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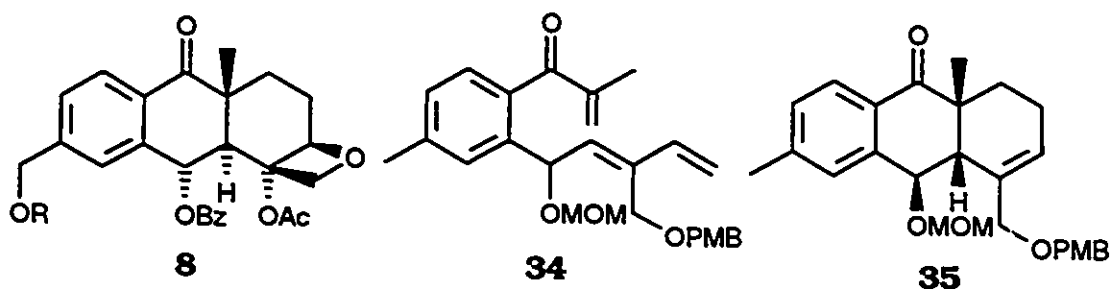


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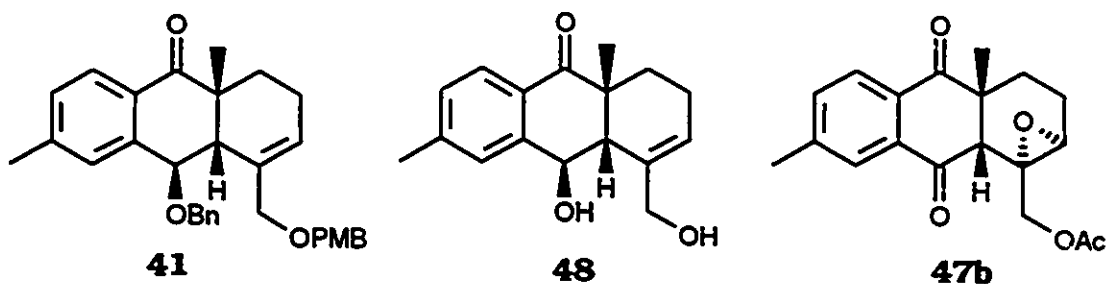
*Kinh tặg Ba Mẹ*

## Abstract

In the cycloaddition approach towards the synthesis of the substituted anthraquinone derivative **8** as a potential antitumor agent, it was found that the tricyclic core of this target analogue could be generated by an intramolecular Diels-Alder reaction. The Diels-Alder precursor **34** was successfully synthesized starting from 3-methyl benzyl alcohol, methacrolein and (2*Z*)-2-(ethenyl)-3-iodo-1-(*p*-methoxybenzyloxy)-2-propene: it readily underwent cycloaddition at approximately 40 °C to generate a *cis*-fused ring system **35**. The stereochemistry of the cycloaddition product was unambiguously determined by X-ray structure of crystalline **41**. Stereoselective epoxidation of the ring C double bond with *m*-chloroperoxybenzoic acid was achieved for diol **48**, where the functionality at C2 was a hydroxyl group. The synthesis of anthraquinone derivative **47b** is also described.



R = Taxol<sup>®</sup> side chain



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## List of Abbreviations

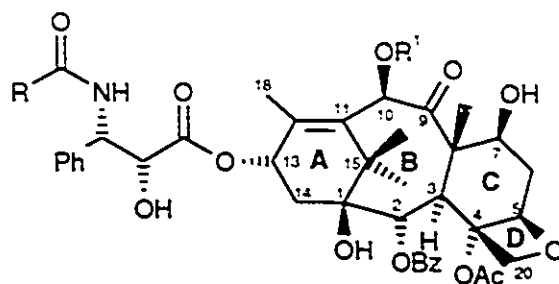
Ac	acetyl
AIBN	2,2'-azo-bis-isobutyronitrile
Anal. Calcd.	elemental analysis calculated
Bn	benzyl
br	broad
Bz	benzoyl
<i>cf.</i>	confer
d	doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DMF	<i>N,N'</i> -dimethylformamide
equiv.	equivalents
Et	ethyl
FTIR	Fourier transform infrared spectroscopy
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
m	multiplet
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point
<i>n</i> -BuLi	<i>n</i> -butyllithium
NBS	N-bromosuccinimide
NCI	National Cancer Institute
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
R	alkyl

R <sub>f</sub>	retention factor
TBAF	tetrabutylammonium fluoride
TBDMS	<i>t</i> -butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMEDA	<i>N,N,N,N</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TPP	triphenylphosphine
triflate	trifluoromethanesulfonate

# 1 Introduction

The mitotic stage of the cell cycle represents an important strategic point where cancerous cell growth can be interrupted. An important biological target in such anticancer chemotherapy is the microtubule. Microtubules are ubiquitous cellular constituents which are required for proper cell maintenance and division. They are in a dynamic equilibrium with tubulin dimers, their basic protein subunits. Modification of this equilibrium by either inhibition or promotion of the assembly of microtubules can disrupt cell mitosis and cause cell death. Classical anti-microtubule agents such as colchicine and podophyllotoxin are known to function by inhibiting the assembly of microtubules.<sup>1</sup> Since normal microtubules are required for cell division, these drugs have been shown to be effective for treating some types of cancer.

Recently, a new class of antimitotic agents was discovered, which promoted microtubule assembly, and was found to have activity against several types of cancer, including breast cancer. This finding was significant since 50,000 woman die annually from breast cancer in North America. Consequently, new drugs are needed to stop this tragedy. Paclitaxel (Taxol<sup>®</sup>, 1), a naturally occurring drug isolated from the Pacific yew *Taxus brevifolia*, and its semisynthetic analogue docetaxel (Taxotere<sup>®</sup>, 2) have been reported to promote microtubule assembly *in vitro* and are used clinically against ovarian, breast, and bronchial carcinomas.<sup>2</sup>



- 1 Taxol<sup>®</sup>,      R = Ph,      R<sup>1</sup> = Ac
- 2 Taxotere<sup>®</sup>,   R = *t*-BuO,   R<sup>1</sup> = H
- 3 10-Deacetyl baccatin III, OH at C13,   R<sup>1</sup> = H

**Figure 1** Taxol<sup>®</sup> and related compounds.

## 1.1 General Background

### 1.1.1 Taxoid History

In the early 1960's, the National Cancer Institute (NCI) identified a crude extract from the bark of *Taxus brevifolia* that possessed activity against several tumor cell lines.<sup>3</sup> Due to its extremely low concentration and complex structural nature, the structure of the active component, Taxol<sup>®</sup>, in the plant extract was not established until 1971.<sup>3</sup> The difficulties associated with procuring and processing Taxol<sup>®</sup> contributed to the lack of interest to further develop the drug. However, interest in Taxol<sup>®</sup> was rekindled in 1979 when Horwitz and coworkers<sup>1</sup> reported that Taxol<sup>®</sup> had a novel mode of action and it promoted the assembly of calf brain microtubules *in vitro*. This new finding led to the initiation of clinical phase I trials by the NCI, in 1983, to determine the maximum tolerated dose in humans and the dose-limiting toxicity of Taxol<sup>®</sup>.<sup>2, 4</sup>

Taxol<sup>®</sup> received greater attention from the scientific community when its activity against ovarian cancer was recognized. In 1989, Taxol<sup>®</sup> treatment of ovarian carcinomas was reported to give a 30% response.<sup>2</sup> This was

considered significant since some of the responding patients had ovarian cancers that were resistant to other chemotherapeutic treatments. Recognition of Taxol<sup>®</sup>'s activity against breast cancer (in 1991) and non-small cell bronchial cancer (in 1992) further emphasized the importance of Taxol<sup>®</sup> as an antineoplastic drug.<sup>2</sup> On December 29, 1992, the US Food and Drug Administration approved Taxol<sup>®</sup> for the treatment of ovarian cancer in patients where other forms of chemotherapy had failed.<sup>2,5</sup> Approval of Taxol<sup>®</sup> and of Taxotere<sup>®</sup> for the treatment of breast cancer followed in 1994 and in 1995, respectively.

### **1.1.2 Taxoid Source**

As mentioned above, Taxol<sup>®</sup> was initially isolated from the stem bark of the Pacific yew *Taxus brevifolia*. This tree is a slow-growing conifer which is usually found in moist soil near streams and lakes, in the understory of old conifers and hardwoods.<sup>6,7</sup> A mature tree rarely exceeds 60 cm in diameter and 12 m in height, and the concentration of Taxol<sup>®</sup> present is in the range of 20–70 ppm in the needles and 70–400 ppm in the bark.<sup>4</sup> The amount of pure Taxol<sup>®</sup> required to treat a cancer patient is approximately 2 g. Using the reported Taxol<sup>®</sup> isolation yield (0.02%) by Wall and Wani<sup>3</sup> as a basis, a total of 10 kg of dry bark would be required to treat a patient. Thus, it is impractical to rely on the yew as the sole source of Taxol<sup>®</sup>, considering the growing need for the drug and the limited availability of yew trees.

To meet the growing demands for the drug, several strategies are currently being studied. Some of these approaches include: total and partial synthesis of Taxol<sup>®</sup>, extraction of Taxol<sup>®</sup> precursors (such as 10-deacetyl baccatin III, **3**) from *Taxus* needles, cultivation of *Taxus* plants,

identification of simpler analogues, and cell culture production. Among the mentioned strategies, extraction of 10-deacetyl baccatin III from *Taxus* needles and cultivated *Taxus* plants, followed by semisynthesis, is favorable in that it utilizes a renewable natural resource. It is this procedure that is now used for the production of both Taxol<sup>®</sup> and Taxotere<sup>®</sup>. In the cell culture production approach, an endophytic fungus associated with *Taxus brevifolia* has been isolated and it was found to be capable of producing Taxol<sup>®</sup>. Unfortunately, the quantitative yields from these cell cultures (24-50 ng Taxol<sup>®</sup> / L of cell culture) are too low for them to be economically viable.<sup>6</sup>

Both partial and total synthetic approaches have their share of shortcomings. In the partial synthetic route, a Taxol<sup>®</sup> precursor 10-deacetyl baccatin III (**3**) is required as a starting material. This compound must be isolated from the *Taxus* plant, and thus the method is still largely dependent on the limited natural resource. On the other hand, the total synthesis of Taxol<sup>®</sup> has proven to be very challenging due to its structural complexity. For example, it is extremely difficult to form the central eight-membered ring of the taxoid nucleus due to entropic and enthalpic factors, in addition to the increase in ring strain introduced by the geminal dimethyl groups. Furthermore, the *trans*-fused C ring with an angular methyl group and the A ring with a bridgehead alkene must be assembled. The difficulty in the construction of the tricyclic nucleus plus the high degree of oxygen functionalities to be introduced require differential protection of the various alkoxy groups. The task is further complicated by the sensitivity of certain functional groups towards different experimental conditions. For example, ring-opening of the oxetane ring can occur under acidic conditions:

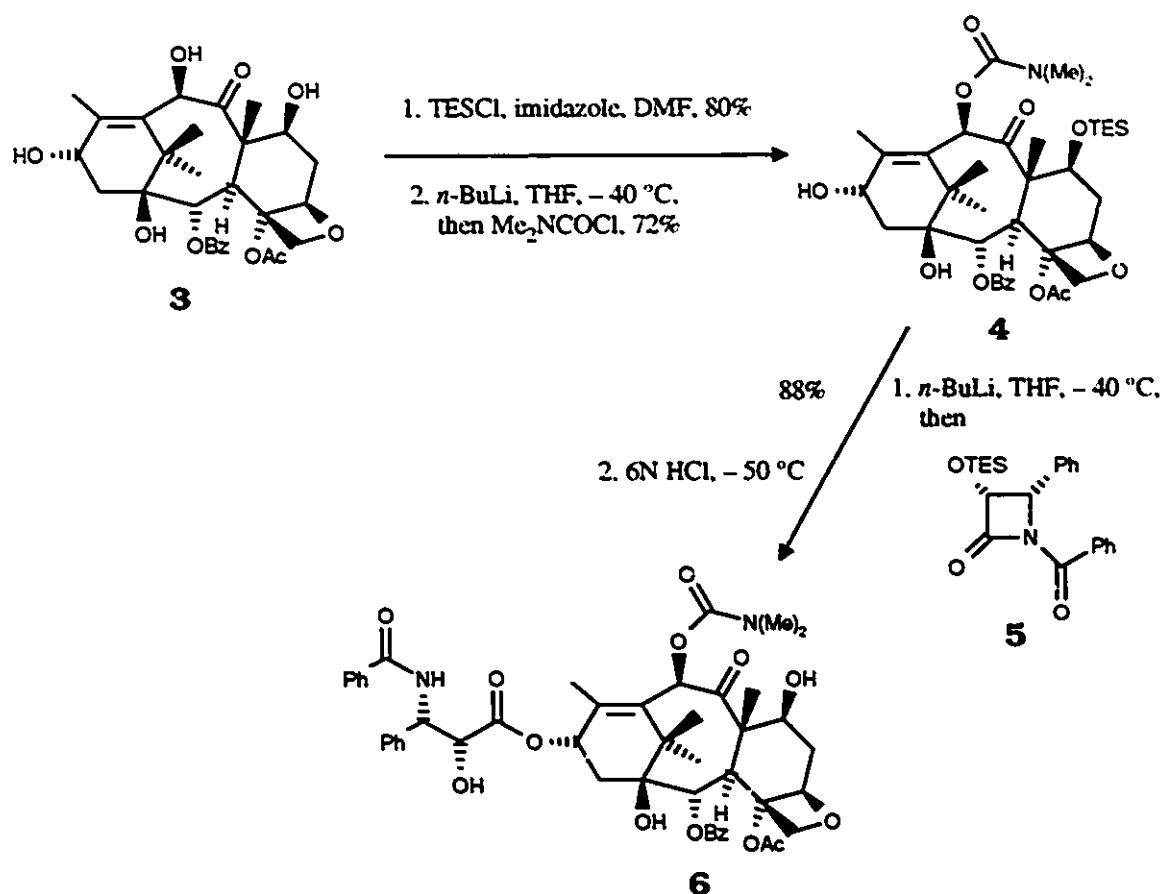
whereas, basic conditions result in epimerization of the hydroxyl group at C7.<sup>7</sup> Thus, it is of no surprise that to date only three research groups have been successful in completing the total synthesis of Taxol<sup>®</sup>.<sup>8,9,10</sup>

### 1.1.3 Taxol<sup>®</sup> Analogues

It is therefore apparent that there is a great need to identify simpler analogues of Taxol<sup>®</sup> which are easier to synthesize. Moreover, drug history has often shown that synthetic analogues were more potent than the naturally occurring parent compound. For example, the Taxol<sup>®</sup> analogue Taxotere<sup>®</sup> (**2**) is reported to be 1.3–12 times more cytotoxic than Taxol<sup>®</sup> in several murine and human tumor cell lines.<sup>11</sup>

Taxol<sup>®</sup> analogues that are presently being studied share one common feature: the taxoid nucleus. A variety of Taxol<sup>®</sup> derivatives, resulting from chemical modifications at C2<sup>12a-c</sup>, C4<sup>12d-e</sup>, C7<sup>12a,f</sup>, C10<sup>12g</sup>, or at the N terminal<sup>12h-j</sup> and C3'<sup>12a,12j-k</sup> of the ring A side chain, and their biological activities have been reported in the literature. An example of a semi-synthetic route employed to generate a C10 modified Taxol<sup>®</sup> analogue is shown in Scheme 1.<sup>12g</sup> There was no need to protect the hydroxyl group at C13 since it is sterically hindered due to its location inside the concave portion of the Taxol<sup>®</sup> skeleton. However, it was necessary to protect the more reactive C7 hydroxyl group prior to selective deprotonation at C10 by an alkyllithium base. The alkoxyllithium anion thus generated can then be treated with a variety of electrophiles to generate different C10 derivatives. Attachment of the A ring side chain *via* Holton's method, followed by acid-promoted deprotection of the alcohols at C7 and C2', then afforded the target Taxol<sup>®</sup> analogues. Interestingly, the C10 carbamate **6** was evaluated for biological activity and was found to be comparable to Taxol<sup>®</sup>.

As mentioned above, current Taxol<sup>®</sup> analogues still possess the diterpene framework of Taxol<sup>®</sup>. Consequently, problems associated with the limiting availability of yew trees and the difficulties encountered in synthesizing Taxol<sup>®</sup> are also faced here. One way of addressing this issue is to identify other Taxol<sup>®</sup> analogues that are simpler in structure, and yet still possess biological activity that is equal to or greater than that of Taxol<sup>®</sup>.



**Scheme 1**

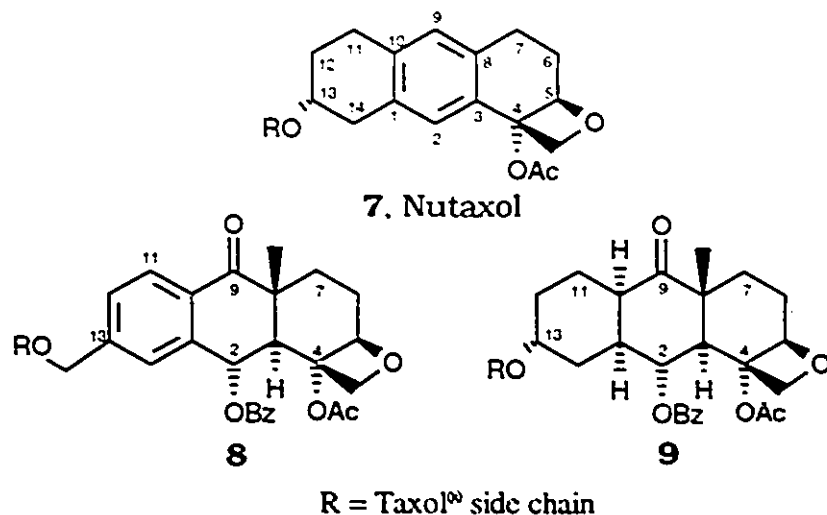
#### 1.1.4 Novel Taxol® Analogues

Our laboratory was interested in identifying and synthesizing simpler analogues of Taxol® in the hope that additional information can be gained which may help elucidate how Taxol® works. We were also motivated by the desire to be able to efficiently synthesize biologically active Taxol® analogues from simple, inexpensive, and readily available starting materials.

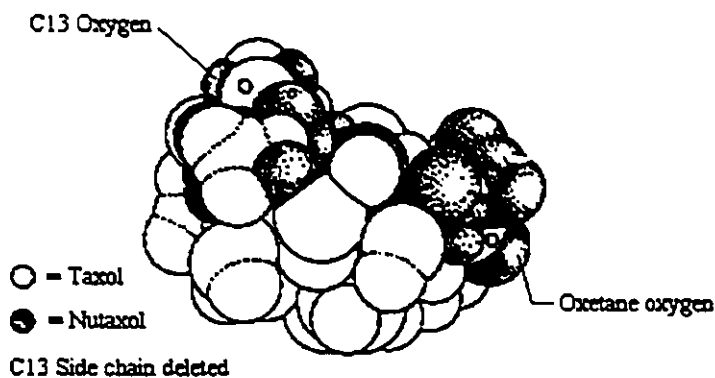
The structure of the target Taxol® analogue(s) was developed based on the structure-activity relationship information reported in the literature. In general, the overall shape of the Taxol® skeleton and the presence of the ring A side chain are essential for Taxol®'s biological activity. Studies have shown that both the side chain alone and baccatin III (Taxol® without side chain) are inactive.<sup>7</sup> It was also found that the oxetane ring is required since its absence resulted in a decrease in activity by more than 20-fold.<sup>13</sup> Overall, the functionalities on the northern part of the Taxol® molecule (**1**) seem to have insignificant effects on activity; whereas, functionalities at C13, C2, C4, and C5 are essential for activity.<sup>12</sup>

In consideration of the mentioned characteristics, we chose the three tricyclic systems **7**, **8**, and **9** as our primary target Taxol® analogues (Taxol® numbering system kept for ease of comparison). Based on molecular modeling, as illustrated for Nutaxol (**7**) (Figure 3), the overall shape of the tricyclic core of Nutaxol is relatively similar to that of the Taxol® skeleton. As a result, the oxygen at C13 and in the oxetane ring of Nutaxol are located in the same region of space as found in Taxol®. This is significant since both the oxetane ring and the Taxol® side chain are essential for biological activity. However, the central ring of Nutaxol is flat, thus analogues **8** and especially **9** should mimic the shape of Taxol® better. Functionalities at C2,

C3, C4, C5, and C8 of Taxol<sup>®</sup> were also retained in target analogues **8** and **9** to ensure biological activity.



