ASYMMETRIC SYNTHESIS USING ORTHO-QUINODIMETHANES

by

Guy L. Plourde

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

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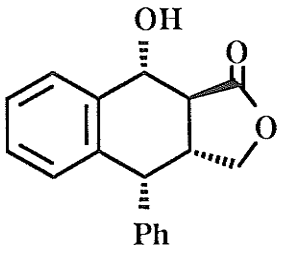
ABSTRACT

A search for a chiral *o*-quinodimethane which can produce high asymmetric induction in Diels-Alder reactions has been carried out. Cycloaddition reactions of dimethyl fumarate with *o*-quinodimethanes bearing α-alkoxy chiral auxiliaries have been shown to proceed diastereoselectively to one face of the *o*-quinodimethanes. Results have been found which are inconsistent with models previously suggested to explain the diastereoselectivity (face selectivity) encountered in these reactions. It has been found that the face selectivity increases for the series of chiral auxiliaries -OCH(Ph)Me, $-OCH(Ph)CH(Me)_2$, and $-OCH(Ph)C(Me)_3$. A mechanism has been proposed to explain the face selectivity in the cycloaddition reactions of these chiral *o*-quinodimethanes. The absolute stereochemistries of the cycloadducts resulting from the cycloaddition of dimethyl fumarate and the chiral *o*-quinodimethanes have been determined to verify the predictions of the model.

The cycloaddition reaction of the fumarate of (S)-methyl lactate with α-hydroxy-*o*-quinodimethane has been found to give a single isomer with diastereoselectivity of at least 95% de. Photolysis of *o*-methylbenzaldehyde, thermolysis of 1-hydroxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide or thermolysis of benzocyclobutenol were used to generate the *o*-quinodimethane. The cycloaddition reaction has been found to be insensitive to the method used in the generation of the *o*-quinodimethane, and identical diastereomeric excess (95% de) and yields (55%) have been obtained in all cases. A 1,2-*trans* stereochemistry has been established for this cycloadduct, which is in contrast to previous work carried out on α-hydroxy-*o*-quinodimethanes, where 1,2-*cis* stereochemistry has always been found for major cycloadducts.

α-Hydroxy-α'-phenyl-*o*-quinodimethane has been found to undergo diastereoselective cycloaddition with the fumarate of (S)-methyl lactate to produce two cycloadducts in a 90:10 ratio. The major cycloadduct (54% isolated yield) has been found to have the same relative stereochemistry (1,2-*trans*) as that of the cycloadduct produced from the reaction with α-hydroxy-*o*-quinodimethane. The minor cycloadduct (5.6% isolated yield) has been found to have the 1,2-*cis*-2,3-*trans* stereochemistry, expected to be produced from an α-phenyl-*o*-quinodimethane. Two analogs of podophyllotoxin **149** and **150**, with the same absolute stereochemistry as the natural product, have been synthesized from the major cycloadduct, in 39% and 16.5% overall yields respectively.



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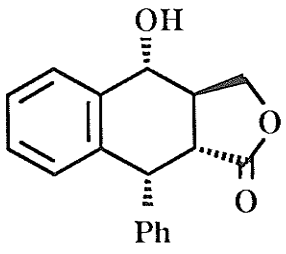

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Compound:

CHAPTER 1

INTRODUCTION

Because this thesis deals with Diels-Alder reactions of *o*-quinodimethanes, the first two Sections of the introduction [**1.1** and **1.2**] will discuss the basics of the Diels-Alder reaction. The remaining Sections will review the work that has been done on *o*-quinodimethanes over the years. This review will include the following Sections: **1.3** Generation of *Ortho*-quinodimethanes; **1.4** E,E- and E,Z-*o*-Quinodimethanes; **1.5** Diastereoselectivity in the Diels-Alder Reaction of *o*-Quinodimethanes; **1.6** Use of *o*-Quinodimethanes in Organic Synthesis; **1.7** Asymmetric Synthesis Using *o*-Quinodimethanes; and finally, **1.8** Objective of this Thesis.

1.1 The Diels-Alder Reaction

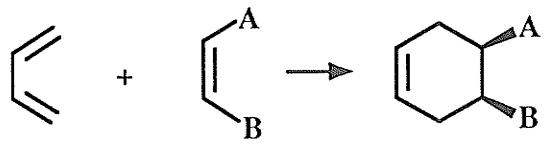
The Diels-Alder reaction was first discovered in 1928 by Diels and Alder[1,2]. The reaction consists of a 4 + 2 cycloaddition of a conjugated diene with an olefin, to generate a cyclohexene ring. The olefin is sometimes referred to as the *dienophile*.

diene **dienophile**

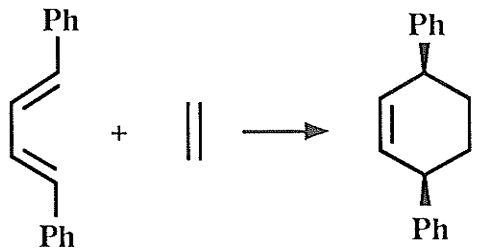
The Diels-Alder reaction is considered to be concerted (pericyclic) with both new bonds being formed simultaneously without intervention of free radical or ionic intermediates. The reaction is normally favoured when electron-withdrawing substituents are located on the dienophile and electron-donating substituents are located on the diene.

When predicting the stereochemistry of the Diels-Alder reaction products, several factors should be noted[3]:

(1) With respect to the dienophile, the reaction is stereoselectively *syn*. This means that substituents which are *cis* to each other in the olefin will also be *cis* in the cyclohexene ring produced. In other words, the reaction takes place on one face of the dienophile.



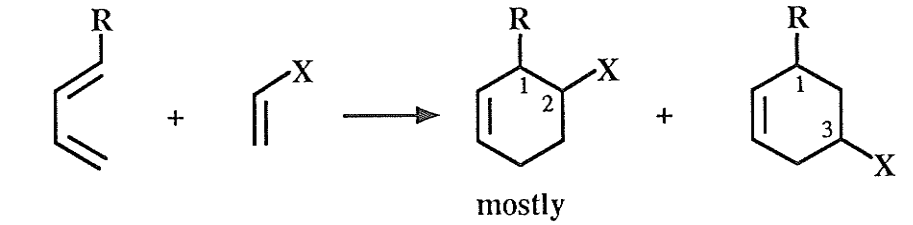
(2) The reaction is also stereoselectively *syn* for 1,4-disubstituted dienes. For example, *trans*,*trans*-1,4-diphenylbutadiene gives only *cis* adducts.



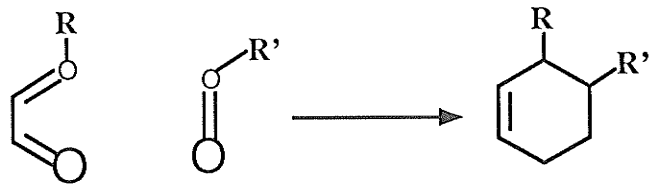
(3) The diene must be able to adopt the *cisoid* conformation. If the diene is in the *transoid* conformation, the reaction cannot take place. The diene must therefore be either frozen into the *cisoid* conformation or be able to achieve it during the reaction if cycloaddition is to take place.

transoid conformation **cisoid conformation**

(4) When both the diene and the dienophile are unsymmetrically substituted, two possible regioisomeric products can arise. Normally the reactions are quite regioselective and one product predominates over the other. Disubstituted cycloadducts with 1,2- and 1,4-regiochemistry are usually favoured over 1,3-adducts.

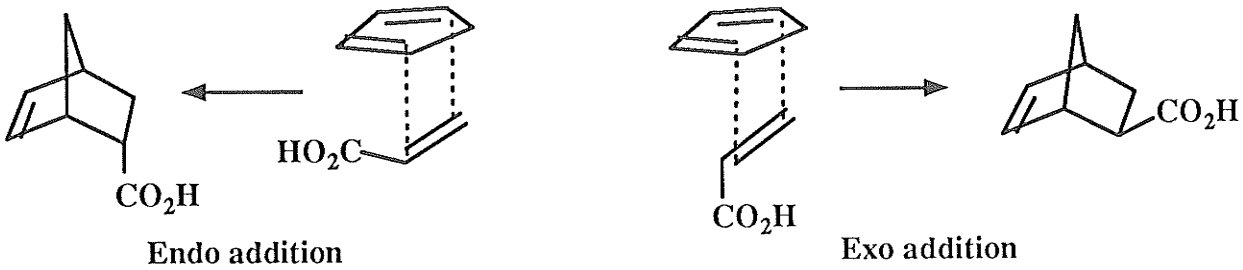


Regioselectivity in Diels-Alder reactions can usually be predicted using frontier molecular orbital theory (FMO)[4]. The rule is: *reactions are allowed only when all overlaps between the highest-occupied molecular orbital* (**HOMO**) *of one reactant and the lowest-unoccupied molecular orbital* (**LUMO**) *of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*[3]. The predictions are based on the most favorable interaction of the **HOMO** of the diene and the **LUMO** of the dienophile. In summary, 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 generally add head-to-head with electron-withdrawing substituted dienophiles. In the case where the primary orbital effects are almost equal, the secondary orbital effect may also affect the regioselectivity[5,6]. If strong orbital effects are non-existent, dipolar interactions may come into play.



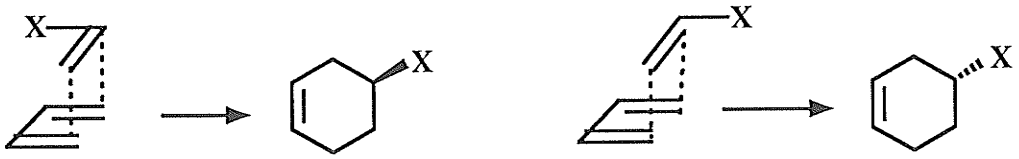
head-to-head addition

(5) For cyclic dienes reacting with unsymmetrical dienophiles, two possible modes of addition can arise. If the substituent on the dienophile is located under the ring, the addition is referred to as *endo*. However, when the substituent on the dienophile is extending away from the diene it is referred to as an *exo* addition. Generally, the addition is predominantly *endo*.



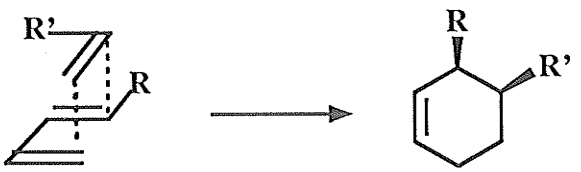
Endo addition **Exo addition**

In the case of non-cyclic dienes, these terms (*endo* and *exo*) are not normally used to describe the products of the reaction. However, they are used to describe the two possible transition states of the reaction. Type A and type B transition states shown below correspond to the *endo* and *exo* modes of addition respectively.

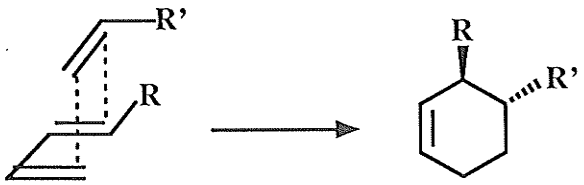


Type A **Type B**

With substituted dienes and substituted dienophiles, isomeric products can be obtained depending on the type of addition (*endo* or *exo*) taking place. The primary orbital interactions (between the atoms to which new bonds are forming) which usually control the regioselectivity [see (4)], do not control the diastereoselectivity (*endo vs exo*). Normally secondary orbital and steric interactions play that role. Hence, favorable secondary orbital overlap between the substituent on the dienophile and carbon 2 of the diene leads to predominantly *endo* products[5,7].



Endo Addition



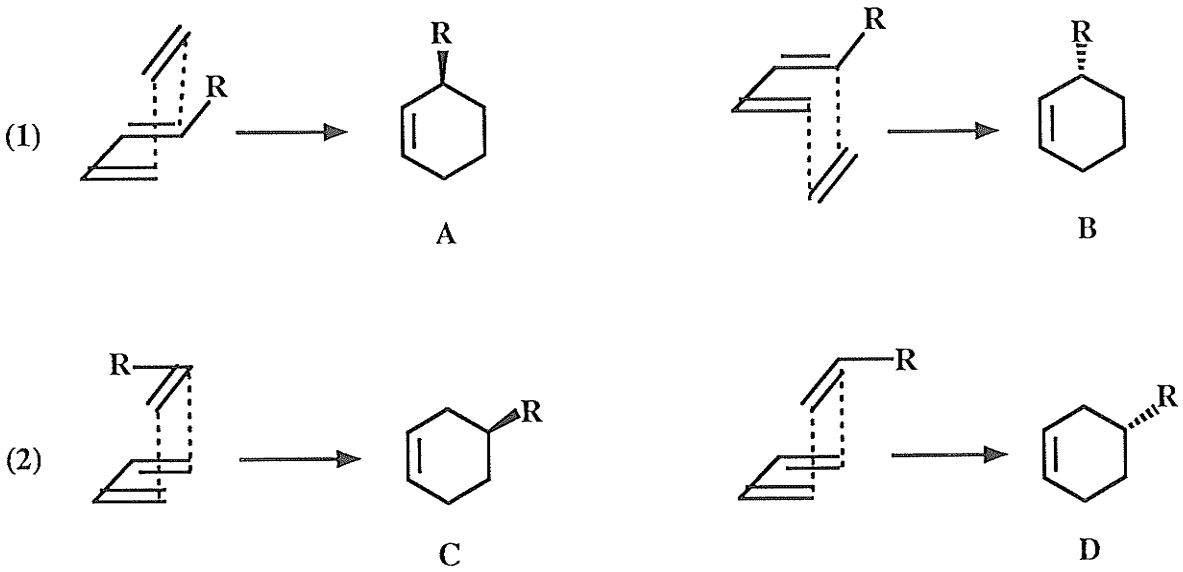
Exo Addition

1.2 Asymmetric, Enantioselective and Diastereoselective Reactions

As the demands for accessibility to enantiomerically pure compounds grow, the synthetic chemist is more and more challenged to find new routes to satisfy those demands. One of the ways of producing enantiomerically pure compounds is by an *asymmetric reaction.* The definition of such a reaction is *any reaction in which an achiral substrate, or achiral unit within a molecule, is converted to a chiral substrate or unit with one of the chiral forms being predominantly produced*[8]. Terminology related to asymmetric reactions can be sometimes quite confusing. A reaction which is *asymmetric* could also be *enantioselective* or *diastereoselective* or both. So, when does one use the terms *asymmetric*, *enantioselective* and/or *diastereoselective* to describe a reaction?

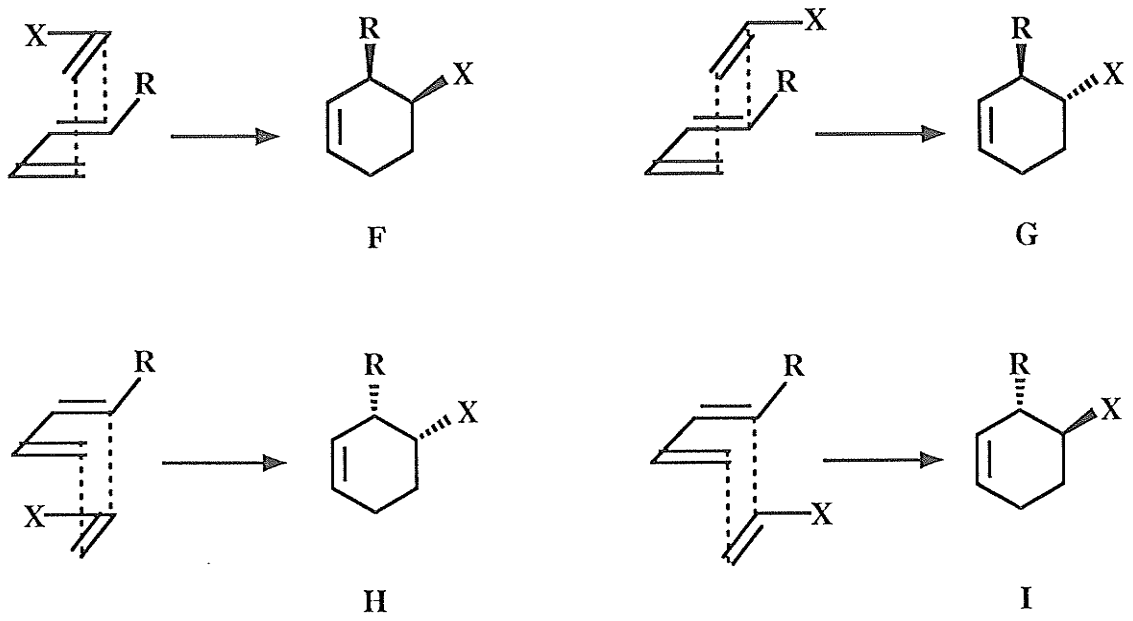
Let us first consider the Diels-Alder reaction in which only one substituent is

present, either at the 1 position on the diene or on the dienophile (there is no chiral center in the substituent group **R**).



In each case, only two enantiomeric products can arise: **A/B** and **C/D**. If products **A** and **B** in (1), as well as **C** and **D** in (2), are produced in equal amounts, the reactions are neither *asymmetric* nor *enantioselective*. The reactions are called *racemic* reactions. If either **A** or **B** in (1), or **C** or **D** in (2), is formed predominantly, then the reactions are *asymmetric* as well as *enantioselective*. In this case, the term *diastereoselective* cannot apply since only one chiral center is produced.

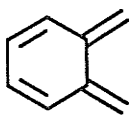
When both the diene and the dienophile are substituted, the situation gets more complicated since four stereoisomers can be produced. Among the four stereoisomers, there are two pairs of enantiomers: **F/H** and **G/I**. The other possible pairs (**F/G**, **F/I**, **H/G**, **H/I**) are diastereomers in which only one of the two chiral centers is different.



With respect to the reactions above, a *diastereoselective* addition is one in which either the *cis* product (**F/H**) or the *trans* product (**G/I**) is formed predominantly. This is true regardless of whether **F/H** or **G/I** are racemic or not. When the ratio of **F/H** or **G/I** is different than one, the reaction is then *enantioselective*. To obtain *asymmetric induction* in the creation of a new chiral center, the reaction must produce the new chiral center with predominance of one absolute configuration. As can be seen in the above diagram, the control of the absolute configuration at the newly created centers is directly related to the faces at which the dienophile and diene react. If neither the diene nor the dienophile is substituted with a chiral auxiliary, the cycloaddition has to be *enantioselective* in order to be classified an *asymmetric* addition. If a chiral auxiliary of one absolute configuration (homochiral) is introduced either on the diene or dienophile, **F**, **G**, **H** and **I** become diastereomers of each other. When one of these four diastereomers is produced in majority over the others, the reaction is *asymmetric* (and *diastereoselective*) since there exists a predominance of one absolute configuration at the newly created centers.

1.3 Generation of *Ortho*-quinodimethanes

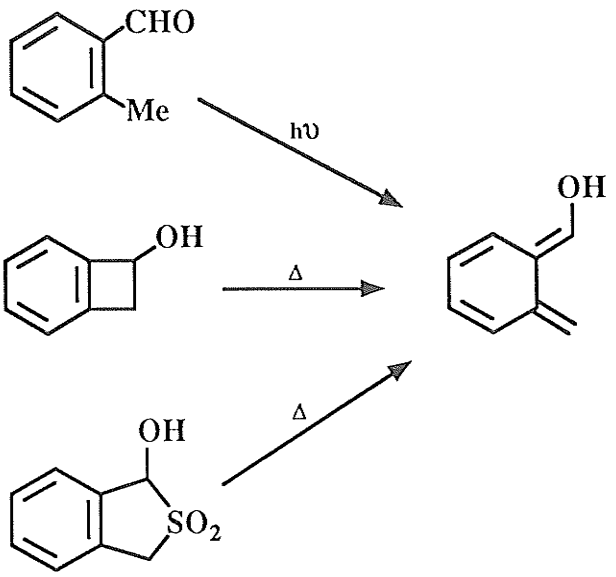
The existence of *ortho*-quinodimethane (*o*-QDM) **1** was verified by chemists about 20 years ago, although the participation of such a molecule as a reaction intermediate was suggested as early as 1957[9]. This compound is also known as *o*-quinodimethide and *o*-xylylene, however, to avoid confusion, only the name *o*-quinodimethane will be used in this thesis. Its discovery, characterization and reactivity will not be discussed here and the reader is referred to a recent review article for further reading material on these subjects[8].



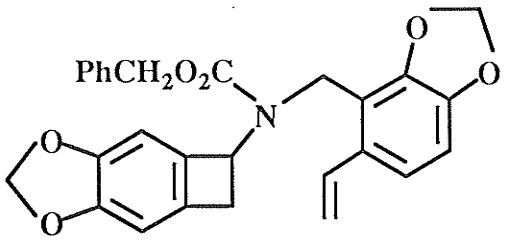
1

Many ways have been developed in the past to generate various substituted and unsubstituted *o*-quinodimethanes. 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 cycloreversion; (5) photochemical expulsion of carbon monoxide or nitrogen; and (6) photoenolization and photorearrangement. These methods were also reviewed by Charlton and Alauddin and are not discussed here except for selected comments[8].

Among these methods, the three most frequently used have been the photoenolization of aldehydes and ketones, the thermolysis of benzocyclobutenes and the thermal elimination of sulfur dioxide from sulfones.



They all possess advantages as well as disadvantages. The most serious drawback in the use of benzocyclobutenes is without a doubt the difficulty of their synthesis[10,11]. For example, although the benzocyclobutene **2** used by Oppolzer could be prepared, several steps were required for its synthesis[10]. Jung *et al.* had difficulty in preparing benzocyclobutenol **3** even though many approaches were used[11]. Benzocyclobutenol **3** has since been synthesized by Durst *et al.*[12], and Jung *et al.*[13]. On the other hand, it would appear that benzocyclobutenes are more versatile precursors of *o*-quinodimethanes, trapping dienophiles more efficiently[14,15].



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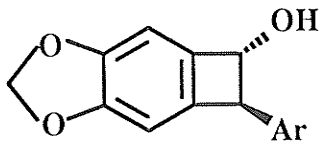
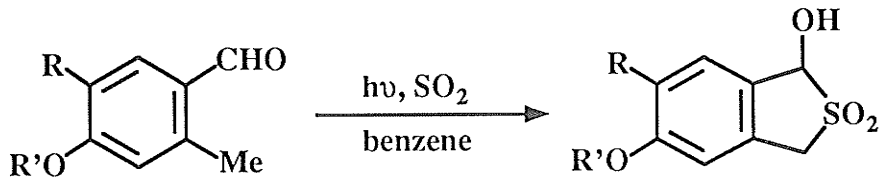


3

Ar= 3,4,5-trimethoxyphenyl

Photochemical production of *o*-quinodimethanes has been used frequently. The advantages of this method is the availability of the precursors, aldehydes or ketones, as well as the stability of these precursors. On the other hand, other photochemical reactions can compete with the formation of *o*-quinodimethanes. *Cis-trans* isomerization of a disubstituted dienophile can also occur, by sensitization from the excited state of the *o*-quinodimethane precursor, resulting in a potential increase in the number of cycloadducts which can eventually be produced[15,16]. Also, not all *o*-quinodimethanes can be formed by photolysis of *o*-methylbenzaldehyde, as shown recently by Charlton and Koh[25]. In that particular case, it was thought that the oxy substituents on the aromatic ring were affecting the excited state of the aldehyde. The authors changed the substituents to acyloxy and sulfonyloxy, as that should reduce the electron donor character of the oxy substituents. After this change they were able to trap the *o*-quinodimethanes with SO_2 to form the sulfones **4**.

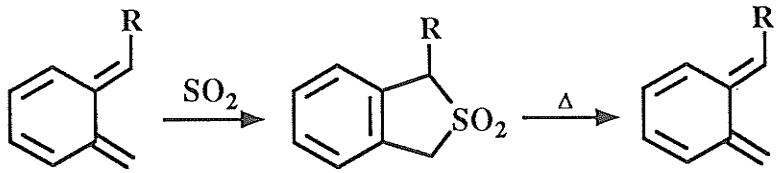


4

R=H; R'=Me (no reaction)
R=OMe; R'=Me (no reaction)
R=H; R'=Ac (no reaction)
R=H; R'=Ms
R=H; R'=Ts
R=OMs; R'=Ms
R=OTs; R'=Ts

Sulfones such as **5** also seem to be preferred *o*-quinodimethane precursors. They can easily be formed by trapping the *o*-quinodimethane itself with sulfur dioxide, as

demonstrated first by Cava *et al.*[17,18]. The *o*-quinodimethanes can then be regenerated by thermolysis of the sulfones. A review article on this reaction appeared in 1980 and since then[10], other articles on this source of *o*-quinodimethanes have been published[6,15,19-29]. The sulfones are usually stable and can also be substituted which is certainly an advantage over the photochemical reaction. This appears to be a straightforward route to *o*-quinodimethane precursors from simple starting materials[6,19,22-29].

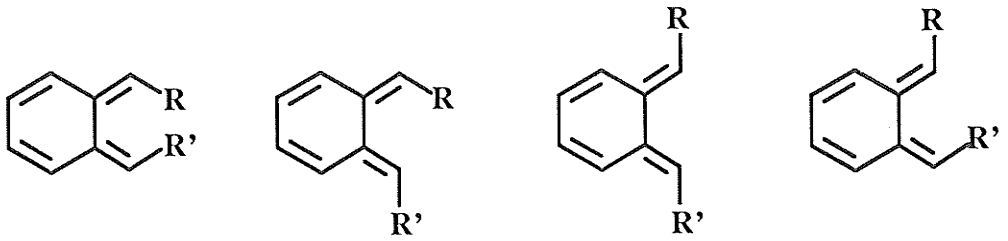


5

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 substituents needed, as well as the tolerance of those substituents to the reaction conditions. One must therefore analyze each method carefully before choosing a particular one.

1.4 E,E- and E,Z-*o*-Quinodimethanes

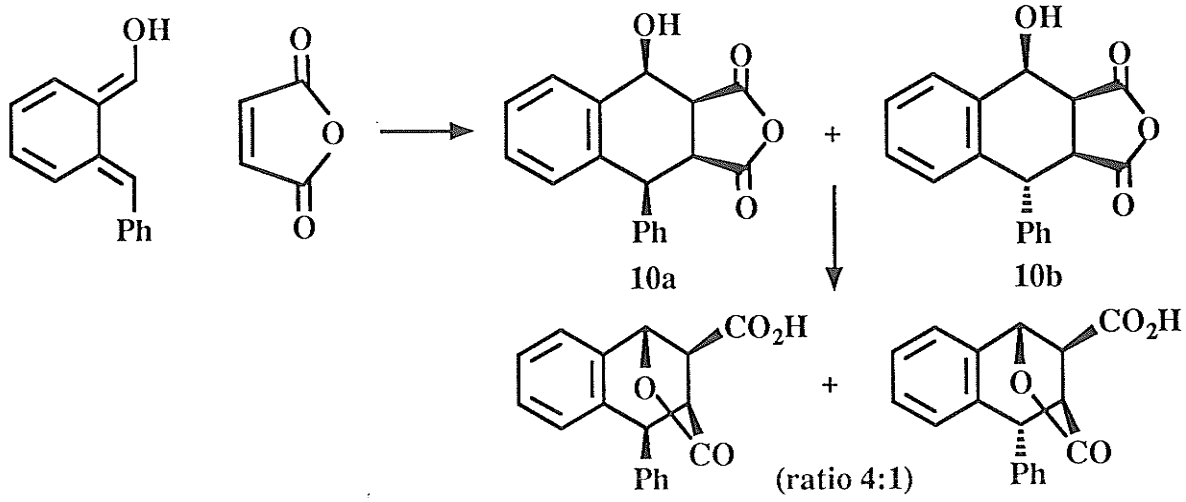
Whether the generation of α,α'-disubstituted *o*-quinodimethanes is performed photochemically or thermally, four geometric isomers can arise. They have the following structures: **6** (Z,Z), **7** (Z,E), **8** (E,E) and **9** (E,Z).



6 7 8 9

Of these four isomeric structures, **8** is the least hindered and should be easiest to form if only steric factors are considered. On the other hand, **6** is the most hindered and should be the most difficult to form. The other two, **7** and **9**, have limited hindrance and their formation should depend on the size of the substituents[30].

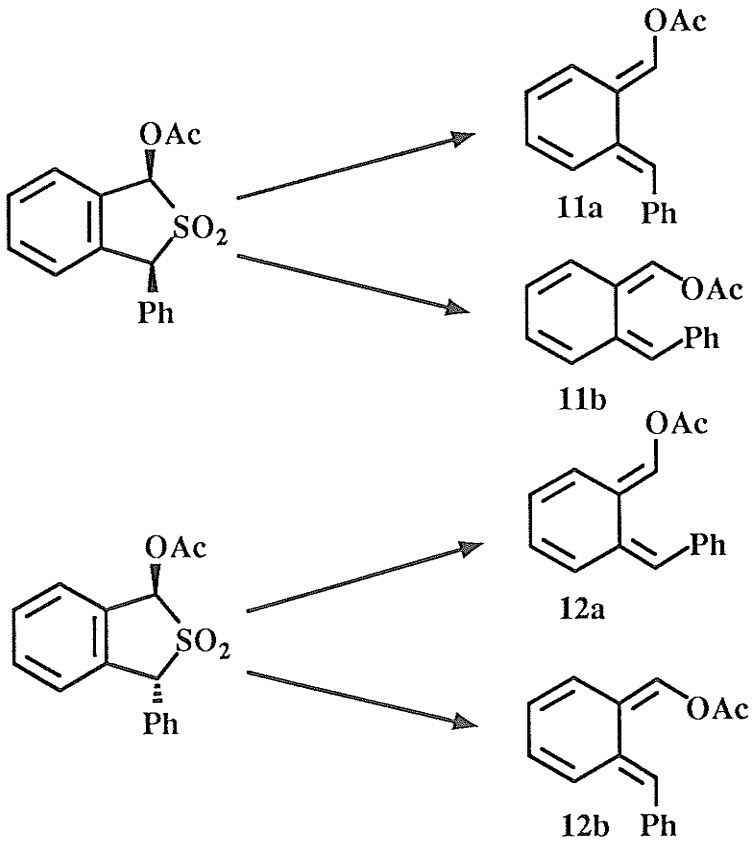
Earlier publications have shown that both the E,E- and E,Z-*o*-quinodimethanes can be formed during photochemical reactions. Sammes *et al.* found that both the E,E- and the E,Z-α-hydroxy-α'-phenyl-*o*-quinodimethanes were generated and could be trapped with maleic anhydride to give a mixture of cycloadducts **10a** and **10b**[31]. They also demonstrated the reluctance of the oxy-substituent to occupy the Z-position in *o*-quinodimethanes[14].



(ratio 4:1)

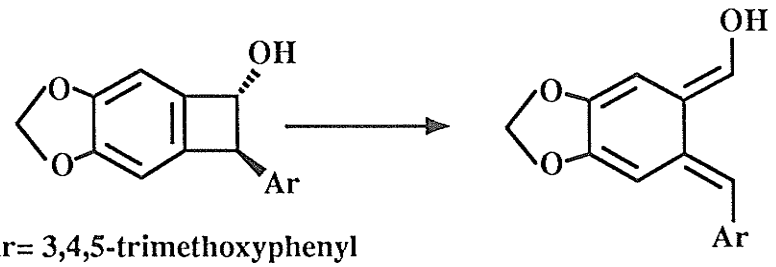
Photochemical generation of an *o*-quinodimethane, similar to that discussed above, was also performed by Durst and Glinski[32]. In this particular case, however, only the E,E-*o*-quinodimethane was trapped with dimethyl fumarate.

Charlton *et al.* later generated α-oxy-α'-phenyl-*o*-quinodimethanes and studied the reactivity of both the E,E- and E,Z-forms[6]. Upon thermolysis of the appropriate sulfones, the four different *o*-quinodimethanes **11a**, **11b**, **12a**, **12b** could, in theory, be produced, depending on the configuration of the precursor used (*cis* or *trans*).



However, only **11a (E,E)** was assumed to be formed from the *cis* sulfone on the basis of steric hindrance in the **Z,Z** conformation **11b**. In addition, *o*-quinodimethane **12a (E,Z)** was assumed to be formed from the *trans* sulfone instead of **12b (Z,E)** on the basis of the arguments put forward by Sammes who noted the reluctance of the oxy substituent to occupy the Z-position in *o*-quinodimethanes[14].

In the case where benzocyclobutenes are used as precursors of *o*-quinodimethanes, the substituents have to be *trans* on the butene ring to produce E,E-*o*-quinodimethanes as shown by Durst *et al.* in their synthesis of podophyllotoxin[12].



Ar= 3,4,5-trimethoxyphenyl

Since there is no contradictory evidence, it is assumed that both the E,E- and E,Z-*o*-quinodimethanes are generally formed in photochemical reactions. However, the E,E-form is more reactive and depending on the dienophile used might be the only one trapped. Thermal reactions, on the other hand, always produce either E,E- or E,Z-*o*-quinodimethanes depending on the stereochemistry of the precursor. As far as the work presented in this thesis is concerned, it is assumed that E,E-*o*-quinodimethanes are produced and are the reacting species unless otherwise noted.

1.5 Diastereoselectivity in the Diels-Alder Reaction of *o*-Quinodimethanes

In order to make generalizations about the diastereoselectivity encountered in the Diels-Alder reaction of *o*-quinodimethanes, it is helpful to classify all the reactions found in the literature according to the type of dienophile and diene used. This is because the diastereoselectivity is dependent on the substitution pattern on the diene and dienophile. As a result, the following literature survey consists of six subsections (**A-F**) which include all the variations encountered. In the case of disubstituted dienes, α and α' represent the positions of the substituents as depicted in Figure 1. The terminology (*endo* and *exo*) used is the same as defined in Section **1.1.**

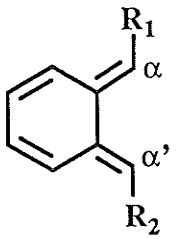
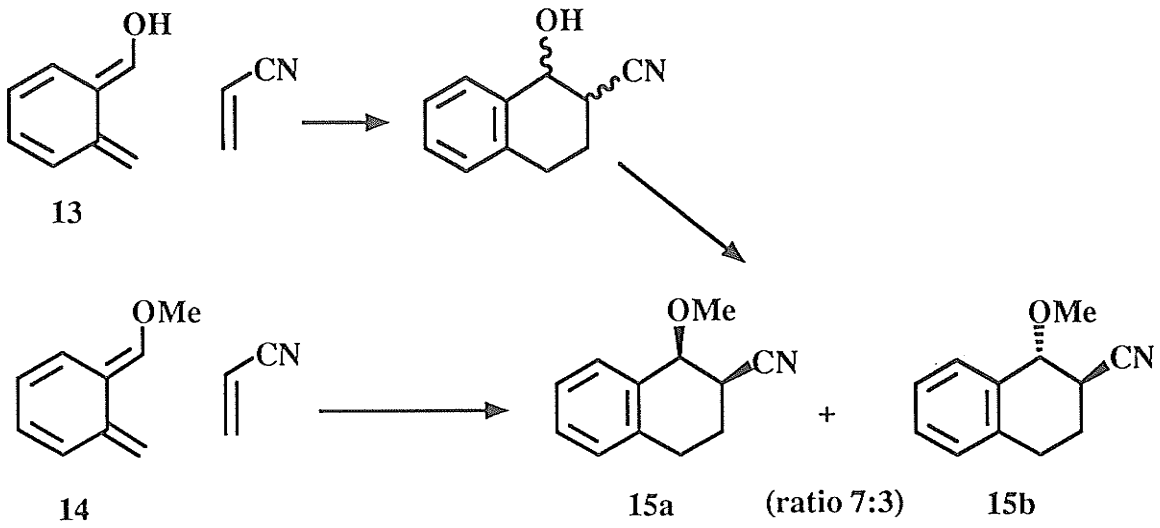


Figure 1. Substitution pattern of disubstituted *o*-QDMs.

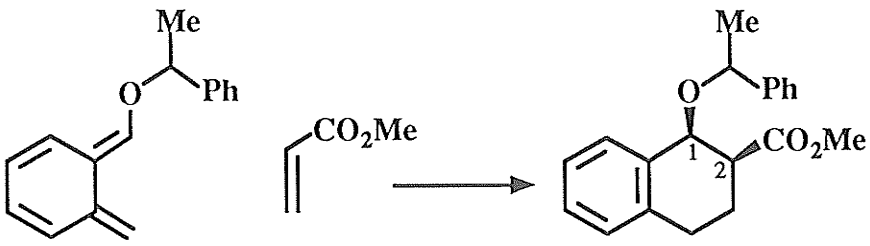
A. Monosubstituted dienes and monosubstituted dienophiles

Only a few examples could be found which fit this category. The first one represents the reaction between the hydroxy-*o*-quinodimethane **13** and acrylonitrile reported by Sammes *et al.* in 1974[33].



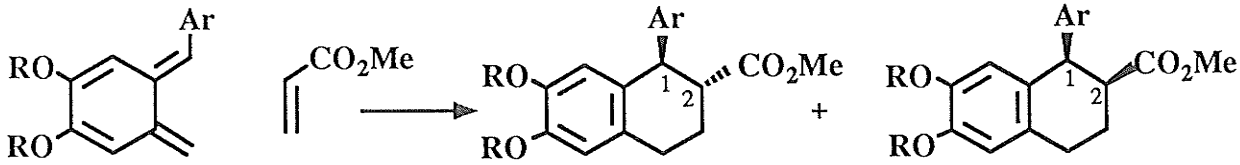
The reaction was highly regioselective giving only 1,2-adducts but the diastereoselectivity could not be determined from the mixture of cycloadducts. It was therefore transformed into its methoxy derivatives **15a** and **15b** from which the isomeric ratio (7:3) could be obtained, the *endo* adducts **15a** being the major isomer in the mixture. Methoxy adducts (**15a** and **15b**) were also formed directly from the *o*-quinodimethane **14** also giving, in this case, a 7:3 ratio of isomers. The authors attributed the low selectivity of this reaction to the known fact that there is less possible secondary orbital overlap for the addition of acrylonitrile than for, for example, the addition of maleic anhydride.

The following reaction also gave predominantly *endo* adducts (1,2-*cis*). This reaction, reported by Charlton in 1986[29], involved the cycloaddition of methyl acrylate with the *o*-quinodimethane **16** which bore a chiral auxiliary (the asymmetric induction obtained in this reaction is not discussed here as this will be the subject of Section **1.7** of this Chapter).



16

The following case is, however, in contradiction with the first two. The dienophile, methyl acrylate, used in this experiment was identical to that of the previous example and was reacted with the *o*-quinodimethane **17**.



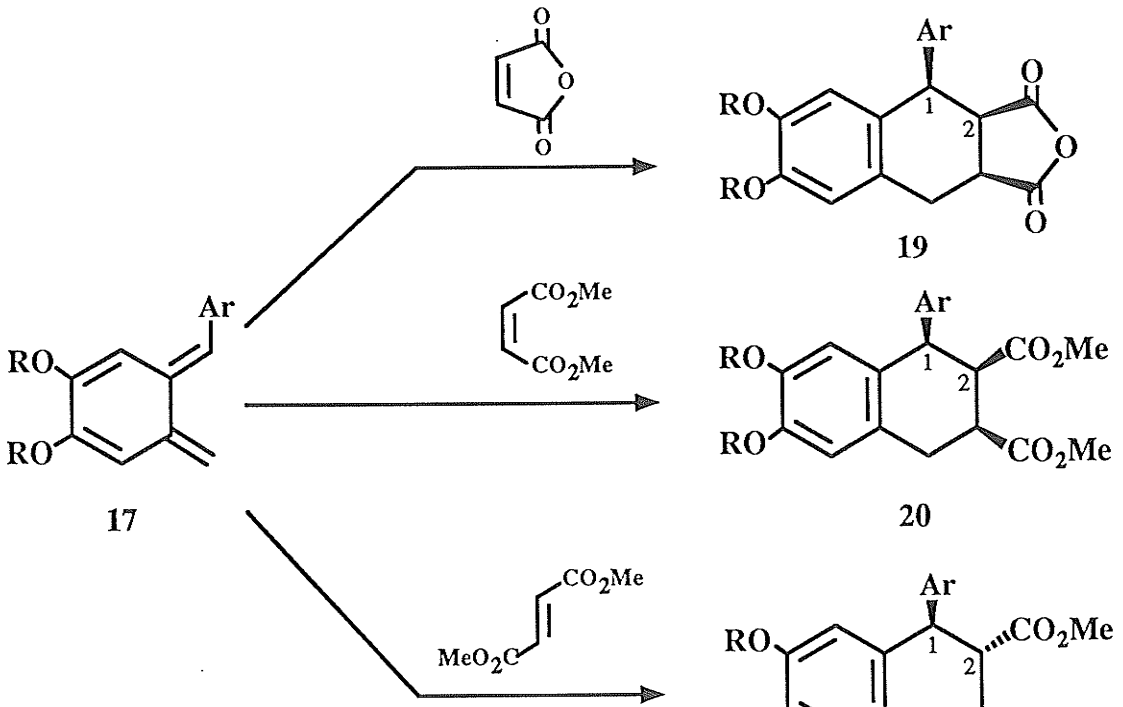
17 **18a** **(ratio 8:2)** **18b**

R=R= -CH_2-; Ar=3,4,5-trimethoxyphenyl
R=Me; Ar=3,4-dimethoxyphenyl

The outcome of the reaction was surprising to the authors since the expected 1,2-*cis* adduct **18b** was obtained only as a minor product[20]. They repeated the reaction under different conditions and finally concluded that the Diels-Alder reaction must be reversible under the elevated temperature conditions used, yielding the thermodynamically more stable product **18a**. Later, Charlton and Durst made similar observations using different dienophiles and a different *o*-quinodimethane, but concluded that the diastereoselectivity was not the result of a reversible Diels-Alder reaction [see subsection B][34].

B. Monosubstituted dienes and disubstituted dienophiles

The following subsection has, compared to the previous one, many more examples from which one can draw generalizations. The first case illustrated here is a continuation of the last case of subsection **A**. The *o*-quinodimethane **17**, which was previously reacted with methyl acrylate, was also reacted with maleic anhydride, dimethyl maleate and dimethyl fumarate.

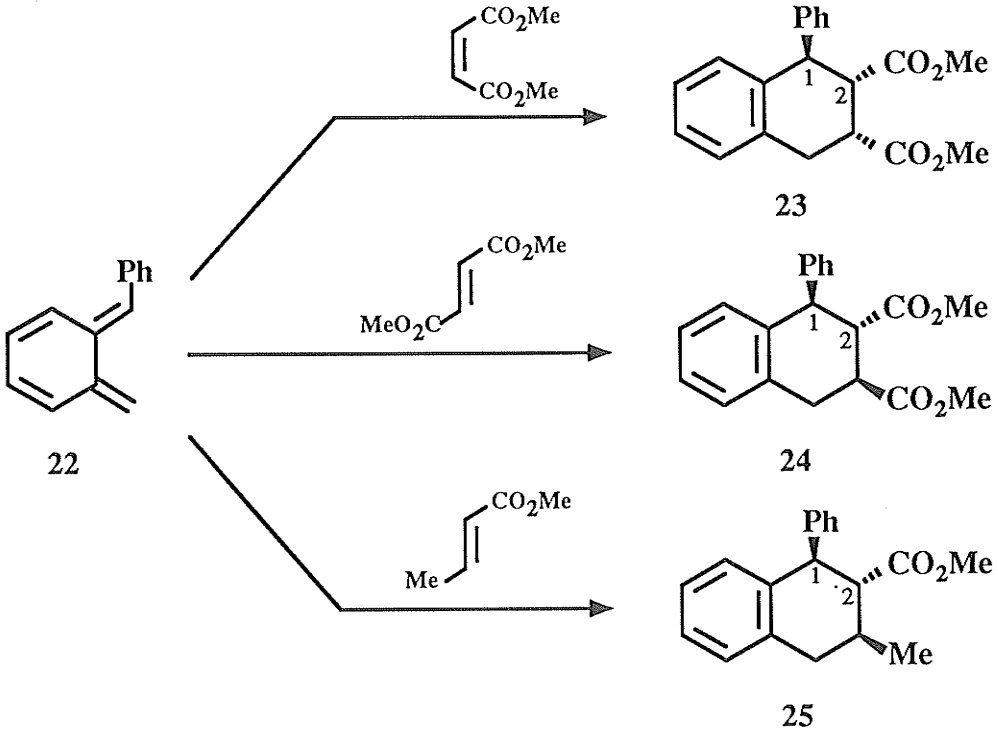


R=R=-CH_2-; Ar=3,4,5-trimethoxyphenyl
R=Me; Ar=3,4-dimethoxyphenyl

The authors observed a different stereochemistry for the adduct **21**, 1,2-*trans* (*exo*), than for **19** and **20**, 1,2-*cis* (*endo*)[20]. Their explanation regarding these differences was the

same as for the case of the reaction with methyl acrylate [see **1.5A**]. They concluded that, in the case of the addition of dimethyl fumarate, under the conditions used, the reaction was reversible, such that the thermodynamic product was preferred.

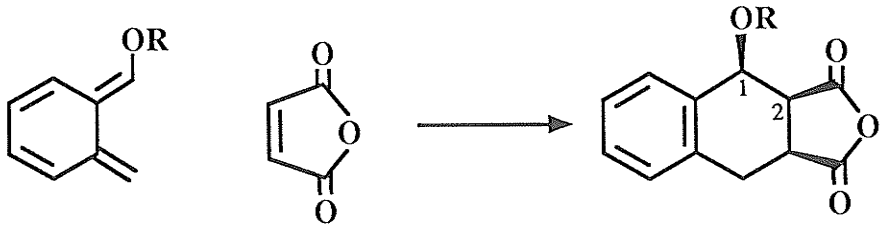
Contradictory conclusions were later published by others, although a slightly different *o*-quinodimethane **22** was used[22,34]. It was added to dimethyl maleate, dimethyl fumarate and methyl crotonate.



Exo adducts (1,2-*trans*) **23**, **24** and **25** were predominantly observed. Furthermore, the reaction with methyl crotonate was highly regioselective giving adduct **25** with the carbomethoxy group located at position 2 and a diastereoselectivity (1,2-*trans*) reported to

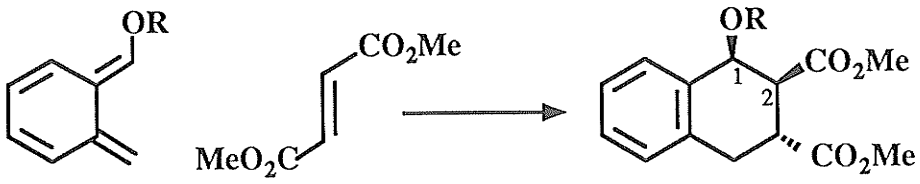
be at least 90%. The major difference between this work and that performed with the *o*-quinodimethane **17**, is the 1,2-*cis* (*endo*) configuration obtained in the reaction of **17** with dimethyl maleate, compared to the 1,2-*trans* (*exo*) configuration obtained from the reaction with **22**. Since the work with **22** was performed at 80°C, the authors claimed that no reversibility of the Diels-Alder reaction was possible and that the configuration of the adducts was 1,2-*trans* arising from a preferred *exo* transition state.

Agreement seems to take place when maleic anhydride is used as dienophile. In all the literature reports, this dienophile cycloadds with *o*-quinodimethanes in the *endo* fashion giving in all cases 1,2-*cis* adducts no matter what the substituent on the diene. Reports using hydroxy-*o*-QDM **13**[14,31,35,36], methoxy-*o*-QDM **24**[14,36], alkoxy-*o*-QDM **26**[29], and acetoxy-*o*-QDM **27**[14,36] gave the same type of cycloadduct.



