PREPARATION AND REACTIONS OF ORTHOQUINODIMETHANES

by

MIAN MOHAMMAD ALAUDDIN

a thesis

submitted to the Faculty of Graduate studies

of the University of Manitoba in partial fulfilment

of the requirments for the degree of

Doctor of Philosophy

The University of Manitoba,

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TO MY PARENTS

ACKNOWLEDGEMENTS

It is a real pleasure to take this oportunity to express my thanks to Dr. J. L. Charlton for his help and guidance during the course of this work.

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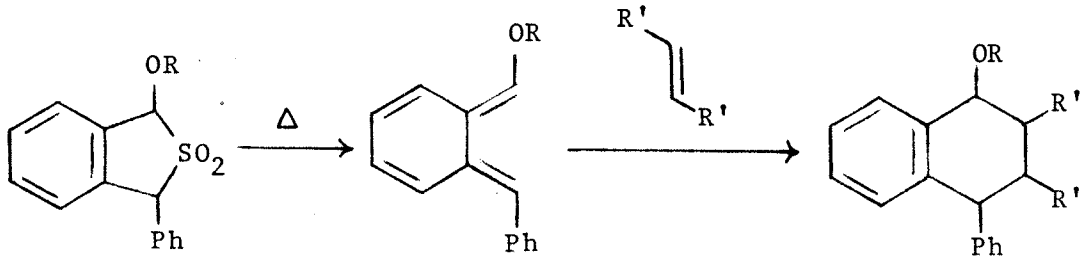
Last but not least, I wish to express my deep sense of gratitude to my wife, Shefali and our children whose sacrifices and support permitted me to undertake this work.

ABSTRACT

There has been, and continues to be, an interest in the use of o-quinodimethanes as intermediates in organic synthesis, especially natural product synthesis, such as steroids, terpenoids, alkaloids, tetracyclines and lignans. A newly discovered, simple route to α-oxy-α'-phenyl-o-quinodimethanes made possible a study of the reactions of these intermediates with various dienophiles to establish routes to a variety of 1-aryl-4-oxy-tetralin systems.



In order to study the electronic and steric factors involved in these cycloaddition reactions, E,E- and E,Z-α-acetoxy-α'-phenyl-o-quinodimethanes **49**, **50**, E,E-α-methoxy-α'-phenyl-o-quinodimethane **51** as well as E,E- and E,Z-α-hydroxy-α'-phenyl-o-quinodimethanes **52** and **53** have been investigated. Preparation and reactions of these o-quinodimethanes with a variety of dienophiles such as dimethyl fumarate, dimethyl maleate, maleic anhydride and methyl crotonate are described. The addition of the dienophiles to the o-quinodimethanes gave

predominantly 1,2-*trans* stereochemistry except the addition of maleic anhydride which gave all *cis* cycloadduct.

An asymmetric synthesis of the lignan (+)-isolariciresinol dimethyl ether **48** in 9 steps and 13% yield (83% optical purity) from veratraldehyde is described. A racemic synthesis was also carried out *via* the methoxy sulfone **84** in 33% yield.

Studies towards a route to an epipodophyllotoxin analogue and a podophyllotoxin analogue, and an attempt to the asymmetric synthesis of deoxypodophyllotoxin are also described.

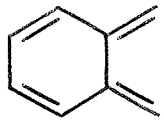
CONTENTS

CHAPTER 1

INTRODUCTION

1.1 Definition of o-quinodimethanes

Compounds having the general structure 1 are known as o-quinodimethanes or ortho-xylylenes(1,2).



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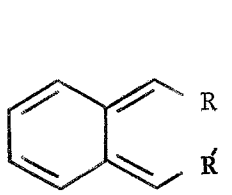
α-Hydroxy-o-quinodimethanes, produced by photoenolization are often referred to simply as dienols(3,4). The name o-quinodimethane will be used in this thesis in preference to ortho-xylylene or dienol.

The o-quinodimethane intermediate 1 with α and α'-substituents has four possible geometric isomers. They are α-cis-α'-cis or Z,Z **2**, α-cis-α'-trans or Z,E **3**, α-trans-α'-trans or E,E **4** and α-trans-α'-cis or E,Z **5**.



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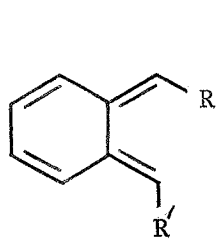

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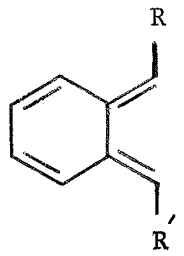

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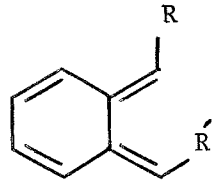

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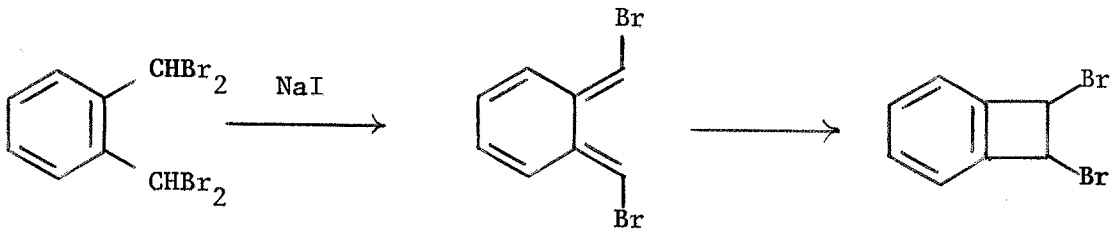
Out of these four isomers, structure **2** i.e. Z,Z is sterically the least favorable and **4** i.e. E,E is the most favorable. The other two isomers **3** and **5** are moderately hindered, depending on the size of the substituents.

1.2 Discovery and characterization of o-quinodimethanes

The intermediate α,α'-dibromo-o-quinodimethane **6** was first postulated by Cava et al(5) in 1957 while repeating an experiment of Finkelstein in which he treated α,α,α',α'-tetrabromo-o-xylene with sodium iodide(6).



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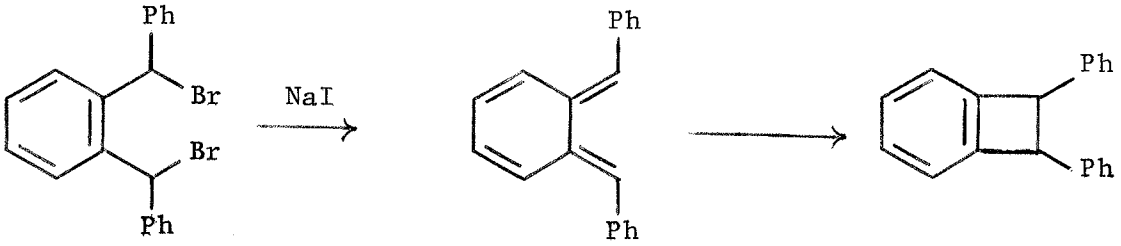
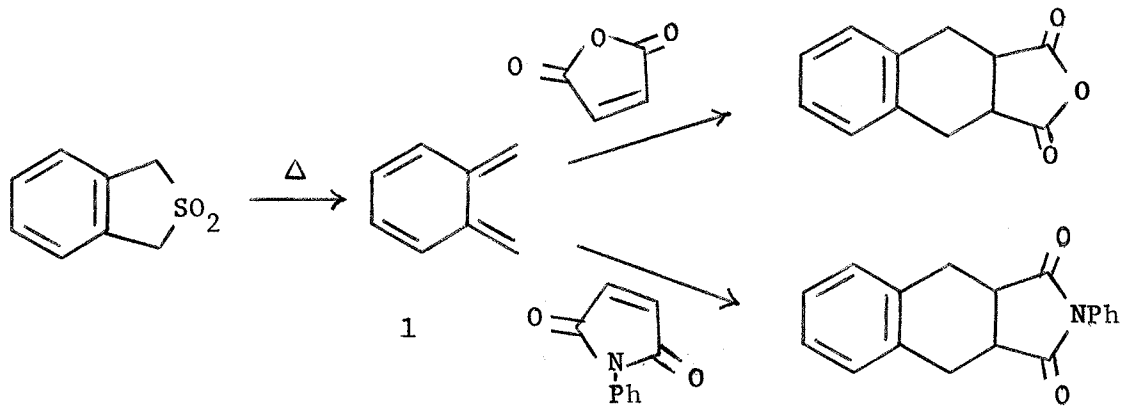
In 1958 Jensen and Coleman also proposed the generation of a disubstituted o-quinodimethane as an intermediate in the preparation of 1,2-diphenyl benzocyclobutene(7).



Later, in 1959, Cava et al generated the o-quinodimethane **1**, by thermal decomposition of 1,3-dihydroisothianaphthene-2,2-dioxide, and trapped it with typical dienophiles in Diels-Alder cycloaddition reactions(8).



Direct observation and characterization of the highly reactive o-quinodimethane **1** was first reported by UV spectroscopy at -196°C in a rigid glass matrix in 1973(9). In other studies, identification of o-quinodimethanes has relied on a combination of spectral and chemical tests(1,8-13). These included absorption spectra, deuterium exchange and trapping with dienophiles. A recent study of o-quinodimethane **1** in an argon matrix (8-30°K) permitted the first measurement of its IR and Raman spectra and provided improved resolution in UV fluorescence and fluorescence excitation spectra(14,15).

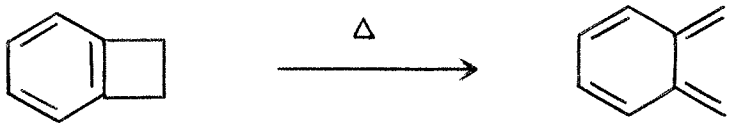
1.3 Methods of generation of o-quinodimethanes

After the discovery and characterization of variously substituted and unsubstituted o-quinodimethanes, it was realised that o-quinodimethanes

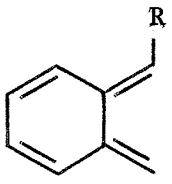
could have a great potential in organic synthesis when employed as Diels-Alder dienes. New ways of generating them were quickly developed which are summarised below.

1.3a Thermolysis of benzocyclobutenes

The most frequent way of generating o-quinodimethanes is the thermal ring opening of benzocyclobutene(16-21).



The transformation proceeds <u>via</u> a thermally allowed con-rotatory electrocyclic ring opening(2,16). Benzocyclobutene having a substituent on the 4-membered ring opens outward to produce the sterically less hindered (E)-o-quinodimethane **7** in preference to the (Z) form **8** (2) and opens at a lower temperature than does unsubstituted benzocyclobutene (alkoxy substituted 110°C, alkyl substituted 140°C, benzocyclobutene, 200°C)(2,22).



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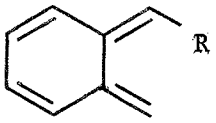

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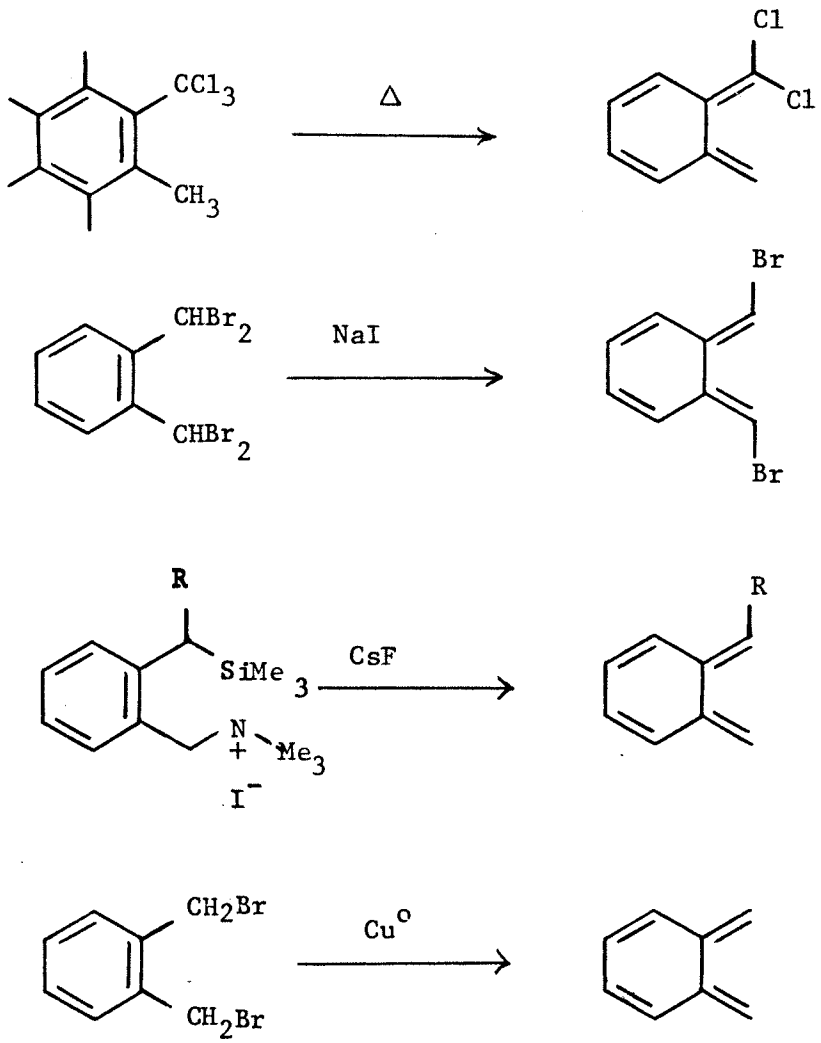
The chemistry and synthesis of benzocyclobutenes have been reviewed(16,23-25) and therefore will not be discussed in this thesis.

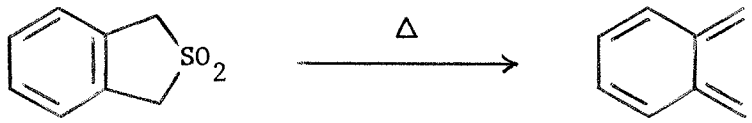
1.3b 1,4-Elimination process

The 1,4-elimination process to generate o-quinodimethanes may involve thermal elimination(26-29), reductive elimination(2,6,30-34), fluoride ion catalysed elimination(30,35,36) or Cu(0) complex catalysed elimination(31). One example of each of these methods is given below.



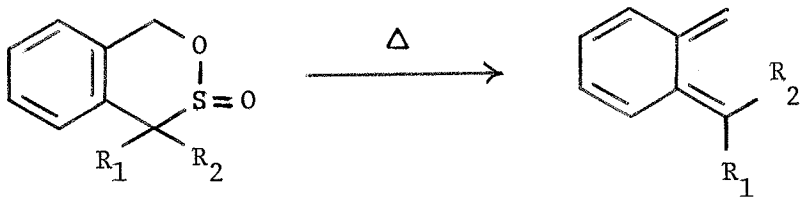
1.3c Thermal elimination of sulfur dioxide from sulfones and sultines

The chelotropic elimination of sulfur dioxide from a benzodihydrothiophene-2,2-dioxide goes back to 1959, when Cava generated an o-quinodimethane and trapped it with dienophiles(8,37).



Oppolzer reviewed previous literature on this reaction(38), which includes the work of Nicolaou et al(39). Charlton et al also generated α-substituted o-quinodimethanes by this method(40).

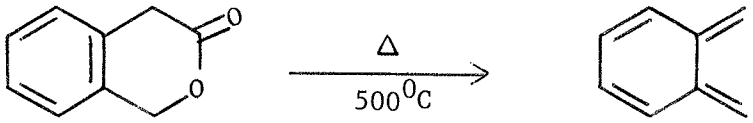
T. Durst et al were the first to generate o-quinodimethanes by thermal elimination of sulfur dioxide from a sultine(41).

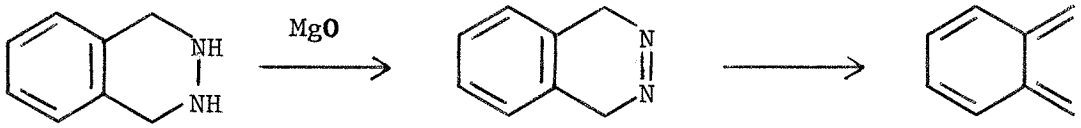


R_1, R_2 = H, CH_3 , Ph etc.

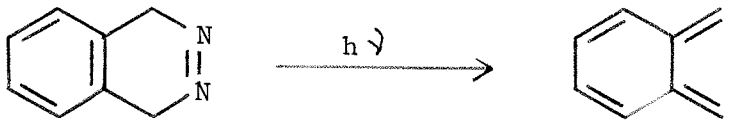
1.3d Diels-Alder cycloreversion

The Diels-Alder cycloreversion process involves loss of carbon dioxide from an isochromanone(42,43) or nitrogen from 1,4-dihydrophthalazine(10,44) to generate o-quinodimethane.



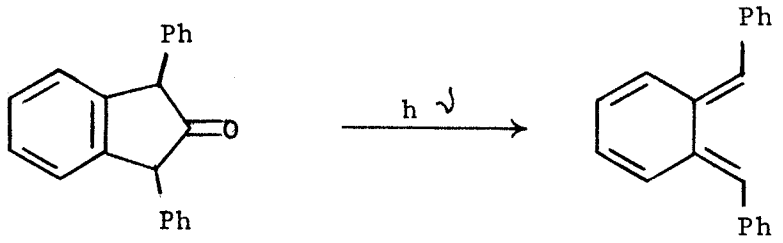


The loss of nitrogen can also be accomplished photochemically(9).



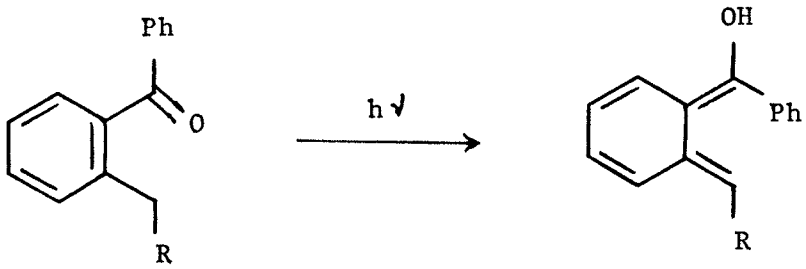
1.3e Photochemical expulsion of carbon monoxide

α,α'-Disubstituted o-quinodimethanes can be generated photochemically from substituted 2-indanones by the loss of carbon monoxide(45,46).



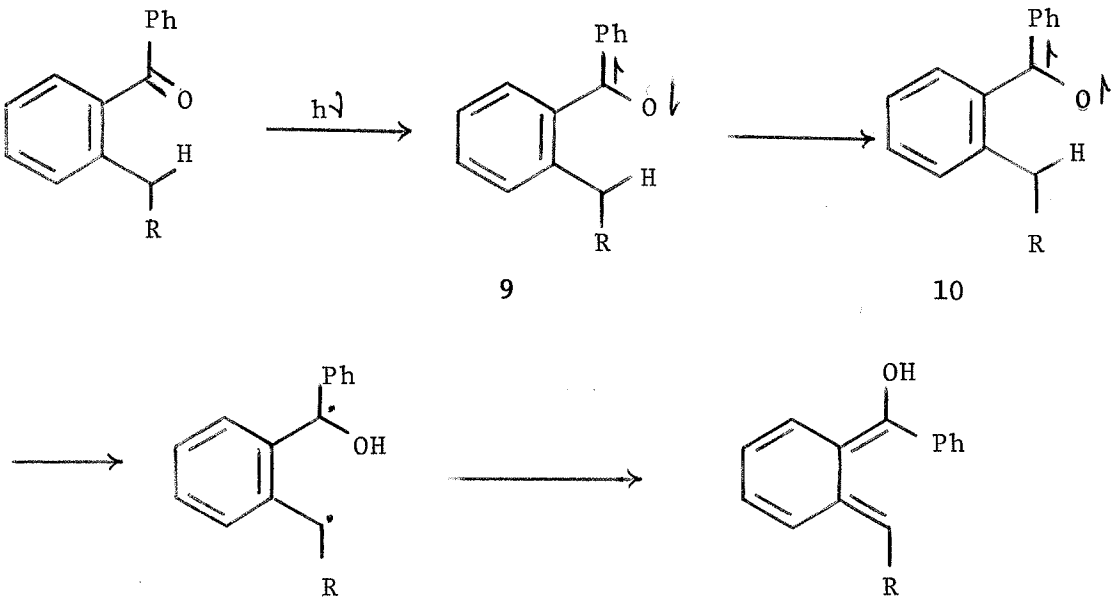
1.3f Photoenolisation

A route to E-α-hydroxy-o-quinodimethane relied on irradiation of an ortho-tolyl-carbonyl compound to induce a [1,5] hydrogen shift(4,47). This photoenolization process was first described by Ullman et al(48) during a study of photochromism effects described earlier by Collie (49). Yang and Rivas had earlier demonstrated the existence of ground state dienol species i.e. α-hydroxy-o-quinodimethanes by reacting them with a variety of trapping agents including Diels-Alder dienophiles(50). Thus irradiation of 2-methyl benzophenone generated α-hydroxy-o-quinodimethane(51).



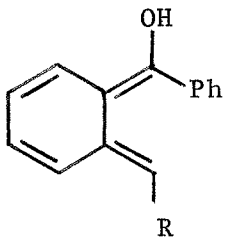
R = H

The most commonly accepted mechanism for the photochemical generation of o-quinodimethanes has been proposed by Sammes as follows(4).



9 10 11 12

The initial process requires excitation of the carbonyl group. Direct irradiation produces an excited singlet state and for simple 2-alkylbenzophenones this state **9** is generally of $n\pi^*$ character which decays very quickly to a triplet $n\pi^*$state **10** by intersystem crossing. This triplet species is mainly responsible for the hydrogen abstraction step(4,52). After abstracting hydrogen, the triplet state of dienol **11** is formed. This species, which can be viewed as a triplet 1,4-diradical, now can return to the singlet ground state by intersystem crossing. Depending on the orientation of the hydoxyl group at the time of intersystem crossing, the diradical will give either the E-o-quinodimethane **12** or its corresponding Z-isomer **13.**



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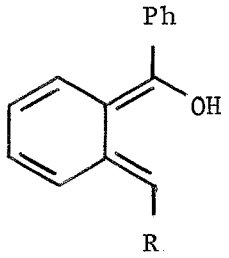

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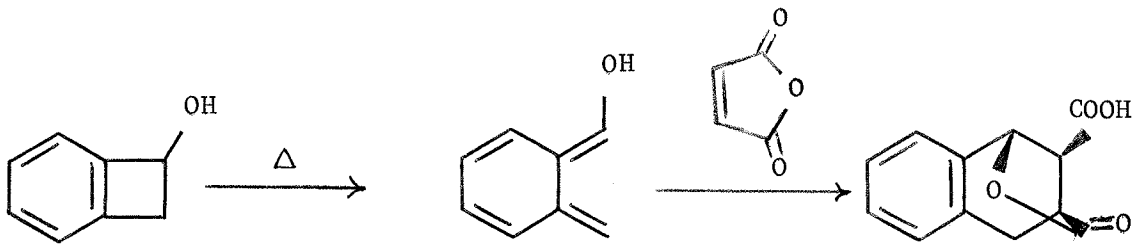
It is thought that the Z-isomer returns rapidly to the starting carbonyl compound by a [1,5] hydrogen shift, while the E-isomer is relatively long lived.

The photochemical formation of the E-dienol (o-quinodimethane) **14** was confirmed by heating 1,2-dihydrobenzocyclobutene-1-ol, which underwent an electrocyclic conrotatory ring opening(53).



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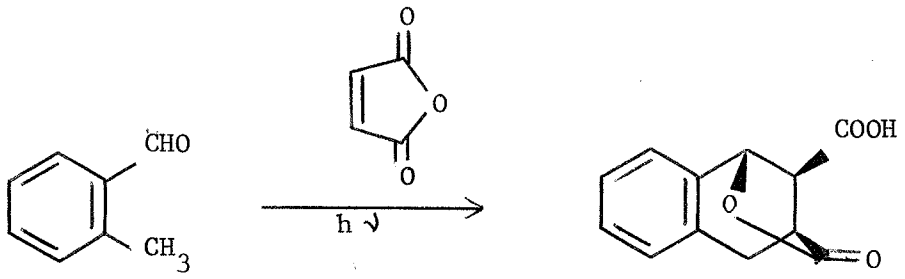
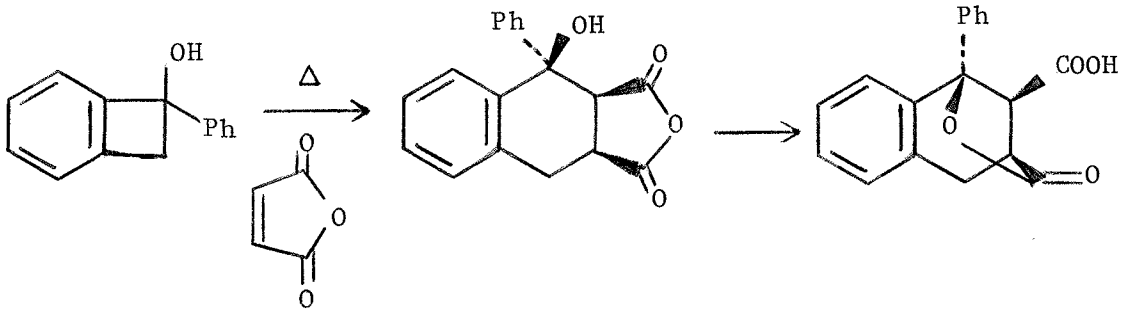
The thermally produced E-o-quinodimethane was trapped with a variety of dienophiles including maleic anhydride. The cycloadduct with maleic anhydride was identical to that obtained in the photochemical reaction of 2-methylbenzaldehyde with maleic anhydride.

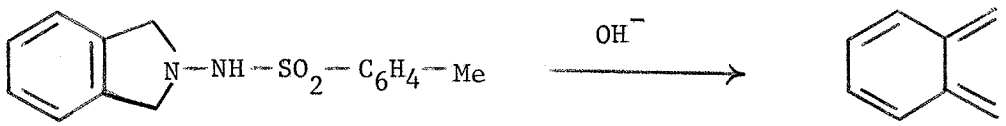


In a following paper Sammes et al demonstrated that for disubstituted benzocyclobutenes containing one oxygen substituent, the oxygen substituent always adopted the E-configuration in the o-quinodimethane(54).

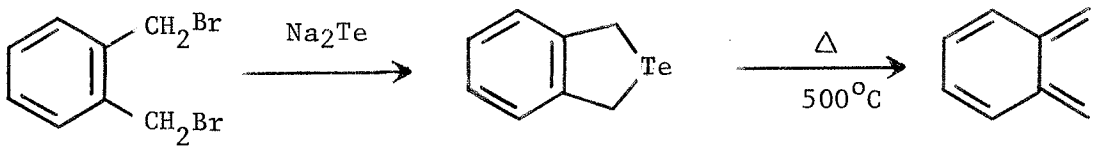


1.3g Other methods

One of the more unusual methods of generating o-quinodimethanes by expulsion of nitrogen was reported by Baker et al(55).

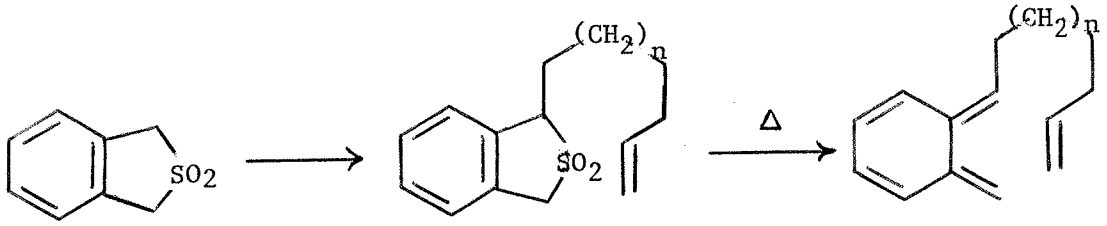


Another method involved thermal extrusion of tellurium from a telluride(56).

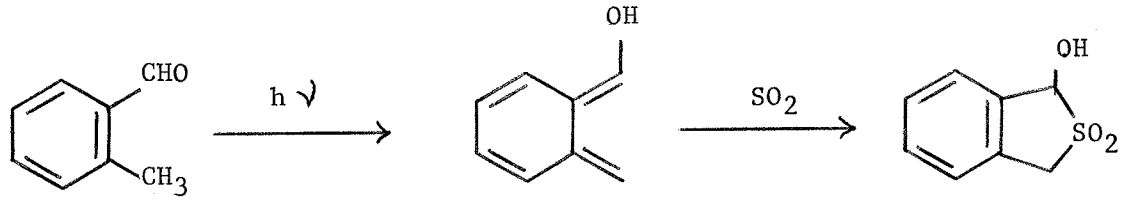


1.3h Summary

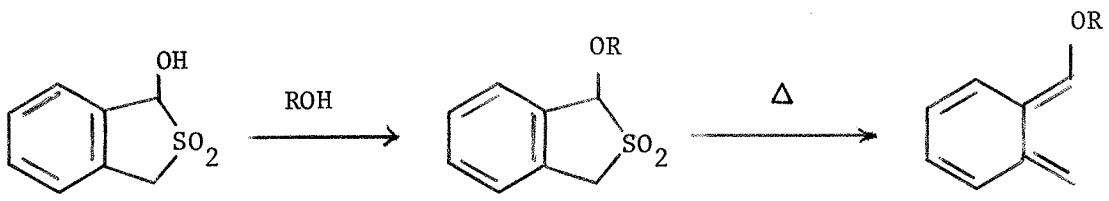
The choice of method for the preparation of an o-quinodimethane depends on the availability of starting materials, the overall yield of the process and the ease with which the method can be carried out. Among all the methods described above, the most frequently used method for producing o-quinodimethanes has been the thermolysis of benzocyclobutenes(2,16-23). However, the most serious drawback to their use is the difficulty in their synthesis(23,38). The photochemical preparation of o-quinodimethanes has the advantage of ease of accessibility of the necessary precursors but is limited by the possibility of photochemical side reactions. Oppolzer et al found that sulfones were preferred precursors for the generation of o-quinodimethanes(38,57). The readily available unsubstituted sulfone could be substituted with appropriate substituents and thermolysed to the o-quinodimethane.



The reversible trapping of o-quinodimethanes by sulfur dioxide(58) was employed by Charlton and Durst to trap a photochemically generated α-hydroxy-o-quinodimethane to give an α-hydroxy sulfone(40). This appears to be a very straight forward route to o-quinodimethane precursors from reasonably simple starting materials.

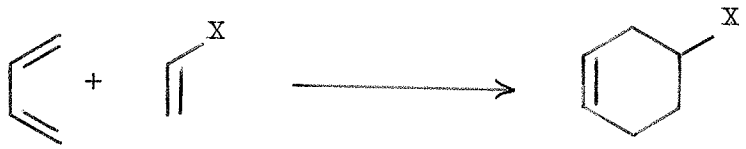


The α-hydroxy sulfones are quite stable, can be stored at low temperature and can be converted into α-alkoxy and α-acetoxy sulfones, which can be used as precursors for the generation of α-subsituted o-quinodimethanes.



1.4 Orthoquinodimethane as a diene in Diels-Alder reaction

The Diels-Alder reaction is a reaction in which a conjugated diene reacts with a substituted alkene (dienophile) to form a six membered ring(59).



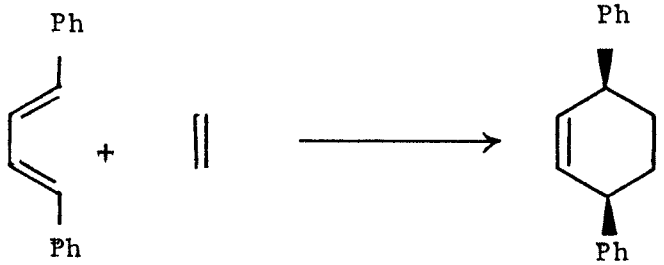
It is a (4+2) cycloaddition involving a system of 4π electrons and a system of 2π electrons. This is a concerted reaction, in which both new bonds are formed in the same transition state. The reaction is normally favored by electron-withdrawing substituents in the dienophile and electron-donating substituents in the diene. In this context, o-quinodimethanes are considered as dienes in the Diels-Alder reaction.

1.4a Stereochemistry and Regiochemistry in the Diels-Alder reaction of o-quinodimethanes

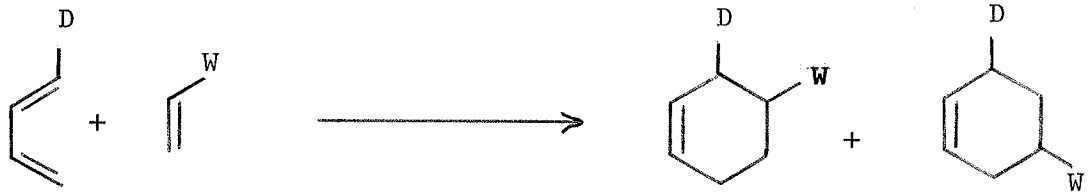
There are several aspects to the stereochemistry of the Diels-Alder reaction(60).

(i) With respect to the dienophiles, the addition is stereospecifically syn, i.e. addition occurs to the dienophile from one face.

(ii) With respect to 1,4-disubstituted dienes the reaction is stereospecific and syn. Thus trans-trans 1,4-diphenylbutadiene gives a cis-1,4-diphenylcyclohexene derivative.



(iii) When an unsymmetrical diene adds to an unsymmetrical dienophile, two possible regioisomers can be formed.

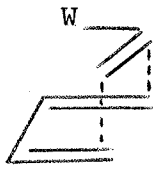


15 16

Although a mixture of products is obtained, usually one predominates. In this case **15** predominates over **16** where D is an electron donating group and W is an electron withdrawing group. This regioselectivity has been explained by frontier orbital theory(61,62). Generally regioselectivity can be predicted on the basis of the most favorable overlap of the HOMO (highest occupied molecular orbital) of the diene with the LUMO (lowest unoccupied molecular orbital) of the dienophile(61). The predicted product has the larger HOMO co-efficient of carbon 1 or 4 of the diene interacting with the larger LUMO co-efficient of the dienophile. Thus, dienes with electron releasing substituents add head-to-head with dienophiles bearing electron withdrawing substituents.

In cases where the primary orbital effects (carbon 1 and 4 of the diene) are approximately equal, secondary orbital effects may also affect the regioselectivity(63). In the absence of any strong orbital effects dipole interactions may come into play to direct regioselectivity.

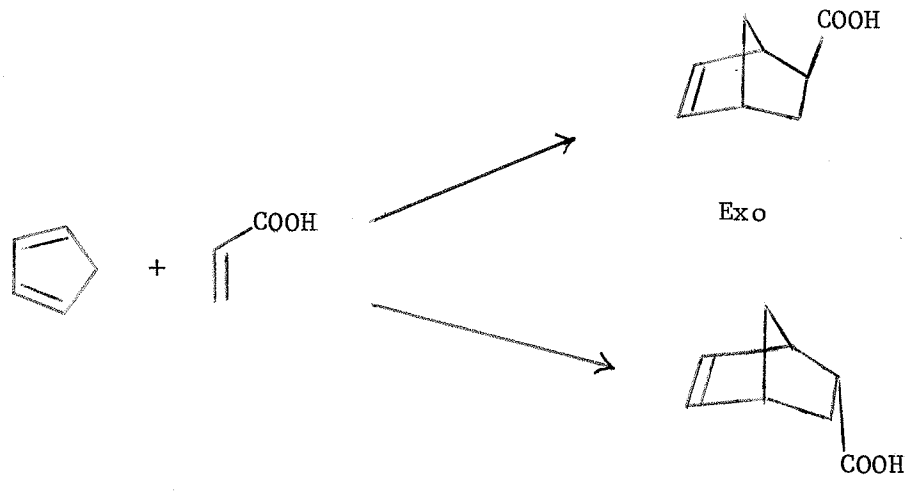
(iv) When the dienophile is substituted there are two possible modes of addition. The substituent group of the dienophile may lie over the diene (endo-addition) or away from the diene (exo-addition).

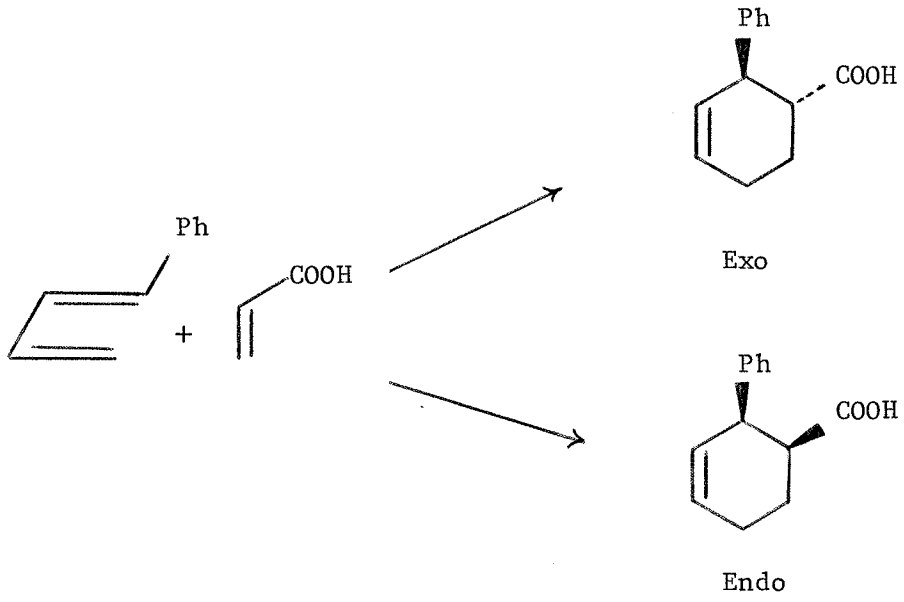


Endo

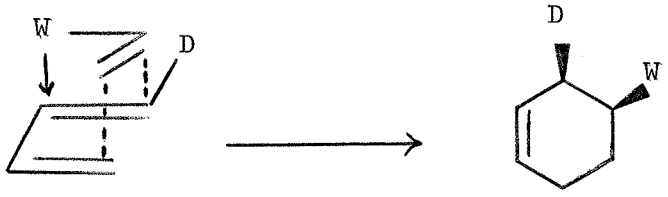
Exo

With substituents on the diene or with cyclic dienes, different products can arise from the two modes of adition.

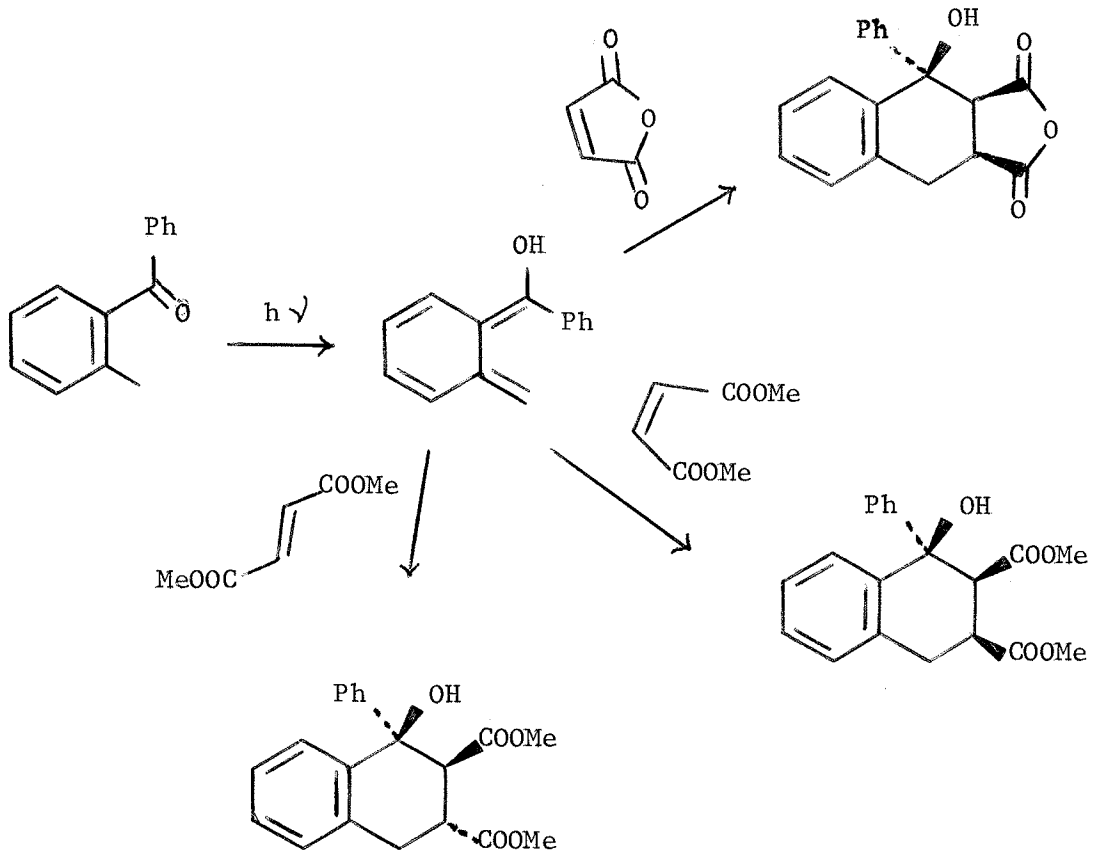




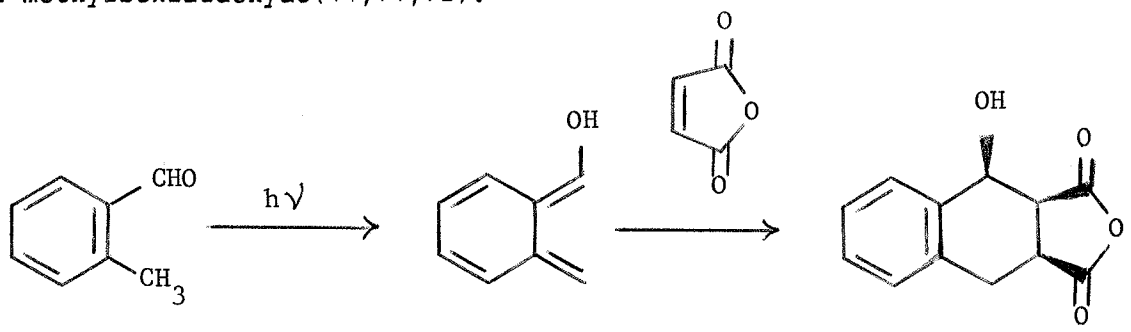
While primary interactions (between atoms to which new bonds are forming) control the regioselectivity of the addition, secondary interactions control the stereoselectivity(63,64) Thus, favorable secondary orbital overlap of the electron acceptor group of the dienophile with carbon 2 of the diene can lead to predominantly <u>endo</u> products(63-66).