**Figure 2** Potential Taxol<sup>®</sup> analogues.

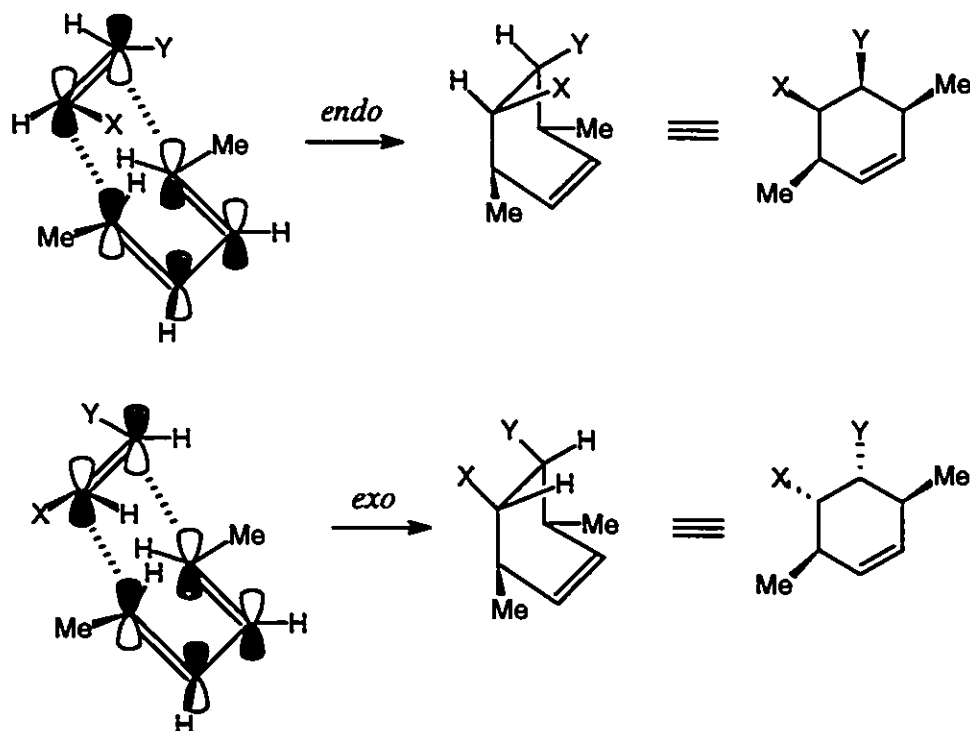


**Figure 3** Molecular model of target analogue superimposed on Taxol<sup>®</sup>.

The structures of target analogues **8** and **9** are compared to that of Taxol<sup>®</sup> in Figure 4. It can be seen that the three molecules are essentially identical on the eastern half of the molecule. The A ring of **8** is flat since it is an aromatic ring; therefore, an extra carbon was used to extend the side chain. This will allow the side chain to hang down from the ring system.



electronic requirement for the reaction to proceed readily is that the diene must be electron-rich while the dienophile must be electron-poor. The mechanism of the reaction involves the diene and dienophile approaching each other in approximately parallel planes to allow  $\sigma$ -overlap of their  $\pi$ -orbitals: thus, the diene must adopt an *s-cis* conformation for the concerted reaction to take place (Figure 5). When the dienophile is unsymmetrical, the reactants can approach each other in two distinct orientations. These two approaches are termed *endo* and *exo*. In the *endo* approach, the reference substituent on the dienophile is oriented toward the  $\pi$ -orbitals of the diene; whereas, it is oriented away from the  $\pi$ -system in the *exo* approach (Figure 5). If the diene is also unsymmetrical, two different stereoisomeric products are generated. The *endo* product is usually preferred when an unsaturated substituent, such as a carbonyl group, is present on the dienophile.<sup>14</sup>

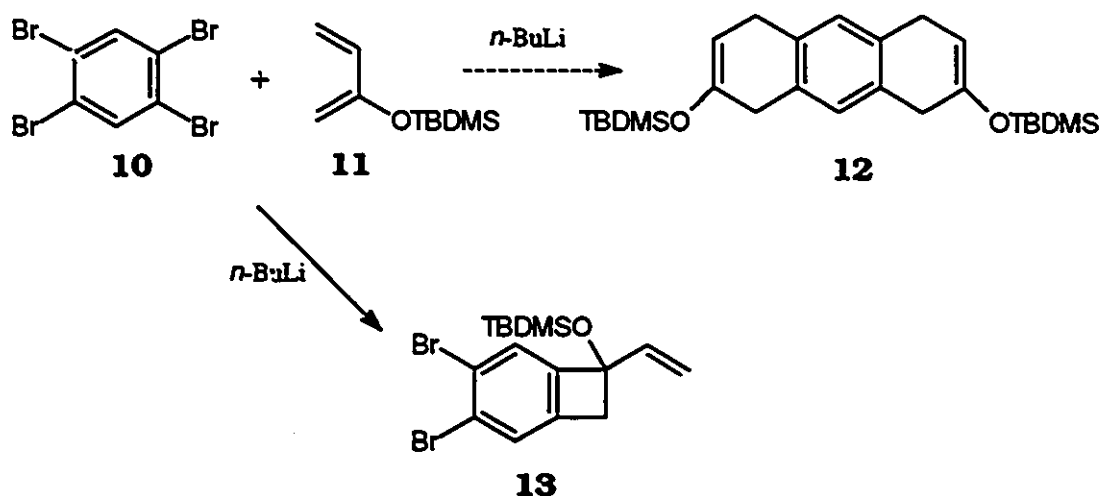


**Figure 5** *Endo* and *exo* approaches in a Diels-Alder reaction.<sup>14</sup>

## 1.2 Research Objectives

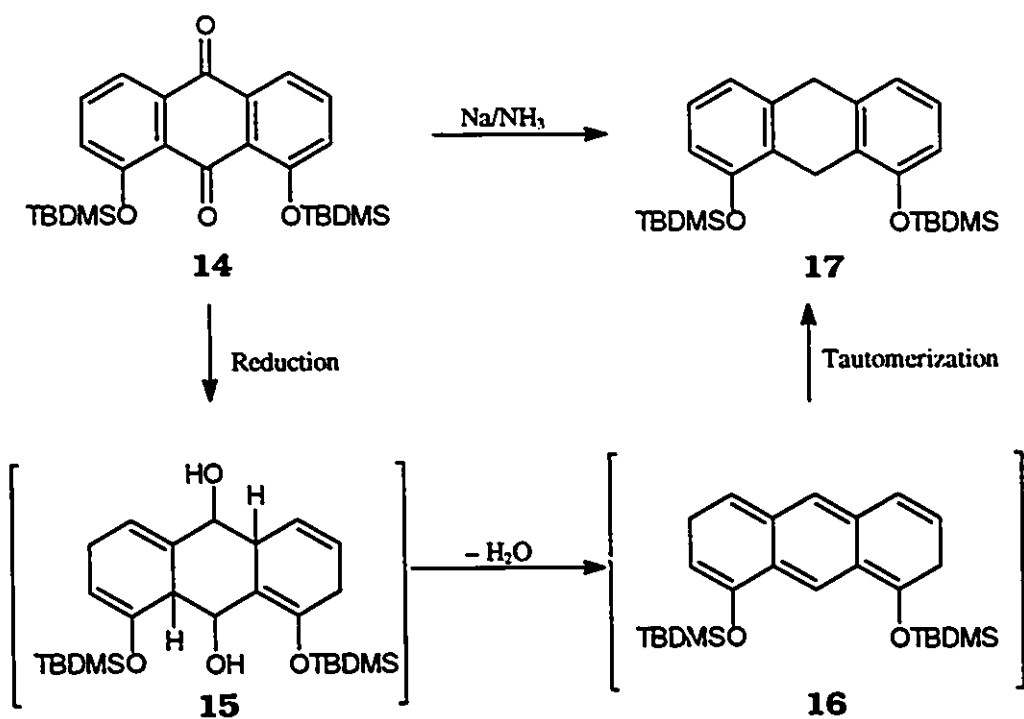
### 1.2.1 Preliminary Work

Initially, the construction of the tricyclic core of Nutaxol (7) was attempted *via* an intermolecular cycloaddition route involving benzyne (Scheme 2). It was hoped that the benzyne generated by treatment of 1,2,4,5-tetrabromobenzene (10) with *n*-butyllithium would undergo Diels-Alder reaction with diene 11 to generate tricyclic system 12. However, analysis by <sup>1</sup>H NMR revealed the presence of a terminal double bond in the isolated product. Thus, the reaction was believed to have proceeded *via* a [2+2] cycloaddition route to generate cyclobutene 13. This observation has also been reported by other researchers.<sup>15</sup> It was reasoned that there was insufficient time for the diene to acquire the *s-cis* conformation required for the [4+2] (Diels-Alder) cycloaddition. A different cyclohexene product can still be obtained by thermal rearrangement of the [2+2] cycloaddition product; however, attempts to perform an additional cycloaddition reaction with the bicyclic compound to generate a tricyclic ring system were unsatisfactory.



**Scheme 2**

Another approach aimed toward the synthesis of the target analogues was based on chemical manipulations of an intact anthraquinone derivative (Scheme 3). Unfortunately, Birch reduction of anthraquinone system **14** resulted in the loss of the two carbonyl oxygens from the molecule. This was believed to proceed by initial reduction of the carbonyl groups and the benzene rings to generate diol **15**. Subsequent loss of water followed by tautomerization generated the tricyclic compound **17**. This type of behavior has been observed before.<sup>16</sup> Another route was sought since it was desirable to retain the oxygen functionalities in the central ring.

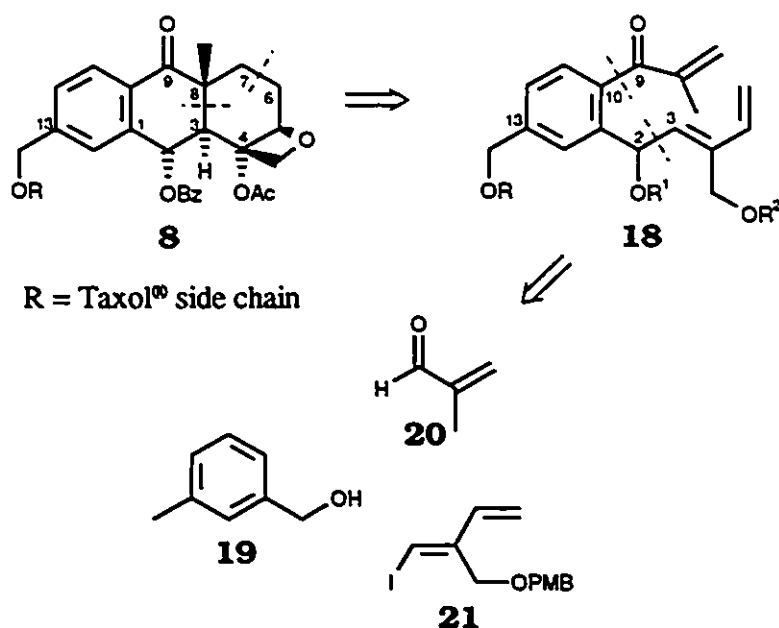


**Scheme 3**

### 1.2.2 Retrosynthetic Plan

Previous synthetic routes met with insurmountable difficulties; therefore, our main objective became the synthesis of the target Taxol<sup>®</sup> analogue **8**. The intramolecular Diels-Alder approach was adopted to

assemble the tricyclic core of this target analogue. In a retrosynthetic representation (Figure 6), removal of the oxetane ring followed by double disconnection between C6–C7 and C3–C8 in ring C should give a Diels-Alder precursor similar to triene **18**. In principle, this precursor can be assembled from **19**, **20**, and **21** by making further disconnections between C2–C3 and C9–C10. These disconnections were chosen because 3-methyl benzyl alcohol (**19**) and methacrolein (**20**) are commercially available at relatively low prices (less than \$2/g), and diene **21** is readily prepared by our laboratory from propargyl alcohol.<sup>17</sup> It was hoped that the chemistry developed here could be extended to the synthesis of target analogue **9**, by proper choice of starting materials.



**Figure 6** Retrosynthetic plan for synthesis of target Taxol<sup>®</sup> analogue **8**.

### 1.2.3 Biological Activity Evaluation

The biological activity of the target Taxol<sup>®</sup> analogue(s) must be tested once it is successfully synthesized. Our laboratory did not have the

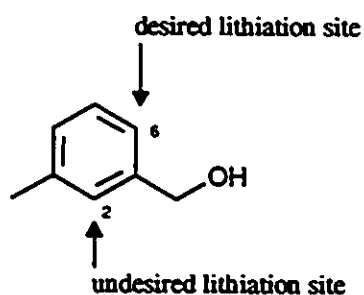
appropriate means for evaluating the biological activity of the target analogue(s): thus, a collaboration with the laboratory of Dr. D.L. Brown, Department of Biology, University of Ottawa was made. The target analogue(s), once synthesized, would be given to the biology laboratory, where microtubule assembly assays and cytotoxicity tests against a range of tumor cell lines would be performed.

## 2 Results and Discussion

### 2.1 Synthesis of the Tricyclic Ring System

It was intended that the tricyclic nucleus of the target analogue **8** would be assembled *via* an intramolecular Diels-Alder reaction. Thus, the first step in this strategy was to synthesize an appropriate Diels-Alder precursor. It was predicted that the desired precursor **18** (Figure 6) could be synthesized starting from 3-methyl benzyl alcohol (**19**).

Benzyl alcohols are known to undergo *ortho*-lithiation upon treatment with an alkyllithium base such as *n*-butyllithium. The *ortho*-lithiated derivative generated can react with a variety of electrophiles to form various *ortho*-substituted benzyl alcohol derivatives.<sup>18</sup> In order to consider this method in the synthetic plan, it was necessary to ensure that treatment of **19** with *n*-butyllithium would result in lithiation at C6 rather than C2 of the aromatic ring (Figure 7). This regioselectivity was crucial since our synthetic strategy required that the dienophile segment of the Diels-Alder precursor must be *para* to the methyl group in **19**.

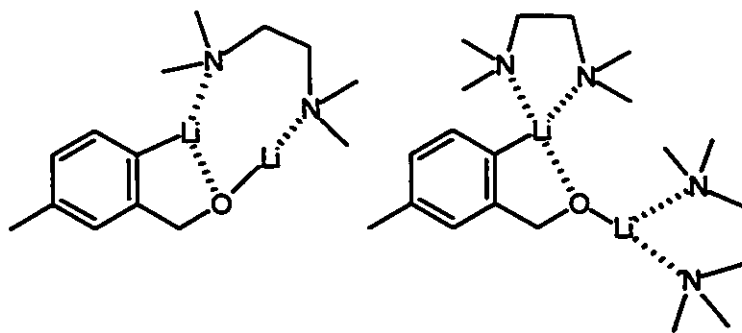


**Figure 7** *ortho*-Lithiation of 3-methyl benzyl alcohol (**19**).

### 2.1.1 Deuteration Experiment

To determine whether the general method for *ortho*-lithiation of benzyl alcohols was applicable in the synthetic plan, deuterium was used as an electrophile in the test system. Benzyl alcohol **19** was treated with *n*-butyllithium (2 equiv.) according to a literature procedure<sup>18</sup> and deuterium was added as an electrophile. The crude product obtained was analyzed by <sup>1</sup>H NMR spectroscopy (500 MHz) and its NMR spectrum was compared to that of benzyl alcohol **19**. Comparison of the aromatic proton signals of the two compounds revealed that there was a significant decrease in intensity of one of the doublet signals in the deuterated compound. Whereas, the singlet signal generated by the proton at C2 did not diminish in intensity. Thus, it was concluded that, as desired, *ortho*-lithiation of the benzyl alcohol **19** occurred preferentially at C6, rather than at C2.

The preference for *ortho*-lithiation at C6 may be due to steric hindrance imposed by the methyl group at C3. *N,N,N,N*-tetramethylethylenediamine (TMEDA) was present in the reaction, thus, it could coordinate with the lithiated species in two possible ways (Figure 8). The bulky nature of the coordinating TMEDA would render it extremely difficult for lithiation to occur at C2 (between two substituents).

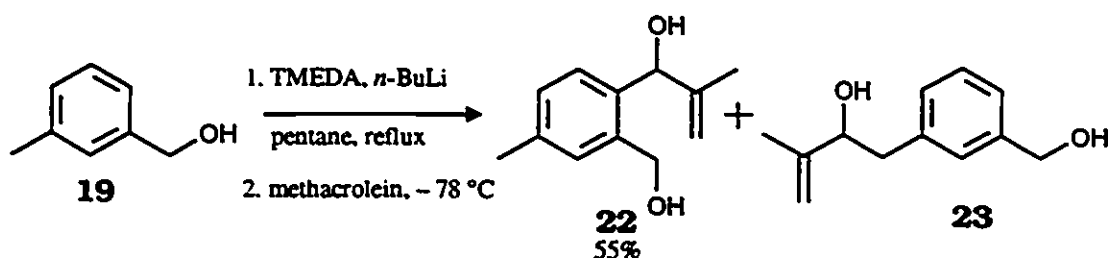


**Figure 8** Coordination of TMEDA to lithiated species of **19**.

### 2.1.2 Attachment of the Dienophile Moiety

These results prompted us to investigate the possibility of attaching the desired dienophile segment to 3-methyl benzyl alcohol (**19**) *via ortho*-lithiation. In this case, methacrolein (**20**) was chosen as the electrophile. As predicted by the results obtained in the deuteration experiment, *ortho*-lithiation occurred at C6 rather than C2 to afford the desired diol **22** in 55% yield.

However, diol **22** was not the only *ortho*-alkylation product obtained. The reaction produced a very complex mixture of relatively nonpolar compounds in addition to diols **22** and **23**, with **22** being the major product. The relatively nonpolar side products were not identified, however, it was very likely that they were composed of unreacted and polymerized methacrolein since they were gelatinous and exhibited odors very similar to that of methacrolein. This was not surprising since methacrolein was used in excess (2.5 equiv.). It was also not surprising that undesired diol **23** was produced since the methyl proton is quite acidic ( $pK_a \approx 41$ ).



**Scheme 4**

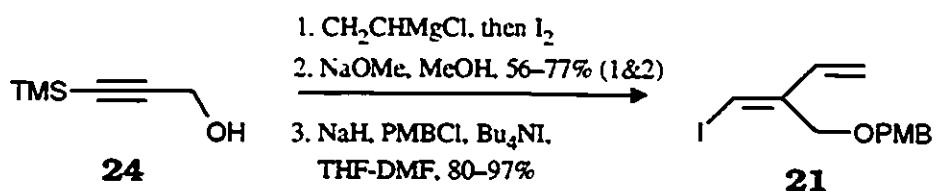
Isolation of the desired product proved to be quite tedious. Attempts to purify the product *via* distillation resulted in decomposition. Purification of the crude by crystallization was not possible because diol **22** did not

crystallize from the crude product mixture, although it was a solid in its pure form. It was found that crystallization occurred only after some of the less polar contaminants had been removed. Consequently, the only workable method for purification was column chromatography. However, there were apparent inconveniences associated with this method. A TLC of the crude mixture revealed that the diols produced were very polar and their  $R_f$  values were very close to each other, with **22** being slightly less polar than **23**. Furthermore, many contaminant spots were found on top of the product spot. Normal chromatographic techniques, whereby the desired solvent system is chosen such that the desired product elutes at an  $R_f$  value between 0.2–0.3, did not work well in this case. Using such a solvent system resulted in poor separation of the two diols due to similar  $R_f$  values. To acquire better separation, a differential solvent system had to be used. Therefore, the crude mixture was initially eluted with 10% ether in petroleum ether, and the polarity of the solvent system was increased incrementally to a final concentration of 60% ether in petroleum ether. This elution method was found to be quite effective since less polar contaminants eluted first and the diols separated sufficiently. It was also found that diol **23** was more difficult to remove from the column. The isolated yield of diol **22** was 55% and as there was no apparent use for diol **23**, no attempt was made to determine the actual yield of **23**.

### **2.1.3 Preparation of Diene 21**

Diene **21** was prepared independently in our laboratory.<sup>17</sup> This procedure allowed the stereoselective synthesis of diene **21** from propargyl alcohol **24** in three chemical steps. Propargyl alcohol **24** was first treated with vinylmagnesium chloride (2.5 equiv.), followed by iodine (1.5 equiv.) in

tetrahydrofuran to afford the desired *Z*-diene derivative. Desilylation of crude product by treatment with sodium methoxide (3.4 equiv.) in methanol resulted in a labile allylic alcohol. The latter was then protected as a *p*-methoxybenzyl ether **21**, which was preferably used immediately after purification. Diene **21** was synthesized in a 45–75% overall yield in three steps.



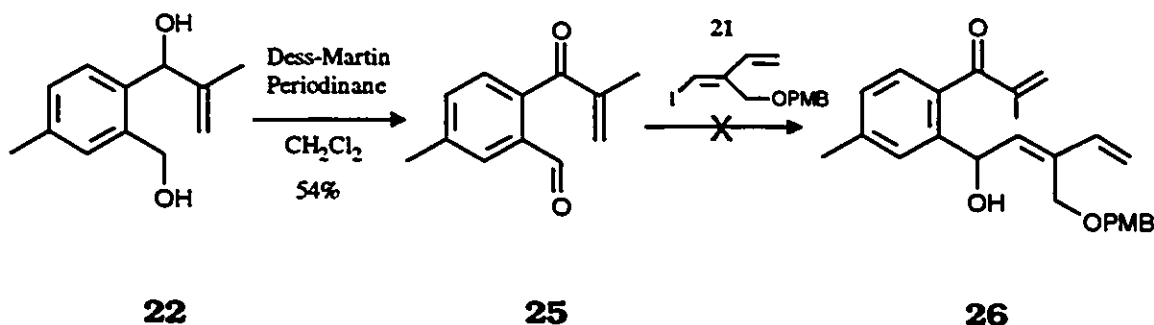
**Scheme 5**

#### 2.1.4 Attachment of the Diene Moiety

After successfully attaching the dienophile segment to the 3-methyl benzyl alcohol (**19**), the attachment of the diene moiety to diol **22** was examined. It was reasoned that if diol **22** was oxidized to form the ketoaldehyde **25**, attachment of the diene segment could be achieved *via* condensation with a vinyl anion. A mild oxidant had to be used to avoid undesirable oxidation of the terminal double bond of ketoaldehyde **25**. Manganese dioxide is a mild oxidant capable of oxidizing allylic and benzylic alcohols, thus it was believed to be an ideal oxidant. However, an overnight treatment of **22** with excess manganese dioxide in dichloromethane resulted in an extremely low yield of the oxidized product (less than 25% yield based on crude product mass). It was therefore necessary to find a more suitable oxidant for this system. Dess-Martin periodinane<sup>19</sup>, also a very mild

oxidant, was tested next. Treatment of **22** with 2.8 equivalents of Dess-Martin periodinane afforded **25** in 54% yield within 10 minutes.