13 R=H
14 R=Me
26 R=alkyl
27 R=Ac

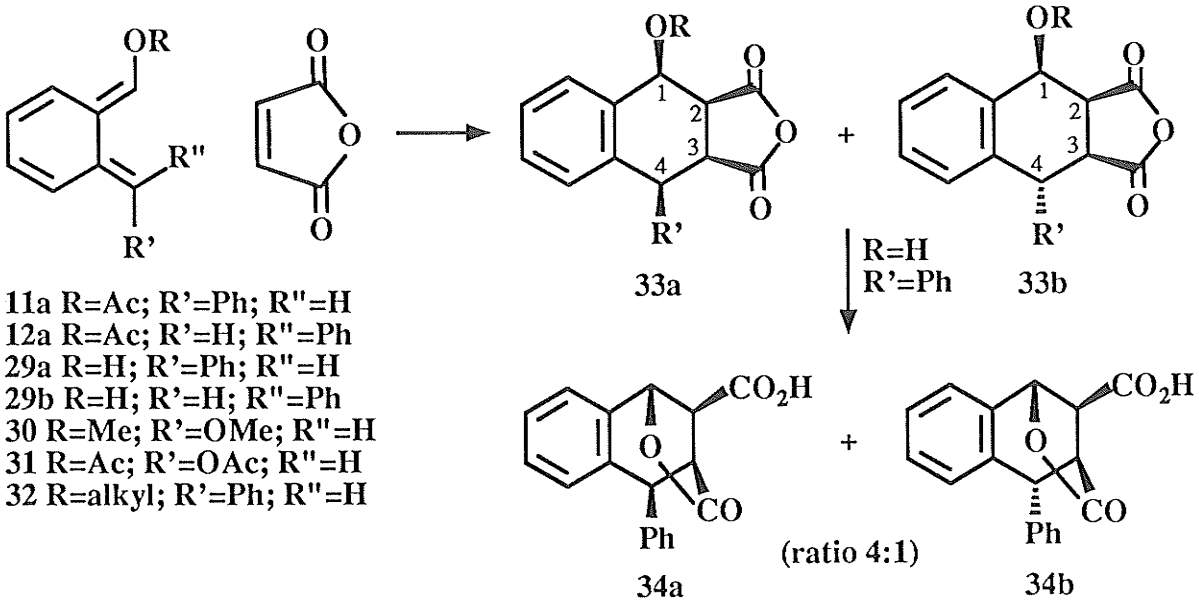
This is also true for the cycloadditions performed with dimethyl fumarate as the dienophile. Only *endo* addition (1,2-*cis*) is obtained regardless of the substituents on the diene[19,29], except, of course, for α-phenyl-*o*-QDM **22** and α-aryl-*o*-QDM **17** which were discussed previously in this subsection.



14 R=Me
26 R=alkyl
27 R=Ac
28 R=TBDMS

C. α,α'-Disubstituted dienes and disubstituted dienophiles

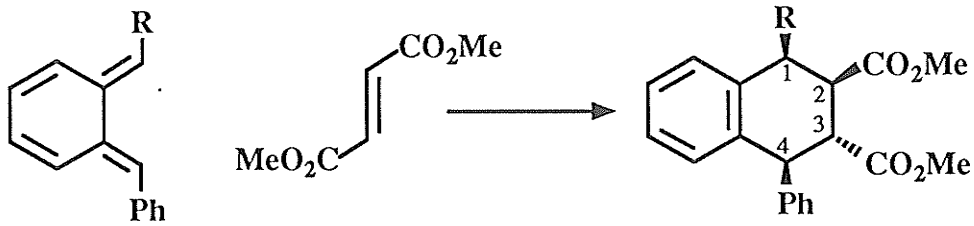
As was the case for the cycloaddition of monosubstituted dienes, the reactions of maleic anhydride with α,α'-disubstituted *o*-quinodimethanes afford only one type of adduct. Once again the substituents on the diene do not affect the outcome of the reaction and 1,2-*cis* adducts (*endo*) **33a** are obtained with α-acetoxy-α'-phenyl-*o*-QDM **11a**[6], α-hydroxy-α'-phenyl-*o*-QDM **29a**[31], α-methoxy-α'-methoxy-*o*-QDM **30**[37], α-acetoxy-α'-acetoxy-*o*-QDM **31**[37] and α-alkoxy-α'-phenyl-*o*-QDM **32**[29].



11a R=Ac; R'=Ph; R"=H
12a R=Ac; R'=H; R"=Ph
29a R=H; R'=Ph; R"=H
29b R=H; R'=H; R"=Ph
30 R=Me; R'=OMe; R"=H
31 R=Ac; R'=OAc; R"=H
32 R=alkyl; R'=Ph; R"=H

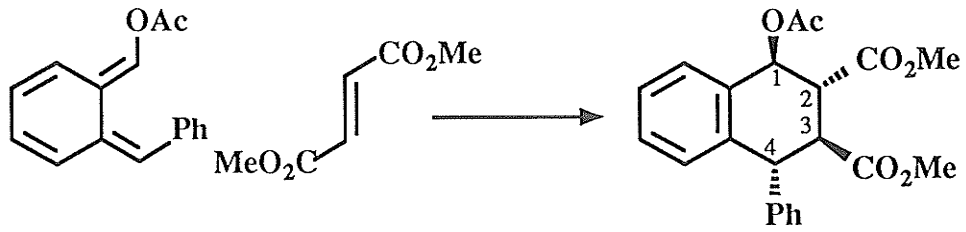
The 1,2-*cis* adducts (*endo*) **33b** were obtained from the E,Z-*o*-quinodimethanes **12a** and **29b**[6,31]. Sammes *et al.* actually obtained both cycloadducts **33a** and **33b** as a 4:1 mixture when *o*-benzylbenzaldehyde was irradiated in presence of maleic anhydride (the structure of **33a** and **33b** (R=H, R'=Ph) were confirmed by conversion to **34a** and **34b**). They explained the two products by proposing that the photolysis had produced the two *o*-quinodimethanes, **29a (E,E)** and **29b (E,Z)**[31]. Sammes' proposal was re-enforced when similar observations on the diastereoselective additions of E,E- and E,Z-*o*-quinodimethanes **11a** and **12a** to maleic anhydride were later made by Charlton *et al.*[6].

Dimethyl fumarate was also reacted with various α,α'-disubstituted *o*-quinodimethanes. The results from the reactions with, α-acetoxy-α'-phenyl-*o*-QDM **11a**[6], α-alkoxy-α'-phenyl-*o*-QDM **32**[29], α-thiophenyl-α'-phenyl-*o*-QDM **35**[28] and α-morpholine-α'-phenyl-*o*-QDM **36**[28] show that cycloadditions are taking place from an *endo* transition state leading to 1,2-*cis* stereochemistry.



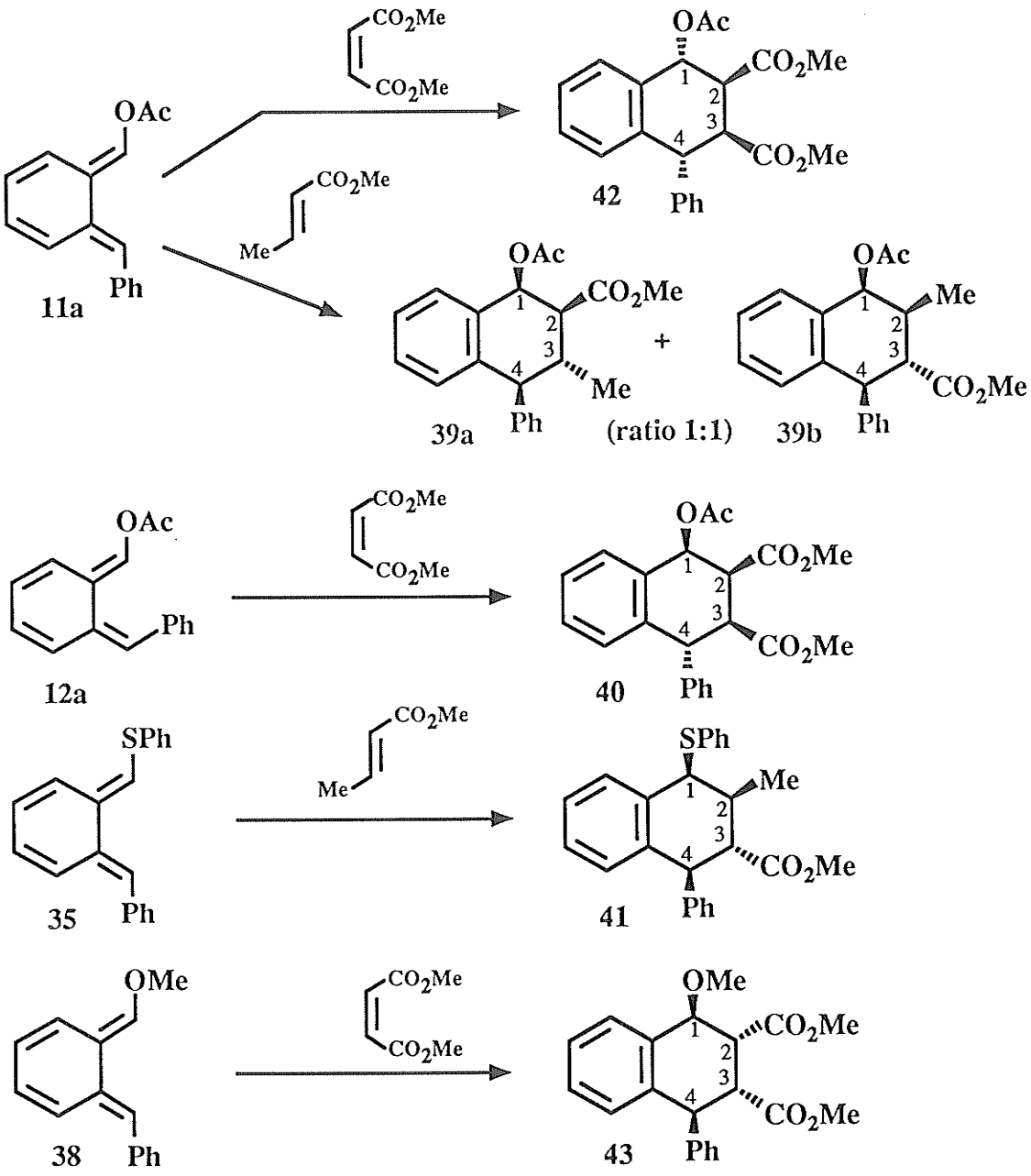
11a R=OAc
32 R=O-alkyl
35 R=SPh
36 R=morpholine

The only time where this reaction did not give *endo* addition is when the E,Z-*o*-quinodimethane **12a** was used giving *exo* addition. The authors suggested that steric factors controlled the outcome of the reaction[6]. The favoured transition state in this case would be one which would produce a cycloadduct **37** with the 3-carbomethoxy and the 4-phenyl *trans* to each other. The reaction for the E,E-*o*-quinodimethanes can produce this 3,4-*trans* stereochemistry in the adducts via an *endo* transition state. For the E,Z-*o*-quinodimethanes, the steric constriction forces the reaction to proceed via an *exo* transition state.



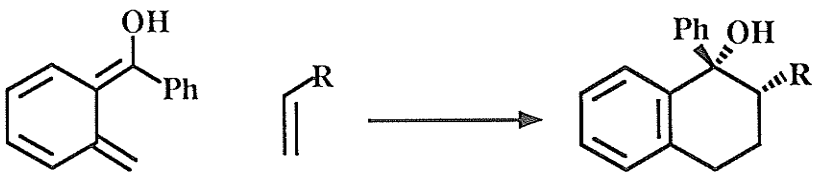
12a (E,Z-o-QDM) **37**

Methyl crotonate and dimethyl maleate also added to *o*-quinodimethanes **11a**[6], **12a**[6], **35**[28] and **38**[22] in an *endo* mode giving 1,2-*cis* adducts **39a**, **39b**, **40** and **41**. However, the cycloaddition of dimethyl maleate proceeded primarily through the *exo* transition state with *o*-quinodimethane **11a** (E,E-*o*-QDM), generating the 1,2-*trans*-3,4-*trans* stereochemistry in the cycloadduct **42**[6], and also with the *o*-quinodimethane **38** giving cycloadduct **43**[22]. The reaction with methyl crotonate and **11a** was not regioselective giving almost a 1:1 mixture of 2-carbomethoxy-3-methyl **39a** and 2-methyl-3-carbomethoxy **39b**. Cycloaddition with *o*-quinodimethane **35**[28] was regioselective.

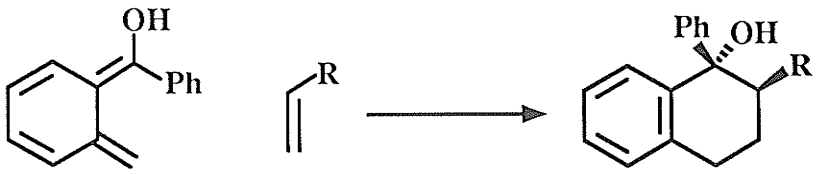


All the reactions encountered in the following subsections (**D**,**E**,**F**) have similarities which need to be noted. In all the cases the substituents at the "α" position are identical, a hydroxyl and a phenyl group. The E-form of the *o*-quinodimethanes, as

depicted below, is assumed in all cases. Because of the two substituents, it is important to define *endo* and *exo* additions. In these cases, the *endo* addition will refer to the transition state generating the 1,2-*cis* stereochemistry between the hydroxyl group and the substituent on carbon 2. The *exo* addition will be, by definition, the opposite and the cycloadduct generated will have the hydroxyl and the substituent on carbon 2 *trans* to each other as depicted below.



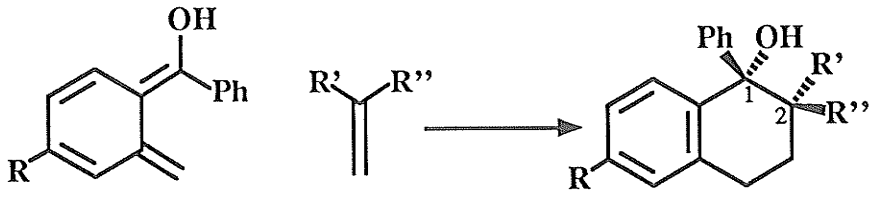
Endo Addition



Exo Addition

D. α,α-Disubstituted dienes and monosubstituted dienophiles

The reactions were found to be regioselective with all three dienophiles, methyl acrylate, acrylonitrile and methyl methacrylate[38]. However, the stereochemistry could not be established experimentally and *endo* addition was assumed to have taken place on the basis of previous examples [see F] giving the product with the carbomethoxy and the phenyl groups *trans* to each other[39].

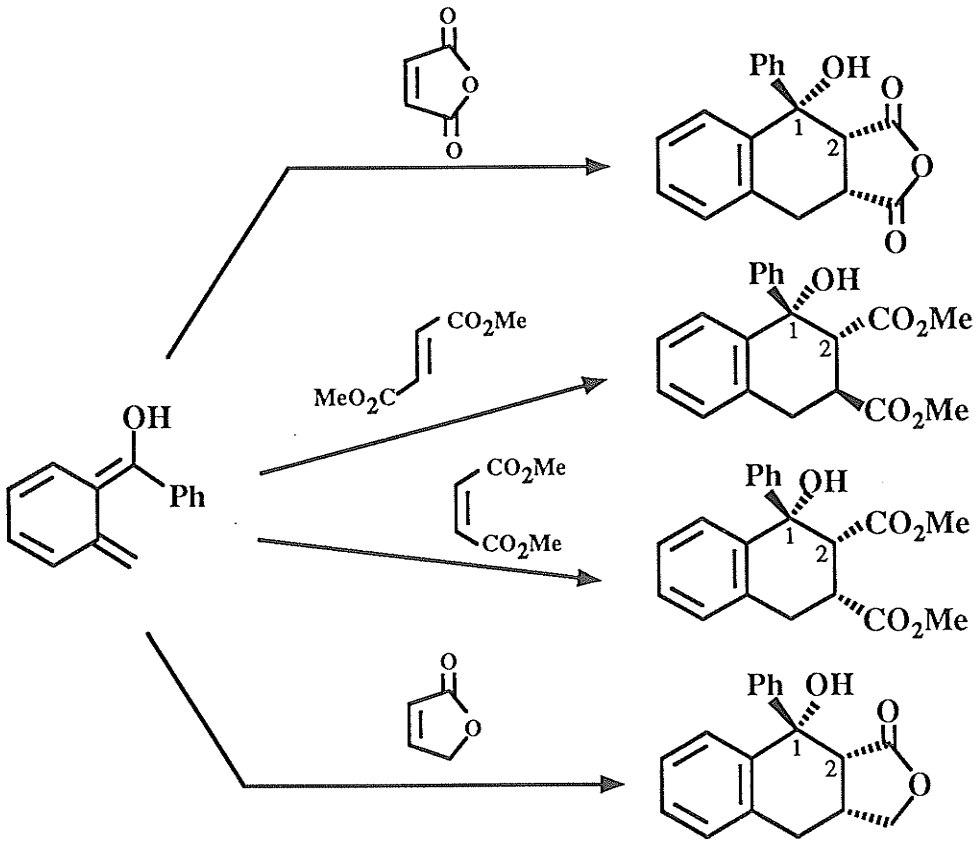


R=H,Me

R'=CO_2Me; R''=H
R'=CN; R''=H
R'=CO_2Me; R''=Me

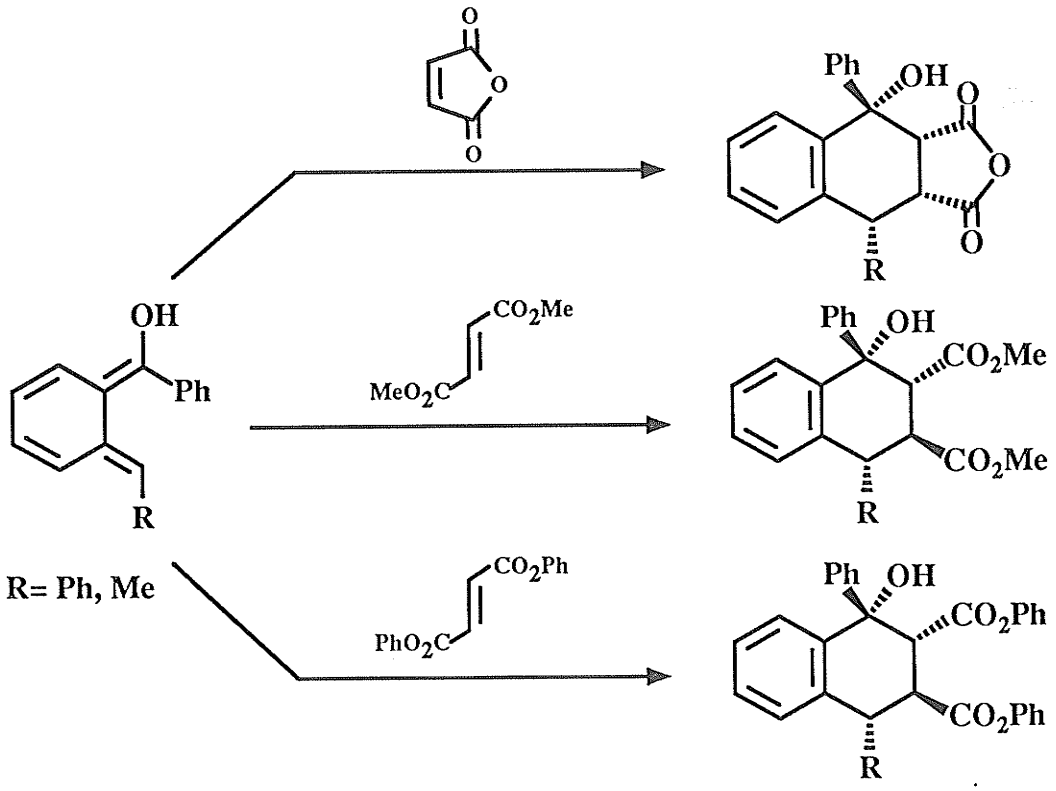
E. α,α-Disubstituted dienes and disubstituted dienophiles

Endo additions were also reported for disubstituted dienophiles[39-42]. All four dienophiles, dimethyl fumarate, dimethyl maleate, maleic anhydride and furanone, added to the *o*-quinodimethane to afford 1,2-*cis* adducts (relative to OH), the reaction with furanone also being highly regioselective.



F. α,α,α'-Trisubstituted dienes and disubstituted dienophiles

The results in this subsection do not differ from the previous two subsections [D and E] and *endo* addition is once again observed in these cases[39].



Summary of Previous Work

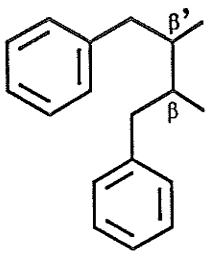
From this literature survey, one can draw the following conclusions about the diastereoselectivity of the Diels-Alder reaction of *o*-quinodimethanes: (1) the outcomes of the reactions do not seem to be different from other Diels-Alder reactions in that 1,2-adducts are usually produced and *endo* addition is predominant; (2) whenever there is

a phenyl or aryl substituent on the diene, the reaction takes place such that the product generated has the neighboring phenyl (aryl) and carbomethoxy substituent *trans* to each other; and (3) maleic anhydride always yields *endo* adducts regardless of the nature of the substituents on the diene. This could be due to lower steric effects and a more important secondary orbital effect in the transition state resulting in *endo* addition.

1.6 Use of *o*-Quinodimethanes in Organic Synthesis

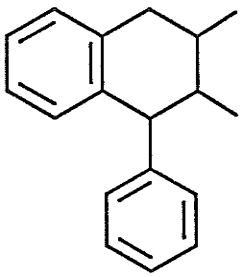
Organic synthesis using *o*-quinodimethanes, based on both inter- and intramolecular Diels-Alder reactions, has received considerable attention in recent years. The literature is so extensive that it is impractical to perform an exhaustive survey. For this reason, and because our interest is directed to a narrower field as far as synthesis is concerned, it is suggested that the reader consults review articles that have appeared for examples of synthesis of alkaloids, steroids, terpenes and anthracyclines[8,10,14,43-46]. In this Section, only a survey of aryltetralin lignans synthesis is made.

Aryltetralin lignans are a sub-class of the larger group of natural product lignans. Lignans and neolignans are formed in nature by the oxidative dimerization of various oxygenated phenylpropanes and the synthesis and biosynthesis of these compounds have been reviewed previously[47]. The name lignan is reserved for compounds in which two C_6-C_3 units are linked by a bond connecting the central β-carbon of each side chain such that the end result is the formation of the 2,3-dibenzylbutane skeleton 44.



44

Lignans having a side chain fused with the aromatic ring can be classified into two groups according to their structures. One of these groups represents the class of compounds known as *aryltetralin lignans*. Their basic carbon skeleton is shown in structure **45**. Structure **46** represents a well known example of a compound from this class, podophyllotoxin.



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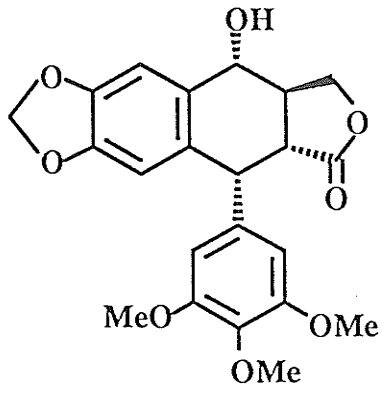
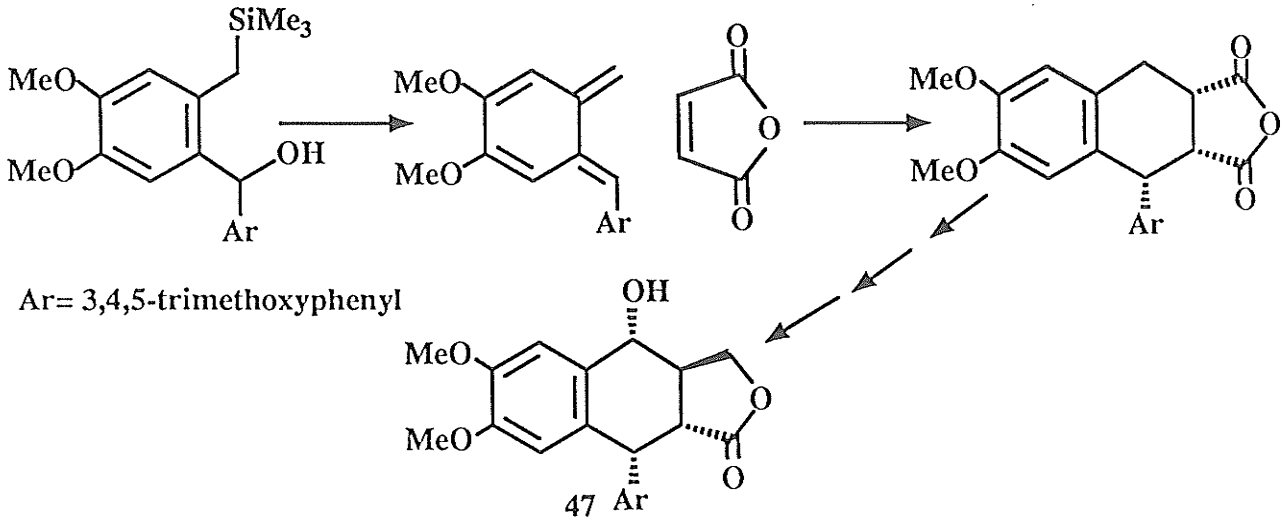
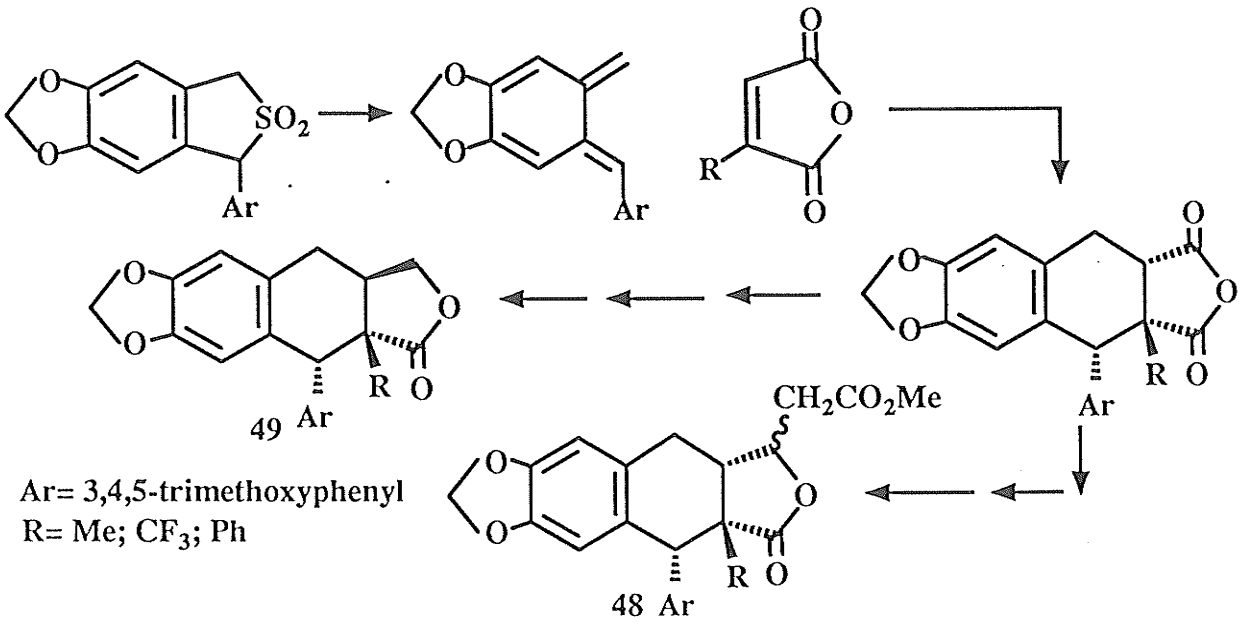


46

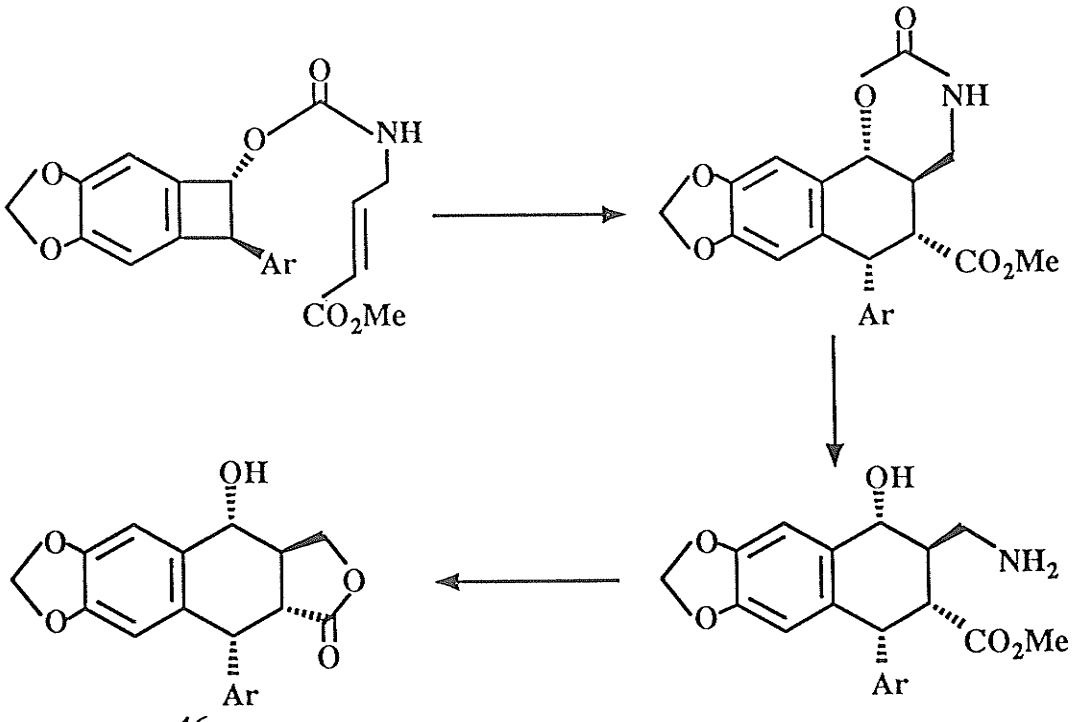
Most of the earlier work using *o*-quinodimethanes in synthesis of aryltetralin lignans and analogs has been covered in Charlton's review[8]. The reader is therefore referred to that article for examples published up to 1986. Since 1986, other examples of such use of *o*-quinodimethanes have appeared[12,48,49]. Sikkimotoxin **47** was recently synthesized by Takano *et al.* using the benzo-Peterson reaction as the key step[49]. Functional group conversion of the cycloadduct finally produced the target molecule **47**.



At about the same time, Mann *et al.* reported the synthesis of deoxypodophyllotoxin analogs[48]. In this case, a sulfone was used to generate the *o*-quinodimethane which was trapped with different 2-substituted maleic anhydrides. Conversion of the functional groups afforded in this case *cis* and *trans* lactone rings 48 and 49.



More recently Durst and MacDonald reported a highly stereoselective synthesis of podophyllotoxin 46 and analogs[12]. The strategy in this case was based on an intramolecular Diels-Alder reaction using an appropriately substituted *o*-quinodimethane to control the diastereoselectivity.



46

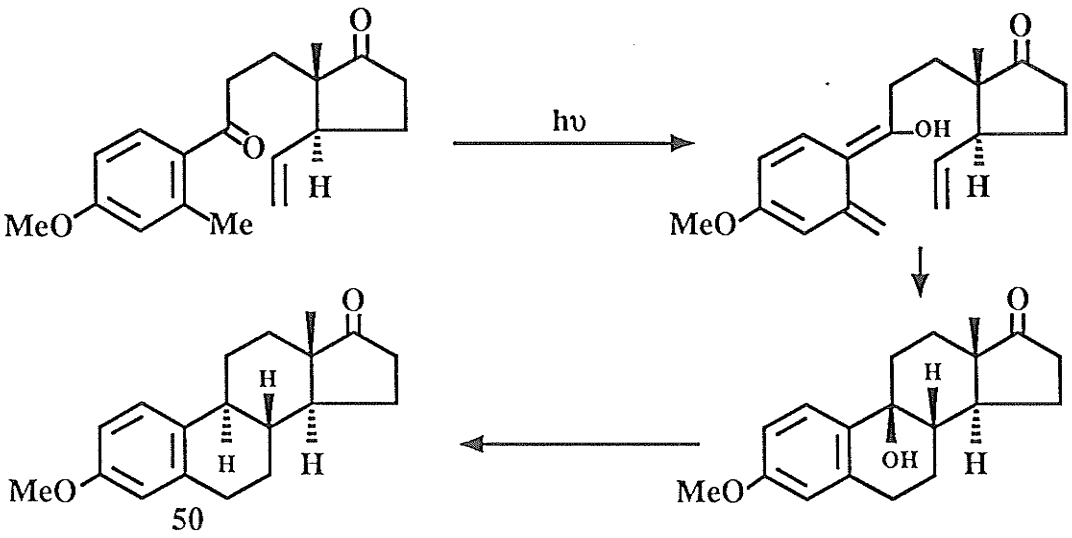
Ar= 3,4,5-trimethoxyphenyl

As demonstrated by the examples found in Charlton's review and by the few examples shown here, *o*-quinodimethanes are versatile intermediates in organic synthesis[8]. The main reason that they attract the interest of so many researchers is, of course, the diastereoselectivity encountered in their reactions. More particularly in the synthesis of aryltetralin lignans, these reactions offer the possibility of controlling the stereochemistry generated around the cyclohexene ring if the appropriate substituents and the proper dienophile are chosen.

1.7 Asymmetric Synthesis Using *o*-Quinodimethanes

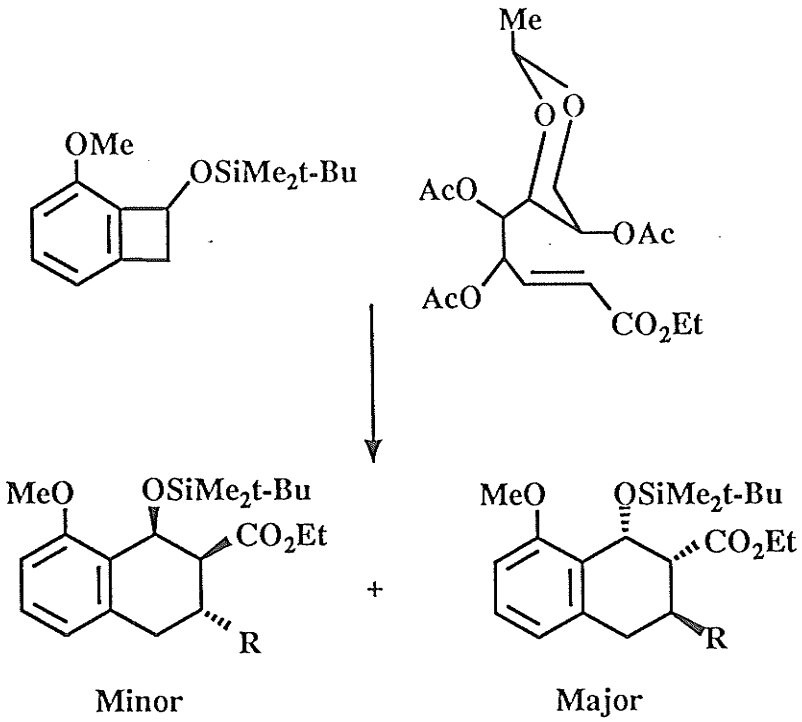
The prospective of controlling the diastereoselectivity of a reaction is always very attractive to synthetic chemists. However, more important is the enantioselective control that one can achieve during an asymmetric synthesis. One of the ways of achieving such a goal, is to introduce in one of the reactants (in this case, the *o*-quinodimethane or the dienophile), an enantiomerically pure control element known as a "*chiral auxiliary*". Such an element is usually used to control the diastereomeric outcome of a reaction before being eventually removed to leave a product of one absolute stereochemistry.

Asymmetric reactions using *o*-quinodimethanes conform to the general principle outlined above as shown by the following examples. Quinkert *et al.* achieved an asymmetric synthesis of estrone **50** by an intramolecular Diels-Alder reaction[44]. The photochemically produced *o*-quinodimethane had a chiral substituent which stereochemically controlled the outcome of the cycloaddition reaction. Other examples of this type can be found in Charlton's review[8].



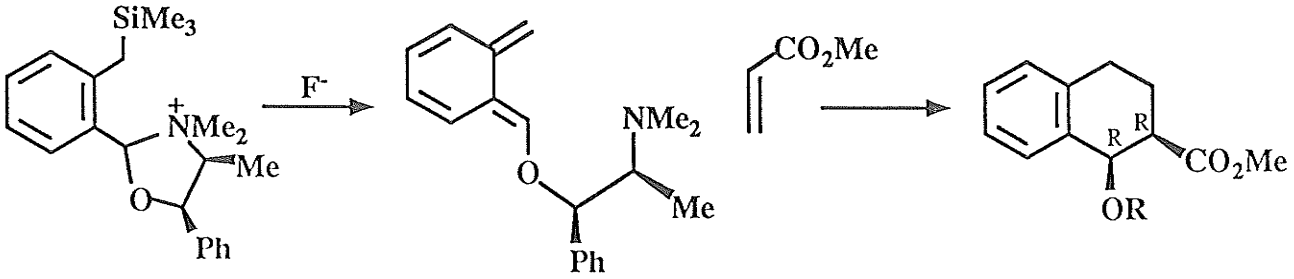
50

In a study of the relative roles of steric effects and secondary orbital interactions on asymmetric induction, Franck *et al.* used an achiral *o*-quinodimethane and a chiral dienophile[50]. They obtained two *endo* adducts in the ratio 4:1 and concluded that orbital interactions predominated over steric interactions in guiding the asymmetric addition.

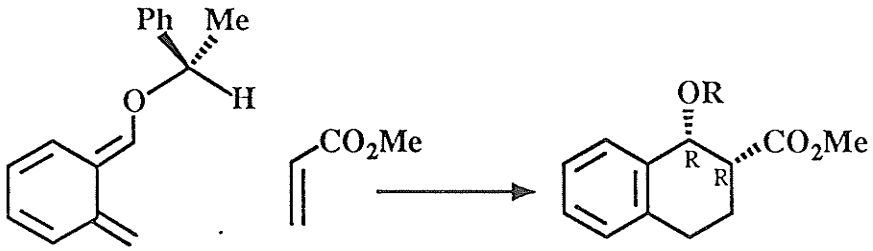


Minor Major

In another example, Ito *et al.* used an oxazolidinium system to produce an *o*-quinodimethane bearing a chiral auxiliary[51]. Reaction with methyl acrylate produced two diastereomers in the ratio 2:1, the major isomer having the **R,R** stereochemistry.

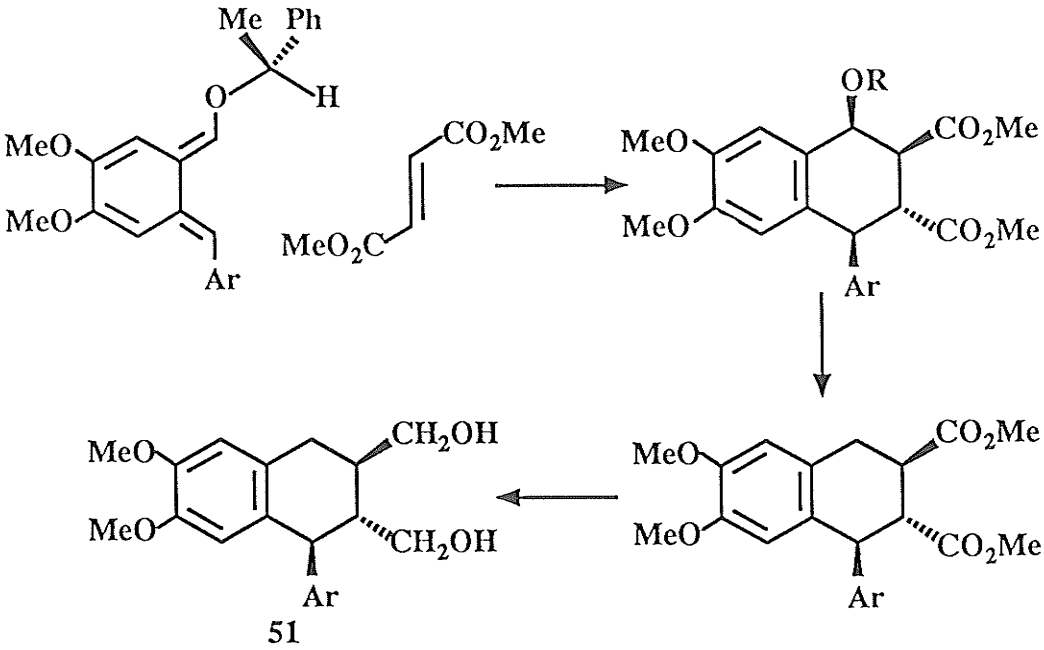


They explained the diastereoselectivity observed in this reaction using a model previously proposed by Trost and Daubin wherein π-stacking interaction serves as a steric factor to block the incoming dienophile from one of the two diastereotopic faces of the diene[52,53]. Ito's explanation of the asymmetric induction was later shown to be incorrect by Charlton [see **Chapter 2**][29]. In Charlton's work, various chiral auxiliaries were studied with the 1-phenylethyl group giving the greatest asymmetric induction.



The (S)-phenylethyl chiral auxiliary produced a cycloadduct (1'S, 1R, 2R) similar to that of Ito *et al.* by blocking the top face (phenyl side) of the *o*-quinodimethane. It was argued that the difference in sizes between the phenyl and the methyl was controlling the approach of methyl acrylate.

The same authors later published an asymmetric synthesis of an aryltetralin lignan, (+)-isolariciresinol dimethylether **51**, using the (S)-phenylethyl chiral auxiliary[23].

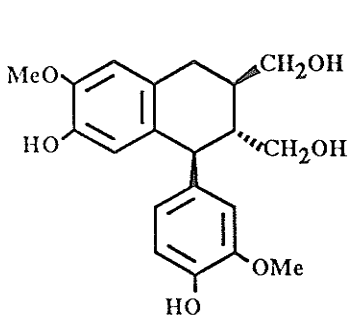


51

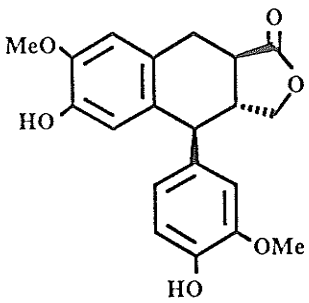
Ar= 3,4-dimethoxyphenyl

One conclusion that is evident from this literature survey is the small amount of work that has been done on asymmetric synthesis using *o*-quinodimethanes. More particularly, in the case of aryltetralin lignan synthesis, only one asymmetric synthesis using an *o*-quinodimethane has been reported[23]. The difficulty in the asymmetric synthesis of such compounds resides in the control of the relative and absolute stereochemistry. From the above, it appears that many different stereochemistries might be accessible. This may be an advantage as many target molecules with different stereochemistries and functionalities can be found in this class of compounds as shown by the few examples drawn in Table 1.

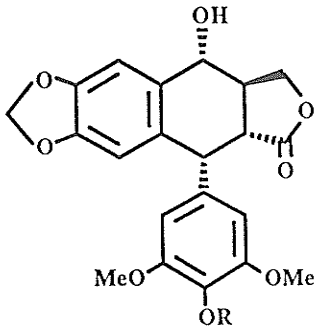
Table 1. Examples of Aryltetralin Lignans



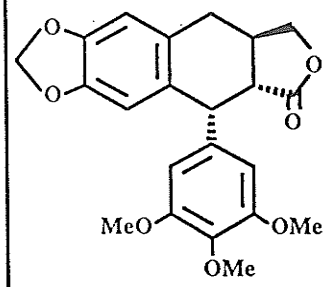
(+)-isolariciresinol



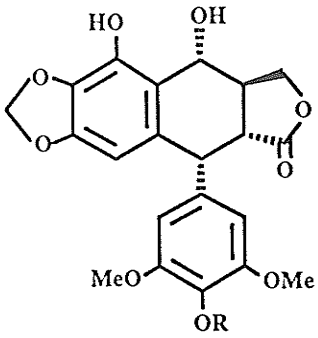
α-conidendrin



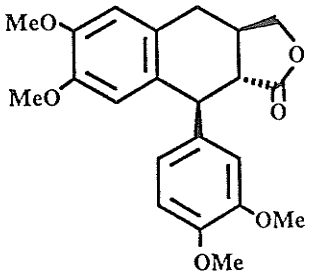
podophyllotoxin (R=Me)
demethyl podophyllotoxin (R=H)



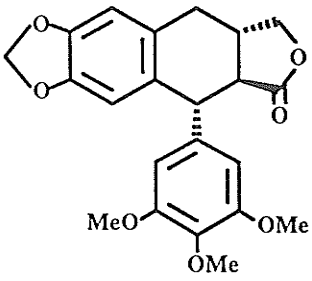
deoxypodophyllotoxin



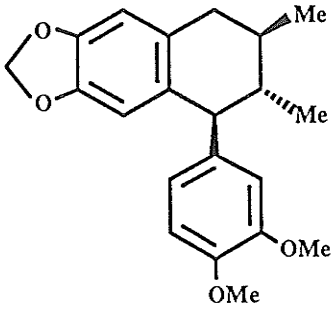
α-peltatin (R=H)
β-peltatin (R=Me)



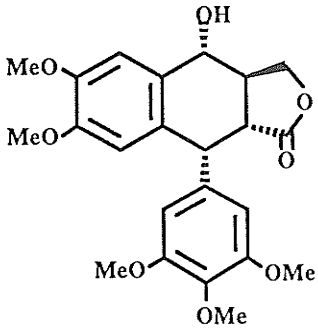
α-retrodendrin dimethyl ether



isodexoypodophyllotoxin



galcetin



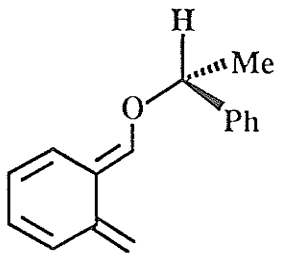
sikkimotoxin

Most of the work related to aryltetralin lignan synthesis encountered in the literature deals with the synthesis of podophyllotoxin or analogs[11,12,32,48,54-72]. However, only one asymmetric synthesis of podophyllotoxin has been published, giving only 5% overall yield in 24 steps[69]. Since the cycloaddition of an *o*-quinodimethane with the appropriate dienophile generates the four chiral centers of the aryltetralin system, it seems that a new chiral auxiliary needs to be designed to provide an asymmetric route to such aryltetralin lignans.

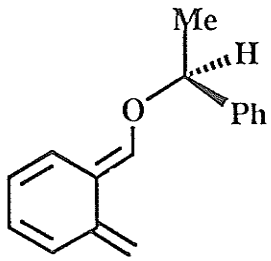
1.8 Objectives of this Thesis

Chiral auxiliaries previously used on *o*-quinodimethanes to control the diastereoselectivity of subsequent Diels-Alder reactions have not been sufficiently selective. The first objective of this work was to find a chiral auxiliary, which could be placed either on the diene or on the dienophile, which would yield high asymmetric induction in the cycloaddition reactions of *o*-quinodimethanes.

Charlton proposed a conformation for the chiral *o*-quinodimethane **52** that would explain the asymmetric induction observed in its cycloaddition reactions[29]. He later suggested that other conformers such as **53** could also explain the results obtained and that further work would be necessary before a definitive answer to the mechanism of the induction could be formulated[8]. Such a mechanistic study was the second objective of this work.



52



53

As a final objective, it was hoped that the chiral auxiliary described as the first objective, could be used to asymmetrically synthesize an aryltetralin lignan or an analog.

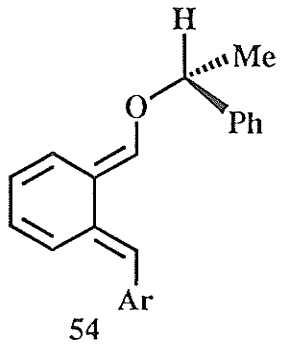
CHAPTER 2

RESULTS AND DISCUSSION

The second chapter of this thesis describes the work that has been done over the last three years. The first four Sections of this chapter explain the work accomplished while searching for a chiral auxiliary which would produce high asymmetric induction in the cycloaddition reactions of *o*-quinodimethanes. The fifth and final Section describes the asymmetric synthesis of two aryltetralin lignan analogs.

2.1 Search for a Better Chiral Auxiliary

To attack the problem of finding a new and hopefully better chiral auxiliary to control the asymmetric induction in the cycloaddition reactions of *o*-quinodimethanes, one must first review previous work in this area. The literature survey performed in Section 1.7 shows that very limited work has been performed in the past on controlling the asymmetric induction in reactions of *o*-quinodimethanes by using a chiral auxiliary. Only a few different chiral auxiliaries were used in the case of intermolecular cycloadditions with the phenylethyl chiral auxiliary (illustrated in structure **54**) used by Charlton *et al.* producing the best results[23,29]. These authors also used this chiral auxiliary to perform the asymmetric synthesis of an aryltetralin lignan, (+)-isolariciresinol dimethyl ether[23].

