NEW CHIRAL DIENOPHILES AND THEIR REACTIONS WITH *ORTHO*-QUINODIMETHANES

BY

PENG GUO

A thesis
Submitted to the Faculty of Graduate Studies
of the University of Manitoba in Partial fulfillment
of the requirements for the Degree of
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ACKNOWLEDGMENTS

This thesis is dedicated to my mother and wife, who make this work possible through their encouragements.

I would like to take this opportunity to thank my supervisor, Dr. J. L. Charlton for his guidance provided during the course of this work and his effort to improve my English.

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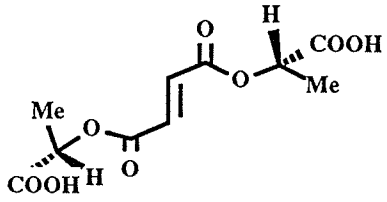
ABSTRACT

This thesis reviews the mechanism of stereoselective Diels-Alder (D-A) reactions, the generation and Diels-Alder reactions of *o*-quinodimethanes (*o*-QDM), and the application of *o*-QDMs as intermediates in asymmetric synthesis of lignans. Hydrogen bonding in diastereoselective control of Diels-Alder reactions is also briefly discussed.

The work described in this thesis focuses on the investigation of the Diels-Alder reactions of new chiral dienophiles with *o*-QDMs. In search of reactions in which hydrogen bonding controls stereoselectivity, dienophiles **87** and **90** were synthesized and reacted with α-methoxy-*o*-QDM. Only *endo* products were formed and there was no evidence of hydrogen bonding control of stereoselectivity.



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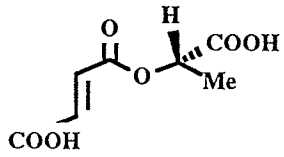
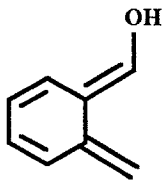


90

The chiral dienophile, mono(methyl (S)-lactyl) fumarate **88**, has also been synthesized by two methods and its use in asymmetric Diels-Alder cycloaddition reactions studied. In the reaction with *o*-QDM **10**, cycloadduct **96** was produced with high relative and absolute stereoselectivity.



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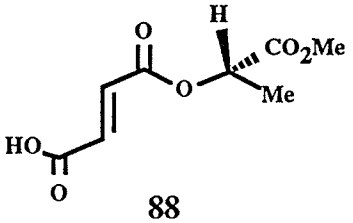

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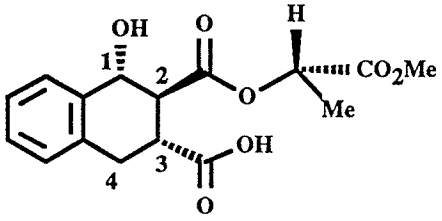
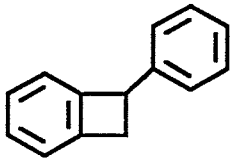


96

The reactions of fumarate **88** with both α-hydroxy-α'-phenyl-*o*-QDM and α-hydroxy-α-phenyl-*o*-QDM were carried out. Both of these reactions gave complicated mixtures of products.

In a study of Lewis acid effects on the stereoselectivity of D-A reactions of **88**, a new method for the synthesis of **100** and **101** was accidently discovered.



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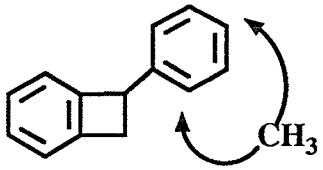
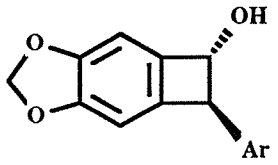


101a: ***ortho*** **1:1 mixture**
101b: ***para***

As this thesis's final goal, the first step in an asymmetric synthesis of the pharmaceutically important compound podophyllotoxin via the reaction of **88** with *o*-QDM **18** has been studied. Two methods for the generation of the *o*-QDM **18** were used.



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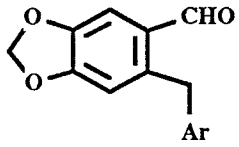
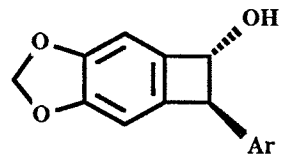


19

Firstly, the aldehyde **19**, which was prepared according to a literature procedure and a modified literature procedure, was irradiated in the presence of the mono(methyl (S)-lactyl) fumarate **88**. No cycloadducts were obtained using this procedure. Secondly, the *o*-QDM precursor benzocyclobutanol **17** was prepared by a literature procedure. Three alternate procedures for the synthesis of benzocyclobutanol **17** were also attempted. **17** was thermolized in the presence of **88** at room temperature to yield a single cycloadduct in high yield.



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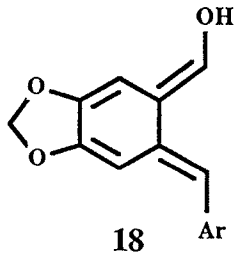

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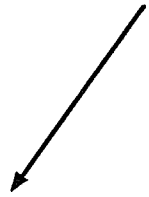

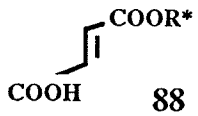

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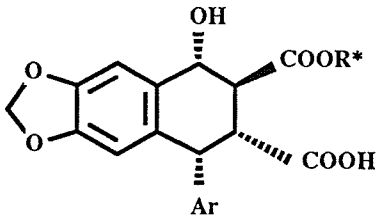
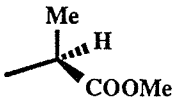


R*:



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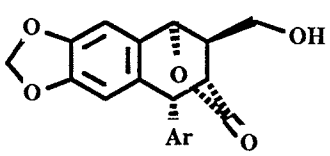
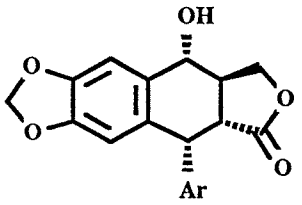
In an attempt to improve a published synthesis of (-)-neopodophyllotoxin which can be converted to (-)-podophyllotoxin, the reaction of the *o*-QDM precursor **17** with the fumarate

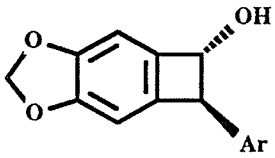
of methyl (S)-mandelate **63** was studied. The key intermediate cycloadduct was produced with better yield and stereoselectivity than those previously reported.



(-) **neopodophyllotoxin**



(-) **podophyllotoxin**



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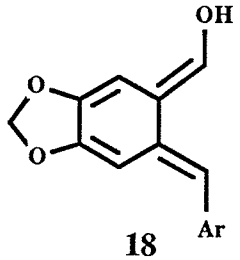

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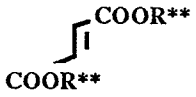

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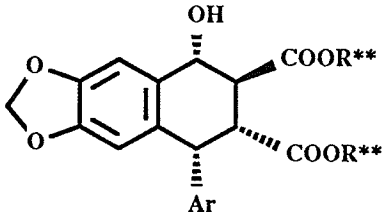

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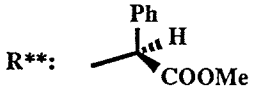

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Chapter 1: INTRODUCTION

CHAPTER 1

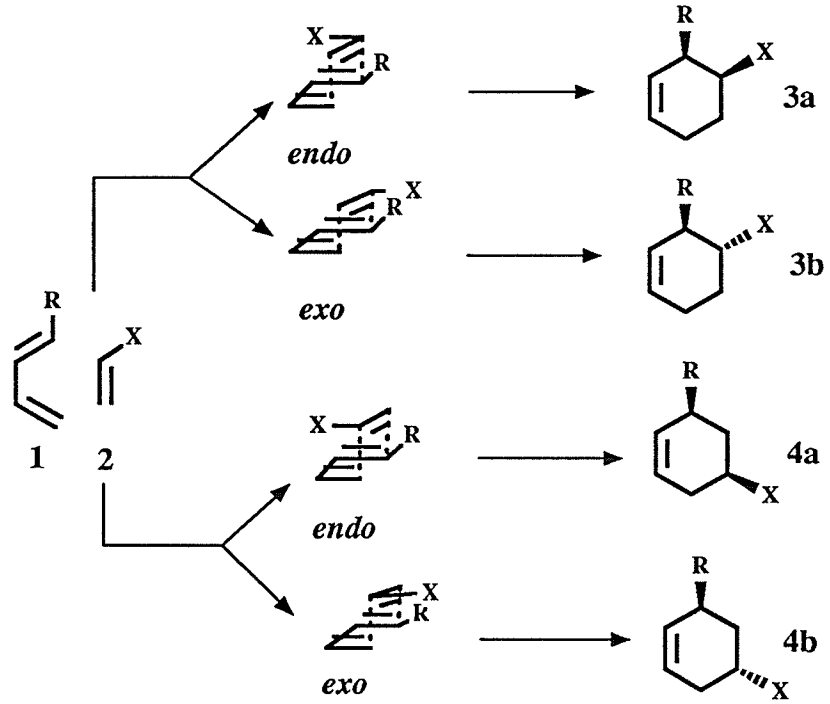
INTRODUCTION

Because many natural products and bioactive compounds contain six-membered rings with incorporated chiral centers, Diels-Alder cycloaddition reactions, which form such rings, have been used extensively in the synthesis of these kinds of compounds. Diels-Alder reactions are pericyclic cycloaddition reactions of dienes with alkenes. *o*-Quinodimethane, a special kind of diene, has been successfully employed in such Diels-Alder reactions for the construction of steroids,[1] complicated alkaloids[2] and other natural compounds.[3] Recent publications have detailed the use of *o*-quinodimethanes in asymmetric synthesis of bioactive compounds such as lignans.[4] Although general asymmetric Diels-Alder cycloaddition reactions using chiral auxiliaries or chiral catalysts have been comprehensively investigated in the last two decades, little work has been done in asymmetric synthesis using *o*-quinodimethanes as dienes. This introductory section will review the Diels-Alder cycloaddition reactions which involve *o*-quinodimethanes, those factors which affect stereoselectivity in these reactions, and applications of unsymmetric synthons in asymmetric synthesis.

1.1 Diels-Alder Cycloaddition Reactions

The Diels-Alder reaction, in which a 1,3-diene reacts with an alkene or alkyne to give a six-membered ring cycloadduct, was discovered separately by Diels and Alder in 1928.[5] Since its discovery, the reaction has been developed into one of the most powerful methods in organic synthesis. Theroretically, a Diels-Alder reaction can give several isomeric

products if there are substituents on the diene and dienophile, but the reaction often gives predominantly only one product. For example, the Diels-Alder reaction between a 1-substituted diene **1** and a monosubstituted dienophile **2** could give four possible products, regio- and stereoisomers **3** and **4**.



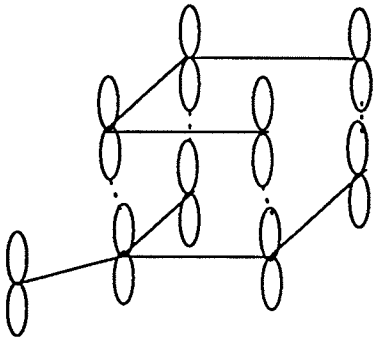
The transition states for these reactions can be classified according to the geometry with which the dienophile approaches the diene. If the substituent X is located over C-2 of the diene, the transition state is called *endo*. If X is extended away from the diene, the transition state is called *exo*.

In the above reaction, it has been observed that if R is an electron-withdrawing group and X is an electron-donating group, the reaction often gives *meta* cycloadducts **4a** and **4b**. These two diastereoiosmers arise via two different transition states, *endo* and *exo* respectively. In those cases in which X is an electron-withdrawing group and R is an electron-donating group, the Diels-Alder reaction usually gives the two *ortho* cycloadducts **3a** and **3b**. Product **3** is a regioisomer of **4** and Frontier Orbital Theory (FOT)[6] has been used to predict the regioselectivity for this reaction, that is, the relative ratio of **3** and **4**. According to FOT, the primary interaction between molecules that eventually leads to reaction is a

mixing of the frontier orbitals of the two reactants. The frontier orbitals are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) on a molecule. Generally, the most significant FOT interactions between two molecules are those that occur between the HOMO of one molecule and the LUMO of the other molecule. The relative size of FOT interaction (orbital overlap) can be predicted by the coefficients of the HOMO and LUMO of the diene and dienophile, and these orbital coefficients can be calculated using molecular orbital theory. In the diagram below, the relative magnitudes of the orbital coefficients of the HOMO and LUMO of diene and dienophile are represented by circles of different sizes. Favorable orbital overlap occurs between centers on which the magnitude of the HOMO and LUMO coefficients are similar e.g. large circle with large circle, small circle with small circle. The orbital overlap in **A**, in which R is an electron-donating group and X is an electron-withdrawing group, gives head-to-head reaction leading to *ortho* cycloadducts **3a** and **3b**. In **B**, in which R is an electron-withdrawing group and X is an electron-donating group, the orbital overlap leads to head-to-tail *meta* cycloadducts **4a** and **4b**.

A **B**

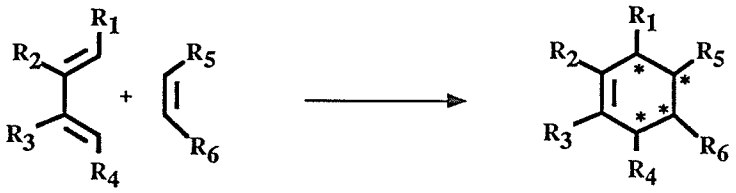
For Diels-Alder reactions, stereoselectivity as well as regioselectivity can be predicted using FOT. The frontier orbital overlap occurs not only between the primary orbitals of the diene and dienophile, but also between the orbital of the diene and the orbital of the substituent on the dienophile.



The latter interaction, called a secondary orbital interaction, occurring between C-2 of the diene and the substituent on the dienophile, leads to the *endo* selectivity.

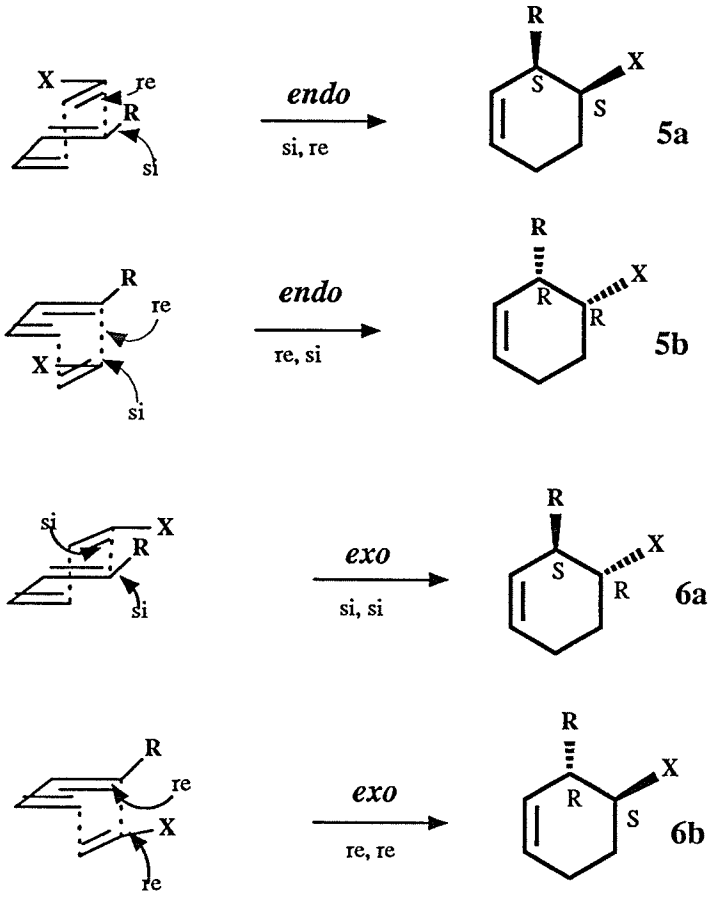
Sometimes the secondary overlap results in conflicting effects on the stereoselectivity. In the case of the reaction of methyl acrylate with the electron-rich 1-substituted diene, 1-phenyl-1,3-butadiene, poor *endo* selectivity was observed despite the secondary orbital interaction.[7] According to molecular orbital (MO) calculations, when an electron-donating substituent is attached to a diene at C-1, it simultaneously increases the magnitude of the secondary HOMO coefficients at C-2 and the exclusion shell (gross orbital charge of $2Pz^2$) at C-2. In this case , the *endo* cycloadduct must be favored through the increased secondary orbital interaction and disfavored through the increased closed-shell repulsion. The balance between the secondary orbital interaction and the closed-shell repulsions contributes to the stereoselectivity.

For Diels-Alder reactions, a most attractive feature is the simultaneous formation of two new bonds with the creation of up to four chiral centers.



If both diene and dienophile bear achiral substituents (R, X) (see below), the two possible

approaches of the diene and dienophile in the *endo* transition state give an equal amount of **5a**, in which reaction has occurred at the *si* and *re* faces of diene and dienophile respectively, and **5b**, in which reaction has occurred at the *re* and *si* faces of diene and dienophile respectively.



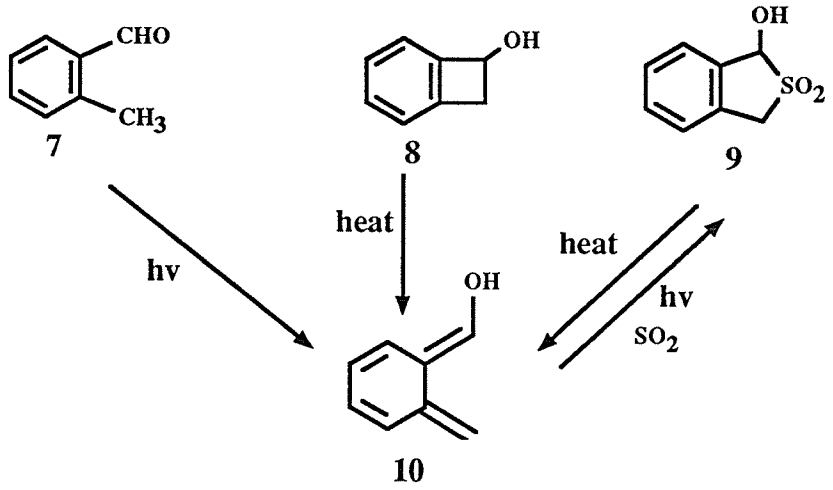
In the *exo* transition state, the two possible approaches give an equal amount of enantiomeric pairs **6a** and **6b**.

When a diene or dienophile bears a chiral group (chiral auxiliary), the previously enantiomeric pairs **5a/5b** and **6a/6b** become diastereomeric pairs and may be produced in unequal amounts. In such cases the reaction becomes an asymmetric synthetic step since the newly created chiral centers are created with an excess of one absolute configuration. The extent of asymmetric induction is measured by quoting the diastereomeric excess (d.e.) of **5a** (**6a**) relative to **5b** (**6b**).

1.2 Diels-Alder Reactions of *o*-Quinodimethanes

1.2.1 Generation of *o*-Quinodimethanes

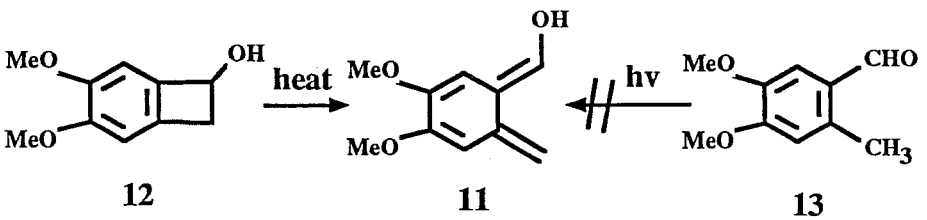
There are a number of reviews detailing generation and reactivity of *o*-quinodimethanes.[4,8] The majority of methods can be classified into three categories. These are, photolysis of *ortho* methyl aromatic ketones or aldehydes,[9,10] elimination reactions of 1,2 substituted *o*-xylenes,[11] and thermal ring openings of unsubstituted and substituted benzocyclobutenes.[12] For example, the photolysis of aldehyde **7** directly gives the expected *o*-QDM **10**. The α-hydroxy sulfone **9**, which can be prepared from trapping of *o*-QDM **10** with sulfur dioxide, regenerates the *o*-QDM **10** via thermolysis. The thermal ring opening of the benzocyclobutanol **8** also directly generates *o*-QDM **10**.



Although the photolysis of an *o*-methylbenzaldehyde is the simplest method for the generation of an *o*-QDM, in certain cases, some aldehydes do not form an *o*-QDM. This may be due to quenching of the excited aldehyde by dienophiles that are present, or inefficient conversion of the aldehyde excited state to *o*-QDM.[13] Even if the photolysis of an aldehyde does occur to form the corresponding *o*-QDM, it may not be trappable by a dienophile if the *o*-QDM has a very short lifetime.

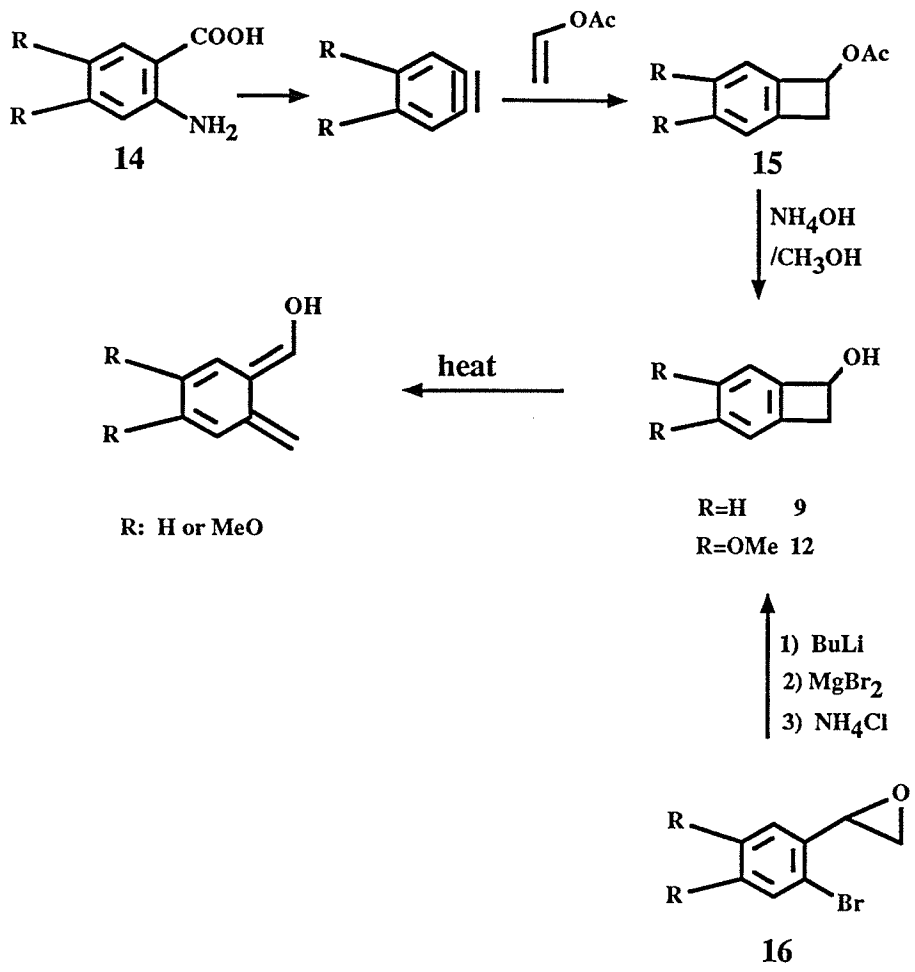
Thermal ring opening of benzocyclobutanols has been effectively used in generation of

o-QDMs. As an example, the *o*-QDM **11**, which could not be generated from photolysis of the aldehyde **13**, was successfully generated from the benzocyclobutanol **12**.[14]

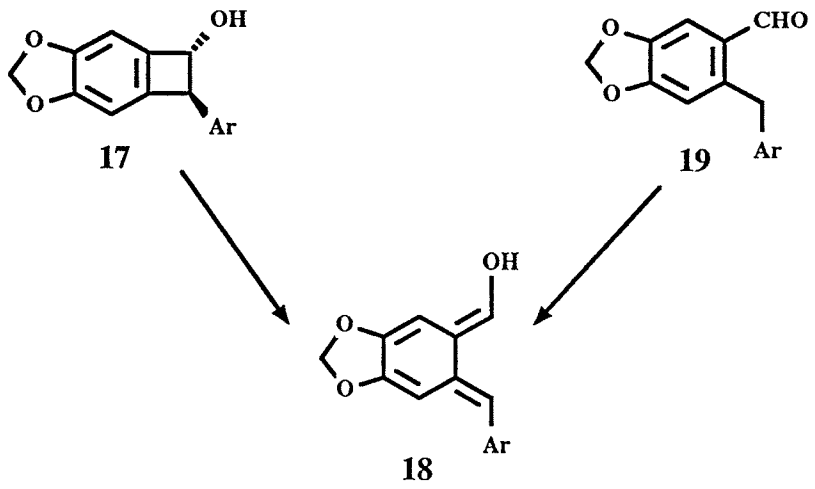


12 **11** **13**

Although benzocyclobutanols often give high yield conversion to *o*-QDMs, it is sometimes difficult to prepare these benzocyclobutanols. Two methods have been frequently used for synthesis of benzocyclobutanols. The unsubstituted or substituted 2-aminobenzoic acid **14** can be diazotized with isoamyl nitrite to generate an intermediate benzyne that reacts with vinyl acetate to give 1-acetoxy benzocyclobutane **15** in a reasonable yield. **15** can be hydrolysed with 30% ammonium hydroxide/methanol to afford the benzocyclobutanol (R=H, **8**; R=MeO, **12**) in 80-85%. The same compounds (R=H, **8**; R=MeO, **12**) can also be synthesized from a cyclization of 6-bromo styrene oxide **16** using n-butyllithium and magnesium bromide etherate in 50-80% yield.[15,16]



The *o*-QDM **18**, an important intermediate in synthesis of the natural product podophyllotoxin, can be generated thermally from the benzocyclobutanol **17** or photochemically from aldehyde **19**.[17]

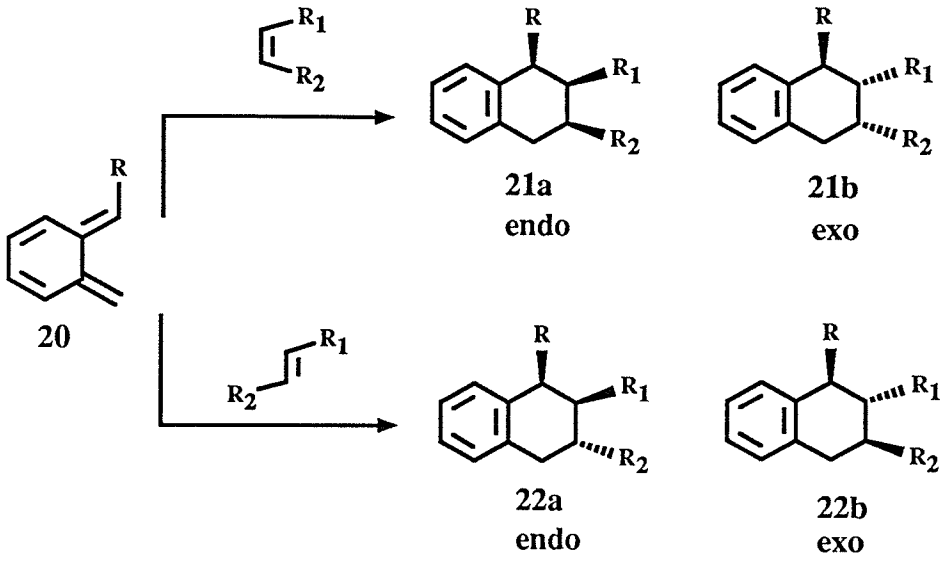


Ar=3,4,5,trimethoxyphenyl

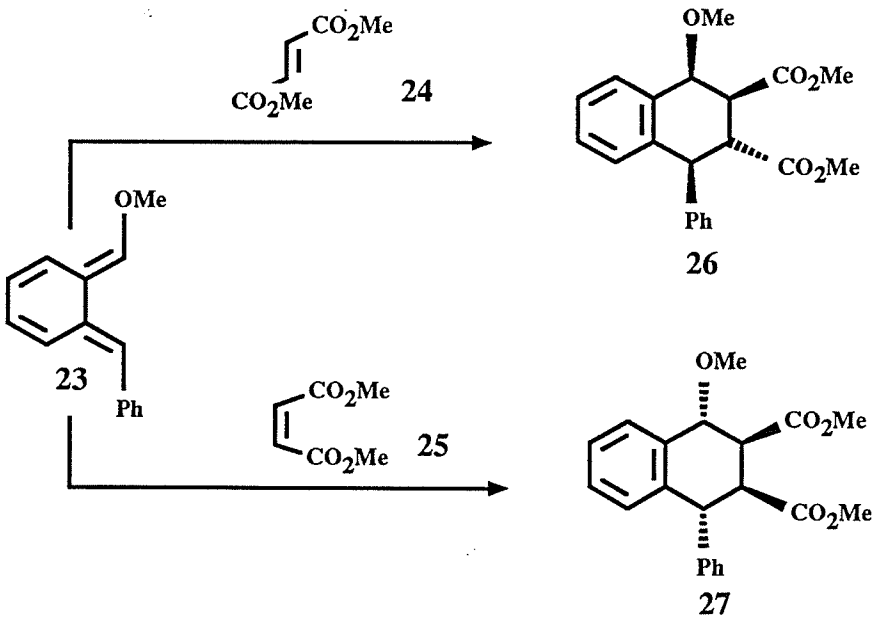
The benzocyclobutanol **17** is thermally unstable above 0°C. Durst *et al* synthesized this compound in 11 steps.[18] Jung *et al* employed a similar method to obtain the same compound.[19]

1.2.2 Diels-Alder Reactions of *o*-Quinodimethanes

o-Quinodimethane **20** reacts with *cis*-disubstituted or *trans*-disubstituted alkenes to give *endo* cycloadducts **21a/22a** and *exo* cycloadducts **21b/22b** respectively with high regioselectivity, in case where R is an electron-donating group and R_1 is an electron-withdrawing group.



The stereoselectivity (*endo*/*exo*) of the above Diels-Alder cycloaddition reaction depends on the substituents on the diene and dienophiles. In almost all cases, α-oxy, α-alkyl and α-aryl *o*-QDMs have been found to yield *endo* adducts,[20] but this trend may be broken for α-oxy-α'-aryl-*o*-QDMs. For example, the α-methoxy-*o*-QDM **23** reacts with dimethyl fumarate **24** to give cycloadduct **26** via the *endo* transition state, but **23** reacts with dimethyl maleate **25** to yield predominately the cycloadduct **27** via the *exo* transition state.[21] If there is no phenyl group in **23**, it reacts with dimethyl maleate to give *endo* cycloadduct rather than *exo* cycloadduct.[21]



1.2.3 Asymmetric Diels-Alder Cycloaddition Reactions of *o*-Quinodimethanes

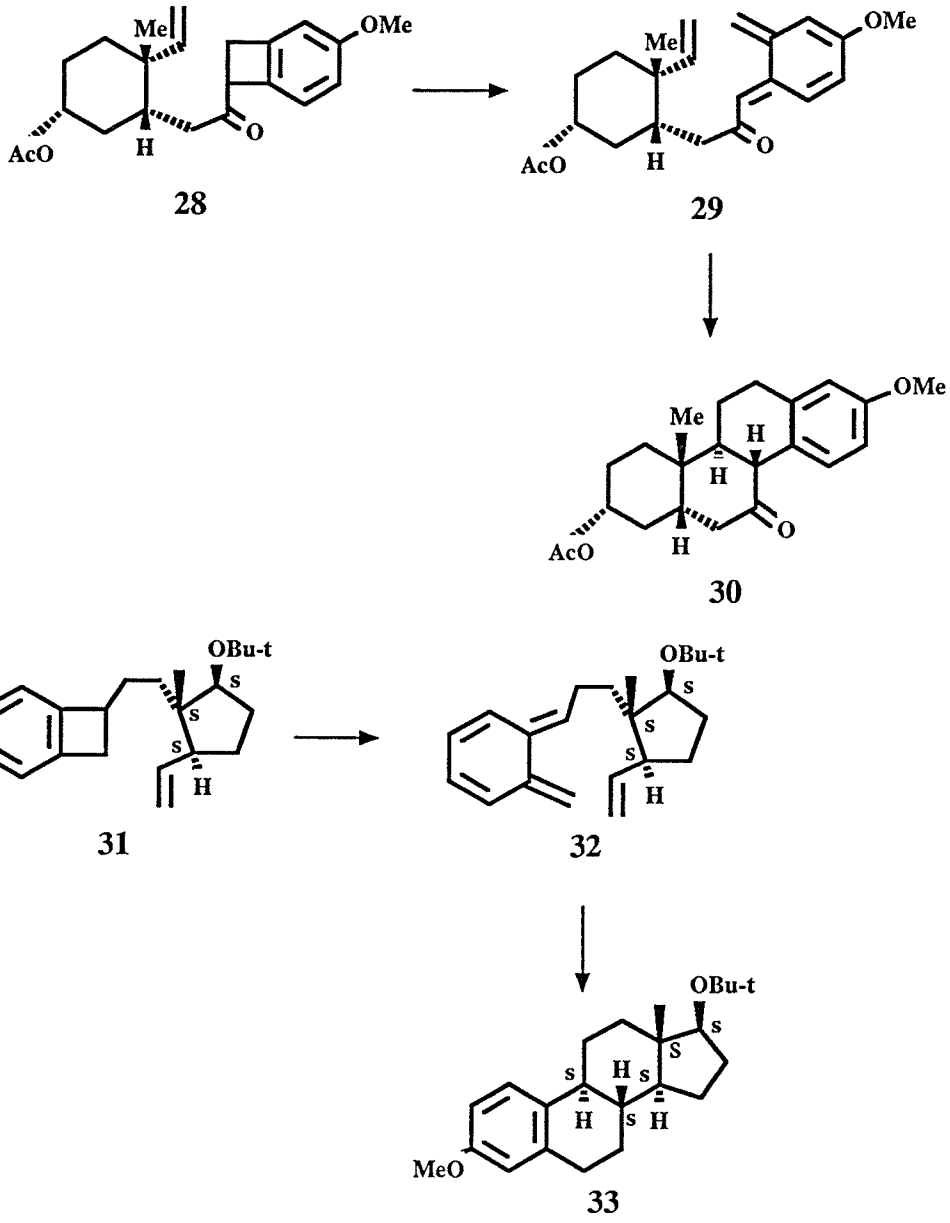
1.2.3.1 Asymmetric Diels-Alder Reactions of Chiral *o*-QDMs With Achiral Dienophiles

Diels-Alder reactions have been incorporated into asymmetric methods in which the chiral induction comes from different sources, for example, from chiral dienes, chiral dienophiles, or chiral Lewis acid catalysts. Most of published work has focused on the Lewis acid catalyzed cycloaddition reactions of achiral dienes and dienophiles, or cycloaddition reactions of chiral dienes and dienophiles catalyzed by achiral Lewis acids.

Thus far, few publications have reported the use of Lewis acids in Diels-Alder reactions of *o*-QDMs. However, chiral *o*-QDMs or chiral dienophiles have been often used in asymmetric Diels-Alder reactions.

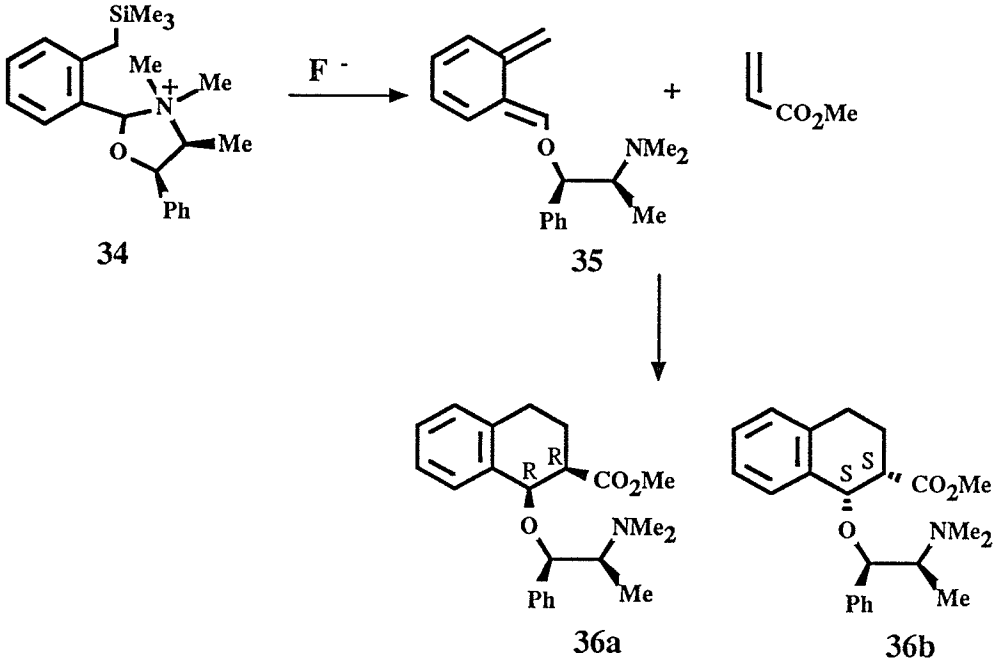
Kametani *et al* were the first to study asymmetric Diels-Alder reactions of *o*-QDMs.[22] They prepared *o*-QDM precursors **28** and **31** with optically pure chiral centers to control the diastereoselectivity of the subsequent cycloaddition reactions of *o*-quinodimethanes **29** and

32. In this way, they synthesized optically pure steroids **30** and **33** via intramolecular Diels-Alder cycloaddition reactions.[23]

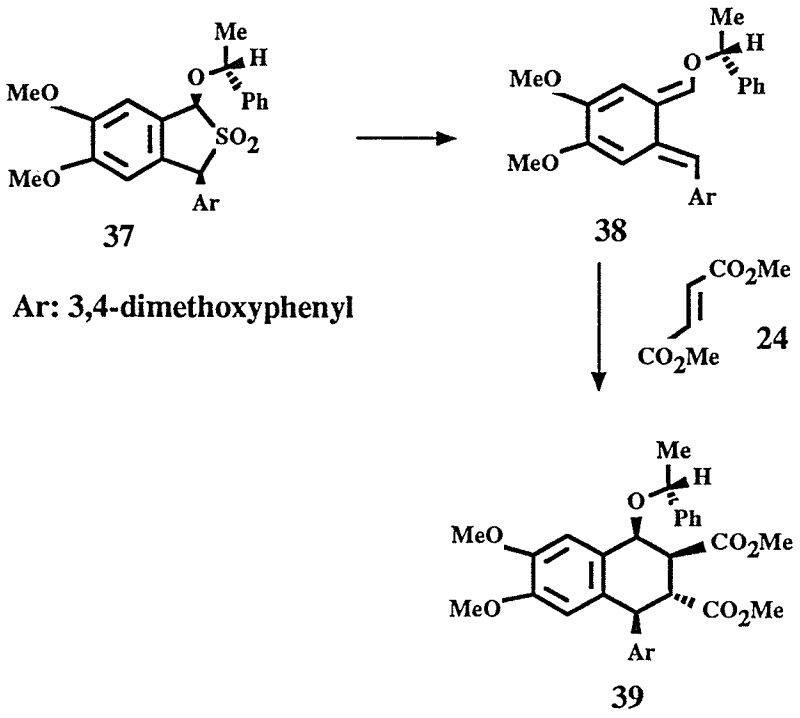


Because of the fixed configuration of intermediates **29** and **33**, the cycloaddition reactions gave 100% regioselectivity, and the steric repulsion between the aromatic and aliphatic rings gave remarkably high stereoselectivity with sterically favored *exo* transition states rather than *endo* transition states. The existing chiral centers in the molecules controlled the absolute stereochemistry of the two new chiral centers introduced by the Diels-Alder reaction.

For an intermolecular cycloaddition reaction, a chiral auxiliary which is attached to the *o*-QDM can control the absolute stereochemistry of the newly formed chiral centers. Ito and co-workers introduced a chiral auxiliary into the *o*-QDM **35** which was generated from a 1,4-elimination of the oxazolidinum system 34.[24] The reaction of **35** with methyl acrylate gave *endo* adduct **36a** and **36b** in a ratio of 2:1.