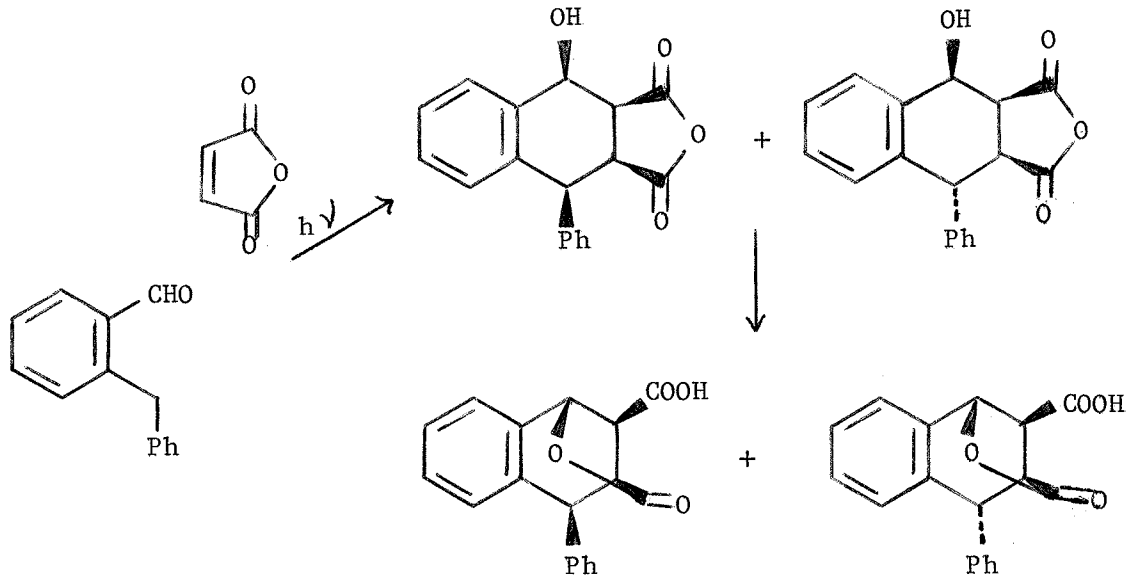
Results from cycloaddition reactions of α-hydroxy (alkoxy, acetoxy etc.) and/or α-phenyl substituted o-quinodimethanes to dienophiles(4,36,40,67-70) indicated that the regio and stereochemical course of the additions followed that expected for a Diels-Alder reaction of substituted dienes with substituted dienophiles. A variety of dienophiles have been added to the photoenol (α-hydroxy-α'-phenyl-o-quinodimethane), generated photochemically from 2-methylbenzophenone(4). Regioselectivity as well as stereoselectivity was observed in these cycloadditions.



The E-dienol was formed, which reacted with the dienophiles giving <u>endo</u> products. Further evidence for the E-dienol was obtained from an examination of the photochemical behavior of 2-methylbenzaldehyde(11,71,72).

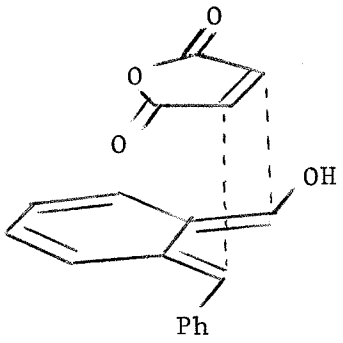


When 2-benzylbenzaldehyde was irradiated in acetone in the presence of maleic anhydride, two isomeric adducts were obtained in the ratio 4:1. When these unstable adducts were heated in toluene they were converted into lactone acids **17** and **18**.

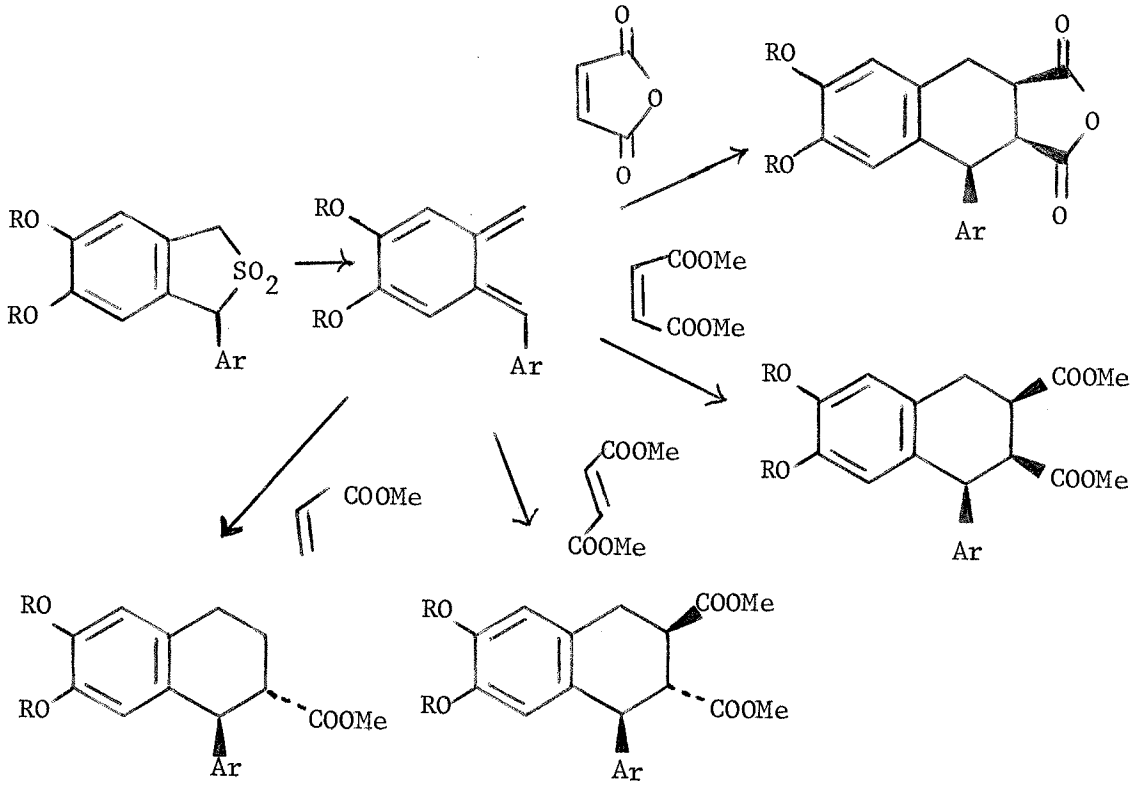


17 18

The authors claimed that these lactone adducts must arise by endo-addition of maleic anhydride to the E,E- and E,Z-dienols(11).



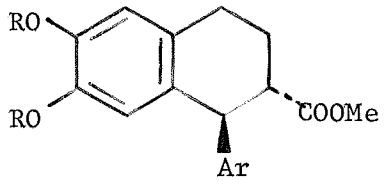
Mann and Piper generated an aryl-substituted o-quinodimethane and added it to a variety of dienophiles(67,68).



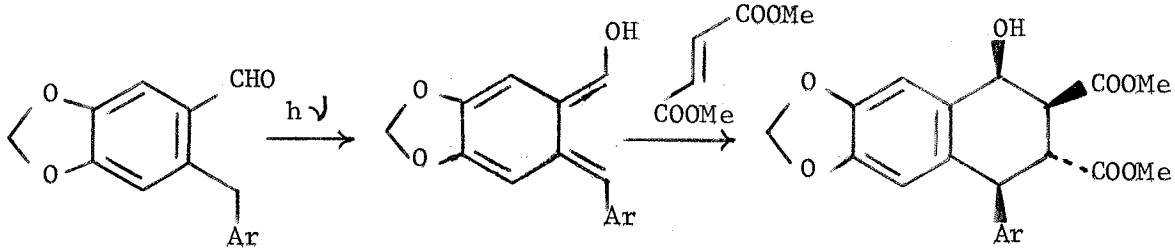
a) R,R = CH_2, Ar = 3,4,5-trimethoxyphenyl

b) R = Me, Ar = 3,4-dimethoxyphenyl

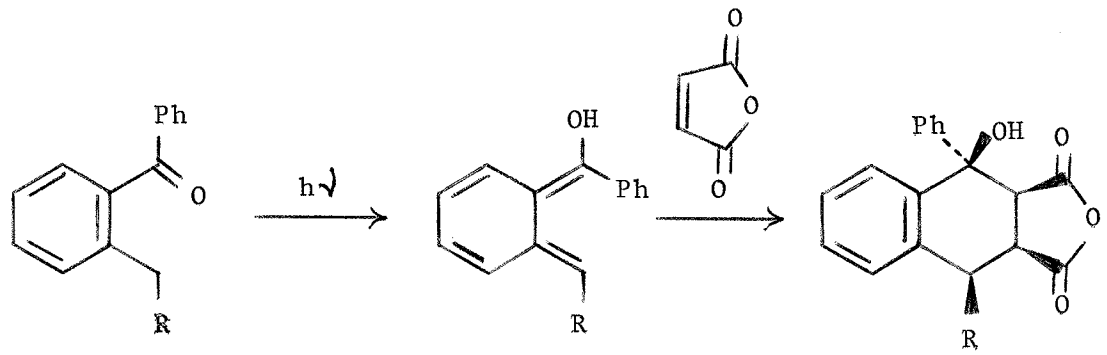
The cycloaddition with maleic anhydride and dimethyl maleate gave mostly endo-adduct i.e. 1,2-cis, which was expected from the E-o-quinodimethane. However, the reaction with dimethyl fumarate and methyl acrylate gave results consistent with exo-addition, i.e. 1,2-trans, >75%. The regioselectivity of the cycloaddition with methyl acrylate was that expected from frontier orbital control, but the stereoselectivity was surprising. They suggested that the abnormal exo selectivity was due to a reversible Diels-Alder reaction that allowed equilibration between the endo(1,2-cis) and exo(1,2-trans) products and eventual accumulation of the thermodynamically more stable exo configuration as the major product(67).



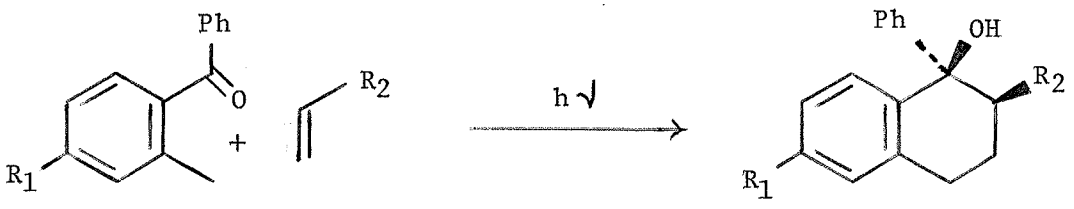
Durst et al generated an E,E-o-quinodimethane photochemically and added it to dimethyl fumarate, to give a 1,2-cis-product presumably via an E-dienol and endo-transition state(69).



Pfau et al produced α-hydroxy-o-quinodimethanes photochemically from 2-benzyl benzophenone and 2-ethyl benzophenone and trapped them by maleic anhydride, methyl fumarate and phenyl fumarate(73). In each case a single adduct was obtained in high yield. Therefore they suggested that the Diels-Alder cycloaddition proceeded from the E,E-dienol (o-quinodimethane) by endo approach.



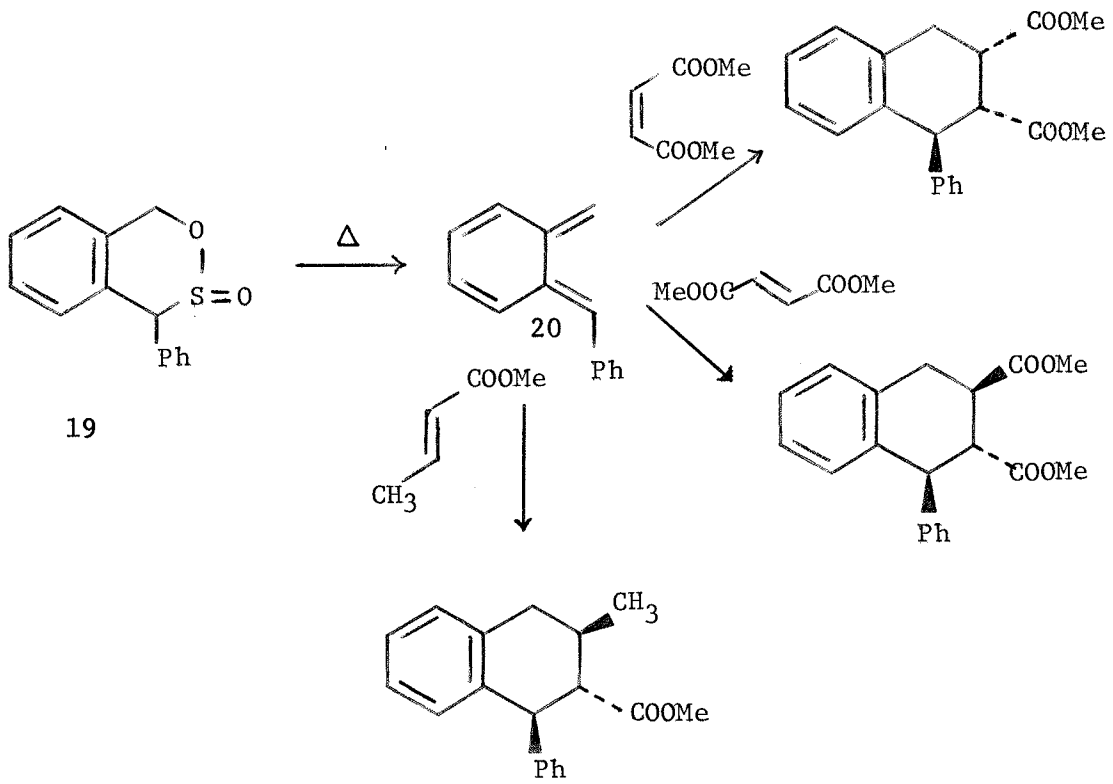
Similarly when 2-methyl benzophenone were irradiated with unsymmetrical dienophiles such as methyl acrylate, acrylonitrile, methyl methacrylate and methyl propiolate, dienol addition proceeded regiospecifically yielding in each case a simple hydroxylic compound having the carboxylate or the carbonitrile group in vicinal positions(74).



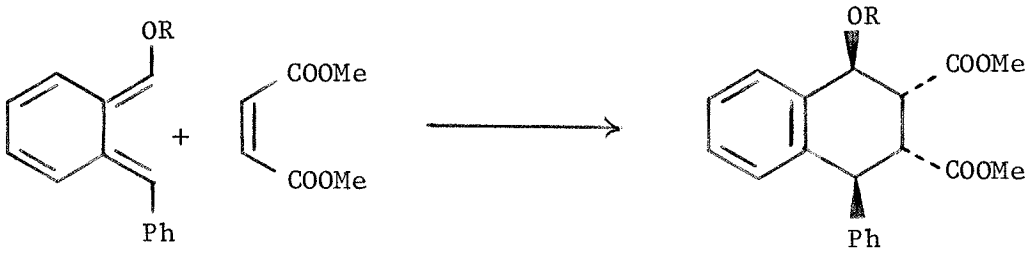
R_1 = H, Me, R_2 = CN, COOMe

Thus the regio and stereochemistry for cycloaddition reactions of o-quinodimethanes follows the prediction of frontier orbital theory.

There have been, however, more recent claims of exceptions to the general pattern which are in contrast to the previously observed directing effect of an aryl group as shown below (70,75). The α-phenyl-o-quinodimethane **20** was generated from the sultine **19** thermally and added to dimethyl maleate, dimethyl fumarate and methyl crotonate. A 1,2-trans-2,3-cis cycloadduct was obtained in each case. It was concluded that the reaction with dimethyl maleate involved an exo-transition state (assuming an E configuration for the o-quinodimethane)(75).



In a later work E,E-α-methoxy-α'-phenyl and α-acetoxy-α'-phenyl-o-quinodimethanes were added to dimethyl maleate, dimethyl fumarate and methyl crotonate. In these reactions also it was claimed that the addition of dimethyl maleate to the E,E-o-quinodimethanes involved exo-transition states(70).

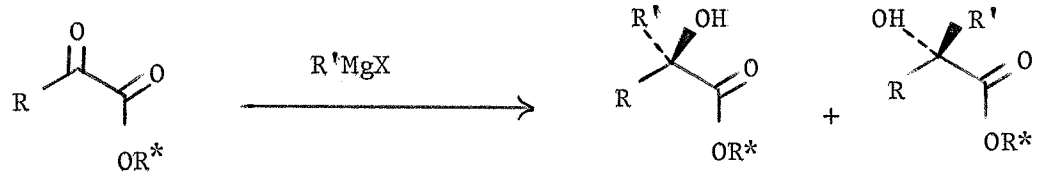


Only in the earlier example of Mann et al had a preference for a trans-1,2-disubstitution pattern been noted, which had been rationalized as arising from a thermodynamically controlled reversible cycloaddition rather than a preference for the exo-transition state(67). In view of the more recent results it would appear that the basis for stereoselectivity in these reactions could bear further study.

1.4b Asymmetric induction in reactions of o-quinodimethanes

At the threshold of synthetic chemistry, one of the main challenges is to find routes which satisfy the demands of industrial accessibility to enantiomerically pure compounds. The definition of asymmetric induction (or asymmetric synthesis) is now accepted as being "any reaction in which an achiral unit (more precisely a prochiral unit) within a substrate molecule is converted by a reactant into chiral unit, such

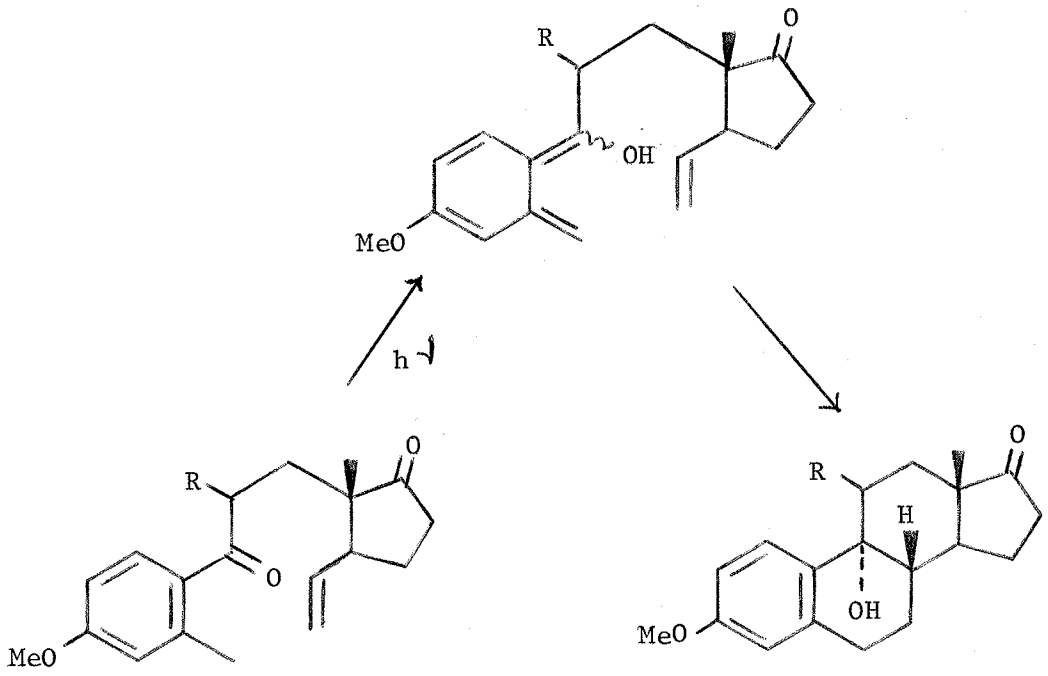
that the resulting two stereoisomers are chiral and are formed in unequal amounts"(76).



R* = menthol

In this example R* is a chiral auxiliary, which controls the face selectivity by steric hindrance and therefore the products (diastereomers) are formed in unequal amounts. In a Diels-Alder reaction a chiral auxiliary in either the diene or the dienophile can cause asymmetric induction.

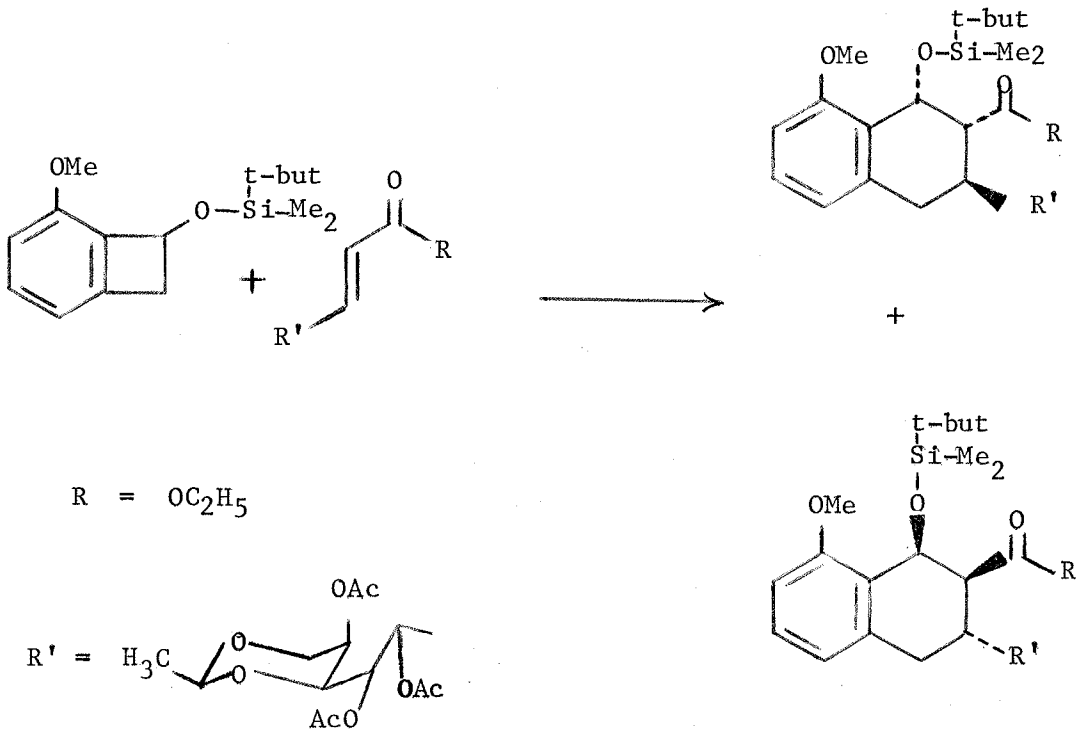
While there has been extensive work carried out on asymmetric induction in Diels-Alder reactions of butadienes(77-79), relatively fewer studies have been made of asymmetric induction in Diels-Alder reactions of o-quinodimethanes(36,80-83). The stereoselectivity of the intramolecular Diels-Alder reaction of o-quinodimethanes have been exploited by many workers in the preparation of optically pure steroids. Quinkert et al achieved an asymmetric synthesis of a steroid by photochemically generating an o-quinodimethane having a chiral substituent which stereochemically controlled an intramolecular Diels-Alder reaction(80).



Several other examples of asymmetric induction in the reaction of o-quinodimethanes are available in the literature(84-88).

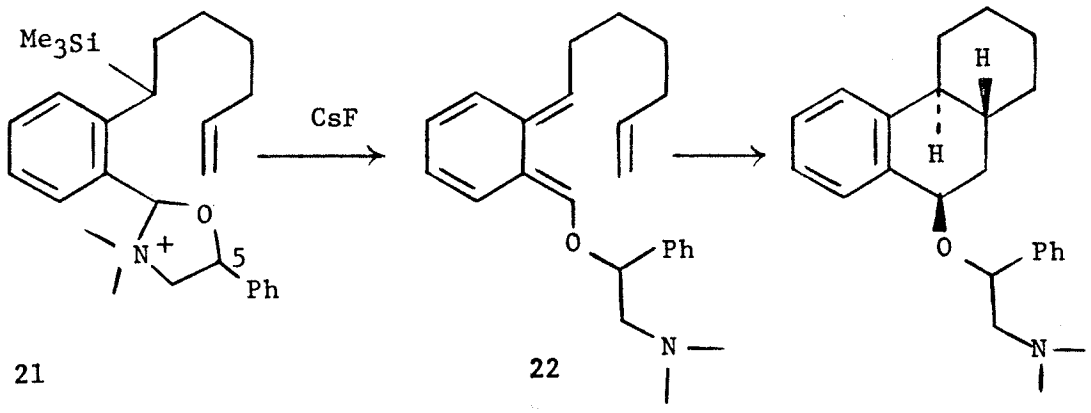
In all of these reactions described in the above references, asymmetric induction was achieved by a chiral auxiliary which became a part of the product molecule. Due to the configuration of the chiral auxiliary the dienophile was sterically constrained to add selectively to one face of the o-quinodimethane thereby ensuring asymmetric induction at the newly created chiral centres.

Frank et al have studied the intermolecular reaction of an achiral o-quinodimethane with a chiral dienophile to determine the relative roles of steric and secondary orbital interactions on the asymmetric induction(81).



Two adducts were formed in the ratio 4:1. Both of the adducts were the results of endo control by the ester function. The orbital interaction appeared to predominate over steric interactions.

More recently Ito et al have reacted the oxazolidinium system **21** with fluoride ion to give the o-quinodimethane **22** bearing a chiral auxiliary that partially controls the stereochemistry of the subsequent addition of dienophile(36). Two diastereomers were found in the ratio 4:1, although the absolute stereochemistry of the products were not determined.

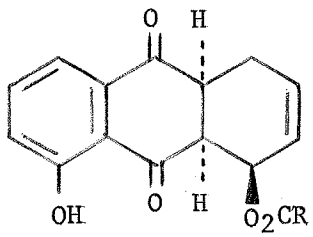


21 22

Various chiral auxiliaries were used to compare the asymmetric induction in these reactions.

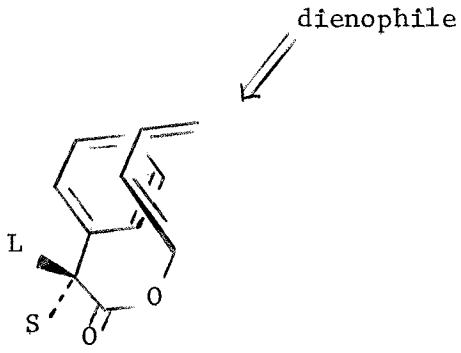
In each case cited so far the asymmetric induction was attributed to the ability of the chiral auxiliary to block one face of the o-quinodimethane or to specifically direct the dienophile to one face of the o-quinodimethane. In the case of the work of Ito et al(36), the presence of an α-phenyl substituent at C_5 of the oxazolidinium ring in **21** remarkably increased the asymmetric induction in the intramolecular Diels-Alder cycloaddition via **22**. The enantioselectivity was accounted for, in accordance with Trost's and Daubin's observation that -stacking interactions may serve as a steric factor to block the incoming dienophile from one of the two enantiotopic faces of the diene(78,79).

Trost et al developed a model of -stacking and described its application to the asymmetric formation of **23** a key intermediate towards the synthesis of tetracycline natural products(78).

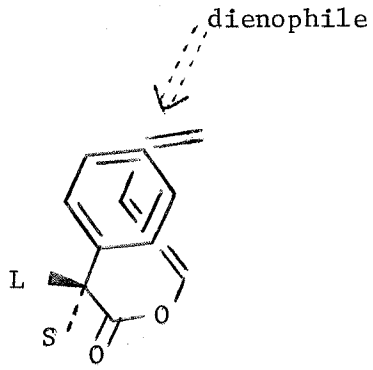


23

On the basis of the π-stacking model, two conformations can be envisioned for a diene such as **24.** In the folded form represented by **24A**, the large group L projects towards the diene producing a severe nonbonded interaction.

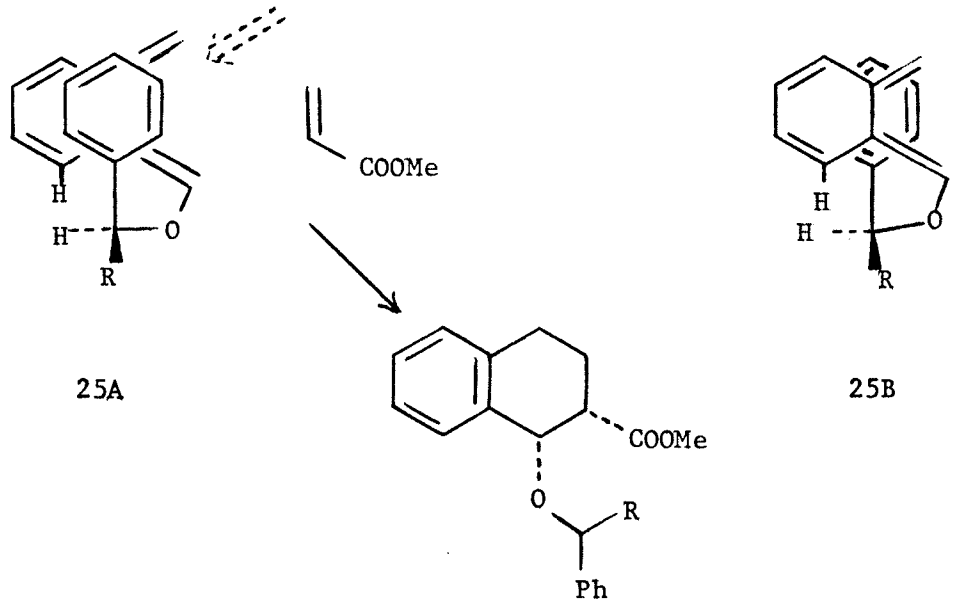


24A



24B

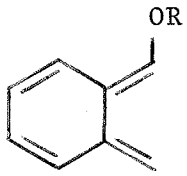
Such a nonbonded interaction is much less between the small group S and the diene in **24B**, and on this basis **24B** should be the favored conformation. The dienophile should preferentially attack from the bottom face. The aromatic ring serves as a steric control element to direct the incoming dienophile to one of the two enantiotopic faces of the diene. However, Ito's contention that -stacking would explain the asymmetric induction in his o-quinodimethane reaction is incorrect. From the diagram **25A** and **25B** it is observed that **25A** should be less hindered, because the nonbonded interaction between the aromatic hydrogen and the benzylic hydrogen adjacent to the ether oxygen is much less than the nonbonded interaction between the aromatic hydrogen and the much more bulky group i.e. $-CH(CH_3)N(Me)_2$ in **25B**. Addition of the dienophile to the open face of **25A** would lead to a product having a stereochemistry opposite to that observed by Ito et al(36).



25A 25B

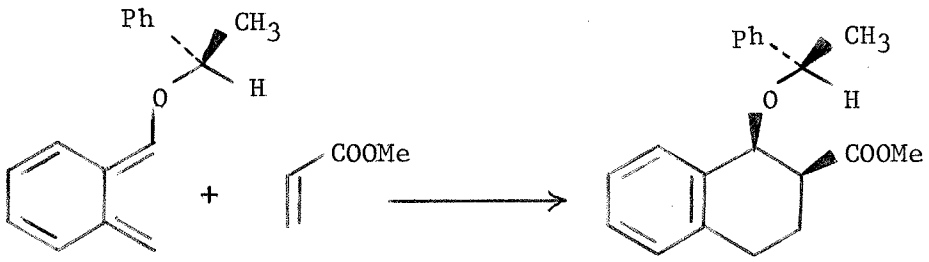
R = $-CH(CH_3)N(Me)_2$

Charlton presented a different explanation for the asymmetric induction in the Diels-Alder reaction of o-quinodimethanes(82,83). He generated the o-quinodimethane **26** by thermal extrusion of SO_2 from a sulfone and added it to the dienophiles, maleic anhydride, dimethyl fumarate and methyl acrylate.

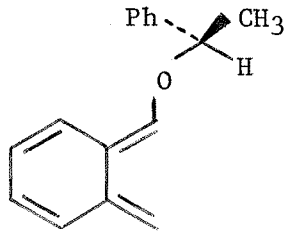


26

Various chiral auxiliaries (R) were used and in all cases some stereoselectivity was observed. The 1-phenylethyl group yielded the greatest asymmetric induction. In the case of the (R)-phenylethyl chiral auxiliary cycloaddition of methyl acrylate to the upper face gave the 1R,1S,2S cycloadduct.



Schaefer et al have shown that in alkyl phenyl ethers the most stable conformation is one in which the alkoxy group lies in the plane of the aromatic ring allowing p-π overlap(89). On the basis of this analogy Charlton suggested that the preferred conformation of the o-quinodimethane **26**,((R)-phenylethoxy) is as in **27**.



27

In this conformation the relative steric bulk of the phenyl and methyl groups serves to block the lower face of the o-quinodimethane and therefore dienophiles add to the upper face. This mechanism is also capable of explaining Ito's earlier results.

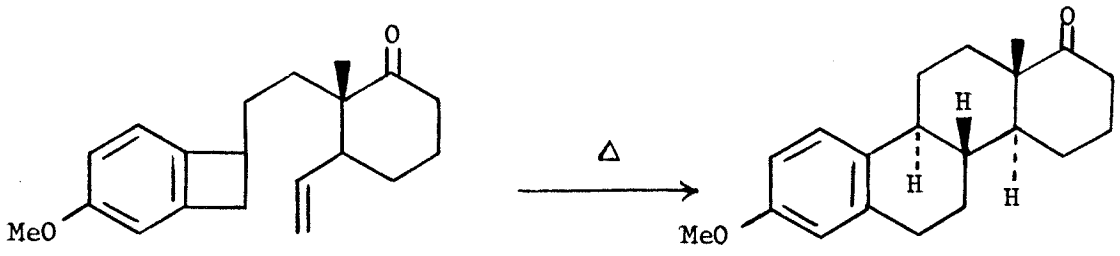
1.5 Use of o-quinodimethanes in organic synthesis

There has been considerable recent interest in the application of o-quinodimethanes in organic synthesis(18-20,90,91). These reactive intermediates are excellent dienes for Diels-Alder cycloadditions and allow the construction of six-membered rings fused to benzene rings . Although it was discovered in the early 1950's that o-quinodimethanes could function as Diels-Alder dienes in the construction of

functionalised tetralin derivatives, they were not used in natural product synthesis until much later. Oppolzer was the first to use o-quinodimethanes in natural product synthesis(92). A brief description on the use of o-quinodimethanes in organic synthesis, especially natural product synthesis, is given below.

1.5a Steroid synthesis

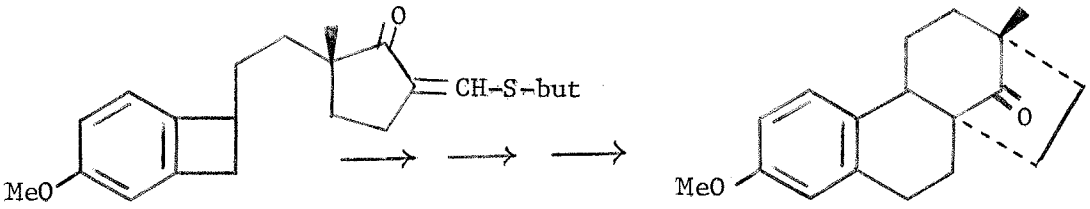
The potential of intramolecular o-quinodimethane cycloadditions for the construction of aromatic steroids has been recognized by different research teams leading to several stereoselective approaches to this ring system. A report on the synthesis of racemic O-methyl-D-homo-estrone reveals an efficient and highly stereocontrolled cycloaddition of an o-quinodimethane. Considerable difficulty was encountered in the preparation of the required benzocyclobutene derivative i.e. coupling the benzocyclobutene with the dienophile carrying future D-ring of the steroid(80).



There are various other examples of steroid synthesis where o-quinodimethanes have been used as intermediates(16,19,85,93-100).

1.5b Terpenoid synthesis

During work originally aimed towards the synthesis of steroids, a novel stereospecific synthesis of an intermediate for the preparation of tetracyclic diterpenes from benzocyclobutene derivatives was discovered. The synthesis involved intramolecular cycloaddition of an o-quinodimethane, derived thermally from 5-n-butylthio methylene-2-[2-(4-methoxydihydrobenzocyclobutene)ethyl]-2-methylcyclopentanone, followed by desulfuration(101).

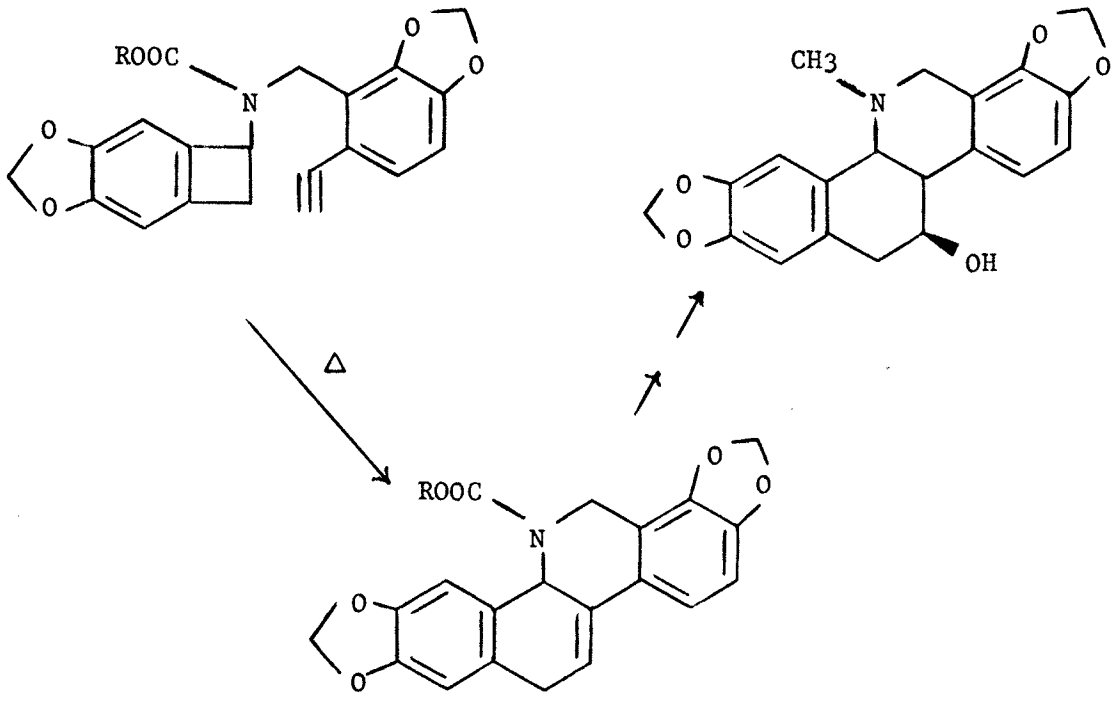


Other examples are total synthesis of hibaol(102) and pentacyclic triterpene intermediates(19,103,104).

1.5c Alkaloid synthesis

The pioneering example of the use of an o-quinodimethane in natural product synthesis is the total synthesis of (+)chelidonine by

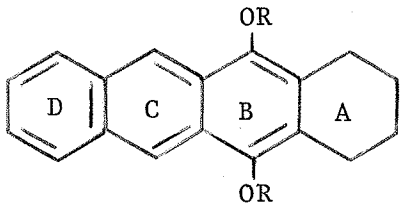
Oppolzer(92). Thus thermolysis of an urethane afforded the cis fused product, which was finally converted to chelidonine.



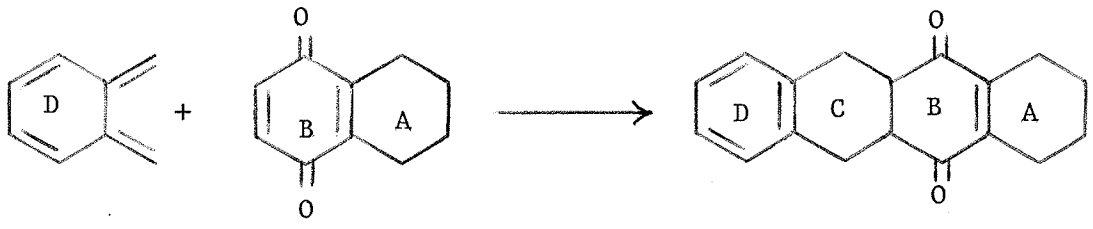
Other application of o-quinodimethanes in alkaloid synthesis involved both intra-molecular and inter molecular cycloaddition reactions(18-21,105,106).

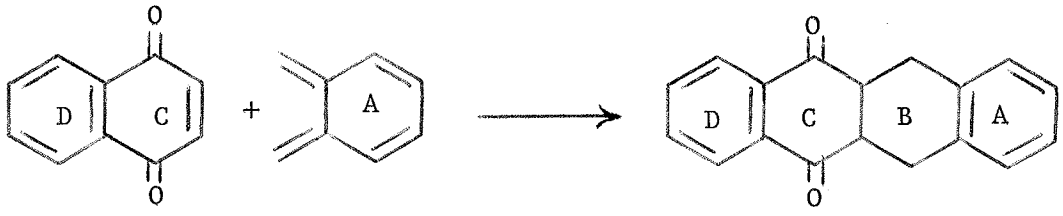
1.5d Anthracycline and other polycyclic synthesis

The basic skeleton of anthracycline and tetracycline antibiotics is a linear tetracyclic system.

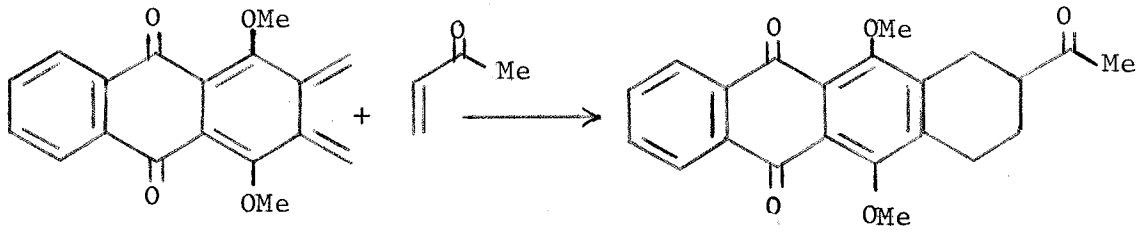


The consruction of this tetracyclic systems via an o-quinodimethane can be achieved in two ways, i) by Diels-Alder reaction of a naphthoquinone (the BA-ring) with an o-quinodimethane, ii) by an analogous reaction whereby a quinone derivative becomes the DC-ring portion.





Cava et al have synthesized the anthracyclinone-type of linear tetracyclic compound by a cycloaddition reaction of an olefin with an o-quinodimethane, generated in situ from 2,3-dibromomethylene anthraquinone(107).

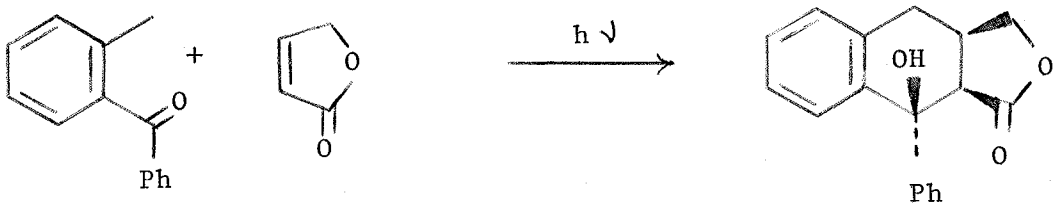


Other workers have also synthesised tetracyclic systems using o-quinodimethanes(19,107-109). The methods of preparation of anthracycline derivative and other tetracyclic systems involving isobenzofuran derivatives and substituted dienes are beyond the scope of this review and they are therefore not included.

