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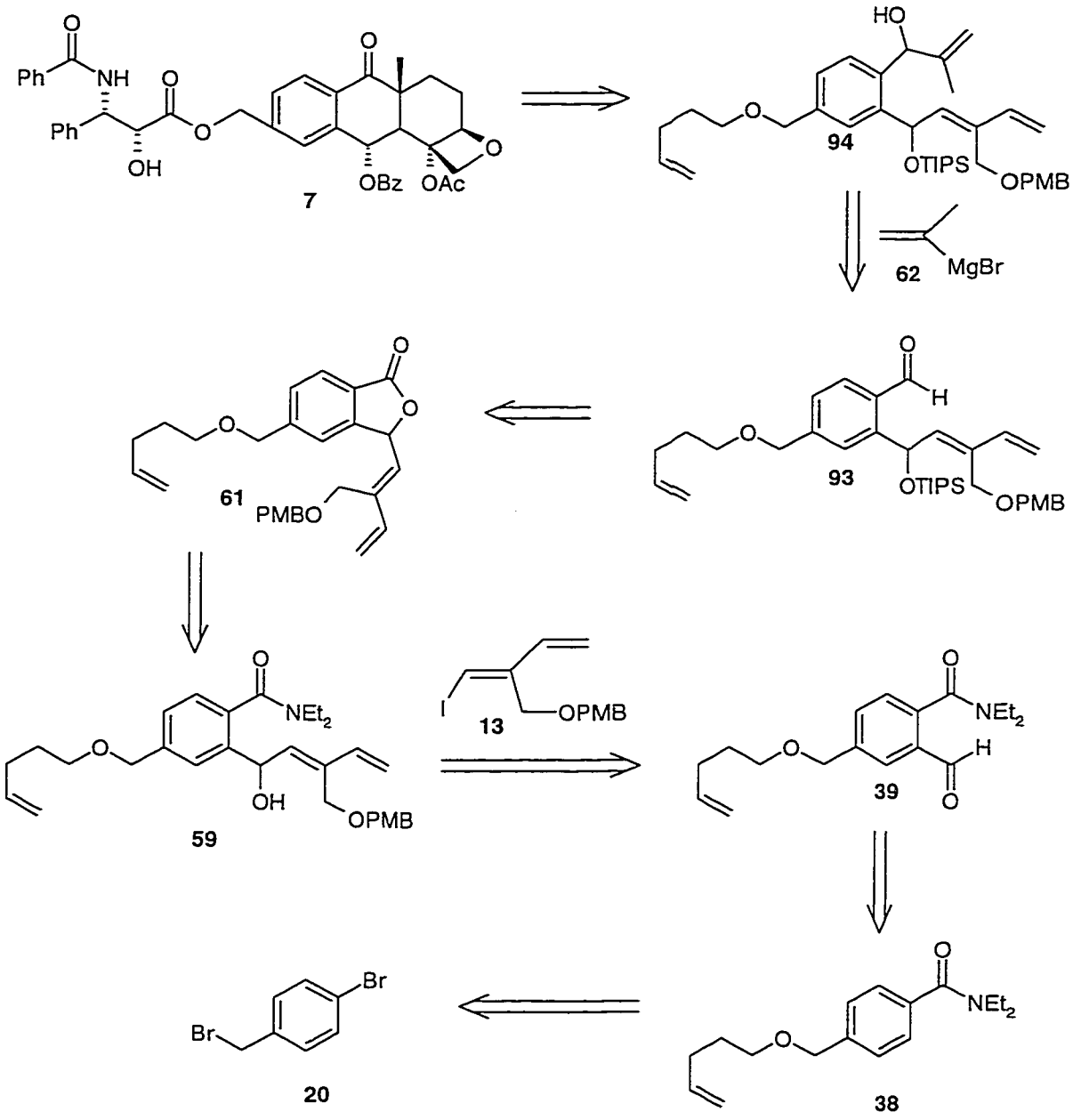
Abstract

The design and synthetic strategy towards a taxoid analogue that contains the important functional groups required for biological activity is described. The key reactions include a directed *ortho* metalation and a tether controlled intramolecular Diels-Alder reaction. Commercially available 4-bromobenzyl bromide (**20**) was successfully converted to the benzamide (**39**) via a metal-halogen exchange reaction, followed by a directed *ortho* metalation reaction. Addition of iododiene (**13**) to the benzamide provided amide **59**. This amide was then lactonized to **61** in quantitative yield. Reduction of the lactone has yielded the diol in good yield. Oxidation of the selectively protected diol would give aldehyde **93**, which after Grignard addition will produce the Diels-Alder precursor **94**.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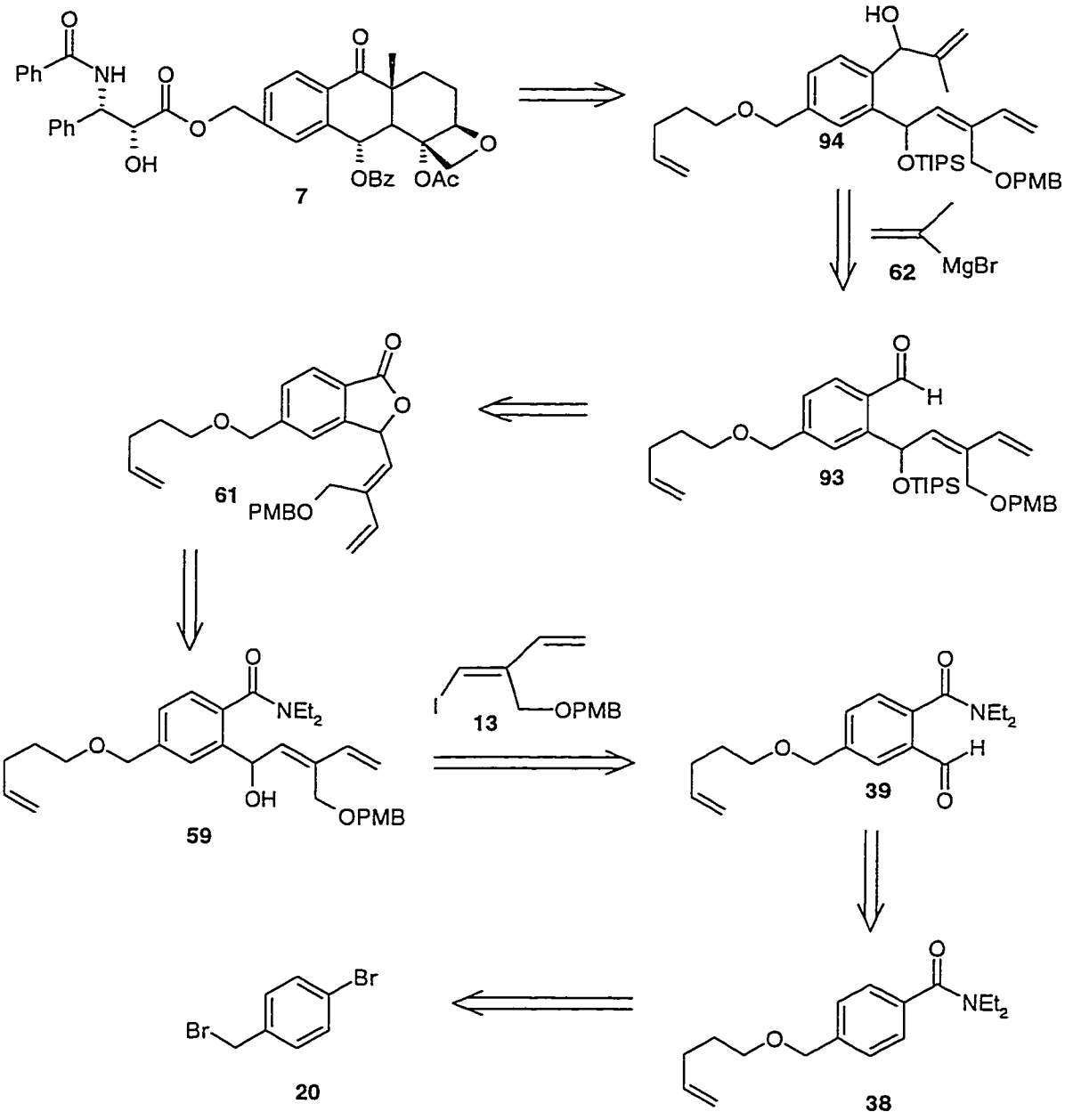
Résumé

La stratégie de synthèse d'un analogue tascoiolique, présentant les groupements fonctionnels principaux requis pour une activité biologique, est presentée. Les étapes clés sont une métalation orientée en ortho et une réaction de Diels-Alder intramoléculaire contrôlée par un groupement téther.

Le bromure benzylique commercial **20** est transformé avec succès en benzamide **39** *via* une réaction d'échange métal-halogène suivie d'une métalation orientée en ortho. L'amide **59** est obtenu par addition du diène iodé **13** à la benzamide **39**. Cette amide donne alors, après une réaction de lactonisation, le dérivé **61** de manière quantitative. Le réduction de la lactone **61** donne accès à un diol avec un bon rendement. L'oxydation du diol, sélectivement protégé, devrait conduire à l'aldéhyde **43** que, après addition d'un réactif de Grignard, permettra l'obtention du précurseur de la réaction de Diels-Alder intramoléculaire.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Acknowledgements

I would like to sincerely thank Dr. Alex Fallis. He accepted me into his group and, in doing so, provided me with a very valuable learning experience. I thank him for all his support, ideas and his encouraging words over the past two years.

A special thank you must also be said to Dr. Peter Wilson for all his creative ideas and advice he gave to this project, and Dr. Simon Woo for his unlimited patience, helpfulness and knowledge. To Pat, thanks for all the help over the last six years and for everything else you've done for me along the way. I wouldn't have gotten this far without you. Also, Simon and Pat, thanks for being my editors, I appreciate all the time you spent proofreading this thesis. Helen (a.k.a. Ben Johnson) thanks for making everything an adventure. Thanks to Shawn for all the laughs and cookies. I'd like to thank Stephanie L. for all her helpful ideas and pour tout l'aides avec mon francais. A big thank you to everyone else in the group for all the little things over the years, Poonam, Irina, Stephanie P. and Tanya. I also must thank Raj Capoor and Dr. Glenn Facey for all the help they've given me over the years and all the NMR samples they've run on last second notice.

Finally, I'd like to thank my family and friends. Mom and Dad....you're the greatest. Al...you're great too. To all my friends, they know who they are, thanks for all the good times.

Table of Contents

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List of Abbreviations

Å	angstrom
Ac	acetyl
Anal. Calcd.	elemental analysis calculated
br	broad
Bz	benzoyl
n-BuLi	*n*-butyllithium
sec-BuLi	*sec*-butyllithium
tert-BuLi	*tert*-butyllithium
d	doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIAD	diisopropylazodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMG	directed metalation group
DMSO	dimethyl sulfoxide
DoM	directed *ortho* metalation
equiv.	equivalents
FTIR	fourier transform infrared spectroscopy
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
IMDA	intramolecular Diels-Alder
IR	infrared spectroscopy
J	coupling constant
LAH	lithium aluminum hydride
LUMO	lowest unoccupied molecular orbital
m	multiplet
m-CPBA	m-chloroperoxybenzoic acid

M	moles per litre
MOM	methoxymethyl
NBS	N-bromosuccinimide
NCI	National Cancer Institute
NMR	nuclear magnetic resonance
PG	protecting group
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
R	alkyl
s	singlet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
p-TsOH	*para*-toluenesulfonic acid

1 Introduction

Cancer is a family of deadly diseases which strikes thousands of Canadians each year. On April 24 1998, Cancer Care Ontario released a report stating that cancer had surpassed heart disease to become the leading cause of premature death in Ontario. In the 1960's, heart disease killed twice as many people as cancer. Today, the cancer mortality rate is 20% higher than that for heart disease.[1] Together, breast, lung, prostate and colon cancer account for more than half of all reported cancer cases.

Breast cancer is the leading cause of death in women, and it alone will affect approximately 10% of females in North America.[2] It is estimated that this year, 19,300 new cases of breast cancer will be reported in Canada, and another 180,300 in the United States. Each year 5,400 die of breast cancer in Canada, while in the U.S., a staggering 40,000 deaths are attributed to the disease annually.[3] The Ontario provincial government will spend in excess of 1.6 billion dollars this year on cancer treatment, prevention education, awareness and support services. The federal and provincial governments both commit billions of dollars to combat cancer; however, the cure continues to elude researchers.

In 1962 extracts from the Pacific Yew *(Taxus brevifolia)* were collected by the National Cancer Institute (NCI) in a large scale screening process designed to find new antitumor compounds of natural origin. Two years later, the extracts from the Yew tree were found to be active in a cytotoxicity assay. This was the beginning of the development of the drug now commonly referred to as Taxol®.

Paclitaxel (Taxol®, **1**, Figure 1) received world-wide interest due to its unique mode of action. At the time, many of the drugs on the market and under development (colchicine, podophyllotoxin, vinblastine) were spindle poisons, meaning they inhibited tubulin polymerization.[4] In contrast, Taxol® actually promotes tubulin polymerization and inhibits the disassembly of the stabilized microtubule[4a], which is necessary for cell replication.[5] Epothilones and eleutherobin are known to have modes of action similar to Taxol.®[6] A smaller and simpler molecule, GS-164, has been recently found to also operate by a similar mechanism.[7]

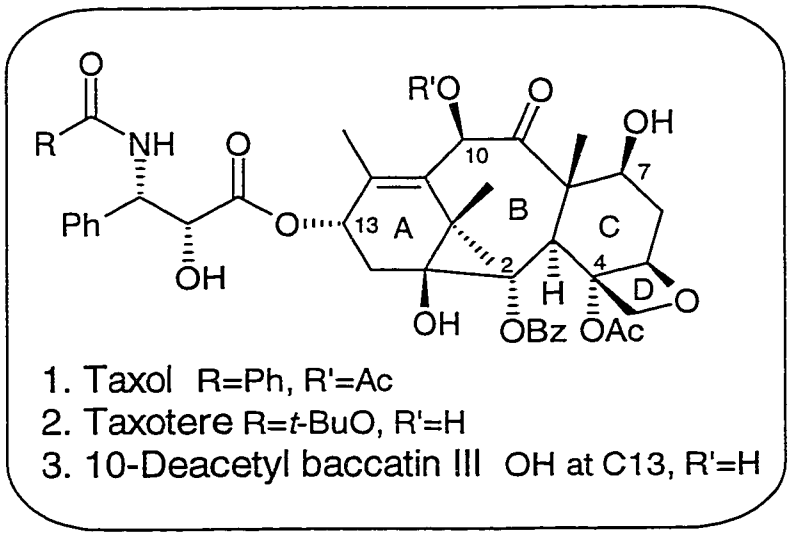


Figure 1: Structure of Taxol® and related compounds.

1.1 General Background

1.1.1 Taxoid Development

For centuries it has been known that the extracts from the Yew tree were fatal to humans. Julius Caesar reported that Catuvolcus committed suicide by taking extracts from the yew tree, and as far back as 50 AD, it was reported that the juice from the tree was used to treat viper bites.[8] Yet, it was not until the twentieth century that Taxol's® full medicinal benefits would be revealed.

In 1963 Taxol® was discovered to have cytotoxicity activity, and in 1967 Taxol® was isolated for the first time. In 1971, the structure of Taxol® and its biological activity were published.[9] It was also found that Taxol® was active against B16 melanoma and MX-1 mammary tumors in 1974 and 1978, respectively.[10] Until this time, Taxol® had yet to receive much attention. The primary concerns were the difficulty in obtaining the compound. However, in 1979 it was discovered by Horowitz and Manfredi that Taxol® had a unique mode of action.[4a] It was this discovery which spawned new interest in the compound, making Taxol® a valuable biochemical tool for studying mitosis, and in the following year Taxol® entered formulation studies and preclinical trials. Within four years, Taxol® entered Phase I Clinical Trials. It was at this time that a serious problem was discovered. Taxol® is very insoluble in water and was formulated as an emulsion with a polyethoxylated castor oil, Cremophor EL. Relatively large doses of Taxol® were required and thus patients also were

administered large quantities of the Cremophor, which for some led to severe allergic reactions, including one death. The problem was eventually solved by lengthening the infusion period and premedicating patients with glucocorticoids and antihistamines.[11] Taxol® then successfully completed both Phase II and III Clinical Trials, and in 1991 the first Canadian woman was treated with the drug.[12]

Taxol® was approved in Canada, the United States and Austria for treatment of ovarian cancer (January) and subsequently approved for breast cancer (December) in 1993.[13] An article in the Toronto Globe and Mail in 1990 read - "Scientists have tried to synthesize the chemical, but ten years of effort have been futile - Taxol's highly complex chemical structure cannot be duplicated." However, in 1994 the first total syntheses were independently reported by both Holton and Nicolaou's groups.[14,15] Since that time, three other groups have published total syntheses of Taxol®.[16]

1.1.2 Taxoid Dosage and Supply

One of the serious concerns over the use of Taxol® as an anti-cancer drug, and the primary reason why it was delayed for clinical use, was the limited supply of the drug. The Pacific yew is a slow-growing conifer which is usually found in moist soils, in the understory of old conifers and hardwoods.[17] A mature tree rarely exceeds 60 cm in diameter and 12 m in height. The concentration of taxol in the needles is 20-70 ppm while the concentration in the bark is 70-140 ppm. Taxol® was initially only isolated from the bark of the yew trees in yields of

approximately 0.007%. The yield from the bark has now doubled to 0.014%.[18] This equates to 100 mg of the drug from 1 kg of dried bark.

A pilot plant contracted to the NCI could only handle about 5000 kg of bark per year to produce only 500 g of pure Taxol® annually.[19] This is below useful quantities, since each patient could require 2 g of Taxol®. The trees are also important roosting habitats for endangered species, such as the spotted owl, and other birds. The collection of large amounts of bark for clinical trials (27000 kg in 1989) raised concerns about the impact of continued collection on the ecology of the U.S. Pacific Northwest and the survival of the *Taxus brevifolia*. It quickly became apparent that due to the slow growth of the trees and the killing of the trees by harvesting bark, Pacific yew bark was not a sustainable resource for Taxol® production. Various solutions to this problem have been proposed and include total synthesis, partial synthesis, Taxol® analogues, plant tissue culture and fungal sources.

Total synthesis, although it has been successfully accomplished, relies on an extensive sequence of steps and results in a low overall yield. The most recently published synthesis of Taxol® is 60 steps![16e] The highly oxygenated, complex nature of the molecule has prevented any economically feasible commercial production. It is known that internal eight-membered rings are difficult to synthesize due to entropic and enthalpic factors,[20] and the synthesis is complicated further by the necessary incorporation of a geminal dimethyl group. In addition, the A ring contains a bridgehead double bond and the C ring

is *trans*-fused with an angular methyl group. Finally, Taxol® contains many defined stereocentres, which further complicates the synthesis.

One of the more favourable routes is semisynthesis. The Taxol® precursor, 10-deacetyl baccatin III (**3**, Figure 1), can be isolated from the needles of *Taxus baccata* and other yews in 0.1% yield, and thus is a more renewable resource than the bark because the tree is not killed from the harvesting.[21] Docetaxel (Taxotere, **2**, Figure 1), is also prepared via a semisynthetic route from 10-deacetyl baccatin III and has been reported to be more active than Taxol® in murine and human tumor cell lines.[22] These options are still far from ideal because they rely on potentially limited resources.

Both plant tissue cultures and fungal production currently yield very low quantities of Taxol®.[23] They might however become feasible using both classical techniques and genetic engineering.

The disadvantages and difficulties in the above methods could be avoided using Taxol® analogues. These analogues ideally would be smaller compounds which are much easier to synthesize and possess cytotoxicities comparable to or better than that of Taxol®. There are four basic types of analogues that may be considered: 1) close chemical analogues prepared from naturally occurring taxanes; 2) close chemical analogues with substituents not accessible from natural taxanes; 3) significantly simplified analogues prepared by total synthesis and retaining only critical shapes, groups and electronic properties; 4) biological analogues binding at the same site on microtubules but with fundamentally different chemical structures. A number of analogues have been prepared under

type 1 classification[24] as well as a few reports of type 2 analogues.[25] A number of structure-activity relationship studies are currently ongoing world-wide in an attempt to gather more data to allow for the design of type 3 analogues. Finally, type 4 analogues give rise to peptide sequences with Taxol®-like activity.

1.1.3 Structure Activity Relationships

Research into structure-activity relationships of Taxol® is still incomplete, although a substantial amount of information has been obtained. The molecule can be divided into three basic areas: the side chain, the northern perimeter and the southern perimeter.

The presence of the C-13 side chain is an absolute requirement for activity. Cleavage of the side chain, to give Baccatin III, significantly reduces the activity in both cytotoxicity assays and tubulin-assembly assays.[8,26] The hydroxyl substituent at C-2' and the phenyl group at C-3' are also both needed for activity.[27] Several analogues have been prepared with substituted 3'-phenyl groups, but all have been less active than Taxol®.[28] Variation of the substituents on the nitrogen at C-3' is tolerated, including aromatic or aliphatic groups such as amides or carbamates. One such analogue, Taxotere®, which has an N-*t*-butoxycarbonyl group in place of the N-benzoyl group (and lacks the C10-acetate), has been found to be about five times as active as Taxol®.[29]

The 'Northern perimeter' of Taxol® includes carbons 6-12, with oxygen functionalities at C-7, C-9 and C-10. In general, structural variations along the

upper edge of the molecule do not affect activity, suggesting this region is not directly involved in binding to microtubules. The alcohol at C7 may be esterified, epimerized or even removed without any significant loss in activity.[30] Very little change in activity is observed with either reduction of the carbonyl[31] at C-9 or removal of the C-10 acetoxy group.[32]

The 'Southern perimeter' of Taxol® comprises C1-5 and C-14, with oxygen functionalities at C-1, C-2 and C-4, and the unusual oxetane ring at C-4 and C-5. In contrast to the flexibility of the functionalities of the upper perimeter, structural changes in the lower portion of the molecule have major effects on activity. The oxetane ring is crucial to activity and ring opening drastically reduces Taxol's® performance in both tubulin-assembly and cytotoxicity assays.[33] The oxetane is relatively chemically inert, suggesting its role may simply be to act as a lock to maintain the conformation of the diterpenoid ring system. The benzoyloxy group at C-2 is also important, since deoxygenation results in an inactive product.[34] Many analogues have been synthesized with substituted benzoyl groups; in general the *m*-substituted derivatives are more active than the corresponding *p*-substituted analogues.[35] π-stacking interactions between the phenyl groups of the side chain and the C-2 benzoyl group have been proposed to rationalize the importance of the benzoyl group.[36] Yet, the difference in *m*- and *p*-substituted benzoyl analogues suggests steric factors must also come into play.

1.1.4 Taxol® Analogues

With the extreme difficulty involved in the total synthesis of Taxol®, it is not surprising that a number of research groups world-wide have worked on or are currently working on analogues. Using the information gathered thus far regarding structure-activity relationships, a number of simpler molecules have been designed and synthesized with the hope of finding a drug more cytotoxic than Taxol® itself. A smaller and simpler molecule, with activity comparable to Taxol®, would allow for efficient large scale industrial production. Most of the analogues are based on the same diterpenoid framework[37], with modifications at C-2[38], C-4[39], C-7[40], C-10[5a, 37a, 39a] or at the N-terminal or C-3' of the side chain[41].

1.1.5 Novel Taxol® Analogues

Our laboratory has had an ongoing interest in the synthesis of Taxol® analogues. A number of analogues have been proposed and synthesized from simple, inexpensive and readily available starting materials. The analogues are designed following the results of structure-activity relationships. The molecules are less complex than Taxol®, although it is still hoped that they will possess activities similar to, or better than, Taxol®. Computer assisted molecular modeling has allowed the design of compounds with similar spatial shape to that of Taxol®. It is hoped that maintaining the same basic shape might give the

molecule the ability to function in a similar manner to Taxol® with respect to the binding sites.

Some of the initial analogues synthesized are shown in Figure 2. In the synthesis of each of these compounds the key step is an intramolecular tether controlled Diels-Alder reaction (IMDA). The tether serves to hold the diene and dienophile in close proximity. The advantage to these types of reactions are two-fold. First, the formation of two rings is observed in a single step. In addition, it has been reported that IMDA reactions can enhance regio- and stereoselectivity.[42] For these reasons, IMDA reactions incorporating removable tethers are commonly used in the synthesis of many natural products.[43] A planar aromatic tether control group was chosen to limit conformational flexibility, which can result in shorter reaction times, lower reaction temperatures and increased stereoselectivity.

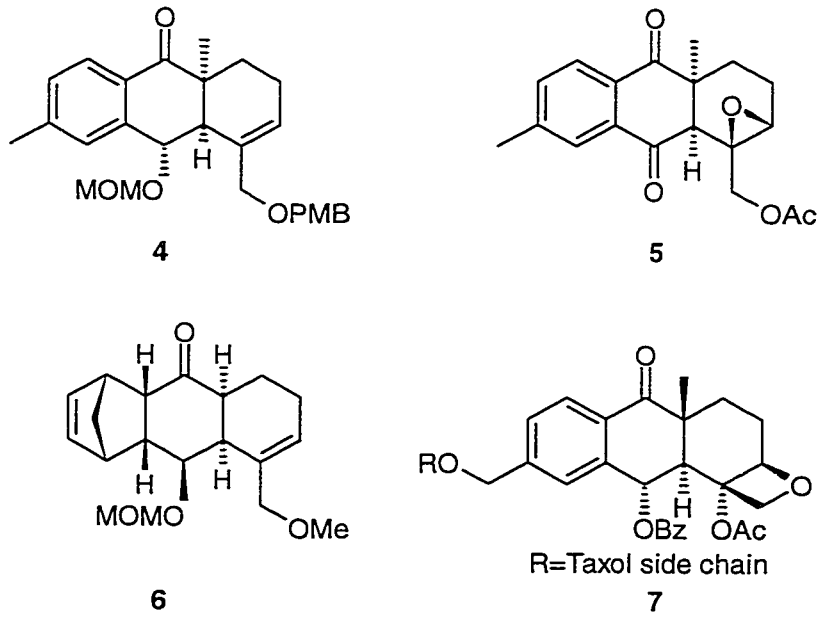


Figure 2: Past (**4-6**) and present (**7**) taxoid analogues.

Compounds **4-6** were successfully synthesized previously as part of a cycloaddition study. Initiallly, it was thought that **7** could be synthesized from a precursor such as **4**; however, this was not the case. It was not possible to functionalize the aryl methyl group. We therefore redesigned our approach to incorporate the oxygen functionality for attachment of the Taxol® side chain at the onset. Analogue **7**, the current target, incorporates all of the necessary moieties for activity. An additional CH_2 spacer was used in the side chain because molecular modeling studies showed the spacer allowed the analogue more flexibility in assuming the general shape of Taxol®. Thus, facilitating complexation into parallel binding sites which may be assisted by π-stacking.

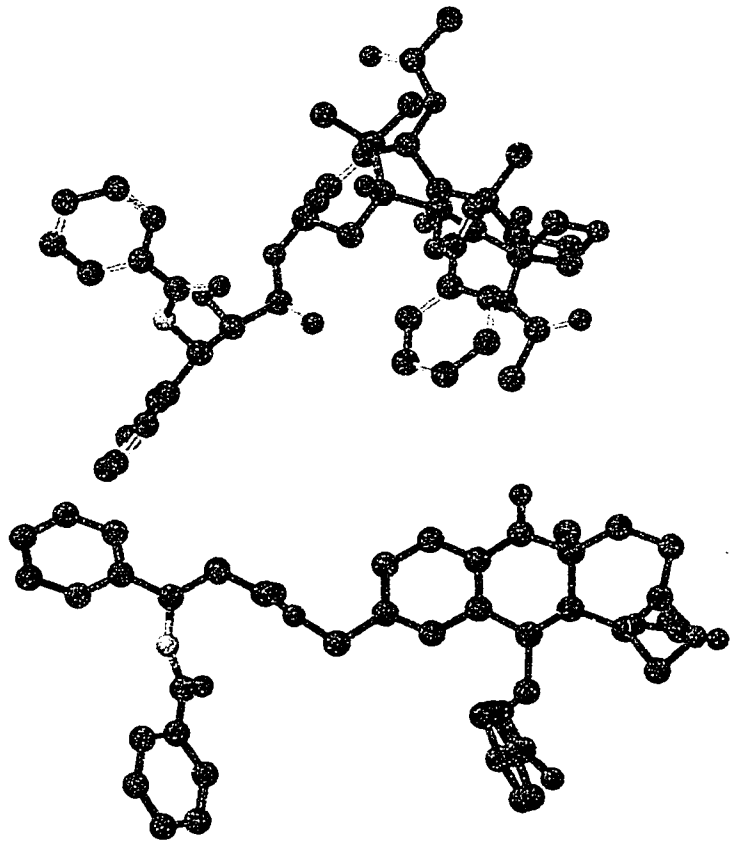


Figure 3: Molecular models of Taxol® (top) and target analogue (bottom).

