# INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

**The quality of this reproduction is dependent upon the quality of the copy submitted.** Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

**UMI**

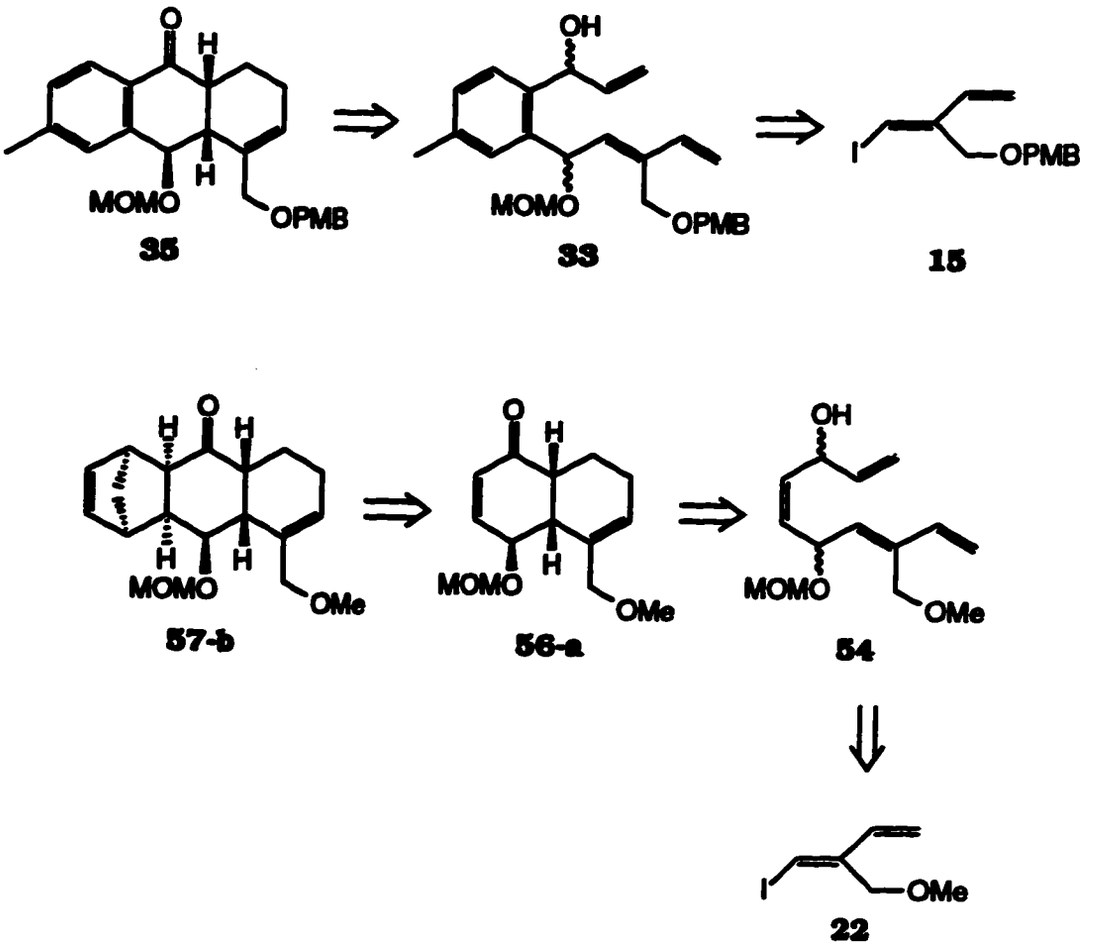
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Université d'Ottawa · University of Ottawa

# Abstract

The syntheses of potential Taxol® analogues **35** and **57-b** are described. The route selected employed a planar group (aromatic ring or a double bond) in the tether to facilitate the key step, an intramolecular Diels-Alder reaction. This approach afforded the tricyclic core of **35** in an efficient and direct manner. The Diels-Alder precursor **33** was synthesized from 3-methylbenzyl alcohol, acrolein, and (*Z*)-1-iodo-2-*p*-methoxybenzyloxymethyl-1,3-butadiene (**15**). The cyclization of alcohol **33** proceeded readily under oxidative conditions at room temperature to afford the *cis*-fused ring system **35**.

The tetracyclic nucleus of **57-b** was prepared by an intermolecular Diels-Alder reaction of cyclopentadiene with intermediate **56-a**. It was found that the bicyclic core of ketone **56-a** could be generated by an intramolecular Diels-Alder reaction in which a tether containing a double bond behaved as a planar control unit. The precursor **54** was synthesized successfully from (*Z*)-2-butene-1,4-diol, vinylmagnesium bromide, and (*Z*)-1-iodo-2-methoxymethyl-1,3-buta-diene (**22**). The intramolecular Diels-Alder cycloaddition of alcohol **54** occurred under oxidative conditions at room temperature and afforded a mixture of diastereomers, of which the major product was the *cis*-fused ring system **56-a**. Collectively these studies have provided new routes to complex ring systems and have demonstrated that improved reactivity and stereochemical control can be derived from appropriately selected tether control groups.


O
H
H
MOMO
OPMB
35
OH
MOMO
OPMB
33
I
OPMB
15
H
O
H
H
H
MOMO
OMe
57-b
O
H
MOMO
H
OMe
56-a
OH
MOMO
OMe
54
I
OMe
22

# Acknowledgements

I would first like to thank Dr. Alex G. Fallis for accepting me in to his group, and for all of his support and guidance. Thanks also to Tham for helping me get settled in the lab when I first arrived.

To Tim, Pete, Scott, Bogdan, Simon and Sandrine, thank you so much for all of the helpful suggestions and advice throughout this research project. Also, to Poonam, Mike, Kristian, Curt, Irina, Jon, Mike T., Martin, and Hélène, thanks for all of the interesting, and often amusing conversations about chemistry and life in general. I would also like to thank Simon, Pete, and Sandrine for their time, and helpful comments in proof-reading this thesis. Overall, I thank all of my colleagues for making my stay in Ottawa a very memorable period of my life.

I must also thank my friends and family back on P.E.I. for their support and continuing words of encouragement. And to Mike Morgan, thank you so much for being here for me and for giving me your support, not to mention keeping me well fed.

Finally, I would like to thank NSERC and the University of Ottawa for their financial support.

# Table of Contents

# List of Figures

# List of Abbreviations

| | |
|---|---|
| Å | angstrom |
| Ac | acetyl |
| Anal. Calcd. | elemental analysis calculated |
| br | broad |
| Bz | benzoyl |
| $Bu_4NI$ | tetrabutylammonium iodide |
| *n*-BuLi | normal butyllithium |
| *sec*-BuLi | secondary butyllithium |
| *tert*-BuLi | tertiary butyllithium |
| *cf.* | confer |
| CSA | 10-camphorsulfonic acid |
| d | doublet |
| DDQ | 2,3-dichloro-5,6-dicyanobenzoquinone |
| DIBAL | diisobutylaluminum hydride |
| DMAP | 4-*N*,*N*-dimethylaminopyridine |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| equiv. | equivalents |
| Et | ethyl |
| $Et_2AlCl$ | diethylaluminum chloride |
| EtOH | ethanol |
| FTIR | Fourier transform infrared spectroscopy |
| h. | hour |
| HOMO | highest occupied molecular orbital |
| HRMS | high resolution mass spectrometry |

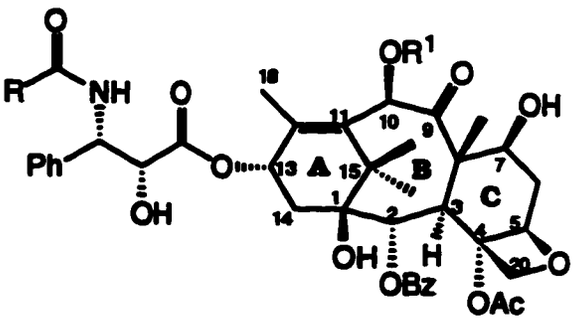
| | |
|---|---|
| Hz | hertz |
| IMDA | intramolecular Diels-Alder |
| IR | infrared spectroscopy |
| *J* | coupling constant |
| LUMO | lowest unoccupied molecular orbital |
| m | multiplet |
| M | moles per liter |
| Me | methyl |
| mmol | millimole |
| MOM | methoxymethyl |
| mp | melting point |
| MHz | megahertz |
| NMR | nuclear magnetic resonance |
| NOE | nuclear Overhauser effect |
| PMB | *p*-methoxybenzyl |
| ppm | parts per million |
| PPTS | pyridinium *p*-toluenesulfonate |
| *i*-$Pr_2EtN$ | *N,N*-diisopropylethylamine |
| R | alkyl |
| $R_f$ | retention factor |
| r.t. | room temperature |
| s | singlet |
| t | triplet |
| TBAF | tetra-*n*-butylammonium fluoride |
| TBDMS | *t*-butyldimethylsilyl |
| TBDPS | *t*-butyldiphenylsilyl |
| Tf | trifluoromethanesulfonyl |

| | |
|---|---|
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMEDA | *N,N,N',N'*-tetramethylethylenediamine |
| TMS | trimethylsilyl |

# 1 Introduction

Cancer is a disease characterized by an unregulated, rapid growth of cells. Worldwide, cancer is a growing health problem, and remains a major issue of both scientific and public concern.[1] Although considerable progress has been made in controlling several forms of cancer, there is a continuing need for new drugs which will help in the fight against this disease.

Paclitaxel (Taxol®, **1**, Figure 1), a naturally occurring drug, has recently attracted considerable attention as a result of its efficacy in the treatment of various types of cancer, particularly ovarian, breast, and bronchial carcinomas.[2,3] Taxol® inhibits cell replication in the mitotic phase of the cell cycle by promoting polymerization of microtubules to produce stable asters that are abnormally resistant to depolymerization.[4] This mode of action is unlike that of the classical antimicrotubule plant products, such as colchicine and podophyllotoxin, which are known to function by inhibiting the assembly of microtubules.[5]




**1** Taxol®, R = Ph, $R^1$ = Ac

**2** Taxotere®, R = *t*-BuO, $R^1$ = H

**3** 10-Deacetyl baccatin III, OH at C13, $R^1$ = H

**Figure 1** Taxol® and related compounds.

## *1.1 General Background*

### 1.1.1 Taxoid Source

The primary source of the highly functionalized diterpenoid Taxol® has been from the dried inner bark of the Pacific yew, *Taxus brevifolia*.[6] The discovery that the crude extract from the bark showed cytotoxic activity against leukemia cells, and inhibitory action against a variety of tumors was made in 1962; however, the structure of the active component of the extract, Taxol®, was not firmly established until 1971 by X-ray crystallographic analysis.[1,7]

The problem in relying on the yew tree as the sole source of Taxol® is the limited availability of these trees. The yew is a slow-growing coniferous tree which is found in moist soil near streams and lakes. The majority of these trees only grow in certain regions of the Pacific Northwest, in the understory of old conifers and hardwoods.[1,6] A typical mature tree rarely exceeds 12 meters in height and 60 centimeters in diameter, and the amount of Taxol® actually present is only 70-140 ppm in the bark of the tree, and 20-70 ppm in the needles . It would therefore require 10,000 kilograms of bark, which is equivalent to 3000 sacrificed yew trees, to obtain 1 kilogram of Taxol®. This 1 kilogram in turn, would only be sufficient for the treatment of 500 patients since each patient may require as much as 2 grams of Taxol® for a successful treatment.[1]

An alternative approach to the Taxol® supply problem involves the extraction of the Taxol® precursor 10-deacetyl baccatin III (**3**, Figure 1) from the needles of the European yew, *Taxus bacata*, followed by semisynthesis. This approach is favourable because yields of approximately 1 kilogram of 10-deacetyl baccatin III can be obtained from

3000 kilograms of needles, and the needles are a more renewable resource than the bark of the tree.[1] In addition, the Taxol® analogue docetaxel (Taxotere®, **2**, Figure 1), which has been reported to be 1.3-12 times more cytotoxic than Taxol® in several murine and human tumor cell lines,[8] can also be prepared in a semisynthetic manner from 10-deacetyl baccatin III. It must be recognized, however, that this method is still largely dependent on a limited natural resource, the European yew *Taxus bacata*.

Another strategy is, of course, the total synthesis of Taxol®. This has, however, been found to be an extremely challenging task because of the highly oxygenated and complex structure of this molecule. For the construction of the tricyclic nucleus, for example, there is the difficulty of forming the *trans*-fused C ring bearing an angular methyl group. Furthermore, the A ring of Taxol® contains a bridgehead alkene, not to mention the formation of the central 8-membered ring. It is known that such 8-membered rings are difficult to synthesize as a result of both entropic and enthalpic factors, and the normally high transannular strain is increased even further by the geminal dimethyl groups which protrude into the center of the molecule.[1] Because of these challenging problems, it is not suprising that despite many attempts to synthesize this complex molecule, only three research groups have successfully completed total syntheses of Taxol®.[9,10,11]

### 1.1.2 Taxol® Analogues

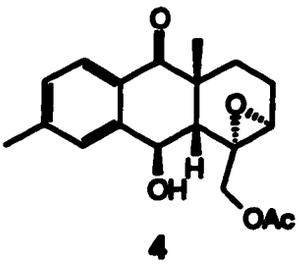
The difficulty involved in the total synthesis of Taxol® has led to many studies dealing with the synthesis of simpler analogues of Taxol® as potential antitumor drugs. A number of Taxol® derivatives have been

reported which involve chemical modifications at C2[12a-c], C4[2,12d], C7[12a,e], C10[4], or at the C3'[12a,f-g] and N terminal[12f,h-i] positions of the A ring side chain. These analogues, however, still involve the construction of the taxoid nucleus, which as described above, can prove to be very challenging.

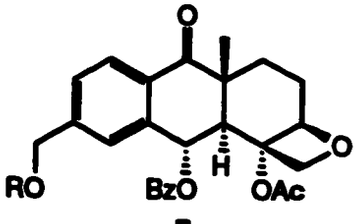
Our laboratory, therefore, has been interested in the synthesis of Taxol® analogues which are simpler in structure, yet may still possess similar, or better cytotoxic biological activity.

### 1.1.3 Potential Taxol® Analogues

Reports have indicated that alteration of the functionalities on the northern part of the Taxol® molecule (**1**) do not dramatically alter the activity of the drug. It has been found, however, that the functionalities at C2, C4, C5, and C13 are essential for activity.[2,4,12] With these characteristics in mind, preliminary work in our laboratory[13] has led to the synthesis of the tricyclic system **4**, which is currently being subjected to further synthetic manipulations[14] in order to obtain the target analogue **5** (Figure 2). It is hoped that this simplified analogue will display cytotoxic biological activity because of the similarity in shape and functionalization to that of Taxol®.[13]




**4**




**5**

R = Taxol® side chain

**Figure 2** Preliminary Taxol® analogues

In order to expand the scope of these tricyclic systems, the decision was made to prepare several variants of compound **4**. The cyclic systems **6**, **7**, and **8** were therefore chosen as our primary synthetic targets as potential analogues of Taxol® (Figure 3). The planned key step in the construction of these compounds, as in the synthesis of **4**,[13] was the Diels-Alder cycloaddition reaction.

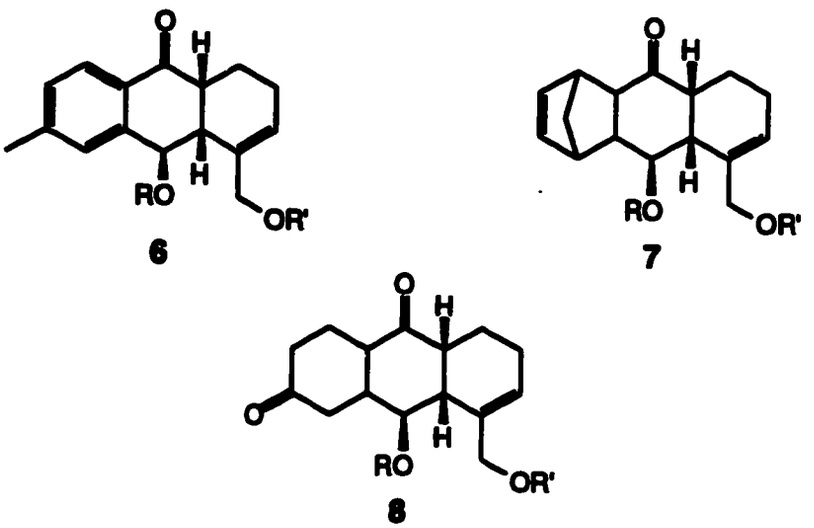



**Figure 3** Potential Taxol® analogues: Synthetic targets.

## *1.2 Diels-Alder Chemistry*

### 1.2.1 General Introduction

The thermally allowed [4+2] cycloaddition has been known for more than half a century as the Diels-Alder reaction. It involves the cycloaddition reaction of conjugated dienes with suitable multiple bond partners (dienophiles) to form the related cyclohexene products. The result, therefore, is the formation of two new $\sigma$ bonds and a $\pi$ bond, with the introduction of up to four new asymmetric centers. Also, with its

typically good yields, mild reaction conditions, high regio- and stereoselectivity, it is no wonder that the Diels-Alder reaction has become one of the most widely used methods for ring construction.[15,16]

The mechanism of the Diels-Alder reaction requires that the diene and dienophile approach each other in approximately parallel planes such that the terminal carbons of one component are directly above the terminal carbons of the other component. The diene must therefore be able to adopt the *cisoid* conformation in order for this concerted reaction to take place. This allows the orbital lobes (which must be of the same symmetry) of the two components to interact efficiently, thus allowing the formation of new σ bonds (Figure 4).[16,17,18]

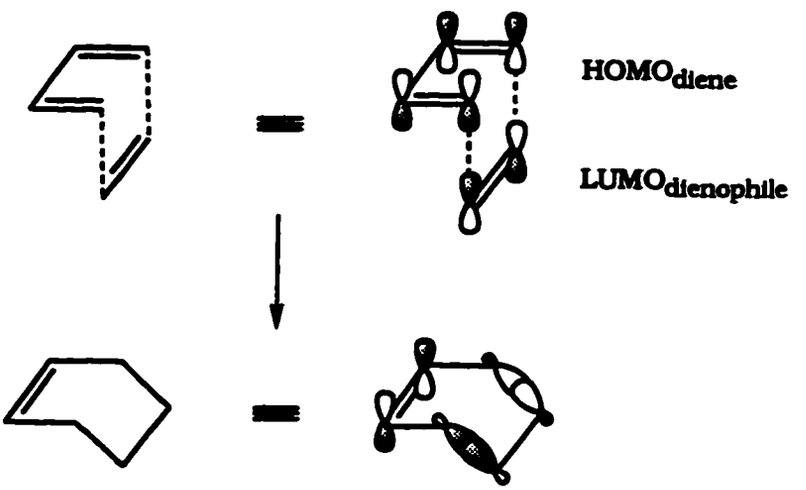



**Figure 4** Diels-Alder reaction of butadiene and ethene.

### 1.2.2 Electronic Requirements

As illustrated above (Figure 4), the Diels-Alder reaction involves the interaction between the HOMO (highest occupied molecular orbital) of one partner, usually the diene, with the LUMO (lowest unoccupied molecular orbital) of the other partner, usually the dienophile. Electron-

withdrawing substituents lower the energy of both HOMO and LUMO, while electron-donating substituents raise their energies; thus, the Diels-Alder reaction works best when there are complementary electronic substituents on the diene and dienophile.

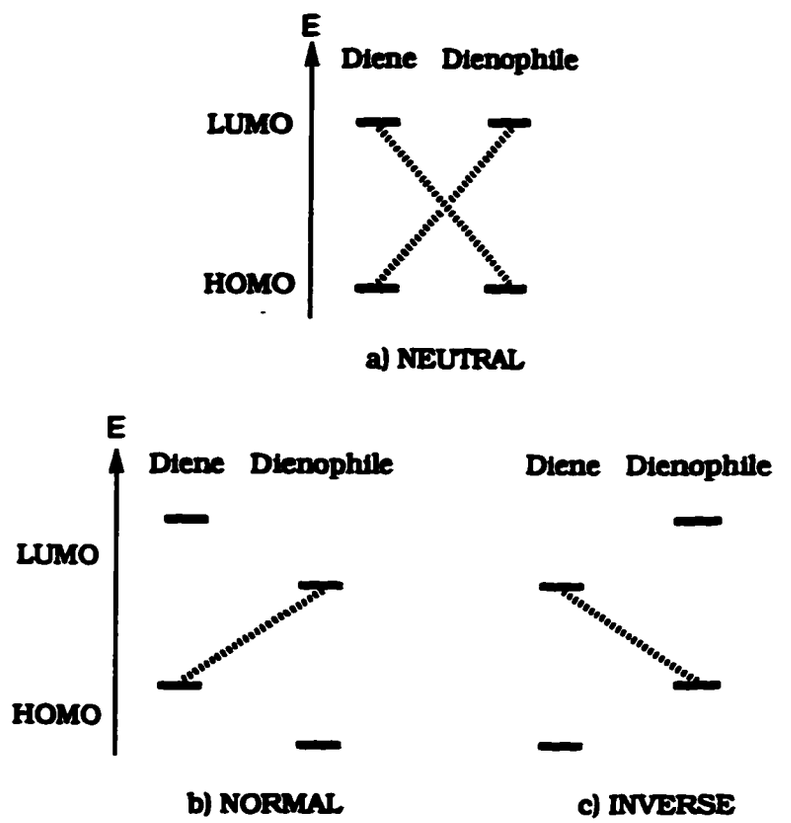


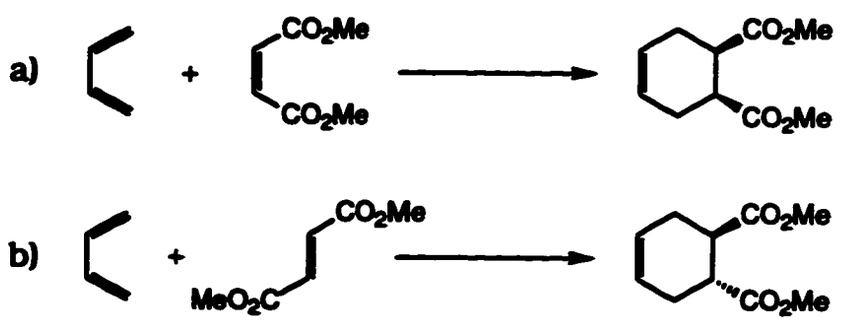

**Figure 5** HOMO-LUMO orbital arrangements for the Diels-Alder reaction.

In comparison with the "neutral electron demand" Diels-Alder (Figure 5a), the "normal electron demand" reaction (Figure 5b) occurs when electron-donating substituents on the diene raise its HOMO energy, and electron-withdrawing substituents on the dienophile lower its LUMO energy (*vice versa* for the "inverse electron demand" reaction, Figure 5c). The net result is a lower energy difference between the HOMO

and LUMO partners, and therefore the reactivity of the diene and dienophile is increased.

### 1.2.3 Stereoselectivity

In the Diels-Alder reaction, the relative configurations of the diene and dienophile are retained in the adduct. This is known as the *cis*-principle.[16,18] For example, the *cis* and *trans* relationship between the alkene substituents in Scheme 1a and 1b, respectively, are retained in their corresponding cycloadducts.




**Scheme 1** Retention of alkene configuration in the Diels-Alder reaction.[18]

In order for the stereochemistry of the diene to be maintained in the adduct, the relative motions of the substituents during the ring formation must be disrotatory (move in opposite directions). This is illustrated in Figure 6.

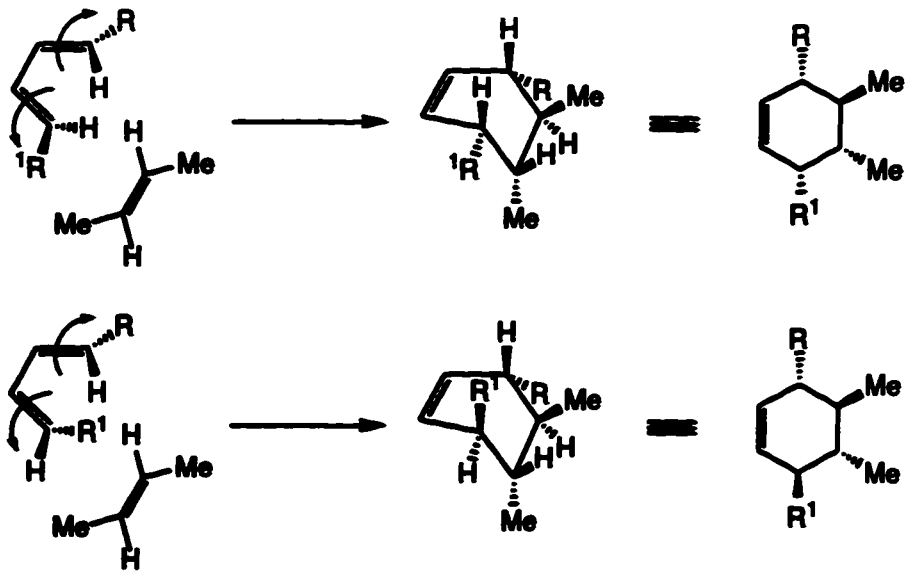


**Figure 6** Retention of diene stereochemistry in the Diels-Alder reaction.[16]

Another issue for consideration in the Diels-Alder reaction occurs when the dienophile is unsymmetrical. In this situation, the diene and dienophile can approach each other in parallel planes in two different orientations. These two approaches are termed *endo* and *exo*. In the *endo* approach, the substituent of the dienophile is tucked under the $\pi$ orbitals of the diene. By contrast, in the *exo* approach, the dienophile substituent is pointing away from the diene (Figure 7). When the dienophile has a substituent bearing a $\pi$ bond, such as a carbonyl group (as depicted in Figure 7), the *endo* approach is favoured as a result of favourable secondary orbital overlap which stabilizes the transition state. As a result, the *endo* product is preferred, and this is referred to as the *endo* rule.[16,17,18]

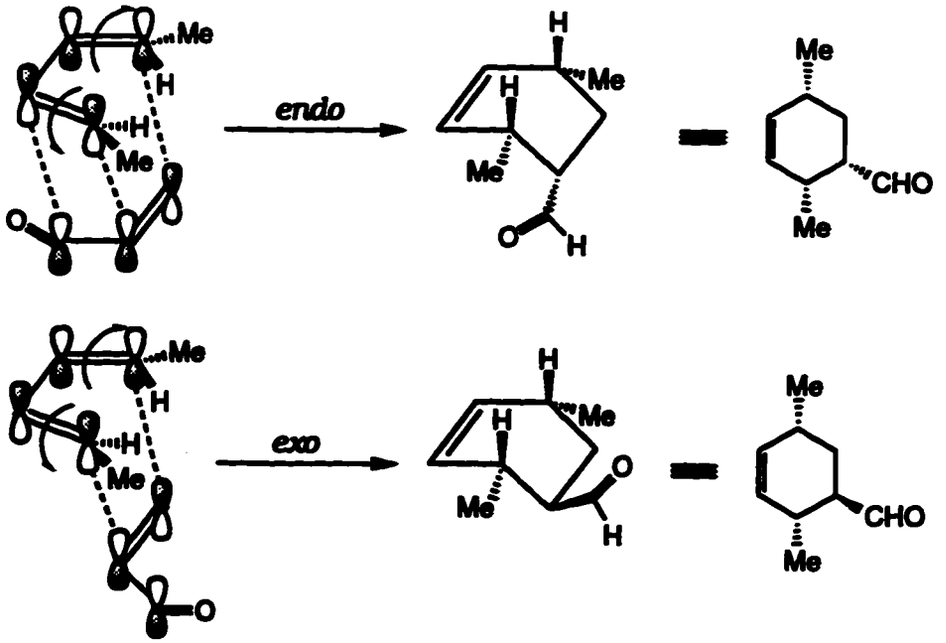
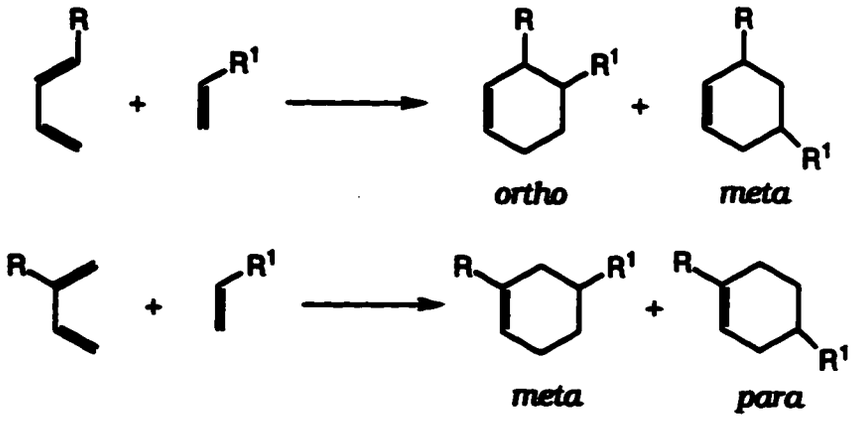



**Figure 7** *Endo* and *exo* transition states in a Diels-Alder reaction.

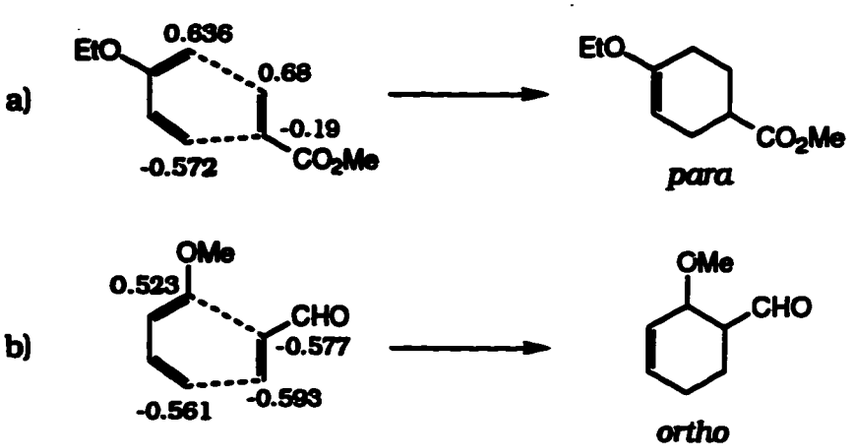
### 1.2.4 Regioselectivity

In the case where both the diene and dienophile are unsymmetrical, the cycloaddition can lead to two regioisomeric adducts resulting from two different orientations of the reactants (Scheme 2).




