ASYMMETRIC DIELS-ALDER REACTIONS OF ORTHO-QUINODIMETHANES

by

Kevin K.S. Koh

a thesis

submitted to the Faculty of Graduate Studies

of the University of Manitoba in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Manitoba

Winnipeg, Manitoba, Canada

September, 1991.

ISBN 0-315-76977-7

ASYMMETRIC DIELS-ALDER REACTIONS OF ORTHO-QUINODIMETHANES

BY

KEVIN K.S. KOH

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

DOCTOR OF PHILOSOPHY

ACKNOWLEDGEMENTS

This thesis is dedicated to my parents, who make this work possible through their love and encouragement. Thank you for having me, mom, dad.

I would like to thank my supervisor, Dr.J.L. Charlton, for the many interesting discussions and guidance provided during the course of this work.

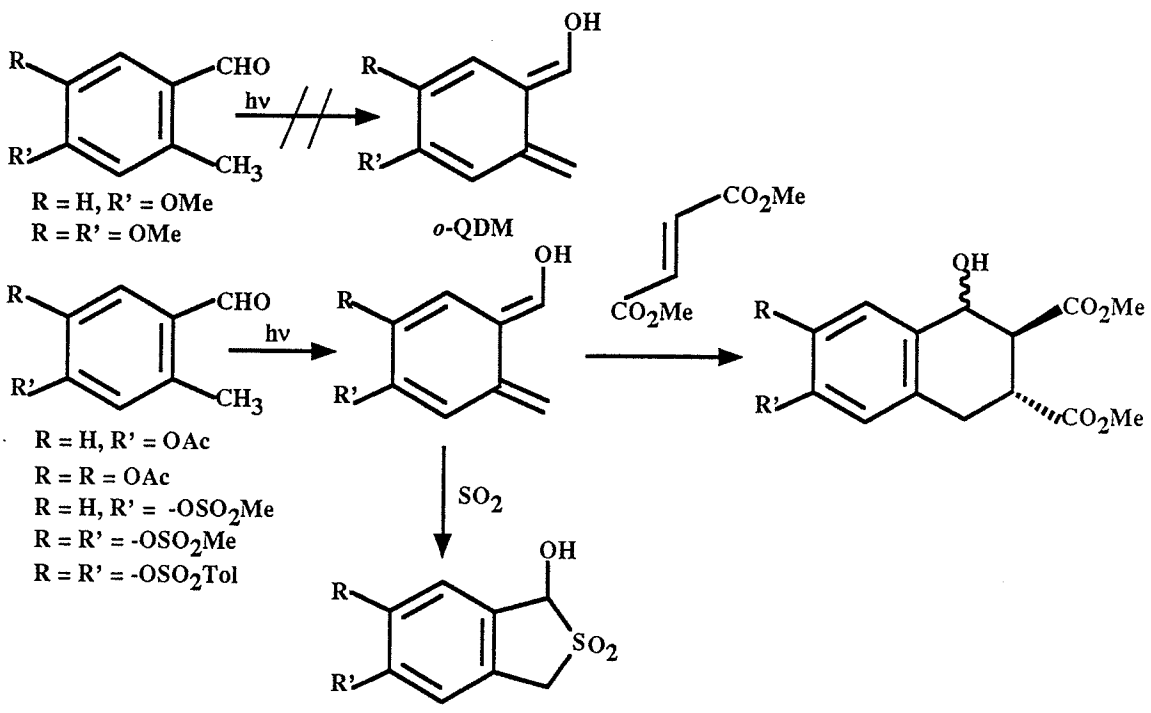
I also express my appreciation to other members of my committee: Dr.D.M. McKinnon and Dr.T. Schaefer.

Thanks to Kirk Marat and Terry Wolowiec for obtaining the nmr spectra, and to Wayne Buchannon for acquiring the numerous mass spectra.

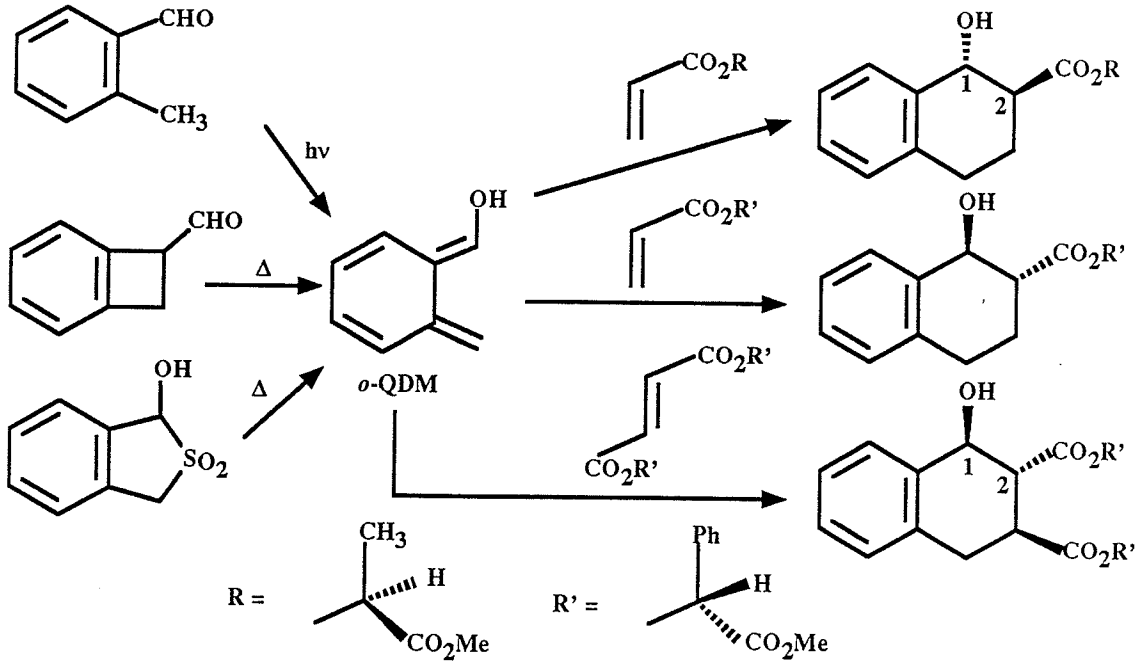
Finally, thanks to the University of Manitoba for the financial assistance provided in the form of Graduate Fellowship

Abstract

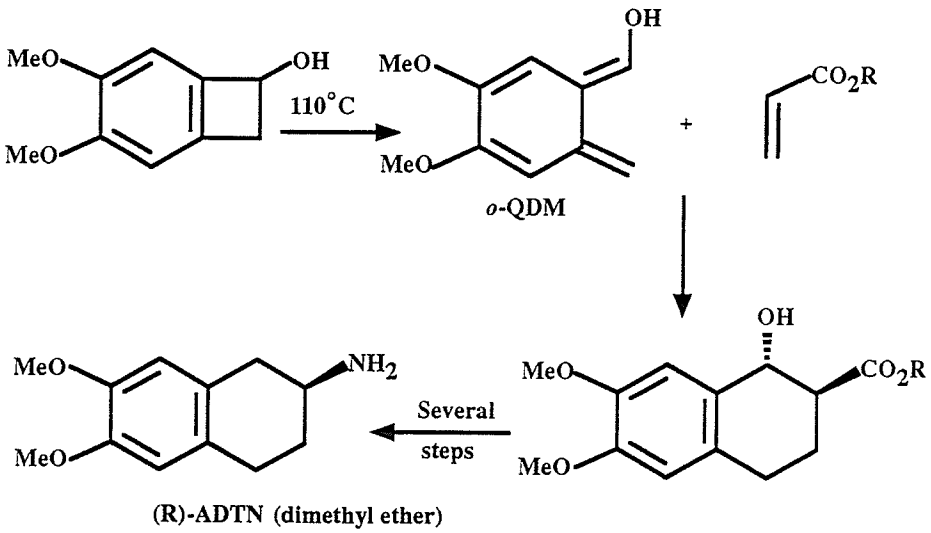
The work described in this thesis focuses on the generation and reaction of *ortho*-quinodimethanes (*o*-QDMs). During the routine photochemical conversion of certain substituted *o*-tolualdehydes to the corresponding *o*-QDMs, anomalous photochemical behaviour was observed. Studies of the photolysis of 4- and 4,5-disubstituted *o*-tolualdehydes have shown that the presence of a 4-methoxy or both 4- and 5-methoxy substituents prevented the formation of trappable *o*-QDMs. However 4-acetoxy and 4,5-diacetoxy-2-methylbenzaldehydes, the corresponding mesylates and tosylates were successfully converted to *o*-QDMs. These *o*-QDMs were trapped with sulfur dioxide and dimethyl fumarate to form the corresponding cycloadducts.



Asymmetric cycloadditions of *o*-QDMs to chiral fumarates and acrylates have also been carried out. The cycloadditions of an α-hydroxy-*o*-quinodimethane with the acrylates of (S)-methyl lactate, (R)-methyl mandelate and the fumarate of (R)-methyl mandelate have been found to give adducts with diastereoselectivities (de) greater than 90%. An unusual 1,2-*trans* stereochemistry has been established for the major products, which is in contrast to previously reported results for similar *o*-QDM reactions where the major products exhibit 1,2-*cis* stereochemistry.

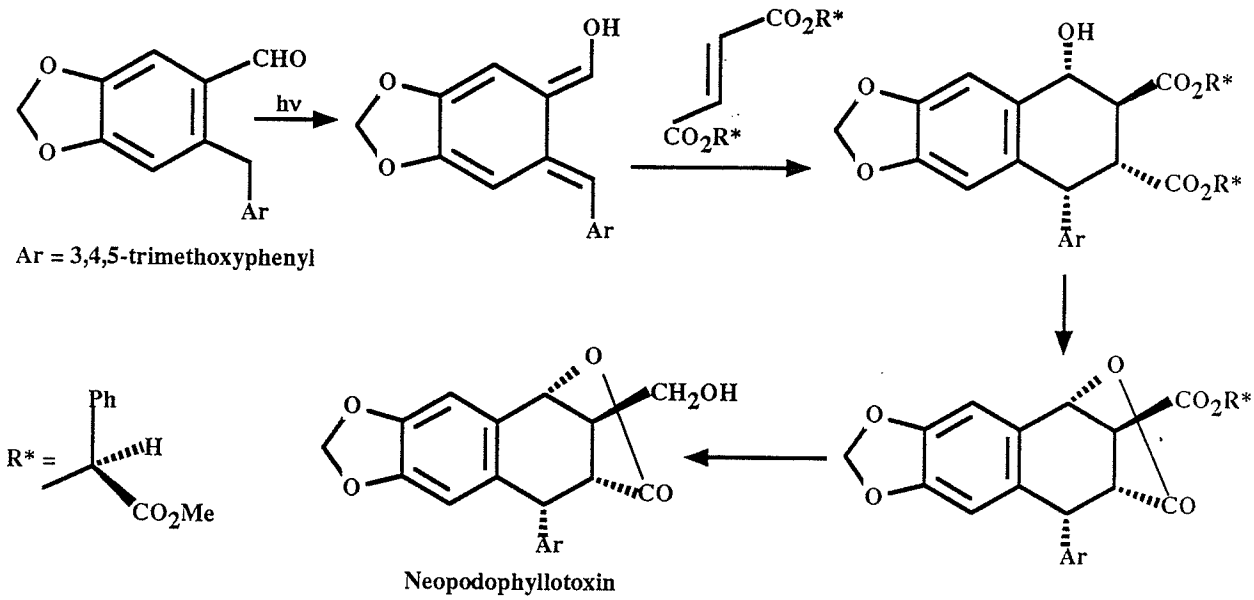


The major adduct from the cycloaddition of the *o*-QDM from 4,5-dimethoxybenzocyclobuten-1-ol to the acrylate of (S)-methyl lactate was successfully converted to the dimethyl ether of the central nervous system active drug ADTN in 11% overall yield and >97% optical purity, starting from 2-amino-4,5-dimethoxybenzoic acid and the acrylate of (S)-methyl lactate.



(R)-ADTN (dimethyl ether)

An asymmetric synthesis of neopodophyllotoxin has been completed in 18% overall yield and >95% optical purity, starting from 6-(3,4,5-trimethoxybenzyl)piperonal and the fumarate of (S)-methyl mandelate.



Ar = 3,4,5-trimethoxyphenyl

Neopodophyllotoxin

TABLE OF CONTENTS

Compound:

Appendix 1: ^{1}H nmr spectra

Compound:

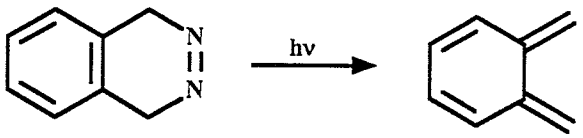
Chapter 1

Introduction

The Diels-Alder reaction occupies a prominent position in the arsenal of the synthetic organic chemist. This versatile reaction allows the formation of two bonds simultaneously and the creation of up to four contiguous chiral centers. Its widespread application is a result of its mild reaction conditions, predictability, and high regio- and stereoselectivity. As a sub group of this class of reactions, the Diels-Alder reactions of *o*-quinodimethanes have been particularly useful, and recently attention has been focused on the asymmetric cycloadditions of these interesting intermediates. This thesis work will deal with the reactions of *o*-quinodimethanes, primarily asymmetric cycloadditions of *o*-quinodimethanes, and applications of these reactions to natural product synthesis. The introduction section of this thesis will consist of a literature review of *o*-quinodimethane cycloadditions. This will include a section on the generation of *o*-quinodimethanes and a brief discussion on the basic rules of the Diels-Alder reaction.

Section 1.1: Generation of *ortho*-quinodimethanes

The highly reactive *ortho*-quinodimethane (*o*-QDM) **1** was first directly observed in 1973 by irradiating the dihydrodiazanaphthalene **2** in a glassy matrix at -196°C[1].

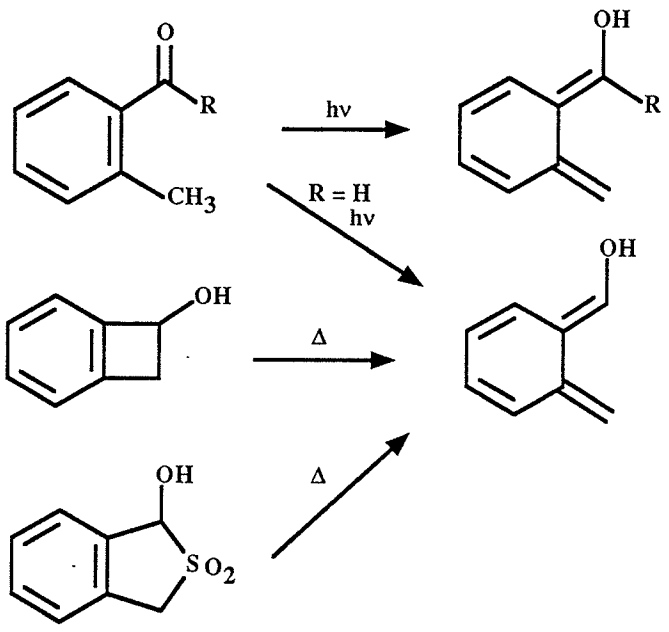


2 **1**

Despite the fact that *o*-QDMs had not been isolated, **1** and its derivatives had been used in organic synthesis much earlier. Its participation in a reaction was first suggested by Cava

in 1957[2]. Later in 1959, the parent *ortho*-quinodimethane **1** was generated and trapped with typical dienophiles in Diels-Alder cycloaddition reactions[3]. Details on its discovery and characterization have been recently reviewed [4]. *Ortho*-quinodimethane is also known as *o*-quinodimethide and *o*-xylylene, however, to avoid confusion, only the name *o*-quinodimethane (*o*-QDM) will be used in this thesis.

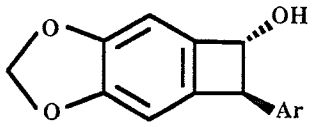
Many methods have been developed in the past to generate variously substituted and unsubstituted *o*-quinodimethanes[4]. They include: (1) thermolysis of benzocyclobutenes and benzocyclobutenols, (2) 1,4-elimination processes, (3) thermal elimination of sulfur dioxide from sultines and sulfones, (4) Diels-Alder cycloreversions, (5) photochemical expulsion of carbon monoxide or nitrogen, and (6) photoenolization or photorearrangement. Among these methods, photoenolization of aldehydes and ketones, the thermolysis of benzocyclobutenes and the thermal elimination of sulfur dioxide from sulfones are the most commonly employed methods used to generate *o*-QDMs.



There are advantages as well as disadvantages with each process. Photochemical generation of *o*-QDM has been used extensively in organic synthesis[4]. It has the advantage of ease of accessibility of the required starting aldehydes or ketones. However,

the method is sometimes limited by the possibility of photochemical side-reactions. For example, *cis-trans* isomerization of dienophiles can occur, often caused by sensitization from the excited state of the *o*-QDM precursor. This can increase the number of isomeric adducts being formed[5,6].

The most serious drawback in using benzocyclobutenes or benzocyclobutenols as *o*-QDM precursor is the difficulty in their synthesis. For instance, Jung had difficulty in preparing benzocyclobutenol **3** even though many different approaches were attempted[7].

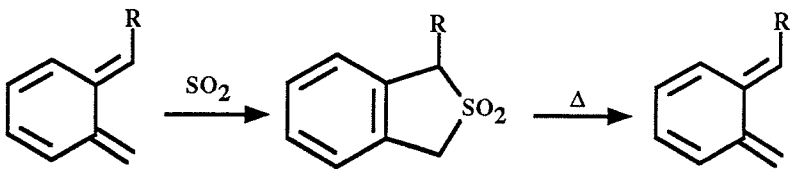


3

Ar = 3,4,5-trimethoxyphenyl

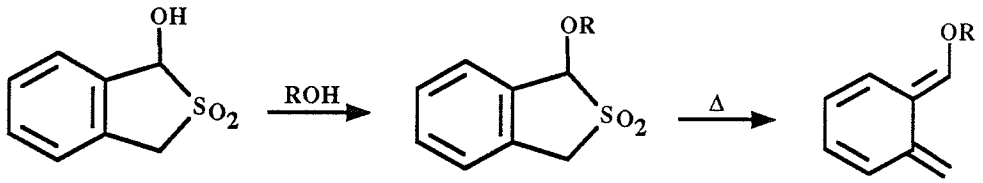
The main reason for the difficulty in preparation of **3** is its instability at temperatures above 0°C. It has only recently been prepared, but by rather lengthy procedures[8,9]. Synthesis of other benzocyclobutenols have also been cited in the literature[10-16]. Despite the difficulty in their preparation, it appears that *o*-QDMs prepared from benzocyclobutenols trap dienophiles more efficiently[5,15].

Sulfones such as **4** have also been used frequently as *o*-QDM precursors in organic synthesis[17]. They can be prepared by trapping photochemically generated *o*-QDMs with sulfur dioxide, as first demonstrated by Charlton and Durst[18]. The *o*-QDM can then be regenerated thermally from the sulfone. Many articles on this subject have appeared in the literature[5,19-29].



4

These sulfones are usually fairly stable and in the case of hydroxy sulfones such as **5** , the hydroxy group can easily be exchanged for an alkoxy group[19,23-24,27-28].



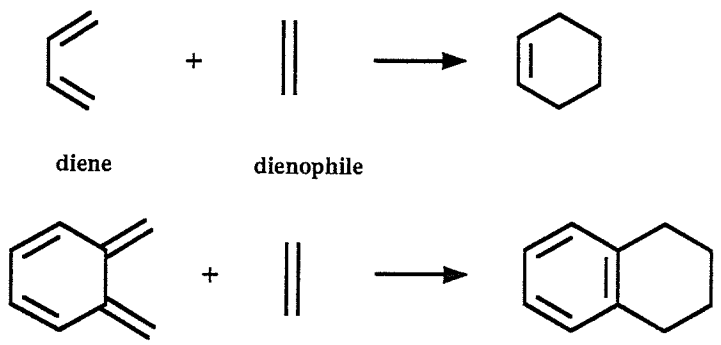
5

In summary, there are several methods that can be used to produce *o*-quinodimethanes. The method chosen for a particular synthesis will depend on the *o*-QDM required, as well as on the sensitivity of the substrates to the reaction conditions.

Section 1.2: The basic rules of the Diels-Alder reactions

The reactions of *o*-QDMs with dienophiles are typical Diels-Alder reactions, it would be appropriate to present a brief discussion of the basic rules of Diels-Alder reactions. They will be discussed in the context of *o*-QDM cycloadditions.

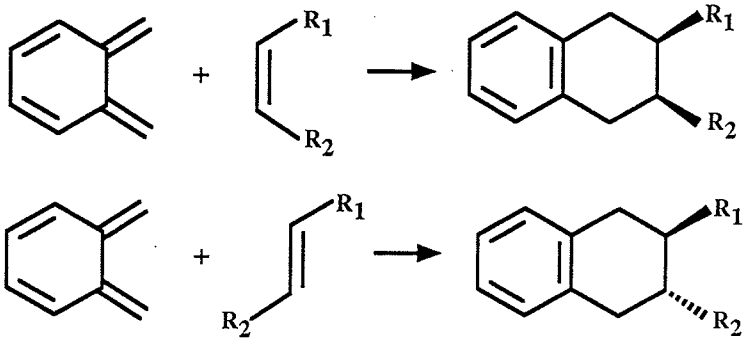
The Diels-Alder reaction was first discovered in 1928 by two German chemists, Otto Diels and Kurt Alder [30-31], who were awarded the Nobel Prize in 1950 for the discovery of this important and versatile reaction. The reaction consists of a 4 + 2 cycloaddition of a conjugated diene with an olefin (often referred to as the dienophile), to generate a six-membered ring. The simplest Diels-Alder reaction consists of the cycloaddition of butadiene with ethylene to form a cyclohexene ring. A Diels-Alder reaction of an *o*-QDM would generate a tetrahydronaphthalene ring.



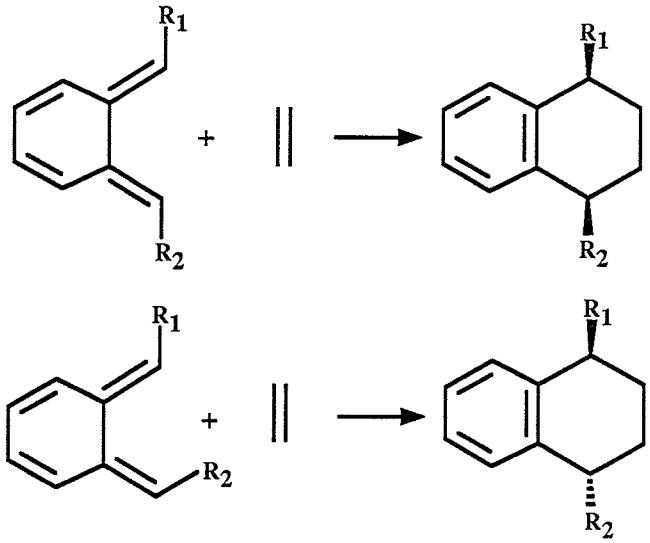
The Diels-Alder reaction is considered to be concerted (pericyclic) with both new bonds being formed simultaneously without intervention of free radical or ionic intermediates. Although the reaction proceeds for the unsubstituted case as shown above, it is most successful when electron-withdrawing substituents are located on the dienophile and electron-donating substituents are located on the diene.

Diels-Alder reactions can be considered from several points of view[32]:

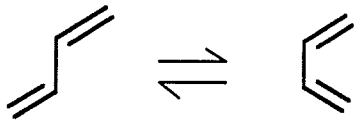
(1) With respect to the dienophile, the reaction is stereoselectively *syn*. That is, the addition to the dienophile takes place from one face. This means that substituents which are *cis* to each other in the olefin will also be *cis* in the six-membered ring that is produced. If they are *trans* in the dienophile they will be *trans* in the six-membered ring as shown below.



(2) The reaction is also stereoselectively *syn* for 1,4-disubstituted dienes. For example, *trans,trans*-1,4-disubstituted diene gives only *cis* adduct while *trans,cis*-1,4-disubstituted diene gives only *trans* adduct.

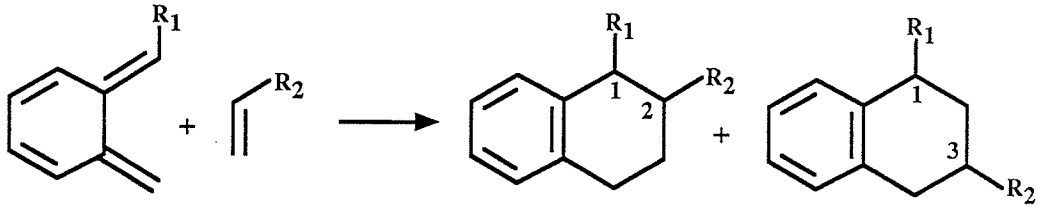


(3) The diene must be able to adopt the cisoid conformation. If the diene is in the transoid conformation, the reaction cannot take place.



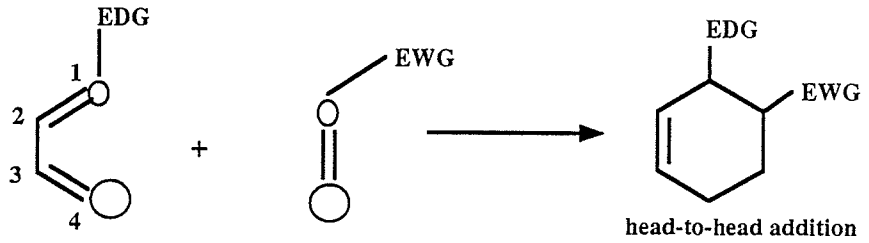
transoid conformation **cisoid conformation**

(4) When both the diene and the dienophile are unsymmetrically substituted, two possible regio isomers can arise. *o*-QDM reactions are very regioselective and disubstituted cycloadducts with 1,2-regiochemistry are favoured over 1,3-adducts.



Predominant isomer

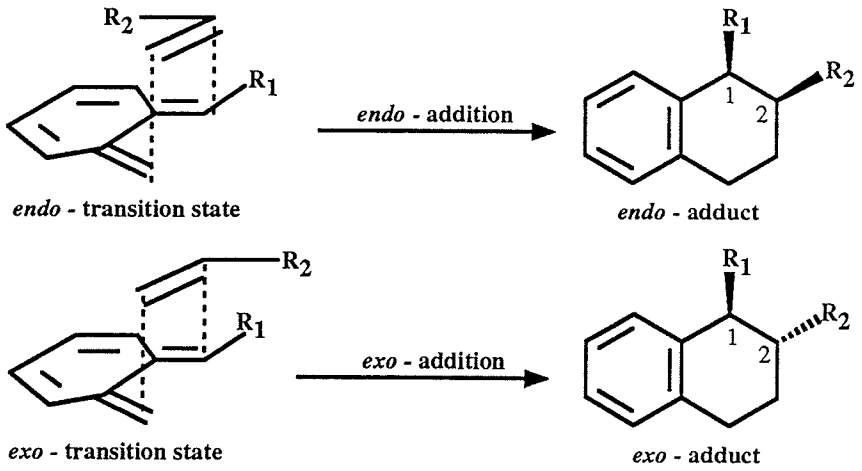
The regioselectivity shown above, and the propensity for electron-donating group on the diene and electron-withdrawing group on the dienophile to enhance Diels-Alder reactions can be rationalized by frontier molecular orbital theory (FMO)[33]. FMO theory states that: *reactions are allowed only when all overlaps between the highest-occupied molecular orbital* (**HOMO**) *of one reactant and the lowest-unoccupied molecular orbital* (**LUMO**) *of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*[32]. The predictions are based on the most favourable interaction of the **HOMO** of the diene and the **LUMO** of the dienophile. An electron-donating group on the diene raises the energy of the diene **HOMO** and an electron-withdrawing group on the dienophile lowers the energy of the dienophile **LUMO**. The result is a strong and dominant **HOMO-LUMO** interaction. Thus the rate of the reaction is enhanced when compared to the unsubstituted case[33]. The explanation of regioselectivity requires a knowledge of the effect of substituents on the coefficients of the **HOMO** and **LUMO** orbitals. An electron-donating group (**EDG**) on the 1 position of the diene leads to differently sized **HOMO** orbital coefficients at the 1 and 4 position of the diene.



The relative sizes of the circles represent the relative magnitudes of the orbital coefficients. The transition state which leads to the predicted adduct possesses the larger **HOMO** coefficient of carbon 1 or 4 of the diene interacting with the larger **LUMO** coefficient of the dienophile. As a result, dienes with electron-donating substituents at position 1 generally add "head-to-head" with dienophiles bearing electron-withdrawing

groups (**EWG**)[35]. For the cases in which primary orbital interactions do not provide a definite preference, secondary orbital effects may determine the resulting regiochemistry. In the absence of any dominant orbital effects, dipolar effects may direct regioselectivity[19,34].

(5) For dienes reacting with unsymmetrical dienophiles, two possible transition states for cycloaddition can arise. If the substituent on the dienophile is located over carbon 2 of the diene, the transition state is referred to as *endo*. However, when the substituent on the dienophile is extended away from the diene, the transition state is referred to as *exo*. The isomeric products from the two transition states are also sometimes referred to as the *exo* or *endo* product.



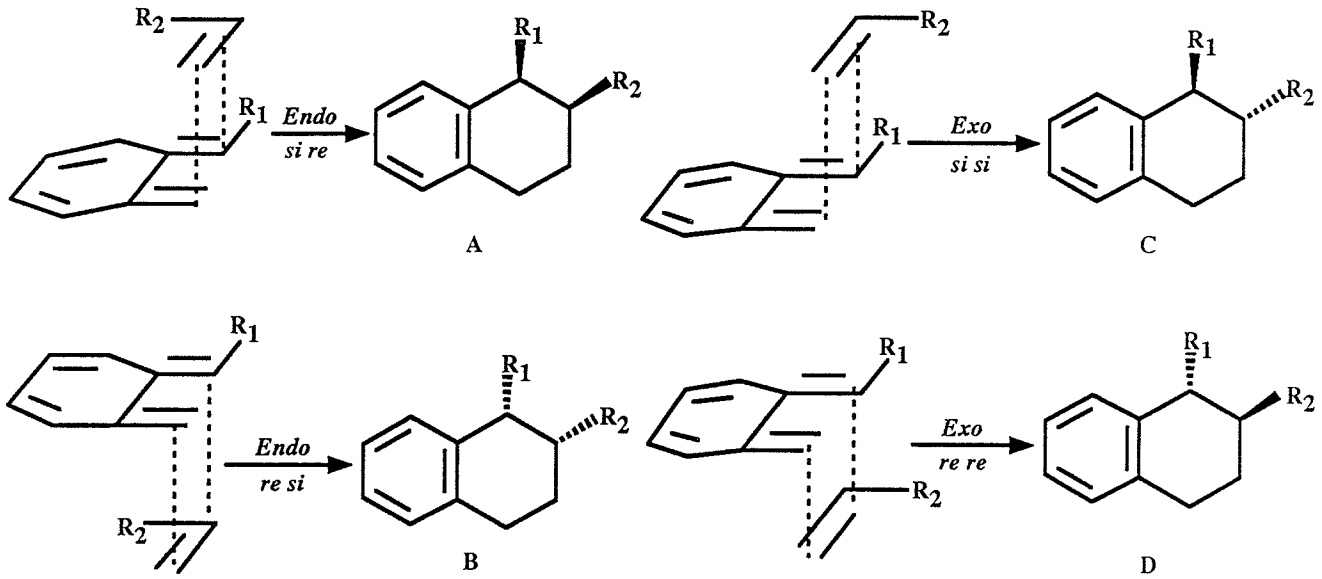
When both diene and dienophile are substituted, isomeric products can be obtained depending on the addition mode (*endo* or *exo*). The primary orbital interactions (between the atoms to which new bonds are forming) which usually control the regioselectivity [see above], do not control the diastereoselectivity (*endo* vs *exo*). Normally secondary orbital and steric interactions play that role. Hence, stabilizing secondary orbital interactions between the substituent on the dienophile and carbon 2 of the diene leads to predominantly *endo* adducts[34,36]. This is often referred to as the Alder *endo* rule. This stabilizing interaction is absent in the *exo* addition mode. Note that the

endo addition leads to adduct with *cis*-1,2-stereochemistry while the *exo* addition produces adduct with *trans*-1,2-stereochemistry.

Section 1.3: Enantioselectivity and diastereoselectivity in asymmetric Diels-Alder reactions

The synthesis of enantiomerically pure compounds is becoming increasingly important in research, development and production chemistry in industry. This is mainly due to the fact that almost all biological systems interact differently with chiral molecules and their optical antipodes. Thus for applications of chiral molecules, it is essential to have access to all stereoisomers of natural products, flavours, fragrances and pharmaceuticals. As the demand for these optically pure compounds grows, chemists are challenged to devise new routes to meet this demand. While there are many different ways of obtaining optically pure compounds, one of the most efficient methods is via asymmetric synthesis. Asymmetric synthesis has been defined as: "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products (enantiomeric or diastereomeric) are produced in unequal amounts. In other words, an asymmetric synthesis is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products results"[4].

Let us consider a Diels-Alder reaction where both the diene and dienophile bear achiral substituents.

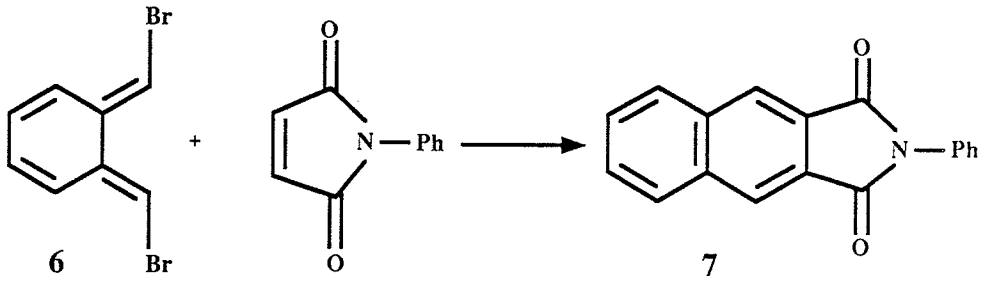


Note : *si re* , *si si* , *re si* and *re re* refer to the prochiral faces of the diene and dienophile

With respect to the above reaction, **A/B** and **C/D** are enantiomeric pairs while A/C, **A/D**, **B/C** and **B/D** are diastereomeric pairs. If the above reaction gives predominantly the *endo* adducts **A** and **B**, then the reaction is said to be diastereoselective towards the *endo* adducts. If the ratio of (**A**+**B**):(**C**+**D**) were 99:1, then one would say that (**A**+**B**) had been generated with a diastereomeric excess (de) of 98%. For the above reaction to be asymmetric, it would have to generate an adduct of predominantly one absolute configuration. That is, the newly created chiral center(s) would be of one absolute configuration. For instance, if **A** were produced predominantly over the other isomers, the above reaction would be asymmetric as well as enantioselective. Notice that the absolute configuration of the adduct obtained is related to the faces at which the diene and dienophile react. Thus to make a Diels-Alder reaction asymmetric, one must be able to direct the reaction in such a way that only the appropriate face of the diene and/or dienophile reacts.

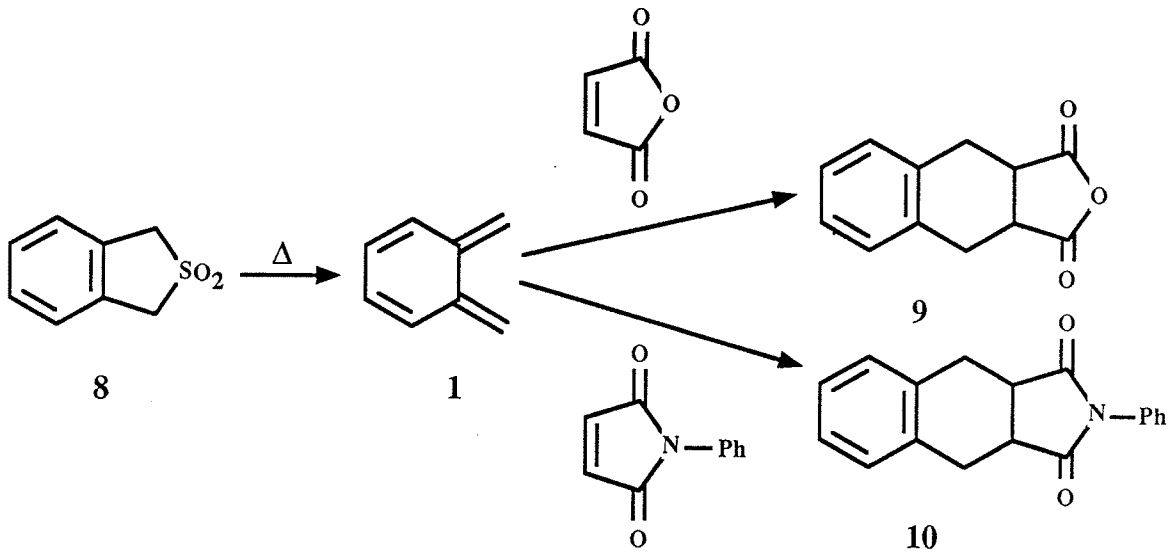
Section 1.4: Non-asymmetric Diels-Alder reactions of *o*-Quinodimethanes

Non-asymmetric Diels-Alder reactions of *o*-quinodimethanes have been studied extensively and as early as 1959, *o*-QDM **6** was reported to react with N-phenylmaleimide to form adduct **7**[37].



6 7

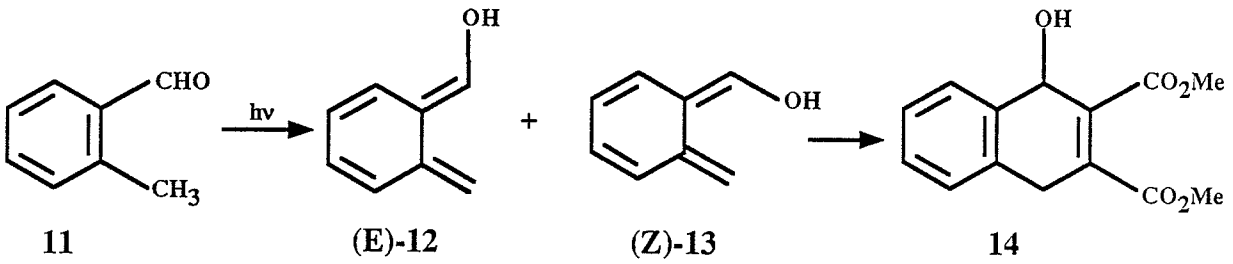
Cava *et al* were the first to generate the parent *o*-QDM **1**, by thermal extrusion of sulfur dioxide from sulfone **8**[38]. Trapping the *o*-QDM with maleic anhydride and N-phenyl maleimide resulted in the formation of the corresponding adducts **9** and **10**.



8 1 9 10

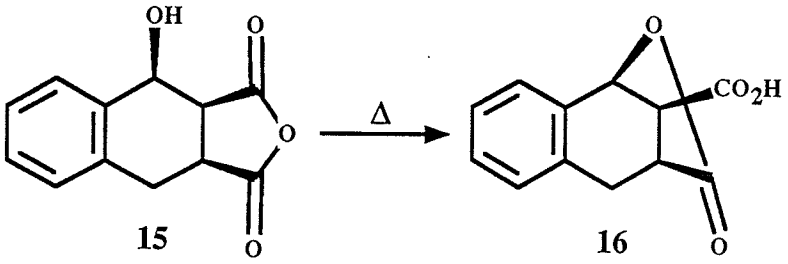
α-Hydroxy-*o*-quinodimethane was firstly generated by Sammes et al[39]. Photolysis

of 2-methylbenzaldehyde generated the intermediate α-hydroxy-*o*-quinodimethane **12**, which was trapped with acetylenedicarboxylic esters to form adduct **14**.



11 **(E)-12** **(Z)-13** **14**

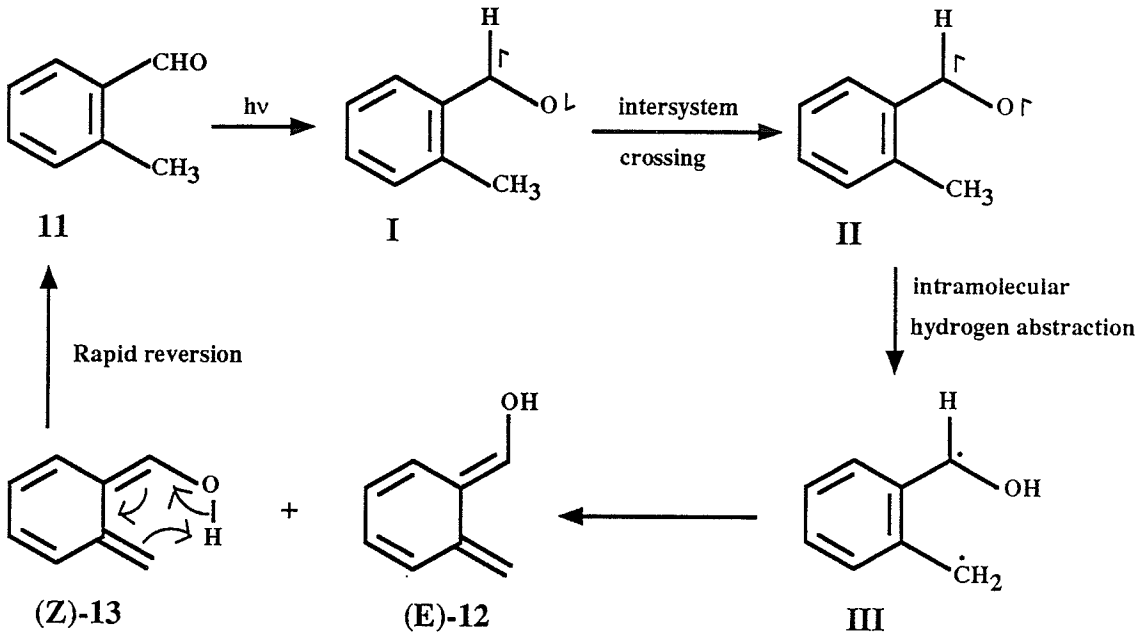
This simple trapping experiment did not reveal whether both isomeric *o*-QDMs **12** and **13** were formed and trapped. Later, it was shown that photolysis of **11** in the presence of maleic anhydride gave one major adduct **15**, which then isomerized to the lactone-acid **16** when heated[39].



15 **16**

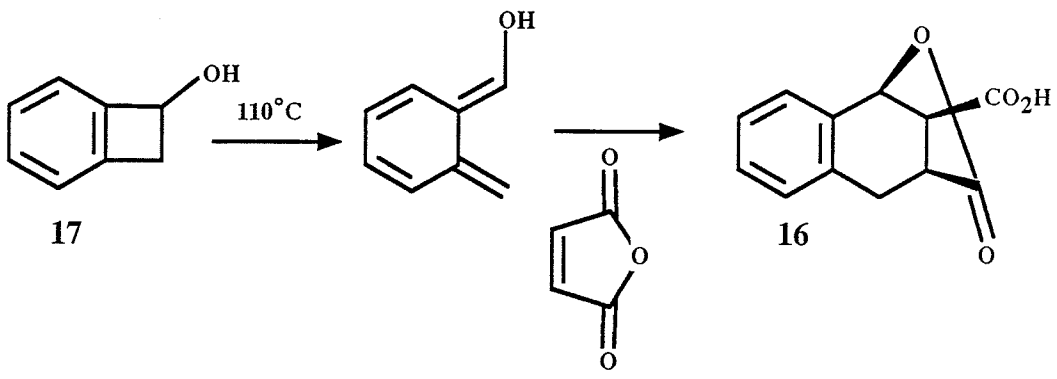
It was concluded that the adduct arose from the *endo* addition of maleic anhydride to the (E)-*o*-QDM **12**. Although *exo* addition of maleic anhydride to the (Z)-*o*-QDM **13** could also lead to **15**, this is a much less favoured mode of addition because of the lack of secondary orbital interactions[33-35]. Recent studies have shown that both **12** and **13** are formed when aldehyde **11** is photolysed[40]. It has been proposed that excitation of the carbonyl group generates an excited nπ* singlet state **I**. This nπ* state then undergoes intersystem crossing to form the nπ* triplet state **II**. It is this triplet state that abstracts a hydrogen atom intramolecularly from the *ortho*-methyl group to form the triplet state dienol **III**. **III** decays to form the two ground state dienols **12** and **13**[39]. The lifetime of

13 as measured by flash photolysis was much shorter than that of **12**, probably because it undergoes a rapid 1,5-sigmatropic hydrogen shift which converts it to the starting aldehyde[40]. This may explain the elusiveness of **13** in chemical trapping experiments. Successful trapping of **13** has yet to be reported.



11 I II III (Z)-13 (E)-12

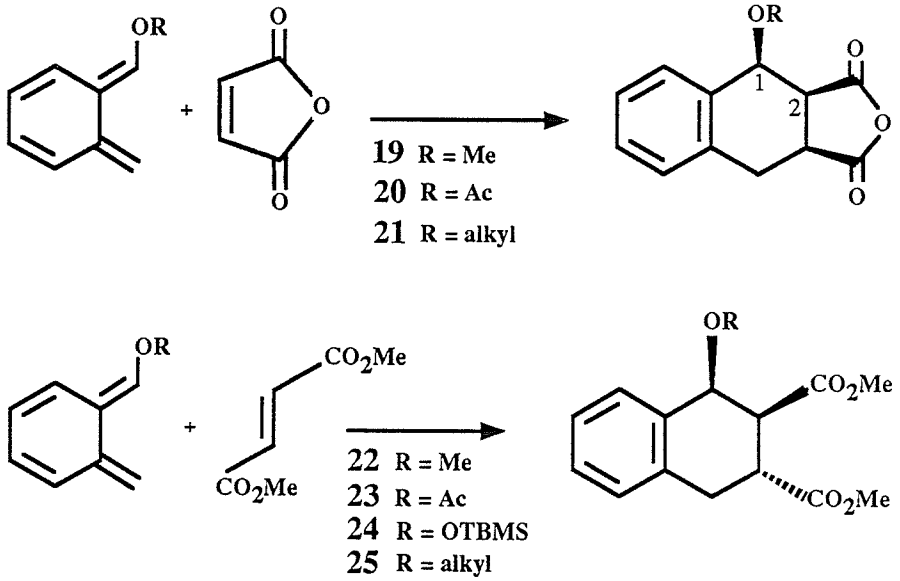
The trapping of *o*-QDM **12** was substantiated when benzocyclobutenol **17** was thermolized in the presence of maleic anhydride[41]. The product isolated was identical to that obtained from the photochemical reaction mentioned above.



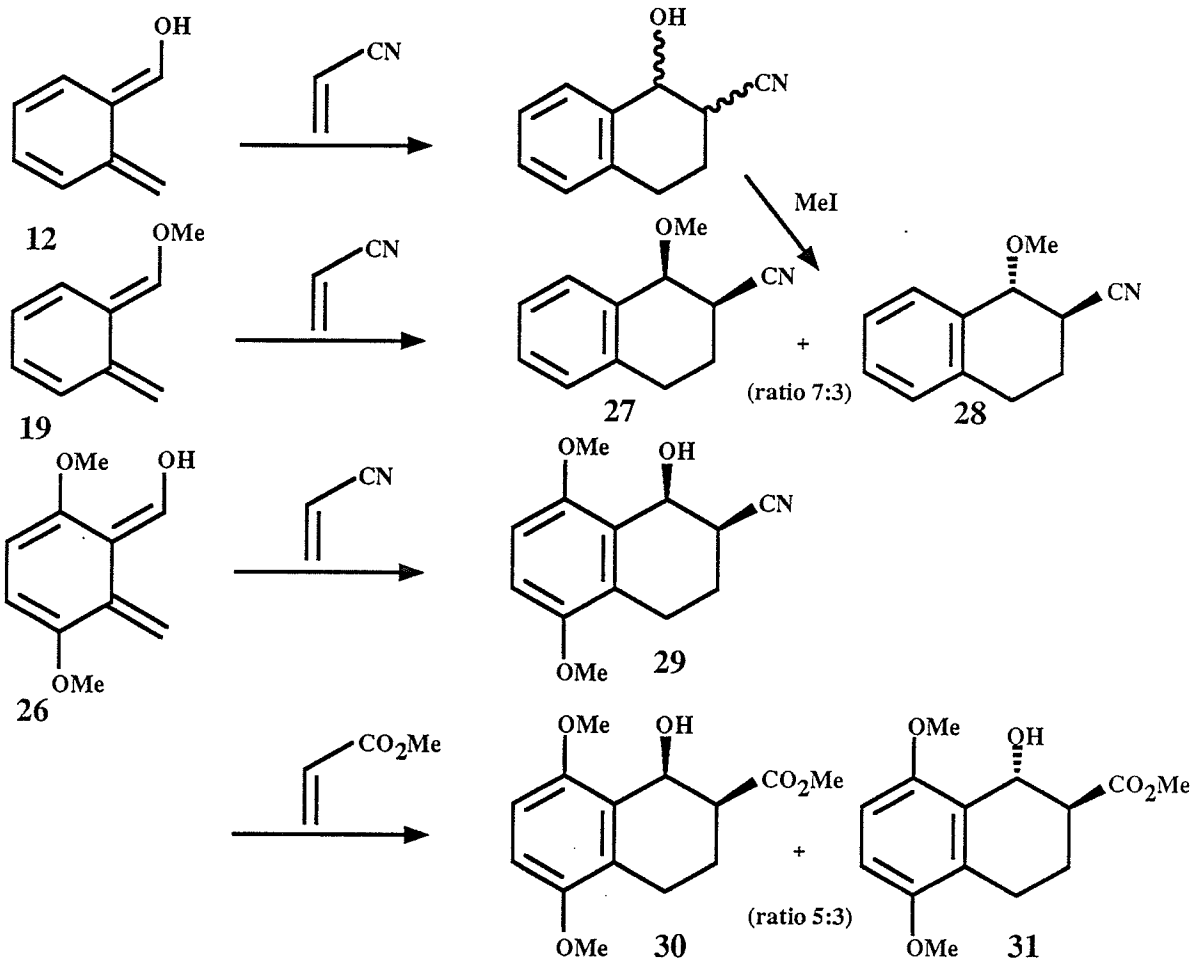
17 16

Other derivatives of *o*-QDM-**12** have also been generated and added to maleic anhydride

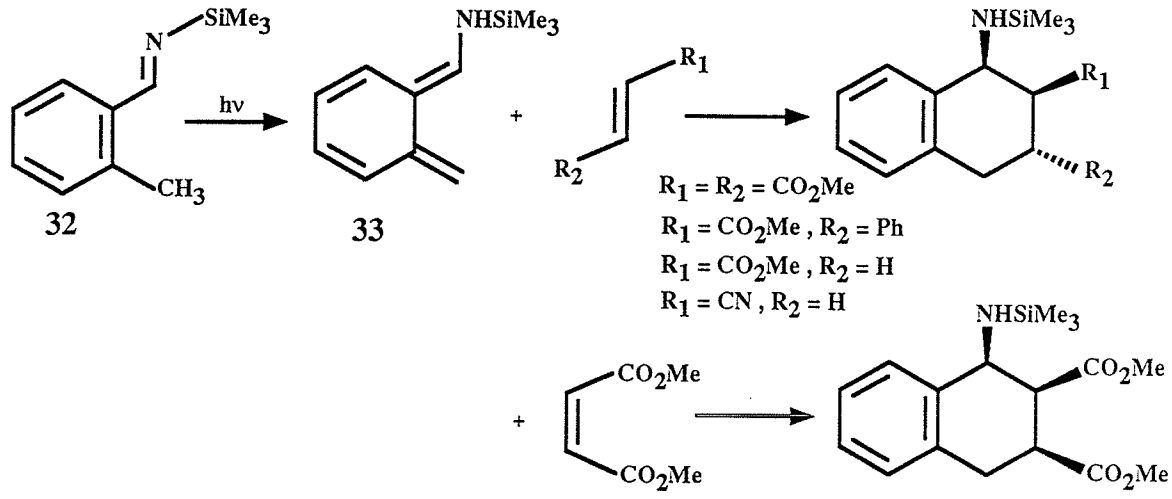
and dimethyl fumarate. In all cases (**19-25**) the cycloaddition proceeded with good *endo*-selectivity forming the expected *endo*-adduct with *cis*-1,2-stereochemistry[18,41-43].



