Studies Towards the Synthesis of Popolohuanone E

by

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GLASGOW G12 8QQ.

...to my butterfly.

I go down to the water

Dive as deep as Man can go

To those back places

Where the underwater flows.....

Exploring the Blue

That's where I'll go

Luka Bloom

Summary

The marine natural product Popolohuanone E has been the target for total synthesis. This C_{42} marine sponge metabolite, which contains two identical *cis*-decalin moieties, was first approached by a route starting from 3,4-dimethylcyclohex-2-enone *via* two stereospecific cuprate addition reactions. The known decalin (±)-3,4,4aβ,5,6,7,8,8a-octahydro-1β-hydroxymethyl-5,6,8aβ-trimethyl-5β-vinyl-2(1*H*)-naphthalenone was synthesised by this route and subsequent elaboration carried out. After deoxygenation of the carbonyl group and further manipulation, the novel aldehyde, (±)-1,2,3,4, 4aβ,5,6,7,8,8a-decahydro-1β-*tert*-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl-5β-formyl naphthalene, was obtained. Further elaboration of the aldehyde to the pseudo-monomeric carbon skeleton of popolohuanone E was not possible.

Secondly a new route to the *cis*-decalin moiety was attempted. This involved synthesis of 1-iodo-3,4-dimethyl-6-trimethylsilylhex-4-ene from tiglic aldehyde by a route involving an Eschenmoser-Claisen rearrangement. Unfortunately due to time constraints the coupling of this iodide with the ketal of 2-bromo-1-cyclohex-2-enone and the subsequent intramolecular Hosomi-Sakurai cyclization were not accomplished.

Finally attention was turned to developing a reliable route to the pseudo-monomer utilising a benzylic cuprate addition. Even after extensive experimentation with various enones, the desired adducts proved to be elusive.

Abbreviations

Ac	acetyl
acac	acetylacetone
aq.	aqueous
AIBN	azobis(isobutyronitrile)
Chex	cyclohexyl
cod	cyclooctadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DPPE	bis(diphenylphosphino)ethane
DPPF	bis(diphenylphosphino)ferrocene
DPPP	bis(diphenylphosphino)propane
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	hexamethylphosphoramide
IR	infra red
LHMDS	lithium hexamethyldisilazide
L.R.M.S.	low resolution mass spectrum
MsCl	methanesulfonyl chloride
mCPBA	*meta*-chloroperbenzoic acid
MVA	mevalonic acid
NCS	*N*-chlorosuccinimide

NMR	nuclear magnetic resonance
Pcy	cyclopentyl
py	pyridine
PP	pyrophosphate
THF	tetrahydrofuran
TBS	*tert*-butyldimethylsilyl
TMS	trimethylsilyl
pTSA	*para*-toluenesulfonic acid
TFA	trifluoroacetic acid
TLC	thin layer chromatography
THP	tetrahydropyran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

Acknowledgements

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The greatest thanks go to Geraldine for tolerating me during this work and as a friend; always in your debt.

Table of Contents

1. Marine Natural Products - Introduction

360 Million years ago animals began to leave the sea and colonise land.[1] Evolution took place in this new land environment and fashioned what we are today. Throughout this time evolutionary processes also took place within the vast oceans of the world to give rise to the variety of marine life now in existence. This environment has given rise to a fascinatingly diverse and different world from that around us on land. It is this fascination which has drawn scientists from all fields back towards the sea in order to investigate the differences that this marine environment has made. The differences are evident at a metabolic level and give rise to a wonderful array of structurally fascinating secondary metabolites of great interest to the chemist. One of the major advantages the human race might gain from this exploration is the discovery of many biologically active marine natural products, which in turn may lead to the next generation of therapeutic agents, essential for the well being of the species.

Approximately 6500 marine natural products have been isolated to date and with the continued interest in this area, and the technological advances that allow for their structural elucidation, this number will continue to grow rapidly.[2] The heightened interest of late is evident within the chemical literature with a large number of excellent review articles appearing in the last three years.[3]

Marine natural products can be subdivided according to which type of marine organism they have been extracted from, microorganisms and phytoplankton,

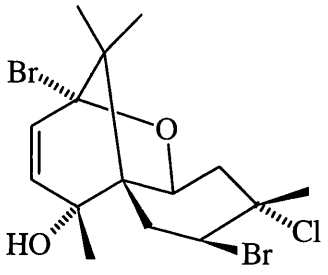
algae, sponges and coelenterates (sea whips, sea fans and soft coral) being the richest sources so far.[2] Chemists in search of new marine natural products have concentrated their efforts on slow moving invertebrates because these animals require a chemical defence mechanism due to their lack of spine or shell. Apart from use as a defence system it is thought that many marine natural products are naturally occurring metal ion chelators. An interesting review by Pattenden and Michael explores this area of research.[4]

Two main areas of research within marine natural product chemistry are the search for 'drugs from the sea' and the isolation and identification of the chemicals responsible for seafood poisoning, the latter being of great social interest due to the many sporadic and unpredictable outbreaks of such poisoning. Both of these areas offer much interest to the synthetic organic chemist as they will almost certainly lead to the discovery of structurally novel natural products. The potential uses as commercial drugs, agrochemicals or as molecular probes are other reasons why many synthetic chemists have entered into this area.

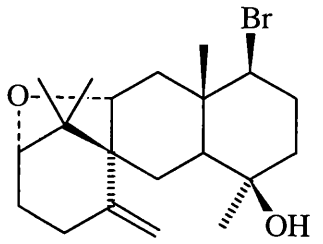
1.1 Structural Diversity

By looking at the complex structures of just a few of these fascinating molecules it is easy to see why this rich source of natural products has drawn so much interest from the synthetic organic chemist. Pacifenol[5] (**1**) from *Laurencia marianensis,* a red algae found at the Great Barrier Reef, is toxic to the aphid *Schizaphis graminium,* and is highly halogenated, containing two bromine atoms and a single

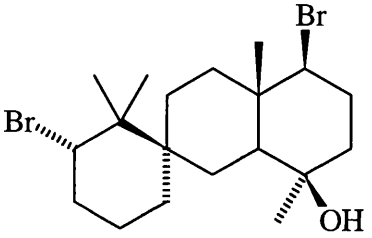
chlorine atom. Kuhukuenes[6] A(**2**) and B(**3**) are unusual brominated diterpenes that were isolated from *Laurencia majuscula.*



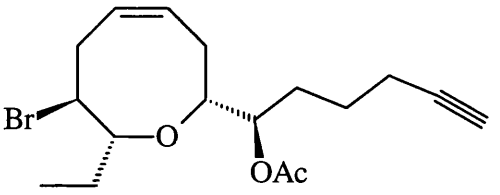
pacifenol (1)



kuhukuene A (2)



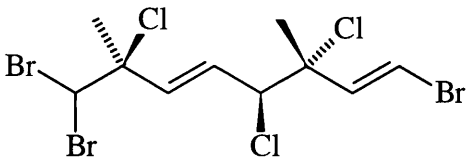
kuhukuene B (3)



(+)-laurencin (4)