**Scheme 2** Regioisomers possible from a Diels-Alder reaction involving unsymmetrical reactants.

The regioselectivity of a Diels-Alder reaction will depend on the electronic effects (electron-donating or electron-withdrawing) of the substituents on the diene and dienophile. The *ortho*, *meta*, or *para* nature of the major cycloadducts can then be predicted upon examination of the orbital coefficients of the interacting HOMO-LUMO pair of the reactants, whereby the larger terminal coefficients of each component will become bonded preferentially in the transition state (Scheme 3).[16,18] A review covering the calculation of molecular orbital coefficients has been reported.[19]



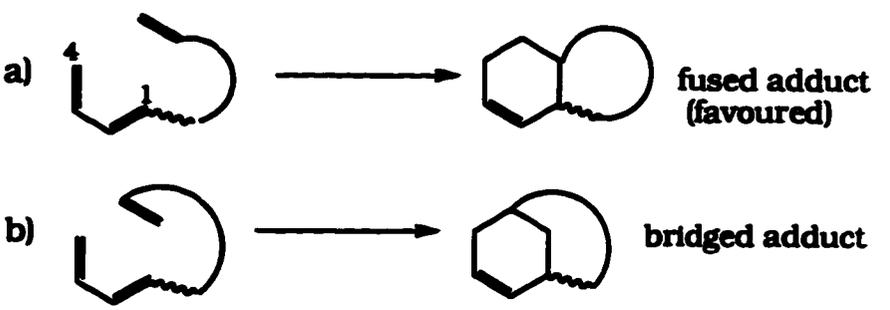

**Scheme 3** Molecular orbital coefficients and regioselectivity in the Diels-Alder reaction.

There is a general rule with respect to regioselectivity in the Diels-Alder reaction. When a dienophile containing a heteroatom reacts with a 1-substituted diene, the *ortho* product is usually preferred and is independent of the nature of the diene substituents. This is known as the *ortho* effect, or *ortho* rule. Scheme 3b shows one such example.

### 1.2.5 Intramolecular Diels-Alder Chemistry

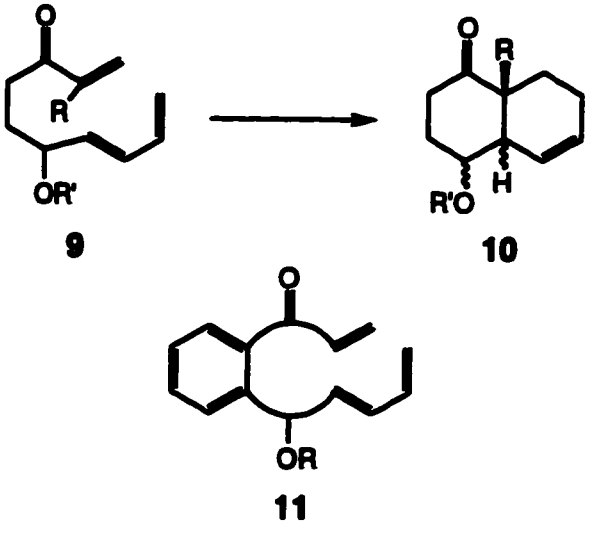
A key step in the planned synthesis of our target molecules **6**, **7**, and **8**, involves an intramolecular Diels-Alder reaction (IMDA). In the IMDA reaction, the diene and dienophile are incorporated into the same compound by a connecting chain of atoms (a tether). The net result of this is that two rings are formed in a single step. Other advantages of the IMDA reaction, such as increased reactivity, regio-, stereo-, and diastereoselectivity, have led to its use in the synthesis of a number of natural products.[15] Removable tethers have also been utilized in the synthesis of monocyclic products in order to take advantage of the enhanced regio- and stereoselectivity induced by the intramolecular cyclization process.[20]

With respect to the regiochemistry of the IMDA reaction, the cycloaddition can actually occur in two different regiochemical modes resulting in either fused or bridged adducts. However, when the tether is attached at C1 of the diene, as illustrated in Scheme 4, a majority of intramolecular Diels-Alder reactions yielded fused adducts exclusively (ie. Scheme 4a).[18]




**Scheme 4** Regioselectivity in the intramolecular Diels-Alder reaction.

Even though a Diels-Alder reaction may be intramolecular in nature, it still may not be able to provide the best levels of reactivity and stereoselectivity. For example, the IMDA reaction of trienes, such as **9**, can frequently require high reaction temperatures, long reaction times, and result in complex mixtures of cycloadducts, such as **10** (Scheme 5).[15,21,22] This problem may be overcome by limiting the flexibility of the molecule through the incorporation of a planar moiety, such as an aromatic ring (i.e. **11**), within the tether.




**Scheme 5**

The conformational constraint should therefore hold the diene and dienophile in close proximity to one another, thus enhancing the transition state interaction between the two components. This interaction would then facilitate the intramolecular Diels-Alder reaction based on entropic grounds. Such conformational constraints have proven to be advantageous in literature examples, such as in Grubbs' work involving the synthesis of eight-membered rings *via* ring-closing metathesis reactions.[23] Also, an aromatic tether control group was

found to be beneficial in the synthesis of compound **4**,[13] so it was decided to use this same control group in the synthesis of the target analogue **6**. For the synthesis of **7** and **8**, it was decided to use a double bond in the tether to determine its potential influence and synthetic utility as a conformational control unit for the intramolecular Diels-Alder reaction.

## *1.3 Research Objectives for the Aromatic Tether Controlled System*

### 1.3.1 Retrosynthetic Plan

The planned synthesis of the tricyclic nucleus of target analogue **6** involved an intramolecular Diels-Alder reaction in which a planar aromatic control group would be utilized within the tether. This is depicted in the retrosynthetic plan shown below (Figure 8, anthraquinone numbering system used), where a double disconnection between C1-C2 and C1a-C4a would provide the tether controlled IMDA precursor **12**. Further disconnections between C4a-C10 and C8a-C9, illustrate that the Diels-Alder precursor could in turn be assembled from commercially available 3-methylbenzyl alcohol (**13**), acrolein (**14**), and the diene **15** which is itself readily prepared in our laboratory from propargyl alcohol.[24]

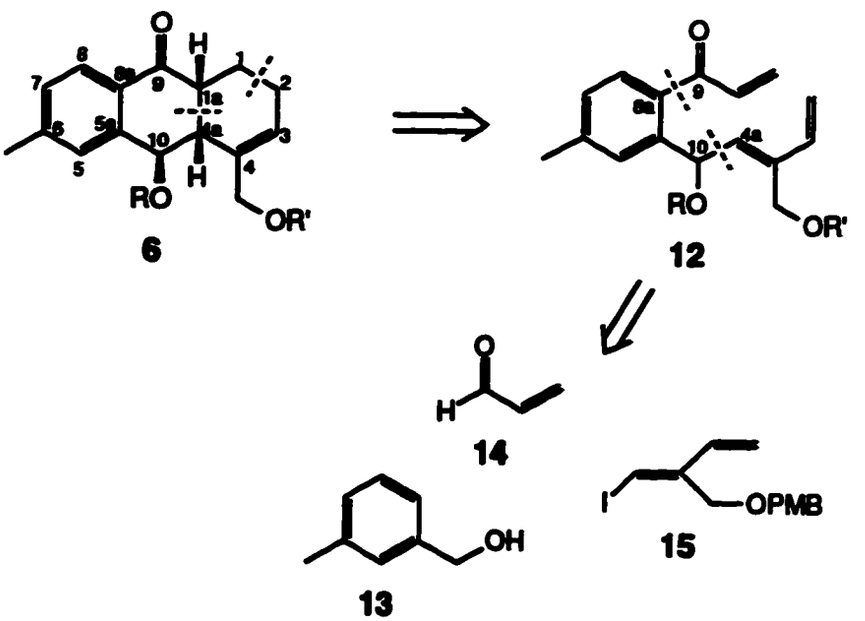



**Figure 8** Retrosynthetic plan for the synthesis of potential Taxol® analogue **6**.

### 1.3.2 Preliminary Work

It is known that benzyl alcohols can undergo *ortho*-lithiation when treated with an alkyllithium base such as *n*-butyllithium. The *ortho*-lithiated species generated can then react with a variety of electrophiles thus enabling the formation of various *ortho*-substituted benzyl alcohol derivatives.[13,25]

In the synthesis of target analogue **6**, as well as the related compound **4**,[13] C6 rather than at C2 lithiation of 3-methylbenzyl alcohol (**13**) would be required upon treatment with *n*-butyllithium (Figure 9). This regioselectivity was essential in order to introduce the dienophile moiety of the Diels-Alder precursor in the required position of the aromatic ring (*para* to the methyl group of **13**).[13]

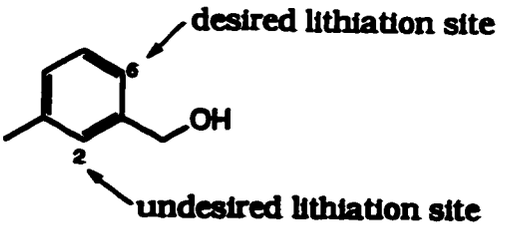



**Figure 9** *ortho*-Lithiation of 3-methylbenzyl alcohol (**13**).[13]

In order to determine the preferred site of *ortho*-lithiation, a deuteration experiment was carried out in our laboratory.[13] The experiment involved the treatment of 3-methylbenzyl alcohol (**13**) with *n*-butyllithium[25], followed by the addition of deuterium oxide as the electrophile. The crude product obtained was then analyzed by $^1$H NMR spectroscopy, from which it was concluded that the *ortho*-lithiation of benzylic alcohol **13** did occur preferentially at the desired C6 position, rather than at C2.[13]

It has been proposed that this preference for *ortho*-lithiation at C6 may be the result of steric hinderance brought about by the methyl group at C3. It is believed that the *N,N,N',N'*-tetramethylethylenediamine present in the reaction coordinates to the lithiated species in two possible ways (Figure 10). The steric bulk of the coordinated TMEDA would therefore make lithiation at C2 extremely difficult.[13]

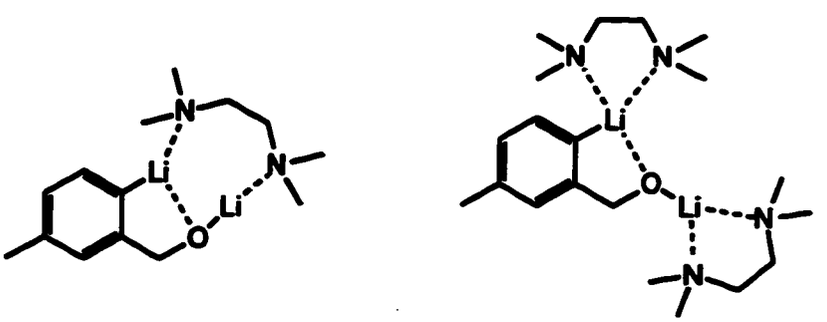



**Figure 10** Coordination of TMEDA to the lithiated species of **13**.[13]

## *1.4 Research Objectives for the Double Bond Tether Controlled System*

### 1.4.1 Retrosynthetic Plan

The planned synthesis of target analogues **7** and **8** involved not only intramolecular, but also intermolecular Diels-Alder reactions. In the retrosynthetic plan (Figure 11, anthraquinone and decalin numbering systems used), the double disconnection between C5-C5a and C8-C8a of both compounds **7** and **8** would afford the common bicyclic dienophile **18** required for the intermolecular Diels-Alder reaction. The diene needed for the synthesis of analogue **7** is cyclopentadiene (**16**) which is easily prepared by cracking[26] commercially available dicyclopentadiene. The diene required for the synthesis of compound **8** is 2-trimethylsilyloxy-1,3-butadiene (**17**), which can be prepared from methyl vinyl ketone.[27]

Double disconnection between C5-C10 and C8-C9 of compound **18** provides the intramolecular Diels-Alder precursor **19**. In this case, a double bond behaves as a planar control group within the tether. Further disconnections of **19** indicate that this Diels-Alder precursor could in turn be assembled from commercially available (*Z*)-2-butene-1,4-diol (**20**), vinylmagnesium bromide (**21**), as well as the diene **22** which is itself readily prepared in our laboratory from propargyl alcohol.[24]

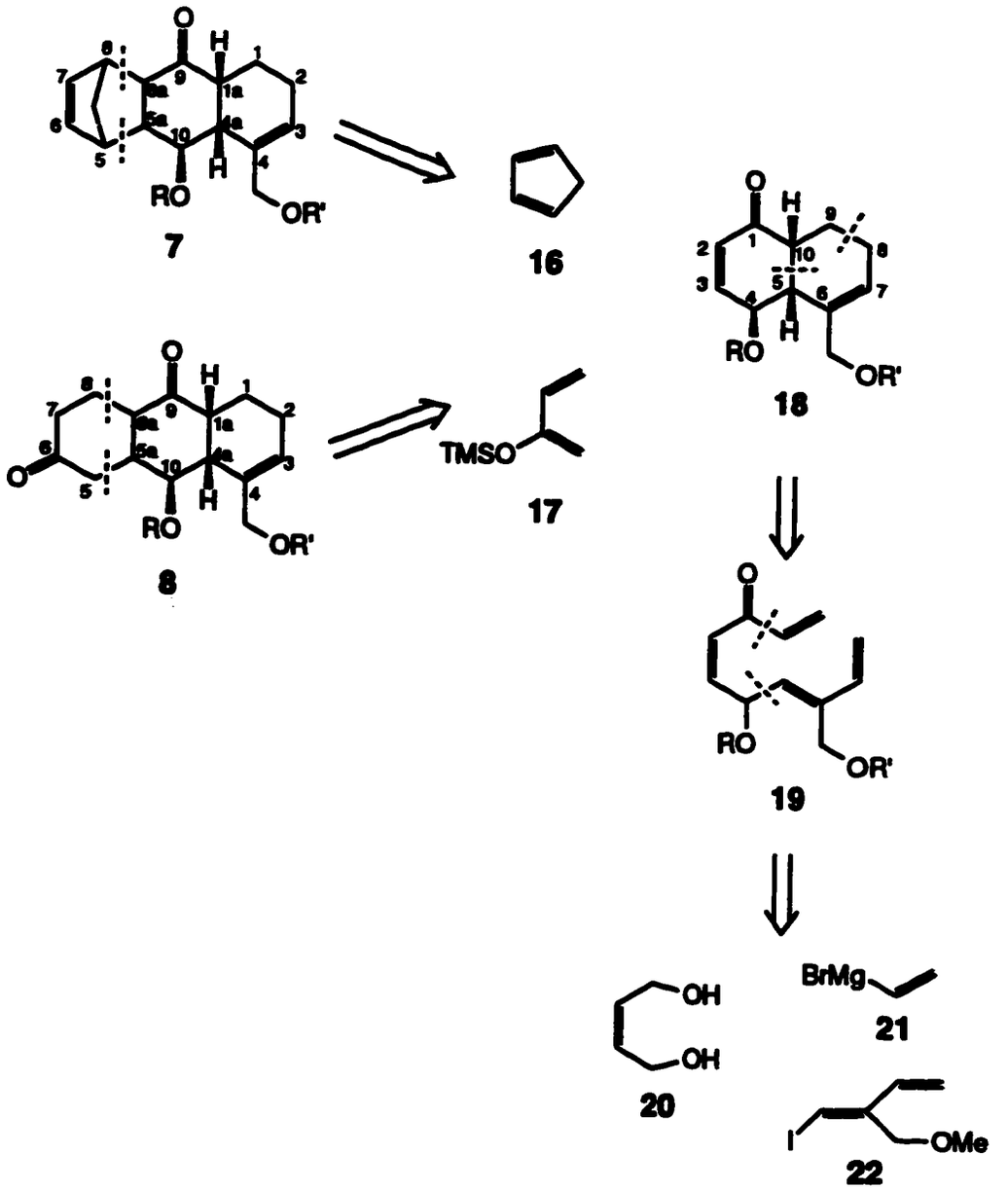


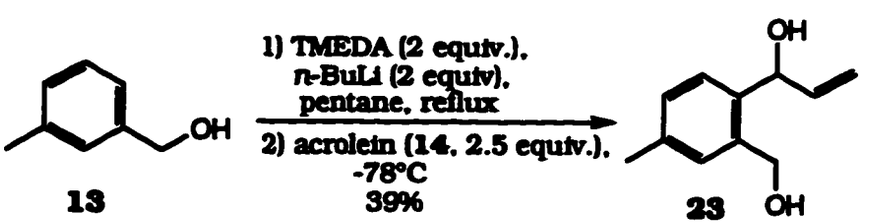

**Figure 11** Retrosynthetic plan for the synthesis of potential Taxol® mimics **7** and **8**.

# 2 Results and Discussion

## *2.1 Synthesis of the Aromatic Tether Controlled System*

### 2.1.1 Attachment of the Dienophile Moiety to the Aromatic Tether

The deuteration experiment described earlier, indicated that the preferred site of *ortho*-lithiation of 3-methylbenzyl alcohol (**13**) was at C6.[13] This was consistent with the suggestion that the bulky TMEDA-lithium complex was deuterated at the least hindered site. In order to attach the dienophile to the aromatic system **13**, acrolein (**14**) was used as the electrophile.




13 23

**Scheme 6**

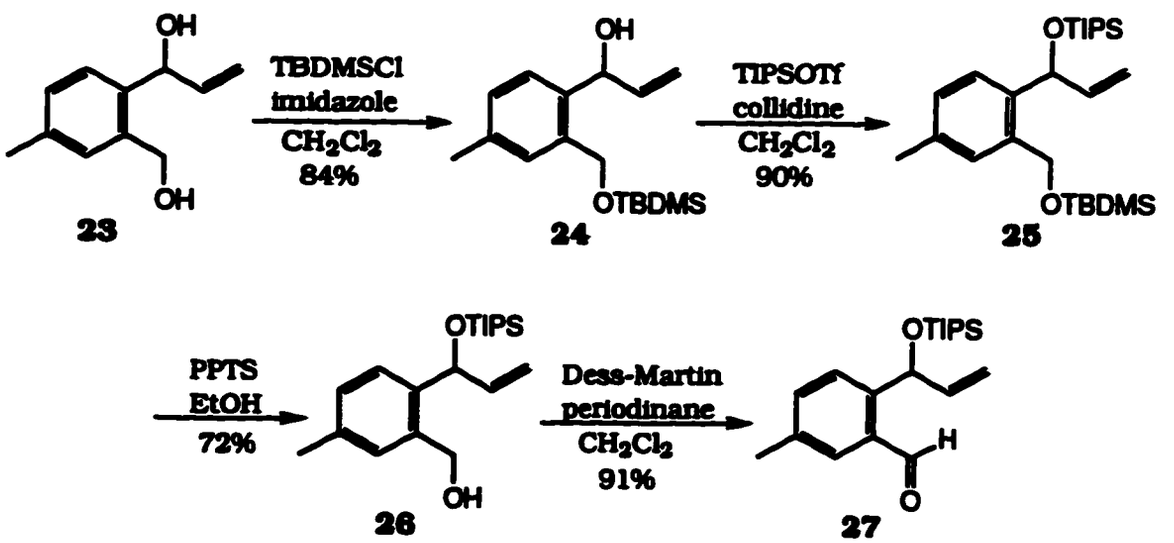
The reaction produced a complex mixture of products from which the desired diol **23** was isolated. The side products were not identified, but it was very likely that they were composed of unreacted and polymerized acrolein since a thick, yellow, gelatinous paste formed which exhibited odors similar to acrolein itself. This thick paste was removed by filtration (through filter paper) of the quenched reaction mixture before any extractions were made.

Purification of the reaction mixture by conventional (drip) column chromatography using a 60% ether/petroleum ether solvent system

afforded desired diol **23** as a clear viscous oil in 39% yield. After prolonged storage at -15 °C, however, this oil afforded a white solid.

### 2.1.2 Preparation of Aldehyde 27

In order to obtain the desired aldehyde **27** for addition of the diene, a series of protection and deprotection steps had to be performed. Initially the more reactive primary alcohol of **23** was protected to afford its corresponding *tert*-butyldimethylsilyl ether **24**. The remaining secondary alcohol was protected as its corresponding triisopropylsilyl ether **25**. The TBDMS group was then removed selectively to provide the alcohol **26** which was subsequently oxidized with Dess-Martin periodinane to afford the required aldehyde **27**.

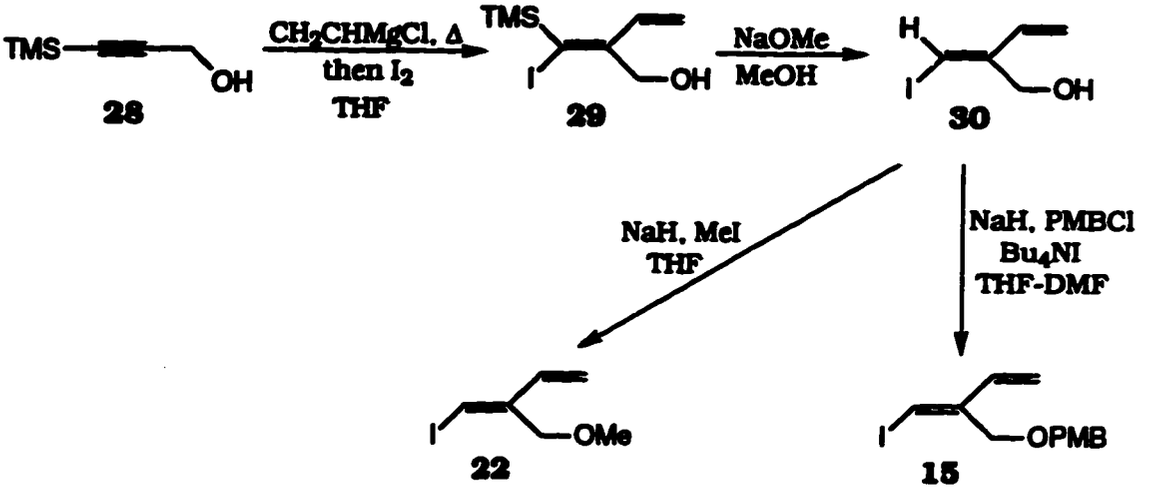



**Scheme 7**

### 2.1.3 Preparation of Dienes 15 and 22

The synthesis of diene **15** was carried out using a route developed in our laboratory.[24] Propargyl alcohol **28** was first treated with

vinylmagnesium chloride (2.5 equiv.) in tetrahydrofuran and heated. Iodine (1.5 equiv.) was then added to afford the desired *Z*-iodo diene **29**. The crude product was desilylated directly by treatment with sodium methoxide (3.4 equiv.) in methanol. The unstable iodo-alcohol **30** was then protected as its corresponding *p*-methoxybenzyl ether to afford the desired diene **15** in an over all yield of 45-75% over the three steps. Diene **15** was used immediately after purification.




**Scheme 8**

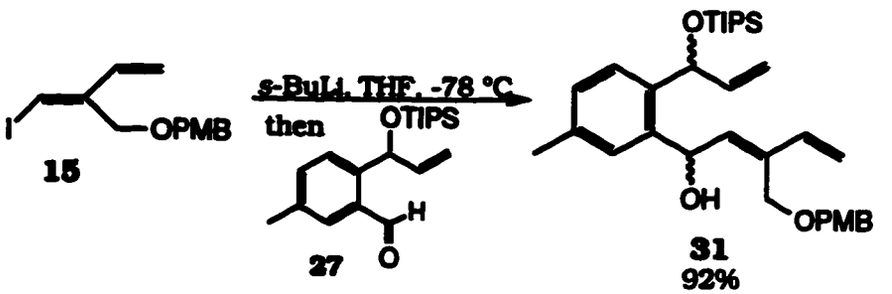
Diene **22** was prepared by protecting the iodo-alcohol **30** as its methyl ether. The use of this diene will be discussed later.

### 2.1.4 Attachment of the Diene Moiety to Aldehyde 27

The diene segment was attached to aldehyde **27** by condensation with the dienyl iodide **15**. This was achieved by the treatment of dienyl iodide **15** (1.6 equiv.), with *sec*-butyllithium (3.4 equiv.), followed by the addition of aldehyde **27**. The resulting adduct **31**, was obtained in 92% yield as a mixture (70:30) of diastereomers consisting of four optical

isomers. The ratio of the diastereomers was determined from the crude $^1$H NMR spectrum.

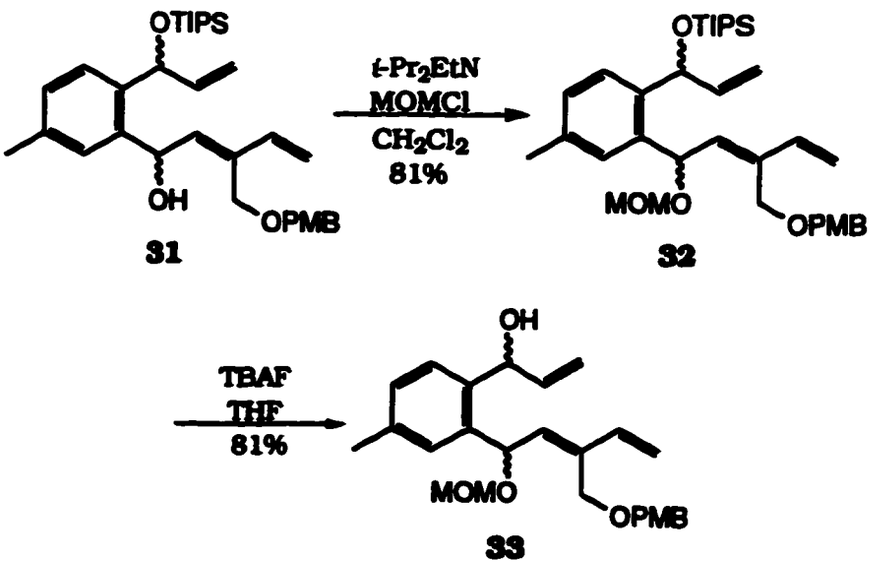
The quality of the dienyl iodide **15** used in this reaction was very important. It was observed that the iodide **15** gradually decomposed on storage, therefore the condensation reaction worked better when freshly prepared dienyl iodide was used. Also, in setting up the reaction, prolonged exposure of **15** to light and heat had to be avoided in order to minimize its decomposition and maximize the reaction yield.




