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Cycloaddition Based Approaches to Nor-taxoids and Aphenes *via* Magnesium and Indium Mediated Reactions

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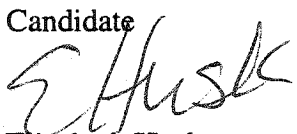
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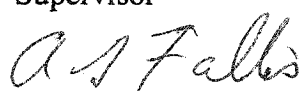
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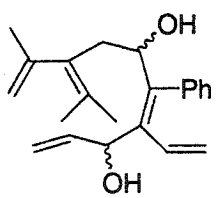
LIST OF OBBREVIATIONS

Ac	acetyl
Bn	benzyl
Bu	butyl
DCM	dichloromethane / methylene chloride
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N, N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
Et	ethyl
IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide
Me	methyl
MEM	(2-methoxyethoxy)methyl
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorphine *N*-oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

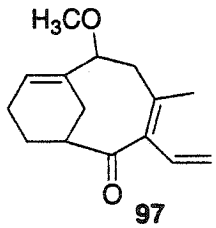
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
Pr	propyl
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TBAB	borano *t*-butylamine
TBAF	tetrabutylammonium fluoride
TCNE	tetracyanoethylene
TEA	triethylamine
THF	tetrahydrofuran
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
TES	triethylsilyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl

ABSTRACT

Various synthetic routes were used in attempt to synthesize nortaxoids that have the potential to be more potent anti cancer reagents than Taxol®. In a previously established pathway to taxoid precursor **66**, aldehyde **65** was difficult to purify and store. An alternative method involved preparing enol ether 79 using carbometallation and Wittig chemistry. Compound **79** was stable to storage and could be easily converted into aldehyde **65** with dilute acid. This sequence represents the first example of an alkylative carbometallation reaction. An attempted synthesis of nortaxoid **97** used indium chemistry as a key step in its synthetic pathway. It was found that the nortaxoids unsubstituented at C10 would not undergo allylic oxidation. The synthesis and successful use of silyl dienes in an appropriate Diels-Alder reaction could alleviate this problem by converting the silyl group into a hydroxyl group *via* Fleming-Tamao oxidation **125**.



66



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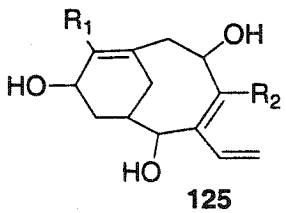
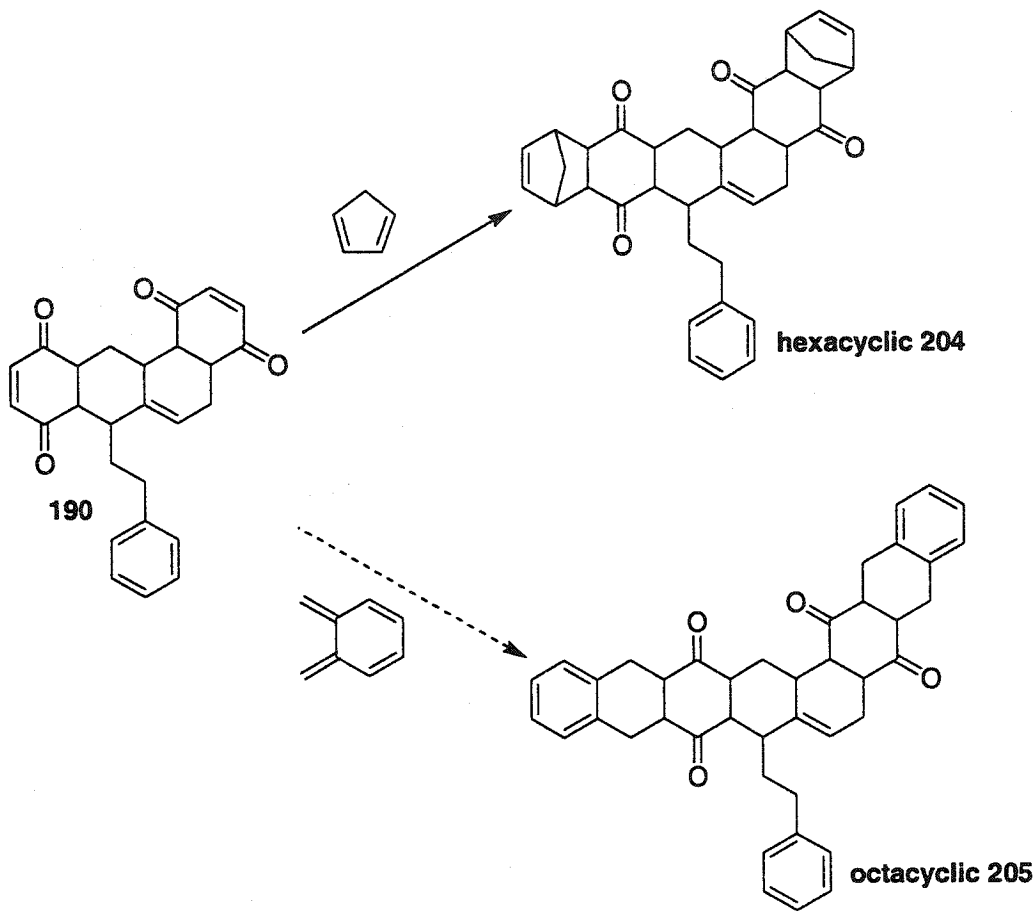


125

The chemical properties of aphenes are not known as well as those of acenes. Acenes are known to have interesting electronic properties. The electronic utility of aphenes is not known. The diene-transmissive Diels-Alder reaction of cross-conjugated trienes with cyclic dienophiles was usedto make the skeleton of butaphene precursor (**190**). The conversion of these skeletons, which can act as dienophiles, into hexaphenes

204 or octaphenes **205** through a second Diels-Alder reaction with cyclic dienes (i.e. cyclopentadiene or o-quinodimethane was investigated.



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1. CHAPTER 1

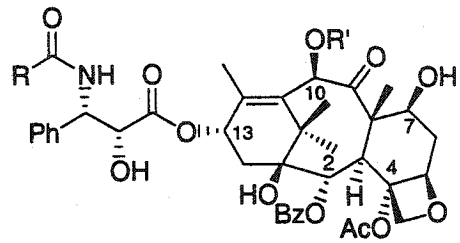
1.1. INTRODUCTION

Cancer is a serious, often deadly disease that affects many people every year. It has been estimated by the National Cancer Institute of Canada that of the 139,900 new cases of cancer reported in 2003, 48% will result in death (67,400).[1] Early diagnosis and treatment has greatly decreased the mortality rate. However, cancer still remains one of the leading causes of death in North America.

Breast cancer and prostate cancer are the most common cancers; lung cancer is the most frequent cause of death from cancer. An estimated 5,300 and 1,550 Canadian women will die as a result of breast and ovarian cancer respectively.[1] The chances for recovery are 80% for breast cancer and 39% for ovarian cancer. These percentages may appear to be increasing in favor of survival, but the probability of survival is still not 100% and the search for a cure will continue until this goal is met.

In 1962 the National Cancer Institute (NCI) conducted a large scale screening process for the discovery of anti-tumor compounds of natural origin. During this process extracts from the bark of *Taxus brevifolia*, the Pacific yew tree, were tested and found to be cytotoxic. This was the first step of many in the development of the drug Taxol®. It created great interest because of its activity on resistant types of cancer. Research towards the synthesis of Taxol® and its analogues (Figure 1) is currently being conducted in order to produce a more facile or efficient reaction pathway to its complex molecular structure.

It should be noted that Taxol® is the trade name specific to the Bristol Myers Squibb drug and paclitaxel is the trivial name of the active ingredient..



1a Taxol R = Ph, R' = Ac
1b Taxotere R = ^{t}BuO, R' = H
2 10-Deacetyl baccatin III, OH at C13, R' = H

Figure 1. The structure of Taxol®, Taxotere® and 10-deacetyl baccatin III.

1.2. HISTORY

In 1962, botanist Authur S. Barclay collected a sample of the Pacific yew tree for a government program aimed at discovering natural chemicals that might be of some use medicinally.[2] It is a slow-growing tree found in the rain forest of the Pacific Northwest United States.

Paclitaxel was found to have cytotoxic and antileukemic activity in 1963 and isolated for the first time in 1967. Wall and Wani in 1971 published its structure and biological activity.[3] The National Cancer Institute conducted a full-scale preclinical development of paclitaxel as an anticancer agent in 1977, when it was discovered that it had promising activity against breast cancer and melanoma. Fuchs and Johnson reported in 1978 that paclitaxel acted as an antimitotic agent and Horwitz reported in 1979 that it acted to promote the irreversible assembly of tubulin into microtubules. The mitotic process is dependent on the tubulin-microtubule equilibrium and at the time paclitaxel

was the only known compound to have this effect. Earlier other antimitotic agents, such as anticancer drugs vinblastine and vincristine, podophyllotoxin and colchicines, had been shown to act by preventing the assembly of tubulin into microtubules (spindle poisons).[4]

In 1981, paclitaxel began its Phase I Clinical Trials after the initial problems due to allergic reactions were solved. Phase II and III Clinical Trials were completed in the mid to late 1980s. In 1989 it was found that paclitaxel showed activity against ovarian cancer and in 1991 breast cancer.[3] These discoveries created great public interest in the drug because it had significant activity against solid tumours.

The Food and Drug Administration approved the use of Taxol® for treating ovarian cancer in 1992 and for breast cancer in 1994.[4] The use of Taxol® has increased in medicinal significance over the years. Today it is used for ovarian, breast, non-small-cell lung, small-cell lung, squamous (head and neck), and other various cancers. Its sales have made it one of the best-selling anticancer drugs in history, with over one billion dollars (US) in 1998.[4]

1.3. BIOLOGY

The discovery of paclitaxel was based on the antileukemic and cytotoxic activities of *T. brevifolia* extracts. Paclitaxel's mode of action is to promote the assembly of tubulin into microtubules. It binds to assembled microtubules without any cofactors and causes the microtubule to be stabilized against dissociation. The equilibrium that exists between microtubules and tubulin is disrupted as a result of the binding, which also causes a disruption in cell division and therefore leads to cell death by apoptosis.[5,6]

A second mechanism of paclitaxel has been revealed to cause apoptosis independently of mitotic arrest. This process involves the second paclitaxel -binding protein Bcl-2 that undergoes hyperphosphorylation in the company of paclitaxel. [7,8] Bcl-2 has an antiapoptotic effect that becomes inactivated *via* phosphorylation. The paclitaxel -promoted assembly of microtubules leads to the activation of Raf-1 and Bcl-2 phosphorylation and thus apoptosis.[9]

Paclitaxel acts mainly on cancerous cells, which divide more often than normal, healthy cells. Despite the advantages of paclitaxel, other cells in the body divide rapidly (blood cells, intestinal cells) and are therefore affected by paclitaxel, resulting in unwanted side effects. These effects may include nausea, baldness, a weakening of the immune system, and killing of nerve cells.

Another disadvantage of paclitaxel is it is only sparingly soluble in water, and thus a difficult drug to formulate for administration by the normal route of injection.[10] As a result, greater amounts are required for treatment, which brings about the limited supply predicament of paclitaxel. A solution to these problems would be to create a more water-soluble analogue that has better specificity and selectivity.

1.4. THE STRUCTURE OF PACLITAXEL

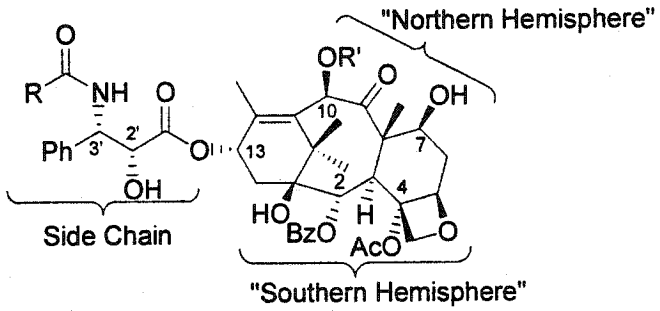
1.4.1. CHEMICAL/PHYSICAL PROPERTIES

Paclitaxel is an off-white crystalline powder, which has a tetracyclic ABCD core with a highly oxygenated pattern and an amino acid side chain. Its empirical formula is $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9 g/mol. The IUPAC name for paclitaxel is

5β, 20-epoxy-1,2α,4,7β,10β,13α-hexahydrotax-11-en-9-on-4,10-diacetate-2-benzoate-13-ester with (2R,3S)-*N*-benzoyl-3-phenylisoserine.

1.4.2. STRUCTURE ACTIVITY RELATIONSHIPS

The paclitaxel molecule can be divided into three areas: the northern hemisphere, southern hemisphere and side chain.



paclitaxel R = Ph, R' = Ac

Figure 2. The three basic regions of paclitaxel.

The "Northern hemisphere" of paclitaxel includes carbons 6 through 12, with oxygen functionalities at C7, C9, and C10. It is thought that this region is not directly involved in binding to microtubules because variation along the upper edge of the molecule does not significantly affect the activity of paclitaxel. The alcohol at C7 can be esterified, epimerized or even removed without any significant loss in activity.[11] It has also been found that little change in activity occurs when either the C9 carbonyl is reduced or the acetoxy group at C10 is removed.[12, 13]

The "Southern hemisphere" consists of C1 to C5 and C14, with oxygen functionalities at C1, C2, and C4, and oxetane ring at C4 and C5. Any structural change to this region of the molecule greatly affects activity. The removal of the benzoyloxy

group at C2 results in an inactive product. Analogues with substituted benzoyl groups have been synthesized and it has been found that *m*-substituted derivatives are more active than the *p*-substituted analogue.[14] It has been suggested that the reason for this difference is a result of the π-stacking interactions between the phenyl groups of the side chain and C2 benzoyl group.[15] A crucial part of the activity is its oxetane ring. Its removal or opening results in drastic reduction of action in tubulin-assembly and cytotoxicity assays.[12] The oxetane ring is relatively inert, since it is thought that it functions as a lock to maintain the conformation of the diterpenoid ring system and provide H-bonding.

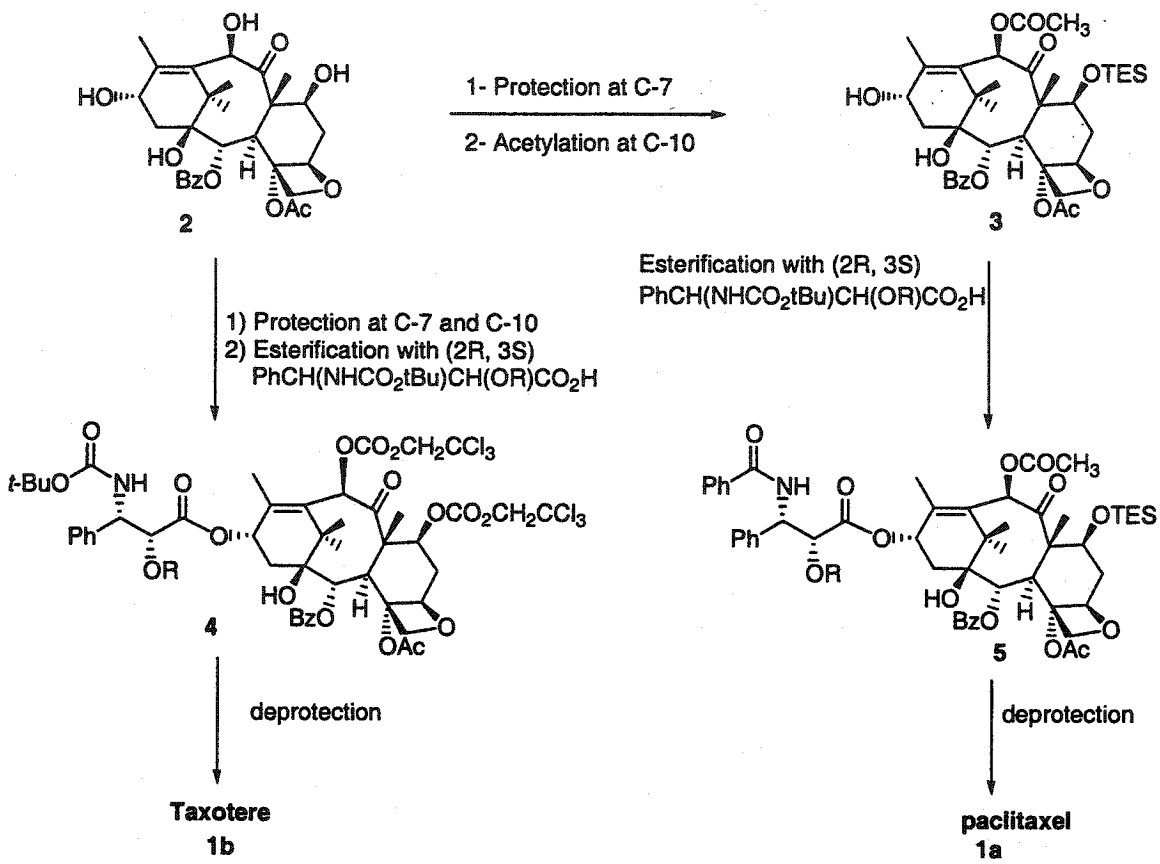
In the early eighties it was found that the side chain at C13 was absolutely necessary for activity. If the side chain was cleaved and Baccatin III formed, the activity was greatly decreased in both cytotoxicity and tubulin-assembly assays.[16] The hydroxyl substituents on C2' and the phenyl group on C3' have both been found to be required for the molecules activity.[17] Any substitution of the 3' phenyl group has led to decreased activity.[18] Aromatic or aliphatic groups such as amides or carbamates are tolerated on the nitrogen at C3'. An example of this is the Taxotere® analogue of Taxol®, which is about five times more active. It contains an *N*-*t*-butoxycarbonyl group instead of *N*-benzoyl group and has a hydroxyl group instead of an acetate group on C10.

1.5. SOURCES OF PACLITAXEL

The initial source of paclitaxel was from inner bark of the Pacific yew tree in yields of 0.014%.[10] From 2,500 yew trees about 25,000 lbs of dried bark can be obtained to produce 1 kg of product sufficient to treat only 500 patients. This caused an

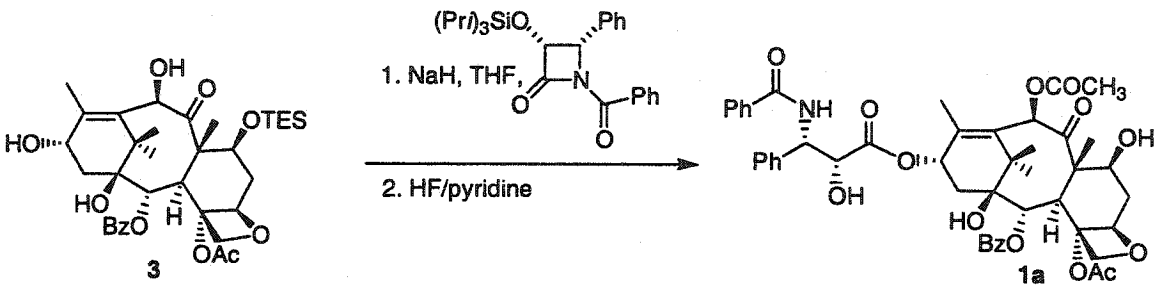
environmental and financial dilemma because the harvesting of the inner bark causes the death of the tree and its resources are limited.[19] Since this tree is rather uncommon, found mainly in old growth forests of the Pacific Northwest of the USA, it was known in the beginning that obtaining an adequate supply of the drug from its natural source would be an unrealistic task. Other potential options for increasing supply of pactilaxel include semisynthesis from other taxoids in the yew tree or related species *via* bioproduction through plant tissue culture, genetic engineering and fermentation procedures. [20]

A breakthrough to the supply problem of pactilaxel came from Potier *et al.* discovery that the needles of the English yew, *T. baccata*, contained precursors of paclitaxel,10-deacetylbaccatin III **2** and baccatin III.[21] A simple procedure was then developed to attach the side chain to the precusor and the first semisynthesis of pactilaxel was achieved and patented in 1986 (Scheme 1).[22] At the same time they discovered another active anticancer molecule called Taxotere® which could be synthesized in a similar manner as paclitaxel (Scheme 1).[23]



Scheme 1. Synthesis of paclitaxel and Taxotere® from 10-deacetylbaccatin III.

Potier's discovery in combination with Holton's synthesis of paclitaxel from a protected baccatin III using a β-lactam as the acylating agent (Scheme 2), allowed for the production of enough paclitaxel to meet the escalating demands. Sales rose from four hundred million dollars (US) in 1994 to an astonishing 1.6 billion dollars (US) in 2000.[24]



Scheme 2. Holton's synthesis of paclitaxel from baccatin III.

Other semisyntheses of paclitaxel and Taxotere® were developed from the renewable natural resource of the European yew tree needles (*Taxus baccata*).[25] This development made large-scale production of paclitaxel feasible through the extraction of its precursors from the yew needles. Until this anticancer drug has been produced *via* Holton's patented semisynthesis, which is licensed to Bristol-Myers Squibb (Taxol®) and Rhône-Poulenc Rorer (Taxotere®). The production of these drugs is both labour intensive and expensive, causing paclitaxel to be very expensive. Thus the next stage of progress is to have chemists develop simpler, better and less expensive analogues that are not dependent on a baccatin as a starting material.

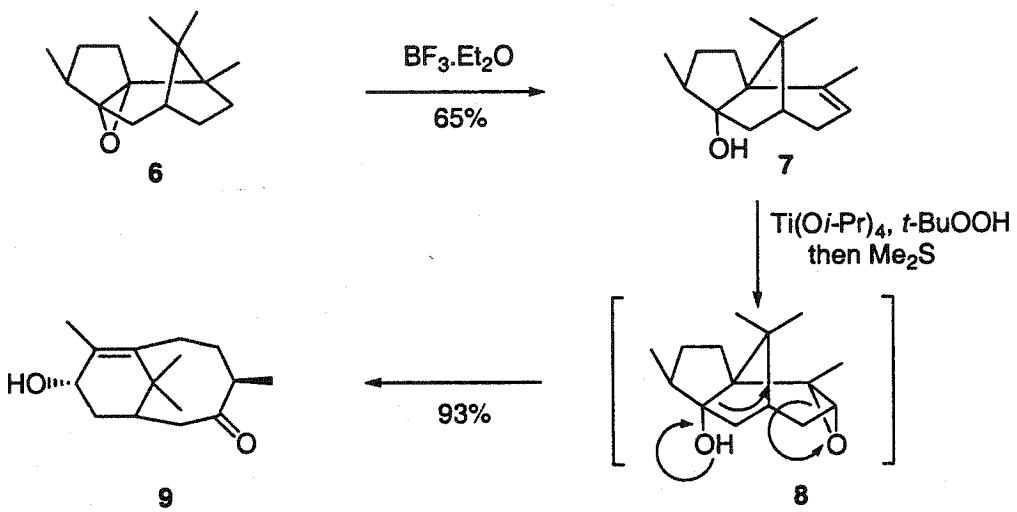
1.6. TOTAL SYNTHESIS OF PACLITAXEL

The total synthesis of paclitaxel has been a difficult endeavor for many synthetic chemists, due to its eleven chiral centers and complex ring system. A validation to its complexity is only six independent syntheses have been completed.[26] In each case the method is targeted at the synthesis of the tricyclic ABC taxane core, which is then coupled with the side chain in a similar fashion to the semisynthesis of paclitaxel and Taxotere®.

Since each synthesis is quite long, only the key construction concepts and a few intermediates are described in each. It is hoped that this will illustrate not only the complexity of each synthesis, but also the imagination required to generate such a complex molecule. A complete description of each synthesis is beyond the scope of this thesis.

1.6.1. HOLTON'S SYNTHESIS

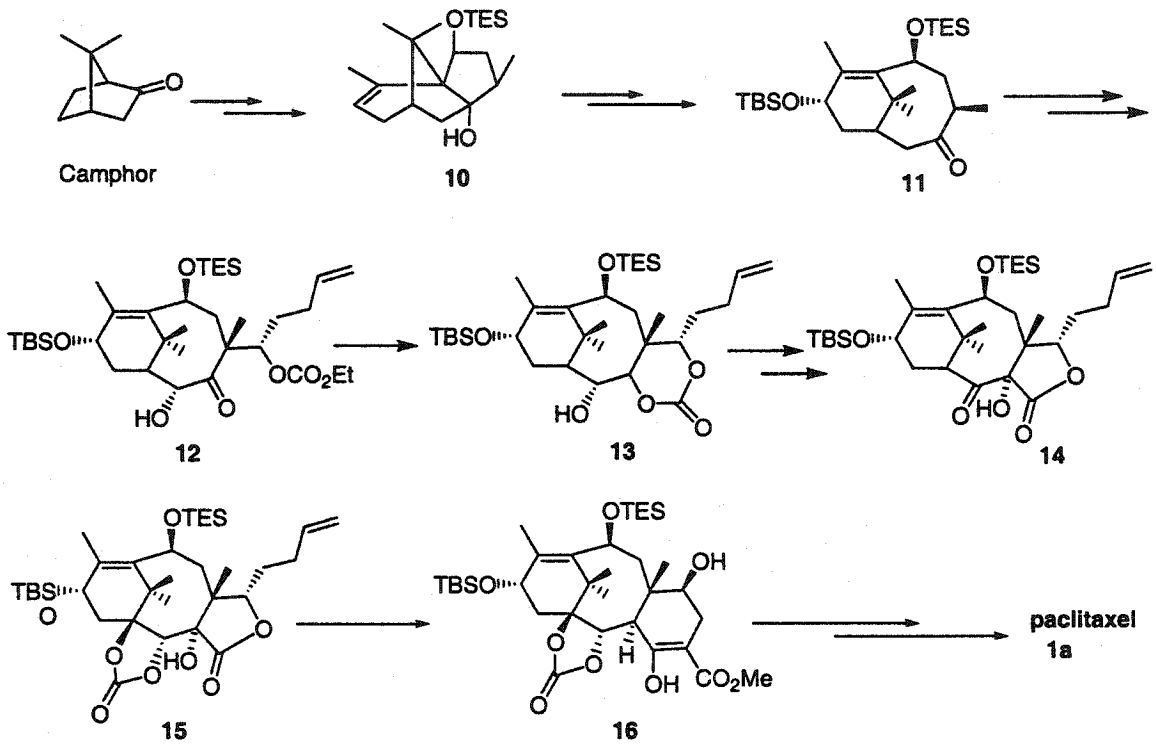
Holton's total synthesis began with the construction of the taxane core from camphor in combination with a previously developed epoxidation-fragmentation sequence (Scheme 3).[27,28] β-Patchoulene oxide **6** was converted into tertiary alcohol **7**, which underwent epoxidation **8** and ring opening to give the AB ring system **9**.



Scheme 3. Epoxidation fragmentation of β-patchoulene oxide.

The same epoxidation-fragmentation sequence allowed for intermediate **10** to be obtained from camphor. This was epoxidized and treated with Lewis acid to produce AB ring system **11** in 93% (Scheme 4). Ketone **11** underwent aldol condensation with 4-pentenal followed by protection of the resulting alcohol and hydroxylation at C-2 to produce hydroxycarbonate **12**. Reduction of **12** produced the cyclic carbonate **13**, which upon Swern oxidation at C-2 followed by treatment with LTMP resulted in ketone **14**. Manipulation of functional groups afforded lactone carbonate **15** in an overall 40% yield.[28]

Completion of the C ring was achieved by having lactone **15** undergo oxidative cleavage of the terminal olefin to produce the required ester. This allowed a Diekmann cyclization to take place yielding enol ester **16**. A series of deprotections and manipulations of functional groups in completed the synthesis of paclitaxel in 4-5% overall yield.

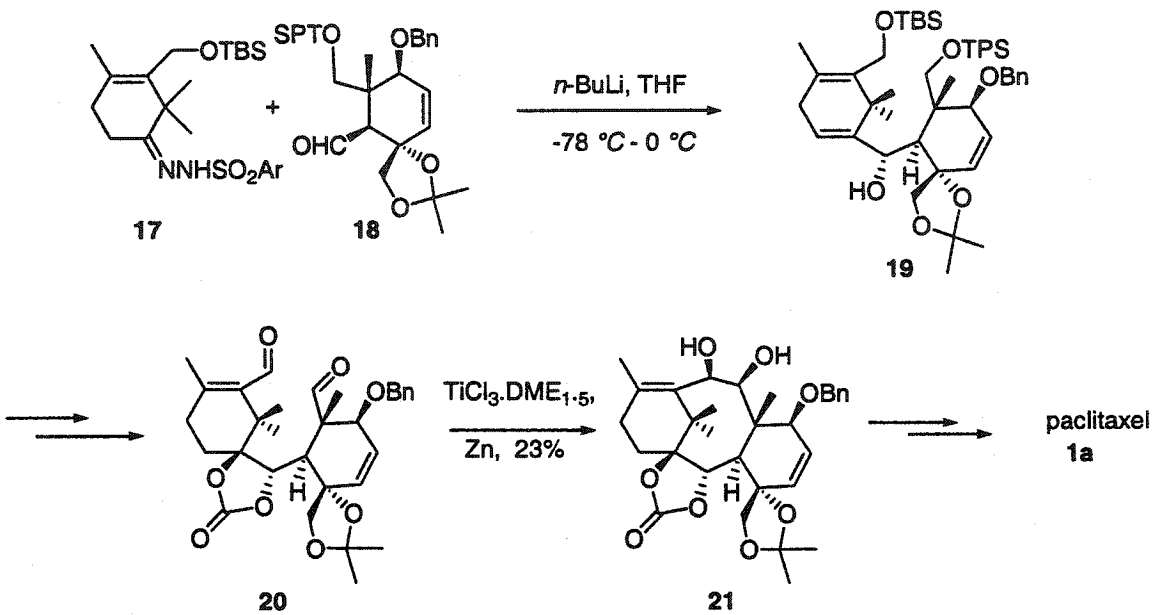


Scheme 4. Holton's synthesis of paclitaxel.