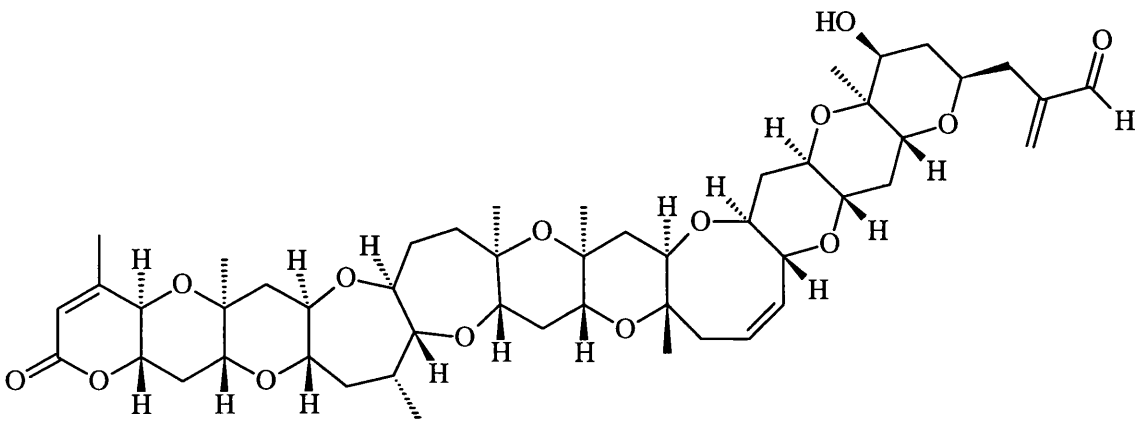
A metabolite of *Laurencia glandulifera*, (+)-laurencin[7] (**4**), has recently been a controversial synthetic target containing a single bromine and a didehydrooxocane ring. During the early 1970's researchers were particularly interested in monoterpenes from red algae, which appeared to be over-endowed with halogens. An example[2] (**5**), from *Plocamium cartilagineum* contains 50 per cent bromine and 22 per cent chlorine by weight. Other examples of highly halogenated marine metabolites are tetrabromopyrrole and carbon tetrabromide from the red algae *Asparagopsis taxiformis.*[2] Although not as structurally interesting, halogenated monoterpenes have been shown to have a wide range of biological activity and thus they may have medical potential and help in the study of the chemical defence

mechanisms of marine invertebrates. Polyhalogenated compounds are now considered to be normal metabolites from sea water dwelling organisms.



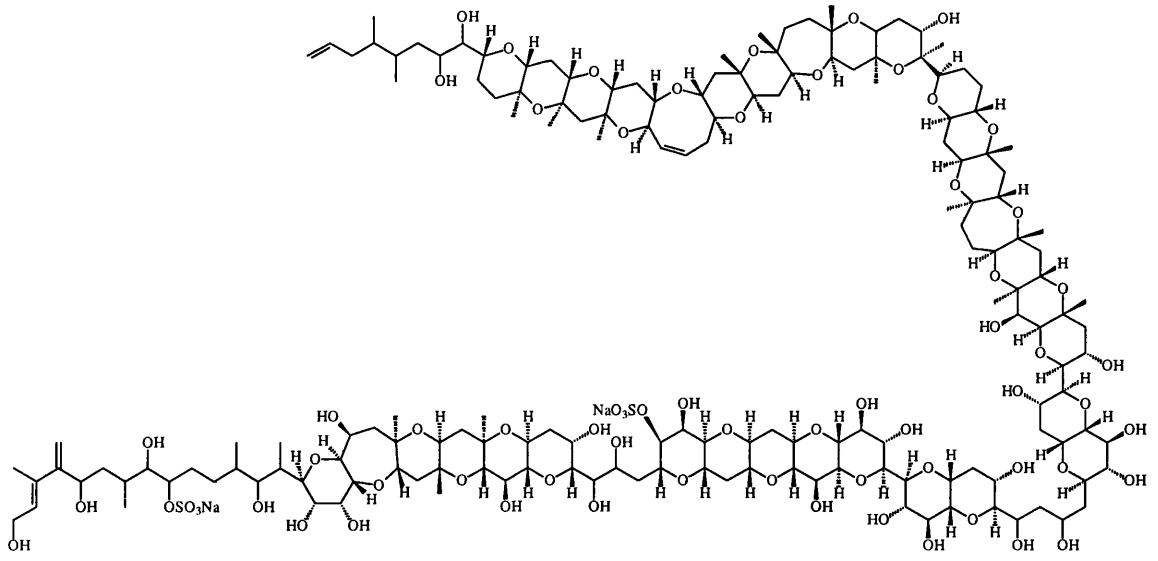
(**5**)

Brevetoxin B[8] (**6**), a marine neurotoxin, which has recently been synthesised by Nicolaou and co-workers, has drawn a great deal of attention.[9] A metabolite of *Gymnodynium breve*, a monocellular algae (phytoplankton), it is the main toxic constituent of a red tide. Red tides, which are caused by vast blooms of the algae, are responsible for massive killings of fish and other marine life, as well as human poisoning. Structurally unprecedented at the time of its discovery brevetoxin B has an intriguing polycyclic skeleton, being composed of only carbon, hydrogen and oxygen, and is endowed with twenty-three stereodefined centres.



brevetoxin B (6)

Comprising a δ-lactone ring, seven tetrahydropyran rings, two oxepane rings, and a didehydrooxocane ring it was a formidable challenge to the synthetic chemist taking over 30 man years to complete. A related natural product of brevetoxin B is maitotoxin, the largest and most toxic non-peptidic natural product known to-date. The structure of maitotoxin[10] (**7**), from *Gambierdiscus toxicus,* was proposed on the basis of chemical and spectroscopic data, and contains thirty-two cyclic ether rings; however, the stereochemistry of the terminal chains is unknown. This gives an added incentive - if one were needed - to the adventurous synthetic organic chemist.

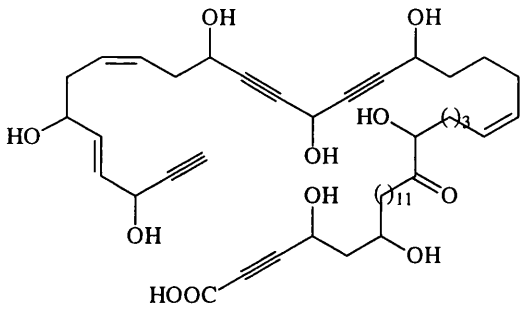


maitotoxin (7)

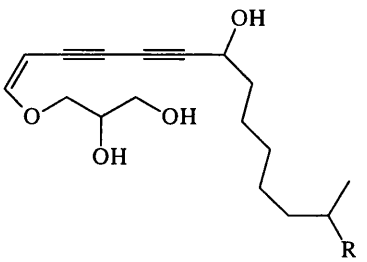
The richest source of marine natural products - 33 per cent of the total number isolated - has been the marine sponge.[2] The polyacetylene petrosyl[3] (**8**) from the *Petrosia* species of sponge is structurally interesting as it contains two *cis* double bonds and one *trans* double bond as well as four acetylenic functions, one of which is propargylic and conjugated to a carboxylic acid group. Not as structurally

interesting are glycerides petrasynes[3] I (**9**) and II (**10**) but they required synthesis to confirm that they occur naturally as a mixture of diastereoisomers.