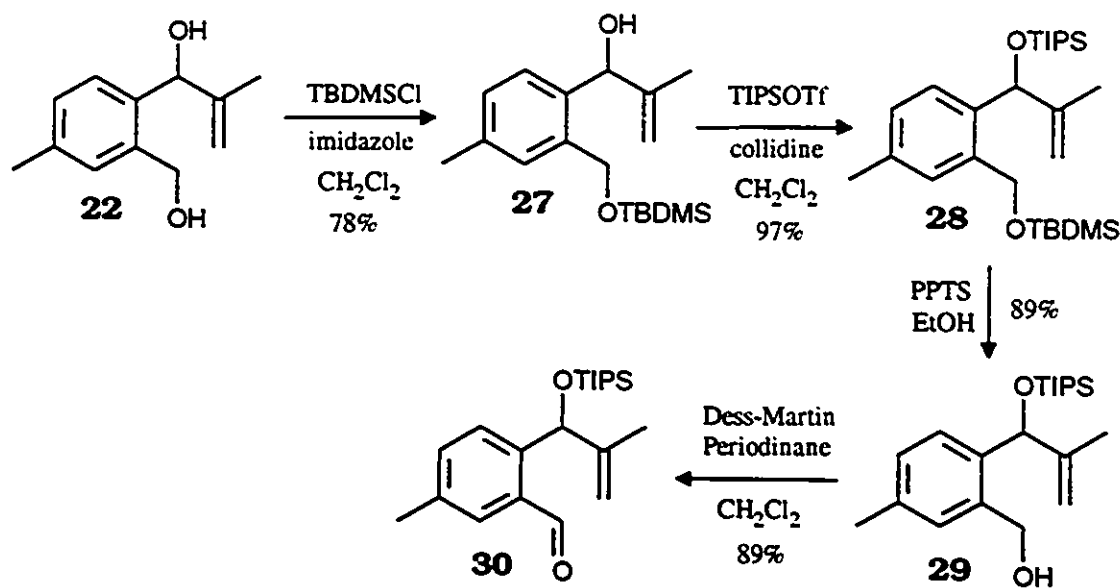
Attachment of the diene segment to ketoaldehyde **25** proved to be much more complicated than anticipated. Attempts to form the adduct **26** via a Grignard-type addition of vinyl iodide **21** to ketoaldehyde **25** with the aid of *sec*-butyllithium<sup>20</sup> or chromium dichloride and catalytic amounts of nickel dichloride<sup>21</sup> met with failure. The reactions would either not proceed or very complex mixtures were produced. This may have been due to competition between the addition to the ketone in the dienophile and the addition to the aldehyde. Therefore, it was reasoned that the keto group must be protected before the diene moiety could be successfully added to the aldehyde.



**Scheme 6**

Aldehydes are more reactive than ketones, thus it would be extremely difficult to selectively protect the keto group while leaving the aldehyde untouched. As a result, a change in the synthetic strategy was made, starting from diol **22**. A sequence of protection and deprotection reactions were performed to acquire the desired aldehyde **30** (Scheme 7). First, the primary hydroxyl group of diol **22** was protected as a *tert*-butyldimethylsilyl

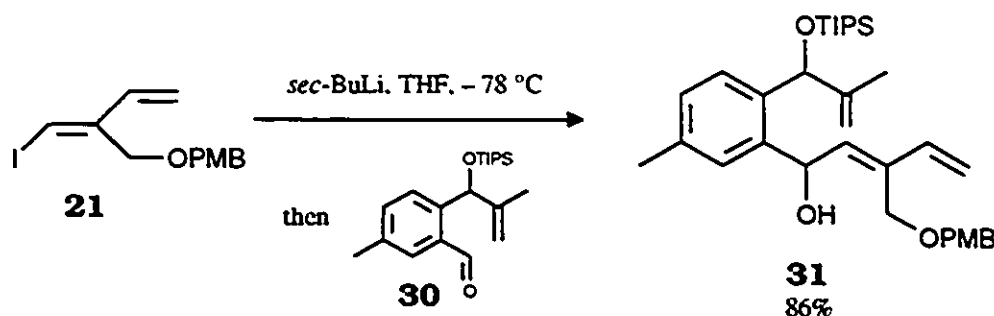
ether (**27**). Then, the remaining less reactive secondary alcohol was protected as a triisopropylsilyl ether (**28**). The desired aldehyde **30** was then obtained by selective desilylation and oxidation of the resulting alcohol with Dess-Martin periodinane. Using this 4-step reaction sequence, aldehyde **30** was produced in a 60% overall yield, starting from diol **22**.



**Scheme 7**

Aldehyde **30** was then ready for condensation with vinyl iodide **21**. As predicted, treatment of vinyl iodide **21** (1.6 equiv.) with *sec*-butyllithium (2.8 equiv.) followed by addition of aldehyde **30** proceeded without incident to afford the desired adduct **31** in 86% yield (Scheme 8). The yield of this reaction was greatly influenced by several factors. It was observed that the quality of the vinyl iodide **21** used was extremely important. Iodide **21** gradually decomposed under storage so the best yields for the condensation reaction were obtained when the vinyl iodide was freshly prepared. Extra care must also be taken to avoid prolonged exposure of compound **21** to

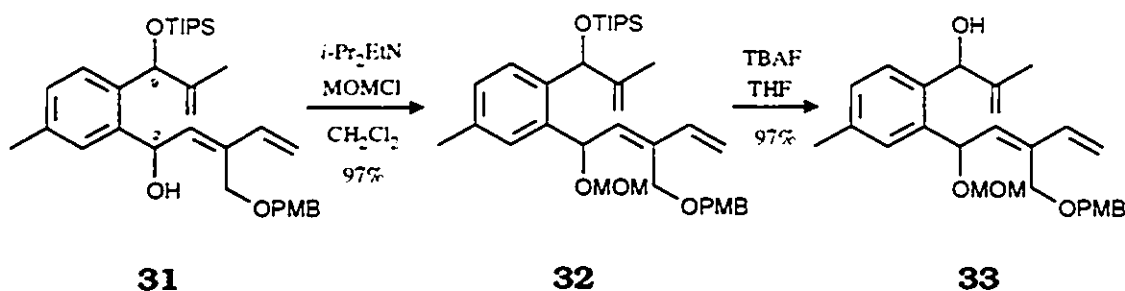
light and heat to minimize its decomposition. In addition, the yield was dependent on the reaction conditions employed. It was found that iodide **21** (0.3 g/mL tetrahydrofuran) must be transferred *via* cannula into a cold solution (-78 °C) of *sec*-butyllithium in tetrahydrofuran at a rate of 5 mL/min. Addition of aldehyde **30** must then follow within one minute after the addition of **21**.



**Scheme 8**

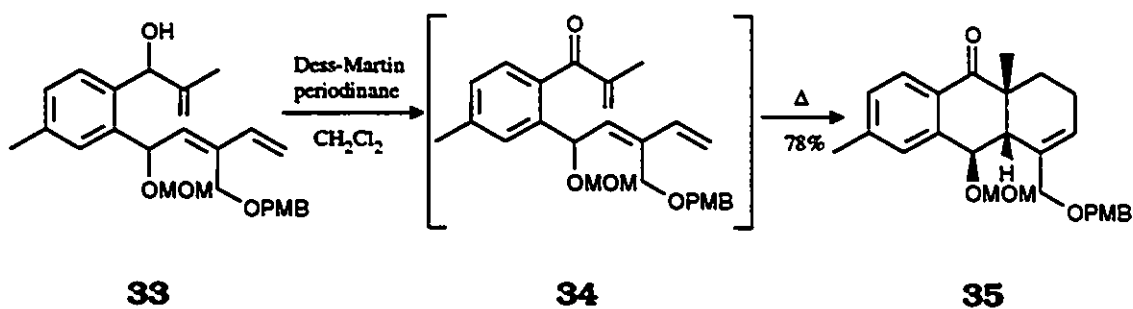
### 2.1.5 The Intramolecular Diels-Alder Reaction

Once the diene moiety had been successfully attached to the dienophile part, triene **31** was prepared for the intramolecular Diels-Alder reaction. To attain the Diels-Alder requirement of an electron-rich diene and electron-poor dienophile, the oxygen functionality at C2 must be retained as an alkoxy group while that at C9 must be oxidized to a carbonyl group. Therefore, the C2 hydroxyl group of compound **31** had to be protected prior to deprotection and oxidation of the C9 alcohol on the dienophile chain. Initially, the C2 hydroxyl group was protected with chloromethyl methyl ether (10 equiv.) to afford **32** (Scheme 9). Removal of the triisopropylsilyl group by treatment with tetrabutylammonium fluoride (5 equiv.) afforded the alcohol **33**. This protection-deprotection reaction sequence gave excellent yields (94% in two steps).



**Scheme 9**

Oxidation of **33** with Dess-Martin periodinane (1.5 equiv.) generated the desired Diels-Alder precursor **34**. The oxidation reaction was monitored by TLC. Two new products were detected in the mixture. These two products were less polar than the alcohol **33**, and so the reaction was terminated once starting material was consumed. Isolation of the two major products formed was attempted *via* column chromatography. It was, however, not possible to isolate the less polar compound since it had rearranged into the more polar product during solvent removal *in vacuo*, using a rotary evaporator with the water bath set at 40 °C. It was later observed that cyclization of the Diels-Alder precursor **34** readily occurred at around 40 °C (in boiling dichloromethane). As a result, only one major product was isolated after Dess-Martin oxidation and was identified as the cyclization product **35** (78%).



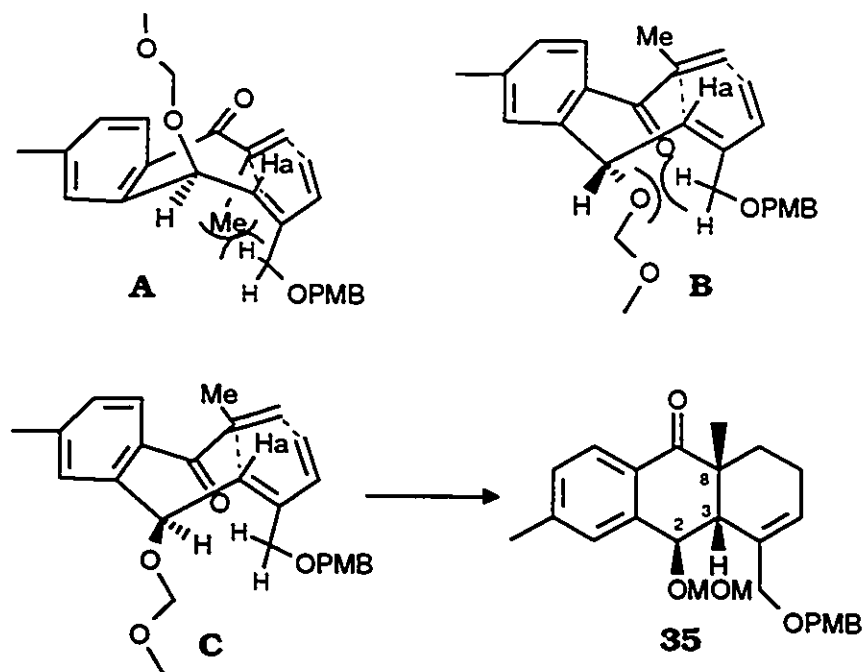
**Scheme 10**

The Diels-Alder precursor **34** could not be isolated easily, nor was this necessary. Thus, the oxidation of **33** by Dess-Martin periodinane was modified to ensure complete cyclization. This was accomplished by subjecting the reaction mixture to refluxing conditions (in dichloromethane) for about one hour, until the two product spots became one on TLC. Precursor **34** was most likely the less polar compound since heating the reaction mixture only increased the size of the more polar cyclized product spot. Furthermore, a splitting pattern typical of a mono-substituted terminal double bond (one doublet of doublets accompanied by two sets of doublets around 5-6 ppm) was observed in a  $^1\text{H}$  NMR of a mixture containing the two compounds.

#### **2.1.6 Characterization of the Cyclized Product**

Close examination of the structure of adduct **34** using molecular models indicated that the dienophile and diene moieties came into close proximity and were properly aligned for the cyclization to take place. The proposed transition states for the Diels-Alder cyclization reaction are represented in Figure 9. It can be seen that an *endo* transition state was favored since proper alignment of the double bonds in the *exo* approach (**A**) would result in steric interactions between the dienophile methyl group and the allylic *p*-methoxybenzyl ether moiety. Therefore, the methyl group on the dienophile and  $\text{H}_a$  on the diene must be pointing in the same direction to avoid this steric interaction (**B** and **C**). This criterion would, of course, lead to the formation of a *cis*-fused ring system. From the transition state, it could be seen that the presence of the methoxymethyl ether would also influence the facial stereochemistry of the cyclized product. To avoid steric interactions, the methoxymethyl ether chain would prefer to point away

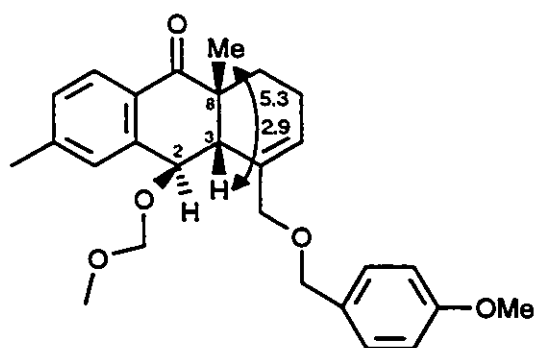
from the allylic *p*-methoxybenzyl ether moiety. This could be accomplished if the diene and dienophile moieties are aligned such that the methoxy-methyl ether is pointing in the same direction with Ha and the methyl group (C). In consideration of the factors mentioned, the cyclized product would have a *cis* relative stereochemistry with respect to C2, C3, and C8.



**Figure 9** Proposed Diels-Alder transition states: **A**, disfavored *exo*; **B**, disfavored *endo*; **C**, favored *endo*.

This predicted stereochemistry was confirmed by NOE experiments done on the cyclized product **35** (Figure 10). Irradiation of the C3 hydrogen resulted in a 4.5% and a 5.3% increase in the C2 proton signal and the C8 methyl proton signal, respectively. This experiment indicated that the newly formed rings were *cis*-fused; whereas, the relative stereochemistry at C2 was ambiguous since the dihedral angle between the two hydrogens (C2 and C3) is close to 90°. Therefore, to solve this problem, the C2 hydrogen and the C8 methyl group were irradiated. Both experiments resulted in signal

enhancement of the C3 proton. However, no signal enhancement of either the methyl group or the C2 hydrogen was observed. Thus, there was a possibility that the C2 hydrogen and the C8 methyl group were on opposite faces of the molecule, and the cycloadduct **35** was tentatively assigned a *cis* relative stereochemistry with respect to C2, C3, and C8. Also, the initial conclusion that the newly formed rings were *cis*-fused was reaffirmed by the observation that irradiation of the C8 methyl resulted in a 2.9% enhancement of the C3 proton signal. This tentative stereochemistry of compound **35** was later confirmed based on X-ray crystallographic study of a similar derivative (*cf.* Section 2.2.2 Benzyl Ether Series).



**Figure 10** Representative NOE enhancements for **35**.

## 2.2 Further Functionalization of the Tricyclic Ring System

Unfortunately, the stereochemistry at C2 and C3 of the cyclized product **35** was not the same as that required in the target analogue **8**. However, it was hoped that inversion of the oxygen functionality could be accomplished *via* a Mitsunobu reaction, and epimerization at C3 could be carried out if C2 is a carbonyl. It is not well known how important the stereochemistry at C2 and C3 was for the activity of Taxol<sup>®</sup> analogues; therefore, the problem of oxetane ring introduction was examined first. This

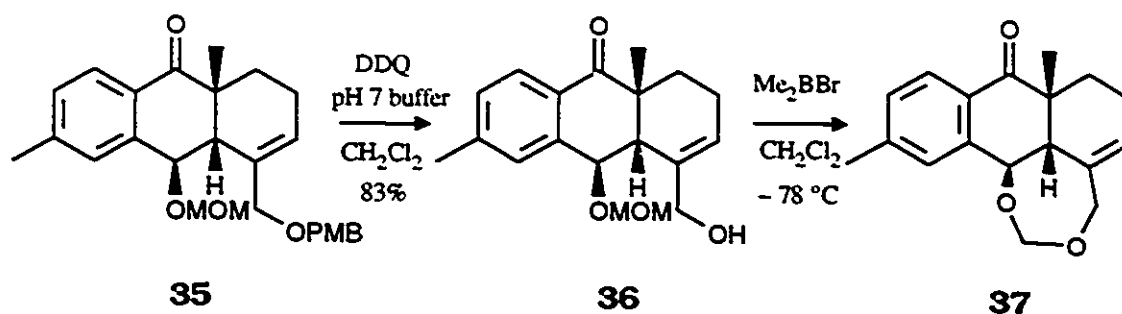
decision was motivated mainly by the desire to determine whether the "wrong" compound would exhibit any biological activity.

### 2.2.1 Epoxidation and Methoxymethyl Ether Cleavage Problem

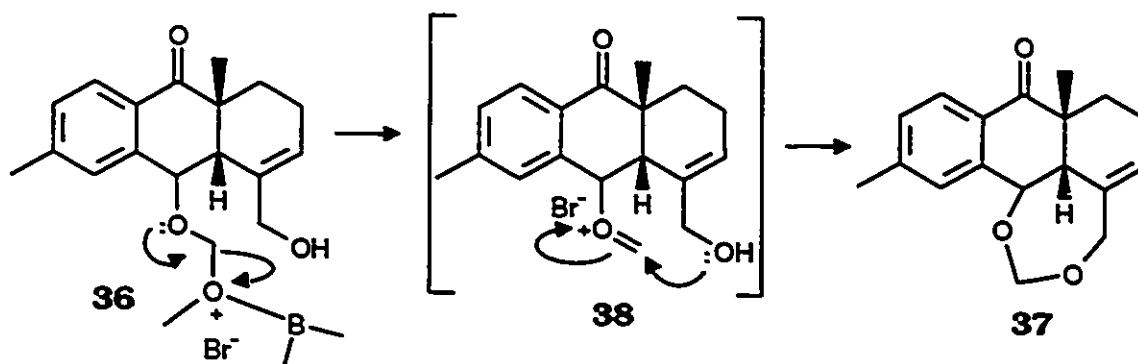
It was intended that the oxetane ring would be formed according to Berkowitz's procedure.<sup>22</sup> Thus, stereoselective epoxidation of the cyclized product **35** was required in order to generate the required  $\beta$ -epoxide. Compound **35** was bent in shape, so it was hoped that classical epoxidation by *m*-chloroperoxybenzoic acid would generate the desired  $\beta$ -epoxide. Unfortunately, the reaction proceeded sluggishly (24 h) and a 1:1 stereochemical mixture was obtained. Hydroxyl groups are known to direct the epoxidation in favoring the approach of the peroxide from the side of the double bond that is closest to the hydroxyl group.<sup>23</sup> Therefore, removal of the *p*-methoxybenzyl protecting group was performed by benzylic oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 2 equiv.) to afford allylic alcohol **36**. However, epoxidation of this allylic alcohol by *m*-chloroperoxybenzoic acid again resulted in a 1:1 isomeric mixture.

Attempts to perform a Sharpless asymmetric epoxidation on the allylic alcohol **36** were unsatisfactory (no reaction or decomposition). Therefore, it was reasoned that the required  $\beta$ -epoxide could be synthesized if the molecule was further bent by the presence of a carbonyl at C2. Thus, the removal of the methoxymethyl protecting group at C2 was attempted. However, micro-scale treatment of the allylic alcohol **36** with trifluoroacetic acid, bromodimethyl borane, or dilute hydrochloric acid resulted in very complex mixtures. In all cases, a much less polar compound was detected in the mixture (by TLC), and this was most prominent when the deprotection was performed using bromodimethyl borane. Finally, a

sufficient amount of a relatively pure product was isolated for  $^1\text{H}$  NMR analysis. Two  $\text{CH}_2\text{O}$  groups were still present while there was no methoxyl group in the new compound. Thus it was proposed that the cyclic acetal **37** was produced in the deprotection reaction. A proposed mechanism for the formation of this acetal is illustrated in Figure 11.