1.6.2. NICOLAOU'S SYNTHESIS

Nicolaou's synthesis has the advantage of making a wide range of taxoids, but the disadvantage of low yields. It consists of constructing the A ring **17** and B ring **18** of paclitaxel by Diels-Alder chemistry and coupling them together *via* a Shapiro reaction to form an AC ring system **19**. The ABC ring **20** was generated by a McMurry pinacol

coupling of **19**, leaving the attachment of the side chain and formation of the D ring for the final stages of the synthesis (Scheme 5).[29]

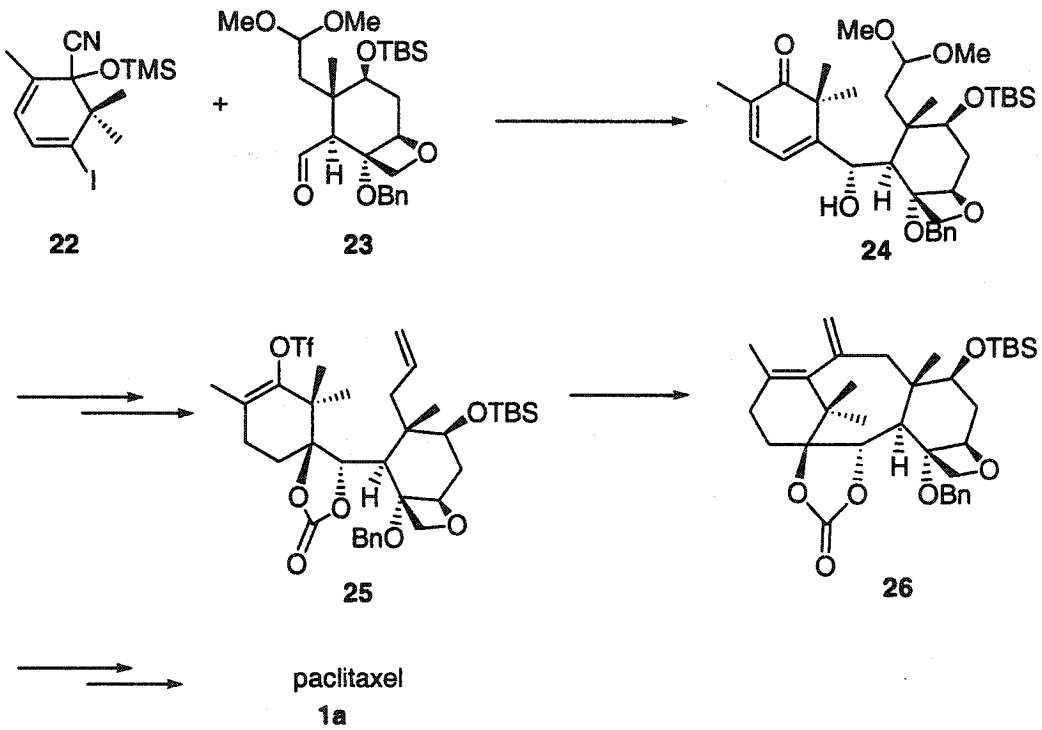


Scheme 5. Nicolaou's synthesis of paclitaxel. .

The Shapiro coupling reaction of sulphonylhydrazone **17** with aldehyde **18** produced allylic alcohol **19** as a single diastereomer. Epoxidation of the A ring followed by regioselective ring opening of the epoxide and treatment of the diol with excess KH and phosgene produced a cyclic carbonate intermediate. Deprotection of the tert-butylsilyl ether followed by oxidation produced dialdehyde **20**. A McMurry reaction permitted the closure of the B-ring and the expected vicinal diol **21** was one of the products formed and purified via chemical resolution. The enatiomerically pure, diol **21** was then used for the formation of the oxetane ring. Oxygenation of the A ring and addition of the side chain afforded paclitaxel.

1.6.3. DANISHEFSKY'S SYNTHESIS

Danishefsky's total synthesis starts with the synthesis of the D ring. The D ring was installed on the C ring to create the CD unit **23**, which was coupled to the A ring fragment **22** to give the ACD unit **24**. Cyclization *via* Heck coupling provided the 8-membered B ring and the tetracyclic ABCD structure (Scheme 6).[30]



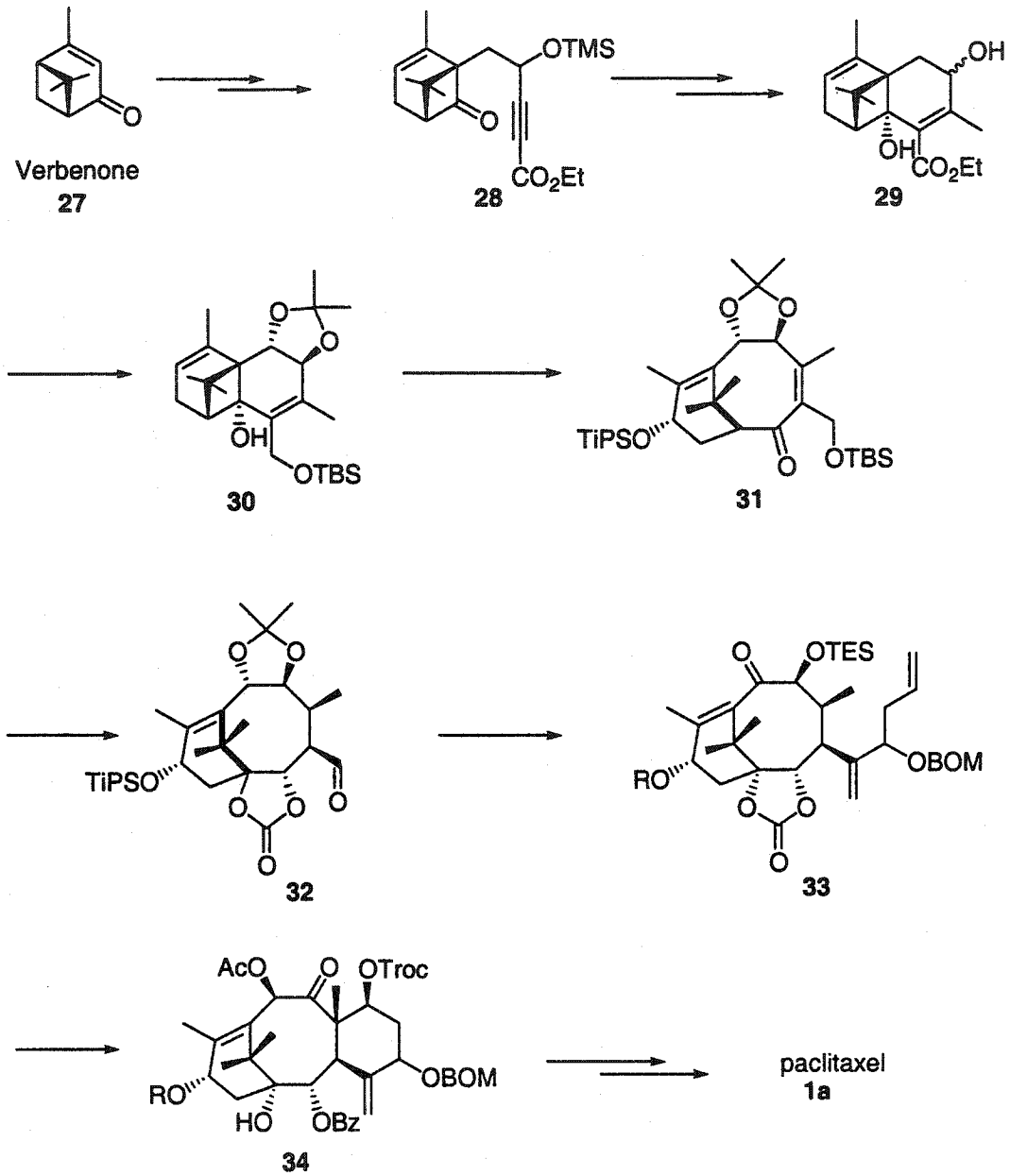
Scheme 6. Danishefsky's synthesis.

Iodine-lithium exchange on the iodocyclohexadiene **22** followed by coupling to the aldehyde unit of the CD unit **23** produced carbinol **24** as a single isomer. Enolization of the ketone **24** to give a vinyl triflate followed by hydrolysis and Wittig olefination of the aldehyde produced substrate **25**, which established a linker arm for the ACD ring system **24** to undergo an intramolecular Heck reaction to make the tetracyclic ABCD ring

system **26**. Further functionalization and attachment of the side chain ultimately gave paclitaxel.

1.6.4. WENDERS SYNTHESIS

Wender's synthesis begins with the natural product verbenone **27**, the air oxidation product of pinene.[31] Verbenone underwent photochemical rearrangement to produce **28** followed by epoxidation and fragmentation. This provided the taxane AB ring system **30**. Subsequent C2-C3 bond formation and fragmentation produced the AB ring system **32**. The addition of the C ring **34** was accomplished by the insertion of a lateral side chain to aldehyde **33** and through a series of deprotection, protection, oxidation and alkylation reactions. Oxidation of the terminal olefin on compound **33** and aldol cyclization gave a mixture of epimers at C7. The interconversion of the undesired epimer to the desired was accomplished by treatment with $NaHCO_3$ and MeOH and protection of the hydroxyl group produced **34** (Scheme 7). Introduction of the D ring and the side chain of paclitaxel completed the synthesis in 37 steps from verbenone.[32]

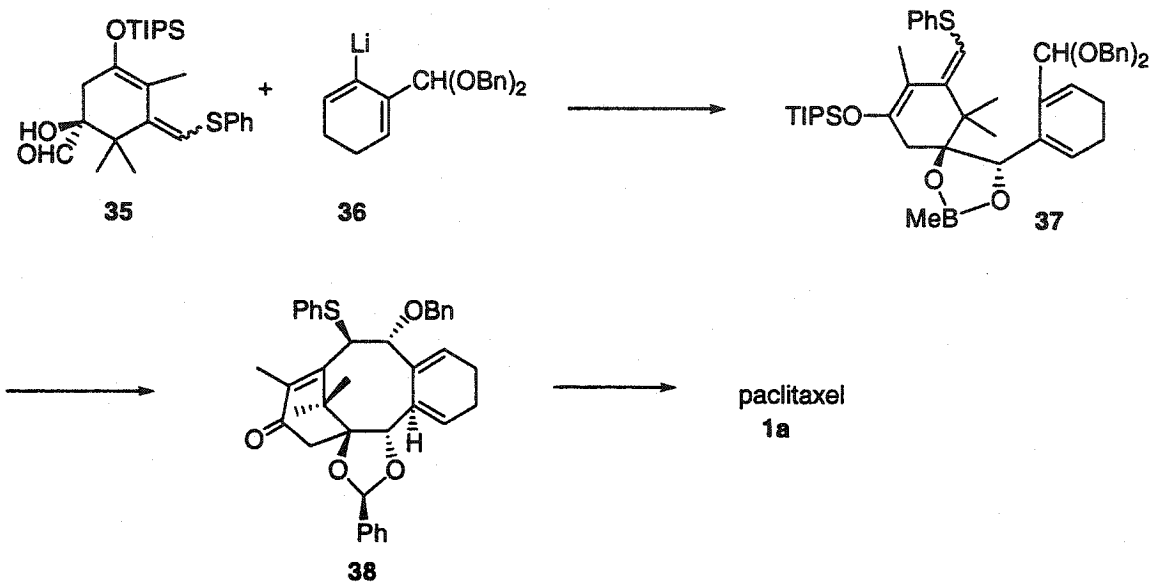


Scheme 7. Wender's synthesis.

1.6.5. KUWAJIMA'S SYNTHESIS

This synthesis features coupling of C ring precursor **36** to **35** to produce AC ring adduct **37**. This intermediate was cyclized in a similar manner to that found in the

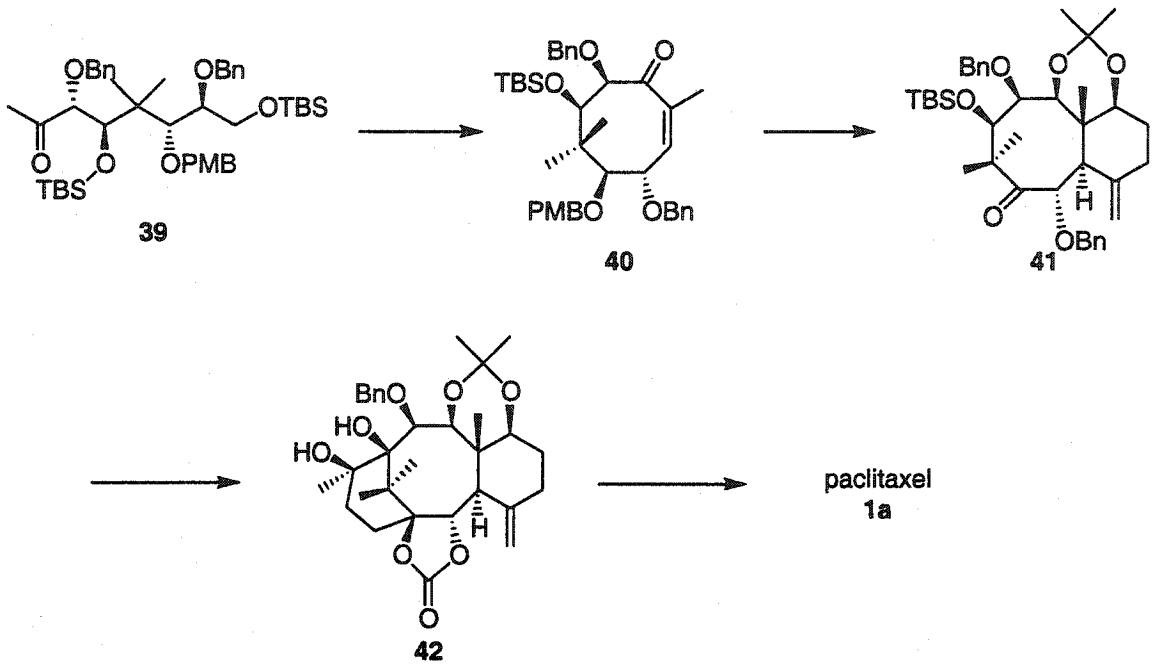
Danishefsky and Holton syntheses to form ABC ring system to provide **38** (Scheme 8).[33] Subsequent functionalizations led to paclitaxel in a total of 46 steps.



Scheme 8. Kuwajima synthesis.

1.6.6. MUKAIYAMA'S SYNTHESIS

This total synthesis differs from the previously discussed syntheses in that it begins with the formation of chiral B ring **40** from the optically active linear polyether **39**. Installation of the C ring involved successive Michael addition and intramolecular aldol reactions to produce **41**. Addition of the A ring component **42** was accomplished through stereoselective homolallylation and intramolecular pinacol coupling cyclization (Scheme 9).[34] The final product was obtained in 59 steps from???.



Scheme 9. Mukaiyama's synthesis.

Due to the large number of steps required for each of the above six syntheses to make paclitaxel, none are suitable for large industrial scale. Other approaches to paclitaxel have been published, but will not be discussed. Only studies using the intramolecular Diels-Alder strategies by the Fallis group to build the tricyclic system will be reviewed since it is closely related to our project studying the use the Diels-Alder reactions to build the AB ring core of paclitaxel.

1.7. DIELS-ALDER STRATEGIES IN THE TAXOID SYNTHESES

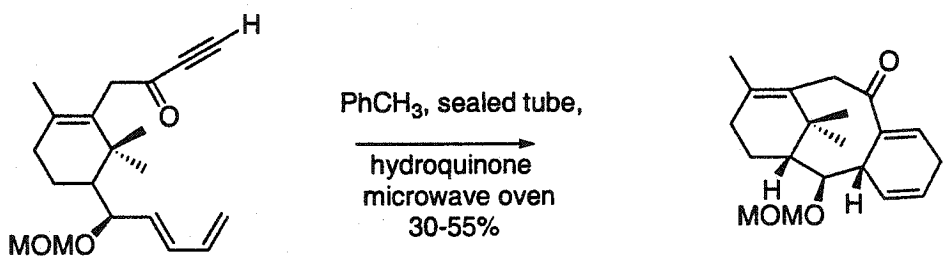
Several groups, including that of Nicolaou (see above), have investigated the synthesis of the taxane core using a Diels-Alder reaction, by developing the synthesis for both the A and C ring synthons. A discussion describing the efforts made by the Fallis

group to achieve the tricyclic taxane core using a Diels-Alder cycloaddition as a key step follows.

1.7.1. FALLIS' APPROACH

The Fallis group has synthesized the AB ring system and the ABC ring system using an intramolecular Diels-Alder reaction as the key step.

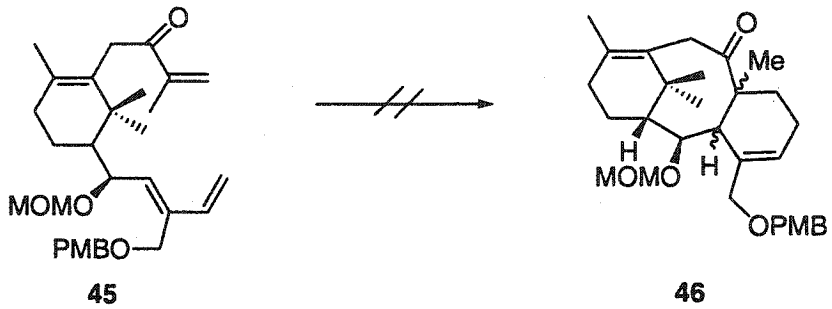
One pathway for the synthesis of the ABC ring system started with a functionalised A ring and achieved the BC ring system *via* a Diels-Alder cycloaddition (Scheme 10).[35]



43 **44**

Scheme 10. IMDA cycloaddition of A ring tethered compound **44**.

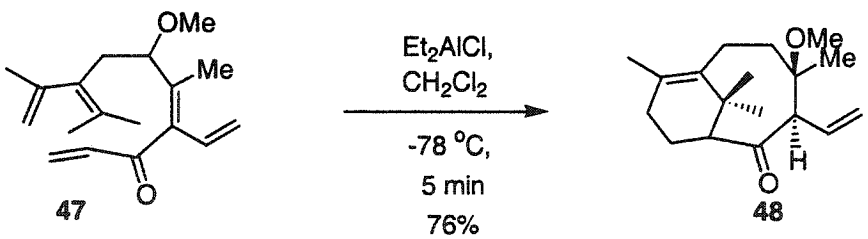
Cycloaddition of compound **43** proceeds in toluene with microwave activation. Unfortunately, this reaction gives compound **44**, not only in low yield, but also with the wrong relative stereochemistry at C1 and C3. Other examples showed that an additional substituent on the diene inhibits the reaction (Scheme 11).



Scheme 11. Influence of substituents on IMDA cycloaddition.

Further investigation showed that bulky protecting groups on the C2 alcohol and on the diene increase the steric hindrance in the transition state and the cycloaddition reaction failed to occur.

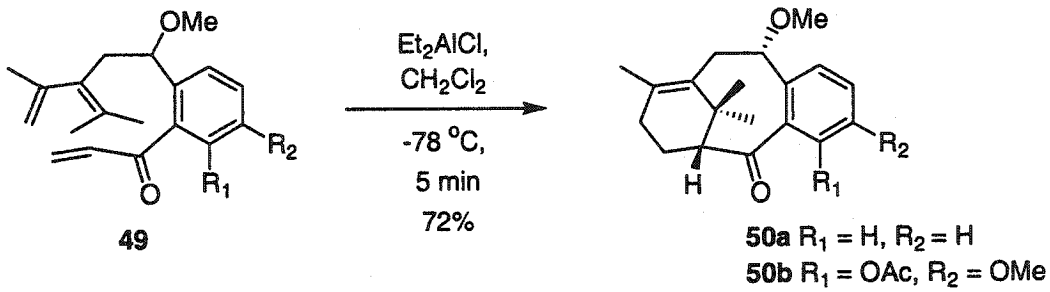
Synthesis of the AB ring system involved the construction of tetraene **47**, a precursor for the AB ring system. Cycloaddition of **47** *via* a Lewis acid catalyzed intramolecular Diels-Alder reaction produced AB building block **48** as a single diastereomer (Scheme 12). This intermediate contains enough functionality for the eventual attachment of the C ring by annulation, cycloaddition, or ring closing metathesis procedures.[36]



Scheme 12. IMDA cycloaddition to construct AB ring system **48**.

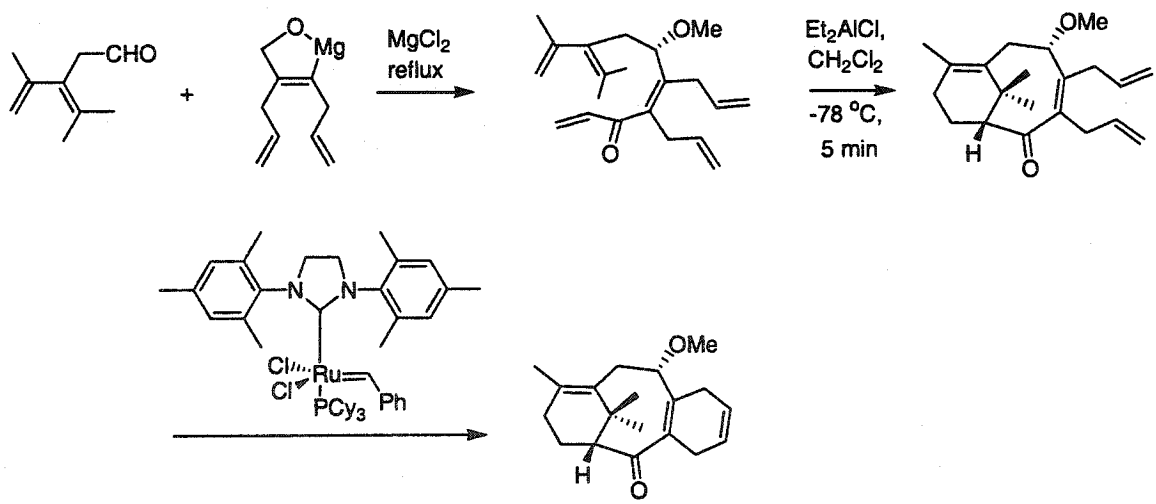
A second pathway used by the Fallis group to acess the tricyclo[9.3.1.0]pentadecane core of aromatic C ring taxanes involved the synthesis a functionalised C ring and the addition of the AB ring *via* an intramolecular Diels-Alder reaction.

Lewis acid catalyzed and chelation controlled IMDA cyclization of **49** afforded aromatic C ring taxane **50** as a single diastereomer (Scheme 13).[37]



Scheme 13. IMDA cycloaddition of functionalised C ring **49**.

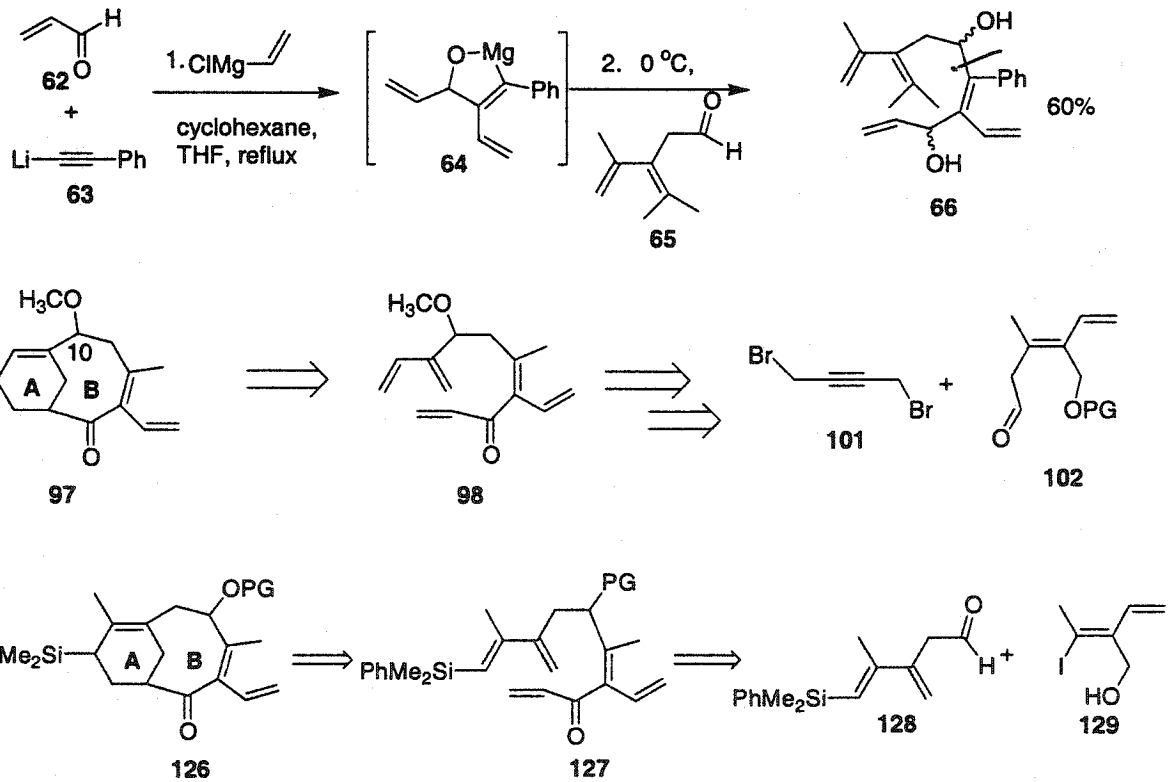
Another pathway to the ABC ring system employs sequential magnesium-mediated carbometallation of allyl-substituted propargyl alcohols followed by Lewis acid catalyzed intramolecular Diels-Alder reactions. The sequence finishes with a ring-closing metathesis to produce the ABC taxane core structure (Scheme 14).[38]



Scheme 14. Carbometallation, intramolecular Diels-Alder, and ring-closing metathesis.

1.8. RESEARCH OBJECTIVES

The initial aim of this thesis was to prepare nor-taxoids, which would be sterically less encumbered, potentially easier to synthesize, and perhaps have better properties for therapeutic application than Taxol®. It was anticipated that these studies would augment parallel investigations in our laboratory that were previously discussed in the Diels-Alder strategies. These research areas encompassed the development of magnesium-mediated carbometallation of propargyl alcohols and the development of intramolecular Diels-Alder reactions with a *cis* alkene in the tether to construct eight membered rings. This combination was expected to lead to rapid assembly of the AB taxane skeleton with appropriate functionality for further manipulation.



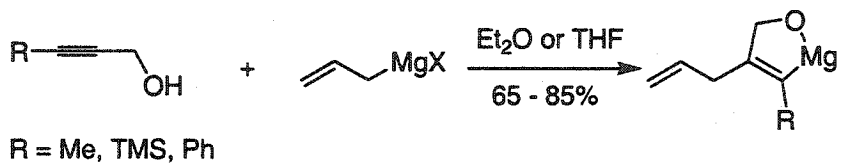
1.9. CARBOMETALLATION

1.9.1. INTRODUCTION

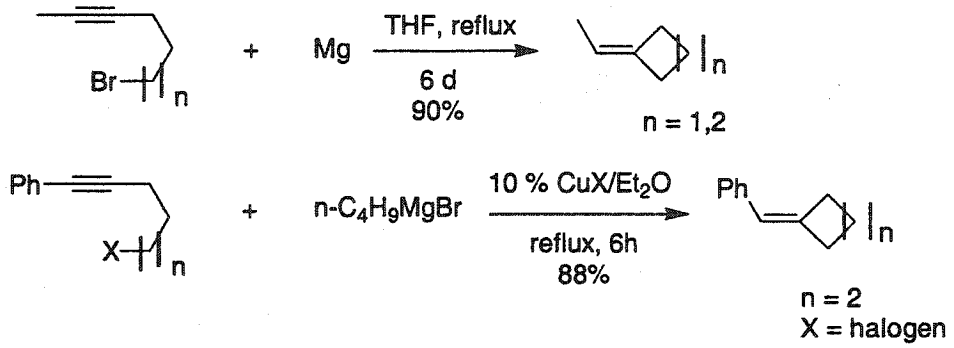
Bähr and Ziegler reported seventy-six years ago the first example of a carbometallation reaction.[39] Negishi defined carbometallation as carbon-metal additions across unsaturated carbon bonds in which result in both a carbon-carbon and a carbon-metal bond. The product thus obtained can be employed in further transformations.[40] The most common type of carbometallation reactions involves an alkyne or alkene acceptor containing an allylic or homallylic heteroatom. Oxygen is generally the most useful complexation substituent, in the form of an alcohol or ether.