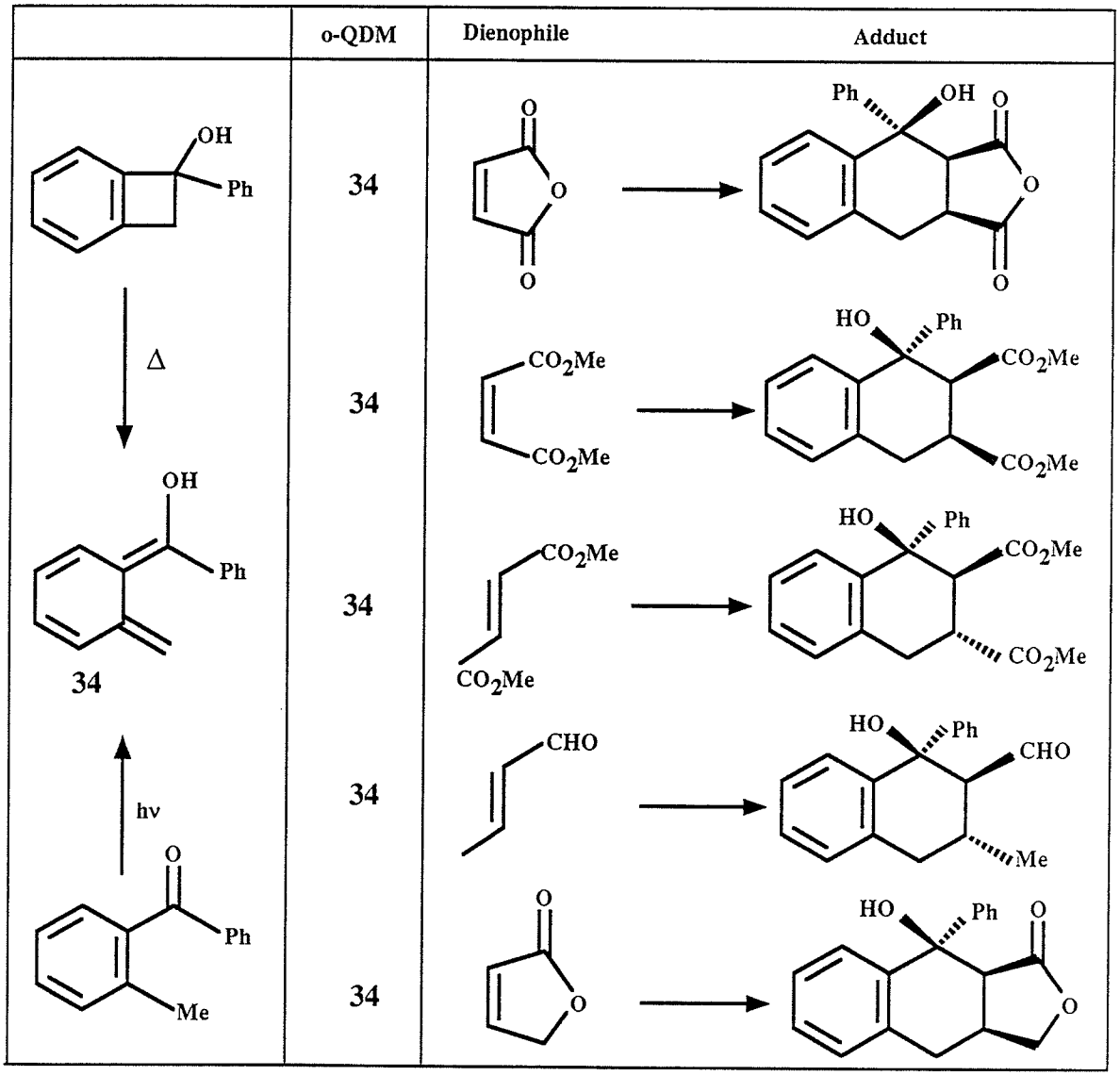
With mono-substituted dienophiles, *o*-QDMs **12**, **19** and **26** gave single regioisomers but the *endo-exo* selectivity varied. Addition of **12** to acrylonitrile gave two adducts[41]. Treatment of the adducts with methyl iodide gave **27** and **28** in the ratio of 7:3. **27** and **28** were also isolated in the same ratio when *o*-QDM **19** was added to acrylonitrile. Recently Wallace *et al* reported the reaction of *o*-QDM **26** with acrylonitrile to give the endo adduct **29** as the sole isolated product[14]. With methyl acrylate as dienophile, endo and exo-isomers **30** and **31** were isolated in the ratio of 5:3[14]. Note that in each case the *endo*-addition product predominated.



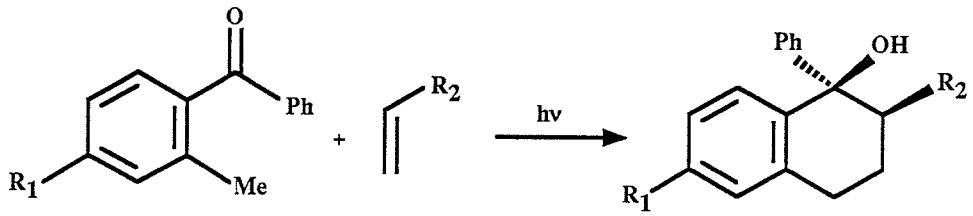
More recently, *o*-QDM **33** generated photochemically from N-silylimine **32** was trapped with a variety of dienophiles[44]. In all cases, the *endo* adducts were isolated.



It was found that products arising from cycloaddition to the *o*-QDM produced either thermally from α-phenyl-α-hydroxybenzocyclobutenol[45] or photochemically from *o*-methylbenzophenone[46-48], could be best interpreted as arising from *endo* addition to *o*-QDM **34**. In cases where unsymmetrical dienophiles were used, addition proceeded with high regioselectivity.



Pfau *et al* photolysed similar benzophenone systems and added the corresponding *o*-QDMs to mono-substituted dienophiles[47-48]. As expected, the cycloadditions were found to proceed via the *endo*-addition mode and with good regioselectivity.



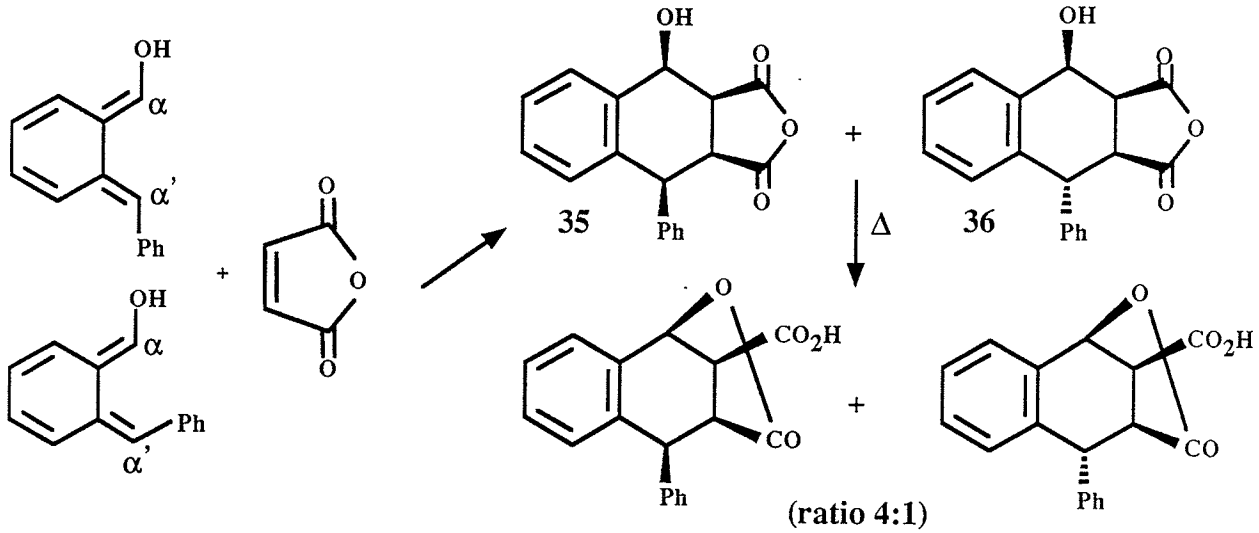
R_1 = H ; R_2 = CO_2Me

R_1 = Me ; R_2 = CO_2Me

R_1 = H ; R_2 = CN

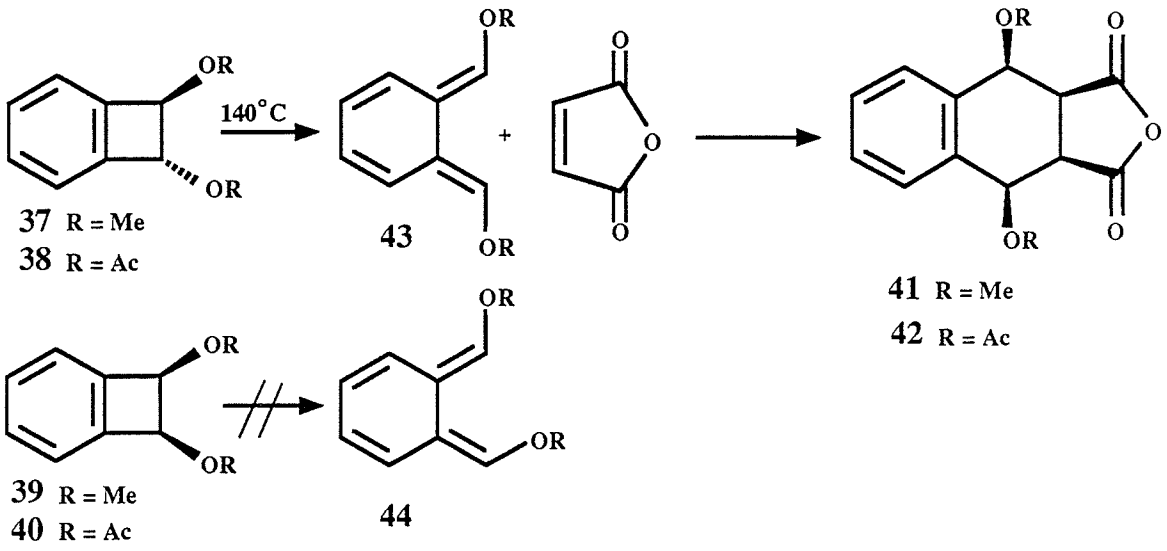
R_1 = Me ; R_2 = CN

Sammes *et al* found that both the (E,E)- and the (E,Z)-α-hydroxy-α'-phenyl-*o*-quinodimethanes were generated photochemically from 2-benzylbenzaldehyde. The two isomeric *o*-QDMs were trapped with maleic anhydride to give a mixture of cycloadducts **35** and **36**[39]. Under thermal condition the adducts isomerised to the corresponding lactone-acids. It was proposed that only *o*-QDMs with the oxy-substituent occupying the (E)-position were trapped.



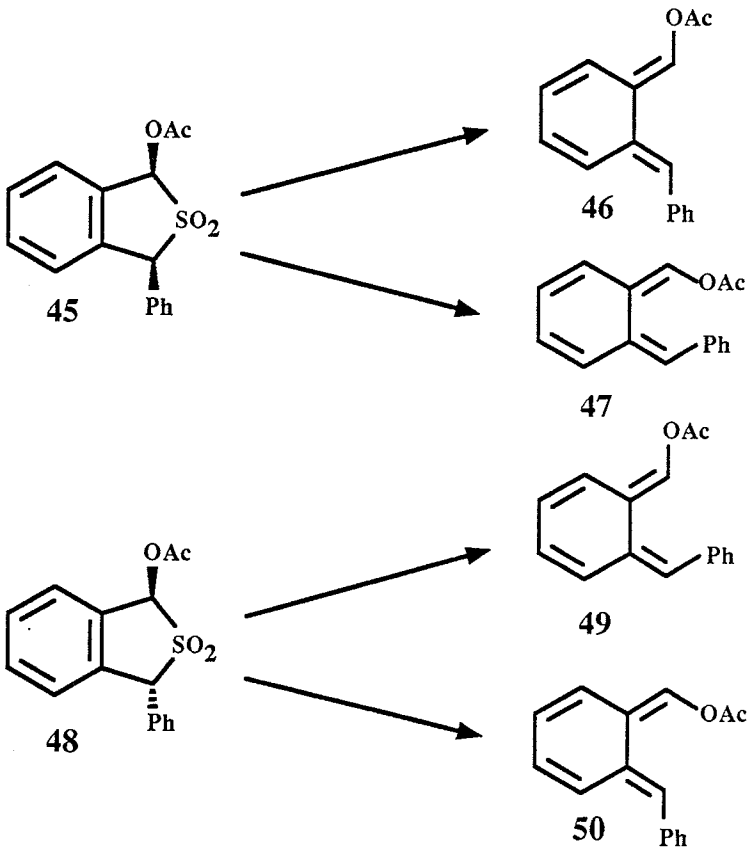
(ratio 4:1)

To further demonstrate that α-oxy-substituents of *o*-QDMs are reluctant to occupy the (Z)-position, Sammes *et al* thermolized benzocyclobutenes **37**-**40** in the presence of maleic anhydride[45].

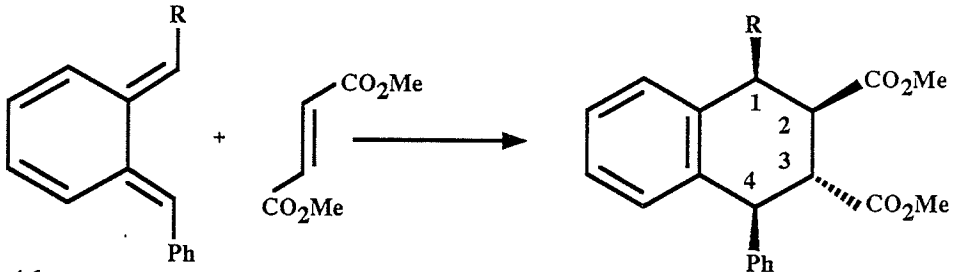


Thermolysis of *trans*-benzocyclobutenes **37** and **38** produced *endo*-adducts **41** and **42**, while thermolysis of *cis*-benzocyclobutenes **39** and **40** under identical conditions did not produce any adduct. At elevated temperatures (>140°C), decomposition of the benzocyclobutenes was observed. These results further indicate that conrotatory ring opening of benzocyclobutenes to *o*-QDM systems of the type **44** is prohibited. From all of the literature examples shown above, one can conclude that *o*-QDMs bearing α-oxy or α-alkoxy substituents prefer to react with the substituents in the (E)-position.

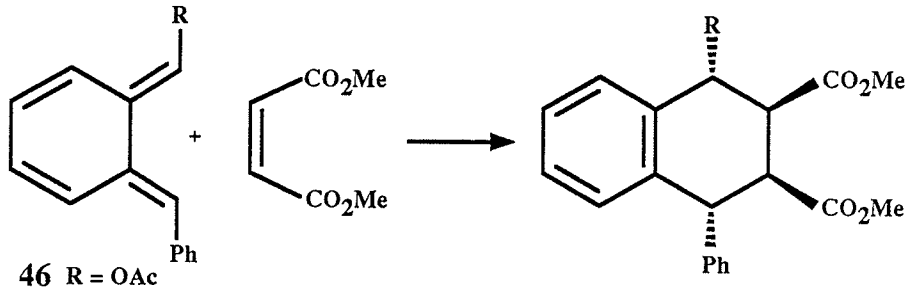
Charlton *et al* have generated α-oxy-α'-phenyl-*o*-QDMs and studied their reactivity with various dienophiles[19]. Thermolysis of the appropriate sulfone could in principle produce *o*-quinodimethanes **46**, **47**, **49** or **50**, depending on the configuration of the precursor used (*cis* or *trans*) and the mode of the pericyclic ring opening of the sulfone.



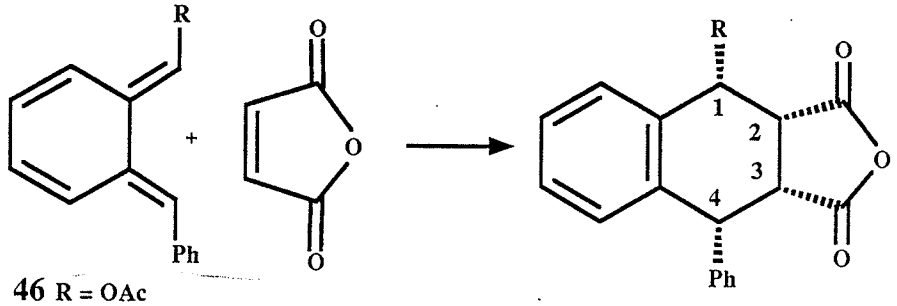
It was assumed that *cis*-sulfone **45** gave only the sterically less hindered (E,E)-*o*-QDM **46** rather than the sterically more hindered **47**. On the basis of the arguments put forward by Sammes *et al*[45], it was also assumed that *trans*-sulfone **48** gave only *o*-QDM **49**. **46** and other similar systems have been added to a variety of dienophiles[27,39,48]. The results are shown below:



46 R = OAc
51 R = OH
52 R = OMe
53 R = SCH_2Ph
54 R = Morpholine



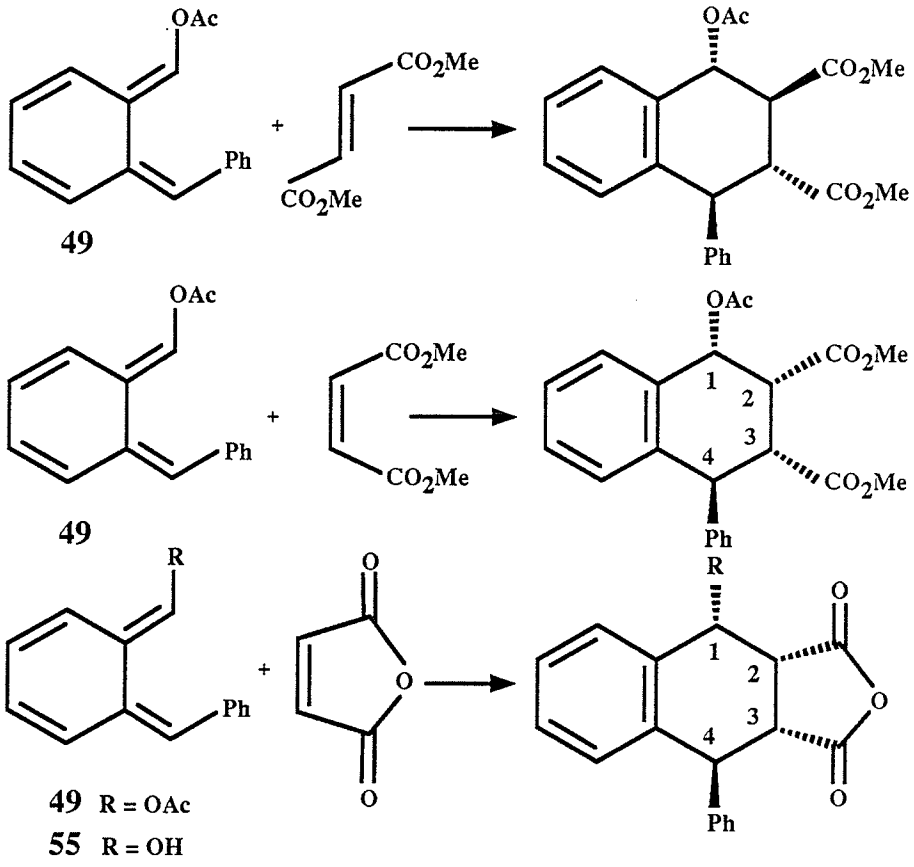
46 R = OAc
52 R = OMe



46 R = OAc
51 R = OH

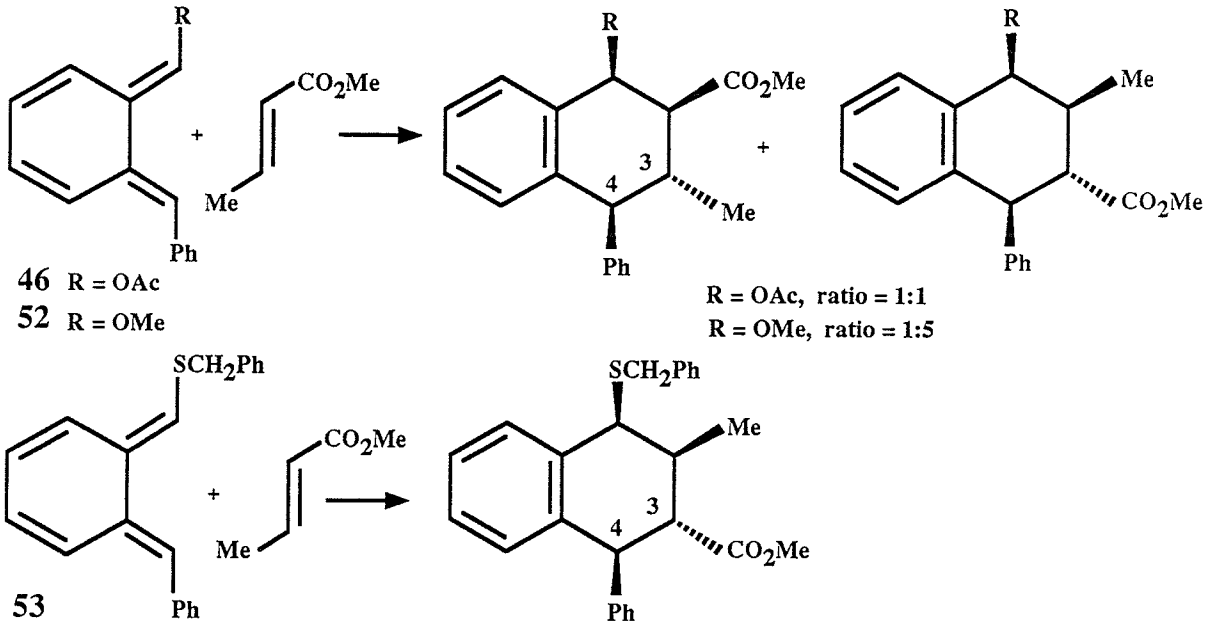
The reaction of *o*-QDMs **46** and **51-54** with dimethyl fumarate always produced the expected *endo*-adduct as the major isomer. However *endo-exo* selectivity varied with the dienophile. In the case of the reaction with dimethyl maleate, *o*-QDM **46** gave primarily *exo*-adduct while reaction with maleic anhydride gave *endo*-adduct exclusively.

The isomeric (E,Z)-*o*-QDM systems **49** and **55** have also been added to dienophiles[19,39].

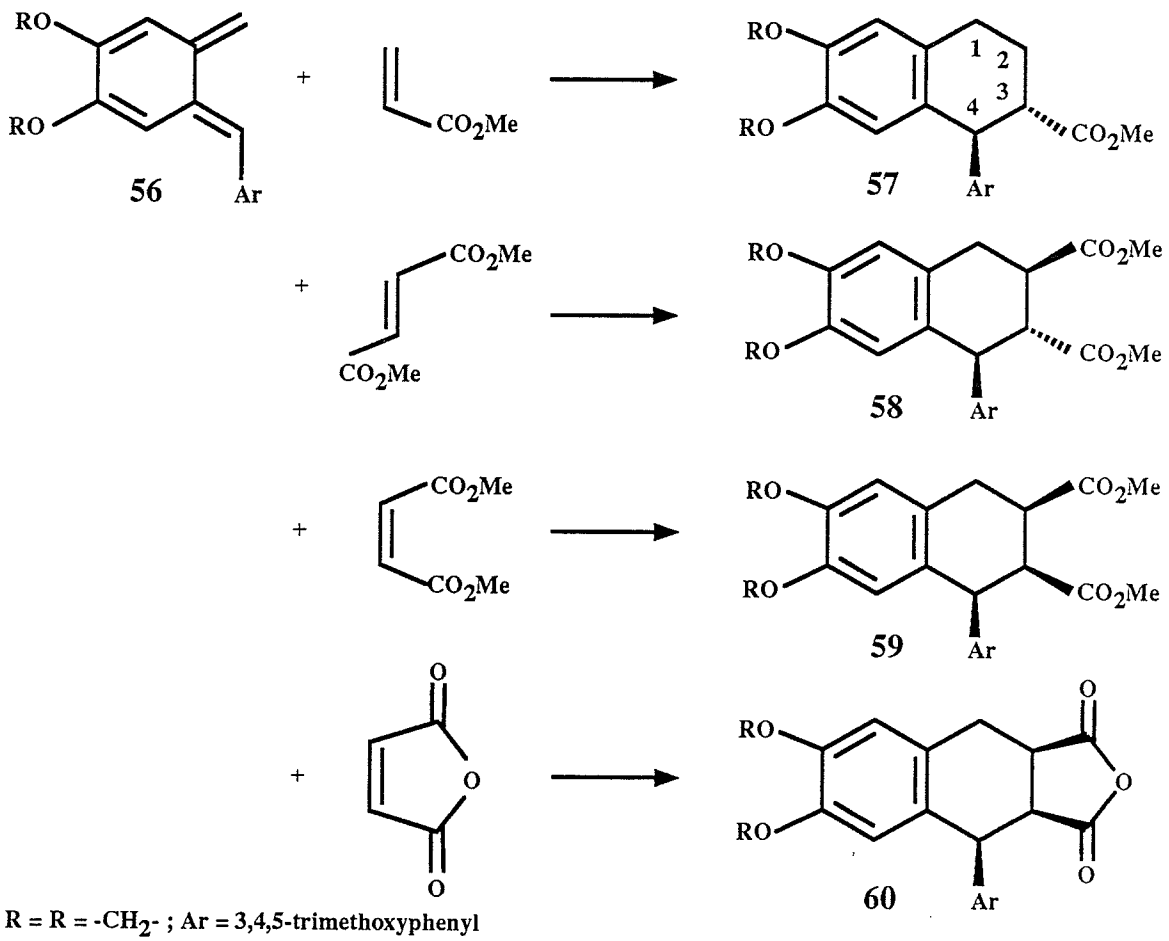


Reaction of *o*-QDM **49** with dimethyl fumarate gave an *exo*-addition product while its reaction with dimethyl maleate and maleic anhydride gave *endo*-adducts. *o*-QDM **55** also gave *endo*-adduct with maleic anhydride as dienophile. The presence of an α'-phenyl group in *o*-QDMs had a directing effect on the stereochemical outcome of the cycloaddition process. For example, the reactions of *o*-QDMs **46**, **49** and **51-54** with dimethyl fumarate and/or dimethyl maleate always gave cycloadducts with 3,4-*trans* stereochemistry. Steric repulsion may have forced the reaction to proceed in such a manner that the resulting adducts have a *trans* disposition between the 4-phenyl and the neighbouring group at the 3-position. However, with maleic anhydride as dienophile (reactions with *o*-QDMs **46**, **49**, **51**, and **55**), secondary orbital interactions were the principle controlling factor in the cycloadditon, overrode the steric repulsion factor, and only *endo*-adducts were produced regardless of the stereochemistry at the 3 and 4 position. Addition of *o*-QDMs **46** and **52** to methyl crotonate proceeded with poor regioselectivity

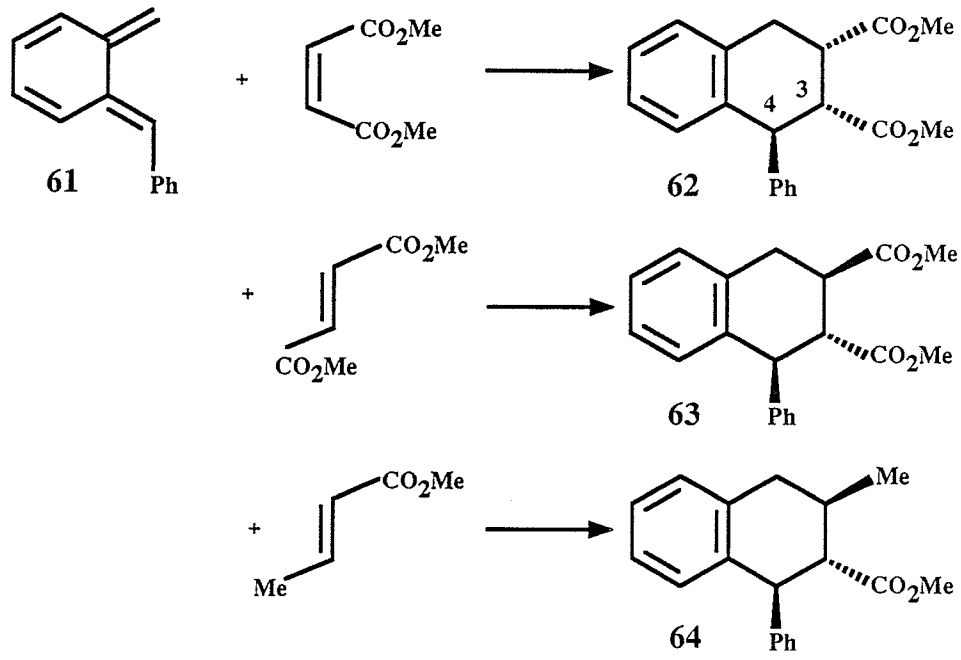
while *o*-QDM **53** proceeded with good regioselectivity[19,27]. The cycloaddition once again produced adducts with *trans*-3,4 stereochemistry.



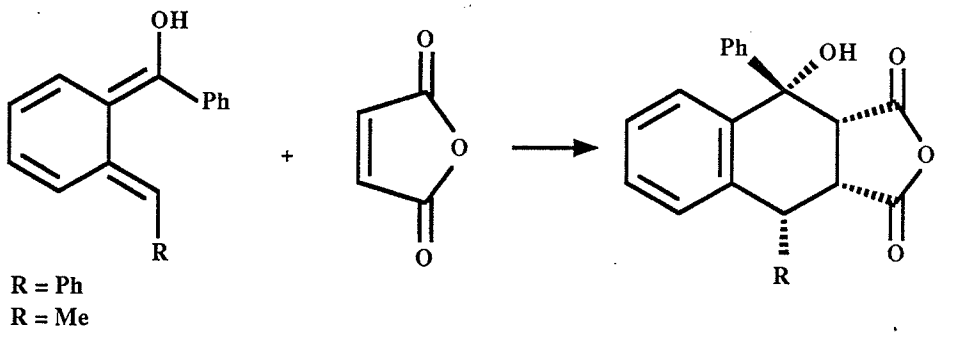
Mann and Piper generated the phenyl substituted *o*-QDM **56** and studied its stereoselectivity in cycloadditions[20]. With dimethyl maleate as dienophile *endo* adduct **59** was reported as the sole product. Dimethyl fumarate gave *exo* adduct with the phenyl group *trans* to the neighbouring ester function. In the case of methyl acrylate, adduct **57** was isolated as the major adduct along with 25% of the 3,4-*cis* isomer. It was claimed that the amount of *cis*-3,4 isomer was increased when addition was carried out at a slightly lower temperature. The authors concluded that the *trans*-3,4-adduct was the result of a retro Diels-Alder addition. In other words, at 200°C (the temperature at which o-QDM **56** was generated) the initially formed adducts with *cis*-3,4-stereochemistry subsequently isomerised to the thermodynamically more stable *trans*-3,4-adducts.

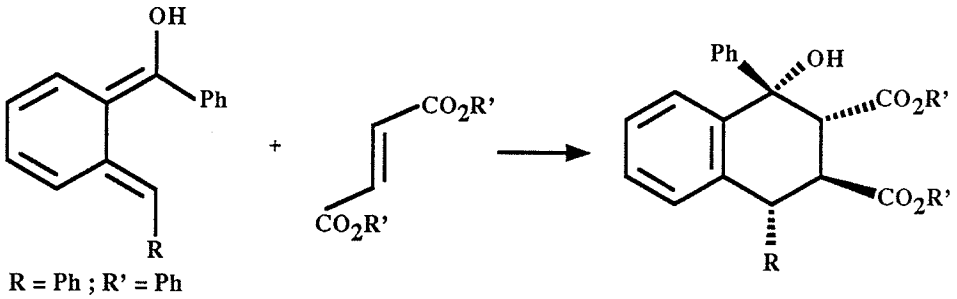


Contradictory results were published later by Charlton and Durst although the *o*-QDM used was slightly different[22]. o-QDM **61** was generated at 80°C and added to dimethyl fumarate, dimethyl maleate and methyl crotonate. With dimethyl maleate the adduct obtained (**62**) had *trans*-3,4-stereochemistry, opposite to what Mann and Piper observed earlier. Since the addition was carried out at a much lower temperature, isomerization of 3,4-*cis* adduct to the 3,4-*trans* adduct (as claimed by Mann and Piper) appeared to be highly unlikely. Methyl crotonate also added regioselectively to formed *exo*-adduct **64.** The adduct **63** formed with dimethyl fumarate was also *exo*, in agreement with results reported by Mann and Piper[20].



α,α,α'-Trisubstituted *o*-QDMs have been generated photochemically, and addition gave predominantly *endo* adducts[48].



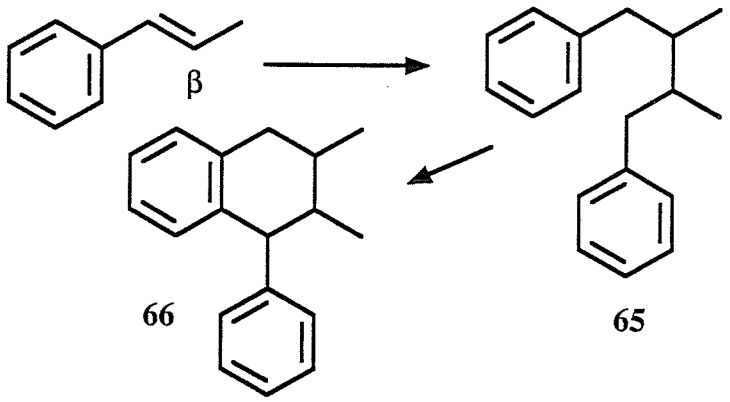


In summary, all of the literature examples on non-asymmetric Diels-Alder reactions of *o*-QDMs indicate that the cycloadditions normally follow the Alder *endo* rule giving predominantly *endo* adducts. The only exceptions appear to be those cases in which the presence of an α-phenyl or α-aryl group in the *o*-QDM leads to cycloadducts with the phenyl or aryl group trans to the neighbouring substituent. Maleic anhydride always reacts via an *endo* transition state.

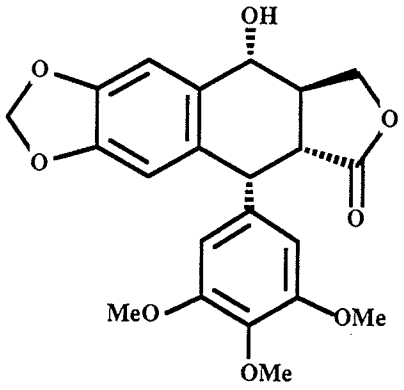
Section 1.5: Application of non-asymmetric Diels-Alder reactions of *o*-quinodimethanes in natural product(s) syntheses

Non-asymmetric Diels-Alder reaction of *o*-QDMs have been applied extensively in organic synthesis. Both inter- and intramolecular processes have been employed. The classes of compounds synthesized using o-quinodimethanes include alkaloids[17,49], steroids[50-52], terpenes[49], anthracyclines[53] and aryltetralin lignans[4]. An exhaustive survey of the literature would be impractical since it is so extensive, and this review will only survey the area of aryltetralin lignans since this thesis research involves the synthesis of these compounds. Readers who are interested in other areas are encouraged to read the review articles referenced.

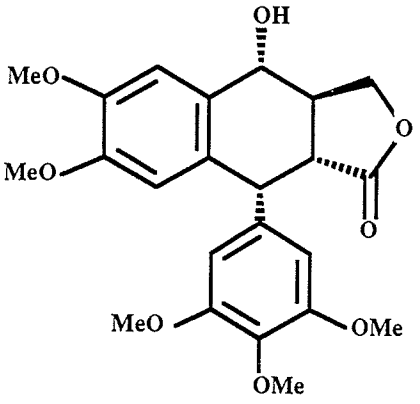
Lignans are a class of natural products (isolated from plants) which contain the basic 2,3-dibenzylbutane skeleton **65**. They are probably formed from two propylphenyl units linked together at the β-carbon of each side chain. Lignans with the side chain fused with the aromatic ring can be classified into two main groups. One of the groups is called the aryltetralin lignans, and they can be represented by the basic structure **66**[54].



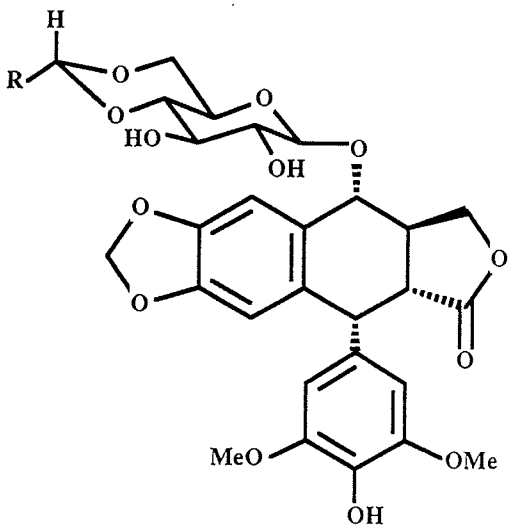
Among the aryltetralin lignans isolated from nature, podophyllotoxin is the most well known because of its antimitotic and tumour damaging activity. Its semisynthetic derivatives etoposide and teniposide are in clinical use as anticancer agents[55]. Sikkimotoxin has also received considerable attention as a potential cancer chemotherapeutic agent.



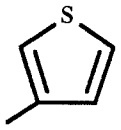
podophyllotoxin



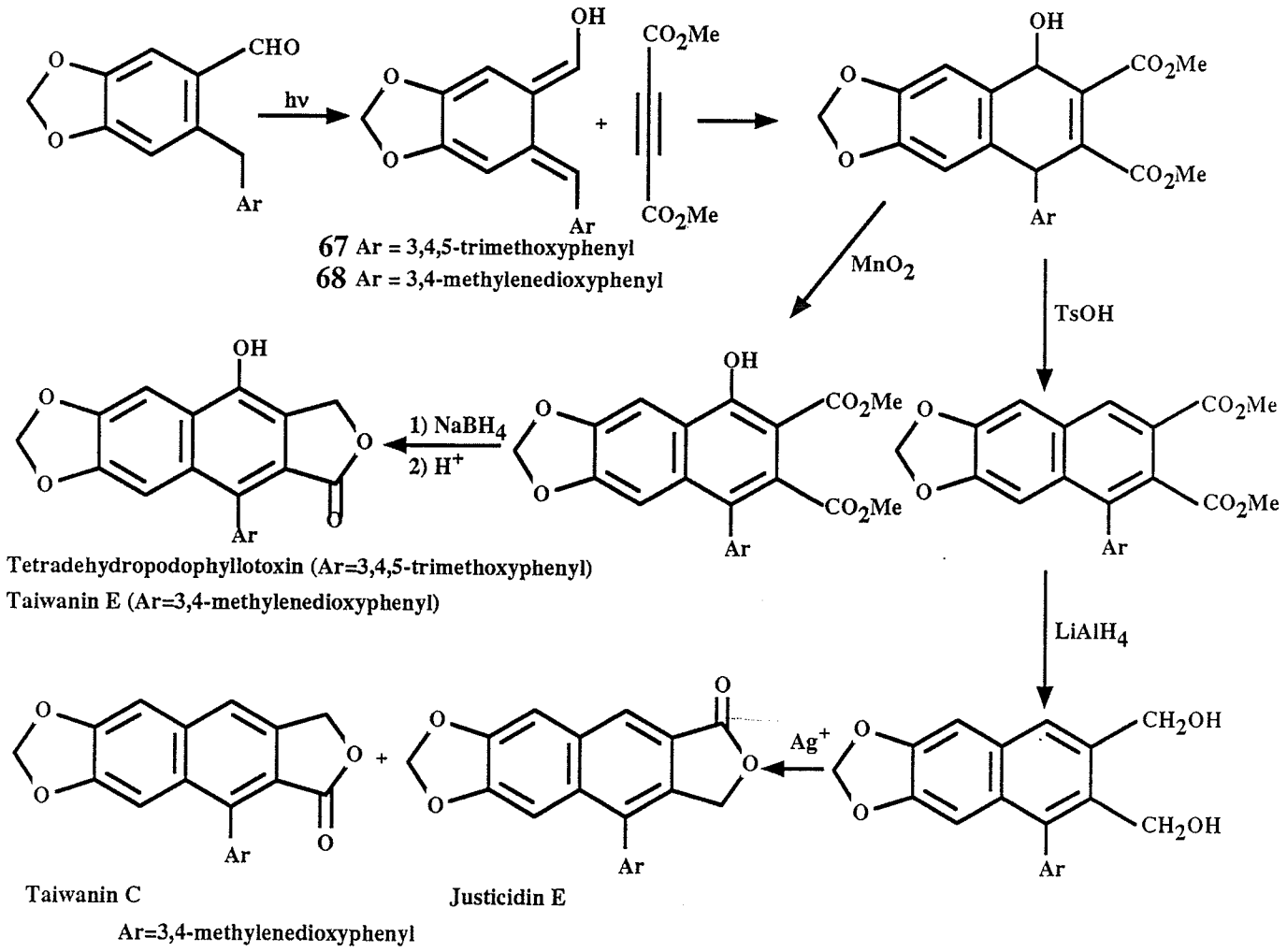
sikkimotoxin



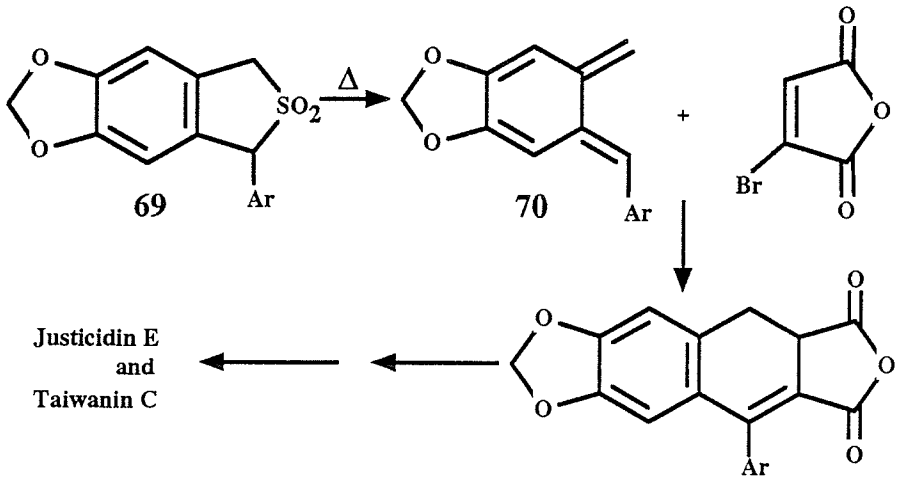
R = Me, etoposide

R =  , teniposide

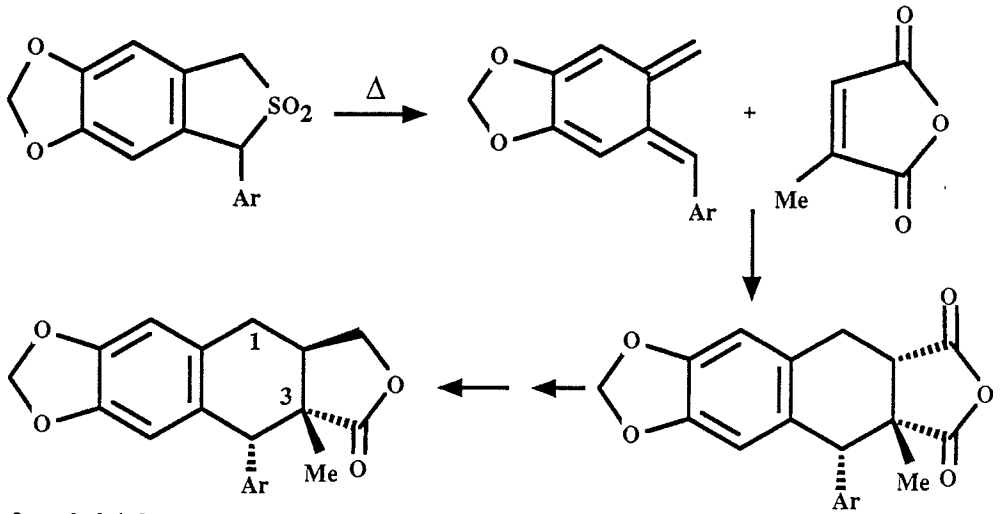
The synthesis of aryltetralin lignans using *o*-QDMs has been reviewed recently[4]. Block and Stevenson first prepared lignan analogs by irradiating 2-methylbenzophenone in the presence of various dienophiles[46]. Later Sammes *et al* synthesized Tetradehydropodophyllotoxin, Justicidin E, Taiwanin C and E via *o*-QDMs **67** and **68**[15].



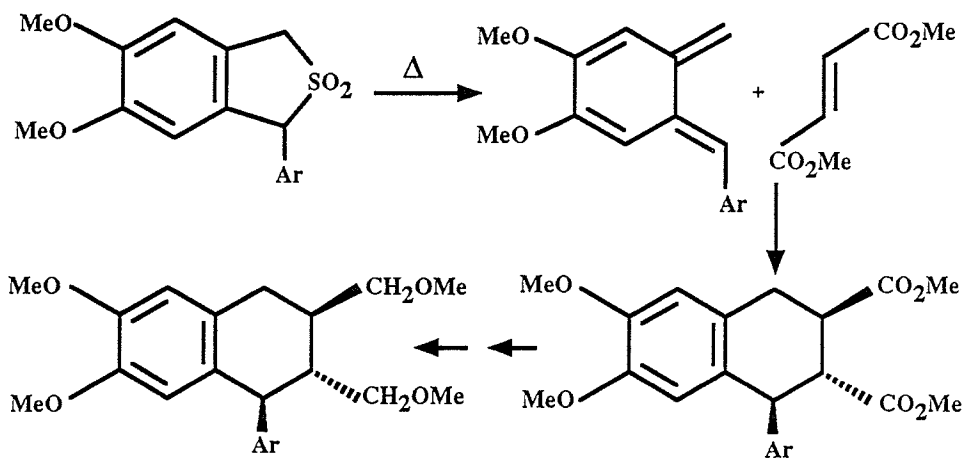
Justicidin E and Taiwanin C were also prepared by Mann *et al* by generating *o*-QDM **70** from sulphone **69**[20-21].



70 was also the key intermediate in the synthesis of 3-methyl-1-deoxypodophyllotoxin[56].

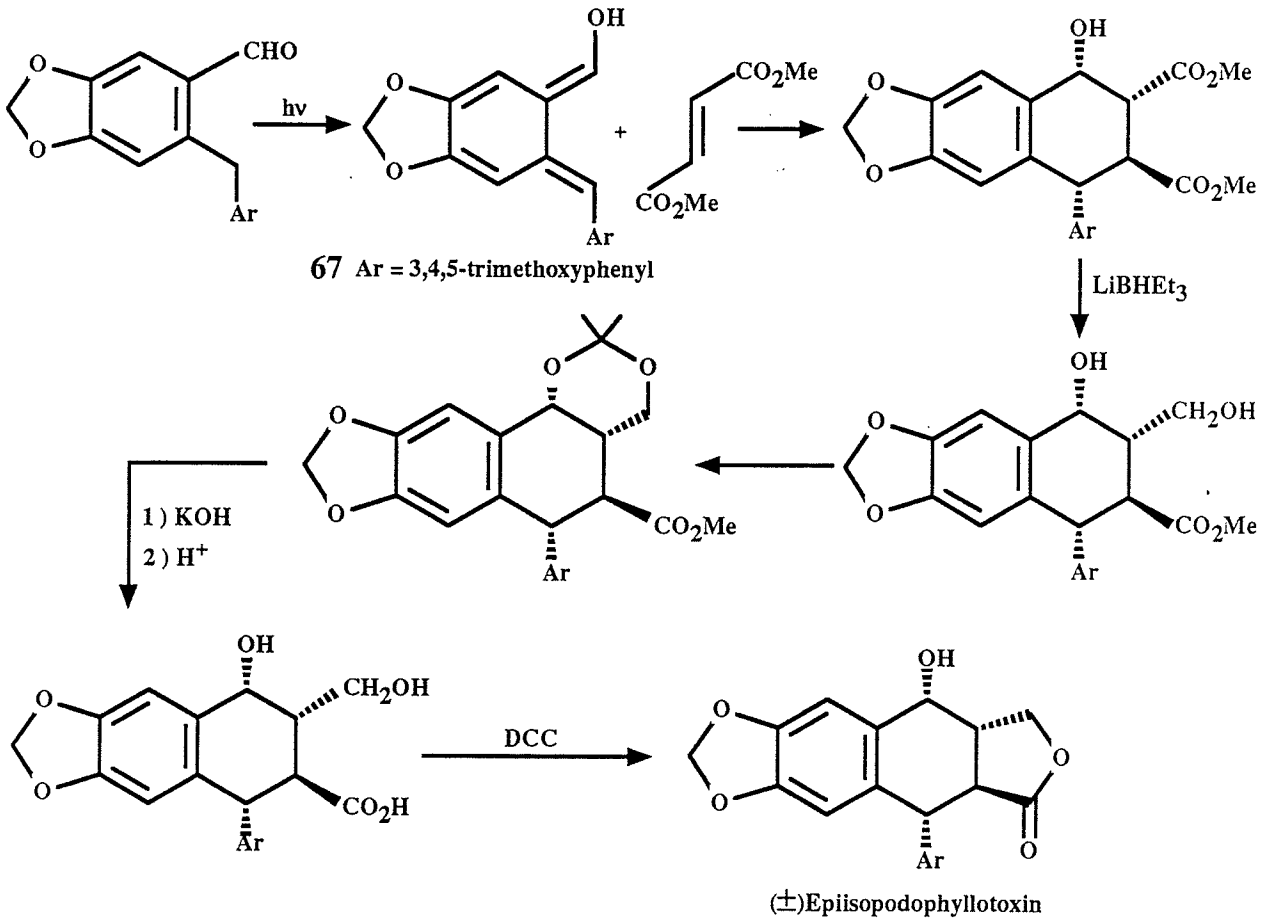


A similar sulfone was generated by Mann for the preparation of (±)-phyltetralin and other lignan analogs[21,57].



(±)Phyltetralin
Ar = 3,4-dimethoxyphenyl

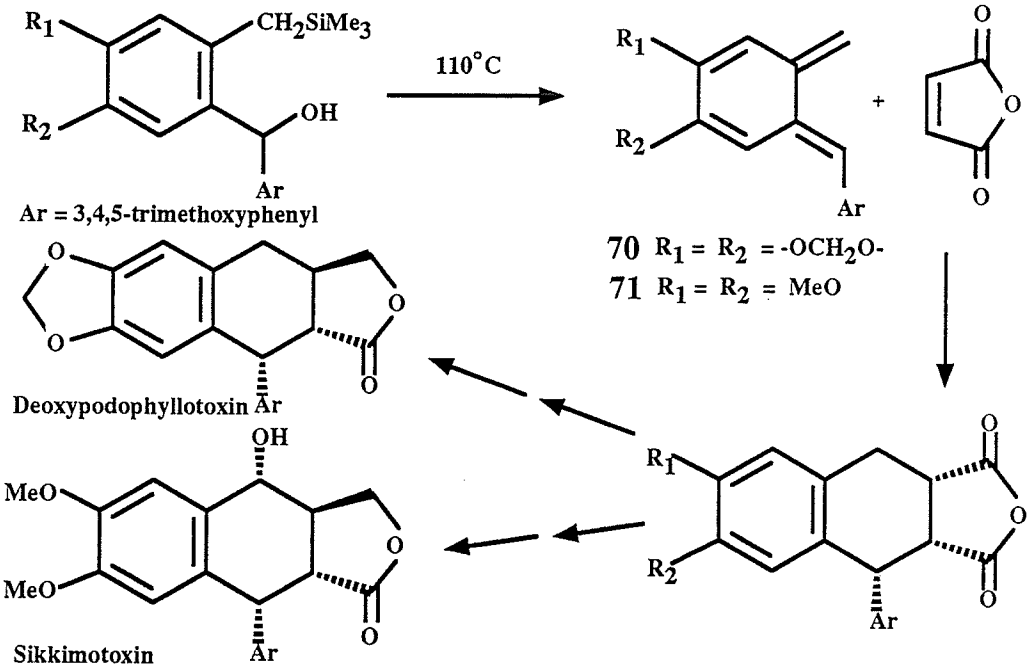
Durst and Glinski generated *o*-QDM **67** and trapped it with dimethyl fumarate to produce the *endo* cycloadduct which was converted to (±)-epiisopodophyllotoxin[58].