The A ring in the analogue is planar and without this spacer, the phenyl groups in the side chain do not have the same spatial relations to the lower perimeter of the molecule as is observed in Taxol®. This spacer then allows the side chain to hang down from the ring system, similar to Taxol® (Figure 3).

An additional advantage to the increased flexibility of the side chain is that it may allow the molecule to more easily attain the proper conformation in the binding site. It was hoped that the resemblance in shape and functional groups to Taxol® would allow the target analogue (**7**) to exhibit similar biological activity. As in the previously synthesized analogues, the key step in the synthesis of the target will be an intramolecular Diels-Alder reaction.

1.1.6 Diels-Alder Chemistry

It was intended that an intramolecular Diels-Alder reaction would be used to gain access to the desired ring system. The Diels-Alder reaction is one of the most powerful tools in modern synthetic chemistry. Discovered in 1928 by Diels and Alder, this thermally allowed [4+2] cycloaddition presents a convenient and highly stereospecific route to six-membered rings.[44] The reaction results in the formation of two new σ bonds and a π bond, with the creation of as many as four new stereogenic centres.

Ideally, the diene has an electron-donating group, and the dienophile an electron-withdrawing group. However, the reaction can occur in the unsubstituted case. These complementary electronic substituents decrease the

HOMO-LUMO gap, and therefore increase the reaction rate, by increasing the energy of the HOMO of the diene and decreasing the energy of the LUMO of the dienophile. Inverse electron demand may also occur when the diene has electron-withdrawing groups and the dienophile has electron-donating groups.

A requirement for the reaction to occur is the diene must be in the *s-cis* conformation in order to allow for correct orbital overlap. Therefore, in general, dienes with an exocyclic double bond cannot react, but endocyclic double bonds react readily. The reactivity of open chain dienes depends on the equilibrium constant for the conformational interconversion. A 1-substituent favours the *s-trans* form and slows the addition rate, while a 2-substituent favours the *s-cis* form and enhances the rate.[45]

One of the most important features of the Diels-Alder reaction is that it is stereospecific. The stereochemistry of the starting dieonophile is maintained during the reaction and a single product diastereomer results, as shown in Figure 4.

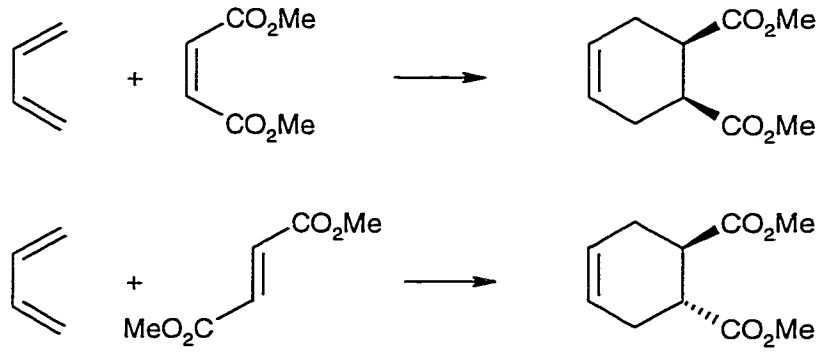


Figure 4: Retention of stereochemistry in a Diels-Alder reaction.[45b]

A second important stereochemical feature is that the *endo* product is preferred over the *exo* product (Figure 5).

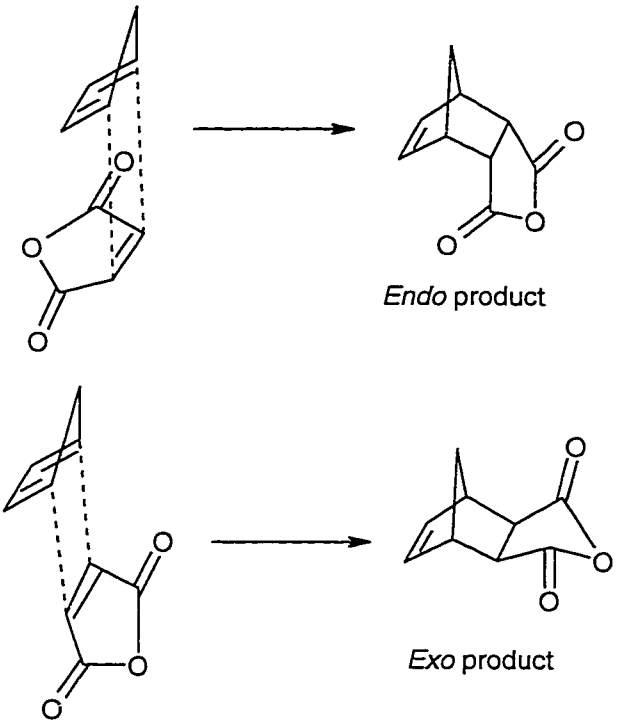


Figure 5: *Endo* and *Exo* approaches in a Diels-Alder reaction.

If the dienophile is unsymmetrical it can approach the diene in two different orientations. In the *endo* approach, the dienophile substituents are under the π orbitals of the diene, whereas in the *exo* approach the dienophile substituents do not overlap with the diene (shown in Figure 6). When the dienophile has an unsaturated substituent, such as a carbonyl group, the secondary orbital overlap observed in the *endo* approach stabilizes the transition state and is favoured.

In the case where both the diene and dienophile are unsymmetrical, two regioisomers can result. When a dienophile containing a heteroatom reacts with

a 1-substituted diene, the *ortho* product is normally preferred over the *meta* product. With 2-substituted dienes, the *para* product usually is generated instead of the *meta* isomer.

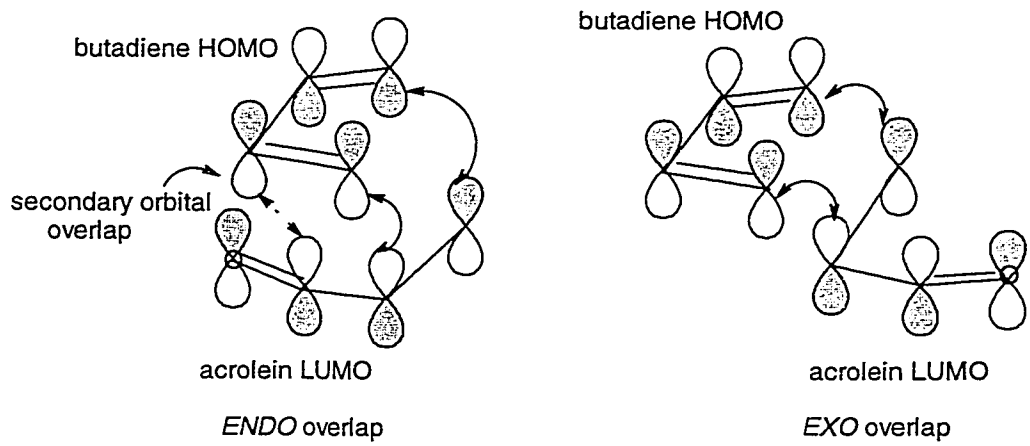


Figure 6: Secondary orbital overlap in *endo* transition state.[46]

1.2 Research Objectives

1.2.1 Retrosynthetic Plan

The previous synthetic routes did not allow for the synthesis of the desired target analogue (**7**). It was decided that following a route which was similar to what had been accomplished previously in the group, beginning with the aromatic tether being fully oxygenated in all the required positions, would allow for the synthesis of **7**. As shown in the retrosynthetic plan in Figure 7, the key step to gain access to the tricyclic core was an *ortho* metalation followed by an intramolecular Diels-Alder reaction in which a planar aromatic group would act as

a tether. Addition of the pentenyl chain to **11**, followed by a metal-halogen exchange reaction and addition of DMF as the electrophile gives **10**. The iododiene (**13**), which is prepared in our laboratory from propargyl alcohol,[47] can then be added to the aldehyde to give **9**. Directed *ortho* metalation of **9**, followed by a quench with methacrolein (**12**) would give the Diels-Alder precursor, **8.**

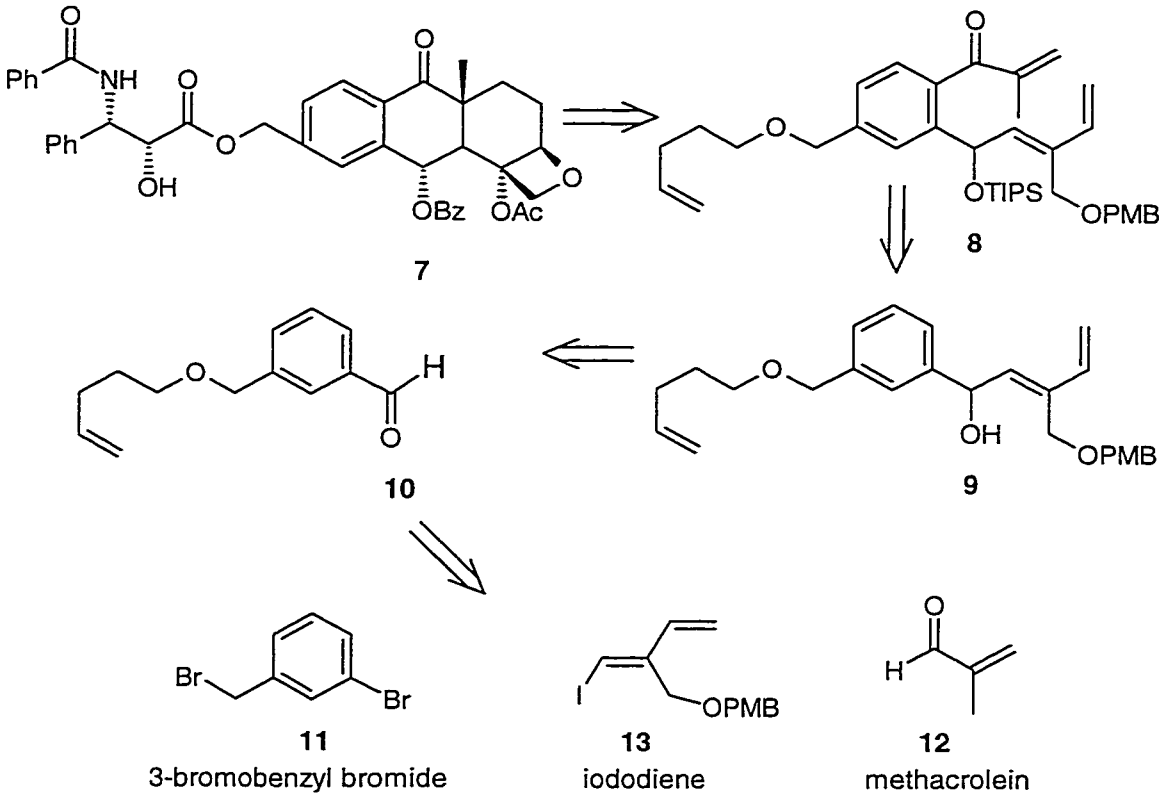


Figure 7: Retrosynthetic plan for the synthesis of Taxol® analogue.

1.2.2 Preliminary Work

It had been shown previously that 3- methylbenzyl alcohol can be lithiated *para* to the methyl group. Quenching of the lithium anion with methacrolein put the dienophile piece in place. The resulting diol was first mono protected

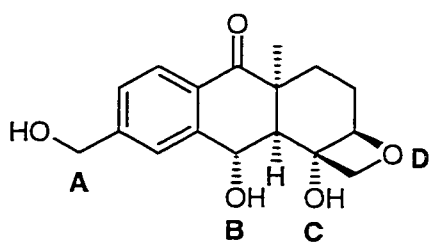
(preferentially protected the 1° over the 2° alcohol) with TBDMSCl, followed by protection of the remaining alcohol with TIPSOTf. The TBDMS group was removed using standard conditions to reveal again the 1° alcohol which was oxidized with Dess-Martin periodinane to the corresponding aldehyde. The iododiene (**13**) was added to the aldehyde via a metal-halogen exchange reaction. The resulting alcohol was then protected as a MOM ether and the TIPS protecting group removed, followed by oxidation to the corresponding ketone. The ketone then underwent an intramolecular Diels-Alder reaction at temperatures slightly higher than room temperature. The tricyclic was further manipulated in an attempt to reach the desired analogue. Unfortunately, it was found that functionalization of the methyl group was impossible, and this was crucial in order to connect the Taxol® side chain. The side chain, as previously discussed, is absolutely necessary for biological activity. A new route was required which would allow for the functionalization to be established at the site of side chain addition.

2 Results and Discussion

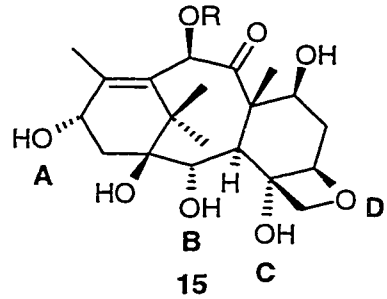
2.1 Molecular Modeling Studies

The target analogue was designed with two factors in mind. The first was that it should contain all functionalities necessary for activity, as defined by structure-activity relationship studies. Secondly, it was felt that it was important that the target have the same general shape as Taxol® for maximum effectiveness in the binding sites. With the use of molecular modeling, the target was designed. As previously explained, the synthetic route would involve an intramolecular Diels-Alder reaction utilizing a planar aromatic group as a tether control element. The CH_2 spacer was then included to increase the flexibility of the side chain. Thus better allowing the molecule to mimic the general shape of Taxol®. The structures were somewhat simplified for modeling purposes due to the limitations of the software. It should also be noted that distances to the side chain oxygen were in fact measured to the carbon attached to the benzene ring. It was believed that this would provide a somewhat more accurate distance than the oxygen itself which is free to orient itself in a variety of positions. This would however result in a slight underestimation of the actual distance to the oxygen. The results of the modeling studies are shown below in Figure 8. As is clearly seen, the similarity in the oxygen separation distances between the target and Taxol® indicate the target analogue's key functionalities possess similar spatial

arrangements to those found in Taxol®. These values are within 2Å for the important centres and thus confirm the suitability of **7** as a promising Taxol® mimic.



14



15

simplified target model	simplified Taxol model
A-B 5.04 Å	A-B 5.16 Å
A-C 7.71 Å	A-C 5.74 Å
A-D 9.22 Å	A-D 8.28 Å
B-C 2.80 Å	B-C 2.76 Å
B-D 5.21 Å	B-D 3.94 Å
C-D 3.12 Å	C-D 3.02 Å

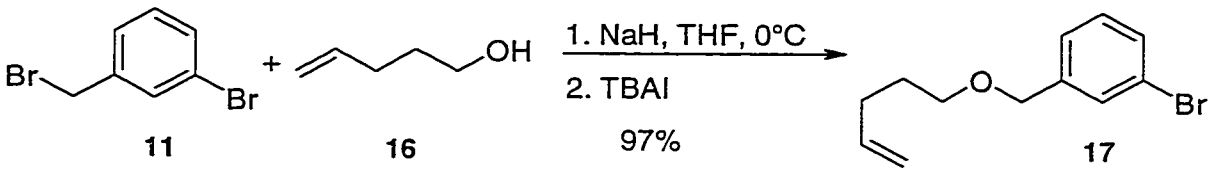
Figure 8: Comparison of important relative oxygen separation distances.

2.2 Initial Synthetic Routes

2.2.1 Previously Established Pathway

The first attempt to synthesize the target (**7**) focused on the use of previously developed chemistry. The difference between the two routes was that now a pentenyl side chain would be put in place in the first step, as opposed to the methyl group previously. This would allow for easier attachment of the Taxol® side chain as this position would already be functionalized. 4-Penten-1-

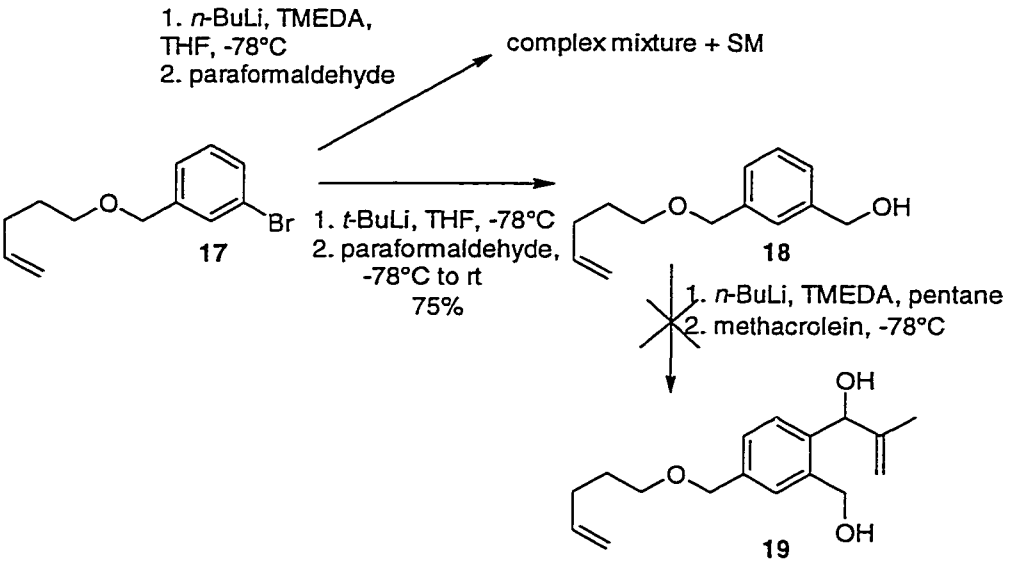
ol (**16**) was deprotonated with sodium hydride using standard conditions and the addition of commercially available 3-bromobenzyl bromide (**9**) resulted in the desired displacement product (**17**), as shown in Scheme 1.



11 **16** **17**

Scheme 1

The next step involved the conversion of bromide **17** to a directed metalation group (DMG). A benzyl alcohol would allow for insertion of methacrolein via a directed *ortho* metalation (DoM) reaction and could then be oxidized to the corresponding aldehyde for addition of the diene (**13**).[48] The conversion of the bromide to the benzyl alcohol proved troublesome; but, conditions were established that allowed for successful lithiation followed by a quench with paraformaldehyde to give the desired product **18** in 75% yield (Scheme 2). Unfortunately *ortho* metalation of this material to give **19** was not possible.



Scheme 2

The problem was there now existed two similar DMG's. Regardless of the conditions it was not possible to isolate any DoM product at the desired site. Three potential lithiation sites were available. The most likely site of lithiation was *ortho* to both DMG's, as it was doubly activated. Therefore, selective metalation was not possible.

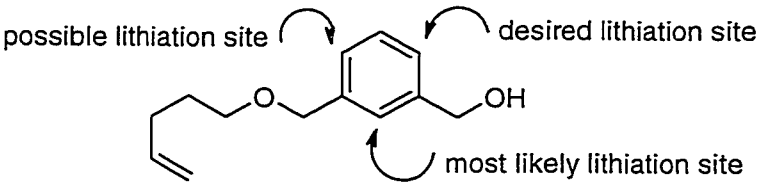
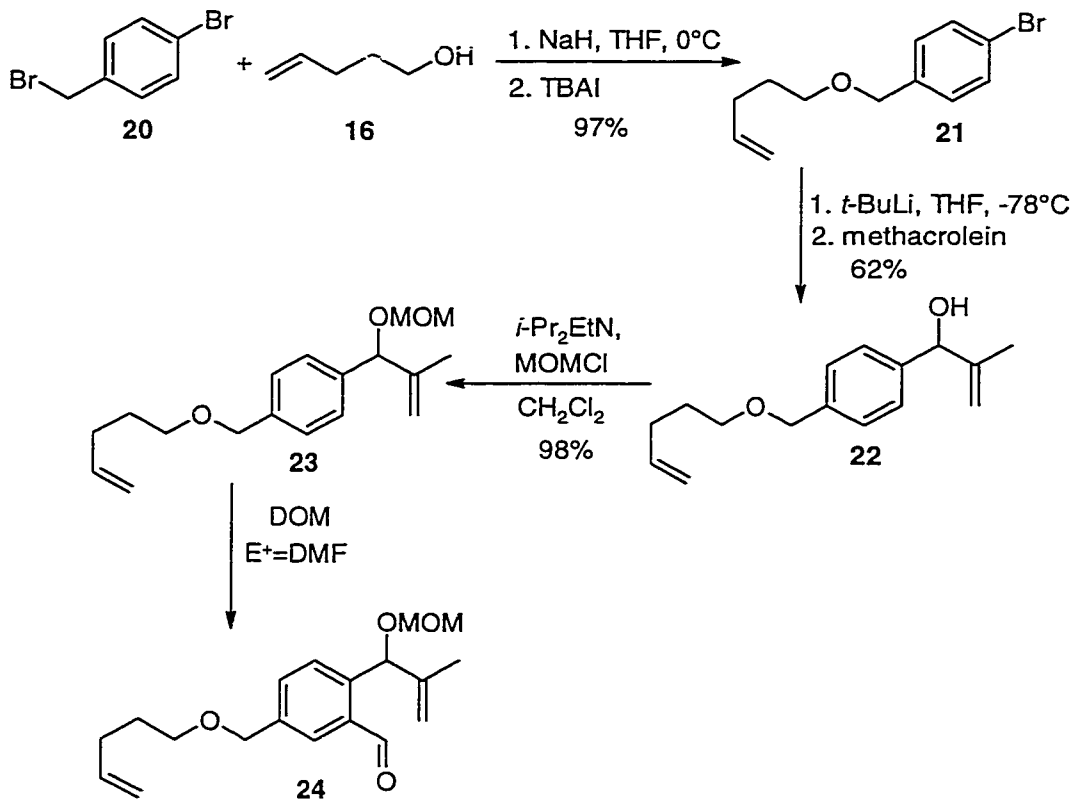


Figure 9: Possible *ortho* lithiation sites of benzyl alcohol **18**.

2.2.2 The Symmetrical Approach

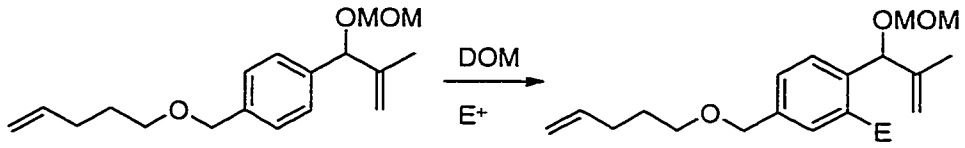
It was thought that starting with 4-bromobenzyl bromide (**20**), rather than 3-bromobenzyl bromide (**11**), would result in a symmetrical molecule and thus minimize the selectivity problem. The only difference was now the bromide would be lithiated and quenched with methacrolein rather than paraformaldehyde, as this was now the upper portion of the molecule. Protection of the resulting alcohol (**22**), as a methoxymethyl ether (**23**), would provide a known DMG.[49] Directed *ortho* metalation and quenching with an electrophile such as DMF would install the aldehyde to give **24.** In contrast with the previous route, the correct oxidation state is obtained immediately, and thus the oxidation step is eliminated. The results are shown in Scheme 3. The pentenyl alcohol was added, using the same conditions as previously established, and resulted in the desired product **21** in quantitative yield. Lithiation of **21**, followed by methacrolein quench provided **22** in 62% yield. The use of *n* and *sec*- butyllithium afforded no improvement in yield. Protection of alcohol **22** using diisopropylethylamine and chloromethyl methyl ether under standard conditions gave the MOM protected material in quantitative yield.



Scheme 3

The DoM reaction again proved very difficult and numerous conditions were attempted, as outlined in Table 1. Entries A and B show typical metalation conditions. In each case, no aldehyde peak was observed in the crude ^{1}H NMR spectra. A D_2O quench was conducted to confirm that the compound was in fact being lithiated and that it was lithiated in the correct site. Unfortunately, the results from this reaction were inconclusive as a very complex mixture was obtained. In an attempt to force the reaction to proceed, the reaction was warmed as indicated in entry D. Changing the butyllithium used again did not lead to any desired product (entries E and F), nor did repeating the reaction without the TMEDA (entry G). Changing solvents also did not result in any

desired product (H, I). Finally, knowing that TMSCl is a very effective electrophile, the reaction was quenched accordingly to provide the TMS compound. Again, only starting material was isolated. Using these conditions another D_2O quench was attempted, and the ^1H NMR clearly showed four aromatic protons were present. This confirmed that the aromatic ring was not being lithiated. Thus, it was necessary to investigate a different directing group, if not a different route.



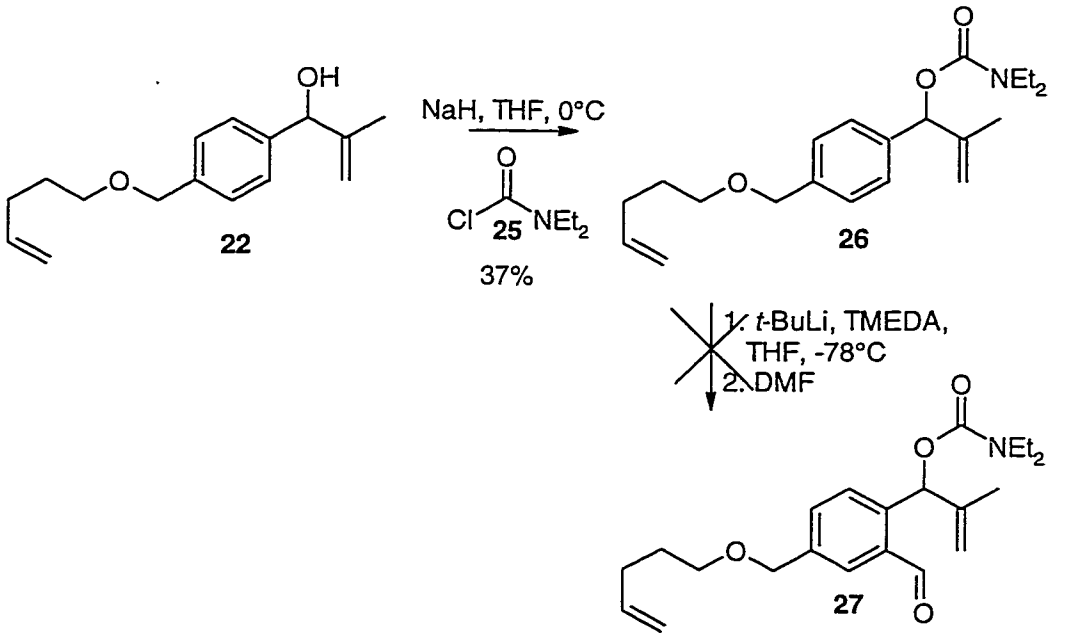
Entry	Conditions	Results
A	1. *n*-BuLi, TMEDA, Et_2O 2. DMF	starting material
B	1. *n*-BuLi, TMEDA, pentane 2. DMF	starting material
C	1. *n*-BuLi, TMEDA, Et_2O 2. D_2O	complex mixture
D	1. *n*-BuLi, TMEDA, pentane, -78°C to rt to reflux 2. DMF	complex mixture
E	1. *s*-BuLi, TMEDA, Et_2O 2. DMF	no CHO signal in crude (^1H NMR)
F	1. *t*-BuLi, TMEDA, Et_2O 2. DMF	no CHO signal in crude (^1H NMR)
G	1. *t*-BuLi, Et_2O 2. DMF	starting material
H	1. *t*-BuLi, THF 2. DMF	complex mixture no CHO signal in crude
I	1. *t*-BuLi, pentane, 0°C 2. DMF	starting material
J	1. *t*-BuLi, TMEDA, Et_2O 2. TMSCl	starting material
K	1. *t*-BuLi, TMEDA, Et_2O 2. D_2O	^1H NMR shows four aromatic protons

note: unless specified, all reactions were conducted at -78°C

Table 1: Attempted DoM conditions on MOM compound.