1.9.2. MAGNESIUM REAGENTS

Organomagnesium compounds are versatile reagents for carbon - carbon bond forming reactions. Addition of these reagents to alkynes is usually enhanced when the alkyne contains functional groups (Scheme 15) or when the reaction is catalyzed with a transition metal (Scheme 16).[41]

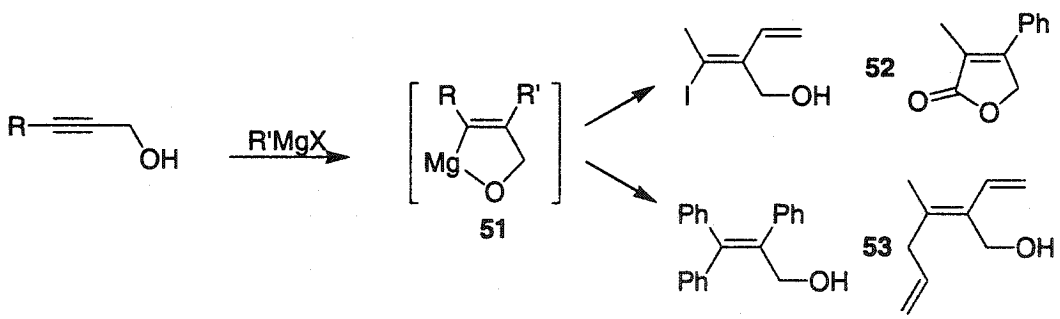


Scheme 15. Carbometallation of functionalized alkynes using magnesium.



Scheme 16. Carbometallation of non-functionalized alkynes with a metal catalyst.

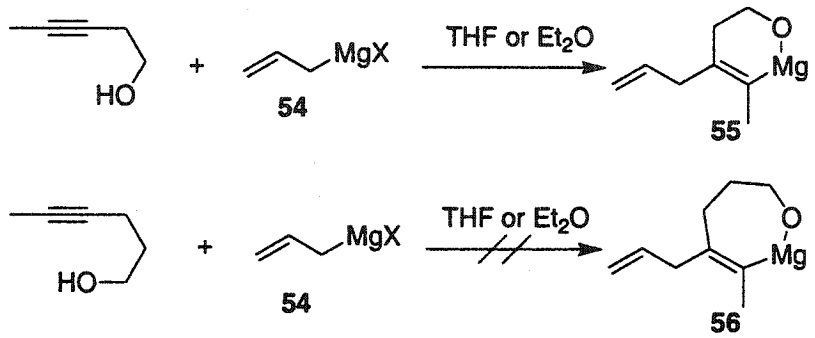
Fallis and coworkers have investigated the addition of various aryl and alkynyl vinyl Grignard reagents to propargyl alcohols.[42,43] The reaction is thought to involve a magnesium chelate intermediate **51**. Intermediate **51** is of great importance because it accounts for the total regio- and stereochemical control (Scheme 17). Compounds such as **52** and **53** are produced from the further reaction of **51** with different electrophiles.



Scheme 17. Magnesium mediated carbometallation of propargyl alcohols.

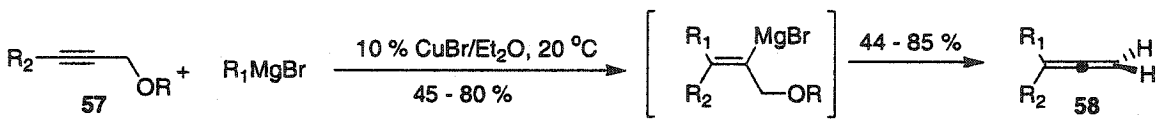
The geometrical alignment with the oxygen, which results in the 5-membered ring chelate **51** is most favourable. The drop in yield to 7% illustrates this when 5-hydroxy-2-pentyne chelates with **54** to form the six membered chelated intermediate **55**. The yield in the cabometalltion reaction drops further to zero when 6-hydroxy-2-hexyne is used;

indicating the seven membered chelated intermediate **56** is not formed (Scheme 18). Clearly the efficiency of chelation decreases as the heteroatom becomes further removed from the alkyne.



Scheme 18. Heteroatom proximity effect of carbometallation reactions with magnesium reagents.

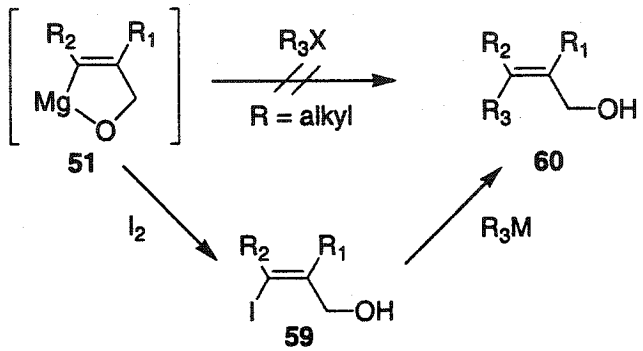
The heteroatom proximity effect of carbometallation reactions with magnesium reagents can be extended to other functionalities other than alcohols, but it adds with the opposite regiochemistry and then eliminates. Propargylic ethers **57**, for example, afford allenes **58** on reaction at high temperatures.[44] The same reaction occurs, but at lower temperatures, when 10% copper (I) bromide is used as shown in Scheme 19.[45]



Scheme 19. Carbometallation with magnesium route to allenes.

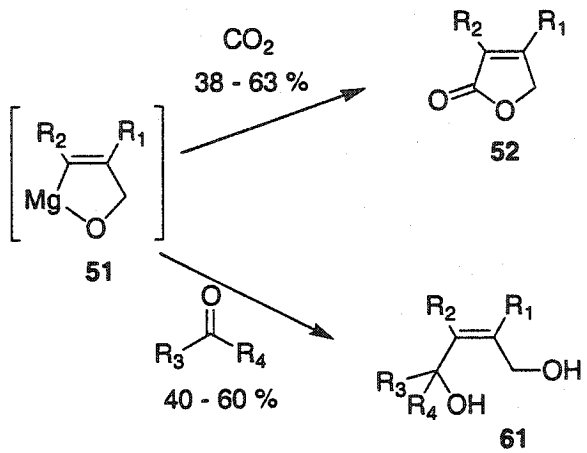
The intermediate for the magnesium mediated carbometallation reaction most likely exists as a cyclic structure **51**. When **51** is exposed to alkylating agents, no

reaction occurs with alkyl iodides, but allylic halides react to give the expected products in fair to good yields (31 - 71%).[46] An indirect route to alkylating cyclic structure **51** can be performed by iodination to **59** followed coupling reactions to afford products such as **60** (Scheme 20).



Scheme 20. Indirect route to cross-coupled products from carbometallation.

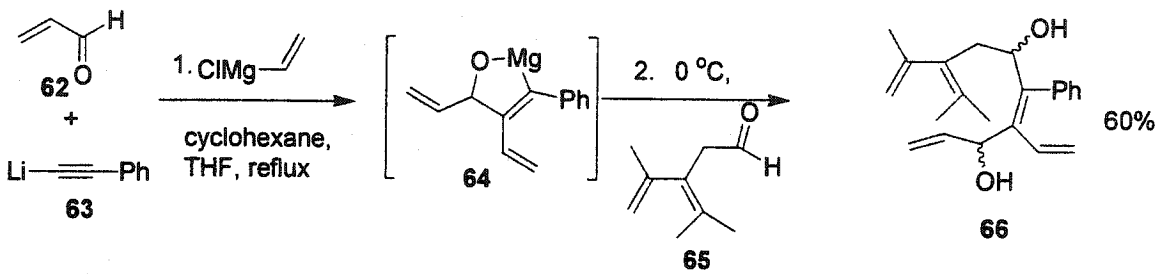
Butenolides **61** can be made directly by reacting the cyclic intermdiate **51** with carbon dioxide. Aldehydes and ketones also react with the cyclic intermediate **51** to form the corresponding diols **52**, as shown in Scheme 21.[47]



Scheme 21. Other electrophiles used to react with the magnesium chelate **51**.

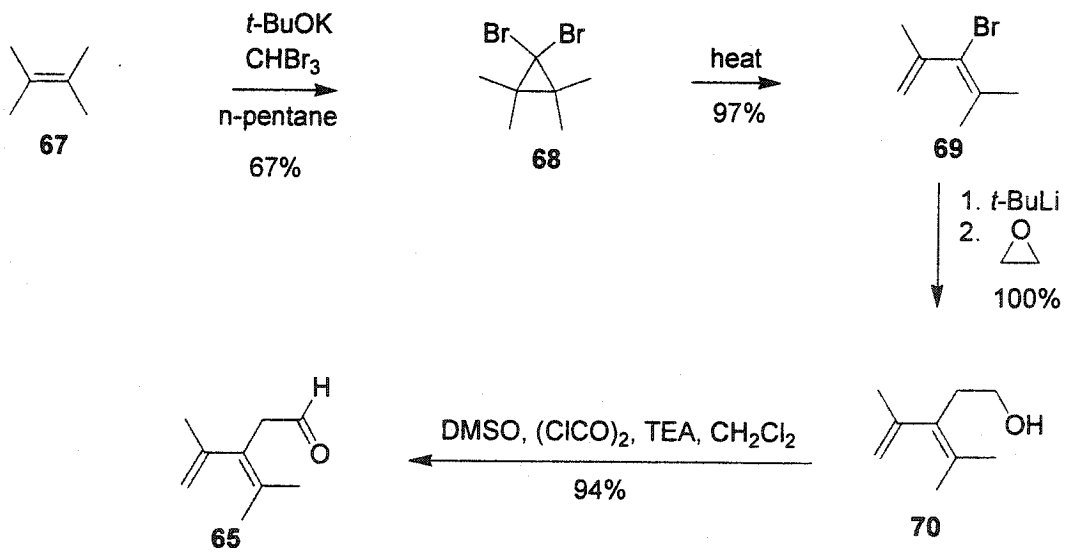
1.9.3. RESEARCH OBJECTIVE

A previously established pathway to the AB ring system for paclitaxel involved the coupling of aldehyde **65** to diene **64** to afford polyene **66** in a moderate 60% yield (Scheme 22).[48]



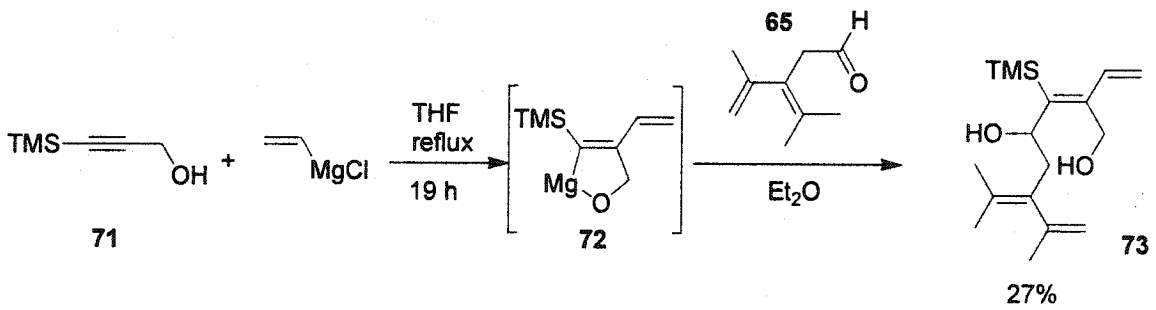
Scheme 22. Carbometallation route to **66**.

The synthesis of the aldehyde **65**, 3-isopropenyl-4-methylpent-3-enal, was a relatively good process yielding 61% of **65** over 4 steps (Scheme 23). The ease of replication and the variation of reaction scale permitted, made this reaction pathway quite reliable.

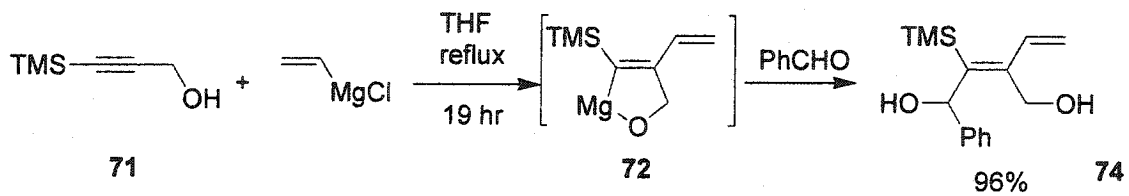


Scheme 23. Original pathway for 3-isopropenyl-4-methylpent-3-enal synthesis.

The low yield of the coupling reaction, shown in Scheme 24, was thought to stem from aldehyde **65**. This compound is rather unstable and had to be used relatively quickly to avoid decomposition. An example of the coupling reaction with two different aldehydes can be seen in Schemes 24 and 25. Scheme 24 illustrates the coupling of aldehyde **65** with **72** occurred in 27% yield, while the coupling of benzaldehyde with **72** proceeded in 96% yield (Scheme 25). This data implied that the low yield of this reaction may be due to the instability of the aldehyde used in the reaction. If it could be generated more easily and isolated more quickly from a precursor than the oxidation process used in Scheme 23 then the yield of the coupling reaction might be improved substantially.



Scheme 24. The coupling of aldehyde **65** with **72**.



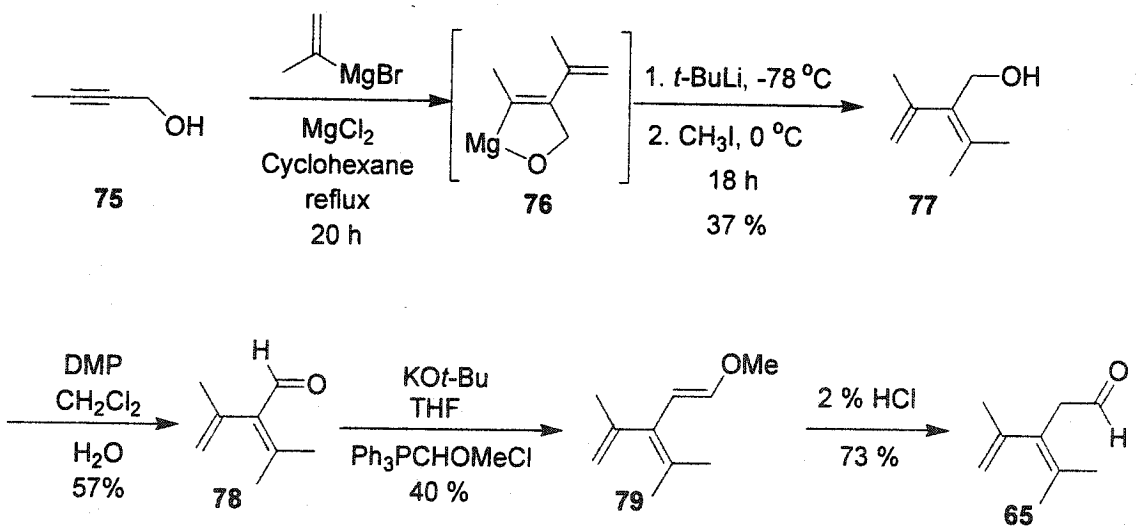
Scheme 25. The coupling of benzaldehyde with **72**.

A possible solution to this problem was to redesign the synthesis and select a stable surrogate for the unstable aldehyde **65** and generate the carbonyl when required. Consequently, compound **79** was selected as a stable precursor for **65**. The established method to synthesize aldehyde **65** involves oxidizing alcohol **77** *via* Swern oxidation followed by purification (column chromatography). The newly formed aldehyde **65** must be used immediately or decomposition will take place. If aldehyde **65** was stored in a –20 °C refrigerator overnight (12 h), about half of the purified material remains and a repeat of the purification procedure need to be done prior to use. Therefore, it would be advantageous to store aldehyde **65** as an enol ether, which upon treatment with dilute acid would form aldehyde **65** and only require only a quick flash column chromatography. In addition, this challenge provided an opportunity to simplify the synthesis and avoid having to heat the dibrompropane with a blowtorch. This could be achieved if a method could be found to alkylate the magnesium chelate **76** with methyl iodide.

1.9.4. RESULTS

An alternative method was investigated for generating aldehyde **65**, involving carbometallation chemistry followed by a Wittig reaction and storing it as an enol ether.

The first step involved reacting 2-butyn-1-ol (**75**) with isopropenyl magnesium bromide, magnesium chloride in cylcohexane for 20 h at reflux to form intermediate **76**. This intermediate **76** was then reacted with *t*-BuLi and methyl iodide to form alcohol **77** in 37 % yield. The allylic alcohol showed the three methyl peaks (1.62, 1.67, 1.73 ppm) and the two-diene protons (4.68 and 4.96 ppm) in the ^{1}H NMR. It is assumed that this reaction occurred *via* equilibrium between the lithium and magnesium salts, which the more reactive lithium anion reacted preferentially. The more reactive lithium salt may be present at equilibrium and it is this material that reacts with methyl iodide to give the desired allylic alcohol **77**.



Scheme 26. A new route to aldehyde **65**.

The Wittig reaction was employed to add an extra carbon onto alcohol **77**. To accomplish this alcohol **77** must be oxidized to aldehyde **78**. Many attempts were made to oxidize the alcohol without any success using only DMP and dichloromethane. The addition of one equivalent of water to the reaction mixture afforded aldehyde **78** in 57% yield.[49] Compound **78** showed the expected aldehyde peak at $\delta = 9.98$ ppm.

The Wittig reaction was attempted *via* two different methods. The first involved the utilization of LDA and triphenylmethoxymethylphosphonium chloride to make the methoxy substituted olefin. Despite many attempts, this reaction did not take place. The second method was successful. It involved the combination of potassium *t*-butoxide and triphenylmethoxymethylphosphonium chloride together with the aldehyde **78** to produce enol ether **79** in 40% yield. The ^{1}H NMR of enol ether **79** showed that both the *cis* and *trans* enol ethers were formed. The hydrogens α to the methoxy group were found at $\delta =$ 7.71 and 8.03 and the β hydrogens at $\delta =$ 7.17 and 7.96 respective to the *cis* and *trans* configurations.

Now that enol ether **79** had been synthesized, its conversion to aldehyde **65** would be necessary in order to validate the storage of **79** as the precursor to aldehyde **65**. Treatment of enol ether **79** with 2% hydrochloric acid resulted in aldehyde **65**, which was purified *via* column chromatography in 73% yield. The spectrum of this compound was identical to that prepared by Fallis and coworkers previously.[35]

This new route to the synthesis of **65** is lower yielding than the previously established pathway. However, it allows for the storage of **65** as enol ether **79** for at least 2 weeks. It allows for the option of conducting reactions in shorter time intervals.

Aldehyde **65** can be made from enol ether **79** in less than an hour and be used in further experimentation; the previous method would take at least 12 hours.

1.10. INDIUM MEDIATED CHEMISTRY

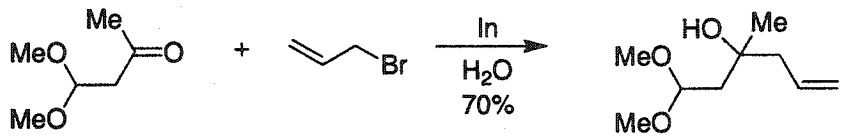
1.10.1. INTRODUCTION

In organic synthesis, transition metal organometallic reagents are of considerable importance. They have been used to supplement Grignard reagents or organolithium compounds, the most established organometallic reagents used in organic synthesis. These reagents have been extensively used to construct carbon-carbon bonds, leading to compounds of greater complexity.[50] A complication with organometallic chemistry is that it is sensitive to moisture and/or oxygen. Anhydrous organic solvents are required for these reactions and extensive protection-deprotection chemistry is often required for reactive hydroxy or acidic groups. Indium metal offers a solution to these problems. It can be used in water and avoids the requirement for the protection of hydroxy groups in the reacting molecule. Its use in carbon-carbon bond forming reactions does not affect acid labile groups.[50] The ability to carry out such reactions in aqueous solution avoids the use and waste of organic solvents. Thus this becomes environmentally more friendly, i.e. green chemistry.

1.10.2. REACTIONS INVOLVING INDIUM

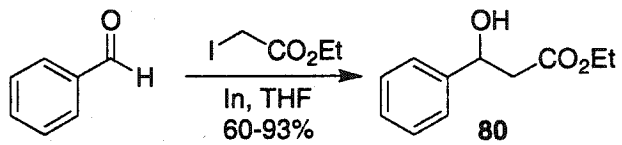
Indium is the metal of choice, along with zinc and tin, for mediating the coupling of allylic halides with carbonyl compounds in aqueous media (Scheme 27).[51] Aldehydes are more reactive under these conditions than ketones, a behaviour also observed with

zinc and tin.[52] Allylation takes place by an addition elimination reaction at the carbon β to the carbon bearing the halide.[51]



Scheme 27. Reaction of an allylic halide and carbonyl compound with indium in aqueous media.[50]

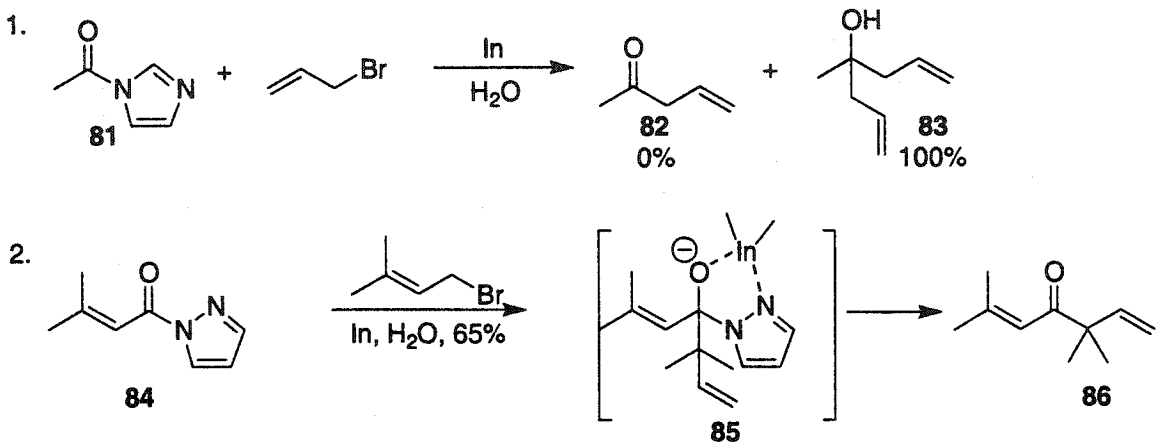
A reaction similar to the Reformansky reaction can be conducted using indium instead of zinc to form secondary and tertiary alcohols. Treatment of ethyl iodoacetate with indium powder in the presence of benzaldehyde produces ester **80** in 60-93% yield (scheme 28).[53]



Scheme 28. Formation of ester **80** through the reaction of an aldehyde with an α-haloester in the presence of indium.

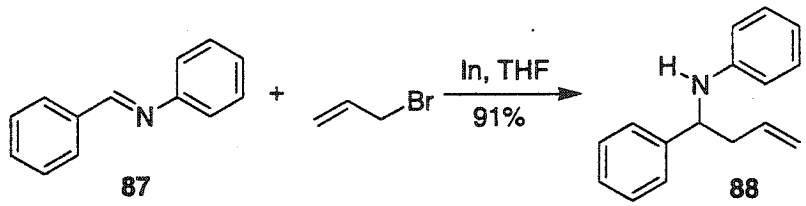
Indium has been mainly used to mediate the allylation of a variety of aldehydes and ketones, but in 1997 Chan and co-workers expanded its use to acyl-imidazoles or pyrazoles.[54] Acyl-imidazole **81** when reacted with allyl bromide in the presence of indium was expected to give both allylic ketone **82** and tertiary alcohol **83** (Equation 1., Scheme 29). Tertiary alcohol **83** was obtained in quantitative yield through the double addition to the allylic ketone. The ketone **86** was the major product, however, when acyl-

pyrazole **84** was used (Equation 2, Scheme 29).[54] It was proposed that the initial intermediate **85** was stabilized by chelation to the second nitrogen in the pyrazole ring. Ketone **85** is much more hindered than **82** and steric hinderance may be the reason for not getting a double addition. Eventual hydrolysis of **85** leads to **86**.



Scheme 29. Formation of tertiary alcohol **83** and ketone **86**.

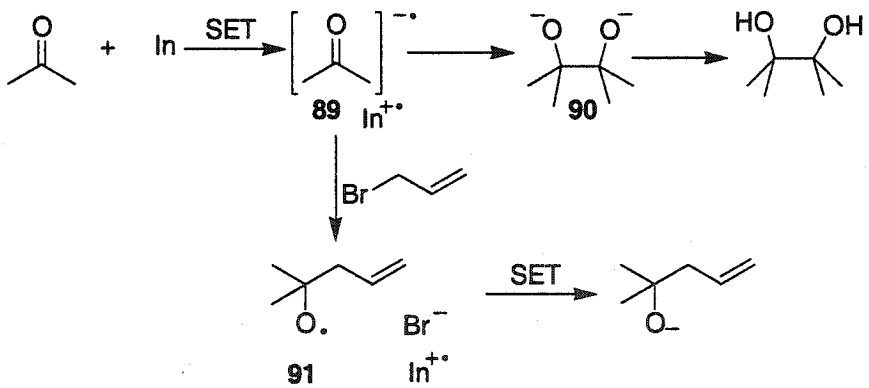
Homoallylic amines are prepared by the addition of allylic organometallics to azomethines and nitriles. This synthetic method has suffered from low yields. However, varying the metal in allylmetallics and selecting magnesium over lithium, zinc, aluminum, boron and tin have improved these yields.[55] Finally the use of indium afforded homoallylic amines in good yields. In Scheme 30, aldimine **87** was allylated in the presence of indium to give the secondary homoallylic amine **88** in 91% yield. Depending on the substituents on nitrogen yields varied from 13% to 91% for this reaction. Low yields occurred when an sp^3 carbon was linked to the nitrogen and high yields were obtained when an sp^2 carbon was linked to the nitrogen in **87**.[56]



Scheme 30. Formation of homoallylic amines.

1.10.3. MECHANISM OF INDIUM MEDIATED ALLYLATION

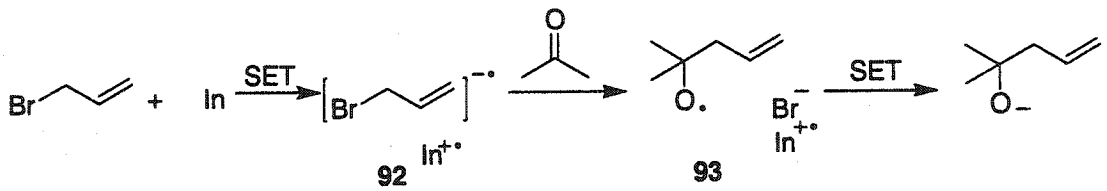
The nature of the mechanism and reactive species involved in the allylation of indium has been investigated. The first possible mechanism involves the single electron transfer (SET) process (Scheme 31). Indium metal reacts with the carbonyl species to form radical anion **89**. This radical may couple with allyl bromide to give the alkoxy radical **91** or couple with itself to form pinacol **90** as a side product. The alkoxy radicial **91** can undergo a second SET to produce the alkoxy anion, which is quenched by water.



Scheme 31. Mechanism of the allylation of a carbonyl species using indium.

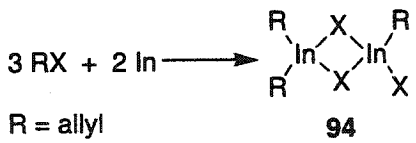
Another possible mechanism is illustrated in Scheme 32. It involves the allylic bromide reacting with indium in a SET process to give radical anion **92**, which reacts

with a carbonyl compound to produce the alkoxy radical **93**. A second SET, followed by protonation of the anion would give the product.[50]



Scheme 32. A second allylation mechanism mediated by indium.

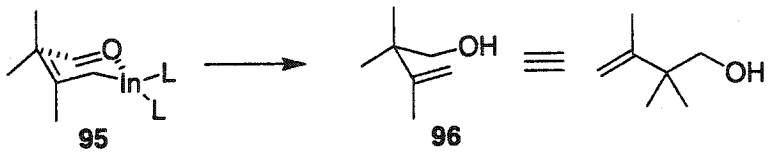
Different complexes of indium have been suggested as the reactive species. It has been suggested that R_2InX and $RInX_2$ are the reactive species. Sesquihalide species **94** has also been proposed by Butsugan and co-workers to be the active species. The allylic indium sesquihalide **94** agrees with results obtained by Gyanane and Worrall (Scheme 33).[57]



Scheme 33. Possible active species for indium mediated allylation.

The allylation transition state for indium mediated allylations has been proposed by Paquette (Scheme 34). It assumes that the indium center is tetravalent based on structure **94**. The transition state of **95** allows a visual depiction of why the allylation occurs β to the carbon attached to indium. **96** and the diastereoselectivities observed.