**Scheme 11**

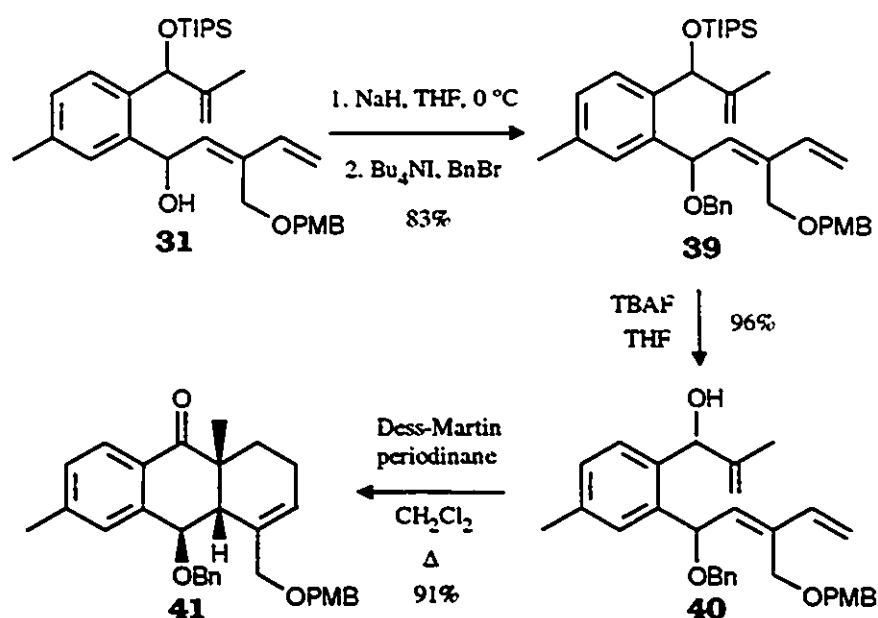


**Figure 11** Proposed mechanism for formation of **37**.

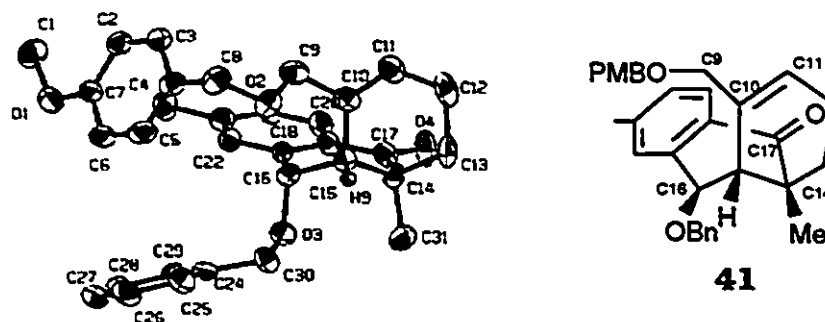
### 2.2.2 Benzyl Ether Series

The methoxymethyl protecting group proved to be quite difficult to remove, so an alternative protecting group at C2 was examined. Thus, the alcohol **31** was protected as a benzyl ether **39**. It was hoped that protection with a benzyl group might lead to a solid cyclized product. This could provide crystals where X-ray analysis could be performed to unambiguously

determine the stereochemistry of the Diels-Alder cyclo-addition product. The same sequence of reactions used for the synthesis of **35** was employed to generate cyclized product **41** (Scheme 12). As desired, benzyl ether **41** was crystalline and its X-ray structure was determined (Figure 12). The X-ray data obtained confirmed that the cyclized product was *cis* with respect to C2, C3, and C8, as previously predicted for cycloadduct **35** ( *cf.* Section 2.1.6 Characterization of the Cyclized Product).

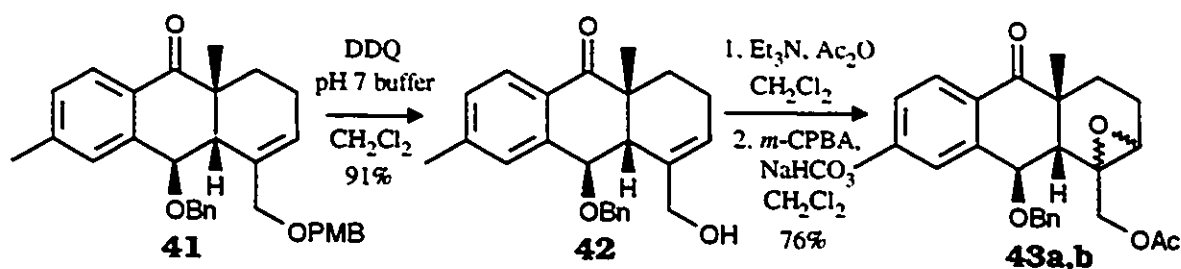


**Scheme 12**



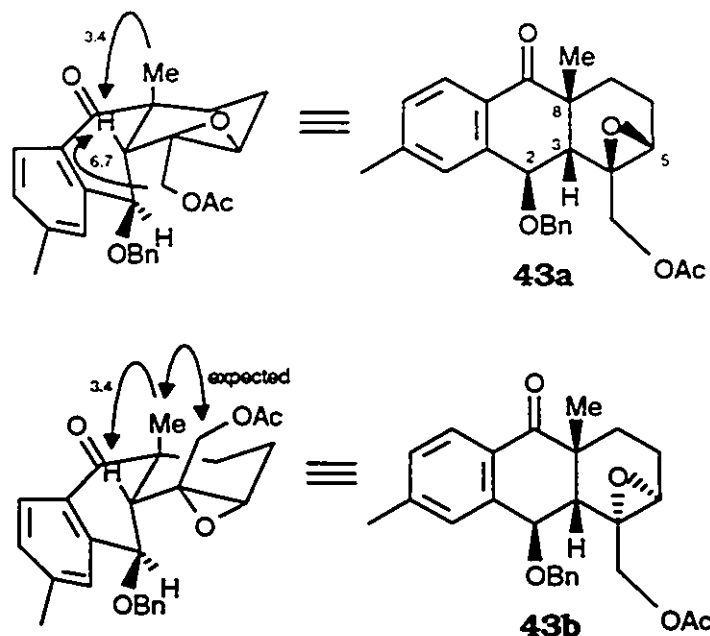
**Figure 12** X-ray structure of **41**.

At this stage of the research project, benzyl ether **41** was prepared independently and methods for removal of the benzyl group were examined.<sup>24</sup> Unfortunately, the benzyl group could not be removed ( $H_2/Pd-C$ , EtOAc;  $H_2/Pd-C$ , 1:1 EtOH/EtOAc). However, it was of interest to determine whether an epoxide derivative of **41** would possess any biological activity and so further chemical manipulation of **41** was carried out (Scheme 13). Again, epoxidation of the allylic alcohol **42** afforded epoxide **43a,b** as a 1:1 isomeric mixture.



**Scheme 13**

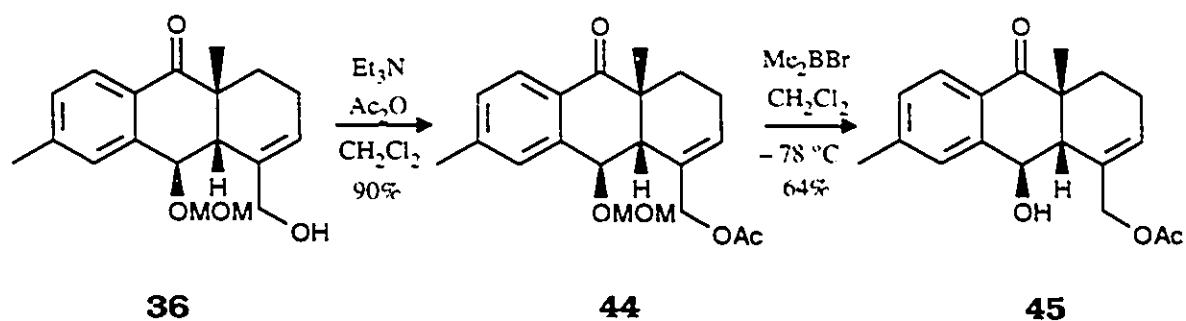
It was, however, possible to isolate one of the two isomers of **43a,b** by flash column chromatography, and this isomer was submitted for biological activity evaluation. Unfortunately, the test results indicated it was inactive. The stereochemistry of the isolated isomer was tentatively assigned based on NOE experiments which indicated that the epoxide was *cis* to the C8 methyl group (**43a**). As illustrated in Figure 13, a *trans* isomer (**43b**) would result in positioning the  $CH_2$  of the acetyloxymethyl group near the C8 methyl group. Irradiation of the former should result in proton signal enhancement of the latter and *vice versa*. The enhancements were not observed and so it was proposed that the isolated epoxide could possess the stereochemistry as drawn for **43a**.



**Figure 13** Representative NOE enhancements and predictions for **43a,b**.

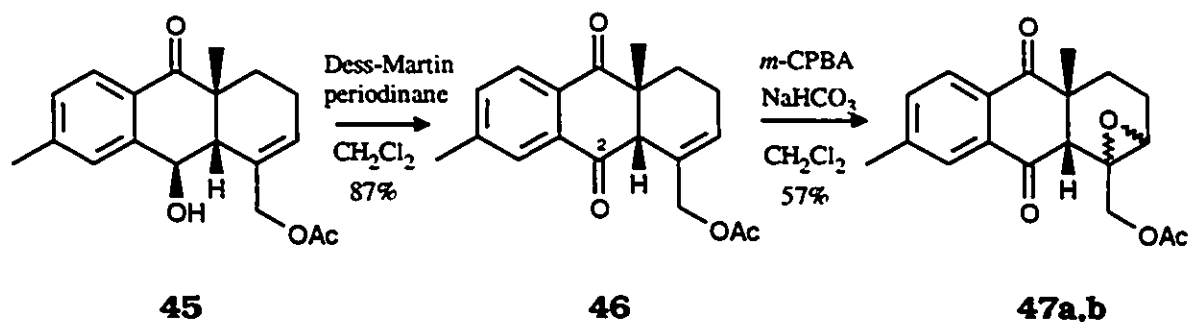
### 2.2.3 Cleavage of Methoxymethyl Ether

It was decided that the methoxymethyl group removal problem was worth further examination since removal of the benzyl protecting group was more difficult than previously anticipated. The cyclic acetalization that occurred in the methoxymethyl group cleavage was believed to be due to the presence of the unprotected allylic alcohol (Figure 11). To avoid this neighboring intervention of the primary allylic alcohol, the latter was protected as an ester. Thus, the acetate **44** was prepared in classical acetylation conditions. Then, removal of the methoxymethyl protecting group from the acetylated product **44** by bromodimethyl borane (8 equiv.) proceeded without incident to afford the desired secondary alcohol **45** in a 64% yield. This low chemical yield was probably due to some migration of the acetate group since another compound which was slightly more polar than the main product was detected in the crude mixture (by TLC).



**Scheme 14**

After removing the methoxymethyl protecting group successfully, oxidation of **45** by Dess-Martin periodinane was carried out to generate anthraquinone derivative **46**. This compound was submitted for biological activity evaluation; unfortunately, it was found to be inactive. Thus further elaboration of **46** was carried out; however, epoxidation by *m*-chloroperoxybenzoic acid proceeded without any stereoselectivity (Scheme 15) to produce **47** as a mixture of diastereomers (**47a** and **47b**).

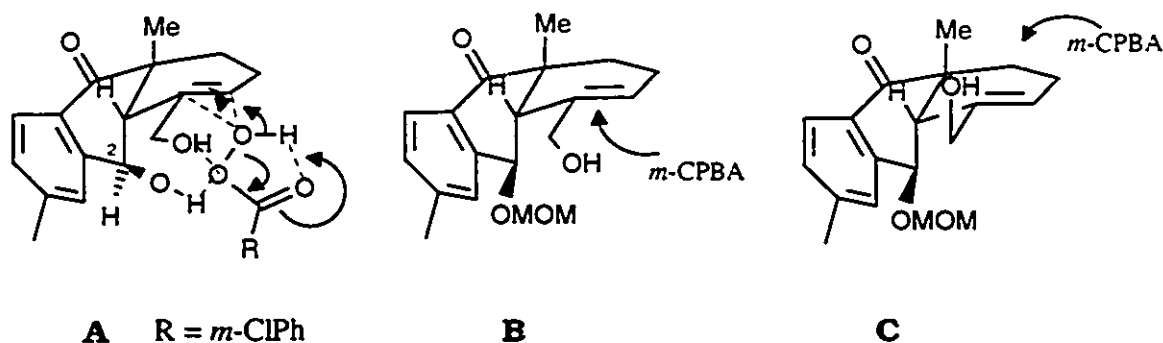


**Scheme 15**

#### 2.2.4 Stereoselective Epoxidation

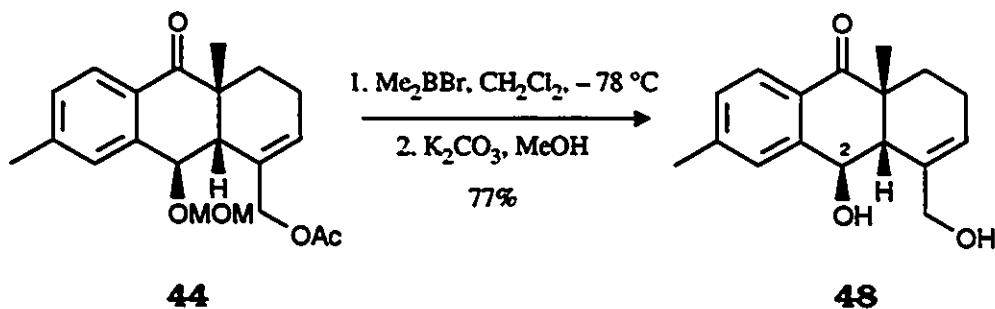
Epoxidations performed thus far were not carried out on a substrate containing a free alcohol at C2. It was thought that such a compound should be examined since there is a possibility that the hydroxyl group is close enough to the double bond to direct a stereoselective epoxidation

(Figure 14, **A**). It is reasonable that no directing effect by the allylic alcohol was observed previously (epoxidation of **36**) because the allylic hydroxyl group is free to rotate as illustrated for **B** and **C** (Figure 14).



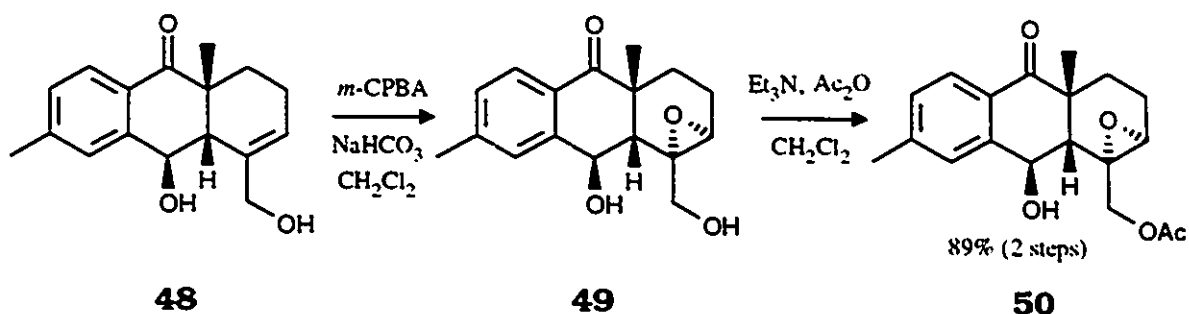
**Figure 14** Proposed transition state for epoxidation with *m*-chloroperoxybenzoic acid.

To test this hypothesis, removal of the acetyl protecting group after the demethoxymethylation of **44** was carried out to generate diol **48**. This deacetylation step was also desirable since the acetate migration byproduct would also be converted to the diol. Diol **48** was then used as a substrate in the *m*-chloroperoxybenzoic acid epoxidation reaction. As predicted, the free alcohol at C2 did play a role in directing the facial selective epoxidation of **48** since only one isomer was obtained. Based on the proposed mechanism for epoxidation (Figure 14), the epoxide generated should be *trans* to the C3 hydrogen and C8 methyl group.



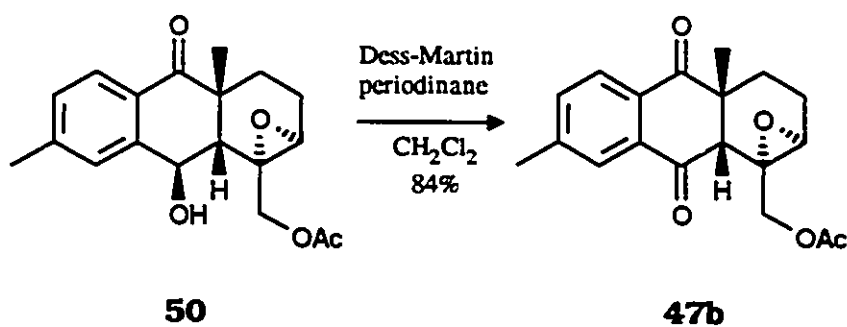
**Scheme 16**

Epoxidation of **48** proceeded cleanly, so the acetylation step was performed without prior purification of epoxide **49**. Only a slight excess (1.05 equiv.) of acetic anhydride and triethylamine was used in order to avoid undesirable acetylation at the less reactive C2 hydroxyl group. The acetylation reaction did not go to completion because this low excess (1.05 equiv.) of reagents was used. A TLC of the reaction mixture indicated that some diacetylated product was formed and so the reaction was terminated.



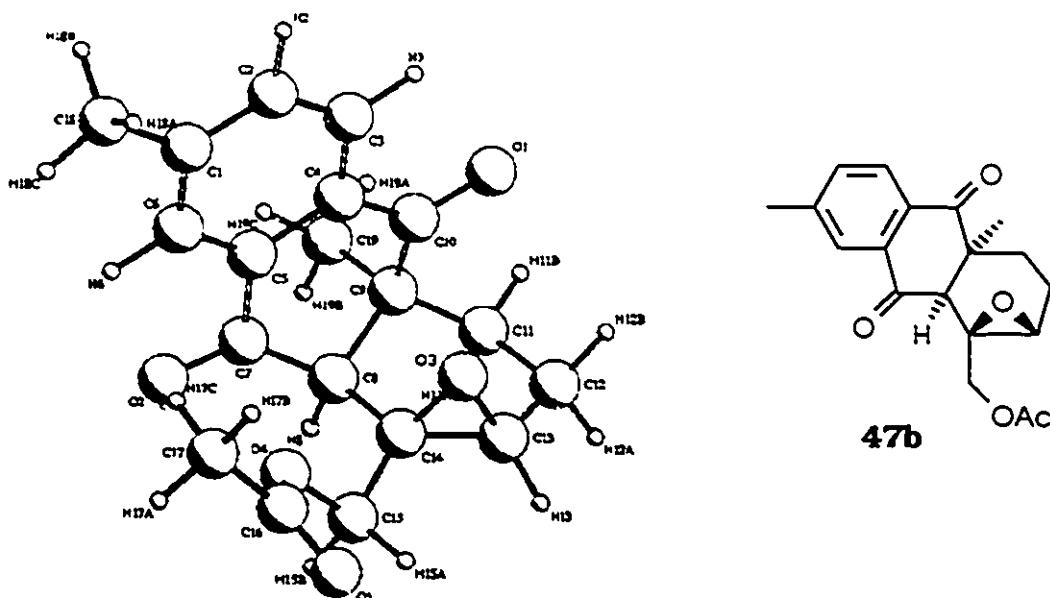
**Scheme 17**

Epoxide **50** was then oxidized with Dess-Martin periodinane to obtain anthraquinone derivative **47b**. This transformation was performed since it was intended that anthraquinone derivatives could possess interesting biological activity, according to precedents.<sup>25</sup>



**Scheme 18**

To our delight, **47b** was a solid and it was possible to grow crystals suitable for X-ray crystallography to unambiguously determine its stereochemistry (Figure 15). The X-ray data confirmed that the epoxide in **47b** was *trans* to the C3 hydrogen and C8 methyl group as predicted by mechanistic considerations of the epoxidation reaction (Figure 14).



**Figure 15** X-ray structure of epoxide **47b**.

### 3 Conclusions

The main objective of this research project was to synthesize substituted anthraquinone systems, having similar structures to that of the target Taxol<sup>®</sup> analogue **8**, via a cycloaddition approach. Anthraquinone systems similar to **46** were successfully synthesized via intramolecular Diels-Alder cyclization. The required Diels-Alder precursor **34** could be assembled from much simpler starting materials (**19**, **20**, and **21**).

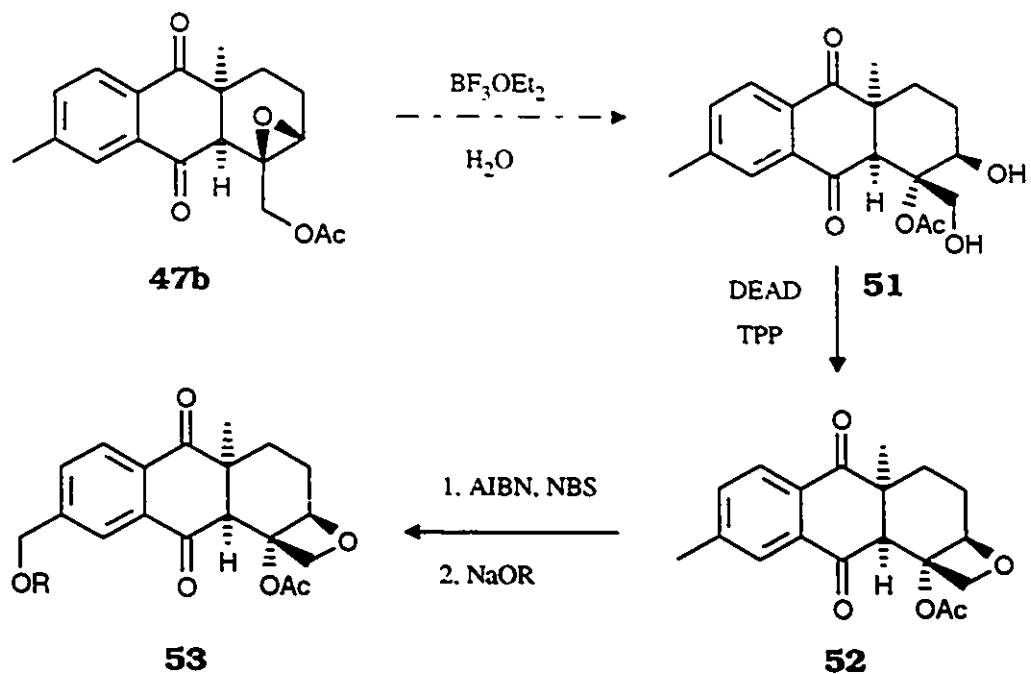
The use of the literature protocol for *ortho*-lithiation of benzyl alcohol<sup>18</sup> was successfully extended to the 3-methyl benzyl alcohol (**19**). Lithiation of the aromatic ring occurred preferably at C6 (*ortho*, *para* rather than *ortho*, *ortho* to the oxymethyl and methyl substituents, respectively), most likely due to steric factors. Although lithiation also occurred at the methyl substituent, the protocol could be used for attachment of the dienophile moiety in the synthesis of the Diels-Alder precursor. Diene moiety attachment via Grignard-type addition reactions could not be done on the ketoaldehyde **25**; however, the same conditions were successfully employed for the attachment of the diene segment to substrate **30**.