2.2.3 Carbamate Directed Metalation Group

The most efficient and well recognized directed metalation group is the carbamate, therefore a carbamate protecting group was investigated. Attempts to deprotonate the alcohol using triethylamine failed; however, sodium hydride was more successful as shown in Scheme 4.



Scheme 4

Deprotonation with sodium hydride, followed by the addition of diethylcarbamoyl chloride (**25**) provided the desired carbamate **26** in 37% yield. *Ortho* metalation to give **27** could not be effected. Regardless of the conditions attempted, the DoM reaction always resulted in a complex mixture which never showed an aldehyde signal in the ^{1}H NMR. After some consideration the reasons for the repeatedly failed directed *ortho* metalation became somewhat obvious. In both the MOM case and the carbamate compound, the DMG is not

directly bound to the aromatic ring, rather it is one carbon removed. In both instances, the most acidic proton is not the required one, as indicated in Figure 10. Therefore, it was necessary to find a new route to the target.

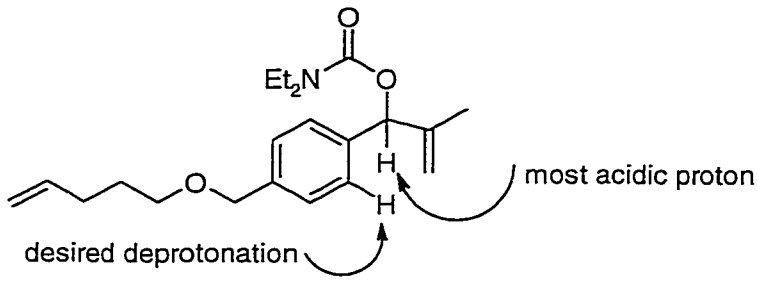
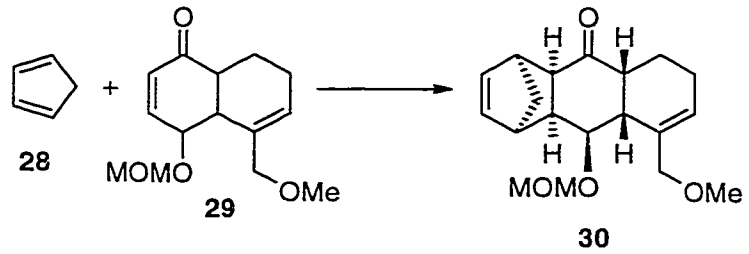


Figure 10: Reasoning for unsuccessful DoM reactions on carbamate **26**.

2.2.4 Diels-Alder Approach

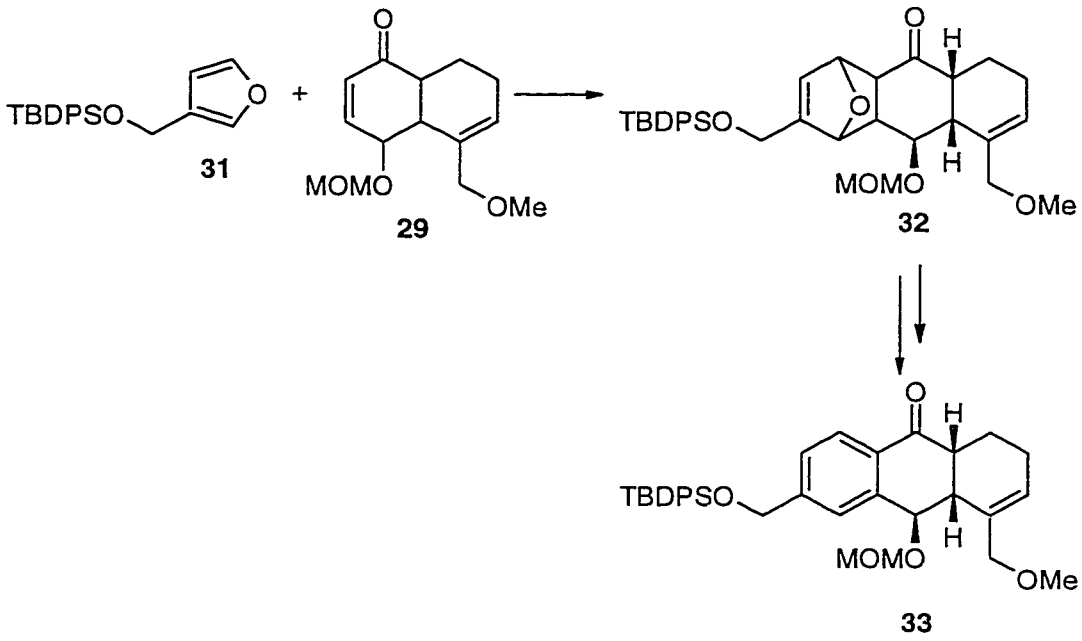
Research previously conducted on taxoid analogues had demonstrated the benefits of intermolecular Diels-Alder chemistry in establishing the ring system. A sample of this chemistry is shown in Scheme 5.



Scheme 5

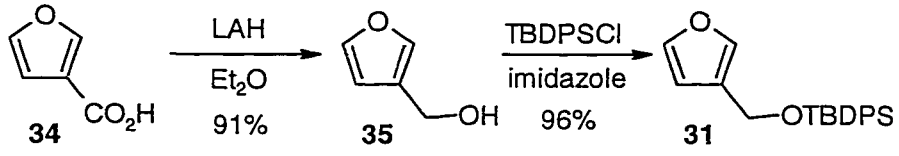
It was proposed that replacement of cyclopentadiene with a substituted furan would yield a tetracyclic ring system which, according to literature precedents, could be opened up and aromatized to the desired corresponding

tricyclic ring system (Scheme 6).[50] The *para* Diels-Alder adduct (**32**) should predominate.



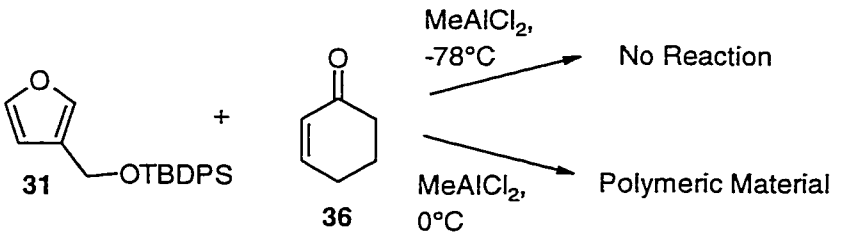
Scheme 6

The substituted furan (**31**) was prepared from commercially available 3-furoic acid (**34**) as shown in Scheme 7. Reduction of the acid using lithium aluminum hydride under standard conditions provided the desired alcohol (**35**) in 91% yield. The alcohol was quantitatively converted into the silyl protected alcohol **31** via reaction with TBDPSCl and imidazole.



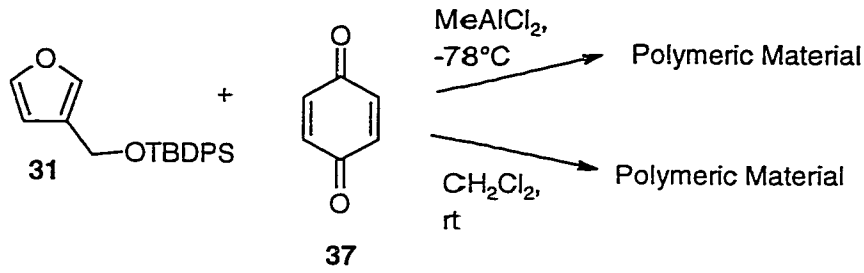
Scheme 7

The Diels-Alder reaction of furan **31** and 2-cyclohexen-1-one, **36** (Scheme 8), with methylaluminum dichloride as catalyst, gave no reaction at -78°C. At 0°C, the reaction gave a black tar, which by ^{1}H NMR appeared to be polymeric in nature.



Scheme 8

The dienophile was changed to 1,4-benzoquinone (**37**), with hopes that the increased reactivity would allow for reaction at low temperatures, thus avoiding the polymerization. 1,4-Benzoquinone is commonly employed as a dienophile in Diels-Alder cycloadditions to form napthoquinones and 1,4-phenanthrenediones.[51] At -78°C, however, a polymeric material was again obtained (Scheme 9). It is assumed that the increased reactivity was such, that even at low temperatures the cycloaddition could not be controlled. The reaction was repeated at room temperature, without the addition of the catalyst, but again a black tar-like material was formed.



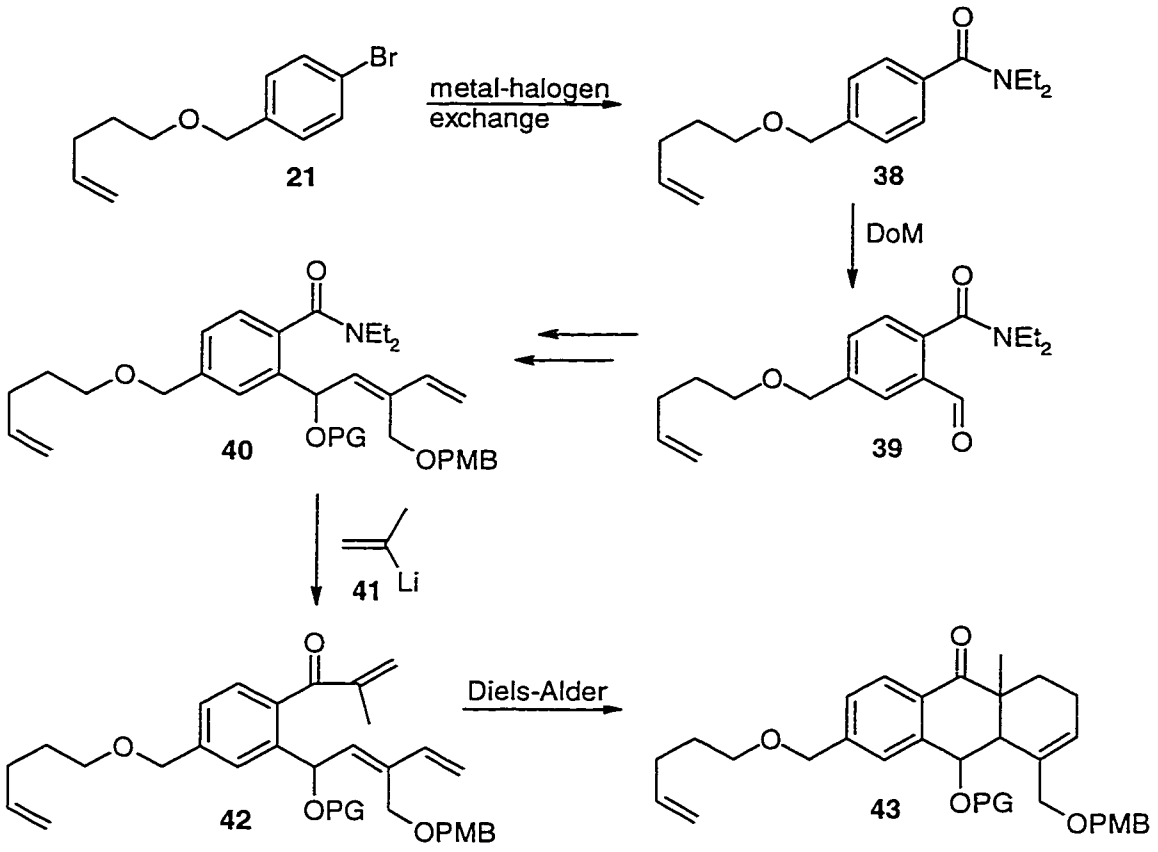
Scheme 9

After this initial investigation into a plausible Diels-Alder route it was decided that the lack of success warranted the termination of this route.

2.3 Current Route

2.3.1 Amide as a Directed Metalation Group

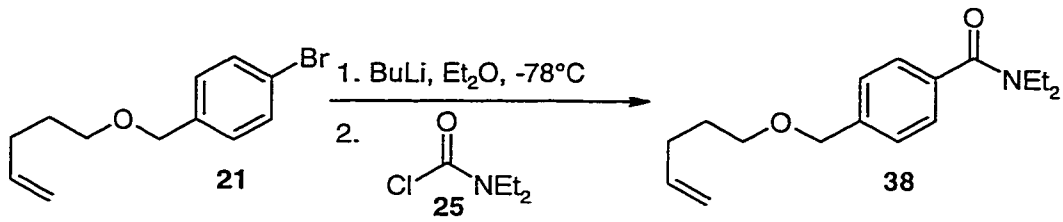
Diethyl amide is a well known directing group and avoids the problem of competing deprotonation. The amide (**38**) was expected to be readily accessible from the bromide precursor (**21**) via metal-halogen exchange. With the amide in hand, the DoM reaction, using DMF as the electrophilic quench, would provide the desired aldehyde (**39**), as shown in Scheme 10. Further manipulation, including addition of the diene (**13**) and protection of the resulting alcohol, followed by addition to the amide would provide access to the Diels-Alder precursor (**42**). Based on past experience in the group, it was believed that the cycloaddition would readily proceed at room temperature.



Scheme 10

2.3.2 Preparation of the Amide

Amide **38** was prepared via metal-halogen exchange. The reaction conditions were optimized and the results of using various BuLi are shown in Table 2.



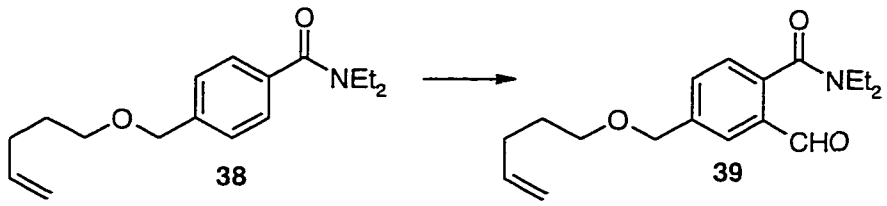
BuLi	Result
n-	SM
sec-	'side product'
tert-	28% 'product' 55% 'side product'

Table 2: Results of conditions for metal-halogen exchange of bromide **21**.

The results, in Table 2, show *n*-BuLi gave no reaction, while *t*-BuLi gave the desired product and an unknown side product with, however, a similar ^{1}H NMR spectrum. The only differences are in one case, for what was believed to be product, the aromatic region is an AA'BB' splitting pattern. The other, which was believed to be a side product, has only a singlet in the aromatic range. In both cases the integration indicated four aromatic protons. The spectrum with the singlet in the aromatic region, displayed broad ethyl group signals with no well defined splitting. This was not the case with the other material, which clearly showed the splitting pattern of both the methylene and the methyl protons. Finally, when the reaction was repeated with *s*-BuLi, it was found that the reaction yielded almost exclusively the unknown side product. The fact the spectra of the product and side product were so similar was of interest, but it was decided to proceed with the synthesis rather than investigate the side product further.

2.3.3 Directed *ortho* Metallation of the Amide.

Various DoM conditions were attempted with the presumed amide product as outlined in Table 3. The most commonly used lithium base for *ortho* metalations is *s*-BuLi.[48] The addition order can sometimes be crucial; thus, entries A and B demonstrate the different reactions. In entry A, the amide was added to the BuLi/TMEDA solution, whereas in entry B, the BuLi was added to a solution of amide and TMEDA. In both cases, the reaction was unsuccessful and yielded a complex mixture. Entry C shows that the D_2O quench again resulted in a complex mixture and the ^1H NMR indicated there were four aromatic protons. In general, these types of reactions are best conducted at -78°C, but it was hoped that warming slightly might promote reaction. Prolonged reaction time (-30°C, 3 days) had no effect. The reaction was repeated using what was originally thought to be side product (the material with a singlet in the aromatic region of the ^1H NMR). As shown in entry E, a trace of aldehyde was observed. Use of paraformaldehyde as the electrophile (entry F) gave no reaction, probably because of solubility limitations. In an attempt to optimize the reaction, *t*-BuLi was substituted for *s*-BuLi (entry G). The optimum conditions are shown in the final entry of the table. The directed *ortho* metalation is most successful when the reaction is warmed to room temperature for 2 hours before cooling it back to -78°C to quench with saturated aqueous ammonium chloride.[52] This is unique because for most DoM reactions it is crucial to maintain the low temperature.



USING 'PRODUCT'

Entry	Conditions	Results
*A	1. *s*-BuLi, TMEDA, THF 2. DMF	complex mixture no CHO
*B	1. *s*-BuLi, TMEDA, THF 2. DMF	complex mixture no CHO
C	1. *s*-BuLi, TMEDA, THF 2. D_2O	complex mixture ^{1}H NMR - 4 aromatic H's
D	1. *s*-BuLi, TMEDA, THF 2. DMF, -30°C, 3 days	complex mixture no CHO

USING 'SIDE PRODUCT'

Entry	Conditions	Results
E	1. *s*-BuLi, TMEDA, THF 2. DMF	trace of CHO signal by ^{1}H NMR
F	1. *s*-BuLi, TMEDA, THF 2. paraformaldehyde	starting material
G	1. *t*-BuLi, TMEDA, THF 2. DMF	CHO in crude little SM remains
H	1. *s*-BuLi, TMEDA, THF 2. DMF, -78°C to rt.	Optimum conditions 76% product

*note: entries A and B involve different addition order (see text)
unless specified, all reactions were conducted at -78°C

Table 3: Attempted DoM conditions on Amide **38**.

The success of the directed *ortho* metalation reaction using what we had believed was side product forced us to go back and examine the metal-halogen exchange reaction further. The ^{1}H NMR spectra of both the product and side product are included in the Appendix. Full characterization of what we had thought was side product conclusively showed that it was in fact desired amide product. The singlet in the aromatic region is surprising because it was not expected that the amide and the ether side chain would be equivalent in terms of

their effect on the shift of adjacent aromatic protons. The poorly defined splitting pattern of the ethyl groups is a result of the hindered rotation of the amide bond and indicates that the signals are close to coalescence. Elemental analysis and high resolution mass spectrometry data support the proposed amide structure.

In order to better understand the nature and reactivity of this side product the material was treated with either tosic acid or HCl, or NaOH, but; in each case the compound was recovered unchanged.

When the reaction was scaled up more of the unknown side product was generated. An initial IR spectrum showed the obvious presence of an alcohol with the broad peak in the 3300cm^{-1} range. After preparing the sample for submission for elemental analysis, another IR was taken to ensure the sample had not decomposed. The alcohol signal was no longer present in the IR spectrum, and in its place there was now a very clear, strong carbonyl stretch. The ^{1}H NMR spectrum was also repeated. The spectrum, as mentioned previously, normally contained broad signals for the ethyl groups of the amide. This time the signals were missing suggesting there no longer was an amide in the compound.

Elemental analysis showed the expected amounts of carbon and hydrogen; however, the amount of nitrogen in the sample was zero. The proposed structure of the elusive side product (**44**) is shown below in Figure 11, and the corresponding proposed mechanism is provided in Scheme 11.

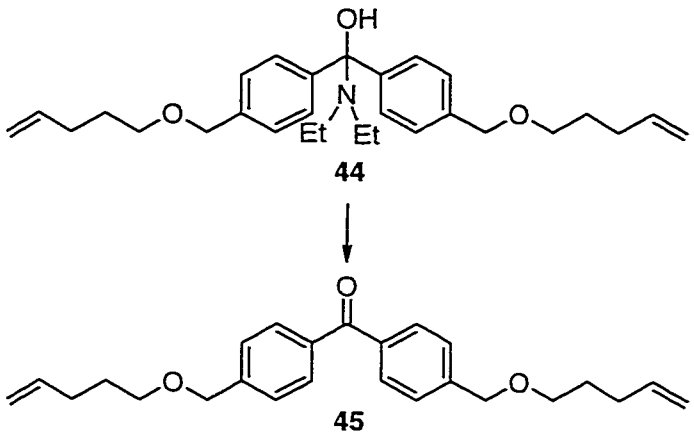
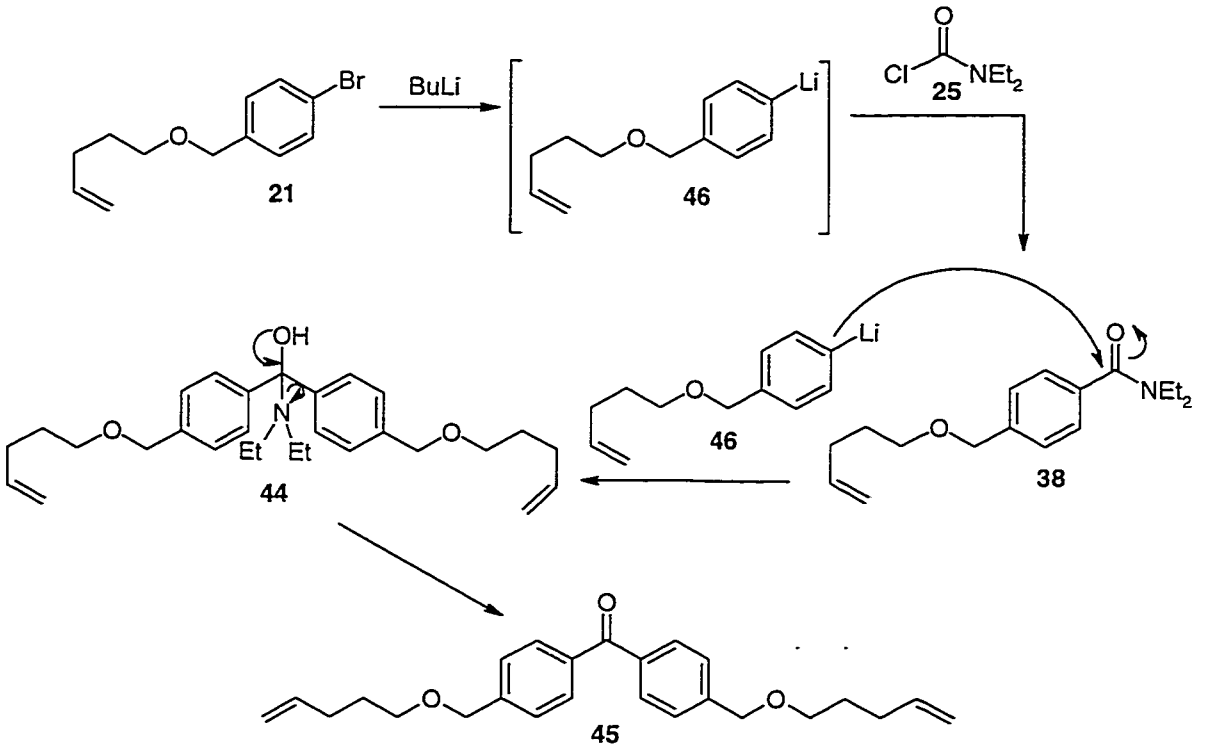


Figure 11: Dimer structure of metal-halogen exchange side product.

The proposed mechanism takes into account why the spectrum for both the IR and ^1H NMR changed over time. After exposure to reduced pressure the spectra show the material no longer contains the NEt_2 group or an alcohol, but rather a carbonyl. The preparation of the amide (**38**) involves the slow addition of diethylcarbamoyl chloride to a cold solution of the bromide (**21**) and BuLi. Nucleophilic substitution with the carbamoyl chloride gives the desired amide (**38**). However, when the amide is generated, in the presence of an excess of the lithium species, the lithium species may then react further with the desired amide product (to give a dimer **44**). Once the dimer is formed, exposure to reduced pressure results in the loss of a small, stable, volatile molecule of diethylamine to give **45**. In an attempt to reduce the amount of dimer generated, the reaction was repeated with a fast addition of the carbamoyl chloride. In this case, only a complex mixture was obtained, and it was determined that it was necessary to add the carbamoyl chloride very slowly. It might be advantageous to repeat the reaction and add a solution of the organolithium reagent to the

carbamoyl chloride. This would ensure there was no excess lithium reagent present during the reaction. The ^{1}H NMR spectra of the side product, before and after loss of diethylamine, are included in the Appendix.

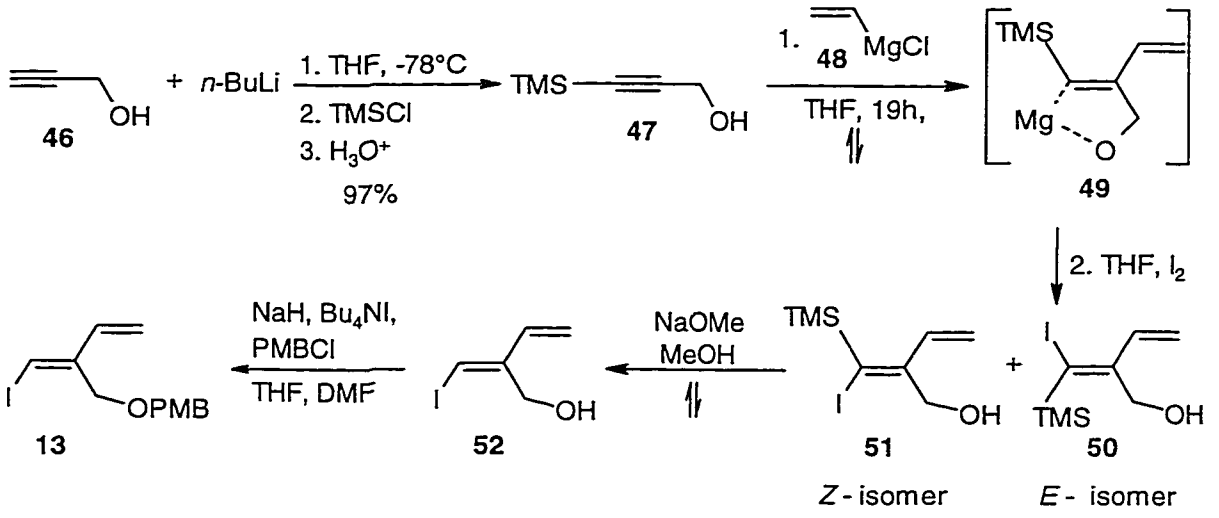


Scheme 11

2.3.4 Iododiene

The iododiene (**13**) is a common building block in the Fallis group for a number of products and is frequently used in a variety of projects. This diene has been synthesized repeatedly by a number of group members, however the reaction was never fully investigated, nor was it completely understood. The reaction commonly yielded two products, the ratio of which changed continually. One of the products was the desired iododiene (*Z* isomer), and the other

compound was believed to be the *E* isomer. The *Z* isomer was normally required and thus little study of the other compound had been completed. The poor reproducibility of the reaction proved to be very troublesome. The preparation of the diene is shown in Scheme 12.

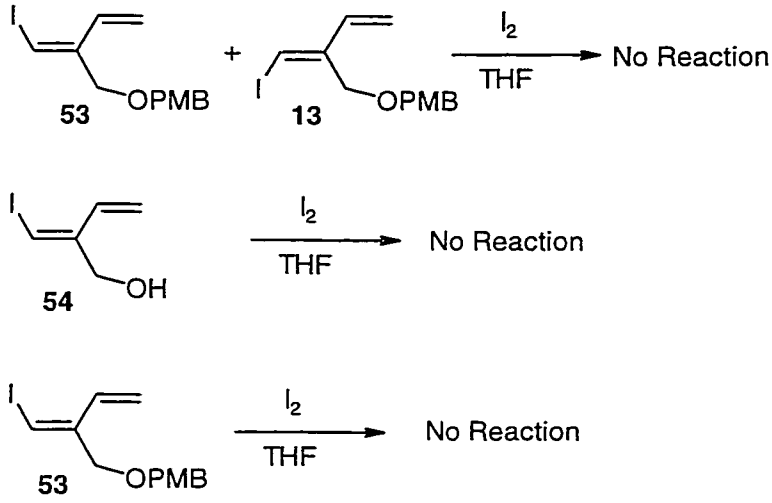


Scheme 12

The diene (**13**) is prepared from commercially available propargyl alcohol, **46,** in 4 steps. The deprotonation is accomplished by treatment of the alcohol with *n*-BuLi. TMSCl is added to the dianion generated *in situ* to yield the desired TMS alcohol (**47**) in quantitative yield. This alcohol is then refluxed overnight with vinylmagnesium bromide (**47**) to provide the proposed chelated intermediate **49**. Addition of iodine to **49** then provides the two isomers of the iododiene. According to the chelated intermediate (**49**) the *Z*-isomer should be formed exclusively. However, it was believed that an excess of iodine or light could isomerize **51**. The material is desilylated using sodium methoxide and

methanol to give **52** and then protected as the PMB ether using standard conditions.