**Scheme 9**

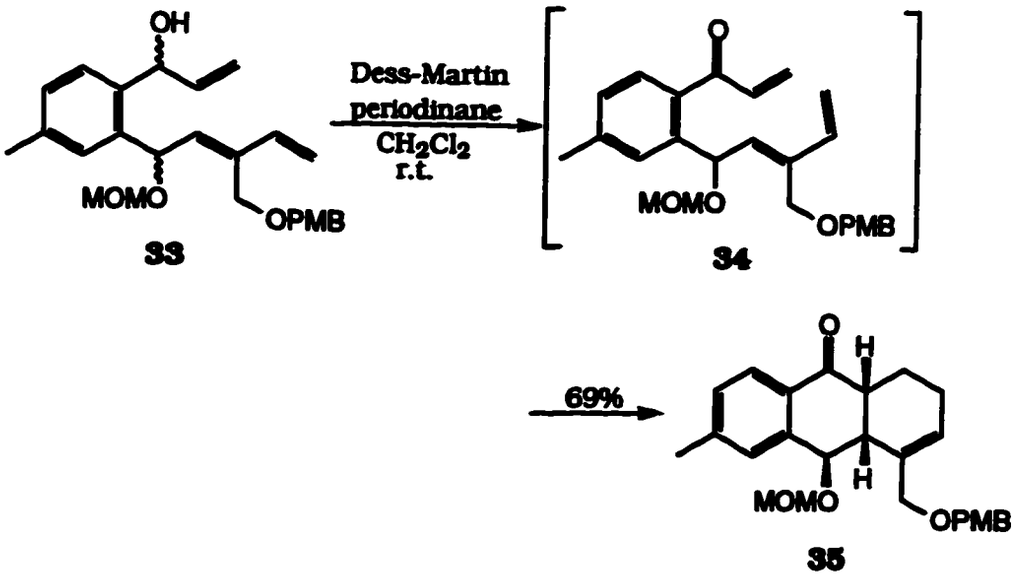
### 2.1.5 The Intramolecular Diels-Alder Reaction of Ketone 34

In order to attain the electronic requirements for a normal electron demand Diels-Alder reaction, the diene must be electron rich, and the dienophile electron poor. This was achieved through another sequence of protection and deprotection steps. First, the secondary alcohol **31** (diastereomeric mixture) was protected as its corresponding methoxymethyl ether to afford the tri-protected triol **32**. The latter already contained the required electron rich diene portion. Next, the triisopropylsilyl ether was selectively deprotected upon treatment with tetra-*n*-butylammonium fluoride (5 equiv.). This provided the alcohol **33** as a mixture of diastereomers.




**Scheme 10**

Oxidation of alcohol **33** with Dess-Martin periodinane (1.5 equiv.) should therefore generate the electron poor dienophile portion and thus provide the desired intramolecular Diels-Alder precursor **34**. It was found, however, that after one hour of stirring at room temperature under Dess-Martin conditions, oxidation of **33** led directly to the cyclized product **35** as a single diastereomer in 69% yield. In fact, the oxidized precursor **34** was not isolated at all. This result indicates that the planarity provided by the aromatic group in the tether was able to hold the diene and dienophile in close proximity to one another. This geometric arrangement was probably very similar to the transition state of the cycloaddition and thus enabled the cyclization to proceed under very mild conditions (oxidation at room temperature). In view of the fact that the oxidation step produces acetic acid, this may also contribute to facilitating the cycloaddition. Coordination with the methoxymethyl ether group would increase the steric bulk of this functionality and thus may enhance the facial selectivity observed.




**Scheme 11**

### 2.1.6 Characterization of the Cyclized Product 35

The proposed transition states for the Diels-Alder reaction are illustrated in Figure 12 (for convenience, the transition states are shown for one optical series only). As described earlier, when the dienophile contains a substituent bearing a π bond such as a carbonyl group, the *endo* product is usually preferred as a result of favourable secondary orbital overlap (*endo* rule). Based on this consideration, it was therefore reasonable to assume that the *endo* approach (**A** and **B**) would be favoured over the *exo* approach (**D** and **F**). This *endo* transition state would thus lead to the formation of a *cis*-fused ring system.

The facial stereoselectivity of the cyclization in the *endo* transition states could also be influenced by the presence of the methoxymethyl ether protecting group. When the diene approaches the dienophile *syn* to the methoxymethyl ether group (transition state **B**), there is the possibility of unfavourable steric interactions between the carbonyl and the protecting group. In order to minimize these interactions, *endo*

transition state **A** would be preferred since the dienophile approaches the diene *anti* to the methoxymethyl ether group. Taking these factors into account, the resulting cyclized product **35** would have a relative *cis* stereochemistry with respect to C1a, C4a and C10, preferentially.

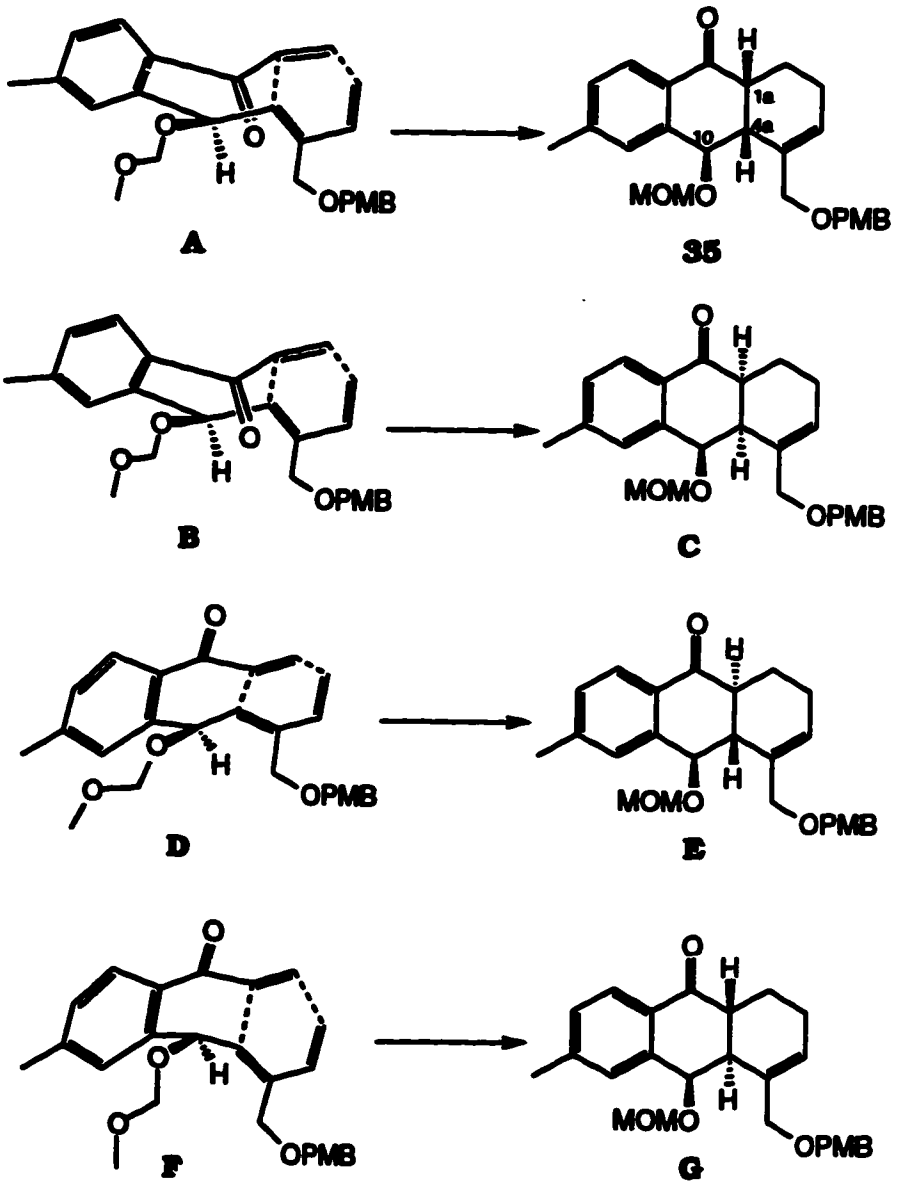



**Figure 12** Proposed Diels-Alder transition states of ketone **34**: **A**, *endo*, *anti* addition; **B**, *endo*, *syn* addition; **D**, *exo*, *anti* addition; **F**, *exo*, *syn* addition.

NOE experiments were performed on the cyclized product **35**. Unfortunately, the C1a and C4a proton signals were overlapping and indistinguishable from one another. As a result, the stereochemistry could not be determined with confidence from the data obtained from these NOE experiments. An X-ray crystallographic study of a similar derivative (Figure 13)[13], however, illustrated its *cis* relative stereochemistry at the same centers of interest. By analogy, and consistent with transition state **A**, the stereochemistry of compound **35** can also be considered to be *cis* with respect to C1a, C4a and C10.

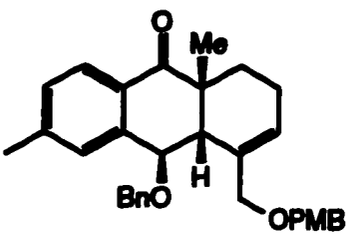



**Figure 13** Stereochemistry of a similar derivative as determined by X-ray crystallography.[13]

## *2.2 Preliminary Synthetic Attempts Toward Synthesis of the Double Bond Tether Controlled System*

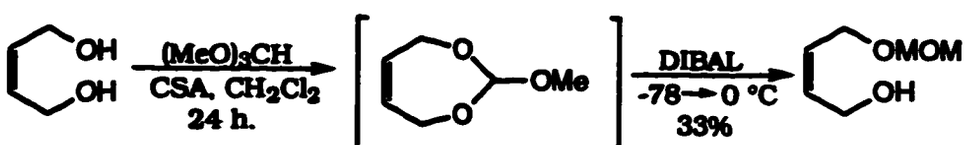
It has been shown above that an aromatic group proved to be beneficial as a planar tether control group in the synthesis of **35**. It was therefore decided to study the use of a double bond as a possible conformational constraint in the tether of another intramolecular Diels-Alder reaction. In this case, the chosen starting material was the commercially available (*Z*)-2-butene-1,4-diol (**20**).

Monoprotection of diol **20** was desirable. It has been reported that acetals and orthoesters provide monoprotected diols upon regioselective

reductive cleavage with diisobutylaluminum hydride.[28] It was therefore decided to utilize this method for the monoprotection of diol **20**.

### 2.2.1 Preparation of Monoprotected Diol 37 *via* Orthoester Cleavage

A methoxymethyl protecting group was employed for the monoprotection of diol **20**. This was accomplished by first forming the cyclic orthoester **36** by treatment of the diol with trimethyl orthoformate (2 equiv.) and a catalytic amount of camphorsulfonic acid in dichloromethane for 24 hours. Without isolation, the crude reaction mixture was treated with excess diisobutylaluminum hydride (DIBAL, 2.8 equiv.). On work up, the alcohol **37** was isolated in 33% yield. This yield was quite low as compared to those reported in the literature which used 10 equivalents of DIBAL.[28b-c] An increase in yield, however, was not observed when a greater excess of DIBAL (up to 5 equiv.) was used.




**20** **36** **37**

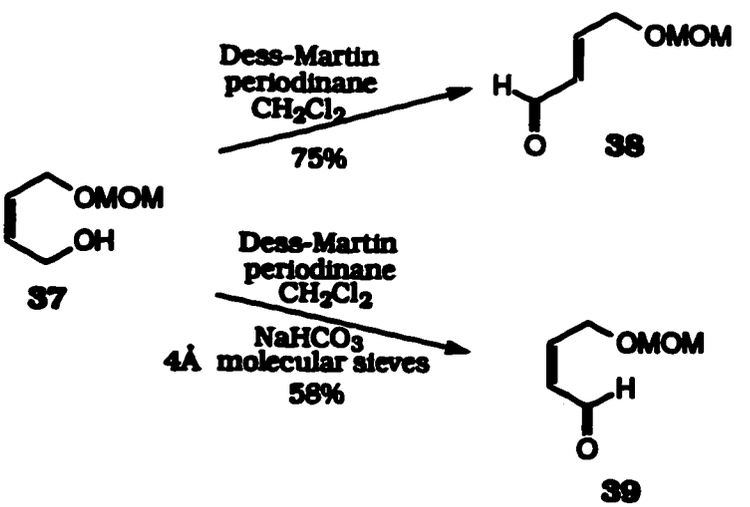
**Scheme 12**

### 2.2.2 Preparation of Aldehyde 39

It was initially believed that treatment of alcohol **37** with Dess-Martin periodinane in dichloromethane would provide the desired (*Z*)-4-methoxymethyloxy-2-butenal (**39**). These conditions, however, turned out to be too acidic and led to the isomerization of the double bond to form the undesired *E* isomer **38**. Other oxidation conditions were

therefore tried, such as manganese dioxide, sulfur trioxide-pyridine-dimethyl sulfoxide complex in triethylamine,[29] as well as Swern oxidation.[30] These conditions, unfortunately, led to the formation of both *cis* and *trans* isomers which were very difficult to separate.

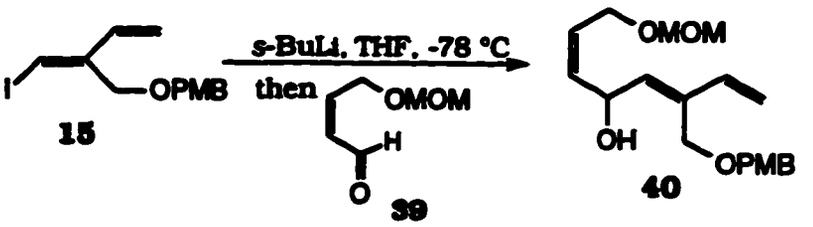
It was therefore decided to perform the Dess-Martin oxidation in the presence of a base. When pyridine (4 equiv.) was added to a solution of the alcohol **37** followed by the addition of Dess-Martin periodinane, again, the net result was the formation of the wrong isomer of the aldehyde. It was finally discovered that the desired *cis* isomer **39** could be formed exclusively when a solution of alcohol **37** was added slowly to a stirred solution of Dess-Martin periodinane (1.2 equiv.), sodium bicarbonate (~4 equiv.) and 4Å molecular sieves in dichloromethane.[31] Once the oxidation was complete (usually about 10 minutes), the reaction mixture was filtered and concentrated, then purified by flash column chromatography to afford the desired aldehyde **39** in 58% yield.




**Scheme 13**

### 2.2.3 Attachment of the Diene Moiety to Aldehyde 39

With the required aldehyde **39** in hand, the diene segment was attached by the condensation reaction described earlier (*cf.* section 2.1.4) with dienyl iodide **15**. Again, this was performed by treating the dienyl iodide **15** with *sec*-butyllithium, and then adding the aldehyde **39**. This condensation afforded the alcohol **40** in 68% yield.



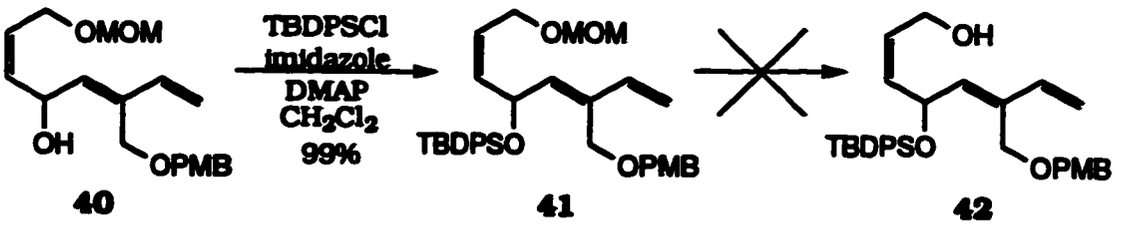

**Scheme 14**

### 2.2.4 Attempted Synthesis of Alcohol 42

In order to obtain the required precursor **42** for the dienophile addition, a sequence of protection and deprotection steps had to be carried out. First, the secondary alcohol of compound **40** was protected as its corresponding *tert*-butyldiphenylsilyl ether (**41**) in 99% yield. The next step required the deprotection of the methoxymethyl group. This, however, proved to be very difficult.

Several attempts were made to cleave the methoxymethyl ether using trimethylsilyl bromide,[32] magnesium bromide etherate with 1-butanethiol,[33] 4% hydrochloric acid, as well as heating at reflux in 2-butanone with pyridinium *p*-toluenesulfonate.[34] Despite this effort, the attempted deprotection of the methoxymethyl group led only to the formation of complex mixtures of products of which the crude NMR

spectra seemed to indicate the disappearance of the diene portion of the molecule.

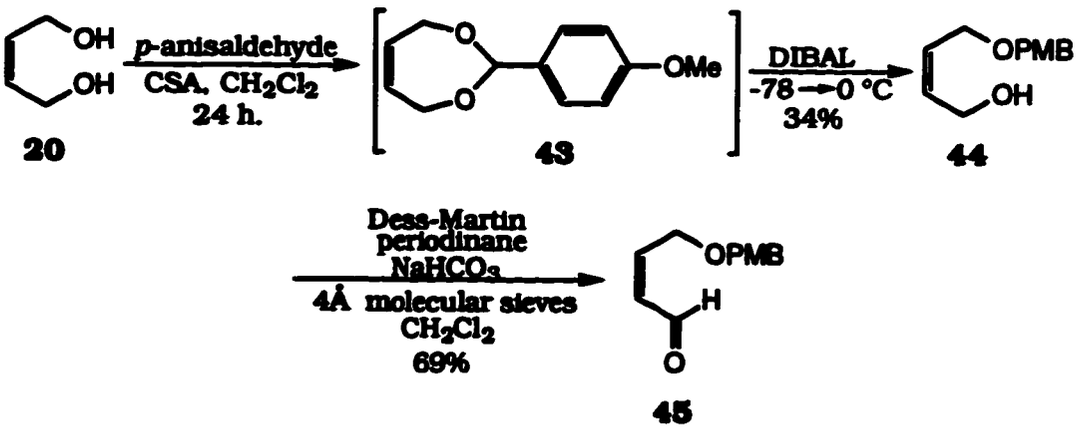



**40** **41** **42**

**Scheme 15**

### 2.2.5 *p*-Methoxybenzyl Ether Series

In view of the fact that the methoxymethyl group utilized for the protection of diol **20** was very difficult to remove in later steps, the use of *p*-methoxybenzyl as an alternate protecting group was examined.




**20** **43** **44** **45**

**Scheme 16**

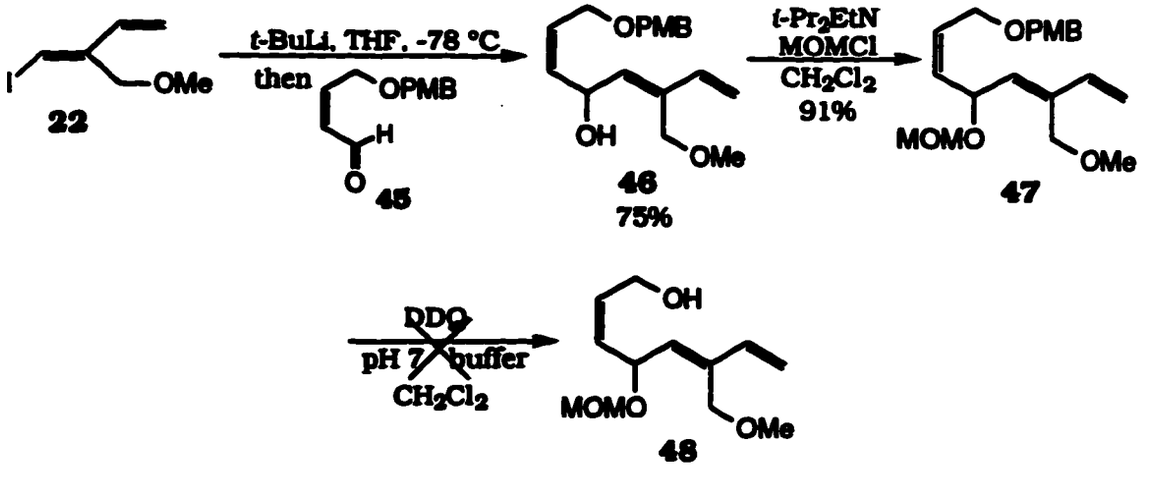
The orthoester **43** was first prepared by treatment of the diol **20** with *p*-anisaldehyde (2 equiv.) and a catalytic amount of camphorsulfonic acid in dichloromethane for 24 hours. As described earlier, the crude orthoester solution was then treated directly with excess diisobutylaluminum hydride (5.3 equiv. were used in this case) to afford the

monoprotected diol **44** in 34% yield. Oxidation was then carried out in the same manner as in the methoxymethyl series, to provide the desired *Z* aldehyde isomer **45** in 69% yield.

The next step was the diene addition to aldehyde **45**. Aldehyde **45** has the same protecting group as dienyl iodide **15** (i.e. *p*-methoxybenzyl ether), so the methyl ether protected diene **22** was therefore used in this series to differentiate between protecting groups.

The condensation reaction between dienyl iodide **22** and aldehyde **45** involved the treatment of **22** (1.5 equiv.) with *tert*-butyllithium (3.1 equiv.), followed by the addition of the aldehyde. This afforded the desired alcohol **46** in 75% yield, which was subsequently protected as its corresponding methoxymethyl ether **47**.

Attempts were made to remove the *p*-methoxybenzyl protecting group with 2,3-dichloro-5,6-dicyanobenzoquinone (2 equiv.), however this was unsuccessful. The $^1$H NMR spectrum of the crude reaction mixture seemed to indicate that the diene portion signals had changed dramatically and it did not appear that any of the desired product (**48**) had been formed.




**Scheme 17**

## *2.3 Synthesis of the Double Bond Tether Controlled System*

### 2.3.1 Preparation of Monoprotected Diol 49

The methoxymethyl and *p*-methoxybenzyl ethers were both difficult to cleave, therefore the use of a silyl ether as a protecting group was examined. The monoprotection of diol **20** was carried out such that a *tert*-butyldimethylsilyl ether was formed.

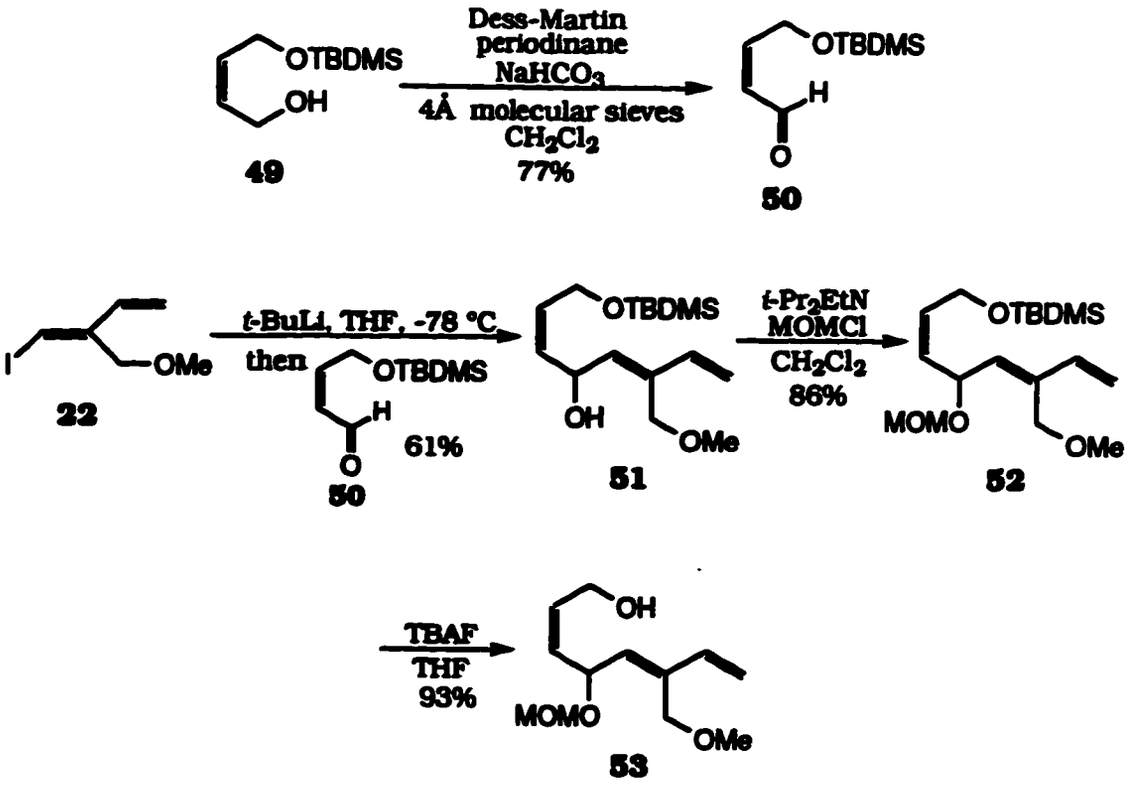
Alcohol **49** was prepared in 88% yield in our laboratory[35] by the treatment of diol **20** with sodium hydride (1 equiv.) and *tert*-butyldimethylsilyl chloride (1 equiv.).


**20** **49**

**Scheme 18**

### 2.3.2 Preparation of Alcohol 53

A series of steps were performed to obtain alcohol **53**. First, alcohol **49** was oxidized to afford the aldehyde **50**, which in turn was condensed with dienyl iodide **22** to form triene **51**. The resulting alcohol functionality of compound **51** was then protected to provide the methoxymethyl ether **52**. The next step required the removal of the *tert*-butyldimethylsilyl protecting group. This was accomplished very easily upon treatment of compound **52** with tetra-*n*-butylammonium fluoride (4 equiv.) and afforded the required alcohol **53**.

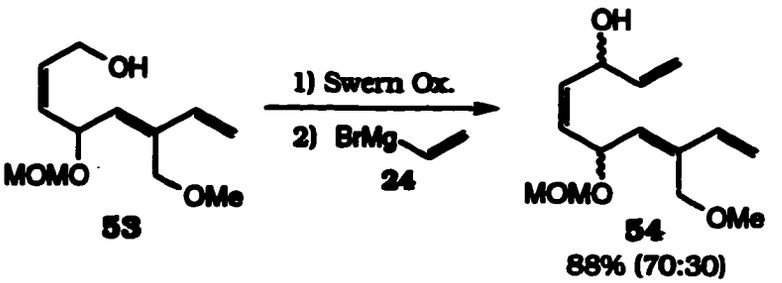



**Scheme 19**

### 2.3.3 Transformation of Alcohol 53 and Attachment of the Dienophile Moiety

The formation of the intramolecular Diels-Alder precursor **54** required oxidation of the alcohol **53** and addition of the dienophile moiety. These two chemical steps were performed in a one pot reaction involving a Swern oxidation, and the addition of the Grignard reagent vinylmagnesium bromide (**24**). The result was the formation of alcohol **54** as a 70:30 mixture of diasteromers in 88% yield (ratio determined from crude $^1$H NMR spectrum). The polarity of these two diastereomers happened to be significantly different (as seen by thin layer chromatography). This enabled their separation (for characterization

purposes) to proceed without difficulty by flash column chromatography. The mixture of diastereomers, however, was carried through to the next step as the oxidized intermediate **55** would present only one chiral centre.



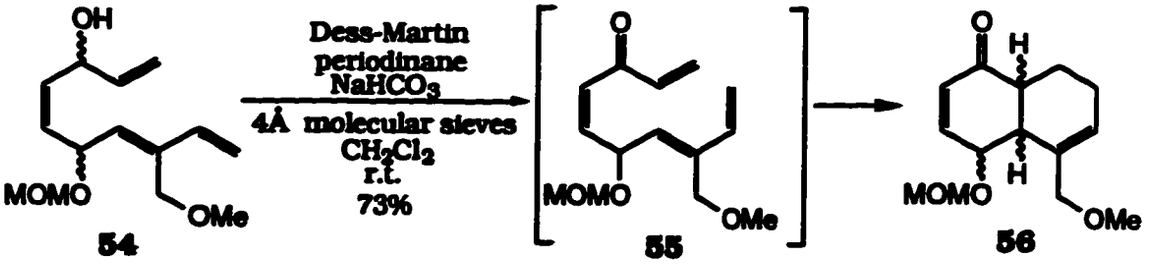

**Scheme 20**

### 2.3.4 The Intramolecular Diels-Alder Reaction of Ketone 55

Alcohol **54** now had the diene and dienophile in place, with the double bond in the connecting tether to act as a conformational constraint. The intramolecular Diels-Alder reaction was therefore performed, as described previously, under oxidation conditions.

To ensure that the *cis* double bond in the tether would not isomerize to *trans* thus inhibiting cyclization, the oxidation was carried out as described previously: a solution of alcohol **54** was added slowly to a stirred solution of Dess-Martin periodinane (1.2 equiv.), sodium bicarbonate (~4 equiv.) and 4Å molecular sieves in dichloromethane. After stirring at room temperature for 4 hours, the reaction was complete. The cyclized product **56** was formed in 73% yield as an apparent 77:23 mixture of diastereomers (ratio determined from crude $^1$H NMR spectrum). Due to the scale of the reaction and difficulty in

separation, only the major isomer of **56** could be isolated for characterization and for use in subsequent reactions.




**Scheme 21**

### 2.3.5 Characterization of the Major Bicyclic Product of 56

The proposed transition states for the Diels-Alder reaction are illustrated in Figure 14 (the transition states are shown for only one optical series only). It was reasonable to assume that the *endo* transition state (**A** and **B**) would be preferred over the *exo* transition state (**C** and **D**) as a result of favourable secondary orbital overlap. The *endo* approach would therefore lead to the formation of a *cis*-fused ring system.