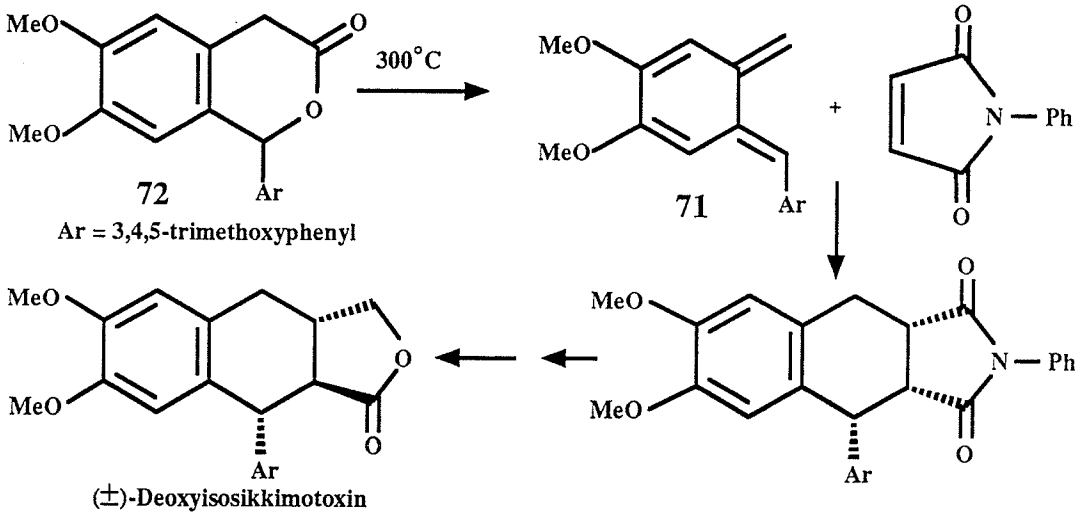
67 Ar = 3,4,5-trimethoxyphenyl

(±)Epiisopodophyllotoxin

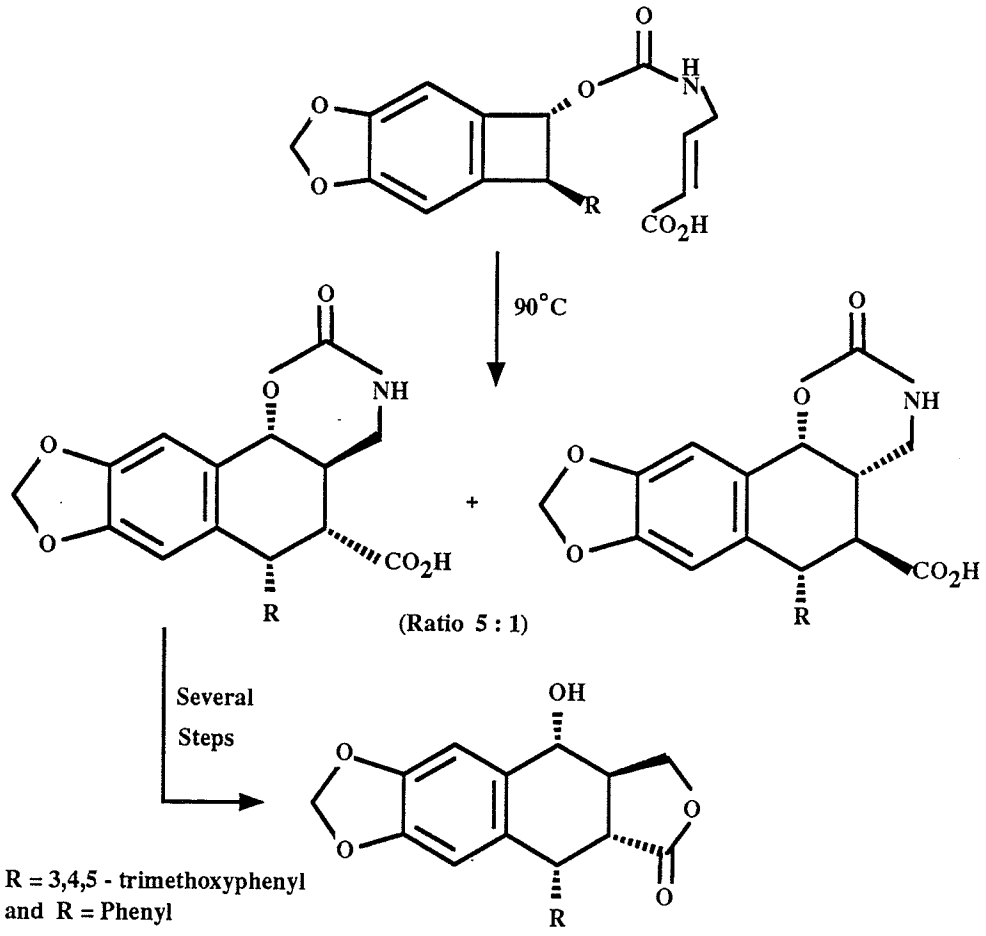
Generation of *o*-QDMs employing the benzo-Peterson reaction was explored by Takano *et al.* Under thermal conditions, *o*-QDMs **70**[59] and **71**[60] were formed by 1,4-elimination from the corresponding *o*-hydroxymethylbenzylsilane. The resulting maleic anhydride *endo* adducts were converted to (±)-deoxypodophyllotoxin and (±)-sikkimotoxin.



Das *et al* also generated *o*-QDM **71** by thermolysis of isochromanone **72**[61]. The adduct with N-phenyl maleimide was subsequently converted to (±)-deoxyisosikkimotoxin.



A racemic synthesis of podophyllotoxin and analogues via intramolecular cycloaddition of *o*-QDM was recently accomplished by McDonald and Durst[8]. Appropriately substituted benzocyclobutenes were thermolised and adducts with the same relative stereochemistry as podophyllotoxin were isolated.

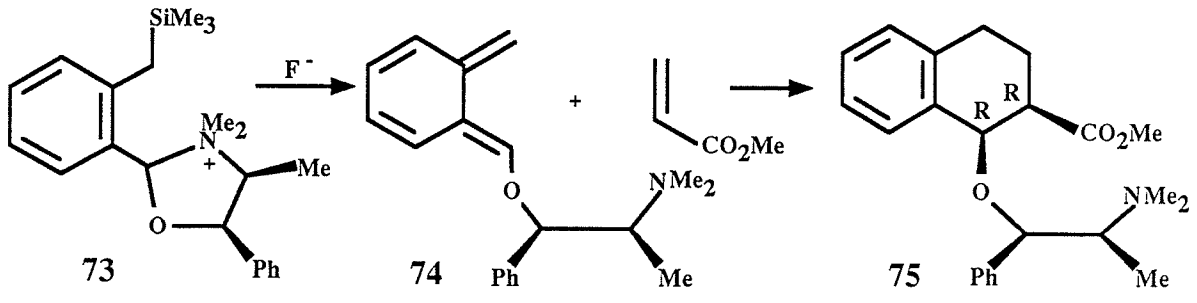


As shown by the literature review and the few examples above, *o*-QDMs are versatile intermediates in organic synthesis.

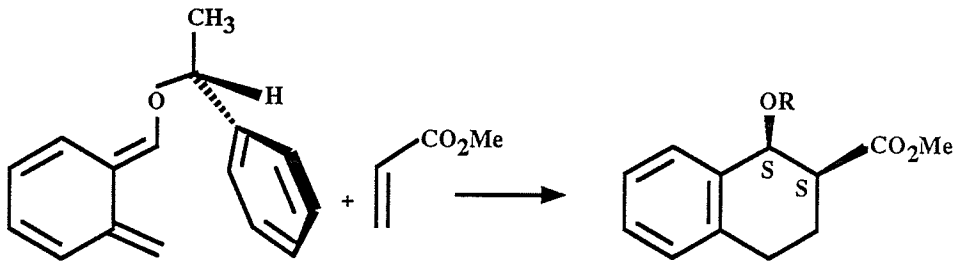
Section 1.6: Asymmetric Diels-Alder reactions of *o*-Quinodimethanes

As mentioned in section 1.3, for a Diels-Alder reaction to be asymmetric, the adduct generated must be of predominantly one absolute configuration. The absolute configuration of the adduct obtained is directly related to the face at which the diene and/or dienophile react. Hence to achieve asymmetric induction during the reaction, one must be able to control the facial selectivity of the reaction. One way of achieving such a goal is to place a control element on the diene. Such a control element is often referred to as a chiral auxiliary and it is usually homochiral (of one absolute configuration). A chiral auxiliary which can be removed easily from the cycloadduct and recovered is also desirable.

Ito *et al* were the first to introduce a chiral auxiliary into an *o*-QDM system[62]. The oxazolidinium system **73** was prepared, and treated with fluoride anion to generate o-QDM **74**. Reaction with methyl acrylate led to the *endo* adduct **75** with a predominance of the (R,R) configuration (ratio of 2:1 over (S,S)). These researchers concluded that the asymmetric induction was due to π-stacking of the phenyl group of the chiral substituent with one face of the *o*-QDM, thereby preventing the dienophile from adding to that face.

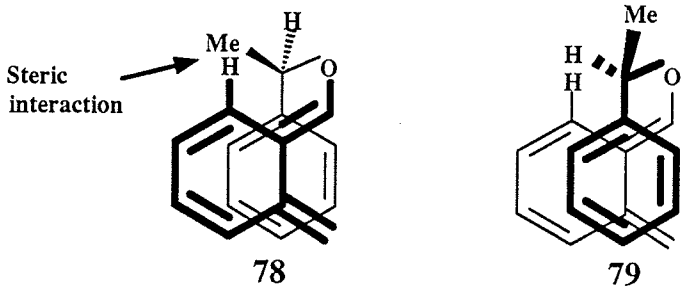


Later, Charlton studied a similar case and showed that π-stacking was not the controlling mechanism[24,28].



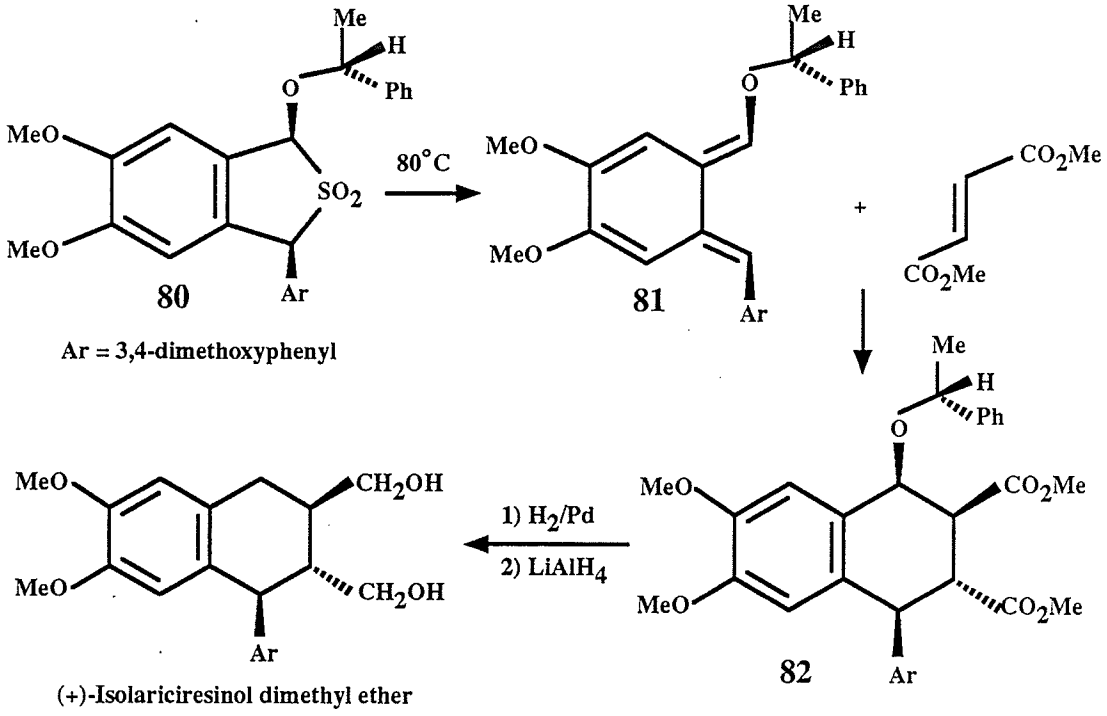
76 **77**

He generated *o*-QDM **76** and reacted it with methyl acrylate to give the major adduct **77**, which had the (S,S) stereochemistry. According to Ito *et al*, **76** should π-stack to form conformations **78** and **79**, with **79** having less non-bonded interactions relative to **78**. *Endo* addition of methyl acrylate to the less sterically hindered face of **79** would have given **77** with the (R,R) configuration, opposite to what was observed experimentally. Charlton proposed that the intermediate *o*-QDM **76** had a preferred conformation as shown above. The phenyl group in the chiral auxiliary would block the bottom face of the diene system thereby leading to asymmetric induction and the absolute stereochemistry observed.



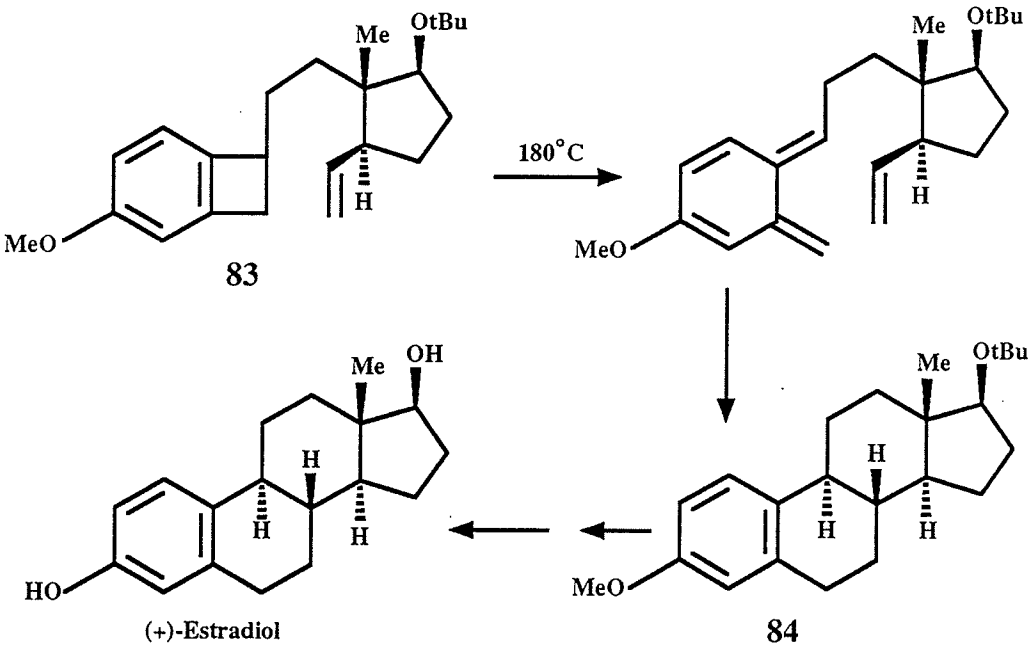
78 **79**

In a following paper, Charlton *et al* exchanged the methyl group in the chiral auxiliary for an isopropyl or t-butyl group[25]. The exchange was found to improve the diastereoselectivity of the cycloaddition. This would suggest that increasing the size of the alkyl group increases the preference for conformation **76.** This new found facial control strategy was later applied to the asymmetric synthesis of (+)-isolariciresinol dimethyl ether[23]. Sulfone **80** bearing the (R)-1-phenylethyl chiral auxiliary was the *o*-QDM precursor used in this synthesis.



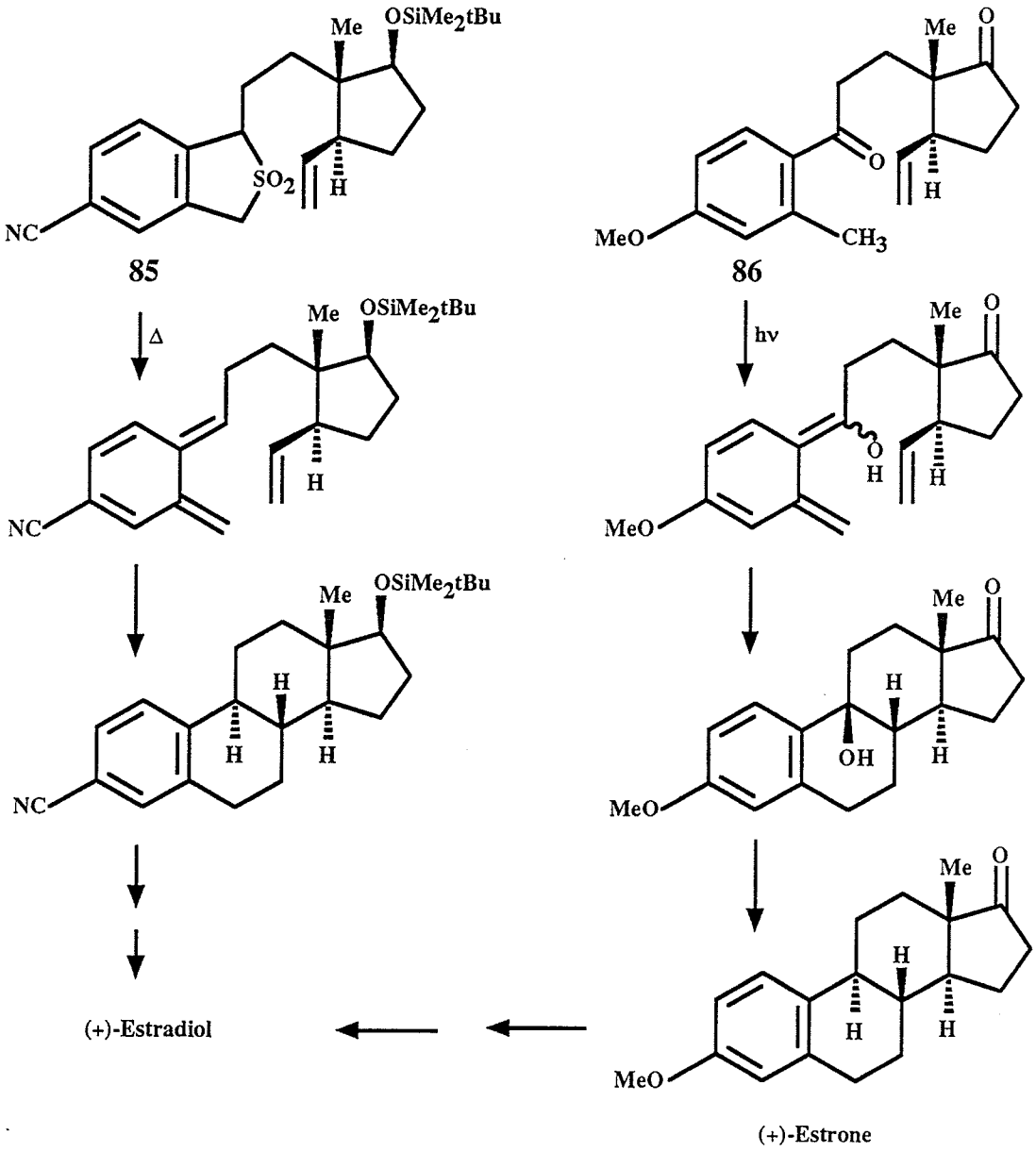
Generation of *o*-QDM **81** in the presence of dimethyl fumarate produced **82** as the major *endo* adduct. Removal of the chiral auxiliary and reduction gave (+)-isolariciresinol with an optical purity of 83%.

An alternate way of controlling the facial selectivity would be to place the control element on the dienophile. Such strategy was employed by Kametani and Nemoto in the asymmetric synthesis of estradiol[63]. Thermolysis of benzocyclobutene **83** gave adduct **84** exclusively. In this case the reaction proceeded through the sterically favoured *exo* transition state and the existing chiral centres near the dienophile controlled the face at which the dienophile reacted. The adduct was converted to (+)-estradiol with an enantiomeric excess of 97%.

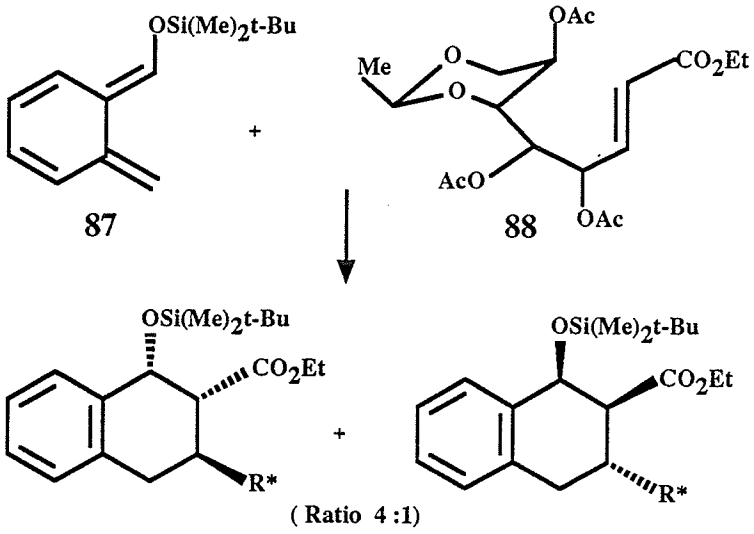


Later Oppolzer *et al* also synthesized optically pure estradiol employing a similar *o*-QDM system[4]. In this case sulfone **85** was the *o*-QDM precursor.

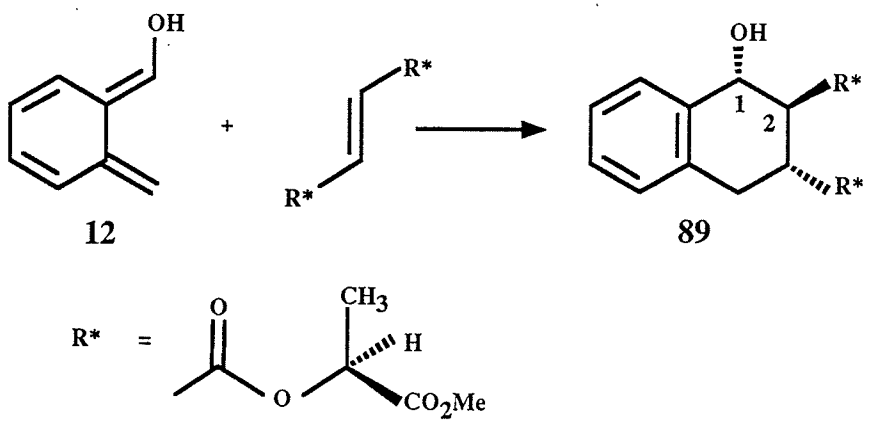
(+)-Estrone which could be converted to (+)-estradiol was prepared by Quinkert and stark[51]. The required *o*-QDM was generated photochemically from the corresponding ketone **86**.



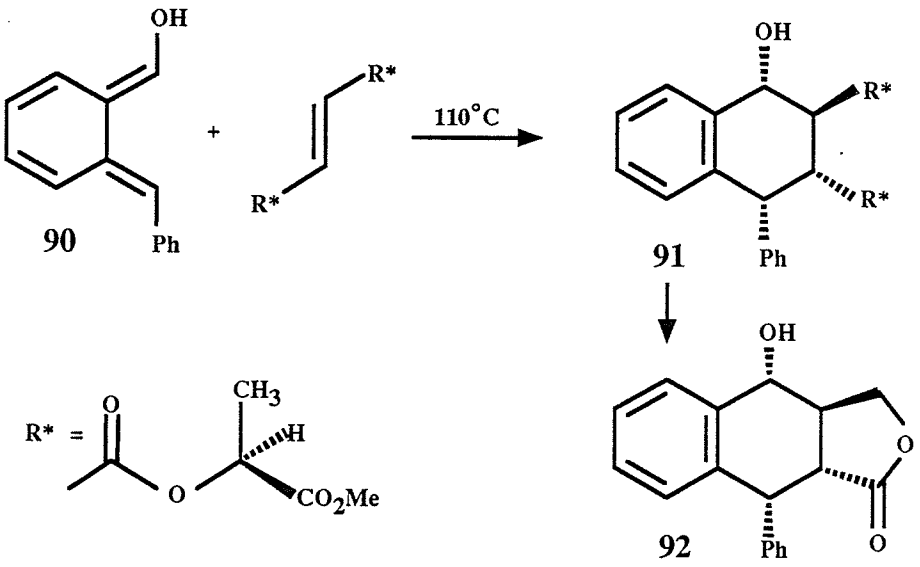
Franck *et al* investigated the addition of *o*-QDM **87** to the chiral dienophile **88**[64]. The addition gave two *endo* adducts in the ratio of 4:1. They concluded that orbital interaction was dominant over steric factors in controlling the facial selectivity at the dienophile.



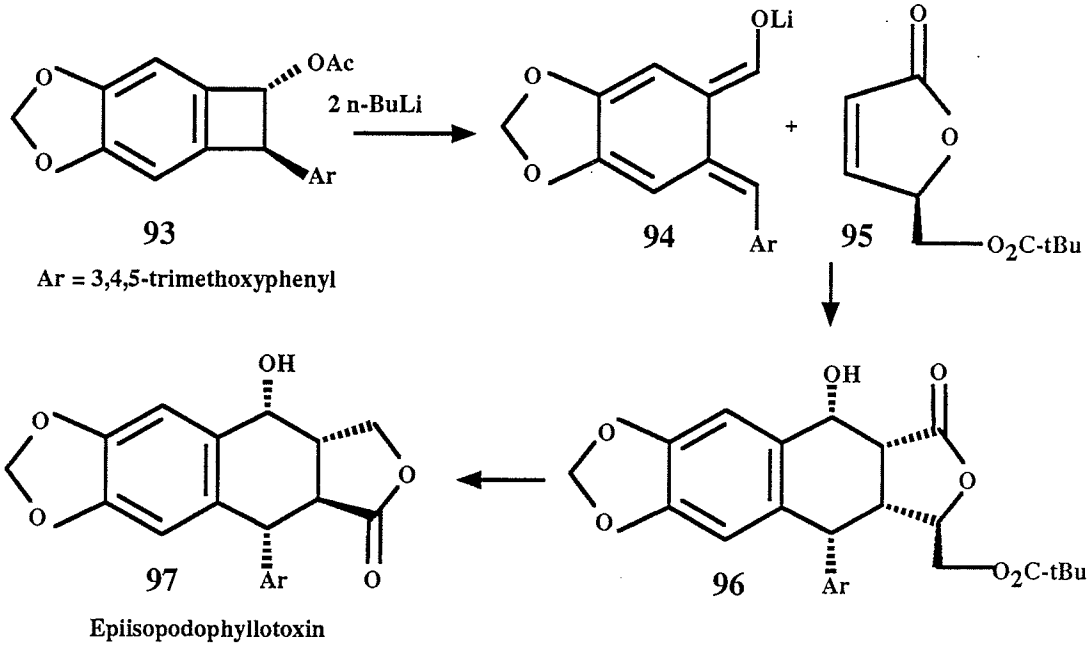
Parallel to this thesis work, a co-worker, Guy Plourde, studied the cycloaddition of the fumarate of (S)-methyl lactate with *o*-QDM **12**[6]. This reaction gave cycloadduct **89** with high asymmetric induction (de >95%), via an unusual *exo* transition state with preferential addition to the *re* face of the dienophile. The adduct possessed the 1,2-*trans* stereochemistry instead of the usual 1,2-*cis* stereochemistry observed from *endo* addition.



This highly diastereoseletive reaction was sucessfully applied to the asymmetric synthesis of a podophyllotoxin analog[65]. Generation of *o*-QDM **90** in the presence of (S)-methyl lactyl fumarate yielded adduct **91**, which was eventually converted to the podophyllotoxin analog **92**.

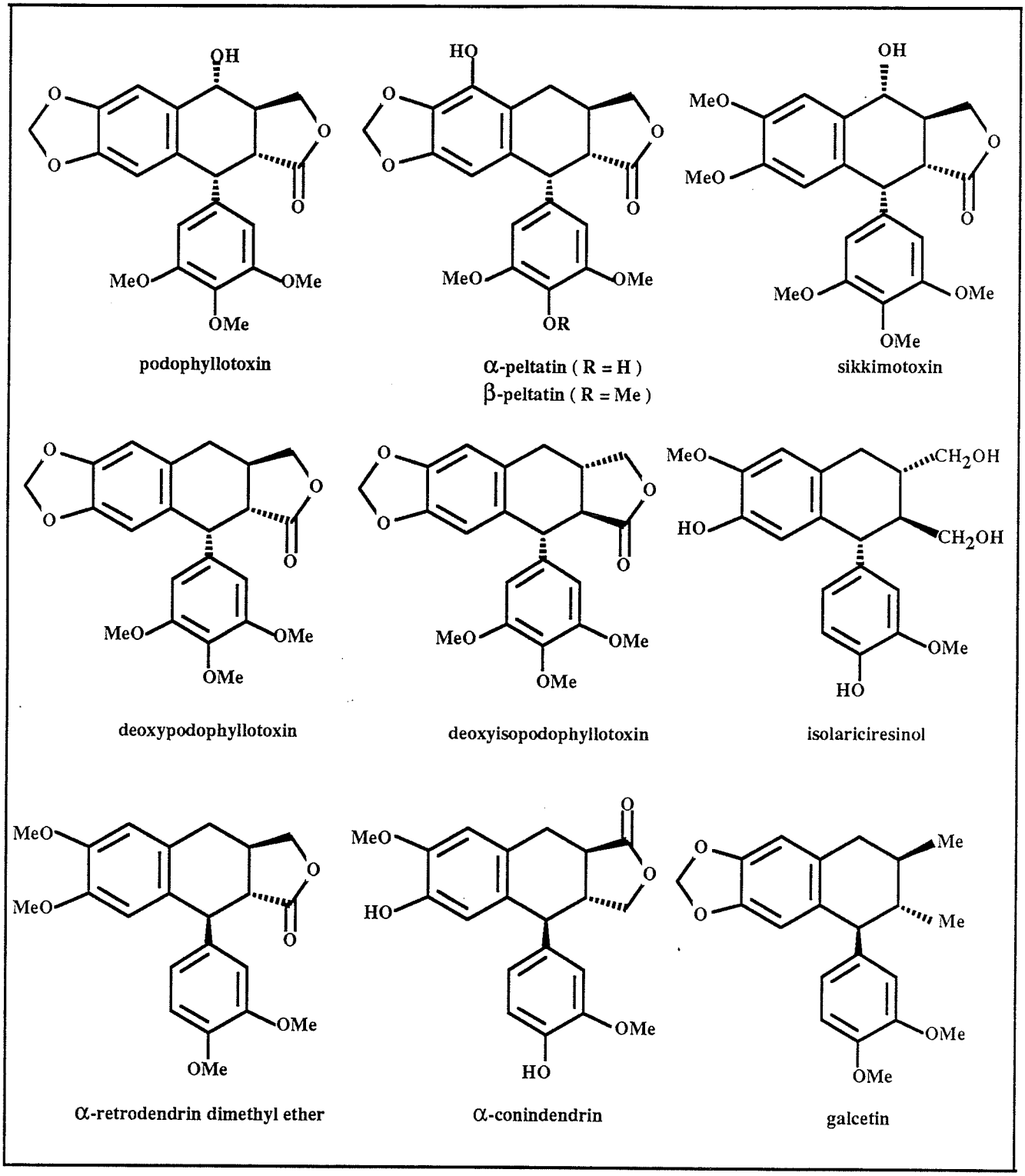


An asymmetric synthesis of epiisopodophyllotoxin **97** was recently attempted by Choy[66]. Treatment of benzocyclobutene acetate **93** with n-BuLi generated *o*-QDM **94**. Addition to the chiral butenolide **95** proceeded regioselectivitely and diastereoselectively to give the *endo* adduct **96** as the major product, which was subsequently converted to **97**.

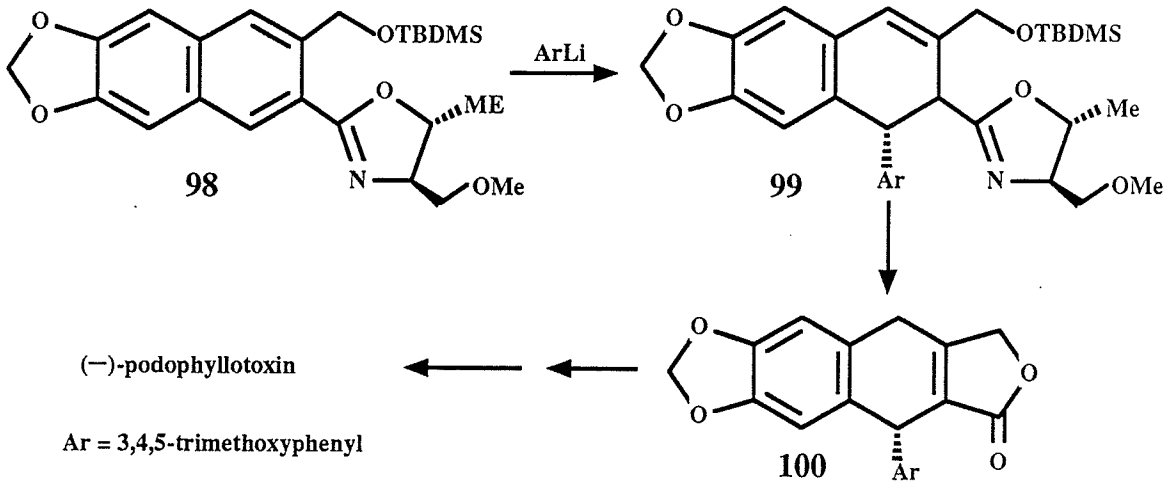


The literature survey above indicates that a limited amount of work has been done in the area of asymmetric Diels-Alder reactions of *o*-QDMs. In the area of aryltetralin lignan synthesis employing *o*-QDMs as a reaction intermediate, only the three asymmetric syntheses cited above have appeared in the literature. The various stereochemistries (both relative and absolute) present in aryltetralin lignans might be accessible by asymmetric Diels-Alder reactions of *o*-QDMs if appropriate chiral auxiliaries were chosen to control the stereochemical outcome. Figure 1 below illustrates some of the stereochemistries present in aryltetralin lignans isolated from the plants *Podophyllum peltatum* (May apple), *podophyllum emodi* and *podophyllum sikkimensis*[55].

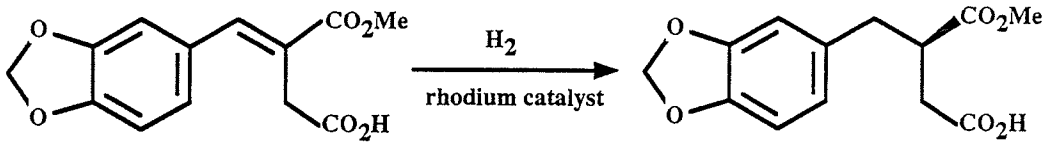
Figure 1:


podophyllotoxin
α-peltatin (R = H)
β-peltatin (R = Me)
sikkimotoxin
deoxypodophyllotoxin
deoxyisopodophyllotoxin
isolariciresinol
α-retrodendrin dimethyl ether
α-conindendrin
galcetin

Among the aryltetralin lignans shown in table 1, podophyllotoxin has received the most attention from organic and medicinal chemists. Its semisynthetic derivatives, etoposide and teniposide, are currently in use as anticancer drugs[55]. Synthetic chemists have been attracted to podophyllotoxin for the stereochemical challenge represented by its four contiguous chiral centers. The difficulty in synthesizing podophyllotoxin and other aryltetralin lignans having the same stereochemistry as podophyllotoxin resides in the control of the relative and absolute stereochemistries. Although there are many syntheses of racemic podophyllotoxin in the literature[67], only one asymmetric synthesis has been published. Meyers *et al* employed the chiral oxazoline system **98** to control the introduction of the 3,4,5-trimethoxyphenyl group. Compound **98** was asymmetrically alkylated with the 3,4,5-trimethoxyphenyl group to give the intermediate **99.** Removal of the chiral oxazoline followed by functional group conversion gave **100**, which was eventually converted to (−)-podophyllotoxin. The whole synthesis was achieved in 24 steps in an overall yield of 5%[68].



An asymmetric synthesis of (−)-deoxypodophyllotoxin, which can be converted to podophyllotoxin, has been accomplished by Achiwa *et al*[69]. The key step in this synthesis was the asymmetric hydrogenation of alkene **101** with a rhodium catalyst to give the intermediate **102**, which was converted to (−)-deoxopodophyllotoxin in 6 steps in an overall yield of 10%.

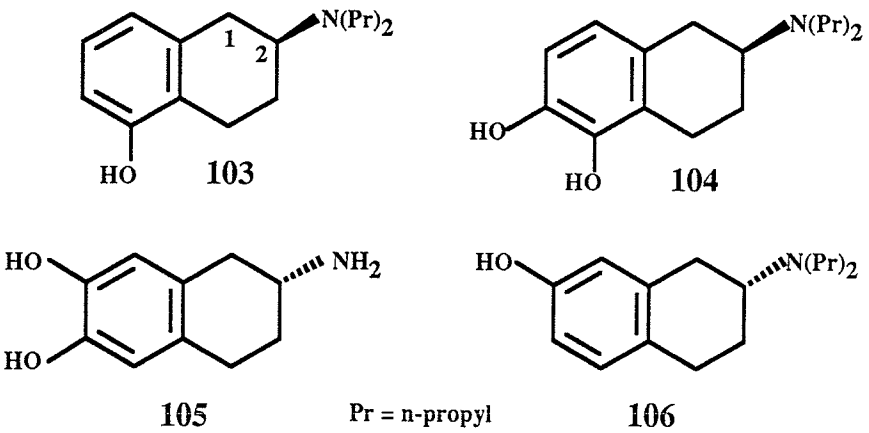


101 **102**

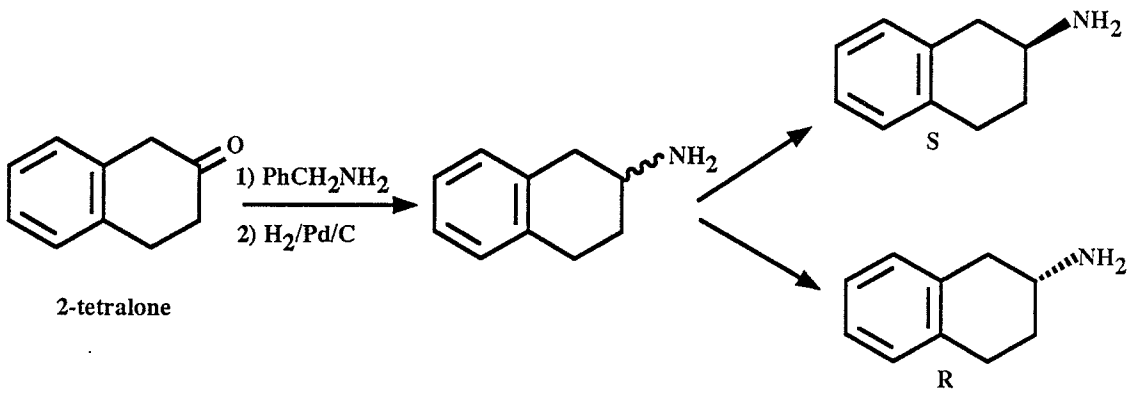
The asymmetric cycloaddition of *o*-QDMs to an appropriate dienophile may present a more efficient route to optically active podophyllotoxin and will be presented in this thesis work.

Another class of compounds which has received considerable attention from medicinal and organic chemists in recent years is the 2-aminotetralins, compounds well known to exhibit central nervous system drug activity[70-73]. Many 2-aminotetralins have been shown to be potent dopamine agonists and are potential antipsychotic and anti-parkinsonian drugs. Figure 2 below shows several 2-aminotetralins which are dopamine agonists[74].

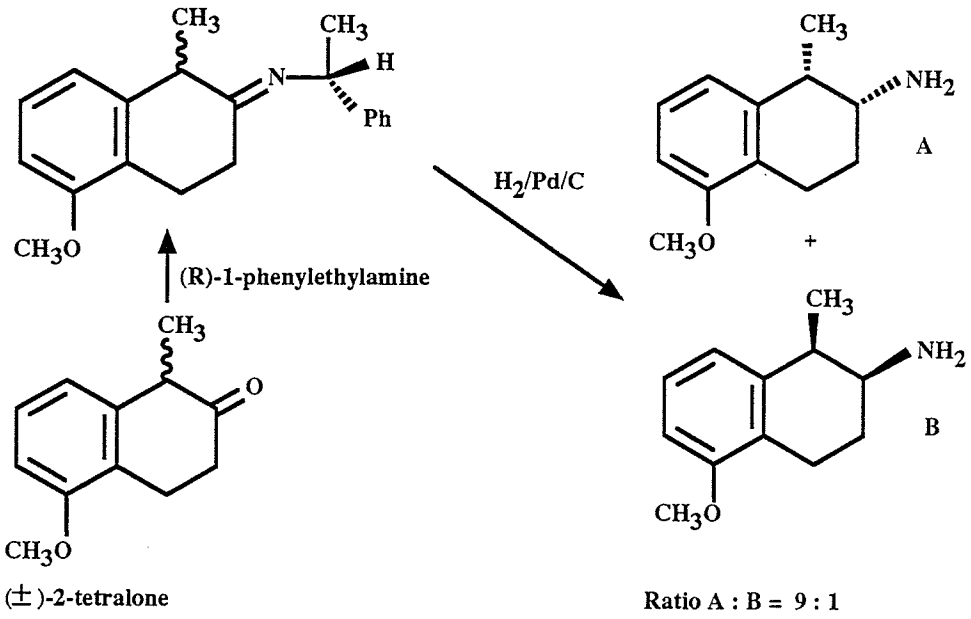
Figure 2:



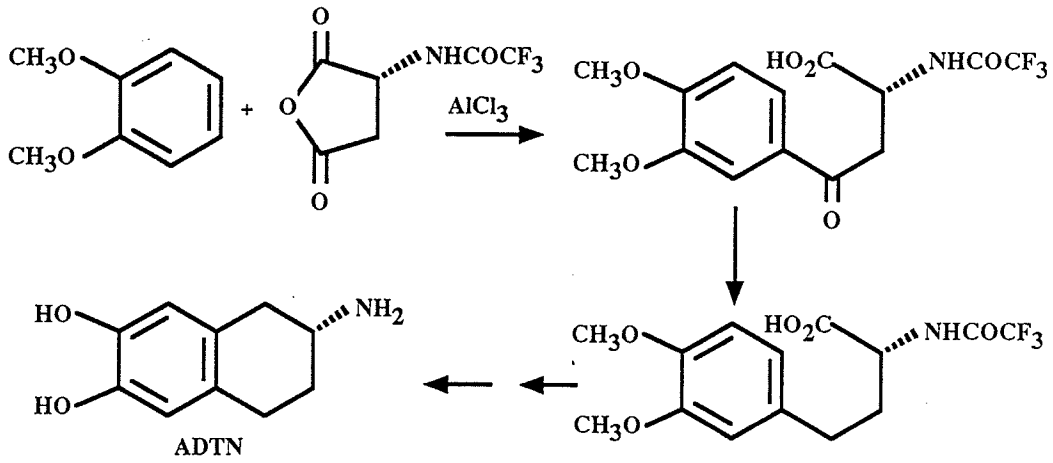
The biological activity in these compounds is directly related to the absolute configuration at C-2. For compounds **103** and **104** it was found that the more active enantiomer had the S configuration at C-2, whereas biological activity in **105** and **106** resided in the enantiomer with the R configuration. Their optical antipodes showed little or no dopaminergic activity. For proper biological testing of members of this class of compounds, the preparation of pure enantiomers is essential. In most cases, optically pure 2-aminotetralins have been obtained by reductive amination of the 2-tetralones followed by resolution of the resulting racemic amines[74].



An asymmetric reductive amination procedure utilizing (R)-1-phenylethylamine for the preparation of nonracemic 1-methyl-5-methoxy aminotetralins has appeared in the literature[75].



A chiral pool synthesis of (R)-2-amino-6,7-dihydroxytetrahydronaphthalene (ADTN) employing (R)-N-(trifluoroacetyl)aspartic anhydride as a chiral synthon has also been published. ADTN was prepared with an optical purity of ≥97%[76].



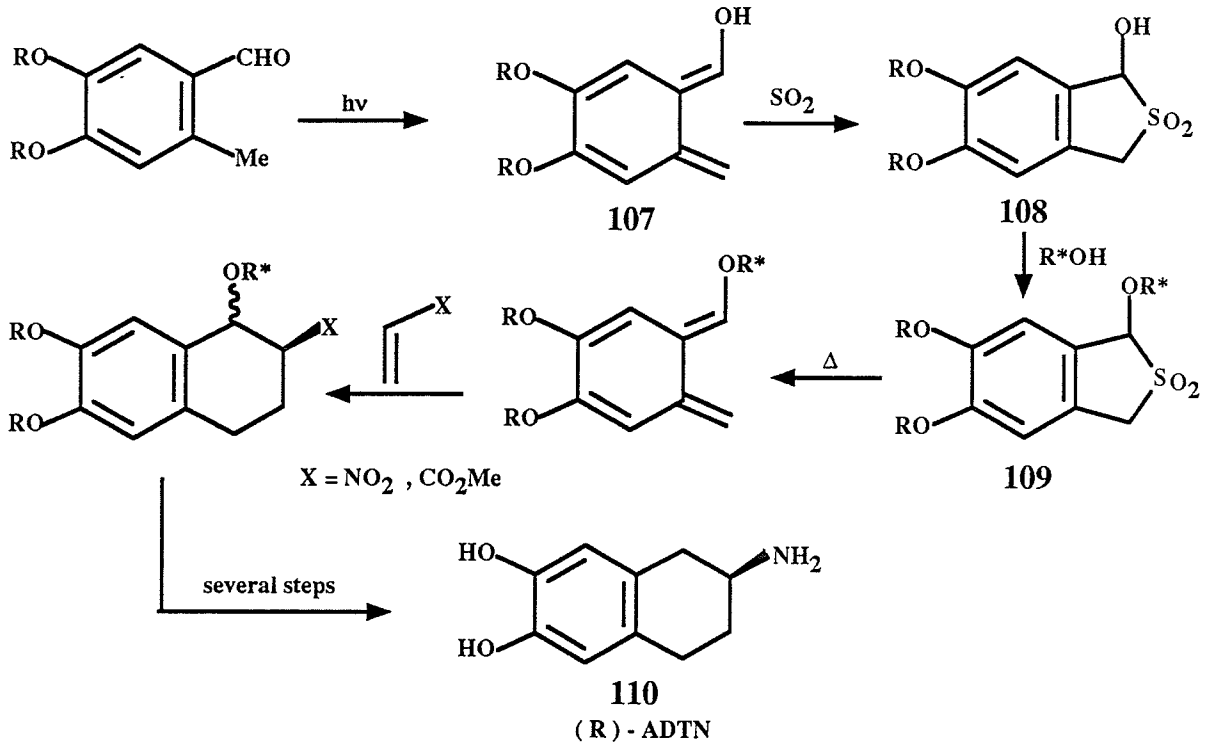
Both of the syntheses shown above lack generality. Synthesis employing asymmetric reductive amination depends on the availability of the required 2-tetralones. The chiral pool synthesis is tied to a specific chiral synthon. In this thesis work, a general asymmetric synthesis of ADTN employing *o*-QDM as a key intermediate will be presented.

CHAPTER 2

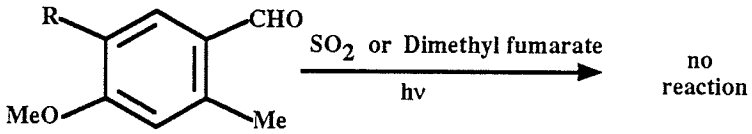
RESULTS AND DISCUSSION

Studies of the cycloaddition reactions of *o*-QDMs and of the application of these reactions to natural product synthesis have been carried out. This section will disclose the details of these studies. At the outset of this thesis research, an asymmetric synthesis of the biologically active 2-aminotetralin **110**[70-72] utilizing an *o*-QDM as an intermediate was proposed. The proposed strategy involved the photolysis of an appropriately substituted 2-methylbenzaldehyde in the presence of sulfur dioxide to give the sulfone **108**, via trapping of the intermediate *o*-QDM **107**. Sulfone **108** would then be converted to alkoxy sulfone **109** bearing a chiral auxiliary (R*), using a method previously developed by Charlton and Durst[18]. The presence of the chiral auxiliary R* in the *o*-QDM generated thermally from **109** would hopefully control the facial selectivity of the subsequent cycloaddition step. The adduct would then be converted to the optically active target molecule **110**.

Proposed Synthesis of ADTN



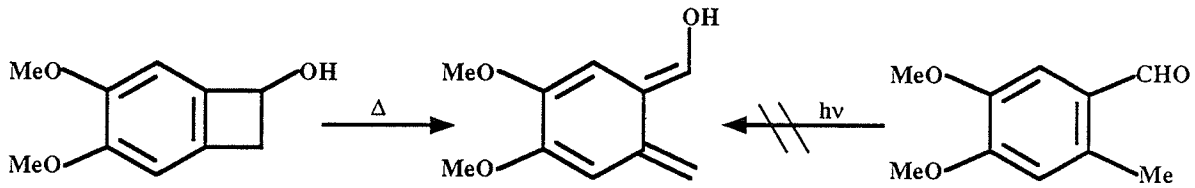
4,5-Dimethoxy-2-methylbenzaldehyde **113** would have been an appropriate starting aldehyde for such a synthetic expedition. However, it had been previously shown that photolysis of this aldehyde with sulfur dioxide under various conditions did not produce any desirable sulfone[76]. As part of this thesis work, photolysis of 4-methoxy-2-methylbenzaldehyde **114** with sulfur dioxide and dimethyl fumarate was investigated, and also failed to produce any of the expected trapping products from the *o*-QDM. Only the starting materials were recovered.



113 R = OMe
114 R = H

The failure of the above reactions may be due to the unsuccessful photoconversion of the aldehydes to *o*-QDMs, or to the unreactive nature of the *o*-QDMs toward dienophiles. The

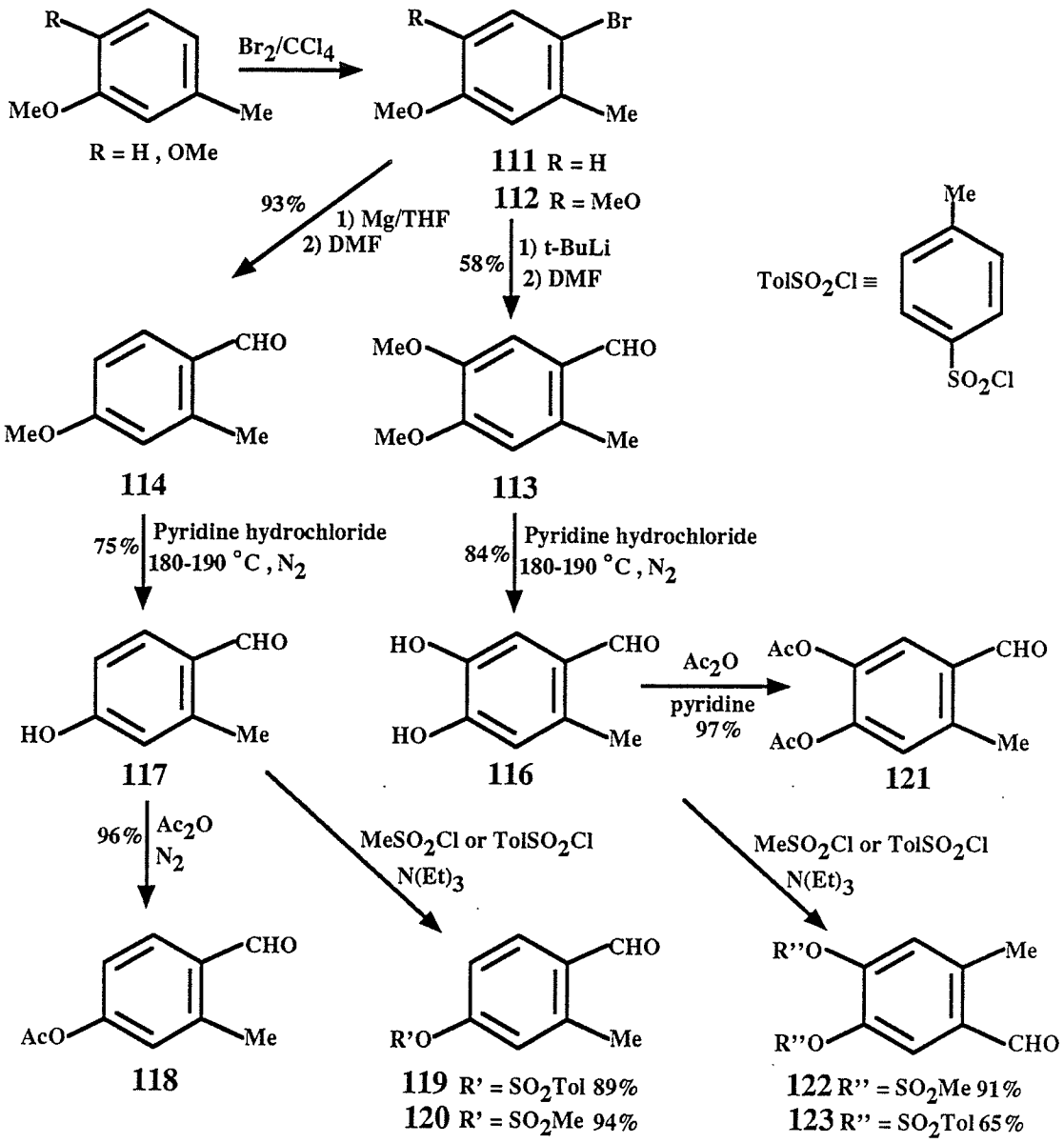
latter suggestion probably does not apply to 4,5-dimethoxy-2-methylbenzaldehyde since the corresponding *o*-QDM **115** has been generated from 4,5-dimethoxybenzocyclobuten-1-ol, and has been shown to be reactive in Diels-Alder reactions[16].



115 **113**

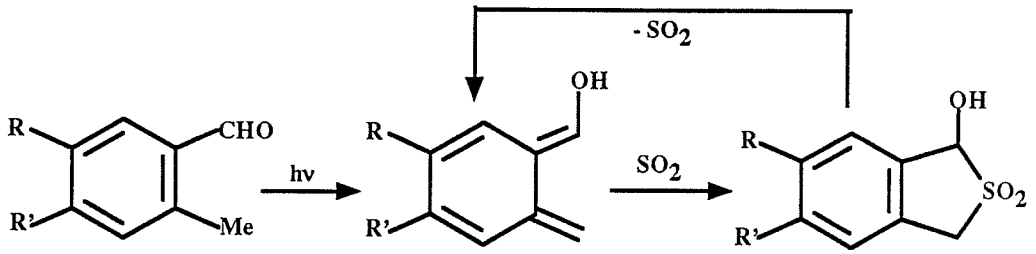
Although there is no direct evidence, the failure of the photochemical step may be due to the presence of the methoxy group *para* to the aldehyde function, which may change the character of the lowest excited triplet state by lowering the $\pi\pi^*$ state below that of the more reactive $n\pi^*$ state. This would inhibit the intramolecular hydrogen abstraction and hence the formation of *o*-QDMs (see section 1.4 for the mechanism of *o*-QDM formation). This rationalization has been used to explain the lack of intramolecular hydrogen abstraction in methoxy substituted valerophenones[77, 78]. Since it was not possible to synthesize **110** starting from 4,5-dimethoxy-2-methylbenzaldehyde, other 2-methylbenzaldehydes with less electron donating substituents at the 4 and 5 position were assessed. The introduction of less electron donating substituents should less affect the excited states of the aldehyde. Acetoxy and sulfonyloxy substituents were chosen as they should reduce the electron donor characteristics of the oxy-substituents.

