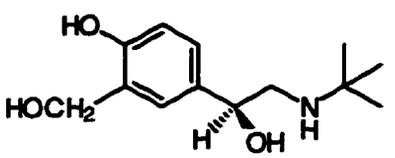

(*S*)-(-)-nicotine (*S*)-(+)-terfenadine

(see Figure 1.6) is not suspected to initiate these problems. One enantiomer may cause worse health problems than just minor side effects. Racemic albuterol is used as an anti-asthmatic but is being changed to only the (*R*)-form as research has shown that the (*S*)-isomer (see Figure 1.7) can induce airway constriction. In extreme cases the unwanted enantiomer may be toxic.

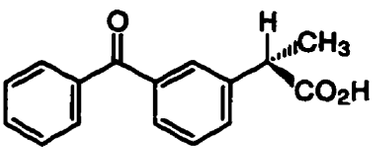
Another situation occurs when each enantiomer of a pair has a distinct and favourable physiological action. The (*S*)-(+)-enantiomer of ketoprofen (see Figure 1.7) is

an anti-inflammatory/analgesic while the (*R*)-(-)-enantiomer might be added to toothpaste for its activity against periodontal disease.

**Figure 1.7**




(*S*)-albuterol




(*S*)-(+)-ketoprofen

### 1.1.2 Methods for Obtaining Single Enantiomers

The four general methods for acquiring a single enantiomer are to isolate it directly from nature, conduct a chiral pool synthesis, perform a resolution of enantiomers, or execute a stereoselective synthesis.

#### 1.1.2.1 Isolation from Natural Sources

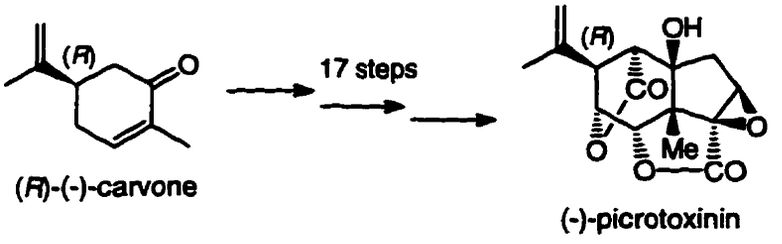
From the smallest bacterium to the largest mammal, chiral compounds are produced from a wide variety of living organisms. Furthermore, a living organism will generally biosynthesize a chiral compound as a single enantiomer. Nature has therefore become a very good source of single enantiomers for the organic chemist.

(*R*)- and (*S*)-carvone are good examples of chiral compounds isolated from natural sources. (*R*)-(-)-Carvone (see Scheme 1.1) is obtained by the simple procedure[8] of steam-distilling the fresh leaves of *Mentha spicata* for one hour and drying the essential oils with anhydrous sodium sulfate. (*R*)-Carvone constitutes 69.9% of the essential oils and is purified by standard flash chromatography on silica gel. The (*S*)-enantiomer is obtained from the ripe fruit of caraway, *Carum carvi*, using the same procedure (51.2% of the essential oils).[8] Apart from the fact that both enantiomers are produced from notably different plant species and as single isomers, a fascinating aspect of this example is that (*R*)-carvone has a strong spearmint odour and (*S*)-carvone has a less intense caraway odour. This shows that the human nose is capable of distinguishing enantiomeric compounds by perceiving differences in odour quality and odour potency.

### 1.1.2.2 Chiral Pool Synthesis

If a single enantiomer isolated from nature is transformed into another compound with incorporation of the existing chiral element, the process is known as a chiral pool synthesis. (*R*)-Carvone, for example, has been used to synthesize picrotoxinin (see

**Scheme 1.1**




(*R*)-(-)-carvone

(-)-picrotoxinin

Scheme 1.1).[9] It is frequently convenient to use a readily available chiral starting material since this choice can avoid the problem of having to introduce chirality in a later step. However, if additional chirality is inserted during the chiral pool synthesis, the synthesis may then be further categorized as stereoselective, as will be discussed in Section 1.1.2.4.

### 1.1.2.3 Resolution of Enantiomers

Resolution of enantiomers is the division of a racemate into single enantiomers. This process is useful when a stereoselective synthesis is difficult to achieve. However, unless both enantiomers of the racemate are desired or the undesired enantiomer can be converted back to a racemic mixture and re-separated, at least 50% of the mixture is waste.

There are four commonly used techniques for resolving enantiomers. One technique encompasses chromatography of the enantiomers on a non-racemic chiral stationary phase. Another method is based on differences in the reaction rates of the individual enantiomers with a non-racemic chiral reagent. This kinetic resolution occurs because the activation energy for the reaction of one enantiomer is lower than that of the other enantiomer, resulting in different rates of diastereomeric transition state formation. Following the selective chemical transformation of one of the enantiomers, the product and remaining enantiomer can be isolated by an appropriate separation technique like simple chromatography, distillation, extraction, or recrystallization. The most popular method of resolving enantiomers is to react them with an enantiomerically pure

compound, a resolving agent, to form a temporary mixture of diastereomers. The physically and chemically distinct diastereomers can then be separated by traditional procedures, and the resolving agent may subsequently be removed. The least utilized resolution technique, limited by the physical properties of the racemate, is preferential crystallization. This method is the same as traditional recrystallization except that the induced crystallization proceeds in a non-equilibrium manner. By treating the saturated or supersaturated solution of a racemate with a crystal of one enantiomer, only that enantiomer is displaced from solution and is separated from the other isomer by filtration.

### 1.1.2.4 Stereoselective Synthesis

Stereoselective synthesis is a very versatile approach to obtaining enantiomerically pure compounds. A stereoselective synthesis of a chiral product results when it is possible for more than one stereoisomer to be formed, but one is formed in excess. A stereoselective reaction should not be confused with a stereospecific reaction in which stereoisomerically different starting materials are converted to stereoisomerically distinct products. A stereospecific reaction is always stereoselective, but stereoselectivity does not necessarily suggest stereospecificity.

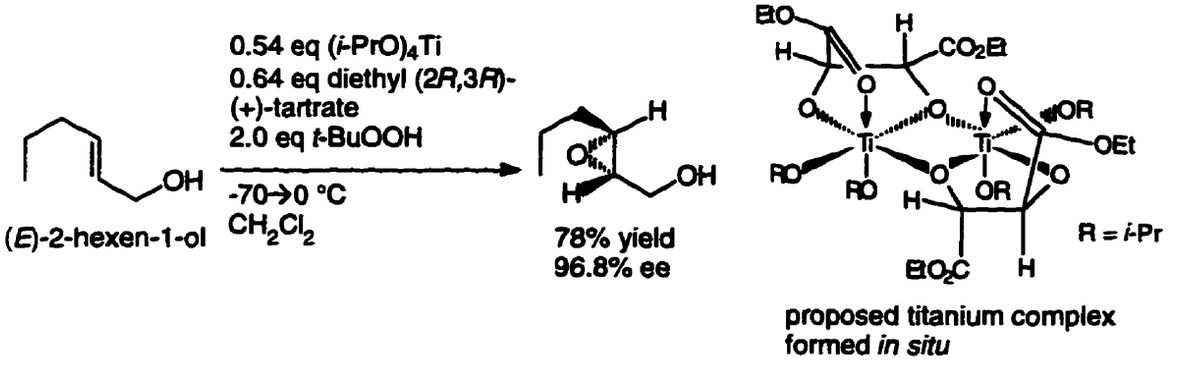
Traditionally, the term asymmetric has been used to describe a stereoselective synthesis that encompasses the production of a new chiral element from a prochiral element in such a way that the new chiral element is produced with a predominance of one absolute configuration. An enantioselective synthesis is the production of unequal

amounts of enantiomeric products from an achiral precursor and is always classed as an asymmetric synthesis. A diastereoselective synthesis is the production of diastereomers, not necessarily from an achiral precursor, in unequal amounts. To control the stereochemical outcome of a synthesis, one must perform an enantioselective, diastereoselective, or in some suitable situations, a double stereodifferentiating reaction.

The enantioselective introduction of chirality into an achiral compound needs to be accomplished by using a chiral catalyst, reagent, or by carrying out the reaction in a chiral environment.

Chiral transition metal complexes are commonly used to catalyze enantioselective epoxidations and hydrogenations of alkenes. Scheme 1.2 shows the selective Katsuki-Sharpless epoxidation of (*E*)-2-hexen-1-ol by *t*-butyl hydroperoxide and a titanium tartrate complex.[10,11] Other enantioselective reactions catalyzed by such complexes include cyclopropanations, alkene isomerizations, hydroborations, hydrosilations, hydroformylations, aldol reactions, and the nucleophilic addition of Grignard reagents.[1]

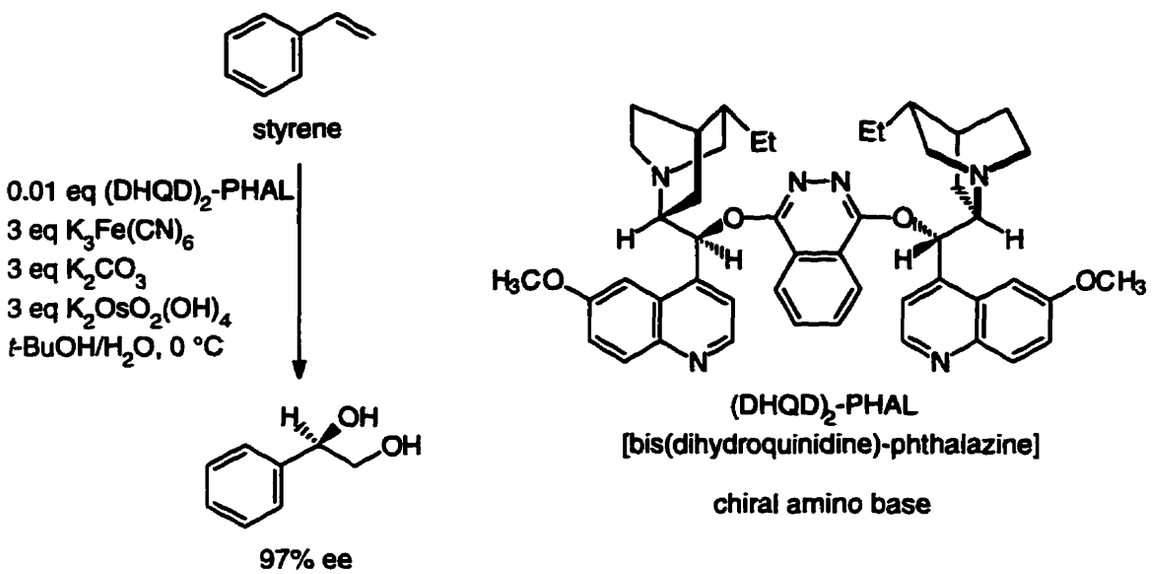
**Scheme 1.2**



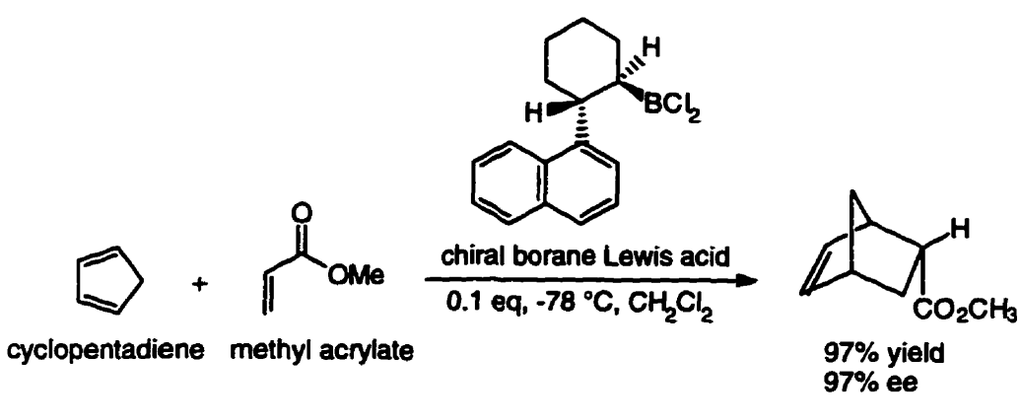

Chiral Lewis bases (see Scheme 1.3)[12] and chiral Lewis acids (see Scheme 1.4),[13] two other main types of chiral catalysts, are predominantly used to catalyze

enantioselective dihydroxylations of alkenes with osmium tetroxide (or potassium osmate) and [4 + 2] cycloadditions respectively.

**Scheme 1.3**




**Scheme 1.4**

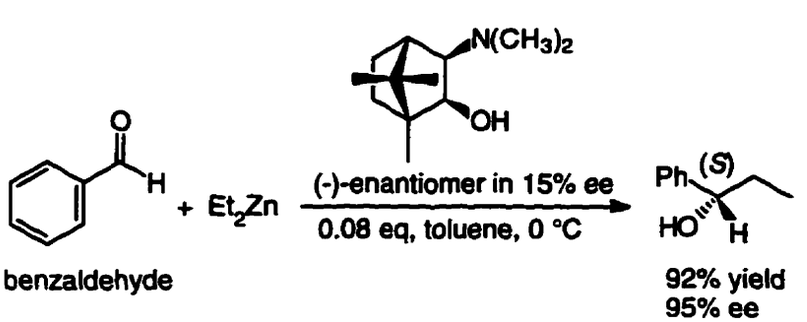



Enzymes, nature's catalysts, are also extensively used by the synthetic organic chemist, often giving 100% enantioselectivity. Hydrolases catalyze the hydrolysis of esters, amides, and glycosides. Transferases promote the transfer of sugar, acyl, and

phosphoryl groups from one compound to another. Lyases facilitate additions to π-bonds and the reverse reactions. Ligases/synthetases assist C-O, C-S, C-N, C-C, and P-O bond forming reactions. *E/Z* isomerizations and the migration of double bonds are promoted by isomerases. Oxidoreductases catalyze various oxidation reactions. Enzymes, while very useful, are not, however, as versatile as other catalysts with regard to acceptable substrates.

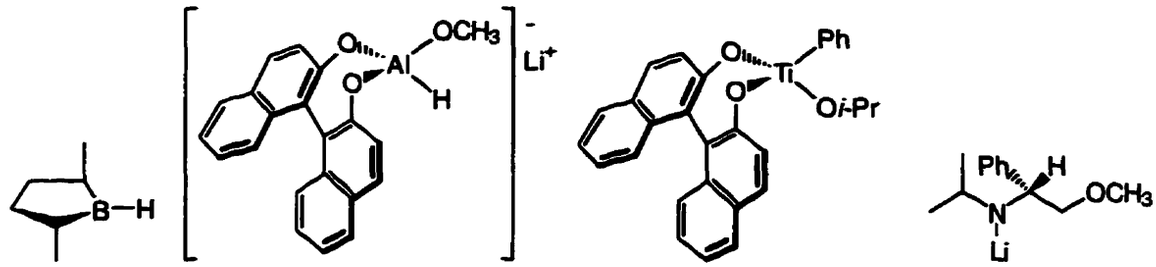
Catalysts do not always have to be very enantiomerically pure to induce high stereoselectivity. The phenomenon of asymmetric amplification, exemplified in Scheme 1.5, occurs when a catalyst of low enantiomeric purity yields a product of higher enantiomeric excess.[14] This observation is explained by the formation of the metal complex catalyst $ML_2$ from the coordination of two chiral and enantiomeric ligands, $L_R$ or $L_S$, to a metal center M. The three possible complexes are $M(L_R)_2$, $M(L_S)_2$, and $ML_RL_S$. When $L_R$ is in excess, the complexes $M(L_R)_2$ and $ML_RL_S$ are predominantly formed. In some cases the meso $ML_RL_S$ complex will be the more effective catalyst, but when the more effective catalyst is $M(L_R)_2$, the enantiomeric excess of the product is enhanced. The effect of $L_R$ is therefore amplified as its influence on the optical purity of the product is greater relative to its enantiomeric excess.

**Scheme 1.5**



The types of chiral reagents that are generally used for enantioselective syntheses are similar to the enantioselective catalysts except that at least a stoichiometric amount of the reagent is required. Some typical chiral reagents, as represented in Figure 1.8, include alkyl boranes for alkene hydroborations, hydride complexes for carbonyl reductions, organometallic complexes for alkylation reactions, and amide bases for the generation and addition of enolates. Of note, the hydride complex and organometallic complex shown in Figure 1.8 are special types of chiral compounds known as atropisomers. Such stereoisomers do not have any tetravalent-atom-based chiral centers but maintain chirality due to the restricted rotation about a single bond.

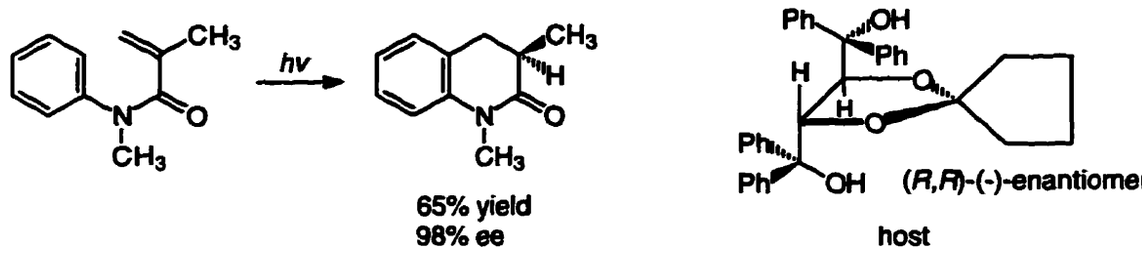
**Figure 1.8**




chiral borane chiral hydride complex chiral organometallic complex chiral amide base

Enantioselectivity can be attained without the use of a chiral reacting species if the reaction takes place in a chiral environment. Chiral solvents, particularly in early attempts at stereoselective control, were used to induce asymmetry, but these reactions were generally very inefficient, giving enantiomeric excesses of less than 10%.[15] More recent experiments have involved solid-state reactions in which the achiral reactant forms a crystalline inclusion complex with an optically active host compound. Scheme 1.6 shows the stereocontrolled photocyclization of an acrylanilide that forms a 1:1 complex with the host.[16]

**Scheme 1.6**

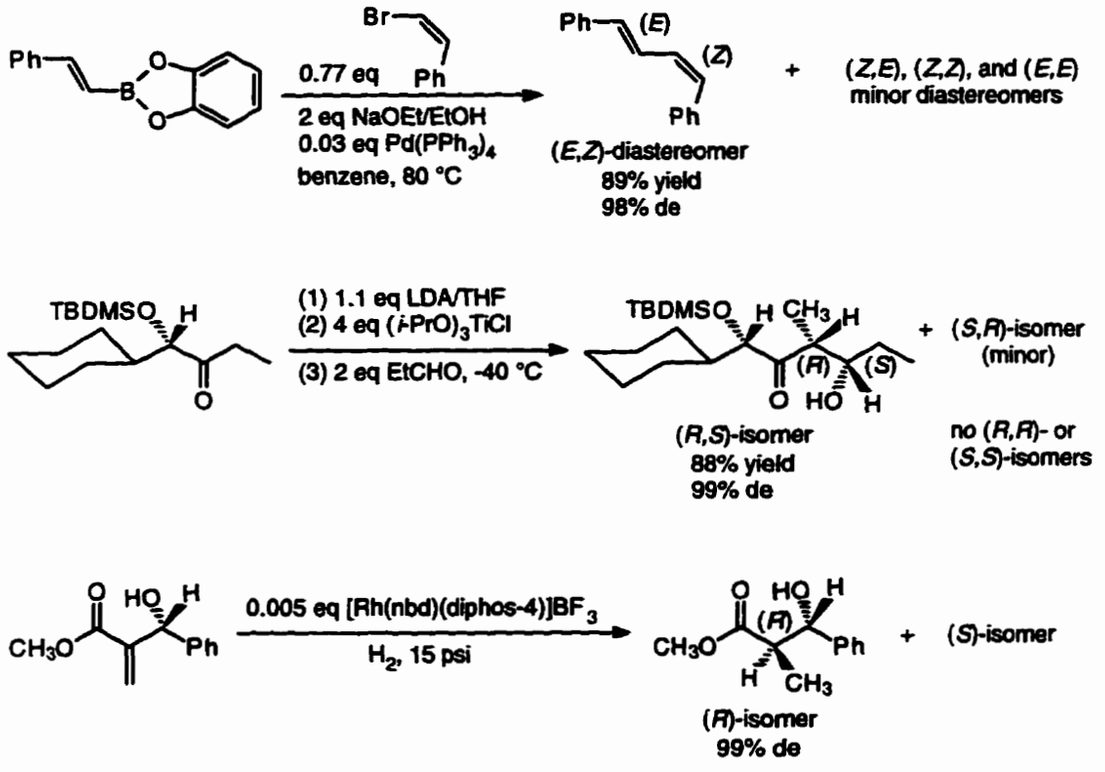



The cause of stereoselectivity is similar for both enantioselective and diastereoselective reactions. For each possible isomer that can be formed, the reactant must go through diastereomeric transition states that are geometrically different and therefore have different free energies. The observed unequal product ratio results from the difference between these transition state free energies leading to the faster rate of formation of one isomer (kinetic control). Diastereoselectivity can also be determined thermodynamically if the diastereomeric products have different ground state free energies, and the more stable isomer forms via an equilibrium process. A minimum of 8 kJ $mol^{-1}$ (2 kcal) difference in the free energies is desired for good stereoselectivity.

Enantioselective syntheses usually entail the transformation of enantiotopic groups or faces of an achiral reactant, and the selectivity is controlled by the reagent. Diastereoselective syntheses, however, are mainly under the stereocontrol of the substrate. Such syntheses, too diverse to describe in detail, can consist of reactants and reagents that are chiral, achiral, or combinations thereof, and incorporate numerous types of reactions. They can be categorized into three broad classes. One class of diastereoselective synthesis involves the formation of achiral diastereomers such as *E* and *Z* alkenes and *cis-trans* diastereomers of achiral cyclic compounds. The second type is concerned with the generation of two or more chiral centers simultaneously in a way that favours one

diastereomer. Examples include the coupling of two molecules at prochiral centers resulting in the development of two new chiral centers as observed with aldol and Michael reactions. The third and most diverse category is the elaboration of new chiral centers in chiral reactants, often by the selective addition of groups to the diastereotopic faces of double bonds. Some reactions that portray these three classes are illustrated in Scheme 1.7.[17,18,19]

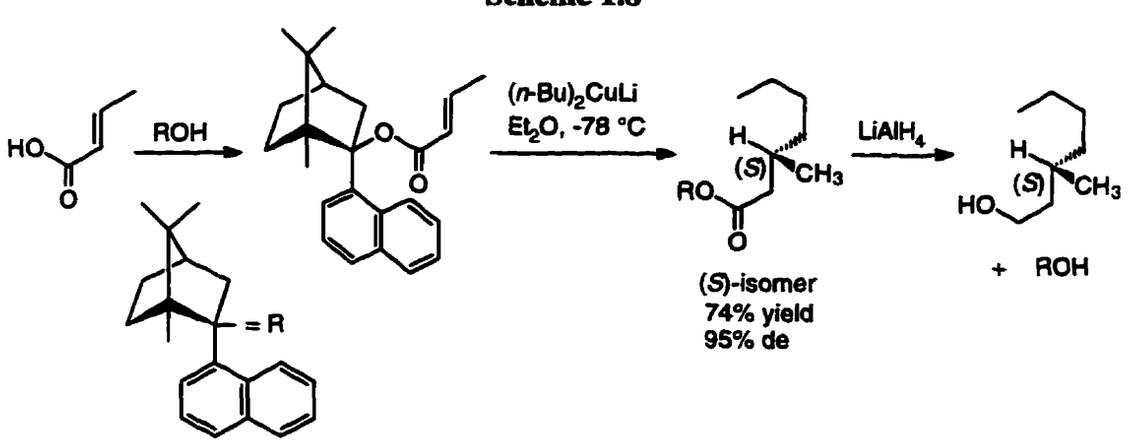
**Scheme 1.7**




One particular strategy for effecting a diastereoselective reaction that has considerable importance in this thesis is the use of a chiral auxiliary. A chiral auxiliary is an enantiomerically pure compound temporarily attached to an achiral substrate in order to induce desired asymmetry during a subsequent diastereoselective reaction. The chiral

auxiliary is then removed and, if possible, recovered. While the chiral auxiliary exerts diastereoselective control over the formation of a new chiral center, the removal of the chiral auxiliary yields unequal amounts of enantiomers. The overall process is therefore an enantioselective synthesis. This special type of enantioselective synthesis has an advantage over others because the diastereomeric intermediates can be easily separated relative to enantiomeric products. In some cases the formation of more than one new chiral center will occur, and the synthesis may be both enantioselective as well as diastereoselective. Scheme 1.8 shows an example of a chiral auxiliary.[20] Crotonic acid is esterified with a chiral camphor derivative and then treated with a lithium dialkyl cuprate. The steric influence of the camphor derivative, especially the naphthalene group, favours 1,4-addition to the *re* face of the double bond giving high diastereoselectively. Reductive cleavage of the chiral auxiliary gives the enantiomerically pure (*S*)-alcohol.

**Scheme 1.8**



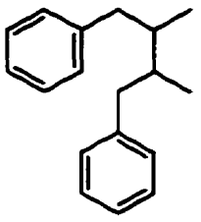

Many stereoselective synthetic strategies involve reactions in which only one of the participants, either the substrate or reagent, is chiral, but some syntheses are comprised of double stereodifferentiating reactions that are stereoselective due to the interactions of

more than one chiral compound. For example, the reaction between two chiral reactants or a chiral reactant and chiral reagent/catalyst will produce a new chiral center(s) by diastereoselection. A unique situation occurs when a mixture of enantiomers undergoes a stereoselective reaction (not involving coupling of the two reactants) with no new chiral centers being produced but with one of the isomers reacting faster than the other. An unbalanced ratio of enantiomeric products is obtained (kinetic resolution was discussed previously as a method for separating enantiomers). Enantioselection is exhibited by this kind of reaction, but it is not an enantioselective synthesis by definition and is more appropriately classified as a double stereodifferentiation.

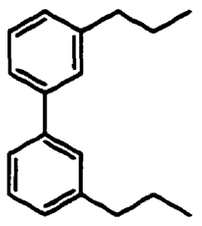
## 1.2 Lignans

Lignans are a class of naturally occurring compounds that are structurally defined by an 18-carbon skeleton (**1**) consisting of two phenylpropanoid units joined at the central atoms of the propyl chains (see Figure 1.9).[21] A similar class of compounds that are dimers of two phenylpropanoid units but do not have the same linkage, such as structure

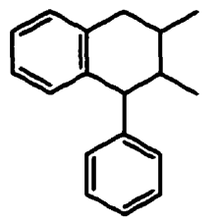
**Figure 1.9**



**1**
lignan skeleton



**2**
neolignan



**3**
aryltetralin lignan skeleton

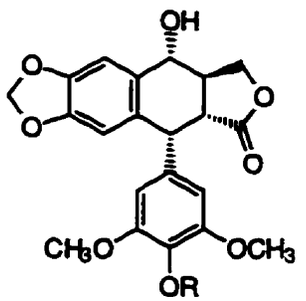
2, are known as neolignans. Aryltetralin lignans are a sub-class of lignans that have the bicyclic skeleton 3. Lignans, and the aryltetralins in particular, have a long history of medicinal use and are just as therapeutically important today as they were hundreds of years ago.

### 1.2.1 General Discovery and Biological Activity of Lignans

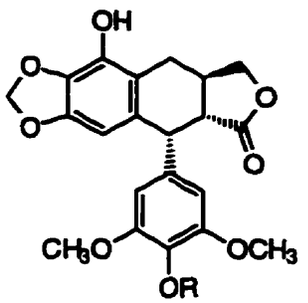
An extract of a herb, known today as *Podophyllum emodi*, was used over two thousand years ago in China for the treatment of tumours.[22] Over one thousand years ago, it was recorded in an early English medical text that the roots of *Anthriscus sylvestris* (wild chervil) were used in an anti-cancer ointment.[23] In approximately 1400-1600 A.D., the natives of the Himalayan region and the American Penobscot Indians of Maine independently found that the roots and rhizomes of different *Podophyllum* species of the family Berberidaceae had biological activity. The roots and rhizomes of these plants were either dried (podophyllum) or extracted with alcohol to give a resinous material (podophyllin). The applications of podophyllum and podophyllin, also incorporated by the American colonists, included snake venom antidote, cathartic, emetic, poison, suicide agent, anthelminthic, vesicant, and chlorotic (induces a form of anemia that is marked by moderate reduction in red blood cells and great reduction in hemoglobin content). Podophyllum became so popular in North America throughout the years that it was designated as a cathartic and cholagogue (promotes the flow of bile) in the first *U.S. Pharmacopoeia* in 1820.[24] Podophyllin was afterward entered into the fourth revision of

the pharmacopoeia in 1863. It would be realized some years later that podophyllum, podophyllin, and the roots of wild chervil consisted of various aryltetralin lignans.

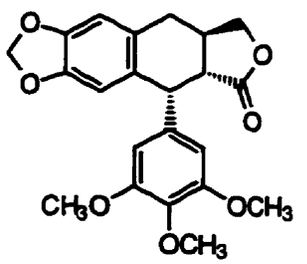
**Figure 1.10**



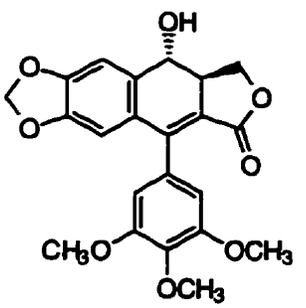
**4** podophyllotoxin: R = $CH_3$
**5** 4'-demethylpodophyllotoxin: R = H



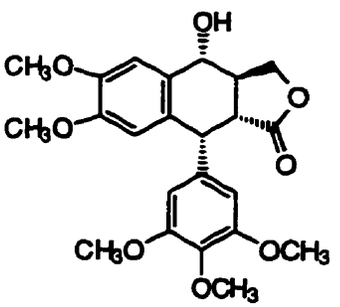
**6** $\alpha$-peltatin: R = H
**7** $\beta$-peltatin: R = $CH_3$



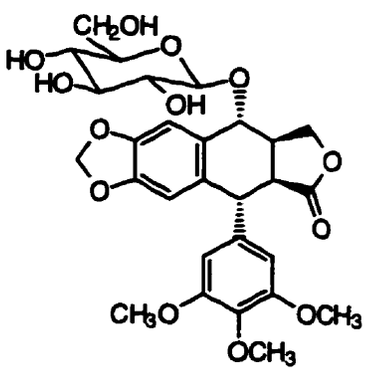
**8** deoxypodophyllotoxin



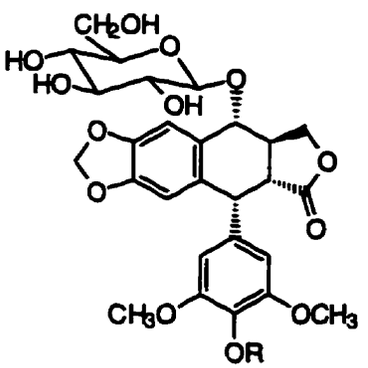
**9** dehydropodophyllotoxin



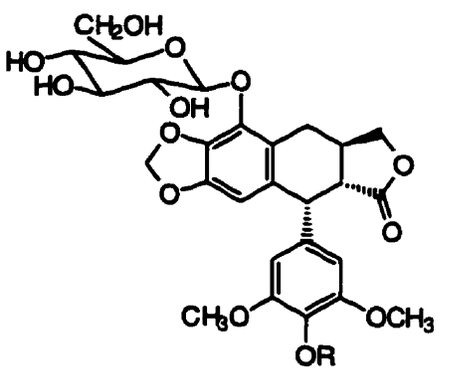
**10** sikkimotoxin



**11** picropodophyllotoxin glucoside



**12** podophyllotoxin glucoside: R = $CH_3$
**13** 4'-demethylpodophyllotoxin glucoside: R = H



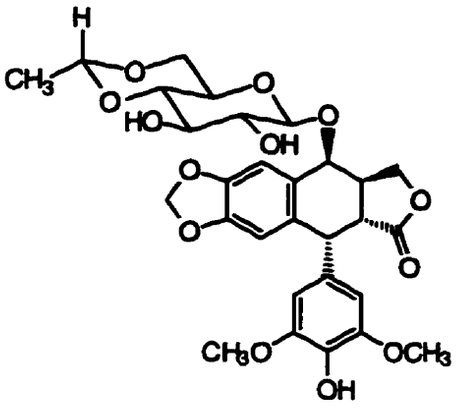
**14** $\alpha$-peltatin glucoside: R = H
**15** $\beta$-peltatin glucoside: R = $CH_3$

The elaboration of the chemical constituents of podophyllin was initiated in 1880 by Podwyssotzki who was the first to isolate and name podophyllotoxin (**4**). The structural formula proposed was not completely correct and remained uncorrected until being established by Hartwell and Schrecker in 1951.[25] In 1936, Haworth defined the lignan classification of compounds.[24] By 1942, podophyllin was discovered to have gastrointestinal toxicity and was removed from the *U.S. Pharmacopoeia*. In the same year, however, Kaplan reported that podophyllin was an effective topical drug for the treatment of *Condylomata acuminata* (venereal warts),[26] and this observation spurred further investigations. The isolation of 4'-demethylpodophyllotoxin (**5**), $\alpha$-peltatin (**6**), $\beta$-peltatin (**7**) along with podophyllotoxin (**4**) from Indian podophyllin (*P. emodi* extracts) soon occurred.[27,28] More studies, extended to include American podophyllin (*P. peltatum* extracts) and *P. sikkimensis* extracts, shortly followed and led to the separation of the new lignans **8-15** plus the flavonols kaempferol, isorhamnetin, quercetin, and quercetin 3-galactoside by 1955.[24] The absolute structures of the first 12 lignans discovered (**4-15**), all aryltetralins, are shown in Figure 1.10.

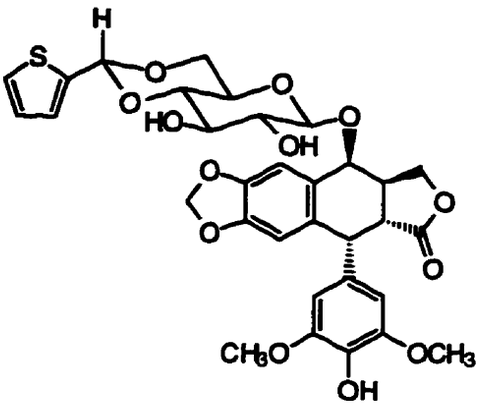
Hundreds of natural[23] and synthetic lignans have since been reported. The lignans that have been most extensively studied are podophyllotoxin (**4**) and two of its semi-synthetic derivatives, etoposide (**16**) and teniposide (**17**) (see Figure 1.11).

Podophyllotoxin is an anti-mitotic compound that inhibits cell division at metaphase.[29] This cytotoxic activity results from the ability of podophyllotoxin to bind to tubulin. Microtubules, the dynamic constituent of eukaryotic cells, are assembled in the cytoplasm by the polymerization of $\alpha$- and $\beta$-tubulin in response to various stimuli. Functions such as intracellular transport, secretion, membrane protein organization,

**Figure 1.11**



**16** etoposide



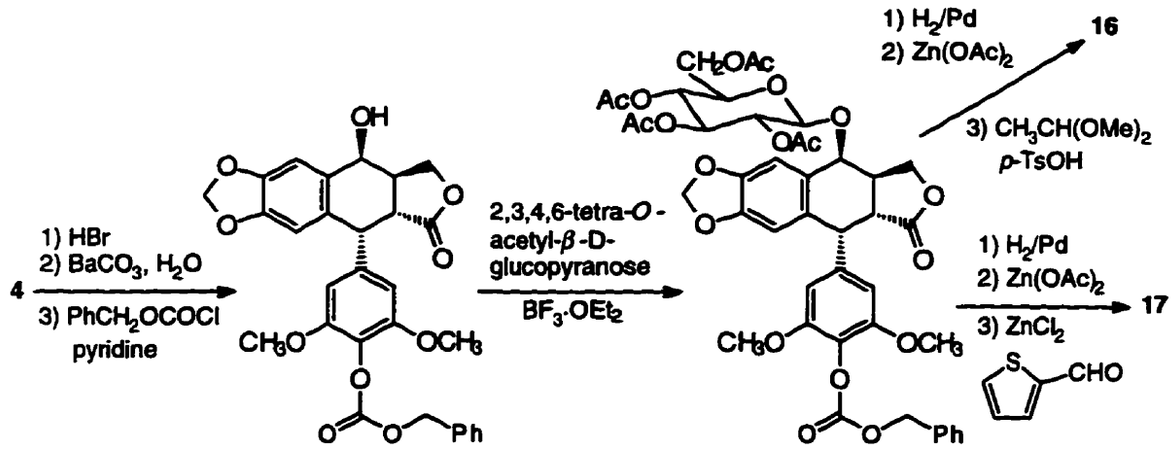
**17** teniposide

cellular motility, cytoplasm organization, and growth factor signaling are dependent on microtubules. When podophyllotoxin binds to tubulin, the equilibrium between microtubule assembly from tubulin and the reverse reaction is disrupted, and the disassembly of microtubules becomes favoured. The microtubule spindle fibers are destroyed and therefore can not separate the duplicated chromosomes, thereby terminating mitosis. A concentration of 0.6 μM ($ID_{50}$ value) of podophyllotoxin is enough to inhibit *in vitro* microtubule assembly by 50%.[29]

There may be a correlation between the anti-mitotic activity of podophyllotoxin and its well-known anti-tumour properties.[21] Lignans that inhibit microtubule assembly are often observed to possess potent anti-tumour activity suggesting that there could be a shared mode of action. However, these lignans tend to be very cytotoxic and are found to readily attack not only cancerous cells but healthy cells as well. Such compounds have limited use in chemotherapy. Podophyllotoxin is restricted to short term topical use, particularly as the major constituent of podophyllin formulations, which remain the chief treatment for venereal warts worldwide.

By using podophyllotoxin as a lead for the design of potential anti-cancer drugs, etoposide (VP-16-213) and teniposide (VM-26) were constructed (see Figure 1.11).[26] These derivatives do not bind to tubulin but have a different mechanism of action that allows for more selective attack on cancer cells. This selectivity permits them to be used clinically for treating various types of diseases such as testicular cancer, small cell lung cancer, non-small cell lung cancer, lymphoma, and leukemia. An example of how etoposide and teniposide can be synthesized from podophyllotoxin is shown in Scheme 1.9.[30-32]

**Scheme 1.9**



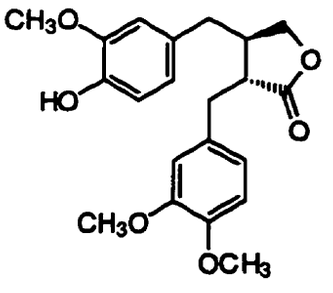

The cytotoxicity of etoposide and teniposide may be due to the inhibition of the enzyme topoisomerase II.[23] This enzyme is involved in DNA functions such as DNA transcription, DNA replication, separation of twisted pairs of newly replicated DNA strands, and chromosome segregation at the end of replication. Etoposide and teniposide interrupt the single- and double-stranded DNA scission/joining processes that are normally catalyzed by the enzyme by interacting with topoisomerase II to form a stabilized DNA-enzyme intermediate. DNA scission is increased, and the rejoining of DNA is halted. Cell

death has been correlated with DNA strand breaks and other cellular effects resulting from topoisomerase II inhibition.

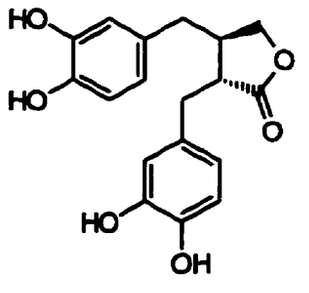
The biological activities of podophyllotoxin (**4**), etoposide (**16**), and teniposide (**17**) as well as other lignans have been thoroughly reviewed.[21,26,33] More recent biological activity studies will be discussed with a focus on lignans other than **4**, **16**, and **17**.

The natural lignan (-)-arctigenin (**18**), isolated from the tropical climbing shrub *Ipomoea cairica*,[34] was recently used as a lead structure to test 30 congeners for their anti-HIV activity and to determine structure-activity relationships.[35] The compounds were tested for their ability to inhibit human immunodeficiency virus-1 (HIV-1) integrase, the protein that controls the integration of HIV DNA into the human genome. The fully demethylated derivative of (-)-arctigenin (**19**) (see Figure 1.12) was found to be a very good inhibitor, but no aryltetralin lignans were found to be effective. Inhibiting activity was dependent on the presence of a lactone group and the number and arrangement of phenolic hydroxyl groups.

**Figure 1.12**




**18**

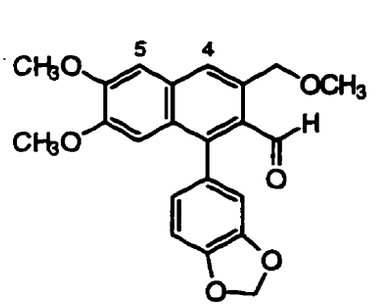



**19**

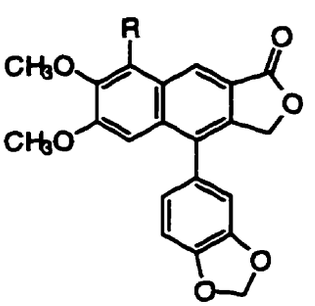
Six lignans (**20-25**) isolated from *Phyllanthus myrtifolius* were also tested for their anti-HIV activity (see Figure 1.13).[36] Phyllamycin B (**20**) and retrojusticidin B (**21**)

displayed strong inhibition of HIV-1 reverse transcriptase (RT), another protein essential to the life cycle of HIV, with $IC_{50}$ values of 3.5 and 5.5 μM respectively. These compounds did not affect human DNA polymerase-$\alpha$ activity to a significant extent, giving $IC_{50}$ values of 289 μM for **20** and 989 μM for **21**. This differential inhibition was poor for the other lignans indicating the importance of lactone ring orientation and lack of methoxy substituents on positions 4 and 5 for potent HIV-1 RT inhibition.

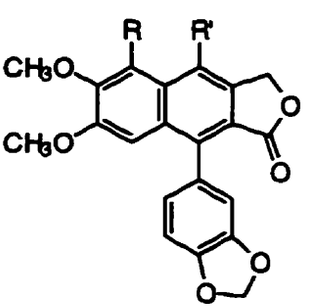
**Figure 1.13**



**20**



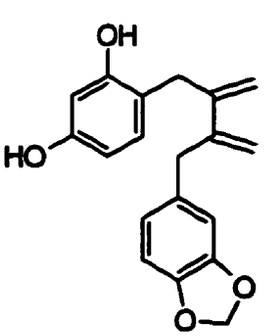
**21**: R = H
**22**: R = $OCH_3$



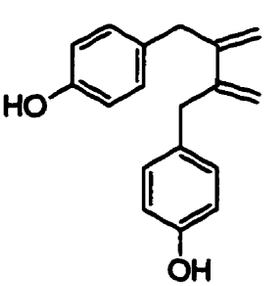
**23**: R = $OCH_3$, R' = H
**24**: R = H, R' = $OCH_3$
**25**: R = H, R' = H

Two new dibenzylbutadiene lignans, anolignan A (**26**) and anolignan B (**27**), from *Anogeissus acuminata* were also found to inhibit HIV-1 RT (see Figure 1.14).[37] The $IC_{50}$

**Figure 1.14**



**26**

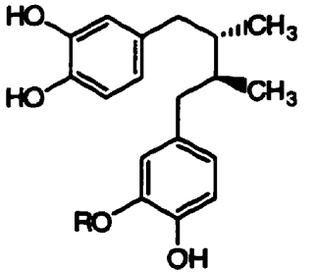


**27**

values of each of these compounds (60.4 μg/mL for **26** and 1072 μg/mL for **27**) could be decreased by using the two compounds in combination.

Mal.4 (**28**), a lignan from *Larrea tridentata*, was reported to suppress HIV basal transcription, Tat-dependent and Tat-independent transactivation, protect human lymphoblastoid CEM-SS cells from HIV infection, and inhibit HIV replication in mitogen-stimulated peripheral blood mononuclear cells (see Figure 1.15).[38,39] The inhibition of transcription and transactivation, and therefore HIV replication, was controlled by mal.4 interfering with the promoter activity of the HIV DNA long terminal repeat. Mal.4 was observed to prevent the binding of the protein transcription factor Sp1 to the promoter, possibly by binding directly to the protein or by interacting with the promoter DNA sequences in the vicinity of the Sp1 site and causing a local structural distortion unfavourable for Sp1 binding.

**Figure 1.15**



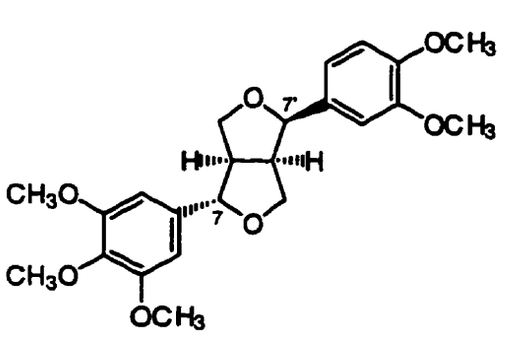

**28**: R = $CH_3$
**38**: R = H

Lignans with anti-viral properties other than anti-HIV activity were reported by San Feliciano *et al.*[40] and MacRae *et al.*[41] San Feliciano *et al.* examined 19 aryltetralin and arylnaphthalene lignans against herpes simplex type 1 and vesicular stomatitis infected cells and observed very potent inhibition of both viruses, especially by the methyl ether of

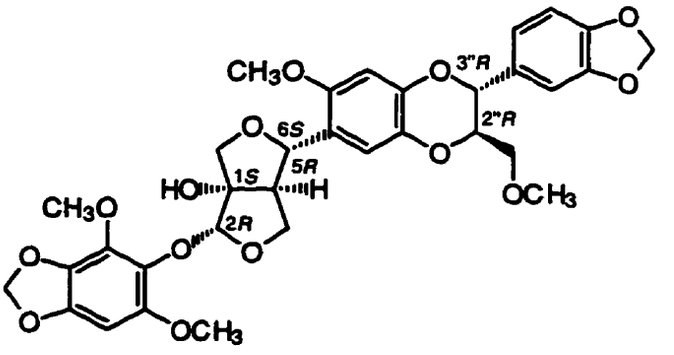
β-peltatin and deoxypodophyllotoxin (**8**) whose $IC_{50}$ values were equal to or less than 0.01 μg/mL. MacRae *et al.* studied 18 structurally diverse lignans for the suppression of the murine cytomegalovirus (MCMV) and Sindbis virus. Podophyllotoxin (**4**) and α-peltatin (**6**) were the most effective agents against MCMV, each inhibiting almost 50% of the virus at a concentration of 0.01 μg/mL. Justicidin B (**25**), however, was the only lignan to act with similar efficiency against the Sindbis virus.

Most lignans have been procured from plant life, so it is no surprise that they have been discovered to be participants in various plant biological processes, particularly in plant defense systems. Some furofuran lignans and neolignans were reported to have insecticidal activity. Miyazawa *et al.* isolated (+)-epimagnolin A (**29**) (see Figure 1.16) from the flower buds of *Magnolia fargesii* and found that it was effective for inhibiting the larval growth of the fruit fly (*Drosophila melanogaster*).[42] Yamauchi *et al.* carried out a

**Figure 1.16**




**29**




**30**

series of studies on compounds structurally related to (+)-haedoxan A (**30**) (see Figure 1.16) to determine their insecticidal effect on the female housefly (*Musca domestica*).[43-49] (+)-Haedoxan A, derived from *Phryma leptostachya*, was known to exhibit high insecticidal activity against the housefly ($LD_{50}$ = 0.25 ng/fly). Prepared analogs of this

compou[illegible] now [illegible]

1*S*,2*R*,5[illegible] 2"*R*,[illegible]"*R*

dioxan-[illegible] moiety [illegible]

[illegible] insects [illegible]

produce [illegible] protect[illegible]

monoox[illegible]enases [illegible]

hydropi[illegible] metabol[illegible]

counter[illegible] this [illegible]

detoxif[illegible]ion enzym[illegible]

increase[illegible] toxicity.

diasesa[illegible] [illegible]

Europe[illegible] [illegible]

methyle[illegible]edi[illegible]

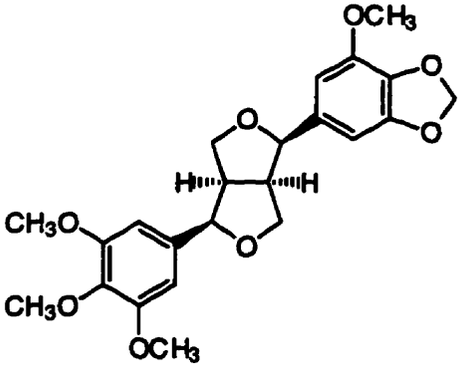
preferen[illegible] to [illegible]

other lig[illegible]

compound showed that the same absolute configurations as the natural lignan, 1*S*,2*R*,5*R*,6*S*,2"*R*,3"*R*, and the (2*R*,3*R*)-2-alkoxymethyl-3-aryl-6-methoxy-1,4-benzodioxan-7-yl moiety were indispensable for producing insecticidal activity.

Some insects have adapted to be able to tolerate the natural insecticides that plants produce to protect themselves. These insects contain gut enzymes called polysubstrate monooxygenases (PSMOs) that can transform a variety of lipophilic plant toxins into more hydrophilic metabolites in order to excrete them. However, some plants have counteracted this problem by producing chemicals that inhibit PSMOs. By inhibiting the detoxification enzymes, the plant toxins are allowed a longer time of action and have increased toxicity. Lignans from the Asteraceae and Piperaceae families, such as diasesartemin (**31**), are known to have good inhibiting activity on the PSMOs of the European corn borer (*Ostrinia nubilalis*).[50] The best PSMO inhibitors possess a methylenedioxyphenyl group in their structure (see Figure 1.17). This group may bind preferentially to the heme of the PSMO giving a stable adduct not easily displaced by other ligands.

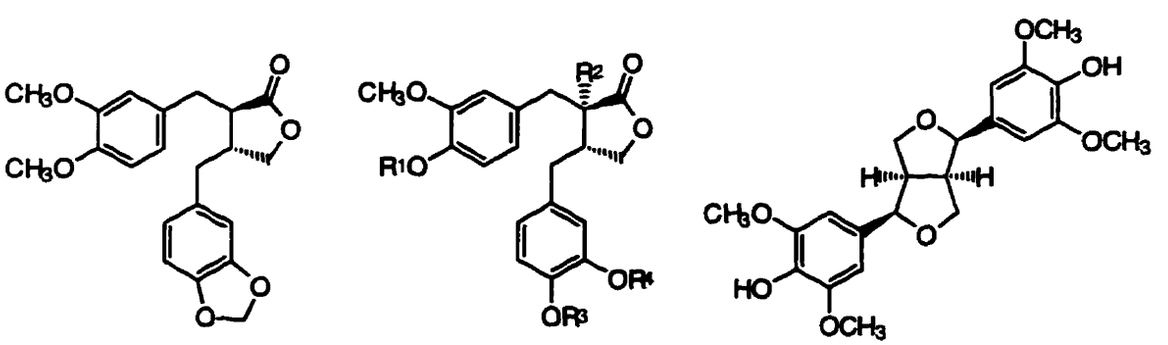
**Figure 1.17**




**31**

Other roles that lignans serve in plant defense include their toxicity against fungi, parasites, and other plants. Figgitt *et al.* were the first to report the anti-fungal activity of lignans.[51] Out of nine aryltetralin lignans tested against *Aspergillus niger*, *Geotrichum flavo-brunneum*, *Microsporum canis*, *Fusarium culmorum*, and *Trichophyton erinacei*, 4'-demethyldeoxypodophyllotoxin, 4'-demethylpodophyllotoxone, and 3',4'-didemethyl-deoxypodophyllotoxin were found to be active with effective inhibitory concentrations being as low as 1 μg/mL. Six lignans from *Bupleurum salicifolium* (**32-37**), particularly bursehernin (**32**) and matairesinol (**33**), were able to inhibit the hatching of potato cyst nematodes *Globodera rostochiensis* and *G. pallida* (see Figure 1.18).[52] Inhibitory activity

**Figure 1.18**



**32**

**33**: $R^1,R^2,R^3 = H$, $R^4 = CH_3$
**34**: $R^1,R^4 = CH_3$, $R^2,R^3 = H$
**35**: $R^1 = CH_3$, $R^2,R^3,R^4 = H$
**36**: $R^1,R^3 = Ac$, $R^2 = OAc$, $R^4 = CH_3$

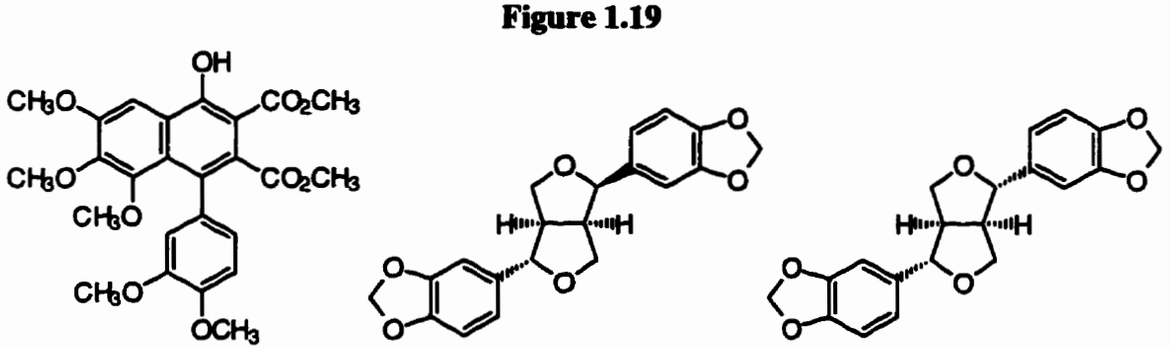
**37**

toward these parasitic worms was favoured by the presence of a methylenedioxy group, but in the absence of this group, activity increased according to the number of free hydroxyl groups. Elakovich and Stevens discovered that nordihydroguaiaretic acid (NDGA; **38**) dramatically reduced the seedling growth and hypocotyl growth of different weed and crop plants (see Figure 1.15).[53] This study was inspired by the observation that

the creosote bush from which NDGA was derived grew in an area almost devoid of annual vegetation. Substances such as NDGA were presumably leached from the aboveground plant parts to the ground and affected the growth of other species. In a recent publication, podophyllotoxin and matairesinol derivatives were tested as plant root growth inhibitors.[54] Consistent with other structure-activity relationships, the methylenedioxy group, the configuration of the lactone junction, and the number of methoxy groups were related to inhibitory activity. Lignans that have plant defense properties therefore have potential use as insecticides, fungicides, pesticides, and herbicides.

Lignans have been discovered to be effective for treating hypercholesterolemia. Hypercholesterolemia is the main contributor to the development of atherosclerosis, a buildup of material within the arteries that leads to heart attacks and strokes. The primary approach to treating hypercholesterolemia is to lower unusually high levels of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). High-density lipoproteins (HDL), however, are known to be anti-atherogenic, so elevated levels of HDLs are desired. Iwasaki *et al.* synthesized various arylnaphthalene lignans and found that some not only reduced total plasma cholesterol but also increased HDL cholesterol in cholesterol fed rats.[55] Lignan **39** (see Figure 1.19) was approximately 100 times more

**Figure 1.19**

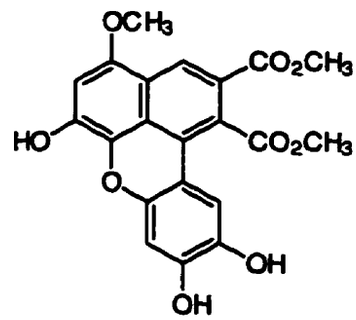



**39** **40** **41**

effective than cholestyramine, a known hypolipidemic agent, and its activity was perhaps in part due to the inhibition of cholesterol absorption into the intestine. Other lignans that were reported to lower cholesterol levels include (+)-episesamin (**40**) and (+)-sesamin (**41**) (see Figure 1.19).[56] These compounds and their enantiomers were also detected to be specific inhibitors of $\Delta^5$-desaturase, an enzyme that catalyzes the biosynthesis of polyunsaturated fatty acids.[57] Like high cholesterol levels, high levels of unsaturated fats are also linked to atherosclerosis.

Another approach to preventing atherosclerosis has been the pursuit of agents that limit lipid peroxidation. Biogenerated superoxide anions are largely scavenged by superoxide dismutase but will to some extent attack lipids when the defense function is weakened, leading to lipid peroxides. Lipid peroxides are believed to damage the intima of the aorta leading to arteriosclerosis and atherosclerosis. Limiting the peroxidation of LDLs by antioxidants was shown to result in atherogenesis suppression.[58] A series of studies by Maeda *et al.*[58-62] on the inhibition of lipid peroxidation in rat liver microsomes revealed potent lignan and neolignan activity, especially by **42** (see Figure 1.20) which had an $IC_{50}$ value of 0.95 μM and was much more effectual than $\alpha$-tocopherol (vitamin E).

**Figure 1.20**

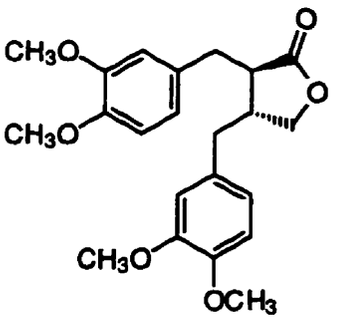



**42**

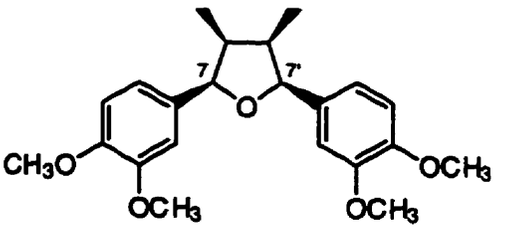
Considering these and other reports on the antioxidant activity of lignans,[63-69] it can be concluded that strong inhibition of lipid peroxidation requires the presence of at least one phenolic hydroxyl group along with multiple alkoxy groups on the same aromatic ring to help stabilize the formation of a phenoxy radical.

Lignans are potential drug candidates for treating inflammatory and respiratory disorders based on their antagonistic activity towards mediators of inflammation. One such inflammation mediator is the phospholipid 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine, better known as platelet activating factor or PAF for its involvement in the aggregation and degranulation of platelets and neutrophils. Lignans interrupt the aggregation of platelets by blocking the receptor to which PAF binds.[70] Epimagnolin A (**29**), with an $IC_{50}$ value of 0.42 μM, is a furofuran lignan that strongly inhibits PAF binding to platelets.[71,72] The PAF antagonistic activity of similar furofuran lignans[71-73] suggests that the presence of hydrophilic groups like phenolic hydroxyl and glucosyl substituents lowers activity. Conversely, the presence of at least one 3,4-dimethoxyphenyl or 3,4,5-trimethoxyphenyl group is required for high activity. PAF inhibition is also improved for furofurans if chiral centers C-7 and C-7' have the opposite configuration (see Figure 1.16). The diarylbutyrolactone dimethylmatairesinol (**43**), which

**Figure 1.21**




**43**

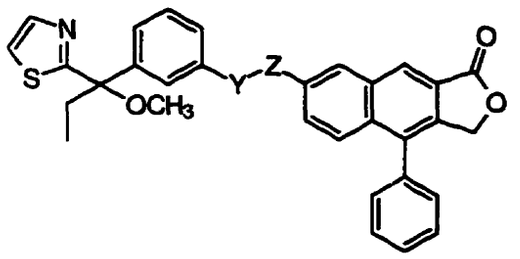



**44**

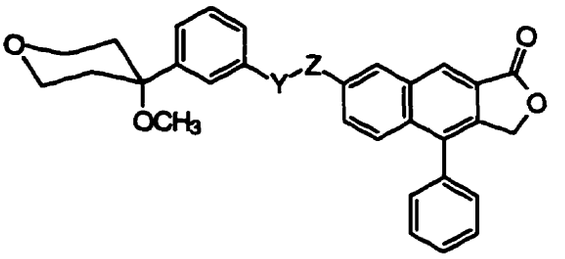
contains the 3,4-dimethoxyphenyl group (see Figure 1.21), has potent PAF inhibition ($IC_{50}$ = 0.56 μM).[71,72] One of the best PAF inhibiting lignans, shown in Figure 1.21, remains to be the 7,7'-diaryltetrahydrofuran lignan **44** ($IC_{50}$ = 0.2 μM).[74] Analogs of **44** show that compounds with this type of structure have the strongest action when C-7 and C-7' have the same configuration, especially the (*S*)-configuration.[75]

Leukotrienes are mediators of inflammation, and their biosynthesis from arachidonic acid, catalyzed by 5-lipoxygenase, is inhibited by the selective interaction of arylnaphthalene lignans **45-48** (see Figure 1.22) with the enzyme.[76] The *in vitro* $IC_{50}$ values of **45**, **46**, **47**, and **48** are 50, 160, 20, and 14 nM respectively.

**Figure 1.22**




**45**: Y = O, Z = $CH_2$
**46**: Y = $CH_2$, Z = O



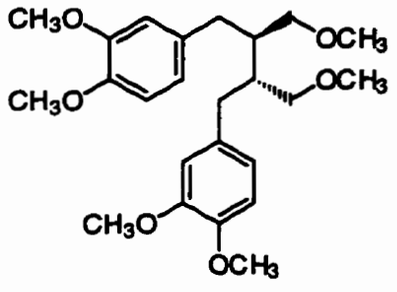

**47**: Y = O, Z = $CH_2$
**48**: Y = $CH_2$, Z = O

Lignans isolated from *Schisandra chinensis* and their derivatives were found to have CNS activity by altering the metabolism of cyclic adenosine-3',5'-monophosphate (cAMP), a second messenger within cells.[77] NDGA (**38**) was effective at suppressing cAMP phosphodiesterase ($IC_{50}$ = 1 μM), the enzyme responsible for catalyzing the irreversible hydrolysis of cAMP to the 5'-phosphate dianion. (-)-Syringaresinol (**37**), its enantiomer, and (+)-syringaresinol-di-*O*-β-D-glucoside displayed the ability to promote neurite outgrowth.[78] Neurite outgrowth is a basic mechanism in the development and

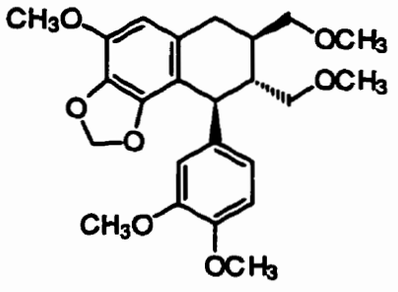
regeneration of nerve tissue and controlling its regulation can lead to the development of drugs for treating dementia disorders like Alzheimer's disease.

Some lignans were discovered to have hepatoprotective,[79] vasodilative,[80] immunosuppressive,[81] and anti-ulcer activity.[82] Other lignans, like phyllanthin (**49**) and hypophyllanthin (**50**) (see Figure 1.23), were able to enhance the action of the cytotoxic drug vinblastine in multidrug-resistant cells.[83] The medicinal plants *Nardostachys jatamansi* and *Aegle marmelos* have been used for treating epilepsy, hysteria, convulsion, heart palpitation, and diabetes. The components of these plants were elucidated and some were found to be lignans.[84,85]

**Figure 1.23**




**49**



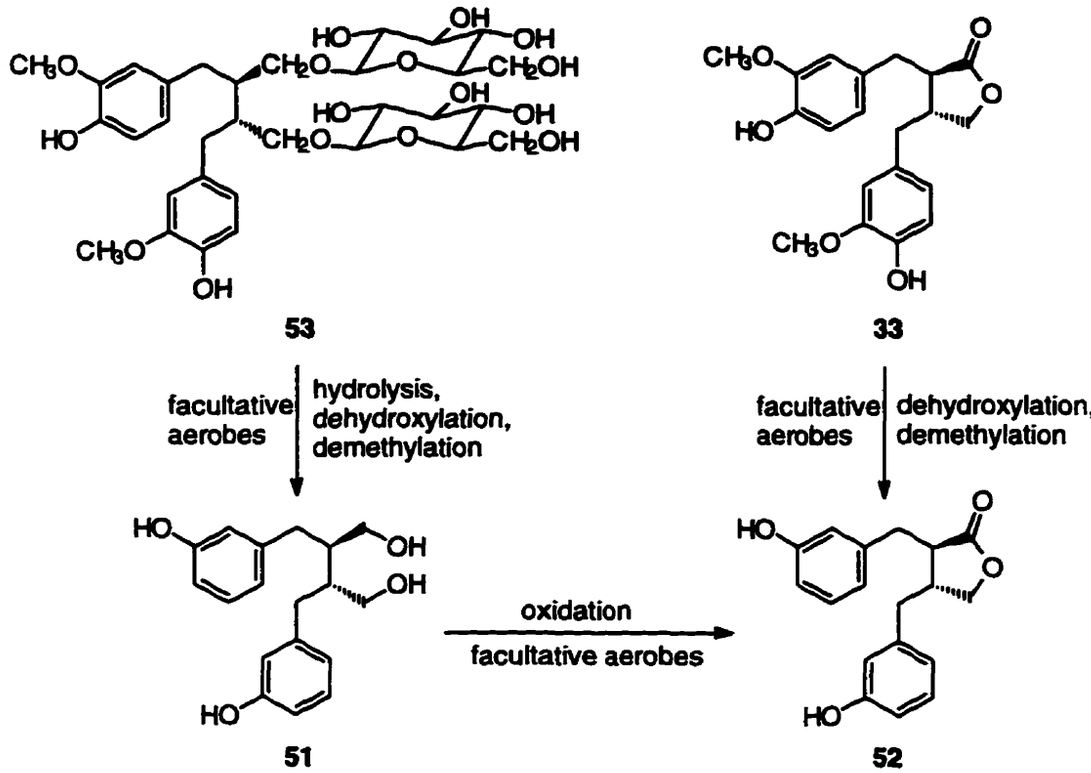

**50**

Numerous papers continue to be published that investigate the anti-tumour properties of etoposide and other lignans. The most recent publications, except those involving etoposide, include those by Miyahara *et al.*,[86] Evans *et al.*,[87] Middel *et al.*,[88] Cho *et al.*,[89,90] and Utsugi *et al.*[91]

Interestingly, lignans have been found in humans and other animals. The two major lignans that have been identified in animal urine, bile, serum, and seminal fluids are enterodiol (**51**) and enterolactone (**52**).[92,93] Mammalian lignans are distinguished from

those derived from plants by the fact that they possess phenolic hydroxyl groups only in the *meta* position of the aryl rings.

**Scheme 1.10**




The dietary plant precursors secoisolariciresinol diglucoside (**53**) and matairesinol (**33**) are converted into compounds **51** and **52** by gastrointestinal bacteria as shown in Scheme 1.10.[94]

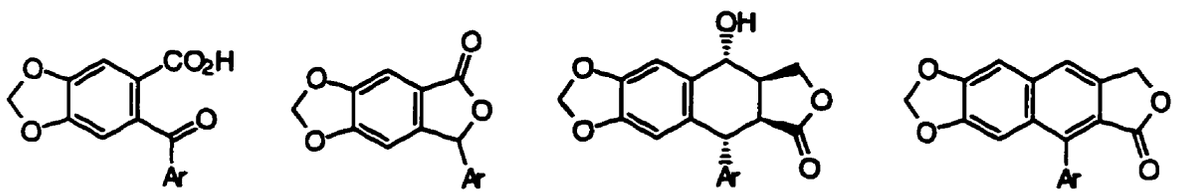
The speculation that mammalian lignans are formed because they may be biologically important is supported by a variety of studies. For example, mammalian lignans enhance the functions of polymorphonuclear leucocytes by stimulating the formyl-methionyl-leucyl-phenylalanine induced production of superoxide (required for killing

bacteria) and may thus increase protection against microbial infection.[95] Mammalian lignans also have notable anti-cancer activity.[23]

### 1.2.2 Discovery and Biological Activity of Deoxypodophyllotoxin

(-)-Deoxypodophyllotoxin (**8**) was first isolated by Noguchi and Kawanami in 1940.[96] The dried roots of *Anthriscus sylvestris* were extracted with diethyl ether, and the brown residue obtained (0.14%) was recrystallized from the same solvent giving a colourless crystalline compound named anthricin. Anthricin was determined to have a molecular formula of $C_{22}H_{22}O_7$. It was insoluble in water but soluble in hot alkali hydroxides. Hydrolysis with aqueous base followed by acidification gave isoanthricin, $C_{22}H_{22}O_7 \cdot H_2O$. The treatment of anthricin with hydrazine gave an acid hydrazide that decomposed to isoanthricin when acidified. Thus, it was assumed that a lactone ring was present. The oxidation of isoanthricin with hot $KMnO_4$ produced 3,4,5-trimethoxybenzoic acid, indicating the presence of a 3,4,5-trimethoxyphenyl nucleus. At room temperature, $KMnO_4$ treatment yielded 3,4-methylenedioxy-6-(3,4,5-trimethoxybenzoyl)benzoic acid

**Figure 1.24**

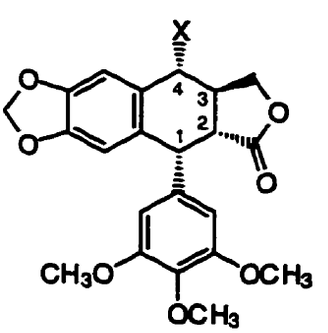



Ar = 3,4,5-trimethoxyphenyl

(**54**) and 5,6-methylenedioxy-3-(3,4,5-trimethoxyphenyl)phthalide (**55**), two products previously obtained from the oxidation of picropodophyllin (**56**).[97,98] The Pd/C mediated dehydrogenation of isoanthricin gave dehydroanhydropicropodophyllin (dehydrodeoxy-podophyllotoxin; **57**), a compound previously synthesized by Haworth and Richardson (see Figure 1.24).[99,100] From this chemical information, Noguchi and Kawanami[96] correctly deduced the general structure of anthricin (**8**) but did not propose the relative or absolute stereochemistry.

In 1942, Hata isolated a compound from the seed oil of *Hernandia ovigera* and named it hernandion.[101] Hernandion gave no melting point depression when mixed with anthricin and was thought to have the same basic structure.

**Figure 1.25**




**4**: X = OH
**8**: X = H
**58**: X = Cl

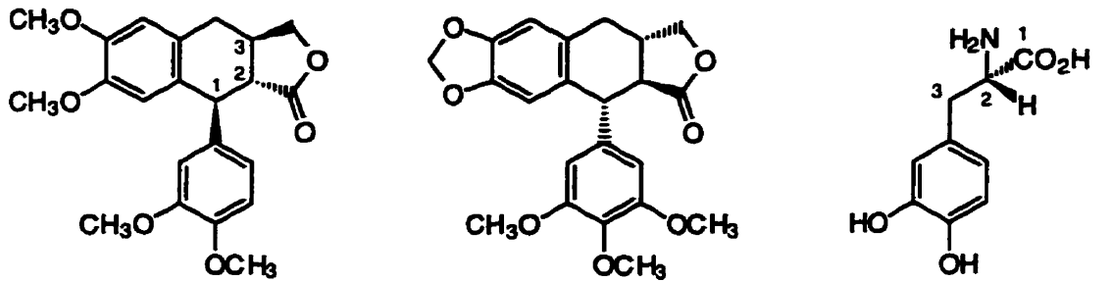
The relative stereochemistry of deoxypodophyllotoxin (**8**) was first established by Hartwell *et al.* in 1953.[102-104] The authors were prompted to find the active components of *Juniperus silicicola* after an aqueous suspension of the pulverized dried needles of this tree was found to damage Sarcoma 37 in mice.[102] A colourless crystalline compound that was very active against the tumour was isolated in 0.11% yield by a process involving a

series of extractions with organic solvents and chromatography on activated alumina followed by recrystallization from absolute ethanol.[102,103] The compound, named silicicolin, gave a positive Gaebel test for a methylenedioxy group. It was insoluble in water and cold 5% aqueous NaOH but soluble in hot 5% aqueous NaOH giving a precipitate upon acidification. This observation was indicative of a lactone group. The ultraviolet spectrum was similar to that of podophyllotoxin (**4**) and so was the infrared spectrum except for the absence of a hydroxyl group absorption at approximately 3450 $cm^{-1}$. The molecular formula of silicicolin, calculated as $C_{22}H_{22}O_7$, was also consistent with that of deoxygenated podophyllotoxin, and silicicolin was tentatively assumed to be a lignan.

Hartwell and Schrecker converted podophyllotoxin to the 4-chloro derivative **58** (see Figure 1.25)[25] and then hydrogenolyzed **58** to give the 4,4-dihydro derivative **8**, named desoxypodophyllotoxin.[103] Considering its method of formation, it was concluded that **8** had the same 1,2-*cis*-2,3-*trans* stereochemistry as that established for podophyllotoxin.[104] The melting point and optical rotation of **8** were found to be identical with those of silicicolin.[103] The authors also discovered that anthricin and hernandion were identical to **8**.[105] These names were henceforth replaced with the terms desoxypodophyllotoxin and deoxypodophyllotoxin, indicating the structural relationship to podophyllotoxin, the first lignan of this type discovered. The first isolation of deoxypodophyllotoxin from a *Podophyllum* species (*P. peltatum*) came in 1955 by Kofod and Jørgensen (0.1% yield).[106]

The absolute stereochemistry of (-)-deoxypodophyllotoxin (**8**) was deduced in 1957 by correlating its stereochemistry with that of (-)-$\alpha$-retrodendrin dimethyl ether

**Figure 1.26**

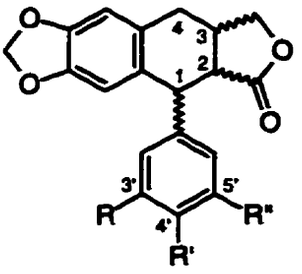



**59** **60** **61**

(**59**).[24] Lignan **59** and the structurally analogous (+)-isodeoxypodophyllotoxin (**60**) (see Figure 1.26) were known to have the 1,2-*trans*-2,3-*trans* stereochemistry. However, the optical rotations of these lignans, although about equal in magnitude, had the opposite sign. It was reasonable to conclude that these compounds had the opposite configurations at C-1, C-2, and C-3 since changes in the alkoxy substituents on the aryl rings of lignans were known to have little effect on their optical rotations. Furthermore, since **60** was proven to differ from deoxypodophyllotoxin by its configurations at C-2 and C-3, it was apparent that deoxypodophyllotoxin had the same configurations at C-2 and C-3 as **59**. Through a series of structural conversions with retention of configuration, the configuration at C-2 of **59** was correlated with that of natural amino acid 3-(3',4'-dihydroxyphenyl)-(S)-alanine (L-DOPA; **61**), the absolute stereochemistry of which was well established. This determined the absolute stereochemistry of (-)-**59** and, therefore, that of (-)-deoxypodophyllotoxin.

The biological activity of deoxypodophyllotoxin has been extensively reviewed and has been found to be very similar to that of podophyllotoxin.[21,26] Both compounds have been reported to have potent anti-mitotic, anti-tumour, and anti-viral activity. Deoxypodophyllotoxin inhibits *in vitro* microtubule assembly with an $ID_{50}$ value of 0.5

**Figure 1.27**



**4** (OH on C-4), **8**, **60**, **62-68**

**Table 1.1**

| No. | R | R' | R" | H(1)-H(2) | H(2)-H(3) | Name | $ID_{50}$ P-815 (mg/mL) |
|---|---|---|---|---|---|---|---|
| **4** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *cis* | *trans* | podophyllotoxin (P) (note: OH on C-4) | 0.005 |
| **8** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *cis* | *trans* | deoxypodophyllotoxin | 0.002 |
| **60** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *trans* | *trans* | (+)-isodeoxy-P | 0.02 |
| **62** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *trans* | *cis* | deoxypicro-P | 0.03 |
| **63** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *trans* | *trans* | (-)-isodeoxy-P | >10 |
| **64** | $OCH_3$ | $OCH_3$ | $OCH_3$ | *cis* | *cis* | isodeoxypicro-P | 0.05 |
| **65** | $OCH_3$ | OH | $OCH_3$ | *cis* | *trans* | 4'-demethyldeoxy-P | 0.005 |
| **66** | $OCH_3$ | $OCH_3$ | H | *trans* | *trans* | 5'-demethoxyisodeoxy-P | 0.4 |
| **67** | H | $OCH_3$ | H | *trans* | *trans* | 3',5'-demethoxyisodeoxy-P | 3 |
| **68** | H | H | H | *trans* | *trans* | 3',4',5'-demethoxyisodeoxy-P | 0.3 |

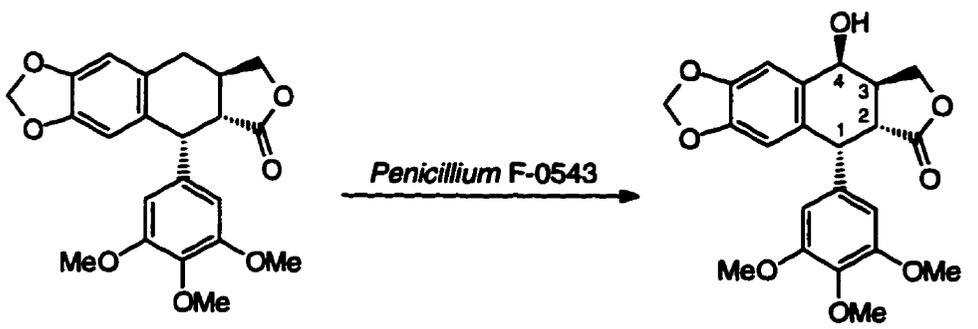
$ID_{50}$ = dose that inhibits mouse tumour cell (P-815) proliferation by 50%

μM while podophyllotoxin gives a slightly higher value ($ID_{50}$ = 0.6 μM).[29] Deoxypodophyllotoxin and podophyllotoxin give $ID_{50}$ values of 2 and 5 ng/mL respectively for inhibiting the proliferation of mouse tumour cells (P-815 mastocytoma) *in*

*vitro*.[26] The cytostatic activity of deoxypodophyllotoxin on these tumour cells has also been compared to that of its stereoisomers (**60, 62-64**) and some derivatives (**65-68**), none of which are as potent (see Figure 1.27 and Table 1.1).[26] Like podophyllotoxin, deoxypodophyllotoxin is also severely toxic to healthy cells, so derivatives such as etoposide (**16**) and teniposide (**17**), with $ID_{50}$ values of 78 and 7.6 nM respectively, have been sought for clinical use.

While it was the manipulation of the (-)-podophyllotoxin structure that led to the first synthesis of etoposide and teniposide, it is important to note that both of these compounds can be readily obtained from (-)-deoxypodophyllotoxin. For example, Kondo *et al.* discovered that deoxypodophyllotoxin (**8**) can be microbially converted to epipodophyllotoxin (**69**) in 100% yield (see Scheme 1.11).[107,108] Therefore, using this

**Scheme 1.11**




**8** **69**

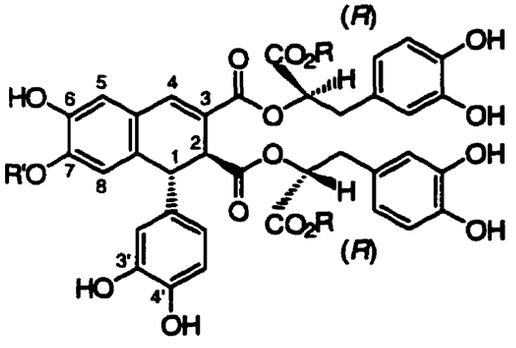
reaction, deoxypodophyllotoxin could be transformed to etoposide and teniposide in a similar route to that used for podophyllotoxin, as shown in Scheme 1.9. The deoxypodophyllotoxin procedure, though, would require fewer steps and give better yields of product. Also, the microbial transformation of deoxypodophyllotoxin is useful for preparing podophyllotoxin. Yamaguchi *et al.* efficiently oxidized the C-4 hydroxyl group

of epipodophyllotoxin (**69**) to give an intermediate ketone (podophyllotoxone) and then stereoselectively reduced the ketone with a variety of reducing agents, one of the best being zinc borohydride, to produce podophyllotoxin in *ca.* 65% yield.[109]

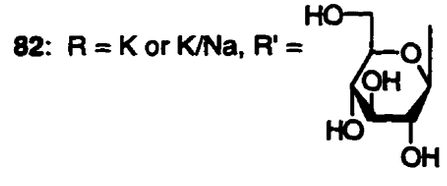
### 1.2.3 Discovery and Biological Activity of Rabdosiin and its (1*S*,2*R*)-Isomer

The isolation and structure determination of (-)-rabdosiin (**70**) by Agata *et al.* was reported in 1988 (see Figure 1.28).[110,111] Rabdosiin was obtained as a chromatographically pure light brown amorphous powder from the ethyl acetate extract of the acidified aqueous acetone homogenate of the powdered stem of *Rabdosia japonica*, the aboveground part of which has been used as a household medicine (enmeiso) in Japan

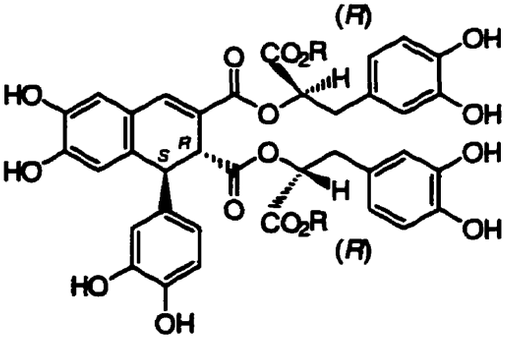
**Figure 1.28**



**70**: R = H, R' = H
**78**: R = Na/H, R' = H
**79**: R = K/H or Na/H (very minor), R' = H
**81**: R = K (major) or Na, R' = H



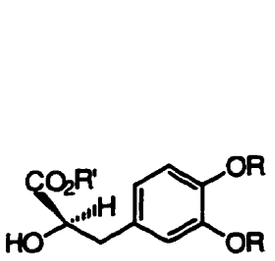
**82**: R = K or K/Na, R' =



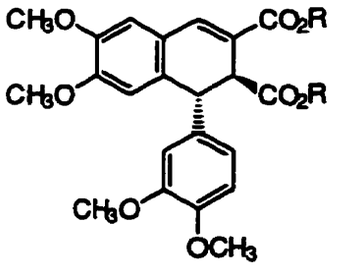
**75**: R = H
**80**: R = K/H or Na/H (very minor)

for treating gastrointestinal disorders. The positive ion and negative ion FAB mass spectra of **70** corresponded with the molecular formula $C_{36}H_{30}O_{16}$. From the $^{1}H$ NMR, $^{13}C$ NMR, and UV spectra of **70**, the authors concluded that this compound contained a 1,2-dihydro-6,7-dihydroxy-1-(3',4'-dihydroxyphenyl)naphthalene-2,3-dicarboxylic acid skeleton and two molecules of 3-(3',4'-dihydroxyphenyl)lactic acid (**71**). Rabdosiin was fully methylated with dimethyl sulfate and potassium carbonate, then hydrolyzed to give compound **72** and the known 3-(3',4'-dimethoxyphenyl)-(*R*)-lactic acid (**73**), as shown in Figure 1.29. The basic structure of **72** was established from its $^{1}H$ NMR spectrum and comparison of its IR, UV, and NMR spectra to those of a synthetic sample. The *trans* relationship of H-1 and H-2 was assigned based on coupling constants and nuclear Overhauser effect studies. The *R* and *S* configurations at C-1 and C-2 respectively were deduced by hydrogenating **72** to its 3,4-dihydro derivative **74**, the CD spectrum of which was analogous to those of structurally similar aryltetralin lignans possessing 1*R*,2*S* stereochemistry. The absolute structure of (-)-rabdosiin (**70**) was therefore elucidated.

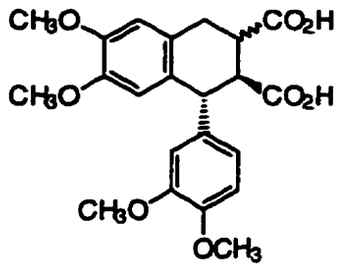
**Figure 1.29**




**71**: R,R' = H
**73**: R = $CH_3$, R' = H
**76**: R,R' = $CH_3$




**72**: R = H
**77**: R = $CH_3$




**74**

In 1990, (-)-rabdosiin (**70**) and its (+)-(1*S*,2*R*)-isomer (**75**) were isolated from the dried root of *Arnebia euchroma*, also known as *Macrotomia euchroma*, by Nishizawa *et*

*al.*[112] The roots of this plant have been used in China for treating epidemic hepatitis and preparing anti-inflammatory, anti-pyretic, and anti-bacterial medicines.[113] This was the first reported isolation of **75** (see Figure 1.28). The absolute structure of **75** was determined using a similar method to that used by Agata *et al.*[110,111] In this case, NMR and mass spectral data indicated that **75** was an isomer of (-)-rabdosiin (**70**). An octamethyl ether dimethyl ester derivative of each lignan, **70** and **75**, was prepared using a combination of diazomethane and dimethyl sulfate/potassium carbonate. Methanolysis of each derivative gave the known 3-(3',4'-dimethoxyphenyl)-(*R*)-lactic acid methyl ester (**76**) as shown in Figure 1.29. However, methanolysis of decamethyl (-)-rabdosiin also gave dimethyl ester **77** while the enantiomer of this compound was obtained from methanolysis of the decamethyl derivative of **75**, as determined from the $[\alpha]_D$ values (-51° and +53° respectively) and CD spectra. Thus, the absolute stereochemistry of **75** was deduced since the absolute stereochemistry of (-)-rabdosiin (**70**) had been already established.

In 1995, Kashiwada *et al.* reported the isolation of the monosodium salt of **70** (**78**), the monopotassium salt of **70** (**79**), the monopotassium salt of **75** (**80**), a mixture of the dipotassium (major) and disodium salts of **70** (**81**), and a mixture of the dipotassium and potassium/sodium salts of rabdosiin 7-*O*-$\beta$-D-glucoside (**82**) from *Arnebia euchroma* (see Figure 1.28).[113] These results suggested that lignans **70** and **75** exist in their salt forms in the plant material. The authors observed that rabdosiin (**70**), its (1*S*,2*R*)-isomer (**75**), and especially the monopotassium and monosodium salts thereof strongly inhibited HIV replication in infected H9 cells. Table 1.2 lists the concentrations at which these lignans inhibited viral replication and H9 cell growth by 50% ($EC_{50}$ and $IC_{50}$ respectively) and the corresponding therapeutic indices (T.I.). Rabdosiin and its isomer were also

**Table 1.2**

| Lignan No. | $EC_{50}$ (mg/mL) | $IC_{50}$ (mg/mL) | T.I. |
|---|---|---|---|
| **70** | 15 | 50 | 3.3 |
| **75** | 13 | 45 | 3.5 |
| **78** | 2.8 | 55 | 19.6 |
| **79** | 4.0 | 50 | 12.5 |
| **80** | 1.5 | 50 | 33.3 |
| **81** | 16 | 50 | 3.1 |
| **82** | 30 | 60 | 2.0 |

$EC_{50}$ = concentration that inhibits HIV replication by 50%
$IC_{50}$ = concentration that inhibits H9 cell growth by 50%
T.I. = therapeutic index ($IC_{50}/EC_{50}$)

potent inhibitors of mammalian DNA topoisomerase I and II *in vitro*.[114] In addition, (-)-rabdosiin was tested by Sakagami *et al.* for its ability to stimulate the iodination of human peripheral blood polymorphonuclear cells and monocytes[115,116] and by Hatano *et al.* for its inhibitory effect on xanthine oxidase,[117] but only weak activity was exhibited.

## 1.3 The Diels-Alder Reaction

In the Diels-Alder reaction, an alkene, the dienophile, adds to a conjugated diene to form a cyclohexene ring (see Scheme 1.12). This reaction is a type of cycloaddition, a reaction in which two unsaturated molecules couple to give a cyclic compound. The Diels-Alder reaction involves a system of four $\pi$-electrons and a system of two $\pi$-electrons

and is therefore classified as a [4 + 2] cycloaddition. The reaction is a concerted process and requires that the diene have the *cisoid* geometry to permit bonding interactions between the terminal carbon atoms of the diene and the carbon atoms of the dienophile. Dienes that are not frozen into the *cisoid* geometry or can not temporarily adopt this geometry are unreactive.[118]

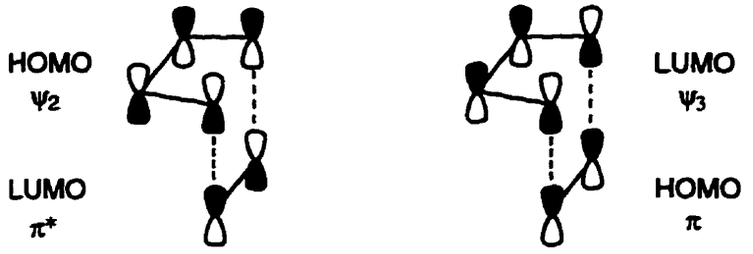
**Scheme 1.12**

Scheme 1.12 depicts the cycloaddition of ethylene, but this compound and other simple alkenes are seldom used in Diels-Alder reactions due to their poor reactivity. Substituted dienophiles containing electron withdrawing groups like COR, $CO_2R$, CN, and $NO_2$ react more readily, a phenomenon that may be rationalized on the basis of frontier molecular orbital (FMO) theory.

According to FMO theory, cycloaddition reactions are thermally allowed only when overlapping lobes between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other reactant have the same phase. The opposite requirement applies to photochemically allowed cycloadditions. Figure 1.30 shows the overlap between the HOMO of the diene and the LUMO of the dienophile and the overlap between the LUMO of the diene and the HOMO of the dienophile. The Diels-Alder reaction is thermally allowed in both processes. Both transition states are shown as being suprafacial meaning that the two new $\sigma$ bonds are

formed on the same face of the π system. It is highly unlikely that the new bonds would form on opposite faces, antarafacially, but this approach may occur in larger ring closures.

**Figure 1.30**

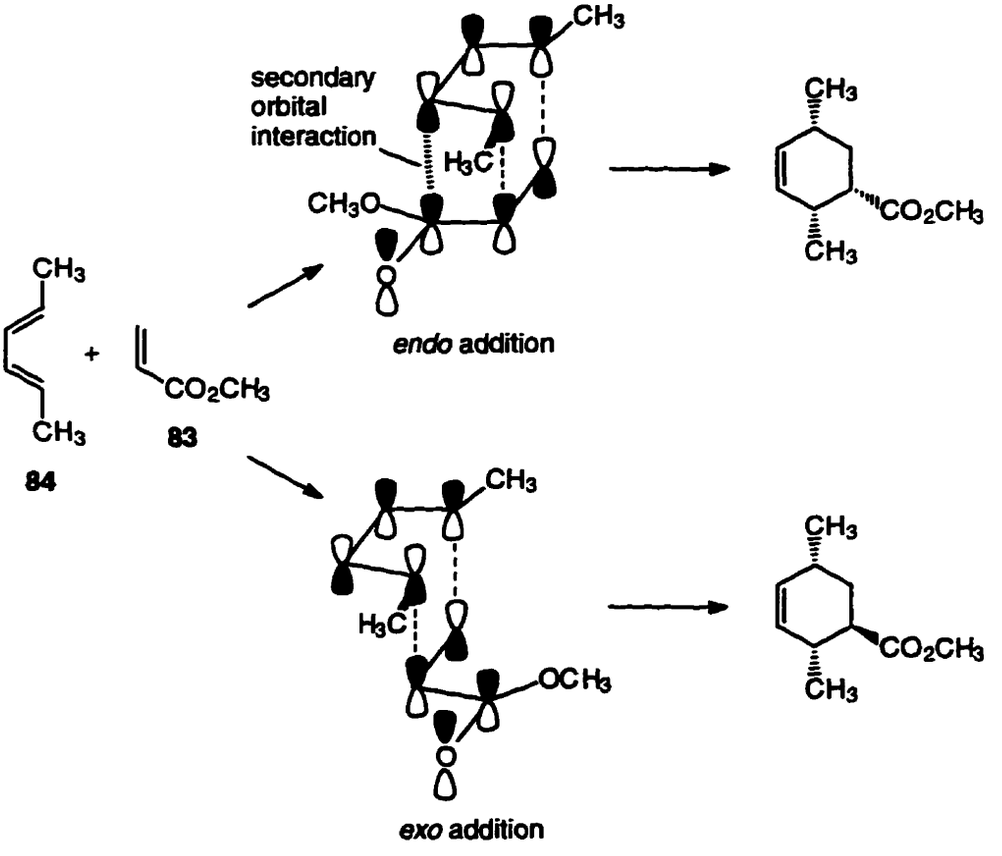



When the diene HOMO interacts with the dienophile LUMO, the diene behaves as a nucleophile and the dienophile behaves as an electrophile. This process is known as normal electron demand because it predominates over diene LUMO and dienophile HOMO interaction (inverse electron demand). The preference of one type of HOMO/LUMO interaction over the other is determined by the relative differences in energy. Placing an electron withdrawing substituent on the dienophile strengthens the dienophile LUMO and diene HOMO interaction by lowering the LUMO energy, therefore bringing it closer in energy to that of the diene HOMO. This theory is used to explain the general observation that electron withdrawing substituents in the dienophile accelerate Diels-Alder reaction rates while electron donating groups decrease reaction rates. The opposite effect is observed for substituted dienes.

The reaction of substituted dienophiles and dienes introduces the concern of stereoselectivity. One such concern is the possible *exo* or *endo* orientation that may occur in the transition state. For *exo* addition, the larger side of the dienophile projects away from the diene, whereas for *endo* addition it is the smaller side. These two orientations can lead to different products, depending on the extent of substitution of the reactants, as

illustrated by the addition of methyl acrylate (**83**) to *trans,trans*-1,4-dimethylbutadiene (**84**) in Scheme 1.13. Although the *endo* mode of addition is often more sterically hindered, it is usually preferred. This preference, known as the Alder rule,[119] is thought to result from the stabilizing interaction of secondary orbitals of like phase (see Scheme 1.13). This explanation however can not be applied to dienophiles that do not contain additional $\pi$ orbitals, and other factors like van der Waals attractions may explain preferred *endo* addition in these cases.

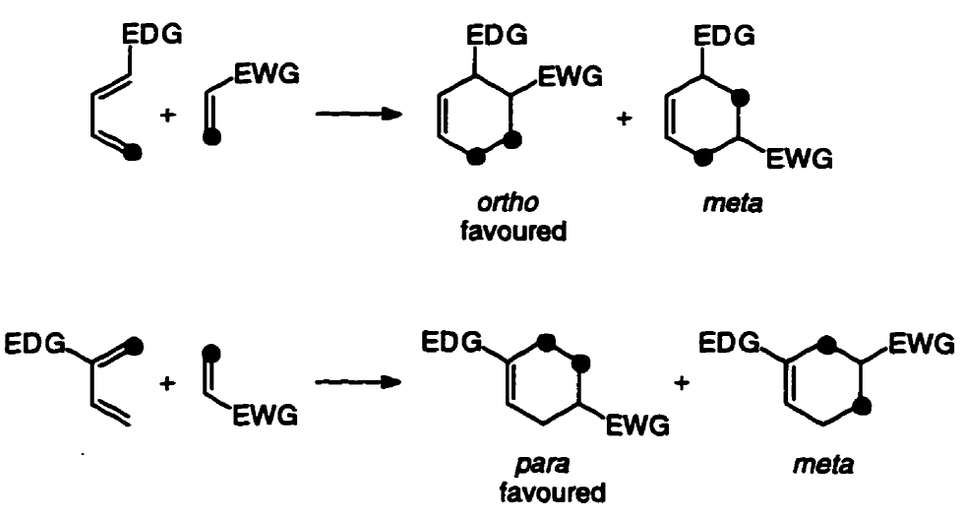
**Scheme 1.13**




When the dienophile and diene are both unsymmetrically substituted, regioselectivity can occur. In terms of normal electron demand, a diene that is substituted

with an electron releasing group at C-1 can react to give either an *ortho* or *meta* cycloadduct (see Scheme 1.14). Generally, the *ortho* product is favoured. Similarly, a diene substituted at C-2 usually prefers to give the *para* cycloadduct over the other possible *meta* regioisomer. FMO theory rationalizes the preference for the *ortho* and *para* regioisomers in that the strongest interaction will occur between the carbon atoms of the reactants having the larger coefficients in the frontier orbitals. That is, the coefficient of C-2 is higher than the coefficient of C-1 in the LUMO of a dienophile containing an electron withdrawing group (EWG). The coefficient of C-4 is higher than the coefficient of C-1 in the HOMO of a diene bearing an electron donating group (EDG) on C-1, but the coefficient of C-1 is higher for a diene substituted on C-2. Matching the carbon atom with the larger coefficient in the dienophile to that in the diene results in the favoured regioisomers shown in Scheme 1.14.

**Scheme 1.14**




●= carbon atom with higher coefficient in the frontier orbitals

Another stereochemical consideration with respect to the dienophile is that addition is stereospecifically *syn*. This means that substituents that are *cis* in the dienophile will be *cis* in the cyclohexene ring as a result of the aforementioned suprafacial transition state. 1,4-Disubstituted dienes also react in a stereospecifically *syn* manner. For example, the *trans,trans* dimethyl groups of **84** (see Scheme 1.13) become situated on the same face in the cycloadducts.

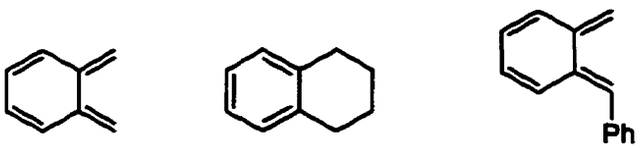
The Diels-Alder reaction produces four new $sp^3$-hybridized carbon atoms from four $sp^2$-hybridized carbon atoms. Therefore, as many as four chiral centers can be generated in the cyclohexene ring, depending on the substitution of the reactants. This implies that sixteen stereoisomers could theoretically be formed. However, due to the stereospecific *syn* addition of the reactants, the maximum number of stereoisomeric products is actually eight. To control the stereochemical outcome of the reaction is nevertheless extremely challenging especially since the possible stereoisomeric cycloadducts can consist of enantiomeric pairs. Thus, not only are *endo/exo* addition and regioselectivity important in providing stereoselectivity for the Diels-Alder reaction, but so is the selectivity that the dienophile may exhibit for one face of the diene if enantiomeric products are possible.

### 1.3.1 *ortho*-Quinodimethanes

The Diels-Alder reaction is a very useful tool for synthesizing many natural products because a cyclohexene ring containing many chiral centers can be produced in a

single step. It is particularly appealing for use in aryltetralin lignan synthesis because an *o*-quinodimethane (*o*-QDM) can function as the diene. *o*-Quinodimethanes, also known as *o*-xylylenes and *o*-quinodimethides, have the general structure **85** shown in Figure 1.31. These compounds are very short lived species, often less than one second in solution, due to the strong driving force to establish aromaticity in the six membered ring. However, for the same reason, they are also very reactive towards dienophiles and will undergo a Diels-Alder reaction when generated *in situ* in the presence of a dienophile. The cycloadduct would have the basic tetralin structure **86**, and placing an aromatic group on C-1 would provide an aryltetralin compound. If an *o*-QDM such as **87**, containing an aromatic substituent on the $\alpha$-position, were to react with a dienophile, an aryltetralin would be formed directly. Either method would provide a very efficient route to obtaining aryltetralin lignans.

**Figure 1.31**

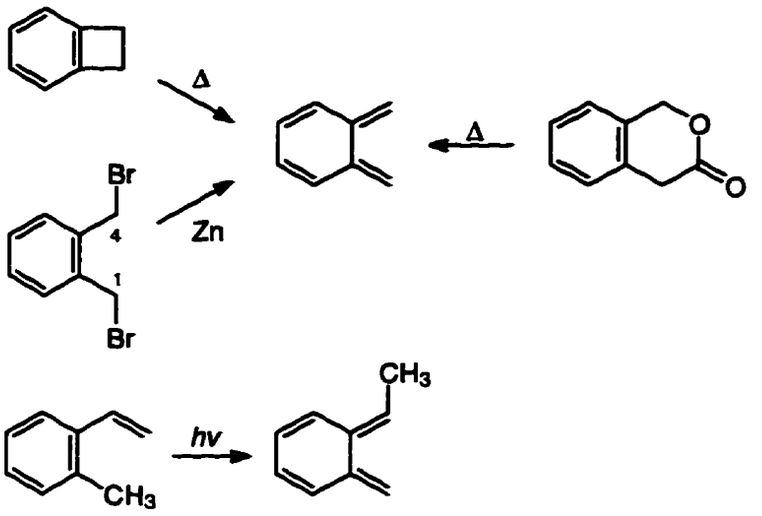



**85** **86** **87**

The various methods that can be used to produce *o*-QDMs include the thermolysis of benzocyclobutenes, 1,4-elimination processes, cheletropic expulsions ($CO_2$, $N_2$, $SO_2$, or CO), and photorearrangements.[120] These processes are represented in Scheme 1.15. The most popular way of preparing *o*-QDMs, which is the method used in this thesis work, is the thermolysis of benzocyclobutenes. The only major drawback of working with the usually unstable benzocyclobutenes is the difficulty in their synthesis, especially if they are

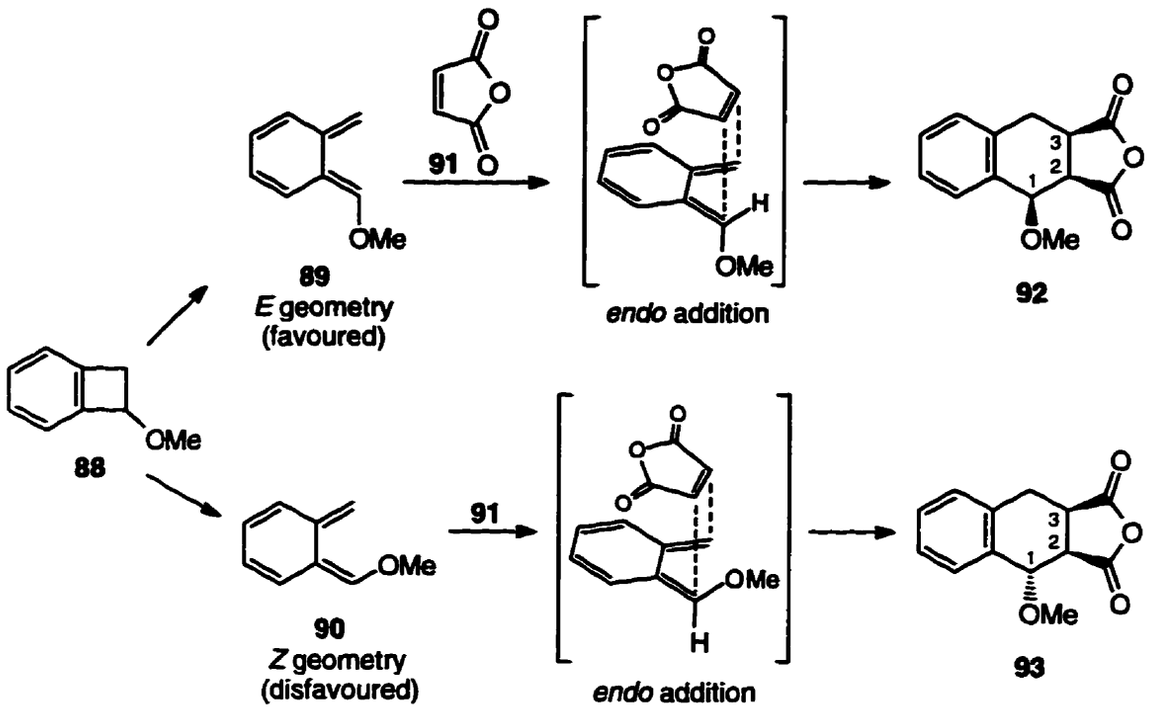
$\alpha$-substituted. The synthesis and reactivity of benzocyclobutenes were recently reviewed by Michellys *et al.*[121]

**Scheme 1.15**



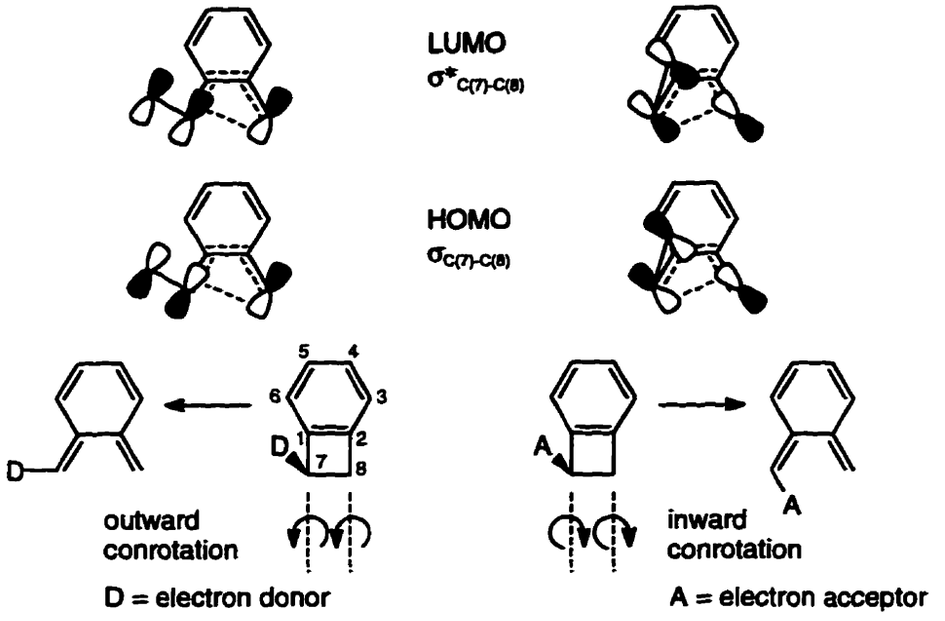

An interesting feature of the electrocyclic ring opening of a benzocyclobutene substituted on the four-membered ring is that as the C-C bond breaks, the substituent will favour rotation to either the outside or inside of the forming diene. For example, the thermolysis of 1-methoxybenzocyclobutene (**88**) results in the formation of *E*-*o*-QDM **89** (see Scheme 1.16) rather than the *Z*-isomer **90**.[122] This twisting preference, termed torquoselectivity, has been studied by Jefford *et al.* and was found to be affected by the type of substitution.[123] Monosubstitution with strong electron donors or weak electron acceptors like alkoxy, amino, alkyl, ester, cyano, and carboxylic acid groups favours outward rotation, but strong electron acceptors like ketone, iminium, amide, and formyl groups prefer inward rotation. Clearly, for inward rotation to occur, torquoselectivity must be controlled by some other factor besides steric effects. The Woodward-Hoffmann rules dictate that the thermally induced ring opening of benzocyclobutenes is a conrotatory

**Scheme 1.16**




process, *i.e.* both bonds C(1)-C(7) and C(2)-C(8) rotate in the same direction.[124] Considering conrotation and FMO theory, Jefford *et al.* believe torquoselectivity is caused by the interaction of molecular orbitals of the substituent and the breaking bond in the transition state (see Scheme 1.17).[123] The outward rotation of a donor group provides a stabilized transition state from the favourable mixing of the lone pair orbital on the donor substituent with the LUMO of the breaking σ* bond. However, inward rotation causes an unfavourable overlap of the doubly occupied donor orbital with the HOMO of the breaking σ bond, destabilizing the transition state. For acceptor groups, the transition state involving inward rotation is more stabilized because of the favourable interaction between the empty acceptor orbital with the HOMO of the breaking σ bond. Torquoselectivity becomes harder to predict for multisubstituted dienes, but outward twisting of the strongest electron donor present is often the trend.

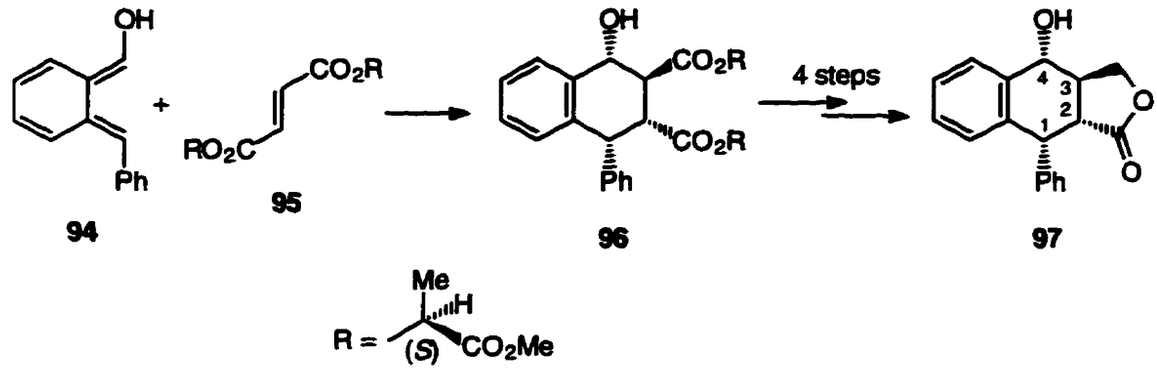
**Scheme 1.17**




Torquoselectivity can have a significant effect on the stereochemical outcome of Diels-Alder reactions. The reaction of thermolyzed benzocyclobutene **88** with maleic anhydride (**91**) shown in Scheme 1.16 is one example.[122] Maleic anhydride typically adds to dienes in an *endo* manner, and this reaction is no exception. Hence, the favoured *E*-*o*-QDM **89** reacts to give the all *cis* cycloadduct **92**. In contrast, if the *Z*-*o*-QDM **90** were preferred, compound **93** containing the 1,2-*trans*-2,3-*cis* geometry would be the prevalent product.

The geometry of certain *o*-quinodimethanes makes them ideal intermediates in the synthesis of the podophyllum type of aryltetralin lignans. These natural lignans have the 1,2-*cis*, and often the 2,3-*trans*, stereochemistry like that of podophyllotoxin (**4**). Charlton *et al.* have achieved this stereochemistry (see Scheme 1.18) by using various *o*-QDMs such as those that are $\alpha$-hydroxy-$\alpha'$-phenyl substituted.[125-127] For instance, the *E,E* geometry of **94** combined with the selective mode of addition of dienophile **95** leads

**Scheme 1.18**

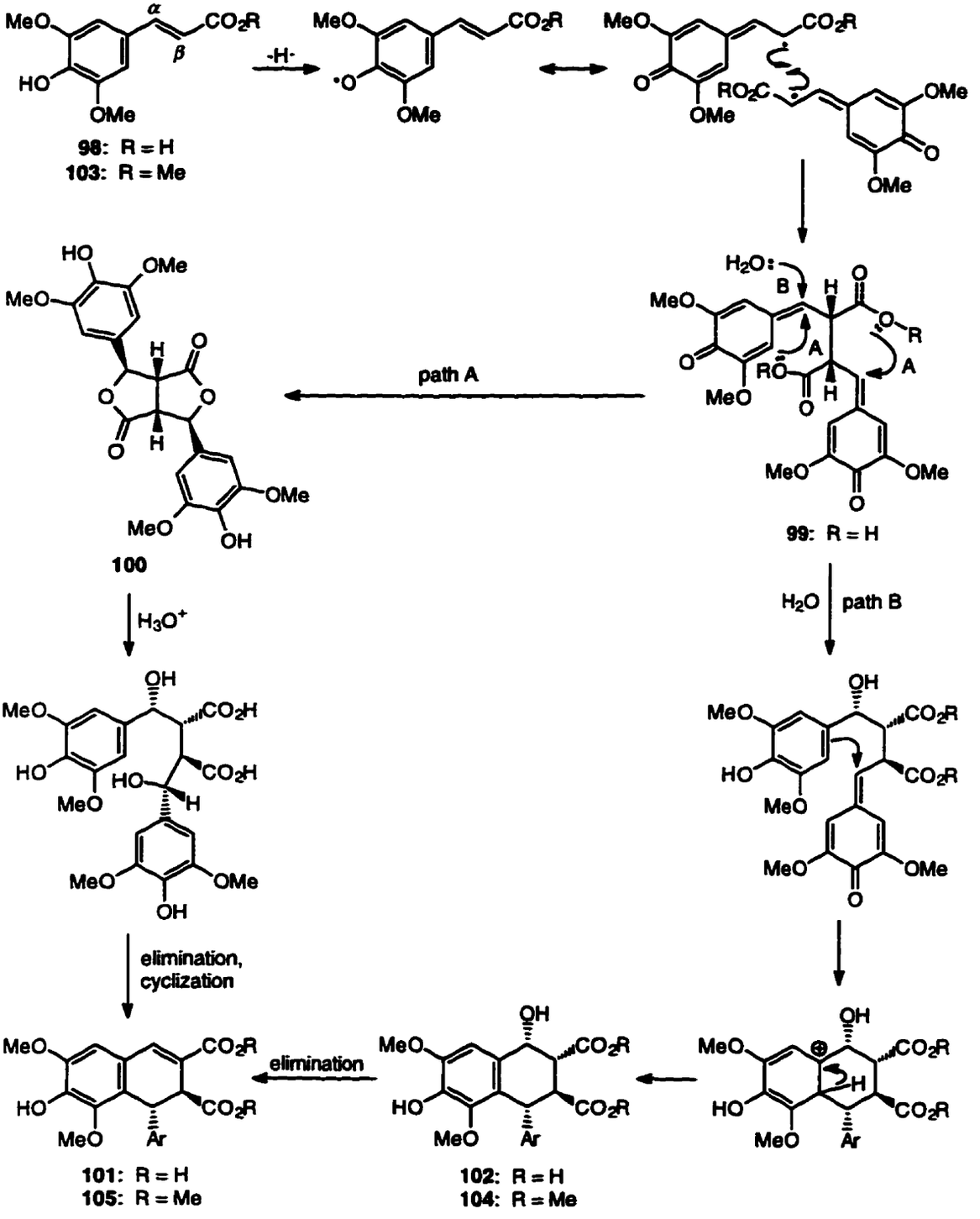



to the formation of major cycloadduct **96**.[125] Not only is the desired relative stereochemistry established in one step in this case, but so is the correct absolute stereochemistry. The (*S*)-chiral groups of **95** diastereoselectively control the addition between the *re* face of the dienophile and the *re* face of the *o*-QDM, thereby giving adduct **96** in 80% diastereomeric excess. By removing the chiral auxiliaries, **96** can subsequently be transformed to the enantiomerically pure (-)-podophyllotoxin analog **97**.[125] *o*-Quinodimethanes can therefore substantially contribute to asymmetric syntheses.

## 1.4 Oxidative Free Radical Coupling Reactions

Lignans are thought to be formed in nature by free radical reactions that join two phenyl propanoid units. One example is the aryltetralin thomasidioic acid (**101**), first isolated (as a racemate) from *Ulmus thomasii*,[128] which is likely biosynthesized by the coupling of two sinapic acid (**98**) molecules. A hypothetical mechanism for this transformation is shown in Scheme 1.19. One electron oxidation of **98** can occur to give

**Scheme 1.19**


98: R = H
103: R = Me
-H·
99: R = H
path A
100
H3O+
H2O
path B
elimination,
cyclization
elimination
101: R = H
105: R = Me
102: R = H
104: R = Me
Ar = 3,5-dimethoxy-4-hydroxyphenyl

the phenoxy radical. This resonance stabilized radical can dimerize with a similar radical at the $\beta$-carbons giving bisquinonemethide **99**. If the carboxylic acid groups of the bisquinonemethide react as shown for path A, intermediate **100** may be obtained. Under acidic conditions, **100** could lead to racemic lignan **101**. If path B is followed, the addition of water could lead to the formation of intermediate **102**, the dehydration of which would also give racemic **101**.

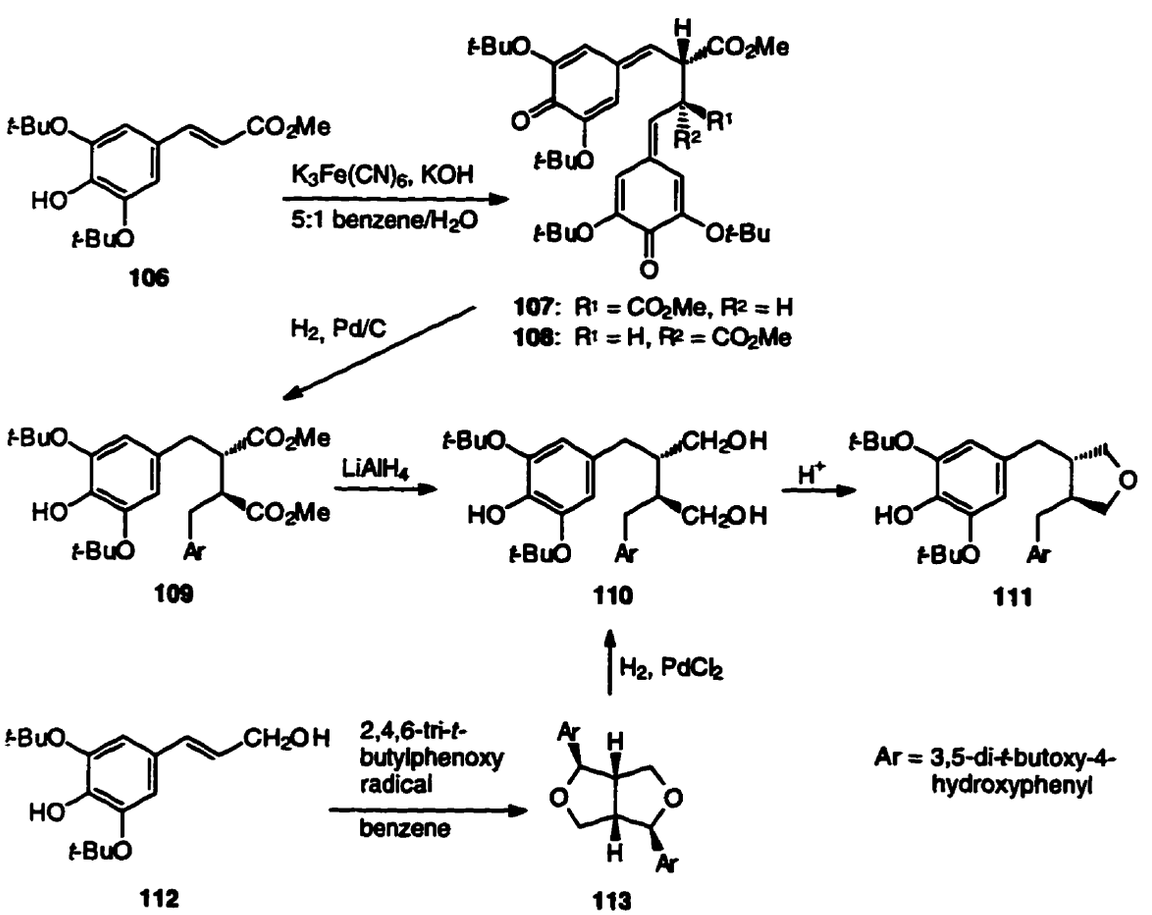
Both reaction pathways are plausible and are supported by experimental evidence published in 1973. Ahmed *et al.* treated sinapic acid (**98**) with the oxidant ferric chloride in a 1:4 methanol/water mixture and obtained dilactone **100** as the major product.[129,130] Treatment of **100** with aqueous acid led to the isolation of racemic **101**. In a similar fashion, Wallis used ferric chloride to oxidize the methyl ester of sinapic acid (**103**) in a 5:4 acetone/water mixture.[131] Both compounds **104** (major) and **105** were produced, and **104** was easily converted to **105** with acid. These reactions strongly suggest that oxidative coupling is the route by which natural lignans form, but more importantly to the synthetic organic chemist, they represent a very efficient one or two step approach to preparing lignans.

Various lignans have since been synthesized by using different oxidizing systems. Of note, the structures obtained from the intermolecular coupling of cinnamyl derivatives are very dependent on the substitution of the starting material and the type of oxidizing system used. This structural selectivity is exemplified by the reactions of sinapic acid (**98**) and methyl sinapate (**103**). The methyl ester group of **103** prevents the formation of dilactone **100**, the oxidation product from **98**, so **103** must form a different compound

(**104**). The methyl ester and carboxylic acid groups exert different structural control, but high diastereoselectivity is achieved in both cases.

The diastereoselectivity of oxidative couplings can be affected by the type of substitution on the aromatic ring. When ester **106** is oxidized by alkaline potassium ferricyanide, *threo*- and *erythro*-bisquinonemethides **107** and **108** are obtained in a 65:35 ratio respectively (see Scheme 1.20).[132] The *threo* stereochemistry is normally exclusively produced for this kind of coupling, as shown in Scheme 1.19. The lower diastereoselectivity for the coupling of **106** is attributed to steric hindrance experienced

**Scheme 1.20**



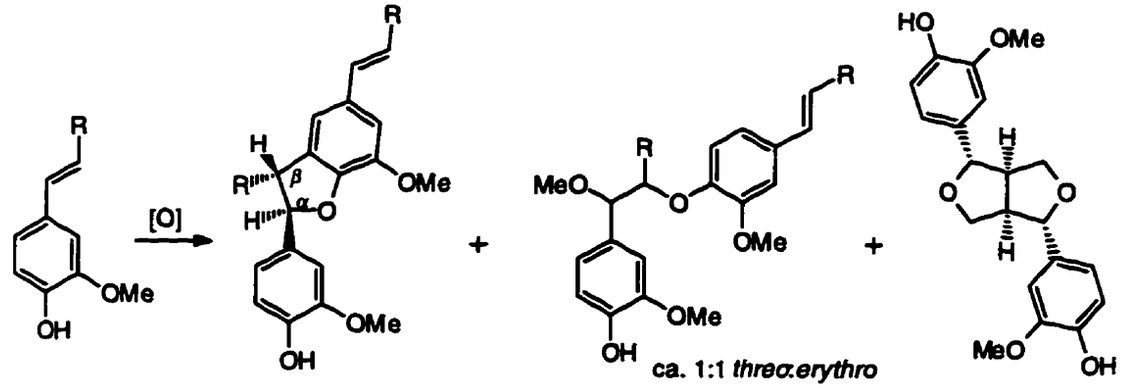
between the bulky *t*-butoxy groups during the formation of a complex that would lead solely to the *threo* product.

The structural selectivity observed for the oxidation of ester **106** is also intriguing. Ester **106** does not cyclize to an aryltetralin in a way analogous to the dimethoxy substituted **103** despite the presence of water, the addition of which is necessary for the cyclization of **103**. In contrast, the cyclization of alcohol **112** to furofuran **113**,[132] a reaction analogous to the formation of dilactone **100**, is not impeded when initiated by 2,4,6-tri-*t*-butylphenoxy radical in a non-aqueous medium. This implies that intramolecular nucleophilic addition of an alcohol is easier than intermolecular addition of water. It is unlikely that the *t*-butoxy groups prevent the cyclization of **106** since the cyclization of **112** is allowed. The prevented cyclization is more likely an effect of the reaction medium. The pH for the cyclization of **106** is much higher than that for **103** and **112**. Also, the reaction takes place in an immiscible two phase system. The relatively non-polar bisquinonemethides may be situated in the benzene phase where there is not much water available for further reaction.