Halichondrin B[11] (**11**), from the marine sponge *Phakellia carteri*, is a member of a group of antimitotic macrolides that have shown potential as antitumour agents.

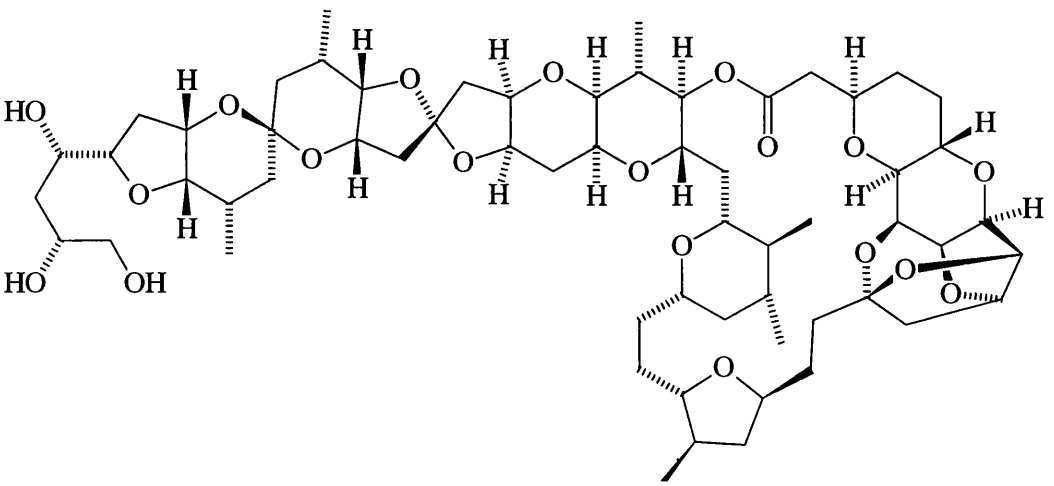


petrosyl (8)



petrasynes I (**9**) R=H
petrasynes II (**10**) R=Me

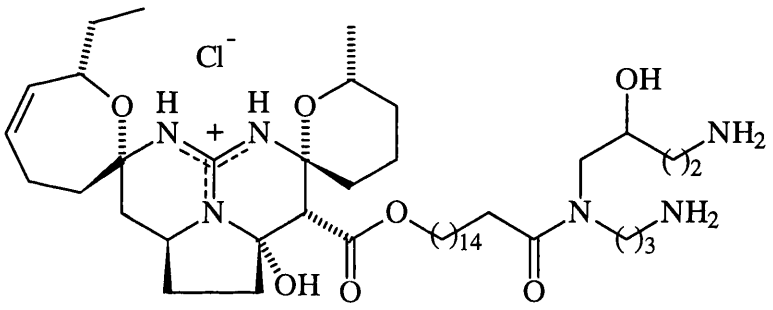
Halichondrin B contains an orthoester group, six tetrahydrofuran rings, seven tetrahydropyran rings and three acetal functions, two of which are spirocyclic, as



halichondrin B (11)

well as the 22-membered macrolide ring. The halichondrin family of marine natural products has received much attention from the synthetic chemist with the total synthesis of halichodrin B being reported in 1992.[11]

Numerous new alkaloids have also been found in marine sponges. Crambescidin 816[3] (**12**), from the Mediterranean sponge *Crambe crambe*, has been shown to be a calcium ion channel blocker. The wide variety of sensitive functionality and lack of symmetry make it a formidable challenge for synthetic analysis.



crambescidin 816 (12)

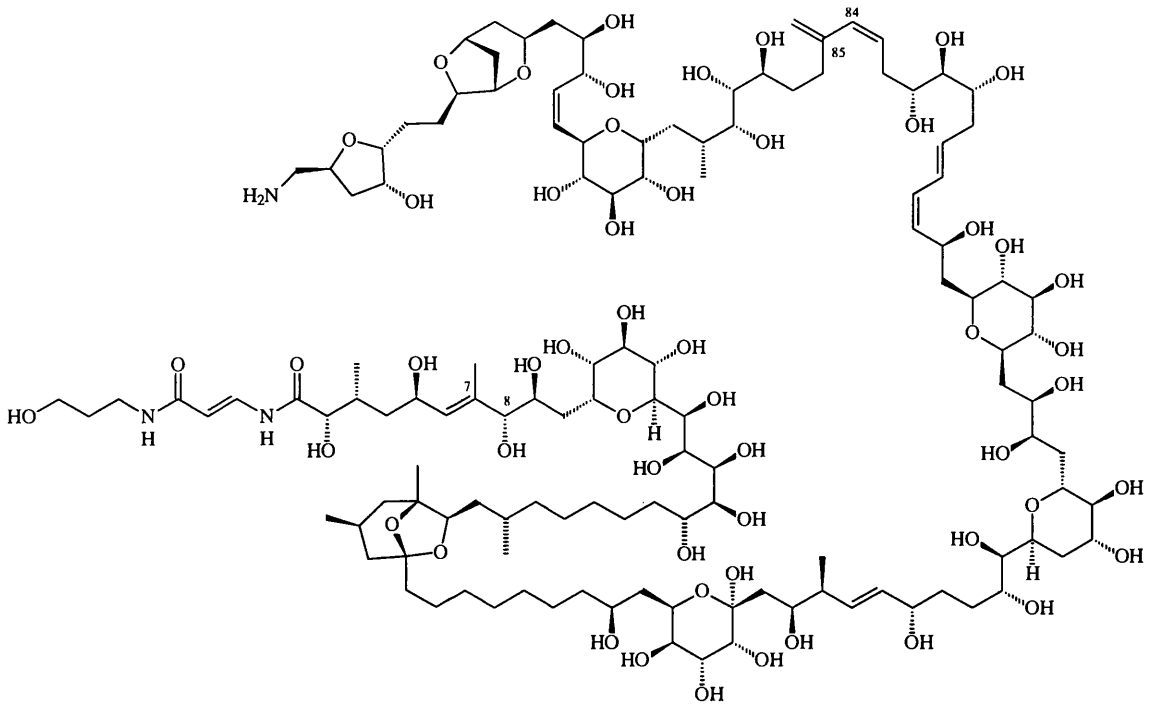
The synthetic organic chemist stands in awe of the architectural diversity and complexity of marine natural products, and can only surmise as to the nature of the complex biosynthetic pathways that lead to such structures.

1.2 Developments in Methodology Through Total Synthesis

The practice of natural product total synthesis provides an opportunity for the chemist to develop new synthetic methods. During many total syntheses new reactions often need to be developed to overcome specific structural problems, or further development of existing reactions is required to allow for more general applicability. The synthesis of three marine natural products, Palytoxin, Brevitoxin B and Arenarol illustrate some interesting developments arrived at through total synthesis of marine natural products.