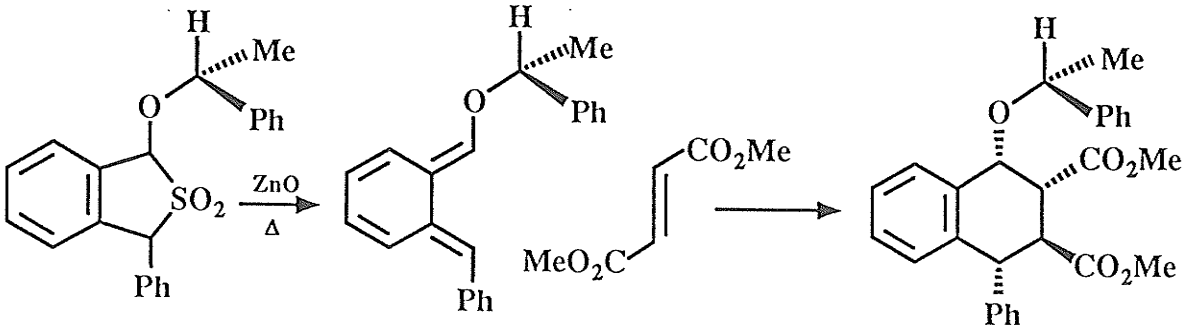


54

Ar= 3,4-dimethoxyphenyl

Although results using this chiral auxiliary were encouraging, they cannot be considered better than average since the isomeric ratio was quite low (ratio of major *endo* to minor *endo* isomers ~2.6:1). Therefore, it seems that more work could be done on this particular chiral auxiliary in the hope of improving these results.

As a first attempt to improve the results, different solvents were used for the cycloaddition reaction. Although higher selectivity is generally achieved in uncatalyzed reactions using nonpolar solvents[71,72], it was felt that this needed to be investigated since this general observation might be different in this case. If this were the case, then perhaps the use of another solvent could increase the asymmetric induction observed in the following reaction.



55

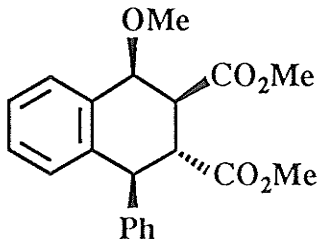
The reaction was first performed under conditions similar to those used by Charlton[29], using toluene as solvent instead of cyclohexane. The higher temperature (~110°C) at which the reaction was performed did not affect the results of the cycloaddition and an isomeric ratio (major *endo* to minor *endo*) of 2.65:1 was observed, compared to 2.6:1 reported by Charlton. In both cases, the ratios of isomers were deduced from the ^{1}H-nmr spectrum of the crude mixture. In our case, integration of the signal for **H-1** in the ^{1}H-nmr spectrum was used to determine isomeric ratios as it is easily distinguished, being located at ~5.0 ppm and usually distant from other signals. In the reaction reported by Charlton, the mixture was primarily made up of two *endo* isomers and the ratios reported were for these two major *endo* isomers. As for the data reported here, the isomeric mixture is also primarily made of two *endo* isomers (1,2-*cis*) (identified by comparison to previously published data[29]), but the isomeric ratios recorded in Tables 2 and 3 take into account all the isomers of the mixture, even those observed in trace amounts (<5% of major isomer) (assuming that doublets near 5 ppm were all due to isomeric cycloadducts). The ratio of isomers represents the proportion of the major isomer to the sum of the minor isomers. Table 2 represents a summary of the results obtained using six different solvents. Those results are in agreement with what is generally observed in Diels-Alder reactions. Increasing the polarity of the solvent generates less selectivity in the reaction to finally reach no selectivity at all in methanol.

Table 2. Solvent Effect on Isomeric Ratio

Solvent	Diastereomeric ratios [ ]**	Type of adduct (major only)
cyclohexane*	2.6:1	*endo*
toluene	2.5:1 [4]	*endo*
ethanol	2.3:1 [3]	*endo*
nitromethane	2.3:1 [3]	*endo*
acetonitrile	2.0:1 [3]	*endo*
methanol	1.2:1 [2]	*endo*

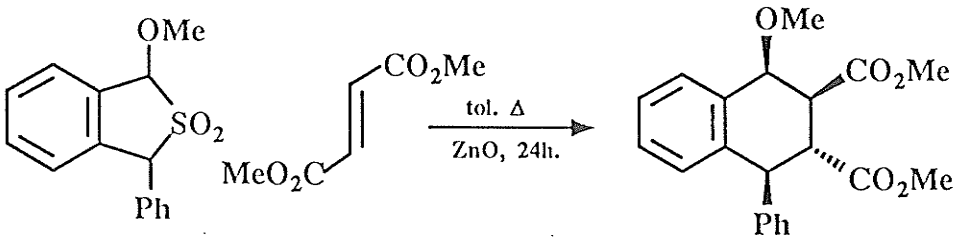
*previously reported[29] **total number of isomers observed (^{1}H-nmr)

In the case of the reaction in methanol, another cycloadduct could be observed in the mixture. It was tentatively assigned the structure **56** on the basis of the three methoxy signals in the ^{1}H-nmr spectrum as well as the absence of the signal (doublet) for the methyl group of the chiral auxiliary.



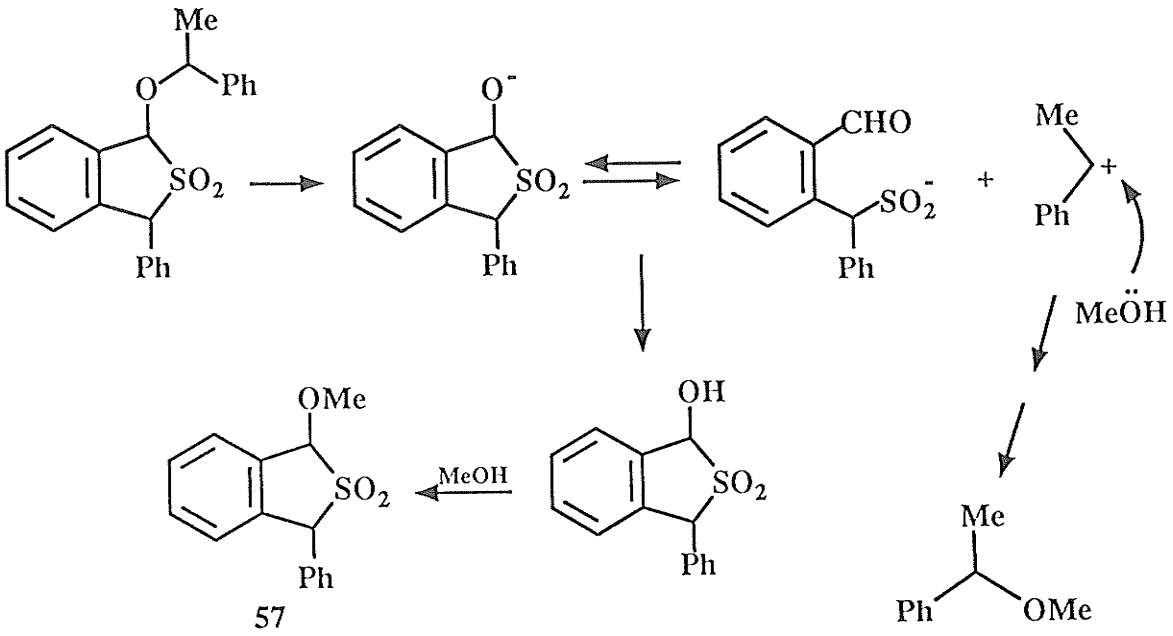
56

Although this product was not isolated, to prove its presence in the reaction mixture, it was directly prepared from the methoxysulfone **57** using the usual conditions (toluene, ZnO, reflux 24h). ^{1}H-nmr spectrum of the cycloaddition product prepared from **57** was identical to the unknown product obtained in the methanol reaction.



57 **56**

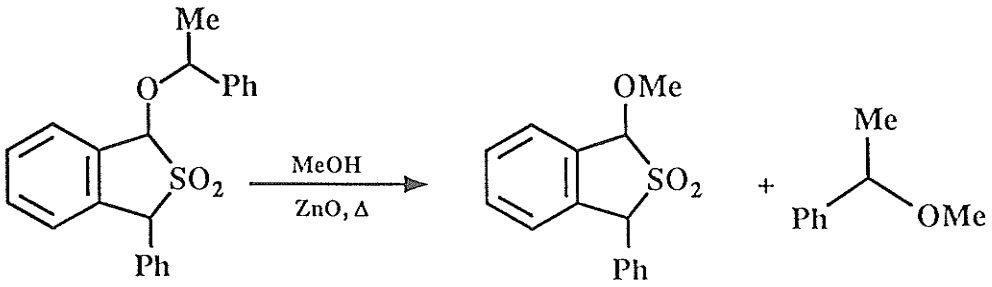
The production of such a product (**56**) would have to arise from an exchange of substituents between the chiral auxiliary on the *o*-quinodimethane and the methanol used as solvent. Cycloadduct **56** could have been formed at two distinct times during the course of the reaction, before or after cycloaddition took place. It seems unlikely that under the reaction conditions used, the substitution would have happened once the cycloadduct was formed. It is more likely that the methoxysulfone **57** is first formed by exchange, followed by thermolysis and cycloaddition of the *o*-quinodimethane with dimethyl fumarate to produce the cycloadduct **56**. Scheme 1 represents a possible mechanism which could explain the formation of the methoxysulfone **57**.



57

SCHEME 1

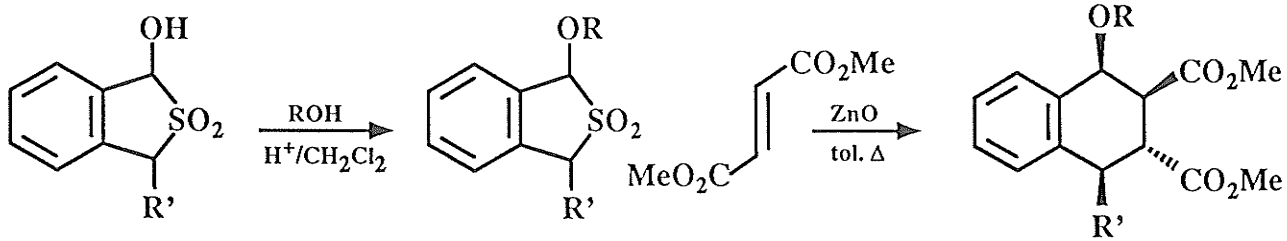
Even though the route described in Scheme 1 to explain the production of cycloadduct **56** seems more reasonable, it was necessary to verify both possibilities. Subjecting the cycloadduct **55** to the cycloaddition reaction conditions (MeOH, ZnO, 80°C, 24h) showed that the exchange of substituents did not occur after cycloaddition, as no methoxy adduct **56** could be found. Only quantitative amounts of cycloadduct **55** were recovered in this reaction. However, treating the phenylethoxysulfone under these identical cycloaddition conditions without the dienophile afforded a mixture of methoxysulfone **57** and 1-phenylethyl methyl ether **58**. This experiment demonstrated that the methoxy adduct **56** did arise from the cycloaddition of dimethyl fumarate and the *o*-quinodimethane generated from the methoxysulfone **57**, and that the exchange of substituents occurred before cycloaddition took place.



57 58

As changing the solvent produced the usual decrease of selectivity with an increase of solvent polarity, our attention and efforts were turned towards the investigation of different chiral auxiliaries. Since the phenylethyl auxiliary used by Charlton gave results good enough that the author could apply them to an asymmetric synthesis[23], the second logical step in our search for a better auxiliary was to try different substituents of the same general nature as that used by Charlton. It was hoped that one of them would generate better asymmetric induction than the phenylethyl auxiliary previously used.

Cycloaddition reactions were performed with dimethyl fumarate using *o*-quinodimethanes bearing eight different chiral auxiliaries with the hope that one would produce high diastereoselectivity. Two different types of *o*-quinodimethane precursors were used to perform these reactions, α-alkoxysulfone **65** and α-alkoxy-α'-phenylsulfones **61-64, 66-68** prepared from the hydroxysulfones **59** and **60** respectively.



59 R'=H
60 R'=Ph

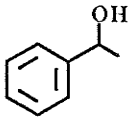
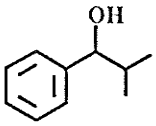
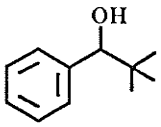
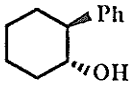
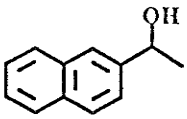
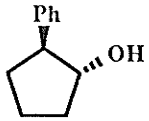
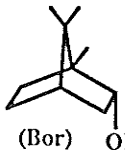
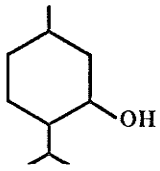
61-68

69-76

The preparation of precursors and cycloaddition reactions proceeded uneventfully, giving good yields 73-82% of alkoxysulfones and 65-81% of cycloadducts. Results are summarized in Table 3, with partial ^{1}H-nmr of each major adduct recorded in Table 4. These ^{1}H-nmr signals for the major adducts were obtained from the crude reaction mixtures. Since this was a preliminary survey, no attempt was made to separate and characterize the individual cycloadducts at this time. As in the previous study, the ratios of cycloadducts were determined from the ratios of signals for **H-1** (~5 ppm) in the ^{1}H-nmr spectra.

It is obvious from these results that none of these chiral auxiliaries generates high enough asymmetric induction to be useful in an asymmetric synthesis. All the isomeric ratios obtained are in the vicinity of what was previously found by Charlton[29]. Only one chiral auxiliary, 2,2-dimethyl-1-phenyl-1-propanol, produced an increase in asymmetric induction (sulfone **62** to cycloadduct **71**) with the generation of only two observable isomers by ^{1}H-nmr. However, even this higher isomeric ratio (3.8:1) is too small for consideration as a control element in an asymmetric synthesis. In the case of cycloadduct **74**, using borneol as the auxiliary, the isomeric ratio could not be determined. It appears that at least two isomers were produced, but the two **H-1** signals in the ^{1}H-nmr spectrum were overlapping, preventing the determination of the diastereomeric ratio. In this case, a rough estimate of the peak areas indicates that the ratio is approximately 1:1.

Table 3. Yields and Diastereomeric ratios (products 61 to 76)

	Hydroxy sulfones	Alcohol	Alkoxy sulfones (% yield)	Cycloadducts (% yield)	Diastereomeric ratios (major/minors)[a]
1	60		61(82)	69(76)	2.5:1 [4]
2	60		62(81)	70(79)	2.8:1 [3]
3	60		63(79)	71(81)	3.8:1 [2]
4	60		64(78)	72(71)	2.0:1 [4]
5	59	 (napht)	65(76)	73(65)	1.5:1 [3]
6	60		66(76)	74(73)	1.4:1 [2][b]
7	60	 (Bor)	67(77)	75(72)	--------
8	60	 (MEN)	68(73)	76(76)	1.6:1 [2]

[a] isomeric ratios obtained from ^{1}H-nmr of crude mixtures. [ ] represents total number of isomers observed. [b] H-1 signals overlapping. Ratio based on H-2 signals

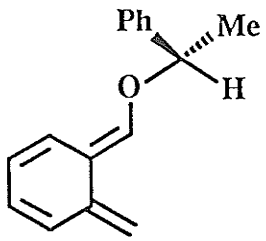
Table 4. Chemical Shifts (δ) and Coupling Constants (Hz)

	69	70	71	72	73	74	75	76
H-1	5.02(d)	4.98(d)	4.93(d)	4.93(d)	4.96(d)	4.87(t)[a]	4.86(t)[a]	4.95(d)
H-2	3.30(dd)	3.22(dd)	3.22(dd)	-----	3.16(dd)	3.26(dd)	3.31(dd)	3.22(dd)
H-3	-----	-----	-----	-----	-----	3.70(dd)	-----	-----
H-4	4.06(d)	4.03(d)	4.04(d)	3.86(d)	2.80(dd) 3.27(dd)	4.02(d)	4.10(d)	4.09(d)
OCH_3	3.52(s)	3.53(s)	3.54(s)	3.40(s)	3.74(s)	3.48(s)	3.53(s)	3.51(s)
OCH_3	3.81(s)	3.81(s)	3.79(s)	3.76(s)	3.86(s)	3.77(s)	3.76(s)	3.72(s)
R	1.44(d) 4.55(q)	0.68(d) 0.98(d) 1.98(m) 4.11(d)	0.87(s)	1.75(m) 2.48(m)	1.47(d) 4.64(q)	1.75(m) 2.10(m)	1.40(m)	1.00(m)
Arom.	7.23(m)	7.20(m)	7.10(m)	7.10(m)	7.35(m)	7.15(m)	7.30(m)	7.25(m)
$J_{1,2}$	2.8	2.5	2.5	2.3	3.1	2.8	2.8	2.5
$J_{2,3}$	12.0	12.0	11.9	-----	10.5	12.1	12.1	12.0
$J_{3,4}$	11.1	10.9	10.9	10.3	10.5	12.0	11.3	10.9
$J_{4a,4e}$	DNA[b]	DNA[b]	DNA[b]	DNA[b]	16.5	DNA[b]	DNA[b]	DNA[b]
J_R	6.4	6.7 7.2	-----	-----	6.4	-----	-----	-----

[a] overlapping with H-1 signal of a minor isomer.
[b] do not apply

Although the diastereoselectivity achieved with these chiral auxiliaries was disappointingly low, it turned out that three results were very interesting from a mechanistic point of view. Entries 1, 2 and 3 show the production of cycloadducts in which the diastereomeric ratios are increasing (from 2.5:1 to 3.8:1). The only difference between these auxiliaries is the size of the alkyl group within the side chain. As a first

observation, it would appear that the larger the alkyl group (methyl *vs* isopropyl *vs* *tert*-butyl), the larger the diastereomeric ratio observed. This is in contradiction with the mechanism proposed by Charlton, who suggested conformation **52** for the chiral auxiliary and explained that the asymmetric induction observed was due to the difference in size between the phenyl and methyl groups[29]. Since in the chiral auxiliaries (in **61**, **62** and **63**) studied here, only the alkyl portion is changing (methyl to isopropyl to *tert*-butyl), the asymmetric induction would be expected to decrease as the size of the alkyl group increases, if the chiral auxiliaries have a conformation similar to that of **52**.



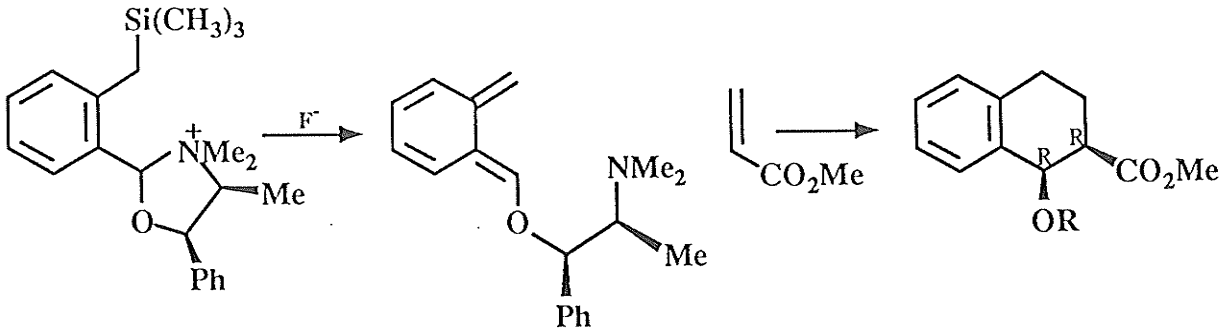
52

Because of these results, it appears that a new mechanism is needed to explain the asymmetric induction encountered in these reactions. Once known, it would then be possible to proceed in searching for a chiral auxiliary generating higher induction. This mechanistic study is the subject of the next Section.

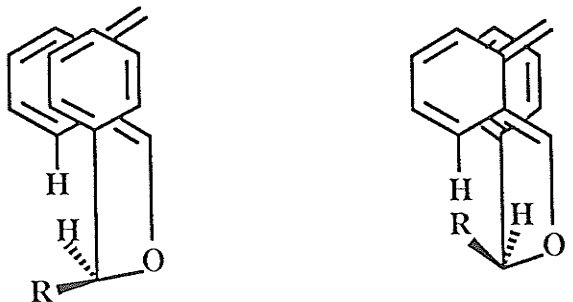
2.2 Mechanism of the Asymmetric Induction

It was previously mentioned [**Section 1.7**] that two mechanisms had been proposed to explain the asymmetric induction in the reaction of *o*-quinodimethanes bearing a

chiral substituent. Ito *et al.* first proposed an explanation for the asymmetric induction observed in the cycloaddition reaction of methyl acrylate and an *o*-quinodimethane produced from an oxazolidinium system[51]. Two diastereomers resulted from this reaction in a ratio of 2:1, with the major adduct reported to have the R,R stereochemistry.

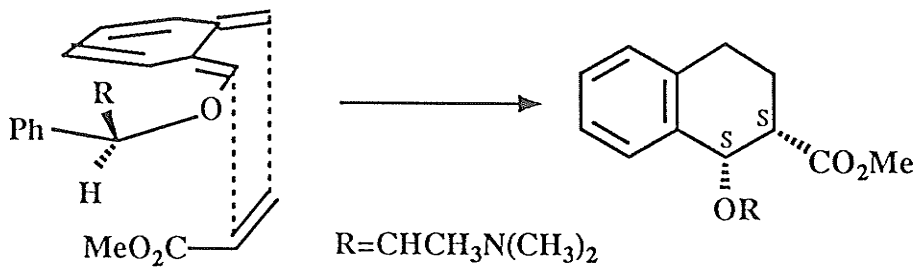


The explanation for the diastereoselectivity observed was based on π-stacking interactions between the phenyl group within the chiral auxiliary and the transitory *o*-quinodimethane. This proposed steric effect would result in blocking one face of the *o*-quinodimethane forcing the dienophile to react at the opposite face. There are two possible conformations (A and B) in which the *o*-quinodimethane can π-stack with the phenyl group as shown below.

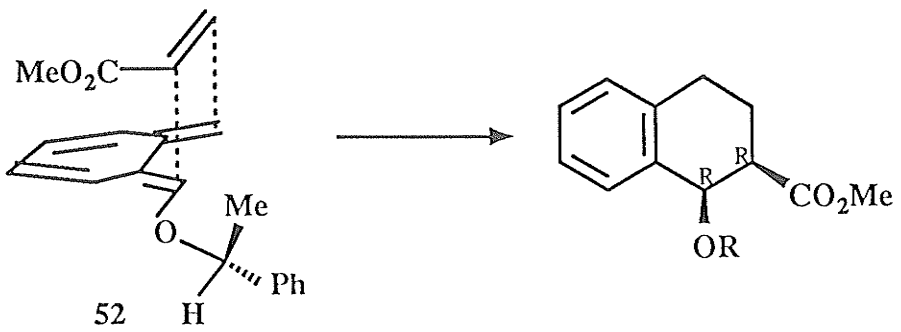


(A) R=$CHCH_3N(CH_3)_2$ (B)

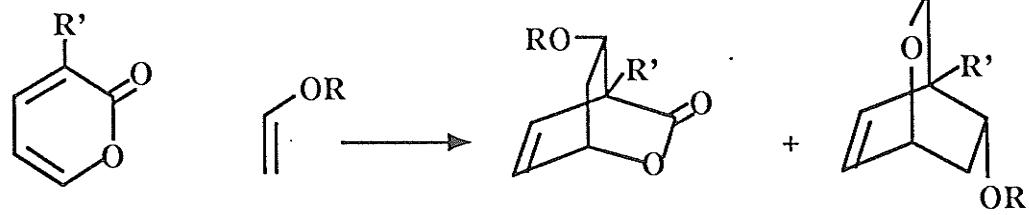
According to the authors, conformation B was favoured and reaction should have occured from that conformer. If this were the case, then the stereochemistry (R,R) observed in the major isomer could be explained. However, a study of molecular models shows that conformer A is less hindered than B and should be the favoured conformation. The reason, as shown in the diagrams above, is that the non-bonding interactions between the aromatic hydrogen and the benzylic hydrogen in A is less than that between the aromatic hydrogen and the bulkier alkyl group R in B. As a result, addition of the dienophile to the open face of the preferred conformer A should have given predominantly an adduct with the S,S stereochemistry. Therefore, the π-stacking model would appear to be wrong and does not explain the asymmetric induction observed.



The inability of Ito's model to explain this asymmetric induction prompted Charlton to suggest a new conformation of the chiral auxiliary capable of explaining the results[29]. After performing a study of various chiral auxiliaries, he suggested that the preferred conformation of the α-substituted *o*-quinodimethane was as depicted below in the *o*-quinodimethane 52. In this conformation, the dienophile approaches from the upper face of the *o*-quinodimethane, because the methyl group in the auxiliary is smaller in size than the phenyl substituent. This proposal also explains the results obtained by Ito *et al.*[51].



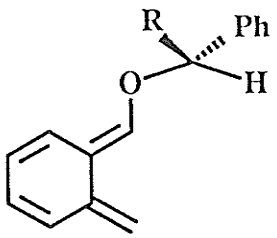
However, the results described in Section 2.1 for cycloadducts 69, 70 and 71 (see Table 3) are not consistent with Charlton's proposal. Other results published by Posner and Wettlaufer are also in contradiction with this proposal[73]. In this article, the authors reported the study of the asymmetric Diels-Alder cycloadditions of a dienylsulfone and eight different chiral vinyl ethers. Of these dienophiles, three of them (77,78,79) had the identical chiral auxiliaries which were used in the formation of cycloadducts 69,70 and 71 (see Table 3).



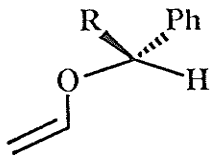
R'=-SO_2Tol

	R	%de
77	-CH(Ph)Me	66
78	-CH(Ph)i-Prop	84
79	-CH(Ph)t-But	90

As was found in **Section 2.1**, the asymmetric induction observed in the cycloaddition reactions of **77**, **78**, and **79** also increased with the increase in size of the alkyl group (methyl to isopropyl to *tert*-butyl) within the chiral auxiliary. Assuming that the chiral auxiliaries of these vinyl ethers have a similar conformation (**80**) as the one proposed by Charlton (**52**), it becomes obvious that the model is inadequate since the asymmetric induction should also have decreased in Posner's case instead of increasing as the size of the alkyl group R became larger. To fully establish the mechanism of the asymmetric induction of these chiral auxiliaries, it is necessary to determine unambiguously at which face the *o*-quinodimethane reacts for each chiral auxiliary. This can be done by determining the absolute configurations of the new chiral centers in the cycloadducts relative to that of the chiral auxiliary.

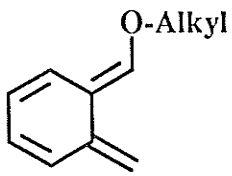


52 (R=Me)

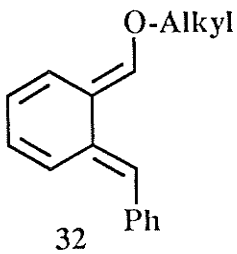


80

To perform this task, α-alkoxy-*o*-quinodimethanes such as **26** were used instead of the α-alkoxy-α'-phenyl-*o*-quinodimethanes **32** which were used in **Section 2.1.**

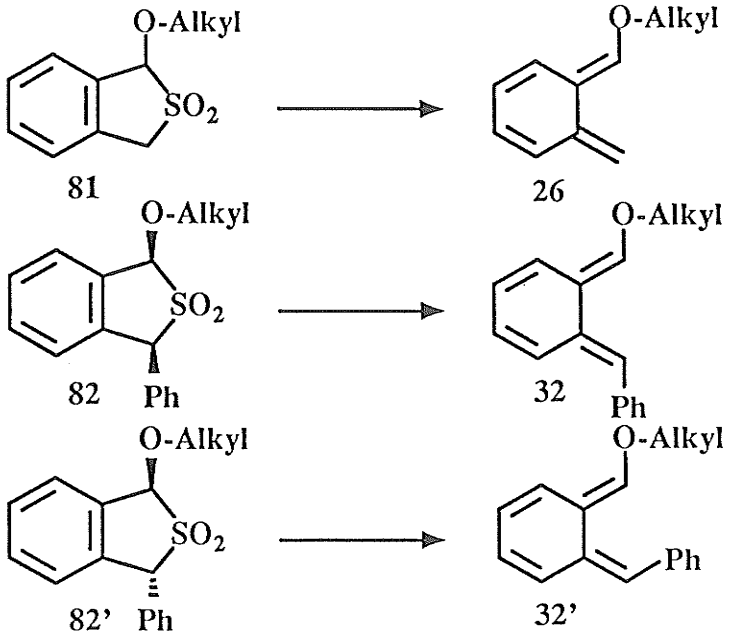


26



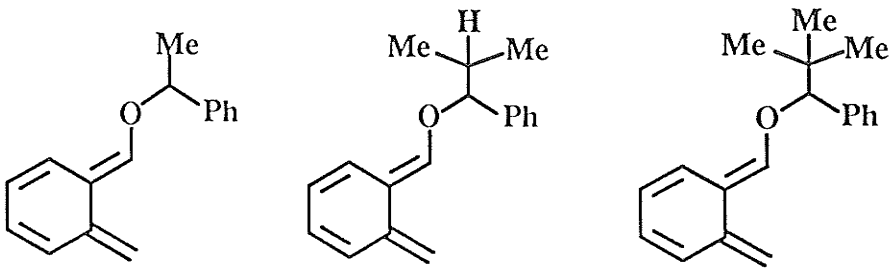
32

There are three reasons to explain this choice. First of all, *o*-quinodimethanes such as 26 are not expected to give results different from those of type 32. This was previously demonstrated by Charlton as the two types of *o*-quinodimethanes gave predominantly *endo* (1,2-*cis*) cycloadducts[29]. Secondly, the alkoxysulfones 81 which are used as precursors for *o*-quinodimethanes 26, have the advantage that their purification is less difficult than that of sulfones 82 used in the generation of *o*-quinodimethanes 32. This is because the production of 32 requires that pure *cis*-sulfones 82 be used so that only E,E-*o*-quinodimethanes 32 are produced during thermolysis. If this is not the case and 82' is also present, then E,Z-*o*-quinodimethanes 32' will be produced. The presence of 32' in the reaction mixture increases the number of possible isomeric cycloadducts that can be formed during cycloaddition, as both the E,E- and E,Z-*o*-quinodimethanes can react with the dienophile. To avoid this problem, sulfones 82 and 82' must therefore be separated by chromatography prior to thermolysis. This is not required for sulfones 81 as thermolysis of this type of sulfones always produces an *o*-quinodimethane of type 26, as explained in Chapter 1.



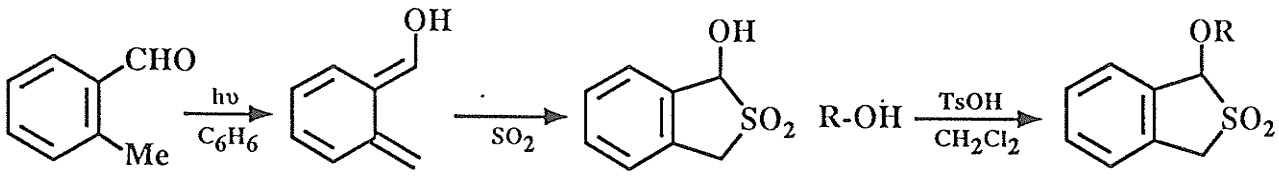
The last reason for choosing *o*-quinodimethanes **26** over those of type **32** is related to the ^{1}H-nmr spectra of the cycloaddition products. It is easier to assign the signal for **H-1**, and therefore the diastereomeric ratios, in the adducts arising from cycloaddition with *o*-quinodimethanes **26**, than it is for the same signal in the cycloadducts arising from **32**. This is due to the fact that the area of the ^{1}H-nmr spectrum where the **H-1** signals of the cycloadducts appear (~4.5-5.0 ppm) is less complicated in the products arising from **26**, since the **H-4** signals (~4.5 ppm in adducts from **32**) are shifted to ~3.0 ppm due to the absence of the phenyl substituent.

Although it is necessary to use an optically pure chiral auxiliary to determine at which face of the *o*-quinodimethane the reaction takes place (by determining the absolute configurations of the new chiral centers), this condition is not compulsory in order to test if a particular auxiliary can induce asymmetry in a cycloaddition reaction[29]. The reason for this is that it is possible to determine the diastereomeric ratio of the cycloadducts from the ^{1}H-nmr spectrum of the racemic mixture of cycloadducts since both enantiomers of a racemic pair produce identical ^{1}H-nmr spectra. Because of this, and also because of the high cost of optically pure chiral auxiliaries, the reactions were first performed using racemic material. In this way, diastereomeric ratios were determined, reaction conditions were optimized and products were characterized, before using the costly optically pure material. The racemic *o*-quinodimethanes **16**, **83** and **84** were therefore generated and reacted with dimethyl fumarate.



16 83 84

The α-alkoxysulfones 85a, 85b and 85c, needed as precursors to the *o*-quinodimethanes, were prepared according to the procedure previously reported and illustrated in Scheme 2[29]. Irradiation of *o*-methylbenzaldehyde in the presence of SO_2 afforded the hydroxysulfone 59 in yield similar to that previously reported[19,22]. Treatment of sulfone 59 with the appropriate alcohols and catalytic amounts of p-toluenesulfonic acid gave the alkoxysulfones 85a, 85b and 85c. The alcohols used in these reactions were either prepared from a Grignard reaction of the proper alkyl halide and benzaldehyde (b and c) or purchased. In all cases the reactions were uneventful giving good yields (82-88%) of α-alkoxysulfones after purification by chromatography on silica gel [see Table 5].

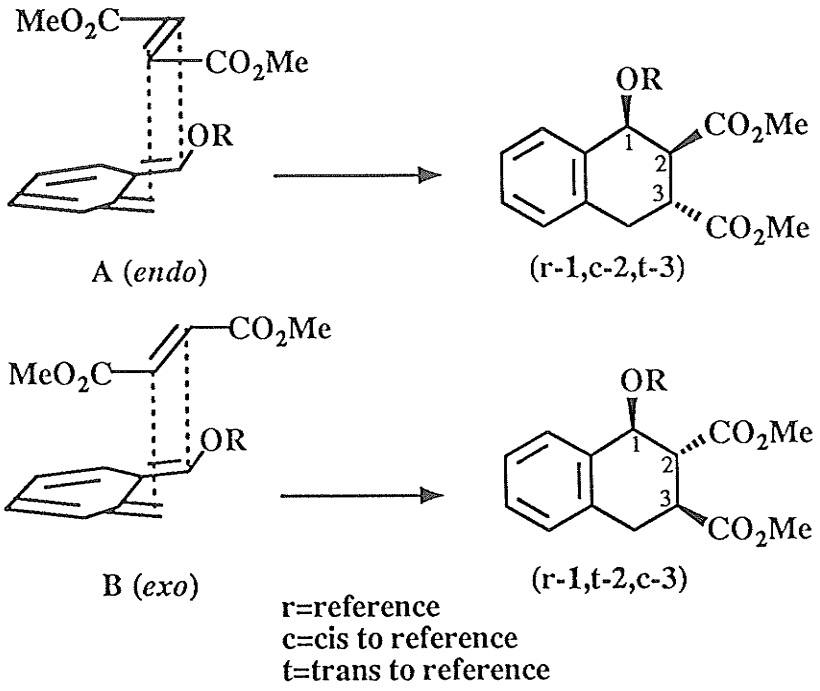


13 59

SCHEME 2

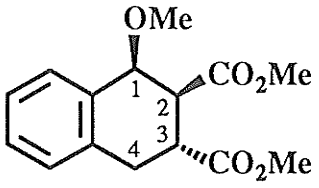
a R=CH(Ph)Me 85a
b R=CH(Ph)i-Prop 85b
c R=CH(Ph)t-But 85c

o-Quinodimethanes and dimethyl fumarate are known to react with each other through two transition states, A (*endo*) and B (*exo*), with the major products (*r-1,c-2,t-3*) arising from A[6,22].

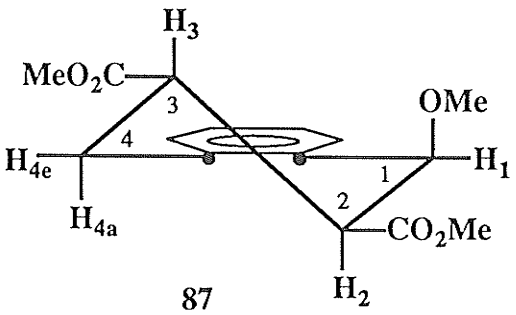


The products arising from these two different modes of addition will be different and therefore the analytical data generated from these adducts will also be different. In particular, ^{1}H-nmr of both type of adducts should prove to be a useful tool in their identification. Chemical shifts and coupling constants of the protons of the cyclohexene ring should be different for *endo* (A) *vs exo* (B) products, since the conformations of the adducts are different.

Durst *et al.* previously carried out the cycloaddition of dimethyl fumarate with α-methoxy-*o*-quinodimethane[22]. The major cycloadduct obtained in that reaction was assumed to have been produced from the *endo* transition state and therefore the (*r-1,c-2,t-3*) relative stereochemistry depicted in 86 was assigned.



86 (r-1,c-2,t-3)

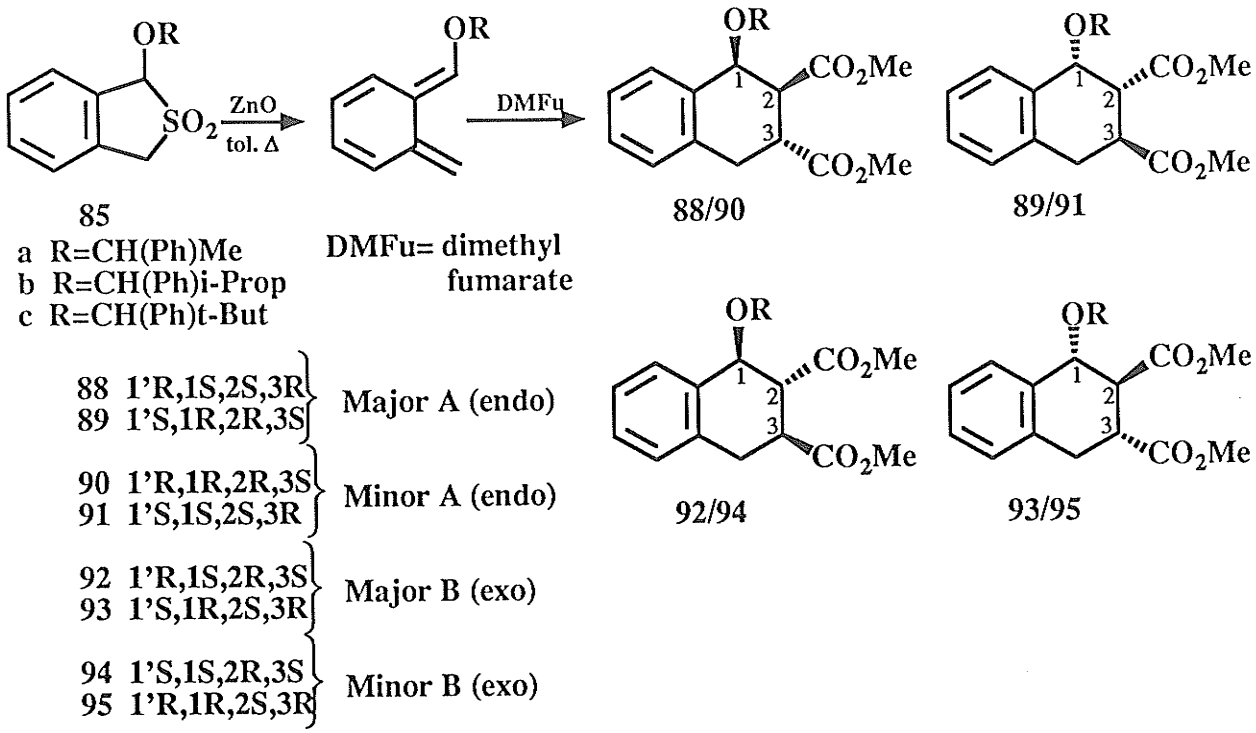


87

Although cycloadduct **86**, as any other cycloadduct of this type, probably does not possess a fixed conformation, Durst *et al.* speculated that conformation **87** would be the favoured conformation of the cycloadduct, as it best explained the ^{1}H-nmr data (coupling constants) obtained ($J_{1,2}$= 3.2; $J_{2,3}$= 11.5; $J_{3,4a}$= 10.9; $J_{3,4e}$= 6.7). These coupling constants can easily be explained from conformer **87**, as they are related to the dihedral angles between the protons concerned. The magnitude of the coupling between two protons on adjacent carbon atoms can be explained using the Karplus equation. The coupling will be large when the dihedral angle α between these protons is ~0° or ~180°. When the angle α is ~90°, the coupling is small. For the cycloaddition reactions carried out in this Section, it was assumed that the *endo* additions would produce cycloadducts with similar ^{1}H-nmr as that of **86** reported by Durst *et al.*[22]. This similarity was the basis of the identification of the *endo* adducts produced in the reactions of *o*-quinodimethanes **16**, **83** and **84**.

The cycloaddition reactions were performed according to a procedure previously reported[24,29]. The alkoxysulfones **85a**, **85b** and **85c** were thermolyzed in refluxing toluene in the presence of dimethyl fumarate and zinc oxide as shown in Scheme 3. The cycloadditions proceeded smoothly to afford in all cases a good yield (80-87%) of product. In each reaction, the product consisted of a mixture of three or four

diastereomers as observed by ^{1}H-nmr spectroscopy. Diastereomeric ratios and yields of cycloadducts are given in Table 5.



85
a R=CH(Ph)Me
b R=CH(Ph)i-Prop
c R=CH(Ph)t-But

DMFu= dimethyl fumarate

88/90

89/91

92/94

93/95

88 1'R,1S,2S,3R
89 1'S,1R,2R,3S } Major A (endo)

90 1'R,1R,2R,3S
91 1'S,1S,2S,3R } Minor A (endo)

92 1'R,1S,2R,3S
93 1'S,1R,2S,3R } Major B (exo)

94 1'S,1S,2R,3S
95 1'R,1R,2S,3R } Minor B (exo)

SCHEME 3

As can be seen from Table 5, the results obtained using *o*-quinodimethanes **16**, **83** and **84** are similar to those obtained with *o*-quinodimethanes generated from sulfones **61**, **62** and **63** [see **Section 2.1**] and also to those results reported by Posner and Wettlaufer[73]. Once again the increase in size of the alkyl group within the chiral auxiliaries affected the asymmetric induction, which increased with the increase in size of the alkyl group of the auxiliaries as shown by the ratios of the major *endo* isomer to the minor *endo* isomer.

Table 5. Yields and Diastereomeric Ratios

Sulfones	Yields[a]	Cycloadduct Yields[a,b]	Diastereomeric ratios (major endo/minor endo)
85a	88	80	2.7:1
85b	82	87	3.0:1
85c	84	84	3.5:1

[a] after chromatography
[b] mixture of diastereomers

In all of the cycloaddition products, the major isomer of the mixture was identified as an *endo* isomer (*r-1,c-2,t-3*) **(type A)** and was assigned the racemic structure **88/89** on the basis of the similarity of its ^{1}H-nmr spectrum with that of **86** previously reported by Durst *et al.*[22]. The minor *endo* isomer (**90/91**) was identified by the similarity of its ^{1}H-nmr spectrum with that of **88/89**. The *exo* isomers (*r-1,t-2,c-3*) **(type B) 92/93, 94/95** were identified in the mixtures by the difference of their ^{1}H-nmr spectra from that of **88/89** or **90/91**. Table 6 shows the chemical shifts and coupling constants for the major isomer arising from **85a** as well as for all the diastereomers for both the reactions of **85b** and **85c**. The data reported by Durst *et al.* for cycloadduct **86** are also included for comparison purposes[22].

As can be seen from Table 6, the *endo* adducts from all of the reactions carried out produced very similar ^{1}H-nmr data. Not only are the chemical shifts similar in all cases, but the coupling constants are also very much the same. These data are comparable to those reported by Durst *et al.* for cycloadduct **86**[22]. These kinds of internal consistencies in chemical shifts and coupling constants were also observed within *exo* isomers.

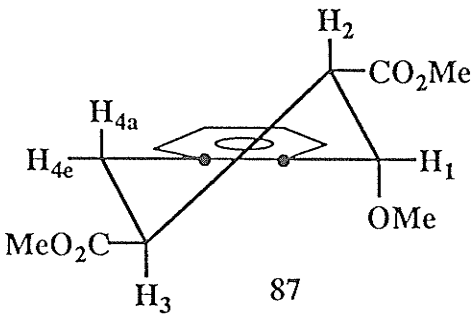
Table 6. Chemical Shifts (δ) and Coupling Constants (Hz)

Cycloadducts	Chemical Shifts (type of signal)								Coupling Constants				
	H-1	H-2	H-3	H-4e	H-4a	OMe	R	Arom.	$J_{1,2}$	$J_{2,3}$	$J_{3,4a}$	$J_{3,4e}$	$J_{4a,4e}$
86	4.63(d)	3.14(dd)	3.52(m)	3.28(dd)	2.83(dd)	3.75(s) 3.78(s)	3.28(s)	7.28(m)	3.2	11.5	10.9	6.7	16.9
88/89a	4.92(d)	3.14(dd)	3.64(ddd)	3.27(dd)	2.81(dd)	3.73(s) 3.83(s)	1.40(d) 4.50(q)	7.20(m)	3.3	11.4	10.9	6.6	16.9
88/89b	4.87(d)	3.07(dd)	3.66(m)	3.26(dd)	2.78(dd)	3.75(s) 3.82(s)	0.64(d) 0.95(d) 1.90(m) 3.99(d)	7.00(m)	2.9	11.2	10.1	7.4	16.8
90/91b	4.58(d)	3.02(dd)	3.71(m)	3.41(dd)	2.89(dd)	3.67(s) 3.79(s)	0.51(d) 0.67(d) 1.72(m) 3.79(d)	7.10(m)	2.7	11.2	9.3	8.0	17.0
92/93b	4.67(d)	3.58(dd)	3.13(m)[a]	2.96(m)	3.13(m)[a]	3.68(s) 3.74(s)	0.69(d) 1.00(d) 2.00(m) 4.16(d)	7.15(m)	4.5	7.9	----	----	----
94/95b	4.59(d)	3.76(m)[a]	3.22(m)	3.00(dd)	3.35(dd)	3.47(s) 3.77(s)	0.55(d) 0.72(d) 1.75(m) 3.76(m)[a]	7.15(m)	2.8	----	9.5	6.1	14.5
88/89c	4.86(d)	3.08(dd)	----[b]	3.27(dd)	2.78(dd)	3.74(s) 3.79(s)	0.82(s) 4.07(s)	6.85(m)	2.8	10.9	9.1	8.2	16.9
90/91c	4.56(d)	3.05(dd)	----[b]	3.40(dd)	2.88(dd)	3.76(s) 3.78(s)	0.65(s) ----[b]	6.90(m)	2.7	11.4	9.7	8.0	17.1
92/93c	4.59(d)	3.69(dd)	3.16(m)[a]	3.16(m)[a]	3.16(m)[a]	3.62(s) 3.75(s)	0.87(s) 4.28(s)	7.15(m)	3.0	7.9	----	----	----
94/95c	4.52(d)	3.84(dd)	----[b]	3.02(dd)	3.37(dd)	3.47(s) 3.80(s)	0.65(s) ----[b]	7.15(m)	2.4	5.7	9.6	6.1	14.4

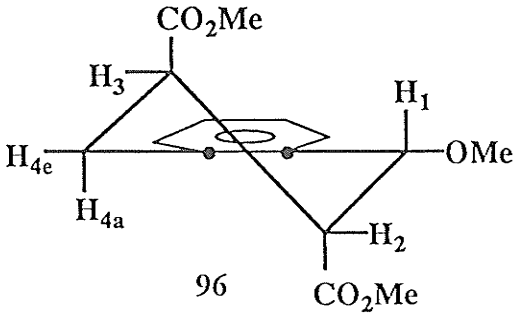
[a] overlapping with other signals [b] hidden under other signals

Many differences exist between the data obtained from *endo* and *exo* isomers. These differences were the basis of the identification of the *exo* isomers in the mixtures of cycloadducts. Typically, one can observe significant differences in the chemical shifts of **H-2**, **H-3**, **H-4a**, and **H-4e** for the *exo* isomers relative to the chemical shifts of the same protons for *endo* isomers. In particular, the **H-2** signal of the *exo* isomers showed a downfield shift of about 0.5-0.8 ppm (~3.1 ppm for *endo vs* ~3.8 ppm for *exo*). Similarly, the **H-3** signal exhibited a upfield shift of about 0.5-0.7 ppm, (~3.7 ppm for *endo vs* ~3.2 ppm for *exo*). The **H-4a/H-4e** pattern of the *endo* isomers (**H-4e** ~3.3 ppm, downfield of **H-4a** at ~2.8 ppm) was completely reversed for the *exo* isomers and **H-4a** was found upfield (~3.2-3.4 ppm) of **H-4e** (~3.0 ppm) in all cases, except for **92/93c** where **H-3**, **H-4a** and **H-4e** were all observed as a combined multiplet centered at 3.16 ppm. The difference in coupling constants between **H-2** and **H-3** was also significant enough to help distinguish between *endo* and *exo* cycloadducts. In the case of *endo* adducts, $J_{2,3}$ is always large (~11 Hz) compared to the smaller values (~6-8 Hz) obtained for the *exo* isomers.