While the direct production of a furofuran lignan provides an efficient lignan synthesis, the formation of a bisquinonemethide can also be useful. Bisquinonemethide **107** can be easily converted with retention of configuration to lignan **109** by hydrogenation.[132] Furthermore, **110**, a precursor to the tetrahydrofuran **111**, can either be obtained from **109** by hydride reduction or from **113** by hydrogenation.[132] The furofuran and bisquinonemethide reaction pathways therefore both have potential for lignan synthesis.

Neolignans are another structurally diverse product obtained from oxidative coupling reactions. These compounds form when coupling occurs at positions other than between two $\beta$-carbons of the cinnamyl precursor. Such a reaction is observed for methyl ferulate (**114**).[133] When **114** is treated with horseradish peroxidase and hydrogen peroxide in a buffered aqueous methanol solution, *$\alpha,\beta$-trans* neolignan **115** (racemic) is diastereoselectively obtained as the major product (see Scheme 1.21). Altering the ester group does not affect the preference for neolignan formation over $\beta$-$\beta$ coupling, as isoeugenol (**116**) gives compounds **117** (major) and **118** (minor), and coniferyl alcohol (**119**) produces compounds **120** (major) and **121** (minor).[133] Coniferyl alcohol also affords a minor amount of furofuran **122** (pinoresinol), the only lignan produced. Between pH 3 and 7.4, compounds **115**, **117**, and **120** are the major products, but yields are best at pH 3. Varying the methanol content from 10% to 90% increases the yields of **118** and **121**, but they remain the minor products. Thus, effects of the reaction medium also appear to be minimal.

**Scheme 1.21**




**114**: R = $CO_2Me$
**116**: R = $CH_3$
**119**: R = $CH_2OH$

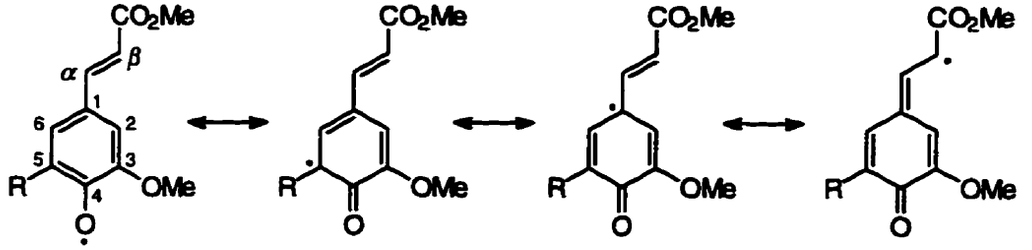
**115**: R = $CO_2Me$
**117**: R = $CH_3$
**120**: R = $CH_2OH$

**118**: R = $CH_3$
**121**: R = $CH_2OH$

**122**

The resonance structures for the methyl sinapyl (**103**) and methyl ferulyl (**114**) radicals are compared in Scheme 1.22. Two of the methyl sinapyl resonance structures are sterically hindered tertiary radicals. The primary radical with the lone electron situated on the oxygen is also sterically hindered by the two adjacent methoxy groups. The least sterically hindered resonance structure for **103** contains the unpaired electron on the $\beta$-carbon, and this is consistent with the fact that only $\beta$-$\beta$ coupling occurs for **103**. For the methyl ferulyl radical, the tertiary resonance structure is the only one that is significantly sterically hindered. Hence, coupling at the oxygen atom and C-5 is as sterically favourable as it is at the $\beta$-carbon for **114**, and this is consistent with neolignan formation in this case.

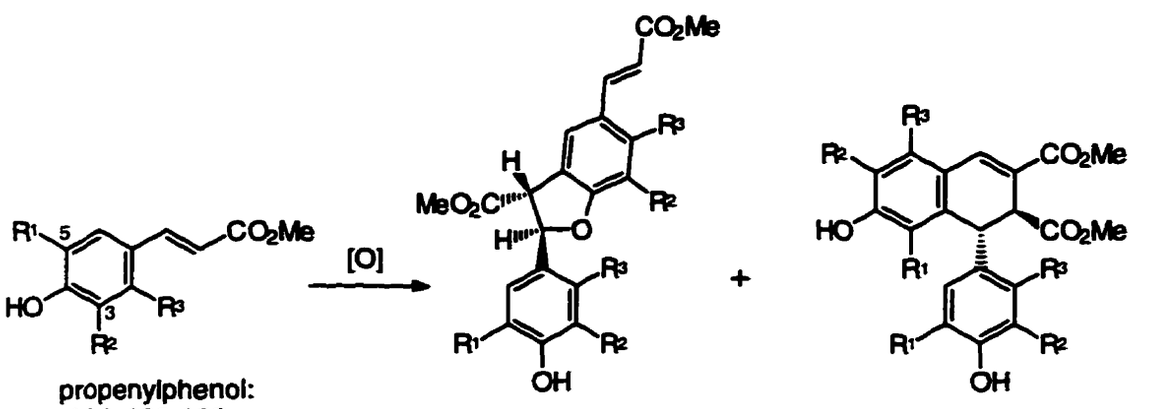
**Scheme 1.22**




**103**: R = OMe
**114**: R = H

The free radical oxidation of **114** and other substituted propenylphenols reveals that a neolignan product can usually be obtained provided that C-3 or C-5 is unsubstituted and sterically unhindered by adjacent groups, but the preference for neolignan versus aryltetralin formation can be dependent on the oxidant used (see Scheme 1.23 and Table 1.3). The conversion of **114** to dihydrobenzofuran **115** can be accomplished using either horseradish peroxidase and hydrogen peroxide,[133] or silver oxide.[58] Compound **115** is also

**Scheme 1.23**




propenylphenol:
**114, 123-126**

dihydrobenzofuran (DHBF):
**115, 127-129**

dihydronaphthalene (DHN):
**130-133**

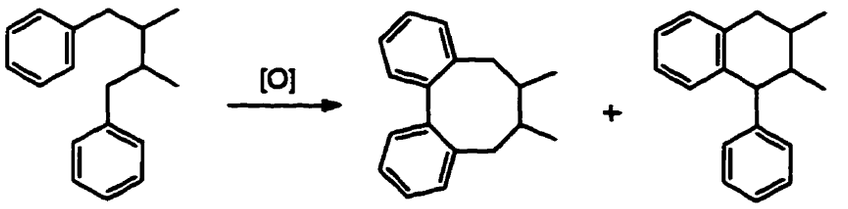
**Table 1.3**

| Propenylphenol | $R^1$ | $R^2$ | $R^3$ | Major Product | Oxidant |
|---|---|---|---|---|---|
| **114** | H | OMe | H | DHBF **115** | $Ag_2O$ |
| **114** | H | OMe | H | DHBF **115** (37%) (+ 31% DHN **130**) | $FeCl_3$ |
| **123** | H | H | OMe | DHBF **127** | $Ag_2O$ or $K_3Fe(CN)_6$ |
| **123** | H | H | OMe | no reaction | $FeCl_3$ |
| **124** | OH | H | OMe | DHN **131** | $Ag_2O$ or $K_3Fe(CN)_6$ |
| **124** | OH | H | OMe | no reaction | $FeCl_3$ |
| **125** | H | OH | OMe | DHBF **128** | $Ag_2O$ |
| **125** | H | OH | OMe | DHN **132** | $FeCl_3$ or $K_3Fe(CN)_6$ |
| **126** | H | OH | H | DHBF **129** | $Ag_2O$ |
| **126** | H | OH | H | DHN **133** | $FeCl_3$ |

the major product obtained when ferric chloride is the chosen oxidant, but a significant amount of dihydronaphthalene **130** is obtained as well.[59] Propenylphenol **123**, sterically unhindered at C-5, gives neolignan **127** on treatment with silver oxide or potassium ferricyanide.[60] Propenylphenol **124** is sterically hindered at both C-3 and C-5, so aryltetralin **131** is the preferred oxidation product.[59] Propenylphenol **125** and methyl caffeate (**126**) are both sterically unhindered at C-5, and their reaction propensities are intermediate between those of **123** and **124**. Silver oxide favours neolignan formation, whereas ferric chloride leads to aryltetralin production in both cases.[61]

While free radical coupling is a valid method for generating a lignan or neolignan from a hydroxycinnamate, it is likewise helpful for elaborating an already established lignan structure. That is, a diarylbutane lignan (**134**) can react with one-electron oxidants to give either a dibenzocyclooctadiene (**135**) or an aryltetralin (**3**) as the major product as shown in Scheme 1.24.[134-145] The structural selectivity of this intramolecular coupling, as for intermolecular coupling, is dependent on the nature of the substituents on the reactant and the type of oxidizing system employed. It should also be noted that both intermolecular[146] and intramolecular couplings[134-136,138,139,141,143-145] can occur without the presence of a phenolic hydroxyl group under the appropriate oxidizing conditions.

**Scheme 1.24**




**134** **135** **3**

Considering the high reactivity and unpredictability of free radical reactions, the fact that many structural isomers are produced from these reactions is not unexpected. This is consistent with the existence of various lignan structures in nature. However, it has been ascertained that this structural selectivity can usually be controlled by the manipulation of substituents and reaction conditions. Oxidative coupling reactions such as those discussed are therefore synthetically useful, especially since high diastereoselectivity is often achieved.

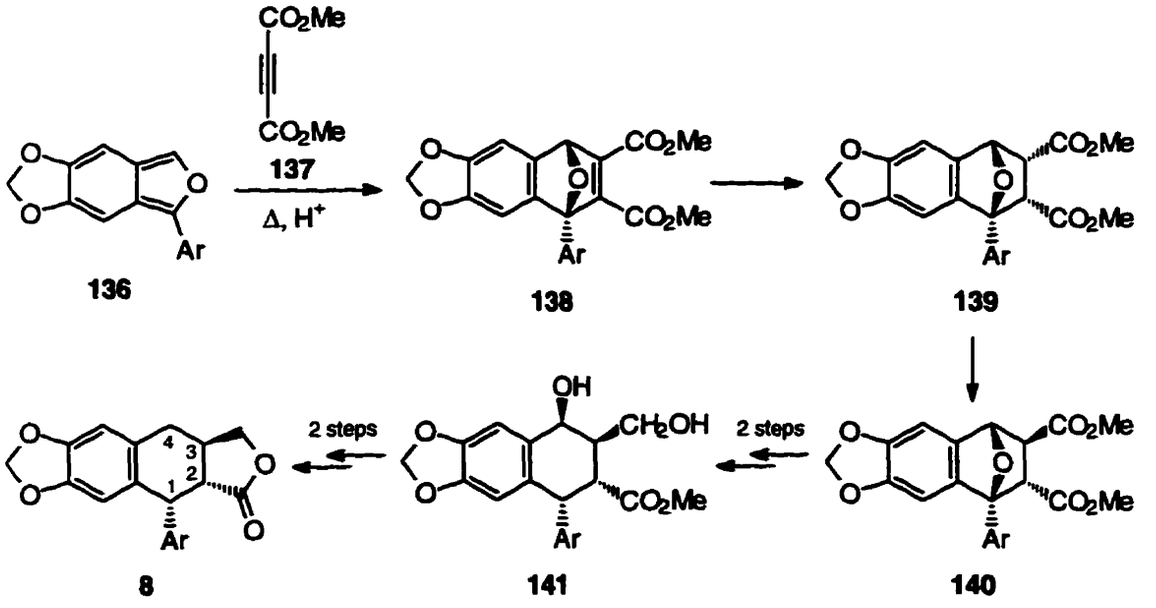
## 1.5 Syntheses of Deoxypodophyllotoxin

There have been numerous published syntheses of lignans over the years, many of which have been reviewed by Whiting,[147-149] Ayres and Loike,[23] and Ward.[150-153] However, few of these synthetic efforts have been directed at forming deoxypodophyllotoxin (**8**) and rabdosiin (**70**). Until now, there has been no reported synthesis of rabdosiin or its 1,2-*trans* isomer. While there are a few syntheses of deoxypodophyllotoxin in the literature, only one of these is an asymmetric synthesis.

All of the most recent racemic syntheses of deoxypodophyllotoxin have utilized a Diels-Alder reaction to establish the aryltetralin moiety. One of these syntheses was by Rodrigo whose approach is outlined in Scheme 1.25.[154] The prepared isobenzofuran **136** was reacted with dimethyl acetylenedicarboxylate (**137**) to give an aryltetralin cycloadduct (**138**) with a C(2)-C(3) double bond. Diastereoselective hydrogenation of the double bond exclusively gave **139** with the desired 1,2-*cis* stereochemistry but undesired 2,3-*cis*

stereochemistry. To obtain an intermediate with the necessary 2,3-*trans* stereochemistry (**140**), C-3 was regioselectively epimerized using sodium methoxide. The C-3 ester group of **140** was selectively reduced using lithium triethylborohydride followed by selective hydrogenolysis of the benzylic ether catalyzed by Raney nickel, giving diol **141**. A second hydrogenolysis removed the benzylic C-4 hydroxyl group, and subsequent acid-catalyzed lactonization gave deoxypodophyllotoxin (**8**).

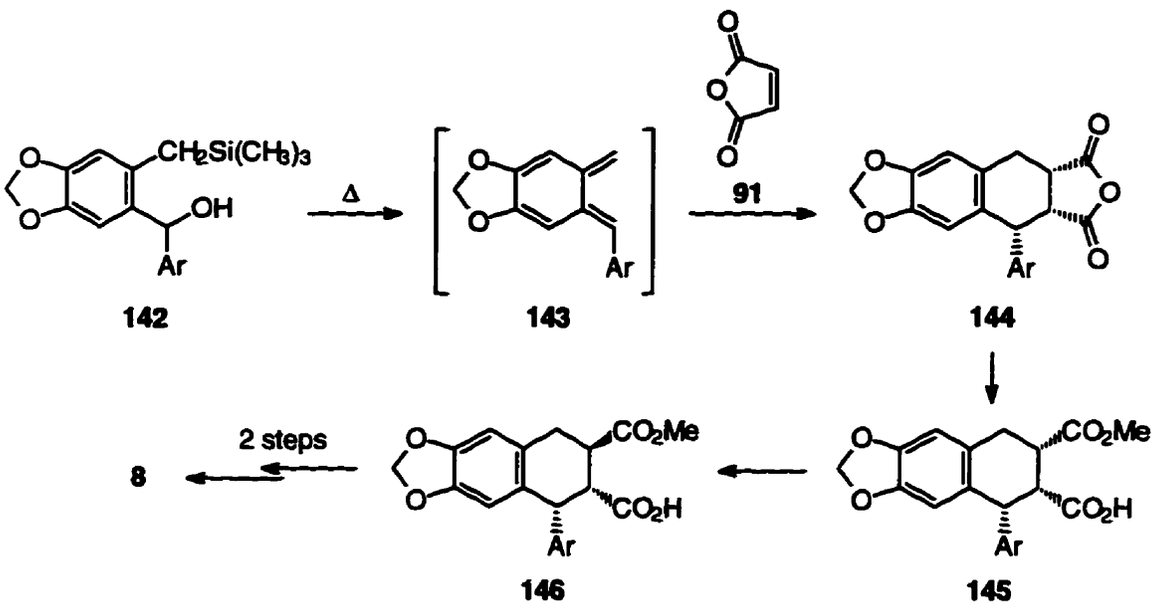
**Scheme 1.25**




A synthesis by Takano *et al.* made use of an *o*-quinodimethane intermediate (**143**) as the diene (see Scheme 1.26).[155] Intermediate **143** was prepared by the thermal 1,4-elimination of an *o*-(hydroxymethyl)benzylsilane (**142**), otherwise known as a Benzo-Peterson reaction. The generation of **143** in the presence of maleic anhydride (**91**) gave cycloadduct **144** via a diastereoselective *endo* transition state. The all *cis* stereochemistry of **144** was changed to the 2,3-*trans* stereochemistry in two steps. Selective methanolysis

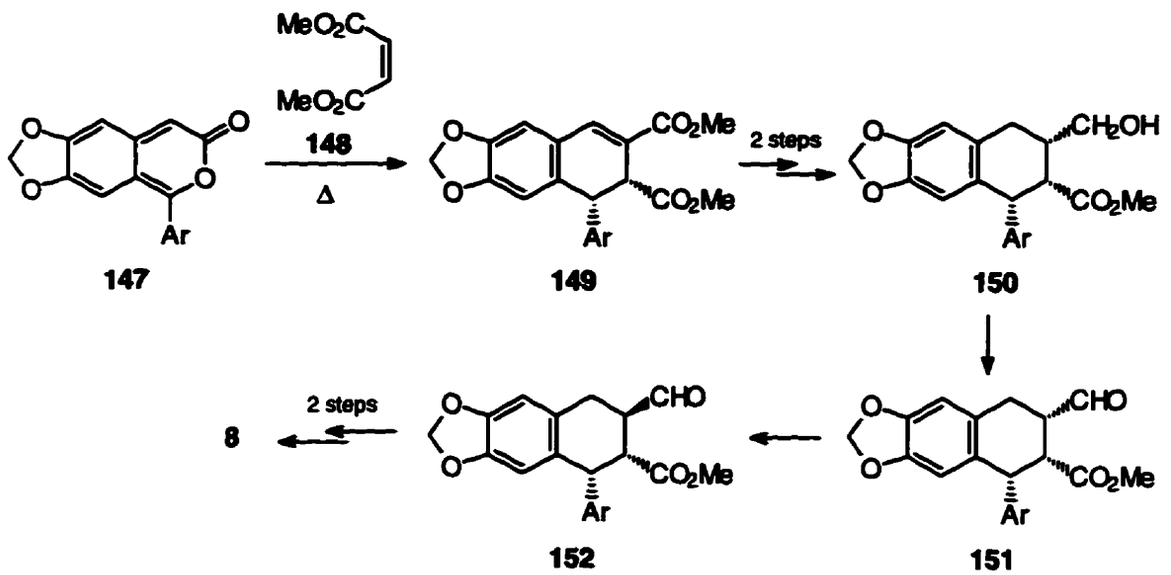
of the anhydride to ester **145** was followed by selective base-catalyzed epimerization at C-3 resulting in the formation of **146**. Compound **146** was reduced at the ester group to give a hydroxy acid intermediate which was lactonized to the desired product (**8**).

**Scheme 1.26**




Jones *et al.* used the Diels-Alder addition of a benzopyranone (**147**) to dimethyl maleate (**148**) to construct the aryltetralin unit (see Scheme 1.27).[156] The reaction proceeded selectively in an *endo* fashion accompanied by decarboxylation giving the 1,2-*cis* cycloadduct **149**. Selective reduction of the ester group on C-3 followed by hydrogenation of the less hindered face of the double bond gave hydroxy ester **150** having the all *cis* stereochemistry. The alcohol was oxidized to aldehyde **151** which was epimerized using DBU to give **152** with the appropriate 2,3-*trans* stereochemistry. Reduction of the aldehyde followed by lactonization afforded **8**.

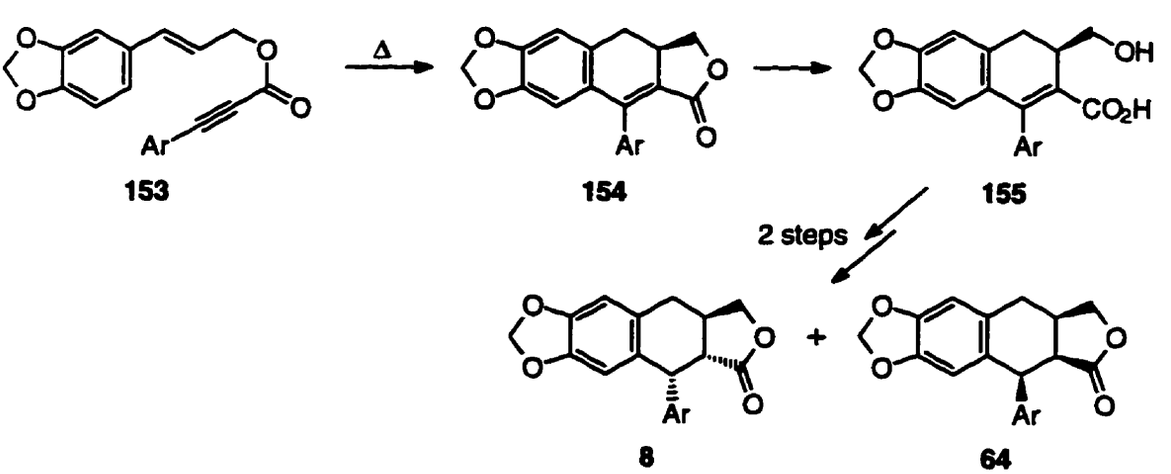
**Scheme 1.27**




Ar = 3,4,5-trimethoxyphenyl

The three racemic syntheses discussed thus far have all used intermolecular Diels-Alder reactions that led to intermediates requiring epimerization at C-3. In a different approach, Kashima *et al.* prepared a 1-aryl-3,4-dihydronaphthalene lactone (**154**) by an intramolecular cycloaddition of a cinnamyl phenylpropiolate (**153**) as shown in Scheme

**Scheme 1.28**

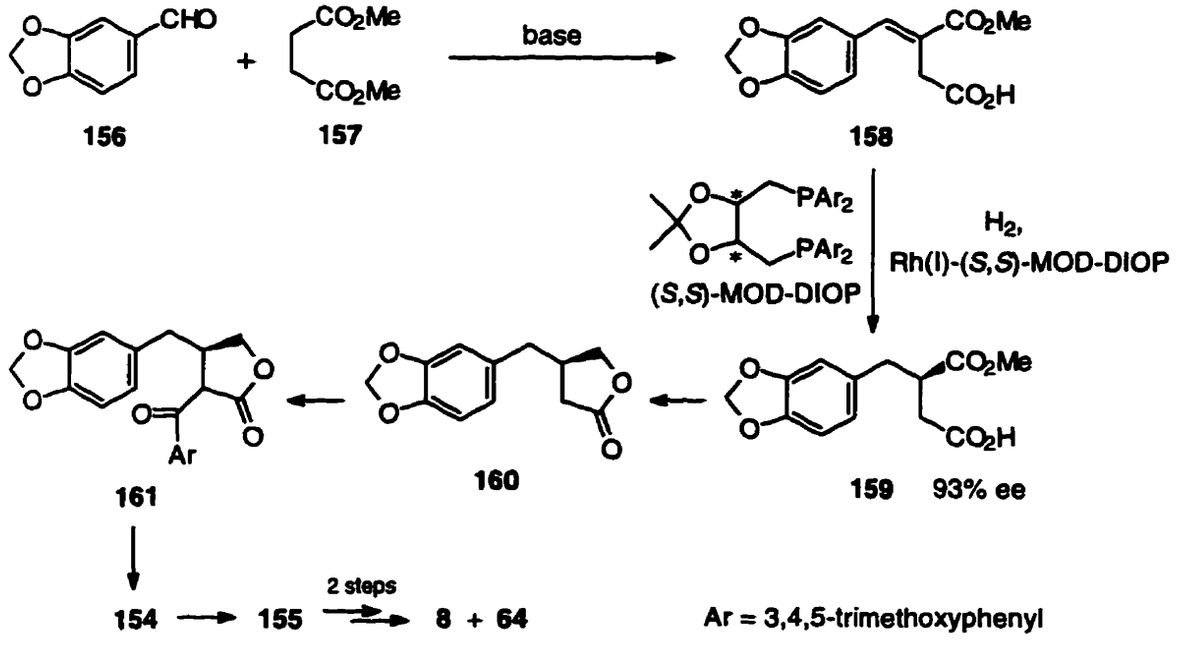



Ar = 3,4,5-trimethoxyphenyl

1.28.[157] Compound **154** was then hydrolyzed to hydroxy acid **155**. The last two steps of the synthesis involved palladium-catalyzed hydrogenation of the C(1)-C(2) double bond followed by direct lactonization without the isolation of any intermediates. An epimerization step was avoided, but unfortunately hydrogenation was not very selective, giving deoxypodophyllotoxin (**8**) and the all *cis* isodeoxypicropodophyllotoxin (**64**) in yields of 35% and 26% respectively from **155**.

An asymmetric synthesis of (-)-deoxypodophyllotoxin by Morimoto *et al.* is depicted in Scheme 1.29.[158-160] The desired absolute stereochemistry at C-3 was introduced in the early steps of the synthesis. After a Stobbe condensation of piperonal (**156**) and dimethyl succinate (**157**), the intermediate **158** was enantioselectively hydrogenated to **159** (93% ee) using a chiral rhodium(I) bisphosphine catalyst. Reductive lactonization to **160** using calcium borohydride, acylation to **161** with 3,4,5-trimethoxy-

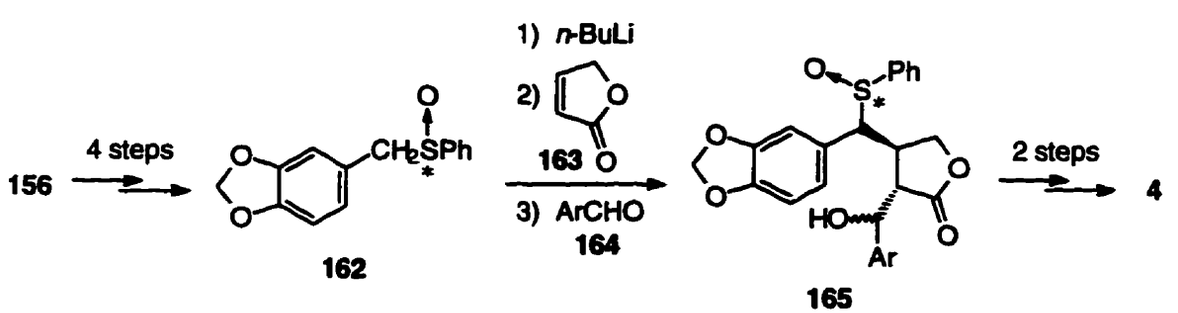
**Scheme 1.29**



benzoyl chloride, followed by dehydrative ring closure afforded aryltetralin **154**. For the conversion of **154** to (-)-deoxypodophyllotoxin, Morimoto *et al.* followed the same procedure used by Kashima *et al.*[157] In this case, palladium-catalyzed hydrogenation of intermediate **155** led to the isolation of (-)-**8** and (+)-**64** in yields of 37% and 25% respectively. The yield for the formation of **158** was not reported, but the overall yield of (-)-deoxypodophyllotoxin (**8**) from **158** was about 9.7%.

It is important to note that deoxypodophyllotoxin can be synthesized from podophyllotoxin (**4**) by catalytic hydrogenolysis of the benzylic hydroxyl group on C-4.[161] Therefore, asymmetric syntheses of podophyllotoxin (see Whiting[149] and Ward[150,151,153]) can also be considered as methods for obtaining enantiomerically pure deoxy-podophyllotoxin. A recent asymmetric synthesis of (-)-podophyllotoxin (**4**) by Hadimani *et al.* was accomplished through a tandem conjugate addition (see Scheme 1.30).[162] The

**Scheme 1.30**

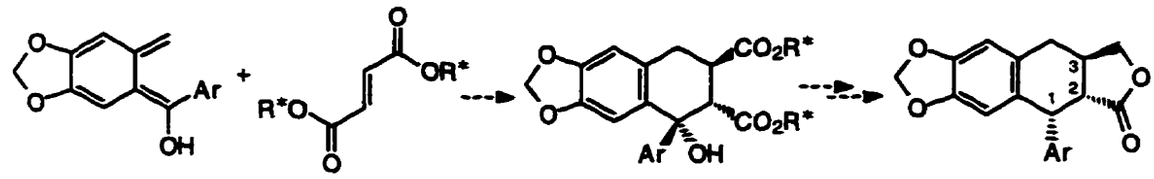



chiral sulfoxide **162** was prepared from piperonal (**156**) by hydride reduction to piperonol, conversion to piperonyl bromide with HBr, alkylation by sodium thiophenolate to piperonyl phenyl sulfide, followed by asymmetric sulfoxidation using a modified Sharpless procedure (*t*-butyl hydroperoxide, water, titanium tetraisopropoxide, and (*R,R*)-(-)-diethyl

tartrate). The anion of (*S*)-(-)-piperonyl phenyl sulfoxide (**162**) added enantioselectively to butenolide **163** giving an intermediate anion that was subsequently reacted with 3,4,5-trimethoxybenzaldehyde (**164**). The resulting lactone (**165**) was converted to (-)-podophyllotoxin by acid-catalyzed cyclization followed by removal of the chiral auxiliary using mercuric oxide and boron trifluoride etherate.

# Thesis Objectives

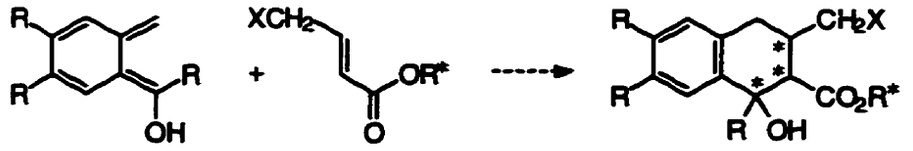
**1) To develop an asymmetric synthesis of the aryltetralin lignan (-)-deoxypodophyllotoxin.**



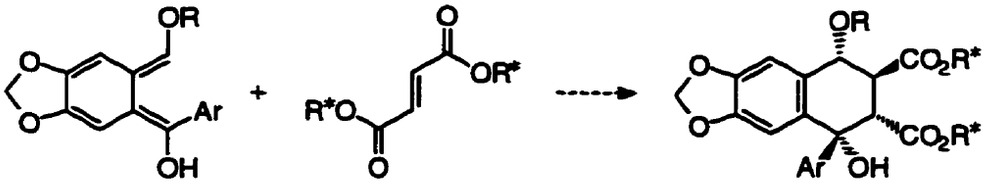

It was previously established that the Diels-Alder reaction of $\alpha$-hydroxy-$\alpha$-phenyl-*ortho*-quinodimethane with bis(methyl (*R*)-mandelyl) fumarate proceeded in a highly diastereoselective manner. A single aryltetralin cycloadduct was obtained possessing three newly formed chiral centers. Based on the relative configurations at these chiral centers, it appeared that this cycloadduct might be a suitable intermediate for the asymmetric synthesis of many biologically active aryltetralin lignans, provided that the reaction could be extended to *o*-quinodimethanes substituted on the aryl rings.

Many biologically active aryltetralin lignans have the 1,2-*cis*-2,3-*trans* stereochemistry found in the natural product podophyllotoxin, and many attempts have been made by others to find efficient synthetic methods to this class of compounds. A new approach to these compounds, based on the cycloaddition reaction of $\alpha$-hydroxy-$\alpha$-phenyl-*o*-quinodimethane, was investigated with the primary goal of preparing the lignan (-)-deoxypodophyllotoxin. To control the absolute stereochemistry, the asymmetric cyclization of an appropriately substituted $\alpha$-aryl-$\alpha$-hydroxy-*o*-QDM with a chiral dienophile was attempted.

**2) To improve upon the Diels-Alder approach for synthesizing aryltetralin lignans.**



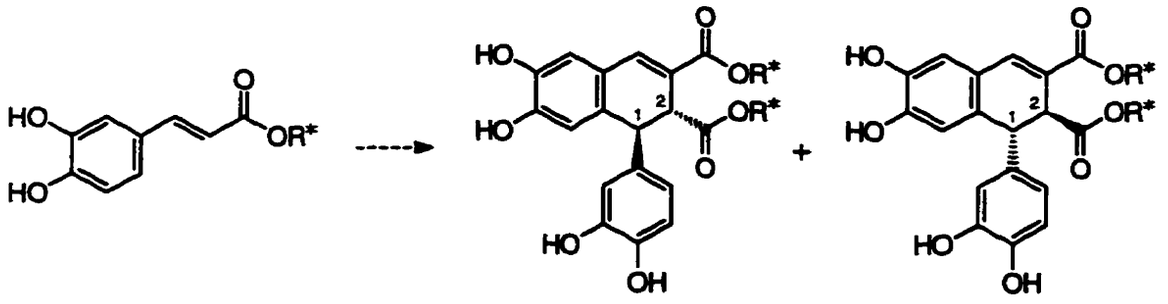

Some asymmetric syntheses of aryltetralin lignans have been accomplished by using a Diels-Alder reaction of a symmetrical fumarate diester with an *o*-QDM. A drawback in using this method is that it can be difficult to chemically differentiate between the two ester groups of the cycloadduct in a later step. A solution to this problem would be to use an unsymmetrical dienophile. Therefore, a study was performed to assess the reactivity and stereoselectivity of 4-halo and 4-oxy derivatives of a chiral crotonate ester when reacted with different *o*-QDMs. The adducts from these dienophiles would be more amenable to later functional group transformations and would provide an efficient route to the butyrolactone moiety found in lignans such as deoxypodophyllotoxin.




The Diels-Alder approach for synthesizing lignans can also potentially be improved by making changes to the *o*-quinodimethane. The generation of an $\alpha$-aryl-$\alpha,\alpha'$-dihydroxy-*o*-QDM and an $\alpha$-aryl-$\alpha$-hydroxy-$\alpha'$-siloxy-*o*-QDM was of interest. Past research showed that an $\alpha$-aryl-$\alpha$-hydroxy-$\alpha'$-alkoxy-*o*-QDM could be generated and converted to racemic podophyllotoxin via an intramolecular Diels-Alder reaction. Thus, the preparation of a different *o*-QDM, one that could possibly undergo an intermolecular cycloaddition, was

pursued by way of a benzocyclobutene precursor. An intermolecular reaction was desired since it could lead to the asymmetric synthesis of (-)-podophyllotoxin.

**3) To achieve a synthesis of (+)-rabdosiin and its (-)-(1*R*,2*S*)-isomer.**




Two oxidative coupling reactions that have been used in lignan synthesis include the dimerization of methyl sinapate to racemic dimethyl thomasidioate and the dimerization of methyl caffeate to an analogous aryltetralin lignan. Based on these precedents, it seemed possible that the aryltetralin (+)-rabdosiin and its (-)-(1*R*,2*S*)-isomer could be synthesized from (*S*)-(-)-rosmarinic acid, a chiral caffeic acid ester, using similar oxidative coupling/cyclization conditions. Furthermore, there was an interest in whether one of these lignans could be formed stereoselectively due to asymmetric induction by the chiral ester group. In order to attempt a synthesis of (+)-rabdosiin and its (1*R*,2*S*)-isomer, a synthetic route to the precursor (*S*)-(-)-rosmarinic acid was pursued. If the oxidative coupling/cyclization of (*S*)-(-)-rosmarinic acid were successful, the process would also be applicable to the synthesis of the (*R*)-isomer, and therefore (-)-rabdosiin and its (1*S*,2*R*)-isomer. These latter compounds are known natural products, and they have significant biological activity.

# Chapter 2

# Results and Discussion

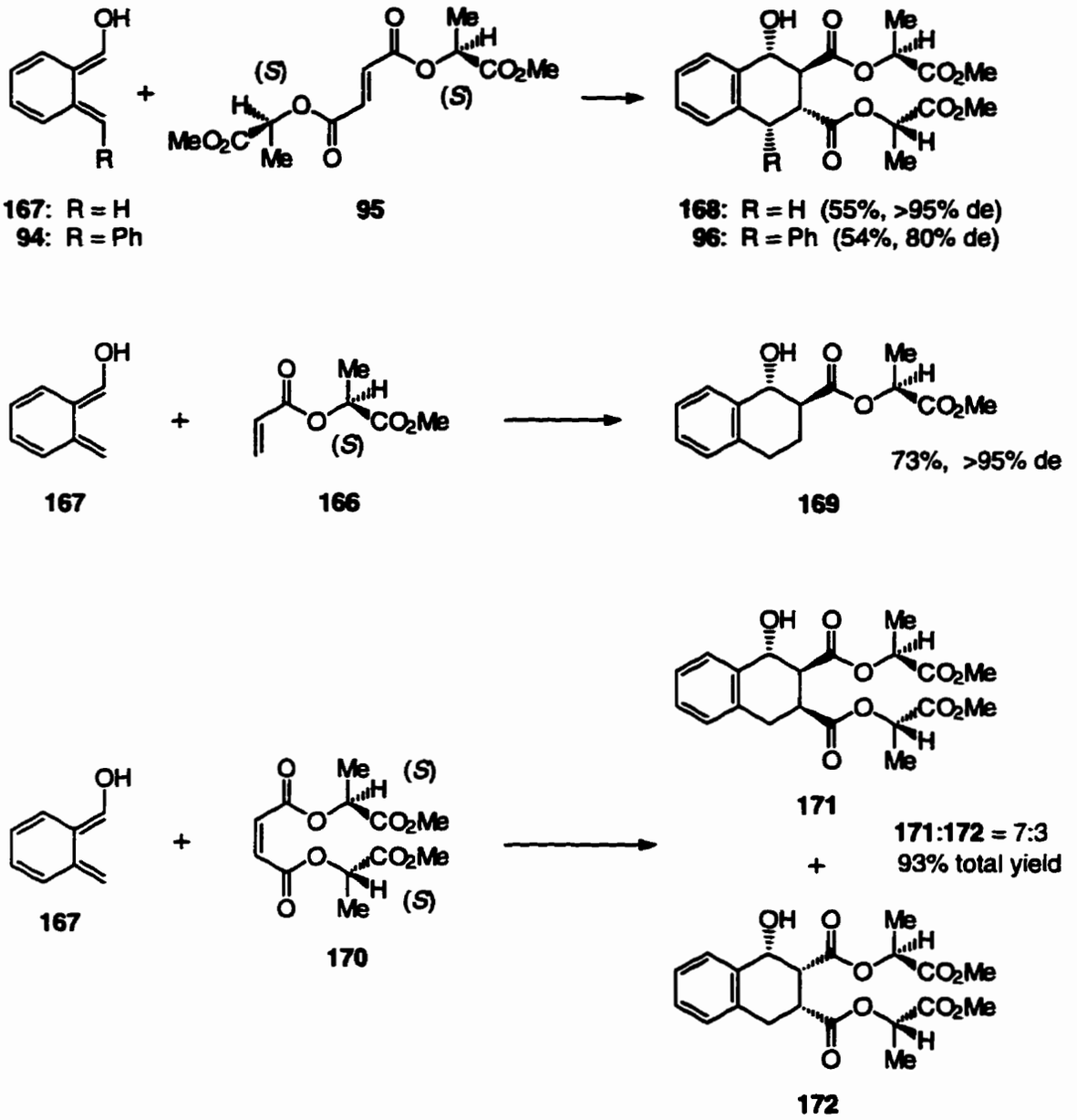
This chapter is divided into three main sections. The first section contains a discussion of the synthesis of enantiomerically pure (-)-deoxypodophyllotoxin along with an examination of an unprecedented stereoselective ionic reduction developed during this synthesis. The second section describes efforts aimed at improving the Diels-Alder approach for synthesizing aryltetralin lignans. The preparation and Diels-Alder reactions of unsymmetrical chiral dienophiles with *o*-QDMs are described. This is followed by a description of attempts that were made to prepare an $\alpha$-aryl-$\alpha,\alpha'$-dihydroxy-*o*-QDM and an $\alpha$-aryl-$\alpha$-hydroxy-$\alpha'$-siloxy-*o*-QDM and to react them with a chiral dienophile. The third section describes a method for synthesizing enantiomerically pure (+)-rabdosiin and its (-)-(1*R*,2*S*)-isomer. This section is introduced by a discussion of a model study of the oxidative coupling/cyclization of (methyl (*R*)-mandelyl) sinapate to produce the corresponding thomasidioate diester.

## 2.1 An Asymmetric Synthesis of (-)-Deoxypodophyllotoxin

### 2.1.1 Basis for the Synthetic Approach

Lignans, as discussed in Section 1.2, have important biological activity, and for this reason, methods for synthesizing these compounds in enantiomerically pure form have

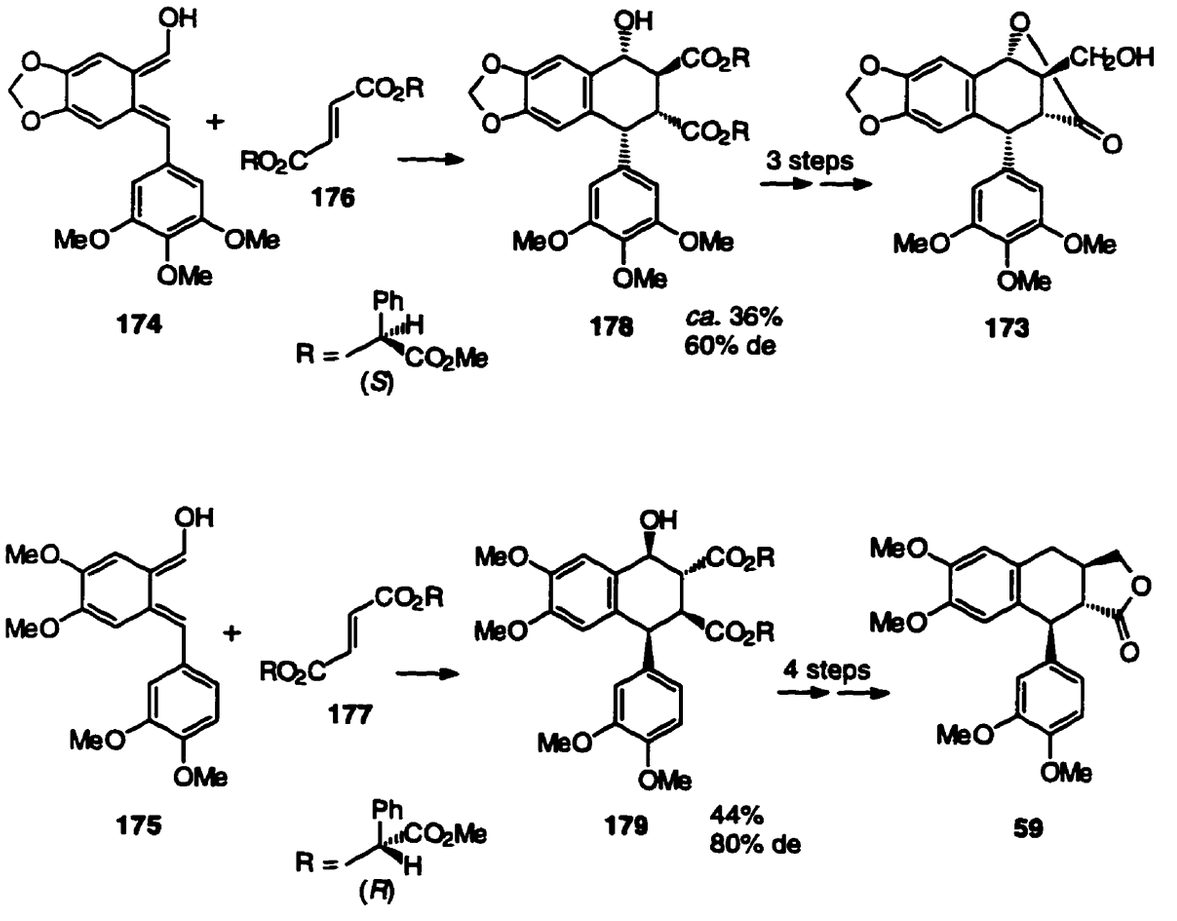
**Scheme 2.1**




been vigorously pursued. Charlton *et al.*,[125-127,163-166] in particular, have done extensive research on the asymmetric synthesis of aryltetralin lignans by investigating diastereoselective Diels-Alder reactions. They discovered that the fumarate (**95**) and acrylate (**166**) of methyl (*S*)-lactate each added to α-hydroxy-*o*-quinodimethane (**167**)

with very high diastereoselectivity (>95% de) to give cycloadducts **168** and **169** respectively (see Scheme 2.1).[163,164] The reactions proceeded by way of an *exo* transition state such that the *re* face of the dienophile added to the *re* face of the diene. Similar results were obtained when the lactate group was replaced with a mandelate group.[165] The maleate of methyl (*S*)-lactate (**170**) also added to *o*-QDM **167** but not as stereoselectively, and cycloadducts **171** and **172** were obtained in a 7:3 ratio respectively.[164] Furthermore, it was found that the fumarate of methyl (*S*)-lactate (**95**) added diastereoselectively to $\alpha$-hydroxy-$\alpha'$-phenyl-*o*-QDM (**94**) via an *exo* transition state giving a cycloadduct (**96**) with the same absolute stereochemistry as (-)-podophyllotoxin

**Scheme 2.2**

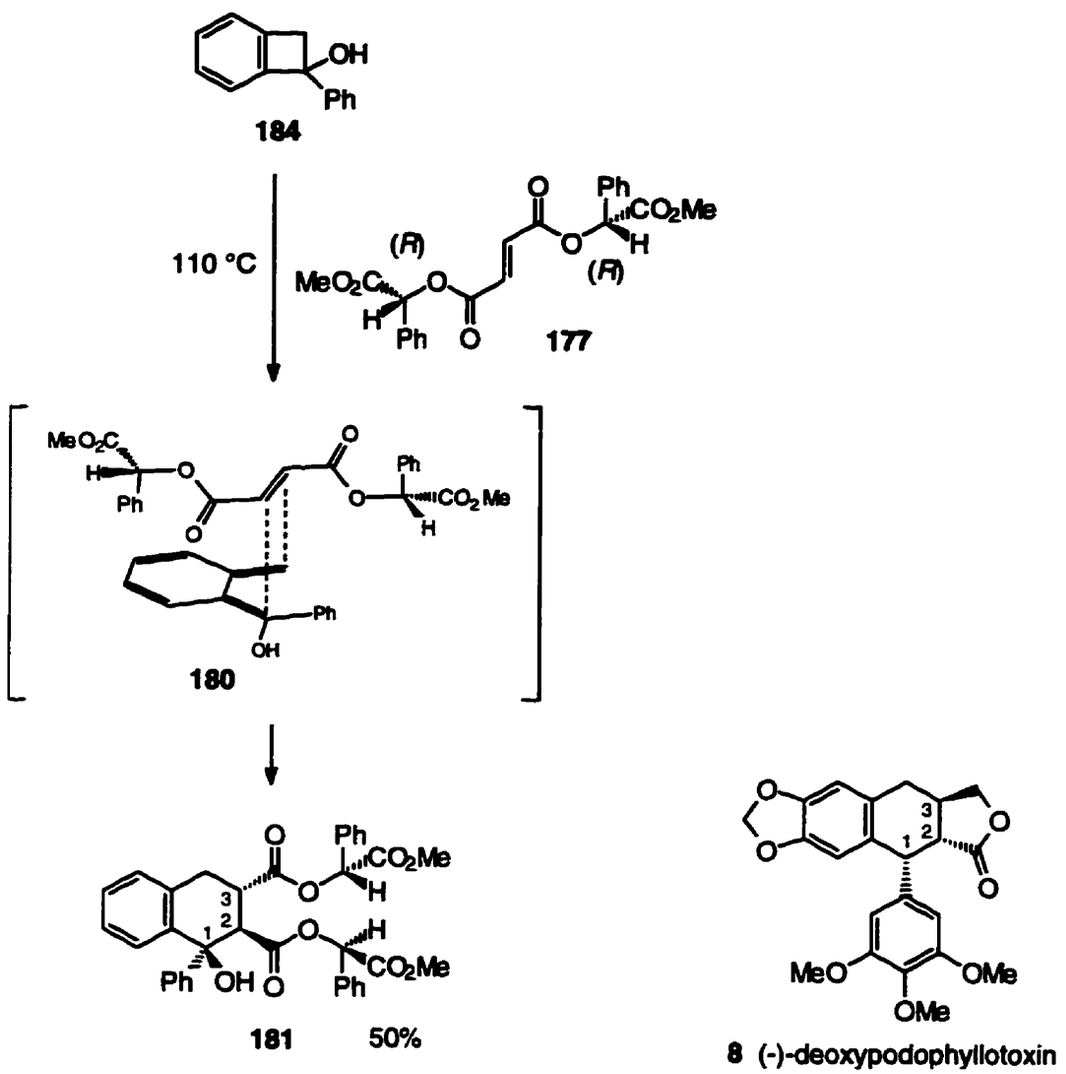


(**4**).[125] This cycloadduct was subsequently transformed to an analog (**97**) of (-)-podophyllotoxin (see Scheme 1.18). Based on this Diels-Alder reaction, (-)-neopodophyllotoxin (**173**)[126] and (-)-$\alpha$-dimethylretrodendrin (**59**),[127] and three diastereomers thereof,[127] were also synthesized (see Scheme 2.2). These syntheses were accomplished by reacting an appropriately substituted $\alpha$-hydroxy-$\alpha'$-aryl-*o*-QDM (**174** or **175**) with the fumarate of methyl (S)-mandelate (**176**) or its enantiomer (**177**) and converting the resulting cycloadduct (**178** or **179**) to the desired aryltetralin lignan.

More recent research by Charlton *et al.* showed that the fumarate of methyl (*R*)-mandelate (**177**) added in a highly diastereoselective manner to $\alpha$-hydroxy-$\alpha$-phenyl-*o*-QDM (**180**) to give a single cycloadduct (**181**) in 50% isolated yield (see Scheme 2.3).[166] Unlike the other diastereoselective Diels-Alder reactions that were studied, this reaction occurred through an unexpected *endo* transition state in which the *si* face of the dienophile added to the *re* face of the *o*-QDM. This reaction was of great interest because the cycloadduct obtained was enantiomerically pure, aryltetralin in nature, and the 2,3-*trans* geometry was the same as that found in many pharmacologically active aryltetralin lignans. The method appeared particularly appropriate for the synthesis of aryltetralins containing the 1,2-*cis*-2,3-*trans* geometry like that of (-)-deoxy-podophyllotoxin (**8**). A decision was therefore made to prepare (-)-deoxypodophyllotoxin by this approach.

For an efficient synthesis, $\alpha$-hydroxy-$\alpha$-aryl-*o*-QDM **182**, containing a methylene dioxy group and trimethoxyphenyl group like that in (-)-deoxypodophyllotoxin, was needed (see Scheme 2.4). Also, to achieve the correct absolute stereochemistry for (-)-deoxypodophyllotoxin, the fumarate of methyl (*S*)-mandelate (**176**) was required

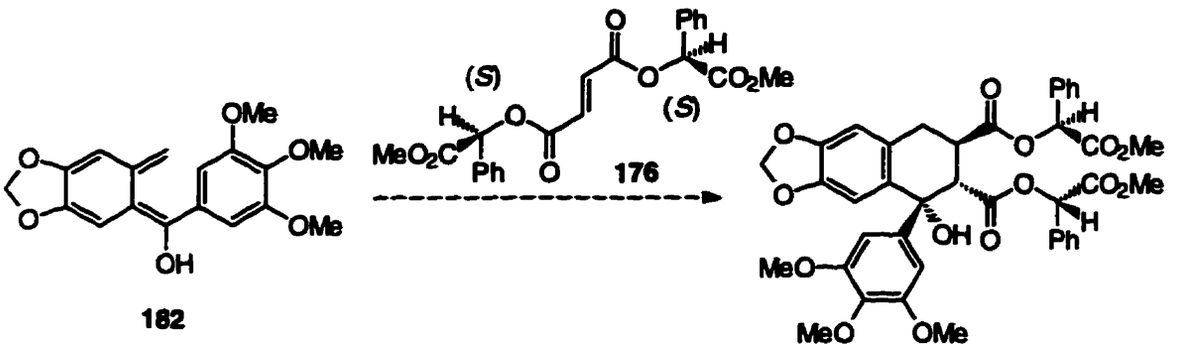
**Scheme 2.3**




instead of its enantiomer (**177**). While there was an uncertainty as to whether the additional substitution on the *o*-QDM would hinder the cycloaddition to give adduct **183**, it seemed reasonable that the reaction would succeed based on the successful reactions of the substituted $\alpha$-hydroxy-$\alpha'$-aryl-*o*-QDMs used in the syntheses of (-)-neo-podophyllotoxin (**173**)[126] and (-)-$\alpha$-dimethylretrodendrin (**59**).[127]

A synthetic approach to (-)-deoxypodophyllotoxin via an $\alpha$-hydroxy-$\alpha'$-aryl-*o*-QDM, rather than the $\alpha$-hydroxy-$\alpha$-aryl-*o*-QDM, could have been chosen. However, the

**Scheme 2.4**




α-hydroxy-α-aryl-*o*-QDM route had a distinct advantage with respect to the formation and reaction of the transient *o*-QDM species. It was known from previous work that 1-hydroxy-1-arylbenzocyclobutenes were relatively stable at room temperature and that these compounds could be thermolyzed to give the corresponding α-hydroxy-α-aryl-*o*-QDMs.[166] For example, *o*-QDM **180**, shown in Scheme 2.3, was prepared by the thermolysis of benzocyclobutene precursor **184**.[166] In contrast, the *trans*-1-hydroxy-2-arylbenzocyclobutene precursors that were required for generating α-hydroxy-α'-aryl-*o*-QDMs like **94**, **174**, or **175** tended to be very difficult to prepare due to their thermal instability at room temperature.[167,168] Photochemical generation of these *o*-QDMs from *o*-benzylbenzaldehydes in the presence of the dienophile was possible, but the reaction was inefficient[126] or failed[125] due to quenching of the triplet aldehyde by the dienophile. Also, trapping the photochemically prepared *o*-QDM as the sulfone, as was done with *o*-QDM **175**,[127] and regenerating the *o*-QDM thermally only led to moderate yields of cycloadduct. Thus, the α-hydroxy-α-aryl-*o*-QDM approach to synthesizing (-)-deoxypodophyllotoxin was more appealing in terms of the potential yield of the cycloadduct and the fact that this route had not been used for any other natural aryltetralin lignan synthesis.

The results of this synthetic approach, which involved preparation of the benzocyclobutenol precursor to *o*-QDM **182**, addition of *o*-QDM **182** to fumarate **176**, and conversion of the resultant cycloadduct (**183**) to (-)-deoxypodophyllotoxin (**8**), are described in detail in the next section.

### 2.1.2 Synthesis of (-)-Deoxypodophyllotoxin

#### 2.1.2.1 Preparation and Asymmetric Diels-Alder Reaction of an $\alpha$-Hydroxy-$\alpha$-aryl-*o*-quinodimethane

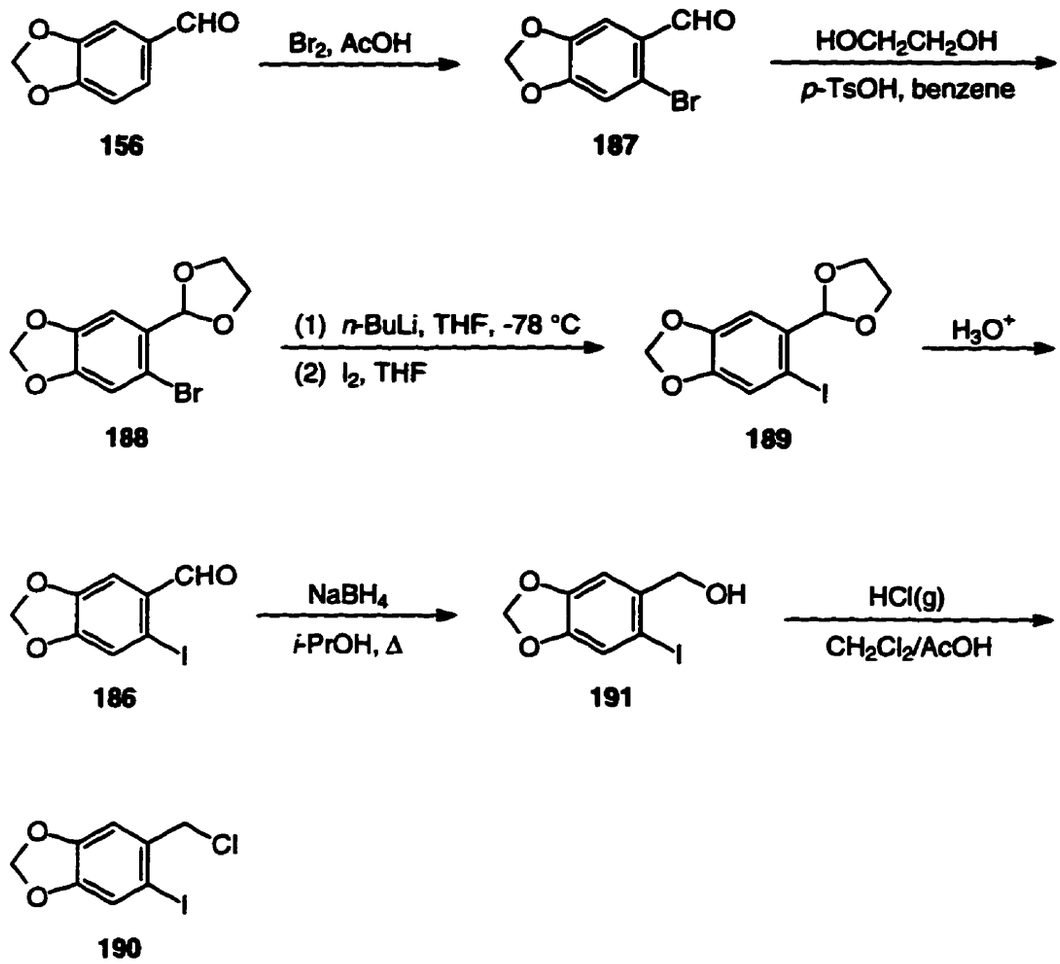
The first few steps in the asymmetric synthesis of (-)-deoxypodophyllotoxin were directed at preparing 1-hydroxy-1-(3,4,5-trimethoxyphenyl)benzocyclobutene **185** (see Scheme 2.6), the precursor to $\alpha$-hydroxy-$\alpha$-aryl-*o*-quinodimethane **182**. This benzocyclobutenol was synthesized according to the convergent pathway shown in Schemes 2.5 and 2.6 following, in part, the earlier work of Aidhen and Narasimhan.[169]

An attempt was made to prepare 6-iodopiperonal (**186**) (see Scheme 2.5) by direct iodination of piperonal (**156**) in acetic acid. However, no aromatic substitution occurred according to TLC analysis and only starting material was recovered.

A multi-step route to 6-iodopiperonal (**186**) was therefore used by first converting piperonal (**156**) to its 6-bromo derivative (**187**). A literature procedure was adapted,[170] in which piperonal and bromine were stirred in acetic acid at room temperature for 17 hours

during which time 6-bromopiperonal (**187**) precipitated from the solution as a colourless solid (98% yield). Only selective monobromination at C-6 was observed for this reaction.

**Scheme 2.5**



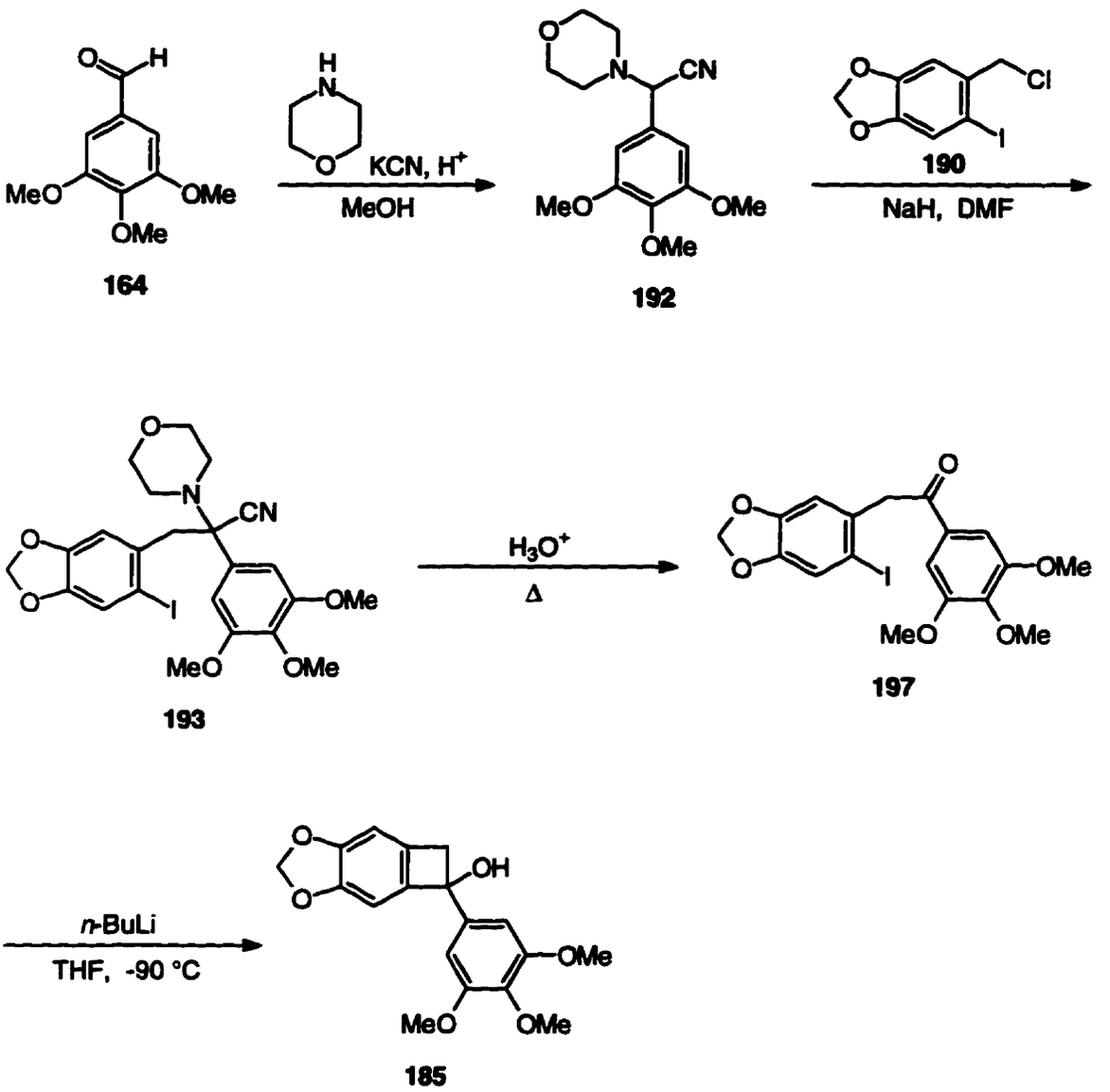

The next three steps needed to prepare 6-iodopiperonal included protecting 6-bromopiperonal as its ethylene glycol acetal (**188**), replacing bromine with iodine, and then removing the protecting group. 6-Bromopiperonal was treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid hydrate in boiling benzene, with azeotropic removal of water, for 15 hours. The resultant colourless crystals, presumed to

be acetal **188**, were treated with excess *n*-butyllithium in tetrahydrofuran at -78 °C followed immediately by the addition of iodine to produce iodo acetal **189**. The protection of 6-bromopiperonal as its acetal prior to the addition of *n*-butyllithium was a necessary step because it avoided undesired nucleophilic attack at the carbonyl group. Hydrolysis of the acetal group gave 6-iodopiperonal (**186**) in good yield (83%) from 6-bromopiperonal. 6-Iodopiperonal has been previously synthesized from 6-bromopiperonal by Ziegler and Fowler by a method involving preparation of the cyclohexylimine of 6-bromopiperonal, bromine-iodine exchange, and hydrolysis of the imine, but the product yield was only 25%.[171]

The conversion of 6-iodopiperonal to 6-iodopiperonyl chloride (**190**), which was required in a subsequent coupling reaction, was accomplished in two steps. 6-Iodopiperonal was reduced with sodium borohydride in boiling isopropyl alcohol to give 6-iodopiperonyl alcohol (**191**) in 97% crude yield. Alcohol **191** was treated with dry hydrochloric acid in 1:1 acetic acid/dichloromethane for 5 hours to produce benzylic chloride **190** in 87% crude yield (69% overall yield from piperonal). Benzylic chloride **190** has been synthesized previously by Abelman *et al.* by an alternative method involving iodination of piperonyl alcohol and replacement of the hydroxy group with chlorine.[172] While this synthesis was shorter than the one depicted in Scheme 2.5, the overall yield (60%) of the benzylic chloride was lower.

The other starting material needed for the synthesis of (-)-deoxypodophyllotoxin, as shown in Scheme 2.6, was 3,4,5-trimethoxybenzaldehyde (**164**). This aldehyde was converted to 1-(3,4,5-trimethoxyphenyl)-1-*N*-morpholinoacetonitrile (**192**) using the Strecker procedure for the synthesis of $\alpha$-amino nitriles.[173] A methanolic solution of

**Scheme 2.6**



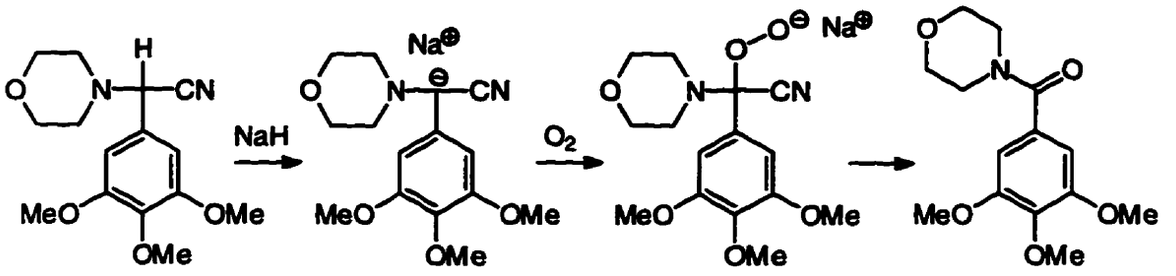

aldehyde **164** was added to a cold aqueous solution of potassium cyanide, morpholine, and hydrochloric acid. Stirring the solution led to formation of $\alpha$-amino nitrile **192** as a colourless solid that precipitated from the solution. A satisfactory product yield of 56% was obtained after a reaction time of 3 hours. However, the yield was improved to 72%

by extending the reaction time to 20 hours and was significantly increased to 92% by allowing a 5 day reaction time.

Initial attempts to synthesize compound **193** by coupling $\alpha$-amino nitrile **192** with benzylic chloride **190** were inefficient. Treating $\alpha$-amino nitrile **192** in THF with lithium diisopropylamide and hexamethylphosphoramide followed by addition of compound **190** (excess) and stirring for 15 hours at room temperature under a nitrogen atmosphere resulted in a 51% yield of alkylation product **193**. A much diminished yield of **193** was obtained by using sodium hydride as the base under the same reaction conditions. In this case, TLC analysis (40% EtOAc/hexanes) of the crude product showed no $\alpha$-amino nitrile **192** but a significant amount of benzylic chloride **190**. Also observed was a minor amount of **193**, and a significant amount of an unknown product with a very low $R_f$ value. Apparently, the unknown compound was a derivative of **192**. Desired product **193** (18% yield) was isolated by chromatography on silica gel using 50% EtOAc/hexanes, but the polar unknown product had to be eluted with 5% *i*-PrOH/EtOAc. The unknown compound exhibited an IR peak at 1634 $cm^{-1}$, indicating that a carbonyl group was present in the structure. The $^1H$ NMR spectrum displayed an eight hydrogen broad singlet at 3.70 ppm that was attributed to the four methylene groups of a morpholino ring. A three hydrogen singlet at 3.86 ppm and a six hydrogen singlet at 3.87 ppm, consistent with three methoxy substituents of an aromatic ring, and a two hydrogen singlet at 6.63 ppm, consistent with aromatic protons, were indicative of a 3,4,5-trimethoxyphenyl ring. The EI mass spectrum gave a parent ion at *m/z* 281 with an exact mass of 281.1269, suggesting that the molecular formula was $C_{14}H_{19}NO_5$. From these results, and from the

$^{13}C$ NMR spectrum, it was concluded that the major product (71% yield) was the amide **194** (see Scheme 2.7).

**Scheme 2.7**



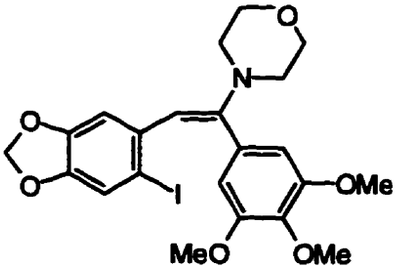

The formation of amide **194** was thought to have resulted from the presence of oxygen in the reaction system. Oxygen, known to oxidize carbanions to peroxides,[118] could have reacted with the resonance stabilized anion of the $\alpha$-amino nitrile (**195**) to give peroxide **196** as illustrated in Scheme 2.7. Decomposition of the peroxide group and loss of cyanide from intermediate **196** could have subsequently produced amide **194**. The presence of oxygen could have been possible if the reaction system were not properly sealed from air. Also, the reaction solvent/solution was at no point degassed.

The use of THF as the solvent may have been a cofactor in favouring the formation of amide **194**. The rate of the desired nucleophilic substitution reaction may be relatively slow in solvents of lower polarity, like THF, such that undesired reaction pathways (e.g. carbanion oxidation) could compete effectively.

To try to increase the rate of the alkylation reaction as well as the yield of alkylation product **193**, a more polar solvent, *N,N*-dimethylformamide, was used and the reaction temperature was raised to 70 °C. Excess $\alpha$-amino nitrile **192** was used relative to benzylic chloride **190**, and sodium hydride was again used as the base. TLC analysis

showed that the reaction was complete (no benzylic chloride **190** remained) after 1.5 hours. While compound **193** appeared to be the major product, two new products were observed. After chromatography, one of the new products was determined from spectral data to be ketone **197**. The other unknown product was obtained as a mixture containing a minor amount of ketone **197**, but $^{1}$H NMR analysis determined that it was likely enamine **198** (see Figure 2.1). This was confirmed by hydrolyzing the mixture at room temperature for 1 hour using 10% HCl(aq) to give only ketone **197**. The results of this coupling reaction were very encouraging considering that the objective was to obtain an intermediate (**193**) that could be transformed to ketone **197**. The coupling reaction was repeated, and the crude reaction product, consisting of ketone **197** and intermediates **193** and **198**, was hydrolyzed with 10% HCl(aq) at 61 °C to directly give ketone **197** in 67% yield.

**Figure 2.1**



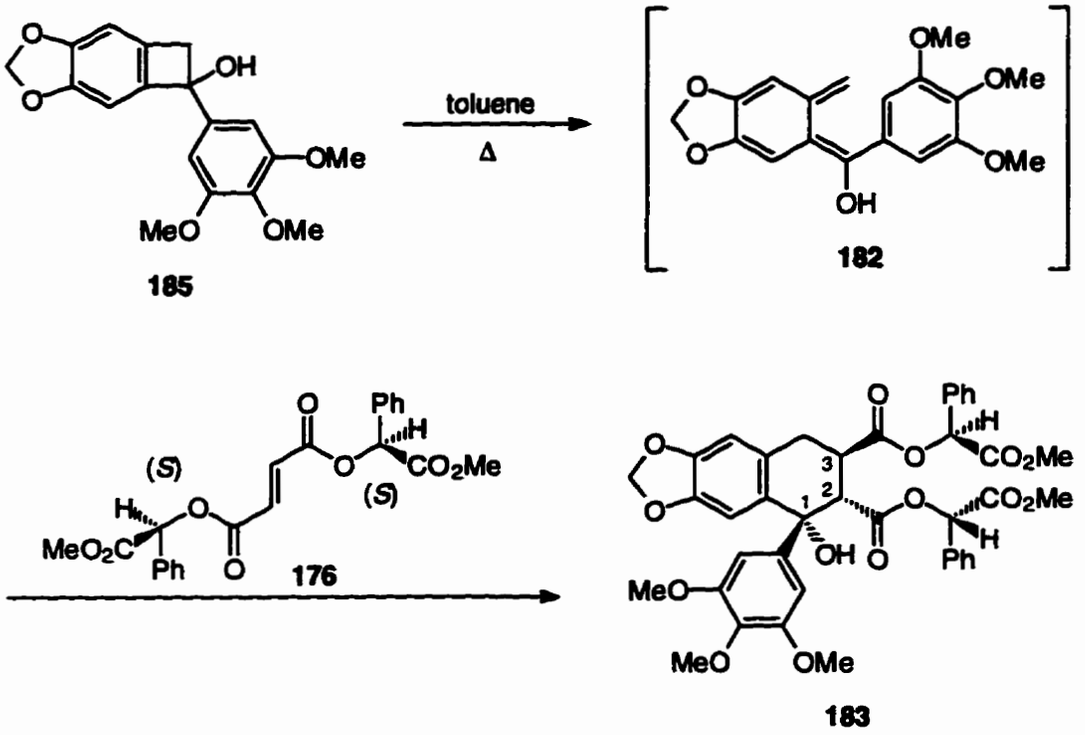

**198**

One more step was needed to prepare benzocyclobutenol **185**. Following a procedure by Aidhen and Narasimhan,[169] *n*-butyllithium was added to a solution of ketone **197** in dry THF at -80 °C under a nitrogen atmosphere. The solution was stirred for 2 minutes, and the reaction was quenched with dilute aqueous acid. Chromatography of the crude product gave benzocyclobutenol **185** in 71% yield (30% from piperonal).

It seemed that the cyclization of iodo ketone **197** might also be feasible for the bromo analog, thereby eliminating the need for the earlier bromine-iodine exchange. However, in their study of the synthesis of 1-arylbenzocyclobutenols, Aidhen and Narasimhan reported that treating the bromo analog of ketone **197** with *n*-butyllithium caused reduction of the C-Br bond and butyl attack on the carbonyl group in addition to intramolecular cyclization.[169] They did not observe these by-products for the cyclization of iodo ketone **197**, and these by-products were not observed for the reaction described above.

The procedure for the synthesis of cycloadduct **183** from benzocyclobutenol **185** (see Scheme 2.8) was the same as that used in previous work on 1-phenylbenzocyclobutenol (**184**) by Charlton *et al.*[166] Two equivalents of the fumarate of methyl (*S*)-mandelate (**176**) (prepared by methylating (*S*)-mandelic acid and coupling the resulting ester (**199**) with fumaryl chloride) and benzocyclobutenol **185** were heated in toluene for 44 hours. Analysis of the crude cycloaddition mixture by $^1$H NMR indicated the presence of two cycloadducts. Integration of the aromatic proton singlets at 6.46 ppm and 6.30 ppm gave a ratio of 9:1 respectively. Separation of the two isomers was possible on a HPLC reverse-phase column (ODS2, octadecylsilyl) using gradient elution (6:4 to 7:3 MeOH/$H_2O$). The major isomer (retention time = 28.7 min) and minor isomer (retention time = 25.8 min) were sufficiently resolved to allow an integration of the peaks. A ratio of 9:1 was observed, in agreement with the $^1$H NMR ratio. Chromatography on silica gel led to isolation of the major cycloadduct in 58% yield. This cycloadduct was assigned the absolute structure **183**, as shown in Scheme 2.8, based on the previous synthesis of cycloadduct **181** (see Scheme 2.3) from 1-phenylbenzocyclobutenol (**184**) and the

**Scheme 2.8**

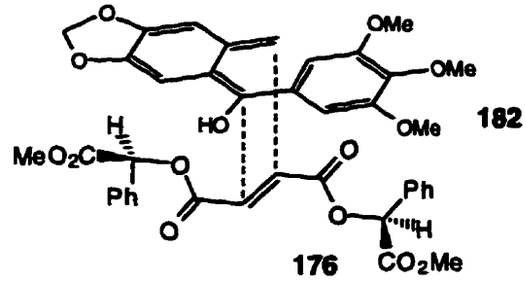



fumarate of methyl (*R*)-mandelate (**177**).[166] The assigned structure was later proven to be correct by the successful transformation of the cycloadduct to (-)-deoxypodophyllotoxin. Cycloadduct **183** exhibited a doublet of doublets at 3.14 ppm for H-4a with a $J_{3,4a}$ of 11.9 Hz and a doublet at 3.80 ppm for H-2 with a $J_{2,3}$ of 11.5 Hz. These coupling constants indicated that protons H-2 and H-3 were *trans* and diaxial, and consequently, that the aryl group on C-1 was located in the pseudo-equatorial position. From the good yield of cycloadduct **183**, it was evident that the substitution on the phenyl rings of the benzocyclobutenol did not hinder the reaction, a concern that was expressed earlier.

For the cycloaddition to proceed, benzocyclobutenol **185** had to be thermolyzed to give a transient *o*-quinodimethane species. This intermediate (**182**) is depicted in Scheme 2.8 as having the hydroxyl group in the *E* geometry. This geometry was presumed on the

basis of past experience by Charlton *et al.*[166] and the torquoselectivity rules set forth by Jefford *et al.*[123] The mechanism of cycloadduct **183** formation involved addition of the *si* face of *o*-QDM **182** to the *re* face of dienophile **176** through an *endo* transition state as shown in Figure 2.2.

**Figure 2.2**

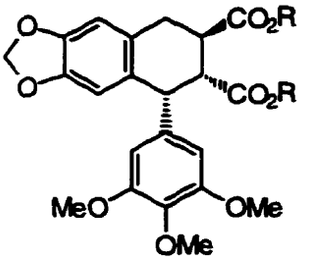



The cycloaddition reaction might have been carried out using the fumarate of methyl (*S*)-lactate (**95**) instead of fumarate **176** since the reactivity and stereoselectivity of the two dienophiles were known to be very similar. However, the mandelate derivative was chosen because the mandelyl groups could be easily removed in a later step by catalytic hydrogenolysis. In contrast, liberation of the lactyl groups would have required stronger conditions such as hydrolysis or transesterification, possibly causing epimerization at the C-2 and C-3 centers.

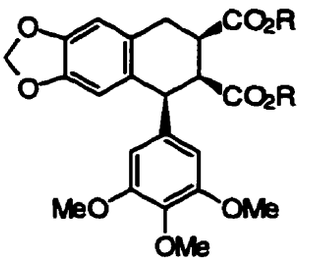
While cycloadduct **183** possessed the same configurations at C-2 and C-3 as those in (-)-deoxypodophyllotoxin, the necessary 1,2-*cis* geometry relative to the aryl group was not present. Reduction of the hydroxyl group with concurrent inversion at C-1 proved to be difficult. An attempt was made to remove the hydroxyl group, invert the C-1 center, and remove the chiral auxiliaries, all at the same time, by catalytic hydrogenolysis. Cycloadduct **183** in acetic acid was treated with 5% Pd/C under a hydrogen atmosphere at

room temperature. The reaction was followed by TLC analysis, and no cycloadduct could be detected after 43 hours. $^1$H NMR analysis of the crude product showed that the product was a mixture of diacids that appeared to be **200** and **201** (see Figure 2.3). The chiral auxiliaries and the hydroxyl group were successfully removed, but there was a mixture of inverted and non-inverted stereochemistry at the C-1 position. Integration of the H-1 doublets at 4.31 ppm ($J$ = 5.9 Hz) and 4.49 ppm ($J$ = 5.6 Hz) gave a 1.0:4.2 ratio (**200**:**201**). Changing the hydrogenolysis solvent to 1:4 methanol/acetic acid led to the

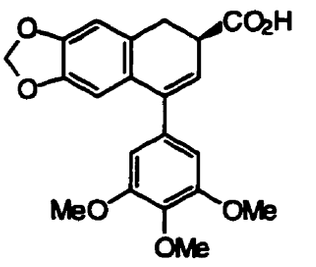
**Figure 2.3**



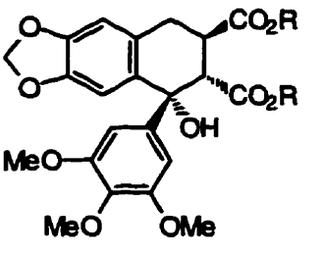
**200**: R = H
**209**: R = Me



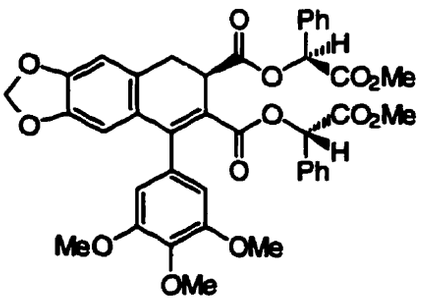
**201**: R = H
**204**: R = Me



**202**



**203**: R = H
**205**: R = Me



**206**

isolation of a significant amount of hydrogenolysis/decarboxylation product **202** (50% yield). Lowering the polarity of the solvent further by using 1:1 methanol/acetic acid resulted in a mixture of diacid **201**, alcohol **203**, and a minor amount of diacid **200** as

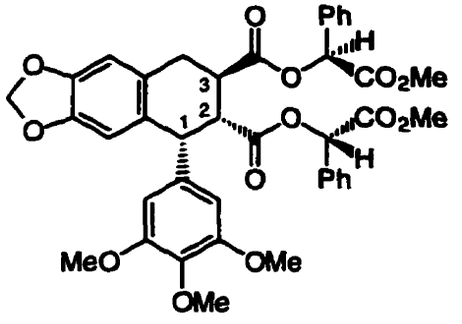
determined by $^1$H NMR. The structures of compounds **201** and **203** were substantiated by converting them to their dimethyl esters **204** and **205** by treating them with diazomethane and isolating the dimethyl esters by chromatography. Compound **203** was the result of removal of the chiral auxiliaries without hydrogenolysis of the C-1 hydroxyl group. All of the results from the catalytic hydrogenolysis experiments in acetic acid could be explained if elimination across the C(1)-C(2) bond were occurring faster than the hydroxyl group could be hydrogenolyzed. An intermediate alkene was possibly being reduced from both faces to give a mixture of diacids **200** and **201**. This theory was supported by catalytically hydrogenating alkene **206**, synthesized by acid-catalyzed dehydration of cycloadduct **183**, in acetic acid to give diacids **200** and **201** in the same ratio as that observed when the cycloadduct was subjected to the same conditions (see above).

### 2.1.2.2 Development of a Stereoselective Ionic Reduction

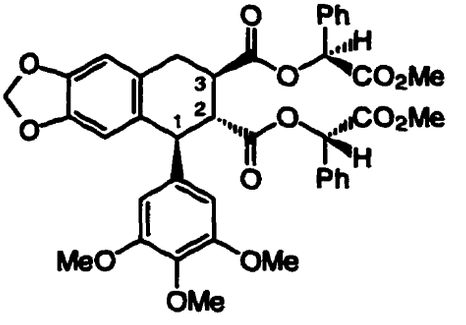
To find a more efficient method of preparing diacid **200** from cycloadduct **183**, a selective ionic reduction of the benzylic alcohol was pursued. The aim of this approach was to identify a reagent system that could remove the hydroxyl group from cycloadduct **183** and selectively reduce the resulting diaryl cation to give inversion product **207** (see Figure 2.4). This goal was very challenging due to the competing processes of reduction to **208** and elimination to **206**.

The first reagent system studied was based on work by Gribble *et al.*[174,175] and Nutaitis *et al.*[176,177] who have reported that mono-, di-, and triarylmethanols can be

**Figure 2.4**




**207**




**208**

conveniently reduced with sodium borohydride/trifluoroacetic acid to afford the corresponding arylmethanes in high yield. Trifluoroacetic acid (500 equivalents) was cooled to -23 °C and treated with powdered sodium borohydride (62.5 equivalents) while being vigorously stirred. This addition had to be made slowly, in small portions, and under a stream of nitrogen in order to prevent combustion of the hydrogen gas produced. A dichloromethane solution of cycloadduct **183** was added to the reducing system. The mixture immediately turned dark blue indicating the formation of the diaryl cation. The blue colour still remained after 30 minutes, so more sodium borohydride was added until the colour was dissipated. $^1$H NMR analysis of the crude product revealed that only elimination product **206** was obtained, as evidenced by the lack of the H-1 and H-2 signals.

The reaction was repeated at -35 °C. Due to the solidification of TFA (mp -15 °C), the mixture had to be slightly warmed to allow for proper mixing of the reagents and reactant. The mixture was partially melted, stirred, cooled again to -35 °C, and the process was continued until the blue colour was discharged. Chromatography (20% EtOAc/hexanes) of the crude product gave three compounds. One of these compounds

exhibited a doublet of doublets at 3.53 ppm for H-2 ($J$ = 11.8, 5.6 Hz) and a doublet at 4.52 ppm for H-1 ($J$ = 5.6 Hz), and was seemingly a reduction product. The large diaxial coupling of H-2 and H-3 (11.8 Hz) was indicative of a 2,3-*trans* geometry with each of the ester groups occupying an equatorial position. The H(1)-H(2) coupling of 5.6 Hz was indicative of a 1,2-*cis* geometry with the aryl group situated in a pseudo-axial position. Thus, the compound was assigned structure **207**. One of the other compounds was also a reduction product, but it showed a doublet at 4.18 ppm for H-1 with a $J_{1,2}$ of 8.5 Hz. This coupling constant indicated that protons H-1 and H-2 were *trans* and diaxial. The compound was therefore assigned the all *trans* structure **208**. The third compound was elimination product **206**. It was interesting to note that the two protons on the 3,4,5-trimethoxyphenyl ring of **206** were magnetically non-equivalent as evidenced by the meta ($^4J$) coupling of 1.9 Hz ($\delta$ = 6.38 ppm). Also, two distinct trimethoxyphenyl methine carbon signals were observed in the $^{13}C$ NMR spectrum suggesting that there was hindered rotation about the C(1)-C(Ar) bond. The isolated yields of the products were low because of their very similar retention times on silica gel. However, before chromatography, $^1H$ NMR integration of the mandelyl methine singlets at 5.67, 5.71, and 5.76 ppm showed that compounds **207**, **208**, and **206** were present in a ratio of 1.2:1.0:1.3 respectively.

The reaction was performed again at -65 °C. $^1H$ NMR analysis showed that compounds **207**, **208**, and **206** were obtained in a 3.6:2.4:1.0 ratio (**207**:**208**:**206**). As no starting material was observed following this reaction, or any of the previous reactions, this ratio represented a potential yield of 51% for desired product **207**. This was the optimum result obtained for this reducing system. It was apparent that low temperatures

were required to give a good yield of **207**, but efforts to improve upon the yield of **207** typically gave irreproducible results, probably due to the necessary intermittent melting of the reaction mixture. It was also determined that a relatively non-polar solvent, such as dichloromethane, was required to help stabilize the intermediate diaryl cation. More polar solvents, such as THF, caused rapid decolourization of the reaction mixture, giving **206** as the sole product. Overall, the moderate selectivity observed for reduction versus elimination and for inversion versus retention was unsatisfactory.

The major drawback to the TFA/$NaBH_4$ reducing system was the use of TFA. The physical properties of TFA meant that the reaction mixture was in a solid state at the low temperatures required, consequently greatly lowering the rate of carbocation formation and reduction. In addition to promoting carbocation formation, TFA also reacted rapidly with $NaBH_4$ to give different trifluoroacetoxyborohydride species and a tetraacyloxyborate (see Scheme 2.9).[175-177] The hydride-donating ability of these reagents

**Scheme 2.9**

$$NaBH_4 + TFA \rightarrow NaBH_3(OCOCF_3) + H_2$$

$$NaBH_3(OCOCF_3) + TFA \rightarrow NaBH_2(OCOCF_3)_2 + H_2$$

$$NaBH_2(OCOCF_3)_2 + TFA \rightarrow NaBH(OCOCF_3)_3 + H_2$$

$$NaBH(OCOCF_3)_3 + TFA \rightarrow NaB(OCOCF_3)_4 + H_2$$

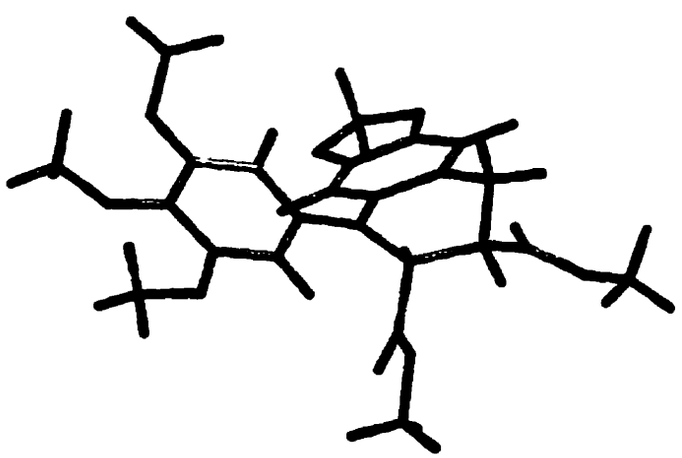
decreases as the number of hydrogen atoms decreases, with the tetraacyloxyborate anion being inert because of the absence of hydride. The decrease in reactivity results from the electronic (electron withdrawing) and steric requirements of a trifluoroacetoxy ligand. Presumably, these reagents were slow in effecting hydride capture of the diaryl cation

intermediate, thereby permitting elimination to effectively compete with simple reduction. A reagent other than TFA that could initiate carbocation formation was therefore desired.

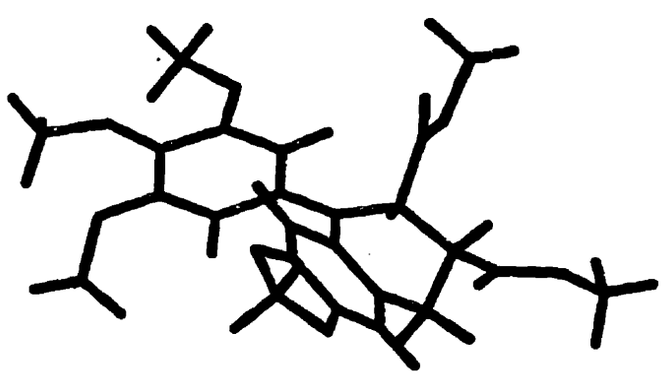
A triethylsilane/boron trifluoride etherate combination has been used by Orfanopoulos and Smonou to reduce diaryl alcohols.[178] Their procedure was adapted to reduce cycloadduct **183** as follows. Cycloadduct **183** and a large excess of triethylsilane (100 equivalents) were stirred in $CH_2Cl_2$ at room temperature while boron trifluoride diethyl etherate (2.5 equivalents) was added. The blue colour associated with diaryl cation formation immediately appeared, remained for 5-10 seconds, and then disappeared. The reaction was worked-up after 25 minutes, and $^1H$ NMR analysis showed that only elimination (**206**) had occurred. The reaction was repeated at -20 °C under a nitrogen atmosphere, and a cation lifetime (blue colour) of 15 minutes was noted. This resulted in minimal formation of reduction products (**207**:**208**:**206** = 1.1:1.0:19.1). Using 21 equivalents of both $Et_3SiH$ and $BF_3{\cdot}OEt_2$ at 0 °C under $N_2$(g) (cation lifetime of 10 min) favoured reduction (4 to 5 fold) over elimination, but there was negligible selectivity between **207** and **208** production. In another trial, the temperature was lowered to -55 °C. Since the blue colour persisted for 50 minutes, the solution was slowly warmed over 50 minutes to -7 °C at which point the colour began to fade. Between -7 °C and -1 °C, in a 25 minute period, the colour was discharged. Again, there was no selectivity between inversion and retention, but the preference for reduction versus elimination was excellent (**207**:**208**:**206** = 11.0:11.1:1.0). This product ratio was reproducible by holding the reaction temperature at -7 °C, giving a cation lifetime of *ca.* 1 hour. Lowering the temperature further was ineffective, causing longer reaction times and no improvement in stereoselectivity. The optimum reduction conditions represented a 48% yield of **207.**

The lack of selectivity between inversion and retention was unexpected considering the bulkiness of the ethyl ligands on triethylsilane. Molecular orbital calculations at the AM1 level with geometry optimization (Spartan SGI version 4.1.1) were used to determine the preferred conformation of a similar diaryl cation in which the mandelyl groups were replaced with methyl groups. Figure 2.5 shows that the *re* face of

**Figure 2.5**



view of the *si* face



view of the *re* face

the cation is more sterically hindered due to the presence of the adjacent ester group. Since cycloadduct **183** should give rise to a cation with a comparable conformation, sterically controlled reduction at the *si* face would be expected to give inversion product **207** as the major product.

Perhaps the transfer of fluoride to the organosilane also affects the stereoselectivity of the reduction of the cation by triethylsilane. The triethylsilane/boron trifluoride etherate reducing system is known to give triethylfluorosilane, $Et_3SiF$, as a by-product[179] indicating that a substitution reaction takes place. Substitution reactions at four-coordinate silicon characteristically do not proceed dissociatively via an intermediate silicenium ion, $R_3Si^+$, but instead, through an associative mechanism involving a five-coordinate transition state.[180] Thus, it is likely that fluoride transfer occurs to give an ionic silicon species, $[Et_3SiHF]^-$, before triethylsilane can reduce the diaryl cation. Since the reaction of boron trifluoride with the C-1 hydroxyl group of **183** probably produces an intimate ion pair, the resulting anion, presumably $[BF_3OH]^-$, would act as the fluoride donor. If this anion is located primarily on the *re* face of the cation, fluoride transfer would bring triethylsilane in closer proximity to the *re* face, thereby facilitating reduction from the same face.

Both the TFA/$NaBH_4$ and $Et_3SiH/BF_3{\cdot}OEt_2$ reducing systems gave approximately the same yield of **207** (*ca.* 50%), but the results from the latter system were more promising. This system established that the diaryl cation could be quickly and easily prepared by using boron trifluoride etherate at temperatures between -10 °C and -20 °C. The diaryl cation was also observed to be quite stable. In the absence of the reducing agent, the blue colour remained for long periods of time at temperatures as high as -5 °C, eventually affording the elimination product. It seemed that boron trifluoride etherate

could be used as an agent to generate the cation, after which various reducing agents could be used to test for their ability to deliver hydride selectively to the *si* face of the cation.

The general reduction conditions were changed slightly in that cycloadduct **183** was first treated with the Lewis acid followed by excess reducing agent. Reduction of **183**, using this method, with a borane-methyl sulfide complex (13 equivalents) at -15 °C gave good selectivity for the retention product (**207**:**208**:**206** = 6.2:14.6:1.0). This was consistent with the size of $BH_3$ compared to $Et_3SiH$. The more bulky 9-borabicyclo[3.3.1]nonane (4 equivalents) was tested in hope that more steric control would be exerted, but only elimination ensued. As $Et_3SiH$, and likely the boron-based reducing agents, had to form an ionic species prior to hydride transfer, it seemed probable that reducing agents that were already ionic in nature, such as sodium borohydride and lithium aluminum hydride, could trap the cation more readily and with better stereoselectivity.

Solid $NaBH_4$ or $LiAlH_4$ (20 equivalents) was added to a solution of the cation in $CH_2Cl_2$ at -15 °C, but elimination was predominant in each case. It was believed that the low solubility of the reducing agents in $CH_2Cl_2$ was a factor, so powdered $LiAlH_4$ was stirred in diethyl ether at room temperature for 5 minutes. Dropwise addition of the ethereal solution to the cation in $CH_2Cl_2$, until the cation colour could no longer be detected, resulted in selective formation of the desired product (**207**:**208**:**206** = 4.6:1.3:1.0). Optimization of these reduction conditions included lowering the reaction temperature, and as ether had been observed to promote elimination, using a more concentrated ethereal solution of $LiAlH_4$. Thus, treating cycloadduct **183** in $CH_2Cl_2$ under

$N_2$(g) with $BF_3$·$OEt_2$ (6 equivalents) at -20 °C followed by the addition of $LiAlH_4$ (0.37 M in ether) at -55 °C resulted in excellent stereoselectivity (**207**:**208**:**206** = 15.0:2.0:1.0). It should be noted that reduction, as well as cation colour (blue or purple), was dependent on the cycloadduct concentration. Reproducible results were obtained for cycloadduct concentrations of 0.005 M to 0.01 M, but at 0.03 M, elimination became favoured. This was probably due to the concurrent increase in ether concentration. The selective addition of hydride to the *si* face of the diaryl cation was attributed to steric control by the adjacent ester group.

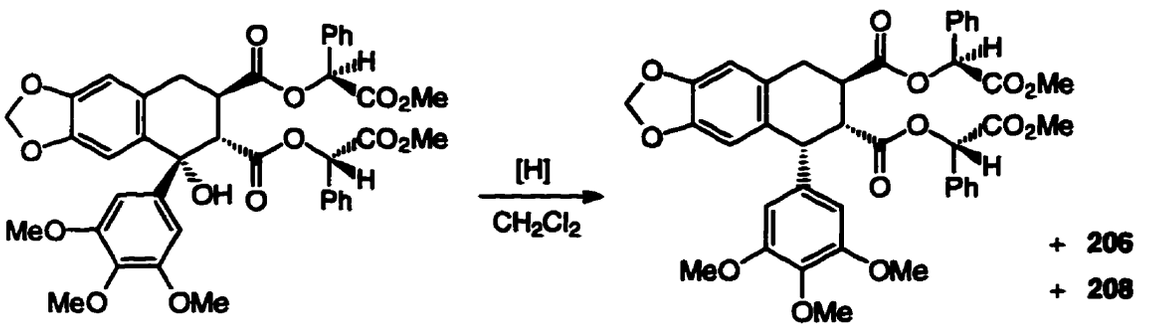
The results of the ionic reduction experiments are summarized in Table 2.1. The compound ratios were determined by $^1$H NMR integration of the crude products. No starting material was identified following any of the reactions. The reactions were also very chemoselective in that no reduction of the ester groups was observed.

Although the $BF_3$·$OEt_2$/$LiAlH_4$ reducing system afforded **207** in about 83% yield, it could be isolated in a pure state by chromatography in only 36% yield because of the very similar retention times of the three products. Since the isolation of **207** was unnecessary at this stage, the crude reduction product was used to synthesize deoxypodophyllotoxin.

### 2.1.2.3 Final Steps

The last few steps in the synthesis were straightforward (see Scheme 2.11). First, the mandelyl groups were removed from **207** by hydrogenolysis. Crude reduction product

**Scheme 2.10**

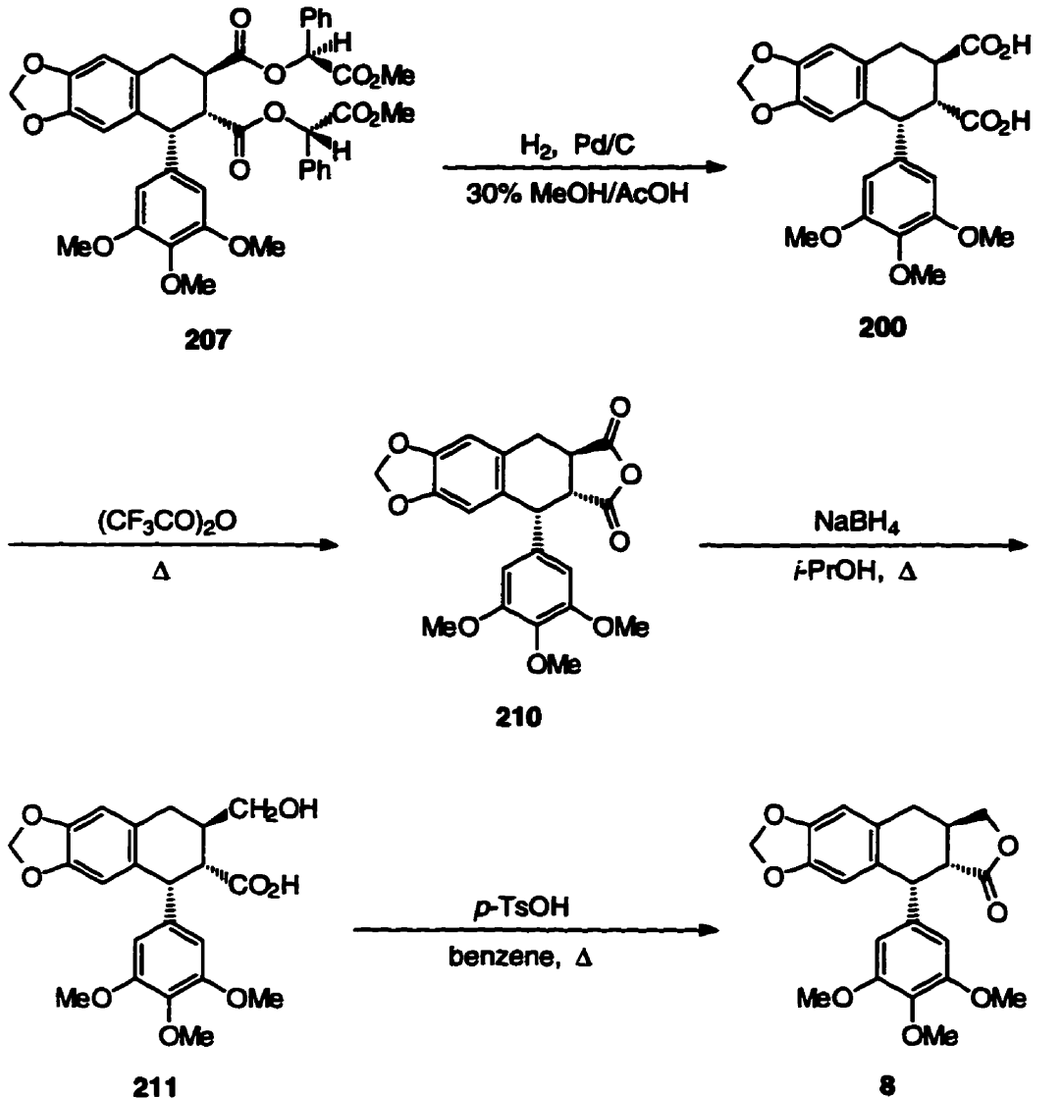



**183** **207**

**Table 2.1**

| Reaction Conditions | | Ratio of Products | | |
|---|---|---|---|---|
| Reagents (equivalents) | Temperature | **207** (Inversion) | **208** (Retention) | **206** (Elimination) |
| TFA/$NaBH_4$ (500:62.5) | -23 °C | 0 | 0 | 1.0 |
| TFA/$NaBH_4$ (500:62.5) | -35 °C | 1.2 | 1.0 | 1.3 |
| TFA/$NaBH_4$ (500:62.5) | -65 °C | 3.6 | 2.4 | 1.0 |
| $Et_3SiH/BF_3{\cdot}OEt_2$ (100:2.5) | 24 °C | 0 | 0 | 1.0 |
| $Et_3SiH/BF_3{\cdot}OEt_2$ (100:2.5) | -20 °C | 1.1 | 1.0 | 19.1 |
| $Et_3SiH/BF_3{\cdot}OEt_2$ (21:21) | 0 °C | 4.7 | 4.2 | 1.0 |
| $Et_3SiH/BF_3{\cdot}OEt_2$ (21:21) | -55 to -7 °C | 11.0 | 11.1 | 1.0 |
| 1) $BF_3{\cdot}OEt_2$ (13 eq)<br>2) $(CH_3)_2S{\cdot}BH_3$ (13 eq) | -15 °C | 6.2 | 14.6 | 1.0 |
| 1) $BF_3{\cdot}OEt_2$ (9 eq)<br>2) 9-BBN (4 eq) | -15 °C | 0 | 0 | 1.0 |
| 1) $BF_3{\cdot}OEt_2$ (6 eq)<br>2) $NaBH_4$ (20 eq) | -15 °C | 0 | 0 | 1.0 |
| 1) $BF_3{\cdot}OEt_2$ (6 eq)<br>2) $LiAlH_4$ (20 eq) | -15 °C | 0 | 0 | 1.0 |
| 1) $BF_3{\cdot}OEt_2$ (6 eq)<br>2) $LiAlH_4$ (0.37 M in $Et_2O$, *ca.* 3.5 eq) | -55 °C | 15.0 | 2.0 | 1.0 |

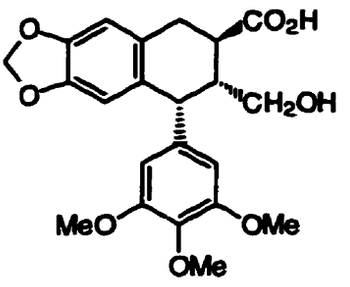
**Scheme 2.11**




**207** **200** **210** **211** **8**

**207** was reduced ($H_2$(g)) in 30% methanol/acetic acid using 5% Pd/C as a catalyst to give the corresponding diacid **200**. Due to difficulties in purifying the diacid, the compound was characterized by conversion to its dimethyl ester **209** with diazomethane (see Figure 2.3). Heating crude diacid **200** in trifluoroacetic anhydride[181] for 2 hours resulted in a crude product presumed to be anhydride **210**. The crude anhydride was regioselectively reduced by heating in isopropyl alcohol with sodium borohydride. The $^1$H NMR spectrum

**Figure 2.6**




**212**

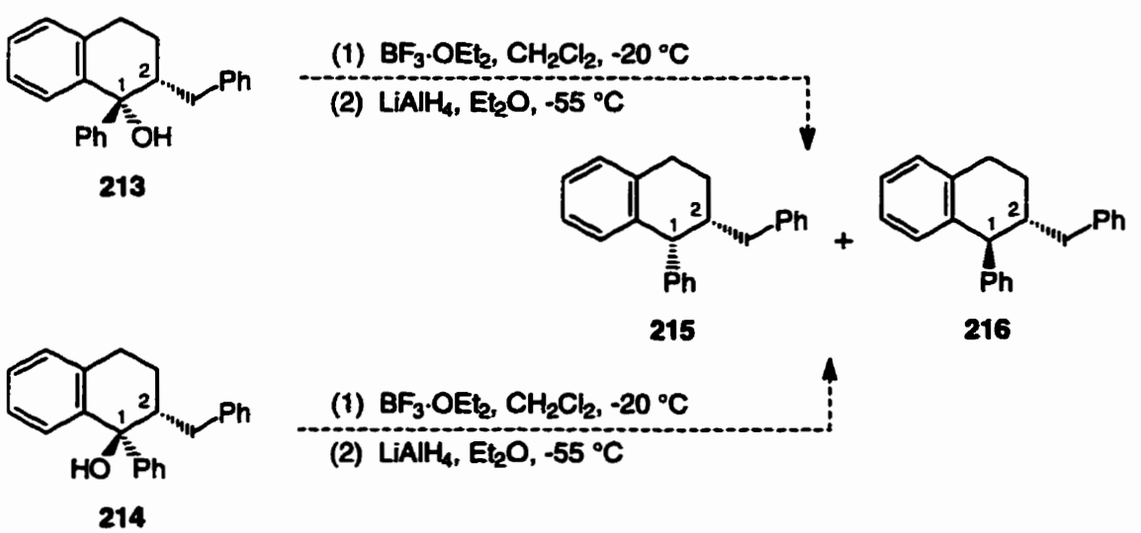
of the crude product was consistent with the presence of γ-hydroxy acids **211** and **212** (see Figure 2.6). Integration of the H-1 doublets appearing at 4.39 ppm ($J$ = 5.4) and 4.48 ppm ($J$ = 5.8) gave a ratio of 3.33:1.00 for **211**:**212**, suggesting that the reduction was sterically controlled by the aryl group on C-1. Compounds **200**, **210**, and **211** were not fully characterized due to difficulty in purifying them by chromatography. Their structural assignments were based on $^1$H NMR spectra of the crude samples. Lactonization of **211** to (-)-deoxypodophyllotoxin (**8**) was effected by boiling a solution of the crude hydroxy acid in benzene with a catalytic amount of *p*-toluenesulfonic acid hydrate.[127] The crude product was chromatographed on silica gel to give enantiomerically pure (-)-deoxypodophyllotoxin in 30% yield from cycloadduct **183** and 6% overall yield from piperonal. The relative structure of deoxypodophyllotoxin was confirmed by preparing an authentic sample of the compound by catalytically hydrogenolyzing the C-4 hydroxyl group of commercially available (-)-podophyllotoxin.[161] The $^1$H NMR spectrum of the synthetic sample was in agreement with that of the authentic sample as well as those in the literature.[29,161] The absolute structure and enantiomeric purity of (-)-deoxypodophyllotoxin was verified by comparing its specific rotation (-112 ° (*c* 0.05, $CHCl_3$)) with the literature value (-113.4 ° (*c* 0.50, $CHCl_3$)).[158]

### 2.1.3 Scope of the $BF_3$·$OEt_2$/$LiAlH_4$ Reducing System

There was no precedent found for the stereoinversion of a diaryl alcohol by reduction with boron trifluoride etherate/lithium aluminum hydride. A study of this reducing system was desired that could define its versatility with respect to the types of aryl alcohols that could be reduced and the stereoselectivity that could be achieved.

Two ideal compounds chosen for this purpose were the diastereomeric diaryl alcohols **213** and **214** (see Scheme 2.12). The *trans* relationship between the phenyl

**Scheme 2.12**

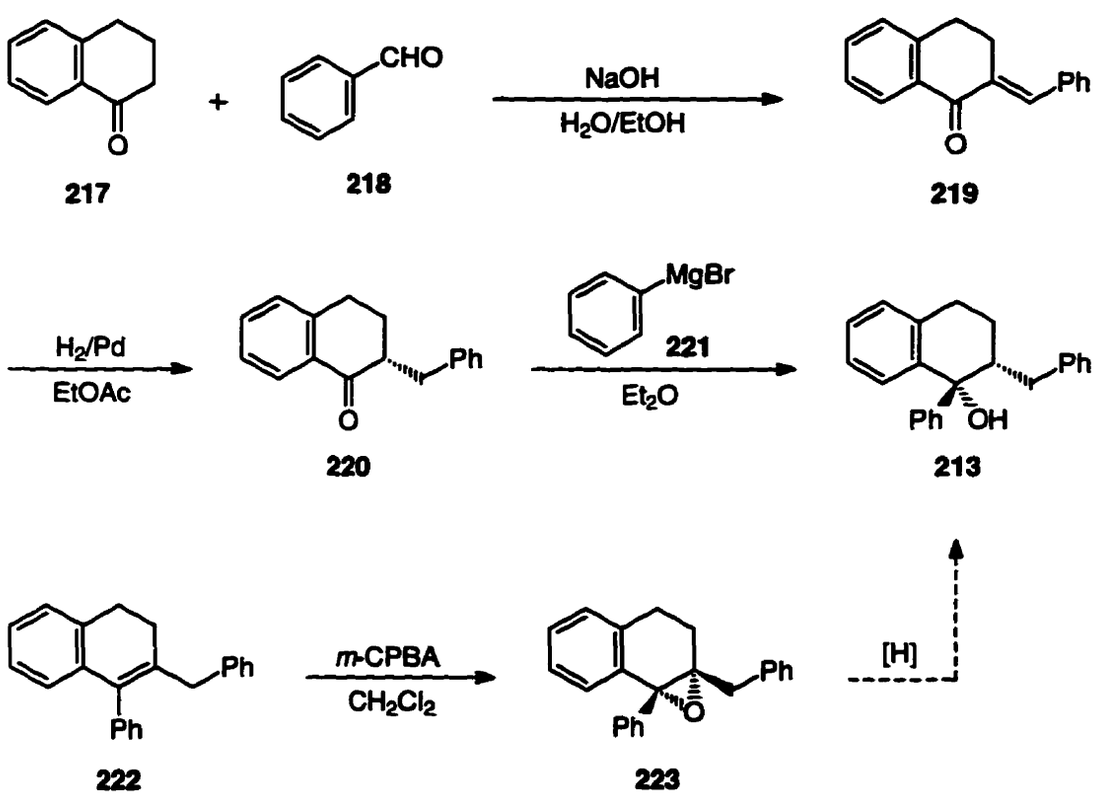



group on C-1 and the benzyl group on C-2 for aryltetralin **213** was analogous to the stereochemistry of cycloadduct **183**. If the stereoselectivity of reduction of **183** were controlled by steric hindrance from the group on C-2, then reduction of **213** should proceed in a similar manner to give 1,2-*cis* **215** (inversion) preferentially over 1,2-*trans* **216**. The stereochemical influence of the C-2 substituent would be further supported if

reduction of aryltetralin **214** were also to result in preferred formation of **215**, the retention product in this case.

Diaryl alcohol **213** (racemic) was synthesized from α-tetralone (**217**) and benzaldehyde (**218**) starting with the preparation of 2-benzaltetralone (**219**) (see Scheme 2.13). Base-catalyzed condensation of α-tetralone and benzaldehyde gave **219** (87% crude yield) with the phenyl group being *trans* to the carbonyl group.[182] Crude enone **219**

**Scheme 2.13**



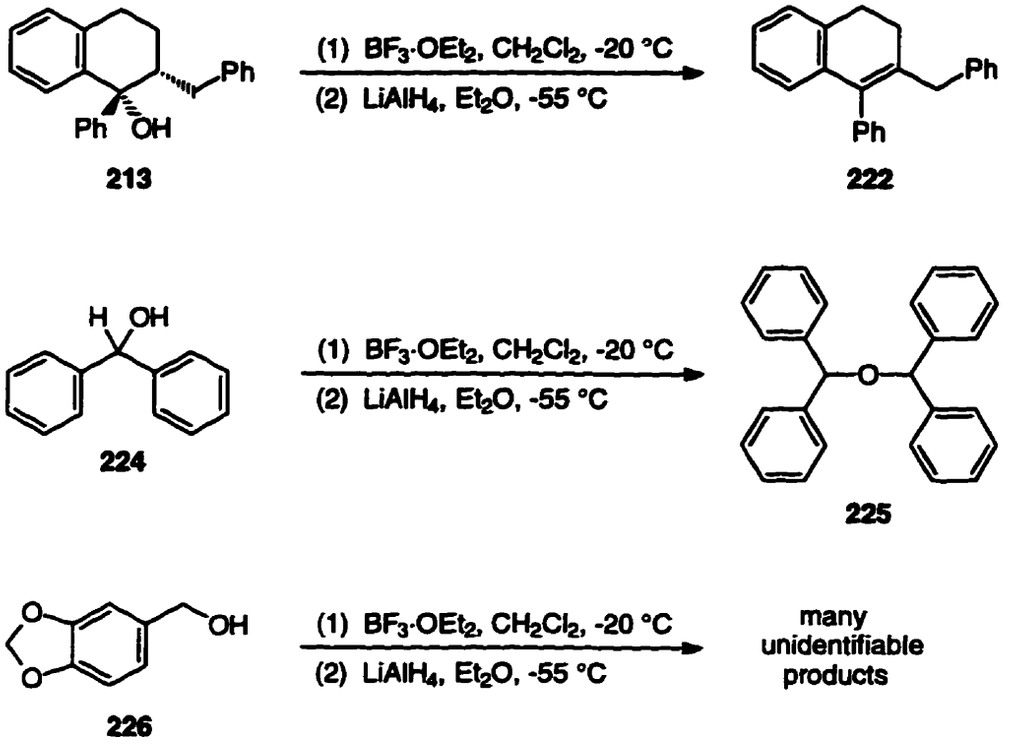

was hydrogenated in ethyl acetate using 5% Pd/C as a catalyst to give ketone **220** in 87% crude yield from α-tetralone.[182] Phenylmagnesium bromide (**221**) was prepared by reacting bromobenzene with magnesium in a refluxing solution of diethyl ether, and the Grignard reagent was then reacted with ketone **220**. Chromatography led to isolation of

only one of the possible two isomeric alcohols in 37% yield from α-tetralone. The $^1$H NOESY spectrum of the racemic alcohol showed Overhauser enhancements between the hydroxyl group proton at 1.92 ppm and each of the methylene protons of the benzyl group at 2.41 ppm and 2.72 ppm. This indicated that the hydroxyl group was *cis* to the benzyl group, and the compound was assigned structure **213**. To confirm the structure, a chemical correlation was attempted. Alcohol **213** was dehydrated by acid catalysis to quantitatively give an alkene (**222**) that was subsequently oxidized to epoxide **223** using *m*-chloroperbenzoic acid. However, reduction of the epoxide to alcohol **213** could not be effected with reducing agents such as lithium aluminum hydride and lithium triethylborohydride, even after prolonged heating at 65 °C.

Alcohol **213** was subjected to the same reduction conditions developed during the synthesis of (-)-deoxypodophyllotoxin. The addition of $BF_3{\cdot}OEt_2$ to **213** at -20 °C gave a dark orange solution that was decolourized by the addition of $LiAlH_4$ at -55 °C. $^1$H NMR analysis of the crude product showed no remaining starting material, but unfortunately, only elimination product **222** was detected (see Scheme 2.14). Since reduction did not occur, the diastereomeric alcohol **214** was not prepared.

Other benzylic alcohols were prepared and treated with $BF_3{\cdot}OEt_2/LiAlH_4$ (see Scheme 2.14). Diphenylmethanol (**224**) was synthesized by reducing benzophenone with sodium borohydride (97% crude yield), and the compound was reacted with $BF_3{\cdot}OEt_2/LiAlH_4$. The major product, isolated by chromatography, gave $^1$H NMR and mass spectra that were indicative of ether **225** (83% yield).[183] This ether has been previously synthesized from alcohol **224** by using cation initiators, such as TFA[184] and $BF_3$,[185] in the absence of reducing agent. No reduction was observed for the reaction.

**Scheme 2.14**



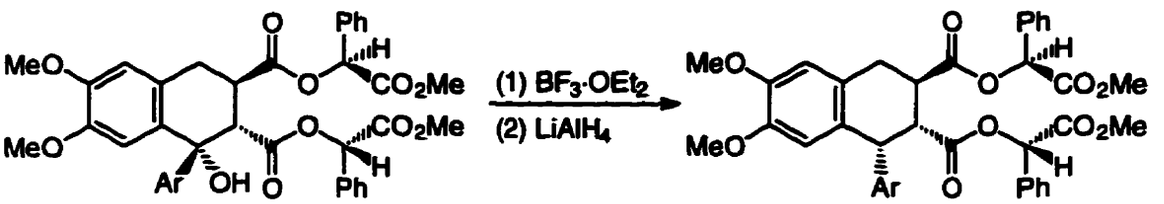

**213** **222** **224** **225** **226**

Piperonyl alcohol (**226**), prepared by reducing piperonal (**156**) with $NaBH_4$, was also treated with the reducing system, but a mixture of many products was obtained that could not be identified by $^1H$ NMR.

From the above results, it was obvious that the $BF_3{\cdot}OEt_2/LiAlH_4$ reducing system was limited in its application, and no further testing was pursued. The products obtained from alcohols **213**, **224**, and **226** suggested that the intermediate benzylic cations were not stable enough to favour reduction. It was reasonable that the cation resulting from cycloadduct **183** would be more stable due to the electron releasing groups situated on both of the aryl groups. This reducing system has since been used successfully by Coltart and Charlton in the syntheses of the lignans (-)-isolariciresinol dimethyl ether and (-)-deoxysikkimotoxin, in which cycloadducts **227** and **228** were stereoselectively reduced

to inversion products **229** and **230** (see Scheme 2.15).[186] Thus, the ionic reduction procedure is synthetically useful, but is specific for well-stabilized diaryl cations.

**Scheme 2.15**




**227**: Ar = 3,4-dimethoxyphenyl
**228**: Ar = 3,4,5-trimethoxyphenyl

**229**: Ar = 3,4-dimethoxyphenyl
**230**: Ar = 3,4,5-trimethoxyphenyl

## 2.2 An Investigation of the Diels-Alder Approach for Synthesizing Aryltetralin Lignans

### 2.2.1 Chiral Crotonate Esters and Their Reactions with *ortho*-Quinodimethanes

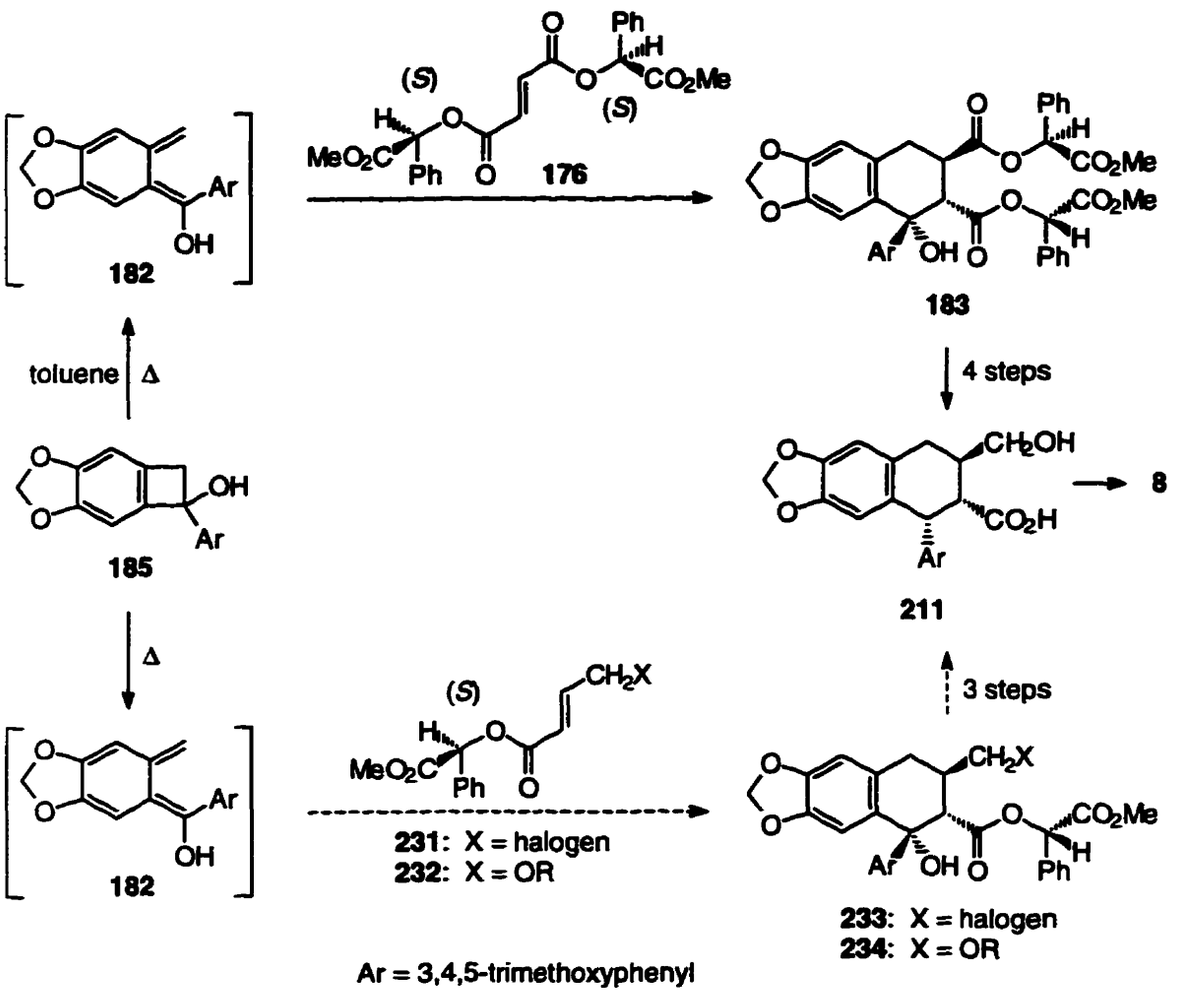
Some asymmetric syntheses of aryltetralin lignans have been accomplished by using a Diels-Alder reaction of a bis(methyl lactyl) fumarate or bis(methyl mandelyl) fumarate with an *o*-quinodimethane (see Section 2.1.1). The asymmetric synthesis of (-)-deoxypodophyllotoxin discussed in Section 2.1.2 can be included in this list. These chiral fumarate diesters are very diastereoselective when reacting with an *o*-QDM and provide an efficient synthetic route to aryltetralin lignans. However, the disadvantage of using these dienophiles is that it can be difficult to selectively modify one of the two ester groups of the resulting cycloadduct in a later step. For instance, in the synthesis of

(-)-deoxypodophyllotoxin (**8**), four steps were required to convert cycloadduct **183** to γ-hydroxy acid **211**, and approximately 23% of the theoretical yield of **211** was lost in the fourth step due to reduction of the carbonyl group on C-2 to give hydroxy acid **212**.