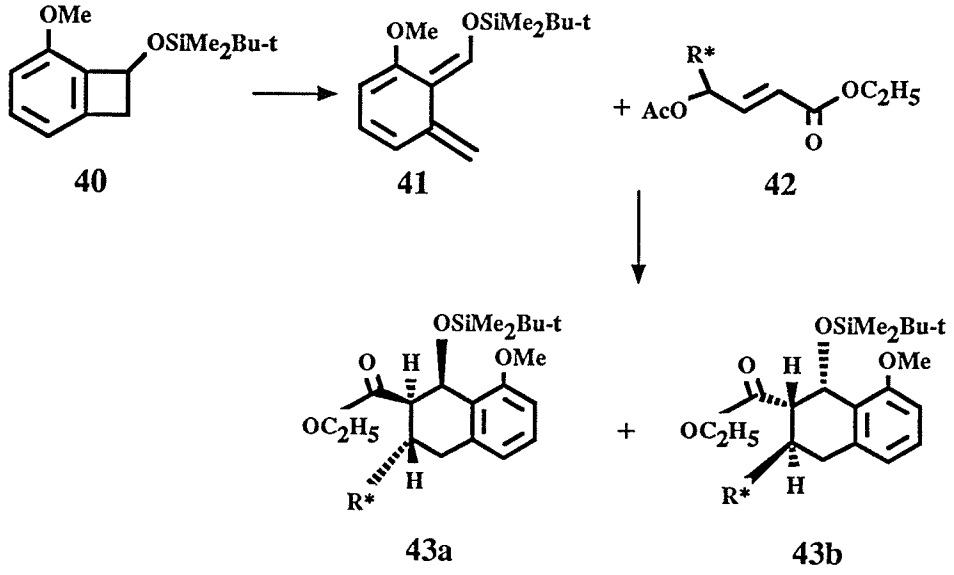
Later, Charlton *et al*, in a similar reaction, introduced a chiral alkoxy group into *o*-quinodimethane **38** and reacted it with dimethyl fumarate to give an *endo* adduct **39** with 83% diastereomeric excess (d.e.):[26]



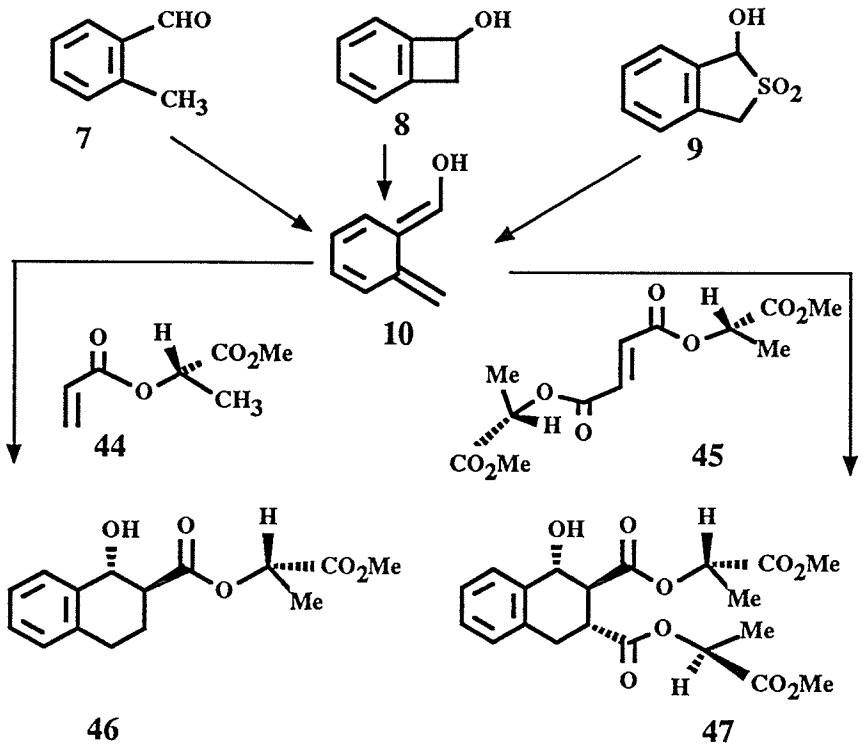
This shows that, in contrast to the intramolecular cycloaddition reactions described above, the intermolecular cycloaddition reactions of **35** and **38** with methyl acrylate and dimethyl fumarate respectively favor *endo*-transition states leading to *endo* adducts **36** and **39**, in which the secondary orbital interaction dominates the reaction, rather than *exo*-transition states. In comparison with intramolecular cycloaddition reactions, intermolecular cycloaddition reactions often yield a lower absolute stereoselectivity.

1.2.3.2 Asymmetric Diels-Alder Reaction of *o*-QDMs with Chiral Dienophiles

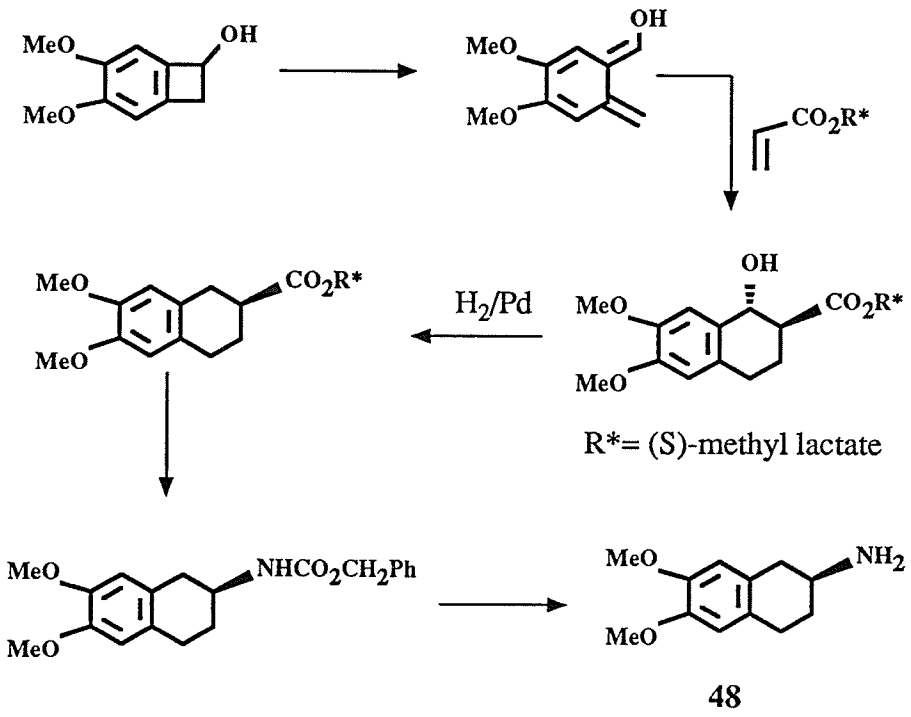
Relative to chiral dienes, dienophiles bearing chiral auxiliaries have been more commonly used in asymmetric Diels-Alder cycloaddition reactions. Franck studied the Diels-Alder cycloaddition reaction of the chiral dienophile **42** with an α-alkylsiloxy-*o*-quinodimethane **41** in which the reaction gave the two *endo* adducts **43a** and **43b** in a ratio of 4:1.[26]



In view of the low diastereoselectivity of the Diels-Alder reaction of the chiral *o*-QDM **38** with dimethyl fumarate, Charlton[27, 28] *et al* introduced a chiral auxiliary methyl (S)-lactate into the acrylate and fumarate dienophile in order to study the diastereoselectivity of the Diels-Alder reactions of these chiral dienophiles with *o*-QDMs. They generated the α-hydroxy-*o*-quinodimethane **10** from precursors **7**, **8** and **9**. **10** was trapped by the acrylate of methyl (S)-lactate **44**, and the fumarate of methyl (S)-lactate **45**, to give the *exo* cycloadducts **46** and **47** respectively with more than 95% d.e.



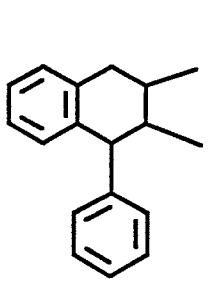
The highly enantioselective synthesis of β-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (ADTN dimethyl ether) **48**, made effective use of the above reaction.[29]



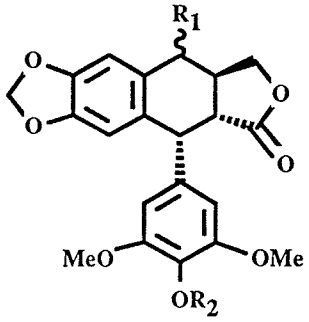
1.3 Asymmetric Synthesis of Lignans

1.3.1 Asymmetric Synthesis of Lignans Using Non Diels-Alder Methods

Aryltetralin lignans, a class of natural products isolated from plants, have a basic structure illustrated by **49**. Among them, podophyllotoxin **50**, a well-known precursor of anticancer agents, and its analogues such as epipodophyllotoxin **51**, deoxypodophyllotoxin **52**, etoposide **53** and teniposide **54**, have received considerable attention. In recent years, many approaches to the synthesis of podophyllotoxin and its lignan analogues have been developed, but most of them have been non-asymmetric syntheses and only a few papers have dealt with asymmetric synthesis.



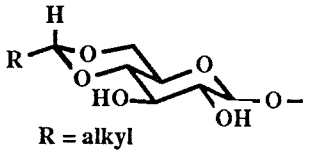
49



50: R_1 = α -OH, R_2 = Me

51: R_1 = β -OH, R_2 = Me

52: R_1 = H, R_2 = Me



R = alkyl

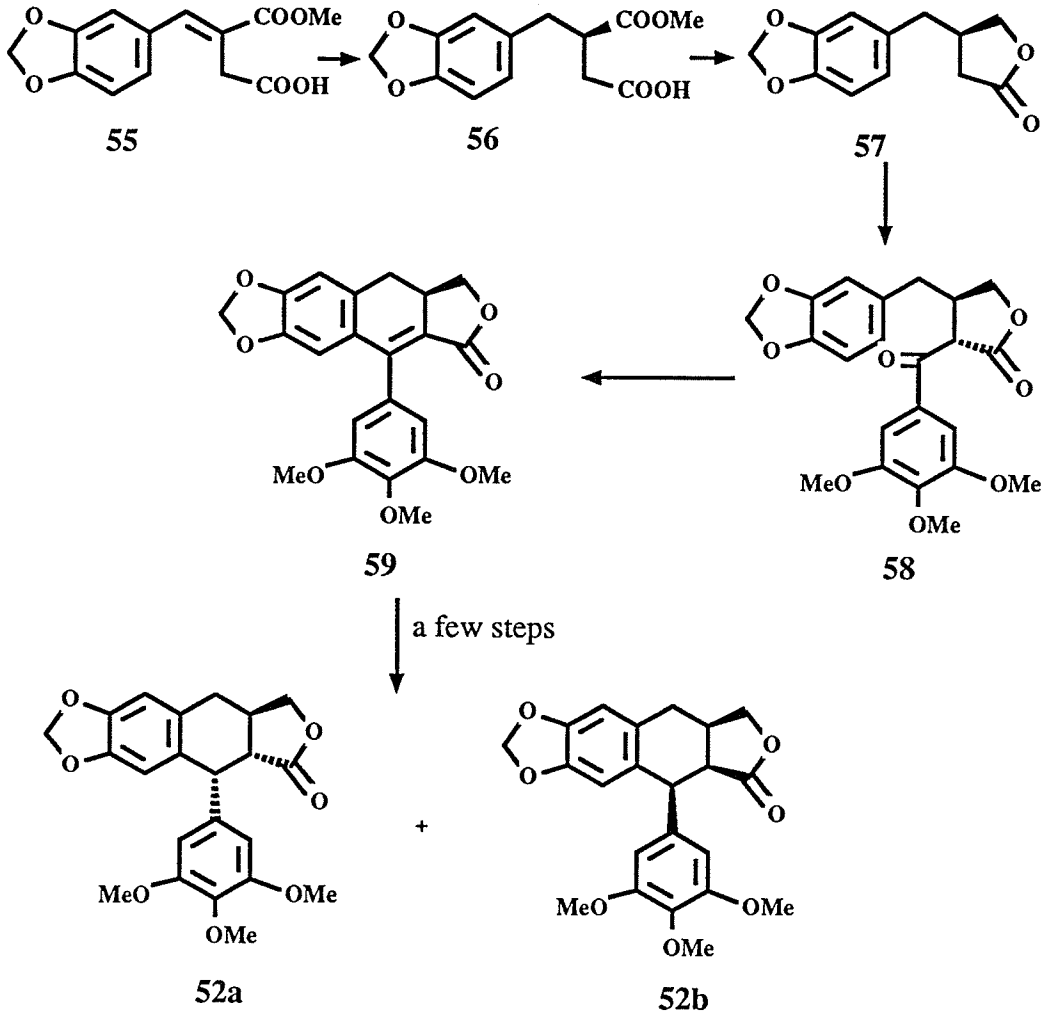
53: R_1 = Me, R_2 = H

54: R_1 = 2'-thenylidene

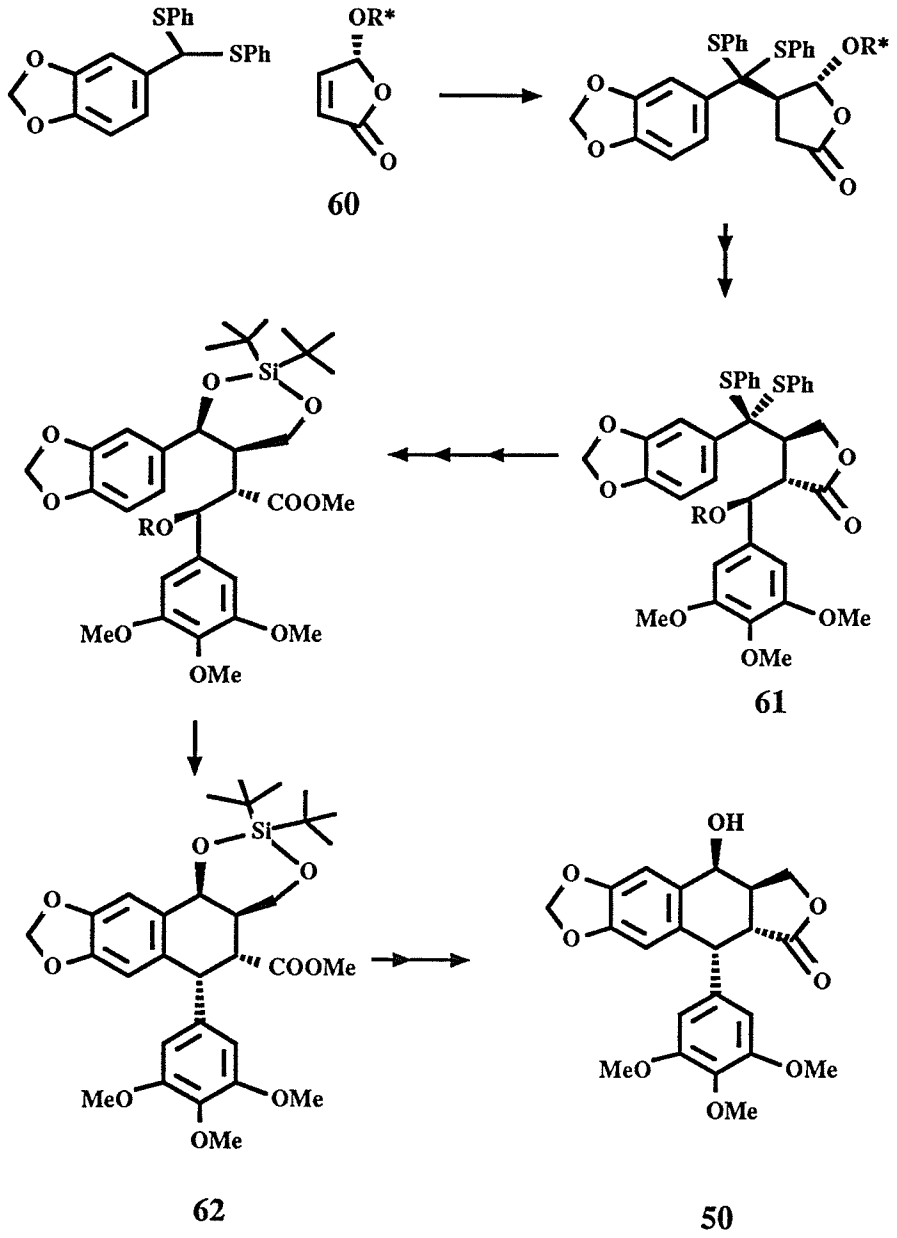
R_2 = H

Meyers reported the first asymmetric synthesis of podophyllotoxin **50** with only a 5% yield in 24 steps via a non Diels-Alder reaction strategy.[30] Achiwa *et al* employed an asymmetric hydrogenation of α-piperonylidenesuccinic acid half-methyl ester **55** using a neutral chiral rhodium (I) complex in the asymmetric synthesis of (-)-deoxypodophyllotoxin **52a**.[31] The overall yield of the procedure was poor and isolation of the product **52a** was complicated by

the concurrent formation of **52b**.



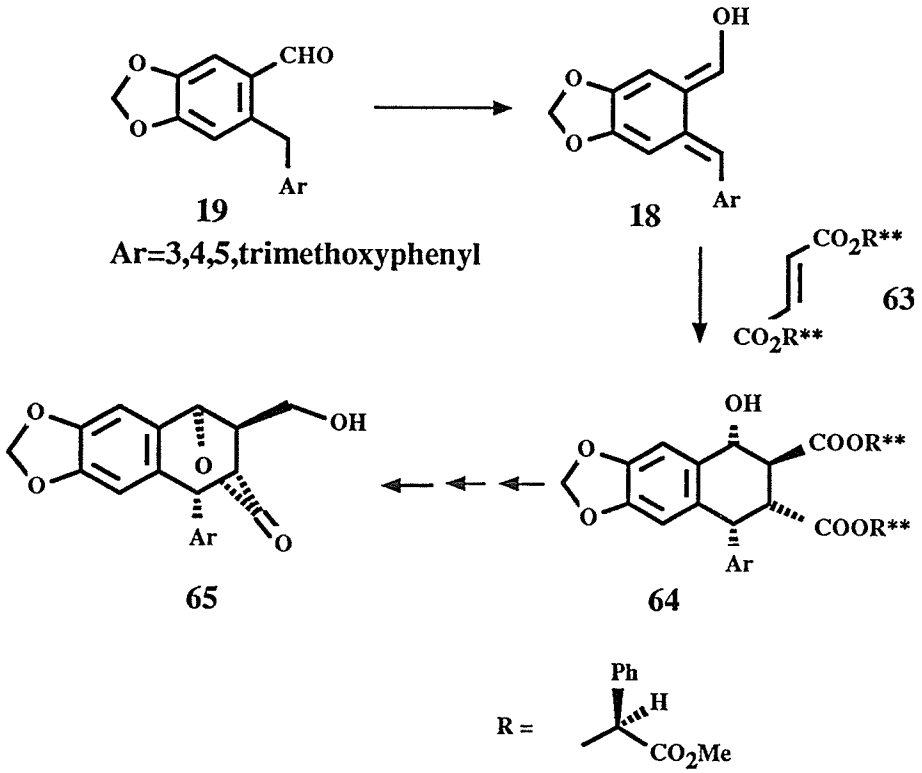
A more recent asymmetric synthesis of podophyllotoxin has been accomplished by Vandewalle via a conjugate addition to a chiral butenolide.[32]



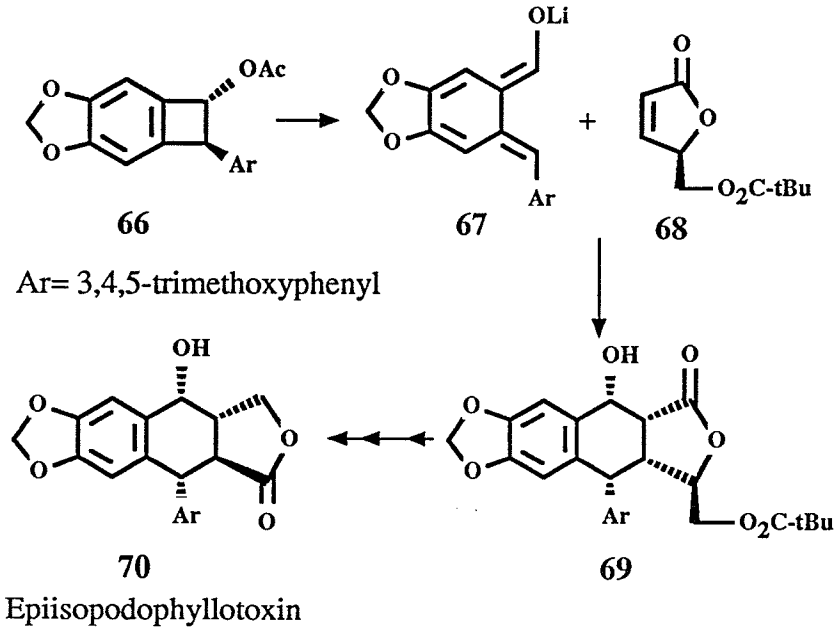
1.3.2 Asymmetric Synthesis of Lignans Using *o*-QDMs in Diels-Alder Reactions

Although some of the existing non-Diels-Alder strategies for the synthesis of podophyllotoxin and its analogues, such as Vandewalle's method, are very good, Diels-Alder approaches also offer some advantages. A Diels-Alder reaction affords the opportunity of

generating the four contiguous chiral centers in arytetralin lignans simultaneously (eg. **50**). Many researchers have employed general Diels-Alder cycloaddition reactions to synthesize racemic lignans.[33,34] Fewer examples of the use of this method in asymmetric lignan synthesis have been published. Charlton and Koh have studied the asymmetric synthesis of (-)-neopodophyllotoxin **65** in a reasonable yield by an intermolecular cycloaddition reaction of the substituted α-hydroxy-α'-aryl-*o*-quinodimethane **18** which was generated from the photolysis of aldehyde (podoaldehyde) **19** in the presence of the fumarate of methyl (S)-mandelate **63**.[17]



Another asymmetric synthesis of (-)-epiisopodophyllotoxin **70** has recently been achieved by Choy[35] via an intermolecular cycloaddition reaction of the *o*-QDM **67** with the chiral butenolide **68**. Treatment of the benzocyclobutene acetate **66** generated **67** which reacted with the chiral butenolide **68** to give the *endo* adduct **69**. The adduct **69** was epimerized, and by a further few steps it afforded (-)-epiisopodophyllotoxin **70**.



66 67 68

Ar= 3,4,5-trimethoxyphenyl

70 69

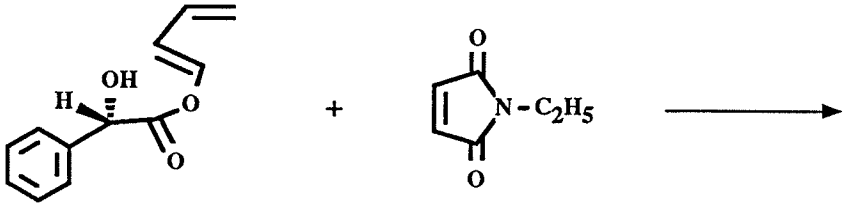
Epiisopodophyllotoxin

The literature survey above indicates that *o*-quinodimethanes have wide application in organic synthesis, especially complicated natural products with multi-chiral centers such as aryltetralin lignans. So far, only a limited amount of work has been done and the highly stereo- and enantioselective cycloaddition reactions of *o*-QDMs still deserves further study.

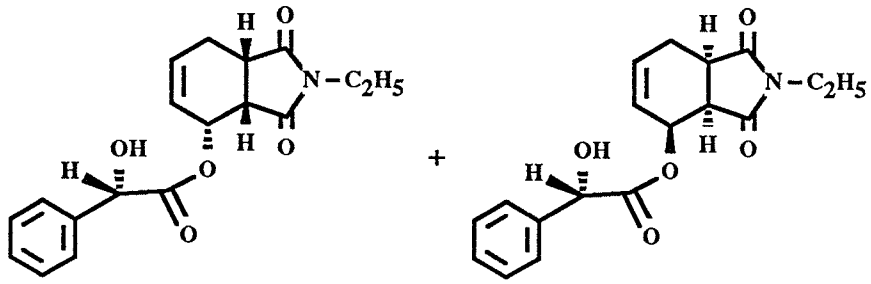
1.4 Hydrogen Bonding in Diastereoselective Control of Diels-Alder Cycloaddition Reactions

From the above discussion, we can see that the diastereoselectivity of the Diels-Alder cycloaddition reaction is dependent on the particular diene-dienophile pair under study. There have been many publications dealing with this interesting field and it seems there are many factors affecting the diastereoselectivity. Among these are Lewis acid effects. It is well-known that Lewis acids can affect the regio and diastereoselectivity of Diels-Alder cycloaddition reactions by complexing with functional groups on the diene or dienophile. Although the proton is the simplest Lewis acid, there have been only a few reports regarding

the proton's role in directing diastereoselectivity of Diels-Alder cycloaddition reactions. Recently, Thornton[36] reacted the 1-alkoxybutadiene **71**, bearing a remote chiral center with N-ethylmaleimide **72**, giving cycloadduct **73b** with high diastereoselectivity.

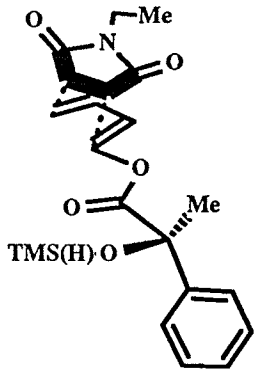


71 **72**

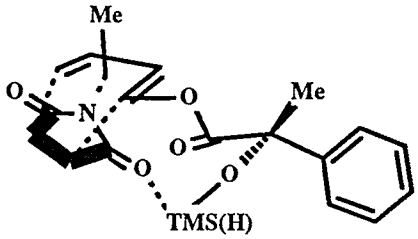


73a **73b**

As discussed in section **1**, a chiral center (or chiral auxiliary) can control the absolute stereochemistry of a Diels-Alder reaction by blocking the top or bottom face of the prochiral diene or dienophile. If the chiral center is far from the center undergoing reaction, it is less able to effectively control the absolute stereochemistry in the reaction. However, in the reaction of diene **71** with dienophile **72**, Thornton proved that control from a remote chiral center is possible if hydrogen bonding occurs in the transition state of the Diels-Alder reaction. He proposed two *endo* transition states **A** and **B**. In transition state **A** as described below, the dienophile approaches the diene from top face of the diene leading to product **73a**.



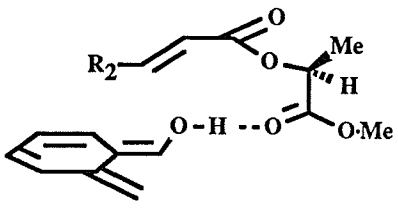
A



B

In transition state **B**, a stereoelectronically less favored form permits intermolecular hydrogen bonding with the carbonyl of the dienophile. In this form, the dienophile attacks the diene from the bottom face, leading to product **73b.** The hydrogen bonding interaction stabilizes transition state **B** to give cycloadduct **73b** as the major product. If the hydroxy group is replaced with a trimethylsiloxy group, as in **71**, so that no hydrogen bonding can occur, the reaction favors transition state **A**, leading to the stereochemistry shown in **73a.** Similar effects of hydrogen bonding on facial selectivity have been reported by other researchers.[37]

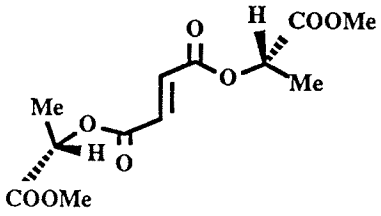
In the Diels-Alder cycloaddition reactions of α-hydroxy-*o*-QDMs with the acrylates and fumarates of methyl (S)-lactate and methyl (S)-mandelate, unusual *exo* stereoselectivity was noted (see the synthesis of **48** and **65** above). Maddaford has recently shown that the stereoselectivity observed in these reactions is the result of intermolecular hydrogen bonding, as shown below.[38]



With this model, both the facial stereoselectivity and the *exo* diastereoselectivity can be explained.

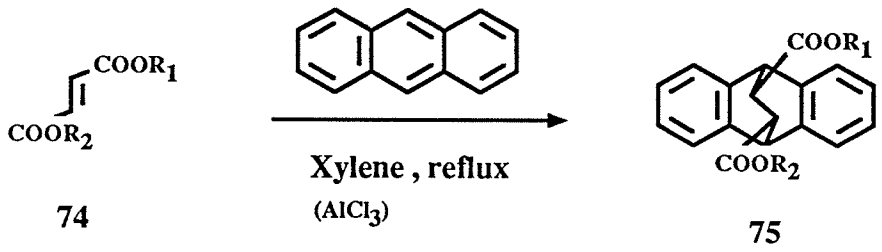
1.5 Symmetric and Unsymmetric Chiral Fumarates in Asymmetric Diels-Alder Reactions

As discussed above, the absolute stereoselectivity of a Diels-Alder reactions originates from a differentiation of the two prochiral faces of a diene or dienophile which bears a chiral auxiliary. If the chiral auxiliary can completely block one prochiral face of the diene or dienophile, the corresponding Diels-Alder cycloaddition reaction will give very high diastereoselectivity. If a dienophile or diene bears two chiral auxiliaries, then the two groups may cooperate in promoting diastereoselectivity. This reaction involving two chiral auxiliaries is called a double asymmetric induction. The disubstituted fumarate ($R_1 = R_2$) is commonly used as a model.



45

As an example, the fumarate of methyl (S)-lactate, which possesses C_2 symmetry, has two methyl (S)-lactate groups cooperating to block the bottom face of the fumarate. If this fumarate undergoes a Diels-Alder cycloaddition reaction, it should theoretically give a higher diastereoselectivity than the fumarate which bears only one methyl (S)-lactate group. Tolbert and Ali[38] observed that in the Diels-Alder reactions of anthracene and chiral fumarate **74**, the fumarate bearing identical chiral auxiliaries **74a** reacted with anthracene to give higher diastereoselectivity than did the fumarate bearing only one chiral auxiliary **74b**. However, few examples of this kind of double asymmetric induction in Diels-Alder reactions have been published.

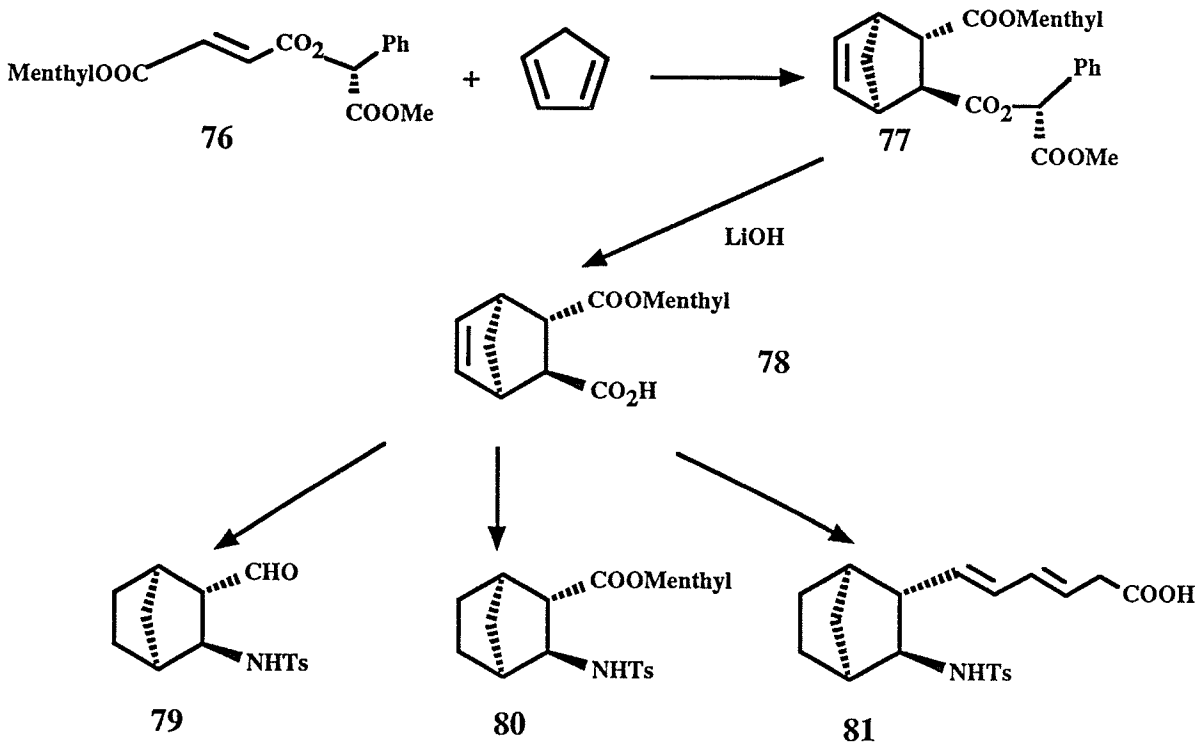


74 75

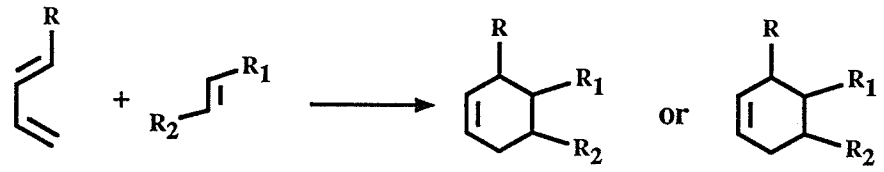
74a = R_1=R_2= Menthyl or Bornyl

74b = R_1= Menthyl or Bornyl , R_2=Methyl

While symmetrical dienophiles bearing identical chiral auxiliaries may lead to higher facial selectivity in a Diels-Alder reactions, disadvantages may arise if subsequent reactions require differentiation of those identical groups. Because syntheses of many natural products and bioactive compounds require differentiation of functional groups, unsymmetric dienophiles rather than symmetric dienophiles have been often employed in these syntheses. For example, Yamamoto[39] introduced two different chiral auxiliaries in fumarate **76** to react with cyclopentadiene. After the reaction, cycloadduct **77** could be selectively hydrolysed to acid **78**. Acid **78** was converted to the target compounds **79**, **80** and **81**.

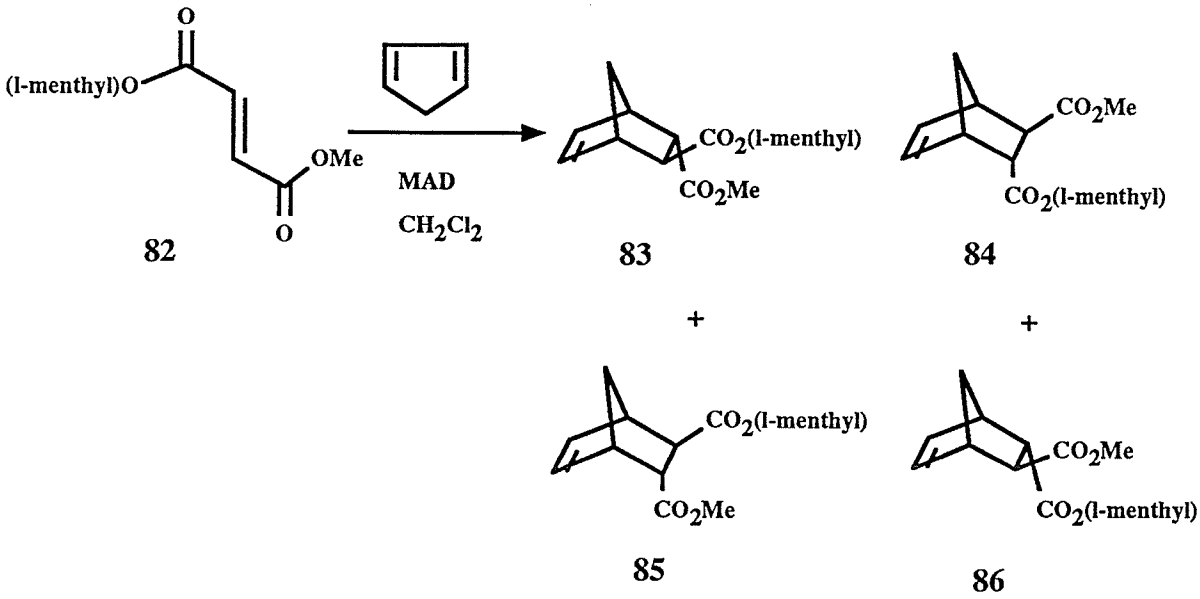


While unsymmetric dienophiles can facilitate the subsequent differentiation of functional groups, they can also lead to an increase in the number of potential regio and/or stereoisomeric products, as shown below.



This problem may be alleviated by selectively complexing a Lewis acid to one of the two functional groups. A dienophile like **82** bearing one chiral auxiliary and one methyl group, provides differentiation between the two esters. The bulky Lewis acid, methyl aluminum bis (2,6-di-tert-butyl-4-methylphenoxide, **MAD**), forms a complex only with the carbonyl group of the methyl ester due to steric interaction with the large (l)-menthyl ester. The selective binding of the Lewis acid makes the Diels-Alder reaction with cyclopentadiene yield four

stereoisomeric cycloadducts **83** to **86** in a ratio of 91.4:7:0.2:1.4.[40]



82 **83** **84** + + **85** **86**

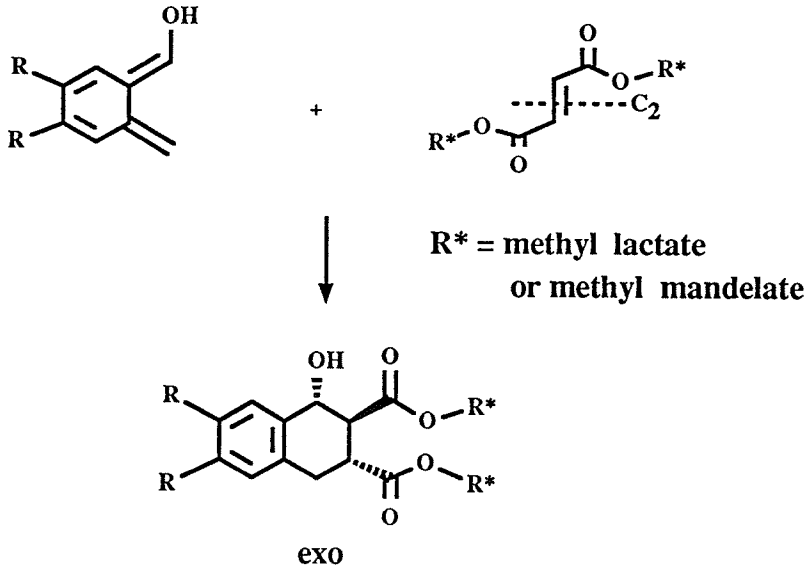
In fact, despite much published work dealing with chiral monofunctional dienophiles in Diels-Alder reactions, not much study of the use of chiral nonsymmetric bifunctional dienophiles in these reactions has been done.

CHAPTER 2

OBJECTIVE OF THIS THESIS

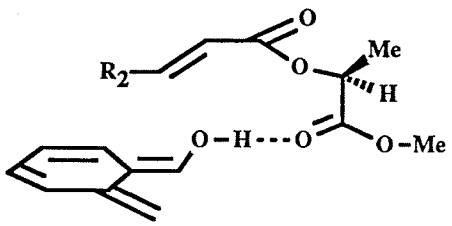
The objective of this thesis work is to explore the reactions of new chiral dienophiles in Diels-Alder reactions of *o*-QDMs, and to attempt to use one of these reactions in a short asymmetric synthesis of podophyllotoxin.

In previous studies, chiral dienophiles with C_2 symmetry, such as the fumarate of methyl (S)-lactate or mandelate, have been used in Diels-Alder cycloaddition reactions of α-hydroxy-*o*-QDMs. These reactions have given exclusively *exo* cycloadducts with more than 95% diastereoselectivity.



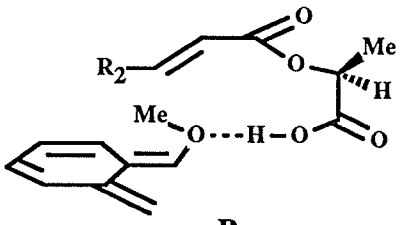
exo

This previous research has also shown that there may be hydrogen bonding in the transition states of these reactions. The hydrogen bond appears to control the relative and absolute stereoselectivity and it is assumed that the hydroxyl group of the *o*-QDM forms a hydrogen bond with the carbonyl group of the lactyl or mandyl group in the dienophile.

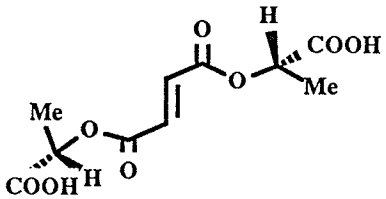


A

It appears possible that other types of hydrogen bonding could be used to control the diastereoselectivity of D-A reactions. The fumarate of lactic acid **87** may form hydrogen bonding from the lactyl carboxylic acid group to the oxy substituents on an *o*-QDM as shown below:



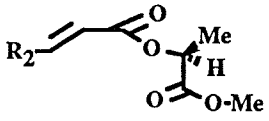
B

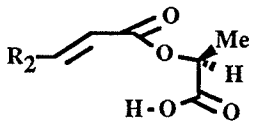


87

These two types of hydrogen bonds, **A** and **B**, are similar. If the latter type of hydrogen bonding does exist in the transition state of the D-A reaction, it may also control the reaction to produce the *exo* cycloadduct. The synthesis of **87** and its reaction with α-methoxy-*o*-QDM will be studied.

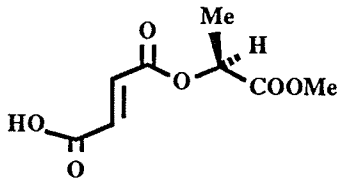
By carefully studying the above D-A reaction transition states which may exhibit hydrogen bonding, it seems possible that only one lactyl group in the fumarate of methyl lactate or lactic acid can form a hydrogen bond with the methoxy group of the *o*-QDM. That means, only one lactyl group takes part in control of the relative and absolute stereoselectivity of the D-A reaction. It could be concluded that one lactyl group in the fumarate is enough to control relative and absolute stereoselectivity of those D-A reactions. This suggests that nonsymmetric fumarates bearing only one chiral lactyl group may react with α-hydroxy-*o*-QDMs to give high relative and absolute stereoselectivity.