An attempt was made to determine the solution conformations of the cycloadducts from their ^{1}H-nmr spectra. The lowest energy conformations for both the *endo* and *exo* isomers were calculated using molecular mechanics (MMP2, performed by Dr. J.L. Charlton) for cycloadduct **86** which was used as a model[74]. Table 7 shows the dihedral angles for all the low energy conformations as well as the expected coupling constants for each conformer. In these conformations, a positive dihedral angle is one where the atom in the background is rotated clockwise relative to the atom in the foreground. Only the chair conformations are represented here, since the steric energies for the boat conformations were always found to be ~3 kcal/mol higher than that of the chair analogs.



87



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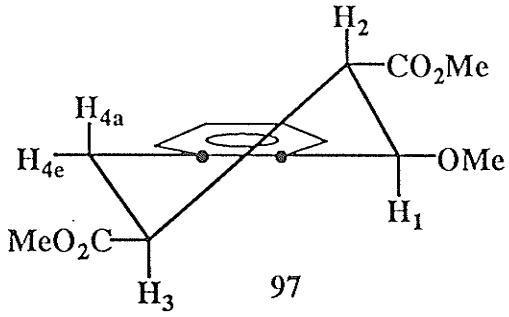

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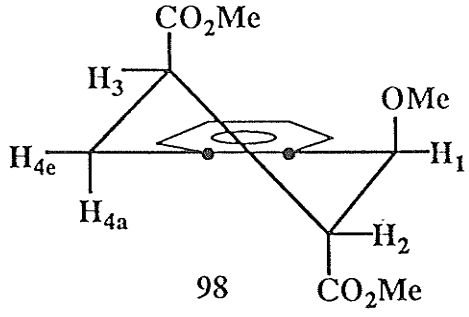
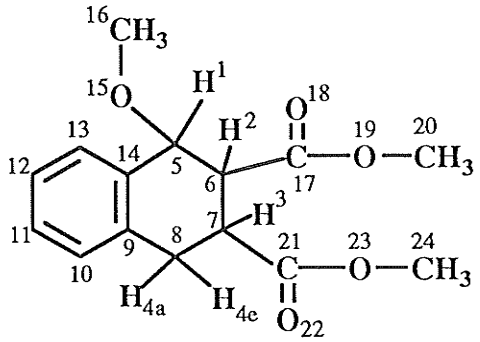


98

According to the MMP2 calculations, the *endo* conformer **87** (Steric Energy: 6.60 Kcal/mol) should be predominant in solution over **96** (Steric Energy: 8.67 Kcal/mol) and the ^{1}H-nmr data of Durst *et al.* are consistent with the *endo* conformer **87**[22]. The ^{1}H-nmr data of the *endo* cycloadducts formed from **16**, **83** and **84**, can also be explained assuming that they are in a conformation similar to **87**. On the other hand, the ^{1}H-nmr data obtained for the *exo* isomers cannot be explained using any of the low energy conformations (**97a**, **97b**, **98**) (**97a** and **97b** are similar to **97**) calculated for the *exo* isomer. The ^{1}H-nmr results of these *exo* isomers seem to be most consistent with a boat conformation although the molecular mechanics program (MMP2) was not able to find any low energy boat conformations.

Table 7. Dihedral Angles and Coupling Constants

86



Conformation

Dihedral Angles (°)	Endo		Exo		
	87	96	97a	97b	98
C_{16}-O_{15}-C_5-H_1	-55.3	45.3	177.9	-6.2	59.3
O_{18}-C_{17}-C_6-H_2	134.9	34.7	149.5	157.5	-119.0
O_{22}-C_{21}-C_7-H_3	147.6	-121.0	138.6	136.8	-117.9
H_1-C_5-C_6-H_2	56.1	-45.9	171.2	171.0	65.2
H_2-C_6-C_7-H_3	176.1	-58.6	176.1	174.3	-57.5
H_3-C_7-C_8-H_{4a}	163.1	-49.3	171.6	169.5	70.4
H_3-C_7-C_8-H_{4e}	45.9	67.3	54.0	52.0	-45.9
Steric Energy (Kcal/mol)	6.60	8.67	6.73	6.71	7.71
Estimated Coupling Constant (Karplus Equation) (Hz)					
$J_{1,2}$	2-3	4-5	9-10	9-10	0-1
$J_{2,3}$	9-10	1-2	9-10	9-10	2-3
$J_{3,4a}$	9-10	3-4	9-10	9-10	0-1
$J_{3,4e}$	4-5	0-1	2-3	2-3	4-5

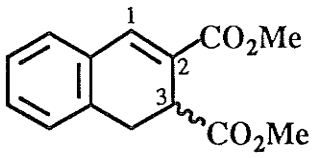
In all of the reactions, the mixture of diastereomers made up more than 95% of the crude reaction mixture, with the major isomer being ~60% of the total. Purification of the cycloadducts was either done by chromatography or crystallization. The major isomers **88/89a, 88/89b, 88/89c** could be crystallized directly from the reaction mixtures and were therefore freed from the minor isomers in each case. The minor isomers (**90/91, 92/93, 94/95**) produced from the reactions of **85b** and **85c** could only be partially separated by flash chromatography[75], and were only characterized using difference ^{1}H-nmr techniques.

To determine at which face of the *o*-quinodimethane the reactions took place, it was necessary to determine the absolute configurations of the new chiral centers relative to that of the chiral auxiliary. To perform this part of the study, optically pure chiral auxiliaries were needed. The cycloaddition reactions were therefore carried out according to Scheme 3 with sulfones **85a** and **85b** generating *o*-quinodimethanes **16** and **83**, bearing optically pure chiral auxiliaries (S)-phenylethyl for **16** and (R)-2-methyl-1-phenylpropyl for **83**.

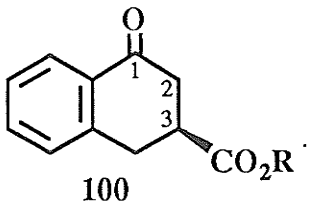
The reactions proceeded in the same fashion as with the racemic material previously used giving in both cases good yields (84 and 81% respectively) of cycloadducts. As in the case of the racemic mixtures, four diastereomers were observed in the crude ^{1}H-nmr spectra with the *endo* addition producing the major isomer in both reactions. The major isomer (**88b**) of the mixture could be crystallized from the reaction of **(R)-83** and was freed from the minor isomers. This diastereomer was further recrystallized to constant melting point (mp: 95-96.5°C) and constant optical rotation ($[\alpha]_D$= -59.4°). In the reaction of **(S)-16**, the major diastereomer (**89a**) could not be crystallized but was enriched by chromatography, giving an 85/15 mixture (from ^{1}H-nmr) with the minor *endo* diastereomer (**91a**) ($[\alpha]_D$= +47°).

To determine the stereochemistry of the newly formed chiral centers of the major diastereomers, two possible methods could be used. The first and most direct method would be by performing X-ray analysis of a suitable crystal. This was thought to be possible for **88b** as that diastereomer was obtained in a pure form. However, all attempts to obtain crystals of that cycloadduct (**88b**) suitable for X-ray analysis failed as the crystals obtained were found to be amorphous. The second method which could be used in the determination of the absolute configurations of the cycloadducts, involves the transformation of the cycloadducts into other product(s) of known stereochemistry. Since crystals suitable for X-ray analysis could not be obtained, this second method was used to determine at which face of the *o*-quinodimethanes reaction predominantly took place.

Two compounds, **99** and **100**, were found to be possible derivatives of the cycloadducts from which the stereochemistry of **89a** and **88b** could be deduced[22,29,76]. Because of its known configuration and rotation, the tetralone **100** was first investigated.

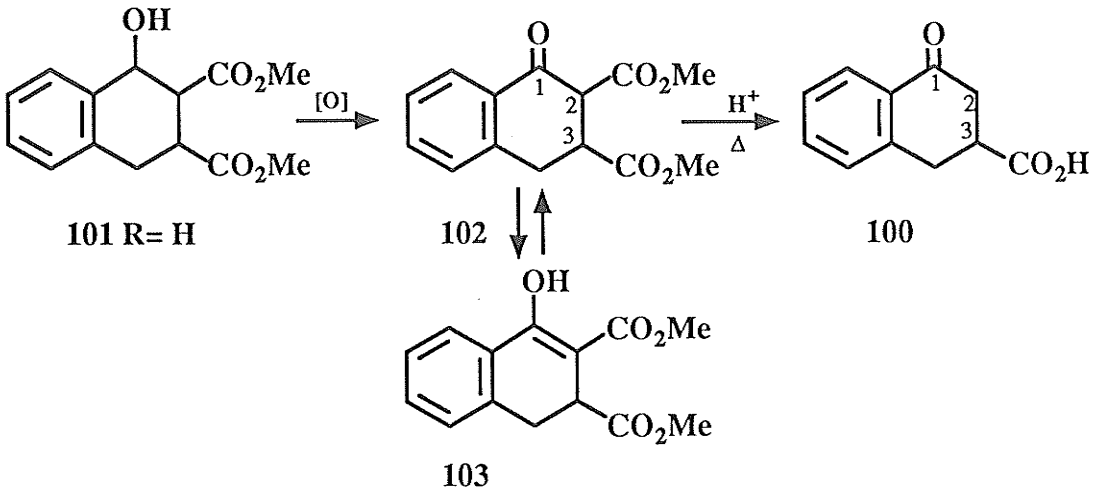


99



100
R=H; CH_3

It was thought that cycloadducts (**88a** and **88b**) could be oxidized to the ketone **102**, which in turn could be decarboxylated to produce the tetralone **100**. In order to investigate this route, the hydroxycycloadduct **101** was first used as a model to determine the reaction conditions for the production of tetralone **100** from **102** as illustrated in Scheme 4.

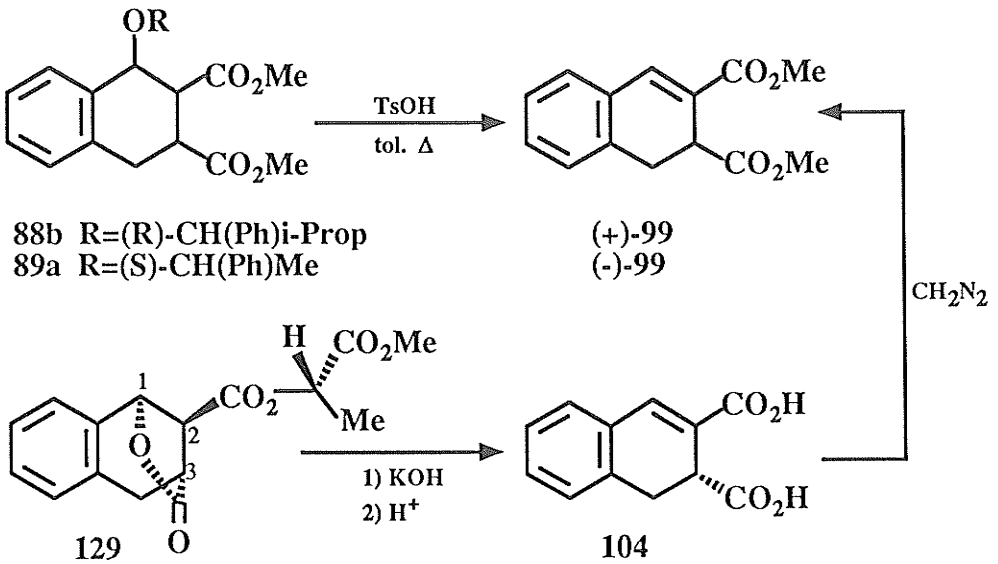


SCHEME 4

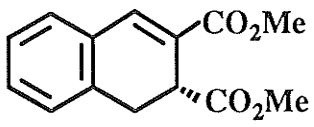
The cycloadduct **101** was prepared by irradiation of *o*-methylbenzaldehyde with dimethyl fumarate in benzene, giving good yield (87%) of a mixture of *endo* and *exo* diastereomers (*endo*/*exo* ratio 74:26). Upon treatment with chromium trioxide in dilute sulfuric acid, the racemic mixture of *endo* and *exo* cycloadducts **101** afforded a good yield (85%) of dicarbomethoxy tetralone **102**. A second product was also observed in the reaction mixture. Purification by chromatography on silica gel did not afford any tetralone **102**, and only the second product of the original reaction mixture was recovered in quantitative yield. This product was later identified as the enol form **103** of the tetralone **102**. The equilibrium between **102** and **103** seems to lie towards the enol **103**, as treating pure **102** with acid afforded a mixture of enol **103** and ketone **102** in an 89:11 ratio. This was not surprising as similar ketones are known to exist largely in the enol form[77]. Recrystallization of the original reaction mixture of tetralone **102** and enol **103** provided tetralone **102** (mp: 84-86°C) free from its enol form **103**. Simultaneous decarboxylation at the 2 position and hydrolysis of the methyl ester at the 3 position afforded the carboxy

tetralone **100** in good yield (86%). Recrystallization of that material was easily achieved from water to give pure tetralone **100** (mp: 147-149°C; ref: 149°C)[76]. Unfortunately, no conditions could be found to prepare the dicarbomethoxy ketone **102** from alkoxycycloadducts **88/89a**, **88/89b** or **88/89c**, which were used as a model for the optically pure alkoxycycloadducts **88a** and **88b**. Even the conditions ($Ce(NH_4)_2(NO_3)_6$; $KBrO_3$; CH_3CN/H_2O; reflux 24h) which were found to work well (84%) with a model (methoxytetralin)[78], afforded only small amounts (<10% from ^{1}H-nmr) of ketone **102**, the major product in the reaction mixture being in all cases the original cycloadduct.

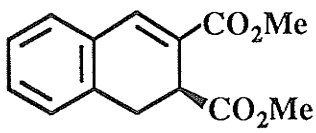
This lack of success in forming the carboxy tetralone **100** from any alkoxycycloadducts directed attention towards the dicarbomethoxy derivative **99**. This derivative was easily prepared according to a procedure previously reported[22,29]. Treatment of the cycloadducts **88/89a**, **88/89b**, **88/89c** with p-toluenesulfonic acid in refluxing toluene gave, after chromatography, good yields (69-90%) of elimination product **99**. Treating the cycloadduct **88b** under the same conditions afforded, after chromatography, pure **(+)-99** in 71% yield ($[\alpha]_D$= +124°). Good yield (92%) was also obtained for **(-)-99** prepared from **89a**, but the magnitude of the optical rotation ($[\alpha]_D$= -92°) was smaller in this case, as an 85:15 mixture (from ^{1}H-nmr) of two *endo* diastereomers (**89/91a**) was used as starting material for the reaction.



The elimination product (+)-**99** could also be prepared from the γ-lactone **129** whose structure was unambiguously established by X-ray analysis (**1S,2S,3R**)[16]. The formation of the lactone **129** is not discussed here as this will be covered in **Section 2.4**. Hydrolysis of lactone **129** in methanolic KOH followed by treatment of the diacid **104** with diazomethane afforded (+)-**99** ($[\alpha]_D$= +128°) in 65% yield. Under those conditions, no inversion of configuration at the 3 position was possible and (+)-**99** was therefore assigned the **R** configuration.

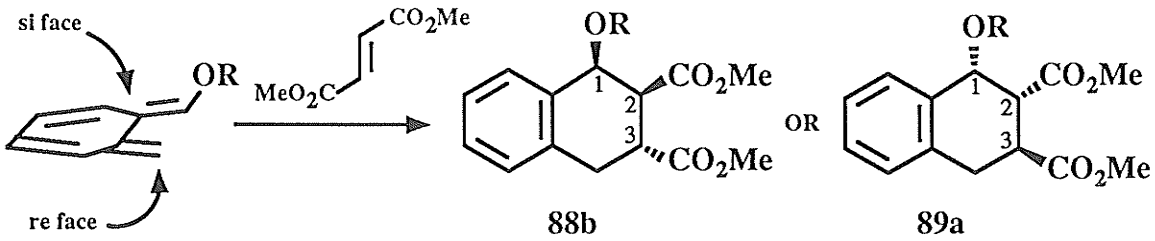


R-(+)-99



S-(-)99

Since the cycloadducts **88b** and **89a** had the relative stereochemistry (*r-1,c-2,t-3*), the absolute configuration of **89a** was determined to be **1'S,1R,2R,3S** and **88b** was **1'R,1S,2S,3R**. As it was found for the *o*-quinodimethane **16**, the **R** chiral auxiliary must partially block the *re* face in **83** to produce the configuration found for the major cycloadduct **88b**[29]. Similarly, the **S** chiral auxiliary partially blocks the *si* face of the *o*-quinodimethane.



88b **89a**

configuration of chiral auxiliary (R)	reacting face of o-quinodimethane	configuration of cycloadduct
R	**si**	**1'R,1S,2S,3R (88b)**
S	**re**	**1'S,1R,2R,3S (89a)**

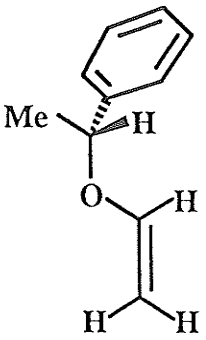
The optically pure form of the chiral auxiliary for **84** was not available and therefore the relative configurations of the chiral centers in the cycloadducts produced from this *o*-quinodimethane were assigned on the basis of the ^{1}H-nmr spectrum of the racemic material. For the reactions of **16** and **83**, the major *endo* cycloaddition products have the signals for **H-1** and **H-2** downfield of the corresponding protons in the minor *endo* isomers. This pattern was also true for the racemic cycloadducts obtained from **84**, which led to the conclusion that the relative configurations of the chiral centers in the cycloadducts obtained from **84** were the same as those of the cycloadducts obtained from

16 and **83**. Thus, the major adduct from the reaction of the racemic **84** was assumed to be a racemic mixture of **88/89c**. If this is the case, the **R** chiral auxiliary in **84** also partially blocks the *re* face of the *o*-quinodimethane.

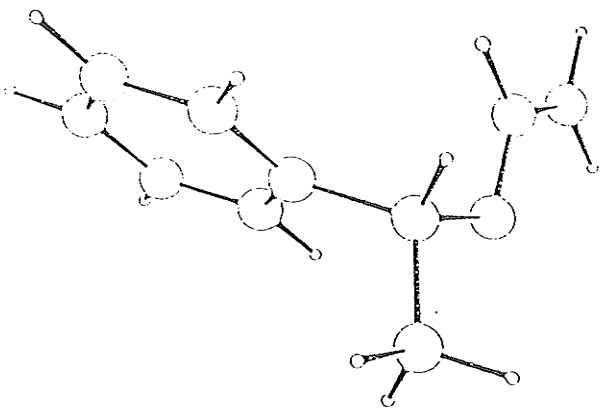
Diels-Alder cycloaddition reactions of *o*-quinodimethanes are expected to be relatively exothermic with early transition states (Hammond postulate) as is the case for most Diels-Alder reactions. Also, the conformation of the *o*-quinodimethane should not substantially change as the *o*-quinodimethane enters the transition state. In such cases, the face selectivity observed in the reaction of *o*-quinodimethanes bearing a chiral auxiliary might be predicted by determining the preferred conformation of the chiral auxiliary on the *o*-quinodimethane. There are precedents in the literature, for other Diels-Alder reactions, of such predictions of face selectivity based on conformational preferences of the diene or dienophile[72].

Ab initio molecular orbital calculations with geometry optimization were carried out (performed by G.H. Penner) on the vinyl ether **77**[26], which was previously used in the Diels-Alder cycloaddition reaction by Posner and Wettlaufer[73]. The vinyl ether **77** was chosen as a model for *o*-quinodimethane **16** so that computational requirements could be reduced.

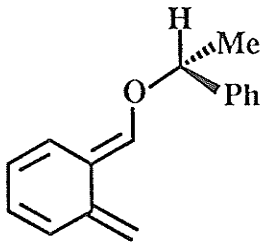
The calculations indicated that the lowest energy conformation of **77** is that in which the methyl group is in plane with the double bond of the olefin as shown in structure **105**. This is illustrated more accurately in the **ORTEP** drawing.



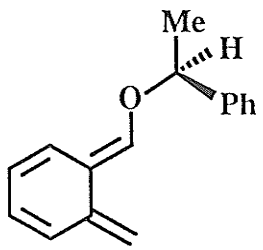
105



It is reasonable to expect the *o*-quinodimethane **16** to have similar conformational preferences and the most stable conformer of **16** is therefore assumed to be the one shown in structure **106**. In this conformation, the difference in the steric bulk of the phenyl and hydrogen substituents will control the face selectivity in the cycloaddition reaction. This is slightly different from the conformation **52** previously proposed by Charlton to explain the cycloaddition diastereoselectivity[29]. In the case of **52**, it was proposed that face selectivity depended on the difference in size of the phenyl and methyl substituents. The new proposal, that reaction occurs from conformer **106**, is more consistent with the experimental data. The diastereoselectivity should be improved (as observed) by exchanging the methyl group in the chiral auxiliary of the *o*-quinodimethane **16** for an isopropyl (*o*-QDM **83**) or *tert*-butyl (*o*-QDM **84**), as preference for conformation **106** is increasing, since this conformation provides the most room for the alkyl substituent.



52



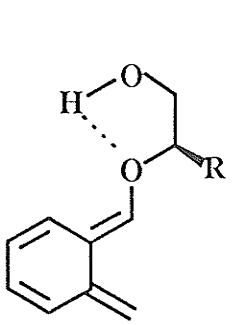
106

Based on these observations and calculations, it appears that further improvement in face selectivity in the Diels-Alder reaction of *o*-quinodimethanes could be achieved if one could more rigidly lock the conformation of the chiral auxiliary on the *o*-quinodimethane. Attempts to perform this task are reported in the next Section.

2.3 Preliminary Studies of Hydrogen Bonding in the Chiral Auxiliary

Note: *The data discussed in this Section were obtained from preliminary experiments only. Elemental compositions (elemental analysis or exact mass/mass spectrum) of the products of the reactions discussed here were not obtained, unless otherwise stated. All of the products in this Section were identified on the basis of their ^{1}H-nmr and/or IR spectra only, often obtained from crude reaction mixtures.*

One method which can be used to lock the conformation of the chiral auxiliary more rigidly, is to introduce another functionality on the alkyl group of the auxiliary capable of hydrogen bonding with the ether oxygen. Such a function could either be an alcohol or an amine properly located in the chiral auxiliary as depicted in structures **107** and **108**.



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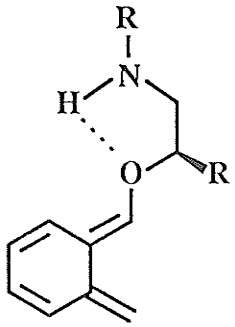
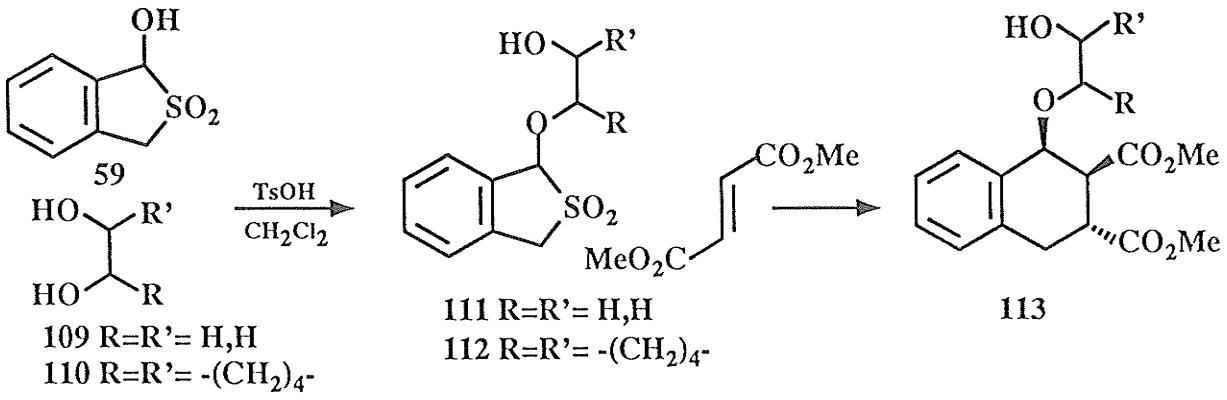


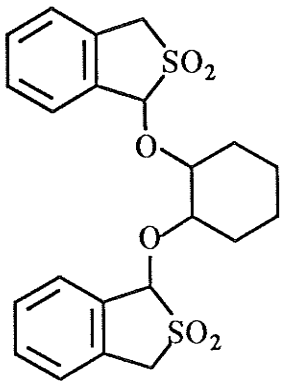
108

The synthesis of the sulfones required to generate **107** was first investigated. Two possibilities can be considered for introducing the terminal hydroxyl group needed for the hydrogen bonding. The first possibility consists of using a starting material which already contains the second hydroxyl group, while the second possibility would be to use a starting alcohol containing a functional group which could later be transformed into the hydroxyl group needed for hydrogen bonding.

The first possibility was initially chosen in this investigation as it was the simpler of the two. Hydroxysulfone **59** was reacted with ethylene glycol **109** in order to establish the feasibility of introducing an auxiliary bearing an hydroxyl group. The reaction proceeded smoothly producing good yields (77%) of alkoxysulfone **111**. Cycloaddition reaction under the usual conditions (toluene, ZnO, dimethyl fumarate, reflux) afforded only moderate yield (54%) of cycloadduct **113**. However, the diastereoselectivity in this reaction was quite high with *endo* addition being predominant as shown by an *endo*/*exo* ratio of ~9:1.

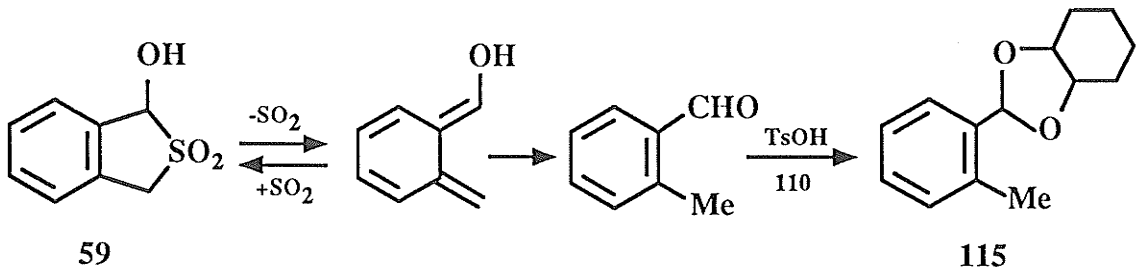


When reacting the diol **110** with the hydroxysulfone 59, a mixture of at least two products was obtained. The two products could be separated by chromatography as their absorptions on silica gel (as shown on tlc) were quite different. The slower running product was completely freed from other material and was easily identified as the sulfone **112** (see above) on the basis of the similarities of its ^{1}H-nmr spectrum with that of other sulfones, as well as its infrared (IR) spectrum [1320, 1207, 1126 (SO), 3551 (OH)] showing typical absorptions for the sulfone and for the hydroxyl group. The faster running product, which could not be completely freed from other impurities, was a white solid (mp: 65-68°C), which could not be further purified nor fully characterized. From the ^{1}H-nmr and IR data [1316, 1202, 1120 (SO)], it was tentatively assigned the structure **114**.



114

Since using an excess of hydroxysulfone **59** produced a mixture of alkoxysulfone **112** and possibly the dialkoxysulfone **114**, it was decided to perform the same reaction with an excess of diol **110** instead of an excess of sulfone **59**. Under these conditions, very poor yield (~25%) of a mixture of products was obtained. The ^{1}H-nmr of the mixture was consistent with the presence of the alkoxysulfone **112**, *o*-methylbenzaldehyde (traces) and a third product which was the major component of the mixture. This third product was later identified as the acetal **115** as this product could be directly prepared in 91% yield from *o*-methylbenzaldehyde. A possible way to produce **115** is by extrusion of SO_2 from the hydroxysulfone **59** generating the *o*-quinodimethane which eventually produces *o*-methylbenzaldehyde and finally the acetal **115** as shown in Scheme 5.



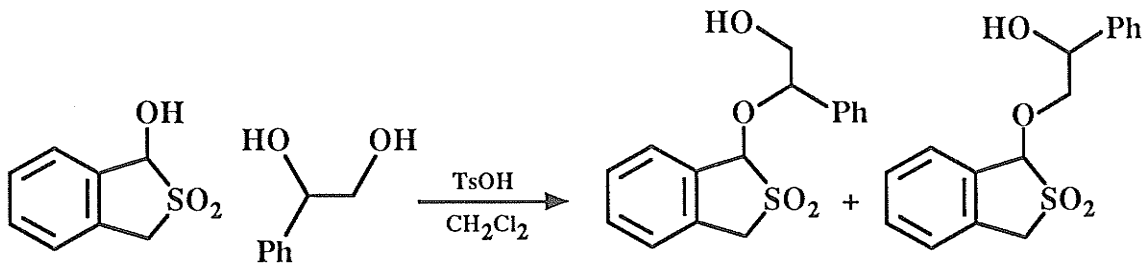
59 **115**

SCHEME 5

The cycloaddition reaction of alkoxysulfone **112** with dimethyl fumarate, performed under the usual conditions (toluene, ZnO, reflux), did not produce any cycloadduct. Only an unidentifiable mixture of products was obtained. Purification for the purpose of identifying the products was not attempted.

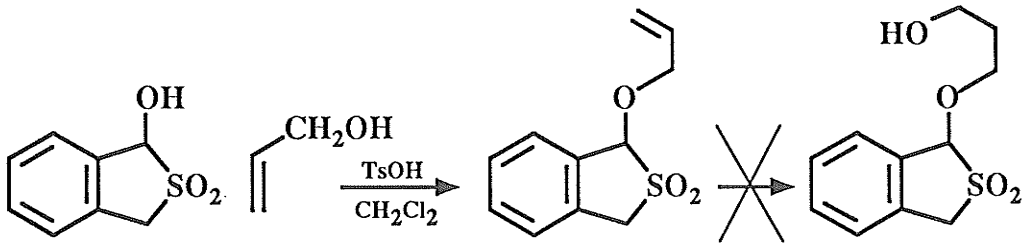
As expected, the use of an unsymmetrical diol created more problems in the formation of the alkoxysulfone. The reaction of hydroxysulfone **59** with 1-phenyl-1,2-ethanediol **116** (prepared by reduction of methyl mandelate) afforded an

inseparable mixture of what appeared to be alkoxysulfones **117a** and **117b**. These sulfones were not cycloadded with dimethyl fumarate.



59 **116** **117a** **117b**

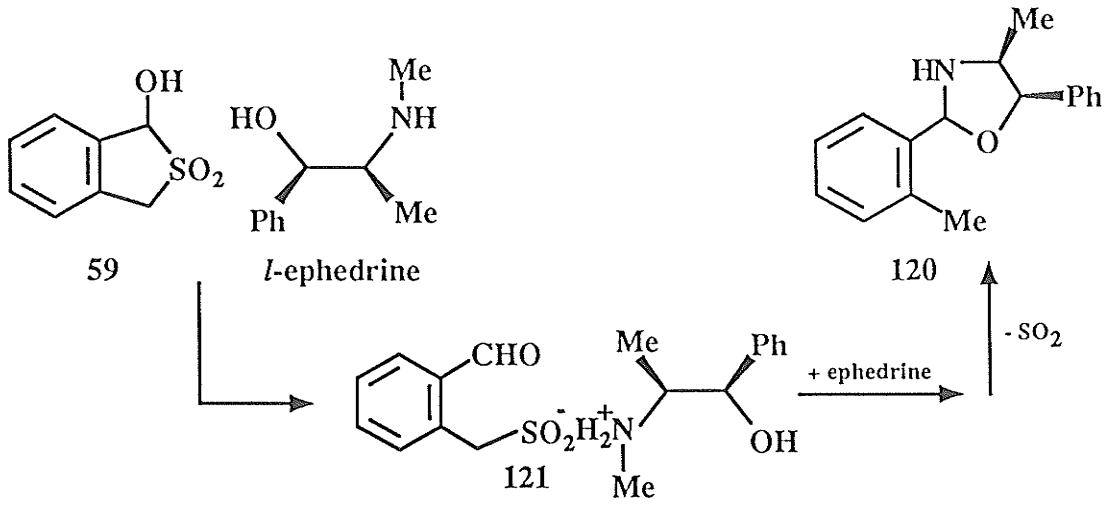
In view of the difficulties encountered above, the synthesis of an alkoxysulfone bearing a masked hydroxyl group was undertaken. Hydroboration-oxidation of alkoxysulfone **118** (1) BH_3-DMS, room temp. 1h; 2) NaOH, H_2O_2, 0°C 4h), prepared in good yield (91%) from **59** and allyl alcohol, did not produce any alkoxysulfone **111**. Because of the lack of promising results, this investigation was abandoned.



59 **118** **111**

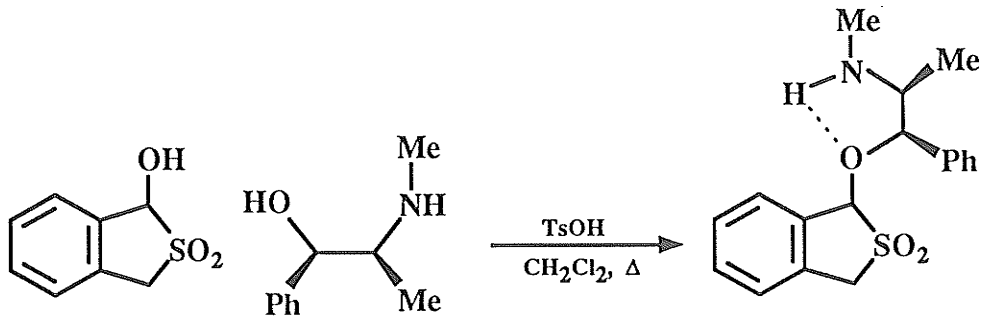
The formation of an alkoxysulfone capable of generating an *o*-quinodimethane such as **108** was also investigated. In this case, the hydroxysulfone **59** was reacted under the usual conditions (CH_2Cl_2, TsOH, reflux) with *l*-ephedrine, in the hope of preparing the sulfone **119**.

of the sulfone **59** to form the aldehyde sulfinic acid salt **121**. The aldehyde group of that salt could then react with another molecule of ephedrine producing the oxazolidine **120** after the loss of sulfur dioxide as shown in Scheme 6.



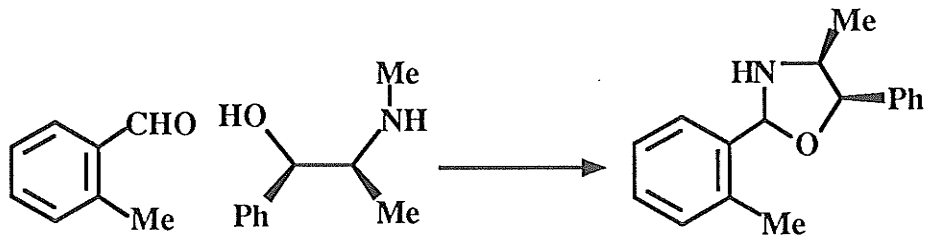
SCHEME 6

The following experiments were performed in an attempt to verify this possible mechanism. First, the formation of the salt **121** was shown to be a possible step in the formation of **120**. The reaction was carried out in a nmr tube in $CDCl_3$, so that the progress of the reaction could be followed by ^{1}H-nmr spectroscopy. Equimolar amounts of hydroxysulfone **59** and *l*-ephedrine were mixed together and the ^{1}H-nmr spectrum was recorded. The ^{1}H-nmr data obtained were consistent with the presence of the sulfinic acid salt **121** (CHO, s 10.17ppm). All of the original signals for *l*-ephedrine and the sulfone **59** were also absent in the ^{1}H-nmr spectrum. The presence of a carbonyl function was also confirmed by IR spectroscopy (1694 cm^{-1}). The formation of sulfinic acid salts from hydroxysulfones has previously been performed at pH=10 in D_2O[19]. As was previously mentioned, the oxazolidine formation between an aldehyde and a hydroxylamine is well



59 *l*-ephedrine **119**

All the attempts to generate the sulfone **119** failed, as the typical signals of an alkoxysulfone could not be observed in the ^{1}H-nmr spectrum of the reaction mixture (**H-1** s ~5.2 ppm, **H-3A** d ~4.5 ppm, **H-3B** d ~4.2 ppm). The characteristic absorptions of the sulfone in the IR spectrum (~1320, 1200, 1120 (SO)) were also absent, re-enforcing the fact that **119** was not present in the reaction mixture. Instead of **119**, chromatography afforded a pure unknown compound which was assigned structure **120** on the basis of its ^{1}H-nmr spectrum. The structure of this crystalline product (mp: 87-89°C) was later proven as it could be prepared from the reaction of *o*-methylbenzaldehyde with *l*-ephedrine and fully characterized. This type of reaction between aldehydes and hydroxyl amines is well documented[79,80].



120

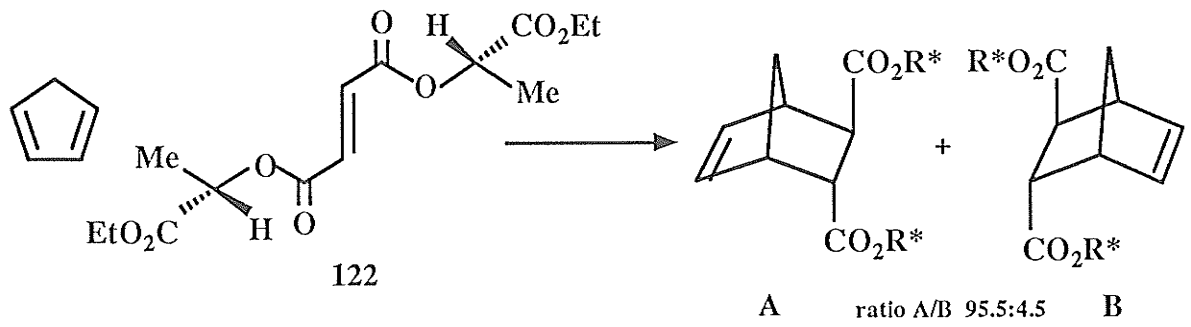
A possible mechanism which could explain the formation of the oxazolidine **120** is described below. It is reasonable to think that the basicity of ephedrine can cause opening

documented[79,80], and the oxazolidine **120** could be directly prepared from *o*-methylbenzaldehyde. This product (**120**) could also be prepared by forming the sulfinic acid salt **121**, followed by treatment of this salt with a second equimolar amount of ephedrine and refluxing in methylene chloride for a few hours.

Since producing an *o*-quinodimethane bearing an unsymmetrical chiral auxiliary capable of hydrogen bonding with the ether oxygen did not afford promising results, a new aspect of the research was undertaken. Instead of working with a chiral auxiliary on the *o*-quinodimethane, attention was directed towards the search of dienophiles bearing chiral auxiliaries which could produce high asymmetric induction. This investigation is the subject of the next Section.

2.4 Search for a Chiral Dienophile

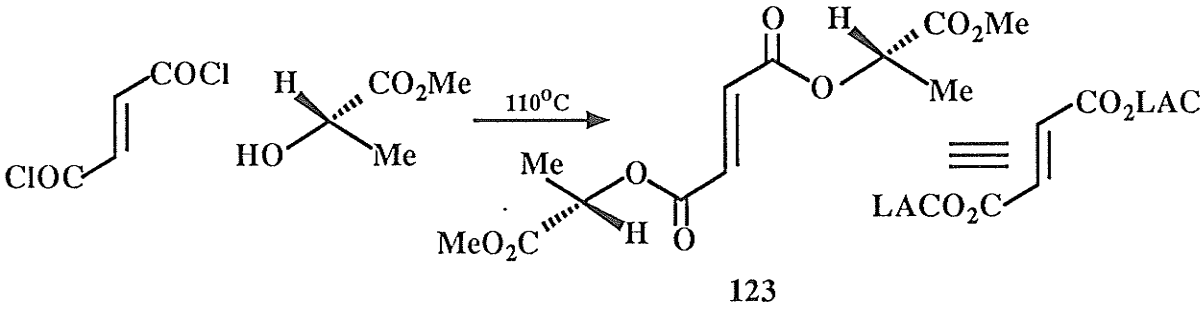
Because the search for a chiral *o*-quinodimethane (**Sections 2.1** to **2.3**) produced results which would have marginal usefulness in asymmetric synthesis, a literature survey was performed in order to find chiral dienophiles that give high diastereoselectivity in Diels-Alder reactions. Two of the more interesting dienophiles found were the acrylate and the fumarate (**122**) of (S)-ethyl lactate[71,72,81]. At 0°C these dienophiles react with cyclopentadiene with diastereoselectivities of 80:20 and 95.5:4.5 respectively (*endo* adduct for addition of acrylate)[71,81].



122

A ratio A/B 95.5:4.5 B

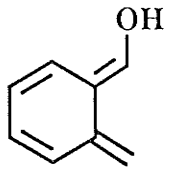
Because (S)-methyl lactate has a ^{1}H-nmr spectrum slightly less complicated than the (S)-ethyl lactate used by Helmchen *et al.*[81], the fumarate of (S)-methyl lactate **123** was chosen for a study of its cycloaddition reactions with o-quinodimethanes. This fumarate (dilactyl fumarate) **123** was prepared by heating a mixture of fumaryl chloride and (S)-methyl lactate at 110°C giving 62% yield after chromatography.



123

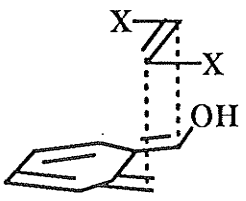
According to Helmchen's report, the most stable conformation of the fumarate of (S)-ethyl lactate is that shown in structure **122** (see above), and addition of dienes to this dienophile occurs to the less hindered *re* (upper) face[81]. This was also expected to be the case for the fumarate **123**, as the structural change in the dienophile was negligible (methyl ester in **123** *vs* ethyl ester in **122**).

In order to investigate the face selectivity in the Diels-Alder reaction of **123** with *o*-quinodimethanes, α-hydroxy-*o*-quinodimethane was initially chosen for study. This *o*-quinodimethane was generated from three sources, photolysis of *o*-methylbenzaldehyde, thermolysis of an hydroxysulfone or thermolysis of benzocyclobutenol. It was assumed that all of these three methods of generation of the *o*-quinodimethane would give the E-dienol shown below (see Chapter 1).

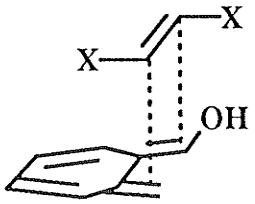


As previously explained (see Chapter 1), four approaches of the fumarate to the α-hydroxy-*o*-quinodimethane are possible. They are classified below according to their prochiral reacting faces. Here, the classification of the α-hydroxy carbon of the *o*-quinodimethane is given first, followed by the classification of the face of the fumarate that will bond to that center.

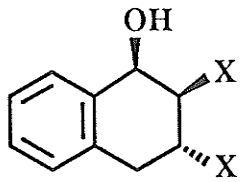
Approaches of diene and dienophile **Resulting cycloadducts**



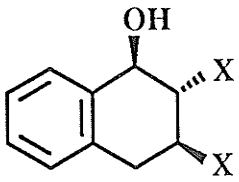
A (endo) *si, re*



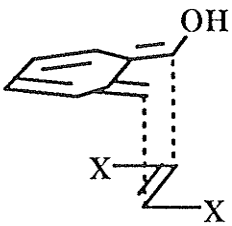
C (exo) *si, si*



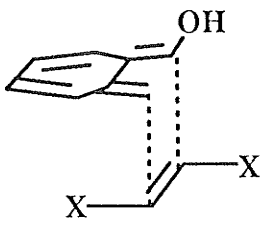
AA



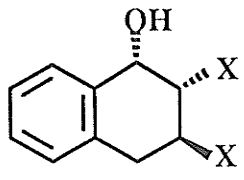
CC



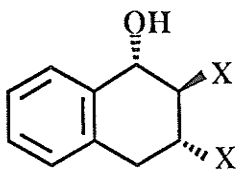
B (endo) *re, si*



D (exo) *re, re*



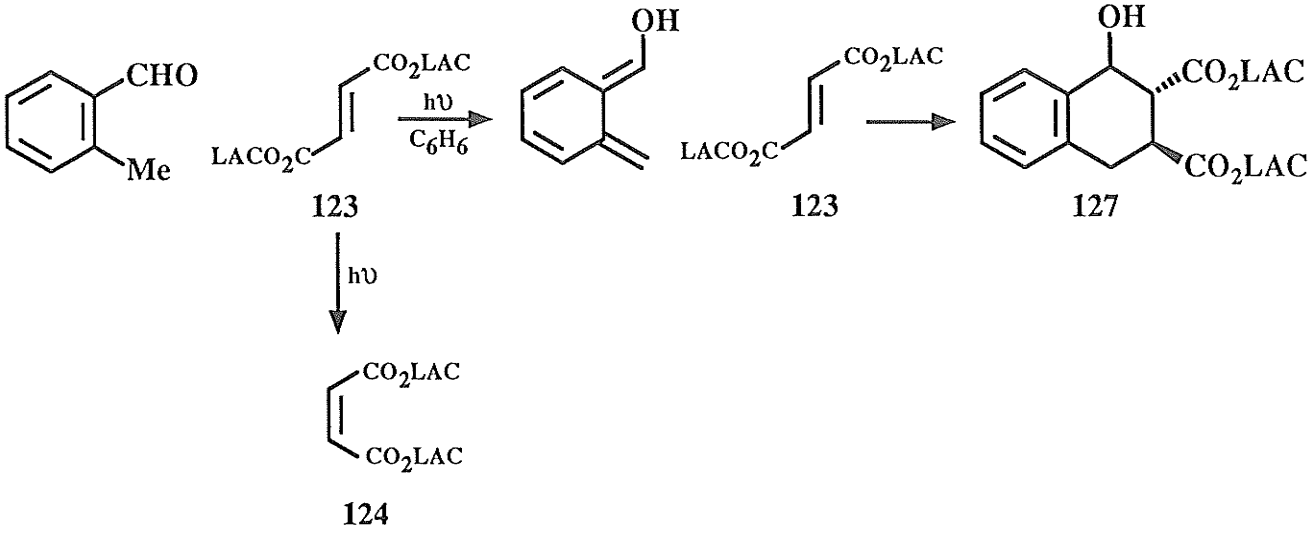
BB



DD

Previous work on E-α-hydroxy-*o*-quinodimethanes (see **Chapter 1**) with achiral dienophiles (dimethyl fumarate or methyl acrylate) has shown that the major adducts are formed via the *endo* transition states A or B, and that the resulting cycloadducts are **AA** or **BB**[8,14,22,38,40]. On the other hand, solvent effects have shown that polar interactions between the diene and dienophile favour the *exo* transition states C and D[83]. Based on the preceding observations, the Diels-Alder cycloaddition between an α-hydroxy-*o*-quinodimethane and the chiral dilactyl fumarate **123** was expected to produce a cycloadduct of configuration **AA** via transition state A.

The reaction was first performed at room temperature with α-hydroxy-*o*-quinodimethane generated by photolysis of *o*-methylbenzaldehyde (hυ, C_6H_6). This method was chosen as it was the easiest way to generate the α-hydroxy-*o*-quinodimethane. Irradiation of the aldehyde with an excess of dilactyl fumarate **123** gave a single crystalline cycloadduct (mp: 84.5-85.0°C; $[\alpha]_D$= -64°) which was isolated in 55% yield by column chromatography. Analysis of the ^{1}H-nmr spectrum of the crude reaction mixture showed that, besides the cycloadduct (**H-1** 4.95 ppm), the only other significant product of the mixture was the maleate of (S)-methyl lactate **124** indicating that the reaction produced a diastereomeric excess of at least 95%. The actual yield of cycloadduct was higher than the 55% isolated chromatographically, but it was very difficult to separate the product from the maleate **124** formed during photolysis, as both products had similar retention times on silica gel.