It was unclear at which step the two isomers formed. A variety of dienes were treated with iodine in an attempt to induce isomerization (Scheme 13). In each case the reactions were protected from light and stirred overnight.



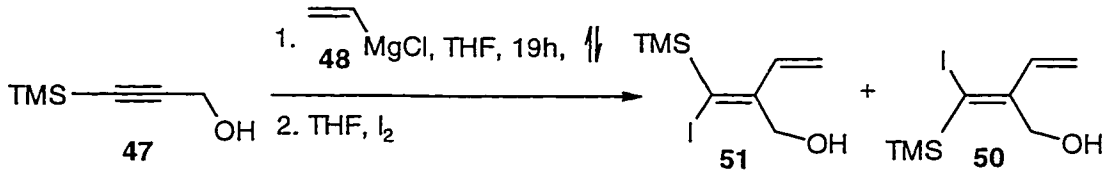
Scheme 13

No isomerization was observed, regardless of the starting diene, and thus an addition-elimination mechanism (with the *E* isomer being the most thermodynamically stable isomer) is improbable. No change in the ratio of isomers was found using a mixture of isomers. Both protected alcohol (**53**) and free alcohol (**54**) were used, but again there was no isomerization observed. The lack of isomerization indicated that the problem must arise at the iodine quench step.

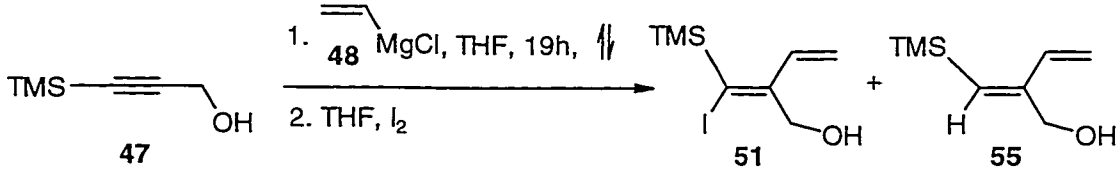
A large quantity of the "*E* isomer" had now been carried through to the PMB diene, and it was decided that the use of this diene would allow us to further study the Diels-Alder reaction. When addition of the diene to the

aldehyde (**39**) was attempted, via a metal-halogen exchange reaction, no desired product was observed. The reaction was repeated with a simple aldehyde, benzaldehyde, and again no addition product was observed. When the diene was further examined, the ^1H NMR spectrum revealed that there was a significant amount of TMS present and a GC-MS indicated the molecule did not contain iodine. Full characterization revealed that it was in fact not the *E* isomer of the iododiene (**13**), but actually the corresponding protonated diene, **55** (PMB protected). Scheme 14 summarizes the products of the reaction.

Initially thought:

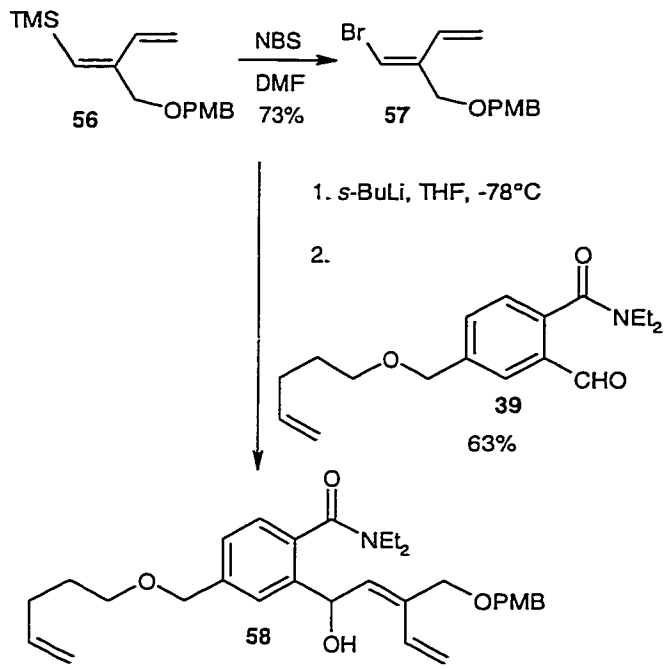


Actually:



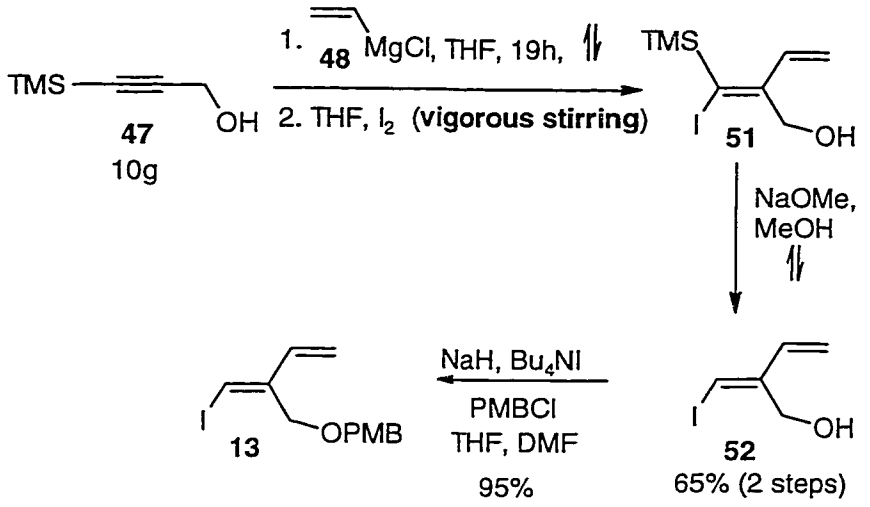
Scheme 14

The protonated diene (**56**) can be converted to the corresponding *E* bromo (**57**) diene using NBS. This bromodiene has been successfully added to the aldehyde (**39**) in 63% yield. (Scheme 15)



Scheme 15

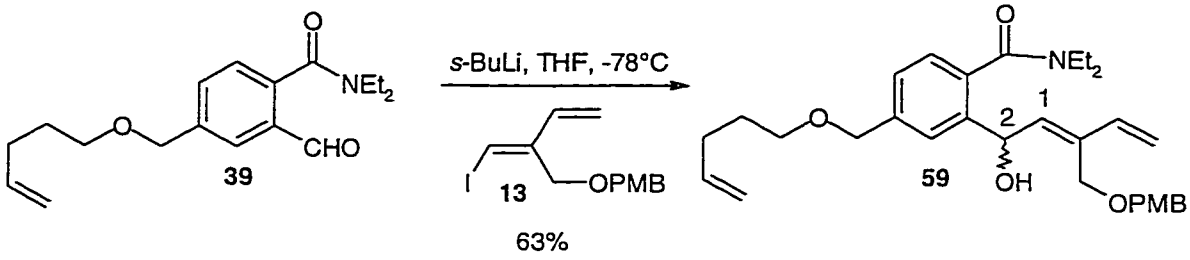
It was now suspected the problem involved the addition of the iodine, although the cause of and solution to the problem were unclear. The reaction had been thoroughly protected from light, so this was not a concern. In the past it had been successfully made with only minimum precautions taken regarding light sensitivity. The reaction had also been attempted using freshly sublimed iodine, yet there was still no answer to the production of the protonated diene. It had been noted that the reaction is quite viscous, and due to its usefulness in the lab, the reagent is commonly prepared on large multigram scales. It is absolutely crucial that after the addition of the iodine that the reaction stir quite vigorously to ensure thorough mixing. The reaction is now very reliable and the iododiene can be successfully prepared on large scale (Scheme 16).



Scheme 16

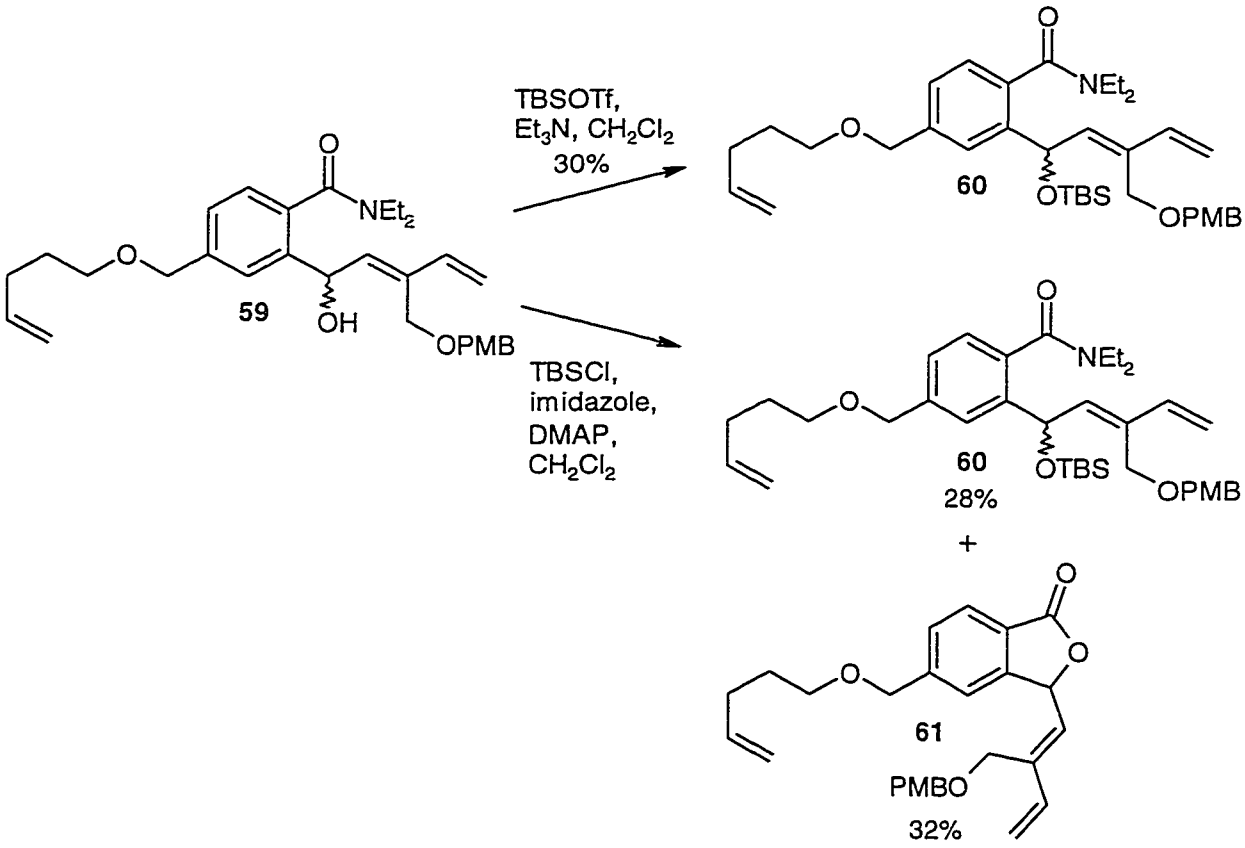
2.3.5 Addition of the Diene

The addition of the iododiene (**13**) to the aldehyde (**39**) proceeded smoothly. A metal halogen exchange reaction provided the lithium anion of the diene which can then be added to the aldehyde. The resulting alcohol (**59**) is isolated in 63% yield. (Scheme 17) It should be noted that according to the ^{13}C NMR spectrum two signals are missing. It is suspected that the signals either coincidentally overlap with others or are buried in the noisy baseline. The signal for H-1 (as labeled in Scheme 17) is present in the ^{1}H NMR spectrum as a doublet, indicating that it must be adjacent to at least one proton; however, the proton to which it is coupled is not visible in the COSY. H-1 should be coupled to H-2, but the reason for its lack of visibility is not clear. It is assumed that the signal is very broad and lost in the baseline. The integration indicates its presence and all other characterization data supports this structure.



Scheme 17

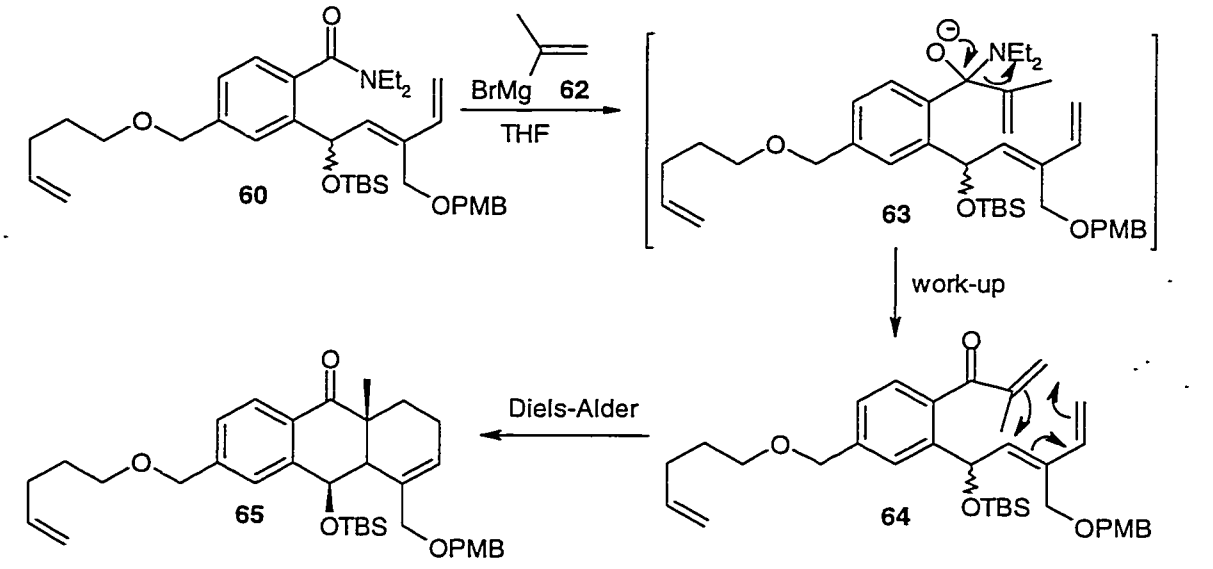
The protection of alcohol **59** proved difficult. The optimum yield of the protected material **60** was 30%. The reaction could be performed using either TBSOTf or TBSCl. When the reaction is perfomed with TBSCl, an equal amount of the lactone (**61**) was obtained as shown in Scheme 18.



Scheme 18

2.3.6 Intramolecular Diels-Alder Reaction

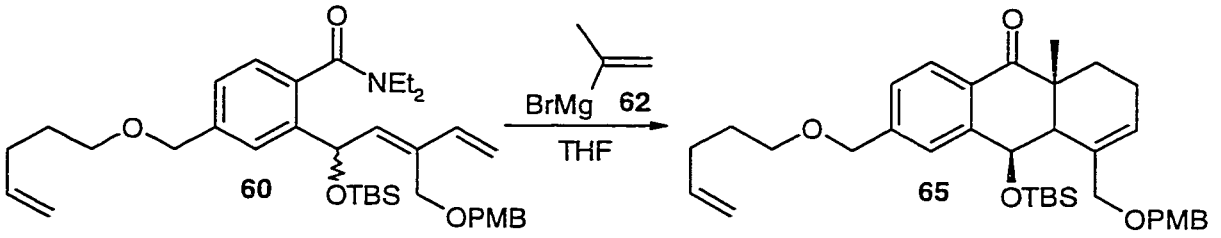
Addition of isopropenylmagnesium bromide to the amide (**60**) was expected to provide the Diels-Alder precursor (**64**). There was literature precedence for the addition, and it was believed that the intermediate would be stable enough that it would not collapse until work-up, thus avoiding the possibility of addition of a second equivalent of Grignard.[53] Results of previous work had shown that the intramolecular Diels-Alder reaction could be accomplished at room temperature. Therefore, we expected that after the addition, the intermediate (**63**) would spontaneously cyclize and give the Diels-Alder adduct **64** (Scheme 19).



Scheme 19

Table 4 shows the results of the many conditions which were attempted for the addition of the vinyl moiety (**62**) to the amide. Theoretically, only one

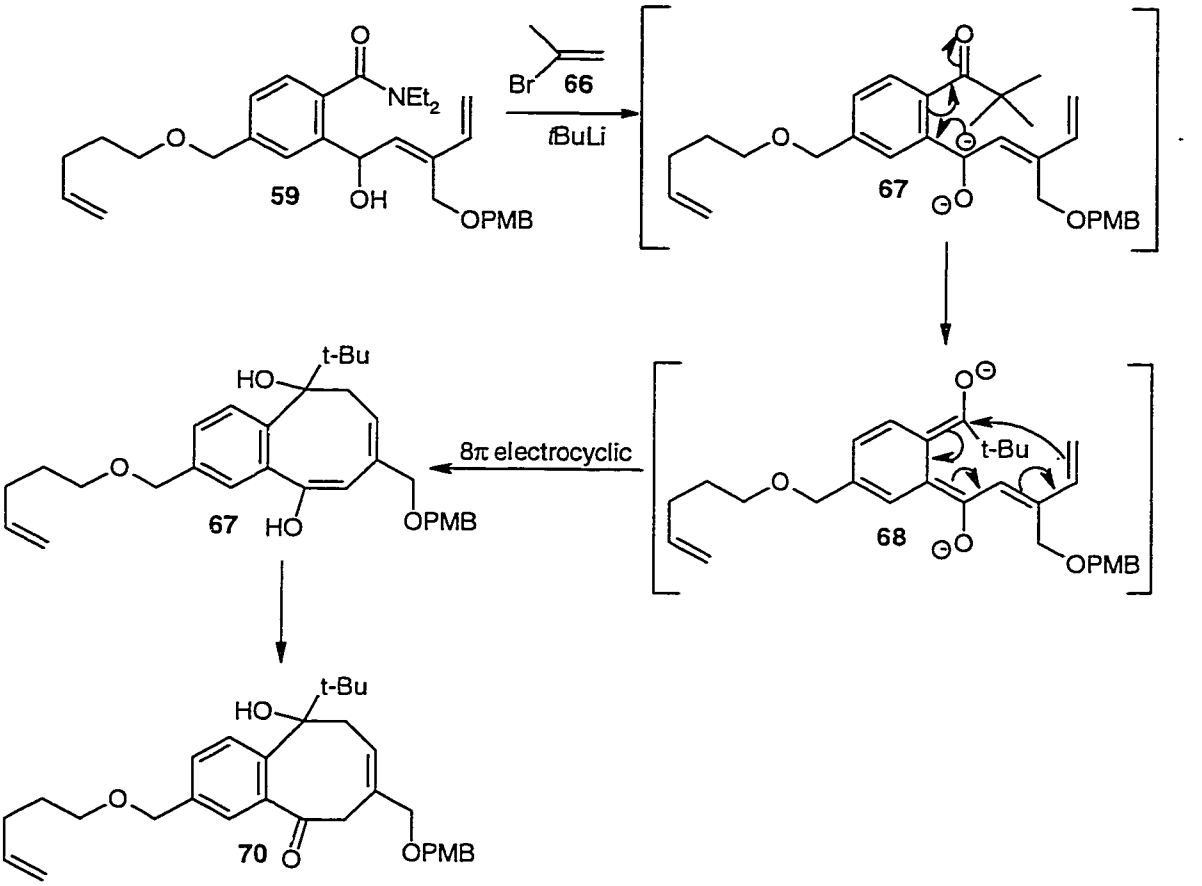
equivalent of Grignard reagent should be required, so the first attempts involved a slight excess at low temperatures (to try to avoid over addition). The reaction was repeated at progressively warmer temperatures and for increasingly longer durations. Finally, it was decided to try a larger excess of the Grignard reagent as the amide may be sterically hindered so that over addition seemed unlikely. Using as much as three equivalents of Grignard reagent at room temperature, there was no trace of product observed. The reactions were then all repeated using a more reactive vinyl source, 2-propenyl lithium (**41**). The isopropenyl lithium was prepared via a metal-halogen exchange reaction using commercially available 2-propenyl bromide. In each case, the reactions did not yield any desired product. Hoping that the addition of TMEDA might further increase the reactivity of the lithium reagent, five equivalents of TMEDA were added and the reaction heated to reflux overnight. The reaction began to decompose, but the amide was still clearly intact and the vinyl group had failed to add. It is unknown why the amide is so resistant to addition. It is possible that the amide is just very sterically hindered.



Entry	Grignard (eq)	Temp (°C)	Time(h)	Result
A	1.5	-78	1	starting material
B	1.5	-60	1	starting material
C	1.5	-30	48	starting material
D	1.5	-10	2.5	starting material
E	3.0	-40	2	starting material
F	3.0	-10	1	starting material
G	3.0	5	16	starting material
H	3.0	rt	2	starting material

Table 4: Conditions attempted for addition of vinyl group.

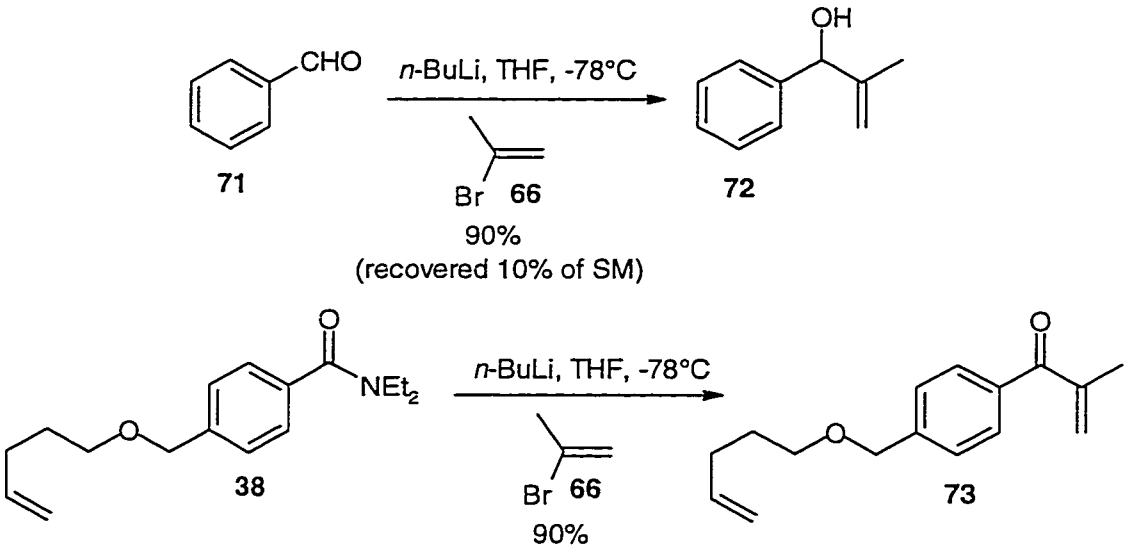
Further investigation into one of the products produced seemed to indicate the formation of an eight-membered ring (**70**). The proposed mechanism and structure are shown in Scheme 20.



Scheme 20

The ^{1}H NMR spectrum clearly shows the presence of a *t*-Bu. As well, the ^{1}H NMR spectrum shows the side chain is intact and the PMB group is still present. The IR spectrum shows the compound contains a carbonyl group (1709 cm^{-1}) and an alcohol (3411 cm^{-1}). The diene fragment is either gone or has been drastically altered, and the vinyl proton in the eight-membered ring couples to the adjacent proton, which is a doublet. This compound was not fully characterized, as it is unstable and decomposes readily, although the spectral data obtained supports the proposed structure.

In order to ensure that the lithiopropene was in fact generated, and to further study the reaction, the vinyl addition was repeated on simple models including benzaldehyde, **71** (Scheme 21) and amide **38**. In both cases, the desired addition products were isolated in excellent yields. The fact that these simple models work so well, and the reaction with the more complex amide (**59**) fails to produce any desired product, indicates that it must be significantly stabilized. The amide (**59**) might be extremely sterically hindered, or there may also be hydrogen bonding of the amide with the alcohol (although the reactions also fail when the alcohol is protected).

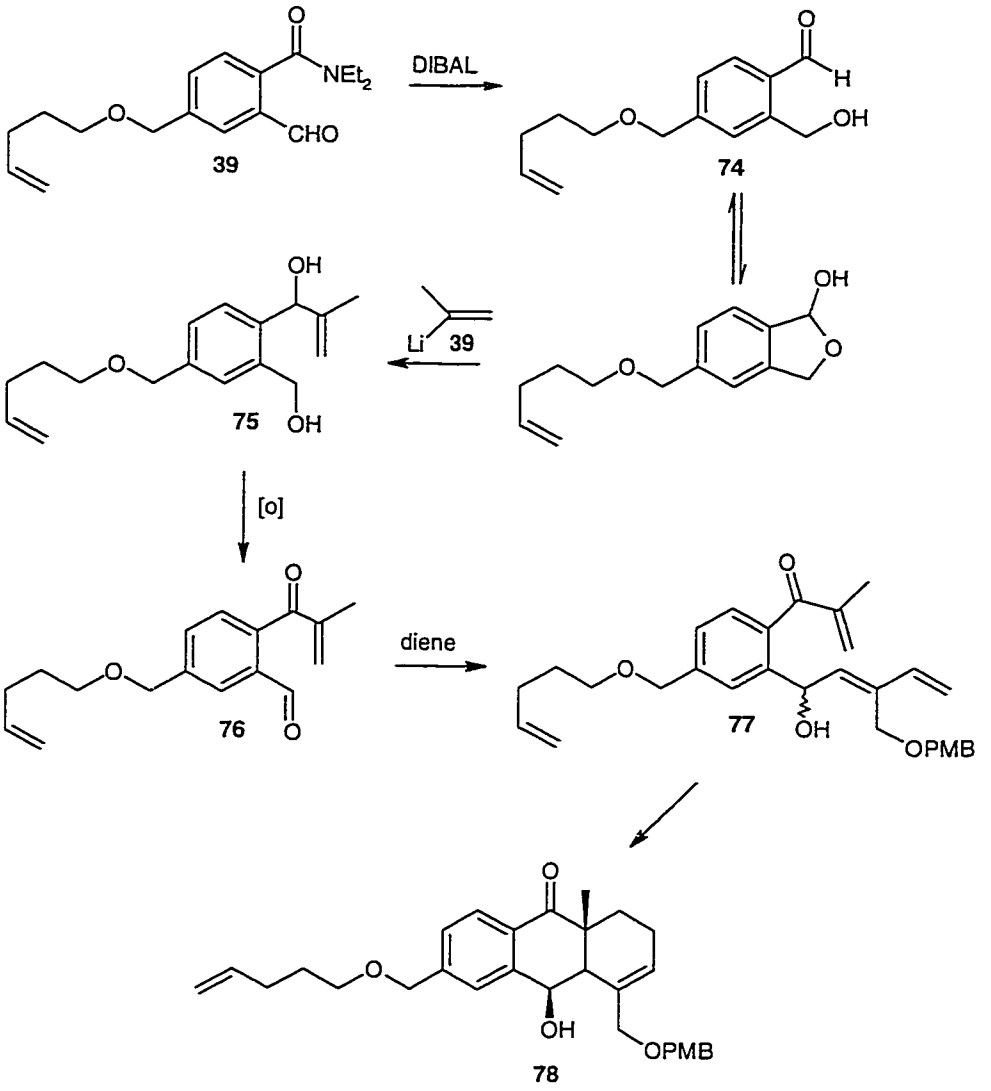


Scheme 21

2.3.7 Reduction of Simple Amide

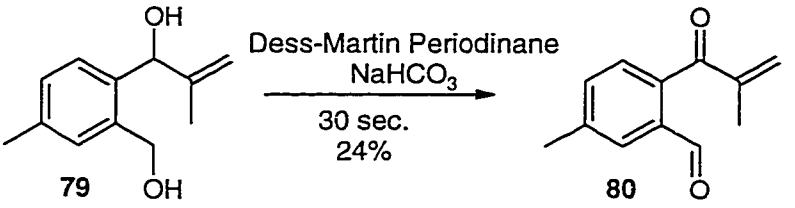
With the difficulties encountered in adding to the amide (**59**) it was decided that we would attempt to reduce the amide functionality. The amide must be in place for the directed *ortho* metallation, as it acts as the directing

group. Thus, the earliest possible step at which it can be altered is after the aldehyde is in place. It was hoped that treatment of the amide (**39**) with an excess of a hydride source, such as DIBAL, would allow for simultaneous reduction of both the amide and the aldehyde functionalities (Scheme 22). The resulting product (**74**) would be in equilibrium with the more stable lactol form. Addition of 2-propenylmagnesium bromide or 2-propenyl lithium to the lactol then would provide the desired diol (**75**). Treatment of this diol with an oxidizing agent such as Dess-Martin periodinane could provide the corresponding ketoaldehyde compound (**76**). There was some concern that if the primary alcohol oxidized much faster than the secondary, it would be possible for the compound to spontaneously cyclize to the lactol, which could be further oxidized to a lactone. However, if the double oxidation were successful, then addition of the iododiene (**13**) selectively to the less sterically hindered aldehyde would again provide a Diels-Alder precursor (**77**), which upon warming would cyclize and give the desired tricyclic core (**78**).