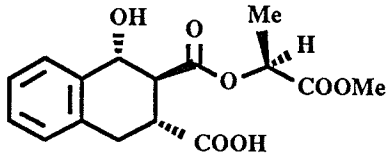


R_2 = any ester, acid or chiral auxiliary

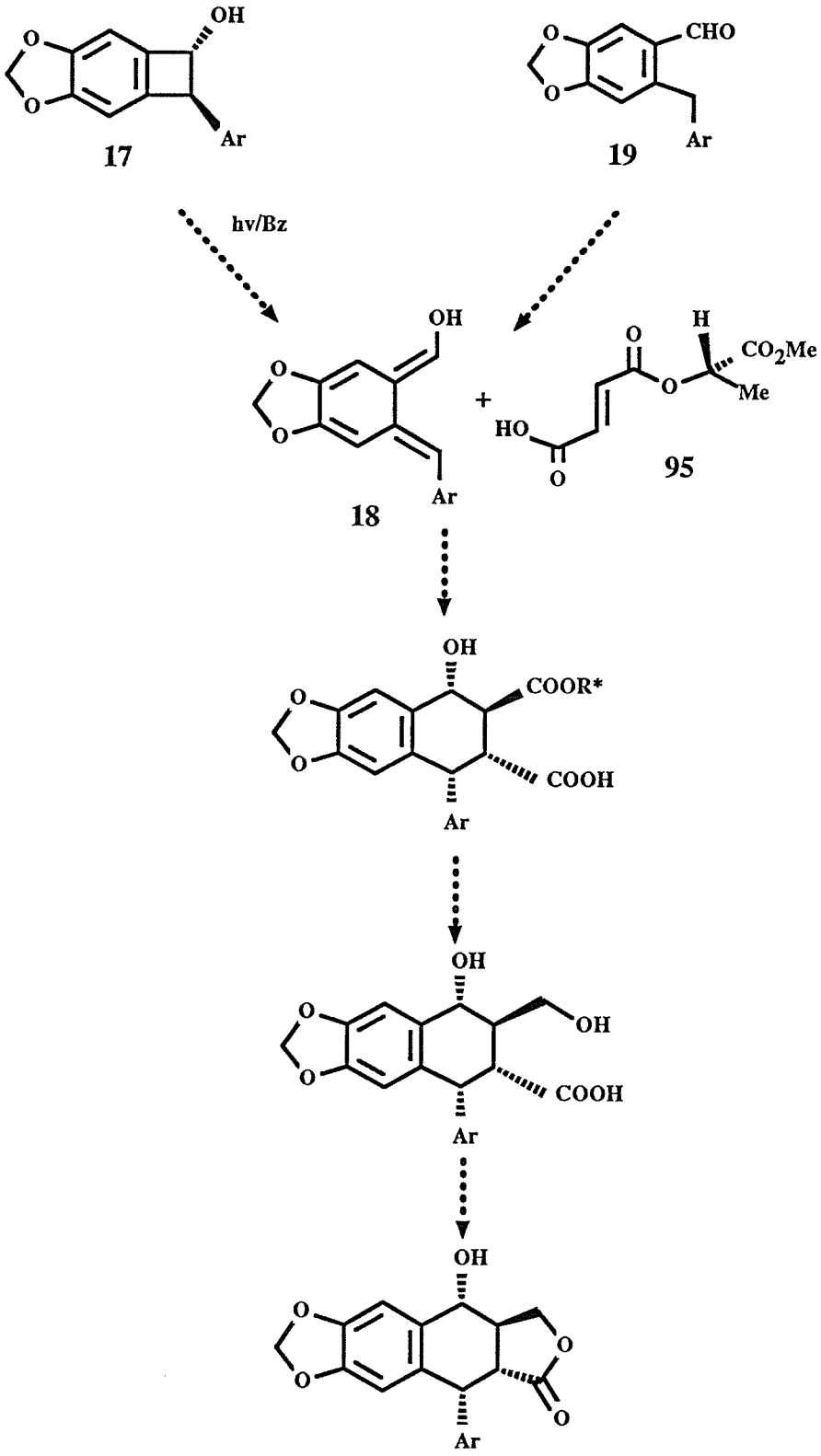
A reaction of an *o*-QDM with a nonsymmetric dienophile, such as a nonsymmetric fumarate, possesses another advantage. A subsequent reaction of a D-A cycloaddition product sometimes requires a differentiation between functional groups. In spite of the usual high diastereoselectivity of D-A reactions involving α-hydroxy-*o*-QDMs and dienophiles with C_2 symmetry, such as the fumarate of methyl lactate or mandelate, it is sometimes difficult to differentiate between nearly identical ester groups in a subsequent reaction. However, the reactions involving nonsymmetric dienophiles, such as mono(methyl (S)-lactyl) fumarate **88**, would lead to cycloadducts in which the carboxylic acid group could be easily distinguished from the ester group. This differentiation would provide an opportunity for selective reaction in a subsequent step. Dienophile **88** will be synthesized and its reactions with α-hydroxy-*o*-QDMs will be studied.



88



If these reactions are successful, a synthesis of podophyllotoxin will be attempted using dienophile **88** as illustrated below.



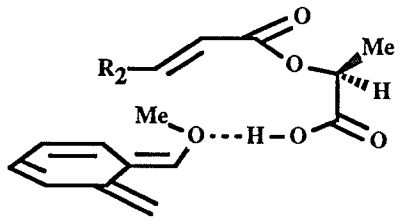
50 Podophyllotoxin

CHAPTER 3

RESULTS AND DISCUSSION

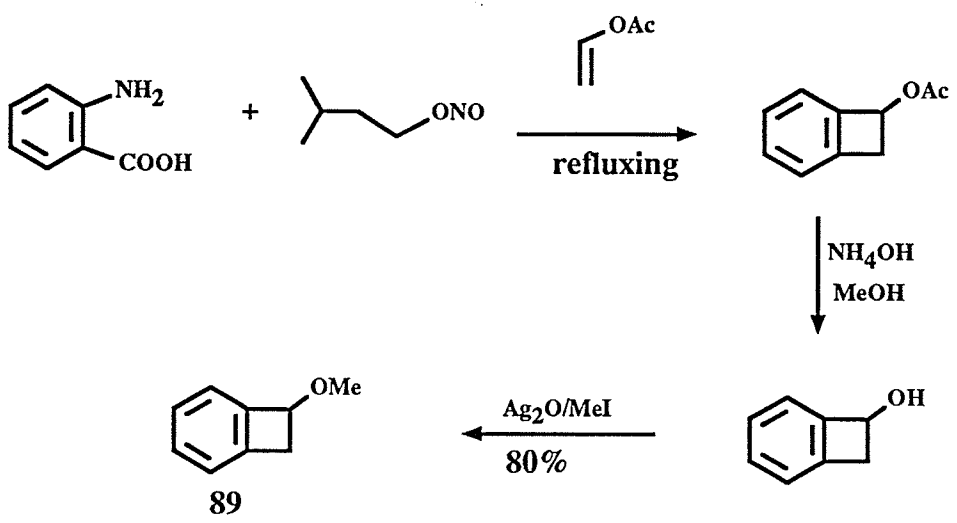
3.1 Preliminary studies of the cycloaddition reactions of dilactyl fumarate and mono lactyl fumarate with α-methoxy-*o*-QDM

In the introduction, hydrogen bonding control of stereoselectivity in Diels-Alder (D-A) reactions was discussed. Maddafford[37] has shown that hydrogen bonding occurs in the Diels-Alder reactions of α-hydroxy-*o*-QDMs with the fumarate of methyl lactate and methyl mandelate. In these reactions, a hydrogen bond forms between the hydroxyl group of the *o*-QDM and the carbonyl group of the lactyl or mandyl group in the dienophile, an interaction that leads to *exo* products. It is also possible that another type of hydrogen bonding might occur in the transition state of the D-A reaction between dilactyl fumarate, having a free carboxyl group in the chiral auxiliary, and α-methoxy-*o*-QDM, also leading to *exo* cycloadduct, as shown below in **B**.



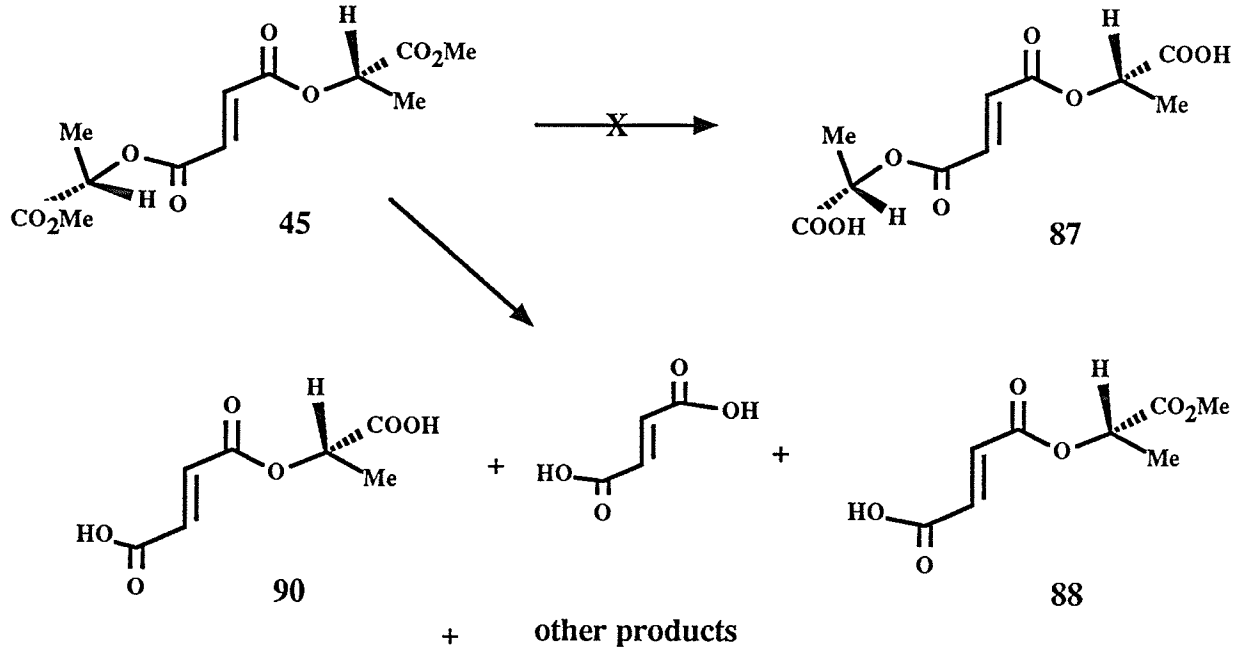
B

To test this idea, the methoxy-*o*-QDM precursor, benzocyclobutanol **89** was prepared from anthranilic acid according to a literature procedure,[41] as shown below.



89

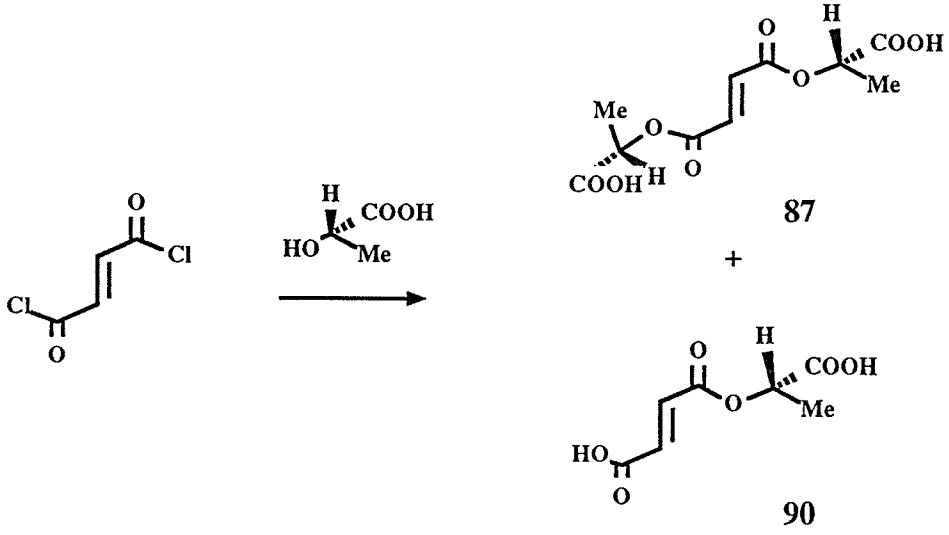
The preparation of (S)-dilactyl fumarate **87** was first attempted via basic hydrolysis of the fumarate of methyl (S)-lactate **45**. **45** in turn was prepared in a 70% yield by heating a 2:1 mixture of methyl (S)-lactate and fumaryl chloride.[27] None of the various hydrolysis conditions tried gave the expected product **87** from **45**, producing instead a mixture of fumaric acid, mono(methyl lactyl) fumarate **88** and monolactyl fumarate **90**.



Hydrolysis of the methyl lactyl group from the fumarate is seemingly easier than the

hydrolysis of the methyl group from the lactyl group.

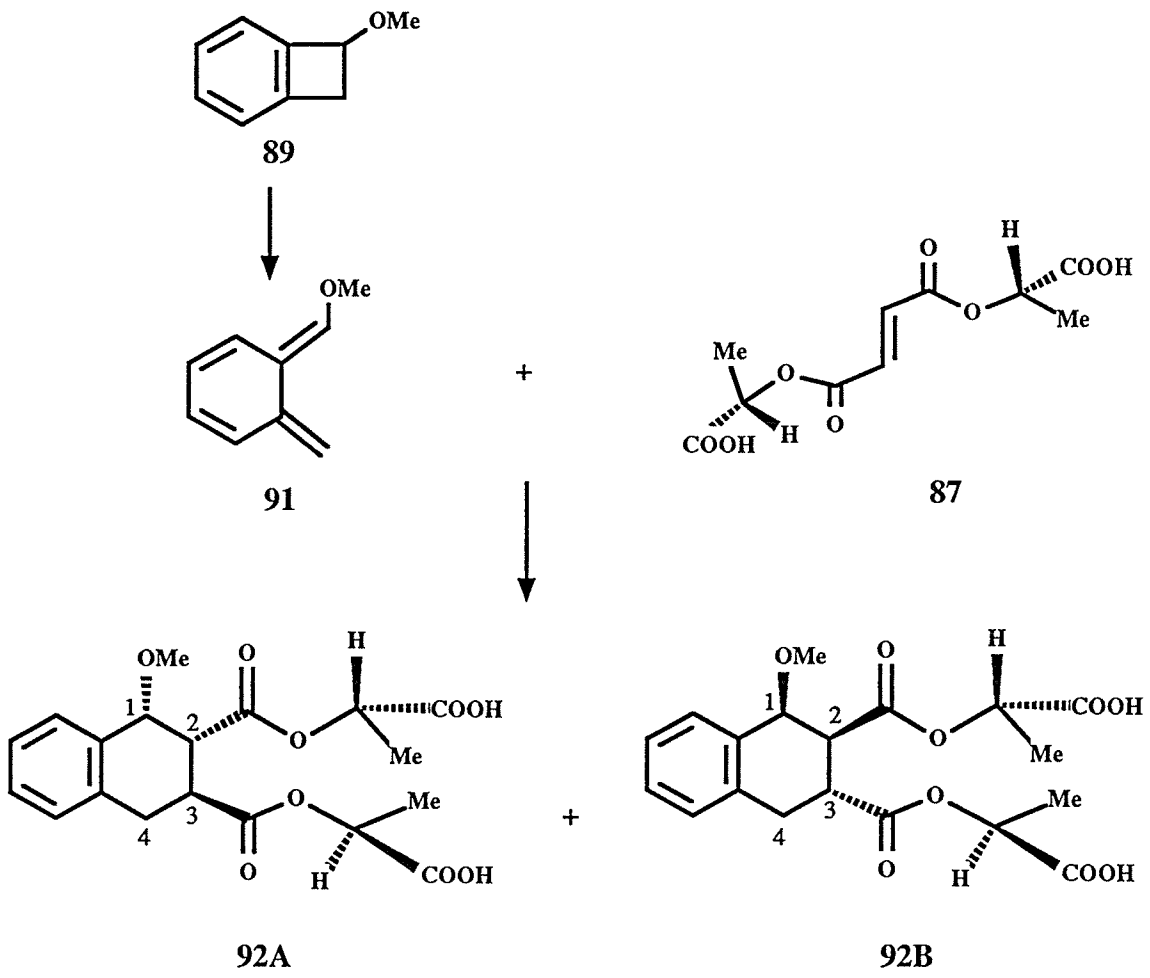
The difficulty in finding suitable hydrolysis conditions for the fumarate of methyl lactate **45** prompted a search for a new method for the preparation of compound **87**. The same method used to prepare the fumarate of methyl (S)-lactate was eventually used to prepare the desired dilactyl fumarate **87**. Fumaryl chloride and (S)-lactic acid (1:2.2) in methylene chloride were slowly warmed to reflux under a gentle flow of nitrogen to remove the generated hydrochloric acid. After neutralizing the mixture with aqueous sodium bicarbonate (5%), the aqueous solution was washed with methylene chloride to remove any impurities. The aqueous solution was acidified with 10% aqueous hydrochloric acid, and then extracted with methylene chloride. Drying and evaporation of the solution afforded a white solid in only 10% yield based on fumaryl chloride. The ^{1}H-nmr spectrum of the solid showed the presence of two products and fractional crystallization from methylene chloride/ether provided these two pure products. These two products were tentatively assigned structures **87** and **90** on the basis of their 300 MHz ^{1}H-nmr spectra.



Before the two products **87** and **90** were fully characterized, their cycloadditon reactions with methoxy-*o*-QDM were attempted. The Diels-Alder cycloaddition reaction of the methoxy-*o*-QDM precursor **89** with the assumed compound **87** was carried out in toluene by

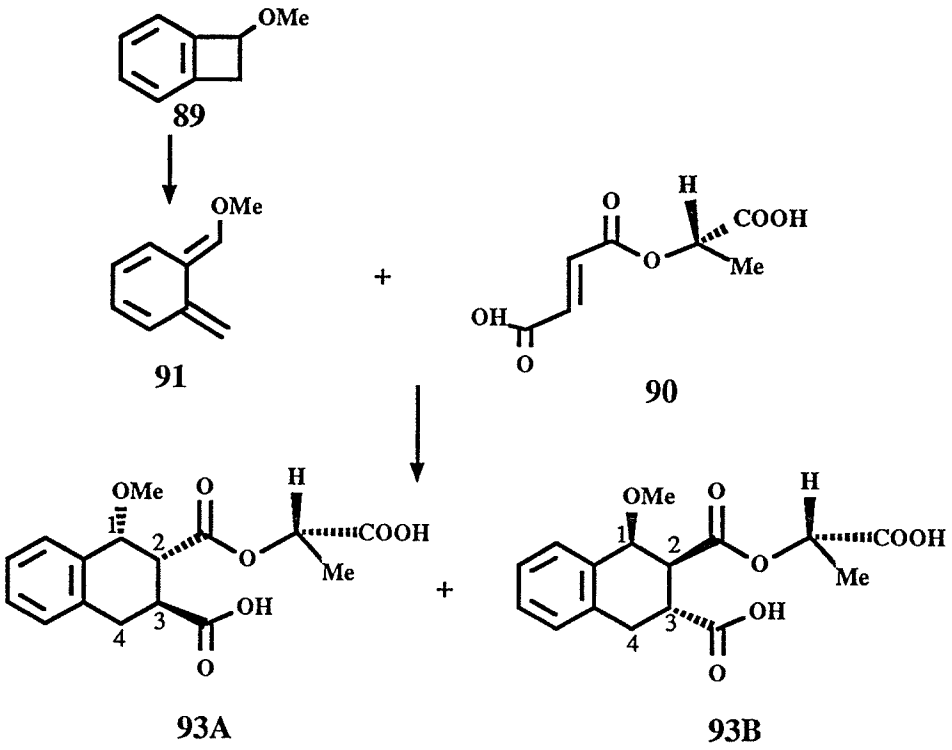
refluxing a mixture of the two compounds. After evaporating the toluene, the ^{1}H-nmr spectrum of the crude reaction mixture showed starting materials and products. The starting materials were removed by chromatography but the products could not be separated. The 300 MHz ^{1}H-nmr spectrum of the products showed two doublets at 4.66_5 and 4.68 ppm with coupling constants J=3.10 Hz and 3.01 Hz respectively in a ratio of 3:2. By inspection of the ^{1}H-nmr spectra of other *o*-QDM/dilactyl fumarate cycloadducts reported in the literature,[13] the doublets at 4.66_5 and 4.68 ppm were tentatively assigned to H-1 of two cycloadducts. The coupling constants of 3.10 and 3.01 Hz suggested a 1,2-*cis* stereochemistry for both cycloadducts, consistent with the two *endo* structures **92A** and **92B**. The lack of evidence for *exo* products suggested that the intermolecular H-bonding control of the stereoselectivity did not occur. Since this preliminary experiment seemed to show very poor diastereoselectivity, complete characterization of the cycloadducts was not carried out.

Scheme 1



Following the same procedure, the other dienophile, assumed to be monolactyl fumarate **90**, was also reacted with methoxy-*o*-QDM precursor **89**. After normal workup, the 300 MHz ^{1}H-nmr spectrum of the chromatographed product also showed the existence of two products. Two doublets at 4.64 and 4.66_5 ppm could be tentatively assigned to H-1 of two cycloadducts, by comparison with similar cycloadducts reported in literature.[13] Coupling constants of 2.9 and 3.1 Hz suggested a 1,2-*cis* stereochemistry for the two products, which indicated two *endo* cycloadducts. The two products in a 5:1 ratio were tentatively assigned structures **93A** and **93B** based on the 300 MHz ^{1}H-nmr spectrum only. There appeared to be only a single regioisomer formed in this D-A reaction.

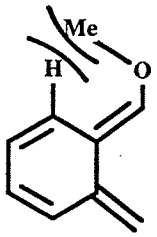
Scheme 2



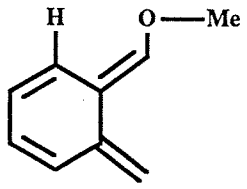
The latter D-A reaction involving the dienophile **90** surprisingly gave higher diastereoselectivity than did the dienophile **87**. As discussed in the introduction, it was expected that the dienophile **87** with C_2 symmetry should give higher diastereoselectivity in a Diels-Alder reaction than the nonsymmetric dienophile **90**.

The above two preliminary experiments yielded similar results in which hydrogen bonding did not appear to be important in the control of stereoselectivity. Therefore, further exploration of these reactions and full characterization of all the compounds were not carried out.

While an explanation for the preferred *endo* transition states in these D-A reactions is not obvious, the conformation of the methoxy *o*-QDM **91** provides a possible explanation. Conformation **91B** seems to be more favorable than **91A** owing to steric repulsion between the methyl group and the aromatic hydrogen in **91A** (as shown below), and **91B** would hinder the expected formation of a hydrogen bond with the carboxylic acid group of the dienophile.



91A



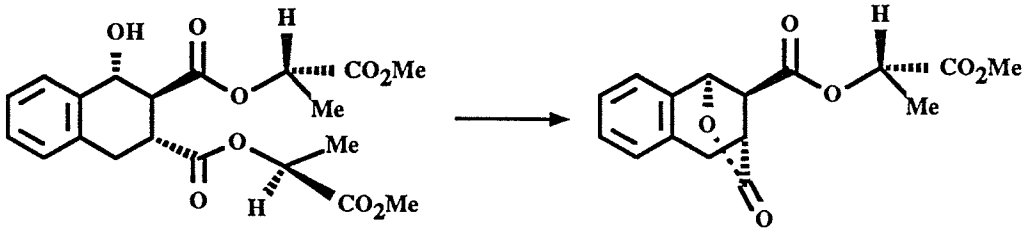
91B

Since these preliminary results were largely negative, showing very low stereoselectivity, a decision was made to abandon this study. However, the high regioselectivity observed in reactions of the dienophile **90** suggested that further studies of mono esters of fumaric acid might be warranted.

3.2 Synthesis and Reactions of Mono(methyl (S)-Lactyl) Fumarate 88

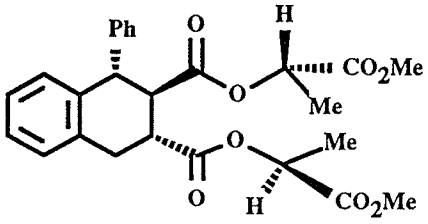
3.2.1 Synthesis and Reactions of Mono(methyl (S)-Lactyl) Fumarate 88 with Simple *o*-QDMs

Using nonsymmetric dienophiles in D-A reactions can provide functional differentiation in products which may be useful in subsequent chemoselective reactions. While the chemoselective differentiation of structurally identical groups may be attained by some specific reactions, a slight change in structure of the reactants may make these specific reactions impossible. For example, cycloadduct **47** could be converted to lactone **94** by treatment with t-butyllithium. In the subsequent reactions, the ester group in **94** could be chemically distinguished from the lactone.



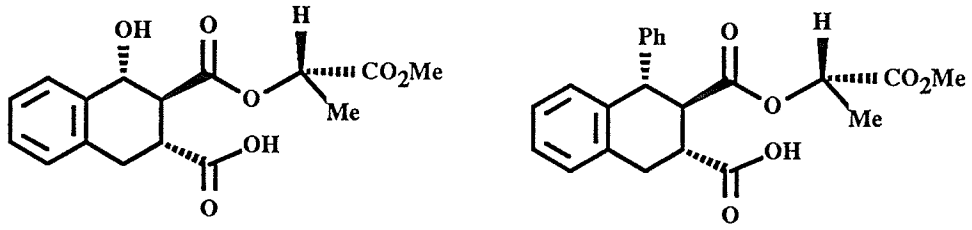
47 94

However, in compounds without a hydroxyl group, such as compound **95**, it is difficult to differentiate between the two ester groups.



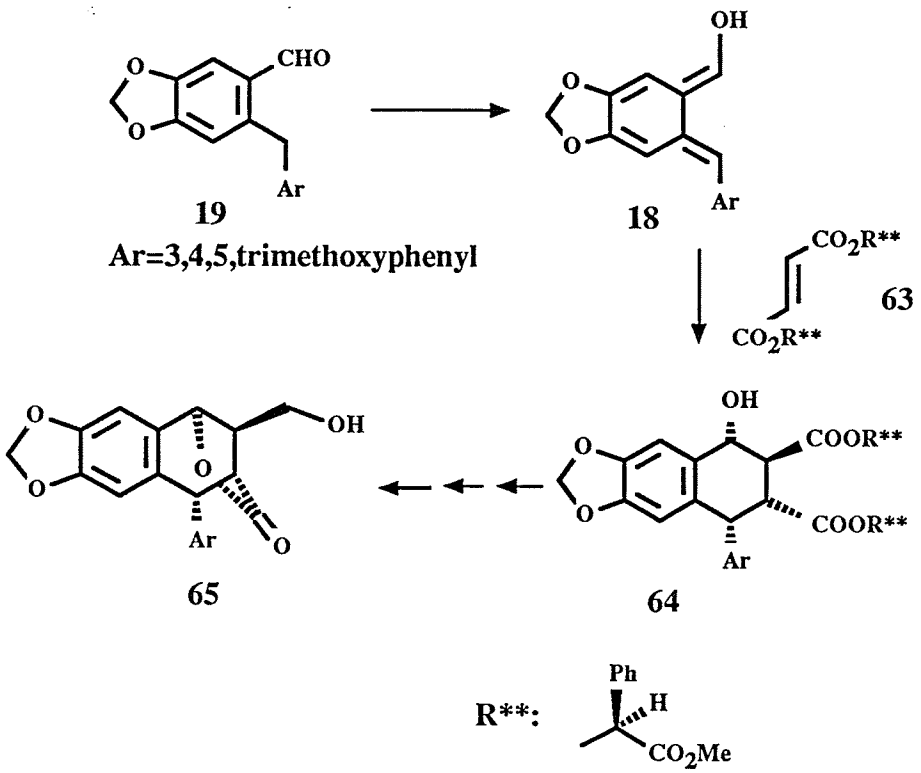
95

If a nonsymmetric dienophile, such as mono(methyl (S)-lactyl) fumarate **88**, is used in a D-A reaction, the resulting cycloadducts **96** or **97** bear functional groups that are easily differentiated in subsequent chemoselective reactions.



96 **97**

The nonsymmetric dienophile mono(methyl (S)-lactyl) fumarate **88**, may provide an opportunity to improve the asymmetric synthesis of podophyllotoxin by eliminating three steps in a previously published preparation.[17] Charlton and Koh reacted the *o*-QDM **18** with the fumarate of methyl (S)-mandelate **63** to yield the cycloadduct **64**. **64** was converted to a lactone which was selectively reduced to give (-)-neopodophyllotoxin **65**.[17]

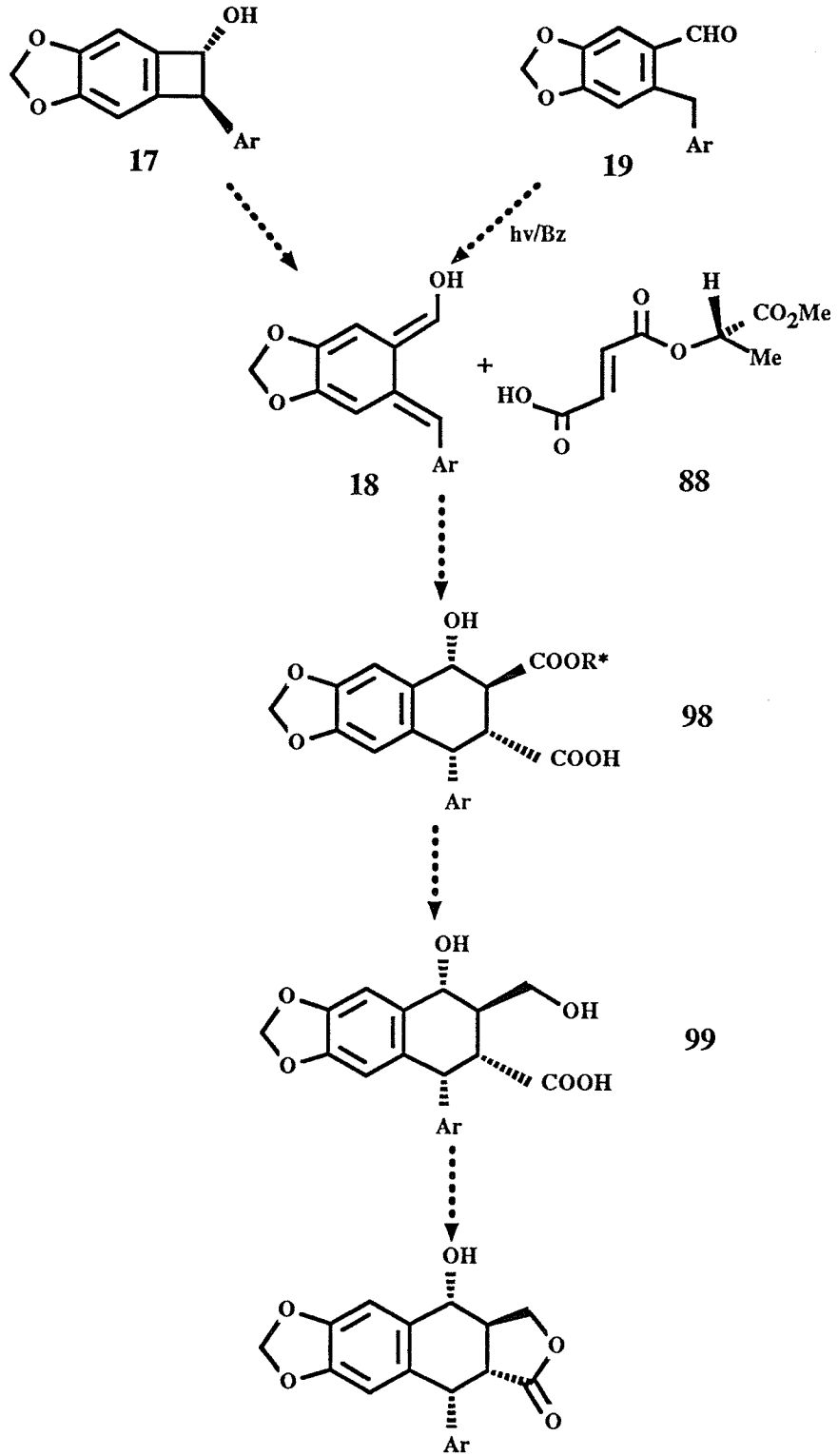


R**:

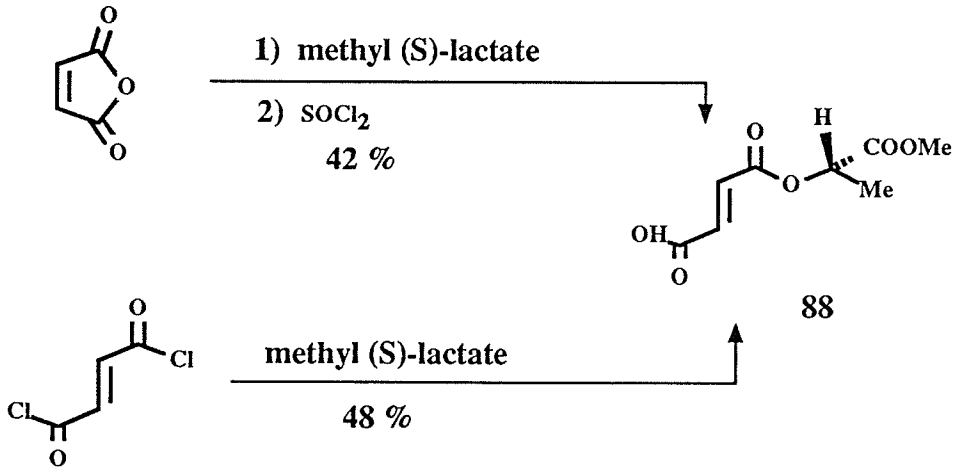
If a nonsymmetric dienophile, such as mono(methyl (S)-lactyl) fumarate **88**, was used to replace the fumarate of methyl (S)-mandelate **63**, the cycloadduct could be selectively converted to the alcohol **99** and then directly converted to podophyllotoxin **50** as shown below.

Proposal:

Scheme 3

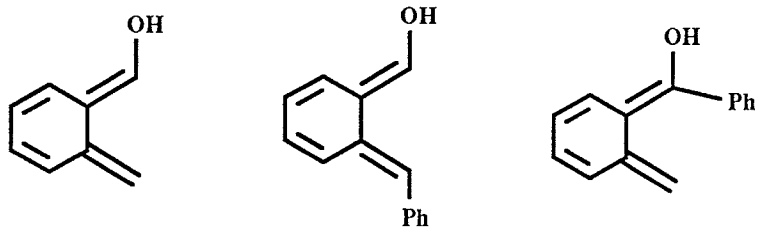

OH
O
O
Ar
17
CHO
19
hv/Bz
18
88
CO2Me
Me
HO
COOR*
COOH
98
99
50 Podophyllotoxin

The nonsymmetric dienophile mono(methyl (S)-lactyl) fumarate **88** was prepared by two methods. Using a modified literature procedure,[42] methyl (S)-lactate was mixed with maleic anhydride (1:1) to give the mono(methyl (S)-lactyl) maleate intermediate. Without purification, this intermediate was isomerized in the presence of a catalytic amount of thionyl chloride to give the product mono(methyl (S)-lactyl) fumarate **88** in a yield of 42%.



The mono(methyl (S)-lactyl) fumarate **88** was also prepared in a yield of 48% by heating a 1:1 mixture of methyl (S)-lactate and fumaryl chloride. The vinyl protons in the ^{1}H-nmr spectrum of **88** appeared as two doublets at 6.90 and 7.08 ppm with coupling constant of 15.6 Hz.

Since the synthesis of the precursor for *o*-QDM **18** is rather difficult, model studies of the reactions of dienophile **88** with the simpler α-hydroxy-*o*-QDM **10**, α-hydroxy-α′-phenyl-*o*-QDM **102** and α-hydroxy-α-phenyl-*o*-QDM **105** were undertaken.



10 **104** **105**

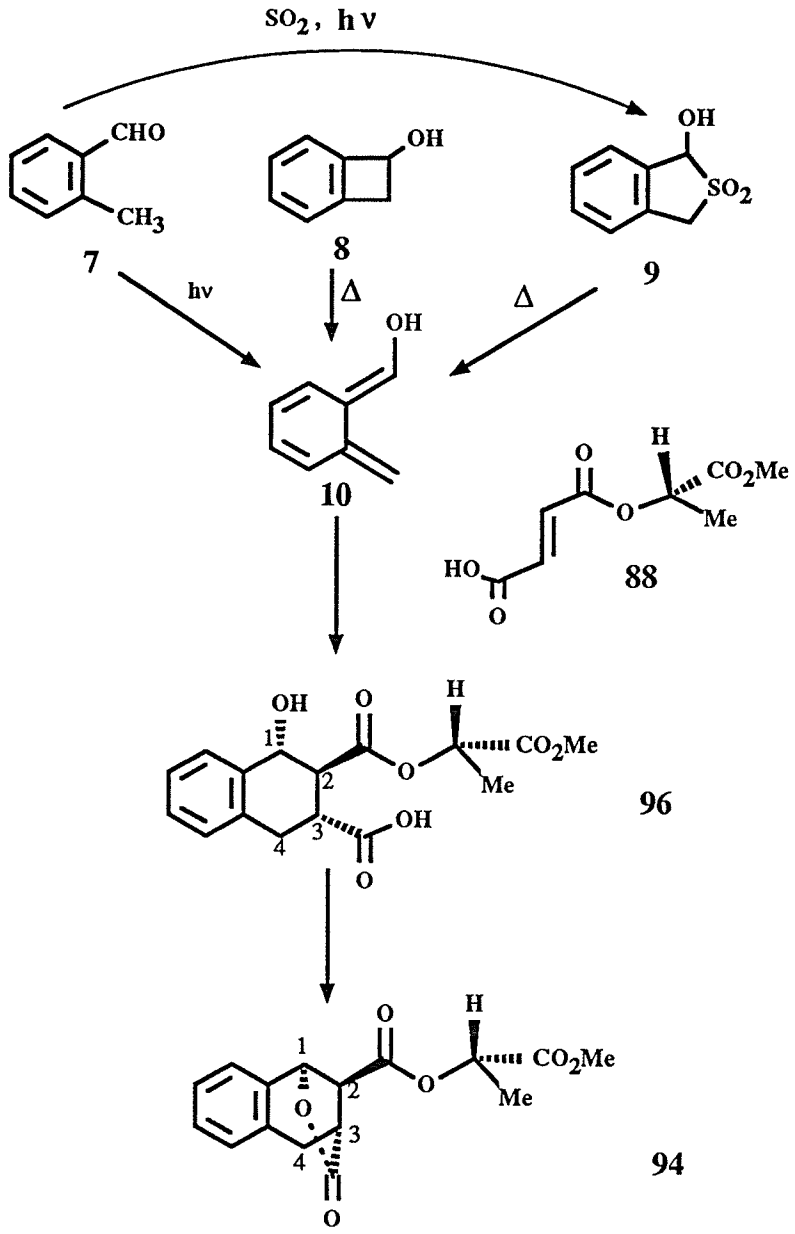
The α-hydroxy-*o*-QDM **10** was generated by photolysis of *o*-methylbenzaldehyde **7**, thermolysis of benzocyclobutanol **8** and thermolysis of sulfone **9**.

The *o*-methylbenzaldehyde **7** with **88** (1:1.14 equivalent) in benzene was flushed with nitrogen and then irradiated for 6 hours using a 450 watt Hanovia medium pressure mercury lamp (Pyrex filter). After evaporation to dryness, the ^{1}H-nmr spectrum of the crude product showed complete consumption of **7** and also showed a new doublet at 4.96 ppm. The product was purified by crystallization from ethyl acetate/hexane (3:1) and tentatively assigned structure **96**, based on a comparison of its ^{1}H-nmr spectrum with that of the cycloadduct **47**, obtained from the reaction of the fumarate of methyl (S)-lactate **45**, with **10**.[13]

Cycloadduct **96** was also produced by the addition of benzocyclobutanol **8** (2.7 equivalent), in methylene chloride, to a refluxing solution of dienophile **88** in toluene (1 equivalent) over 20 minutes. After the reaction was complete, the toluene was evaporated to leave an oil.

Following the procedure used with benzocyclobutanol **8**, the reaction of the sulfone **9** with **88** (1:2.1 equivalent) was carried out in refluxing toluene. The ^{1}H-nmr spectra of the crude products from **8** and **9** showed two doublets at 4.96 (J=9.5 Hz) and 5.48 (J=5.1 Hz)ppm in a 5:1 and 10:1 ratio respectively. No *o*-methylbenzaldehyde (from decomposition of benzocyclobutanol or sulfone) was observed in the product mixture from either reaction. Fractional crystallization afforded two pure products **A** and **B**. The ^{1}H-nmr spectrum of **A**, with a doublet at 4.96 ppm, was identical to that of adduct **96** described above. It was further characterized by IR, ^{13}C-nmr, MS and elemental analysis. The product **B**, with a doublet at 5.48 ppm was assigned structure **94**. The ^{1}H-nmr spectrum, melting point and optical rotation of the lactone **94** were identical to data previously reported for this compound.[43]

Scheme 4

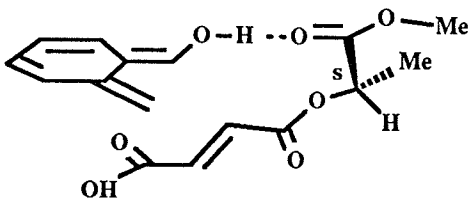


Cycloadduct **96** was obtained in a similar yield from all three *o*-QDM precursors **7**, **8** and **9** by crystallization of the product from the crude reaction mixtures. Thus it was obtained in 41% yield from **7**, 32% from **8** and 42% from **9**. The lactone **94** was also separated by fractional crystallization in 7% and 5% yields respectively from the reactions using the thermal precursors **8** and **9**. No lactone was observed in the photochemical reaction of aldehyde **7** with **88**. It appears that lactone **94** was produced by the elimination of water from

cycloadduct **96** at the higher temperature used in the thermal reactions. It was observed that the cycloadduct **96** was spontaneously converted to lactone **94** on standing in methylene chloride solution for three days.

Based on the facile conversion to lactone **94**, whose relative and absolute stereochemistry has been previously determined by X-ray crystallography, cycloadduct **96** was assigned the stereochemistry 1-R, 2-S, 3-R as shown. This assignment was further supported by the *trans* diaxial coupling constant of 9.5 Hz observed for $J_{1,2}$.