The photoisomerization of the fumarate **123** to the maleate **124** was probably sensitized by energy transfer from the excited state of the *o*-methylbenzaldehyde, since irradiation of the fumarate **123** in benzene alone gave only traces of the maleate **124**. On the other hand, the same reaction performed in the presence of benzophenone afforded a photostationary state equilibrium between maleate **124** and fumarate **123** of 92:8 (determined by ^{1}H-nmr).

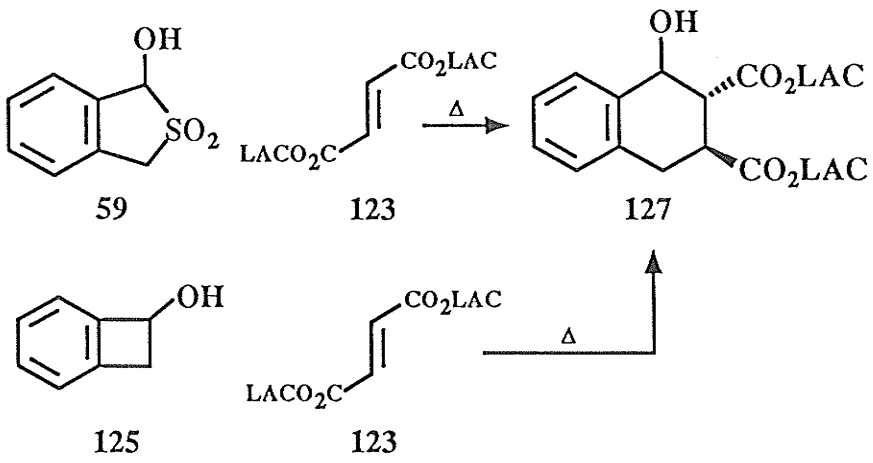
The production of a single crystalline cycloadduct seemed to be dependent on the reaction time. When irradiation was performed for 6 hours, only one cycloadduct (**H-1** signal 4.95 ppm) could be detected from the ^{1}H-nmr spectrum of the crude mixture. After 12 hours a second cycloadduct appeared (~5% of the major) as observed by a new doublet signal at ~5.4 ppm representing **H-1** of the minor isomer. After 24 hours, the ratio of the minor isomer to the major was ~10%, and did not further increase with an increase of the reaction time. This second isomer could have arisen from the reaction of the *o*-quinodimethane and the dilactyl maleate **124** as this dienophile was predominant in

solution over the fumarate **123** after the initial 6 hours of the reaction (ratio of maleate/fumarate left in solution after 6 hours, 90:10, ^{1}H-nmr of crude mixture).

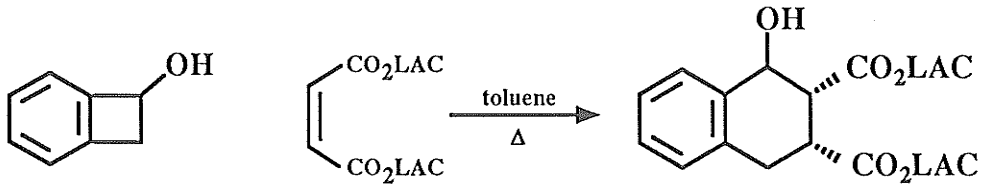
To verify the possibility of having produced a maleate adduct, the following experiments were performed. Firstly, the cycloaddition reaction was repeated under the same conditions (hυ, C_6H_6, 6 h), but with pure dilactyl maleate **124** as dienophile. After irradiation of the solution for 6 hours, a mixture of two cycloadducts was obtained. Both isomers of the mixture were identical (^{1}H-nmr, major **H-1** 4.95, minor **H-1** 5.4 ppm) to those obtained in the reaction with fumarate **123**. The only difference encountered between this reaction and that performed with the fumarate **123** was in the ratio of isomers. The minor isomer (**H-1** 5.4 ppm) of this reaction was produced in ~20% of the major isomer (**H-1** 4.95 ppm) compared to ~10% in the reaction with fumarate **123**. The large production of the same major adduct (**H-1** 4.95 ppm) in these two cycloaddition reactions seems to indicate that the fumarate **123** is more reactive than the maleate **124**. It was later found that the production of the second isomer in the photolysis reactions could be avoided by using a shorter reaction time and also an increased concentration of dilactyl fumarate **123**.

Thermolysis of the hydroxysulfone **59** under the usual conditions (toluene, ZnO, reflux 10 h) with the fumarate **123** afforded disappointingly small amounts (~10%) of cycloadduct. Performing the reaction under slightly different conditions (addition of CH_2Cl_2 solution of **59** to refluxing toluene solution of fumarate **123**) afforded only one cycloadduct (**H-1** 4.95 ppm) in 58% yield. In this case, the purification was much easier to perform than in the case of the photolysis experiment, as no maleate **124** was present in the reaction mixture. Separation of the cycloadduct and the fumarate **123** was possible as these two compounds were retained differently on silica gel. The thermal reaction,

forming this unique cycloadduct (**H-1** 4.95 ppm) from the hydroxysulfone **59**, not only had the advantage that the purification of the product was easier than in the photolysis reaction, but also, the chromatography afforded unreacted dilactyl fumarate **123** which could be recovered and reused. In the photolysis reaction this was not possible as the fumarate **123** was isomerized to the maleate **124**. The production of only one cycloadduct (**H-1**, 4.95 ppm) in this thermal reaction confirms that the minor isomer (**H-1** 5.4 ppm) produced in the photolysis reaction was a maleate adduct, since dilactyl maleate **124** could not have been produced here and only one diastereomer was obtained. The same major cycloadduct (**H-1**, 4.95 ppm) was also produced as the only cycloadduct in the reaction of fumarate **123** and benzocyclobutenol **125**.

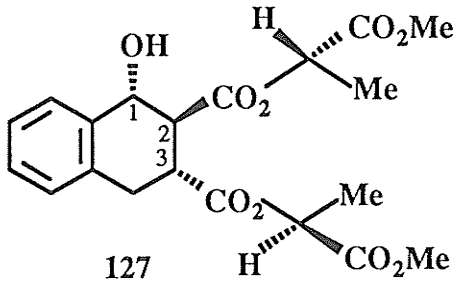


The minor isomer (**H-1** 5.4 ppm), obtained in the photolysis reaction of *o*-methylbenzaldehyde and dilactyl fumarate **123**, was later indeed shown to be a maleate adduct (**126**), as it was prepared as one of the diastereomers in an inseparable mixture of diastereomers (~70:30, $[\alpha]_D$= -28.6°) from the reaction of dilactyl maleate **124** and benzocyclobutenol **125** (toluene, 3Å molecular sieves, reflux 5 h). Attempts to produce this cycloadduct (**126**) from the hydroxysulfone **59** failed and only dilactyl maleate **124** and *o*-methylbenzaldehyde could be recovered from the reaction.



125 **124** **126 (70:30 mixture)**

The **H-1** signal (4.95 ppm) in the ^{1}H-nmr spectrum of the major cycloadduct from the reaction of dilactyl fumarate **123** with α-hydroxy-*o*-quinodimethane was a doublet with a splitting ($J_{1,2}$) of 9.8 Hz suggesting a *trans* stereochemistry of the substituents on carbons 1 and 2. Similar compounds having a *cis* stereochemistry of the C-1 and C-2 substituents have been found to exhibit a $J_{1,2}$ less than 5 Hz (see **Section 2.2**)[22,32]. This 1,2-*trans* stereochemistry suggests that the cycloadduct would have formed via an unusual *exo* transition state (**C** or **D**). Thus, the major cycloadduct was tentatively assigned the structure **127** (shown below), which represents the absolute stereochemistry that would arise from the expected addition to the *re* face of the fumarate.

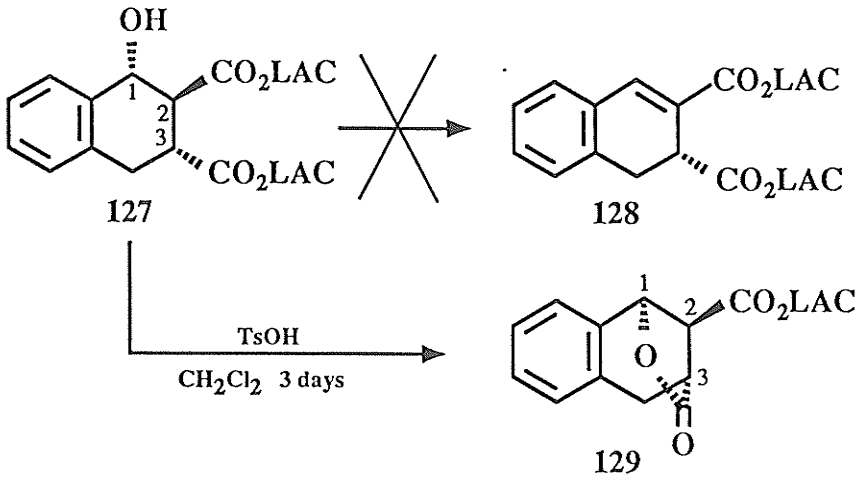


127

Treating the cycloadduct **127** with toluenesulfonic acid at reflux in methylene chloride did not produce the expected alkene **128**. Instead, elimination of one molecule of methyl lactate was observed (determined by ^{1}H-nmr), giving a product which was identified as the lactone **129** (IR: 1788 cm^{-1}). The lactone **129** (mp: 130-130.5°C, $[\alpha]_D$=

-22°) could also be produced by treating the cycloadduct **127** with toluenesulfonic acid in methylene chloride for 3 days at room temperature. Purification of the lactone **129** by chromatography on silica gel was quite difficult. Although ^{1}H-nmr of the crude reaction mixture of **129** showed that the product was at least 90% pure, only a moderate yield (51%) of lactone **129** could be achieved after purification by chromatography. This yield was difficult to reproduce, as chromatography afforded lactone **129** in yields ranging from 21% to 50% under seemingly identical conditions. This could have been due to the lactone **129** reacting with the silica gel used for chromatography.

The fact that treatment of the cycloadduct **127** with acid produced the lactone **129** reinforced the assumption that cycloadduct **127** was an *exo* isomer, since only an *exo* isomer (with 1,3-*cis* stereochemistry) could produce a lactone such as **129**, assuming that no inversion of chiral centers occurred under the conditions used. The formation of a γ-lactone between the 1-hydroxyl and the 3-carboxy group has been observed previously in similar molecules[31,82].



The lactone **129** also produced crystals suitable for X-ray crystallography[16]. It was therefore possible to determine the relative stereochemistry of the chiral centers in **129** as shown in the ORTEP diagram of **129** (Figure 2).

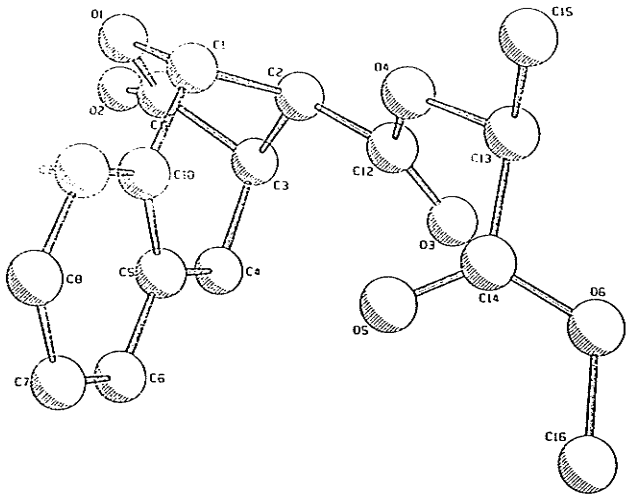
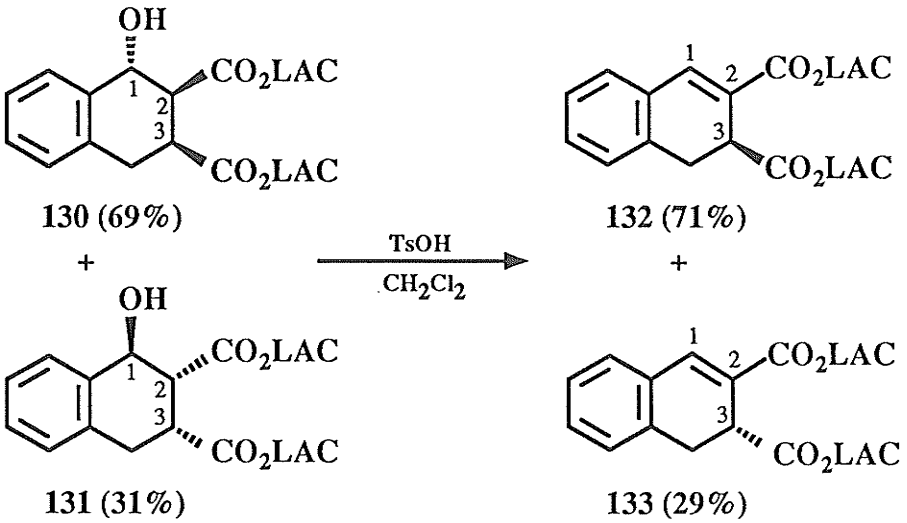


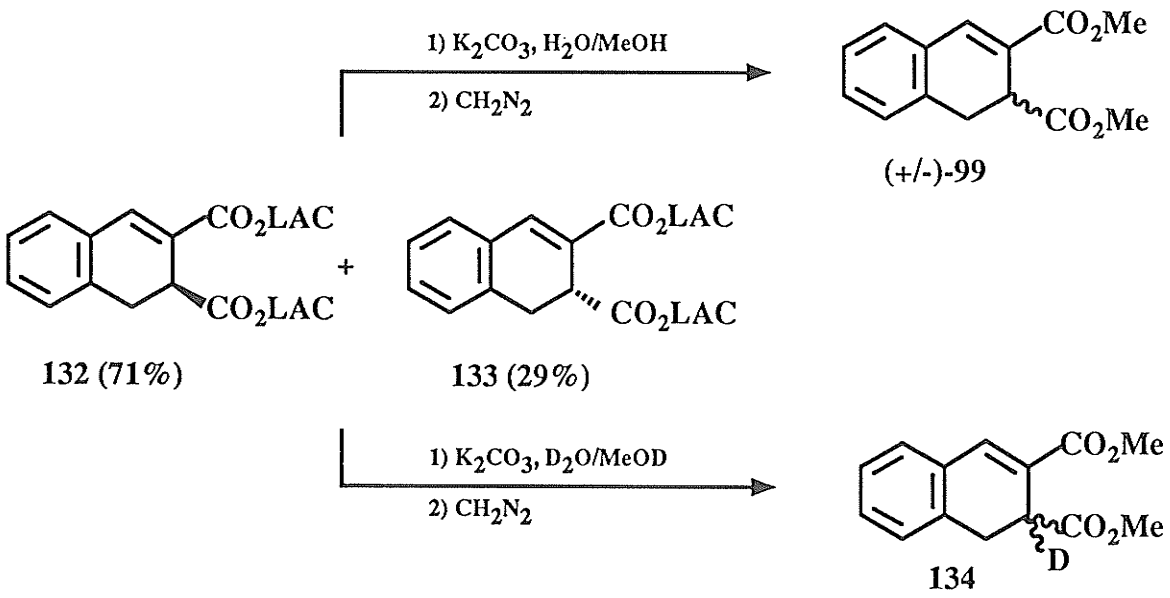
Figure 2. ORTEP diagram of lactone **129**

Since the absolute configuration of the lactate center in lactone **129** was known (S), it was possible to assign the absolute configurations of the other centers as **1R,2S,3R**. By inference, the absolute configurations of centers 2 and 3 in the cycloadduct **127** were also **2S,3R**. The relative stereochemistry of center 1 in **127** was based primarily on the ^{1}H-nmr ($J_{1,2}$= 9.8 Hz), since inversion of this center could have occurred during the conversion of **127** to **129**. The absolute configuration of the cycloadduct produced from dilactyl fumarate **123** is therefore that shown in structure **127** (**1R,2S,3R**), since centers 1 and 2 are *trans* to each other.

Although the two isomers obtained in the cycloaddition of dilactyl maleate **124** and benzocyclobutenol **125** had a smaller coupling constant ($J_{1,2}$= 6.0 Hz for the major isomer, $J_{1,2}$= 5.5 Hz for the minor isomer in C_6D_6, decoupled OH for both isomers) than in the case of the reaction with dilactyl fumarate **123** ($J_{1,2}$= 9.8 Hz), these isomers were also assigned the 1,2-*trans* stereochemistry being produced from the *exo* transition states C and **D**. This was based on the fact that lactonization of the 1-hydroxy and the 3-carboxy group could not be achieved. In this case, the production of a γ-lactone would have been possible if *endo* isomers had been produced. Instead, a mixture of elimination products **132** and **133** (71/29 $[\alpha]_D$ = -48°) were produced in a ratio (^{1}H-nmr) similar to that of the original mixture of hydroxycycloadducts (69/31). The two *exo* diastereomers produced in the reaction of dilactyl maleate **124** were therefore assigned the structure **130** (major) and **131** (minor), assuming that the major isomer of this reaction was also produced from addition to the *re* face of the dienophile[15].



Attempts to determine unambiguously the absolute stereochemistry of the major adduct in the reaction with maleate **124** (by preparing the dimethyl ester **99** from the mixture of **132** and **133**) were all unsuccessful. Under the conditions used (1) K_2CO_3, 20% H_2O/MeOH, reflux 20h; 2) CH_2N_2/ether, r.t.), epimerization at the 3 position occurred as only racemic (no optical activity) dicarbomethoxy alkene **99** was obtained. This reaction was repeated in deuterated solvent (20% D_2O/MeOD) and hydrogen-deuterium exchange at the C-3 position occurred confirming the epimerization at C-3.



To summarize, the cycloaddition of a hydroxy-*o*-quinodimethane to the fumarate of (S)-methyl lactate **123** occurred between the *re* face of the dienophile and the *re* face of the *o*-quinodimethane (mode **D**) giving cycloadduct of type **DD** (*exo* addition) with high diastereoselectivity (>95% de). This represents the first report of the production of a cycloadduct from this highly unusual mode of addition (*exo* addition) for intermolecular

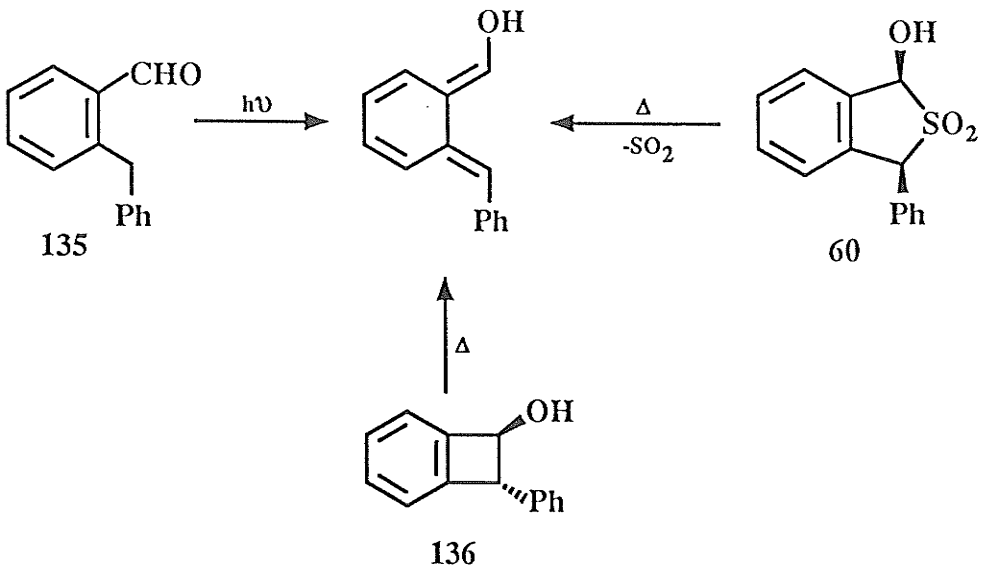
cycloadditions of *o*-quinodimethanes, with the exception of α-oxy-*o*-quinodimethanes bearing an α'-phenyl substituent (see **Chapter 1**)[6,32]. This type of addition (*exo* addition) is more common in intramolecular cycloadditions due to conformational preferences in the transition state[43]. The thermal generation of the α-hydroxy-*o*-quinodimethane seems to be the preferred method of producing this reactive species, as it facilitates the purification of the final product.

It is possible that hydrogen bonding between the α-hydroxy group of the *o*-quinodimethane and the lactyl substituted dienophiles used in this study make the Diels-Alder addition more analogous to an intramolecular cycloaddition. Examples of the effect of hydrogen bonding in the stereochemical control in other reactions have recently been published[84,85]. Polar effects could also have been a factor in the high diastereoselectivity observed. Further studies of the mechanism controlling the diastereoselectivity in these reactions are now in progress[86]. Nevertheless, it would appear that this highly selective reaction could be synthetically useful. In particular, a short asymmetric synthesis of aryltetralin lignans such as podophyllotoxin (**46**) or analogs seems possible, if the dilactyl fumarate **123** and α-hydroxy-α'-aryl-*o*-quinodimethanes add with the same selectivity as observed for α-hydroxy-*o*-quinodimethane. This will be the subject of the next Section.

2.5 Asymmetric Synthesis of Aryltetralin Lignan Analogs

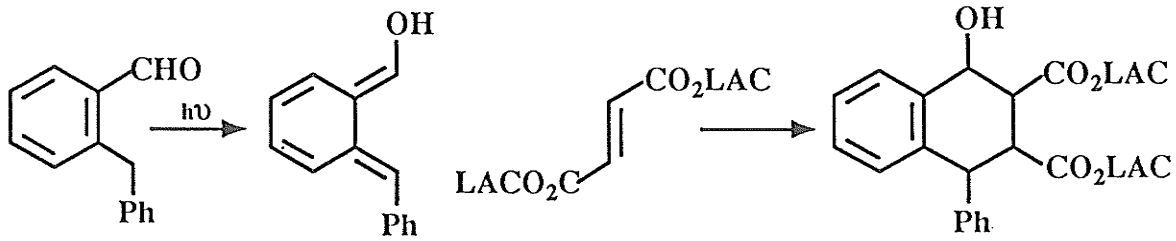
The first step in synthesizing analogs of aryltetralin lignans (such as podophyllotoxin) was to determine if an α-hydroxy-α'-phenyl-*o*-quinodimethane would react with dilactyl fumarate **123** in the same fashion as the α-hydroxy-*o*-quinodimethane described in **Section 2.4**. Three possible methods of generating the E,E-*o*-quinodimethane

required in this reaction could be used. Photolysis of *o*-benzylbenzaldehyde **135**, thermolysis of the *cis*-hydroxysulfone **60**, prepared from **135**, or thermolysis of the *trans*-benzocyclobutenol **136**. The thermolysis of the *trans*-phenyl-benzocyclobutenol **136** was only considered as a possibility in the event that the other two methods were not successful, since *trans*-benzocyclobutenol **136** is thermally unstable above 0°C and very difficult to synthesize (see **Chapter 1**).



o-Benzylbenzaldehyde **135** was prepared from the corresponding acid using standard procedures (1) $LiAlH_4$, THF; 2) 5% CrO_3 in 10% H_2SO_4) giving quantitative yield of aldehyde **135**. Irradiation of **135** in the presence of dilactyl fumarate **123** for 6 hours at room temperature did not produce any cycloadduct. The only signals which could be observed in the ^{1}H-nmr spectrum of the crude mixture were those of the *o*-benzylbenzaldehyde **135**, the dilactyl fumarate **123** and the dilactyl maleate **124**. The last two compounds (**124/123**) were present in the mixture in a similar ratio (90:10) to that

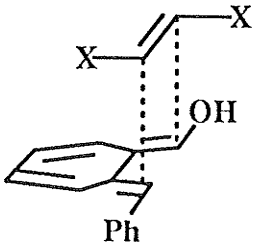
which was obtained previously in the photolysis of *o*-tolualdehyde with dilactyl fumarate **123** (see Section 2.4). Repeating the photolysis of *o*-benzylbenzaldehyde **135** with dilactyl fumarate **123** for a longer reaction time (30 hours) did not change the outcome of the reaction, and only the same three compounds (**123**, **124** and **135**) were observed in the ^{1}H-nmr spectrum of the crude mixture. Increasing the reaction temperature to 50°C (8 hours) produced a cycloadduct but in very small amounts estimated by ^{1}H-nmr to be ~5% relative to the fumarate and maleate left in the mixture. At 50°C for 24 hours, the production of the cycloadduct did not increase. Increasing the temperature to 80°C (refluxing benzene) for 24 hours produced ~10% of cycloadduct as estimated from the ^{1}H-nmr spectrum of the crude mixture. The photolysis was also performed at 110°C (refluxing toluene) for 20 hours, but under these conditions the percentage of cycloadduct produced did not change. This method of producing the cycloadduct was abandoned at this point, since increasing the temperature further was not expected to improve the production of the cycloadduct.



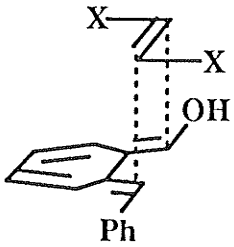
135 29 123

Conditions	Results (% cycloadduct)
benzene, r.t., 6h	0
benzene, r.t., 30h	0
benzene, 50°C, 8h	5
benzene, 50°C, 24h	5
benzene, 80°C, 24h	10
toluene, 120°C, 20h	10

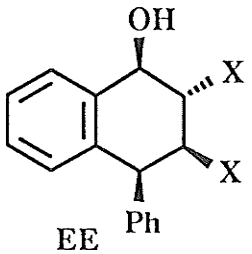
Although the yield obtained in this photochemical cycloaddition reaction was not very impressive, it was very interesting to note that the reaction produced a cycloadduct which seemed to be similar to that obtained in the photochemical cyclization of *o*-tolualdehyde with the fumarate **123**. The **H-1** signal of the cycloadduct could be easily observed (4.98 ppm) in the ^{1}H-nmr spectrum of the crude mixture and a coupling constants ($J_{1,2}$) of ~9-10 Hz was estimated. These values were very similar to those of cycloadduct **127** (**H-1**, 4.95 ppm, $J_{1,2}$= 9.8 Hz) previously prepared (see **Section 2.4**), suggesting that the cycloadduct arising from the reaction of *o*-quinodimethane **29** with dilactyl fumarate **123** was also formed through an *exo* transition state (E or F) giving 1,2-*trans*-3,4-*cis* cycloadduct **EE** or **FF** as shown in the diagrams below. In these diagrams, the transition states are classified according to the prochiral face of the α-hydroxy carbon of the *o*-quinodimethane and the face of the fumarate that will bond to that center.



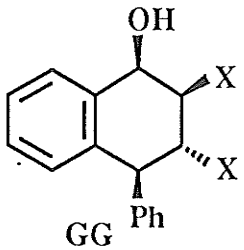
E (exo) *si, si*



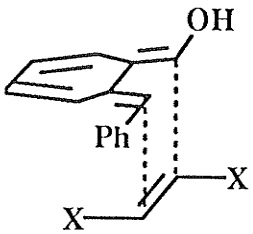
G (endo) *si, re*



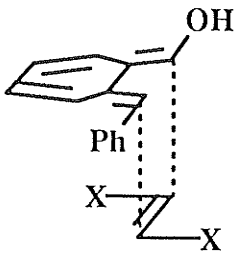
EE



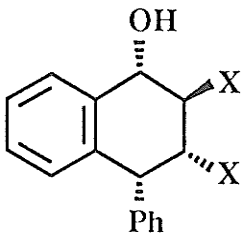
GG



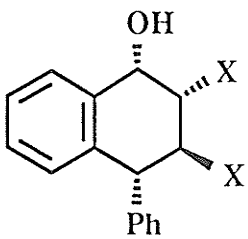
F (exo) *re, re*



H (endo) *re, si*



FF

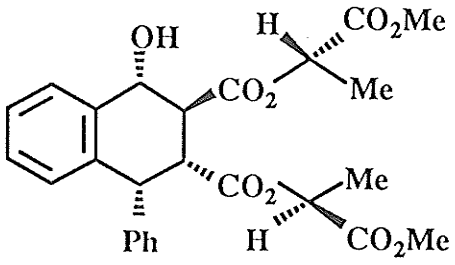


HH

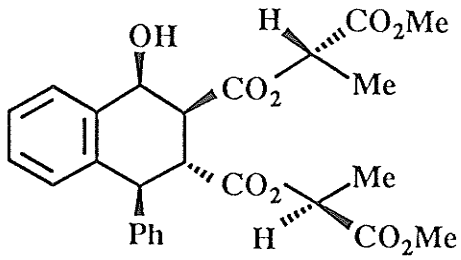
Thermolysis of the hydroxysulfone **60** with dilactyl fumarate **123** under the usual conditions (toluene, ZnO, reflux 20 h) afforded a very low yield of cycloadduct (~10% estimated from ^{1}H-nmr of crude mixture). As was the case for the formation of **127** from hydroxysulfone **59** and fumarate **123**, adding a CH_2Cl_2 solution of sulfone **60** to a refluxing toluene solution of fumarate **123** produced a larger amount of cycloadduct. While only one cycloadduct was observed from the ^{1}H-nmr of the reaction mixture, purification by chromatography on silica gel revealed that there were two diasteromers (9:1 ratio) present, isolated in 54% (major, **H-1** 4.98 ppm) and 5.6% (minor, **H-1** 5.44 ppm) yields based on sulfone **60**. A mixed fraction (17%) was also obtained from chromatography containing a mixture of the same two isomers in a 9:1 ratio (^{1}H-nmr). The major isomer (**H-1**, 4.98 ppm) was crystalline and could be recrystallized from isopropyl alcohol to constant melting point (mp: 142-143°C) and constant optical rotation ($[\alpha]_D$= -215°). It was later found that the major isomer (**H-1**, 4.98 ppm) could also be crystallized directly from the crude reaction mixture in ~40% yield. The minor isomer (**H-1**, 5.44 ppm, $[\alpha]_D$= +50°) was obtained as an oil from the chromatography and could not be crystallized.

The coupling constant ($J_{1,2}$) of the major isomer (**H-1**, 4.98 ppm) was indeed found to be large (9.5 Hz) suggesting a 1,2-*trans* stereochemistry in the cycloadduct arising from an *exo* transition state. On the other hand, the minor isomer (**H-1**, 5.44 ppm) had a smaller coupling constant ($J_{1,2}$= 3.1 Hz) suggesting a 1,2-*cis* stereochemistry in the adduct which would have arisen from an *endo* transition state. It was assumed that both cycloadducts were derived from addition to the *re* face of the dilactyl fumarate **123**, through the transition state F for the major adduct giving a product of type FF, and through the transition state G for the minor adduct giving a cycloadduct of type GG. Thus, the major adduct (**H-1**, 4.98 ppm) was tentatively assigned the structure **137**, while structure **138**

was assigned to the minor cycloadduct (**H-1**, 5.44 ppm).



137

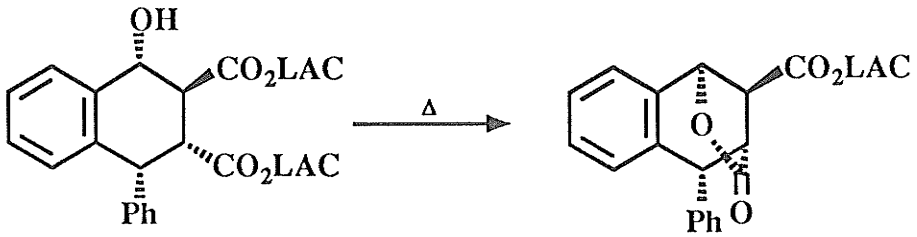


138

The predominant formation of an *exo* adduct (**137**) over that of an *endo* adduct (**138**) was even more surprising in this case than it was in the case of **127**. It was previously mentioned (see **Chapter 1**) that α'-phenyl-*o*-quinodimethanes usually react with dienophiles like fumarate, in such a way that the resulting product has the phenyl and the neighboring carboxy group *trans* to each other due to steric preferences. In the formation of **137**, an *exo* (1,2-*trans*) addition means that the 3-carboxy and the 4-phenyl substituents will be *cis* to each other in the resulting cycloadduct. This suggests that the steric repulsion of the 4-phenyl and the 3-carboxy substituents, which usually seems to be the controlling factor in the cycloaddition of α-phenyl-*o*-quinodimethanes, does not predominate in this case.

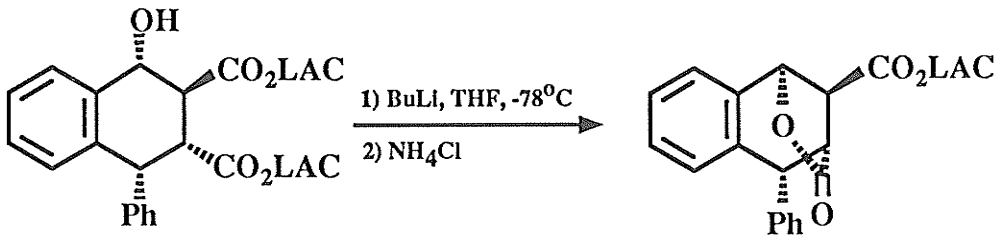
Treating the major cycloadduct **137** with toluenesulfonic acid in methylene chloride for four days at room temperature did not afford any γ-lactone **139**. Only unreacted cycloadduct **137** was recovered from this reaction. Increasing the temperature of the reaction (refluxing CH_2Cl_2) gave a very small amount of lactone **139**, as determined from the similarities of its crude ^{1}H-nmr spectrum (**H-1**, 5.5 ppm) with that of the

γ-lactone **129** previously described (see **Section 2.4**). Increasing the reaction temperature to 80°C (refluxing benzene) and 110°C (refluxing toluene) did not increase the amount of γ-lactone **139** produced. Unidentifiable material was obtained from these reactions.



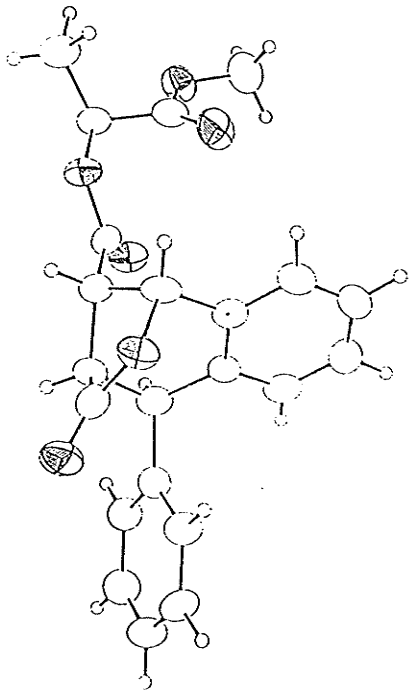
137 **139**

A recent communication published by Choy *et al.* suggested that the lactonization of **137** to **139** might be achieved by forming the oxy anion of the hydroxyl group in **137**[82]. Treating the cycloadduct **137** with n-butyllithium at -78°C for 30 minutes, followed by acid work-up, afforded a product (90%) which was identified as the γ-lactone **139** from its ^{1}H-nmr spectrum which was similar to that of lactone **129**.



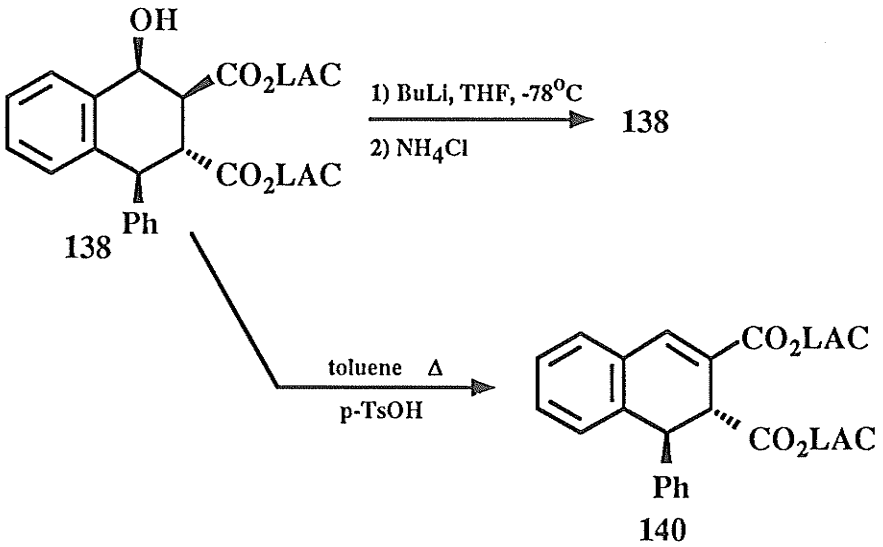
137 **139**

The purity of lactone **139** was estimated to be at least 90% from the ^{1}H-nmr spectrum of the crude reaction mixture. However, as was the case for the γ-lactone **129** (Section 2.4), purification of the lactone **139** was difficult as chromatography afforded variable yields of product. The maximum yield from chromatographic workup, which was attained only twice, was 50%. As for **129**, reaction of the lactone with silica gel may explain the low yield obtained after chromatography of **139**. Nevertheless, the product obtained was a pure crystalline material which could be recrystallized to constant melting point (mp: 135-136°C) and constant optical rotation ($[\alpha]_D$= -39°). This lactone **139** also produced crystals suitable for X-ray crystallography[88], and it was therefore possible to determine the relative configuration of the chiral centers as shown in the ORTEP diagram.

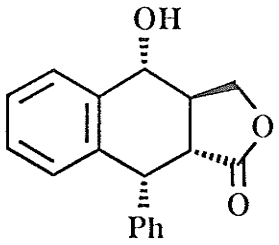


As was the case for the lactone **129**, it was possible to determine the absolute configuration of the chiral centers in **139** since the absolute configuration of the lactate center was known (S). The absolute configuration of the lactone **139** was therefore determined to be **1R,2S,3R,4S**, which is that shown in structure **139**. By inference, the absolute configuration of the cycloadduct **137** was also **1R,2S,3R,4S** (shown in structure **137**).

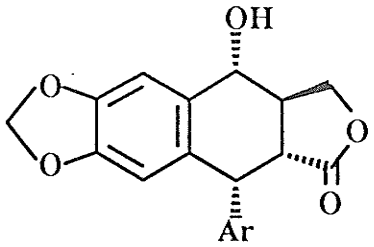
Treating the minor cycloadduct **138** under the same conditions (BuLi, THF, -78°C) did not afford any product similar to a γ-lactone, and only the cycloadduct **138** was recovered in this reaction. This suggested that the cycloadduct **138** had the 1,3-*trans* stereochemistry which could not produce a γ-lactone. Treating **138** with acid under refluxing conditions at 110°C afforded the elimination product **140** (as shown by the **H-1** signal at 7.85 ppm) in good yield (74%). This reaction, which is typical for *endo* adducts (see **Section 2.2**), reinforced the assumption that cycloadduct **138** was formed through an *endo* transition state.



Having determined that the dilactyl fumarate **123** reacts with α-hydroxy-α'-phenyl-*o*-quinodimethane as it did with α-hydroxy-*o*-quinodimethane (see Section 2.4) to produce a cycloadduct with the same absolute configuration as that of podophyllotoxin (46), an asymmetric synthesis of the analog **150** was undertaken.

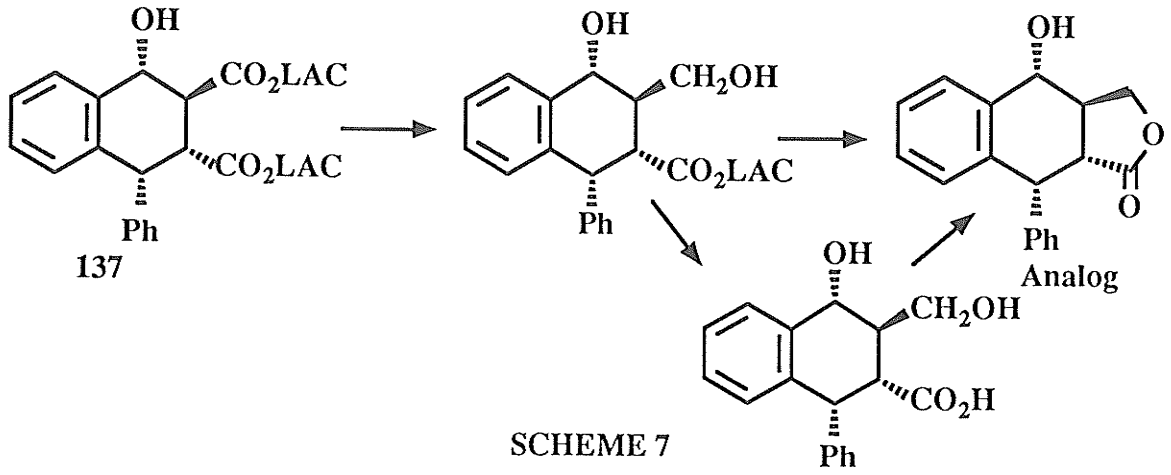


150
podophyllotoxin analog



46
Ar= 3,4,5-trimethoxyphenyl

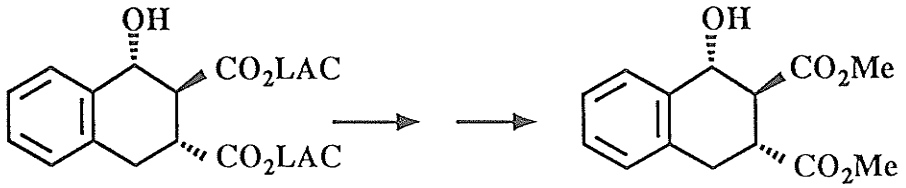
The transformation of the carboxyl groups at C-2 and C-3 in **137** into other functional groups capable of forming the 2,3-lactone ring of the analog, could be carried out starting from either the cycloadduct **137** or from its γ-lactone **139**. Because the use of γ-lactone **139** would increase the number of steps in the synthesis (therefore reducing the total yield of the synthesis), the transformation to the podophyllotoxin analog was first attempted from the cycloadduct **137**. Scheme 7 represents a possible route in the synthesis of the podophyllotoxin analog from cycloadduct **137**.



SCHEME 7

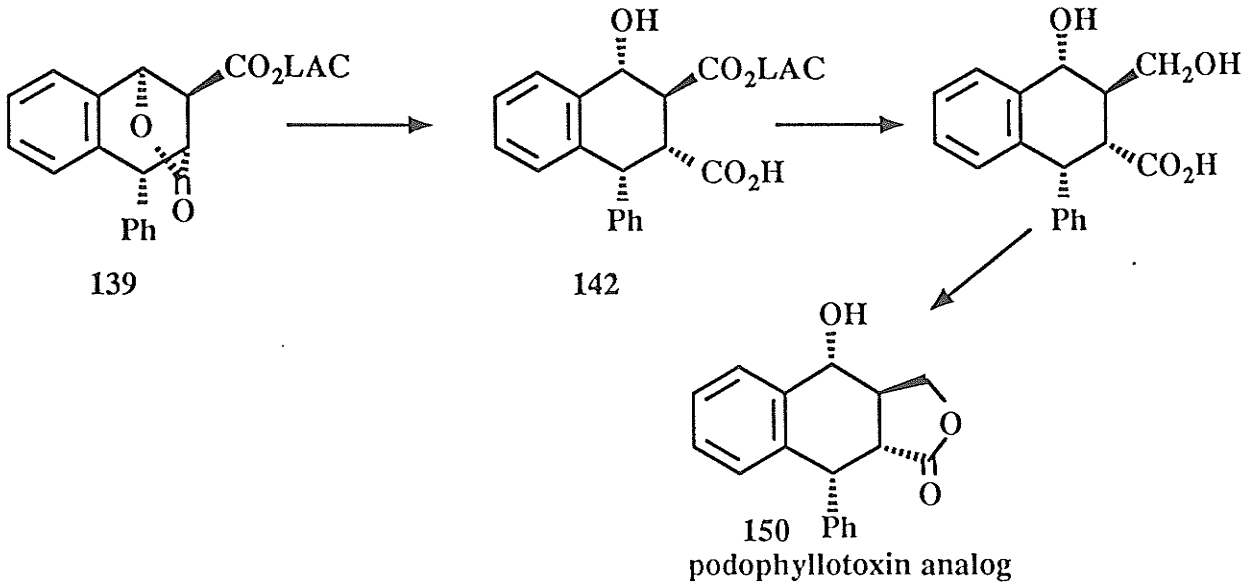
Selective reduction of the ester function at C-2 has been previously reported for molecules similar to **137**[32,69]. Although these reported reductions were carried out on molecules containing methyl esters, the selective reduction of the C-2 ester in **137** was attempted under the conditions previously used by others. The reduction was carried out on both cycloadduct **127** (used as a model for **137**) and cycloadduct **137**. Treating either one of these cycloadducts with lithium triethylborohydride ($LiBHEt_3$) at -78°C afforded a mixture of compounds. Purification (chromatography) was attempted, but was unsuccessful as only a small amount of material was recovered from which it was not possible to identify any components of the mixture.

Since this reduction was previously successful on a similar system which contained methyl esters, attempts to form the dicarbomethoxy adduct **141** from the cycloadducts **127** and **137** were carried out[32]. All attempts to hydrolyze the lactyl esters in **127** or **137** failed under acidic conditions (20% HCl, EtOH, reflux) or enzymatic conditions (THF, pH=9, room temp., subtilisin, chymotrypsin, trypsin, thermolysin). Basic conditions were not investigated as it was previously shown that treatment of cycloadducts with base leads to elimination (**Section 2.4**).



127 141

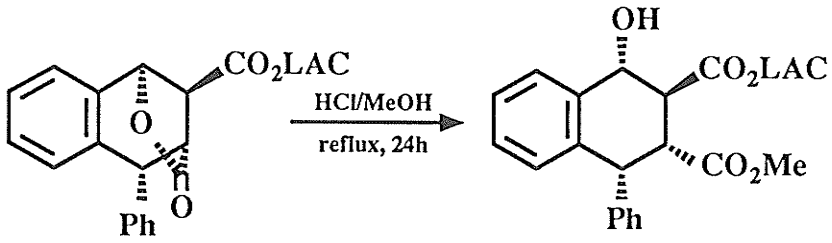
Since all attempts to selectively reduce the C-2 ester or hydrolyse both the C-2 and C-3 esters from **127** or **137** failed to produce satisfactory results, a route to the podophyllotoxin analog from the γ-lactone **139** was considered (scheme 8). The key step in this new route would be the opening of the γ-lactone to form the hydroxy acid **142**. The carboxyl group at the 3 position could then be protected as its carboxylate anion during reduction of the ester group at the 2 position[49,61]. Methods for the closure of the resulting 2-hydroxymethyl-3-carboxylic acid derivative to the 2,3-lactone of the analog have been previously published[32,69].



139 142 150 podophyllotoxin analog

SCHEME 8

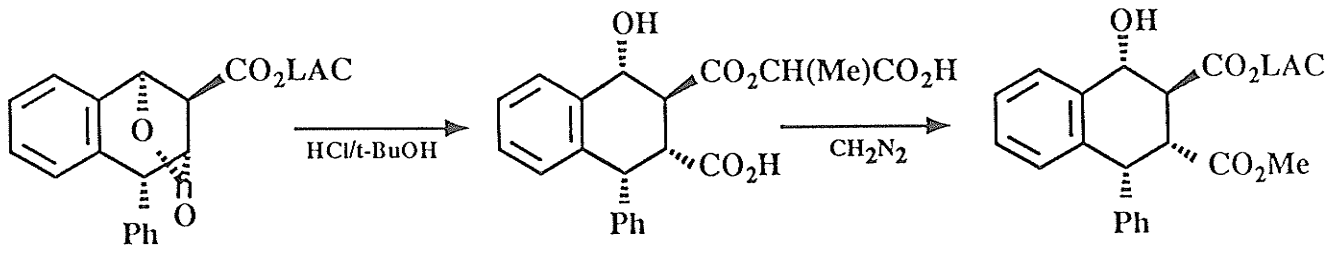
The γ-lactone **139** was first treated with 10% aqueous HCl/MeOH at reflux temperature. Under these conditions, no acidic products were formed. The crude ^{1}H-nmr spectrum of the neutral product did not correspond to the γ-lactone **139**, but was more similar (doublet ~5 ppm, J= 9.7 Hz) to that of the cycloadduct **137**. Two methoxy signals (3.58 ppm and 3.82 ppm) were also observed, but only one lactyl group was present in the molecule as shown by the single doublet-quartet pattern (d ~1.6 ppm, q ~5.3 ppm) in the ^{1}H-nmr spectrum. This product was tentatively assigned the structure **143** on the basis of the ^{1}H-nmr observations of the crude reaction mixture.