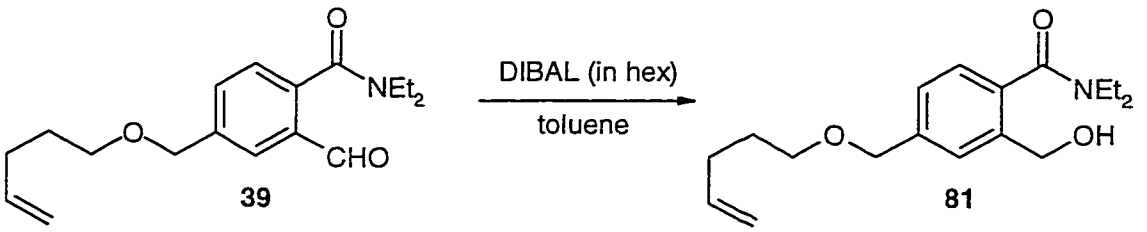
Scheme 22

The questionable double oxidation was performed on a simple diol model (**79**) and was found to proceed (although with limited success) as shown in Scheme 23.



Scheme 23

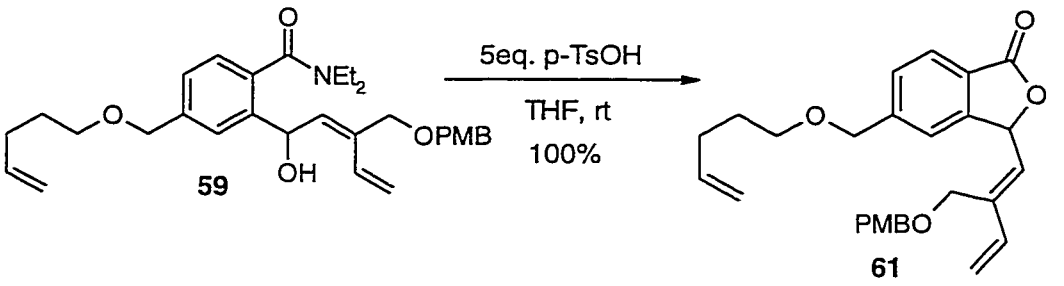
DIBAL was chosen for the reduction, instead of LAH, in hopes of avoiding over-reduction to the diol. However, when the reduction was attempted, it was found that even with a large excess of DIBAL, the amide remained intact and only the aldehyde was reduced to the alcohol (**81**) (Scheme 24). All attempts to add a vinyl moiety to this amide (**81**) resulted in recovered starting material.



Scheme 24

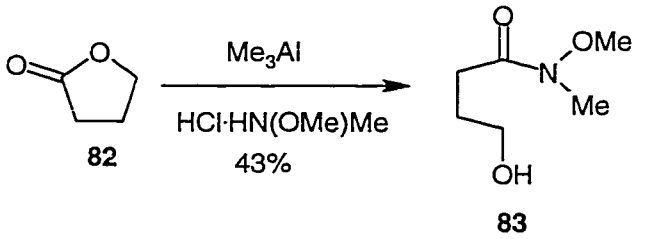
There was literature precedence for the reduction of diethylbenzamides to the corresponding aldehydes using an "ate" complex.[54] The complex is a mixture of DIBAL and n-BuLi. Unfortunately, all attempts to reduce the amide (**60**) were unsuccessful. LAH was also tried as a reducing agent. However, rather than either the aldehyde or the over-reduced alcohol being isolated, the reaction yielded a complex mixture, containing starting material with the OPMB group cleaved (HOPMB was isolated). It was also found that the amide was stable to bases such as NaOH and $Ba(OH)_2$/MeOH. The only successful method

of altering the amide functionality is treatment with acid to give the corresponding lactone (**61**) (Scheme 25). Treatment of the amide (**59**) with an excess of *para*-toluenesulfonic acid resulted in lactonization in quantitative yield. In the ^{13}C NMR spectrum of the lactone one of the quaternary signals are not visible. It is suspected that the signal is buried under another signal and all other spectral data and elemental analysis support the lactone structure (**61**).



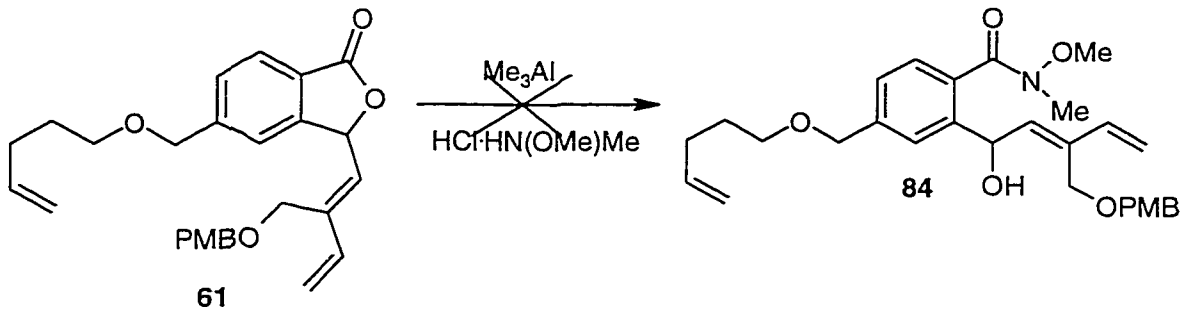
Scheme 25

It should also be noted that attempts were made to use a Weinreb amide.[55] It was hoped that like the diethylamide, it too would act as a directing group for a DoM reaction. The Weinreb amide should then be easier to add to than the diethylbenzamide. A simple model was used to determine the conditions (Scheme 26). The reaction provided a modest yield with butyrolactone (**82**).



Scheme 26

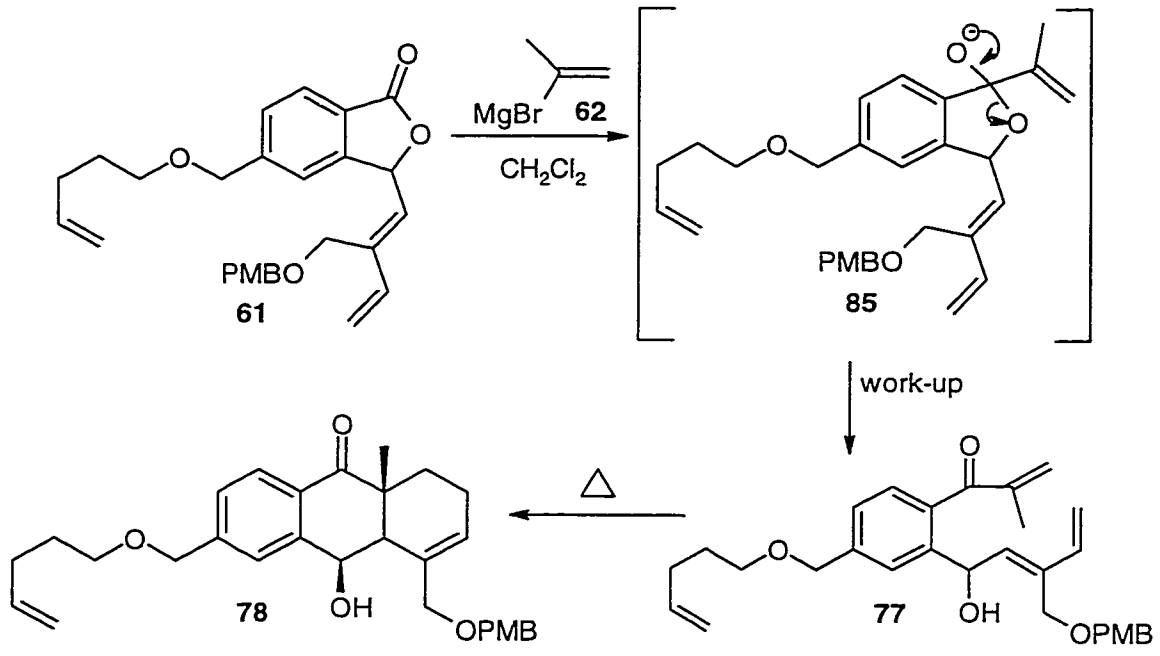
The same conditions were unsuccessful with the complex lactone (**61**) (Scheme 27). The literature indicates a reaction temperature of -40°C for up to 48 hours.[52] In this case, the reaction was conducted at progressively higher temperatures, to a maximum of 80°C, for 24 hours and there was still only starting material present. The lack of any trace of product led us to abandon this route.



Scheme 27

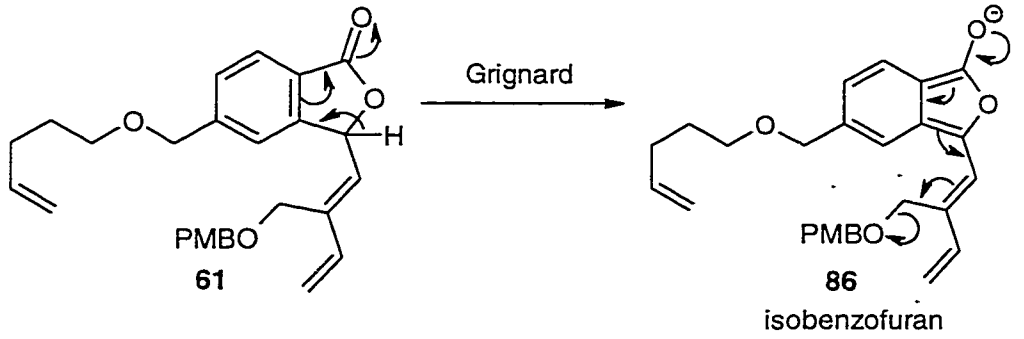
2.3.8 Manipulation of Lactone

It was believed that addition of a vinyl moiety to the lactone (**61**) would provide direct access to the tricyclic system (**78**) (Scheme 28). Unfortunately, when the reaction was conducted at low temperatures (0°C and below), only starting material was isolated. When the reaction was warmed to room temperature a black tar-like material was formed. When the reactions were repeated using the corresponding 2-propenyl lithium, rather than the Grignard, the OPMB group was cleaved from the starting material.



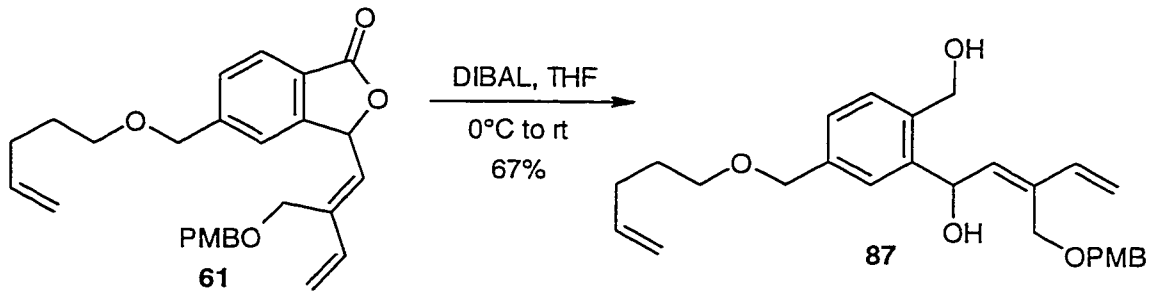
Scheme 28

The possible mechanisms for both the polymerization and decomposition are shown below in Scheme 29. In the case of the polymerization, deprotonation leads to the generation of an isobenzofuran, which is a very reactive diene. The loss of *para*-methoxybenzylalcohol could also be explained if the isobenzofuran loses the OPMB group before it reacts.



Scheme 29

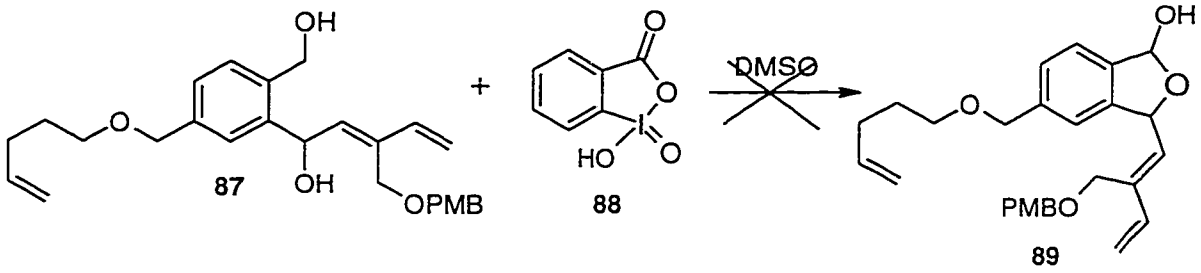
The lactone (**61**) could be synthesized in quantitative yield from the amide (**59**). However, all attempted additions to the lactone had failed. It was believed that the lactol would be easier to add to than the lactone; however, the molecule decomposes when treated with LAH. Treatment of the lactone with DIBAL at -78°C resulted in only starting material being recovered. When the reduction was repeated at 0°C, rather than starting material or lactol, the diol (**87**) was isolated (Scheme 30). Warming the reduction to room temperature results in the optimized yield of 67% of diol **87**.



Scheme 30

2.3.9 Selective Oxidation of 1,4 diols

In the last few years a number of papers have been published on the use of the Dess-Martin periodinane intermediate for selective oxidation of 1,4 diols.[56] With the lactol (**89**) in hand, the addition could again be attempted using a vinyl Grignard. The *o*-iodoxybenzoic acid was prepared using literature procedures, with special care taken due to the explosive nature of the material. Treatment of the diol (**87**) with the oxidizing agent in DMSO only resulted in complex mixtures and no product could be isolated (Scheme 31).



Scheme 31

As reported earlier, a double oxidation of a 1,4 diol could give the corresponding ketoaldehyde, as demonstrated on a simple model (**79**). It was decided that the oxidation should be tried on the complex diol **87**. Treatment of the alcohol with Dess-Martin periodinane unfortunately did not yield any of the desired product. The next option, although less elegant, seemed more likely to succeed. The plan involved the protection of the primary alcohol as a TBS ether, followed by protection of the secondary alcohol as a TIPS ether. The TBS group could then be removed in the presence of the TIPS using PPTS. The protection of the primary alcohol proceeded smoothly, under standard conditions, to give

the desired product. The protection of the remaining secondary alcohol has proven more difficult than anticipated. At this time, both TIPSOTf and TBDPSCl have failed to protect the second alcohol. Work is currently ongoing to protect the remaining free alcohol.

3 Conclusions

The main objective of this research project was to synthesize the target Taxol® analogue, **7**, via an intramolecular Diels-Alder approach, using an aromatic ring as the tether control group. Although the final target was not realized, a few more steps will give the Diels-Alder precursor, from commercially available starting materials, **20**, diethyl carbamoyl chloride and the diene, **13**.

Initially, it was believed that it would be possible to follow a similar route to those previously established in our lab for the synthesis of these types of analogues. However, that was not true and it was necessary to develop a novel route to the analogue. A number of routes were attempted, but many of them led to major difficulties and were therefore abandoned. The final sequence, which has been successful, utilizes a metal-halogen exchange followed by an *ortho*-metallation as the key steps. Metal-halogen exchange on the substituted aromatic bromide, **21**, followed by the addition of diethyl carbamoyl chloride as a quench affords the desired benzamide, **38**. The literature protocol for *ortho*-lithiations of diethyl benzamides[45] was successfully extended to our *para*-substituted benzamide, **38**, after some initial setbacks with difficulties in identifying the products of the reaction and optimizing the reaction to avoid the dimer side product, **45**. With the aldehyde, **39**, in hand the iodo diene, **13**, was then successfully added. Manipulation of the amide proved to be very difficult. Difficulties in removing the amide have been reported in the literature[45]; however, it was found that treatment with tosic acid led to quantitative lactonization, **61**.

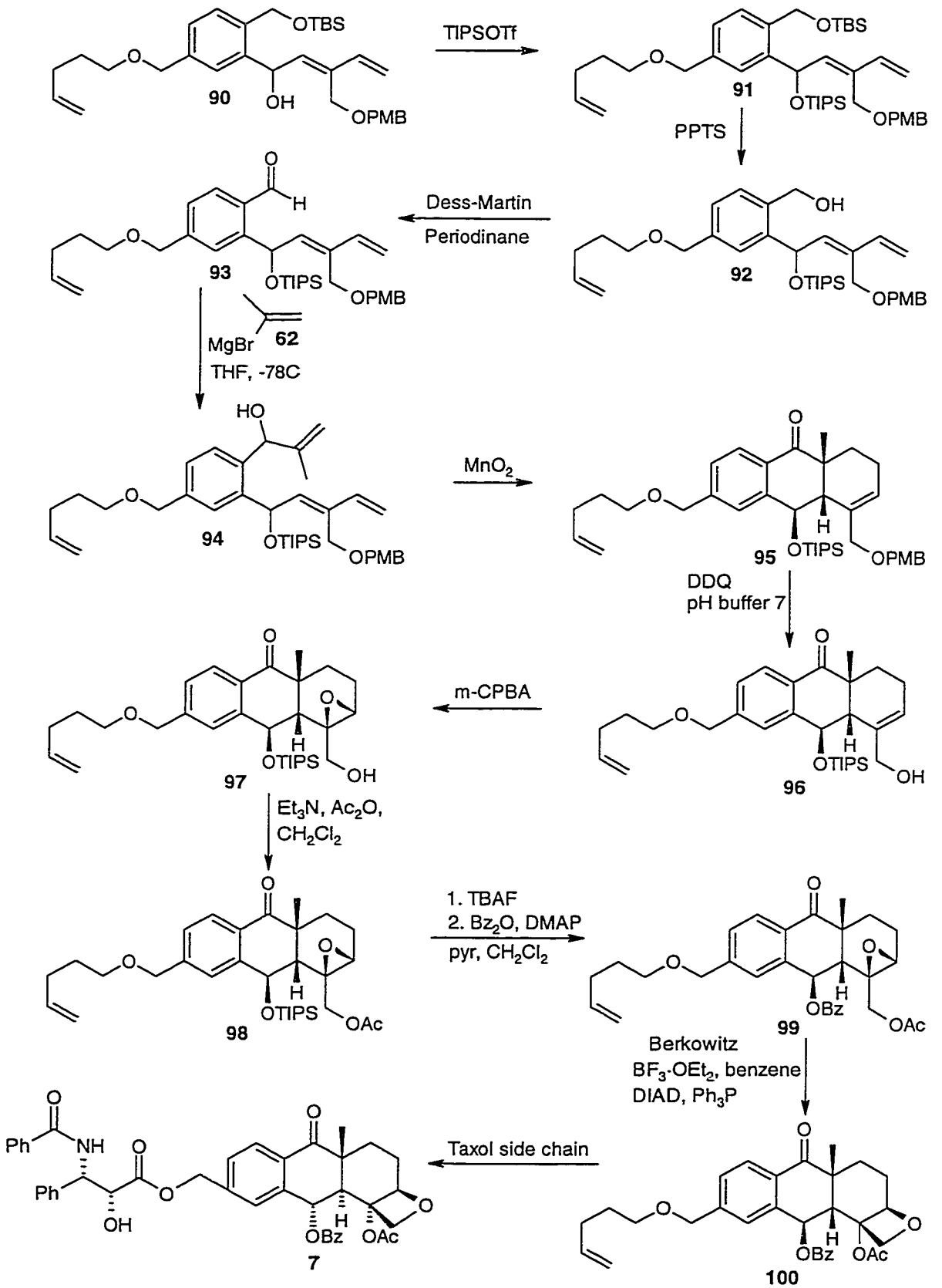
Again, manipulation of the lactone was difficult. After initial attempts to reduce the lactone to the lactol failed, as did direct addition to the lactone, it was found that treatment with DIBAL-H successfully led to the corresponding diol, **87**. This diol has now been successfully mono-protected and is currently in the process of having the secondary alcohol protected.

The difficulties with the inconsistent yield of the iododiene (**13**) have been resolved. In addition, Organic Synthesis has asked us to submit this procedure for publication. After further investigation, it was found that the problem was that the very viscous mixture required vigorous stirring after the iodine had been added. It was found that the iododiene does not isomerize, but rather desired iododiene and the corresponding protonated diene are produced.

3.1 Future Studies

Additional work is required to complete the synthesis of the target Taxol® analogue, **7**. The Diels-Alder precursor will be attainable through a simple series of protection, deprotections and oxidations (Scheme 32). Protection of the secondary alcohol (**91**), followed by deprotection of the primary alcohol (**92**) and oxidation gives the corresponding aldehyde **93**. Addition of isopropenylmagnesium bromide to **93**, followed by oxidation of the resulting alcohol (**94**) will give the Diels-Alder precursor. This material should cyclize at temperatures only slightly above room temperature; however, if it is necessary to reflux the precursor at temperatures in excess of 100°C, it should not be a problem as the earlier material has shown tremendous heat stability. It is also

possible that the cyclization could be aided by the use of microwave radiation, rather than classical means. Work is currently being done to establish the conditions for removal of the pentenyl chain followed by attachment of the Taxol® side chain. Conditions for the introduction of the oxetane and benzoate moieties have been previously established.


TIPSOTf
PPTS
Dess-Martin
Periodinane
MgBr
62
THF, -78C
MnO2
DDQ
pH buffer 7
m-CPBA
Et3N, Ac2O,
CH2Cl2
1. TBAF
2. Bz2O, DMAP
pyr, CH2Cl2
Berkowitz
BF3·OEt2, benzene
DIAD, Ph3P
Taxol side chain
90
91
92
93
94
95
96
97
98
99
100
7

Scheme 32

4 Experimental Section

General Procedures and Instrumentation

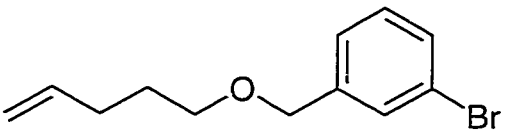
Infrared (IR) spectra were recorded on a Bomem Michelson 100 FTIR spectrometer (neat) and the data are reported in reciprocal centimetres (cm^{-1}). All NMR spectra were measured in $CDCl_3$ relative to an internal lock on the deuterium in $CDCl_3$. ^1H NMR (200 or 500 MHz) and ^{13}C NMR (50.3 or 125.8 MHz) spectra were run on a Varian Gemini or Bruker WM500, respectively. All NMR data are reported in parts per million (ppm) on the δ-scale. ^1H NMR data are reported as follows: chemical shift, multiplicity, integration, and coupling constants (Hz). High resolution mass spectroscopy 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. Molecular modeling studies were conducted using MOPAC and MM2 prgrams within CAChe Editor, version 3.7, supplied from CAChe Scientific Inc.

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. Reactions performed at room temperature were conducted at approximately 21°C. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates (E. Merck, type 5554). TLC spots were viewed under ultraviolet light and developed

by heating the plate after treatment with either a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or a *p*-anisaldehyde staining solution (80 mL 95% ethanol, 2.9 mL sulfuric acid, 0.86 mL acetic acid, 2.1 mL *p*-anisaldehyde). Product purification by conventional and flash column chromatography 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 -25°C in vials flushed with nitrogen.

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

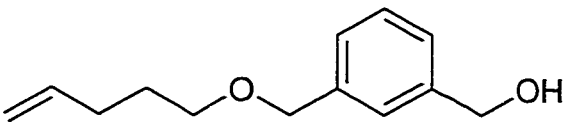
3-Bromo-(2-oxa-6-heptenyl)-benzene (17)



A solution of 4-penten-1-ol (8.26 mL, 0.080 mol) in dry tetrahydrofuran (10 mL) was added to a washed suspension of 80% sodium hydride (2.16 g, 0.072 mol) in dry tetrahydrofuran (50 mL) at 0°C. The mixture was stirred for 30 min. The reaction was protected from light and then 3-bromobenzyl bromide (10 g, 40 mmol) in dry tetrahydrofuran (25 mL) was added, followed by tetrabutylammonium iodide (296 mg, 0.80 mmol). The reaction was warmed to room temperature and stirred for 20 h. The reaction was cooled to 0°C and quenched with wet diethyl ether (25 mL), then water (25 mL) and stirred for 10 min. The resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x20 mL) and the combined organic extracts were washed with water (1x10 mL) and brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (5% ether/petroleum ether) afforded 9.66 g (95%) of the desired product as a colourless oil. IR (neat) 3072, 2932, 2858, 1640, 1571, 1474, 1428, 1356, 1200, 1108, 995, 912, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (p, 2H, J=7.0 Hz), 2.13 (q, 2H, J=7.2 Hz), 3.47 (t, 2H, J=6.5 Hz), 4.45 (s, 2H), 4.94-4.97 (dm, 1H), 5.02 (dq, 1H, J_1=12.0 Hz, J_2=1.8 Hz), 5.80 (dddd, 1H, J_1=17.2 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.17-7.25 (m, 1H), 7.39 (d with additional splitting, 1H, J=4.6 Hz), 7.48 (s with additional splitting, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ

141.0, 138.1, 130.5, 130.4, 129.9, 125.9, 122.5, 114.8, 72.0, 69.9, 30.2, 28.8; HRMS calcd for $C_{12}H_{15}BrO$ 254.0306, found 254.0319.

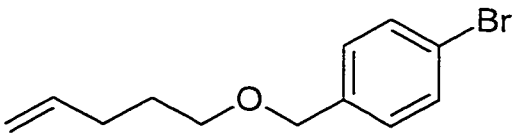
3-(2-Oxa-6-heptenyl)-benzylalcohol (18)



Tert-butyllthium (1.45 M, 0.54 mL) was added to a solution of bromide **17** (100 mg, 0.392 mmol) in dry tetrahydrofuran (2 mL) at -78°C. The reaction stirred for 30 min and then paraformaldehyde (12 mg, 0.392 mmol) was added. After warming to room temperature the reaction was stirred for 3 days. The reaction was quenched with saturated ammonium chloride (2 mL) and the resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x10 mL) and the combined organic extracts were washed with water (1x15 mL) and brine (1x15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (10-75% ether/petroleum ether) afforded the desired product as a colourless oil. IR (neat) 3371 (br), 2930, 2861, 1640, 1445, 1361, 1154, 1087, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (br, 1H), 1.70 (p, 2H, *J*=7.0 Hz), 2.13 (q, 2H, *J*=7.2 Hz), 3.48 (t, 2H, *J*=6.5 Hz), 4.49 (s, 2H), 4.68 (s, 2H), 4.93-4.96 (dm, 1H), 4.98-5.02 (dm, 1H), 5.80 (dddd, 1H, J_1=17.1 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.24-7.34 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 141.0, 139.1, 138.3, 128.6, 126.9, 126.1, 114.7,

72.8, 69.9, 65.3, 30.3, 28.9; HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1286. Note M^+-H calcd 205.1229, found 205.1217.