The high relative and absolute stereoselectivity, and high regioselectivity of this cycloaddition reaction can be rationalized by a mechanism involving intramolecular hydrogen bonding similar to that previously proposed by Maddaford for comparable reactions.[37] Hydrogen bonding from the hydroxyl group in the *o*-QDM to the carbonyl in the chiral auxiliary favors the *exo* transition state and controls facial selectivity in the reaction. It also ensures the high regioselectivity since the lactyl ester group will be adjacent to the hydroxyl in the final product.

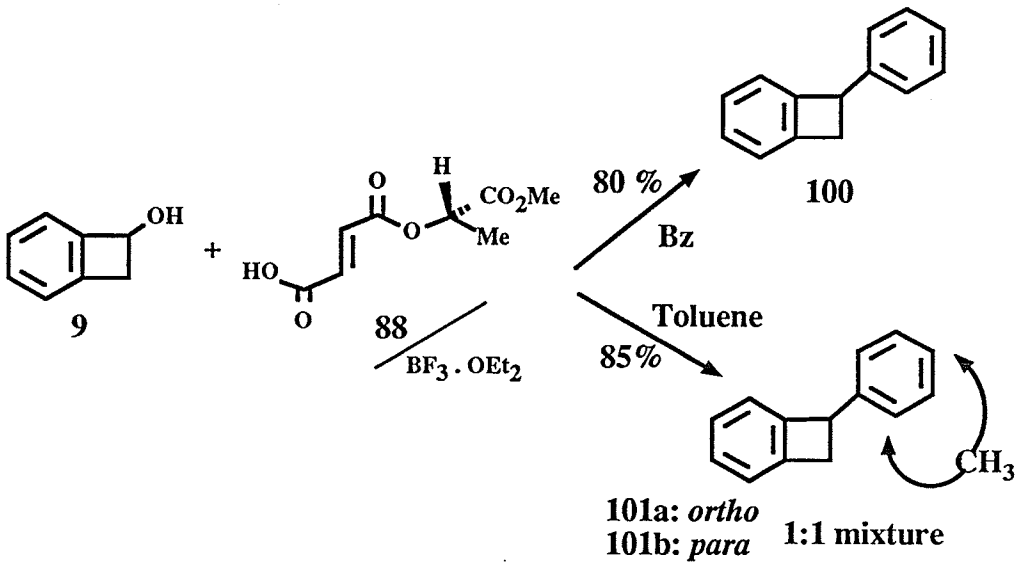


While the reaction of dienophile **88** with *o*-QDM **10** gave exclusively *exo* cycloadduct **96**, there are situations in which it would be more desirable to obtain the *endo* cycloadduct. It is well known that Lewis acids can affect the stereoselectivity of Diels-Alder reactions by complexing either the dienophile or diene. A study of the effect of a Lewis acid on the stereoselectivity of the Diels-Alder reaction of α-hydroxy-*o*-QDM **10** with mono(methyl (S)-lactyl) fumarate **88** was undertaken.

In a preliminary experiment, the benzocyclobutanol **8** (1 equivalent) was added to a refluxing solution of mono(methyl (S)-lactyl) fumarate **88** with boron triflouride etherate

(1:2) in benzene. After refluxing a further two hours the solution was evaporated, dissolved in ethyl acetate and extracted with dilute aqueous bicarbonate solution. Drying and evaporation of the organic phase followed by chromatography gave two fractions. The first fraction was mono(methyl (S)-lactyl) fumarate **88** which was recovered in 90% yield. The second fraction was assigned the structure **100** on the basis of its ^{1}H-nmr and Mass spectra, the ^{1}H-nmr spectrum being identical to that previously reported in the literature.[44] The same procedure, performed in toluene instead of benzene, gave a mixture of two products which were assigned as **101a** and **101b** based on the ^{1}H-nmr and mass spectra only. Both reactions gave a good yield.

Scheme 5



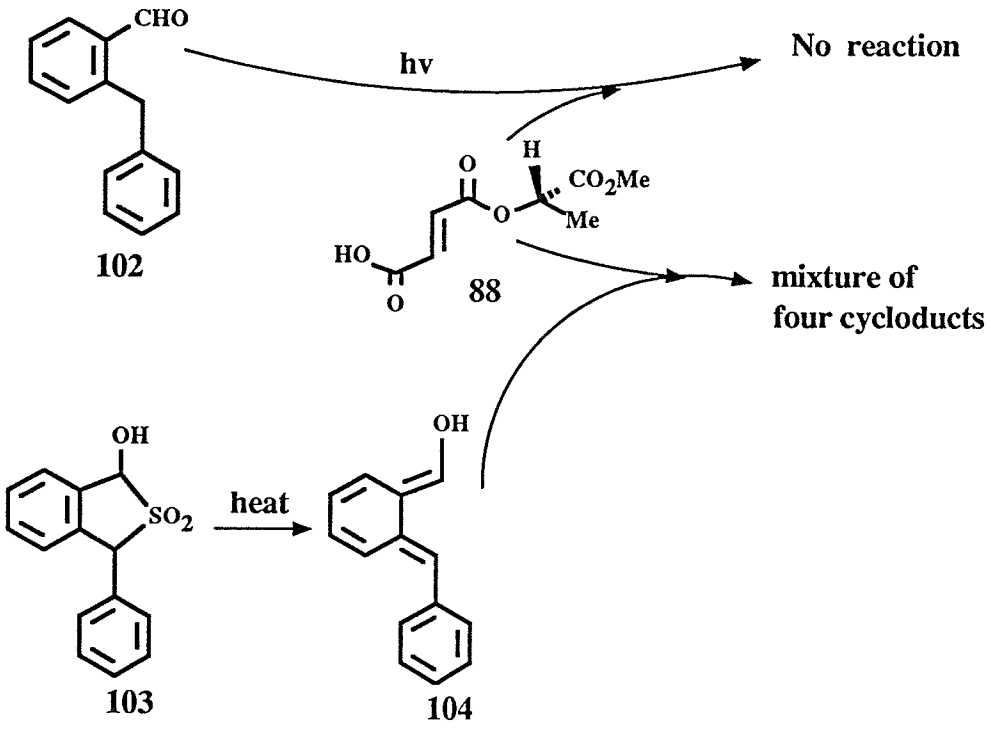
The formation of **100** and **101** can be rationalized on the basis of a mechanism involving a boron trifluoride catalyzed conversion of the benzocyclobutanol to a benzylic cation that subsequently undergoes a Friedel-Crafts reaction with the benzene or toluene solvent.

Only a few papers in the literature have reported the preparation of the phenyl benzocyclobutene **100**, the most successful method being the hydrogenolysis of 1-phenylbenzocyclobutanol.[44] The procedure reported in this thesis is better in both yield and ease of preparation of starting material.

The success of the Diels-Alder cycloaddition reaction of mono(methyl (S)-lactyl) fumarate **88** with α-hydroxy-*o*-QDM **10** encouraged further exploration of this new dienophile's use. According to the literature,[21] α-hydroxy-α′-phenyl-*o*-QDM **104**, generated from photolysis of *o*-benzylbenzaldehyde **102**, reacts with the fumarate of methyl (S)-lactate to give a cycloadduct with a high diastereoselectivity, but in very poor yield. Using a similar procedure, *o*-benzylbenzaldehyde **102** with excess mono(methyl (S)-lactyl) fumarate **88** was irradiated for 6 hours with a 450 watt Hanovia medium pressure mercury lamp using a Pyrex filter. After evaporating the solvent, no cycloadduct was observed in the 300 MHz ^{1}H-nmr spectrum of the crude product. The only product isolated by chromatography on silica gel was tentatively identified as mono(methyl (S)-lactyl) maleate, on the basis of its 300 MHz ^{1}H-nmr spectrum only. It appears that the mono(methyl (S)-lactyl) fumarate **88** quenches the excited state of the *o*-benzylbenzaldehyde generating the isomeric maleate and stops the conversion of the excited state aldehyde to the *o*-QDM. Due to this quenching problem another method for the generation of α-hydroxy-α′-phenyl-*o*-QDM (**104**) was sought. It had been previously reported that **104** can be generated from the thermolysis of **103**, a sulfone that can be prepared by trapping of the photochemically generated *o*-QDM by sulfur dioxide[43]. *o*-Benzylbenzaldehyde was dissolved in benzene containing 10% sulfur dioxide, flushed with nitrogen, and irradiated for 20 hours at room temperature with a 450 watt Hanovia medium pressure mercury lamp (Pyrex filter). Evaporation of the benzene gave an oil which was triturated with carbon tetrachloride to afford the pure crystalline sulfone **103** with 1,4-*cis* stereochemistry. **103** was found to be unstable above 0°C giving a mixture of *cis* and *trans* **103** (1:1) after standing two days at room temperature. Sulfone **103** in methylene chloride was added to a refluxing solution of mono(methyl (S)-lactyl) fumarate **88** (1 equivalent) in toluene over 1 hour. After thin layer chromatography indicated that the reaction was complete, the solvent was evaporated. The ^{1}H-nmr spectrum of the crude yellow oil showed four new doublets in an approximate ratio of 1:1: 0.1: 0.3. By comparing the chemical shifts of the four doublets at 4.46 (J=5.5), 4.95 (J=9.6), 5.09 (J=4.0) and 5.41

(J=3.0) ppm to those of known cycloadducts, it was concluded that each doublet represented a different stereoisomeric cycloadduct. The coupling constants suggested a mixture of 1,2-*cis* and 1,2-*trans* stereochemistry, that is, a mixture of *endo* and *exo* cycloadducts. The reason why this cycloaddition reaction yielded a mixture is not clear. No attempt was made to study this complicated reaction mixture further.

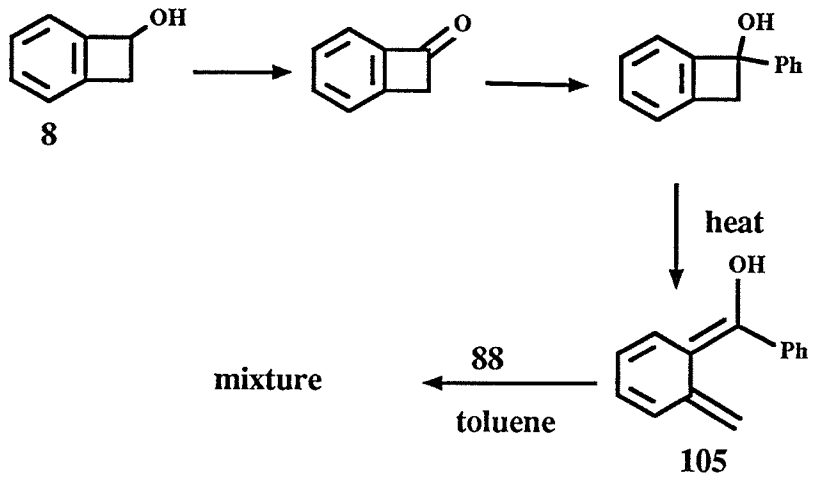
Scheme 6



During the completion of the above research, co-worker Kevin Koh was investigating the Diels-Alder cycloaddition reactions of α-phenyl-α-hydroxy-*o*-QDM **105** generated from thermal ring opening of 1-phenylbenzocyclobutanol[45]. He reacted the α-phenyl-α-hydroxy *o*-QDM **105** with the fumarate of methyl (S)-mandelate **63** and obtained a cycloadduct with very high diastereoselectivity.[45] That preliminary result prompted the use of the dienophile **88** in a similar Diels-Alder cycloaddition reaction. The reaction of mono(methyl (S)-lactyl) fumarate **88** with α-phenyl-α-hydroxy-*o*-QDM **105** generated from 1-phenylbenzocyclobutanol in refluxing toluene gave a complicated mixture of at least four cycloadducts in a ratio of 1:1.5:1:2, as measured from the ^{1}H-nmr spectrum of the crude

product. No attempt was made to separate this mixture of adducts.

Scheme 7

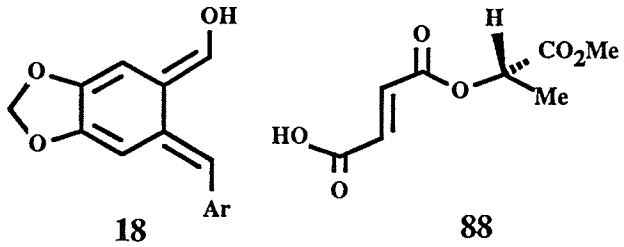


It was concluded that the reaction of the mono(methyl (S)-lactyl) fumarate **88** with simple α-hydroxy-*o*-QDM **10** gave exclusively *exo* cycloadduct, but with α-hydroxy-α'-phenyl-*o*-QDM **104** and α-hydroxy-α-phenyl-*o*-QDM **105** it gave complicated product mixtures. The lack of stereoselective reactions with **104** and **105** might be due to a change in orbital coefficients which affects secondary orbital interactions. Steric interactions with the α′-phenyl group of **104** or the α-phenyl group of **105** may also affect the stereoselectivity. However, no further study was attempted to explore these effects.

3.2.2 Use of Mono(Methyl (S)-Lactyl) Fumarate 88 in an Approach to the Asymmetric Synthesis of Podophyllotoxin 50

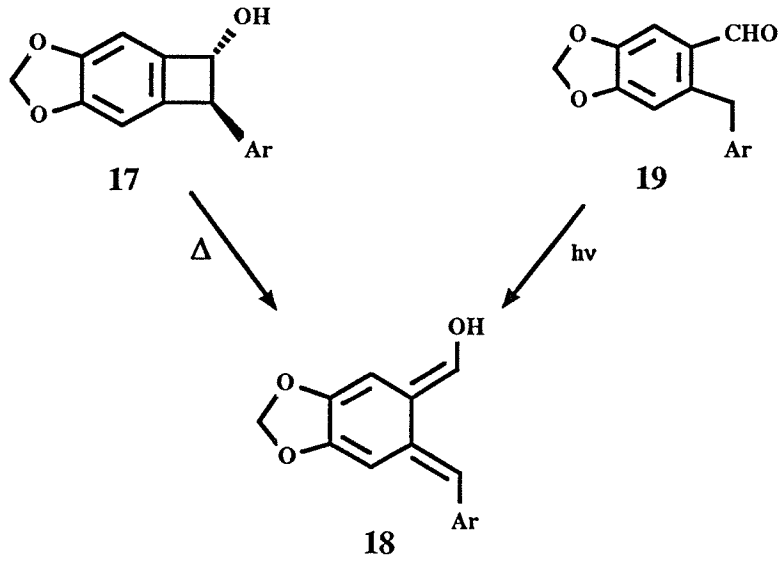
The Diels-Alder cycloaddition reaction of the mono(methyl (S)-lactyl) fumarate **88** with the α-hydroxy-*o*-QDM **10** gave the *exo* cycloadduct **96** with high absolute stereoselectivity. The cycloadduct **96** possesses the same relative and absolute stereochemistry as (-)-podophyllotoxin. As mentioned previously using *o*-QDM **18** in place of **10** would generate a cycloadduct which could be easily converted to (-)-podophyllotoxin. Despite the discouraging results with the α-hydroxy-α′-phenyl-*o*-QDM **102**, an *o*-QDM similar to **18**, a

decision was made to prepare precursors to *o*-QDM **18** and test their reactions with dienophile **88.**



18 **88**

The *o*-QDM **18** has been successfully generated photochemically from the podoaldehyde **19** and thermally from the substituted benzocyclobutanol **17.**



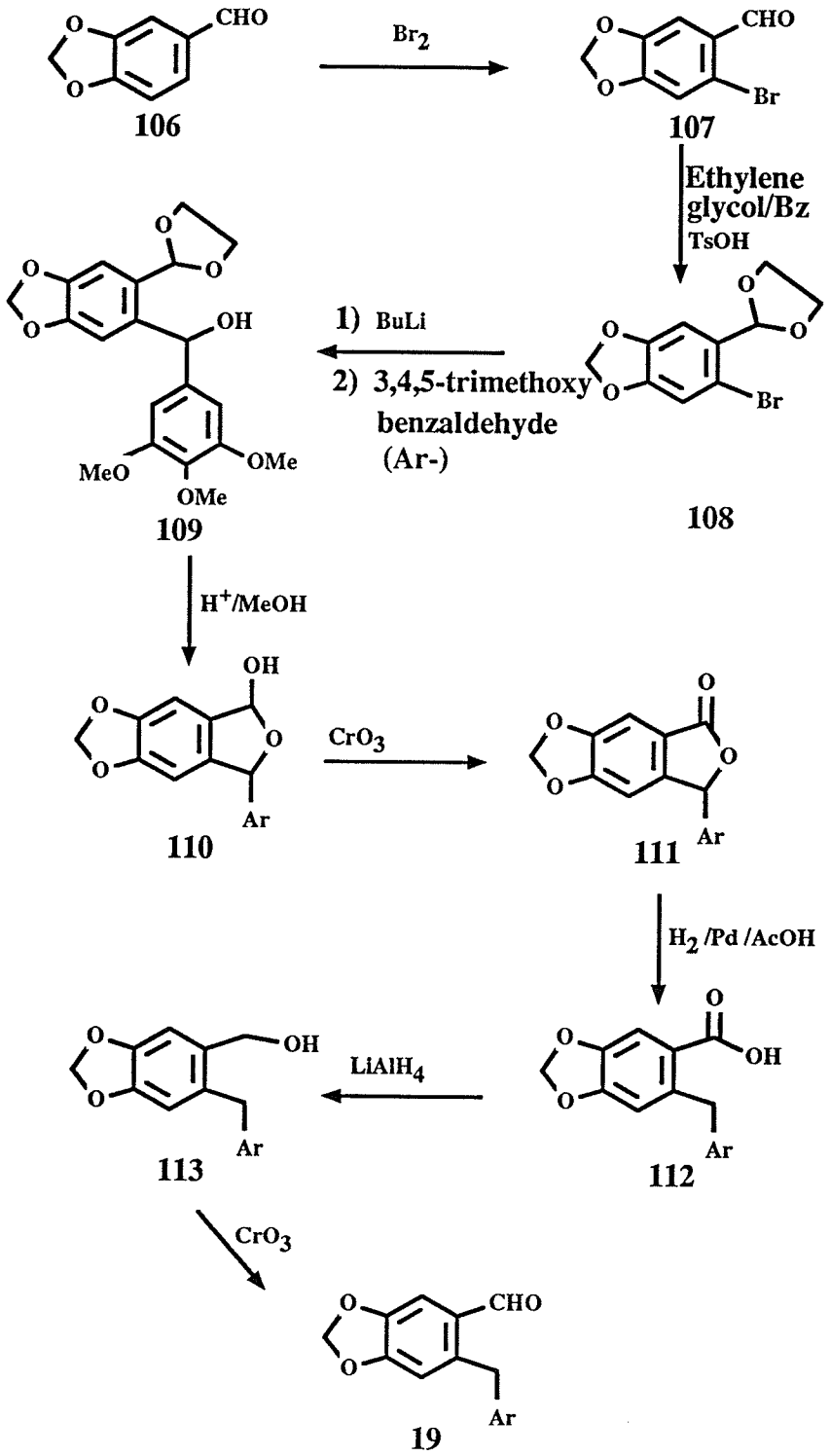
17 **19** **18**

Charlton and Koh[34] successfully reacted the *o*-QDM **18,** which was generated from photolysis of aldehyde **19,** with the fumarate of methyl (S)-mandelate to give a cycloadduct in reasonable yield. In view of this success and since it is easier to prepare the podoaldehyde **19** than the benzocyclobutanol **17**, the synthesis of podoaldehyde **19** and its photoreaction with **88** was attempted first.

3.2.2.1 Synthesis of 3,4-Methylenedioxy-6-(3,4,5-trimethoxyphenyl)benzaldehyde (Podoaldehyde) 19 and Attempted Photochemical Reaction with 88

The aldehyde **19** was prepared from piperonal using a literature procedure in an overall yield of 20%[34], as shown below. The bromopiperonal **107** was prepared in 75% yield by bromination of piperonal **106** in acetic acid. Aldehyde **107**, ethylene glycol (1:2) and a catalytic amount of p-toluenesulfonic acid (TsOH) were refluxed in a benzene solution for 2 hours. Evaporation of the benzene and chromatography using a short silica gel column afforded pure acetal **108**. Acetal **108** (1 equivalent) in THF was transmetalated with n-butyllithium (1 equivalent) at -78°C, and then 3,4,5-trimethoxybenzaldehyde (1 equivalent) added to the solution. After stirring 40 minutes at -78°C the reaction was quenched with aqueous ammonium chloride. Normal workup yielded product **109**. Acetal **109** was hydrolysed using Dowex 50W-X4 in methanol/water, and isolated by removal of the resin, evaporation and extraction with ethyl acetate. The resulting crude cyclic hemiacetal **110**, was oxidized to lactone **111** using a two phase mixture of ether and 5% chromic anhydride in 10% sulfuric acid. The crude oxidation product, isolated from the organic phase, was chromatographed on silica gel to provide pure **111**. Hydrogenolysis of lactone **111** in acetic acid using Pd/C catalyst yielded **112**. Reduction of **112** with lithium aluminum hydride gave alcohol **113** which was subsequently oxidized with a two phase solution of 5% chromic anhydride in 10% sulfuric acid and ether/methylene chloride to give aldehyde **19**. All physical data and spectra of **19** are identical to that reported in the literature[17].

Scheme 8

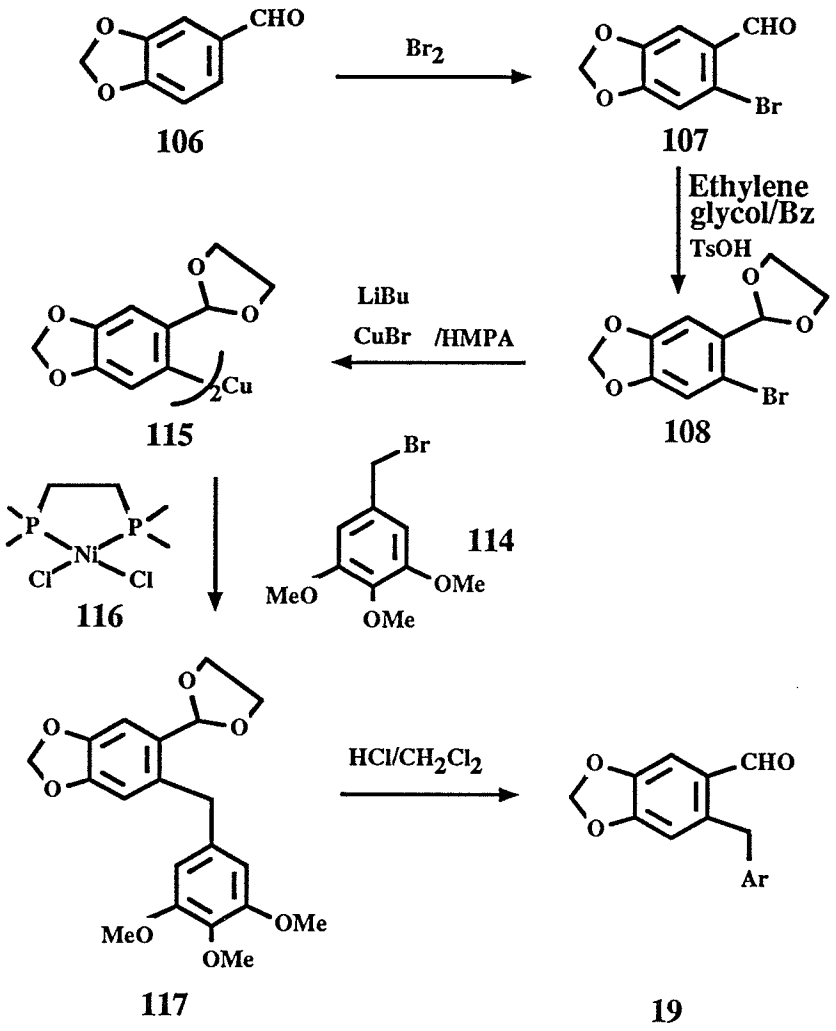


Although the reactions of above procedure were simple, the synthesis involved eight steps. Durst *et al*[46] reported a shorter synthesis of the aldehyde **19** in which a crucial step was the coupling of 3,4,5-trimethoxybenzyl bromide with the aryl anion prepared by transmetalation

of **108**. This coupling reaction required the preparation of the tri-n-butylphosphine/cuprous iodide complexed aryl anion and Charlton *et al* later reported that the yields for the coupling were quite variable.[25]

After a review of the literature, an improvement in the synthesis was attempted. Starting from piperonal **106**, the acetal **108** was prepared following the same procedure as described above. 3,4,5-Trimethoxybenzyl bromide **114** was prepared according to the literature procedure by reduction of trimethoxybenzaldehyde with lithium aluminum hydride and treatment of the corresponding alcohol with phosphorus tribromide. The ^{1}H-nmr spectrum of **114** was consistent with that reported in literature.[47] The compound **114** was unstable so that it was prepared when needed or stored at low temperature. Instead of using tri-n-butylphosphine/cuprous iodide, the organocupper compound **115** was prepared by treating the lithium carbanion, prepared from **108** and n-butyllithium (1:1 equivalent), with cuprous bromide dissolved in hexamethylphosphoramide (HMPA). 3,4,5-Trimethoxybenzyl bromide **114** (1 equivalent) was added to a solution of **115**, followed by addition of a catalytic amount of [1,2-bis(diphenylphosphino)ethane]nickel (II) chloride complex **116**. The resulting mixture was stirred for 12 hours and then worked up by quenching with aqueous ammonium chloride and extraction with ethyl acetate. The crude product was hydrolysed using 10% hydrochloric acid in methylene chloride (1:4 volume) to yield aldehyde **19** in 15% yield.

Scheme 9

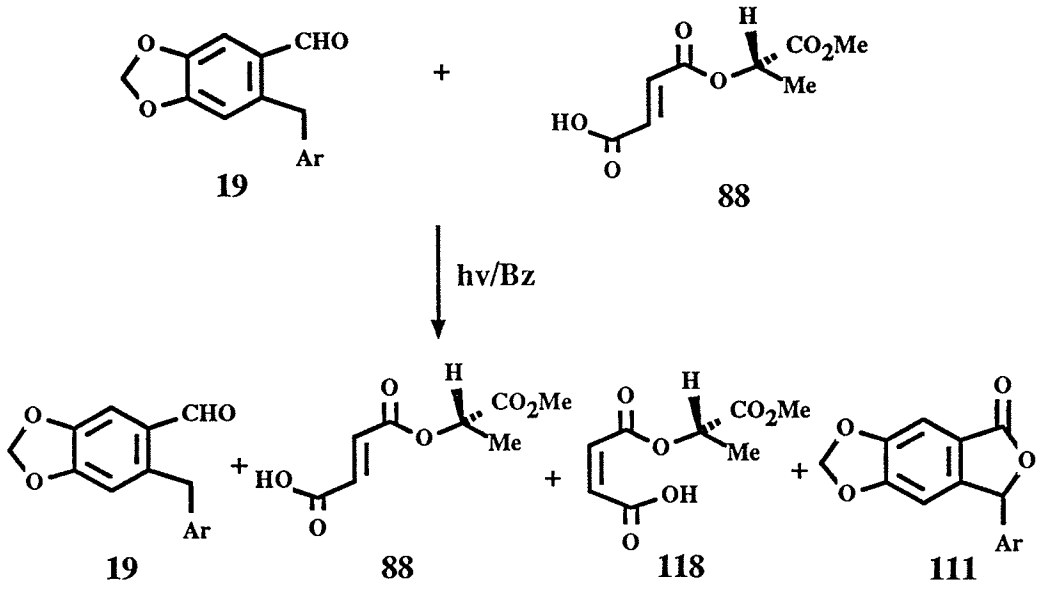


The above procedure involves only five steps for the synthesis of aldehyde **19**, but the yield in the coupling step was very low (15%). The yield might be improved by changing the catalyst and solvent. However, no attempt was made to improve this procedure since another short synthesis was accomplished by co-workers.[46]

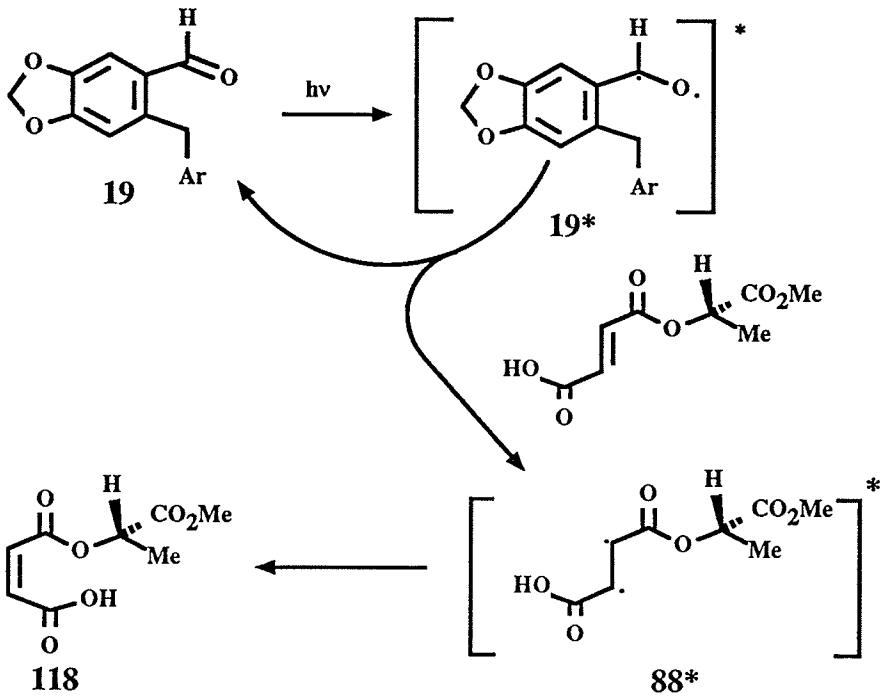
Following the literature procedure, the photoconversion of aldehyde **19** to the *o*-QDM **18** and subsequent reaction with **88** was attempted in benzene at room temperature. The aldehyde **19** in benzene was deoxygenated with nitrogen and irradiated at room temperature while mono(methyl (S)-lactyl) fumarate **88** (5 equivalents) was slowly added over 4 hours. After six hours, the benzene was evaporated to give an oil. The ^{1}H-nmr spectrum of the crude oil showed it to be a mixture of four compounds. Chromatography (40% ethyl

acetate/hexane) gave four pure compounds, two of which were the starting materials, aldehyde **19** and mono(methyl (S)-lactyl) fumarate **88.** The other two compounds were identified as mono(methyl (S)-lactyl) maleate **118** and lactone **111.**

Scheme 10



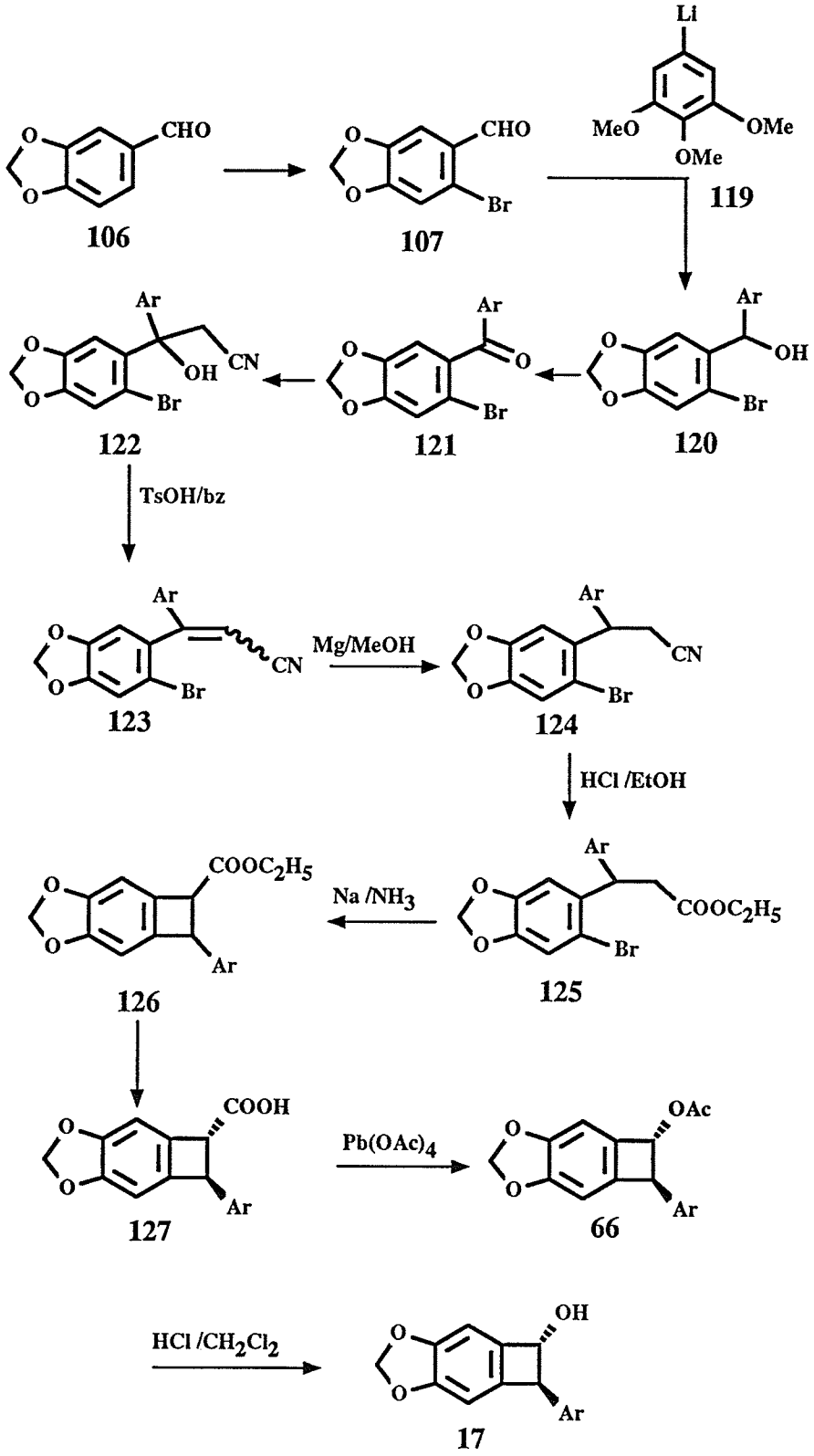
A possible explanation for the formation of **111** could be the reaction of *o*-QDM **18** with oxygen. In the absence of aldehyde **19**, irradiation of dienophile **88** in benzene solution gave no isomerized product **118.** This indicated that the isomerization of **88** occurred due to energy transfer from the excited state of aldehyde **19** to the fumarate **88** followed by *cis-trans* isomerization of the fumarate to maleate. In other words, the dienophile **88** quenched the excited aldehyde **19** and stopped formation of the *o*-QDM **18** (as shown below).



3.2.2.2 Preparation of Substituted Benzocyclobutanol 17

In view of the failure of the photochemical preparation of *o*-QDM **18** in the presence of mono(methyl (S)-lactyl) fumarate **88**, the synthesis of the benzocyclobutanol precursor **17** was attempted for use in the Diels-Alder cycloaddition reaction with **88**. Both Durst *et al*[18] and Jung *et al*[19] have synthesized compound **17** in 11 steps. As an attempt to test the cycloaddition reaction of the new dienophile **88** with the *o*-QDM **18**, the benzocyclobutanol precursor **17** was first prepared by following Durst's procedure as shown below.

Scheme 11

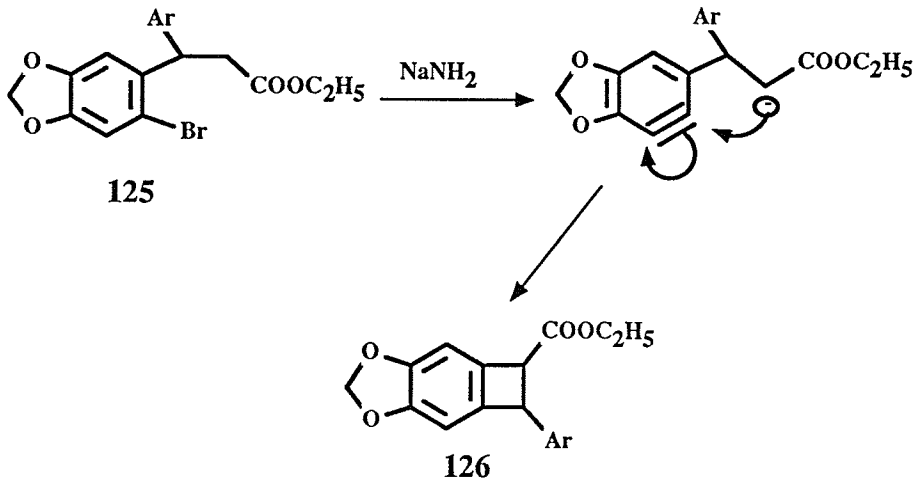

Li
MeO
OMe
OMe
CHO
Br
106
107
119
Ar
OH
CN
Br
122
121
120
TsOH/bz
Mg/MeOH
123
124
HCl /EtOH
$COOC_2H_5$
Na /NH_3
125
126
COOH
$Pb(OAc)_4$
OAc
127
66
HCl /CH_2Cl_2
17

The 3,4,5-trimethoxyphenylbromide was prepared in a 37% yield from 3,4,5-trimethoxyaniline. Isoamyl nitrite (1 equivalent) was mixed with cupric bromide (1.1 equivalent) in acetonitrile and 3,4,5-trimethoxyaniline in acetonitrile added to the solution at 0°C. After stirring 2 hours, the reaction was worked up by dilution with ethyl acetate, filtration through silica, washing with dilute acid and finally chromatography on silica gel. The yield of pure 3,4,5-trimethoxyphenylbromide was 37%.

3,4,5-Trimethoxyphenyllithium **119** was prepared by reacting the 3,4,5-trimethoxyphenylbromide (1 equivalent) with n-butyllithium (1.05 equivalent) at -78°C in THF. Bromopiperonal **107** (1 equivalent) in dry THF was added to the above solution of **119**. After normal workup, alcohol **120** was obtained in a yield of 90%. The crude alcohol was directly oxidized in a two phase system of ether/methylene chloride and 5% chromic anhydride in 10% sulfuric acid to yield ketone **121** in 90% yield after chromatography. The addition of the lithio acetonitrile anion (3 equivalents), prepared from reaction of acetonitrile with lithium diisopropylamide (LDA), to the ketone **121** yielded the alcohol **122** which, without isolation, was refluxed with TsOH in benzene to eliminate water giving a mixture of *cis* and *trans* alkenes **123** in an approximate ratio of 4:1. The mixed *cis* and *trans* alkenes **123** were reduced using magnesium in methanol at -10°C to yield the pure nitrile **124** in a yield of 90%. **124** was treated with ethanol/dry hydrogen chloride to give the ester **125** in 57% yield, which is somewhat lower than that reported in the literature.[18]

Cyclization of **125** was carried out in a flask equipped with a dry ice condenser. The system was purged with dry nitrogen, dry ice added to the condenser and ammonia distilled into the apparatus. Sodium (3.5 equivalents), cut in pieces, was added to the liquid ammonia and after evolution of hydrogen had stopped, a trace of ferric chloride was added. After the dissipation of the blue colour and the formation of a grey precipitate, ester **125** in dry THF was added. After 10 minutes the reaction was quenched by adding solid ammonium chloride. Following evaporation of the ammonia, the residue was dissolved in water, extracted with methylene chloride, dried and evaporated to leave a pale yellow oil. The ^{1}H-nmr spectrum of

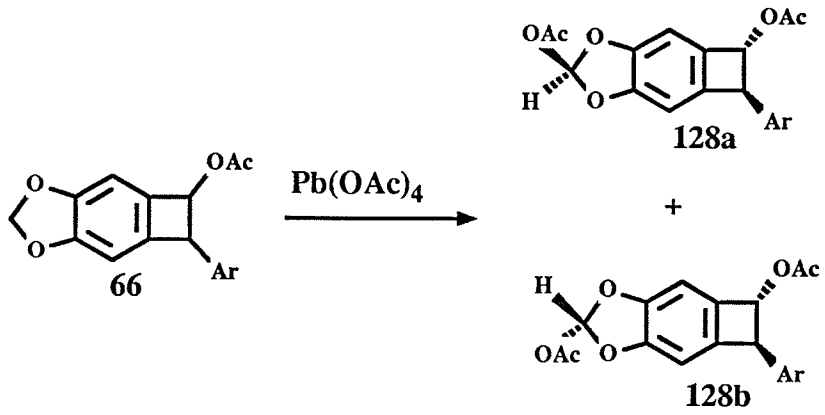
the crude product showed both the *cis* and *trans* benzocyclobutane products **126**, identical to those reported in the literature,[18] and also two other unidentified compounds. Chromatography gave the pure *trans* diastereomer (33%) and the *cis* diastereomer (ca 13%) containing approximately 20% of an impurity. Cyclization of the ester **125** is a key step in this synthesis. LDA was tried in place of sodium amide as the base for this cyclization step as Jung had reported that it was equally effective (34% yield of **126**). Unfortunately, Jung's results were not repeatable and only the starting material **125** and a by-product were recovered. The final procedure using sodium amide for the cyclization step, which is described above, was achieved only after some experimentation. When sodamide was made by adding sodium to liquid ammonia, it was necessary to add a catalytic amount of ferric chloride. The complete reaction of sodium to form sodamide is important since Birch reduction might occur if excess metallic sodium is present. The reaction time and ratio of ester to sodamide were other critical factors for a successful cyclization. If the reaction lasted too long, complicated product mixtures resulted. The best ratio of sodamide to ester was in the range of 3.5 to 4. The mechanism for this cyclization reaction was considered to be an intramolecular addition of an enolate anion to a benzyne as shown below.



125 **126**

The mixture of the *cis* and *trans* isomers **126** were treated with DMSO/50% aqueous KOH (1:1) to give the *trans* acid **127.** Evidently the *cis* isomer of **126** is epimerized to the *trans* isomer before hydrolysis to the acid. The *trans* acid **127** was treated with lead tetraacetate in

acetic acid to give the acetate **66**. Using exactly one equivalent of lead tetraacetate for the decarboxylation was very important. Excess lead tetraacetate led to the by-products **128a** and **128b** whose structures were tentatively assigned on the basis of their ^{1}H-nmr spectra.