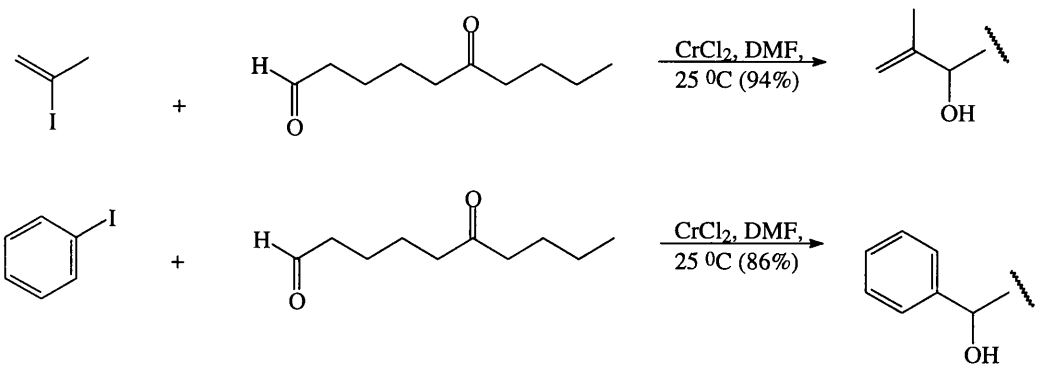
1.2.1 Palytoxin

Palytoxin[12,13] (**13**), from certain soft corals of the genus *Palythoa*, was first synthesised by Kishi and co-workers in 1994 and is a landmark achievement in total synthesis.[14] At the time it claimed - excluding peptides - to be the most poisonous substance known to man but has since been relegated to second place following the discovery of maitotoxin (**7**). The structural elucidation of palytoxin itself took many years, culminating in two groups simultaneously reporting the gross structure in 1981.



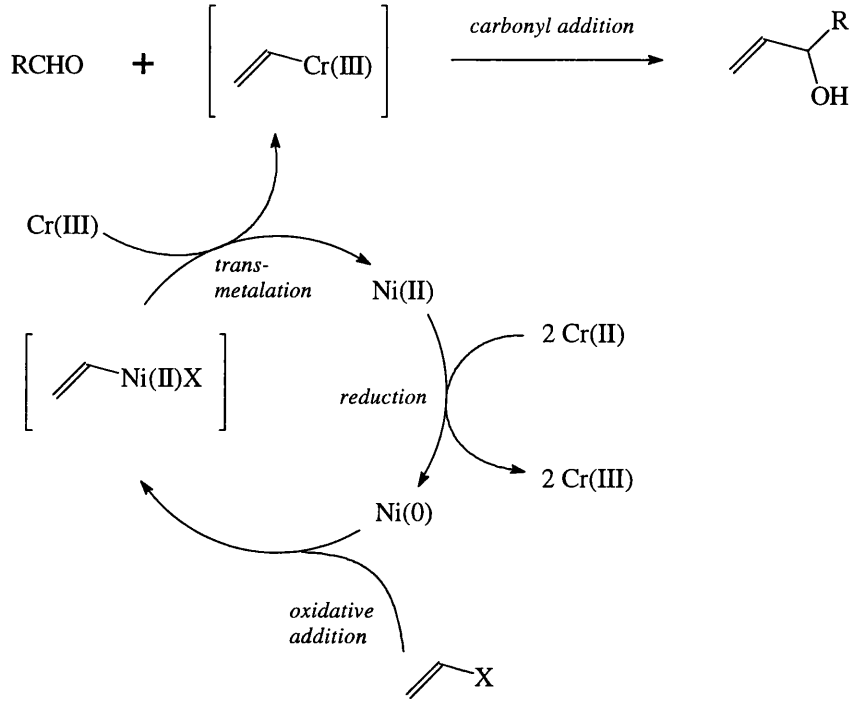
palytoxin (13)

During the synthesis some useful developments and new discoveries in synthetic methodology emerged. One such reaction that was improved during the synthesis was the $NiCl_2/CrCl_2$-catalyzed coupling between vinyl iodides and aldehydes. Originally discovered by Nozaki and co-workers[15] in 1983, the reaction entails reduction of a vinyl/aryl bromide or iodide with $CrCl_2$ and trapping the resultant organochromium(III) species with an aldehyde, under mild conditions. This gave excellent yields of allylic or benzylic alcohols, Scheme 1.1.



Scheme 1.1

By a similar mechanism allylic bromides can also undergo this nucleophilic reaction. However, when Kishi and co-workers began to develop this reaction for their synthesis they found that the outcome of the coupling was dependant upon the source of the $CrCl_2$.[12] The Kishi group then began systematically examining the effect of transition metal salts on the reaction, having suspected the presence of impurities in the $CrCl_2$. It was found that $NiCl_2$ was essential for this reaction and it has since been presumed to have a catalytic role, Scheme 1.2. The advantages of this reaction, over other carbonyl addition reactions - Grignard reagents, organolithium reagents or organocuprates - when employed in a complex synthesis like that of palytoxin, is that the vinyl halide can be activated in the presence of the aldehyde and that the reaction is chemospecific; aldehyde carbonyl groups are exclusively attacked. In the construction of palytoxin this reaction was employed to couple two pairs of intermediates together forming bonds C7-C8 and C84-C85.

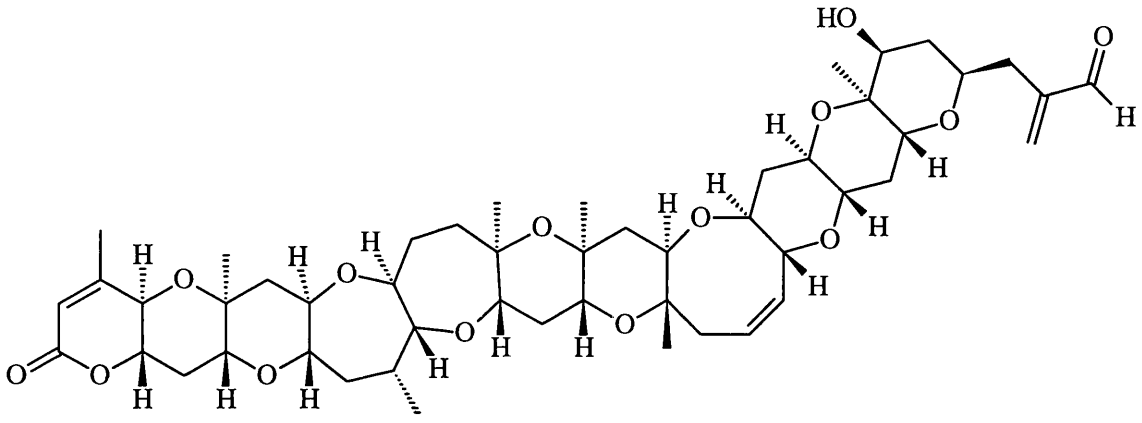


Scheme 1.2

The scope of this useful reaction to natural product synthesis is evident from the numerous total syntheses[16] that have reported its use, none of which would have been possible without the additional insight that Kishi and co-workers gained during their palytoxin work.