1.5e Lignan synthesis

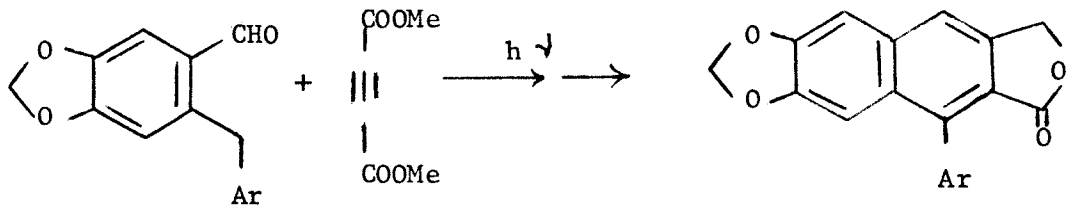
Lignans as a class of natural products present an interesting challenge to synthetic organic chemists. In a recent comprehensive review(110) various methods of synthesis of lignans have been described, including Diels-Alder reactions. Synthesis of lignans involving o-quinodimethanes was first reported by Block et al(71) and Sammes et al(47).

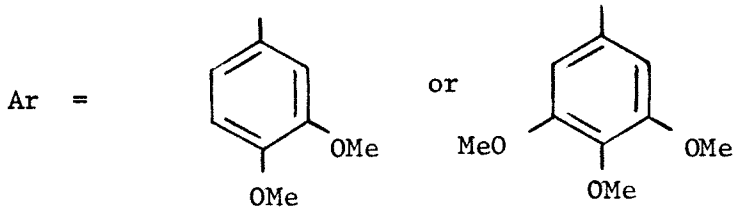
Block reported that irradiation of o-methylbenzophenone in the presence of unsymmetrical dienophiles, such as 4-hydroxybut-2-enoic acid lactone, produced an aryl-tetralin lignan analogue(72).



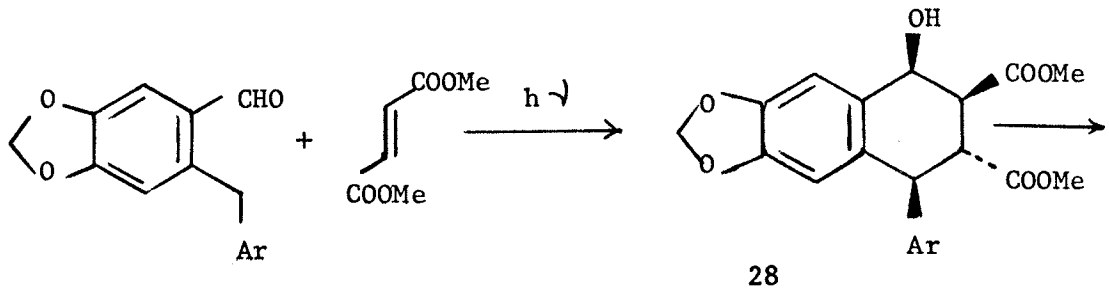
In a following paper(71) they examined the irradiation of 2-methyl benzophenone in the presence of dimethylacetylenedicarboxylate, tetracyanoethylene, dimethyl maleate dimethyl fumarate and crotonaldehyde to establish the stereochemistry of the aryltetralin poducts.

Sammes et al described the synthesis of arylnaphthalene lignans using photochemically generated o-quinodimethanes(47). Thus an ortho-benzylbenzaldehyde was irradiated in the presence of dimethyl acetylenedicarboxylate and the cycloadduct then converted into an arylnaphthalene lignan.

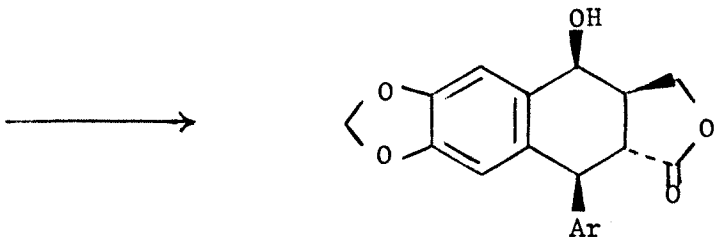




Synthesis of (+/-)epiisopodophyllotoxin was described by Durst et al in which the intermediate α-hydroxy-o-quinodimethane was generated photochemically(69). Thus irradiation of 6-(3',4',5'-trimethoxybenzyl)-piperonal in THF in the presence of dimethyl fumarate afforded the cycloadduct diester **28** which was converted into epiisopodophyllotoxin.

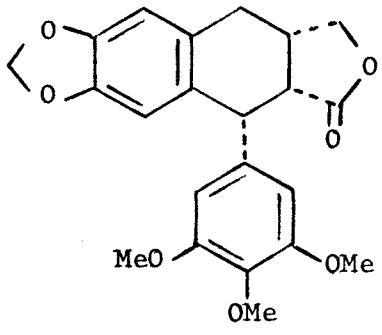


28

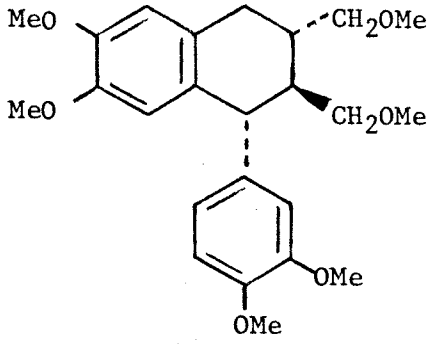


Ar = 3,4,5-trimethoxyphenyl

Mann and Piper reported the synthesis of the basic ring systems of lignans. The key step was an intermolecular cycloaddition between o-quinodimethanes and various dienophiles(67,68). These methods were used for the synthesis of isodeoxypicropodophyllin **29**, phyltetralin **30** and a large number of analogues of arylnaphthalene lignans.

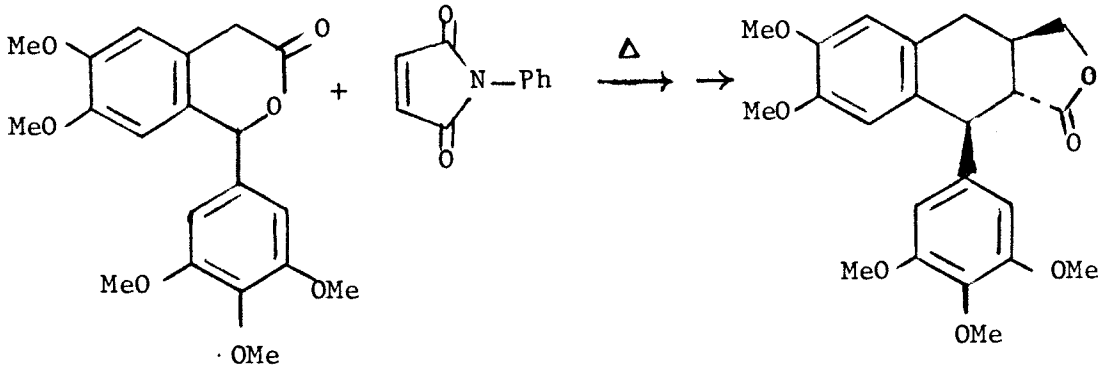


29

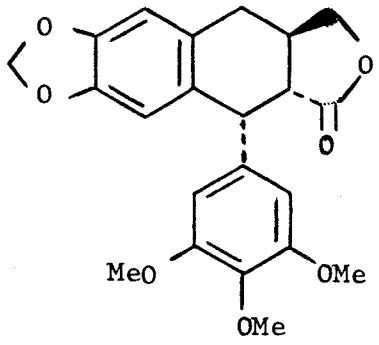


30

Another synthesis of 1-aryltetralin lignan lactones has been provided by Das et al(111). Deoxyisosikkimotoxin has been synthesized by an intermolecular cycloaddition of o-quinodimethane generated from isochromanone.

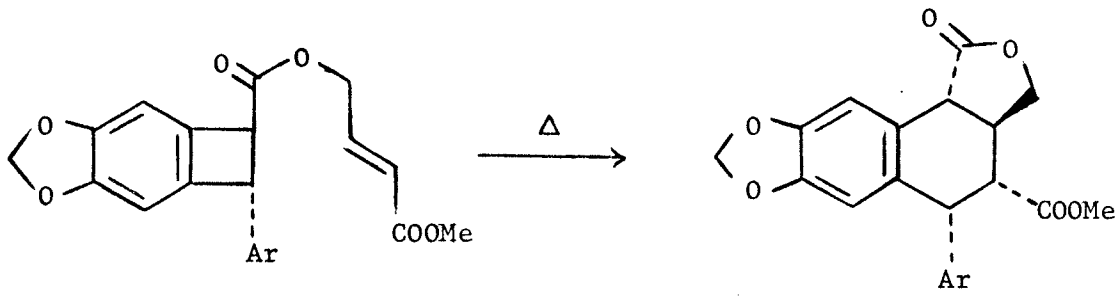


A recent synthesis of deoxypodophyllotoxin **31** involves an intermolecular Diels-Alder reaction of an o-quinodimethane with maleic anhydride(112).



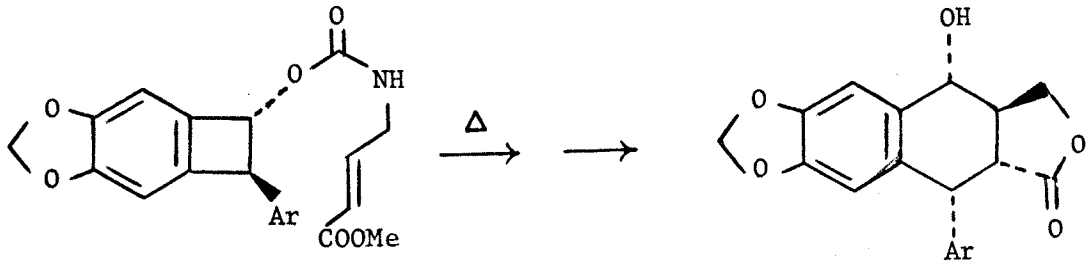
31

Synthesis of lignans involving isobenzofuran remains beyond the scope of discussion in this review(113). A podophyllotoxin analogue has also been synthesized by an intramolecular Diels-Alder cycloaddition of o-quinodimethane. Thus heating the benzocyclobutene derivative generated an o-quinodimethane, which underwent intramolecular cycloaddition to give the lignan-like structure(23).



Ar = 3,4,5-trimethoxyphenyl

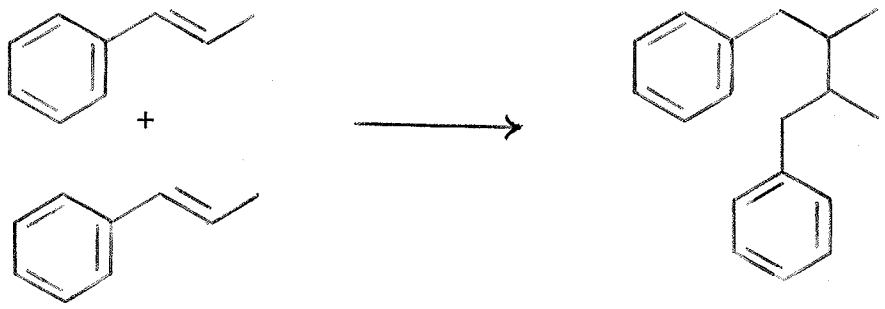
Recently Durst et al have described the synthesis of podophyllotoxin by an intramolecular Diels-Alder reaction of an o-quinodimethane, generated from a benzocyclobutene derivative(114).



Ar = 3,4,5-trimethoxyphenyl

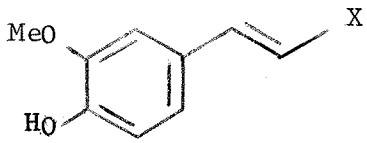
1.6 Medicinally important lignans and lignan stereochemistry

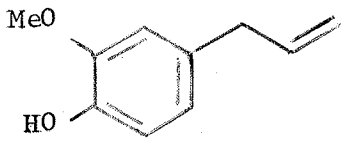
Lignans and neolignans are formed in nature by the oxidative dimerization of various C_6C_3 phenols(115). Lignans were defined by Haworth as a class of optically active plant products which contain the 2,3-dibenzyl butane skeleton **32** and are probably derived by the dimerization of C_6-C_3 units at the ß-carbon atoms of the side chains(116-118).



32

Another related class of compounds, the neolignans has been defined as those compounds deriving from a dimerization of propenyl phenols and/or allyl phenols **35**, **36**. Both lignans and neolignans are derived biologically from coupling cinnamyl alcohols and propenyl phenols such as **33**, **35**.





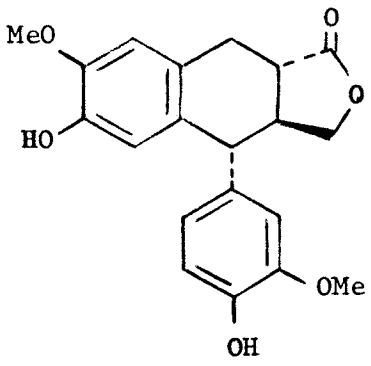
33 X = CH_2OH

34 X = COOH

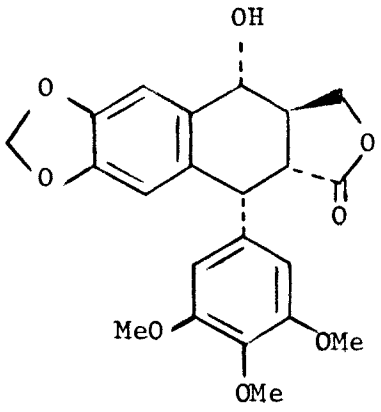
35 X = CH_3

36

The name lignan was reserved for compounds in which the two C_6-C_3 units were linked by a bond connecting the central ß-carbon atoms of each side chain and the name neolignan was used to designate compounds in which the two C_6-C_3 units were not linked by a ß-ß bond. According to a more recent definition lignans can be distinguished from neolignans by the fact that lignans are formed by oxidative coupling of cinnamyl alcohols and/or cinnamic acids **33/34** whereas neolignans are formed by oxidative coupling of propenyl phenols and/or allyl phenols **35/36**. Since the latter definition does not identify any fundamental structural difference between the two series of compounds the former definition was adopted by R. S. Ward(110). Therefore lignans are defined as a class of compounds having a basic 18-carbon skeleton formed by the dimerization of C_6-C_3 units at the ß-positions. Conidendrin **37**, podophyllotoxin **38** and steganone **39** are some examples of lignans.



37



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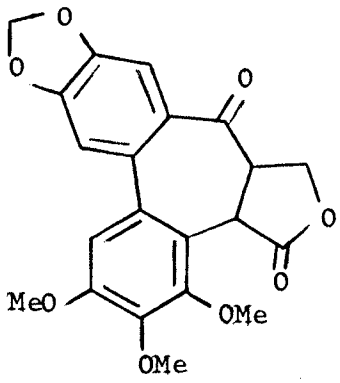
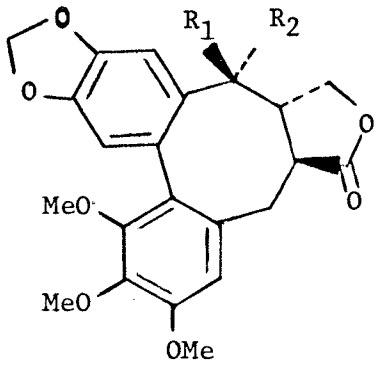


39

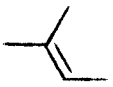
Lignans with a side chain fused with the aromatic ring can be classified into two groups according to their structures,

i) aryltetralin lignans such as **38** and

ii) dibenzocyclooctadiene lignans such as **39**. In both subclasses one finds medicinally important compounds. Thus steganangin **40** and steganacin **41** have shown significant antileukemic activity(119).



40 R_1 = OAc, R_2 = H

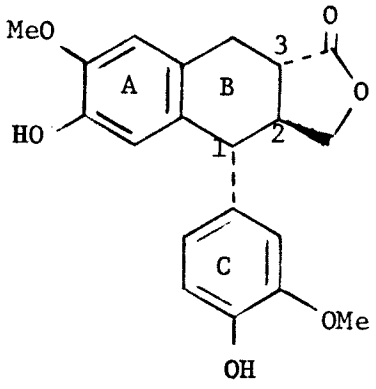
41 R_1 = OOC 

R_2 = H

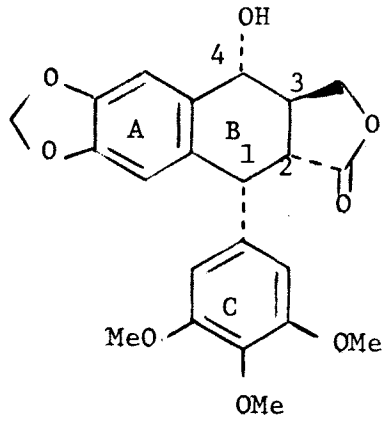
The phyllanthus lignans, from the plant Phyllanthus niruri linn have reportedly been used in the treatment of jaundice, asthma and bronchial infections(120). Phyltetralin, nertetralin and phyllanthin were isolated from that plant(120-122). Podophyllum lignans have antimitotic activity(118) and podophyllotoxin has been used clinically and experimentally as a potent cytotoxic agent.

Podophyllum lignans as a class of aryltetralin lignans differ from other known aryltetralin lignans such as conidendrin, isotaxiresinol,

isoolivil etc. in several respects(118). Firstly, they are the only ones in which ring C is a fully or partially methylated pyrogallol nucleus, whereas in the other aryltetralin lignans both A and C rings are derived from catechol.



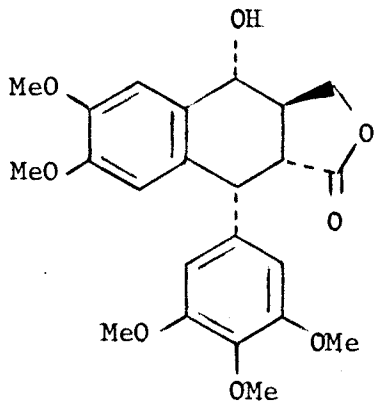
α-Conidendrin



Podophyllotoxin

Secondly, most have a 1,2-cis-2,3-trans configuration, whereas other aryltetralin lignans have the thermodynamically more stable 1,2-trans configuration. Thirdly, the lactone carbonyl group is located at C_2 in podophyllotoxin and at C_3 in conidendrin.

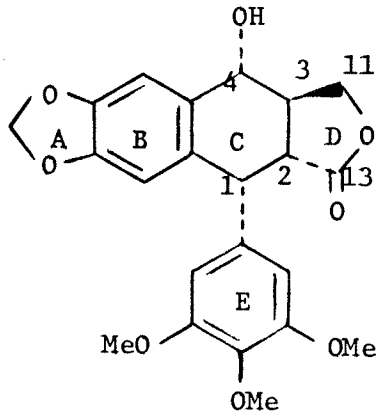
Another analogue of the Podophyllum lignans known as sikkimotoxin (6,7-dimethoxy analogue of podophyllotoxin) has also recieved considerable attention as a cancer chemotherapeutic agent(111).



Sikkimotoxin

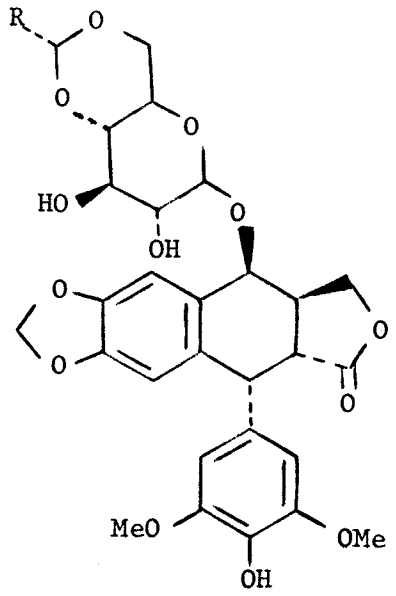
The Podophyllum lignans are unique in their biological (especially antimitotic and tumor-damaging) activity, a property not shared by other known lignans and which is closely associated with their configuration at C_1, C_2 and C_3. A review of the chemistry, stereochemistry and biological activity of lignans, especially the Podophyllum lignans, remains beyond the scope of the dicussion in this thesis(118,123). However, a brief discussion about the stereochemistry and structure-activity relationships in Podophyllum lignans is presented.

Podophyllum lignans include 12 isolated compounds from naturally occuring Podophyllum species(118). Out of these 12 compounds podophyllotoxin **38** has been shown to have anticancer properties(123). Hartwell and Schrecker pointed out that the podophyllotoxin was unique in its antimitotic and tumor damaging activity, which was closely associated with its configuration at C_1, C_2 and C_3 with its highly strained trans-fused γ-lactone system(118).

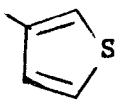


38

The stereochemistry of podophyllotoxin is 1,2-cis-2,3-trans-3,4-trans. However, the semisynthetic derivatives etoposide **42** and teniposide **43** having 3,4-cis configuration are also in clinical use as anticancer agents(23,124).



42 R = Me

43 R = 

Jardin concluded that the relationship between the structural modifications and the resulting antimitotic activity supports the suggestions that the C and D rings of these compounds (see **38**) are involved in their interaction with tubulin(123). Tubulin is a constituent protein of microtubules which are cylindrical structures involved in regulating shape, internal organization and movement of eukaryotic cells(125). Specifically the activity of these compounds is sensitive to the configuration, size and/or hydrophilic character of substituents at the C_4 position in the C-ring, and to the steric features of substituents at the 12 position of D-ring.

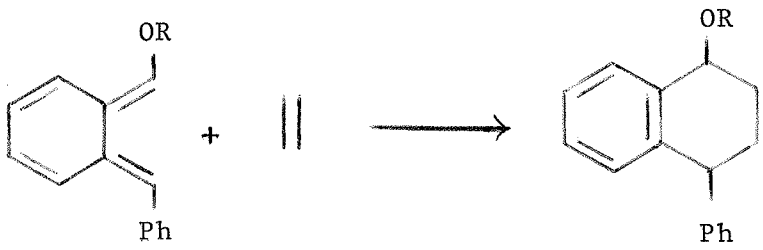
The mode of action of podophyllotoxin and semisynthetic derivatives etoposide (VP-16-213) and teniposide (VM-26) are different(126). Podophyllotoxin inhibits assembly of microtubules, whereas the semisynthetic derivatives inhibit cell cycle progression prior to mitosis. Evidence now indicates that cytotoxicity of VP-16-213 and VM-26 may be due to the DNA breakage resulting from the exposure of cells to the drugs. The congeners of VP-16-213 require a free hydroxyl group at the 4' position for DNA breakage activity and this activity can be influenced by the configuration at the 4-carbon position. Glycosylation diminishes breakage activity and abolishes antimicrotubule activity. Aldehyde condensation with the OH-group at the C_4 and C_6 position of the pyranose moiety greatly enhances breakage activity, and also influences anticancer activity.

NMR studies suggest that all of these compounds(podopyllotoxin, etoposide and teniposide) have a favored conformation in solution in which the pendant aryl group(E-ring) is perpendicular (quasi-axial) to the rest of the system (ABCD ring)(127). The reduced biological activity of the related compound picropodophyllin (1,2-trans-2,3-cis-3,4-trans) has been ascribed to a favored conformation in solution in which the aryl ring is roughly co-planar (quasi-equatorial) with respect to the ABCD ring system.

CHAPTER 2

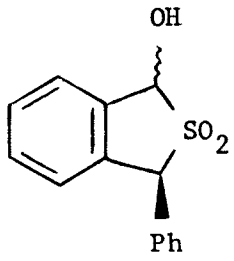
AIM OF THIS WORK

The recent discovery of a simple route to α-oxy-α'-phenyl-o-quinodimethane(40,70) has allowed an investigation of the reactions of these intermediates with dienophiles in order to establish routes to the various diastereomers of the 1-aryl-4-oxy tetralin system.



Until now only the reactions of E,E-α,α'-disubstituted o-quinodimethanes with various dienophiles have been studied in attempts to synthesise podophyllotoxin analogues(69,70). The study of E,Z-α,α'-disubstituted-o-quinodimethanes remains unexplored. Their cycloaddition reactions with dienophiles may provide a route to the aryl tetralins having the podophyllotoxin stereochemistry. Therefore in order to elucidate further the steric and electronic factors involved in the cycloaddition reaction of o-quinodimethanes, a study of the Diels-Alder reactions of both E,E- and E,Z-α-acetoxy-α'-phenyl-o-quinodimethanes with dienophiles such as dimethyl fumarate, dimethyl maleate, maleic anhydride and methyl crotonate is proposed. Cis and trans 1-phenyl-3-acetoxy sulfone **46** and

47 will be prepared and their reactions with dienophiles will be investigated. In addition cis-1-phenyl-3-methoxy and 1-phenyl-3-hydroxy sulfones **45** and **44** will also be investigated.



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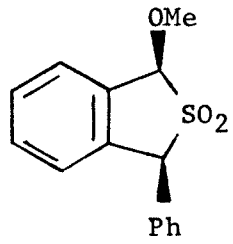
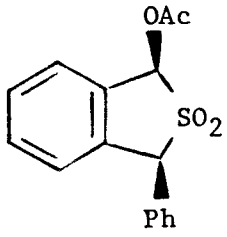
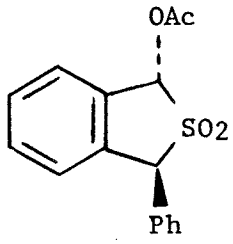


45

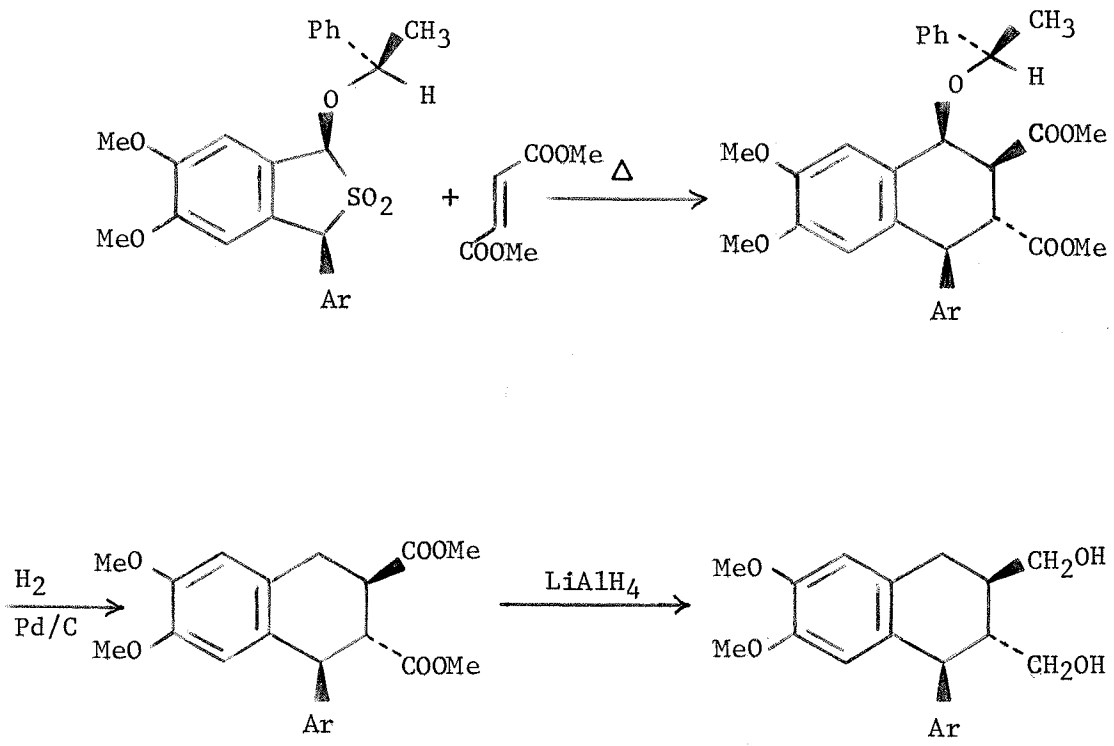


46



47

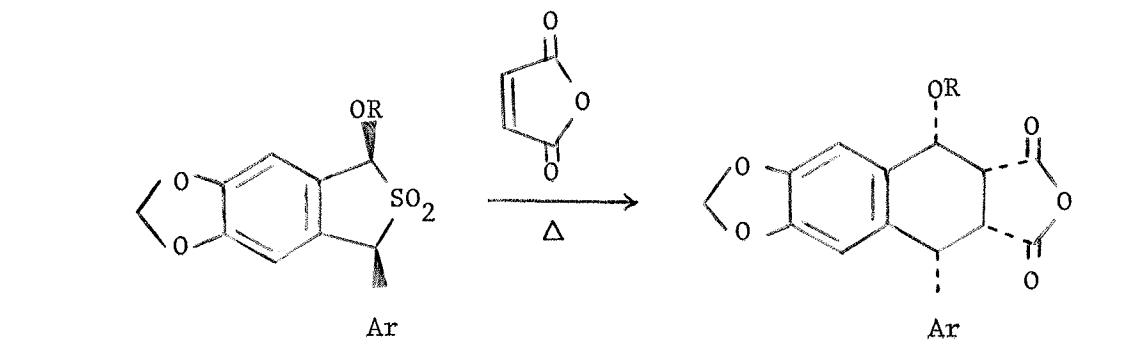
An enantioselective synthesis of (+)-isolariciresinol dimethyl ether **48** (outlined) will be attempted to demonstrate that asymmetric addition to an o-quinodimethane is applicable to the synthesis of a typical lignan.

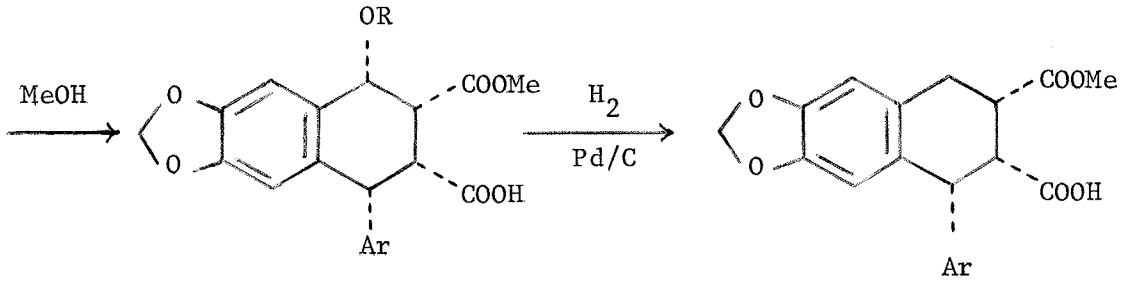


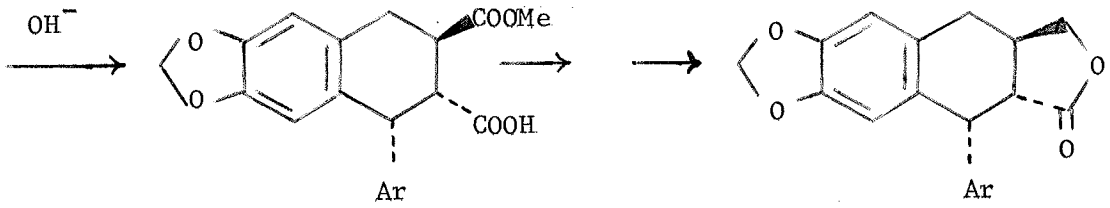
Ar = 3,4-dimethoxyphenyl

48

An enantioselective synthesis of deoxypodophyllotoxin **31** (outlined) will also be attempted.

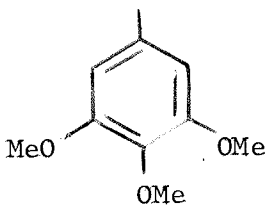

OR
O
O
SO2
Ar
O
O
Δ
OR
O
O
O
O
Ar


MeOH
OR
O
O
COOMe
COOH
Ar
H2
Pd/C
COOMe
COOH
Ar


OH⁻
O
O
COOMe
COOH
Ar
O
O
O
O
Ar

31

Ar =

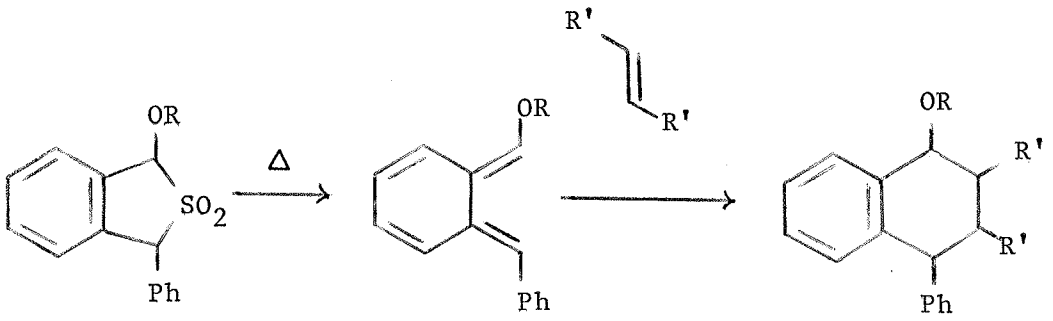

MeO
OMe
OMe

CHAPTER 3

RESULTS AND DISCUSSION

3.1 E,E- and E,Z-o-quinodimethanes

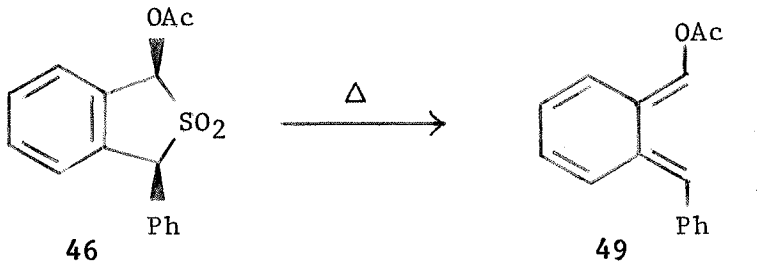
Recently there has been an interest in the use of o-quinodimethanes as intermediates in natural product synthesis(16,23,36,67-70). The recent discovery of a simple route to α-oxy-α'-phenyl-o-quinodimethanes prompted us to investigate the reactions of these intermediates with dienophiles, to establish routes to the various diastereomers of the tetralin system(40,70).



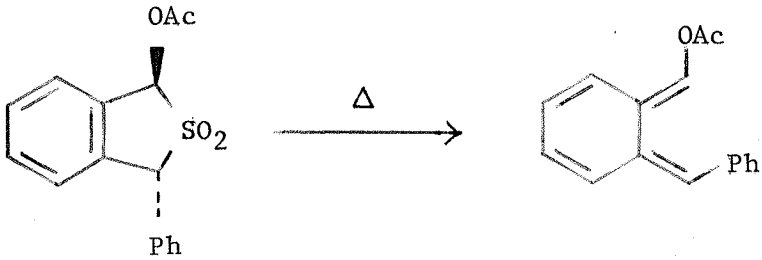
Previous work on the addition of oxy and phenyl substituted o-quinodimethanes to alkenes indicated that the regio and stereochemical course of the addition followed that expected from the Diels-Alder reaction of substituted dienes with alkenes (70). However, there have been more recent claims of exceptions to the general pattern, which are in contrast to the previously observed directing effect of an aryl group(36,70,75). Therefore in order to elucidate further the steric and electronic factors involved in the cycloadditions of o-quinodimethanes

we have carried out a study of the Diels-Alder reactions of E,E- and E,Z-α-oxy-α'-phenyl-o-quinodimethanes such as E,E- and E,Z-α-acetoxy-α'-phenyl-o-quinodimethanes **49**, **50**, E,E-α-methoxy-α'-phenyl-o-quinodimethane **51** as well as E,E- and E,Z-α-hydroxy-α'-phenyl-o-quinodimethanes **52** and **53**. The dienophiles used in this study included dimethyl fumarate, dimethyl maleate, maleic anhydride and methyl crotonate. We have also attempted to carry out Lewis acid catalysed Diels-Alder reactions of E,E-α-acetoxy-α'-phenyl-o-quinodimethane with the dienophile dimethyl fumarate.

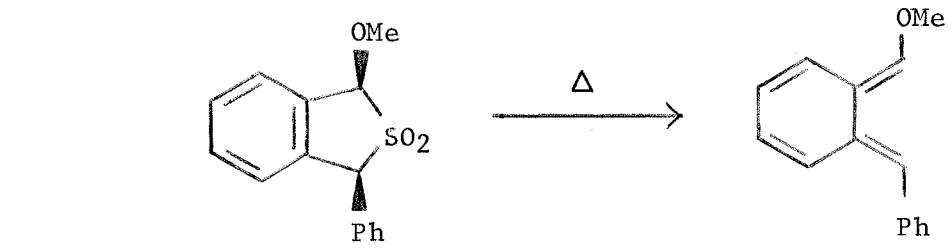
The E,E- and E,Z-α-acetoxy-α'-phenyl-o-quinodimethanes **49** and **50** were prepared by thermal elimination of SO_2 from <u>cis</u> and <u>trans</u> acetoxyphenyl sulfones **46**, and **47** respectively. The E,E-α-methoxy-α'-phenyl, E,E-α-hydroxy-α'-phenyl and E,Z-α-hydroxy-α'-phenyl-o-quinodimethanes **51**, **52** and **53** were prepared from the <u>cis</u>-methoxyphenyl sulfone **45** and a mixture of <u>cis</u> and <u>trans</u>-hydroxyphenyl sulfone **44** respectively.



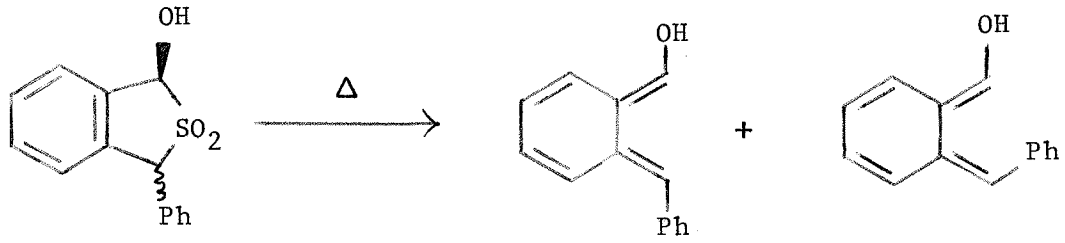
46 **49**



47 **50**



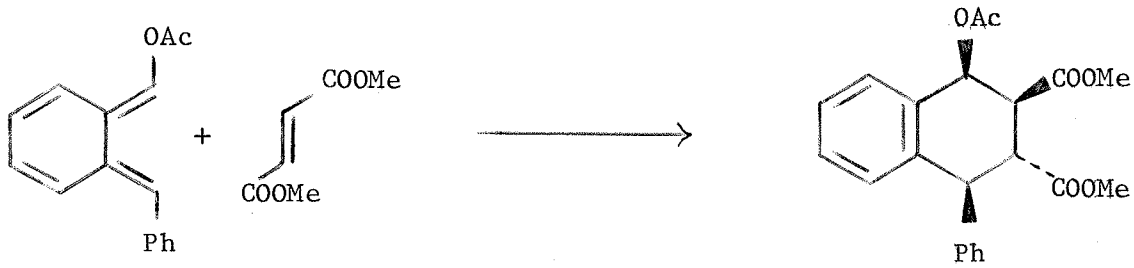
45 51



44 52 53

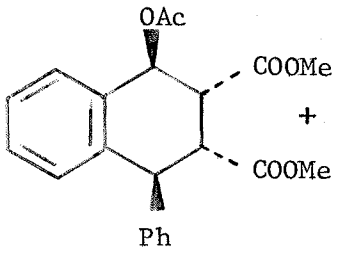
The hydroxy, methoxy and acetoxy sulfones were prepared following the literature procedure(70). It was assumed that cis-acetoxyphenyl sulfone **46** generated the E,E-o-quinodimethane **49** as it is much less sterically hindered than the Z,Z configuration, which could have also formed by pericyclic extrusion of SO_2 from **46**. We also assumed that the trans-acetoxyphenyl sulfone **47** yielded the o-quinodimethane **50** with the E-acetoxy and Z-phenyl configuration, on the basis of arguments put forward by Sammes et al who have demonstrated that the oxy-substituents always adopted the E-configuration in the o-quinodimethane(54). In methoxy and hydroxy sulfones we also assumed that the methoxy and hydroxy substituents adopted the E-configuration in the o-quinodimethanes. The reaction products, their structures and yields are given in scheme 1 and 2.