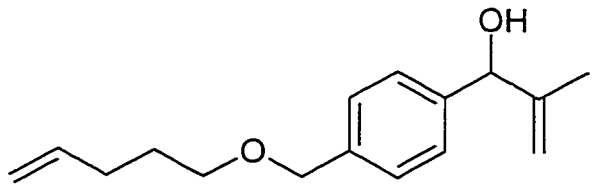
4-Bromo-(2-oxa-6-heptenyl)-benzene (21)



A solution of 4-penten-1-ol (20.66 mL, 0.20 mol) in dry tetrahydrofuran (25 mL) was added to a washed suspension of 60% sodium hydride (7.20 g, 0.18 mol) in dry tetrahydrofuran (100 mL) at 0°C. The mixture was stirred for 30 min. The reaction was protected from light and then 4-bromobenzyl bromide (25 g, 0.10 mol) in dry tetrahydrofuran (30 mL) was added, followed by tetrabutylammonium iodide (740 mg, 2.0 mmol). The reaction was warmed to room temperature and stirred for 18 h. The reaction was cooled to 0°C and quenched with wet diethyl ether (50 mL), then water (50 mL) and stirred for 10 min. The resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x20 mL) and the combined organic extracts were washed with water (1x10 mL) and brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (2.5% ether/petroleum ether) afforded 16.0 g (97%) of the desired product as a colourless oil. IR (neat) 3075, 2933, 2858, 1640, 1593, 1487, 1447, 1397, 1358, 1104, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.69 (p with additional splitting, 2H, J=6.6 Hz), 2.13 (q with

additional splitting, 2H, J=7.2 Hz), 3.45 (t, 2H, J=6.5 Hz), 4.43 (s, 2H), 4.93-4.96 (dm, 1H), 4.98-5.03 (dm, 1H), 5.80 (dddd, 1H, J_1=17.2 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.19 (d with additional splitting, 2H, J=8.4 Hz), 7.45 (d with additional splitting, 2H, J=8.4 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.2, 137.7, 131.4, 129.2, 121.3, 114.8, 72.1, 69.9, 30.3, 28.9; HRMS calcd for $C_{12}H_{15}BrO$ 254.0306, found 254.0331; Anal Calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.92; Found: C, 56.47; H, 5.70.

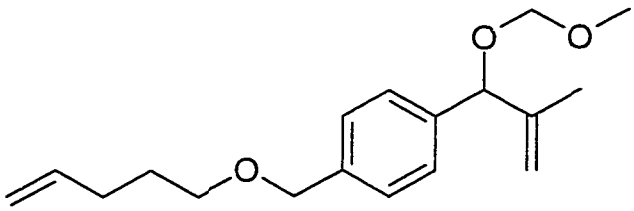
(1R,S)-2-Methyl-1-(4-(2-oxa-6-heptenyl)phenyl)-2-propenol (22)



Tert-butyllithium (1.58 M, 10.9 mL) was added to a solution of bromide **21** (2.0 g, 7.84 mmol) in dry tetrahydrofuran (12 mL) at -78°C. The reaction was stirred for 30 min then methacrolein (1.62 mL, 19.6 mmol) was added and the mixture stirred for another 15 min. The reaction was quenched with saturated ammonium chloride (10 mL) and warmed to room temperature. The resulting phases were separated and the aqueous phase was extracted with ethyl acetate (3x10 mL) and the combined organic extracts were washed with brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (5-20-50% ether/petroleum ether) afforded 1.20 g

(62%) of the desired product as a colourless oil. IR (neat) 3402 (br), 3074, 2932, 2860, 1646, 1446, 1365, 1090, 907; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.69 (p, 2H, J=7.0 Hz), 2.12 (q, 2H, J=7.2 Hz), 3.46(t, 2H, J=6.5 Hz), 4.47 (s, 2H), 4.92-5.02 (m, overlapping signals, 3H), 5.11 (s, 1H), 5.18 (s, 1H), 5.79 (dddd, 1H, J_1=17.1 Hz, J_2=10.3 Hz, J_3=7.0 Hz, J_4=6.7 Hz), 7.29 (d, 2H, J=8.3 Hz), 7.33 (d, 2H, J=8.2 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) 146.8, 141.2, 138.2, 138.0, 127.6, 126.4, 114.7, 111.1, 77.6, 72.6, 69.7, 30.3, 28.9, 18.2; HRMS calcd for $C_{16}H_{22}O_2$ 246.1621, found 246.1613.

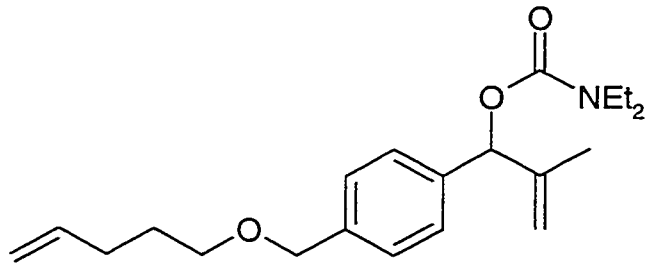
(1R,S)-1-(Methoxymethyloxy-2-methyl-2-propenyl)-4-(2-oxa-6-heptenyl) benzene (23)



Diisopropylethylamine (9.32 mL, 53.5 mmol) and chloromethyl methyl ether (2.71 mL, 35.7 mmol) were added to a solution of the alcohol **22** (878 mg, 3.57 mmol) in dry dichloromethane (9 mL) at 0°C. The reaction was warmed to room temperature and stirred for 18 h. The mixture was quenched with saturated ammonium chloride (10 mL) and the resulting phases were separated and the aqueous phase was extracted with ether (3x20 mL) and the combined organic extracts were washed with brine (1x25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (30-70%

ether/petroleum ether) afforded 540 mg (52%) of the desired product as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.70 (p, 2H, J=7.0 Hz), 2.13 (q, 2H, J=7.2 Hz), 3.47 (t, 2H, J=6.5 Hz), 4.47 (s, 2H), 4.59 (d, 1H, J=6.6 Hz), 4.68 (d, 1H, J=6.6 Hz) 4.92-5.13 (m,overlapping signals, 5H), 5.80 (dddd, 1H, J_1=17.1 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.28-7.33 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) 144.4, 139.4, 138.2, 137.8, 129.6, 127.5, 126.8, 114.6, 113.0, 93.7, 80.4, 72.6, 69.8, 55.5, 32.1, 30.3, 28.9, 18.0.

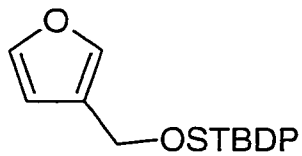
1-((1R,S)-Diethylcarbamate-2-methyl-2-propene)-4-(2-oxa-6-heptenyl) benzene (26)



A washed suspension of 60% sodium hydride (89 mg, 2.2 mmol) in dry tetrahydrofuran (2 mL) was added to a solution of **22** (500 mg, 2.0 mmol) in dry tetrahydrofuran (3 mL) to at 0°C. The reaction was stirred at 0°C for 45 min. and then diethylcarbamoyl chloride (515 μL, 4.1 mmol) was added. The reaction was heated to 80°C and stirred for 30 h. The reaction was cooled to 0°C and quenched with wet ether (1 mL), then water (1 mL). The resulting phases were separated and the aqueous phase was extracted with ethyl acetate (3x2 mL) and the combined organic extracts were washed with 10% aqueous hydrochloric acid

(4x2 mL), water (1x2 mL) and brine (1x2 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatrography (20 % ether/petroleum ether) afforded 261 mg (37%) of the desired product as a colourless oil. IR (neat) 3075, 2974, 2932, 2861, 1703, 1652, 1475, 1422, 1271, 1167; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, br, 6H), 1.62 (s, 3H), 1.69 (p, 2H, *J*=6.6 Hz), 2.09-2.14 (m, 2H), 3.30 (s, br, 4H), 3.47 (t, 2H, *J*=6.5 Hz), 4.46 (s, 2H), 4.91-4.94 (m, 2H), 4.99 (dq, 1H, J_1=12.0 Hz, J_2=1.58 Hz), 5.09 (s, 1H), 5.76-5.82 (m, 1H), 6.08 (s, 1H), 7.23-7.31 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) 154.9, 144.0, 138.7, 138.3, 138.1, 127.6, 127.0, 114.7, 112.0, 79.0, 72.6, 69.8, 30.9, 30.3, 29.7, 28.9, 18.8; HRMS calcd for $C_{21}H_{31}NO_3$ 345.2305, found 345.2320.

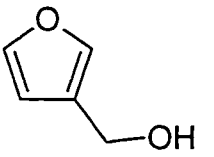
3-(*tert*-Butyldiphenylsilyloxymethyl)-furan (31)



Imidazole (3.05 g, 44.8 mmol) and *tert*-butyldiphenylsilyl chloride (5.83 mL, 22.4 mmol) were added to a solution of 3-(hydroxymethyl)furan (2.0 g, 20.4 mmol) in dry dimethylformamide (20 mL) at room temperature. The reaction was stirred for 17 h. and then diluted with diethyl ether (100 mL) and the resulting phases were separated. The organic phase was washed with brine (3x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by

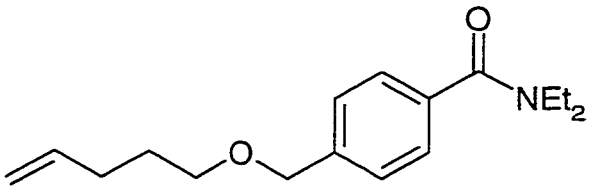
flash chromatography (2% ether/petroleum ether) afforded 6.60 g (96%) of the desired product as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 4.61 (s, 2H), 6.32 (s, 1H), 7.29-7.69 (m, 12H); ^{13}C NMR (125.8 MHz, $CDCl_3$) 143.0, 139.4, 135.6, 134.8, 133.6, 129.7, 127.7, 109.6, 58.3, 26.8, 19.2. ^{1}H NMR data matches well with literature.[56]

3-(Hydroxymethyl)furan (35)



A solution of 3-furoic acid (10.0 g, 0.089 mmol) in dry diethyl ether (150 mL) was added slowly to a suspension of lithium aluminum hydride (3.39 g, 0.089 mmol) in dry diethyl ether (50 mL) at 0°C. The reaction was stirred at 0°C for 40 min and then warmed to room temperature and stirred for 2 h. After being cooled back to 0°C the solution was treated dropwise with ethyl acetate (10 mL), water (3.4 mL), 15% aqueous sodium hydroxide (3.4 mL) and water (10.2 mL). Anyhydrous magnesium sulfate was added and the solution was stirred for 15 min and then filtered through Celite and concentrated to afford 4.53 g (52%) of the desired product, which was not purified before further use. Note: The material is volatile and thus after continued exposure to reduced pressure, the yield of 52% is an observed minimum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 1H), 4.51 (s, 2H), 6.41 (s, 1H), 7.33-7.41 (m, 2H) ^{1}H NMR data matches well with literature.[57]

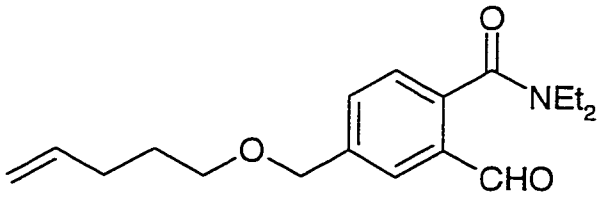
N,N-Diethyl-4-(2-oxa-6-heptenyl) benzamide (38)



Sec-butyllithium (1.3 M, 13.5 mL) was slowly added to a solution of **21** (4.09 g, 0.016 mol) in dry tetrahydrofuran (50 mL) at -78°C. The reaction was stirred for 30 min. and then diethyl carbamoyl chloride (5.08 mL, 0.040 mol) was added over 10 min. The reaction was stirred for 25 min. and then quenched with saturated ammonium chloride (18 mL) and allowed to warm to room temperature. The resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x50 mL) and the combined organic extracts were washed with water (1x10 mL) and brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (20-60% ether/petroleum ether) afforded 2.38 g (54%) of the desired product as a pale yellow oil. IR (neat) 3078, 2973, 2934, 2864, 1629, 1570, 1512, 1443, 1370, 1294, 1220, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09-1.22 (br, 6H), 1.69 (p, 2H, J=6.8 Hz), 2.12 (q, 2H, J=7.0 Hz), 3.17-3.32 (br, 2H), 3.42-3.57 (br, 2H), 3.47 (t, 2H, J=6.5 Hz), 4.48 (s, 2H), 4.91-4.94 (dm, 1H), 4.97-5.01 (dm, 1H), 5.78 (dddd, 1H, J_1=17.1 Hz, J_2=10.4 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.32 (s, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.1, 139.7, 138.1, 136.4,

127.4, 126.3, 114.7, 72.4, 69.9, 43.1 (br), 39.2 (br), 30.2, 28.8, 14.1 (br), 13.0 (br); HRMS calcd for $C_{17}H_{25}NO_2$ 275.1886, found 275.1862; Anal Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09; Found: C, 72.24; H, 8.52; N, 5.03.

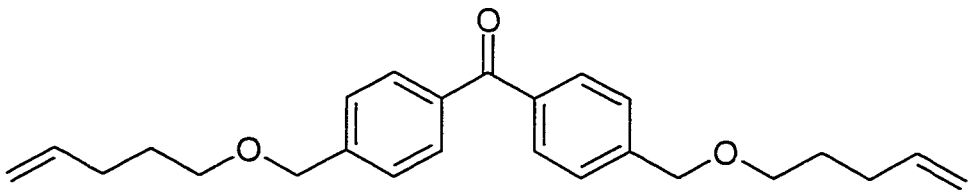
N,N-Diethyl-2-formyl-4-(2-oxa-6-heptenyl)-benzamide (39)



Tetramethylethylenediamine (0.68 mL, 4.5 mmol) was added to a solution of **38** (1.04 g, 3.76 mmol) in dry tetrahydrofuran (20 mL). The mixture was cooled to -78°C and *sec*-butyllithium (1.3 M, 3.47 mL) was added dropwise over 12 min. The resulting yellow mixture turned orange and then red. The reaction was stirred at -78°C for 1 h. Anhydrous dimethylformamide (0.58 mL, 7.5 mmol) was added over 10 min. and the and the resulting mixture was stirred at -78°C for 30 min. The reaction was warmed to room temperature and stirred for 2 h and then was cooled to 0°C. and quenched with saturated ammonium chloride (15 mL) and allowed to warm to room temperature. The reaction was diluted with ether and the resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x5 mL) and the combined organic extracts were washed with water (1x5 mL) and brine (1x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (70-85%

ether/petroleum ether) afforded 530 mg (46%) of the desired product as a yellow oil. IR (neat) 3502, 3074, 2975, 2935, 2863, 2752, 1698, 1627, 1442, 1288, 1099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J*=7.1 Hz), 1.28 (t, 3H, *J*=7.1 Hz), 1.97 (p, 2H, *J*=7.0 Hz), 2.14 (q with additional splitting, 2H, *J*=6.8 Hz), 3.09 (q, 2H, *J*=7.1 Hz), 3.51 (t, 2H, *J*=6.5 Hz), 3.59 (q, 2H, *J*=7.1 Hz), 4.54 (s, 2H), 4.93-4.96 (dm, 1H), 4.99-5.03 (dm, 1H), 5.79 (dddd, 1H, J_1=17.0 Hz, J_2=10.3 Hz, J_3=7.0 Hz, J_4=6.7 Hz), 7.31 (d, 1H, *J*=7.7 Hz), 7.60 (dd, 1H, J_1=7.7 Hz, J_2=1.7 Hz), 7.87 (d, 1H, *J*=1.2 Hz), 10.02 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 190.5, 168.6, 140.2, 138.7, 138.0, 132.9, 132.6, 128.5, 126.9, 114.9, 71.8, 70.3, 42.9, 39.1, 30.2, 28.8, 13.9, 12.6; HRMS calcd for $C_{18}H_{25}NO_3$ 303.1835, found 303.1859; Anal Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.30; N, 4.62; Found: C, 71.14; H, 8.16; N, 4.47.

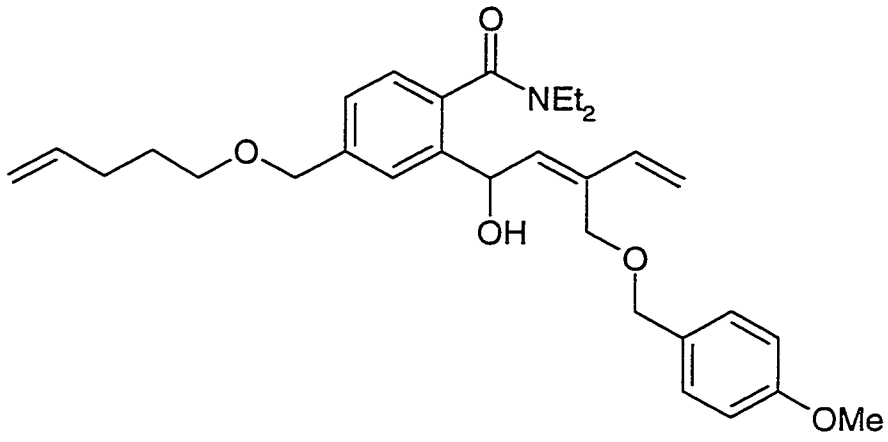
Bis (4-(2-oxa-6-heptenyl)phenyl) ketone (45)



Sec-butyllithium (1.19 M, 18.3 mL) was added slowly to a solution of **21** (5.05 g, 0.020 mol), in dry tetrahydrofuran (100 mL) at -78°C. The reaction was stirred for 30 min. and then diethyl carbamoyl chloride (3.01 mL, 0.024 mol) was added over 10 min. The reaction was stirred for 25 min. and then quenched with

saturated ammonium chloride (40 mL) and allowed to warm to room temperature. The resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x50 mL) and the combined organic extracts were washed with water (1x15 mL) and brine (1x15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (20-100% ether/petroleum ether) afforded 1.02 g (19%) of the material as a pale yellow oil. IR (neat) 3074, 2931, 2859, 1739, 1655, 1609, 1447, 1408, 1360, 1284, 1106, 920; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (p, 2H, J=6.8 Hz), 2.15 (q, 2H, J=7.2 Hz), 3.51 (t, 2H, J=6.5 Hz), 4.56 (s, 2H), 4.94-4.97 (dm, 1H), 5.00-5.04 (dm, 1H), 5.81 (dddd, 1H, J_1=17.1 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 7.43 (d, 2H, J=8.5 Hz), 7.76 (d, 2H, J=8.3 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) 196.1, 143.5, 138.1, 136.9, 130.2, 127.0, 114.8, 72.3, 70.1, 30.3, 28.9; MS calcd for $C_{25}H_{30}O_3$ 378, found 378; Anal Calcd for $C_{25}H_{30}O_3$ C,79.33; H, 7.99; Found C, 79.85; H, 7.40.

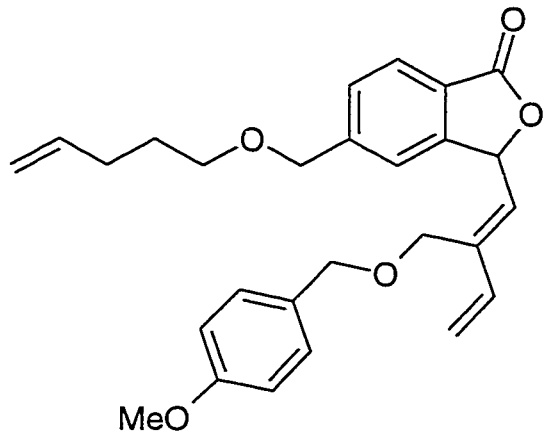
(*E*)-N,N-Diethyl-2-(1-hydroxy-3-(4-methoxybenzyloxymethyl)-2,4-pentadienyl)-4-(2-oxa-6-heptenyl) benzamide (59)



A solution of 1-iodo-2-(4-methoxybenzyloxymethyl)-1,3-butadiene (**13**) (5.26 g, 15.9 mmol) in dry tetrahydrofuran (12 mL) was added to a solution of *sec*-butyllithium (1.3 M, 24.5 mL) in dry tetrahydrofuran (75 mL) at -78°C. The reaction was stirred at -78°C for 3 min and then aldehyde **39** (3.72 g, 12.3 mmol) in dry tetrahydrofuran (9 mL) was added. The reaction was stirred at -78°C for 15 min and then the cold bath was removed and the reaction stirred at room temperature for 10 min. The reaction was quenched with water (20 mL) and the resulting phases were separated and the aqueous phase extracted with diethyl ether (3x20 mL) and the combined organic extracts were washed with brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (75% ether/petroleum ether) afforded 4.15 g (67%) of the desired product as a yellow oil. IR (neat) 3381 (br), 2974, 2935, 2863, 1613, 1512, 1460, 1369, 1292, 1248, 1088, 1033 cm^{-1}; ^1H NMR (500 MHz,

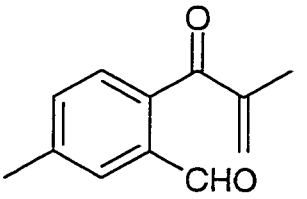
$CDCl_3$) δ 1.01 (t, 3H, *J*=7.1 Hz), 1.18 (t, 3H, *J*=7.0 Hz), 1.70 (p, 2H, *J*=6.6 Hz), 2.12 (q, 2H, *J*=6.7 Hz), 3.01-3.13 (m br, 2H), 3.43-3.48 (m, overlapping signals, 4H), 3.50-3.65 (s br, 1H), 3.77 (s, 3H), 4.05-4.16 (s br, 2H), 4.31 (ABq, 2H, J_1=11.3 Hz, J_2=9.3 Hz), 4.45 (s, 2H), 4.93-4.95 (dm, 1H), 4.98-5.01 (dm, 1H), 5.08 (d, 1H, *J*=10.9 Hz), 5.31 (d, 1H, *J*=17.4 Hz), 5.33-5.62 (s br, 1H), 5.80 (dddd, 1H, J_1=17.1 Hz, J_2=10.3 Hz, J_3=6.9 Hz, J_4=6.6 Hz), 6.01 (d, 1H, *J*=7.6 Hz), 6.20-6.35 (s br, 1H), 6.82 (d, 2H, *J*=8.5 Hz), 7.13-7.27 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.2, 140.3, 138.2, 138.1, 134.4, 130.0, 129.4, 126.4, 126.1, 114.7, 114.4, 113.7, 72.3, 71.8, 70.0, 65.8, 64.0, 55.2, 43.3, 39.1, 30.3, 28.9, 15.2, 13.7, 12.5; HRMS calcd for $C_{31}H_{41}NO_5$ 507.2986, found 507.3112; Anal Calcd for $C_{31}H_{41}NO_5$: C, 73.35; H, 8.14; N, 2.76; Found: C, 73.19; H, 7.94; N, 2.60.

(*E*)-3-((2-Methoxybenzyloxymethyl)-1,3-butadienyl-5-(2-oxa-6-heptenyl) phthalide (61)



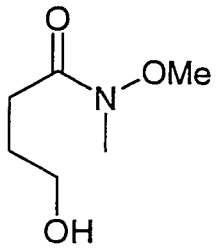
Para-toluenesulfonic acid (7.65 g, 0.040 mol) was added to a solution of **59** (4.08 g, 8.04 mmol) in dry tetrahydrofuran (160 mL) at room temperature. The reaction was stirred for 3 h. and then quenched with saturated sodium bicarbonate (60 mL). Note the reaction changes from colourless to dark cherry red upon addition of sodium bicarbonate. The reaction was diluted with ether and the resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x50 mL) and the combined organic extracts were washed with water (1x25 mL) and brine (1x25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. During extractions, solution changes colour from red to green to yellow. Purification by flash chromatography (60% ether/petroleum ether) afforded 3.27 g (94%) of the desired product as a colourless oil. IR (neat) 2931, 2859, 1766, 1613, 1513, 1447, 1366, 1289, 1248, 1091, 1051, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (p, 2H, *J*=6.4 Hz), 2.12 (q, 2H, *J*=6.8 Hz), 3.47 (t, 2H, *J*=6.5 Hz), 3.77 (s, 3H), 4.37 (ABq, 2H, J_1=11.5 Hz, J_2=5.7 Hz), 4.48 (s, 2H), 4.55 (ABq, 2H, J_1=11.5 Hz, J_2=5.8 Hz), 4.93-4.95 (dm, 1H), 4.97-5.01 (dm, 1H), 5.18 (d, 1H, *J*=11.0 Hz), 5.41 (d, 1H, *J*=17.6 Hz), 5.46 (d, 1H, *J*=9.2 Hz), 5.78 (dddd, 1H, J_1=17.2 Hz, J_2=10.1 Hz, J_3=6.9 Hz, J_4=6.7 Hz), 6.29 (dd, 1H, *J*=10.2 Hz), 6.31 (d, 1H, *J*=9.9 Hz), 6.85 (d, 2H, *J*=8.7 Hz), 7.28 (d, 2H, *J*=8.7 Hz), 7.36 (s, 1H), 7.47 (d, 1H, *J*=7.9 Hz), 7.82 (d, 1H, *J*=7.9 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.3, 159.5, 149.5, 146.0, 139.8, 138.0, 137.4, 129.7, 129.5, 128.2, 125.5, 125.0, 121.7, 115.9, 114.9, 113.8, 77.7, 72.6, 72.2, 70.4, 64.2, 55.2, 30.2, 28.8; HRMS calcd for $C_{27}H_{30}O_5$ 434.2299, found 434.2448; Anal Calcd for $C_{27}H_{30}O_5$: C, 74.62; H, 6.96; Found: C, 74.45; H, 6.78.

2-(2-Methyl-1-oxo-2-propenyl)-5-methyl benzaldehyde (80)



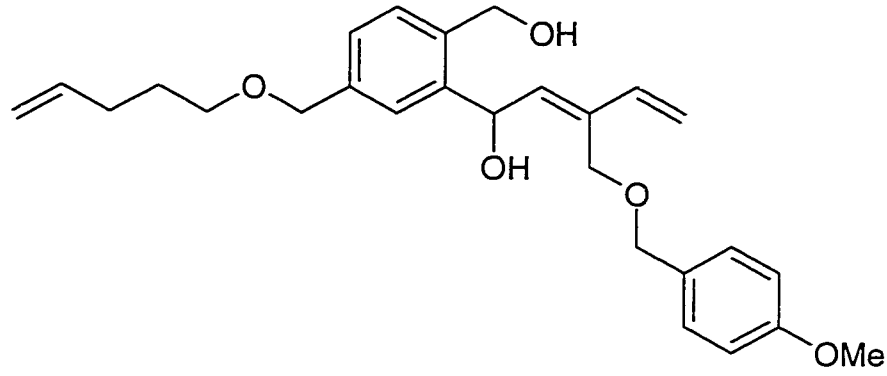
Sodium bicarbonate (1.22g, 14.5 mmol) was added to a solution of 2-(1-hydroxy-2-methyl-2-propenyl)-5-methyl benzyl alcohol (518 mg, 2.69 mmol) in dry dichloromethane (10 mL) at room temperature. Dess-Martin Periodinane (2.71 g, 6.39 mmol) was added and the reaction was stirred for 5 min., during which time it changed from colourless to dark blue. The reaction was quenched with a 1:1 mixture of saturated sodium bicarbonate : 1 M sodium thiosulfate (30 mL) and stirred for 10 min. The reaction was diluted with ether and the resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x5 mL) and the combined organic extracts were washed with brine (1x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (20% ether/petroleum ether) afforded 91.1 mg (18%) of the desired product as a colourless oil. IR (neat) 2958, 2925, 2857, 2738, 1678, 1605, 1564, 1449, 1376, 1328, 1245, 1203; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.43 (s, 3H), 5.41 (s, 1H), 5.87 (s, 1H), 7.30 (d, 1H, J=4.5 Hz), 7.40 (d, 1H, J=4.1 Hz), 7.70 (s, 1H), 9.92 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 190.8, 145.8, 140.6, 135.2, 133.8, 130.8, 129.0, 128.5, 21.1, 17.3; HRMS calcd for $C_{12}H_{12}O_2$ 188.0838, found 188.0826.

4-Hydroxy-N-methoxy-N-methyl butanamide (83)



Trimethylaluminum (2.0M in hexanes, 5.20 mmol) was added to a solution of N,O-dimethylhydroxylamine (508 mg, 5.20 mmol) in dry toluene (10 mL) at room temperature. The reaction was stirred for 15 min and then butyrolactone (224 mg, 2.60 mmol) was added and the reaction stirred for 3 h. Dilute aqueous hydrochloric acid (10%, 7.5 mL) was added and the resulting phases were separated and the aqueous phase was extracted with dichloromethane (3x10 mL) and the combined organic extracts were washed with brine (1x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude mixture was clean and afforded 172 mg (45%) of the desired product as a colourless oil. Note the product was found to be volatile and extended exposure to reduced pressure resulted in a loss of material, therefore the quoted yield is a minimum. IR (neat) 3412 (br), 2975, 2937, 2875, 2244, 1647, 1441, 1387, 915, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (p, 2H, *J*=6.4 Hz), 2.56 (t, 2H, *J*=6.5 Hz), 2.62-2.88 (s br, 1H), 3.16 (s, 3H), 3.64-3.66 (m, overlapping signals, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) 174.8, 62.4, 61.2, 32.2, 29.1, 27.2; HRMS calcd for $C_6H_{13}NO_3$ 147.0896, found 147.0876.