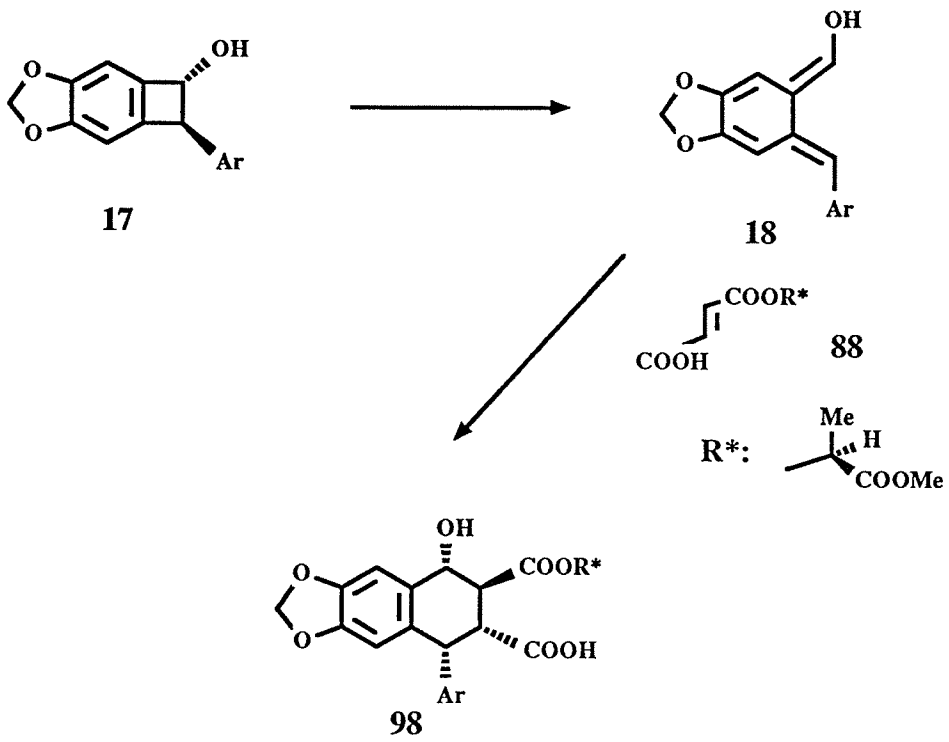
Compound **66** is relatively more stable than **126** and **127** which decompose after two weeks at 4°C. Since the benzocyclobutanol **17** was reported to decompose above 0°C, a carefully designed operation was used in the hydrolysis of the acetate **66**. The hydrolysis was carried out between -8° and -15°C using a mixture of 1 part methylene chloride and 3 parts 20% hydrochloric acid/methanol (prepared by adding acetyl chloride to cooled methanol 1:3). After hydrolysis and dilution with methylene chloride the solution was washed with water and dried with sodium sulfate. The volume of the solution was reduced under high vacuum to leave a concentrated solution of the benzocyclobutanol in methylene chloride. It was essential to keep the temperature below -4°C throughout all of these operations.

3.2.2.3 The Diels-Alder Cycloaddition Reactions of Benzocyclobutanol 17 with the Fumarate of Methyl (S)-mandelate 63 and Mono(methyl (S)-Lactyl) Fumarate 88

The ultimate aim in preparing the benzocyclobutanol **17** as a precursor to *o*-QDM **18** was to attempt the cycloaddition reaction of **18** with the nonsymmetric dienophile **88**. As discussed in section **3.2.1**, the D-A reaction of mono(methyl (S)-lactyl) fumarate **88** with

α-hydroxyl-α'-phenyl-*o*-QDM **102** gave a mixture of regioisomeric cycloadducts. Because of the lower reaction temperature it was hoped that the D-A reaction of **88** with *o*-QDM **18** would be more regioselective. The mono(methyl (S)-lactyl) fumarate **88** (3 equivalents) in toluene was added to a solution of the benzocyclobutanol **17** in methylene chloride. The methylene chloride was evaporated at high vacuum at -4°C. The remaining solution was stirred at room temperature for 40 hours. The toluene was evaporated to give a pale yellow oil. The ^{1}H-nmr spectrum of this crude product showed the presence of not only the acetate **66** and fumarate **88**, but also another new product. Two doublets appeared at 4.51 (J=5.4 Hz) and 4.89 (J=9.3 Hz) ppm as well as two unresolved multiplets at 3.4 and 3.6 ppm. A comparison was made with the ^{1}H-nmr spectrum of the cycloadduct **129** reported in literature,[34] in which two doublets appear at 4.49 (J=5.8 z) and 4.95 (J=9.4 Hz) ppm representing H_1 and H_2 of the cycloadduct. The similarity in the two spectra indicated that they probably had the same relative stereochemistry and structure leading to the assignment of structure **98** for the new cycloadduct. The remarkable result for this reaction was that there were no other isomeric cycloadducts observable in the nmr spectrum of the crude cycloadduct. Attempted purification of the cycloadduct by silica gel chromatography led to a complete loss of the material on the silica gel column. A lack of starting material and time prevented a repeat of these experiments. Nevertheless, it appears that the cycloaddition of the nonsymmetric dienophile **88** to the *o*-QDM **18** occurs with high regioselectivity and stereoselectivity. The stereochemistry appears to be the same as that found in (-)-podophyllotoxin and the cycloadduct should be convertible to podophyllotoxin by simple reduction using Lithium Triethyl Borohydride (Super Hydride) and lactone formation (DCC). Another student is now pursuing this goal.

Scheme 12

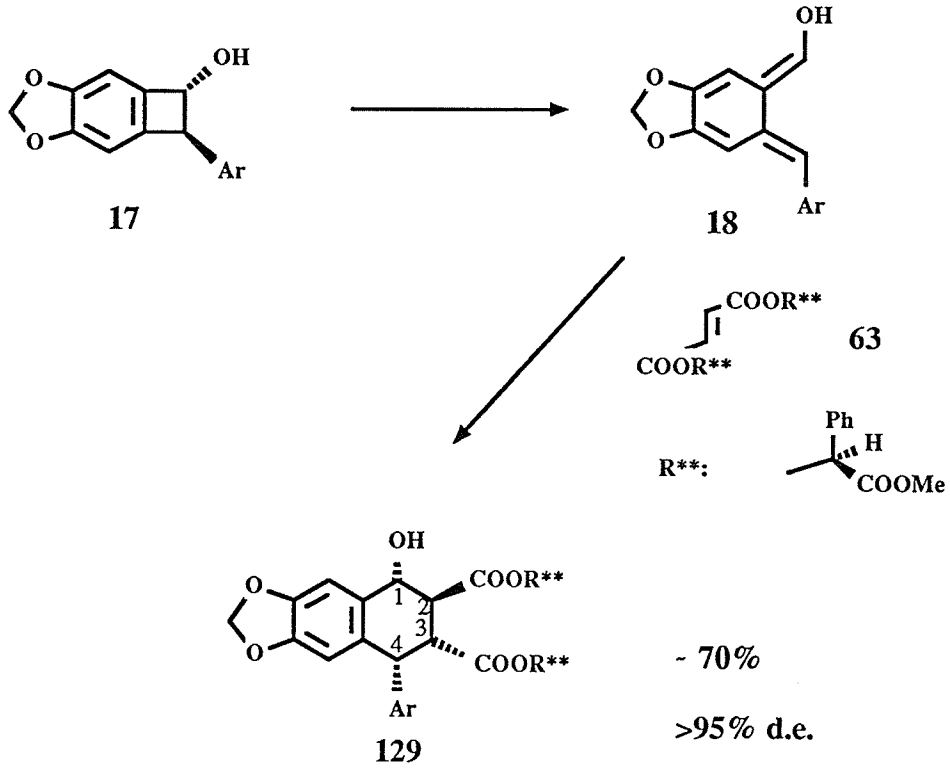


The high diastereoselectivity of the above reaction and the availability of the *o*-QDM precursor **17** provided an opportunity to improve Koh's synthesis of (-)neopodophyllotoxin. In Koh's synthesis, the *o*-QDM **18** was generated photochemically from the corresponding podoaldehyde **19** and reacted with dienophile **63**. However, the yield and stereospecificity of this cycloaddition reaction were poor.[17] The reaction of the *o*-QDM precursor **17** with **63** seemed to be a method to improve both diastereoselectivity and chemical yield.

Following the procedure described above, the dienophile **63** (5 equivalents based on the amount of acetate **66** which was hydrolysed to **17**) in toluene was added to a solution of **17** in methylene chloride at -4° to -8°C and then evaporated under high vacuum to remove the methylene chloride. After the methylene chloride was completely removed, the remaining toluene solution was warmed to room temperature (ca 20°C) and maintained at that temperature for 24 hours. After evaporation of the toluene, the 300 MHz ^{1}H-nmr spectrum of

crude product showed the presence of dienophile **63**, acetate **66** (remaining from incomplete hydrolysis) and what appeared to be a single cycloadduct identical to the major cycloadduct **129** previously isolated by Koh. There were no signals remaining for the benzocyclobutanol **17**, nor was there any podoaldehyde **19** present. This meant that all of the precursor **17** had been converted to *o*-QDM **18** which was subsequently trapped to form cycloadduct **129**. Chromatography (ethyl acetate/hexane, 30%) of the crude product gave a pale yellow solid (approximate yield 70%, corrected for recovered acetate **66**), mp 95-97°C (lit. 97-99°C).[17] The ^{1}H-nmr of the purified product was identical to that reported in the literature.[34] Two double doublets at 3.41 (J=9.4, 12.4 Hz) and 3.61 (J=5.8, 12.4 Hz) ppm and two doublets at 4.49 (J=5.8 Hz) and 4.95 (J=9.4 Hz) ppm indicated that this cycloadduct had a 1,2-*trans*, 2,3-*trans* and 3,4-*cis* stereochemistry. Approximately 40% of the starting acetate **66** was recovered.

Scheme 13



In comparison to Koh's synthesis of **129**[17], this Diels-Alder cycloaddition reaction gave a

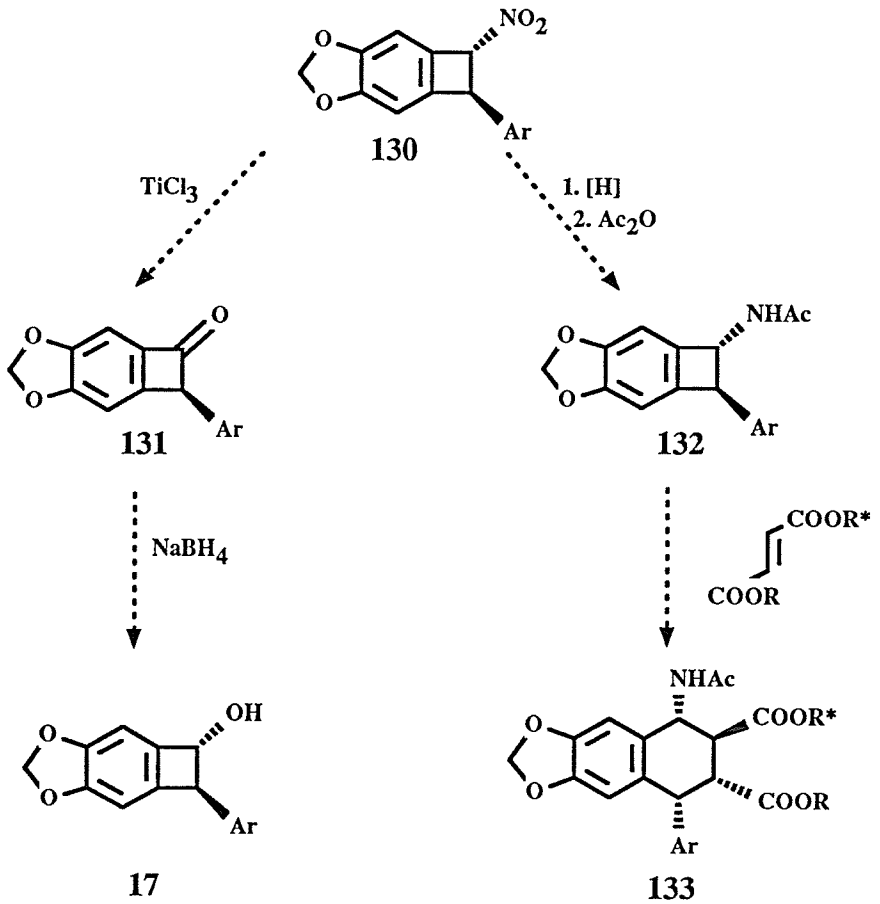
better yield (approximate 70%) and higher diastereoselectivity (>95% d.e.) as determined by 300 MHz ^{1}H-nmr spectroscopy.

3.2.2.4 Attempts to Improve the Synthesis of the Substituted Benzocyclobutanol 17

The Diels-Alder reaction of the *o*-QDM precursor **17** with both dienophiles **63** and **88** gave excellent results with reasonable chemical yield and high diastereoselectivity, but the existing method for the preparation of **17** required 11 steps with only 8 to 10% yield. It would be desirable very practical to develop a shorter synthesis of **17**. As an first attempt, the following strategy was proposed.

Proposal:

Scheme 14

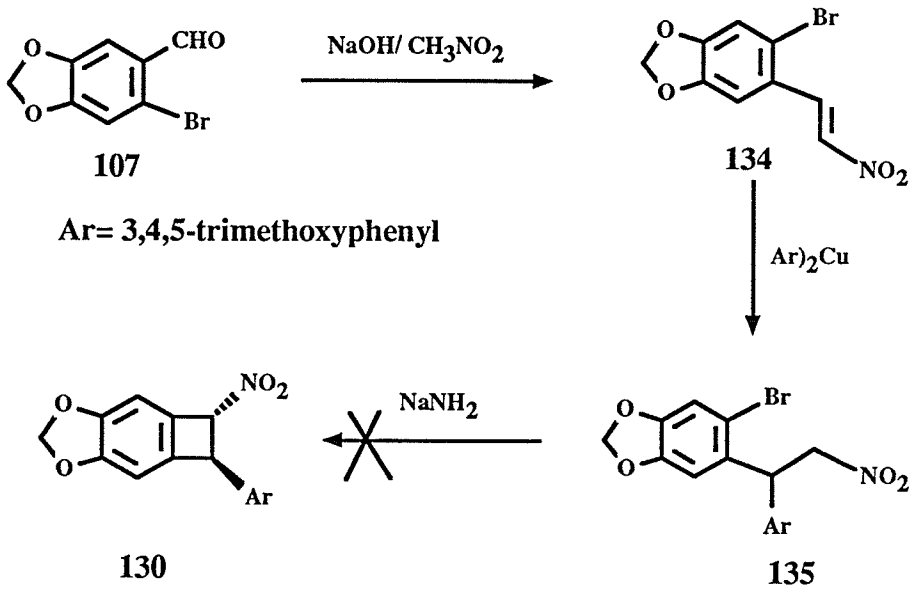


If nitro compound **130** could be synthesized, it might be possible to convert it to ketone

131 with titanium trichloride and subsequently reduce it with $NaBH_4$ at low temperature to yield **17**. Compound **130** could also possibly be converted to the acetaminobenzocyclobutene **132** which could react with the dienophile to give **133**. Compound **133** might then be converted to an analogue of podophyllotoxin.

Synthesis of compound **130** was attempted by the following sequence of reactions:

Scheme 15



107

Ar= 3,4,5-trimethoxyphenyl

134

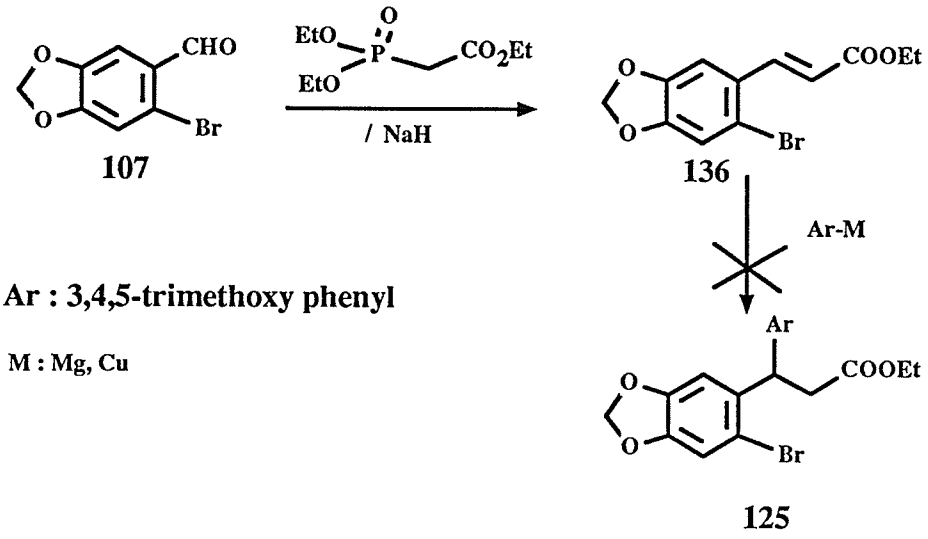
130

135

Condensation of bromopiperonal **107** with nitromethane was carried out by adding bromopiperonal to a solution of sodium hydroxide in methanol/nitromethane. After stirring 1.5 hours at room temperature the solution was partially evaporated and the residue diluted with ethyl acetate. The organic phase was separated and washed with 10% aqueous hydrochloric acid. Drying and evaporation of the organic phase gave an oil that was subsequently treated with TsOH in benzene to provide **134** in 43% yield after chromatography. The diarylcopper was prepared by reacting 3,4,5-trimethoxyphenyllithium with cuprous bromide/dimethylsulfide (DMS). Compound **134** was added to a solution of the diarylcopper in THF and the mixture stirred at room temperature for 24 hours to give the Michael addition product **135** in 61% yield after workup and chromatography. Unfortunately, all attempts to cyclize compound **135** to give **130** were unsuccessful. An example of one of these attempts is given in the experimental.

Since the new procedure via the nitro compound **130** was unsuccessful, an attempt was made to modify the existing Durst procedure. Because Durst's synthesis of **125** took seven steps from piperonal **106**, it seemed that some improvements could be made. Based on the successful addition of an aryllithium to nitrostyrene **134**, it was considered likely that compound **136**, prepared from bromopiperonal **107**, might undergo a similar Michael addition reaction. **136** was prepared in 51% by the condensation of bromopiperonal with ethyl 2-diethylphosphonoacetate/sodium hydride in ether. **136** in THF was added to a solution of the arylcopper (1 equivalent, prepared according to the same procedure as described above). However, the Michael addition reaction was unsuccessful.

Scheme 16

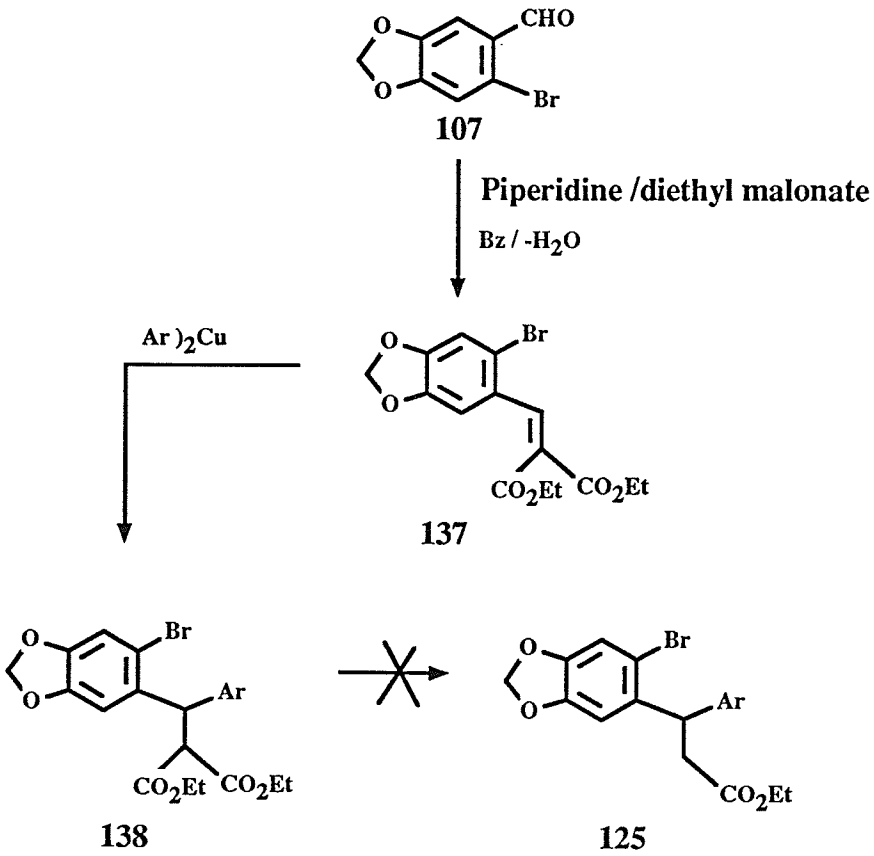


The failure of the Michael addition reaction was probably due to the fact that the double bond of **136** is conjugated to the aryl ring and is insufficiently activated towards Michael addition. Based on this idea, another electron-withdrawing group was introduced at the double bond. Obviously, an ester group such as in compound **137** was the best candidate for this activation. If a Michael addition of the compound with the arylcopper did work, a subsequent decarboxylation could remove one ester group to afford **125**.

A review of the literature indicated that compound **137** could be obtained by reacting bromopiperonal with diethyl malonate in the presence of a catalytic amount of piperidine.[49]

The bomopiperonal and diethyl malonate (1 equivalent) with a small amount of piperidine in toluene were refluxed using a Dean-Stark trap to remove water. After the reaction, the toluene was evaporated and the remaining oil purified by chromatography to give compound **137.** Compound **137** underwent Michael addition with the diarylcopper (1 equivalent, prepared following the same procedure as described above) to give a product in 78% yield after chromatography. The product was tentatively assigned structure **138** on the basis of its ^{1}H nmr spectrum. Attempt to decarboxylate **138** directly to ester **125** by refluxing a mixture of **138**, dimethylsulfoxide (DMSO)/water (100:1) and a trace of lithium chloride was unsuccessful[50].

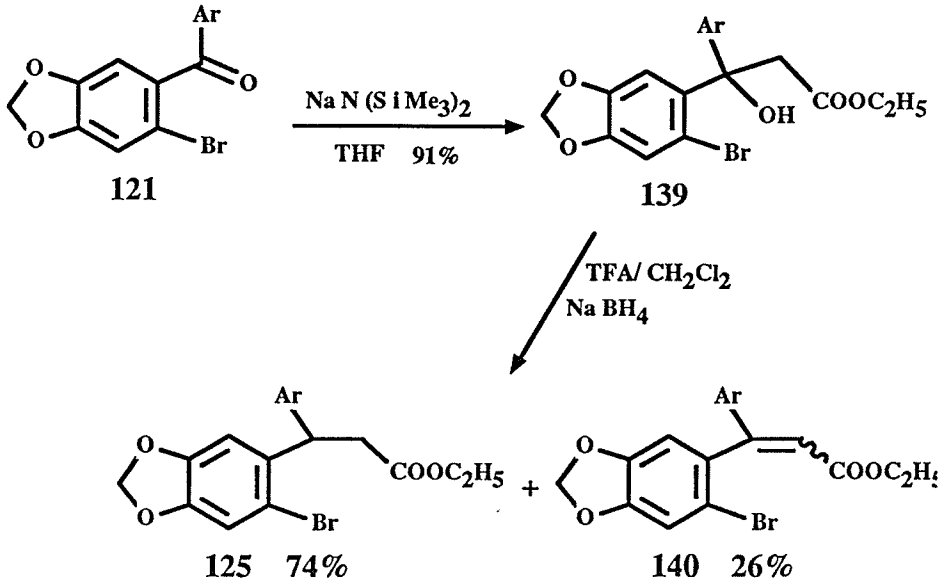
Scheme 17



Ar = 3,4,5-Trimethoxy phenyl

A re-examination of Durst's procedure for the preparation of **17** indicated that the conversion of **121** to **125** not only took four steps, but also gave a low yield for the conversion of nitrile **124** to ester **125**. It appeared that a simpler conversion of **121** to **125** could be achieved by the addition of ethyl acetate anion followed by hydrogenolysis of the resulting benzylic alcohol. According to the literature,[51] a conversion of a ketone to a β-hydroxy ester can be achieved in very high yield by the reaction of the ketone with lithio ethyl acetate at -78°C. Relative to the lithio derivative, sodio ethyl acetate, prepared from sodium bis(trimethylsilyl)amide and ethyl acetate at -78°C, gave lower yields in these reactions.[52] However, owing to the availability of sodium bis(trimethylsilyl)amide, sodio ethyl acetate was prepared and reacted with ketone **121**. Ethyl acetate (15 equivalents) was added slowly to a solution of sodium bis(trimethylsilyl)amide (10 equivalents) in THF at -78°C. After 1 minute, the ketone **121** in THF was added to the above solution and mixture stirred for 15 minute at -78°C. The reaction was quenched with 10% hydrochloric acid and aqueous solution extracted with methylene chloride. Drying and evaporating gave an oil which was chromatographed to yield **139** in 91% yield.

Removal of the hydroxyl group from **139** to yield the ester **125** was challenging because elimination of water from **139** to give alkene **140** was very likely. Hydrogenolysis of **139** in trifluoroacetic acid (TFA)/sodium borohydride[48] at 0°C gave a 90% yield of alkene **140**. Better results were obtained by carrying out the hydrogenolysis in a mixture of TFA and methylene chloride below -10°C, conditions which, after recrystallization from ethanol, gave the ester **125** in 74% yield.

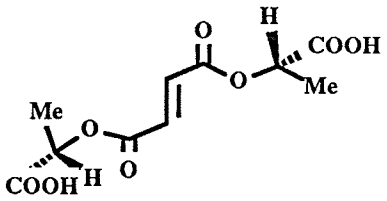


Inserting these new steps into Durst's procedure reduces the total number of steps for the synthesis of **66** from piperonal to eight steps from ten.

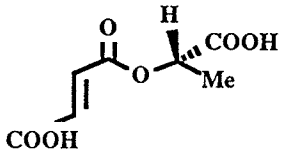
CHAPTER 4

CONCLUSION

The research of this thesis has dealt with the use of new chiral dienophiles in Diels-Alder (D-A) cycloaddition reactions with *o*-quinodimethanes (*o*-QDMs). The reaction of both the dilactyl fumarate **87** and monolactyl fumarate **90** with α-methoxy-*o*-QDM led to apparent *endo* cycloadducts.

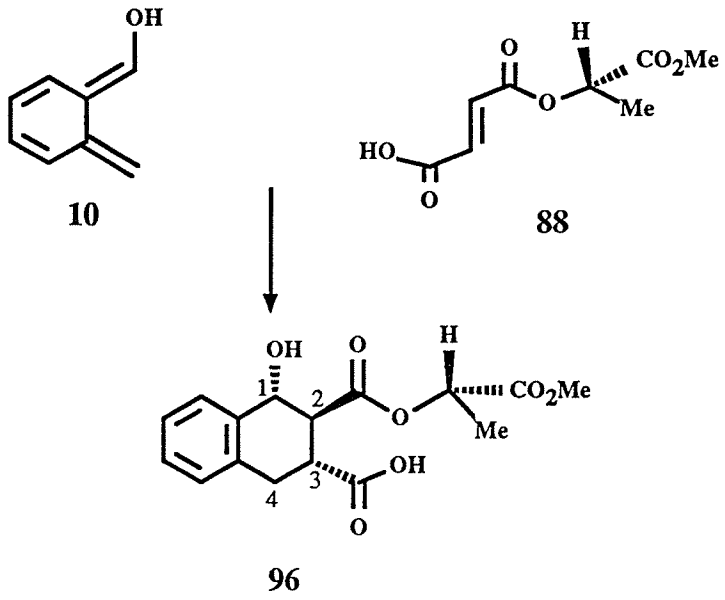


87



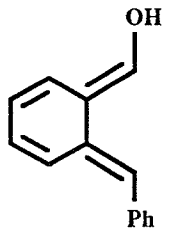
90

The *endo* stereoselectivity apparently indicated the absence of hydrogen bonding in the transition states of these reactions, an interaction expected to favour *exo* adducts. The reaction of dienophile **90** with α-methoxy-*o*-QDM gave unexpectedly higher diastereoselectivity than did the reaction of **87**. This encouraged the synthesis and testing of a new nonsymmetric dienophile, mono(methyl (S)-lactyl) fumarate **88**. This new dienophile was prepared easily by the reaction of maleic anhydride or fumaryl chloride with methyl (S)-lactate. It reacted with the α-hydroxy-*o*-QDM **10** to give an *exo* cycloadduct **96** with more than 95% d.e.

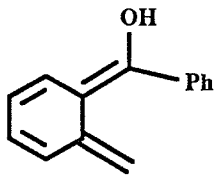


An attempt to alter the stereoselectivity of this reaction by Lewis acid catalysis was unsuccessful but did lead to a new and efficient synthesis of α-phenylbenzocyclobutane.

The high regio and diastereoselectivity of the non Lewis acid catalyzed reaction indicated the possible presence of hydrogen bonding in the transition state of that reaction. The result also presented the opportunity for an improvement in the asymmetric synthesis of podophyllotoxin. In some preliminary model reactions to this end, mono(methyl (S)-lactyl) fumarate **88** was reacted with the substituted *o*-QDMs α-hydroxy-α'-phenyl-*o*-QDM **104** and α-hydroxy-α-phenyl-*o*-QDM **105**, but gave disappointingly complicated mixtures of regio and stereoisomers.



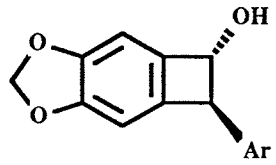
104



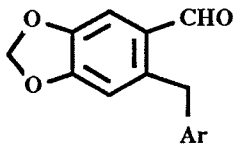
105

Despite these discouraging results, efforts were made to photochemically react dienophile

88 with the *o*-QDM precursor **19**, a reaction that could provide the cycloadduct leading to podophyllotoxin. Generating *o*-QDM **18** photochemically from **19** in the presence of mono(methyl(S)-lactyl) fumarate **88** led to no cycloadduct. It appeared that energy transfer from the excited aldehyde to the dienophile made the conversion of the aldehyde to the *o*-QDM impossible.

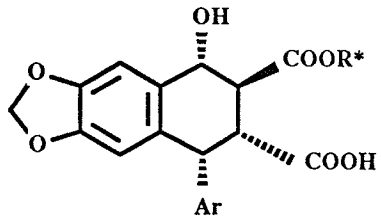


17

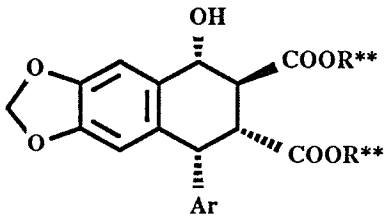


19

As an alternate precursor to *o*-QDM **18**, benzocyclobutanol **17** was prepared in 11 steps using a literature procedure in a very low yield, and in 9 steps using a modified procedure in a much higher yield. The D-A reaction of precursor **17** with mono(methyl(S)-lactyl) fumarate **88** was completely stereoselective, giving a single product **98**, whose structure was tentatively assigned by ^{1}H-nmr spectroscopy. This striking result presents the opportunity for a very practical synthesis of (-)-podophyllotoxin **50** in only three steps from **17**, a compound which has already been described in the literature.



98



129

The availability of *o*-QDM precursor **17** provided the opportunity to test this precursor in a D-A reaction with the fumarate of methyl (S)-mandelate **63** following the same procedure as described above. This reaction was also very successful giving the cycloadduct **129** in more than 90% d.e. and approximately 70% yield. This was far superior to the previous work of Koh who generated the *o*-QDM from precursor **19** and obtained the cycloadduct in only 60% d.e. and <40% yield. Obviously, the thermal reaction conditions involving precursor **17** gives much better results than the photochemical reaction.

CHAPTER 5

EXPERIMENTAL

Melting points were determined on a hot stage instrument and are uncorrected. The infrared spectra (IR) were recorded in methylene chloride solution on a Perkin Elmer 881 spectrometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AM-300 instrument in deuterated chloroform ($CDCl_3$) using TMS as an internal standard. The mass spectra (MS) and high resolution mass spectra (HRMS) were obtained with an Analytical V6 7070E-HF instrument. The elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guleph, Ontario, Canada. The optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument. The thin layer chromatography (TLC) was carried out on precoated Whatman PE SIL G/UV (Cat no 4410 222) plates. Aldrich 28,859-4, or Terochem 339385 silica gel was used for all chromatography. The THF was dried over sodium/benzophenone under nitrogen before distillation. All organic solutions were dried with magnesium sulfate unless otherwise specified.

Fumarate of methyl (S)-lactate **45**

This compound was prepared according to a previously reported procedure.[27] Fumaryl chloride (2.8 mL, 26.1 mmol) and methyl (S)-lactate (5 mL, 52.4 mmol) were heated at 110°C under nitrogen for 18 hours. The mixture was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate (5%). The organic phase was dried (Na_2SO_4) and evaporated to give a yellow oil (5.74g, 76%). The crude product was purified by chromatography on silica gel using 30% ethyl acetate/hexane as eluant to give a colorless oil (4.4 g, 59%). All spectral data were identical to those in the literature.[27]

Benzocyclobutanol **8**

This compound was prepared according to the literature procedure.[43] To a refluxing solution of vinyl acetate (200 mL) and isoamyl nitrite (30 mL, 0.22 mol), anthranilic acid (20 g, 0.15 mol) was added over 40 minutes. The resulting dark solution was refluxed for an additional hour. The vinyl acetate was evaporated and the residue oil was distilled under reduced pressure (0.1 mm Hg, 80-90°C) to give a yellow oil (20 g, 83%). The crude product, 1-acetyoxybenzocyclobutene (4.76 g, 29.4 mmol) was stirred with methanol (105 mL) and ammonium hydroxide (45 mL) at room temperature for 3 hours. The solution was extracted twice with diethyl ether (50 mL) and the extracts were washed with saturated aqueous sodium chloride. Drying and evaporation gave an oil (3.12 g). The oil was recrystallized from petroleum ether to afford colorless needles (1.63 g, 34%), mp 56-58°C. ^{1}H-nmr ($CDCl_3$)δ: 2.24 (d, 1H, J=7.0, OH), 3.05 (dd, 1H, J=2.0, 14.4), 3.63 (dd, 1H, J=2.0, 14.4), 5.3 (dd, 1H, J=2.0, 4.5), 7.1-7.3 (m, 4H, aromatics), was identical to that previously reported.[43]

Methoxybenzocyclobutanol **89**

Benzocyclobutanol (0.413 g, 3.44 mmol) in chloroform (40 mL), methyl iodide (1 mL, 16 mmol), silver oxide (1.5 g, 6.5 mmol) and 4Å molecular sieves (0.4 g) were stirred at room temperature for 26 hours. The mixture was filtered and the solid washed with chloroform. The combined organic fractions were evaporated to give a colourless oil (0.37 g, 80%). ^{1}H-nmr ($CDCl_3$)δ: 3.12 (dd, 1H, J=1.6, 12.5), 3.45 (m, 1H), 3.48(s, 3H, OCH_3), 4.98 (m, 1H), 7.15-7.26m(m, 4H, aromatics), was the identical to that previously reported.[41]

Compound **87** *and* **90**

(S)-Lactic acid (2.0 g, 22 mmol), fumaryl chloride (1 mL, 9.3 mmol) and methylene chloride (20 mL) were refluxed for 24 hours under nitrogen. The mixture was filtered and the filtrate kept at 4°C for 24 hours resulting in the precipitate of colourless crystals. These

crystals had the same melting point and Rf on TLC as fumaric acid. The methylene chloride solution was evaporated. The solid was purified by chromatography (ethyl acetate:hexane:acetic acid/3:7:0.4) to afford two fractions, fraction 1 (0.12 g) and fraction 2 (0.10 g).

Fraction 1, colourless solid, mp 128.5-129.5°C, ^{1}H-nmr (D_2O)δ: 1.57 (d, 3H, J=7.1, CH_3), 5.18 (q, 1H, J=7.1, CH), 6.91 (d, 1H, J=15.9), 7.0 (d, 1H, J=15.9), was consistent with that of the compound **90**.

Fraction 2, colourless crystal, mp 144-145.5°C, ^{1}H-nmr (D_2O)δ: 1.58 (, 6H, J=7.1, $2CH_3$), 5.19 (q, 2H, J=7.1, 2CH), 7.04 (s, 2H), was consistent with that of compound **87**.

Fraction 1 and fraction 2 were not further characterized.

Cycloaddition of methoxybenzocyclobutane with **87** *and* **90**

Methoxybenzocyclobutanol (63 mg, 0.47 mmol) and dilactyl fumarate **87** in toluene (7 mL) were refluxed for 5 hours. The toluene was evaporated and the remaining oil was chromatographed (ethyl acetate:hexane:acetic acid/3:7:0.3) to give a colourless solid. The ^{1}H-nmr ($CDCl_3$) spectrum of the solid exhibited two double peaks at 4.66_5 and 4.68 ppm with coupling constants 3.01 Hz and 3.10 Hz respectively in a ratio of 3 to 2. The ^{1}H-nmr spectra of these two products appears to be consistent with the assumed structure **92A** and **92B**, and no attempt was made to further identify these products.

Following the same procedure, the reaction of methoxybenzocyclobutane with **90** gave a colourless solid. ^{1}H-nmr spectrum of the solid showed two double peaks at 4.64 and 4.66_5 ppm with coupling constants 2.9 and 3.1 Hz respectively. The 5:1 ratio of the two peaks was determined from integrations. The ^{1}H-nmr spectrum of the two products were consistent with the assumed structures **93A** and **93B**. No attempt was made to identify these products further.

Mono(methyl (S)-lactyl) fumarate **88**

Method 1:

This compound was prepared by a modified literature procedure used for preparing monomethyl fumarate.[42] Maleic anhydride (1.02 g, 10.4 mmol) and methyl (S)-lactate (1.4 mL, 15 mmol) were mixed until a homogeneous solution was obtained. Thionyl chloride (0.05 mL) was added to the mixture. The mixture was heated on a steam bath for 10 min. After cooling, the solution was made basic with aqueous sodium carbonate (5%) and then washed with methylene chloride to remove the unreacted methyl (S)-lactate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and then extracted with methylene chloride. The combined organic fractions were dried and evaporated to give a colourless oil (0.85 g, 42%). The ^{1}H-nmr spectrum of the crude product exhibited impurity peaks (~6%) which were consistent with those expected for mono(methyl lactyl) maleate, ^{1}H-nmr ($CDCl_3$)δ: 1.57 (d, 3H, J=7.1, CH_3), 3.78 (S, OCH_3), 5.25 (q, 1H, J=7.1), 6.41 (d, 1H, J=12.5), 6.47 (d, 1H, J=12.6). The crude oil was crystallized from petroleum ether to give a colourless solid (0.63 g, 31.1%) with a low melting point. $[\alpha]^{20}_D = -8.6$ (c 0.91, $CHCl_3$). IR (CH_2Cl_2): 1736 (ester), 1711 (carboxylic acid) cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 1.55 (d, 3H, J=7.1, CH_3), 3.76(s, CH_3), 5.21 (q, 1H, J=7.1, CH), 6.90 (d, 1H, J=15.7, CH), 7.08 (d, 1H, J=15.6, CH), 10.6(bs, 1H, acid). ^{13}C-nmr ($CDCl_3$)δ: 16.9 (CH_3), 52.7 (CH_3), 69.6 (CH), 133.9 (CH), 134.4 (CH), 164.0, 169.2, 170.9 (CO). Mass spectrum *m/e* (rel.%): 157 (2), 143 (23), 113 (25), 99 (100), 85 (6). Elemental analysis calculated for $C_8H_{10}O_6$ C 47.65, H 4.99, found C 47.30, H 4.99.

Method 2

Fumaryl chloride (5 mL, 47.4 mmol) and methyl (S)-lactate (5 mL, 52.4 mmol) were heated at 100-110°C under nitrogen for 30 hours. Water (30 mL) was added and the aqueous phase was made basic with solid sodium carbonate. The aqueous phase was extracted with methylene chloride, and then acidified with aqueous hydrochloric acid (10%), followed by

extraction with methylene chloride. The organic phase was dried and evaporated to give a dark oil (5.5 g, 58%). The oil was purified by chromatography on a silica gel column using 30% ethyl acetate/hexane as an eluant to give a colourless oil (4.56 g, 47.6%). All physical properties were identical to those given above.

o-Methylbenzaldehyde **7**:

This compound was prepared according to the literature procedure.[42] To a suspension of $LiAlH_4$ (3.8 g, 100 mmol) in dry THF (100 mL), solid *o*-toluic acid (13.6 g, 99.9 mol) was added portionwise under nitrogen at 0°C. The mixture was stirred at room temperature for 1 hour, then refluxed for half an hour. After cooling, water (15 mL) was added followed by the addition of 10% aqueous sodium hydroxide (20 mL) at 0°C. The mixture was refluxed for another half hour, and then filtered, washing the solid with ethyl acetate. The combined organic phases were dried and evaporated to give an oil (11.8 g, 96%). ^{1}H-nmr ($CDCl_3$)δ: 2.33 (*s*, 3H, CH_3), 3.39 (s, 1H, OH), 4.63 (s, 2H, CH_2), 7.1-7.4 (m, 4H, aromatics).