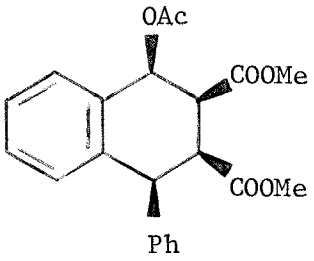
Scheme 1

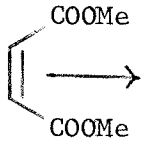


49

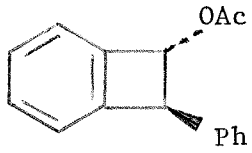
54 (90%)



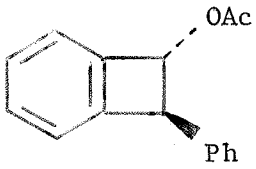


49 + 

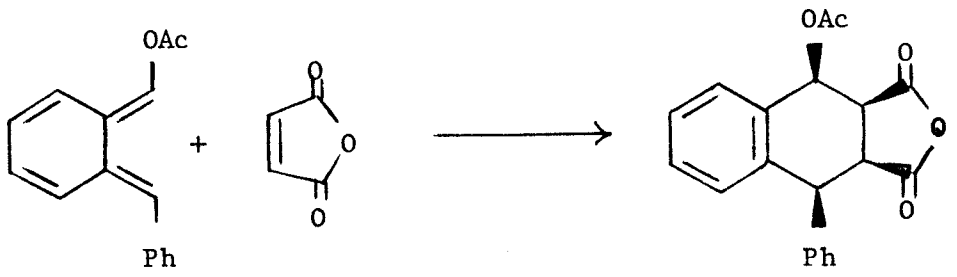
55 (43%) + **56** (18%)



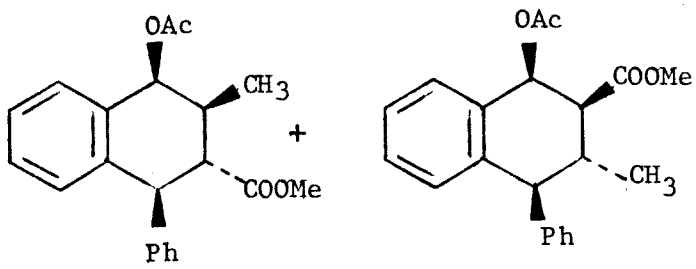
57 (20%)

49 

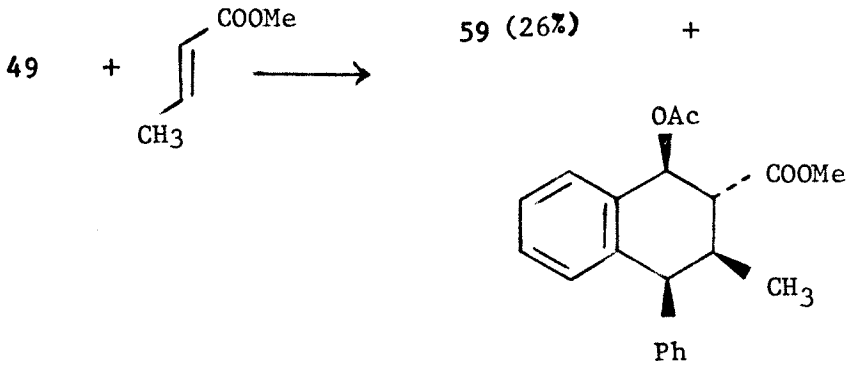
57 (76%)



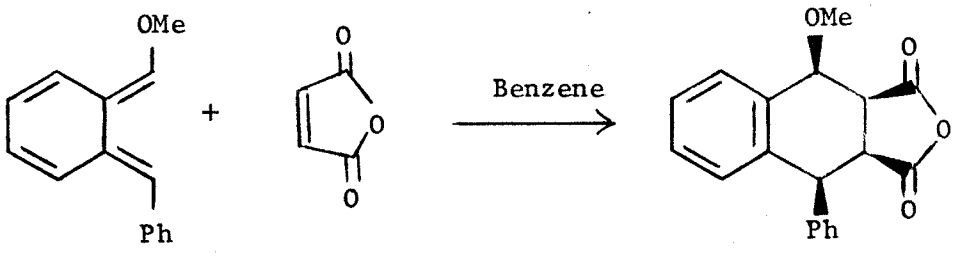
49 58 (90%)



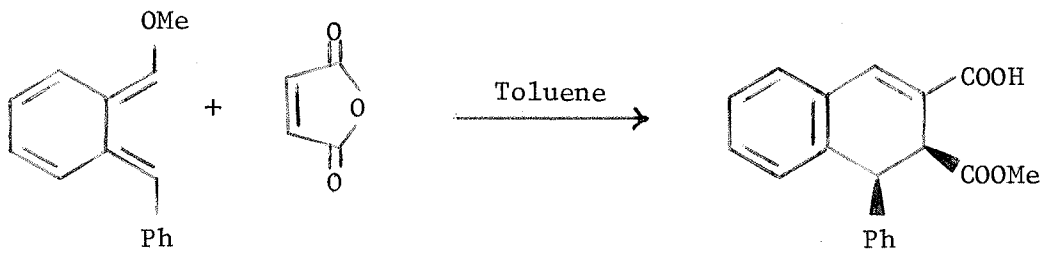
59 (26%) + 60 (27%)



61 (8%)

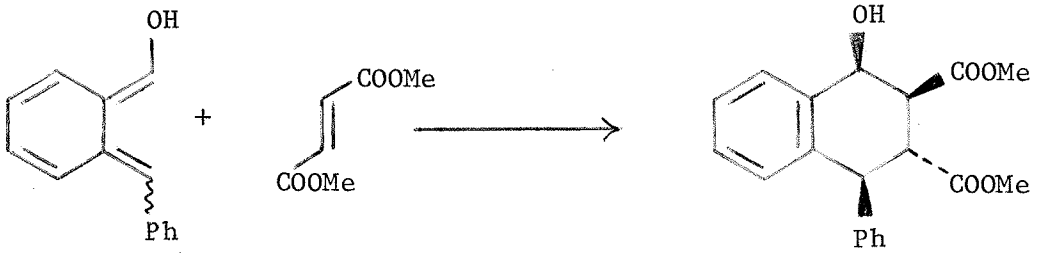


51 62 (98%)



51

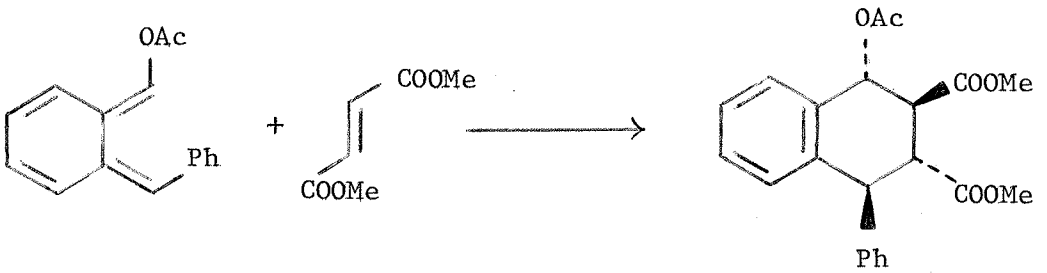
63 (95%)



52/53

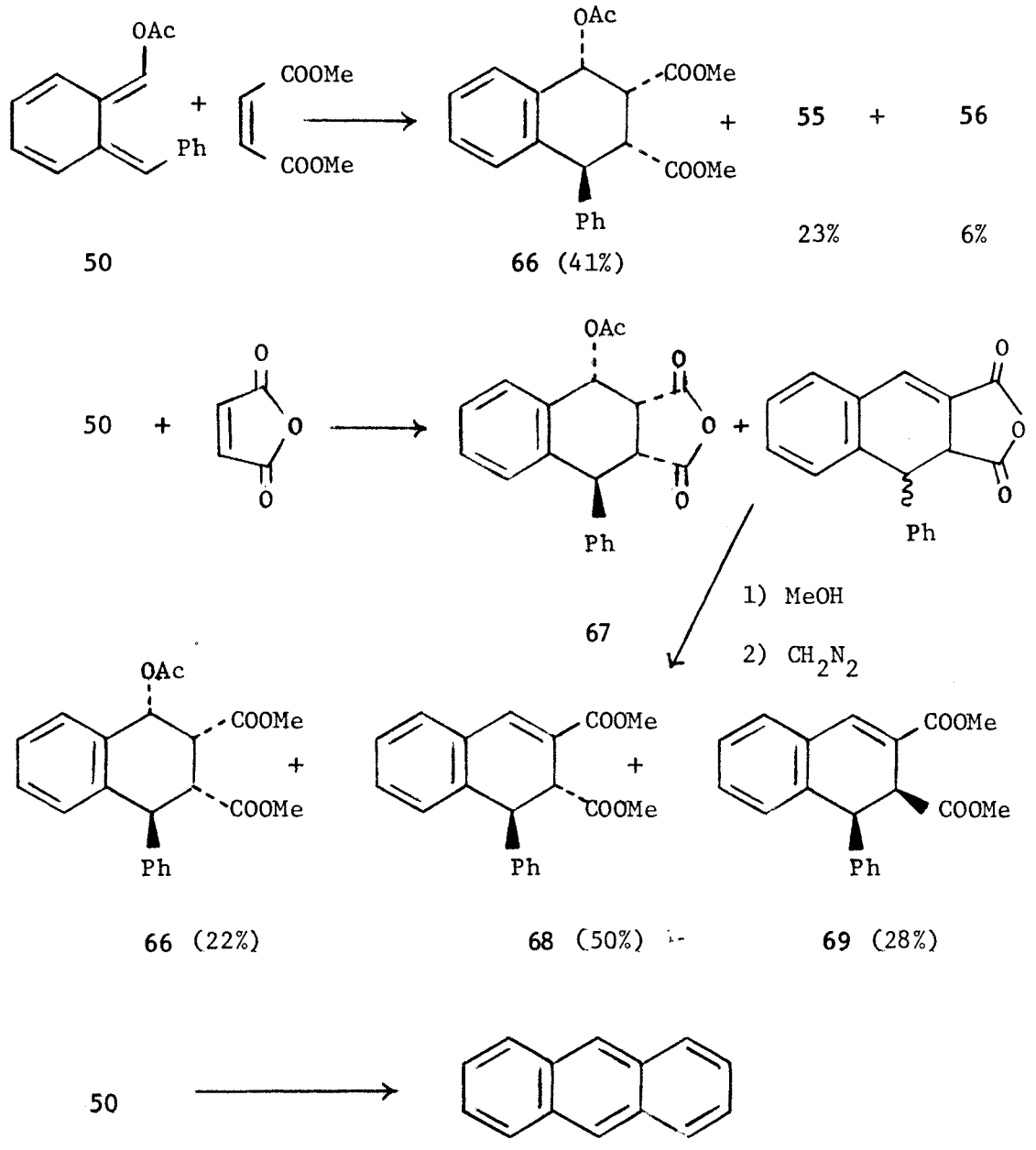
64 (46%)

Scheme 2



50

65 (94%)



The reaction conditions for cycloadditions are given in table 1.

The structures of the products were determined primarily on the basis of 300 MHz ^{1}H NMR, IR and mass spectra. The ^{1}H NMR data are given in table 2.

TABLE 1

Reaction Conditions for Cycloadditions.

Reactant	Diene	Solvent	Temperature(°C)	Time (hrs)
5	DMF	T	140	5
5	DMM	T	180	5
5	MA	T	140	5
5	MC	T	140	10
5	-	T	110	15
16	DMF	T	180	5
16	DMM	T	180	18
16	MA	T	180	11
16	-	X	140	23

Key:

DMF = dimethylfumarate

DMM = dimethylmaleate

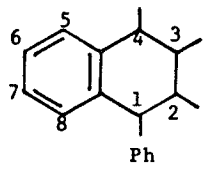
MA = maleic anhydride

MC = methyl crotonate

T = toluene

X = xylene

TABLE 2
Chemical Shifts and Coupling Constants.



	54[a]	55[a]	56	58	59[d]	60[d]	61[d]	65[a]	66	
H(1)	4.02	5.04	4.39	4.45	4.33	3.58	4.14	4.37	4.95	
H(2)	3.82	3.76	3.68	3.98	3.10	2.71	2.55	3.48	3.43	
H(3)	3.56	2.72	3.38	4.14	2.42	2.80	2.84	3.60	3.48	
H(4)	6.69	6.93	6.63	6.14	6.13	6.38	6.47	6.80	6.49	
OCH_3	3.22	3.13	3.43	-	3.72	3.54	3.72	3.45	3.62	
OCH_3	3.78	3.21	3.77	-	-	-	-	3.65	3.67	
OAc	1.60	1.67	2.04	2.27	2.12	2.10	2.19	2.18	2.10	
CH_3	-	-	-	-	1.04	0.97	0.82	-	-	
Arom	6.8-7.2[b]	6.8-7.2[c]	7.12-7.55	7.1-7.6	6.7-7.45	6.7-7.45	6.7-7.45	7.1-7.4	6.9-7.2	
H(8)	6.71	-	7.13	-	-	-	-	-	-	
$J_{1,2}$	11.26	7.24	5.32	5.59	11.20	10.28	6.6	10.69	10.69	
$J_{2,3}$	12.26	4.49	4.1	9.99	-	12.16	2.8	10.76	10.76	
$J_{3,4}$	3.16	4.99	4.26	7.45	3.00	2.72	9.39	8.85	8.85	
$J_{x,CH}$	-	-	-	-	6.75	6.20	6.85			
Sol	C_6D_6	C_6D_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	C_6D_6	$CDCl_3$	

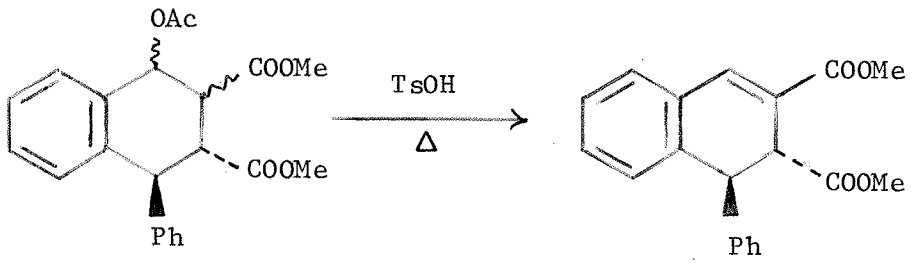
[a] for spectrum in $CDCl_3$ see reference (9)

[b] also 7.47 (d,1H)

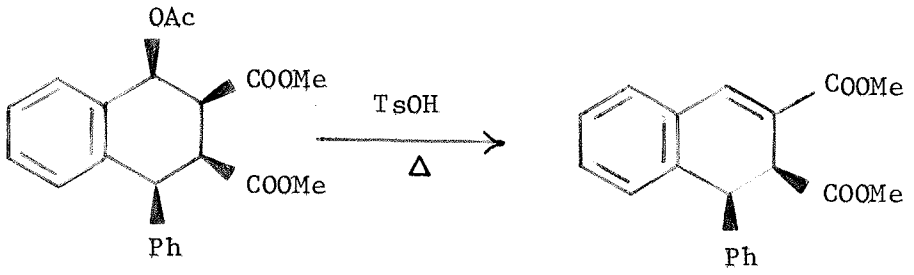
[c] also 7.31(d,1H), 7.45(d,1H)

[d] 59, 60 and 61 were not individually isolated

The structures were further confirmed by elimination of acetic acid from the acetoxy cycloadducts to form the 1-phenyl-2,3-dicarbomethoxy-1,2-dihydronaphthalenes **68** and **69.**



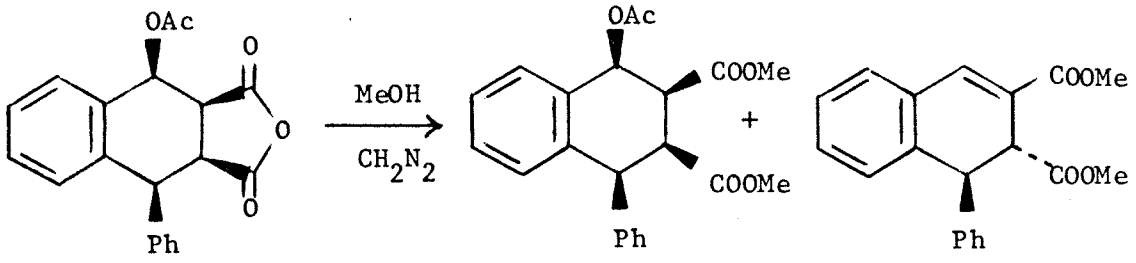
54, 55, 65, 66 68



56 69

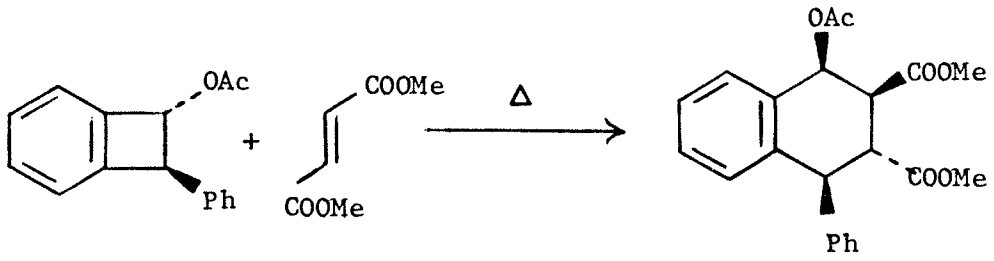
Thus **54**, **55**, **65** and **66** were converted to the known 1,2-trans-alkene **68**(70) and the cycloadduct **56** was converted to the cis-alkene **69.** The structure of the cis-alkene **69** was determined by ^{1}H NMR, IR and exact mass/mass spectrometry. The structure of the maleic anhydride adduct **58** was determined by ^{1}H NMR, IR and mass spectrum as well as elemental analysis. It was further confirmed by treatment with methanol (reflux)

followed by treatment with diazomethane, which converted it to the adduct **56** with a small amount of the trans-alkene **68** (25%).



58 56 68

The formation of **68** in the above reaction is unusual but could be due to the presence of a trace of base which could cause elimination as well as epimerisation at the C_2 centre to produce **68**. The benzocyclobutenol acetate **57** which was formed as a minor product from the reaction of **49** and dimethyl maleate and as a major product in the absence of dienophiles was identified by its ^1H NMR, IR, mass spectrum and elemental analysis. It could also be converted to the cycloadduct **54** by heating with dimethyl fumarate, which further confirmed its structure.

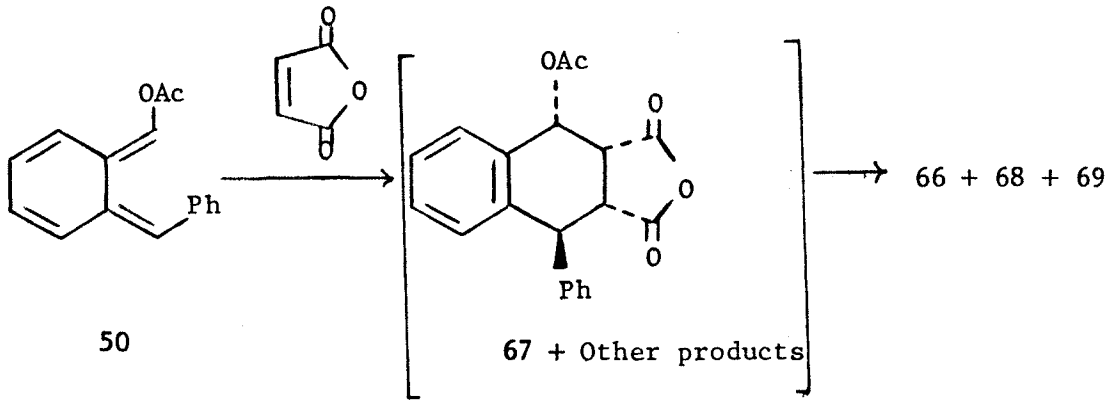


57 54

The trans-1-acetoxy-2-phenyl benzocyclobutene **57** opens in a conrotatory fashion to generate the E,E-α-acetoxy-α'-phenyl-o-quinodimethane, which reacts with dimethyl fumarate to produce the cycloadduct **54**.

The products **59**, **60** and **61**, obtained as a mixture from the reaction of E,E-α-acetoxy-α'-phenyl-o-quinodimethane with methyl crotonate (61% yield), were not isolated individually. Their structures were deduced solely from ^{1}H NMR spectrum of the mixture using decoupling techniques to decipher the spectrum.

The E,Z-o-quinodimethane **50** on reacting with maleic anhydride gave a mixture of products. The mixture, on successive treatment with methanol (reflux) and diazomethane gave **66** (22%), **68** (50%) and **69** (28%). The major product was the 1,2-trans-alkene **68**, which could be produced by the loss of acetic acid from the cycloadduct **67** prior to treatment with methanol and diazomethane, or from the product **66**, another minor component of the reaction. It appears that the product **66** and its elimination product **68** arise from the initial endo-adduct **67**.



50

67 + Other products

The minor component **69**, the elimination product with 1,2-cis stereochemistry, must have been produced via exo-addition of maleic anhydride to the E,Z-o-quinodimethane.

The E,E-α-methoxy-α'-phenyl-o-quinodimethane gave the half ester **63**, with 1,2-cis stereochemistry, when reacted with maleic anhydride in toluene. However, the cycloadduct **62** was obtained when the solvent was changed to benzene. The E,E- and E,Z-α-hydroxy-α'-phenyl-o-quinodimethane **52** and **53** with dimethyl fumarate gave a mixture of the cycloadduct **64** (46%) and the starting aldehyde.

From the results of the cycloaddition reactions of E,E- and E,Z-o-quinodimethanes with dienophiles it was observed that the most notable features of these reactions was the contrast between stereoselectivity for addition of dimethyl fumarate and dimethyl maleate versus maleic anhydride. For fumarate and maleate the major products always have the 1,2-trans stereochemistry i.e. phenyl and carbomethoxy groups are always trans, irrespective of other factors. On the other hand maleic anhydride added to both E,E- and E,Z-o-quinodimethanes **49**, **50** and **51** to give predominantly the 3,4-cis stereochemistry, i.e. acetoxy or methoxy group and the neighboring carbomethoxy group are cis, a stereochemistry which arises via an endo-transition state, (assuming acetoxy and methoxy groups are in the E configuration in **49**, **50**, and **51**). Only a small amount of the elimination product **69** was observed in the maleic anhydride addition to the E,Z-o-quinodimethane after subsequent treatment of the cycloadduct with methanol and diazomethane. This

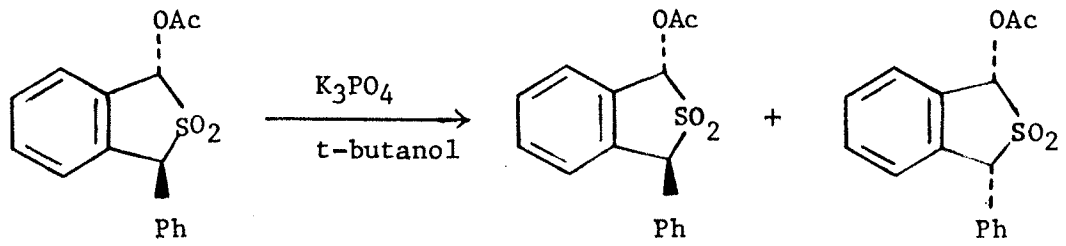
product could arise from the exo-transition state. The reaction of methyl crotonate with E,E-o-quinodimethane gave a mixture of regioisomers. The stereochemistry of addition was 1,2-trans (26%), 3,4-cis (27%) and 3,4-trans (8%). The E,E- and E,Z-α-hydroxy-α'-phenyl-o-quinodimethanes **52** and **53** with dimethyl fumarate also gave primarily the endo-adduct. Only the reaction of dimethyl fumarate with the E,Z-o-quinodimethane **50** gave exclusively the exo-adduct. Dimethyl maleate with the E,E-o-quinodimethane **49** also gave exo-adduct as the major product. The phenyl group was the controlling factor which gave exo-adduct with 1,2-trans-stereochemistry except the addition of maleic anhydride. According to frontier molecular orbital theory endo selectivity is controlled by a favourable secondary orbital interaction between the carbonyl group of the dienophile and the o-quinodimethane. However, if large substituents are present in the diene and/or dienophile, the steric interaction also has to be taken into account. Thus in Diels-Alder reactions where the steric interaction is greater than the secondary orbital interaction the reaction may proceed through an exo-transition state. In our studies, the reaction of the E,E-o-quinodimethane with dimethyl maleate and the E,Z-o-quinodimethane with dimethyl fumarate proceeded through an exo-transition state due to the fact that, in these cases the steric interaction is greater than the secondary orbital interaction. Similar results were also observed by other workers(36,70,75).

From the reaction conditions for cycloadditions (Table 1) it should be noted that the formation of E,Z-α-acetoxy-α'-phenyl-o-quinodimethane

50 required a higher temperature than did the E,E-o-quinodimethane **49**. Thus **46** could be converted to **49** and then **57** at 110°C whereas **47** was unaffected at this temperature.

Our attempt to prepare the cis-1-acetoxy-2-phenylbenzocyclobutene from the E,Z-o-quinodimethane did not work. At the high temperature necessary to generate the E,Z-o-quinodimethane it underwent intramolecular ring closure to form anthracene. However, the preparation of the trans-1-acetoxy-2-phenylbenzocyclobutene **57** is of significant synthetic interest, since difficulty in preparing a benzocyclobutenol similar to **57** has been noticed by other workers(23).

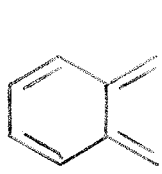
The formation of **55** and **56** from the attempted reaction of **47** and dimethyl maleate was due to the isomerisation of **47** to **46**. Although ZnO, added to the reaction mixture as an acid scavenger, is relatively neutral, it may catalyse the conversion of trans-acetoxy sulfone **47** to the cis compound **46** at high temperature. We have observed that this interconversion of trans to cis sulfone and vice-versa is readily catalysed by potassium phosphate in t-butyl alcohol or triethylamine in benzene. Thus refluxing the trans-acetoxyphenyl sulfone **47** in t-butyl alcohol with K_3PO_4 gave a mixture of the cis (45%) and trans (55%)



47 **47** (55%) **46** (45%)

The cis-sulfone on refluxing with K_3PO_4 in t-butyl alcohol also gave the same mixture. Similar observations were made on refluxing in benzene with triethylamine.

Recently ab initio calculations have been made to find the optimum geometry, charge distribution and molecular orbital co-efficients for o-quinodimethane **1**, α-phenyl-o-quinodimethane **20**, α-hydroxy-o-quinodimethane **14** and α-hydroxy-α'-phenyl-o-quinodimethane **52**(128).



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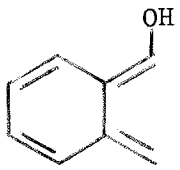

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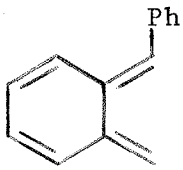

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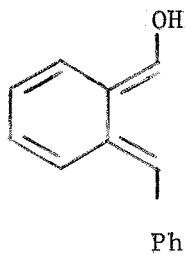
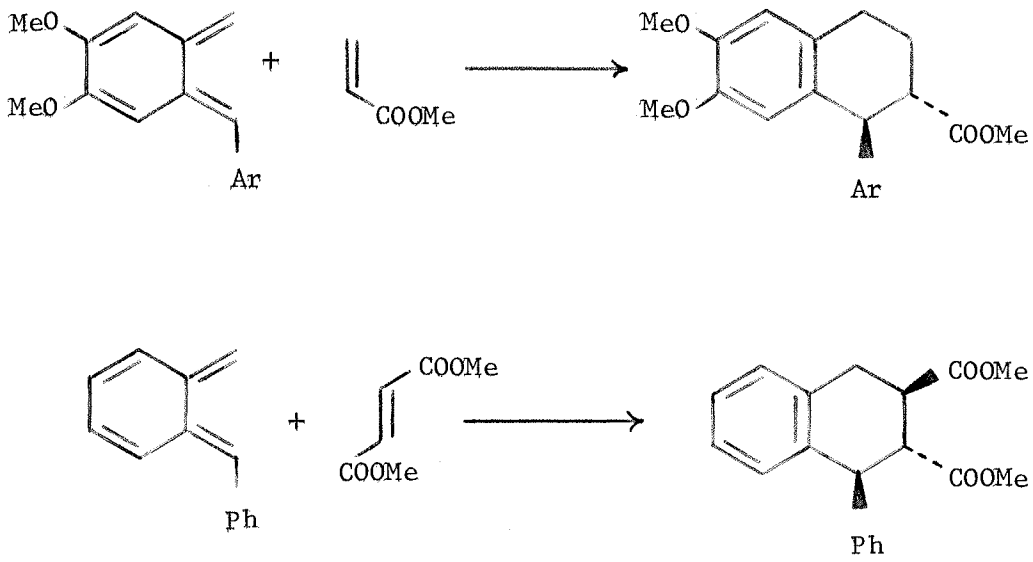
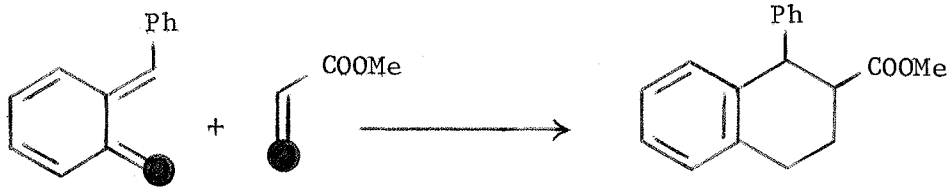


52

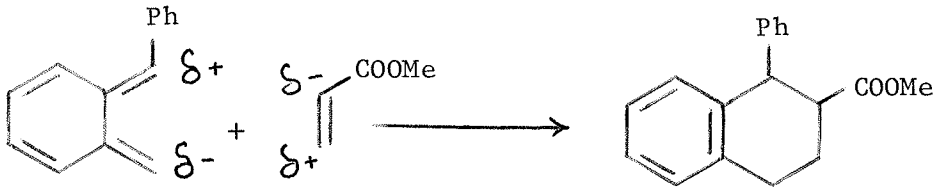
These calculations indicate that an E-α-phenyl substituent is rotated out of the plane of the o-quinodimethane and has a little effect on orbital co-efficients relative to unsubstituted o-quinodimethane **1**. However, it was observed previously that the α-phenyl-o-quinodimethane adds in a head-to-head manner with monoactivated dienophiles(67,70,75).



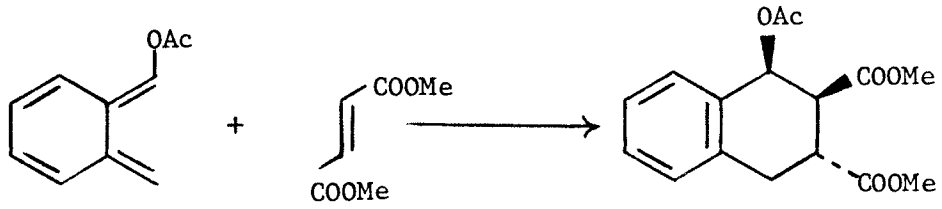
Although Mann et al reported that this head-to-head addition was due to the frontier molecular orbital interaction(67,68), it does not agree with the calculated results. According to the frontier molecular orbital theory, the highest occupied molecular orbital (HOMO) of the diene interacts with lowest unoccupied molecular orbital (LUMO) of the dienophile. The orientation of interaction of the diene with the dienophile is controlled by the size of the orbital co-efficients.



Thus the carbon in the diene with largest HOMO co-efficient interacts with the carbon in the dienophile with largest LUMO co-efficient. In the o-quinodimethane **20** the orbital co-efficients on C_1 and C_4 are almost equal, therefore regioselectivity is not expected, and a mixture of two regioisomers should be formed. Nevertheless the observed regioselectivity can be explained on the basis of polar effects. The <u>ab initio</u> calculation shows that the phenyl group in the E-phenyl-o-quinodimethane decreases the electron density on the carbon atom bearing the phenyl group. Therefore the relatively electron deficient carbon of the o-quinodimethane interacts with the relatively electron rich carbon of the dienophile.



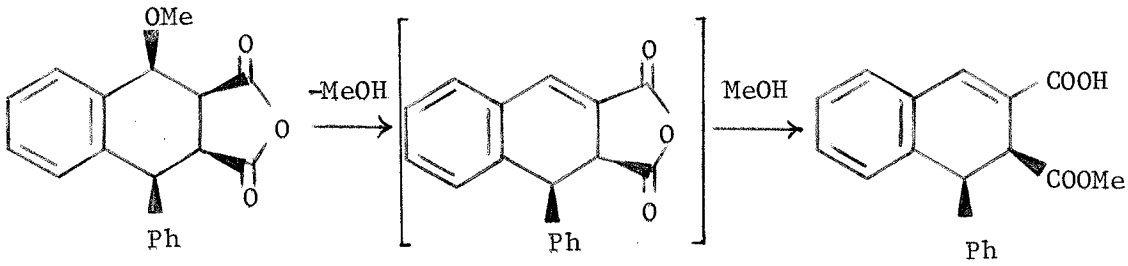
It may also be due to the fact that the α-phenyl-o-quinodimethane exists in the Z-configuration, where orbital factors may be larger and direct the regiochemistry of addition. In the case of α-oxy-o-quinodimethane there are both a polar effect and a secondary and primary orbital effect, all of which favour head-to-head addition. The secondary orbital effect should be large (large coefficient on C_2) and should favour a 1,2-<u>cis</u>-adduct stereochemistry when dimethyl fumarate is added. The α-oxy-o-quinodimethanes do indeed give <u>endo</u> head-to-head addition as predicted(36,70).



An analogous case dealing specifically with dimethyl fumarate addition to 1-substituted dienes has been provided by Kakushima(64). However, in our work with α-oxy-α'-phenyl o-quinodimethanes, maleic anhydride always gave endo-adducts, dimethyl fumarate gave endo-adducts with E,E-o-quinodimethane and exo-adduct with E,Z-o-quinodimethane, and dimethyl maleate gave an endo-adduct with E,Z-o-quinodimethane and an exo-adduct with E,E-o-quinodimethane. Methyl crotonate also gave a mixture of endo- and exo-adduct irrespective of the regiochemistry. Only in two reactions i.e. dimethyl fumarate with the E,Z- and dimethyl maleate with the E,E-o-quinodimethane was exo-addition observed. In view of the out of plane rotation of the α-phenyl group in the E-α-phenyl-o-quinodimethane, it is likely that the preference for exo-addition of the above mentioned reactions is rooted in steric factors.

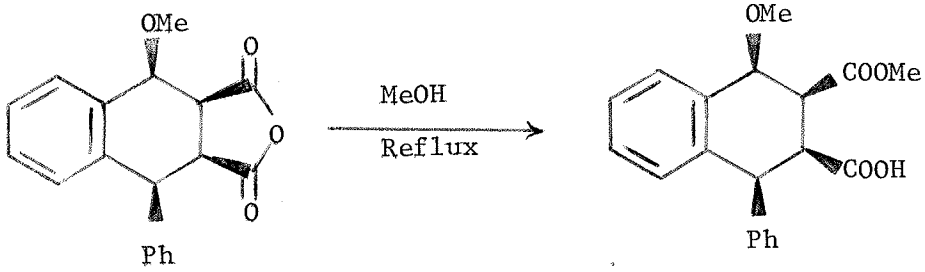
The reaction of methyl crotonate with E,E-o-quinodimethane gave a mixture of two regioisomers i.e. the o-quinodimethane added head-to-head and head-to-tail with the dienophile. This indicates that the directive effects of the phenyl and acetoxy group on the regiochemistry of addition are almost equal.

The addition of maleic anhydride to α-methoxy-α'-phenyl-o-quinodimethane **51** is noteworthy. In toluene, the product was **63**, i.e. an elimination product with the carboxyl group esterified. The product was formed from the cycloadduct **62** by the elimination of methanol. The methanol generated <u>in situ</u> attacked the elimination product **70** to produce **63**.



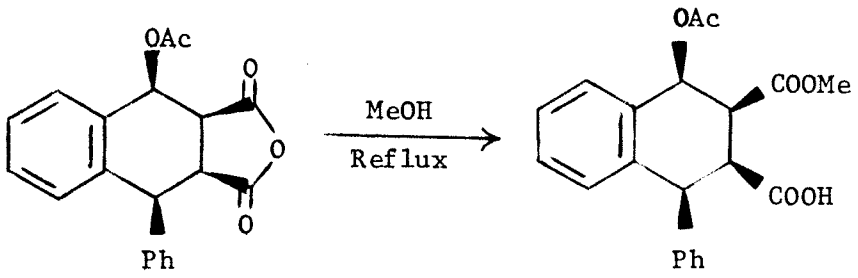
62 70 63

The intermediate compound **70** was not isolated in this reaction. The cycloadduct **62** was prepared in benzene in the presence of ZnO. The product was identified by ^{1}H NMR, IR, and exact mass/mass spectrometry. When the product **62** was refluxed in methanol compound **71** was obtained, which is another half ester.



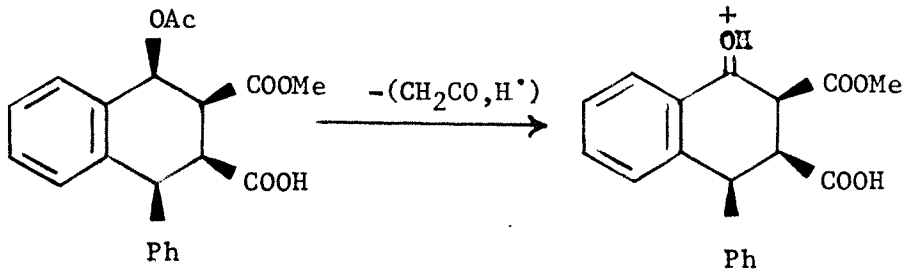
62 71

Similarly when the maleic anhyride adduct with the E,E-actoxyphenyl-o-quinodimethane **58** was refluxed in methanol, compound **72** was obtained.



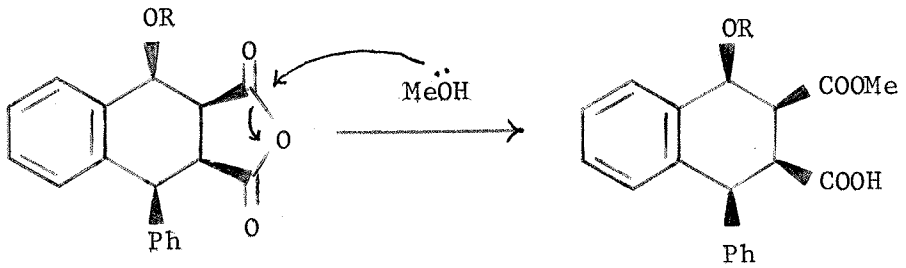
58 72

Compound **72** was characterized by ^1H NMR, IR and mass spectrometry. In the EI mass spectrum the molecular ion was not observed but M-43 was observed, which indicates that the molecular ion was not very stable at the ambient temperature. The loss of 43 mass units can be explained as follows.

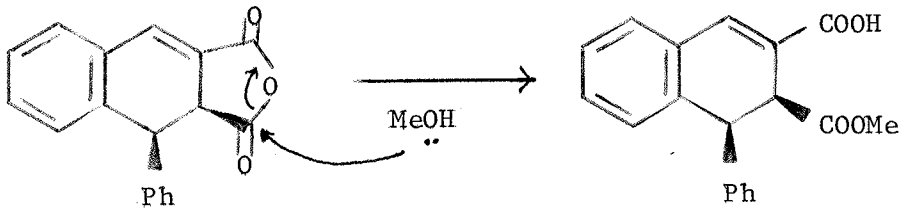


72 m/z 325

The structure of **72** was further confirmed by elimination of acetic acid, which gave the cis-elimination product **73.** It should be mentioned here that the position of carboxyl group in **63** is different than in **71** and **72.** This indicates that the selectivity of the addition of methanol to the maleic anhydride ring is different in the elimination product and the cycloadducts. Methanol attacks at the C_3 in the cycloadduct whereas it attacks at the C_2 carbonyl in the elimination product.



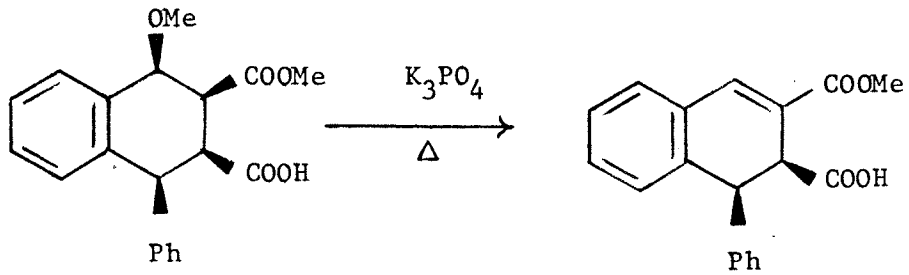
58/62 71/72



70 63

The difference in selectivity in the above two reactions may be due to the fact that in **58** or **62** the C_3 carbonyl carbon is more electrophilic than the C_2 carbonyl. In **70** the C_3 carbonyl is conjugated, therefore the C_2 carbonyl carbon is more electrophilic and methanol attacks at that position.

The compound **71** was converted into **73** by heating with K_3PO_4 in methylene chloride in the presence of water.



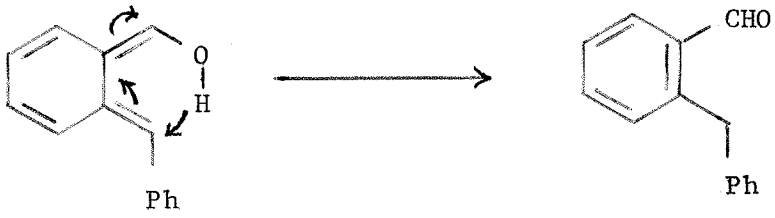
71 73

The ^1H NMR and IR spectra of **63** and **73** were different. The structural difference of these two isomeric compounds was further confirmed by IR spectroscopy. The IR spectrum of **63** gave two strong bands for the carbonyl groups at 1732 cm^{-1} and 1685 cm^{-1}. This compound was converted into its triethylammonium salt by treating with triethylamine. The IR spectrum of the salt gave one strong band at 1730 cm^{-1} two bands at 1610 cm^{-1} and 1382 cm^{-1}. Comparing these IR spectra it appears that the peak at 1732 cm^{-1} remained almost unchanged in the salt, but the peak at 1685 cm^{-1} disappeared, giving new peaks at 1610 cm^{-1}(carboxylate asymmetric stretch) and at 1382 cm^{-1}(carboxylate symmetric stretch). This

observation indicates that the unchanged peak at 1732 cm^{-1} arises from the ester carbonyl group and this frequency is close to the expected value of 1735 cm^{-1}(129). The expected frequency of carboxylic acids is between 1730-1700 cm^{-1}. However, α-ß-unsaturated acids appear at lower frequency(129). Therefore the peak at 1685 cm^{-1} must be due to the α,ß-unsaturated acid, i.e. in **63** the carboxyl group is conjugated at C_3 and the ester group is at C_2 confirming structure **63** as shown. The compound **73** gave a band at 1712 cm^{-1} with a shoulder at 1720 cm^{-1}, possibly both the ester and acid carbonyl groups stretch at close to this frequency. The triethyl ammonium salt gave one strong band at 1712 cm^{-1} and other bands at 1640 cm^{-1}, 1470-1450 cm^{-1}(broad) and 1385 cm^{-1}. In these two spectra the peak at 1712 cm^{-1} remained unchanged and the shoulder at higher frequency disappeared, giving new peaks at 1605 cm^{-1} and 1382 cm^{-1} which are characteristic frequencies for carboxylate anions(129). From this observation it appears that the peak at 1712 cm^{-1} which remained unchanged on salt formation is due to an α,ß-unsaturated ester and the shoulder at 1720 cm^{-1} is due to a saturated carboxylic acid. These data thus confirm the structure of **73** as shown.

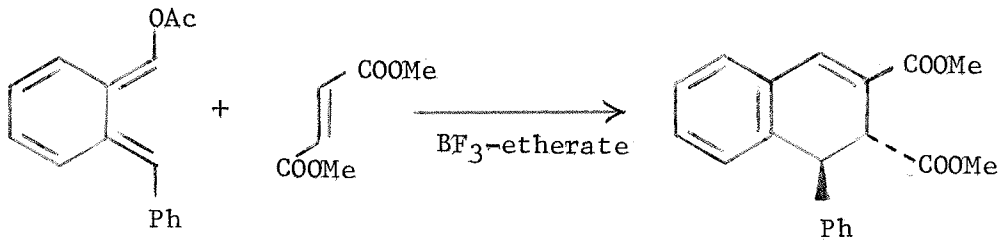
The thermolysis of α-hydroxy-α'-phenyl-sulfones with dimethyl fumarate gave a mixture of cycloadduct **64** and the starting aldehyde. The major product was the cycloadduct **64** with a hydroxyl group at the C_4 position. It is important to mention that in this experiment a mixture of cis- and trans-hydroxy sulfone was used. However, only one cycloadduct was obtained, which is surprising. The reason may be due to

the fact that trans-hydroxy sulfone requires a higher temperature to generate the E,Z-o-quinodimethane as was observed for the trans-acetoxy sulfone. Therefore only the cis-hydroxy sulfone reacted to produce the E,E-o-quinodimethane which underwent cycloaddition with the dienophile. We also observed that these oxy-sulfones (at least the acetoxy sulfones) were interconvertable, therefore it might also be possible that by the time when cis-sulfone reacted, the trans-sulfone was converted into cis and as a two step process all of the sulfone reacted to produce only one cycloadduct. The other product in this reaction was the starting aldehyde. This aldehyde could be formed from the highly reactive α-hydroxy-α'-phenyl-o-quinodimethane **52/53** by abstracting hydrogen from a trace of water which might be present in the reaction. Another possibility of forming the aldehyde could be from the E,Z-o-quinodimethane which can undergo 1,5 hydrogen shift to form the aldehyde.



However, according to Sammes et al the formation of E,Z-o-quinodimethane is not very common. In some reactions of acetoxyphenyl o-quinodimethane we also observed the formation of aldehyde in small amounts.

The use of a Lewis acid catalyst in the Diels-Alder reaction is common, and enhances rate, regiochemistry and endo-selectivity(77,130-135). In an attempt to use a Lewis acid as a catalyst in the Diels-Alder reaction of o-quinodimethane, BF_3 etherate and $TiCl_4$ were used. In the presence of BF_3 etherate the product obtained was the elimination product **68**.