1.2.2 Brevetoxin B

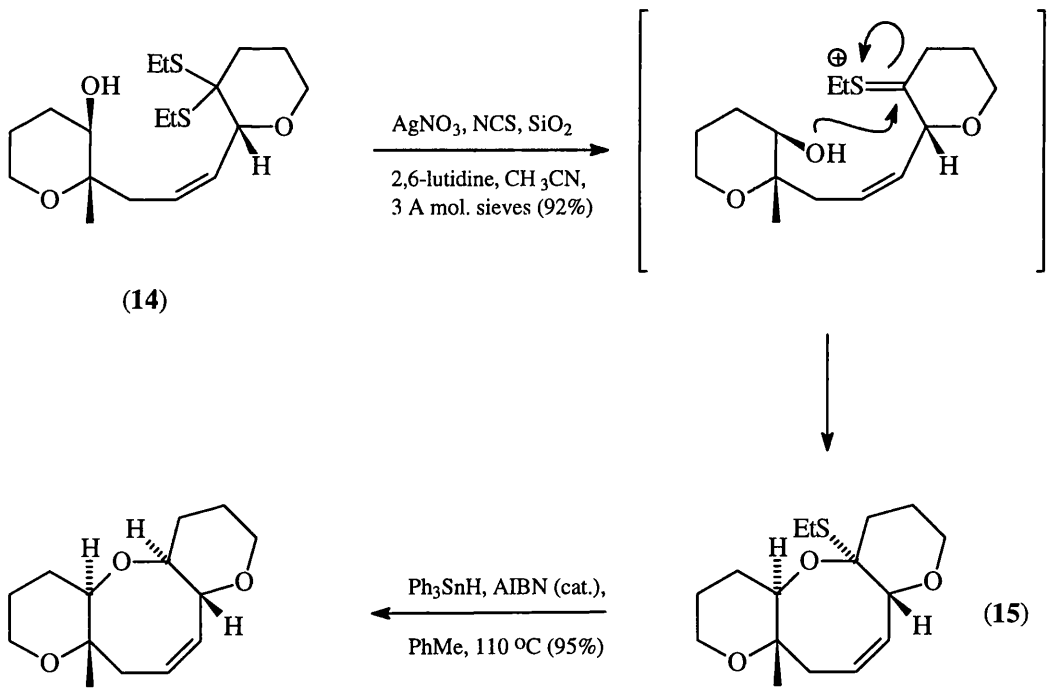
Brevetoxin B[8,9,12] (**6**) is another marine natural product which required the development of novel methodologies to allow for its total synthesis.



brevetoxin B (6)

En route to the total synthesis Nicolaou and co-workers developed many new methods for the construction of cyclic ethers, tetrahydropyran rings, didehydrooxocane rings, and (bis)oxepane rings. In the case of the (bis)oxepane medium ring ethers the inherent difficulty was seized upon by the group and overcome in a number of ways. Unfortunately most of the new reactions were not applicable to the brevetoxin B synthesis, and in reality a long stepwise approach was needed. An extensive body of work[17] has been published which is too large to review here. This pioneering work has given the synthetic chemist many new tools which otherwise may not have been discovered although they found little application in the synthesis of brevetoxin B. The inherent problems involved with the synthesis of the 8-membered didehydrooxocane rings were initially approached by a seemingly difficult route, that of direct cyclization of an

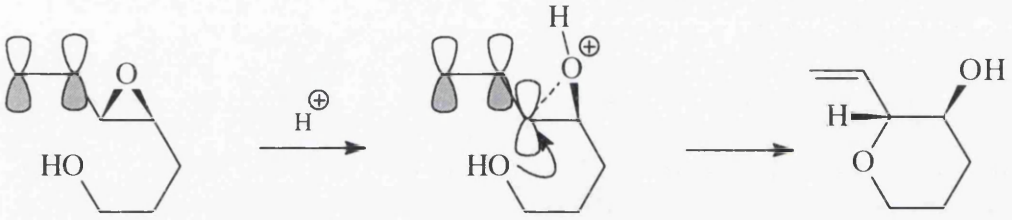
acyclic precursor. Nicolaou postulated that if sufficient conformational rigidity could be conferred to the precursor - by the *cis*-double bond and pre-constructed tetrahydropyran rings at each terminus - an intramolecular capture of a highly electrophilic species by a hydroxyl group would give the desired oxocene ring. After a great deal of effort it was found that treatment of a hydroxy dithioketal (**14**) with NCS and $AgNO_3$ in the presence of 2,6-lutidine, dry silica gel and 3Å molecular sieves resulted in the hoped cyclization to give the didehydrooxocane containing tricycle (**15**) in good yield.[12,18] Removal of the ethylthio function by tin mediated radical reduction, proceeded with complete diastereoselectivity to give the correct *trans*-ring fusion required in brevetoxin B, Scheme 1.3.



Scheme 1.3

A simple and concise solution to the tetrahydropyran problem was also developed which utilised the premise that a suitably functionalized epoxide could be opened by acid catalysis *via* the oxonium ion (**17**) and trapped in a 6-*endo* cyclization by a suitably placed hydroxyl group.[12,19] Ring closure in systems such as these generally

proceed *via* a 5-*exo* process to give the tetrahydrofuran system. Placement of a carbon-carbon double bond adjacent to the epoxide, *e.g.* (**16**), after treatment with acid, resulted in ring closure to give the desired tetrahydropyran (**18**), presumably by stabilization of the ensuing electron-deficient orbital of the carbocation by conjugation with the vinyl π-orbital, Scheme 1.4.



(**16**) (**17**) (**18**)

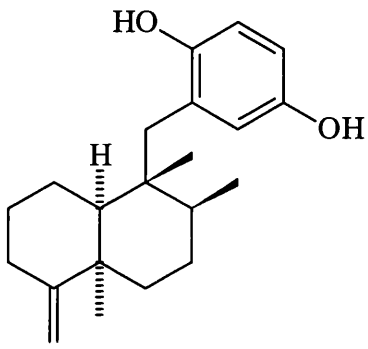
Scheme 1.4

The vinyl group also allows for further elaboration and hence construction of the adjacent cyclic ether.

Through the efforts of Nicolaou and co-workers many new and versatile methods for the synthesis of cyclic ethers have been established, all of which had their origin in the studies towards the synthesis of the marine natural product brevetoxin B.

1.2.3 Arenarol

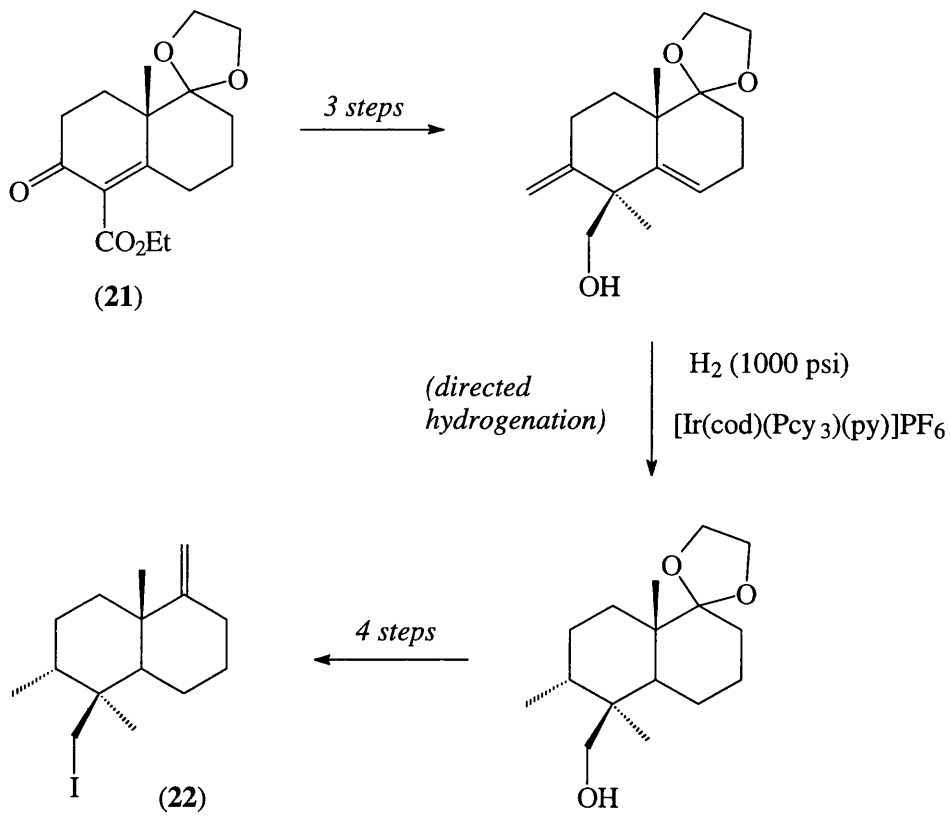
The synthesis of arenarol[20,21] (**19**) is worthy of inclusion because of the similarity in structure and approach with that of popolohuanone E[22] (**20**), although at the outset of this work the synthesis had not been published.