The acetate, mesylate and tosylate derivatives of 4-hydroxy- and 4,5-dihydroxy-2-methylbenzaldehyde were prepared as shown in the scheme below.



3-Methoxy and 3,4-dimethoxytoluene were brominated in carbon tetrachloride to give the corresponding bromides **111** and **112** in 88 and 85% yield respectively. Treatment of **111** with magnesium, and **112** with *t*-butyllithium followed by N,N-dimethyl formamide produced aldehydes **114** and **113**. The demethylation of **113** and **114** to form hydroxyaldehydes **116** and **117** was accomplished using pyridine hydrochloride[79]. The aldehydes **116** and **117** were smoothly converted to the corresponding acetate, mesylate and tosylate derivatives in good yields.

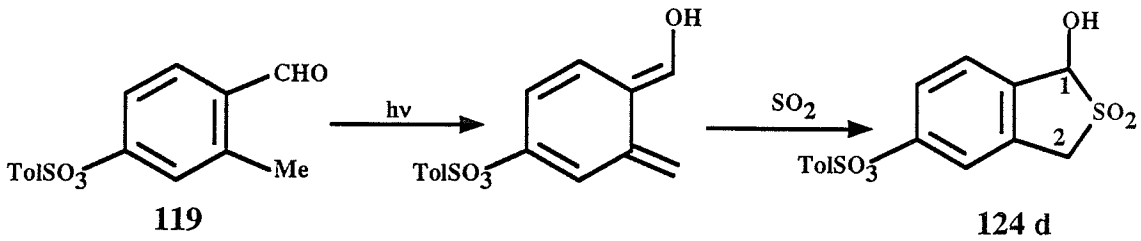
Irradiation of aldehydes **118, 121** or **123** in benzene in the presence of excess sulfur dioxide using a 450 watt medium pressure mercury lamp and a pyrex filter led to slow disappearance of the starting aldehyde. The formation of a new compound (presumably sulfone adduct) was evident on TLC. However, attempted isolation of the sulfone product by evaporation of the benzene and base extraction led only to isolation of the starting aldehyde. The sulfones **124a-c** appear to be unstable at room temperature, slowly reverting to the starting aldehydes during the isolation procedure. The above isolation procedure had been successfully used to isolate other sulfones[22].



118 R = H , R' = OAc
121 R = R' = OAc
123 R = R' = OSO_2Tol

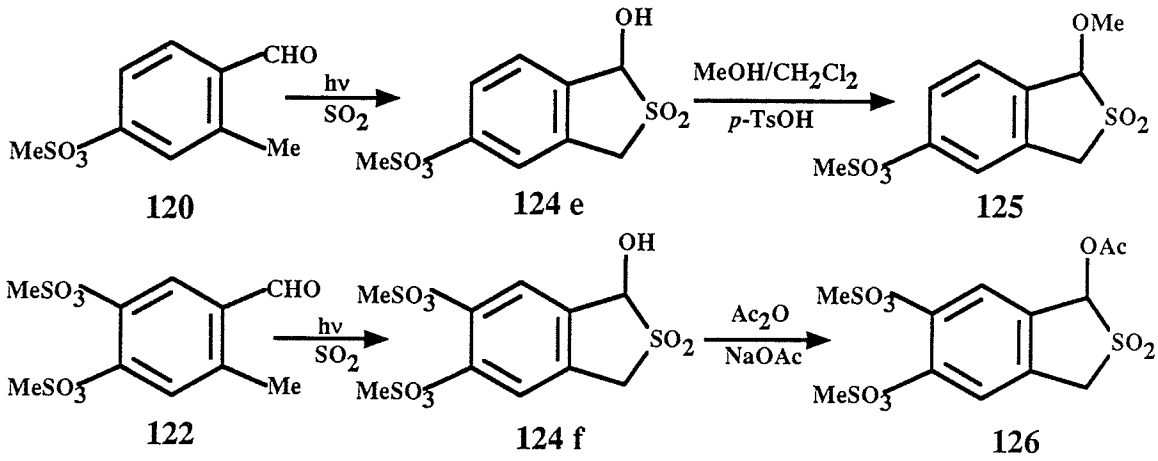
124 a R = H , R' = OAc
124 b R = R' = OAc
124 c R = R' = OSO_2Tol

The mono-tosylate **119**, on the other hand, was cleanly converted to hydroxysulfone **124d** which could be isolated in good yield (67%). It could be characterized despite being somewhat thermally unstable, decomposing back to aldehyde **119** over a few days at room temperature. Its ^1H nmr showed the presence of H-1 as a singlet at 5.59 ppm, and the two H-2 protons appeared as an AB quartet at 4.25 ppm with $J_{a,b}$= 16.06 Hz. The spectroscopic data (including infrared) are consistent with those previously reported for similar types of sulfones[22].



119 **124 d**

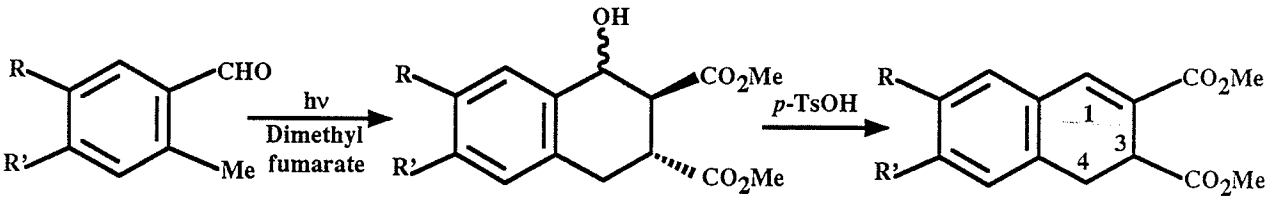
The mono-mesylate **120** could also be converted to hydroxysulfone **124e** (70%). Unfortunately it was insoluble in most organic solvents. For characterization purposes, **124e** was converted to the more soluble methoxy derivative **125** in refluxing dichloromethane / methanol containing a trace of *p*-toluenesulfonic acid. In addition to the singlet for the mesylate group at 3.18 ppm, the ^{1}H nmr of **125** also showed the presence of a methoxy singlet at 3.84 ppm. The dimesylate aldehyde **122** was converted to hydroxy sulfone **124f** in 67% yield. It was also insoluble in most organic solvents and was converted to the more soluble acetoxy derivative **126**. The conversion was effected in acetic anhydride / sodium acetate at room temperature. However, **126** could only be isolated in 32% yield presumably due to the decomposition of the starting sulfone during the course of the reaction. A substantial amount of aldehyde **122** was isolated from the reaction mixture. The nmr of **126** showed the presence of two mesylate methyl groups (3.30 and 3.31 ppm) and one acetoxy methyl group at 2.25 ppm.



120 **124 e** **125**

122 **124 f** **126**

In view of the thermal instability of sulfones **124d** and **124f**, it seemed likely that aldehydes **119**, **121** and **123** did form *o*-QDMs upon irradiation but that the sulfone adducts were too unstable to be isolated. To show conclusively that these aldehydes did form *o*-QDMs upon irradiation, **119**, **121** and **123** along with **122** were photolysed in the presence of dimethyl fumarate, which is known to trap *o*-QDMs irreversibly[22]. Fumarate adducts **127-130** were isolated in good yields (50-90%). The adducts consisted of a mixture of two diastereomers in the ratio of approximately 2:1 (evident from proton nmr), but they were not separated and individually characterized. The diastereomeric mixture of adducts from **118** (**127**) was dehydrated (methanol / *p*-toluenesulfonic acid at room temperature) with simultaneous deacetylation to give the dihydronaphthalene **131** in quantitative yield. Similarly the diastereomeric mixture **128** gave **132**. **129** and **130** were dehydrated in refluxing toluene / *p*-toluenesulfonic acid to give the elimination product **133** (90%) and **134** (74%). Proton nmr spectra of **131-134** were consistent with those previously reported for compounds of similar structure[25]. The characteristic H-1 alkene protons of the elimination products were present as singlets between 7.50-7.60 ppm.



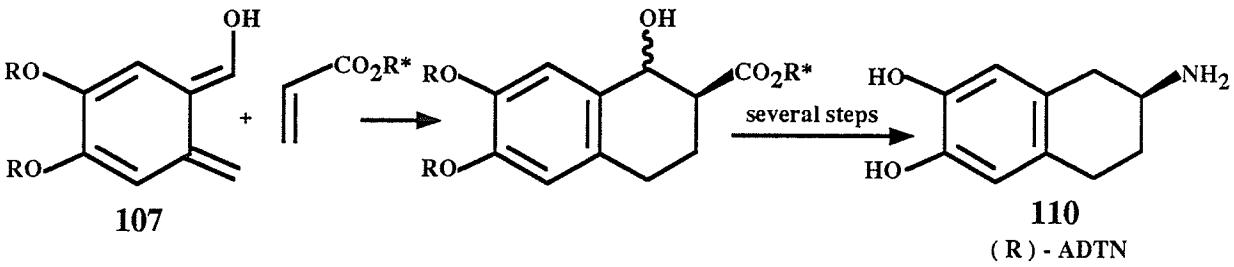
118 R = H , R' = OAc
121 R = R' = OAc
122 R = R' = OSO_2Me
123 R = R' = OSO_2Tol

127 R = H , R' = OAc
128 R = R' = OAc
129 R = R' = OSO_2Tol
130 R = R' = OSO_2Me

131 R = H , R' = OH
132 R = R' = OH
133 R = R' = OSO_2Tol
134 R = R' = OSO_2Me

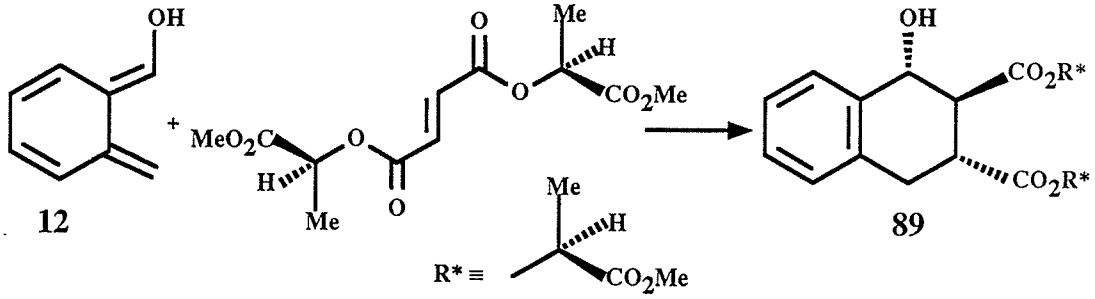
From the above experimental results, one can conclude that 4- and 4,5-diacetoxy, dimesyloxy and ditosyloxy-2-methylbenzaldehydes can be photochemically converted to *o*-QDMs and trapped with sulfur dioxide. However, in view of their thermal instability, the outlook for introducing a chiral auxiliary into the 4,5-diacetoxy-, dimesyloxy- and ditosyloxy- sulfones does not appear promising. The facial control strategy for the

asymmetric synthesis of 2-aminotetralin **110** was therefore revised. Attention was directed towards the possibility of controlling the asymmetric Diels-Alder reaction of an *o*-QDM, such as **107**, with acrylate, by placing the facial control element on the acrylate. The resulting adduct could then be converted to 2-aminotetralin **110**.



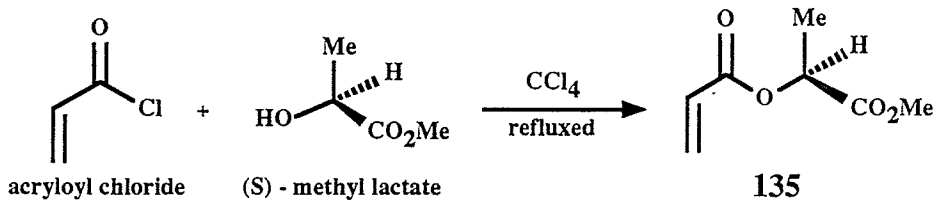
107 **110**
(R) - ADTN

While the above research was being carried out, co-worker Guy Plourde was investigating the reaction of *o*-QDM **12** with the fumarate of (S)-methyl lactate[6]. He found that this cycloadditon proceeded with very high asymmetric induction (de >95%), giving a single *exo* adduct **89** possessing 1,2-*trans* stereochemistry. The addition took place on the *re* face of *o*-QDM **12** and the *re* face of the dienophile.



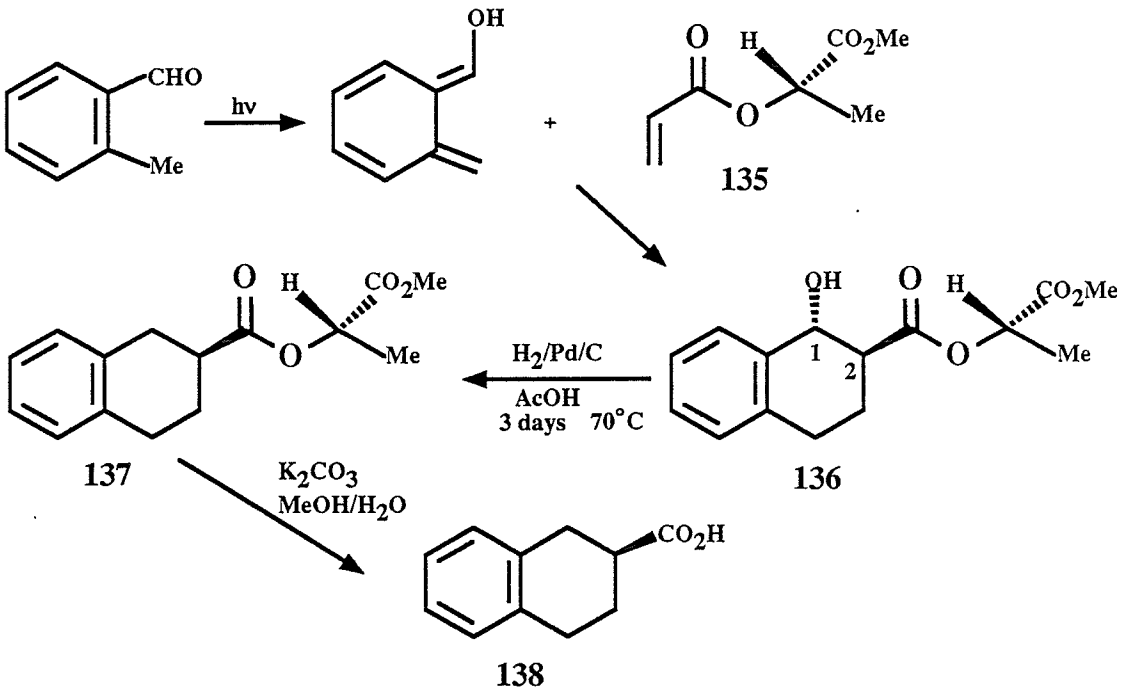
12 **89**

An asymmetric synthesis of **110** should be possible if the cycloaddition of the acrylate of (S)-methyl lactate (**135**) (as opposed to the fumarate used by Plourde) with an α-hydroxy-*o*-QDM such as **107** also proceeded with high asymmetric induction. To assess the diastereoselectivity of such a reaction, acrylate **135** was prepared in 87% yield by refluxing an excess of acryloyl chloride with (S)-methyl lactate in carbon tetrachloride[80].

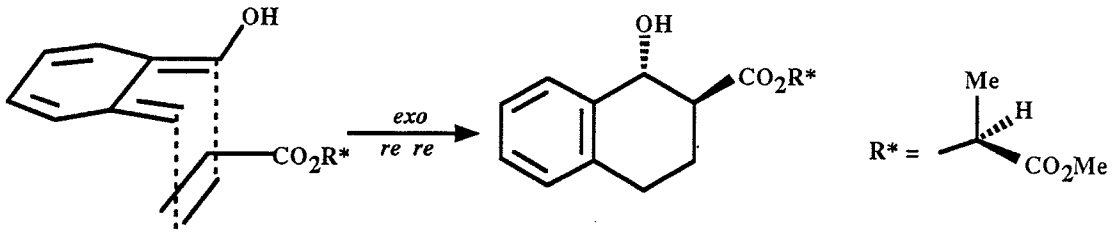


acryloyl chloride (S) - methyl lactate **135**

A model reaction was then carried out. Irradiation of a benzene solution of 2-methylbenzaldehyde with excess (1.3 molar equivalents) acrylate **135** and traces of hydroquinone (to prevent the polymerisation of the acrylate) gave predominantly a single adduct, which was isolated in 55% yield after chromatography. The nmr of the crude reaction mixture before chromatography showed that in addition to the signals due to the excess acrylate and the major adduct, signals due to traces of other diastereomeric adducts were also present. From integration of the signals, the major adduct was estimated to have been formed with a diastereomeric excess (de) of at least 95%. The major adduct exhibited a doublet at 5.00 ppm for H-1 with a $J_{1,2}$ of 9.30 Hz, similar to that reported for **89** ($J_{1,2}$ 9.80 Hz). This result suggested a *trans* disposition of the substituents on carbon 1 and 2. Similar compounds having a *cis* disposition of the 1 and 2 substituents show a $J_{1,2}$ of less than 5 Hz[14]. Based on the magnitude of $J_{1,2}$ and the structural similarity to **89**, the major adduct was tentatively assigned the structure **136**.

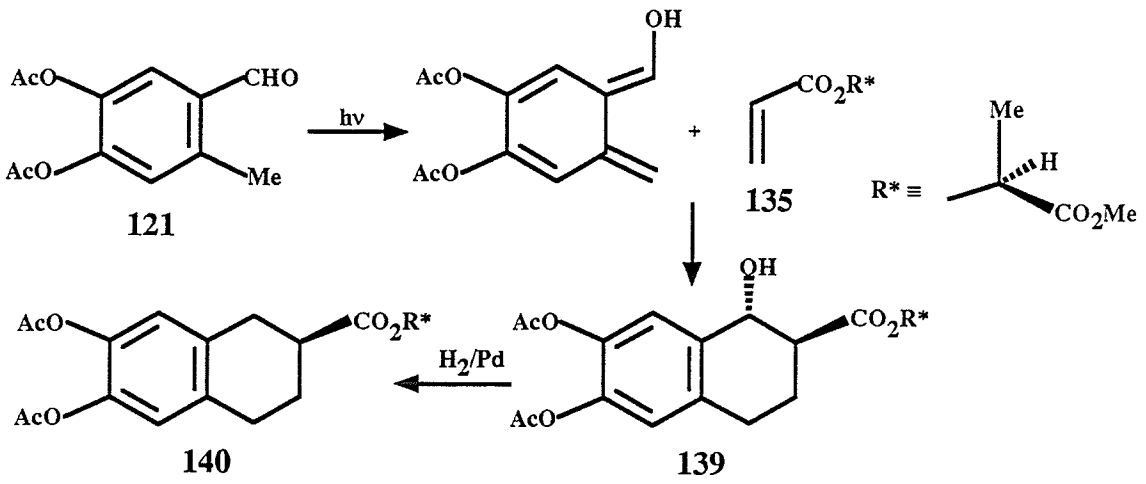


136 was hydrogenolysed with hydrogen (1 atm) over 5% Pd/C in acetic acid at 70°C for 3 days to give a single product which was tentatively assigned structure **137**. The infrared spectrum of **137** showed the absence of a hydroxyl function signalling the successful removal of the hydroxyl group from **136**. Hydrolysis of **137** furnished the known (S)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **138** ($[\alpha]_D^{20}$ -53° (lit.[81] $[]_D^{20}$ +55.5° for (R)), confirming the absolute configuration for center 2. Since the configuration of the lactate center is known to be (S), then the absolute configurations of **136** must be (1R,2S,S). The absolute stereochemistry of centers 1 and 2 of cycloadduct **136** can only arise from the addition of the *re* face of *o*-QDM **12** to the *re* face of acrylate **135** via an unexpected *exo* transition state. It is noteworthy that the acrylate of (S)-methyl lactate, like the fumarate of (S)-methyl lactate, gives the exo cycloadduct with *o*-QDM **12**, rather than the endo adduct predicted by the Alder *endo* rule.

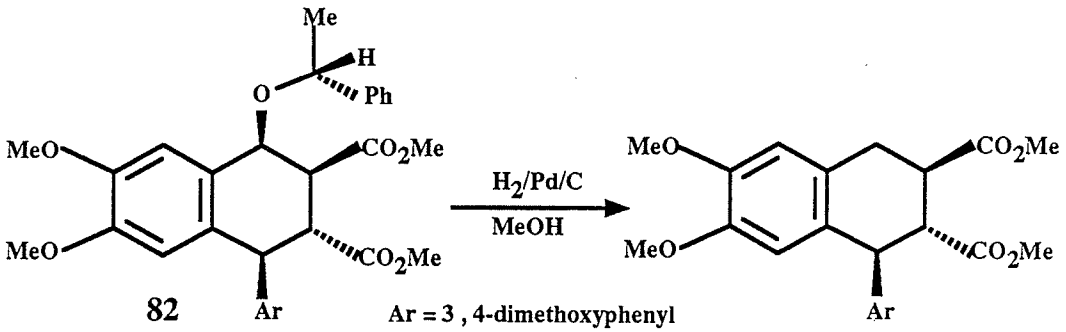


***re re* refers to the prochiral faces of the diene and dienophile**

Since the reaction of acrylate **135** with an α-hydroxy-*o*-QDM proceeded with excellent diastereoselectivity, an attempted synthesis of **110** was carried out with aldehyde **121** as the *o*-QDM precursor. Photolysis of a benzene solution of **121** with excess acrylate **135** (1.5 molar equivalents) produced predominantly a single adduct (85%) with a $J_{1,2}$ of 9.54 Hz. Although the stereochemistry of the adduct was not directly determined, it was assigned structure **139** since the reaction of the *o*-QDM from aldehyde **121** with acrylate **135** was expected to proceed with the same stereoselectivity as was observed for *o*-QDM **12.** Hydrogenolysis of **139** over 5% Pd/C in acetic acid at 70°C for four days resulted in a less than 20% yield of the desired compound **140** (evident from nmr). Most of **139** remained unreacted. The reaction was then carried out at a higher temperature (90°C for 4 days) in hopes of forcing the reaction to completion. However, the nmr of the high temperature reaction product showed the presence of at least three compounds, two of which were **139** and **140**. The other compounds presumably arose from competing dehydration/reduction reactions. Compound **140** could not be obtained in high yield. Hydrogenolysis of **139** in other solvent systems (5% Pd/C in refluxing methanol or ethyl acetate) only resulted in recovered starting material.

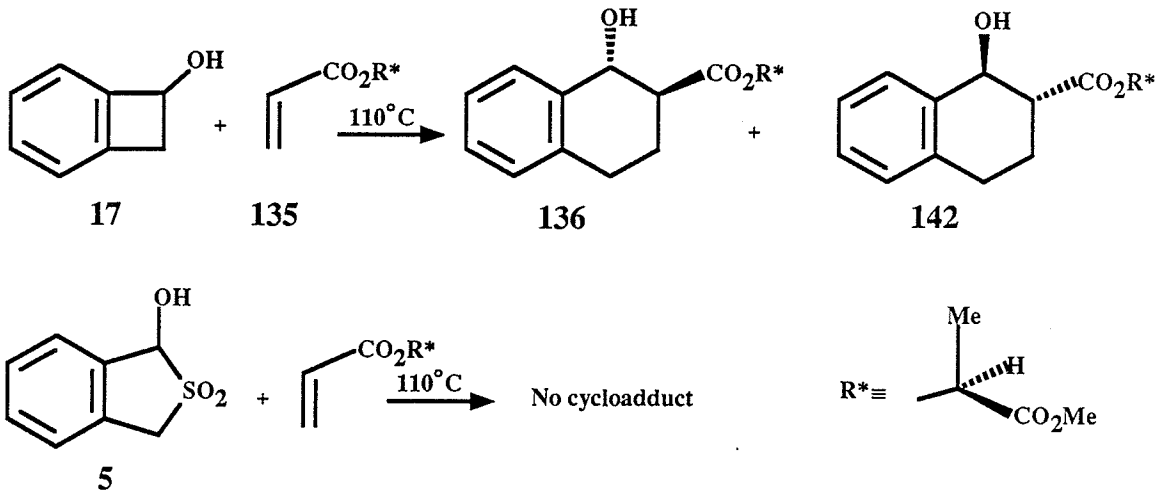


Comparing the hydrogenolysis of **136** and **139** under identical conditions (H_2, 5% Pd/C, 70°C, acetic acid), it appeared that the acetoxy substituents in **139** had an adverse effect on the hydrogenolysis process. In contrast, cycloadduct **82**, having the more electron donating methoxy substituents, has been shown to undergo hydrogenolysis readily[23].



In view of the difficulties encountered with the hydrogenolysis of **139**, a synthesis via the 4,5-dimethoxy-*o*-QDM **115** was reconsidered. As shown above, **115** could be generated from 4,5-dimethoxybenzocyclobuten-1-ol at 110°C. However, the stereoselectivity of the reaction of an *o*-QDM such as **115** with acrylate **135** at the higher temperature required (110°C) remains to be assessed. For a model study, benzocyclobutenol **17** was synthesized by using a modified literature procedure[12]. Diazotization of anthranilic acid (2-aminobenzoic acid) with isoamyl nitrite in boiling vinyl acetate produced 1-acetoxy benzocyclobutene **141** in 47% yield. **141** was deacetylated in methanol in the presence of

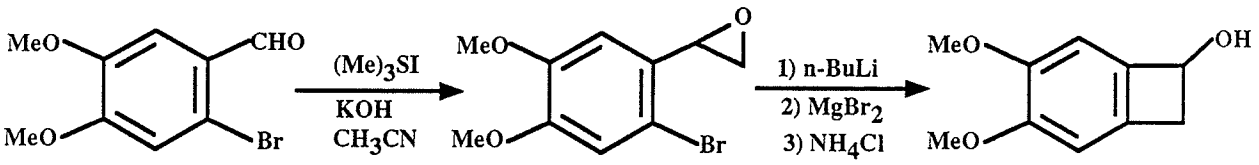
a cation exchange resin (acid form)[10] to give benzocyclobutenol **17** in 68% yield. Thermolysis of **17** with excess acrylate **135** (3 molar equivalents) at 110°C for 6 hours gave **136** along with other diasteromers (9:1 by nmr integration) in a total yield of 73%. The minor diastereomers could not be separated and hence were not individually characterized. One of these isomers exhibited a doublet for H-1 at 5.11 ppm with a $J_{1,2}$ of 9.42 Hz. It was assigned the structure **142** based on its large *trans*-1,2 coupling constant.



To assess the reactivity of an *o*-QDM prepared from a hydroxysulfone, the cycloaddition was also performed with hydroxysulfone **5** as the *o*-QDM precursor, but failed to generate any cycloadduct. The only products isolated from the reaction were unreacted acrylate and 2-methylbenzaldehyde. The presence of sulfur dioxide (from sulfone **5**) might have shortened the lifetime of the *o*-QDM by combining with traces of water in the reaction mixture to formed sulfurous acid, which subsequently catalysed the tautomerization of the *o*-QDM to 2-methylbenzaldehyde. The use of zinc oxide in the reaction, which had been successfully employed previously to scavenge acid in similar reactions[28], did not change the outcome of the reaction.

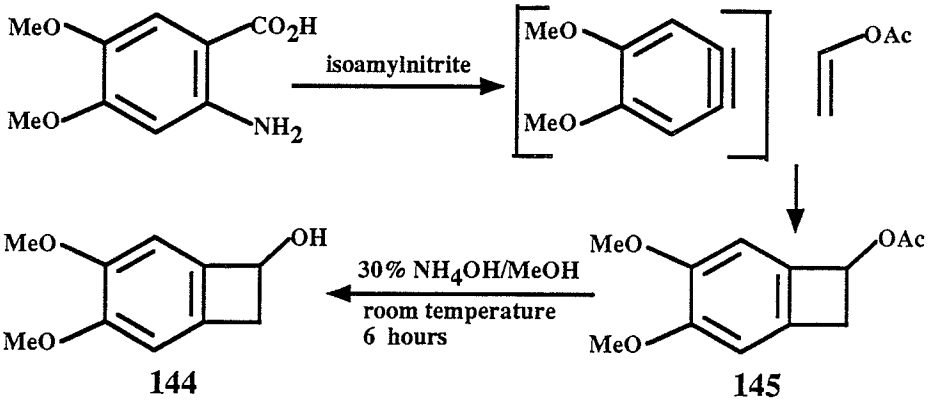
Since a higher temperature reaction (110°C) of acrylate **135** with α-hydroxy-*o*-QDM proceeded with good stereoselectivity, the stage was set for the synthesis of ADTN. The required 4,5-dimethoxybenzocyclobuten-1-ol **144** has been

prepared by Kametani *et al*, but by a rather lengthy procedure (8 steps), and in an overall yield of only 8%[16,82]. A more efficient route to this compound was needed. More recently, Akgün *et al* reported the synthesis of various benzocyclobutenols starting from *o*-bromostyrene oxides in 50-80% yield[13]. Thus the synthesis of **144** employing Durst's method was attempted. Treatment of 2-bromo-4,5-dimethoxybenzaldehyde with trimethylsulfonium iodide and potassium hydroxide in acetonitrile furnished the styrene oxide **143** in 78% yield[83]. Reaction of **143** with n-butyllithium and magnesium bromide etherate at -78°C followed by mild acid quenching at room temperature gave the desired benzocyclobutenol **144** initially in 47% yield, but in subsequent reactions, under nominally identical conditions, in lower and variable yields (20-30%).

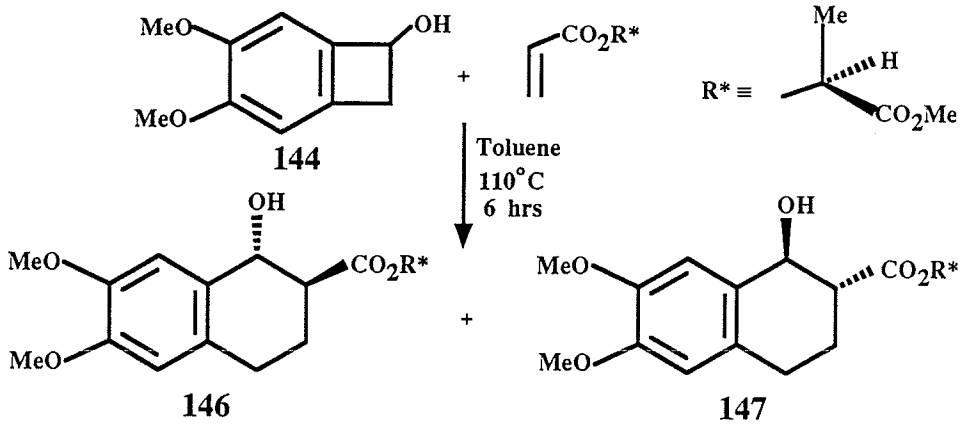


143 **144**

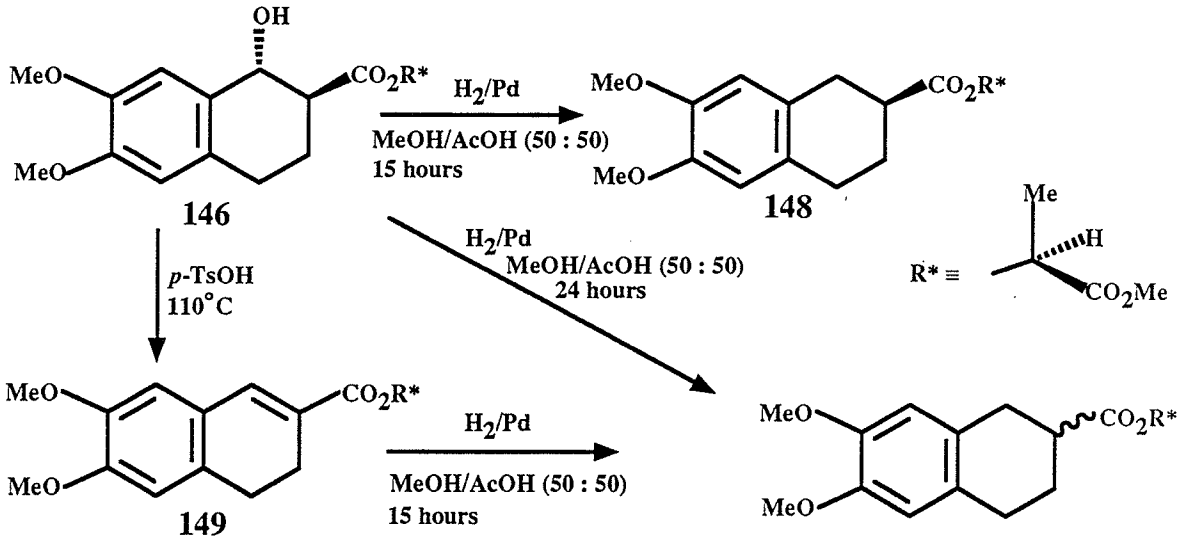
In view of the unpredictability of the above procedure, a more reliable procedure was sought. Although Jung *et al* had little success preparing 1-acetoxy-4,5-methylenedioxybenzocyclobutene employing a benzyne route (8% yield from diazotization of 2-amino-4,5-methylenedioxybenzoic acid with isoamyl nitrite in vinyl acetate), this route was nevertheless examined[7]. The 2-amino-4,5-dimethoxybenzoic acid was diazotized with isoamyl nitrite in refluxing vinyl acetate to generate the intermediate benzyne, which was then trapped by vinyl acetate to give 1-acetoxy-4,5-dimethoxybenzocyclobutene **145** in a reproducible yield of 45% after purification[12]. The benzocyclobutene **145** was deacetylated in 30% ammonium hydroxide / methanol to give **144** in 85% yield after chromatography. The spectroscopic properties of **144** were identical to those previously reported[16].



Heating benzocyclobutenol **144** in a toluene solution of acrylate **135** (3 equivalents) gave one major and three minor cycloadducts (evident by nmr) in a total yield of 93% after chromatography to remove the excess acrylate. From nmr integration, the total amount of minor isomers was estimated to be 10%. Fortunately, the major isomer could be separated from its diastereomers by a more careful column chromatography on silica gel employing 25% ethyl acetate / hexanes as the mobile phase. The yield of the major isomer after isomer separation was 80%. It was assigned structure **146** based on previous experience (see above). The nmr of **146** exhibited a doublet for H-1 at 4.92 ppm with a $J_{1,2}$ of 9.12 Hz. A small amount of one of the minor isomer was also isolated. This minor isomer exhibited a doublet for H-1 at 5.08 ppm with a large $J_{1,2}$ of 9.11 Hz and hence was assigned the structure **147.** The remaining minor isomers could not be isolated in pure form and hence were not characterized.

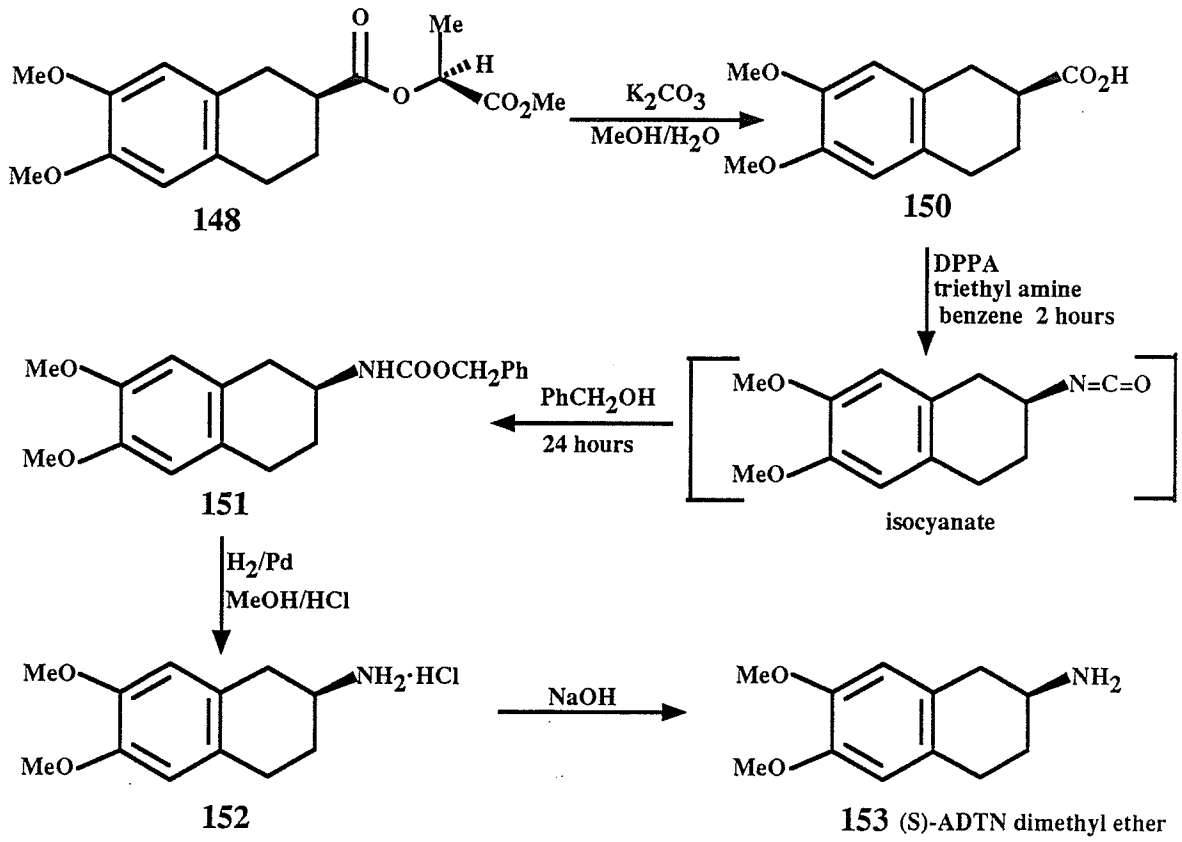


Hydrogenolysis of **146** with 5% Pd/C in acetic acid / methanol (50:50) at room temperature for 15 hours gave the ester **148** cleanly, and in 80% yield. The reaction time for the hydrogenolysis reaction appeared to be crucial. Products from longer reaction time (24 hours) showed appreciable epimerization of the C-2 center, presumably due to dehydrogenation / rehydrogenation of **148**. The nmr of the epimerized product in C_6D_6 clearly showed the presence of **148** and its epimer. The same two diastereomers were obtained (in the ratio of approximately 50:50) when **149** was hydrogenated under identical condition (15 hours). Alkene **149** was obtained from the dehydration of cycloadduct **146** in refluxing toluene containing traces of *p*-toluenesulfonic acid.



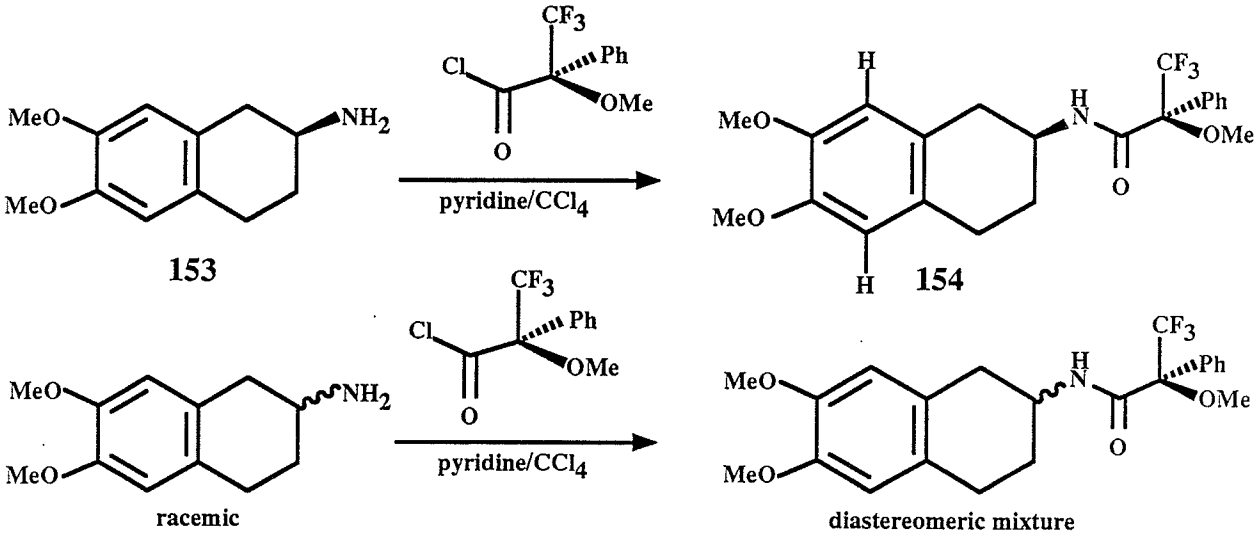
The ester **148** could be hydrolysed to the corresponding optically active carboxylic acid **150** ($[\alpha]_D^{20}$ -41.8°, mp 145.5-147°C, lit.[84] mp 141.5-142.5°C (racemic)) with potassium carbonate in methanol / water without epimerization of the C-2 chiral center. Carboxylic acid **150** was converted to (S)-ADTN dimethyl ether following a literature procedure[84]. A modified Curtius reaction of **150** with diphenylphosphoryl azide (DPPA) and triethyl amine in dry benzene produced the intermediate isocyanate, which was then reacted with benzyl alcohol to furnish the benzyloxycarbamate **151** in 80% yield ($[\alpha]_D^{20}$ -23.3°, mp

130-131.5°C, lit.[84] mp 122-123°C (racemic))[85]. It was reasonable to assume in this case, that the modified Curtius reaction would proceed with retention of configuration.



Hydrogenolysis of **151** in methanol / anhydrous hydrogen chloride furnished the hydrochloride salt of (S)-ADTN dimethyl ether **152** in 97% yield ($[\alpha]_D^{20}$ -65.1°, lit.[75] $[]_D^{20}$ +73.2° for (R), mp 213-214°C, lit.[75] mp 212-214°C). Dissolution of the hydrochloride salt **152** in sodium hydroxide solution (0.1 M) followed by extraction with methylene chloride, gave, after concentration, the free amine **153** as a colourless solid in 60% yield ($[\alpha]_D^{20}$ -85.7°, lit.[75] $[\alpha]_D^{20}$ +86.5° for (R), mp 85-86°C). **153** was previously reported as a yellow oil[75]. The infrared spectrum of **153** showed the expected primary amine N-H bands at 3378 and 3299 cm^{-1}. The proton nmr was consistent with the structure **153** although it was slightly different from that reported by Norlander *et al*[75]. The two aromatic protons appeared as two singlets at 6.55 and 6.58 ppm, and had previously been reported as a

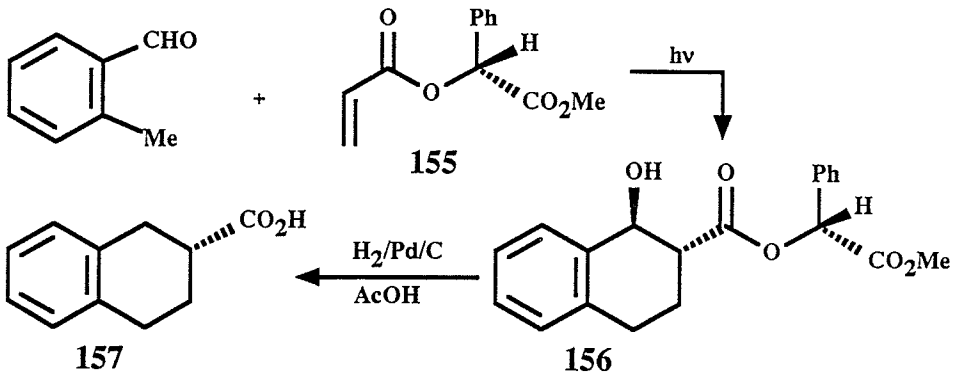
singlet at 6.50 ppm. To assess the configurational purity of **153**, its amide, derived from (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's Acid) was prepared[75,86]. The Mosher's acid chloride was prepared from the corresponding acid by a literature procedure[87]. The free amine **153** (crude) was reacted with Mosher's acid chloride in CCl_4 / pyridine to give the amide **154**. For comparison purposes, a mixture of diastereomeric amides was also prepared from (±)-4,5-dimethoxy-2-aminotetralin. The racemic 4,5-dimethoxy-2-aminotetralin was prepared via hydrogenation of the alkene **149** followed by the same procedures used for the preparation of **153**.



The proton nmr of **154** and the corresponding diastereomeric mixture were acquired in benzene-D_6. The best region of the spectra for analysis of the enantiomeric purity of **153** was that of the aromatic protons. The diastereomeric amide exhibited four well resolved singlets at 6.24, 6.29, 6.32 and 6.35 ppm, while **154** showed the two inner singlets with barely perceptible outer signals. From the integration, it was estimated that the two outer signals of **154** were less than 2% of the total integration. Assuming that the purity of Mosher's acid was >99%, then the optical purity of **153** would be >97%. The didemethylation of **153** to give (S)-ADTN **110** has been described elsewhere and has been shown to proceed without epimerization of the chiral center[88]. The above procedure

constitutes an asymmetric synthesis of 6,7-dimethyl-(S)-ADTN in eight steps in 11% overall yield and >97% optical purity, starting from 2-amino-4,5-dimethoxybenzoic acid and acrylate **135**. The above methodology could be applied to the asymmetric synthesis of a variety of 2-aminotetralin systems.

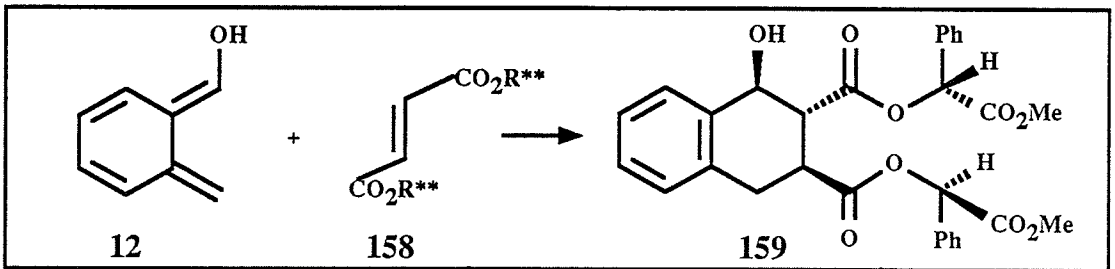
Although (S)-methyl lactate has been shown to be an excellent chiral auxiliary in the reactions of α-hydroxy-*o*-QDMs and acrylate **135**, there are certain drawbacks to the use of the lactyl chiral auxiliary. In particular, (R)-methyl lactate is not readily available, which limits the method to the preparation of only one enantiomer of target molecules. In addition, removal of the lactyl chiral auxiliary by hydrolysis requires fairly harsh basic conditions (potassium carbonate / methanol) which may be unsuitable in certain cases. In searching for a better chiral auxiliary, mandelic acid appeared to be an appropriate candidate. While both enantiomers of mandelic acid are readily available, their methyl ester is structurally similar to methyl lactate. The methyl ester also offers the advantage that it can be removed by mild hydrogenolysis although this procedure precludes recovery of the chiral auxiliary. The stereoselectivity of the reactions of the fumarate and acrylate of (R)-methyl mandelate with α-hydroxy-*o*-QDMs were therefore investigated. (R)-methyl mandelate was prepared by esterification of (R)-mandelic acid (methanol / sulfuric acid) in 92% yield ($[\alpha]_D^{20}$ -140.5°). The acrylate of (R)-methyl mandelate **155** was prepared in 69% yield using the procedure for preparing acrylate **135**. Photolysis of a benzene solution of 2-methylbenzaldehyde with excess acrylate **155** (1.5 molar equivalents) at room temperature for 20 hours produced essentially a single adduct. The nmr of the crude reaction product (before chromatography) showed signals due to traces of minor diastereomers and the major adduct was estimated to be formed with a diastereomeric excess (de) of >95%. The major adduct exhibited a large $J_{1,2}$ of 9.25 Hz suggesting a *trans*-1,2 stereochemistry, and therefore was tentatively assigned the structure **156** based on the large $J_{1,2}$ and by comparison to adduct **136** produced from the acrylate **135**.



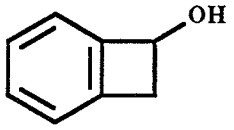
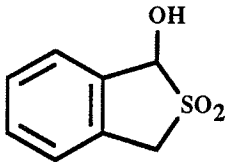
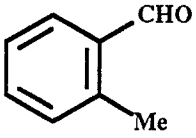
Hydrogenolysis of **156** over H_2/Pd/C in acetic acid furnished the known (R)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **157** in 70% yield ($[\alpha]_D^{20}$ +53.3°, lit.[81] $[\alpha]_D^{20}$ +55°), thus confirming the absolute configuration of **156**. The major adduct in this case arose from the addition of the *si* face of *o*-QDM **12** to the *si* face of the acrylate **155**. Thermolysis of a toluene solution of benzocyclobuten-1-ol **17** with an excess of acrylate **155** also generated **156** along with three minor isomers (in the ratio of 9:1 by nmr) in a combined yield of 56%. The minor isomers could not be separated and hence were not individually characterized. As in the case of the acrylate of (S)-methyl lactate, cycloaddition of acrylate **155** with sulfone **5** as *o*-QDM precursor produced no expected cycloadduct. Only 2-methylbenzaldehyde and unreacted acrylate were isolated. From the above results, one could conclude that the reaction of acrylate **155** with an α-hydroxy-*o*-QDM proceeds with the same stereoselectivity as that of acrylate **135**.

The fumarate of (R)-methyl mandelate **158** was prepared in 83% yield by heating fumaryl chloride with (R)-methyl mandelate (2 molar equivalents) at 110°C for 15 hours ($[\alpha]_D^{20}$ -99.8°, mp 141-143°C). A longer reaction time resulted in a lower yield of the fumarate. The *o*-QDM **12**, generated from 2-methylbenzaldehyde, benzocyclobutenol **17** or sulfone **5**, was reacted with **158** to give a single adduct in all three cases ($[\alpha]_D^{20}$ -43.4°, mp 124-126°C). The nmr of the crude product from all three reactions showed no signals consistent with other possible diastereomers indicating a de > 95%. The isolated adduct exhibited a $J_{1,2}$ of 9.56 Hz suggesting a *trans*-1,2 disposition of the substituents on carbon

1 and 2, as was observed for the adduct of *o*-QDM **12** with the fumarate of (S)-methyl lactate ($J_{1,2}$ 9.8 Hz)[6]. The adduct was tentatively assigned structure **159**. The yields of the reactions varied and highest yield was obtained when benzocyclobutenol **17** was used as the *o*-QDM precursor. It appears that *o*-QDM prepared from benzocyclobutenol traps the dienophile more efficiently.