This problem could be potentially solved by using an unsymmetrical dienophile. A number of unsymmetrical chiral dienophiles have been used in Diels-Alder reactions (see references cited by Mathivanan and Maitra[187]), but there was a particular interest in studying 4-halo and 4-oxy derivatives of chiral crotonate esters. The 4-halo and 4-oxy substituents, being hydroxyl group equivalents, would furnish a route to the butyrolactone moiety found in lignans such as deoxypodophyllotoxin. For example, if (methyl (*S*)-mandelyl) 4-halocrotonate (**231**) or (methyl (*S*)-mandelyl) 4-oxycrotonate (**232**) were to react with α-hydroxy-α-aryl-*o*-QDM **182** with the same stereoselectivity as bis(methyl (*S*)-mandelyl) fumarate (**176**), cycloadducts **233** and **234** would be afforded (see Scheme 2.16). These cycloadducts could be converted to hydroxy acid **211** in a similar manner to cycloadduct **183**, but the reduction step needed for the diester would be avoided along with the loss of yield associated with that step. Therefore, an improved yield of deoxypodophyllotoxin would be achieved.

Although 4-halo and 4-oxy derivatives of chiral crotonate esters would be more useful than their fumarate counterparts in later functional group transformations, it remained to be determined if they would show sufficiently high yield, regioselectivity, diastereoselectivity (*endo* versus *exo*), and asymmetric induction to make them synthetically useful. To get this information, the (methyl (*S*)-lactyl) esters of 4-bromocrotonate and 4-acetoxycrotonate, **235** and **236**, were synthesized and reacted with α-hydroxy-*o*-quinodimethane (**167**).

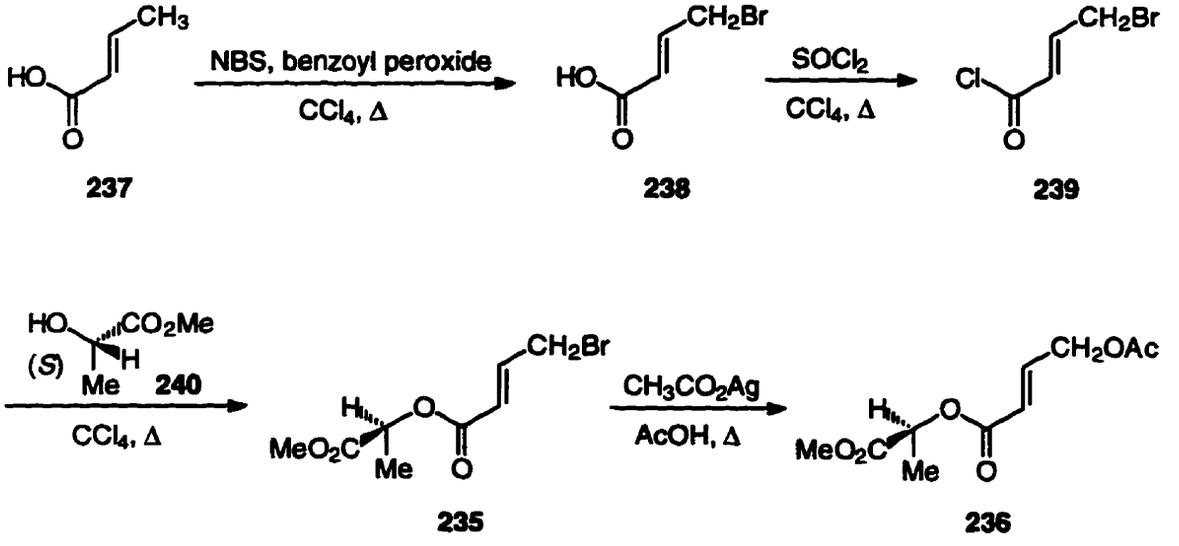
**Scheme 2.16**




Crotonate esters **235** and **236** were synthesized from crotonic acid (**237**) according to the pathway shown in Scheme 2.17. Following a method by Pinza and Pifferi,[188] crotonic acid was monobrominated on the methyl group by heating in a solution of carbon tetrachloride containing *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide. After 4.5 hours, the mixture was cooled to 5 °C and then filtered. $^1$H NMR integration of the filtrate showed that the 4-bromocrotonic acid (**238**):crotonic acid (**237**) ratio was 7:3. The solution was treated with excess thionyl chloride and warmed to 60 °C for 4 hours to

generate acid chloride **239**. Heating the crude acid chloride with excess methyl (*S*)-lactate (**240**) in $CCl_4$ followed by chromatography gave 4-bromocrotonate **235** in 40% yield from crotonic acid. It was assumed that no epimerization of the lactyl group occurred during these steps based on past experience with this group.[163] Replacement of bromine with an acetoxy group was achieved by stirring silver acetate, prepared from sodium acetate trihydrate and silver nitrate, and crotonate **235** in acetic acid at 100 °C. Chromatographically pure 4-acetoxycrotonate **236** was obtained in 75% yield.

**Scheme 2.17**

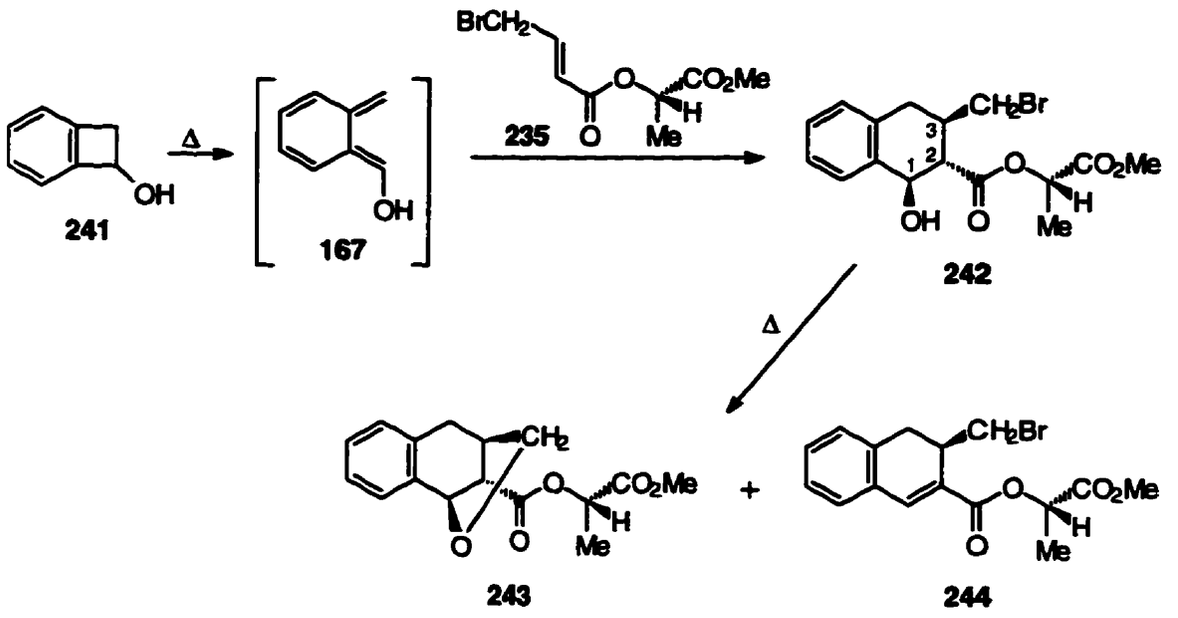



Thermolysis of benzocyclobutenol (**241**) was used as the method for generating $\alpha$-hydroxy-*o*-QDM (**167**) and assessing its reactivity with crotonates **235** and **236** (for the preparation of benzocyclobutenol, see the work of Bubb and Sternhell[189]). Benzocyclobutenol (2.1 equivalents) and 4-bromocrotonate **235** were heated in toluene for 71 hours. Evaporation of the solvent and analysis of the crude product by $^1$H NMR showed a mixture of three tetralin compounds, possibly implying that three diastereomeric

cycloadducts had formed. The three compounds, and the *o*-methylbenzaldehyde by-product, were isolated by chromatography on silica gel (5% EtOAc/hexanes). Comparing their retention times by developing a TLC plate with 30% EtOAc/hexanes revealed that one compound had a noticeably lower $R_f$ value than the other two. This compound was the only one to display an infrared absorption band for a hydroxyl group (3504 $cm^{-1}$). It was also the only one to give parent ions in its mass spectrum, at *m/z* 372 ($C_{16}H_{19}O_5{}^{81}Br$) and *m/z* 370 ($C_{16}H_{19}O_5{}^{79}Br$), that were consistent with the molecular weight of a cycloadduct. NMR and infrared absorption data showed that the other two compounds were tetralin in nature and contained the methyl lactyl ester group, but their molecular weights were lower than that of the expected cycloadduct. It was therefore deduced that the Diels-Alder reaction produced a single cycloadduct and that this adduct had reacted further to give two derivatives.

The cycloadduct was assigned the absolute structure **242** as shown in Scheme 2.18 based on the reactions of the fumarate (**95**) and acrylate (**166**) of methyl (*S*)-lactate with $\alpha$-hydroxy-*o*-quinodimethane (**167**).[163,164] The $^1H$ NMR spectrum exhibited a doublet of doublets at 2.80 ppm for H-2 with a $J_{1,2}$ of 9.6 Hz and a $J_{2,3}$ of 10.6 Hz. These coupling constants substantiated that the groups on C-1, C-2, and C-3 were all *trans* and equatorial. The relative structure of **242** was also proven by the structure of one of the secondary products formed from **242**. No bromine isotopic patterns were observed in the mass spectrum for this derivative, and a parent ion at *m/z* 290 was obtained, indicating that HBr had been lost from the cycloadduct. From this and other spectral properties, it was concluded that the secondary product was ether **243**. Clearly, if the groups on C-1 and C-3 were *trans*, ether formation would not have been possible due to the severe angle and

**Scheme 2.18**



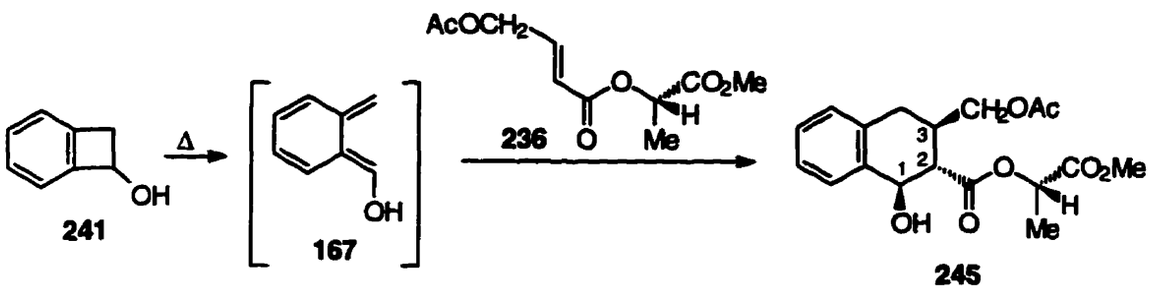

torsional strain that would have been placed on the system. The other secondary product produced parent ion peaks at *m/z* 354 ($C_{16}H_{17}O_4{}^{81}Br$) and *m/z* 352 ($C_{16}H_{17}O_4{}^{79}Br$), 18 mass units ($H_2O$) less than those of the cycloadduct, and was determined to be elimination product **244**. $^1H$ NMR integration of the crude cycloaddition mixture prior to chromatography indicated that cycloadduct **242**, ether **243**, and alkene **244** were present in a 4.5:1.7:1.0 ratio respectively.

The Diels-Alder reaction was examined again by heating 1.8 equivalents of benzocyclobutenol (**241**) and 4-bromocrotonate **235** in benzene instead of toluene. After 70 hours, $^1H$ NMR showed that about 25% of the dienophile was unreacted relative to the amount of cycloadduct formed. More benzocyclobutenol (1.6 equivalents) was added, and the solution was heated for a further 95 hours. The $^1H$ NMR spectrum of the crude product showed that there was no crotonate remaining and that ether **243** and alkene **244** were also absent. Cycloadduct **242** was obtained in 89% yield after chromatography

(8% EtOAc/hexanes). Apparently the temperature of the refluxing benzene solution (*ca.* 80 °C) was preferable to that of the toluene solution (ca 111 °C) for this reaction. A temperature of 80 °C was high enough to thermolyze the benzocyclobutenol, yet low enough to prevent cyclization or dehydration of the cycloadduct.

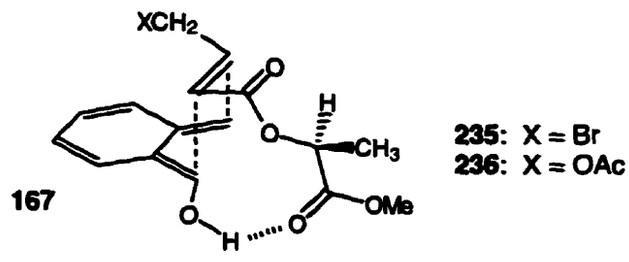
The cycloadduct of 4-acetoxycrotonate **236** and *α*-hydroxy-*o*-QDM (**167**) was likewise prepared by heating **236** with 2 equivalents of benzocyclobutenol in toluene for 67 hours. Evaporation of the toluene followed by chromatography (5-10% EtOAc/hexanes) gave enantiomerically pure cycloadduct **245** (see Scheme 2.19) in 76% yield. The cycloadduct was presumed to have the same absolute stereochemistry as **242**. Like **242**, cycloadduct **245** displayed large couplings between H-1 and H-2 (9.6 Hz) and between H-2 and H-3 (10.9 Hz) meaning that these protons were all *trans* and axial. No derivatives such as an ether or elimination product were isolated, and such compounds were not observed in the $^1$H NMR spectrum of the crude product. Although the precise levels of diastereoselectivity and regioselectivity for the formation of **242** and **245** were undetermined, there were only very minor peaks in the $^1$H NMR spectra of the crude products that could have been attributed to isomeric cycloadducts.

**Scheme 2.19**



The absolute stereochemistry of cycloadducts **242** and **245** was tentatively assigned based on the work of Charlton *et al.*[163,164] Presuming that it is correct, the cycloadducts were produced from *exo* addition of the *re* face of the crotonate to the *re* face of the *o*-QDM. This *exo* transition state differs from the *endo* transition state encountered for the formation of cycloadduct **183** in the synthesis of deoxypodophyllotoxin in which an $\alpha$-hydroxy-$\alpha$-aryl-*o*-QDM was used. An interesting fact is that Diels-Alder reactions of $\alpha$-hydroxy- or $\alpha$-alkoxy-*o*-QDMs with dienophiles lacking mandelyl or lactyl substituents have predominantly produced 1,2-*cis* adducts via *endo* transition states.[120,190,191] In studying the reactions of fumarates and acrylates of lactate and mandelate with $\alpha$-hydroxy-*o*-QDM (**167**), Charlton and Maddaford found that the preference for the *exo* transition state geometry was likely controlled by intermolecular hydrogen bonding between the hydroxyl group on the *o*-QDM and the lactyl or mandelyl carbonyl.[191] Taking this proposal into account, Figure 2.7 shows a possible transition state for the Diels-Alder reaction of (methyl (*S*)-lactyl) crotonate **235** or **236** with $\alpha$-hydroxy-*o*-QDM (**167**).

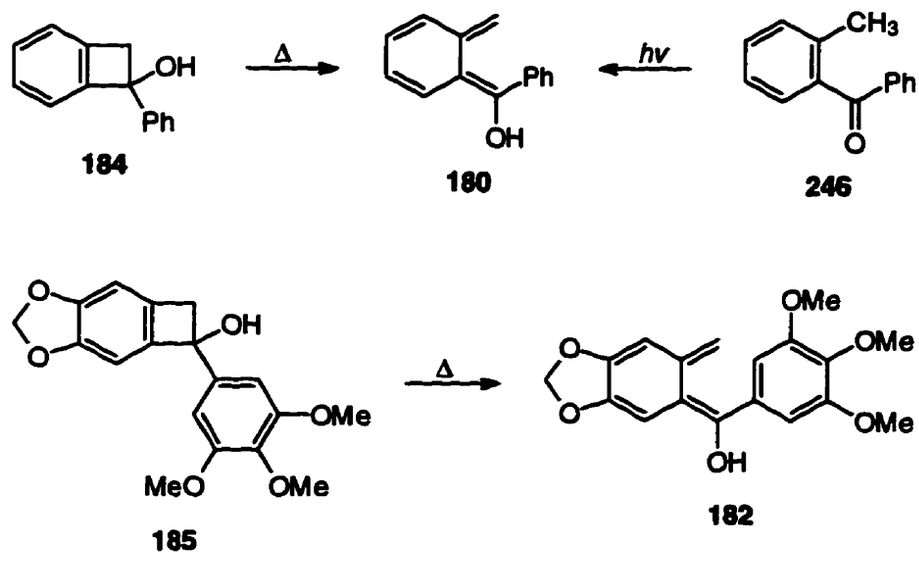
**Figure 2.7**




In view of the successful additions of crotonates **235** and **236** to $\alpha$-hydroxy-*o*-QDM (**167**), attempts were made to react these dienophiles with other *o*-QDMs such as $\alpha$-hydroxy-$\alpha$-phenyl-*o*-QDM (**180**) and $\alpha$-hydroxy-$\alpha$-aryl-*o*-QDM **182** (see Scheme

2.20). Successful reactions with these *o*-QDMs would be the first steps in using these dienophiles in asymmetric lignan synthesis. 4-Bromocrotonate **235** and an excess of 1-phenylbenzocyclobutenol (**184**) were heated in toluene for 44 hours (for the preparation of benzocyclobutenol **184**, see the work of Arnold *et al.*[192]). The crude product, as determined by $^1$H NMR, mainly consisted of unreacted dienophile. No benzocyclobutenol remained, and no cycloadducts could be detected. The same results were obtained for 4-acetoxycrotonate **236**. To photochemically generate *o*-QDM **180**,[193] 2 equivalents of 2-methylbenzophenone (**246**) and crotonate **235** in benzene were irradiated at room temperature for 23 hours using a 450 Watt Hanovia medium pressure mercury lamp. Again, no cycloadducts were obtained. Not surprisingly, the dienophiles were also found to be unreactive towards the thermally generated *o*-QDM **182**. The crotonates were evidently less reactive than the corresponding fumarates in these circumstances. The lower reactivity was attributed to the lower electrophilicity associated with the presence of only one electron withdrawing substituent.

**Scheme 2.20**



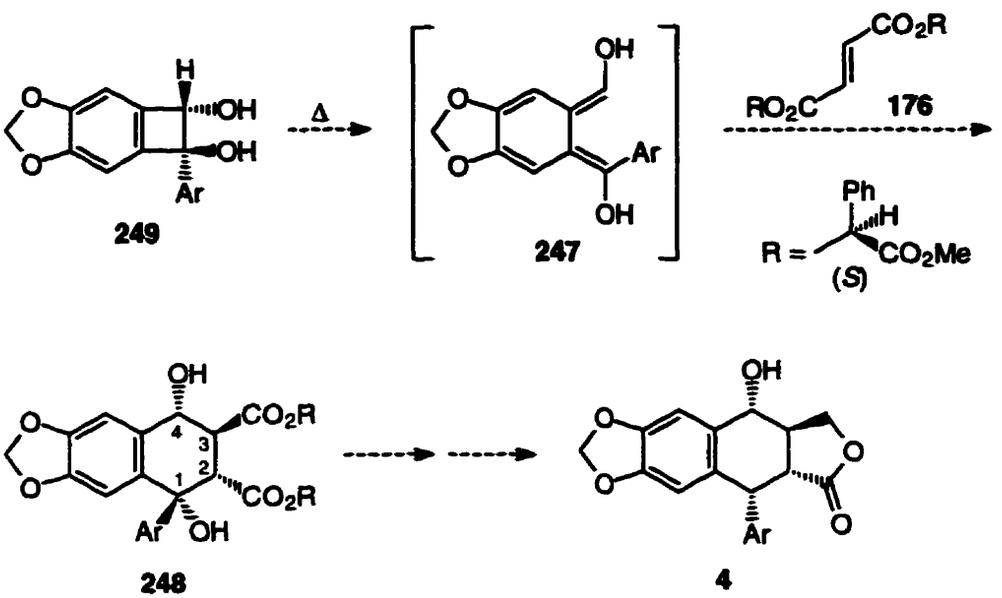
It was unfortunate that crotonates **235** and **236** did not react with α-hydroxy-α-aryl-*o*-QDMs since this meant that a monoesterified aryltetralin, such as shown in Scheme 2.16, could not be obtained in a single step. However, the high yield and stereoselectivity shown by these dienophiles with α-hydroxy-*o*-QDM (**167**) was encouraging. It might even be possible to use these reactions for aryltetralin lignan synthesis, although extra steps would be needed following cycloaddition to add an aryl group to C-1.

### 2.2.2 Attempts to Prepare α-Aryl-α,α'-dioxy-*o*-quinodimethanes and to React Them with a Chiral Dienophile

In the synthesis of (-)-deoxypodophyllotoxin (see Section 2.1.2), the aryltetralin unit was constructed asymmetrically by reacting an α-aryl-α–hydroxy-*o*-QDM with a chiral dienophile. It seemed possible that an α-aryl-α,α'-dihydroxy-*o*-QDM (**247**) could likewise react with a chiral fumarate to give cycloadduct **248** as shown in Scheme 2.21. The advantage of such a reaction was that it could be used to asymmetrically synthesize (-)-podophyllotoxin (**4**), the C-4 hydroxy analog of (-)-deoxypodophyllotoxin.

There was some uncertainty as to whether *o*-QDM **247** or analogs thereof could be prepared and undergo a Diels-Alder reaction. Since 1-aryl-2-hydroxybenzocyclobutenes were known to be thermally unstable,[167,168] it was conceivable that 1-aryl-1,2-dihydroxybenzocyclobutene **249**, the precursor to **247**, would also be unstable. However, there was precedent for the formation of similar benzocyclobutenes (see Scheme 2.22).[194,195] Coll *et al.* stereoselectively prepared *trans*-1-aryl-2-methoxy-

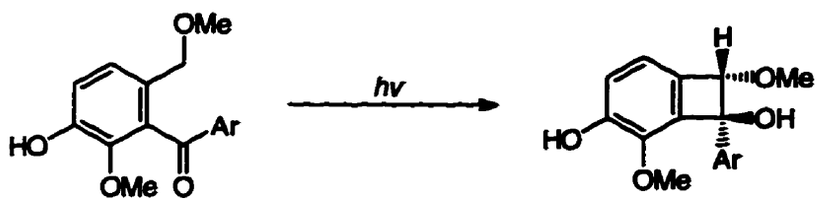
**Scheme 2.21**




Ar = 3,4,5-trimethoxyphenyl

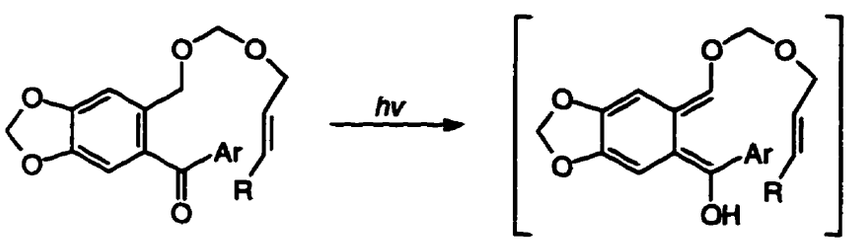
benzocyclobutenols **250-252** in over 90% purity by photolysis of the corresponding benzophenones (**253-255**).[194] These compounds were too unstable to be chromatographed, and heating them in solvent for recrystallization led to the starting benzophenones. Nevertheless, these compounds were adequately stable to be successfully used in subsequent reactions such as solvolysis and hydrogenolysis. There was no reported attempt to use these benzocyclobutenols to prepare and trap *o*-QDMs. Kraus and Wu prepared 1-phenyl-2-alkoxybenzocyclobutenol **256** as a mixture of diastereomers by photoenolization/cyclization of benzophenone **257**.[195] By altering the alkoxy and aryl substituents, it was found that an intramolecular Diels-Alder reaction was preferred over benzocyclobutene formation. That is, *o*-QDM **259** was generated by irradiation of benzophenone **260** and was subsequently trapped as cycloadduct **261** in 60% yield. No benzocyclobutene products were isolated. Cycloadduct **261** was later used in the formal total synthesis of racemic podophyllotoxin (**4**).[195] These results suggested that

**Scheme 2.22**



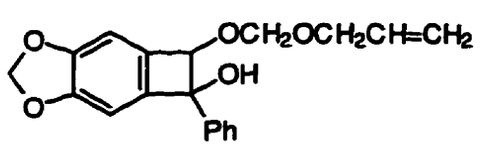

**253**: Ar = 2-methoxyphenyl
**254**: Ar = 2,3-dimethoxyphenyl
**255**: Ar = 2,4-dimethoxyphenyl

**250**: Ar = 2-methoxyphenyl
**251**: Ar = 2,3-dimethoxyphenyl
**252**: Ar = 2,4-dimethoxyphenyl

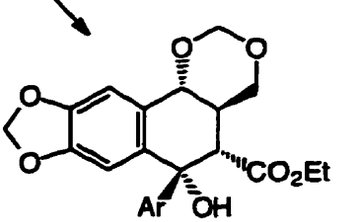



**257**: Ar = Ph, R = H
**260**: Ar = 3,4,5-trimethoxyphenyl
R = $CO_2Et$

**258**: Ar = Ph, R = H
**259**: Ar = 3,4,5-trimethoxyphenyl
R = $CO_2Et$




**256**

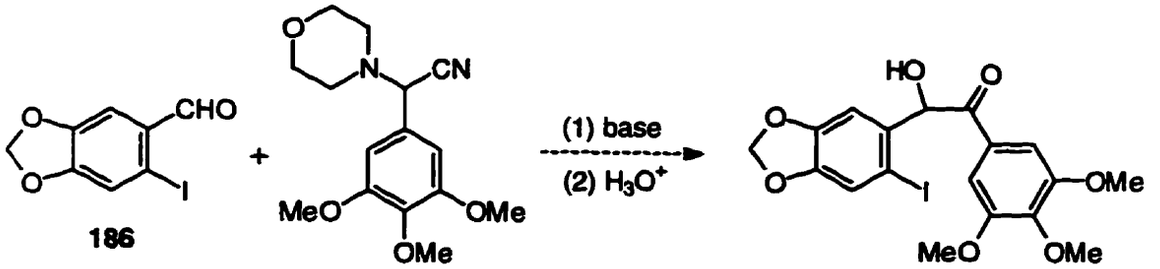



**261**: Ar = 3,4,5-trimethoxyphenyl

benzocyclobutenediol **249** would be a feasible precursor to *o*-QDM **247**. In light of the intramolecular Diels-Alder reaction of *o*-QDM **259**, an intermolecular Diels-Alder reaction of *o*-QDM **247** seemed at least possible. Thus, the synthesis of precursor **249** was pursued with the intention of generating *o*-QDM **247** and testing its reactivity with a chiral dienophile.

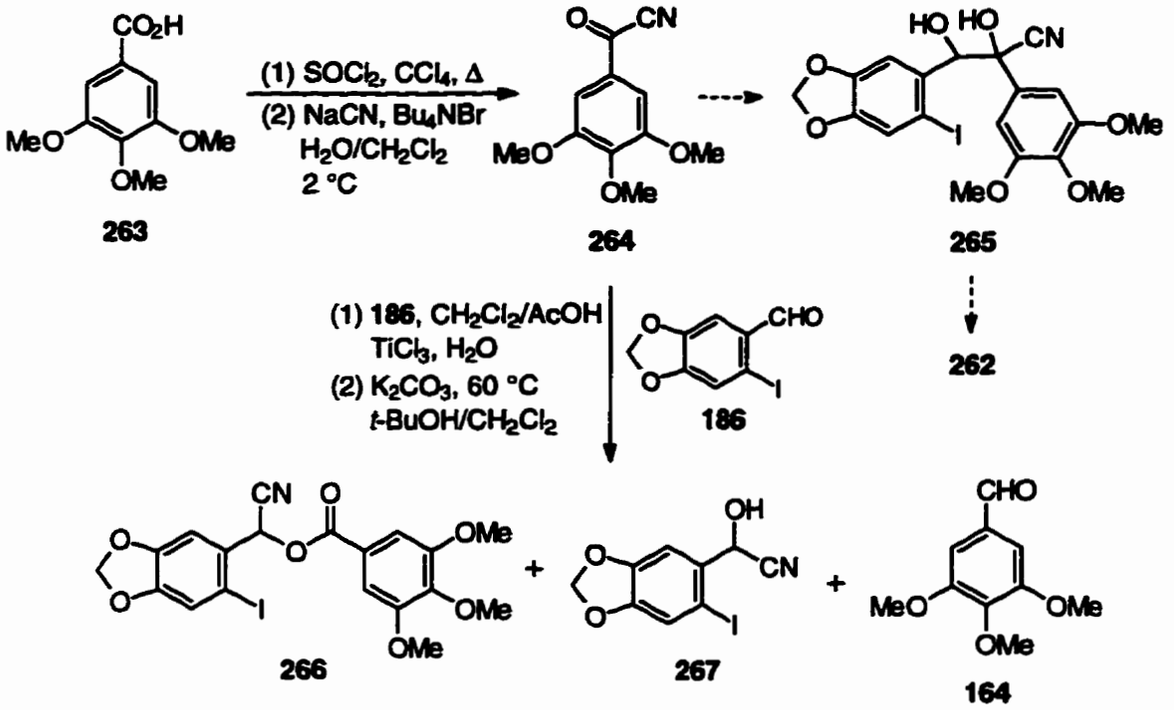
To synthesize benzocyclobutenediol **249**, a non-photochemical method was chosen based on the cyclization of benzyl aryl ketone **197** to benzocyclobutenol **185** in the deoxypodophyllotoxin synthesis. Hence, $\alpha$-hydroxy ketone **262** (see Scheme 2.23) was synthesized on the premise that it would cyclize in a similar manner. Initial attempts at preparing ketone **262** were unproductive and are outlined in Schemes 2.23-2.25. The first attempt followed closely the procedure described in Section 2.1.2 for the synthesis of ketone **197** in that $\alpha$-amino nitrile **192** was to be coupled with 6-iodopiperonal (**186**) instead of its benzylic chloride derivative (**190**). A mixture of aldehyde **186** and excess **192** in either DMF or THF was treated with sodium hydride, LDA, or lithium bis(trimethylsilyl)amide at temperatures ranging from -55 °C to 25 °C and stirred for as long as 2.5 hours. The crude products contained mostly starting materials, and no coupling products were observed for any of the trials.

**Scheme 2.23**




A second attempt to obtain ketone **262** was made according to a recent report on the synthesis of mixed benzoins using aqueous titanium(III) ions to reductively couple benzoyl cyanide and carbonyl compounds.[196] 3,4,5-Trimethoxybenzoic acid (**263**) was used to prepare 3,4,5-trimethoxybenzoyl cyanide (**264**) as shown in Scheme 2.24. Compound **263** was heated in $CCl_4$ with thionyl chloride for 16 hours. The resulting

**Scheme 2.24**

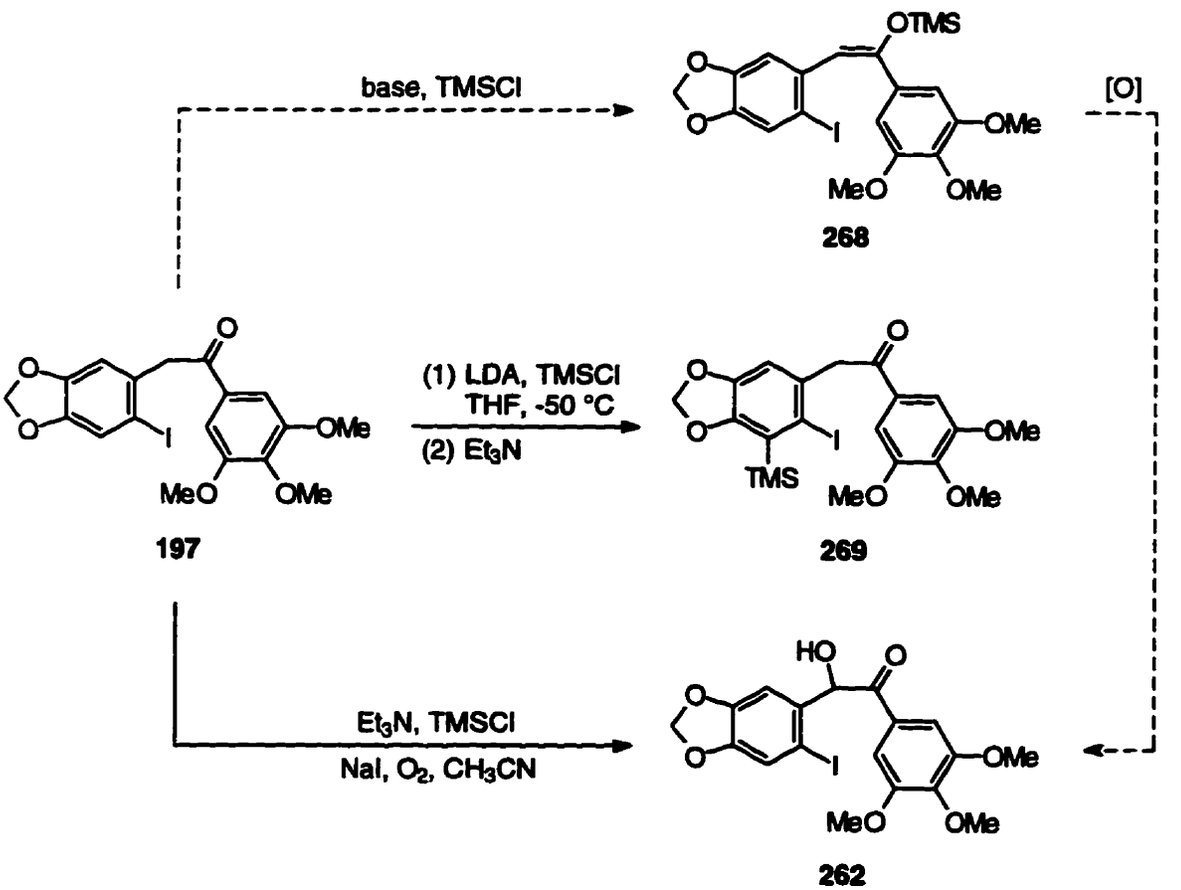



crude acid chloride was dissolved in $CH_2Cl_2$ and treated with an aqueous sodium cyanide solution at 2 °C for 1.5 hours using tetra-*n*-butylammonium bromide as a phase transfer catalyst.[197] Chromatography of the crude product gave 3,4,5-trimethoxybenzoyl cyanide (**264**) in 32% yield. To effect coupling of nitrile **264** and 6-iodopiperonal (**186**), an acetic acid/dichloromethane solution of **264** and **186** was treated with an aqueous solution of titanium trichloride for 4 hours.[196] The desired diol (**265**) could not be distinguished by $^1H$ NMR spectroscopy in the mixture of products obtained. The crude mixture was dissolved in $CH_2Cl_2$/*t*-BuOH and treated with potassium carbonate at 60 °C for 4.5 hours in hope that ketone **262** would be produced.[196] After chromatography, the only coupling product isolated appeared to be benzoylmandelonitrile **266** (13% yield). Other products included

the cyanohydrin of 6-iodopiperonal (**267**), 3,4,5-trimethoxybenzaldehyde (**164**), and unreacted **186**.

The third attempt to synthesize **262** was based on the fact that silyl enol ethers can be oxidized to $\alpha$-hydroxy ketones using *m*-chloroperbenzoic acid[198] and other oxidizing agents.[118] It was desired to convert ketone **197** to enol ether **268** and subsequently oxidize the enol ether to $\alpha$-hydroxy ketone **262** (see Scheme 2.25). While this approach was not immediately successful, **262** was eventually obtained in an unexpected manner. In an attempt to prepare **268**, ketone **197** was treated with trimethylsilyl chloride (1.5 equivalents) and triethylamine (3.5 equivalents) in DMF following a standard

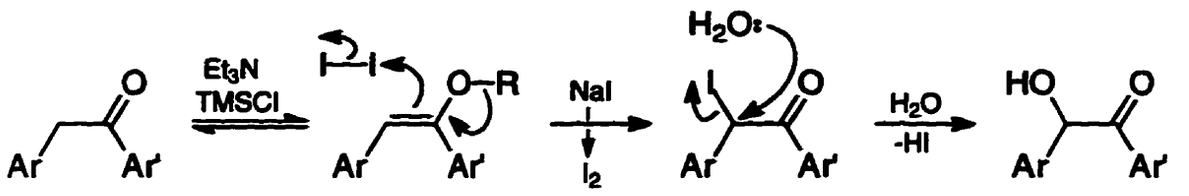
**Scheme 2.25**



method.[199,200] Mostly starting material was obtained suggesting that if the silyl enol ether had been formed, it was perhaps too labile to be isolated. A different procedure was attempted, in which ketone **197** was reacted with LDA (2 equivalents) and TMSCl (6 equivalents) in THF at -50 °C for 2 minutes followed by the addition of $Et_3N$ (15 equivalents).[199-201] This led to selective silylation of the iodopiperonyl ring, giving **269** in 100% crude yield. Starting ketone **197** was recovered by treating **269** with fluoride ion (RbF) in DMF for 45 minutes. It was interesting to find that the aromatic ring could be selectively lithiated, but as the above results indicated, **268**, if formed, was presumably too unstable to be isolated. Nevertheless, ketone **197** was again treated with TMSCl following a procedure by Cazeau *et al.*[202] In this case, **197** in acetonitrile was treated with 1.3 equivalents of $Et_3N$, 1.2 equivalents of TMSCl, and 1.4 equivalents of sodium iodide at room temperature for 20 hours. $^1H$ NMR analysis of the crude product showed that the starting material had completely reacted to give one major compound, but it did not contain any trimethylsilyl groups. A carbonyl group (IR 1689 $cm^{-1}$) was present, but there was only one benzylic proton and it displayed a higher chemical shift (6.13 ppm) than those of ketone **197** (4.33 ppm). After treating the compound with $D_2O$, the doublet ($J = 5.2$) for the benzylic proton became a singlet, and the doublet at 4.51 ppm ($J = 5.3$) was removed. Considering that the IR spectrum (3472 $cm^{-1}$) and the proton/deuterium exchange were indicative of a hydroxyl group, it was concluded that the compound was the desired $\alpha$-hydroxy ketone **262**. This was later confirmed by spectral analysis of a pure sample.

To establish the mechanism for the hydroxylation of ketone **197**, a series of qualitative tests were carried out in which one or more of the variables were changed. It

**Scheme 2.26**




**197** **268**: R = TMS; **270**: R = H **271** **262**

Ar = 2-iodo-4,5-methylenedioxyphenyl
Ar' = 3,4,5-trimethoxyphenyl

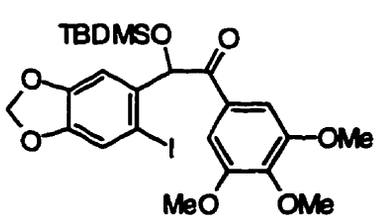
was found that passing a stream of dry air through the solution increased the reaction rate whereas no reaction occurred when an inert atmosphere was used. There was also no reaction when sodium iodide was omitted. However, **262** was produced when sodium iodide was replaced with iodine. Treating **197** with only $Et_3N$ and iodine or only sodium iodide in acetonitrile also led to the formation of **262**. From these results, the general mechanism displayed in Scheme 2.26 was proposed. Iodide salts are known to oxidize readily to iodine.[203] Since the reaction required air and sodium iodide or iodine in place of NaI, it was likely that iodine was the reactive species. Under the basic conditions, the ketone would have been in tautomerism with its enol form (**270**) or may have reacted to give the silyl enol ether **268**. Although the reaction was not dependent on TMSCl being present, TMSCl did enhance the reaction. Therefore, either **268** or **270**, or perhaps both species, could have reacted with iodine to give $\alpha$-iodo ketone **271**. The reactions of enols, enolates, and silyl enol ethers with halogens are methods that are frequently used for preparing $\alpha$-halo carbonyl compounds.[118] Since **271** was not isolated, the $\alpha$-iodo group must have been displaced by water to give ketone **262**. The water for the hydrolysis could have come from trace moisture in the atmosphere or solvent, because no

water was added prior to or following the reaction. Such susceptibility to hydrolysis can be explained by the generally high rates at which $\alpha$-halo ketones undergo $S_N2$ reactions[204,205] and the fact that benzylic halides are known to be easily hydrolyzed.[206]

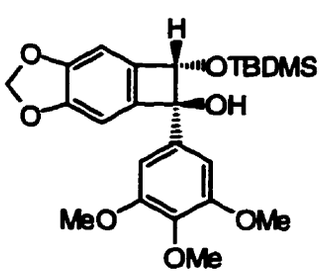
During the qualitative tests, it was found that the most efficient way to synthesize **262** was to treat **197** with $Et_3N$, TMSCl, and NaI while passing air through the system. This gave chromatographically pure $\alpha$-hydroxy ketone in 95% yield.

An attempt to cyclize **262** to benzocyclobutenediol **249** was made by applying the same conditions used for the cyclization of ketone **197**. $\alpha$-Hydroxy ketone **262** in THF was treated with excess *n*-BuLi under a nitrogen atmosphere at -80 °C for 2 minutes. The crude product obtained after work-up was a mixture of many unidentifiable compounds. If **262** cyclized, **249** was too unstable to exist at room temperature.

**Figure 2.8**




**272**




**273**

The *t*-butyldimethylsilyl ether of **262** was prepared and treated with *n*-BuLi. Compound **262** was treated with TBDMS triflate[207] and triethylamine in $CH_2Cl_2$ to give $\alpha$-*t*-butyldimethylsiloxy ketone **272** in 99% yield (see Figure 2.8). The TBDMS group was incorporated in order to prevent possible abstraction of the hydroxyl proton by *n*-BuLi, a process that could have hindered cyclization. Also, in considering previous research,[194,195] the corresponding $\alpha'$-siloxybenzocyclobutenol **273** may have been more

stable than **249**. However, treating **272** with *n*-BuLi also gave a large number of unidentifiable products.

Assuming that the benzocyclobutenols, **249** and **273**, were being formed, it was possible that they were being thermolyzed to the respective *o*-QDMs at a much lower temperature than expected. Choy and Yang reported[208] that benzocyclobutenols or their acetates, on treatment with *n*-BuLi, were converted to $\alpha$-oxy-*o*-QDMs at temperatures of 0 °C and -78 °C as proven by trapping the *o*-QDMs *in situ* with dienophiles such as dimethyl maleate (**148**), $\gamma$-crotonolactone (**163**), and dimethyl fumarate. Choy subsequently exploited this method in the enantioselective synthesis of (-)-epiisopodophyllotoxin by preparing and reacting an $\alpha$-aryl-$\alpha'$-oxy-*o*-QDM with a chiral butenolide at -78 °C.[209] The fumarate of methyl (*S*)-mandelate (**176**) was therefore used to see if ketones **262** and **272** could also afford cycloadducts at low temperature. To either **262** or **272** in THF at -80 °C was added *n*-BuLi followed by 2 equivalents of fumarate **176**. The solution was allowed to warm to 0 °C over 1.5 hours then acidified. Unfortunately, no cycloadducts were obtained. While the lack of cycloadduct formation did not mean that the intermediate *o*-QDMs were not being generated, it was apparent that this approach was not synthetically useful and was not studied further.

In retrospect, there were two interesting discoveries made during this investigation. One was that benzyl aryl ketone **197** could be selectively lithiated at the position *ortho* to the iodo group. Secondly, ketone **197** could be efficiently oxidized to $\alpha$-hydroxy ketone **262** in a single step.

## 2.3 A Synthesis of (+)-Rabdosiin and its (-)-(1*R*,2*S*)-Isomer

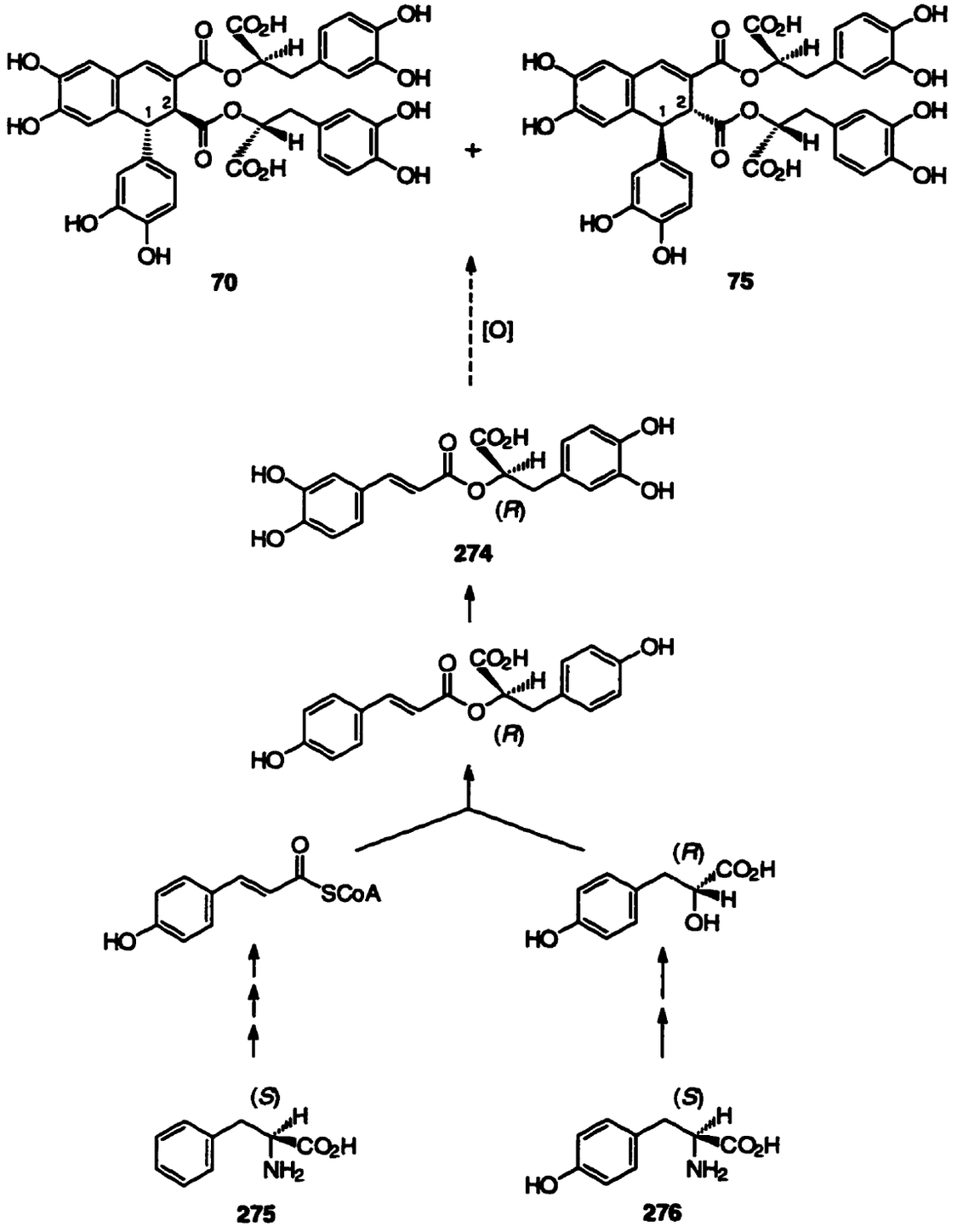
### 2.3.1 Basis for the Synthetic Approach

As discussed in Section 1.2.3, natural rabdosiin has been isolated in a (-)-(1*R*,2*S*) form (**70**). The (+)-(1*S*,2*R*)-diastereomer of rabdosiin (**75**) has also been obtained from one of the same natural sources. Considering that these compounds are formally dimers of (*R*)-(+)-rosmarinic acid (**274**), it seems possible that they are biosynthesized by the diastereoselective oxidative coupling/cyclization of two molecules of rosmarinic acid (see Scheme 2.27).

(*R*)-(+)-Rosmarinic acid (**274**) is a natural caffeic acid dimer whose structure was first elucidated by Scarpati and Oriente almost 40 years ago.[210] This compound has been the subject of many studies due to its anti-inflammatory properties.[211-219] It is one of the active constituents of the Chinese drug dan-shen which has been used for the treatment of heart disease.[220] Its other biological activities include anti-oxidative,[213,221-224] anti-histamine,[225] anti-bacterial,[219,226,227] anti-viral,[228] and anti-hormonal[229] effects. Rosmarinic acid was originally isolated from extracts of *Rosmarinus officinalis*,[210] but it can be found throughout the plant kingdom in such families as Apiaceae, Boraginaceae, and Lamiaceae.[222]

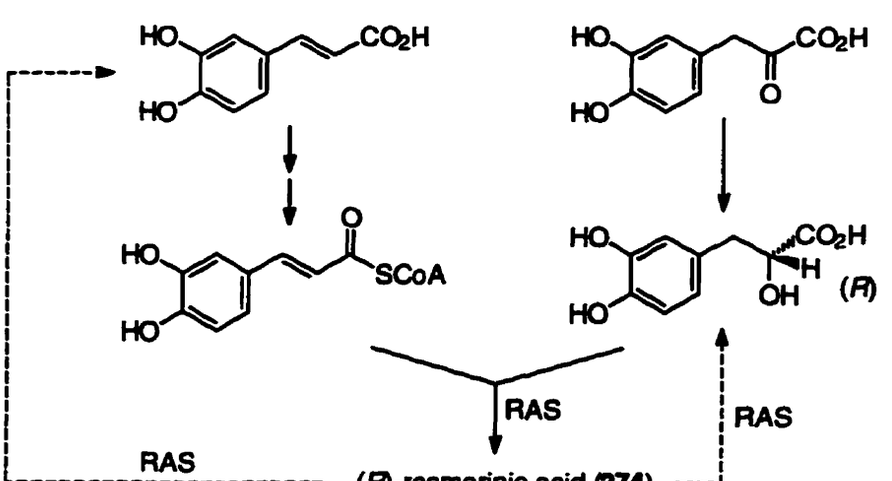
The biosynthetic pathway for rosmarinic acid production has been determined from investigations of *Coleus blumei* and *Anchusa officinalis* plant cell suspension cultures.[230-235] (*S*)-Phenylalanine (**275**) and (*S*)-tyrosine (**276**) (see Scheme 2.27) were first established as precursors to (*R*)-rosmarinic acid in 1970 by introducing radioactively

**Scheme 2.27**



labelled amino acids to plants of *Mentha*.[236] With the subsequent discovery that cell cultures of *Coleus blumei*[230,231] and *Anchusa officinalis*[232] generated large amounts of rosmarinic acid, these cell cultures became the focus of research. In 1977, the *Coleus blumei* cell cultures were used to confirm the biosynthetic precursors **275** and **276** and to determine that phenylalanine ammonia-lyase was one of the enzymes involved in the biosynthesis.[230] The other enzymes of the biosynthetic pathway were unknown until ten years later when tyrosine aminotransferase activity was observed.[233,234] Determination of the remaining enzymes soon followed (see Petersen *et al.*[235] and literature cited therein). This led to a chemo-enzymatic synthesis of (*R*)-rosmarinic acid (**274**)[217] (see Scheme 2.28) and the proposal of a total biosynthetic pathway[235] (see Scheme 2.27). However, no non-enzymatic route to this compound has been published, and no one has investigated the possibility that it may be involved in the biosynthesis of (-)-rabdosiin (**70**) or its (1*S*,2*R*)-isomer (**75**).

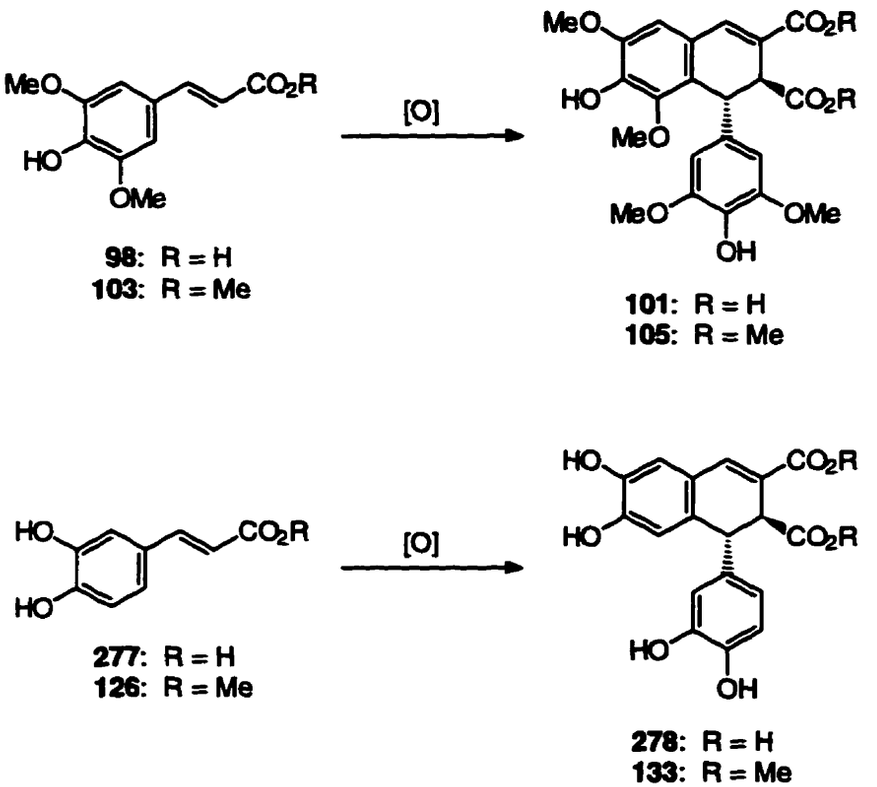
**Scheme 2.28**




RAS = rosmarinic acid synthase

Although the possibility that aryltetralin lignans **70** and **75** may be formed by the oxidative coupling and cyclization of rosmarinic acid has not been investigated, similar studies have been carried out for other hydroxycinnamyl compounds analogous to rosmarinic acid. For instance, sinapic acid (**98**) was converted to racemic thomasidioic acid (**101**) in about 59% yield on oxidation with ferric chloride in aqueous methanol

**Scheme 2.29**




**98**: R = H
**103**: R = Me

**101**: R = H
**105**: R = Me

**277**: R = H
**126**: R = Me

**278**: R = H
**133**: R = Me

followed by treatment with acid,[129,130] and a quantitative conversion was achieved on treatment with oxygen in aqueous base at pH 8.5 (see Scheme 2.29).[237] Methyl sinapate (**103**) in aqueous acetone also afforded racemic dimethyl thomasidioate (**105**) using ferric chloride (45% yield),[131] or hydrogen peroxide with horseradish peroxidase (41% yield) as the oxidant.[238] Caffeic acid (**277**) formed diacid **278** on treatment with oxygen in aqueous

base at pH 8.5,[239] and methyl caffeate (**126**) was converted to the corresponding aryltetralin **133** in 55% yield on oxidation with ferric chloride in aqueous acetone.[111] Based on these precedents, it seemed at least possible that rabdosiin and its 1,2-*trans* isomer could be prepared from rosmarinic acid by oxidative coupling/cyclization.

Rabdosiin and its 1,2-*trans* isomer have synthetically challenging structures that are unique relative to other natural aryltetralin lignans such as deoxypodophyllotoxin. In addition to the chiral centers contained in the tetralin ring, there are also chiral centers outside of the ring in the lactyl ester groups. Oxidative coupling of enantiomerically pure rosmarinic acid would provide the chiral centers in the side chains of rabdosiin and would possibly stereoselectively direct the introduction of the chiral centers of the aryltetralin unit.

Before attempting to synthesize rabdosiin and its 1,2-*trans* isomer, two preliminary studies were performed. First, the oxidative coupling/cyclization of methyl sinapate (**103**) was studied to determine which oxidizing conditions would give the best yield of dimethyl thomasidioate (**105**). In the second study, sinapic acid (**98**) was esterified with the chiral and bulky methyl (*R*)-mandelyl group and subsequently treated with an oxidizing agent. This study was undertaken primarily to determine the effect of the bulkier ester group on coupling/cyclization and to look for asymmetric induction. Having made these investigations, as discussed in the next Section (2.3.2), the synthesis of the rosmarinic acid dimers was then pursued.

In order to synthesize rabdosiin and its 1,2-*trans* isomer in high enantiomeric purity, an enantiomerically pure form of rosmarinic acid was required. A practical non-enzymatic route to both the (*R*)- and (*S*)-enantiomers of rosmarinic acid was devised and

used to synthesize the (*S*)-enantiomer. While attempts to oxidatively couple and cyclize (*S*)-(-)-rosmarinic acid to the desired aryltetralin lignans were unsuccessful, the conversion of a protected form of (*S*)-rosmarinic acid was accomplished. All of these results are discussed in Section 2.3.3.

### 2.3.2 Oxidative Coupling and Cyclization of Sinapic Acid Esters

As reviewed in Section 1.4, the free radical oxidative coupling of a propenylphenol is very dependent on the oxidizing system used and the structure of the starting material. It therefore seemed worthwhile to investigate these properties before attempting the rabdosiin synthesis. To determine the optimum oxidation conditions needed to convert a propenylphenol to the desired 1,2-*trans* aryltetralin structure, methyl sinapate (**103**) was chosen as the model compound. Likewise, (methyl (*R*)-mandelyl) sinapate (**279**) was chosen to study structural effects. Like rosmarinic acid, both **103** and **279** contain an acid residue that is known to readily cyclize to an aryltetralin on oxidative coupling.

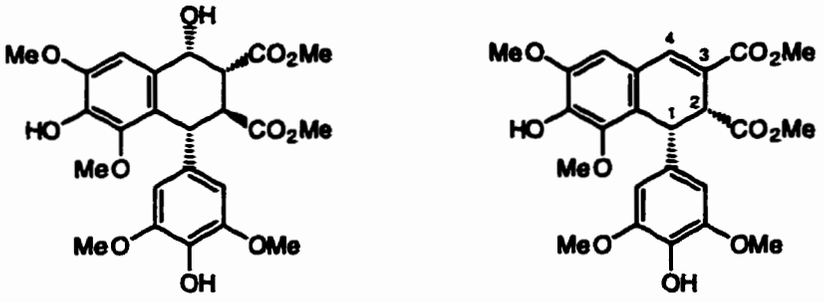
#### 2.3.2.1 Effects of the Oxidation System on the Conversion of Methyl Sinapate to Dimethyl Thomasidioate

It has already been established that sinapic acid (**98**)[237] and caffeic acid (**277**)[239] can be converted to the respective aryltetralins, **101** and **278**, on treatment with aqueous base

while being exposed to air. Compound **98** gives quantitative conversion to **101**, whereas **277** leads to a mixture of products. The yield of **278** from **277**[239] appears to be comparable to those obtained for the conversion of methyl sinapate (**103**)[131] and methyl caffeate (**126**)[111] to aryltetralins **105** and **133** using ferric chloride. Hence, although rosmarinic acid is soluble in aqueous base, air oxidation would probably not give a better yield of rabdosiin than could be obtained with other one electron oxidants. In addition, the lactyl groups of rosmarinic acid, and the dimeric products, would be susceptible to hydrolysis and epimerization in the alkaline environment. Various oxidizing conditions other than base promoted oxidations were therefore explored for their potential use in the rabdosiin synthesis by analyzing for their ability to couple/cyclize methyl sinapate (**103**) to dimethyl thomasidioate (**105**).

To survey the effects of different oxidizing conditions efficiently, methyl sinapate was treated with an oxidant and the crude product was analyzed by $^1$H NMR. A more detailed analysis of a preliminary reaction was carried out in order to identify other products formed in the oxidation. Methyl sinapate (**103**) was treated with ferric chloride (2.1 equivalents) in aqueous acetone for 30 minutes following, in part, the procedure of Wallis.[131] The $^1$H NMR of the crude product indicated that alcohol **104** was the major product (see Figure 2.9).[131] The crude alcohol was heated in benzene with *p*-toluenesulfonic acid hydrate for 45 minutes to give, after chromatography, dimethyl thomasidioate (**105**) in 60% yield along with two other products. These two products were impure, but the $^1$H NMR signals of one of the products were sufficiently distinct to allow its structure to be tentatively assigned. This compound displayed a doublet of doublets for H-2 at 4.13 ppm, a doublet for H-1 ($J$ = 9.0) at 4.80 ppm, and a doublet for

**Figure 2.9**




**104** **280**

H-4 ($J = 2.7$) at 7.41 ppm. These coupling patterns suggested that the compound was the 1,2-*cis* aryltetralin **280** (see Figure 2.9). The second compound gave a very similar $^1$H NMR spectrum ($CDCl_3$) to that of **105**. This included a doublet for H-2 ($J$ = 1.2) at 4.00 ppm, a broad singlet for H-1 at 4.96 ppm, and a singlet for H-4 at 7.63 ppm. There were also unique doublets at 6.07 ppm and 6.35 ppm ($J$ = 1.8) that were characteristic of the vinyl protons of a 2,5-dimethoxy-2,5-cyclohexadienone ring.[238] However, the spectrum was not consistent with any products that have been reported for the oxidative coupling of methyl sinapate,[131,238] and the presence of impurities made it difficult to propose a structure. This compound will henceforth be referred to as unknown **281**. Other than **280** and **281**, only very minor by-products were detected for the ferric chloride oxidation of methyl sinapate.

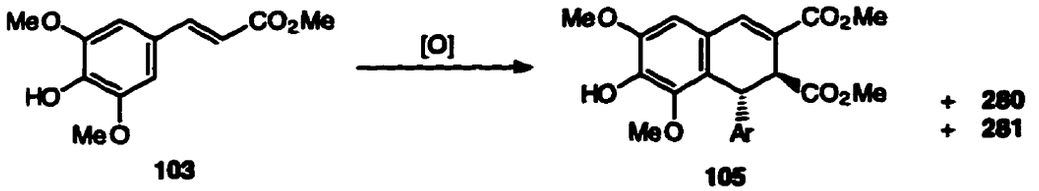
The oxidation variables that were studied included the type of oxidant, the type of solvent, and to some extent, the temperature of the medium. A typical procedure involved the dropwise addition of 2.2 equivalents of the oxidant in water (0.3 mL) to a solution of methyl sinapate (5 mg) in organic solvent (0.6 mL) and stirring the mixture for 30 minutes. The reaction progress was followed by TLC. For reactions using iron-based oxidants, the reaction progress could also be monitored visually by the change in the colour of the

solution from yellow to brown. Following the reaction, the solvent was evaporated, and the residue was heated in benzene with *p*-TsOH·$H_2O$ between 30 minutes and 1 hour. The crude product was isolated by extraction (water and $CH_2Cl_2$) and analyzed by $^1H$ NMR. The relative yield of dimethyl thomasidioate (**105**) was determined by comparing the area of its H-1 signal to the area of the signals given by 1,2-*cis* aryltetralin **280** (H-1 at 4.80 ppm), unknown compound **281** (H-1 at 4.96 ppm), and starting material **103** (aromatic protons at 6.77 ppm). The oxidizing conditions used and the corresponding ratios of products to remaining starting material (**105**:**281**:**280**:**103**) are summarized in Table 2.2.

The oxidation of methyl sinapate with ferric chloride[61,111,129-131] was performed in five different aqueous organic solvents at room temperature. The amount of unreacted starting material was negligible for all solvents except for THF in which the reaction rate was noticeably slower. Two hours were required for most of the methyl sinapate to react in THF. The yield of desired product **105** relative to products **280** and **281** was approximately the same for all solvents, with the formation of **105** being favoured, except for acetonitrile, in which a significant amount of **281** was obtained. Altering the procedure by adding methyl sinapate in acetonitrile or acetic acid to the oxidant also increased the formation of **281**.

Other oxidants were no better than ferric chloride. Ceric ammonium nitrate[131] gave about the same quantities of **105** and **281** in acetone, the formation of **281** was favoured in acetonitrile, and **281** was exclusively produced at 5 °C in acetonitrile. It should be noted that ceric ammonium nitrate oxidation also led to the formation of a number of other minor products, possibly polymers, but these were not identifiable in the crude mixture by $^1H$ NMR. The oxidant potassium ferricyanide[59-62,131,132] had the lowest

## Scheme 2.30




103 105

Ar = 3,5-dimethoxy-4-hydroxyphenyl

## Table 2.2

| Reaction Conditions | | | | | Ratio of Products to Starting Material | | | |
|---|---|---|---|---|---|---|---|---|
| Oxidant | Solvent | Time (hours) | Temp. (°C) | I.A. | **105** (1,2-*trans*) | **281** (?) | **280** (1,2-*cis*) | **103** (S.M.) |
| $FeCl_3$ | acetone/$H_2O$ | 0.5 | 25 | | 4.3 | 1.0 | 0.60 | 0.14 |
| $FeCl_3$ | *i*-PrOH/$H_2O$ | 1.0 | 25 | | 6.6 | 1.0 | 1.4 | 0.15 |
| $FeCl_3$ | $CH_3CN/H_2O$ | 0.5 | 25 | | 1.0 | 1.2 | 0.13 | 0.036 |
| $FeCl_3$ | $CH_3CN/H_2O$ | 0.5 | -5 | yes | 1.0 | 2.2 | 0 | 0.056 |
| $FeCl_3$ | AcOH/$H_2O$ | 0.25 | 25 | | 4.5 | 1.0 | N.A. | 0.38 |
| $FeCl_3$ | AcOH/$H_2O$ | 0.5 | 25 | yes | 1.0 | 1.2 | 0.21 | 0.022 |
| $FeCl_3$ | THF/$H_2O$ | 1.0 | 25 | | 4.5 | 1.0 | N.A. | 0.87 |
| $FeCl_3$ | THF/$H_2O$ | 2.0 | 25 | | 4.4 | 1.0 | N.A. | 0.24 |
| $(NH_4)_2Ce(NO_3)_6$ | acetone/$H_2O$ | 1.0 | 25 | | 1.2 | 1.0 | 0.23 | 0.24 |
| $(NH_4)_2Ce(NO_3)_6$ | $CH_3CN/H_2O$ | 0.25 | 25 | | 1.0 | 4.1 | 0 | 0.23 |
| $(NH_4)_2Ce(NO_3)_6$ | $CH_3CN/H_2O$ | 0.25 | 5 | | 0 | 23 | 0 | 1.0 |
| $K_3Fe(CN)_6$ | acetone/$H_2O$ | 48 | 25 | | 0 | 0 | 0 | 1.0 |
| $K_3Fe(CN)_6$ | AcOH/$H_2O$ | 69 | 25 | | 1.6 | 1.0 | 0 | 3.7 |
| $K_3Fe(CN)_6$ | acetone/2.0 M $H_2SO_4$(aq) | 20 | 25 | | 2.3 | 0 | 0.29 | 1.0 |
| $Fe(ClO_4)_3 \cdot xH_2O$ | acetone/$H_2O$ | 0.5 | 25 | | 2.8 | 1.0 | 0.33 | 0.11 |
| $Fe(ClO_4)_3 \cdot xH_2O$ | $CH_3CN/H_2O$ | 0.5 | 25 | | 1.9 | 1.0 | 0.30 | 0.20 |
| $Fe(ClO_4)_3 \cdot xH_2O$ | AcOH/$H_2O$ | 0.5 | 25 | | 5.5 | 0 | 0.77 | 1.0 |
| DDQ | acetone/$H_2O$ | 1.5 | 25 | | 1.0 | 1.4 | 0.12 | 0.16 |
| DDQ | $CH_3CN/H_2O$ | 0.5 | 5 | | 1.0 | 4.8 | 0 | 0.047 |

Temp. = Temperature, I.A. = Inverse Addition, S.M. = Starting Material, N.A. = Not Available

reactivity. No reaction occurred when potassium ferricyanide was used in acetone, but lowering the pH of the medium by using acetic acid or sulfuric acid resulted in partial dimerization. Ferric perchlorate hydrate[240] readily reacted with methyl sinapate in acetone or acetic acid to give **105** in similar yields to those obtained with ferric chloride. The product ratios obtained for oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[241-244] in acetone or acetonitrile closely paralleled those obtained with ceric ammonium nitrate.

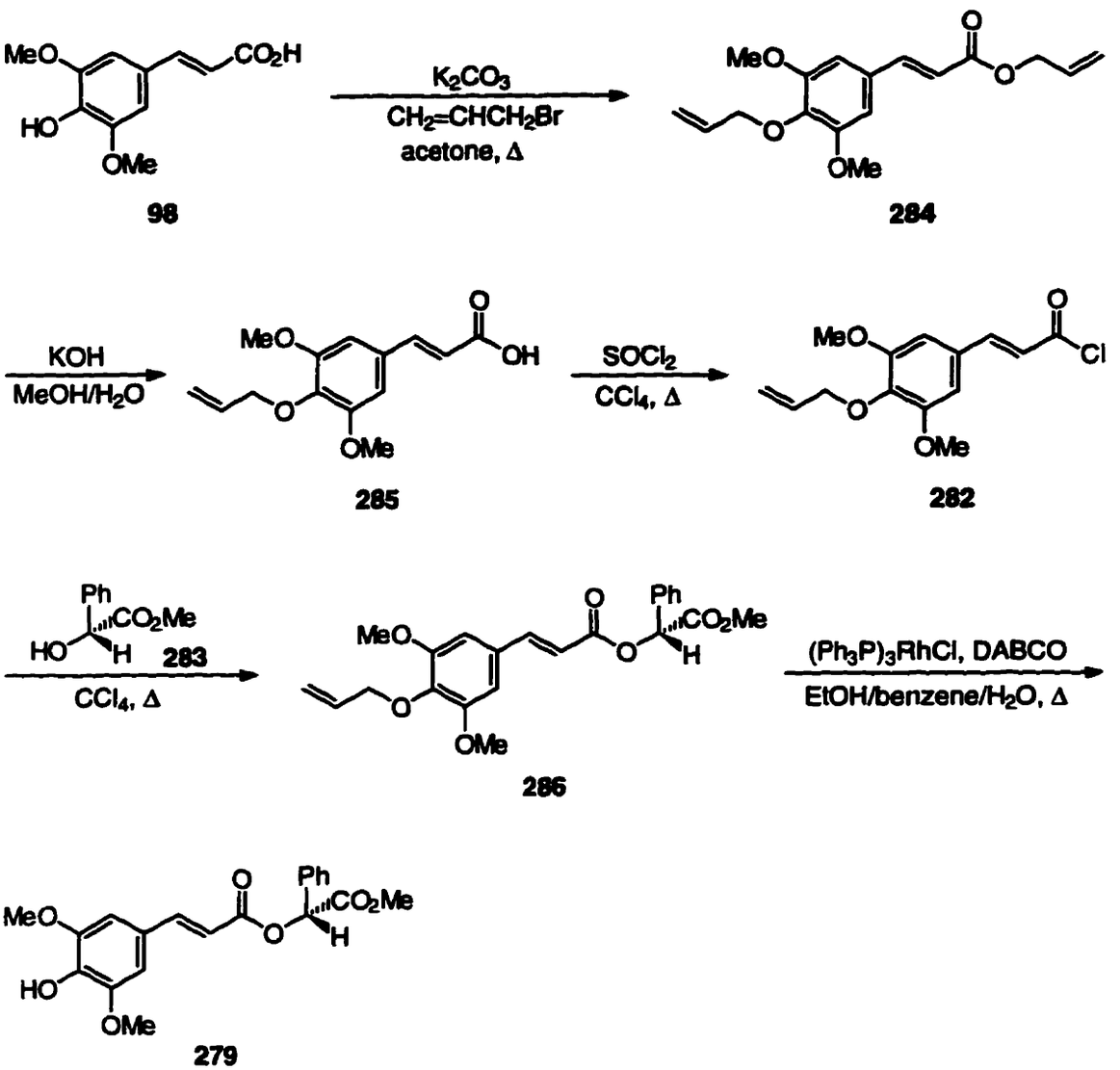
Regarding the oxidative dimerization of methyl sinapate to dimethyl thomasidioate, the following conclusions were reached. Ceric ammonium nitrate, DDQ, acetonitrile, low temperatures, and inverse addition were all inappropriate oxidizing conditions due to their selectivity for the production of **281**. Potassium ferricyanide was also unsuitable because of its low reactivity. Dimerization did proceed in aqueous THF and acetic acid solutions, but these were not the best solvents since the reaction was relatively slow in THF and a close to neutral pH was preferred. The optimum oxidation method involved adding a solution of ferric chloride or ferric perchlorate hydrate in water to a solution of methyl sinapate in acetone or isopropyl alcohol at room temperature. This procedure produced dimethyl thomasidioate in about 70% yield (see Table 2.2). This approximate yield was consistent with the 60% isolated yield of **105** that was obtained by using $FeCl_3$ in aqueous acetone (see above), especially considering that some product would have been lost during chromatography. It was hoped that these oxidation conditions would likewise give high yields for the dimerization of (methyl (*R*)-mandelyl) sinapate in the study of structural effects.

### 2.3.2.2 Preparation and Dimerization of (Methyl (*R*)-Mandelyl) Sinapate

(Methyl (*R*)-mandelyl) sinapate (**279**) contains an ester portion that is very similar to that found in rosmarinic acid (see Scheme 2.31). By treating **279** with an oxidant, it could be determined whether such a bulky ester group would allow coupling and cyclization to occur with the same efficiency as was observed for the methyl ester. It would also indicate whether the chiral ester group could stereoselectively control the introduction of the chiral centers of the aryltetralin unit.

The methyl (*R*)-mandelyl ester of sinapic acid (**279**) was prepared, as shown in Scheme 2.31, by the coupling of 4-*O*-allylsinapoyl chloride (**282**) with methyl (*R*)-mandelate (**283**). Direct coupling to sinapic acid chloride was not possible. Attempts to prepare sinapic acid chloride by treating sinapic acid with thionyl chloride or triphenylphosphine/carbon tetrachloride resulted in polymerization. To prevent interference from the phenolic hydroxyl group, an allyl protecting group was used. Sinapic acid (**98**) was heated in 2:1 acetone/allyl bromide with anhydrous potassium carbonate to give allyl 4-*O*-allylsinapate (**284**).[245] The allyl ester group was removed by base hydrolysis to give 4-*O*-allylsinapic acid (**285**) in 98% crude yield from sinapic acid. Acid **285** was transformed to the acid chloride (**282**) with thionyl chloride and subsequently reacted with 2 equivalents of methyl (*R*)-mandelate (**283**) to produce ester **286** in 79% yield. Ester **286** was heated in 7:3:1 ethanol/benzene/water for 4 hours with 0.07 equivalents of tris(triphenylphosphine)rhodium(I) chloride and 0.5 equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO).[246,247] This effected both the isomerization and hydrolysis of the allyl group to produce the deprotected sinapic acid ester **279** in 98%

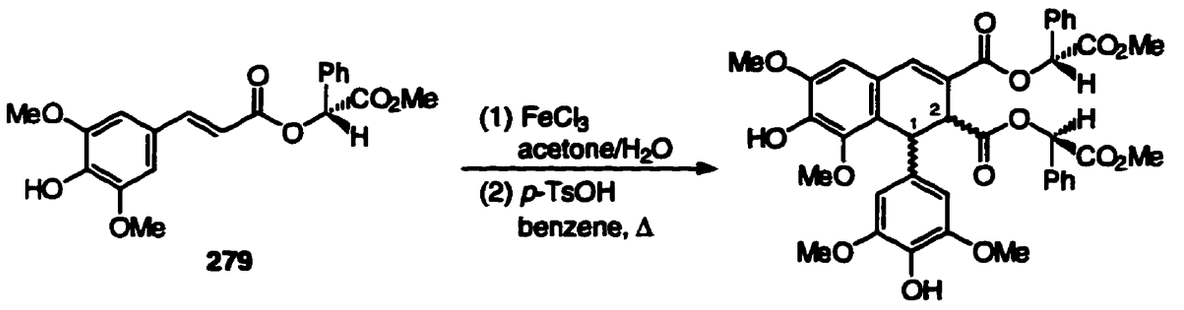
**Scheme 2.31**




yield (76% overall yield). DABCO was included in the procedure to impede the deactivation of the rhodium catalyst.[248,249] DABCO slows the hydrolysis of the intermediate enol ether, which would give propionaldehyde that in turn would be decarbonylated by $(Ph_3P)_3RhCl$ to form the less catalytically active $(Ph_3P)_2Rh(CO)Cl$.

Mandelyl sinapate **279** was oxidized and cyclized using one of the optimum methods found for the dimerization of methyl sinapate (**103**). Treatment of **279** with ferric

**Scheme 2.32**




**287**: 1,2-*trans* (major)
**288**: 1,2-*trans* (minor)
**289**: 1,2-*cis*

chloride in 2:1 acetone/water for 25 minutes at room temperature followed by acid catalyzed dehydration gave a crude product that appeared by $^1$H NMR to be a mixture of two isomers of the desired lignan and very little remaining starting material. Integration of the H-4 proton singlets at 7.79 ppm and 7.81 ppm suggested that these isomers were present in a 2.0:1.0 ratio respectively. Due to the similar retention times of the compounds on silica gel, the crude product was chromatographed on a preparative HPLC reverse-phase column. Three isomeric aryltetralin lignans were isolated in a 6.8:3.0:1.0 ratio with the favoured isomer being isolated in 53% yield. The HPLC chromatogram indicated the presence of these aryltetralins in a ratio of 8.1:4.0:1.0. Each of the two major dimers displayed a H-2 doublet with a H(1)-H(2) coupling of 1.2 Hz in their $^1$H NMR spectra. As this low coupling constant was the same as that given by the H-2 proton of dimethyl thomasidioate (**105**), these dimers, **287** and **288**, were assigned the 1,2-*trans* stereochemistry (see Scheme 2.32). The $J_{1,2}$ of 8.8 Hz exhibited by the minor dimer (**289**) indicated that it had the 1,2-*cis* geometry. The absolute configurations at C-1 and C-2 for compounds **287**, **288**, and **289** were not determined. Since the reaction rate and product yield observed for the dimerization of **279** was similar to that of methyl

sinapate, it was apparent that the bulky methyl mandelyl group did not cause significant steric hindrance. Surprisingly, the formation of 1,2-*cis* aryltetralins by the oxidation of propenylphenols, as had been observed earlier with the formation of **280** and here with the formation of **289**, has not been reported previously.

A brief study was conducted to ascertain if the diastereoselectivity with respect to the two *trans* isomers could be improved by altering the reaction medium. The results of the study are displayed in Table 2.3. Similar to the methyl sinapate investigation, the general procedure was to add 2.2 equivalents of ferric chloride in water to mandelyl sinapate **279** in organic solvent (2:1 organic solvent/$H_2O$) at room temperature, dehydrate the product with a catalytic amount of acid, and analyze by $^1H$ NMR spectroscopy. The solvents that were effective for the dimerization of methyl sinapate also provided good yields of aryltetralins **287** and **288**. The aqueous acetone solvent gave the best diastereoselectivity for the major 1,2-*trans* isomer (**287**) relative to the minor *trans* isomer

**Table 2.3**

| Reaction Conditions | | | Ratio of Products to Starting Material | | |
|---|---|---|---|---|---|
| Solvent | Temperature | Time | Major 1,2-*trans* Isomer (**287**) | Minor 1,2-*trans* Isomer (**288**) | Starting Material (**279**) |
| acetone/$H_2O$ | 25 °C | 30 min | 12.1 | 6.0 | 1.0 |
| $CH_3CN/H_2O$ | 25 °C | 30 min | 7.3 | 3.8 | 1.0 |
| *i*-PrOH/$H_2O$ | 25 °C | 1 h | 5.6 | 3.5 | 1.0 |
| AcOH/$H_2O$ | 25 °C | 10 min | 1.9 | 1.0 | 1.6 |
| THF/$H_2O$ | 25 °C | 20 h | 1.6 | 1.2 | 1.0 |
| acetone/$H_2O$ | 2 °C | 20 h | 7.9 | 4.8 | 1.0 |

(**288**) and resulted in the least unreacted starting material. Most of the solvents resulted in similar diastereoselectivity (*ca.* 2:1 **287**:**288**) except for THF, in which the reaction was very slow and unselective. Performing the reaction at a lower temperature also resulted in decreased diastereoselectivity and lower yields. It should be noted that, while acetonitrile furnished little remaining starting material, other unidentified products were obtained in significant quantities in this solvent, and the yields of aryltetralins **287** and **288** were not as high as they were in solvents such as acetone, isopropyl alcohol, and acetic acid.

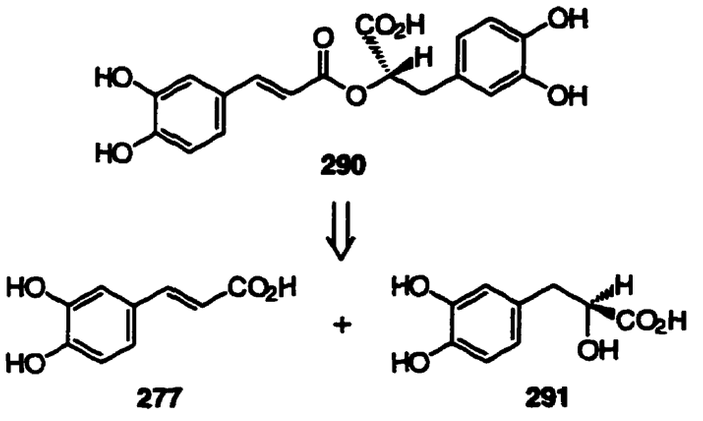
The discovery that the methyl (*R*)-mandelyl group can induce diastereoselectivity in the oxidative dimerization of a sinapate ester was very promising. A future examination of the ability of other chiral ester groups to induce stereoselectivity in similar reactions would be beneficial. This type of reaction, especially if the diastereomeric excess could be augmented, would be useful for asymmetrically synthesizing lignans such as thomasidioic acid since the chiral groups can be readily removed following the cyclization. The good yield of the two 1,2-*trans* diastereomers was also very impressive considering the bulkiness of the ester group. This meant that the same oxidation technique should also be effective for the dimerization of rosmarinic acid.

### 2.3.3 Synthesis of (+)-Rabdosiin and its (-)-(1*R*,2*S*)-Isomer

In considering the retrosynthesis of rosmarinic acid (**290**), the disconnection of the caffeic acid ester bond was an obvious first step. This disconnection gave caffeic acid (**277**) and 3-(3',4'-dihydroxyphenyl)lactic acid (**291**) as synthetic precursors (see Scheme

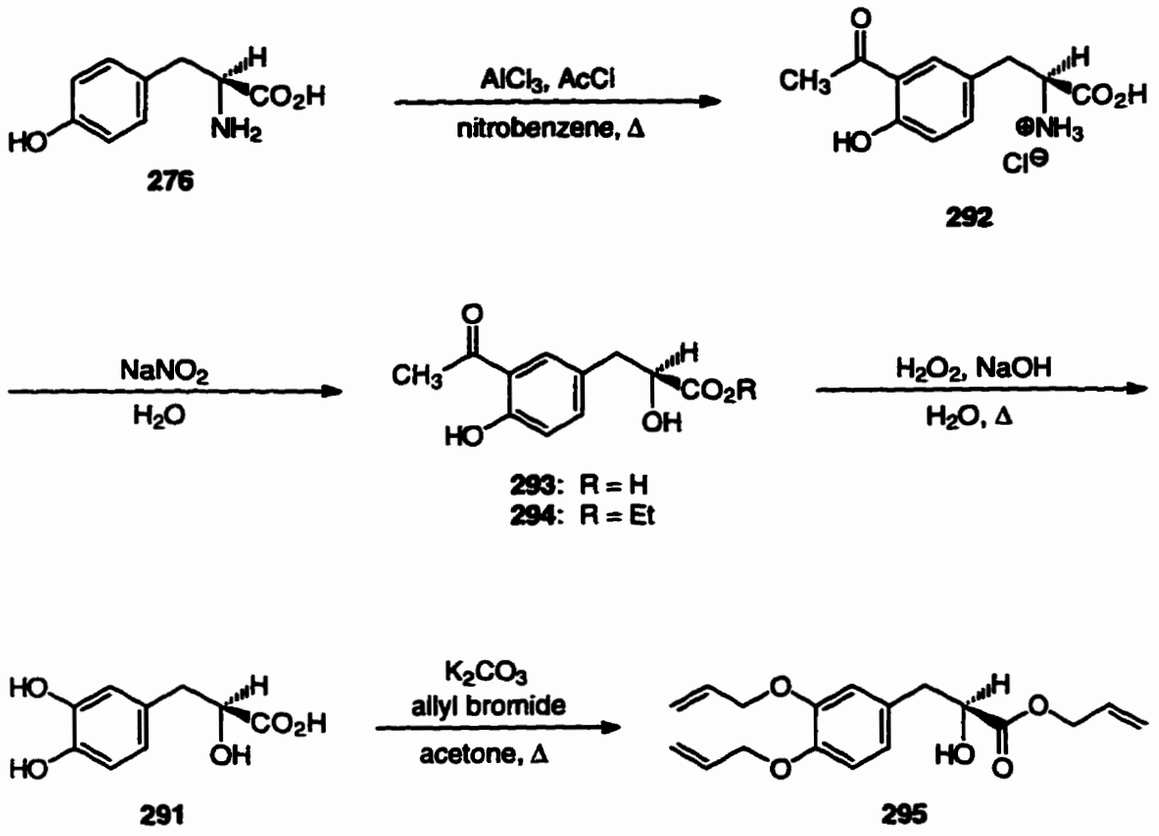
2.33). A synthetic route involving these compounds as intermediates was pursued since it appeared to be a practical convergent synthesis not unlike the one that occurs in nature (see Scheme 2.27).

**Scheme 2.33**




The complete synthesis of (*S*)-rosmarinic acid (**290**) is depicted in Schemes 2.34 and 2.35. The problem of establishing the chiral center was overcome at the beginning of the synthesis by making use of enantiomerically pure (*S*)-tyrosine (**276**) as the starting material for the synthesis of 3-(3',4'-dihydroxyphenyl)-(*S*)-lactic acid (**291**). (*S*)-Tyrosine was selectively acetylated using a Friedel-Crafts method that was described by Boger and Yohannes[250] (aluminum chloride/acetyl chloride/nitrobenzene) to give the hydrogen chloride salt of 3-acetyl-(*S*)-tyrosine (**292**) in 70% yield. $\alpha$-Amino acid **292** was transformed to $\alpha$-hydroxy acid **291** by using the two-step procedure developed by Wünsch and Zott.[251] Diazotization of **292** with aqueous sodium nitrite was followed by *in situ* hydrolysis resulting in the formation of $\alpha$-hydroxy acid **293** (81% yield) with retention of configuration. The enantiomeric purity of **293** was confirmed by converting it to the known ester **294**, and comparing its specific rotation to those reported in the literature.[251]

**Scheme 2.34**




**276** **292** **293**: R = H **294**: R = Et **291** **295**

Aryllactic acid **293** was then subjected to Baeyer-Villiger oxidation by treatment with aqueous sodium hydroxide and 30% hydrogen peroxide at 46 °C. The resulting base-sensitive phenolic acetate was not isolated but was directly hydrolyzed to **291** (61% yield) in the alkaline environment. The moderate yield was attributed to the loss of the highly polar polyhydroxy acid during chromatographic purification. It should be noted that the (*R*)-form of 3-(3',4'-dihydroxyphenyl)lactic acid (**291**), also known as danshensu, has a wide range of pharmacological activities and is found in traditional Chinese medicine.[252,253]

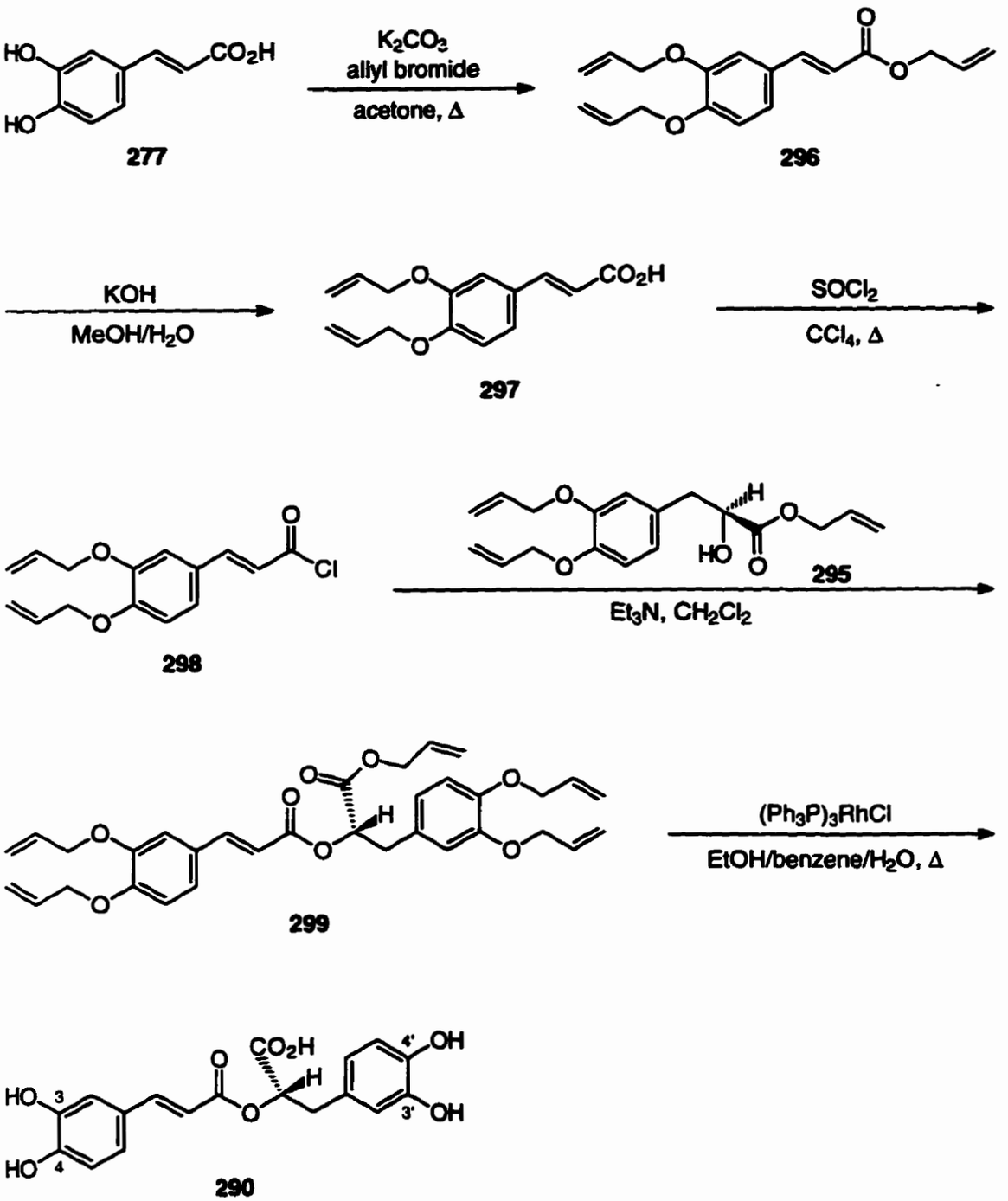
(*S*)-Tyrosine was not the initial choice for starting material to prepare **291**. Based on the work of Wünsch and Zott,[251] it was thought that 3-(3',4'-dihydroxyphenyl)-(*S*)-

alanine (L-DOPA; **61**) could be deaminated like **292** to give **291** in a single step. However, this endeavor failed, necessitating the alternative three-step method.

To facilitate the coupling of aryllactic acid **291** with caffeic acid (**277**), the phenolic and carboxylic hydroxyl groups were protected by allyl groups. Treating **291** in acetone with 3.0 equivalents of potassium carbonate and 17 equivalents of allyl bromide gave compound **295**.[245] Only the $\alpha$-hydroxyl group, needed in the subsequent coupling reaction, was left unprotected. The moderate yield of alcohol **295** (42%) was unexpected since TLC and $^1$H NMR analyses of the crude product were indicative of a complete reaction. It appeared that some product was lost during chromatography. The overall yield of the protected aryllactic acid (**295**) from (*S*)-tyrosine was improved from 15% to 30% by not chromatographing intermediates **293** and **291**.

Caffeic acid (**277**), as shown in Scheme 2.35, was also allylated using allyl bromide and anhydrous base to provide ester **296** in good yield (86%). Hydrolysis of **296** with a solution of potassium hydroxide in 9:1 methanol/water afforded the diallyl ether of caffeic acid (**297**) in 83% yield. The coupling of alcohol **295** and acid **297** was accomplished by preparing the acid chloride of **297** (**298**) using thionyl chloride and subsequently reacting **298** with 0.5 equivalents of alcohol **295** in the presence of triethylamine. Fully allylated (*S*)-rosmarinic acid (**299**) was obtained in 65% yield. The overall yield of **299**, like that of alcohol **295**, was increased from 9% to 29% by omitting all of the intermediate chromatographic steps. The deprotection of **299** was more problematic than removing the allyl group from mandelyl 4-*O*-allylsinapate **286**. Treatment of **299** with 0.07 equivalents of Wilkinson's catalyst and 0.5 equivalents of DABCO,[246,247] as for **286**, resulted in only partial removal of the allyl groups. Increasing the amount of the rhodium catalyst to as

**Scheme 2.35**




high as 4 equivalents also led to inadequate deallylation. The problem was eventually rectified by omitting DABCO from the procedure. Using small quantities of Wilkinson's

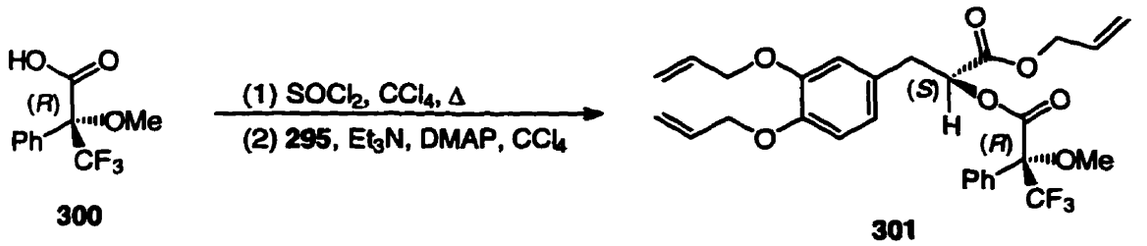
catalyst (0.1 to 0.2 equivalents) was still ineffective, but total deallylation was achieved on treating **299** with 0.4 to 0.7 equivalents of the catalyst. Chromatographically pure (*S*)-(-)-rosmarinic acid (**290**) was obtained from **299** in 29% yield and in 3% overall yield (9% overall yield when chromatography was not performed prior to the isolation of **299**). However, the crude rosmarinic acid, isolated in 60% yield in the final step by aqueous base extraction, would probably be sufficiently pure for most purposes, and the loss of material that occurred during chromatography on silica gel could be avoided.

Although all of the spectral data were consistent with the structure of rosmarinic acid,[254,255] it was disconcerting to observe that the magnitude of the specific rotation of the pure sample ($[\alpha]_D^{25}$ -86°, *c* 0.53, 95% EtOH) was considerably different than that reported for the natural product ($[\alpha]_D^{25}$ +145°, *c* 1.4, 95% EtOH),[210] indicative of only 59% enantiomeric excess for the synthetic material. In order to verify the enantiomeric purity of the synthetic rosmarinic acid, various stages of the synthesis were investigated for possible isomerization. Derivatization and analysis by GC on a chiral column revealed that the (*S*)-tyrosine starting material had greater than 99% enantiomeric purity. As mentioned above, the optical purity of hydroxy acid **293** was examined by converting it to ester **294**. Ester **294**, formed by the acid catalyzed condensation of **293** with ethanol, was obtained in 49% yield from amino acid **292**. The specific rotation of **294**, $[\alpha]_D^{25}$ -30° (*c* 2.7, $CHCl_3$), compared well with those previously reported, $[\alpha]_{546}$ -38.8° and $[\alpha]_{578}$ -34.2° (*c* 2.39, $CHCl_3$).[251]

To verify the enantiomeric purity of alcohol **295**, it was esterified with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-Mosher's acid; **300**).[256,257] (*R*)-Mosher's acid was treated with thionyl chloride, and the resulting acid chloride was

reacted with alcohol **295** (0.25 equivalents), triethylamine, and 4-(dimethylamino)pyridine to give crude diester **301** (see Scheme 2.36). Only a single diastereomer could be detected in the $^{1}H$ NMR spectrum, and no remaining alcohol was present. The $^{19}F$ NMR spectrum displayed one major signal (-75.00 ppm) and 4 very minor signals. From the 92:8 integrated ratio of the major singlet to the largest of the remaining signals (-75.11 ppm), it was calculated that **295** had a minimum enantiomeric purity of 84%. An attempt was made to isomerize **301** with strong base. Crude diester **301** in THF was treated with a 1.0 M solution of lithium bis(trimethylsilyl)amide in hexanes (5 equivalents) under a nitrogen atmosphere at -55 °C for 10 minutes and was then acidified with 10% HCl(aq). However, this gave back only recovered starting material, indicating that it was also unlikely that **291** would have been isomerized during allylation.

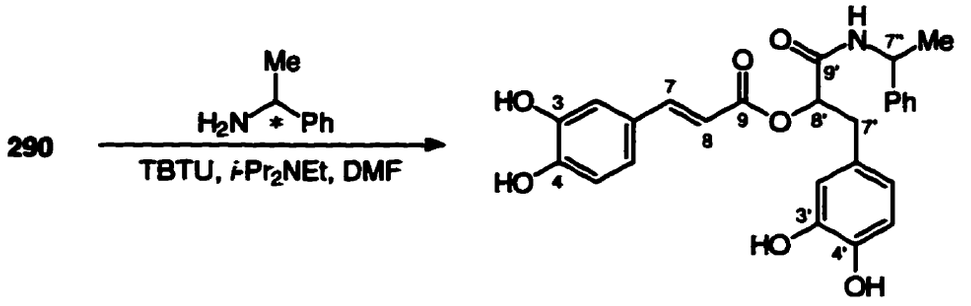
**Scheme 2.36**




**300** **301**

Finally, the enantiomeric purity of rosmarinic acid was tested. A mixture of diastereomeric salts was prepared by adding 1.2 equivalents of racemic $\alpha$-methylbenzylamine to rosmarinic acid in acetone. Unfortunately, these diastereomeric salts were not distinguishable by $^{1}H$ NMR (DMSO-$d_6$), so the corresponding diastereomeric amides were synthesized (see Scheme 2.37). Rosmarinic acid (**290**) in DMF under a nitrogen atmosphere was reacted with 1.2 equivalents of

**Scheme 2.37**




**302**: 8'*S*,7"*S*/8'*R*,7"*R*
**303**: 8'*S*,7"*R*/8'*R*,7"*S*
**304**: 8'*R*,7"*R*
**305**: 8'*S*,7"*R*

*N*,*N*-diisopropylamine, 1.1 equivalents of *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyl-uronium tetrafluoroborate (TBTU), and 1.3 equivalents of racemic $\alpha$-methylbenzylamine for 25.5 hours.[258] The $^1$H NMR spectrum (acetone-$d_6$) of the crude product exhibited no starting material, and the isomeric amides, (8'*S*,7"*S*)/(8'*R*,7"*R*)-diastereomer **302** and (8'*S*,7"*R*)/(8'*R*,7"*S*)-diastereomer **303**, were easily distinguishable. The best separation of diastereomeric signals was observed for an aromatic doublet at 6.71 ppm ($J$ = 8.0, (*S*,*R*)/(*R*,*S*)-isomer) and an aromatic doublet at 6.72 ppm ($J$ = 8.0, (*S*,*S*)/(*R*,*R*)-isomer). Integration of these signals indicated that the formation of the (*S*,*S*)/(*R*,*R*)-isomer was slightly favoured by a ratio of 1.3:1.0. The amidation reaction was repeated using optically pure (*R*)-(+)-$\alpha$-methylbenzylamine instead of the racemate. The $^1$H NMR spectrum of the crude amide in deuterated acetone exhibited only very minor peaks that could possibly be attributed to the (*R*,*R*)-diastereomer (**304**). A ratio of 9:1 was obtained from integration of the (*S*,*R*)-isomer (**305**) doublet at 6.71 ppm and signals that could possibly be attributed to a (*R*,*R*)-isomer doublet at 6.72 ppm respectively. Thus, the rosmarinic acid sample was at least 90% *S*. The discrepancy between the specific rotation

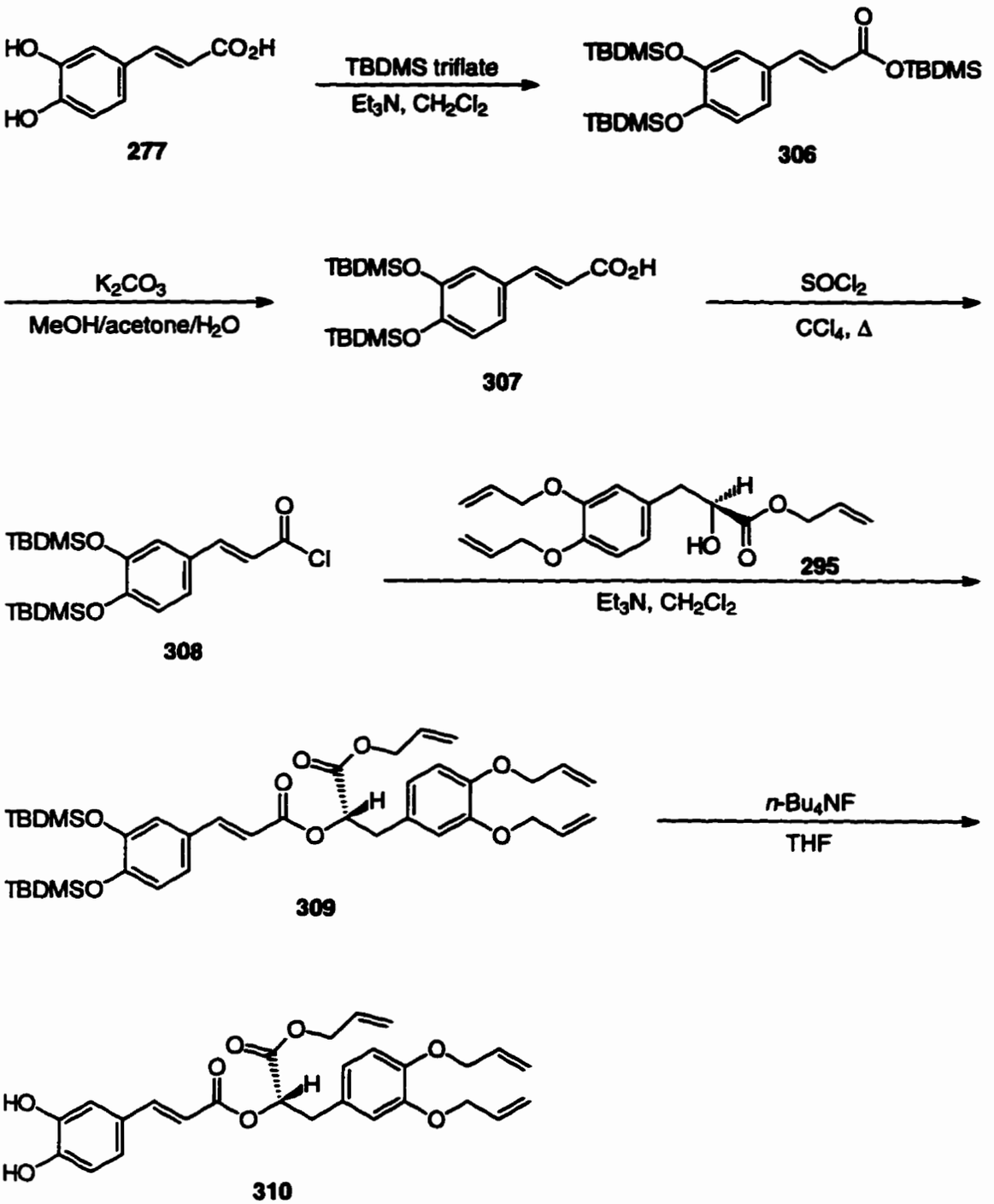
of the synthetic material and that reported in the literature for natural rosmarinic acid remains unexplained.

The synthesis of rosmarinic acid that has been described has advantages over the previously reported synthesis using an enzymatic procedure.[217] In the enzymatic process, rosmarinic acid synthase (RAS) not only catalyzes the formation of rosmarinic acid but also catalyzes its hydrolysis (see Scheme 2.28), thereby diminishing its yield. Furthermore, the non-enzymatic synthesis is applicable to both the (*R*)- and (*S*)-forms of rosmarinic acid.

Efforts to convert (*S*)-rosmarinic acid (**290**) to (+)-rabdosiin and its (-)-(1*R*,2*S*)-isomer with ferric chloride failed as no aryltetralin lignans could be observed in the $^1$H NMR spectrum of the crude product. To verify that methyl caffeate (**126**) can be oxidatively dimerized as efficiently as reported,[111] methyl caffeate, prepared by methylation of caffeic acid (**277**), was treated with ferric chloride in aqueous acetone for 18 hours. The $^1$H NMR spectrum (acetone-$d_6$) of the crude product showed by integration that the desired aryltetralin product **133** (doublet at 4.44 ppm, $J$ = 2.4)[111] was present in a ratio of 1.3:1.0 relative to the starting material (doublet at 6.27 ppm, $J$ = 15.9). This ratio was in agreement with the reported 55% yield of **133**.[111] In view of the successful preliminary work with mandelyl sinapate, it was not likely that the failure to dimerize **290** was a consequence of the size of the aryllactyl ester group. In contrast, it was believed that the poor reactivity was due to the coordination of the phenolic hydroxyl groups on C-3' and C-4' with the oxidant.

To overcome this problem, (*S*)-rosmarinic acid was prepared with only the two phenolic hydroxyl groups on C-3 and C-4 unprotected as shown in Scheme 2.38. Caffeic

**Scheme 2.38**

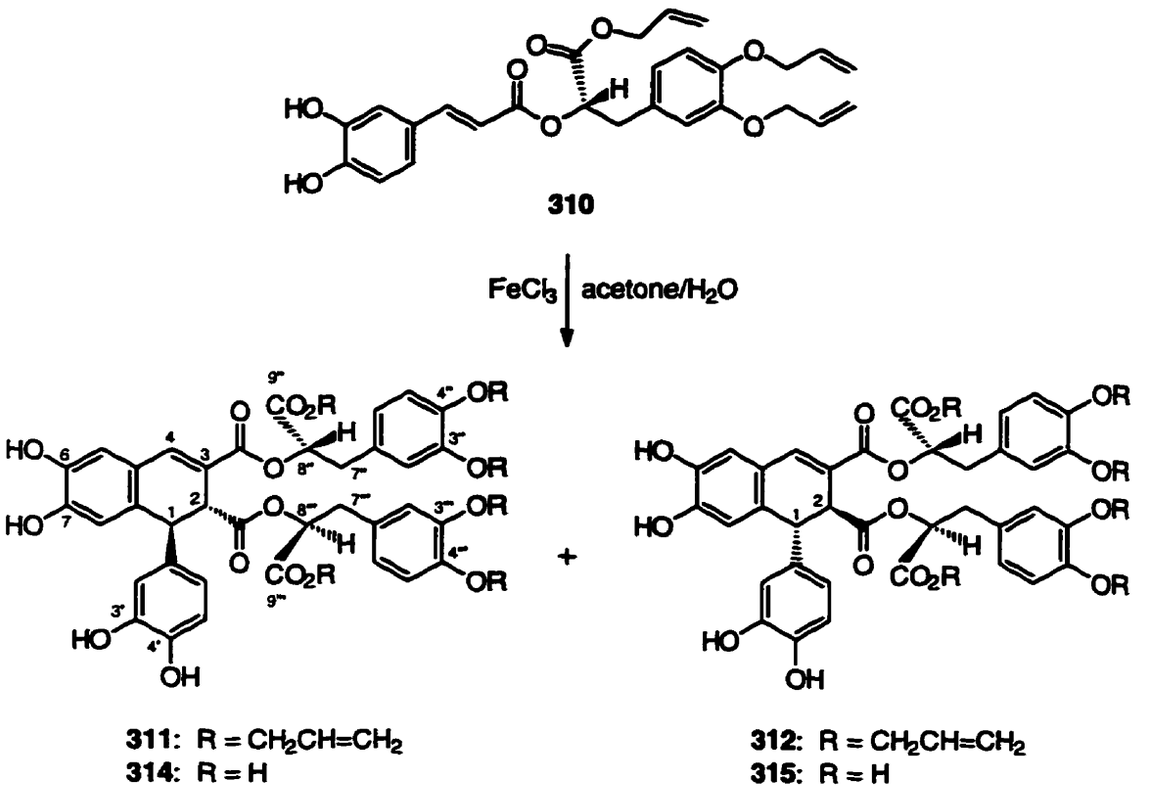



acid (**277**) was fully silylated to **306** using 4.5 equivalents of TBDMS triflate and 6.6 equivalents of triethylamine.[207] This compound was not completely characterized because

on standing, it was slowly hydrolyzed to acid **307**. Since **307** was a desired intermediate, the hydrolysis was enhanced by treating ester **306** with potassium carbonate in aqueous methanol/acetone to give the disilyl ether of caffeic acid in 76% yield from **277**. Acid **307** was coupled with alcohol **295** via an acid chloride intermediate (**308**) resulting in the formation of fully protected (*S*)-rosmarinic acid **309** in 97% yield. Selective removal of the two *t*-butyldimethylsilyl protecting groups was achieved with 2 equivalents of fluoride ion (1.0 M tetra-*n*-butylammonium fluoride in THF)[200] to afford triallyl (*S*)-rosmarinate **310** in 51% yield after chromatography.

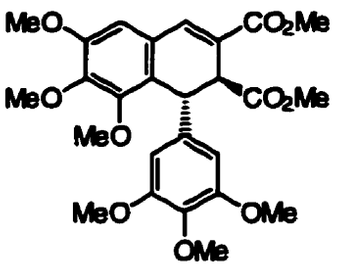
Protected (*S*)-rosmarinic acid **310** was treated with ferric chloride in aqueous acetone for 23 hours on a small scale, and the $^1$H NMR spectrum of the crude product showed the presence of aryltetralins along with a significant amount of starting material. The crude product was chromatographed on a preparative HPLC reverse-phase column, and two aryltetralin lignans were isolated. A comparison of the $^1$H NMR spectra of both lignans with those reported[110-113] for (-)-rabdosiin (**70**) and its (1*S*,2*R*)-isomer (**75**) led to the conclusion that these compounds were the allylated enantiomers of these natural lignans. The minor diastereomer was tentatively assigned structure **311** (see Scheme 2.39) based on the higher chemical shift of its H-1 signal (*ca.* 4.54 ppm) relative to that of the major diastereomer (4.31 ppm). Consequently, the major diastereomer was assigned structure **312**. Diastereomers **311** and **312** were obtained in a ratio of 1.0:1.6 as shown by integration of their H-2 doublets at 3.94 ppm and 3.97 ppm respectively in the crude product. HPLC analysis also gave the same product ratio. The low isolated yields of **311** (5.5%) and **312** (6.4%) may have been the result of steric hindrance from the allyl groups.

**Scheme 2.39**




Although **311** and **312** could not be deprotected effectively with tris(triphenylphosphine)rhodium(I) chloride,[246,247] an efficient procedure was found based on the work that Guibe *et al.*[259-261] and Keinan and Gleize[262] have done involving palladium catalysts and tributyltin hydride. Triallyl (*S*)-rosmarinate **310** was used as a model to find the conditions needed to completely remove the allyl groups. These conditions were then tested on the dimethyl ether of dimethyl thomasidioate (**313**) (see Figure 2.10), prepared by methylation of dimethyl thomasidioate (**105**), since it was known that $\alpha,\beta$-unsaturated carbonyl compounds can be reduced at the double bond under the reaction conditions cited.[260,262] No reduction of the double bond was observed for either **310** or **313**. Thus, the compounds to be deprotected, **311** and **312**, were

**Figure 2.10**



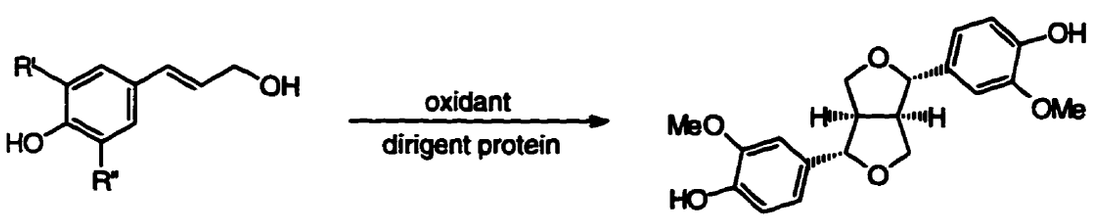

**313**

separately stirred with 0.4 equivalents of bis(triphenylphosphine)palladium dichloride,[263] and 20 equivalents of acetic acid in acetone at room temperature while 30 equivalents of tributyltin hydride was added portionwise (6 equivalents) over 40 minutes. The crude products were isolated by extraction with aqueous base, giving (+)-rabdosiin (**314**) from **311** and the (-)-(1*R*,2*S*)-isomer of (+)-rabdosiin (**315**) from **312**. The identities of the crude products were confirmed from the directions of their optical rotations and their $^1$H NMR data as compared with those of their enantiomers in the literature.[110-113]

The observation that the (1*R*,2*S*)-isomer **315** was produced selectively over (+)-rabdosiin (**314**) was unexpected. Extraction of their enantiomers from natural sources has always led to greater yields of the (1*R*,2*S*)-isomer, (-)-rabdosiin (**70**).[112,113] This implies that the production of the natural isomers may be diastereoselectively controlled, not only by the chiral aryllactyl groups, but also by the oxidizing system as well. It could also mean that the natural isomers are not formed by the oxidative coupling of two rosmarinic acid molecules. Perhaps the basic aryltetralin structure is first established by the non-asymmetric dimerization of caffeic acid (**277**), and the aryllactyl moieties are subsequently added selectively to the (1*R*,2*S*)-enantiomer. This possibility is not as likely as the former in consideration of the recent work by Davin *et al.*[264] These authors were

the first to discover a natural protein that, in the presence of an oxidant, effects asymmetric bimolecular phenoxy radical coupling. This 78 kD protein was isolated from *Forsythia suspensa*, a plant that produces the lignan (+)-pinoresinol (**122**). Racemic pinoresinol has been synthesized by the oxidative dimerization of coniferyl alcohol (**119**).[133,264] When the dimerization of **119** was carried out in the presence of the 78 kD protein, (+)-pinoresinol (**122**) was obtained in over 99% enantiomeric excess (see Scheme 2.40).[264] The activity of the protein was substrate specific since no enantioselectivity was

**Scheme 2.40**




**119**: R' = OMe, R" = H

**316**: R',R" = H
**317**: R',R" = OMe

**122**

shown for the coupling of either coumaryl alcohol (**316**) or sinapyl alcohol (**317**). The protein itself lacks a catalytically active oxidative center and had to be used in conjunction with a non-specific oxidase or non-enzymatic one electron oxidant. This new class of protein was described as dirigent based on the Latin word "dirigere", meaning to align or guide. Although rosmarinic acid is a chiral compound, unlike **119**, a dirigent protein may also be involved in the biosynthesis of (-)-rabdosiin.

# Chapter 3

# Conclusion

The three research objectives presented at the beginning of the thesis were all undertaken, and the results obtained were satisfactory.

An asymmetric synthesis of (-)-deoxypodophyllotoxin was accomplished using piperonal and 3,4,5-trimethoxybenzaldehyde as the starting materials. The key step in the synthesis was the diastereoselective Diels-Alder reaction between the fumarate of methyl (*S*)-mandelate and $\alpha$-aryl-$\alpha$-hydroxy-*o*-quinodimethane **182**. The reaction proceeded through an *endo* transition state to give, in 58% isolated yield, an aryltetralin cycloadduct (**183**) having the same absolute configurations at C-2 and C-3 as those found in (-)-deoxypodophyllotoxin.

Elaboration of cycloadduct **183** to the final product involved the inversion of the C-1 chiral center. For this purpose, a highly stereoselective method for reducing the C-1 hydroxyl group was developed by using a combination of boron trifluoride etherate and lithium aluminum hydride at low temperature. This unprecedented reduction procedure was found to be specific for well-stabilized diaryl cations, intermediates in the procedure, and the method has since been used successfully by others.[186] Enantiomerically pure (-)-deoxypodophyllotoxin was obtained in 6% overall yield from piperonal.

The synthesis proved that the previously reported[166] Diels-Alder reaction of $\alpha$-hydroxy-$\alpha$-phenyl-*o*-QDM with a chiral dienophile can be extended to $\alpha$-aryl-$\alpha$-hydroxy-*o*-QDMs containing substitution on the aryl rings and that these *o*-QDMs are

useful intermediates for the synthesis of natural aryltetralin lignans having the 1,2-*cis*-2,3-*trans* stereochemistry. This is the second asymmetric synthesis of (-)-deoxypodophyllotoxin that has been reported. Morimoto *et al.*[158-160] did not describe the yields for all of the steps that were used in their asymmetric strategy, but it appears that the overall yields for the two asymmetric syntheses are comparable.

The Diels-Alder approach for synthesizing aryltetralin lignans was investigated by studying the additions of unsymmetrical chiral dienophiles to *o*-quinodimethanes. 4-Bromo and 4-acetoxy derivatives of (methyl (*S*)-lactyl) crotonate were prepared, but they were unreactive with $\alpha$-aryl-$\alpha$-hydroxy-*o*-QDMs. However, both dienophiles did undergo highly stereoselective cycloadditions with $\alpha$-hydroxy-*o*-QDM. In each case, a single cycloadduct, resulting from an *exo* transition state, was obtained in high yield (76-89%). The reactivity of the chiral crotonates seems to be superior to that of structurally analogous dienophiles such as the fumarate and acrylate of methyl (*S*)-lactate. The reactions of the lactyl fumarate and lactyl acrylate with $\alpha$-hydroxy-*o*-QDM, also generated thermally from 1-benzocyclobutenol, reportedly gave cycloadducts in only 55% and 73% yields respectively.[164] Another synthetically important advantage that chiral crotonates provide is that they establish functional groups at the C-2 and C-3 centers in the resulting adducts that can be easily differentiated in later functional group transformations.

The Diels-Alder approach for synthesizing aryltetralin lignans was also investigated by attempting to prepare and react $\alpha$-aryl-$\alpha,\alpha'$-dioxy-*o*-QDMs with a chiral dienophile. This investigation was not successful as no cycloaddition was observed, and there was no evidence that the benzocyclobutene precursors to these *o*-QDMs were formed. However,

two interesting discoveries were made that may have other useful applications. It was found that ketone **197** could be selectively lithiated at the position *ortho* to the iodo group, and that **197** could also be efficiently oxidized to the $\alpha$-hydroxy ketone **262**.

As a prelude to the preparation of (+)-rabdosiin and its (1*R*,2*S*)-isomer, two model studies were conducted. The first study determined that one of the optimum methods for oxidatively dimerizing methyl sinapate to dimethyl thomasidioate was to use ferric chloride in aqueous acetone. The same oxidizing conditions were then used in a second study to couple/cyclize (methyl (*R*)-mandelyl) sinapate, synthesized in 76% overall yield, to give three isomeric aryltetralin lignans. The two predominant isomers had the 1,2-*trans* thomasidioate structure and were produced in a 2:1 ratio. The major diastereomer was isolated in 40% overall yield from sinapic acid. The 1,2-*cis* geometry of the third isomer (minor) has not been previously reported for the coupling of propenylphenols This study proved that a bulky chiral ester group does not hinder the efficient dimerization of a sinapate ester and that it induces diastereoselectivity.

The synthesis of (+)-rabdosiin and its (1*R*,2*S*)-diastereomer was achieved by oxidatively coupling/cyclizing allyl 3',4'-di-*O*-allyl-(*S*)-rosmarinate and subsequently removing the allyl groups. (*S*)-Rosmarinic acid (9% overall yield) and its triallyl derivative (15% overall yield) were both synthesized from (*S*)-tyrosine and caffeic acid. While (*S*)-rosmarinic acid could not be dimerized to the desired aryltetralin lignans using ferric chloride, its protected form was converted to the corresponding hexaallyl intermediates **311** and **312** in a 1.0:1.6 ratio (11.9% combined yield). Deallylation to the final products was easily effected, but the low yields of the coupling products indicates that this is not an efficient synthetic route to these lignans. However, considering that rosmarinic acid

probably undergoes free radical self-coupling in nature, the dimerization of rosmarinic acid and its triallyl derivative can likely be made more successful by using more suitable oxidizing conditions. Interestingly, the observed ratio for the formation of adducts **311** and **312** is not consistent with the isolated yields of (-)-rabdosiin and its (1*S*,2*R*)-isomer from natural sources. Thus, further studies are required in order to better understand how these lignans are biosynthesized and what factors control the predominant formation of one isomer over the other. This work represents the first reported non-enzymatic synthesis of enantiomerically pure rosmarinic acid. As well, this is the first synthesis of enantiomerically pure rabdosiin, or any of its stereoisomers, that has been reported.

# Experimental

$^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded on a Bruker AM-300 spectrometer with tetramethylsilane as the internal standard. Signal assignments for $^{13}C$ NMR spectra were based on DEPT experiments. A Perkin-Elmer 881 spectrometer was used to record IR spectra. Exact mass/mass spectra were recorded on a VG Analytical 7070E-HF instrument. Optical rotations were obtained on a Rudolf Research Autopol III instrument. Melting points were measured on a hot stage. A Fisher Accumet® pH meter model 600 fitted with a Baxter combination pH/sealed reference electrode was used to measure pH values. HPLC separations and analyses were performed using a Varian 9010 solvent delivery system, a Varian 9050 variable wavelength UV-VIS detector, and a 5 μm CSC-S ODS2 (25 × 0.46 cm) reverse-phase column.

THF was always freshly distilled from sodium and benzophenone under a nitrogen atmosphere prior to use. All solutions/suspensions were stirred using a magnetic stirring apparatus unless otherwise noted. Reactions conducted at temperatures below 0 °C were performed by immersing the reaction vessel in an external dry-ice/acetone bath unless otherwise noted. Aldrich silica gel (230-400 mesh, 60 Å) was used for all chromatography.