arenarol (19)

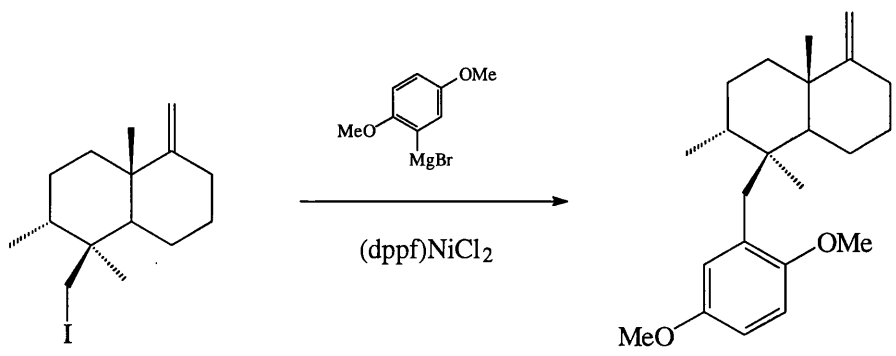
The successful approach to arenarol relied on two key steps: (i) a directed hydrogenation of an unsaturated neopentyl alcohol and (ii) the application to total synthesis of a nickel-mediated neopentyl cross coupling reaction.[23] Disconnection of the arene-decalin bond gives rise to two fragments, one a hydroquinone and the other a *cis*-decalin. In the synthetic direction this bond forming reaction is inherently difficult due to the steric nature of both fragments, one a neopentyl centre and the other an *ortho*-substituted arene.

Wiemer's approach to the required *cis*-decalin began from the known decalin (**21**) and *via* a multi-step process - including the hydroxyl directed hydrogenation - gave the desired iodide (**22**) (Scheme 1.5). It was known at the time that (dppf)$NiCl_2$



Scheme 1.5

was the preferred catalyst for neopentyl coupling; however, it had only been used with common unfunctionalized neopentyl halides. Cross coupling of this iodide and (2,5-dimethoxyphenyl)magnesium bromide in the presence of (dppf)$NiCl_2$ gave the coupled dimethyl protected arenarol in 45% yield, Scheme 1.6.



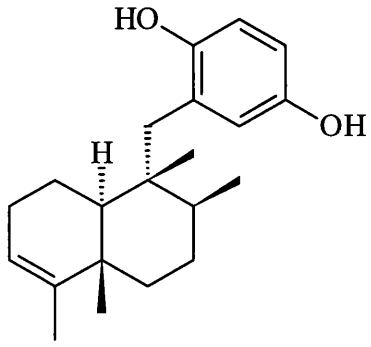
Scheme 1.6

After minor manipulation - exposure to ceric ammonium nitrate then reduction with sodium thiosulphate - the first synthesis of a *cis*-decalin containing C_{21} compound, biogenetically derived from a sesquiterpene and a benzenoid moiety, was complete.

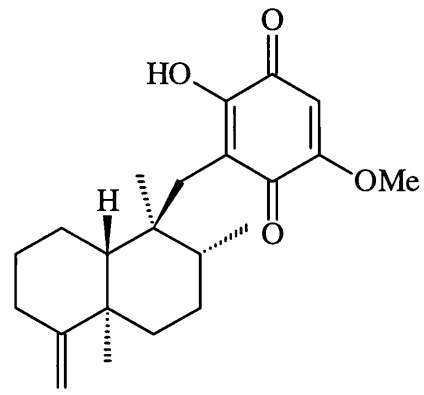
2. Related Marine Natural Products

2.1 Avarol Family

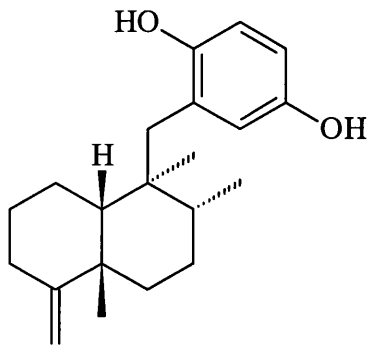
Some C_{21} compounds, which are biogenetically derived from sesquiterpene and benzenoid moieties, have been isolated from marine sponges and brown algae. Interest in these compounds has been heightened by reports of biological properties, which include antileukemia activity, anti-HIV activity and inhibition of various enzymatic processes. Avarol[24] (**23**) from the Mediterranean sponge *Dysidea avara* and illimaquinone[25] (**24**) from the Pacific sponge *Hippiosongia metachromia* were two of the earliest known marine natural products of this type. Both of these compounds contain a *trans*-decalin portion (a rearranged drimane skeleton) and are present in most species of *Dysidea* sponge. Compounds containing a drimane skeleton with *cis*-decalin stereochemistry have also been isolated. Arenarol (**19**) and arenarone (**25**) are two such examples, with the absolute stereochemistry of the diacetate of arenarol having been established by X-ray diffraction.[26]



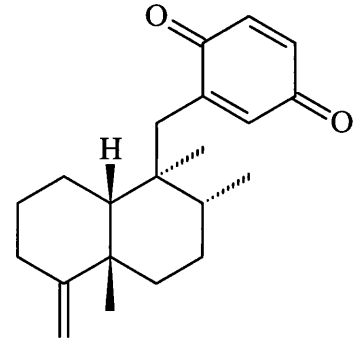
(**23**)



(**24**)

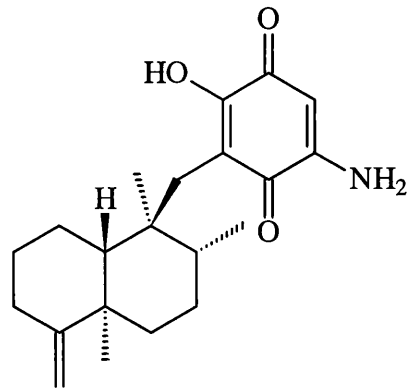


(**19**)



(**25**)

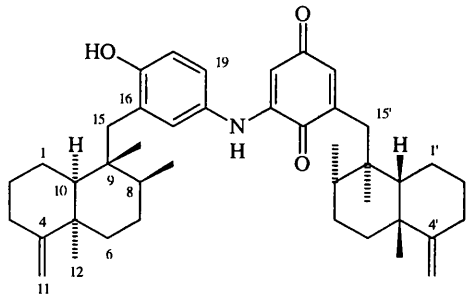
Nitrogenous derivatives of the hydroquinone bearing natural products have also been reported in which the quinone moiety bears an amine function; amine bearing marine natural products are very uncommon. One such compound, smenospongine[27] (**26**), was extracted from the Red Sea sponge *Smenospongia aureus* with the sesquiterpene moiety having *trans*-decalin stereochemistry. Unfortunately, due to the lack of material, the absolute stereochemistry was not determined. Smenospongine is cytotoxic towards L1210 leukemia cells (IC_{50} = 1 μg/mL).