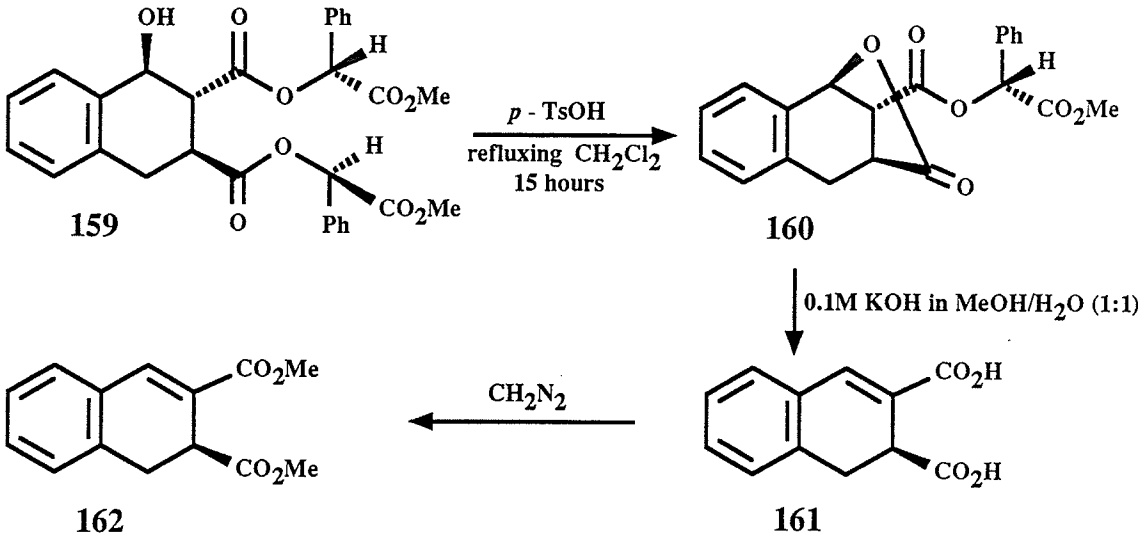


12 **158** **159**

Precursor of 12	Dienophile	Reaction conditions	Yield of 159 (%)
	158	Toluene , 110°C , 6 hours	96
	158	Toluene , 110°C , 2 hours	55
	158	Benzene , hv , room temperature 6 hours	52

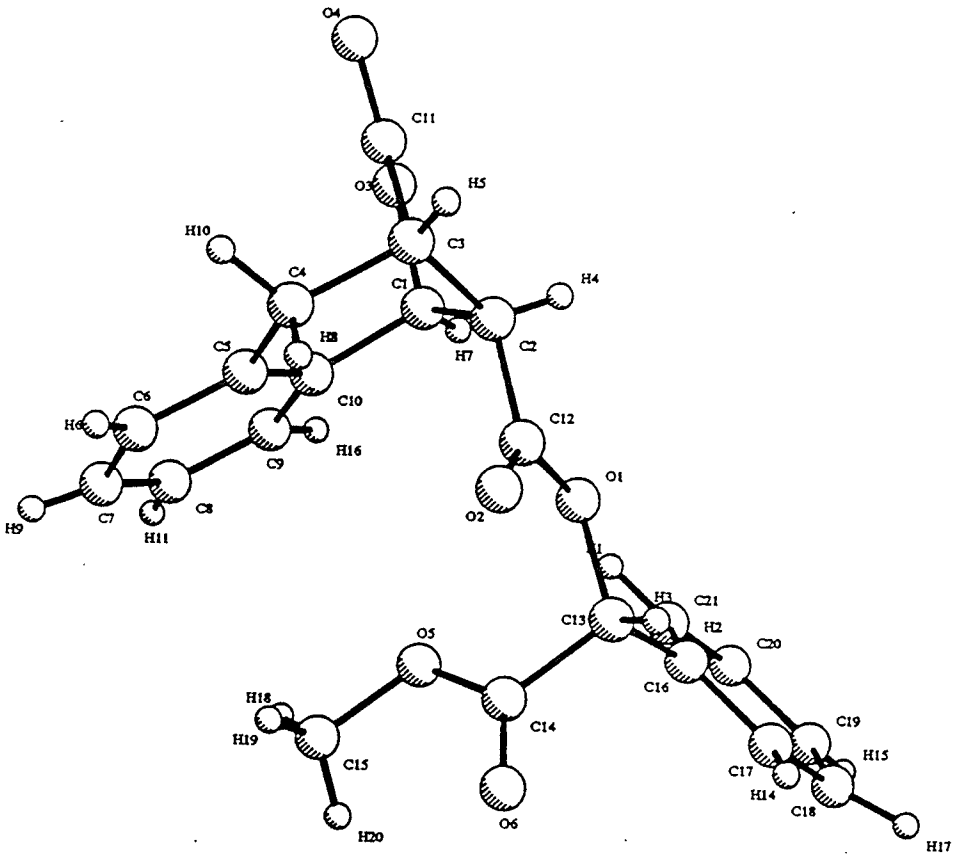
Refluxing **159** in methylene chloride containing traces of *p*-toluenesulfonic acid (for 15 hours) caused the elimination of one molecule of methyl mandelate giving lactone **160** in 71% yield after chromatography ($[\alpha]_D^{20}$ -60.9°, mp 86-88°C, IR 1788 cm^{-1}). Lactone formation between the 1-hydroxyl and the 3-carboxyl is not unreasonable and has been reported previously in similar systems[14,41,65]. The methyl mandelate eliminated during

the lactone formation was isolated from the reaction mixture by chromatography. Hydrolysis of lactone **160** in methanolic potassium hydroxide (0.2M potassium hydroxide in methanol / water (1:1)) furnished the diacid **161** (not characterized), which was methylated with diazomethane to give the known (S)-dimethyl-3,4-dihydronaphthalene-2,3-dicarboxylate **162** ($[\alpha]_D^{20}$ -128°, lit.[25] $[\alpha]_D^{20}$ +128° for (R)). This confirmed the absolute configuration of (S) at center 3 and the absolute configuration of **159** and **160** (by inference).

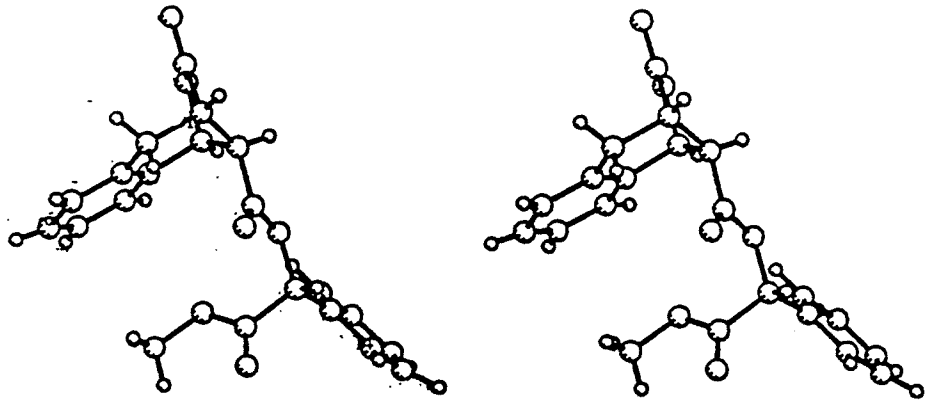


Further information on the absolute stereochemistry of the lactone **160** was obtained when crystals of **160** (from methylene chloride) were obtained and the structure determined by X-ray analysis[89]. It was therefore possible to determine the relative stereochemistry of the chiral centers in **160** as shown in the ORTEP diagram below.

ORTEP diagram of lactone **160**



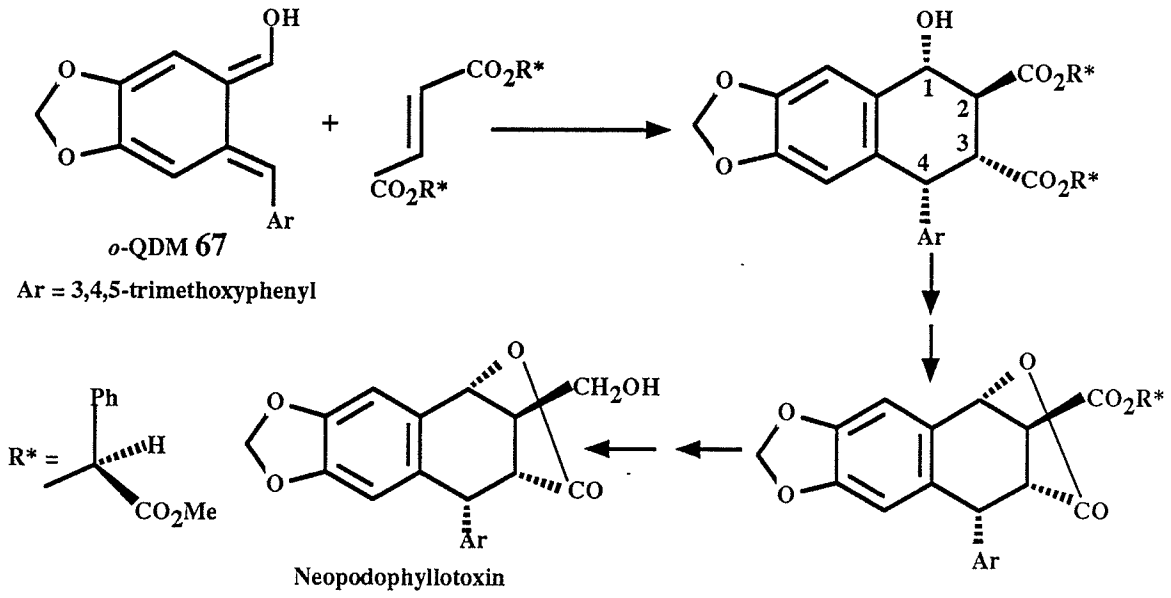
stereo view of **160**



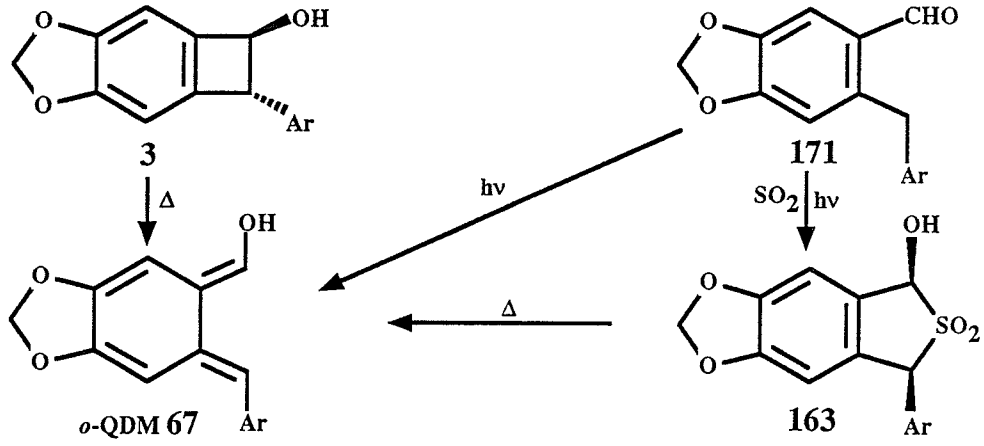
Since the absolute stereochemistry of the mandelate center in **160** was known to be (R), then the absolute configurations of the other centers must be (1S,2R,3S). From the above results, one can conclude that the cycloaddition of the fumarate of (R)-methyl mandelate proceeded with very high asymmetric induction (de >95%). Cycloadduct **159** formed from the expected addition of the *si* face of *o*-QDM **12** to the *si* face of **158** via an *exo* transition state.

Since the addition of fumarate **158** with an α-hydroxy-*o*-QDM **12** proceeded with excellent stereoselectivity, giving an adduct with the same relative stereochemistry as neopodophyllotoxin (1,2-*trans*, 2,3-*trans*), an asymmetric synthesis of neopodophyllotoxin was considered possible. It would be necessary to generate *o*-QDM **67** and add it to the fumarate of (S)-methyl mandelate. Hopefully the cycloaddition would proceed with good stereoselectivity giving an adduct with the required relative stereochemistries (1,2-*trans*, 2,3-*trans* and 3,4-*cis*). The adduct could then be converted to neopodophyllotoxin.

Proposed Synthesis of Neopodophyllotoxin

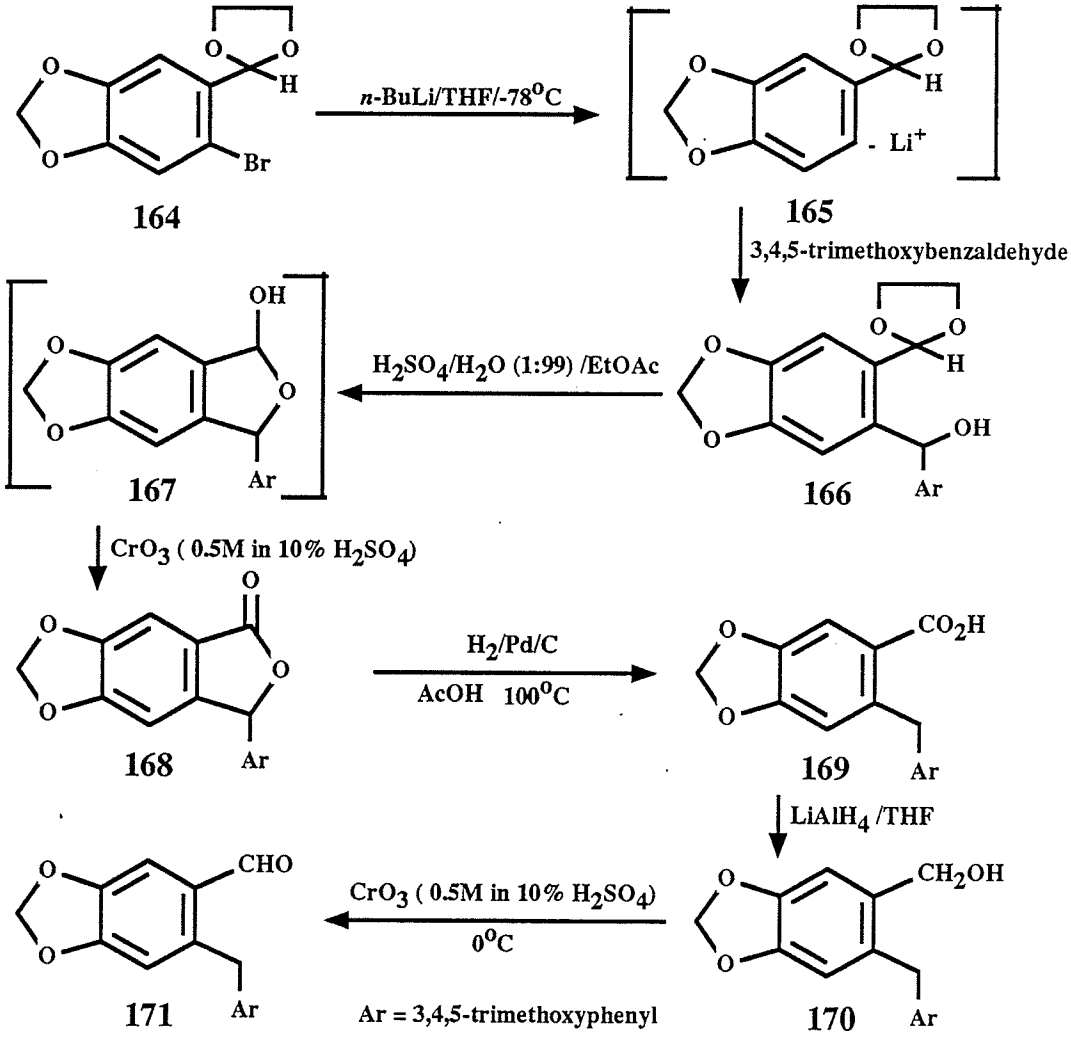


In principle, *o*-QDM **67** could be generated thermally from benzocyclobutenol **3** or the sulfone **163**, or photochemically from aldehyde **171**. The benzocyclobutenol **3** has been prepared by lengthy procedures[8,9] and has been shown to be thermally unstable[8]. The sulfone **163** has been prepared in poor yield from **171** and has also been shown to be thermally unstable[29]. The more easily accessible aldehyde **171** was therefore chosen as the precursor to *o*-QDM **67**.

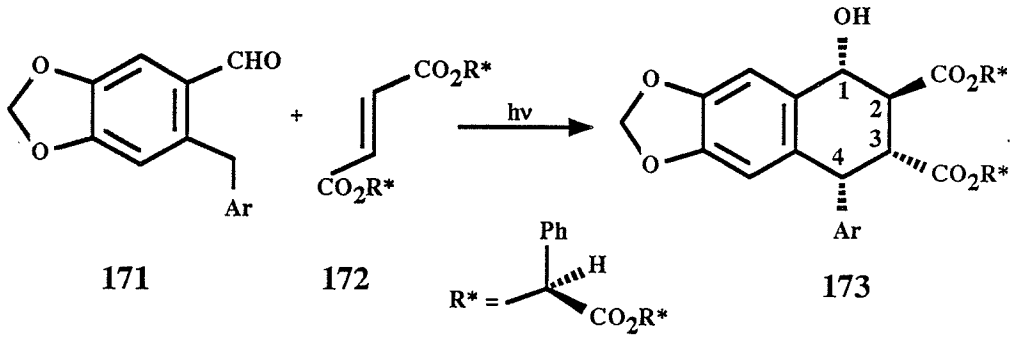


Aldehyde **171** has been prepared by Glinski and Durst[58], Jung *et al*[7] and Arnold *et al*[90]. While according to Durst's procedure, aldehyde **171** can be prepared in 84% yield in two steps from *o*-bromopiperonal, difficulty with the procedure has been reported[29]. Jung's procedure gives a poor yield of **171**. To avoid complication, the simpler but longer procedure (modified) of Sammes was chosen for the preparation of **171**. Treatment of bromoacetal **164** with a slight excess of *n*-butyllithium (1.1 molar equivalents) at -78°C (dryice / acetone) generated the intermediate anion **165**, which was subsequently reacted with 3,4,5-trimethoxybenzaldehyde to furnish the alcohol **166** in 95% yield after chromatography (IR 3499 cm^{-1}). Hydrolysis of **166** with sulfuric acid / water (1:99) furnished the lactol **167** (not isolated) which was oxidized with chromium trioxide to give lactone **168** in 70% yield (IR 1759 cm^{-1}, lit[90]. 1760 cm^{-1}, mp 220-222°C, lit[90]. mp 217-223°C). The lactone **168** was selectively hydrogenolysed over H_2/Pd/C in acetic acid

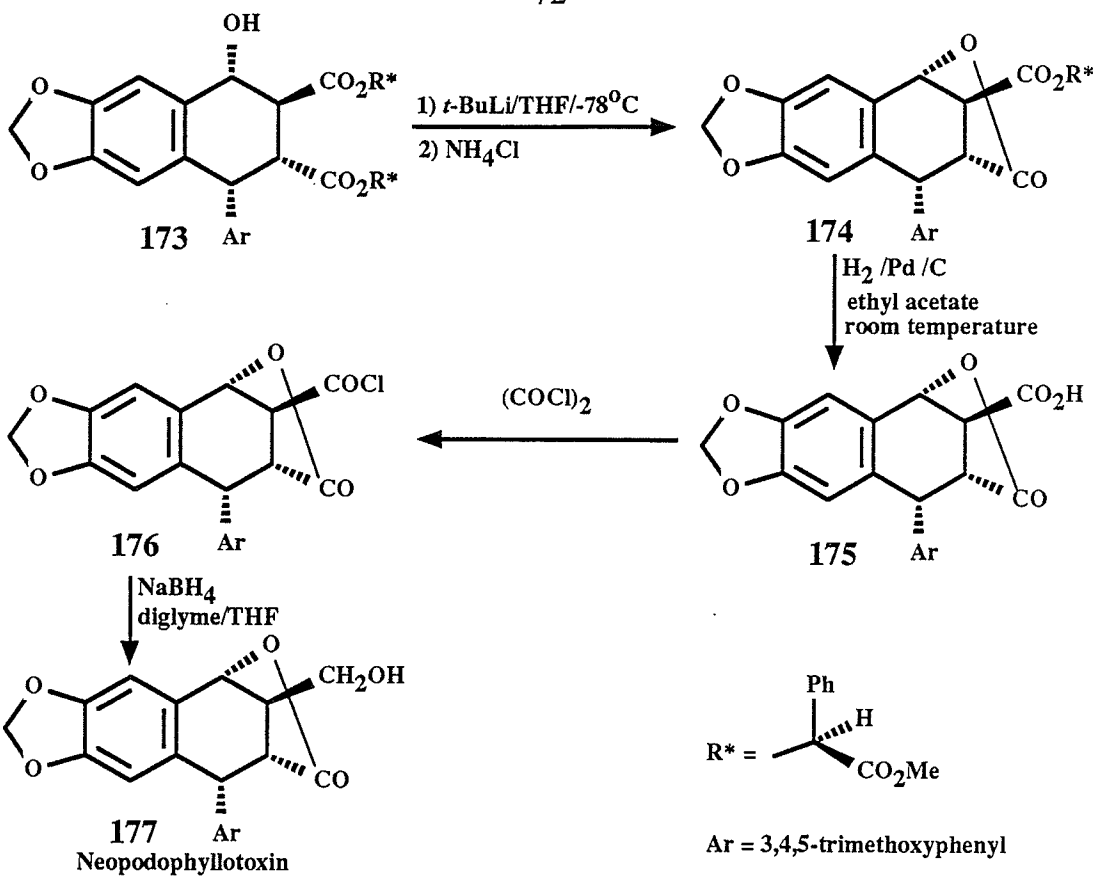
at 100°C to give 6-(3,4,5-trimethoxybenzyl)piperonylic acid **169** in 94% yield (mp 164-166°C, lit[90]. mp 165-168°C). Reduction of **169** with lithium aluminium hydride in THF furnished the corresponding alcohol **170** in 87% yield (IR 3606 cm^{-1}, mp 90-92°C, lit[90]. mp 89-90°C). Oxidation of **170** with chromium trioxide (0.5M in 10% sulfuric acid / water) at 0°C furnished aldehyde **171** in 85% yield (mp 112-114°C, lit[90]. mp 124-125°C). The ^1H nmr of **171** was identical to those previously reported[7,58].



Esterification of (S)-mandelic acid with sulfuric acid / methanol gave (S)-methyl mandelate in 96% yield ($[\alpha]_D^{20}$ +140.4°). The fumarate of (S)-methyl mandelate **172** was prepared in 90% yield by heating fumaryl chloride with (S)-methyl mandelate (2 molar equivalents) at 110°C for 15 hours ($[\alpha]_D^{20}$ +115.5°). With the aldehyde **171** and fumarate **172** in hand, the photogeneration and cycloaddition of the *o*-QDM was next attempted. The aldehyde **171** was irradiated with one equivalent of fumarate (**172**) at room temperature under nitrogen in dry benzene. A further two molar equivalents of fumarate (in benzene solution) was added dropwise to the irradiated solution over a period of 5 hours. The ^{1}H nmr (300 MHz) of the crude product showed that signals due to two isomeric adducts were present (ratio of major : minor = 8 : 2 by nmr integration). Chromatography of the crude reaction mixture gave the two adducts in a total yield of 45%. Unfortunately the major isomer could not be fully separated from the minor isomer and hence the minor isomer was not characterized. For characterization purposes, a small sample of the pure major adduct was isolated by careful rechromatography of the isomeric mixture ($[\alpha]_D^{20}$ -23.7°). It exhibited a doublet for H-4 at 4.50 ppm with a $J_{4,3}$ of 5.80 Hz, and a doublet of doublets for H-1 at 4.95 ppm with a $J_{1,2}$ of 9.32 Hz. These coupling constants suggested a 1,2-*trans* and 3,4-*cis* stereochemistry. A similar adduct with a 1,2-*trans* and 3,4-*cis* stereochemistries, obtained from the *exo*-addition of the fumarate of (S)-methyl lactate with an α-hydroxy-α'-phenyl-*o*-QDM, also exhibited a large $J_{1,2}$ of 9.5 Hz and a $J_{3,4}$ of 5.70 Hz[65]. A similar adduct with a 1,2-*cis* and 3,4-*trans* stereochemistry exhibited a small $J_{1,2}$ of 3 Hz and a large $J_{3,4}$ of 10 Hz[58]. Based on previous experience with the cycloaddition of the fumarate of (R)-methyl mandelate with α-hydroxy-*o*-QDM **12** (*exo*-addition) and analogy to similar compounds, the above major adduct was tentatively assigned structure **173**.



Treatment of the above isomeric mixture with *t*-butyllithium at -78°C followed by mild acid quenching furnished essentially a single product in 54% yield after chromatography ($[\alpha]_D^{20}$ +5.27). The nmr of the product showed the elimination of one molecule of mandelate from **173** and infrared showed the presence of a lactone carbonyl at 1787 cm^{-1}. The lactone was assigned structure **174**. Lactone formation between 1-hydroxyl and 3-carboxyl group under similar reaction conditions has been previously described[65]. Hydrogenolysis of **174** over 5% Pd/C in ethyl acetate at room temperature occurred selectively to give the corresponding lactone-carboxylic acid **175** in 87% yield ($[\alpha]_D^{20}$ -26.7, mp 209-211, IR 3400-2800(broad), 1787 cm^{-1}). The selective hydrogenolysis of a similar lactone without cleavage of the lactone function has been reported[67d].



The lactone-acid was then treated with oxalyl chloride ($(COCl)_2$) to form the corresponding acid chloride **176** which was isolated but not characterized. The acid chloride **176** was subsequently reduced with sodium borohydride in "Diglyme" / THF to furnish the target compound neopodophyllotoxin **177** in 88% yield ($[\alpha]_D^{20}$ -50.77°, lit [91]$[\alpha]_D^{20}$ -52.4°, mp 232-234°C, lit[67a] mp 230-231 (racemic), IR 1781 cm^{-1}). The proton nmr of **177** was identical to those previously reported[67a,91]. A comparison of the observed optical activity of **177** with that reported by Wartburg *et al*[91], indicated an optical purity of >95%. Therefore an asymmetric synthesis of neopodophyllotoxin was accomplished in 4 steps in an overall yield of 18% and >95% optical purity, starting from aldehyde **171** and fumarate **172**. As neopodophyllotoxin has been converted to podophyllotoxin in 54% yield without configurational alteration[67d], the above synthetic route also constitutes an asymmetric synthesis of podophyllotoxin. The above synthetic route may also be applicable to the synthesis of other aryltetralin lignan systems.

Chapter 3

CONCLUSIONS

The research work presented in this thesis could be summarized as follow:

(1) In contrast to the 4- and 4,5-dimethoxy-2-methylbenzaldehydes, the corresponding 4- and 4,5-disubstituted acetoxy, mesyloxy and tosyloxy-2-methylbenzaldehydes could be converted to *o*-QDMs photochemically. The *o*-QDMs were trapped with sulfur dioxide to form the corresponding sulfones, but most of the sulfones were too unstable to be isolated. The *o*-QDMs were trapped irreversibly with dimethyl fumarate to form the expected cycloadducts.

(2) The acrylate of (S)-methyl lactate has been found to react with an α-hydroxy-*o*-quinodimethane (generated photochemically from 2-methylbenzaldehyde) to form cycloadduct with high asymmetric induction (de >95%). The adduct arose from the addition of the *re* face of the *o*-QDM to the *re* face of the acrylate via the unexpected *exo* transition state. The same addition was carried out with the α-hydroxy-*o*-quinodimethane generated thermally (110°C) from benzocyclobuten-1-ol. The reaction was found to proceed with slightly lower diastereoselectivity giving one major adduct along with three minor adducts in the ratio of 9 : 1 (major : total minor). Cycloaddition with α-hydroxy-sulfone as an *o*-QDM precursor did not generate any expected adduct.

(3) The major adduct from the cycloaddition of the acrylate of (S)-methyl lactate with the *o*-QDM generated from 4,5-dimethoxybenzocyclobuten-1-ol was successfully converted to (S)-ADTN dimethyl ether with an optical purity of >97%. The method developed could be applied to the asymmetric synthesis of other aminotetralin systems.

(4) Cycloaddition of the acrylate of (R)-methyl mandelate with an α-hydroxy-*o*-quinodimethane was found to proceed with the same diastereoselectivity as that of the acrylate of (S)-methyl lactate. The major adduct formed from the cycloaddition of the *si* face of the α-hydroxy-*o*-quinodimethane to the *si* face of the acrylate giving an adduct with 1,2-*trans* stereochemistry.

(5) Cycloaddition of the fumarate of (R)-methyl mandelate with an α-hydroxy-*o*-quinodimethane was found to be highly diastereoselective, giving a single adduct with de >95%. The cycloaddition proceeded via an *exo* transition state with the reaction taking place on the *si* of the *o*-QDM and on the *si* of the fumarate.

(6) A short asymmetric synthesis of neopodophyllotoxin was accomplished, with the cycloaddition of the fumarate of (S)-methyl mandelate to an α'-phenyl-α-hydroxy-*o*-QDM as the key synthetic step. Neopodophyllotoxin was synthesized with an optical purity of >95%.

CHAPTER 4

EXPERIMENTAL

The ^1H nmr spectra were recorded on a Bruker AM-300 instrument in deuterated chloroform ($CDCl_3$, unless otherwise specified) using tetramethylsilane as internal standard. The infrared spectra (IR) were recorded in dichloromethane solution on a Perkin Elmer 881 spectrometer. Aldrich 28,859-4 or Terochem 339385 silica gel was used for all chromatography. All thin layer chromatography (TLC) was carried out on precoated Whatman PE SIL G/UV (CAT NO 4410 222) plates. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada. Exact Mass / spectra were obtained on an Analytical VG 7070E-HF instrument. Melting points (mp) were measured on a hot stage instrument and are uncorrected. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument. All organic solutions were dried with magnesium sulfate ($MgSO_4$) unless otherwise specified. Tetrahydrofuran (THF) was distilled from sodium / benzophenone under nitrogen.

2-Bromo-5-methoxytoluene **111**

This compound was prepared by a modified literature procedure[92]. A solution of bromine (13.0 g, 81.25 mmol) in carbon tetrachloride (30 mL) was added dropwise to a solution of 3-methoxytoluene (10.0 g, 81 mmol), in carbon tetrachloride (100 mL) with stirring at room temperature until the colour of bromine persisted. The mixture was washed with water, dried and evaporated to give a red oil (15 g). The red oil was purified by simple distillation (at 1 atm) to give a pale yellow oil (14.5 g, 88%). Bp 231-235°C. IR (CH_2Cl_2) cm^{-1}: 3051, 3009, 2962, 1242. ^1H nmr ($CDCl_3$) δ: 2.36 (s, 3H), 3.76 (s, 3H), 6.65 (dd, 1H, J= 3.0, 8.75), 6.78 (d, 1H, J= 3.0), 7.39 (d, 1H, J= 8.80). Mass spectrum *m/e*

(rel. %): 202 (97), 200 (100), 187 (13), 185 (13), 159 (15) 157 (15); exact mass calculated for $C_8H_9O_1{}^{79}Br$ 199.9846, found 199.9836; exact mass calculated for $C_8H_9O_1{}^{81}Br$ 201.9831, found 201.9816. The ^1H nmr was identical to that reported in the literature[92].

2-Bromo-4,5-dimethoxytoluene **112**

A solution of bromine (1.15 g, 7.20 mmol) in carbon tetrachloride (20 mL) was added dropwise to a solution of 3,4-dimethoxytoluene (1.04 g, 6.85 mmol) in carbon tetrachloride (15 mL) with stirring at room temperature until the colour of bromine persisted. The mixture was washed with water (2 x 30 mL), dried ($MgSO_4$) and evaporated to give a red oil. The red oil was purified by chromatography on silica gel (ethyl acetate / hexanes, 5/95) to give a colourless oil (1.34 g, 85%). IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 1505, 1465, 1420, 1225, 1220, 1150, 1030. ^1H nmr ($CDCl_3$) δ: 2.32 (s, 3H), 2.82 (s, 3H), 2.83 (s, 3H), 6.72 (s, 1H), 6.99 (s, 1H). Mass spectrum *m/e* (rel. %): 232 (97), 230 (100), 217 (28), 215 (23), 189 (11), 187 (12); exact mass calculated for $C_9H_{11}O_2{}^{79}Br$ 229.9942, found 229.9955.

2-Methyl-4,5-dimethoxybenzaldehyde **113**

2-Bromo-4,5-dimethoxytoluene (0.221 g, 0.96 mmol) in THF (2 mL) was added to a solution of *t*-butyllithium (1.53 mL, 1.25 M in pentane, 1.92 mmol) in THF (3 mL) at -78°C under nitrogen. After 45 seconds, N,N-dimethylformamide (0.140 g, 1.92 mmol, anhydrous) in THF (1 mL) was added. The solution was stirred for 5 minutes at -78°C and then at room temperature for 2 hours. The reaction was quenched with aqueous 10% HCl (10 mL), saturated with sodium chloride, extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give an oil (0.144 g). Chromatography of the oil (ethyl acetate / hexanes) gave a colourless solid (100 mg, 58%). Mp 71-72°C. IR (CH_2Cl_2) cm^{-1}: 1733 (CO). ^1H nmr ($CDCl_3$) δ: 2.63 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.35 (s, 1H), 10.22 (s, 1H). Mass spectrum *m/e* (rel. %): 181 (11), 180 (100), 179 (45), 165 (19),

151 (15), 109 (17); exact mass calculated for $C_{10}H_{12}O_3$ 180.0783, found 180.0786. The ^1H nmr was identical to that reported in the literature[93].

2-Methyl-4-methoxybenzaldehyde **114**

This compound was prepared by a modified literature procedure[92]. A round bottom flask with magnesium turnings (1.66 g, .0682 mol) was flamed for 20 seconds with a stream of nitrogen flushing the flask, and then cooled under the stream of nitrogen. 2-Bromo-5-methoxytoluene (12.47 g, 0.0620 mol) in dry THF (70 mL) was introduced. A small crystal of iodine was added to initiate the formation of the Grignard reagent and the mixture was refluxed for one hour (until all of the magnesium had reacted). N,N-dimethylformamide (9.10 g, 0.124 mol) was added and the solution was stirred for three hours. Aqueous 10% HCl (40 mL) was added and the mixture was stirred for an hour. The mixture was extracted with ethyl acetate (3 x 40 mL), washed with with water (40 mL), dried ($MgSO_4$) and concentrated in vacuo to give a pale red oil (8.68 g, 93%) which was >95% pure by nmr (300 MHz). IR (CH_2Cl_2) cm^{-1}: 3058, 2971, 2844, 2730, 1687 (CO), 1249. ^1H nmr ($CDCl_3$) δ: 2.65 (s, 3H), 3.86 (s, 3H), 6.74 (d, 1H, J= 2.10), 6.83 (dd, 1H, J= 2.40, 8.70), 7.75 (d, 1H, J= 8.70), 10.13 (s, 1H). Mass spectrum *m/e* (rel. %) 150 (84), 149 (100), 121 (15), 91 (13), 78 (10) 77 (15); exact mass calculated for $C_9H_{10}O_2$ 150.0674, found 150.0681. The ^1H nmr was identical to that reported in the literature[92].

2-Methyl-4,5-dihydroxybenzaldehyde **116**

2-Methyl-4,5-dimethoxybenzaldehyde (0.47 g, 2.61 mmol) was mixed with pyridine hydrochloride (1.21 g, 10.44 mmol) and heated to 180 to 190°C under nitrogen for 4 hours. The mixture was cooled and digested in aqueous 10% HCl (50 mL). Some residual tar was removed by filtration and the filtrate extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation gave a pale green solid (0.336 g, 84%) which could be purified by chromatography on silica (ethyl acetate / hexanes, 60/40). Mp 171-173°C. IR

(CH_2Cl_2) cm^{-1}: 3538 (OH), 1684 (CO), 1138, 1104. ^1H nmr ($CDCl_3/CD_3CN$) δ: 2.54 (s, 3H), 6.70 (s, 1H), 7.27 (s, 1H), 10.07 (s, 1H). Mass spectrum *m/e* (rel. %): 153 (8), 152 (90), 151 (100), 124 (5), 123 (45), 77 (17); exact mass calculated for $C_8H_8O_3$ 152.0474, found 152.0472.

2-Methyl-4-hydroxybenzaldehyde **117**

2-Methyl-4-methoxybenzaldehyde (1.42 g, 9.43 mmol) with pyridine hydrochloride (4.31 g, 38 mmol) were fused at 170-180°C under nitrogen for four hours. TLC showed that the starting aldehyde had reacted completely. The hot reaction mixture was poured into aqueous 10% HCl (100 mL) and stirred for half an hour. The mixture was filtered to removed residual tar. The filtrate was extracted with dichloromethane (3 x 40 mL), dried ($MgSO_4$) and concentrated in vacuo to give a pale green solid (0.96 g, 75%). The sample was pure enough for further reaction. A small sample was recrystallized (dichloromethane / hexanes) to give a colourless solid. Mp 107-108°C. IR (CH_2Cl_2) cm^{-1}: 3560, 3060. 2980, 1695 (CO), 1505, 1270, 1120. ^1H nmr ($CDCl_3$) δ: 2.63 (s, 3H), 6.73 (d, 1H, J= 2.13), 6.83 (dd, 1H, J= 2.43, 8.35), 7.73 (d, 1H, J= 8.43), 10.08 (s,1H). Mass spectrum *m/e* (rel. %): 136 (76), 135 (100), 107 (42), 77 (30); exact mass calculated for $C_8H_8O_2$ 136.0524, found 136.0521.

4-Acetoxy-2-methylbenzaldehyde **118**

2-Methyl-4-hydroxybenzaldehyde (0.579 g, 4.25 mmol), acetic anhydride (25 mL) and sodium acetate (30 mg) were stirred at room temperature under nitrogen for 15 hours. The mixture was poured into water (150 mL) and stirred for an hour. The mixture was extracted with dichloromethane (4 x 30 mL), washed with sodium bicarbonate solution (5%, 50 mL), dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil (0.73 g, 96%). IR (CH_2Cl_2) cm^{-1}: 3063, 2867, 2743, 1764 (CO), 1694 (CO), 1602, 1580, 1371, 1208, 1018. ^1H nmr ($CDCl_3$) δ: 2.31 (s, 3H, OAc), 2.66 (s, 3H, Me), 7.00 (d, 1H, J= 2.30),

7.09 (dd, 1H, J= 2.33, 8.40), 7.81 (d, 1H, J= 8.37), 10.26 (s, 1H). Mass spectrum *m/e* (rel. %): 178 (10), 152 (100), 136 (35), 135 (83), 107 (16), 77 (17), 43(94); exact mass calculated for $C_{10}H_{10}O_3$ 178.0630, found 178.0618.

2-Methyl-4-tosyloxybenzaldehyde **119**

2-Methyl-4-hydroxybenzaldehyde (0.281 g, 2.07 mmol), *p*-toluenesulfonyl chloride (0.395 g, 2.07 mmol) and triethylamine (0.21 g, 2.07 mmol) in acetone (25 mL) were stirred for half an hour (reaction was followed by TLC). The mixture was poured in aqueous 10% HCl (50 mL) and stirred for an hour. The mixture was then extracted with dichloromethane (4 x 25 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid. Recrystallization from dichloromethane / hexanes gave a colourless solid (0.537 g, 89%). Mp 110-113°C. IR (CH_2Cl_2) cm^{-1}: 3040, 1710 (CO), 1502, 1382, 1199, 1175, 965. ^1H nmr ($CDCl_3$) δ: 2.46 (s, 3H), 2.62 (s, 3H), 6.93-6.98 (m, 2H), 7.32-7.35 (m, 2H), 7.71-7.75 (m, 3H), 10.20 (s, 1H). Mass spectrum *m/e* (rel. %): 290 (18), 155 (48), 135 (4), 91 (100), 77 (8), 65 (15); exact mass calculated for $C_{15}H_{14}O_4S_1$ 290.0613, found 290.0622.

2-Methyl-4-mesyloxybenzaldehyde **120**

The compound was prepared using the procedure for synthesizing 2-methyl-4-tosyloxybenzaldehyde, starting with the following reagents: 2-methyl-4-hydroxybenzaldehyde (0.727 g, 5.34 mmol), methanesulfonyl chloride (0.612 g, 5.34 mmol), triethylamine (0.648 g, 6.41 mmol). Chromatography of the crude product (silica gel, 30% ethyl acetate / hexanes) gave a pale yellow oil (1.074 g, 94%). A sample was recrystallized from dichloromethane / hexanes to give a colourless solid. Mp 68-70°C. IR (CH_2Cl_2) cm^{-1}: 3060, 2989, 2742, 1702 (CO), 1603, 1577, 1374, 1227, 1180, 1143, 950. ^1H nmr ($CDCl_3$) δ: 2.70 (s, 3H, Me), 3.21 (s, 3H, OMs), 7.21 (d, 1H, J= 2.1), 7.27 (dd, 1H, J= 2.40, 8.40), 7.86 (d, 1H, J= 8.40) 10.25 (s, 1H). Mass spectrum *m/e* (rel.

%): 215 (8), 214 (77), 213 (19), 136 (89), 135 (100), 107 (25), 77 (40); exact mass calculated for $C_9H_{10}O_4S_1$ 214.0300, found 214.0304.

2-Methyl-4,5-diacetoxybenzaldehyde **121**

2-Methyl-4,5-dihydroxybenzaldehyde (0.206 g, 1.35 mmol), acetic anhydride (0.291 g, 0.27 mL, 2.84 mmol) and pyridine (0.32 g, 4.05 mmol) were dissolved in dichloromethane (15 mL) and stirred for 1.5 hours. The mixture was poured into water (100 mL), stirred for an hour, then extracted with dichloromethane, washed with aqueous 10% HCl, dried ($MgSO_4$) and evaporated to give a pale yellow solid (0.31 g, 97%) which could be recrystallized from dichloromethane. Mp 93-96°C. IR (CH_2Cl_2) cm^{-1}: 1775 (CO), 1705 (CO), 1694 (CO), 1501, 1372, 1280, 1209, 1180, 1088 cm^{-1}. ^1H nmr ($CDCl_3$) δ: 2.30 (s, 3H, OAc), 2.31 (s, 3H, OAc), 2.66 (s, 3H, Me), 7.12 (s, 1H), 7.64 (s, 1H), 10.12 (s, 1H). Mass spectrum *m/e* (rel. %): 236 (3), 194 (25), 152 (100), 151 (29), 124 (23); exact mass calculated for $C_{12}H_{12}O_5$ 236.0685, found 236.0670.

2-Methyl-4,5-dimesyloxybenzaldehyde **122**

The experimental procedure used was identical to that for 2-methyl-4-mesyloxybenzaldehyde, starting with the following reagents: 2-methyl-4,5-dihydroxybenzaldehyde (0.68 g, 4.47 mmol), methanesulfonyl chloride (1.024 g, 8.94 mmol), triethylamine (0.905 g, 8.94 mmol). Chromatography of the crude product (silica gel, 30% ethyl acetate / hexanes) gave a colourless solid (0.893 g, 65%). Mp 114-116°C. IR (CH_2Cl_2) cm^{-1}: 3060, 2980, 2875, 1708 (CO), 1379, 1257, 1164, 1184, 1086, 968. ^1H nmr ($CDCl_3$) δ: 2.70 (s, 3H, Me), 3.29 (s, 3H, OMs), 3.31 (s, 3H, OMs), 7.41 (s, 1H), 7.87 (s, 1H), 10.25 (s, 1H). Mass spectrum *m/e* (rel. %): 309 (4), 308 (27), 230 (11), 229 (16), 152 (10), 151 (100), 123 (15), 79 (22); exact mass calculated for $C_{10}H_{12}O_7S_2$ 308.0024, found 308.0016.

2-Methyl-4,5-ditosyloxybenzaldehyde **123**

The compound was synthesized using the procedure for making 2-methyl-4-tosyloxybenzaldehyde, starting with the following reagents: 2-methyl-4,5-dihydroxybenzaldehyde (0.063 g, 0.415 mmol), *p*-toluenesufonyl chloride (0.1584 g, 0.83 mmol), triethylamine (0.085 g, 0.83 mmol). The resulting crude product was purified by chromatography on silica gel (50% ethyl acetate / hexanes) to give a colourless solid (0.175 g, 91%). Mp 124-126°C. IR (CH_2Cl_2) cm^{-1}: 3060, 2988, 2758, 1707 (CO), 1599, 1494, 1383, 1295, 1195, 1179, 1063. ^1H nmr ($CDCl_3$) δ: 2.46 (s, 6H), 2.63 (s, 3H), 7.20-7.35 (m, 5H), 7.58-7.70 (m, 5H), 10.14 (s, 1H). Mass spectrum *m/e* (rel. %): 461 (4), 460 (15), 156 (9), 155 (100), 91 (72), 65 (13); exact mass calculated for $C_{22}H_{22}O_7S_2$ 460.0650, found 460.0638.

1-Hydroxy-5-tosyloxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **124d**

2-Methyl-4-tosyloxybenzaldehyde (0.241 g, 8.30 mmol) in benzene (40 mL) was deoxygenated by flushing with nitrogen. Sulfur dioxide (2.0 g) was added and the solution was irradiated (Hanovia 450-W, medium pressure mercury lamp, through 1 mm Pyrex tube) for 14 hours. The solvent was evaporated (at room temperature) and the residue was dissolved in ethyl acetate (40 mL) followed by extraction with aqueous 5% sodium bicarbonate (3 x 15 mL). The combined bicarbonate extracts were acidified with aqueous 10% HCl, extracted with ethyl acetate (4 x 15 mL), dried ($MgSO_4$) and evaporated to give a colourless solid (0.198 g, 67%). Mp 113-115°C. IR (CH_2Cl_2) cm^{-1}: 3530 (OH), 3070, 2990, 1380, 1323, 1195, 1180, 955. ^1H nmr ($CDCl_3$) δ: 2.46 (s, 3H, Me), 4.20, 4.32 (AB_q, 2H, J= 16.04), 5.59 (s, 1H), 6.97 (dd, 1H, J= 2.36, 8.45), 7.04 (d, 1H, J= 2.13), 7.32 (d, 1H, J= 8.37), 7.47 (d, 1H, J= 8.46), 7.71 (d, 1H, J= 8.31). Mass spectrum *m/e* (rel. %): 290 (45, $M^+ - SO_2$), 280 (15), 166 (16), 84 (27), 64 (100), 48 (40).

1-Hydroxy-5-mesyloxy-1,3-dihydroxybenzo[c]thiophene-2,2-dioxide **124e**

This compound was prepared according to the procedure for sulfone **124d**, starting with the following reagents: 2-methyl-4-mesyloxybenzaldehyde (0.222 g, 1.04 mmol) and sulfur dioxide (1.88 g). Total irradiation time was 7 hours. The product was a yellow oil (0.196 g, 70%). The oil was insoluble in deuterated chloroform and dichloromethane, and was converted to the more soluble methoxy derivative **125** for characterisation.

1-Methoxy-5-mesyloxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **125**

The sulfone **124e** (0.196 g, 7.06 mmol) with *p*-toluenesulfonic acid (10 mg) in dichloromethane / methanol (1:1, 50 mL) was warmed to 40-50°C for 24 hours. The solvent was evaporated and the crude product was filtered through a short column of silica gel (ethyl acetate). Evaporation of solvent gave the product as a colourless oil (0.146 g, 71%). IR (CH_2Cl_2) cm^{-1}: 3061, 2939, 1611, 1486, 1357, 1375, 1321, 1214, 1182, 1126, 969, 945. ^1H nmr ($CDCl_3$) δ: 3.18 (s, 3H, OMs), 3.84 (s, 3H, OMe), 4.26, 4.40 (AB_q, 2H, J= 16.03), 5.28 (s, 1H), 7.26 (d, 1H, J= 2.22), 7.33 (d, 1H, J= 2.36, 8.48), 7.55 (d, 1H, J= 8.46). Mass spectrum *m/e* (rel. %): 229 (38), 228 (100, $M^+ - SO_2$), 213 (50), 149 (45), 135 (92), 121 (62). 91 (27), 77 (35), 64 (71), 48 (35); exact mass calculated for $C_{12}H_{12}O_4S_1$ 228.0456, found 228.0418.

1-Hydroxy-5,6-dimesyloxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **124f**

The experimental procedure used to prepare this sulfone was identical to that for sulfone **124d**, starting with the following reagents: 2-methyl-4,5-dimesyloxybenzaldehyde (0.193 g, 0.625 mmol), sulfur dioxide (4.0 g). The product (0.155 g, 67%) was insoluble in deuterated chloroform and dichloromethane and was converted to the more soluble acetoxy derivative **126** for characterisation.

1-Acetoxy-5,6-dimesyloxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **126**

The sulfone **124f** (0.1995 g, 0.417 mmol), sodium acetate (85 mg) and acetic anhydride (20 mL) were stirred at room temperature for 10 hours. Water (150 mL) was cautiously added and the mixture was stirred for 2 hours. The mixture was extracted with dichloromethane (3 x 20 mL), dried ($MgSO_4$) and the solvent was removed at reduced pressure. Chromatography of the crude product (silica gel, ethyl acetate / hexanes) gave a colourless solid (54.9 mg, 32%). Mp 70-72°C. IR (CH_2Cl_2) cm^{-1}: 3056, 2988, 1770 (CO), 1422, 1381, 1342, 1271, 1187, 1165, 1136, 1123, 1107, 968. ^1H nmr ($CDCl_3$) δ: 2.25 (s, 3H, OAc), 3.30 (s, 3H, OMs), 3.31 (s, 3H, OMs), 4.39, 4.42 (AB_q, 2H, J= 16.26), 6.54 (s, 1H), 7.52 (s, 1H), 7.64 (s, 1H). Mass spectrum *m/e* (rel. %): 350 (0.4, M^+ - SO_2), 308 (14), 229 (10), 151 (50), 117 (12), 84 (12), 64 (100).

Dimethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate **127-130**

These compounds were prepared as follow: Aldehyde (**119**, **121-123**) with 5 molar equivalents of dimethyl fumarate in acetone (50 mL) were deoxygenated by flushing with nitrogen. The solution was irradiated (Hanovia 450-W, medium pressure mercury lamp, through a 1 mm Pyrex tube) for 15 hours. The solvent was evaporated and most of the excess dimethyl fumarate was removed by sublimation at 90°C at reduced pressure (0.2 mm Hg). The resulting crude product was purified by chromatography on silica gel (40% ethyl acetate / hexanes). The cycloadducts (colourless oil) consisted of a mixture of diastereomers and were not separated and individually characterized. The ^1H nmr and infrared spectra of the mixtures were acquired.

127 (85%). IR (CH_2Cl_2) cm^{-1}: 3596 (OH), 3058, 1763 (CO), 1742 (CO), 1439, 1272, 1209. ^1H nmr ($CDCl_3$) δ: 2.26 (s, OAc), 2.85 (dd, J= 11.85, 16.86), 2.94 (dd, J= 9.30, 10.35), 3.00-3.20 (m), 3.34 (ddd, J= 5.58, 11.79), 3.70 (s, $-CO_2Me$), 3.74 (s, $-CO_2Me$), 3.75 (s, $-CO_2Me$), 4.90 (bd, 1H), 5.10 (bd, 1H), 6.80 (m, aromatics), 6.95 (m, aromatics),

7.35 (d, 1H, J= 8.40), 7.55 (d, 1H, J= 8.50).

128 (90%). IR (CH_2Cl_2) cm^{-1}: 3588 (OH), 3064, 2956, 1772 (CO), 1740 (CO), 1504, 1439, 1372, 1211, 1097, 910. ^1H nmr ($CDCl_3$) δ: 2.27 (s, OAc), 2.85(dd, J= 12.30, 16.95), 2.950 (dd, J= 9.45, 10.56), 3.00-3.20 (m), 3.35 (ddd, J= 5.58, 11.61), 3.71 (s,-CO_2Me), 3.75 (s, -CO_2Me) 3.76 (s, -CO_2Me), 3.77(s, -CO_2Me), 4.90 (bd, 1H), 5.05 (bd, 1H), 6.92 (s, aromatic), 6.96 (s, aromatic), 7.19 (s, aromatic), 7.39 (s, aromatic)

129 (65%). IR (CH_2Cl_2) cm^{-1}: 3591 (OH), 3064, 2957, 1739 (CO), 1598, 1499, 1439, 1380, 1196, 1177, 1094, 872, 814. ^1H nmr ($CDCl_3$) δ: 2.44 (s, Me), 2.83 (dd, J= 11.25, 16.95), 2.97 (dd, J= 9.48, 10.44), 3.01-3.20 (m), 3.36 (ddd, J= 5.73, 11.43), 3.71 (s,-CO_2Me), 3.74 (s, -CO_2Me) 3.76 (s, -CO_2Me), 3.77 (s, -CO_2Me), 4.89 (bd, 1H), 5.00 (bd, 1H), 7.20-7.90 (m, aromatics).

130 (54%). IR (CH_2Cl_2) cm^{-1}: 3579 (OH), 3058, 1740 (CO), 1502, 1439, 1378, 1184, 1171, 968. ^1H nmr ($CDCl_3$) δ: 2.91 (dd, J= 10.98, 17.34), 2.99 (dd, J= 9.39, 10.05), 3.04-3.20 (m), 3.23 (s, OMs), 3.24(s, OMs), 3.36 (ddd, J= 5.67, 11.01), 3.72 (s,-CO_2Me), 3.75 (s, -CO_2Me) 3.77 (s, -CO_2Me), 3.77 (s, -CO_2Me), 4.92 (bd, 1H), 5.08 (bd, 1H), 7.20 (s, aromatic), 7.25 (s, aromatic), 7.47 (s, aromatic), 7.65 (s, aromatic)

Dimethyl-3,4-dihydronaphthalene-2,3-dicarboxylate **131** and **132**

The cycloadduct(**127** or **128**, ~100 mg) with *p*-toluenesulfonic acid (10 mg) in methanol (10 mL) was stirred at room temperature for 12 hours. Most of the methanol was evaporated and the residue was dissolved in dichloromethane (50 mL). The solution was washed with aqueous 5% sodium bicarbonate (20 mL), dried ($MgSO_4$) and concentrated in vacuo.

131 (97%). a colourless solid with mp 168-170°C. IR (CH_2Cl_2) cm^{-1}: 3575 (OH), 3405

(OH), 3058, 1734 (CO), 1707 (CO), 1206; ^{1}H nmr (CD_3CN) δ: 3.06 (dd, 1H, J= 8.00, 16.31, H-4), 3.21 (dd, 1H, J= 3.51, 16.33, H-4), 3.58 (s, 3H, -CO_2Me), 3.78 (s, 3H, -CO_2Me), 3.79 (dd, 1H, J= 3.72, 7.74, H-3), 6.67 (d, 1H, J= 8.50), 7.12 (d, 1H, J= 8.88), 7.20 (s, 1H), 7.56 (s, 1H, H-1). Mass spectrum *m/e* (rel. %) 263 (5), 262 (32), 204 (13), 203 (100), 172 (7), 172 (51), 159 (19), 145 (10), 144 (83), 115 (43), 59 (34); exact mass calculated for $C_{14}H_{14}O_5$ 262.0841, found 262.0849

132 (98%). a colourless solid with mp 202-205°C. IR (nujol) cm^{-1}: 3348 (OH), 3058, 1724 (CO), 1691 (CO), 1582, 1255; ^{1}H nmr (CD_3CN) δ: 3.00 (dd, 1H, J= 7.92, 16.24, H-4), 3.10 (dd, 1H, J= 3.63, 16.24, H-4), 3.55 (s, 3H, -CO_2Me), 3.73 (dd, 1H, J= 3.67, 7.83, H-3), 3.75 (s, 3H, -CO_2Me), 6.68 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 6.86 (broad s, 2H, OH), 7.51 (s, 1H, H-1). Mass spectrum *m/e* (rel. %) 279 (6), 278 (41), 220 (13), 219 (98), 218 (71), 188 (13), 187 (100), 161 (13), 160 (89), 129 (17), 114 (22), 77 (14), 59 (34); exact mass calculated for $C_{14}H_{14}O_6$ 278.0790, found 278.0799.

Dimethyl-3,4-dihydronaphthalene-2,3-dicarboxylate **133** and **134**

The cycloadduct (**129** or **130**, ~50 mg) with *p*-toluenesulfonic acid (10 mg) in toluene (20 mL) were refluxed (110°C) for approximately one hour (followed reaction by TLC). The solvent was evaporated and the residue was dissolved in dichloromethane (50 mL) and filtered through a short column of silica gel. Evaporation of solvent gave the corresponding product.