*6-Bromopiperonal* (**187**)

6-Bromopiperonal was synthesized by a modification of the literature procedure.[170] To a solution of piperonal (**156**) (10.23 g, 68.14 mmol) in acetic acid (63 mL) was added

$Br_2$ (10 mL, 190 mmol), and the solution was stirred at rt for 17 h. Ice-cold $H_2O$ (100 mL) was added, and the resultant precipitate was collected by filtration, washed with sat. $NaHSO_3$(aq) (*ca.* 10 mL), and dissolved in EtOAc (200 mL). The organic layer was washed successively with sat. $NaHCO_3$(aq) (2 × 40 mL) and $H_2O$ (50 mL), dried ($MgSO_4$), and evaporated to give a colourless crystalline solid (15.32 g, 98%): $^1$H NMR ($CDCl_3$) $\delta$: 6.08 (s, 2H, $CH_2$), 7.07 (s, 1H, aromatic), 7.37 (s, 1H, aromatic), 10.19 (s, 1H, CHO). The $^1$H NMR spectrum was consistent with that previously reported.[265]

*6-Iodopiperonal* (**186**)

To a solution of 6-bromopiperonal (**187**) (7.34 g, 32.0 mmol) in benzene (250 mL) was added ethylene glycol (3.80 mL, 68.1 mmol) and a catalytic amount of *p*-TsOH·$H_2O$ (5 mg, 0.03 mmol), and the mixture was heated at reflux for 15 h using a Dean-Stark trap to remove water. The solution was concentrated *in vacuo* and filtered through silica gel (40% EtOAc/hexanes) to remove excess ethylene glycol. Evaporation of the solvent gave colourless crystals, presumed to be acetal **188**, that were subsequently dissolved in dry THF (100 mL). The stirred colourless THF solution was cooled to -78 °C under a nitrogen atmosphere, and *n*-BuLi (2.0 M in hexanes, 19 mL, 40 mmol) was added, giving a yellow solution, immediately followed by a solution of iodine (9.80 g, 38.6 mmol) in THF (30 mL). The solution was warmed to rt, acidified with sat. $NH_4Cl$(aq) (30 mL), and $NaHSO_3$(s) was added until the solution (red) was decolourized. The mixture was extracted with EtOAc (1 × 100 mL, 3 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated to give a yellow residue presumed to be acetal **189**. To a solution of the crude acetal in 15% MeOH/benzene (70 mL) was added 20% HCl(aq) (50

mL), and the mixture was stirred at rt for 16 h. The aqueous layer was removed and extracted with EtOAc (3 × 25 mL). The combined organic portions were concentrated *in vacuo*, filtered through silica gel (40% EtOAc/hexanes), and evaporated to give a light yellow solid (7.34 g, 83%). Some of the crude product was recrystallized from 40% AcOH/$H_2O$ to give a pure sample of colourless crystals: mp: 102-104 °C (lit.[171] mp: 108.5-110.5 °C, from MeOH); IR ($CH_2Cl_2$): 1684 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 6.08 (s, 2H, $CH_2$), 7.34 (s, 1H, aromatic), 7.37 (s, 1H, aromatic), 9.89 (s, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) $\delta$: 93.2 (C), 102.6 ($CH_2$), 108.9 (CH), 119.4 (CH), 129.6 (C), 149.1 (C), 153.5 (C), 194.3 (CH); mass spectrum *m/z* (relative intensity): 276 ($M^+$, 100), 247 (10), 148 (15), 120 (22); HRMS calcd for $C_8H_5O_3I$: 275.9283; found: 275.9290. The $^1H$ NMR spectrum was consistent with that previously reported.[171]

*6-Iodopiperonyl Alcohol* (**191**)

To a solution of 6-iodopiperonal (**186**) (5.63 g, 20.4 mmol) in *i*-PrOH (60 mL) was added $NaBH_4$ (753 mg, 19.9 mmol), and the mixture was heated at reflux for 16 h. The mixture was cooled to rt, acidified with 10% HCl(aq) (10 mL), diluted with $H_2O$ (20 mL), and extracted with EtOAc (1 × 60 mL, 3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a yellow solid (5.49 g, 97%). A portion of the crude alcohol was recrystallized from AcOH to give a pure sample of colourless crystals: mp: 107-108 °C (lit.[172] mp: 110-111 °C, from $CHCl_3$; lit.[266] mp: 106-107 °C, from benzene); IR ($CH_2Cl_2$): 3605 (OH) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.92 (s, 1H, OH), 4.58 (s, 2H, $CH_2$), 5.97 (s, 2H, $CH_2$), 6.98 (s, 1H, aromatic), 7.23 (s, 1H, aromatic); $^{13}C$ ($CDCl_3$) $\delta$: 69.2 ($CH_2$), 85.3 (C), 101.7 ($CH_2$), 109.0 (CH), 118.5 (CH), 136.2 (C), 147.9

(C), 148.6 (C); mass spectrum *m/z* (relative intensity): 278 ($M^+$, 100), 261 (13), 149 (17), 122 (14); HRMS calcd for $C_8H_7O_3I$: 277.9440; found: 277.9450. The $^1H$ NMR spectrum was consistent with that previously reported.[266]

*6-Iodopiperonyl Chloride* (**190**)

A solution of 6-iodopiperonyl alcohol (**191**) (3.98 g, 14.3 mmol) in 1:1 AcOH/$CH_2Cl_2$ (50 mL) was saturated with HCl(g) and stirred at rt for 5 h. The solution was diluted with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$(aq) (2 × 20 mL) and $H_2O$ (40 mL), dried ($MgSO_4$), and evaporated to give a light brown solid (3.67 g, 87%). Some of the crude product was recrystallized from *i*-PrOH to afford a pure sample of colourless crystals: mp: 59-60 °C (lit.[172] mp: 65-66 °C, from ether/hexane); $^1H$ NMR ($CDCl_3$) $\delta$: 4.61 (s, 2H, $CH_2$), 5.98 (s, 2H, $CH_2$), 6.96 (s, 1H, aromatic), 7.24 (s, 1H, aromatic); $^{13}C$ ($CDCl_3$) $\delta$: 51.4 ($CH_2$), 88.1 (C), 101.9 ($CH_2$), 110.0 (CH), 118.8 (CH), 133.1 (C), 148.6 (2 × C); mass spectrum *m/z* (relative intensity): 296 ($M^+$, 41), 261 (100), 134 (16), 127 (9); HRMS calcd for $C_8H_6O_2I^{35}Cl$: 295.9101; found: 295.9110. The $^1H$ NMR spectrum was consistent with that previously reported.[172]

*1-(3,4,5-Trimethoxyphenyl)-1-N-morpholinoacetonitrile* (**192**)

Water (5 mL) was cooled to 0 °C and stirred while KCN (1.83 g, 28.1 mmol), morpholine (2.35 mL, 26.8 mmol), and conc. HCl (2.34 mL) were added sequentially. The solution was warmed to rt and added to a stirred solution of 3,4,5-trimethoxybenzaldehyde (**164**) (5.02 g, 25.6 mmol) in MeOH (52 mL). The mixture was

stirred for 5 days (116 h), and the resulting colourless precipitate was collected by filtration. Dichloromethane (100 mL) was added to the precipitate, and the mixture was manually stirred, dissolving most of the precipitate. The solution was dried ($MgSO_4$), the insoluble portion of the precipitate and the drying agent were removed by filtration, and the solvent was evaporated to give a colourless solid (6.84 g, 92%): mp: 136-138 °C; IR ($CH_2Cl_2$): 2231 (CN) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.59 (m, 4H, $CH_2$), 3.75 (m, 4H, $CH_2$), 3.86 (s, 3H, $CH_3$), 3.89 (s, 6H, $CH_3$), 4.75 (s, 1H, CH), 6.77 (s, 2H, aromatic); $^{13}C$ ($CDCl_3$) $\delta$: 50.0 (2 × $CH_2$), 56.3 (2 × $CH_3$), 60.8 ($CH_3$), 62.5 (CH), 66.7 (2 × $CH_2$), 105.0 (2 × CH), 115.2 (C), 127.9 (C), 138.4 (C), 153.5 (2 × C); mass spectrum *m/z* (relative intensity): 292 ($M^+$, 7), 265 (4), 206 (100), 181 (25), 176 (10), 149 (27); HRMS calcd for $C_{15}H_{20}O_4N_2$: 292.1423; found: 292.1433.

*Alkylation Product* **193**

Lithium diisopropylamide was freshly prepared by adding HMPA (0.10 mL, 0.57 mmol) to a solution of diisopropylamine (0.11 mL, 0.78 mmol) in THF (1 mL) under a nitrogen atmosphere, cooling the solution to -78 °C, adding *n*-BuLi (2.1 M in hexanes, 0.30 mL, 0.63 mmol), and stirring the solution for 5 min. $\alpha$-Amino nitrile **192** (149 mg, 0.510 mmol) in THF (2 mL) was added to the LDA, the mixture was stirred for 2 min, and benzylic chloride **190** (154 mg, 0.519 mmol) in THF (0.8 mL) was added. The mixture was stirred for 1 h, warmed to rt, stirred for 15 h, diluted with $H_2O$ (6 mL), and extracted with $CH_2Cl_2$ (3 × 3.5 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel (30% EtOAc/hexanes) to give colourless crystals (142 mg, 50%): mp: 153-155 °C; $^1H$ NMR ($CDCl_3$) $\delta$: 2.65 (m,

2H, $CH_2$), 2.83 (m, 2H, $CH_2$), 3.14 (d, 1H, $J$ = 13.6, $CH_2$), 3.73 (d, 1H, $J$ = 13.6, $CH_2$), 3.77 (s, 6H, $CH_3$), 3.79 (m, 4H, $CH_2$), 3.83 (s, 3H, $CH_3$), 5.89 (d, 1H, $J$ = 1.2, $CH_2$), 5.90 (d, 1H, $J$ = 1.0, $CH_2$), 6.38 (s, 1H, aromatic), 6.62 (s, 2H, aromatic), 7.12 (s, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 47.5 ($CH_2$), 48.9 (2 × $CH_2$), 56.3 (2 × $CH_3$), 60.9 ($CH_3$), 66.9 (2 × $CH_2$), 71.5 (C), 91.2 (C), 101.7 ($CH_2$), 105.1 (2 × CH), 110.3 (CH), 116.8 (C), 118.8 (CH), 130.1 (C), 131.2 (C), 138.4 (C), 147.5 (C), 147.9 (C), 153.0 (2 × C); mass spectrum *m/z* (relative intensity): 525 ([M - HCN]$^+$, 100), 510 (9), 398 (45), 367 (16), 312 (9), 282 (9), 261 (21), 195 (13), 181 (8); HRMS calcd for $C_{22}H_{24}NO_6I$ ([M - HCN]$^+$): 525.0648; found: 525.0628.

*N-(3,4,5-Trimethoxybenzoyl)morpholine* (**194**)

A solution of $\alpha$-amino nitrile **192** (149 mg, 0.510 mmol) in THF (7 mL) was treated with NaH (57% dispersion in mineral oil, 127 mg, 3.02 mmol) at rt under a nitrogen atmosphere and stirred for 15 min. The suspension was treated with a solution of benzylic chloride **190** (155 mg, 0.523 mmol) in THF (2 mL) and stirred for an additional 15 h. The mixture was diluted with $H_2O$ (6 mL) and extracted with $CH_2Cl_2$ (3 × 6 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel (12-60% EtOAc/hexanes followed by 5% *i*-PrOH/EtOAc) to give colourless crystals (102 mg, 71%): mp: 118-120 °C; IR ($CH_2Cl_2$): 1634 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.70 (br s, 8H, $CH_2$), 3.86 (s, 3H, $CH_3$), 3.87 (s, 6H, $CH_3$), 6.63 (s, 2H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 56.3 (2 × $CH_3$), 60.9 ($CH_3$), 66.9 (4 × $CH_2$), 104.4 (2 × CH), 130.6 (C), 139.4 (C), 153.3 (2 × C), 170.1 (C); mass spectrum *m/z*

(relative intensity): 281 ($M^+$, 31), 266 (5), 195 (100), 167 (12); HRMS calcd for $C_{14}H_{19}NO_5$: 281.1263; found: 281.1269.

Compound **193** was also isolated (52 mg, 18%).

*Benzyl Aryl Ketone* **197**

A solution of benzylic chloride **190** (3.6 g, 12 mmol) and $\alpha$-amino nitrile **192** (3.96 g, 13.5 mmol) in dry DMF (50 mL) was stirred at rt under a nitrogen atmosphere while NaH (57% dispersion in mineral oil, 4.0 g, 95 mmol) was added. The mixture was warmed to 70 °C, stirred for 1 h, and cooled to rt. Water (10 mL) and 10% aqueous HCl (40 mL) were added to the solution, and the solution was stirred at 61 °C for 16 h. The solution was cooled to rt, saturated with NaCl, and extracted with $CH_2Cl_2$ (4 × 25 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the brown residue was recrystallized from AcOH to afford light yellow crystals (3.7 g, 67%): mp: 176-178 °C; IR ($CH_2Cl_2$): 1684 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.92 (s, 9H, $CH_3$), 4.33 (s, 2H, $CH_2$), 5.96 (s, 2H, $CH_2$), 6.75 (s, 1H, aromatic), 7.27 (s, 2H, aromatic), 7.29 (s, 1H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 50.2 ($CH_2$), 56.4 (2 × $CH_3$), 60.9 ($CH_3$), 88.9 (C), 101.7 ($CH_2$), 106.0 (2 × CH), 110.2 (CH), 118.6 (CH), 131.6 (2 × C), 142.7 (C), 147.6 (C), 148.6 (C), 153.1 (2 × C), 195.5 (C); mass spectrum *m/z* (relative intensity): 456 ($M^+$, 1), 329 (17), 278 (52), 261 (10), 230 (9), 195 (95), 181 (43); HRMS calcd for $C_{18}H_{17}O_6I$: 456.0070; found: 456.0027.

*1-Hydroxy-1-(3',4',5'-trimethoxyphenyl)-6,7-(methylenedioxy)benzocyclobutene* (**185**)

A solution of ketone **197** (1.21 g, 2.65 mmol) in dry THF (36 mL) was placed under a nitrogen atmosphere, cooled in a liquid $N_2$/hexanes bath (-80 °C), and treated with *n*-BuLi (2.0 M in hexanes, 3.3 mL, 6.6 mmol). The solution was stirred for 2 min and then acidified with sat. $NH_4Cl$(aq) (3 mL). The mixture was warmed to rt, diluted with $H_2O$ (25 mL), and saturated with NaCl. The THF layer was collected, and the aqueous layer was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting yellow crystalline solid was chromatographed on silica gel (20% EtOAc/hexanes) to give colourless crystals (622 mg, 71%): mp: 141-143 °C (lit.[169] mp: 142-144 °C); IR ($CH_2Cl_2$): 3587 (OH) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.75 (s, 1H, OH), 3.36 (d, 1H, $J$ = 13.6, $CH_2$), 3.43 (d, 1H, $J$ = 13.5, $CH_2$), 3.82 (s, 9H, $CH_3$), 5.92 (d, 1H, $J$ = 1.3, $CH_2$), 5.93 (d, 1H, $J$ = 1.3, $CH_2$), 6.67 (s, 2H, aromatic), 6.73 (s, 1H, aromatic), 6.76 (s, 1H, aromatic); $^{13}C$ ($CDCl_3$) $\delta$: 48.7 ($CH_2$), 56.1 (2 × $CH_3$), 60.8 ($CH_3$), 79.9 (C), 100.4 ($CH_2$), 102.9 (2 × CH), 103.1 (CH), 105.9 (CH), 134.8 (C), 137.3 (C), 139.4 (C), 140.8 (C), 147.4 (C), 148.9 (C), 153.0 (2 × C); mass spectrum *m/z* (relative intensity): 330 ($M^+$, 48), 313 (15), 299 (72), 283 (26), 268 (15), 255 (10), 195 (100); HRMS calcd for $C_{18}H_{18}O_6$: 330.1103; found: 330.1135.

*Methyl (S)-Mandelate* (**199**)

Methyl (*S*)-mandelate was synthesized according to the literature procedure.[267] A solution of (*S*)-mandelic acid (18.01 g, 118.4 mmol) and $H_2SO_4$ (1.0 mL, 19 mmol) in MeOH (30 mL) was heated at reflux for 69 h. The solution was concentrated *in vacuo* and then diluted with EtOAc (90 mL). The solution was washed with sat. $NaHCO_3$(aq) (3

× 20 mL) followed by $H_2O$ (30 mL). The combined aqueous layers were extracted with EtOAc (20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a colourless crystalline solid (16.84 g, 86%): $^1$H NMR ($CDCl_3$) $\delta$: 3.76 (s, 3H, $CH_3$), 5.18 (s, 1H, CH), 7.37 (m, 5H, aromatic). The spectrum was identical to that previously reported.[267]

*Bis(methyl (S)-mandelyl) Fumarate* (**176**)

Bis(methyl (*S*)-mandelyl) fumarate was synthesized according to the literature procedure.[267] Methyl (*S*)-mandelate (**199**) (16.84 g, 101.3 mmol) and fumaryl chloride (5.60 mL, 51.8 mmol) were heated at reflux under a drying tube ($CaCl_2$) for 23 h. The crude product was allowed to cool to rt and was dissolved in EtOAc (90 mL). The solution was washed successively with sat. $NaHCO_3$(aq) (3 × 20 mL) and $H_2O$ (30 mL), and the combined aqueous phases were extracted with EtOAc (20 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel (15% EtOAc/hexanes) to give a colourless crystalline solid (15.61 g, 64% from (*S*)-mandelic acid): $^1$H NMR ($CDCl_3$) $\delta$: 3.74 (s, 6H, $CH_3$), 6.04 (s, 2H, CH), 7.06 (s, 2H, CH), 7.43 (m, 10H, aromatic). The spectrum was identical to that previously reported.[267]

*Cycloadduct* **183**

A solution of fumarate **176** (1.42 g, 3.44 mmol) in toluene (6 mL) was warmed to *ca.* 50 °C. A solution of benzocyclobutenol **185** (567 mg, 1.72 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise to the stirred toluene solution, the methylene chloride was allowed to boil off, and the solution was heated at reflux for 44 h. The solution was slightly cooled,

the solvent was evaporated, and the crude product was chromatographed on silica gel (20-30% EtOAc/hexanes) to give a colourless solid (743 mg, 58%): mp: 186-188 °C; $[\alpha]_D^{25}$: +132° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): 3417 (OH), 1743 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.14 (dd, 1H, $J$ = 16.3, 11.9, H-4a), 3.41 (dd, 1H, $J$ = 16.4, 4.5, H-4b), 3.62 (s, 3H, $CH_3$), 3.71 (m, 1H, H-3), 3.72 (s, 3H, $CH_3$), 3.80 (d, 1H, $J$ = 11.5, H-2), 3.80 (s, 6H, $CH_3$), 3.90 (s, 3H, $CH_3$), 3.96 (s, 1H, OH), 5.73 (s, 1H, CH), 5.88 (d, 1H, $J$ = 1.3, $CH_2$), 5.89 (d, 1H, $J$ = 1.3, $CH_2$), 5.89 (s, 1H, CH), 6.46 (s, 1H, aromatic), 6.63 (s, 1H, aromatic), 6.73 (s, 2H, aromatic), 6.93 (m, 2H, aromatic), 7.24 (m, 3H, aromatic), 7.38 (m, 3H, aromatic), 7.45 (m, 2H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 32.7 ($CH_2$), 39.7 (CH), 52.6 ($CH_3$), 52.8 ($CH_3$), 54.7 (CH), 56.2 (2 × $CH_3$), 60.9 ($CH_3$), 74.8 (CH), 75.0 (CH), 76.4 (C), 101.1 ($CH_2$), 104.0 (2 × CH), 107.4 (CH), 109.3 (CH), 126.9 (C), 127.0 (2 × CH), 127.6 (2 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.1 (CH), 129.3 (CH), 132.7 (C), 133.2 (C), 133.5 (C), 137.0 (C), 142.0 (C), 146.7 (C), 147.3 (C), 152.9 (2 × C), 169.2 (C), 169.6 (C), 171.6 (C), 174.0 (C); mass spectrum *m/z* (relative intensity): 742 ($M^+$, 3), 530 (18), 365 (18), 339 (52), 324 (13), 308 (17), 149 (70), 121 (25), 107 (100), 91 (23), 79 (58); HRMS calcd for $C_{40}H_{38}O_{14}$: 742.2261; found: 742.2268.

*Hydrogenolysis/Decarboxylation Product* **202**

To a solution of cycloadduct **183** (105 mg, 141 mmol) in 1:1 MeOH/EtOAc (1 mL) was added 5% Pd/C (18 mg), and the mixture was stirred under an $H_2$ atmosphere at rt for 2.6 h. The catalyst was removed by filtration, washed with EtOAc, and the combined filtrates were evaporated. The $^1H$ NMR spectrum ($CDCl_3$) of the crude residue showed that *ca.* 50% of the starting material was still present. A solution of the crude

mixture in 4:1 AcOH/MeOH (2.5 mL) was stirred over 5% Pd/C (20 mg) under an $H_2$ atmosphere at rt for 19 h. The catalyst was removed by filtration, washed with EtOAc, and the combined filtrates were evaporated. EtOAc (5 mL) and sat. $NaHCO_3$(aq) (3 mL) were added to the residue, the mixture was shaken, and the EtOAc layer was removed and extracted with sat. $NaHCO_3$(aq) (4 × 2 mL). The combined aqueous layers were acidified with 10% HCl(aq) to pH 1-2 and extracted with $CH_2Cl_2$ (4 × 5 mL). The combined $CH_2Cl_2$ layers were dried ($MgSO_4$) and evaporated to give a colourless solid (27 mg, 50%): $^1$H NMR ($CDCl_3$) $\delta$: 3.00 (dd, 1H, $J$ = 15.3, 6.9, H-4a), 3.08 (dd, 1H, $J$ = 15.2, 12.3, H-4b), 3.51 (ddd, 1H, $J$ = 12.1, 7.0, 3.8, H-3), 3.85 (s, 6H, $CH_3$), 5.92 (s, 2H, $CH_2$), 6.03 (d, 1H, $J$ = 3.6, H-2), 6.54 (s, 2H, aromatic), 6.59 (s, 1H, aromatic), 6.76 (s, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 30.8 ($CH_2$), 40.5 (CH), 56.2 (2 × $CH_3$), 101.0 ($CH_2$), 105.9 (2 × CH), 107.0 (CH), 108.6 (CH), 121.3 (CH), 128.0 (C), 128.7 (C), 135.5 (C), 141.0 (C), 146.3 (C), 146.7 (C), 153.0 (2 × C), 179.4 (C); mass spectrum *m/z* (relative intensity): 384 ($M^+$, 11), 367 (6), 338 (42), 323 (29), 308 (10), 158 (23), 105 (27), 91 (95), 55 (100).

*1,2-cis-2,3-cis-Dimethyl Ester* **204** *and 1-Hydroxy-2,3-trans-dimethyl Ester* **205**

To a solution of cycloadduct **183** (21.4 mg, 0.0288 mmol) in 1:1 MeOH/AcOH (2 mL) was added 5% Pd/C (18 mg), and the mixture was stirred under an $H_2$ atmosphere at rt for 50 h. The catalyst was removed by filtration, washed with EtOAc, and the combined filtrates were evaporated. The colourless residue was dissolved in sat. $NaHCO_3$(aq) (5 mL) and washed with EtOAc (3.5 mL). The aqueous layer was acidified with 10% HCl(aq), saturated with NaCl, and extracted with $CH_2Cl_2$ (5 × 3.5 mL). The

combined $CH_2Cl_2$ portions were dried ($MgSO_4$) and evaporated to give a colourless amorphous solid (10.3 mg). A suspension of the crude solid in diethyl ether (0.5 mL) was cooled to 0 °C. A freshly prepared solution of diazomethane in diethyl ether[173] was added dropwise to the stirred suspension (dissolving the solid) until no more gas ($N_2$) was evolved and a yellow colour was persistent. The solution was stirred at rt for 10 min, the solvent was evaporated, and the residue was chromatographed on silica gel (15-20% EtOAc/hexanes) to give dimethyl esters **204** (*ca.* 2 mg) and **205** (*ca.* 3 mg) as colourless amorphous solids.

*1,2-cis-2,3-cis-dimethyl ester* **204**: IR ($CH_2Cl_2$): 1738 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.99 (dd, 1H, $J$ = 16.3, 5.4, H-4a), 3.13 (ddd, 1H, $J$ = 12.5, 5.6, 3.7, H-3), 3.36 (s, 3H, $CH_3$), 3.46 (dd, 1H, $J$ = 6.2, 3.7, H-2), 3.58 (m, 1H, H-4b), 3.72 (s, 3H, $CH_3$), 3.79 (s, 6H, $CH_3$), 3.85 (s, 3H, $CH_3$), 4.28 (d, 1H, $J$ = 6.0, H-1), 5.87 (d, 1H, $J$ = 1.4, $CH_2$), 5.89 (d, 1H, $J$ = 1.4, $CH_2$), 6.40 (s, 2H, aromatic), 6.41 (s, 1H, aromatic), 6.65 (s, 1H, aromatic); mass spectrum *m/z* (relative intensity): 458 ($M^+$, 85), 398 (26), 365 (26), 339 (62), 283 (29), 252 (19), 231 (30), 195 (20), 155 (90), 141 (27), 71 (100), 57 (40); HRMS calcd for $C_{24}H_{26}O_9$: 458.1577; found: 458.1585.

*1-hydroxy-2,3-trans-dimethyl ester* **205**: IR ($CH_2Cl_2$): 1740 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.12 (dd, 1H, $J$ = 16.8, 11.5, H-4a), 3.22 (dd, 1H, $J$ = 16.7, 5.8, H-4b), 3.35 (d, 1H, $J$ = 11.9, H-2), 3.46 (s, 3H, $CH_3$), 3.64 (ddd, 1H, $J$ = 11.7, 11.7, 5.9, H-3), 3.72 (s, 3H, $CH_3$), 3.81 (s, 6H, $CH_3$), 3.86 (s, 3H, $CH_3$), 4.31 (s, 1H, OH), 5.86 (d, 1H, $J$ = 1.3, $CH_2$), 5.89 (d, 1H, $J$ = 1.3, $CH_2$), 6.31 (s, 1H, aromatic), 6.55 (s, 2H, aromatic), 6.59 (s, 1H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 32.3 ($CH_2$), 39.8 (CH), 52.1 ($CH_3$), 52.3 ($CH_3$), 54.0 (CH), 56.2 (2 × $CH_3$), 60.9 ($CH_3$), 76.0 (C), 101.1 ($CH_2$), 103.8 (2 × CH), 107.7

(CH), 109.0 (CH), 127.4 (C), 132.7 (C), 135.1 (C), 140.5 (C), 146.4 (C), 147.6 (C), 152.7 (2 × C), 173.8 (C), 174.7 (C); mass spectrum *m/z* (relative intensity): 474 ($M^+$, 15), 456 (6), 396 (25), 381 (9), 365 (18), 328 (37), 313 (10), 299 (25), 195 (23), 149 (100), 57 (64); HRMS calcd for $C_{24}H_{26}O_{10}$: 474.1526; found: 474.1508.

*Elimination Product* **206**, *Inversion Product* **207**, *and Retention Product* **208**

A 0.37 M solution of $LiAlH_4$ in diethyl ether was prepared[173] by heating a suspension of $LiAlH_4$ (2.51 g, 66.1 mmol) in diethyl ether (100 mL) at reflux under a nitrogen atmosphere for 1 h. The solution was cooled to rt, filtered under an inert atmosphere, and titrated[173] twice as follows. A solution of iodine (1.029 g, 4.054 mmol) in benzene (20 mL) was gently shaken with the $LiAlH_4$/ether solution (2.0 mL), and the mixture was allowed to stand for 10 min. $H_2O$ (20 mL) and glacial AcOH (0.8 mL) were added to the solution, and the excess iodine was titrated with a 0.2 M aqueous thiosulfate solution (50 mL). A volume of 25.70 mL of the thiosulfate solution was required to dissipate the iodine colour.

A solution of cycloadduct **183** (155 mg, 0.209 mmol) in $CH_2Cl_2$ (41 mL) was placed under a nitrogen atmosphere and cooled to -20 °C. As $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) was added dropwise, the stirred solution turned dark purple. After the addition of $BF_3{\cdot}OEt_2$ was complete, the temperature of the solution was lowered to -55 °C, and $LiAlH_4$ (0.37 M in diethyl ether, *ca.* 2 mL) was slowly added dropwise until the solution was decolourized (*ca.* 15 min). The solution was treated dropwise with 50% MeOH/$H_2O$ (20 mL), stirred for 20 min, warmed to rt, and acidified with 10% HCl(aq) (1 mL). The $CH_2Cl_2$ layer was collected, washed with 10% HCl(aq) (20 mL), and the combined

aqueous layers were extracted with $CH_2Cl_2$ (5 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a purple amorphous solid (145 mg). $^1H$ NMR ($CDCl_3$) integration of the methine singlets at 5.76, 5.67, and 5.71 ppm indicated that compounds **206**, **207**, and **208** were present in a ratio of 1.0:15.0:2.0 respectively. Chromatography on silica gel (20% EtOAc/hexanes) gave pure samples of compounds **206** (colourless crystals), **207** (colourless amorphous solid), and **208** (colourless amorphous solid).

*elimination product* **206**: mp: 184-186 °C; $[\alpha]_D^{25}$: +78° (*c* 0.16, $CHCl_3$); IR ($CH_2Cl_2$): 1749 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.29 (dd, 1H, $J$ = 15.7, 6.3, H-4a), 3.37 (dd, 1H, $J$ = 16.1, 4.5, H-4b), 3.58 (s, 3H, $CH_3$), 3.63 (s, 3H, $CH_3$), 3.64 (s, 3H, $CH_3$), 3.81 (s, 6H, $CH_3$), 4.08 (dd, 1H, $J$ = 6.8, 4.3, H-3), 5.76 (s, 1H, CH), 5.91 (s, 2H, $CH_2$), 5.93 (s, 1H, CH), 6.28 (s, 1H, aromatic), 6.38 (d, 2H, $J$ = 1.9, aromatic), 6.74 (s, 1H, aromatic), 7.03 (m, 2H, aromatic), 7.20-7.36 (m, 8H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 31.5 ($CH_2$), 41.3 (CH), 52.4 ($CH_3$), 52.5 ($CH_3$), 56.0 ($CH_3$), 60.9 (2 × $CH_3$), 74.6 (CH), 74.9 (CH), 101.3 ($CH_2$), 105.5 (CH), 106.3 (CH), 108.5 (CH), 109.2 (CH), 120.7 (C), 127.3 (4 × CH), 128.4 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.8 (2 × C), 133.3 (C), 133.8 (C), 134.0 (C), 137.4 (C), 146.5 (C), 148.5 (C), 149.3 (C), 153.0 (2 × C), 167.2 (C), 168.8 (C), 168.9 (C), 172.0 (C); mass spectrum *m/z* (relative intensity): 724 ($M^+$, 6), 530 (2), 408 (23), 393 (12), 365 (15), 338 (5), 323 (2), 307 (2), 149 (42), 121 (13), 107 (38), 91 (61), 77 (31), 57 (100); HRMS calcd for $C_{40}H_{36}O_{13}$: 724.2155; found: 724.2158.

*inversion product* **207**: $[\alpha]_D^{25}$: -49° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$): 1745 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.01 (dd, 1H, $J$ = 18.3, 13.1, H-4a), 3.39 (m, 2H, H-3, H-4b), 3.53

(dd, 1H, $J$ = 11.8, 5.6, H-2), 3.59 (s, 3H, $CH_3$), 3.63 (s, 6H, $CH_3$), 3.68 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 4.52 (d, 1H, $J$ = 5.6, H-1), 5.67 (s, 1H, CH), 5.90 (s, 2H, $CH_2$), 6.05 (s, 1H, CH), 6.12 (s, 2H, aromatic), 6.40 (s, 1H, aromatic), 6.66 (s, 1H, aromatic), 7.02-7.12 (m, 4H, aromatic), 7.18-7.44 (m, 6H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 32.1 ($CH_2$), 37.3 (CH), 46.5 (CH), 48.0 (CH), 52.5 (2 × $CH_3$), 56.2 (2 × $CH_3$), 60.6 ($CH_3$), 74.1 (CH), 74.7 (CH), 100.9 ($CH_2$), 107.2 (2 × CH), 107.6 (CH), 109.4 (CH), 126.6 (C), 126.9 (2 × CH), 127.9 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 128.8 (CH), 129.2 (CH), 129.5 (C), 133.3 (C), 133.5 (C), 136.9 (C), 137.3 (C), 146.5 (C), 146.8 (C), 152.6 (2 × C), 168.8 (C), 169.4 (C), 171.0 (C), 174.0 (C); mass spectrum *m/z* (relative intensity): 726 ($M^+$, 35), 532 (13), 499 (22), 411 (73), 384 (14), 365 (42), 339 (66), 324 (14), 308 (19), 283 (11), 149 (100), 121 (100), 107 (31), 91 (58), 77 (41), 57 (27); HRMS calcd for $C_{40}H_{38}O_{13}$: 726.2312; found: 726.2324.

*retention product* **208**: $[\alpha]_D^{25}$: +77° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$): 1750 (CO) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.12-3.42 (m, 4H, H-2, H-3, H-4a, H-4b), 3.59 (s, 3H, $CH_3$), 3.71 (s, 3H, $CH_3$), 3.75 (s, 6H, $CH_3$), 3.86 (s, 3H, $CH_3$), 4.18 (d, 1H, $J$ = 8.5, H-1), 5.71 (s, 1H, CH), 5.84 (s, 1H, CH), 5.88 (s, 2H, $CH_2$), 6.28 (s, 1H, aromatic), 6.39 (s, 2H, aromatic), 6.64 (s, 1H, aromatic), 7.16 (m, 2H, aromatic), 7.24-7.42 (m, 8H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 32.1 ($CH_2$), 42.9 (CH), 48.8 (CH), 50.1 (CH), 52.4 ($CH_3$), 52.6 ($CH_3$), 56.0 (2 × $CH_3$), 60.8 ($CH_3$), 74.8 (2 × CH), 100.9 ($CH_2$), 106.4 (2 × CH), 107.8 (CH), 109.2 (CH), 126.9 (C), 127.2 (2 × CH), 127.6 (2 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.0 (CH), 129.2 (CH), 130.7 (C), 133.2 (C), 133.5 (C), 137.0 (C), 138.7 (C), 146.3 (C), 146.5 (C), 153.2 (2 × C), 168.5 (C), 169.1 (C), 172.8 (C), 173.2 (C); mass spectrum *m/z* (relative intensity): 726 ($M^+$, 15), 532 (8), 499 (18), 412 (35), 383 (10), 365

(32), 339 (39), 324 (10), 308 (13), 283 (10), 149 (100), 121 (69), 107 (44), 91 (80), 77 (54), 57 (36); HRMS calcd for $C_{40}H_{38}O_{13}$: 726.2312; found: 726.2314.

*(-)-Deoxypodophyllotoxin* (**8**)

To a solution of crude reduction product **207** (145 mg) in 30% MeOH/AcOH (20 mL) was added 5% Pd/C (36 mg), and the mixture was stirred under an $H_2$ atmosphere at rt for 4 days (89 h). The catalyst was removed by filtration, washed with EtOAc, and the combined filtrates were evaporated. The resultant light yellow solid was dissolved in sat. $NaHCO_3$(aq) (10 mL) and washed with EtOAc (2 × 5 mL). The combined organic layers were extracted successively with sat. $NaHCO_3$(aq) (3 mL) and $H_2O$ (3 mL) three times. The combined aqueous layers were acidified with 10% HCl(aq) to pH 1-2, saturated with NaCl, and extracted with $CH_2Cl_2$ (7 × 12 mL). The combined $CH_2Cl_2$ layers were dried ($MgSO_4$) and evaporated to give a light yellow solid presumed to be diacid **200** (67 mg): $^1$H NMR ($CDCl_3$) $\delta$: 2.88 (dd, 1H, $J$ = 15.7, 11.9, H-4a), 3.08 (ddd, 1H, $J$ = 11.8, 11.8, 5.5, H-3), 3.22 (dd, 1H, $J$ = 16.0, 5.4, H-4b), 3.29 (dd, 1H, $J$ = 11.8, 5.6, H-2), 3.69 (s, 6H, $CH_3$), 3.76 (s, 3H, $CH_3$), 4.47 (d, 1H, $J$ = 5.5, H-1), 5.90 (s, 2H, $CH_2$), 6.16 (s, 2H, aromatic), 6.41 (s, 1H, aromatic), 6.62 (s, 1H, aromatic), 8.14 (s, 2H, $CO_2H$).

The crude diacid (**200**) (67 mg) was dissolved in trifluoroacetic anhydride (6.5 mL), and the solution was heated at reflux under a drying tube ($CaCl_2$) for 2 h. The solution was slightly cooled and then evaporated to give the presumed anhydride **210** as a light brown amorphous solid: $^1$H NMR ($CDCl_3$) $\delta$: 3.03-3.39 (m, 4H, H-2, H-3, H-4a, H-4b), 3.76 (s, 6H, $CH_3$), 3.81 (s, 3H, $CH_3$), 4.72 (d, 1H, $J$ = 4.1, H-1), 5.95 (d, 1H, $J$ =

1.3, $CH_2$), 5.97 (d, 1H, $J$ = 1.2, $CH_2$), 6.31 (s, 2H, aromatic), 6.52 (s, 1H, aromatic), 6.71 (s, 1H, aromatic).

To a solution of the crude anhydride (**210**) in *i*-PrOH (7.5 mL) was added $NaBH_4$ (8.0 mg, 0.21 mmol), and the mixture was heated at reflux for 15 h. The solution was cooled to rt and acidified with 10% HCl(aq) to pH 1-2. Most of the *i*-PrOH was evaporated, and the concentrated solution was diluted with EtOAc (5.5 mL) and $H_2O$ (5.5 mL). The aqueous layer was removed, saturated with NaCl, and then extracted with $CH_2Cl_2$ (6 × 3 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a brown solid presumed to be hydroxy acid **211**. The $^1H$ NMR spectrum ($CDCl_3$) of the crude material displayed a doublet at 4.39 ppm ($J$ = 5.4) and a doublet at 4.48 ppm ($J$ = 5.8), in an integrated ratio of 3.33:1.00, that were consistent with the H-1 protons of γ-hydroxy acids **211** and **212** respectively.

To a solution of the crude hydroxy acid (**211**) in benzene (7.0 mL) was added a catalytic amount of *p*-TsOH·$H_2O$ (2 mg, 0.01 mmol), and the mixture was heated at reflux for 17.5 h. The mixture was cooled to rt and washed with $H_2O$ (5 mL). The aqueous layer was saturated with NaCl and then extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, dried ($MgSO_4$), evaporated, and the resulting brown solid was chromatographed on silica gel (20% EtOAc/hexanes) to give (-)-deoxypodophyllotoxin (**8**) as a colourless amorphous solid (24.5 mg, 30% from cycloadduct **183**): $[\alpha]_D^{25}$: -112° ($c$ 0.05, $CHCl_3$) [lit.[158] $[\alpha]_D^{25}$: -113.4° ($c$ 0.50, $CHCl_3$)]; IR ($CH_2Cl_2$): 1781 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.74 (br s, 2H, H-2, H-3), 2.76 (m, 1H, H-4a), 3.07 (m, 1H, H-4b), 3.75 (s, 6H, $CH_3$), 3.81 (s, 3H, $CH_3$), 3.92 (m, 1H, $CH_2$), 4.46 (m, 1H, $CH_2$), 4.60 (br s, 1H, H-1), 5.93 (d, 1H, $J$ = 1.3, $CH_2$), 5.95 (d, 1H, $J$ = 1.3, $CH_2$), 6.35 (s, 2H, aromatic), 6.52

(s, 1H, aromatic), 6.67 (s, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 32.8 (CH), 33.1 ($CH_2$), 43.7 (CH), 47.5 (CH), 56.2 (2 × $CH_3$), 60.7 ($CH_3$), 72.0 ($CH_2$), 101.2 ($CH_2$), 108.3 (2 × CH), 108.4 (CH), 110.4 (CH), 128.2 (C), 130.6 (C), 136.2 (C), 137.1 (C), 146.7 (C), 147.0 (C), 152.5 (2 × C), 174.8 (C); mass spectrum *m/z* (relative intensity): 398 ($M^+$, 40), 244 (8), 181 (10), 173 (9), 129 (8), 86 (68), 84 (100), 57 (12); HRMS calcd for $C_{22}H_{22}O_7$: 398.1380; found: 398.1365. The $^1$H NMR spectrum was in agreement with that previously reported.[29,161]

*Dimethyl Ester* **209**

Diazomethane was freshly prepared from Diazald® according to a standard procedure.[173]

Crude diacid **200** (18 mg, 0.042 mmol) was suspended in diethyl ether (0.5 mL) and cooled to 0 °C. A solution of diazomethane in diethyl ether was added dropwise to the stirred suspension until no more gas ($N_2$) was evolved and the solution remained yellow. The solution was stirred for 5 min, warmed to rt, and the ether was evaporated to give a yellow solid. Chromatography on silica gel (15% EtOAc/hexanes) gave **209** as a colourless amorphous solid (14 mg, 73%): $[\alpha]_D^{25}$: -121° (*c* 0.08, $CHCl_3$); IR ($CHCl_3$): 1735 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 2.85 (dd, 1H, $J$ = 17.8, 13.4, H-4a), 3.17 (m, 2H, H-3, H-4b), 3.35 (dd, 1H, $J$ = 12.1, 5.6, H-2), 3.57 (s, 3H, $CH_3$), 3.70 (s, 3H, $CH_3$), 3.74 (s, 6H, $CH_3$), 3.79 (s, 3H, $CH_3$), 4.48 (d, 1H, $J$ = 5.6, H-1), 5.90 (d, 1H, $J$ = 1.3, $CH_2$), 5.90 (d, 1H, $J$ = 1.3, $CH_2$), 6.11 (s, 2H, aromatic), 6.41 (s, 1H, aromatic), 6.60 (s, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 32.4 ($CH_2$), 37.2 (CH), 46.5 (CH), 47.8 (CH), 51.5 ($CH_3$), 52.0 ($CH_3$), 56.1 (2 × $CH_3$), 60.8 ($CH_3$), 101.0 ($CH_2$), 106.7 (2 × CH), 107.5

(CH), 109.5 (CH), 126.7 (C), 129.5 (C), 137.1 (C), 137.3 (C), 146.6 (C), 146.8 (C), 152.8 (2 × C), 172.5 (C), 175.5 (C); mass spectrum *m/z* (relative intensity): 458 ($M^+$, 90), 398 (50), 339 (100), 324 (15), 308 (16), 283 (32), 252 (23), 231 (19), 149 (23), 57 (44); HRMS calcd for $C_{24}H_{26}O_9$: 458.1577; found: 458.1570.

*Diaryl Alcohol* **213**

2-Benzaltetralone (**219**) was synthesized by a modification of the literature procedure for the preparation of benzalacetophenone (chalcone).[173] To an ice-cold solution of NaOH (113 mg, 2.83 mmol) in $H_2O$ (1 mL) was added a solution of $\alpha$-tetralone (**217**) (308 mg, 2.11 mmol) and benzaldehyde (**218**) (230 mg, 2.17 mmol) in EtOH (0.6 mL). The solution was stirred at rt for 22 h, and the resultant yellow precipitate was collected by filtration, washed with $H_2O$, and dissolved in $CH_2Cl_2$ (2 mL). The organic solution was dried ($MgSO_4$) and evaporated to give enone **219** as light yellow crystals (431 mg, 87%): $^1$H NMR ($CDCl_3$) $\delta$: 2.93 (m, 2H, $CH_2$), 3.12 (m, 2H, $CH_2$), 7.23 (d, 1H, $J$ = 7.8, aromatic), 7.31-7.50 (m, 7H, aromatic), 7.87 (br s, 1H, CH), 8.13 (dd, 1H, $J$ = 7.8, 1.2, aromatic). The spectrum was in agreement with that previously reported.[182]

A solution of the crude enone (**219**) in EtOAc (3.2 mL) was stirred over 5% Pd/C (60 mg) under an $H_2$ atmosphere at rt for 4 h. The catalyst was removed by filtration, washed with EtOAc, and the combined filtrates were evaporated to give ketone **220** as a light yellow oil (434 mg, 87% from $\alpha$-tetralone): $^1$H NMR ($CDCl_3$) $\delta$: 1.70-1.83 (m, 1H, $CH_2$), 2.05-2.13 (m, 1H, $CH_2$), 2.60-2.78 (m, 2H, CH, $CH_2$), 2.90 (m, 2H, $CH_2$), 3.48 (dd, 1H, $J$ = 13.3, 3.6, $CH_2$), 7.17-7.32 (m, 7H, aromatic), 7.44 (m, 1H, aromatic), 8.06

(dd, 1H, $J$ = 7.8, 1.2, aromatic). The spectrum was in agreement with that previously reported.[182]

Magnesium turnings (89.0 mg, 3.66 mmol) were placed in a 2-necked 25 mL round-bottom flask fitted with a reflux condenser and separatory funnel with drying tubes attached ($CaCl_2$). One crystal of iodine (12 mg, 0.047 mmol) and diethyl ether (1 mL) were added to the magnesium, and the system was purged with $N_2$(g). A solution of bromobenzene (800 mg, 5.1 mmol) in diethyl ether (2 mL) was slowly added via the separatory funnel, and the mixture was heated at reflux until the magnesium turnings were completely reacted (as indicated by their disappearance). The crude ketone (**220**) in diethyl ether (2 mL) was slowly added at rt via the separatory funnel, and the solution was heated at reflux for 20 min. The solution was cooled to 0 °C and acidified with sat. $NH_4Cl$(aq) (1 mL). The mixture was diluted with $H_2O$ (5 mL), and the aqueous phase was extracted with EtOAc (4 × 3 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the resulting brown oil was chromatographed on silica gel (4-10% EtOAc/hexanes) to give alcohol **213** as a yellow amorphous solid (245 mg, 37% from $\alpha$-tetralone (**217**)): $^1$H NMR ($CDCl_3$) $\delta$: 1.76-1.84 (m, 2H, $CH_2$), 1.92 (s, 1H, OH), 2.20-2.29 (m, 1H, CH), 2.41 (dd, 1H, $J$ = 13.5, 10.9, $CH_2$), 2.72 (dd, 1H, $J$ = 13.5, 2.3, $CH_2$), 2.78-2.92 (m, 2H, $CH_2$), 6.86 (dd, 1H, $J$ = 7.8, 0.7, aromatic), 6.94-7.47 (m, 8H, aromatic).

*Alkene* **222**

To a solution of diaryl alcohol **213** (190 mg, 0.60 mmol) in benzene (6.5 mL) was added $p$-TsOH·$H_2O$ (2 mg, 0.01 mmol), and the mixture was heated at reflux for 20 h.

The solution was cooled to rt, washed with $H_2O$ (4 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 2 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a brown oil (179 mg, 100%): $^1H$ NMR ($CDCl_3$) $\delta$: 2.29 (m, 2H, $CH_2$), 2.80 (m, 2H, $CH_2$), 3.41 (s, 2H, $CH_2$), 6.64 (m, 1H, aromatic), 6.99-7.41 (m, 8H, aromatic).

*Epoxide* **223**

To a solution of crude alkene **222** (45 mg, 0.15 mmol) in $CH_2Cl_2$ (4.5 mL) was added *m*-chloroperoxybenzoic acid (53 mg, 0.31 mmol), and the solution was stirred at rt for 3 h. Saturated $Na_2SO_3$(aq) (2 mL) was added to the solution, and the mixture was stirred for 10 min. The $CH_2Cl_2$ layer was washed with $H_2O$ (3 mL), dried ($MgSO_4$), and evaporated to afford a light yellow amorphous solid (47 mg, 100%): $^1H$ NMR ($CDCl_3$) $\delta$: 1.88 (ddd, 1H, $J$ = 14.3, 13.5, 5.5, $CH_2$), 2.25 (ddd, 1H, $J$ = 14.4, 6.3, 2.0, $CH_2$), 2.56 (d, 1H, $J$ = 14.4, $CH_2$), 2.59 (ddd, 1H, $J$ = 15.6, 5.4, 1.9, $CH_2$), 2.68 (d, 1H, $J$ = 14.5, $CH_2$), 2.85 (ddd, 1H, $J$ = 15.4, 13.6, 6.3, $CH_2$), 6.91 (dd, 1H, $J$ = 7.8, 1.1, aromatic), 7.00-7.72 (m, 8H, aromatic).

*Diphenylmethanol* (**224**)

To a solution of benzophenone (200 mg, 1.10 mmol) in *i*-PrOH (6 mL) was added $NaBH_4$ (46 mg, 1.2 mmol), and the mixture was heated at reflux for 30 min. The solution was cooled to rt, acidified with 10% HCl(aq) to pH 1-2, and the *i*-PrOH was evaporated. The residue was dissolved in $CH_2Cl_2$ (8 mL), the solution was washed with $H_2O$ (5 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 2 mL). The combined organic

portions were dried ($MgSO_4$) and evaporated to give colourless crystals (196 mg, 97%): $^1$H NMR ($CDCl_3$) $\delta$: 2.31 (s, 1H, OH), 5.79 (s, 1H, CH), 7.30 (m, 10H, aromatic). The spectrum was consistent with that previously reported.[268]

*Bis(diphenylmethyl) Ether* (**225**)

A stirred solution of alcohol **224** (151 mg, 0.820 mmol) in $CH_2Cl_2$ (4.5 mL) was cooled to -20 °C under a nitrogen atmosphere and treated with $BF_3$·$OEt_2$ (0.6 mL, 4.9 mmol). The solution, which turned brilliant yellow, was stirred for 2 min and then cooled to -55 °C. $LiAlH_4$ (0.37 M in diethyl ether, 1 mL, 0.37 mmol) was added dropwise until the solution was decolourized, and 1:1 MeOH/$H_2O$ (1 mL) was added. The mixture was warmed to rt, diluted with $H_2O$ (6 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3.5 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting brown solid was chromatographed on silica gel (10% EtOAc/hexanes) to give a colourless crystalline solid (120 mg, 83%): $^1$H NMR ($CDCl_3$) $\delta$: 5.39 (s, 2H, CH), 7.30 (m, 10H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 80.0 (2 × CH), 127.2 (8 × CH), 127.4 (4 × CH), 128.3 (8 × CH), 142.2 (4 × C); mass spectrum *m/z* (relative intensity): 183 ([M - $Ph_2CH]^+$, 53), 167 (100), 152 (28), 105 (33), 77 (22); HRMS calcd for $C_{13}H_{11}O$ ([M - $PH_2CH]^+$): 183.0810; found: 183.0798. The mass spectrum and $^1$H NMR spectrum were consistent with those previously reported.[183]

*(Methyl (S)-Lactyl) 4-Bromocrotonate* (**235**)

To a solution of crotonic acid (**237**) (5.01 g, 58.2 mmol) in $CCl_4$ (50 mL) was added NBS (10.53 g, 59.16 mmol) and benzoyl peroxide (210 mg, 0.867 mmol), and the

mixture was heated at reflux under a nitrogen atmosphere for 4.5 h. The mixture was cooled, kept at 5 °C for 16 h, and the resulting colourless precipitate (succinimide) was removed by filtration. The $^1$H NMR spectrum of the solution indicated that the 4-bromocrotonic acid:crotonic acid ratio was 7:3 by integration of the signals. The solution was treated with thionyl chloride (6.40 mL, 87.7 mmol) and stirred at 60 °C under a drying tube ($CaCl_2$) for 4 h. The solution was cooled to rt, the solvent was evaporated, and $CCl_4$ (10 mL) was added and evaporated twice to remove traces of $SOCl_2$ from the remaining liquid. The crude acid chloride (**239**) was dissolved in $CCl_4$ (20 mL). The solution was treated with methyl (*S*)-lactate (**240**) (8.30 mL, 86.9 mmol) and heated at reflux under a drying tube ($CaCl_2$) for 66.5 h. After cooling the solution to rt and evaporating the solvent, the crude product was chromatographed on silica gel (8% EtOAc/hexanes) to give a light yellow liquid (5.83 g, 40%): $[\alpha]_D^{25}$: -13° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$): 1719 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 1.53 (d, 3H, $J$ = 7.1, $CH_3$), 3.76 (s, 3H, $CH_3$), 4.03 (dd, 2H, $J$ = 7.2, 1.2, $CH_2$), 5.17 (q, 1H, $J$ = 7.1, CH), 6.11 (d, 1H, $J$ = 15.4, CH), 7.08 (dt, 1H, $J$ = 15.4, 7.3, CH); $^{13}$C NMR ($CDCl_3$) $\delta$: 17.0 ($CH_3$), 28.9 ($CH_2$), 52.4 ($CH_3$), 68.8 (CH), 123.7 (CH), 143.0 (CH), 164.6 (C), 171.0 (C); mass spectrum ($NH_4^+$ CI) *m/z* (relative intensity): 253/251 ($[M + H]^+$, 3), 221/219 (3), 193/191 (12), 171 (15), 166/164 (9), 149/147 (100), 121/119 (8), 113 (13), 68 (70); anal. calcd for $C_8H_{11}O_4Br$: C 38.27, H 4.42; found: C 38.49, H 4.34.

*(Methyl (S)-Lactyl) 4-Acetoxycrotonate* (**236**)

Silver acetate was prepared by adding a solution of sodium acetate trihydrate (1.27 g, 9.33 mmol) in $H_2O$ (11 mL) dropwise to a stirred solution of silver nitrate (1.10 g,

6.48) in $H_2O$ (10 mL) at rt. The mixture was stirred for five min, and the resultant colourless precipitate was collected by filtration (848 mg, 79%).

A solution of (methyl (*S*)-lactyl) 4-bromocrotonate (**235**) (1.00 g, 3.98 mmol) and silver acetate (731 mg, 4.38 mmol) in acetic acid (26 mL) was stirred at 100 °C under a drying tube ($CaCl_2$) for 22 h. The resultant precipitate was removed by filtration and washed with EtOAc. The combined filtrates were diluted with aqueous NaCl (1.0 M, 80 mL), and the mixture was extracted with EtOAc (5 × 20 mL). The EtOAc layers were combined, washed successively with sat. $NaHCO_3$(aq) (3 × 15 mL) and $H_2O$ (20 mL), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (10% EtOAc/hexanes) to give a colourless liquid (685 mg, 75%): $[\alpha]_D^{25}$: -11 ° (*c* 2.30, $CHCl_3$); IR ($CHCl_3$): 1742 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.53 (d, 3H, $J$ = 7.1, $CH_3$), 2.13 (s, 3H, $CH_3$), 3.76 (s, 3H, $CH_3$), 4.76 (dd, 2H, $J$ = 4.5, 2.0, $CH_2$), 5.18 (q, 1H, $J$ = 7.1, CH), 6.11 (dt, 1H, $J$ = 15.8, 2.0, CH), 7.02 (dt, 1H, $J$ = 15.8, 4.5, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 17.0 ($CH_3$), 20.7 ($CH_3$), 52.4 ($CH_3$), 62.4 ($CH_2$), 68.7 (CH), 121.1 (CH), 142.6 (CH), 164.9 (C), 170.2 (C), 171.1 (C); mass spectrum ($NH_4^+$ CI) *m/z* (relative intensity): 231 ($[M + H]^+$, 1), 171 (22), 127 (21), 85 (100), 55 (24); HRMS calcd for $C_8H_{11}O_4$ ($[M - CH_3CO_2]^+$): 171.0657; found: 171.0657.

*Cycloadduct* **242**

A solution of benzocyclobutenol (**241**) (37.5 mg, 0.312 mmol) and (methyl (*S*)-lactyl) 4-bromocrotonate (**235**) (42.8 mg, 0.170 mmol) in benzene (3.0 mL) was heated at reflux under a drying tube ($CaCl_2$) for 70 h, and the solvent was evaporated. The $^1H$ NMR spectrum ($CDCl_3$) of the crude product showed that 4-bromocrotonate **235** (minor)

was present in a ratio of 1:3 relative to cycloadduct **242** (major) and that benzocyclobutenol (**241**) was absent. The crude product was dissolved in benzene (3.0 mL), more benzocyclobutenol (33.0 mg, 0.275 mmol) was added, and the solution was heated at reflux for 95 h. The solvent was evaporated, and the $^1$H NMR spectrum ($CDCl_3$) of the crude product showed that no crotonate remained. The crude product was chromatographed on silica gel (8% EtOAc/hexanes) to give a light yellow liquid (56.3 mg, 89%): $[\alpha]_D^{25}$: -66° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$): 3504 (OH), 1747 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 1.58 (d, 3H, $J$ = 7.2, $CH_3$), 2.55 (m, 1H, H-3), 2.80 (dd, 1H, $J$ = 10.6, 9.6, H-2), 2.95 (d, 2H, $J$ = 8.0, $CH_2$), 3.52 (dd, 1H, $J$ = 10.3, 3.4, H-4a), 3.57 (dd, 1H, $J$ = 10.3, 5.7, H-4b), 3.83 (s, 3H, $CH_3$), 4.04 (br s, 1H, OH), 4.99 (d, 1H, $J$ = 9.5, H-1), 5.31 (q, 1H, $J$ = 7.2, CH), 7.12 (m, 1H, aromatic), 7.24 (m, 2H, aromatic), 7.67 (m, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 16.7 ($CH_3$), 32.9 ($CH_2$), 35.8 (CH), 37.3 ($CH_2$), 53.0 ($CH_3$), 53.5 (CH), 69.0 (CH), 71.7 (CH), 126.3 (CH), 126.6 (CH), 127.5 (CH), 128.1 (CH), 133.9 (C), 136.8 (C), 172.5 (C), 173.5 (C); mass spectrum ($NH_4^+$ CI) *m/z* (relative intensity): 390-388 ($[M + NH_4]^+$, 32), 372-370 ($M^+$, 90), 355-353 (38), 308 (28), 273 (30), 251-249 (100), 240-238 (31), 187 (88), 158 (36), 141 (61), 128 (52), 115 (27), 91 (28); HRMS calcd for $C_{16}H_{19}O_5{}^{81}Br$: 372.0395; found: 372.0394; HRMS calcd for $C_{16}H_{19}O_5{}^{79}Br$: 370.0415; found: 370.0418.

*Ether* **243** *and Elimination Product* **244**

A solution of benzocyclobutenol (**241**) (98.8 mg, 0.822 mmol) and (methyl (*S*)-lactyl) 4-bromocrotonate (**235**) (99.5 mg, 0.396 mmol) in toluene (3.5 mL) was heated at reflux under a drying tube ($CaCl_2$) for 71 h, and the solvent was evaporated. The $^1$H

NMR spectrum ($CDCl_3$) of the crude product mixture indicated that cycloadduct **242**, ether **243**, and alkene **244** were present in a ratio of 4.5:1.7:1.0 respectively. Chromatography on silica gel (5% EtOAc/hexanes) gave pure samples of compounds **243** and **244** as light yellow liquids.

*ether* **243**: $[\alpha]_D^{25}$: -33° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$): 1744 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.36 (d, 3H, $J$ = 7.0, $CH_3$), 2.81 (d, 1H, $J$ = 17.5, H-4a), 3.04 (m, 1H, H-3), 3.42 (m, 2H, H-2, H-4b), 3.50 (s, 3H, $CH_3$), 3.83 (d, 1H, $J$ = 8.3, $CH_2$), 4.16 (ddd, 1H, $J$ = 8.3, 5.2, 2.4, $CH_2$), 4.95 (q, 1H, $J$ = 7.1, CH), 5.01 (d, 1H, $J$ = 5.1, H-1), 7.16 (m, 4H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 16.7 ($CH_3$), 33.8 ($CH_2$), 35.6 (CH), 48.6 (CH), 52.2 ($CH_3$), 68.7 (CH), 74.3 ($CH_2$), 76.8 (CH), 126.1 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH), 133.7 (C), 137.6 (C), 168.9 (C), 170.6 (C); mass spectrum *m/z* (relative intensity): 290 ($M^+$, 7), 186 (19), 158 (19), 142 (71), 129 (100), 115 (13), 91 (19), 71 (60); HRMS calcd for $C_{16}H_{18}O_5$: 290.1155; found: 290.1152.

*elimination product* **244**: $[\alpha]_D^{25}$: +35° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$): 1713 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.60 (d, 3H, $J$ = 7.1, $CH_3$), 3.04 (m, 2H, H-4a, $CH_2$), 3.29 (m, 2H, H-3, H-4b), 3.55 (ddd, 1H, $J$ = 9.7, 3.3, 1.1, $CH_2$), 3.78 (s, 3H, $CH_3$), 5.26 (q, 1H, $J$ = 7.0, CH), 7.28 (m, 4H, aromatic), 7.68 (s, 1H, H-1); $^{13}C$ NMR ($CDCl_3$) $\delta$: 17.0 ($CH_3$), 30.5 ($CH_2$), 33.2 ($CH_2$), 34.8 (CH), 52.4 ($CH_3$), 68.9 (CH), 127.1 (CH), 128.5 (C), 128.8 (CH), 129.0 (CH), 130.6 (CH), 131.2 (C), 134.4 (C), 139.2 (CH), 165.6 (C), 171.2 (C); mass spectrum *m/z* (relative intensity): 354-352 ($M^+$, 5), 251-249 (8), 169 (18), 155 (100), 141 (33), 128 (13), 115 (13), 59 (11); HRMS calcd for $C_{16}H_{17}O_4{}^{81}Br$: 354.0289; found: 354.0300; HRMS calcd for $C_{16}H_{17}O_4{}^{79}Br$: 352.0310; found: 352.0324.

*Cycloadduct* **245**

A solution of benzocyclobutenol (**241**) (220 mg, 1.83 mmol) and (methyl (*S*)-lactyl) 4-acetoxycrotonate (**236**) (206 mg, 0.895 mmol) in toluene (2.0 mL) was heated at reflux under a drying tube ($CaCl_2$) for 67 h, and the solvent was evaporated. The crude product was chromatographed on silica gel (5-10% EtOAc/hexanes) to give a light yellow liquid (240 mg, 76%): $[\alpha]_D^{25}$: -46° (*c* 0.70, $CHCl_3$); IR ($CH_2Cl_2$): 3484 (OH), 1736 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.56 (d, 3H, *J* = 7.1, $CH_3$), 2.05 (s, 3H, $CH_3$), 2.57 (m, 1H, H-3), 2.71 (dd, 1H, *J* = 10.9, 9.6, H-2), 2.79 (dd, 1H, *J* = 16.4, 10.2, H-4a), 2.93 (dd, 1H, *J* = 16.6, 5.7, H-4b), 3.82 (s, 3H, $CH_3$), 3.97 (d, 1H, *J* = 4.1, OH), 4.06 (dd, 1H, *J* = 11.1, 4.3, $CH_2$), 4.16 (dd, 1H, *J* = 11.1, 5.8, $CH_2$), 5.00 (dd, 1H, *J* = 9.4, 3.3, H-1), 5.27 (q, 1H, *J* = 7.2, CH), 7.10 (d, 1H, *J* = 7.1, aromatic), 7.23 (m, 2H, aromatic), 7.65 (m, 1H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 16.6 ($CH_3$), 20.8 ($CH_3$), 31.3 ($CH_2$), 34.3 (CH), 51.8 (CH), 52.9 ($CH_3$), 66.1 ($CH_2$), 69.0 (CH), 71.6 (CH), 126.2 (CH), 126.6 (CH), 127.4 (CH), 128.0 (CH), 133.9 (C), 137.0 (C), 170.8 (C), 172.3 (C), 173.9 (C); mass spectrum *m/z* (relative intensity): 350 ($M^+$, 2), 272 (54), 203 (40), 187 (62), 168 (87), 158 (100), 141 (61), 129 (57), 115 (20), 91 (24), 85 (32), 59 (18); HRMS calcd for $C_{18}H_{22}O_7$: 350.1365; found: 350.1365.

*3,4,5-Trimethoxybenzoyl Cyanide* (**264**)

3,4,5-Trimethoxybenzoyl cyanide (**264**) was synthesized by following, in part, the literature procedure for the preparation of benzoyl cyanide.[197] A solution of 3,4,5-trimethoxybenzoic acid (**263**) (8.02 g, 37.8 mmol) and $SOCl_2$ (4.40 mL, 60.3 mmol) in $CCl_4$ (80 mL) was heated at reflux under a drying tube ($CaCl_2$) for 16 h. Evaporation of

the solvent gave a colourless solid, presumed to be the acid chloride, that was subsequently dissolved in $CH_2Cl_2$ (50 mL). The solution was treated with tetra-*n*-butylammonium bromide (50 mg, 0.16 mmol), cooled to 0 °C, and then treated with sodium cyanide (2.04 g, 41.6 mmol) followed by $H_2O$ (3.0 mL). The mixture was stirred for 1.5 h, and the precipitate that formed was removed by filtration and washed with $CH_2Cl_2$. The combined filtrates were dried ($MgSO_4$), evaporated, and the resultant dark yellow solid was chromatographed on silica gel (20% EtOAc/hexanes) to give brilliant yellow crystals (2.65 g, 32%): mp: 133-135 °C; IR ($CH_2Cl_2$): 2224 (CN), 1671 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.95 (s, 6H, $CH_3$), 4.01 (s, 3H, $CH_3$), 7.37 (s, 2H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: 56.5 (2 × $CH_3$), 61.3 ($CH_3$), 107.7 (2 × CH), 112.8 (C), 128.2 (C), 146.2 (C), 153.5 (2 × C), 166.4 (C); mass spectrum *m/z* (relative intensity): 221 ($M^+$, 100), 206 (43), 195 (7), 178 (12), 163 (11), 135 (11), 124 (14); HRMS calcd for $C_{11}H_{11}NO_4$: 221.0688; found: 221.0684.

*Benzoylmandelonitrile* **266** *and Cyanohydrin* **267**

To a stirred solution of 6-iodopiperonal (**186**) (769 mg, 2.79 mmol) and 3,4,5-trimethoxybenzoyl cyanide (**264**) (306 mg, 1.38 mmol) in 1.0:1.6 $CH_2Cl_2$/AcOH (6.5 mL) was added an ice-cold solution of $TiCl_3$ (478 mg, 3.10 mmol) in $H_2O$ (2.7 mL). The solution was stirred under a nitrogen atmosphere at rt for 4 h and then diluted with $H_2O$ (6 mL). The mixture was extracted with EtOAc (2 × 7 mL), and the combined organic phases were washed with $H_2O$ (2 × 5 mL), dried ($MgSO_4$), and evaporated. The crude product was dissolved in 1:4 $CH_2Cl_2$/*t*-BuOH (10 mL), $K_2CO_3 \cdot 1\frac{1}{2}H_2O$ (244 mg, 1.48 mmol) was added to the solution, and the mixture was stirred for 4.5 h at 60 °C. The

solution was cooled to rt, diluted with EtOAc (20 mL), and the precipitate was removed by filtration. The filtrate was washed with $H_2O$ (10 mL), dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel (10-20% EtOAc/hexanes) to give an amorphous solid presumed to be **266** (88 mg, 13%): IR ($CH_2Cl_2$): 1729 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.90 (s, 6H, $CH_3$), 3.92 (s, 3H, $CH_3$), 6.07 (m, 2H, $CH_2$), 6.69 (s, 1H, CH), 7.27 (s, 1H, aromatic), 7.31 (s, 2H, aromatic), 7.33 (s, 1H, aromatic); mass spectrum *m/z* (relative intensity): 497 ($M^+$, 19), 286 (46), 212 (10), 195 (100), 159 (8).

No other coupling products were isolated. Along with unreacted **186**, two additional products isolated were the known 3,4,5-trimethoxybenzaldehyde (**164**) and a compound presumed to be cyanohydrin **267**: $^1H$ NMR ($CDCl_3$) $\delta$: 3.21 (br s, 1H, OH), 5.68 (d, 1H, $J$ = 4.7, CH), 6.03 (s, 2H, $CH_2$), 7.22 (s, 1H, aromatic), 7.26 (s, 1H, aromatic).

*Trimethylsilyl Derivative* **269**

LDA was generated by cooling a stirred solution of diisopropylamine (0.04 mL, 0.29 mmol) in THF (1 mL) to 0 °C under a nitrogen atmosphere, adding *n*-BuLi (2.5 M in hexanes, 0.07 mL, 0.18 mmol), and cooling the solution to -50 °C. A solution of TMSCl (0.07 mL, 0.55 mmol, freshly distilled from $CaCl_2$) in 0.5 mL of THF was cooled to -50 °C and added to the LDA solution followed by the dropwise addition of ketone **197** (42 mg, 0.092 mmol) in THF (2 mL). The solution was stirred for 2 min and then treated with $Et_3N$ (0.2 mL, 1.4 mmol) followed by sat. $NaHCO_3$(aq) (1 mL). The mixture was warmed to rt, diluted with $H_2O$ (5 mL), and extracted with EtOAc (2 × 3 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a light yellow solid

(49 mg, 100%): $^1$H NMR ($CDCl_3$) $\delta$: 0.47 (s, 9H, $CH_3$), 3.92 (s, 9H, $CH_3$), 5.89 (s, 2H, $CH_2$), 6.72 (s, 1H, aromatic), 7.28 (s, 1H, aromatic).

*α-Hydroxy Ketone* **262**

To benzyl aryl ketone **197** (253 mg, 0.555 mmol) was added triethylamine (0.10 mL, 0.72 mmol) followed consecutively by acetonitrile (2 mL), trimethylsilyl chloride (0.084 mL, 0.66 mmol), and a solution of NaI (117 mg, 0.781 mmol) in acetonitrile (2 mL). Air, dried over Drierite® (anhydrous $CaSO_4$ with indicator, 8 mesh), was slowly passed through the solution that was stirred at rt for 4.5 h. The resultant dark brown solution was concentrated *in vacuo*, and to the residue was added EtOAc (4 mL) and $H_2O$ (4 mL). The mixture was acidified with 10% HCl(aq) (0.5 mL), saturated with NaCl, and the aqueous phase was extracted five times with $CH_2Cl_2$ (2 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the crude brown residue was chromatographed on silica gel (25% EtOAc/hexanes) to give colourless crystals (249 mg, 95%): mp: 124-125 °C; IR ($CH_2Cl_2$): 3472 (OH), 1689 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.88 (s, 6H, $CH_3$), 3.89 (s, 3H, $CH_3$), 4.51 (d, 1H, $J$ = 5.3, OH), 5.92 (d, 1H, $J$ = 1.3, $CH_2$), 5.94 (d, 1H, $J$ = 1.3, $CH_2$), 6.13 (d, 1H, $J$ = 5.2, CH), 6.49 (s, 1H, aromatic), 7.17 (s, 2H, aromatic), 7.30 (s, 1H, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 56.6 (2 × $CH_3$), 60.9 ($CH_3$), 80.1 (CH), 88.9 (C), 102.0 ($CH_2$), 106.6 (2 × CH), 107.7 (CH), 118.9 (CH), 127.7 (C), 135.5 (C), 143.3 (C), 148.9 (C), 149.4 (C), 153.0 (2 × C), 197.5 (C); mass spectrum *m/z* (relative intensity): 472 ($M^+$, 1), 275 (7), 195 (100), 149 (23), 128 (20), 81 (14), 69 (13), 57 (40); HRMS calcd for $C_{18}H_{17}O_7I$: 472.0019; found: 471.9987.

*α-t-Butyldimethylsiloxy Ketone* **272**

TBDMS triflate was freshly prepared according to the literature procedure[207] by adding triflic acid (14 mL, 160 mmol) to TBDMSCl (24 g, 160 mmol) at rt and stirring the mixture at 65 °C for 12 h. The solution was distilled at reduced pressure (*ca.* 2.5 mmHg). A minor amount of TBDMSCl was collected first at *ca.* 60 °C followed by TBDMS triflate, a colourless liquid, at *ca.* 83 °C (33.4 g, 79%).

A solution of α-hydroxy ketone **262** (145 mg, 0.307 mmol) in $CH_2Cl_2$ (3 mL) was stirred at rt while TBDMS triflate (0.14 mL, 0.61 mmol) was added followed by $Et_3N$ (0.13 mL, 0.93 mmol). The solution was stirred under a drying tube ($CaCl_2$) for 1 h, the solvent was evaporated, and the resultant yellow amorphous solid was chromatographed on silica gel (20% EtOAc/hexanes) to afford a colourless oil (178 mg, 99%): IR ($CH_2Cl_2$): 1692 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 0.08 (s, 3H, $CH_3$), 0.18 (s, 3H, $CH_3$), 0.92 (s, 9H, $CH_3$), 3.88 (s, 3H, $CH_3$), 3.90 (s, 6H, $CH_3$), 5.92 (d, 1H, $J$ = 1.3, $CH_2$), 5.96 (d, 1H, $J$ = 1.3, $CH_2$), 6.15 (s, 1H, CH), 6.90 (s, 1H, aromatic), 7.22 (s, 2H, aromatic), 7.24 (s, 1H, aromatic); $^{13}C$ NMR ($CDCl_3$) $\delta$: -4.2 (2 × $CH_3$), 18.3 (C), 25.9 (3 × $CH_3$), 56.5 (2 × $CH_3$), 60.8 ($CH_3$), 81.1 (CH), 87.5 (C), 101.9 ($CH_2$), 106.3 (2 × CH), 109.2 (CH), 118.5 (CH), 130.0 (C), 135.5 (C), 142.4 (C), 148.6 (C), 149.0 (C), 152.9 (2 × C), 196.2 (C); mass spectrum *m/z* (relative intensity): 571 ($[M - CH_3]^+$, 2), 529 (16), 459 (1), 391 (100), 343 (10), 195 (20), 73 (79); HRMS calcd for $C_{23}H_{28}O_7SiI$ ($[M - CH_3]^+$): 571.0649; found: 571.0638.

*Methyl Sinapate* (**103**)

A solution of sinapic acid (**98**) (500 mg, 2.23 mmol) and $H_2SO_4$ (0.05 mL, 0.9 mmol) in MeOH (10 mL) was heated at reflux for 2.5 h. The solution was concentrated *in vacuo* to approximately half of the original volume, then diluted with EtOAc (8 mL), and washed with $H_2O$ (6 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the crude brown solid was recrystallized from 1:1 MeOH/$H_2O$ (3 mL) to give a light brown crystalline solid (465 mg, 88%): IR ($CH_2Cl_2$): 3526 (OH), 1710 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.80 (s, 3H, $CH_3$), 3.92 (s, 6H, $CH_3$), 5.74 (br s, 1H, OH), 6.30 (d, 1H, $J$ = 15.9, CH), 6.77 (s, 2H, aromatic), 7.60 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 51.6 ($CH_3$), 56.3 (2 × $CH_3$), 105.1 (2 × CH), 115.6 (CH), 125.9 (C), 137.1 (C), 145.1 (CH), 147.2 (2 × C), 167.5 (C); mass spectrum *m/z* (relative intensity): 238 ($M^+$, 100), 223 (9), 207 (31), 180 (9), 175 (16), 163 (15), 149 (18), 135 (9), 119 (9), 91 (8), 57 (10); HRMS calcd for $C_{12}H_{14}O_5$: 238.0841; found: 238.0840.

*Dimethyl Thomasidioate* (**105**) *and its 1,2-cis Isomer* (**280**)

Dimethyl thomasidioate (**105**) was synthesized by a slight modification of the literature procedure.[131] A solution of methyl sinapate (**103**) (20 mg, 0.084 mmol) in acetone (1.0 mL) was stirred at rt while $FeCl_3$ (30 mg, 0.18 mmol) in $H_2O$ (0.5 mL) was added dropwise over 3 min, giving a yellow solution. After 30 min, the solution, which had turned brown, was diluted with EtOAc (4 mL), $H_2O$ (3 mL), and 10% HCl(aq) (0.5 mL). The aqueous layer was removed and extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give a brown amorphous

solid (20 mg). The $^1$H NMR spectrum ($CDCl_3$) of the crude material indicated that alcohol **104** was the major product by comparison to its previously reported $^1$H NMR spectrum.[131]

*alcohol* **104**: $^1$H NMR ($CDCl_3$) $\delta$: 3.05 (dd, 1H, $J$ = 12.0, 1.9, H-3), 3.22 (s, 3H, $CH_3$), 3.49 (dd, 1H, $J$ = 12.1, 8.9, H-2), 3.63 (s, 3H, $CH_3$), 3.70 (s, 3H, $CH_3$), 3.79 (s, 6H, $CH_3$), 3.91 (s, 3H, $CH_3$), 4.40 (d, 1H, $J$ = 9.0, H-1), 5.03 (d, 1H, $J$ = 1.8, H-4), 5.40 (s, 1H, OH), 5.52 (s, 1H, OH), 6.43 (s, 2H, aromatic), 6.67 (s, 1H, aromatic).

The crude mixture was dissolved in benzene (1.2 mL), *p*-TsOH·$H_2O$ (2 mg, 0.01 mmol) was added to the solution, and the mixture was heated at reflux for 45 min. The solution was diluted with $CH_2Cl_2$ (5 mL), washed with $H_2O$ (6 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel (45:53:2 EtOAc/hexanes/AcOH) to give **105** as a light brown amorphous solid (12 mg, 60%): IR ($CH_2Cl_2$): 3529 (OH), 1727, 1712 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.65 (s, 6H, $CH_3$), 3.76 (s, 9H, $CH_3$), 3.93 (s, 3H, $CH_3$), 4.03 (d, 1H, $J$ = 1.2, H-2), 5.00 (s, 1H, H-1), 5.35 (s, 1H, OH), 5.76 (s, 1H, OH), 6.28 (s, 2H, aromatic), 6.71 (s, 1H, aromatic), 7.64 (s, 1H, H-4); $^{13}$C NMR ($CDCl_3$) $\delta$: 39.5 (CH), 46.5 (CH), 51.9 ($CH_3$), 52.5 ($CH_3$), 56.3 (3 × $CH_3$), 60.6 ($CH_3$), 104.3 (2 × CH), 107.3 (CH), 122.9 (C), 123.4 (C), 123.8 (C), 133.5 (2 × C), 137.5 (CH), 140.9 (C), 144.9 (C), 146.7 (C), 146.8 (2 × C), 167.0 (C), 172.4 (C); mass spectrum *m/z* (relative intensity): 474 ($M^+$, 45), 414 (100), 383 (64), 351 (30), 330 (12), 289 (19), 262 (11), 247 (11), 59 (28); HRMS calcd for $C_{24}H_{26}O_{10}$: 474.1526; found: 474.1519. The $^1$H NMR spectrum was consistent with that previously reported.[131]

A compound presumed to be 1,2-*cis* aryltetralin **280** was also produced (relatively low yield) but was not obtained completely pure after chromatography: $^1$H NMR ($CDCl_3$) $\delta$: 3.35 (s, 3H, $CH_3$), 3.50 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 3.77 (s, 6H, $CH_3$), 3.93 (s, 3H, $CH_3$), 4.13 (dd, 1H, $J$ = 9.0, 2.7, H-2), 4.80 (d, 1H, $J$ = 9.0, H-1), 5.33 (s, 1H, OH), 5.67 (s, 1H, OH), 6.33 (s, 2H, aromatic), 6.63 (s, 1H, aromatic), 7.41 (d, 1H, $J$ = 2.7, H-4).

*Allyl 4-O-Allylsinapate* (**284**)

To a solution of sinapic acid (**98**) (706 mg, 3.15 mmol) in acetone (13 mL) was added allyl bromide (7 mL, 81 mmol) and anhydrous $K_2CO_3$ (1.76 g, 12.7 mmol), and the mixture was heated at reflux under a drying tube ($CaCl_2$) for 22 h. The solution was cooled to rt, diluted with $CH_2Cl_2$ (15 mL), and washed with $H_2O$ (20 mL). After extracting the aqueous layer four times with $CH_2Cl_2$ (10 mL), the combined organic layers were dried ($MgSO_4$) and evaporated to give an orange liquid (960 mg, 100%). A portion of the crude product was chromatographed on silica gel (25% EtOAc/hexanes) to afford a pure sample of a colourless liquid: IR ($CH_2Cl_2$): 1708 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.87 (s, 6H, $CH_3$), 4.56 (dt, 2H, $J$ = 6.1, 1.2, $CH_2$), 4.71 (dt, 2H, $J$ = 5.7, 1.4, $CH_2$), 5.17-5.41 (m, 4H, $CH_2$), 5.93-6.06 (ddt, 1H, $J$ = 17.1, 10.4, 5.7, CH), 6.02-6.15 (ddt, 1H, $J$ = 17.2, 10.3, 6.1, CH), 6.37 (d, 1H, $J$ = 15.8, CH), 6.75 (s, 2H, aromatic), 7.62 (d, 1H, $J$ = 15.9, CH); $^{13}$C NMR ($CDCl_3$) $\delta$: 56.2 (2 × $CH_3$), 65.2 ($CH_2$), 74.2 ($CH_2$), 105.3 (2 × CH), 117.0 (CH), 118.0 ($CH_2$), 118.2 ($CH_2$), 129.8 (C), 132.3 (CH), 134.1 (CH), 138.8 (C), 145.0 (CH), 153.6 (2 × C), 166.5 (C); mass spectrum *m/z* (relative intensity): 304 ($M^+$, 13), 263 (100), 247 (6), 177 (13); HRMS calcd for $C_{17}H_{20}O_5$: 304.1310; found: 304.1274.

*4-O-Allylsinapic Acid* (**285**)

To a solution of diallyl sinapate **284** (832 mg, 2.73 mmol) in 9:1 MeOH/$H_2O$ (20 mL) was added KOH (1.82 g, 32.4 mmol), and the mixture was stirred at rt for 3 h. The solution was concentrated *in vacuo* and then diluted with $H_2O$ (10 mL). The mixture was extracted with EtOAc (30 mL), and the organic extract was washed with sat. $NaHCO_3$(aq) (3 × 10 mL) followed by $H_2O$ (10 mL). The combined aqueous layers were washed once with EtOAc (10 mL), acidified with 10% HCl(aq), and then extracted with $CH_2Cl_2$ (4 × 20 mL). The combined $CH_2Cl_2$ extracts were dried ($MgSO_4$) and evaporated to give beige crystals (708 mg, 98%). Some of the crude product was recrystallized from 10% EtOAc/hexanes to afford a pure sample of colourless crystals: mp: 99-100 °C; IR ($CH_2Cl_2$): 1690 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.89 (s, 6H, $CH_3$), 4.57 (dt, 2H, $J$ = 6.1, 1.2, $CH_2$), 5.20 (m, 1H, $CH_2$), 5.32 (m, 1H, $CH_2$), 6.03-6.16 (ddt, 1H, $J$ = 17.1, 10.3, 6.1, CH), 6.35 (d, 1H, $J$ = 15.9, CH), 6.77 (s, 2H, aromatic), 7.70 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 56.2 (2 × $CH_3$), 74.2 ($CH_2$), 105.6 (2 × CH), 116.3 (CH), 118.1 ($CH_2$), 129.5 (C), 134.1 (CH), 139.2 (C), 147.1 (CH), 153.6 (2 × C), 172.2 (C); mass spectrum *m/z* (relative intensity): 264 ($M^+$, 14), 223 (100), 163 (17), 149 (36), 119 (19), 81 (44), 69 (90); HRMS calcd for $C_{14}H_{16}O_5$: 264.0998; found: 264.0984.

*Methyl (R)-Mandelate* (**283**)

Methyl (R)-mandelate was synthesized in the same manner as methyl (*S*)-mandelate (**199**) (see procedure above) using (*R*)-mandelic acid (1.54 g, 10.1 mmol), $H_2SO_4$ (0.30 mL, 5.6 mmol), and MeOH (15 mL). The crude product was obtained as a

colourless solid (1.59 g, 95%): $^1$H NMR ($CDCl_3$) $\delta$: 3.76 (s, 3H, $CH_3$), 5.18 (s, 1H, CH), 7.37 (m, 5H, aromatic). The spectrum was identical to that previously reported.[267]

*(Methyl (R)-Mandelyl) 4-O-Allylsinapate* (**286**)

A solution of monoallyl sinapic acid **285** (201 mg, 0.761 mmol) and $SOCl_2$ (0.16 mL, 2.2 mmol) in $CCl_4$ (7 mL) was heated at reflux under a drying tube ($CaCl_2$) for 19.5 h. After the solution was allowed to cool to rt, the solvent was evaporated, and $CCl_4$ (4 mL) was added and evaporated twice to remove traces of $SOCl_2$ from the residue. The crude acid chloride (**282**) and methyl (*R*)-mandelate (**283**) (255 mg, 1.53 mmol) were dissolved in $CCl_4$ (2.5 mL), and the solution was heated at reflux under a drying tube ($CaCl_2$) for 23 h. The solution was slightly cooled, the solvent was evaporated, and the resulting crude yellow solid was chromatographed on silica gel (10% EtOAc/toluene) to give colourless crystals (249 mg, 79%): mp: 83-84 °C (hexanes); $[\alpha]_D^{25}$: -67° (*c* 0.51, $CHCl_3$); IR ($CH_2Cl_2$): 1757 (CO), 1717 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.75 (s, 3H, $CH_3$), 3.87 (s, 6H, $CH_3$), 4.56 (dt, 2H, $J$ = 6.1, 1.2, $CH_2$), 5.19 (m, 1H, $CH_2$), 5.31 (m, 1H, $CH_2$), 6.02-6.15 (ddt, 1H, $J$ = 17.2, 10.3, 6.1, CH), 6.09 (s, 1H, CH), 6.48 (d, 1H, $J$ = 15.9, CH), 6.76 (s, 2H, aromatic), 7.41 (m, 3H, aromatic), 7.53 (m, 2H, aromatic), 7.69 (d, 1H, $J$ = 15.9, CH); $^{13}$C NMR ($CDCl_3$) $\delta$: 52.7 ($CH_3$), 56.2 (2 × $CH_3$), 74.2 ($CH_2$), 74.4 (CH), 105.4 (2 × CH), 116.1 (CH), 118.0 ($CH_2$), 127.7 (2 × CH), 128.8 (2 × CH), 129.3 (CH), 129.6 (C), 134.0 (C), 134.1 (CH), 139.0 (C), 146.3 (CH), 153.6 (2 × C), 166.0 (C), 169.3 (C); mass spectrum *m/z* (relative intensity): 412 ($M^+$, 4), 371 (12), 237 (33), 149 (100), 121 (25), 117 (77), 71 (47), 57 (97); HRMS calcd for $C_{23}H_{24}O_7$: 412.1522; found: 412.1526.

*(Methyl (R)-Mandelyl) Sinapate* (**279**)

To a solution of monoallyl (methyl mandelyl) sinapate **286** (170 mg, 0.412 mmol) in 7:3:1 ethanol/benzene/$H_2O$ (5 mL) was added tris(triphenylphosphine)rhodium(I) chloride (26 mg, 0.028 mmol) and DABCO (24 mg, 0.21 mmol), and the mixture was heated at reflux for 4 h. The solution was cooled to rt, acidified with 10% HCl(aq) (2 mL), diluted with $H_2O$ (5 mL), and then extracted with $CH_2Cl_2$ (4 × 5 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the yellow residue was chromatographed on silica gel (55% EtOAc/hexanes) to yield a colourless amorphous solid (150 mg, 98%): $[\alpha]_D^{25}$: -63° (*c* 1.2, $CHCl_3$); IR ($CH_2Cl_2$): 3523 (OH), 1752 (CO), 1714 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.75 (s, 3H, $CH_3$), 3.92 (s, 6H, $CH_3$), 5.78 (s, 1H, OH), 6.09 (s, 1H, CH), 6.43 (d, 1H, $J$ = 15.9, CH), 6.79 (s, 2H, aromatic), 7.42 (m, 3H, aromatic), 7.54 (m, 2H, aromatic), 7.69 (d, 1H, $J$ = 15.8, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 52.6 ($CH_3$), 56.4 (2 × $CH_3$), 74.4 (CH), 105.3 (2 × CH), 114.6 (CH), 125.7 (C), 127.7 (2 × CH), 128.8 (2 × CH), 129.2 (CH), 134.0 (C), 137.4 (C), 146.5 (CH), 147.2 (2 × C), 166.2 (C), 169.4 (C); mass spectrum *m/z* (relative intensity): 372 ($M^+$, 46), 223 (27), 207 (100), 180 (25), 149 (11), 121 (15), 105 (17), 91 (22) 77 (20); HRMS calcd for $C_{20}H_{20}O_7$: 372.1209; found: 372.1193.

*Aryltetralin Lignans* **287**, **288**, and **289**

A solution of mandelyl sinapate **279** (24 mg, 0.064 mmol) in acetone (0.6 mL) was stirred at rt while a solution of $FeCl_3$ (24 mg, 0.15 mmol) in $H_2O$ (0.4 mL) was added dropwise over 3 min. After 25 min, the brown solution was diluted with EtOAc (4 mL) and $H_2O$ (4 mL), and the mixture was acidified with 10% HCl(aq) (1 mL). The aqueous

layer was removed and extracted with $CH_2Cl_2$ (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered, stirred with Amberlite® IRC-718 ion-exchange resin for 5 min, filtered, and evaporated to give a brown amorphous solid. The crude residue was dissolved in benzene (1.3 mL), *p*-TsOH·$H_2O$ (2 mg, 0.01 mmol) was added to the solution, and the mixture was heated at reflux for 40 min. The solution was diluted with $CH_2Cl_2$ (4 mL), washed with $H_2O$ (5 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a brown amorphous solid (24 mg). The $^1H$ NMR spectrum ($CDCl_3$) of the crude material indicated the presence of the 1,2-*trans* diastereomers **287** and **288** in a ratio of 2.0:1.0 respectively (from the ratio of the H-4 singlets at 7.79 ppm and 7.81 ppm respectively). A portion of the crude product (7.8 mg) was chromatographed on a preparative HPLC reverse-phase column using 53:47 MeOH/$H_2O$ to give the 1,2-*trans* diastereomer **287** (4.1 mg, 53%), and what was assumed to be the 1,2-*trans* diastereomer **288** (1.8 mg, 23%) and the 1,2-*cis* diastereomer **289** (0.6 mg, 8%), as colourless amorphous solids. The HPLC chromatogram (UV-VIS detector, λ = 254 nm) indicated the presence of **287**, **288**, and **289** in a ratio of 8.1:4.0:1.0 respectively.

*1,2-trans aryltetralin lignan* **287**: $[\alpha]_D^{25}$: -160° (*c* 0.10, $CHCl_3$); IR ($CH_2Cl_2$): 3525 (OH), 1754, 1715 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.62 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$), 3.78 (s, 6H, $CH_3$), 3.92 (s, 3H, $CH_3$), 4.26 (d, 1H, $J$ = 1.2, H-2), 5.10 (s, 1H, H-1), 5.35 (s, 1H, OH), 5.77 (s, 1H, OH), 5.86 (s, 1H, CH), 6.01 (s, 1H, CH), 6.41 (s, 2H, aromatic), 6.71 (s, 1H, aromatic), 7.26-7.45 (m, 10H, aromatic), 7.79 (s, 1H, H-4); $^{13}C$ NMR ($CDCl_3$) $\delta$: 39.2 (CH), 45.8 (CH), 52.5 (2 × $CH_3$), 56.3 (3 × $CH_3$), 60.6 ($CH_3$), 74.6 (CH), 74.9 (CH), 104.3 (2 × CH), 107.7 (CH), 121.5 (C), 122.7 (C),

124.5 (C), 127.3 (2 × CH), 127.6 (2 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.0 (CH), 129.1 (CH), 133.7 (3 × C), 134.0 (C), 139.3 (CH), 141.3 (C), 145.0 (C), 146.6 (C), 146.8 (2 × C), 165.6 (C), 168.8 (C), 169.1 (C), 171.0 (C); mass spectrum *m/z* (relative intensity): 742 ($M^+$, 10), 548 (31), 457 (8), 426 (16), 400 (36), 383 (30), 356 (11), 274 (12), 231 (11), 149 (84), 121 (41), 107 (99), 91 (100), 79 (45), 69 (33), 57 (58); HRMS calcd for $C_{40}H_{38}O_{14}$: 742.2262; found: 742.2251.

*1,2-trans aryltetralin lignan* **288**: $^1$H NMR ($CDCl_3$) $\delta$: 3.56 (s, 3H, $CH_3$), 3.64 (s, 3H, $CH_3$), 3.65 (s, 3H, $CH_3$), 3.73 (s, 6H, $CH_3$), 3.94 (s, 3H, $CH_3$), 4.25 (d, 1H, $J$ = 1.2, H-2), 5.01 (s, 1H, H-1), 5.33 (s, 1H, OH), 5.77 (s, 1H, OH), 5.83 (s, 1H, CH), 6.00 (s, 1H, CH), 6.35 (s, 2H, aromatic), 6.75 (s, 1H, aromatic), 7.26-7.45 (m, 10H, aromatic), 7.81 (s, 1H, H-4).

*1,2-cis aryltetralin lignan* **289**: $^1$H NMR ($CDCl_3$) $\delta$: 3.46 (s, 3H, $CH_3$), 3.57 (s, 6H, $CH_3$), 3.64 (s, 3H, $CH_3$), 3.73 (s, 3H, $CH_3$), 3.92 (s, 3H, $CH_3$), 4.29 (dd, 1H, $J$ = 8.8, 2.7, H-2), 4.85 (d, 1H, $J$ = 8.8, H-1), 5.11 (s, 1H, OH), 5.49 (s, 1H, OH), 5.68 (s, 1H, CH), 6.18 (s, 1H, CH), 6.30 (s, 2H, aromatic), 6.68 (s, 1H, aromatic), 7.03-7.55 (m, 10H, aromatic), 7.60 (d, 1H, $J$ = 2.7, H-4).

*3-(3'-Acetyl-4'-hydroxyphenyl)-(S)-alanine Hydrochloride* (**292**)

Acetyl (*S*)-tyrosine hydrochloride **292** was synthesized according to the literature procedure.[250] Nitrobenzene and acetyl chloride were freshly distilled. A solution of (*S*)-tyrosine (**276**) (14.5 g, 80.0 mmol) in nitrobenzene (350 mL) was stirred at rt while anhydrous $AlCl_3$ (42.4 g, 318 mmol) was added portionwise. The mixture was stirred until a homogeneous solution was achieved (*ca.* 5 min), and acetyl chloride (7.8 mL, 110

mmol) was added. The solution was warmed to 116 °C and stirred for 5.5 h. After slightly cooling the solution, it was poured over a mixture of ice (500 g) and conc. HCl (800 mL), and the mixture was manually stirred until all of the ice had melted. The aqueous phase was separated from the nitrobenzene layer and divided into approximately 2 equal volumes that were each extracted twice with EtOAc (100 mL). The combined aqueous phases were concentrated *in vacuo* to *ca.* 200 mL and stored at 4 °C for 14 h. The resulting light brown crystals were collected by filtration and recrystallized from 5 M HCl(aq) to give beige crystals (14.6 g, 70%): IR (KBr): 3418 (OH), 1747 (CO) $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$: 2.67 (s, 3H, $CH_3$), 3.22 (dd, 1H, $J$ = 14.7, 7.3, $CH_2$), 3.32 (dd, 1H, $J$ = 14.7, 5.8, $CH_2$), 4.27 (dd, 1H, $J$ = 7.3, 5.9, CH), 7.00 (d, 1H, $J$ = 8.6, aromatic), 7.49 (dd, 1H, $J$ = 8.6, 2.2, aromatic), 7.82 (d, 1H, $J$ = 2.2, aromatic); $^{13}C$ NMR ($D_2O$) $\delta$: 27.5 ($CH_3$), 36.0 ($CH_2$), 55.6 (CH), 119.5 (CH), 121.0 (C), 126.6 (C), 133.6 (CH), 138.9 (CH), 161.0 (C), 173.0 (C), 208.2 (C); mass spectrum *m/z* (relative intensity): 223 ([M - HCl]$^+$, 2), 177 (13), 149 (100), 131 (44), 107 (13), 77 (20). The $^1H$ NMR spectrum was similar to that previously reported.[250]

*3-(3'-Acetyl-4'-hydroxyphenyl)-(S)-lactic Acid* (**293**)

$\alpha$-Hydroxy acid **293** was synthesized according to the literature procedure.[251] A solution of acetyl (*S*)-tyrosine hydrochloride **292** (3.00 g, 11.6 mmol) in $H_2O$ (50 mL) was cooled to 0 °C and then added dropwise over 40 min to a stirred ice-cold solution of $NaNO_2$ (1.20 g, 17.4 mmol) in $H_2O$ (33 mL). The solution was slowly warmed to rt over 2 h, stirred for 18 h, treated with ammonium sulfate (611 mg, 4.62 mmol), and stirred for a further 1 h. To the solution was added conc. HCl (1 mL) followed by EtOAc (25 mL),

and the mixture was stirred until all of the formed precipitate had dissolved. The aqueous layer was removed and extracted five times with EtOAc (25 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting yellow oil was chromatographed on silica gel (200:32:5:1 $CHCl_3$/MeOH/AcOH/$H_2O$) to afford a yellow amorphous solid (2.10 g, 81%): $[\alpha]_D^{25}$: -12° (*c* 0.64, MeOH); IR ($CHCl_3$): 3674 (OH), 1729 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.62 (s, 3H, $CH_3$), 2.97 (dd, 1H, $J$ = 14.3, 6.8, $CH_2$), 3.16 (dd, 1H, $J$ = 14.3, 4.1, $CH_2$), 4.50 (dd, 1H, $J$ = 6.8, 4.2, CH), 6.92 (d, 1H, $J$ = 8.5, aromatic), 7.37 (dd, 1H, $J$ = 8.5, 2.1, aromatic), 7.63 (d, 1H, $J$ = 2.0, aromatic), 12.16 (s, 1H, OH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 26.6 ($CH_3$), 39.1 ($CH_2$), 70.8 (CH), 118.5 (CH), 119.5 (C), 126.3 (C), 131.6 (CH), 137.7 (CH), 161.4 (C), 177.4 (C), 204.4 (C); mass spectrum *m/z* (relative intensity): 224 ($M^+$, 3), 206 (1), 191 (2), 178 (3), 149 (100), 131 (47), 117 (42), 77 (13), 43 (34); HRMS calcd for $C_{11}H_{12}O_5$: 224.0685; found: 224.0699.

*Ethyl 3-(3'-Acetyl-4'-hydroxyphenyl)-(S)-lactate* (**294**)

Acetyl (*S*)-tyrosine hydrochloride **292** (200 mg, 0.77 mmol) was converted to crude aryllactic acid **293** by appropriately scaling the amounts of reagents and solvents used in the procedure above (see *3-(3'-Acetyl-4'-hydroxyphenyl)-(S)-lactic Acid* (**293**)). The crude aryllactic acid (**293**) thus obtained was dissolved in EtOH (4 mL). The solution was treated with $H_2SO_4$ (0.02 mL, 0.4 mmol), heated at reflux for 3 h, and then concentrated *in vacuo*. The residue was dissolved in EtOAc (8 mL), the solution was washed with $H_2O$ (6 mL), and the aqueous layer was extracted three times with EtOAc (3.5 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting light yellow crystals were chromatographed on silica gel (40:8:1

hexanes/EtOAc/AcOH) to afford colourless crystals (95 mg, 49%): mp: 96-98 °C ($CHCl_3$) (lit.[251] mp: 97-98 °C, from *i*-$Pr_2O$); $[\alpha]_D^{25}$: -30° (*c* 2.7, $CHCl_3$) [lit.[251] $[\alpha]_{546}$: -38.8°, $[\alpha]_{578}$: -34.2° (*c* 2.39, $CHCl_3$)]; IR ($CH_2Cl_2$): 3537 (OH), 1733 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 1.30 (t, 3H, $J$ = 7.2, $CH_3$), 2.62 (s, 3H, $CH_3$), 2.93 (dd, 1H, $J$ = 14.2, 6.6, $CH_2$), 3.10 (dd, 1H, $J$ = 14.2, 4.3, $CH_2$), 4.24 (q, 2H, $J$ = 7.1, $CH_2$), 4.41 (dd, 1H, $J$ = 6.5, 4.3, CH), 6.91 (d, 1H, $J$ = 8.5, aromatic), 7.34 (dd, 1H, $J$ = 8.5, 2.2, aromatic), 7.61 (d, 1H, $J$ = 2.1, aromatic), 12.15 (s, 1H, OH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 14.3 ($CH_3$), 26.6 ($CH_3$), 39.3 ($CH_2$), 61.9 ($CH_2$), 71.0 (CH), 118.3 (CH), 119.4 (C), 126.8 (C), 131.5 (CH), 137.7 (CH), 161.3 (C), 174.0 (C), 204.3 (C); mass spectrum *m/z* (relative intensity): 252 ($M^+$, 6), 234 (5), 179 (8), 149 (100), 131 (36), 77 (12), 55 (10); HRMS calcd for $C_{13}H_{16}O_5$: 252.0997; found: 252.0988. The $^1H$ NMR spectrum was consistent with that previously reported.[251]

*3-(3',4'-Dihydroxyphenyl)-(S)-lactic Acid* (**291**)

$\alpha$-Hydroxy acid **291** was synthesized according to the literature procedure.[251] A suspension of aryllactic acid **293** (2.04 g, 9.10 mmol) in $H_2O$ (20 mL) was stirred at rt while a solution of NaOH (1.27 g, 31.8 mmol) in $H_2O$ (6.4 mL) was added, dissolving the acid. The solution was cooled to 0 °C under a nitrogen atmosphere and stirred while 30% $H_2O_2$(aq) (1.56 g, 13.8 mmol) was added in one portion. The solution was slowly warmed over 5 min to allow for the remaining ice in the reaction vessel to melt and was then heated at 46 °C for 30 min, giving a colour change from orange to dark brown. After cooling the stirred solution to rt, $Na_2SO_3$ (0.60 g, 4.8 mmol) in $H_2O$ (6 mL) was added. The solution was cooled further to 0 °C and acidified with conc. HCl (4 mL). The

solution was saturated with NaCl and extracted with EtOAc (14 mL) eight times. The combined organic layers were dried ($MgSO_4$), evaporated, and the yellow residue was chromatographed on silica gel (200:50:5:1 $CHCl_3$/MeOH/AcOH/$H_2O$) to give a yellow amorphous solid (1.10 g, 61%): $[\alpha]_D^{25}$: -10° (*c* 0.50, MeOH); IR (neat): 3651 (OH), 1726 (CO) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$: 2.78 (dd, 1H, $J$ = 14.0, 7.5, $CH_2$), 2.97 (dd, 1H, $J$ = 13.9, 4.3, $CH_2$), 4.32 (dd, 1H, $J$ = 7.5, 4.3, CH), 6.60 (dd, 1H, $J$ = 8.0, 2.0, aromatic), 6.71 (d, 1H, $J$ = 8.0, aromatic), 6.78 (d, 1H, $J$ = 2.0, aromatic); $^{13}C$ NMR (acetone-$d_6$) $\delta$: 40.6 ($CH_2$), 72.2 (CH), 115.7 (CH), 117.5 (CH), 121.7 (CH), 130.0 (C), 144.4 (C), 145.4 (C), 175.3 (C); mass spectrum *m/z* (relative intensity): 198 ($M^+$, 4), 152 (9), 136 (5), 123 (100), 77 (16), 44 (35); HRMS calcd for $C_9H_{10}O_5$: 198.0529; found: 198.0508.

*Allyl 3-(3',4'-Diallyloxyphenyl)-(S)-lactate* (**295**)

3-(3',4'-Dihydroxyphenyl)lactic acid (**291**) (940 mg, 4.7 mmol) was dissolved in acetone (14 mL), and the solution was stirred at rt while allyl bromide (7 mL, 80 mmol) and anhydrous $K_2CO_3$ (1.97 g, 14.3 mmol) were added. The mixture was heated at reflux under a drying tube ($CaCl_2$) for 22 h and cooled to rt. The insoluble salts were removed by filtration, washed with $CH_2Cl_2$, and the combined filtrates were evaporated. The residue was dissolved in $CH_2Cl_2$ (10 mL), the solution was washed with $H_2O$ (10 mL), and the aqueous layer was extracted three times with $CH_2Cl_2$ (5 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the crude product (1.28 g) was chromatographed on silica gel (20% EtOAc/hexanes) to give colourless crystals (640 mg, 42%): mp: 72-73 °C; $[\alpha]_D^{25}$: -29° (*c* 0.73, $CHCl_3$); IR ($CH_2Cl_2$): 3545 (OH), 1738 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 2.91 (dd, 1H, $J$ = 14.1, 6.5, $CH_2$), 3.06 (dd, 1H, $J$ = 14.0, 4.4,

$CH_2$), 4.44 (dd, 1H, $J$ = 6.5, 4.5, CH), 4.58 (m, 4H, $CH_2$), 4.65 (dt, 2H, $J$ = 5.8, 1.3, $CH_2$), 5.23-5.44 (m, 6H, $CH_2$), 5.84-5.97 (ddt, 1H, $J$ = 17.1, 10.4, 5.9, CH), 6.01-6.14 (m, 2H, CH), 6.73 (dd, 1H, $J$ = 8.1, 2.0, aromatic), 6.78 (d, 1H, $J$ = 1.9, aromatic), 6.82 (d, 1H, $J$ = 8.2, aromatic); $^{13}$C NMR ($CDCl_3$) $\delta$: 40.0 ($CH_2$), 66.2 ($CH_2$), 70.0 (2 × $CH_2$), 71.3 (CH), 114.2 (CH), 115.7 (CH), 117.4 ($CH_2$), 117.5 ($CH_2$), 119.2 ($CH_2$), 122.1 (CH), 129.1 (C), 131.4 (CH), 133.4 (CH), 133.6 (CH), 147.6 (C), 148.4 (C), 173.7 (C); mass spectrum *m/z* (relative intensity): 318 ($M^+$, 40), 259 (29), 229 (24), 203 (100), 161 (32), 123 (38), 81 (62); HRMS calcd for $C_{18}H_{22}O_5$: 318.1467; found: 318.1445.

*Allyl 3,4-Di-O-allylcaffeate* (**296**)

A solution of caffeic acid (**277**) (1.50 g, 8.33 mmol) in acetone (22 mL) was stirred at rt while allyl bromide (11 mL, 130 mmol) and anhydrous $K_2CO_3$ (5.18 g, 37.5 mmol) were added. The mixture was heated at reflux under a drying tube ($CaCl_2$) for 19 h and then cooled to rt. The insoluble salts were removed by filtration, washed with $CH_2Cl_2$, and the combined filtrates were evaporated. The residue was dissolved in $CH_2Cl_2$ (15 mL), the solution was washed with $H_2O$ (10 mL), and the aqueous layer was extracted three times with $CH_2Cl_2$ (3 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the crude product (2.50 g) was chromatographed on silica gel (20% EtOAc/hexanes) to give colourless crystals (2.15 g, 86%): mp: 50-51 °C; IR ($CH_2Cl_2$): 1711 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 4.64 (m, 4H, $CH_2$), 4.70 (dt, 2H, $J$ = 5.7, 1.4, $CH_2$), 5.25-5.47 (m, 6H, $CH_2$), 5.93-6.15 (m, 3H, CH), 6.30 (d, 1H, $J$ = 15.9, CH), 6.87 (d, 1H, $J$ = 8.9, aromatic), 7.08 (dd, 1H, $J$ = 8.8, 2.0, aromatic), 7.08 (d, 1H, $J$ = 2.0, aromatic), 7.63 (d, 1H, $J$ = 15.9, CH); $^{13}$C NMR ($CDCl_3$) $\delta$: 65.1 ($CH_2$), 69.7 ($CH_2$), 70.0 ($CH_2$),

112.7 (CH), 113.4 (CH), 115.6 (CH), 117.9 (2 × $CH_2$), 118.1 ($CH_2$), 122.7 (CH), 127.5 (C), 132.4 (CH), 132.9 (CH), 133.1 (CH), 144.9 (CH), 148.5 (C), 150.7 (C), 166.8 (C); mass spectrum *m/z* (relative intensity): 300 ($M^+$, 100), 259 (73), 243 (33), 229 (63), 173 (32), 145 (41), 133 (74), 117 (34), 105 (34), 77 (54); HRMS calcd for $C_{18}H_{20}O_4$: 300.1362; found: 300.1342.

*3,4-Di-O-allylcaffeic Acid* (**297**)

To a solution of triallyl caffeate **296** (2.14 g, 7.13 mmol) in 9:1 MeOH/$H_2O$ (48 mL) was added KOH (4.00 g, 71.3 mmol), and the mixture was stirred at rt for 4 h. The solution was concentrated *in vacuo* to approximately half of the original volume and was then acidified with 10% HCl(aq) (30 mL) followed by conc. HCl (5 mL). The mixture was saturated with NaCl and extracted with EtOAc (10 mL) five times. The combined organic layers were dried ($MgSO_4$), evaporated, and the crude product (1.85 g) was recrystallized twice from 10% MeOH/$CHCl_3$ to give colourless crystals (1.54 g, 83%): mp: 157-159 °C; IR ($CH_2Cl_2$): 1686 (CO) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$: 4.65 (dt, 2H, $J$ = 5.1, 1.6, $CH_2$), 4.68 (dt, 2H, $J$ = 5.2, 1.6, $CH_2$), 5.26 (m, 2H, $CH_2$), 5.47 (m, 2H, $CH_2$), 6.04-6.18 (m, 2H, CH), 6.39 (d, 1H, $J$ = 15.9, CH), 7.02 (d, 1H, $J$ = 8.3, aromatic), 7.20 (dd, 1H, $J$ = 8.3, 2.0, aromatic), 7.34 (d, 1H, $J$ = 2.0, aromatic), 7.60 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR (acetone-$d_6$) $\delta$: 70.0 ($CH_2$), 70.2 ($CH_2$), 113.5 (CH), 114.4 (CH), 116.8 (CH), 117.3 ($CH_2$), 117.4 ($CH_2$), 123.5 (CH), 128.5 (C), 134.4 (CH), 134.6 (CH), 145.4 (CH), 149.6 (C), 151.5 (C), 167.9 (C); mass spectrum *m/z* (relative intensity): 260 ($M^+$, 100), 219 (72), 189 (53), 179 (26), 145 (28), 133 (25), 117 (32), 105 (21), 91 (21), 77 (47); HRMS calcd for $C_{15}H_{16}O_4$: 260.1048; found: 260.1044.

*Allyl 3,4,3',4'-Tetra-O-allyl-(S)-rosmarinate* (**299**)

A solution of diallyl caffeic acid **297** (1.05 g, 4.03 mmol) and thionyl chloride (0.90 mL, 12 mmol) in $CCl_4$ (15 mL) was heated at reflux under a drying tube ($CaCl_2$) for 17.5 h. The solution was concentrated *in vacuo*, and $CCl_4$ was added and evaporated once to remove traces of $SOCl_2$ from the residue. A solution of alcohol **295** (585 mg, 1.84 mmol) in $CH_2Cl_2$ (6 mL) was added to the crude acid chloride (**298**), and the solution was stirred at rt while freshly distilled triethylamine (2.25 mL, 16.1 mmol) was added. The solution was stirred under a drying tube ($CaCl_2$) for 3.5 h and evaporated. The residue was dissolved in $CH_2Cl_2$ (10 mL), and the solution was extracted successively with 10% HCl(aq) (2 × 5 mL), $H_2O$ (5 mL), sat. $NaHCO_3$(aq) (2 × 5 mL), and $H_2O$ (5 mL). The aqueous layers, except for the acidic layers, were combined and extracted twice with $CH_2Cl_2$ (1 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the crude product was chromatographed on silica gel (20% EtOAc/hexanes) to give a colourless oil (673 mg, 65%): $[\alpha]_D^{25}$: -42° (*c* 1.08, $CHCl_3$); IR ($CH_2Cl_2$): 1753 (CO), 1715 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.11 (dd, 1H, $J$ = 14.3, 7.9, $CH_2$), 3.18 (dd, 1H, $J$ = 14.4, 5.2, $CH_2$), 4.56-4.66 (m, 10H, $CH_2$), 5.21-5.46 (m, 11H, CH, $CH_2$) 5.80-5.93 (ddt, 1H, $J$ = 17.1, 10.5, 5.7, CH), 5.99-6.14 (m, 4H, CH), 6.29 (d, 1H, $J$ = 15.9, CH), 6.82 (m, 4H, aromatic), 7.07 (m, 2H, aromatic), 7.61 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 37.1 ($CH_2$), 65.9 ($CH_2$), 69.7 ($CH_2$), 70.0 (3 × $CH_2$), 73.0 (CH), 112.7 (CH), 113.4 (CH), 114.2 (CH), 114.7 (CH), 115.6 (CH), 117.5 (2 × $CH_2$), 117.9 ($CH_2$), 118.0 ($CH_2$), 118.7 ($CH_2$), 122.0 (CH), 123.0 (CH), 127.3 (C), 128.8 (C), 131.5 (CH), 132.8 (CH), 133.0 (CH), 133.4 (CH), 133.5 (CH), 145.9 (CH), 147.6 (C), 148.4 (C), 148.6 (C), 150.9 (C), 166.3 (C), 169.5 (C); mass spectrum *m/z* (relative intensity): 560 ($M^+$, 2), 300 (100),

259 (37), 243 (27), 229 (23), 201 (11), 173 (14), 161 (10), 145 (15), 133 (24), 117 (12), 105 (10), 81 (21); HRMS calcd for $C_{33}H_{36}O_8$: 560.2410; found: 560.2412.

*(S)-(-)-Rosmarinic Acid* (**290**)

To a solution of pentaallyl (*S*)-rosmarinate **299** (645 mg, 1.15 mmol) in 7:3:1 ethanol/benzene/$H_2O$ (22 mL) was added tris(triphenylphosphine)rhodium(I) chloride (700 mg, 0.757 mmol), and the mixture was heated at reflux under a drying tube ($CaCl_2$) for 43 h. The solution was concentrated *in vacuo*, and EtOAc (40 mL) was added to the residue. The mixture was extracted sequentially with $H_2O$ (2 × 10 mL), sat. $NaHCO_3$(aq) (3 × 10 mL), $H_2O$ (10 mL), sat. $NaHCO_3$(aq) (3 × 10 mL), and $H_2O$ (10 mL). The combined aqueous layers were washed once with $CH_2Cl_2$ (10 mL), filtered, and acidified with conc. HCl to approximately pH 1-2. The mixture was filtered, saturated with NaCl, and extracted ten times with EtOAc (20 mL). The combined EtOAc layers were dried ($MgSO_4$), evaporated, and the crude product (247 mg) was chromatographed on silica gel (200:40:5:1 $CHCl_3$/MeOH/AcOH/$H_2O$) to give a light yellow amorphous solid. A colourless amorphous solid was obtained by lyophilization of the product in $H_2O$ (121 mg, 29%): $[\alpha]_D^{25}$: -86° (*c* 0.54, 95% EtOH); IR (neat): 3316 (OH), 1729 (CO), 1690 (C) $cm^{-1}$; $^1H$ NMR (acetone-$d_6$) $\delta$: 3.03 (dd, 1H, $J$ = 14.3, 8.4, $CH_2$), 3.13 (dd, 1H, $J$ = 14.3, 4.4, $CH_2$), 5.22 (dd, 1H, $J$ = 8.4, 4.4, CH), 6.29 (d, 1H, $J$ = 15.9, CH), 6.67 (dd, 1H, $J$ = 8.1, 2.0, aromatic), 6.75 (d, 1H, $J$ = 8.0, aromatic), 6.86 (m, 2H, aromatic), 7.05 (dd, 1H, $J$ = 8.2, 2.0, aromatic), 7.16 (d, 1H, $J$ = 2.1, aromatic), 7.56 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR (acetone-$d_6$) $\delta$: 37.4 ($CH_2$), 73.6 (CH), 114.9 (CH), 115.2 (CH), 115.9 (CH), 116.3 (CH), 117.2 (CH), 121.6 (CH), 122.6 (CH), 127.4 (C), 129.1 (C), 144.7 (C), 145.6 (C),

146.2 (C), 146.4 (CH), 148.8 (C), 166.7 (C), 171.0 (C); mass spectrum ($FAB^+$) *m/z* (relative intensity): 361 ($[M + H]^+$, 13), 180 (63), 163 (100), 123 (17). The NMR spectra were in agreement with those previously reported for the (*R*)-isomer.[254,255]

*(R)-Mosher's Acid Ester of Alcohol* **295** **(301)**

To a solution of (*R*)-(+)-$\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetic acid ((*R*)-Mosher's acid; **300**) (19 mg, 0.081 mmol) in $CCl_4$ (0.5 mL) was added $SOCl_2$ (0.56 mL, 7.7 mmol), and the solution was heated at reflux under a drying tube ($CaCl_2$) for 4 h. The solution was concentrated *in vacuo*, and $CCl_4$ was added and evaporated once to remove traces of $SOCl_2$ from the residue. A solution of freshly distilled $Et_3N$ (37 µL, 0.27 mmol), DMAP (2 mg, 0.02 mmol), and alcohol **295** (7.0 mg, 0.02 mmol) in $CCl_4$ (0.4 mL) was added to the crude acid chloride at rt, immediately giving a colourless precipitate. The mixture was stirred under a drying tube ($CaCl_2$) for 1 h, diluted with $CH_2Cl_2$ (6 mL), and washed successively with 10% HCl(aq) (2 × 3 mL), sat. $NaHCO_3$(aq) (2 × 3 mL), and $H_2O$ (3 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a yellow oil (11.8 mg, 100%): $^1$H NMR ($CDCl_3$) $\delta$: 3.04 (dd, 1H, $J$ = 14.5, 10.0, $CH_2$), 3.25 (dd, 1H, $J$ = 14.5, 3.6, $CH_2$), 3.36 (d, 3H, $J$ = 1.1, $CH_3$), 4.48 (dt, 2H, $J$ = 5.3, 1.5, $CH_2$), 4.58 (dt, 2H, $J$ = 5.3, 1.5, $CH_2$), 4.65 (dt, 2H, $J$ = 5.9, 1.2, $CH_2$), 5.22-5.43 (m, 7H, CH, $CH_2$), 5.80-5.93 (ddt, 1H, $J$ = 17.2, 10.4, 5.9, CH), 5.96-6.13 (m, 2H, CH), 6.74 (m, 2H, aromatic), 6.81 (d, 1H, $J$ = 8.0, aromatic), 7.32 (m, 5H, aromatic). The $^1$H NMR spectrum ($CDCl_3$) showed no alcohol present, and only one diastereomer could be detected. The $^{19}$F NMR spectrum ($CDCl_3$) displayed one major signal (-75.00 ppm) and 4

very minor signals, and the ratio of the major signal to the largest minor signal (-75.11 ppm) was 92:8 by integration.

*(S)- and (R)-α-Methylbenzyl Amide of (S)-Rosmarinic Acid* (**302** and **303**)

A solution of (*S*)-rosmarinic acid (**290**) (7.5 mg, 0.021 mmol) in DMF (0.2 mL) was stirred at rt under a nitrogen atmosphere while (*i*-Pr)$_2$NEt (3.3 mg, 0.026 mmol) in DMF (0.2 mL) was added. The solution was cooled at 0 °C for 7 min, treated with TBTU (7.5 mg, 0.023 mmol), stirred for 5 min to allow the TBTU to dissolve, stirred at rt for 10 min, cooled at 0 °C for 7 min, and then treated dropwise with a solution of racemic α-methylbenzylamine (3.4 mg, 0.028 mmol) in DMF (0.2 mL). The solution was stirred for 1.5 h, slowly warmed to rt, and stirred for an additional 24 h. The solution was diluted with EtOAc (7 mL) and washed with sat. $NaHCO_3$(aq) (3 × 2 mL) followed by 10% HCl(aq) (2 mL). The combined aqueous phases were extracted with EtOAc (3 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a yellow amorphous solid (7.9 mg, 82%). The $^1$H NMR spectrum (acetone-$d_6$) of the crude product mixture showed the presence of the (*S*,*S*)/(*R*,*R*)-diastereomer (**302**) and the (*S*,*R*)/(*R*,*S*)-diastereomer (**303**) in a ratio of 1.3:1.0 respectively, and no starting material was observed. The best separation of diastereomeric signals was observed for an aromatic doublet at 6.71 ppm ($J$ = 8.0, (*S*,*R*)/(*R*,*S*)-isomer) and an aromatic doublet at 6.72 ppm ($J$ = 8.0, (*S*,*S*)/(*R*,*R*)-isomer).

*(R)-α-Methylbenzyl Amide of (S)-Rosmarinic Acid* (**305**)

Compound **305** was synthesized in the same manner as the (*S*)/(*R*)-α-methylbenzyl amide of (*S*)-rosmarinic acid (**302/303**) (see procedure above) using (*S*)-rosmarinic acid (**290**) (7.3 mg, 0.020 mmol), (*i*-Pr)$_2$NEt (2.6 mg, 0.020 mmol), TBTU (6.9 mg, 0.021 mmol), (*R*)-(+)-α-methylbenzylamine (3.3 mg, 0.027 mmol), and the same volumes of DMF. The crude product was obtained as a light yellow amorphous solid (7.0 mg, 74%). The $^1$H NMR spectrum (acetone-$d_6$) of the crude product showed minor peaks that could possibly be attributed to the (*R*,*R*)-diastereomer (**304**). A ratio of 9:1 was obtained by integration of the (*S*,*R*)-isomer (**305**) doublet at 6.71 ppm and signals that could possibly be attributed to a (*R*,*R*)-isomer (**304**) doublet at 6.72 ppm respectively. No starting material was observed.

*Methyl Caffeate* (**126**)

A solution of caffeic acid (**277**) (102 mg, 0.566 mmol) and $H_2SO_4$ (0.01 mL, 0.2 mmol) in MeOH (2 mL) was heated at reflux for 3 h. The solution was concentrated *in vacuo*, diluted with EtOAc (8 mL), and washed with $H_2O$ (6 mL). The aqueous phase was extracted with EtOAc (3 × 3.5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give light brown crystals (110 mg, 100%): IR (KBr): 3482 (OH), 1679 (CO) cm$^{-1}$; $^1$H NMR (acetone-$d_6$) $\delta$: 3.72 (s, 3H, $CH_3$), 6.28 (d, 1H, $J$ = 16.0, CH), 6.87 (d, 1H, $J$ = 8.2, aromatic), 7.04 (dd, 1H, $J$ = 8.2, 2.1, aromatic), 7.15 (d, 1H, $J$ = 2.1, aromatic), 7.54 (d, 1H, $J$ = 15.9, CH), 8.14 (s, 1H, OH), 8.41 (s, 1H, OH); $^{13}$C NMR (acetone-$d_6$) $\delta$: 51.4 ($CH_3$), 115.0 (CH), 115.2 (CH), 116.2 (CH), 122.4 (CH), 127.4 (C), 145.6 (CH), 146.2 (C), 148.6 (C), 167.7 (C); mass spectrum *m/z* (relative

intensity): 194 ($M^+$, 87), 163 (100), 145 (16), 135 (26), 117 (19), 89 (28), 77 (14), 63 (13), 55 (7); HRMS calcd for $C_{10}H_{10}O_4$: 194.0579; found: 194.0580.