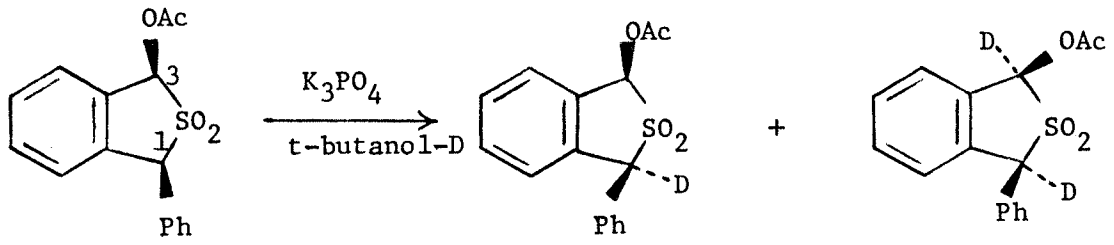


68

In the $TiCl_4$ catalysed reaction the product was anthracene. From these results it appears that $TiCl_4$ did not catalyse the reaction at all and that BF_3 etherate might catalyse the reaction but it also catalysed the elimination reaction. Thus the use of Lewis acid catalysts in the Diels-Alder reaction of o-quinodimethane was not pursued further.

In order to compare the acidity of the two hydrogens in the cis-acetoxyphenyl sulfone **46** we carried out a deuterium exchange experiment

in t-butyl alcohol-D in the presence of K_3PO_4. After one hour refluxing the sulfone **46** in t-butanol-D with K_3PO_4, the ^1H NMR spectrum showed that H_1 was totally exchanged and H_3 was partially exchanged.



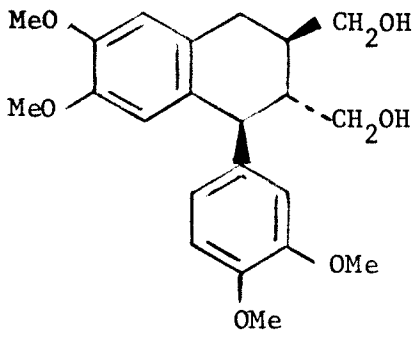
46

This observation indicates that H_1 is more acidic than H_3. Epimerization was also observed in this experiment.

From the results of our study of o-quinodimethanes it may be concluded that Diels-Alder reaction of both the E,E- and E,Z-o-quinodimethanes follow the endo rule except in two reactions, where the steric interaction is greater than the secondary orbital interaction. The directive effects of the acetoxy and phenyl group on the regiochemistry of addition are almost equal. Lewis acid catalysts are not useful in the Diels-Alder reactions of o-quinodimethanes. Concerning acetoxyphenyl sulfone i.e. 1-phenyl-3-acetoxybenzothiaphene-2-2-dioxide, the dibenzylic hydrogen H_1 is more acidic than H_3.

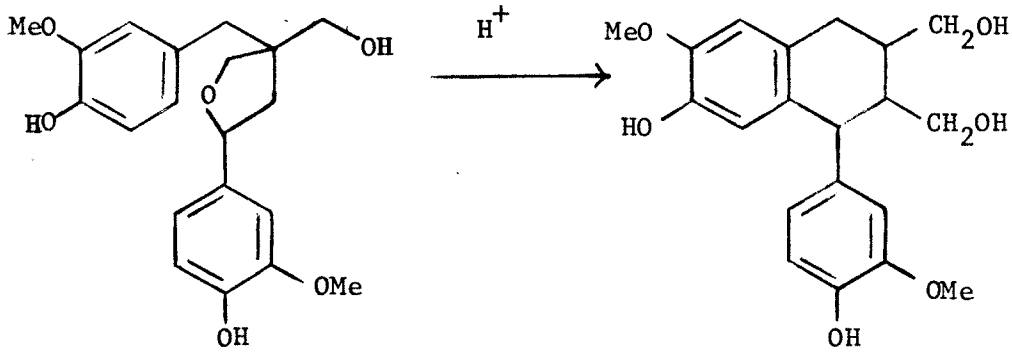
3.2 Asymmetric synthesis of (+)-isolariciresinol dimethyl ether

An asymmetric synthesis of (+)-isolariciresinol dimethyl ether **48** has been carried out in nine steps in 13% yield and 83% enantiomeric excess.



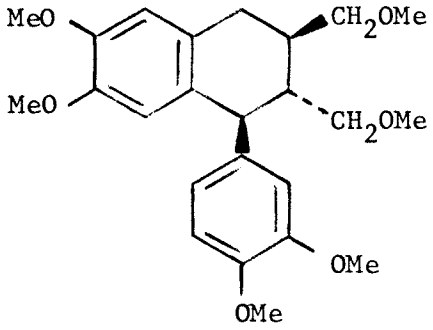
48

Laricіresinol **74** has been isolated from the phenolic resins, collected from European larches growing in County Durham, (U.K.). The resin exudes from wounds(136).

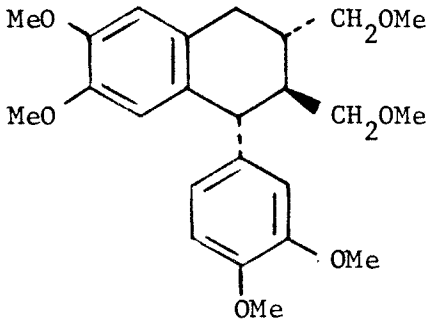


74 **75**

Isolariciresinol **75** was prepared from lariciresinol by boiling with aqeuous formic acid, and then converted to isolariciresinol dimethyl ether **48**, by treatment with dimethyl sulfate and NaOH(136). Isolariciresinol tetramethyl ether **76** is enantiomeric with phyltetralin **30**, which has been isolated from Phylanthus plants(137). Phylanthus plants were used for the treatment of jaundice, asthma and bronchial infections (120,137).



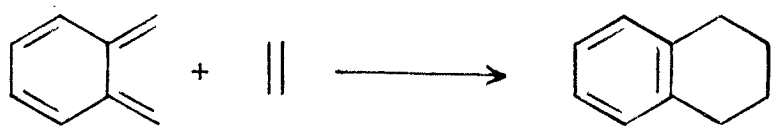
76



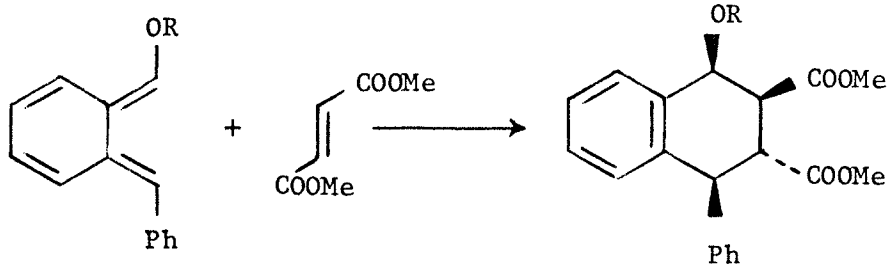
30

The lignan (+)-isolariciresinol dimethyl ether was prepared from α-conidendrin dimethyl ether(138) and the racemic isolariciresinol dimethyl ether and phyltetralin have been synthesised by Mann et al(68). However, an asymmetric synthesis of (+)-isolariciresinol dimethyl ether has not been reported. Therefore an asymmetric synthesis of (+)-isolariciresinol dimethyl ether was planned in order to demonstrate that the asymmetric addition to an o-quinodimethane is applicable to the synthesis of a typical lignan.

It is well known that the tetralin ring system can be easily prepared by the Diels-Alder reaction of an o-quinodimethane with a dienophile(67,70,128).



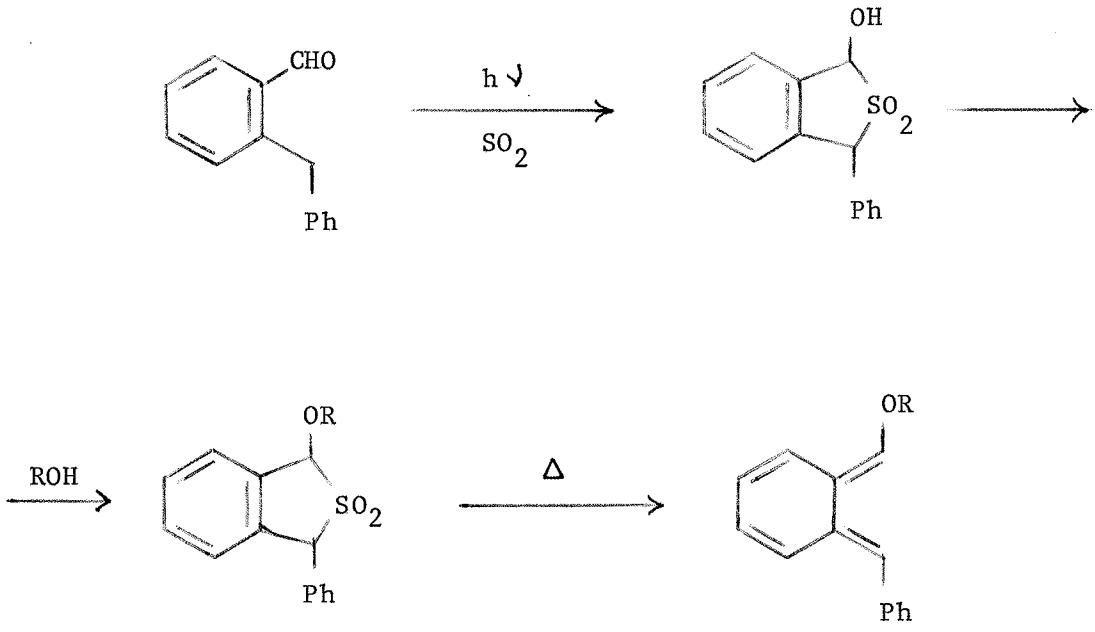
Substituted o-quinodimethanes with substituted dienophiles produce substituted tetralins. Thus when α-alkoxy-α'-phenyl-o-quinodimethanes were reacted with dienophiles such as dimethyl fumarate, 1-phenyl-2,3-dicarbomethoxy-4-alkoxy 1,2,3,4-tetrahydro naphthalenes were obtained.



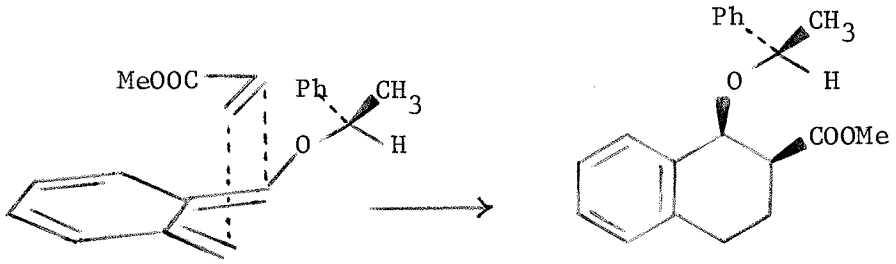
It should be noted here that the addition of dimethyl fumarate to the E,E- and E,Z-α-alkoxy-α'-phenyl or E,E- and E,Z-α-acetoxy-α'-phenyl-o-quinodimethanes gave exclusively the products with 1,2-trans

stereochemistry i.e. the 1-phenyl and 2-carbomethoxy groups are trans to each other(128).

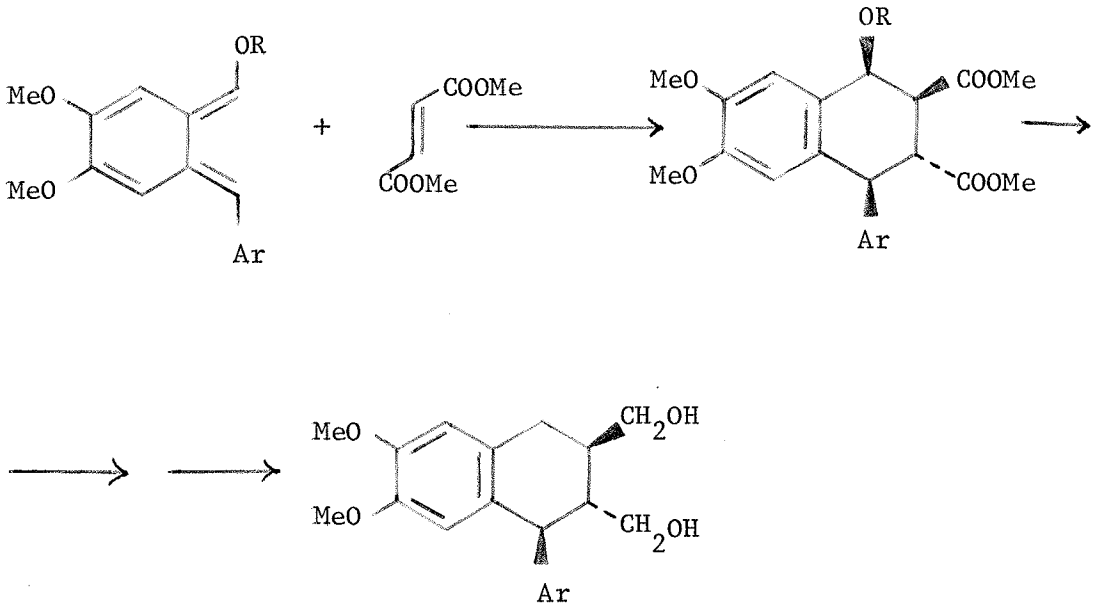
The facile synthesis of α-alkoxy-α'-phenyl-o-quinodimethanes is well documented(40,69,70).



It has been demonstrated that the use of a chiral auxiliary in an o-quinodimethane can control the face selectivity of the cycloaddition(82,83). Thus when a phenylethyl substituent was used in an o-quinodimethane as a chiral auxiliary, it blocked one face of the o-quinodimethane and the dienophile added preferentially to the other face.



Based on the preceding information it seemed feasible to carry out an asymmetric synthesis of (+)-isolariciresinol dimethyl ether by adding dimethyl fumarate to an appropriately substituted E,E-o-quinodimethane as the key step.

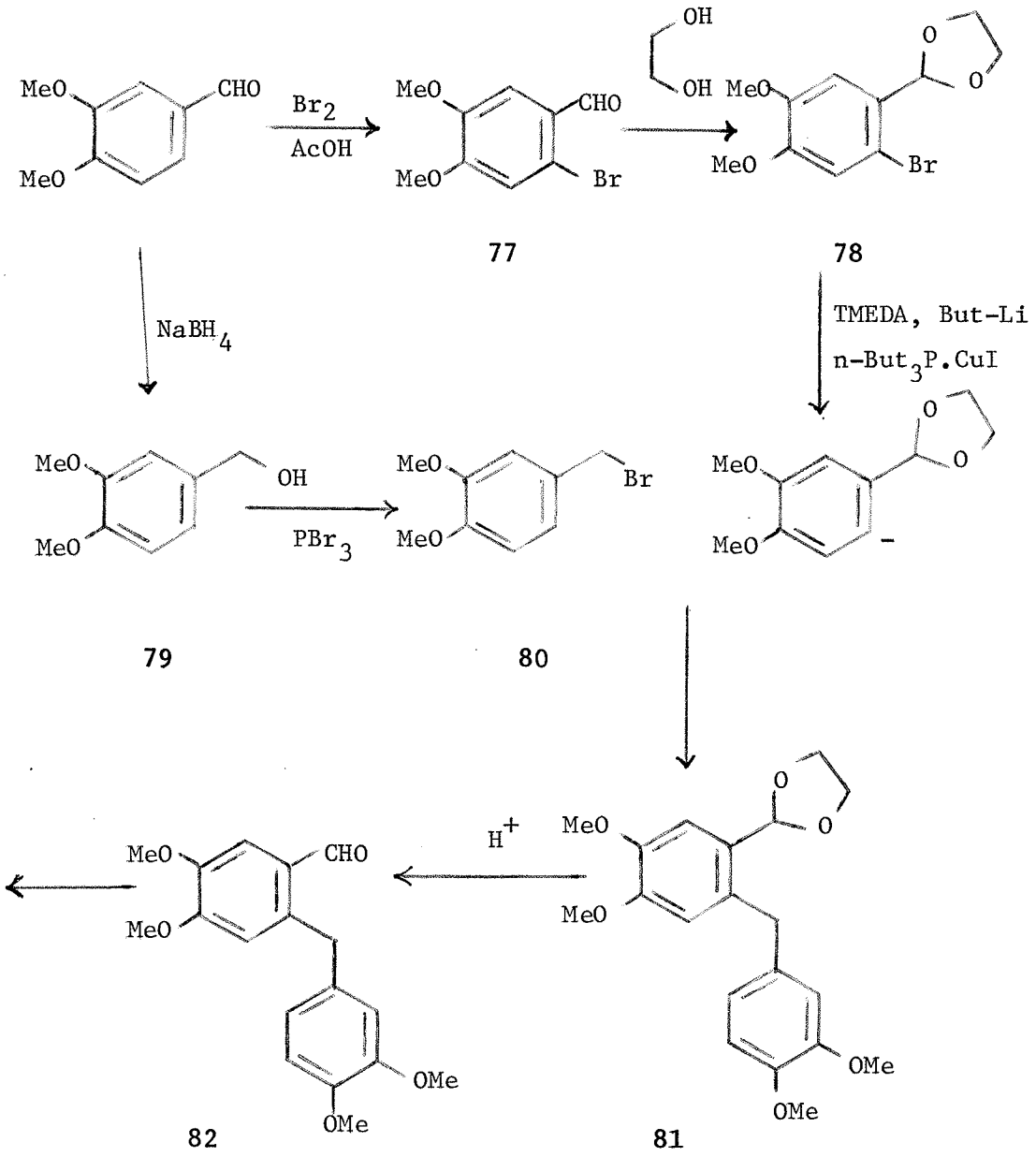


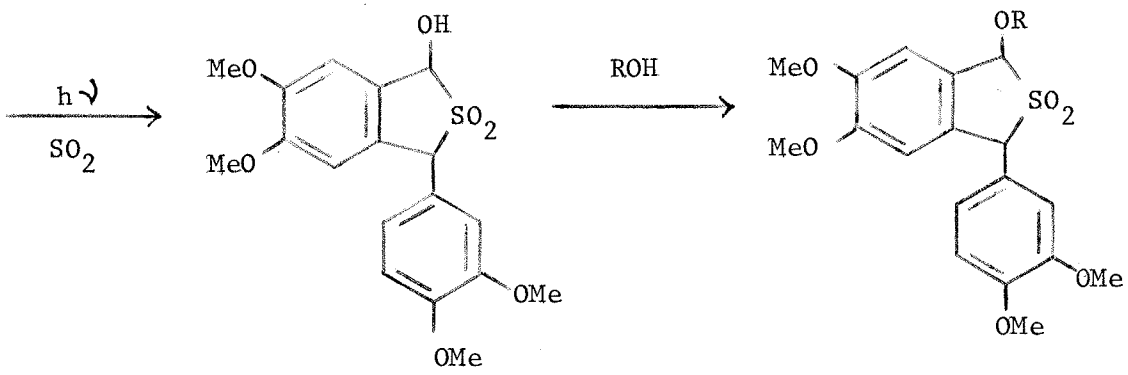
48

Ar = 3,4-dimethoxyphenyl

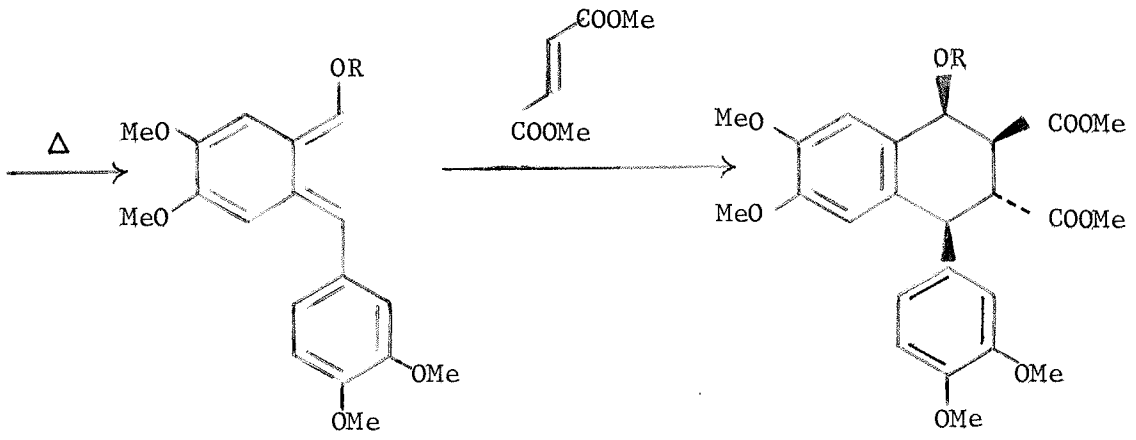
A racemic synthesis of the lignan was also carried out in 33% yield using a mixture of E,E- and E,Z-α-methoxy-α'-aryl-o-quinodimethanes. A general scheme for the synthesis of isolariciresinol dimethyl ether is given below.

Scheme 3

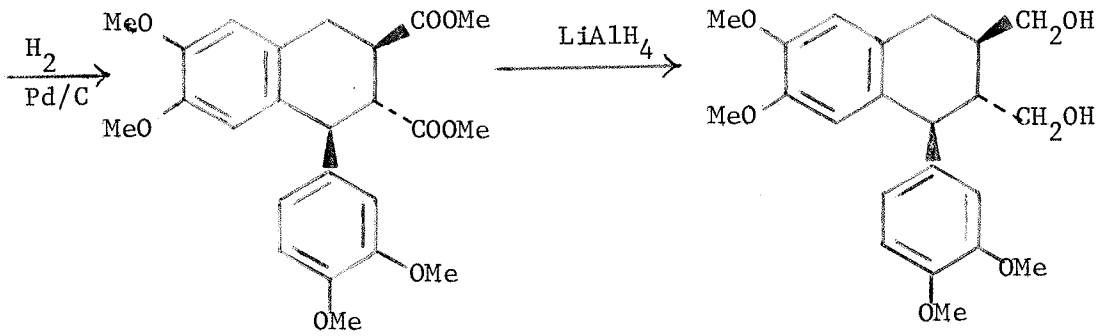




83 84/85



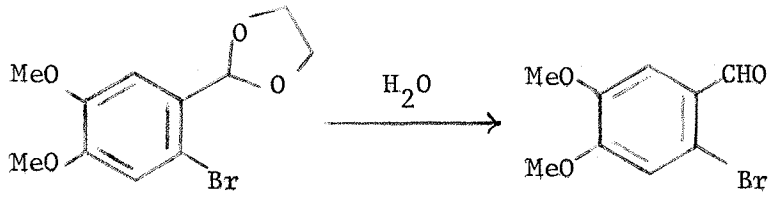
86/87 88/89



90 48

The starting material for this synthesis was veratraldehyde which was commercially available and inexpensive. Veratraldehyde was converted to 6-bromo-veratraldehyde by treating with bromine in acetic acid, according to the literature procedure(139). However, the yield was improved to 80% when two equivalents of bromine were used instead of one equivalent. The compound could be recrystallized from a methanol water mixture and the melting point was consistent with the literature value(139). The ^1H NMR spectrum was identical to that reported in the literature(140).

6-Bromoveratraldehyde ethylene glycol acetal **78** was prepared from 6-bromoveratraldehyde and ethylene glycol in 98% yield following a standard procedure with special caution(47). Traces of acid and water easily hydrolysed the acetal back to the starting aldehyde (exposure to the atmosphere for two weeks).



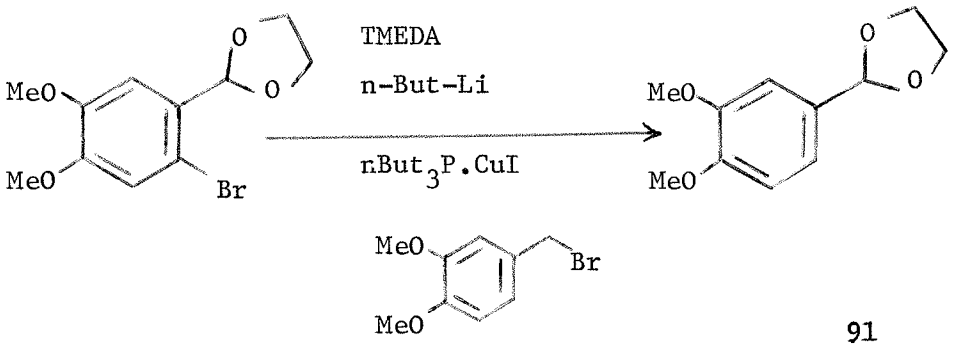
78 77

During recrystallization some of the compound always hydrolysed and therefore it was used without recrystallization. The compound could be preserved in a desiccator at room temperature in the absence of air.

Veratraldehyde was also reduced by $NaBH_4$ to veratryl alcohol **79** as an oil in 100% yield, which was converted to veratryl bromide **80**. Compound **80** was very unstable decomposing to HBr and unidentified products. It was prepared by treating veratryl alcohol with PBr_3 (overnight) followed by evaporation and workup with $NaHCO_3$ The initial product was an oil which solidified after pumping at high vacuum for five hours. The solid compound could be stored for only one week at 0^oC and was generally used immediately in the coupling reaction. Materials that are absolutely free of HBr are essential to the success of the coupling reaction that follows. Elemental analysis of the bromide could not be carried out because of its instability.

Compound **81** was prepared from **78** and **80** by coupling, following a procedure similar to that outlined by Durst et al(69). In contrast to Durst's procedure tetramethylethylenediamine (TMEDA) was used to promote the generation of the ortho-lithiated species. The reaction was carried out at -78^oC in a nitrogen atmosphere. When n-butyllithium was added to the solution of **78** and TMEDA in dry THF, a light yellow coloured solution was obtained. The anion was converted to the organo-copper complex by adding one equivalent of $(nBu)_3PCuI$ complex. Then veratryl bromide in dry THF was added quickly through the serum cap. The sequence of n-butyllithium, $(nBu)_3PCuI$ complex and veratryl bromide addition was carried out as quickly as possible.

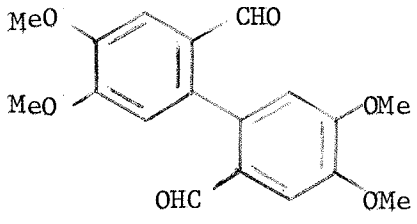
The coupling reaction of **78** and **80** was a challenging step and initial attempts gave very poor yields. In a few coupling reactions only reduced acetal **91** was obtained instead of any coupled product **81**.



91

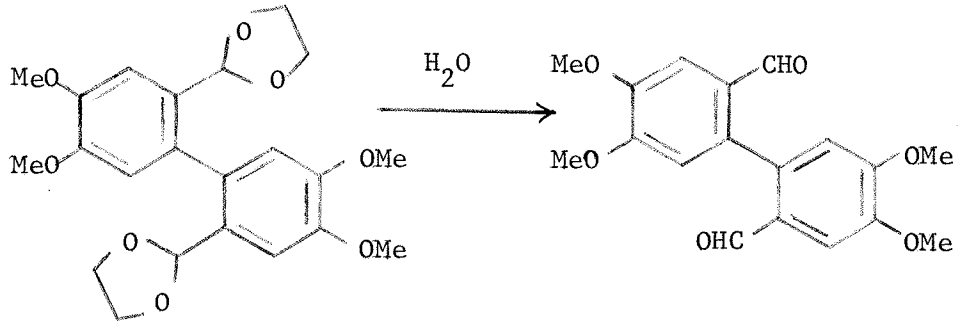
Finally it was understood that the veratryl bromide **80** can very easily lose HBr, especially if stored for a long time. This acid destroys the highly reactive anion by protonation. The metalated acetal was also very unstable even at -78°C. Therefore the yield of this reaction was variable. With care, the highest yield of coupled product obtained was 76% based on ^{1}H NMR integration. The remaining 24% was mainly reduced acetal **91**.

From this coupling reaction trace amounts of two other byproducts were isolated. One of these compounds was identified as a dimer of veratraldehyde, compound **92**.



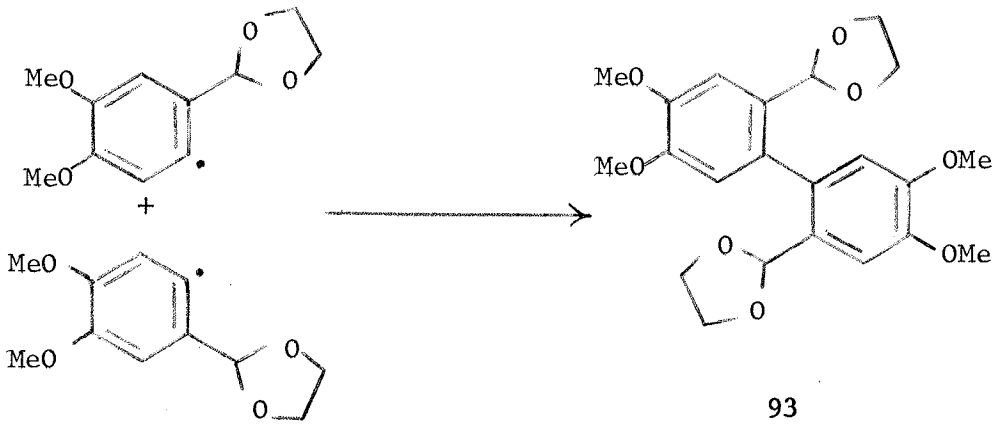
92

This compound was obtained after chromatograhpy of the hydrolysed product from the coupling reaction. Therefore the dimer must arise from the dimer acetal **93.**



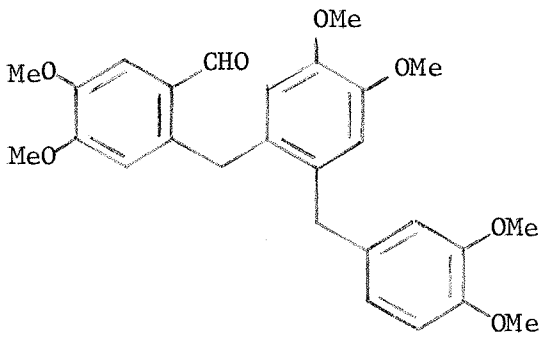
93 92

The formation of the non-isolated compound **93** was possibly preceded by radical coupling. During the generation of the metalated acetal from **78**, some radicals were formed, which coupled with each other to form **93.**



93

The other byproduct was tentatively assigned structure **94**.

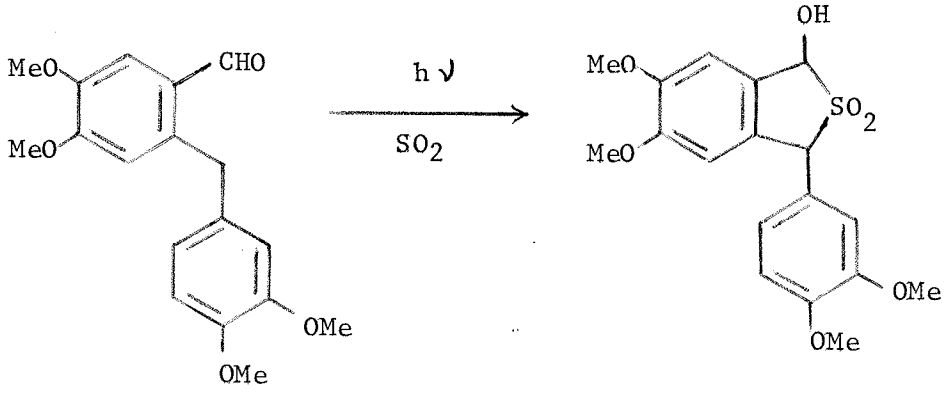


94

The molecular ion M^+ of the compound **94** was 466 consistent with the above structure. ^1H NMR and ^{13}C NMR spectra were reasonably consistent with the compound as **94**. TLC showed that the compound was not perfectly pure and because of this the NMR spectra were not completely unambiguous. However, as the compound was isolated in a very small quantity, further attempts at purification and characterization were not pursued.

Hydrolysis of **81** in ethereal solution with dil HCl at room temperature gave **82** in 95% yield. The compound **82** could be purified by chromatography followed by recrystallization.

The hydroxy sulfones were prepared following the standard procedure(40,69,70). Thus when the aldehyde **82** was irradiated in benzene(thiophene free) in the presence of SO_2, the sulfone **83** was obtained as a mixture of cis- and trans-isomers, in 77% yield based on the aldehyde consumed.

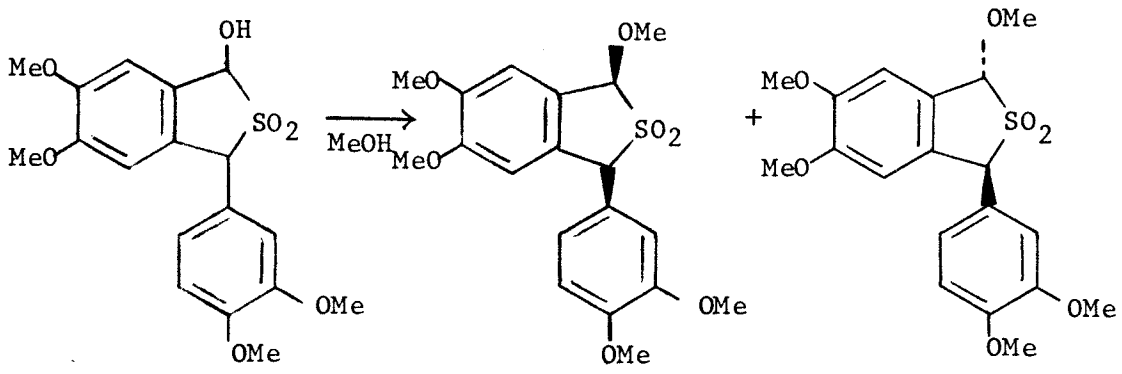


83

The cis- and trans-hydroxy sulfones were not separated, but were identified from the ^1H NMR spectrum. The H_1 and H_3 protons of both cis- and trans-hydroxy sulfones were assigned by ^1H NMR, and from their integration it was observed that 55% of the sulfone was cis-, and 45% was the trans-isomer (see experimental). The H_1 and H_3 of these hydroxy sulfones were identified by comparing the line broadening of their signals. H_1, being coupled with three aromatic ortho-protons of the two phenyl rings, gave a broader peak than the sharper peak of H_3 which coupled with only one aromatic ortho-protons. This line broadening of H_1 was further confirmed for the methoxy sulfones by difference

decoupling techniques which will be discussed later. The time period of irradiation was also important. Thus in a typical reaction when the sample was irradiated for a relatively longer time (9.5 hrs.) the yield was lowered. The optimum time observed was 7 hours. Lower yield of hydroxy sulfone with longer irradiation time may be due to photodecomposition of hydroxy sulfone.

The methoxy sulfone **84** was prepared from the hydroxy sulfone **83** by refluxing in a 50:50 mixture of methanol in methylene chloride containing a catalytic amount of p-toluenesulfonic acid, in 98% yield. The product was a mixture of cis- and trans-methoxy sulfones **84A** and **84B**.

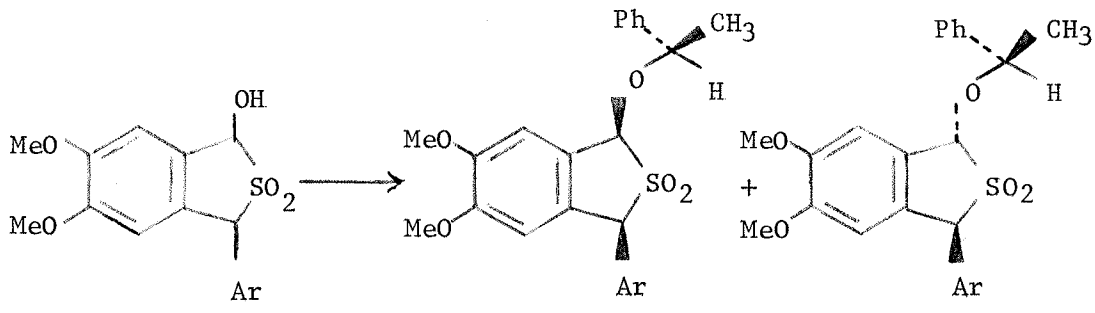


83 **84A** **84B**

The ^{1}H NMR spectrum of the mixture indicated 65% cis- and 35% trans-isomer. The mixture was separated by chromatography using 35% ethyl acetate in hexane as eluent. The NMR spectra of these two isomers were

different. H_1 and H_3 were assigned by a difference decoupling technique, which showed that H_1 coupled with 3 aromatic ortho-protons and H_3 coupled with only one aromatic ortho-proton. H_1 was relatively much broader than H_3 because of this coupling to ortho-protons. It is interesting to note that in the cis-sulfone H_1 resonates at lower field than H_3, whereas in the trans-sulfone the H_1 resonates at higher field than H_3. Thus in the cis-sulfone the chemical shift for H_1 = 5.232 ppm and H_3 = 5.337 ppm, whereas in the trans-sulfone the chemical shift for H_1 = 5.479 ppm and H_3 = 5.306 ppm.

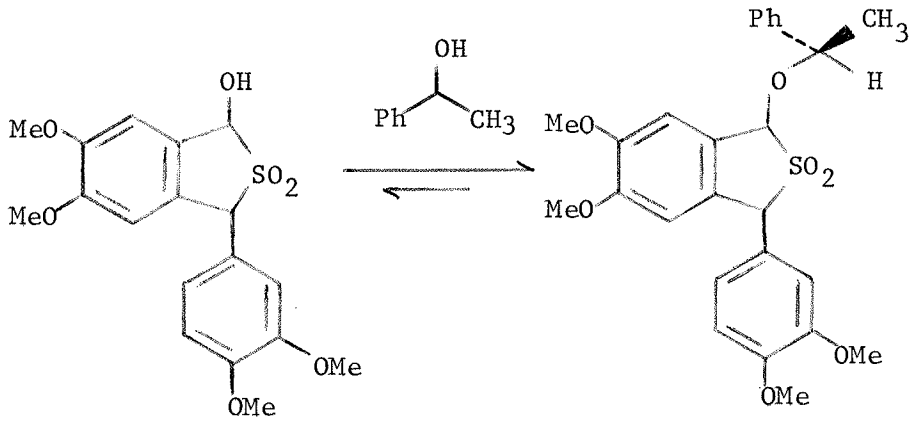
The phenylethoxy sulfone **85** was prepared from the hydroxy sulfone **83** by the treatment of **83** with phenylethyl alcohol in the presence of a catalytic amount of p-toluenesulfonic acid. The reaction conditions were different from those used for preparing the methoxy sulfones. The reaction was carried out at room temperature with an excess of alcohol (15 equivalent) in 6 hours. A mixture of cis- and trans-isomers was obtained in the ratio 86:14.



83 **85A** **85B**

Ar = 3,4-dimethoxyphenyl

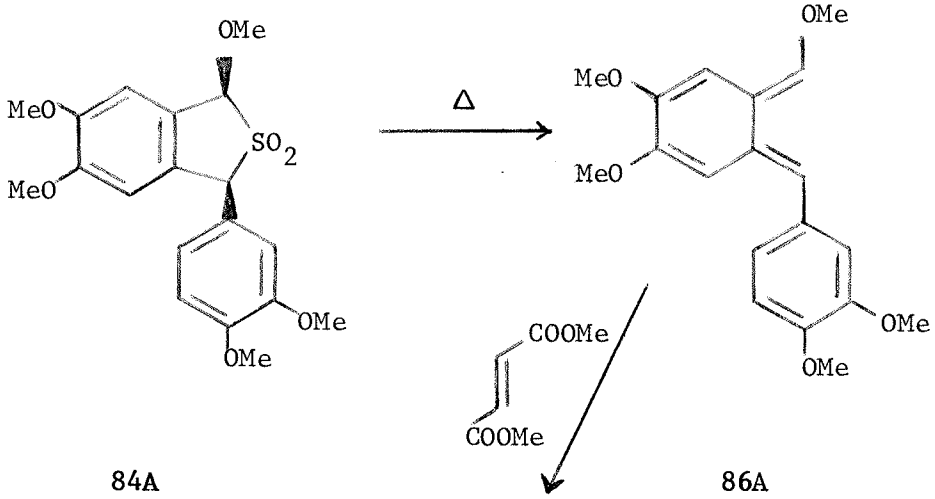
The phenylethoxy sulfone **85** contains 3 chiral centres, therefore 4 diastereomers were possible, 2 cis-diastereomers **85A** and 2 trans-diastereomers **85B**. However, the reaction produced predominantly only one of the cis-diastereomers. Four diastereomers did form when the reaction was worked up after 2.5 hours, 2 cis- and 2 trans-isomers were observed by ^{1}H NMR with the cis-isomers predominating. When less phenylethyl alcohol (2 equivalents) was used no significant amount of the product was observed. It appeared that the amount of alcohol and time of the reaction was important. Thus with excess alcohol and longer time only two diastereomers were formed, although four diastereomers could form at shorter time. This indicates that the formation of phenylethoxy sulfone was a thermodynamically controlled reaction. Kinetically four isomers were formed but they finally formed two thermodynamically more stable isomers, one cis **85A** and one trans **85B** with the cis-isomer predominating.



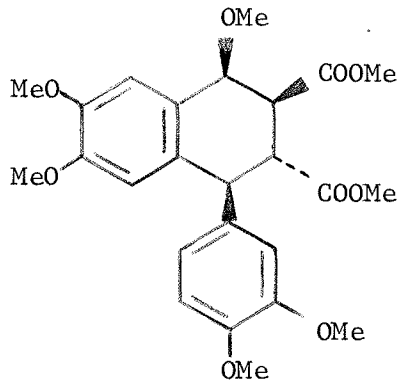
83 85

In some of the preparations of the alkoxy sulfone **85**, a small amount of the starting aldehyde **82** was observed as a byproduct. It was found that the addition of a small amount of anhydrous $MgSO_4$ to the reaction mixture prevented the aldehyde formation.

The cis-methoxy sulfone was treated with dimethyl fumarate in benzene at reflux in the presence of ZnO, to prepare the cycloadduct **88A**. A Diels-Alder reaction took place between the E,E-α-methoxy-α'-aryl-o-quinodimethane **86A**, generated from the cis-sulfone **84A**.