133 (90%). a colourless oil. IR (CH_2Cl_2) cm^{-1}: 3064, 2960, 1740 (CO), 1720 (CO), 1599, 1497, 1438, 1376, 1245, 1179, 1046. ^{1}H nmr ($CDCl_3$) δ: 2.45 (s, 6H, Me), 3.10 (dd, 1H, J= 8.21, 16.46, H-4), 3.31 (dd, 1H, J= 3.39, 16.57, H-4), 3.64 (s, 3H, -CO_2Me), 3.84 (s, 3H, -CO_2Me), 3.89 (dd, 1H, J= 3.35, 8.18, H-3), 7.12 (s, 1H, aromatic), 7.14 (s, 1H, aromatic), 7.22-7.30 (m, 4H, aromatics), 7.50 (s, 1H, H-1), 7.59-7.66 (m, 4H, aromatics). Mass spectrum *m/e* (rel. %) 586 (1), 306 (43), 155 (100), 151 (38), 139 (13), 123 (17), 91

(100), 65 (26); exact mass calculated for $C_{28}H_{26}O_{10}S_2$ 586.0967, found 586.0952.

134 (74%). a colourless oil. IR (CH_2Cl_2) cm^{-1}: 3064, 2975, 1736 (CO), 1716 (CO), 1505, 1450, 1379, 1243, 1182, 1079, 975, 890. ^1H nmr ($CDCl_3$) δ: 3.14 (dd, 1H, J= 8.28, 16.56, H-4), 3.25 (s, 3H, OMs), 3.26 (s, 3H, OMs), 3.41 (dd, 1H, J= 2.99, 16.64, H-4), 3.64 (s, 3H, -CO_2Me), 3.85 (s, 3H, -CO_2Me), 3.92 (dd, 1H, J= 2.94, 8.25, H-3), 7.33 (s, 1H, aromatic), 7.36 (s, 1H, aromatic), 7.57 (s, 1H, H-1). Mass spectrum *m/e* (rel. %) 434 (15), 376 (10), 375 (95), 343 (25), 295 (46), 237 (35), 217 (100), 189 (25), 159 (44), 102 (22), 59 (51); exact mass calculated for $C_{16}H_{18}O_{10}S_2$ 434.0342, found 434.0335.

Acrylate of (S)-methyl lactate **135**,

A mixture of (S)-methyl lactate (4.42 g, 42.2 mmol), acryloyl chloride (11.53 g, 10.4 mL, 127 mmol) and 3 Å molecular sieves (9 g, flamed dried) in carbon tetrachloride (80 mL) were refluxed under nitrogen for 4 days. The mixture was filtered, evaporation of solvent and chromatography of the crude oil (20% ethyl acetate / hexanes) gave a colourless oil (5.83 g, 87%) which was >97% pure by nmr (300 MHz). $[\alpha]_D^{20}$ -43.5° (c 0.433, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 2969, 1768 (CO), 1740 (CO), 1415, 1197, 1105, 987. ^1H nmr ($CDCl_3$) δ: 1.55 (d, 3H, J= 7.1, Me), 3.76 (s, 3H, -CO_2Me), 5.16 (q, 1H, J= 7.1), 5.88 (dd, 1H, J= 1.3, 10.4), 6.20 (dd, 1H, J= 10.4, J = 17.2), 6.46 (dd, 1H, J= 1.3, 17.2). Mass spectrum *m/e* (rel. %) neohexane chemical ionization: 159 (12, M+1), 127 (20), 71 (55), 55 (100); ammonia chemical ionization: 176 (10, M·NH_4), 159 (25, M+1), 127 (20), 72 (17), 55 (100); electron impact: 114 (18), 99 (25), 55 (100).

(1R,2S)-(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **136**

A solution of 2-methylbenzaldehyde (133 mg, 1.1 mmol), acrylate **135** (0.228 g, 1.44 mmol) and hydroquinone (1 mg) in benzene (30 mL) was purged with nitrogen and

irradiated with a Hanovia 450 watt medium pressure mercury lamp through a pyrex filter from a distance of 10 cm for 17 h. The solvent was evaporated and the residue chromatographed (40% ethyl acetate / hexanes) to give an oil (107 mg, 55%). $[\alpha]_D^{20}$ -36.3° (c 1.35 , $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3499 (OH), 3065, 2958, 1739 (CO), 1457, 1220, 1160, 1103. ^1H nmr ($CDCl_3$) δ: 1.55 (d, 3H, J = 7.1, Me), 2.00 (m, 1H), 2.20 (m, 1H), 2.84 (m, 3H), 3.79 (s, 3H, $-CO_2Me$), 5.00 (d, 1H, J= 9.30, H-1), 5.23 (q, 1H, J= 7.1), 7.20 (m, aromatics). Mass spectrum *m/e* (rel. %) 278 (3), 173 (21), 156 (28), 146 (86), 129 (100), 118 (33), 91 (65); exact mass calculated for $C_{15}H_{18}O_5$ 278.1154, found 278.1153.

(2S)-(-)-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **137**,

Cycloadduct **136** (146 mg, 0.525 mmol) and 5% palladium on charcoal (30 mg) in acetic acid (10 mL) was stirred under hydrogen (1 atm) at 70°C for 3 days. The mixture was filtered, diluted with dichloromethane (40 mL), washed with water and 5% aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to give a colourless oil (118 mg, 87%). $[\alpha]_D^{20}$ -38.4° (c 0.55, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3058, 2993, 1740 (CO), 1168, 1137, 1102. ^1H nmr ($CDCl_3$) δ: 1.50 (d, 3H, J= 7.05, Me), 1.85-1.95 (m, 1H), 2.19-2.31 (m, 1H), 2.77-2.91 (m, 3H), 2.97-3.14 (m, 2H), 3.75 (s, 3H, $-CO_2Me$), 5.15 (q, 1H, J= 7.05), 7.10 (m, aromatics). Mass spectrum *m/e* (rel. %) 262 (2), 159 (8), 131 (37), 130 (100), 129 (26), 115 (14); exact mass calculated for $C_{13}H_{18}O_4$ 262.1205, found 262.1201.

(S)-(-)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **138**

A solution of the methyl lactyl ester of **137** (118 mg, 0.45 mmol) and potassium carbonate (200 mg) in methanol (15 mL) and water (2 mL) were refluxed for 4 hours. Most of the methanol was evaporated, the solution diluted with water and washed with dichloromethane. The aqueous portion was then acidified with 10% HCl and extracted with dichloromethane, dried ($MgSO_4$) and evaporated to give crystals (69 mg, 86%).

Recrystallization from dichloromethane / hexanes gave colourless needles. Mp 98-100°. $[\alpha]_D^{20}$ -53° (c 0.788, $CHCl_3$), lit[81] $[\alpha]_D^{20}$ +55.5° for (R). IR (CH_2Cl_2) cm^{-1}: 3400-3000 (broad, $-CO_2H$), 1707 (CO), 1495, 1455, 1438, 1421, 1136, 1111. ^1H nmr ($CDCl_3$) δ: 1.83-1.96 (m, 1H), 2.20-2.31 (m, 1H), 2.77-2.90 (m, 3H), 3.02-3.05 (m, 2H), 7.08-7.14 (m, aromatics). Mass spectrum *m/e* (rel. %) 177 (4), 176 (35), 131 (32), 130 (100), 115 (17), 104 (20), 91 (27); ezact mass calculated for $C_{11}H_{12}O_2$ 176.0837, found 176.0843.

(1R,2S)-(-)-1-Hydroxy-6,7-diacetoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **139**

2-Methyl-4,5-diacetoxybenzaldehyde (0.093 g, 0.394 mmol), the acrylate of (S)-methyl lactate (0.094 g, 0.591 mmol) and hydroquinone (2 mg) were dissolved in benzene and deoxygenated by flushing with nitrogen. The solution was irradiated (Hanovia 450 watt, medium pressure mercury lamp, through 1 mm pyrex) for 24 h, the solvent was evaporated and the residue was chromatographed on silica gel (35-75% ethyl acetate / hexanes) to give a colourless oil (0.132 g, 85%). $[\alpha]_D^{20}$-24° (c 1.43, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3575 (OH), 3492 (OH), 3061, 2959, 1771 (CO), 1504, 1372, 1213, 1176, 1099. ^1H nmr ($CDCl_3$) δ: 1.54 (d, 3H, J= 7.09, Me), 1.90-2.07 (m, 1H), 2.10-2.24 (m, 1H), 2.26 (s, 3H, OAc), 2.27 (s, 3H, OAc), 2.72-2.88 (m, 3H), 3.78 (s, 3H, $-CO_2Me$), 4.90 (d, H-1, J= 9.54), 5.25 (q, 1H, J= 7.09), 6.91 (s, 1H, aromatic), 7.47 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 394 (7), 352 (20), 310 (48), 292 (36), 249 (35), 223 (42), 205 (57), 188 (44), 179 (22), 178 (100), 166 (55), 161 (60), 149 (36); exact mass calculated for $C_{19}H_{22}O_9$ 394.1264, found 394.1266.

(2S)-(-)-6,7-diacetoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **140**

Cycloadduct **139** (227.5 mg, 0.58 mmol) with 5% Pd/C (50 mg) in acetic acid (10 mL) were stirred under hydrogen (1 atm) at 70 °C for four days. The mixture was filtered

and the solvent was evaporated to give a yellow oil. Chromatography of the crude oil (silica gel, ethyl acetate / hexanes) gave **140** as a colourless oil (37 mg, 17%). $[\alpha]_D^{20}$-25° (c 0.89, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3064, 2958, 1766 (CO), 1741 (CO), 1506, 1372, 1216, 1178, 1097. ^1H nmr ($CDCl_3$) δ: 1.51 (d, 3H, J= 7.05, Me), 1.80-1.95 (m, 1H), 2.17-2.35 (m, 1H, overlapped by OAc singlets), 2.26 (s, 3H, OAc), 2.27 (s, 3H, OAc), 2.75-2.88 (m, 3H), 2.94-3.11 (m, 2H), 3.74 (s, 3H, $-CO_2Me$), 5.13 (q, 1H, J= 7.08), 6.90 (s, 1H, aromatic), 6.92 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 378 (3), 336 (11), 295 (12), 294 (72), 275 (7), 205 (14), 163 (26), 162 (100), 149 (18); exact mass calculated for $C_{19}H_{22}O_8$ 378.1315, found 378.1306.

1-Acetoxybenzocyclobutene **141**

This compound was prepared by a modified literature procedure[12]. To a refluxing solution of vinyl acetate (100 mL) and isoamyl nitrite (10 mL, 74.4 mmol), anthranilic acid (9.00 g, 65.6 mmol) was added in small portions over a period of half an hour and refluxed for an additional half an hour. The excess vinyl acetate was evaporated and the resulting dark oil was distilled under reduced pressure (0.3 mm Hg, 80-90°C) to give a yellow oil (5.455 g, 47%). ^1H nmr ($CDCl_3$) δ: 2.11 (s, 3H, OAc), 3.22 (dd, 1H, J= 1.91, 14.55), 3.66 (dd, 1H, J= 4.55, 14.53), 5.91 (dd, 1H, J= 1.91, 4.56), 7.01-7.45 (m, 4H, aromatics), identical to that previously reported[12].

Benzocyclobuten-1-ol **17**

1-Acetoxybenzocyclobutene **141** (5.00 g, 28.0 mmol) and cation exchange resin (Dowex 50W-X8, acid form, 5 g) in methanol (20 mL) was stirred at 70°C for 17 hours. The mixture was filtered and the solvent was evaporated. The resulting crude oil was chromatographed to give a pale yellow oil (2.296 g, 68%). ^1H nmr ($CDCl_3$) δ: 2.09 (s, 1H, OH), 3.05 (dd, 1H, J= 2.00, 14.44), 3.63 (dd, 1H, J= 4.50, 14.41), 5.30 (dd, 1H, J= 2.02, 4.50), 7.12-7.27 (m, 4H, aromatics), identical to that previously reported[12].

(1R,2S)-(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **136**

Benzocyclobuten-1-ol **17** (32 mg, 0.268 mmol), acrylate **135** (0.1272 g, 0.804 mmol) and hydroquinone (2 mg) in toluene (7.0 mL) were refluxed for 6 hours. The solvent was evaporated and the residue was chromatographed (40% ethyl acetate / hexanes) to give an oil (54.4 mg, 73%). The major isomer had an ^{1}H nmr spectrum identical to the product obtained from the photochemical reaction.

2-Bromo-4,5-dimethoxy styrene oxide **143**

2-Bromo-4,5-dimethoxybenzaldehyde (0.804 g, 3.30 mmol), trimethyl sulfonium iodide (1.346 g, 6.58 mmol)and potassium hydroxide (0.35 g, 6.26 mmol) in acetonitrile (50 mL) with two drops of water were stirred at 60°C for five hours. Water (40 mL) was added and the mixture was extracted with dichloromethane (3 x 40 mL). The combined extract was dried ($MgSO_4$) and evaporation of solvent followed by chromatography of the crude oil (silica gel, 10% ethyl acetate / hexanes) gave colourless crystals (0.6642 g, 78%). Mp 87-89°C. IR (CH_2Cl_2) cm^{-1}: 3061, 2969, 1606, 1507, 1464, 1394, 1247, 1211, 1164, 1031, 942, 863, 792. ^{1}H nmr ($CDCl_3$) δ: 2.83 (dd, 1H, J = 2.64, 5.67), 3.16 (dd, 1H, J= 4.14, 5.70), 3.85 (s, 1H, -OCH_3), 3.87 (s, 3H, -OCH_3), 4.10 (dd, 1H, J = 2.58, 4.02), 6.72 (s, 1H), 7.00 (s, 1H). Mass spectrum *m/e* (rel. %): 260 (26), 259 (5), 258 (26), 231 (93), 229 (100), 149 (25), 107 (14); exact mass calculated for $C_{10}H_{11}O_3{}^{79}Br$ 257.9892, found 257.9897.

4,5-Dimethoxybenzocyclobuten-1-ol **144**

A solution of 2-bromo-4,5-dimethoxystyrene oxide **143** (0.359 g, 1.39 mmol) in anhydrous ether (30 mL) was cooled to -78°C under nitrogen. *n*-Butyllithium (2.44 M in pentane, 1.60 mmol, 0.66 mL) was introduced, followed by $MgBr_2$ etherate (2.78 mmol).

The mixture was stirred at -78°C for half an hour and then allowed to warm slowly to room temperature. The mixture was quenched with 10% ammonium chloride solution (30 mL), extracted with ether (2 x 30 mL) and dried ($MgSO_4$). Evaporation of solvent followed by chromatography of the crude oil (silica gel, 35% ethyl acetate / hexanes) gave a colourless solid (117 mg, 47%). Mp 107-109°C, lit.[16] mp 104-105°C. IR (CH_2Cl_2) cm^{-1}: 3593 (OH), 3061, 2961, 1593, 1482, 1304, 1209, 1099, 1073, 1046, 973, 898. ^1H nmr ($CDCl_3$) δ: 2.30 (s, 1H), 2.95 (dd, 1H, J = 1.4, 13.72) 3.50 (dd, 1H, J = 4.20 13.72), 3.84 (s, 3H), 3.85 (s, 3H), 5.20 (dd, 1H, J = 1.4, 4.2), 6.70 (s, 1H), 6.80 (s, 1H). Mass spectrum *m/e* (rel. %): 181 (12), 180 (100), 179 (58), 165 (24), 151 (53), 109 (23), 77 (21), 65 (19); exact mass calculated for $C_{10}H_{12}O_3$ 180.0787, found 180.0781. The physical properties were identical to those previously reported[16].

1-Acetoxy-4,5-dimethoxybenzocyclobutene **145**

A solution of 2-amino-4,5-dimethoxybenzoic acid (1.40 g, 7.08 mmol) in tetrahydrofuran (20 mL) was added to a refluxing solution of vinyl acetate (70 mL) and *iso*-amyl nitrite (1.67 g, 1.9 mL, 14.16 mmol) over a period of 30 min. After refluxing for 15 hours, the vinyl acetate was evaporated on a rotary evaporator and the resulting brown-red oil was distilled in a short path distillation apparatus (0.05 mm Hg, 130°C) to give a red oil (1.24 g). This oil was chromatographed on silica gel (ethyl acetate / hexanes) to give a pale yellow oil (0.71 g, 45%, solidified on cooling) which nmr indicated was essentially free of impurities. Mp 33-35°C. IR (CH_2Cl_2) cm^{-1}: 3057, 2966, 1737 (CO), 1484, 1466, 1383, 1304, 1241, 1211, 1073, 1036. ^1H nmr ($CDCl_3$) δ: 2.10 (s, 3H, OAc), 3.14 (dd, 1H, J = 1.52, 13.9), 3.53 (dd, 1H, J = 4.30, 13.9), 3.85 (s, 3H, $-OCH_3$), 3.86 (s, 3H, $-OCH_3$), 5.80 (dd, 1H, J = 1.63, 4.30), 6.71 (s, 1H, aromatic), 6.82 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 222 (20), 181 (11), 180 (100), 179 (47), 165 (16), 163 (15), 162 (21); exact mass calculated for $C_{12}H_{14}O_4$ 222.0892, found 222.0891.

4,5-Dimethoxybenzocyclobuten-1-ol **144**

Dimethoxybenzocyclobutenyl acetate **145** (0.458 g, 2.06 mmol) was stirred in a mixture of methanol / 30% aqueous ammonia (7:3, 10 mL) at room temperature for 6 hours . The mixture was acidified with aqueous 10% HCl and extracted with dichloromethane. The resulting crude product (yellow solid) was chromatographed on silica gel (ethyl acetate / hexanes) to give colourless crystals (0.317 g, 85%), which had physical properties identical to those previously reported[16].

(1R,2S)-(-)-1-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **146**

Dimethoxybenzocyclobutenol **144** (88 mg, 0.49 mmol), the acrylate of (S)-methyl lactate (232 mg, 1.47 mmol) and hydroquinone (2 mg) were dissolved in toluene (7 mL) and refluxed for 6 hours. The solvent was concentrated in vacuo and the resulting oil was chromatographed on silica gel (eluant ethyl acetate / hexanes) to give a pale yellow oil (153 mg, 93%) which appeared by nmr to be a mixture of one major and three minor (<9%) isomers). Careful rechromatography on silica gel (25% ethyl acetate / hexanes) gave the major cycloadduct as a colourless oil which solidified on cooling (132 mg, 80%). Mp 76-78°C. $[\alpha]_D^{20}$-31.6° (c 1.33, $CHCl_3$). IR (CH_2Cl_2)cm^{-1}: 3492 (OH), 3062, 2960, 1739(CO), 1512, 1461, 1244, 1209, 1159, 1118. ^1H nmr ($CDCl_3$) δ: 1.55 (d, 3H, J = 7.12, Me), 1.91-2.05 (m, 1H), 2.12-2.20 (m, 1H), 2.71-2.92 (m, 3H), 3.79 (s, 1H, $-CO_2Me$), 3.84 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-OCH_3$), 4.92 (d, 1H, J= 9.12, H-1), 5.25 (q, 1H, J= 7.12), 6.55 (s, 1H, aromatic), 7.17 (s, 1H, aromatic). ^{13}C nmr (75.5 MHz $CDCL_3$) δ: 16.75 (CH_3), 23.73 (CH_2), 27.79 (CH_2), 48.84 (CH), 52.85 (CH_3), 55.81 (CH_3), 55.86 (CH_3), 68.68 (CH), 70.59 (CH), 109.43 (CH), 110.55 (CH), 127.51 (C), 129.30 (C), 147.56 (C), 148.12 (C), 172.19 (C), 174.54 (C). Mass spectrum *m/e* (rel. %): 339 (10), 338 (52), 321 (10), 320 (34), 251 (20), 233 (42), 217 (28), 207 (21), 206 (63), 189 (100), 177 (68), 151 (35), 115 (16), 91 (16), 77 (16), 55 (30); exact mass calculated for $C_{17}H_{22}O_7$ 338.1367,

found 338.1372.

(1S,2R)-1-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-methyl lactate **147**

Only 2 mg of the pure minor adduct was isolated by chromatography and it was characterized by ^{1}H nmr only. ^{1}H nmr ($CDCl_3$) δ: 1.55 (d, 3H, J = 7.09, Me), 1.91-2.05 (m, 1H), 2.27-2.34 (m, 1H), 2.72-2.94 (m, 3H), 3.78 (s, 1H, $-CO_2Me$), 3.85 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 5.08 (d, 1H, J= 9.11, H-1), 5.25 (q, 1H, J= 7.08), 6.56 (s, 1H, aromatic), 7.13 (s, 1H, aromatic)

(2S)-(-)-6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carbox ylate of (S)-methyl lactate **148**

Cycloadduct **146** (123 mg, 0.36 mmol) and 5% Pd/C (120 mg) were stirred in acetic acid / methanol (50:50, 15 mL) under H_2 (1 atm) at room temperature for 15 hours. The mixture was then filtered, evaporated to near dryness, dissolved in dichloromethane (50 mL), washed with 5% aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to a colourless oil which crystallized on standing (95.5 mg, 82%). Mp 67-68°C. $[\alpha]_D^{20}$-37.3° (c 0.88, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3064, 2959, 1740 (CO), 1516, 1462, 1242, 1168, 1115. ^{1}H nmr ($CDCl_3$) δ: 1.51 (d, 3H, J = 7.05, Me), 1.82-1.91 (m, 1H), 2.18-2.27 (m, 1H), 2.76-2.84 (m, 3H), 2.86-3.08 (m, 2H), 3.75 (s, 3H, $-CO_2Me$), 3.85 (s, 6H, $-OCH_3$), 5.14 (q, 1H, J = 7.05), 6.57 (s, 1H, aromatic), 6.60 (s, 1H, aromatic). ^{1}H nmr (C_6D_6) δ: 1.29 (d, 3H, J = 7.07, Me), 1.80-1.95 (m, 1H), 2.07-2.16 (m, 1H), 2.44-2.73 (m, 3H), 2.93-3.13 (m, 2H), 3.31 (s, 3H, $-CO_2Me$), 3.44 (s, 3H, $-OCH_3$), 3.46 (s, 3H, $-OCH_3$), 5.14 (q, 1H, J = 7.07), 6.39 (s, 2H, aromatics). ^{13}C nmr (75.5 MHz, $CDCL_3$), δ: 16.85 (CH_3), 25.61 (CH_2), 27.94 (CH_2), 31.09 (CH_2), 39.72 (CH), 52.25 (CH_3), 55.76 (CH_3), 66.28 (CH_3), 68.32 (CH), 111.33 (CH), 111.52 (CH), 126.35 (C), 127.19 (C), 147.02 (C), 147.09 (C), 171.19 (C), 174.72 (C). Mass spectrum *m/e* (rel. %): 322 (96), 192 (7), 191 (58), 190 (100), 189 (21), 175 (24), 176 (11), 159 (13), 96 (16); exact mass calculated for

$C_{17}H_{22}O_6$ 322.1416, found 322.1425.

(2S)-(-)-6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **150**

The ester **148** (113 mg, 0.35 mmol) and potassium carbonate (200 mg) was stirred in a methanol / water (20:1, 20 mL) mixture at room temperature for 15 hours. Most of the solvent was then evaporated and the residue dissolved in 5% aqueous sodium bicarbonate, washed with dichloromethane, acidified with 10% aqueous HCl and finally extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation gave a colourless solid which could be recrystallized from dichloromethane / hexanes (79.5 mg, 95%). Mp 145.5-147°C, lit.[84] mp 141.5-142.5 (racemic). $[\alpha]_D^{20}$-41.8° (c 0.67, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3400-2800 (broad, -CO_2H), 1708 (CO), 1517, 1243, 1224, 1116, 909. ^1H nmr ($CDCl_3$) δ: 1.81-1.94 (m, 1H), 2.19-2.27 (m, 1H), 2.72-2.83 (m, 3H), 2.95 (d, 2H, J= 7.70), 3.840 (s, 3H, -OCH_3), 3.843 (s, 3H, -OCH_3), 6.58 (s, 1H, aromatic), 6.59 (s, 1H, aromatic), 11.72 (bs, 1H, -CO_2H). Mass spectrum *m/e* (rel. %): 237 (13), 236 (100), 191 (9), 190 (22), 175 (21), 164 (26), 159 (15); exact mass calculated for $C_{13}H_{16}O_4$ 236.1049, found 236.1046.

Benzyloxycarbamate of (2S)-(-)-1-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene **151**

Dimethoxytetralincarboxylic acid **150** (76.5 mg, 0.33 mmol), diphenylphosphoryl azide (107 mg, 0.39 mmol) and triethylamine (39.4 mg, 0.39 mmol) were refluxed in dry benzene for 2 hours. Benzyl alcohol (105 mg, 0.97 mmol) was added and the mixture was refluxed a further 24 hours. The solvent was then evaporated and the residual yellow oil chromatographed on silica gel (20% ethyl acetate / hexanes) to give a colourless solid (88.5 mg, 80%). Mp 130-131.5°C, lit.[84] mp 122-123°C (racemic). $[\alpha]_D^{20}$-23.3° (c 0.56, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3437 (NH), 3060, 2940, 1720 (CO), 1512, 1249, 1214, 1136, 1114. ^1H nmr ($CDCl_3$) δ: 1.73-1.84 (m, 1H), 2.01-2.10 (m, 1H), 2.60 (dd, 1H, J = 16.0,

7.0), 2.68-2.90 (m, 1H), 3.05 (dd, 1H, J = 16.0, 4.80), 3.82 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$), 3.92-4.10 (bm, 1H), 4.80 (bd, 1H, J = 6.0), 5.10 (s, 2H), 6.52 (s, 1H, aromatic), 6.57 (s, 1H, aromatic), 7.32-7.36 (m, 5H, aromatics). Mass spectrum *m/e* (rel. %): 341 (7), 233 (11), 191 (14), 190 (100), 175 (11), 164 (22), 108 (13), 107 (11), 91 (37), 79 (17), 77 (15); exact mass calculated for $C_{20}H_{23}O_4N$ 341.1627, found 341.1589.

Hydrochloride of (2S-(-)-1-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene **152**

A mixture of carbamate **151** (69.5 mg, 0.20 mmol), 5% Pd/C (40 mg) in 10% anhydrous HCl in methanol (30 mL) was stirred under hydrogen (1 atm) at room temperature for 8 hours. The solution was filtered, and evaporated, giving a beige solid (48 mg, 97%) which could be recrystallized from methanol / ether. Mp 213-214°C, lit.[75] 212-214°C. $[\alpha]_D^{20}$ -65.1° (c 0.215, CH_3OH), lit.[75] $[\alpha]_D^{20}$ +73.2 for (R). ^1H nmr ($CDCl_3$) δ: 1.97-2.11 (m, 1H), 2.32-2.44 (m, 1H), 2.76-2.92 (m, 2H), 2.06 (dd, 1H, J = 15.4, 10.7), 3.25 (dd, 1H, J = 15.4, 4.38), 3.54-3.68 (m, 1H), 3.78 (s, 3H, $-OCH_3$), 3.82 (s, 3H, OCH_3), 6.54 (s, 1H, aromatic), 6.56 (s, 1H, aromatic), 8.6 (bs, 3H, $-NH_2 \cdot HCl$). Mass spectrum *m/e* (rel. %): 208 (7) 207 (52), 192 (8), 191 (11), 190 (88), 175 (25), 165 (19), 164 (100), 159 (15), 149 (25), 121 (22), 105 (13), 91 (12), 77 (19).

(2S)-(-)-1-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene **153**

The hydrochloride salt of **152** (see above) (32 mg, 0.13 mmol) was dissolved in dilute aqueous sodium hydroxide (0.1 M, 20 mL) and saturated aqueous sodium chloride (5 mL) was added. Extraction with dichloromethane, drying ($MgSO_4$) and evaporation gave a colourless oil (16.1 mg, 60%) which solidified on cooling. Mp 85-86°C. $[\alpha]_D^{20}$ -85.7° (c 0.105, CH_3OH), lit.[75] +86.5 for (R). IR (CH_2Cl_2) cm^{-1}: 3378 (NH), 3299 (weak, NH), 3050, 2929, 1611, 1517, 1467, 1250, 1216, 1116, 853. ^1H nmr ($CDCl_3$) δ: 1.58 (m, 1H), 1.66 (s, 2H, $-NH_2$), 1.94-2.03 (m, 1H), 2.50 (dd, 1H, J = 9.23, 15.75), 2.70-2.85 (m, 2H), 2.92 (dd, 1H, J = 4.68, 15.75), 3.12-3.21 (m, 1H), 3.84 (s, 6H, $-OCH_3$), 6.55 (s, 1H,

aromatic), 6.58 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 208 (6) 207 (51), 192 (8), 191 (10), 190 (85), 175 (34), 165 (18), 164 (100), 159 (14), 149 (20), 91 (12), 77 (14); exact mass calculated for $C_{12}H_{17}O_2N$ 207.1259, found 207.1259.

Mosher's acid chloride

This compound was prepard according to the literature procedure[87]. (S)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (Aldrich, 0.471 g, 2.01 mmol) with sodium chloride (100 mg) in thionyl chloride (30 mL) was refluxed for 50 hours. The excess thionyl chloride was removed at reduced pressure. The reaction mixture was dissolved in carbon tetrachloride (50 mL) and the sodium chloride was removed by filtration. The organic solution was concentrated in vacuo to give a colourless oil (0.5020 g, 99%). ^{1}H nmr ($CDCl_3$) δ: 3.75 (q, 3H, J= 1.91, -OCH_3), 7.43-7.55 (m, 5H, aromatics).

Mosher's acid amide of (2S)-(-)-1-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene **154**

The S-(-)-amide was prepared from the crude amine **153** using the literature method[75]: Crude (S)-(-)-2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (14 mg, 0.068 mmol) in carbon tetrachloride (2 mL) was stirred continously at room temperature under nitrogen. Dry pyridine (0.30 mL) and Mosher's acid chloride (23.9 mg, 0.095 mmol, in carbon tetrachloride (1.0 mL)) were introduced sucessively. The mixture was stirred for 15 hours and dichloromethane (20 mL) was added. The mixture was washed sucessively with 10% HCl (2 x 10 mL), 5% sodium bicarbonate (10 mL) and saturated sodium chloride solution (10 mL). The organic phase was dried ($MgSO_4$) and evaporation of solvent gave the amide as a colourless oil (21.5 mg, 75%). ^{1}H nmr (C_6H_6) δ: 1.30-1.42 (m, 1H), 1.62-1.74 (m, 1H), 2.29 (dd, 1H, J = 15.8, 8.49), 2.37-2.56 (m, 2H), 2.81 (dd, 1H, J = 15.8, 5.05), 3.13 (m, 3H), 3.41 (s, 3H), 3.44 (s, 3H), 4.24-4.34 (m, 1H), 6.29 (s, 1H), 6.32 (s, 1H), 6.42 (d, 1 H, J = 7.72), 7.02-7.12 (m, 3H), 7.74 (d, 2H, J = 7.75). The amide

from the racemic amine exhibited the signals above as well as the signals for the other diastereomer. The two sets of signals were well resolved only in the aromatic region where the other diastereomer showed signals at δ 6.24 and 6.35.

Mosher's acid amide of (±)-2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene

This compound was prepared using the procedure for optically pure amide **154** and has the following nmr. ^{1}H nmr (C_6H_6) δ: 1.10-1.50 (m, 2H), 1.55-1.80 (m, 1H), 2.19 (dd, 1H, J= 8.50, 15.70), 2.29 (dd, 1H, J = 15.8, 8.49), 2.32-2.58 (m, 2H), 2.72 (dd, 1H, J= 4.75, 15.92), 2.81 (dd, 1H, J = 4.99, 15.78), 3.11-3.13 (m, 6H), 3.405 (s, 3H), 3.411 (s, 3H), 3.421 (s, 3H), 3.438 (s, 3H,), 4.22-4.38 (m, 1H), 6.24 (s, 1H), 6.29 (s, 1H), 6.32 (s, 1H), 6.35 (s, 1H,), 6.42 (d, 1 H, J = 7.72), 6.45 (d, 1H, J= 8.10), 7.02-7.2 (m, 3H), 7.74 (t, 2H, J = 7.25).

6,7-Dimethoxy-3,4-dihydronaphthalene-2-carboxylate of (S)-methyl lactate **149**

Cycloadduct **146** (92.5 mg, 0.274 mmol) with *p*-toluenesulfonic acid (1 mg) in benzene (20 mL) was refluxed for 30 minutes. Most of the solvent was evaporated and the residue was filtered through a short silica gel column (50% ethyl acetate / hexanes). The solvent was evaporated to give a colourless oil (82 mg, 94%). $[\alpha]_D^{20}$ +33.5° (c 0.65, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3022, 2958, 1754 (CO), 1703 (CO), 1570, 1519, 1217, 1127, 1103. ^{1}H nmr ($CDCl_3$) δ: 1.57 (d, 3H, J = 7.05, Me), 2.56-2.64 (m, 2H), 2.78-2.86 (m, 2H), 3.77 (s, 3H, -CO_2Me), 3.87 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 5.21 (q, 1H, J = 7.05), 6.71 (s, 1H, aromatic), 6.77 (s, 1H, aromatic), 7.56 (s, H_1). Mass spectrum *m/e* (rel. %): 321 (5), 320 (32), 218 (3), 217 (21), 189 (19), 188 (21), 149 (23), 88 (22), 86 (88), 84 (100); exact mass calculated for $C_{17}H_{20}O_6$ 320.1260, found 320.1275.

The (S)-methyl lactate of (±)-6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid

Alkene **149** (145 mg, 0.453 mmol) with 5% Pd/C (50 mg) in methanol (30 mL) was stirred under hydrogen (1 atm) at room temperature for 15 hours. The mixture was filtered and evaporation of solvent gave a colourless oil. The ^{1}H nmr of the oil in benzene-D_6 showed that it is a mixture of two diastereomers (approximately 50:50). ^{1}H nmr (C_6D_6) δ: 1.27 (d, J= 7.08), 1.29 (d, J = 7.05, Me), 1.78-2.00 (m), 2.06-2.15 (m), 2.16-2.26 (m), 2.24-2.74 (m), 2.80-3.11 (m, 2H), 3.29 (s, -CO_2Me), 3.31 (s, -CO_2Me), 3.43 (s, -OCH_3), 3.44 (s, -OCH_3), 3.45 (s, -OCH_3), 3.46 (s, -OCH_3), 5.13 (q, J = 7.05), 6.358 (s, aromatic), 6.369 (s, aromatic), 6.374 (s, aromatic), 6.394 (s, aromatic).

Racemic 6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid

The compound was prepared in a manner identical to that used for the preparation of **150**, starting from the corresponding diastereomeric mixture. The resulting racemic acid had a ^{1}H nmr identical to **150**.

(R)-(-)-methyl mandelate

(R)-mandelic acid (Aldrich, 2.376 g, 15.6 mmol) and concentrated sulfuric acid (1.0 mL) in methanol (50 mL) were refluxed for 3 hours. Most of the methanol was evaporated and the residue was dissolved in dichloromethane (50 mL). The mixture was washed with 5% sodium bicarbonate (3 x 30 mL) and then water until neutral. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a colourless oil which solidified to a colourless solid on cooling (2.3845 g, 92%). Mp 54-55°C. $[\alpha]_D^{20}$ -140.5° (c 0.39, CH_3OH). IR (CH_2Cl_2) cm^{-1}: 3540 (OH), 3050, 2929, 1725 (CO), 1480, 1360, 1190, 1290, 1140. ^{1}H nmr ($CDCl_3$) δ: 3.53 (d, 1H, J = 5.58), 3.76 (s, 3H, -CO_2Me), 5.18 (d, 1H, J= 5.25), 7.34-7.41 (m, 5H, aromatics). Mass spectrum *m/e* (rel. %): 167 (1) 166 (7), 107 (100), 79 (47), 77 (29).

Acrylate of (R)-methyl mandelate **155**

This compound was synthesised using the procedure for preparing the acrylate of (S)-methyl lactate, starting with the following reagents: (R)-methyl mandelate (2.01 g, 12.1 mmol), acryloyl chloride (3.0 mL, 36.3 mmol) and molecular sieves (3Å, 8 g). The product was a colourless oil (1.841 g, 69%). $[\alpha]_D^{20}$ -140.0° (c 0.60, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3067, 2958, 1758 (CO), 1732 (CO), 1407, 1173. ^1H nmr ($CDCl_3$) δ: 3.73 (s, 3H, $-CO_2Me$), 5.92 (dd, 1H, J= 1.38, 10.41), 6.01 (s, 1H), 6.24 (dd, 1H, J= 10.41, 17.23), 6.53 (dd, 1H, J= 1.34, J = 17.34), 7.37-7.49 (m, 5H, aromatics). Mass spectrum *m/e* (rel. %): 221 (2), 220 (14), 189 (8), 188 (68), 166 (4), 165 (34), 162 (11), 161 (100), 106 (12) 105 (85), 90 (17), 77 (55); exact mass calculated for $C_{12}H_{12}O_4$ 220.0736, found 220.0724.

(1S, 2R)-(-)-*1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxy late of (R)-methyl mandelate* **156**

2-Methylbenzaldehyde (159 mg, 1.33 mmol), the acrylate of (R)-methyl mandelate **155** (437 mg, 1.99 mmol) and hydroquinone (2 mg) were irradiated in benzene solution (30 mL) for 20 hours using a 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter). Evaporation and chromatography (silica gel, ethyl acetate / hexanes) gave the adduct as a pale yellow oil (234 mg, 51%). $[\alpha]_D^{20}$-51.9° (c 0.45, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3598 (OH), 3498 (OH), 3065, 2957, 1741 (CO), 1495, 1456, 1438, 1217, 1152, 1038, 789. ^1H nmr ($CDCl_3$) δ: 1.96-2.22 (m, 2H), 2.76-3.00 (m, 3H), 3.75 (s, 3H, $-CO_2Me$), 3.84 (d, 1H, J = 4.0), 5.20 (d, H-1, J = 3.21, 9.25), 6.07 (s, 1H), 7.07 (d, 1H, J = 7.2), 7.15-7.28 (m, 2H), 7.3-7.52 (m, 5H), 7.67 (d, 1H, J = 7.32). Mass spectrum *m/e* (rel. %): 340 (0.1), 191 (38), 174 (12), 173 (68), 158 (7), 157 (60), 151 (8), 150 (85), 146 (20) 145 (27), 130 (23), 129 (100), 104 (58), 91 (56), 77 (40). Analysis calculated for $C_{20}H_{20}O_5$: C 70.58, H 5.92, found C 70.24, H 5.93.

(R)-(+)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **157**

The cycloadduct **156** (11.3 mg, 0.33 mmol) with 5% Pd/C (100 mg) in acetic acid (15 mL) were stirred under 1 atm of hydrogen at room temperature for 6 hours. The mixture was filtered and most of the acetic acid was removed at reduced pressure. The residue was dissolved in dichloromethane (40 mL) and extracted with 5% sodium bicarbonate (2 x 20 mL). The bicarbonate extract was acidified with aqueous 10% HCl and then extracted with dichloromethane (3 x 20 mL). The dichloromethane layer was dried ($MgSO_4$) and concentrated in vacuo to give a colourless oil which crystallized on cooling (40.9 mg, 70%). Mp 97-99°C. $[\alpha]_D^{20}$+53.3° (c 0.0975, $CHCl_3$), lit.[81] $[\alpha]_D^{20}$ +55.5. IR , ^1H nmr and mass spectrum of this compound were identical to that of its optical antipode **138**. Exact mass calculated for $C_{11}H_{12}O_2$ 176.0837, found 176.0830.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (R)-methyl mandelate

Benzocyclobuten-1-ol **17** (19.5 mg, 0.163 mmol), acrylate of (R)-methyl mandelate (71.5 mg, 0.325 mmol) and hydroquinone (2 mg) in toluene (5.0 mL) were refluxed for 5 hours. The solvent was evaporated and the residual oil was chromatographed (silica gel, ethyl acetate / hexanes) to give a pale yellow oil (31 mg, 56%). $[\alpha]_D^{20}$-46.7° (c 2.37, $CHCl_3$). The major isomer has a ^1H nmr identical to compound **156**.

Fumarate of (R)-methyl mandelate **158**

Fumaryl chloride (0.674 g, 4.41 mmol) with (R)-methyl mandelate (1.464 g, 8.82 mmol) in a 25-mL round bottom flask were stirred at 110°C for 15 hours. The crude oil was chromatographed (silica gel, 15% ethyl acetate / hexanes) to give a colourless oil (1.5155 g, 83%). Mp 82-84°C. $[\alpha]_D^{20}$ -99.8° (c 1.10, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3059, 2988, 1759 (CO), 1734 (CO), 1272, 1138. ^1H nmr ($CDCl_3$) δ: 3.74 (s, 6H, $-CO_2Me$), 6.04 (s, 2H), 7.06 (s, 2H), 7.39-7.48 (m, 10H, aromatics). Mass spectrum *m/e* (rel. %): 380 (1),

255 (6), 248 (9), 150 (24), 149 (100), 121 (32), 107 (24), 105 (17), 82 (16) 79 (12), 77 (16). Analysis calculated for $C_{22}H_{20}O_8$: C 64.39, H 5.29, found C 64.08, H 4.89.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (R)-methyl mandelate **159**

2-Methylbenzaldehyde (13.5 mg, 0.113 mmol) and the fumarate of (R)-methyl mandelate **158** (46.5 mg, 0.113 mmol) were irradiated in benzene solution (20 mL) for 6 hours using a 450 watt Hanovia medium pressure mercury lamp (1 mm Pyrex filter). Evaporation of solvent and chromatography (silica gel, ethyl acetate / hexanes) gave the adduct as a colourless oil (31 mg, 52%). The adduct could be recrystallized from ethyl acetate / Hexanes to give colourless needles. Mp 124-126°C. $[\alpha]_D^{20}$-43.4° (c 0.21, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3493 (OH), 3056, 2959, 1744 (CO), 1227, 1175, 1156, 1119. ^1H nmr ($CDCl_3$) δ: 3.12 (dd, 1H, J = 17.80, 13.40), 3.22 (dd, 1H, J = 9.60, 10.96), 3.30-3.43 (m, 2H), 3.68 (s, 3H, $-CO_2Me$), 3.75 (s, 3H, $-CO_2Me$), 5.03 (d, 1H, J = 9.56, H-1), 5.91 (s, 1H), 6.11 (s, 1H), 7.14 (d, 1H, J= 7.13), 7.12-7.50 (m, 12H), 7.74 (d, 1H, J= 7.38). Mass spectrum *m/e* (rel. %): 166 (8), 159 (28), 129(17), 128 (12), 107 (100), 79 (57), 77 (42). Analysis Calculated for $C_{30}H_{28}O_9$: C 67.66, H 5.30, found C 68.07, H 5.18.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (R)-methyl mandelate **159**

Benzocyclobuten-1-ol **17** (134 mg, 1.12 mmol) and the fumarate of (R)-methyl mandelate **158** (461 mg, 1.12 mmol) in toluene (5 mL) were refluxed for 6 hours. Evaporation of solvent and chromatography of the crude oil (silica gel, ethyl acetate / hexanes) gave the adduct as a colourless oil (573.5 mg, 96%). Spectral properties were identical to those given earlier.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (R)-methyl mandelate **159**

The hydroxy sulfone **5** (29.6 mg, 0.161 mmol) in dichloromethane (2.0 mL) was added dropwise (over a period of half hour) to a refluxing toluene solution (5.0 mL) of the fumarate of (R)-methyl mandelate (73 mg, 0.177 mmol). The solution was refluxed for another 2 hours. Evaporation of solvent and chromatography of the crude oil (silica gel, ethyl acetate / hexanes) gave the adduct as a colourless oil (47.5 mg, 55%). Spectral properties were identical to those given earlier.

Lactone **160**

The cycloadduct **159** (115 mg) and *p*-toluenesulfonic acid (10 mg) in dichloromethane (15 mL) were refluxed for 15 hours. Evaporation of the solvent and chromatography of the crude oil (silica gel, ethyl acetate / hexanes) gave a colourless oil (56 mg, 71%). The oil solidified and could be recrystallized from ethyl acetate / hexanes. Mp 86-88°C. $[\alpha]_D^{20}$-60.9° (c 0.35 $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3066, 3031, 2959, 1788 (lactone CO), 1750 (CO), 1438, 1218, 1142. ^1H NMR ($CDCl_3$) δ: 3.05 (d, 1H, J = 16.83), 3.37 (m, 1H), 3.42 (dd, 1H, J = 17.13, 5.18), 3.51 (s, 3H, -CO_2Me), 3.90 (t, 1H, J = 5.0), 5.50 (d, 1H, J = 5.11, H-1), 5.74 (s, 1H), 7.10-7.50 (m, 9H, aromatics). Mass spectrum *m/e* (rel. %): 201 (5), 173 (10), 155(5), 151 (10), 150 (100), 145 (16), 130 (8), 129 (68), 121 (24), 91 (12), 77 (13). Analysis caculated for $C_{21}H_{18}O_6$: C 68.85, H 4.95, found C 68.62, H 5.19.

(S)-(-)-Dimethyl-3,4-Dihydronaphthalene-2,3-dicarboxylate **162**

Lactone **160** (87.0 mg, 0.238 mmol) in potassium hydroxide (10 ml, 0.2 M in 1:1 water / methanol) was refluxed for 2 hours. The methanol was evaporated and the residue was dissolved in ethyl acetate (50 mL). The solution was extracted with 5% sodium bicarbonate (3 x 20 mL). The bicarbonate extract was acidified (10% HCl), extracted with

ethyl acetate (4 x 20 mL), dried ($MgSO_4$) and evaporated to give the diacid **161** as white solid (72 mg). Diazomethane in ether was added dropwise to the diacid until the yellow colour persisted. Evaporation of solvent follow by chromatography of the crude oil gave the product as a colourless oil (31.0 mg, 53%). $[\alpha]_D^{20}$ -128.3° (c 0.385, $CHCl_3$), lit.[25] $[\alpha]_D^{20}$ -128.3°. IR (CH_2Cl_2) cm^{-1}: 3058, 2957, 1735 (CO), 1711 (CO), 1637, 1455, 1438, 1255, 1211, 1117. ^1H nmr ($CDCl_3$) δ: 3.13 (dd, 1H, J = 8.02, 16.23, H-3), 3.35 (dd, 1H, J= 3.44, 16.26, H-4), 3.60 (s, 3H, $-CO_2Me$), 3.84 (s, 3H, $-CO_2Me$), 3.87 (dd, 1H, J = 3.43, 8.03, H-4), 7.17-7.32 (m, 4H, aromatics), 7.65 (s, $1H_1$). Mass spectrum *m/e* (rel. %): 247 (1.3), 246 (7.6), 215(2), 214 (7), 188 (9), 187 (79), 163 (15), 156 (5), 155 (44), 144 (5), 143 (41), 129 (10), 128 (100), 77 (10); exact mass calculated for $C_{14}H_{14}O_4$ 246.0892, found 246.0883.

Compounds **166-171** were prepared by a modified literature procedure[90].

Alcohol **166**

Dry THF (15 mL) in a flame dried 100-mL flask was cooled to -78°C under nitrogen. *n*-Butyllithium (5.0 mL, 2.03 M in hexane) was added. Bromoacetal **164** (2.517 g, 9.22 mmol) in dry THF (5 mL) was added over a period of two minutes. 3,4,5-Trimethoxybenzaldehyde (1.90 g, 9.68 mmol) in dry THF (5 mL) was added over a period of two minutes and the mixture was stirred at -78°C for an hour. The reaction flask was then removed from the cold bath and allowed to warm slowly to room temperature. Aqueous ammonium chloride solution (10%, 50 mL) was added and the mixture was stirred 10 minutes. The organic phase was separated and the aqueous phase was extracted with dichloromethane (4 x 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil (4.5515 g). Chromatography of the crude oil (40% ethyl acetate / hexanes) gave a pale yellow oil (3.411 g, 95%). IR (CH_2Cl_2) cm^{-1}: 3594 (OH), 3499 (OH), 3062, 2897, 1594, 1506, 1486, 1465, 1419, 1249, 1129,

1098, 1041. ^{1}H nmr ($CDCl_3$) δ: 3.32 (d, 1H, J= 3.51, OH), 3.82 (s, 6H, -OCH_3), 3.84 (s, 3H, -OCH_3), 4.00-4.20 (m, 4H), 5.93 (s, 2H), 5.99 (s, 1H), 6.09 (d, 1H, J= 3.41), 6.64 (s, 2H,aromatic), 6.65 (s, 1H, aromatic), 7.07 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 391 (6), 390 (29), 372 (6), 345 (10), 344 (12), 329 (34), 328 (100), 314 (13), 313 (47) 297 (18), 178 (11), 177 (95), 149 (21); exact mass calculated for $C_{20}H_{22}O_8$ 390.1315, found 390.1326. The spectral properties were identical to those reported in the literature[90].

5,6-Methylenedioxy-3-(3,4,5-trimethoxyphenyl)phthalide **168**

The alcohol **166** (3.380 g, 8.658 mmol) in ethyl acetate (40 mL) and concentrated sulfuric acid / water (1:99 by volume, 20 mL) were stirred vigorously for 2 hours. TLC showed complete disappearance of the starting material and formation of white precipitate was observed. Additional ethyl acetate was added to dissolved the precipitate. The solution was cooled in an ice-water bath and chromium trioxide (0.5M in 10% sulfuric acid, 17.32 mmol, 34 mL) was added dropwise and vigorous stirring continued until the reaction was completed (followed by TLC, 6 hours). The organic layer was separated and the aqueous phase was extracted with dichloromethane(6 x 30 mL). The combined organics was washed with 5% sodium bicarbonate (50 mL), dried ($MgSO_4$) and evaporated to give a pale yellow solid (2.10 g, 70%) which was >95% pure by ^{1}H nmr (300 MHz). A small sample was recrystallized (dichloromethane / hexanes) to give crystals with mp 220-222°C, lit.[90] mp 217-223°C. IR (CH_2Cl_2) cm^{-1}: 3063, 2945, 1759 (CO), 1597, 1506, 1476, 1466, 1315, 1132. ^{1}H nmr ($CDCl_3$) δ: 3.83 (s, 6H, -OCH_3), 3.84 (s, 3H, -OCH_3), 6.11 (s, 1H), 6.12 (S, 1H), 6.16 (s, 1H), 6.45 (s, 2H, aromatics), 6.68 (s, 1H, aromatic), 7.25 (s, 1H,aromatic). Mass spectrum *m/e* (rel. %): 344 (4), 168 (5), 107 (16), 91 (16), 84 (100), 70 (16), 69 (18); exact mass calculated for $C_{18}H_{16}O_7$ 344.08961, found 344.08963. The spectral properties were identical to those reported in the literature[90].

6-(3,4,5-trimethoxybenzyl)piperonylic acid **169**

The phthalide **168** (2.2050 g, 6.4043 mmol) and 5% Pd/C (800 mg) in acetic acid (100 mL) were stirred under hydrogen (1 atm) at 100°C for 48 hours. TLC showed that some lactone remain unreacted. Fresh 5% Pd/C (400 mg) was added and the mixture was stirred for an additional 48 hours. The mixture was filtered and evaporation of solvent gave the a colourless solid (2.074 g, 94%). The solid could be recrystallized from dichloromethane / hexanes to give colourless crystals. Mp 164-166°C, lit.[90] mp 165-168°C. IR (CH_2Cl_2) cm^{-1}: 3400-2800 (broad, $-CO_2H$), 3063, 1690 (CO), 1592, 1507, 1488, 1465, 1423, 1242, 1128, 1041. ^1H nmr ($CDCl_3$) δ: 3.80 (s, 6H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 4.33 (s, 2H), 6.02 (s, 2H), 6.41 (S, 2H), 6.45 (s, 1H), 7.53 (s, 1H), 11.85 (bs, 1H,$-CO_2H$). Mass spectrum *m/e* (rel. %): 347 (20), 346 (100), 328 (10), 313 (20), 297 (27), 270 (14), 178 (10), 177 (59), 163 (26), 149 (22), 84 (35), 69 (33); exact mass calculated for $C_{18}H_{18}O_7$ 346.1053, found 346.1047. The spectral properties were identical to those reported in the literature[90].

6-(3,4,5-trimethoxybenzyl)piperonol **170**

Carboxylic acid **169** (2.074 g, 5.99 mmol) in dry THF (50 mL) was added dropwise to a cooled (ice-water bath) suspension of lithium aluminium hydride (12 mmol, 0.46 g) in dry THF (30 mL). The mixture was stirred at room temperature for 18 hours. Water (0.46 mL), aqueous 15% sodium hydroxide (0.46 mL) and water (1.29 mL) were added successively and the mixture was stirred for half an hour. The mixture was filtered and the solution was dried ($MgSO_4$). Evaporation of solvent gave a colourless oil which solidified (1.72 g, 87%). The solid could be recrystallized from dichloromethane / hexanes to give colourless crystals. Mp 90-92°C, lit.[90] mp 89-90°C. IR (CH_2Cl_2) cm^{-1}: 3606 (OH), 3056, 2942, 1591, 1505, 1487, 1465, 1422, 1237, 1130, 1042. ^1H nmr ($CDCl_3$) δ: 1.60 (bs, 1H, OH), 3.79 (s, 6H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 3.92 (s, 2H), 4.58 (s, 2H), 5.94 (s, 2H), 6.35 (s, 2H), 6.64 (s, 1H), 6.90 (s, 1H). Mass spectrum *m/e* (rel. %): 333 (8),

332 (39), 316 (11), 284 (11), 283 (50), 253 (6), 252 (13), 170 (10), 169 (100), 164 (34), 163 (28), 152 (14), 139 (16), 129 (18), 69 (40), 57 (52); exact mass calculated for $C_{18}H_{20}O_6$ 332.1260, found 332.1258.