A solution of 5% chromic anhydride in 10% sulfuric acid (135 mL, 67.5 mmol) was added to the *o*-methylbenzyl alcohol (6.6 g, 54 mmol) in diethyl ether (200 mL) at 0°C. After the addition, the stirring was continued for half an hour. Ethyl acetate (30 mL) was added and the two phases separated. The organic fraction was washed with 5% sodium bicarbonate, then dried and evaporated to give a colourless oil (4.6 g, 71%). IR (CH_2Cl_2): 1698 (CO) cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 2.67 (s, 3H, CH_3), 7.1-7.9 (m, 4H, aromatics), 10.3 (s, 1H, CHO), was identical to that reported in the literature.[43]

1-Hydroxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **9**:

This compound was prepared according to a previously reported procedure.[43] *o*-Methylbenzaldehyde (4.6 g, 38.3 mmol) in benzene (100 mL) was added to a solution of sulfur dioxide (10 g, 156 mmol) in benzene (50 mL). The solution was irradiated for 22 hours using a 450 watt Hanovia medium pressure mercury lamp located in a water cooled,

Pyrex probe immersed in the solution. The benzene was evaporated. The residue was dissolved in ethyl acetate and extracted with 5% aqueous sodium bicarbonate. The aqueous extract was re-acidified (10% HCl) and extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated to give a dark oil which was triturated with carbon tetrachloride (0°C) to remove impurities, leaving a pale green solid (2.7 g, 38%). IR (CH_2Cl_2): 3532 (OH), 1321, 1203, 1123 (SO_2) cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 4.26 (, 1H, J=15.6, CH), 4.38 (d, 1H, J=15.6, CH), 4.52 (broad s, 1H, OH), 5.64 (s, 1H, CH), 7.23-7.55 (m, 4H, aromatics), identical to that reported in the literature.[43]

*(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-3-carboxy-2-carboxy late of (S)-m*ethyl*l lactate* **96**

Method A

A solution of *o*-methylbenzaldehyde (0.352 g, 2.93 mmol) and mono(methyl (S)-lactyl) fumarate (0.67 g, 3.33 mmol) in dry benzene (100 mL) in three Pyrex test tubes were flushed with nitrogen and then irradiated for 6 hours using a 450 watt Hanovia medium pressure mercury lamp located in a Pyrex water cooled probe. After irradiation, the solvent was evaporated to give a dark oil. The oil was recrystallized from ethyl acetate/hexane (3:1) to yield colourless crystals **A** (0.383 g, 40.6%), mp 151-153°C. Product **A**: $[\alpha]^{20}_D$ = -78.4 (c 0.9, $CHCl_3$), mp 151-153°C. IR (CH_2Cl_2): 3503 (OH), 1738 (COO) cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 1.60 (t, 3H, J=7.15, CH_3), 3.05 (m, 2H, CH), 3.25 (m, 2H, CH), 3.82 (s, 3H, OCH_3), 4.96 (d, 1H, J=9.5, H-1), 5.34 (q, 1H, J=7.16, CH), 7.13-7.26(m, aromatics), 7.71(d, 1H, J=7.4). ^{13}C-nmr ($CDCl_3$)d: 16.6 (CH_3), 31.4 (CH_2), 40.4 (CH), 50.4 (CH), 53.1 (CH_3), 69.1 (CH), 70.9 (CH), 126.8 (CH), 126.9(CH), 127.6(CH), 127.9 (CH), 132.8 (C), 136.5 (C), 172.9(C), 173.9(C), 179.1 (C). Mass spectrum *m/e* (rel.%): 304 (3), 200 (17), 156 (27), 128 (100), 45 (53). Elemental analysis calculated for $C_{16}H_{18}O_7$ C 59.62, H 5.63, found C 59.30, H 5.64.

Method B

Mono(methyl (S)-lactyl) fumarate (0.333 g, 1.6 mmol) and 4Å molecular sieves (0.5 g) in toluene (12 mL) were heated to reflux. The 1-hydroxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide (sulfone) (0.62 g, 3.37 mmol) in methylene chloride (3 mL) was added portionwise over 20 min. After the addition of the sulfone, refluxing was continued for another half an hour. The solution was passed through a short silica gel column to remove polymeric materials. The solvent was evaporated to give an oil (0.78 g). The oil was partly purified by chromatography (30% ethyl acetate/hexane). The resulting colourless oil was crystallized from petroleum ether to afford colourless crystals (0.17 g, 32%), mp 151-152 °C. ^{1}H-nmr of this material was identical to that of **A** obtained from method A. Further concentration and cooling of the mother liquors gave a second compound **B** (0.033 g, 6.6%), mp 126-128°C.

Product **B**: $[\alpha]^{20}_D$ = -20.4 (c 0.27, $CHCl_3$), mp 126-128°C. IR(CH_2Cl_2): 1786 (CO, lactone), 1747 (CO ester) cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 1.38 (d, 3H, J=7.1, CH_3), 3.10 (d, 1H, J=17.7, H-4a), 3.35 (m, 1H, H-3), 3.48 (dd, 1H, J=5.2, 17.7, H-4b), 3.50 (s, 3H, OCH_3), 3.85 (t, 1H, J=5.1, H-2), 4.96 (q, 1H, J=7.1, CH), 5.48 (d, 1H, J=5.1, H-1), 7.13-7.35 (m, 4H, aromatics), melting point and ^{1}H-nmr spectra for **B** were identical to that reported in the literature.

Method C

Mono(methyl (S)-lactyl) fumarate **88** (0.247 g, 1.2 mmol) and 4Å molecular sieves (0.2 g) in toluene (6 mL) were heated to reflux. Benzocyclobutanol (0.38 g, 3.2 mmol) in methylene chloride (5 mL) was added portionwise over 20 min. After the addition, the stirring was continued for another two hours (TLC showed complete consumption of the benzocyclobutanol). The mixture was passed through a short silica gel column. The toluene was evaporated to leave an oil which was crystallized from ethyl acetate/hexane (4:1) to give

colourless crystals (0.164 g, 42%), mp 152-153°C. ^{1}H-nmr of this product was identical to **A** obtained from method A. Further concentration and cooling of the mother liquors gave another colourless crystalline compound (0.019 g, 5.1%), mp 127-128.5°C, ^{1}H-nmr of this crystal was identical to that of compound **B** obtained from method B.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-3-carboxy-1,3-lactone-2-carboxylate of methyl (S)-lactate **94**

As well as by direct isolation from the cycloaddition reaction described above, the lactone could also be prepared by direct elimination of water from the cycloadduct. The cycloadduct was dissolved in ethyl acetate/hexane (10:1, 2 mL) and the solution, refrigerated for a few days, deposited colourless needles whose physical data were identical to the lactone **B** described above.

o-Benzylbenzaldehyde **97**

To a suspension of $LiAlH_4$ (3 g, 79 mmol) in dry tetrahydrofuran (80 mL) was added a solution of *o*-benzylbenzoic acid (9.5 g, 44 mmol) at 0°C. After the addition, the mixture was stirred at room temperature for half an hour, then refluxed for another hour. After cooling, water (10 mL) was slowly added to the mixture followed by 15% sodium hydroxide (10 mL) and water (10 mL). The mixture was filtered and the precipitate washed with ethyl acetate. The organic phase was dried and evaporated to give an oil (8.45 g, 96%).

The oil was dissolved in diethyl ether (80 mL) and cooled in an ice-bath. A solution of chromic anhydride (5%) in 10% aqueous sulfuric acid (75 mL, 37.5mmol) was added dropwise to the above solution with vigorous stirring. After the addition, the stirring was continued for another 20 minutes. Ether (50 mL) was added and the organic phase separated, washing with 5% aqueous sodium bicarbonate. Drying and evaporation left an oil (8 g, 96%). The ^{1}H-nmr spectrum was identical to that reported in the literature.[48]

1-Hydroxy-3-phenyl-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **103**

This compound was prepared according to the literature procedure.[21] Sulfur dioxide (6 g, 96 mmol) in benzene (80 mL) was added to a solution of *o*-benzylbenzaldehyde (5.4 g, 27 mmol) in dry benzene (100 mL). The final volume of solvent was adjusted to 260 mL with benzene. The solution was flushed with nitrogen and irradiated for 20 hours using a 450 watt Hanovia medium pressure mercury lamp located in a water cooled Pyrex probe immersed in the solution. The solvent was evaporated at room temperature to give a yellow oil which was triturated with carbon tetrachloride to yield a yellow solid (4.5 g, 62%). The ^{1}H-nmr was identical to that previously reported in the literature.[21]

Cycloaddition of sulfone with mono(methyl (S)-lactyl) fumarate **88**

A solution of mono(methyl (S)-lactyl) fumarate **88** (0.368 g, 1.9 mmol) in toluene (7 mL) was heated to reflux. The above sulfone (0.53 g, 1.9 mmol) in methylene chloride (10 mL) was added portionwise over 1 hour. After the addition of the sulfone, the solution was refluxed for another 25 minutes. The mixture was passed through a short silica gel column and washed with ethyl acetate. The solvent was evaporated to give an oil. ^{1}H-nmr ($CDCl_3$) of the crude product was complicated but exhibited doublets at 4.46 (J=5.5), 4.95 (J=9.6), 5.09 (J=4.0), 5.41 (J=3.0) in the approximate ratio of 1:1:0.1:0.3.

α-*Phenylbenzocyclobutene* **100**

Benzocyclobutanol **9** (0.2 g, 1.7 mmol) in methylene chloride (3 mL) was added to a refluxing solution of boron trifluoride etherate (0.43 mL, 3.3 mmol) in benzene (5 mL). The solution was refluxed for 2 hours. After cooling, the benzene solution was washed with 5% aqueous sodium bicarbonate, dried and evaporated to give a yellow oil. The crude product was purified by chromatography (10% ethyl acetate/hexane) to give a pale yellow oil (0.27 g, 82%). ^{1}H-nmr ($CDCl_3$)δ: 3.06 (d, 1H, J=13.9), 3.69 (bd, 1H), 4.67 (m, 1H), 7.13-7.25 (m, 9H, aromatics), identical to that reported in the literature.[44]

(Methyl phenyl) benzocyclobutene **101**

A solution of benzocyclobutanol **9** (0.14 g, 0.17 mmol) in methylene chloride was added to a solution of boron trifluoride etherate (0.34 mL, 3.3 mmol) in toluene (7 mL) and was refluxed for 30 minutes. The mixture was washed with 5% aqueous sodium bicarbonate. The organic phase was dried and evaporated to give a pale yellow oil. Chromatography of the oil (10% ethyl acetate/hexane) afforded a colourless oil (0.15 g, 66%). TLC showed the oil to be a mixture of two compounds. ^{1}H-nmr ($CDCl_3$)δ: 2.35 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.97 (dd, 1H, J=2.9, 10.8), 3.08 (dd, 1H, J=2.7, 11.2), 3.73 (dd, 1H, J=5.6, 11.4), 3.80 (dd, 1H, J=5.5, 11.1), 6.68 (dd, 1H, J=2.3, 2.9), 4.85 (dd, 1H, J=2.3, 2.9), 7.1-7.34 (m, 8H, aromatics). No attempt was made to separate the mixture of the products formed.

Benzocyclobutanone

A solution of benzocyclobutanol (0.23 g, 1.92 mmol) in diethyl ether (30 mL) was stirred vigorously and chromic anhydride solution (CrO_3 0.5M in 10% sulfuric acid, 15 mL, 7.5mmol) was added dropwise at 0°C. After the addition, the solution was stirred in an ice-bath for another 20 minutes. More ether (20 mL) was added and the phases separated. The aqueous layer was extracted with ether and the combined ether fractions washed with 5% aqueous sodium bicarbonate until the organic layer became colourless. The organic extract was dried and evaporated to give a colourless oil (0.2 g, 88%). ^{1}H-nmr ($CDCL_3$)δ: 3.98 (s, 2H), 7.23-7.43 (m, 4H, aromatics). Comparison to the literature spectra[48] showed the material to be greater than 90% pure and it was used in following reaction without further purification.

1-Phenyl-1-benzocyclobutanol

Butyllithium (2.6 mL, 4.2 mmol) was added to a solution of bromobenzene (0.44 mL, 4.2 mmol) at -78°C. After 5 minutes, benzocyclobutanone (0.33 g, 2.8 mmol) in THF (2 mL)

was added. The initial wine-red solution slowly changed to yellow. The solution was stirred for another 10 minutes. The dry-ice bath was removed and saturated aqueous ammonium chloride (10 mL) was added. The aqueous layer was extracted with ethyl acetate. The combined organic phases were dried and evaporated to give a yellow oil. The oil was purified by chromatography (20% ethyl acetate/hexane) to afford a colourless solid (0.268 g, 60%). ^{1}H-nmr ($CDCl_3$)δ: 3.42 (d, 1H, J=14), 3.52 (d, 1H, J=14), 7.13-7.39 (m, 9H, ArH), was identical to that previously reported.[45]

Cycloaddition of 1-phenyl-1-benzocylobutanol with mono(methyl (S)-lactyl) fumarate **88**

A solution of 1-phenyl-1-benzocyclobutanol (0.238 g, 1.21 mmol) in toluene (2 mL) was added to a refluxing solution of mono(methyl (S)-lactyl) fumarate (0.484 g, 2.4 mmol) in toluene (5 mL) and the refluxing continued for 1 hour. The toluene was evaporated to give an oil (0.68 g). ^{1}H-nmr of the crude product was very complicated but exhibited doublets at 1.16, 1.29, 1.48, 1.58 (J=7, CH_3, ratio: 1:1.5:1:2). No attempt was made to separate the mixture of adducts.

6-(3',4',5'-Trimethoxybenzyl)piperonal (podoaldehyde) 19

Method A

This compound was prepared according to a literature procedure.[13]

Bromopiperonal **107**

Bromine (16.9 mL, 0.32 mol) was added dropwise to a solution of piperonal (24.4 g, 0.16 mol) in glacial acetic acid (240 mL). The mixture was stirred at room temperature for 23 hours. Water (250 mL) was added and the solution was cooled to 4°C for 5 hours. Filtration

gave a dark solid. The solid was washed with cold 40% acetic acid/water (300 mL) to afford a pale yellow solid (32 g) which was recrystallized from ethyl acetate to give colourless needles (28 g, 75.1%), mp 127.5-129°C (lit. 127-129°C)[13]. ^{1}H-nmr of the product was identical to that of the literature.[13]

5,6-Methylenedioxy-3-(3',4',5'-trimethoxyphenyl) phthalide **111**

Bromopiperonal **107** (4.5 g, 16.5 mmol), ethylene glycol (2 mL, 33 mmol) and *p*-toluenesulfonic acid (TsOH) (500 mg) in benzene (100 mL) were refluxed for 2 hours using a Dean-Stark trap for water separation. The mixture was passed through a short silica gel column to remove ethylene glycol and TsOH. Evaporation of the solvent left a colourless solid (3.86 g). The bromoacetal (3.86 g, 14.1 mmol) in THF (20 mL) was added to a solution of butyllithium (8.7 mL, 14.1 mmol) in dry THF (30 mL) at -78°C. After 2 minutes, 3,4,5-trimethoxybenzylaldehyde (2.82 g, 14.12 mmol) in THF (20 mL) was added. The mixture was stirred at -78°C for 40 minutes and then saturated aqueous ammonium chloride (10 mL) added. Ethyl acetate (20 mL) was added to the above solution and the phases separated. The organic fraction was dried and evaporated to give an oil (6.22 g). The oil was hydrolysed by stirring with Dowex 50W-X4 (10g) in methanol/water (9:1, 100 mL) at room temperature for 3 hours. The resin was filtered off and the methanol evaporated. The remaining aqueous solution was extracted with ethyl acetate. The organic fractions were dried and evaporated to give a yellow oil. The oil, in diethyl ether (100 mL), was added dropwise to a vigorously stirred solution of chromic anhydride (CrO_3 5% in 10% H_2SO_4, 75 mL) at 0°C. The stirring was continued for another 20 minutes in an ice-bath. Diethyl ether (50 mL) was added and the organic layer separated. The ether solution was washed with 5% aqueous sodium bicarbonate. The organic phase was dried and evaporated to give a pale yellow solid (2.76 g). The crude product was chromatographed (30% ethyl acetate/hexane to give a colourless solid (1.82 g, 32% based on bromopiperonal used). The physical data and spectral properties were identical to those reported in the literature.[13]

6-(3',4',5'-Trimethoxybenzyl) piperonylic acid **112**

The above lactone (1.0 g, 2.9 mmol) with 5% Pd/C (50 mg) in acetic acid (20 mL) was hydrogenolyzed at 90-105°C at atmospheric pressure for 32 hours (monitored by TLC). After the reaction was complete, ethyl acetate was added, the solution filtered and extracted with water. The organic phase was dried and evaporated to give a pale yellow solid. The crude product was recrystallized from methylene chloride/hexane (1:3) to afford a colourless solid (0.82 g, 68%), mp 99-100°C lit. 98-99°C).[13]

6-(3',4',5'-Trimethoxybenzyl) piperonal **19**

To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry THF (50 mL) was added a solution of the piperonylic acid (0.42 g, 1.2 mmol) in THF (20 mL). The mixture was refluxed for 20 minutes. Water (10 mL), followed by 15% sodium hydroxide (5 mL), was added at 0°C. The precipitate was washed with ethyl acetate and the aqueous layer extracted with ethyl acetate. The combined organic phases were dried and evaporated to give a pale yellow solid (0.33 g). A solution of chromic anhydride ($CrO_3$5% in 10% H_2SO_4, 10 mL) was added dropwise to a solution of the above crude product (0.33 g) in diethyl ether (50 mL) with vigorous stirring at 0°C. The stirring was continued for another 40 minutes at 0°C. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with 5% aqueous sodium bicarbonate, then dried and evaporated to give a pale yellow solid which was chromatographed (40% ethyl acetate/hexane) to afford colourless crystals (0.22 g, 55%), mp 110-111.5°C. IR (CH_2Cl_2): 1691(CHO) cm^{-1} . ^{1}H-nmr ($CDCl_3$)δ: 3.79 (s, 6H, OCH_3), 3.82(s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 6.05 (S, 2H, CH_2), 6.69 (s, 1H), 7.35 (s, 1H). Mass spectrum *m/e*: 330, 329. The spectral properties were identical to those previously reported.[13]

Method B

[1,2-Bis(diphenylphosphino)ethane]nickel (II) chloride

116

A solution of 1,2-bis(diphenylphosphino)ethane (0.344 g, 0.863 mmol) in ethanol (5 mL) was added to a solution of nickel (II) chloride (0.21 g, 0.83 mmol) in 95% ethanol (5 mL). The resulting brown-red precipitate was filtered and dried to give a brown-red powder (0.412 g, 92%).

3,4,5-Trimethoxybenzylbromide **114**

3,4,5-Trimethoxybenzylalcohol (2 g, 10.1 mmol) was added to a solution of phosphorus tribromide (2 g, 7.4 mmol) in methylene chloride (20 mL). The mixture was stirred at room temperature for 24 hours. The solvent was evaporated to give brown-red oil. The oil was subjected to high vacuum for 2 hours to give a dark solid (2.15 g, 81.6%). ^{1}H-nmr ($CDCl_3$)δ: 3.83 (s, 3H, OCH_3), 3.89 (s, 6H, OCH_3), 4.45 (s, 2H), 6.75 (s, 2H), was identical to that reported in the literature.[47]

6-(3',4',5'-Trimethoxybenzyl)piperonal **19**

To a solution of bromopiperonal acetal (0.182 g, 0.67 mmol) in dry THF (5 mL) was added butyllithium (0.4 mL, 0.67 mmol) at -78°C. After 2 minutes, dry copper cyanide (0.07 g, 0.85 mmol) in HMPA (1 mL) was added, followed by the addition of the above nickel complex (15 mg). After another 2 minutes, 3,4,5-trimethoxybenzyl bromide in THF (5 mL) was added. The mixture was stirred at -78°C for 3 hours, and then at room temperature for 12 hours. Saturated aqueous ammonium chloride (5 mL) was added. After separation, the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride, then dried and evaporated to give a low melting solid. The crude product was hydrolysed in a two phase solution of methylene chloride (40 mL) and 10% aqueous hydrochloric acid (10 mL) at room temperature for 12 hours. The mixture was separated and the aqueous phase extracted with methylene chloride. The

combined organic layers were washed with 5% aqueous sodium bicarbonate, then dried and evaporated to give a pale yellow solid which was chromatographed (40% ethyl acetate/hexane) to afford a colourless solid (35 mg, 16%), mp 110-112°C. IR, ^{1}H-nmr and mass spectrum were identical to the aldehyde prepared by **method A**.

Attempted photochemical addition of 6-(3',4',5'-trimethoxy benzyl)piperonal to mono(methyl (S)-lactyl) fumarate **88**

A solution of 6-(3',4',5'-Trimethoxylbenzyl)piperonal **19** (30 mg, 0.09 mmol) in dry benzene (20 mL) was purged with nitrogen. One fourth of a solution of mono(methyl (S)-lactyl) fumarate **88** (100 mg, 0.5 mmol) in benzene (4 mL) (solution purged with nitrogen) was added to the solution. The mixture was irradiated at room temperature (450 Watt Hanovia Medium Pressure mercury lamp) and the remaining solution of mono(methyl (S)-lactyl) fumarate **88** in benzene was added over 4 hours. At the end of this time, the solution was irradiated for a further 6 hours. The benzene was evaporated to give a pale yellow oil (124 mg) which was chromatographed (40% ethyl acetate/ hexane) to yield four fractions. The ^{1}H-nmr spectrum and Rf of the first fraction was identical to that of mono(methyl (S)-lactyl) fumarate **88**. The third fraction was consistent with 6-(3',4',5-trimethoxyphenzyl)piperonal and the fourth, 5,6-methylenedioxy-3-(3',4',5'-trimethoxyphenyl)phthalide. The ^{1}H-nmr of the second fraction was identical to that of the product prepared from treating maleic anhydride with (S)-methyl lactate and was assumed to be mono(methyl (S)-lactyl) maleate **118**.

Preparation of trans 2-(3,4,5-trimethoxyphenyl)benzocyclobutanol 17

This compound was prepared by a modified literature procedure.[18]

3,4,5-Trimethoxybromobenzene

Isoamyl nitrite (4.2 mL, 29.8 mmol) was added to a solution of copper (II) bromide (7 g, 31.4 mmol) in acetonitrile (40 mL) cooled in an ice-salt bath (-3 to -6°C). 3,4,5-Trimethoxyaniline (5.6 g, 30.6 mmol) in acetonitrile (40 mL) was added dropwise. Evolution of nitrogen was observed. After the addition, the mixture was stirred for 2 hours below 0°C. The solution was evaporated to dryness, the residue dissolved in ethyl acetate and the solution passed through a short silica gel column to remove inorganic salts. The organic phase was washed with 20% aqueous hydrochloric acid until the extract was colourless. The organic layer was dried and evaporated to give a dark oil which was chromatographed (10% ethyl acetate/ hexane) to give colorless crystals (2.8 g, 37%), mp 74-75°C. ^{1}H-nmr ($CDCl_3$)δ: 3.89 (s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 6.72 (s, 2H, aromatics), was identical to that in the literature.[49]

Benzophenone **121**

Butyllithium (1.69 M in hexane, 3.2 mL, 5.4 mmol) was added to a solution of 3,4,5-trimethoxybromobenzene (1.31 g, 5.3 mmol) in THF (20 mL) at -78°C. After 2 minutes, bromopiperonal (1.5 g, 5.5 mmol) in THF (10 mL) was added. The mixture was stirred at -78°C for 1 hour, then warmed slowly to room temperature. Saturated aqueous ammonium chloride (20 mL) was added to quench the reaction. The aqueous layer was separated and extracted with ethyl acetate. The combined organic phases were dried and evaporated to give an oil which was purified by chromatography (20% ethyl acetate/hexane) to yield a colourless solid (1.9 g, 90%). ^{1}H-nmr ($CDCl_3$)δ: 2.02 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.81 (s, 6H, OCH_3), 5.94_4 (d, 2H, J=5.5), 5.94_0(d, 1H, J=5.5), 6.05 (s, 1H, CH), 6.63 (s, 2H), 6.95 (, 1H), 6.96 (s, 1H), was identical to that reported in literature.[18]

A solution of 5% chromic anhydride in 10% sulfuric acid (30 mL) was added dropwise to a solution of the above alcohol (0.625 g, 1.57 mmol) in diethyl ether (50 mL) and methylene chloride (15 mL) at 0°C. The solution was stirred for a further 20 minutes. The organic phase

was diluted with ether and separated. The aqueous phase was extracted with ether. The combined organic extracts were washed with 5% aqueous sodium bicarbonate, dried and evaporated to yield an oil which was purified by chromatography (30% ethyl acetate/hexane) to give a colourless solid (0.52 g, 80%). ^{1}H-nmr ($CDCl_3$)δ: 3.81 (s, 6H, OCH_3), 3.88 (s, 3H, OCH_3), 6.07 (s, 2H), 6.50 (s, 2H), 6.77(s, 2H), 7.12 (s, 1H) was identical to that previously reported.[18]

3-(3',4',5'-trimethoxyphenyl)-3-(2"-bromo-4", 5"-methylenedioxyphenyl) propylnitrile **124**

Butyllithium (1.69 M in hexane, 1.7 mL, 2.85 mmol) was added to a solution of isopropylamine (0.4 mL, 2.85 mmol) in THF (5 mL)) at -78°C. After 10 minutes, acetonitrile (0.4 mL, 7.6 mmol) was added and the resulting suspension was stirred for 7 minutes. The above ketone **121** (0.38 g, 0.96 mmol) in THF (5 mL) was added and the mixture was stirred for 15 minutes at -78°C, then at room temperature for 15 minutes. Saturated aqueous ammonium chloride (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with methylene chloride. The combined organic phases were dried and evaporated to give an oil which was purified by a short silica gel column (30% ethyl acetate/hexane) to afford a pale yellow solid (0.40 g, 95%). ^{1}H-nmr ($CDCl_3$)δ: 3.36 (d, 1H, J=16.5), 3.44 (d, 1H, J=16.5), 3.53 (s, 1H, OH), 3.79 (s, 6H, OCH_3), 6.06 (s, 2H), 6.5 (s, 2H), 7.26 (s, 1H), 7.37 (s, 1H). The above oil and TsOH (15 mg) in benzene (50 mL) were refluxed for 2 hours. After evaporation of the benzene, the residue in methylene chloride was passed through a short silica gel column to remove TsOH. Recrystallization from ethyl acetate/hexane (1:3) gave 3-(3',4',5'-trimethoxyphenyl)-3-(2"-bromo-4", 5"-methylenedioxyphenyl)-2-propylene nitrile **123** (0.31 g, 85%), mp 154-156°C. ^{1}H-nmr ($CDCl_3$)δ: 3.81 (s, 6H, OCH_3), 3.88 (s, 3H, OCH_3), 5.91 (s, 1H), 6.07 (s, 2H), 6.50 (s, 2H), 6.77 (s, 1H), 7.12 (, 1H). Mass spectrum *m/e* (rel.%): 419 (11), 417 (11), 309 (5), 307 (100), 129 (64), was identical to the literature spectrum.[18]

A crystal of iodine was added to a mixture of magnesium turnings (1.3 g, 54 mmol) in dry methanol (40 mL). When hydrogen began evolving vigorously, the flask was immersed in a carbon tetrachloride-dry ice bath (-20°C) and the above alkene **123** (0.32 g, 0.8 mmol) in THF (7 mL) was added. The mixture was stirred at -20 to 0°C for 2 hours until reduction was complete (the reaction was monitored by TLC). The remaining magnesium turnings were filtered off and the methanol evaporated. The residue was dissolved in ethyl acetate and the solution washed with 10% aqueous hydrochloric acid. The organic phase was dried and evaporated to give an oil (0.307 g, 96%). Recrystallization from ethanol gave colourless crystals, mp 154.5-155.5°C. ^{1}H-nmr ($CDCl_3$)δ: 2.96 (d, 2H, J=7.4), 3.84 (s, 9H, OCH_3), 4.77 (t, 1H, J=7.4), 5.97 (s, 2H), 6.47 (s, 2H), 6.64 (s, 1H), 7.04 (s, 1H). Mass spectrum *m/e* (rel.%): 421 (31), 419 (32), 381 (18), 379 (18), 300 (100), 299 (52), 269 (71), were identical to that previously reported.[18]

Ethyl 3,3-diarylpropionate **125**

Compound **124** (0.367 g, 0.9 mmol) in dry ethanol (20 mL) was saturated with dry hydrogen chloride gas. The saturated solution was refluxed for 1.5 hours. Half of the solvent was evaporated and 20% water/ethanol (36 mL) was added. The mixture was refluxed for another 4 hours. After cooling, water (20 mL) was added and the solution extracted with methylene chloride. The combined organic phases were dried and evaporated to give an oil which was purified by chromatography (30% ethyl acetate/hexane) to yield a pale yellow oil (0.205 g, 57%). The oil was crystallized from ethanol/water (5:1) to give colourless crystals, mp 110-112°C. ^{1}H-nmr ($CDCl_3$)δ: 1.16 (t, 3H, J=7.1), 2.93 (d, 2H, J=8.1), 3.81, 3.82 (s, 9H, OCH_3), 4.07 (q, 2H, J=7.1), 4.94 (t, 1H, J=8.1), 5.93 (dd, 2H, J=1.3, 3.1, CH_2), 6.48 (s, 2H), 6.67 (s, 1H), 7.01 (s, 1H), identical to that reported in the literature.[18]

Cyclization of the ethyl 3,3-diarylpropionate **125**

Sodium (0.1 g, 4.3 mmol) was added to liquid ammonia (15 mL) at -78°C. After 5

minutes, a trace of ferric chloride was added to the resulting blue solution. The solution was warmed to -33°C for 10 minutes until the blue colour had disappeared and a grey precipitate formed. The solution was cooled again at -78°C and the bromo ester **125** (0.37 g, 0.79 mmol) in THF (15 mL) was added in one portion. The resulting brown solution was stirred at -78°C for 10 minutes followed by the addition of solid ammonium chloride (5 g) to quench the reaction. The solution was warmed to room temperature to allow the ammonia to boil off. Water (10 mL) was added and mixture extracted with methylene chloride. The combined organic fractions were dried and evaporated to give a yellow oil (0.372 g). A ^{1}H-nmr spectrum of the crude product showed that there were four products. The crude oil was chromatographed (30% ethyl acetate/hexane) to afford fraction 1 (102 mg, 33%), fraction 2 (73 mg, 13%) and fraction 3. The ^{1}H-nmr ($CDDCl_3$)δ of fraction 1, a pure product (**A**): 1.32 (t, 3H, J=7.1), 3.48(d, 1H, J=2.3), 3.82 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 3.91 (d, 1H, J=2.3), 4.24 (q, 2H, J=7.1), 5.94_5 (d, 1H, J=5.2), 5.94_0 (d, 1H, J=5.2), 6.52(s, 2H), 6.74 (s, 1H), 6.80(s, 1H), was identical to the *trans*-diastereomer **126** reported in the literature,[18] major product (**B**) from fraction 2 which contained 20% of another compound: 0.81 (t, 3H, J=7.2), 3.74 (q, 2H, J=7.2), 3.79 (s, 6H), 3.80 (s, 3H), 4.48 (d, 1H, J=5.8), 4.85 (d, 1H, J=5.8), 5.94 (d, 1H, J=1.3), 5.97 (d, 1H, J=1.3), 6.40 (s, 2H), 6.70(s, 1H), 6.79 (s, 1H), was identical to that the *cis*-diastereomer **126** reported in the literature.[18] The ^{1}H-nmr spectrum of fraction 3 showed a mixture of two products. No further purification or characterization was undertaken for these by-products (fraction 3).

Hydrolysis of the ester **126**

Both ester **A** (102 mg) and ester **B** (73 mg) were hydrolysed separately using the same procedure. The ester was dissolved in DMSO (2 mL) and 50% sodium hydroxide (2 mL) added. The solution was stirred at room temperature for 1 hour and then acidified with concentrated hydrochloric acid at 0°C. The mixture was diluted with ethyl acetate (20 mL) and then washed with 10% hydrochloric acid. The organic phase was dried and evaporated to

give a light yellow oil **A'** (0.08 g, 85%) and **B'** (0.058 g, ca 86%). ^{1}H-nmr ($CDCl_3$)δ of **A'**: 3.82 (s, 6H), 3.83 (s, 3H), 3.94 (d, 1H, J=2.2), 4.70 (d, 1H, J=2.2), 5.92 (d, 1H, J=1.0), 5.97 (d, 1H, J=1.0), 6.50 (s, 2H), 6,72 (s, 1H), 6.79 (s, 1H), identical to the trans diastereomer **127** reported in the literature.[18] The ^{1}H-nmr spectrum of **B'** was the same as **A'**.

Decarboxylation of acid **127**

The acid **127** (0.072 g, 0.2 mmol) in dry THF (8 mL) and redistilled acetic acid (2 mL) was immersed in a water bath. Lead tetraacetate (99%, 1.1 equivalent) was added as a solid under nitrogen. The mixture was stirred for 4 hours at room temperature. Following the reaction, water (10 mL) was added. The resulting red aqueous solution was extracted with sodium bicarbonate (5%). Drying and evaporation gave an oil which was chromatographed (ethyl acetate:hexane/3:7) to give two fractions. Fraction 1 (18 mg, 24%), ^{1}H-nmr ($CDCl_3$)δ: 2.14 (s, 3H), 3.83 (s, 6H), 3.84 (s, 3H), 4.40 (broad s), 5.47 (d, 1H, J=1.4), 5.94 (d, 1H, J=1.3), 5.97 (d, 1H, J=1.3), 6.47 (s, 2H), 6.72 (, 1H), 6.85 (s, 1H), was identical to that of compound **66** reported in the literature.[18] Fraction 2 (34 mg), ^{1}H-nmr ($CDCl_3$)δ: 2.04 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 3.82-3.84 (m, 18H), 4.44 (bs, 1H), 4.45 (bs, 1H), 5.51 (d, 1H, J=1.4 Hz), 5.53 (d, 1H, J=1.4 Hz), 6.46 (s, 2H), 6.49 (s, 2H), 6.88_2 (s, 1H), 6.88_4 (s, 1H), 7.01 (s, 1H), 7.02 (s, 1H), 7.69_7 (s, 1H), 7.70_4 (s, 1H).

Cycloaddition reaction of benzocyclobutanol **17** *with mono(methyl (S)-lactyl) fumarate* **88**

Methanolic hydrochloric acid (25%) was prepared by adding acetyl chloride (0.5 mL) to methanol (1.5 mL) cooled in a ice bath. Acetate **66** (12 mg, 0.032 mmol) in methylene chloride (1.5 mL) was added to the above solution. The solution was stirred for 4 hours between -8°C and -5°C followed by dilution with methylene chloride (10 mL, -5°C) and washing with ice-water until neutral. The organic phase was dried with sodium sulfate (-5°C). The methylene chloride solution was evaporated to 0.5 mL under high vacuum at -4°C. Mono(methyl (S)-lactyl) fumarate **88** (67 mg, 0.2 mmol) in toluene (1 mL) was added

and evaporation at high vacuum continued in order to remove the remaining methylene chloride. The resulting solution was stirred for 30 hours at room temperature. The toluene was evaporated to give a colourless oil. The ^{1}H-nmr spectrum of the crude product exhibited all peaks of mono(methyl (S)-lactyl) fumarate **88** and acetate **66**, along with new doublets at 4.51 (J=5.4 Hz) and 4.89 (J=9.3 Hz) ppm. The ratio of the new doublets to the doublet of **66** is 1:1. An attempt to purify the mixture by chromatography (30% ethyl acetate/hexane), was unsuccessful as the compound appeared to bind irreversibly to the silica gel.

Fumarate of Methyl (S)-Mandelate **63**

This compound was provided by a co-worker.

Preparation of the benzocyclobutanol **17** *and it's cycloaddition reaction with fumarate of methyl (S)-mandelate* **63**

Redistilled acetyl chloride (0.5 mL) was added to dry methanol (2 mL) in an ice bath. The mixture was stirred for 10 minutes and recooled in a dry ice-carbon tetrachloride bath (-8°C to -15°C). Compound **66** (13 mg, 0.04 mmol) in methylene chloride (1.5 mL) was added to the above solution and stirred for 4 hours between -8° and -15°C. Methylene chloride (10 mL) was added to dilute the above solution (-5°C). The mixture was washed with ice-water until neutral. The organic phase was dried with sodium sulfate. All operations were carried out below -5°C.

The fumarate of methyl (S)-mandelate **63** (68 mg, 0.2 mmol) in toluene (5 mL) was added to the above solution and evaporation at high vacuum continued at -5°C in order to remove the remaining methylene chloride. The remaining solution (approximately 3 mL in volume) was stirred for 24 hours at room temperature. Toluene was evaporated to give a pale yellow oil (85 mg). Chromatography of the oil (30% ethyl acetate/hexane) gave two fractions. Fraction 1 (59 mg), a colourless oil, was identical to the starting material, the fumarate of methyl (S)-mandelate **63**. Fraction 2 (10 mg) was a pale yellow solid, mp 95-97°C. ^{1}H-nmr

($CDCl_3$)δ: 3.41 (dd, 1H, J=9.4, 12.4), 3.56 (s, 3H), 3.61 (dd, 1H, J=5.8, 12.4), 3.62 (s, 6H), 3.66 (s, 3H), 3.78 (s, 3H), 4.49 (d, 1H, J=5.8), 4.71 (bs, 1H, OH), 4.95 (d, 1H, J=9.4), 5.55 (s, 1H), 5.92 (s, 2H), 6.16 (s, 2H), 6.22 (s, 1H), 6.38 (s, 1H), 6.95-7.45 (m, 10H), was identical to that reported in literature.[17] Mass spectra *m/e* (rel.%): 742 (0.2), 577 (0.4), 576 (1.2), 530 (0.4), 408 (8.6), 393 (3.8), 365 (3), 86 (100).

Attempt to improve the synthesis of 17

2-Bromo-4,5-methylenedioxy-β-nitrostyrene **134**

At room temperature, nitromethane (15 mL, 277 mmol) was added to a suspension of sodium hydroxide (5 g, 125 mmol) in water (20 mL). Bromopiperonal (1.8 g, 7.9 mmol) in nitromethane (10 mL) was added dropwise to this solution and the mixture was stirred for 1.5 hours at room temperature. TLC showed the disappearance of starting materials. The solution was partially evaporated and diluted with ethyl acetate (50 mL). The ethyl acetate was separated, washed with 10% aqueous hydrochloric acid, dried and evaporated to give a colourless oil which was refluxed with TsOH (30 mg) in benzene (50 mL) for 26 hours. After the evaporation of the benzene, the remaining yellow solid was purified by chromatography (20% ethyl acetate/hexane) to give a yellow solid (0.886 g, 43%), mp 141-143°C. IR (CH_2Cl_2): 1631, 1621, 1519, 1506 cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 6.08 (s, 2H, CH_2), 7.00 (s, 1H, aromatic), 7.12 (s, 1H, aromatic), 7.43 (d, 1H, J=13.5, CH), 8.36 (d, 1H, J=13.5, CH). ^{13}C-nmr ($CDCl_3$)δ: 102.7 (CH_2), 106.6 (CH), 113.2(CH), 119.9(C), 123.2 (C), 137.2(CH), 137.6 (CH), 148.2 (C), 151.6 (C). Mass spectrum *m/e* (rel.%): 273 (34), 271 (35), 226 (31), 224 (30), 162 (65), 161 (49), 146 (76),145 (15), 55 (100), 53 (24); high resolution mass calculated for $C_9H_6O_4N^{81}Br$ 272.9460, found 272.9470.

1-(3',4',5'-Trimethoxyphenyl)-1-(2"-bromo-4",5"-methylenedioxyphenyl)-2-nitroethane **135**

To a solution of 3,4,5-trimethoxybromobenzene (0.922 g, 3.73 mmol) in dry THF was added butyllithium (1.62 M in hexane, 2.3 mL, 3.7 mmol) at -78°C. After 2 minutes, dry cuprous bromide (0.60 g, 4.2 mmol) in THF containing dimethyl sulfide (DMS) (2 mL) was added. The resulting dark blue solution was warmed to -30°C followed by addition of 2-bromo-4,5-methylenedioxy-β-nitrostyrene (0.6 g, 2.2 mmol) in THF (8 mL). The solution was stirred at -30°C for half an hour and then at room temperature for 2 hours. Saturated aqueous ammonium chloride (15 mL) was added and the aqueous layer extracted with ethyl acetate. The combined organic fractions were dried and evaporated to give a pale yellow oil which was chromatographed (30% ethyl acetate/hexane) to afford a colourless solid (0.594 g, 61%), mp 121-123°C. IR (CH_2Cl_2): 1594, 1557 cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 3.82 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 4.87 (d, 2H, J=8.2, CH_2), 5.31 (t, 1H, J=8.2, CH), 5.96 (s, 2H, CH_2), 6.46 (s, 2H, aromatic), 6.64 (s, 1H, aromatic), 7.04(s, 1H, aromatic). ^{13}C-nmr ($CDCl_3$)δ: 47.6 (CH), 56.3 (CH_3), 60.8 (CH_3), 77.5 (CH_2), 102.1 (CH_2), 105.0 (CH), 108.2 (CH), 113.4 (CH), 115.0 (C), 131.1 (C), 133,3 (C), 137.6 (C), 147.8 (C), 147.9 (C), 153.6 (C). Mass spectrum *m/e* (rel.%): 441 (25), 439 (24), 300 (23), 283 (50), 282 (100), 129 (77), 71 (51); high resolution mass calculated for $C_{18}H_{18}O_7N^{79}Br$ 439.0267, found 439.0270.