The readily synthesized Diels-Alder precursor underwent cyclization when subjected to a slight increase in temperature (about 40 °C). The newly formed rings were *cis*-fused, resulting from an *endo* transition state. The ease of this cyclization is a consequence of the benzene group in the tether which holds the reactive components in a geometry resembling that required for the transition state. The epoxidation of the C ring double bond proceeded much more slowly and required more reagents when the allylic oxygen functionality was an ether. Facial selective epoxidation of the ring C

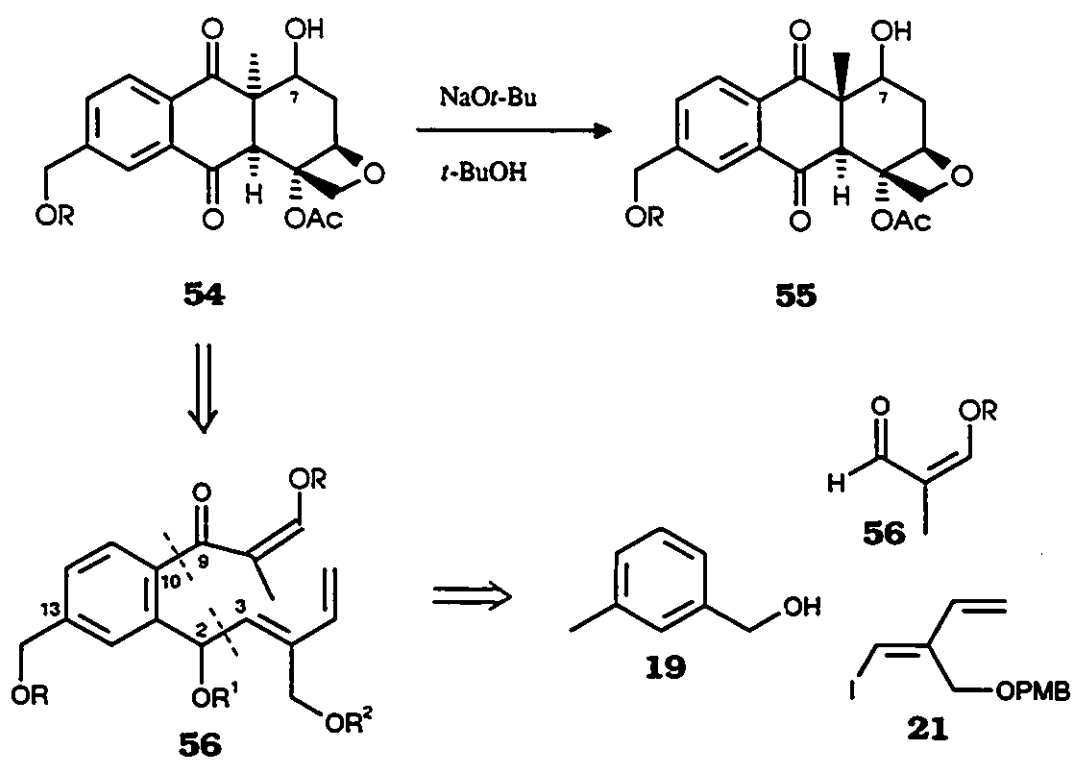
double bond was achieved when both the oxygen functionalities on the southern part of the ring system were unprotected. Removal of the methoxymethyl protecting group at C2 by bromodimethyl borane to generate diol **48** could be achieved only when the allylic alcohol was protected as an acetate ester. The stereochemistry of the ring systems synthesized were based on NOE experiments and on the X-ray structure of compounds **41** and **47b**. Finally, compounds **43a** and **46** were submitted for biological activity evaluation and were found to be inactive.

### **3. 1 Future Studies**

Tricyclic systems **43** and **46** were biologically inactive; however, this does not imply that the proposed tricyclic analogues **7**, **8**, and **9** are themselves inactive. Additional work is required to examine means for the attachment of the Taxol<sup>®</sup> C13 side chain and the introduction of the oxetane ring. Introduction of the oxetane functionality could be attained by treatment of epoxide **47b** according to Berkowitz's procedure for oxetane ring formation (Scheme 19).<sup>22</sup> This work is presently being carried out in our laboratory.<sup>24</sup> Compound **52** has been prepared and the stereochemistry will be established by X-ray analysis. Unfortunately, initial attempts to oxidize and/or brominate the methyl group at C13 have proven challenging. However, attachment of the Taxol<sup>®</sup> side chain should be possible once the benzyl methyl group at C13 is functionalized. It would be interesting to determine the biological activity of anthraquinone derivative **53** since it possesses a different C8 stereochemistry as compared to that of Taxol<sup>®</sup>. Epimerization at C8 should be possible if there is an oxygen functionality at C7 (Scheme 20). It should be possible to synthesize the required compound **54** from the Diels-Alder precursor **56**.



**Scheme 19**



**Scheme 20**

## 4 Experimental Section

### General Procedures and Instrumentation

Infrared (IR) spectra were recorded on a Bomem Michelson 100 FTIR spectrometer (in KBr, CH<sub>2</sub>Cl<sub>2</sub>, or neat) and the data are reported in reciprocal centimetres (cm<sup>-1</sup>). All NMR spectra were measured in CDCl<sub>3</sub> relative to an internal lock on the deuterium in CDCl<sub>3</sub>. <sup>1</sup>H NMR (200 or 500 MHz) and <sup>13</sup>C NMR (50.3 or 125.8 MHz) spectra were run on a Varian Gemini or Bruker WM500 spectrometer, respectively. All NMR data are reported in parts per million (ppm) on the δ-scale. <sup>1</sup>H NMR data are reported as follows: chemical shift, multiplicity, integration, and coupling constants (Hz). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. High resolution mass spectroscopy was performed on a Kratos Concept-IIA mass spectrometer at 70 eV ionizing energy. Elemental analyses were performed at M-H-W Laboratories, Phoenix, Arizona, or were performed in house on a Perkin Elmer<sup>xl</sup>.

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 employed in handling air and moisture sensitive materials. Reactions were monitored by TLC using commercial aluminum-backed silica gel plates (E. Merck, type 5554). TLC spots were viewed under ultraviolet light and 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 were performed with 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.

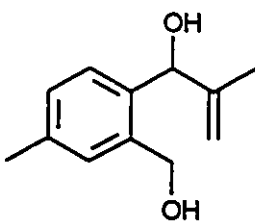
Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30–60 °C and ether refers to diethyl ether. Tetrahydrofuran and ether were freshly distilled from potassium and benzophenone ketyls, respectively. Dichloromethane, triethylamine and diisopropylethylamine were distilled from calcium hydride. *N,N,N,N*-tetramethylethylenediamine was distilled from potassium hydroxide. Pentane was stored on 4Å molecular sieves for at least 24 hours prior to use. All other chemicals were used as supplied without prior purification. Dess-Martin periodinane was prepared according to the procedures described by Dess and Martin<sup>19a</sup> and by Ireland and Liu<sup>19b</sup> (Appendix).

#### **General Procedure for Dess-Martin Oxidation Reaction**

Dess-Martin periodinane (1.5 equiv.) was added to a stirred solution of alcohol in dichloromethane (0.05–0.15 M) and the reaction mixture was stirred at room temperature until no more starting material was detected by TLC (5–30 minutes). Saturated sodium bicarbonate solution (5–50 mL), sodium thiosulfate (2–15 g), and ether (5–50 mL) were added and the mixture stirred for 20 minutes further. (Either saturated sodium thiosulfate solution or sodium thiosulfate salt can be used, and sufficient amounts must be added to obtain a clear aqueous layer or else difficult workups will result.) The layers were separated and the aqueous phase extracted with

ether (3x25 mL). The combined organic fractions were washed once with 20% sodium thiosulfate solution (20 mL), once with 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 *in vacuo*.

**2-Hydroxymethyl-1-(1-hydroxy-2-methyl-2-propenyl)-4-methylbenzene  
(22)**



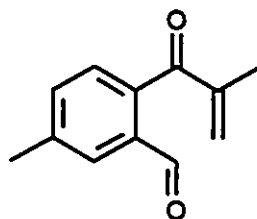
A modified version of the general procedure for *ortho*-lithiation of substituted aromatic rings<sup>18</sup> was employed. To a cooled, flame-dried three-necked round bottomed flask (500 mL), equipped with a magnetic stir bar and a water condenser, was added di-*n*-pentane (100 mL), 3-methyl benzyl alcohol (4.6 g, 37 mmol), and *N,N,N,N*-tetramethylethylenediamine (8.7 g, 75 mmol). The resulting clear mixture was stirred vigorously while one half of the *n*-butyllithium (34.7 mL, 2.16 M, 75 mmol) was cautiously added dropwise to avoid coagulation. White gel-like precipitates formed as the mixture began to reflux. The remaining half of the *n*-butyllithium was then introduced rapidly and the red-brown mixture was refluxed (~36 °C) overnight.<sup>†</sup> The reaction mixture was then cooled to -78 °C and methacrolein (6.6 g, 94 mmol), which has been passed through a plug of basic alumina, was introduced all at once. The mixture was stirred for

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<sup>†</sup> Circulation of ice water through the water condenser by a pump is required during the summer.

15 minutes at  $-78\text{ }^{\circ}\text{C}$  and then allowed to warm to room temperature. Saturated sodium bicarbonate solution (50 mL) was added slowly. The layers were separated and the aqueous phase extracted with ether (3x50 mL). The combined organic fractions were washed once with water (50 mL) and once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the viscous crude oil by flash column chromatography (350 g silica gel, 1:9 ether/petroleum ether then gradually increased to 3:2 ether/petroleum ether) afforded 4.0 g (55%) of diol **22** as a white solid (mp  $85.0\text{--}85.5\text{ }^{\circ}\text{C}$ ). IR (KBr): 3334 (br), 3070, 1646, 1026, 887  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.56 (s, 3H), 2.30 (s, 3H), 3.91–4.23 (br s, 2H), 4.50 (d, 1H,  $J = 12.1\text{ Hz}$ ), 4.56 (d, 1H,  $J = 12.1\text{ Hz}$ ), 4.99–5.00 (m, 1H), 5.09 (br s, 1H), 5.18–5.19 (m, 1H), 7.06 (d, 1H,  $J = 7.4\text{ Hz}$ ), 7.07 (s, 1H), 7.17 (d, 1H,  $J = 8.4\text{ Hz}$ );  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.7, 20.9, 63.2, 74.6, 77.0, 110.7, 128.4, 128.9, 130.8, 137.2, 137.8, 138.8, 145.6; HRMS exact mass calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}$  ( $\text{M}^+ - \text{H}_2\text{O}$ ) 174.1045, found 174.1034.

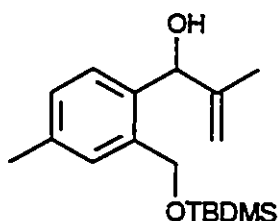
**5-Methyl-2-(2-methyl-1-oxo-2-propenyl)benzenecarboxaldehyde (25)**



The general protocol for Dess-Martin oxidation was followed using benzyl alcohol **22** (2.8 g, 15 mmol) and Dess-Martin periodinane (17.3 g, 49 mmol) in dichloromethane (150 mL). The reaction was completed in 10 minutes and purification of the crude product (150 g silica gel, 3:7 ether/petroleum ether) afforded 1.5 g (54%) of ketoaldehyde **25** as a

yellowish oil:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.06 (s, 3H), 2.43 (s, 3H), 5.41 (br s, 1H), 5.88 (br s, 1H), 7.29 (d, 1H,  $J = 8.0$  Hz), 7.41 (br d, 1H,  $J = 8.0$  Hz), 7.69 (br s, 1H), 9.91 (s, 1H). Product decomposed during storage. Additional material was not synthesized since there was no apparent need for it.

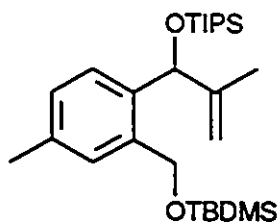
**2-(*t*-Butyldimethylsilyloxy)methyl-1-(1-hydroxy-2-methyl-2-propenyl)-4-methylbenzene (27)**



To a stirred solution of diol **22** (4.0 g, 21 mmol) in dichloromethane (50 mL), was added imidazole (2.8 g, 42 mmol) and *tert*-butyldimethylsilyl chloride (3.7 g, 25 mmol). After stirring at room temperature for 3 minutes, the reaction was quenched with saturated sodium bicarbonate solution (25 mL) and the layers were separated. The aqueous layer was extracted with ether (3x25 mL) and the combined organic fractions were washed once with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (250 g silica gel, 1:9 ether/petroleum ether) to afford 4.9 g (78%) of alcohol **27** as a slightly yellow, viscous oil: IR (neat): 3380 (br), 1652, 1254, 1059, 897  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.13 (s, 6H), 0.93 (s, 9H), 1.60 (s, 3H), 2.34 (s, 3H), 3.52 (d, 1H,  $J = 5.1$  Hz), 4.77 (s, 2H), 5.02–5.07 (m, 1H), 5.20 (br d, 1H,  $J = 4.8$  Hz), 5.26–5.30 (m, 1H), 7.10 (d, 1H,  $J = 7.6$  Hz), 7.13 (br s, 1H), 7.26 (d, 1H,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.3, 18.2, 19.8, 21.0, 25.9, 54.0, 74.7, 110.8, 127.9, 128.6, 129.6.

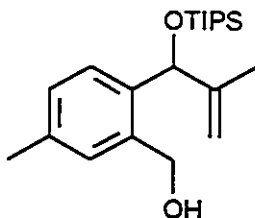
137.3 (2x), 138.2, 145.4: HRMS exact mass calcd. for  $C_{14}H_{21}O_2Si$  ( $M^+ - t\text{-Bu}$ ) 249.1311, found 249.1326.

**2-(*t*-Butyldimethylsilyloxy)methyl-4-methyl-1-(1-triisopropylsilyloxy-2-methyl-2-propenyl)benzene (28)**



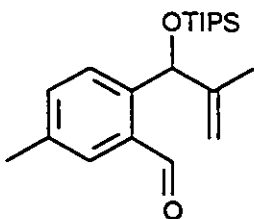
To a stirred solution of alcohol **27** (4.7 g, 16 mmol) in dichloromethane (30 mL) was added 2,4,6-collidine (4.5 g, 37 mmol) and triisopropylsilyl triflate (5.7 g, 19 mmol). After 15 minutes, the reaction was quenched with saturated sodium bicarbonate solution (25 mL) and the layers were separated. The aqueous layer was extracted with ether (3x30 mL) and the combined organic fractions were washed once with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Column chromatography (75 g silica gel, petroleum ether) afforded 7.0 g (97%) of protected diol **28** as a colorless oil: IR (neat): 1650, 1252, 1085, 884  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.08–1.12 (m, 30H), 1.51 (s, 3H), 2.32 (s, 3H), 4.71 (d, 1H,  $J = 14$  Hz), 4.84 (s, 1H), 4.86 (d, 1H,  $J = 14$  Hz), 5.09–5.13 (m, 1H), 5.24–5.28 (m, 1H), 7.01 (br d, 1H,  $J = 7.8$  Hz), 7.29 (br s, 1H), 7.35 (d, 1H,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  -5.3, 12.3, 17.7, 18.0 (2x), 18.5, 21.3, 26.0, 62.0, 76.0, 110.8, 126.7, 126.9, 127.2, 136.0, 136.5, 137.9, 146.3.

**2-Hydroxymethyl-4-methyl-1-(1-triisopropylsilyloxy-2-methyl-2-propenyl)benzene (29)**



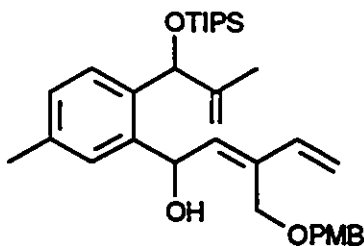
To a stirred solution of protected diol **28** (7.0 g, 15 mmol) in 99% ethanol (100 mL) was added pyridinium *p*-toluenesulfonate (1.9 g, 7.5 mmol) and the mixture was allowed to stir at room temperature overnight. Ethanol was then removed *in vacuo* and the crude oil was dissolved in dichloromethane (50 mL) and washed once with brine (15 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (250 g silica gel, 1:9 ether/petroleum ether) afforded 4.7 g (89%) of benzyl alcohol **29** as a slightly yellow oil: IR (neat): 3355 (br), 1650, 1059, 889  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.83–1.15 (m, 21H), 1.51 (s, 3H), 2.31 (s, 3H), 2.82–2.90 (m, 1H), 4.53 (dd, 1H,  $J = 12.6, 8.6$  Hz), 4.82 (dd, 1H,  $J = 12.6, 4.3$  Hz), 4.91–4.95 (br m, 1H), 5.29 (br s, 1H), 5.31–5.35 (br m, 1H), 7.05 (br d, 1H,  $J = 7.8$  Hz), 7.13 (br s, 1H), 7.30 (d, 1H,  $J = 7.8$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.2, 17.9, 18.0, 18.6, 21.0, 62.9, 77.9, 110.6, 127.9, 129.0, 130.3, 137.2, 137.4, 138.4, 146.4; HRMS exact mass calcd. for  $\text{C}_{18}\text{H}_{29}\text{O}_2\text{Si}$  ( $\text{M}^+ - i\text{-Pr}$ ) 305.1937, found 305.1957.

**5-Methyl-2-(1-triisopropylsilyloxy-2-methyl-2-propenyl)benzenecarboxaldehyde (30)**



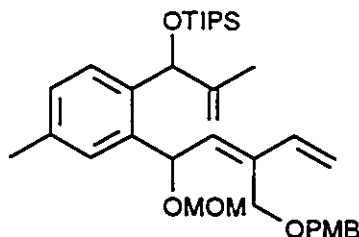
The general protocol for Dess-Martin oxidation was followed using benzyl alcohol **29** (4.5 g, 13 mmol) and Dess-Martin periodinane (9.6 g, 23 mmol) in dichloromethane (100 mL). The reaction was completed in 5 minutes and purification of the crude product (250 g silica gel, 1:19 ether/petroleum ether) afforded 3.9 g (89%) of aldehyde **30** as a yellowish oil: IR (neat): 1696, 1609, 1081, 883  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.85–1.13 (m, 21H), 1.53 (s, 3H), 2.36 (s, 3H), 4.80–4.84 (br m, 1H), 5.26–5.30 (br m, 1H), 5.93 (br s, 1H), 7.31 (br dd, 1H,  $J = 7.8, 1.4$  Hz), 7.51 (d, 1H,  $J = 7.9$  Hz), 7.61 (br d, 1H,  $J = 1.6$  Hz), 10.42 (s, 1H);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.1, 17.8, 17.9, 18.2, 20.8, 74.7, 110.6, 128.5, 131.2, 133.2, 134.0, 137.2, 143.1, 147.3, 192.9; HRMS exact mass calcd. for  $\text{C}_{18}\text{H}_{27}\text{O}_2\text{Si}$  303.1780, found 303.1787.