As formerly described, the major cyclized product would likely be formed *via endo* transition state **A** in which the dienophile approaches the diene *anti* to the methoxymethyl ether group thus reducing steric interactions between the carbonyl and the protecting group. It was therefore predicted that the major product would have a relative *cis* stereochemistry with respect to C4, C5, and C10 (**56-a**).

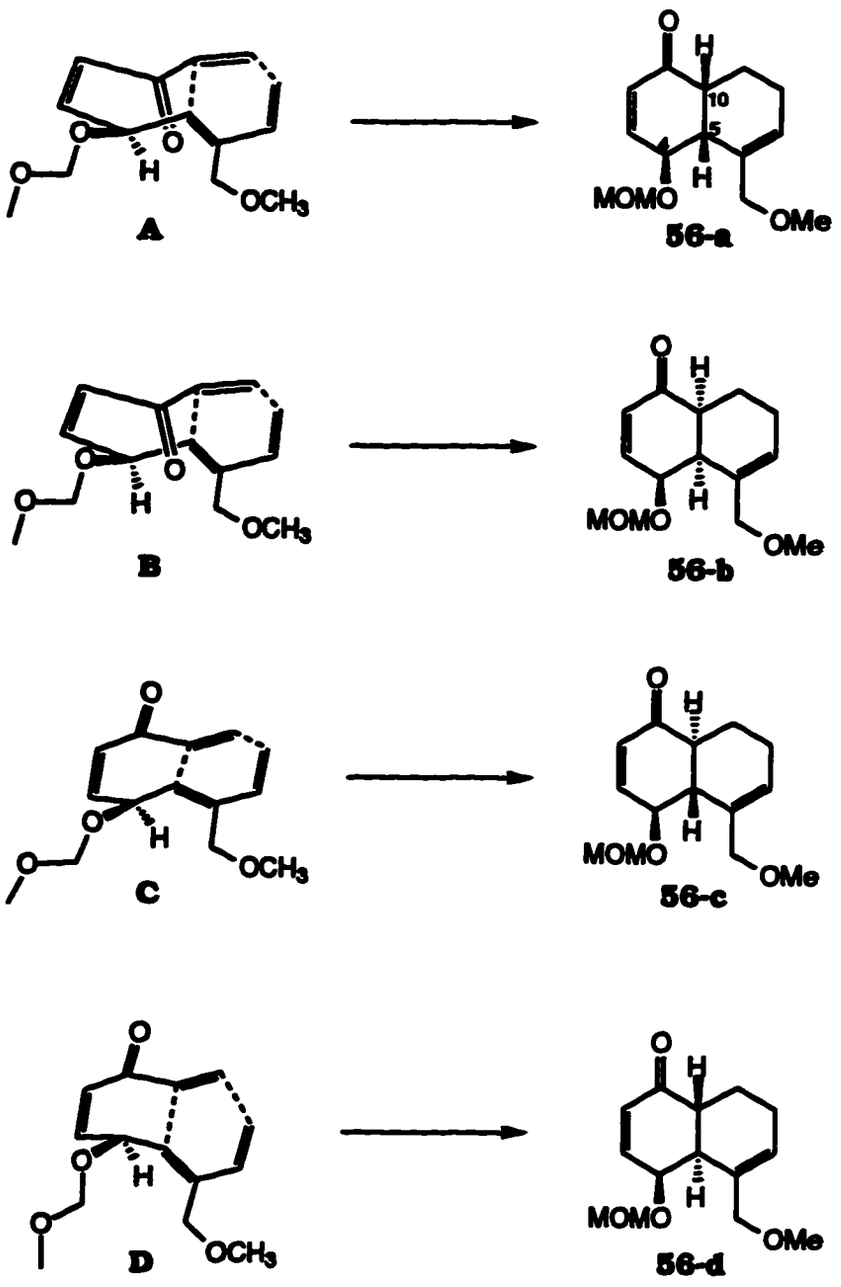



**Figure 14** Proposed Diels-Alder transition states of ketone **55**: **A**, *endo*, *anti* addition; **B**, *endo*, *syn* addition; **C**, *exo*, *anti* addition; **D**, *exo*, *syn* addition.

NOE experiments were performed on the major cyclized product of **56** (Figure 15) in order to confirm the predicted stereochemistry. Irradiation of the C5 hydrogen resulted in a 3.5% increase of the C10

proton signal, as well as a 3.6% increase of the C4 proton signal. This experiment indicated that the two rings were *cis*-fused. The relative stereochemistry of C4, however, was still ambiguous because the dihedral angle between the C4 and C5 hydrogens is almost orthogonal. In order to eliminate this uncertainty, the C4 hydrogen and the C10 hydrogen were irradiated. Both experiments resulted in the enhancement of the C5 proton signal. There was, however, no enhancement observed for either the C10 proton signal by irradiation of C4, or the C4 proton signal by irradiation of C10. It was therefore possible that the C4 and C10 hydrogens were on opposite sides of the molecule, thus the major cycloadduct was tentatively considered to be **56-a**. An X-ray crystallographic study of the derivative **57-b**, later unambiguously confirmed that this relative *cis* stereochemistry of **56-a** was correct.

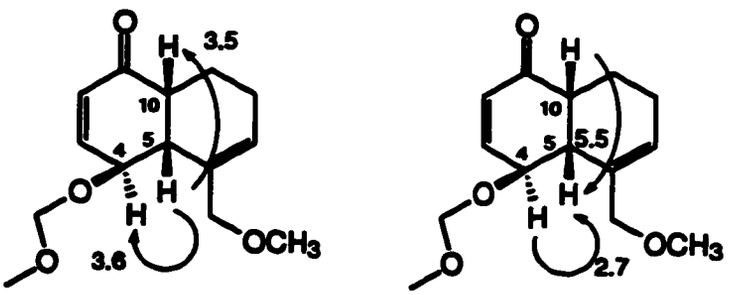


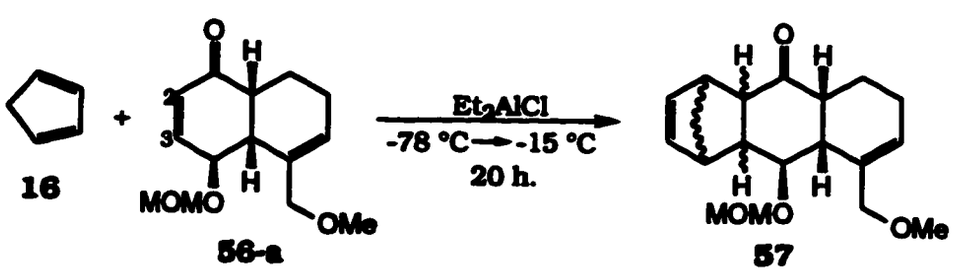

**Figure 15** Representative NOE enhancements of decalone **56-a**.

### 2.3.6 The Intermolecular Diels-Alder Reaction of Decalone 56-a with Cyclopentadiene

With the cycloadduct **56-a** in hand, it was decided to utilize the double bond between C2 and C3 as a dienophile in a subsequent intermolecular Diels-Alder reaction. Cyclopentadiene (**16**) was first chosen as the diene for this reaction because its symmetric character

would reduce the number of possible adducts formed from the cyclization.

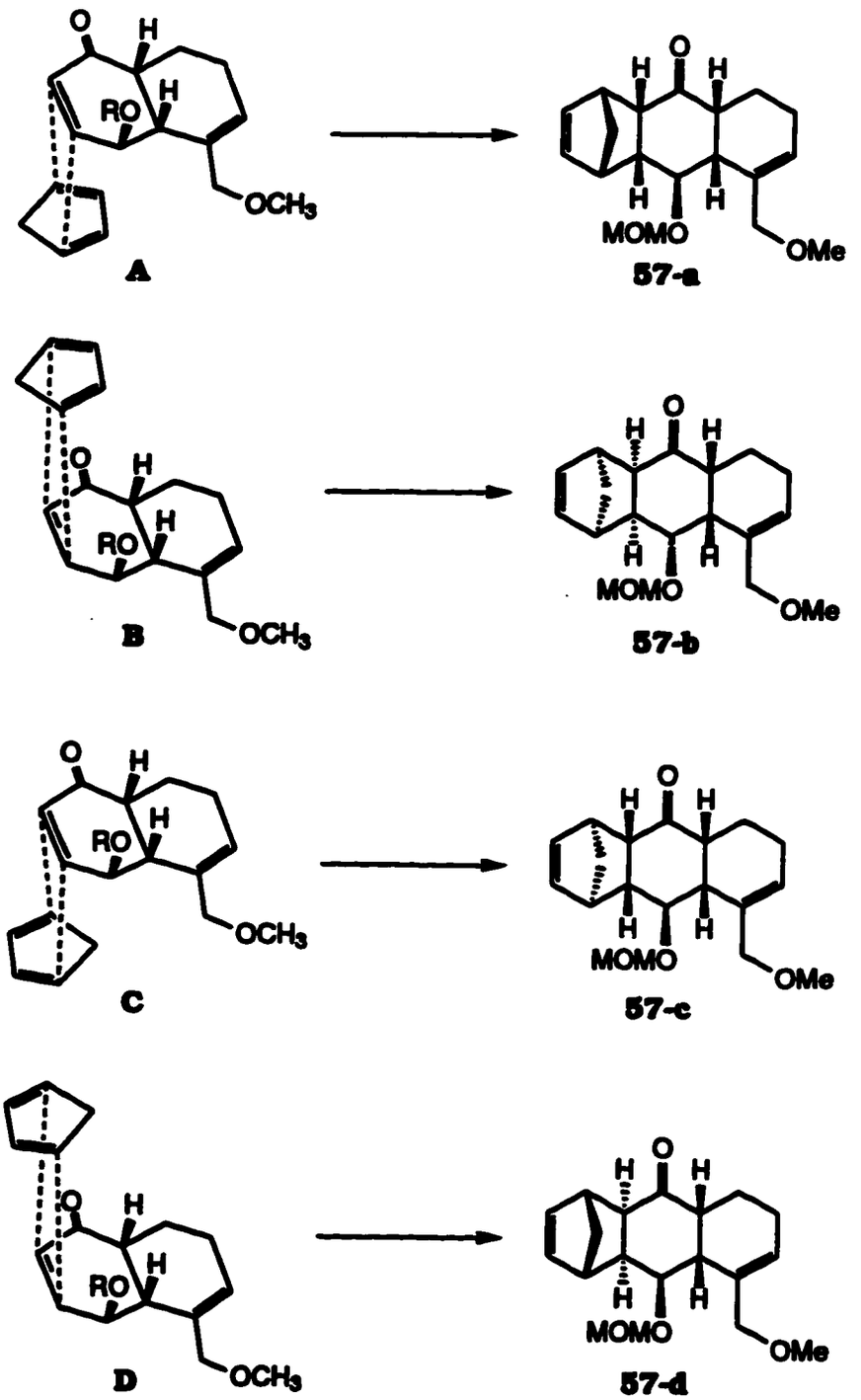
The cyclopentadiene (**16**, bp = 41 °C) used for the reaction was obtained from the fractional distillation (cracking) of dicyclopentadiene (bp = 160 °C) into receiving flasks submersed in a -78 °C dry ice/acetone bath. The freshly distilled, cold (-78 °C) cyclopentadiene was then transfered, *via* cannula, to a cold (-78 °C) solution of ketone **56-a** and diethylaluminum chloride (1.4 equiv.) in dichloromethane. The reaction flask was placed in the freezer (-15 °C) for 20 hours after which time the intermolecular Diels-Alder reaction had apparently reached completion. The cycloadduct **57** had been formed as a 90:10 mixture of diasteromers (ratio determined from crude $^1$H NMR spectrum) in an 87% yield. Again, because of the small scale of the reaction, only the major cycloadduct was isolated for characterization.




**Scheme 22**

### 2.3.7 Characterization of the Major Intermolecular Diels-Alder Product of 57

The proposed transition states for the intermolecular Diels-Alder reaction between cyclopentadiene (**16**) and decalone **56-a** are illustrated in Figure 16.




R = -$OCH_2OCH_3$

**Figure 16** Proposed intermolecular Diels-Alder transition states: **A**, *endo*, *anti* addition; **B**, *endo*, *syn* addition; **C**, *exo*, *anti* addition; **D**, *exo*, *syn* addition.

Once again, it was reasonable to assume that the *endo* transition state (**A** and **B**) would be preferred over the *exo* transition state (**C** and **D**) due to favourable secondary orbital overlap. It was also believed that the major cycloadduct would be formed *via endo* transition state **A** where the dienophile aproaches the diene *anti* to the bulky methoxymethyl ether group. Based on these considerations, it was initally predicted that the major cycloadduct would have the relative *cis* stereochemistry as depicted by the product **57-a**.

NOE experiments were performed on what was believed to be the major product **57-a** (Figure 17) in order to confirm this predicted stereochemistry. Irradiation of the hydrogen designated $H_A$ in Figure 17, resulted in a 5.2% increase of the C5a proton signal, as well as a 4.2% increase of the C8a proton signal. Irradiation of the C8a hydrogen gave rise to an increase of ~2.6% of the $H_A$ proton signal, and irradiation of the C5a hydrogen led to an increase of ~3.5% of the $H_A$ proton signal. These results seem to indicate that the bridge between C5 and C8 is *cis* to the C5a and C8a hydrogens. This is consistent with the *endo* transition states in Figure 15.

An increase of ~5.8% of the C10 proton signal was also observed upon irradiation of the C5a hydrogen, while C10 irradiation led to an ~5.4% increase of the C5a proton signal. Unfortunately, the relative stereochemistry of C5a was still ambiguous since the dihedral angle between the C5a and C10 hydrogens is almost orthogonal. Further NOE experiments were not found to be beneficial as a result of the overlapping of proton signals which made them indistinguishable from one another. Therefore, it was possible that these results could correspond to the product **57-b** (Figure 17).

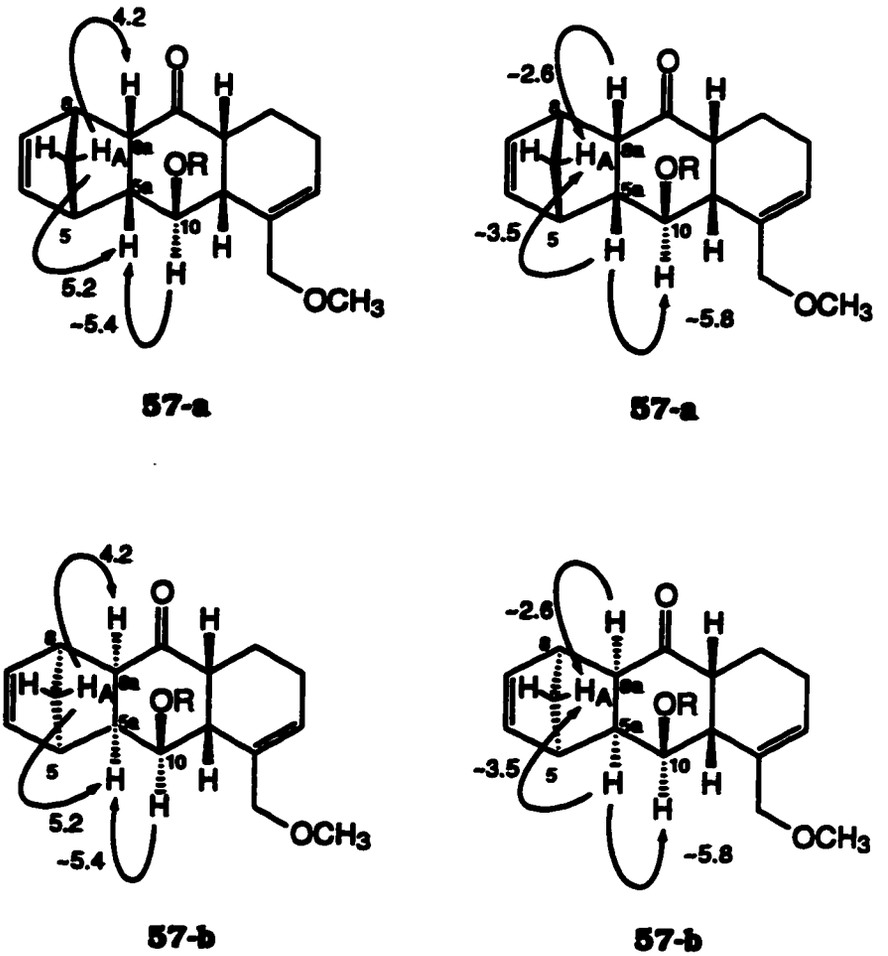



**Figure 17** Representative NOE enhancements of ketone **57-a** or **57-b**.

Fortunately the major cycloadduct of **57** was crystalline, and after submission of this thesis, the X-ray results were obtained (Figure 18). It turns out that the major product was actually the result of an *endo, syn* addition and thus has the structure of **57-b**. This overall geometry of the tetracyclic compound will not be as good a taxoid mimic as anticipated (*cf* page 48).

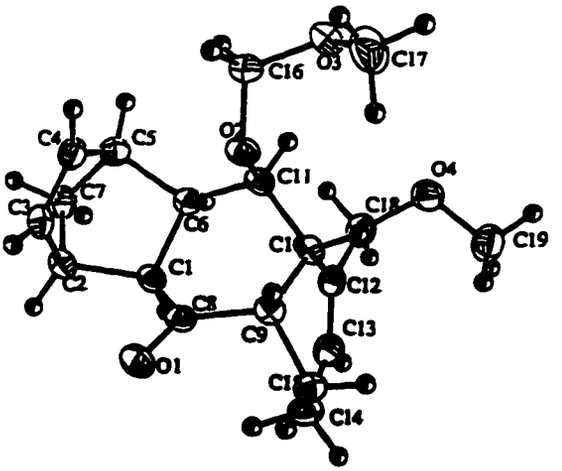



**Figure 18** X-ray structure of **57-b**.

This result might be better understood if we look at the transition state interactions in a different manner (Figure 19; these structures are drawn for the opposite optical series for clarity). It appears that the *endo*

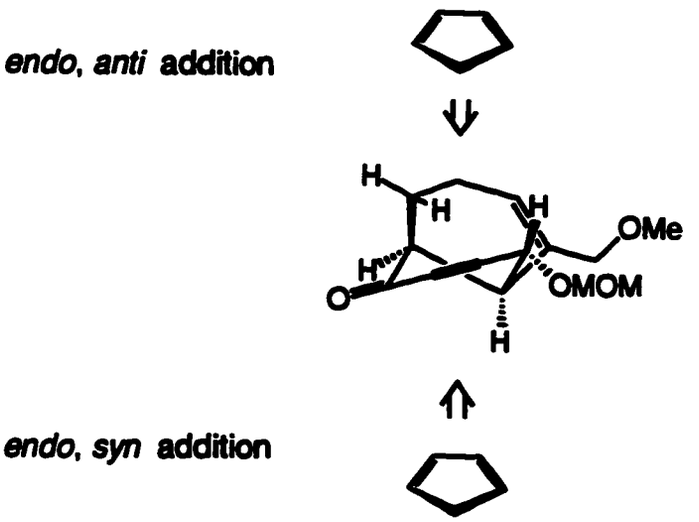


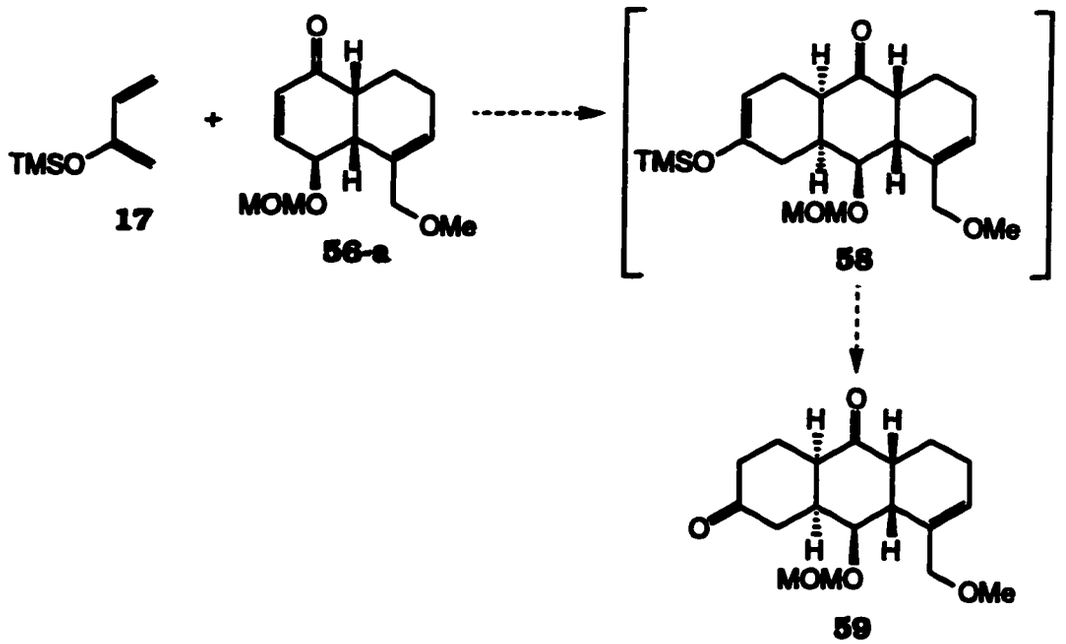

**Figure 19** Transition state interactions between cyclopentadiene and decalone **56-a**.

*anti* approach is actually more sterically hindered than the *endo, syn* addition which explains why we see **57-b** as the major cycloadduct.

### 2.3.8 Alternative Intermolecular Diels-Alder Reaction Attempt

In order to expand the scope of this research, another intermolecular Diels-Alder reaction involving a different diene with ketone **56-a** was investigated. 2-Trimethylsilyloxy-1,3-butadiene (**17**) was selected and prepared as described in the literature.[27]

The dienophile **56-a** was first treated with diene **17** (1.5 equiv.) in dichloromethane. After stirring at room temperature for 24 hours, there was no change indicated by TLC. The dichloromethane was therefore removed *in vacuo* and replaced with *m*-xylene. The reaction then continued under reflux conditions at ~140 °C for 4.5 days. TLC analysis of the reaction mixture at this point did show some change, but the reaction did not appear to be progressing any further. The reaction mixture was therefore allowed to cool to room temperature and diethylaluminum chloride (1.4 equiv.) was added. The reaction mixture was then allowed to stir at room temperature for 1 day, 110 °C for 4-5 hours, then 30-40 °C for 2 days. At this point, there was little evidence of starting material by TLC thus the reaction was stopped. Unfortunately, the NMR spectra of the products obtained under these conditions did not show any evidence for the formation of the expected products **58** or **59** (Scheme 23).




**Scheme 23**

# 3 Conclusions

The main objective of this research project was to synthesize substitued anthraquinone systems as potential analogues of Taxol®. The anthraquinone derivatives **35** and **57-b** were successfully prepared *via* cycloaddition approaches, based on the concept of suitable tether control groups to facilitate the intramolecular reactions.

The tricyclic core of ketone **35** was prepared by an intramolecular Diels-Alder reaction. The required precursor **33** was readiiy synthesized from 3-methylbenzyl alcohol (**13**), acrolein (**14**), and (*Z*)-1-iodo-2-*p*-methoxybenzyloxymethyl-1,3-butadiene (**15**). *Ortho*-lithiation of the benzylic alcohol **13** occurred preferentially at C6 rather than C2 as a consequence of steric factors. This enabled the dienophile moiety to be attached in the required position of the aromatic ring. Attachment of the diene was achieved *via* a Grignard-type addtition reaction. The Diels-Alder precursor **33** readily underwent cyclization under oxidative conditions at room temperature to afford the *cis*-fused ring system **35**. The latter resulted from an *endo* transition state in which the dienophile approached the diene *anti* to the bulky methoxymethyl ether group. The ease of this cyclization was the result of the placement of an aromatic group in the tether which likely held the diene and dienophile in a geometric arrangement resembling that required for the transition state. The stereochemistry of ketone **35** was based on the X-ray structure of a similar derivative.[13]

The decalone system **56-a** was also synthesized *via* an intramolecular Diels-Alder cyclization. Its precursor **54** was prepared from (*Z*)-2-butene-1,4-diol (**20**), vinylmagnesium bromide (**21**), and (*Z*)-1-iodo-

2-methoxymethyl-1,3-butadiene (**22**). Synthetic pathways involving the monoprotection of diol **20** as its methoxymethyl or *p*-methoxybenzyl ether (*via* orthoester cleavage with DIBAL) were unsuccessful due to difficulty in removing these protecting groups in later steps. Monoprotection with a *tert*-butyldimethylsilyl group, however, readily enabled the synthesis of precursor **54**. The intramolecular Diels-Alder reaction proceeded upon oxidation of alcohol **54** at room temperature to afford the cyclized product **56** as a 77:23 mixture of diastereomers. The major product formed was the *cis*-fused ring system **56-a** resulting from an *endo* transition state in which the dienophile approached the diene *anti* to the methoxymethyl ether group.

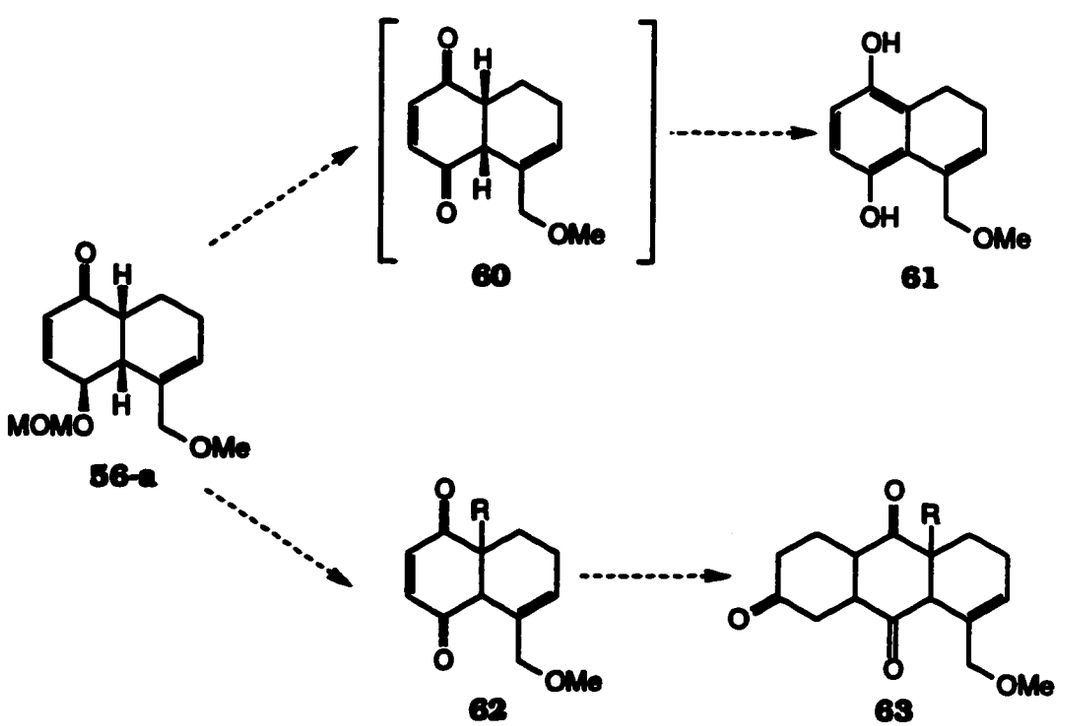
The substituted anthraquinone system **57-b** was prepared *via* an intermolecular Diels-Alder reaction between cyclopentadiene and the major decalone product **56-a**. Cyclization proceeded in the presence of diethylaluminum chloride at -15 °C to afford the cycloadduct **57** as a 90:10 mixture of diastereomers. The stereochemistry of the ring systems **56-a** and **57-b** were unambiguously determined by the X-ray structure of the adduct **57-b**.

## *3.1 Future Studies*

The intramolecular Diels-Alder reactions examined above involved an aromatic group or a double bond as conformational control units in the tether. Many other groups in the side chain could also influence the stereochemical outcome of such intramolecular reactions. Thus, tether control groups which are chiral should also merit study due to their potential to produce a homochiral product. Additional work is also

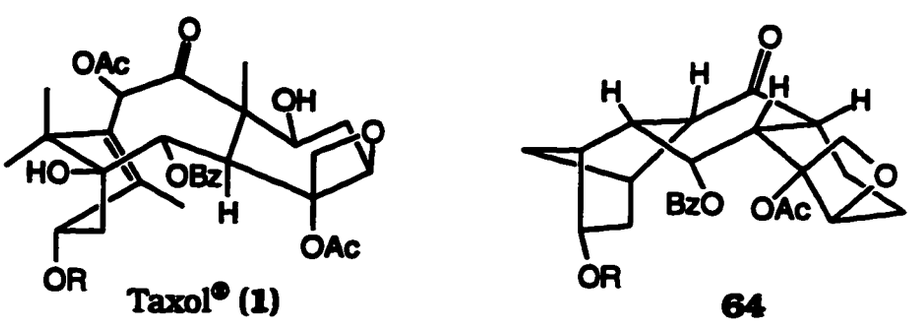
required to study the oxidative cleavage and/or further manipulations of the newly formed double bond of cycloadduct **57-b** which would provide access to interesting fused systems as potential taxol analogues.