Even though structure **94** and transition state **95** have been proposed, no evidence can fully support either of these formulas.[58]

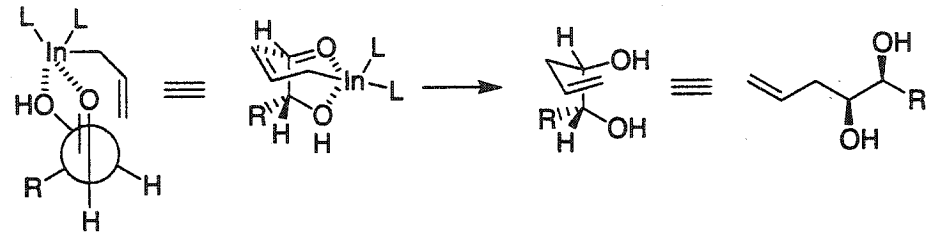


95 **96**

Scheme 34. The proposed transition state for indium mediated allylation and the product that results.

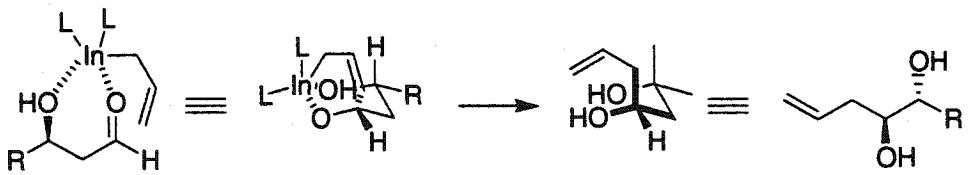
1.10.4. STEREOCHEMICAL CONSIDERATIONS

Organometallic reagents are used under anhydrous conditions due to moisture sensitivity. The Cram and Felkin-Anh models have been proposed for rationalization of the direction of attack of the nucleophile on a carbonyl compound. These two models have not been applied to the metal indium because its reactions are often conducted under aqueous conditions. The isomer formed by attacking a carbonyl compound depends on the π-facial selectivity of the indium attack. Addition of allylindium reagents to α- and β-hydroxy aldehydes in water have been found to be highly stereoselective and as a result synthetically useful. α-Chelation of both the carbonyl and hydroxy group occurs on the less sterically hindered *re* face of the aldehyde (Scheme 35). A stereochemical bias (10.2:1) in favour of the *syn* diastereomer resulted.[59]



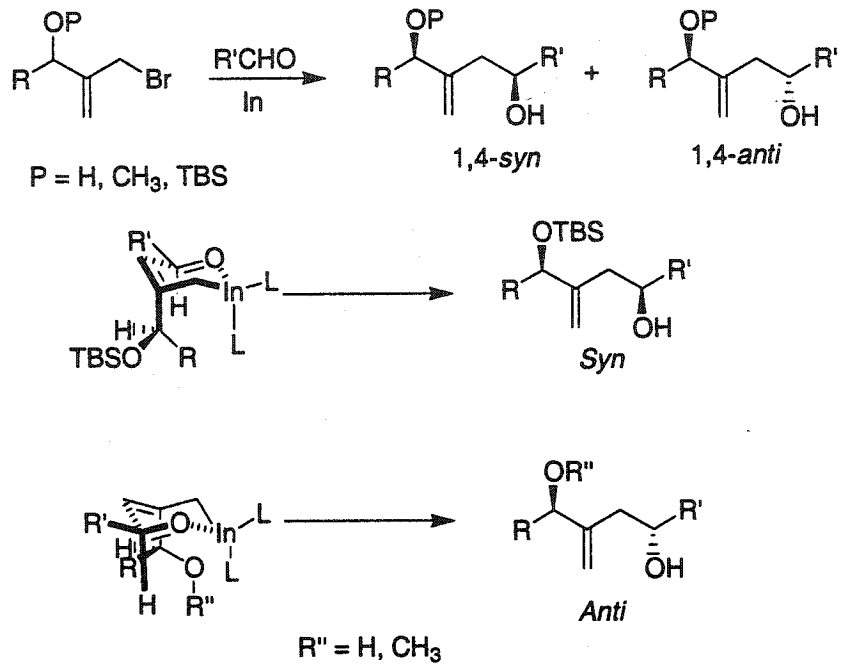
Scheme 35. α-Hydroxy-aldehyde is *syn* allylated by indium.

β-Chelation seems to follow the same influences as that of α-chelation, except that the anti stereoisomer is favoured (Scheme 36).



Scheme 36. β-Hydroxy-aldehyde in anti allylated by indium.[58]

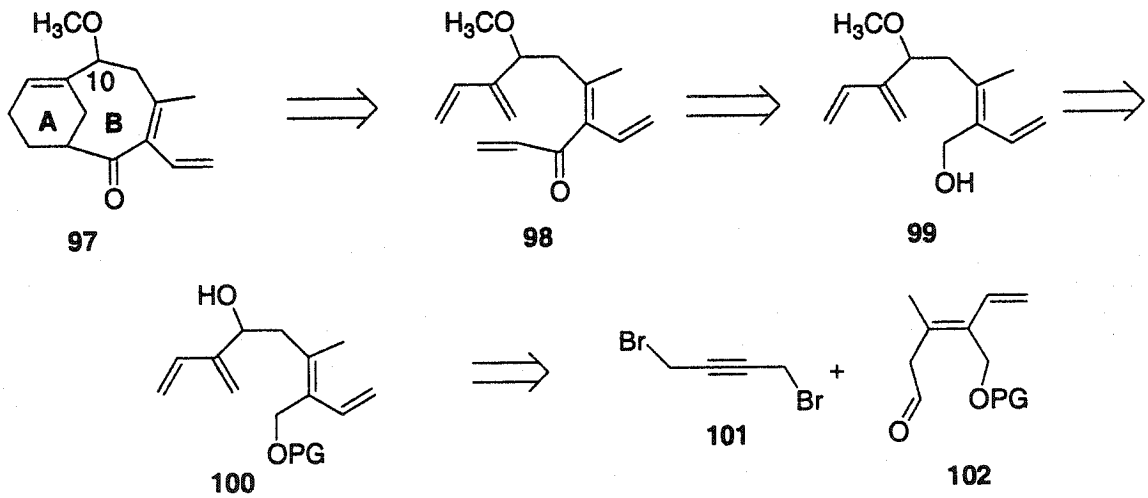
If a β-hydroxyallyl bromide reacts with an aldehyde, the hydroxyl group reacts differently compared to its ether. A TBS protected hydroxyl group will result in a syn stereoisomer. If the hydroxyl group is free or an ether, then chelation with the oxygen will give a more rigid transition state and result in anti stereoisomers (Scheme 37).[59]



Scheme 37. The allylation transition state models of hydroxy-bromides.

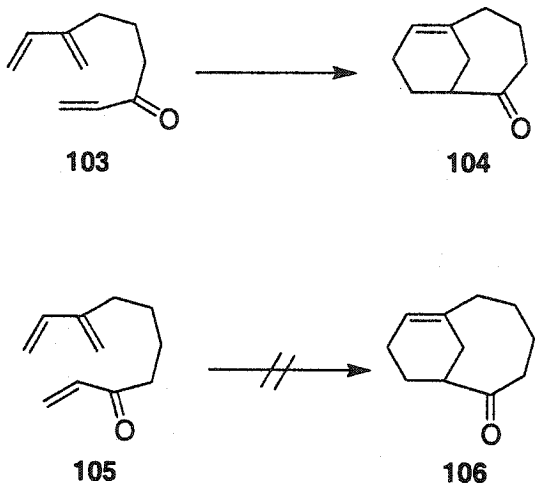
1.10.5. RESEARCH OBJECTIVE

In principle the AB nor-taxoid ring system **97** can be obtained *via* an intramolecular Diels-Alder reaction of **98**. Essentially all of the carbon skeleton of **98** can be envisaged as arising from 1,4-dibromo-2-butyne **101** and aldehyde **102** *via* Chan's indium chemistry.[60] The use of indium chemistry would enable the insertion of a mono-substituted diene to make compound **100**. After deprotection and reprotection, **99** can be formed from **100**, which can be oxidized and treated with vinyl Grignard to form **98**. Compound **98** can undergo intramolecular Diels-Alder reaction to form nortaxoid **97** (Scheme 38).



Scheme 38. Retrosynthetic analysis of nor-taxoid **97** using indium chemistry.

Chan has previously conducted similar experiments.[60] He has successfully constructed the 6-membered A ring and a 7-membered B ring **104**, but failed to make an 8-membered ring **106** because the transition state required for its formation cannot be achieved without a *cis* alkene.



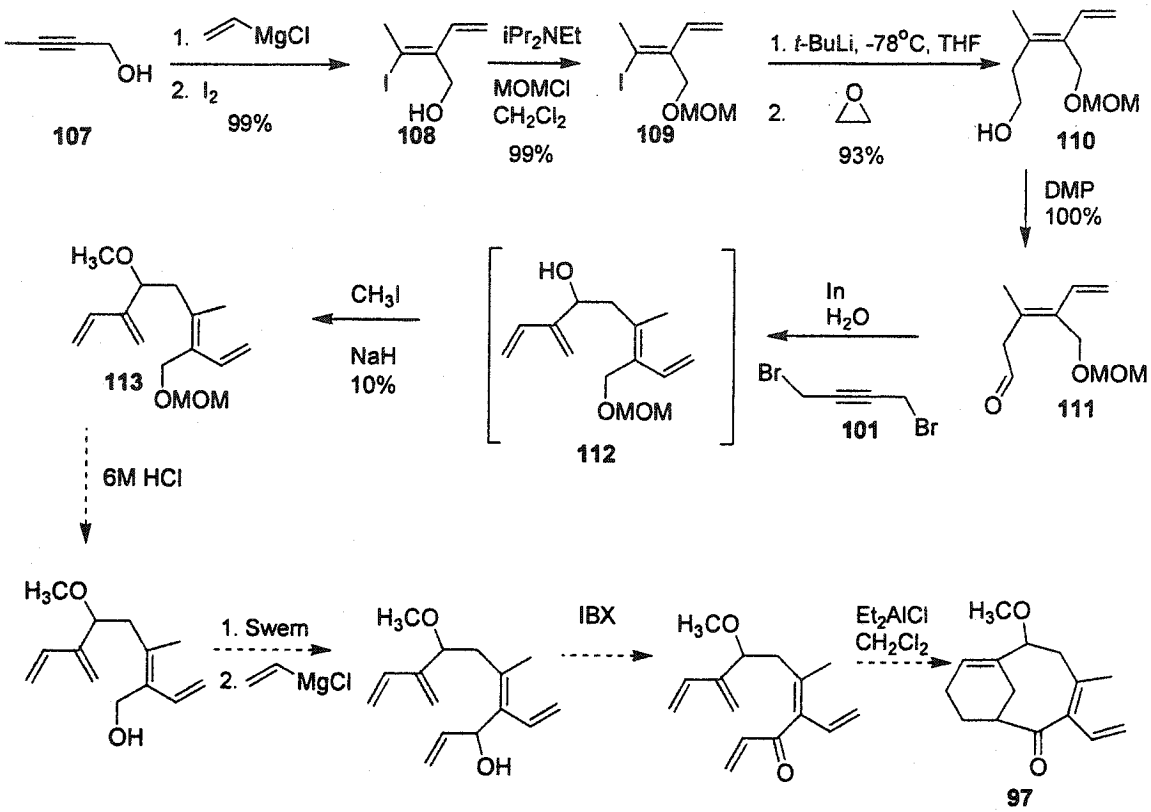
103 104

105 106

Scheme 39. Intramolecular Diels-Alder reaction of Chan's compounds **103** and **105**.

1.10.6. RESULTS

The synthesis of the precursor for the intramolecular Diels-Alder reaction began with commercially available 2-butyn-1-ol (**107**) (Scheme 40). It underwent carbometallation with vinyl magnesium chloride Grignard and was quenched with iodine to give **108** in 99% yield. Protection of **108** with MOMCl using diisopropylethylamine as the base gave a quantitative yield of **109**.[61] Attachment of a side chain *via* the removal of iodine with *t*-butyllithium and the insertion of ethylene oxide, required extensive experimentation. Considerable experimentation resulted in a 93% yield of **110** by controlled addition of ethylene oxide (liquid, 10 equiv.) to the vinyl anion generated from treatment of **109** *t*-butyllithium. Compound **110** showed the expected three proton peaks of the vinyl group in the ^{1}H NMR (5.09, 5.30, 6.70 ppm) along with the two-methyl groups (1.90 ppm and 3.37 ppm for MOM).



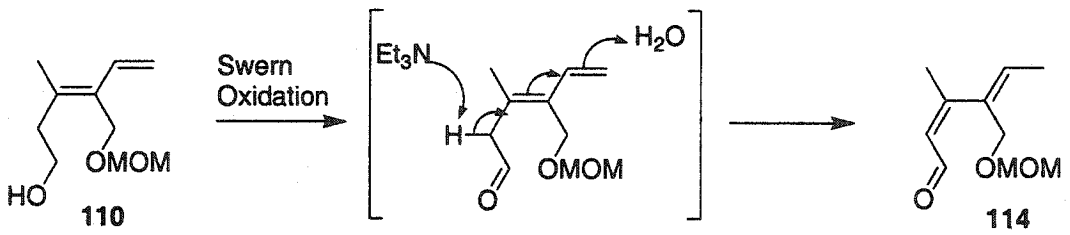
Scheme 40. The synthetic route to nor-taxoid **97**.

Oxidation of alcohol **110** also was found to be technically difficult. Various oxidizing agents were investigated for the oxidation of alcohol **110.** Only Dess-Martin periodinane afforded acceptable results (Table 1).

Entry	Conditions	Results
A	TPAP, NMO, 4 Å sieves, CH_2Cl_2, 21 °C	Starting Material
B[62]	IBX, DMSO, 21 °C	10%
C	Dess-Martin Periodinane, CH_2Cl_2, 21 °C	100% Crude
D[63]	PCC, Celite, CH_2Cl_2, 0 - 21 °C	Decomposition
E[64]	PDC, 4 Å sieves	Starting Material
F	Trichloroisocyanuric acid, TEMPO, CH_2Cl_2, 21 °C	Decomposition
G[65]	DMSO, Oxaylyl chloride, Triethylamine, CH_2Cl_2 -78 - 0 °C	Rearrangement

Table 1. Oxidation reactions attempted on alcohol **110**.

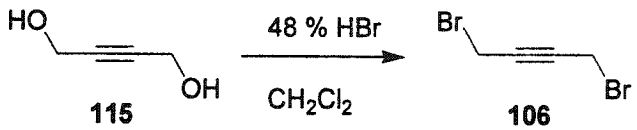
Both TPAP and PDC oxidants resulted in the recovery of starting materials, while entry D and F caused decomposition of the alcohol. Entry B, the IBX oxidation of alcohol **110**, provided the desired aldehyde **111**, in 10% yield. The Dess-Martin periodinane, entry C was tried next in the hopes of increasing the yield. The crude ^1H NMR suggested that 100% conversion of the alcohol to the aldehyde had occurred with two methyl singlets at δ = 1.63 and 3.19 ppm and an aldehyde peak at δ = 9.25 ppm. Upon purification the yield dropped drastically for both B and C, so the crude material was used directly. Entry G, the Swern oxidation, resulted in the conjugated aldehyde **114** (Scheme 41). This feature was easily established from the ^1H NMR spectrum in which three methyl singlets were found at δ = 1.91, 3.37, and 4.61 ppm and an aldehyde peak at δ = 10.12 ppm. It was likely the rearrangement of the aldehyde to the more stable conjugated aldehyde was due to the triethylamine used during the Swern oxidation reaction. Triethylamine acts as a base that removes the α-proton of the aldehyde to make the more thermodynamically favourable conjugated aldehyde **114**.



Scheme 41. Oxidation of alcohol **110** *via* Swern oxidation conditions.

Before any indium chemistry could be performed a precursor **101**, (1,4-dibromo-2-butyne), had to be synthesized. The starting material 2-butyne-1,4-diol (**115**) was

treated with tribromophosphine in benzene at 0 °C.[66] A thick, black sludge was formed and upon ^{1}H NMR analysis it was determined that neither the dibromide nor the diol were present. An alternative method for the synthesis of **101** was tried. It involved dissolving **115** in dichloromethane and adding 48% hydrobromic acid (Scheme 42). ^{1}H NMR analysis, determined that dibromide **101** was present and the reaction had gone to completion.



Scheme 42. The synthesis of dibromide **101**.

The isolation of **101** proved to be very challenging. Various purification procedures are listed in Table 2. It should be noted that the dibromide **101** was extracted with dichloromethane, unless stated in Table 2.

Entry	Purification	Results
1	Extraction with Et_2O, Distillation	Mix
2	Fraction Column Distillation	Mix
3	Changed solvent to Ether (1 and 2)	Mix
4	Nitrogen Bubbler	35%
5	Nitrogen Flow	8.03% (2:1; product / ether)
6	Rotoevaporator	0

Table 2. Purification procedures attempted for 1,4-dibromo-2-butyne **101**.

Difficulties were encountered upon removal of the solvent. If the solvent was simply removed with a rotoevaporator, both product and solvent were lost. Both column

chromatography and fractional distillation resulted in a mixture of the product along with starting material. The use of ether in the place of dichloromethane provided no improvement. The solvent could be removed in a nitrogen stream (2h) but the yield was reduced. Bubbling nitrogen through the solution and *via* a syringe needle exit provided the purified product **101** in 35% yield.

The synthesis of olefin **113** could now be attempted using indium chemistry, since both precursors had been prepared. This key step in the reaction pathway involved placing the aldehyde and the dibromide **101** in water, DMF or DMSO. Indium powder was added in one portion while stirring vigorously. After 12 hours, ether was added to the reaction, followed by work up. This reaction procedure was attempted on both benzaldehyde and aldehyde **111** without any success. Various equivalents of dibromide **101** were tried (1.5 to 5) in the attempt to start the reaction, however, the ^{1}H NMR spectrum of the crude product showed that starting materials were still present.

When aldehyde **111** was reacted with **101**, the ^{1}H NMR spectrum of the crude product looked promising (proton peaks expected in the product were present, i.e. the diene proton peaks at δ = 4 to 5 ppm). However, upon work up these peaks disappeared and the product appeared to decompose. Consequently, the intermediate alcohol **112** was protected with methyl iodide and sodium hydride in THF prior to purification in an effort to produce compound **113**. This resulted in promising ^{1}H NMR spectra data, with the characteristic diene peaks found between 4 and 5 ppm. Unfortunately, upon purification the product decomposed to provide a mixture of unknown products (no starting materials remained).

Due to the failed attempts at the indium diene formation, another reaction pathway involving silyl dienes was attempted.

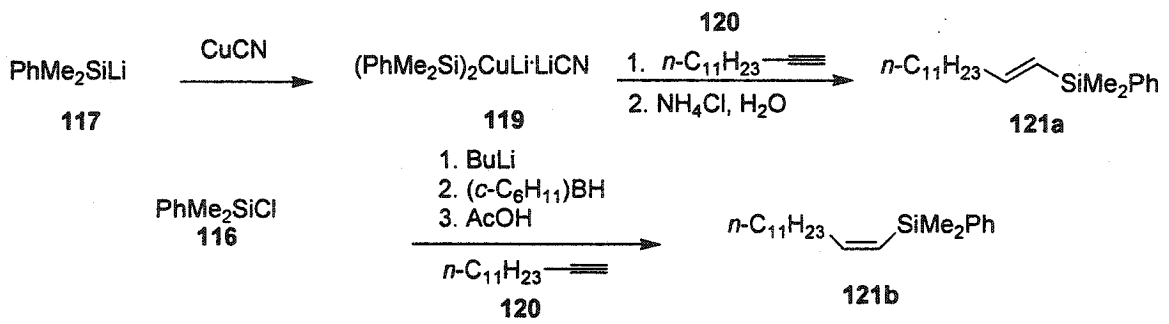
1.11. SILYL DIENE CHEMISTRY

1.11.1. INTRODUCTION

In 1963, Gilman discovered a route to prepare phenyldimethylsilyllithium **117** by reaction of phenyldimethylsilyl chloride **116** and lithium in THF (Scheme 43). [67] Treatment of **117** with a second equivalent of phenyldimethylsilyl chloride **116** led to the formation of disilane **118**, which could then be converted back to the phenyldimethylsilyllithium **117** through cleavage with of the silicon-silicon bond with lithium. This cleavage requires an unsubstituted phenyl group attached to each silicon.. For example, *p*-tolydimethylsilyl chloride treated with lithium will form a disilane that cannot be cleaved by lithium.

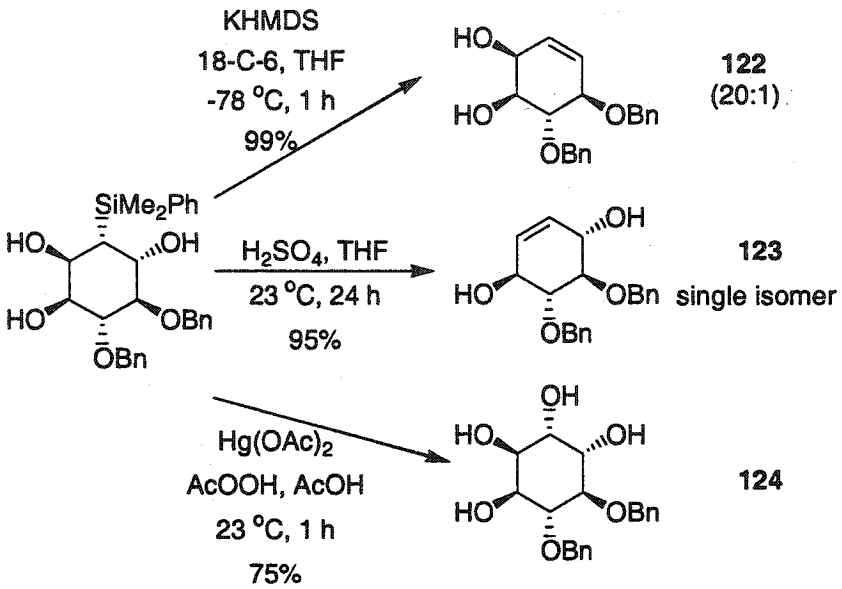
Scheme 43. The formation of silyllithium reagent **117**.

Treatment of silyllithium **117** with copper cyanide creates lithium dimethylphenylsilyl cuprous cyanate **119**, which can be used to make *cis* or *trans* vinylsilanes. A completely regioselective and *syn* stereospecific silyl-cupration of terminal acetylene **120** with **119** produces pure *trans* vinylsilane **121a** in 95% yield. In contrast, treatment of acetylene **120** with phenyldimethylsilyl chloride **116** followed by *syn* reduction with a boron species created the *cis* vinylsilane **121b** in 75% yield (Scheme 44).[68]



Scheme 44. Formation of *cis* and *trans* vinylsilanes **121b** and **121a**.

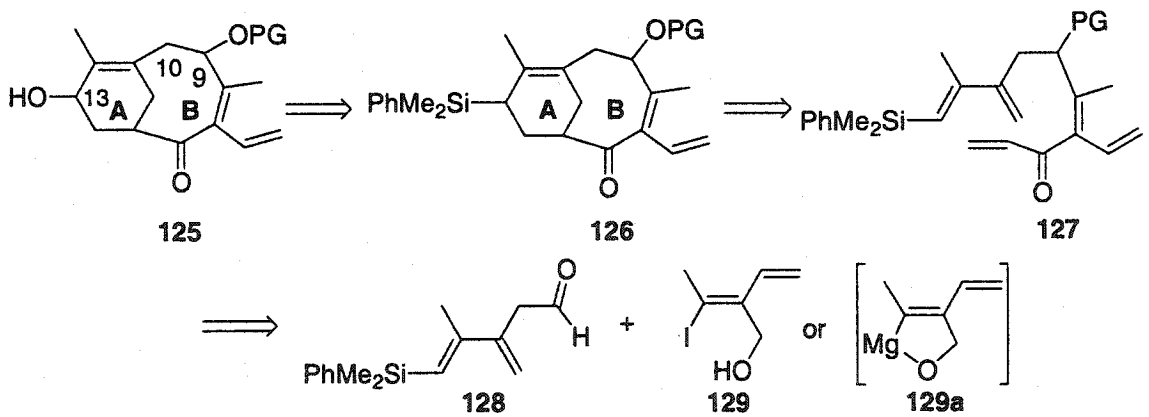
The elimination of the phenyldimethylsilyl group from β-hydroxy silanes can be accomplished *via* the Peterson elimination of the *cis*-hydroxysilane to produce **122.** Two mechanisms are possible depending on reaction conditions. A cis hydroxyl group is eliminated under basic conditions, but the trans hydroxyl group is lost under acidic conditions. The Fleming-Tamao oxidation gives **124** (Scheme 45). The Fleming-Tamao oxidation allows phenyldimethylsilane to act as a surrogate for a hydroxyl group.[69] This idea can be applied to introduce the allylic C13 alcohol in taxoids.



Scheme 45. The elimination and conversion of the silyl group.

1.11.2. RESEARCH OBJECTIVE

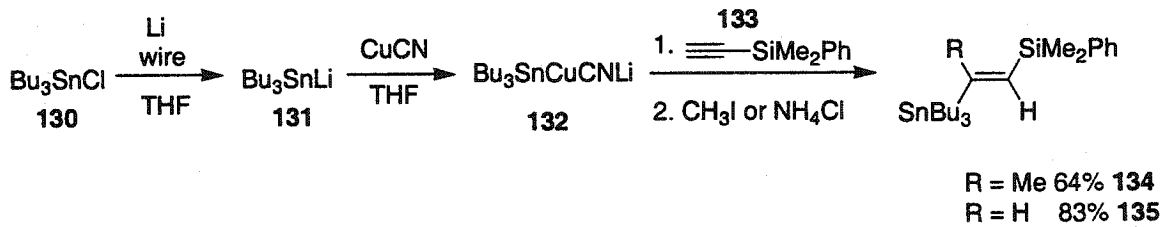
In order to properly evaluate the taxoid AB ring system, the paclitaxel or docetaxel side chain must be incorporated at C13. Currently the carbonyl functional group can only be introduced at C13 *via* allylic oxidation when C10 is substituted. If C10 is unsubstituted allylic oxidation at C13 is not possible. A new approach to the introduction of the side chain is to have a silyl group on C13 (**126**), which would then be converted to alcohol **125** *via* the Fleming oxidative silyl cleavage.[68] This method converts the phenyldimethylsilyl group into a hydroxyl with the retention of configuration. Scheme 46 shows a retrosynthetic analysis of taxoid **125** that utilizes the above concepts. It was thought that olefin **127** could be made from precursors **128** and **129** (or **129a**), which is prepared from phenyldimethylsilyl diene and an alcohol respectively.



Scheme 46. The retrosynthetic analysis of the taxoid AB ring system.

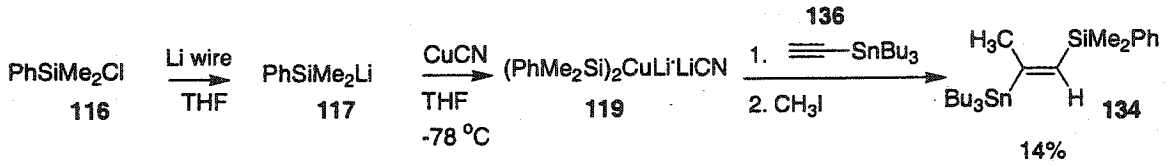
1.11.3. RESULTS

The synthesis of diene **128** involved the utilization of a stannylcupration reaction.[70] Tributyltin chloride **130** was reacted with lithium wire in dry THF under argon, producing **131**, which was subsequently treated with CuCN to give intermediate **132**. Adding silyl acetylene **133** to **132** and quenching the reaction with either methyl iodide or ammonium chloride produced compounds **134** and **135** in yields of 64% and 83%, respectively (Scheme 47). These results are consistent with those found by Fleming and coworkers[72] with ^{1}H NMR peaks for the five phenyl protons at δ = 7.54-7.57 and 7.30-7.37 and the vinyl hydrogen at δ = 6.06.



Scheme 47. Synthesis of olefin **134** *via* tributyl tin salt.

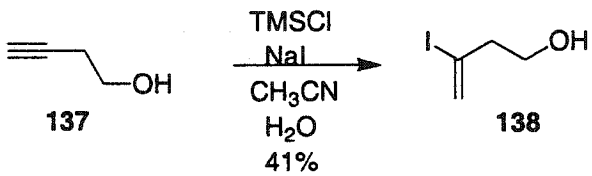
Based on literature precedence[70] the silyl salt **119** was also synthesized in an effort to compare yields of each preparation. Phenyldimethylsilyl chloride **116** was treated with lithium wire in THF at 0 °C to create phenyldimethylsilyl lithium **117**. Silyllithium **117** was then treated with CuCN forming **119**, which was subsequently treated with **131** and methyl iodide to produce olefin **134** in 14% yield (Scheme 48).



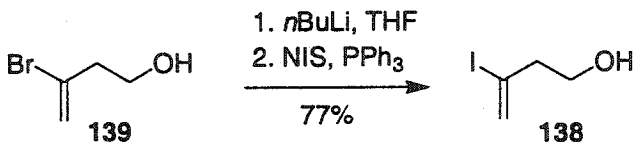
Scheme 48. Synthesis of olefin **134** *via* **119**.

Due to the higher yield produced from the tributyltin chloride synthesis (Scheme 47), it was selected for further experimentation.

The next step involved the synthesis of alcohol **138** from alkyne **137** *via* Ishii conditions.[73] TMSCl and NaI were reacted with **137** followed by the addition of water to form **138** in 41% yield (Scheme 49). It should be noted that **138** could have been made from commercially available 3-bromo-3-butyn-1-ol, **139**, using NIS in 77% yield (Scheme 50)[74]; however, it was unavailable at the time that it was required.