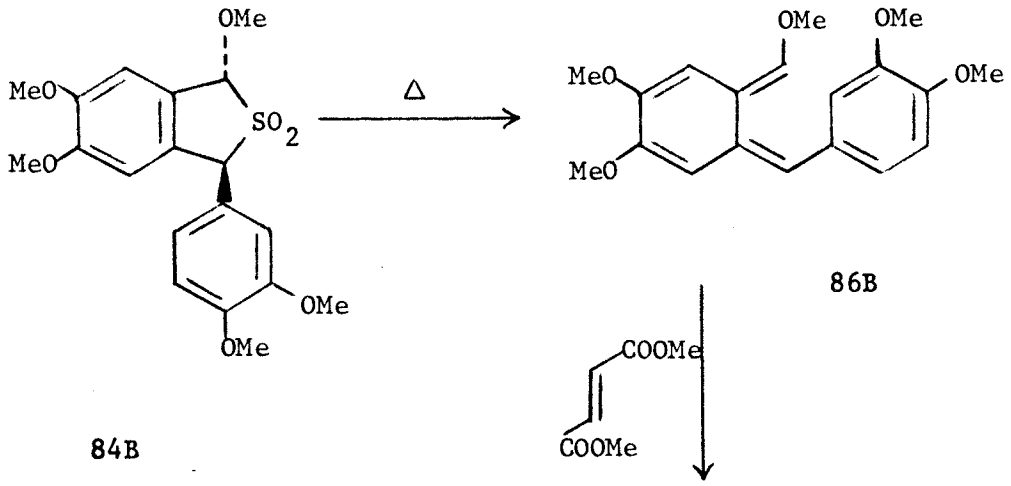
84A **86A**

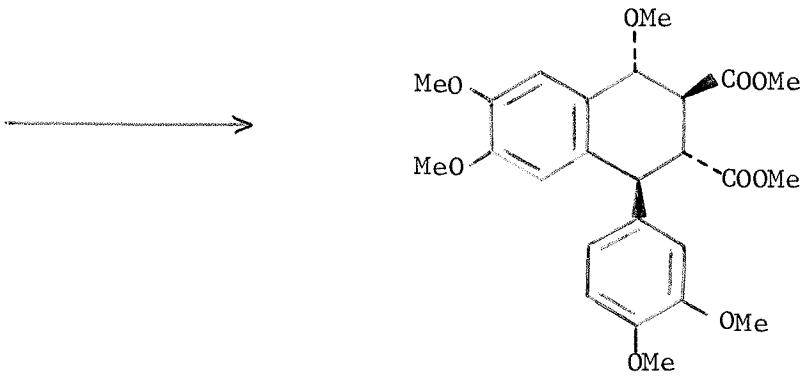


88A

In this reaction only one product was formed which indicated that dimethyl fumarate added stereospecifically to the o-quinodimethane **86A**. The structure of **88A** was assigned by ^{1}H NMR spectrum as the 1,2-trans-2,3-cis-3,4-cis configuration. This result allowed assignment of the cis geometry to the methoxy sulfone **84A**, since only cis-sulfone would be able to produce the E,E-o-quinodimethane **86A**. The alternative Z,Z configuration for **86A**, also attainable by pericyclic extrusion of SO_2 from **84A** was considered unlikely for steric reasons.

The racemic synthesis of isolariciresinol dimethyl ether (+/-)-**48** involved the Diels-Alder reaction of a mixture of E,E- and E,Z-α-methoxy-α'-aryl-o-quinodimethanes with dimethyl fumarate. Thus the mixture of cis- and trans-methoxy sulfones **84** was thermolysed with dimethyl fumarate without separation. On the basis of analogy to my earlier work(see page 57), the trans-sulfone **84B** should generate the E,Z-o-quinodimethane **86B** which would react with dimethyl fumarate to give presumably the cycloadduct **88B**.

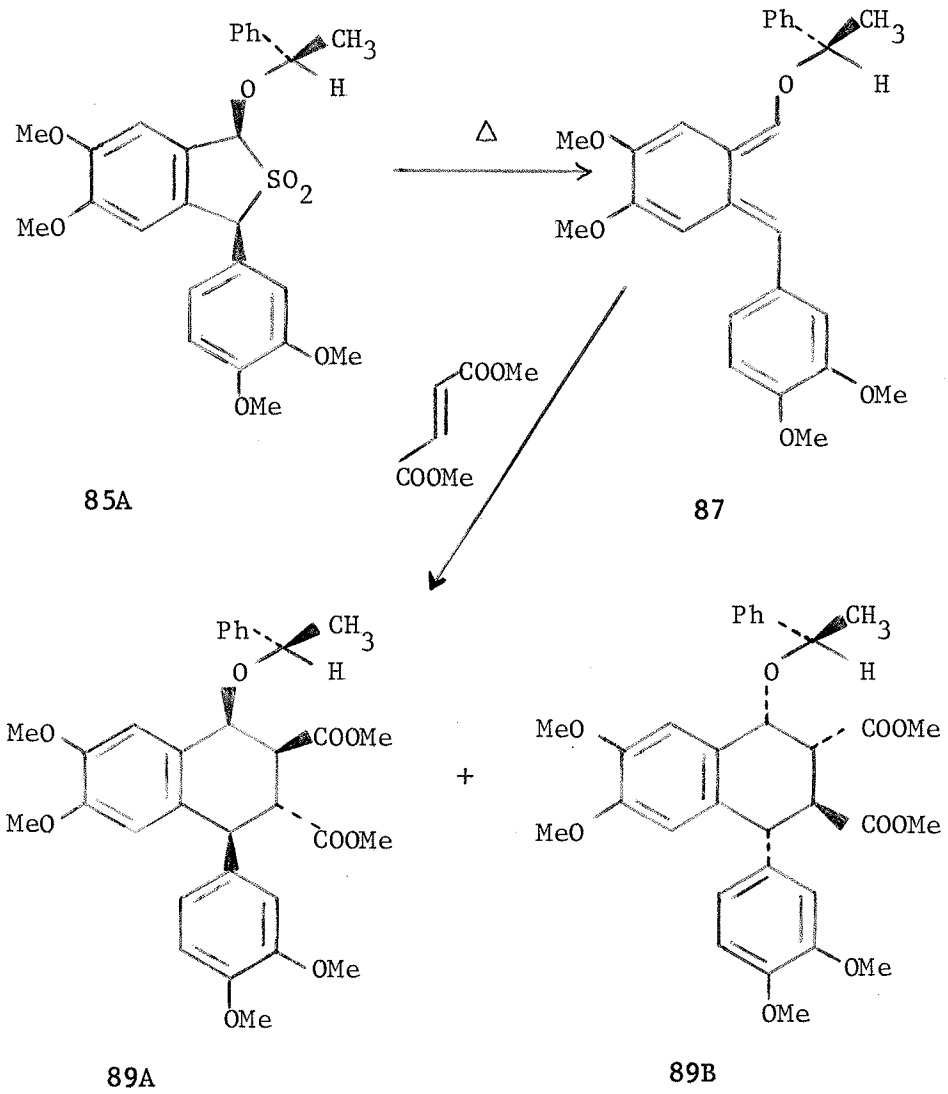




88B

However, after hydrogenolysis, both **88A** and **88B** should give the same product **90**. This was found to be true as hydrogenolysis of the mixture of cycloadducts gave only the diester **90**. Compound **90** on treatment with $LiAlH_4$ gave the lignan **48** as a racemic mixture in an overall yield of 33%. The ^1H NMR spectrum of the racemic isolariciresinol dimethyl ether has been recorded and assigned previously(68). Our ^1H NMR spectrum was identical to that published except for the assignment of the CH_2 on C_2 (see experimental). Our assignment of the CH_2 on C_2 was confirmed by difference decoupling techniques.

The Diels-Alder cycloaddition of o-quinodimethane **87** with dimethyl fumarate was also stereospecific to produce the cycloadducts **89A** and **89B**. The E,E-o-quinodimethane **87** was generated from the cis-alkoxy sulfone **85A**.



85A

87

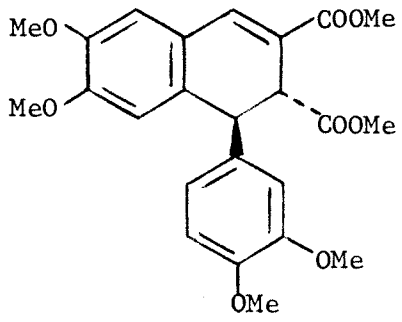
89A

89B

The chiral auxiliary (R)-phenylethoxy group blocked the bottom face of the o-quinodimethane **87** and as a result the dienophile added preferentially to the top face giving the cycloadduct **89A** as the major product. The minor product **89B** was formed by the addition of the dienophile to the more sterically hindered bottom face. The cycloadducts **89A** and **89B** (70:30 mixture) were separated by column

chromatography using 25% ethyl acetate in hexane as eluent. The absolute configuration of the major product **89A** was presumed to be 1S,2R,3S,4S on the basis of the previous model studies(82,83). The major product was hydrogenolysed using Pd/C and H_2 to get the optically active diester **90A**

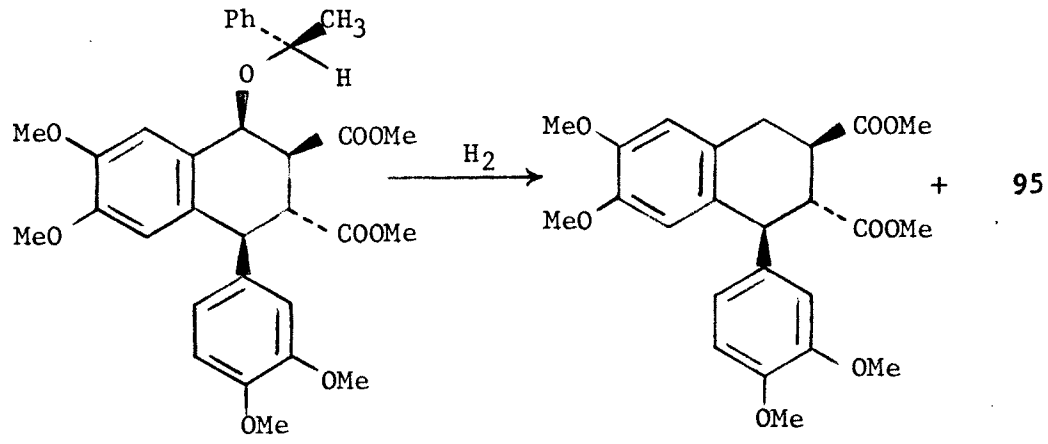
In the cycloaddition reaction of the o-quinodimethane having the chiral auxiliary, a significant amount of the elimination product **95** was observed.



95

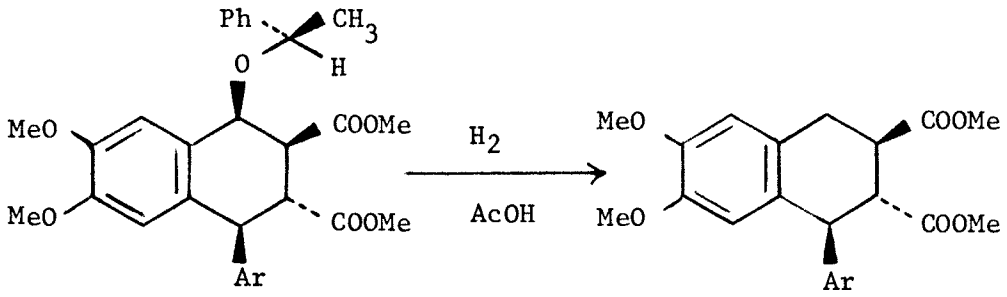
The cycloadduct **89A** (perhaps also **89B**) was very sensitive to acids and the alkoxy group was very labile. Thus when a solution of **89A** in $CDCl_3$ was kept at room temperature for 24 hours, most of the compound was converted to **95**. After this observation a small amount of anhydrous K_2CO_3 was used in the reaction mixture during the cycloaddition reaction in order to prevent the elimination and in fact the addition of K_2CO_3 prevented the elimination.

Compound **90A** was prepared by hydrogenolysis of the major cycloadduct **89A** after separation.



89A **90A**

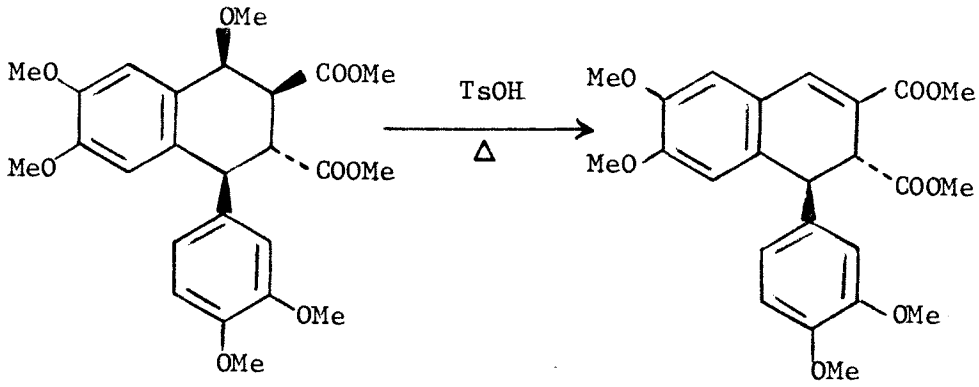
It should be noted here that the cycloadduct **88**, i.e. the cycloadduct from the reaction of methoxy sulfone and dimethyl fumarate, could be hydrogenolysed without causing any elimination. However, the hydrogenolysis of **89A** always produced some elimination product **95**. The reason for this elimination may be due to the fact that the phenylethoxy group was much more bulky and may be lost more easily than the less bulky methoxy group. When the hydrogenolysis of **89A** was carried out in acetic acid, no elimination product was observed. Therefore either the hydrogenolysis rate is much faster in acetic acid or, more likely the elimination occurs followed by hydrogenation of **95** to give the diester **90A** as the only product.



Ar = 3,4-dimethoxyphenyl 90A

The catalytic hydrogenation of compounds analogous to **95** gave a mixture of 2,3-trans- and 2,3-cis-isomers in the ratio 2:1(137,141). During our hydrogenolysis of **89A**,no isomer of **90A** with 2,3-cis configuration was obtained.

The elimination product **95** could also be prepared by refluxing the cycloadduct **88** in toluene with a catalytic amount of p-toluenesulfonic acid.



88 95

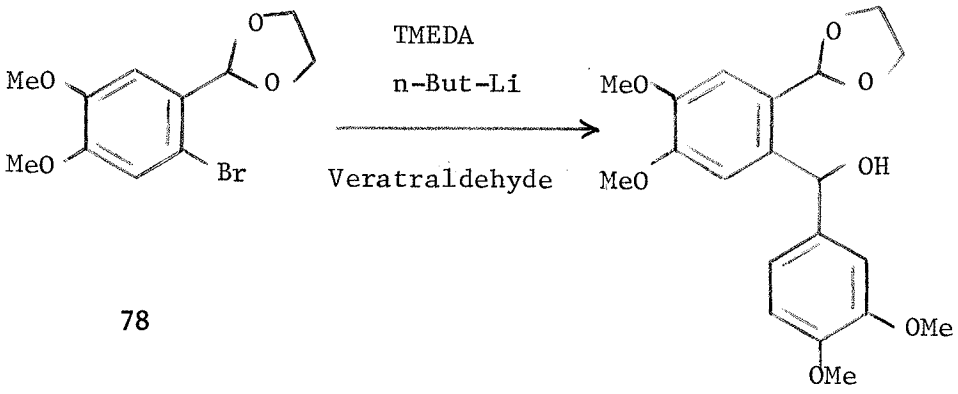
The diester **90A** upon recrystallization from 2-propanol gave melting point 143-145°C, which was higher than that of racemic diester (126-127°C). The specific rotation of the diester was +19.9°.

The (+)-isolariciresinol dimethyl ether **48** was prepared from the compound **90A** by reducing with $LiAlH_4$. The product was recrystallized from ethyl acetate/ hexane as a white crystalline solid with melting point 164-169°C, which was considerably above that of the racemic mixture (150-153°C). The specific rotation of **48** was +13.2°. Schrecker and Hartwell have determined the melting point and specific rotation of (+)-isolariciresinol dimethyl ether to be 167-169°C and +15.8° respectively, although higher values have been recorded(138). On the basis of the specific rotation reported by Schrecker and Hartwell our material was 83% optically pure. The fact that our compound was not 100% optically pure is probably due to the difficulty in separating the major diastereomer **89A** from the minor one **89B** by chromatography. The sign of rotation nevertheless confirmed that the prediction of the effect of the (R)-chiral auxiliary on the diastereoselectivity of the cycloaddition was correct and that all four chiral centres could be introduced selectively in a single step.

Therefore it may be concluded that an o-quinodimethane with a chiral auxiliary such as a phenylethoxy group could be prepared and that these o-quinodimethanes can be used for the asymmetric synthesis of a typical lignan. Thus using (R)-phenylethoxy group as a chiral auxiliary it was possible to carry out an asymmetric synthesis of (+)-isolariciresinol

dimethyl ether. It should also be possible to carry out an asymmetric synthesis of phyltetralin, which is enantiomeric to (+)-isolariciresinol tetramethyl ether, using the (S)-phenylethoxy group as a chiral auxiliary. Therefore our synthesis demonstrates asymmetric synthesis of a typical class of aryl-tetralin lignans.

Alternative routes for preparing the aldehyde **82** were attempted. One of these was partially succesful with low overall yields. Thus the 6-bromoveratraldehyde ethylene glycol acetal **78** was ortho-lithiated and then treated with veratraldehyde to produce the alcohol **97**.

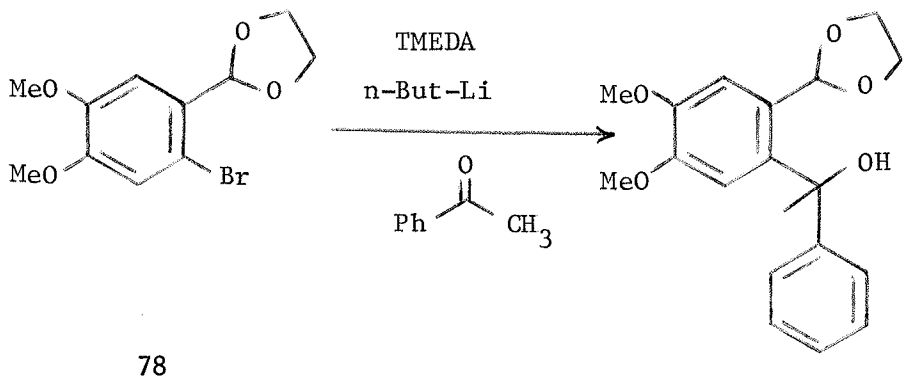


78

97

The yield of the coupling reaction was 90% for the alcohol **97** and 10% for the reduced acetal **91** based on ^{1}H NMR integration.

A model study was carried out for the coupling reaction using acetophenone instead of veratraldehyde.

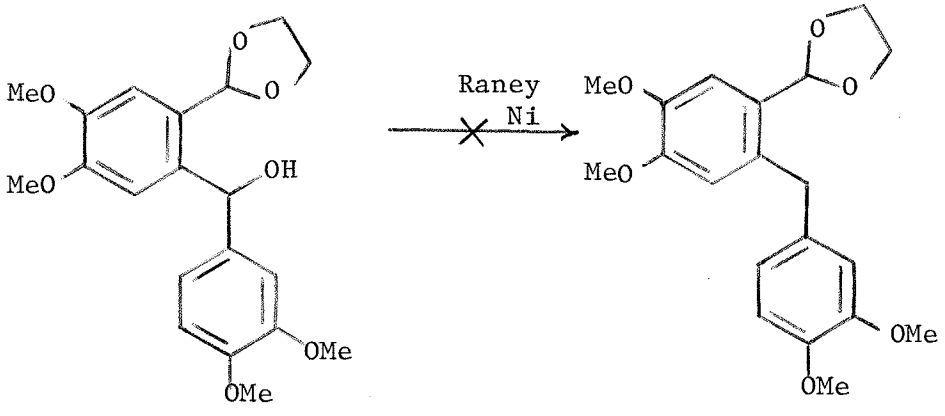


78

96

Compound **96** was obtained in 58% yield after purification by chromatography and recrystallization. Two other products separated were reduced acetal **91** and a product tentatively identified as an adduct between the butyllithium and the actophenone.

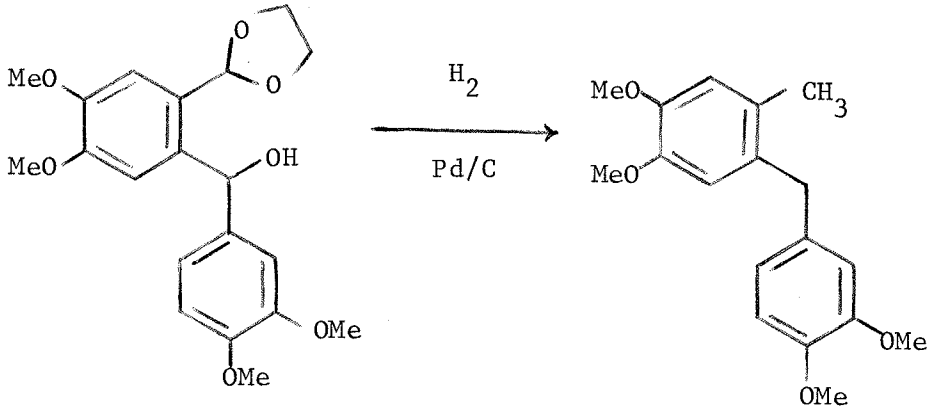
The alcohol **97** could not be reduced to the acetal **81** using Raney Ni.



97

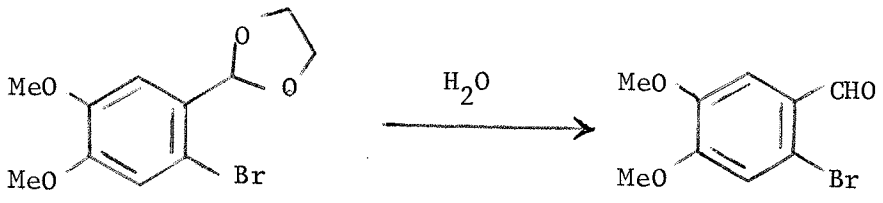
81

Catalytic hydrogenolysis reduced the acetal as well as the hydroxyl group, to give the hydrocarbon **98**.



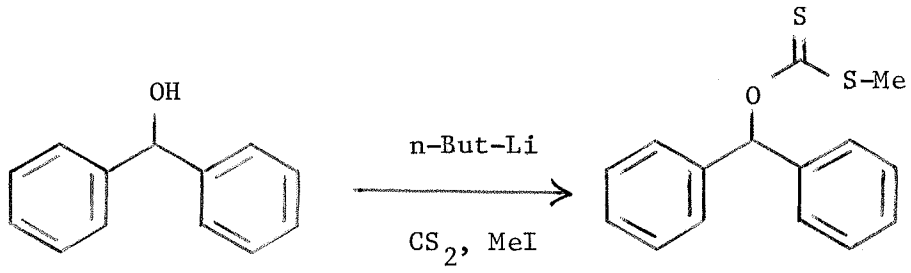
97 **98**

In this experiment the conversion of the acetal group into a methyl group was surprising. However, as we observed that the bromoacetal **78** was sensitive to moisture, the acetal group in **97** was possibly hydrolysed to aldehyde, which was then reduced to the methyl group.



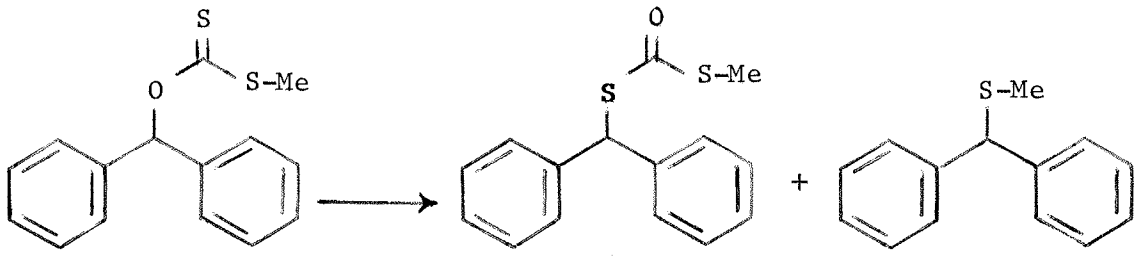
Therefore the selective reduction of the alcohol **97** to the acetal **81** could neither be done by Raney Ni nor by catalytic hydrogenolysis.

Deoxygenation of alcohols <u>via</u> thiocarbonyl derivatives with $(nBu)_3SnH$ is well known(142). Therefore at first a model study was carried out using benzhydrol. The thiocarbonyl derivative (xanthate) **99** was prepared by treating benzhydrol with n-butyllithium at -78°C followed by the addition of CS_2 and MeI.



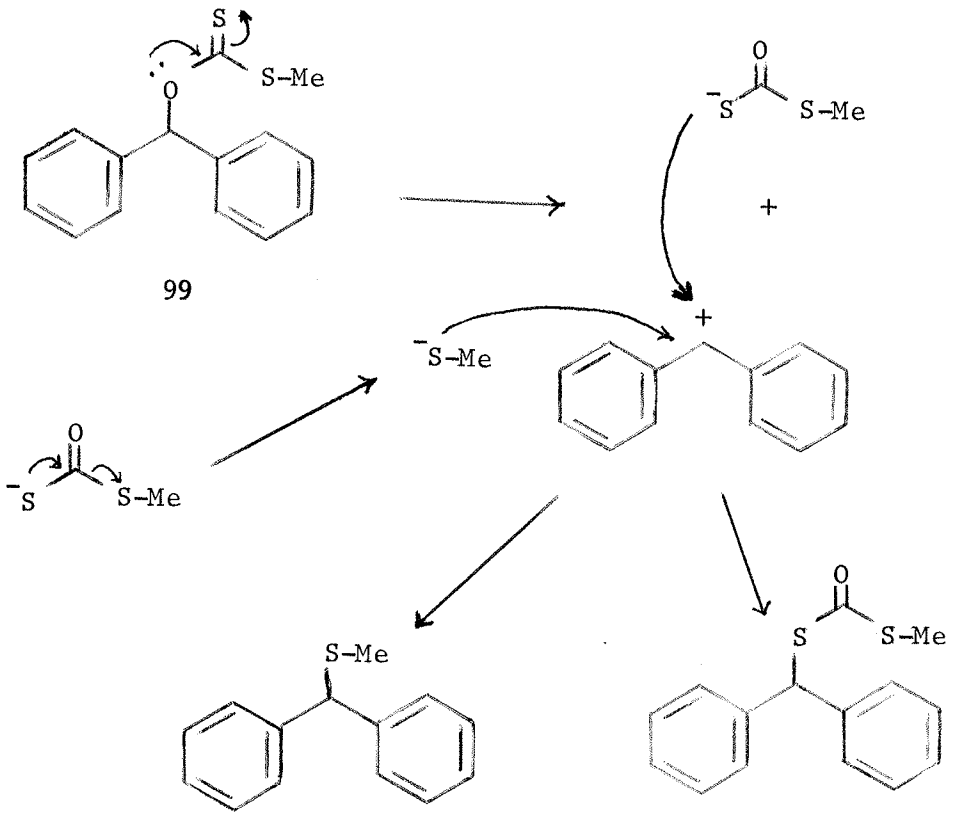
99

When purification of compound **99** was attempted by chromatography, it underwent rearrangement. Thus after chromatography two new compounds were isolated and identified as compound **100** and **101**.

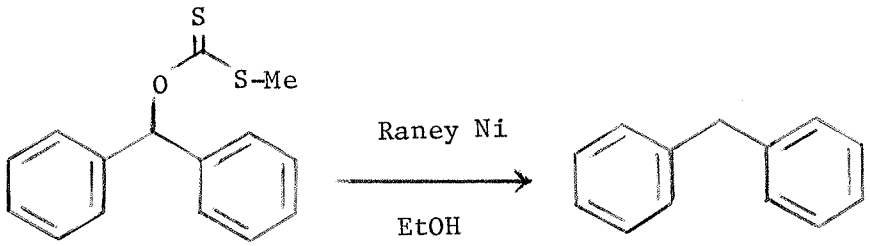


99 **100** **101**

The reason for this rearrangement was not known, however a possible mechanism is as follows.

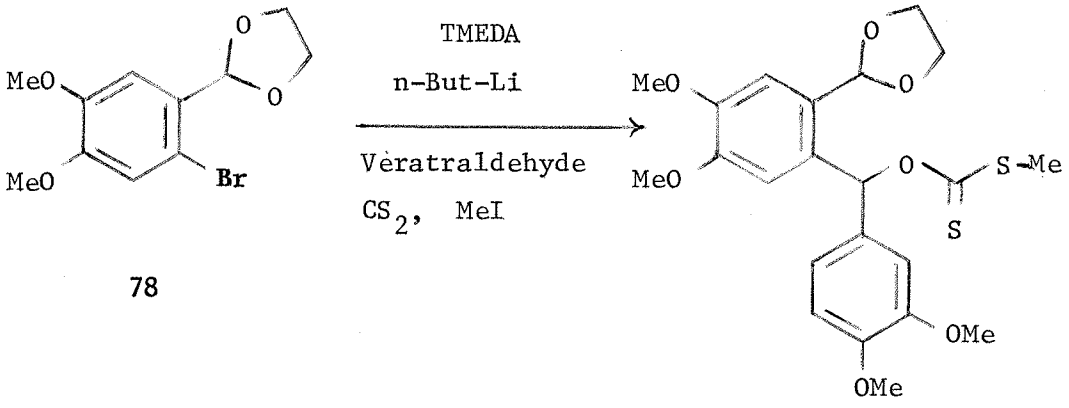


The xanthate **99** could be reduced to diphenylmethane and the rearranged products **100**, **101** on treatment with $(nBu)_3SnH$. However, the xanthate **99** could be reduced to the hydrocarbon in very high yield using Raney Ni in ethanol (reflux).



99

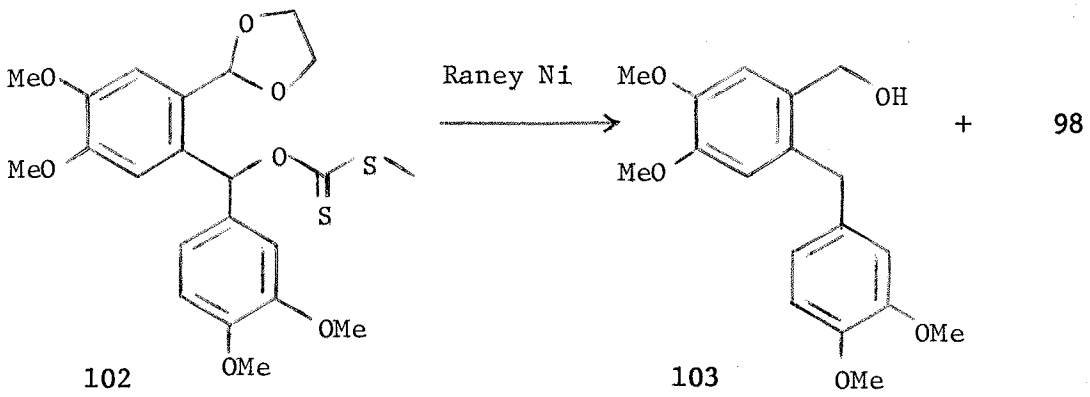
Following the above procedure the xanthate **102** was prepared from the bromoacetal **78.**



78

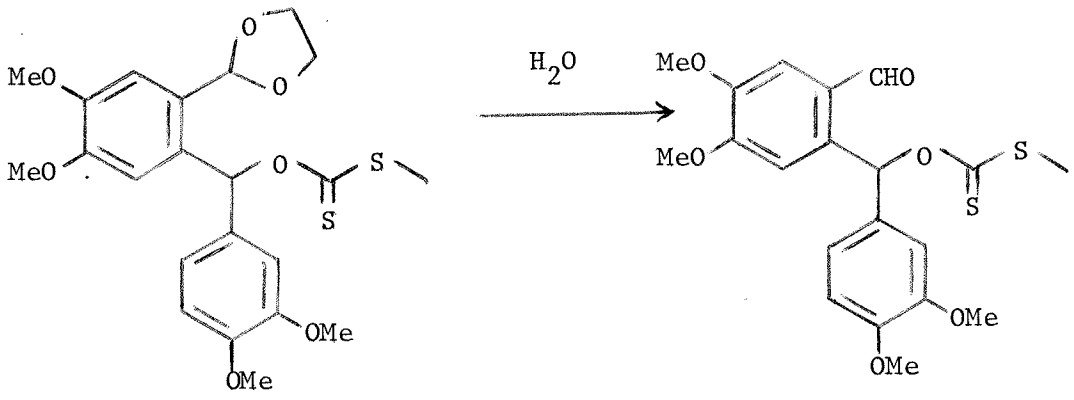
102

The compound **102** was refluxed for 3 hours with Raney Ni in ethanol yielding the alcohol **103.** In this reaction a small amount of the totally reduced compound **98** was also observed.



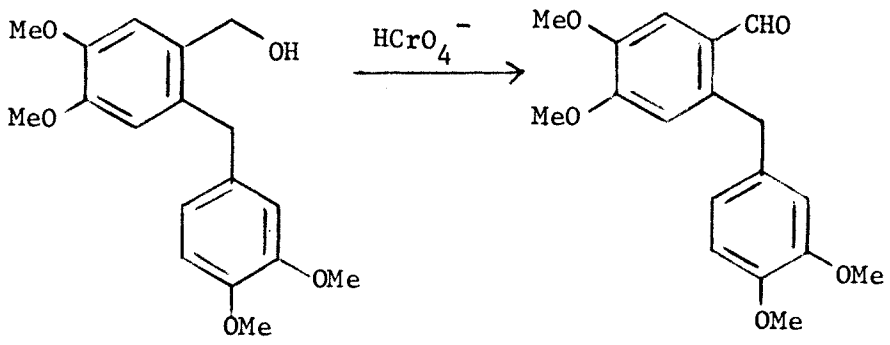
102 103

The acetal **102** was possibly hydrolysed to aldehyde, which was also reduced by Raney Ni to the alcohol **103** and the hydrocarbon **98** in addition to the reduction of the thiocarbonyl group. The xanthate **102** could be easily hydrolysed to the xanthate **104.**



102 104

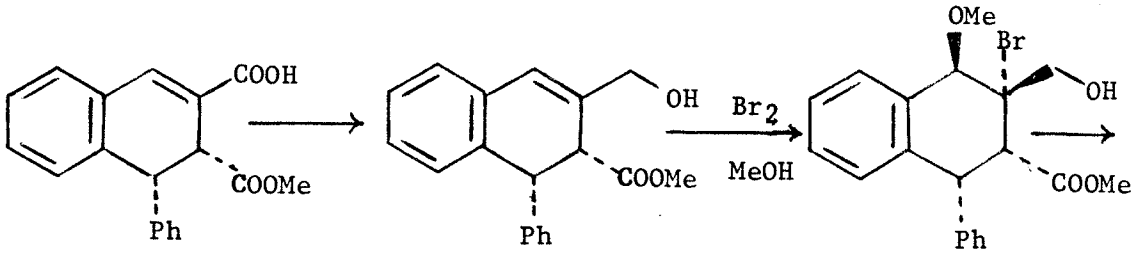
The alcohol **103** obtained from the xanthate **102** was oxidised by $HCrO_4^-$ to the desired aldehyde **82.**



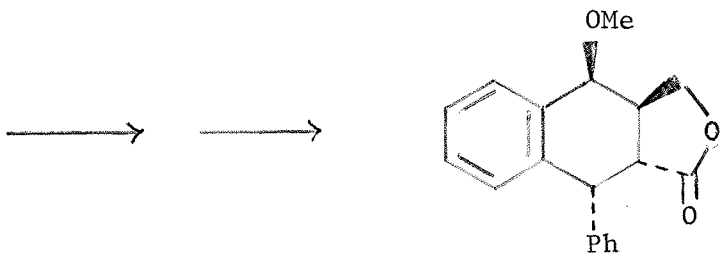
103 82

3.3 Epipodophyllotoxin and podophyllotoxin analogue

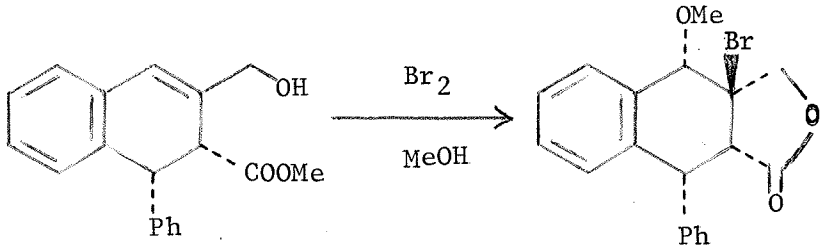
Epipodophyllotoxin and podophyllotoxin are two of several naturally occuring lignans isolated from extracts of a variety of species of Podophyllum(118,123). These compounds have held a long standing interest among synthetic chemists, because of their utility in the synthesis of glycosidic clinical antitumor agents VP-16 and VM-26(123,143,144). Our earlier synthesis of compound **63** suggested a possible route to epipodophyllotoxin analogues as shown below.



63 105 106



An effort was made to study the possibility of the above route to an epipodophyllotoxin analogue. Thus compound **105** was prepared from **63** by BH_3.DMS reduction. BH_3.DMS selectively reduced the carboxylic acid to alcohol. In order to prepare the compound **106**, **105** was treated with bromine in methanol and methylene chloride. The bromolactone **107** was obtained instead of **106**.

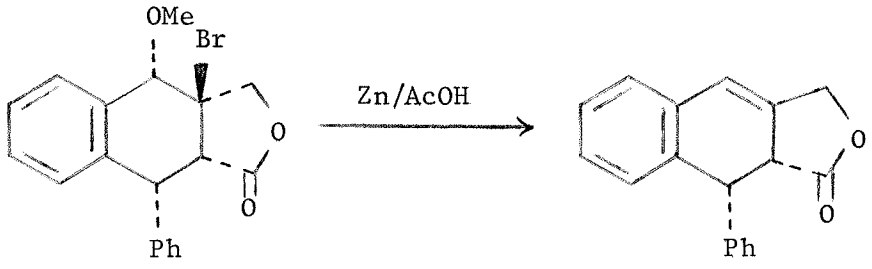


105 107

In this reaction the addition of bromine and the methoxy group to the double bond and lactonization took place in one step. However, the lactone formed with the undesired 2,3-cis stereochemistry. The methoxy

group and bromine were trans to each other as expected. The structure of this bromolactone **107** was confirmed by 300 MHz ^{1}H NMR using COZY techniques and the measurement of nuclear overhauser effect. NOE between H_1 and H_4 was observed indicating that H_1 and H_4 are cis to one another and that the ring is in a boat conformation.

An attempt to reduce the bromolactone **107** was unsuccesful, reductive elimination taking place instead. Thus **107** on treatment with Zn/acetic acid gave the compound **108**.

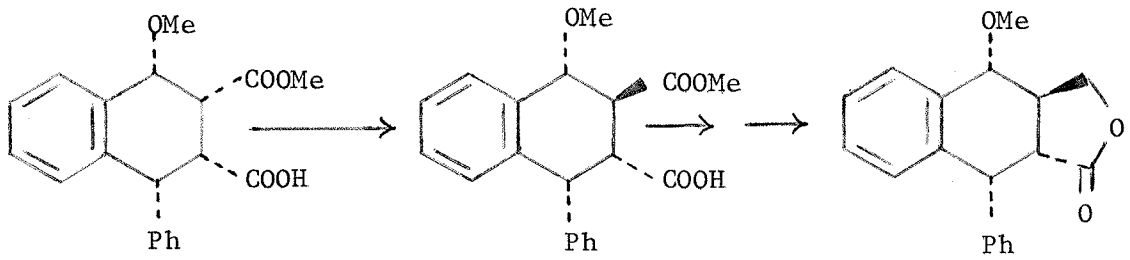


107 **108**

As the addition of bromine and methanol to compound **105** gave **107** with the undesired stereochemistry this route to an epipodophyllotoxin analogue was not pursued further.

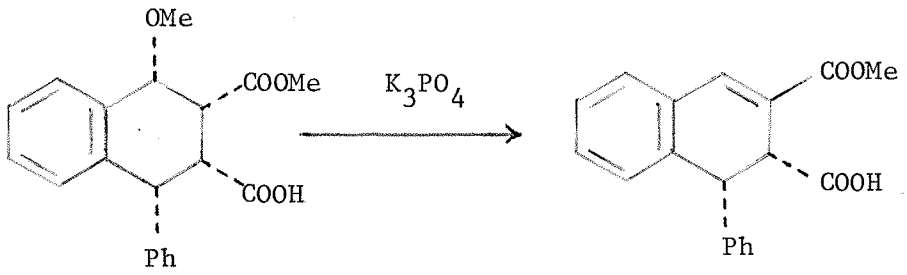
Our synthesis of compound **71** suggested a possible route to a podophyllotoxin analogue as outlined in the scheme 4.

Scheme 4



71 109

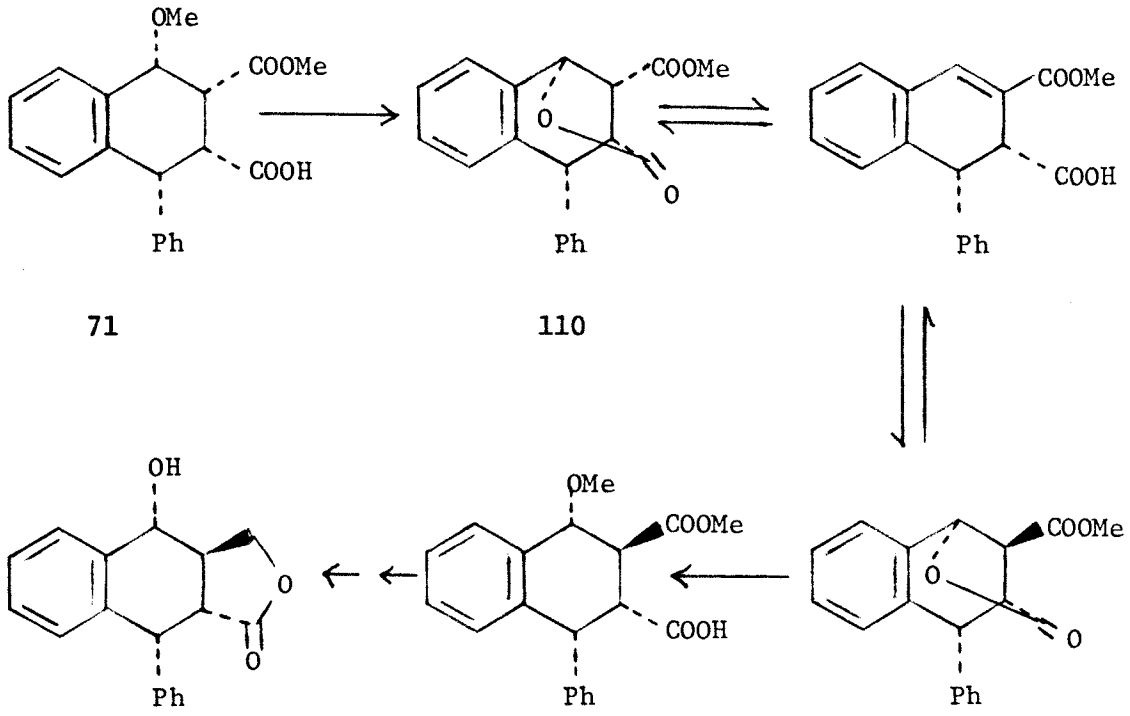
The base catalyzed epimerization of **71** to **109** was attempted but only an elimination product was obtained. Thus treatment of **71** with K_3PO_4 or potassium-t-butoxide gave **73.**



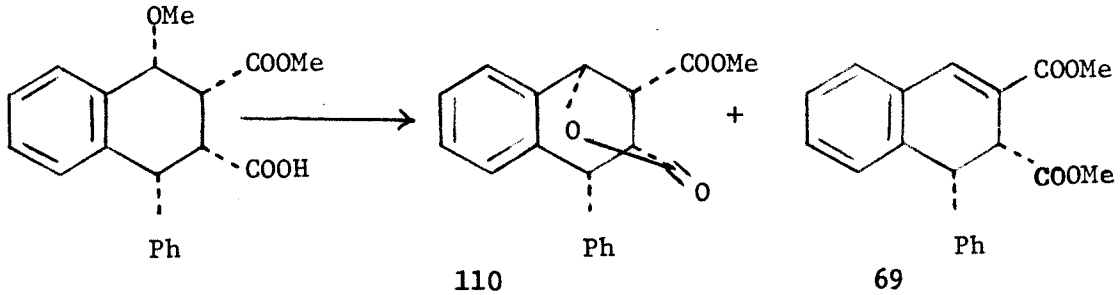
71 73

An alternative possible route was the acid catalysed epimerization <u>via</u> lactonization, elimination/addition and lactonization as outlined below, scheme 5.