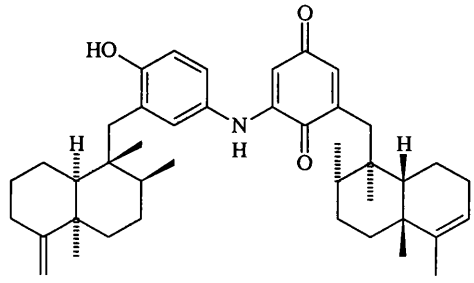
(**26**)

2.2 Popolohanone A-D

In 1990, P. J. Scheuer identified two compounds, popolohuanone A (**27**) and B[28] (**28**), from *Dysidea* species of sponge, in which two C_{21} entities, one a quinone and one a hydroquinone, derived from arenarone and arenarol like structures, were coupled *via* an amine link. Both compounds are purple-blue in colour and were named after the Hawaiian word for 'purplish-blue as the sea', Popolohua.

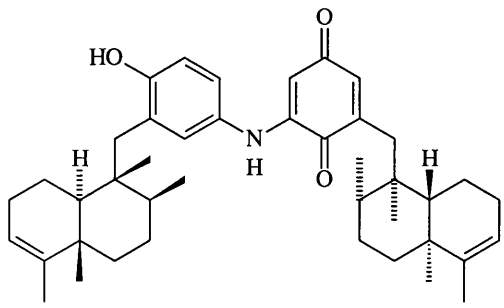


popolohuanone A (27)

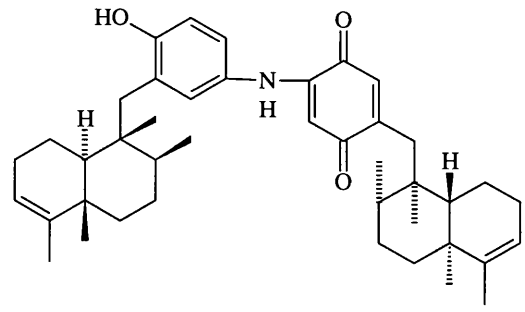


popolohuanone B (28)

The structural elucidation was carried out using NMR spectroscopic techniques and only the relative stereochemistry is known. The sesquiterpene moiety is a *cis*-decalin with a syn relationship of the two methyl groups on C-8/8' and C-9/9'. A syn relationship also exists between the benzylic bond (C-9/9' to C-15/15') and the C-10/10' proton. Both decalin moieties in popolohuanone A contain an exocyclic olefin. B differs from A by having an exocyclic and an endocyclic olefin. *cis*-Decalins, although not rare, are still more unusual in marine natural products than *trans*. Unfortunately neither of these interesting marine natural products has shown any biological activity. Shortly afterwards, in 1992, Crews and co-workers[29] isolated the third and fourth members of the popolohuanone family, C (**29**) and D (**30**), from the sponge *Dysidea avera*.



popolohuanone C (29)



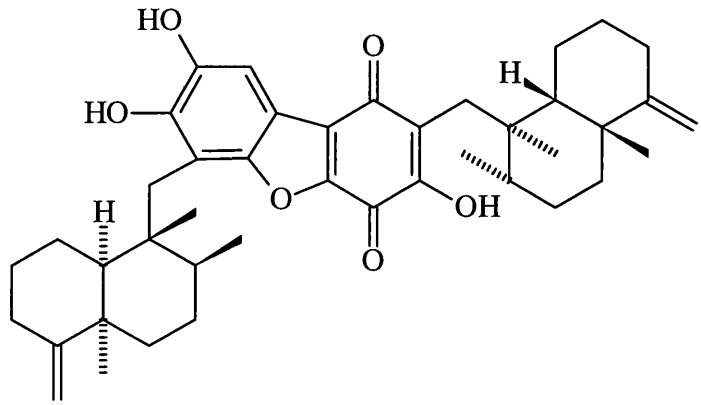
popolohuanone D (30)

Structurally C and D consist of two *trans*-decalin portions, a quinone portion and a derivatised hyroquinone. As with popolohuanone A and B the two C_{21} entities are connected *via* an amine bridge. The syn relationship between the benzylic bonds and the ring junction proton is conserved. C and D however, contain endocyclic olefins and differ from one another only in the geometrical attachment of the hydroquinone entity to the quinone entity; attachment in C is at C-18' and in D at C-19'. Once again neither of these compounds has shown any biological activity.

2.3 Popolohuanone E

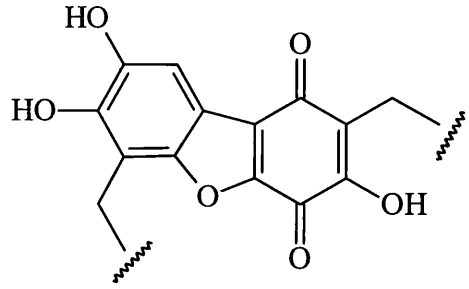
More interesting was the discovery of the fifth member of the family, popolohuanone E[22] (**20**), by P. J. Scheuer in 1993. Popolohuanone E, an oxidatively-dimerised arenarol derivative, was isolated from a *Dysidea* sponge collected at Pohnpei. The structure of popolohuanone E is similar to that of the other members in that it contains two C_{21} moieties made up of a benzenoid fragment and a sesquiterpenoid derived decalin. However, popolohuanone E does not contain an amine bridge but instead the quinone and hydroquinone are fused together to form a furan ring. The benzenoid moieties each carry an extra hydroxyl

function and the decalin portions are both *cis* and contain only exocyclic olefins. The relationship of the other features is consistent with that of popolohuanone A.



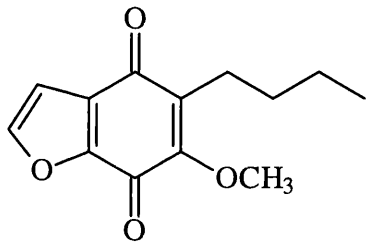
popolohuanone E (20)

Elucidation of the structure was carried out mainly by NMR spectroscopy using HMBC to determine the relative stereochemistry. The substitution patterns of the quinone and the aromatic rings were unequivocal, but the orientation of the two C_{21} moieties to one another through the furan ring could not be determined by NMR spectroscopy. Thus it was established by comparison of the carbonyl carbon shifts of the two possible orientations with that of two compounds - (**31**) and (**32**) - prepared *via* unambiguous synthetic routes (Scheme 2.1(a) shows the carbonyl carbon shifts for popolohuanone E and Scheme 2.1(b) shows the carbonyl carbon shifts for the two synthetic compounds).