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



To a round bottomed flask was added tetrahydrofuran (75 mL) and *sec*-butyllithium (18.7 mL, 1.3 M, 25 mmol). This resulting bright yellow solution was maintained at  $-78\text{ }^{\circ}\text{C}$  for 15 minutes. Vinyl iodide **21** (4.6 g, 14 mmol) in tetrahydrofuran (15 mL) was then introduced *via* cannula over a period of no more than three minutes to yield a yellow-brown solution. Aldehyde **30** (3.0 g, 8.7 mmol) in tetrahydrofuran (15 mL) was introduced dropwise *via* cannula within one minute after the vinyl iodide addition. The resulting pale yellow solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for an additional 15 minutes, then allowed to warm up to room temperature. The reaction was carefully quenched with a few drops of water. Water (50 mL) and ether (50 mL) were added and the layers were separated. The aqueous layer was extracted with ether (3x50 mL), and the combined organic phase was washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification using flash column chromatography (200 g silica gel, 1:4 ether/petroleum ether) afforded 4.8 g (86%) of alcohol **31** as a light yellow, viscous oil: IR (neat): 3428 (br), 1647, 1248, 1061, 894  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.88–1.12 (m, 21H), 1.52 (s, 3H), 2.31 (s, 3H), 3.47 (s, 1H), 3.78 (s, 3H), 4.17 (d, 1H,  $J = 11.3\text{ Hz}$ ), 4.26 (d, 1H,  $J = 11.3\text{ Hz}$ ), 4.39 (br s, 1H), 4.87–4.91 (br s, 1H), 5.11 (d, 1H,  $J = 11.3\text{ Hz}$ ), 5.20–5.23 (br s, 1H), 5.24 (br s, 1H), 5.35 (d, 1H,  $J = 17.4\text{ Hz}$ ), 5.93–6.04 (m, 2H), 6.33 (dd, 1H,  $J = 17.4, 11.2\text{ Hz}$ ), 6.80–6.88 (m, 2H), 7.02–7.04 (m, 1H), 7.17–7.24 (m, 2H), 7.32 (br s, 1H), 7.35 (d, 1H,  $J = 7.6\text{ Hz}$ );  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.2, 17.9, 18.0, 18.3, 21.2, 55.2, 64.6, 65.1, 72.1, 77.2, 111.0, 113.8, 114.3, 127.0, 127.8, 128.5, 129.5, 129.9, 136.1, 136.8, 137.5, 137.6, 138.1, 140.5, 146.5, 159.2.

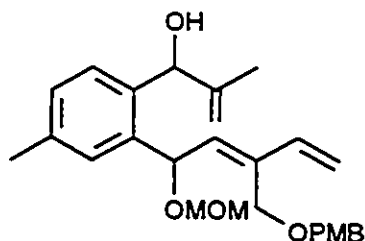
**2-[3-(*p*-Methoxybenzyloxy)methyl-1-methoxymethyloxy-2,4-pentadienyl]-4-methyl-1-(1-triisopropylsilyloxy-2-methyl-2-propenyl)benzene (32)**



To a stirred solution of alcohol **31** (4.4 g, 7.9 mmol) in dichloromethane (50 mL) at 0 °C was added dropwise diisopropylethylamine (15.4 g, 119 mmol) and chloromethyl methyl ether (6.4 g, 79 mmol). The resulting mixture was warmed to room temperature and stirred overnight. Saturated sodium bicarbonate solution (50 mL) was then added and the layers separated. The aqueous layer was extracted with ether (3x30 mL) and the combined organic fractions were washed once with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (250 g silica gel, 1:9 ether/petroleum ether) afforded 4.6 g (97%) of triene **32** as a clear, yellowish oil: IR (neat): 1647, 1249, 1059, 896  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.81–1.05 (m, 21H), 1.58 (s, 3H), 2.34 (s, 3H), 3.28 (s, 3H), 3.80 (s, 3H), 4.29 (d, 1H,  $J = 10.4$  Hz), 4.37 (d, 1H,  $J = 10.4$  Hz), 4.49 (d, 1H,  $J = 6.7$  Hz), 4.54 (br s, 2H), 4.69 (d, 1H,  $J = 6.6$  Hz), 4.81–4.85 (br m, 1H), 5.04–5.08 (br m, 1H), 5.10 (d, 1H,  $J = 11.5$  Hz), 5.29 (br s, 1H), 5.34 (d, 1H,  $J = 17.0$  Hz), 5.53 (d, 1H,  $J = 9.8$  Hz), 5.83 (d, 1H,  $J = 9.8$  Hz), 6.22 (dd, 1H,  $J = 17.6, 11.0$  Hz), 6.85–6.93 (m, 2H), 7.08 (br dd, 1H,  $J = 1.4, 8.0$  Hz), 7.27–7.34 (m, 2H), 7.35 (br d, 1H,  $J = 1.6$  Hz), 7.55 (d, 1H,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.1, 16.7, 17.9, 18.0, 21.3, 55.2, 55.5, 64.4, 67.8, 72.7, 74.2, 93.3.

111.7, 113.7, 115.4, 126.4, 126.7, 127.9, 129.8, 130.1, 133.8, 137.0, 137.2, 137.4, 137.9 (2x), 147.2, 159.3.

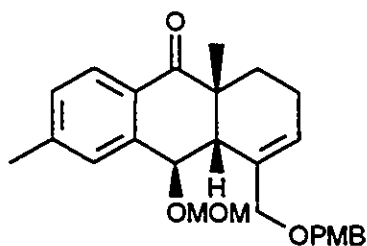
**1-(1-Hydroxy-2-methyl-2-propenyl)-2-[3-(*p*-methoxybenzyloxy)methyl-1-methoxymethoxy-2,4-pentadienyl]-4-methylbenzene (33)**



To a stirred solution of triene **32** (2.1 g, 3.5 mmol) in tetrahydrofuran (20 mL) was added dropwise tetrabutylammonium fluoride (17.3 mL, 1 M, 17 mmol). The resulting mixture was stirred at room temperature for 20 minutes. Water (25 mL) and ether (25 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x30 mL) and the combined organic fractions were washed once with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (250 g silica gel, 7:13 ether/petroleum ether) afforded 1.5 g (97%) of alcohol **33** as a yellow oil: IR (neat): 3452, 1653, 1248, 1050, 909  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.52 (s, 3H), 2.32 (s, 3H), 2.86 (d, 1H,  $J = 4.0$  Hz), 3.30 (s, 3H), 3.79 (s, 3H), 4.21 (d, 1H,  $J = 11.0$  Hz), 4.31 (d, 1H,  $J = 11.0$  Hz), 4.40 (d, 1H,  $J = 11.5$  Hz), 4.45 (d, 1H,  $J = 11.5$  Hz), 4.53 (d, 1H,  $J = 6.8$  Hz), 4.67 (d, 1H,  $J = 6.7$  Hz), 5.04–5.06 (br s, 1H), 5.09 (d, 1H,  $J = 11.0$  Hz), 5.27 (br s, 1H), 5.30 (d, 1H,  $J = 17.5$  Hz), 5.35 (br s, 1H), 5.87 (d, 1H,  $J = 9.2$  Hz), 5.89 (d, 1H,  $J = 9.3$  Hz), 6.30 (dd, 1H,  $J = 11, 17.5$  Hz), 6.86 (br d, 2H,  $J = 8.7$  Hz), 7.07 (br d, 1H,  $J = 8.0$  Hz), 7.20–7.26 (m, 4H);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):

$\delta$  20.0, 21.2, 55.2, 55.5, 63.7, 69.5, 72.0, 72.3, 93.5, 111.1, 113.8, 114.8, 127.5, 128.4, 129.1, 129.8, 129.9, 135.3, 136.7 (2x), 137.8, 138.3, 138.8, 146.0, 159.4.

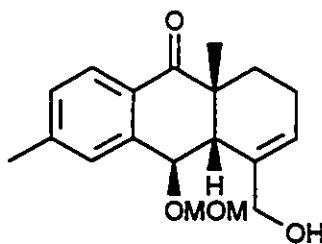
**(4aR\*,9R\*,9aS\*)-3,4,4a,9,9a-Pentahydro-1-(p-methoxybenzyloxy)methyl-9-methoxymethoxy-4a,7-dimethyl-10-anthracenone (35)**



The general protocol for Dess-Martin oxidation was followed using alcohol **33** (1.5 g, 3.4 mmol) and Dess-Martin periodinane (2.1 g, 5.0 mmol) in dichloromethane (20 mL). The oxidation reaction was completed after 30 minutes, whereupon it was refluxed for one hour to ensure complete cyclization. After cooling to room temperature, the reaction was worked up as outlined in the general Dess-Martin oxidation protocol. Purification using flash column chromatography (100 g silica gel, 1:3 ether/petroleum ether) afforded 1.1 g (78%) of ketone **35** as a yellow oil: IR (neat): 1726, 1676, 1246, 1050  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.44 (s, 3H), 1.45–1.49 (m, 1H), 1.99–2.03 (br s, 2H), 2.21–2.25 (m, 1H), 2.34 (s, 3H), 2.94 (br s, 1H), 3.39 (s, 3H), 3.76 (d, 1H,  $J = 11.7$  Hz), 3.80 (s, 3H), 3.90 (d, 1H,  $J = 11.5$  Hz), 4.31 (d, 1H,  $J = 11.4$  Hz), 4.40 (d, 1H,  $J = 11.4$  Hz), 4.65 (d, 1H,  $J = 6.7$  Hz), 4.77 (d, 1H,  $J = 6.7$  Hz), 5.07 (d, 1H,  $J = 4.0$  Hz), 5.71 (br s, 1H), 6.86 (d, 2H,  $J = 8.7$  Hz), 7.06 (s, 1H), 7.18 (d, 1H,  $J = 8.0$  Hz), 7.25 (d, 2H,  $J = 8.7$  Hz), 7.88 (d, 1H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.7, 22.8, 27.4, 32.7, 44.8, 46.5, 55.3, 55.8, 71.8, 73.5, 74.0, 95.1,

113.7, 127.5, 128.8, 129.6, 129.7 (2x), 129.9, 130.2, 133.4, 140.1, 144.3, 159.2, 202.2; Anal. Calcd. for  $C_{27}H_{32}O_5$  : C, 74.29; H, 7.39. Found: C, 74.31; H, 7.43.

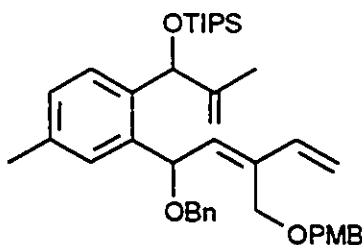
**(4aR',9R',9aS')-3,4,4a,9,9a-Pentahydro-1-hydroxymethyl-9-methoxy-methoxy-4a,7-dimethyl-10-anthracenone (36)**



To a stirred mixture of ketone **35** (725 mg, 1.7 mmol) in pH 7 buffer (10 mL) and dichloromethane (15 mL) was added 2,3-dichloro-5,6-dicyano-benzoquinone (754 mg, 3.3 mmol). After stirring at room temperature for 1.5 hours, saturated sodium bicarbonate solution (15 mL), water (50 mL), and ether (50 mL) were added. The layers were separated and the aqueous phase was extracted with ether (3x75 mL). The combined organic fractions were washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification using flash column chromatography (75 g silica gel, 7:3 ether/petroleum ether) afforded 435 mg (83%) of allylic alcohol **36** as a slightly yellow solid (mp 99–100 °C). IR (KBr): 3495, 1669, 1246, 1018  $cm^{-1}$ ;  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  1.37 (s, 3H), 1.40–1.52 (m, 1H), 2.01–2.19 (m, 4H), 2.38 (s, 3H), 2.87–2.92 (m, 1H), 3.43 (s, 3H), 4.00 (d, 1H,  $J = 10.4$  Hz), 4.11 (d, 1H,  $J = 10.4$  Hz), 4.72 (d, 1H,  $J = 6.7$  Hz), 4.82 (d, 1H,  $J = 6.8$  Hz), 5.02 (d, 1H,  $J = 5.4$  Hz), 5.72 (br s, 1H), 7.19 (d, 1H,  $J = 7.7$  Hz), 7.21 (s, 1H), 7.87 (d, 1H,  $J = 7.5$  Hz);  $^{13}C$  NMR (50.3 MHz,  $CDCl_3$ ):  $\delta$  21.8, 22.5, 25.9, 31.2, 44.8, 46.4, 56.1, 66.5, 74.9.

95.8, 127.3, 127.7, 128.6, 129.6, 136.3, 140.6, 144.5, 202.0; Anal. Calcd. for C<sub>19</sub>H<sub>24</sub>O<sub>4</sub> : C, 72.13; H, 7.65. Found: C, 72.41; H, 7.73.

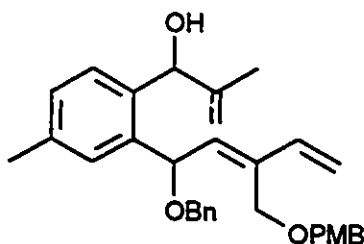
**2-[1-Benzyloxy-3-(*p*-methoxybenzyloxy)methyl-2,4-pentadienyl]-4-methyl-1-(1-triisopropylsilyloxy-2-methyl-2-propenyl)benzene (39)**



To a round bottomed flask was added sodium hydride in mineral oil (80%, 403 mg, 13 mmol). The sodium hydride was then washed with dry tetrahydrofuran (2x5 mL). Tetrahydrofuran (40 mL) was added and the suspension was cooled to 0 °C. A solution of **31** (4.1 g, 7.5 mmol) in tetrahydrofuran (10 mL) was introduced dropwise and the mixture stirred for 5 minutes before warming up to room temperature. Tetrabutylammonium iodide (138 mg, 0.37 mmol) and benzyl bromide (2.8 g, 16 mmol) were added and the reaction mixture stirred at room temperature for 23 hours. The reaction was quenched with a few drops of water; then saturated sodium bicarbonate solution (20 mL) and ether (20 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x20 mL) and the combined organic fractions were washed once with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification *via* flash column chromatography (200 g silica gel, 1:9 ether/petroleum ether) afforded 4.1 g (83%) of benzyl ether **39** as a colorless oil: IR (neat): 3067, 1647, 1249, 1060, 894 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 0.82–1.02 (m, 21H), 1.57 (s, 3H), 2.36 (s, 3H), 3.80 (s,

3H), 4.20 (d, 1H,  $J = 10.8$  Hz), 4.30 (d, 1H,  $J = 10.8$  Hz), 4.36 (s, 2H), 4.44 (s, 2H), 4.71 (br s, 1H), 4.90 (br s, 1H), 5.11 (d, 1H,  $J = 11.0$  Hz), 5.27 (s, 1H), 5.36 (d, 1H,  $J = 17.7$  Hz), 5.60 (d, 1H,  $J = 10.2$  Hz), 5.66 (d, 1H,  $J = 9.8$  Hz), 6.24 (dd, 1H,  $J = 11.0, 17.6$  Hz), 6.86 (br d, 2H,  $J = 8.6$  Hz), 7.10 (br d, 1H,  $J = 7.7$  Hz), 7.22–7.33 (m, 7H), 7.43 (br s, 1H), 7.57 (d, 1H,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.1, 16.8, 17.9, 18.0, 21.3, 55.3, 64.5, 70.0, 71.9, 72.3, 74.5, 112.0, 113.8, 115.2, 126.2, 127.0, 127.4, 127.9, 128.0, 128.3, 129.6, 130.1, 134.9, 137.1, 137.4, 137.6 (2x), 138.1, 138.6, 147.2, 159.3.

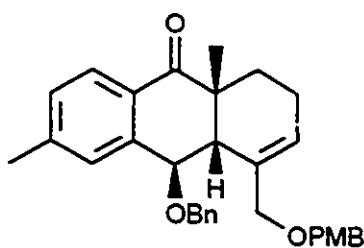
**1-(1-Hydroxy-2-methyl-2-propenyl)-2-[1-benzyloxy-3-(*p*-methoxybenzyl-oxy)methyl-2,4-pentadienyl]-4-methylbenzene (40)**



The reaction procedure for the preparation of **33** was followed using benzyl ether **39** (3.8 g, 5.7 mmol) and tetrabutylammonium fluoride (28.6 mL, 1 M, 29 mmol) in tetrahydrofuran (20 mL). Purification by flash column chromatography (200 g silica gel, 7:13 ether/petroleum ether) afforded 2.7 g (96%) of **40** as a yellowish oil: IR (neat): 3446 (br), 1651, 1248, 1055, 905  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.58 (s, 3H), 2.34 (s, 3H), 2.79–1.89 (m, 1H), 3.79 (s, 3H), 4.15 (br s, 2H), 4.36 (br s, 2H), 4.49 (br s, 2H), 5.03 (br s, 1H), 5.12 (d, 1H,  $J = 11.1$  Hz), 5.18–5.24 (br s, 2H), 5.32 (d, 1H,  $J = 17.6$  Hz), 5.60 (br d, 1H,  $J = 8.9$  Hz), 5.99 (br d, 1H,  $J = 9.0$  Hz), 6.35 (dd, 1H,  $J = 11.1, 17.6$  Hz), 6.84 (br d, 2H,  $J = 7.6$  Hz), 7.06–7.35 (m,

10H);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.1, 21.3, 55.2, 63.7, 70.1, 72.3 (2x), 73.4, 111.2, 113.8, 114.8, 127.6, 127.8, 128.0, 128.3, 128.4, 129.0, 129.6, 129.7, 129.8, 135.9, 136.7, 136.8, 137.8, 138.3, 138.9, 145.9, 159.3.

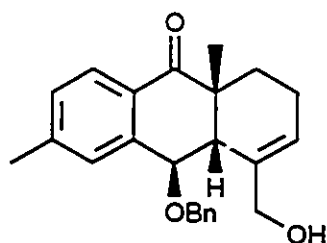
**(4aR\*,9R\*,9aS\*)-9-Benzoyloxy-3,4,4a,9,9a-pentahydro-1-(*p*-methoxybenzyloxy)methyl-4a,7-dimethyl-10-anthracenone (41)**



The general protocol for Dess-Martin oxidation was followed using **40** (2.5 g, 5.0 mmol) and Dess-Martin periodinane (3.2 g, 7.5 g) in dichloromethane (50 mL). The oxidation reaction was complete after 15 minutes, whereupon, the reaction mixture was refluxed for 2.5 hours. After cooling to room temperature, the reaction was worked up as outlined in the general Dess-Martin oxidation protocol. Purification using column chromatography (200 g silica gel, 1:3 ether/petroleum ether) afforded 2.3 g (91%) of cyclized product **41** as a white solid (mp 86–87 °C). IR (KBr): 3062, 1668, 1248, 1056  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.49 (s, 3H), 1.42–1.58 (m, 1H), 2.05 (br s, 2H), 2.14–2.30 (m, 1H), 2.35 (s, 3H), 3.06 (br s, 1H), 3.79 (d, 1H,  $J = 11.6$  Hz), 3.80 (s, 3H), 3.96 (d, 1H,  $J = 11.5$  Hz), 4.26 (d, 1H,  $J = 11.4$  Hz), 4.40 (d, 1H,  $J = 11.5$  Hz), 4.63 (s, 2H), 4.86 (br d, 1H,  $J = 4.9$  Hz), 5.76 (br s, 1H), 6.87 (br d, 2H,  $J = 8.6$  Hz), 7.01 (br s, 1H), 7.21 (br d, 3H,  $J = 8.4$  Hz), 7.28–7.38 (m, 5H), 8.91 (d, 1H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.8, 22.7, 26.5, 32.1, 45.0, 45.6, 55.3, 71.5, 71.6, 73.5, 77.5, 113.6, 113.7, 127.6, 128.4, 128.7, 129.1, 129.3, 129.6, 130.2.

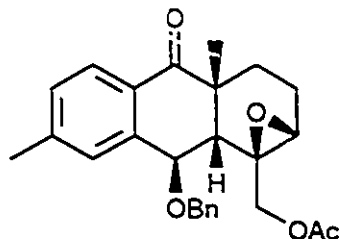
133.8, 138.4, 140.6, 144.3, 159.2, 202.3. Anal. Calcd. for  $C_{32}H_{34}O_4$ : C, 76.64; H, 7.10. Found: C, 76.50; H, 7.31.

**(4aR\*,9R\*,9aS\*)-9-Benzoyloxy-3,4,4a,9,9a-pentahydro-1-hydroxymethyl-4a,7-dimethyl-10-anthracenone (42)**



The reaction procedure for the preparation of **36** was followed using cyclized product **41** (500 mg, 1.0 mmol), 2,3-dichloro-5,6-dicyano-benzoquinone (455 mg, 2.0 mmol), pH 7 buffer (3 mL), and dichloromethane (5 mL). The reaction was complete after 30 minutes. Purification by column chromatography (50 g silica gel, 9:11 ether/petroleum ether) afforded 309 mg (91%) of allylic alcohol **42** as a yellow, viscous oil: IR ( $CH_2Cl_2$ ): 3457 (br), 1672, 1266, 1058  $cm^{-1}$ ;  $^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  1.37 (s, 3H), 1.40-1.55 (m, 1H), 1.98-2.15 (br m, 3H), 2.25-2.45 (m, 4H), 2.91 (br d, 1H,  $J = 6.8$  Hz), 4.03 (d, 1H,  $J = 12.0$  Hz), 4.12 (d, 1H,  $J = 12.0$  Hz), 4.65 (d, 1H,  $J = 12.0$  Hz), 4.72 (d, 1H,  $J = 12.0$  Hz), 4.84 (br d, 1H,  $J = 7.0$  Hz), 5.72 (br s, 1H), 7.15-7.40 (m, 7H), 7.90 (br d, 1H,  $J = 8.3$  Hz);  $^{13}C$  NMR (50.3 MHz,  $CDCl_3$ ):  $\delta$  22.0, 22.4, 24.4, 30.1, 45.1, 45.9, 66.8, 72.4, 78.2, 126.2, 127.7, 127.9, 128.0, 128.3, 128.5, 129.5, 137.0, 137.7, 141.4, 144.6, 202.3; HRMS exact mass calcd. for  $C_{17}H_{18}O_2$  ( $M^+ - HOBn$ ) 254.1307, found 254.1284.