Scheme 5

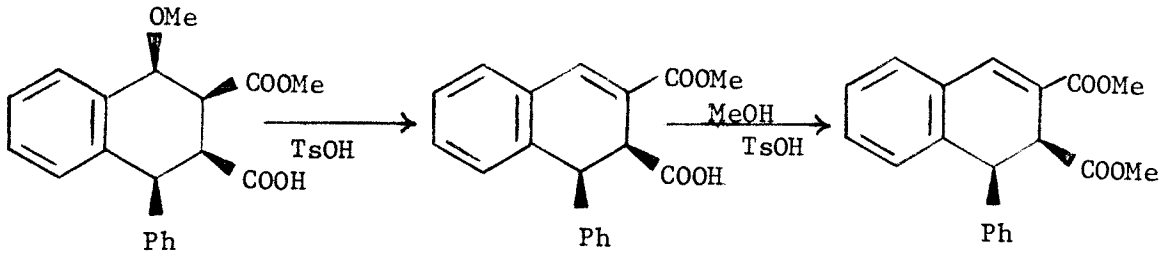


A study of podophyllotoxin analogue synthesis following the above route was carried out. Compound **71** was warmed with p-toluenesulfonic acid in methylene chloride to prepare the compound **110** and eventually **111**. Compound **110** was obtained in addition to the compound **69**.



Based on ^{1}H NMR integration the ratio of **110** and **69** was 45:55. These two compunds could be separated by chromatography using 30% ethyl acetate-hexane as eluent. The NMR spectrum of **110** was reported previously(11). While our spectrum was similar to that published, there are slight differences in chemical shifts, possibly due to the more precise higher field measurements in this work (see experimental). As only compound **110** was obtained instead of **111** in low yield, this route to the podophyllotoxin analogue synthesis was not pursued.

The formation of the elimination product **69** in the above reaction may be due to formation of methanol by elimination as well as lactone formation. This methanol generated <u>in situ</u> reacts with the carboxylic acid of **73** in the presence of p-toluenesulfonic acid to produce **69**.



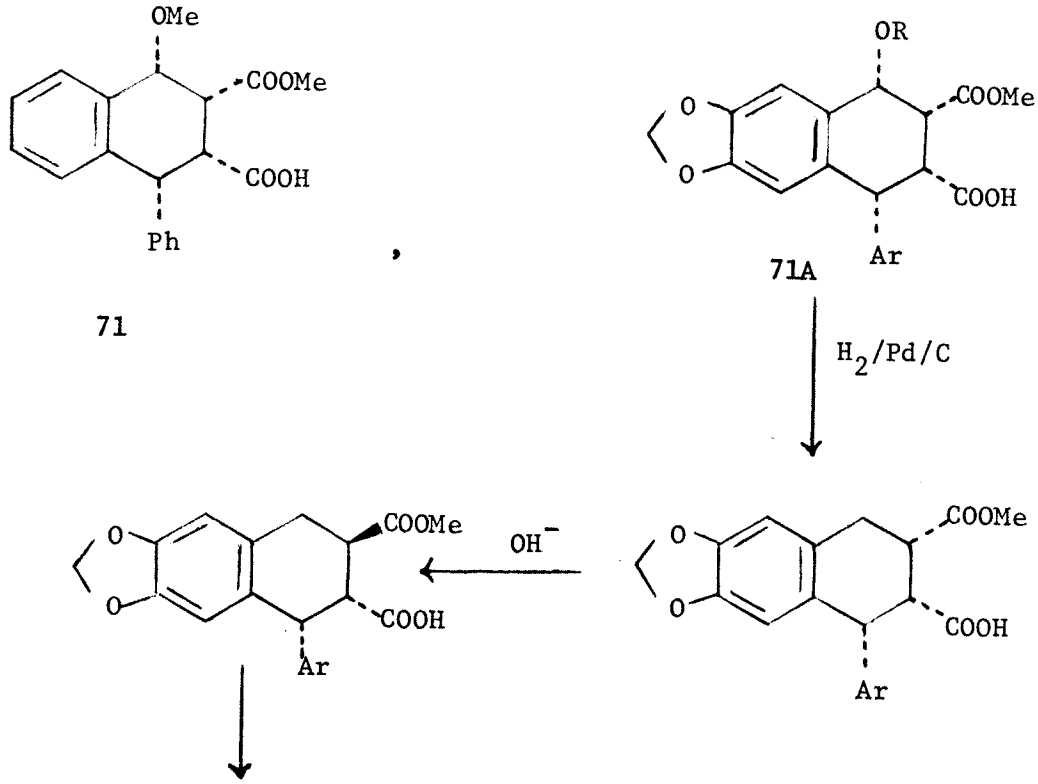
71 **73** **69**

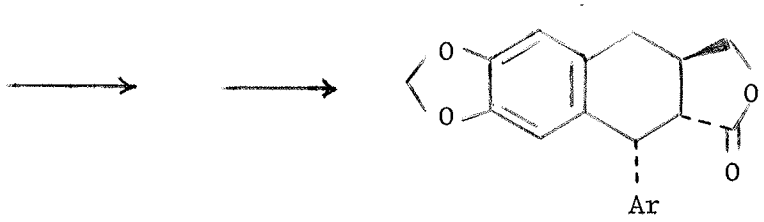
Compound **69** was characterized by comparing the ^{1}H NMR spectrum with that previously reported(128). The intermediate compound **73** was also observed when the reaction was worked up after a shorter time of reflux.

3.4 Deoxypodophyllotoxin

The potent antimitotic activity of the Podophyllum lignans has been the subject of much chemical and biochemical study. Deoxypodophyllotoxin, a compound isolated from Podophyllum and other plants(118), also having antitumor activity is of much interest among synthetic organic chemists(145-147). Although racemic syntheses of deoxypodophyllotoxin have been reported in the literature(112,113), an asymmetric synthesis is not known.

The availability of compound **71** suggested that if the appropriately substituted analogue could be synthesised it could be converted to deoxypodophyllotoxin by the following route.

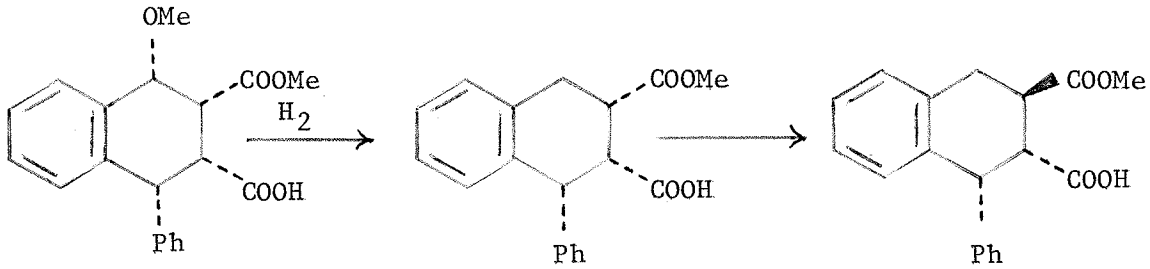




31

Ar = 3,4,5-trimethoxyphenyl

The steps following the hydrogenolysis have been already reported in a recently published racemic synthesis of deoxypodophyllotoxin(112). The challenge would be to prepare the optically active **71A** via an asymmetric cycloaddition. As a first step in this project the hydrogenolysis and epimerization steps were carried out on **71**. Thus compound **112** was prepared from **71** by catalytic hydrogenolysis in 87% yield. Compound **112** was then epimerized by refluxing with NaOMe in methanol to obtain **113**.

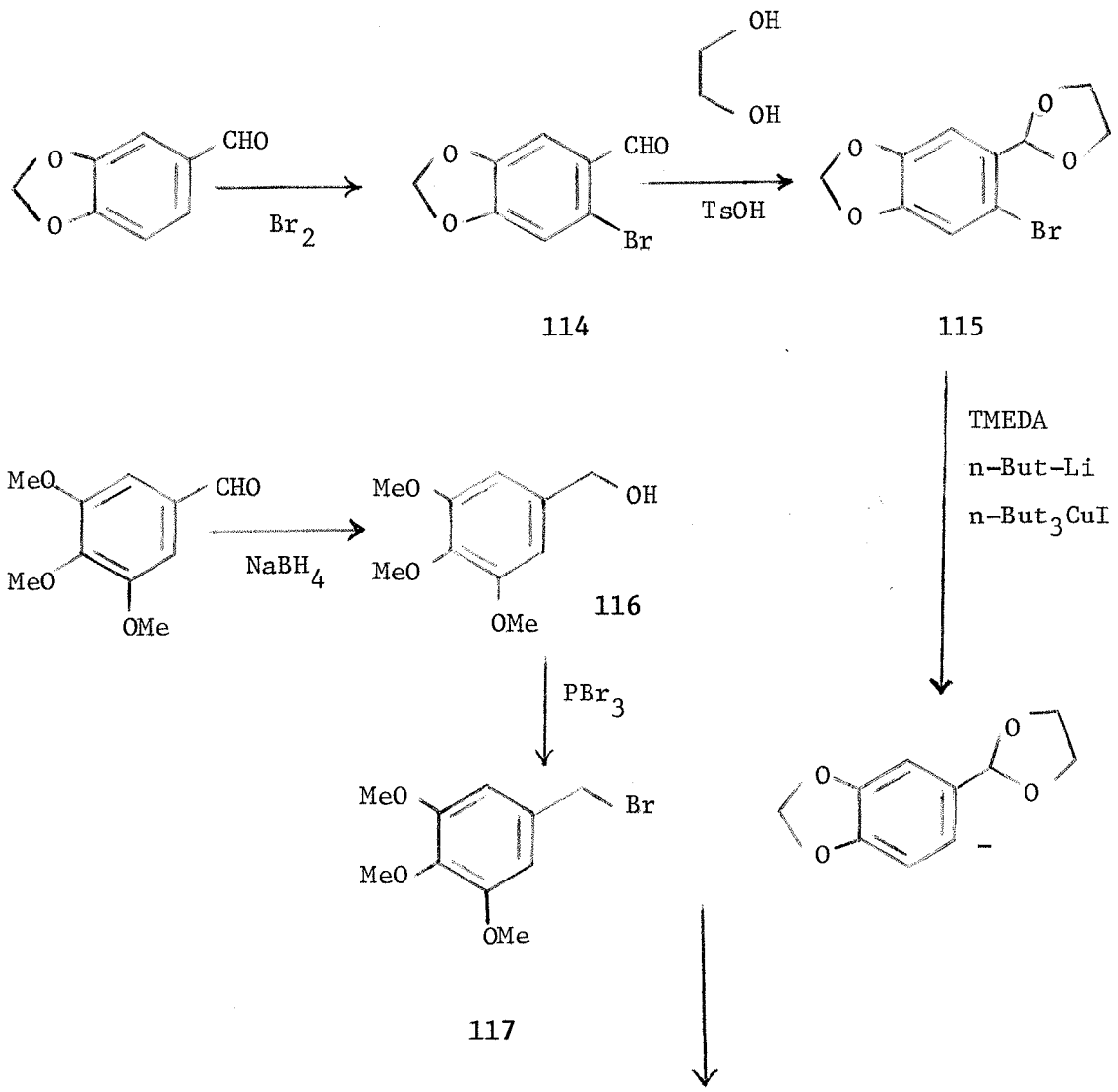


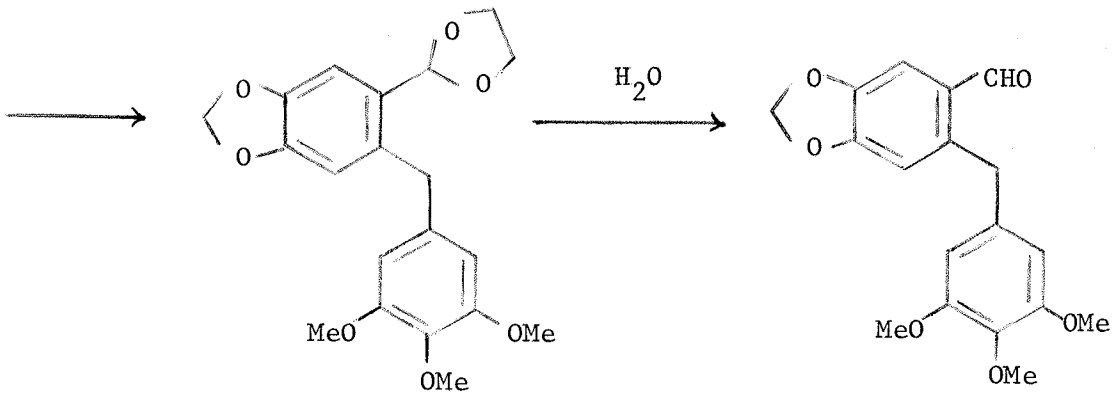
71 112 113

The IR spectrum of **113** was similar to that of **112**, but the ^1H NMR spectrum was different (see experimental). From compound **113** a deoxypodophyllotoxin analogue could be prepared following the literature procedure(112).

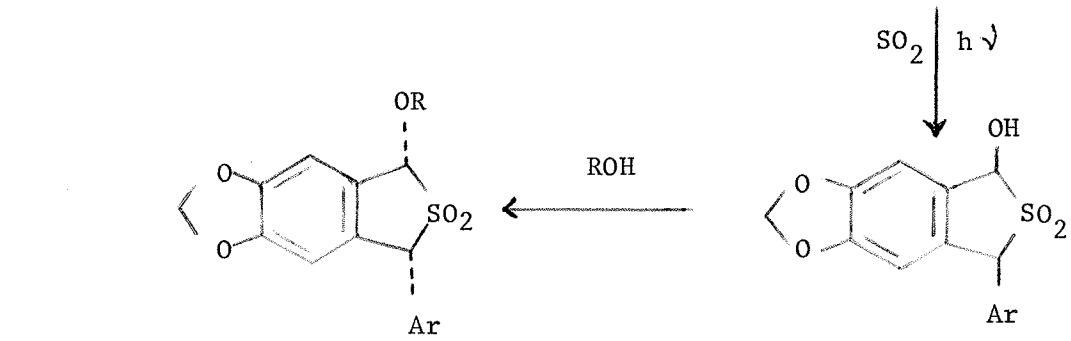
The asymmetric synthesis of deoxypodophyllotoxin was attempted according to scheme 6.

Scheme 6

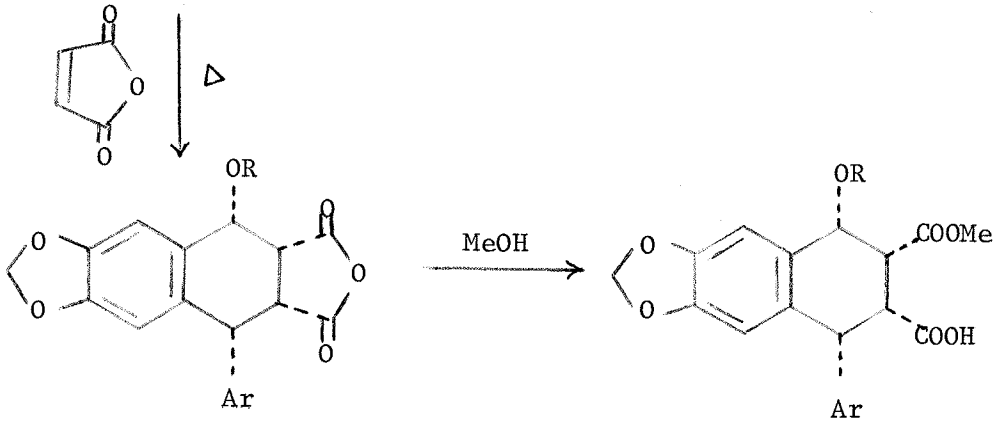




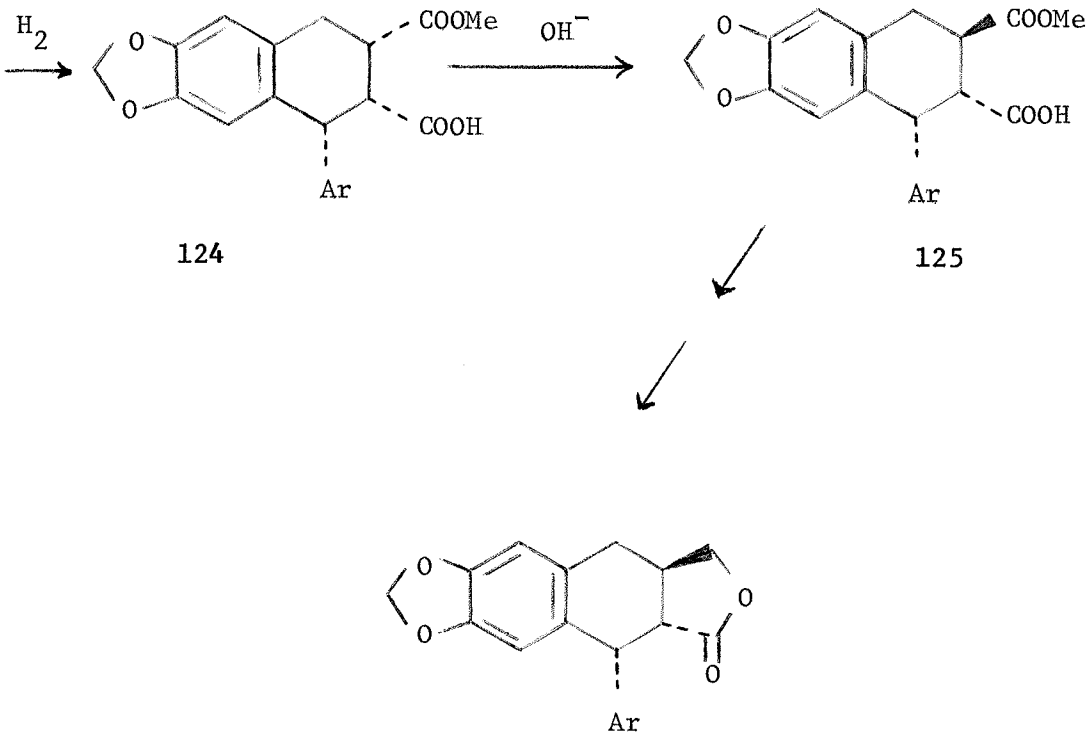
118 119



121 120



122 123



124 125

31

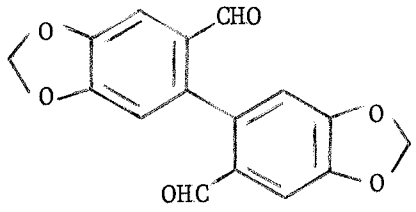
Ar = 3,4,5-trimethoxyphenyl

6-Bromopiperonal **114** was prepared from piperonal following the literature procedure(139). 6-Bromopiperonal ethylene glycol acetal **115** was prepared from **114** following the literature procedure (47). The melting point was consistent with that reported in the literature, but the ^{1}H NMR spectrum was slightly different due to the fact that the reported spectrum was not well resolved. Our spectrum taken at 300 MHz was well resolved and all of the peaks were assigned.

The 3,4,5-trimethoxybenzyl alcohol **116** was prepared from the corresponding aldehyde following a standard procedure(148). 3,4,5-Trimethoxy benzyl bromide, **117**, was prepared following our previously described procedure(148). This compound was not very stable, but could be stored at low temperature. Generally it was freshly prepared and was used immediately in the coupling reaction with the metalated acetal.

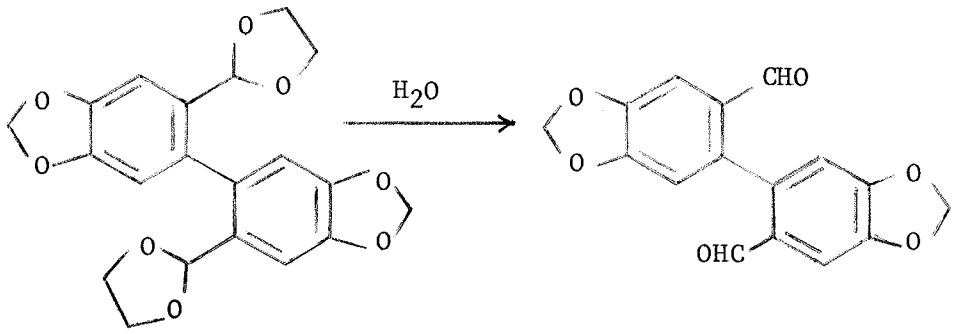
Compound **118** could not be isolated after the coupling reaction of **115** and **117**. The coupling reaction was carried out following our previously reported method(148). When the crude product of the coupling reaction was chromatographed, the aldehyde **119** was isolated instead of the acetal **118**, which indicated the acetal **118** was hydrolysed in the silica gel column. The melting point of the aldehyde was consistent with the literature(47) and the spectral data were also identical. The yield for this reaction was 36% in two steps and three other byproducts were isolated from the reaction mixture.

One of the byproducts isolated from the coupling reaction was compound **126**.



126

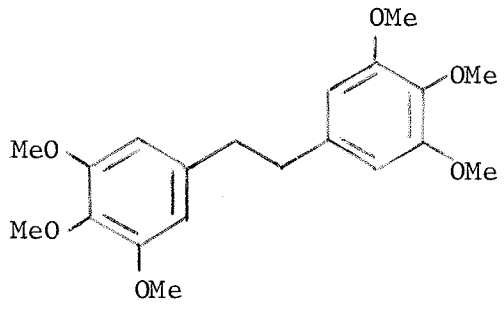
Compound **126** was a dimer of piperonal. This compound possibly arose from hydrolysis of the acetal dimer **127** during workup.



127 126

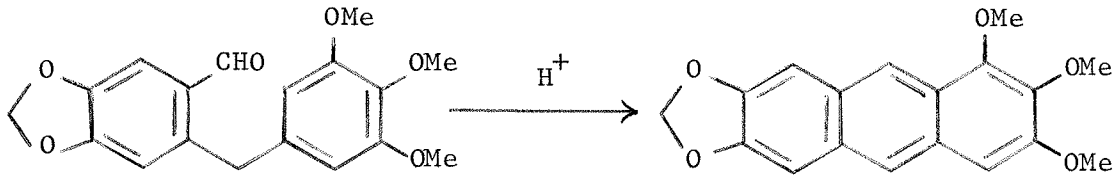
The acetal dimer **127** was probably formed by a radical coupling reaction. A similar dimerization was also observed in our earlier work, when 6-bromoveratraldehyde ethylene glycol acetal was coupled with 3,4-dimethoxy benzyl bromide.

The other byproduct of the coupling reaction was compound **128**, which is a dimer of the 3,4,5-timethoxy benzyl bromide.



128

This dimer was also probably formed by radical coupling. The third byproduct was the anthracene derivative **129**. This compound appeared to form after the coupling reaction. The aldehyde **119** generated during chromatography gradually cyclized due to catalysis by traces of acid.

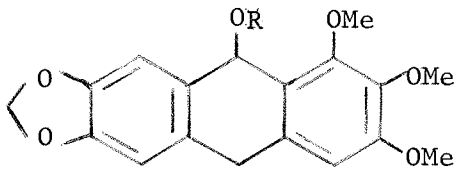


119 129

It was observed that the aldehyde **119** could be purposely converted to the anthracene **129** by treating with a trace of p-toluenesulfonic acid at room temperature, or reflux for half an hour in methylene chloride.

The hydroxy sulfone **120** was prepared by irradiation of the aldehyde **119** in benzene with SO_2 following our previously reported procedure(148). The yield of this reaction was 42%. From the reaction mixture a significant amount of the anthracene **129** was isolated. The formation of the anthracene, which lowers the yield of the hydroxy sulfone, may be due to the fact that traces of water in benzene react with SO_2 to produce H_2SO_3, which catalyses the formation of the

anthracene. Therefore it should be possible to improve the yield in this reaction by using dry benzene and a trace of acid scavenger. From the ^{1}H NMR spectrum of the hydroxy sulfone **120**, it appeared to be a mixture of cis- and trans-isomers in the ratio 55:45. The hydroxy sulfone was quite unstable but could be stored at low temperature. In an attempt to prepare the chiral alkoxy sulfone **121** (R = trans-2-phenyl cyclohexyl), the hydroxy sulfone was refluxed with the alcohol in methylene chloride with a trace of p-toluenesulfonic acid. The trans-2-phenylcyclohexyl chiral auxiliary was used as recent work had shown it to be more effective than the phenylethyl auxiliary in reactions of o-quinodimethanes(148). Unfortunately, the reaction of the hydroxy sulfone **120** with this alcohol yielded only the anthracene **129**. When the reaction was carried out at room temperature for 48 hours the compound **130** was obtained.



130

The structure of **130** was tentatively assigned by ^{1}H NMR spectroscopy. M^+, the molecular ion of the compound was not observed by EI mass spectrometry. More information is necessary to confirm the structure of **130**.

In view of the lack of success in preparation of the alkoxy sulfone this approach to deoxypodophyllotoxin was abandoned. It is possible that the alkoxy sulfone **121** can be prepared with other chiral auxiliaries such as the phenylethyl group, as was used to synthesize (+)-isolariciresinol dimethyl ether. However, this repetition of an already established asymmetric method was not pursued.

All Compounds were analysed by a combination of NMR, IR, mass spectrometry and elemental analysis.

CHAPTER 4

EXPERIMENTAL

4.1 Instrumentation

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian EM 360 spectrometer operating at 60 MHz and/or on a Bruker AM 300 spectrometer operating at 300 MHz. Unless otherwise stated, deuterochloroform ($CDCl_3$) was used as the solvent with tetramethylsilane (TMS) as the internal reference. ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Infrared (IR) spectra were recorded on a Unicam 1000 spectrometer. Mass spectra were recorded on a Finnigan 1015 Spectrometer and a VG analytical 7000E mass spectrometer. Only the molecular ions and major fragments of diagnostic value are reported. Exact mass/ mass spectra were obtained on an analytical VG 7070-E instrument at the University of Ottawa, Ottawa, Canada and on a VG 7000-E mass spectrometer at the University of Manitoba.

Melting points were recorded on a hot stage instrument and are uncorrected. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. Guelph, Ontario, Canada. Specific rotations were measured by Michael Hrytsak at the University of Ottawa, Ottawa, Canada.

Thin layer chromatography (tlc) was carried out on Kieselgel DSF-5. Column chromatography was carried out on Merck Kieselgel-60, 230-400 mesh and Terochem silica gel, 20-45 microns, using the flash chromatography technique(150).

4.2 E,E- and E,Z-o-quinodimethanes

1-Phenyl-3-hydroxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide 44

o-Benzyl benzaldehyde (9.3g, 0.47 mmol) was dissolved in thiophene free benzene (300 mL) containing SO_2 (20 g). The solution was irradiated for 19 hours, under nitrogen through a 1 mm pyrex filter, with a water-jacketed 450-W Hanovia medium pressure mercury lamp immersed in the solution. The solvent was evaporated in vacuo to give a brown coloured paste (12.5 g). This was dissolved in methylene chloride (100 mL) and extracted 3 times with 5% $NaHCO_3$ solution. The aqueous layer was acidified with 10% HCl and extracted 9 times with methylene chloride (50 mL). The organic extract was dried ($MgSO_4$) and evaporated to give the pure compound (8 g), 65% yield. The product was a glassy solid, ^1H NMR spectrum showed it to be a mixture of cis- and trans-isomers. The spectral data were consistent with the literature(70).

Cis-1-phenyl-3-methoxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide 45

The hydroxy sulfone **44**, (2 g, 7.7 mmol) was dissolved in 50% methanol in methylene chloride (40 mL). p-Toluenesulfonic acid (30 mg) was added and the solution refluxed for 1.5 hours at which time TLC showed that no starting material remained. The solvent was evaporated giving a paste. The crude mass was dissolved in a small amount of methylene chloride and filtered through a short silica gel column. The column was washed with 50% ethyl acetate in hexane. After evaporating the solvent, the sulfone **45** (4.04 g) was obtained as a mixture of 90% cis- and 10% trans-isomers, in 97% yield. This methoxy sulfone was used for cycloaddition reactions

without further purification. The spectral data were consistent with those reported in the literature(70).

1-phenyl-3-acetoxy-1,3-dihydrobenzo[c]thiophene-2,2-dioxide 46 and **47**
The hydroxy sulfone **44** (2 g, 7.7 mmol) was added to acetic anhydride (130 mL). The solution was heated at 55°C for 2 hours. After cooling, excess acetic anhydride was removed at room temperature on a rotary evaporator and finally on a high vacuum line, to give the crude product in 99% yield. The product was a mixture of cis- and trans-acetoxy sulfones. The mixture of products was chromatographed using 2% ethyl acetate in benzene to give 1.09 g (47%) of the trans-sulfone **47**, 0.87 g (38%) of the cis-sulfone **46** and 0.13 g of the mixture of cis- and trans-sulfones. The cis-sulfone was recrystallized from methylene chloride in hexane, mp 163-165°C. The trans-sulfone was also recrystallized from methylene chloride in hexane, mp 105-108°C. The spectral data of both cis- and trans-isomers were consistent with those reported in the literature(70).

Cycloaddition reactions

The cycloaddition reactions of cis- and trans-acetoxyphenyl sulfones with dienophiles were similar, solvents, reaction conditions and time of the reactions are give in table 1. A representative procedure is described here.

Acetoxy sulfone **46** or **47** (100-200 mg) was dissolved in toluene (10-20 mL) containing 30-40 mg of anhydrous, powdered ZnO. Four equivalents of

the dienophiles were added and the reaction mixture was heated (as described in table 1) in a sealed flask in a nitrogen atmosphere. After 5 hours the reaction mixture was cooled and filtered through a short silica gel column, which was washed with methylene chloride. The organic solution was evaporated and then heated at 100°C under high vacuum to remove excess dienophile. The cycloadduct was then purified by chromatography and/or recrystallization as described below. In the case of the maleic anhydride adduct the cycloadduct was not filtered through silica gel, but rather through filter paper.

Purification methods are summarised below

Compound 54

Recrystallized from ethyl acetate-hexane, mp 109-110°C, for spectral properties see ref. 70. and for the ^{1}H NMR spectrum in deuterobenzene see table 2.

Compound 55

Chromatography, with 20% ethyl acetate in hexane as eluent and recrystallized from methylene chloride-hexane, mp 136-138°C (lit. 139-140°C)(70). For spectral data see ref. 70 and for the ^{1}H NMR spectrum in deuterobenzene, see table 2.

Compound 56

Chromatography, with 20% ethyl acetate in hexane, recrystallized from methylene chloride-hexane, mp 150-153°C; ir (CH_2Cl_2): 1747 cm^{-1}(C=O, ester); NMR data, see Table 2; mass spectrum, m/z (relative abundance):

382 (10), 339 (33), 322 (40), 307 (40), 262 (43), 221 (43), 203 (47), 188 (100). Anal. calcd. for $C_{22}H_{22}O_6$: C 69.10, H 5.80; found: C 68.92, H 6.09.

Compound 58

Recrystallized from ethyl acetate-hexane, mp 168-170°C; ir (CH_2Cl_2): 1750 cm^{-1}, 1760 cm^{-1}, 1795 cm^{-1}; NMR data, see Table 2; mass spectrum, m/z (relative abundance): 336 (12), 293 (12), 276 (21), 248 (38), 204 (35), 195 (44), 178 (100). Anal. calcd. for $C_{20}H_{16}O_5$: C 71.42, H 4.79; found: C 71.55, H 5.09.

Compounds 59, 60 and 61

Chromatography with 10% ethyl acetate-hexane. Separation of the three isomers was not possible by chromatography. The identity of the three isomers was based solely on the 300 MHz ^1H NMR spectrum of the mixture, which was analysed using decoupling and COZY techniques. The NMR data are given in table 2.

Compound 65

Recrystallized from methylene chloride-hexane, mp 135-137°C; ir (CH_2Cl_2): 1742 cm^{-1} (C=O); NMR data, see Table 2; mass spectrum, m/z (relative abundance): 322 (7)(M-AcOH), 262 (36), 176 (44), 131 (65), 117 (76), 91 (100). Anal. calcd. for $C_{22}H_{22}O_6$: C 69.10, H 5.80, found: C 68.82, H 6.02.

Compound 66

Chromatography with 10% ethyl acetate-hexane; recrystallized from methylene chloride-hexane, mp 130-132°C; ir (CH_2Cl_2): 1745 cm^{-1} (C=O); NMR data, see Table 2; mass spectrum, m/z (relative abundance): 382 (1), 351 (1), 339 (1.5), 322 (31), 294 (28), 231 (20), 204 (25), 43(100). Anal. calcd. for $C_{22}H_{22}O_6$: C 69.10, H 5.80; found: C 68.98, H 6.00.

Trans-1-acetoxy-2-phenylbenzocyclobutene 57

This compound was first isolated as a minor product from the reaction of the cis-acetoxyphenyl sulfone **46** with dimethyl maleate by chromatography using 20% ethyl acetate-hexane. It was further prepared by refluxing the sulfone **46** (101.5 mg) in toluene (10 mL) with 33 mg of ZnO for 15 hours. The crude product was chromatographed with 20% ethyl acetate-hexane to give 42 mg of **57** and 32.5 mg of the unreacted sulfone **46**. The yield was 76% on the basis of sulfone reacted. The pure compound was recrystallized from hexane, mp 50-53°C; ir (CH_2Cl_2): 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 2.15 (s, 3 H, acetoxy), 4.67 (d, 1 H, J = 1.63 Hz), 5.65 (d, 1 H), 7.20-7.50 (m, 9 H, aromatic); mass spectrum, m/z (relative abundance): 196 (67)(M-42), 195 (47), 178 (100), 167 (67). Anal. calcd. for $C_{16}H_{14}O_2$: C 80.65, H 5.92; found: C 80.40, H 6.19. Refluxing **46** with ZnO in xylene (138°C) gave only anthracene.

Compound 62

The methoxy sulfone **45** (2.04 g, 7.45 mmol) was dissolved in benzene (60 mL) and maleic anhydride (4 equivalents) was added to the solution. The

reaction mixture was refluxed for 8 hours in the presence of ZnO (500 mg). The solvent was evaporated and excess maleic anhydride was removed at 100°C using a high vacuum line to give the crude product (2.25 g), 98% yield. This mass recrystallized from methylene chloride-hexane, mp 159-161°C; ir (CH_2Cl_2): 1790 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 3.44 (s, 3 H, OMe), 3.70 (dd, 1 H, H_3, J = 5.24, 10.26), 3.93 (dd, 1 H, J = 10.26, 9.12 Hz), 4.63 (d, 1 H, J = 9.12 Hz), 4.70 (d, 1 H, H_4, J = 5.24), 7.10-7.45 (m, 9 H, aromatic); mass spectrum, m/z (relative abundance): 308 (21), 276 (15), 264 (18), 210 (47), 206 (12), 205 (69), 204 (41), 203 (27), 202 (22), 179 (56), 178 (100), 165 (21). Exact mass for $C_{19}H_{16}O_4$: calculated 308.1048, found 308.1075.

Compound 63

Compound **62** (1.28 g) was dissolved in toluene (15 mL). To this solution p-toluenesulfonic acid (20 mg) was added and the solution was refluxed for 2 hours. After cooling, the solvent was evaporated and the crude product was recrystallized from 2-propanol to give the pure compound (780 mg), 67% yield. Mp 227-230°C; ir (CH_2Cl_2): 3400-2500 cm^{-1} (COOH), 1732 cm^{-1} (C=O), 1682 cm^{-1} (α-ß-unsaturated acid); ^1H NMR ($CDCl_3$): 3.34 (s, 3 H, OMe), 4.01 (d, 1 H, H_2, $J_{1,2}$ = 8.19 Hz), 4.63 (d, 1 H, H_1), 6.99-7.03 (m, 1 H, aromatic), 7.18-7.38 (m, 8 H, aromatic), 7.84 (s, 1 H, vinyl); mass spectrum, m/z (relative abundance): 308 (9), 290 (27), 276 (6), 262 (13), 248 (27), 231 (27), 205 (100), 204 (43), 203 (84), 202 (73), 178 (65), 155 (14), 127 (44). Exact mass for $C_{19}H_{16}O_4$: calculated 308.1048, found 308.1048.

Compound 64

The hydroxy sulfone **44** (50 mg) was dissolved in toluene (10 mL). To this solution dimethyl fumarate (110 mg) and ZnO (30 mg) were added. The reaction mixture was heated in a sealed flask at 140°C for 5 hours. After cooling, the reaction mixture was filtered, evaporated on a rotary evaporator and the excess dienophile was removed by heating at 100°C under high vacuum. The crude product was recrystallized from methylene chloride-hexane to give a white solid in 46% yield, mp 136-138°C; ir (CH_2Cl_2): 3200-3000 cm^{-1} (OH), 1748 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 2.74 (broad, 1 H, OH), 3.28 (dd, 1 H, H_3, J = 2.97 Hz), 3.46 (s, 3 H, OMe), 3.55 (dd, 1 H, H_2, J = 11.10 Hz), 3.76 (s, 3 H, OMe), 4.21 (d, 1 H, H_1, J = 11.10 Hz), 5.22 (d, 1 H, H_4), 6.80 (d, 1 H, aromatic), 7.10-7.45 (m, 8 H, aromatic); mass spectrum, m/z (relative abundance): 340 (1), 322 (3), 262 (17), 231 (10), 205 (4), 204 (6), 203 (6), 202 (4), 178 (17), 43 (100). The structure of the compound was further confirmed by converting it to the known compound **68**, as described below in the elimination reactions.

Treatment of 67 and other prroducts with methanol and diazomethane

The cycloadduct from the trans-acetoxyphenyl sulfone **47** and maleic anhydride appeared to be a mixture by ^1H NMR spectrum. The crude reaction mixture was refluxed with methanol for 1 hour, evaporated to dryness and then treated with excess diazomethane in ether. The ^1H NMR analysis showed the resulting product to be a mixture of **68** as the major product (50%), **69** (28%) and **66** (22%).

Elimination reactions to prepare 68 and 69

The cycloadducts **54**, **55**, **64**, **65** and **66** were converted to **68** by refluxing (20 mg) in toluene (10 mL) with p-toluenesulfonic acid (5 mg) for 2 hours. After cooling, the product mixture was filtered through a short silica gel column with methylene chloride and evaporated to give quantitative yield of the alkene in each case. For properties see ref. 70. The all cis-tetralin **56** was treated in the same way to give the cis-alkene **69** as an oil; ir (CH_2Cl_2): 1720 cm^{-1} and 1735 cm^{-1}; ^1H NMR ($CDCl_3$): 3.34 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.02 (d, 1 H, J = 8.15 Hz), 4.61 (d, 1 H), 7.01 (m, 1 H, aromatic), 7.18-7.38 (m, 9 H, aromatic), 7.73 (s, 1 H, vinyl); mass spectrum, m/z (relative abundance): 322 (28), 290 (50), 262 (57), 204 (95), 203 (98), 202 (93), 178 (64), 105 (100). When compound **69** was dissolved in 0.1M NaOMe and left at room temperature for 15 hours, it was converted quantitatively to the alkene **68**.

Treatment of 58 with methanol and diazomethane

Compound **58** (10 mg) was refluxed in methanol for 1.5 hours, evaporated and then treated with diazomethane in ether; ^1H NMR spectrum showed the product of the reaction to be mainly **56** with a small amount of **68** (25%).

Compound 71

The cycloadduct **62** (200 mg) was dissolved in methanol (35 mL) and refluxed for 20 hours. After cooling, the solvent was evaporated to give the crude product (220 mg), 99.5% yield. The product could not be recrystallized, ir (CH_2Cl_2): 1745 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 3.33 (dd,

1 H, H_3, J = 3.35, 5.49 Hz), 3.58 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.83 (dd 1 H, H_2, J = 5.49 Hz), 4.52 (d, 1 H, H_1, J = 8.41 Hz), 4.98 (d, 1 H, H_4, J = 3.35 Hz), 7.09-7.44 (m, 9 H, aromatic); mass spectrum, m/z (relative abundance): 340 (1), 308 (12), 248 (10), 231 (12), 210 (8), 205 (45), 196 (25), 195 (29), 194 (31), 179 (56), 178 (100), 165 (54). The relative abundance of the molecular ion was too low for exact mass measurement. Exact mass for $C_{19}H_{16}O_4$(M-32): calculated 308.1048, found 308.1059.

Compound 72

The cycloadduct **58** (15 mg) was dissolved in methanol (3 mL) and the solution was refluxed for 2.5 hours. After cooling, the solvent was evaporated to dryness to give the crude product (16.5 mg), 100% yield. The product was recrystallized from methylene chloride-hexane , mp 194-196°C; ir (CH_2Cl_2): 36000-2500 cm^{-1} (broad), 1790 cm^{-1}, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): 1.79 (s, 3 H, OAc), 3.41 (t, 1 H, H_3, J = 3.65 Hz), 3.66 (t, 1 H, H_2, J = 4.73 Hz), 3.78 (s, 3 H, OMe), 4.34 (d, 1 H, H_1), 6.58 (d, 1 H, H_4), 7.16-7.51 (m, 10 H, aromatic); mass spectrum, m/z (relative abundance): 325 (16)(M-43), 308 (22), 248 (25), 247 (24), 231 (17), 221 (29), 186 (22), 178 (36), 165 (19), 91 (30), 43 (100). The compound was converted to **73** by treatment with p-toluenesulfonic acid in toluene.

Compound 73

Compound **71** (17 mg) was dissolved in chloroform (3 mL). To this solution K_3PO_4 (10 mg in 1 mL of D_2O) was added. The reaction mixture

was heated on a steam bath for 2 hours. After cooling, the solution was acidified and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and evaporated to give the product (15 mg), 97% yield. IR (CH_2Cl_2): 3500-2800 cm^{-1}(broad), 1745 cm^{-1}(C=O), 1712 cm^{-1} (α,β-unsaturated ester); ^1H NMR ($CDCl_3$): 3.81 (s, 3 H, OMe), 3.99 (d, 1 H, H_2, J = 7.81 Hz), 4.60 (d, 1 H, H_1), 7.02 (q, 1 H, aromatic), 7.20-7.40 (m, 8 H, aromatic), 7.70 (s, 1 H, vinyl); mass spectrum, m/z (relative abundance): 308 (67), 262 (18), 237 (27), 205 (100), 195 (99), 165 (24), 137 (80), 105 (70), 91 (22), 77 (53). Exact mass for $C_{19}H_{16}O_4$: calculated 308.1048, found 308.1059.

Isomerisation of acetoxyphenyl sulfones

Pure acetoxyphenyl sulfone (**46** or **47**) (50 mg) was dissolved int-butyl alcohol (5 mL). Potassium phosphate (125 mg) was added to this solution and refluxed for 1 hour. After cooling, the solvent was evaporated. The crude product was dissolved in methylene chloride, filtered and evaporated to give a mixture of sulfones (44 mg). The NMR spectrum of this mixture showed to be cis and trans acetoxyphenyl sulfone in the ratio 45:55 respectively.

Deuterium exchange on the cis-acetoxyphenyl sulfone

Pure cis-acetoxyphenyl sulfone (21 mg) was dissolved in t-butyl alcohol-D (2 mL). Potassium phosphate (50 mg) was added and the solution refluxed for 1 hour. After working up (as in the isomerisation) NMR spectrum of the product showed to be a mixture of cis and trans 1-phenyl-3-acetoxy-1-deutero sulfone in the ratio 45:55.