139 **143**

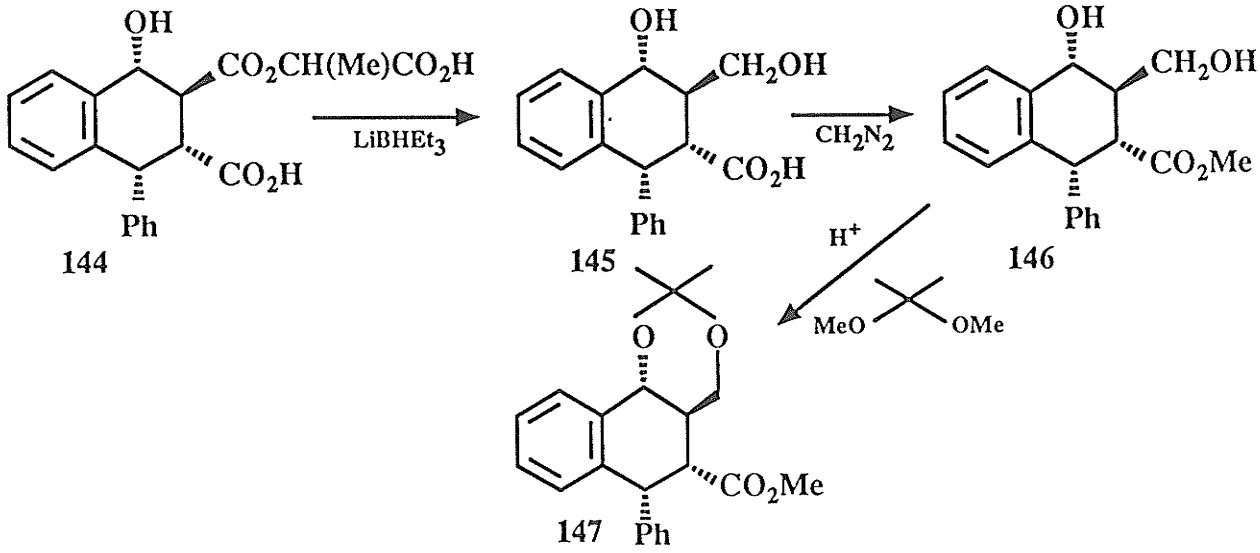
The reaction was repeated in isopropyl alcohol hoping that the size of the alkyl group in the alcohol would prevent the esterification of the open form of the lactone **139**. Under similar conditions to those used above (10% aqueous HCl/isopropyl alcohol, 80°C, 2 days), ~50% of the material was recovered in the basic extract. The rest of the material was found in the neutral organic layer. Repeating the reaction in *tert*-butyl alcohol proved to be more successful and only an acidic product was formed with no material recovered from the organic layer after the base extraction. Upon reacidification of the base extract (10% aqueous HCl) and extraction with ethyl acetate, a white solid (72%, mp: 122-130°C) was obtained. This product was estimated to be ~90% pure by ^{1}H-nmr, but it could not be recrystallized nor chromatographed. It was assigned the structure **144** on the basis of the ^{1}H-nmr spectrum (**H-1** 4.98 ppm, $J_{1,2}$= 9.8 Hz, no methoxy signals, one d-q pattern of the

lactyl group) obtained from the crude mixture and also on the fact that treating **144** with diazomethane gave a ^{1}H-nmr spectrum consistent with **143**.



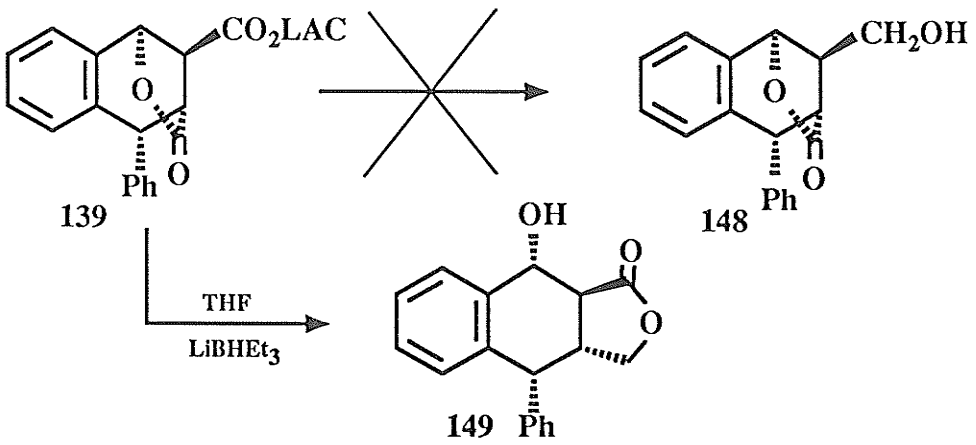
139 **144** **143**

Reduction of the ester group at C-2 in **144** proceeded smoothly. Treating the hydroxy diacid with lithium triethylborohydride in THF afforded a product which appeared, by ^{1}H-nmr, to be ~80% pure. Attempts to crystallize the product from the crude mixture failed. Identification of the product as **145** was based on its ^{1}H-nmr spectrum obtained from the crude mixture, on the ^{1}H-nmr spectrum of its methyl ester (**146**) obtained by treatment with diazomethane, and also on its methyl ester acetonide (**147**) which was prepared according to a literature procedure and was fully characterized[32].

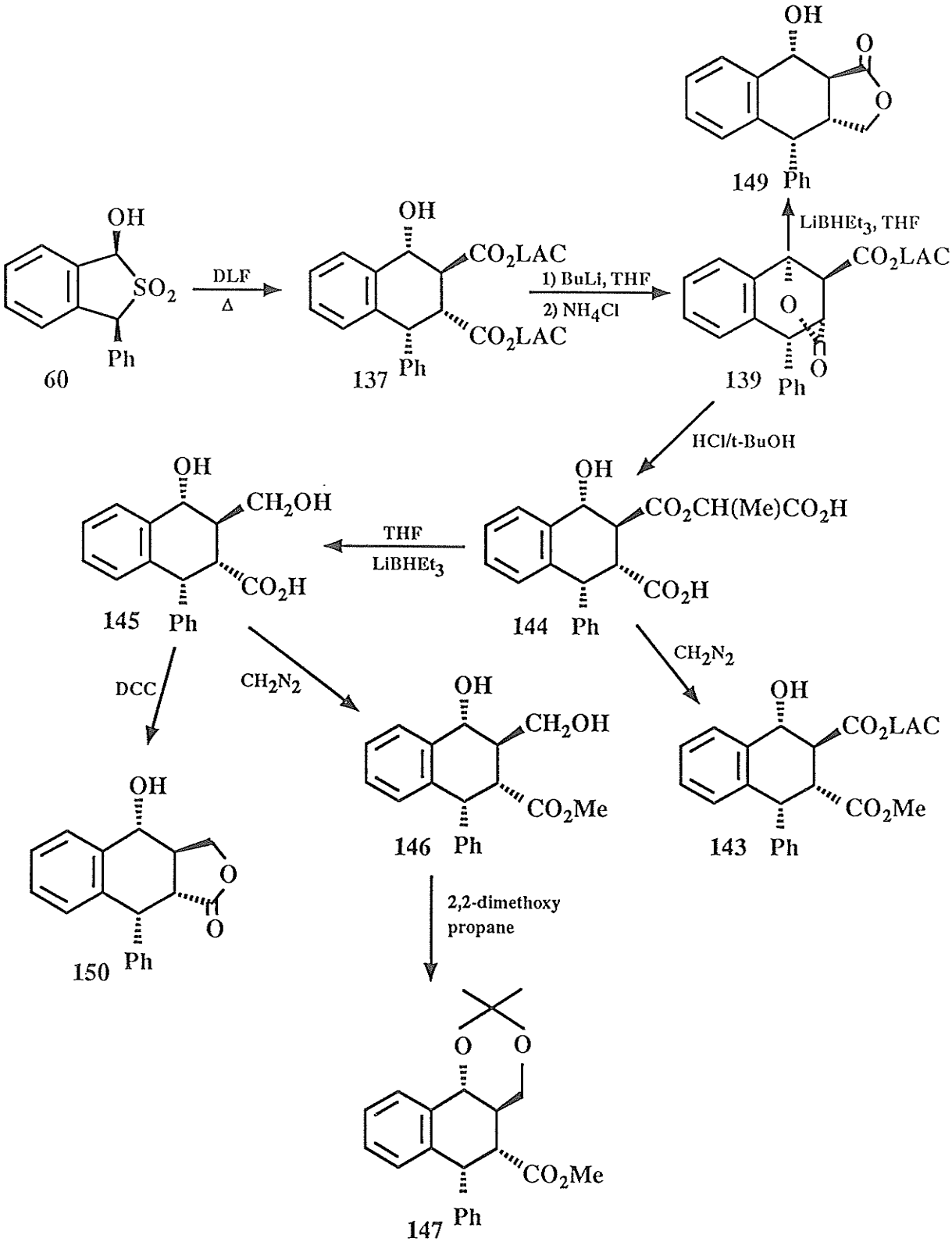


144 **145** **146** **147**

An attempt to reduce the C-2 ester directly from the lactone **139** was also made. It was hoped that the reaction would selectively reduce the C-2 ester to produce the hydroxy lactone **148**. Instead of **148**, a crystalline product (mp: 162-164°C) was obtained (71%) which was assigned the structure **149**. The production of this pericarbonyl lactone opens the possibility of using a similar route for the synthesis of aryltetralin lignans having the reverse 2,3-lactone.



Attempt to lactonize the dihydroxy methyl ester **146** to the podophyllotoxin analog **150**, under conditions ($ZnCl_2$, THF, molecular sieves) previously reported[64], failed and only the ester **146** was recovered. Lactonization to the podophyllotoxin analog **150** was achieved by treating the dihydroxy acid **145** with dicyclohexylcarbodiimide (DCC) according to a procedure previously reported[32]. The podophyllotoxin analog **150** was easily identified as its ^{1}H-nmr data were identical to those previously reported for the racemic material[32]. The entire asymmetric synthesis of optically pure analog **150** from the hydroxysulfone **60** was achieved in 16.5% (total yield) (30% from the cycloadduct **137**). The total synthesis from the hydroxysulfone **60** to the podophyllotoxin analog **150** is outlined in scheme 9.


OH
O
O
149 Ph
LiBHEt3, THF
OH
SO2
DLF
Δ
60
Ph
OH
CO2LAC
CO2LAC
137 Ph
1) BuLi, THF
2) NH4Cl
CO2LAC
O
O
O
139 Ph
HCl/t-BuOH
OH
CH2OH
CO2H
145 Ph
THF
LiBHEt3
OH
CO2CH(Me)CO2H
CO2H
144 Ph
CH2N2
DCC
CH2N2
OH
CH2OH
CO2Me
146 Ph
OH
CO2LAC
CO2Me
143 Ph
OH
O
O
150 Ph
2,2-dimethoxy
propane
O
O
CO2Me
147 Ph

SCHEME 9

Chapter 3

CONCLUSIONS

The work presented in this thesis has resulted in three major achievements. These are: (1) the proposal of a new mechanism to explain the asymmetric induction encountered in the Diels-Alder cycloaddition reactions of chiral o-quinodimethanes, (2) the discovery of a highly diastereoselective reaction of α-hydroxy-o-quinodimethanes with dilactyl fumarate and (3) the short and efficient asymmetric syntheses of two podophyllotoxin analogs.

While searching for a chiral o-quinodimethane which would produce high asymmetric induction in Diels-Alder reactions, it was discovered that the results were inconsistent with the two proposals previously suggested to explain the diastereoselectivity encountered in these reactions. For this reason, three new chiral α-alkoxy-o-quinodimethanes were prepared to help elucidate the mechanism controlling the diastereoselectivity. It was concluded that the diastereoselectivities observed were related to the preferred conformation of the chiral auxiliary which controlled the approach of the dienophile to the o-quinodimethane. This conformation of the chiral auxiliary not only explained our results, but also those reported by others in similar reactions. It was proposed that asymmetric induction could be improved by more rigidly locking the conformation of the chiral auxiliary. Attempts to carry out this latter suggestion by introducing hydrogen bonding into the chiral o-quinodimethanes were made, but the work was discontinued due to difficulties in introducing the chiral auxiliaries into the o-quinodimethane precursors.

In view of the difficulties encountered in the search for a chiral o-quinodimethane producing high diastereoselectivity in Diels-Alder reactions, attention was turned towards chiral dienophiles. A literature survey suggested that the fumarate of (S)-methyl lactate might lead to high asymmetric induction in a Diels-Alder cycloaddition reaction with o-quinodimethanes. The reactions of this chiral dienophile with α-hydroxy and α-hydroxy-α'-phenyl-o-quinodimethane were found to be highly diastereoselective, producing predominantly one cycloadduct in at least 95% de. It was determined that the reactions took place from the expected *re* face of the chiral dienophile, but via an unexpected *exo* transition state.

Taking advantage of the highly diastereoselective reaction of the fumarate of (S)-methyl lactate and α-hydroxy-α'-phenyl-o-quinodimethane, two short asymmetric syntheses (5 and 3 steps) of podophyllotoxin analogs were carried out. These analogs were prepared in 16.5% and 39% overall yields, and the methods developed should provide a new route for synthesizing optically pure aryltetralin lignans.

Chapter 4

EXPERIMENTAL

Melting points were determined on a hot stage instrument and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 881 spectrometer. ^{1}H-nmr spectra were recorded on a Bruker AM-300 instrument using tetramethylsilane as internal standard. Exact mass/mass spectra were obtained on an Analytical V6 7070E-HF instrument. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario Canada. Analytical thin layer chromatography (tlc) were carried out on precoated silica gel sheets, 60 F_{254} (EM reagents) of 0.2 mm thickness. Merck Kieselgel 60 or Aldrich (230-400 mesh, 60Å) silica gel was used for all column chromatography.

o-Methylbenzaldehyde:

To a suspension of $LiAlH_4$ (3.0 g, 79 mmol) in dry tetrahydrofuran (100 mL) was slowly added at 0°C a solution of *o*-methylbenzoic acid (10 g, 74 mmol) in dry tetrahydrofuran (50 mL). The solution was then refluxed for one hour, cooled and water (3 mL) was added followed by 15% aqueous sodium hydroxide (3 mL) and water (9 mL). The solution was stirred at room temperature for 15 minutes, the precipitate was filtered, washed with ethyl acetate and the combined organic solvents were evaporated to give a white solid (8.7 g, mp: 32-32.5°C). The solid was dissolved in diethyl ether (75 mL) and a solution of chromium trioxide (5%) in 10% aqueous H_2SO_4 was slowly added. The organic and aqueous layers were separated and the aqueous layer extracted with diethyl

ether. The organic fractions were combined, washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to afford a colourless liquid (8.6 g, 98%).
IR (CH_2Cl_2) cm^{-1}: 1699 (CO). ^{1}H-nmr ($CDCl_3$) δ: 2.67 (s, 3H, CH_3), 7.1-7.9 (m, 4H, aromatics), 10.17 (s, 1H, CHO).

2-Methyl-1-phenyl-1-propanol (b):

To a suspension of magnesium (1.22 g, 0.05 mol) in diethyl ether (50 mL) was added in a dropwise fashion isopropyl bromide (6.15 g, 0.05 mol). The solution was stirred at room temperature until all the magnesium was consumed. Freshly distilled benzaldehyde (5.3 g, 0.05 mol) in diethyl ether (50 mL) was then added dropwise at 0°C and the resulting solution was refluxed for 30 minutes. The solution was cooled, water was added followed by aqueous HCl (10%) until both layers were clear. The organic layer was separated and the aqueous layer extracted with methylene chloride. The organic fractions were combined, dried ($MgSO_4$) and evaporated to give a yellowish liquid (6.7 g, 89%). The crude product was purified by distillation under reduced pressure (89-93°C/1.25mm Hg) to give a colourless oil (4.96 g, 66%).
IR (CH_2Cl_2) cm^{-1}: 3607 (OH). ^{1}H-nmr ($CDCl_3$) δ: 0.72 (d, 3H, J= 7.0, CH_3), 0.91 (d, 3H, J= 7.0, CH_3), 1.83 (m, 1H, CH), 2.92 (s, 1H, OH), 4.15 (d, 1H, J= 7.0, benzylic CH), 7.18 (s, 5H, aromatics). Mass Spectrum, *m/e* (rel %): 150(4), 117(5), 108(10), 107(100), 105(14), 91(5), 79(37), exact mass calcd. for $C_{10}H_{14}O$: 150.1045, found: 150.1060.

2,2-Dimethyl-1-phenyl-1-propanol (c):

To a suspension of magnesium (1.22 g, 0.05 mol) in diethyl ether (50 mL) was added in a dropwise fashion t-butyl chloride (4.62 g, 0.05 mol). The solution was stirred at room temperature until all the magnesium was consumed. Freshly distilled benzaldehyde (5.3 g, 0.05 mol) in diethyl ether (50 mL) was then added dropwise at 0°C

and the resulting solution was refluxed for 30 minutes. The solution was cooled, water was added followed by aqueous HCl (10%) until both layers were clear. The organic layer was separated and the aqueous layer extracted with methylene chloride. The organic fractions were combined, dried ($MgSO_4$) and evaporated to give a yellowish liquid (6.1 g, 93%). The crude product was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to give colourless flakes (3.36 g, 41%, mp: 36-37°C).
IR (CH_2Cl_2) cm^{-1}: 3609 (OH). ^{1}H-nmr ($CDCl_3$) δ: 0.93 (s, 9H, t-butyl), 4.30 (s, 1H, CH), 7.30 (s, 5H, aromatics). Mass Spectrum, *m/e* (rel %): 164(1), 108(22), 107(100), 106(27), 105(49), 91(6), 79(40), 77(44), exact mass calcd. for $C_{11}H_{16}O$: 164.1201, found 164.1229.

1-Hydroxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **59**:

This compound was prepared according to a procedure previously reported[19,22]. To a solution of *o*-methylbenzaldehyde (7.6 g, 63.3 mmol) in benzene (100 mL) was added a solution of sulfur dioxide (17 g) in benzene (75 mL). The volume of the solution was then adjusted to fill the reaction vessel (~300 mL), the solution was flushed with nitrogen and irradiated for 24 hours using a 450 watt Hanovia medium pressure mercury lamp located in a water cooled, Pyrex probe immersed in the solution. The probe was cleaned every five hours. The solution was evaporated, the residue dissolved in ethyl acetate and extracted with aqueous sodium bicarbonate (5%). The aqueous extract was re-acidified (10% aqueous HCl) and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and the solvent evaporated. The resulting oil was then triturated with carbon tetrachloride to free the product from *o*-methylbenzoic acid and afforded a pale green solid (3.69 g, 32%).
IR (CH_2Cl_2) cm^{-1}: 3531 (OH), 1320, 1203, 1123 (SO). ^{1}H-nmr ($CDCl_3$) δ: 4.26 (d, 1H, J= 15.6, H-3A), 4.38 (d, 1H, J= 15.6, H-3B), 4.52 (broad s, 1H, OH), 5.64 (s, 1H, H-1), 7.23-7.55 (m, 4H, aromatics), identical to that previously reported[19,22].

1-Hydroxy-3-phenyl-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **60**:

This compound was prepared according to a procedure previously reported[22]. To a solution of *o*-benzylbenzaldehyde (4.35 g, 22.2 mmol) in benzene (100 mL) was added a solution of sulfur dioxide (18 g) in benzene (50 mL). The volume of the solution was adjusted to fill the reaction vessel (~ 300 mL), the solution was flushed with nitrogen and irradiated for 20 hours using a 450 watt Hanovia medium pressure mercury lamp located in a water cooled, Pyrex probe immersed in the solution. The probe was cleaned every five hours. The solution was evaporated and the residue was triturated with carbon tetrachloride to afford a yellowish solid (4.0 g, 69%) corresponding to the *cis*-hydroxysulfone **60**.

^{1}H-nmr ($CDCl_3$) δ: 3.1 (broad s, 1H, OH), 5.3 (s, 1H, H-3), 5.67 (s, 1H, H-1), 7.1-7.7 (m, 9H, aromatics), identical to that previously reported[22].

1-Alkoxy-3-phenyl-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **61-64, 66-68** and *1-alkoxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide* **65**:

These sulfones were prepared according to a procedure previously reported[29]. To a solution of the appropriate alcohol (80-150 mg) in methylene chloride (15 mL) was added either the hydroxysulfone **59** or **60** (1.5 equivalent) and p-toluenesulfonic acid (10 mg). The solution was refluxed for 7-10 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated to afford 73-82% of the alkoxysulfone **61-68**. No further purifications were attempted for these products. Only ^{1}H-nmr spectroscopy was used to identify these sulfones. Products were at least 95% pure by ^{1}H-nmr.

^{1}H-nmr ($CDCl_3$) δ:

61 (82%): 1.73 (d, 3H, J= 6.4, CH_3), 5.23 (q, 1H, J= 6.4, CH), 5.29 (s, 1H, H-3), 5.51 (s, 1H, H-1), 7.3 (m, 14H, aromatics).

62 (81%): 0.70 (d, 3H, J= 7.1, CH_3), 1.07 (d, 3H, J= 7.1, CH_3), 2.13 (m, 1H, CH), 4.75 (d, 1H, J= 8.0, CH), 5.32 (s, 1H, H-3), 5.40 (s, 1H, H-1), 7.5 (m, 14H, aromatics).

63 (79%): 0.95 (s, 9H, t-butyl), 4.88 (s, 1H, CH), 5.25 (s, 1H, H-3), 5.38 (s, 1H, H-1), 7.25 (m, 14H, aromatics).

64 (78%): 1.2-2.9 (m, 9H, cyclohexane protons), 4.07 (m, 1H, cyclohexane proton), 5.08 (s, 1H, H-3), 5.15 (s, 1H, H-1), 7.35 (m, 14H, aromatics).

65 (76%): 1.69 (d, 3H, J= 6.5, CH_3), 4.19 (d, 1H, 15.6, H-3A), 4.47 (, 1H, J= 15.6, H-3B), 5.23 (s, 1H, H-1), 5.39 (q, 1H, J= 6.5, CH), 7.55 (m, 11H, aromatics).

66 (76%): 1.8-2.5 (m, 7H, cyclopentane protons), 4.38 (m, 1H, cyclopentane proton), 5.05 (s, 1H, H-3), 5.18 (s, 1H, H-1), 7.25 (m, 14H, aromatics).

67 (77%): 0.90 (s, 6H, CH_3), 0.93 (s, 3H, CH_3), 1.0-2.4 (m, 7H, borneol protons), 5.36 (s, 1H, H-3), 5.66 (s, 1H, H-1), 7.4 (m, 9H, aromatics).

68 (73%): 0.8-2.6 (m, 18H, menthol protons), 3.83 (m, 1H, menthol proton), 5.30 (s, 1H, H-3), 5.80 (s, 1H, H-1), 7.35 (m, 9H, aromatics).

1-Alkoxy-4-phenyl-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **69-72, 74-76** and *1-alkoxy-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene* **73**:

These cycloadducts were prepared according to a procedure previously reported[29]. To a solution of the alkoxysulfone **61-68** (~150 mg) in benzene (10 mL) was added dimethyl fumarate (4 equivalents) and zinc oxide (~50 mg). The solution was refluxed for 10-12 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant and evaporated. The excess of dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to afford 65-81% of a mixture of cycloadducts. No further purification was attempted. The cycloadducts made up at least 95% of the crude reaction mixture (from ^{1}H-nmr). The diastereomeric products were identified only on the basis of their ^{1}H-nmr spectra. ^{1}H-nmr spectrum for the major diastereomer produced in each

reaction was obtained from the crude reaction mixtures.

^{1}H-nmr ($CDCl_3$) δ: major diastereomer only.

69 (76%): 1.44 (d, J= 6.4, CH_3), 3.30 (dd, J= 2.8, 12.0, H-2), 3.52 (s, OCH_3), 3.81 (s, OCH_3), 4.06 (d, J= 11.1, H-4), 4.55 (q, J= 6.4, CH), 5.02 (d, J= 2.8, H-1), 7.23 (m, aromatics), H-3 not observed.

70 (79%): 0.68 (d, J= 6.7, CH_3), 0.98 (d, J= 6.7, CH_3), 1.98 (m, CH), 3.22 (dd, J= 2.5, 12.0, H-2), 3.53 (s, OCH_3), 3.81 (s, OCH_3), 4.03 (d, J= 10.9, H-4), 4.11 (d, J= 7.2, CH), 4.98 (d, J= 2.5, H-1), 7.20 (m, aromatics), H-3 not observed.

71 (81%): 0.87 (s, t-butyl), 3.22 (dd, J= 2.5, 11.9, H-2), 3.54 (s, OCH_3), 3.79 (s, OCH_3), 4.04 (d, J= 10.9, H-4), 4.93 (d, J= 2.5, H-1), 7.10 (m, aromatics), H-3 not observed.

72 (71%): 1.75 (m, cyclohexane protons), 2.48 (m, cyclohexane protons), 3.40 (s, OCH_3), 3.76 (s, OCH_3), 3.86 (d, J= 10.3, H-4), 4.93 (d, J= 2.3, H-1), 7.10 (m, aromatics), H-2 and H-3 not observed.

73 (65%): 1.47 (d, J= 6.4, CH_3), 2.80 (dd, J= 10.5, 16.5, H-4), 3.16 (dd, J= 3.1, 10.5, H-2), 3.27 (dd, J= 10.5, 16.5, H-4'), 3.74 (s, OCH_3), 3.86 (s, OCH_3), 4.64 (q, J= 6.4, CH), 4.96 (d, J= 3.1, H-1), 7.35 (m, aromatics), H-3 not observed.

74 (73%): 1.75 (m, cyclopentane protons), 2.10 (m, cyclopentane protons), 3.26 (dd, J= 2.8, 12.1, H-2), 3.48 (s, OCH_3), 3.70 (dd, J= 12.0, 12.1, H-3), 3.77 (s, OCH_3), 4.02 (d, J= 12.0, H-4), 4.87 (d*, H-1), 7.15 (m, aromatics), *overlapping with other signals.

75 (72%): 1.40 (m, borneol protons), 3.31 (dd, J= 2.8, 12.1, H-2), 3.53 (s, OCH_3), 3.76 (s, OCH_3), 4.10 (d, J= 11.3, H-4), 4.86 (d*, H-1), 7.30 (m, aromatics), *overlapping with other signals, H-3 not observed.

76 (76%): 1.00 (m, menthol protons), 3.22 (dd, J= 2.5, 12.0, H-2), 3.51 (s, OCH_3), 3.72 (s, OCH_3), 4.09 (d, J= 10.9, H-4), 4.95 (d, J= 2.5, H-1), 7.25 (m, aromatics), H-3 not observed.

1-(1-Phenyl-1-ethoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **85a**:

To a solution of (±)-1-phenyl-1-ethanol **(a)** (0.5 g, 4.1 mmol) in methylene chloride (15 mL) was added the hydroxysulfone **59** (0.85 g, 4.62 mmol, 1.13 eq.) and p-toluenesulfonic acid (20 mg). The solution was refluxed for 7 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated to afford a yellow oil. The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexane as eluant to give a pale yellow oil (1.04 g, 88%).
IR (CH_2Cl_2) cm^{-1}: 1319, 1202, 1122 (SO). ^{1}H-nmr ($CDCl_3$) δ: 1.61 (d, 3H, J= 6.5, CH_3), 4.20 (d, 1H, J= 15.7, H-3A), 4.46 (d, 1H, J= 15.7, H-3B), 5.20 (s, H-1), 5.23 (q overlapping with s at 5.20, J= 6.5, H-1'), 7.23-7.47 (m, 9H, aromatics), identical to that previously reported[29].

1-(2-Methyl-1-phenyl-1-propoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **85b**:

To a solution of (±)-2-methyl-1-phenyl-1-propanol **(b)** (210 mg, 1.4 mmol) in methylene chloride (15 mL) was added the hydroxysulfone **59** (370 mg, 2.0 mmol, 1.6 eq.), p-toluenesulfonic acid (11 mg) and magnesium sulfate (200 mg). The solution was then refluxed for 22 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and the solvent was evaporated to give a yellow oil (450 mg, 100%). The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexane as eluant to afford a pale yellow solid (363 mg, 82%, mp: 102-105°C).
IR (CH_2Cl_2) cm^{-1}: 1318, 1202, 1123 (SO). ^{1}H-nmr ($CDCl_3$) δ: 0.75 (d, 3H, J= 6.7, CH_3), 1.15 (d, 3H, J= 6.7, CH_3), 2.0-2.2 (m, 1H, H-2'), 4.17 (d, 1H, J= 15.6, H-3A), 4.42 (d, 1H,

J= 15.6, H-3B), 4.74 (d, 1H, J= 8.1, H-1'), 5.19 (s, 1H, H-1), 7.2-7.5 (m, 9H, aromatics). Mass Spectrum, *m/e* (rel %): 273(2), 252(3), 167(3), 133(62), 120(32), 117(15), 103(20), 91(100). Anal. calcd. for $C_{18}H_{20}SO_3$: C 68.33, H 6.38, S 10.11, found: C 68.09, H 6.42, S 10.17.

1-(2,2-Dimethyl-1-phenyl-1-propoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **85c**:

To a solution of (±)-2,2-dimethyl-1-phenyl-1-propanol (**c**) (200 mg, 1.22 mmol) in methylene chloride (20 mL) was added the hydroxysulfone **59** (340 mg, 1.85 mmol, 1.5 eq.), p-toluenesulfonic acid (10 mg) and magnesium sulfate (200 mg). The solution was refluxed for 14 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated to give a yellow oil (400 mg, 100%). The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexane as eluant and afforded a pale yellow solid (339 mg, 84%, mp: 116-118°C).
IR (CH_2Cl_2) cm^{-1}: 1318, 1201, 1124 (SO). ^{1}H-nmr ($CDCl_3$) δ: 0.98 (s, 9H, t-butyl), 4.15 (d, 1H, J= 15.5, H-3A), 4.41 (d, 1H, J= 15.5, H-3B), 4.90 (s, 1H, H-1'), 5.18 (s, 1H, H-1), 7.3-7.5 (m, 9H, aromatics). Mass Spectrum, *m/e* (rel %): 273(5), 239(7), 209(11), 167(8), 147(63), 120(24), 105(67), 103(55), 91(100). Anal. calcd. for $C_{19}H_{22}SO_3$: C 69.06, H 6.72, S 9.68, found: C 68.96, H 6.73, S 9.70.

1-((S)-1-Phenyl-1-ethoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **(S)-85a**:

To a solution of (S)-1-phenyl-1-ethanol (**a**) (235 mg, 1.92 mmol) in methylene chloride (10 mL) was added the hydroxysulfone **59** (400 mg, 2.17 mmol, 1.13 eq.) and p-toluenesulfonic acid (19 mg). The solution was refluxed for 5 1/2 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated to afford a yellow oil (520 mg, 94%). The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexane as eluant to give a pale yellow oil (446 mg,

80%). ^{1}H-nmr ($CDCl_3$) δ: identical to that of **85a**.

1-((R)-2-Methyl-1-phenyl-1-propoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **(R)-85b**:

To a solution of (R)-2-methyl-1-phenyl-1-propanol **(b)** (200 mg, 1.33 mmol) in methylene chloride (10 mL) was added the hydroxysulfone **59** (400 mg, 2.17 mmol, 1.6 eq.), p-toluenesulfonic acid (15 mg) and magnesium sulfate (150 mg). The solution was then refluxed for 5 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated to give a pale yellow oil (389 mg, 92%). The crude product was purified by chromatography on silica gel using 10% ethyl acetate/hexane as eluant to afford a pale yellow solid (282 mg, 67%).
^{1}H-nmr ($CDCl_3$) δ: identical to that of **85b**.

1-(1-Phenyl-1-ethoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **88/89a**:

To a solution of alkoxysulfone **85a** (390 mg, 1.35 mmol) in toluene (25 mL) was added dimethyl fumarate (800 mg, 5.56 mmol, 4.1 eq.) and zinc oxide powder (150 mg). The solution was then refluxed for 3 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated. The excess dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to give a yellowish oil (400 mg, 80%). The crude product was crystallized from hexane to give colourless needles (301 mg, 60%, mp: 78-79°C) corresponding to the major diastereomer of the mixture.
IR (CH_2Cl_2) cm^{-1}: 1737 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.40 (d, 3H, J= 6.4, CH_3), 2.81 (dd, 1H, J= 10.9, 16.9, H-4a), 3.14 (dd, 1H, J= 3.3, 11.4, H-2), 3.27 (dd, 1H, J= 6.6, 16.9, H-4e), 3.64 (ddd, 1H, J= 6.6, 11.3, H-3), 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.50 (q, 1H, J= 6.4, H-1'), 4.92 (d, 1H, J= 3.3, H-1), 6.68 (d, 1H, J= 7.1, H-5), 7.0-7.4 (m, 8H, aromatics), identical to that previously reported[29]. ^{1}H-nmr spectrum is shown in

Appendix 1.

1-(2-Methyl-1-phenyl-1-propoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **88/89b, 90/91b, 92/93b, 94/95b:**

To a solution of alkoxysulfone **85b** (133 mg, 0.42 mmol) in toluene (5 mL) was added dimethyl fumarate (200 mg, 1.39 mmol, 3.3 eq.) and zinc oxide powder (20 mg). The solution was then refluxed for 10 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant and evaporated. The excess of dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to afford a colourless oil (145 mg, 87%). The crude product was crystallized from pentane to give colourless needles [mp: 89-91°C] corresponding to the major diastereomer of the mixture. The minor diastereomers were only partially purified by chromatography using 5% ethyl acetate/benzene as eluant and only ^{1}H-nmr was used for their identification.

***Major endo* 88/89b**

IR (CH_2Cl_2) cm^{-1}: 1750 (CO). ^{1}H-nmr ($CDCl_3$) δ: 0.64 (d, 3H, J= 6.8, CH_3), 0.95 (d, 3H, J= 6.8, CH_3), 1.90 (m, 1H, H-2'), 2.78 (dd, 1H, J= 10.1, 16.8, H-4a), 3.07 (dd, 1H, J= 2.9, 11.2, H-2), 3.26 (dd, 1H, J= 7.4, 16.8, H-4e), 3.61-3.71 (m, 1H, H-3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.99 (d, 1H, J= 7.3, H-1'), 4.87 (d, 1H, J= 2.9, H-1), 6.53 (d, 1H, J= 7.6, H-5), 6.8-7.2 (m, 8H, aromatics). Anal. calcd. for $C_{24}H_{28}O_5$: C 72.69, H 7.12, found: C 72.92, H 6.98.

***Minor endo* 90/91b**

^{1}H-nmr ($CDCl_3$) δ: 0.51 (d, J= 6.8, CH_3), 0.67 (d, J= 6.8, CH_3), 1.72 (m, H-2'), 2.89 (dd, J= 9.3, 17.0, H-4a), 3.02 (dd, J= 2.7, 11.2, H-2), 3.41 (dd, J= 8.0, 17.0, H-4e), 3.67-3.75 (m, H-3), 3.67 (s, OCH_3), 3.75 (s, OCH_3), 3.79 (d, J= 7.2, H-1'), 4.58 (d, J= 2.7, H-1), 6.8-7.4 (m, aromatics).

Major exo **92/93b**

^{1}H-nmr ($CDCl_3$) δ: 0.69 (d, J= 6.7, CH_3), 1.00 (d, J= 6.7, CH_3), 2.00 (m, H-2'), 2.96 (m, H-4e), 3.13 (m, H-3, H-4a), 3.58 (dd, J= 4.5, 7.9, H-2), 3.68 (s,OCH_3), 3.74 (s, OCH_3), 4.16 (d, J= 7.8, H-1'), 4.67 (d, J= 4.5, H-1), 6.9-7.4 (m, aromatics).

Minor exo **94/95b**

^{1}H-nmr ($CDCl_3$) δ: 0.55 (d, J= 6.8, CH_3), 0.72 (d, J= 6.8, CH_3), 1.75 (m, H-2'), 3.00 (dd, J= 6.1, 14.5, H-4e), 3.22 (m, H-3), 3.35 (dd, J= 9.5, 14.5, H-4a), 3.47 (s, OCH_3), 3.77 (s, OCH_3), 3.72-3.80 (m, H-2, H-1'), 4.59 (d, J= 2.8, H-1), 6.9-7.4 (m, aromatics).

1-(2,2-Dimethyl-1-phenyl-1-propoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **88/89c, 90/91c, 92/93c, 94/95c:**

To a solution of alkoxysulfone **85c** (47 mg, 0.14 mmol) in toluene (5 mL) was added dimethyl fumarate (100 mg, 0.69 mmol, 5 eq.) and zinc oxide powder (21 mg). The solution was then refluxed for 17 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant and evaporated. The excess of dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to afford a white solid (49 mg, 84%). The crude product was recrystallized from hexane to give colourless needles [mp: 136-137°C] corresponding to the major diastereomer of the mixture. The minor diastereomers were only partially purified by chromatography using 5% ethyl acetate/benzene as eluant and only ^{1}H-nmr was used for their identification.

Major endo **88/89c**

IR (CH_2Cl_2) cm^{-1}: 1735 (CO). ^{1}H-nmr ($CDCl_3$) δ: 0.82 (s, 9H, t-butyl), 2.78 (dd, 1H, J= 9.1, 16.9, H-4a), 3.08 (dd, 1H, J= 2.8, 10.9, H-2), 3.27 (dd, 1H, J= 8.2, 16.9, H-4e), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.07 (s, 1H, H-1'), 4.86 (d, 1H, J= 2.8, H-1), 6.7-7.0 (m, 9H, aromatics), H-3 hidden under other signals. ^{1}H-nmr spectrum is shown in Appendix 1. Anal. calcd. for $C_{25}H_{30}O_5$: C 73.13, H 7.37, found: C 73.46, H 7.45.

(-)-1-((R)-2-Methyl-1-phenyl-1-propoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **88b**:

To a solution of alkoxysulfone **(R)-85b** (259 mg, 0.82 mmol) in toluene (10 mL) was added dimethyl fumarate (500 mg, 3.5 mmol, 4.3 eq.) and zinc oxide powder (150 mg). The solution was then refluxed for 3 1/2 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated. The excess of dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to afford a colourless oil (263 mg, 81%). The crude product was crystallized from pentane to give colourless needles [mp: 95-96.5°C] corresponding to the major diastereomer of the mixture.

$[\alpha]_D$= -59.4° (c: 0.74, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: identical to that of **88/89b**. ^{1}H-nmr spectrum is shown in Appendix 1.

2,3-Dicarbomethoxy-3,4-dihydronaphthalene **99**:

This compound was prepared by elimination of the alcohol from the cycloadducts as previously reported[6,22]. A solution of the desired cycloadduct in toluene (10 mL) was refluxed in the presence of p-toluenesulfonic acid (5 mg) for 7 hours. The solution was then filtered through a short silica gel column using methylene chloride as eluant and evaporated. The residue was chromatographed on silica gel using 10% ethyl acetate/hexane as eluant to afford in all cases a colourless oil.

(±)-99

Prepared from **88/89a** (77 mg, 0.21 mmol); obtained 36 mg (69%). Prepared from **88/89b** (13 mg, 0.03 mmol); obtained 7 mg (82%). Prepared from **88/89c** (10 mg, 0.03 mmol); obtained 6 mg (90%). ^{1}H-nmr ($CDCl_3$) δ: 3.13 (dd, 1H, J= 8.0, 16.2, H-4e), 3.35 (dd, 1H, J= 3.5, 16.2, H-4a), 3.60 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.88 (dd, 1H, J= 3.5, 8.0, H-3), 7.17-7.23 (m, 4H, aromatics), 7.65 (s, 1H, H-1), identical in all cases to that

Minor endo **90/91c**

^{1}H-nmr ($CDCl_3$) δ: 0.65 (s, t-butyl), 2.88 (dd, J= 9.7, 17.1, H-4a), 3.05 (dd, J= 2.7, 11.4, H-2), 3.40 (dd, J= 8.0, 17.1, H-4e), 3.76 (s, OCH_3), 3.77 (s, OCH_3), 4.56 (d, J= 2.7, H-1), 6.7-7.05 (m, aromatics), H-3 and H-1' hidden under other signals.

Major exo **92/93c**

^{1}H-nmr ($CDCl_3$) δ: 0.87 (s, t-butyl), 2.96 and 3.16 (m, H-3, H-4a, H-4e), 3.69 (dd, J= 3.2, 7.9, H-2), 3.62 (s, OCH_3), 3.75 (s, OCH_3), 4.28 (s, H-1'), 4.59 (d, J= 3.0, H-1), 6.9-7.4 (m, aromatics).

Minor exo **94/95c**

^{1}H-nmr ($CDCl_3$) δ: 0.65 (s, t-butyl), 3.02 (dd, J= 9.6, 14.4, H-4e), 3.37 (dd, J= 6.1, 14.4, H-4a), 3.47 (s, OCH_3), 3.80 (s, OCH_3), 3.84 (dd, J= 2.4, 5.7, H-2), 4.52 (d, J= 2.4, H-1), 6.9-7.4 (m, aromatics), H-3 and H-1' hidden under other signals.

(+)-1-((S)-1-Phenyl-1-ethoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **89a**:

To a solution of alkoxysulfone **(S)-85a** (306 mg, 1.06 mmol) in toluene (20 mL) was added dimethyl fumarate (620 mg, 4.31 mmol, 4.1 eq.) and zinc oxide powder (200 mg). The solution was then refluxed for 3 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated. The excess of dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to give a yellowish oil (329 mg, 84%). The crude product could not be crystallized in this case, but the major isomer was obtained as a 85:15 mixture (^{1}H-nmr) with the minor *endo* isomer by chromatography using 5% ethyl acetate/benzene as eluant.

$[\alpha]_D$= +47° (c: 0.54, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: identical to that of **88/89a**.

previously reported[29]. ^{1}H-nmr spectrum is shown in Appendix 1.

(S)-(-)-**99**

Prepared from an 85:15 mixture (major/minor *endo* isomer) of **89a** (11 mg, 0.03 mmol); obtained 7 mg (92%). $[\alpha]_D$= -92° (c: 0.33, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: identical to that of (±)-**99**.

(R)-(+)-**99**

A) Prepared from **88b** (16 mg, 0.04 mmol); obtained 7 mg (71%). $[\alpha]_D$= +124° (c: 0.74, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: identical to that of (±)-**99**.

B) Prepared from γ-lactone **129**:

A solution of γ-lactone **129** (68 mg, 0.22 mmol) in methanolic KOH (0.2M, 10 mL) was refluxed for 2 hours. The solution was concentrated to half of its original volume by evaporation, diluted with aqueous sodium bicarbonate (5%) and extracted with ethyl acetate. The aqueous solution was acidified (10% aqueous HCl), extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to give an oily material. The oil was dissolved in diethyl ether (5 mL) and an excess of diazomethane in ether was added. After 15 minutes at room temperature the solvent was evaporated to give a yellowish oil (47 mg, 90%). Purification by chromatography on silica gel using 15% ethyl acetate/hexane as eluant afforded a colourless oil (37 mg, 65%).

$[\alpha]_D$= +128° (c: 0.58, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: identical to that of (±)-**99**.

(±)-3-Carboxy-1,2,3,4-tetrahydronaphthalene-1-one **100**:

A solution of dicarbomethoxy ketone **102** (75 mg, 0.29 mmol) in 40% aqueous H_2SO_4 (25 mL) was refluxed for 2 1/2 hours. The solution was then extracted with methylene chloride, the organic layer was washed with aqueous sodium bicarbonate (5%), the aqueous extract re-acidified (10% aqueous HCl), extracted with methylene chloride,

dried ($MgSO_4$) and evaporated to give a yellowish solid (47 mg, 86%). The crude product was recrystallized from water to afford a colourless solid [mp: 147-149°C; ref 149°C[76]]. IR (CH_2Cl_2) cm^{-1}: 3200 (OH), 1713 (CO, acid), 1689 (CO, ketone). ^{1}H-nmr ($CDCl_3$) δ: 2.80-3.05 (m, 2H), 3.20-3.30 (m, 3H), 7.30-8.10 (m, 4H, aromatics). Mass Spectrum, *m/e* (rel %): 190(32), 177(13), 149(64), 145(100), 127(8), 118(32), 115(25), 90(37), exact mass calcd. for $C_{11}H_{10}O_3$: 190.0630, found: 190.0628.

1-Hydroxy-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **101**:

To a solution of *o*-methylbenzaldehyde (105 mg, 0.88 mmol) in benzene (30 mL) was added dimethyl fumarate (360 mg, 2.5 mmol, 2.9 eq.). The solution was flushed with nitrogen and irradiated at room temperature for 4 hours using a 450 watt Hanovia medium pressure mercury lamp housed in a Pyrex probe. The solvent was evaporated, the excess fumarate was removed by sublimation at 100°C under reduced pressure, and the residue purified by chromatography on silica gel using 50% ethyl acetate/hexane as eluant to afford a colourless oil (200 mg, 87%) corresponding to a mixture of isomers (*endo*/*exo*: 74/26 from ^{1}H-nmr).

IR (CH_2Cl_2) cm^{-1}: 3600 (OH), 1750 (CO). ^{1}H-nmr ($CDCl_3$) δ: ***Endo Isomer*** 2.25 (d, J= 4.9, OH), 2.91 (dd, J= 11.7, 16.8, H-4a), 3.14 (dd, J= 3.4, 11.7, H-2), 3.21 (dd, J= 5.6, 16.8, H-4e), 3.40 (ddd, J= 5.6, 11.7, H-3), 3.77 (s, OCH_3), 3.79 (s, OCH_3), 5.13 (broad dd, H-1), 7.25 (m, aromatics), ***Exo Isomer*** 2.63 (d, J= 6.4, OH), 3.03 (dd, J= 9.2, 10.3, H-4a), 3.20 (dd, J= 5.8, 10.3, H-4e), 3.73 (s, OCH_3), 3.79 (s, OCH_3), 5.01 (dd, J= 7.6, H-1), 7.25 (m, aromatics), H-2 and H-3 were not observed for this isomer. Mass Spectrum, *m/e* (rel %): 264(1), 256(1), 246(11), 214(19), 204(28), 187(100), 186(60), 155(45), 145(87), 128(72), exact mass calcd. for $C_{14}H_{16}O_5$: 264.0998, found: 264.1006. All data were obtained from the mixture.

(±)-*2,3-Dicarbomethoxy-1,2,3,4-tetrahydronaphthalene-1-one* **102**:

To a solution of hydroxycycloadduct **101** (112 mg, 0.42 mmol) in diethyl ether (7 mL) was slowly added at 0°C a solution of chromium trioxide (5%) in 10% aqueous H_2SO_4. The solution was stirred for 1 1/2 hours and extracted with diethyl ether. The organic solution was washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to give a white solid (95 mg, 85%). The crude product (consisting of the ketone and its enol form **103**) was recrystallized from isopropyl alcohol to afford colourless flakes [mp: 84-86°C] corresponding to the ketone **102**.

IR (CH_2Cl_2) cm^{-1}: 1743 (CO, ester), 1690 (CO, ketone). ^{1}H-nmr ($CDCl_3$) δ: 3.18 (dd, 1H, J= 11.1, 16.7, H-4a), 3.37 (dd, 1H, J= 4.6, 16.7, H-4e), 3.63 (ddd, 1H, J= 4.6, 11.1, H-3), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.91 (d, 1H, J= 11.1, H-2), 7.10-8.10 (m, 4H, aromatics). Mass spectrum, *m/e* (rel %): 262(10), 231(6), 230(2), 203(84), 171(100), 143(19), 115(34), exact mass calcd. for $C_{14}H_{14}O_5$: 262.0841, found: 262.0837.

***Enol* 103**

^{1}H-nmr ($CDCl_3$) δ: 3.15 (dd, J= 7.3, 16.0, H-4a), 3.27 (dd, J= 2.6, 16.0, H-4e), 3.58 (s, OCH_3), 3.80 (dd, J= 2.6, 7.3, H-3), 3.83 (s, OCH_3), 7.10-8.10 (m, aromatics). Obtained from crude reaction mixture.

1-(2-Hydroxy-1-ethoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **111**:

To a solution of hydroxysulfone **59** (89 mg, 0.48 mmol) in methylene chloride (10 mL) was added ethylene glycol (100 mg, 1.61 mmol) and p-toluenesulfonic acid (10 mg). The solution was refluxed for 20 hours, cooled, filtered through a short silica gel column using methylene chloride as eluant to afford a yellowish oil (84 mg, 77%).