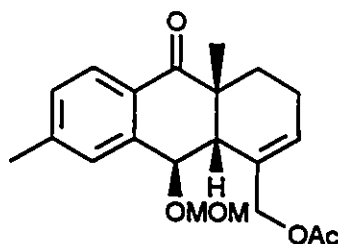
(1R',2R',4aR',9R',9aS')-1-Acetyloxymethyl-9-benzyloxy-1,2-epoxy-1,2,3,4,4a,9,9a-heptahydro-4a,7-dimethyl-10-anthracenone (43a)



To a stirred solution of allylic alcohol **42** (575 mg, 1.7 mmol) in dichloromethane (7 mL) was added triethylamine (474  $\mu$ L, 3.4 mmol) and acetic anhydride (321  $\mu$ L, 3.4 mmol). The reaction mixture was stirred overnight. Water (10 mL) and ether (10 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x10 mL) and the combined organic fractions washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude oil was redissolved in dry dichloromethane (10 mL) and cooled to 0 °C. Sodium bicarbonate (285 mg, 3.4 mmol) and *m*-chloroperoxybenzoic acid (50%, 1.2 g, 3.4 mmol) were added and the reaction mixture stirred at room temperature for 3 hours. Water (10 mL) and ether (10 mL) were added and the two layers separated. The aqueous phase was extracted with ether (3x10 mL) and the combined organic fractions washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. NMR of the crude product indicated that it was a 1:1 isomeric mixture. Purification by flash column chromatography (50 g silica gel, 1:3 ether/petroleum ether) and recrystallization from ether/petroleum ether afforded 273 mg (38%) of isomer **43a** as colorless crystals (mp 102-102 °C). IR (KBr): 3067, 1733, 1672, 1225, 1072  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.18 (s, 3H), 1.42–1.48 (m, 1H), 1.61–1.70 (m, 1H), 2.00

(s, 3H), 2.02–2.17 (m, 2H), 2.37 (s, 3H), 2.47 (d, 1H,  $J = 10.6$  Hz), 3.34 (br s, 1H), 4.06 (d, 1H,  $J = 11.4$  Hz), 4.44 (d, 1H,  $J = 11.4$  Hz), 4.83 (d, 1H,  $J = 10.6$  Hz), 4.90 (d, 1H,  $J = 10.9$  Hz), 5.13 (d, 1H,  $J = 10.9$  Hz), 7.16 (d, 1H,  $J = 7.9$  Hz), 7.29–7.35 (m, 2H), 7.36–7.42 (m, 2H), 7.50 (br d, 2H,  $J = 7.1$  Hz), 7.84 (d, 1H,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.4, 20.8, 22.1, 22.4, 23.8, 43.1, 46.1, 57.9, 58.2, 68.0, 74.8, 75.0, 116.2, 125.3, 127.3, 127.9, 128.2 (2x), 128.6, 128.8, 137.9, 144.5, 145.0, 170.3, 202.3. Anal. Calcd. for  $\text{C}_{26}\text{H}_{28}\text{O}_5$ : C, 74.26; H, 6.71. Found: C, 74.12; H, 6.86.

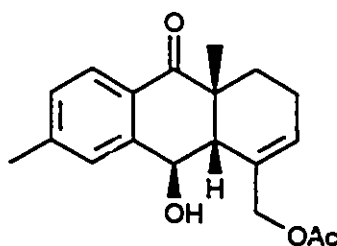
**(4aR',9R',9aS')-1-Acetyloxymethyl-3,4,4a,9,9a-pentahydro-9-methoxymethoxy-4a,7-dimethyl-10-anthracenone (44)**



To a stirred solution of allylic alcohol **36** (336 mg, 1.1 mmol) in dichloromethane (10 mL) was added triethylamine (218 mg, 2.2 mmol) and acetic anhydride (216 mg, 2.1 mmol), and the resulting mixture stirred overnight. Saturated sodium bicarbonate solution (10 mL), water (10 mL), and ether (20 mL) were added and the layers separated. The aqueous layer was extracted with ether (3x20 mL), and the combined organic fractions were washed once with brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (30 g silica gel, 7:13 ether/petroleum ether) afforded 342 mg (90%) of acetylated product **44** as a yellow oil:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.39 (s, 3H), 1.42–1.55 (m, 1H), 2.03–2.22 (m, 3H), 2.39 (s, 3H), 2.85–2.92 (br m,

1H). 3.43 (s, 3H), 4.40 (br d, 1H,  $J = 12.4$  Hz), 4.58 (br d, 1H,  $J = 12.5$  Hz), 4.71 (d, 1H,  $J = 7.0$  Hz), 4.78 (d, 1H,  $J = 6.8$  Hz), 4.90 (br d, 1H,  $J = 5.1$  Hz), 5.80 (br s, 1H), 7.19–7.22 (br m, 2H), 7.89 (d, 1H,  $J = 8.2$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.9, 21.8, 22.7, 26.1, 31.3, 44.7, 46.3, 56.0, 67.8, 74.5, 95.5, 127.7, 128.5, 128.8, 129.7, 130.9, 131.6, 140.2, 144.6, 170.8, 201.8.

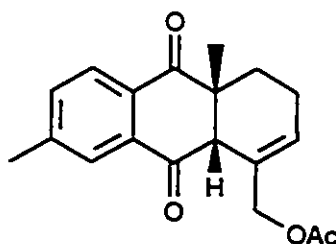
**(4aR',9R',9aS')-1-Acetyloxymethyl-3,4,4a,9,9a-pentahydro-9-hydroxy-4a,7-dimethyl-10-anthracenone (45)**



To a stirred solution of protected alcohol **44** (330 mg, 0.92 mmol) in dichloromethane (9 mL) at  $-78$  °C was added dropwise bromodimethyl borane (965 mg, 8.0 mmol) in dichloromethane (8 mL). The resulting mixture was stirred at  $-78$  °C for 10 minutes. Saturated sodium bicarbonate solution (15 mL) and tetrahydrofuran (15 mL) were added and the reaction mixture warmed to room temperature. Brine (15 mL) and ether (15 mL) were then added and the layers separated. The aqueous layer was extracted with ether (3x30 mL), and the combined organic fractions were washed once with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification using flash column chromatography (30 g silica gel, 1:1 ether/petroleum ether) afforded 189 mg (64%) of alcohol **45** as an oil:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.18 (s, 3H), 1.40–1.55 (m, 1H), 1.69–1.89 (m, 1H), 2.06 (s, 3H), 2.20–2.34 (m, 3H), 2.38 (s, 3H), 3.88 (d, 1H,  $J = 6.5$  Hz), 4.66 (d, 1H,  $J = 12.8$  Hz), 4.78 (d, 1H,  $J = 13.0$  Hz), 4.77–4.84

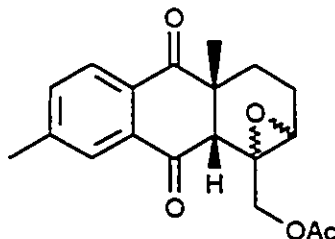
(br m, 1H), 5.80–5.85 (br m, 1H), 7.16 (d, 1H,  $J = 8.0$  Hz), 7.52 (br s, 1H), 7.88 (d, 1H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.4, 21.0, 21.9, 22.3, 26.3, 44.7, 49.0, 68.8, 72.1, 125.7, 126.2, 127.2, 127.9, 128.8, 134.0, 144.5, 145.1, 171.7, 201.5; Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{O}_4$  : C, 72.59; H, 7.05. Found: C, 72.80; H, 7.03.

**(4aR',9aS')-1-Acetyloxymethyl-3,4,4a,9a-tetrahydro-4a,7-dimethyl-9,10-anthraquinone (46)**



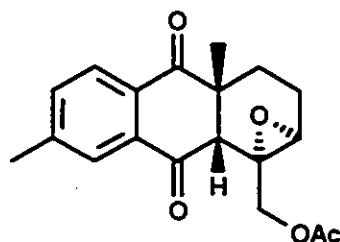
The general protocol for Dess-Martin oxidation was followed using alcohol **45** (162 mg, 0.52 mmol) and Dess-Martin periodinane (328 mg, 0.77 mmol) in dichloromethane (10 mL). The reaction was completed after 15 minutes. Flash column chromatography (10 g silica gel, 1:1 ether/petroleum ether) afforded 163 mg (87%) of diketone **46** as a yellow solid (mp 141–142 °C). IR (KBr): 1738, 1682, 1250, 1026  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.28 (s, 3H), 1.34–1.42 (m, 1H), 1.84 (s, 3H), 2.11–2.18 (br m, 1H), 2.24–2.35 (m, 2H), 2.45 (s, 3H), 3.45–3.51 (br m, 1H), 4.34 (d, 1H,  $J = 12.4$  Hz), 4.47 (d, 1H,  $J = 12.4$  Hz), 5.76–5.84 (br m, 1H), 7.50–7.52 (br m, 1H), 7.72–7.74 (br m, 1H), 7.95 (d, 1H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.7, 21.7, 22.8, 24.7, 30.2, 47.9, 58.2, 66.7, 126.5, 127.4, 129.4, 130.3, 130.9, 134.2, 135.2, 145.4, 170.4, 198.7, 199.5; Anal. Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_4$  : C, 73.06; H, 6.45. Found: C, 73.34; H, 6.35.

**(4aR',9aR')-1-Acetyloxymethyl-1,2-epoxy-1,2,3,4,4a,9a-hexahydro-4a,7-dimethyl-9,10-anthraquinone (47)**



To a stirred solution of diketone **46** (75 mg, 0.24 mmol) in dichloromethane (5 mL) at 0 °C was added sodium bicarbonate (40 mg, 0.48 mmol) and *m*-chloroperoxybenzoic acid (50%, 165 mg, 0.48 mmol). The reaction was warmed to room temperature and stirred overnight. Water (5 mL) and ether (5 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x5 mL) and the combined organic fractions were washed once with brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (7 g silica gel, 1:1 ether/petroleum ether) afforded 45 mg (57%) of epoxide **47(a,b)** as a 1:1 isomeric mixture. (NMR data are too complex for peak assignment.)

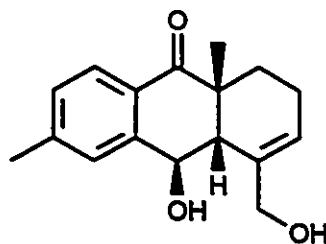
**(1R',2R',4aR',9aR')-1-Acetyloxymethyl-1,2-epoxy-1,2,3,4,4a,9a-hexahydro-4a,7-dimethyl-9,10-anthraquinone (47b)**



The general protocol for Dess-Martin oxidation was followed using epoxide **50** (792 mg, 2.4 mmol) and Dess-Martin periodinane (1.5 g,

3.5 mmol) in dichloromethane (25 mL). The reaction was complete after 3 hours. Purification by column chromatography (80 g silica gel, 7:13 ethylacetate/petroleum ether) afforded 663 mg (84%) of diketone **47b** as a slightly yellow solid (mp 142–143 °C). IR (KBr): 1739, 1693, 1240, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.07–1.14 (m, 1H), 1.16 (s, 3H), 1.94–1.98 (m, 1H), 2.00 (s, 3H), 2.15–2.24 (m, 2H), 2.43 (s, 3H), 3.16 (d, 1H,  $J = 4.9$  Hz), 3.20 (s, 1H), 3.95 (d, 1H,  $J = 12.2$  Hz), 4.11 (d, 1H,  $J = 12.2$  Hz), 7.52 (d, 1H,  $J = 7.9$  Hz), 7.78 (s, 1H), 7.96 (d, 1H,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.4, 20.6, 21.7, 26.6, 28.4, 45.8, 57.1, 58.3, 58.9, 64.6, 126.7, 127.1, 132.3, 134.4, 135.5, 144.5, 170.0, 197.3, 197.3; Anal. Calcd. for  $\text{C}_{19}\text{H}_{20}\text{O}_5$ : C, 69.50; H, 6.14. Found: C, 69.54; H, 6.03.

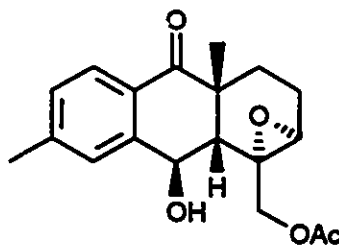
**(4aR\*,9R\*,9aS\*)-3,4,4a,9,9a-Pentahydro-9-hydroxy-1-hydroxymethyl-4a,7-dimethyl-10-anthracenone (48)**



To a stirred solution of protected alcohol **44** (3.4 g, 9.5 mmol) in dichloromethane (50 mL) at  $-78$  °C was added dropwise bromodimethyl borane (9.2 g, 76 mmol) in dichloromethane (20 mL). The resulting mixture was stirred at  $-78$  °C for 10 minutes. Saturated sodium bicarbonate solution (20 mL) and tetrahydrofuran (20 mL) were added and the reaction mixture warmed to room temperature. Brine (20 mL) and ether (20 mL) were then added and the layers separated. The aqueous layer was extracted with ether (3x50 mL) and the combined organic fractions were washed once

with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was then dissolved in methanol (50 mL). Potassium carbonate (2.6 g, 19 mmol) was added and the mixture stirred overnight. Methanol was removed *in vacuo* and the crude product redissolved in ether (20 mL). The ether fraction was washed once with water (5 mL) and once with brine (5 mL). The resulting organic fraction was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (200 g silica gel, 3:1 ether/petroleum ether) afforded 2.0 g (77%) of diol **48** as an extremely viscous oil that solidified over time (mp 51–52). IR (KBr): 3329 (br), 1667, 1289, 1007  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.12 (s, 3H), 1.30–1.45 (m, 1H), 1.57–1.75 (m, 1H), 2.30 (s, 3H), 2.16–2.40 (m, 3H), 3.97 (br d, 1H,  $J = 11.3$  Hz), 4.16 (br d, 1H,  $J = 11.5$  Hz), 4.59 (br d, 1H,  $J = 9.8$  Hz), 5.75–5.85 (br s, 1H), 7.11 (br d, 1H,  $J = 7.5$  Hz), 7.44 (br s, 1H), 7.84 (br d, 1H,  $J = 7.9$  Hz);  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ):  $\delta$  20.0, 21.9, 22.3, 26.2, 45.0, 51.3, 68.5, 70.6, 126.2, 126.8, 127.7, 128.4, 128.8, 137.2, 144.2, 145.1, 201.8; Anal. Calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}_3$  : C, 74.97; H, 7.40. Found: C, 75.19; H, 7.19.

**(1R',2R',4aR',9R',9aS')-1-Acetyloxymethyl-1,2-epoxy-1,2,3,4,4a,9,9a-heptahydro-9-hydroxy-4a,7-dimethyl-10-anthracenone (50)**



To a stirred solution of diol **48** (1.5 g, 5.5 mmol) in dichloromethane (50 mL) at 0 °C was added sodium bicarbonate (555 mg, 6.6 mmol) and *m*-chloroperoxybenzoic acid (50%, 2.3 g, 6.6 mmol). The reaction was stirred for 2.5 hours. Water (30 mL) and ether (30 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x50 mL) and the combined organic fractions were washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was dissolved in dichloromethane (50 mL); triethylamine (584 mg, 5.8 mmol) and acetic anhydride (590 mg, 5.8 mmol) were added. The resulting mixture was stirred at room temperature overnight. Water (25 mL) and ether (25 mL) were added and the layers separated. The aqueous phase was extracted with ether (3x50 mL), and the combined organic fractions were washed once with brine (30 mL), dried over anhydrous magnesium sulfated, and concentrated *in vacuo*. Purification by flash column chromatography (100 g silica gel, 3:7 ethylacetate/petroleum ether then gradually increasing solvent polarity to 100% ethylacetate) afforded 1.1 g (89% at 68% conversion) of epoxide **50** as an orange-red foam: IR (neat): 3440, 1737, 1667, 1256, 1038 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 1.13 (s, 3H), 1.25–1.55 (m, 2H), 2.00 (s, 3H), 1.95–2.10 (m, 2H), 2.25 (d, 1H, *J* = 10.9 Hz), 2.35 (s, 3H), 3.30 (br s, 1H), 3.83 (d, 1H, *J* = 6.0 Hz), 4.33 (d, 1H, *J* = 11.2 Hz), 4.52 (d, 1H, *J* = 11.4 Hz), 4.99 (br dd, 1H, *J* = 10.4, 5.3 Hz), 7.11 (br d, 1H, *J* = 7.9 Hz), 7.53 (br s, 1H), 7.79 (d, 1H, *J* = 7.9 Hz); <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): δ 20.2, 20.6, 21.6, 21.9, 23.5, 42.8, 47.0, 57.5, 66.0, 67.0, 125.3, 126.7, 127.8, 128.5, 145.1, 145.2, 170.8, 200.7; HRMS exact mass calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>3</sub> (M<sup>+</sup> - HOAc) 270.1256, found 270.1243.

## Appendix

### Preparation of Dess-Martin Periodinane

To a three-neck 2 L round bottomed flask, equipped with a strong mechanical stirrer and a thermometer, containing 2-iodobenzoic acid (85.2 g, 0.34 mol) was added sulfuric acid (1.5 L, 0.73M) in several portions. While adding the sulfuric acid, the stirrer was turned on to help mix the 2-iodobenzoic acid (fluffy and preferred to float on sulfuric acid) into the aqueous solution. Once all of the 2-iodobenzoic acid has mixed with sulfuric acid to form a suspension, potassium bromate (76.0 g, 0.45 mol) was added in small portions at a time in order to maintain the reaction temperature below 55 °C. After completing the addition of potassium bromate (about 1 hour), the third neck of flask was connected to a tube containing a funnel at one end. The mouth of the funnel was suspended 1 mm in a solution of sodium hydroxide. The orange reaction mixture was heated to and maintained at 65 °C, with stirring, until no more bromine evolved (5–6 hours). The reaction mixture was cooled to 0 °C and white solids settled to the bottom of the reaction flask. The mixture was filtered (suction) and the white solids washed with cold distilled water (4x250 mL), 99% ethanol (2x100 mL), and dry ether (2x75 mL). Drying in a desiccator overnight afforded 87.5 g (91%) of 1-hydroxy-1,2-benziodoxol-3(1H)-one (**A**) as a fine, slightly fluffy, white crystalline (mp 220 °C, decomposition).

In a one-neck round bottomed flask under a flow of nitrogen was stirred a solution of *p*-toluenesulfonic acid (0.25 g, 0.09 mol) in acetic anhydride (200 mL). Intermediate **A** (50 g, 0.18 mol) was added and a water condenser equipped with a drying tube was connected to the flask. The

reaction was stirred at 80 °C for 2 hours and all of the starting material dissolved. The solution was cooled to 0 °C and Dess-Martin periodinane precipitated out as a white solid. The suspension was suction filtered through a sintered glass funnel (aspirator line connected to a drying tube) under a flow of nitrogen and the precipitate washed with anhydrous ether (5x20 mL). The dry white solid was quickly transferred to small vials, flushed with nitrogen, capped, weighed, covered with aluminum foil, and stored immediately at -15 °C. This reaction afforded 61.7 g (82%) of Dess-Martin periodinane. (No analysis was carried out since the material was quite insoluble in most solvents. Its quality was tested by performing a micro-scale oxidation on an alcohol that was known to be easily oxidized. This reaction was best performed at a 50 g scale since larger scales resulted in lower yields of the product. (A large funnel connected to a nitrogen line was anchored above the filtering system. The diameter of the funnel's opening was increased by extending the cone with aluminum foil.)

### **Summary of Data Collection, Structure Solution, and Refinement**

#### **Details for Adduct 41**

##### ***Crystal Data***

empirical formula	C <sub>32</sub> H <sub>34</sub> O <sub>4</sub>
formula weight	482.62
crystal color, habit	white, prism
crystal dimensions	0.200 x 0.300 x 0.400 mm
crystal system	orthorhombic
lattice parameters:	
a	22.966(1) Å
b	27.903(1) Å

c	7.976(2) Å
V	5111(2) Å <sup>3</sup>
space group	Pbca (#61)
Z value	8
F(000)	2064
$d_{\text{calc}}$	1.254 g·cm <sup>-3</sup>
$\mu$	0.76 cm <sup>-1</sup>

#### ***Data Acquisition<sup>a</sup>***

temperature	-150 °C
unit cell reflections (2 $\theta$ range)	12 (25.0–28.2°)
max. 2 $\theta$ for reflections	50.0°
take-off angle	6.0°
detector aperture	6.0 mm horizontal, 6.0 mm vertical
crystal to detector distance	40 cm
scan type	$\omega$
scan rate	4.0° / min. (in omega, 3 rescans)
scan width	(1.09 + 0.30 tan $\theta$ )°
total reflections measured	4619
variation in 150 reflections	none (no decay correction)
Corrections	Lorentz-polarization

#### ***Structure Solution and Refinement<sup>b</sup>***

structure solution	direct methods
refinement	full-matrix least-squares
anomalous dispersion	all non-hydrogen atoms
observations with $I > 2.50\sigma(I)$	2646
number of variables in least-squares	325

reflection/parameter ratio	8.14
residue: R: R <sub>w</sub>	0.060: 0.073
goodness of fit indicator	3.22
final max. shift/error ratio	0.02
Δ-map	- 0.66, 0.69 e Å <sup>-3</sup>

<sup>a</sup> Data collection on a Rigaku AFC6S diffractometer with graphite monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71069 \text{ \AA}$ ) and a 12 KW rotating anode generator.

<sup>b</sup> All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation. The structure was solved by direct methods (MITHRIL: Glimore, C.J. *J. Appl. Cryst.* **1984**, *17*, 42 and DIRDIF: Beurskens, P.T. *Technical Report 1984/1* Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands).