The intermolecular Diels-Alder reaction between 2-trimethylsilyl-oxy-1,3-butadiene (**17**) and decalone **56-a** proved to be unsuccessful. A related target system of **59** could certainly be prepared by using a diactivated dienophile such as the diketone **60** which is expected to be more reactive. Unfortunately, cleavage of the methoxymethyl ether followed by oxidation of compound **56-a** will not afford the reactive diketone **60**, but instead will lead to the phenol derivative **61**. The versatility of the adduct **56-a**, however, could be expanded in the future by preparing the diactivated dienophile **62** (Scheme 24) which should readily generate the tricyclic nucleus related to **59**, (i.e. **63**).




**Scheme 24**

The stereochemical result from the intermolecular Diels-Alder reaction with cyclopentadiene was expected to provide some of the adduct **57-a**. This structure has potential as a Taxol® analogue due to its concave nature that resembles the "butterfly" conformation of the taxiods. The addition of key functional groups could afford compound **64** which should have a high probability of displaying useful biological activity. Unfortunately, the *cis-trans-cis* arrangement of the major product **57-b** is less favourable as a taxoid mimic. Epimerization of the norbornane hydrogens of **57-b** will be required to achieve the stereochemical relationships depicted in **64**.




R = Taxol® side chain

**Figure 20** Structure comparison between Taxol® and potential analogue **64**.

# 4 Experimental Section

## General Procedures

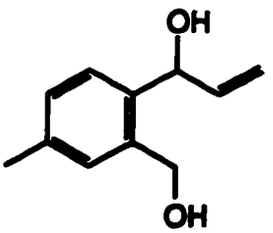
Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane or ether solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR) and the data are reported in reciprocal centimeters ($cm^{-1}$). Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. All nuclear magnetic resonance (NMR) spectra were obtained from deuterochloroform ($CDCl_3$) solutions relative to an internal lock on the deuterium in $CDCl_3$. $^1H$ NMR (200 or 500 MHz), and $^{13}C$ NMR (50.3 or 125.8 MHz) spectra were run on either a Varian Gemini or Bruker WM500 spectrometer. All NMR data are reported in parts per million (ppm) on the δ-scale. $^1H$ NMR data are reported as follows: chemical shift, multiplicity, integration, and coupling constants (Hz). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer with a 70 eV ionizing energy. Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona, or were performed in house.

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in oven-dried, or flame-dried glassware equipped with a magnetic stir bar. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates (E. Merck, type 5554). TLC plates were

viewed under ultraviolet light and developed by heating the plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a *p*-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). Product purification by conventional and flash column chromatography was performed using E. Merck Silica Gel 60 (70-230 or 230-400 mesh, respectively). Excess solvents were removed *in vacuo* at pressures obtained by a water aspirator drawing on a Buchi R110 Rotovapour. Trace solvents were removed on a vacuum pump. All compounds were stored at -15 °C in vials flushed with nitrogen.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C, and ether refers to diethyl ether. Tetrahydrofuran and ether were freshly distilled from benzophenone/sodium. Dichloromethane, triethylamine and diisopropylethylamine were distilled from calcium hydride. *N,N,N',N'*-tetramethylethylenediamine was distilled from potassium hydride. Pentane was stored over 4Å molecular sieves for at least 24 hours prior to use.

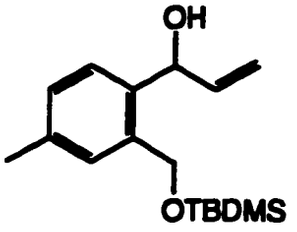
**2-Hydroxymethyl-1-(1-hydroxy-2-propenyl)-4-methylbenzene (23)**




To a dry three-necked flask equipped with a magnetic stir bar and a water condenser was added dry pentane (100 mL), 3-methylbenzyl alcohol (5.0 mL, 42 mmol), and *N,N,N',N'*-tetramethylethylenediamine (12.5 mL, 83.0 mmol). The mixture was stirred vigorously while one half of the *n*-butyllithium (33.2 mL, 2.5 M solution in hexane, 83.0 mmol) was slowly added dropwise. During this addition, thick white precipitates began to form and the mixture began to reflux. Coagulation stopped and the remaining half of the *n*-butyllithium was added rapidly to the red-brown mixture which was then refluxed (~35 °C) overnight. The reaction mixture was cooled to -78 °C and acrolein (7.0 mL, 104 mmol), which had been passed through a plug of basic alumina, was added. The mixture was stirred at -78 °C for ~5 minutes and then allowed to warm to room temperature. Saturated sodium bicarbonate solution (50 mL) was added and a thick yellow precipitate formed which was filtered off and discarded. The layers were separated and the aqueous phase was extracted with ether (3 × 25 mL). The combined organic extracts were washed once with water (50 mL), and once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the viscous crude oil by column chromatography (250 g silica gel, 60% ether/petroleum ether) afforded 2.9 g (39%) of the diol **23** as a clear

viscous oil which, upon prolonged storage at -15 °C, afforded a white solid (mp 41.5 - 42.0 °C): IR (ether): 3436 (br), 1490, 1448, 1291, 842 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.55-3.69 (br s, 1H), 3.79-3.89 (br s, 1H), 4.58 (d, 2H, $J$ = 3.6 Hz), 5.20-5.38 (m, 3H), 5.99-6.16 (m, 1H), 7.08 (d, 1H, $J$ = 6.4 Hz), 7.10 (s, 1H), 7.22 (d, 1H, $J$ = 8.6 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 20.9, 63.5, 72.6, 114.9, 127.9, 128.9, 130.9, 137.8, 137.9, 138.4, 139.1; HRMS exact mass calcd. for $C_{11}H_{12}O$ ($M^+$ - $H_2O$) 160.0889, found 160.0914.

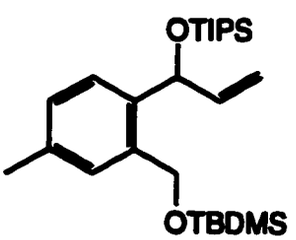
**2-(*t*-Butyldimethylsilyloxy)methyl-1-(1-hydroxy-2-propenyl)-4-methylbenzene (24)**




To a stirred solution of the diol **23** (5.05 g, 28.3 mmol) in dry dichloromethane (140 mL) was added imidazole (3.81 g, 56.0 mmol) and *tert*-butyldimethylsilyl chloride (5.06 g, 33.6 mmol). After stirring at room temperature for 10 minutes, saturated sodium bicarbonate solution (30 mL) was added and the layers were separated. The aqueous phase was extracted with ether (2 × 25 mL), and the combined organic extracts were washed once with brine (35 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash column chromatography (100 g silica gel, 30% ether/petroleum ether) afforded 6.9 g (84%) of alcohol the **24** as a slightly yellow oil: IR (neat): 3383 (br),

2943, 1615, 1062, 842 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 6H), 0.91 (s, 9H), 2.33 (s, 3H), 3.45-3.49 (m, 1H), 4.76 (dd, 2H, $J$ = 14.0, 12.0 Hz), 5.21-5.47 (m, 3H), 6.02-6.18 (m, 1H), 7.10 (m, 2H), 7.28 (d, 1H, $J$ = 8.2 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ -5.2, 18.3, 21.1, 25.9, 64.4, 72.1, 114.6, 127.7, 128.8, 129.8, 137.5, 137.9, 138.4, 139.2; HRMS exact mass calcd. for $C_{13}H_{19}O_2Si$ ($M^+$ - *t*-Bu) 235.1192, found 235.1166.

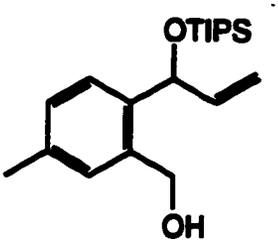
**2-(*t*-Butyldimethylsilyloxy)methyl-4-methyl-1-(1-triisopropylsilyloxy-2-propenyl)benzene (25)**




To a stirred solution of the alcohol **24** (1.38 g, 4.71 mmol) in dichloromethane (9.4 mL) was added 2,4,6-collidine (1.5 mL, 11 mmol) and triisopropylsilyl triflate (1.5 mL, 5.7 mmol). After 20 minutes, the reaction was quenched with saturated sodium bicarbonate solution (15 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed once with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash column chromatography (150 g silica gel, 2.5% ether/petroleum ether) afforded 1.9 g (90%) of the protected diol **25** as a colourless oil: IR (neat): 2943, 1638, 1465, 1068, 883 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.09(s, 6H), 0.89-1.03 (m, 30H), 2.33 (s, 3H), 4.77 (dd, 2H, $J$ = 16.9, 13.5 Hz), 5.01 (ddd, 1H, $J$ = 10.2, 1.6, 1.6

Hz), 5.23 (ddd, 1H, $J$ = 15.4, 1.6, 1.6 Hz), 5.38 (d, 1H, $J$ = 5.0 Hz), 5.84-6.00 (m, 1H), 7.04 (d, 1H, $J$ = 8.2 Hz), 7.24 (s, 1H), 7.33 (d, 1 H, $J$ = 7.8 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ -5.3, 12.2, 18.0 (2x), 21.3, 26.0, 62.6, 73.1, 112.6, 126.6, 127.3, 127.7, 136.5, 137.3, 137.5, 141.1; HRMS exact mass calcd. for $C_{26}H_{48}O_2Si_2$ 448.3195, found 448.3200; Anal. calcd. for $C_{26}H_{48}O_2Si_2$ : C, 69.58; H, 10.77. Found: C, 69.62; H, 10.95.

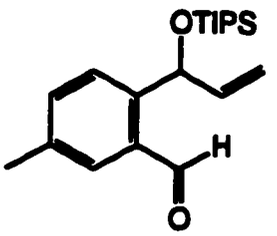
**2-Hydroxymethyl-4-methyl-1-(1-triisopropylsilyloxy-2-propenyl)-benzene (26)**




To a stirred solution of the protected diol **25** (3.00 g, 6.68 mmol) in 99% ethanol (45 mL) was added pyridinium *p*-toluenesulfonate (0.84 g, 3.3 mmol). After stirring at room temperature overnight, the ethanol was removed *in vacuo*. The crude oil was then dissolved in ether (20 mL) and washed once with $H_2O$ (20 mL). The layers were separated and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic extracts were washed once with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash column chromatography (100 g silica gel, 10% ether/petroleum ether) afforded 1.6 g (72%) of the benzyl alcohol **26** as a colourless oil: IR (neat): 3351 (br), 2867, 1464, 1047, 883 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.83-1.13 (m, 21H), 2.31 (s, 3H), 2.68-2.74 (m, 1H), 4.54 (dd,

1H, $J$ = 12.6, 8.0 Hz), 4.82 (dd, 1H, $J$ = 12.4, 4.6 Hz), 5.09 (ddd, 1H, $J$ = 10.4, 1.6, 1.6 Hz), 5.30 (ddd, 1H, $J$ = 17.2, 1.6, 1.6 Hz), 5.40-5.42 (m, 1H), 5.94-6.10 (m, 1H), 7.07 (d, 1H, $J$ = 7.6 Hz), 7.14 (s, 1H), 7.26 (d, 1H, $J$ = 7.6 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 12.2, 17.7, 17.9, 18.0, 21.0, 63.4, 75.4, 113.5, 128.1, 128.5, 130.3, 138.5, 138.2, 140.9; HRMS exact mass calcd. for $C_{17}H_{27}O_2Si$ ($M^+$ - *i*-Pr) 291.1781, found 291.1795.

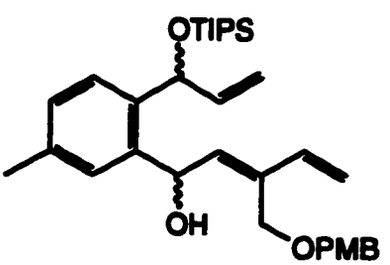
**5-Methyl-2-(1-triisopropylsilyloxy-2-propenyl)benzenecarboxaldehyde (27)**




To a stirred solution of the benzyl alcohol **26** (1.62 g, 4.84 mmol) in dichloromethane (48 mL) was added Dess-Martin periodinane (3.08 g, 7.25 mmol). After stirring at room temperature for 20 minutes, saturated sodium bicarbonate solution (30 mL) was added, followed by sodium thiosulfate pentahydrate (2.0 g) and ether (30 mL). The mixture was allowed to stir for another 20 minutes, and then the layers were separated and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic extracts were washed once with a saturated sodium thiosulfate solution (40 mL), once with a saturated sodium bicarbonate solution (40 mL), and once with brine (40 mL). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification of the crude oil by flash column

chromatography (60 g silica gel, 5% ether/petroleum ether) afforded 1.5 g (91%) of the aldehyde **27** as a slightly yellow oil: IR (neat): 2867, 2728, 1464, 1062, 883 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.95 (d, 9H, $J$ = 2.9 Hz), 1.00 (d, 9H, $J$ = 2.9 Hz), 1.04-1.56 (m, 3H), 2.38 (s, 3H), 5.01-5.04 (m, 1H), 5.27-5.31 (m, 1H), 5.98-6.04 (m, 2H), 7.36 (dd, 1H, $J$ = 7.9, 1.4 Hz), 7.54 (d, 1H, $J$ = 7.9Hz), 7.60 (s, 1H), 10.31 (s, 1H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 12.1, 17.9, 18.0, 20.9, 72.3, 113.2, 127.6, 132.6, 134.6, 137.3, 141.5, 143.7, 193.4; HRMS exact mass calcd. for $C_{17}H_{25}O_2Si$ ($M^+$ - *t*-Pr) 289.1625, found 289.1637.

**2-[(2Z)-1-Hydroxy-3-(*p*-methoxybenzyloxy)methyl-2,4-pentadienyl]-4-methyl-1-(1-triisopropylsilyloxy-2-propenyl)benzene (31)**

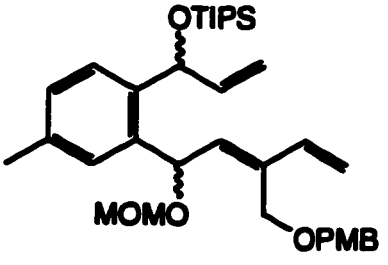



To a round bottomed flask at -78 °C was added dry tetrahydrofuran (29 mL) and *sec*-butyllithium (3.6 mL, 1.4 M in hexanes, 5.02 mmol). The resulting bright yellow solution was stirred at -78 °C for 15 minutes, and then a solution of the dienyl iodide **15** (790 mg, 2.39 mmol) in dry tetrahydrofuran (4.4 mL) was added *via* cannula over a period of 1-1.5 minutes to yield an orange/yellow solution. After stirring for an additional 1.5 minutes at -78 °C, a solution of the aldehyde **27** (497 mg, 1.49 mmol) in dry tetrahydrofuran (4.4 mL) was added *via* cannula over a period of ~1.5 minutes. The resulting yellow solution was stirred at -78

°C for 15 minutes, and then was allowed to warm up to room temperature during which time the solution turned blue/green. The reaction was quenched slowly with a few drops of water, and the solution turned yellow. Additional water (25 mL) was added and the layers were separated. The aqueous phase was extracted with ether (2 × 15 mL) and the combined organic extracts were washed once with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (100 g silica gel, 30% ether/petroleum ether) afforded 735 mg (92%) of the alcohol **31** as a 70:30 mixture of diastereomers as a viscous yellow oil: major product: IR (neat): 3416 (br), 2943, 1612, 1067, 883 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.92-1.07 (m, 21H), 2.31 (s, 3H), 3.19 (br s, 1H), 3.78 (s, 3H), 4.18 (d, 1H, $J$ = 11.3 Hz), 4.25 (d, 1H, $J$ = 11.5 Hz), 4.41 (d, 1H, $J$ = 8.4 Hz), 4.43 (d, 1H, $J$ = 8.9 Hz), 5.01 (ddd, 1H, $J$ = 10.4, 1.6, 1.6 Hz), 5.11 (d, 1H, $J$ = 11.0 Hz), 5.17 (ddd, 1H, $J$ = 17.1, 1.6, 1.6 Hz), 5.31-5.32 (m, 1H), 5.34 (d, 1H, $J$ = 17.5 Hz), 5.84 (d, 1H, $J$ = 8.4 Hz), 5.90-5.96 (m, 1H), 5.93 (d, 1H, $J$ = 8.8 Hz), 6.31 (dd, 1H, $J$ = 17.6, 11.1 Hz), 6.84 (d, 2H, $J$ = 8.7 Hz), 7.05 (dd, 1H, $J$ = 7.9, 1.2 Hz), 7.20 (d, 2H, $J$ = 8.6 Hz), 7.31 (d, 1H, $J$ = 7.5 Hz), 7.32 (br s, 1H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 12.2, 12.3, 18.0 (2×), 21.2, 55.2, 64.4, 66.0, 72.2, 74.0, 113.5, 113.9, 114.4, 126.7, 127.5, 128.3, 129.5, 129.9, 136.9, 137.4 (2×), 137.5, 138.1, 139.7, 141.1, 159.3; Anal. calcd. for $C_{33}H_{48}O_4Si$ : C, 73.83; H, 9.01. Found: C, 73.72; H, 8.99: minor product: IR (neat): 3429 (br), 2943, 1612, 1048, 883 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.95 (d, 9H, $J$ = 7.2 Hz), 1.00 (d, 9H, $J$ = 7.0 Hz), 1.03-1.10 (m, 3H), 2.31 (s, 3H), 2.88 (br s, 1H), 3.78 (s, 3H), 4.24 (d, 1H, $J$ = 11.4 Hz), 4.33 (d, 1H, $J$ = 11.4 Hz), 4.48 (s, 2H), 4.97 (ddd, 1H, $J$ = 10.4, 1.6, 1.6 Hz), 5.08 (d, 1H, $J$ = 11.0

Hz), 5.17 (ddd, 1H, $J$ = 17.1, 1.7, 1.7 Hz), 5.29 (d, 1H, $J$ = 17.6 Hz), 5.48 (d, 1H, $J$ = 5.2 Hz), 5.85 (d, 1H, $J$ = 8.2 Hz), 5.87-5.92 (m, 1H), 5.91 (d, 1H, $J$ = 7.5 Hz), 6.27 (dd, 1H, $J$ = 17.6, 11.0 Hz), 6.86 (d, 2H, $J$ = 8.6 Hz), 7.07 (dd, 1H, $J$ = 7.9, 1.5 Hz), 7.26 (d, 2H, $J$ = 8.5 Hz), 7.30 (br s, 1H), 7.37 (d, 1H, $J$ = 7.9 Hz); $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 12.3, 18.0 (2×), 21.2, 55.2, 64.5, 66.5, 72.1, 72.5, 112.9, 113.9, 114.2, 126.8, 127.4, 128.6, 129.6, 129.7, 136.4, 137.2, 138.1, 138.3, 138.5, 140.0, 171.7, 159.4; Anal. calcd. for $C_{33}H_{48}O_4Si$ : C, 73.83; H, 9.01. Found: C, 73.67; H, 9.21

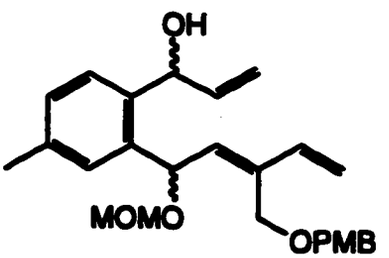
**2-[(2Z)-3-(p-Methoxybenzyloxy)methyl-1-methoxymethyloxy-2,4-pentadienyl]-4-methyl-1-(1-triisopropylsilyloxy-2-propenyl)benzene (32)**




To a stirred solution of the alcohol **31** (714 mg, 1.33 mmol) in dichloromethane (26.6 mL) at 0 °C was added dropwise diisopropylethylamine (3.5 mL, 20 mmol) and chloromethyl methyl ether (1.0 mL, 13 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, and was then warmed to room temperature and stirred overnight. Saturated sodium bicarbonate solution (20 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 15 mL), and the combined organic extracts were washed once with brine (25 mL),

dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (40 g silica gel, 20% ether/petroleum ether) afforded 625 mg (81%) of the triene **32** as a 70:30 inseparable mixture of diastereomers as a viscous yellow oil: $^1$H NMR (200 MHz, $CDCl_3$): δ 0.83-1.04 (m, 21H), 2.30 and 2.32 (two s, 3H), 3.30 and 3.33 (two s, 3H), 3.79 and 3.80 (two s, 3H), 4.19-4.32 (m, 2H), 4.46-4.52 (m, 3H), 4.64-4.70 (m, 1H), 4.89-5.39 (m, 5H), 5.54-6.01 (m, 2H), 5.65 (d, 1H, $J$ = 17.0 Hz), 6.24 and 6.25 (two dd, 1H, $J$ = 17.4, 10.9 and 17.6, 12.8 Hz), 6.87 and 6.88 (two d, 2H, $J$ = 8.2 and 8.0 Hz), 7.06-7.10 (m, 1H), 7.20-7.31 (m, 3H), 7.46 and 7.48 (two d, 1H, $J$ = 8.2 and 8.0 Hz).

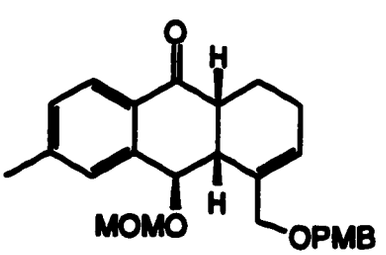
**1-(1-Hydroxy-2-propenyl)-2-[(2*Z*)-3-(*p*-methoxybenzyloxy)methyl-1-methoxymethyloxy-2,4-pentadienyl]-4-methylbenzene (33)**




To a stirred solution of the triene **32** (737 mg, 1.27 mmol) in tetrahydrofuran (6.3 mL) was added tetra-*n*-butylammonium fluoride (6.3 mL, 1M in THF, 6.3 mmol) dropwise over a period of 1.5 minutes. The resulting dark orange solution was stirred at room temperature for 20 minutes. Water (20 mL) was then added and the layers were separated. The aqueous phase was extracted with ether (3 × 7 mL), and the combined organic extracts were washed once with saturated sodium bicarbonate solution (15 mL), and once with brine (20 mL), dried over

anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (35 g silica gel, 40% ether/petroleum ether) afforded 435 mg (81%) of the alcohol **33** as a mixture of diastereomers as a viscous orange oil: major product: IR (neat): 3422 (br), 2918, 1612, 1029 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.88 (br s, 1H), 3.30 (s, 3H), 3.78 (s, 3H), 4.20 (d, 1H, $J$ = 11.1 Hz), 4.31 (d, 1H, $J$ = 11.1 Hz), 4.39 (d, 1H, $J$ = 11.5 Hz), 4.44 (d, 1H, $J$ = 11.5 Hz), 4.53 (d, 1H, $J$ = 6.8 Hz), 4.65 (d, 1H, $J$ = 6.8 Hz), 5.09 (d, 1H, $J$ = 11.0 Hz), 5.21 (ddd, 1H, $J$ = 10.4, 1.6, 1.6 Hz), 5.31 (d, 1H, $J$ = 17.6 Hz), 5.36 (ddd, 1H, $J$ = 17.2, 1.8, 1.8 Hz), 5.52 (d, 1H, $J$ = 4.3 Hz), 5.84 (d, 1H, $J$ = 9.2 Hz), 5.89 (d, 1H, $J$ = 9.2 Hz), 6.02-6.07 (m, 1H), 6.31 (dd, 1H, $J$ = 17.5, 11.1 Hz), 6.86 (d, 2H, $J$ = 8.7 Hz), 7.08 (dd, 1H, $J$ = 7.9, 1.5 Hz), 7.23 (d, 2H, $J$ = 8.6 Hz), 7.25 (s, 1H), 7.28 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 21.2, 55.3, 55.5, 63.7, 69.7, 69.8, 72.3, 93.5, 113.8, 114.6, 114.8, 127.6, 128.4, 129.0, 129.8, 135.2, 136.8, 137.7, 137.8, 138.1, 138.3, 139.9, 159.4.

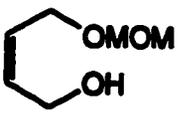
**(1a*RS*,4a*SR*,10*RS*)-1,1a,2,4a,10-Pentahydro-4-(*p*-methoxybenzyloxy)-methyl-10-methoxymethyloxy-6-methyl-9-anthracenone (35)**




To a stirred solution of the alcohol **33** (416 mg, 0.980 mmol) in dichloromethane (9.8 mL) was added Dess-Martin periodinane (623 mg,

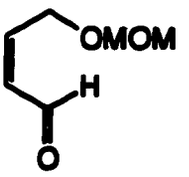
1.47 mmol). The resulting solution was stirred at room temperature for one hour. Saturated sodium bicarbonate solution (10 mL), and saturated sodium thiosulfate solution (20 mL) were added and the resulting mixture was stirred for two hours. The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed once with a saturated sodium thiosulfate solution (15 mL), once with a saturated sodium bicarbonate solution (20 mL), and once with brine (20 mL). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by column chromatography (40 g silica gel, 35% ether/petroleum ether) afforded 285 mg (69%) of the ketone **35** as a yellow oil: IR (neat): 2908 (br), 1678, 1452, 1059, 829 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.55-1.64 (m, 1H), 1.96-2.09 (m, 2H), 2.31 (s, 3H), 2.57-2.60 (m, 1H), 3.30 (br s, 2H), 3.35 (s, 3H), 3.60 (d, 1H, $J$ = 11.4 Hz), 3.73 (d, 1H, $J$ = 11.4 Hz), 3.80 (s, 3H), 4.20 (d, 1H, $J$ = 11.4 Hz), 4.42 (d, 1H, $J$ = 11.4 Hz), 4.62 (d, 1H, $J$ = 6.9 Hz), 4.64 (d, 1H, $J$ = 6.9 Hz), 5.01 (d, 1H, $J$ = 2.6 Hz), 5.62 (br s, 1H), 6.88 (s, 1H), 6.88 (d, 2H, $J$ = 8.7 Hz), 7.17 (dd, 1H, $J$ = 8.0, 1.1 Hz), 7.25 (d, 2H, $J$ = 8.2 Hz), 7.88 (d, 1H, $J$ = 7.9 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 21.6, 22.2, 22.7, 40.7, 41.6, 55.3, 55.4, 71.7, 72.3, 73.0, 94.1, 113.8, 127.1, 129.7, 129.8 (2×), 130.1, 130.5 (2×), 132.9, 139.0, 144.2, 159.3, 198.9; HRMS exact mass calcd. for $C_{26}H_{30}O_5Si$ 422.2094, found 422.2102.

**(Z)-4-Methoxymethyloxy-2-buten-1-ol (37)**



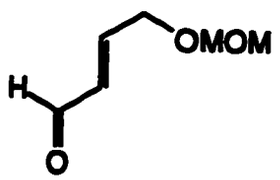

A solution of trimethyl orthoformate (2.7 mL, 24 mmol), (Z)-2-butene-1,4-diol (1.0 mL, 12 mmol) and 10-camphorsulfonic acid (31.4 mg, 0.24 mmol) in dry dichloromethane (12 mL) was stirred at room temperature for 24 hours. The resulting red/brown solution was cooled to -78 °C, then diisobutylaluminum hydride (34.0 mL, 1M in hexanes, 34.0 mmol) was added dropwise. Stirring was continued at -78 °C for 1.5 hours, and then at 0 °C for 10 minutes. Ethyl acetate (~30 mL) was added slowly, and then 2M NaOH (20 mL) was added. A white precipitate formed which was filtered off and discarded. The layers were separated and the aqueous phase was extracted with ether (3 × 15 mL). The combined organic extracts were washed once with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (30 g silica gel, 60% ether/petroleum ether) afforded 523 mg (33%) of alcohol the **37** as a clear colourless oil: IR (neat): 3382 (br), 2910 (br), 1649, 1434, 1209 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.14 (br s, 1H), 3.26 (s, 3H), 4.02-4.10 (m, 4H), 4.52 (s, 2H), 5.54-5.72 (m, 2H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.2, 58.1, 62.4, 95.3, 127.5, 132.7; HRMS exact mass calcd. for $C_6H_{10}O_2$ ($M^+ - H_2O$) 114.0681, found 114.0681.