*Aryltetralin* **133**

Methyl caffeate (**126**) was dimerized by a modification of the literature procedure.[111] A solution of methyl caffeate (**126**) (4.9 mg, 0.025 mmol) in acetone (0.6 mL) was cooled to 0 °C and stirred while $FeCl_3$ (10 mg, 0.06 mmol) in $H_2O$ (0.3 mL) was added dropwise over 5 min. The solution was stirred at 0 °C for 3 h and then stored at 5 °C for 15 h. The solution was acidified with 10% HCl(aq) (3 mL), diluted with $H_2O$ (3 mL), and extracted with EtOAc (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a dark brown amorphous solid (6.9 mg). The $^1$H NMR spectrum (acetone-$d_6$) of the crude product showed by integration that the oxidative coupling product **133** (doublet at 4.44 ppm, $J$ = 2.4)[111] was present in a ratio of 1.3:1.0 relative to the starting material (doublet at 6.27 ppm, $J$ = 15.9) respectively.

*aryltetralin* **133**: $^1$H NMR (acetone-$d_6$) $\delta$: 3.57 (s, 3H, $CH_3$), 3.68 (s, 3H, $CH_3$), 3.89 (d, 1H, $J$ = 2.7, H-2), 4.44 (d, 1H, $J$ = 2.4, H-1), 6.43 (br d, 1H, $J$ = 8.1, aromatic), 6.46 (br s, 1H, aromatic), 6.62 (s, 1H, aromatic), 6.68 (d, 1H, $J$ = 8.0, aromatic), 6.94 (s, 1H, aromatic), 7.56 (s, 1H, H-4). The spectrum was consistent with that previously reported.[111]

*3,4-Di-O-(t-butyldimethylsilyl)caffeic Acid* (**307**)

Caffeic acid (**277**) (4.00 g, 22.2 mmol) was stirred as a suspension in $CH_2Cl_2$ (100 mL) at rt while TBDMS triflate (23 mL, 100 mmol) was added followed by freshly

distilled $Et_3N$ (20.5 mL, 147 mmol). The $Et_3N$ had to be added carefully due to the exothermicity of the reaction. The mixture immediately became a homogeneous dark brown solution that was stirred under a nitrogen atmosphere for 17 h. The solution was washed successively with 10% HCl(aq) (2 × 20 mL) and $H_2O$ (20 mL), and the organic layer was dried ($MgSO_4$) and evaporated to give crude trisilyl caffeate **306** as a mixture of a brown oil and light brown solid (11.5 g, 99%): $^1$H NMR ($CDCl_3$) $\delta$: 0.21 (s, 6H, $CH_3$), 0.22 (s, 6H, $CH_3$), 0.33 (s, 6H, $CH_3$), 0.98 (s, 9H, $CH_3$), 0.99 (s, 9H, $CH_3$), 1.00 (s, 9H, $CH_3$), 6.20 (d, 1H, $J$ = 15.8, CH), 6.82 (d, 1H, $J$ = 8.7, aromatic), 7.00 (m, 2H, aromatic), 7.50 (d, 1H, $J$ = 15.8, CH).

The crude trisilyl caffeate (**306**) was dissolved in 1:1 MeOH/acetone (220 mL), and the solution was stirred at rt while $H_2O$ (20 mL) was slowly added over 5 min followed by $K_2CO_3 \cdot 1\frac{1}{2}H_2O$ (3.63 g, 22.0 mmol). The mixture was stirred for 3 h, filtered, and the filtrate was concentrated *in vacuo* to *ca.* 50% of the original volume. EtOAc (150 mL) and $H_2O$ (20 mL) were added to the solution. The mixture was acidified with conc. HCl at 0 °C, warmed to rt, and then saturated with NaCl. The aqueous phase was removed and extracted four times with EtOAc (20 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the resultant grey crystalline solid was chromatographed on silica gel (5:1 $CHCl_3$/MeOH) to give **307** as a colourless crystalline solid (6.90 g, 76% from **277**): mp: 152-155 °C; IR ($CH_2Cl_2$): 1686 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 0.22 (s, 6H, $CH_3$), 0.23 (s, 6H, $CH_3$), 0.99 (s, 9H, $CH_3$), 1.00 (s, 9H, $CH_3$), 6.25 (d, 1H, $J$ = 15.8, CH), 6.84 (d, 1H, $J$ = 8.8, aromatic), 7.05 (m, 2H, aromatic), 7.67 (d, 1H, $J$ = 15.9, CH); $^{13}$C NMR ($CDCl_3$) $\delta$: -4.1 (2 × $CH_3$), -4.0 (2 × $CH_3$), 18.5 (2 × C), 25.9 (6 × $CH_3$), 114.7 (CH), 120.6 (CH), 121.1 (CH), 122.6 (CH), 127.6 (C), 147.0

(CH), 147.2 (C), 149.9 (C), 172.1 (C); mass spectrum *m/z* (relative intensity): 408 ($M^+$, 1), 351 (6), 335 (6), 219 (55), 149 (14), 73 (100), 57 (11); HRMS calcd for $C_{21}H_{36}O_4Si_2$: 408.2152; found: 408.2169.

*Allyl 3,4-Di-O-(t-butyldimethylsilyl)-3',4'-di-O-allyl-(S)-rosmarinate* (**309**)

A solution of disilyl caffeic acid **307** (4.31 g, 10.5 mmol) and $SOCl_2$ (2.4 mL, 33 mmol) in $CCl_4$ (40 mL) was heated at reflux under a drying tube ($CaCl_2$) for 4.75 h. The solution was concentrated *in vacuo*, and $CCl_4$ (10 mL) was added and evaporated once to remove traces of $SOCl_2$ from the residue. Triallyl alcohol **295** (2.13 g, 6.69 mmol) in $CH_2Cl_2$ (20 mL) was added to the crude acid chloride (**308**), and the resulting homogeneous solution was stirred at rt while freshly distilled $Et_3N$ (5.9 mL, 42 mmol) was added. The solution was stirred under a drying tube ($CaCl_2$) for 4 h and then concentrated *in vacuo*. EtOAc (50 mL) was added to the residue, and the mixture was washed successively with 10% HCl(aq) (2 × 11 mL) and $H_2O$ (11 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting yellow oil was chromatographed on silica gel (20% EtOAc/hexanes) to afford a light yellow oil (4.61 g, 97%): $[\alpha]_D^{25}$: -34° (*c* 0.50, $CHCl_3$); IR ($CH_2Cl_2$): 1751 (CO), 1719 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 0.21 (s, 6H, $CH_3$), 0.22 (s, 6H, $CH_3$), 0.98 (s, 9H, $CH_3$), 0.99 (s, 9H, $CH_3$), 3.11 (dd, 1H, $J$ = 14.3, 7.9, $CH_2$), 3.18 (dd, 1H, $J$ = 14.3, 5.2, $CH_2$), 4.57 (m, 4H, $CH_2$), 4.63 (dt, 2H, $J$ = 5.7, 1.3, $CH_2$), 5.21-5.43 (m, 7H, CH, $CH_2$), 5.80-5.93 (ddt, 1H, $J$ = 17.1, 10.5, 5.7, CH), 5.99-6.12 (m, 2H, CH), 6.25 (d, 1H, $J$ = 16.0, CH), 6.81 (m, 4H, aromatic), 7.00 (m, 2H, aromatic), 7.59 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: -4.1 (2 × $CH_3$), -4.0 (2 ×

$CH_3$), 18.4 (C), 18.5 (C), 25.9 (6 × $CH_3$), 37.1 ($CH_2$), 65.9 ($CH_2$), 70.0 (2 × $CH_2$), 73.0 (CH), 114.2 (CH), 114.5 (CH), 115.5 (CH), 117.5 (2 × $CH_2$), 118.7 ($CH_2$), 120.5 (CH), 121.1 (CH), 121.9 (CH), 122.5 (CH), 127.8 (C), 128.9 (C), 131.5 (CH), 133.3 (CH), 133.5 (CH), 146.0 (CH), 147.2 (C), 147.6 (C), 148.4 (C), 149.7 (C), 166.4 (C), 169.6 (C); mass spectrum *m/z* (relative intensity): 708 ($M^+$, 1), 465 (3), 408 (3), 391 (11), 351 (19), 335 (15), 300 (6), 261 (8), 236 (5), 219 (100), 191 (10), 115 (17), 73 (100), 59 (17); HRMS calcd for $C_{39}H_{56}O_8Si_2$: 708.3514; found: 708.3460.

*Allyl 3',4'-Di-O-allyl-(S)-rosmarinate* (**310**)

A solution of disilyl triallyl (*S*)-rosmarinate **309** (4.23 g, 5.97 mmol) in THF (30 mL) was stirred at rt under a nitrogen atmosphere while tetra-*n*-butylammonium fluoride (1.0 M in THF, 12 mL, 12 mmol) was added over *ca.* 1 min. The resultant dark brown solution was stirred for 15 min and then acidified with 10% HCl(aq) (10 mL). The mixture was diluted with $H_2O$ (10 mL) and extracted with EtOAc (1 × 35 mL, then 3 × 10 mL). The combined organic phases were dried ($MgSO_4$), evaporated, and the resulting yellow oil was chromatographed on silica gel (25:25:1 EtOAc/hexanes/AcOH) to give a colourless crystalline solid (1.47 g, 51%): mp: 116-118 °C (EtOAc); $[\alpha]_D^{25}$: -51° (*c* 0.51, $CHCl_3$); IR ($CH_2Cl_2$): 3542 (OH), 3369 (OH), 1741 (CO), 1717 (CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.12 (dd, 1H, $J$ = 14.3, 7.7, $CH_2$), 3.18 (dd, 1H, $J$ = 14.2, 5.1, $CH_2$), 4.57 (m, 4H, $CH_2$), 4.65 (dt, 2H, $J$ = 5.7, 1.2, $CH_2$), 5.21-5.42 (m, 7H, CH, $CH_2$), 5.80-5.93 (ddt, 1H, $J$ = 17.1, 10.5, 5.7, CH), 5.98-6.11 (m, 3H, CH, OH), 6.17 (s, 1H, OH), 6.20 (d, 1H, $J$ = 16.0, CH), 6.80 (m, 4H, aromatic), 6.91 (dd, 1H, $J$ = 8.2, 1.9, aromatic), 6.99 (d, 1H, $J$ = 1.9, aromatic), 7.51 (d, 1H, $J$ = 15.9, CH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 37.1 ($CH_2$), 66.1

($CH_2$), 70.0 ($CH_2$), 70.1 ($CH_2$), 73.0 (CH), 114.2 (2 × CH), 114.4 (CH), 115.4 (CH), 115.7 (CH), 117.7 (2 × $CH_2$), 119.0 ($CH_2$), 122.1 (CH), 122.5 (CH), 127.2 (C), 128.7 (C), 131.2 (CH), 133.2 (CH), 133.4 (CH), 143.9 (C), 146.2 (CH), 146.6 (C), 147.6 (C), 148.3 (C), 166.6 (C), 170.1 (C); mass spectrum *m/z* (relative intensity): 480 ($M^+$, 2), 318 (14), 300 (53), 259 (32), 229 (18), 219 (10), 203 (50), 191 (6), 175 (14), 163 (100), 145 (20), 135 (28), 117 (22), 105 (15), 89 (23), 77 (23), 55 (20); HRMS calcd for $C_{27}H_{28}O_8$: 480.1784; found: 480.1752.

*3'',3''',4'',4''',9'',9'''-Hexa-O-allyl-(+)-rabdosiin* (**311**) *and its (1R,2S)-Isomer* (**312**)

A slow stream of oxygen was passed through a stirred solution of triallyl rosmarinate **310** (26 mg, 0.054 mmol) in acetone (2.4 mL) at rt while a solution of $FeCl_3$ (19.3 mg, 0.119 mmol) in $H_2O$ (1.2 mL) was added dropwise over 2 min. The dark green reaction mixture, protected from light, was stirred for 23 h and then diluted with $H_2O$ (5 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to give a brown amorphous solid (30 mg). The $^1H$ NMR spectrum (acetone-$d_6$) of the crude residue showed that a significant amount of starting material was present and that diastereomers **311** and **312** were present in a ratio of 1.0:1.6 by integration of their H-2 doublets at 3.94 ppm and 3.97 ppm respectively. Due to the low yield of products, the reaction was repeated in the same manner as described above using **310** (21 mg, 0.044 mmol), $FeCl_3$ (16 mg, 0.099 mmol), and the same volumes of solvents. The crude products from both reactions were combined and chromatographed on a preparative HPLC reverse-phase column using 72:28 MeOH/0.06% TFA(aq) to give 1,2-*trans* diastereomers **311** (2.6 mg, 5.5%) and **312** (3.0

mg, 6.4%) as colourless amorphous solids. The HPLC chromatogram (UV-VIS detector, $\lambda = 254$ nm) indicated the presence of **311** and **312** in a ratio of 1.0:1.6 respectively.

*3'',3''',4'',4''',9'',9'''-hexa-O-allyl-(+)-rabdosiin* (**311**): $^1$H NMR (acetone-$d_6$) $\delta$: 3.07 (m, 4H, $CH_2$), 3.94 (d, 1H, $J$ = 1.6, H-2), 4.54 (m, 13H, H-1, $CH_2$), 5.09-5.29 (m, 10H, CH, $CH_2$), 5.38-5.46 (m, 4H, $CH_2$), 5.74-5.90 (m, 2H, CH), 6.01-6.13 (m, 4H, CH), 6.40 (m, 2H, aromatic), 6.62-6.97 (m, 9H, aromatic), 7.65 (s, 1H, H-4).

*(1R,2S)-diastereomer of 3'',3''',4'',4''',9'',9'''-hexa-O-allyl-(+)-rabdosiin* (**312**): $^1$H NMR (acetone-$d_6$) $\delta$: 3.01 (m, 4H, $CH_2$), 3.97 (d, 1H, $J$ = 2.1, H-2), 4.31 (d, 1H, $J$ = 1.9, H-1), 4.45-4.58 (m, 12H, $CH_2$), 5.06 (dd, 1H, $J$ = 8.0, 4.8, CH), 5.11-5.25 (m, 9H, CH, $CH_2$), 5.38-5.46 (m, 4H, $CH_2$), 5.68-5.86 (m, 2H, CH), 6.01-6.14 (m, 4H, CH), 6.39 (dd, 1H, $J$ = 8.1, 2.1, aromatic), 6.44 (d, 1H, $J$ = 2.1, aromatic), 6.53 (s, 1H, aromatic), 6.67 (d, 1H, $J$ = 8.1, aromatic), 6.76 (m, 2H, aromatic), 6.90 (m, 5H, aromatic), 7.66 (s, 1H, H-4).

*Dimethyl Ether of Dimethyl Thomasidioate* (**313**)

Thomasidioic acid (**101**) was prepared according to the literature procedure.[237,269] A solution of aqueous ammonium bicarbonate (0.3 M, 120 mL) was adjusted to pH 8.6 by dropwise addition of 30% aqueous ammonium hydroxide. Sinapic acid (**98**) (1.02 g, 4.55 mmol) was dissolved in the buffer, and the solution stirred at rt while maintaining the solution at pH 8.6 by intermittently adding the appropriate amount of conc. HCl. After 64 h, conc. HCl was added until the solution reached pH 1.7. The solution was extracted with EtOAc (9 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to give a brown amorphous solid presumed to be thomasidioic acid (**101**) (958

mg, 94%): $^1$H NMR ($CDCl_3$) $\delta$: 3.64 (s, 3H, $CH_3$), 3.74 (s, 6H, $CH_3$), 3.92 (s, 3H, $CH_3$), 4.00 (s, 1H, H-2), 5.02 (s, 1H, H-1), 6.28 (s, 2H, aromatic), 6.73 (s, 1H, aromatic), 7.74 (s, 1H, H-4). The $^1$H NMR spectrum was consistent with that previously reported.[128-130,237,269]

A solution of the crude thomasidioic acid (**101**) in 3% HCl/MeOH (30 mL) was heated at reflux for 23 h. The solution was concentrated *in vacuo,* diluted with EtOAc (40 mL), and then washed with $H_2O$ (20 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to give a brown amorphous solid presumed to be dimethyl thomasidioate (**105**) (967 mg, 95%): $^1$H NMR ($CDCl_3$) $\delta$: 3.65 (s, 6H, $CH_3$), 3.76 (s, 9H, $CH_3$), 3.93 (s, 3H, $CH_3$), 4.03 (d, 1H, $J$ = 1.2, H-2), 5.00 (s, 1H, H-1), 5.35 (s, 1H, OH), 5.76 (s, 1H, OH), 6.28 (s, 2H, aromatic), 6.71 (s, 1H, aromatic), 7.64 (s, 1H, H-4). The $^1$H NMR spectrum was consistent with that obtained from the oxidative dimerization of methyl sinapate (see *Dimethyl Thomasidioate* (**105**)) and with that previously reported.[129-131]

To a solution of the crude dimethyl ester (**105**) and dimethyl sulfate (0.48 mL, 5.1 mmol) in acetone (30 mL) was added $K_2CO_3 \cdot 1\frac{1}{2}H_2O$ (1.01 g, 6.11 mmol), and the mixture was heated at reflux for 16.5 h. The mixture was cooled to rt, and the insoluble material was removed by filtration and washed with EtOAc. The combined filtrates were washed with $H_2O$ (20 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and the resulting brown oil was chromatographed on silica gel (15% EtOAc/hexanes) to give **313** as colourless crystals (584 mg, 51% from sinapic acid (**98**)): IR ($CH_2Cl_2$): 1729, 1708 (CO) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$: 3.65 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 3.72 (s, 6H, $CH_3$), 3.77 (s, 3H,

$CH_3$), 3.78 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 3.89 (s, 3H, $CH_3$), 4.06 (d, 1H, $J$ = 1.2, H-2), 4.99 (s, 1H, H-1), 6.26 (s, 2H, aromatic), 6.72 (s, 1H, aromatic), 7.65 (s, 1H, H-4); $^{13}C$ NMR ($CDCl_3$) $\delta$: 39.6 (CH), 46.3 (CH), 52.0 ($CH_3$), 52.5 ($CH_3$), 56.1 (3 × $CH_3$), 60.8 ($CH_3$), 60.9 (2 × $CH_3$), 104.6 (2 × CH), 108.3 (CH), 123.2 (C), 124.3 (C), 127.0 (C), 136.8 (C), 137.3 (CH), 138.2 (C), 144.4 (C), 151.4 (C), 152.8 (C), 153.0 (2 × C), 166.9 (C), 172.3 (C); mass spectrum *m/z* (relative intensity): 502 ($M^+$, 84), 443 (95), 411 (100), 396 (26), 380 (52), 303 (55), 211 (34), 195 (99), 181 (25), 149 (33), 69 (39); HRMS calcd for $C_{26}H_{30}O_{10}$: 502.1839; found: 502.1836. The $^1H$ NMR spectrum was consistent with that previously reported.[128-130]

*(+)-Rabdosiin* (**314**)

Bis(triphenylphosphine)palladium dichloride was prepared according to the previously reported procedure.[263] Palladium dichloride (1.50 g, 8.46 mmol) and lithium chloride (0.72 g, 17 mmol) were stirred in MeOH (12.7 mL) at rt while triphenylphosphine (4.66 g, 17.8 mmol) was added. The mixture was heated at reflux under a nitrogen atmosphere for 1 h, then cooled to rt, and placed in an ice bath for 10 min. An orange solid was collected by filtration, washed with $H_2O$ followed by MeOH, and recrystallized from chloroform to afford yellow crystals (3.42 g, 58%).

To a stirred mixture of hexaallyl (+)-rabdosiin **311** (2.6 mg, 0.0027 mmol), bis(triphenylphosphine)palladium dichloride (0.8 mg, 0.001 mmol), acetic acid (0.0030 mL, 0.052 mmol), and acetone (0.3 mL) at rt was added tributyltin hydride (0.0050 mL, 0.019 mmol) every 10 min for a total of 5 additions (0.0250 mL, 0.093 mmol) over 40 min. The mixture was stirred for 10 min and then diluted with EtOAc (5 mL), sat.

$NaHCO_3$(aq) (1 mL), and $H_2O$ (2 mL). The organic phase was removed and extracted twice with sat. $NaHCO_3$(aq) (0.5 mL) and $H_2O$ (2 mL). The combined aqueous phases were filtered, washed once with EtOAc (1 mL), carefully acidified to pH 1-2 using conc. HCl, and evaporated. Acetone was added to the residue, the mixture was filtered, and the filtrate was evaporated to give a light yellow amorphous solid (1.9 mg, 100%): $^1$H NMR (acetone-$d_6$) $\delta$: 3.05 (m, 4H, $CH_2$), 3.94 (d, 1H, $J$ = 1.3, H-2), 4.57 (br s, 1H, H-1), 5.06 (dd, 1H, $J$ = 6.2, 6.2, CH), 5.09 (dd, 1H, $J$ = 7.1, 5.4, CH), 6.39-6.93 (m, 11H, aromatic), 7.63 (s, 1H, H-4). Plane polarized light was rotated in a clockwise direction (positive optical rotation). The $^1$H NMR spectrum of **314** was consistent with that reported for its enantiomer.[110-113]

*(-)-(1R,2S)-Diastereomer of (+)-Rabdosiin* (**315**)

The (1*R*,2*S*)-diastereomer of (+)-rabdosiin (**315**) was prepared in the same manner as (+)-rabdosiin (**314**) (see procedure above) using the (1*R*,2*S*)-isomer of hexaallyl (+)-rabdosiin (**312**) (3.0 mg, 0.0031 mmol), bis(triphenylphosphine)palladium dichloride (0.9 mg, 0.001 mmol), acetic acid (0.0036 mL, 0.063 mmol), tributyltin hydride (5 × 0.0051 mL, 0.019 mmol; 0.0255 mL, 0.095 mmol total), and the same volume of acetone. The crude product was obtained as a yellow amorphous solid (2.1 mg, 95%): $^1$H NMR (acetone-$d_6$) $\delta$: 3.01 (m, 4H, $CH_2$), 3.96 (d, 1H, $J$ = 2.0, H-2), 4.22 (d, 1H, $J$ = 2.0, H-1), 5.01 (dd, 1H, $J$ = 8.6, 4.6, CH), 5.12 (dd, 1H, $J$ = 6.2, 6.2, CH), 6.35-6.90 (m, 11H, aromatic), 7.62 (s, 1H, H-4). Plane polarized light was rotated in a counterclockwise direction (negative optical rotation). The $^1$H NMR spectrum of **315** was consistent with that reported for its enantiomer.[112]

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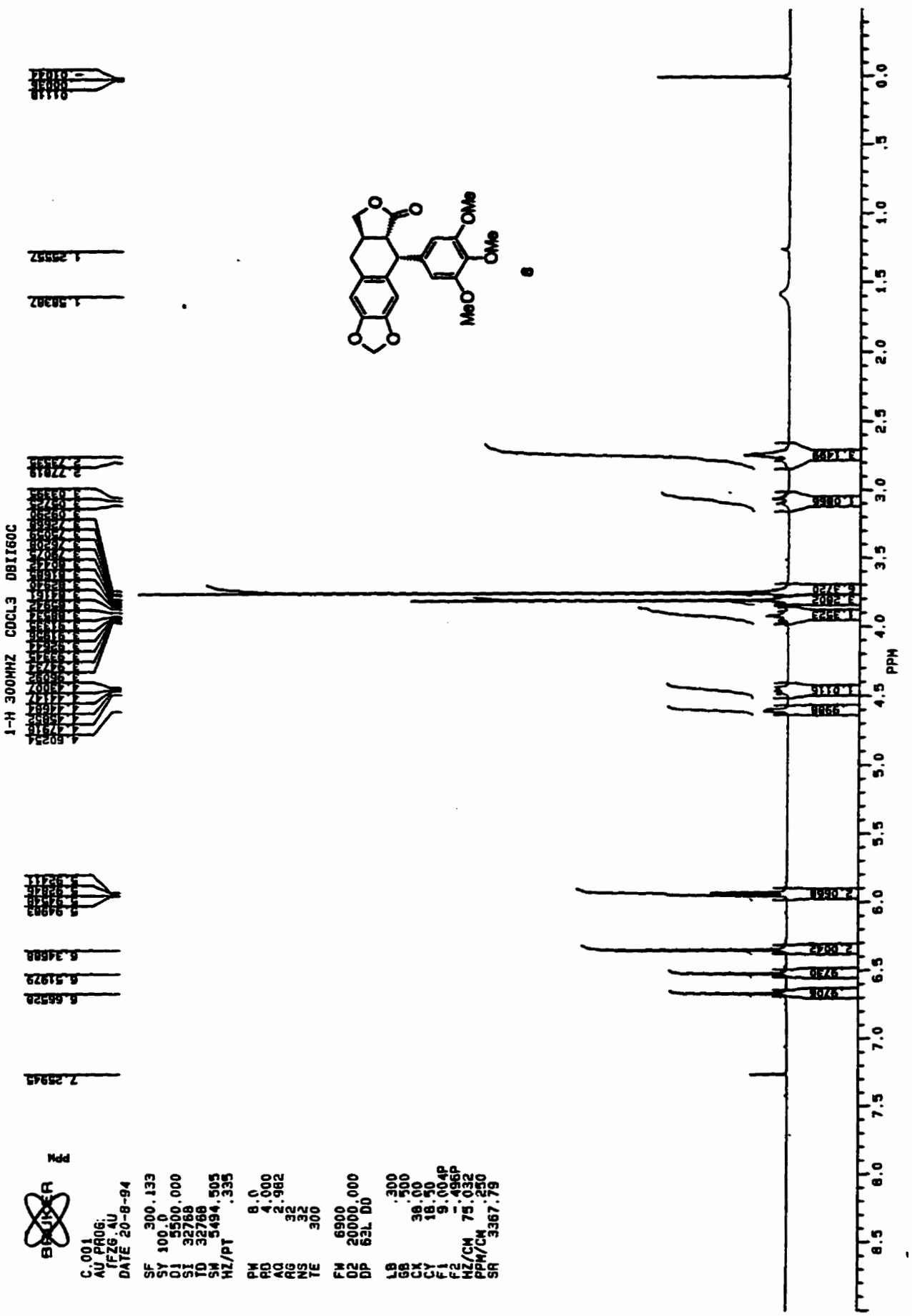
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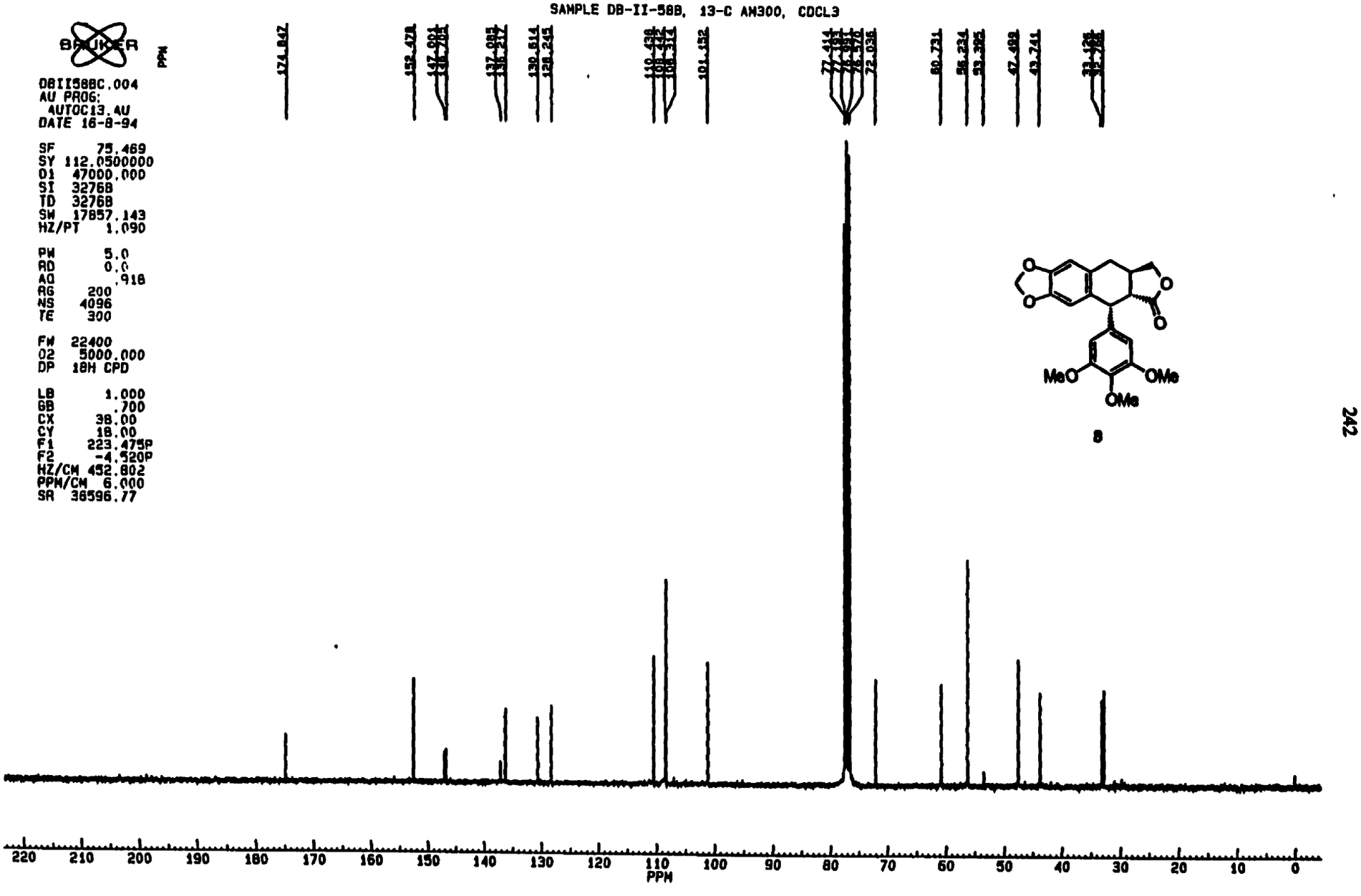
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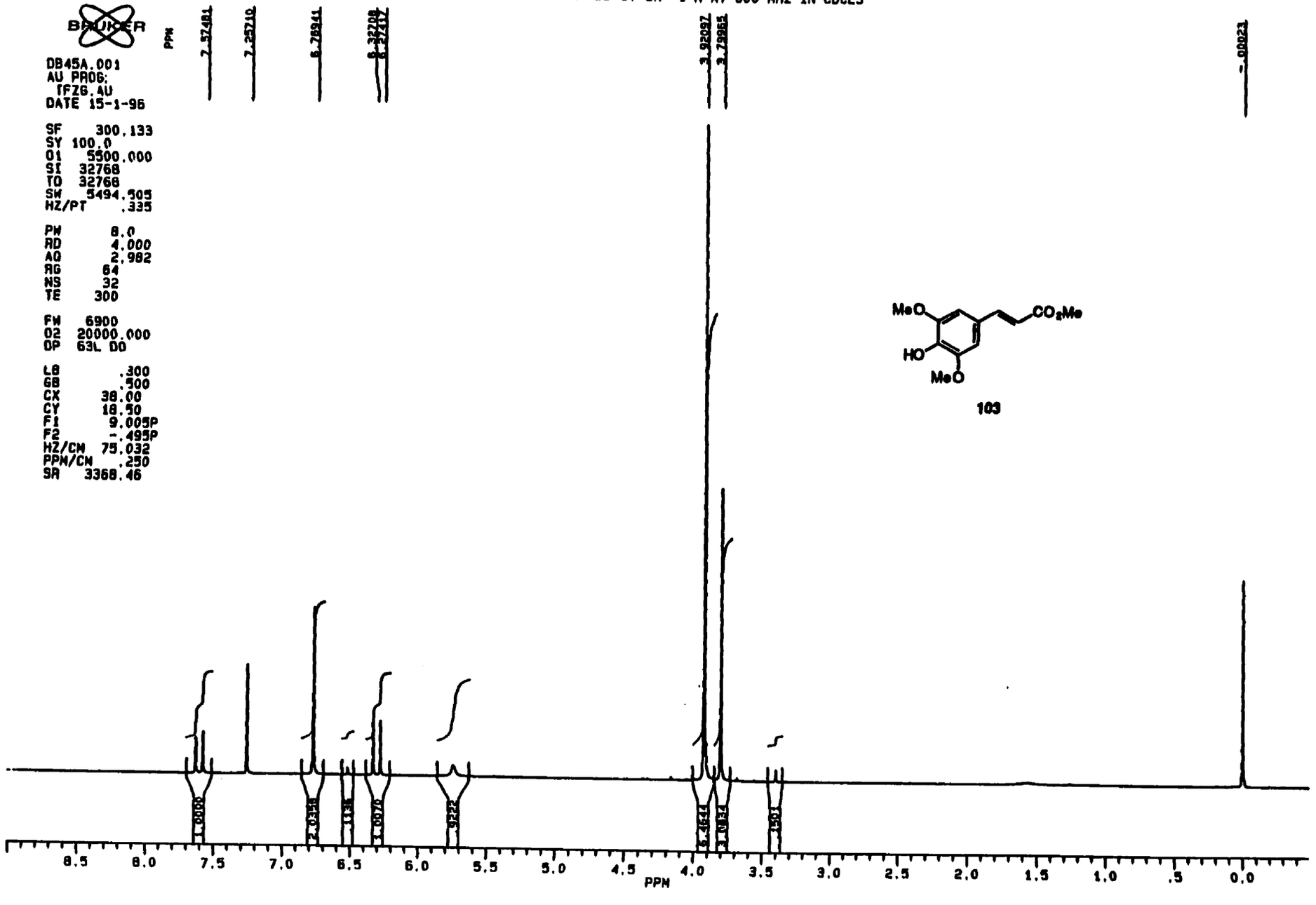

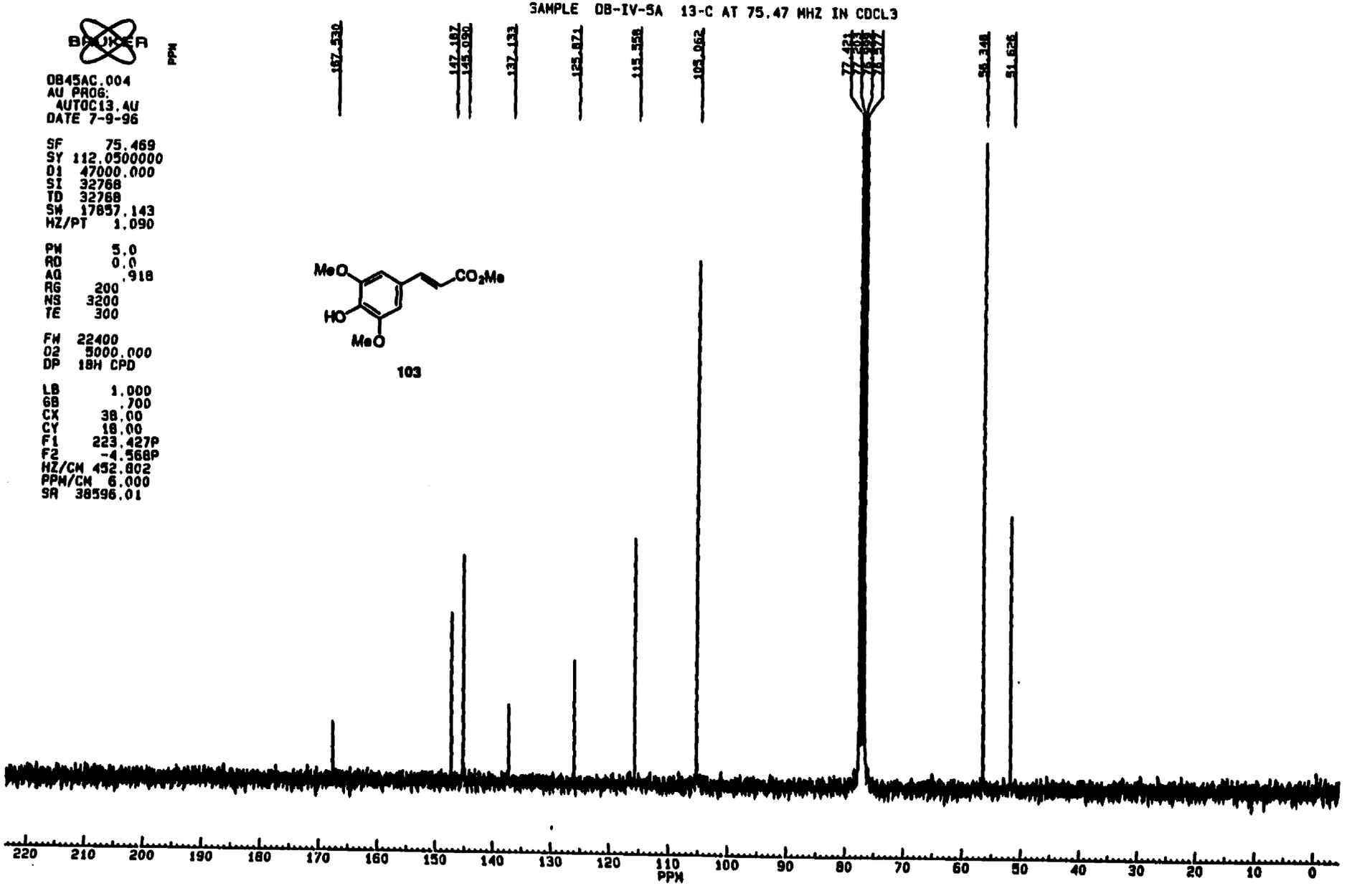
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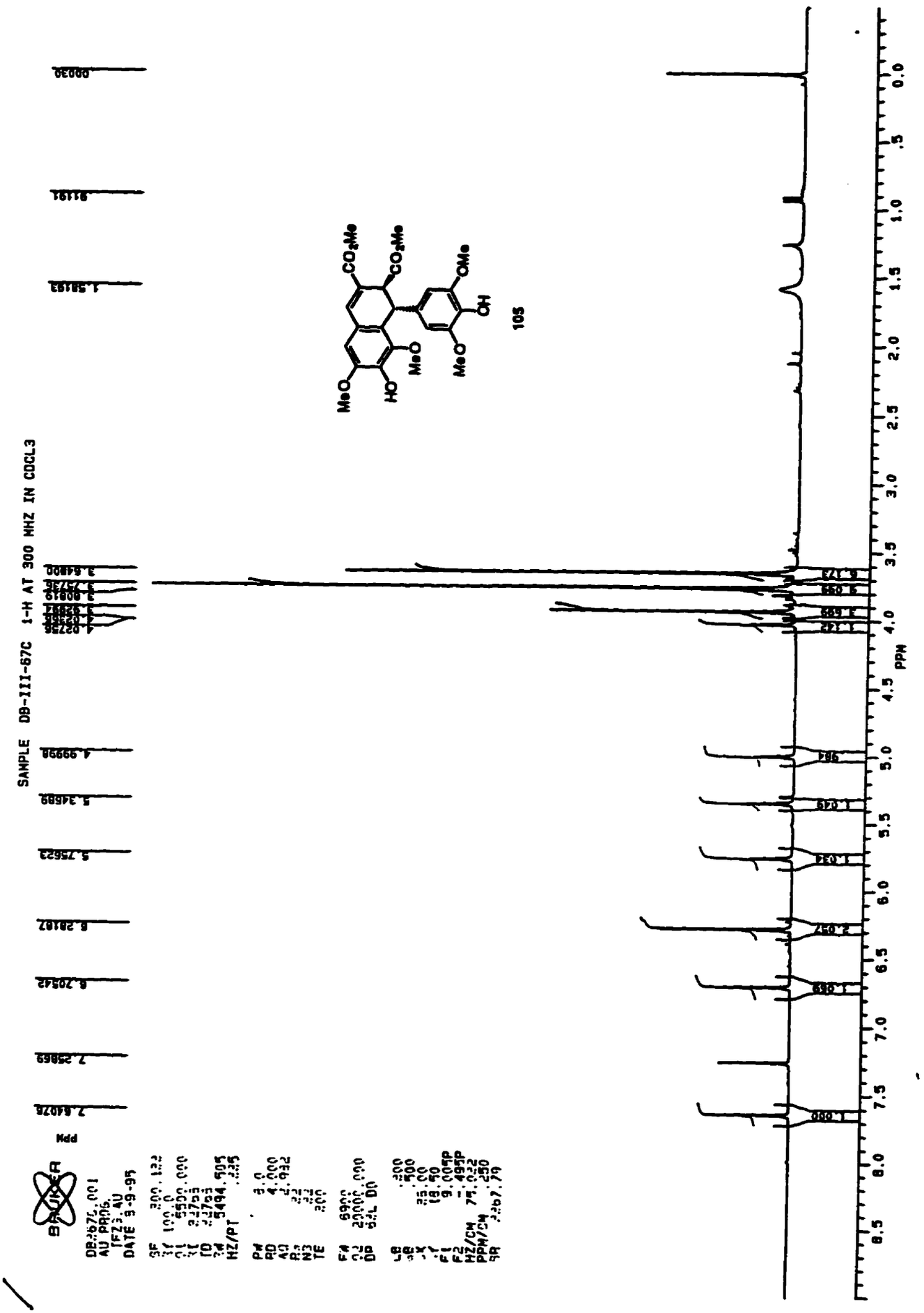
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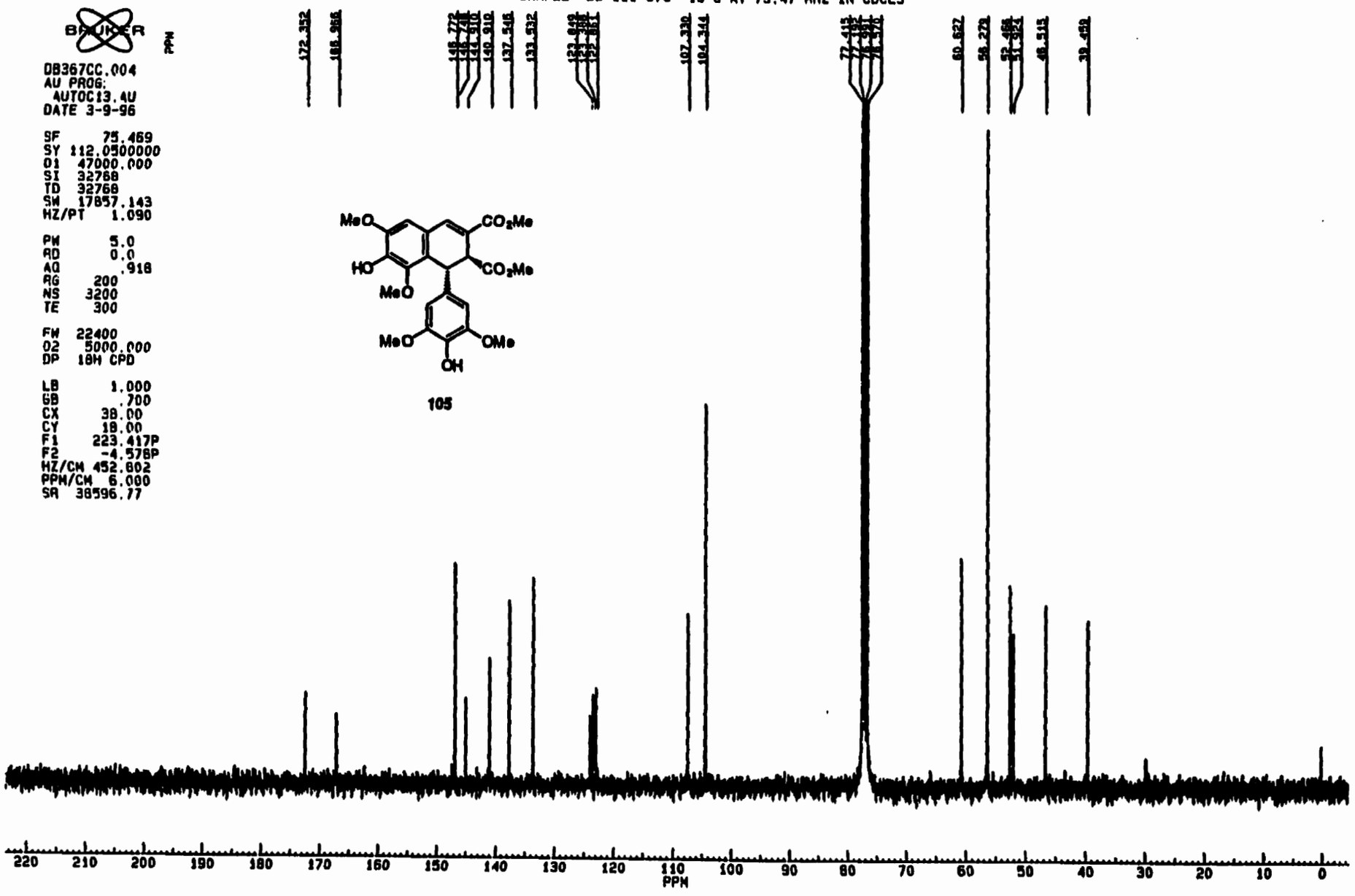

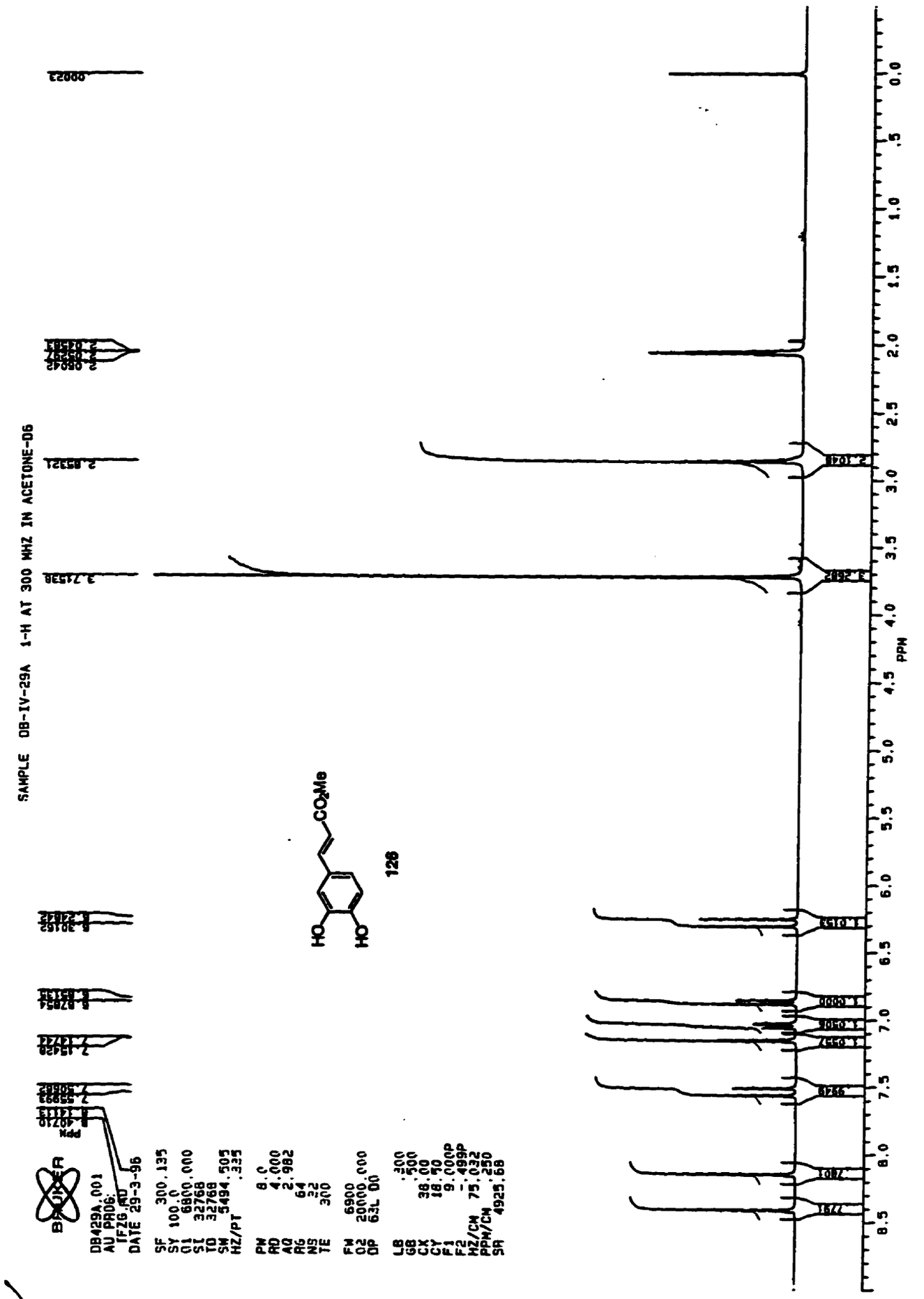
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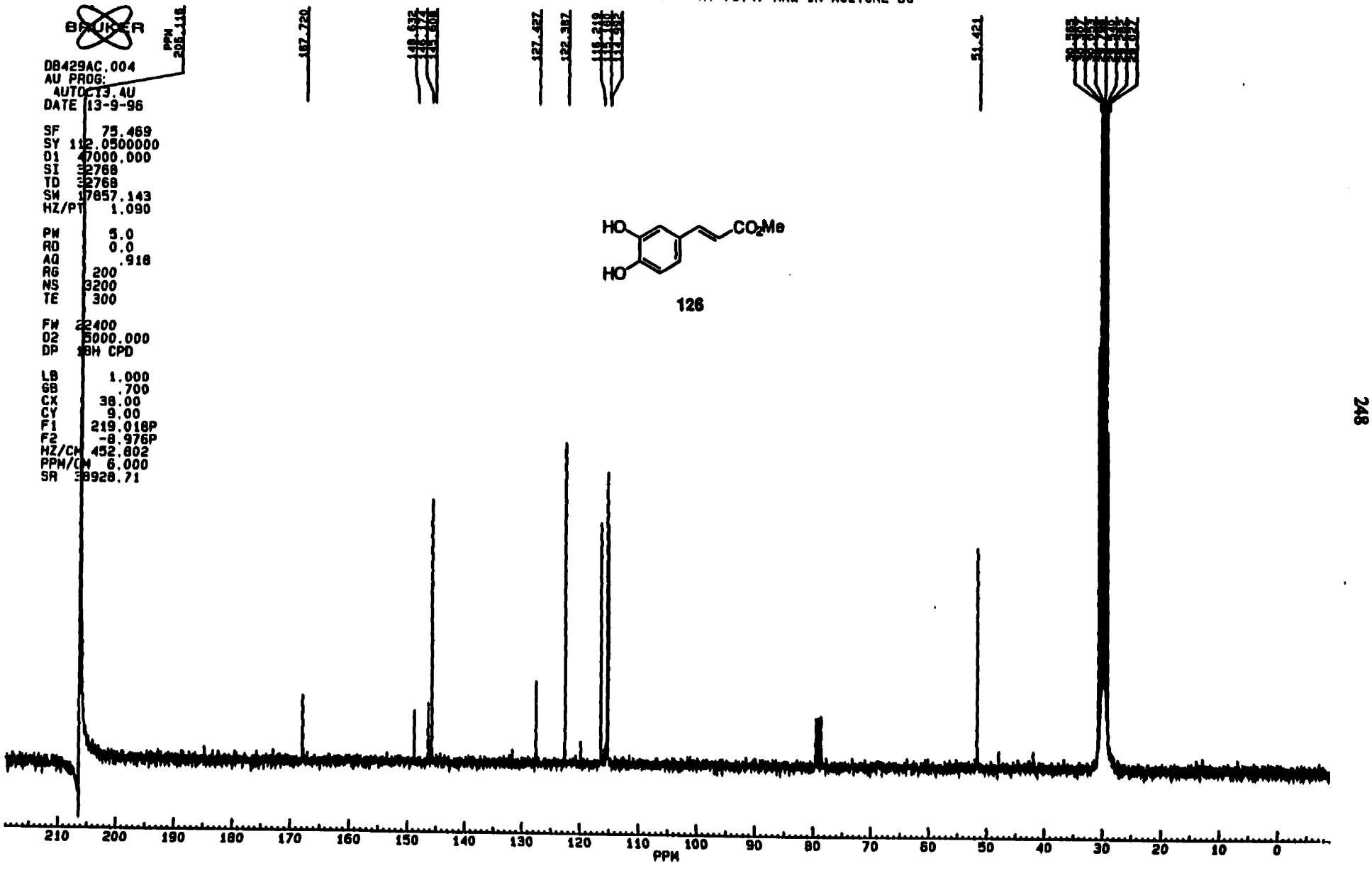

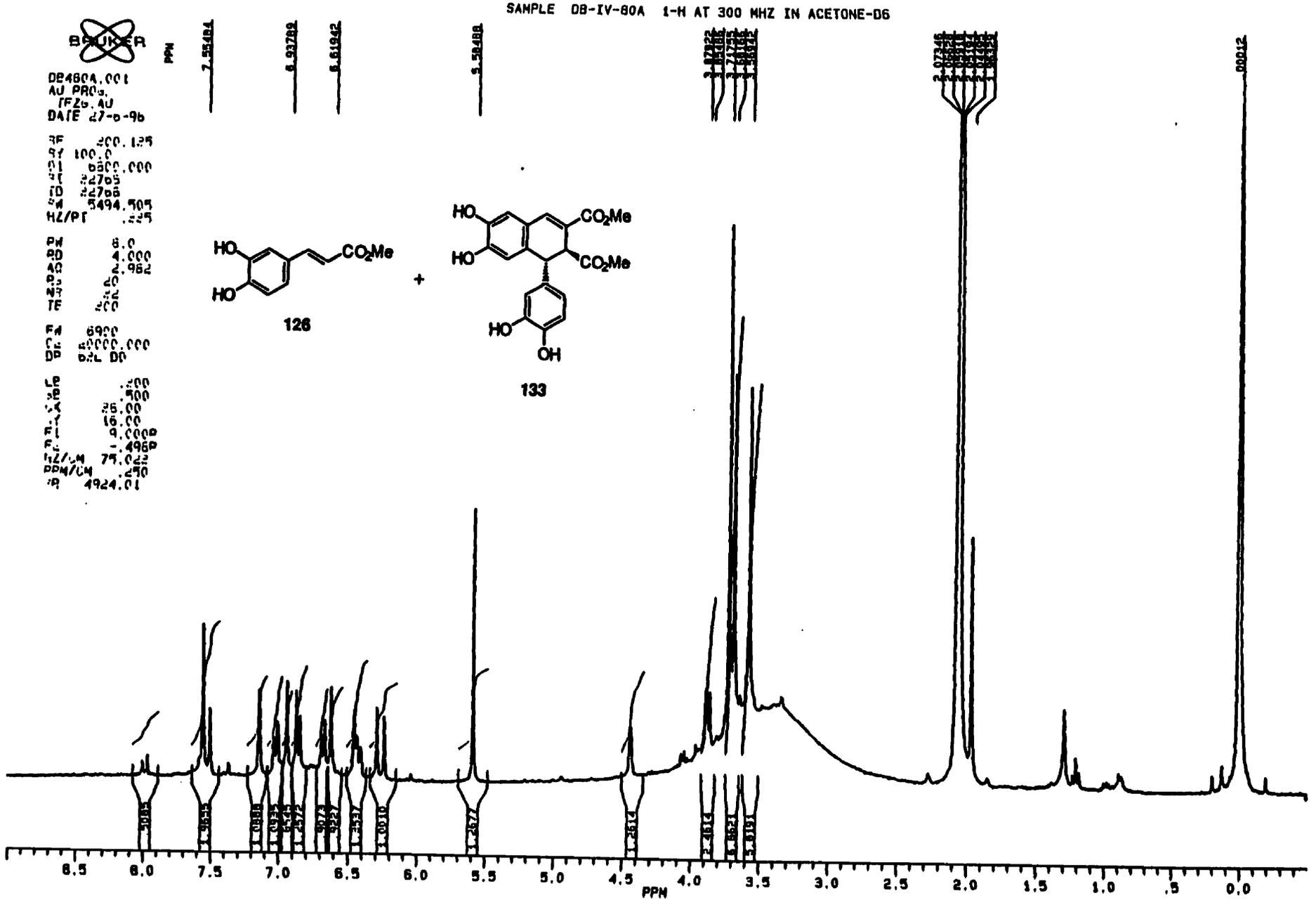
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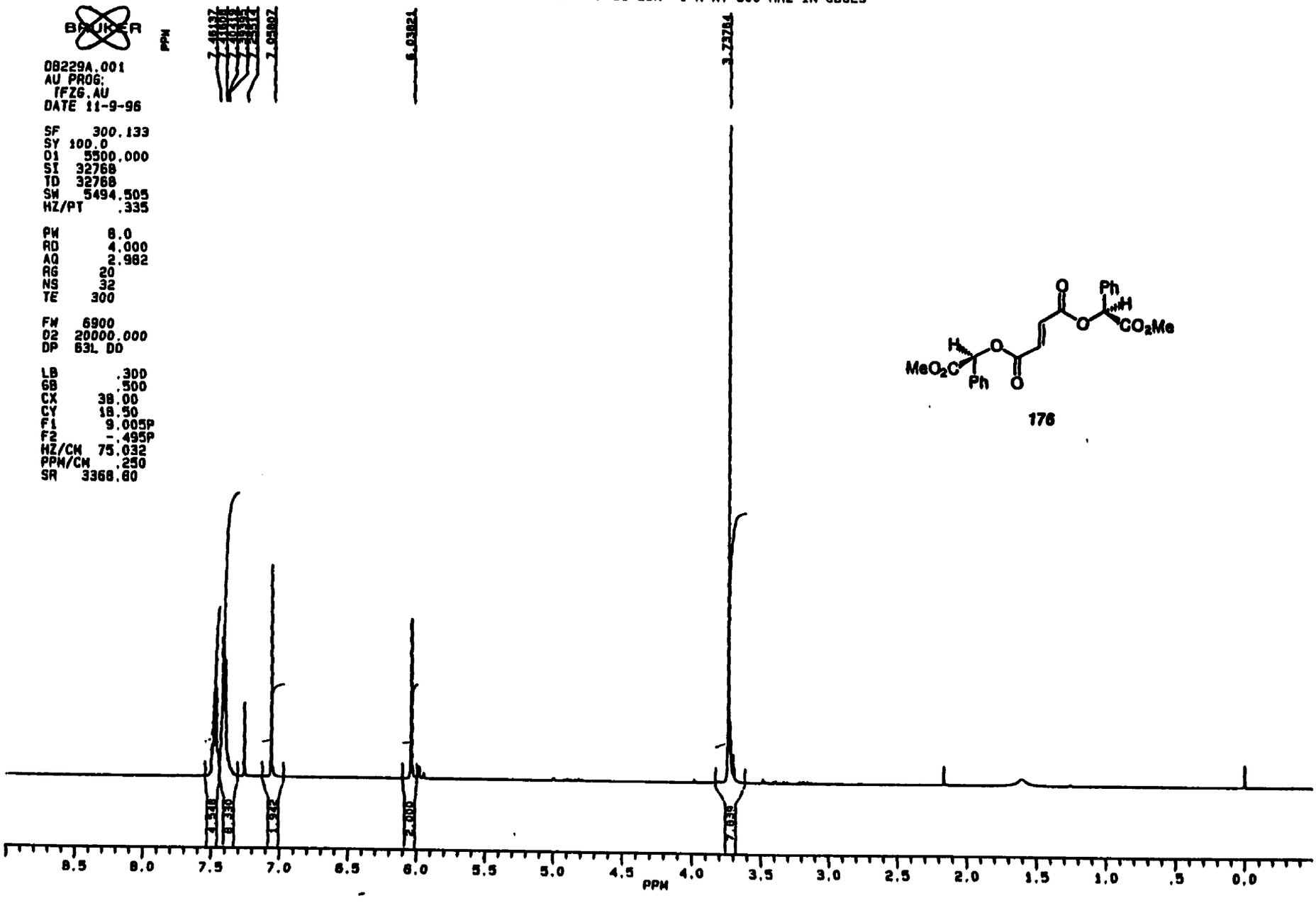





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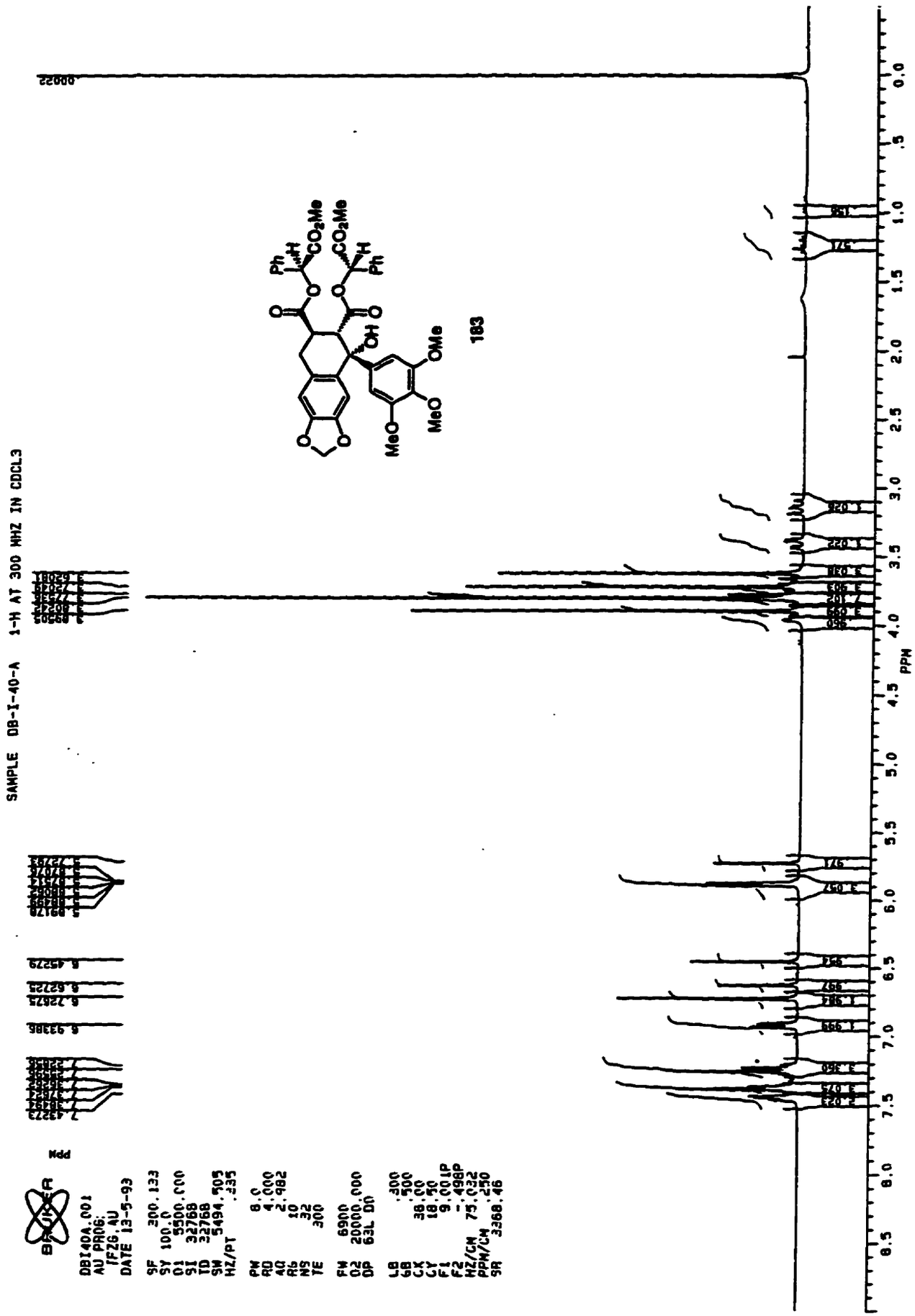
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TO 32768
SW 17857.143
HZ/PT 1.090

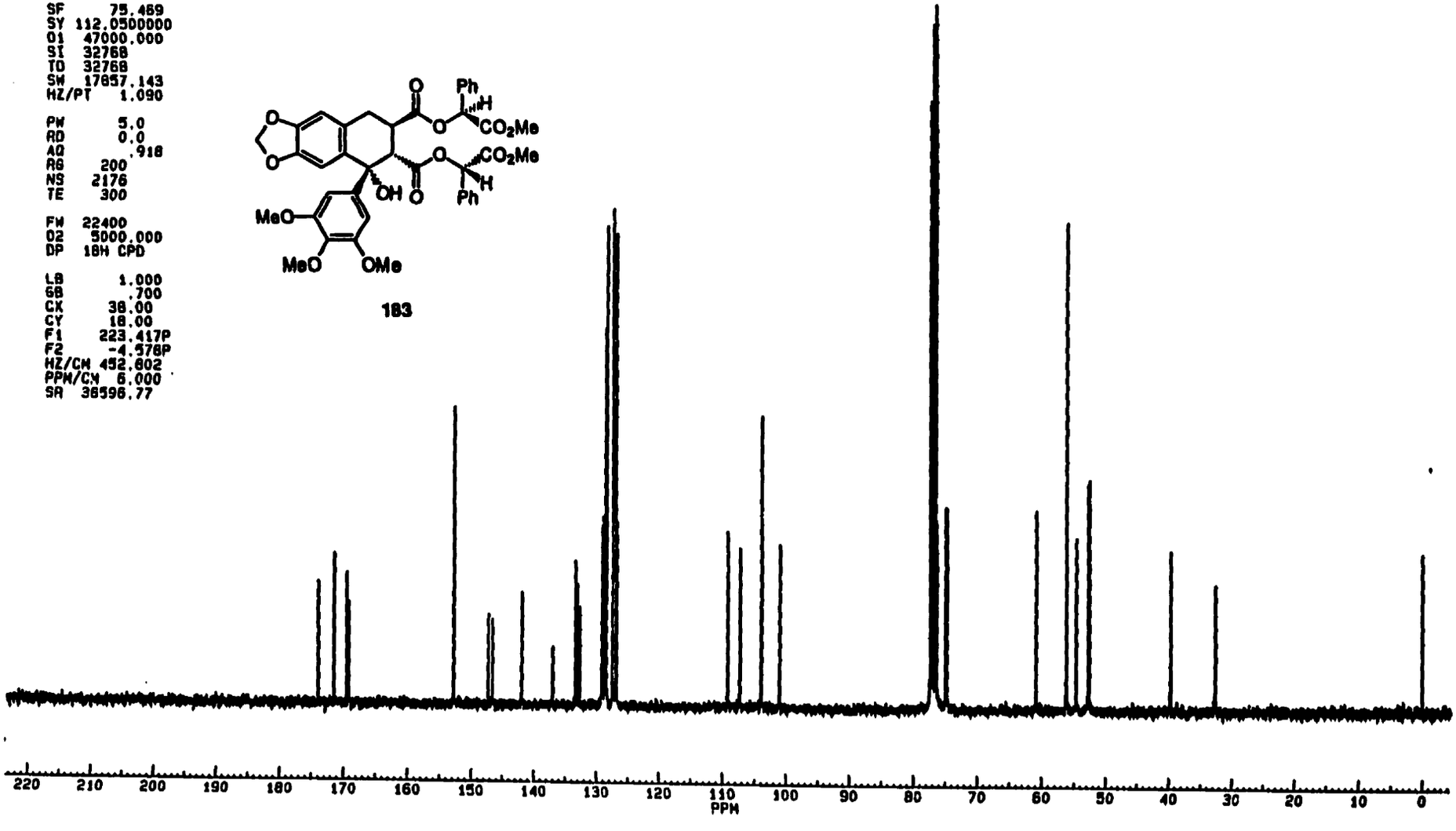
PW 5.0
RD 0.0
AQ .918
RG 200
NS 2176
TE 300

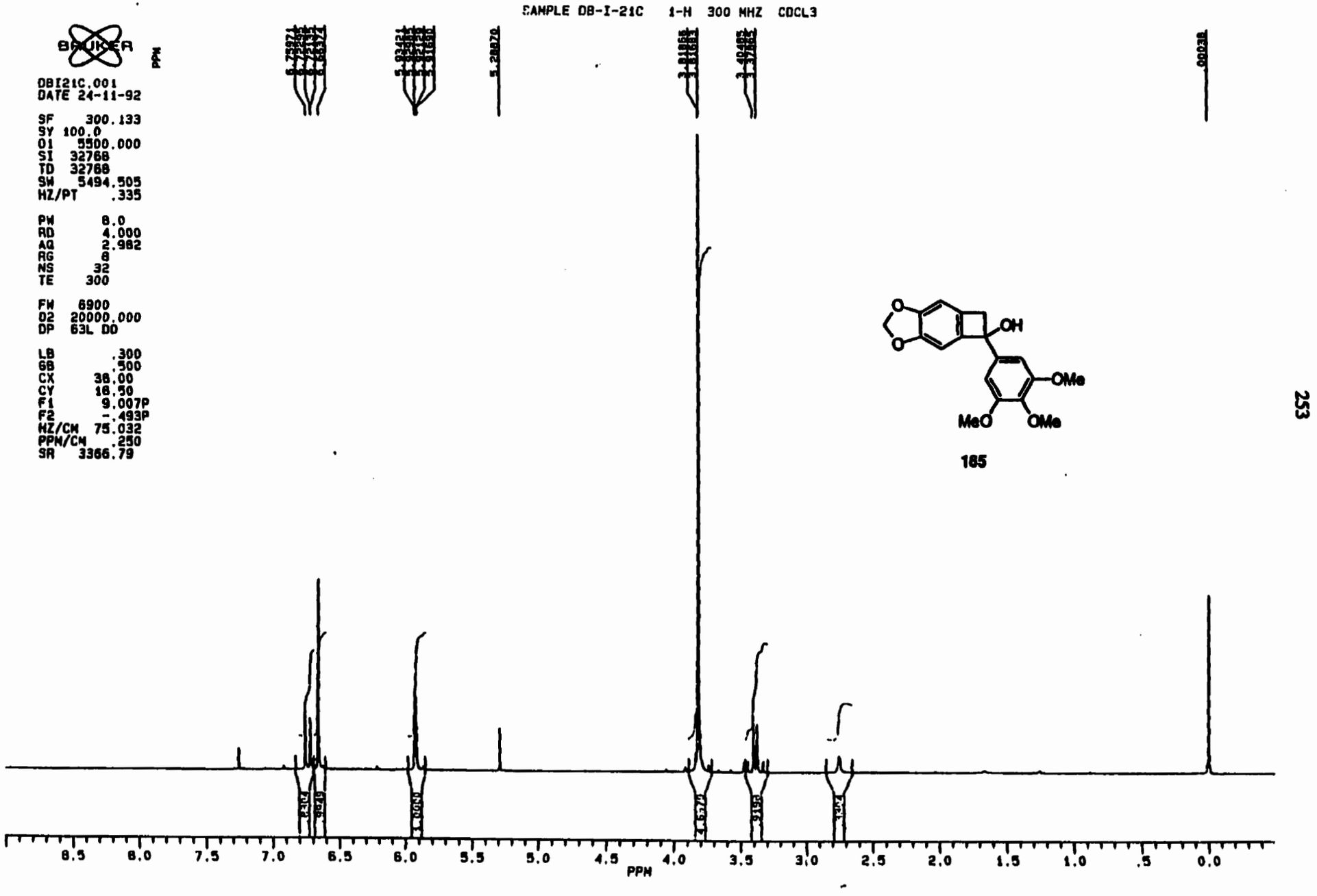
FW 22400
O2 5000.000
DP 18H CPD

LB 1.000
GB .700
CK 38.00
CY 18.00
F1 223.417P
F2 -4.576P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77

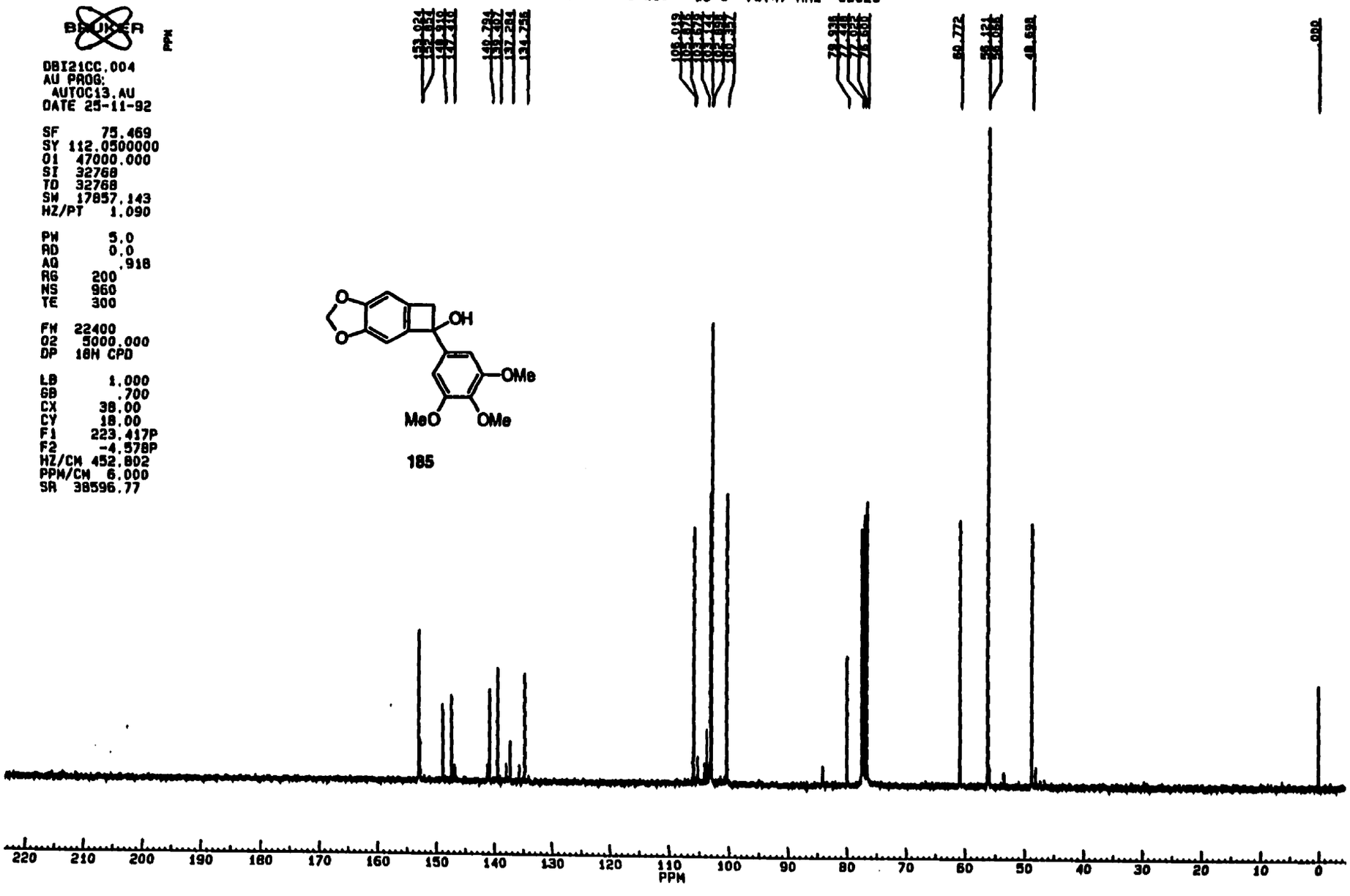


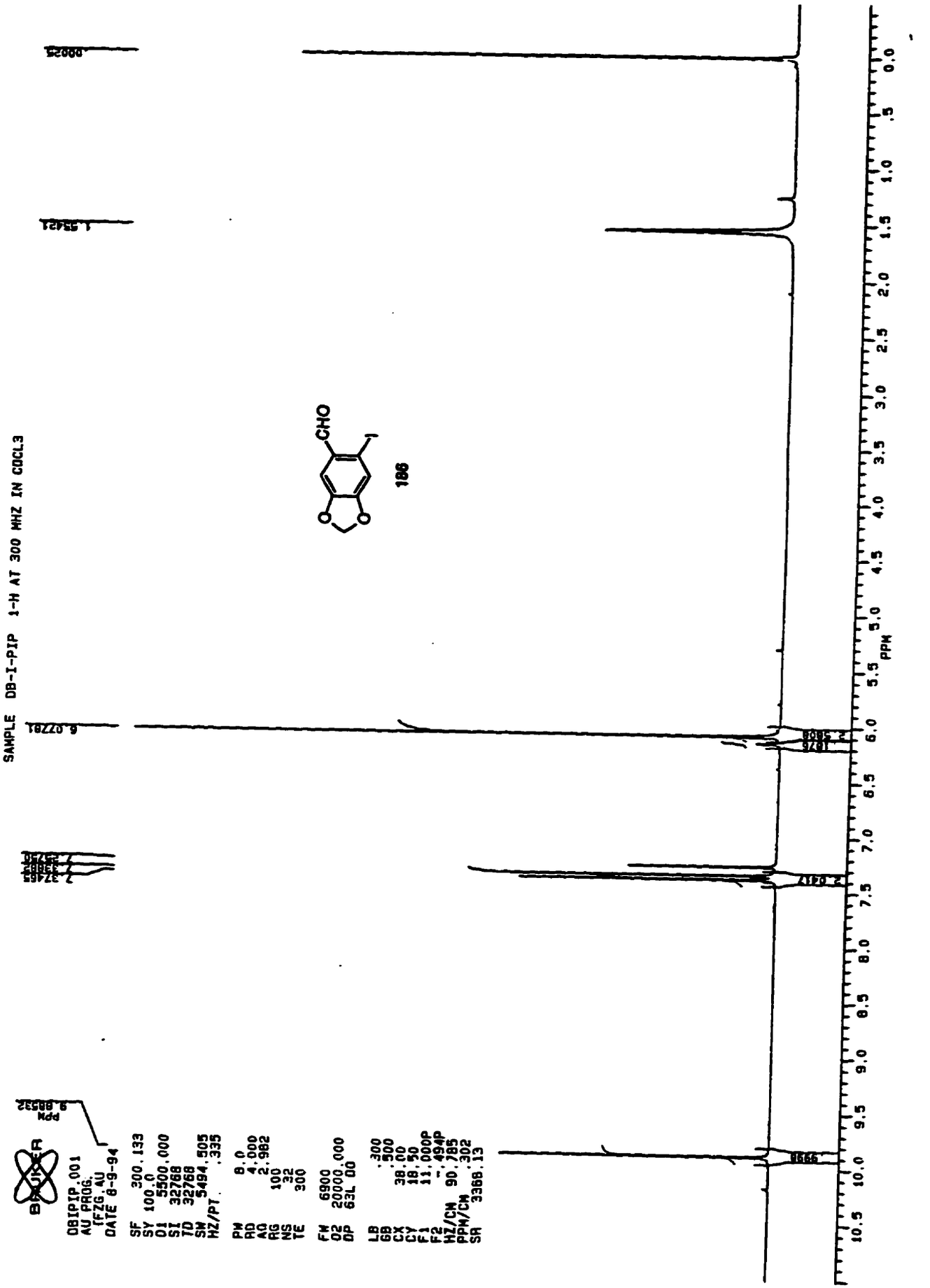

183

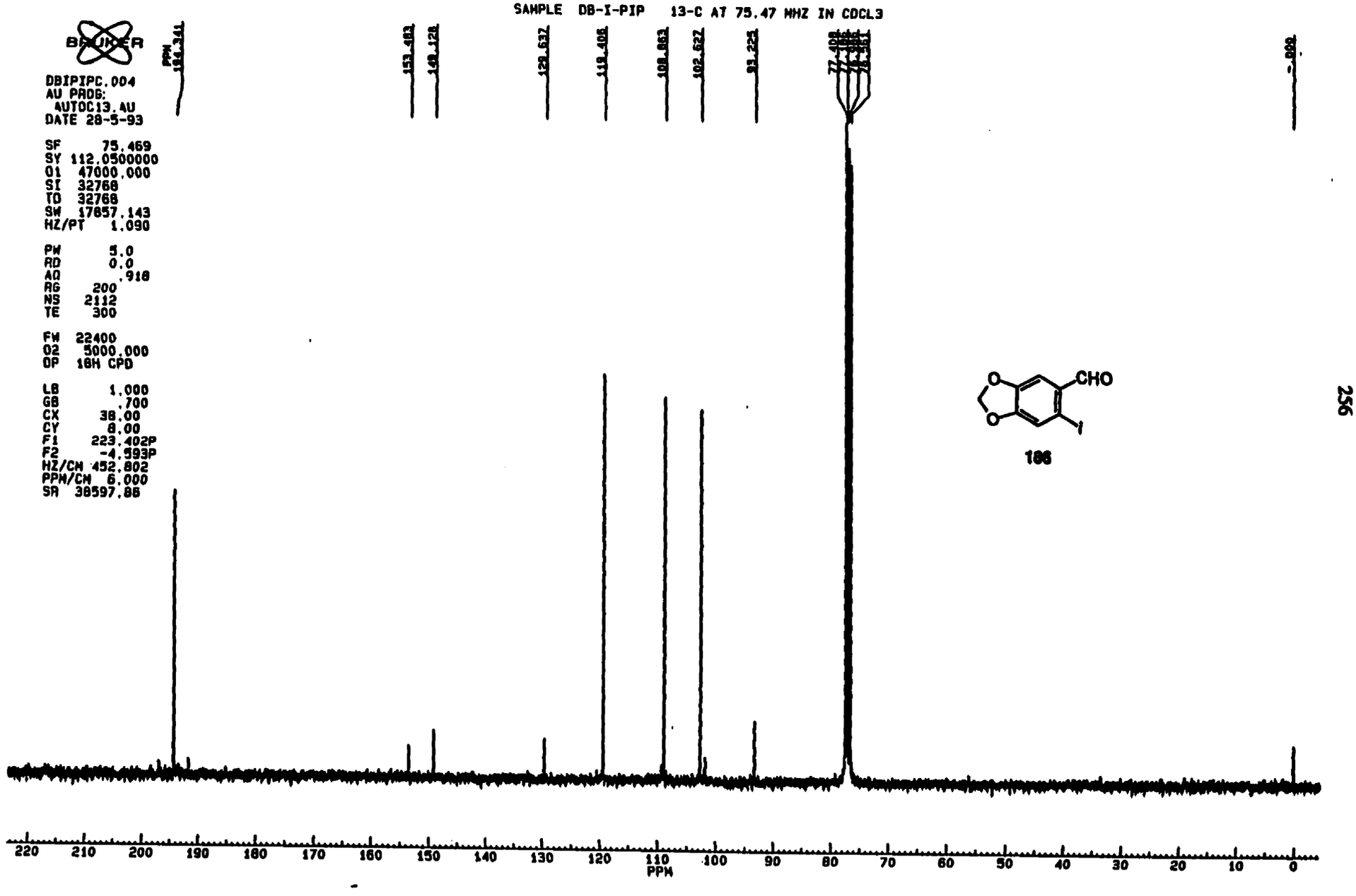



SAMPLE DB-I-21C 1-H 300 MHZ CDCL3
BRUKER
PPM
DBI21C.001
DATE 24-11-92
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.007P
F2 -.493P
HZ/CM 75.032
PPM/CM .250
SR 3366.79
OH
OMe
MeO
OMe
165
PPM

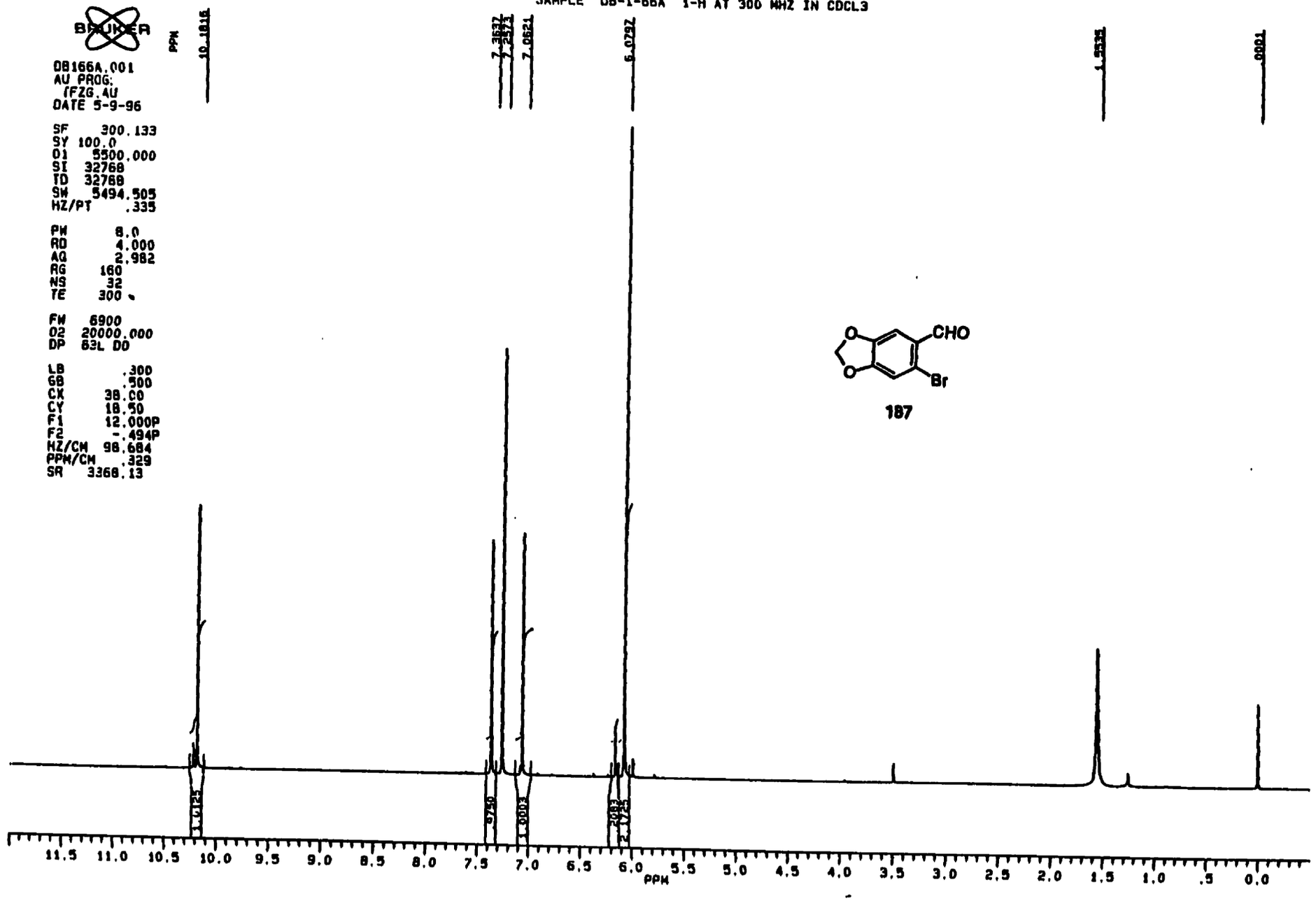
SAMPLE DB-I-21c 13-C 75.47 MHZ CDCL3

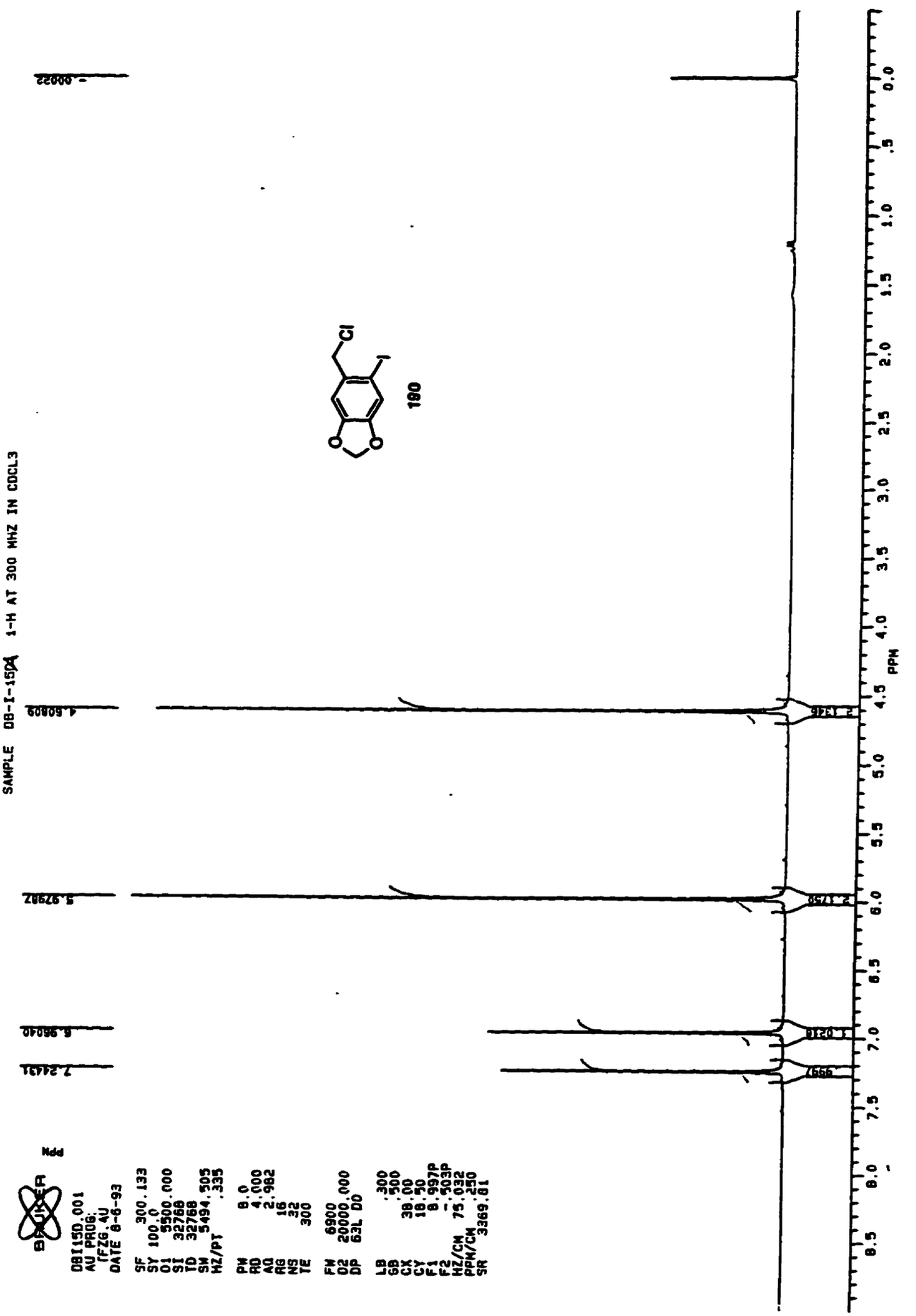


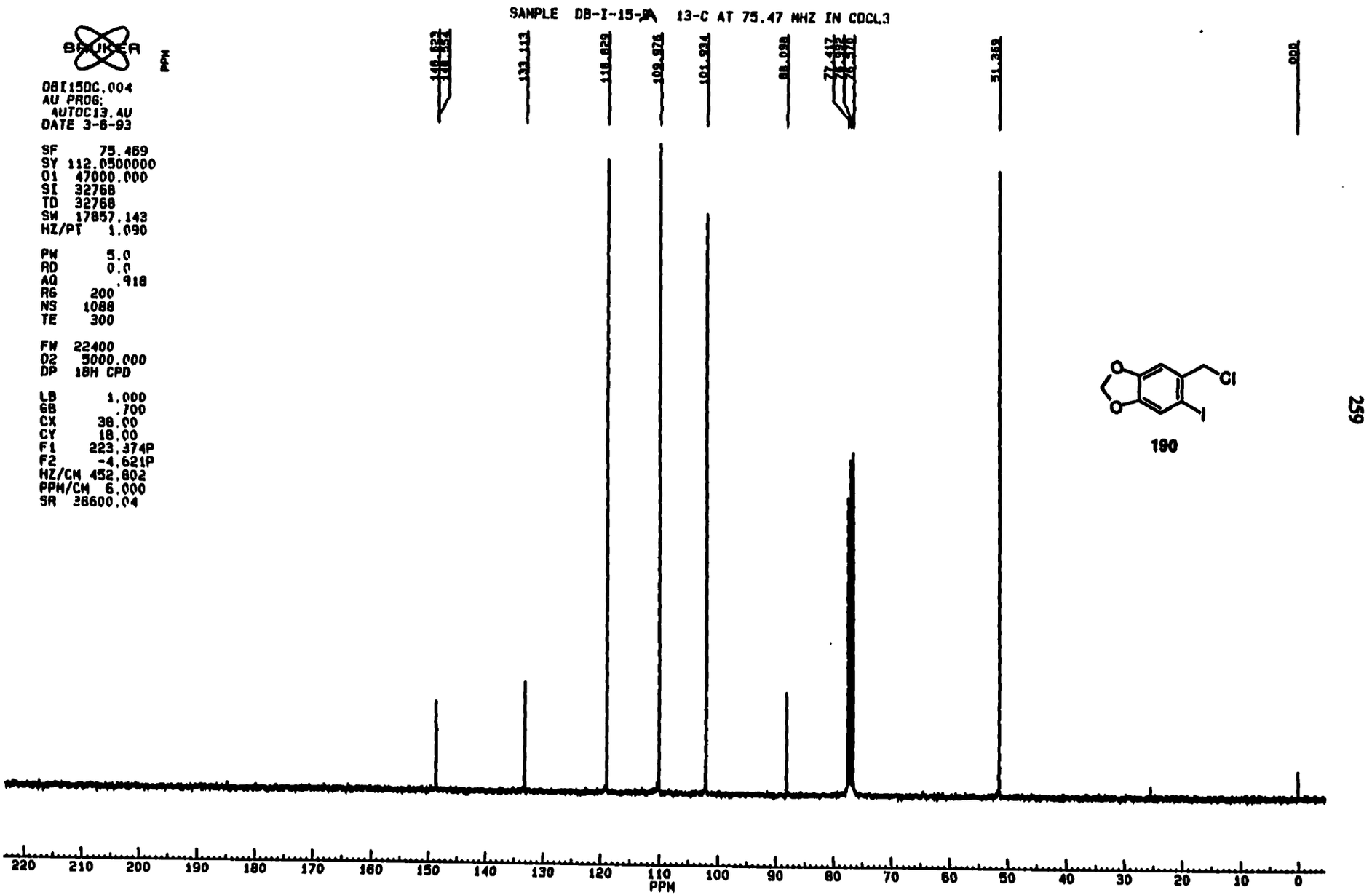

SAMPLE DB-I-PIP 1-H AT 300 MHZ IN CDCL3
CHO
186
PPM

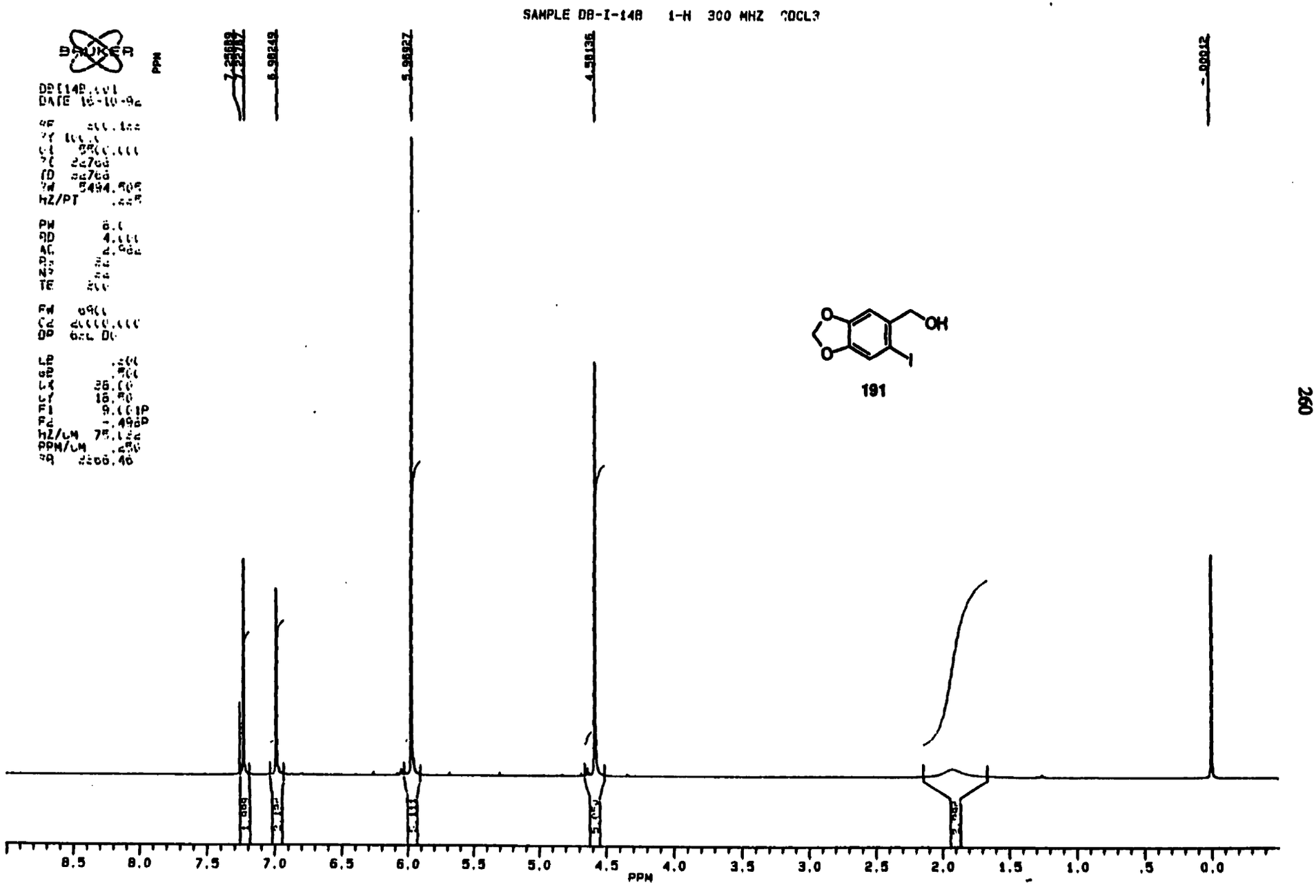

SAMPLE DB-I-PIP 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
154.341
153.483
149.128
129.637
119.408
108.863
102.622
93.225
77.408
77.151
76.894
76.261
-0.000
DBIPIPC.004
AU PROG:
AUTOC13.AU
DATE 28-5-93
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 2112
TE 300
FW 22400
O2 5000.000
OP 16H CPD
LB 1.000
GB .700
CX 38.00
CY 8.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.88
O
O
CHO
I
186
256
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

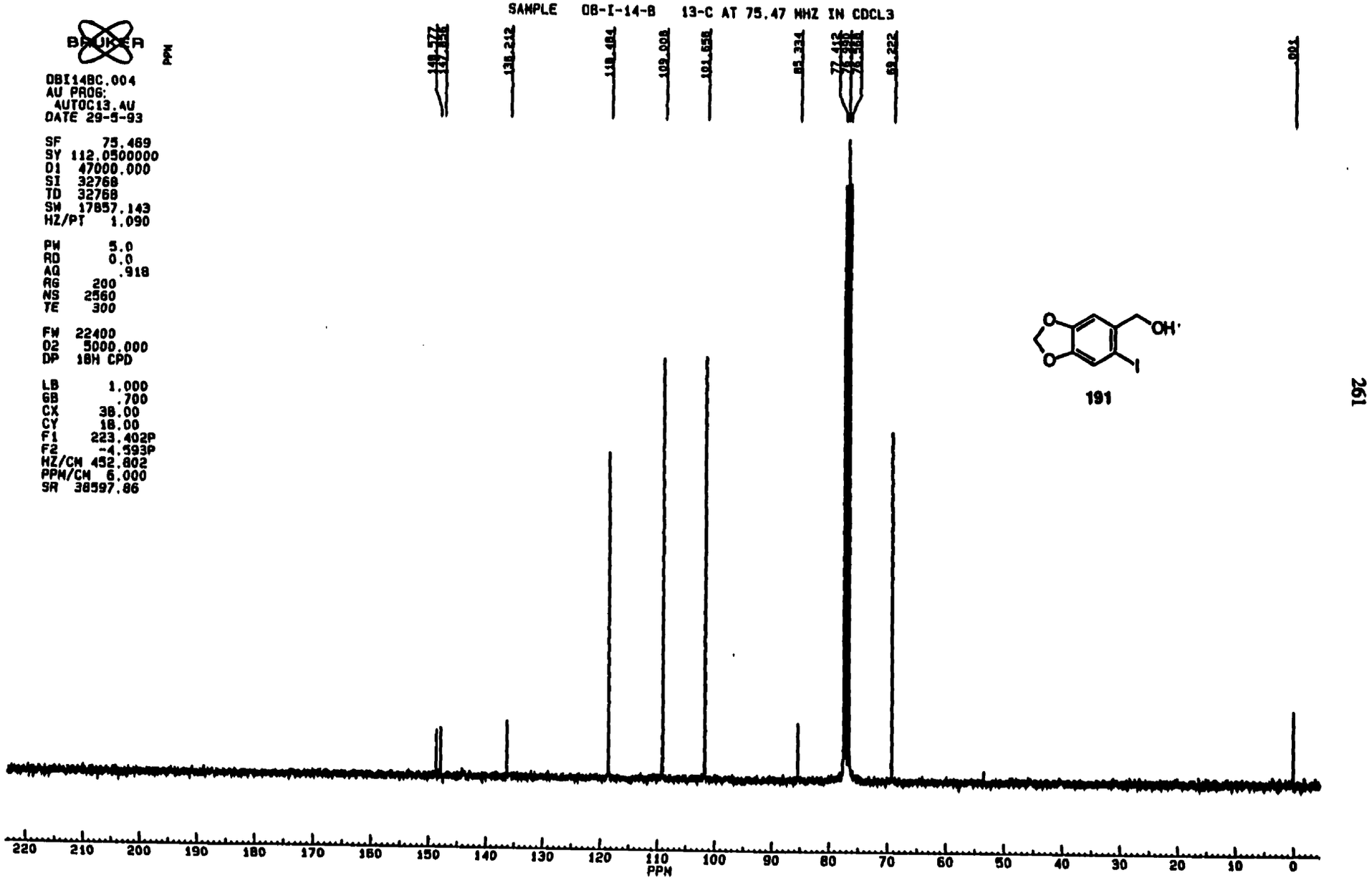
SAMPLE DB-I-66A 1-H AT 300 MHZ IN CDCL3

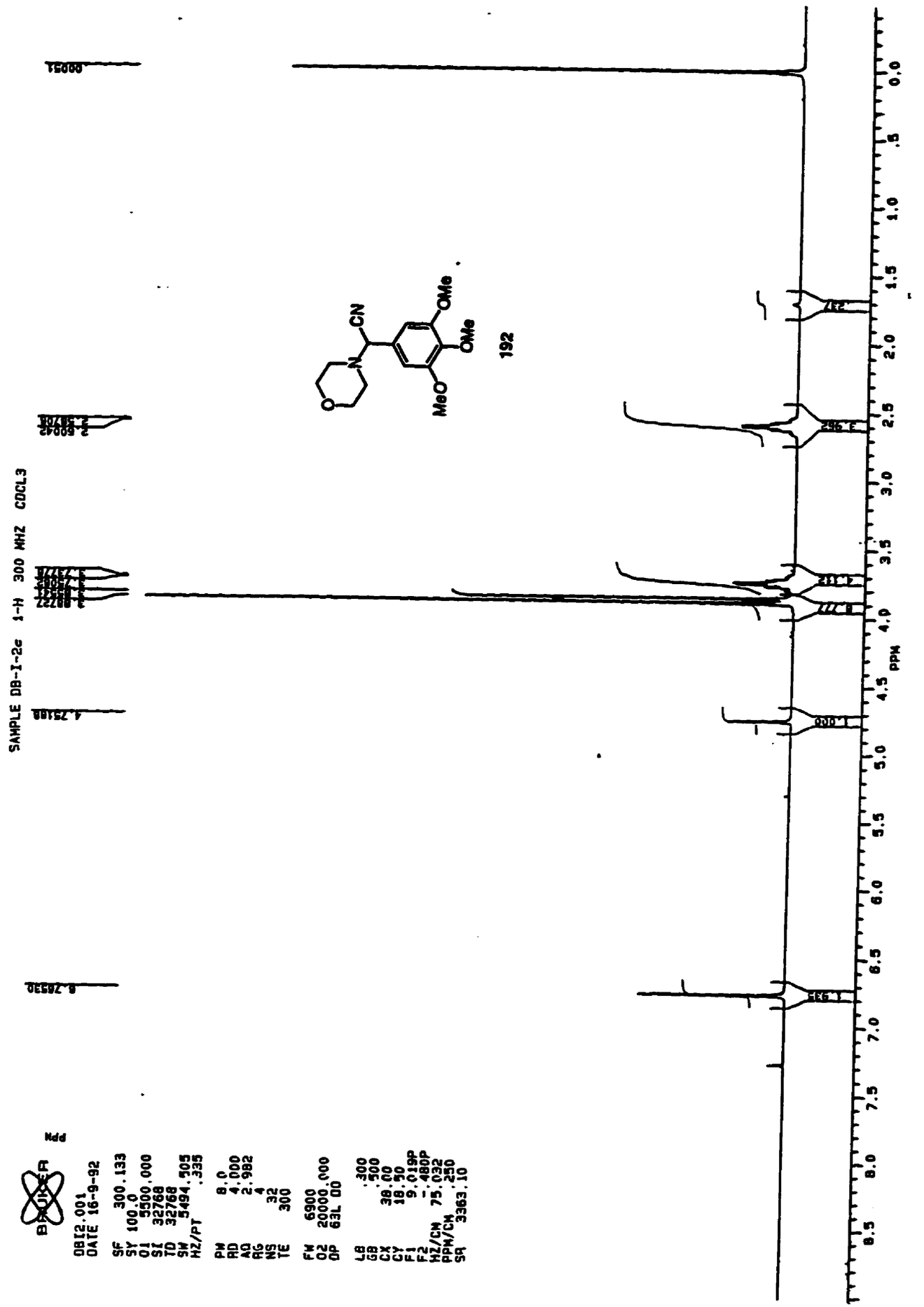


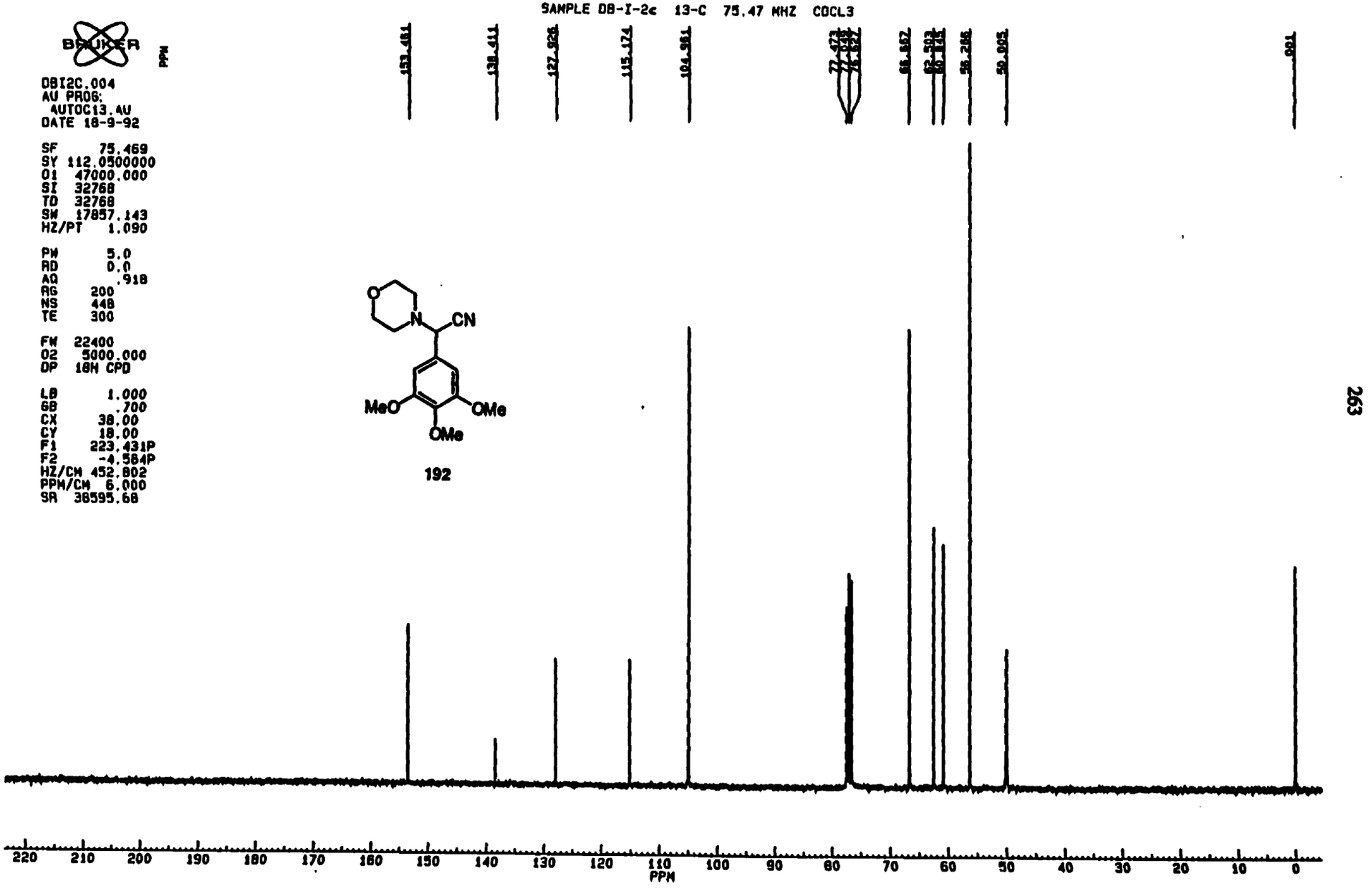

SAMPLE DB-I-150A 1-H AT 300 MHZ IN CDCL3
DB1150.001
AU PROG:
rFZ6.AU
DATE 8-6-93
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.997P
F2 .503P
HZ/CM 75.032
PPM/CM .250
SR 3369.81
PPM
180

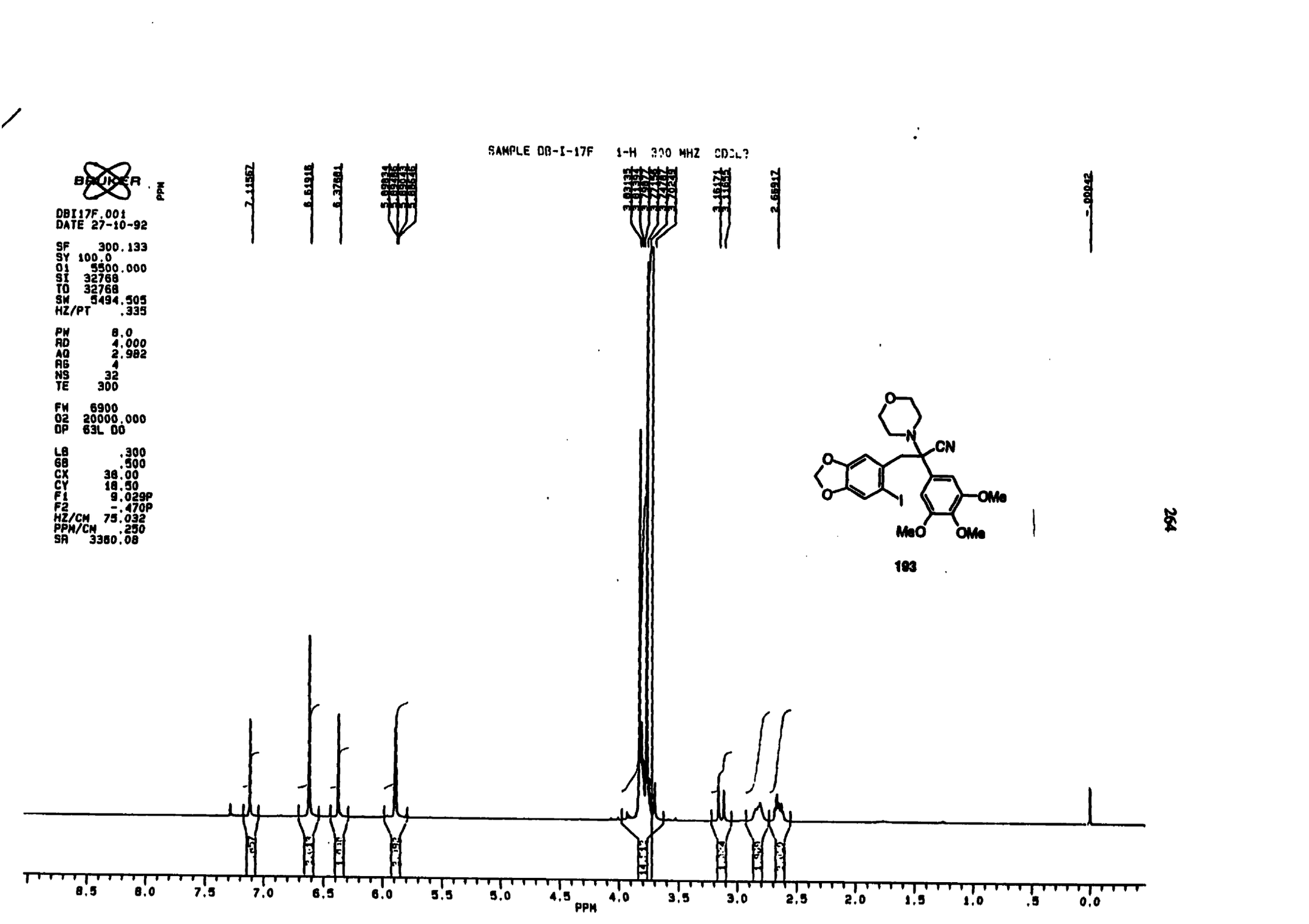

SAMPLE DB-I-15-A 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DBI15DC.004
AU PROG:
AUTOC13.AU
DATE 3-6-93
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1088
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.374P
F2 -4.621P
HZ/CM 452.802
PPM/CM 6.000
SR 38600.04
133.113
118.829
109.976
101.934
88.098
77.417
51.362
.000
Cl
I
190
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

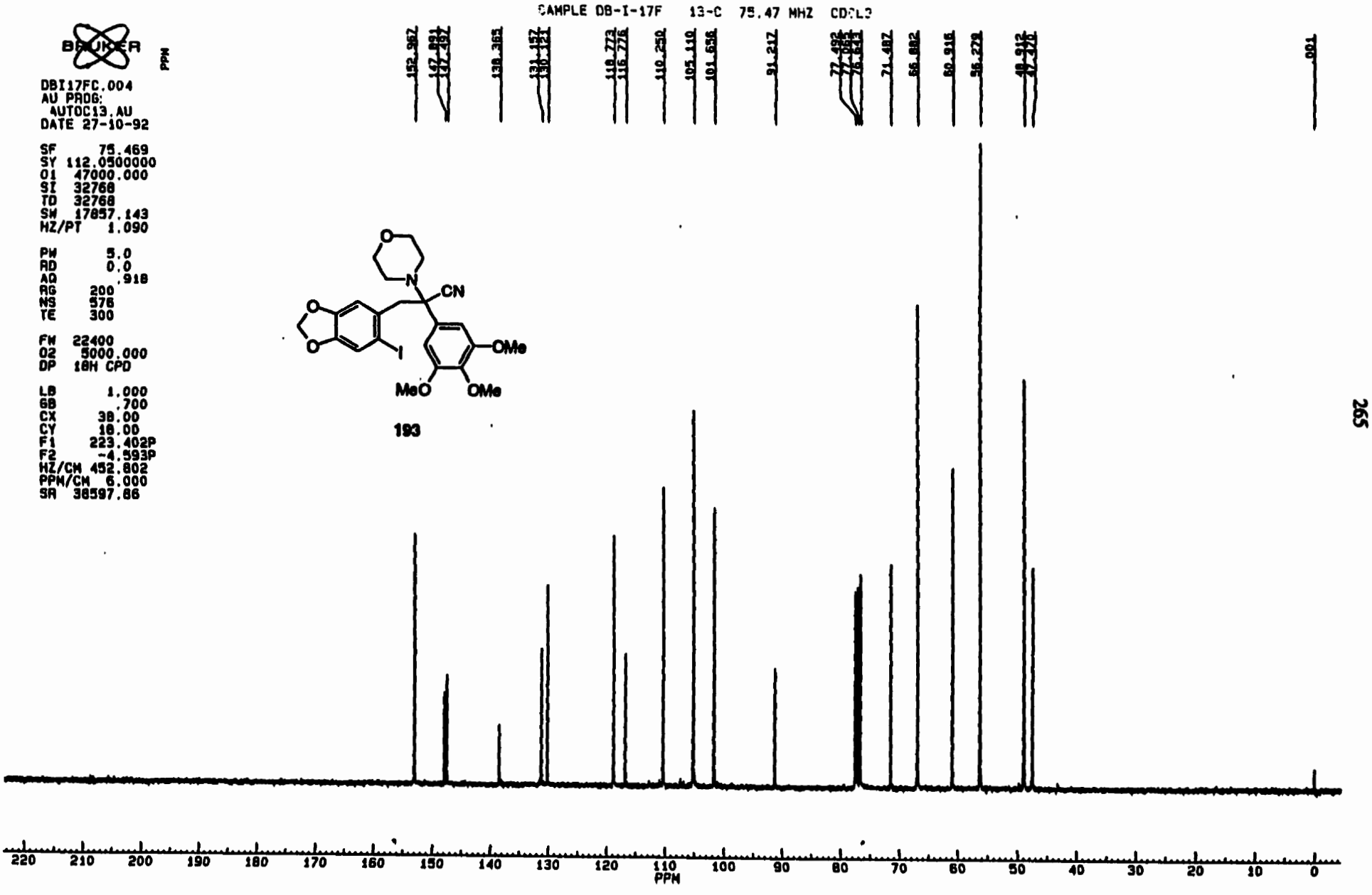

SAMPLE DB-I-148 1-H 300 MHZ CDCL3
BRUKER
PPM
6.98249
5.96927
4.58136
OH
191
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

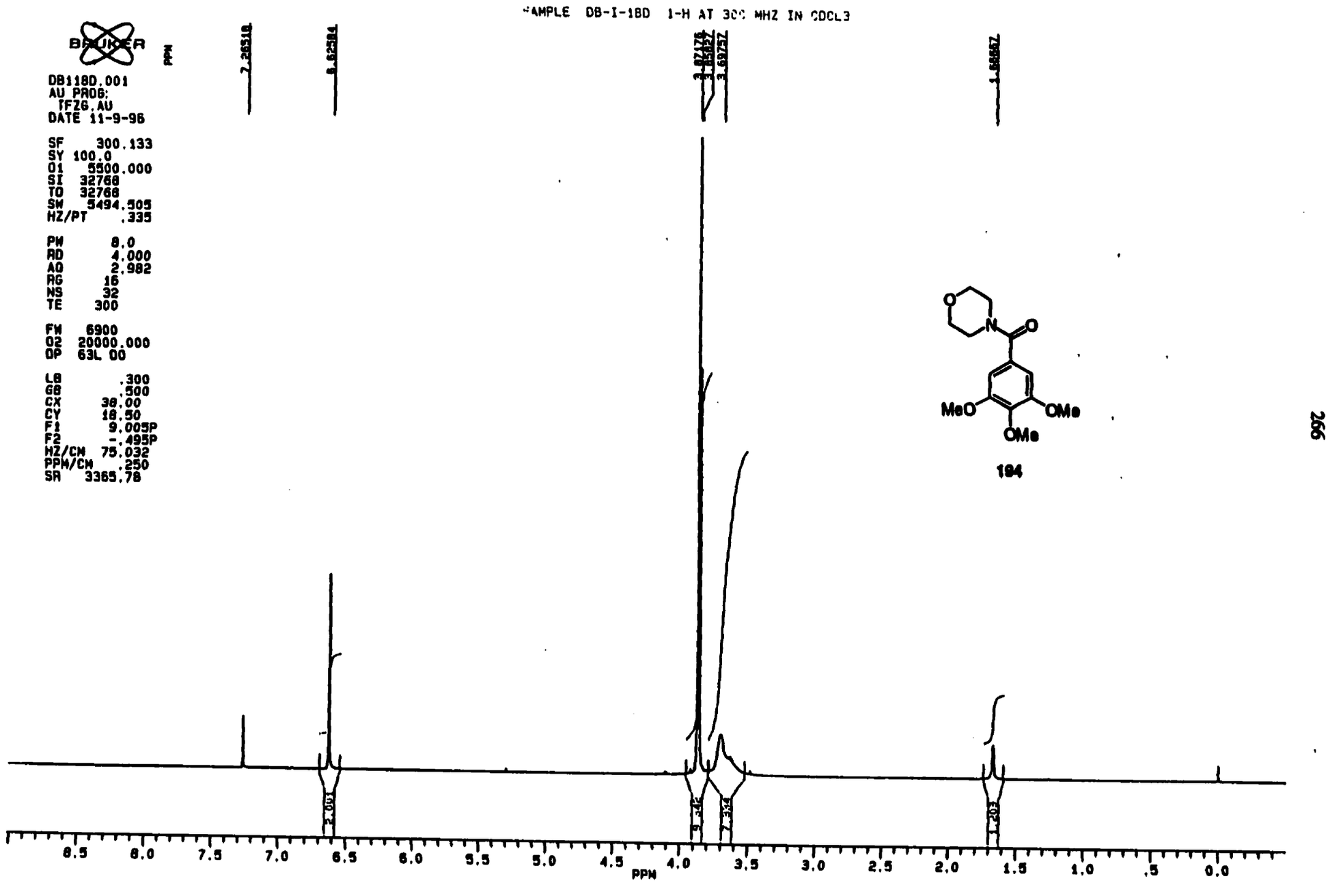

SAMPLE OB-I-14-B 13-C AT 75.47 MHZ IN CDCL3
PPM
OBI14BC.004
AU PROG:
AUTOC13.AU
DATE 29-5-93
SF 75.469
SY 112.0500000
D1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 2560
TE 300
FW 22400
D2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.86
OH
I
191
PPM