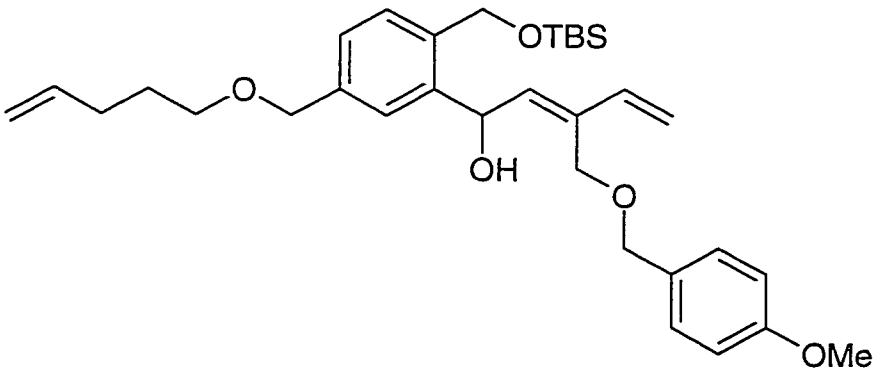
(*E*)-2-(1-Hydroxy-3-(4-methoxybenzyloxymethyl)-2,4-pentadienyl)-4-(2-oxa-6-heptenyl)-1-benzyl alcohol (87)



Diisobutylaluminum hydride (1.0 M in hexanes, 15.0 mL) was added dropwise to a solution of the lactone **61** (3.26 g, 7.50 mmol) in dry tetrahydrofuran (60 mL) at 0°C. The reaction was warmed to room temperature and stirred for 3.5 h. and then cooled to 0°C. The reaction was quenched with potassium sodium tartrate (0.5 M, 30 mL) and stirred for 15 min. Extensive emulsion was minimized by the addition of aqueous hydrochloric acid (10%, 30 mL). The resulting phases were separated and the aqueous phase was extracted with diethyl ether (3x25 mL) and the combined organic extracts were washed with water (1x10 mL) and brine (1x10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (80% ether/ petroleum ether) afforded 2.63 g (80%) of the desired product as a pale yellow oil. IR (neat) 3365 (br), 3075, 2896, 1640, 1611, 1586, 1513, 1453, 1363, 1247, 1053; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (p, 2H, *J*=6.8 Hz), 2.11 (q, 2H, *J*=7.2 Hz), 3.05 (t, 1H, *J*=6.0 Hz),

3.41-3.46 (m, 1H), 3.44 (t, 2H, J=6.5 Hz), 3.78 (s, 3H), 4.23 (s, 2H), 4.43 (d, 2H, J=4.4 Hz), 4.45 (s, 2H), 4.59 (d of ABq, 2H, J_1=16.8 Hz, J_2=5.8 Hz), 4.92-5.02 (dm, 2H), 5.11 (d, 1H, J=11.0 Hz), 5.30 (d, 1H, J=17.6 Hz), 5.74-5.83 (m, overlapping signals, 2H), 5.99 (d, 1H, J=8.1 Hz), 6.32 (dd, 1H, J_1=11.0 Hz, J_2=6.6 Hz), 6.85 (d, 2H, J=8.7 Hz), 7.18-7.29 (m, 4H), 7.35 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.4, 141.3, 138.8, 138.2, 138.1, 137.7, 136.7, 136.6, 130.2, 129.6, 129.4, 127.1, 126.4, 114.7, 114.5, 113.9, 72.4, 72.3, 69.8, 68.6, 63.9, 63.4, 55.2, 30.3, 28.9; HRMS calcd for $C_{27}H_{34}O_5$ 438.2407, found 438.2728; Anal Calcd for $C_{27}H_{34}O_5$: C,73.95; H,7.81; Found: C,74.16; H,7.80.

(*E*)-2-(1-Hydroxy-3-(4-methoxybenzyloxymethyl)-2,4-pentadienyl)-4-(2-oxa-6-heptenyl)-1-(*tert*-butyl-dimethylsilyl) benzyl alcohol (90)



4-Dimethylaminopyridine (28.5 mg, 0.233 mmol) was added to a solution of alcohol **87** (102 mg, 0.234 mmol) in dry dichloromethane (2 mL) at 0°C. *Tert*-butyldimethylsilyl chloride (35.2 mg, 0.233 mmol) was added and the reaction was warmed to room temperature. The reaction was stirred reaction for 17 h.

and then diluted with dichloromethane (2 mL). The reaction was washed with water (1x5 mL) and saturated ammonium chloride (1x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by flash chromatography (50% ether/petroleum ether) afforded 58.4 mg (47%) of the desired product as a pale yellow oil. IR (neat) 3414 (br), 3075, 2938, 2857, 1640, 1611, 1586, 1513, 1464, 1250, 1067; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (d, 6H, J=15.9 Hz), 0.89 (s, 9H), 1.68 (p, 2H, J=6.8 Hz), 2.12 (q, 2H, J=7.2 Hz), 3.45 (t, 2H, J=6.5 Hz), 3.57 (d, 1H, J=3.3 Hz), 3.78 (s, 3H), 4.20 (ABq, 2H, J_1=11.5 Hz, J_2=4.6 Hz), 4.37 (ABq, 2H, J_1=11.5 Hz, J_2=6.8 Hz), 4.46 (s, 2H), 4.61 (d, 1H, J=12.6 Hz), 4.74 (d, 1H, J=12.5 Hz), 4.92-5.02 (dm, 2H), 5.11 (d, 1H, J=11.0 Hz), 5.35 (d, 1H, J=17.6 Hz), 5.73-5.82 (m, 2H), 6.01 (d, 1H, J=8.0 Hz), 6.34 (dd, 1H, J_1=11.0 Hz, J_2=6.5 Hz), 6.83 (d, 2H, J=8.7 Hz), 7.17 (d, 2H, J=8.7 Hz), 7.24 (dd, 1H, J_1=6.0 Hz, J_2=1.7 Hz), 7.29 (d, 1H, J=7.8 Hz), 7.39 (d, 1H, J=1.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.2, 141.4, 138.5, 138.3, 138.2, 137.0, 136.9, 136.4, 129.3, 129.4, 128.6, 126.6, 125.9, 114.6, 114.3, 113.8, 72.6, 71.9, 69.7, 67.5, 64.2, 63.8, 55.2, 30.3, 28.9, 25.8, 18.2, -5.2, -5.3; HRMS calcd for $C_{33}H_{48}O_5Si$ 552.3273, found 552.3027; Anal Calcd for $C_{33}H_{48}O_5Si$: C,71.70; H,8.75; Found: C,71.86; H,8.65.

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Claims to Original Research

1. Expanded directed *ortho* metalation chemistry to include a complex diethylbenzamide.

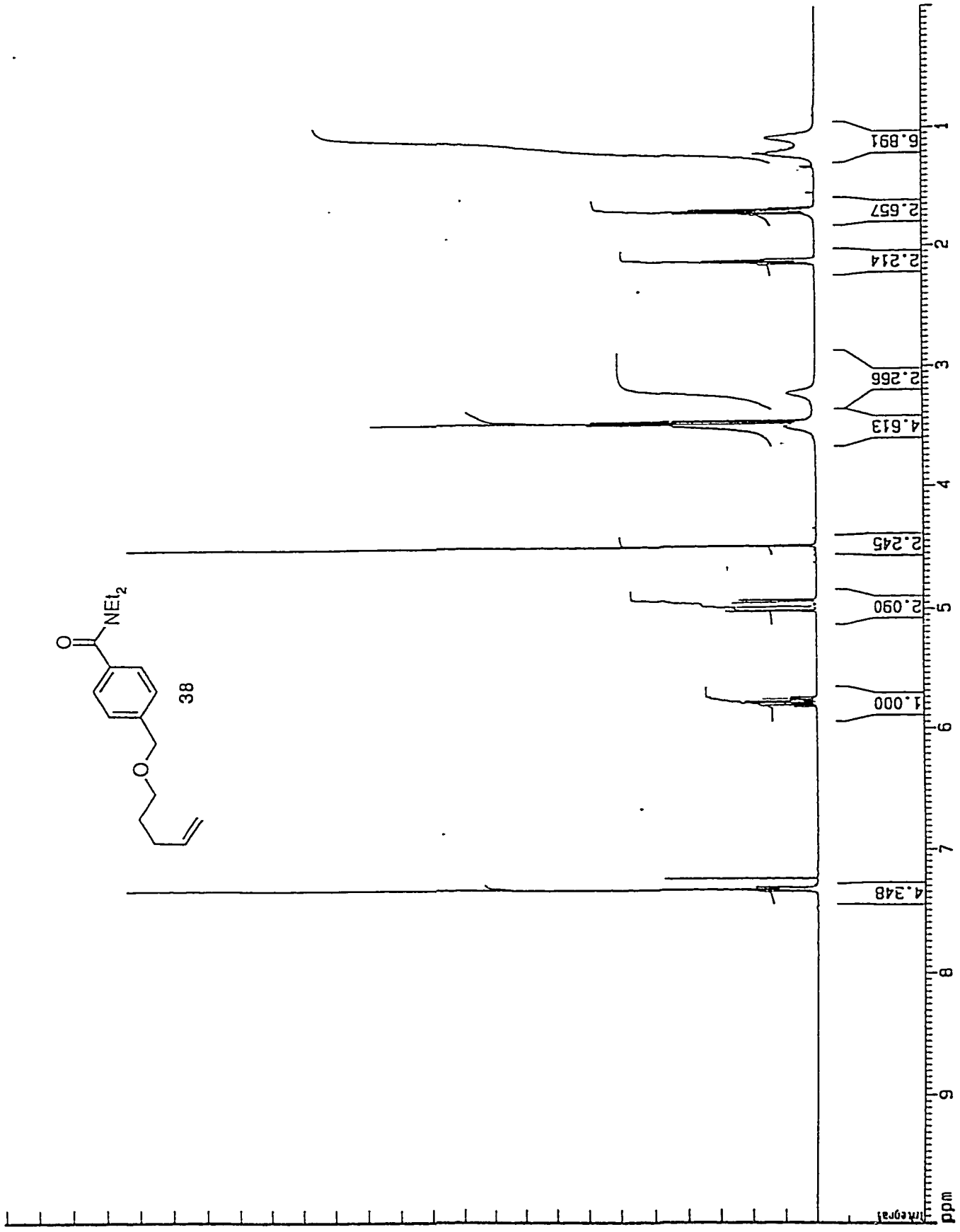
2. Developed effective route for the synthesis of 2-(1-hydroxy-3-(4-methoxybenzyloxymethyl)-2,4-pentadienyl)-4-(2-oxa-6-heptenyl)-1-*tert*-butyl-dimethylsilyl) benzyl alcohol.

3. Improved knowledge and understanding of reproducibility of preparation of iododiene.

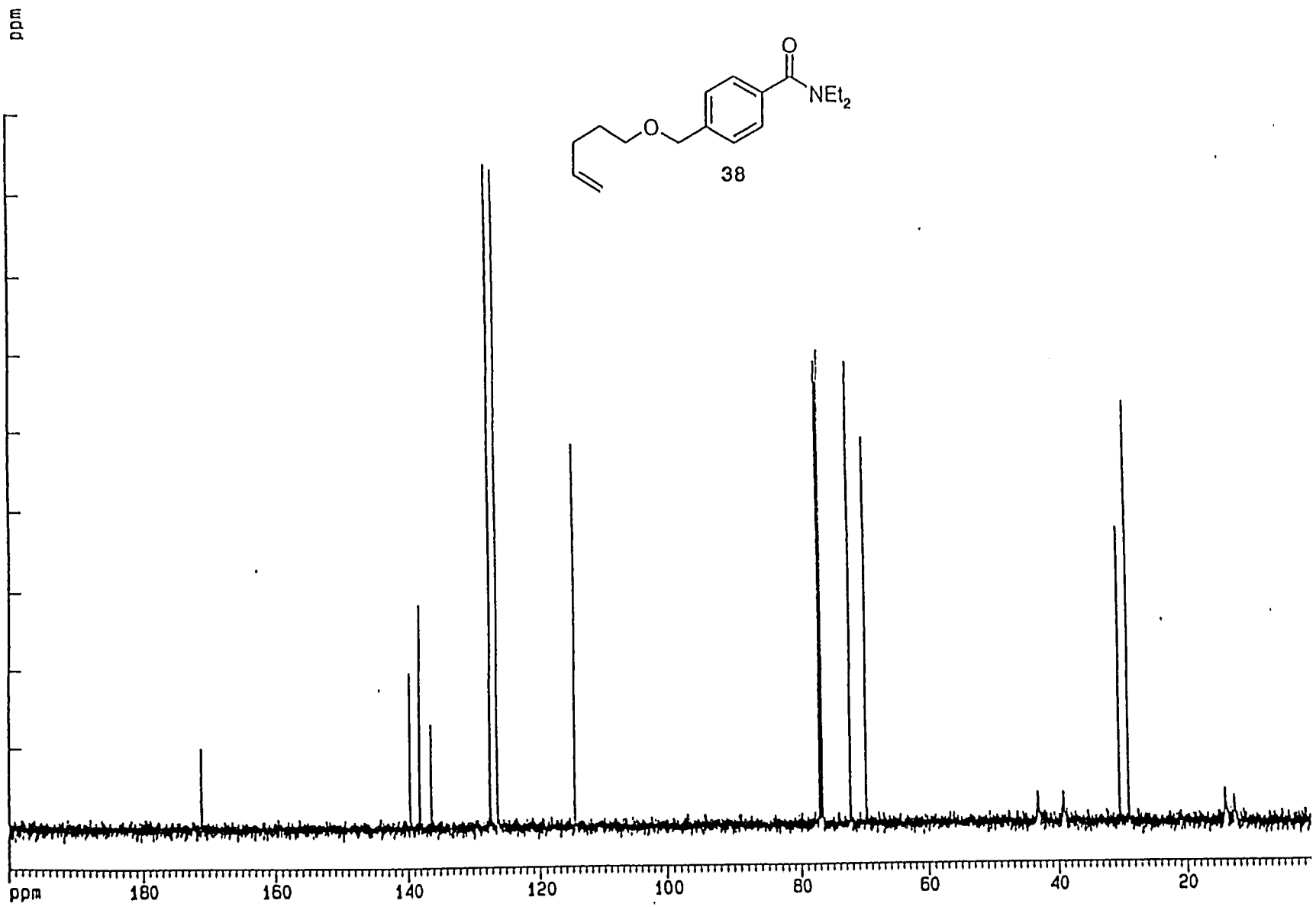
4. Extension of this research to the synthesis of the target Taxol® analogue can now be investigated.

Appendix I

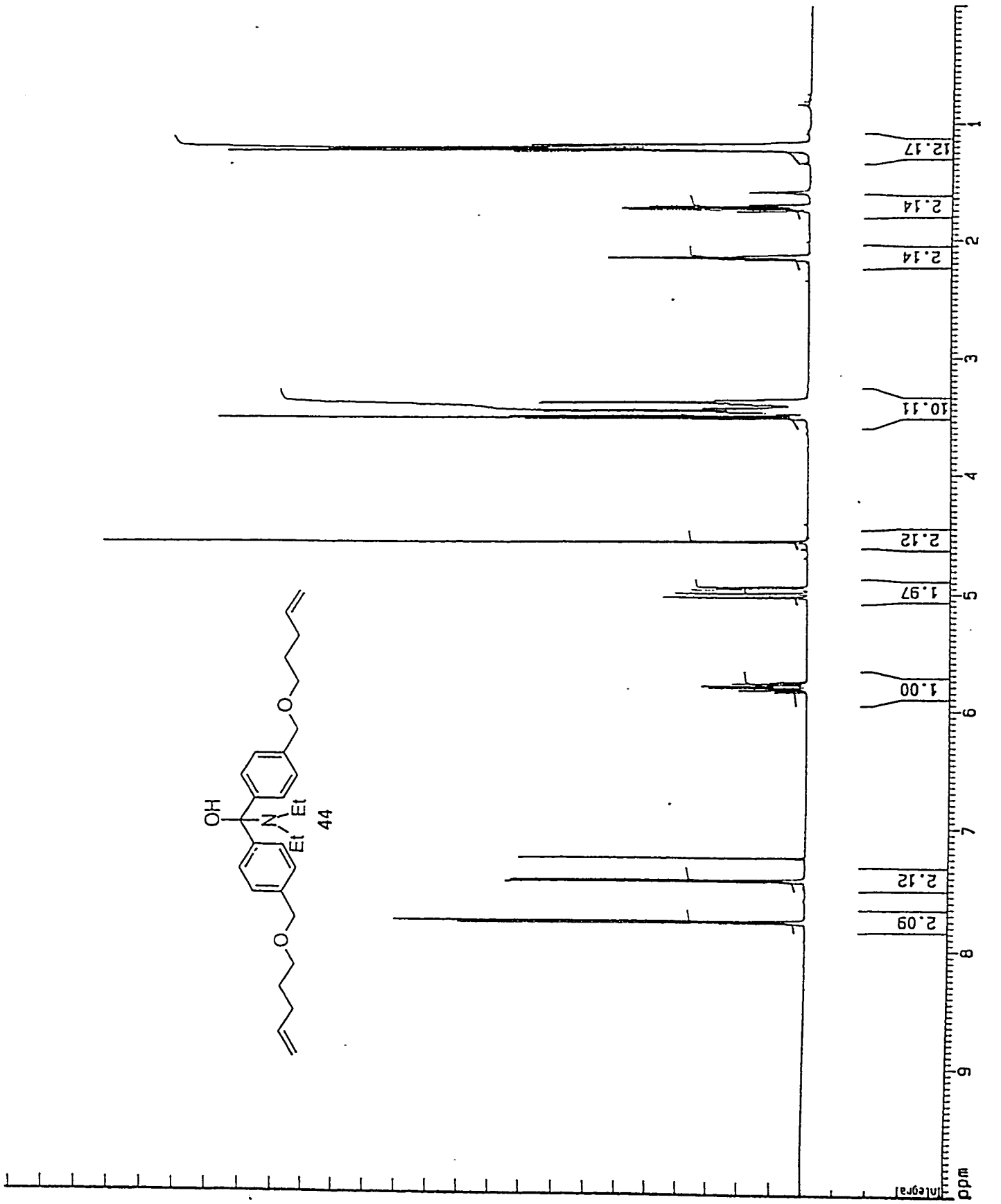
Selected Spectra



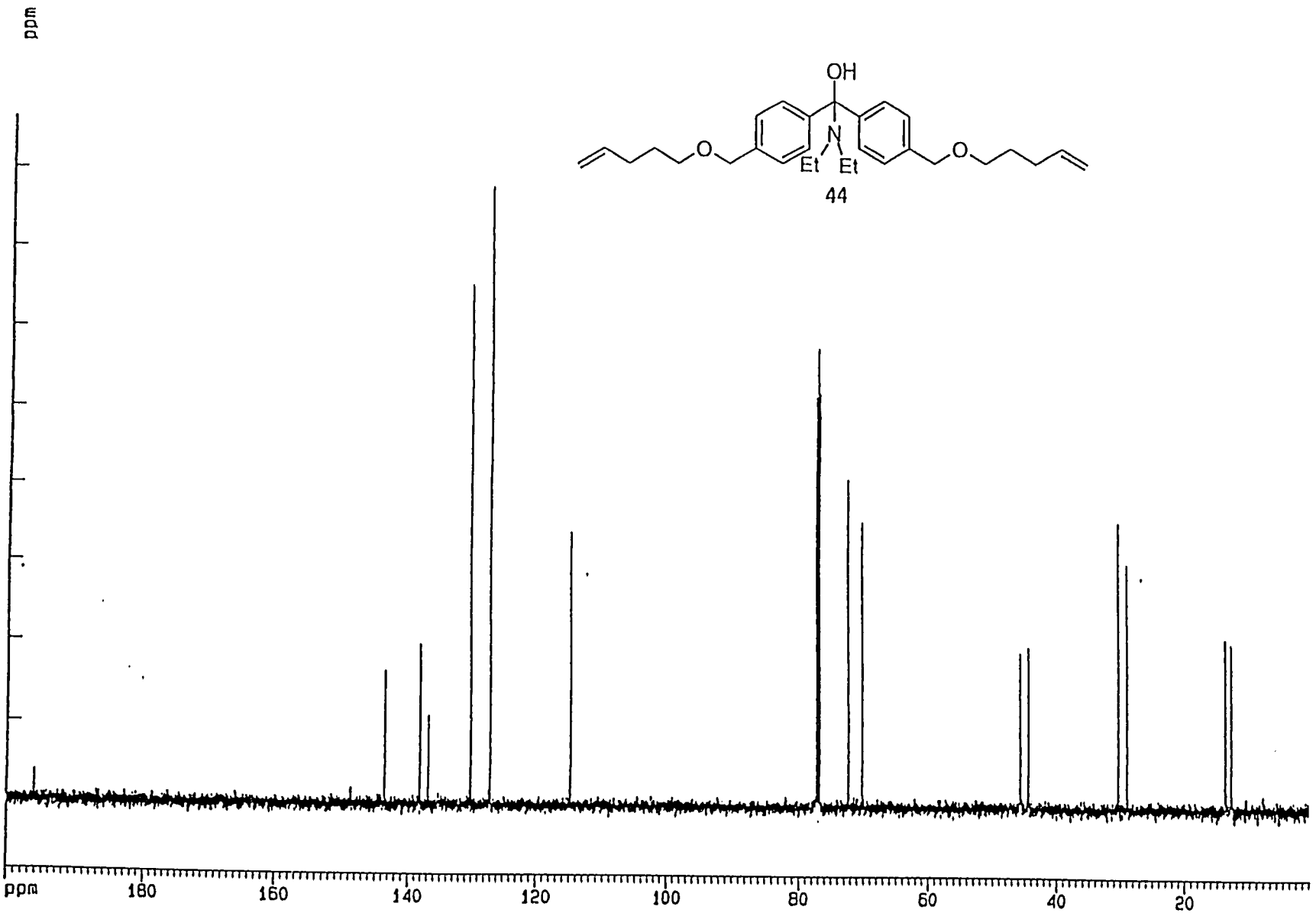
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **38**



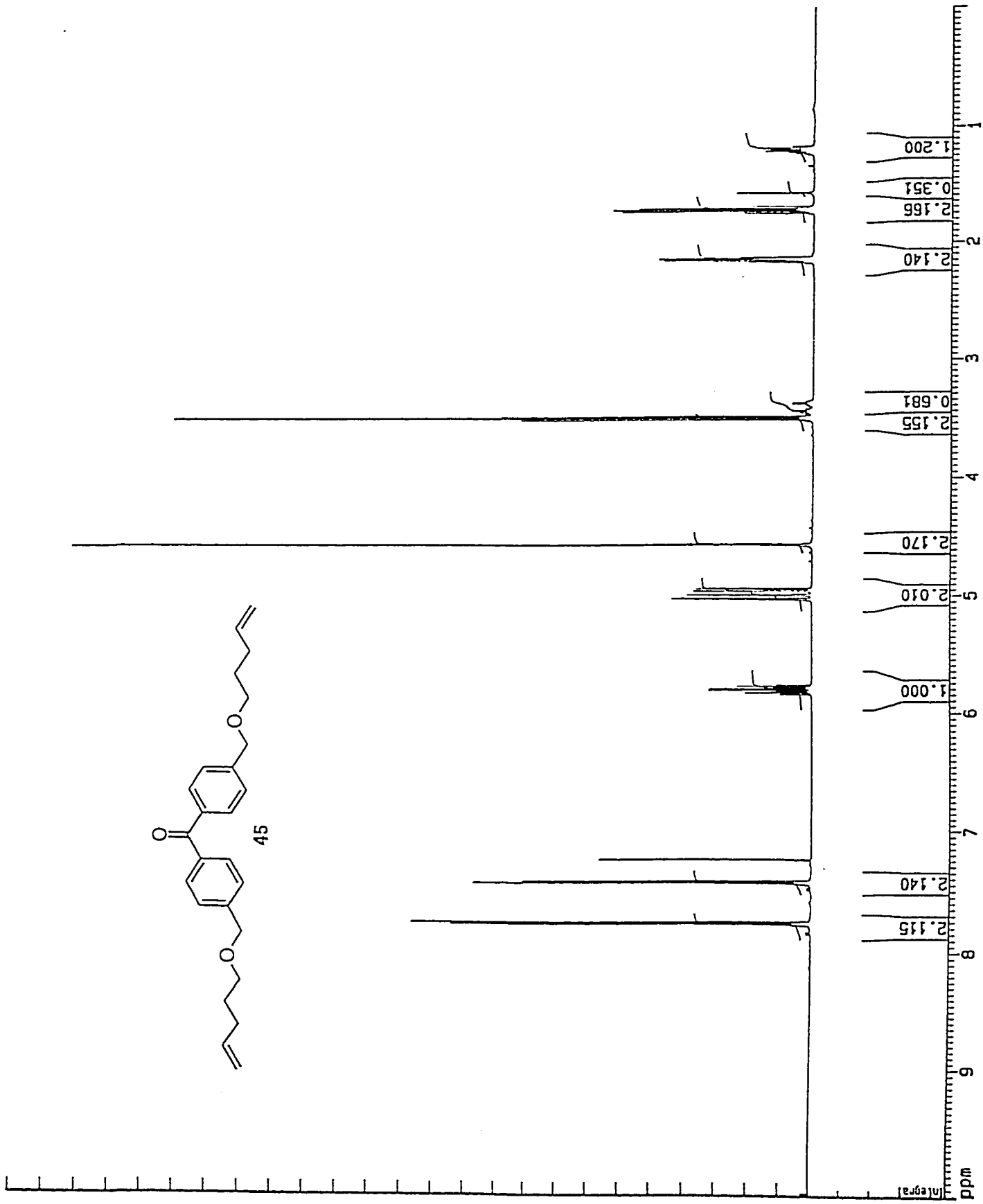
^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of **38**



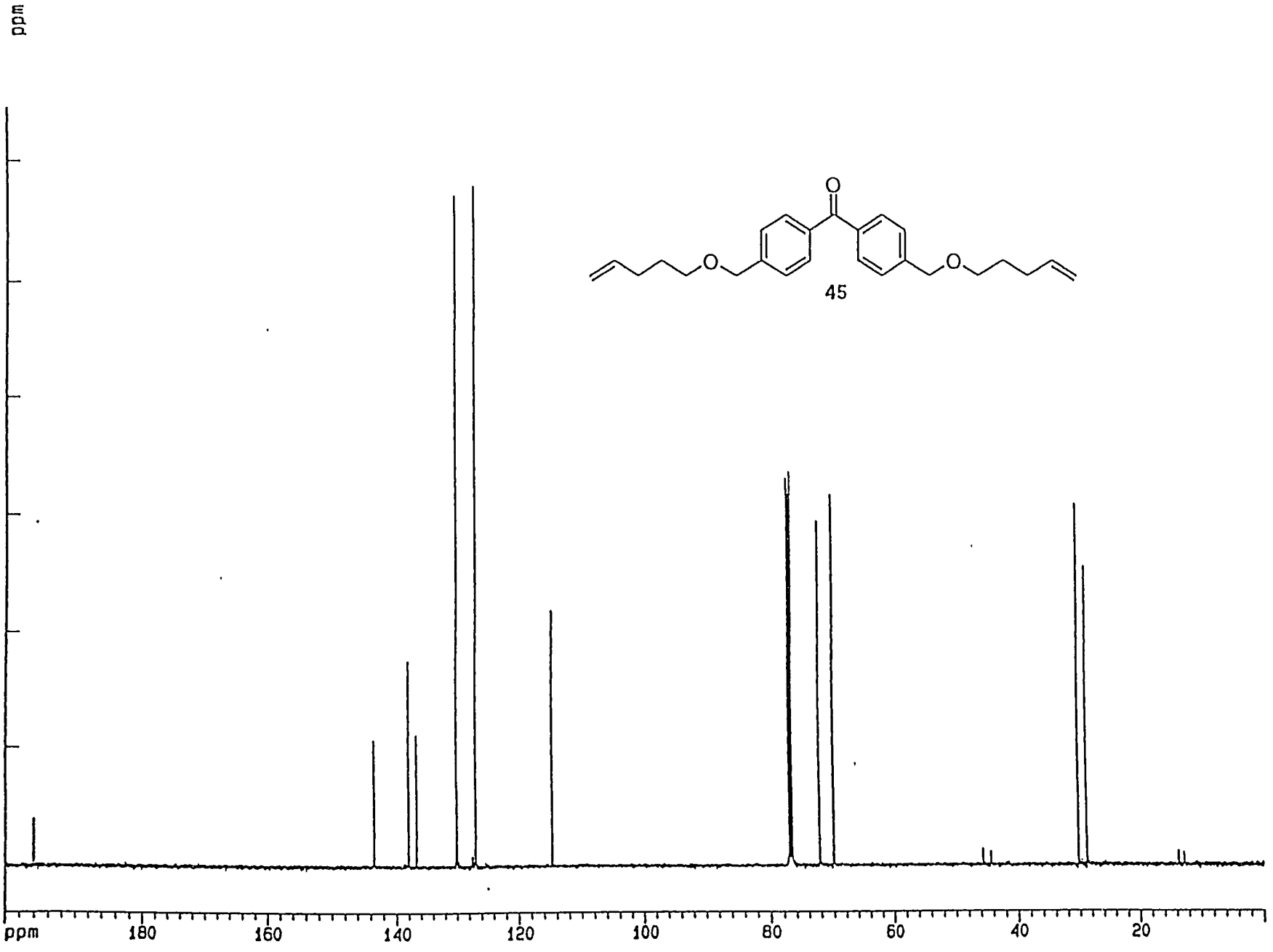
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **44**