**(Z)-4-Methoxymethyloxy-2-butenal (39)**



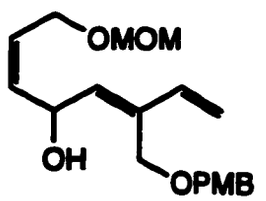

To a stirred solution of Dess-Martin periodinane (2.05 g, 4.82 mmol), sodium bicarbonate (1.35 g, 16.1 mmol) and 4Å molecular sieves (0.70 g) in dichloromethane (30 mL) was added dropwise a solution of the alcohol **37** (531 mg, 4.02 mmol) in dichloromethane (10 mL). After stirring at room temperature for 10 minutes, the reaction mixture was filtered and concentrated. Purification by column chromatography (15 g silica gel, 60% ether/petroleum ether) afforded 306 mg (58%) of the aldehyde **39** as a slightly yellow oil: IR (neat): 2889, 1681, 1612, 1086 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.35 (s, 3H), 4.55 (dd, 2H, $J$ = 5.8, 2.0 Hz), 4.65 (s, 2H), 5.98-6.07 (m, 1H), 6.53-6.62 (m, 1H), 10.04 (d, 1H, $J$ = 6.8 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.5, 64.1, 96.2, 129.8, 147.1, 191.2; HRMS exact mass calcd. for $C_4H_5O_2$ ($M^+$ - $H_2O$) 85.0290, found 85.0219.

**(*E*)-4-Methoxymethyloxy-2-butenal (38)**




To a stirred solution of the alcohol **37** (789 mg, 5.97 mmol) in dichloromethane (60 mL) was added Dess-Martin periodinane (3.80 g, 8.96 mmol) and stirring was continued for 25 minutes. Saturated sodium bicarbonate solution (20 mL), and sodium thiosulfate pentahydrate (5 g) were added and the resulting mixture was stirred for one hour. The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed once with saturated sodium bicarbonate solution (15 mL), once with saturated sodium thiosulfate solution (20 mL), and once with brine (25 mL). The resulting organic phase was dried over magnesium sulfate, filtered, and concentrated. Purification by column chromatography afforded 579 mg (75%) of the aldehyde **38** as a slightly yellow oil: IR (neat): 2921, 2734, 1690, 1086 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.30 (s, 3H), 4.25-4.28 (m, 2H), 4.60 (s, 2H), 6.22-6.35 (m, 1H), 6.74-6.86 (m, 1H), 9.50 (d, 1H, $J$ = 8.0 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.3, 65.6, 96.0, 131.4, 152.7, 193.1; HRMS exact mass calcd. for $C_4H_5O_2$ ($M^+$ - $H_2O$) 85.0290, found 85.0242.

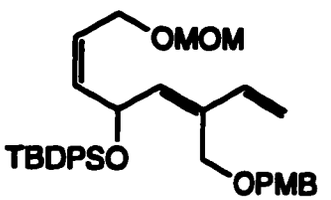
**(2Z,5Z)-6-(*p*-Methoxybenzyloxy)methyl-1-methoxymethyloxy-2,5,7-octatrien-4-ol (40)**




To a round bottomed flask at -78 °C was added dry tetrahydrofuran (75 mL) and *sec*-butyllithium (11.8 mL, 1.09 M in hexanes, 12.9 mmol). The resulting bright yellow solution was stirred at -78 °C for 15 minutes, then a solution of the dienyl iodide **15** (2.03 mg, 6.15 mmol) in dry tetrahydrofuran (11.2 mL) was added *via* cannula over a period of 2 minutes to yield an orange/brown solution. After stirring for an additional 4-5 minutes at -78 °C, a solution of the aldehyde **39** (0.50 g, 3.8 mmol) in dry tetrahydrofuran (11.2 mL) was added *via* cannula over a period of 1-2 minutes. The resulting yellow solution was stirred at -78 °C for 15 minutes, and then was allowed to warm up to room temperature during which time the solution turned green/brown. The reaction was quenched slowly with a few drops of water, and the solution turned yellow. Additional water (25 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 15 mL), and the combined organic extracts were washed once with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (30 g silica gel, 80% ether/petroleum ether) afforded 873 mg (68%) of the alcohol **40** as a yellow oil: IR (neat): 3407 (br), 2912, 1611, 1458, 1058 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.63 (d, 1H, $J$ = 5.0 Hz), 3.33 (s, 3H), 3.78 (s, 3H),

4.17-4.22 (m, 2H), 4.18 (d, 1H, $J$ = 12.5 Hz), 4.21 (d, 1H, $J$ = 12.5 Hz), 4.43 (d, 1H, $J$ = 12.0 Hz), 4.45 (d, 1H, $J$ = 12.0 Hz), 4.56 (d, 1H, $J$ = 10.0 Hz), 4.60 (d, 1H, $J$ = 10.0 Hz), 5.09 (d, 1H, $J$ = 11.0 Hz), 5.24-5.27 (m, 1H), 5.31 (d, 1H, $J$ = 20.5 Hz), 5.58-5.68 (m, 2H), 5.71 (d, 1H, $J$ = 11.0 Hz), 6.28 (dd, 1H, $J$ = 18.3, 12.0 Hz), 6.86 (d, 2H, $J$ = 9.0 Hz), 7.25 (d, 2H, $J$ = 10.5 Hz); $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 55.2, 55.3, 62.9, 64.0, 64.2, 72.1, 95.5, 113.9, 114.6, 127.6, 129.6, 129.9, 134.2, 136.3, 136.4, 138.2, 159.4.

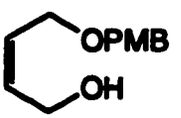
**(3*Z*,6*Z*)-5-(*t*-Butyldiphenylsilyloxy)-3-(*p*-Methoxybenzyloxy)methyl-8-methoxymethyloxy-1,3,6-octatriene (41)**




To a stirred solution of the alcohol **40** (751 mg, 2.25 mmol) in dichloromethane (11.2 mL) was added imidazole (306 mg, 4.49 mmol), 4-*N*,*N*-dimethylaminopyridine (54 mg, 0.45 mmol), and *t*-butyldiphenylsilyl chloride (2.5 g, 9.0 mmol). After stirring at room temperature for 50 minutes, saturated sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 5 mL), and the combined organic extracts were washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (40 g silica gel, 35% ether/petroleum ether) afforded 1.3 g (99%) of the protected triol **41** as a slightly yellow oil: IR (neat): 2939, 2857, 1612, 1467, 1046 cm$^{-1}$; $^1$H

NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 9H), 3.23 (s, 3H), 3.52 (d, 1H, $J$ = 11.4 Hz), 3.68 (d, 1H, $J$ = 11.3 Hz), 3.74-3.80 (m, 2H), 3.77 (s, 3H), 4.07 (d, 1H, $J$ = 11.4 Hz), 4.12 (d, 1H, $J$ = 11.4 Hz), 4.39 (d, 1H, $J$ = 6.5 Hz), 4.41 (d, 1H, $J$ = 6.5 Hz), 5.03 (d, 1H, $J$ = 11.2 Hz), 5.19 (d, 1H, $J$ = 6.8 Hz), 5.21 (s, 1H), 5.40-5.45 (m, 1H), 5.59-5.64 (m, 1H), 5.71 (d, 1H, $J$ = 8.9 Hz), 6.21 (dd, 1H, $J$ = 17.6, 11.0 Hz), 6.78 (d, 2H, $J$ = 8.6 Hz), 7.07 (d, 2H, $J$ = 8.6 Hz), 7.30-7.43 (m, 6H), 7.62-7.66 (m, 4H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 19.2, 26.8, 55.1, 55.2, 63.6, 64.1, 66.6, 71.8, 95.8, 113.6, 114.4, 126.4, 127.5, 127.7, 129.4, 129.6, 130.2, 132.8, 133.7, 133.8, 133.9, 134.8, 135.9 (2x), 136.0, 138.3, 159.1.

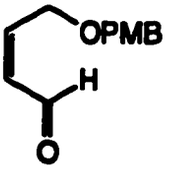
**(Z)-4-(*p*-Methoxybenzyloxy)-2-buten-1-ol (44)**




To a solution of (*Z*)-2-butene-1,4-diol (2.0 g, 23 mmol) in dichloromethane (20 mL) was added D-10-camphorsulfonic acid (57 mg, 0.23 mmol) and *p*-anisaldehyde (5.5 mL, 45 mmol). After stirring at room temperature for 24 hours, the mixture was cooled to -78 °C and diisobutylaluminum hydride (120 mL, 1M in hexanes, 120 mmol) was added dropwise *via* cannula. Stirring was continued at -78 °C for 45 minutes, then at 0 °C for 15 minutes. Ethyl acetate (200 mL) was added slowly to quench the reaction, then a saturated sodium potassium tartrate solution (200 mL) was added. To the resulting thick slurry which formed, was added additional ethyl acetate (200 mL), and the resulting solution was stirred at room temperature for 3 hours. The

layers were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed once with brine (300 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (100 g silica gel, 80% ether/petroleum ether) afforded 1.6 g (34%) of the alcohol **44** as a slightly yellow oil: IR (neat): 3380 (br), 2889, 2353, 1612, 1458, 1053, $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.19 (br t, 1H, $J$ = 5.3 Hz), 3.78 (s, 3H), 4.04 (d, 2H, $J$ = 5.4 Hz), 4.12 (d, 1H, $J$ = 5.0 Hz), 4.14 (d, 1H, $J$ = 5.0 Hz), 4.43 (s, 2H), 5.66-5.82 (m, 2H), 6.86 (d, 2H, $J$ = 8.8 Hz), 7.24 (d, 2H, $J$ = 8.8 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.2, 58.6, 65.3,72.1, 113.8, 128.2, 129.5, 129.8, 132.3, 159.2; HRMS exact mass calcd. for $C_{12}H_{16}O_3$ 208.1100, found 208.1105.

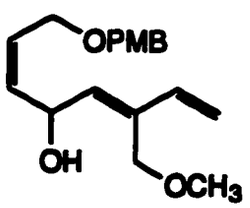
**(Z)-4-(*p*-Methoxybenzyloxy)-2-butenal (45)**




To a stirred solution of Dess-Martin periodinane (3.59 g, 8.48 mmol), sodium bicarbonate (2.37 g, 28.3 mmol) and 4Å molecular sieves (2.0 g) in dichloromethane (60 mL) was added dropwise a solution of the alcohol **44** (1.47 g, 7.06 mmol) in dichloromethane (10 mL). After stirring at room temperature for 10 minutes, the reaction mixture was filtered and concentrated. Purification by flash column chromatography (50 g silica gel, 30% ether/petroleum ether) afforded 1.00 g (69%) of the aldehyde **45** as a slightly yellow oil: IR (neat): 3003, 2883, 1680, 1457,

1091 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.77 (s, 3H), 4.44-4.48 (m, 4H), 5.95 (m, 1H), 6.54-6.65 (m, 1H), 6.86 (d, 2H, $J$ = 8.8 Hz), 7.24 (d, 2H, $J$ = 8.8 Hz) 10.01 (d, 1H, $J$ = 7.0 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.1, 66.5, 72.6, 113.8, 129.3, 129.4, 129.6, 147.6, 159.3, 191.4.

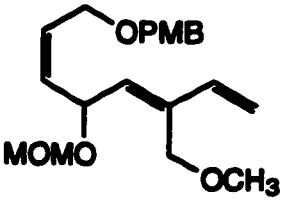
**(2*Z*,5*Z*)-1-(*p*-Methoxybenzyloxy)-6-methoxymethyl-2,5,7-octatrien-4-ol (46)**




To a stirred, cold (-78 °C) solution of the dienyl iodide **22** (783 mg, 3.50 mmol) in dry tetrahydrofuran (15 mL) was added *tert*-butyllithium (4.5 mL, 1.6 M in pentane, 7.2 mmol) dropwise over a period of 1 minute. The resulting orange/brown solution was stirred at -78 °C for 1.5 minutes, then at 0 °C for 15 minutes. The dark red/brown mixture was recooled to -78 °C for 7 minutes, then a solution of the aldehyde **45** (481 mg, 2.33 mmol) in dry tetrahydrofuran (5 mL) was added quickly *via* cannula. Stirring was continued at -78 °C for 15 minutes, then at 0 °C for another 15 minutes during which time the solution turned bright green/yellow. The reaction was quenched slowly with a few drops of water and the solution turned bright orange/yellow. Additional water (20 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic extracts were washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column

chromatography (35 g silica gel, 75% ether/petroleum ether) afforded 447 mg (63%) of the alcohol **46** as a slightly yellow oil: IR (neat): 3398 (br), 2901, 1611, 1459,1092 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.60 (d, 1H, $J$ = 3.0 Hz), 3.29 (s, 3H), 3.78 (s, 3H), 4.03-4.14 (m, 4H), 4.44 (s, 2H), 5.10 (d, 1H, $J$ = 11.0 Hz), 5.24-5.27 (m, 1H), 5.33 (d, 1H, $J$ = 17.6 Hz), 5.63-5.70 (m, 3H), 6.26 (ddd, 1H, $J$ = 17.6, 11.0, 0.6 Hz), 6.86 (d, 2H, $J$ = 8.7 Hz), 7.24 (d, 2H, $J$ = 8.7 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 55.3, 58.1, 64.5, 65.6, 66.8, 72.1, 113.9, 114.4, 128.2, 129.5, 130.0, 133.9, 136.2, 136.3, 138.3, 159.3.

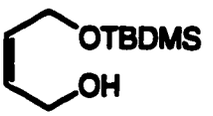
**(3Z,6Z)-8-(p-Methoxybenzyloxy)-3-methoxymethyl-5-methoxymethyl-oxy-1,3,6-octatriene (47)**




To a stirred solution of the alcohol **46** (343 mg, 1.13 mmol) in dichloromethane (23 mL) at 0 °C was added dropwise diisopropylethylamine (2.9 mL, 17 mmol) and chloromethyl methyl ether (0.86 mL, 11.3 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, and was then warmed to room temperature and stirred overnight. Saturated sodium bicarbonate solution (20 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic extracts were washed once with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated.

Purification by flash column chromatography (25 g silica gel, 30% ether/petroleum ether) afforded 358 mg (91%) of the protected triol **47** as a slightly yellow oil: IR (neat): 2904, 1611, 1460, 1094 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.26 (s, 3H), 3.32 (s, 3H), 3.78 (s, 3H), 4.09-4.22 (m, 4H), 4.40 (d, 1H, $J$ = 12.2 Hz), 4.47 (d, 1H, $J$ = 12.2 Hz), 4.55 (d, 1H, $J$ = 6.8 Hz), 4.59 (d, 1H, $J$ = 6.8 Hz), 5.12 (d, 1H, $J$ = 11.0 Hz), 5.24-5.60 (m, 4H), 5.70-5.81 (m, 1H), 6.28 (dd, 1H, $J$ = 17.5, 10.9 Hz), 6.86 (d, 2H, $J$ = 8.8 Hz), 7.25 (d, 2H, $J$ = 8.8 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 55.2, 55.3, 57.9, 65.7, 66.5, 66.7, 72.1, 92.8, 113.7, 114.9, 129.3, 129.9, 130.1, 130.2, 133.1, 136.8, 138.0, 159.2; Anal. calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.03; H, 7.92.

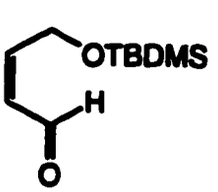
**(*Z*)-4-(*t*-Butyldimethylsilyloxy)-2-buten-1-ol (49)**




To a flame-dried, three-necked 250 mL flask equipped with a 100 mL addition funnel was added a 60% dispersion of sodium hydride in mineral oil (2.40 g, 60.0 mmol) which was washed with dry tetrahydrofuran (1 × 50 mL). After the sodium hydride powder had settled out of the suspension, the tetrahydrofuran was discarded using a pipette. Dry tetrahydrofuran (60 mL) was added to the washed sodium hydride, and the resulting suspension was stirred and cooled to 0 °C. A solution of (*Z*)-2-butene-1,4-diol (4.8 mL, 58 mmol) in dry tetrahydrofuran (30 mL) was placed in the addition funnel and was added dropwise to the reaction flask at 0 °C over a period of 6 minutes.

Stirring was continued at room temperature for 1.5 hours, then a solution of *tert*-butyldimethylsilyl chloride (9.06 g, 60.0 mmol) in dry tetrahydrofuran (60 mL) was placed in the addition funnel and was added to the reaction flask over a period of 10 minutes. Stirring was continued at room temperature for 2 hours, then water (60 mL) was added to the reaction mixture, and the layers were separated. The aqueous phase was extracted with ether (3 × 30 mL), and the combined organic extracts were washed once with brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (300 g silica gel, 25% ether/petroleum ether) afforded 10.4 g (88%) of the alcohol **49** as a colourless liquid: IR (neat): 3352 (br), 2943, 1468, 1069 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.88 (s, 9H), 2.11 (br s, 1H), 4.16-4.18 (m, 2H), 4.23-4.24 (m, 2H), 5.63-5.71 (m, 2H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ -5.3, 18.3, 25.9, 58.8, 59.6, 130.1, 131.3; HRMS exact mass calcd. for $C_6H_{13}O_2Si$ ($M^+$ - *t*-Bu) 145.0685, found 145.0670.

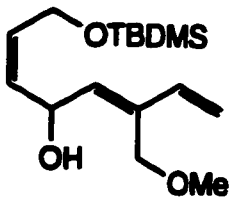
**(*Z*)-4-(*t*-Butyldimethylsilyloxy)-2-butenal (50)**




To a stirred solution of Dess-Martin periodinane (5.83 g, 13.7 mmol), sodium bicarbonate (3.85 g, 15.8 mmol) and 4Å molecular sieves (2.4 g) in dichloromethane (80 mL) was added dropwise a solution of the alcohol **49** (2.32 g, 11.4 mmol) in dichloromethane (30 mL). After

stirring at room temperature for 10 minutes, the reaction mixture was filtered and concentrated *in vacuo*. A white precipitate remained, therefore saturated sodium thiosulfate solution (100 mL), saturated sodium bicarbonate solution (50 mL), and ether (100 mL) were added and the resulting mixture was stirred for 20 minutes. The layers were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed once with a saturated sodium thiosulfate solution (150 mL), once with a saturated sodium bicarbonate solution (150 mL), and once with brine (200 mL). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated. A yellow precipitate remained which was separated upon purification by flash column chromatography (100 g silica gel, 10% ether/petroleum ether) which afforded 1.76 g (77%) of the aldehyde **50** as a yellow oil: IR (neat): 2932, 1685, 1609, 1097 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.06 (s, 9H), 4.64-4.66 (m, 2H), 5.89-6.00 (m, 1H), 6.48-4.59 (m, 1H), 10.12 (d, 1H, $J$ = 6.8 Hz); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ -5.4, 18.2, 25.8, 61.2, 128.5, 150.6, 191.8; HRMS exact mass calcd. for $C_{10}H_{20}O_2Si$ 200.1232, found 200.1213.

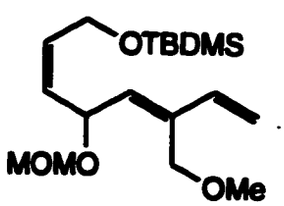
**(2Z,5Z)-1-(*t*-Butyldimethylsilyloxy)-6-methoxymethyl-2,5,7-octatrien-4-ol (51)**




To a stirred, cold (-78 °C) solution the dienyl iodide **22** (2.64 g, 11.8 mmol) in dry tetrahydrofuran (80 mL) was added *tert*-butyllithium (15.2 mL, 1.6 M in pentane, 24.3 mmol) dropwise over a period of 6 minutes. The resulting mixture was stirred at -78 °C for 10 minutes, then at 0 °C for 15 minutes. The red/brown mixture was recooled to -78 °C for 10 minutes, then a solution of the aldehyde **50** (1.57 g, 7.84 mmol) in dry tetrahydrofuran (20 mL) was added quickly *via* cannula. Stirring was continued at -78 °C for 20 minutes, then at 0 °C for another 20 minutes during which time the solution turned dark green. The reaction was quenched slowly with a few drops of water and the solution turned orange. Additional water (35 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 15 mL), and the combined organic extracts were washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (500 g silica gel, 30% ether/petroleum ether) afforded 1.42 g (61%) of the alcohol **51** as a slightly yellow oil: IR (neat): 3390 (br), 2939, 1606, 1092 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.88, (s, 9H), 2.72 (br s, 1H), 3.33 (s, 3H), 4.15 (s, 2H), 4.22-4.24 (m, 1H), 4.30-4.34 (m, 1H), 5.09 (d, 1H, $J$ = 11.0 Hz), 5.28 (dd, 1H, $J$ = 8.9, 8.9 Hz), 5.34 (d, 1H, $J$ = 17.6 Hz), 5.52-

5.56 (m, 1H), 5.59-5.61 (m, 1H), 5.70 (d, 1H, $J$ = 8.4 Hz), 6.27 (ddd, 1H, $J$ = 17.6, 11.0, 0.7 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ -5.2, 18.3, 25.9, 58.1, 59.7, 64.5, 66.9, 114.3, 131.3, 131.7, 136.0, 136.5, 138.3; HRMS exact mass calcd. for $C_{16}H_{28}O_2Si$ ($M^+$ - $H_2O$) 280.1860, found 280.1866.

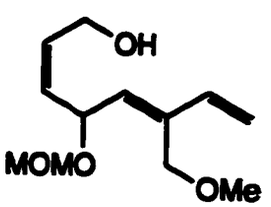
**(3Z,6Z)-8-(*t*-Butyldimethylsilyloxy)-3-methoxymethyl-5-methoxymethyloxy-1,3,6-octatriene (52)**




To a stirred solution of the alcohol **51** (123 mg, 0.412 mmol) in dichloromethane (8.2 mL) at 0 °C was added dropwise diisopropylethylamine (1.1 mL, 6.2 mmol) and chloromethyl methyl ether (0.31 mL, 4.1 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, and was then warmed to room temperature and stirred overnight. Saturated sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 5 mL), and the combined organic extracts were washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (25 g silica gel, 10% ether/petroleum ether) afforded 121 mg (86%) of the protected triol **52** as a slightly yellow oil: IR (neat): 2940, 1607, 1095, 1032 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 3.31 (s, 3H), 3.34 (s, 3H), 4.12 (d, 1H, $J$ = 11.3 Hz), 4.16 (ddd, 1H, $J$ = 13.6, 6.5, 1.7 Hz), 4.24 (ddd, 1H, $J$ = 13.6, 5.6, 1.8 Hz), 4.33 (ddd, 1H, $J$ = 13.6, 6.5, 1.7 Hz), 4.55 (d,

1H, $J$ = 6.7 Hz), 4.57 (d, 1H, $J$ = 6.8 Hz), 4.11 (d, 1H, $J$ = 11.0 Hz), 5.26 (dd, 1H, $J$ = 9.0, 9.0 Hz), 5.35-5.40 (m, 1H), 5.39 (d, 1H, $J$ = 16.9 Hz), 5.57 (d, 1H, $J$ = 9.2 Hz), 5.64-5.69 (m, 1H), 6.27 (dd, 1H, $J$ = 17.5, 11.0 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ -5.2 (2×), 18.3, 25.9, 55.3, 58.0, 59.5, 66.7, 66.8, 92.9, 114.8, 127.9, 133.3, 133.4, 136.8, 138.1; HRMS exact mass calcd. for $C_{16}H_{29}O_2Si$ ($M^+$ - $OCH_2OCH_3$) 281.1938, found 281.1940.

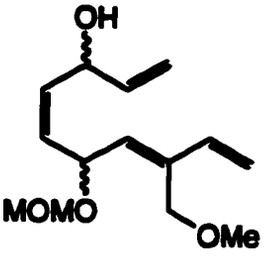
**(2Z,5Z)-6-Methoxymethyl-4-methoxymethyloxy-2,5,7-octatrien-1-ol (53)**




To a stirred solution of the triene **52** (114 mg, 0.333 mmol) in tetrahydrofuran (2.1 mL) was added tetra-*n*-butylammonium fluoride (1.3 mL, 1 M in THF, 1.3 mmol) dropwise over a period of 1 minute. The resulting yellow solution was stirred at room temperature for 20 minutes. Water (10 mL) was then added and the layers were separated. The aqueous phase was extracted with ether (3 × 3 mL), and the combined organic extracts were washed once with saturated sodium bicarbonate solution (7 mL), and once with brine (15 mL), then dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (6 g silica gel, 65% ether/petroleum ether) afforded 71 mg (93%) of the alcohol **53** as a colourless oil: IR (neat): 3417 (br), 2912, 1606, 1095, 1030 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ

2.67 (t, 1H, $J$ = 7.0 Hz), 3.32 (s, 3H), 3.35 (s, 3H), 4.09 (d, 1H, $J$ = 11.4 Hz), 4.18 (dd, 2H, $J$ = 6.2, 6.1 Hz), 4.21 (d, 1H, $J$ = 11.4 Hz), 4.56 (d, 1H, $J$ = 6.8 Hz), 4.63 (d, 1H, $J$ = 6.8 Hz), 5.11 (d, 1H, $J$ = 11.0 Hz), 5.35 (d, 1H, $J$ = 17.6 Hz), 5.41-5.47 (m, 2H), 5.62 (d, 1H, $J$ = 8.6 Hz), 5.83 (dt, 1H, $J$ = 10.2, 7.0 Hz), 6.29 (dd, 1H, $J$ = 17.5, 11.3 Hz); $^{13}$C NMR (125.8 MHz, $CDCl_3$): δ 55.3, 58.1, 58.3, 66.6, 66.7, 92.9, 114.7, 130.0, 132.1, 133.8, 136.6, 138.2.

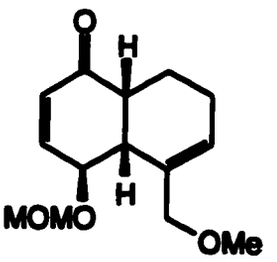
**(4Z,7Z)-8-Methoxymethyl-6-methoxymethyloxy-1,4,7,9-decatetraen-3-ol (54)**




To a stirred, cold (-78 °C) solution of dry dimethyl sulfoxide (89 μL, 1.3 mmol) in dry dichloromethane (2.0 mL), was added oxalyl chloride (61 μL, 0.64 mmol) dropwise over a period of 1 minute. The resulting mixture was allowed to stir at -78 °C for 15 minutes, and then a solution of the alcohol **53** (66.5 mg, 0.291 mmol) in dry dichloromethane (0.65 mL) was added slowly over a period of 3 minutes. After stirring at -78 °C for 1 hour, dry triethylamine (0.18 mL, 1.3 mmol) was added dropwise over a period of 30 seconds. Stirring was continued at 0 °C for 1 hour, then the reaction mixture was cooled down to -78 °C. Vinylmagnesium bromide (1.2 mL, 1.0 M in THF, 1.2 mmol) was added to the solution and stirring was continued at -78 °C for 3 minutes, then at 0 °C for 1 hour.

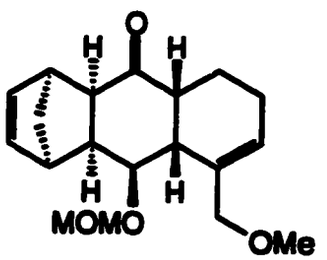
Saturated ammonium chloride solution (6 mL) was added to the reaction mixture and the layers were separated. The aqueous phase was extracted with ether (2 × 4 mL), and the combined organic extracts were washed once with saturated ammonium chloride solution (10 mL), and once with brine (15 mL). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by flash column chromatography (10 g silica gel, 65% ether/petroleum ether) afforded 65 mg (88%) of the alcohol **54** as a 70:30 mixture of diastereomers as a colourless oil: major product: IR (neat): 3413 (br), 2923, 2362, 1095, 1028 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.93 (d, 1H, $J$ = 3.3 Hz), 3.33 (two s, 6H), 4.12 (d, 1H, $J$ = 11.5 Hz), 4.28 (d, 1H, $J$ = 11.5 Hz), 4.55 (d, 1H, $J$ = 6.8 Hz), 4.58 (d, 1H, $J$ = 6.8 Hz), 5.01 (br s, 1H), 5.12 (d, 1H, $J$ = 11.0 Hz), 5.13 (ddd, 1H, $J$ = 10.4, 1.4, 1.4 Hz), 5.30 (ddd, 1H, $J$ = 17.3, 1.5, 1.5 Hz), 5.34 (d, 1H, $J$ = 17.6 Hz), 5.44-5.50 (m, 2H), 5.58-5.66 (m, 2H), 5.87-5.93 (m, 1H), 6.32 (dd, 1H, $J$ = 17.6, 11.0 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 55.3, 58.1, 66.5, 66.8, 68.3, 92.8, 114.5, 115.2, 129.1, 134.0, 134.3, 136.5, 138.5, 139.2: minor product: IR (neat): 3418 (br), 2915, 1607, 1096, 1028 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 2.89 (d, 1H, $J$ = 2.6 Hz), 3.30 (s, 3H), 3.38 (s, 3H), 4.10 (d, 1H, $J$ = 11.4 Hz), 4.16 (d, 1H, $J$ = 11.4 Hz), 4.59 (d, 1H, $J$ = 7.0 Hz), 4.72 (d, 1H, $J$ = 7.0 Hz), 5.02 (m, 1H), 5.11-5.13 (m, 2H), 5.27 (ddd, 1H, $J$ = 17.2, 1.5, 1.5 Hz), 5.38 (d, 1H, $J$ = 17.6 Hz), 5.43-5.48 (m, 2H), 5.61-5.66 (m, 2H), 5.85-5.88 (m, 1H), 6.29 (dd, 1H, $J$ = 17.5, 11.0 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 55.4, 58.1, 66.8, 67.0, 68.3, 92.9, 115.0, 115.1, 129.2, 133.1, 134.6, 136.9, 138.1, 138.9.