6-(3,4,5-trimethoxybenzyl)piperonal **171**

The alcohol **170** (99.5 mg, 0.30 mmol) in ether (15 mL) was cooled in an ice-water bath with stirring. Chromium trioxide (0.5M in 10% sulfuric acid, 0.60 mmol, 1.25 mL) was added dropwise and the mixture was stirred vigorously for half an hour. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined ether extracts were washed with 5% sodium bicarbonate (3 x 20 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid. Chromatography (silica gel, 25% ethyl acetate / hexanes) gave a white solid (84 mg, 85%). Mp 112-114°C, lit.[90] mp 124-125°C. IR (CH_2Cl_2) cm^{-1}: 3067, 2955, 1691 (CO), 1665, 1601, 1568, 1514, 1492, 1380, 1134, 1044. ^1H nmr ($CDCl_3$) δ: 3.79 (s, 6H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 4.29 (s, 2H), 6.05 (s, 2H), 6.34 (s, 2H), 6.69 (S, 1H), 7.35 (s, 1H), 10.16 (s, 1H). Mass spectrum *m/e* (rel. %): 331 (19), 330 (100), 329 (59), 313 (38), 312 (54), 300 (10), 299 (38), 298 (13), 282 (19), 269 (13), 268 (14); exact mass calculated for $C_{18}H_{18}O_6$ 330.1103, found 330.1090. The ^1H nmr was identical to that reported in the literature[7,29,58,90].

(S)-(+)-methyl mandelate

(S)-mandelic acid (Aldrich, 7.34 g, 48.2 mmol) and concentrated sulfuric acid (1.0 mL) in methanol (50 mL) were refluxed for 4 hours. Most of the methanol was evaporated and the residue was dissolved in dichloromethane (60 mL). The mixture was washed with 5% sodium bicarbonate (3 x 30 mL) and then water until neutral. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a colourless oil which solidified to a colourless solid on cooling (7.69 g, 96%). Mp 53-54°C. $[\alpha]_D^{20}$ +140.4° (c 0.39, CH_3OH). The ^1H nmr and IR were identical to those of (R)-methyl mandelate (see

above).

Fumarate of (S)-methyl mandelate **172**

Fumaryl chloride (1.353 g, 8.85 mmol) with (S)-methyl mandelate (2.937g, 17.7 mmol) in a 25-mL round bottom flask were stirred at 110°C for 15 hours. The crude oil was chromatographed (silica gel, 15% ethyl acetate / hexanes) to give a colourless oil which solidified (3.599 g, 98%). Mp 85-87°C. $[\alpha]_D^{20}$ +115.5° (c 1.10, $CHCl_3$). The ^1H nmr and IR were identical to those of the fumarate of (R)-methyl mandelate (see above).

Cycloadduct **173**

Aldehyde **171** (0.438 g, 1.33 mmol) in dry benzene (100 mL) was purged with nitrogen continuously. One third of a solution of fumarate **172** (1.64 g, 2.65 mmol, in benzene (90 mL), purged with nitrogen) was added and the mixture was irradiated at room temperature (450 Watt Hanovia medium pressure mercury lamp, 1 mm pyrex filter). The remaining fumarate solution was added dropwise over a period of 5 hours. The total irradiation time was 6 hours and 30 minutes. The solvent was evaporated and the crude product was chromatographed (30% ethyl acetate / hexanes) to the product as a colourless foam (399 mg, 45% based on reacted aldehyde) and unreacted aldehyde (46 mg). The ^1H nmr of the foam indicated the presence of two isomeric compounds. Careful rechromatography (20% ethyl acetate / hexanes) of the isomeric mixture gave a small sample of the pure major isomer as a colourless foam. Mp 97-99°C. $[\alpha]_D^{20}$-23.7° (c 0.228, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3488 (OH), 3056, 2960, 1746 (CO), 1593, 1504, 1484, 1333, 1235, 1129, 1040. ^1H NMR ($CDCl_3$) δ: 3.40 (dd, 1H, J = 9.39, 12.61), 3.56 (s, 3H), 3.60 (dd, 1H, J= 12.56, 6.10), 3.61 (s, 6H), 3.65 (s, 3H), 3.72 (d, 1H, J= 3.14, OH), 3.78 (s, 3H), 4.50 (d, 1H, J= 5.80, H-4), 4.94 (dd, 1H, J = 2.70, 9.32, H-1), 5.49 (s, 1H), 5.91 (s, 2H), 6.17 (s, 2H), 6.22 (s, 1H), 6.37 (s, 1H), 6.93-7.02 (m, 4H), 7.10-7.50 (m, 7H). Mass spectrum *m/e* (rel. %): 742 (3), 724 (2), 577 (10), 576 (26), 548 (7), 530 (10) 471 (4), 427

(4), 410 (30), 408 (32), 393 (16), 383 (19), 365 (43), 339 (32), 324 (17), 308 (20), 168 (18), 149 (42), 121 (39), 107 (100), 79 (97), 77 (76); exact mass calculated for $C_{40}H_{38}O_{14}$ 742.2262, found 742.2214. Analysis calculated for $C_{40}H_{38}O_{14}$ C 64.69, H 5.16, found C 65.04, H 5.29.

Lactone **174**

The cycloadduct **173** (isomeric mixture, 64 mg, 0.086 mmol) in dry THF (5 mL) was cooled to -78°C under nitrogen. Then *t*-butyllithium (0.068 ml, 1.26 M in pentane) was added dropwise and the mixture stirred for 5 minutes. The reaction flask was removed from the cold bath and stirred at room temperature for 15 minutes. Aqueous ammonium chloride solution (10%, 15 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Chromatography of the crude oil (silica gel, 40% ethyl acetate / hexanes) gave a colourless foam (27 mg, 54%). Mp 89-91°C. $[\alpha]_D^{20}$+5.27° (c 1.10, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3063, 2988, 1787 (lactone CO), 1750, 1592, 1507, 1486, 1250, 1129. ^1H NMR ($CDCl_3$) δ: 3.32 (dt, 1H, J = 0.87, 4.82, H-3), 3.60 (s, 3H), 3.75 (s, 6H), 3.61 (s, 6H), 3.84 (s, 3H), 3.95 (t, 1H, J= 5.08, H-2), 4.62 (d, 1H, J= 4.69, H-4), 5.43 (d, 1H, J= 4.90, H-1), 5.86 (s, 1H), 5.97 (s, 2H), 6.21 (s, 2H), 6.43 (s, 1H), 6.83 (s, 1H), 7.32-7.42 (m, 5H, aromatics). ^{13}C nmr (75.5 MHz, $CDCL_3$) δ: 44.45 (CH), 46.51 (CH), 49.72 (CH), 52.67 (CH_3), 56.20 (CH_3), 60.83 (CH_3), 75.04 (CH), 77.55 (CH), 101.38 (CH_2), 106.70 (CH), 108.22 (CH), 110.30 (CH), 127.56 (CH), 128.06 (C), 128.90 (CH), 129.61 (CH), 129.77 (C), 133.05 (C), 136.41 (C), 137.47 (C), 146.55 (C), 148.55 (C), 153.03 (C), 166.53 (C), 167.90 (C), 173.36 (C). Mass spectrum *m/e* (rel. %): 577 (12), 576 (33), 410 (23), 409 (11), 408 (41), 393 (16), 383 (21), 365 (33), 339 (36), 324 (17), 308 (23), 168 (14), 149 (22), 121 (20), 111 (20), 107 (100), 79 (55), 77 (48); exact mass calculated for $C_{31}H_{28}O_{11}$ 576.1632, found 576.1633.

Lactone-acid **175**

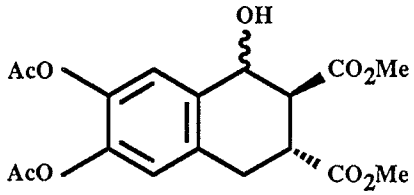
The lactone **174** (27 mg, 0.047 mmol) with 5% Pd/C (15 mg) in ethyl acetate (10 mL) were stirred under hydrogen (1 atm) at room temperature for 2 hours. The mixture was filtered and the solvent was evaporated. The residue was dissolved in dichloromethane (20 mL) and extracted with 5% sodium bicarbonate (3 x 10 mL). The combined bicarbonate extracts were acidified (10% HCl), saturated with sodium chloride and extracted with ethyl acetate (3 x 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colourless solid (17.5 mg, 87%). The solid could be recrystallized from dichloromethane / hexanes to give colourless crystals. Mp 209-211°C. $[\alpha]_D^{20}$ -26.74° (c 0.43, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3400-2800 (broad, $-CO_2H$), 1787 (lactone CO), 1734 (CO), 1592, 1505, 1485, 1464, 1423, 1250, 1130. ^1H nmr ($CDCl_3$) δ: 3.30 (t, 1H, J = 4.75, H-3), 3.78 (s, 6H, $-OCH_3$), 3.85 (s, 3H), 3.89 (t, 1H, J= 5.05, H-2), 4.76 (d, 1H, J= 4.77, H-4), 5.38 (d, 1H, J= 5.12, H-1), 5.95, 5.97 (ABq, 2H, J= 1.27, OCH_2O), 6.27 (s, 2H, aromatics), 6.46 (s, 1H, aromatic), 6.79 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 428 (5), 408 (2), 384 (13), 383 (5), 382 (15), 367 (8), 339 (24), 338 (47), 324 (12), 323 (30), 308 (8), 168 (11), 149 (13), 137 (11), 129 (10), 109 (11), 97 (16), 83 (23), 81 (51), 73 (29), 69 (100), 57 (47), 55 (48); exact mass calculated for $C_{22}H_{20}O_9$ 428.1107, found 428.1090.

(-)-Neopodophyllotoxin **177**

The lactone-acid **175** (23.5 mg, 0.055 mmol) in dry dichloromethane (3 mL, dried with 3Å molecular sieves) and oxalyl chloride (5 mL) were stirred at room temperature for 4 days. The excess oxalyl chloride was evaporated. Sodium borohydride (20 mg), dry THF (3 mL) and diglyme (1 mL) were added and the mixture was stirred for 2 hours. Water (20 mL) was added and stirred for half hour (until all the excess sodium borohydride was destroyed). The solution was saturated with sodium chloride and the

organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 x 10 mL) and the combined organic extracts were dried ($MgSO_4$). Evaporation of solvent and recrystallisation of the crude product (ethyl acetate / hexanes) gave white solid (20 mg, 88%). Mp 232-234°C. $[\alpha]_D^{20}$ -50.77° (c 0.26, $CHCl_3$), lit.[91] $[\alpha]_D^{20}$ -52.4°. IR (CH_2Cl_2) cm^{-1}: 3617 (OH), 3330 (OH), 3059, 2990, 1781 (lactone CO), 1592, 1507, 1485, 1463, 1425, 1331, 1247, 1130, 1041. ^1H NMR ($CDCl_3$) δ: 3.02 (t, 1H, J = 4.38, H-3), 3.16 (m, 1H, H-2), 3.66 (dd, 1H, J= 7.69, 10.82), 3.75 (1H, overlapped by -OMe singlet), 3.78 (s, 6H, -OMe), 3.85 (s, 3H, -OMe), 4.25 (d, 1H, J= 4.54, H-4), 5.19 (d, 1H, J= 4.75, H-1), 5.95, 5.97 (ABq, 2H, J= 1.30, OCH_2O), 6.28 (s, 2H, aromatics), 6.49 (s, 1H, aromatic), 6.74 (s, 1H, aromatic). Mass spectrum *m/e* (rel. %): 415 (11), 414 (54), 396 (19), 395 (9), 394 (36), 379 (17), 352 (10), 351 (13), 339 (19), 338 (13), 324 (10), 308 (11), 168 (24), 153 (16), 129 (15), 98 (32), 97 (25), 95 (26), 83 (37), 81 (49), 73 (36), 69 (100), 57 (70), 55 (77); exact mass calculated for $C_{22}H_{22}O_8$ 414.1315, found 414.1304. The ^1H nmr was identical to that reported in the literature[67a,91].

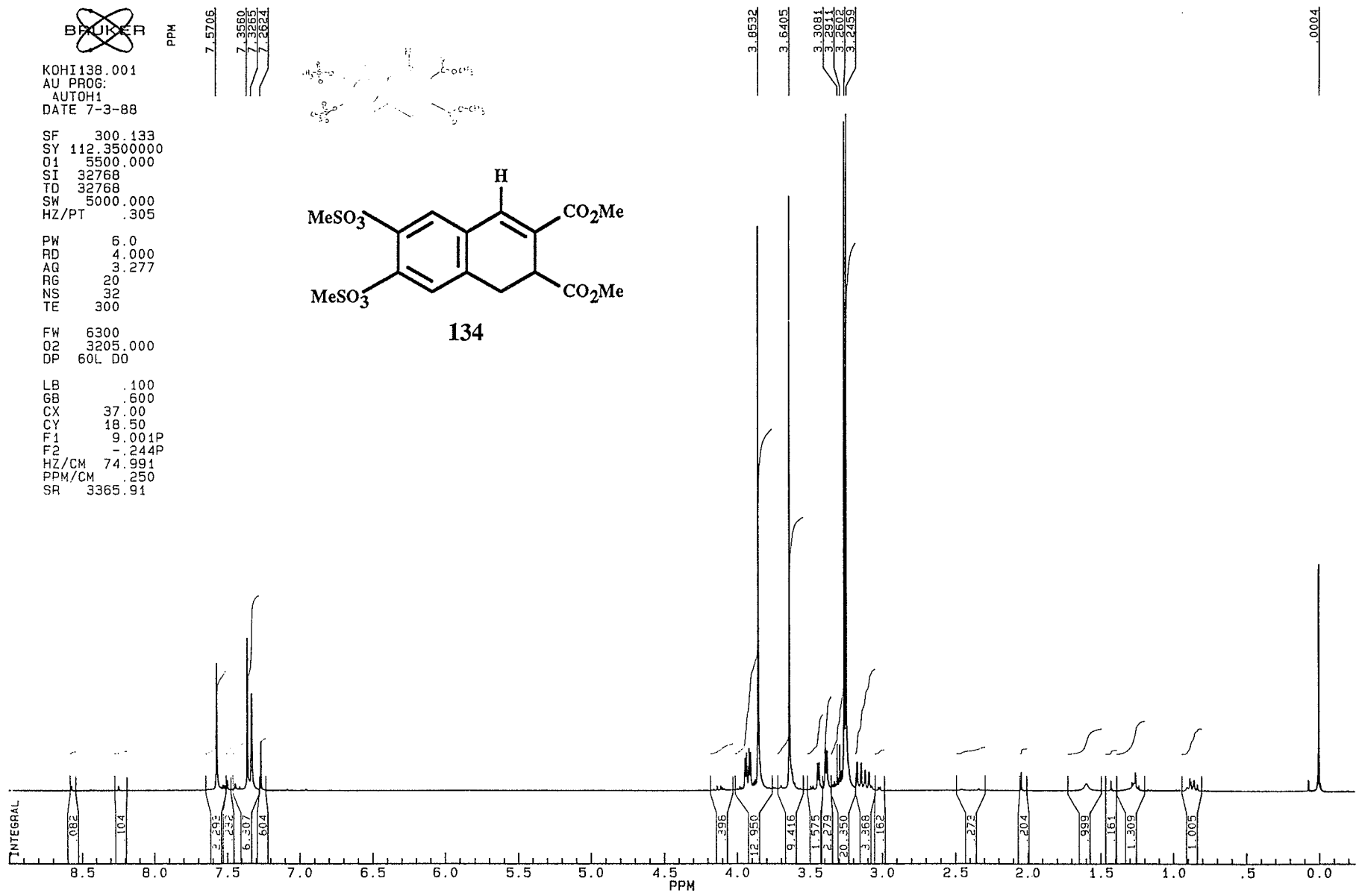
KOH-I-162 1-H AT 300 MHZ IN CDCL3

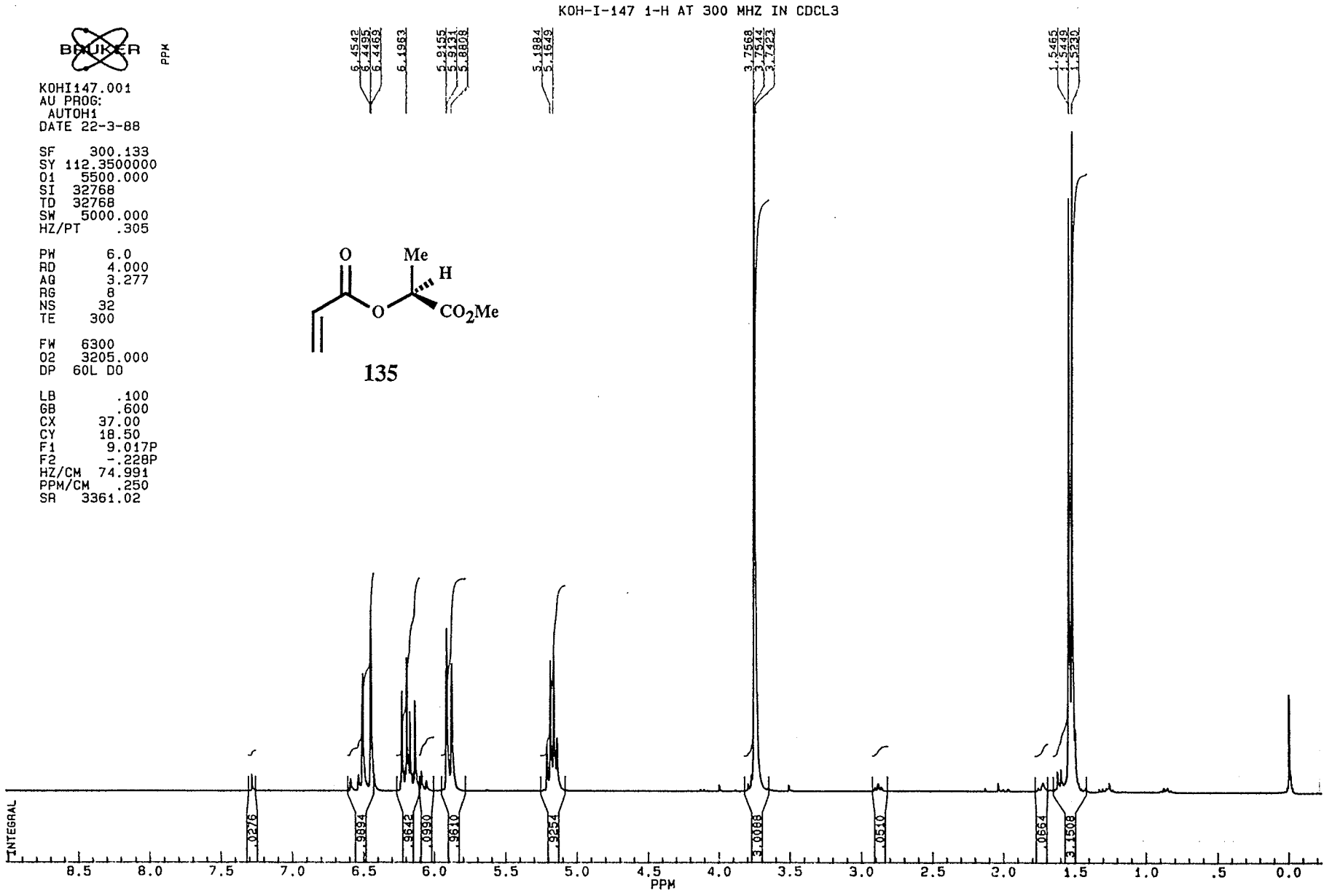


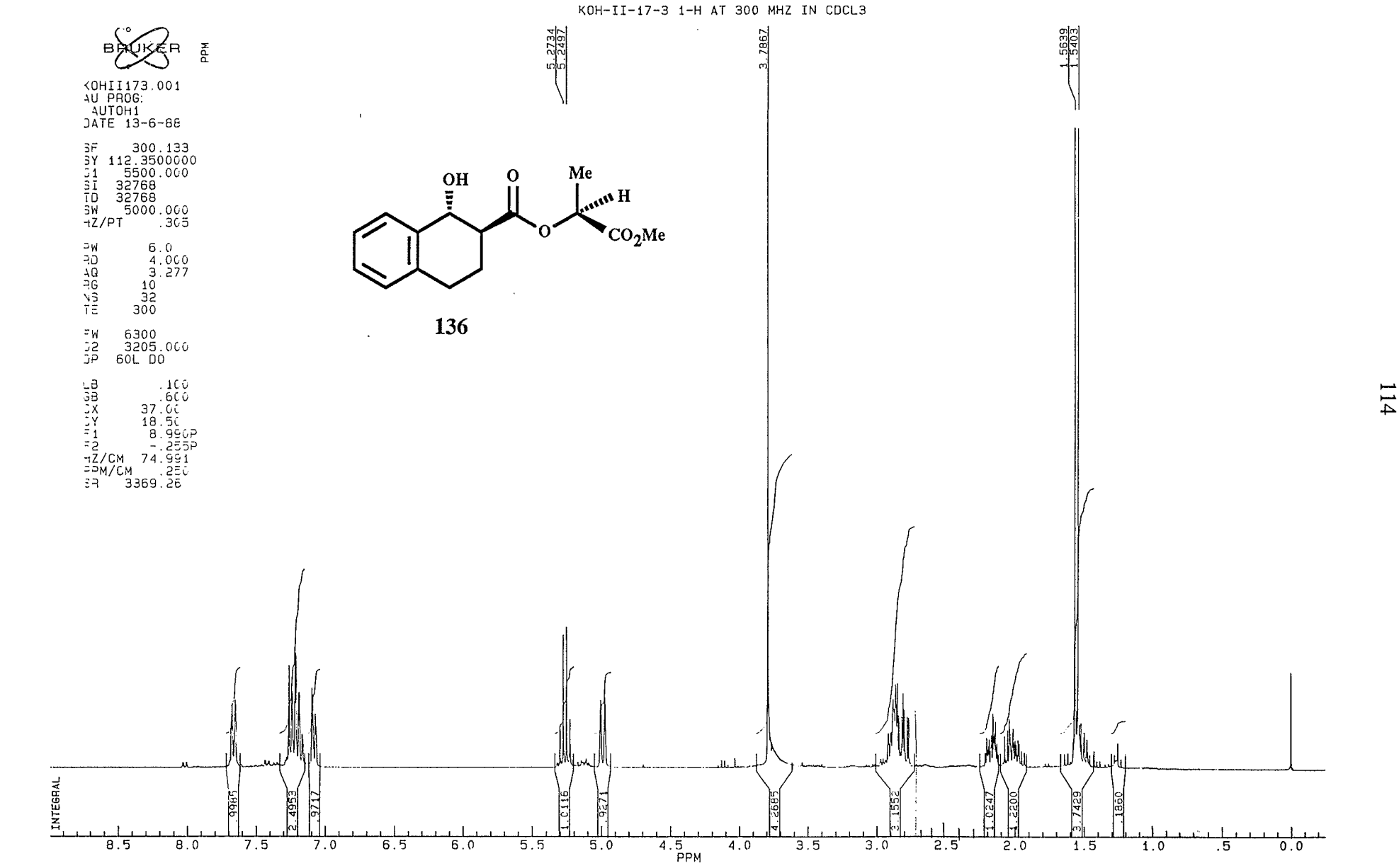
128

```
KOHI162.001
AU PROG:
 AUTOH1
DATE 10-5-88

SF    300.133
SY 112.3500000
O1   5500.000
SI   32768
TD   32768
SW   5000.000
HZ/PT    .305

PW       6.0
RD       4.000
AQ       3.277
RG        10
NS        32
TE       300

FW    6300
O2   3205.000
DP  60L DO

LB        .100
GB        .600
CX      37.00
CY      18.50
F1       9.003P
F2       -.242P
HZ/CM  74.991
PPM/CM    .250
SR   3365.30
```

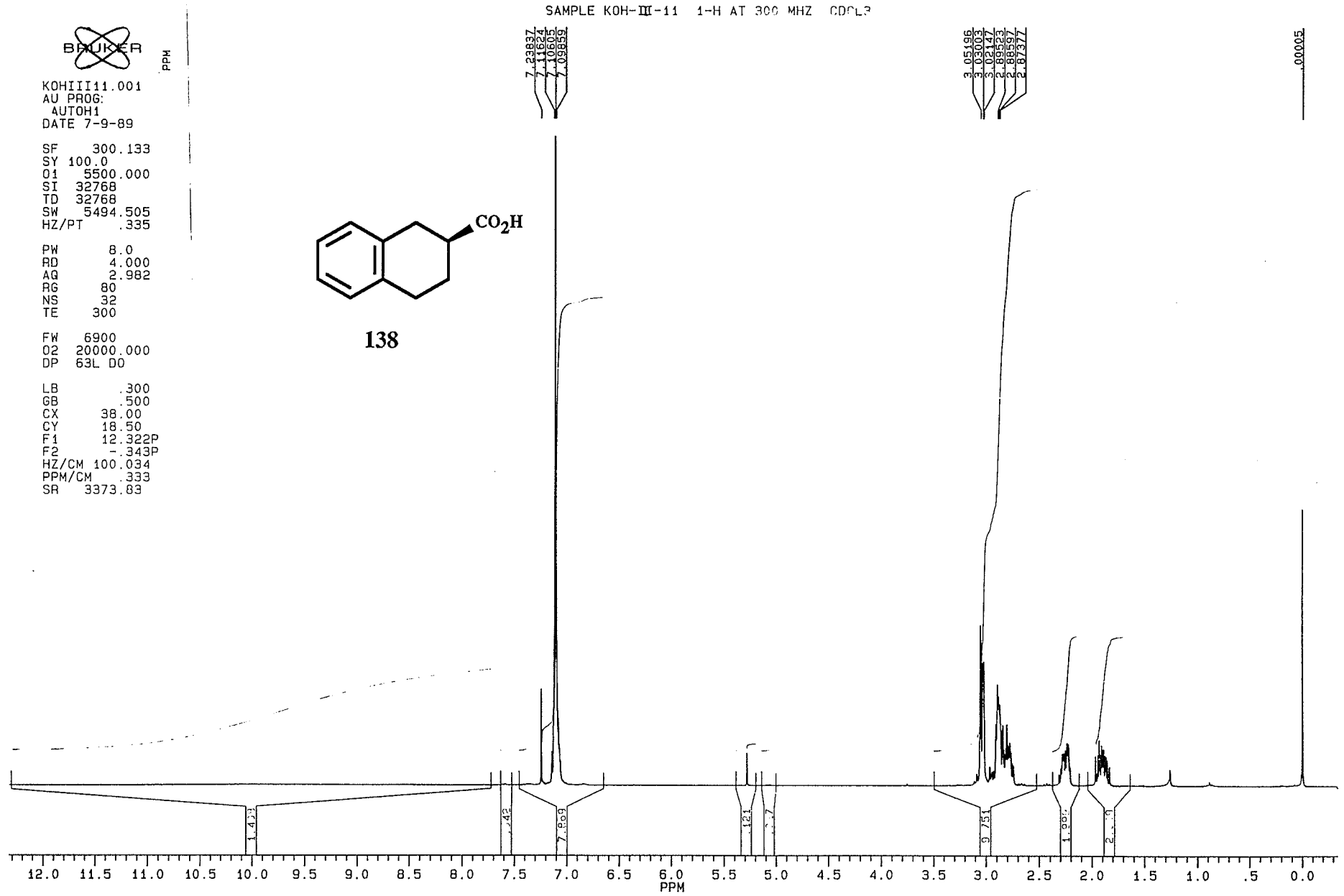
KOH-I-138 1-H AT 300 MHZ IN CDCL3

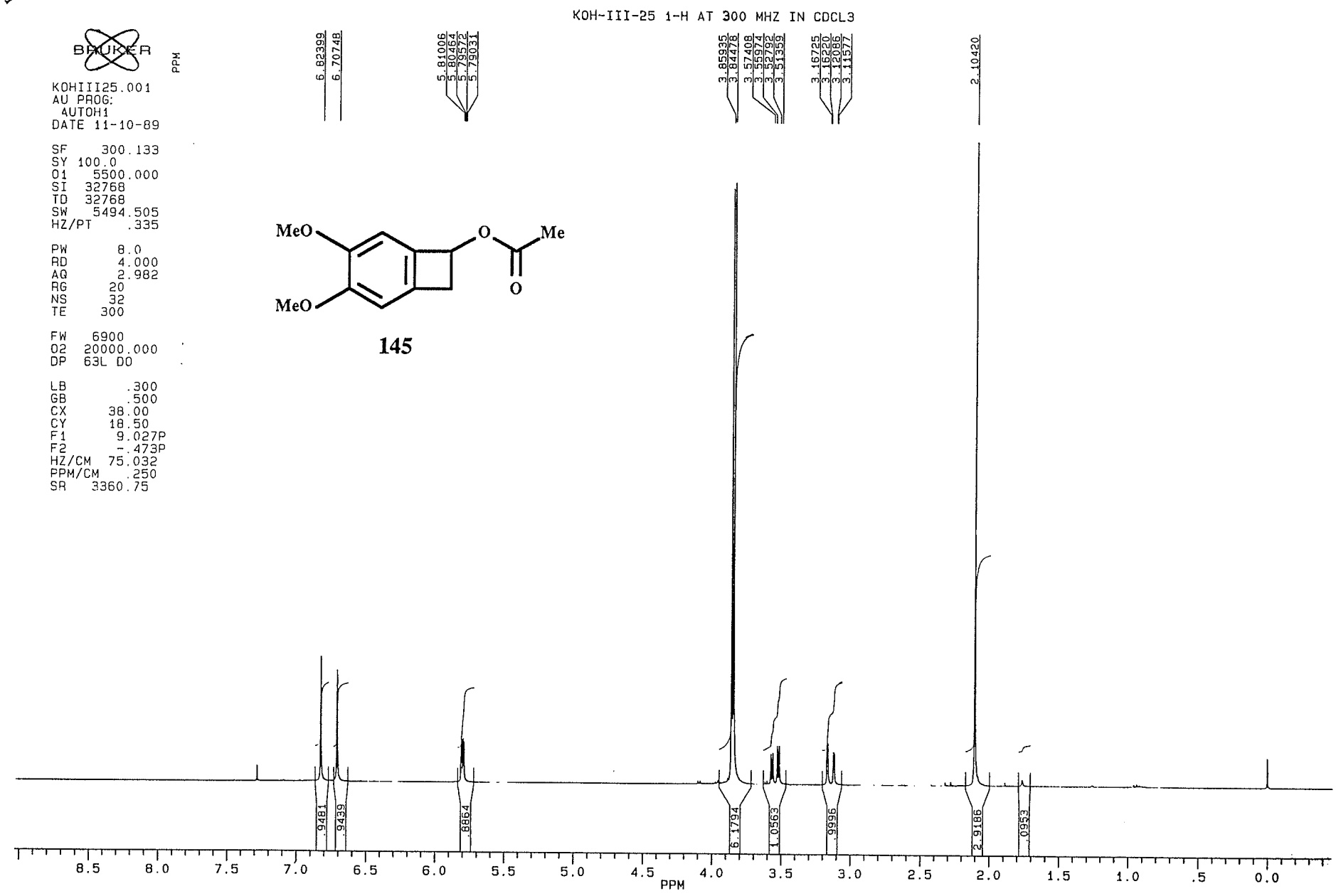



KOH-I-147 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
KOHI147.001
AU PROG:
AUTOH1
DATE 22-3-88
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 8
NS 32
TE 300
FW 6300
O2 3205.000
DP 60L D0
LB .100
GB .600
CX 37.00
CY 18.50
F1 9.017P
F2 -.228P
HZ/CM 74.991
PPM/CM .250
SR 3361.02
6.4542
6.4495
6.4469
6.1963
5.9155
5.8131
5.8809
5.1884
5.1649
3.7568
3.7244
3.7422
1.5465
1.5449
1.5230
O
Me
H
O
CO2Me
135
INTEGRAL
.0276
.9894
.9642
.0990
.9610
.9254
3.0068
.0510
.0564
3.1508
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


KOH-II-17-3 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
<OHII173.001
AU PROG:
AUTOH1
DATE 13-6-88
SF 300.133
SY 112.3500000
S1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 10
NS 32
TE 300
FW 6300
S2 3205.000
SP 60L DO
LB .100
GB .600
SX 37.00
SY 18.50
F1 8.9950P
F2 -.2555P
HZ/CM 74.991
PPM/CM .250
SR 3369.26
5.2734
5.2497
3.7867
1.5639
1.5403
OH
O
Me
H
O
CO2Me
INTEGRAL
9965
2.4953
.9717
1.0116
.9271
4.2685
3.1552
1.0247
1.2200
3.7429
.1860
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

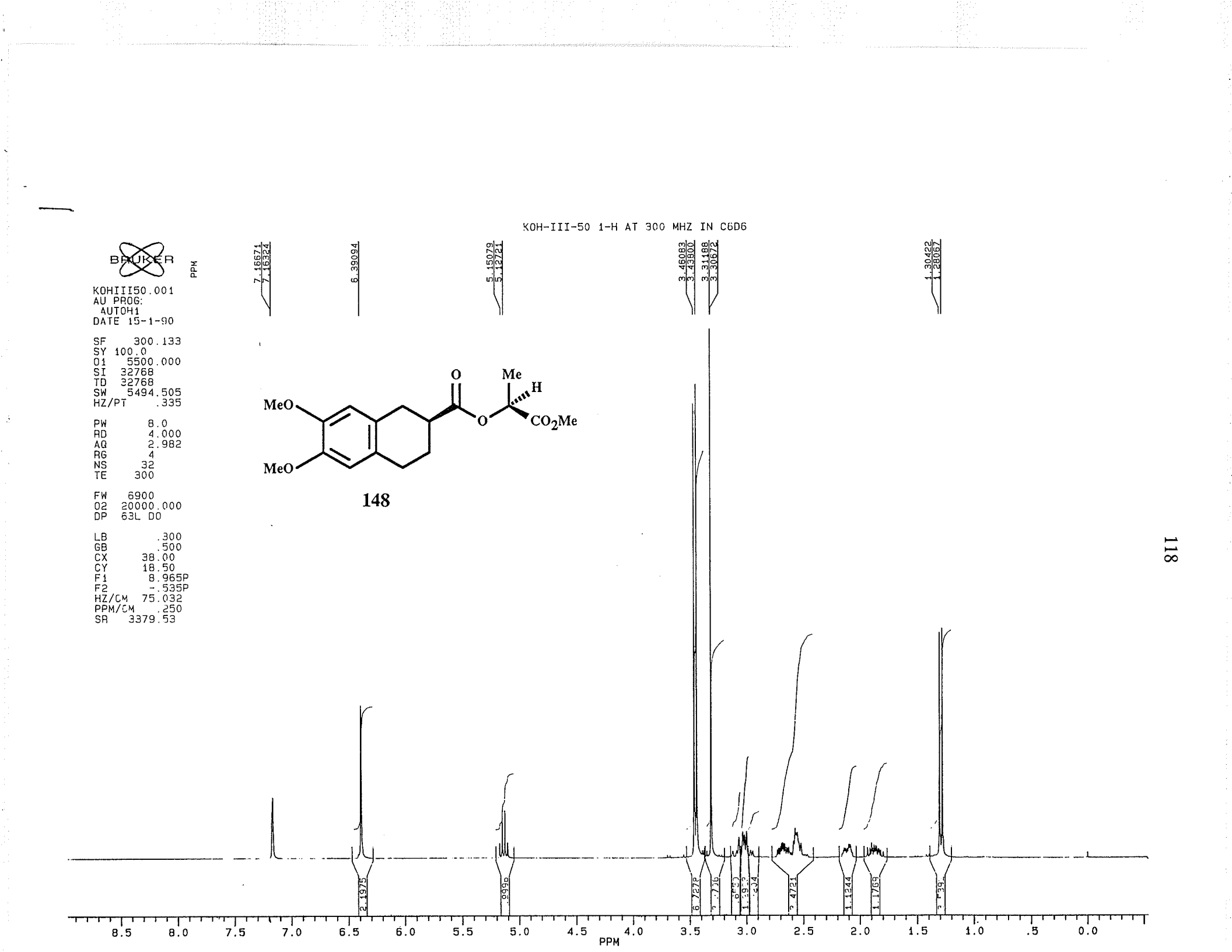
136

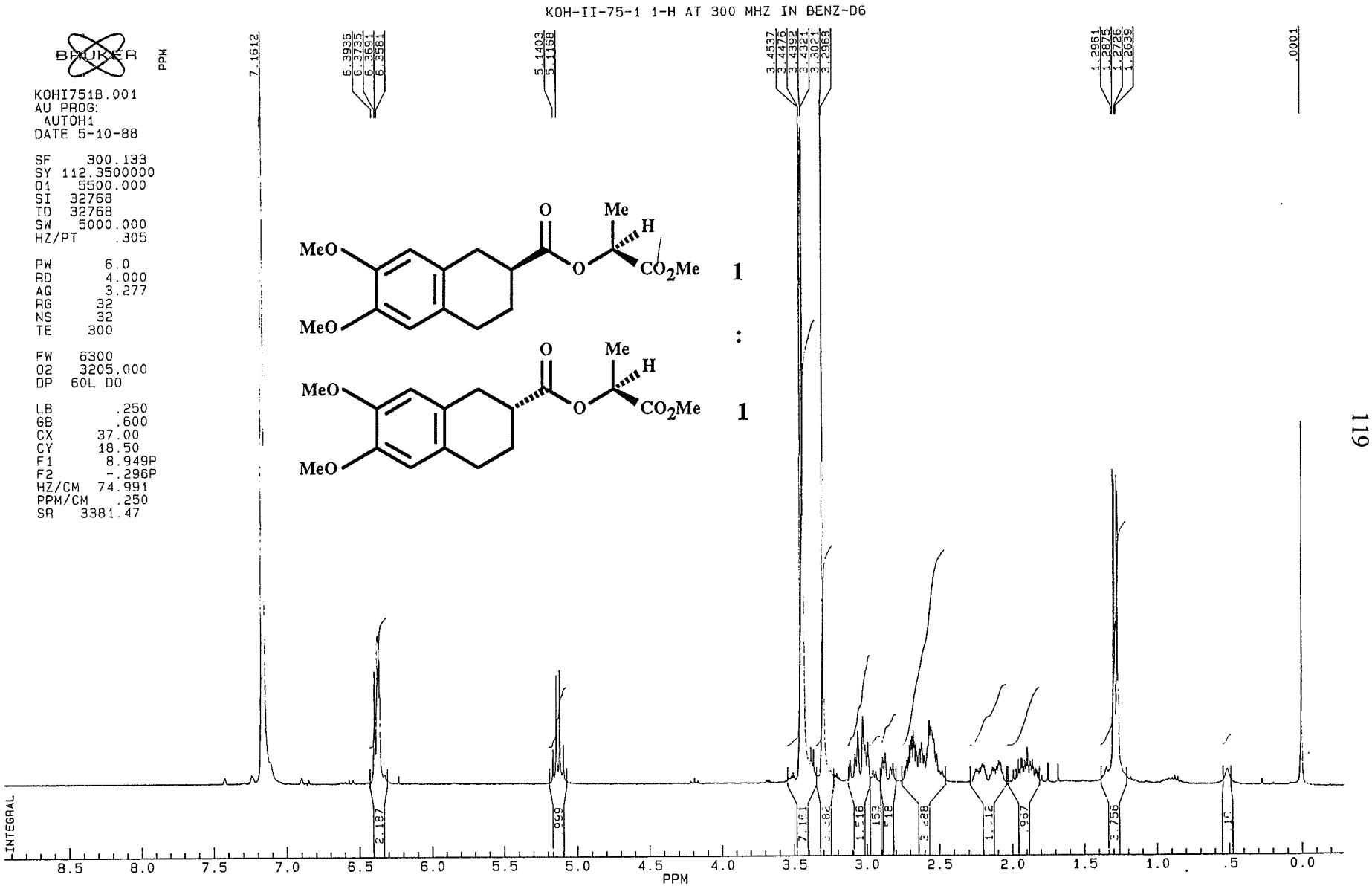

SAMPLE KOH-III-11 1-H AT 300 MHZ CDCL3
BRUKER
PPM
KOHIII11.001
AU PROG:
AUTOH1
DATE 7-9-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 80
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 12.322P
F2 -.343P
HZ/CM 100.034
PPM/CM .333
SR 3373.83
7.23837
7.11624
7.10605
7.09859
3.05196
3.03003
3.02147
2.89523
2.88597
2.87377
.00005
CO2H
138
1.42
.42
7.869
1.21
.77
9.751
1.980
2.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


KOH-III-25 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
KOHIII25.001
AU PROG:
AUTOH1
DATE 11-10-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.027P
F2 -.473P
HZ/CM 75.032
PPM/CM .250
SR 3360.75
6.82399
6.70748
5.81006
5.80464
5.79872
5.79031
3.85935
3.84478
3.57408
3.55974
3.52792
3.51356
3.16725
3.16220
3.12086
3.11577
2.10420
MeO
MeO
O
Me
O
145
.9481
.9439
.8864
6.1794
1.0563
.9996
2.9186
.0953
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

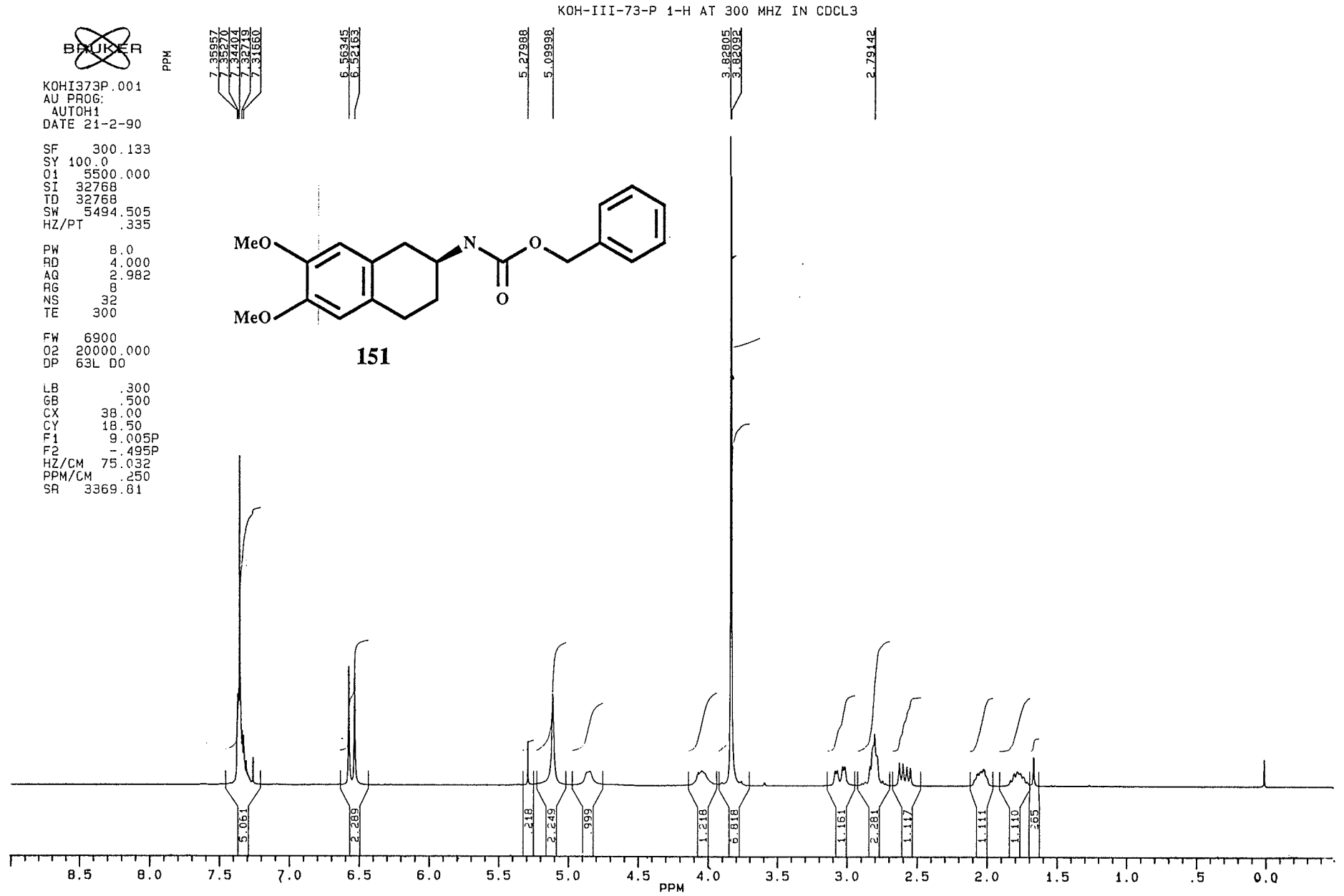

KOH-II-137 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
KOHII137.001
AU PROG:
AUTOH1
DATE 1-2-89
SF 300.133
SY 100.0500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AG 3.277
RG 16
NS 32
TE 300
FW 6300
O2 20000.000
DP 60L DO
LB .250
GB .600
CX 37.00
CY 18.50
F1 8.999P
F2 -.246P
HZ/CM 74.991
PPM/CM .250
SR 3366.52
7.26295
7.17347
6.55284
5.28315
5.25931
4.94240
4.91181
3.88066
3.85825
3.84863
3.79573
3.77509
2.80928
2.79821
2.77789
2.76830
2.75856
2.73801
2.72775
1.56674
1.54285
-.00003
OH
O
Me
H
MeO
MeO
O
CO2Me
146
.027
1.049
1.065
.999
1.005
9.675
3.467
1.105
1.126
3.012
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

KOH-III-50 1-H AT 300 MHZ IN C6D6

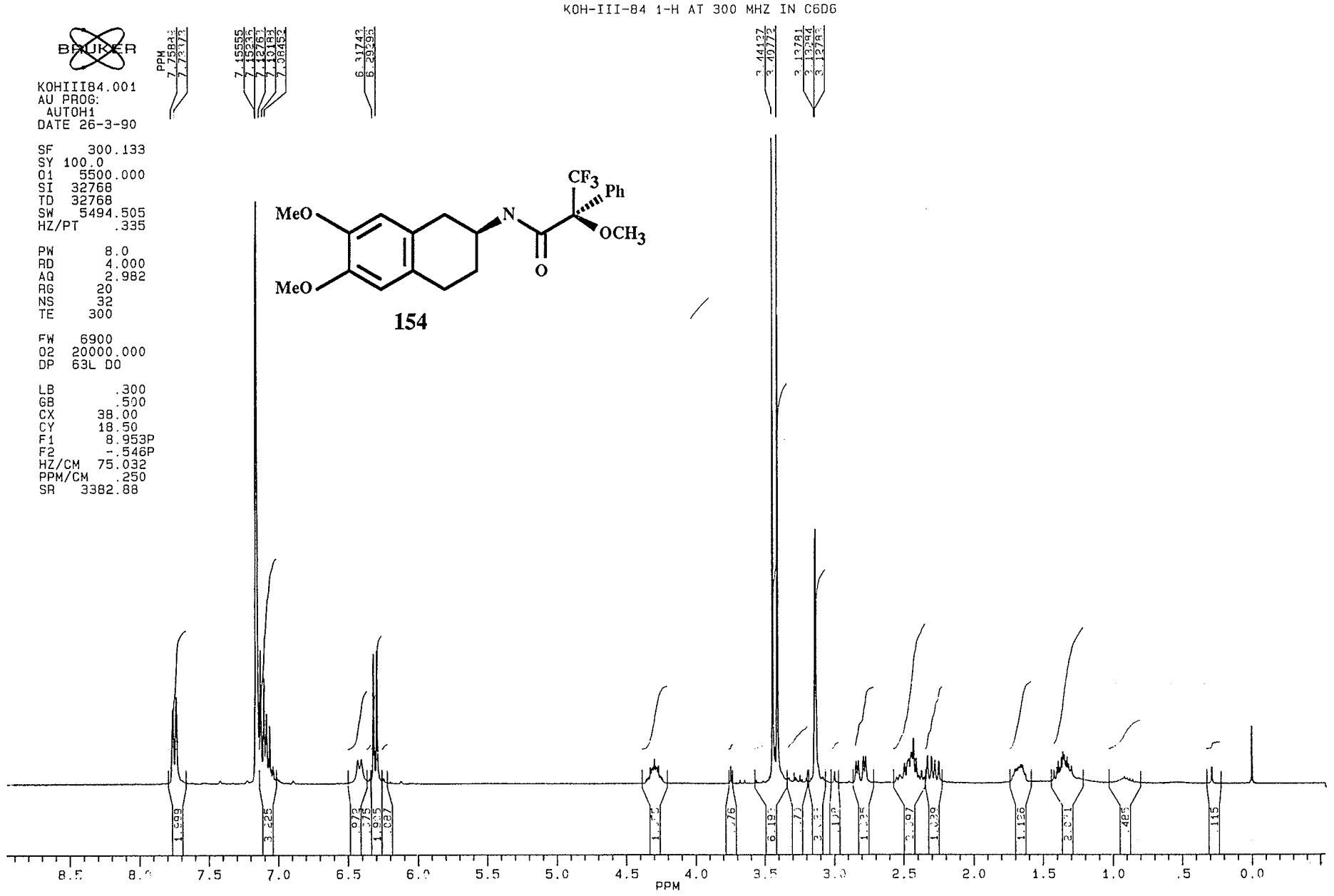


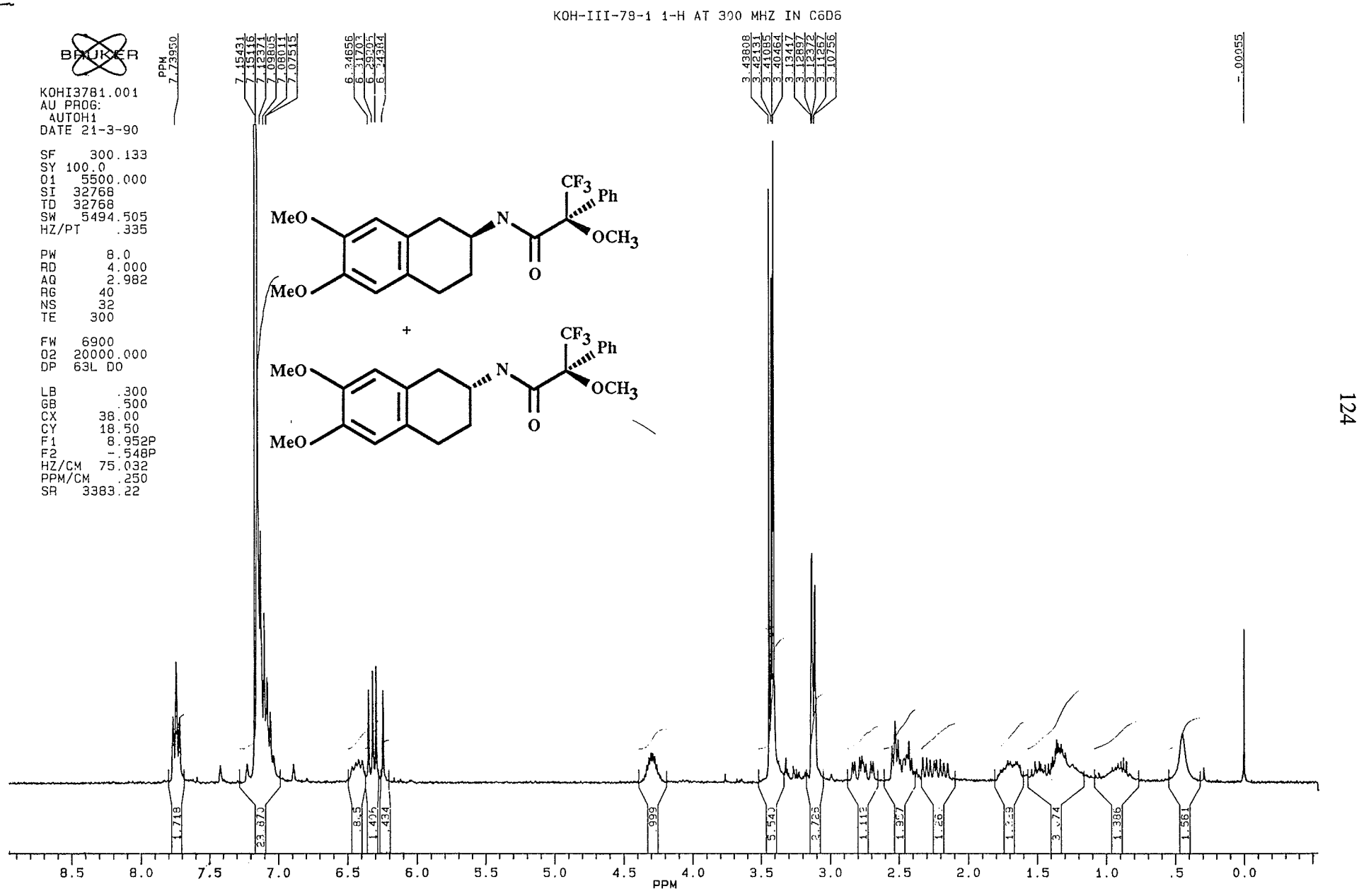

KOH-II-75-1 1-H AT 300 MHZ IN BENZ-D6
BRUKER
PPM
KOHI751B.001
AU PROG:
AUTOH1
DATE 5-10-88
SF 300.133
SY 112.3500000
O1 5500.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 6.0
RD 4.000
AQ 3.277
RG 32
NS 32
TE 300
FW 6300
O2 3205.000
DP 60L DO
LB .250
GB .600
CX 37.00
CY 18.50
F1 8.949P
F2 -.296P
HZ/CM 74.991
PPM/CM .250
SR 3381.47
7.1612
6.3936
6.3735
6.3591
6.3381
5.1403
5.1168
3.4537
3.4476
3.4392
3.4321
3.3021
3.2968
1.2961
1.2875
1.2726
1.2639
.0001
MeO
MeO
O
Me
H
O
CO2Me
1
:
1
INTEGRAL
PPM