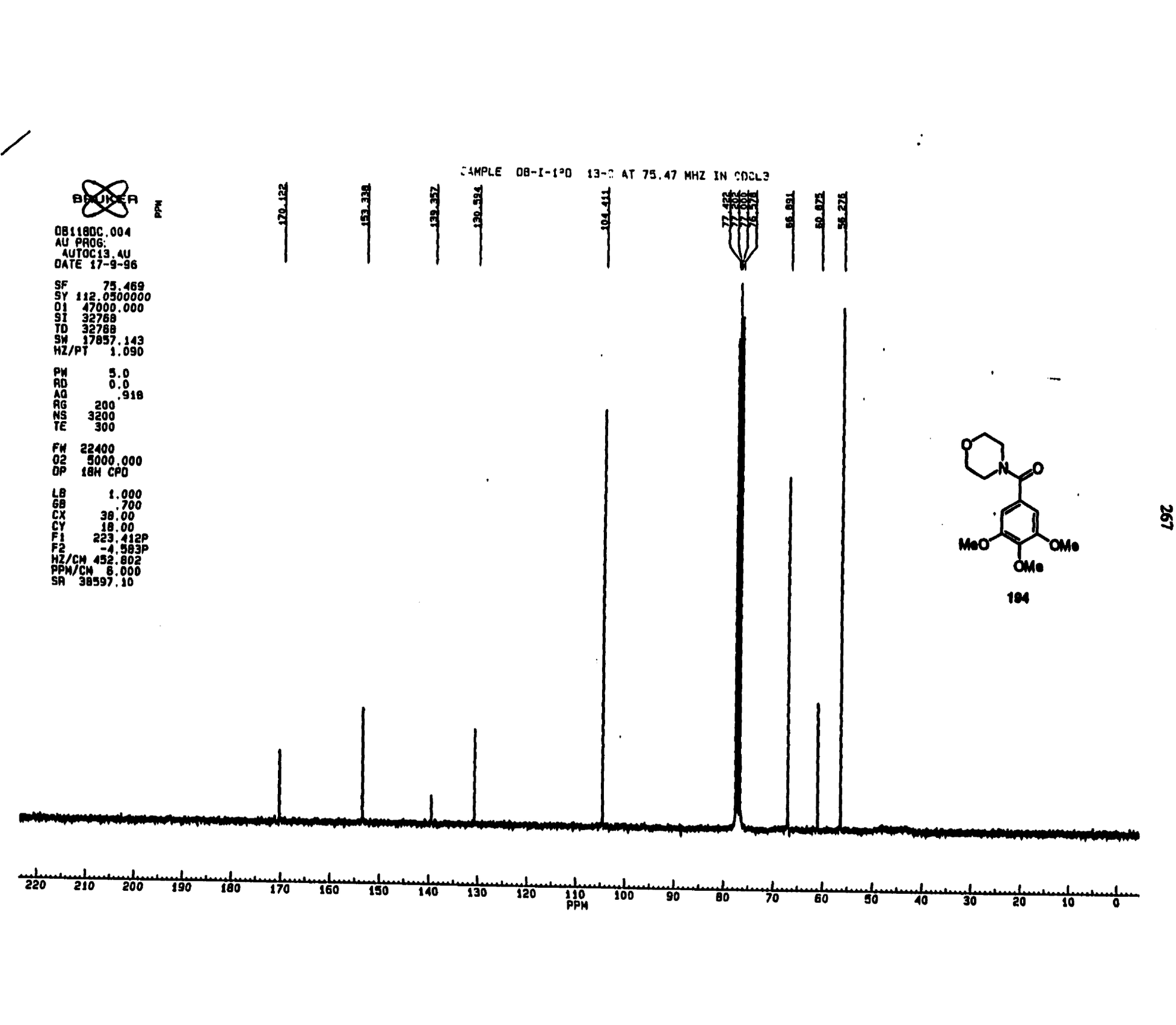

SAMPLE DB-I-2a 1-H 300 MHZ CDCL3
BRUKER
PPM
DB12.001
DATE 16-9-92
SF 300.133
SY 100.0
OI 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.019P
F2 -.480P
HZ/CM 75.032
PPM/CM .250
SR 3363.10
CN
N
O
OMe
OMe
MeO
192
PPM


SAMPLE DB-I-2c 13-C 75.47 MHZ CDCL3
BRUKER
PPM
153.481
138.411
127.928
115.174
104.961
77.473
77.053
76.632
68.862
62.303
60.111
56.286
50.005
.001
DBI2C.004
AU PR06:
AUTOC13.AU
DATE 18-9-92
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 448
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.431P
F2 -4.584P
HZ/CM 452.802
PPM/CM 6.000
SR 38595.68
O
N
CN
MeO
OMe
OMe
192
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

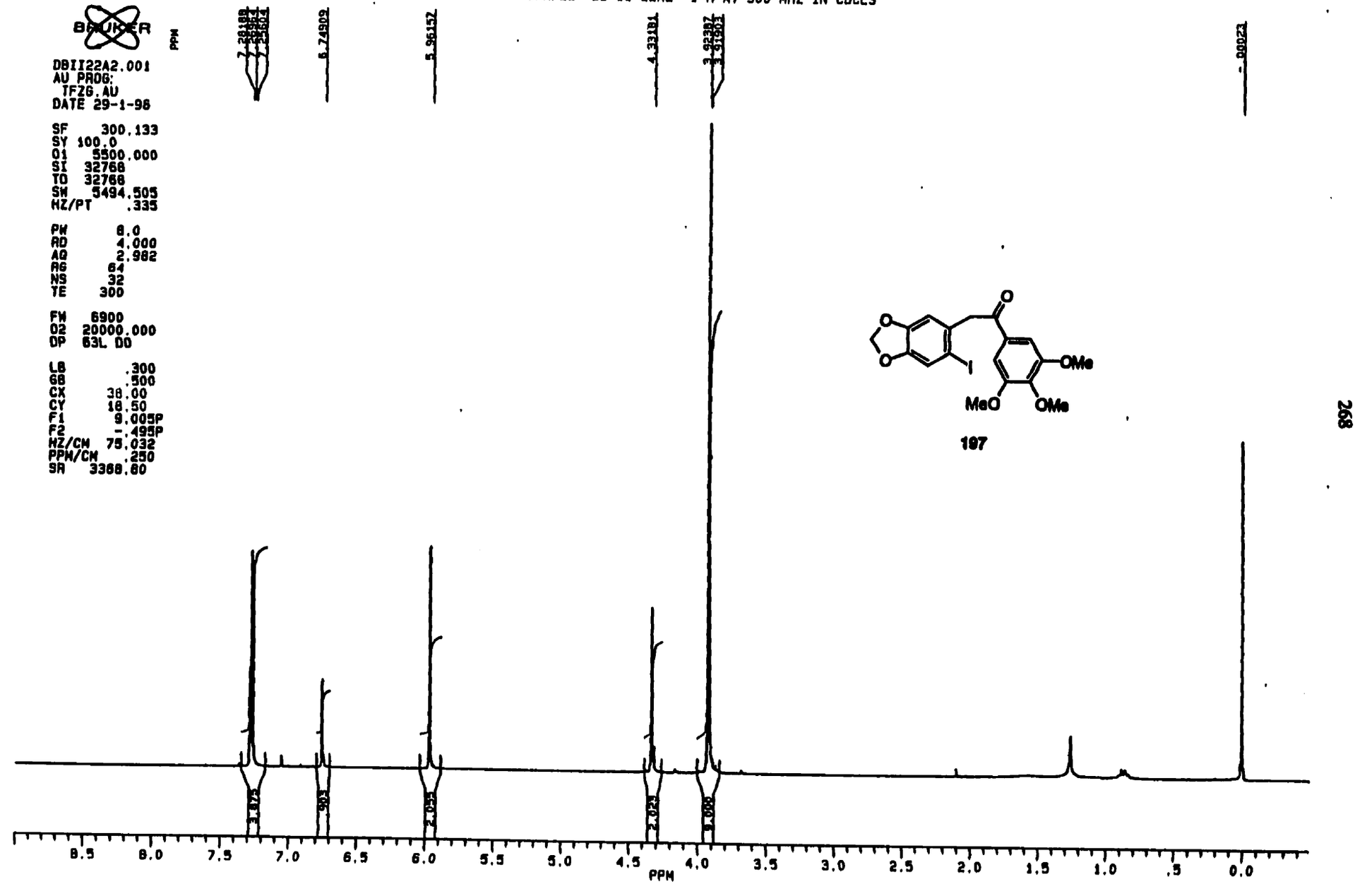

SAMPLE DB-I-17F 1-H 300 MHZ CDCL3
BRUKER
PPM
DBI17F.001
DATE 27-10-92
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 4
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.029P
F2 -.470P
HZ/CM 75.032
PPM/CM .250
SR 3360.08
7.11367
6.61918
6.37881
3.16171
3.11851
2.66917
-.00042
CN
OMe
MeO
OMe
193
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


SAMPLE DB-I-17F 13-C 75.47 MHZ CDCL3
BRUKER
PPM
DBI17FC.004
AU PROG:
AUTOC13.AU
DATE 27-10-92
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 576
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 16.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.86
152.982
147.891
147.497
138.365
131.157
130.121
110.773
110.776
110.250
105.110
101.658
91.217
77.482
77.000
76.844
71.487
66.882
60.916
56.229
40.912
40.376
0.01
O
N
CN
O
O
I
OMe
MeO
OMe
193
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

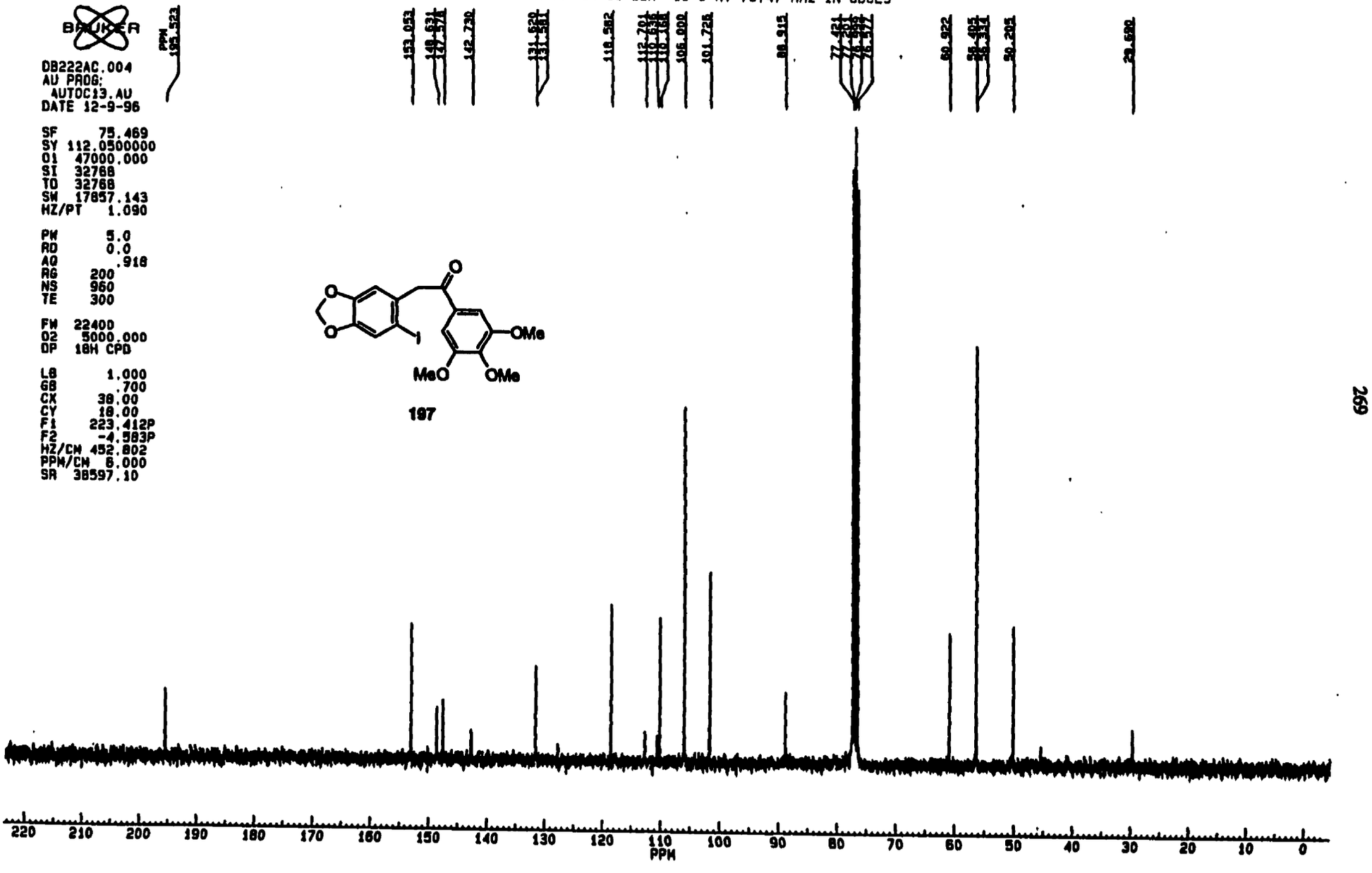

SAMPLE DB-I-18D 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DB118D.001
AU PROG:
TFZG.AU
DATE 11-9-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
OP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3365.78
7.26518
6.62584
3.87478
3.85822
3.69757
1.66867
MeO
OMe
OMe
O
N
O
194
2.001
9.345
7.334
1.203
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

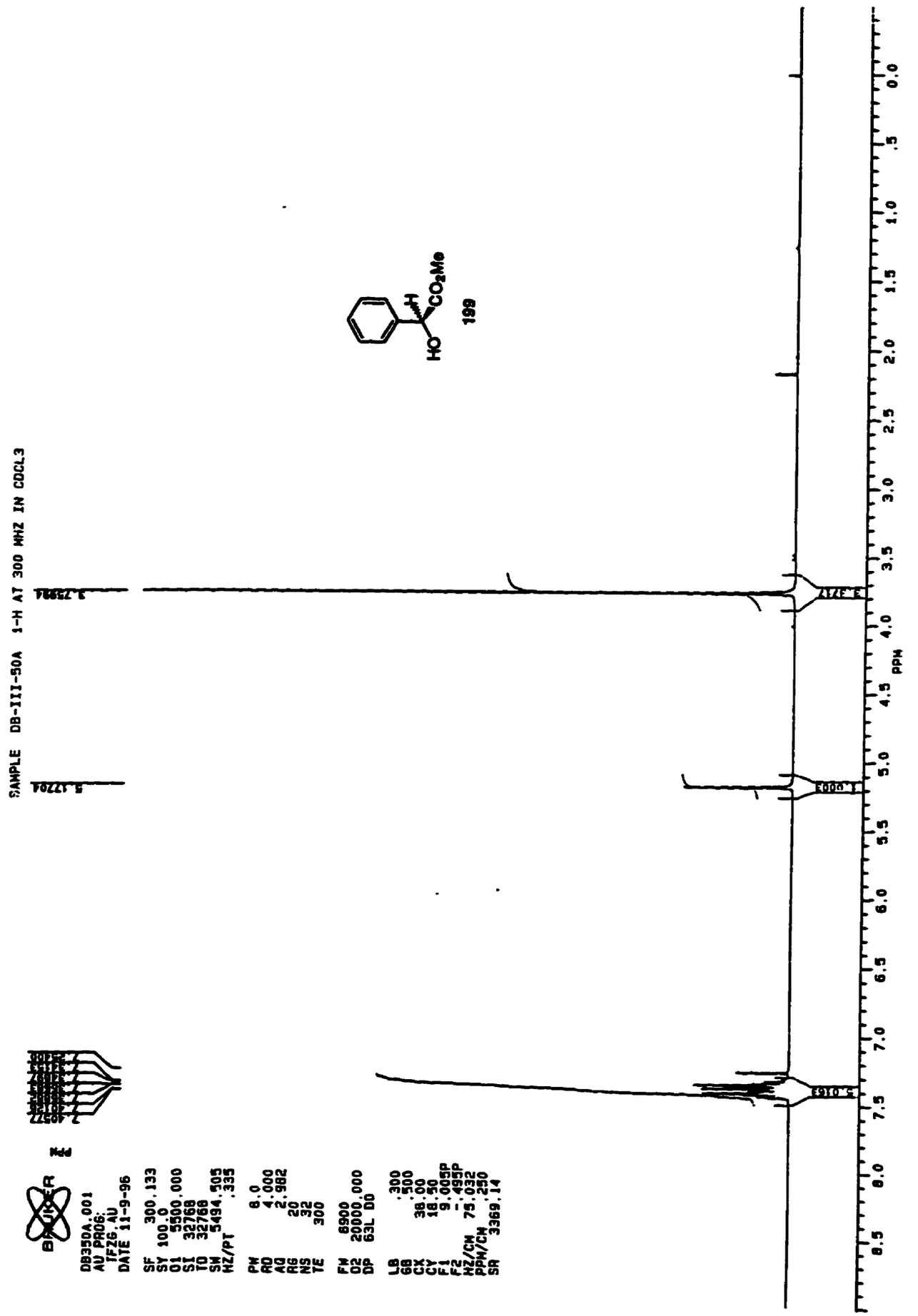

SAMPLE 08-I-180 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
170.122
153.338
139.357
130.594
104.411
77.422
77.205
77.000
76.578
66.891
60.875
56.276
08118DC.004
AU PROG:
AUTOC13.AU
DATE 17-9-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.412P
F2 -4.583P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.10
MeO
OMe
OMe
184
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

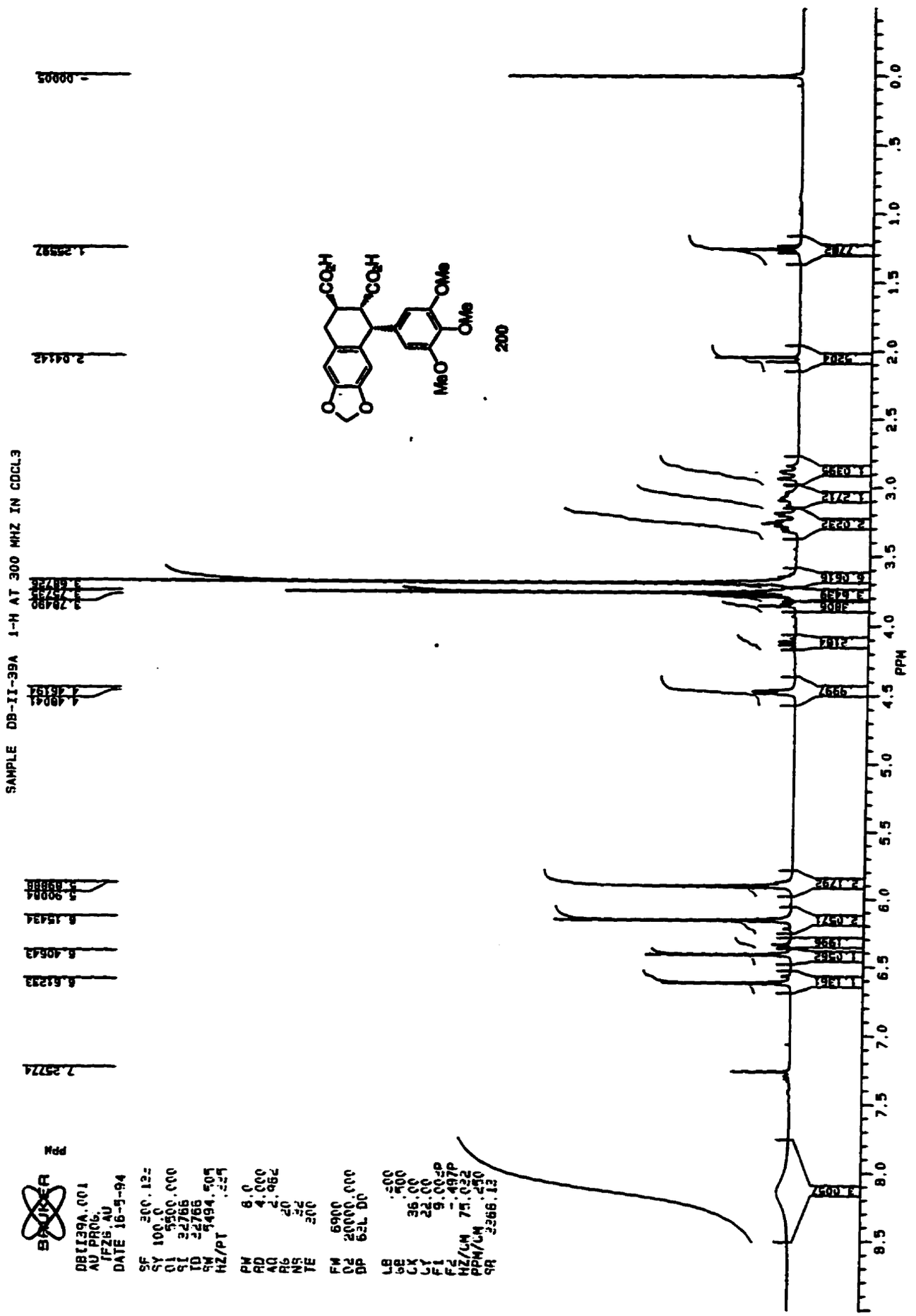
SAMPLE DB-II-22A2 1-H AT 300 MHZ IN CDCL3

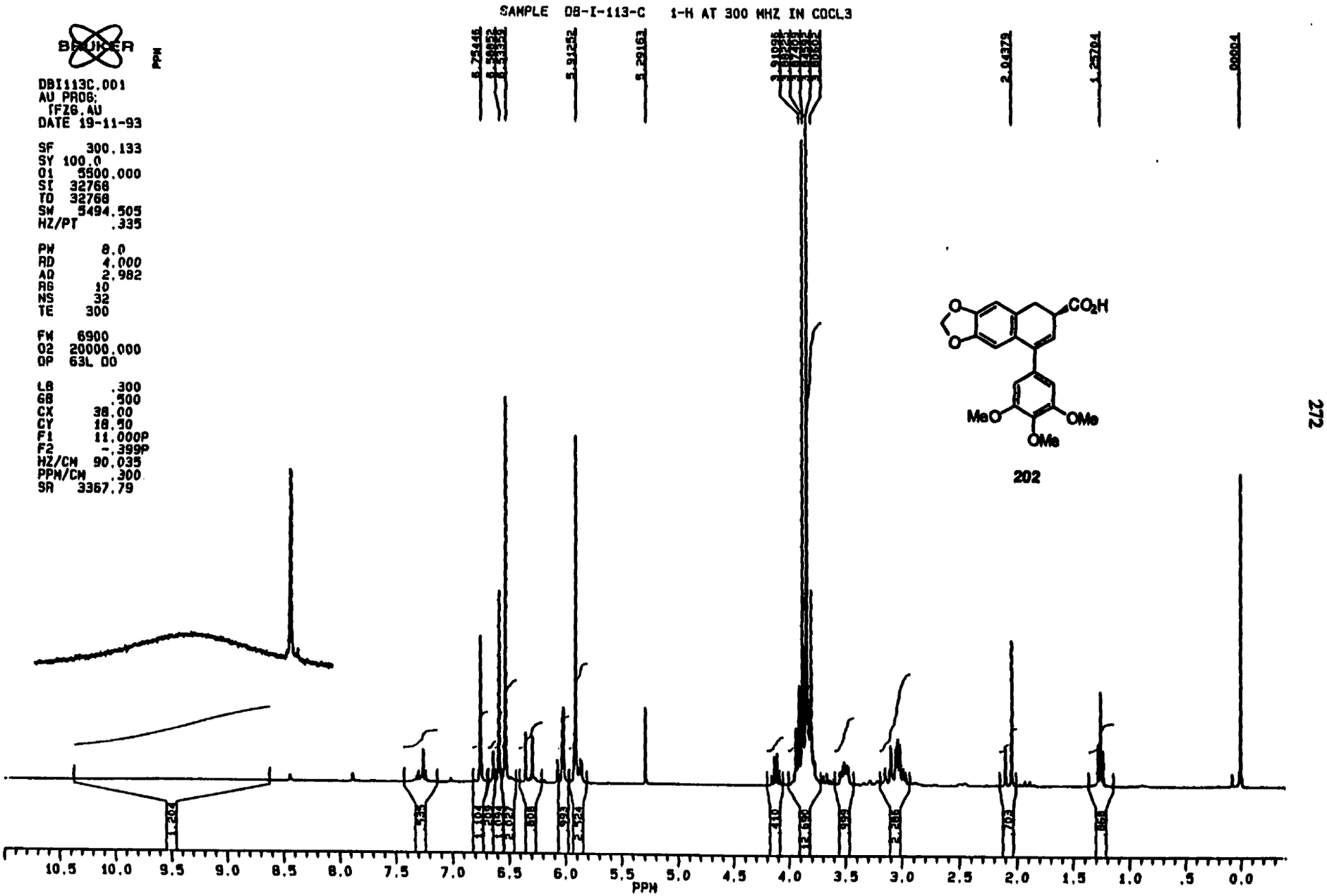


SAMPLE DB-II-22A 13-C AT 75.47 MHZ IN CDCL3




SAMPLE DB-III-50A 1-H AT 300 MHZ IN CDCL3
3.17704
3.27994
HO
CO2Me
H
199
PPM
DB350A.001
AU PROG:
TFZ6.AU
DATE 11-9-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 8900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.90
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3369.14


SAMPLE DB-II-39A 1-H AT 300 MHZ IN CDCL3
DBII39A.001
AU PROG.
IPZ6.AU
DATE 16-9-94
PPM
PPM


SAMPLE DB-I-113-C 1-H AT 300 MHZ IN COCL3
BRUKER
PPM
DBI113C.001
AU PROG:
IFZG.AU
DATE 19-11-93
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
OP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 11.000P
F2 -.399P
HZ/CM 90.035
PPM/CM .300
SR 3367.79
5.91252
5.29163
2.04379
1.25704
.00004
CO2H
MeO
OMe
OMe
202
10.5 10.0 9.5 9.0 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 DB-I-113-C 13-C AT 75.47 MHZ IN COCL3



DBI113CC.004
AU PROG:
4UTOC13.AU
DATE 22-11-93

SF 75.469
SY 112.0500000
D1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090

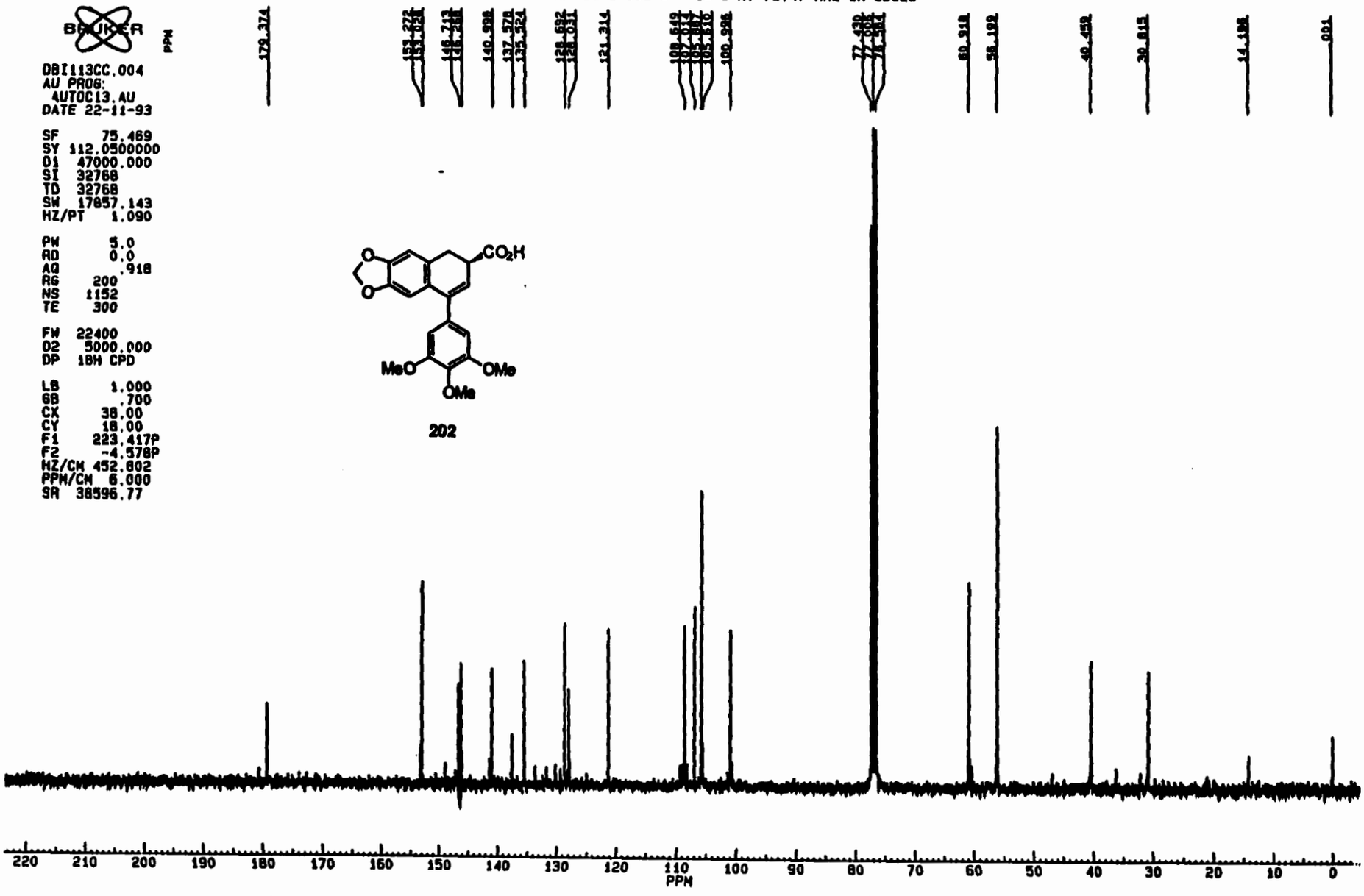
PW 5.0
RD 0.0
AQ .918
RG 200
NS 1152
TE 300

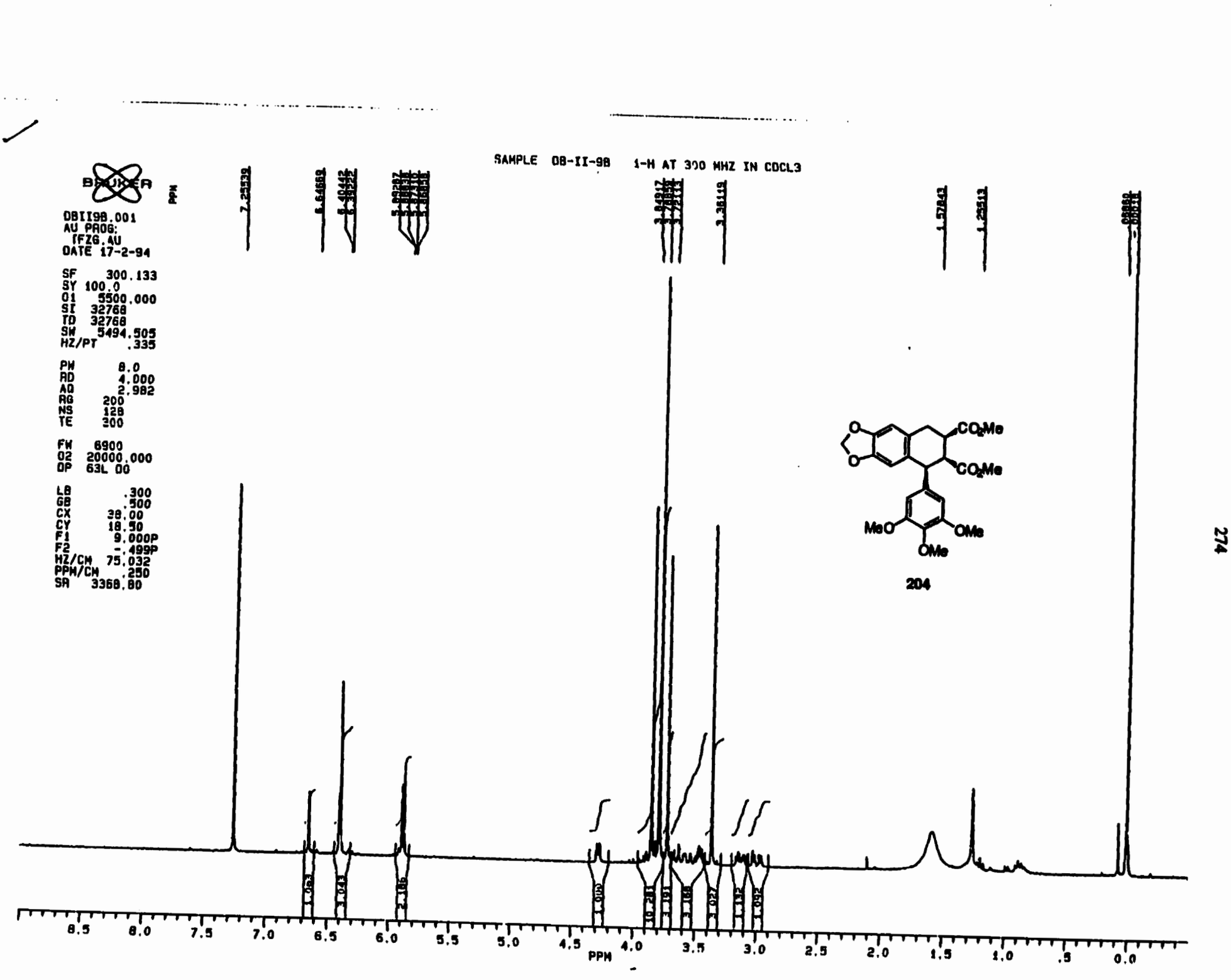
FW 22400
D2 5000.000
DP 18H CPD

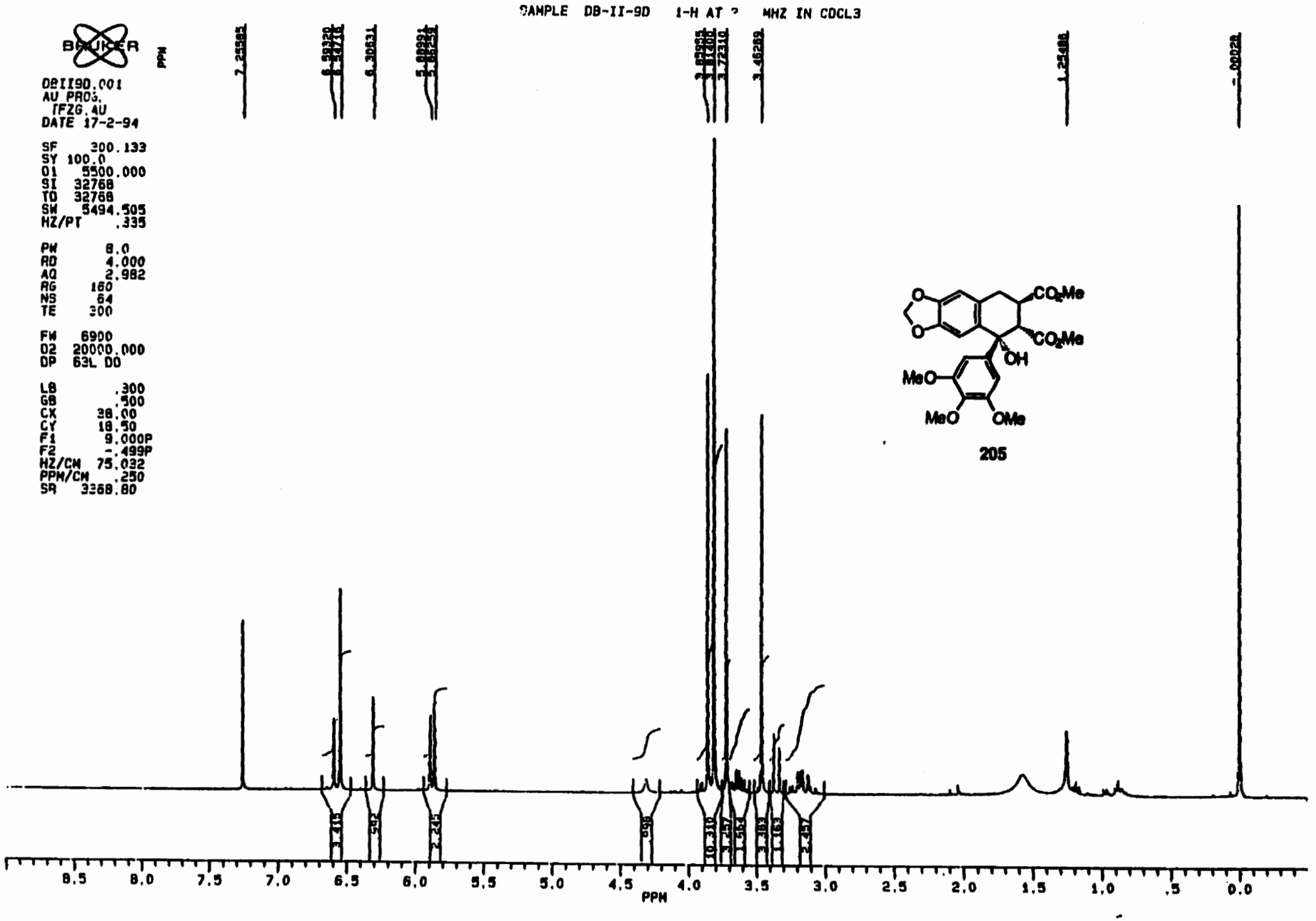
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77

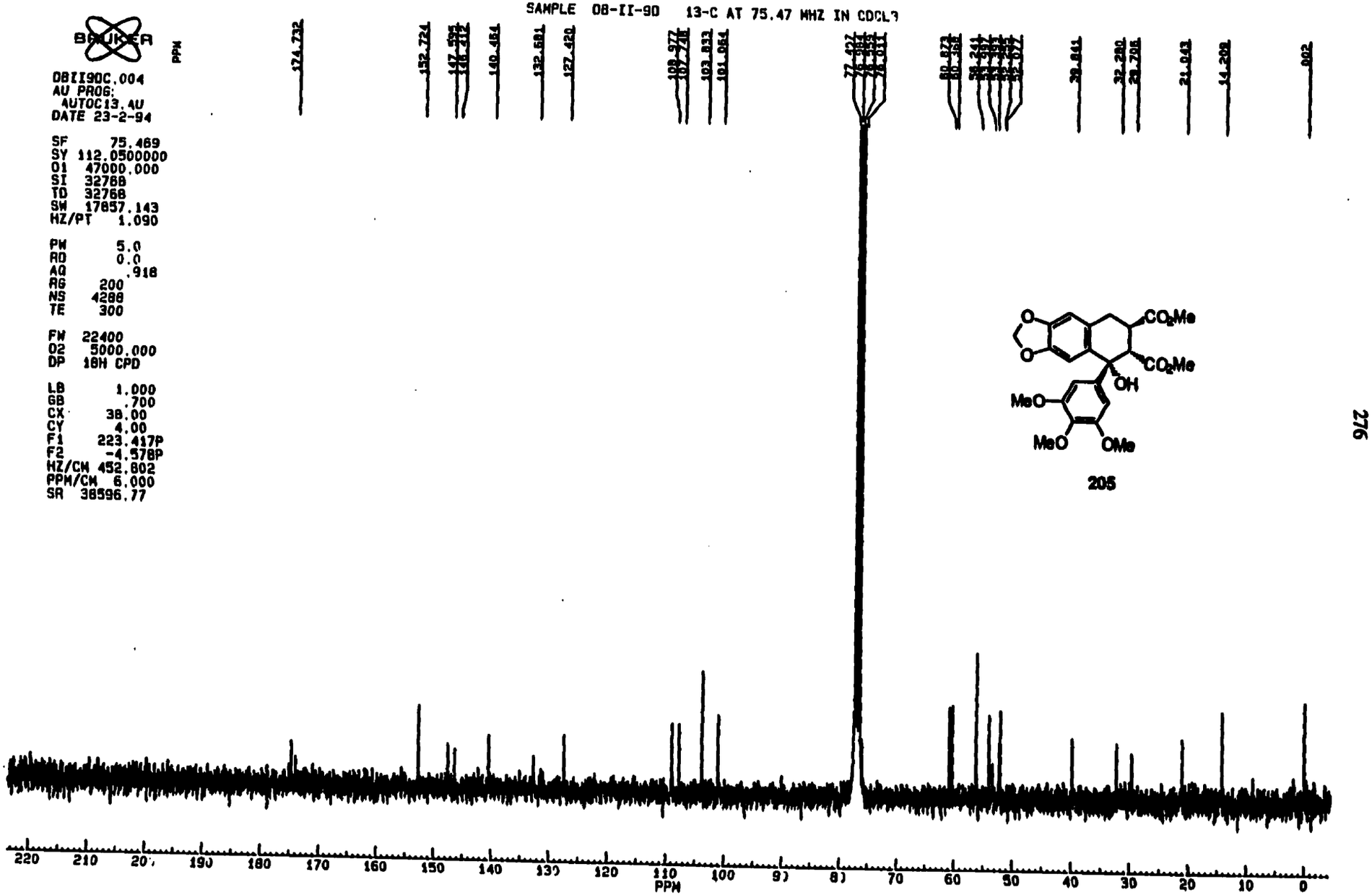



202




SAMPLE 08-II-98 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DBII98.001
AU PROG:
fFZG.AU
DATE 17-2-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 200
NS 128
TE 300
FW 6900
O2 20000.000
OP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.000P
F2 -.499P
HZ/CM 75.032
PPH/CM .250
SR 3368.80
7.25539
5.64869
5.40442
5.38122
3.84817
3.36119
1.57843
1.25513
.08868
-.00018
CO2Me
CO2Me
MeO
OMe
OMe
204
1.083
1.045
2.186
1.000
10.281
3.191
3.168
3.027
1.112
1.092
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 DB-II-9D 1-H AT ? MHZ IN CDCL3
BRUKER
PPM
DBII9D.001
AU PROG.
TFZG.AU
DATE 17-2-94
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 160
NS 64
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.000P
F2 -.499P
HZ/CM 75.032
PPM/CM .250
SR 3368.80
CO2Me
CO2Me
OH
MeO
MeO
OMe
205
PPM


SAMPLE 08-II-90 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
174.732
152.724
147.535
146.212
140.484
132.681
127.420
109.977
107.718
103.833
101.984
77.422
80.873
80.368
56.241
39.841
32.280
29.708
21.043
14.208
002
DBII90C.004
AU PROG:
AUTOC13.AU
DATE 23-2-94
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 4288
TE 300
FW 22400
O2 5000.000
DP 10H CPD
LB 1.000
GB .700
CX 38.00
CY 4.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
CO2Me
CO2Me
OH
MeO
MeO
OMe
205
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 DB-II-31H 1-H AT 300 MHZ IN CDCL3

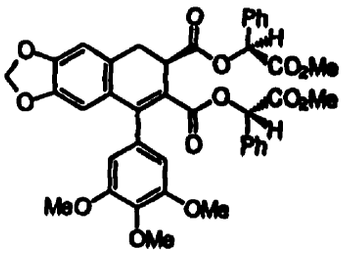
DBII31H.001
AU PROG:
(FZG.AU
DATE 9-5-94

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

PW 8.0
RD 4.000
AQ 2.982
RG 64
NS 32
TE 300

FW 6900
O2 20000.000
DP 63L DD

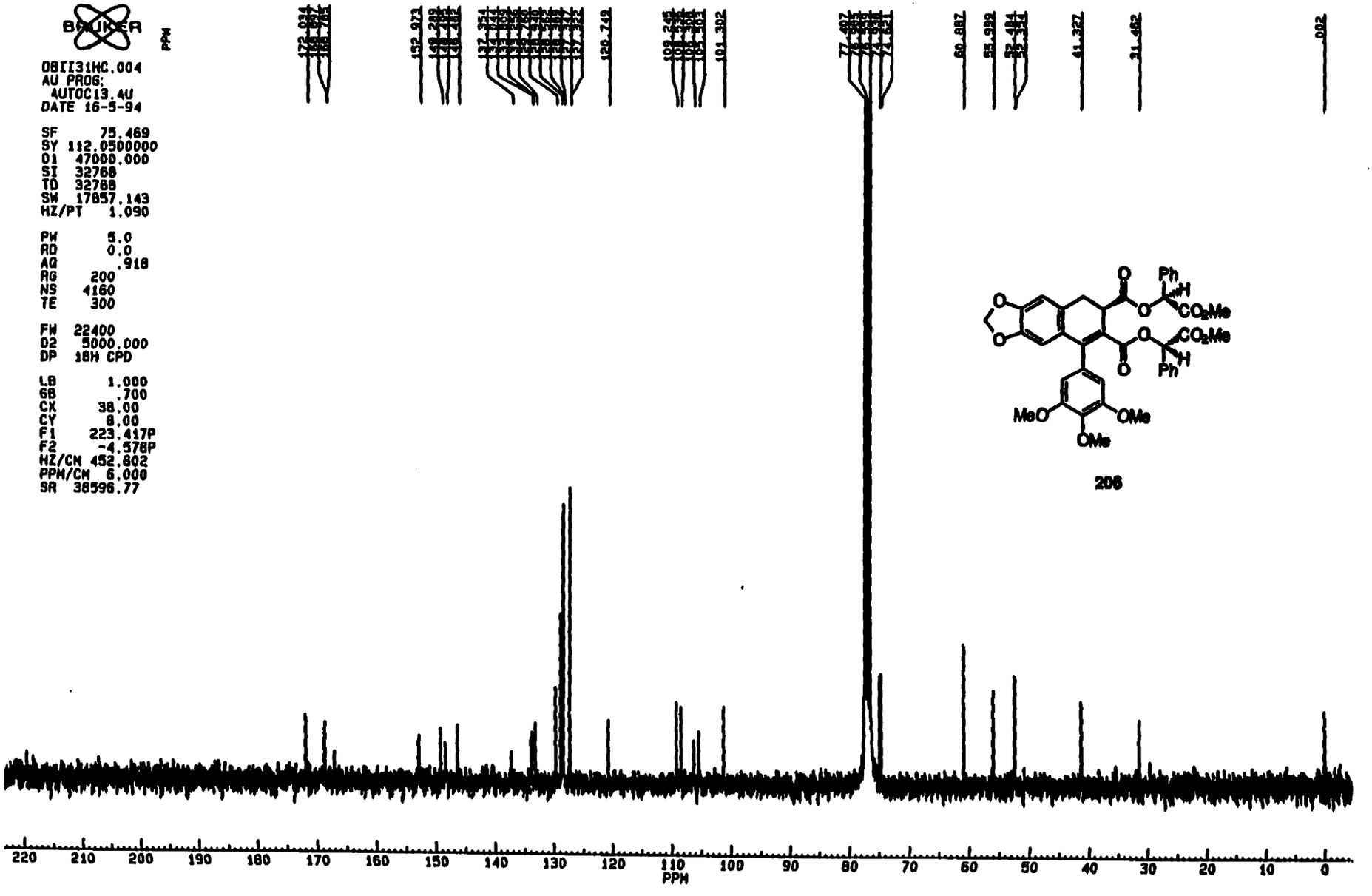
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.000P
F2 -.499P
HZ/CM 75.032
PPM/CM .250
SR 3368.80



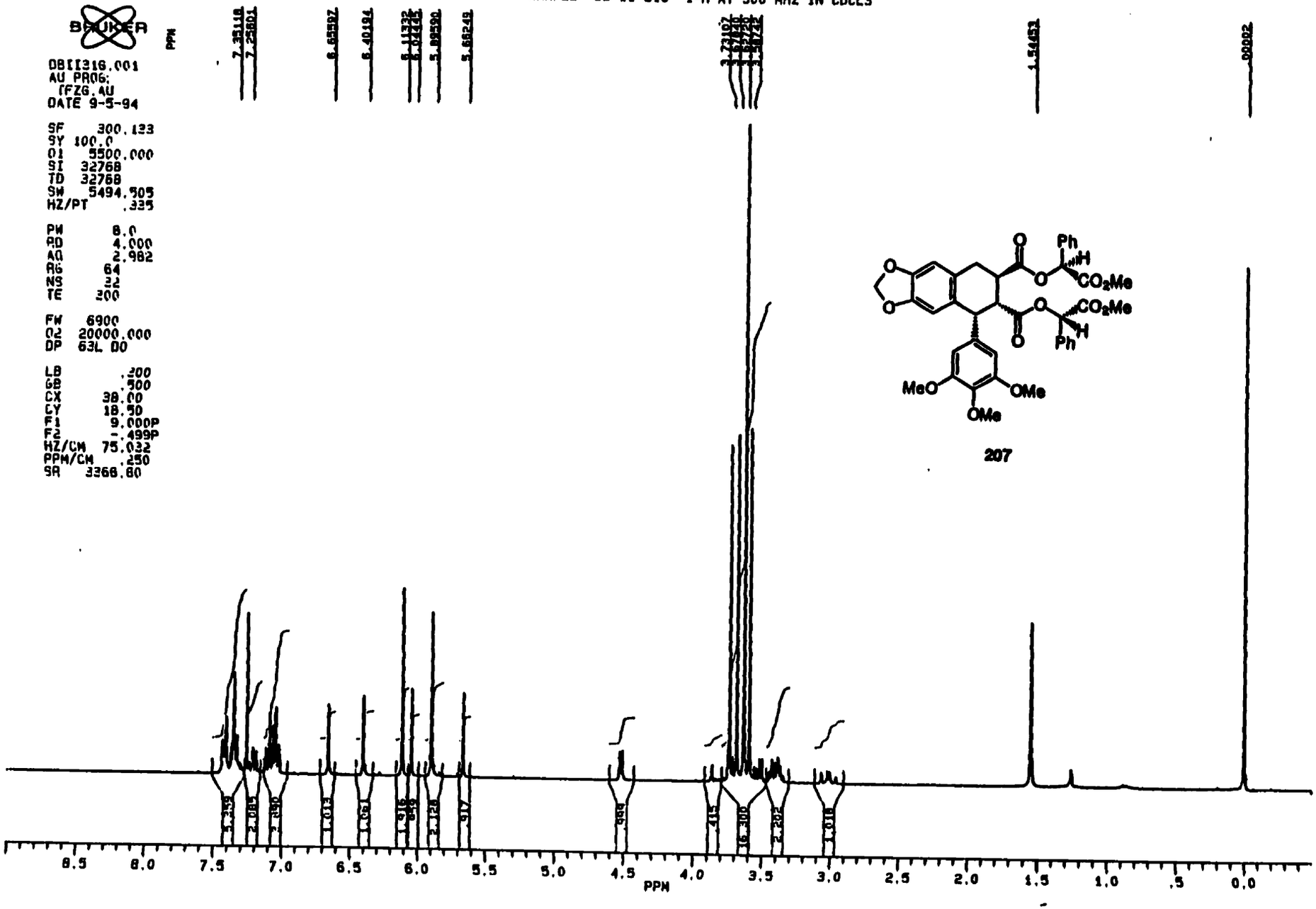

208

PPM

SAMPLE DB-II-31-H 13-C AT 75.47 MHZ IN CDCL3



SAMPLE DB-II-316 1-H AT 300 MHZ IN CDCL3







207

SAMPLE DB-II-31-G 13-C AT 75.47 MHZ IN CDCL3

BRUKER

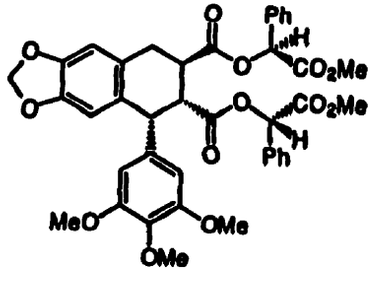
DBII316C.004
AU PROG:
AUTOC13.AU
DATE 15-9-94

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

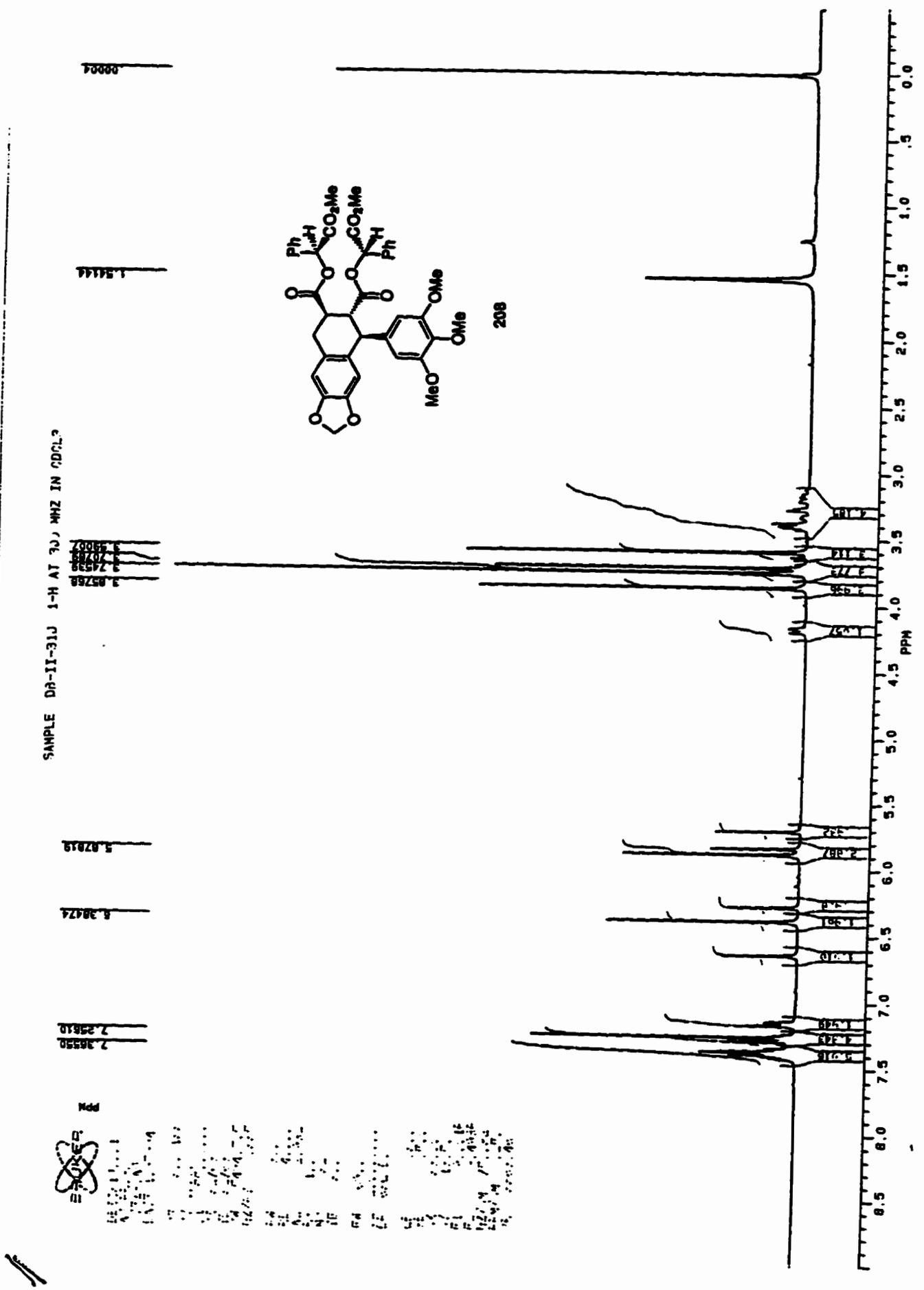
PW 5.0
RD 0.0
AQ .918
RG 200
NS 5760
TE 300

FW 22400
O2 5000.000
DP 18H CPD

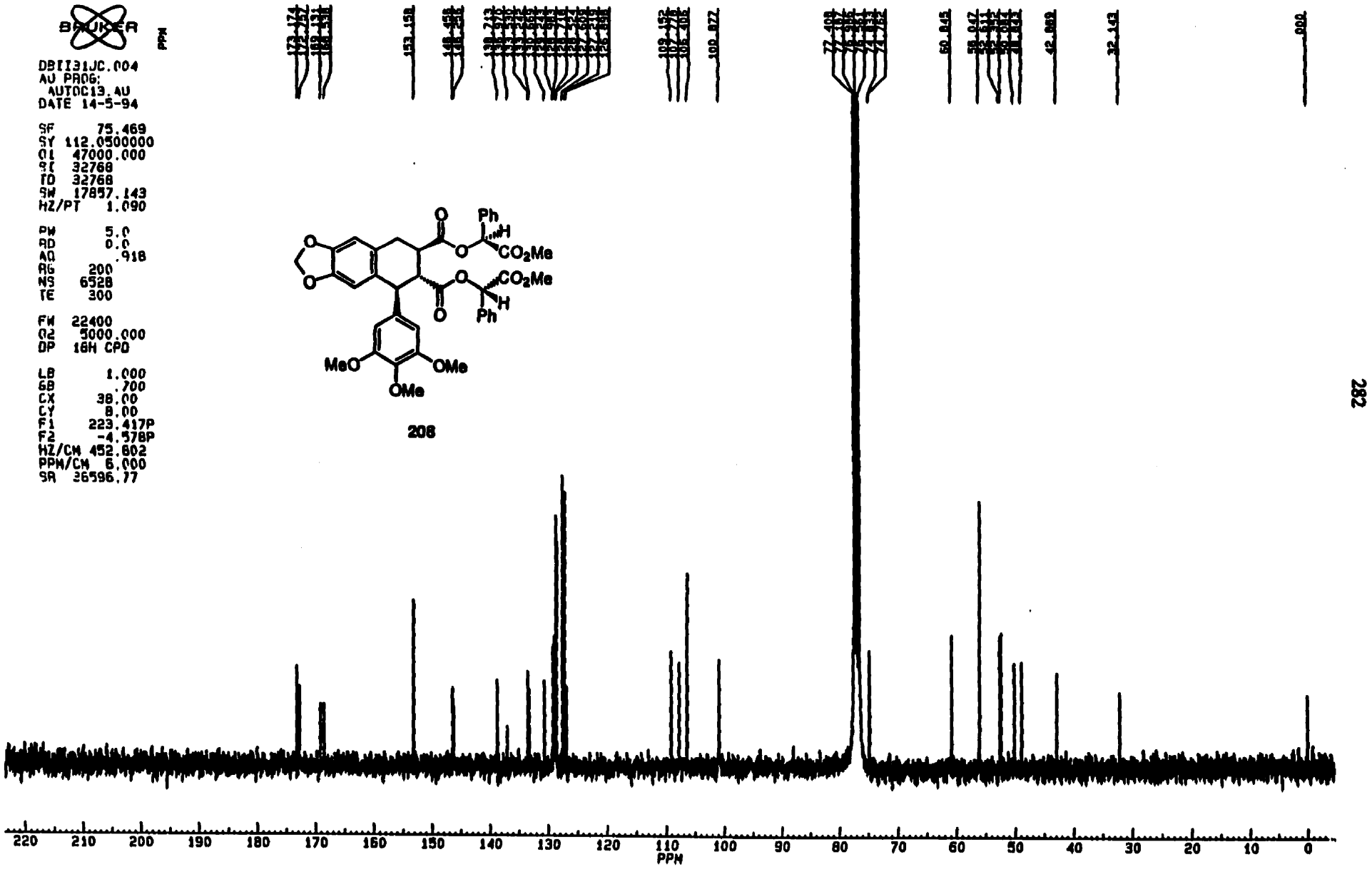
LB 1.000
GB .700
CX 38.00
CY 10.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77

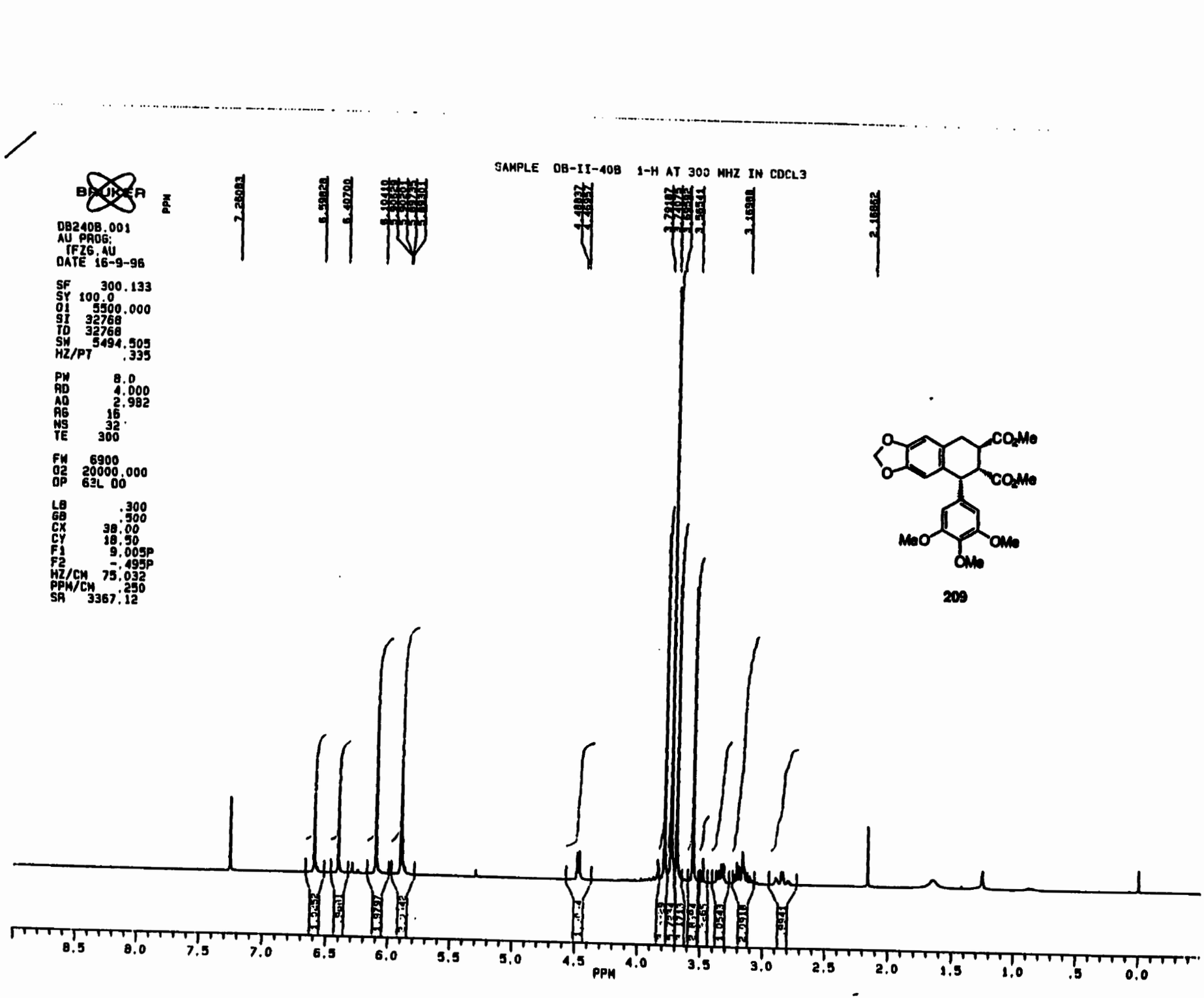



207


SAMPLE DB-II-31J 1-H AT 300 MHZ IN CDCL3
208
PPM

SAMPLE DB-II-31-J 13-C AT 75.47 MHZ IN CDCL3




SAMPLE OB-II-40B 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DB240B.001
AU PROG:
TFZ6.AU
DATE 16-9-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300
FW 6900
O2 20000.000
OP 62L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.12
7.28083
6.59828
6.40700
4.48037
4.46857
3.72107
3.71074
3.69882
3.56544
3.16388
2.16862
CO2Me
CO2Me
MeO
OMe
OMe
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

209

SAMPLE DB-II-40-B 13-C AT 300 MHZ IN CDCL3

BRUKER

PPM

175.454
172.541
152.786
148.818
148.492
137.341
137.148
129.519
128.738
103.453
103.273
100.950
77.418
77.000
76.577
60.725
56.177
56.101
52.908
51.592
47.804
47.673
37.240
32.422
-0.001

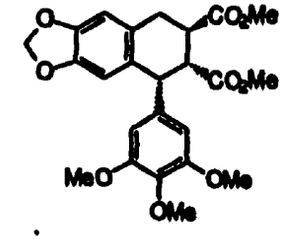
DBII40BC.004
AU PROG:
AUTOC13.AU
DATE 26-6-94

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

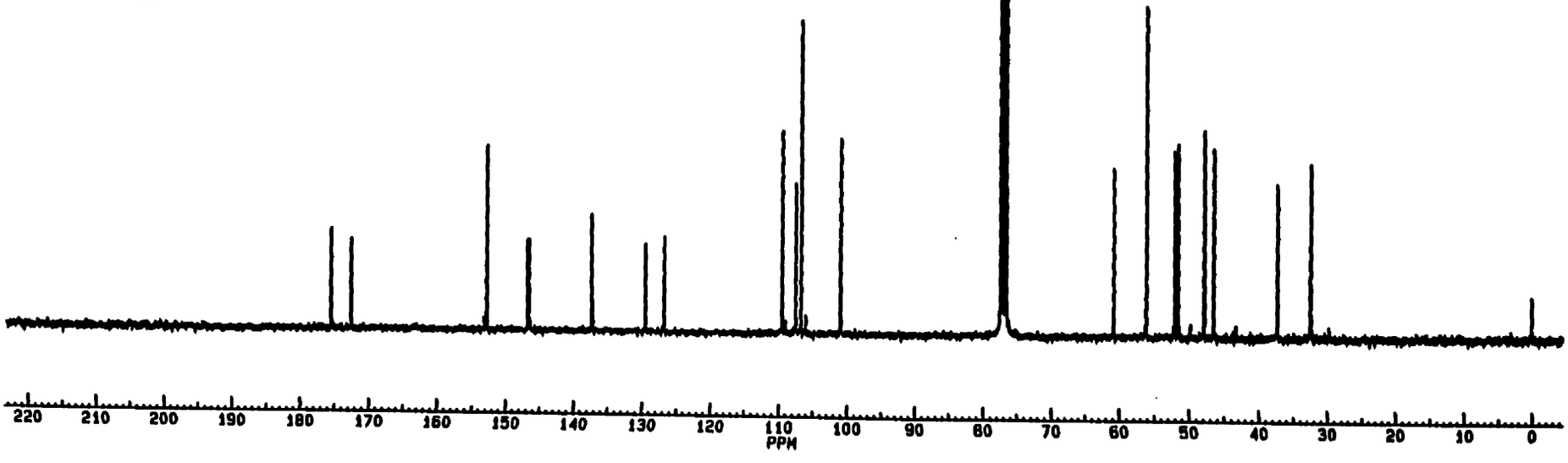
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300

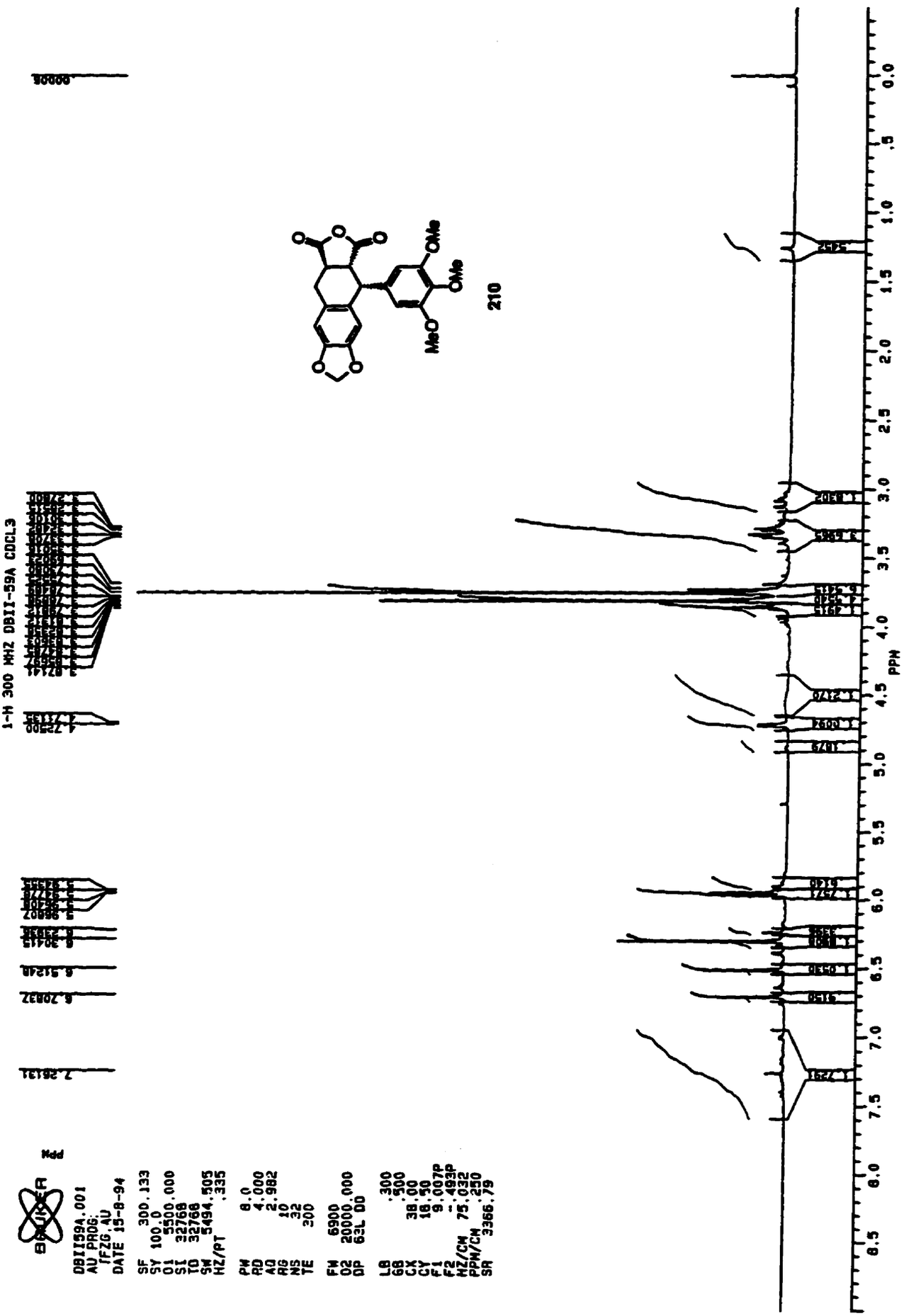
FW 22400
O2 5000.000
DP 18H CPD

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

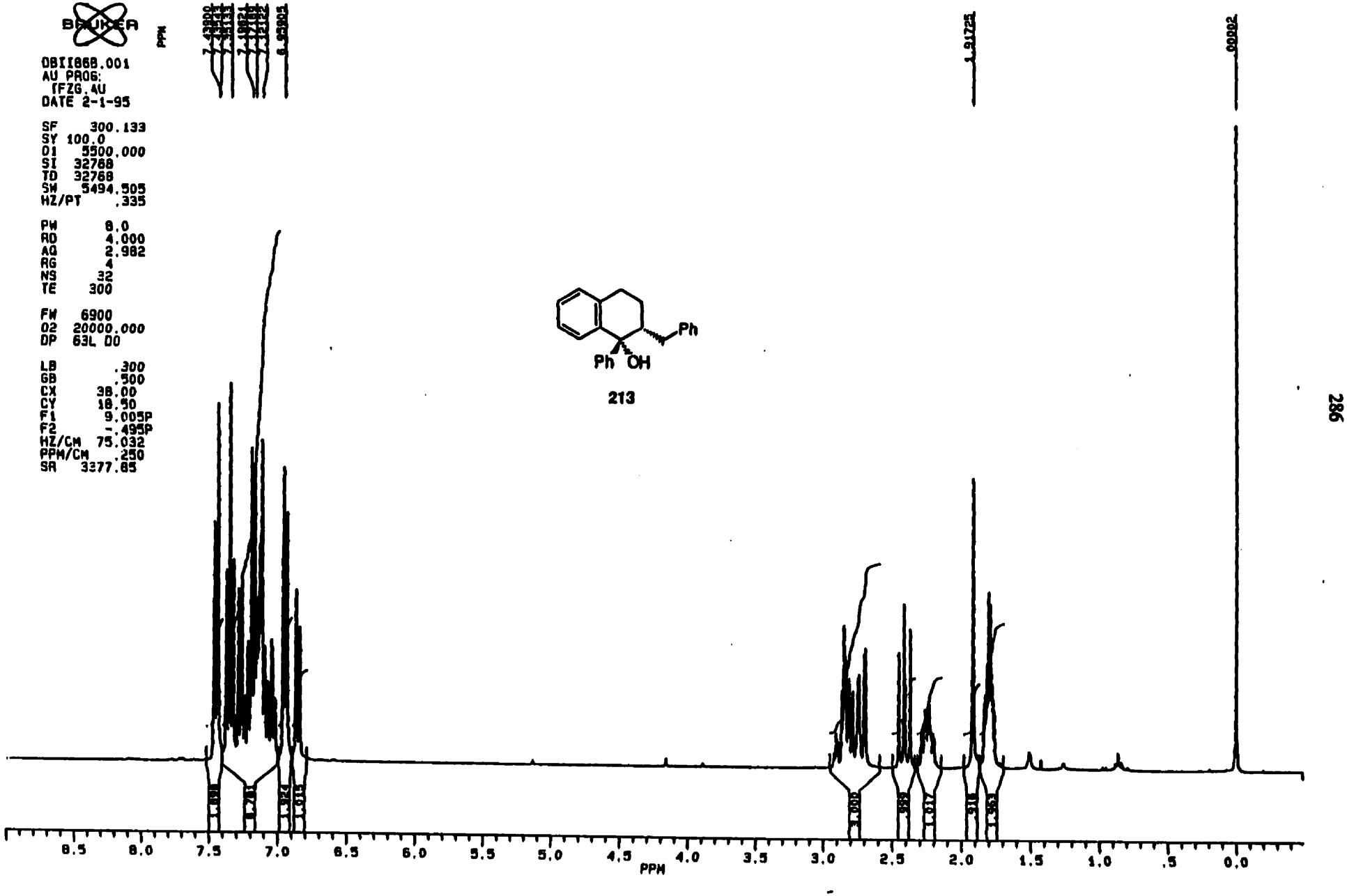


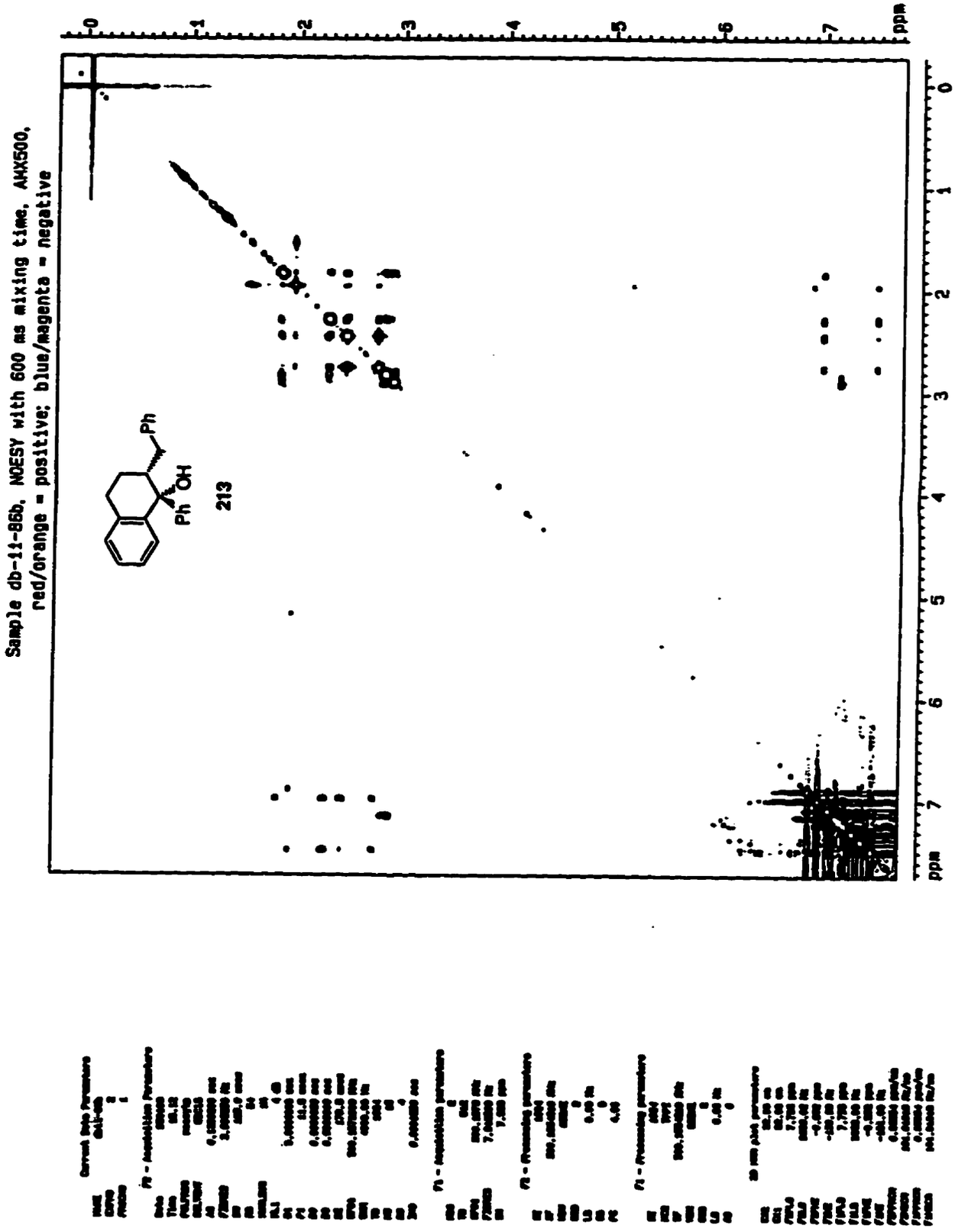

209



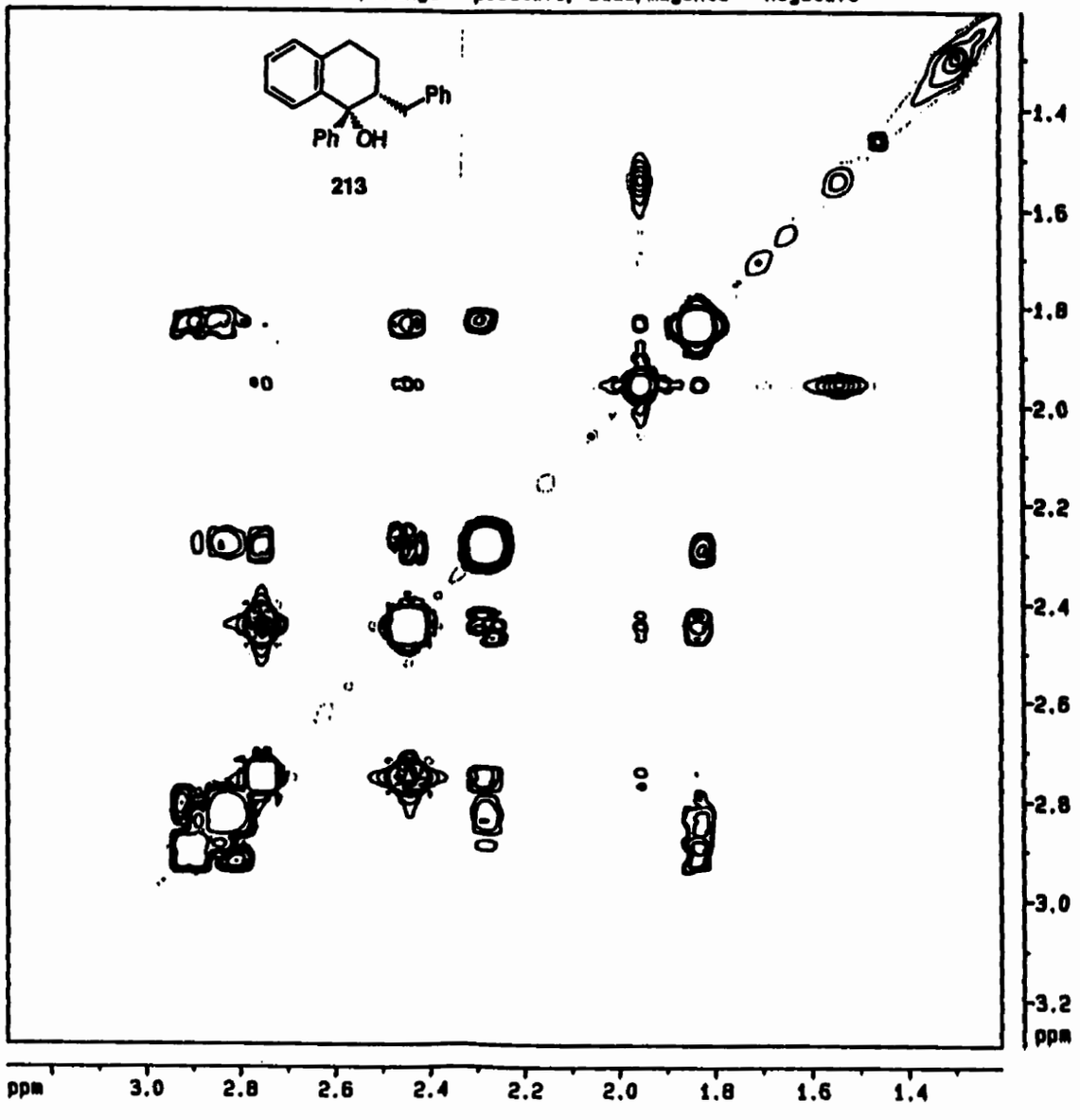

1-H 300 MHZ DBII-59A CDCL3
DBII59A.001
AU PROG:
TFZG.AU
DATE 15-8-94
SF 300.133
SW 3494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.007P
F2 -.493P
HZ/CM 75.032
PPM/CM .250
SR 3366.79
PPM
MeO
OMe
OMe
210

SAMPLE 08-II-86-8 1-H AT 300 MHZ IN COCL3

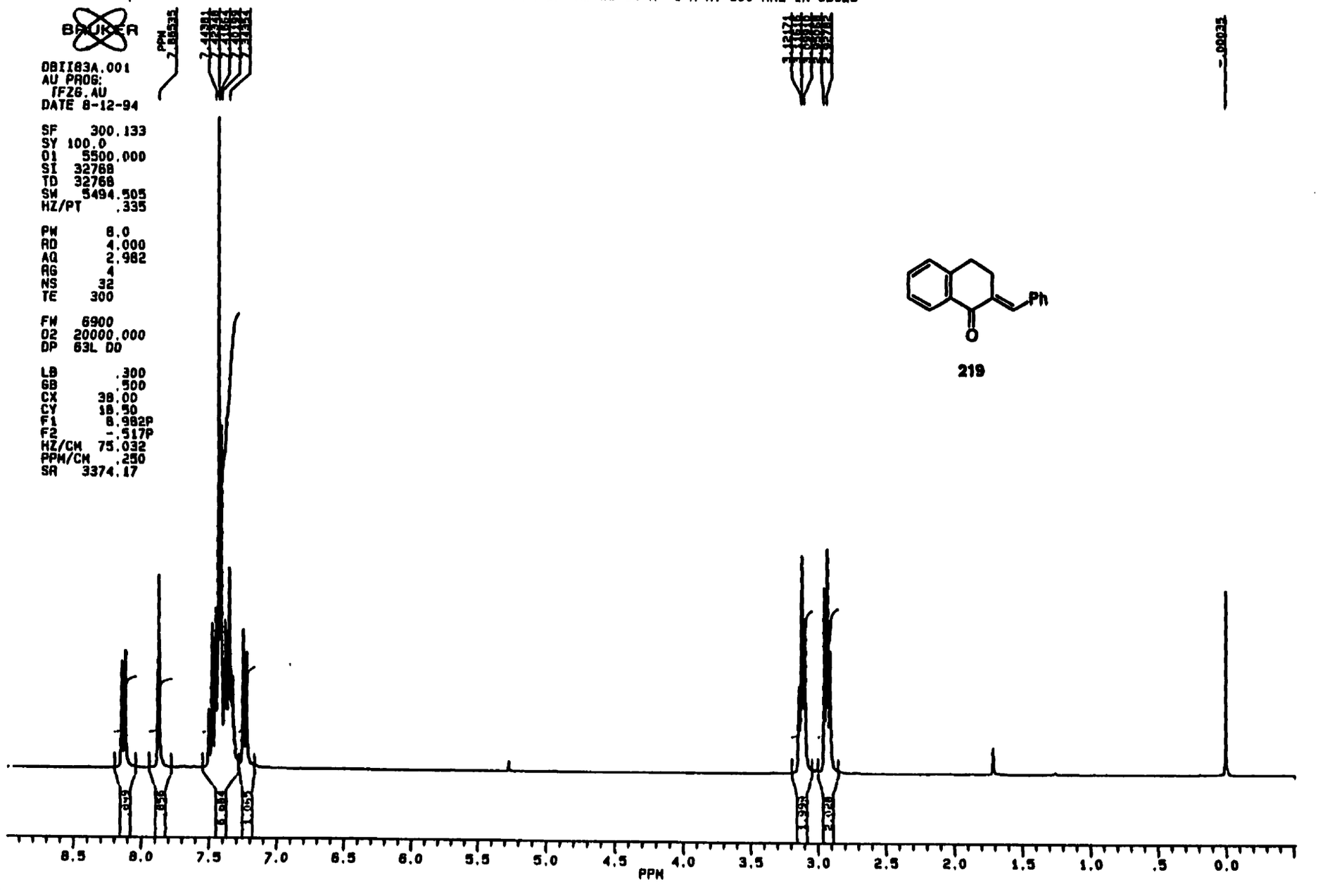



Sample db-11-86b, NOESY with 600 ms mixing time, AMX500,
red/orange = positive; blue/magenta = negative
Ph
Ph
OH
213
ppm
ppm

Sample db-ii-86b, NOESY with 600 ms mixing time, AMX500,
red/orange = positive; blue/magenta = negative



SAMPLE DB-II-83-A 1-H AT 300 MHZ IN CDCL3

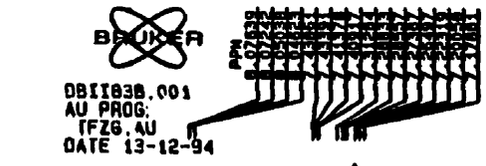






219

SAMPLE DB-II-83-B 1-H AT 300 MHZ IN CDCL3



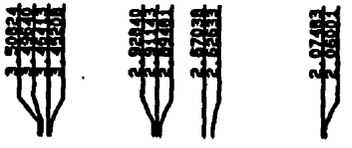
DBII83B.001
AU PROG:
IFZG.AU
DATE 13-12-94

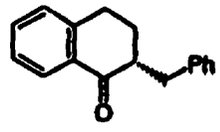
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

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

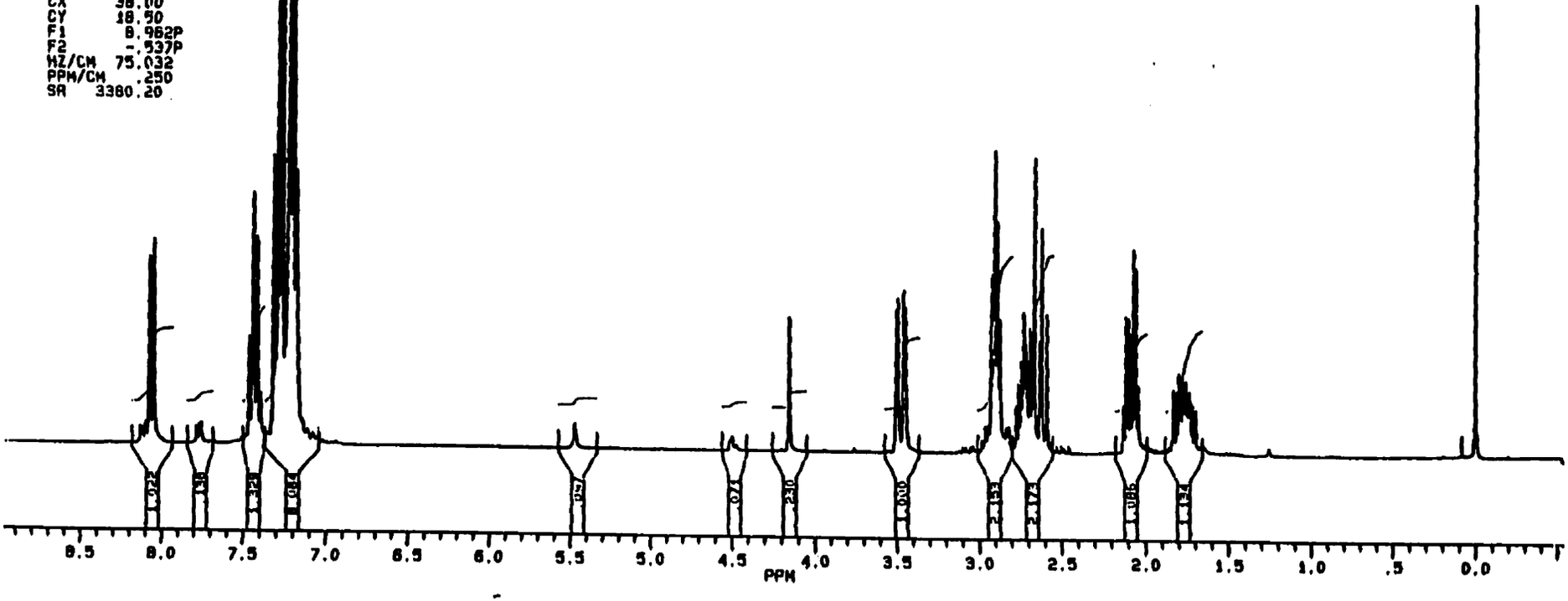
FW 6900
O2 20000.000
OP 63L 00

LB .300
GB .500
CX 38.00
CY 18.50
F1 8.982P
F2 -.537P
HZ/CM 75.032
PPM/CM .250
SR 3380.20



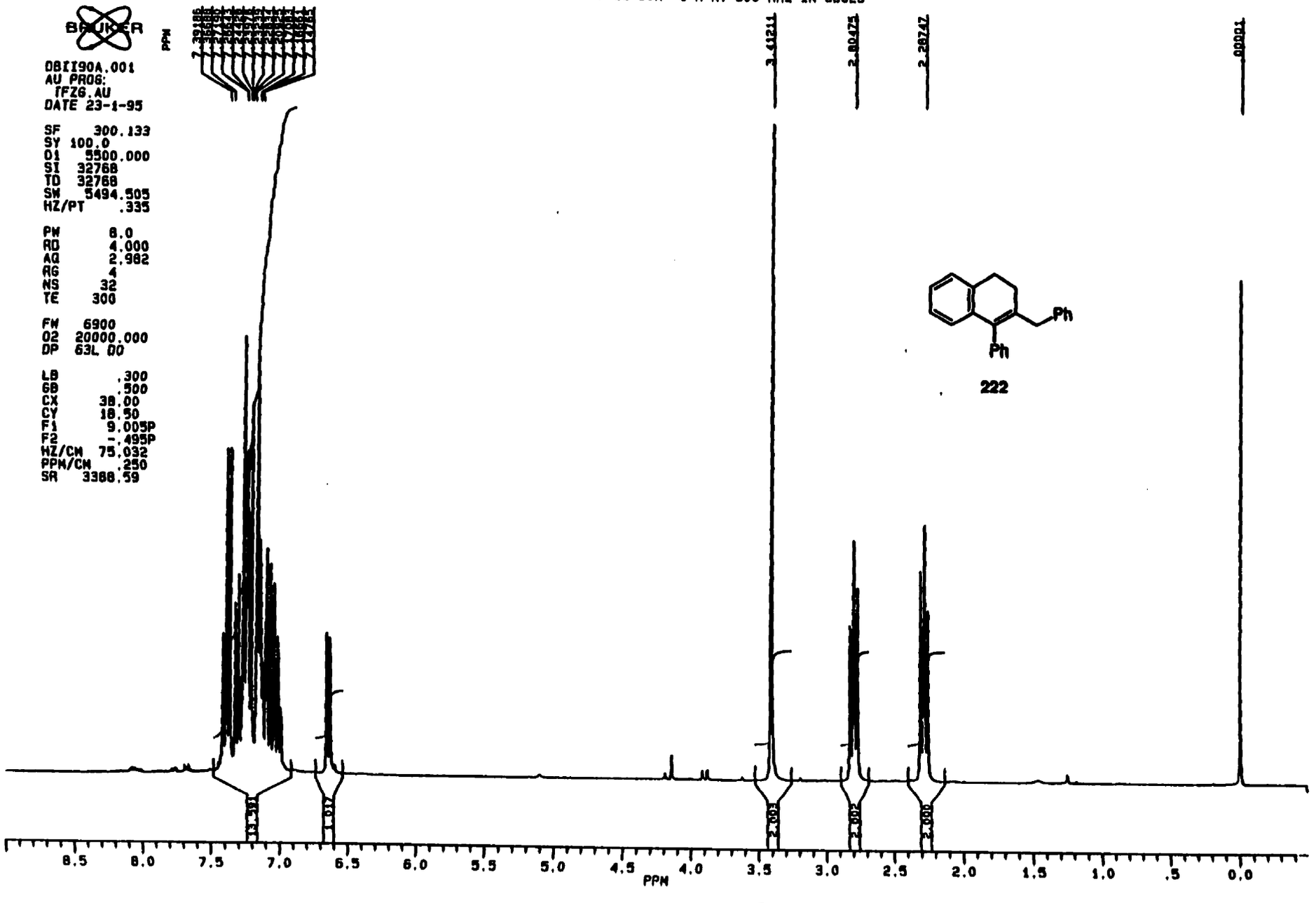


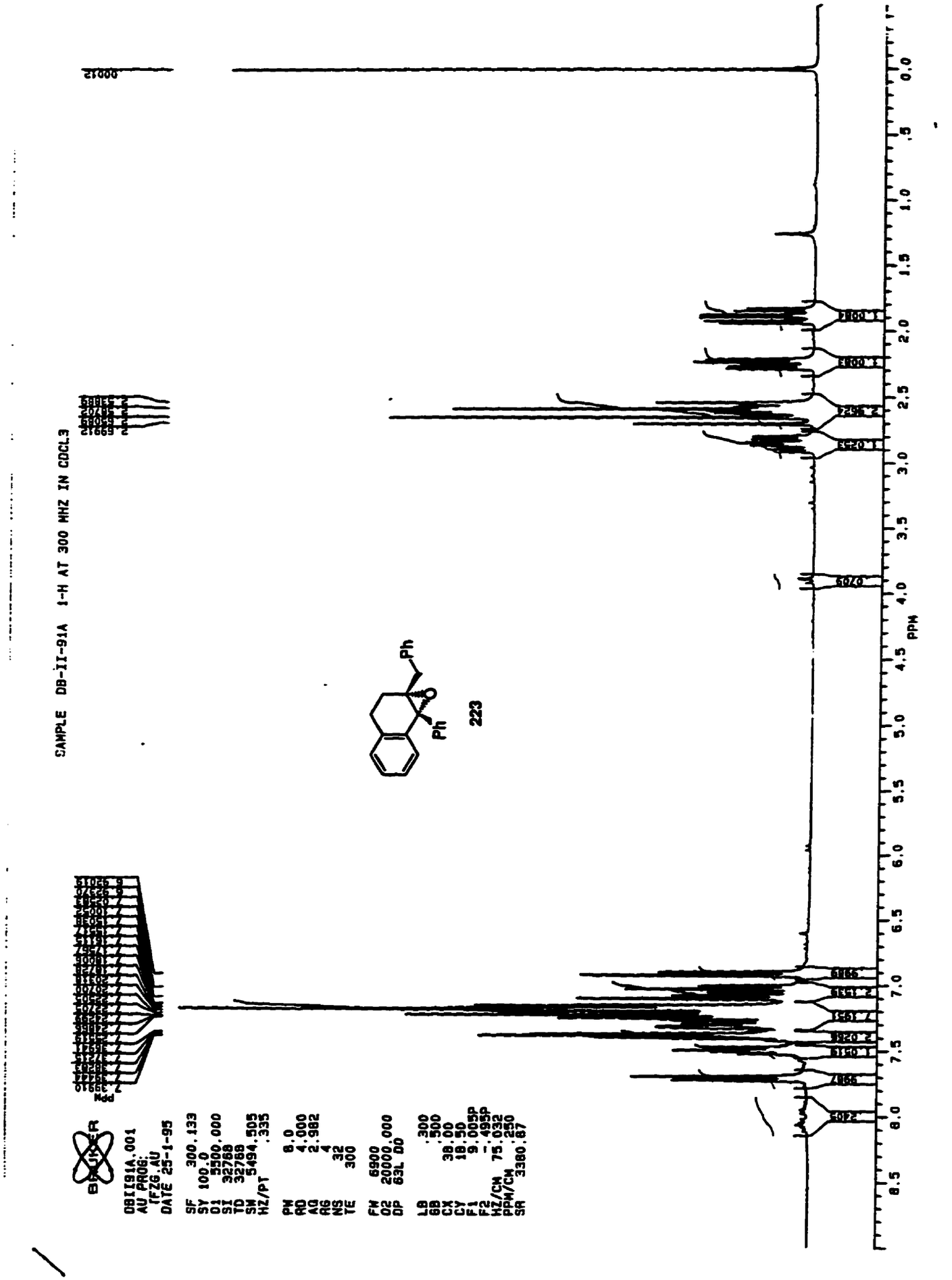

220

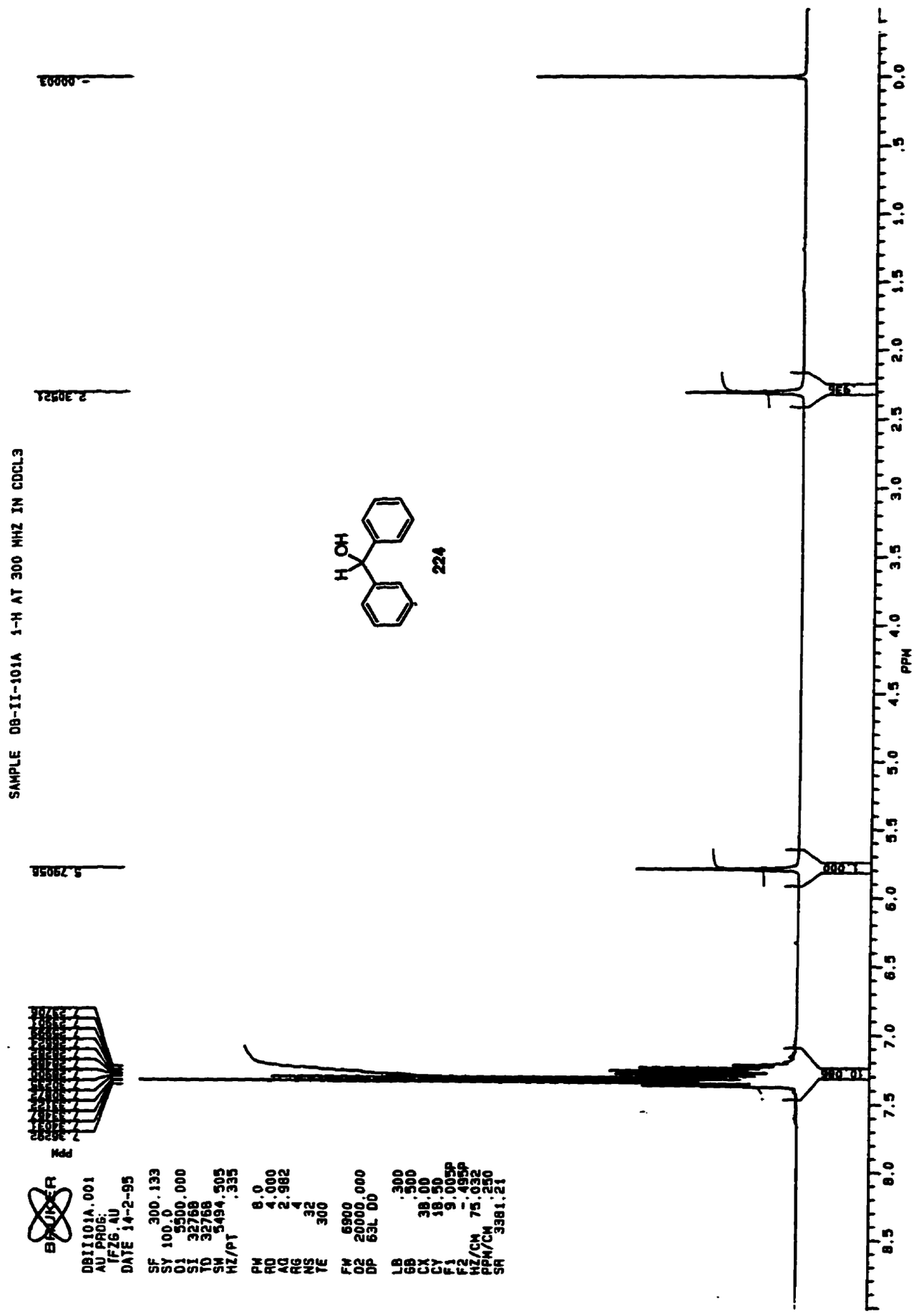


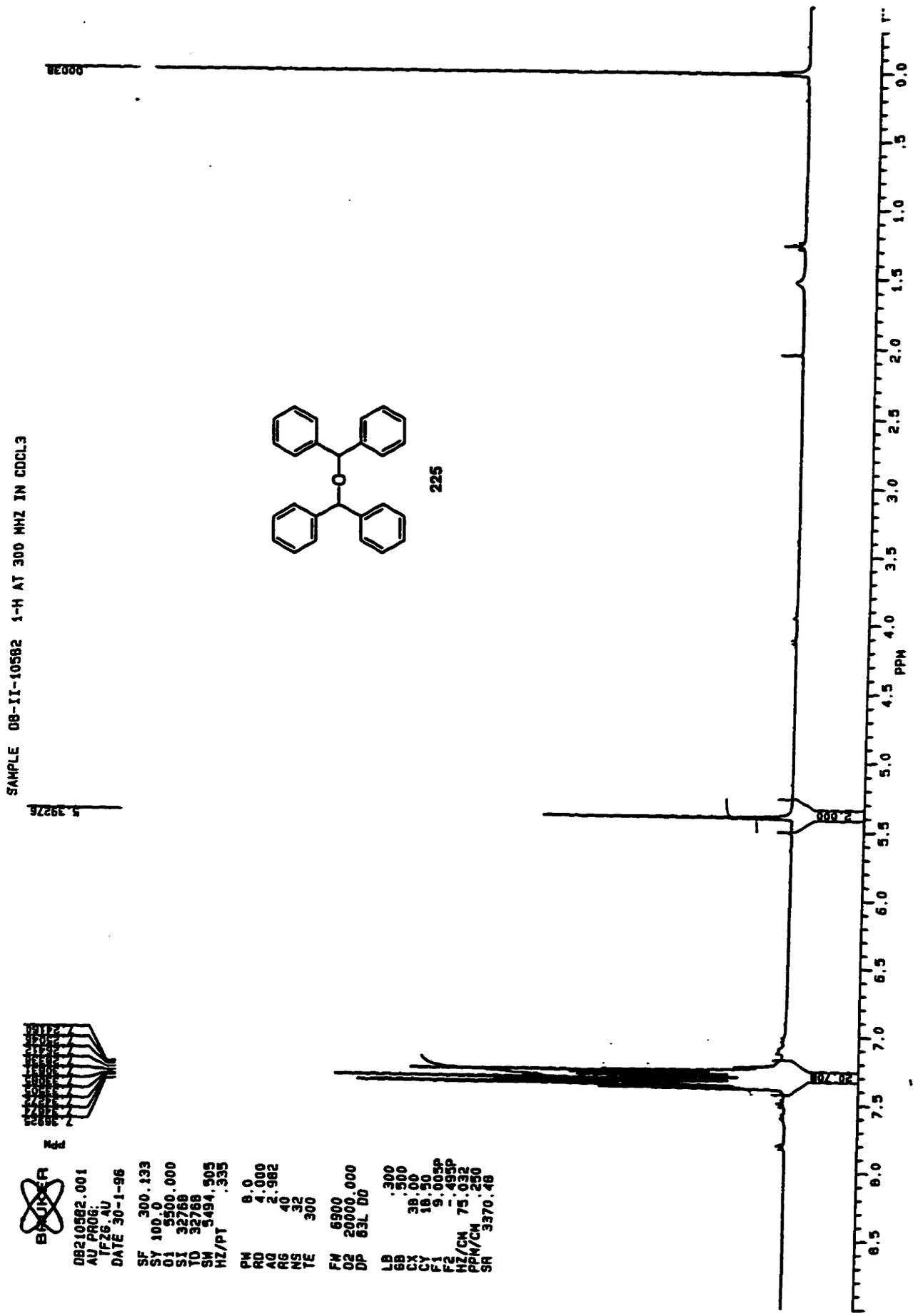

290

SAMPLE DB-II-90A 1-H AT 300 MHZ IN CDCL3




SAMPLE DB-II-91A 1-H AT 300 MHZ IN CDCL3
Ph
Ph
O
223
PPM


SAMPLE DB-II-101A 1-H AT 300 MHZ IN CDCL3
DBII101A.001
AU PROG:
TFZ6.AU
DATE 14-2-95
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 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.0059
F2 -.4959
HZ/CM 75.032
PPM/CM .250
SR 3381.21
PPM
OH
224


SAMPLE 08-II-10582 1-H AT 300 MHZ IN CDCL3
225
BRUKER
DB210582.001
AU PROG:
TF26.4U
DATE 30-1-96
SF 300.133
SY 100.0
DI 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3370.48
PPM
PPM

SAMPLE 08-II-10582 13-C AT 75.47 MHZ IN CDCL3

PPM

DB10582C.004
AU PROG:
AUTOC13.AU
DATE 31-8-96

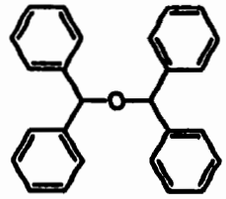
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090

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

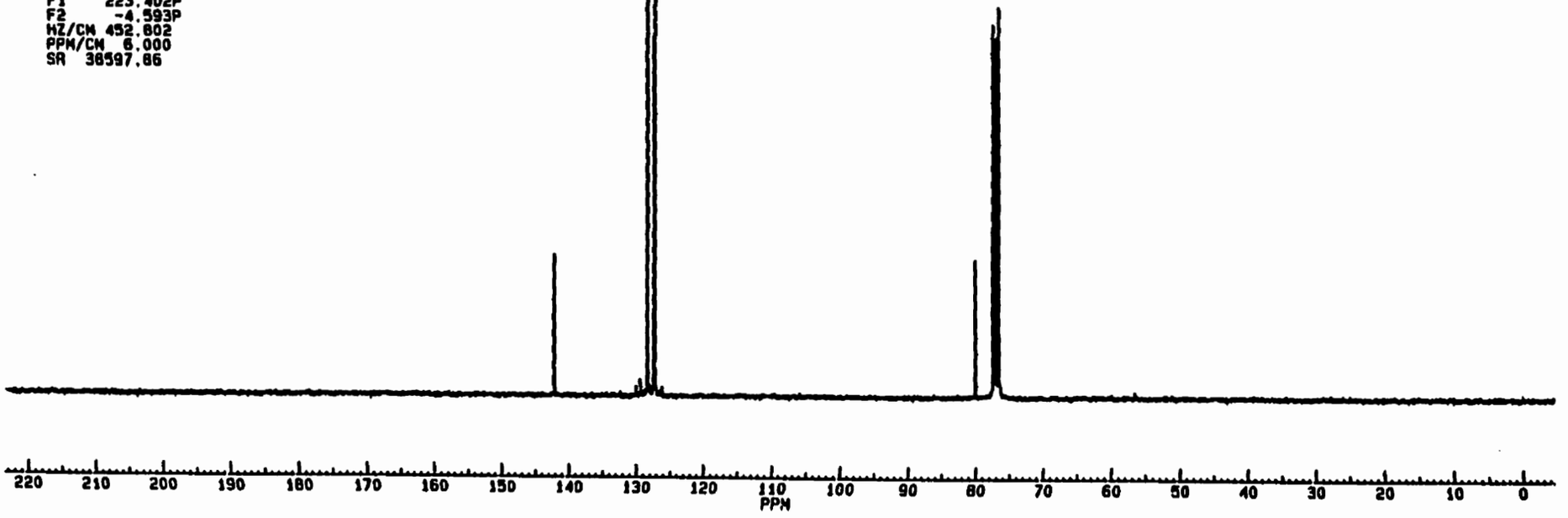
FW 22400
O2 5000.000
DP 18H CPD

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

142.153
129.317
128.384
127.211
79.958
77.406
76.980
76.558



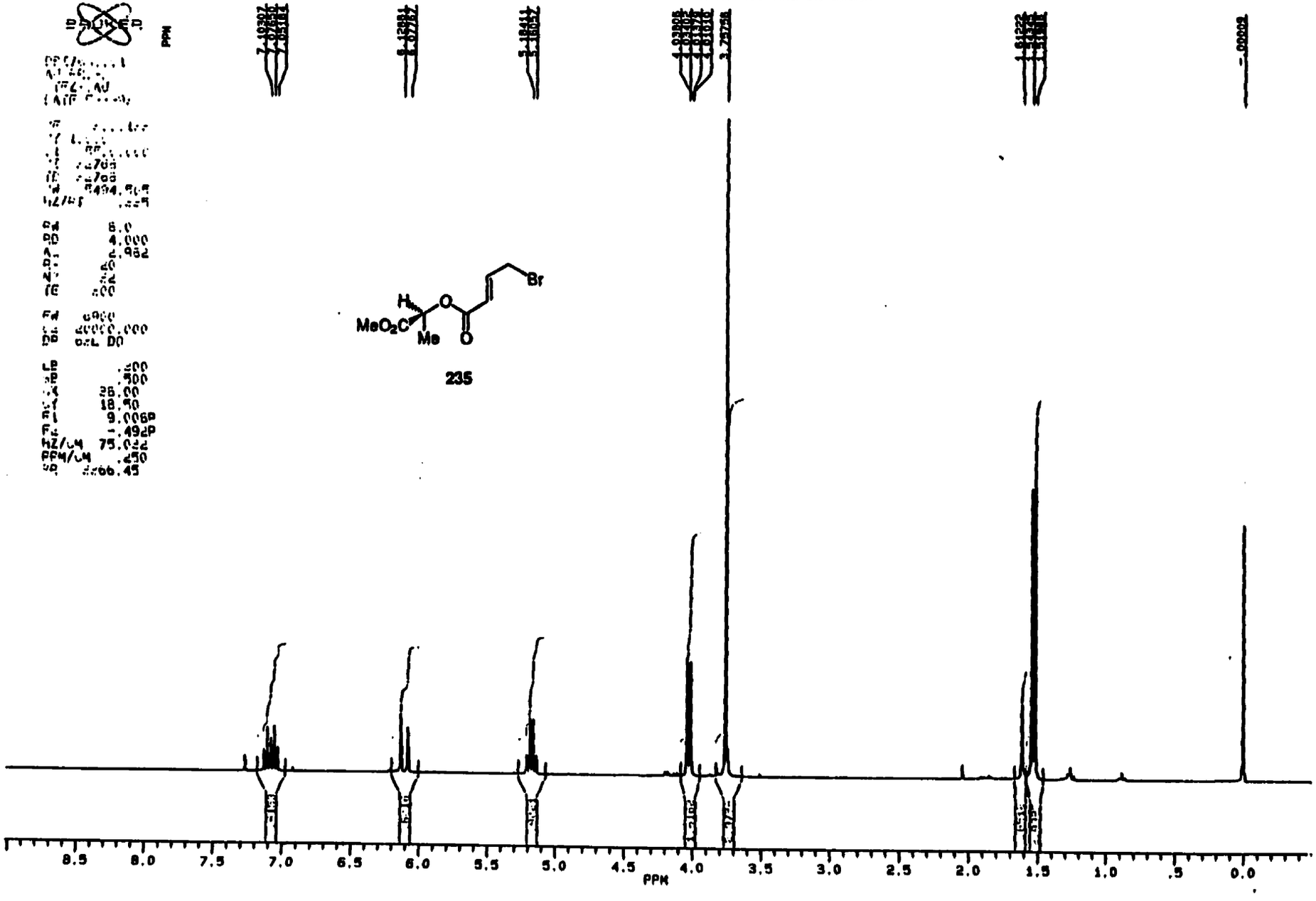
225



SAMPLE DB--I--76--C 1-H AT 300 MHZ IN CDCL3




235



SAMPLE DB-I-76-C 13-C AT 75.47 MHZ IN CDCL3



DBI76CC.004
AU PROG:
AUTOC13.AU
DATE 6-8-93

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

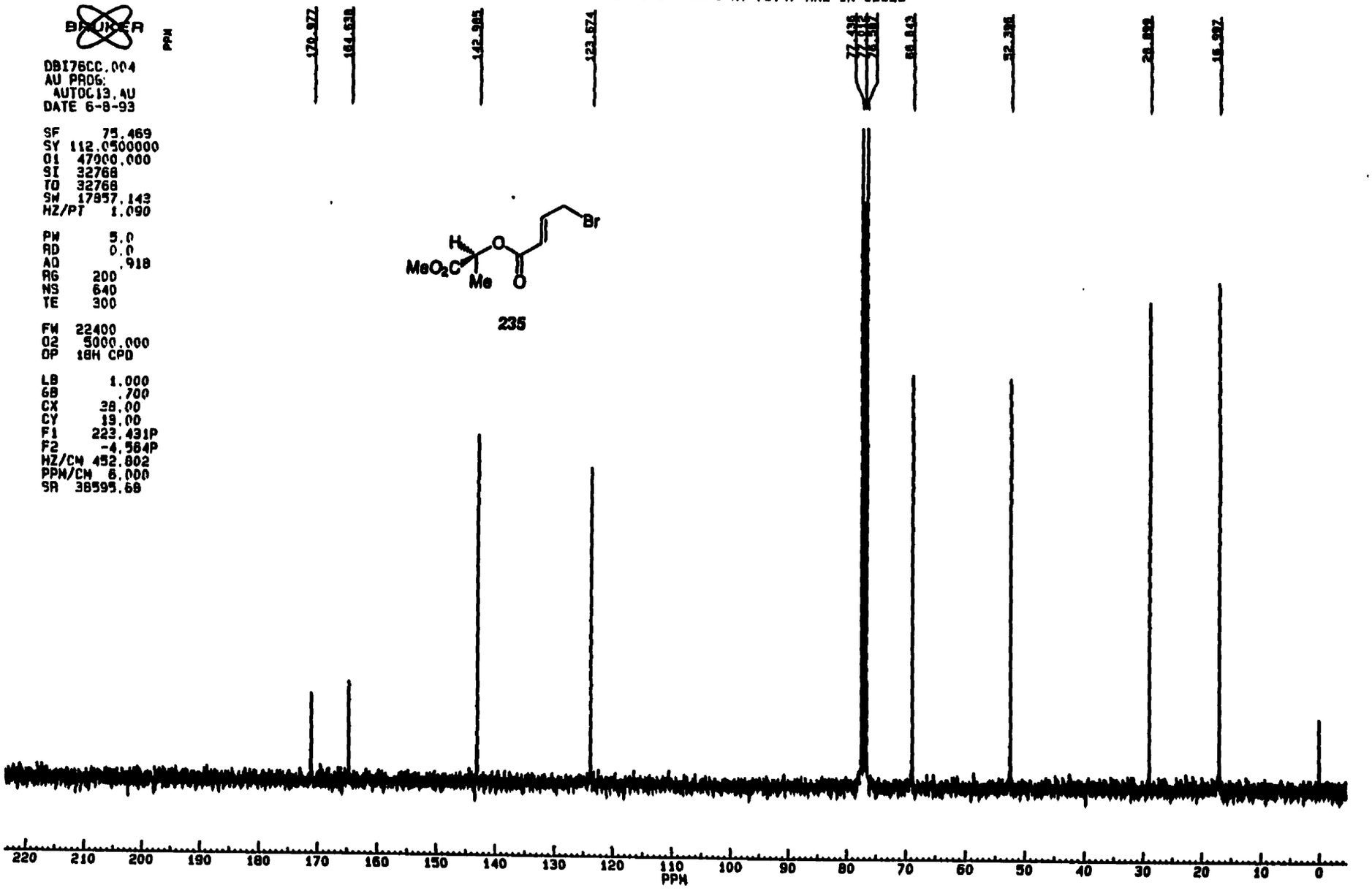
PW 5.0
RD 0.0
AQ .918
RG 200
NS 640
TE 300

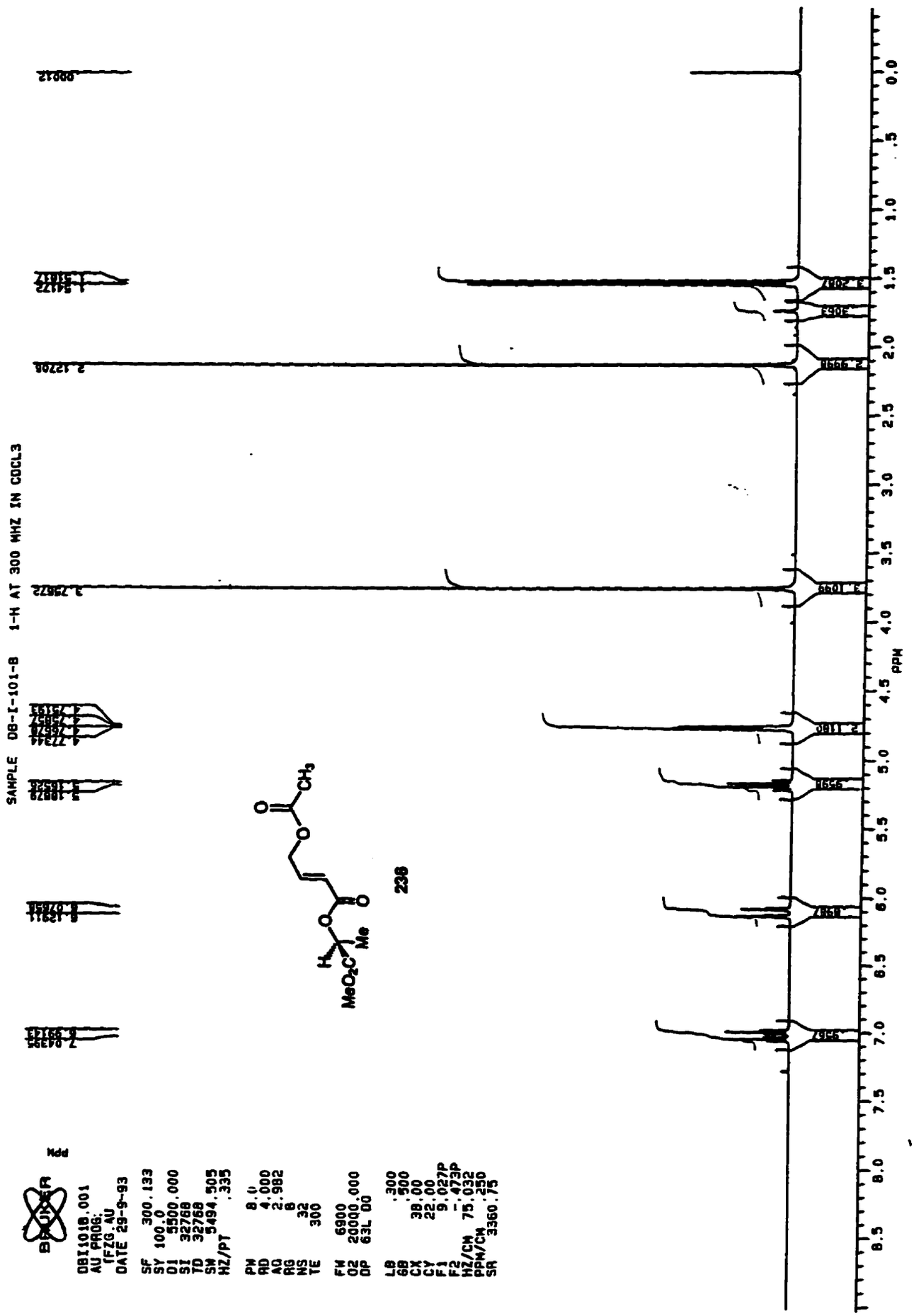
FW 22400
O2 5000.000
OP 18H CPD

LB 1.000
GB .700
CX 38.00
CY 19.00
F1 223.431P
F2 -4.564P
HZ/CM 452.802
PPM/CM 6.000
SR 38595.68

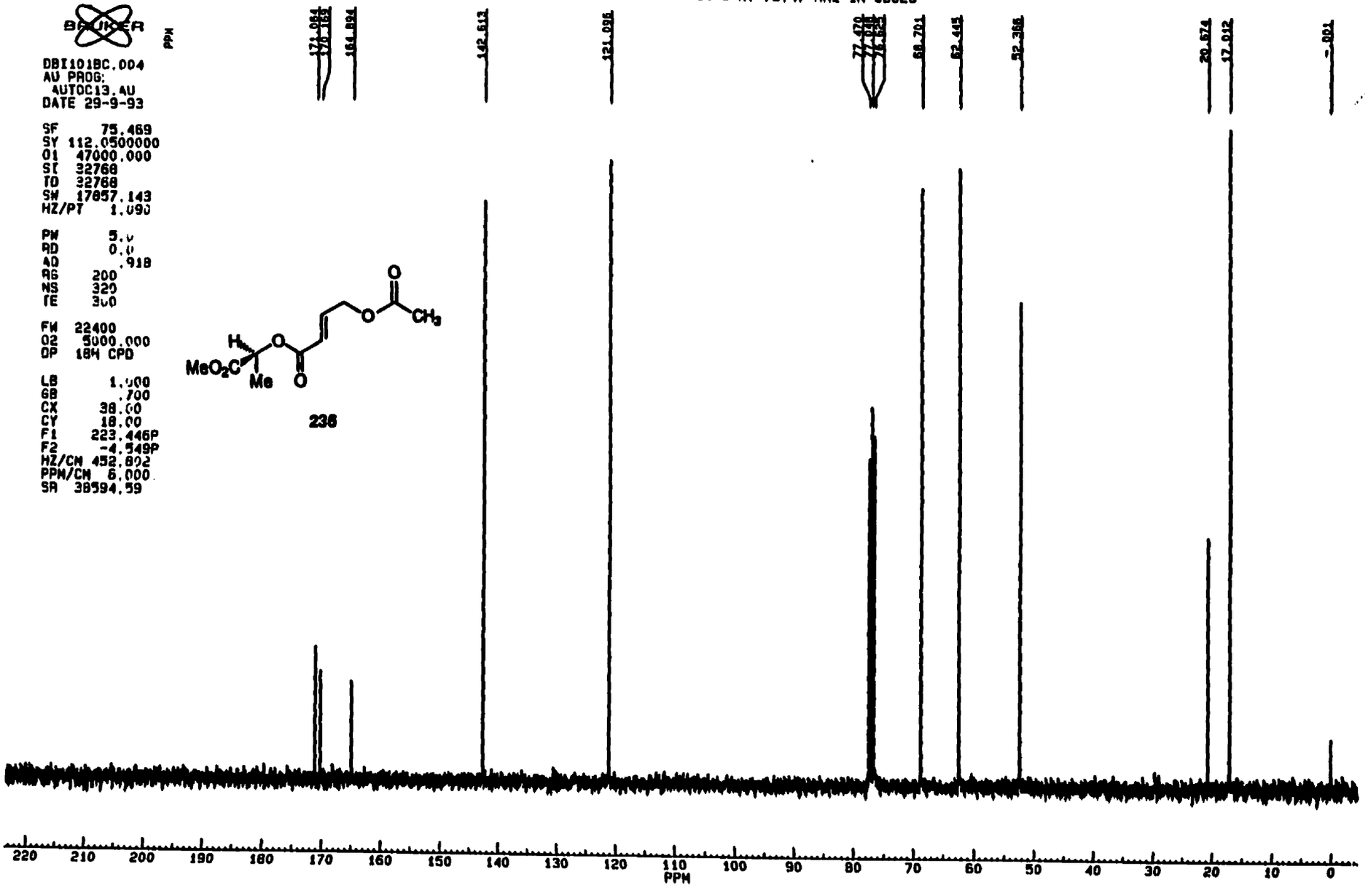



235

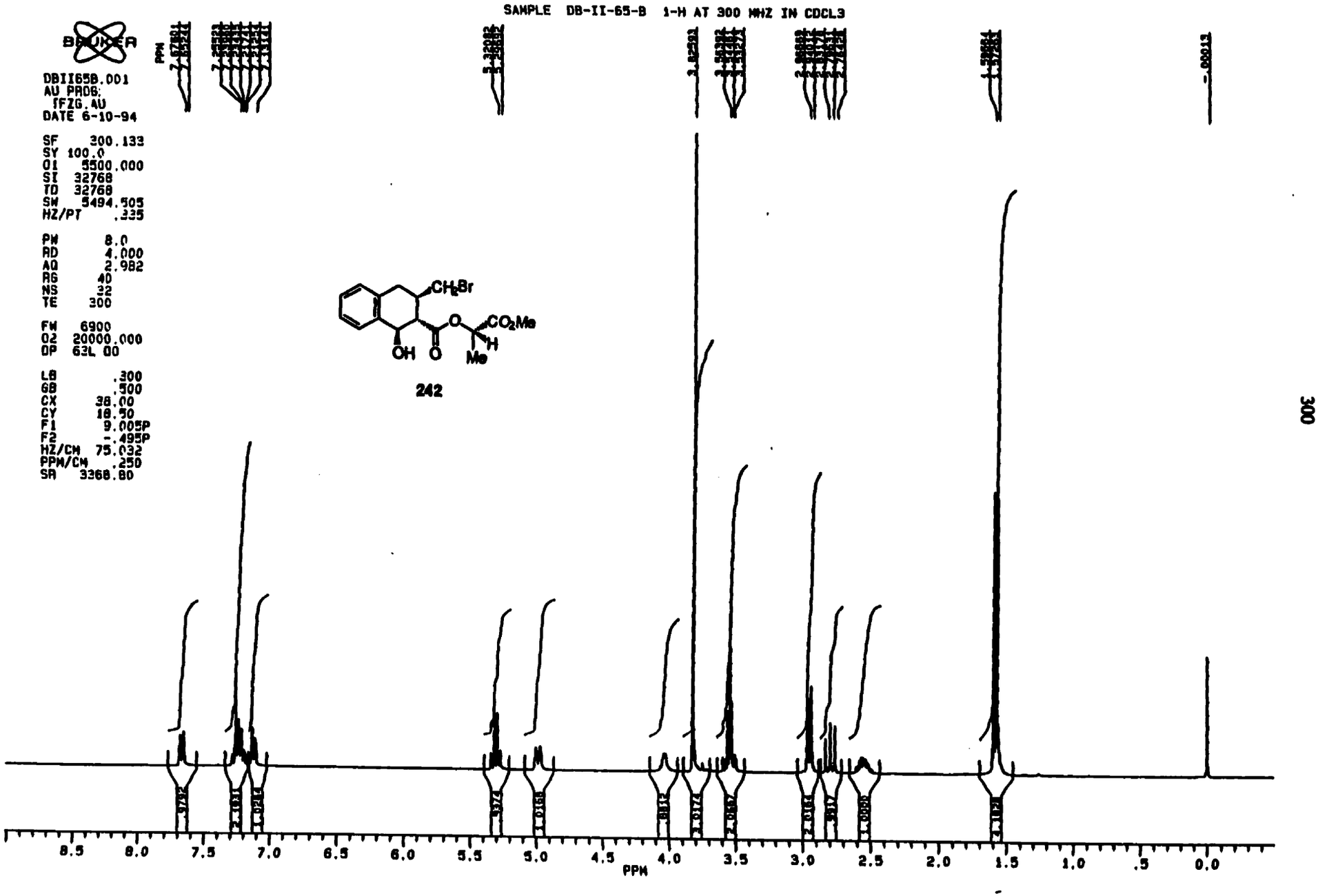



SAMPLE DB-I-101-B 1-H AT 300 MHZ IN CDCL3
DBI1018.001
AU PROG:
TFZG.AU
DATE 29-9-93
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 22.00
F1 9.027P
F2 -.473P
HZ/CM 75.032
PPM/CM .250
SR 3360.75
PPM
238