**(4*RS*,5*RS*,10*SR*)-6-Methoxymethyl-4-methoxymethyloxy-2,6-didehydro-1-decalone (56-a)**




To a stirred solution of Dess-Martin periodinane (199 mg, 0.469 mmol), sodium bicarbonate (131 mg, 1.56 mmol) and 4Å molecular sieves (100 mg) in dichloromethane (1.5 mL) was added dropwise a solution of the alcohol **54** (99 mg, 0.39 mmol) in dichloromethane (3.4 mL). After stirring at room temperature for 4 hours, the reaction mixture was filtered and concentrated. Purification by flash column chromatography (30 g silica gel, 30% ether/petroleum ether) afforded 72 mg (73%) of the ketone **56-a** as a 77:23 mixture of diastereomers as a slightly yellow oil: major product: IR (neat): 2904, 1677, 1095, 1038 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.59-1.66 (m, 1H), 1.94-2.02 (m, 1H), 2.11-2.22 (m, 2H), 2.70-2.71 (m, 1H), 2.88-2.89 (m, 1H), 3.23 (s, 3H), 3.37 (s, 3H), 3.79 (d, 1H, $J$ = 11.8 Hz), 3.92 (d, 1H, $J$ = 11.8 Hz), 4.37-4.39 (m, 1H), 4.72 (d, 1H, $J$ = 6.9 Hz), 4.74 (d, 1H, $J$ = 6.9 Hz), 5.75-5.77 (m, 1H), 5.94 (ddd, 1H, $J$ = 10.2, 1.2, 1.2 Hz), 6.84-6.88 (m, 1H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 21.9, 23.8, 41.1, 43.9, 55.7, 57.6, 74.6, 76.2, 96.7, 129.3, 129.0, 134.4, 147.4, 201.1; HRMS exact mass calcd. for $C_{14}H_{20}O_4$ 252.1362, found 252.1366.

**(1a*RS*,4a*SR*,5*RS*,5a*SR*,8*SR*,8a*RS*,10*SR*)-1,1a,2,4a,5,5a,8,8a,10-Nonahydro-5,8-methano-4-methoxymethyl-10-methoxymethyloxy-9-anthracenone (57-b)**




To a stirred, cold (-78 °C) solution of the ketone **56-a** (39 mg, 0.16 mmol) in dry dichloromethane (0.5 mL) was added diethylaluminum chloride (0.22 mL, 1 M in hexanes, 0.22 mmol). Freshly distilled, cold (-78 °C) cyclopentadiene (1.0 mL, 12 mmol) was added *via* cannula, and the resulting solution was stirred at -78 °C for two hours. The reaction mixture was placed in the freezer (-15 °C) for 20 hours, then saturated sodium bicarbonate solution (10 mL) was added and the layers were separated. The aqueous phase was extracted with ether (3 × 4 mL), and the combined organic extracts were washed once with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification by column chromatography (3 g silica gel, 55% ether/petroleum ether) afforded 43 mg (87%) of the ketone **57-b** as a 90:10 mixture of diasteromers as a colourless oil: major product as a white solid (mp 41.5 - 42.0 °C): IR ($CH_2Cl_2$): 2911, 1698, 1096, 1036 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.23 (d, 1H, $J$ = 8.2 Hz), 1.36 (ddd, 1H, $J$ = 8.2, 1.8, 1.8 Hz), 1.50-1.57 (m, 1H), 1.91-2.00 (m, 1H), 2.00-2.14 (m, 2H), 2.38 (dd, 1H, $J$ = 10.6, 5.7 Hz), 2.65-2.68 (m, 1H), 2.71-2.75 (m, 1H), 2.78 (br s, 1H), 2.94 (br s, 1H), 3.20 (br s, 1H), 3.31 (s, 3H), 3.33 (s, 3H),

3.79 (d, 1H, $J$ = 11.8 Hz), 4.02 (d, 1H, $J$ = 11.7 Hz), 4.32 (dd, 1H, $J$ = 5.9, 5.9 Hz), 4.58 (d, 1H, $J$ = 6.8 Hz), 4.60 (d, 1H, $J$ = 6.8 Hz), 5.84 (br s, 1H) 6.04 (d, 1H, $J$ = 5.8 Hz), 6.06 (d, 1H, $J$ = 6.9 Hz); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): δ 22.6, 24.1, 38.1, 42.9, 44.4, 45.1, 45.4, 50.0, 51.7, 55.9, 58.0, 73.5, 75.7, 95.3, 128.1, 134.4, 134.5, 135.7, 215.8; HRMS exact mass calcd. for $C_{17}H_{21}O_3$ ($M^+$ - $CH_2OCH_3$) 273.1491, found 273.1476.

# References


1. Nicolaou, K. C.; Dai, W. -M.; Guy R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.

2. Chen, S. -H.; Kadow, J. F.; Farina, V. *J. Org. Chem.* **1994**, *59*, 6156.

3. (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Paxdur, R.; Kudelka, A. P.; Kavenagh, J. J.; Cohen, P. R.; Raber, M. N. *Cancer Treat. Rev.* **1993**, *19*, 351.

4. Kant, J.; O'Keefe, W. S.; Chen, S. -H.; Farina, V.; Fairchild, C.; Johnston, K.; Kadow, J. F.; Long, B. H.; Vyas, D. *Tetrahedron Lett.* **1994**, *35*, 5543.

5. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *227*, 665.

6. Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214.

7. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

8. Riou, J. F.; Naudin, A.; Lavelle, F. *Biochem. and Biophys. Res. Comm.* **1992**, *187*, 164

9. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P.G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.

10. (a) Holton, R. A.; Somoza, C.; Kim, H. -B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H. -B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

11. Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723.

12. (a) Grover, S.; Rimoldi, J. M.; Molinero, A. A.; Chaudhary, A. G.; Kingston, D. G. I.; Hamel, E. *Biochemistry* **1995**, *34*, 3927. (b) Georg, G. I.; Harriman, G. C. B.; Ali, S. M.; Datta, A.; Hepperle, M. *Bioorg. & Med. Chem. Lett.* **1995**, *5*, 115. (c) Chen, S. -H.; Farina, V.; Wei, J. -M.; Long, B.; Fairchild, C.; Mamber, S. W.; Kadow, J. F.; Vyas, D.; Doyle, T. W. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 479. (d) Chen, S. -H.; Fairchild, C.; Long, B. *J. Med. Chem.* **1995**, *38*, 2263. (e) Chen, S. -H.; Kant, J.; Mamber, S. W.; Roth, G. P.; Wei, J. -M.; Marshall, D.; Vyas, D.; Farina, V. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 2223. (f) Swindell, C. S.; Heerding, J. M.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1531. (g) Georg, G. I.; Harriman, G. C. B.; Hepperle, M; Himes, R. H. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1381. (h) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M; Park, H. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 335. (i) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M; Park, H. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1825.

13. Pham, T. *MSc. Thesis*, University of Ottawa, **1996**.

14. Millan, D. S. Postdoctoral Fellow, Department of Chemistry, University of Ottawa, unpublished results.

15. Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

16. Smith, M. B. *Organic Synthesis*; McGraw-Hill, Inc.: New York, **1994**, pp 1113-1165.

17. Baker, A. D.; Engel, R. *Organic Chemistry*; West Publishing Company: New York, **1992**, pp 475-480.

18. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reation*; John Wiley & Sons, Inc.: New York, **1990**, pp 1-31.

19. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Inc.: London, **1976**.

20. (a) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885. (b) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585. (c) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. (d) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595.

21. Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.

22. Millan, S.; Pham, T.; Lavers, J.; Fallis, A. G. unpublished results.

23. Miller, S. J.; Kim, S. -H.; Chen, S. -R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

24. Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **1996**, *37*, 755.

25. Meyer, N.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 521.

26. Fieser, L. F.; Williamson, K. L. *Organic Experiments*; 7th Ed.; D.C. Heath & Company: Lexington, **1992**, p 287.

27. (a) Jung, M. E.; McCombs, C. A. *Organic Sunthesis*; John Wiley & Sons: New York, **1988**; Vol. 6, p 445. (b) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, **1995**; Vol. 7, p 5294.

28. (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947. (c) Schreiber, S. L.; Wang, S.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085. (d) Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555.

29. Smith, III, A. B.; Hale, K. J.; Laakso, L. M.; Chen, K.; Riéra, A. *Tetrahedron Lett.* **1989**, *30*, 6963.

30. Mancuso, A. J.; Huang, S. -L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

31. Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88.

32. Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.

33. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183.

34. (a) Monti, H.; Léandri, H.; Klos-Ringuet, M.; Corriol, C. *Synthetic Comm.* **1994**, *59*, 394. (b) Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394.

35. Wong, T. Postdoctoral Fellow, Department of Chemistry, University of Ottawa, unpublished results.

# Claims to Original Research

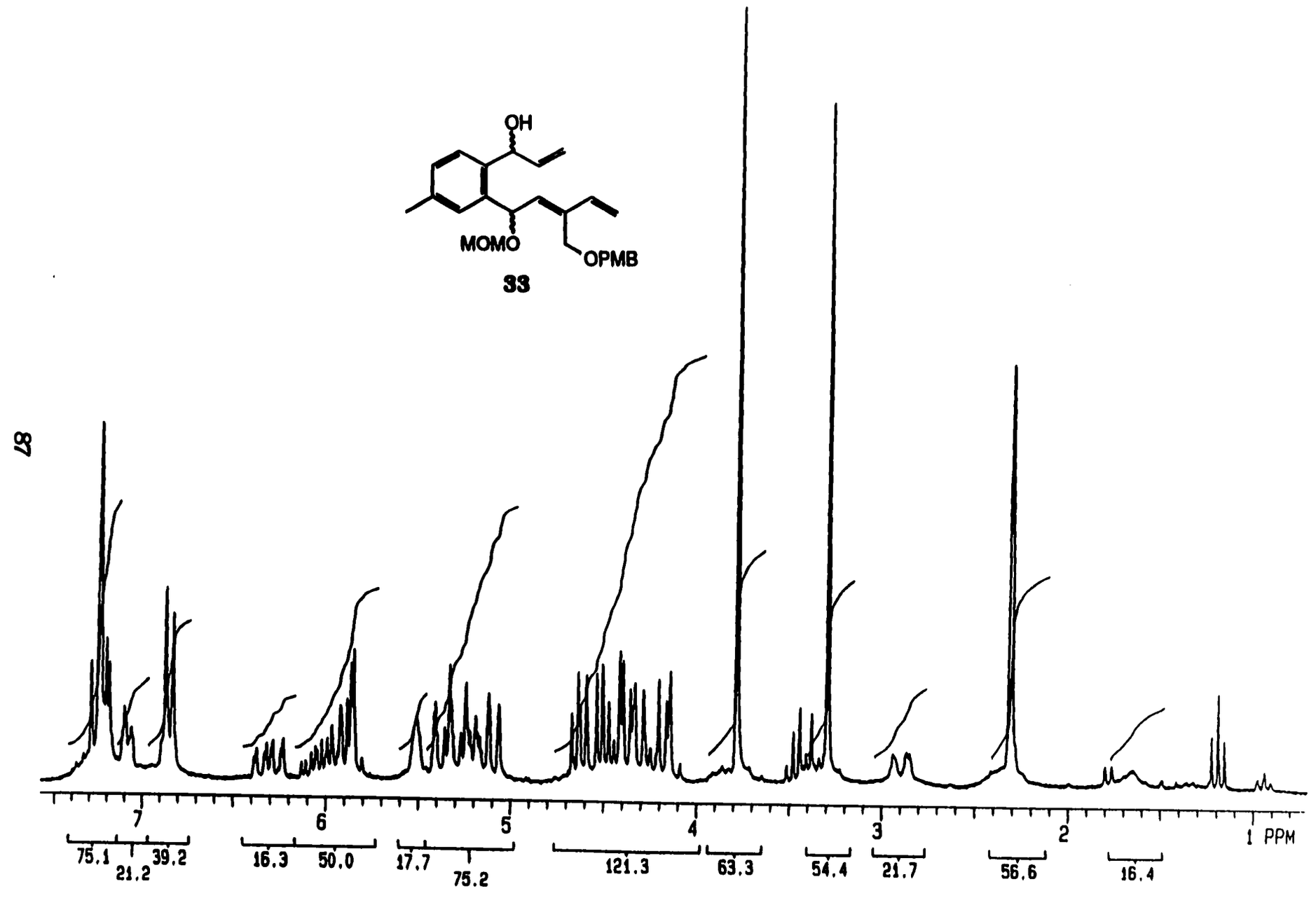
1. General and effective routes for the synthesis of multicyclic systems have been developed.

2. Planar (aromatic ring or double bonds) tether control groups result in intramolecular Diels-Alder reactions under very mild conditions.

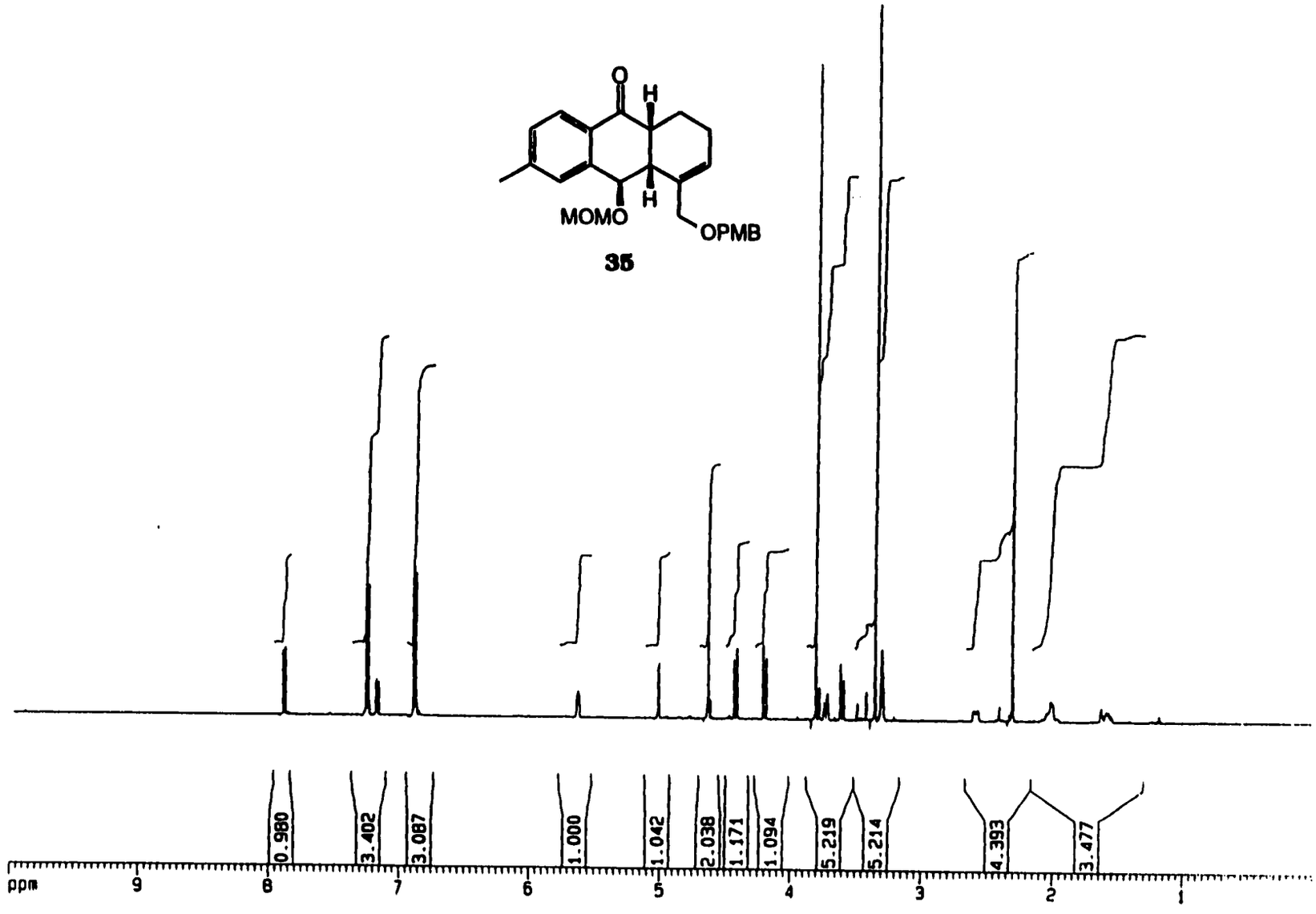
3. Improved knowledge and understanding of the facial selectivity in these reactions has been discovered.