4.3 Isolariciresinol dimethyl ether

6-Bromoveratraldehyde 77

A solution of bromine (10 g) in acetic acid (20 mL) was added over 15 min at 22-25°C to a solution of veratraldehyde (5 g, 0.3 mol) in acetic acid (50 mL). The mixture was stirred for 5 hours at room temperature, an equal volume of water added and the mixture then cooled to 4°C. The product was filtered off and recrystallized from methanol/water (6:1) to yield 5.9 g (80%). Mp 148-150°C. Lit 149-151°C(151).

6-Bromoveratraldehyde ethylene glycol acetal 78

6-Bromoveratraldehyde (3.6 g, 1.48×10^{-2}mol), ethylene glycol (1.8 g, 2.9×10^{-2}mol, 2 equivalents) and p-toluenesulfonic acid (50 mg) were mixed in benzene (40 mL). The reaction mixture was refluxed under a Dean-Stark trap for 2 hours. After cooling, sodium bicarbonate (0.3 g) was added and the mixture filtered through a short silica gel column with 50% EtOAc/hexane. The eluent was evaporated to yield 4.17 g (98%). Recrystallized from benzene/hexane, mp 110-112°C, ^{1}H NMR ($CDCl_3$): 3.87 (s, 6 H, OMe), 4.00-4.28 (m, 4 H), 6.00 (s, 1 H, acetal), 7.01 (s, 1 H, aromatic), 7.14 (s, 1 H, aromatic); mass spectrum, m/z (relative abundance) 290 (40), 289 (44), 288 (44), 287 (42), 246 (32), 245 (47), 243 (48), 229 (40), 218 (92), 216 (100), 209 (12), 149 (96), 119 (52). Anal. Calcd. for $C_{11}H_{13}BrO_4$: C 45.70, H 4.53, Br 27.64. Found: C 45.46, H 4.65, Br 27.53.

3,4-Dimethoxybenzylalcohol 79

$NaBH_4$ (1.14 g, 0.03 mol) was added slowly to a solution of veratraldehyde (10 g, 0.06 mol) in 2-propanol (50 mL). The reaction mixture was stirred at room temperature for 15 min and then refluxed for 10 min. Dilute HCl (10%) was cautiously added until the solution was acidic. After removing most of the 2-propanol in vacuo the solution was extracted with CH_2Cl_2, the extract washed with 5% $NaHCO_3$, dried ($MgSO_4$) and evaporated giving a viscous liquid (10 g, 99%). ^1H NMR ($CDCl_3$): 3.06 (br s, 1 H, OH) 3.86 (s, 6 H, OMe), 4.53 (s, 2 H, benzylic), 6.80-6.93 (m, 3 H, aromatic). The NMR spectrum was identical to that given in the literature(151).

3,4-Dimethoxybenzyl bromide 80

3,4-Dimethoxybenzyl alcohol (3.0 g,.018 mol) and PBr_3 (3.24 g, 2 equivalents) were stirred in CH_2Cl_2 (30 mL) overnight at room temperature. CH_2Cl_2 and PBr_3 were removed in vacuo, the residue dissolved in CH_2Cl_2 and stirred with a moist paste of $NaHCO_3$. The solution was filtered through $MgSO_4$, evaporated to dryness and pumped at high vacuum for 5 hours during which time the sample solidified to yield 3.35 g (82%). ^1H NMR ($CDCl_3$): 3.90 (s, 6 H, OMe), 4.55 (s, 2 H, benzylic), 6.80-7.20 (m, 3 H, aromatic); mass spectrum, m/z (relative abundance): 232 (67), 230 (66), 217 (4), 215 (4), 186 (10), 151 (100), 135 (62). The bromide was quite unstable and had to be stored at low temperature under nitrogen.

6-(3,4-Dimethoxybenzyl)veratraldehyde ethylene glycol acetal 81

The 6-bromoveratraldehyde ethylene glycol acetal (1.0 g) was dissolved in THF (5 mL), cooled to -78°C and tetramethylethylenediamine (TMEDA) (0.5 mL) added. n-Butyllithium in hexane (2.8 mL, 1.1 M) was added followed immediately by $(nBu)_3PCuI$ (1.0 g in 3 mL of THF) and 3,4-dimethoxybenzyl bromide (1.05 g in 4 mL THF). The mixture was stirred at -78°C for 15 min, at room temperature for 0.5 hour, then quenched with saturated NH_4Cl (10 mL). Water (20 mL) was added, the mixture extracted (CH_2Cl_2), the organic phase dried ($MgSO_4$) and evaporated <u>in vacuo</u>. Chromatography (30% EtOAc/hexane) yielded 0.94 g of the coupled acetal (75%) which could be recrystallized from hexane/CH_2Cl_2. Mp 122-124°C; ^1H NMR ($CDCl_3$): 3.783 (s, 3 H, OMe), 3.811 (s, 3 H, OMe), 3.849 (s, 3 H, OMe), 3.902 (s, 3 H, OMe), 3.995-4.020 (m, 2 H), 4.037 (s, 2 H), 4.135-4.158 (m, 2 H), 5.888 (s, 1 H), 6.602 (s, 1 H), 6.712-6.795 (m, 3 H, aromatic), 7.151 (s, 1 H); mass spectrum, m/z (relative abundance): 360 (24), 299 (27), 298 (65), 284 (10), 283 (9), 269 (6), 268 (7), 221 (13), 222 (100) 194 (8), 151 (6), 150 (6). Anal. Calcd. for $C_{20}H_{24}O_6$: C 66.65, H 6.71. Found: C 66.80, H 6.91.

6-(3,4-Dimethoxybenzyl)veratraldehyde 82

Acetal **81** (165 mg) was dissolved in ether (10 mL) and HCl (10%) added with stirring at room temperature. After 2 hours, the ether was separated, the aqueous layer extracted (CH_2Cl_2), the organic extracts combined, dried ($MgSO_4$) and evaporated to give 138 mg of aldehyde (95%) which was recrystallized from hexane/CH_2Cl_2. mp 91-92.5°C. ^1H NMR

($CDCl_3$): 3.813 (s, 3 H, OMe), 3.845 (s, 3 H, OMe), 3.897 (s, 3 H, OMe), 3.939 (s, 3 H, OMe), 4.330 (s, 2 H, benzylic), 6.60-6.80 (m, 4 H, aromatic), 7.418 (s, 1 H), 10.200 (s, 1 H, aldehyde); ir (CH_2Cl_2): 1682 cm^{-1} (C=O); mass spectrum, m/z (relative abundance): 316 (90), 301 (19), 299 (28), 298 (20), 285 (47), 254 (20), 253 (14), 178 (28), 151 (43), 150 (100), 115 (80). Anal. Calcd. for $C_{18}H_{20}O_5$: C 68.33, H 6.38. Found: C 67.99, H 6.68.

1-(3,4-Dimethoxyphenyl)-3-hydroxy-5,6-dimethoxy -1,3-dihydrobenzo[c]thiophene-2,2-dioxide 83

The aldehyde **82** was dissolved in thiophene free benzene (300 mL) containing SO_2 (20 g) and the solution irradiated with a water-jacketed 450-W Hanovia medium-pressure mercury lamp immersed in the solution, for 8 h under a blanket of nitrogen. The solvent was evaporated in vacuo, the residue dissolved in CH_2Cl_2 and this extracted three times with 5% aqueous sodium bicarbonate. The basic extract was acidified with HCl (10%), extracted (CH_2Cl_2), the organic extract dried ($MgSO_4$) and evaporated to leave a glassy solid (790 mg, 67%). Unreacted aldehyde **82**, (120 mg) was isolated from the neutral organic material. Yield, based on aldehyde consumed is 77%. A mixture of two isomers could be discerned in the NMR spectrum. ^1H NMR ($CDCl_3$), [isomer 1]: 3.782 (s, 3 H, OMe), 3.810 (s, 3 H, OMe), 3.891 (s, 3 H, OMe), 3.945 (s, 3 H, OMe), 5.315 (s, 1 H, H_1), 5.687 (s, 1 H, H_3), 6.557 (s, 1 H), 6.77-6.95 (m, 3 H, OMe), 7.066 (s, 1 H); [isomer 2]: 3.774 (s, 3 H, OMe), 3.828 (s, 3 H, OMe), 3.906 (s, 3 H, OMe), 3.945 (s, 3 H, OMe), 5.473 (s, 1 H, H_1), 5.646 (s, 1 H, H_3), 6.522 (s, 1 H), 6.77-6.95 (m, 3 H, aromatic), 7.066

(s, 1 H); the OH protons were not observed and were probably obscured beneath the methoxy signals; ir (CH_2Cl_2): 3600, 1522, 1472, 1232, 1120, 1030 cm^{-1}; mass spectrum, m/z (relative abundance): 316 (51)(M - SO_2), 285 (51), 178 (51), 165 (56), 151 (61), 150 (100), 139 (61), 115 (66).

1-(3,4-Dimethoxyphenyl)-3,5,6-trimethoxy-1,3-dihydrobenzo[c] thiophene-2,2-dioxide 84

Hydroxy sulfone **83** (104 mg) and p-toluenesulfonic acid (30 mg) were refluxed in a 50:50 mixture of methanol and CH_2Cl_2 (7 mL) for 1 h. The solvent was evaporated <u>in vacuo</u> at 20°C and the residue passed through a short silica gel column with 90% EtOAc/hexane. Evaporation of the eluent yielded an oil (105 mg, 98%). ^1H NMR spectrum indicated the presence of two isomers in the approximate ratio of 65:35 (<u>cis</u>/<u>trans</u>). These could be separated by chromatography (35% EtOAc/hexane). ^1H NMR ($CDCl_3$) <u>cis</u>-isomer: 3.782 (s, 3 H, OMe), 3.808 (s, 3 H, OMe), 3.860 (s, 3 H, OMe), 3.892 (s, 3 H, OMe), 3.949 (s, 3 H, OMe), 5.232 (s, 1 H, H_1), 5.337 (s, 1 H, H_3), 6.541 (s, 1 H), 6.718-6.915 (m, 3 H, aromatic), 6.984 (s, 1 H); <u>trans</u>-isomer: 3.763 (s, 3 H, OMe), 3.835 (s, 3 H, OMe), 3.878 (s, 3 H, OMe), 3.913 (s, 3 H, OMe), 3.950 (s, 3 H, OMe), 5.306 (s, 1 H, H_3), 5.479 (s, 1 H, H_1), 6.502 (s, 1 H), 6.665-6.932 (m, 3 H, aromatic), 6.995 (s, 1 H); ir (CH_2Cl_2): 1612, 1532, 1472, 1232, 1120-1170 cm^{-1}; mass spectrum (of mixture), m/z (relative abundance): 330 (11)(M-SO_2), 316 (49), 299 (26), 298 (18), 285 (32), 240 (23), 224 (37), 209 (67), 194 (67), 193 (50), 166 (52), 165 (98), 154 (100), 151 (67), 139 (67). Elemental analysis not possible due to instability.

(R)-Phenylethoxy sulfone 85

The hydroxy sulfone **83** (234 mg) and (R)-1-phenylethanol (Aldrich) (1.1 g) were added to CH_2Cl_2 (12 mL) followed by p-toluenesulfonic acid (20 mg) and $MgSO_4$ (100 mg). After 6 hours at room temperature the solution was evaporated in vacuo and chromatographed using 25% EtOAc/hexane as eluent to yield 230 mg (77%). ^1H NMR ($CDCl_3$): 1.583 (d, 3 H, J = 6.45 Hz), 3.760 (s, 3 H, OMe), 3.826 (s, 3 H, OMe), 3.895 (s, 3 H, OMe), 3.905 (s, 3 H, OMe), 5.152 (s, 1 H, H_1), 5.166 (q, 1 H, J = 6.45 Hz), 5.267 (s, 1 H, H_3), 6.520 (s, 1 H, aromatic), 6.727 (s, 1 H, aromatic), 6.747-6.887 (m, 3 H, aromatic), 7.389-7.545 (m, 5 H, aromatic); mass spectrum, m/z (relative abundance): 420 (<1)($M-SO_2$), 329 (9), 316 (50), 315 (54), 299 (27), 298 (18), 285 (31), 166 (22), 165 (45), 154 (68), 151 (27), 150 (54), 139 (100). Elemental analysis was not possible due to instability.

(+/-)-Cycloadduct 88

ZnO (30 mg, anhydrous) was added to a solution of the sulfone **84** (99.5 mg) and dimethyl fumarate (143 mg, 4 eq) in benzene (8 mL). The reaction mixture was flushed with nitrogen, refluxed 15 hours, evaporated and chromatographed through a short silica gel column (30% EtOAc/hexane) to yield an oil (98 mg, 82%). ^1H NMR ($CDCl_3$): 3.263 (dd, 1 H, H_3, J = 2.91, 12.15 Hz), 3.415 (s, 3 H, OMe), 3.512 (s, 3 H, OMe), 3.519 (dd, 1 H, H_2, J = 10.86, 12.15 Hz), 3.622 (s, 3 H, OMe), 3.761 (s, 3 H, OMe), 3.791 (s, 3 H, OMe), 3.882 (s, 3 H, OMe), 3.922 (s, 3 H, OMe), 3.966 (d, 1 H, H_1, J = 10.86 Hz), 5.653 (d, 1 H, H_4, J = 2.91 Hz), 6.324 (s, 1 H), 6.617-6.929 (m, 4 H, aromatic); ir (CH_2Cl_2): 1742,

1732, 1522, 1242 cm^{-1}; mass spectrum, m/z (relative abundance): 474 (28), 382 (100), 381 (42), 351 (57), 252 (43), 222 (28), 59 (42); exact mass for $C_{25}H_{30}O_9$: calculated 474.1889, found 474.1861.

(+/-)-Diester 90

The cycloadduct **88** (98 mg) and Pd/C (5%, 150 mg, Aldrich) were stirred in methanol (20 mL) under hydrogen for 15 hours. The mixture was filtered and evaporated to give a solid (88 mg, 96%) which could be recrystallized from 2-propanol. Mp 126-127°C, lit. 127°C.(68). The NMR and IR spectra were identical to those reported previously(68). Mass spectrum, m/z (relative abundance): 444 (60), 384 (45), 325 (100), 259 (60), 222 (45), 151 (45).

(+/-)-Isolariciresinol dimethyl ether 48

(+/-)-Diester **90A** (13 mg) was dissolved in dry THF (3 mL), cooled to 0°C and $LiAlH_4$ (4 mg) added. The solution was stirred for 1 h at 20°C and then refluxed for 15 min. Water (1 drop) and 10% aqueous HCl (ca 0.5 mL) were added and then the solution dried ($MgSO_4$) and evaporated to give a solid (12 mg, ca 100%). Recrystallization from EtOAc/hexane gave crystals, mp 150-153°C; lit. 150-152°C(68). ^1H NMR ($CDCl_3$): 1.788-1.895 (m, 1 H, H_2), 1.945-2.185 (m, 1 H, H_3), 2.295-2.615 (br s, 1 H, OH), 2.723 (dd, 1 H, H_4 <u>cis</u> to H_3, J = 5.1, 15.0 Hz), 2.821 (dd, 1 H, H_4 <u>trans</u> to H_3, J = 11.3, 15.0 Hz), 3.505 (dd, 1 H, one of the CH_2 protons at C_2, J = 5.2, 11.2 Hz), 3.571 (s, 3 H, OMe), 3.772-3.880 (m, 4 H, H_1, one of the CH_2 protons at C_2 and the CH_2 protons at C_3), 3.802 (s, 3 H, OMe), 3.847 (s, 3 H, OMe), 3.878 (s, 3 H, OMe), 6.201 (s, 1 H),

6.596-6.603 (m, 2 H), 6.65-6.68 (m, 2 H); ir spectrum was identical to that in the literature; mass spectrum, m/z (relative abundance): 388 (100), 340 (92), 269 (73), 189 (42), 151 (73).

Elimination product 95

The cycloadduct **88** (12 mg) and p-toluenesulfonic acid (5 mg) were refluxed in toluene (3 mL) for 16 hours. The mixture was filtered through a silica gel column to give an oil (11 mg, 99%). ^{1}H NMR ($CDCl_3$): 3.642 (s, 3 H, OMe), 3.755 (s, 3 H, OMe), 3.789 (s, 3 H, OMe), 3.809 (s, 3 H, OMe), 3.828 (s, 3 H, OMe), 3.911 (s, 3 H, OMe), 4.002 (d, 1 H, H_2, J = 2.6 Hz), 4.642 (d, 1 H, H_1, J = 2.6 Hz), 6.450 (dd, 1 H), 6.620-6.700 (m, 3 H, aromatic), 6.873 (s, 1 H, aromatic), 7.672 (s, 1 H, H_4); IR (CH_2Cl_2) 1740, 1710, 1517 cm^{-1}; mass spectrum, m/z (relative abundance): 442 (28), 383 (43), 382 (100), 352 (16), 351 (68), 324 (8), 128 (17), 91 (16). Exact mass for $C_{24}H_{26}O_8$: calculated 442.1628, found 442.1643.

Cycloadduct 89A

The alkoxysulfone **85** (230 mg) was dissolved in benzene (10 mL) with dimethyl fumarate (280 mg). ZnO (100 mg) and K_2CO_3 (90 mg) were added and the mixture refluxed for 1 hour. The mixture was chromatographed using 40% EtOAc/hexane to give an oil (208 mg, 78%). TLC and NMR spectrum indicated the presence of two isomeric adducts. Rechromatography using 25% EtOAc/hexane gave the major isomer as an oil (116 mg, 43%). ^{1}H NMR ($CDCl_3$): 1.422 (d, 3 H, J = 6.5 Hz), 3.241(dd, 1 H, H_3, J = 2.9, 12.0 Hz), 3.530 (s, 3 H, OMe), 3.553 (s, 3 H, OMe),

3.565 (s, 3 H, OMe), 3.645 (dd, 1 H, H_2, J = 11.0, 12.0 Hz), 3.694 (s, 3 H, OMe), 3.823 (s, 3 H, OMe), 3.878 (s, 3 H, OMe), 3.925 (d, 1 H, J = 11.0 Hz), 4.578 (q, 1 H, J = 6.5 Hz), 4.922 (d, 1 H, H_4, J = 2.85 Hz), 6.068 (s, 1 H, aromatic), 6.209 (s, 1 H, aromatic), 6.55-6.85 (m 3 H, aromatic), 7.20-7.50 (m, 5 H, aromatic); ir ($CDCl_3$): 1740, 1520, 1250 cm^{-1}; mass spectrum, m/z (relative abundance): 564 (3.5), 442 (27), 383 (43), 382 (100), 352 (16), 351 (65), 316 (10), 315 (11), 122 (18). Exact mass for $C_{32}H_{36}O_9$: calculated 564.2359, found 564.2342.

Diester 90A (1S,2R,3R).

The cycloadduct **89** (113 mg) was dissolved in methanol containing 25% acetic acid (13 mL) with Pd/C (5%, 50 mg) and the mixture stirred under hydrogen for 15 h at 20°C. the mixture was filtered, evaporated and chromatographed (25% EtOAc/hexane) to give a solid (84 mg, 92%) which was recrystallized from 2-propanol. Mp 143-145°C. The spectra (NMR and IR) were identical to those of racemic **90A**. $[\alpha]^{20}$ +19.9 (c 0.44 chloroform).

(+)-Isolariciresinol dimethyl ether 48

The optically active diester **90A** (35.5 mg) was reduced in a manner identical to that used for racemic **48** to yield 29.5 mg (100%). Spectra (NMR and IR) were identical to the racemic material. Mp 167-169°C; lit 167-169°C(138). $[\alpha]^{20}$ +13.2 (c 0.58 chloroform).

Compound 92

This compound was isolated as a byproduct during the coupling reaction of **78** and **79**. Chromatography and recrystallization from ethyl acetate-

hexane gave mp 208-210°C. ^{1}H NMR ($CDCl_3$): 3.96 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 6.79 (s,1 H, aromatic), 7.56 (s, 1 H, aromatic), 9.67 (s, 1 H, aldehyde); mass spectrum, m/z (relative abundance): 330 (10), 316 (32), 301 (100), 285 (42), 178 (8), 151 (15), 150 (38). As the compound was obtained in a very small amount, exact mass/mass spectrometry was not performed.

Compound 94

This compound was isolated as another byproduct from the coupling reaction of **78** and **79**, after chromatography. IR (CH_2Cl_2): 1690 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): 3.72 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.84 (s, 6 H, OMe), 3.89 (s, 2 H, dibenzylic), 3.93 (s, 3 H, OMe), 4.25 (s, 2 H, dibenzylic), 6.44 (d, 2 H, aromatic), 6.60-6.83 (m, 4 H, aromatic), 7.39 (s, 1 H, aromatic), 10.03 (s, 1 H, aldehyde); mass spectrum, m/z (relative abundance): 466 (5), 315 (31), 301 (20), 287 (100), 151 (44).

Compound 96

6-Bromoveratraldehyde ethylene glycol acetal **78** (250 mg) was dissolved in dry THF (8 mL), TMEDA (0.13 mL, 1 equivalent) was added at -78°C, then n-butyllithium (0.8 mL, 1.25M) was added, followed by the addition of 0.1 mL acetophenone. The reaction mixture was warmed to room temperature, quenched with saturated solution of ammonium chloride (10 mL), and extracted with methylene chloride. The organic extract was dried ($MgSO_4$) and solvent was evaporated to give 284 mg of crude product. After chromatography with 25% ethyl acetate-hexane, the pure compound (165 mg) was obtained, 58% yield. The compound was

recrystallized from methylene chloride-hexane, mp 119-121°C; ir (CH_2Cl_2): 3600-3200 cm^{-1}(broad); ^1H NMR ($CDCl_3$): 1.88 (d, 3 H, CH_3, J = 0.39 Hz), 3.76-3.88 (m, 2 H), 3.90 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.97-4.05 (m, 2 H), 4.41 (s, 1 H, OH), 5.25 (s, 1 H, acetal), 7.18-7.38 (m, 7 H, aromatic); mass spectrum, m/z (relative abundance): 330 (10), 259 (15), 210 (57), 209 (52), 182 (42), 167 (26), 165 (26), 138 (94), 121 (100), 105 (42). Exact mass for $C_{19}H_{22}O_5$: calculated 330.1473, found 330.1470.

Compound 97

The bromoacetal **78** (250 mg) was dissolved in dry THF (8 mL) and cooled to -87°C. TMEDA (0.13 mL), n-butyllithium in hexane (0.8 mL) and veratraldehyde (145 mg) were added follwing the procedure for compound **96.** After chromatography with 70% ethyl acetate-hexane an oil (223 mg) was obtained, 68% yield, ir (CH_2Cl_2): 3600-3200 cm^{-1} (broad); ^1H NMR ($CDCl_3$): 3.24 (d, 1 H, OH, J = 3.98 Hz), 3.76 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 4.00-4.20 (m, 4 H, ethylenic), 5.91 (s, 1 H, acetal), 6.13 (d, 1 H, benzylic), 6.77 (s, 1 H, aromatic), 6.81-6.90 (m, 2 H, aromatic), 6.99 (d, 1 H, aromatic), 7.13 (s, 1 H, aromatic); mass spectrum, m/z (relative abundance): 376 (2), 315 (4), 210 (5), 209 (4), 193 (9), 169 (11), 168 (100), 167 (15), 151 (19), 139 (27), 121 (77).

Compound 98

The alcohol **97** (30 mg) was dissolved in ethyl acetate (5 mL). Pd/C (30 mg) was added to the solution and this stirred under the H_2 atmosphere,

for 24 hours. The solution was filtered and evaporated to give a colourless oil (20 mg), 83% yield. IR (CH_2Cl_2): no OH absorption; ^1H NMR ($CDCl_3$): 2.20 (s, 3 H, methyl), 3.81 (s, 6 H, OMe), 3.92 (m, 8H, OMe and benzylic), 6.70-6.80 (m, 5 H, aromatic); mass spectrum, m/z (relative abundance): 302 (7), 166 (23), 152 (100), 137 (30), 109 (27), 91 (23), 74 (61), 73 (46).

Compound 99

Benzhydrol (184 mg) was dissolved in dry THF (7 mL) and cooled to -78°C. n-Butyllithium in hexane (0.8 mL, 1 equivalent) was added, followed by the addition of CS_2 (0.125 mL) and MeI (0.28 g). The reaction mixture was warmed to room temperature and stirred for 0.5 hour. The reaction mixture was evaporated to dryness, dissolved in methylene chloride, washed with water, dried ($MgSO_4$) and evaporated again to give the crude product (0.28 g), 100% yield. IR (CH_2Cl_2): 1062 cm^{-1}, 1212 cm^{-1}; ^1H NMR ($CDCl_3$): 2.53 (s, 3 H, S-Me), 7.33 (s, 10 H, aromatic), 7.63 (s, 1 H, benzylic); mass spectrum, m/z (relative abundance): 274 (1), 197 (4), 183 (60), 167 (93), 163 (67), 152 (17), 138 (40), 109 (51), 91 (100), 77 (47).

Compound 100 and 101

These two compound were obtained when the crude product of **99** was chromatographed using 5% ethyl acetate-hexane. **100:** IR (CH_2Cl_2): 1643 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 2.37 (s, 3 H, S-Me), 6.15 (s, 1 H, benzylic), 7.20-7.40 (m, 10 H, aromatic); mass spectrum, m/z (relative abundance): 274 (3), 238 (3), 209 (2), 183 (19), 168 (15), 167 (100),

165 (23), 105 (15). **101:** ^{1}H NMR ($CDCl_3$): 2.00 (s, 3 H, S-Me), 5.06 (s, 1 H, benzylic), 7.20-7.50 (m, 10 H, aromatic); mass spectrum, m/z (relative abundance): 214 (9), 167 (100), 165 (28), 152 (12), 126 (10), 75 (20).

Compound 102

The procedure was similar to that for **99**. Thus 6-bromoveratraldehyde ethylene glycol acetal (250 mg) was dissolved in THF (8 mL). To this solution TMEDA (0.13 mL), n-butyllithium in hexane (0.8 mL), veratraldehyde (150 mg), CS_2 (0.12 mL) and MeI (0.12 mL) were added. After working up, the crude product was chromatographed using 20% ethyl acetate-hexane as eluent to give the pure product (240 mg), 70% yield. ^{1}H NMR ($CDCl_3$): 2.40 (s, 3 H, S-Me), 3.80 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.00-4.24 (m, 4 H, ethylenic), 6.04 (s, 1 H, acetal), 6.50 (s, 1 H, benzylic), 6.75-7.35 (m, 5 H, aromatic); mass spectrum, m/z (relative abundance): 466 (2), 406 (4), 391 (22), 360 (35), 359 (100), 358 (27), 165 (16), 151 (16).

Compound 103

Compound **102** (40 mg) was dissolved in 95% ethanol (4 mL). Raney Ni (30 mg) was added and the solution was refluxed for 3 hours. After cooling, the solution was filtered and evaporated to give 27 mg of the product, 99% yield. Later this compound was prepared from **82** by reduction with sodium borohydride. The aldehyde **82** (360 mg) was dissolved in 2-propanol (15 mL), sodium borohydride (25 mg) was added to the solution and refluxed for 15 minutes. After cooling, the solution was acidified

with 10% HCl, diluted with 10 mL water and extracted with methylene chloride (3X, 15 mL). The organic extract was dried ($MgSO_4$) and evaporated to give the product (360 mg), 99.4% yield. This was recrystallized from methylene chloride-hexane, mp 103-105°C; ir (CH_2Cl_2): 3650 cm^{-1} (OH); ^1H NMR ($CDCl_3$): 1.59 (s, broad, 1 H, OH) 3.81 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.97 (s, 2 H, dibenzylic), 4.59 (s, 2 H, benzylic), 6.60-6.79 (m, 4 H, aromatic), 6.96 (s, 1 H, aromatic); mass spectrum, m/z (relative abundance): 318 (3), 269 (4), 223 (4), 179 (11), 168 (100), 151 (89). Exact mass for $C_{18}H_{22}O_5$: calculated 318.1467, found 318.1467.

Compound 104

The xanthate **102** (22 mg) was dissolved in ether (3 mL) and stirred at room temperature with a few drops of 10% HCl for 2 hours. The solution was washed with water (5 mL), the aqueous extract, back washed with ether (5 mL), the organic extract evaporated and finally filtered through a short silica gel column using 25% ethyl acetate-hexane. The solvent was evaporated to yield the product (13 mg), 65% yield. IR (CH_2Cl_2): 1682 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 2.40 (s, 3 H, S-Me), 3.835 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 6.77-6.99 (m, 4 H, benzylic and aromatic), 7.09 (s, 1 H,aromatic), 7 37 (s, 1 H, aromatic), 10.22 (s, 1 H, aldehyde); mass spectrum, m/z (relative abundance): 422 (4), 362 (5), 347 (20), 316 (76), 315 (100), 285 (42), 151 (22).

4.4 Epipodophyllotoxin and podophyllotoxin analogue

Compound 105

The half ester **63** (10 mg) was dissolved in dry THF (5 mL). BF_3.DMS (0.5 mL, 2M in ether) was added at room temperature and the solution was stirred for 1.5 hours. A solution (8 mL) of 5 drops of acetyl chloride in 10 mL methanol was added and the reaction mixture stirred for another 2 hours. The solvent was evaporated to dryness and the compound was chromatographed using 35% ethyl acetate-hexane to give the pure product (55 mg), 58% yield. IR (CH_2Cl_2): 3600-3200 cm^{-1} (OH), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 2.40 (broad, 1 H, OH), 3.50 (s, 3 H, OMe), 3.71 (d, 1 H, H_2, J = 7.5 Hz), 4.26 (s, 2 H), 4.50 (d, 1 H, H_1), 6.70 (s, 1 H, vinyl), 7.08-7.45 (m, 9 H, aromatic); mass spectrum, m/z (relative abundance): 294 (3), 276 (17), 262 (23), 217 (54), 202 (34), 119 (95), 117 (100), 105 (55). Exact mass for $C_{19}H_{18}O_3$: calculated 294.1256, found 294.1256.

Compound 107

The alcohol **105** (55 mg) was dissolved in methylene chloride (5 mL), methanol (5 mL) and bromine (3-4 drops) were added to the solution and stirred for 5 minutes. The reaction mixture was evaporated to dryness and chromatographed using 15% ethyl acetate-hexane to give the pure compound (36 mg), 52% yield. IR (CH_2Cl_2): 1790 cm^{-1} (strong band, C=O, lactone); ^1H NMR ($CDCl_3$): 3.80 (s, 3 H, OMe), 3.91 (d, 1 H, J = 4.45 Hz), 4.52 (d, 1 H, J = 11.05 Hz), 4.53 (d, 1 H, H_1), 4.72 (d, 1 H,), 4.74 (s, 1 H, H_4), 7.04 (d, 2 H, aromatic), 7.22-7.60 (m, 7 H,

aromatic); ^{1}H NMR (C_6D_6): 3.29 (s, 3 H, OMe), 3.51 (d, 1 H, H_2), 4.10 (dd, 1 H), 4.22 (d, 1 H, H_1), 4.33 (s, 1 H, H_4), 4.60 (d, 1 H,), 6.99-7.29 (m, 7 H, aromatic), 7.59 (m, 1 H, aromatic); mass spectrum, m/z (relative abundance): 374. (4), 372 (4), 261 (4), 217 (34), 215 (13), 210 (100), 179 (40), 178 (67).

Compound 108

The bromolactone **107** (26 mg) was dissolved in glacial acetic acid (3 mL), Zn dust (100 mg) was added to the solution and this stirred at room temperature for 2 hours. Acetic acid was removed under high vacuum, then the reaction mixture was filtered through a short silica gel column using 15% ethyl acetate-hexane to give the crude product (17 mg), 92% yield. IR (CH_2Cl_2): 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$): 3.99-4.03 (m, 1 H, H_2), 4.56 (d, 1 H, H_1, J = 8.16 Hz), 4.79-4.85 (m, 1 H) 4.96-5.03 (m, 1 H), 6.57-6.60 (m, 1 H, H_4), 6.88 (d, 1 H, aromatic), 7.10-7.35 (m, 9 H, aromatic); mass spectrum, m/z (relative abundance): 276 (M-2, 8), 262 (7), 261 (16), 260 (82), 232 (26), 231 (76), 203 (35), 202 (61), 149 (100).

Compound 110

The half ester **71** (15 mg) was dissolved in methylene chloride (4 mL), p-toluenesulfonic acid (10 mg) was added and the solution refluxed for 3 hours. After cooling, the reaction mixture was washed with water. The organic solution was dried ($MgSO_4$) and evaporated to give 13 mg of crude product. The compound was chromatographed using 20% ethyl acetate-hexane to give the pure compound (3 mg), ir (CH_2Cl_2): 1796 cm^{-1} (C=O, lactone), 1744 cm^{-1} (C=O ester); ^{1}H NMR ($CDCl_3$): 3.40 (s,broad 1 H,

H_3), 3.43 (dd, 1 H, H_2), 3.81 (s, 3 H, OMe), 4.65 (d, 1 H, J = 4.9 Hz), 5.59 (d, 1 H, H_4, J = 1.1 Hz), 7.08-7.11 (m, 2 H, aromatic), 7.26-7.35 (m, 7 H, aromatic); mass spectrum, m/z (relative abundance): 308 (40), 262 (25), 205 (77), 204 (42), 203 (38), 202 (35), 195 (100), 149 (65), 105 (62), 77 (40).

4.5 Deoxypodophyllotoxin

Compound 112

The half ester **71** (20 mg) was dissolved in distilled methanol (5 mL). Pd/C (10 mg) was added and the solution stirred under an atmosphere of H_2 for 18 hours. The solution was filtered and evaporated to give a white solid (18 mg), 99% yield. The compound was recrystallized from methylene chloride hexane, mp 174-175°C; ir (CH_2Cl_2): 1742 cm^{-1} (C=O ester), 1714 cm^{-1} (C=O, acid); ^1H NMR ($CDCl_3$): 3.10 (dd, 1 H, J = 16.5 Hz, 5.6 Hz), 3.22 (m, 8 lines, 1 H, J = 12.3 Hz, J = 3.7 Hz), 3.53 (dd, 1 H, J = 6.1 Hz), 3.61 (dd, 1 H), 3.72 (s, 3 H, OMe), 4.49 (d, 1 H), 6.92 (d, 1 H, aromatic), 7.01 (m, 1 H, aromatic), 7.17-7.28 (m, 7 H, aromatic); mass spectrum, m/z (relative abundance): 310 (23), 292 (12), 264 (22), 250 (38), 232 (16), 206 (20), 205 (100), 204 (40), 179 (31), 178 (25), 91 (18). Exact mass for $C_{19}H_{18}O_4$: calculated 310.1204, found 310.1223

Compound 113

The half ester **112** (28 mg) was dissolved in a solution of NaOMe in methanol (3 mL 1M). Another 1 mL of methanol was added to the solution and this refluxed for 6 hours. After cooling, the solvent was

evaporated, the residue dissolved in water and the aqueous solution was extracted with methylene chloride (10 mL, 2 times). The aqueous solution was acidified with 10% HCl and extracted with methylene chloride (10 mL, 2X). The organic extract was dried ($MgSO_4$) and evaporated to give the product (24 mg), 85% yield. IR spectrum was similar to the other isomer **112**; ^1H NMR ($CDCl_3$): 2.96 (dd, 1 H, J = 16.3 Hz, J = 11.9 Hz), 3.17 (m, 1 H, H_3, J = 11.9 Hz, J = 5.7 Hz), 3.34 (dd, 1 H), 3.43 (dd, 1 H, H_2), 3.66 (s, 3 H, OMe), 4.68 (d, 1 H, H_1, J = 5.5 Hz), 6.89-6.99 (m, 2 H, aromatic), 7.06-7.30 (m, 7 H, aromatic).

6-Bromopiperonal 114

Piperonal (1.5 g) was dissolved in acetic acid (5 mL). Bromine (3.2 g) in acetic acid (5 mL) was added to the above solution slowly with cooling in an ice bath. The solution was stirred overnight. An equal volume of water was added to the reaction mixture. The crystals were filtered off and recrystallized from methanol-water (6:1 by vol.) to give white needles, 64% yield, mp 127-129°C (Lit. 129°C) (47).

6-Bromopiperonal ethylene glycol acetal 115

6-Bromopiperonal **114** (1.118 g) was dissolved in benzene (15 mL). Ethylene glycol (0.70 g, 2 equivalent) and p-toluenesulfonic acid (50 mg) were added to the solution and this refluxed under a Dean-Stark trap for 16 hours. After cooling, the reaction mixture was filtered through a short silica gel column with benzene. After evaporating the solvent, a solid mass (1.28 g) was obtained, 98% yield. After recrystallization from ethyl acetate-hexane, mp 67-69°C (lit. 68-69°C)(47).

3,4,5-trimethoxybenzylalcohol 116

3,4,5-Trimethoxybenzaldehyde (1.96 g) was dissolved in 2-propanol (10 mL). Sodium borohydride (200 mg) in 2-propanol (5 mL) was added slowly. The reaction mixture was refluxed for 15 minutes. After cooling, the solution was acidified with 10% HCl. Excess 2-propanol was removed on a rotary evaporator and the solution was then extracted with methylene chloride (15 mL, 3 times). The organic extract was washed with 5% sodium bicarbonate solution, dried ($MgSO_4$) and the solvent evaporated to give an oil (1.94 g), 98% yield. ^1H NMR spectrum was identical to that reported in the literature(153).

3,4,5-Trimethoxybenzyl bromide 117

The alcohol **116** (1.94 g) was dissolved in methylene chloride (25 mL). PBr_3 (0.885 g) was added to the solution and stirred overnight at room temperature. Excess PBr_3 was removed in vacuo and the residue dissolved in methylene chloride and washed with 5% sodium bicarbonate solution. The organic solution was dried ($MgSO_4$) and evaporated to dryness by pumping at high vacuum for 6 hours, when the sample solidified to yield the product (1.95 g), 76%. ^1H NMR ($CDCl_3$): 3.89 (s, 9 H, OMe), 4.50 (s, 2 H), 6.66 (s, 2 H, aromatic); mass spectrum, m/z (relative abundance): 262 (29), 260 (29), 182 (75), 181 (100), 165 (17), 148 (57), 138 (25), 137 (30), 136 (45). The bromide was quite unstable and had to be stored at low temperature under nitrogen.

6-(3',4'.5'-Trimethoxybenzyl)piperonal 119

6-Bromopiperonal ethylene glycol acetal (1 g) was dissolved in dry THF (12 mL) and cooled to -78°C. TMEDA (0.52 mL), n-butyllithium in hexane (1.4 mL, 1.2 equivalents), $(nBu)_3PCuI$ complex (1.36 g), and 3,4,5-trimethoxybenzyl bromide (0.9 g) in THF were added to the solution. The reaction mixture was warmed to room temperature and stirred for 0.5 hours, then quenched with saturated ammonium chloride solution (15 mL), water (20 mL) was added and the solution was extracted with methylene chloride (20 mL,3 times). The organic extract was evaporated to dryness. The crude product was dissolved in ether (20 mL) and stirred with 10% HCl (2 mL). The ether layer was separated, dried ($MgSO_4$) and evaporated to dryness. After chromatography with 30% ethyl acetate-hexane the desired aldehyde was obtained (400 mg), 36% yield in 2 steps. Recrystallized from ethyl acetate-hexane, mp 123-125°C (lit. 124-125°C) (47).

1-(3',4',5'-Trimethoxyphenyl)-3-hydroxy-5,6-methylenedioxy-1,3 dihydrobenzo[c]thiophene-2,2-dioxide 120

This compound was prepared following our previously reported procedure in 35% yield(128). The product was a mixture of cis- and trans-diastereomers. ^1H NMR ($CDCl_3$): [isomer 1]: 3.80 (s, 6 H, OMe), 3.87 (s, 3 H, OMe), 5.22 (s, 1 H, H_3), 5.66 (s, 1 H, H_1), 6.00-6.03 (dd, 2 H, methylenedioxy), 6.47 (s, 2 H,aromatic), 6.55 (s, 1 H, aromatic), 7.01 (s, 1 H, aromatic). [Isomer 2]: 3.82 (s, 6 H, OMe), 3.88 (s, 3 H, OMe), 5.44 (s, 1 H, H_1), 5.61 (s, 1 H, H_3), 6.04-6.06 (dd, 2 H, methylenedioxy), 6.49 (s, 2 H, aromatic), 6.55 (s, 1 H, aromatic), 7.01

(s, 1 H, aromatic); mass spectrum, m/z (relative abundance): 330 (100, M-SO_2), 313 (75), 312 (35), 299 (37), 297 (30), 282 (15), 169 (20), 124 (40).

Compound 126

This compound was isolated as a byproduct during the coupling reaction of **115** and **116**. Chromatography and recrystallization from ethyl acetate-hexane gave mp 238-240°; ir (CH_2Cl_2): 1684 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 6.13 (s, 4 H, methylenedioxy), 6.76 (s, 2 H, aromatic), 7.47 (s, 2 H, aromatic), 9.62 (s, 2 H, aldehyde); mass spectrum, m/z (relative abundance): 298 (.1), 270 (16), 269 (100), 212 (41), 183 (33), 127 (33), 126 (50), 74 (58).

Compound 128

This compound was also isolated as another byproduct in the coupling reaction of **115** and **116** by chromatography. ^1H NMR ($CDCl_3$): 2.85 (s, 4 H, benzylic), 3.83 (s, 18 H, OMe), 6.36 (s, 4 H, aromatic); mass spectrum, m/z (relative abundance): 362 (15), 312 (23), 297 (10), 182 (12), 181 (100), 149 (5).

Compound 129

This compound was first isolated from the coupling reaction as a byproduct, later it was prepared from the aldehyde **119**. Thus the aldehyde **119** (9 mg) was dissolved in methylene chloride (5 mL). The solution was refluxed with p-toluenesulfonic acid (3 mg) for 0.5 hour. After cooling and filtering through a short silica gel column, the solvent was evaporated to give the product (8 mg), 94% yield. IR

(CH_2Cl_2): 1600 cm^{-1}, 1462 cm^{-1}; ^1H NMR ($CDCl_3$): 3.99 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 4.12 (s, 3 H, OMe), 6.03 (s, 2 H, methylenedioxy), 6.96 (s, 1 H, aromatic), 7.14 (s, 1 H), 7.21 (s, 1 H), 8.01 (s, 1 H), 8.36 (s, 1 H); mass spectrum, m/z (relative abundance): 312 (100), 297 (41), 269 (18), 254 (31), 225 (22), 183 (77), 155 (59), 127 (50), 125 (54), 91 (52).

Compound 130

Hydroxy sulfone **120** (10 mg) was dissolved in methylene chloride (3 mL). Trans-2-phenylcyclohexyl alcohol (40 mg), p-toluenesulfonic acid (2 mg), and $MgSO_4$ (10 mg) were added and the solution stired for 24 hours. After chromatography with 30% ethyl acetate-hexane the product (5 mg) was obtained, 40% yield. ^1H NMR ($CDCl_3$): 1.35-1.95 (m, 7 H), 2.45-2.55 (m, 1 H), 2.67-2.75 (m, 1 H), 3.80 (s, 6 H, OMe), 3.85 (s, 3 H, OMe), 3.91-4.10 (m, 1 H), 4.95 (s, 2 H), 5.73 (s, 1 H), 5.90-5.93 (m, 2 H, methylenedioxy), 6.38 (s, 1 H, aromatic), 6.42 (s, 2 H, aromatic), 7.40-7.42 (m, 5 H, aromatic).

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