IR (CH_2Cl_2) cm^{-1}: 1319, 1205, 1124 (SO), 3554 (OH). ^{1}H-nmr ($CDCl_3$) δ: 3.78-4.25 (m, 4H, ethylene glycol), 4.27 (d, 1H, J= 15.6, H-3A), 4.43 (d, 1H, J= 15.6, H-3B), 5.45 (s, 1H, H-1), 7.3-7.5 (m, 4H, aromatics).

1-(1,2-cis-2-Hydroxy-1-cyclohexyloxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **112**:

To a solution of hydroxysulfone **59** (201 mg, 1.09 mmol) in methylene chloride (10 mL) was added 1,2-*cis*-hexanediol (80 mg, 0.69 mmol) and p-toluenesulfonic acid (10 mg). The solution was refluxed for 24 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant and evaporated. The crude product (160 mg, 82%) was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford a colourless oil (55 mg, 28%).

IR (CH_2Cl_2) cm^{-1}: 1320, 1207, 1126 (SO), 3551 (OH). ^{1}H-nmr ($CDCl_3$) δ: 1.3-2.1 (m, 8H, cyclohexane protons), 3.9-4.2 (m, 2H, cyclohexane protons), 4.27 (d, 1H, J= 15.7, H-3A), 4.42 (d, 1H, J= 15.7, H-3B), 5.50 (s, 1H, H-1), 7.2-7.6 (m, 4H, aromatics).

1-(2-Hydroxy-1-ethoxy)-2,3-dicarbomethoxy-1,2,3,4-tetrahydronaphthalene **113**:

To a solution of alkoxysulfone **111** (80 mg, 0.35 mmol) in toluene (10 mL) was added dimethyl fumarate (200 mg, 1.39 mmol) and zinc oxide (50 mg). The solution was then refluxed for four hours, cooled, filtered through a short silica gel column using methylene chloride as eluant and evaporated. The excess dimethyl fumarate was removed by sublimation at 100°C under reduced pressure to afford a yellowish oil (58 mg, 54%) corresponding to a 9:1 mixture of *endo* and *exo* diastereomers.

IR (CH_2Cl_2) cm^{-1}: 1729 (CO), 3549 (OH). ^{1}H-nmr ($CDCl_3$) δ: **(major isomer, *endo*)** 2.86 (dd, J= 11.3, 16.8, H-4a), 3.17 (dd, J= 3.3, 11.7, H-2), 3.27 (dd, J= 6.6, 16.8, H-4e), 3.5-3.7 (m, H-3, H-1', H-2'), 3.76 (s, OCH_3), 3.78 (s, OCH_3), 4.77 (d, J= 3.3, H-1), 7.1-7.4 (m, aromatics), obtained from crude reaction mixture.

o-Methylbenzaldehyde 1,2-cis-cyclohexanediol acetal **115**:

To a solution of *o*-methylbenzaldehyde (47 mg, 0.39 mmol) in benzene (10 mL) was added 1,2-*cis*-cyclohexanediol (57 mg, 0.49 mmol) and p-toluenesulfonic acid (10

mg). The solution was refluxed for 20 hours, cooled, diluted with ethyl acetate, washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to afford a colourless oil (77 mg, 91%).

^{1}H-nmr ($CDCl_3$) δ: 1.2-2.1 (m, 8H, cyclohexane protons), 2.41 (s, 3H, CH_3), 4.20 (m, 2H, cyclohexane protons), 6.08 (s, 1H, O-CH-O), 7.1-7.6 (m, 4H, aromatics).

1-(1-Phenyl-2-hydroxy-1-ethoxy)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **117**:

To a solution of hydroxysulfone **59** (90 mg, 0.49 mmol) in methylene chloride (10 mL) was added 1-phenyl-1,2-ethanediol (91 mg, 0.66 mmol) and p-toluenesulfonic acid (10 mg). The solution was refluxed for 21 hours, filtered through a short silica gel column using methylene chloride as eluant and evaporated to afford a yellowish oil (110 mg, 74%) corresponding to a mixture of isomers.

IR (CH_2Cl_2) cm^{-1}: 1325, 1207, 1126 (SO), 3457 (OH). ^{1}H-nmr ($CDCl_3$) δ: the ^{1}H-nmr spectra of these two isomers could not be assigned as most of the signals were overlapping.

1-(1-Propoxy-2-ene)-1,3-dihydrobenzo[c]thiophene-2,2-dioxide **118**:

To a solution of hydroxysulfone **59** (209 mg, 1.13 mmol) in methylene chloride (10 mL) was added allyl alcohol (51 mg, 0.88 mmol) and p-toluenesulfonic acid (10 mg). The solution was refluxed for 5 hours, cooled, pushed through a short silica gel column using methylene chloride as eluant and evaporated to afford a yellowish oil (180 mg, 91%).

IR (CH_2Cl_2) cm^{-1}: 1321, 1201, 1129 (SO). ^{1}H-nmr ($CDCl_3$) δ: 4.23 (d, 1H, J= 15.6, H-3A), 4.42 (d, 1H, J= 15.6, H-3B), 4.44 (m, 1H, H-1'A), 4.68 (m, 1H, H-1'B), 5.38 (m, 2H, H-3'), 5.42 (s, 1H, H-1), 6.00 (m, 1H, H-2'), 7.3-7.5 (m, 4H, aromatics).

Oxazolidine **120**:

Method A:

To a solution of *o*-methylbenzaldehyde (220 mg, 1.83 mmol) in methylene chloride (10 mL) was added *l*-ephedrine (300 mg, 1.83 mmol). The solution was refluxed for 8 hours, cooled, diluted with ethyl acetate, washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and solvent evaporated. The resulting semi-crystalline material was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford colourless crystals (330 mg, 68%, mp: 87-89°C).

Method B:

To a solution of hydroxysulfone **59** (222 mg, 1.21 mmol) in methylene chloride (15 mL) was added *l*-ephedrine (199 mg, 1.21 mmol). The solution was stirred at room temperature for 15 minutes, then another molar equivalent (199 mg) of *l*-ephedrine was added. The solution was refluxed for four hours, filtered through a short silica gel column using ethyl acetate as eluant and the solvent was evaporated to afford a white solid (228 mg, 71%, mp: 86-88°C). No further purification was attempted on this product. ^{1}H-nmr was identical in both cases.

$[\alpha]_D$= -69° (c: 0.56, $CHCl_3$). ^{1}H-nmr ($CDCl_3$) δ: 0.79 (d, 3H, J= 6.4, CH_3), 2.22 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.98 (m, 1H, H-4), 5.01 (s, 1H, H-1), 5.14 (d, 1H, J= 8.1, H-3), 7.15-7.4 (m, 8H, aromatics), 7.89 (d, 1H, aromatic). Mass Spectrum, *m/e* (rel %): 267(1), 266(3), 210(15), 195(29), 181(35), 167(12), 162(18), 161(100), 160(90), 148(24), 147(26), 146(76), exact mass calcd. for $C_{18}H_{21}NO$: 267.1623, found: 267.1577.

Benzylsulfinic acid salt of ephedrine **121**:

In a nmr tube was dissolved the hydroxysulfone **59** (34 mg, 0.18 mmol) in $CDCl_3$ (~1.5 mL). One molar equivalent of *l*-ephedrine (31 mg, 0.18 mmol) was added and the ^{1}H-nmr spectra was recorded.

IR ($CDCl_3$) cm^{-1}: 3250 (OH), 1694 (CO). ^{1}H-nmr ($CDCl_3$) δ: 0.91 (d, 3H, J= 6.7, CH_3), 2.41 (s, 3H, CH_3), 2.98 (broad q, 1H, J= 6.7, CH_3-CH-N), 4.04 (q, 2H, CH_2), 5.09 (d, 1H, J= 1.8, HO-CH-Ph), 7.2-7.5 (m, 8H, aromatics), 7.83 (d, 1H, J= 6.8, aromatic), 10.17 (s, 1H, CHO).

Fumarate of (S)-methyl lactate **123**:

To (S)-methyl lactate (3.32 g, 31.9 mmol) was added fumaryl chloride (2.44 g, 15.9 mmol) and the resulting mixture was heated at 110°C for 17 hours. The mixture was then diluted with ethyl acetate and washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to give a yellowish oil (4.24 g, 92%). The crude product (1.0 g was typically used) was purified by chromatography on silica gel using 15% ethyl acetate/hexane as eluant and afforded a colourless oil (0.62 g, 62%). $[\alpha]_D$= -15.5° (c: 0.32, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1733 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.56 (d, 3H, J= 7.1, CH_3), 3.77 (s, 3H, OCH_3), 5.22 (q, 1H, J= 7.1, CH), 6.97 (s, 1H, alkene CH). Mass Spectrum, *m/e* (rel %): 288(0.1), 258(1), 185(54), 140(6), 113(13), 99(17), 87(100), 82(16), exact mass calcd. for $C_{12}H_{16}O_8$: 288.0848, found: 288.0845, chemical ionization (NH_4^+), *m/e* (rel %): 306(26) [M^++18], 289(14) [M^++1], 257(22), 244(12), 202(15), 185(100), 140(18), 113(47), 98(47), 87(73), 82(46).

Maleate of (S)-methyl lactate **124**:

To a solution of (S)-dilactyl fumarate **123** (527 mg) in benzene (300 mL) was added benzophenone (70 mg). The solution was flushed with nitrogen and irradiated for 6 1/2 hours using a 450 watt Hanovia medium pressure mercury lamp located in a water cooled, Pyrex probe immersed in the solution. The solution was cooled and the solvent evaporated to give a yellowish oil. Chromatography on silica gel using 15% ethyl

acetate/hexane as eluant gave a colourless oil (421 mg, 80%).

$[\alpha]_D$ = -69.8° (C: 0.79, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1748 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.52 (d, 3H, J= 7.1, CH_3), 3.76 (s, 3H, OCH_3), 5.23 (q, 1H, J= 7.1, CH), 6.36 (s, 1H, alkene CH). Mass spectrum, *m/e* (rel %): 288(0.1), 258(2), 185(29), 155(6), 129(4), 128(4), 121(34), 119(99), 117(100), 99(7), 87(42), chemical ionization: 306(14) [M^+ + 18], 289(32) [M^+ + 1], 257(5), 202(28), 185(100), 170(5), 113(13), 98(56), exact mass calcd. for $C_{12}H_{16}O_8$: 288.0845, found: 288.0847.

Benzocyclobutenol **125**:

This compound was prepared according to a procedure previously reported[89]. To refluxing vinyl acetate (75 mL) was added simultaneously isoamyl nitrite (5 g, 42.7 mmol) and a suspension of anthranilic acid (5 g, 36.5 mmol) in vinyl acetate (50 mL) over a period of 30 minutes. The solution was then refluxed for 40 minutes and evaporated to give a dark oil (11 g). The oil was distilled under reduced pressure (80°C/0.2 mm Hg) to afford a yellow liquid (2.12 g, 36%). This residue was dissolved in methanol (15 mL) and aqueous sodium bicarbonate (5%, 27 mL) was added. The solution was stirred overnight and extracted with ether. The organic extract was washed with water, dried ($MgSO_4$) and evaporated to give a yellow solid. Recrystallization from light petroleum ether gave colourless needles (289.6 mg, 18%).

mp: 56-58°C [ref 59-60°C[89]]. ^{1}H-nmr ($CDCl_3$) δ: 2.09 (d, 1H, J= 8.8, OH), 3.05 (dd, 1H, J= 2.0, 14.4, H-2A), 3.63 (dd, 1H, J= 4.5, 14.4, H-2B), 5.30 (m, 1H, H-1), 7.13-7.27 (m, 4H, aromatics), identical to that previously reported[89].

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (S)-methyl lactate **127**:

Method A:

To a solution of *o*-methylbenzaldehyde (97 mg, 0.81 mmol) in benzene (30 mL) was added (S)-dilactyl fumarate **123** (331 mg, 1.15 mmol, 1.4 eq.). The solution was then flushed with nitrogen and irradiated for 6 hours using a 450 watt Hanovia medium pressure mercury lamp located in a Pyrex water cooled probe 10 cm from the solution. After irradiation, the solvent was evaporated to give a colourless oil (441 mg). The crude product was purified by chromatography on silica gel using 15% ethyl acetate/hexane as eluant to afford a colourless oil (181 mg, 55%). Recrystallization from hexane afforded colourless flakes [mp: 84.5-85.0°C].

Method B:

To a solution of benzocyclobutenol **125** (28 mg, 0.23 mmol) in toluene (5 mL) was added (S)-dilactyl fumarate **123** (221 mg, 0.77 mmol, 3.3 eq.) and 4Å molecular sieves (20 mg). The solution was refluxed for 4 hours, cooled and the solvent evaporated. Chromatography on silica gel using 15% ethyl acetate/hexane as eluant afforded a white solid (55 mg, 58%). Recrystallization from hexane afforded colourless flakes [mp: 81-82°C].

Method C:

To a refluxing solution of (S)-dilactyl fumarate **123** (292 mg, 1.01 mmol, 1.5 eq.) in toluene (5 mL), containing zinc oxide (50 mg), was slowly added a methylene chloride solution (10 mL) of hydroxysulfone **59** (124 mg, 0.67 mmol). After addition of the methylene chloride solution, the mixture was refluxed for another 20 minutes, cooled, filtered through a short silica gel column with ethyl acetate and evaporated. The residual oil was purified by chromatography on silica gel using 20% ethyl acetate/hexane as eluant to afford a white solid (152 mg, 55%). Recrystallization from hexane gave colourless flakes [mp: 82-84°C]. ^{1}H-nmr spectrum was identical for all three methods.

$[\alpha]_D$= -64° (c: 0.74, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3471 (OH), 1743 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.52 (d, 3H, J= 7.1, CH_3), 1.58 (d, 3H, J= 7.1, CH_3), 3.05 (m, 2H, H-2, H-4a), 3.27 (m, 2H, H-3, H-4e), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.53 (broad s, 1H, OH), 4.95 (d, 1H, J= 9.8, H-1), 5.13 (q, 1H, J= 7.1, CH), 5.31 (q, 1H, J= 7.1, CH), 7.11-7.27 (m, 3H, aromatics), 7.70 (d, 1H, J= 7.2, H-8). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 408(2), 304(12), 276(17), 258(37), 201(34), 200(24), 173(35), 172(44), 171(19), 156(28), 155(100), 145(87), 129(78), 128(93), 127(24), exact mass calcd. for $C_{20}H_{24}O_9$: 408.1420, found: 408.1430. Anal. calcd. for $C_{20}H_{24}O_9$: C 58.80, H 5.93, found: C 58.81, H 5.70.

(-)-1-Hydroxy-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid-1,3-lactone-2-carboxylate of (S)-methyl lactate **129**:

To a solution of hydroxycycloadduct **127** (340 mg, 0.83 mmol) in methylene chloride (40 mL) was added p-toluenesulfonic acid (100 mg). The solution was stirred at room temperature for 3 days, filtered through a short silica gel column using ethyl acetate as eluant and evaporated. The crude product was purified by chromatography on silica gel using 25% ethyl acetate/hexane as eluant to afford a white solid (131 mg, 52%). Recrystallization from hexane/methylene chloride (traces) gave colourless needles [mp: 130-130.5°C], suitable for X-ray analysis.

$[\alpha]_D$= -22° (c: 1.18, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1788 (CO lactone), 1747 (CO ester). ^{1}H-nmr ($CDCl_3$) δ: 1.38 (d, 3H, J= 7.0, CH_3), 3.10 (d, 1H, J= 17.7, H-4a), 3.35 (m, 1H, H-3), 3.48 (dd, 1H, J= 5.2, 17.7, H-4b), 3.50 (s, 3H, OCH_3), 3.85 (t, 1H, J= 5.0, H-2), 4.95 (q, 1H, J= 7.0, CH), 5.48 (d, 1H, J= 5.0, H-1), 7.23 (m, 4H, aromatics), **COSY** experiment was performed to determined which signals (3.35 ppm and 3.85 ppm) corresponded to H-2 and H-3. Normal ^{1}H-nmr spectrum as well as **COSY** ^{1}H-nmr spectrum are shown in

Appendix 1. Mass Spectrum, *m/e* (rel %): 304(16), 201(19), 200(34), 172(10), 156(18), 145(17), 144(25), 129(68), 128(100), 127(16), 117(11), 115(12), exact mass calcd. for $C_{16}H_{16}O_6$: 304.0947, found: 304.0944. Anal. calcd. for $C_{16}H_{16}O_6$: C 63.14, H 5.30, found: C 62.96, H 5.51.

1-Hydroxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (S)-methyl lactate **130** and **131**:

To a solution of benzocyclobutenol **125** (170 mg, 1.41 mmol) in toluene (20 mL) was added (S)-dilactyl maleate **124** (833 mg, 2.89 mmol, 2 eq.) and 3Å molecular sieves (50 mg). The solution was refluxed for 5 hours, cooled and the solvent evaporated. The residue was purified by chromatography on silica gel using 25% ethyl acetate/hexane as eluant to afford a colourless oil (535 mg, 93%) corresponding to an inseparable mixture of two *exo* diastereomers (69/31, from ^{1}H-nmr).

$[\alpha]_D$= -28.6° (c: 1.57, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3594 (OH), 1745 (CO). ^{1}H-nmr ($CDCl_3$) δ: **(Major isomer 130)** 1.44 (d, J= 7.1, CH_3), 1.49 (d, J= 7.1, CH_3), 3.02 (d, J= 3.5, OH), 3.21 (dd, J= 6.2, 17.2, H-4), 3.35 (m, H-2, H-3, H-4'), 3.64 (s, OCH_3), 3.67 (s, OCH_3), 5.03 (q, J= 7.1, CH), 5.15 (q, J= 7.1, CH), 5.38 (dd, J= 3.5, 6.4, H-1), 7.18 (m, aromatics), 7.50 (m, aromatics), **(Minor isomer 131)** most of the signals for this isomer were hidden under the signals of the major isomer except: 2.73 (d, J= 3.7, OH), 3.60 (s, OCH_3), 3.68 (s, OCH_3). ^{1}H-nmr (C_6D_6) δ: **(Major isomer 130)** 1.15 (d, J= 7.0, CH_3), 1.28 (d, J= 7.0, CH_3), 2.61 (d, J= 3.9, OH), 2.89 (dd, J= 5.6, 16.6, H-4), 3.13 (s, OCH_3), 3.20 (s, OCH_3), 3.43 (m, H-2, H-3, H-4'), 4.99 (q, J= 7.0, CH), 5.16 (q, J= 7.0, CH), 5.51 (dd, J= 3.9, 6.0, H-1), 6.95 (m, aromatics), 7.48 (d, J= 7.5, H-8), **(Minor isomer 131)** 1.12 (d, J= 7.0, CH_3), 1.29 (d, J= 7.1, CH_3), 2.25 (d, J= 4.3, OH), 3.16 (s, OCH_3), 3.18 (s, OCH_3), 4.98 (q, J= 7.0, CH), 5.18 (q, J= 7.1, CH), 5.44 (overlapping dd, J~ 4.9, H-1), other signals of the minor isomer were not observed. Decoupling of the hydroxyl groups

(2.25 ppm and 2.61 ppm) gave the following coupling constants for **H-1** (**Major 130** $J_{1,2}$= 6.0, **Minor 131** $J_{1,2}$= 5.5). Mass spectrum, *m/e* (rel %): 408(1), 390(1), 305(15), 201(8), 185(8), 172(35), 155(38), 145(100), 144(28), 129(29), 121(26), 119(81), 117(84), exact mass calcd. for $C_{20}H_{24}O_9$: 408.1420, found: 408.1424. All data were obtained using the diastereomeric mixture.

(-)-3,4-Dihydronaphthalene-2,3-dicarboxylate of (S)-methyl lactate **132** and **133**:

To a mixture (69/31) of hydroxycycloadducts **130/131** (268 mg, 0.66 mmol) in toluene (10 mL) was added p-toluenesulfonic acid (20 mg). The solution was refluxed for 5 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant and evaporated to give an oil (236 mg, 92%). Chromatography on silica gel using 20% ethyl acetate/hexane as eluant gave a colourless oil (233 mg, 91%) corresponding to a mixture of two diastereomers (71/29, from ^{1}H-nmr).

$[\alpha]_D$= -48° (c: 0.45, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1742, 1714 (CO). ^{1}H-nmr ($CDCl_3$) δ: **(Major isomer 132)** 1.39 (d, J= 7.0, CH_3), 1.57 (d, J= 7.0, CH_3), 3.20 (dd, J= 8.0, 16.2, H-4a), 3.40 (dd, J= 3.7, 16.2, H-4e), 3.52 (s, OCH_3), 3.77 (s, OCH_3), 3.96 (dd, J= 3.7, 7.7, H-3), 5.02 (q, J= 7.0, CH), 5.23 (q, J= 7.0, CH), 7.26 (m, aromatics), 7.75 (s, H-1), **(Minor isomer 133)** 1.45 (d, J= 7.1, CH_3), 1.60 (d, J= 7.0, CH_3), 3.24 (dd, J= 8.0, 16.2, H-4a), 3.59 (s, OCH_3), 3.77 (s, OCH_3), 5.04 (q, J= 7.1, CH), 5.22 (q, J= 7.0, CH_3), 7.26 (m, aromatics), 7.76 (s, H-1), H-4e and H-3 of **133** were partially hidden under the corresponding signals of the major isomer **132**. Mass spectrum, *m/e* (rel %): 390(0.1), 359(1), 258(5), 185(8), 155(28), 149(13), 121(31), 119(96), 117(100), 82(24), exact mass calcd. for $C_{20}H_{22}O_8$: 390.1314, found: 390.1295. All data were obtained using the isomeric mixture.

2,3-Dicarbomethoxy-3-deutero-4-hydronaphthalene **134**:

To a mixture (71/29) of alkene **132/133** (94 mg, 0.24 mmol) in 20% D_2O/MeOD (10 mL) was added potassium carbonate (135 mg). The solution was refluxed overnight, diluted with ethyl acetate and washed with aqueous sodium bicarbonate (5%). The aqueous portion was acidified (10% aqueous HCl), extracted with methylene chloride, dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in diethyl ether (5 mL) and an excess of diazomethane in ether was added. The solution was stirred at room temperature for 15 minutes and evaporated. The residue was purified by chromatography on silica gel using 15% ethyl acetate/hexane as eluant to give a colourless oil (34 mg, 57%).

$[\alpha]_D$= no rotation was observed. IR (CH_2Cl_2) cm^{-1}: 1735, 1711 (CO). ^{1}H-nmr ($CDCl_3$) δ: 3.13 (d, 1H, J= 16.2, H-4a), 3.34 (d, 1H, J= 16.2, H-4e), 3.60 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 7.24 (m, 4H, aromatics), 7.65 (s, 1H, H-1). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 247(6), 215(5), 189(17), 188(73), 187(42), 156(38), 144(39), 130(23), 129(100), 128(44), 127(13), 116(5), exact mass calcd. for $C_{14}H_{13}DO_4$: 247.0954, found: 247.0946.

o-Benzylbenzaldehyde **135**:

To a suspension of $LiAlH_4$ (2.0 g, 53 mmol) in dry tetrahydrofuran (60 mL) was slowly added at 0°C a solution of *o*-benzylbenzoic acid (10 g, 47 mmol) in dry tetrahydrofuran (60 mL). The solution was then refluxed for one hour, cooled, and water (2 mL) was added followed by 15% aqueous sodium hydroxide (2 mL) and water (6 mL). The white precipitate was filtered, washed with ethyl acetate and the combined filtrates evaporated to afford a colourless oil (9.2 g). The oil was dissolved in diethyl ether (75 mL) and a solution of chromium trioxide (5%) in 10% aqueous H_2SO_4 was slowly added at 0°C. The mixture was stirred for 15 minutes at 0°C. Organic and aqueous layers were

separated and the aqueous extracted with diethyl ether. The organic fractions were combined, washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and evaporated to afford a colourless oil (8.4 g, 91%).

IR (CH_2Cl_2) cm^{-1}: 1698 (CO). ^{1}H-nmr ($CDCl_3$) δ: 4.45 (s, 2H, CH_2), 7.1-7.8 (m 9H, aromatics), 10.25 (s, 1H, CHO).

(-)-1-Hydroxy-4-phenyl-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate of (S)-methyl lactate **137** and **138**:

To a refluxing solution of dilactyl fumarate **123** (973 mg, 3.38 mmol, 1.5 eq.) in toluene (20 mL) containing zinc oxide (200 mg) was slowly added over a period of 1 hour a solution of hydroxysulfone **60** (580 mg, 2.23 mmol) in methylene chloride (25 mL). The solution was then refluxed for 20 minutes, filtered through a short silica gel column using ethyl acetate as eluant and evaporated to give a yellow oil (2 isomers, 90:10 ratio). The crude product was purified by chromatography using 15% ethyl acetate/hexane as eluant to afford a semi-crystalline material (583 mg, 54%, major isomer **137**) and a colourless oil (61 mg, 5.6%, minor isomer **138**), (644 mg, 60%, total yield). Recrystallization of the major isomer **137** from isopropyl alcohol afforded colourless needles [mp: 142-143°C]. The major isomer could also be obtained in 40% yield by crystallization from the crude reaction mixture with isopropyl alcohol. The minor isomer could not be crystallized.

(Major isomer 137, *exo*)

$[\alpha]_D$= -215.4° (c: 0.2, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3476 (OH), 1742 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.09 (d, 3H, J= 7.0, CH_3), 1.53 (d, 3H, J= 7.2, CH_3), 3.33 (dd, 1H, J= 9.5, 12.5, H-2), 3.55 (dd, 1H, J= 5.7, 12.5, H-3), 3.73 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.69 (d, 1H, J= 5.7, H-4), 4.91 (q, 1H, J= 7.0, CH), 4.98 (d, 1H, J= 9.5, H-1), 5.32 (q, 1H, J= 7.2, CH), 7.13 (m, 8H, aromatics), 7.82 (d, 1H, J= 7.4, H-8). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 484(0.1), 362(2), 335(17), 334(75), 249(13),

248(16), 247(9), 232(20), 231(100), 221(14), 220(17), 205(38), 204(49), 203(23), 202(15), 192(17), 178(11), 165(12), 128(9), 115(13), exact mass calcd. for $C_{26}H_{28}O_9$: 484.1733, found: 484.1698.

(Minor isomer 138, *endo*)

$[\alpha]_D$= +50° (c: 0.18, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3477 (OH), 1737 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.32 (d, 3H, J= 6.9, CH_3), 1.59 (d, 3H, J= 7.2, CH_3), 3.41 (dd, 1H, J= 3.1, 11.9, H-2), 3.60 (s, 3H, OCH_3), 3.71 (overlapping dd, 1H, J= 11.5, H-3), 3.81 (s, 3H, OCH_3), 4.02 (d, 1H, J= 4.0, OH), 4.17 (d, 1H, J= 11.1, H-4), 4.97 (q, 1H, J= 6.9, CH), 5.27 (q, 1H, J= 7.2, CH), 5.44 (overlapping dd, 1H, J= 3.5, H-1), 6.76 (d, 1H, J= 7.8, H-5), 7.12-7.35 (m, 7H, aromatics), 7.43 (d, 1H, J= 7.8, H-8). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 484(0.1), 334(18), 250(19), 249(16), 248(17), 247(12), 232(22), 231(100), 221(19), 220(14), 205(42), 204(35), 203(19), 202(12), 195(7), 178(10), 165(9), 131(8), 115(12), exact mass calcd. for $C_{26}H_{28}O_9$: 484.1733, found: 484.1709.

(-)-1-Hydroxy-4-phenyl-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid-1,3-lactone-2-carboxylate of (S)-methyl lactate **139**:

To a solution of hydroxycycloadduct **137** (449 mg, 0.93 mmol) in dry tetrahydrofuran (20 mL) was added, at -78°C under nitrogen, n-butyllithium in hexanes (2.5 M, 0.37 mL, 0.93 mmol). The solution was stirred at -78°C for 15 minutes, then at room temperature for 1/2 hour. Aqueous ammonium chloride (5%, 30 mL) was added, the solution stirred for 15 minutes, extracted with methylene chloride, dried ($MgSO_4$) and evaporated to give an oil (316 mg, 90%). The crude product was at least 90% pure by ^{1}H-nmr. Chromatography on silica gel using 15% ethyl acetate/hexane as eluant afforded a white solid (185 mg, 51%). Recrystallization from hexane/methylene chloride gave colourless flakes [mp: 135-136°C] suitable for X-ray analysis.

$[\alpha]_D$= -39.3° (c: 0.18, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1788 (CO, lactone), 1748 (CO, ester).

^{1}H-nmr ($CDCl_3$) δ: 1.42 (d, 3H, J= 7.0, CH_3), 3.35 (td, 1H, J= 0.8, 4.9, H-3), 3.51 (s, 3H, OCH_3), 3.94 (t, 1H, J= 5.1, H-2), 4.95 (d, 1H, J= 4.9, H-4), 5.00 (q, 1H, J= 7.0, CH), 5.52 (d, 1H, J= 5.1, H-1), 7.0-7.4 (m, 9H, aromatics). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 380(1), 362(4), 334(32), 276(16), 248(32), 231(79), 220(22), 205(68), 204(100), 192(39), 178(11), 165(17), 128(21), 127(14), exact mass calcd. for $C_{22}H_{20}O_6$: 380.1259, found: 380.1254.

4-Phenyl-3,4-dihydronaphtalene-2,3-dicarboxylate of (S)-methyl lactate **140**:

To a solution of hydroxycycloadduct **138** (20 mg, 0.04 mmol) in toluene (10 mL) was added p-toluenesulfonic acid (5 mg). The solution was refluxed for 20 hours, cooled, filtered through a short silica gel column using ethyl acetate as eluant to afford a colourless oil (14 mg, 74%).

$[\alpha]_D$: +213° (c: 0.72, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1744, 1711 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.48 (d, 3H, J= 7.1, CH_3), 1.55 (d, 3H, J= 7.0, CH_3), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.15 (d, 1H, J= 2.2, H-3), 4.84 (d, 1H, J= 2.2, H-4), 5.08 (q, 1H, J= 7.1, CH), 5.18 (q, 1H, J= 7.0, CH), 7.05-7.40 (m, 9H, aromatics), 7.85 (s, 1H, H-1). Mass Spectrum, *m/e* (rel %): 466(1), 335(12), 334(50), 232(21), 231(100), 205(8), 204(19), 203(28), 202(18), 185(9), exact mass calcd for $C_{26}H_{26}O_8$: 466.1628, found 466.1613.

1-Hydroxy-3-carboxy-4-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate of (S)-lactic acid **144**:

To a solution of γ-lactone **139** (58 mg, 0.15 mmol) in *tert*-butyl alcohol (7 mL) was added aqueous HCl (10%, 15 mL). The solution was heated for 3 days using a sand bath maintained at 80°C. The solution was cooled and aqueous sodium bicarbonate (5%) slowly added until the solution was basic. The solution was extracted with methylene

chloride, the aqueous layer re-acidified (10% aqueous HCl) and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and the solvent evaporated to give a white solid (42 mg, 72%, mp: 122-130°C). The product (~90% pure, ^{1}H-nmr) could not be recrystallized and was therefore used without any purification.

^{1}H-nmr ($CDCl_3$) δ: 1.54 (d, J= 7.1, CH_3), 3.24 (dd, J= 9.8, 12.4, H-2), 3.54 (dd, J= 5.6, 12.4, H-3), 4.67 (d, J= 5.4, H-4), 4.98 (d, J= 9.8, H-1), 5.31 (q, J= 7.1, CH), 6.95-7.33 (m, aromatics), 7.74 (d, J= 7.8, H-8), obtained from crude product.

The dimethyl ester **143** of the diacid **144** was also obtained by treating the crude diacid **144** with diazomethane followed by chromatography on silica gel (15% ethyl acetate/hexane). ^{1}H-nmr ($CDCl_3$) δ: 1.54 (d, 3H, J= 7.2, CH_3), 3.28 (dd, 1H, J= 9.7, 12.4, H-2), 3.52 (dd, 1H, J= 5.8, 12.4, H-3), 3.58 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.68 (d, 1H, J= 5.8, H-4), 4.73 (d, 1H, J= 3.4, OH), 4.97 (dd, 1H, J= 3.1, 9.7, H-1), 5.28 (q, 1H, J= 7.2, CH), 6.90-7.35 (m, 8H, aromatics), 7.81 (d, 1H, J= 7.9, H-8). Mass Spectrum, *m/e* (rel %): M^+ not observed, 394(1), 334(30), 263(36), 262(78), 249(10), 248(11), 247(10), 232(20), 231(100), 221(17), 220(13), 219(11), 205(31), 204(31), 203(25), 202(15), 195(21), 192(10).

1-Hydroxy-2-hydroxymethyl-3-carboxy-4-phenyl-1,2,3,4-tetrahydronaphthalene **145**:

To a solution of crude hydroxy diacid **144** (78 mg, 0.2 mmol) in dry tetrahydrofuran (40 mL) was added, at 0°C under nitrogen, lithium triethylborohydride in tetrahydrofuran (1M, 1.3 mL, 1.3 mmol, 6.5 eq.). The solution was stirred at 0°C for 5 minutes, then at room temperature for 20 hours. Dilute aqueous HCl (10%) was added, the solution was stirred for 1 1/2 hours, saturated with NaCl and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated to give an oily material (59 mg, 98%). The product (~80% pure by ^{1}H-nmr) could not be crystallized and was therefore used without purification.

IR (CH_2Cl_2) cm^{-1}: 3695 (OH), 1744 (CO). ^{1}H-nmr ($CDCl_3$) δ: 2.53 (m, H-2), 3.06 (dd, J= 6.3, 12.1, H-3), 4.35 (dd, J= 4.6, 10.7, H-11), 4.62 (d, J= 6.3, H-4), 4.86 (d, J= 10.1, H-1), 6.85-7.31 (m, aromatics), 7.75 (d, J= 7.7, H-8), H-11' was not observed. Data were obtained from crude product.

The methyl ester **146** was also obtained by treating the dihydroxy acid **145** with diazomethane. ^{1}H-nmr ($CDCl_3$) δ: 2.59 (m, H-2), 3.05 (dd, J= 6.5, 12.1, H-3), 3.49 (s, OCH_3), 4.31 (dd, J= 4.5, 10.6, H-11), 4.59 (d, J= 6.5, H-4), 4.85 (d, J= 10.2, H-1), 6.88-7.32 (m, aromatics), 7.73 (d, H= 7.7, H-8), obtained from crude product. The dihydroxy acid **145** was fully characterized as its methyl ester acetonide **147**.

(-)-1-Hydroxy-2-hydroxymethyl-3-carbomethoxy-1,2,3,4-tetrahydronaphthalene acetonide **147**:

This compound was prepared according to a procedure previously reported[32,59]. To a solution of crude dihydroxy ester **146** (65 mg, 0.21 mmol) in 2,2-dimethoxypropane (5 mL) was added p-toluenesulfonic acid. The solution was stirred at room temperature overnight. Ethyl acetate was added and the organic solution was washed with aqueous sodium bicarbonate (5%), dried ($MgSO_4$) and solvent evaporated to give a yellowish oil (45 mg, 61%). Chromatography on silica gel using 15% ethyl acetate/hexane as eluant gave a colourless oil (95% pure by ^{1}H-nmr) which could not be crystallized. $[\alpha]_D$= -179.4° (c: 0.36, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 1742 (CO). ^{1}H-nmr ($CDCl_3$) δ: 1.56 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.50 (m, 1H, H-2), 3.02 (dd, 1H, J= 6.7, 12.3, H-3), 3.40 (s, 3H, OCH_3), 3.68 (t, 1H, J= 10.9, H-11), 4.14 (dd, 1H, J= 4.3, 11.1, H-11'), 4.57 (d, 1H, J= 6.7, H-4), 4.79 (d, 1H, J= 10.4, H-1), 6.87-7.26 (m, 8H, aromatics), 7.56 (d, 1H, J= 7.8, H-8). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 352(2), 337(12), 277(73), 217(100), 205(42), 195(32), 178(18), 167(81), 149(83), 119(97),

117(99), 99(52), exact mass calcd. for $C_{22}H_{24}O_4$: 352.1674, found: 352.1671.

(-)-1-Hydroxy-3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid-2,3-lactone **149**:

To a solution of γ-lactone **139** (228 mg, 0.60 mmol) in dry tetrahydrofuran (25 mL) was added, at 0°C under nitrogen, lithium triethylborohydride in tetrahydrofuran (1M, 1.8 mL, 1.8 mmol, 3 eq.). The solution was stirred at 0°C for 10 minutes then at room temperature for 5 hours. Aqueous HCl (10%, 20 mL) was added and the solution was stirred overnight. The solution was diluted with water, extracted with methylene chloride, dried ($MgSO_4$) and evaporated to give a white solid (120 mg, 71%). Recrystallization from carbon tetrachloride afforded colourless needles [mp: 162-164°C]. $[\alpha]_D$= -75.6° (c: 0.18, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3577 (OH), 1776 (CO). ^{1}H-nmr ($CDCl_3$) δ: 2.74 (dd, 1H, J= 9.9, 14.5, H-2), 2.91-3.03 (m, 1H, H-3), 3.35 (broad s, 1H, OH), 3.56 (dd, 1H, J= 8.6, 11.1, H-11), 4.43 (dd, 1H, J= 7.0, 8.6, H-11'), 4.51 (d, 1H, J= 5.7, H-4), 5.07 (d, 1H, J= 9.9, H-1), 6.91-7.80 (m, 9H, aromatics). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 280(30), 217(8), 202(5), 195(6), 178(7), 165(11), 118(10), 117(100), 115(10), 105(19), 91(25), 85(15), exact mass calcd. for $C_{18}H_{16}O_3$: 280.1099, found: 280.1076.

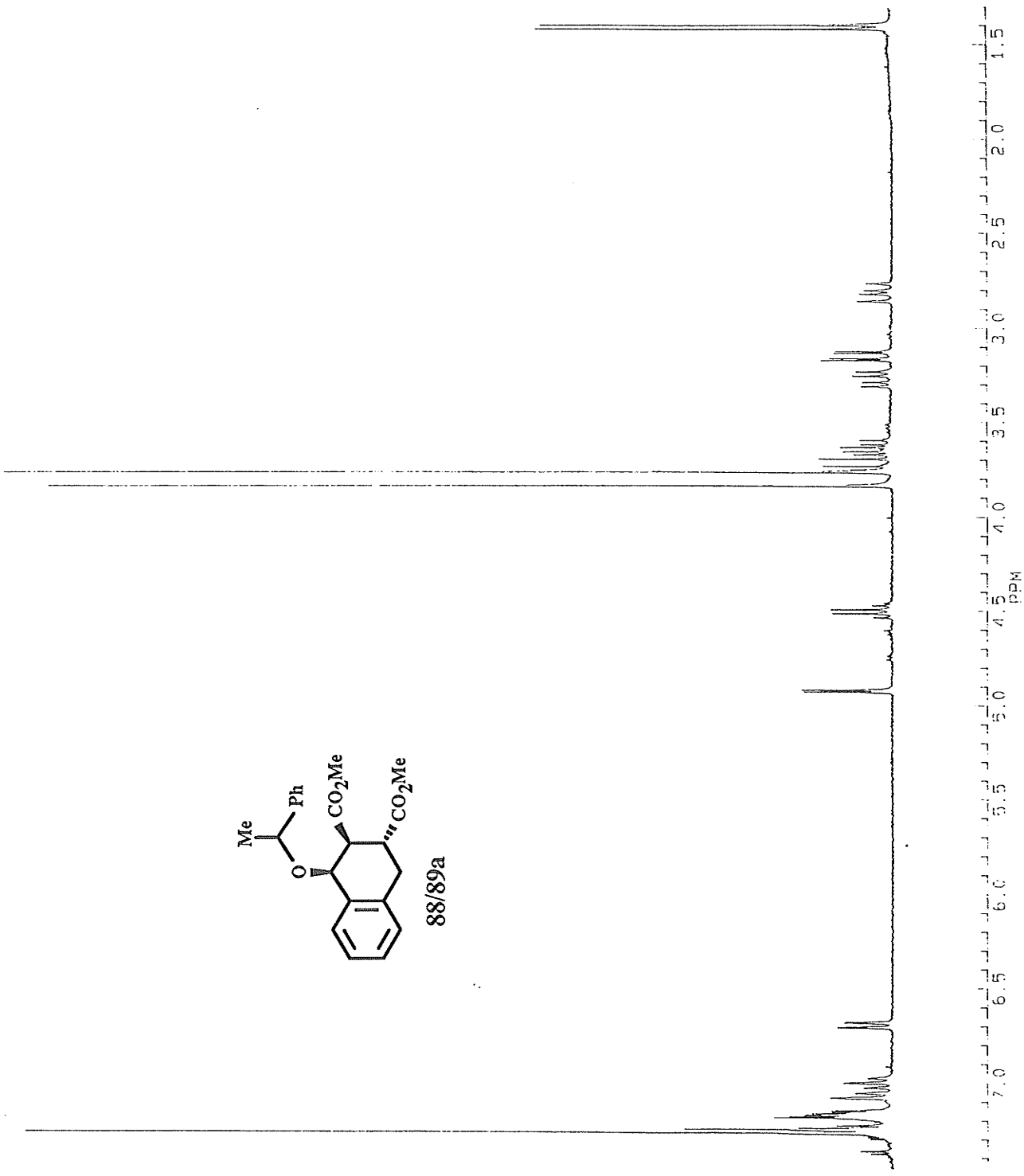
Podophyllotoxin analog **150**:

The hydroxycycloadduct **137** (533 mg, 1.1 mmol) was treated with n-BuLi according to the procedure given for product **139**. The lactone **139** (445 mg) was then hydrolysed (see experimental for **144**) and the residual hydroxy diacid **144** (287 mg) was reduced with lithium triethylborohydride ($LiBHEt_3$) (see experimental for **145**). No purification was performed for any of these first three steps. To a solution of this crude dihydroxy acid **145** (187 mg) in dry tetrahydrofuran (15 mL) was added

dicyclohexylcarbodiimide (DCC, 145 mg, 0.7 mmol) in tetrahydrofuran (1 mL). The solution was stirred at room temperature for 24 hours and worked up according to literature procedures previously reported[32,59]. Addition of water and acetic acid followed by evaporation of the solvent gave a semi-crystalline material (241 mg). Purification by trituration with methylene chloride followed by chromatography on silica gel using 25% ethyl acetate/hexane as eluant gave a white solid (92.1 mg, 30% from **137**, 16.5% overall from hydroxysulfone **60**). Recrystallization from hexane/methylene chloride afforded colourless plates [mp: 225-227°C, ref. 226-227°C for racemic material[12]]. $[\alpha]_D$= -151° (c: 0.12, $CHCl_3$). IR (CH_2Cl_2) cm^{-1}: 3320 (OH), 1777 (CO). ^{1}H-nmr ($CDCl_3$) δ: 2.18 (d, 1H, J= 7.7, OH), 2.87 (m, 2H, H-2, H-3), 4.11 (broad t, 1H, J= 9.5, H-11), 4.61 (dd, 1H, J= 6.6, 8.8, H-11'), 4.78 (d, 1H, J= 4.3, H-4), 4.89 (broad t, 1H, J= 8.5, H-1), 7.05-7.39 (m, 8H, aromatics), 7.70 (d, 1H, J= 7.8, H-8). ^{1}H-nmr spectrum is shown in Appendix 1. Mass Spectrum, *m/e* (rel %): 280(51), 262(35), 218(45), 217(54), 205(20), 203(27), 202(26), 195(18), 185(20), 178(25), 165(29), 128(17), 119(52), 117(100), 105(19), 98(21), exact mass calcd. for $C_{18}H_{16}O_3$: 280.1099, found: 280.1104.