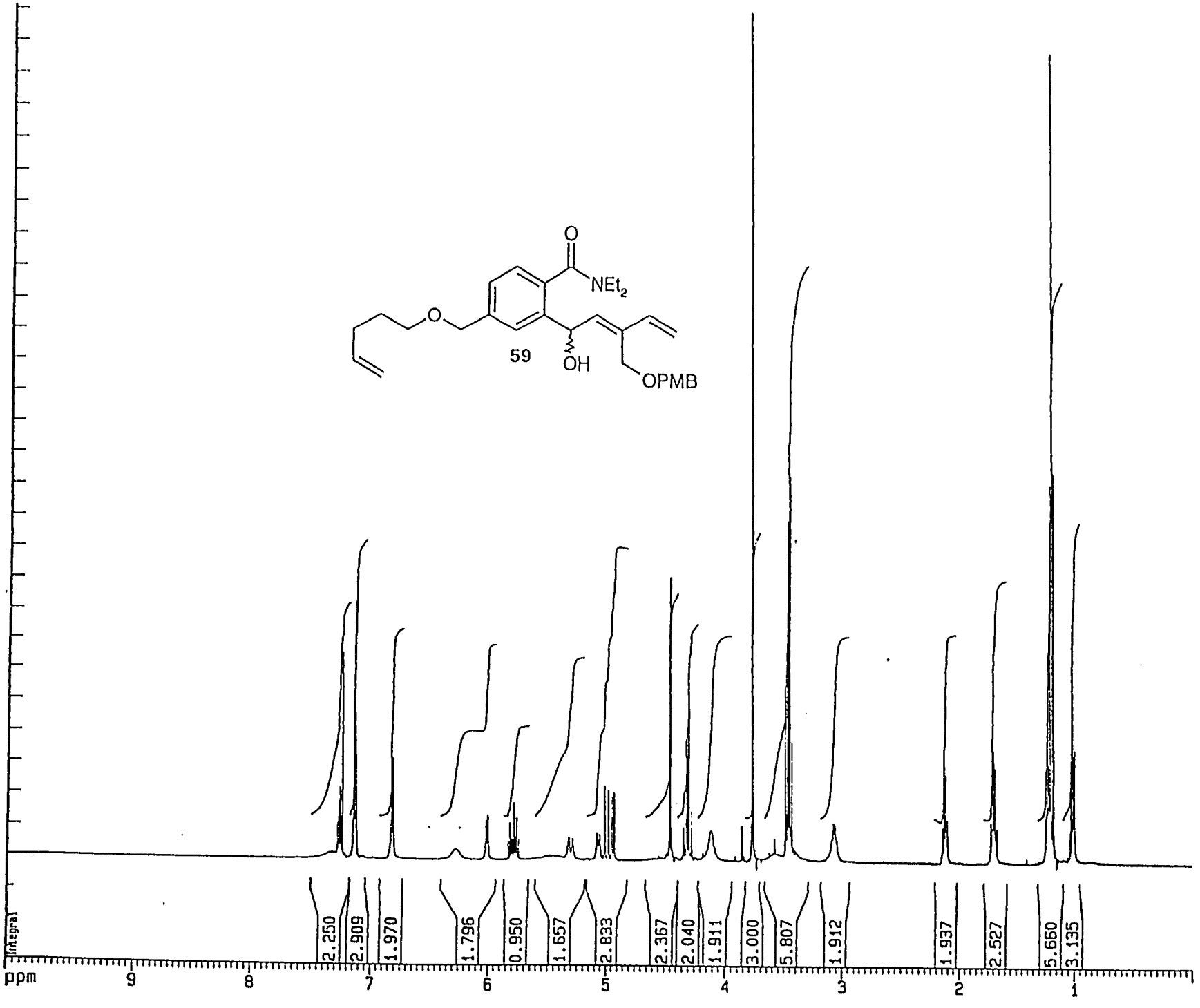
^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of **44**



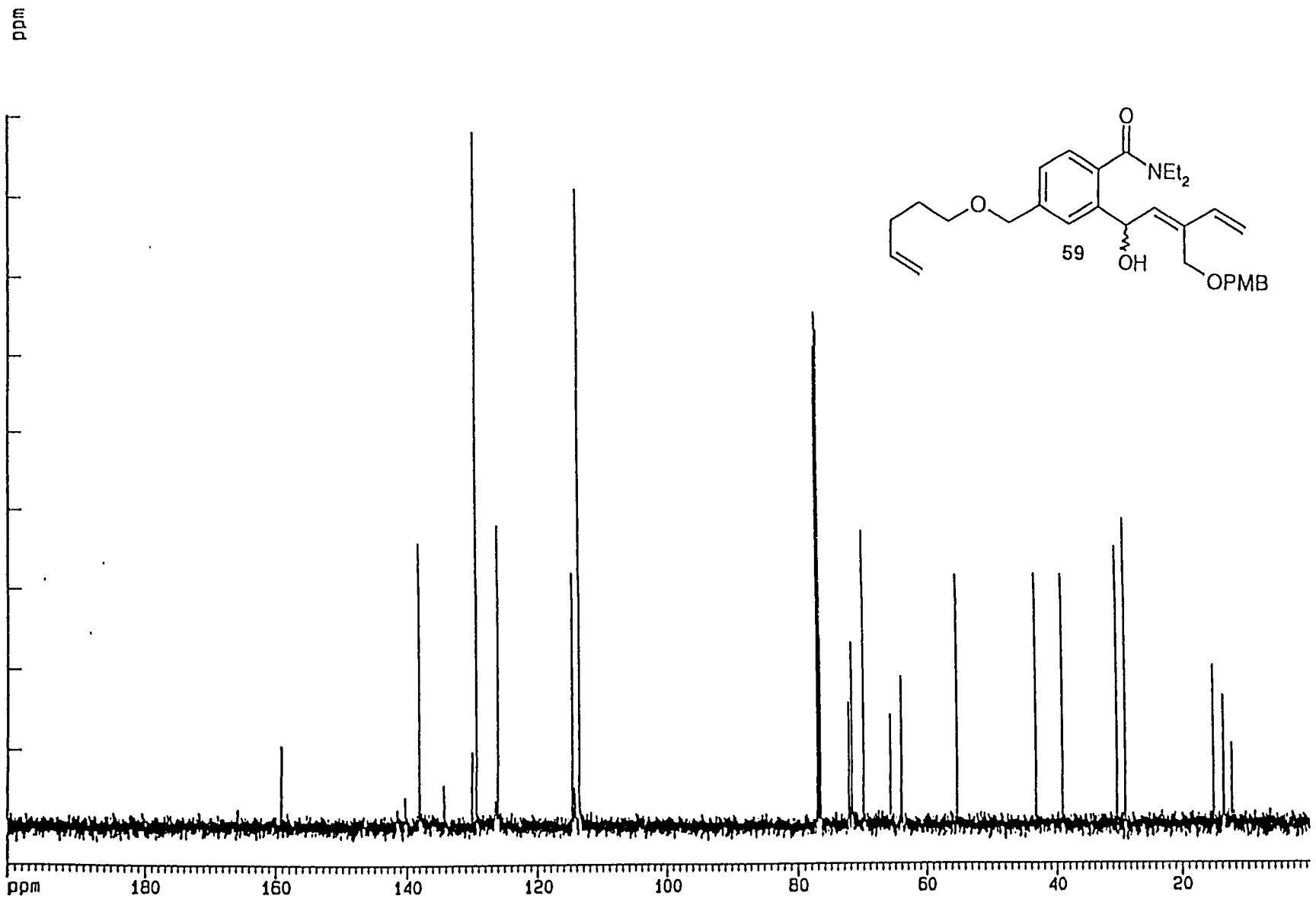
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **45**



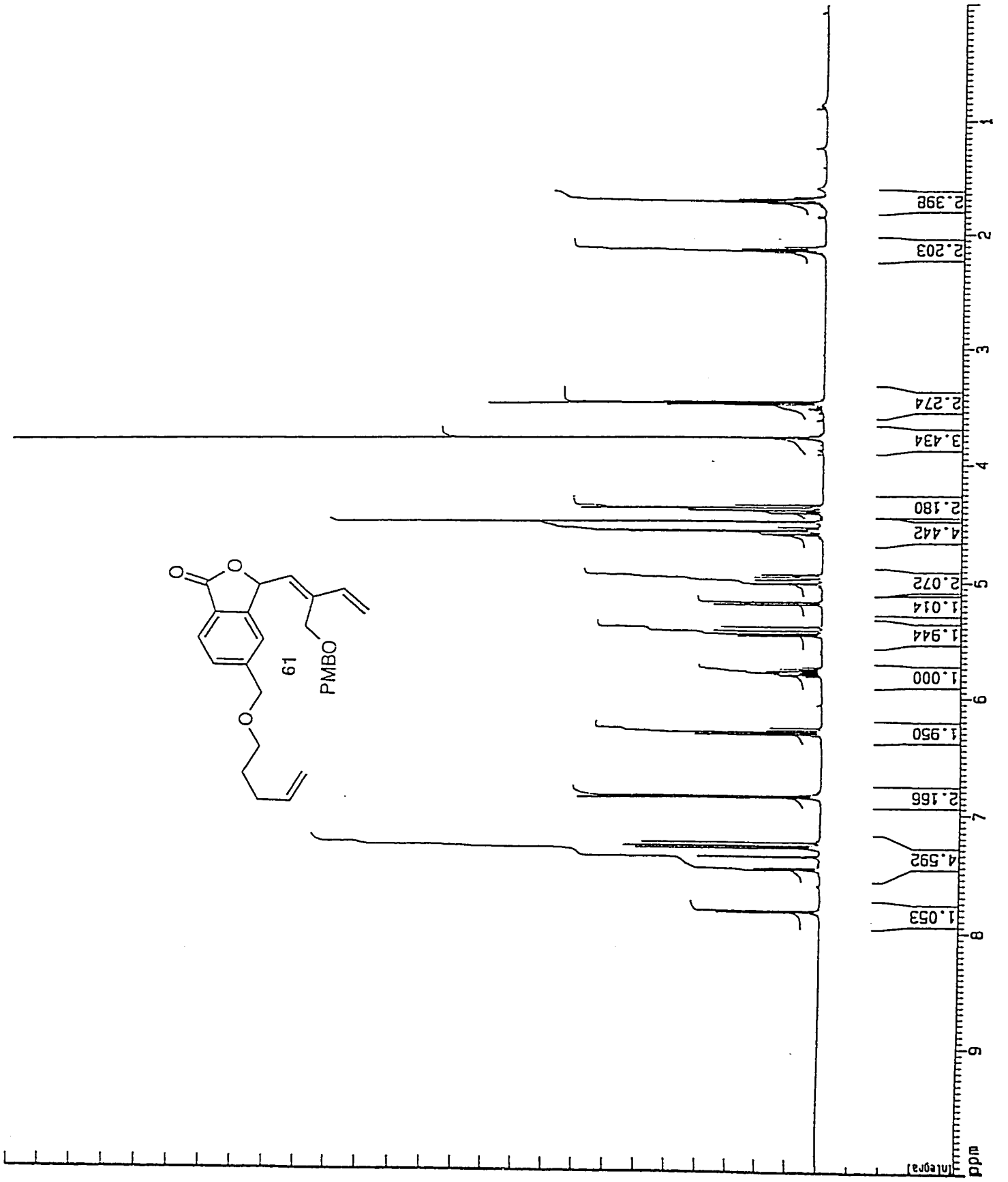
^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of **45**



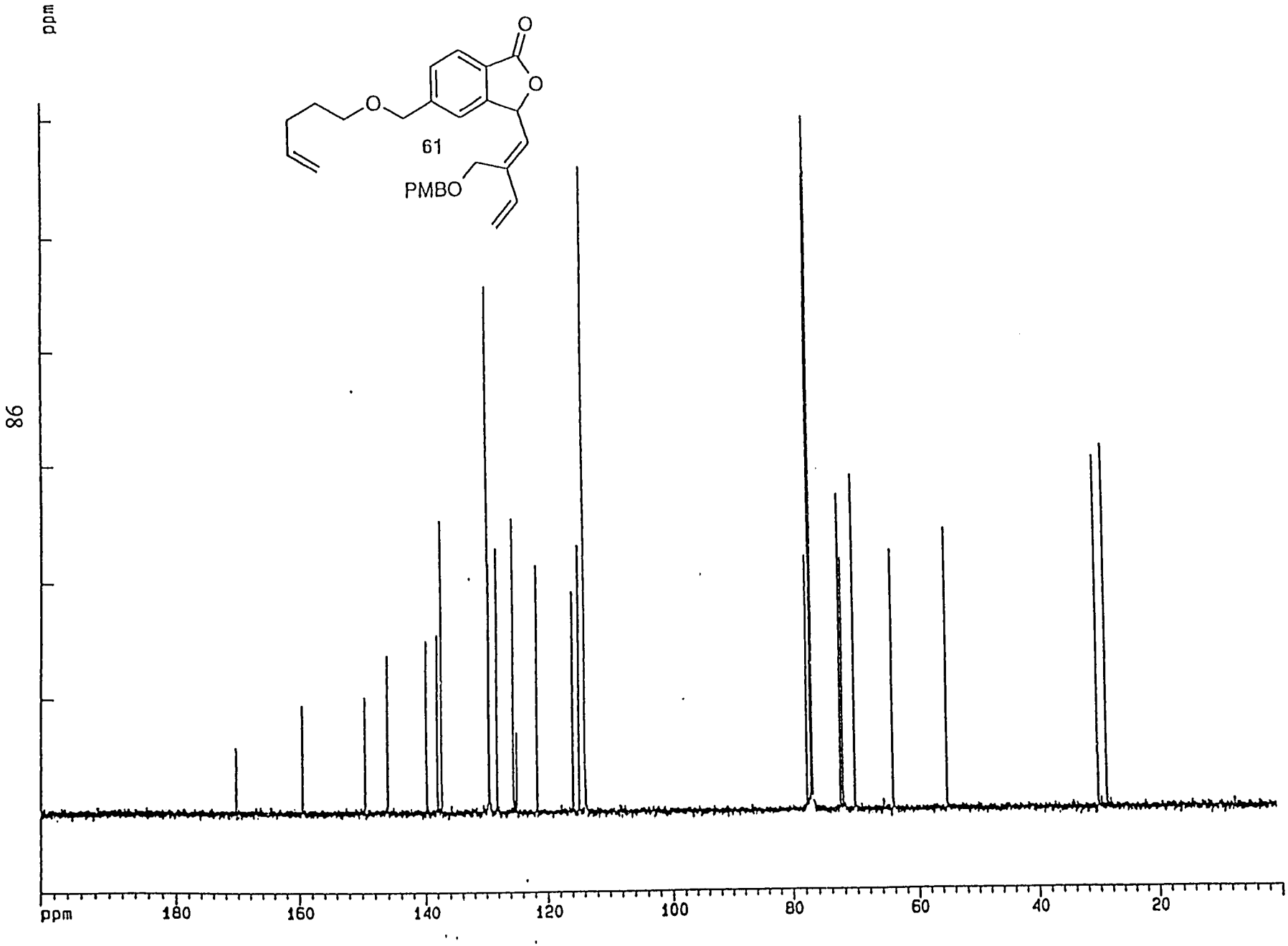
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **59**



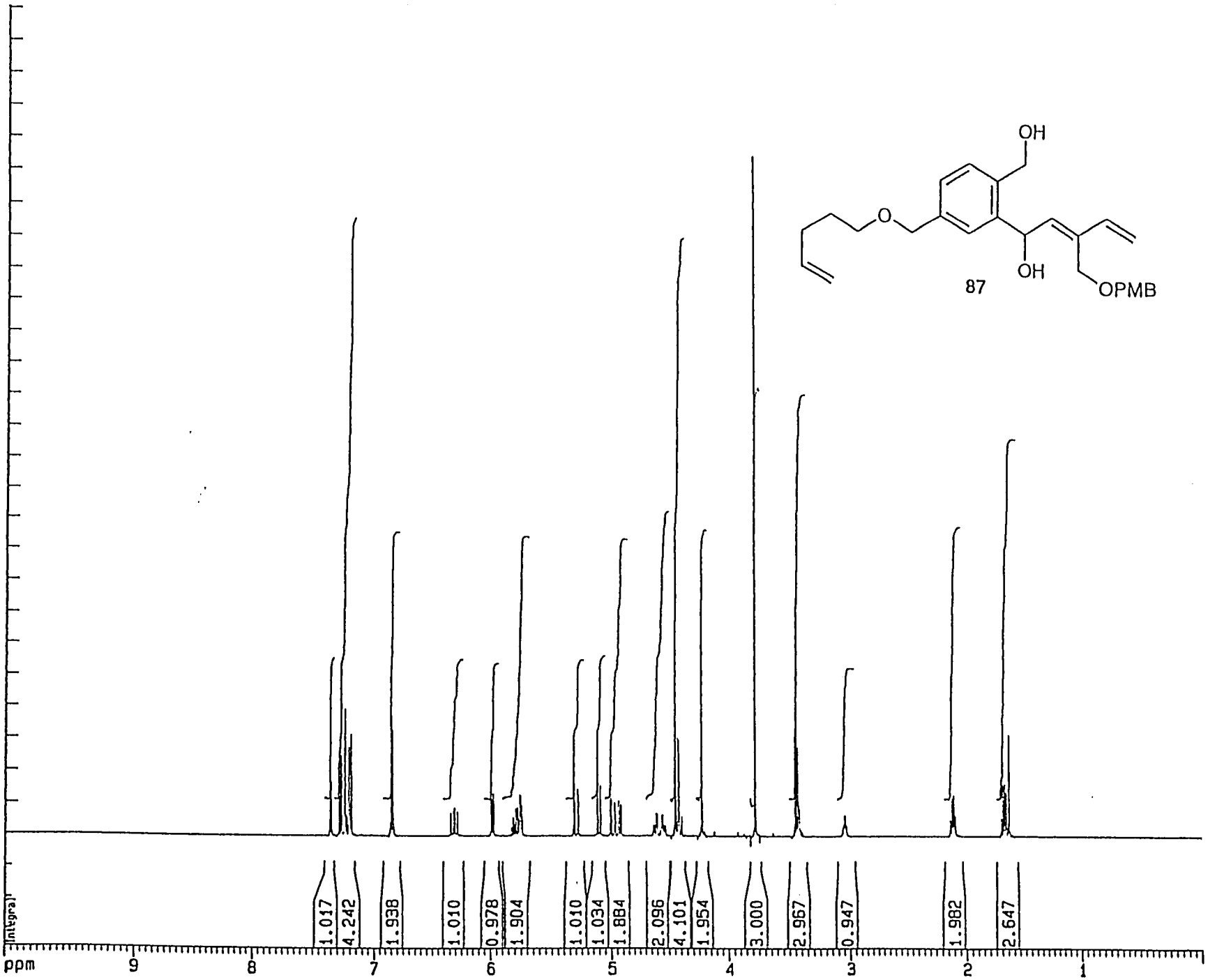
^{13}CNMR spectrum (125.8 MHz, $CDCl_3$) of **59**



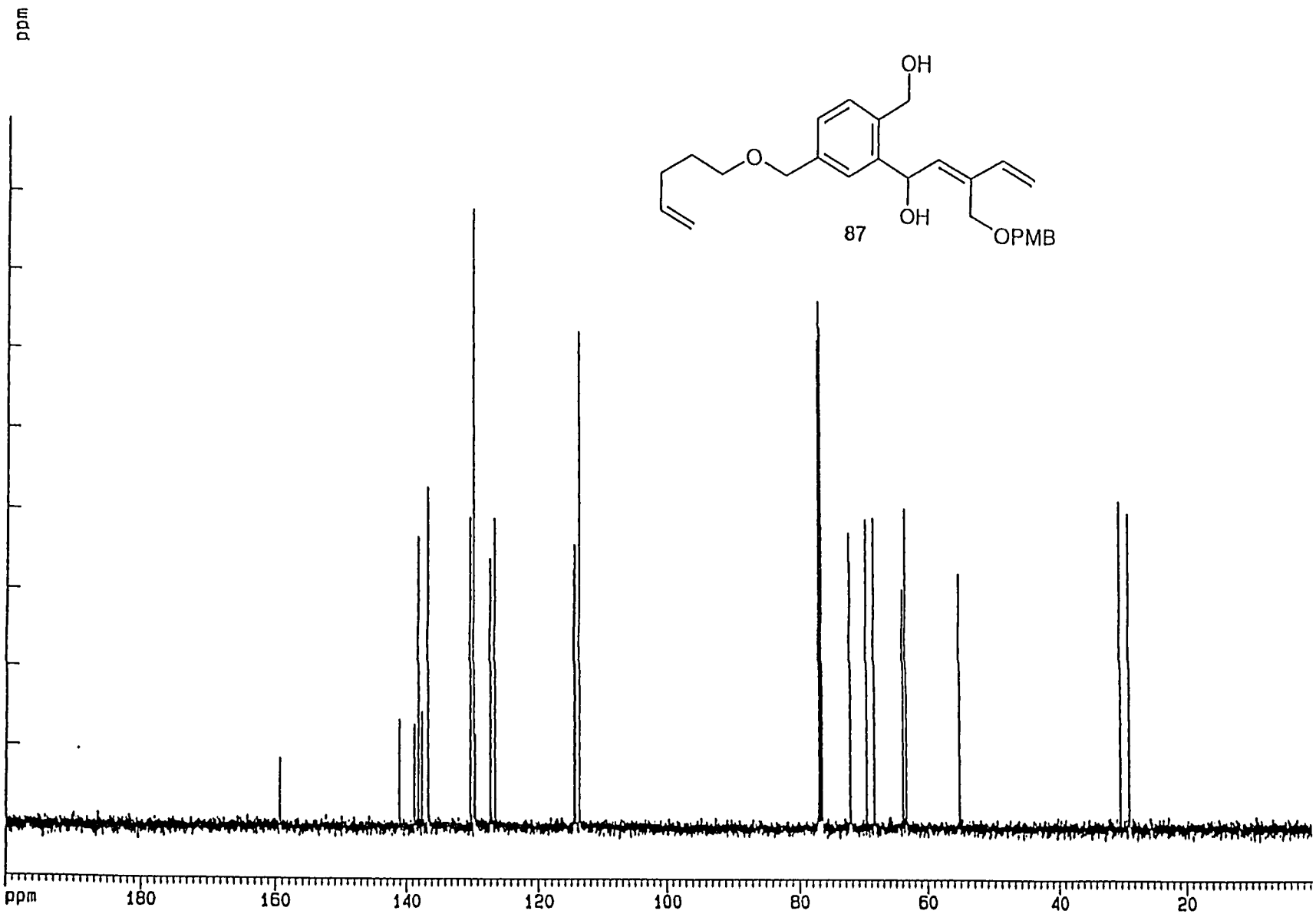
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **61**



^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of **61**

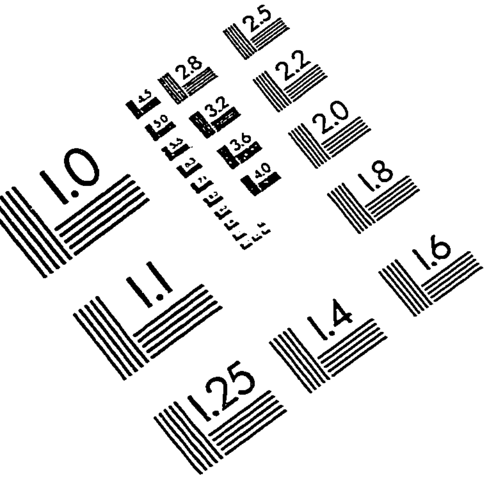


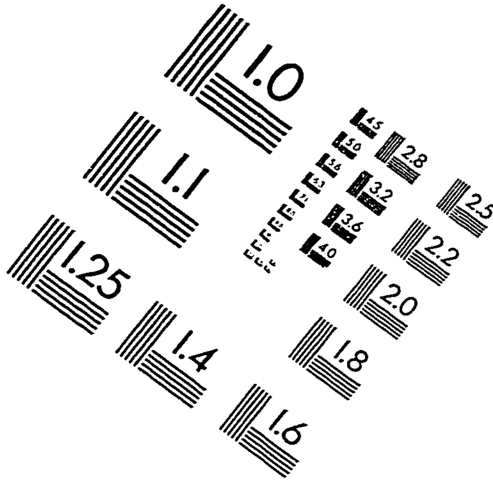
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **87**

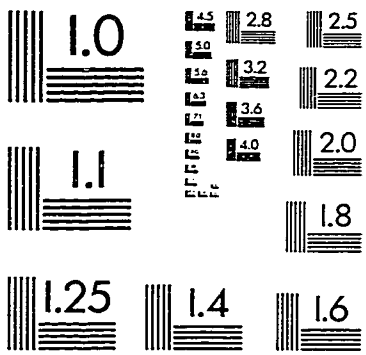


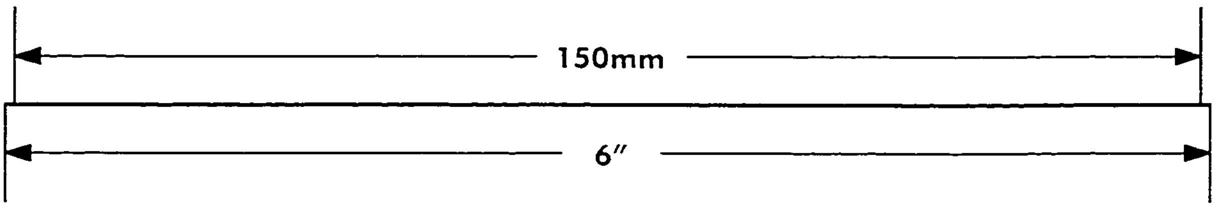
^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of **87**

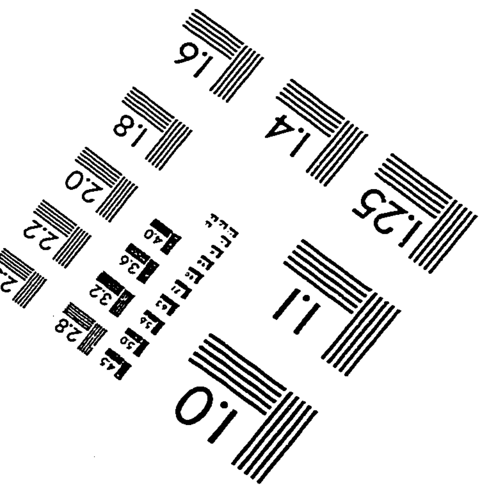
IMAGE EVALUATION TEST TARGET (QA-3)











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