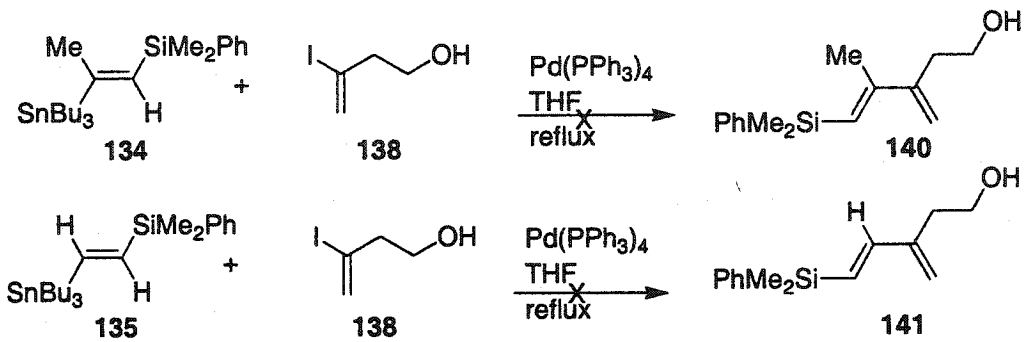


Scheme 49. Synthesis of alcohol **138** *via* Ishii conditions.



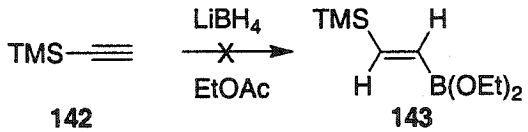
Scheme 50. Alternative synthesis for **133**.[74]

Stille reaction conditions were used to try and couple precursors **134** and **138** (Scheme 51). This reaction was monitored *via* TLC for up to 3 days; no reaction appeared to take place.



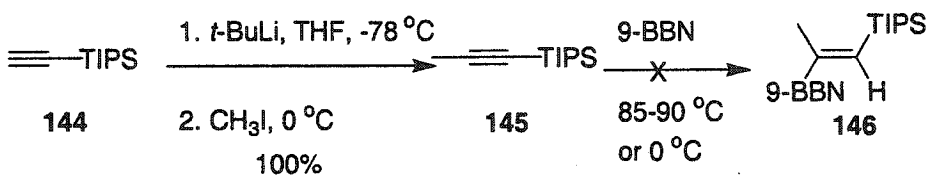
Scheme 51. Stille coupling of both olefins **134** and **135** to **138**.

Since the Stille coupling reaction was unsuccessful, perhaps the Suzuki coupling reaction would work. The boron substituted compound **143** was required to attempt such an interconversion. Trimethylsilyl acetylene **142** was reacted with $LiBH_4$ in ethyl acetate; we were not successful in isolating **143**, possibly due to its high volatility (Scheme 52).[75]



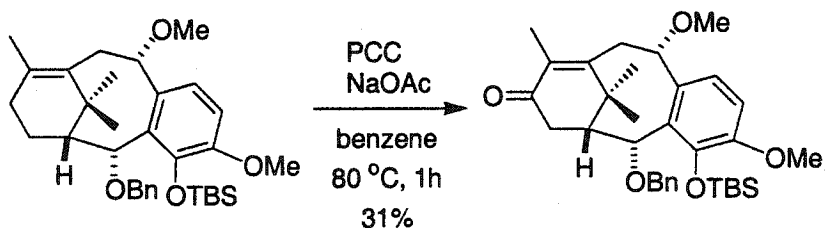
Scheme 52. Treatment of **142** with lithium borohydride.

Employing a larger silyl group and a methyl group diminished the volatility of the boron-substituted olefin. Alkyne **145** was prepared in quantitative yield from alkyne **144** by *t*-BuLi and methyl iodide (Scheme 53). 9-BBN was reacted with alkyne **145** at both 85 °C[76] and 0 °C[77] without any success in creating olefin **146**.



Scheme 53. Attempted synthesis of **146** *via* hydroboration.

During the time this project was being persued another member of the group found that PCC oxidation gave the desired allylic oxidation in fair yield (Scheme 54). Thus the proposal to use a silyl substiuent as a masked hydroxy group lost its urgency an thus it was abandoned.



Scheme 54. The successful oxidation of C13 with PCC.

2. CHAPTER 2

2.1. INTRODUCTION TO DIELS-ALDER CHEMISTRY

Discovered in 1928 by Diels and Alder, the Diels-Alder reaction is one of the most powerful tools in modern synthetic chemistry. Thermally allowed [4 +2] cycloadditions and result in two new σ bonds and a π bond, with the creation of up to four new stereogenic centers. This method provides a convenient and stereoselective route to six-membered rings. [78]

The ideal reaction conditions involve a diene that has an electron-donating group and the dienophile an electron-withdrawing group. However, the reaction can occur without any substituents on the diene and dienophile. The HOMO-LUMO gap is affected by the nature of the substituents. The smaller the gap the greater the rate of the reaction. Electron donating substituents increase the energy of the HOMO of the diene while electron-withdrawing substituents decrease the energy of the LUMO of the dienophile. The electronic demand may be inverted when the diene has an electron-withdrawing group and the dienophile has and electron-donating group.

Correct orbital overlap is required for the Diels-Alder reaction to occur, and therefore the diene must be in the *s-cis* conformation. Another important aspect of the Diels-Alder reaction is the *endo* product is favoured over the *exo* product.[79,80,81]

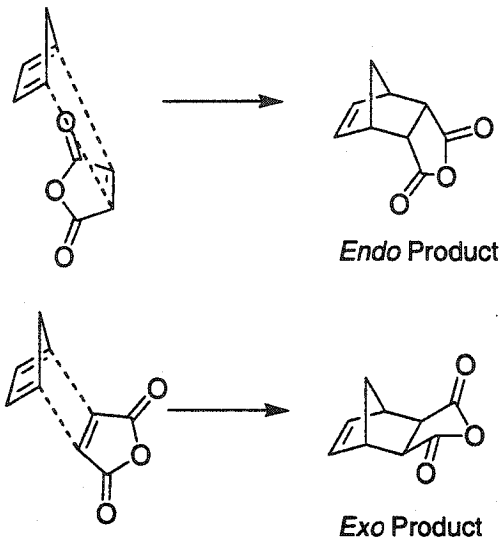


Figure 4. *Endo* and *Exo* products formation in Diels-Alder Reaction.

Unsymmetrical dienes can be approached by both the *endo* and *exo* orientations. For the *endo* approach, the dienophile's substituents are under the π orbitals of the diene, while for the *exo* approach the dienophile substituents do not overlap with the diene. When the substituents on the dienophile are unsaturated, such as a carbonyl group, the secondary orbital overlap observed in the *endo* approach stabilizes the transition state and is favoured.[82]

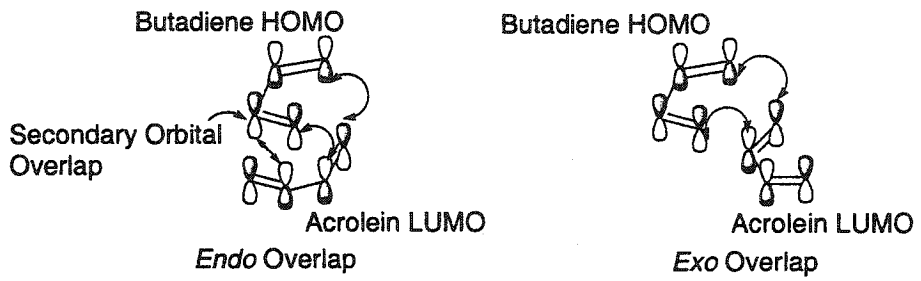
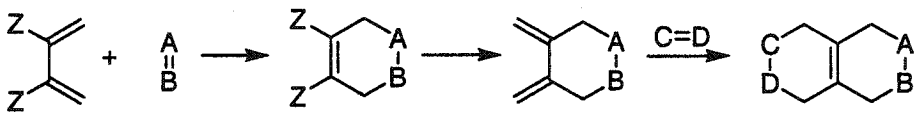


Figure 5. Secondary orbital overlap in *endo* transition state.

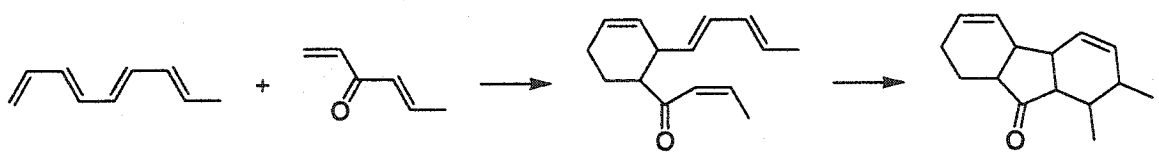
2.2. MULTIPLE DIELS-ALDER REACTIONS

Multiple Diels-Alder reactions are useful tools in synthetic organic chemistry. These include tandem, timed, domino and transmissive Diels-Alder reactions. Tandem Diels-Alder reactions are based on the sequence of two cycloadditions in which the mono-adduct resulting from the first is converted into a diene or dienophile, which then undergoes a second cycloadditon. A general reaction sequence can be found in Scheme 55.



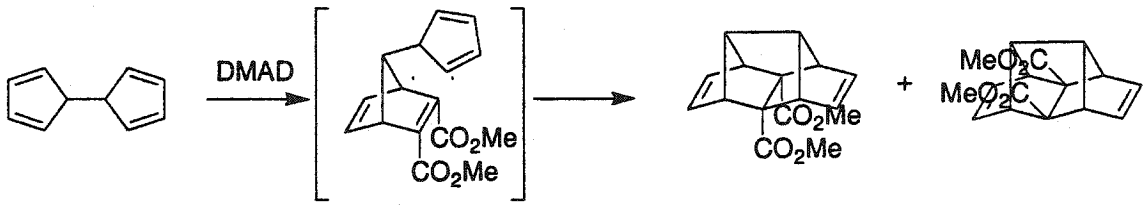
Scheme 55. General sequence for the tandem Diels-Alder reaction.

Another type of multiple Diels-Alder reaction is the timed reaction. It involves and intermolecular Diels-Alder reaction followed by an intramolecular Diels-Alder reaction (Scheme 56).



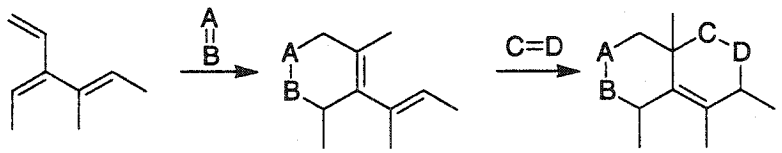
Scheme 56. The general reaction sequence for the timed Diels-Alder reaction.

The domino Diels-Alder reaction differs from the tandem and timed. In the first Diels-Alder reaction, the initial Diels-Alder adduct forms the dienophile, which undergoes a second Diels-Alder reaction with the diene already present in the reaction.



Scheme 57. The domino Diels-Alder reaction.

The final multiple Diels-Alder reaction discussed will be the diene-transmissive Diels-Alder reaction. It consists of two intermolecular cycloadditions. The initial cycloaddition involves a condensation of a cross-conjugated triene with one equivalent of a dienophile, affording a monoadduct containing a new diene unit. This new diene unit undergoes a second intermolecular cycloaddition with a second equivalent of a dienophile forming a two-fused six membered ring system (Scheme 58).[80,83]

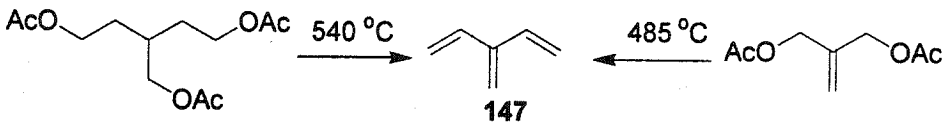


Scheme 58. The transmissive Diels-Alder reaction.

2.3. CROSS-CONJUGATED TRIENES

2.3.1. 3-METHYLENE-1,4-PENTADIENE

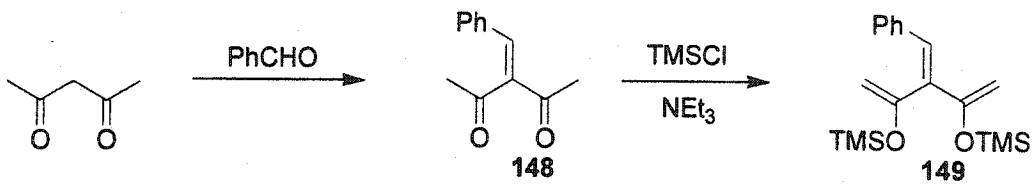
The first cross-conjugated triene **147** described was 3-methylene-1,4-pentadiene. In 1955, Blomquist and Bailey prepared triene **147** from the pyrolysis of 1,5-diactoxy-3-acetoxymethylpentane or 3-methylene-1,5-pentadiol diacetate. They found that triene **147** was very unstable and polymerized at temperatures below zero (-5 °C). As a result of this instability and therefore limited utility of triene **147**, various derivatives were synthesized to overcome the triene **147** defects.[84,85]



Scheme 59. Formation of 3-methylene-1,4-pentadiene through pyrolysis.

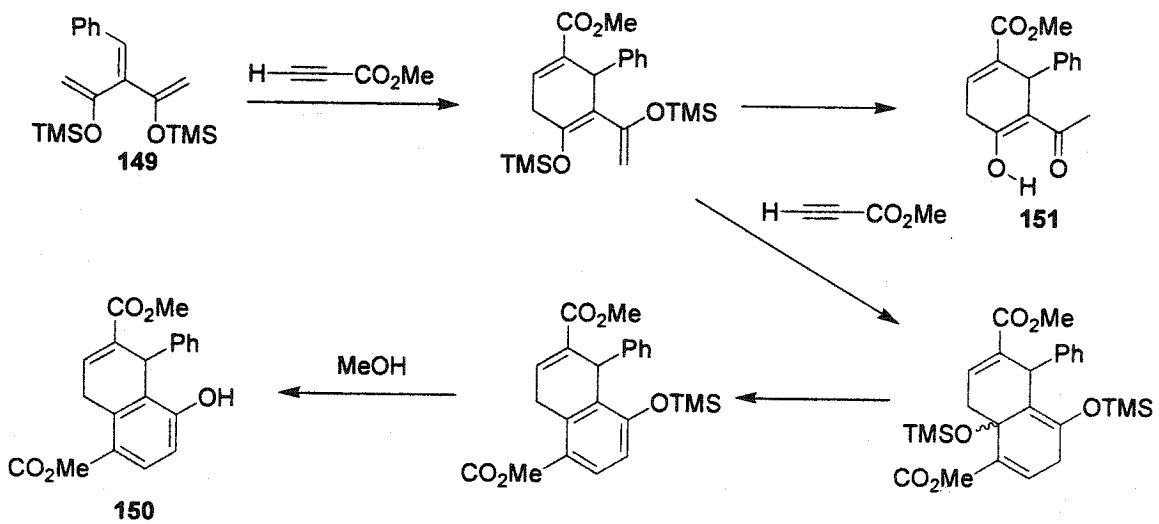
2.3.2. ACYCLIC DERIVATIVES OF TRIENE 147

A number of substituted cross-conjugated trienes have been synthesized. Tsuge and coworkers, in 1983, were able to make the first acyclic cross-conjugated triene that was stable enough to be used successfully in organic reactions. Their synthesis began with condensation of 2,4-pentanedione with benzaldehyde to give 3-benzylidene-2,4-pentadione (**148**). Treatment of **148** with TMSCl and NEt_3 produced cross-conjugated triene **149**.



Scheme 60. Synthesis of bis(silyloxy) cross-conjugated trienes **149**.

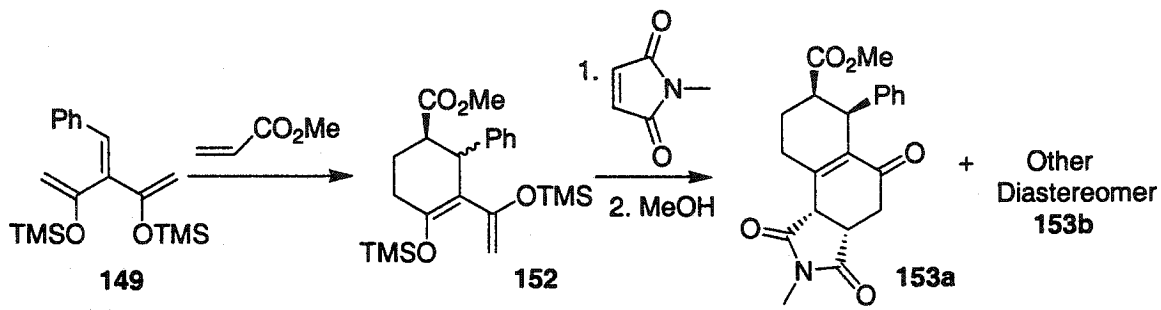
Tsuge reacted triene **149** with various dienophiles such as DMAD, methyl propiolate, *N*-methylmaleimide, *N*-phenylmaleimide, and maleic anhydride. Treatment of triene **149** with excess methyl propiolate, followed by elimination of TMSOH and deprotection of the phenol, formed **150** in 47% yield, Scheme 61. Mono-adduct **151** was also isolated in 2% yield and was found to exist mainly in the enol form.[86]



Scheme 61. The diene-transmissive Diels-Alder reaction using triene **149**.

Tsuge and coworkers also explored the possibility of synthesizing mixed adducts. They reacted triene **149** with different cyclic and acyclic dienophiles. Reaction of a cyclic dienophile (maleic anhydride, *N*-phenylmaleimide, or *N*-methylmaleimide) for the first cycloaddition followed by a second cycloaddition with a different dienophile lead to diastereoselective bis-adducts.

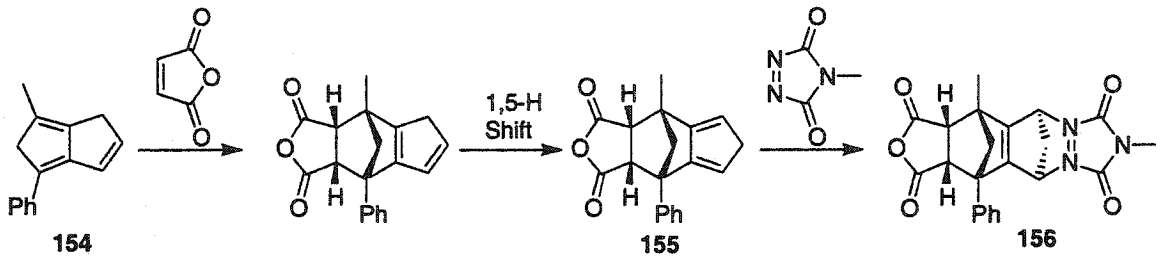
The reaction of **149** with an acyclic dienophile followed by a second cycloaddition with a cyclic or acyclic dienophile did not always produce diastereoselective cross bis-adducts. When triene **149** was reacted with methyl acrylate to produce mono-adduct **152**, it then underwent a second cycloaddition with *N*-methylmaleimide to produce diastereomers **153a** and **153b** (Scheme 62).[87]



Scheme 62. Diene transmissive Diels Alder with triene **149** and different dienophiles.

2.3.3. CYCLIC DERIVATIVES

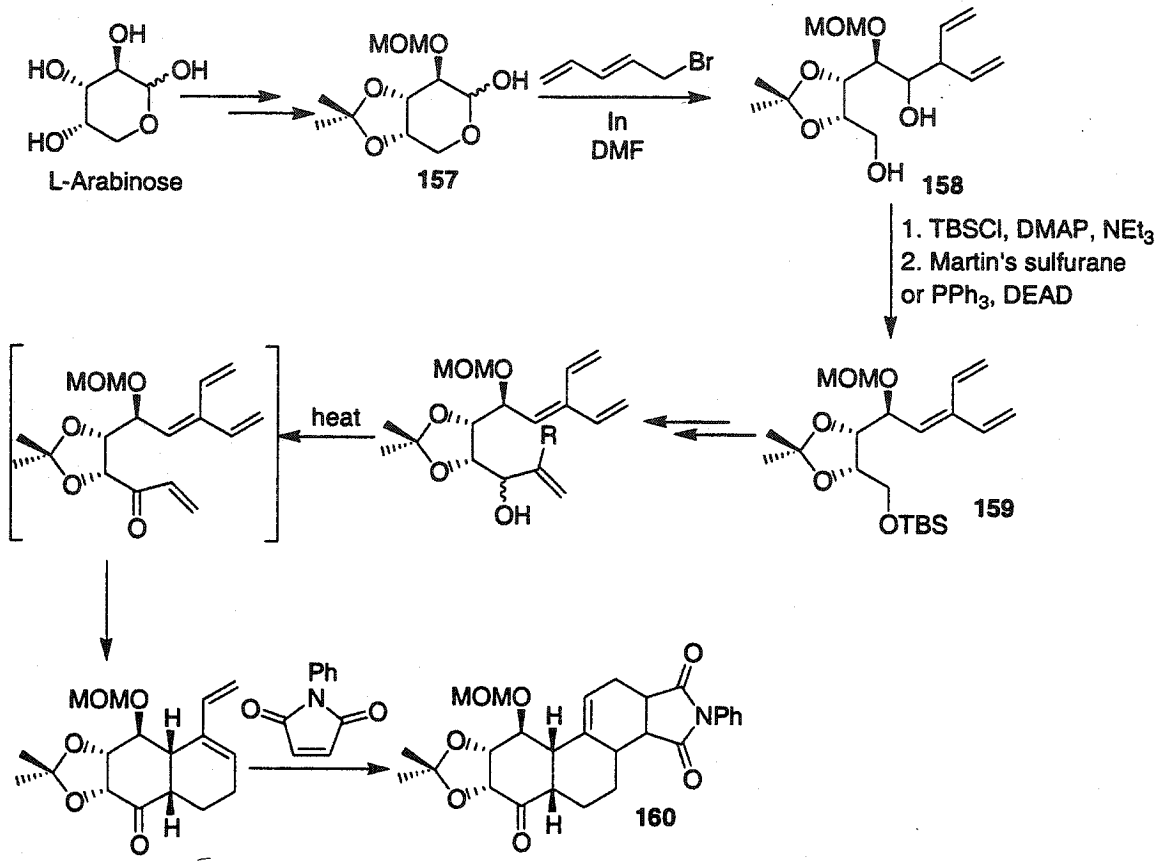
Hirt and coworkers carried out diene-transmissive Diels-Alder reactions with 1,5-dihydropentadiene and its derivatives. Similarly, treatment of triene **154** with high concentrations of maleic anhydride, produced the bis-adduct. While treatment with only one equivalent of dienophile, followed by isomerization of the intermediate cyclopentadiene **155** (1,5-hydrogen shift) and a second equivalent of a different dienophile, NMTAD, result in a cross-bis-adduct **156** (Scheme 63).[88]



Scheme 63. Diene-transmissive Diels-Alder reaction production of a cross bis-adduct.

2.3.4. DIENE-TRANSMISSIVE DIELS-ALDER STUDIES WITH TRIENES

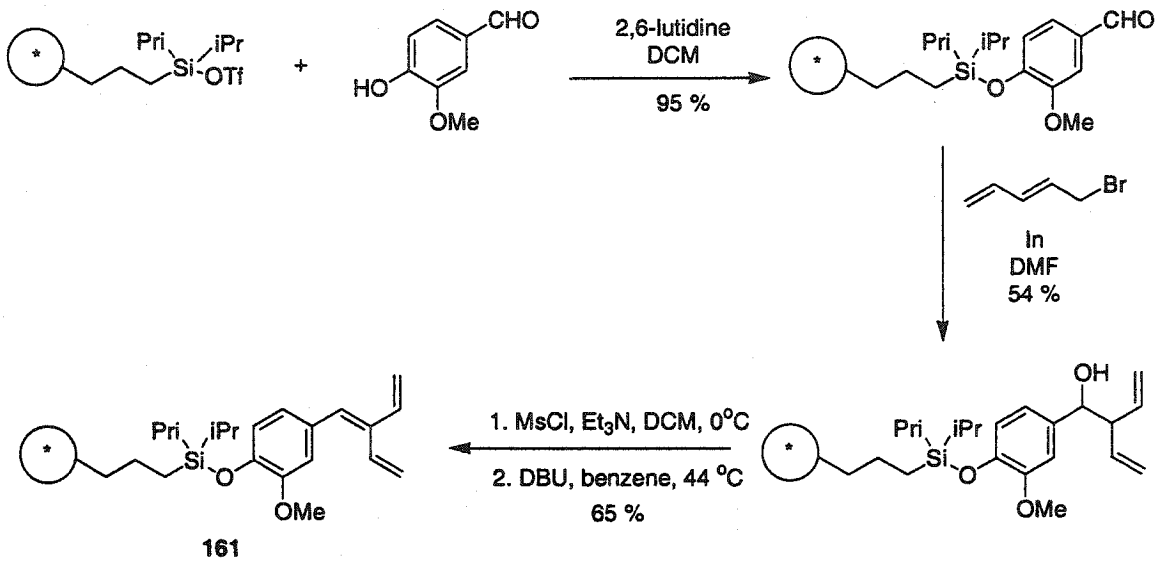
In 1999, Fallis and coworkers studied and published their studies on the diene-transmissive Diels-Alder reactions with cross-conjugated trienes. They utilized this reaction to prepare efficiently nor-terpeneoids, nor-steroids, as illustrated by the tetracyclic skeleton in compound **160** in one reaction vessel. The lactol **157,** prepared from L-arabinose was converted to secondary alcohol **158** by reaction with 5-bromo-1,3-pentadiene in the presence of indium. Dehydration of alcohol **158** with either Martin's sulfurane or PPh_3 and DEAD produced cross-conjugated triene **159**, which was later used in the diene-transmissive Diels-Alder reaction to produce steroidal and tetracyclic skeletons, such as **160** (Scheme 64).



Scheme 64. Synthesis of tetracycle **160** *via* diene-transmissive Diels-Alder reaction.

2.3.6. MACROBEAD-LOADED TRIENES

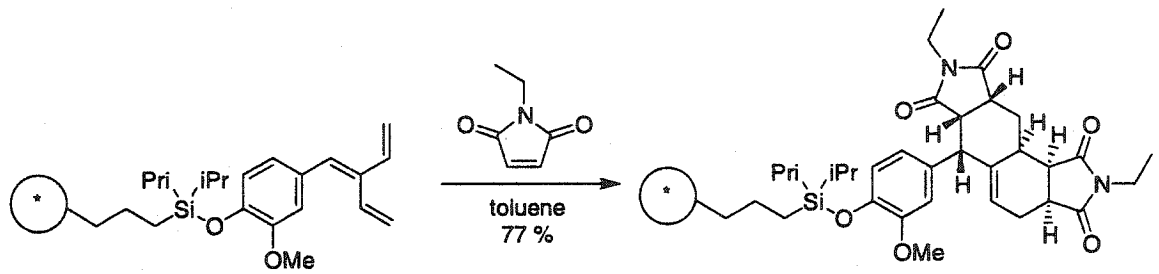
Schreiber and coworkers used the unique method established by Fallis and coworkers to form 53 disubstituted- and 44 tri- or tetrasubstituted cyclic dienophiles. It involved the synthesis of macrobead-loaded triene **161** (Scheme 65), which was reacted with various dienophiles in consecutive Diels-Alder reactions. They discovered that reacting triene **161** reacted with acyclic dienophiles to produce stereoisomeric mixtures of double cycloadducts, while cyclic dienophiles yielded products stereoselectively.



161

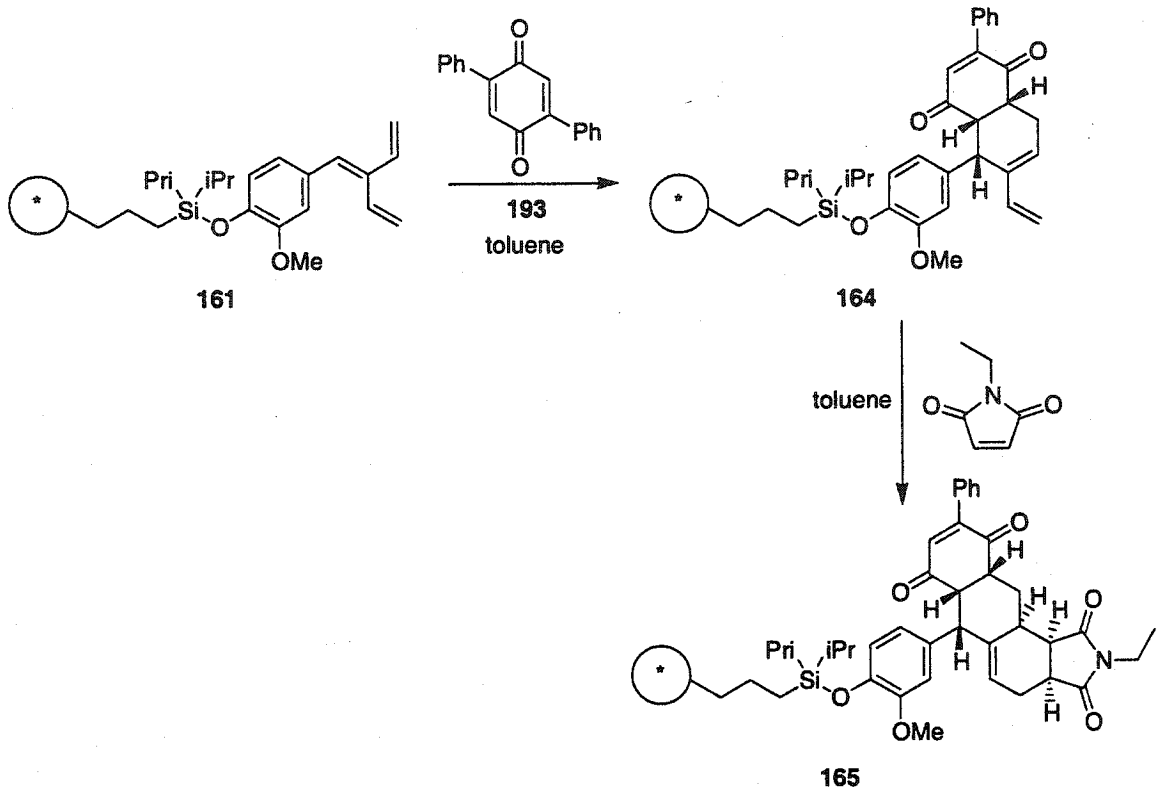
Scheme 65. Formation of cross-conjugated macrobead-loaded triene **161**.