APPENDIX 1

^{1}H-nmr Spectra


Me
Ph
O
CO2Me
CO2Me
88/89a
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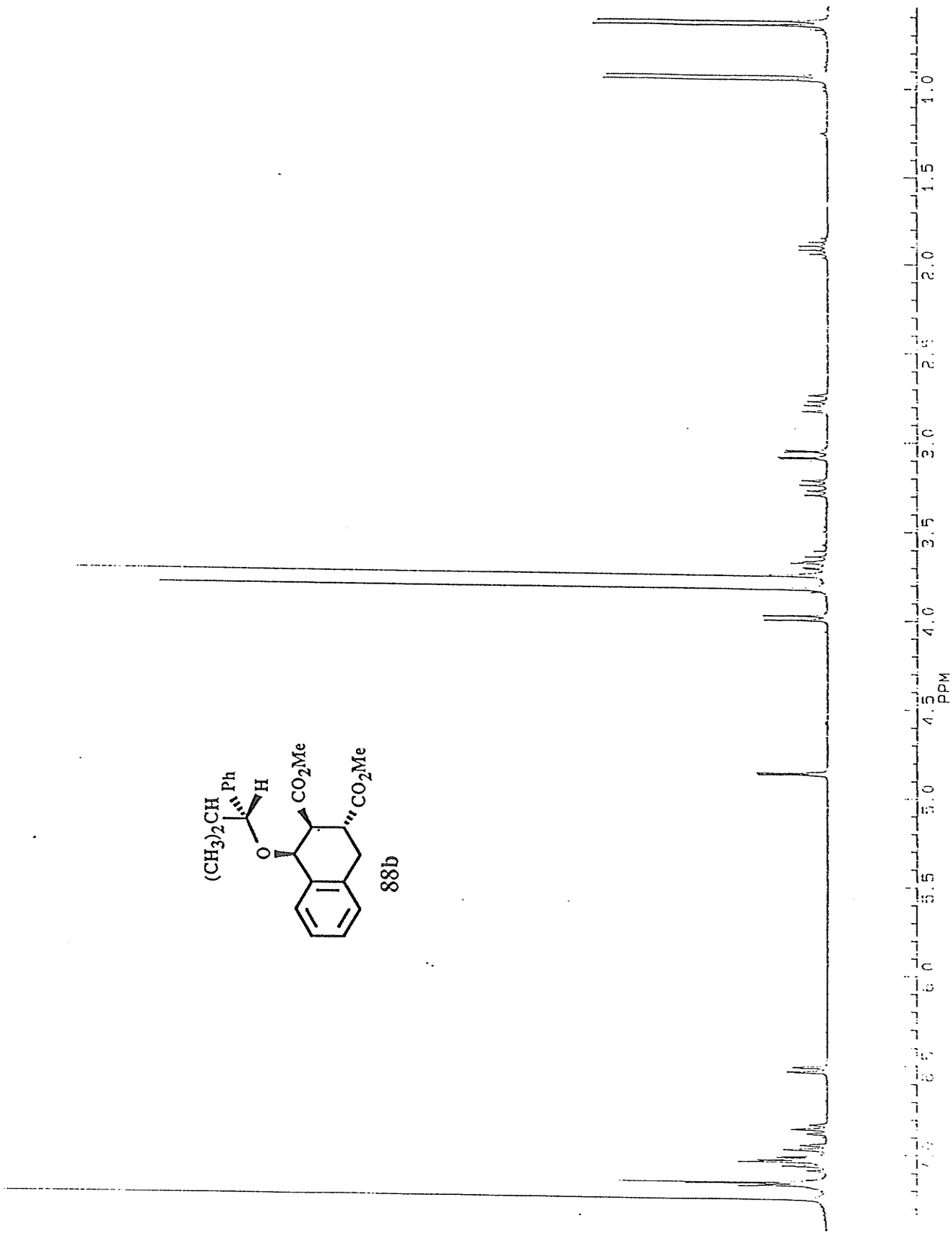
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
PPM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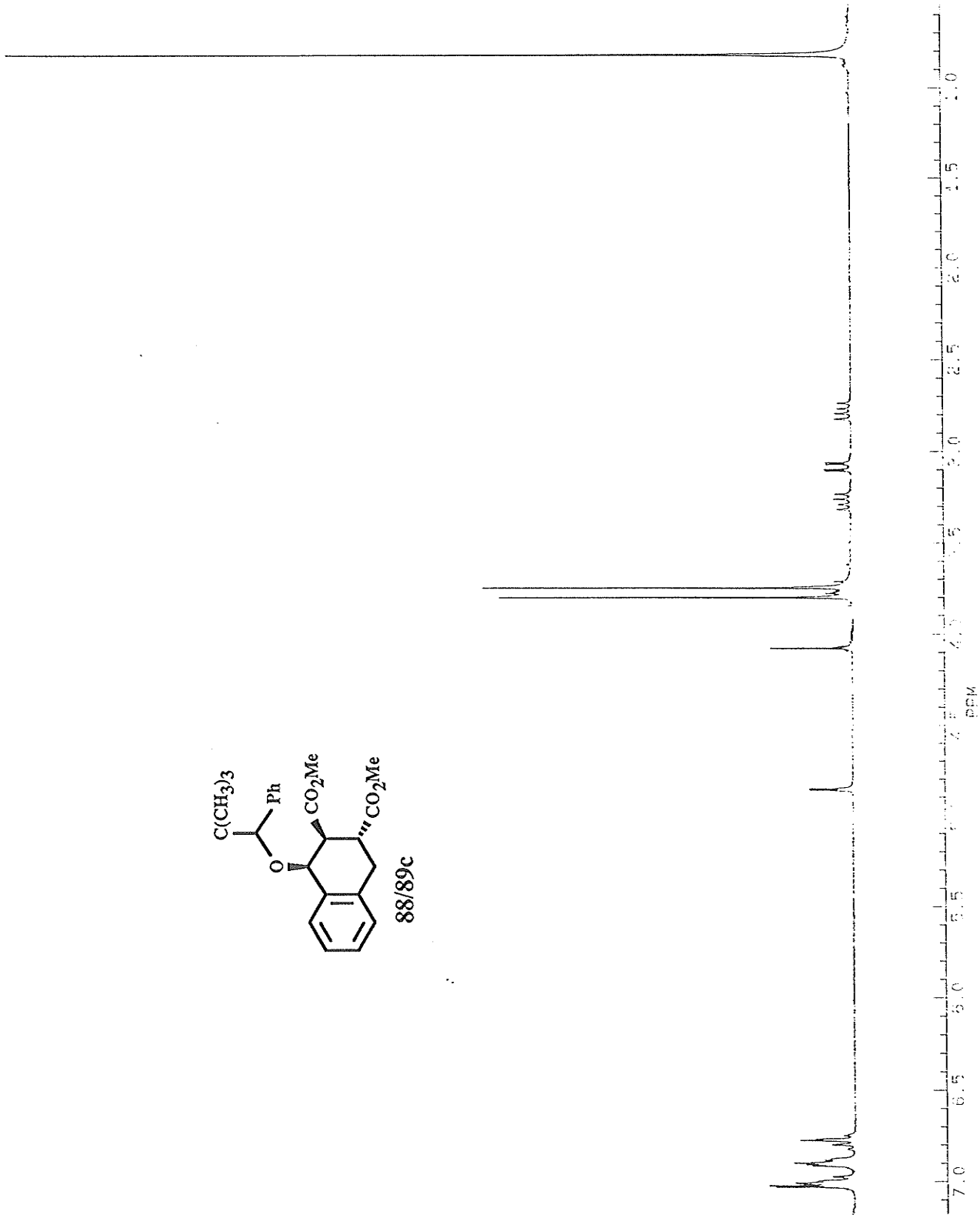
H
O
CO2Me
CO2Me
88b
PPM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Ph
O
CO2Me
CO2Me
88/89c
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6.5
6.0
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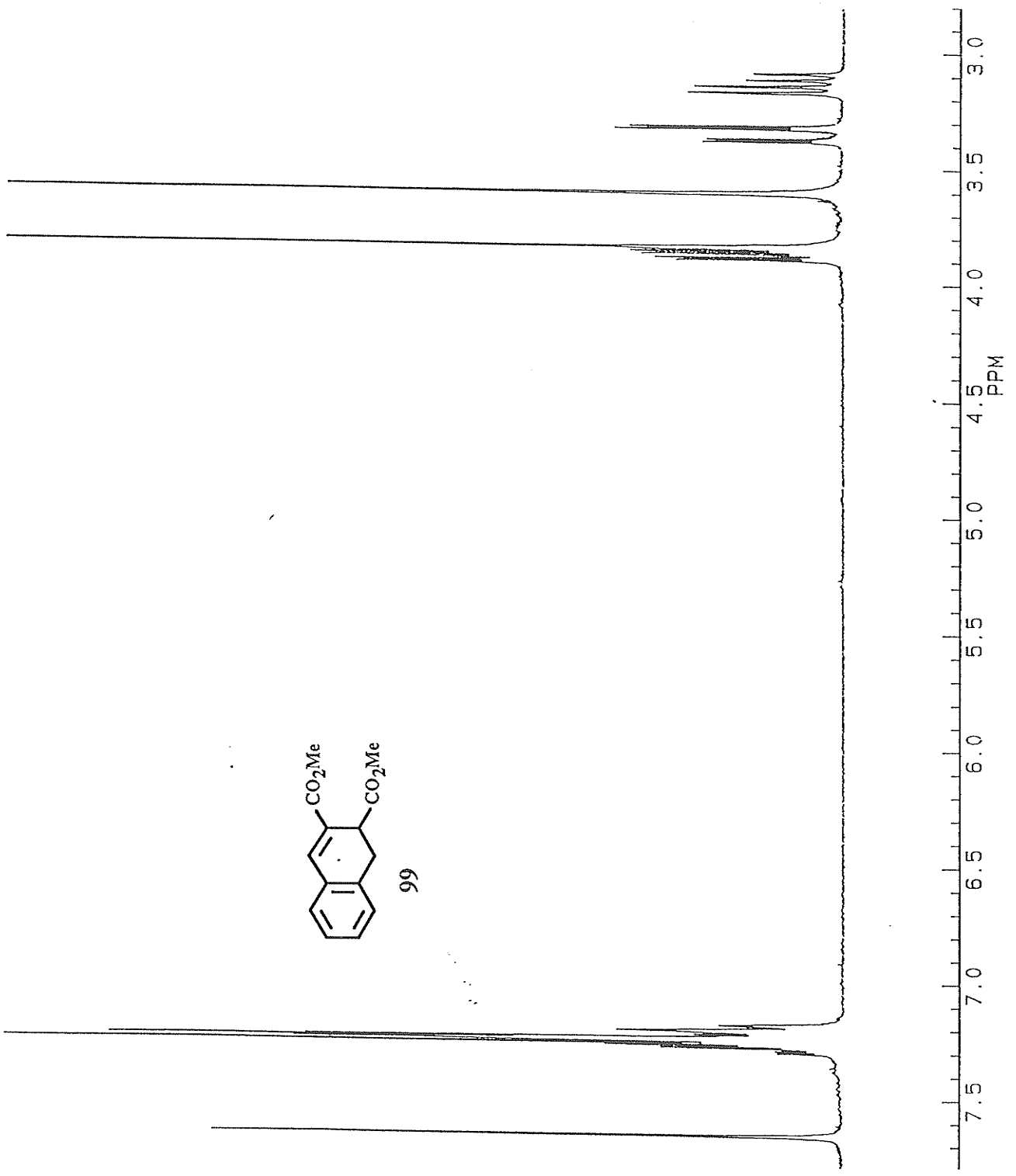
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM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CO2Me
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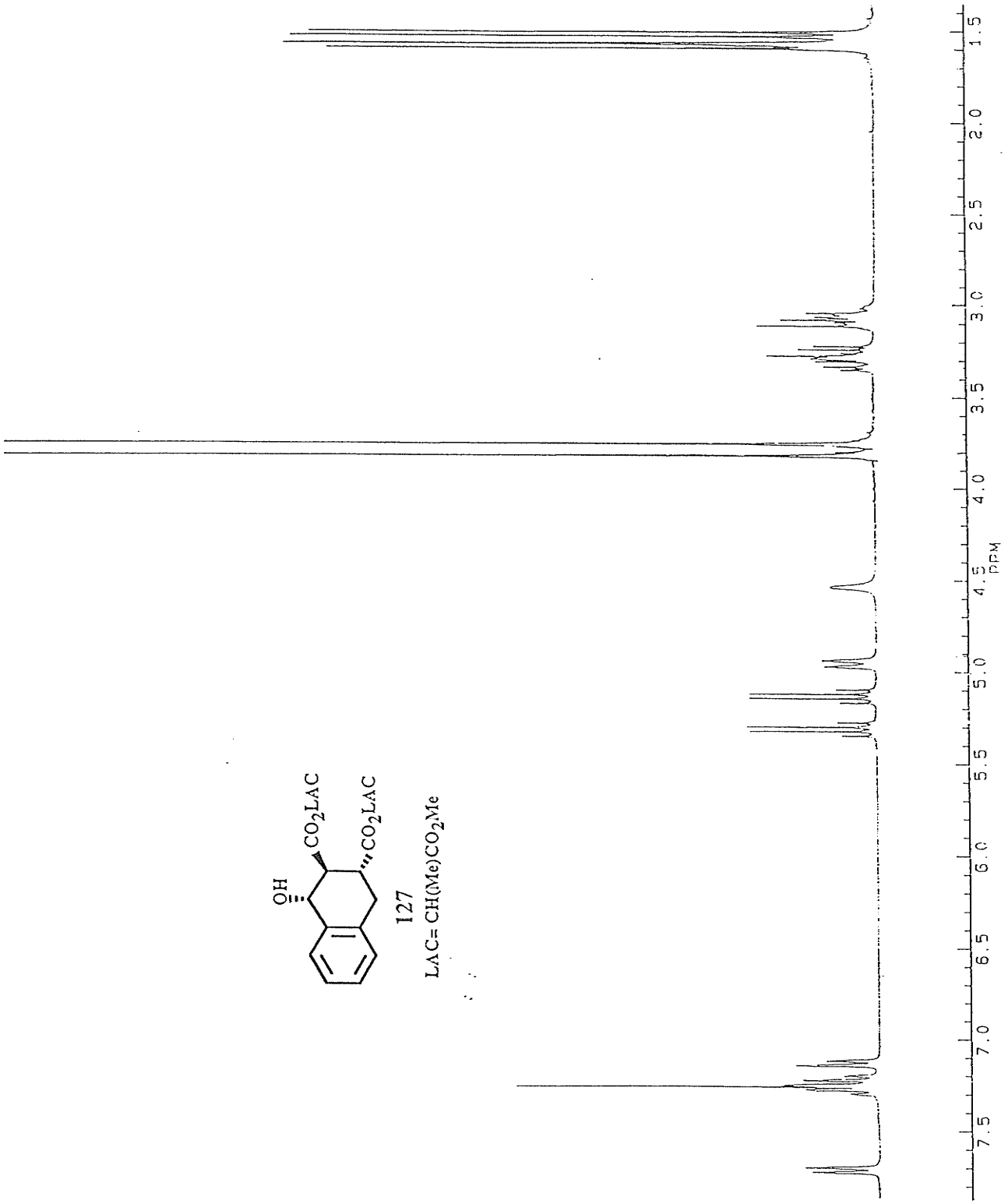
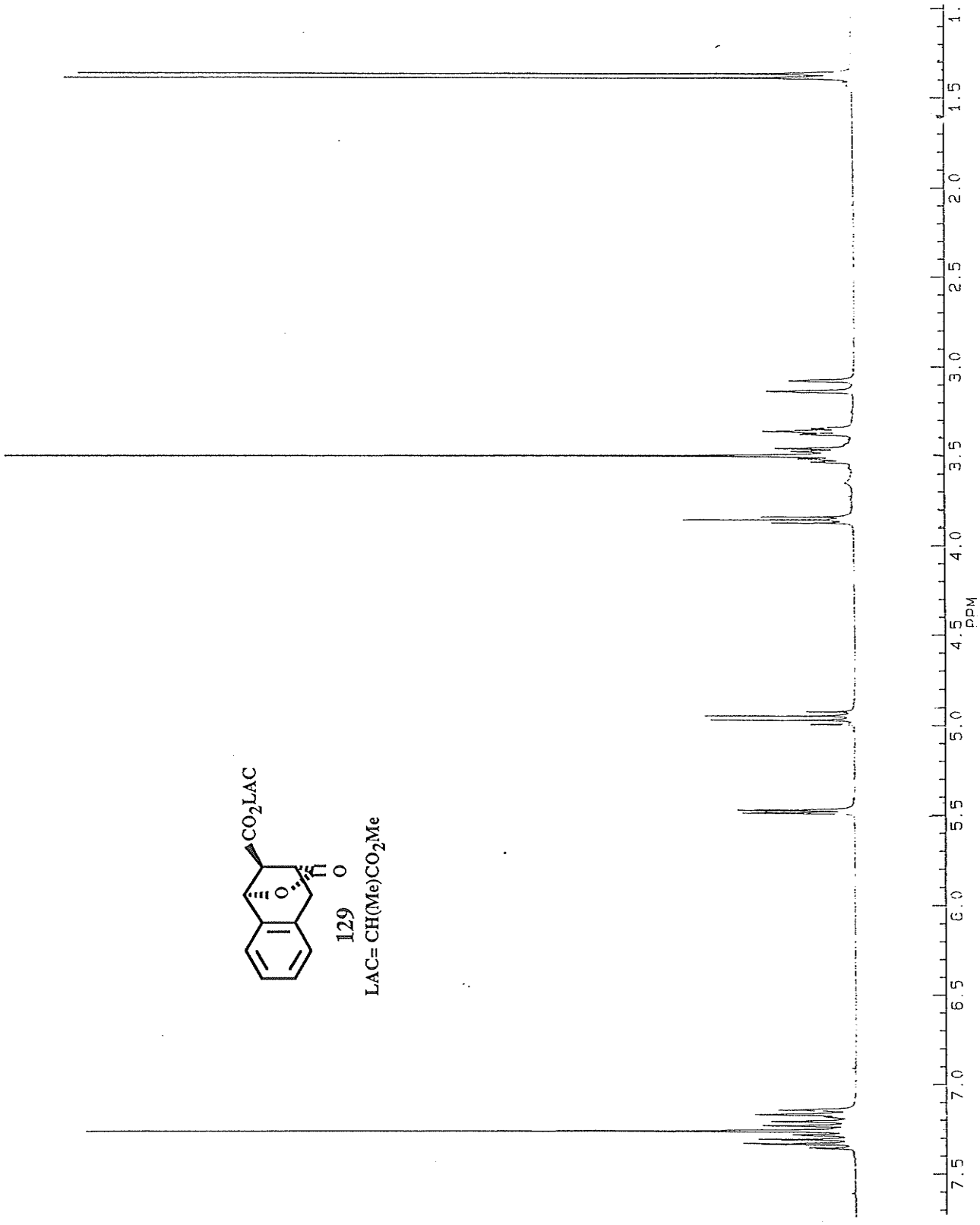
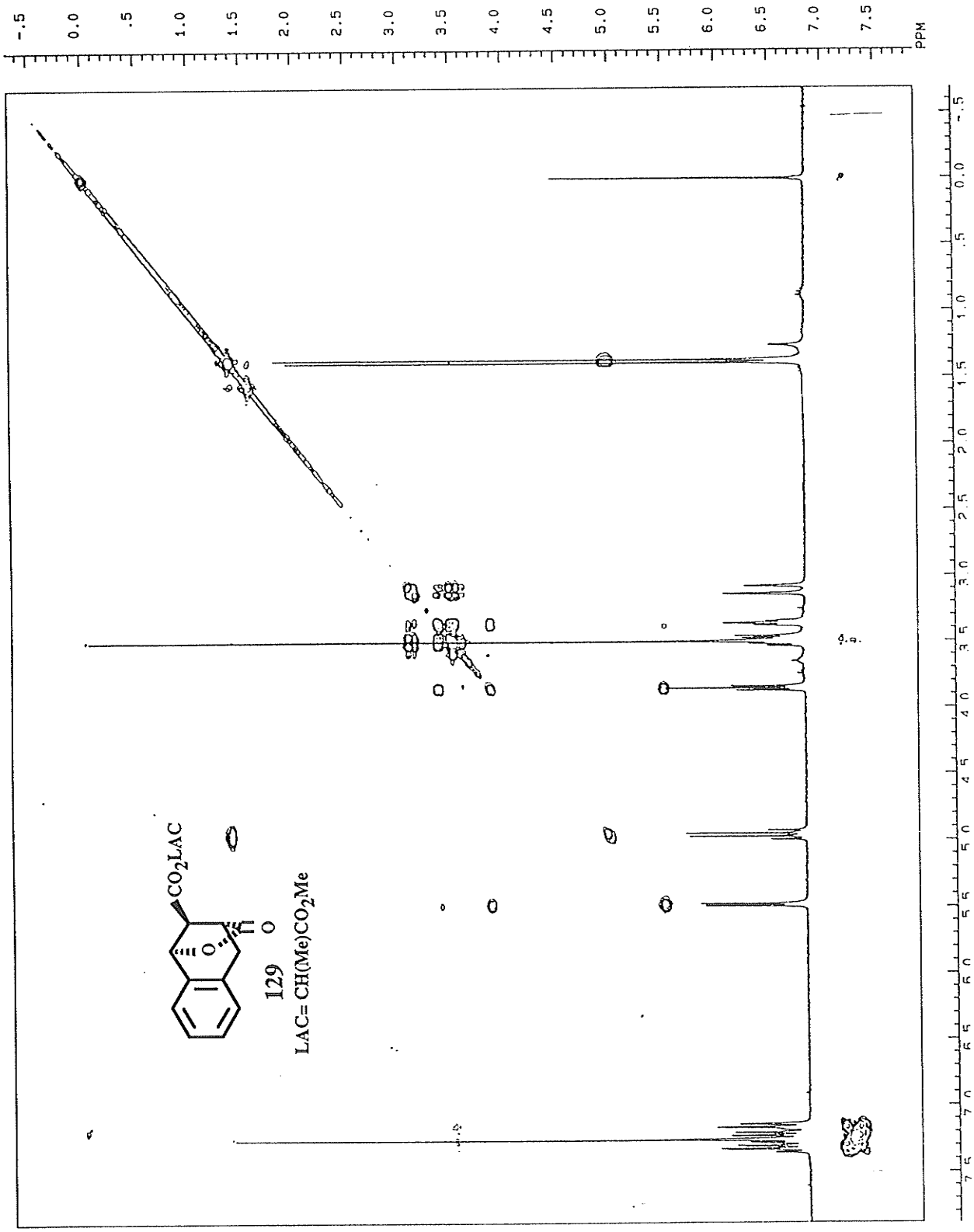
4.0
3.5
3.0
PPM



127

LAC= CH(Me)CO_2Me


CO2LAC
O
O
129
LAC= CH(Me)CO2Me
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.
PPM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.5
1.0
1.5
2.0
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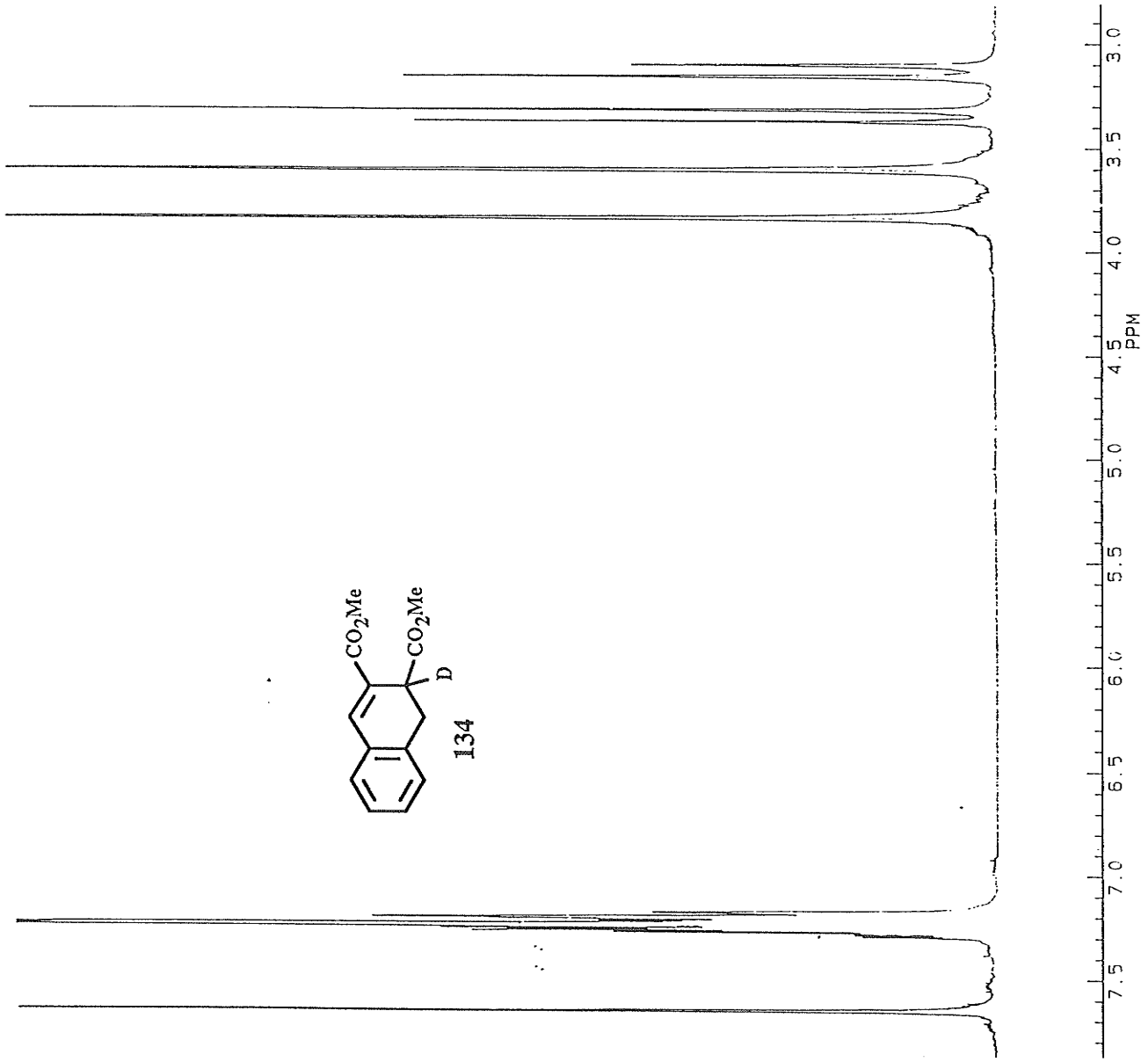
6.0
6.5
7.0
7.5
PPM
CO2LAC
O
129
LAC= CH(Me)CO2Me


CO2Me
CO2Me
D
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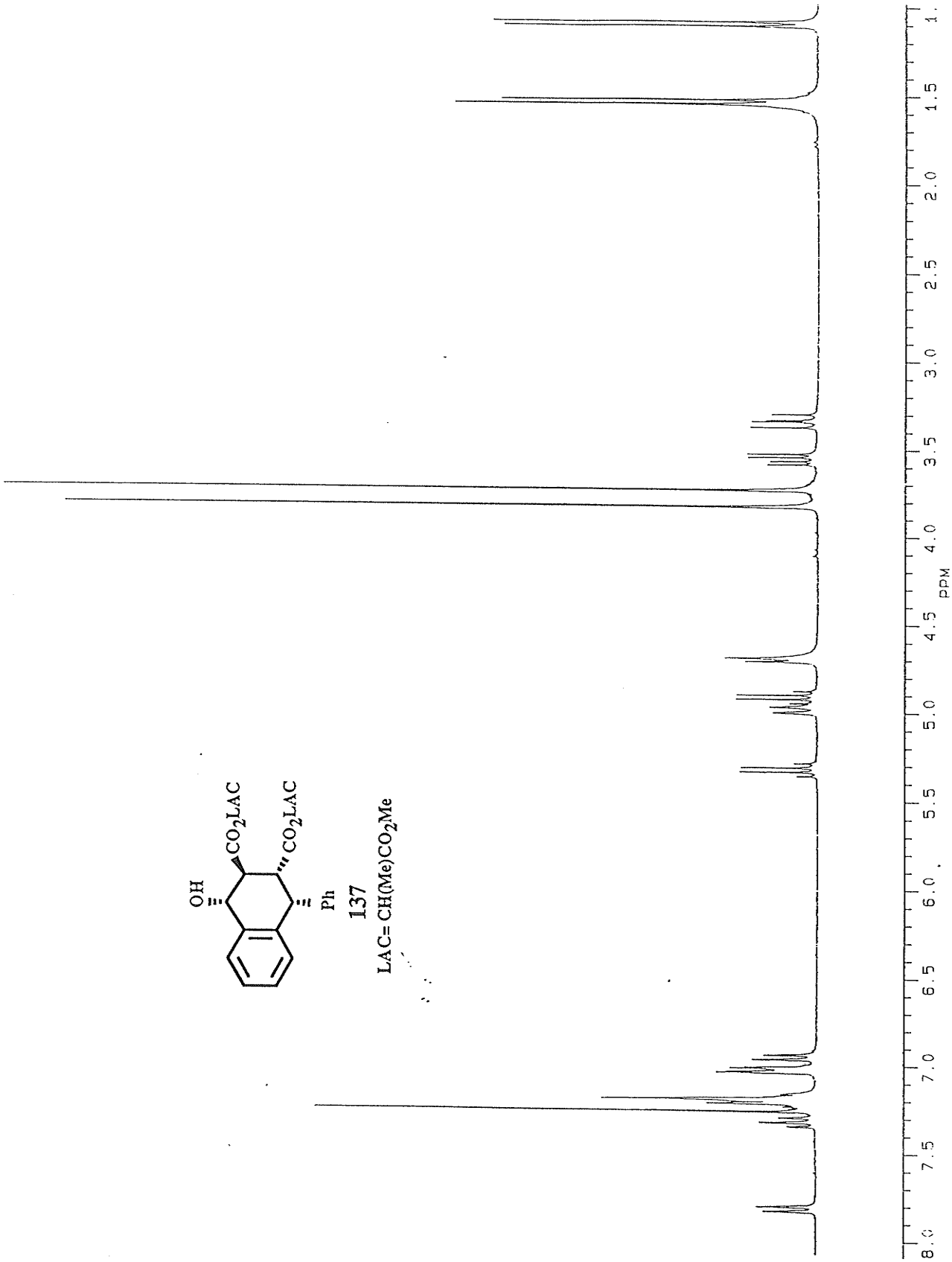
4.5
4.0
3.5
3.0
PPM


OH
CO2LAC
CO2LAC
Ph
137
LAC=CH(Me)CO2Me
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7.5
7.0
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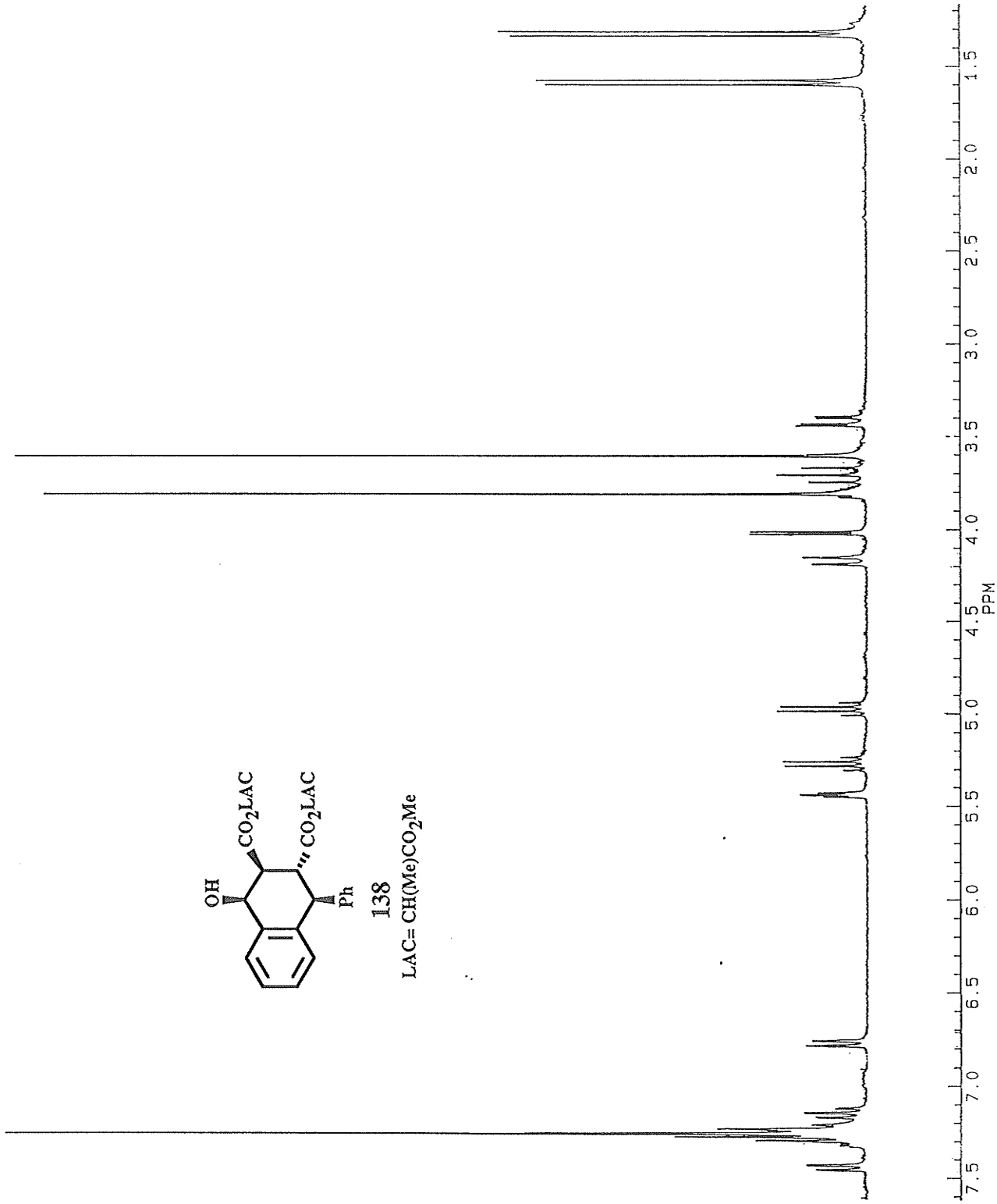
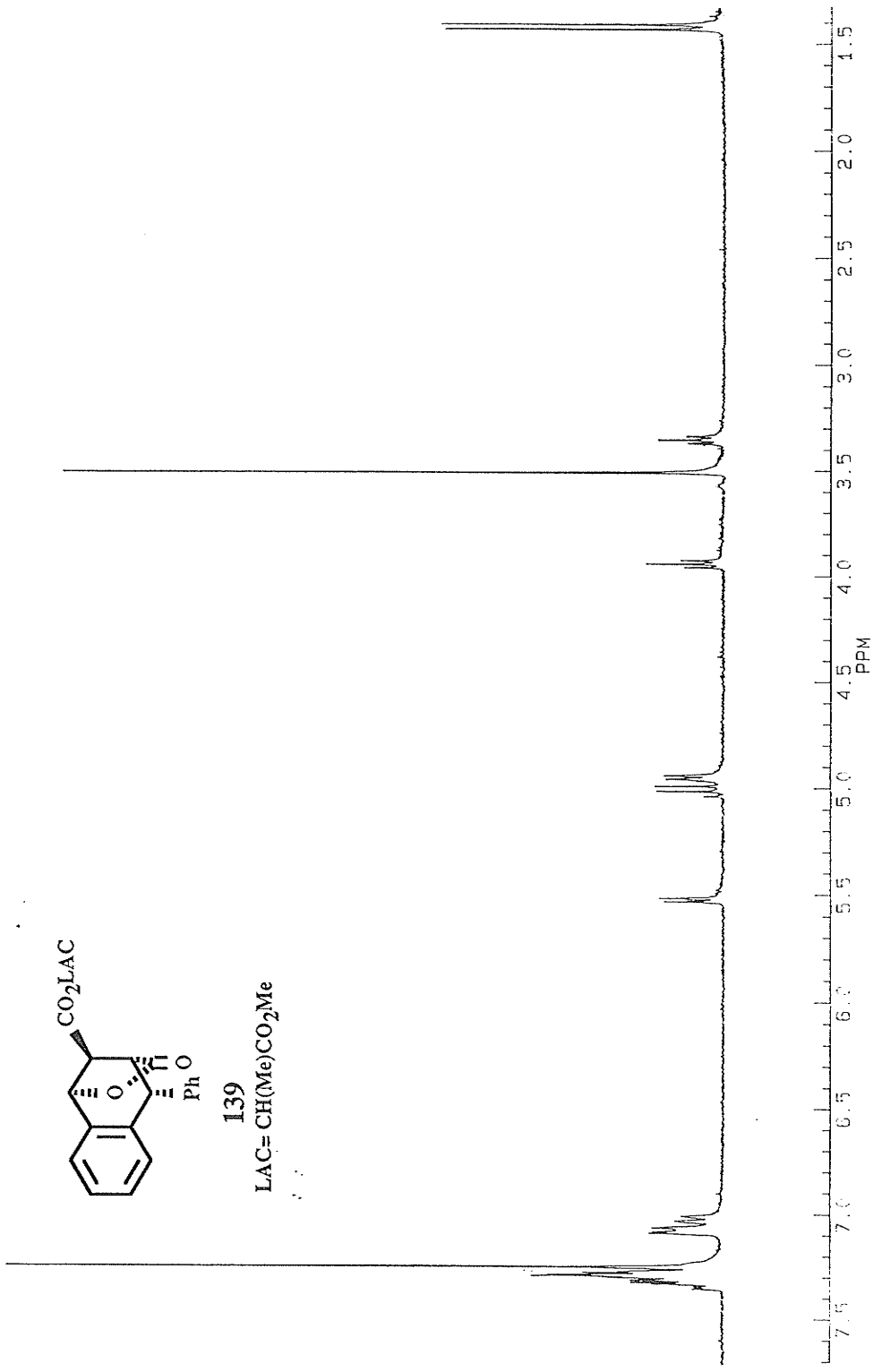
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.
PPM



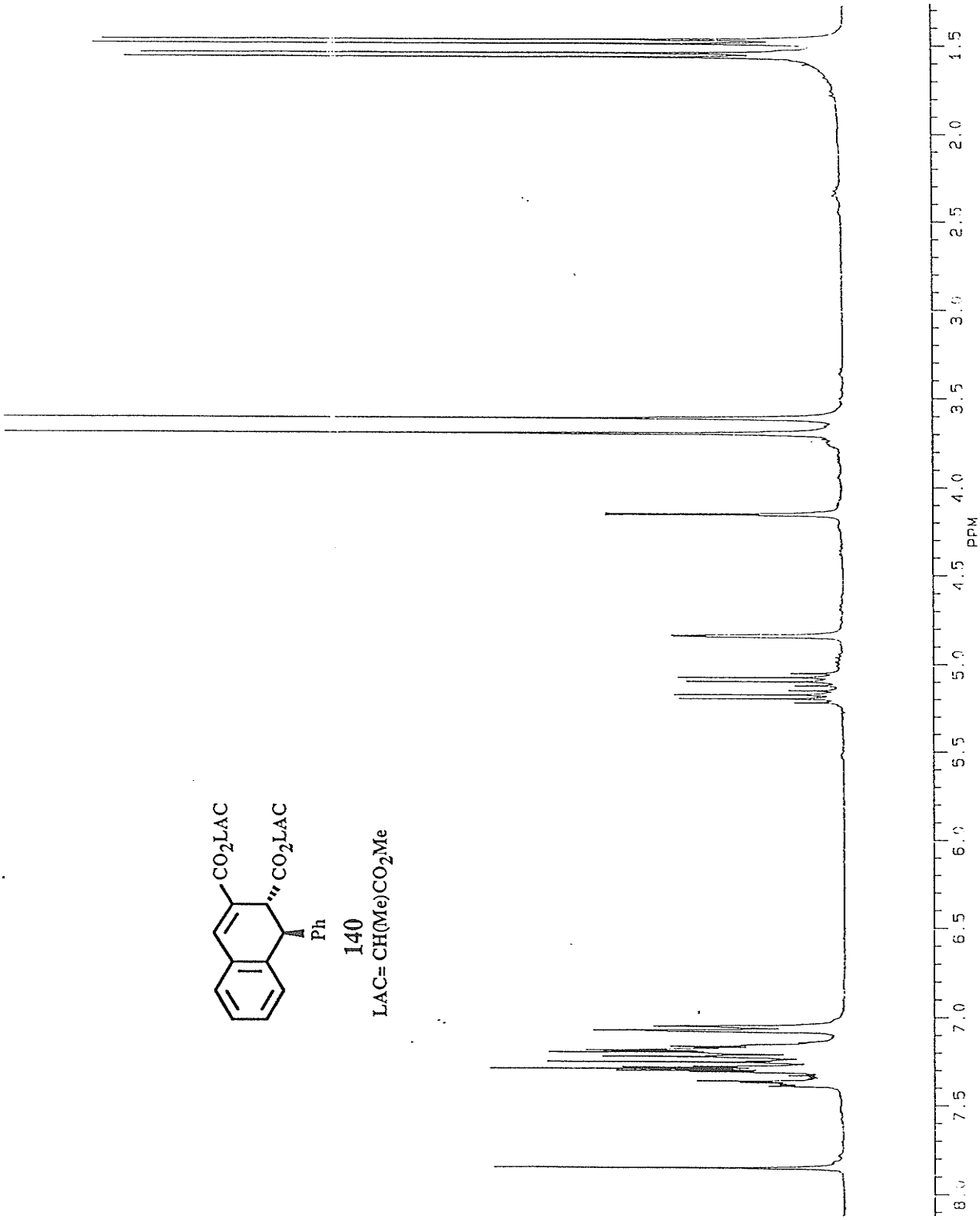
138

LAC= $CH(Me)CO_2Me$



139

LAC= CH(Me)CO_2Me


CO2LAC
CO2LAC
Ph
140
LAC= CH(Me)CO2Me
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7.5
7.0
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5.5
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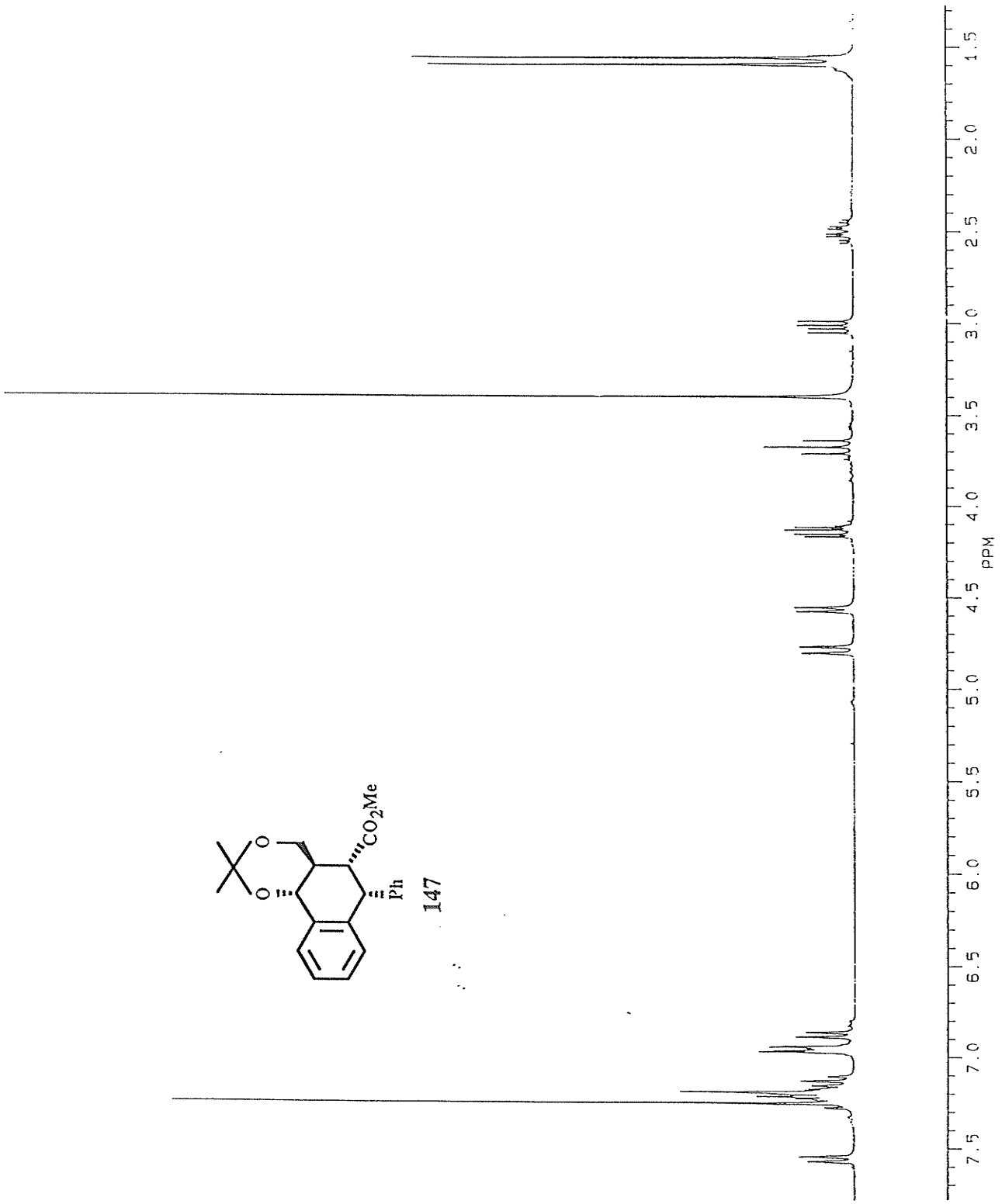
3.5
3.0
2.5
2.0
1.5
PPM


CO2Me
Ph
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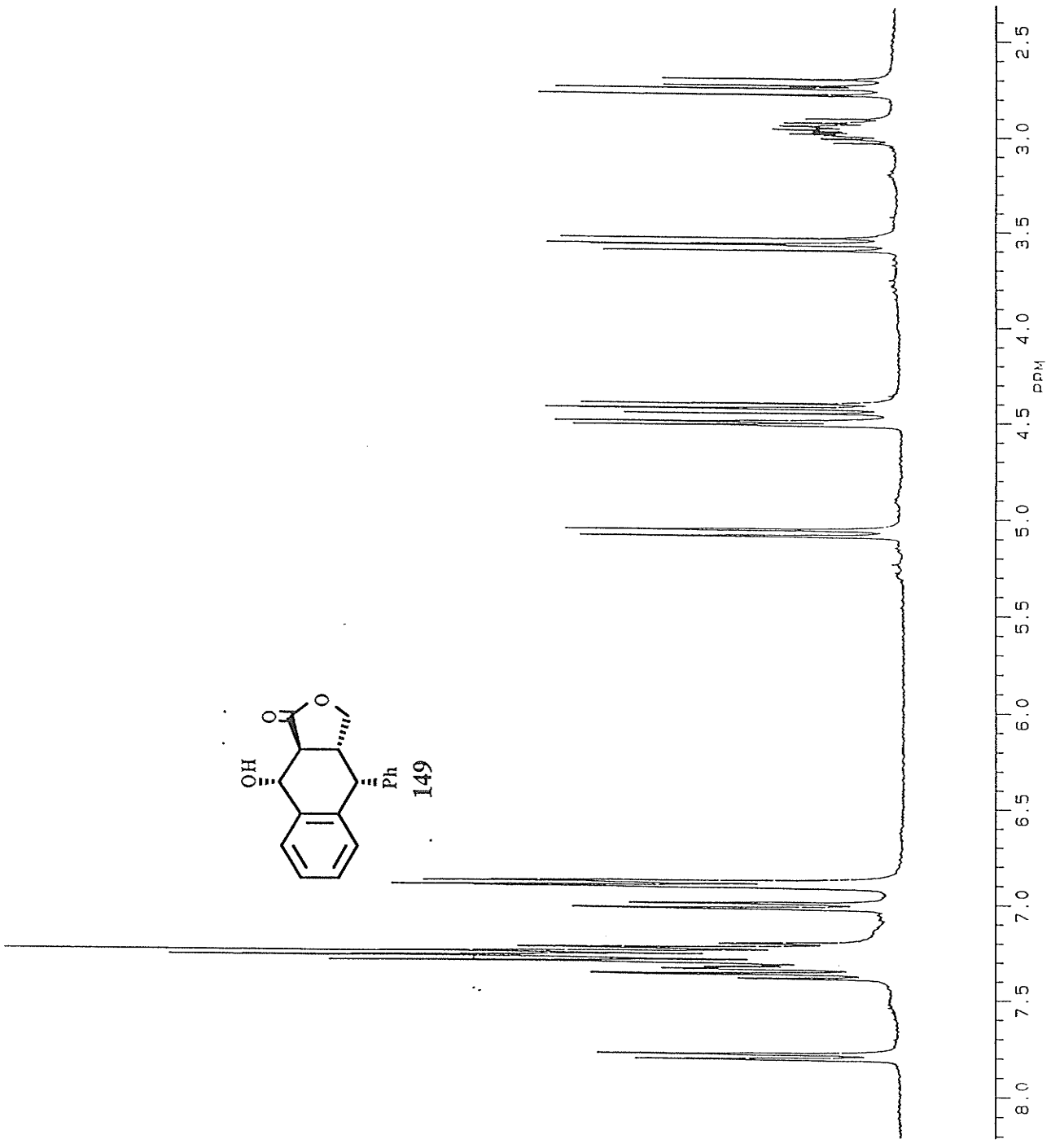
3.0
2.5
2.0
1.5
PPM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Ph
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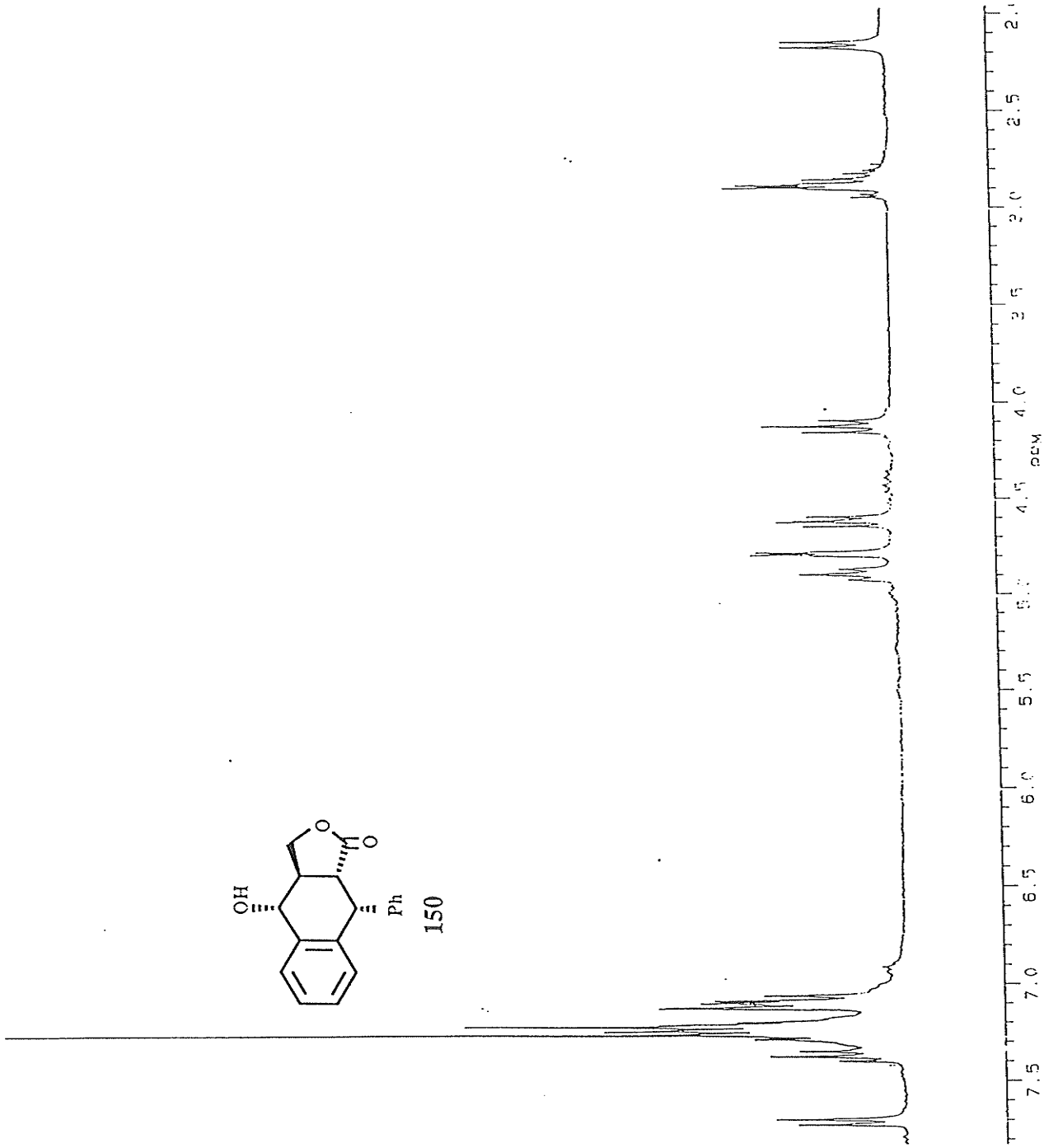
3.0
2.5
PPM


OH
O
O
Ph
150
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4.0
2.5

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