Attempted cyclization of compound **135**

Sodium (0.05 g, 2.17 mmol) was added to liquid ammonia (20 mL) at -78°C. After 5 minutes, a trace of ferric chloride was added. The mixture was warmed to -33°C for 10 minutes until the blue colour disappeared and a deep brown color formed. The solution was cooled again to -78°C and compound **135** (0.15 g, 0.34 mmol) in THF (3 mL) added all at once. After the mixture was stirred for another 10 minutes, ammonium chloride (2 g) was added portionwise. The dry-ice bath was removed and the excess ammonia boiled off. Water (10 mL) was added and solution acidified to pH 2. The aqueous layer was extracted with methylene chloride. The combined organic phases were dried and evaporated to give an oil. The ^{1}H-nmr spectrum of the crude product was identical to that of the starting material

135. After chromatography (30% ethyl acetate/hexane), only the starting material was recovered (0.069 g).

Ethyl 2-bromo-4,5-methylenedioxycinnamate **136**

Ethyl 2-diethylphosphonoacetate was prepared by refluxing ethyl bromoacetate (8 mL, 71 mmol) and triethylphosphite (12.6 mL, 71 mmol) for 1 hour. The solution was distilled at 0.08 mm Hg to give two fractions. Fraction 1: 40 to 50°C (2 g), fraction 2: 80 to 85°C (10 g, 63%). The ^{1}H-nmr spectrum of the fraction 2 was consistant with that of ethyl 2-diethylphosphonoacetate.

Ethyl 2-diethylphosphonoacetate (3 g, 13.4 mmol) in ether (20 mL) was added to a stirred suspension of sodium hydride (57% in oil, 2 g, 47.5 mmol) in anhydrous ether (15 mL) at room temperature. The evolution of hydrogen stopped after 20 minutes and bromopiperonal (1.5 g, 5.5 mmol) in ether (20 mL) was added in one portion. After stirring 1 hour, water (10 mL) was added to destroy excess sodium hydride. More ether (20 mL) was added and the phases separated. The organic phase was dried and evaporated to give a colourless oil which was purified by chromatography (20% ethyl acetate/hexane) to afford a colourless solid (0.83 g, 51%), mp 110-111°C. IR (CH_2Cl_2): 1710, 1700 cm^{-1}. ^{1}H-nmr ($CDCl_3$)δ: 1.34 (t, 3H, J=7.2, CH_3), 4.27 (q, 2H, J=7.1, OCH_2), 6.02 (s, 2H, CH_2), 6.24 (d, 1H, J=16, CH), 7.05 (s, 1H), 7.06(s, 1H), 7.98 (d, 1H, J=16, CH). ^{13}C-nmr ($CDCl_3$)δ: 14.3 (CH_3), 60.6 (CH_2), 102.2 (CH_2), 106.4 (CH), 113.1 (CH), 117.7 (C), 119.1 (CH), 127.7 (C), 142.6 (CH), 147.9 (C), 149.9 (), 166.5 (). Mass spectrum *m/e* (rel.%): 300 (10), 298 (8), 219 (36), 191 (100), 189 (5), high resolution mass calculated for $C_{12}H_{11}O_4{}^{81}Br$ 299.9820, found 299.9842.

Ethyl α-carbethoxy-2-bromo-4,5-methylenedioxycinnamate **137**

Bromopiperonal (0.7 g, 3.06 mmol), diethyl malonate (0.464 g, 3.06 mmol) and piperidine (0.1 mL) in toluene (40 mL) were refluxed for 24 hours using a Dean-Stark trap to remove water. Toluene was evaporated to give a pale yellow oil which was dissolved in ether (30

mL) and washed with 10% aqueous hydrochloric acid. The ether solution was dried and evaporated to give a colourless oil which was chromatographed (30% ethyl acetate/hexane) to afford two fractions. The ^{1}H-nmr spectrum and melting point of fraction **1** (0.26 g) were identical to those of bromopiperonal. Fraction 2 (0.375 g, 53%): mp 54-55.5°C. ^{1}H-nmr ($CDCl_3$)δ: 1.28 (t, 3H, J=7.1, CH_3), 1.33 (t, 3H, J=6.9, CH_3), 4.30 (q, 2H, J=7.2, CH_2), 4.31 (q, 2H, J=7.1, CH_2), 6.00 (s, 2H, CH_2), 6.93 (s, 1H, aromatic), 7.05 (s, 1H, aromatic), 7.90(s, 1H, CH). ^{13}C-nmr ($CDCl_3$)δ: 13.9 (CH_3), 14.1 (CH_3), 61.7 (CH_2+CH_2), 102.3 (CH_2), 108.5 (CH), 113.2 (CH), 117.6 (C), 126.5 (C), 127.1 (C), 141.0 (CH), 147.5 (C), 149.9 (), 163.8 (C), 166.0 (C). The ^{1}H-nmr spectrum was identical to that reported in the literature.[49]

Compound **138**

3,4,5-Trimethoxyphenylbromide (0.2 g, 0.8 mmol) in THF (6 mL) was cooled in a dry-ice/acetone bath. Butyllithium (1.62 M in hexane, 0.5 mL, 0.81 mmol) was added to the above solution. After 1 minute, cuprous bromide (0.065 g, 0.45 mmol) in dimethyl sulfide was added, resulting in a red solution. After 10 minutes, compound **137** (0.12 g, 0.3 mmol) in THF (4 mL) was added. The mixture was stirred for 30 minutes at -78°C, and then for 1 hour at room temperature. Saturated ammonium chloride was added and the aqueous solution extracted with methylene chloride. Drying and evaporation of the organic phase gave an oil. The oil was purified by chromatography (30% ethyl acetate/hexane) to yield a colourless oil (0.135g, 78%). ^{1}H-nmr ($CDCl_3$)δ: 1.07 (t, 3H, J=7.1), 1.11 (t, 3H, J=7.1), 3.78 (s, 3H), 3.83 (s, 6H), 4.05 (q, 2H, J=7.1), 4.06 (q, 2H, J=7.1), 4.22 (d, 1H, J=12.2), 5.23 (d, 1H, J=12.2), 5.92 (d, 1H, J=1.3), 5.95 (d, 1H, J=1.3), 6.57 (s, 2H), 6.85 (s, 1H), 6.99 (s, 1H). No further characterization was attempted.

Decarboxylation of **138**

A mixture of **138** (30 mg), dimethylsulfoxide (DMSO) (10 mL), water (0.1 mL), and a small quaulity of lithium chloride (about 1 mg) was refluxed for 3 hours. Ethyl acetate (20

mL) was added. After the DMSO was washed with water and the organic phase dried, evaporated, the resulted colourless oil showed the same Rf as **138**, and ^{1}H-nmr spectrum of the oil was identical to that of starting material **138**. No further experiments were carried out.

Synthesis of Compound **139**

Sodium bis-(trimethylsilyl)amide (0.865 g, 47 mmol) in THF (15 mL) was cooled to -78°C. Ethyl acetate (2 mL, 20 mmol) was added to the above solution over 2 minutes. After the addition, the solution was stirred another 1 minute and then ketone **121** (0.2 g, 0.5 mmol) in THF (8 mL) was added. The mixture was stirred at -78°C for 15 minutes, and then quenched by the addition of aqueous hydrochloric acid (10%, 10 mL). The aqueous solution was extracted with methylene chloride. The organic phase was dried and evaporated to give pale yellow oil. The oil was purified by chromatography (20% ethyl acetate/hexane) to give a pale yellow oil (0.221 g, 91%), IR (CH_2Cl_2): 3456 (bs, OH), 3077 (w, aromatic), 1720, 1713, 1603, 1513. ^{1}H-nmr ($CDCl_3$)δ: 1.20 (t, 3H, J=7.2 Hz), 3.37 (d, 1H, J=16Hz), 3.69 (d, 1H, J=16 Hz), 3.79 (s, 6H), 3.83 (s, 3H), 4.13_7 (q, 1H, J=7.2 Hz), 4.13_9 (q, 1H, J=7.2 Hz), 5.20 (s, 1H, OH), 5.99 (s, 2H), 6.55 (s, 2H), 6.99 (s, 1H), 7.34_3(s, 1H). ^{13}C-nmr ($CDCl_3$)δ: 14.0 (CH_3), 43.1 (CH_2), 56.2 ($2CH_3$), 60.8 (CH_3), 61.1 (CH_2), 101.9 (CH_2), 104.4 ($2CH_2$), 109.0 (CH), 112.4 (C), 114.9 (CH), 137.0 (C), 137.4 (C), 139.7 (2C), 147.1 (C), 147.5 (C), 152.7 (C), 172.9 (C). Mass spectrum *(m/e)*: 484 (M^+, 15), 482 (14) 397 (32), 395 (32), 385 (63), 229 (95), 227 (100), high resolution mass calculated for $C_{21}H_{23}O_8{}^{81}Br$ 484.0555, found 484.0536.

The improved synthesis of **125**

Trifluoroacetic acid (4 mL) and methylene chloride (2 mL) was cooled in a dry ice-carbon tetrachloride bath (-21°C). Sodium borohydride (100 mg, 2.6 mmol) was added portionwise, and then alcohol **139** (140 mg, 0.3 mmol) in methylene chloride (3 mL) was added dropwise. More sodium borohydride (200 mg) was added slowly to the resulting blue solution until the

blue had colour disappeared. Methylene chloride (15 mL) and water (10 mL) were added. After separation, the aqueous phase was extracted with methylene chloride. The combined organic phase was dried and evaporated to give a pale yellow oil which when recrystallized from ethanol gave pure product (74%). Melting point and ^{1}H-nmr were identical to that previously obtained.

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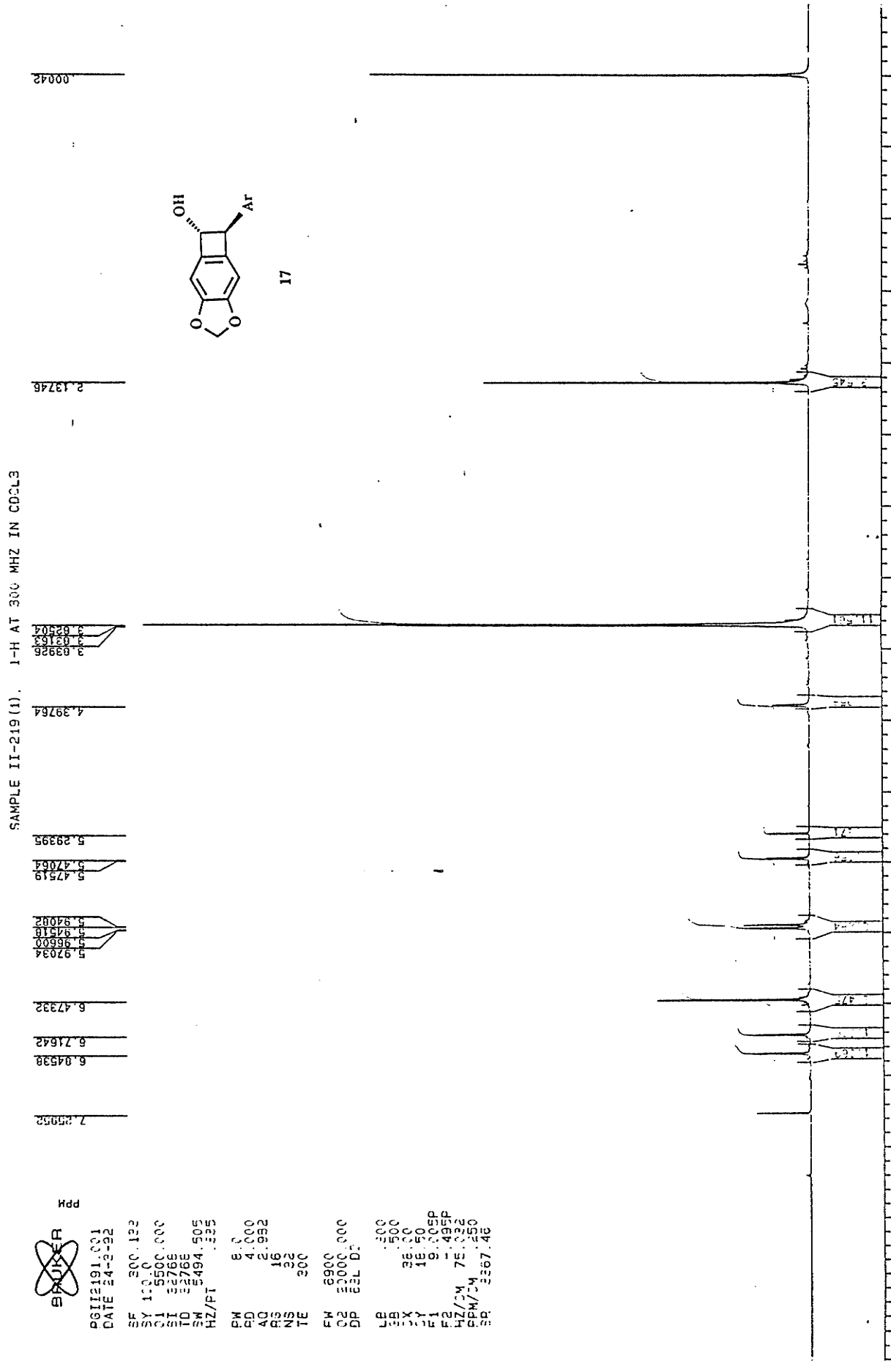
Appendix 1

^{1}H-nmr and ^{13}C-nmr spectra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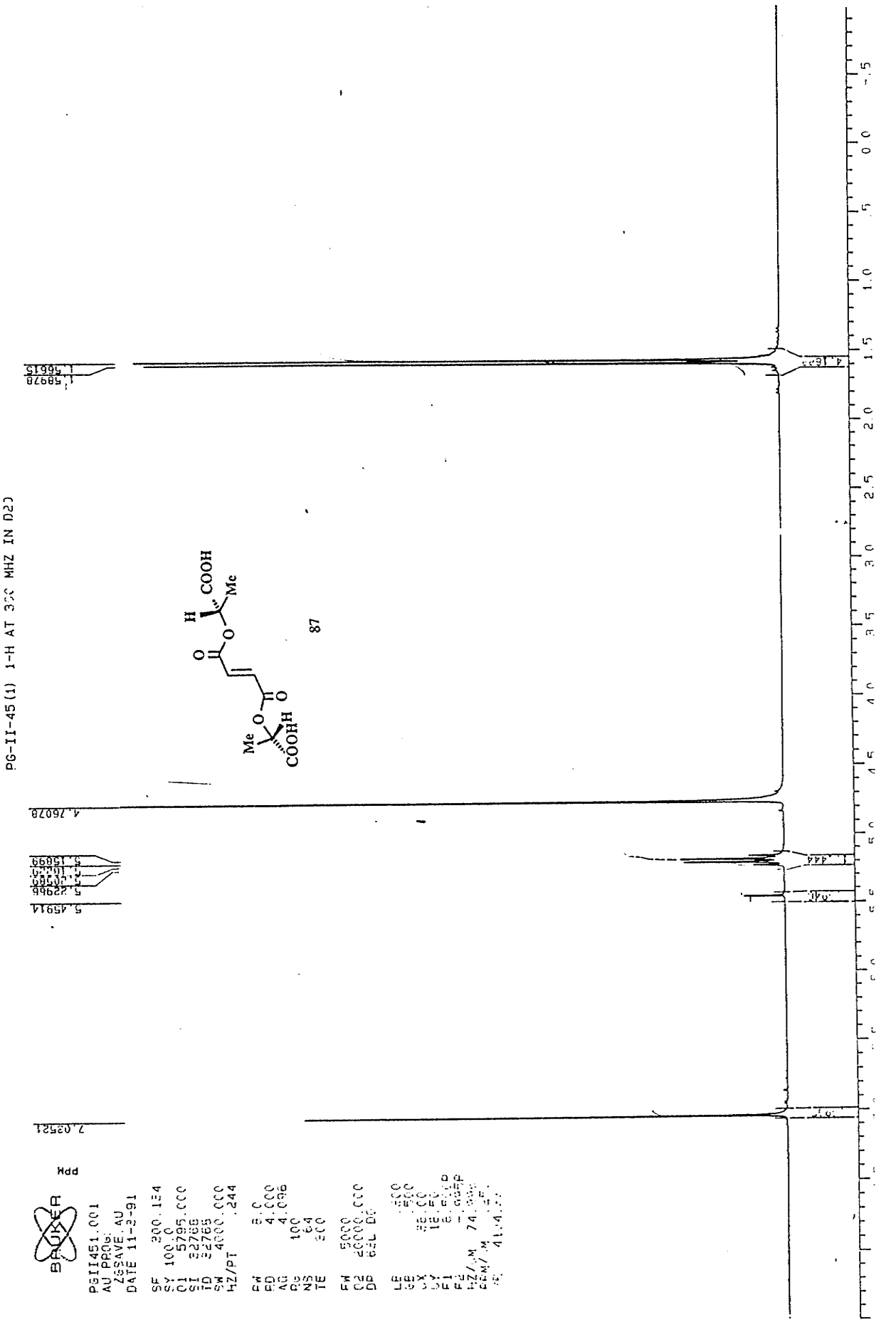
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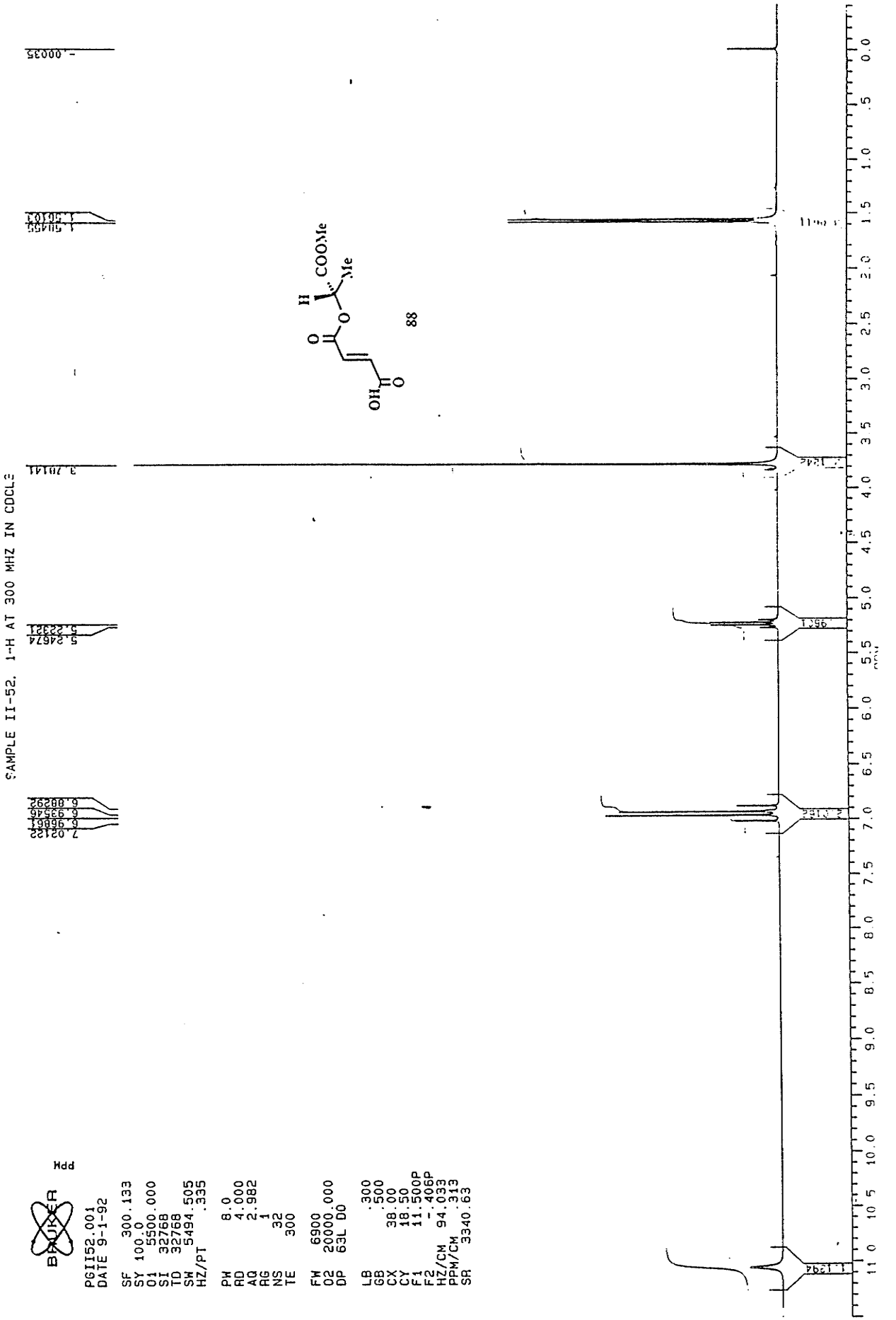
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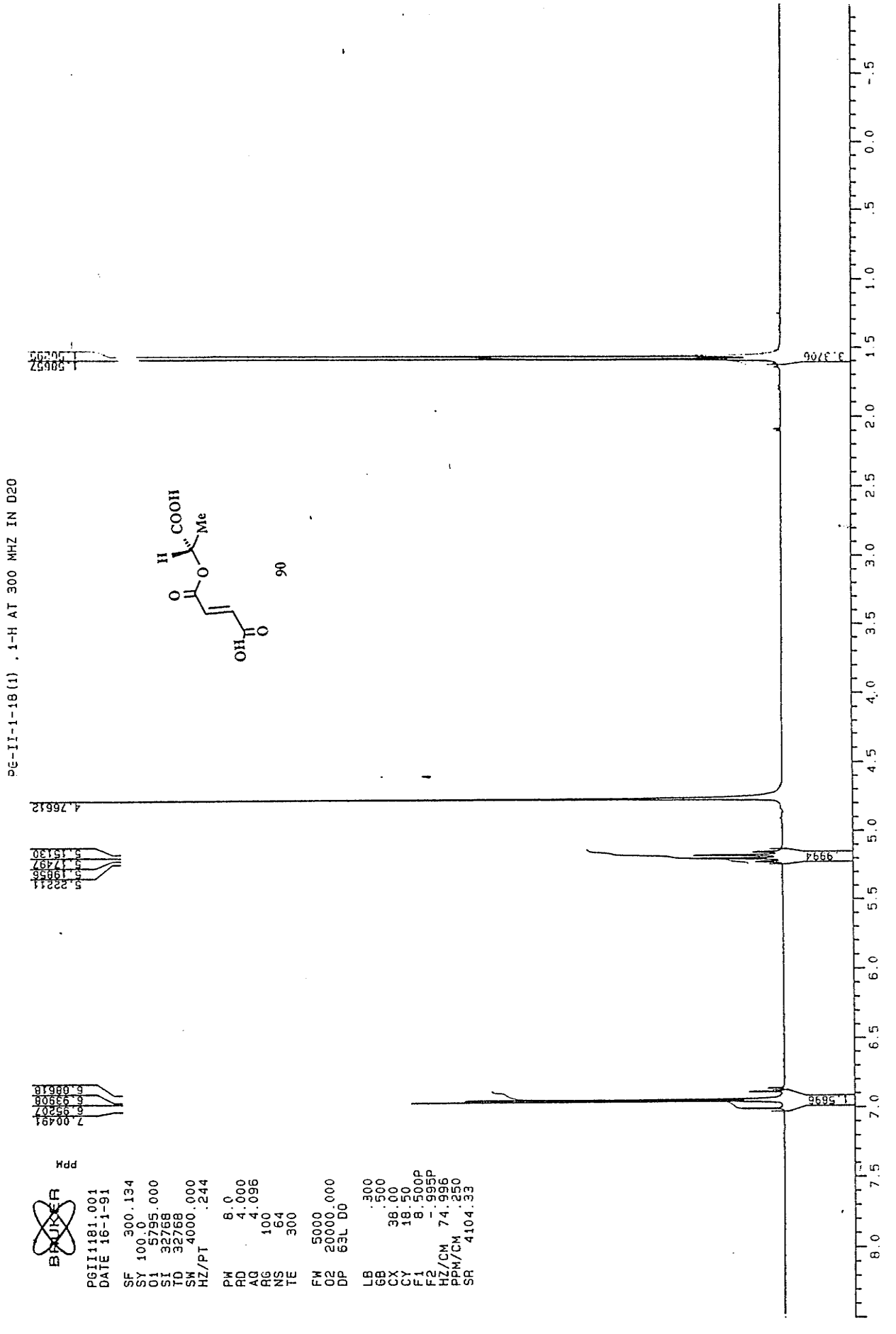
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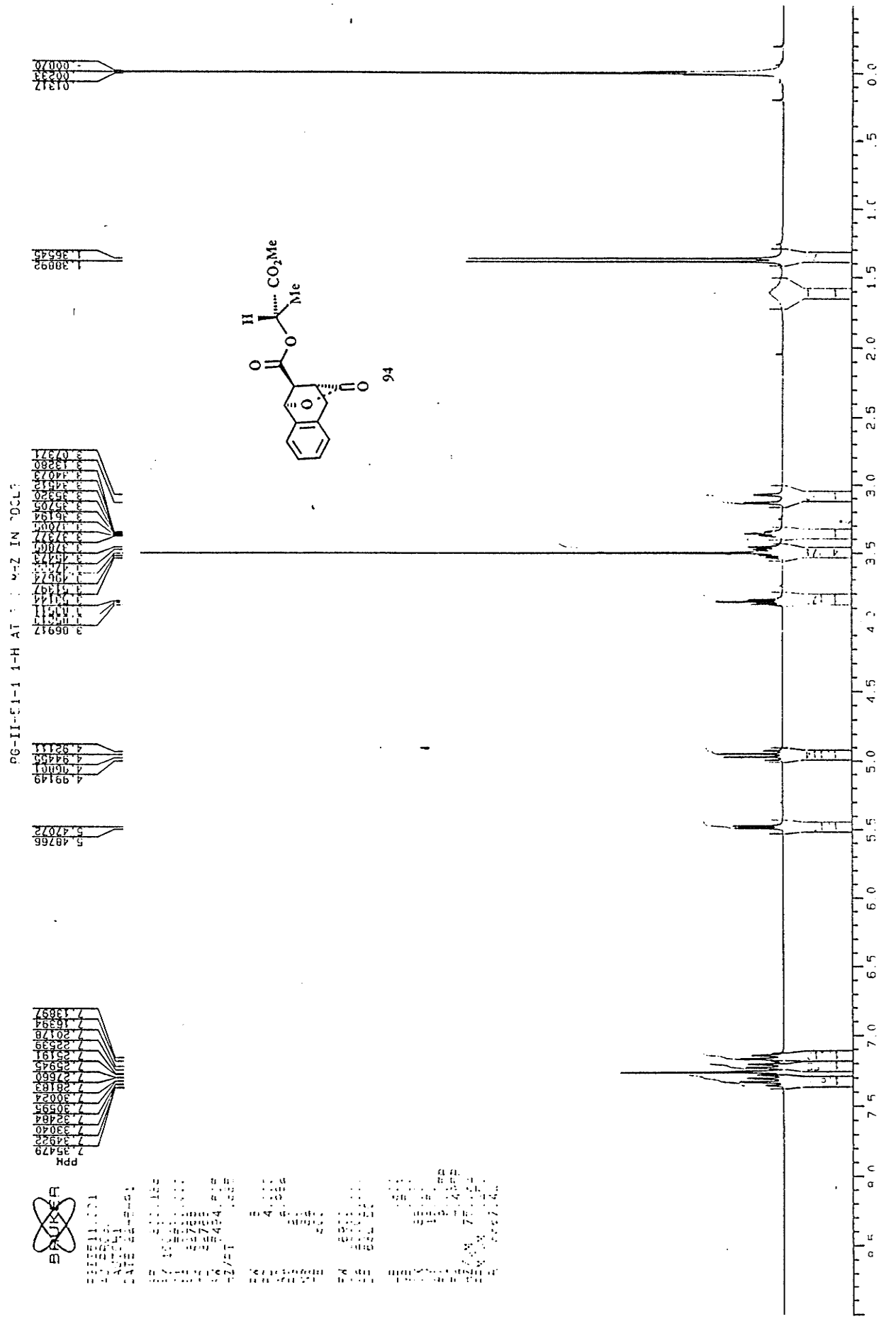
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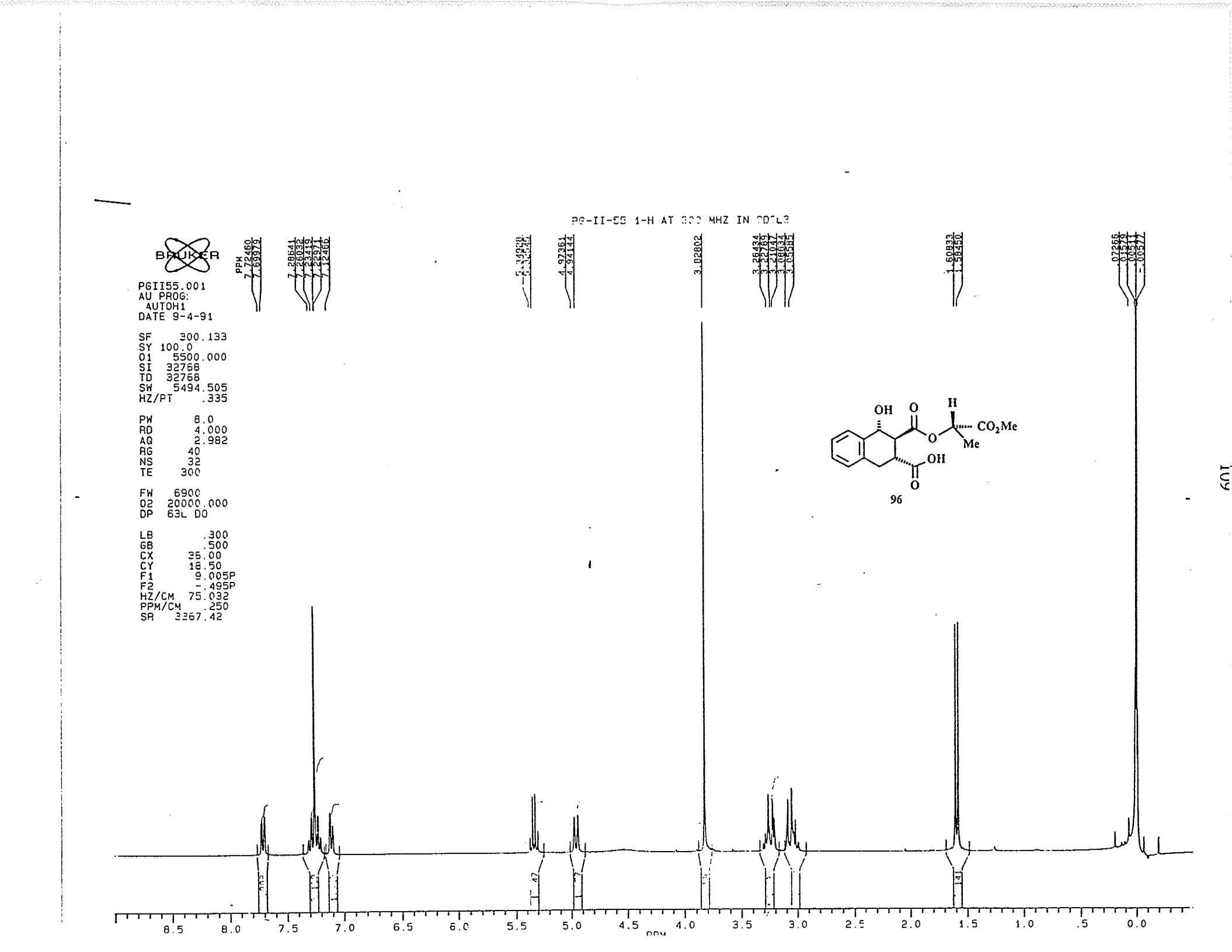
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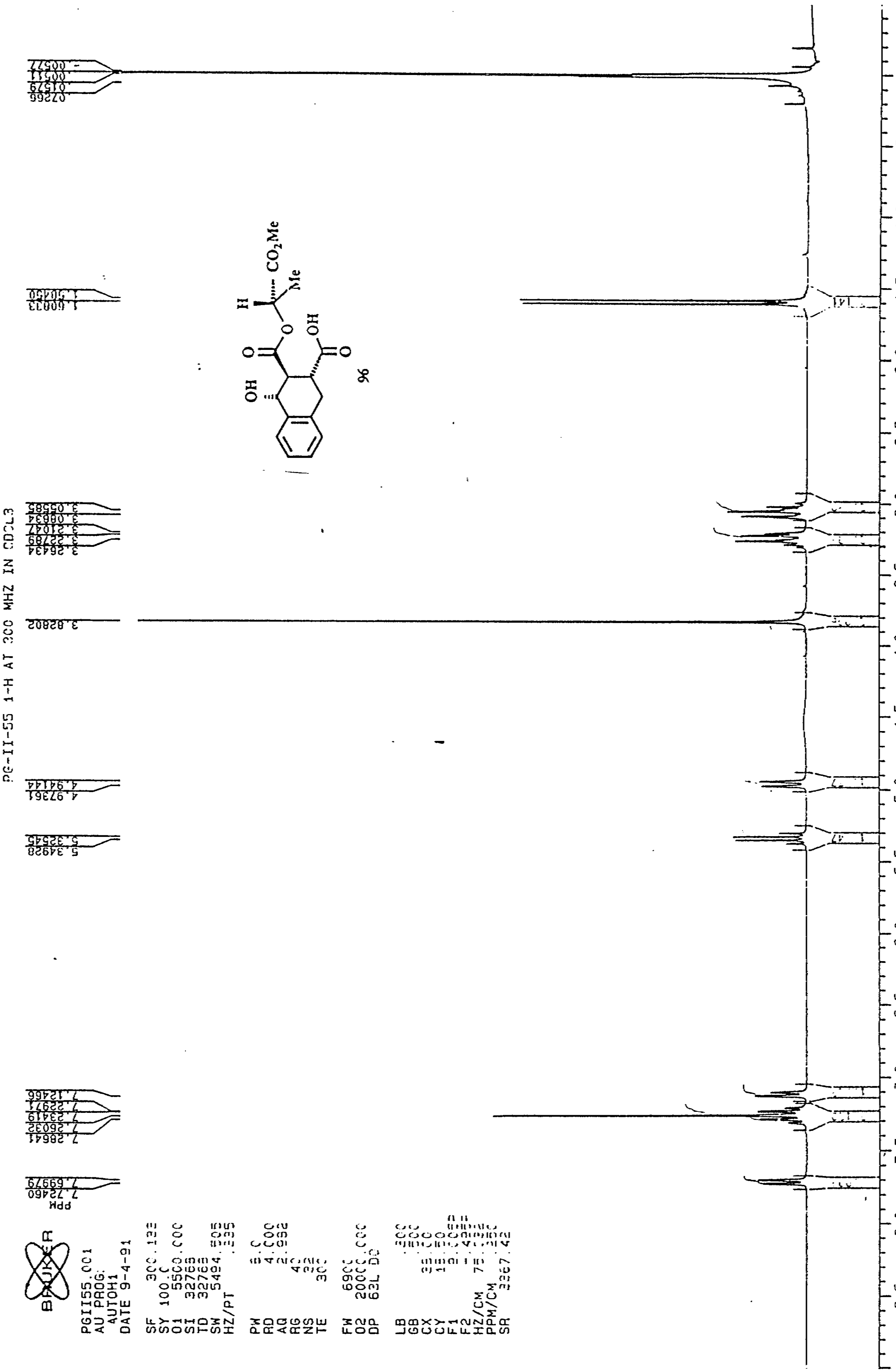
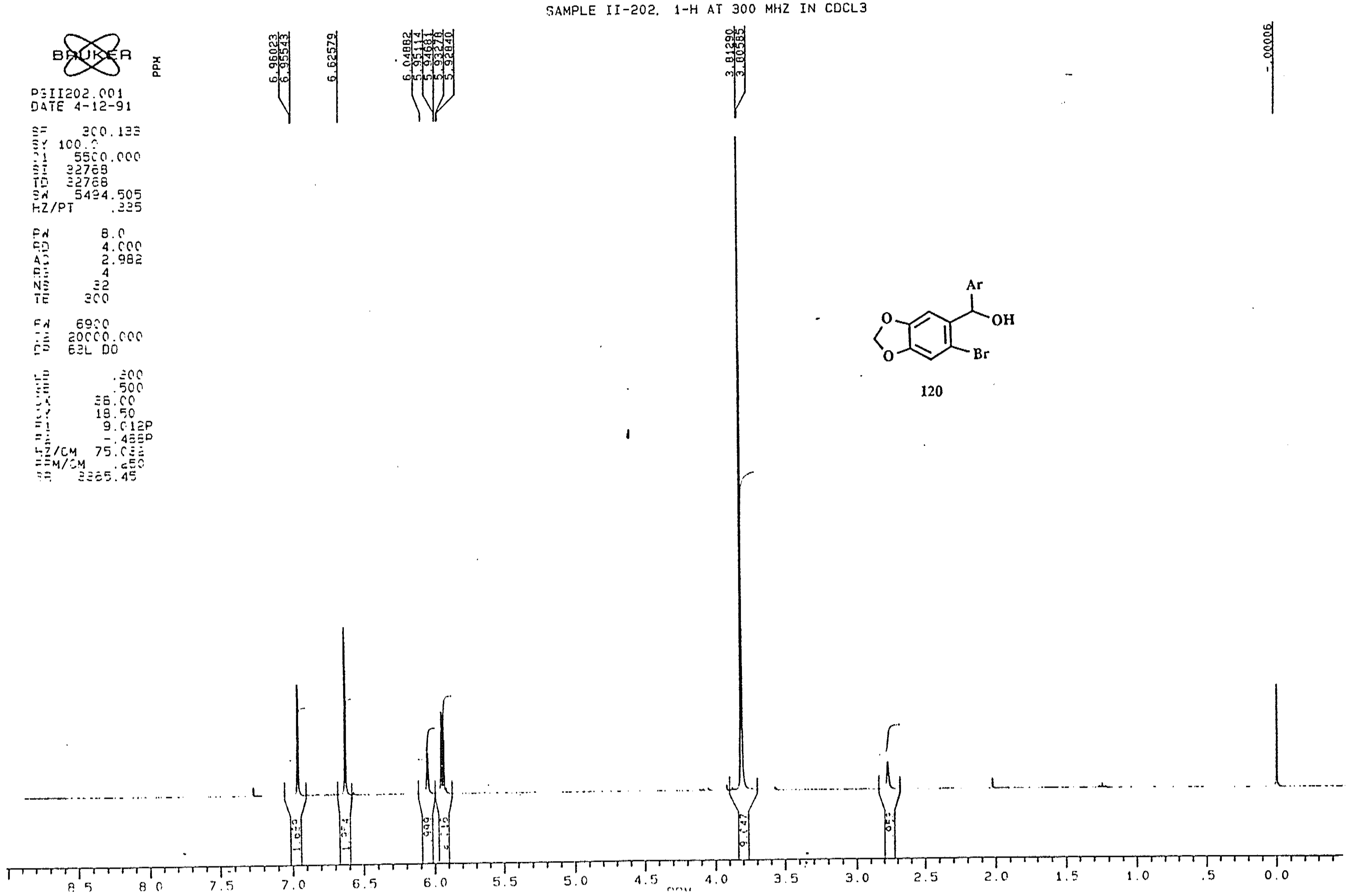
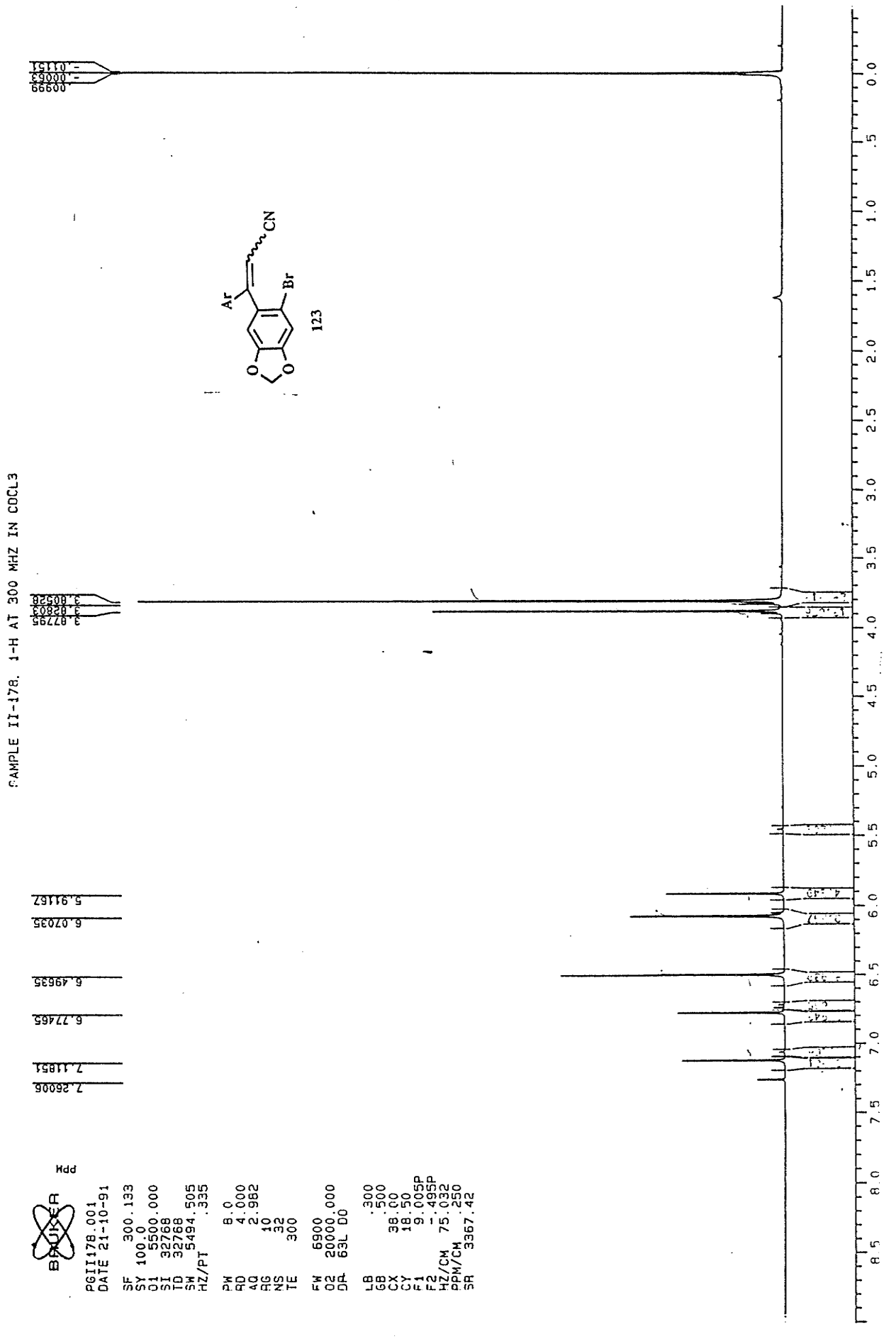
.5
0.0
PPM