Reacting two equivalents of *N*-ethylmaleimide with triene **161** produced bis-adduct **162** in high purity as a single diastereomer in 95% yield (Scheme 66). The consecutive Diels-Alder reactions could be performed with one dienophile **163** to form the mono-adduct **164** as a single isomer, which could be further reacted with another dienophile (*N*-ethylmaleimide) to produce bis-adduct **165** again as a single isomer (Scheme 67).[89]



161 162

Scheme 66. Formation of bis-adduct **162**.

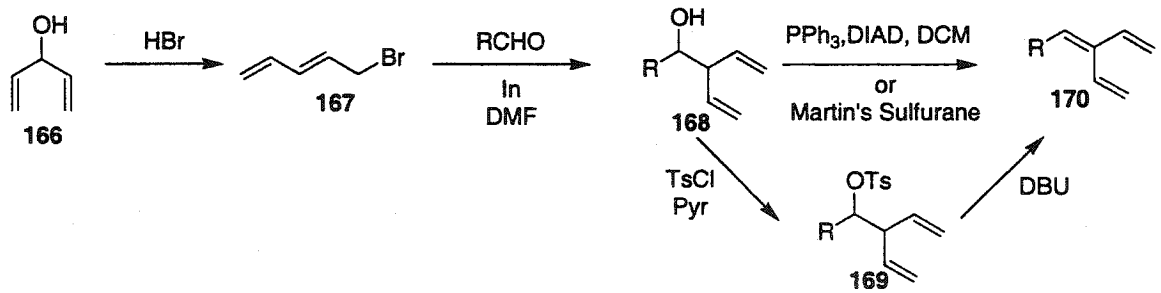


Scheme 67. Single isomeric synthesis of **164** and **165**.

2.4. RESEARCH OBJECTIVES

2.4.1. PROPOSED METHOD FOR CROSS-CONJUGATED TRIENES PREPARATION

The synthesis of cross-conjugated trienes was accomplished by dehydrating secondary alcohols that were made *via* indium chemistry from desired aldehydes and allyl bromide species (Scheme 68). Treatment of 1,4-pentadiene-3-ol **166** with HBr produces 5-bromo-1,3-pentadiene **167**.[90] Reacting bromodiene **167** with aldehydes in the presence of indium will create a secondary alcohol, such as **168** when the substitution of the bromodiene is at the γ position to the bromide. If an alkyllithium were to be used substitution of the bromodiene **167** would be at the α position of the bromide. These alcohols could be dehydrated using different methods.



Scheme 68. The route to 3-methylene substituted cross-conjugated trienes.

2.4.2. DEHYDRATION OF SECONDARY ALCOHOLS

There are various ways in which to dehydrate secondary alcohols (Scheme 68). One method would be to generate the tosylate **169**, followed by elimination with DBU,

170. Other methods would the use of Martin's Sulfurane, (carboxysulfamoyl) triethylammonium hydroxide inner salt methyl ester[91,92] or the PPh_3/DIAD, **170**. Due to the ease of a one step process and the cost of Martin's Sulfurane the PPh_3/DIAD method was chosen. The secondary alcohols would be treated with PPh_3/DIAD and heated to 50 °C for 18 h.

2.5. DIENE-TRANSMISSIVE DIELS-ALDER REACTION FOR THE SYNTHESIS OF APHENES

2.5.1. APHENES

A hydrocarbon parent component that consists of *n* ortho-fused benzene rings (*n*>3) and comprises two linear arrangements of (*n* + 1)/2 and (*n* + 1)/2 (if *n* is odd) or *n*/2 and (*n*/2)+1 rings (if *n* is even) with a common benzene ring and which makes a formal angle of 120 ° is named by citing the numerical prefix denoting the total number of benzene rings followed by the ending '-aphene' (derived from phenanthrene). In an attached component prefix the ending '-aphene' is changed to '-apheno'.

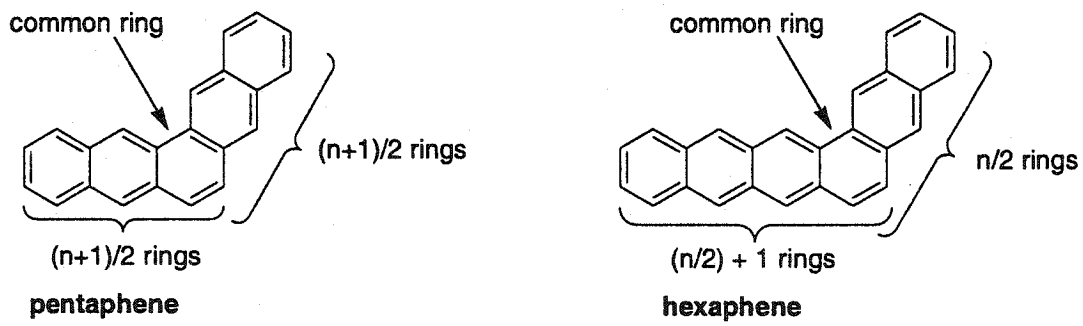


Figure 6. Components of pentaphene and hexaphene that make them aphenes.

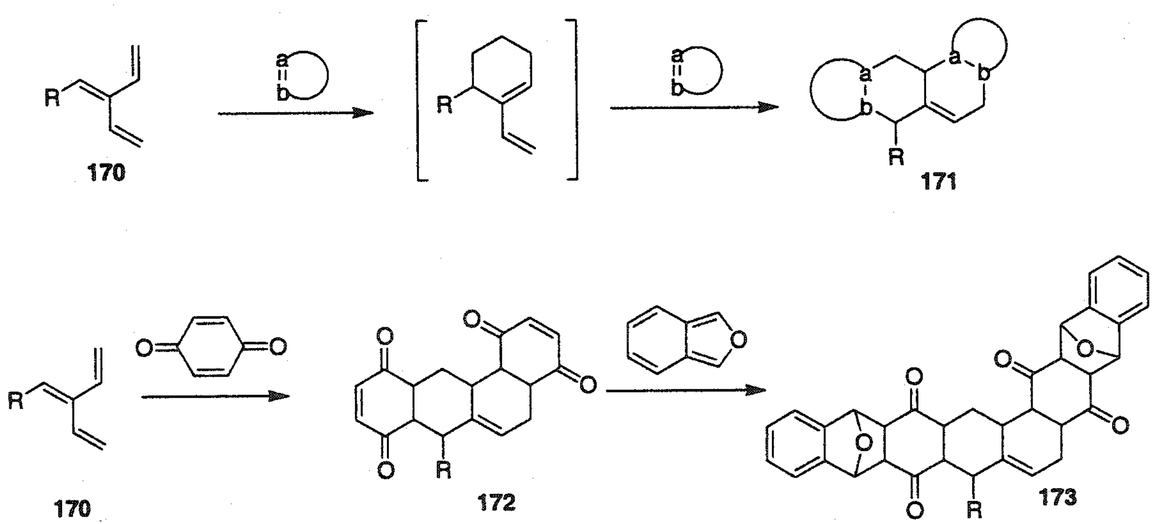
Aphenes, unlike acenes, are not well known in literature. Some are known to have utilities such as hexaphene is an embalming agent and butaphene is a contact herbicide for post-emergence weed control in cereals. They are of theoretical interest, as their electronic properties are not understood compared to acenes. It has been suggested

that the cyclic conjugation in phanes increases toward the center of the molecule.[93] If valid the terminal aromatic rings should posses diene character in contrast to acenes in which the central ring are the most reactive in [4 + 2] cycloaddition sites.

Through the synthesis of aphenes it is hoped that the knowledge of their utility and function will expand.

2.5.2. PROPOSED ROUTE TO APHENES USING THE DIENE-TRANSMISSIVE DIELS-ALDER REACTION

The diene-transmissive Diels-Alder reaction will be investigated with a cross-conjugated triene **170** and cyclic dienophiles (1,4-benzoquinone, cyclopentadiene, *N*-methylmaleimide, isobenzofuran and derivatives). If successful this would create an aphene precursor **171** consisting of four rings.



Scheme 69. The diene-transmissive approach to aphene precursers.

Based on the introduction to this chapter we envisaged that the aphene precursor **171** consisting of four rings could be created in a single operation involving the cross-conjugated diene **170** and cyclic dienophiles such as 1,4-benzoquinone, cyclopentadiene, *N*-methylmaleimidem or isobenzofuran. The extended aphene precusor **173** could result from the reaction of 1,4-benzoquinone with cross-conjugated triene **170** to form bis-adduct **172**. This compound is a potential double dienophile; such as isobenzofuran a second Diels-Alder reaction with two equivalents of a second diene should produce **173** (Scheme 69). Full aromatisation of **173** appears feasible.

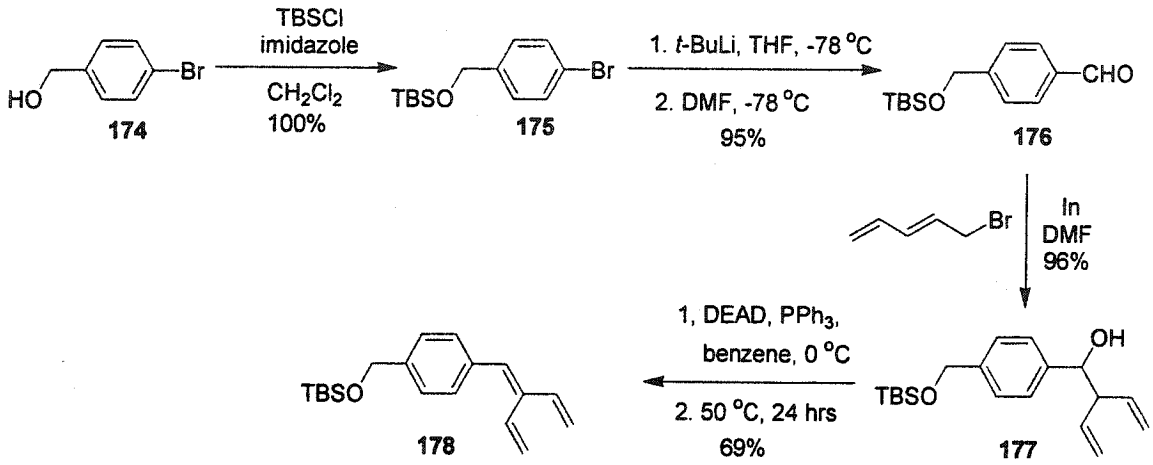
2.6. RESULTS

The first cross-conjugated triene **178** was synthesized in four steps from 4-bromobenzyl alcohol (**174**). Alcohol **174** was treated with TBSCl and imidazole in DCM to produce **175** in quantitative yield. Subsequent treatment of **175** with *tert*-butyl lithium at –78 °C in THF followed by DMF created aldehyde **176** in 95% yield. The ^{1}H NMR spectrum showed a doublet of doublets at δ = 7.47 (J = 0.3, 8.05 Hz) for two aromatic protons and a doublet at δ = 7.82 (J = 8.13 Hz) for the other two aromatic protons. The aldehyde peak was also found at δ = 9.97 and at 192.2 ppm in the ^{13}C NMR sprectrum.

The secondary alcohol **177** was then generated in 96% yield by vigorously stirring aldehyde **176** with indium metal at 0 °C in DMF followed by the addition of 5-bromo-1,3-pentadiene for 18h.[94] The identification of alcohol **177** was accomplished *via* ^{1}H and ^{13}C NMR, IR and HRMS. ^{1}H NMR spectrum had the four aromatic peaks in a multiplet at δ = 7.26, an allylic proton quartet at δ = 3.08, and a doublet for the proton on the same carbon as the hydroxyl group at δ = 4.56.

Conversion of alcohol **177** into cross-conjugated triene **178** involved a dehydration reaction, which consisted of treating **177** with triphenylphosphine and DEAD in benzene at 0 °C followed by heating the reaction mixture to 50 °C for 18 h. The reaction was cooled to room temperature (22 °C), diluted with petroleum ether to form a cloudy solution, filtered through a 1 cm pad of silica gel and washed with petroleum ether to afford a pale yellow oil. The crude material was then purified *via* flash column chromatography (10:1, petroleum ether/ether) to produce **178** in 69% yield (Scheme 84). The ^{1}H NMR for triene **178** had a singlet at δ = 6.62 for the vinyl proton closest to the aromatic ring, terminal vinyl proton peaks between δ = 5.17 and δ = 5.53

and the vinyl protons at δ = 6.51-6.56 (J = 0.90, 6.73, 10.72Hz) and δ = 6.67-6.72 (J = 6.63, 11.12, 17.76Hz).

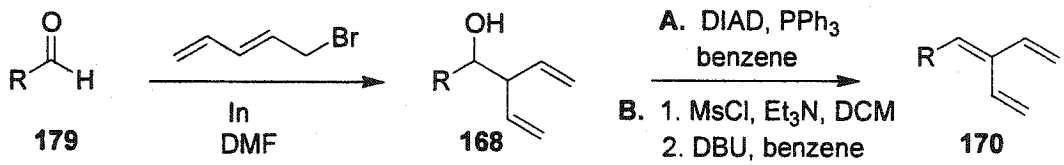


Scheme 70. The four step synthesis to triene **178**.

Other cross-conjugated trienes were synthesized from their corresponding aldehydes *via* indium mediated addition and elimination reactions (Scheme 71). Aldehydes such as **179** were treated with 5-bromo-1,3-pentadiene, indium and DMF and stirred for 18 h. They were worked up in the usual manner and purified by column chromatography (3:1, pet. ether/ether) to produce secondary alcohols **168**. Table 3 shows the relative yields of each aldehyde, which ranged from 64% to 99%. All alcohols that upon dehydration became cross–conjugated with an aromatic ring proved to be difficult to handle due to their quick decomposition and necessity to be utilized within one hour of purification.

All the secondary alcohols **168** were treated with triphenylphosphine and DIAD/DEAD in benzene at 0 °C. These reactions were heated to 50 °C for 18 h before being worked up to produce trienes **170**. All trienes with the general structure of **170**

were purified *via* column chromatography (pure pet. ether). The yields of the trienes (**185** to **187**) ranged from as low as 5% to 72%. The triene **184** (R = CH_3 in **280**) was very volatile and could not be isolated.



Scheme 71. The general reaction pathway for the synthesis of cross-conjugated trienes.

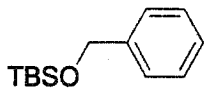
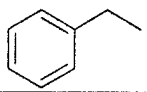
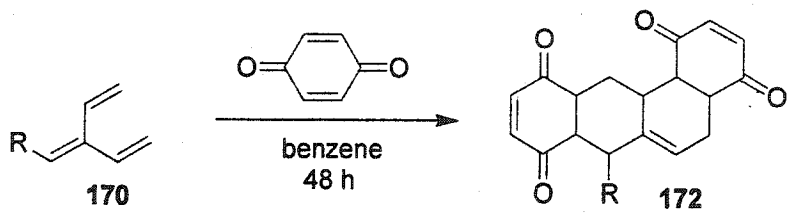
	R	Alcohol Yield (%)	Conditions		Triene Yield (%)
177		96	A	**178**	69
180	CH_3	64	A and B	**184**	not isolated
181		92	A	**185**	5
182		92	B	**186**	66
183		99	A	**187**	72

Table 3. The alkyl groups(R) of each aldehyde and their corresponding yields for secondary alcohols and trienes.

The first diene transmissive Diels-Alder reaction was conducted on TBS substituted triene **178** with 1,4-benzoquinone in benzene at reflux for 18 h.[96] A new spot was observed *via* TLC . The reaction mixture was cooled and a precipitate was observed. The powder recovered upon simple filtration was found to be hydroquinone. The same

result was observed when the reaction was attempted in toluene. It was thought that heating the reaction was causing 1,4-benzoquinone to aromatise prior to reacting, so the reaction was carried out in benzene at room temperature (22 °C) for 3 days. The result again was the total recovery of hydroquinone. Due to 1,4-benzoquinone's ability to aromatize in light, the next reaction was conducted in the absence of light for 2 days. This again simply yielded the hydroquinone in quantitative yield. The reaction was then conducted in DCM at room temperature for 2 days. Again, 1,4-benzoquinone and hydroquinone were recovered as the only products. At this point it was thought that the triene **178** may be decomposing rather than reacting with the dienophile (1,4-benzoquinone) or triene **178** was being oxidized at the benzylic alcohol position by 1,4-benzoquinone to form an extended quinomethide species. As a result the reaction was conducted at −78 °C in DCM with and without Lewis acid Et_2AlCl. The results were consistent with previous results and only benzoquinone was recovered and bis-adduct was not obtained.

The other trienes (**185** to **187**) were then reacted with 1,4-benzoquinone in benzene for 2 days. Triene **185** and **187** both produced bis-adduct **188** and **190** in 13% and 84% respectively (Scheme 72, Table 4). Triene **186** did not react with 1,4-benzoquinone in benzene, DCM, or toluene. The lack of reactivity of triene **186** was not unexpected due its structure, the benzene ring being directly conjugated with the cross-conjugated triene. It is known that styrene and highly conjugated compounds in general, polymerize on exposure to light, so it is not surprising that cross-conjugated trienes that are brought into further conjugation with an aromatic ring are also unstable.[95]



Scheme 72. The transmissive Diels-Alder reaction with dienophiles **185**, **186** and **187**.

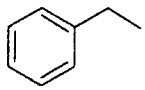
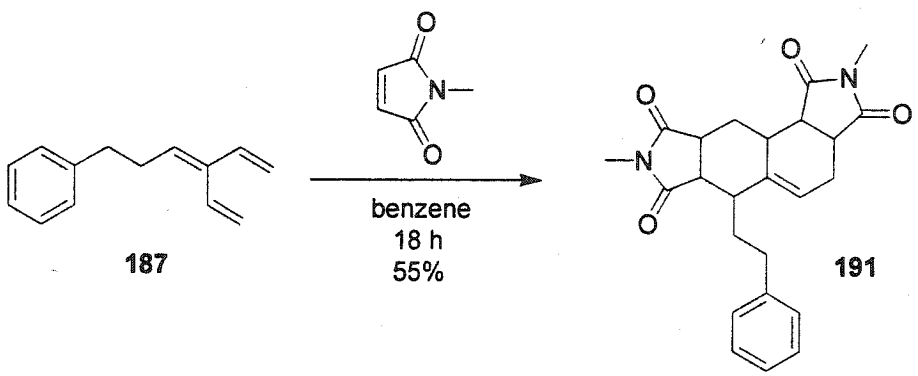
	R		Yield (%)
185		**188**	13
186		**189**	not isolated
187		**190**	84

Table 4. The adduct yields of each triene when reacted with 1,4-benzoquinone.

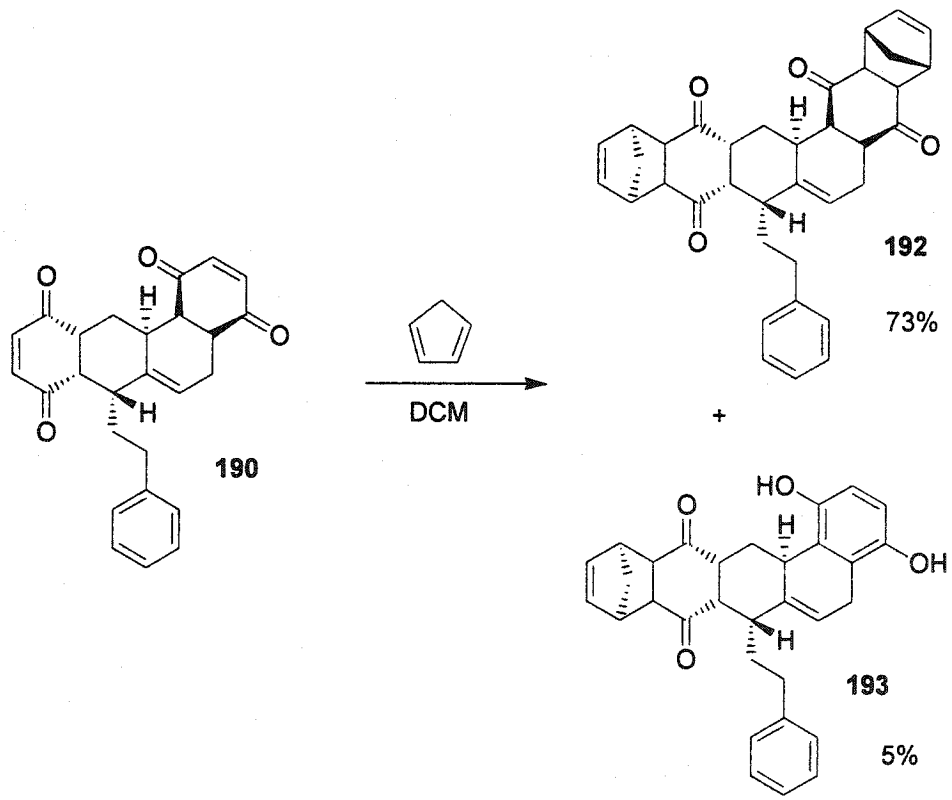
Triene **187** also underwent the transmissive Diels-Alder reaction with *N*-methylmaleimide in benzene for 18 hours to produce bis-adduct **191** in 55% yield (Scheme 73). The structure of compound **191** was verified by NMR, IR and HRMS. The ^{1}H NMR contained the six methyl protons of *N*-methylmaleimide at δ = 2.88-2.89 as a multiplet, the vinyl proton at δ = 5.61-5.62 as a multiplet and the five phenyl protons at δ = 7.15-7.27 also as a multiplet.



Scheme 73. The transmissive Diels-Alder reaction of **187** with *N*-methylmaleimide.

The improved yield with **187** compared to **185** for the respective bis-adducts (**188** and **190**), led to its selection for further transmissive Diels-Alder reactions. Bis-adduct **190** (dienophile) was reacted with a variety of dienes.

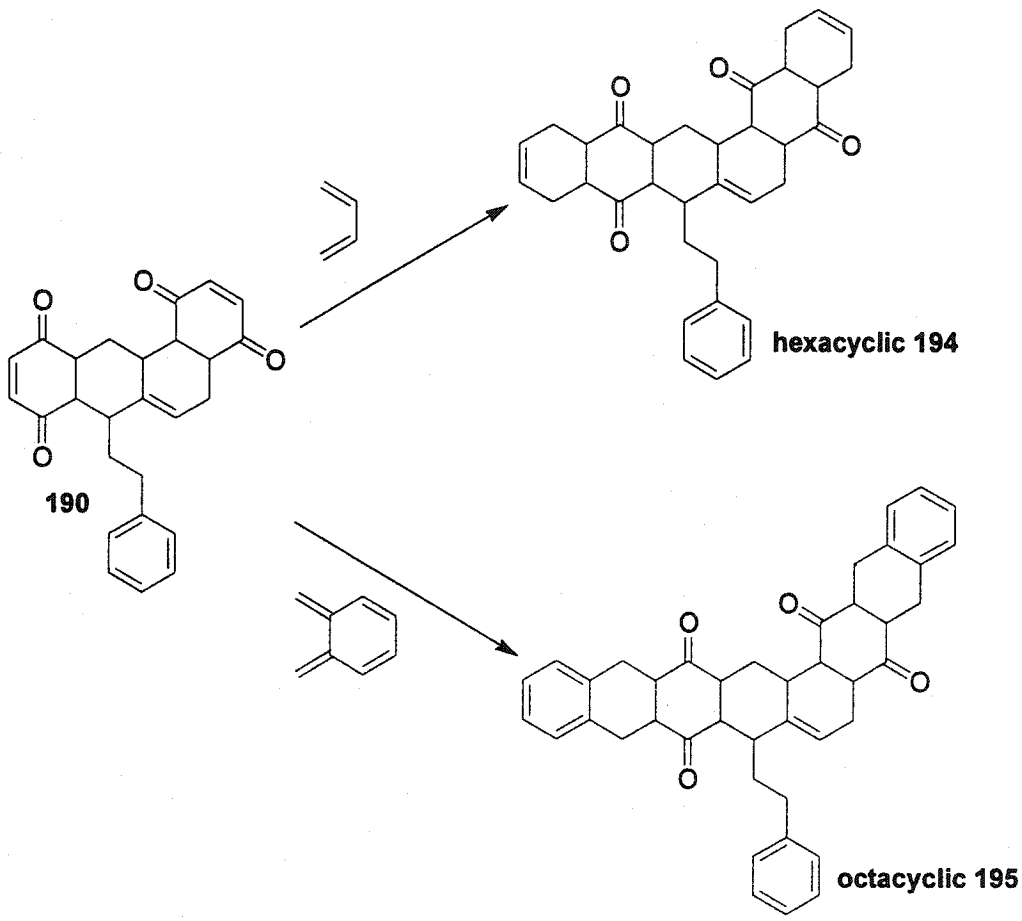
The first diene to be reacted with adduct **190** was cyclopentadiene a repetition of work previously completed.[96] Two equivalents of freshly distilled cyclopentadiene were added to a solution of adduct **190** in DCM. After stirring for 2 days at room temperature bis-adduct **192** and mono-adduct **193** were generated in 73% and 5% respectively (Scheme 74). Adducts **192** and **193** were identical in ^{1}H and ^{13}C NMR spectra to previously obtained spectra of these compounds.



Scheme 74. Transmissive Diels-Alder reaction of dienophile **190** with cyclopentadiene.

2.7. RING EXTENSION STUDIES

Various other dienes were reacted with tetraketone **190** in an attempt to extend the tetracyclic ring system into a hexacyclic or octacyclic ring system (Scheme 75).

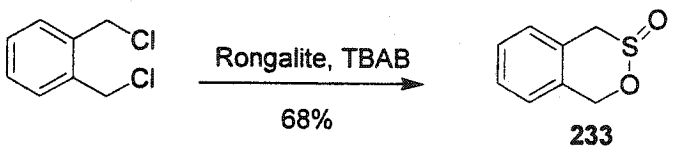


Scheme 75. Proposed general reaction sequence for the extention of **190**'s ring system.

2.7.1. O-QUINODIMETHANE

Sultine **196** was synthesized by reaction of α,α'-dichloro-o-xylene with rongalite (sodium hydroxymethane sulfinate) and TBAB in DMF for 12 h. Purification involved the removal of solvents to produce sultine **196** in 68% (Scheme 76). The ^{1}H NMR

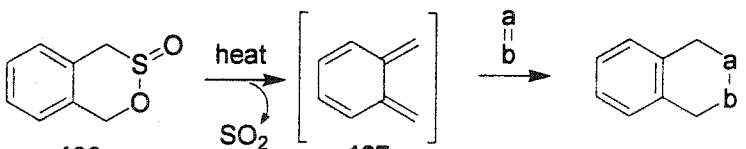
spectrum showed a doublet of doublets at δ = 3.51 and 4.37 (J = 14.8Hz) and δ = 4.91 and5.27 (J = 13.8Hz) in addition to four aromatic hydrogens. This data compares closely with that reported by Dittmer.[97]



233

Scheme 76. Synthesis of sultine **196**.

Upon exposure to heat, sulfur dioxide is removed from sultine **196** to produce the short-lived o-quinodimethane **197**. This highly reactive intermediate must be made *in situ* to react with a dienophile to create adducts such as **198** (Scheme 77). The additional driving force that makes **197** an outstanding diene in Diels-Alder reactions is the regeneration of aromaticity as shown in **198**.