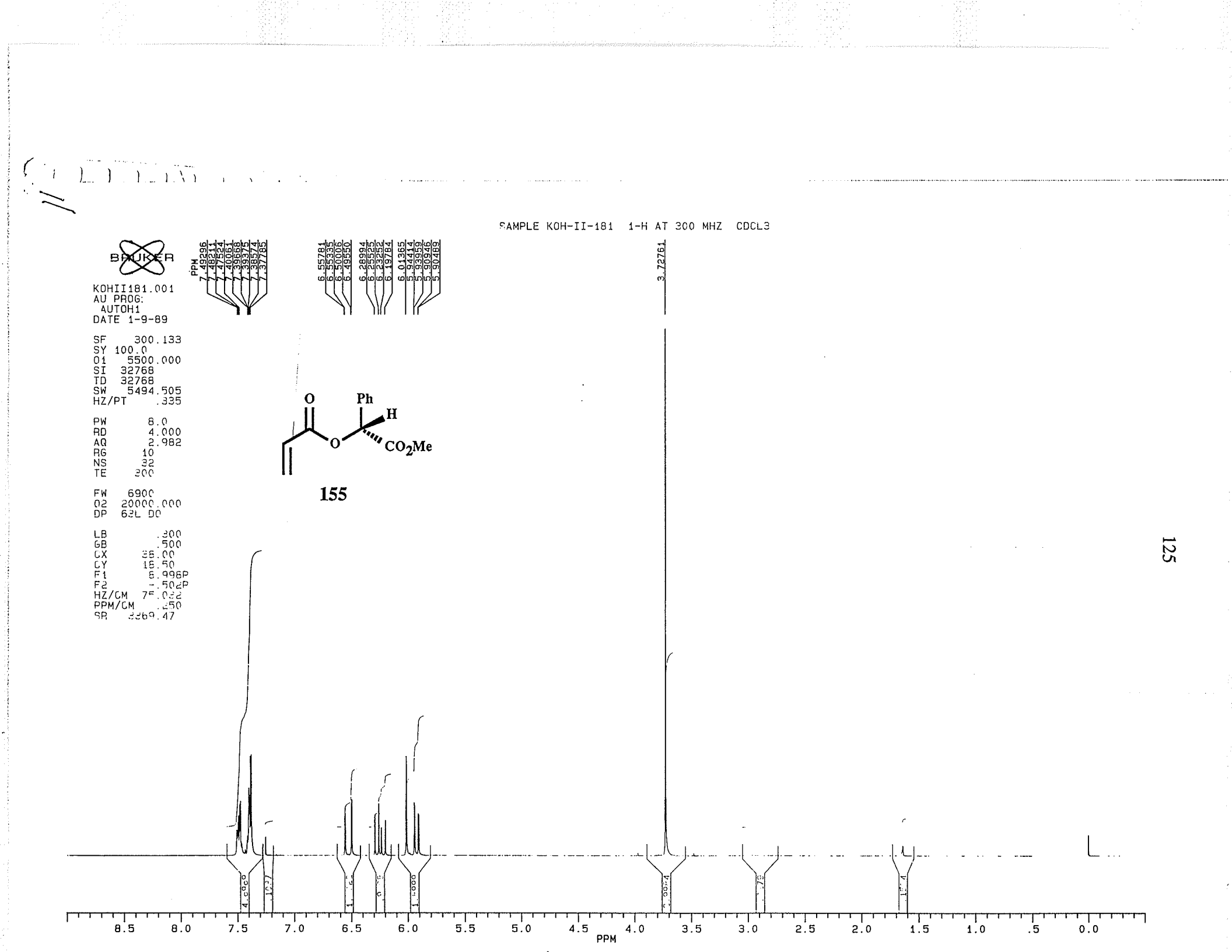

KOH-III-55 1-H AT 300 MHZ IN CDCL3
KOHIII55.001
AU PROG:
AUTOH1
DATE 27-2-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.999P
F2 -.501P
HZ/CM 75.032
PPM/CM .250
SR 3369.14
MeO
MeO
CO2H
150
EOX
PPM

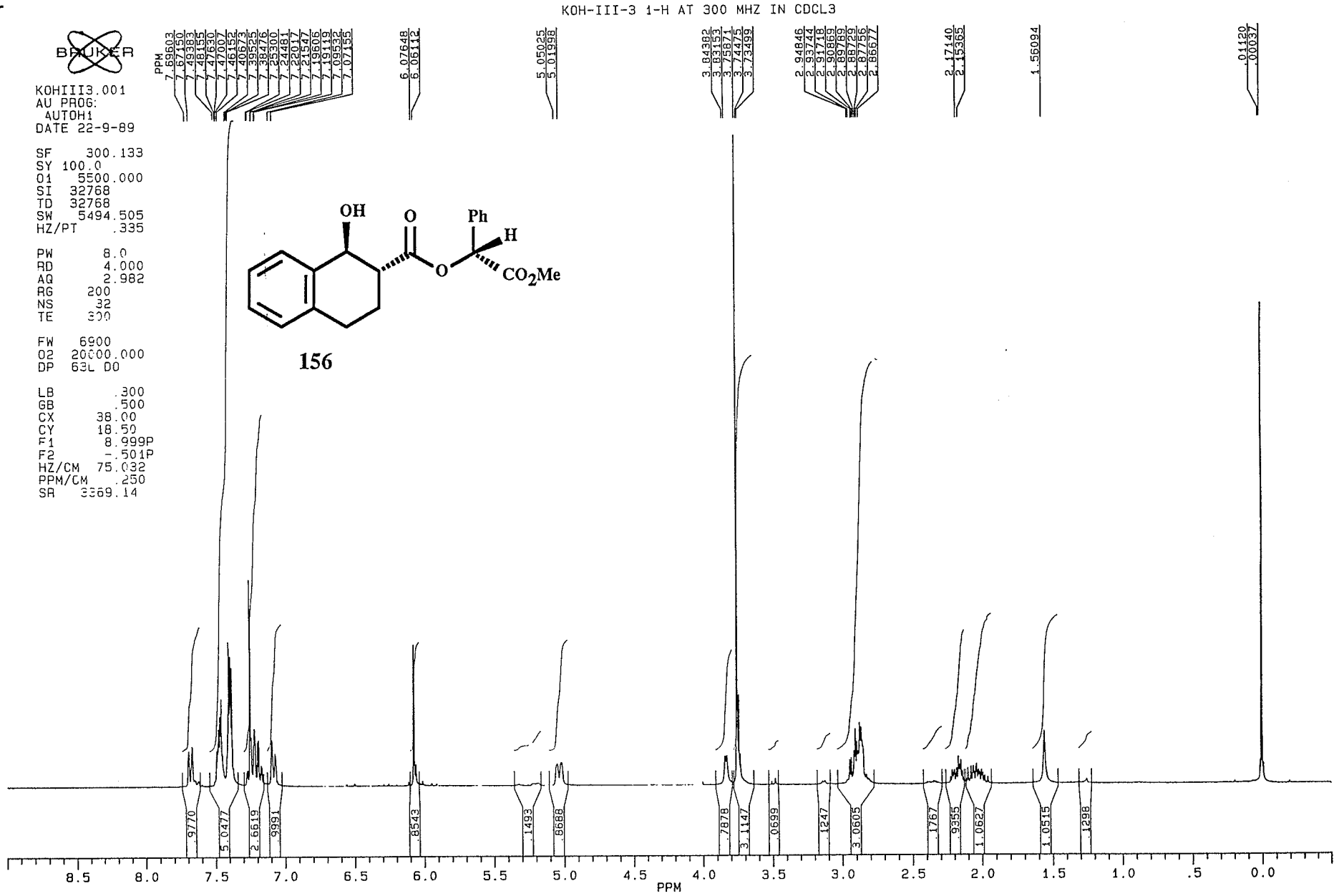

KOH-III-73-P 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
KOHI373P.001
AU PROG:
AUTOH1
DATE 21-2-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 8
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3369.81
7.35957
7.35270
7.34404
7.32219
7.31660
6.56345
6.52163
5.27988
5.09998
3.82805
3.82092
2.79142
MeO
MeO
N
O
O
151
5.061
2.289
.218
2.249
.999
1.218
6.818
1.161
2.281
1.117
1.111
1.110
.265
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

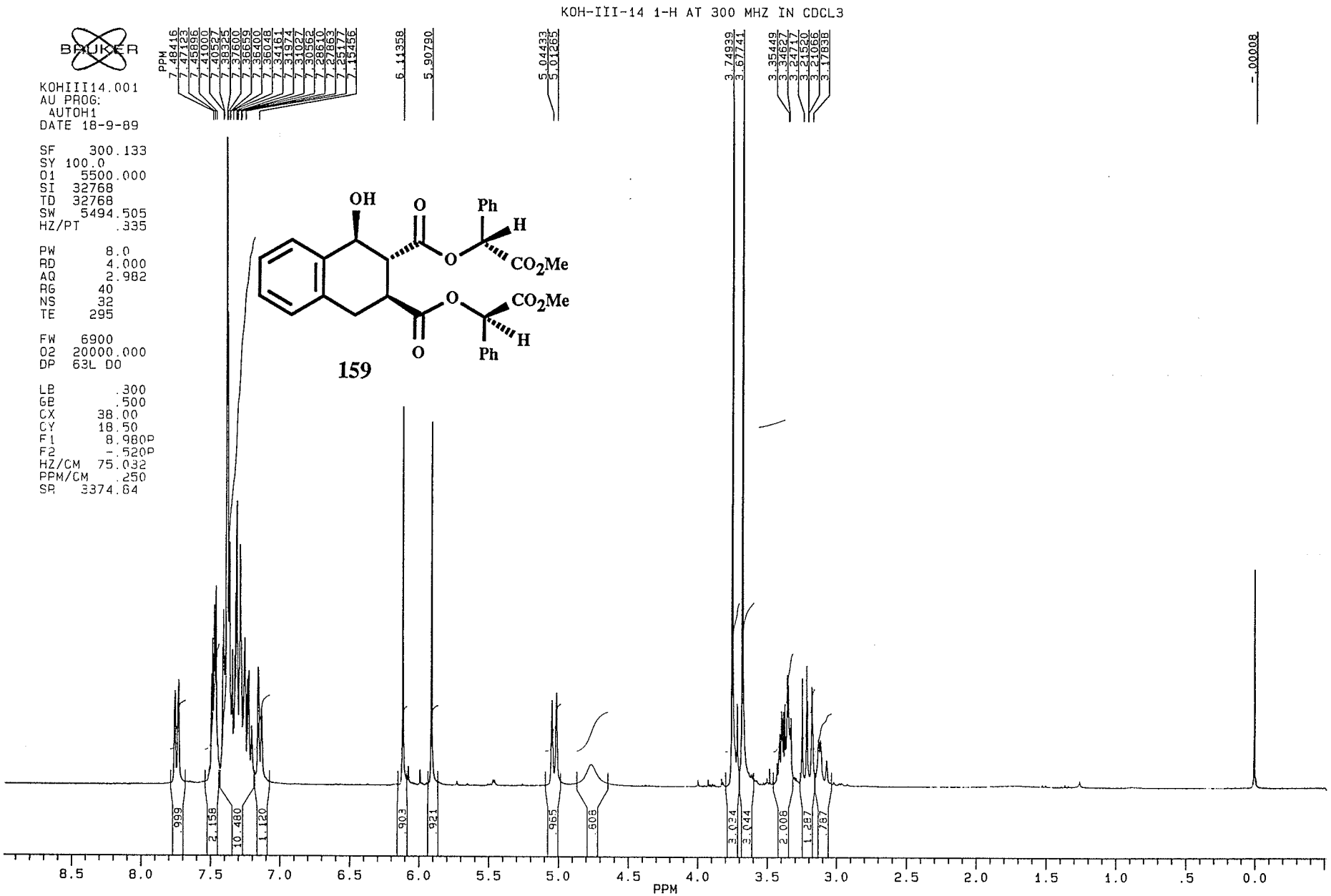
KOH-III-82 1-H AT 300 MHZ IN CDCL3


KOH-III-84 1-H AT 300 MHZ IN C6D6
KOHIII84.001
AU PROG:
AUTOH1
DATE 26-3-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 20
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.953P
F2 -.546P
HZ/CM 75.032
PPM/CM .250
SR 3382.88
MeO
MeO
N
CF3
Ph
OCH3
O
154
PPM


KOH-III-78-1 1-H AT 300 MHZ IN C6D6
BRUKER
KOHI3781.001
AU PROG:
AUTOH1
DATE 21-3-90
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.952P
F2 -.548P
HZ/CM 75.032
PPM/CM .250
SR 3383.22
PPM
7.73950
7.15431
7.15116
7.12371
7.09805
7.08011
7.07515
6.34656
6.31703
6.29205
6.24384
3.43808
3.42131
3.41085
3.40464
3.13417
3.12897
3.12372
3.11267
3.10756
-.00055
MeO
MeO
N
O
CF3
Ph
OCH3
+
MeO
MeO
N
O
CF3
Ph
OCH3
1.718
23.870
8.45
1.405
.434
.999
5.540
3.725
1.112
1.957
1.26
1.239
3.974
1.386
1.561
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


SAMPLE KOH-II-181 1-H AT 300 MHZ CDCL3
KOHII181.001
AU PROG:
AUTOH1
DATE 1-9-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 10
NS 32
TE 300
FW 6900
O2 20000.000
DP 62L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 6.998P
F2 4.502P
HZ/CM 75.022
PPM/CM .250
SR 3269.47
PPM
7.49296
7.48211
7.47124
7.40624
7.40061
7.39698
7.39375
7.38574
7.37785
6.55781
6.55335
6.50006
6.49550
6.28994
6.25525
6.23252
6.19784
6.01365
5.94414
5.93959
5.90946
5.90489
3.72761
O
Ph
H
O
CO2Me
155
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


KOH-III-3 1-H AT 300 MHZ IN CDCL3
KOHIII3.001
AU PROG:
AUTOH1
DATE 22-9-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 200
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.999P
F2 -.501P
HZ/CM 75.032
PPM/CM .250
SR 3369.14
OH
O
Ph
H
O
CO2Me
156
PPM


KOH-III-14 1-H AT 300 MHZ IN CDCL3
KOHIII14.001
AU PROG:
AUTOH1
DATE 18-9-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 295
FW 6900
O2 20000.000
DP 63L DO
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.980P
F2 -.520P
HZ/CM 75.032
PPM/CM .250
SR 3374.64
OH
O
Ph
H
CO2Me
159
PPM

KOH-III-41-R 1-H AT 300 MHZ IN CDCL3

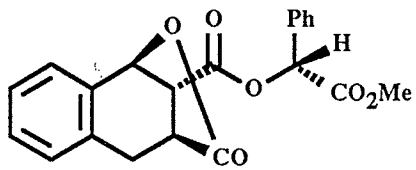
KOHI341R.001
AU PROG:
AUTOH1
DATE 8-12-89

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

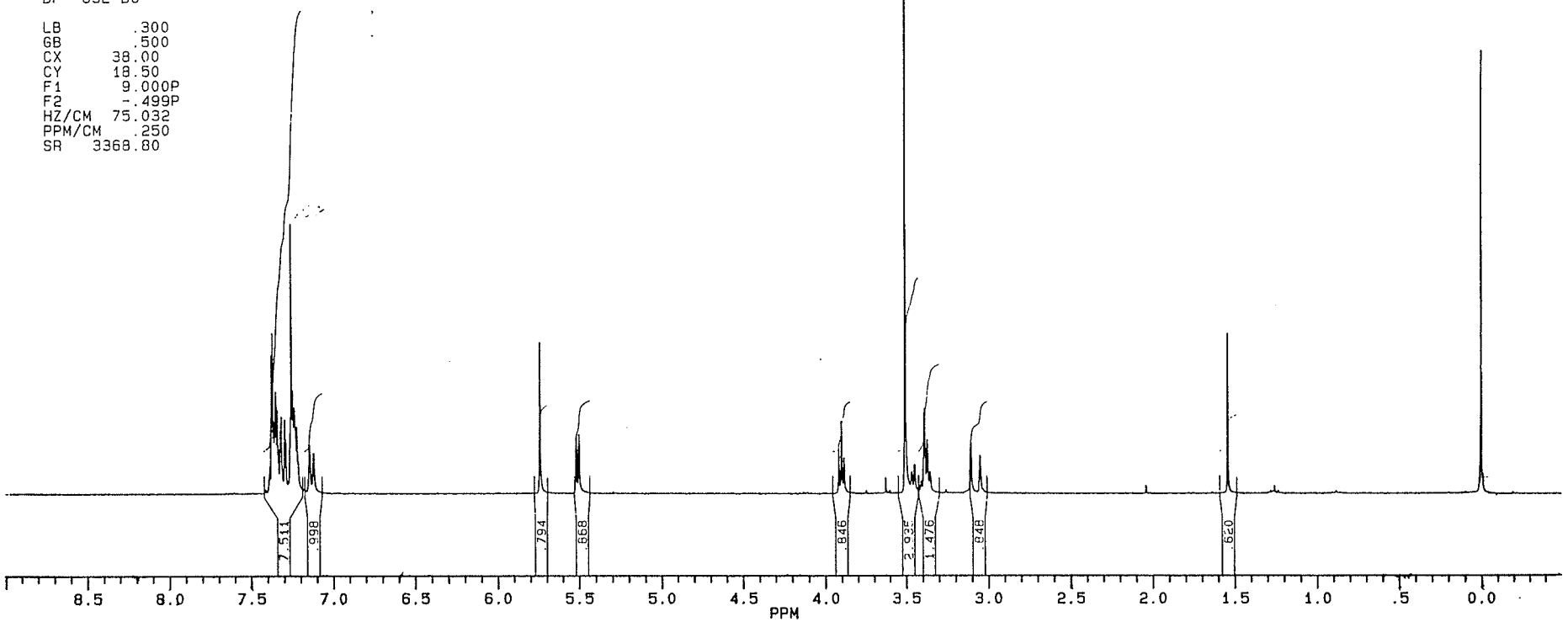
PW 8.0
RD 4.000
AQ 2.982
RG 40
NS 32
TE 300

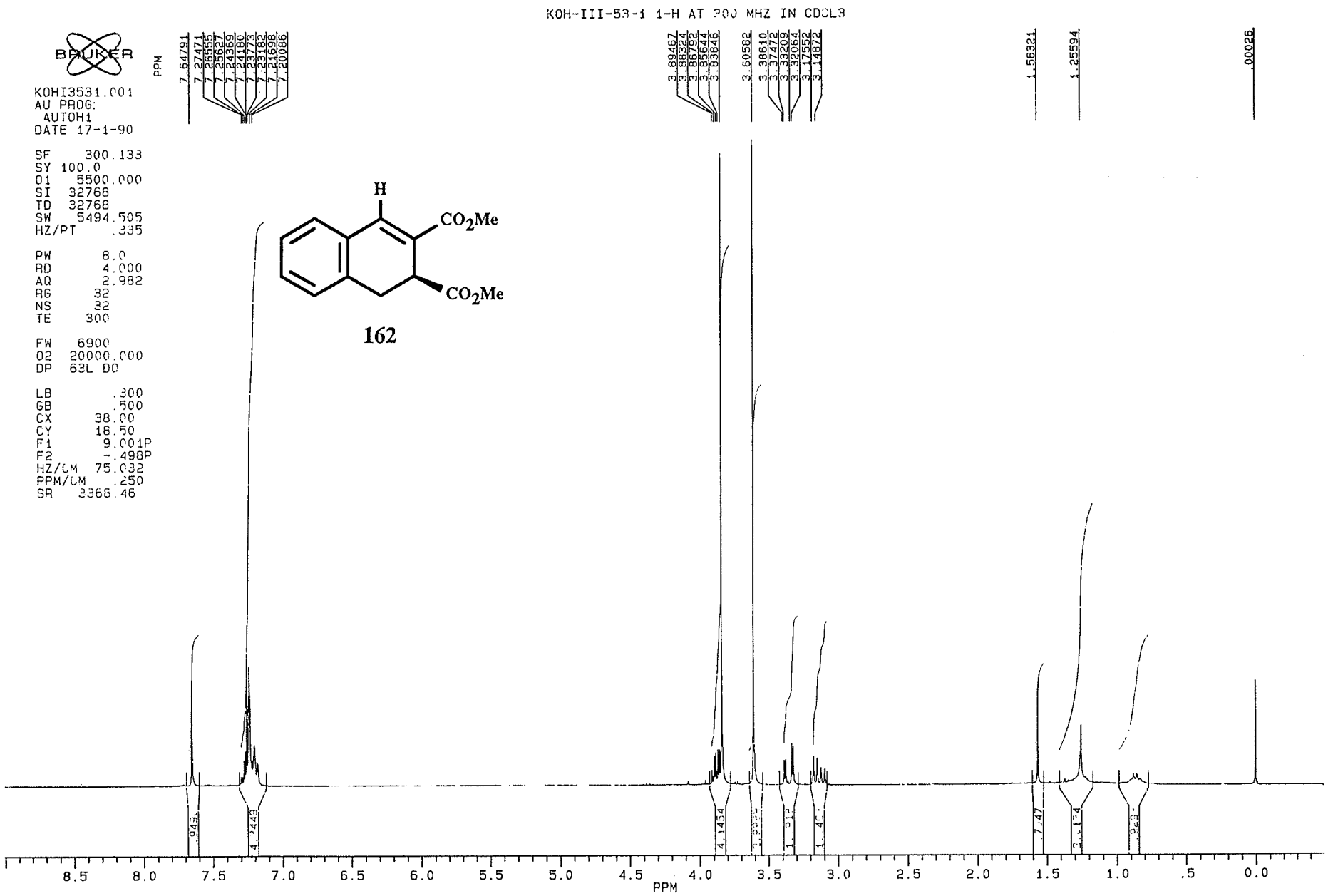
FW 6900
O2 20000.000
DP 63L DO

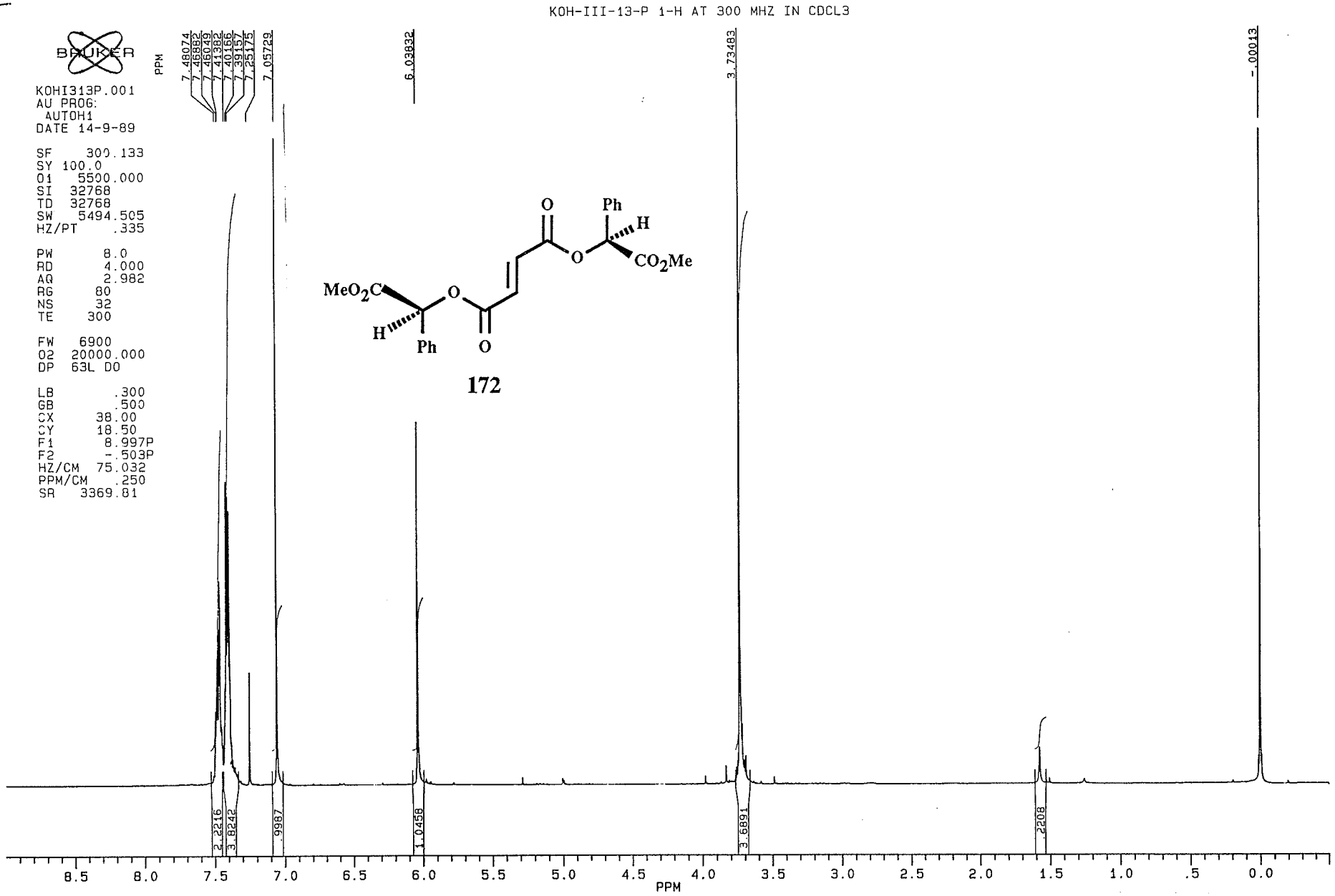
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.000P
F2 -.499P
HZ/CM 75.032
PPM/CM .250
SR 3368.80

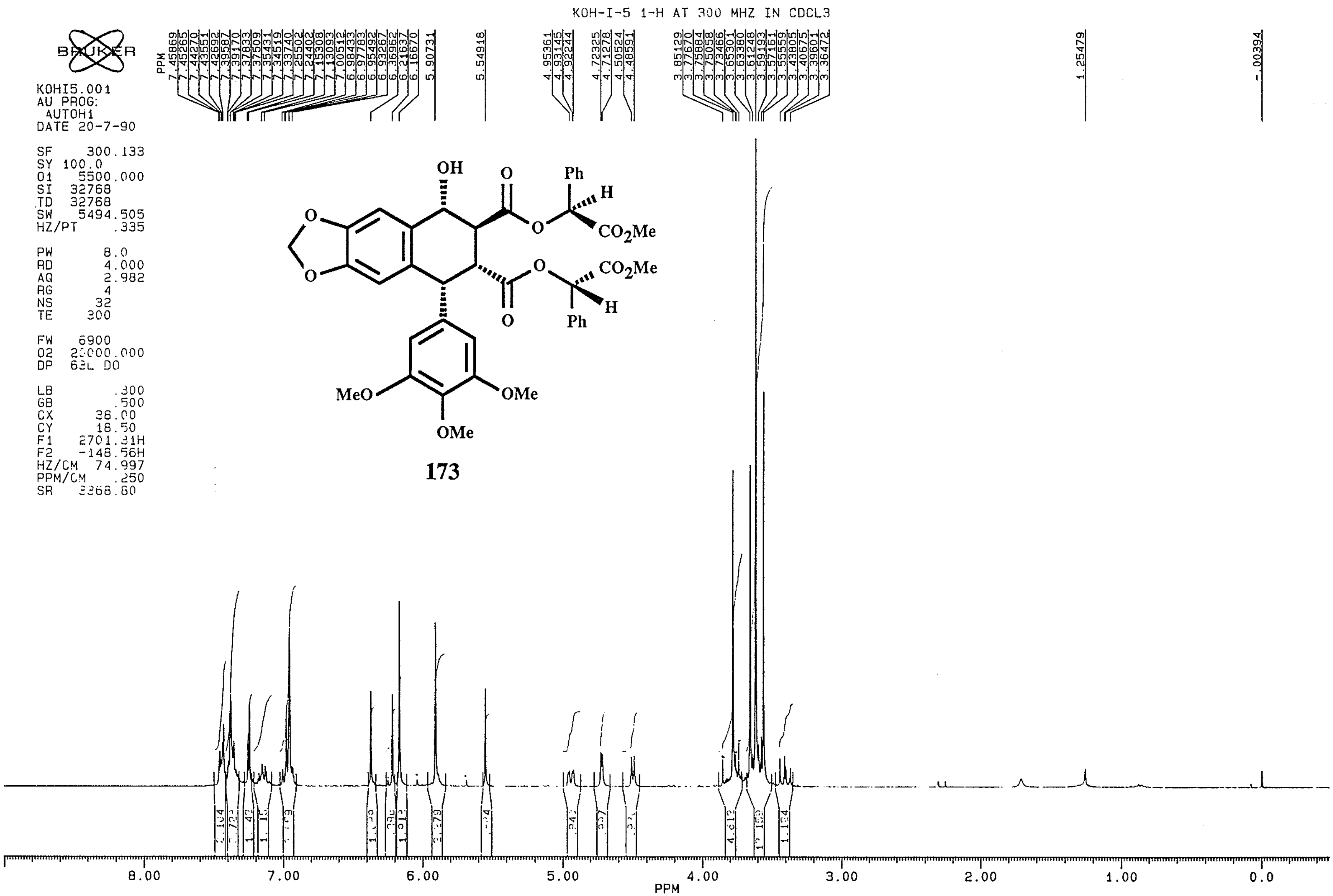


160




KOH-III-53-1 1-H AT 300 MHZ IN CDCL3
KOHI3531.001
AU PROG:
AUTOH1
DATE 17-1-90
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 32
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 16.50
F1 9.001P
F2 -.498P
HZ/CM 75.032
PPM/CM .250
SR 3366.46
PPM
7.64791
7.27471
7.26555
7.25627
7.24360
7.24180
7.23775
7.23162
7.21696
7.20086
3.89467
3.88324
3.86792
3.85644
3.83846
3.60582
3.38610
3.37472
3.33209
3.32064
3.17552
3.14872
1.56321
1.25594
.00026
H
CO2Me
CO2Me
162
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


KOH-III-13-P 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
KOHI313P.001
AU PROG:
AUTOH1
DATE 14-9-89
SF 300.133
SY 100.0
O1 5500.000
SI 32768
TD 32768
SW 5494.505
HZ/PT .335
PW 8.0
RD 4.000
AQ 2.982
RG 80
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 8.997P
F2 -.503P
HZ/CM 75.032
PPM/CM .250
SR 3369.81
7.48074
7.46982
7.46049
7.41382
7.40166
7.39157
7.25175
7.05729
6.03832
3.73483
.00013
2.2216
3.8242
.9987
1.0458
3.6891
.2208
MeO2C
O
Ph
H
CO2Me
172
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


KOH-I-5 1-H AT 300 MHZ IN CDCL3
BRUKER
KOHI5.001
AU PROG:
AUTOH1
DATE 20-7-90
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 36.00
CY 16.50
F1 2701.31H
F2 -148.56H
HZ/CM 74.997
PPM/CM .250
SR 3268.60
PPM
7.45869
7.45265
7.44270
7.43551
7.42692
7.39587
7.39170
7.37833
7.37509
7.35431
7.34519
7.33740
7.25502
7.24402
7.15308
7.13093
7.00512
6.98433
6.97783
6.95494
6.93267
6.36962
6.21637
6.16670
5.90731
5.54918
4.95361
4.93145
4.92244
4.72325
4.71278
4.50524
4.48591
3.85129
3.77670
3.75884
3.75058
3.73466
3.65301
3.63380
3.61248
3.59193
3.57161
3.55559
3.43805
3.40675
3.39601
3.36472
1.25479
-.00394
OH
O
Ph
H
CO2Me
O
O
O
CO2Me
O
H
O
Ph
MeO
OMe
OMe
173
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

KOH-IV-28 1-H AT 300 MHZ IN CDCL3

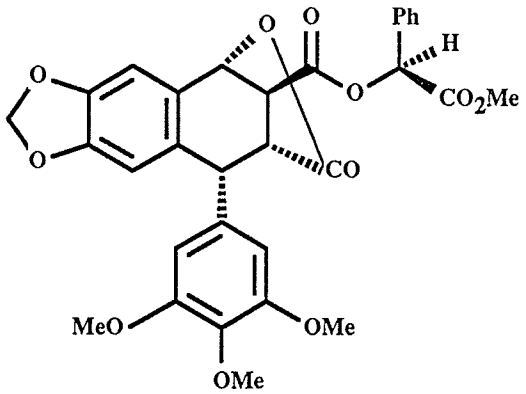
KOHIV28.001
AU PROG:
AUTOH1
DATE 24-1-91

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

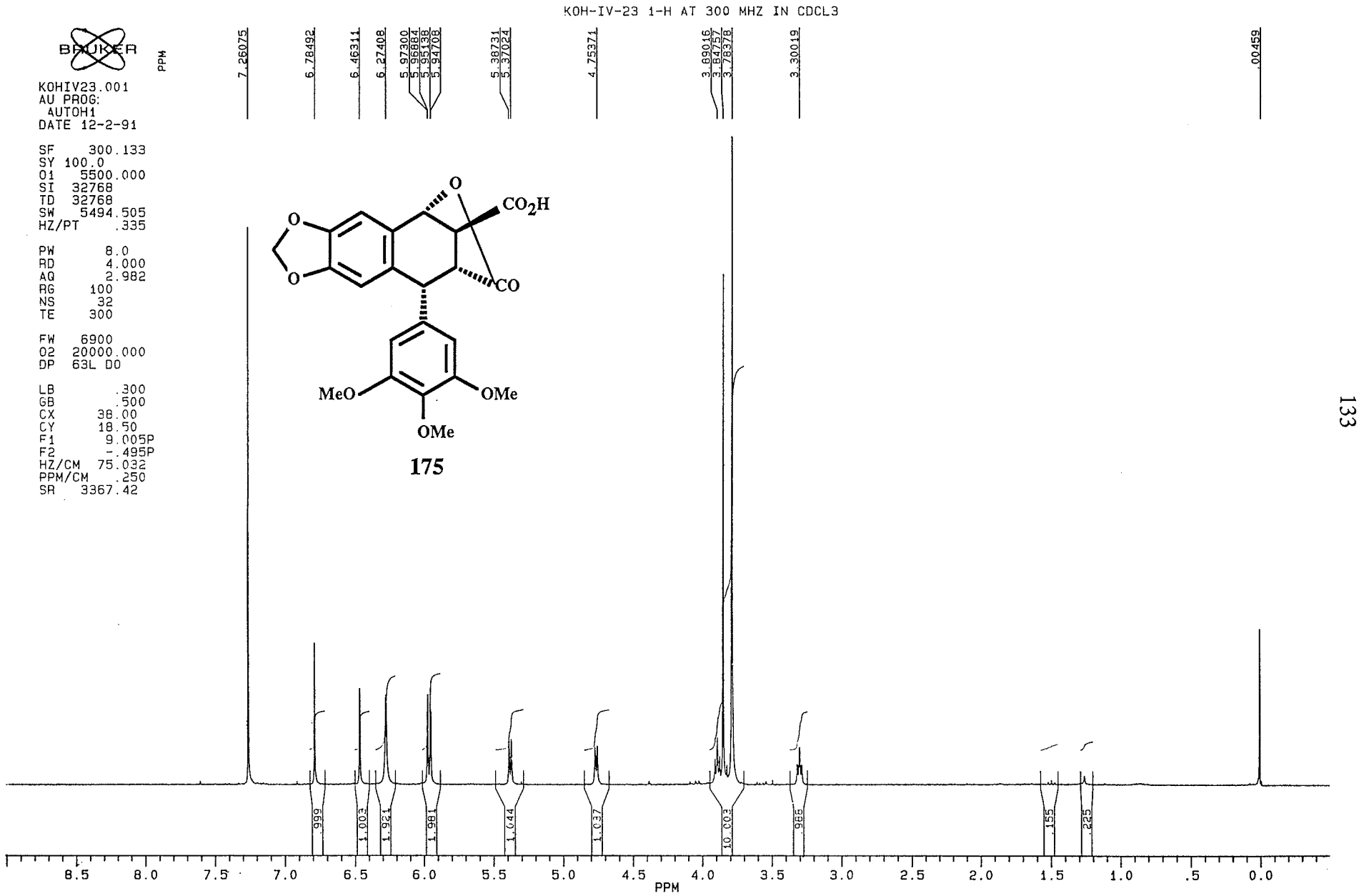
PW 8.0
RD 4.000
AQ 2.982
RG 16
NS 32
TE 300

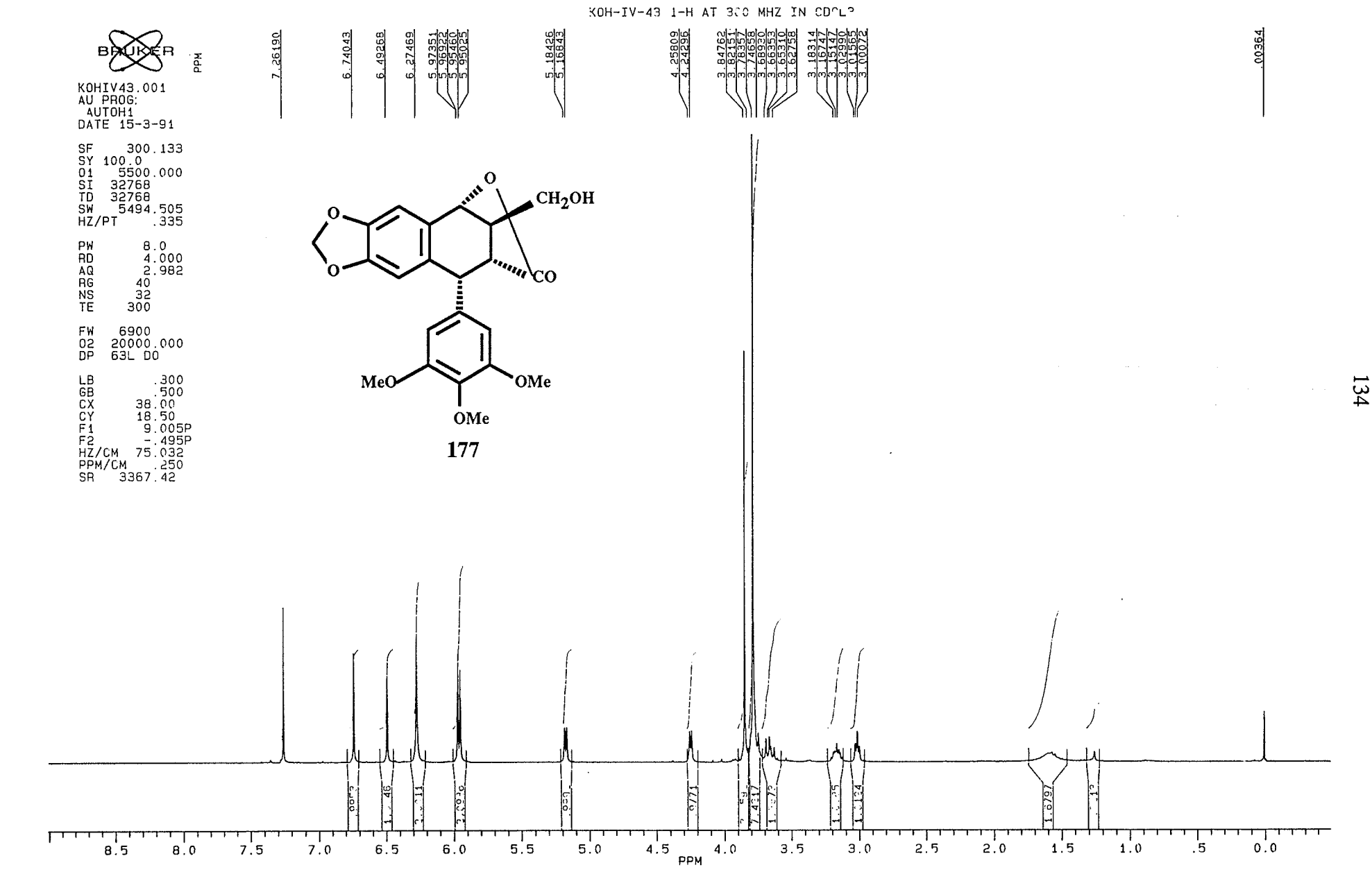
FW 6900
O2 20000.000
DP 63L DO

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



174


KOH-IV-23 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.26075
6.78492
6.46311
6.27408
5.97300
5.96884
5.95138
5.94709
5.38731
5.37024
4.75371
3.89016
3.84757
3.78378
3.30019
.00459
KOHIV23.001
AU PROG:
AUTOH1
DATE 12-2-91
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 100
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.42
O
CO2H
O
O
CO
MeO
OMe
OMe
175
.999
1.003
1.921
1.981
1.644
1.037
10.003
.966
.155
.225
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


KOH-IV-43 1-H AT 300 MHZ IN CDCL3
BRUKER
PPM
7.26190
6.74043
6.49268
6.27469
5.97351
5.96922
5.95460
5.95025
5.18426
5.16843
4.25809
4.24296
3.84762
3.82151
3.78357
3.74658
3.68930
3.66353
3.65310
3.62758
3.18314
3.16747
3.15147
3.02990
3.01565
3.00072
.00364
KOHIV43.001
AU PROG:
AUTOH1
DATE 15-3-91
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 40
NS 32
TE 300
FW 6900
O2 20000.000
DP 63L D0
LB .300
GB .500
CX 38.00
CY 18.50
F1 9.005P
F2 -.495P
HZ/CM 75.032
PPM/CM .250
SR 3367.42
O
CH2OH
O
O
CO
MeO
OMe
OMe
177
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

REFERENCES

1. C.R. Flynn and J. Michl. J. Am. Chem. Soc. **95**, 5802 (1973).
2. M.P. Cava and D.R. Napier. J. Am. Chem. Soc. **79**, 1701 (1957).
3. M.P. Cava, A.A. Deanna,and K. Muth. J. Am. Chem. Soc. **81**, 6458 (1959).
4. J.L. Charlton and M.M. Alauddin. Tetrahedron, **43**, 2873 (1987).
5. J.L. Charlton, K. Koh, and G.L. Plourde. Tetrahedron lett, **30**, 3279 (1989).
6. J.L. Charlton, G.L. Plourde, K. Koh, and A.S Secco, Can. J. Chem. **67**, 574 (1989).
7. M.E. Jung, P.W. Lam, M.M. Mansuri, and L.M. Spetz. J. Org. Chem. **50**, 1087 (1985).
8. D.I. McDonald and T. Durst. J. Org. Chem. **53**, 3663 (1988).
9. M.E Jung and G.T. Lowen. Tetrahedron Lett. **27**, 5319 (1986).
10. M.P. Cava and K. Muth. J. Am. Chem. Soc. **82**, 652 (1960).
11. H.H. Wasserman and J. Solodar. J. Am. Chem. Soc. **87**, 4002 (1965).
12. W.A. Bubb and S. Sternhell. Aust. J. Chem. **29**, 1685 (1976).
13. E. Akgün, M.B. Glinski, K.L. Dhawan, and T. Durst. J. Org. Chem. **46**, 2730 (1981).
14. M. Azadi-Ardakani and T.W. Wallace. Tetrahedron, **44**, 5939 (1988).
15. P.G. Sammes. Tetrahedron, **32**, 405 (1976).
16. T. Kametani, Y. Katoh, and K. Fukumoto. J. Chem. Soc. Perkin. Trans. I, 1712 (1974).
17. W. Oppolzer. Heterocycles, **14**, 1615 (1980).
18. J.L. Charlton and T. Durst. Tetrahedron Lett. **25**, 2663 (1984).
19. J.L. Charlton, M.M. Alauddin, and G.H. Penner. Can. J. Chem. **64**, 793 (1986).
20. J. Mann and S.E. Piper. J. Chem. Soc. Chem. Comm. 430 (1982).
21. J. Mann, S.E. Piper, and L.K.P. Yeung. J. Chem. Soc. Perkin Trans. I, 2081 (1984).
22. T. Durst, E.C. Kozma, and J.L. Charlton. J. Org. Chem. **50**, 4829 (1985).

23. J.L. Charlton and M.M. Alauddin. J. Org. Chem. **51**, 3490 (1986).

24. J.L. Charlton. Tetrahedron Lett. **26**, 3413 (1985).

25. J.L. Charlton, G.L. Plourde, and G.H. Penner. Can. J. Chem. **67**, 1010 (1989).

26. M. Hrytsak, N. Etkin, and T. Durst. Tetrahedron Lett. **27**, 5679 (1986).

27. Z. Khan and T. Durst. Can. J. Chem. **65**, 482 (1987).

28. J. Charlton. Can. J. Chem. **64**, 720 (1986).

29. M.M. Alauddin. Ph.D. Thesis. University of Manitoba (1987).

30. Otto Diels (1876-1954), Ph.D. thesis, Berlin (E. Fisher), Kiel, Nobel Prize 1950.

31. Kurt Alder (1902-1958), Ph.D. thesis, Kiel (O. Diels), Cologne, Nobel Prize 1950.

32. J. March, *In* Advanced Organic Chemistry (3^{rd} edition). John Wiley and Sons, New York. 1985. pp. 745-753.

33. I. Fleming, *In* Frontier Orbitals and Organic Reactions. John Wiley and Sons, New York. 1978. pp. 87-135.

34. T. Cohen, R.J. Ruffner, D.W. Shull, W.M. Daniewski, R.M. Ottenbrite, and P.V. Alston. J. Org. Chem. **43**, 4052 (1978).

35. T.H Lowry, K.H. Richardson, *In* Mechanism and Theory in Organic Chemistry (2^{nd} edition). Harper & Row, New York. 1981. pp. 841-848.

36. M. Kakushima, Can. J. Chem. 57, 2564 (1979).

37. M.P. Cava, A.A. Deanna, and K. Muth. J. Am. Chem. Soc. **81**, 6458 (1959).

38. M.P. Cava and A.A. Deanna. J. Am. Chem. Soc. **81**, 4266 (1959).

39. B.J. Arnold, S.M. Mellows, P.G. Sammes, and T.W. Wallace. J. Chem. Soc. Chem. Comm. 401 (1974).

40. P.K. Das, M.V. Encinas, R.D. Small, and J.C. Scaino. J. Am. Chem. Soc. **101**, 6965 (1979).

41. B.J. Arnold, P.G. Sammes, and T.W. Wallace. J. Chem. Soc. Perkin Trans. I, 409 (1974).

41. S.M. Mellows and P.G. Sammes. J. Chem. Soc. Chem. Comm. 21 (1971).

43. B.J. Arnold and P.G. Sammes. J. Chem. Soc. Chem. Comm. 30 (1972).

44. S.V. Kessar, T. Singh, and A.K.S Mankotia. J. Chem. Soc. Chem. Comm. 1692 (1989).

45. B.J. Arnold, P.G. Sammes and T.W. Wallace. J. Chem. Soc. Perkin Trans. I, 415 (1974).

46. E. Block and R. Stevenson. J. Chem. Soc. Perkin Trans. I, 308 (1973).

47. M. Pfau, J.E. Rowe Jr., and N.D. Heindel. Tetrahedron, **34**, 3469 (1978).

48. M. Pfau, S. Combrisson, J.E. Rowe Jr., and N.D. Heindel. Tetrahedron, **34**, 3459 (1978).

49. T. Kametani and K. Fukumoto. Heterocycles, **8**, 465 (1977).

50. A.G. Fallis. Can. J. Chem. **62**, 183 (1984).

51. G. Quinkert and H. Stark. Angew. Chem. Int. Ed. Engl. **22**, 637 (1983).

52. R.L. Funk and K.P.C. Vollhardt. Chem. Soc. Rev. **9**, 41 (1980).

53. T. Kametani and K. Fukomoto. Med. Res. Rev. **1**, 23 (1981).

54. R.S. Ward. Chem. Soc. Rev. **11**, 75 (1982).

55. H. Stähelin and A. Von Wartburg. Prog. Drug. Res. **33**, 169 (1989).

56. A.R. Beard, M.G.B. Drew, J. Mann, and L.T.F. Wong. Tetrahedron, **43**, 4207 (1987).

57. J. Mann, L.T. Wong, and A. Beard, Tetrahedron Lett. **26**, 1667 (1985).

58. M.B. Glinski and T. Durst. Can. J. Chem. **61**, 573 (1983).

59. S. Takano, S. Otaki, and K. Ogasawara. J. Chem. Soc. Chem. Comm. 485 (1985).

60. S. Takano, N. Sato, S. Otaki, and K. Ogasawara. Heterocycles, **25**, 69 (1987).

61. K.G. Das, J. Afzal, B.G. Hazra, and B.M. Bhawal. Synthetic Comm. **13**, 787 (1983).

62. Y. Ito, Y. Amino, M. Nakatsuka, and T. Saegusa. J. Am. Chem. Soc. **105**, 1586 (1983).

63. T. Kametani and H. Nemoto. Tetrahedron, **37**, 3 (1981).

64. R.W. Franck, T.V. John, and K. Olejniczak. J. Am. Chem. Soc. **104**, 1106 (1982).

65. J.L. Charlton, G.L. Plourde, K. Koh, and A.S. Secco. Can. J. Chem. **68**, 2022 (1990).

66. W. Choy. Tetrahedron, **46**, 2281 (1990).

67. (a) S.P. Forsey, R. Rodrigo, D. Rajapaksa, and N.J. Taylor. J. Org. Chem. **54**, 4280 (1989); (b) D.M. Vyas, P.M. Skonezny, T.A. Jenks, and T.W. Doyle. Tetrahedron Lett. **27**, 3099 (1986); (c) J. Van der Eycken, P. De Clercq, and M. Vandewalle. Tetrahedron Lett. **26**, 3871 (1985); (d) T. Kaneko and H. Wong. Tetrahedron Lett. **28**, 517 (1987); (e) D.W. Jones and A.M. Thompson. J. Chem. Soc. Chem. Comm. 1370 (1989).

68. R.C. Andrews, S.J. Teague, and A.I. Meyers. J. Am. Chem. Soc. **110**, 7854 (1988).

69. T. Morimoto, M. Chiba, and K. Achiwa. Tetrahedron Lett. **31**, 261 (1990).

70. C. Kaiser and T. Jain. Med. Res. Rev. **5**, 145 (1985).

71. J.G. Cannon. Prog. Drug. Res. **29**, 303 (1985).

72. A.M. Johansson, K. Fredriksson, U. Hacksell, C.J. Grol, K. Svensson, A. Carlsson, and S. Sundell. J. Med. Chem. **33**, 2925 (1990), and references cited within (1, 2a, 5c, 5d, 5f).

73. H. Wikstrum, B. Andersson, D. Sanchez, P. Linberg, L. Arvidsson, A.M. Johansson, J.L.G. Nilsson, K. Svensson, S. Hjorth, and A. Carlsson. J. Med. Chem. **28**, 215 (1985).

74. A.M. Johansson, L. Arvidsson, U. Hacksell, J.L.G. Nilsson, and K. Svensson. J. Med. Chem. **30**, 602 (1987).

75. J.E. Nordlander, M.J. Payne, F.G. Njoroge, V.M. Vishwanath, G.R. Han, G.D. Laikos, and M.A. Balk. J. Org. Chem. **50**, 3619 (1985).

76. G.L. Plourde. personal communication.

77. P.J. Wagner. Pure & Appl. Chem. **49**, 259 (1977).

78. W.A. Noyes, G.S. Hammond, and J.N. Pitts. *In* Advances In Photochemistry. Vol. 5. Interscience Publishers. 1968. pp. 99-107.

79. L.F. Fieser and M. Fieser. *In* Reagents for Organic Synthesis, John Wiley and Sons, Inc .1967. p. 964.

80. A.R. Banks, R.F. Fibiger, and T. Jones. J. Org. Chem. **42**, 3965 (1977).

81. A. Schoofs, J.P. Guette, and A. Horeau. Bull. Chim. Soc. Fr. 1215 (1976).

82. T. Kametani and K. Fukumoto. Heterocycles, **3**, 29 (1975).

83. E. Borredon and M. Delmas et Antoine Gaset. Tetrahedron Lett. **23**, 5283 (1982).

84. A.P.S. Narula and D.I. Schuster. Tetrahedron Lett. **22**, 3707 (1981).

85. K. Ninomiya, T. Shiori, and S. Yamada. Tetrahedron, **30**, 2151 (1974).

86. N. Kalyanam and D.A. Lightner. Tetrahedron Lett. 415 (1979).

87. J.A. Dale, D.L. Dull, and H.S. Mosher. J. Org. Chem. **34**, 2543 (1969).

88. J.D. McDermed, G.M. McKenzie, and A.P. Phillips. J. Med. Chem. **18**, 362 (1975)

89. Crystal structure of lactone 160 was determined by C. Choo and Dr. A.S. Secco, University of Manitoba, personal communication.

90. B.J. Arnold, S.M. Mellows, and P.G. Sammes. J. Chem. Soc. Perkin Trans. I, 1266 (1973).

91. J. Renz, M. Kuhn, and A.V. Wartburg. Liebigs Ann. Chem. 207 (1965).

92. G. Quinkert, Wolf-Dietrich. Weber, U. Schwartz, H. Stark, and H. Baier, G. D3rner. Liebigs Ann. Chem. 2335 (1981).

93. J.R. Falk, L.L. Miller, and F.R. Stermitz. J. Am. Chem. Soc. **96**, 2981 (1974).