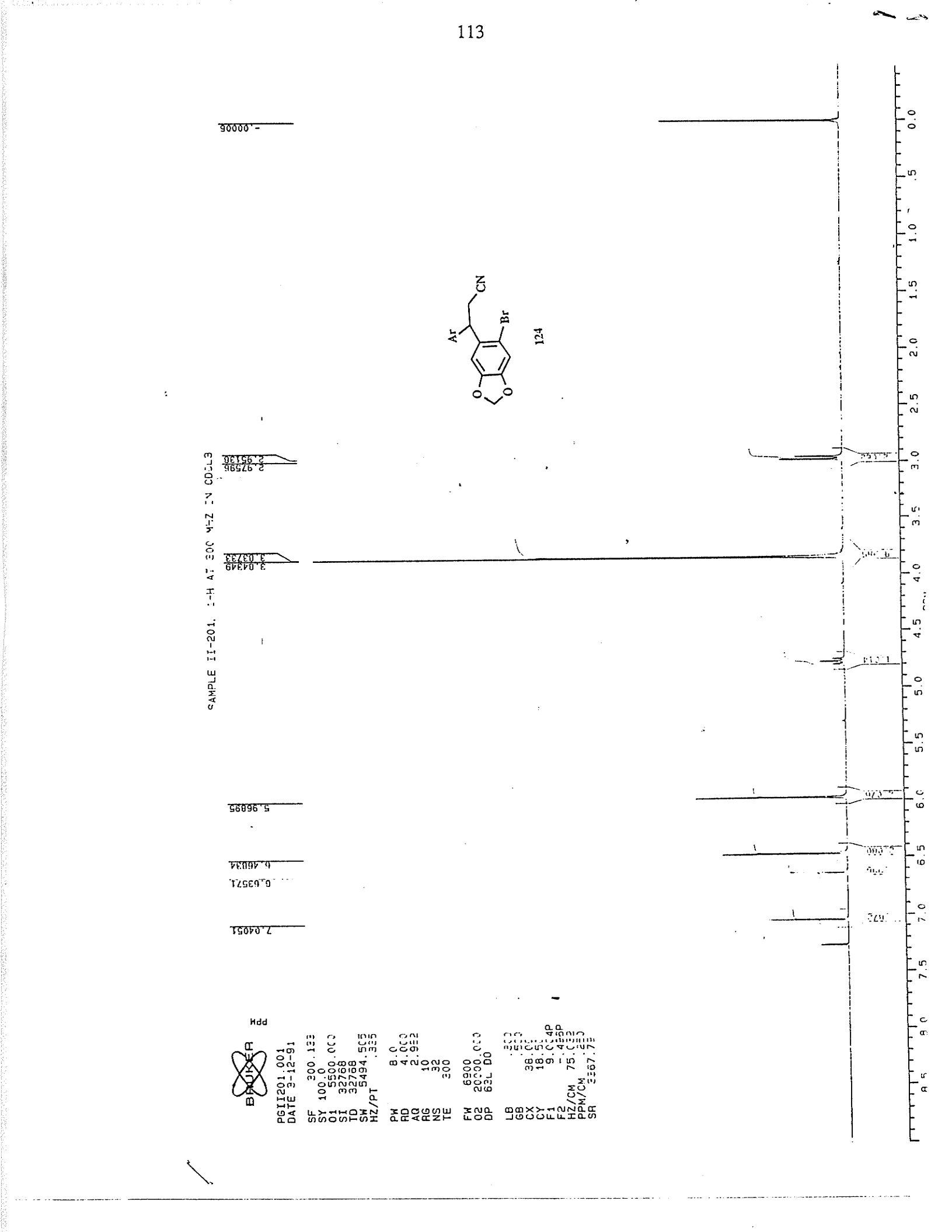

PG-II-55 1-H AT 300 MHZ IN CDCL3
PGII55.001
AU PROG:
AUTOH1
DATE 9-4-91
OH
O
H
CO2Me
Me
OH
O
96

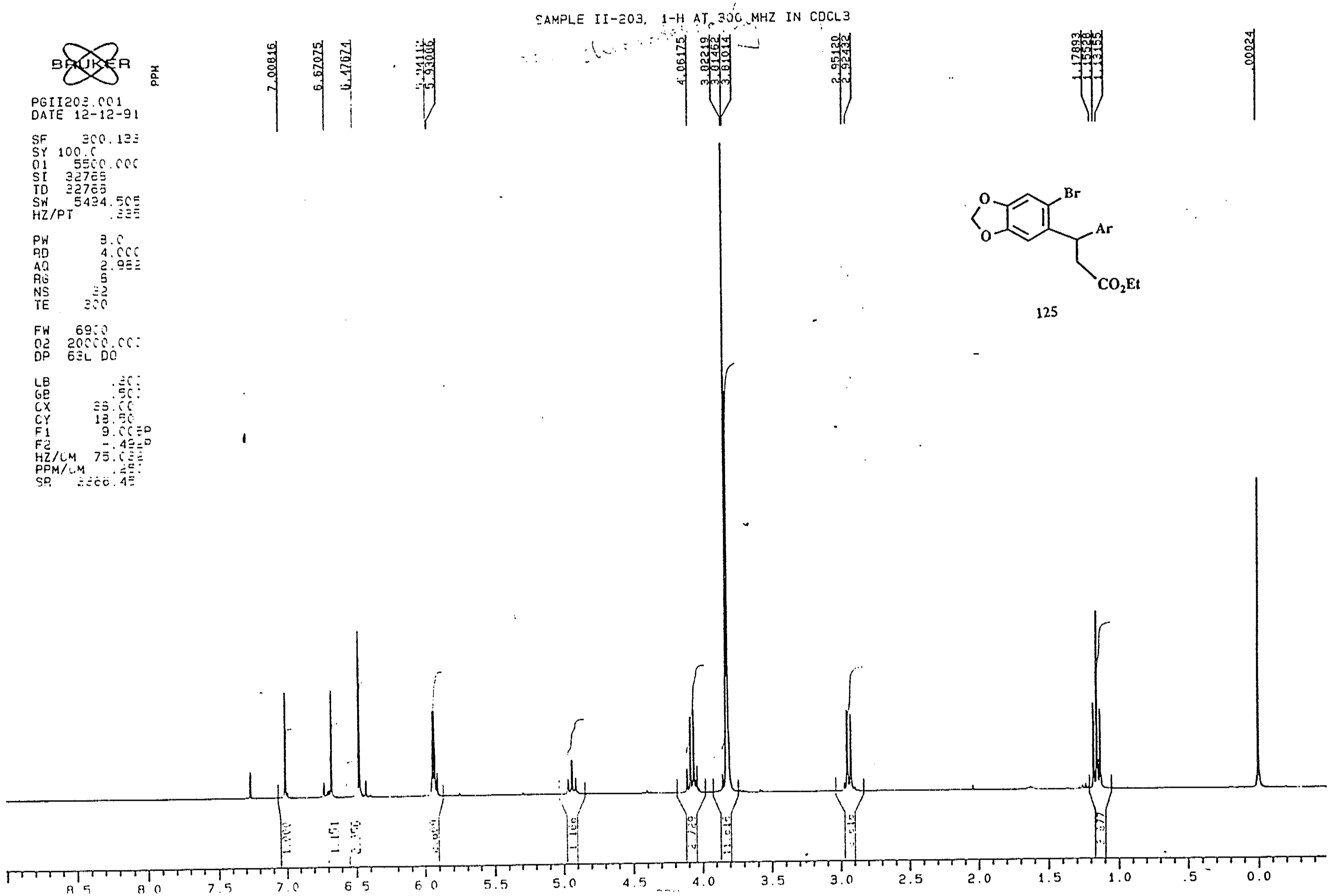
SAMPLE II-202, 1-H AT 300 MHZ IN CDCL3

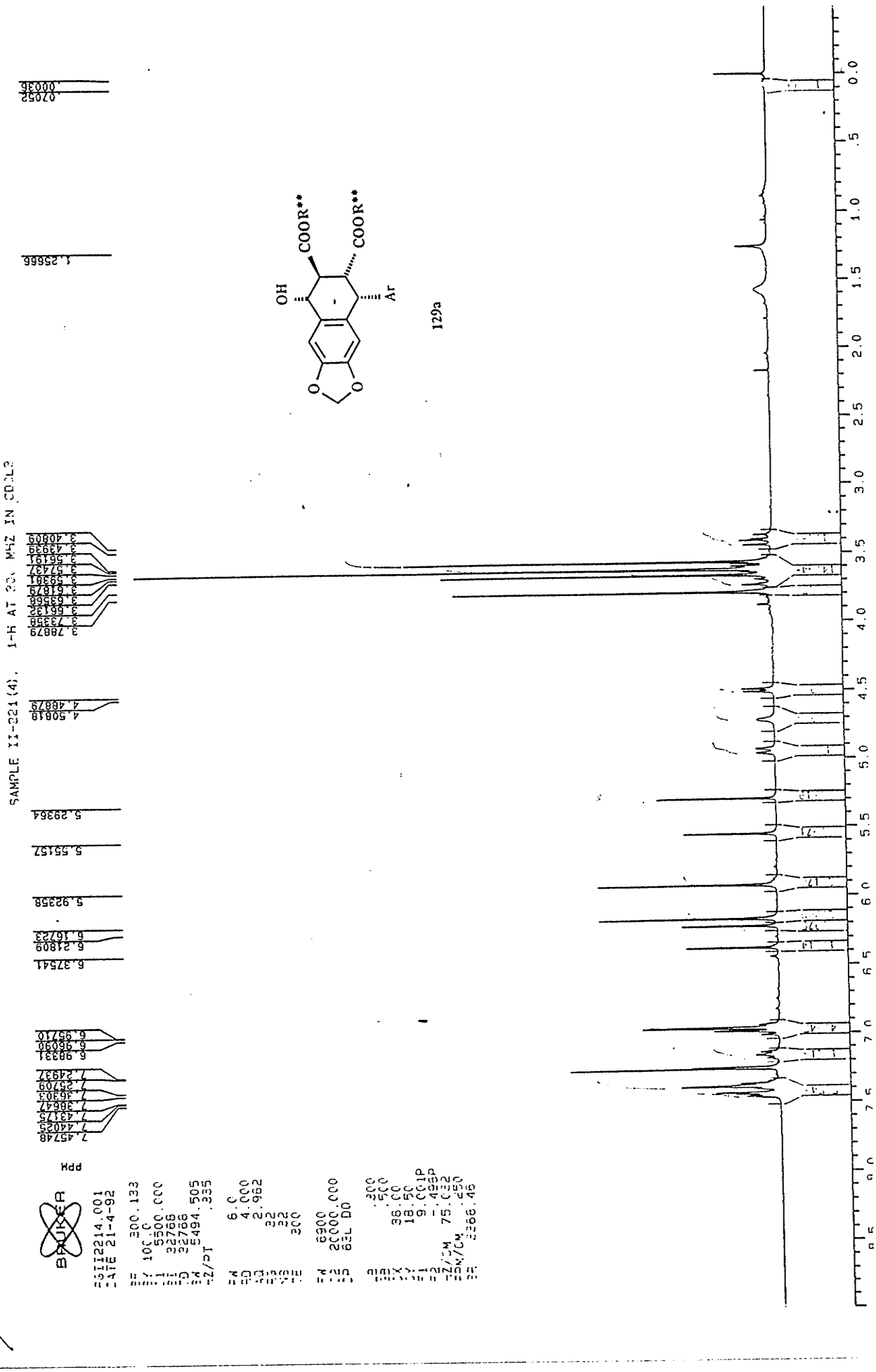


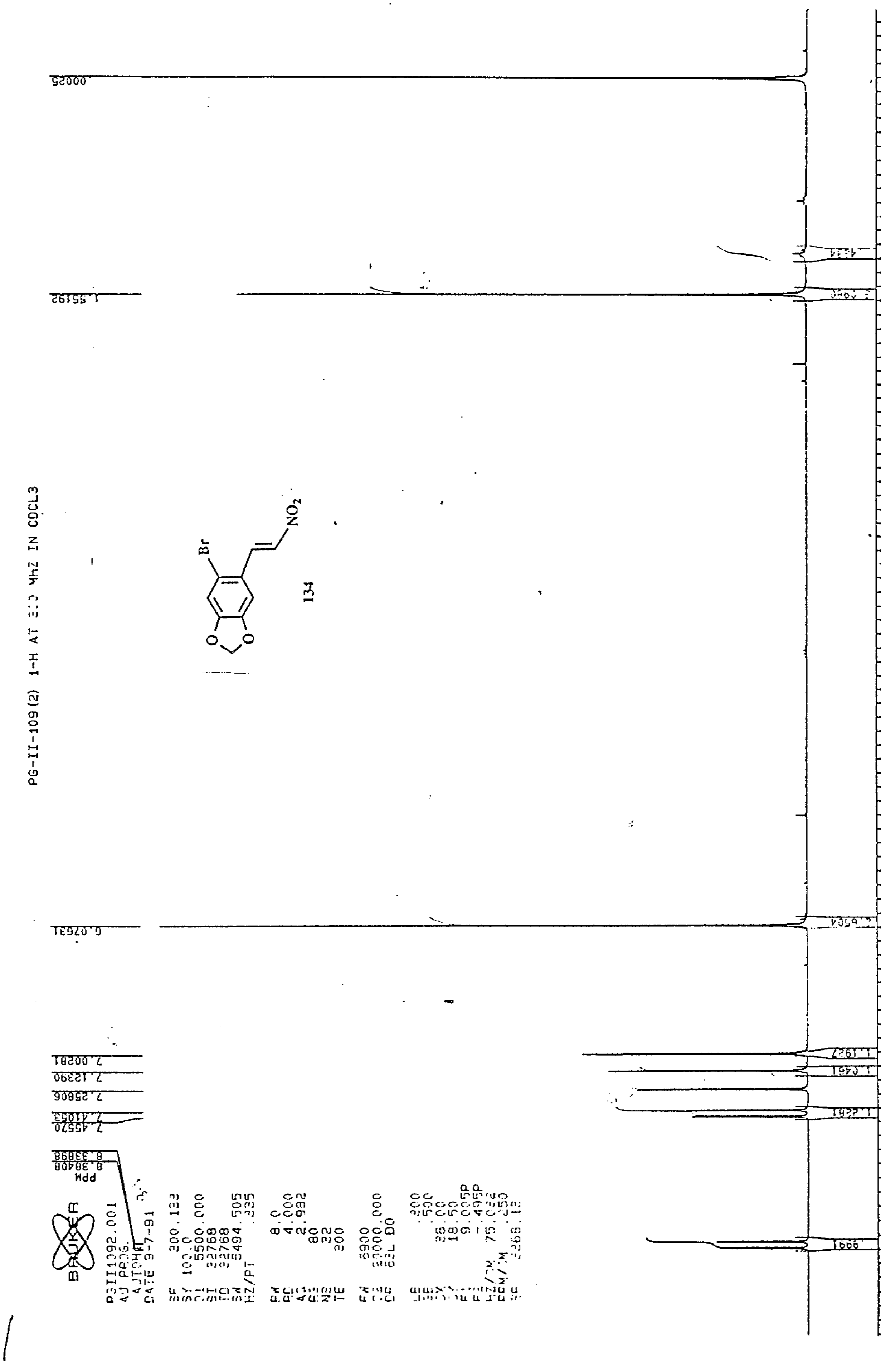
120

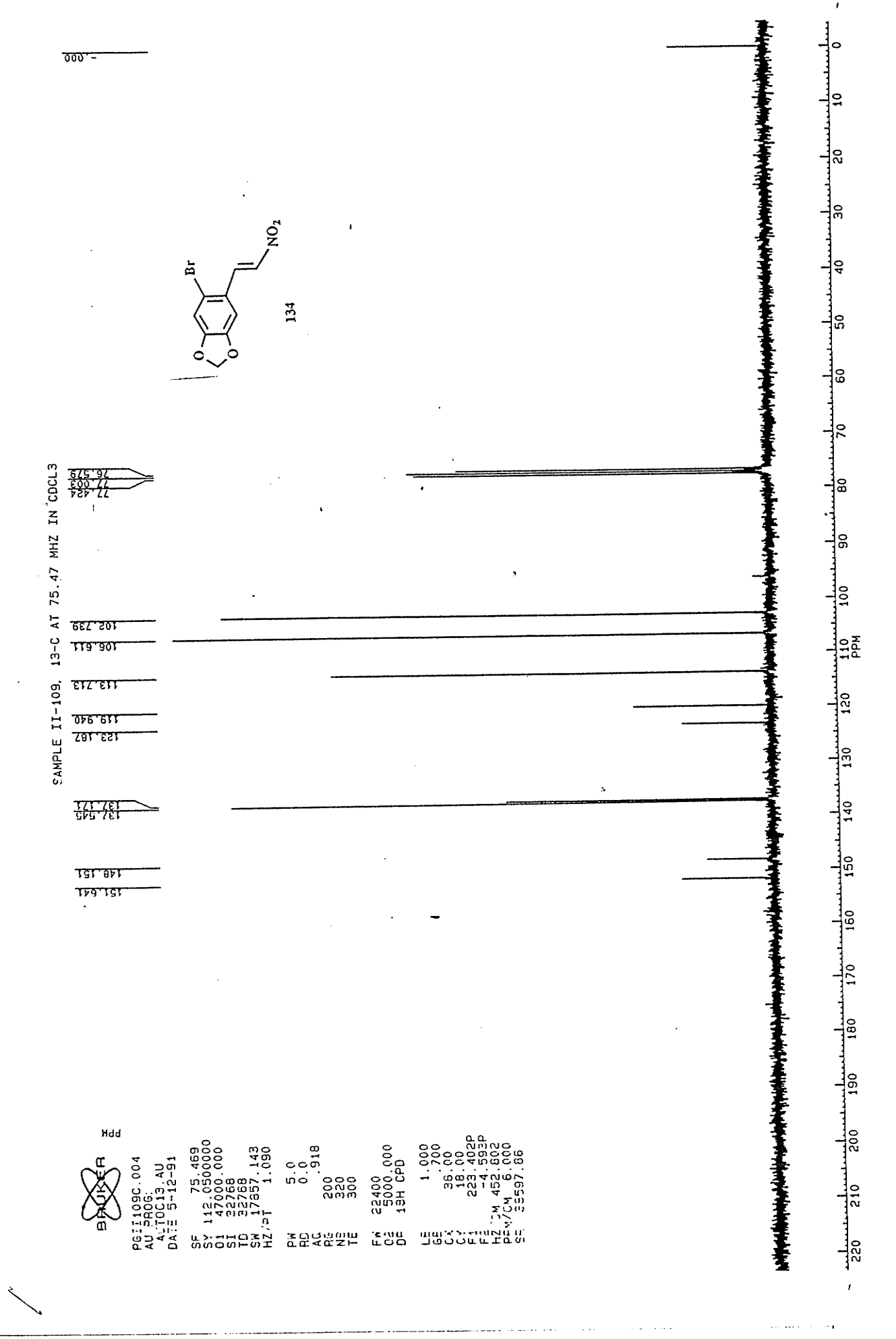

SAMPLE II-178. 1-H AT 300 MHZ IN CDCL3
PPM
PGII178.001
DATE 21-10-91
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DA 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.42
7.26006
7.11851
6.77465
6.49635
6.07035
5.91167
3.87795
3.82803
3.80528
Ar
Br
CN
O
O
123

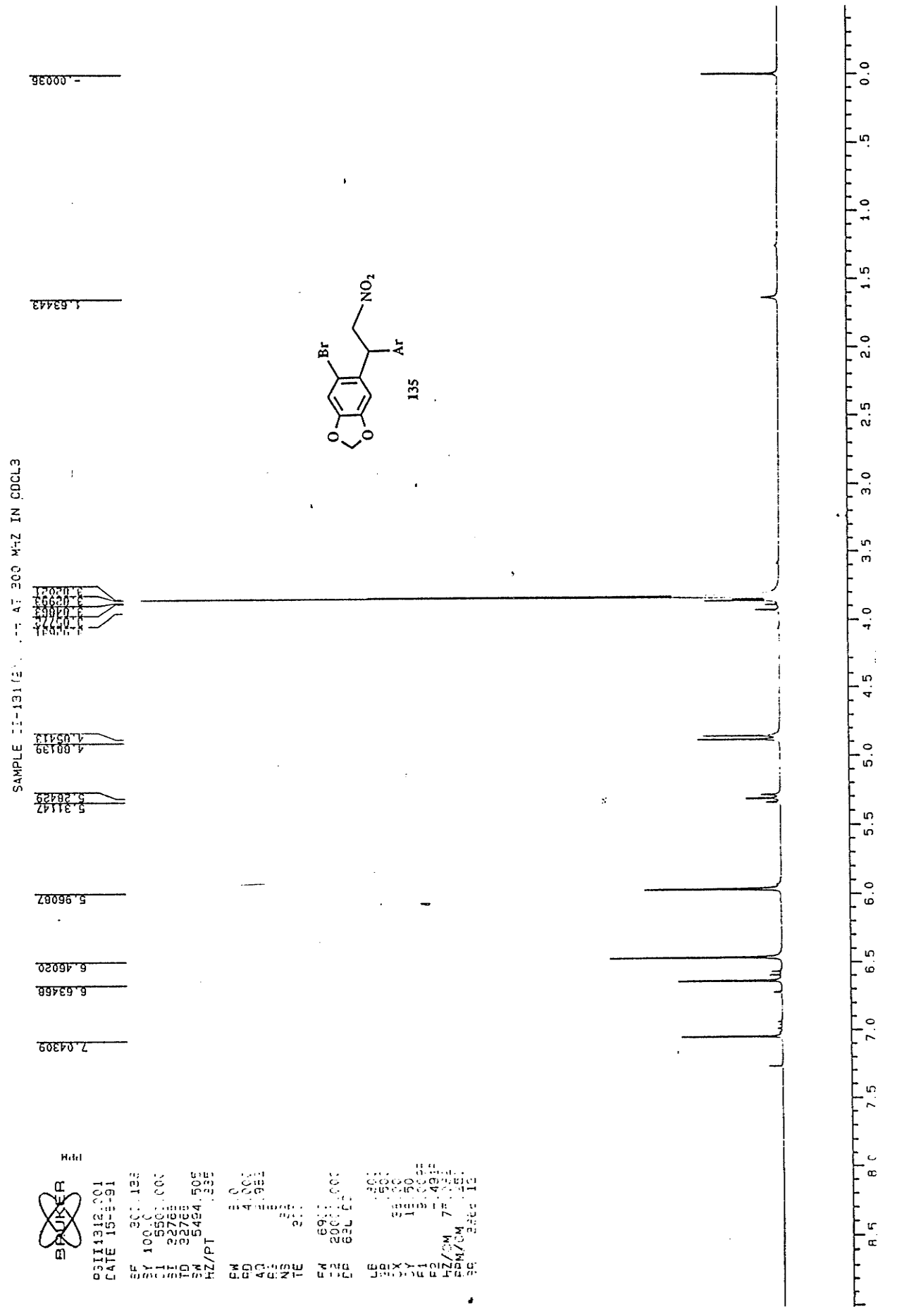

CN
Ar
Br
O
O
124
SAMPLE II-201, 1-H AT 300 MHZ IN CDCL3
PGII201.001
DATE 3-12-91
PPM

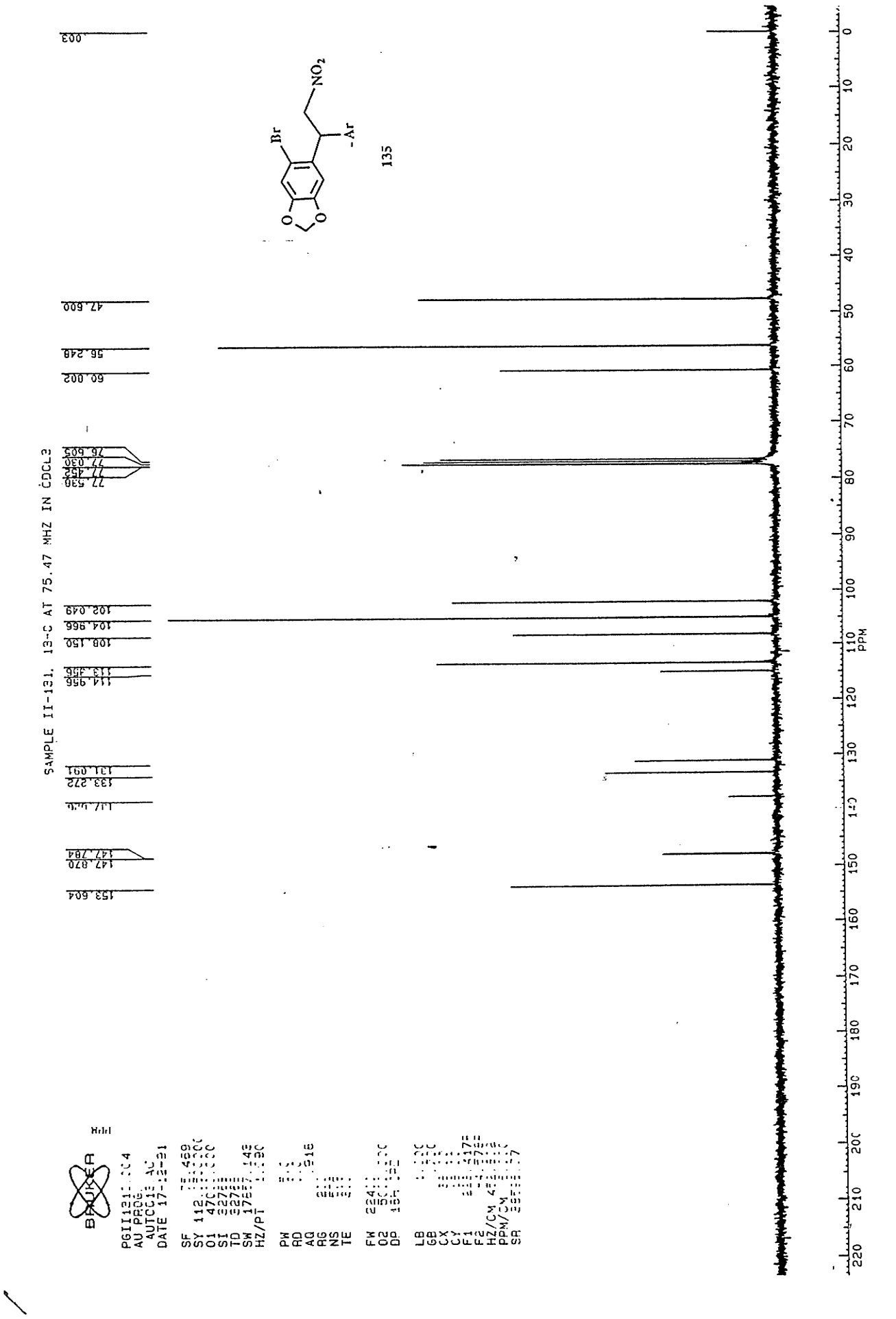

SAMPLE II-203, 1-H AT 300 MHZ IN CDCL3
BRUKER
PGII203.001
DATE 12-12-91
SF 300.123
SY 100.0
01 5500.000
SI 32768
TD 32768
SW 5434.505
HZ/PT .332
PW 3.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
02 20000.000
DP 63L DO
LB .300
GB .500
CX 35.00
CY 18.50
F1 9.000P
F2 -.492P
HZ/CM 75.032
PPM/CM .251
SR 2266.45
PPM
7.00816
6.67075
6.47674
5.94111
5.93006
4.06175
3.82219
3.81462
3.81014
2.95120
2.92432
1.17893
1.15528
1.13155
.00024
Br
Ar
CO2Et
125
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

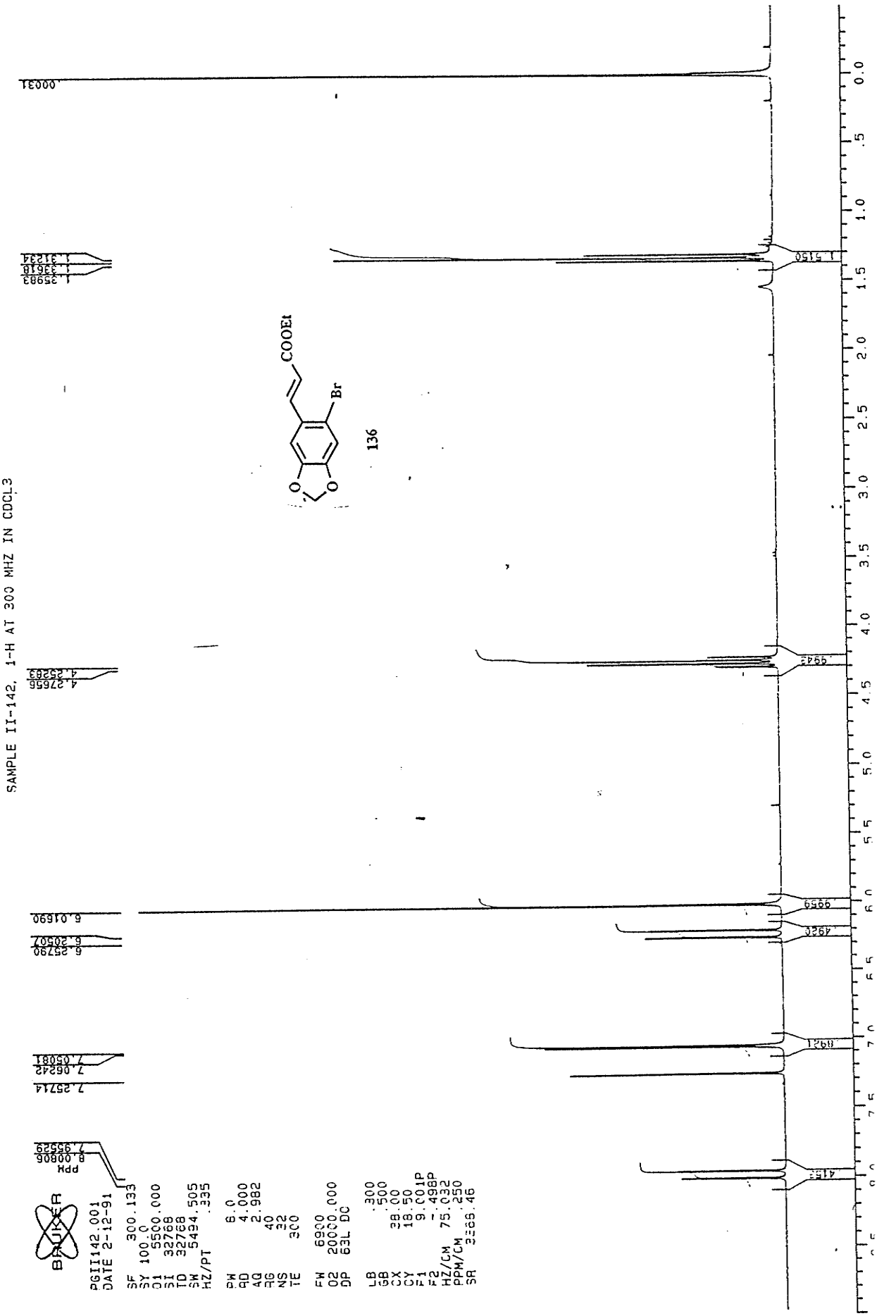

COOR**
COOR**
OH
Ar
129a
SAMPLE II-221(4), 1-H AT 300 MHZ IN CDCL3
BRUKER
ppm

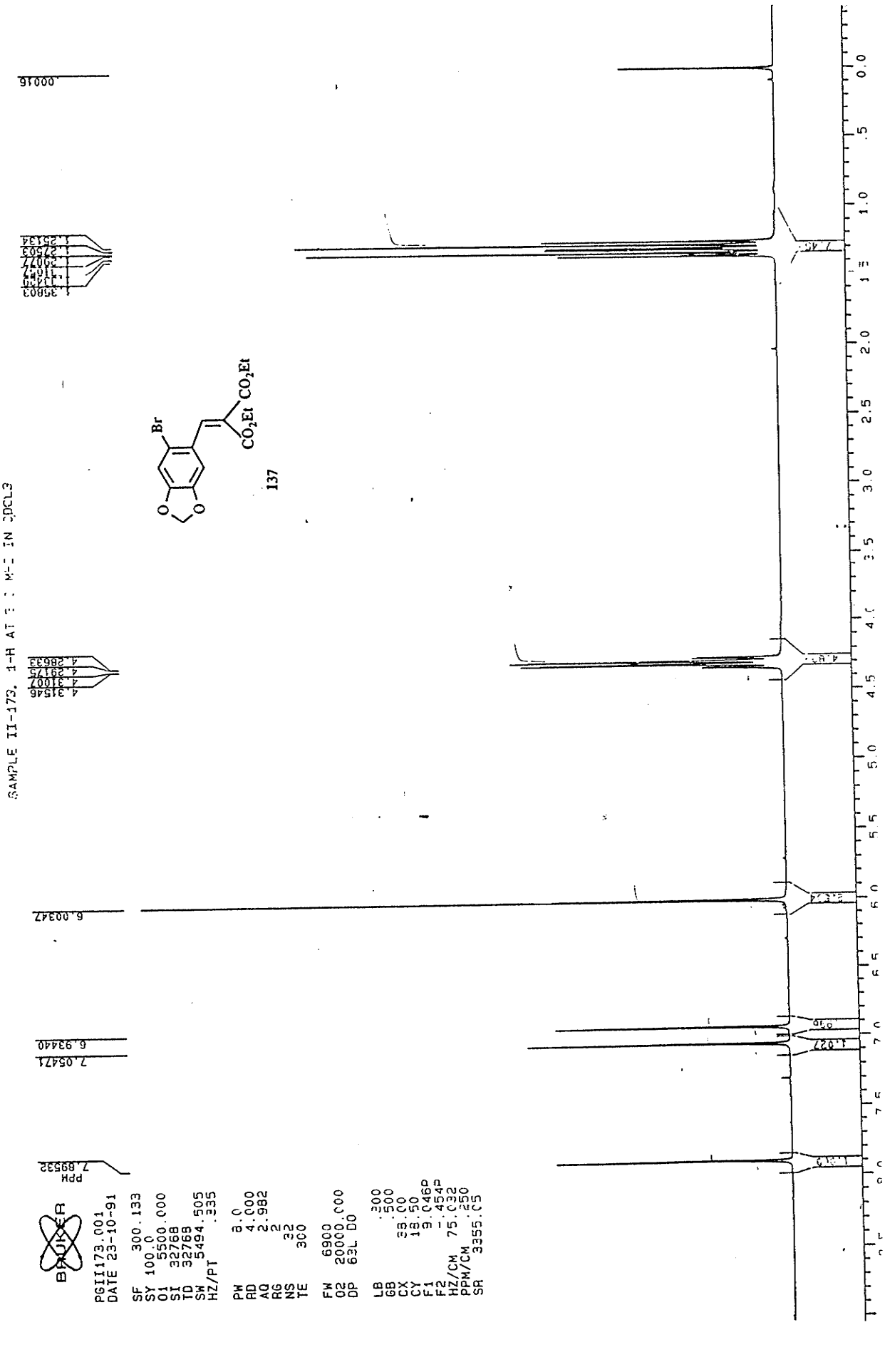

PG-II-109(2) 1-H AT 300 MHz IN CDCL3
Br
NO2
134
BRUKER
PPM

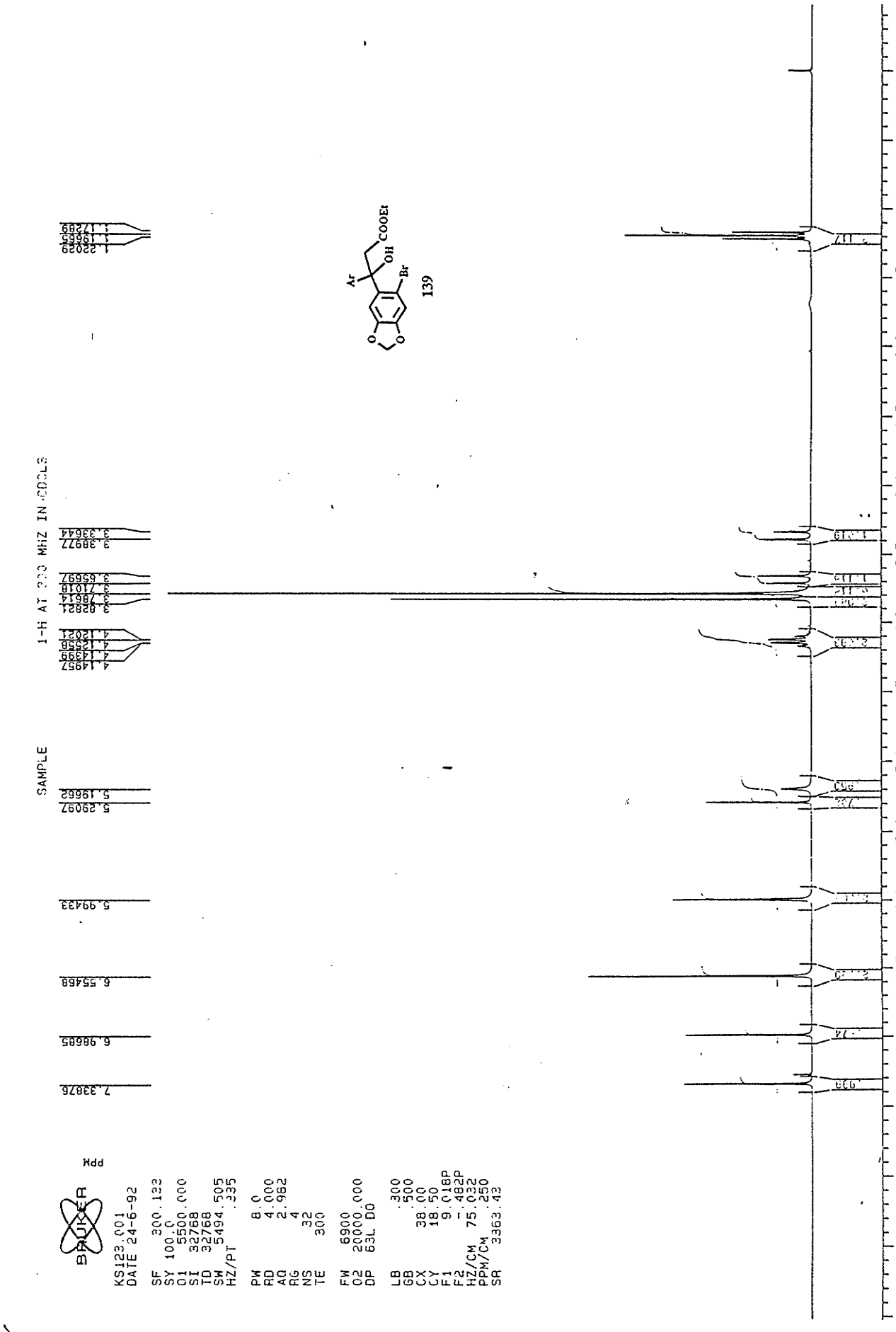

SAMPLE II-109, 13-C AT 75.47 MHZ IN CDCL3
77.424
77.003
76.579
102.739
106.611
113.713
119.940
123.187
137.545
137.171
148.151
151.641
Br
NO2
O
O
134
PPM
BRUKER
PGII1109C.004
AU PROG:
ACTOC13.AU
DATE 5-12-91
SF 75.469
SY 112.0500000
01 47000.000
SI 32768
TD 32768
SW 17857.143
HZ/PT 1.090
PW 5.0
RD 0.0
AG .918
RE 200
NB 320
TE 300
FW 22400
CS 5000.000
DE 18H CPD
LB 1.000
GB .700
CX 36.00
CY 18.00
F1 223.402P
F2 -4.593P
HZ/CM 452.602
PPM/CM 6.000
SE 33597.86


SAMPLE II-131(2) .. AT 300 MHZ IN CDCL3
7.04309
6.63466
6.46020
5.96087
5.31147
5.28429
4.80139
4.05413
1.63443
1.00036
Br
Ar
NO_2
O
O
135
BRUKER
PSII1312.001
DATE 15-E-91
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


SAMPLE II-131, 13-C AT 75.47 MHZ IN CDCL3
153.604
147.870
147.784
131.091
133.222
114.956
113.346
108.150
104.966
102.049
77.536
77.246
77.030
76.605
60.002
56.248
47.600
003
Br
-Ar
NO_2
O
O
135
PPM


SAMPLE II-142, 1-H AT 300 MHZ IN CDCL3
COOEt
Br
136
PGII142.001
DATE 2-12-91
SF 300.133
SY 100.0
D1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 6.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
D2 20000.000
DP 63L DC
LB .300
GB .500
GX 38.00
GY 18.50
F1 9.001P
F2 -.498P
HZ/CM 75.032
PPM/CM .250
SR 3366.46
PPM


SAMPLE II-173, 1-H AT
IN CDCL3
PGII173.001
DATE 23-10-91
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 2
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 33.00
CY 18.50
F1 9.046P
F2 -.454P
HZ/CM 75.032
PPM/CM .250
SR 3355.05
PPH
7.89532
7.05471
6.93440
6.00347
4.31546
4.31007
4.29175
4.28633
Br
CO2Et
CO2Et
O
O
137


Ar
COOEt
OH
Br
O
O
139
SAMPLE
1-H AT 300 MHz IN CDCL3
KS123.001
DATE 24-6-92
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 DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.018P
F2 -.482P
HZ/CM 75.032
PPM/CM .250
SR 3363.43
PPM