SAMPLE DB-I-101-B 13-C AT 75.47 MHZ IN CDCL3




236


SAMPLE DB-II-65-B 1-H AT 300 MHZ IN CDCL3
BRUKER
DBII65B.001
AU PROG:
TFZG.AU
DATE 6-10-94
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 40
NS 32
TE 300
FW 6900
O2 20000.000
OP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.80
CH2Br
CO2Me
OH
O
Me
H
242
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

300

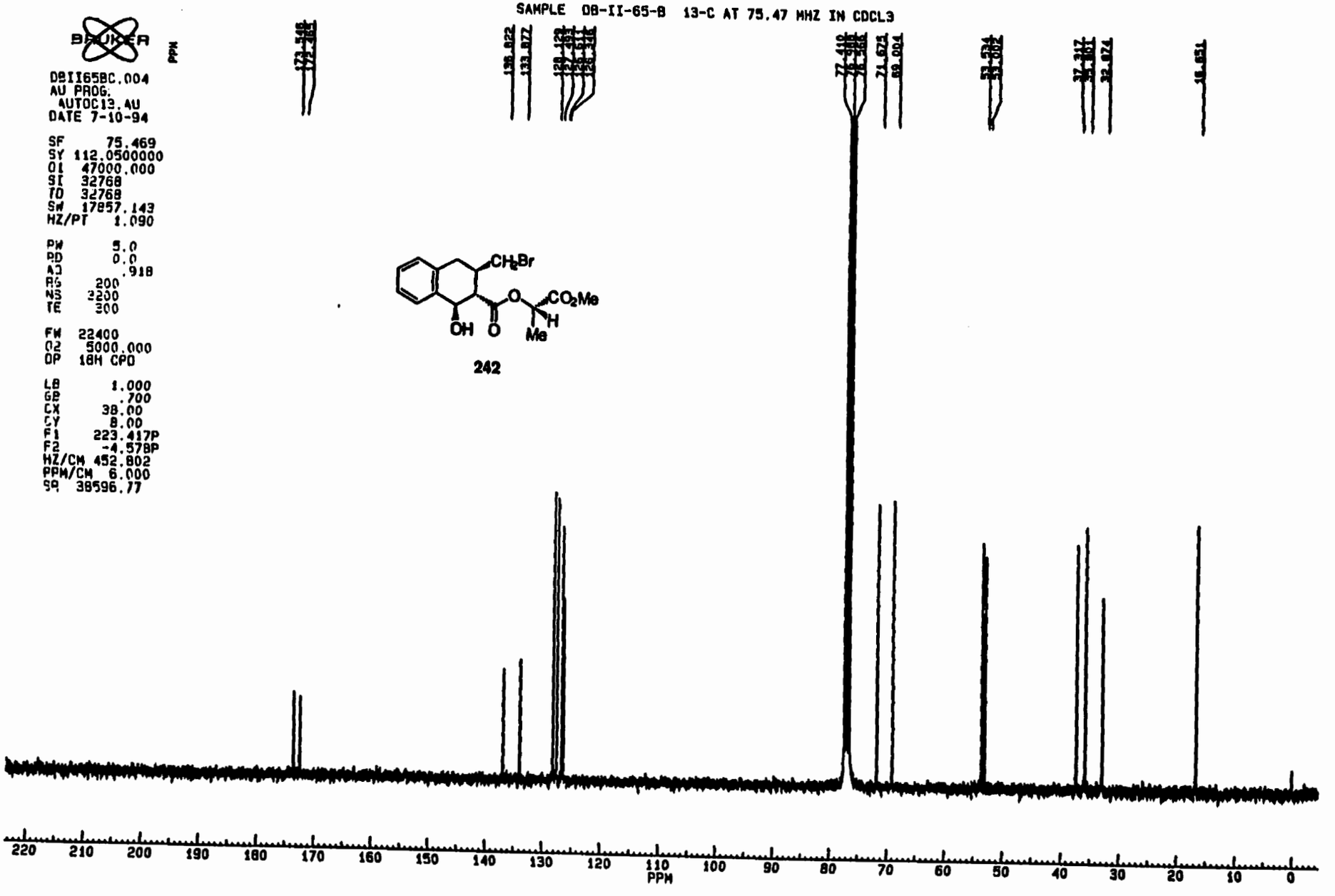
SAMPLE DB-II-65-B 13-C AT 75.47 MHZ IN CDCL3

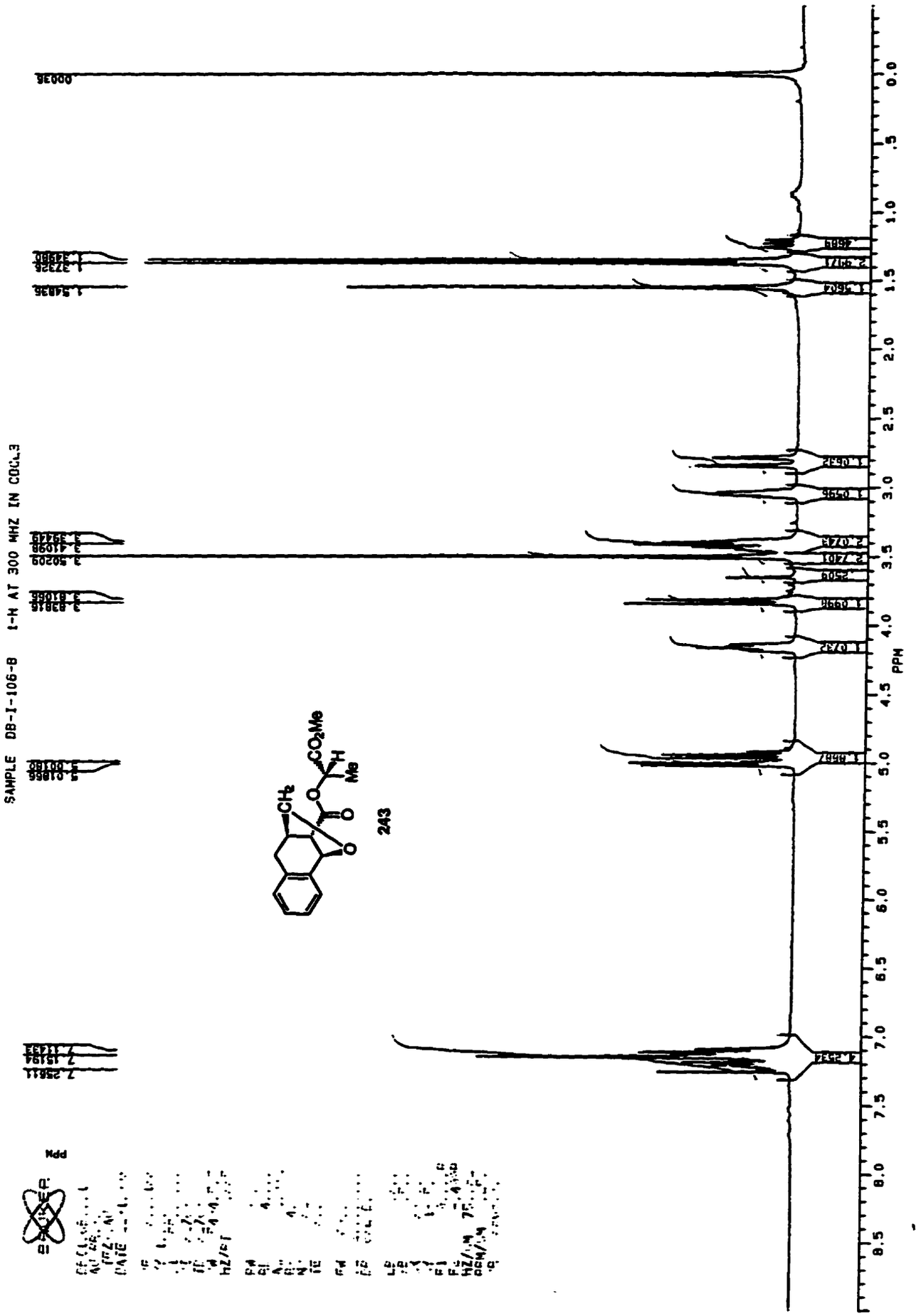




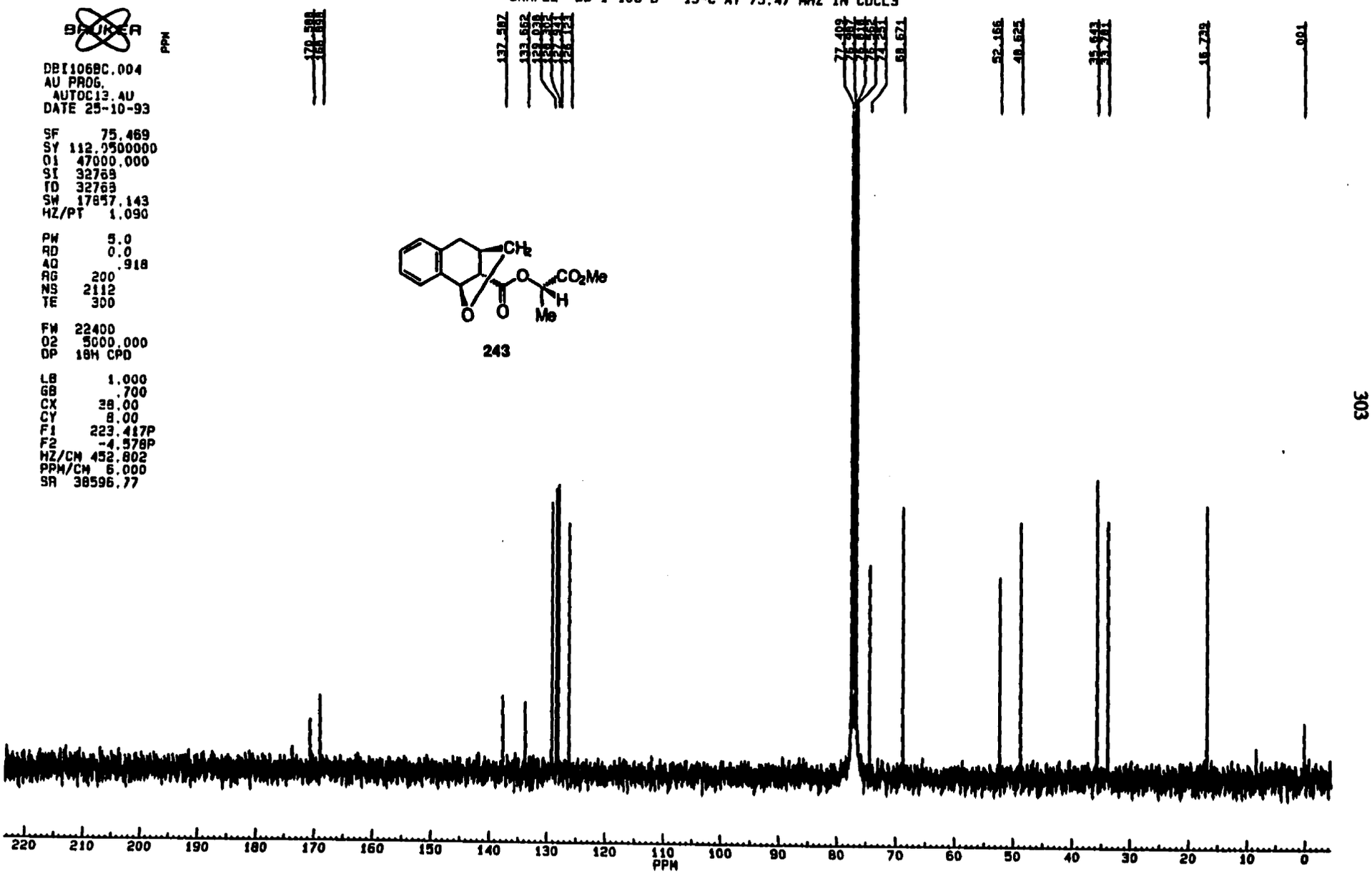


242

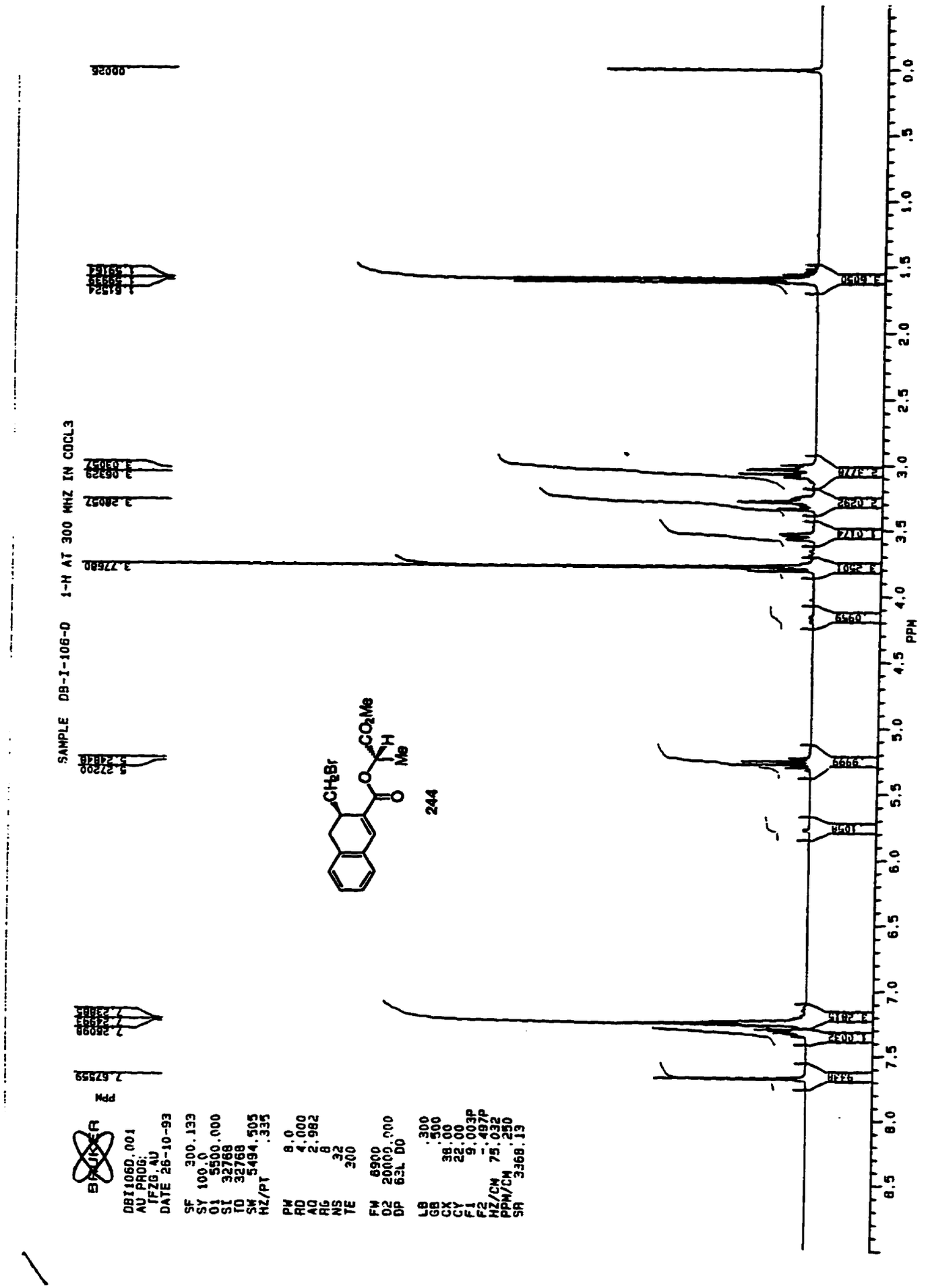


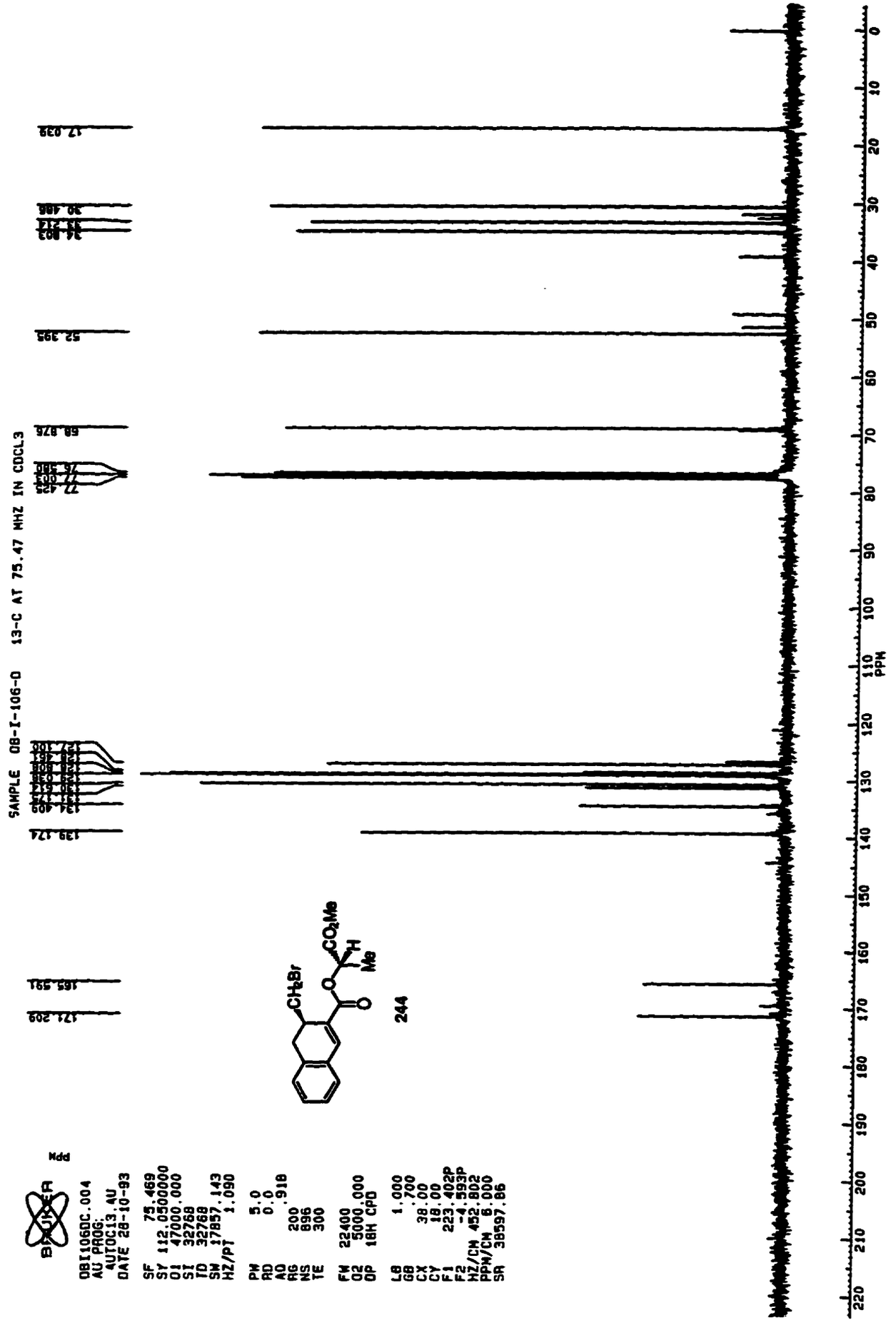

SAMPLE DB-I-106-B 1-H AT 300 MHZ IN CDCL3
CO2Me
H
Me
CH2
O
O
O
243
PPM

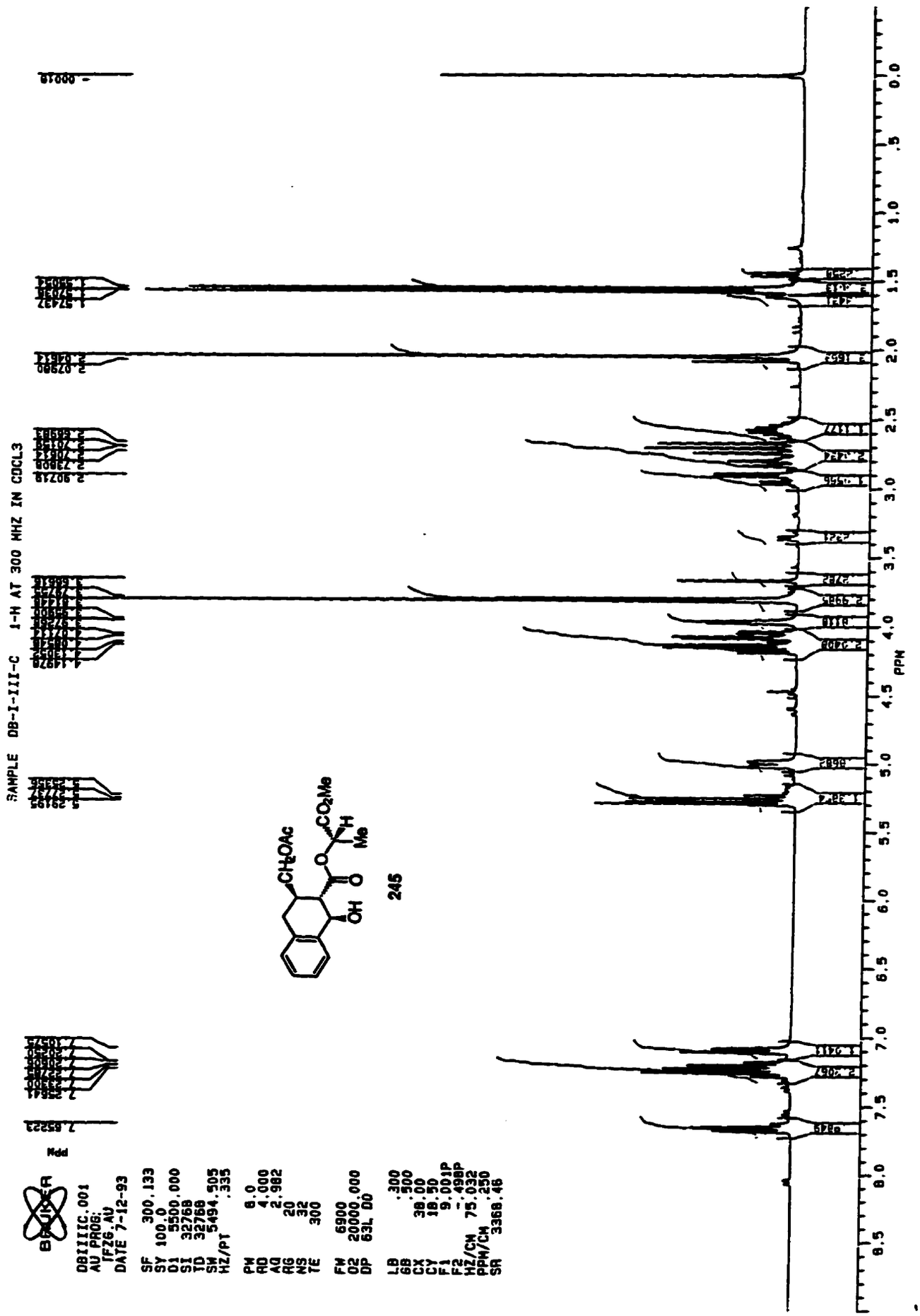
SAMPLE DB-I-106-B 13-C AT 75.47 MHZ IN CDCL3



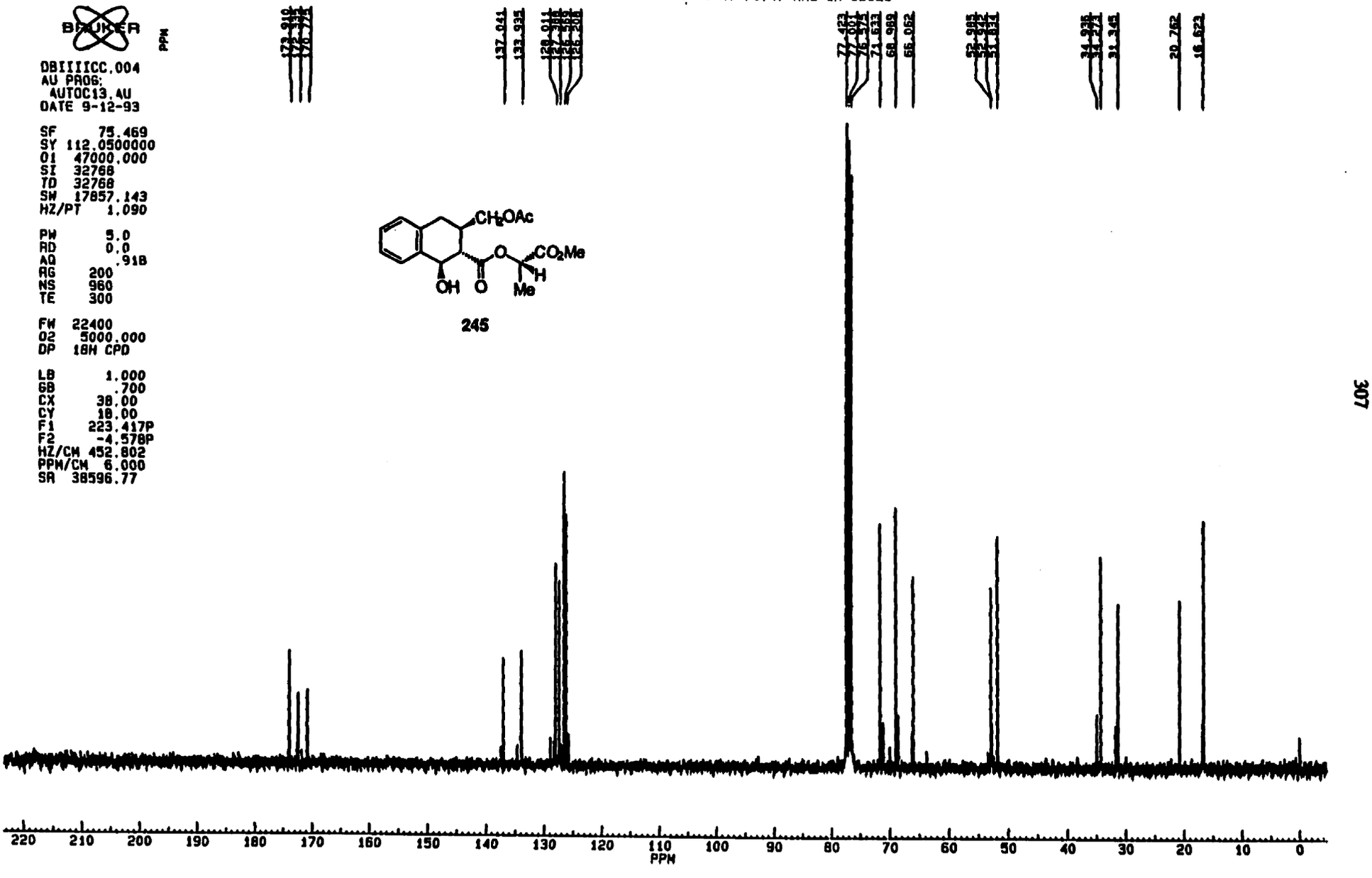

243


SAMPLE DB-I-106-D 1-H AT 300 MHZ IN COCL3
DBI106D.001
AU PROG:
IFZG.AU
DATE 26-10-93
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
D2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 22.00
F1 9.003P
F2 -.497P
HZ/CM 75.032
PPM/CM 25.250
SR 3368.13
PPM
CH2Br
CO2Me
H
Me
O
244

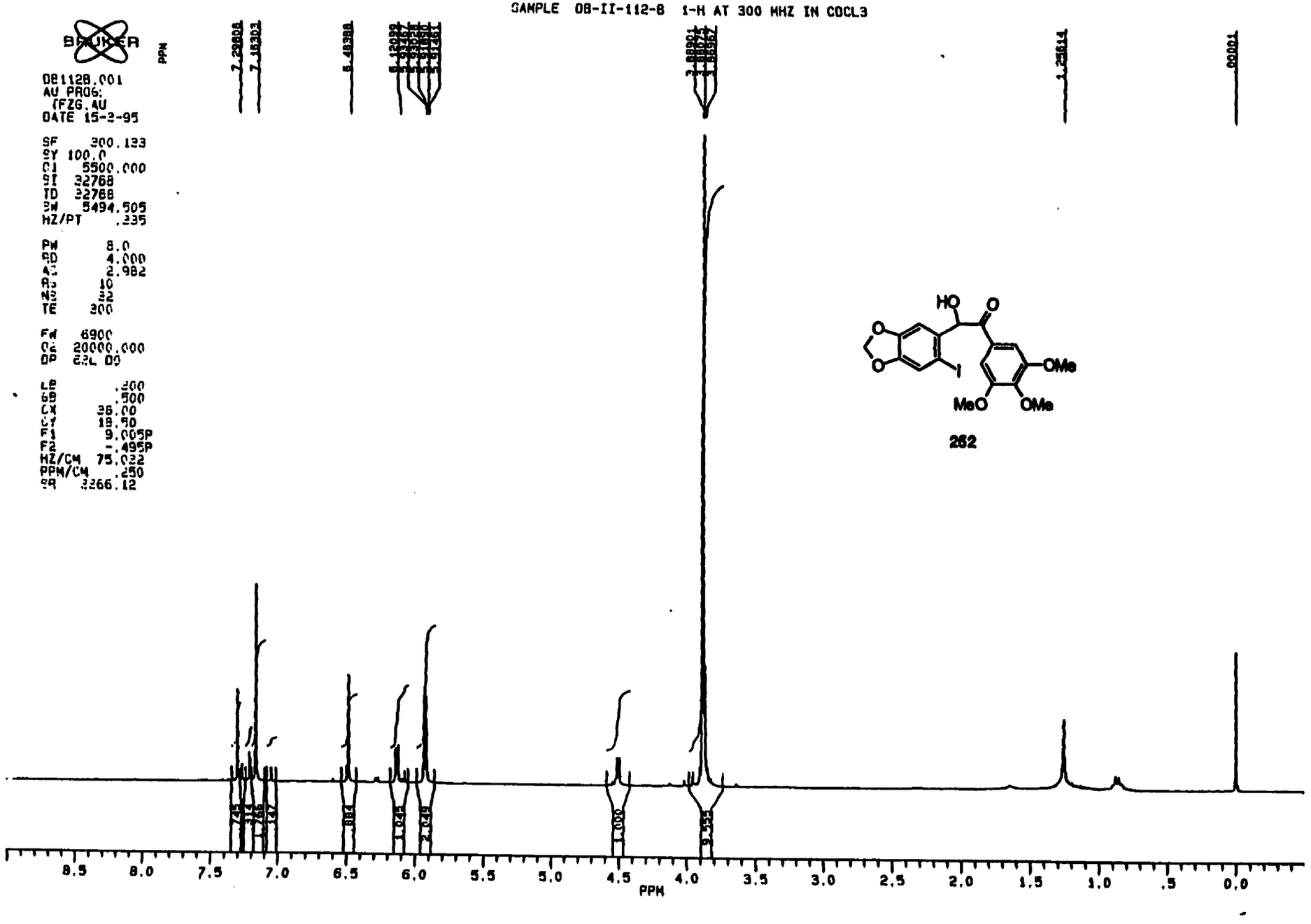

SAMPLE 08-I-106-D 13-C AT 75.47 MHZ IN CDCL3
DBI1060C.004
AU PROG.
AUTOC13.AU
DATE 28-10-93
SF 75.469
SY 112.0500000
OI 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 896
TE 300
FM 22400
O2 5000.000
OP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.802
PPM/CM 6.000
SR 38597.86
PPM
CH2Br
CO2Me
H
Me
O
O
244


SAMPLE DB-I-III-C 1-H AT 300 MHZ IN CDCL3
DBIIIIC.001
AU PROG:
IFZ6.AU
DATE 7-12-93
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.001P
F2 -.498P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
PPM
CH2OAc
CO2Me
H
Me
O
O
OH
245

SAMPLE DB-I-III-C 13-C AT 75.47 MHZ IN CDCL3



SAMPLE 08-II-112-B 1-H AT 300 MHZ IN COCL3




262

SAMPLE DB-III-6A 13-C AT 75.47 MHZ IN CDCL3



0836AC.004
AU PROG:
AUTOC13.AU
DATE 1-4-95

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

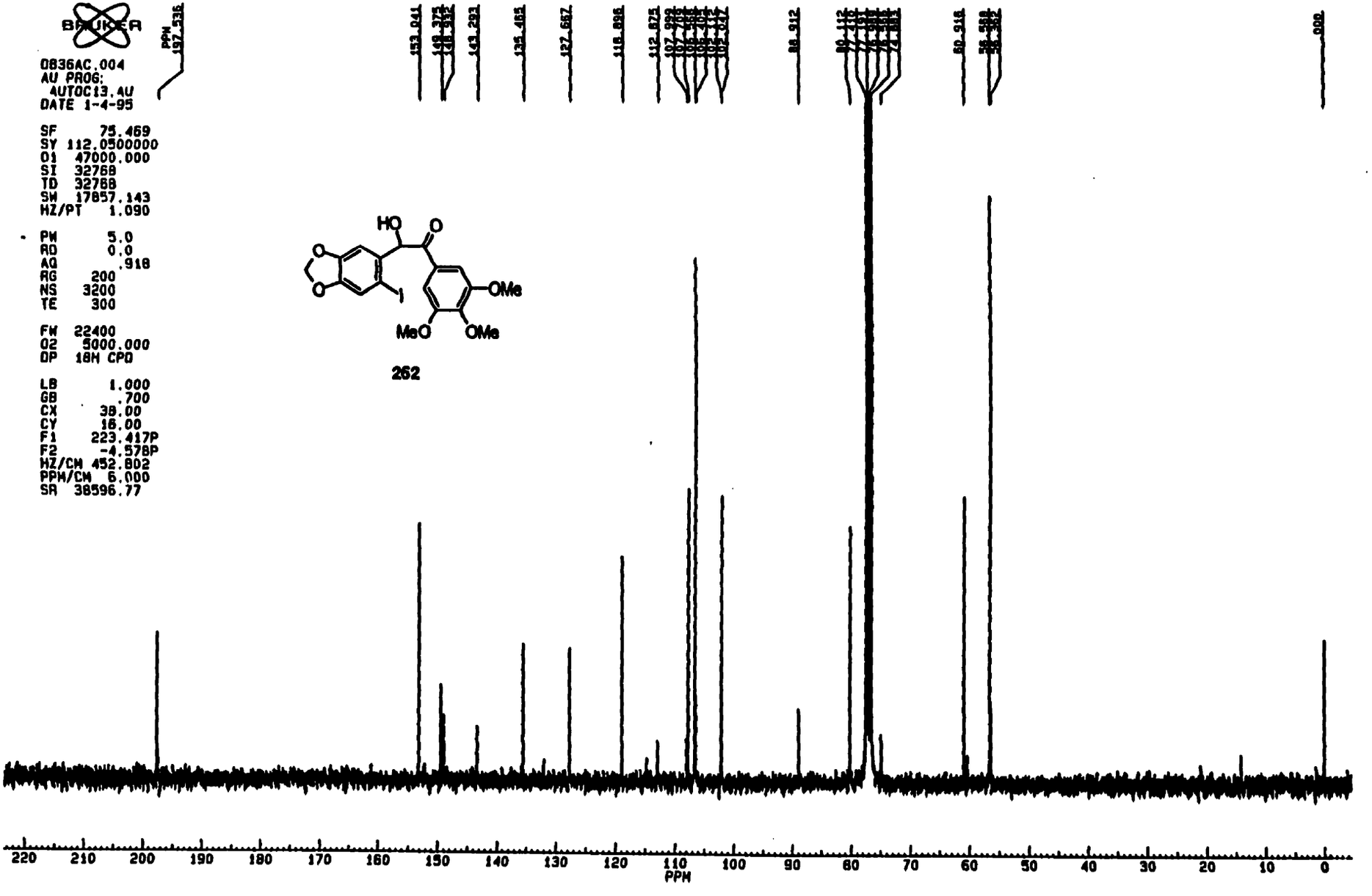
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300

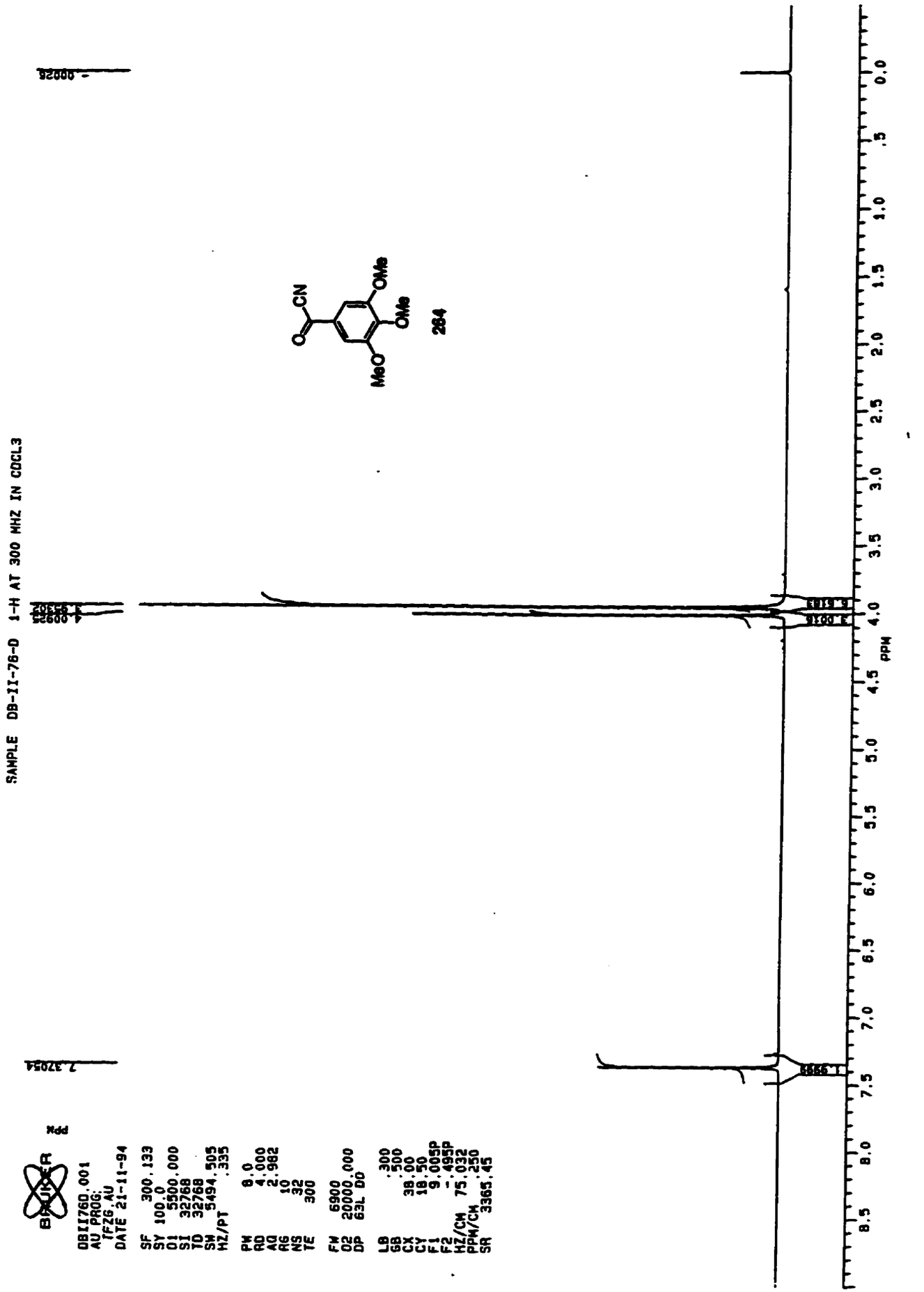
FW 22400
O2 5000.000
DP 18H CPD

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

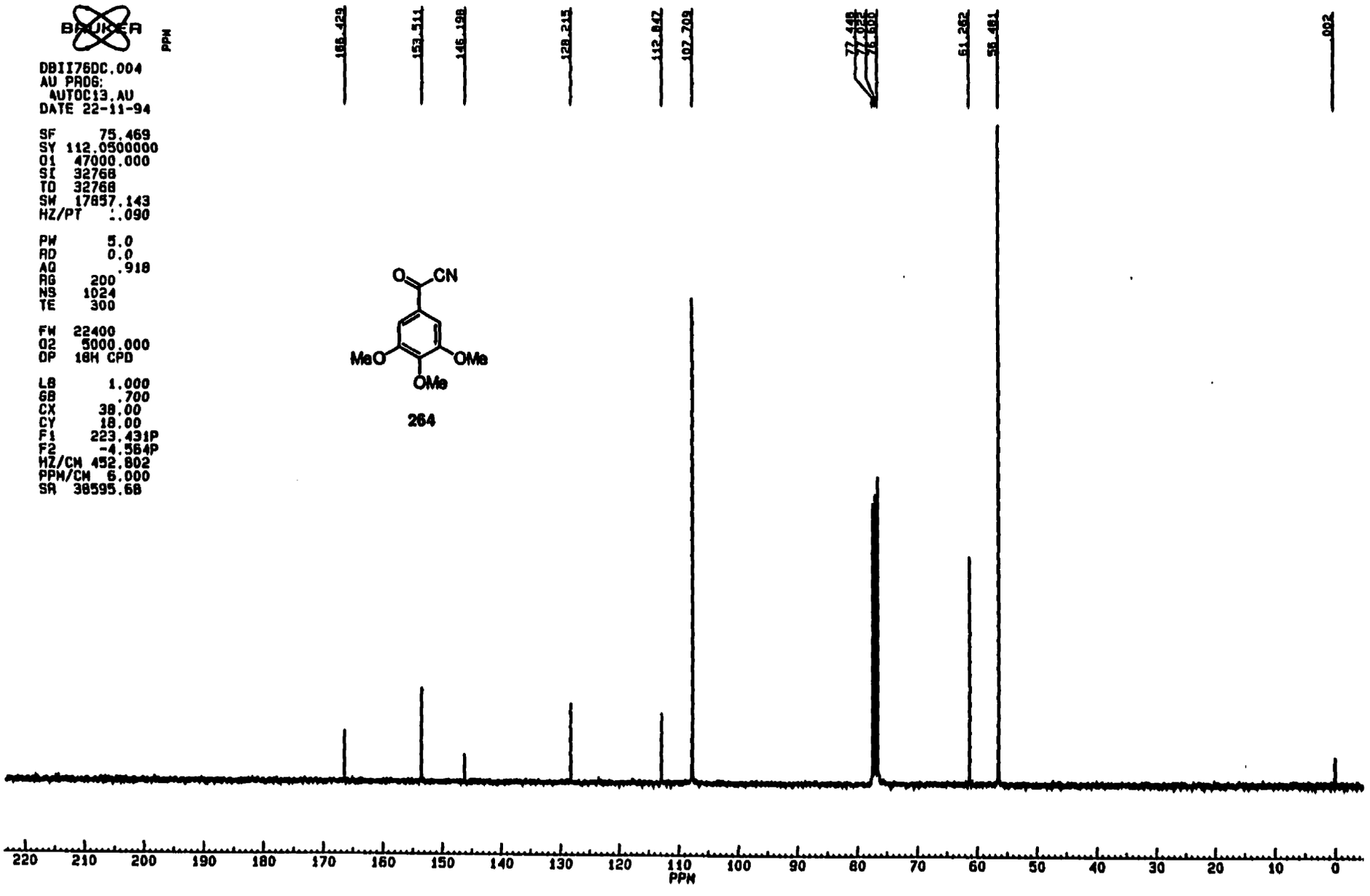


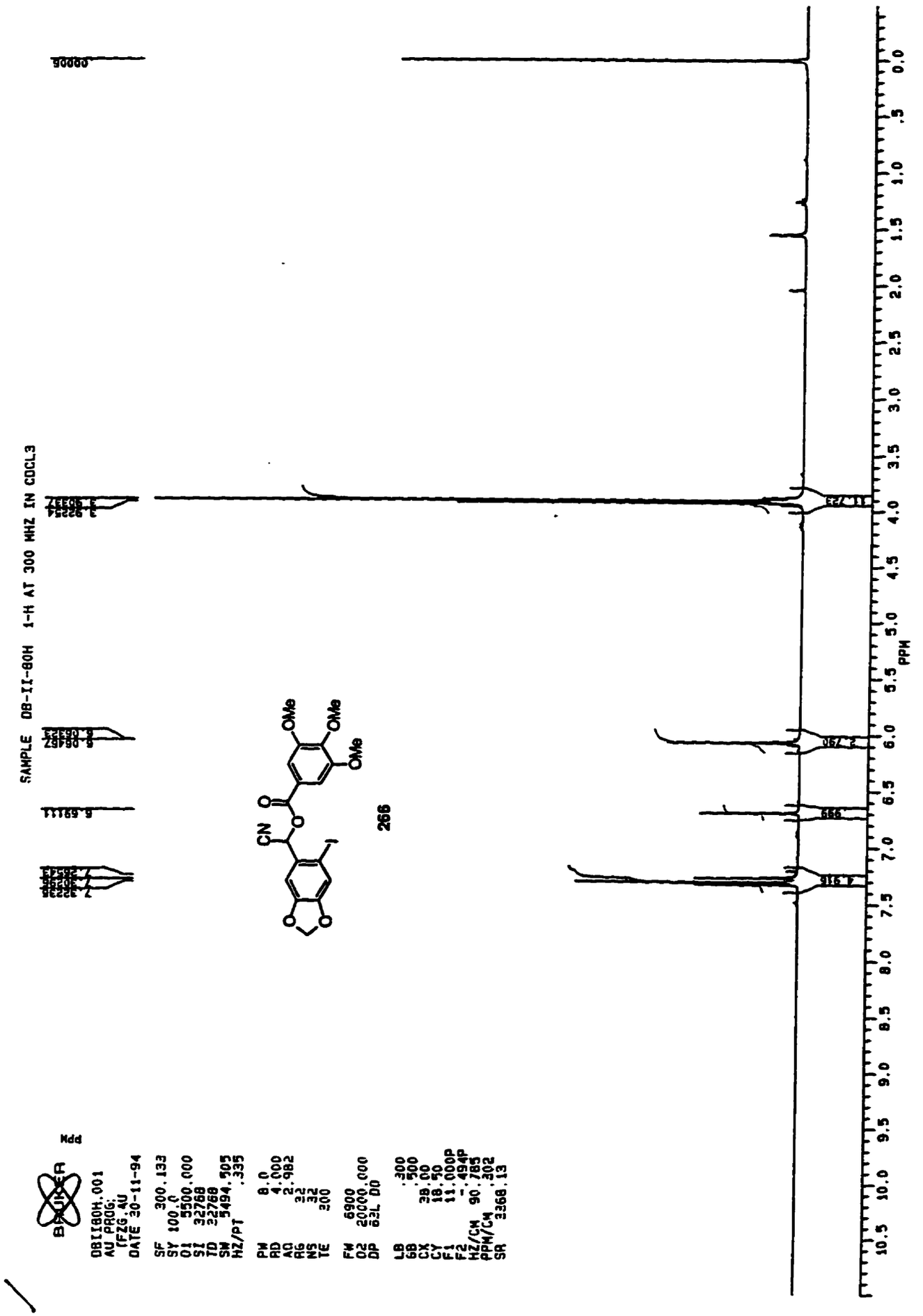

262

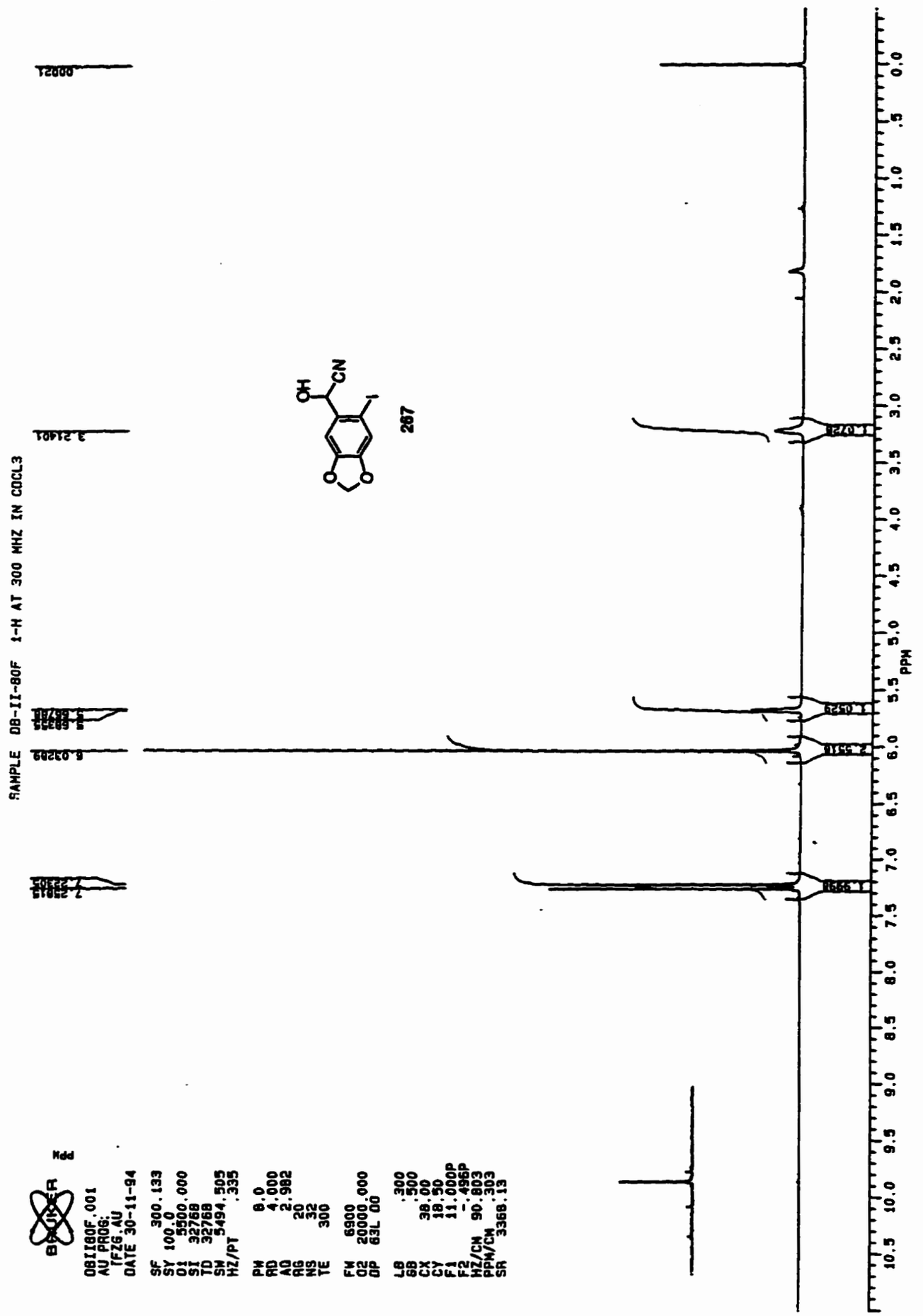



SAMPLE DB-II-76-D 1-H AT 300 MHZ IN CDCL3
284
MeO
OMe
OMe
CN
O
PPM
BRUKER
DBII760.001
AU PROG:
TFZ6.AU
DATE 21-11-94
SF 300.133
SY 100.0
DI 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3365.45

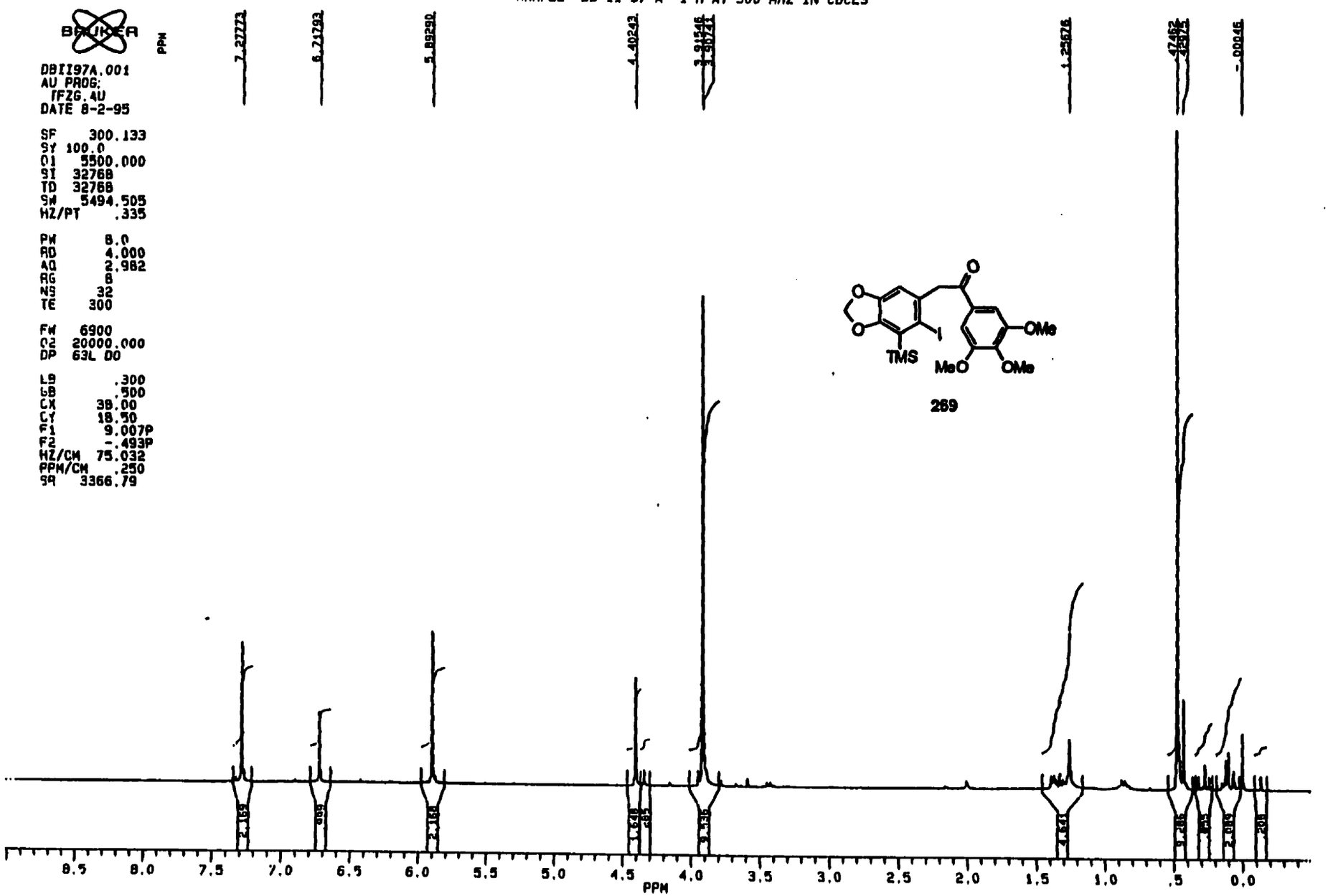
SAMPLE DB-II-76-D 13-C AT 75.47 MHZ IN CDCL3




SAMPLE DB-II-80H 1-H AT 300 MHZ IN CDCL3
OMe
OMe
OMe
CN
O
O
I
266
PPM

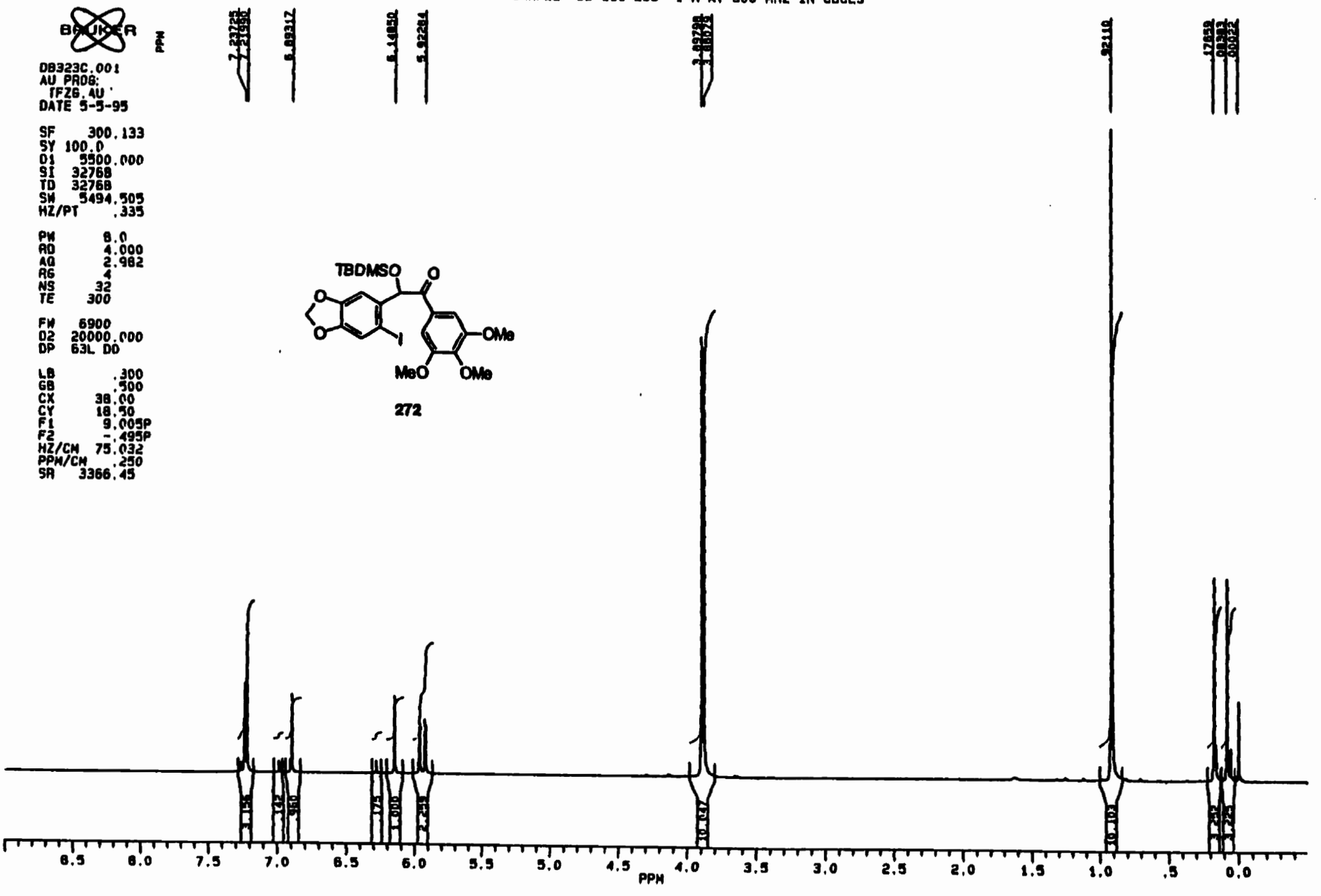

SAMPLE DB-II-80F 1-H AT 300 MHZ IN COCL3
267
PPM

SAMPLE DB-II-97-A 1-H AT 300 MHZ IN CDCL3




289

SAMPLE DB-III-23C 1-H AT 300 MHZ IN CDCL3



SAMPLE DB-III-23-C 13-C AT 75.47 MHZ IN CDCL3



DB323CC.004
AU PROG:
AUTOC13.AU
DATE 8-5-95

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

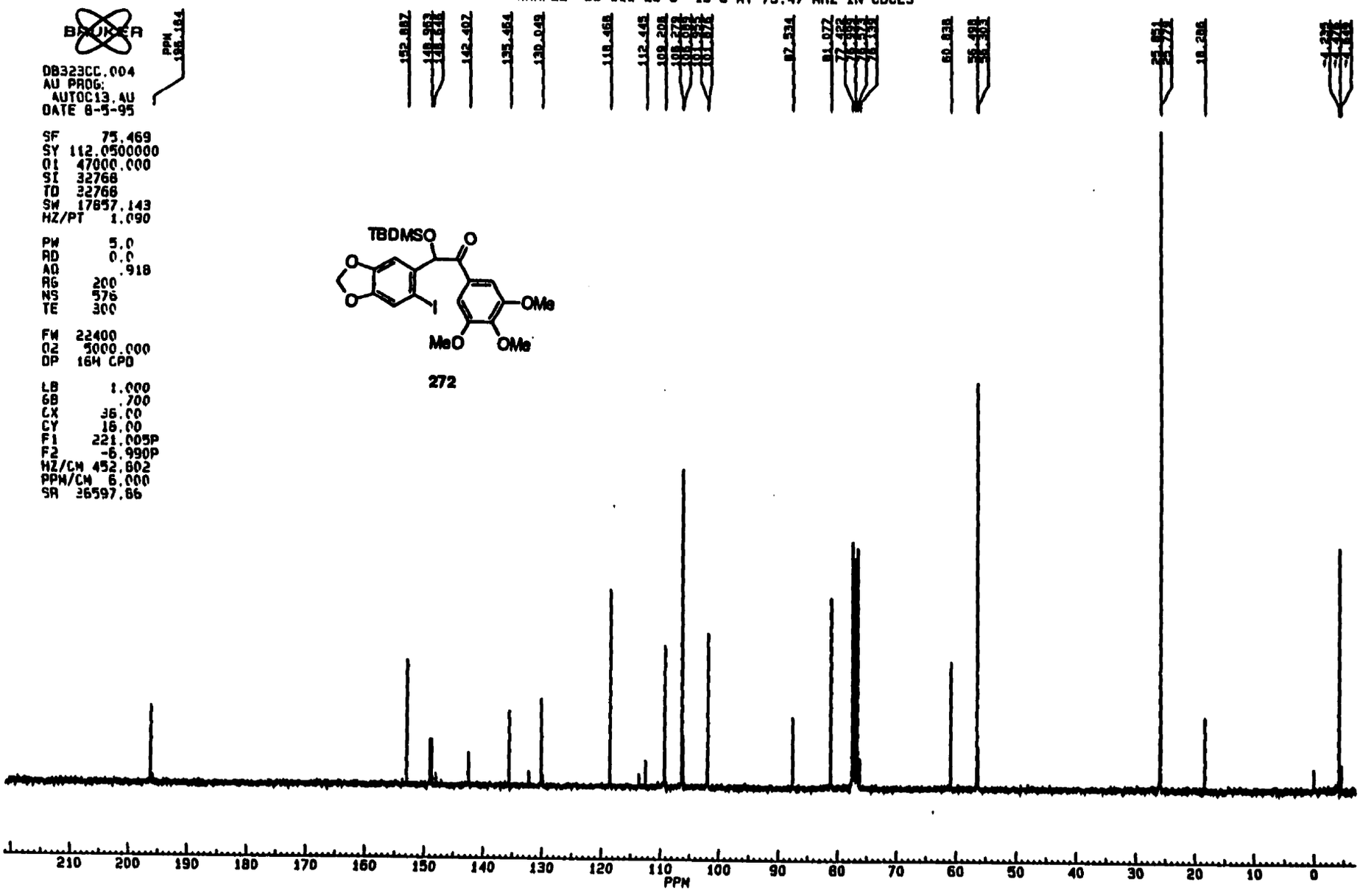
PW 5.0
RD 0.0
AQ .918
RG 200
NS 576
TE 300

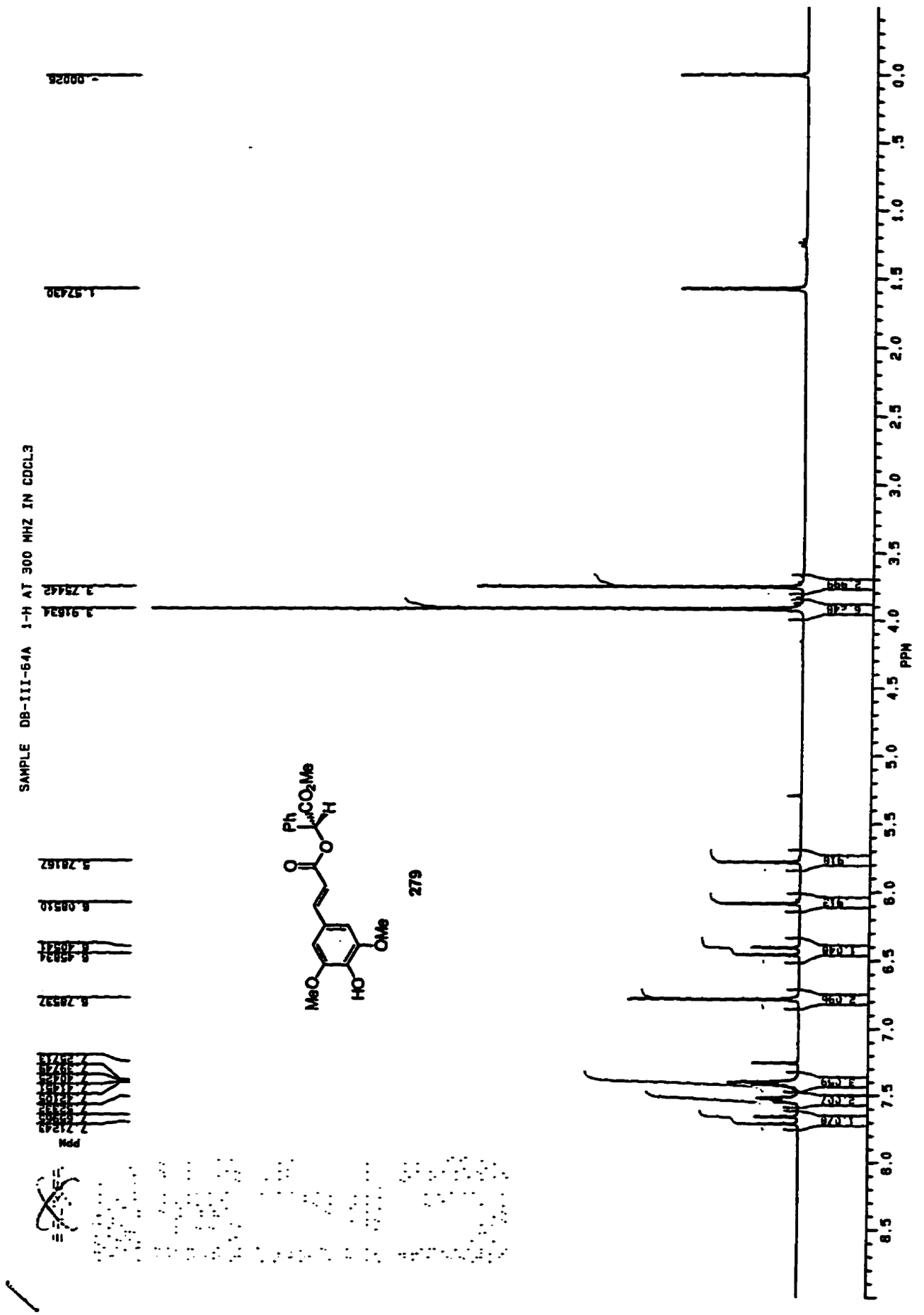
FW 22400
O2 5000.000
DP 16W CPD

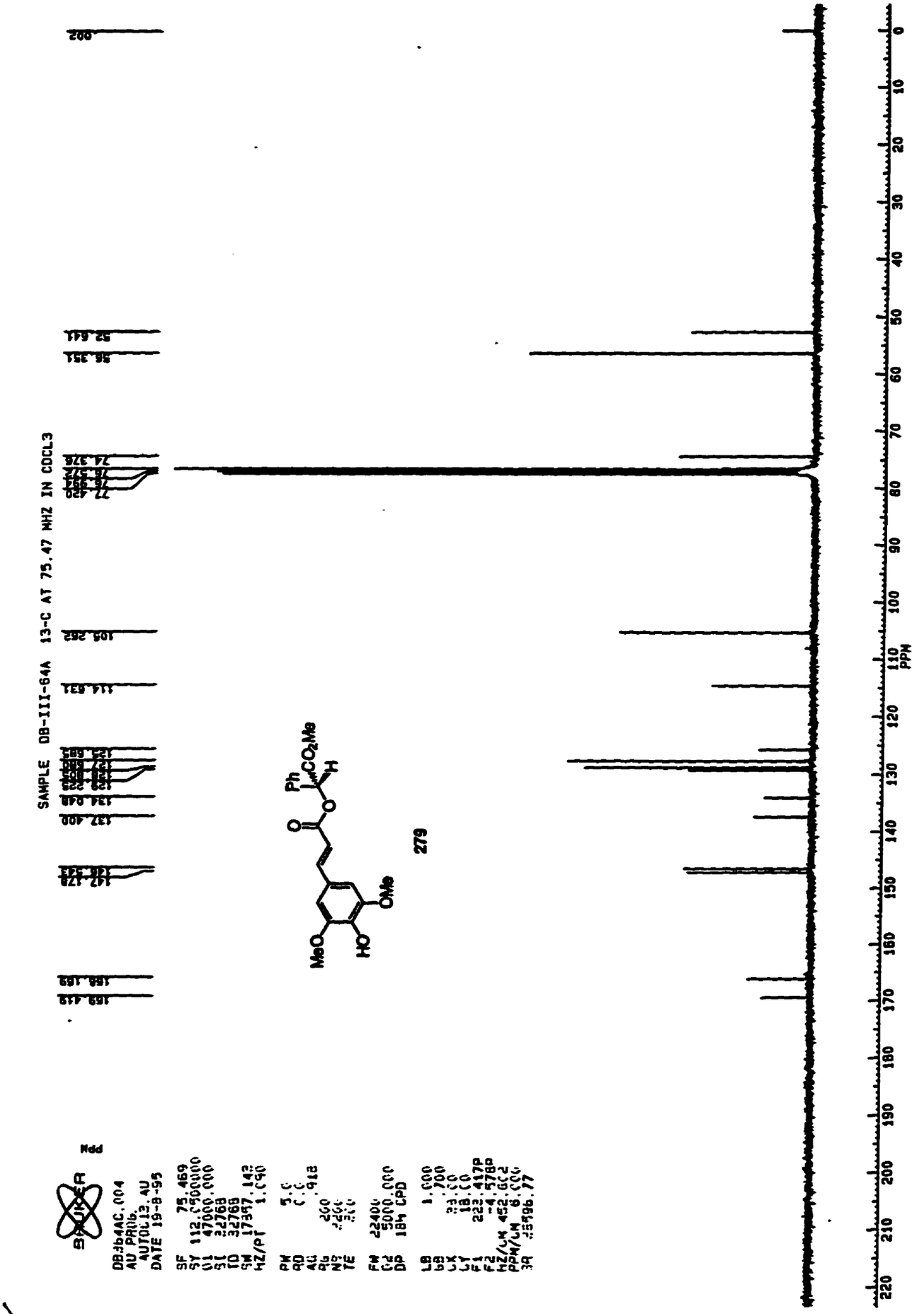
LB 1.000
GB .700
CX 36.00
CY 16.00
F1 221.005P
F2 -6.990P
HZ/CM 452.802
PPM/CM 6.000
SR 36597.66

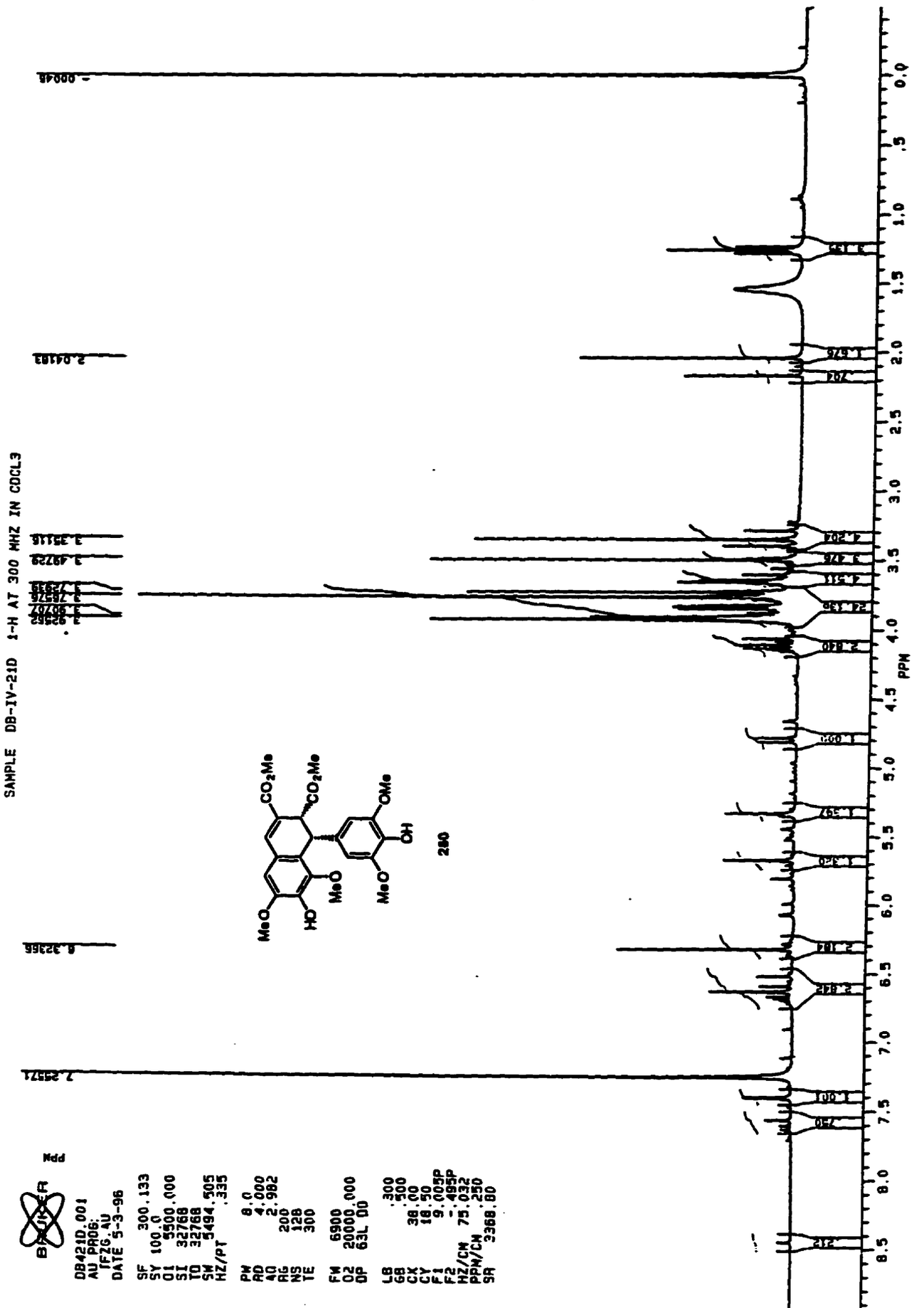



272

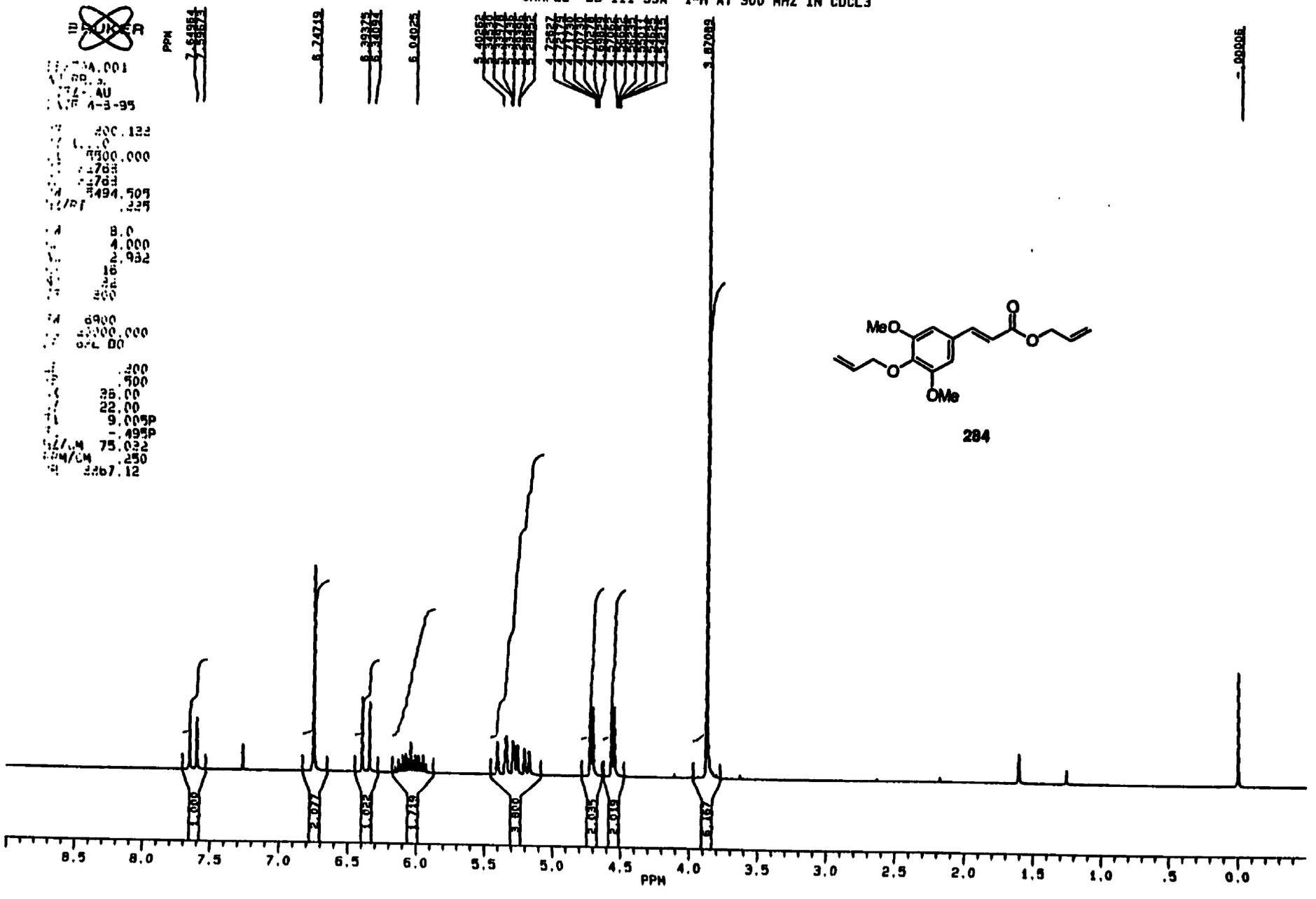



SAMPLE DB-III-64A 1-H AT 300 MHZ IN CDCL3
PPM
279
Ph
CO2Me
H
O
MeO
OMe
HO

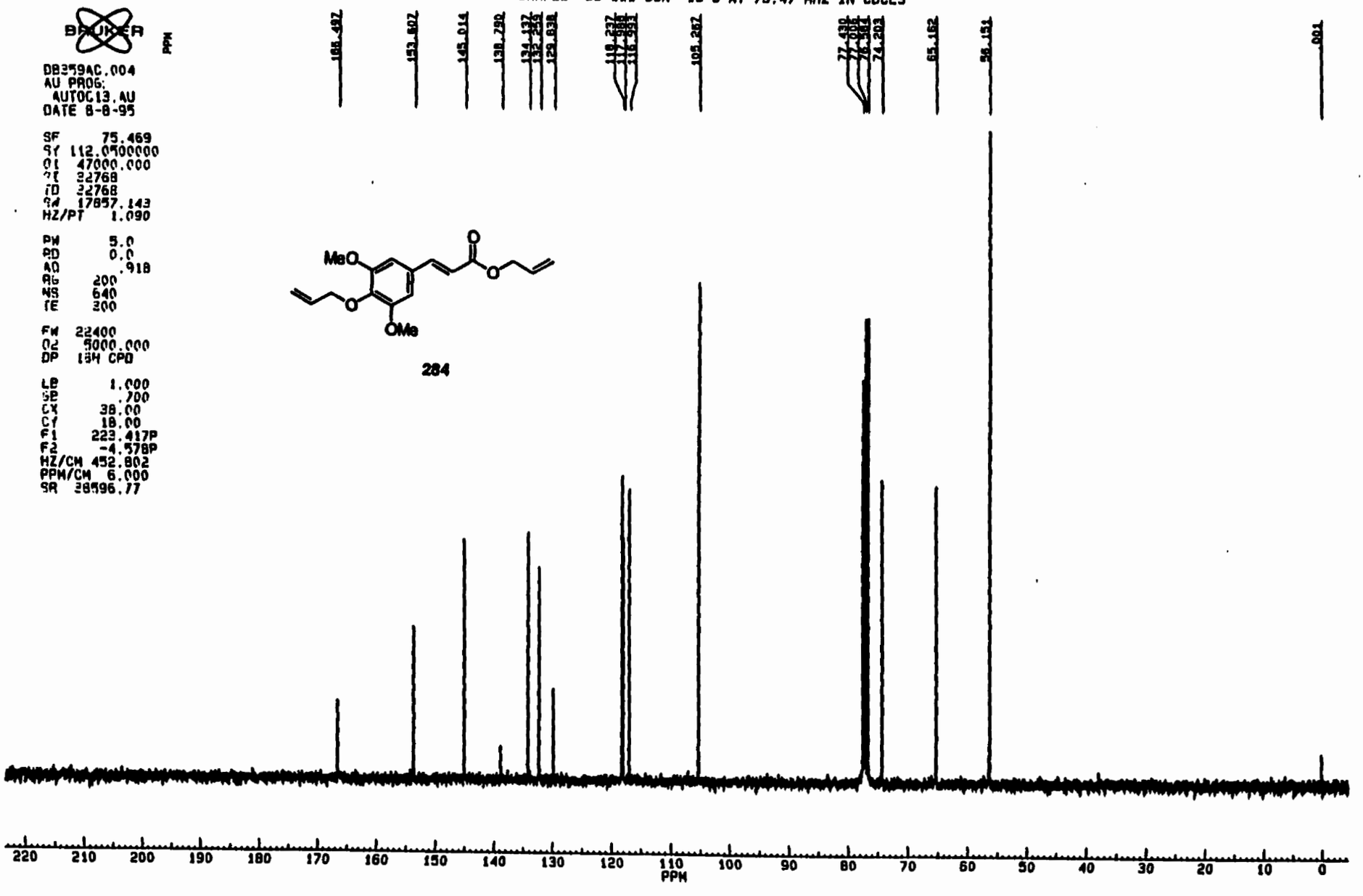

SAMPLE DB-III-64A 13-C AT 75.47 MHZ IN CDCL3
DB3b4AC.004
AU PROG.
AUTOL13.AU
DATE 19-8-95
PPM
PPM
Ph
CO2Me
H
O
O
MeO
OMe
HO
279

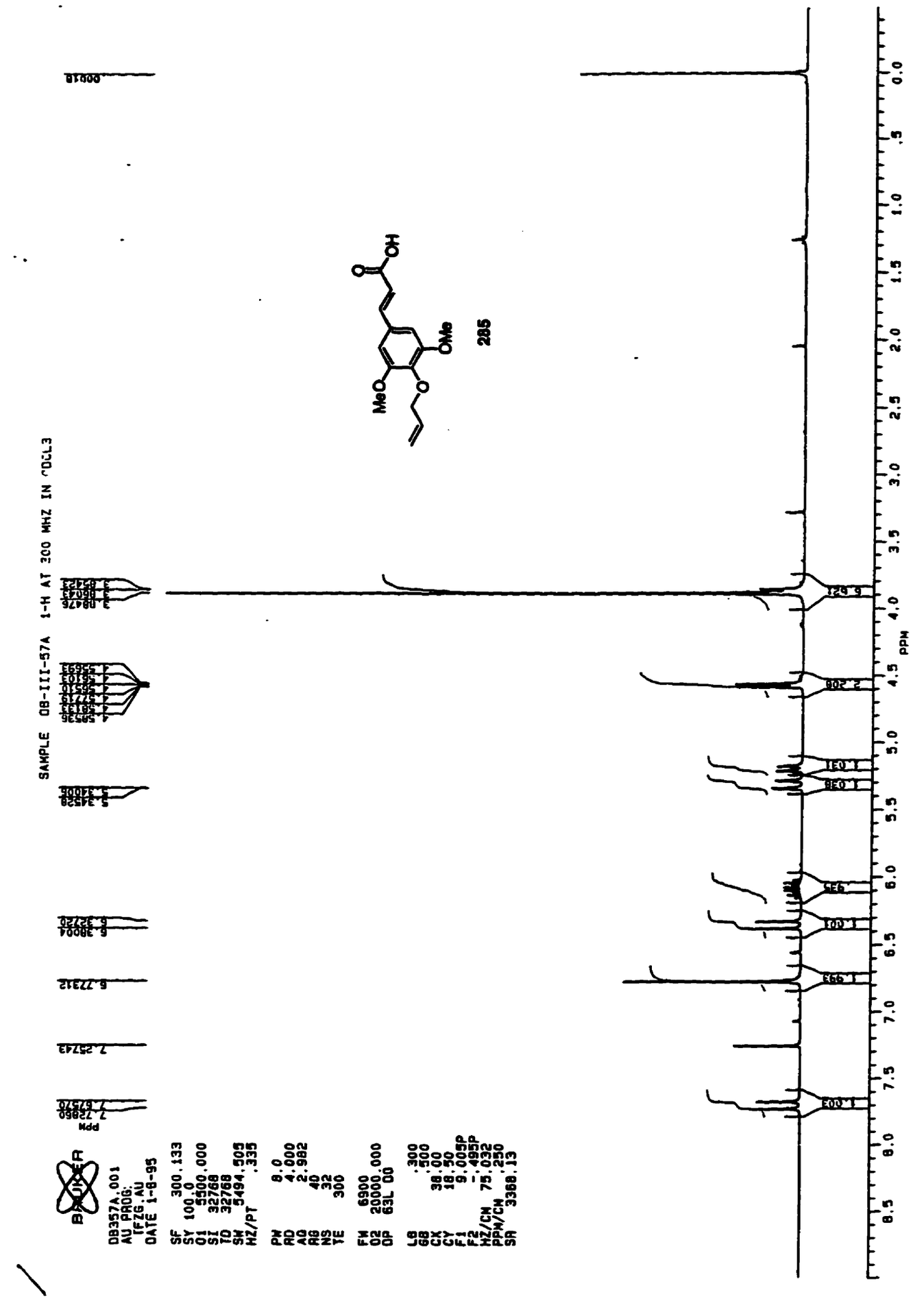

SAMPLE DB-IV-21D 1-H AT 300 MHZ IN CDCL3
DB421D.001
AU PROG:
IFZG.AU
DATE 5-3-96
SF 300.133
SY 100.0
DI 9900.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 200
NS 128
TE 300
FW 6900
O2 20000.000
DP 63L DD
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.80
PPM
CO2Me
CO2Me
OMe
OH
MeO
MeO
HO
280

SAMPLE DB-III-59A 1-H AT 300 MHZ IN CDCL3

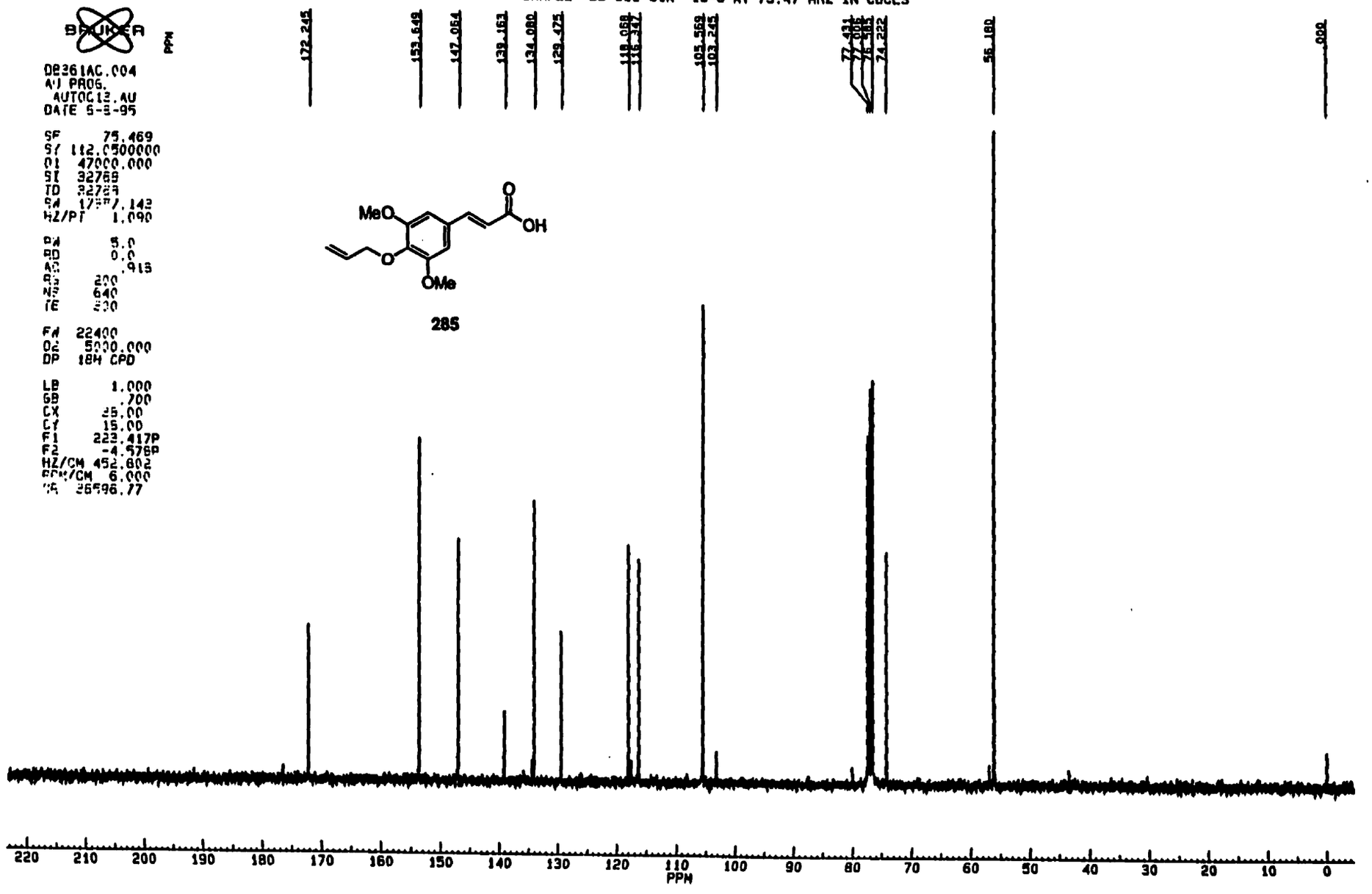


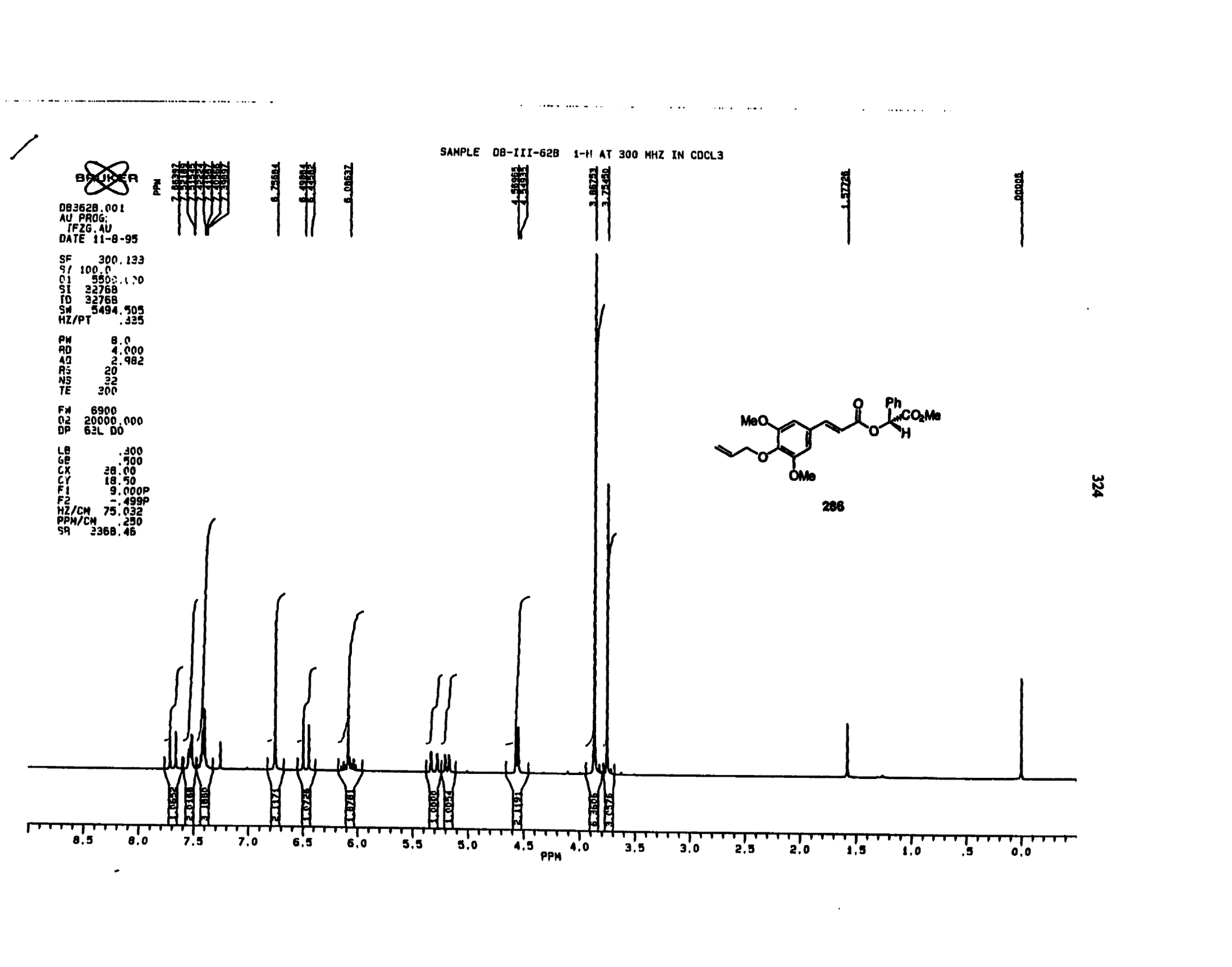

284


SAMPLE DB-III-59A 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
DB359AC.004
AU PROG:
AUTOC13.AU
DATE 8-8-95
SF 75.469
SI 112.0000000
DI 47000.000
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
D2 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
MeO
OMe
284
165.497
153.802
145.014
138.280
134.132
132.256
129.838
118.237
116.991
105.267
77.430
74.203
65.162
56.151
.001
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 OB-III-57A 1-H AT 300 MHZ IN CDCL3
DB357A.001
AU PROG:
[FZG.AU
DATE 1-8-95
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.13
MeO
OMe
OH
285
PPM

SAMPLE DB-III-61A 13-C AT 75.47 MHZ IN CDCL3




SAMPLE DB-III-62B 1-H AT 300 MHZ IN CDCL3
DB362B.001
AU PROG:
IFZG.AU
DATE 11-8-95
SF 300.133
SI 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
LB .300
GB .000
CX 28.00
CY 18.50
HZ/CM 75.032
PPM/CM .250
SR 3368.46
MeO
Ph
CO2Me
H
OMe
286
PPM

SAMPLE OB-III-62B 13-C AT 75.47 MHZ IN CDCL3

BRUKER

PPM

169.348
166.000
153.602
146.302
139.017
134.117
131.374
129.641
129.211
128.811
128.674
127.674
118.010
116.052
105.435
77.423
77.001
76.579
74.438
74.256
56.185
52.854
0.01

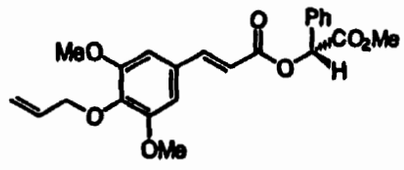
OB2628C.004
AU PROG.
AUTOC13.AU
DATE 14-8-95

SF 75.469
SI 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.142
HZ/PT 1.090

PW 5.0
PD 0.0
AQ .918
RG 200
NS 960
TE 300

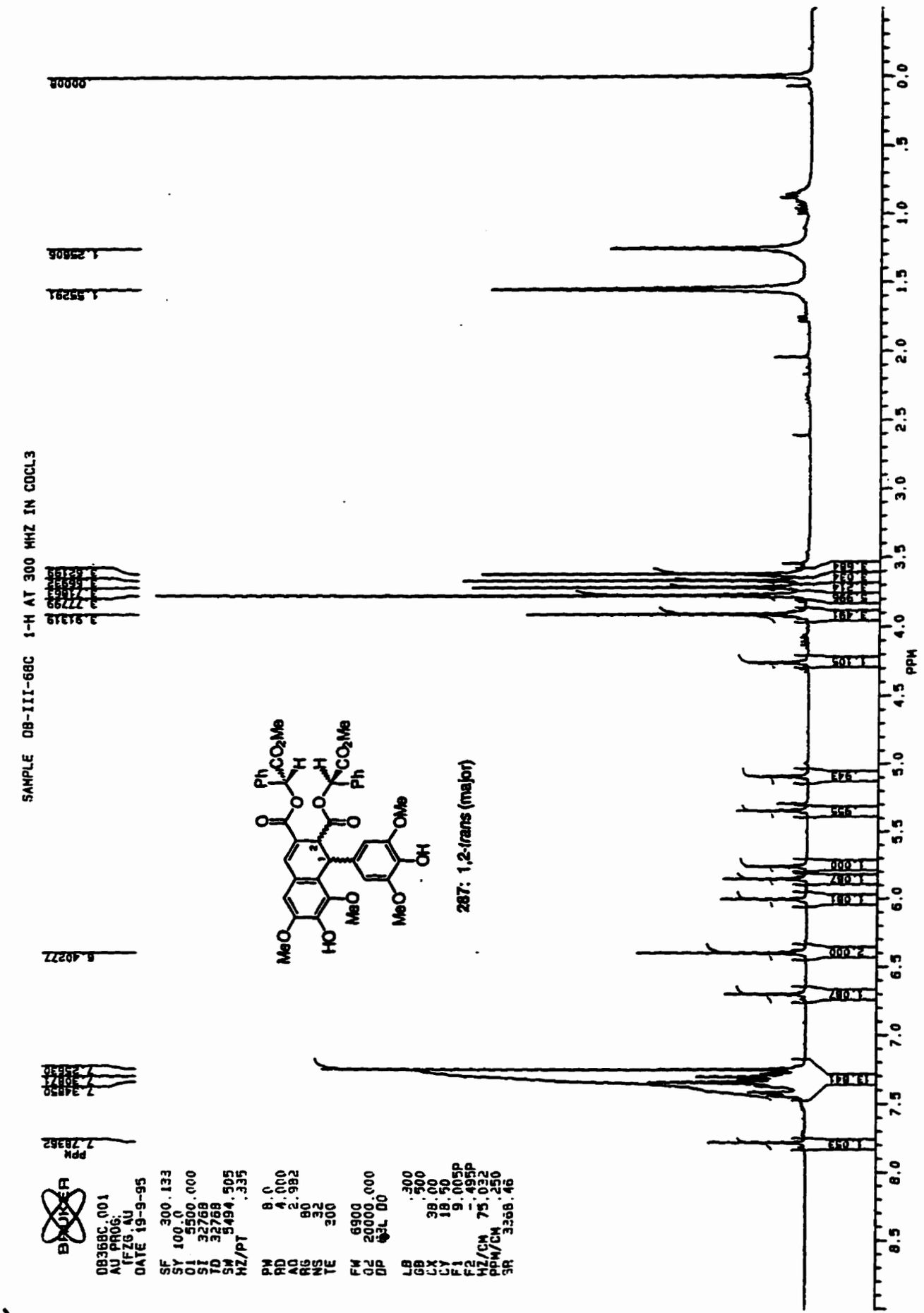
FW 22400
O2 5000.000
DP 1BH CPD

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 26596.77




286

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 DB-III-68C 1-H AT 300 MHZ IN CDCL3
DB368C.001
AU PROG:
(FZG.AU
DATE 19-9-95
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 80
NS 32
TE 300
FW 6900
O2 20000.000
DP
LB .300
GB .500
LX 38.00
LY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46
PPM
MeO
HO
MeO
OMe
OH
Ph
CO2Me
287: 1,2-trans (major)

SAMPLE DB-III-68C 13-C AT 75.47 MHZ IN CDCL3



DB368CC.001
AU PROG:
POWSTORE.AU
DATE 22-9-96

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

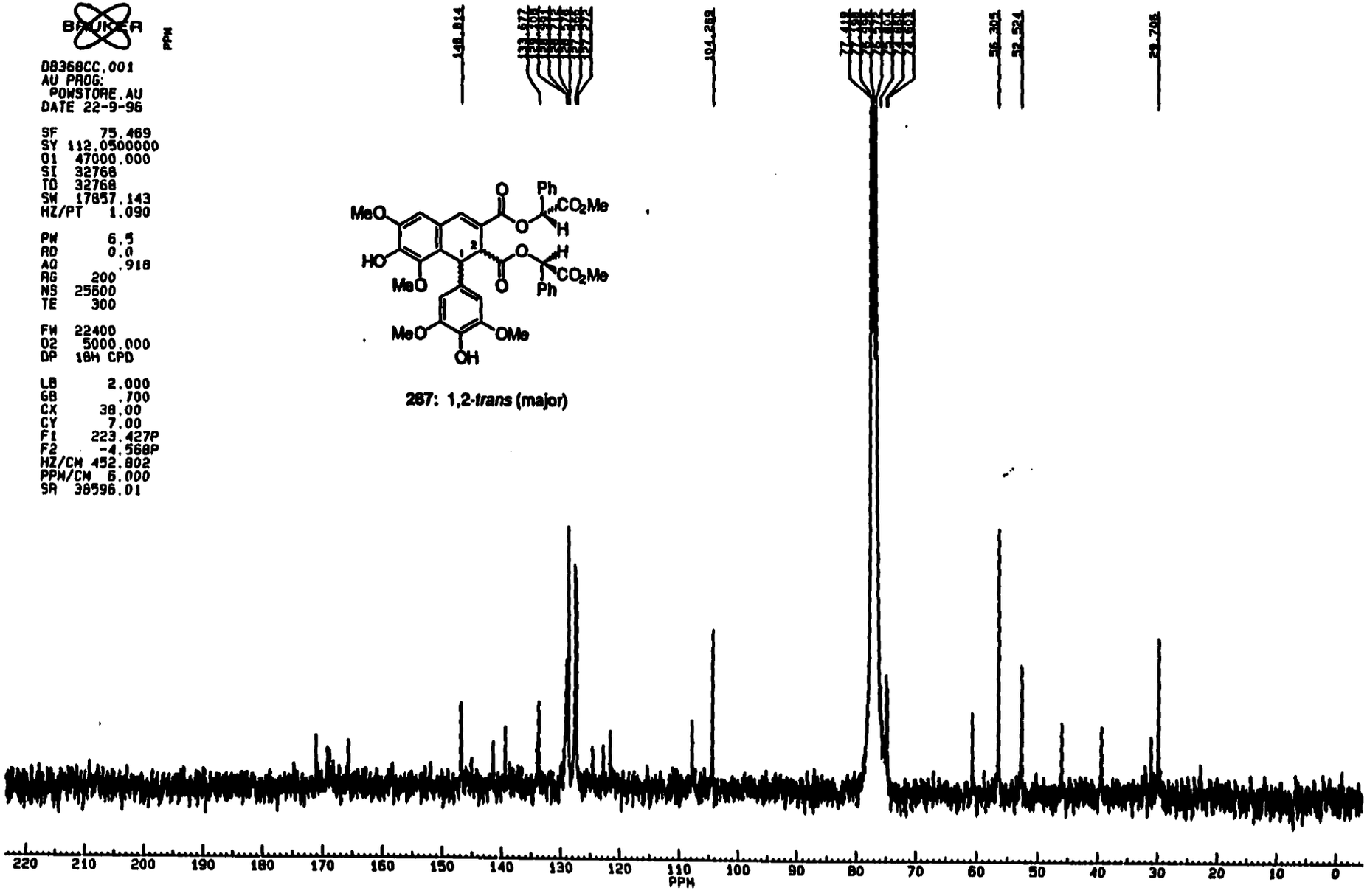
PW 6.5
RD 0.0
AQ .918
RG 200
NS 25600
TE 300

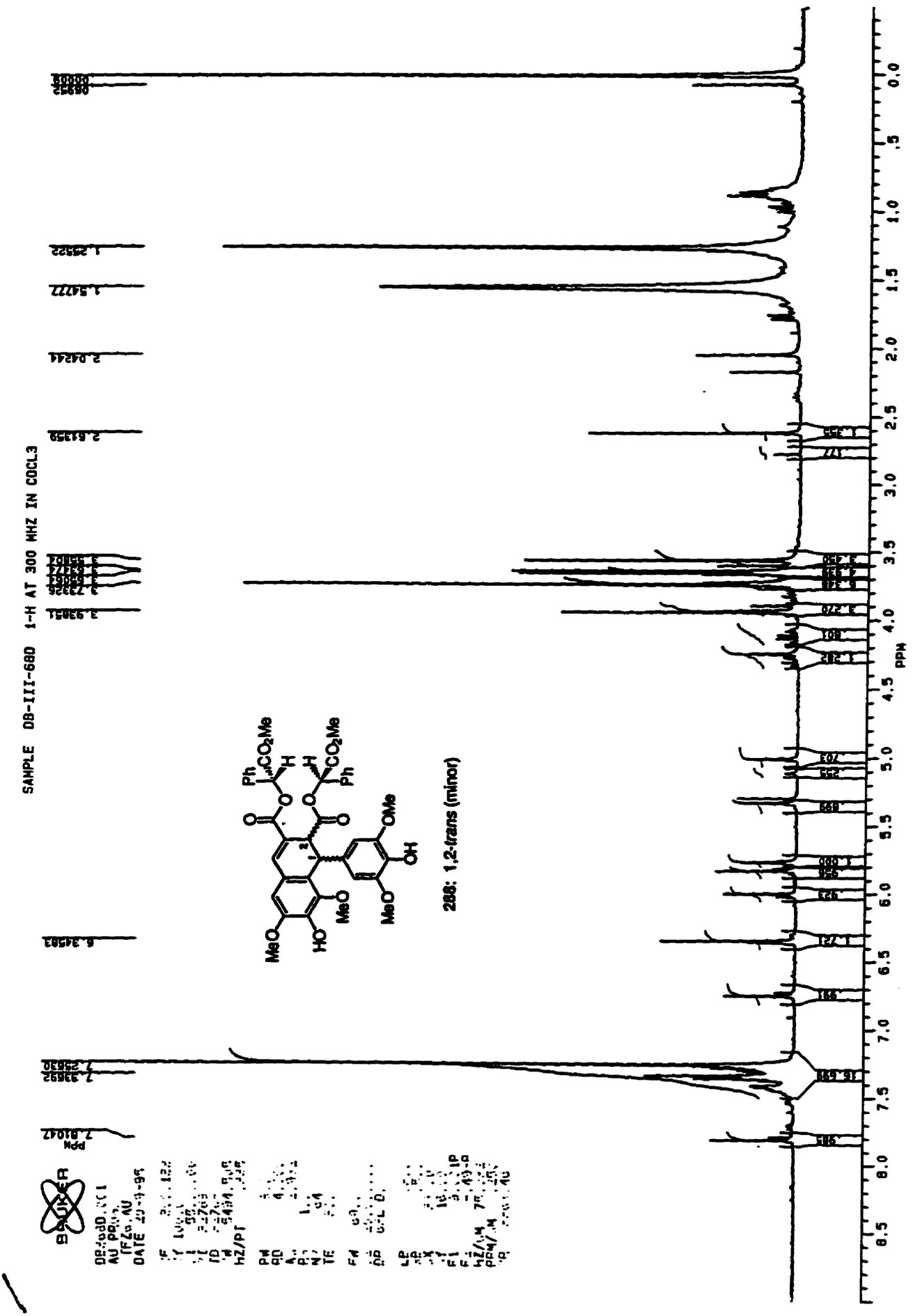
FW 22400
O2 5000.000
DP 1BH CPD

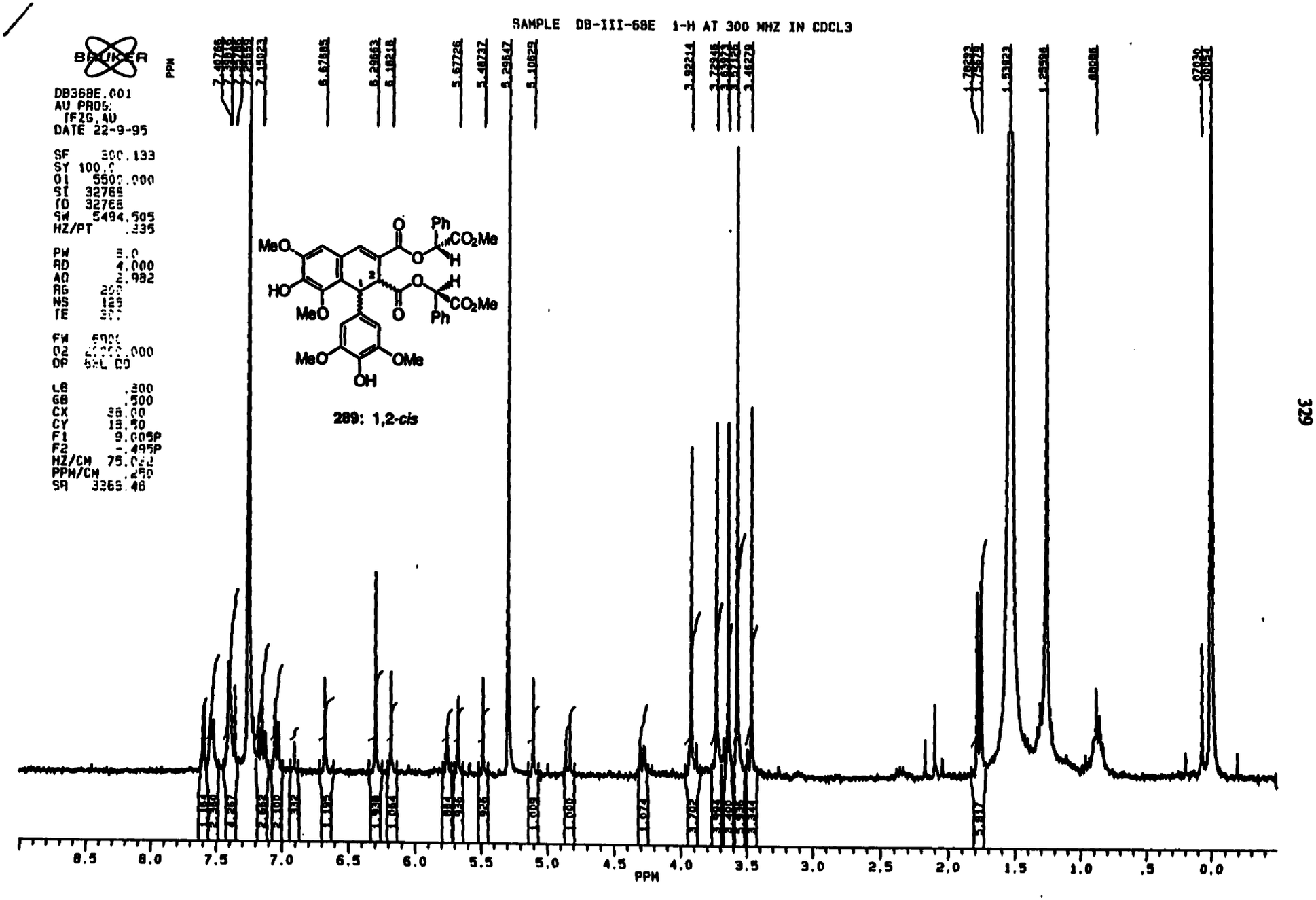
LB 2.000
GB .700
CX 38.00
CY 7.00
F1 223.427P
F2 -4.568P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.01

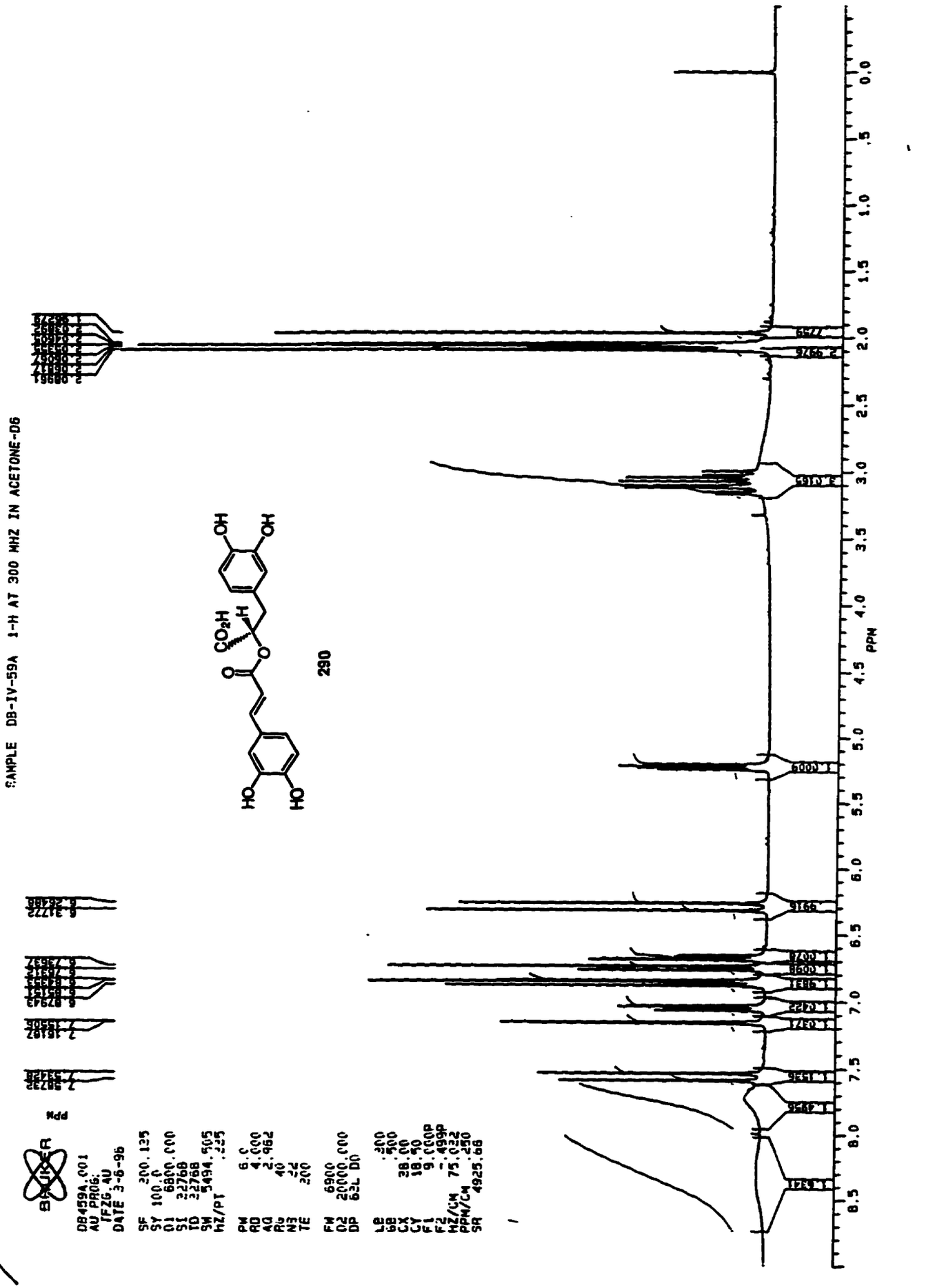


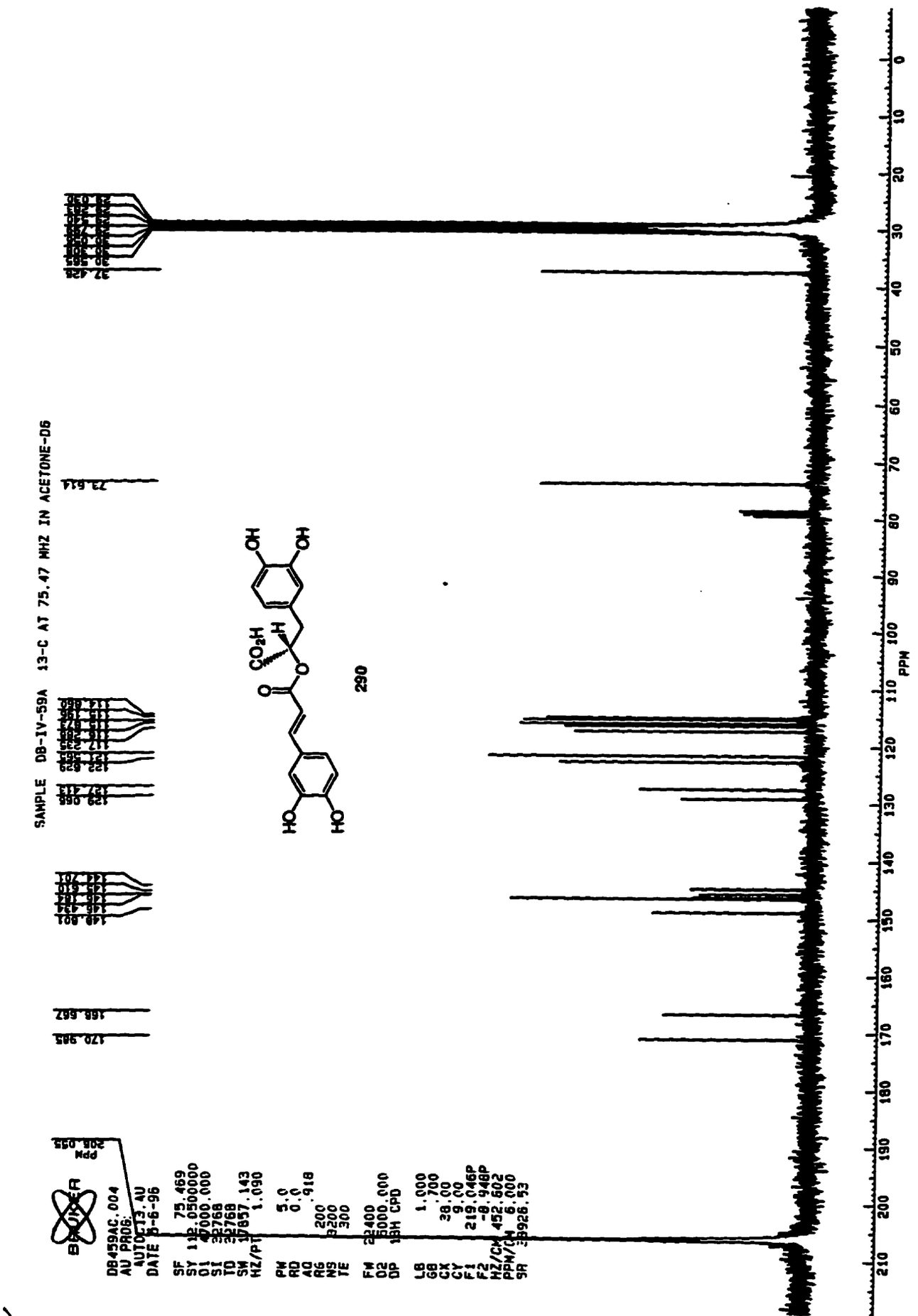

287: 1,2-*trans* (major)