### **Summary of Data Collection, Structure Solution, and Refinement**

#### **Details for Anthraquinone 47b**

##### ***Crystal Data***

empirical formula	C <sub>19</sub> H <sub>20</sub> O <sub>5</sub>
formula weight	328.36
crystal color, habit	white, prism
crystal dimensions	0.20 x 0.20 x 0.20 mm
crystal system	monoclinic
lattice parameters:	
a	9.6338(3) Å
b	10.4708(5) Å

c	16.2597(1) Å
V	1522.49(3) Å <sup>3</sup>
space group	P 21/c
Z value	4
F(000)	698.23
d <sub>calc</sub>	1.344 g·cm <sup>-3</sup>
μ	0.84 mm <sup>-1</sup>

### ***Data Acquisition<sup>a</sup>***

temperature	
unit cell reflections (2θ range)	24 (40.00–50.00°)
max. 2θ for reflections	99.9°
take-off angle	4.0°
detector aperture	6.0 mm horizontal, 6.0 mm vertical
crystal to detector distance	40 cm
scan type	θ / 2θ
scan rate	4.0° / min. (in omega, 4 rescans)
scan width	(1.09 + 0.30 tanθ)°
total reflections measured	1796
variation in 150 reflections	≈ 5% for the 3 standard
Corrections	Lorentz-polarization

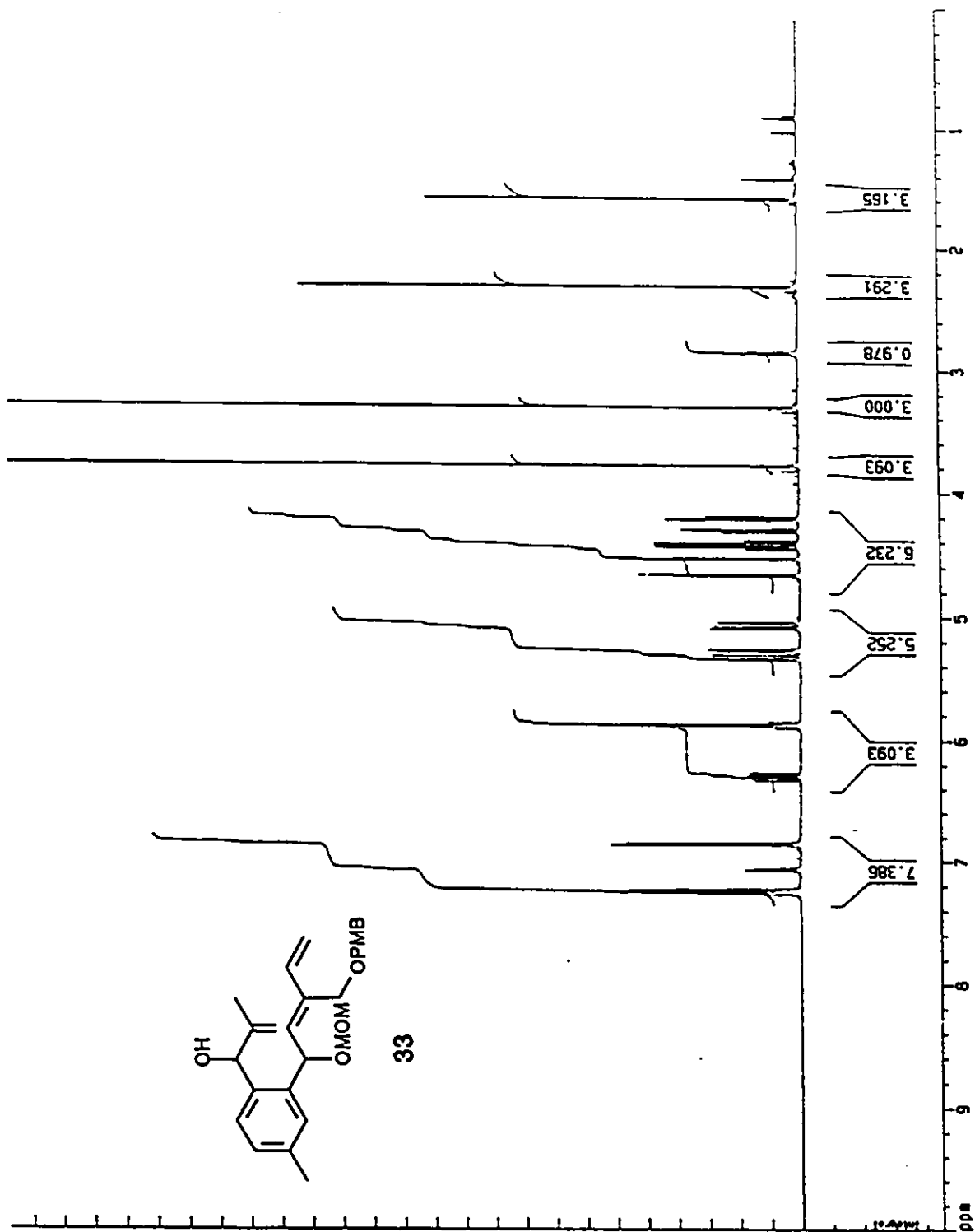
### ***Structure Solution and Refinement<sup>b</sup>***

structure solution	direct methods
refinement	full-matrix least-squares
anomalous dispersion	all non-hydrogen atoms
observations with I > 2.50σ(I)	1495
number of variables in least-squares	122

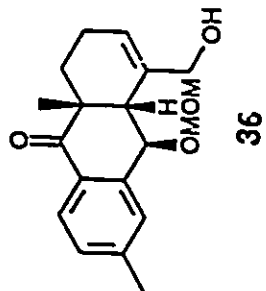
reflection/parameter ratio	12.25
residue: R; R <sub>w</sub>	0.193; 0.238
goodness of fit indicator	10.78
final max. shift/error ratio	0.235
Δ-map	- 1.550, 1.650 e Å <sup>-3</sup>

<sup>a</sup> Data collection on a Rigaku AFC6S diffractometer with graphite monochromated Cu K $\alpha$  radiation ( $\lambda = 1.54056 \text{ \AA}$ ) and a 12 KW sealed tube.

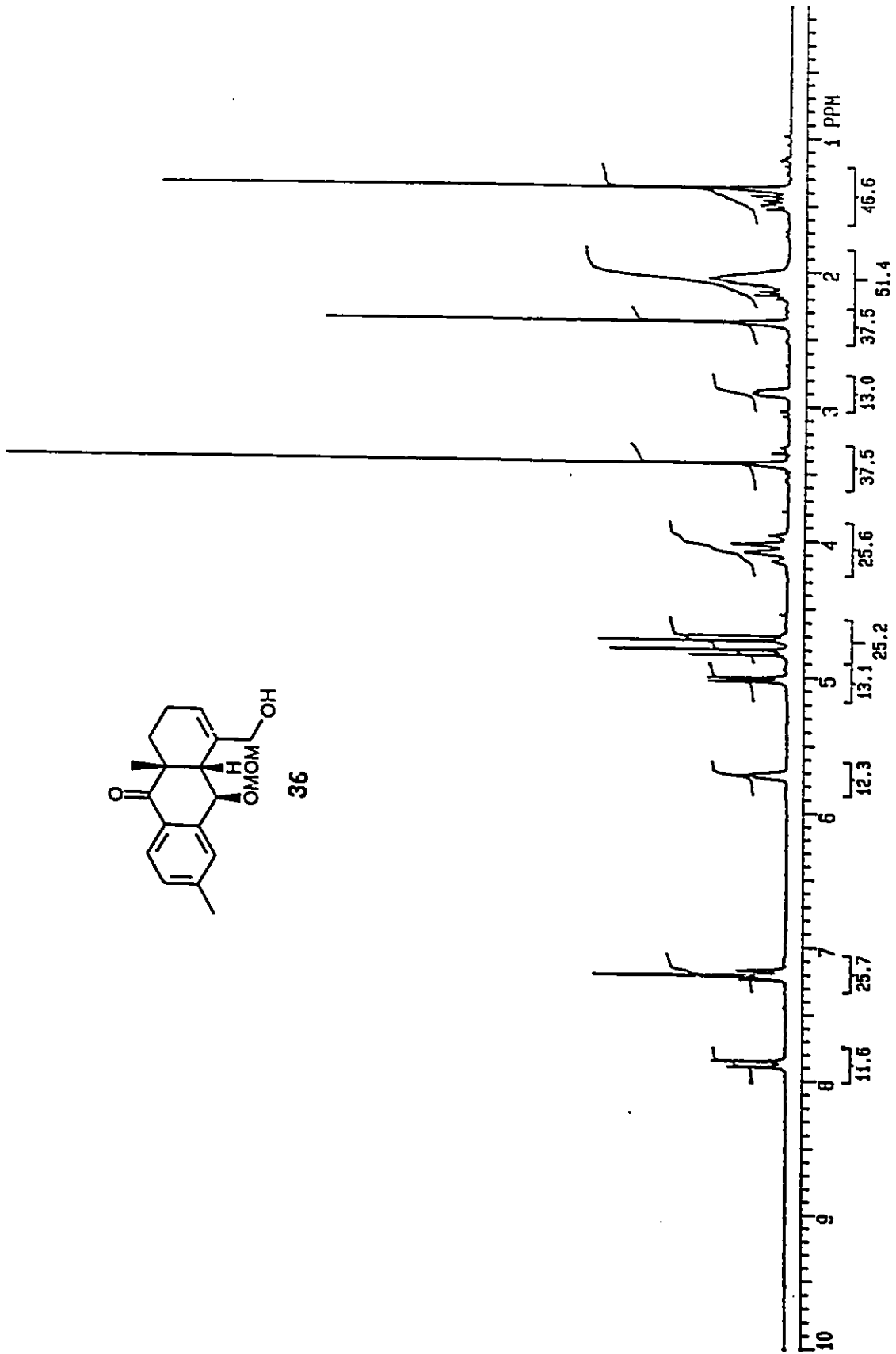
<sup>b</sup> All calculations were performed using the NRCVAX crystallographic software package. The structure was solved by direct methods (Solver: Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.L. and White, P.S. (1989) *J. Appl. Cryst.*, **22**, 384-387).



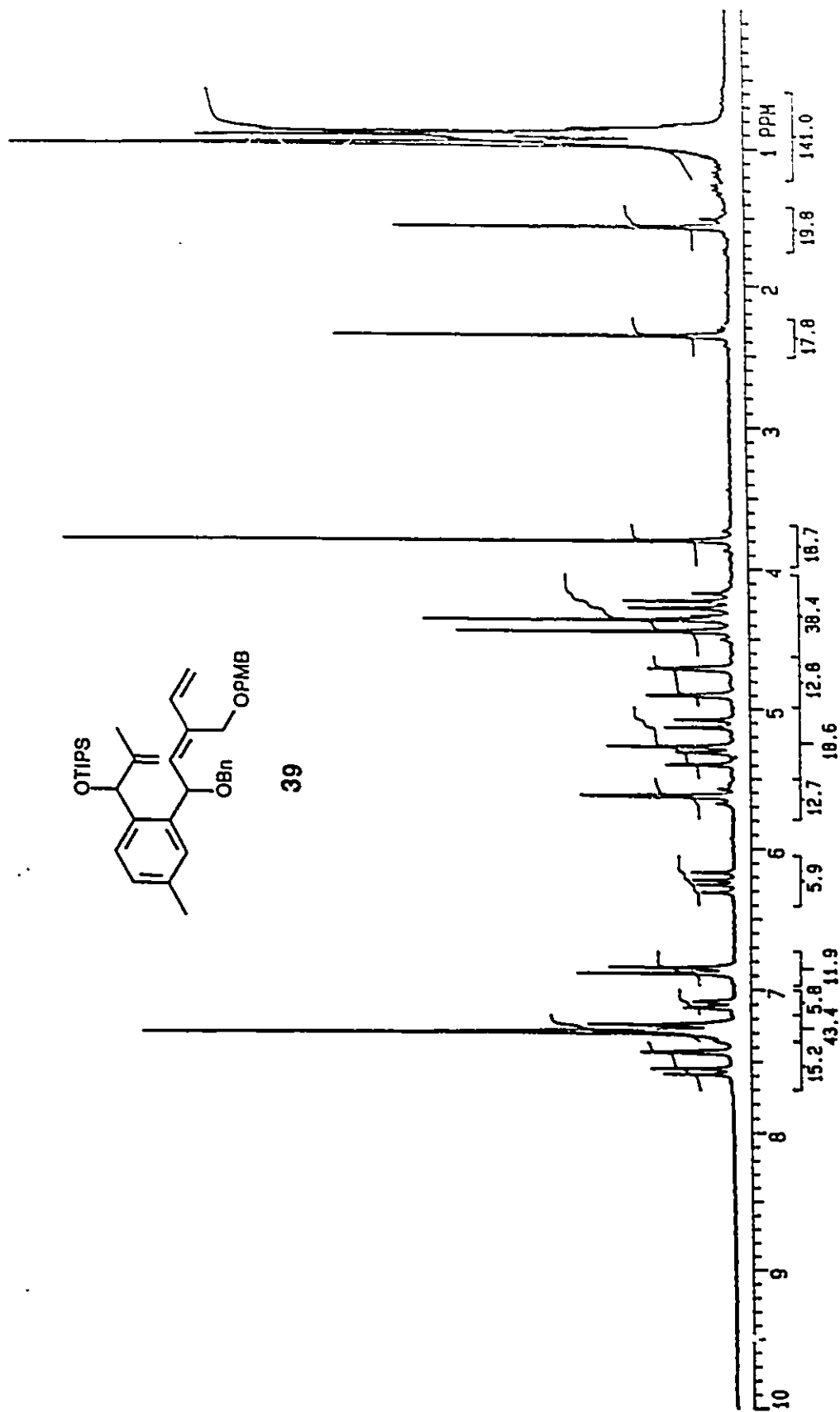
<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, 500 MHz) of 33.



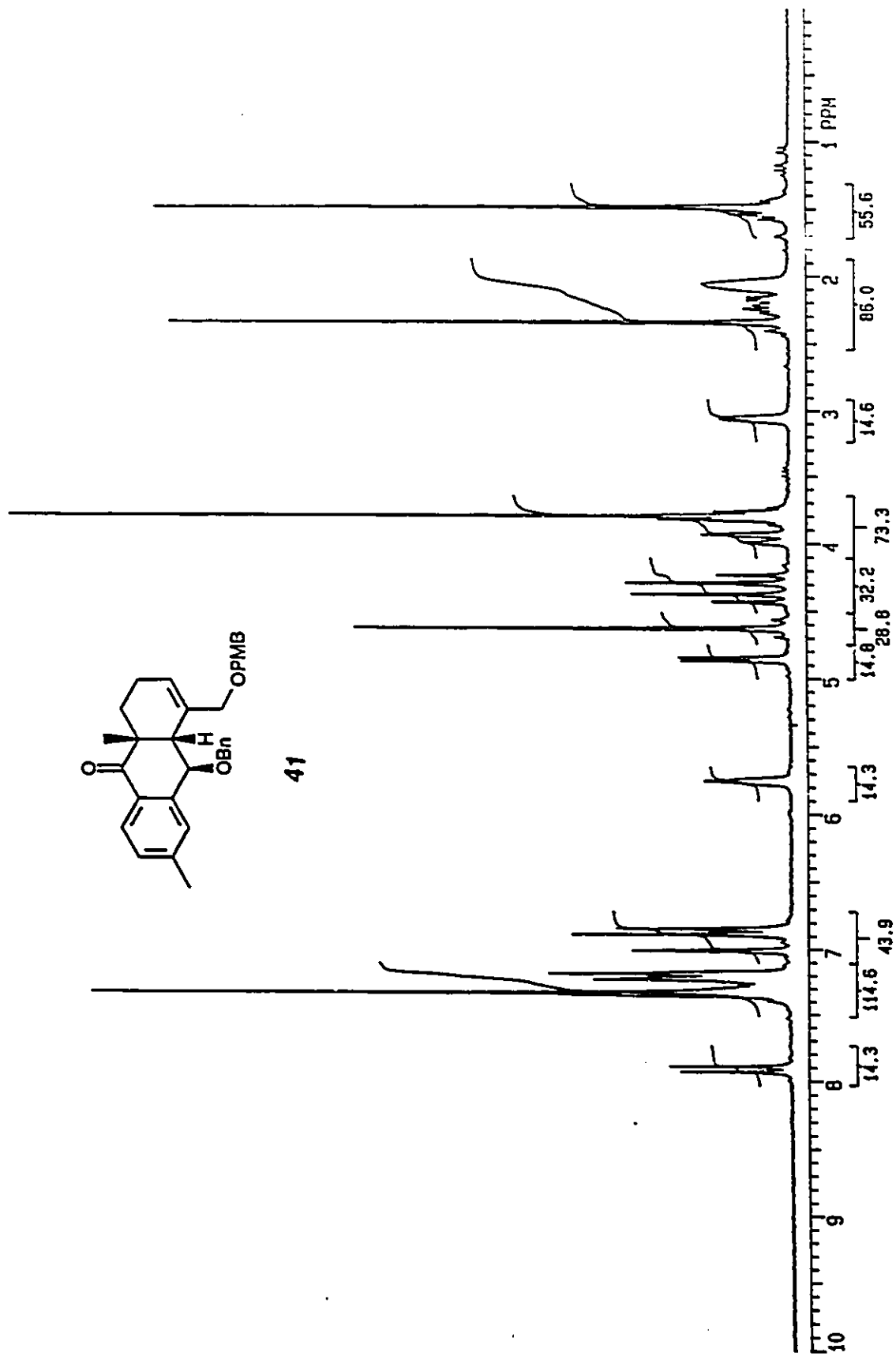
36



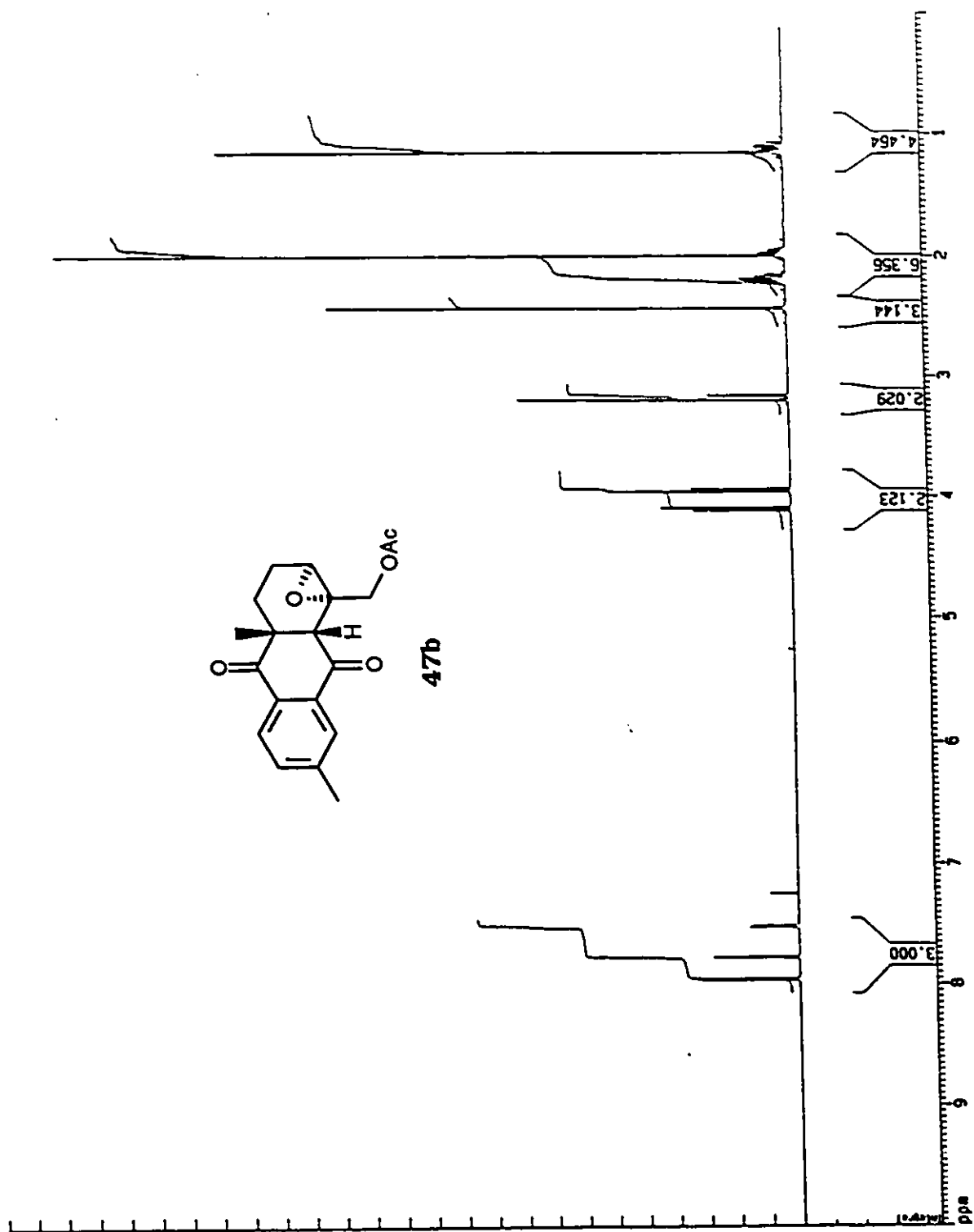
$^1\text{H}$  NMR spectrum (CDCl<sub>3</sub>, 200 MHz) of 36.



<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, 200 MHz) of 39.



<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, 200 MHz) of 41.



<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>, 500 MHz) of **47b**.

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- <sup>25</sup> These compounds possess a structural similarity to some under investigation by Bio Chem Pharma in Montreal.