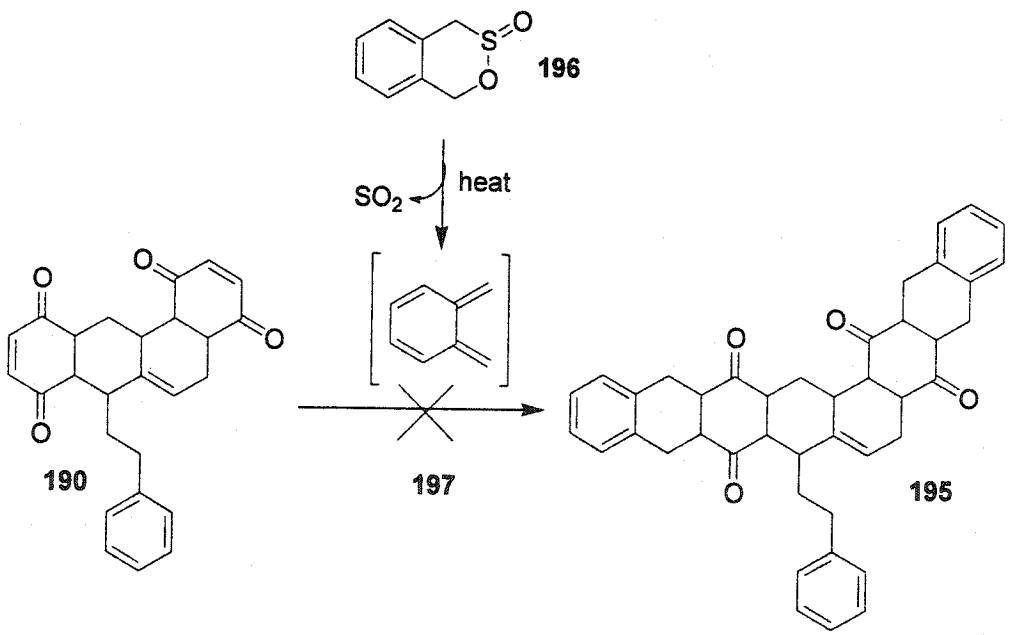
196 **197** **198**

Scheme 77. Sultine **196**'s mode of action in the Diels-Alder reaction.

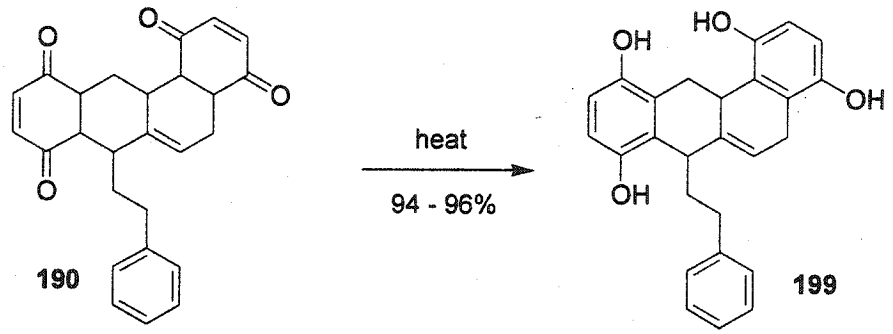
Various conditions were tried in order to add diene **197** to tetraketone **190**. Both tetraketone **190** and sultine **196** were heated to reflux in benzene and toluene without obtaining bis-adduct **195** (Scheme 78). The heat (120 °C) and pressure (100 psi) from a microwave reactor were examined in toluene in an attempt to cause the double

cycloaddition of tetraketone **190** to sultine **196**. Unfortunately this was unsuccessful. Heating tetraketone **190** and sultine **196** in a sealed tube in toluene and higher boiling *m*-xylene (138 °C), gave only a thick brown sludge thought to be polymerized **197**. Column chromatography of the brown sludge in dichloromethane and methanol produced tetra-phenol **199** in 94%. The ^{1}H NMR showed the vinyl proton at δ = 5.79 - 5.80 as a multiplet, the five aromatic protons and the four protons for the benzene-1,4-diols at δ = 6.56 as a multiplet.

At this point it was discovered that the only recoverable product from each reaction involving the heating of tetraketone **190** was tetra-phenol **199**. Tetraketone **190** was aromatizing rapidly upon exposure to heat (Scheme 79).



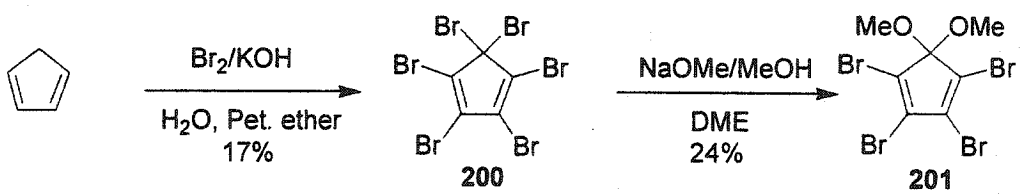
Scheme 78. Reaction of sultine **196** with tetraketone **190**.



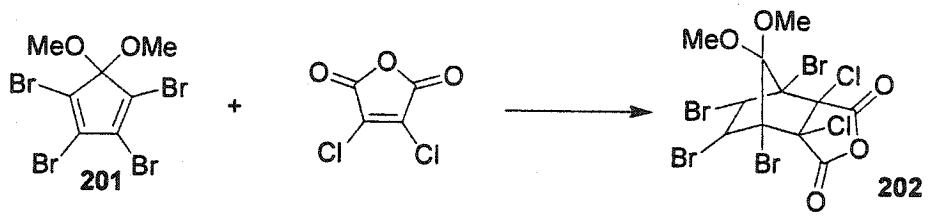
Scheme 79. Aromatization of **190** upon exposure to heat.

2.7.2. 1,2,3,4-TETRABROMO-5,5-DIMETHOXYCYCLOPENTA-1,3-DIENE

1,2,3,4-Tetrabromo-5,5-dimethoxycycopenta-1,3-diene (**201**) was an attractive diene to introduce more functionality into the adduct. It was prepared from cyclopentadiene according to scheme 80.[98] This compound was obtained in low yield and its spectroscopic properties matched those reported.[98] Diene **201** could be added, like cyclopentadiene, without the use of heat, which would avoid aromatization of tetraketone **190**. It is known that diene **201** will react with dichloromaleic anhydride to form adduct **202** (Scheme 81).

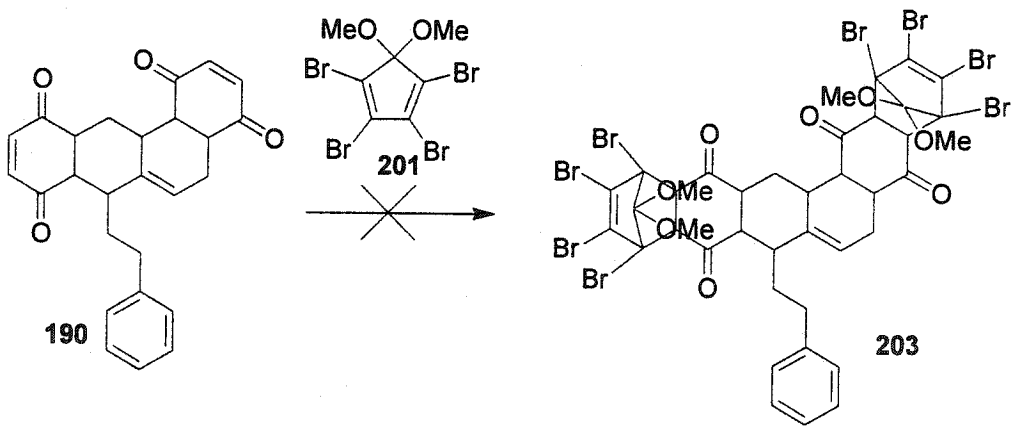


Scheme 80. Synthesis of diene **201** from cyclopentadiene.



Scheme 81. Example of **201** coupling to a dienophile.

Tetraketone **190** was mixed with diene **201** in dichloromethane, benzene and toluene for 2 to 5 days without obtaining the desired bis-adduct **203**(Scheme 82). Both starting materials were recovered in quantitative yields. Heating any of the reactions caused the formation of tetra-phenol **199**.

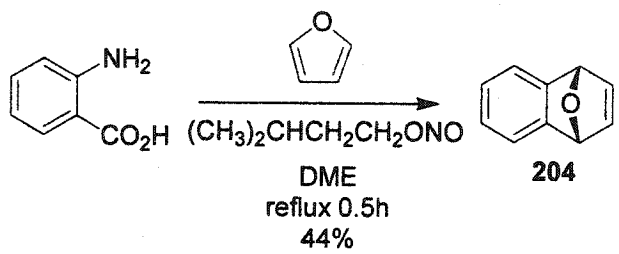


Scheme 82. Reaction of tetraketone **190** with diene **201**.

2.7.3. ISOBENZOFURAN AND DERIVATIVES

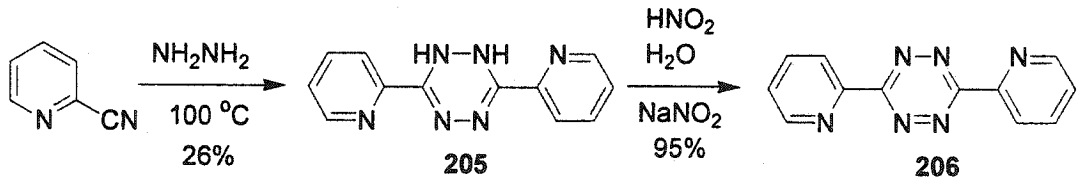
The synthesis of **204** utilized a method developed by Newman and coworkers. This method involved reacting anthranilic acid with isoamyl nitrate in DME for 1.5 h

followed by the addition of a refluxing solution of furan and DME.[99] The resulting isobenzofuran precursor **204** was obtained in 44% yield (Scheme 83).



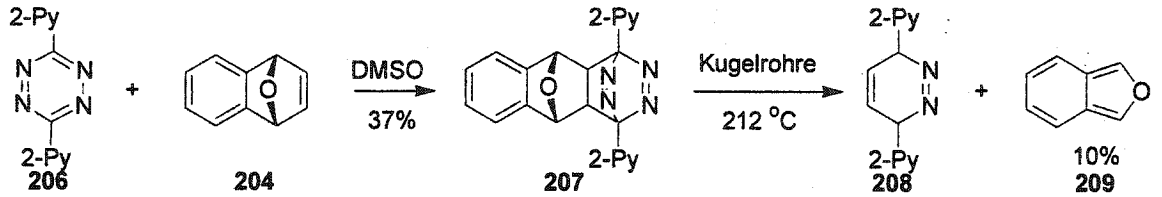
Scheme 83. Newman method to create precursor **204**.

The second precusor **206** was synthesized *via* intermediate **205**, which was made from 2-cyanopyridine and excess hydrazine hydrate in 26% yield. Intermediate **205** was converted to precursor **206** in 95% yield by dissolving **205** in glacial acetic acid and water at 0 °C followed by the slow addition of sodium nitrite (Scheme 84). NMR spectroscopy was the same as that published by Geldard.[100]



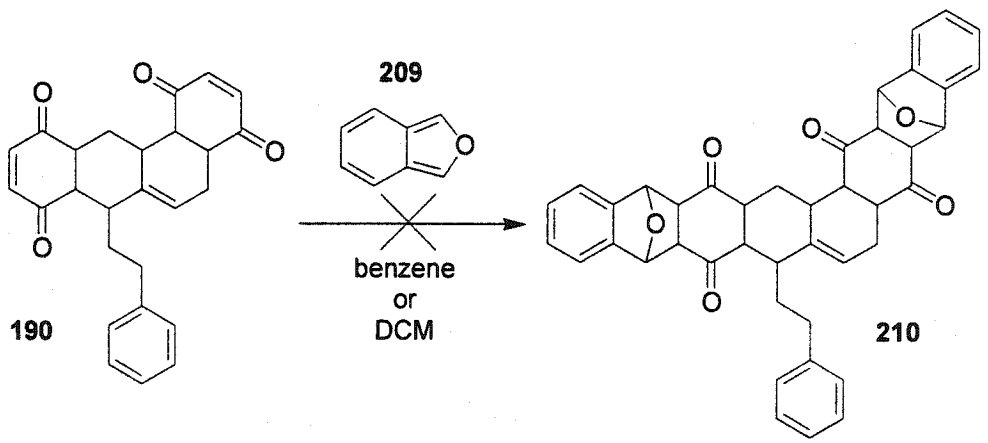
Scheme 84. The synthesis of precursor **206** from 2-cyanopyridine.

Precursors **204** and **206** were reacted together to form derivative **207** in 37% yield. Derivative **207** was then placed in a Kugelrohre and heated to 212 °C under water aspirator conditions to produce pyridazine **208** and isobenzofuran **209** in 10% yield (Scheme 85).



Scheme 85. Synthesis of isobenzofuran **206**.

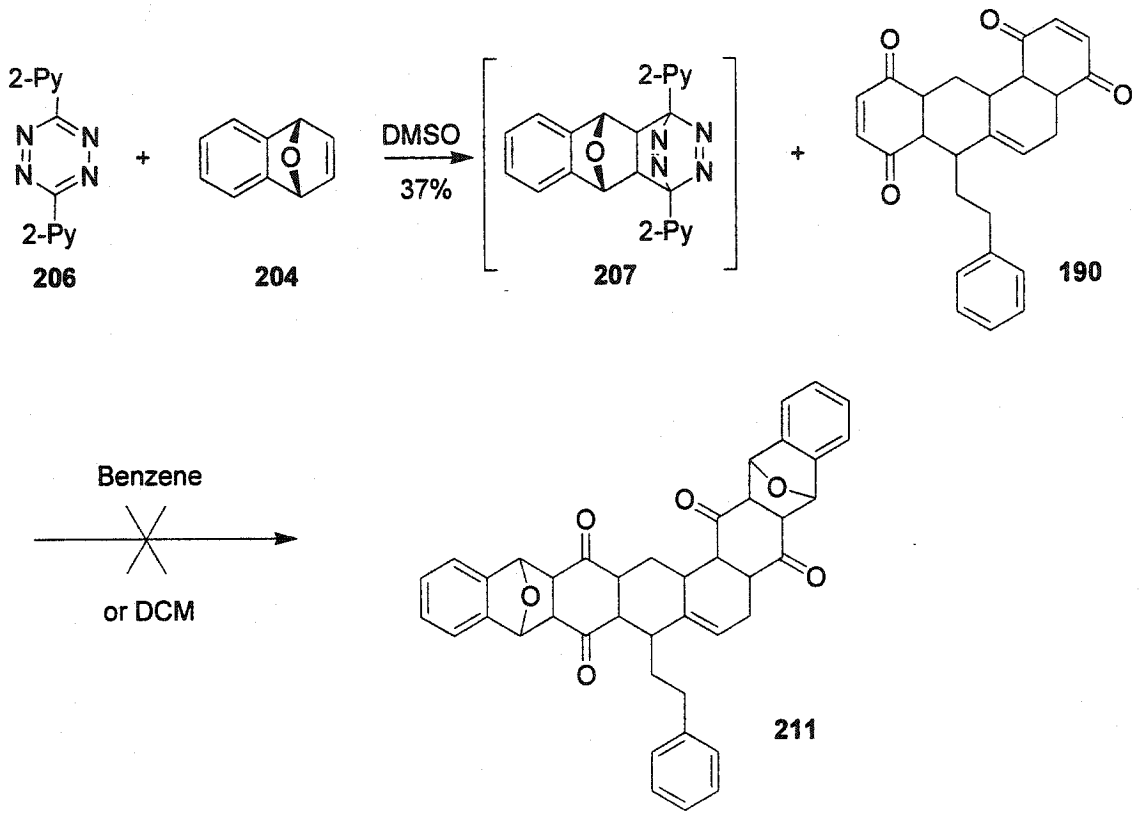
The newly formed isobenzofuran **209** was immediately partitioned into two equal portions and reacted with tetraketone **190** in both dichloromethane and benzene (Scheme 101). Both reactions resulted in the total recovery of tetraketone **190** instead of the desired bis-adduct **210**. This outcome was not surprising because isobenzofuran **209** was known to be unstable.[101]



Scheme 86. Attempted reaction of isobenzofuran **209** with tetraketone **190**.

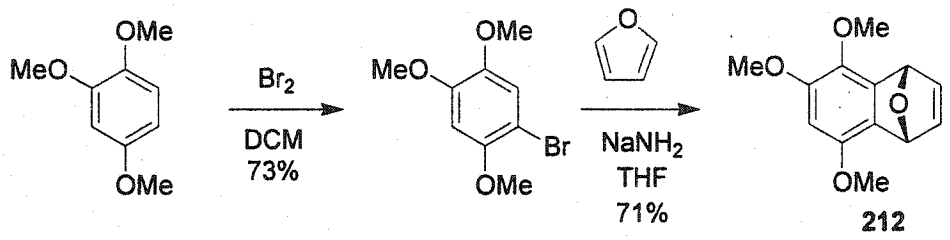
It was also known that derivative **207** was unstable in the solid state, but quite stable in solution below –20 °C. Decomposition was rapid at room temperature in both solid and solution state. Derivative **207** was also known to decompose into pyridazine **208** and isobenzofuran **209**.[101]As a result, a newly formed solution of **207** was reacted

with tetraketone **190** in both dichloromethane and benzene (Scheme 87). Both reactions were allowed to stir for 5 days and monitored by TLC. No reaction took place due to the rapid polymerization of isobenzofuran **209**. This reaction was faster than the transmissive Diels-Alder reaction.



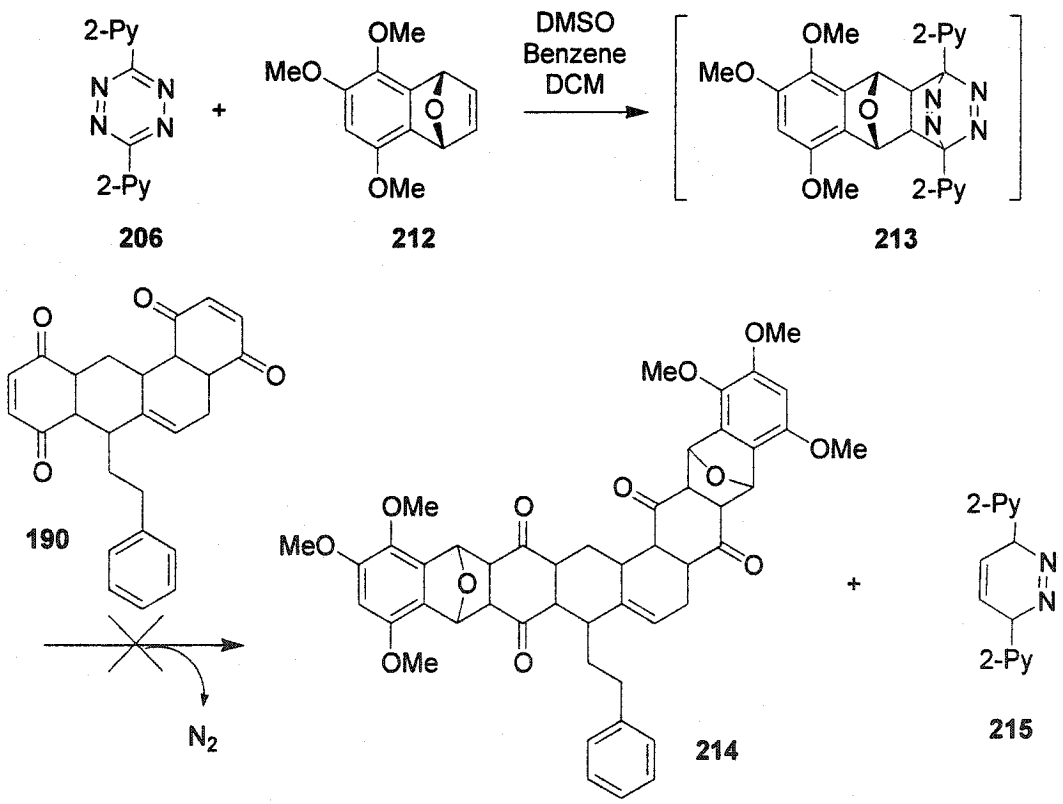
Scheme 87. Reaction of derivative **207** solution with tetraketone **190**.

Since isobenzofuran **209** was too unstable to isolate, thus its trisubstituted derivative **212** was synthesized from1,2,4-trimethoxybenzene in two steps in 72% yield overall yield (Scheme 88).[101]



Scheme 88. Synthesis of trisubstituted isobenzofuran derivative **212**.

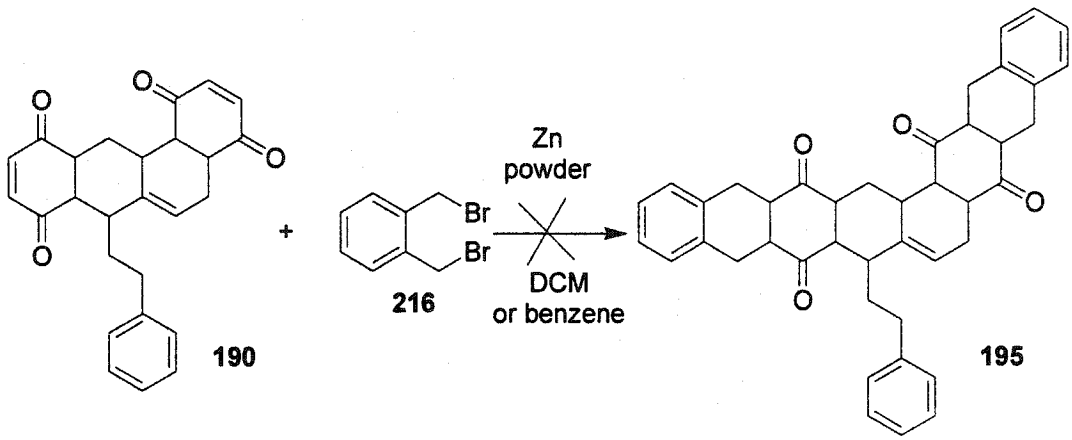
Precursor **206** was reacted with **212** in various solvents (dichloromethane, dimethylsulfoxide, and benzene) to produce intermediate **213** in the presence of tetraketone **190** (Scheme 89). The desired product **214** was again not obtained.



Scheme 89. Reaction of tetraketone **190** with intermediate **213**.

2.7.4. α,α'-DIBROMO-o-XYLENE

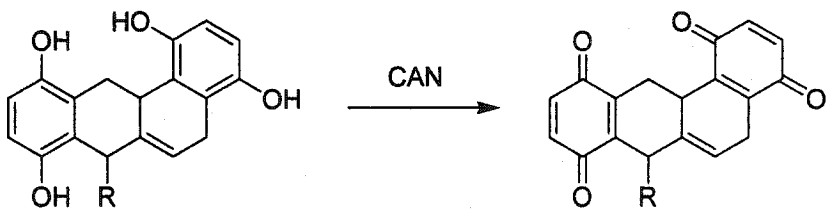
α,α'-Dibromo-o-xylene **216** was known to form diene **197** in the presence of zinc in THF.[102] Dibromine **216** and tetraketone **190** were dissolved in THF and Zn was added and put into a sonicator for various periods of time (1 to 24 h) resulting in the total recovery of starting materials (Scheme 90).



Scheme 90. The use of dibromine **216** to produce **195**.

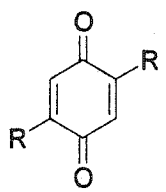
2.8. FUTURE WORK

If more time were available other options could have been considered. One option is to reoxidize tetraphenol compound and make compounds such as **220** and react again with o-quinodimethane species. An attractive possibility in future studies is to change the reactivity and stability of the various components. One possibility is to increase the reactivity of the quinone *via* the addition of electron withdrawing groups (Figure 7, Scheme 91). Activated quinones could be reacted with cross-conjugated trienes **160** to produce bis-adducts **217** that would act as a better dienophile than tetraketone **190**. These activated quinones would also potentially enable regiochemical control with non-symmetrical dienes.



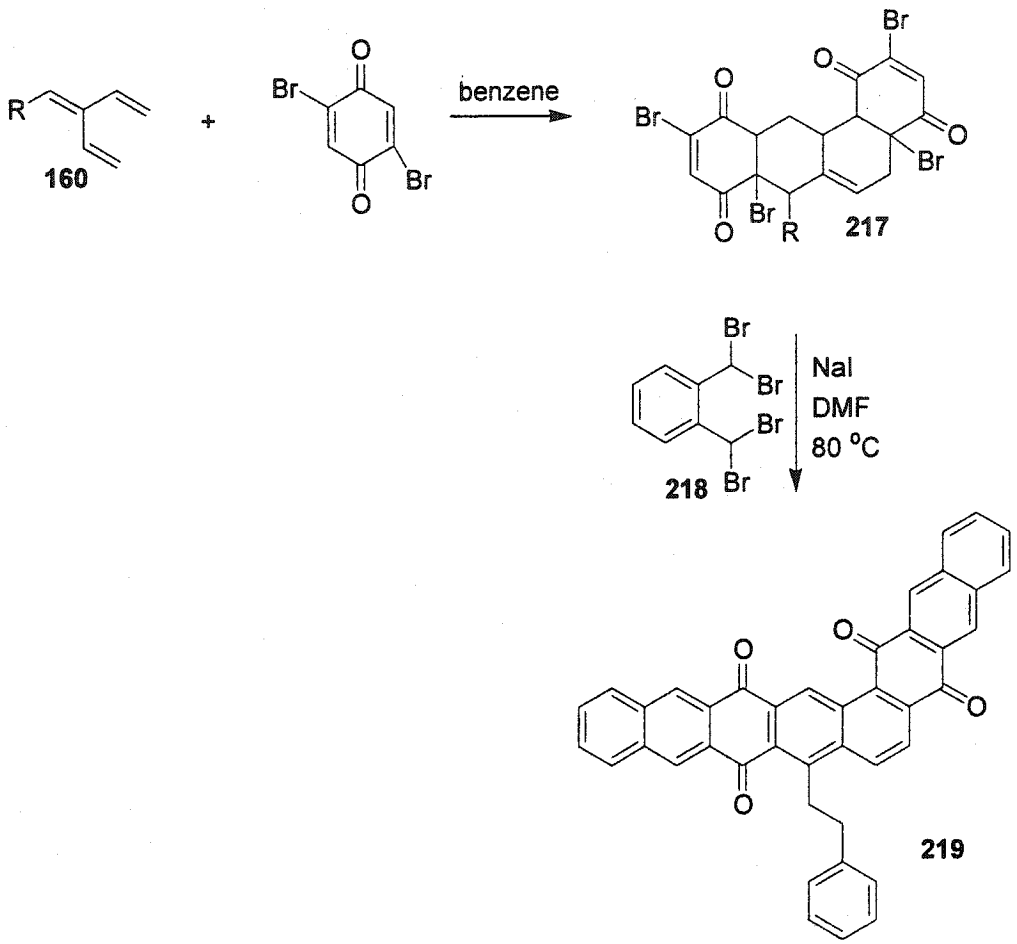
217 **218**

Scheme 91. Reoxidize tetraphenol with CAN.



R = Br, CO_2Me, CN, NO_2, CF_3

Figure 7. Activated quinones.



Scheme 92. Proposed synthesis of octaphene **219**.

3. CLAIMS TO ORIGINAL RESEARCH

1. The first example of a direct alkylation of the intermediate from the magnesium mediated carbometallation of propargyl alcohols was developed to provide diene alcohol **77**.
2. Alcohol **77** was converted to the stable enol ether **79** a new precursor for the unstable aldehyde **65**.
3. Progress has also been made in several routes by which nortaxoids can be synthesized.
4. Access to cross conjugated trienes generated *via* indium mediated chemistry has been expanded.
5. Discovered that triene **178** was being oxidized at the benzylic alcohol position by 1,4-benzoquinone to form an extended quinonethide species because triene **187** works without giving the hydroquinone.
6. Developed a better understanding of aphenes precursors including their preparation and reactivity towards dienophiles such as 1,2,3,4-tetrabromo-5,5-dimethoxycyclopenta-1,3-diene (**201**), isobenzofuran (**207** or **212**) or orthoquinodimethanes.

4. EXPERIMENTAL

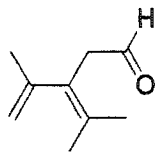
General. Melting points were determined in capillary tubes with a Thomas-Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were obtained either as a neat film on sodium chloride discs or as solutions in the solution cells. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FT-IR) and the data are reported in reciprocal centimetres (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were measured at 500MHz with a Bruker AMX500, at 300MHz with a Bruker Avance300, or at 200MHz with a Varian Gemini 200 spectrometer in deuterated chloroform unless otherwise stated. Carbon magnetic resonance was measured (^{13}C NMR) at 125MHz with a Bruker AMX500 in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad), number of protons and coupling constants (reported in Hz) are indicated in parentheses. Optical rotations were recorded on a Perkin-Elemer 241 polarimeter operating at 589nm. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using ionization energy of 70 eV.

Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in flame or oven dried glassware equipped with a magnetic stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. All reactions were monitored by thin layer chromatography (TLC) using commercial aluminum sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). The TLC spots were viewed under ultraviolet light and by heating the TLC plate after treatment with a stain, either with a

5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or permanganate (3.0 g $KMnO_4$, 20.0 g K_2CO_3, 5.0mL 5% NaOH, 300.0mL H_2O). Product purification by conventional and flash column chromatography was performed using E. Merck Silica Gel (70-230 or 2230-400 mesh), unless otherwise stated. Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a rotary evaporator connected to an air or water aspirator. Trace solvents were removed on a vacuum pump. All compounds were stored at –15 °C in vials flushed with nitrogen. All Grignard reagents were purchased from Aldrich Chemical Company or Fluka Chemika-BioChemika and titrated against diphenyl ditelluride prior to their use.