4. The extension of these ideas to chiral tether control groups can now be investigated.

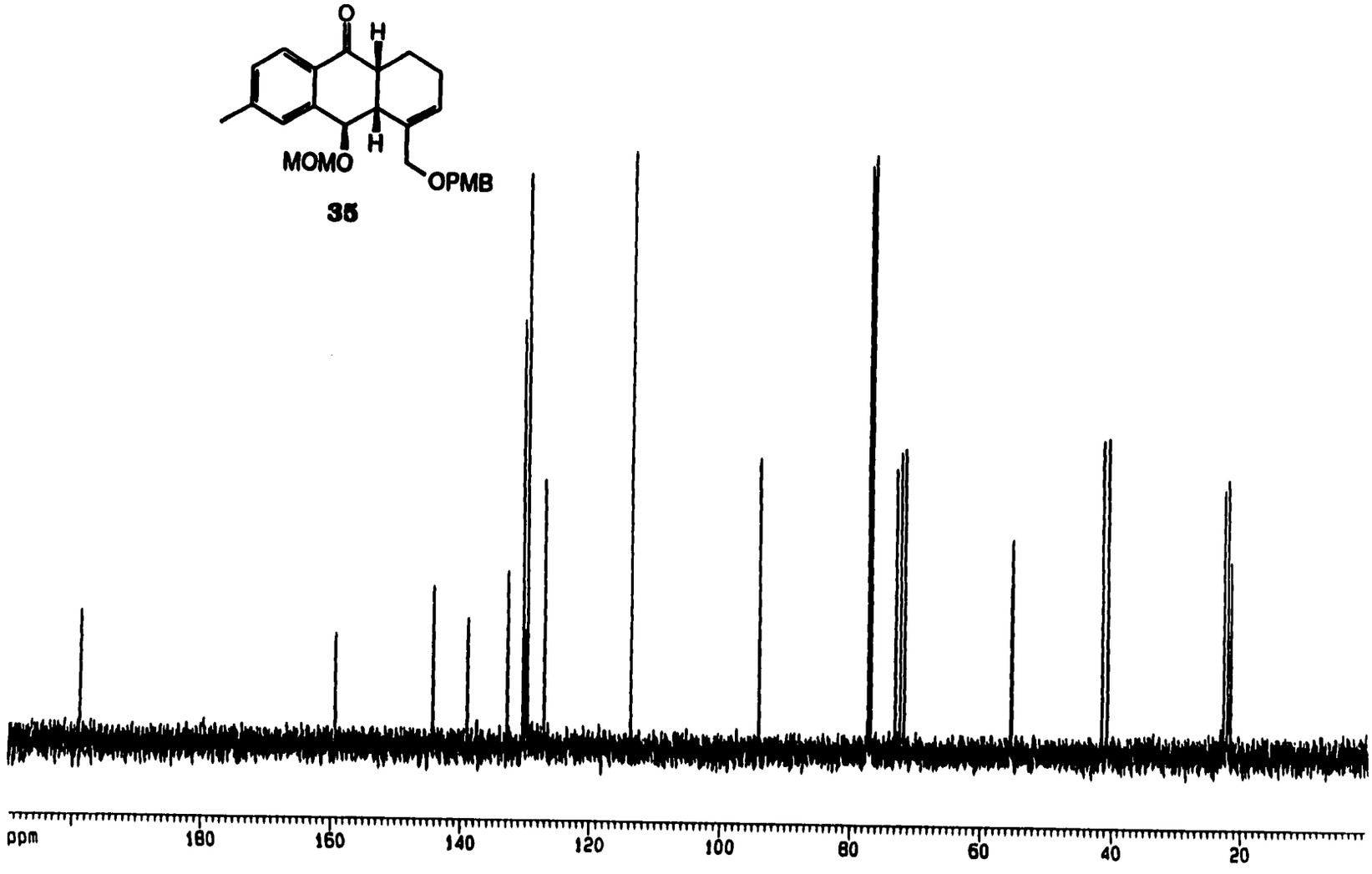
# Appendix I
# Selected Spectra



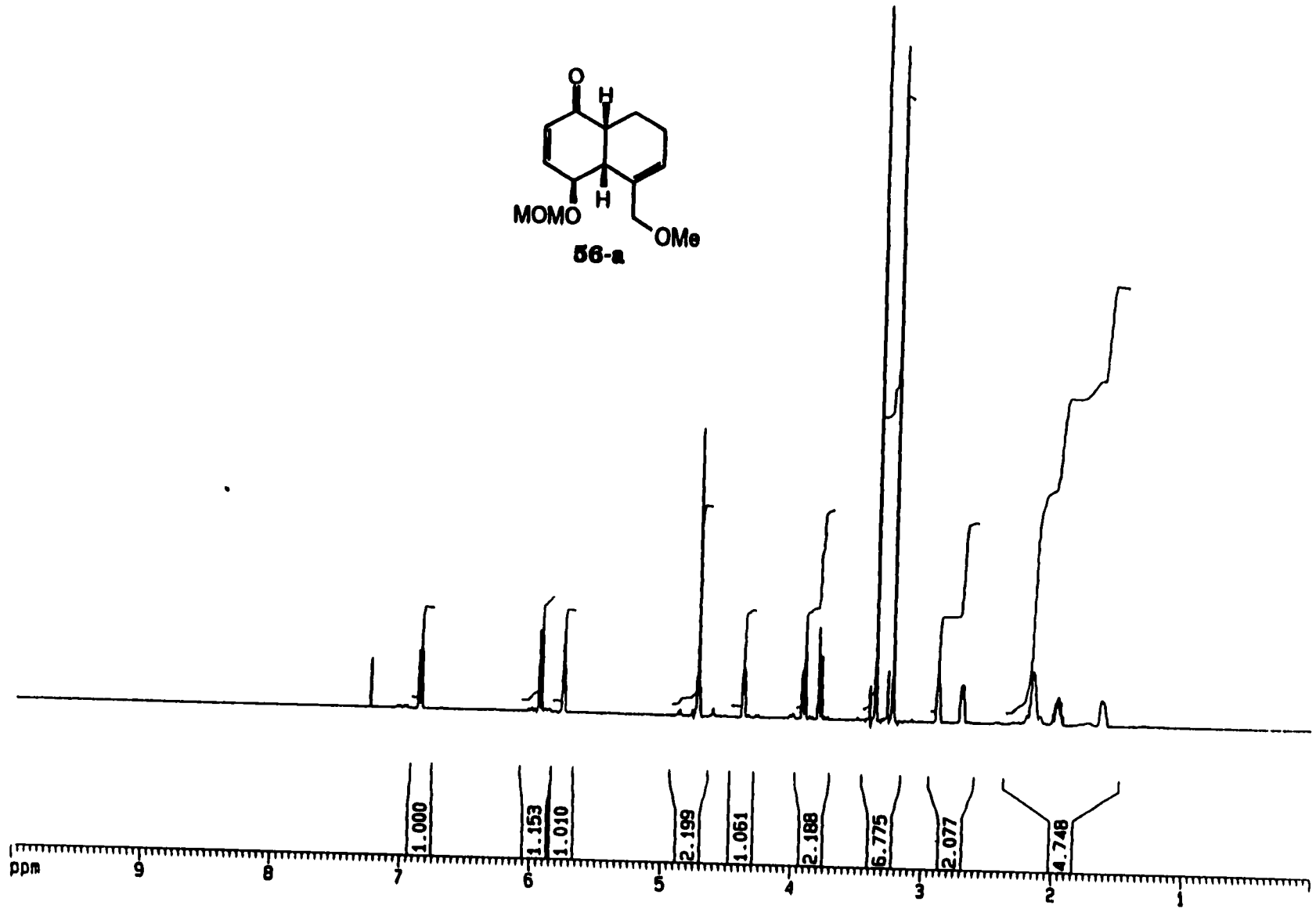

$^1$H NMR Spectrum (200 MHz, $CDCl_3$) of **33**



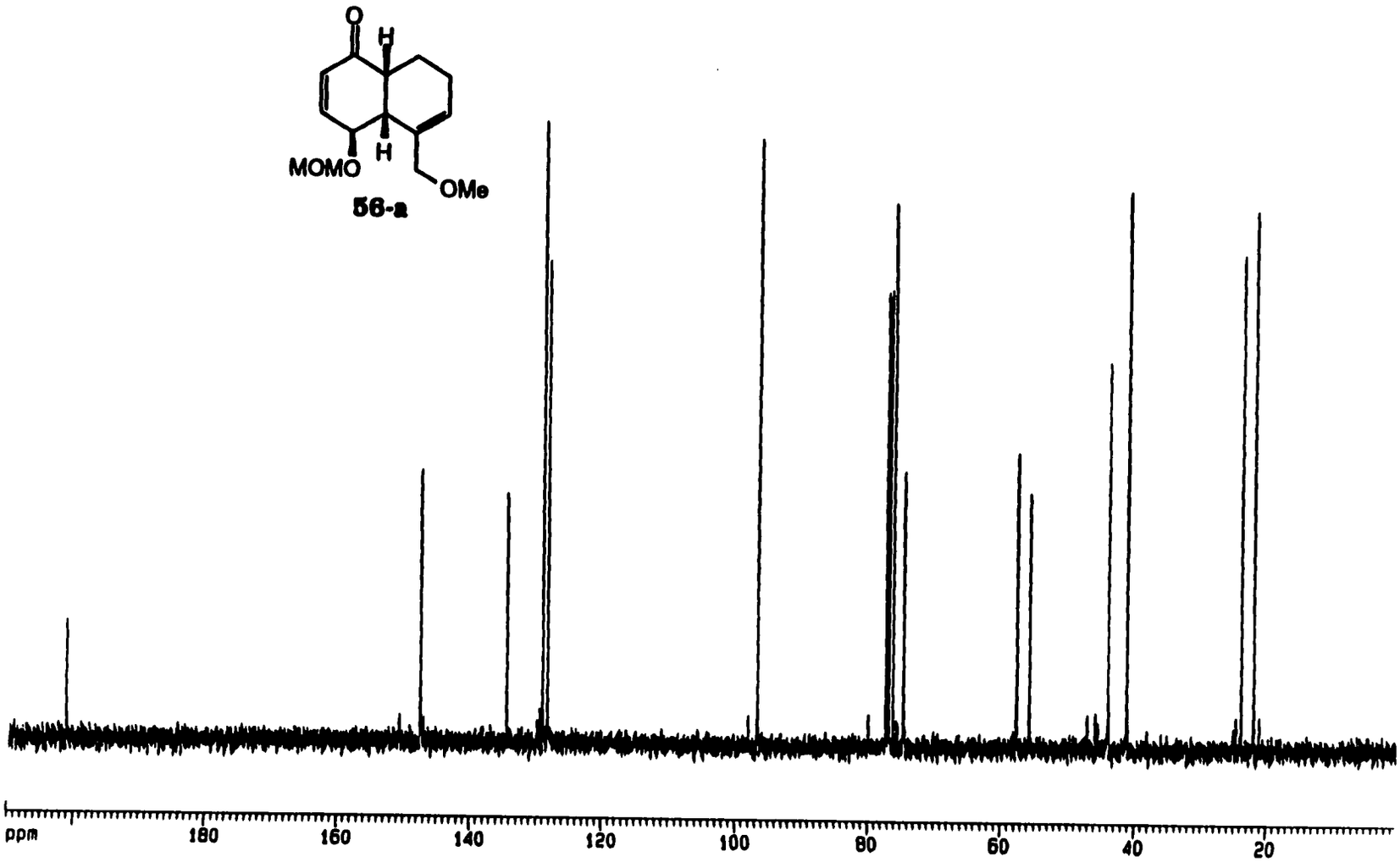

$^1$H NMR Spectrum (500 MHz, $CDCl_3$) of **35**



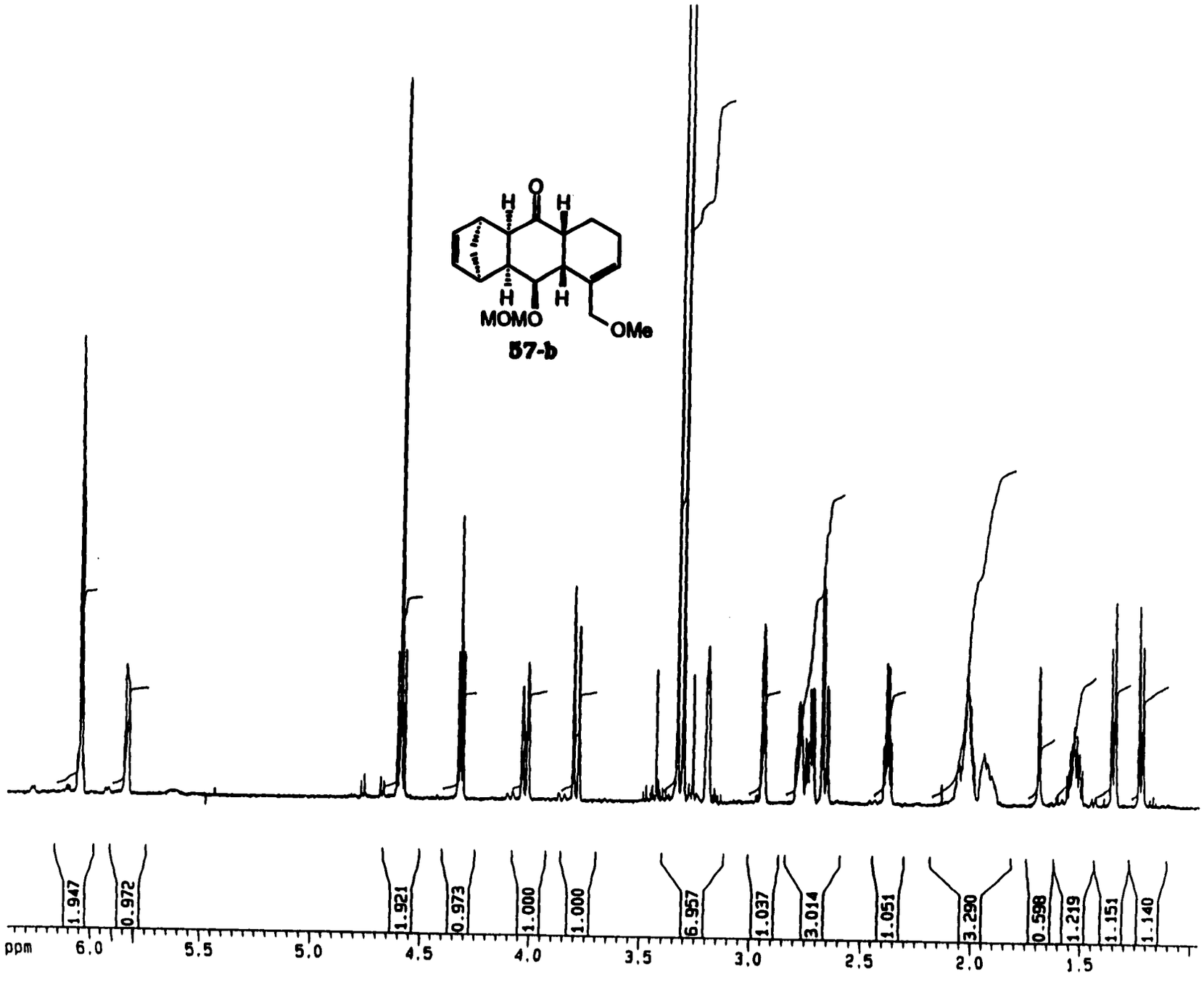

$^{13}C$ NMR Spectrum (125.8 MHz, $CDCl_3$) of **35**



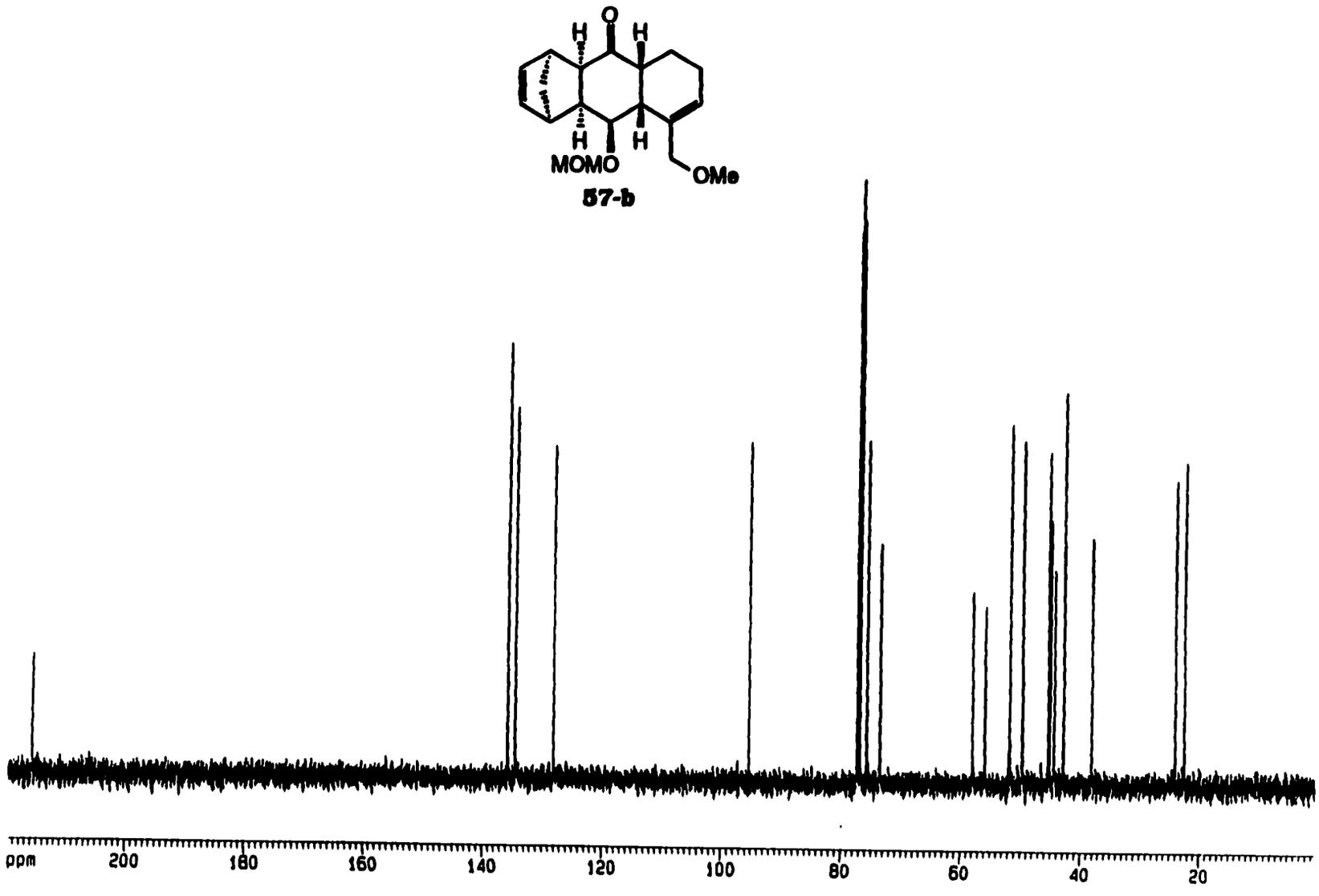

$^1$H NMR Spectrum (500 MHz, $CDCl_3$) of **56-a**




$^{13}C$ NMR Spectrum (125.8 MHz, $CDCl_3$) of **56-a**

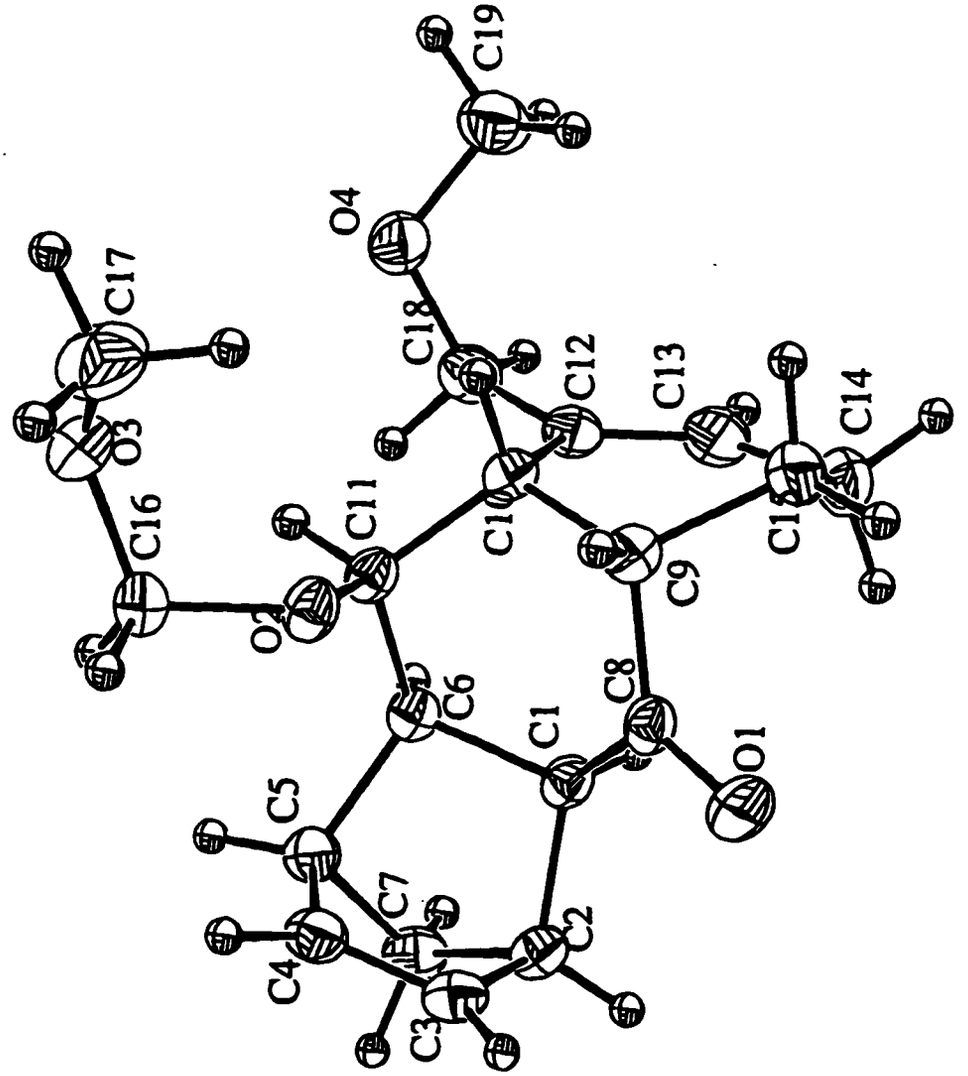



$^1$H NMR Spectrum (500 MHz, $CDCl_3$) of **57-b**




$^{13}C$ NMR Spectrum (125.8 MHz, $CDCl_3$) of **57-b**

# Appendix II
# X-ray Data of Compound 57-b




**Compound 57-b**

Space Group and Cell Dimensions  Monoclinic,  P 21/c
a 11.5034(3)  b 9.66010(20)  c 14.9000(3)
beta 95.4750(20)
Volume 1648.19(6)A**3

Empirical formula : O4 C19 H26

Cell dimensions were obtained from 24 reflections with 2Theta angle
in the range 3.00 - 57.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.20 mm

FW = 318.41  Z = 4  F(000) = 688.28

Dcalc 1.283Mg.m-3, mu 0.08mm-1, lambda 0.70930A, 2Theta(max) 57.0

The intensity data were collected on a Siemens diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -15 15; Kmin,max 0 12; Lmin,max 0 20
No. of reflections measured 11411
No. of unique reflections 4182
No. of reflections with Inet > 2.5sigma(Inet) 2694
Merging R-value on intensities 0.027
No correction was made for absorption

The last least squares cycle was calculated with
49 atoms, 313 parameters and 2694 out of 4182 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.044, Rw 0.043 GoF 1.57
For all reflections, RF 0.080, Rw 0.047.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.396.

In the last D-map, the deepest hole was -0.180e/A**3,
and the highest peak 0.280e/A**3.

Secondary ext. coeff. 30.9524microns  sigma 9.4581

Table of Atomic Bond Distances in Angstroms

| | | | |
|---|---|---|---|
| O1-C8 | 1.2173(19) | C9-C10 | 1.5406(22) |
| O2-C11 | 1.4398(18) | C9-C15 | 1.5380(24) |
| O2-C16 | 1.4109(19) | C9-H9 | 1.022(15) |
| O3-C16 | 1.4039(21) | C10-C11 | 1.5374(23) |
| O3-C17 | 1.4217(24) | C10-C12 | 1.5219(22) |
| O4-C18 | 1.4339(22) | C10-H10 | 1.004(14) |
| O4-C19 | 1.4192(23) | C11-H11 | 0.990(14) |
| C1-C2 | 1.5638(24) | C12-C13 | 1.3326(24) |
| C1-C6 | 1.5636(22) | C12-C18 | 1.5091(23) |
| C1-C8 | 1.5061(22) | C13-C14 | 1.500(3) |
| C1-H1 | 1.007(15) | C13-H13 | 1.009(16) |
| C2-C3 | 1.5175(23) | C14-C15 | 1.526(3) |
| C2-C7 | 1.5400(24) | C14-H14a | 1.028(18) |
| C2-H2 | 0.980(15) | C14-H14b | 1.030(17) |
| C3-C4 | 1.3272(23) | C15-H15a | 1.003(16) |
| C3-H3 | 0.972(15) | C15-H15b | 1.004(18) |
| C4-C5 | 1.5207(23) | C16-H16a | 1.009(15) |
| C4-H4 | 1.010(15) | C16-H16b | 1.063(15) |
| C5-C6 | 1.5661(23) | C17-H17a | 0.968(20) |
| C5-C7 | 1.5468(23) | C17-H17b | 1.032(20) |
| C5-H5 | 1.010(14) | C17-H17c | 1.075(22) |
| C6-C11 | 1.5263(22) | C18-H18a | 1.016(17) |
| C6-H6 | 1.020(14) | C18-H18b | 1.040(16) |
| C7-H7a | 0.992(15) | C19-H19a | 0.976(19) |
| C7-H7b | 1.002(16) | C19-H19b | 0.998(17) |
| C8-C9 | 1.5305(24) | C19-H19c | 1.035(18) |

Table of Atomic Bond Angles in Degrees

| | | | |
|---|---|---|---|
| C11-O2-C16 | 113.69(11) | C11-C10-C12 | 112.63(13) |
| C16-O3-C17 | 112.29(14) | C11-C10-H10 | 107.3(8) |
| C18-O4-C19 | 112.10(13) | C12-C10-H10 | 107.2(8) |
| C2-C1-C6 | 103.49(13) | O2-C11-C6 | 112.69(13) |
| C2-C1-C8 | 115.12(13) | O2-C11-C10 | 106.38(12) |
| C2-C1-H1 | 109.7(9) | O2-C11-H11 | 107.5(8) |
| C6-C1-C8 | 115.02(13) | C6-C11-C10 | 110.33(12) |
| C6-C1-H1 | 109.5(9) | C6-C11-H11 | 109.2(8) |
| C8-C1-H1 | 104.0(9) | C10-C11-H11 | 110.7(8) |
| C1-C2-C3 | 105.36(13) | C10-C12-C13 | 122.33(15) |
| C1-C2-C7 | 100.59(13) | C10-C12-C18 | 117.38(14) |
| C1-C2-H2 | 114.5(10) | C13-C12-C18 | 120.15(15) |
| C3-C2-C7 | 99.57(13) | C12-C13-C14 | 124.87(15) |
| C3-C2-H2 | 115.8(9) | C12-C13-H13 | 117.0(9) |
| C7-C2-H2 | 118.6(9) | C14-C13-H13 | 118.1(9) |
| C2-C3-C4 | 107.53(14) | C13-C14-C15 | 110.84(14) |
| C2-C3-H3 | 123.2(9) | C13-C14-H14a | 110.5(10) |
| C4-C3-H3 | 128.8(9) | C13-C14-H14b | 110.5(9) |
| C3-C4-C5 | 108.23(14) | C15-C14-H14a | 109.4(9) |
| C3-C4-H4 | 128.3(8) | C15-C14-H14b | 109.8(9) |
| C5-C4-H4 | 123.4(8) | H14a-C14-H14b | 105.7(13) |
| C4-C5-C6 | 109.46(13) | C9-C15-C14 | 110.68(14) |
| C4-C5-C7 | 99.44(13) | C9-C15-H15a | 110.4(10) |
| C4-C5-H5 | 117.0(8) | C9-C15-H15b | 108.7(10) |
| C6-C5-C7 | 98.15(12) | C14-C15-H15a | 111.3(9) |
| C6-C5-H5 | 113.2(9) | C14-C15-H15b | 110.5(10) |
| C7-C5-H5 | 117.3(8) | H15a-C15-H15b | 105.0(13) |
| C1-C6-C5 | 101.89(13) | O2-C16-O3 | 112.37(14) |
| C1-C6-C11 | 115.18(13) | O2-C16-H16a | 113.1(8) |
| C1-C6-H6 | 108.6(8) | O2-C16-H16b | 105.2(8) |
| C5-C6-C11 | 119.94(13) | O3-C16-H16a | 104.3(9) |
| C5-C6-H6 | 105.7(9) | O3-C16-H16b | 112.0(8) |
| C11-C6-H6 | 104.9(9) | H16a-C16-H16b | 110.0(12) |
| C2-C7-C5 | 94.15(12) | O3-C17-H17a | 105.8(11) |
| C2-C7-H7a | 113.4(9) | O3-C17-H17b | 109.5(11) |
| C2-C7-H7b | 113.7(9) | O3-C17-H17c | 110.6(12) |
| C5-C7-H7a | 113.8(9) | H17a-C17-H17b | 109.9(17) |
| C5-C7-H7b | 112.4(9) | H17a-C17-H17c | 108.3(16) |
| H7a-C7-H7b | 108.9(13) | H17b-C17-H17c | 112.5(16) |
| O1-C8-C1 | 121.85(15) | O4-C18-C12 | 112.56(14) |
| O1-C8-C9 | 119.75(14) | O4-C18-H18a | 104.4(9) |
| C1-C8-C9 | 118.31(13) | O4-C18-H18b | 109.0(9) |
| C8-C9-C10 | 113.93(13) | C12-C18-H18a | 111.0(9) |
| C8-C9-C15 | 109.53(13) | C12-C18-H18b | 109.2(9) |
| C8-C9-H9 | 104.7(9) | H18a-C18-H18b | 110.6(13) |
| C10-C9-C15 | 110.99(14) | O4-C19-H19a | 105.7(11) |
| C10-C9-H9 | 109.0(9) | O4-C19-H19b | 110.5(11) |
| C15-C9-H9 | 108.4(9) | O4-C19-H19c | 112.6(11) |
| C9-C10-C11 | 109.45(13) | H19a-C19-H19b | 110.6(15) |
| C9-C10-C12 | 112.60(13) | H19a-C19-H19c | 109.3(15) |
| C9-C10-H10 | 107.4(8) | H19b-C19-H19c | 108.0(14) |

Torsion angles

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C16 | O2 | C11 | C6 | -100.25(24) | C16 | O2 | C11 | C10 | 138.7( 3) |
| C16 | O2 | C11 | H11 | 20.1(13) | C11 | O2 | C16 | O3 | -76.49(21) |
| C11 | O2 | C16 | H16a | 41.3(15) | C11 | O2 | C16 | H16b | 161.4(14) |
| C17 | O3 | C16 | O2 | -71.43(24) | C17 | O3 | C16 | H16a | 165.7(15) |
| C17 | O3 | C16 | H16b | 46.8(14) | C16 | O3 | C17 | H17a | -177.3(19) |
| C16 | O3 | C17 | H17b | 64.3(19) | C16 | O3 | C17 | H17c | -60.2(19) |
| C19 | O4 | C18 | C12 | 68.79(23) | C19 | O4 | C18 | H18a | -170.7(16) |
| C19 | O4 | C18 | H18b | -52.5(15) | C18 | O4 | C19 | H19a | 175.0(19) |
| C18 | O4 | C19 | H19b | 55.2(17) | C18 | O4 | C19 | H19c | -65.7(17) |
| C6 | C1 | C2 | C3 | -72.49(22) | C6 | C1 | C2 | C7 | 30.62(16) |
| C6 | C1 | C2 | H2 | 159.0(15) | C8 | C1 | C2 | C3 | 53.87(20) |
| C8 | C1 | C2 | C7 | 157.0( 3) | C8 | C1 | C2 | H2 | -74.6(15) |
| H1 | C1 | C2 | C3 | 170.7(15) | H1 | C1 | C2 | C7 | -86.2(15) |
| H1 | C1 | C2 | H2 | 42.2(21) | C2 | C1 | C6 | C5 | 7.68(14) |
| C2 | C1 | C6 | C11 | 139.2( 3) | C2 | C1 | C6 | H6 | -103.6(14) |
| C8 | C1 | C6 | C5 | -118.7( 3) | C8 | C1 | C6 | C11 | 12.76(14) |
| C8 | C1 | C6 | H6 | 130.0(14) | H1 | C1 | C6 | C5 | 124.6(15) |
| H1 | C1 | C6 | C11 | -103.9(15) | H1 | C1 | C6 | H6 | 13.3(20) |
| C2 | C1 | C8 | O1 | 25.88(16) | C2 | C1 | C8 | C9 | -157.5( 3) |
| C6 | C1 | C8 | O1 | 146.1( 3) | C6 | C1 | C8 | C9 | -37.33(17) |
| H1 | C1 | C8 | O1 | -94.1(15) | H1 | C1 | C8 | C9 | 82.5(15) |
| C1 | C2 | C3 | C4 | 69.01(24) | C1 | C2 | C3 | H3 | -103.5(16) |
| C7 | C2 | C3 | C4 | -34.86(19) | C7 | C2 | C3 | H3 | 152.6(16) |
| H2 | C2 | C3 | C4 | -163.3(15) | H2 | C2 | C3 | H3 | 24.2(22) |
| C1 | C2 | C7 | C5 | -56.80(20) | C1 | C2 | C7 | H7a | 61.4(15) |
| C1 | C2 | C7 | H7b | -173.4(15) | C3 | C2 | C7 | C5 | 50.95(19) |
| C3 | C2 | C7 | H7a | 169.2(16) | C3 | C2 | C7 | H7b | -65.7(15) |
| H2 | C2 | C7 | C5 | 177.5(15) | H2 | C2 | C7 | H7a | -64.2(21) |
| H2 | C2 | C7 | H7b | 60.9(21) | C2 | C3 | C4 | C5 | 1.59(15) |
| C2 | C3 | C4 | H4 | -174.7(15) | H3 | C3 | C4 | C5 | 173.5(16) |
| H3 | C3 | C4 | H4 | -2.8(21) | C3 | C4 | C5 | C6 | -70.13(24) |
| C3 | C4 | C5 | C7 | 32.06(18) | C3 | C4 | C5 | H5 | 159.4(14) |
| H4 | C4 | C5 | C6 | 106.4(14) | H4 | C4 | C5 | C7 | -151.4(15) |
| H4 | C4 | C5 | H5 | -24.1(19) | C4 | C5 | C6 | C1 | 60.07(20) |
| C4 | C5 | C6 | C11 | -68.47(21) | C4 | C5 | C6 | H6 | 173.5(14) |
| C7 | C5 | C6 | C1 | -43.02(18) | C7 | C5 | C6 | C11 | -171.6( 3) |
| C7 | C5 | C6 | H6 | 70.4(14) | H5 | C5 | C6 | C1 | -167.5(14) |
| H5 | C5 | C6 | C11 | 64.0(13) | H5 | C5 | C6 | H6 | -54.0(19) |
| C4 | C5 | C7 | C2 | -49.85(19) | C4 | C5 | C7 | H7a | -167.7(16) |
| C4 | C5 | C7 | H7b | 67.9(15) | C6 | C5 | C7 | C2 | 61.56(21) |
| C6 | C5 | C7 | H7a | -56.3(15) | C6 | C5 | C7 | H7b | 179.3(15) |
| H5 | C5 | C7 | C2 | -176.9(14) | H5 | C5 | C7 | H7a | 65.2(20) |
| H5 | C5 | C7 | H7b | -59.2(20) | C1 | C6 | C11 | O2 | -80.93(22) |
| C1 | C6 | C11 | C10 | 37.81(16) | C1 | C6 | C11 | H11 | 159.7(14) |
| C5 | C6 | C11 | O2 | 41.32(16) | C5 | C6 | C11 | C10 | 160.1( 3) |
| C5 | C6 | C11 | H11 | -78.0(13) | H6 | C6 | C11 | O2 | 159.8(14) |
| H6 | C6 | C11 | C10 | -81.5(14) | H6 | C6 | C11 | H11 | 40.4(19) |
| O1 | C8 | C9 | C10 | -174.6( 3) | O1 | C8 | C9 | C15 | 60.44(22) |
| O1 | C8 | C9 | H9 | -55.6(15) | C1 | C8 | C9 | C10 | 8.74(14) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C1 | C8 | C9 | C15 | -116.2( 3) | C1 | C8 | C9 | H9 | 127.7(15) |
| C8 | C9 | C10 | C11 | 42.50(17) | C8 | C9 | C10 | C12 | -83.59(24) |
| C8 | C9 | C10 | H10 | 158.7(14) | C15 | C9 | C10 | C11 | 166.7( 3) |
| C15 | C9 | C10 | C12 | 40.60(18) | C15 | C9 | C10 | H10 | -77.1(14) |
| H9 | C9 | C10 | C11 | -74.0(15) | H9 | C9 | C10 | C12 | 159.9(15) |
| H9 | C9 | C10 | H10 | 42.1(20) | C8 | C9 | C15 | C14 | 65.65(22) |
| C8 | C9 | C15 | H15a | -58.1(16) | C8 | C9 | C15 | H15b | -172.8(17) |
| C10 | C9 | C15 | C14 | -61.01(22) | C10 | C9 | C15 | H15a | 175.3(16) |
| C10 | C9 | C15 | H15b | 60.5(16) | H9 | C9 | C15 | C14 | 179.4(15) |
| H9 | C9 | C15 | H15a | 55.6(22) | H9 | C9 | C15 | H15b | -59.1(22) |
| C9 | C10 | C11 | O2 | 56.05(18) | C9 | C10 | C11 | C6 | -66.47(21) |
| C9 | C10 | C11 | H11 | 172.6(14) | C12 | C10 | C11 | O2 | -177.9( 3) |
| C12 | C10 | C11 | C6 | 59.60(20) | C12 | C10 | C11 | H11 | -61.4(13) |
| H10 | C10 | C11 | O2 | -60.2(14) | H10 | C10 | C11 | C6 | 177.3(14) |
| H10 | C10 | C11 | H11 | 56.3(19) | C9 | C10 | C12 | C13 | -10.39(17) |
| C9 | C10 | C12 | C18 | 174.0( 3) | C11 | C10 | C12 | C13 | -134.8( 3) |
| C11 | C10 | C12 | C18 | 49.62(19) | H10 | C10 | C12 | C13 | 107.5(14) |
| H10 | C10 | C12 | C18 | -68.1(14) | C10 | C12 | C13 | C14 | -1.06(16) |
| C10 | C12 | C13 | H13 | 179.7(16) | C18 | C12 | C13 | C14 | 174.5( 3) |
| C18 | C12 | C13 | H13 | -4.8(16) | C10 | C12 | C18 | O4 | 60.08(20) |
| C10 | C12 | C18 | H18a | -56.6(15) | C10 | C12 | C18 | H18b | -178.7(16) |
| C13 | C12 | C18 | O4 | -115.7( 3) | C13 | C12 | C18 | H18a | 127.7(16) |
| C13 | C12 | C18 | H18b | 5.5(15) | C12 | C13 | C14 | C15 | -18.39(17) |
| C12 | C13 | C14 | H14a | -139.9(17) | C12 | C13 | C14 | H14b | 103.6(16) |
| H13 | C13 | C14 | C15 | 160.9(16) | H13 | C13 | C14 | H14a | 39.4(23) |
| H13 | C13 | C14 | H14b | -77.2(22) | C13 | C14 | C15 | C9 | 48.38(20) |
| C13 | C14 | C15 | H15a | 171.6(16) | C13 | C14 | C15 | H15b | -72.1(16) |
| H14a | C14 | C15 | C9 | 170.5(17) | H14a | C14 | C15 | H15a | -66.3(23) |
| H14a | C14 | C15 | H15b | 50.0(23) | H14b | C14 | C15 | C9 | -73.9(16) |
| H14b | C14 | C15 | H15a | 49.3(22) | H14b | C14 | C15 | H15b | 165.6(23) |