SAMPLE DB-III-68D 1-H AT 300 MHZ IN CDCL3
288: 1,2-trans (minor)
PPM


SAMPLE DB-III-68E 1-H AT 300 MHZ IN CDCL3
DB368E.001
AU PROG:
IFZG.AU
DATE 22-9-95
SF 300.133
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
NS 128
TE 300
LB .300
GB .500
CX 38.00
CY 19.50
F1 9.005P
F2 -.495P
HZ/CM 75.062
PPM/CM .250
SR 3365.46
MeO
HO
MeO
MeO
OMe
OH
Ph
CO2Me
H
O
289: 1,2-cis
PPM


SAMPLE DB-IV-59A 1-H AT 300 MHZ IN ACETONE-D6
290
PPM


SAMPLE DB-IV-59A 13-C AT 75.47 MHZ IN ACETONE-D6
290
PPM

SAMPLE DB-IV-44C 1-H AT 300 MHZ IN ACETONE-D6

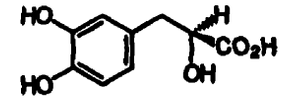
DB444C.001
AU PROG:
IFZG.AU
DATE 29-4-96

SF 300.135
SY 100.0
O1 6800.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

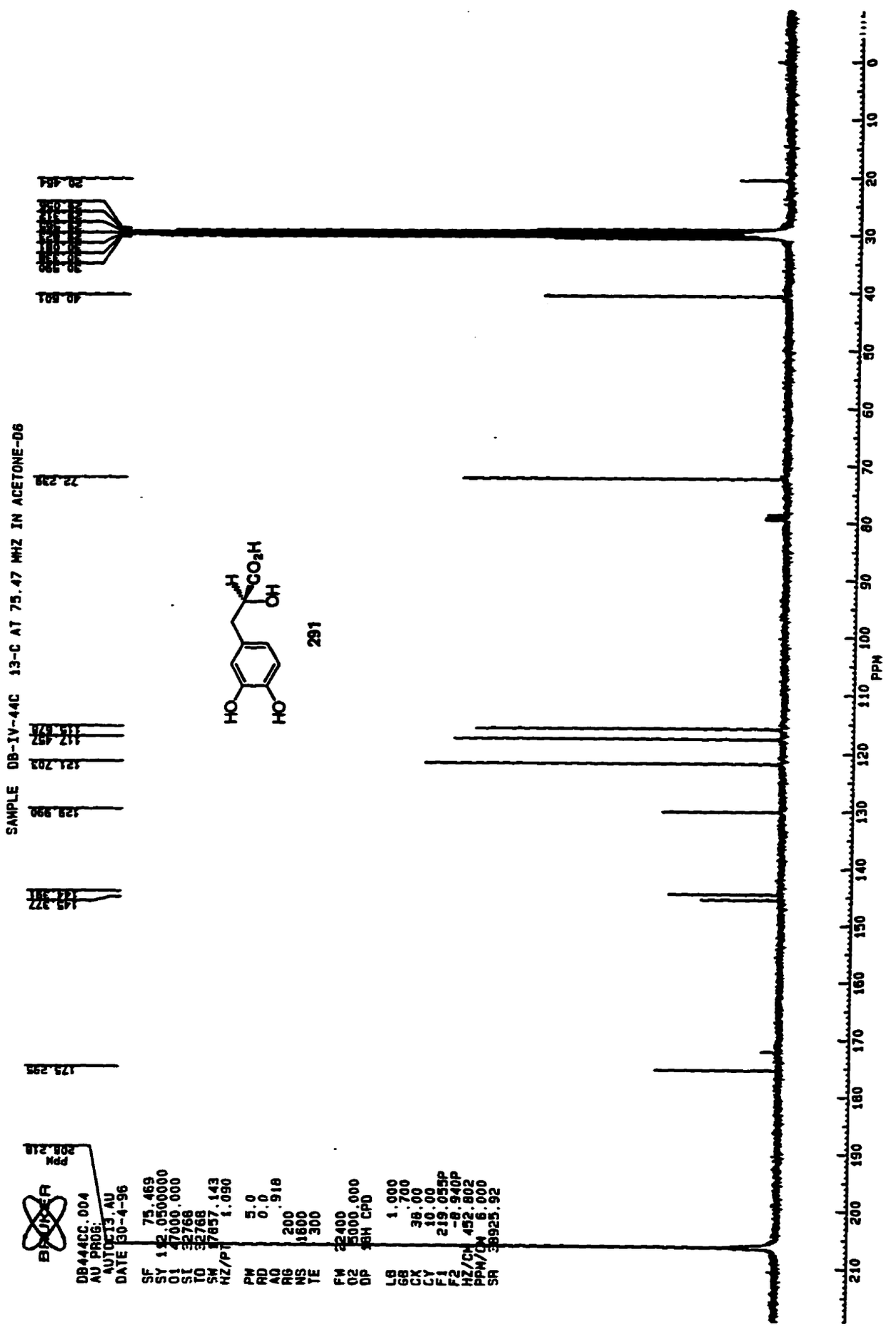
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300

FW 6900
O2 20000.000
DP 63L DO

LB .300
GB .500
CX 38.00
CY 16.00
F1 11.000P
F2 -.498P
HZ/CM 90.820
PPM/CM .303
SR 4925.01



291


SAMPLE DB-IV-44C 13-C AT 75.47 MHZ IN ACETONE-D6
291
PPM

SAMPLE DB-III-113B 1-H AT 300 MHZ IN D2O

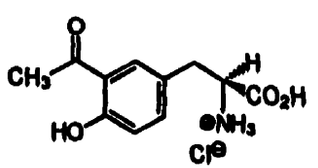
DB3113B.001
AU PROG:
IFZG.AU
DATE 16-8-96

SF 200.134
SY 100.0
O1 5795.000
SI 32768
TD 32768
SW 4000.000
HZ/PT .244

PW 8.0
RD 4.000
AQ 4.096
RG 16
NS 32
TE 200

FW 5000
O2 20000.000
DP 62L DO

LB .300
GB .300
CK 26.00
CY 18.50
F1 9.000P
F2 -.499P
HZ/CM 75.028
PPM/CM .250
SR 4104.33




292

SAMPLE DB-III-113B 13-C AT 75.47 MHZ IN D2O

DB3113BC.004
AU PROG:
AUTOC13.40
DATE 20-8-96

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

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

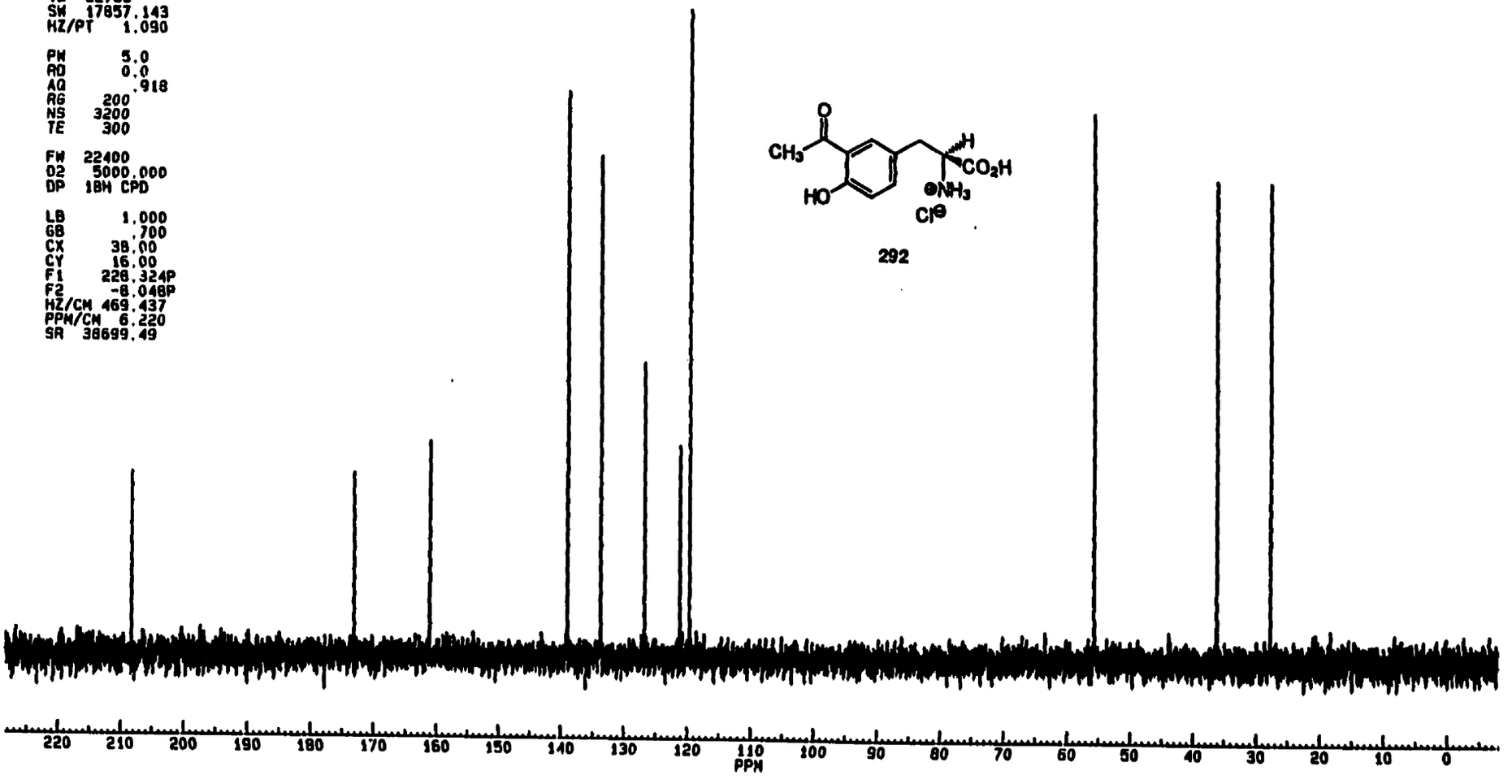
FW 22400
D2 5000.000
DP 1BH CPD

LB 1.000
GB .700
CX 38.00
CY 16.00
F1 226.324P
F2 -8.048P
HZ/CM 469.437
PPM/CM 6.220
SR 38699.49

172.993
160.951
138.858
133.574
128.570
121.018
119.289
55.602
36.018
27.542



292



SAMPLE OB-IV-42A 1-H AT 300 MHZ IN COCL3

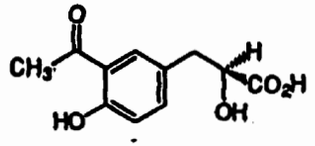
OB442A.001
AU PHOG:
TFZG.AU
DATE 25-4-96

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

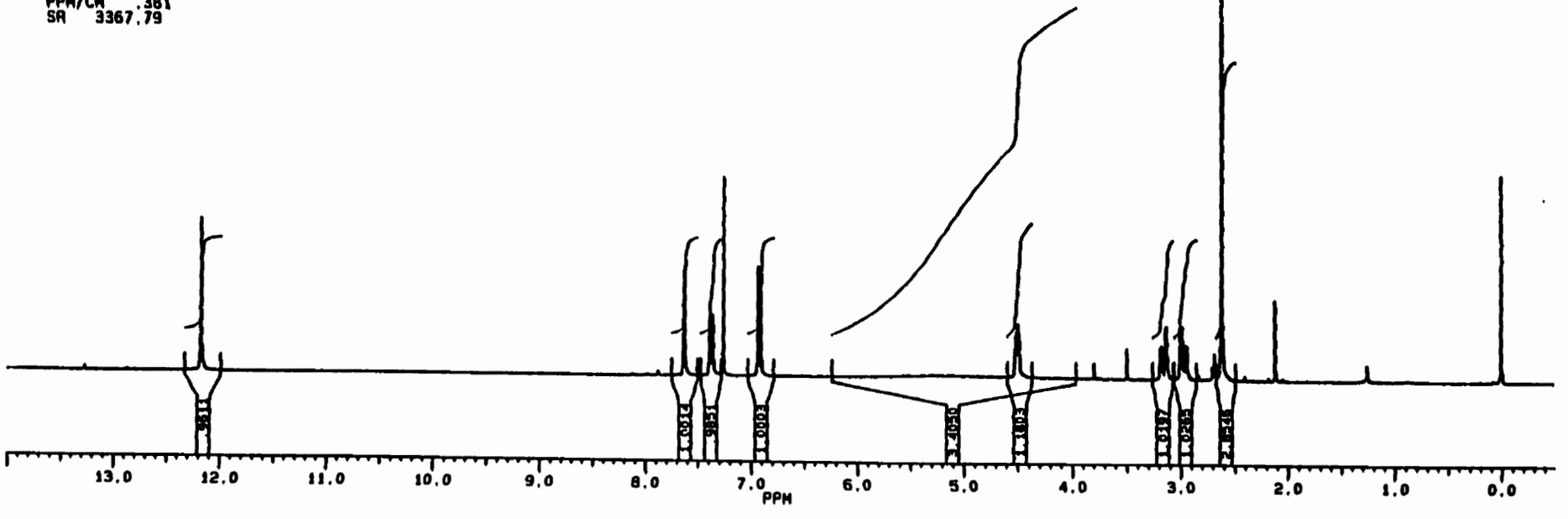
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300

FW 6900
O2 20000.000
DP 63L DD

LB .300
GB .500
CX 38.00
CY 18.50
F1 14.001P
F2 -.493P
HZ/CM 114.472
PPM/CM .381
SR 3367.79



293



SAMPLE DB-IV-42A 13-C AT 75.47 MHZ IN CDCL3
293
DB442AC.004
AU PROG:
AUTOC13.AU
DATE 26-4-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AO .918
RG 200
NS 1600
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 39.00
CY 8.00
F1 223.4177P
F2 -4.5788P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77
PPM

SAMPLE DB-IV-368 1-H AT 300 MHZ IN CDCL3



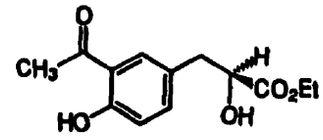
DB4368.001
AU PROG:
IFZG.AU
DATE 11-4-96

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

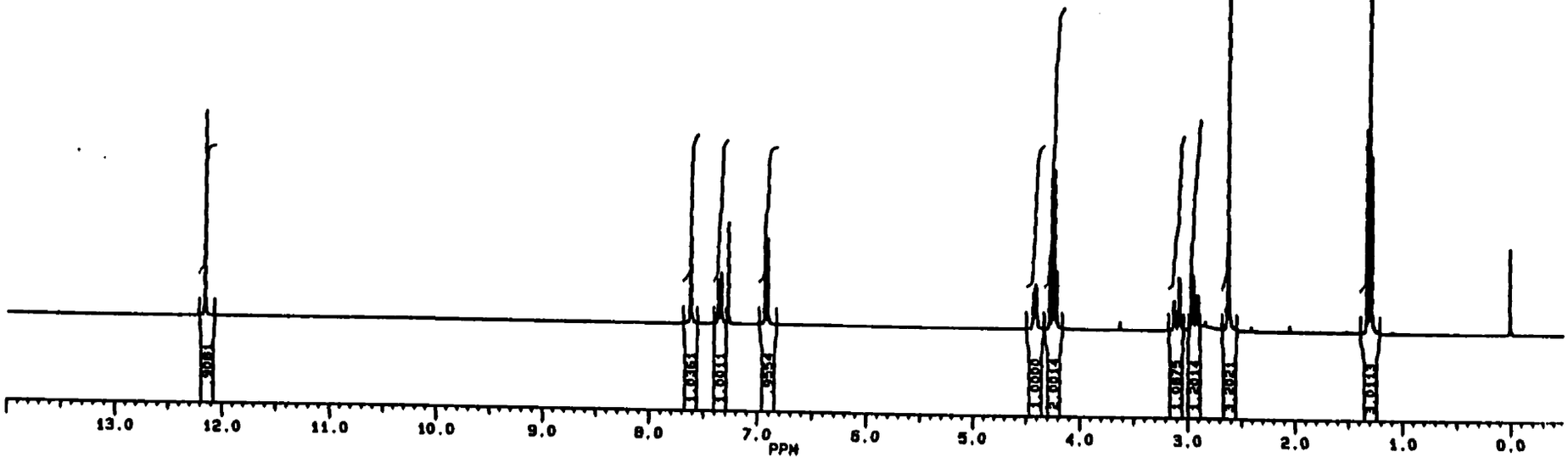
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300

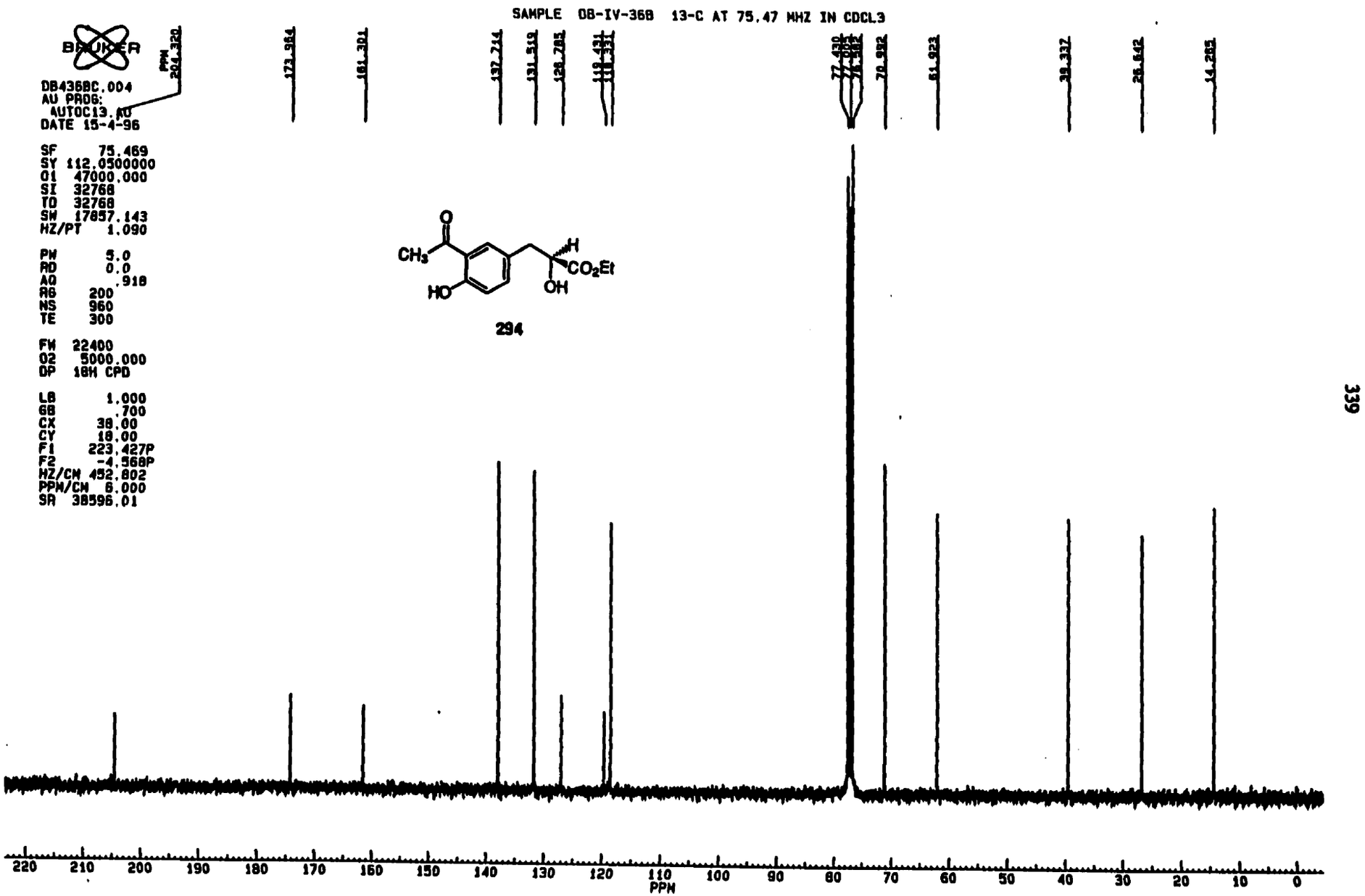
FW 6900
O2 20000.000
OP 63L 00

LB .300
GB .500
CX 38.00
CY 18.50
F1 14.001P
F2 -.497P
HZ/CM 114.507
PPM/CM .382
SR 3367.46

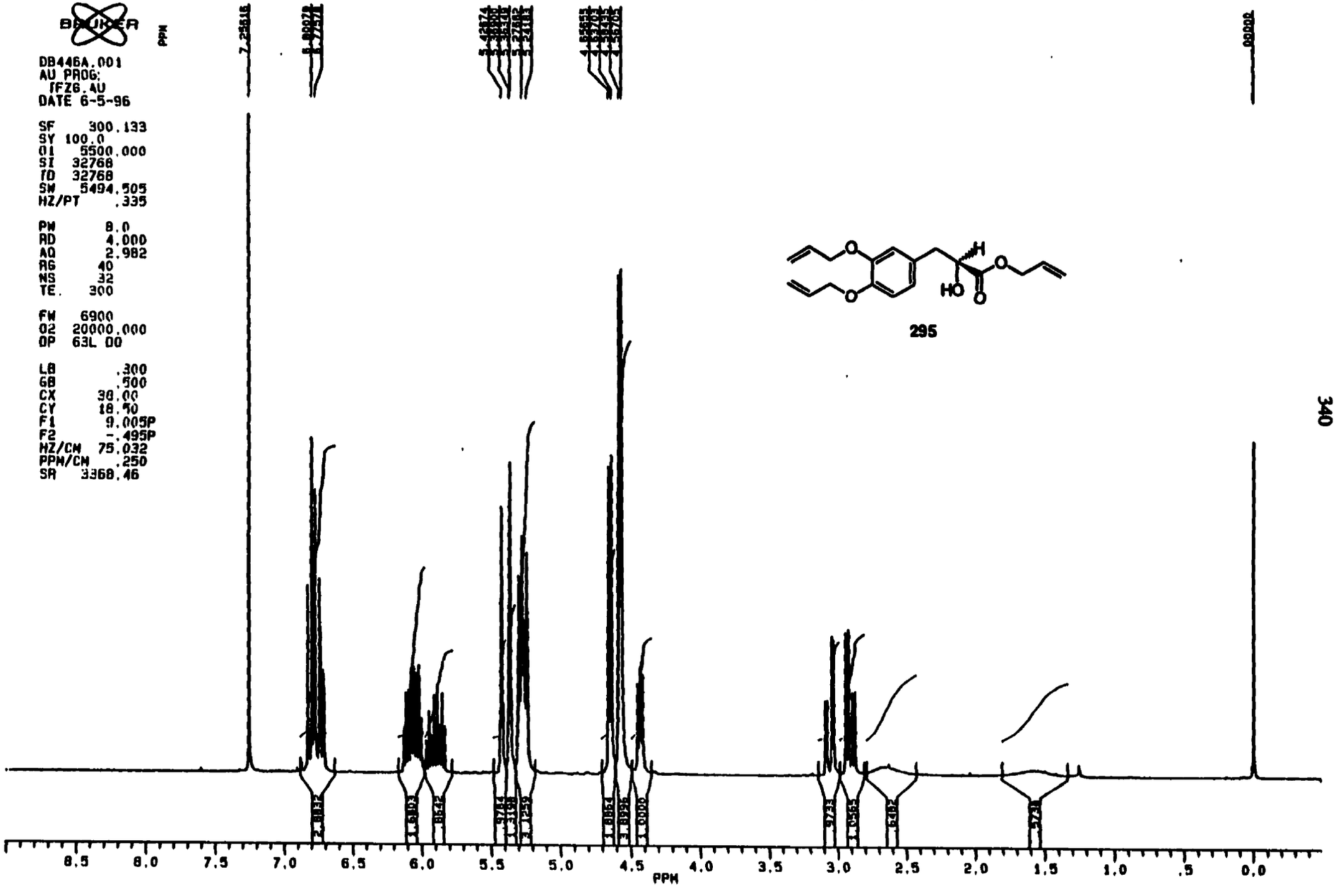



294




SAMPLE 08-IV-368 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
204.320
173.984
161.301
137.214
131.519
128.785
118.431
118.331
77.430
77.005
76.580
70.982
61.923
38.337
28.642
14.283
DB436BC.004
AU PROG:
AUTOC13.AU
DATE 15-4-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 960
TE 300
FW 22400
O2 5000.000
OP 18M CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 223.427P
F2 -4.568P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.01
O
CH3
H
CO2Et
HO
OH
294
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

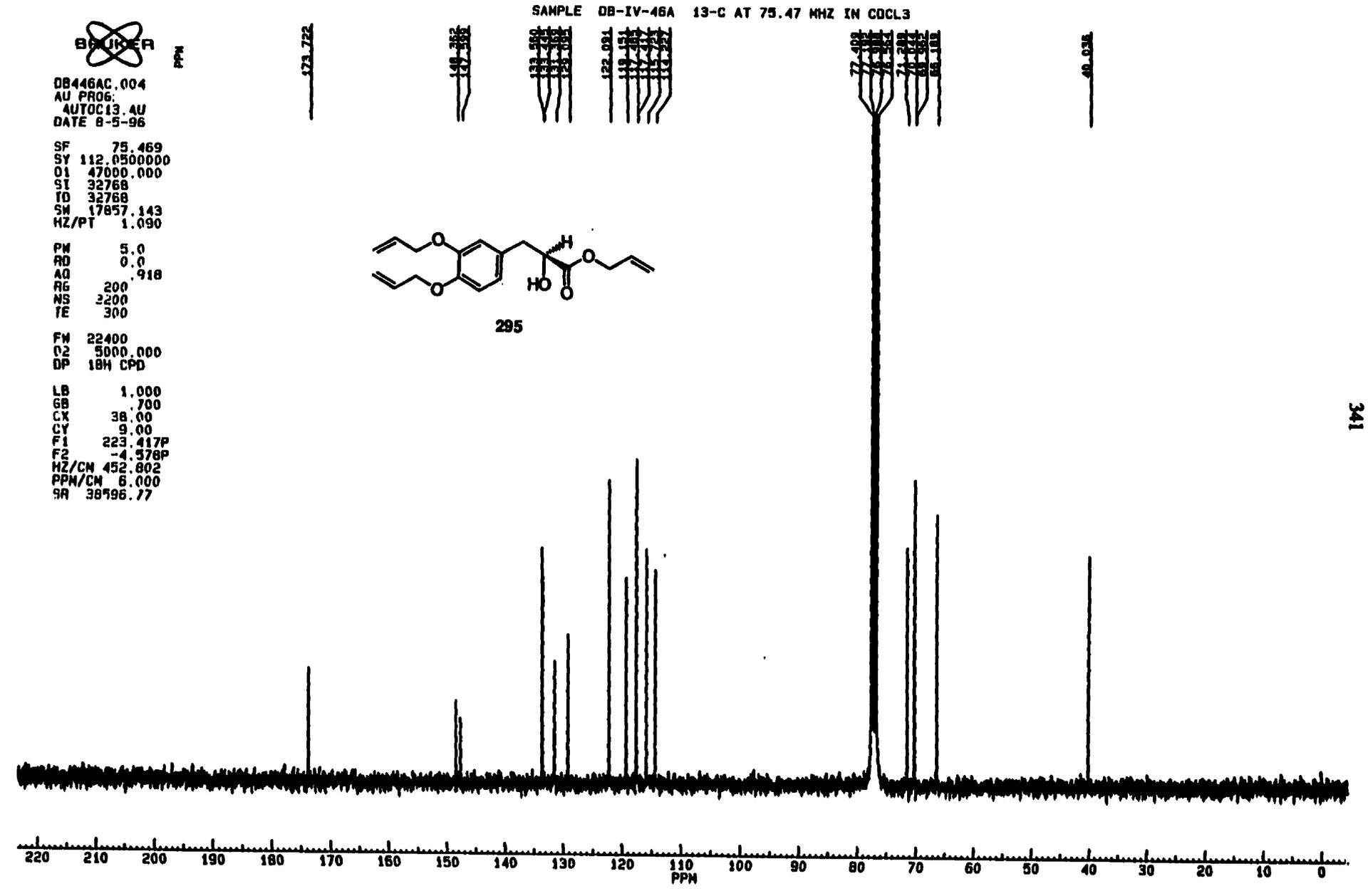
SAMPLE DB-IV-46A 1-H AT 300 MHZ IN CDCL3



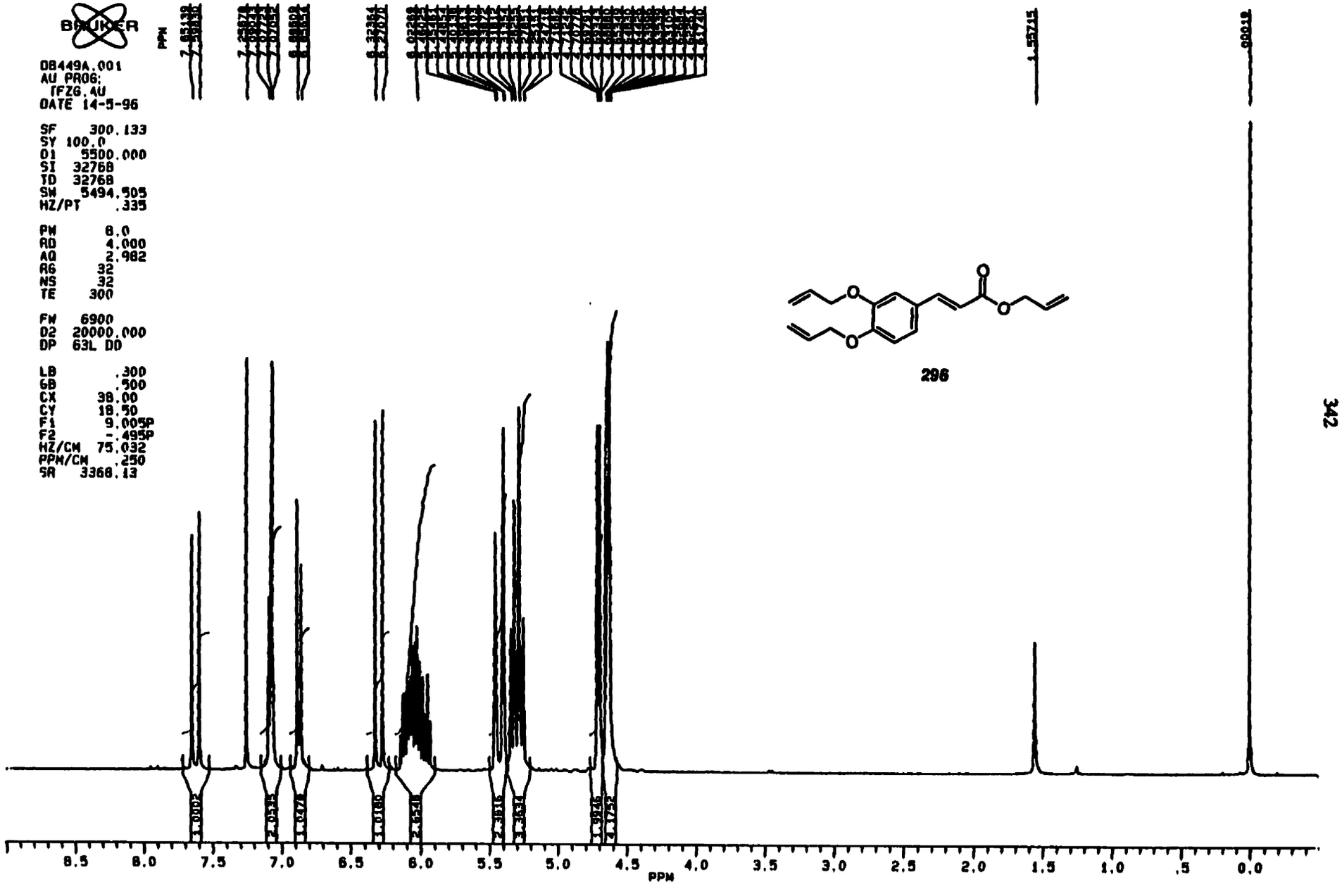




295

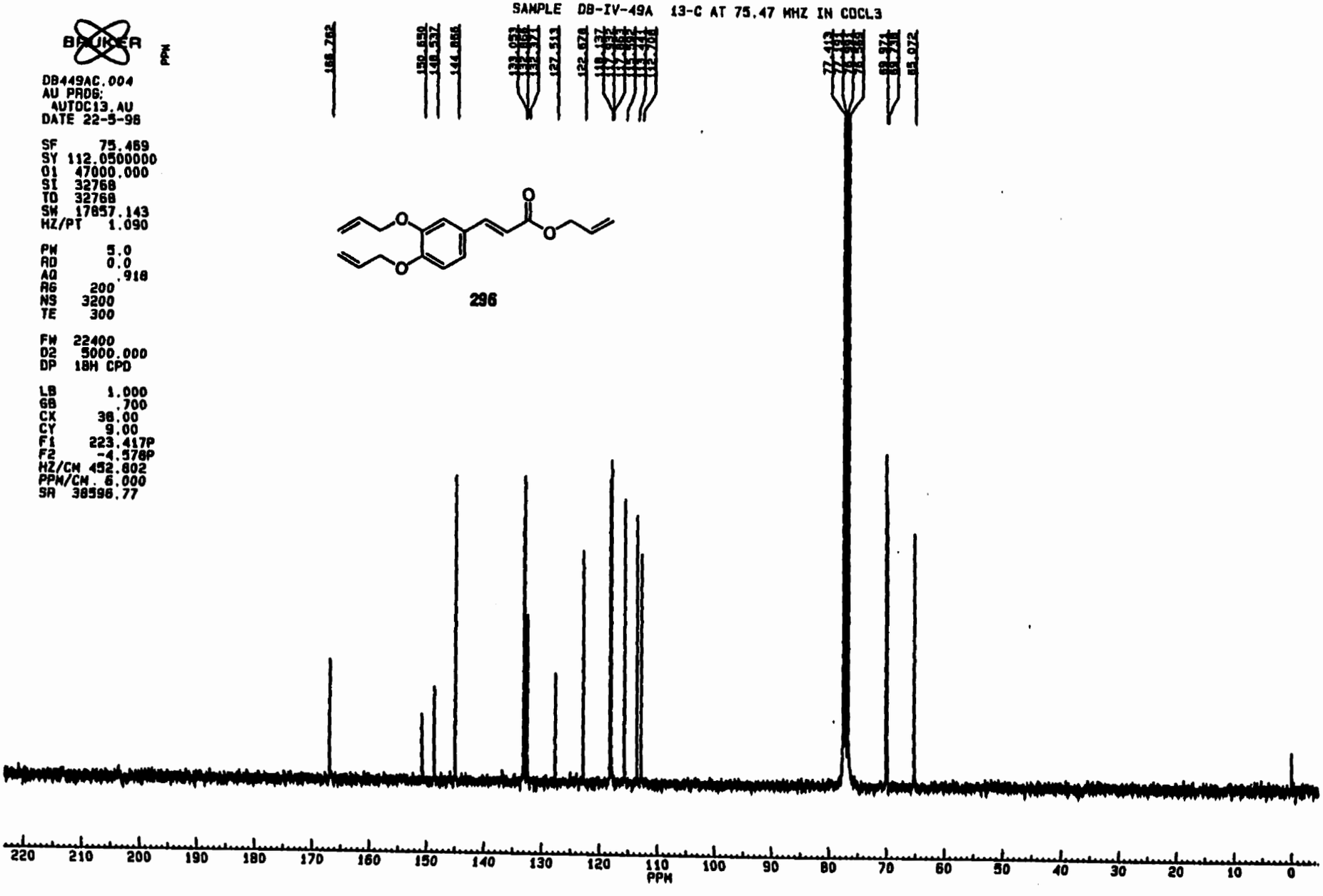

SAMPLE DB-IV-46A 13-C AT 75.47 MHZ IN COCL3
BRUKER
PPM
DB446AC.004
AU PROG:
AUTOC13.AU
DATE 8-5-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 9.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPN/CM 6.000
SR 38596.77
173.722
122.091
40.038
295
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 DB-IV-49A 1-H AT 300 MHZ IN CDCL3

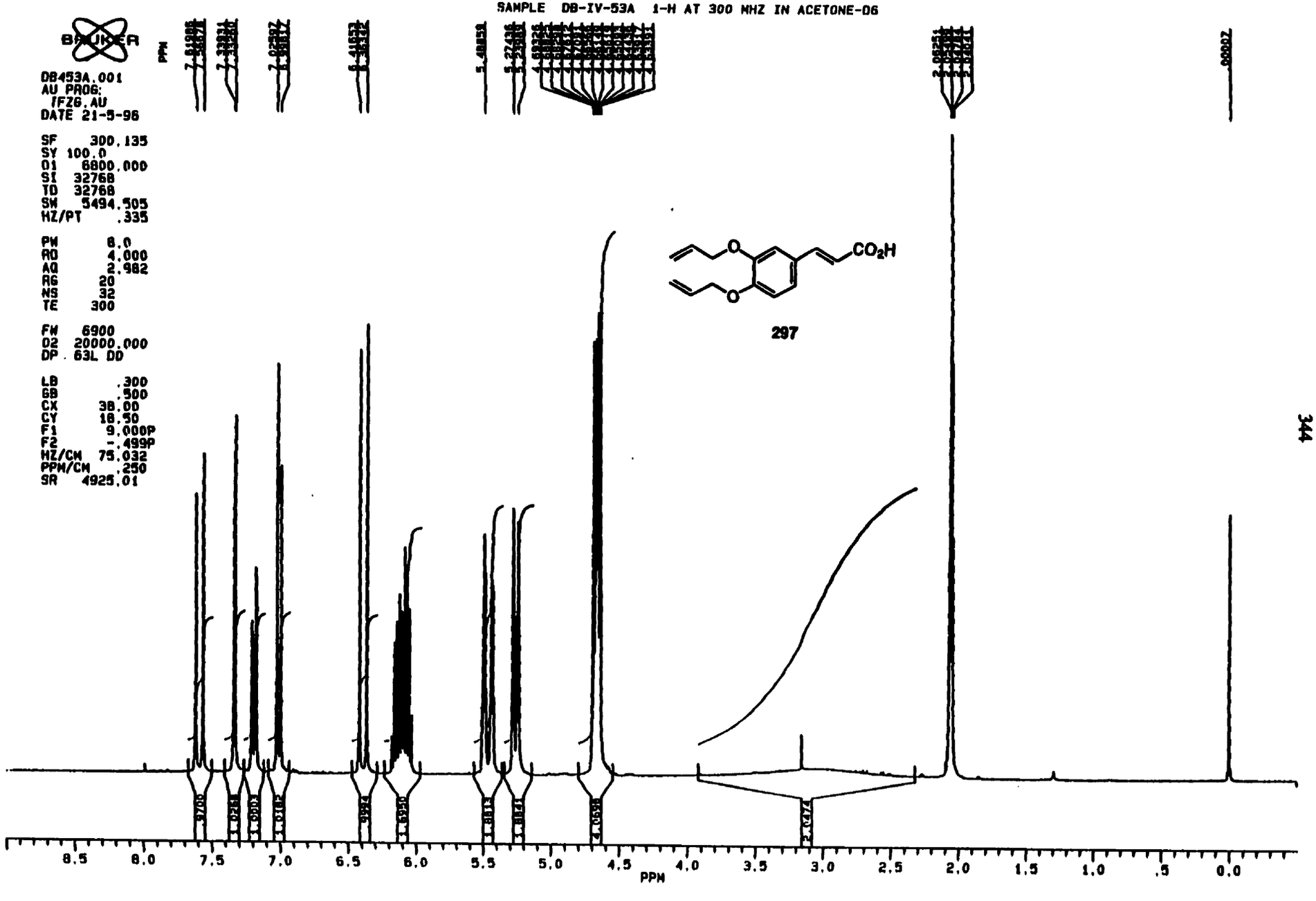


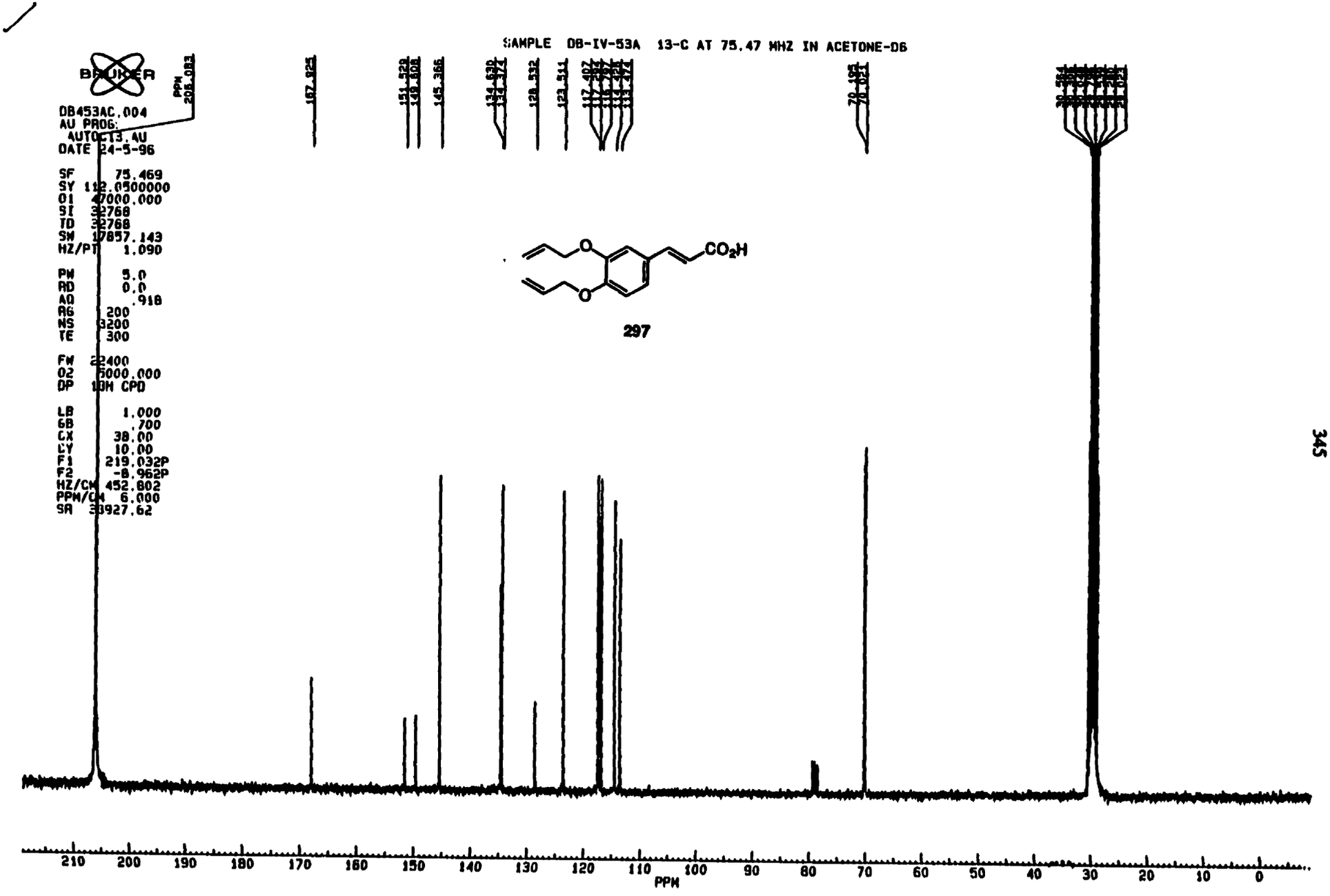

296

SAMPLE DB-IV-49A 13-C AT 75.47 MHZ IN COCL3

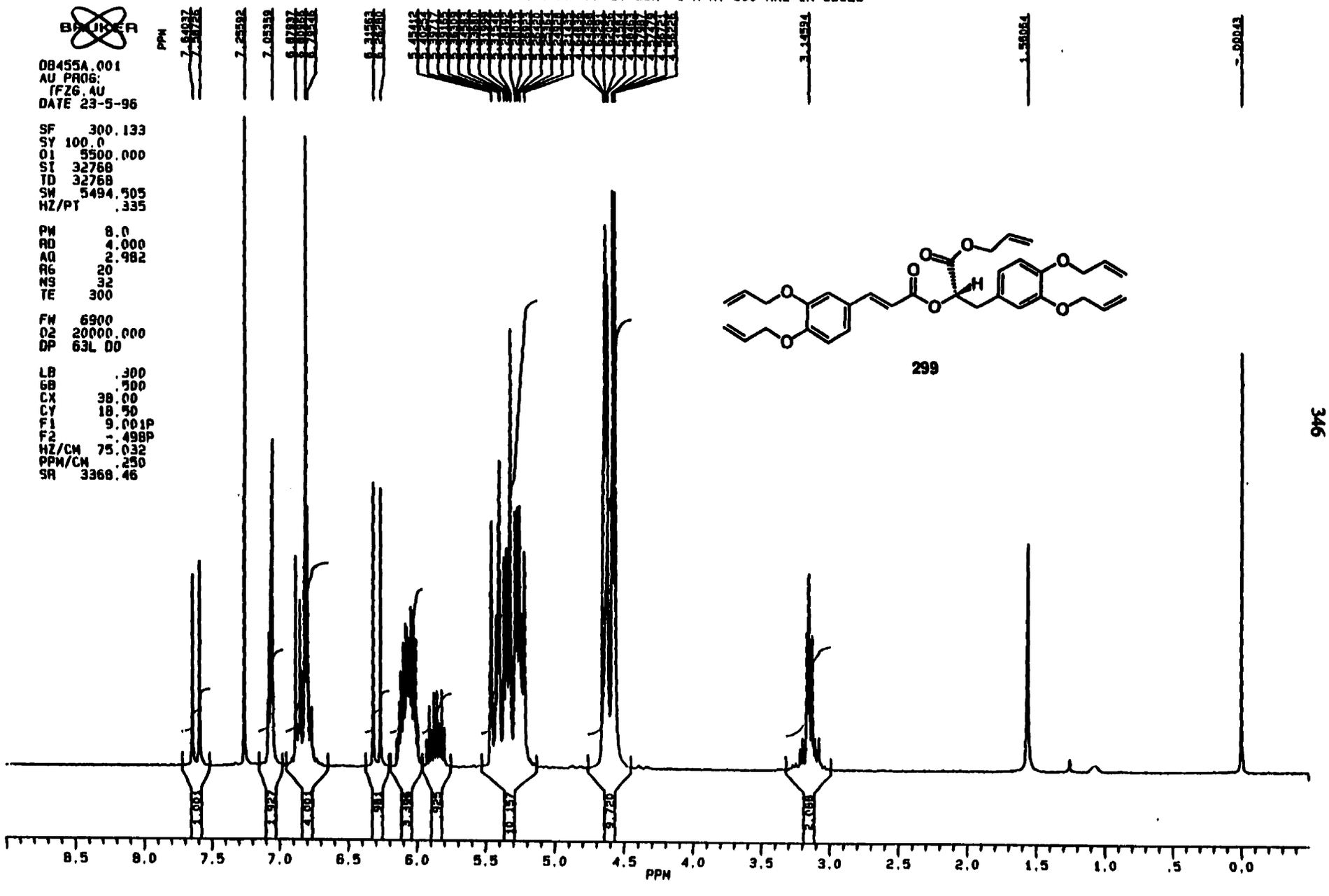


SAMPLE DB-IV-53A 1-H AT 300 MHZ IN ACETONE-D6



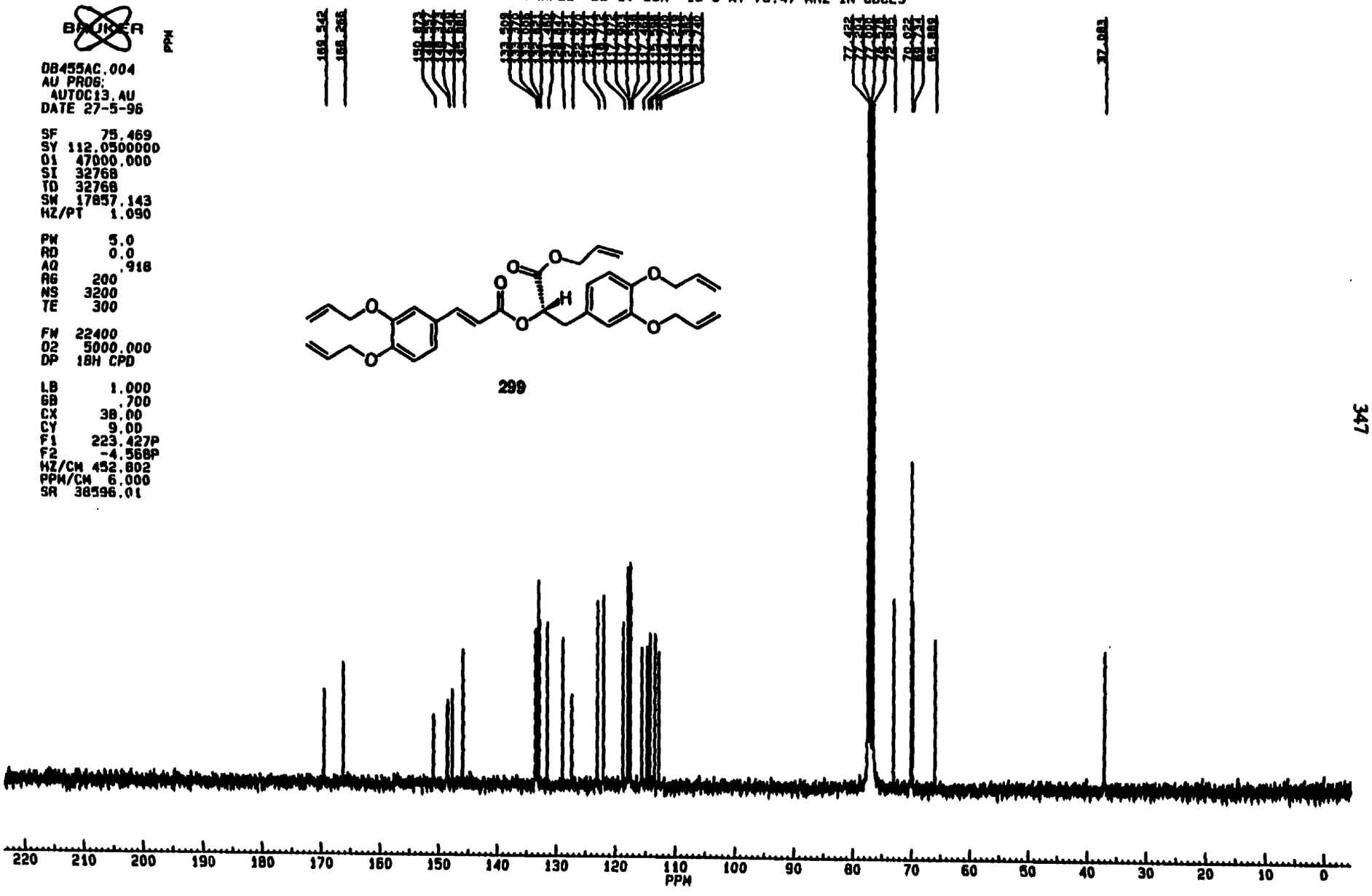

SAMPLE DB-IV-53A 13-C AT 75.47 MHZ IN ACETONE-D6
BRUKER
DB453AC.004
AU PROG:
AUTOC13.AU
DATE 24-5-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300
FW 22400
O2 5000.000
DP 10M CPD
LB 1.000
GB .700
CX 38.00
CY 10.00
F1 219.032P
F2 -8.962P
HZ/CM 452.802
PPM/CM 6.000
SR 30927.62
167.925
151.320
148.804
145.366
134.630
134.372
128.532
123.511
117.402
116.787
116.424
111.272
70.185
70.021
CO2H
297
345
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

SAMPLE DB-IV-55A 1-H AT 300 MHZ IN COCL3



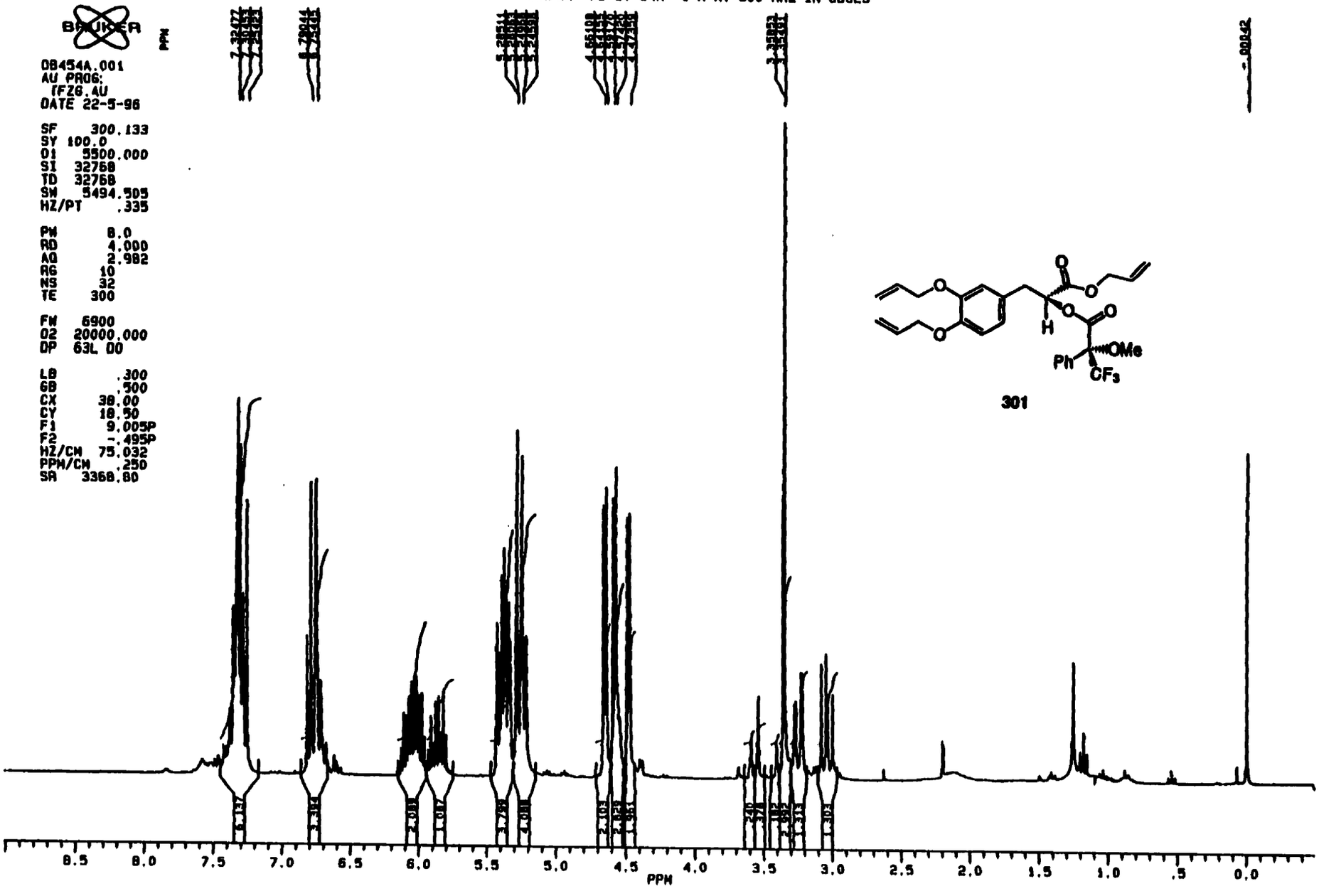

299

SAMPLE DB-IV-55A 13-C AT 75.47 MHZ IN CDCL3




299

SAMPLE DB-IV-54A 1-H AT 300 MHZ IN COCL3






301

SAMPLE DB-IV-54A 19-F AT 282.4 MHZ IN CDCL3

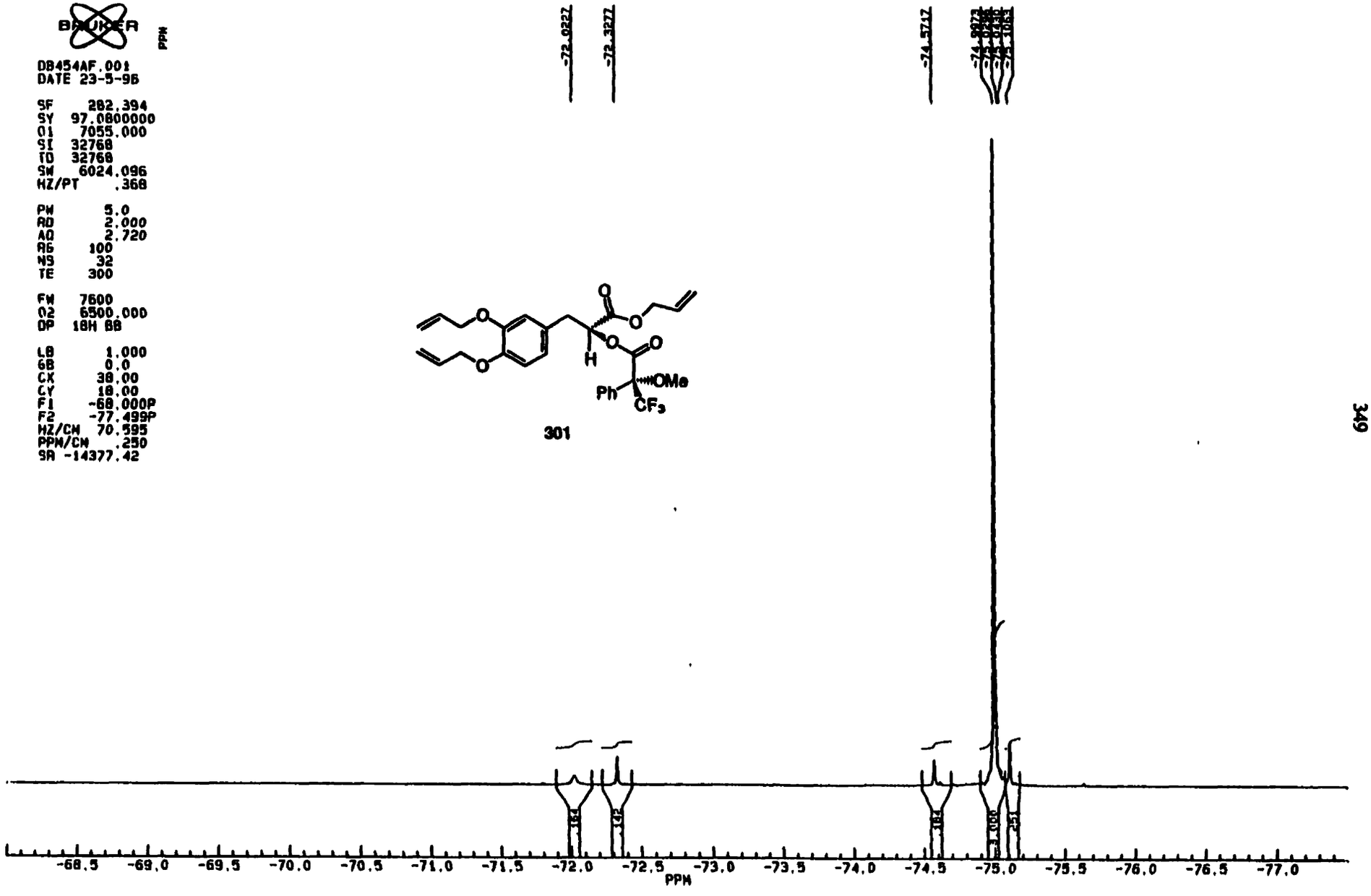


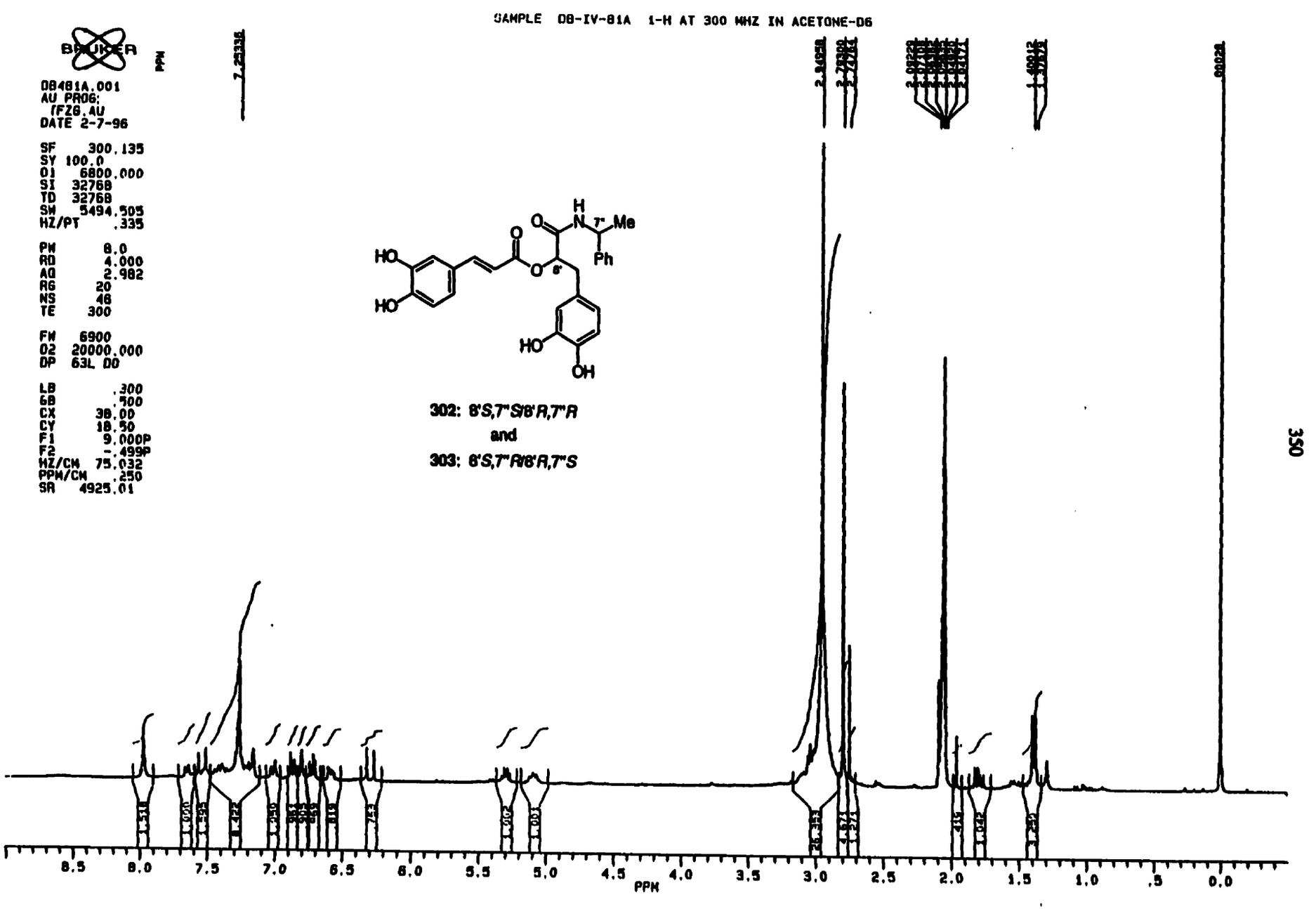
DB454AF.001
DATE 23-5-96

| | |
|---|---|
| SF | 282.394 |
| SY | 97.0800000 |
| O1 | 7055.000 |
| SI | 32768 |
| TD | 32768 |
| SW | 6024.096 |
| HZ/PT | .368 |
| PW | 5.0 |
| RD | 2.000 |
| AQ | 2.720 |
| RG | 100 |
| NS | 32 |
| TE | 300 |
| FW | 7600 |
| O2 | 6500.000 |
| DP | 18H BB |
| LB | 1.000 |
| GB | 0.0 |
| CX | 38.00 |
| CY | 18.00 |
| F1 | -68.000P |
| F2 | -77.499P |
| HZ/CM | 70.595 |
| PPM/CM | .250 |
| SR | -14377.42 |



301

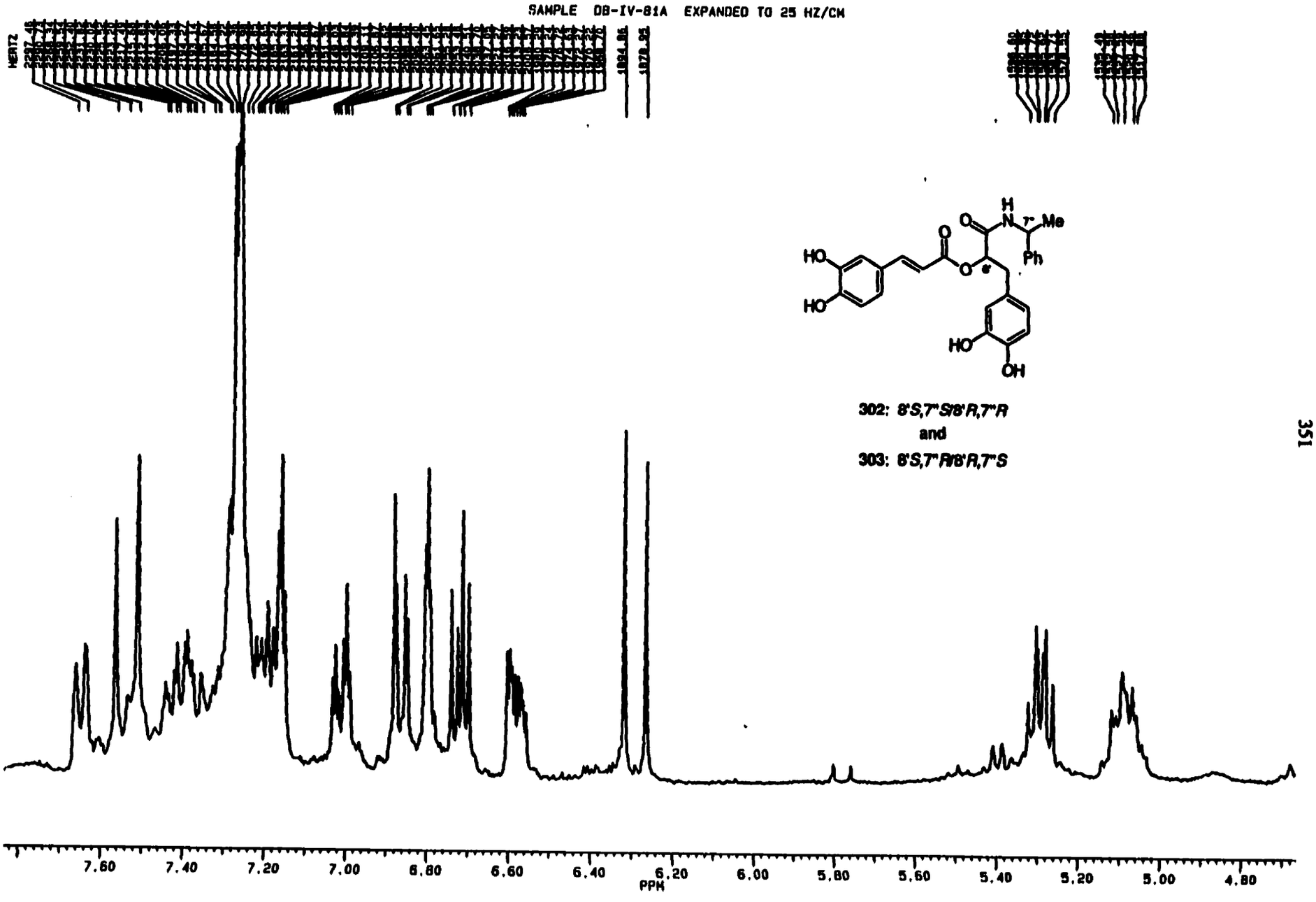





302: 6'S,7"S/6'R,7"R

and

303: 6'S,7"R/6'R,7"S

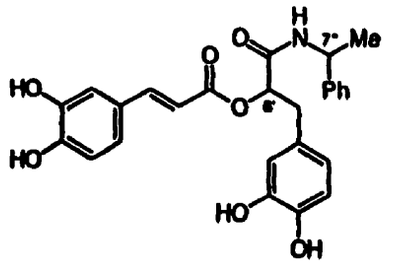



**302:** *8'S,7"S/8'R,7"R*

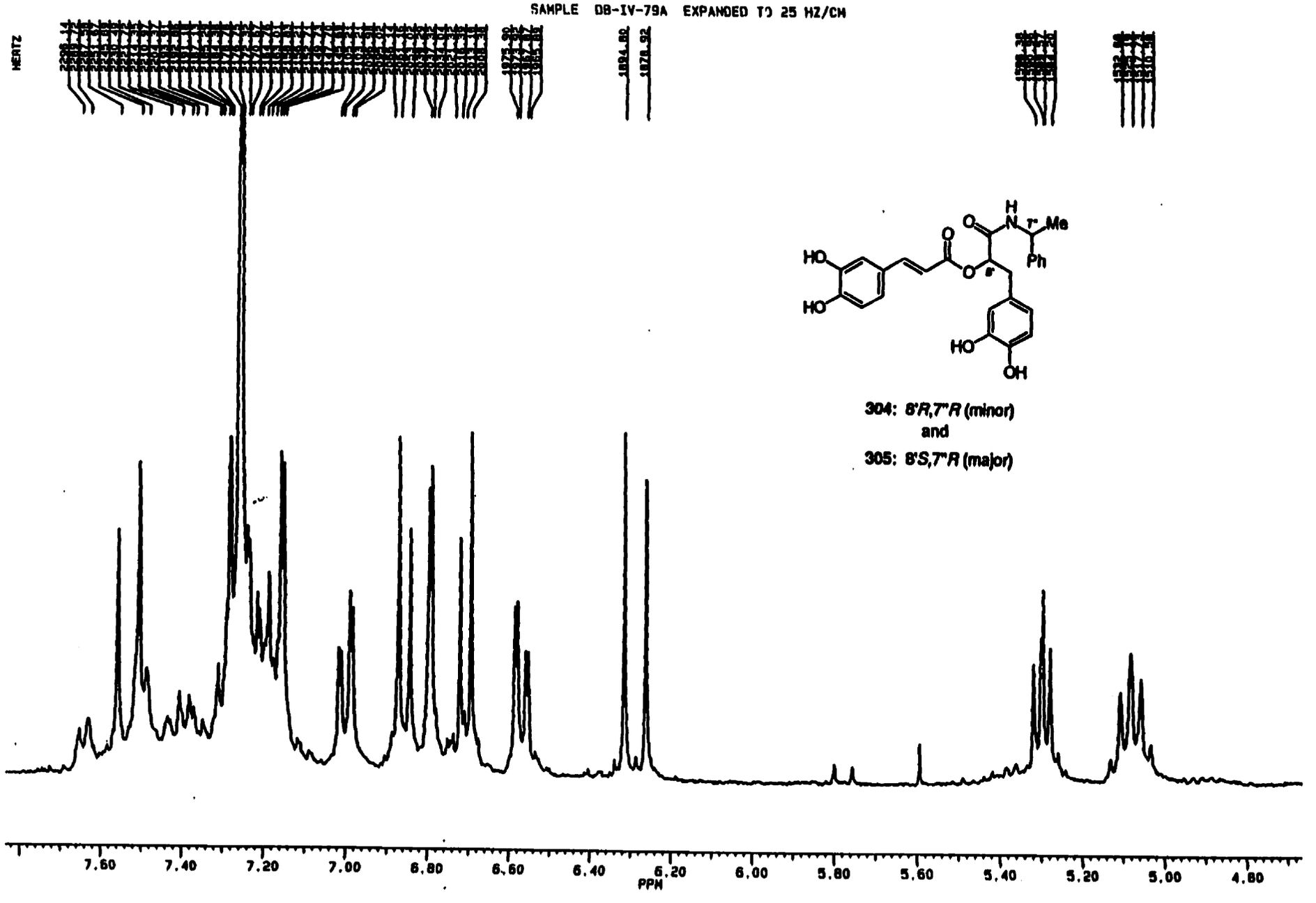
**and**

**303:** *8'S,7"R/8'R,7"S*

SAMPLE DB-IV-79A 1-H AT 300 MHZ IN ACETONE-D6



304: 8'*R*,7"*R* (minor)
and
305: 8'*S*,7"*R* (major)




304: 8'*R*,7"*R* (minor)
and
305: 8'*S*,7"*R* (major)

SAMPLE DB-IV-50A 1-H AT 300 MHZ IN CDCL3




DB450A.001
AU PROG:
 IFZG.AU
DATE 14-5-96

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

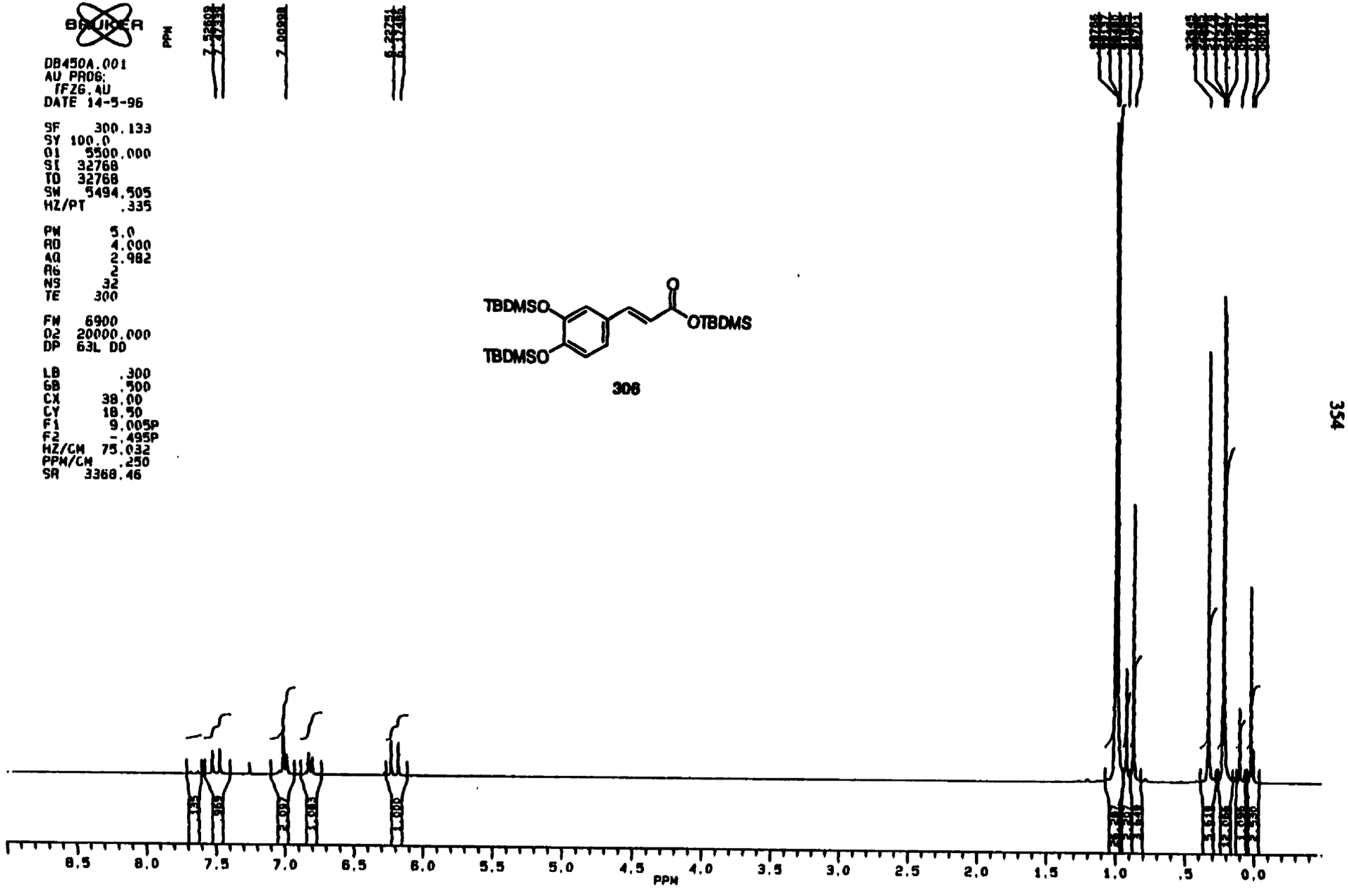
PW 5.0
RD 4.000
AQ 2.982
RG 2
NS 32
TE 300

FW 6900
D2 20000.000
DP 63L DD

LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3368.46




308



SAMPLE OBIV-71A, 1-H AT 300 MHZ IN COCL3



DBIV71A.001
AU PROG:
IFZ6.AU
DATE 13-6-96

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

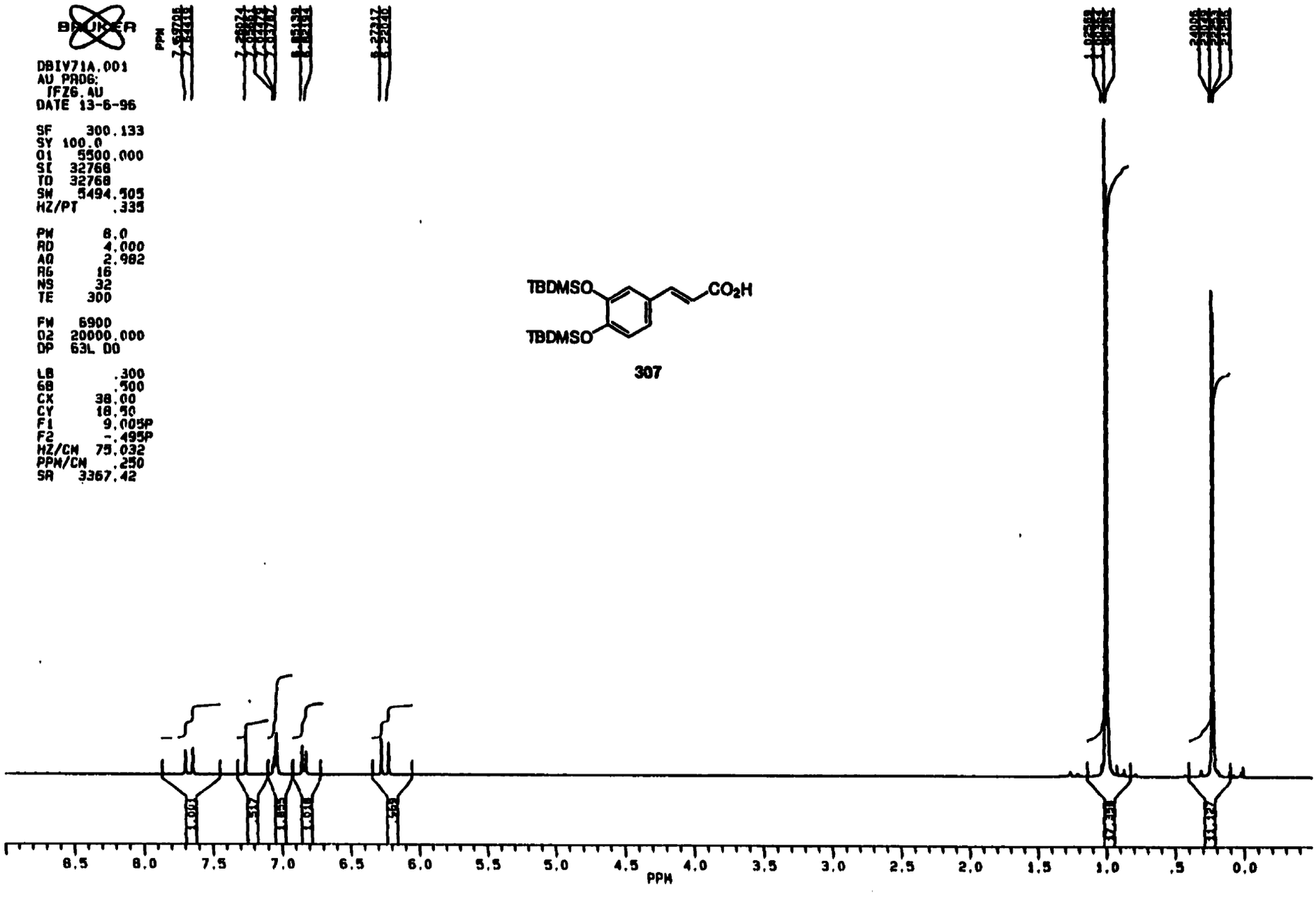
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300

FW 6900
O2 20000.000
DP 63L DO

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




307



SAMPLE OB-IV-72A 13-C AT 75.47 MHZ IN COCL3



PPM

DB472AC.004
AU PROG:
AUTOC13.AU
DATE 18-6-96

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

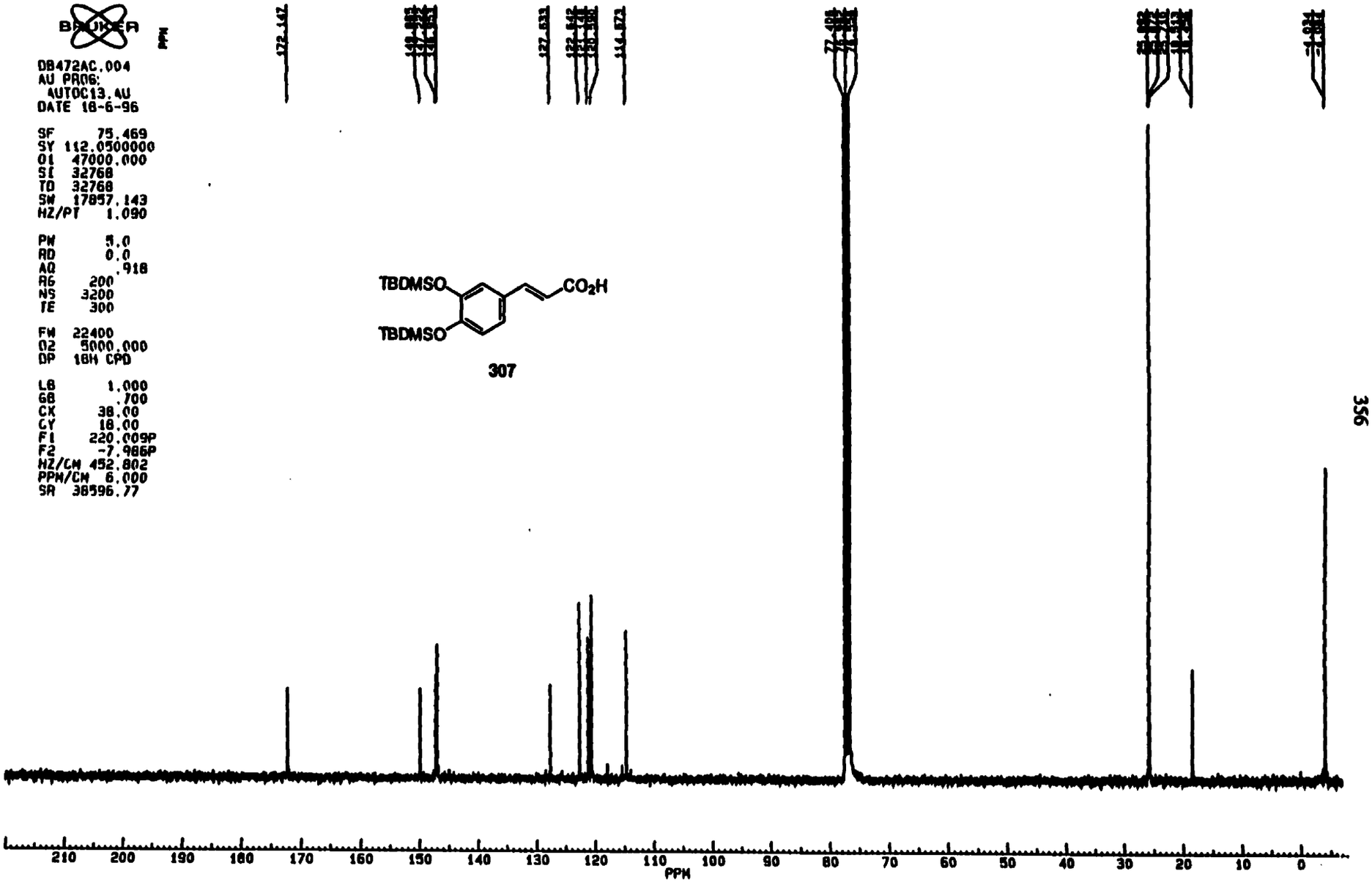
PW 5.0
RD 0.0
AQ .918
RG 200
NS 3200
TE 300

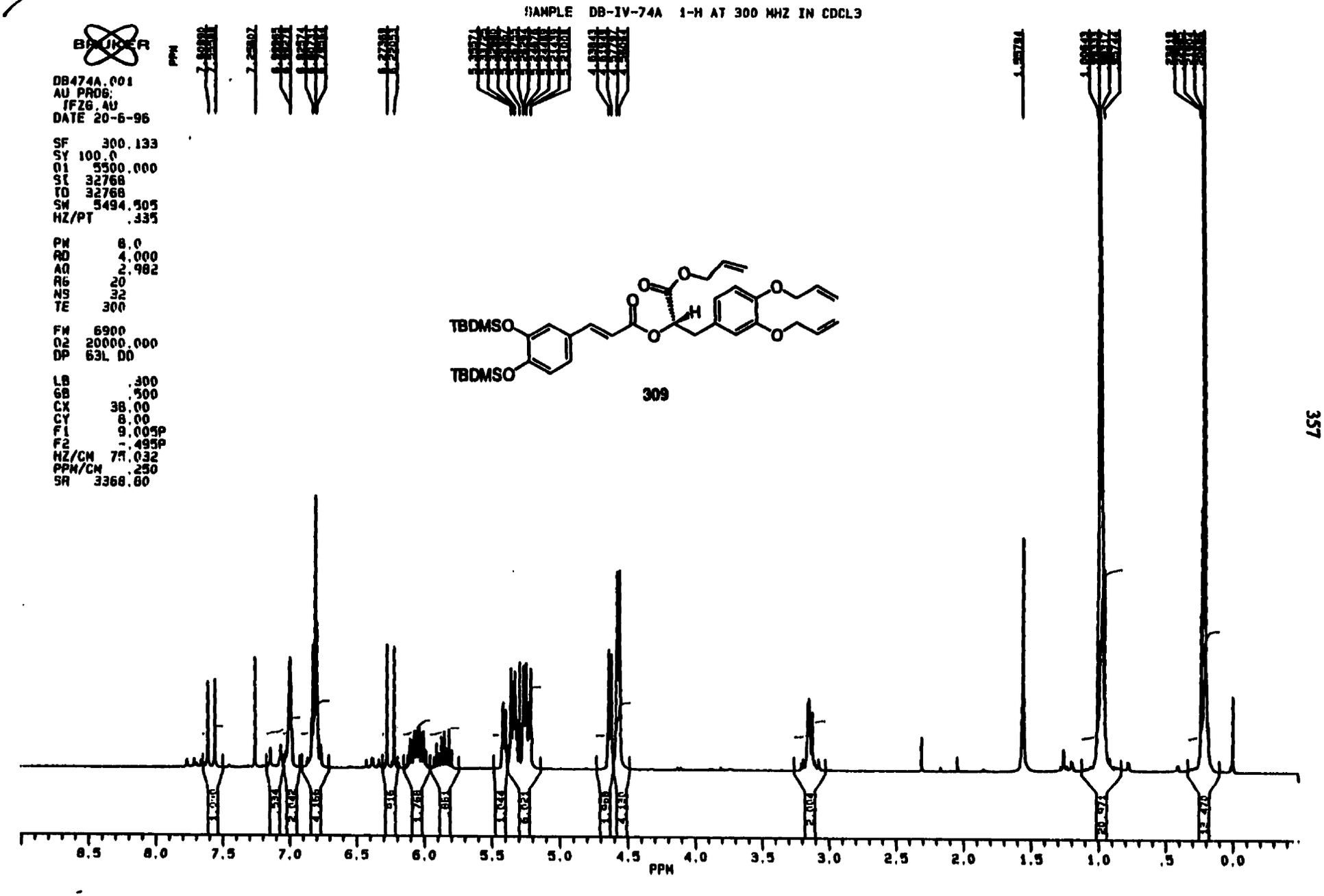
FW 22400
O2 5000.000
DP 18H CPD

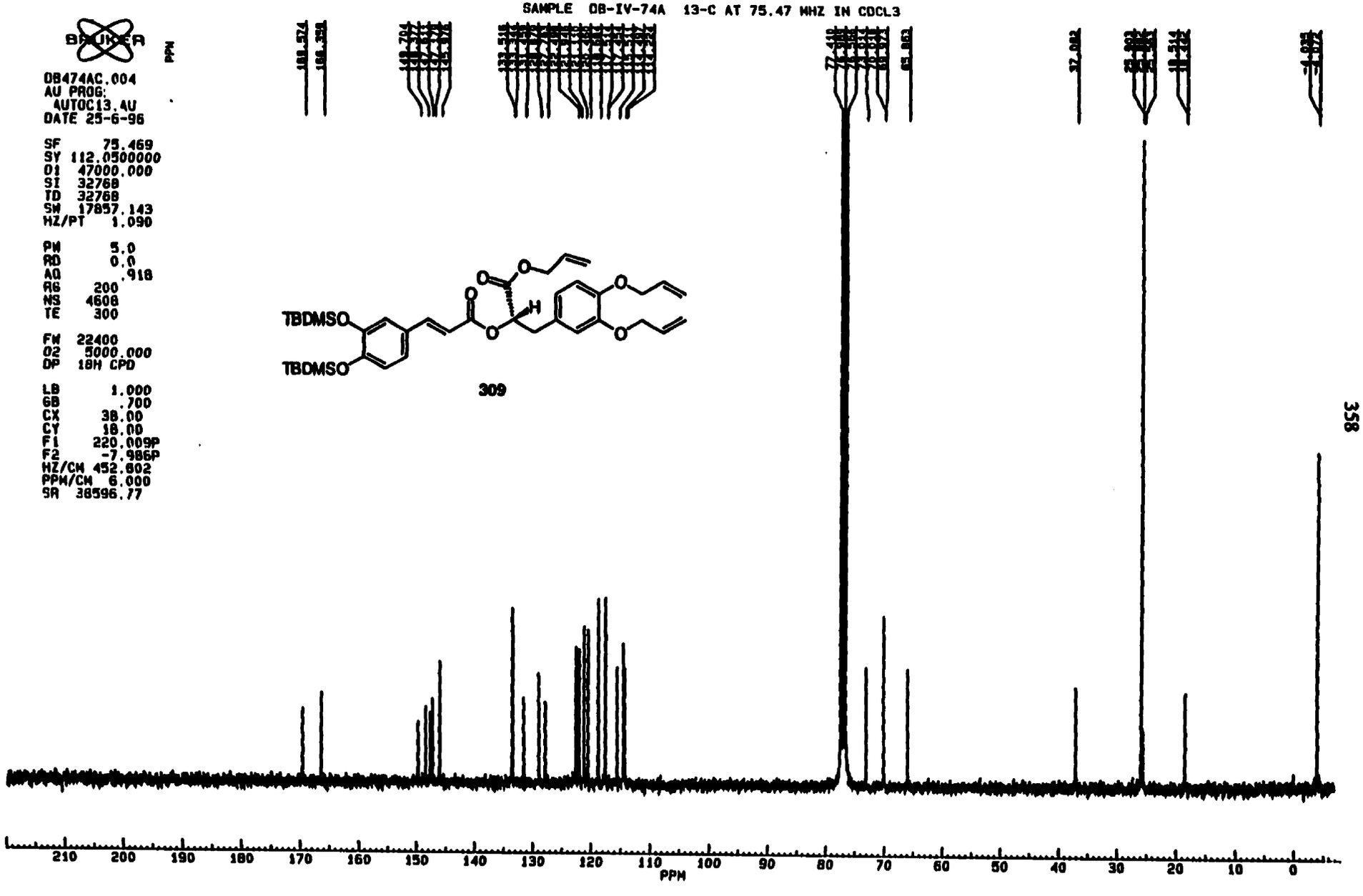
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 220.009P
F2 -7.986P
HZ/CM 452.802
PPH/CM 6.000
SR 38596.77

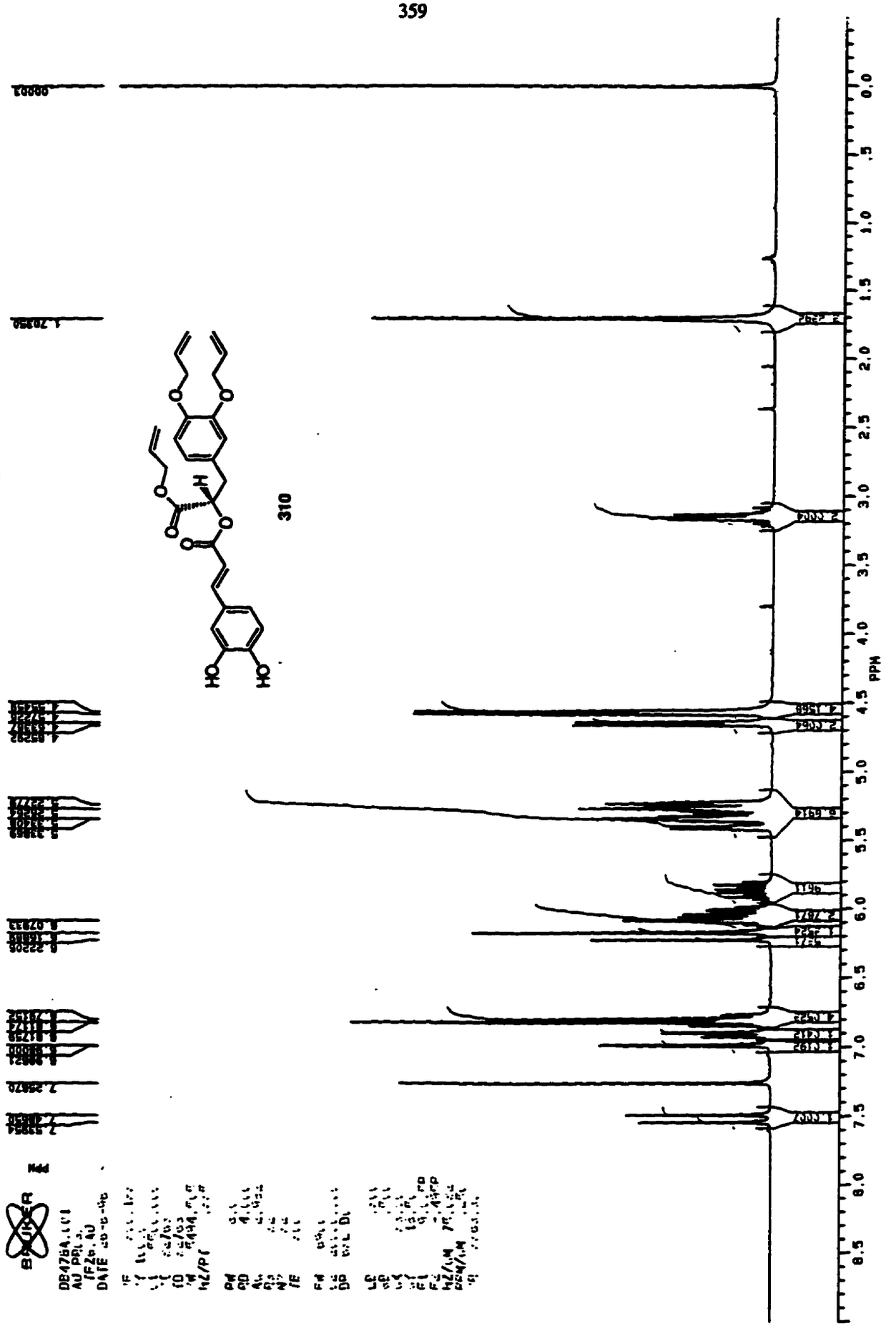



307




SAMPLE DB-IV-74A 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
DB474A.001
AU PROG:
IFZG.AU
DATE 20-6-96
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 8.00
F1 9.005P
F2 -.495P
HZ/CM 79.032
PPM/CM .250
SR 3368.80
TBDMSO
TBDMSO
H
309
PPM


SAMPLE OB-IV-74A 13-C AT 75.47 MHZ IN CDCL3
BRUKER
PPM
OB474AC.004
AU PROG:
AUTOC13.AU
DATE 25-6-96
SF 75.469
SY 112.0500000
O1 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AQ .918
RG 200
NS 4608
TE 300
FW 22400
O2 5000.000
DP 18H CPD
LB 1.000
GB .700
CX 38.00
CY 18.00
F1 220.009P
F2 -7.986P
HZ/CM 452.602
PPM/CM 6.000
SR 38596.77
TBDMSO
TBDMSO
309
358
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


SAMPLE DB-IV-78A 1-H AT 300 MHZ IN CDCL3
310
PPM

SAMPLE DB-IV-78A 13-C AT 75.47 MHZ IN CDCL3



DB478AC.004
AU PROG:
AUTOC13.AU
DATE 27-6-96

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

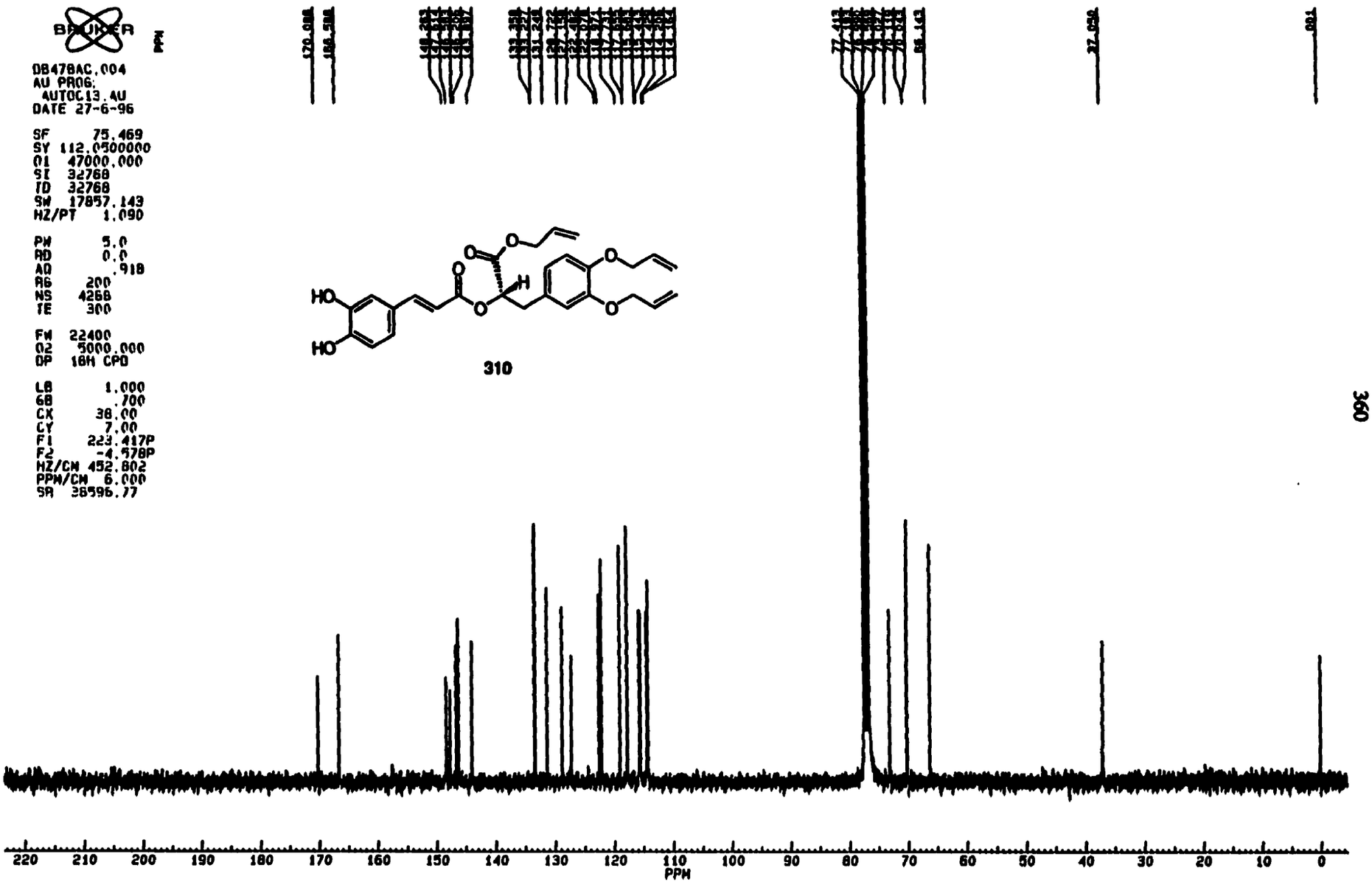
PW 5.0
RD 0.0
AQ .918
RG 200
NS 4268
TE 300

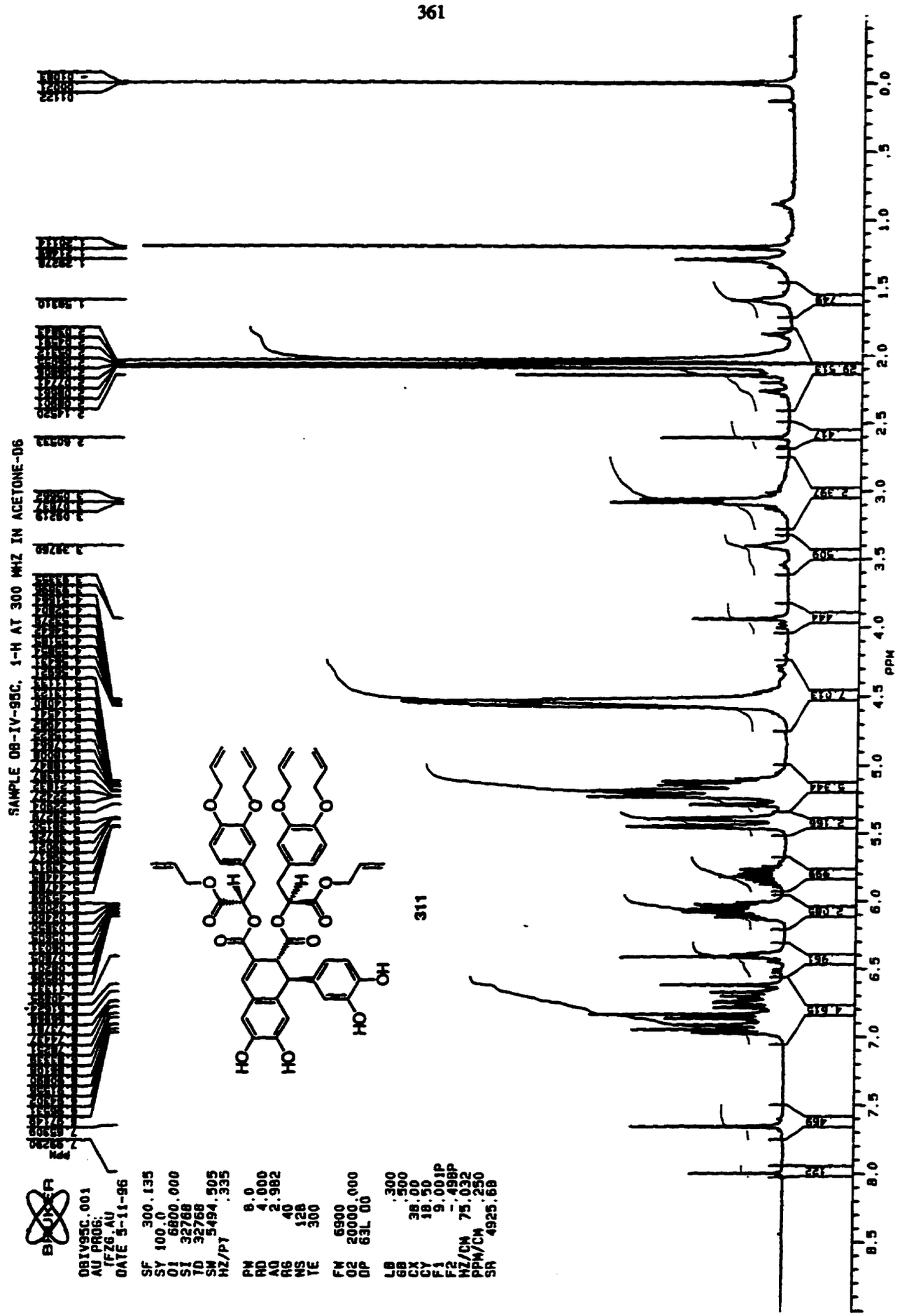
FW 22400
O2 5000.000
DP 18H CPD

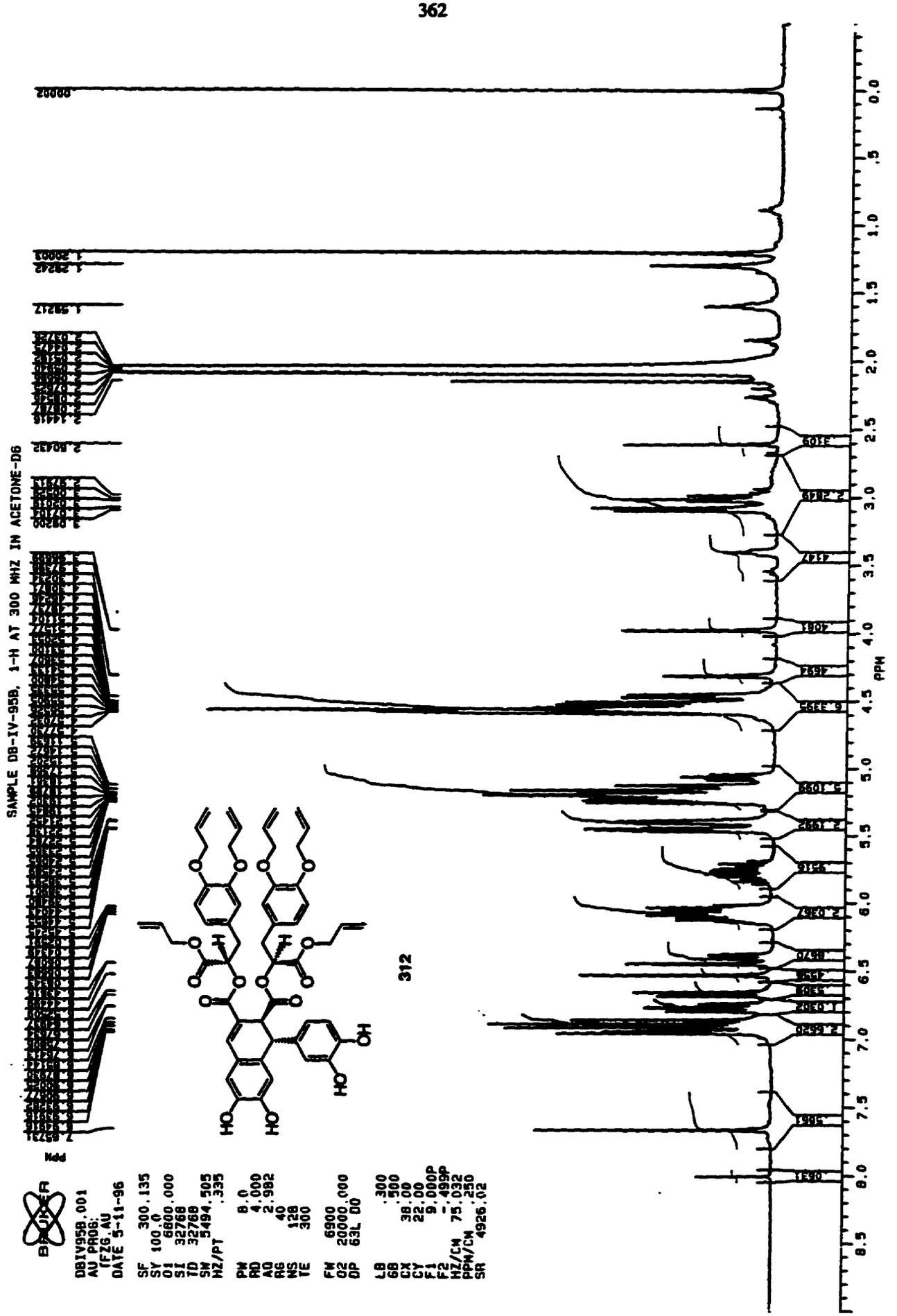
LB 1.000
GB .700
CX 38.00
CY 7.00
F1 223.417P
F2 -4.578P
HZ/CM 452.802
PPM/CM 6.000
SR 38596.77



310




SAMPLE 08-IV-95C, 1-H AT 300 MHZ IN ACETONE-D6
BRUKER
DBIV95C.001
AU PROG:
(FZ6.AU
DATE 5-11-96
SF 300.135
SY 100.0
OI 6800.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 128
TE 300
FW 6900
O2 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.001P
F2 -.498P
HZ/CM 75.032
PPM/CM .250
SR 4925.68
311
PPM


SAMPLE DB-IV-95B, 1-H AT 300 MHZ IN ACETONE-D6
BRUKER
DB1V95B.001
AU PROG:
(FZ6.AU
DATE 5-11-96
SF 300.135
SY 100.0
01 6800.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 128
TE 300
FW 6900
02 20000.000
DP 63L 00
LB .300
GB .500
CX 38.00
CY 22.000
F1 9.000P
F2 .499P
HZ/CM 75.032
PPM/CM .250
SR 4926.02
PPM
312

SAMPLE DB-III-29A 1-H AT 30. 4MHZ IN CDCL3

BRUKER

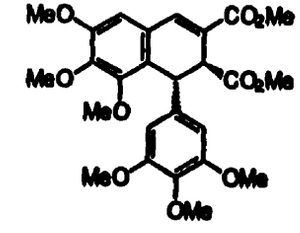
DB329A.001
AU PR06;
FFZ6.AU
DATE 19-5-95

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

PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300

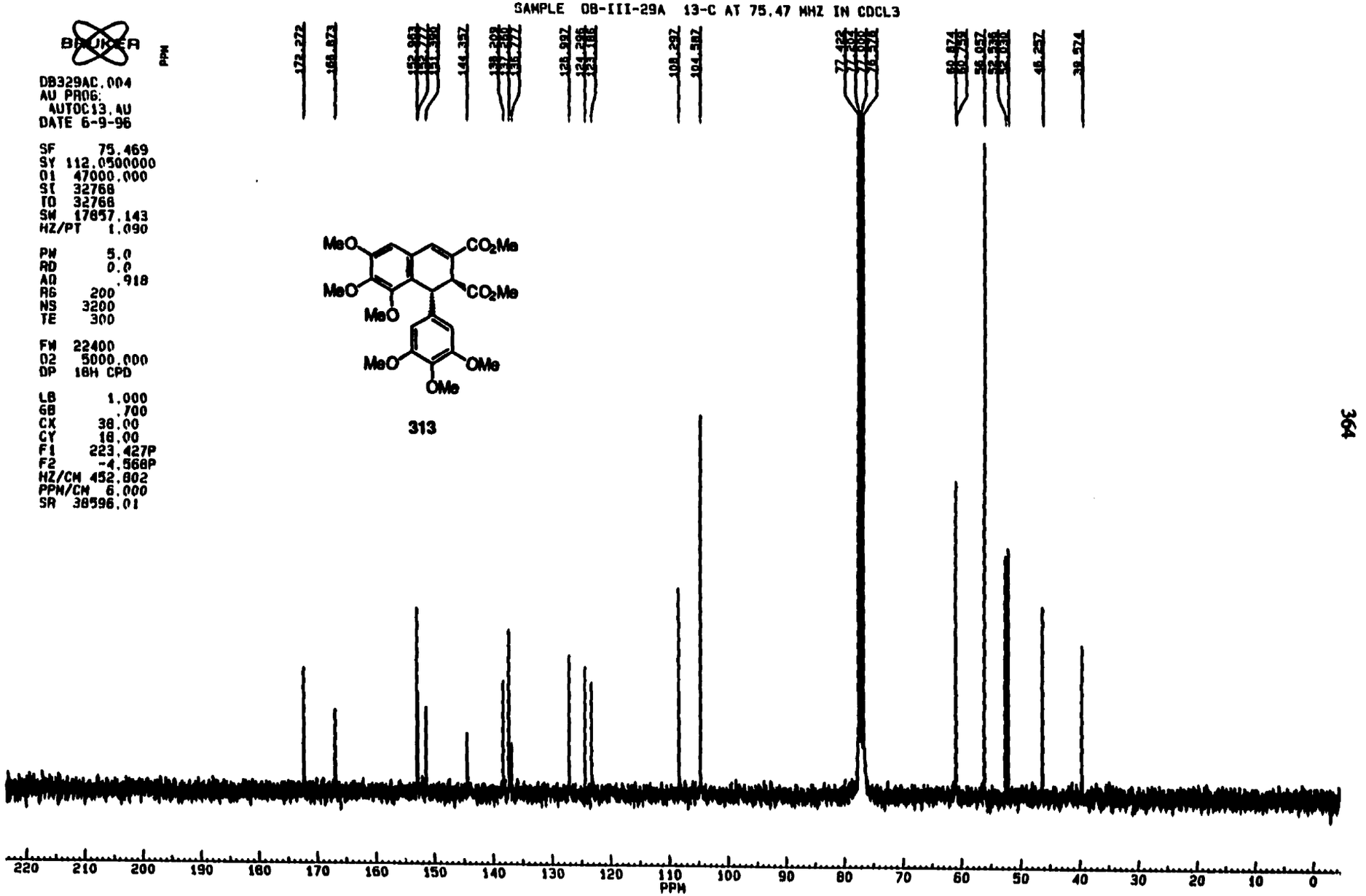
FW 6900
O2 20000.000
DP 63L 00

LB .300
GB .500
LK 38.00
LY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.46

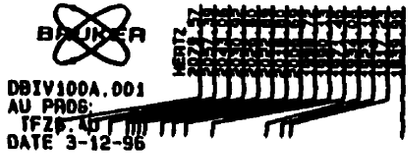



313

SAMPLE DB-III-29A 13-C AT 75.47 MHZ IN CDCL3



SAMPLE DB-IV-100A, 1-H AT 300 MHZ IN ACETONE-D6



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DBIV100A.001
AU PROG:
 TFZP.40
DATE 3-12-96

SF     300.135
SY 100.0
O1    6800.000
SI   32768
TD   32768
SW    5494.505
HZ/PT     .335

PW        8.0
RD        4.000
AQ        2.982
RG       64
NS      128
TE      300

FW     6900
O2   20000.000
DP   63L D0

LB         .300
GB         .500
CK       38.00
CY        8.00
F1        7.149P
F2        2.930P
HZ/CM   33.324
PPN/CM     .111
SR     4926.02
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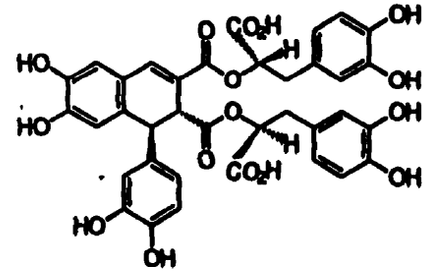
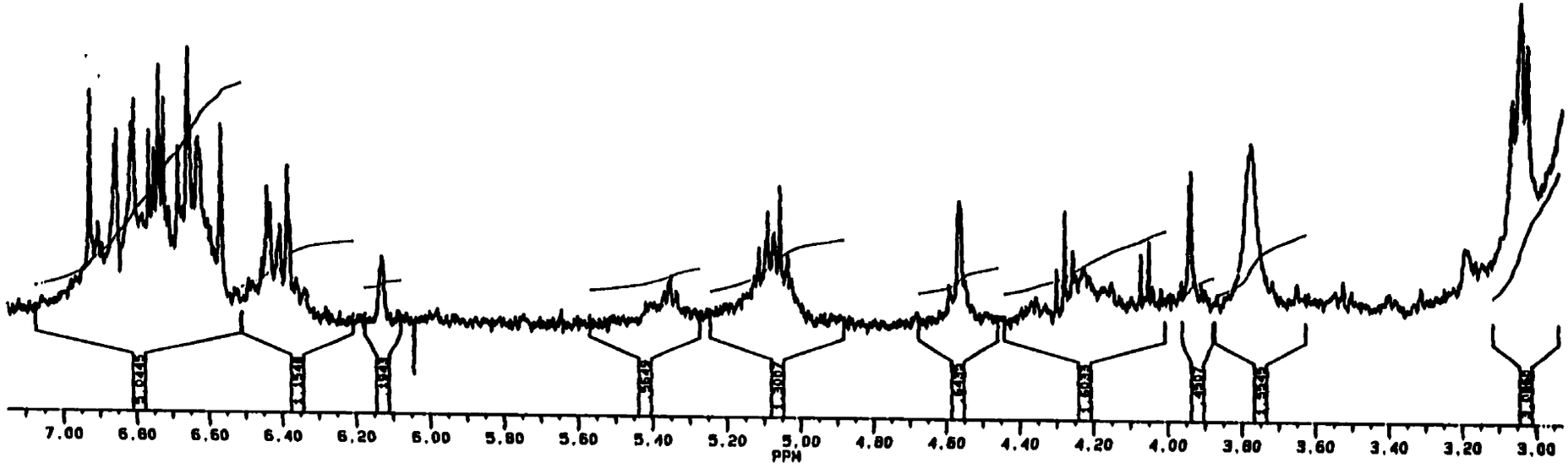
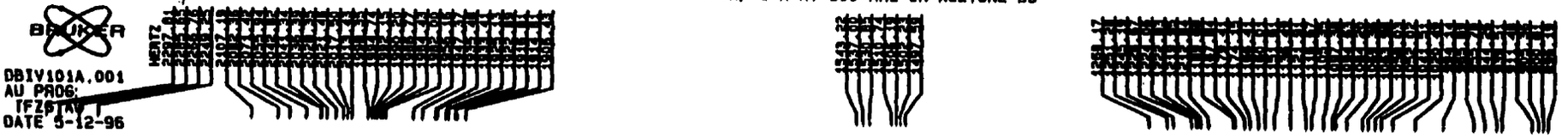


314



SAMPLE DB-IV-101A, 1-H AT 300 MHZ IN ACETONE-D6



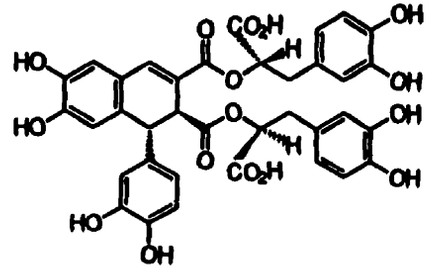
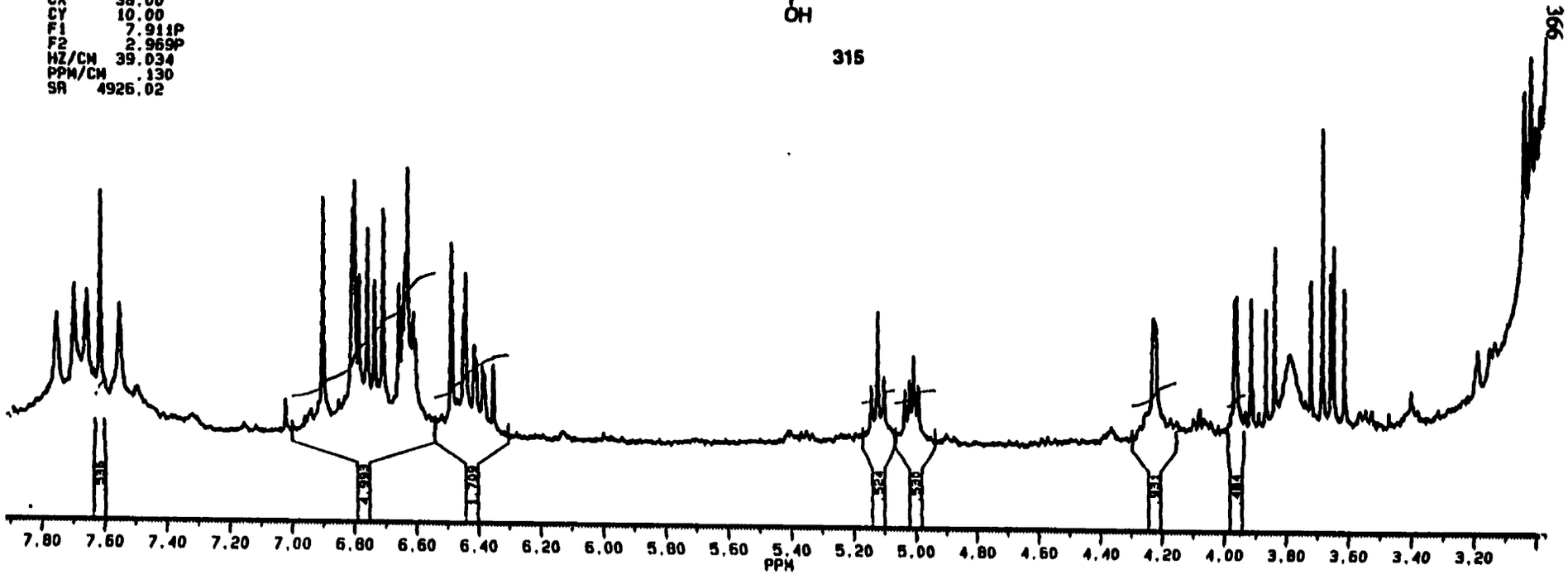
DBIV101A.001
AU PROG:
TFZ5TAV
DATE 5-12-96

SF 300.135
SY 100.0
O1 6800.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335

PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 256
TE 300

FW 6900
O2 20000.000
DP 63L DO

LB .300
GB .500
CX 38.00
CY 10.00
F1 7.911P
F2 2.969P
HZ/CM 39.034
PPM/CM .130
SR 4926.02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