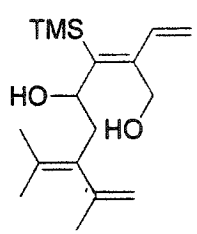
Petroleum ether is a mixture of hydrocarbons with boiling point range of 30 to 60 °C. Anhydrous diethyl ether (a.k.a. ether), anhydrous tetrahydrofuran (THF) were freshly distilled from a benzophenone/sodium still. Dry benzene, toluene, dimethylformamide (DMF), dichloromethane (DCM), triethylamine, diisopropylamine, diisopropylethylamine and cyclohexane were distilled from NaH or CaH or were purchased as analytical grade reagents and placed over activated molecular sieves. All commercial starting materials were purchased from Aldrich Chemical Company unless otherwise stated.

3-Isopropenyl-4-methyl-pent-3-enal (65)



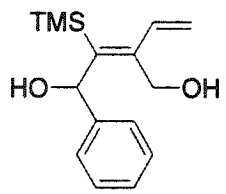
CH_2Cl_2 (20 mL) and enol ether **79** (0.20 g, 1.31 mmol) were placed in a 50 mL flask. The flask and its contents were cooled to 0 °C and 2% hydrochloric acid (1 mL, 1.8 mmol) was added. After 5 minutes water (10 mL) was added and the two layers were separated. The aqueous layer was washed with ether (3 x 50 mL). The organic extracts were combined, washed with saturated sodium chloride solution (3 x 50 mL) dried over $MgSO_4$, filtered and concentrated. Product was purified *via* flash chromatography (10:1, petroleum ether/ether) resulting in 73% (0.10 g) yield. ^1H NMR ($CDCl_3$, 300MHz): δ 1.63 (s, 3H), 1.71 (s, 6H), 3.11 (d, 2H), 4.60-4.62 (m, 1H), 4.91-4.92 (m, 1H), 9.50 (t, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 20.2, 22.2 22.8, 47.2, 114.5, 127.4, 131.9, 146.4, 200.3; IR (neat) *v* 3077, 2969, 2722, 1725, 1444, 1374, 899 cm^{-1}; HRMS for $C_9H_{14}O$ calculated 138.1045; found 138.1048.

6-Isopropenyl-7-methyl-3-trimethylsilanyl-2-vinyl-octa-2, 6-diene-1, 4-diol (73)



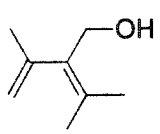
Alcohol **71** (0.61 g, 4.76 mmol) was added to a 100 mL flask containing THF (20 mL). The solution was cooled to 0 °C and vinylmagnesium chloride (6.2 mL, 10.89 mmol) was added dropwise. The reaction mixture was then allowed to warm to 21 °C and heated to reflux for 20 h. After cooling to –78 °C, the aldehyde **65** (0.22 g, 1.59 mmol) was added. The reaction was allowed to warm to 21 °C and stir for 18 h. Saturated ammonium (20 mL) was added to the reaction at 0 °C. The aqueous layer was washed with ether (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. Product was purified *via* column chromatography (1:1, pet. ether/ether) in 27% (0.13 g) yield. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.16 (s, 9H), 1.65 (s, 3H), 1.66 (s, 3H), 1.74 (m, 3H), 2.20 (dd, J = 5.3, 14.1Hz, 1H), 2.54 (s, 1H), 2.62 (dd, J = 8.4, 14.1Hz, 1H), 4.24 (d, J = 12.0Hz, 1H), 4.36 (d, J = 12.0Hz, 1H), 4.66 (m, 1H), 4.84 (dd, J = 5.3, 8.4 Hz, 1H), 4.96-4.98 (m, 1H), 5.10 (dd, J = 1.2, 11.2Hz, 1H), 5.42 (dd, J = 1.2, 17.7Hz, 1H), 6.63 (dd, J = 11.2, 17.5Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 1.6, 13.1, 20.2, 22.2, 37.0, 57.2, 70.2, 114.1, 114.3, 129.0, 131.9, 133.4, 134.9, 141.1, 146.4; IR (neat) ν 3469, 2941, 2856, 1635, 1475, 1053 cm^{-1}; HRMS for $C_{17}H_{30}O_2Si$ calculated 294.2015; found 294.2007.

1-Phenyl-2-trimethylsilanyl-3-vinyl-but-2-ene-1, 4-diol (74)



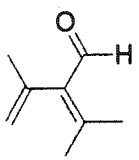
Alcohol **71** (0.52 g, 3.90 mmol) and THF (10 mL) were added to a 3-neck 50 mL flask equipped with a condenser and dropping funnel. The solution was cooled to 0 °C and vinylmagnesium chloride (6.10 mL, 10.37 mmol, 1.7 M) was added drop wise through the dropping funnel over 10 min. The reaction mixture was then heated at reflux for 18 h forming a cloudy suspension with a slight brown/green colour. Again the reaction was cooled to 0 °C and benzaldehyde (1.1 mL, 10.33 mmol, 1.044 g/mL) was added *via* dropping funnel. An additional amount of THF was added and the reaction was stirred for 15 min. Upon warming the reaction to 21 °C, it was stirred for 1 h. The reaction was worked up in the usual manner followed by column chromatography (3:1, pet. ether/ether) to produce **74** in 96% (0.99 g) yield. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.09 (s, 9H), 4.32 (s, 2H), 5.28 (d, J = 11.07 Hz, 1H), 5.51 (d, J = 17.36Hz, 1H), 5.86 (s, 1H), 6.80 (dd, J = 17.44, 11.17 Hz, 1H), 7.23 – 7.33 (m, 5H). ^{13}C NMR ($CDCl_3$, 75MHz): δ 1.8, 58.1, 73.4, 115.3, 126.3, 127.1, 128.4, 137.8, 143.8, 147.1, 148.6; IR (NaCl) v 3379, 2956, 2898, 1494, 1450 cm^{-1}; HRMS calculated for $C_{15}H_{23}O_2Si$ (M^+ - H_2O) 244.1284; found 244.1279.

2-Isopropenyl-3-methyl-but-2-en-1-ol (77)



2-Butyn-1-ol (2.34 g, 33.42 mmol, 0.937 g/mL) was placed in a 250 mL flask containing $MgCl_2$ (3.50 g, 36.76 mmol) partially dissolved in cyclohexane (230 mL) and allowed to stir for 5 to 10 min. The reaction mixture was cooled to –78 °C and isopropenyl magnesium bromide (153.74 mL, 76.87 mmol, 0.935 g/mL) was added drop wise. The reaction was warmed to 21 °C and then heated to reflux for 18 h. *t*-BuLi (25.71 mL, 33.42 mmol, 1.30 M) was added at –78 °C and allowed to stir for 45 min. The reaction was warmed to 0 °C and CH_3I (31.21 mL, 501.13 mmol, 2.280 g/ml) was added drop wise and stirred for another 2 h. Saturated ammonium chloride was added and the organic and aqueous phases were separated. The aqueous phase was washed with ether (2 x 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The product was purified *via* column chromatography (4:1, pet. ether/ether) to produce pale yellow oil in 37% (1.56 g) yield. ^1H NMR ($CDCl_3$): δ 1.62 (s, 3H), 1.67 (s, 3H), 1.73 (s, 3H), 4.06 (s, 2H), 4.68 (m, 1H), 4.96 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 19.5, 21.9, 22.7, 60.5, 114.7, 129.8, 136.2, 145.1; IR (neat) *v* 626, 2920, 3032, 3388 cm^{-1}; HRMS calculated for $C_8H_{14}O$ 126.1045; found 126.1031.

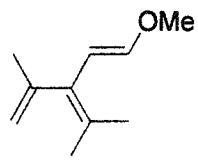
2-Isopropenyl-3-methyl-but-2-enal (78)



Alcohol 77 (0.089 g, 0.71 mmol) was added to a solution of DMP (0.43 g, 1.48 mmol) in DCM (8 mL) and H_2O (0.013 mL, 0.71 mmol, 1.0 g/mL) and stirred at room

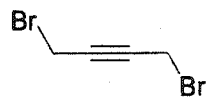
temperature for 3 h. The reaction was worked up in the usual way and purified *via* column chromatography (1:1, Pet. Ether/ether) to produce **78** in 57% (0.05 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 6H), 1.67 (s, 3H), 4.25-4.30 (m, 1H), 4.58-4.62 (m, 1H), 9.98 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.5, 21.9, 22.7, 114.7, 127.8, 131.2, 145.1, 200.6; IR (neat) *v* 1671, 2857, 2905, 3079, 3467 cm^{-1}; HRMS calculated for $C_8H_{12}O$ 124.0888; found 124.0825.

3-(2-Methoxy-vinyl)-2,4-dimethyl-penta-1,3-diene (79)



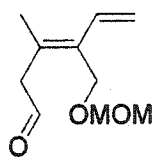
Potassium *t*-butoxide (0.65 mL, 4.81 mmol, 0.902 g/mL) and triphenylmethoxyphosphonium chloride (1.64 g, 4.81 mmol) were dissolved in THF (20 mL). Aldehyde **78** (0.50 g, 4.00 mmol) was then added dropwise to the reaction mixture. The reaction was worked up in the usual manner and purified *via* column chromatography (3:2, pet. ether/ether) to produce enol **79** in 40% (0.20 g). ^{1}H NMR ($CDCl_3$): δ 1.70 (s, 3H), 1.74 (s, 3H), 1.80 (s, 3H), 4.16 (s, 3H), 4.69 (m, 1H), 5.04 (m, 1H), 7.17 (dt, J = 1.66, 5.96Hz, 1H), 7.41 (dt, J = 1.00, 6.71Hz, 1H), 7.96 (dd, J = 1.16, 6.17Hz, 1H), 8.03 (dd, J = 0.83, 7.09Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.6, 19.7, 22.1, 22.3, 60.6, 115.1, 122.4, 128.1, 132.0, 133.5, 142.0, 201.3; IR (neat) *v* 626, 2920, 3032, 3388 cm^{-1}; HRMS calculated for $C_{10}H_{16}O$ 152.1201; found 152.1195.

1, 4-Dibromobut-2-yne (101)



2-Butyne-1, 4-diol (10.8 g, 0.13 mol) was dissolved in DCM in a round bottom flask with the aid of a heat gun. The solution was cooled to 0 °C and 48% HBr (15.0 mL, 0.28 mol) was added dropwise. The reaction mixture was then allowed to warm to room temperature (21 °C) and stir for one hour. The resulting biphasic mixture was separated. The aqueous phase was extracted with diethyl ether (3 x 20 mL), dried over $MgSO_4$ and concentrated by blowing nitrogen gas over it. The aqueous product was isolated from the solid starting material by filtration to obtain the pure product in 35% (9.94 g). ^{1}H NMR ($CDCl_3$, 200MHz): δ 5.26 (4H, s, CH_2Br); ^{13}C NMR ($CDCl_3$): δ 19.6, 75.5; IR (neat) *v* 2857, 2905, 3080, 3467 cm^{-1}.

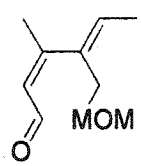
4-Methoxymethoxymethyl-3-methyl-hexa-3, 5-dienal (111)



IBX (1.31 g, 4.67 mmol) was dissolved in DMSO (20 mL). Alcohol **110** was then added as a solution of DMSO (10 mL). The reaction was monitored via TLC. No change in R_f occurred over a 1 h period. H_2O (10 mL) was added and the white

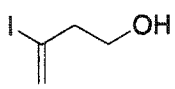
precipitate formed was filtered. The organic layer was separated from the aqueous layer, which was washed with ether (3 x 50 mL). Organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. The product was purified via flash chromatography (2:1, pet. ether/ether) in a 10% (1.18 g) yield. **Or** alcohol **110** (0.12 g, 0.64 mmol) was dissolved in CH_2Cl_2 (10 mL) and placed in a 50 mL flask containing DMP (0.21 g, 0.71 mmol) dissolved in DCM (10 mL). After stirring for 1 h the reaction mixture was a light, creamy yellow. The reaction mixture was diluted with ether (10 mL). The resulting suspension of iodinane was added to 1.3 M NaOH solution (20 mL) to hydrolyze the 2-iodobenzate. The reaction was then stirred for another 10 min. The ether layer was extracted with 1.3 M NaOH solution (20 mL) and H_2O (20 mL). The organic layer was then collected and the aqueous layer was washed with ether (3 x 25 mL). Organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. Crude yield of aldehyde was 100% (11.78 g). ^1H NMR ($CDCl_3$MHz): δ 1.63 (s, 3H), 3.19 (s, 3H), 5.10 (m, 1H), 5.53 (m, 1H), 6.67 (dd, J = 11.16, J = 6.22, 1H), 9.25 (t, J = 0.89, 1H); ^{13}C NMR ($CDCl_3$): δ 19.3, 36.1, 55.4, 63.0, 70.8, 95.7, 114.1, 128.4, 134.9, 200.1; IR (neat) ν 953, 1031, 1094, 1369, 1444, 1626, 1738, 2884, 2947, 3091, 3436 cm^{-1}; HRMS calculated for $C_{13}H_{16}O_3$ 184.1099; found 184.1059.

4-(2-Methoxy-ethyl)-3-methyl-hexa-2, 4-dienal (114)



A solution of DMSO (12.0 mL, 169.44 mmol, 1.101 g/mL) and DCM (60 mL) was cooled to –78 °C. Oxalyl chloride (7.4 mL, 84.72 mmol, 1.455 g/mL) was added and the reaction mixture was stirred for 10 min. Alcohol **110** (7.01 g, 38.51 mmol) was dissolved in DCM (36 mL) and added to the reaction mixture. The reaction was then stirred for 1 h at –78 °C. Triethylamine (27.0 mL, 192.54 mmol, 0.726 g/mL) was added and the reaction was warmed to 0 °C. 1M sodium thiosulfate solution (75 mL) was then added and the organic layer was separated. The aqueous layer was washed with ether (3 x 50 mL). Organic extacts were combined, dried over $MgSO_4$, filtered and concentrated. Product was purified *via* flash chromatography (10:1, pet. ether/ether) in 72% (5.10 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.91 (d, J = 7.03Hz, 3H), 2.29 (s, 2H), 3.37 (s, 3H), 4.30 (s, 2H), 4.61 (s, 3H), 6.19 (d, J = 7.71Hz, 1H), 6.35 (q, J = 7.07Hz, 1H), 10.12 (d, J = 7.83Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.5, 55.6, 61.4, 95.8, 126.2, 134.1, 137.7, 156.4, 191.9; IR (neat) ν 1662, 2884, 2934 cm^{-1}; HRMS calculated for $C_{10}H_{16}O_3$ 183.9750; found 184.1080.

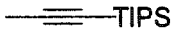
3-Iodo-but-3-en-1-ol 1 (138)



CH_3CN (20 mL) was placed in a 100 mL flask, 3-butyn-1-ol (1.0 mL, 13.2 mmol, 0.926 g/mL) was then added followed by trimethylsilylchloride (1.68 mL, 13.2 mmol, 0.856 g/mL) and sodium iodide (1.98 g, 13.2 mmol). The reaction was stirred for 10 min before H_2O (10 mL) was added. The reaction mixture was then allowed to stir for 18 h.

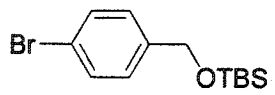
Saturated ammonium chloride solution (25 mL) was added and the aqueous layer was separated and washed with ether (2 x 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. Product was purified by column chromatography (7:3, pet. ether/ether) in 41% (1.07 g) yield. ^1H NMR ($CDCl_3$, 500MHz): δ 2.63 (td, J = 5.43, 0.99Hz, 2H), 3.85 (t, J = 5.43Hz, 2H), 6.12 (d, J = 1.59Hz, 1H) 6.15 (dd, J = 1.59, 0.99Hz, 1H). ^{13}C NMR ($CDCl_3$, 500MHz): δ 44.5, 62.1, 97.6, 122.5; IR (neat) ν 900, 1617, 2954, 3442 cm^{-1}; HRMS for C_4H_7OI calculated 197.9542; found 197.9503.

Triisopropyl-prop-1-ynyl-silane (145)



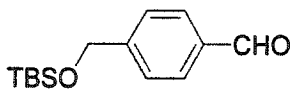
Triisopropylacetylene (1.3 mL, 5.80 mmol, 0.813 g/mL) was added to THF (20 mL) which was cooled to 0 °C. *t*-BuLi (3.86 mL, 5.80 mmol, 1.5 M) was then added and stirred for 45 min. Methyl iodide (0.72 mL, 11.59 mmol, 2.275 g/mL) was added next and stirred for 15 min before being warmed to 21 °C and stirred for 30 min. Saturated ammonium chloride solution (20 mL) was added and the organic layer was separated. The aqueous layer was washed with ether (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Product was made in 100% yield. ^1H NMR ($CDCl_3$): δ 1.19 – 1.22 (m, 21H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 4.8, 12.2, 19.3; IR (neat) ν 2177, 2866, 2950 cm^{-1}; HRMS calculated for $C_{12}H_{24}Si$ 196.1648; found 196.1639.

(4-Bromo-benzyloxy)-*tert*-butyldimethylsilane (175)



4-Bromobenzyl alcohol (4.52 g, 24.19 mmol) was added to a solution of TBSCl (4.01 g, 26.61 mmol), imidazole (1.81 g, 26.61 mmol) and DCM (50 mL) at 0 °C for 1 h. The reaction was then worked up in the usual manner. Bromine **175** was purified via column chromatography (3:1, pet. ether/ether) in 100% (1.14 g). ^{1}H NMR ($CDCl_3$): δ0.010 (s, 6H), 0.94 (s, 9H), 4.68 (s, 2H), 7.43 (d, J = 8.5Hz, 2H), 7.45 (d, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ-5.1, 18.6, 25.9, 26.1, 64.5, 120.8, 127.9, 131.5, 140.7; IR (neat) ν 2956, 2930, 2885, 2857 cm^{-1}; HRMS calculated for $C_{13}H_{21}BrOSi$ 300.5045; found 300.5023.

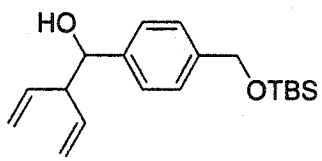
4-(*tert*-butyl-dimethyl-silanyloxymethyl)-benzaldehyde (176)



Bromine **175** (2.09 g, 6.95 mmol) and THF (50 mL) were added to a 250 mL round bottom flask and cooled to –78 °C. A 1.2 M solution of *t*-BuLi (12.17 mL, 1.2 M, 14.60 mmol) was then added dropwise, turning the solution from pale yellow to orange colour. The reaction was permitted to stir for 15 min before DMF (1.62 mL, 20.86 mmol, 0.944 g/mL) was added causing the solution to change from orange to pale yellow

in colour. After stirring for 40 min at –78 °C, the reaction was warmed to 22 °C and saturated ammonium chloride solution was added. The aqueous layer was washed with diethyl ether (3x). Organic extracts were combined, dried over $MgSO_4$ and concentrated. The product was purified *via* column chromatography (3:1; pet. ether/ether; R_f = 0.69) resulting in 95% (1.65 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.096 (s, 6H), 0.94 (s, 9H), 4.79 (s, 2H), 7.47 (dd, *J* = 0.3Hz, 8.05Hz, 2H), 7.82 (d, *J* = 8.13Hz, 2H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$): δ-5.1, 18.6, 26.1, 64.7, 126.4, 130.0, 135.6, 148.9, 192.2; IR (neat) *v* 2956, 2930, 2885, 2857, 1728 cm^{-1}; HRMS for $C_{14}H_{22}O_2Si$ calculated 250.1390; found 250.1357.

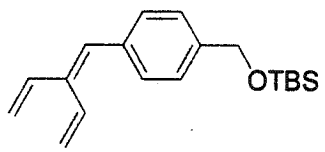
1-[4-(tert-Butyl-dimethyl-silanyloxymethyl)-phenyl]-2-vinylbut-3-en-1-ol (177)



Indium metal (0.60g, 5.19 mmol), 100 mesh, was added in one portion to a vigorously stirred solution of aldehyde **176** (1.00g, 4.00 mmol) and 5-bromo-1,3-pentadiene (1.18g, 7.99 mmol) in DMF at 0 °C. The reaction mixture was stirred at room temperature for 18 h and diluted with DCM (50 mL). The diluted solution was then poured slowly to stirring EtO_2 (100 mL) and the resulting cloudy solution was filtered through a pad of silica, which was washed with portions of EtO_2 (3 x 20 mL). Solvent was then removed and the resulting oil was purified via column chromatography (3:1; pet. ether/ether) in 96% (1.22 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.084 (s, 6H), 0.93 (s, 9H), 2.21 (s, 1H), 3.08 (q, *J* = 7.24, 7.82Hz, 1H), 4.56 (d, *J* = 7.04Hz, 1H), 4.72 (s, 2H), 4.98-

5.04 (m, 2H), 5.14-5.22 (m, 2H), 5.63-5.70 (dddd, J = 6.84, 7.06, 7.13,10.35Hz, 1H), 5.80-5.87 (dddd, J = 7.06, 8.13, 8.20, 9.73Hz, 1H), 7.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ -5.2, 18.4, 26.0, 56.1, 64.8, 76.1, 116.9, 118.1, 125.9, 126.7, 136.8, 136.9, 140.5, 140.9; IR (neat) ν 3455, 3080, 2956, 2930, 2885, 2858 cm^{-1}; HRMS for $C_{19}H_{30}O_2Si$ (-$C_6H_{15}OSi$) calculated 187.1142; found 187.1099.

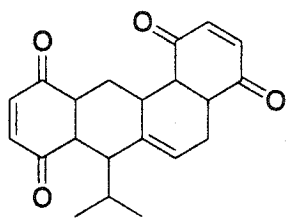
Tert-butyldimethyl-[4-(2-vinylbuta-1,3-dieny)-benzyloxy]silane (178)



DEAD (0.87 mL, 5.54 mmol, 1.106 g/mL) was added dropwise to a solution containing alcohol **177** (1.18 g, 3.69 mmol) and triphenyl phosphine (1.45 g, 5.54 mmol) in benzene (50 mL) at 0 °C. The initially yellow solution decolourised quickly, but upon complete addition the reaction became yellow again. The solution was heated to 50 °C for 24 h. After allowing the reaction to cool to 22.1 °C, the reaction was diluted with petroleum ether, forming a cloudy solution. The mixture was filtered through a 1 cm pad of silica and washed with petroleum ether forming an orange coloured solution. Solvent was removed to make an orange oil that was purified *via* flash column chromatography (10:1; petroleum ether/ether) forming a pale pink oil in 69% (0.77 g) yield (R_f = 0.95). ^{1}H NMR ($CDCl_3$): δ 0.088 (s, 6H), 0.96 (s, 9H), 4.73 (s, 2H), 5.17-5.20 (dd, J = 0.37, 0.53Hz, 1H), 5.32-5.35 (dd, J = 1.37, 1.63Hz, 1H), 5.41-5.45 (dd, J = 0.58, 0.61Hz, 1H), 5.50-5.53 (d, J = 1.58Hz, 1H), 6.51-6.56 (ddd, J = 0.90, 6.73, 10.72Hz, 1H) 6.62 (s, 1H),

6.67-6.72 (ddd, J = 6.63, 11.12, 17.76Hz, 1H), 7.23-7.33 (m, 4H); ^{13}C NMR ($CDCl_3$): δ – 5.2, 18.4, 25.9, 29.7, 64.8, 115.8, 118.2, 125.8, 129.5, 129.6, 133.6, 135.8, 137.6, 137.9, 140.4; IR (neat) ν 3020, 2956, 2930, 2885, 2858 cm^{-1}; HRMS for $C_{19}H_{28}OSi$ calculated 300.1911; found 300.1849.

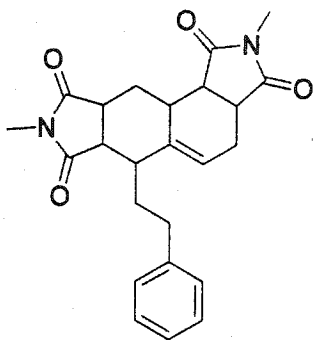
7-Isopropyl-4a, 5, 7, 7a, 11a, 12,12a, 12b-octahydro-benzo[a]anthracene-1, 4, 8, 11-tetraone (188)



Triene **185** (0.096 g, 0.78 mmol) was added to a solution of 1,4-benzoquinone (0.17 g, 1.57 mmol) and benzene (10 mL). The reaction was allowed to stir at room temperature for 2 days. The resulting cream powder was filter, washed with Et_2O (3 x 20 mL) and dried to produce tetraketone **188** in 13% (0.34 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.61 – 0.62 (d, J = 6.0 Hz, 3H), 0.67 – 0.68 (d, J = 6.5 Hz, 3H), 0.95 –1.01 (td, J = 5.7, 12.8Hz, 1H), 1.44 – 1.48 (m, 1H), 2.06 – 2.11 (dd, J = 4.8, 18.5Hz, 1H), 2.15 – 2.18 (m, 1H), 2.27 –2.30 (dd, J = 5.4, 9.9Hz, 1H), 2.47 – 2.50 (m, 1H), 2.87 –2.91 (dd, J = 4.8, 18.5Hz, 1H), 2.99 –3.02 (t, J = 5.6 Hz, 1H), 3.15- 3.17 (t, J = 6.0Hz, 1H), 3.22 – 3.25 (t, J = 6.8 H, 1Hz), 3.29 – 3.31 (t, J = 6.3 Hz, 1H), 5.48 – 5.49 (m, 1H), 6.70 – 6.83 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.4, 23.9, 26.7, 29.2, 32.3, 43.7, 46.1, 49.7, 55.1, 56.7, 119.4,

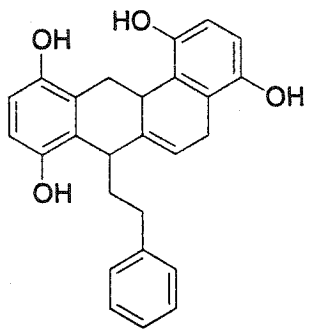
139.1, 141.0, 141.2, 141.5, 141.9, 198.1, 198.7, 200.4, 200.6; IR (neat) ν 2966, 2920, 1674 cm^{-1}; HRMS for $C_{21}H_{22}O_4$ calculated 338.1518; found 338.1498.

2, 8-Dimethyl-6-phenethyl-3a, 4, 6, 6a, 9a, 10, 10a, 10b-octahydro-isoindolo[5, 6-e] isoindole-1, 3, 7, 9-tetraone (191)



Triene **187** (0.10 g, 0.54 mmol) was placed in a 10 mL round bottom flask containing benzene (5 mL). *N*-methylmaleimide (0.19 g, 1.09 mmol) was then added and the reaction was allowed to stir at 21 °C for 24h. The reaction mixture was then filtered with at sintered glass funnel and a pale grey powder was collected in 55% (0.1207g) yield. ^1H NMR ($CDCl_3$): δ 1.92-2.13 (m, 4H), 2.32-2.36 (m, 1H), 2.46-2.48 (m, 1H), 2.55-2.58 (m, 1H), 2.70-2.82 (m, 3H), 2.88-2.89 (m, 6H), 3.00-3.05 (m, 2H), 3.14-3.22 (m, 2H), 5.61-5.62 (m, 1H), 7.15-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 23.0, 24.7, 24.8, 24.8, 29.7, 33.5, 33.9, 37.2, 39.8, 40.0, 41.5, 43.2, 120.4, 126.0, 128.3, 128.5, 140.4, 141.8, 177.6, 177.7, 179.4, 179.8; IR (neat) ν 2938, 1768, 1681 cm^{-1}; HRMS: Calculated for $C_{24}H_{26}N_2O_4$ 406.1893; found, 406.1897.

7-Phenethyl-5,7,12,12a-tetrahydro-benzo[a]antracene-1,4,8,11-tetraol (199)



Tetraketone **190** (0.10 g, 0.26 mmol) was placed in a 10 mL flask containing benzene (5 mL). MnO_2 (0.22 g, 2.57 mmol) was added to the solution and the reaction was heated to reflux for 18 h. The reaction was cooled to room temperature, filtered and dried to produce **199** as a light brown powder in 96% (0.10 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.80-1.87 (m, 1H), 2.04-2.06 (m, 1H), 2.17-2.22 (dd, J = 11.74, 16.68Hz, 1H), 2.43-2.49 (m, 1H), 2.61-2.74 (m, 2H), 3.01 (s, 4H), 3.24-3.29 (m, 1H), 3.42-3.48 (dt, J = 3.85, 14.78Hz, 1H), 3.62-3.65 (dd, J = 2.94, 7.95Hz, 1H), 3.85-3.89 (dd, J = 5.74, 10.98Hz, 1H), 4.00-4.05 (m, 1H), 5.79-5.80 (m, 1H), 6.56 (dq, J = 8.47, 12.36, 16.04Hz, 4H), 7.09-7.13 (m, 1H), 7.21-7.24 (m, 4H), 7.44 (s, 1H), 7.63 (s, 1H), 7.67 (s, 1H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.9, 34.3, 35.2, 35.7, 44.9, 112.9, 113.1, 113.3, 113.6, 118.3, 126.3, 129.0, 129.3, 138.4, 143.7, 148.5, 148.7, 149.0; IR (neat) ν 3598, 3500, 2938, 2920 cm^{-1}; HRMS calculated for $C_{26}H_{24}O_4$ 400.1682; found 400.1683.

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