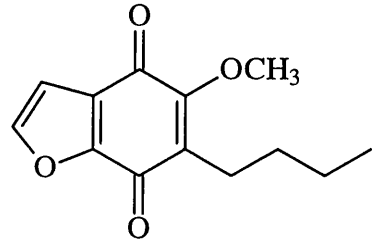
δ 185.4 and 170.8

Scheme 2.1(a)



δ 182.7 and 171.9

(31)



δ 179.0 and 176.5

(32)

Scheme 2.1(b)

2.3.1 Biological Activity

Unlike the first four members of the family popolohuanone E has shown some interesting biological activity.[22] Topoisomerase-II, a member of the family of enzymes responsible for the coiling and uncoiling of DNA and thus essential for cell replication, is inhibited at relatively low concentrations (IC_{50} = 400 nmol) by popolohuanone E. It is worth noting that topoisomerase-II is the target enzyme for several of the most potent agents against lung cancer, and that the topoisomerase-II content appears to be related to the sensitivity of that cell type to these compounds. Popolohuanone E is not appreciably cytotoxic (> 20 μg/mL) to the CV-1 strain of nontumour monkey kidney cells or the HT-29 strain of human

colon tumour cells but is slightly cytotoxic to P388 murine leukaemia cell line (IC_{50} = 20 μg/mL). Most interesting of all is that popolohuanone E is cytotoxic (IC_{50} = 2.5 μg/mL) to A549 non-small cell lung cancer cells. This is of added significance because of the two distinct human lung cancer phenotypes - small or "oat" cell and non-small cell - the non-small cell lung cancer cell line is to-date the least responsive to anticancer agents. Furthermore, the inhibitory concentrations of popolohuanone E in the topoisomerase-II and A549 bioassays are comparable with those of the epipodophyllotoxins and other anticancer agents currently in clinical use for lung cancer.

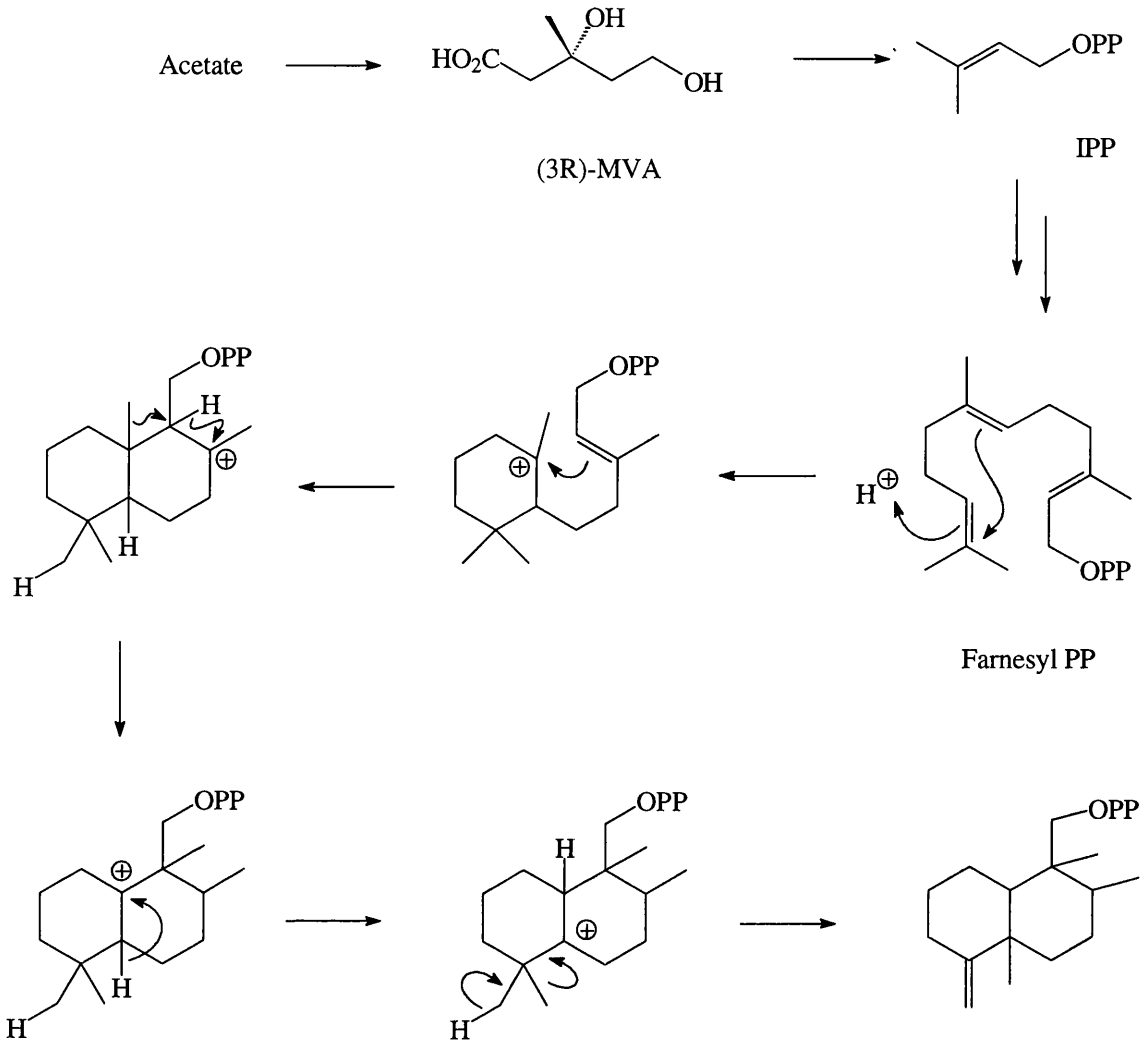
The challenging structure, the potential biological or medical use, the possibility of probing the mechanism of topoisomerase-II, and the need to unequivocally establish the structure and stereochemistry make popolohuanone E an obvious choice for synthetic studies and moreover, total synthesis.

3. Postulated Biosynthesis[30]

Before devising a synthetic strategy towards any natural product it may be advantageous to explore its biosynthesis, as this may give added insight into possible routes to the natural product. If, as in may cases, the biosynthetic pathway is not known it may be possible to postulate such a pathway from other structurally related natural products with known biosynthetic pathways. In the case of popolohuanone E it is possible to postulate a pathway by considering that late stage oxidative dimerisation takes place, thus assuming that it is derived from two arenarol type molecules. The monomer biosynthesis is that of the two main fragments, a rearranged drimane skeleton and the benzenoid/quinonoid moieties.

3.1 Decalin Biosynthesis

Biosynthetic pathways to decalin skeletons are well established. The biosynthesis starts from acetate and *via* mevalonic acid (MVA) furnishes isopentenyl pyrophosphate (IPP), the C_5 building block for all sesquiterpene based natural products. Combining three such units gives rise to farnesyl PP. Biogenetic folding of farnesyl PP gives a decalin skeleton which, after rearrangement, produces the carbon skeleton required in popolohuanone E, Scheme 3.1.



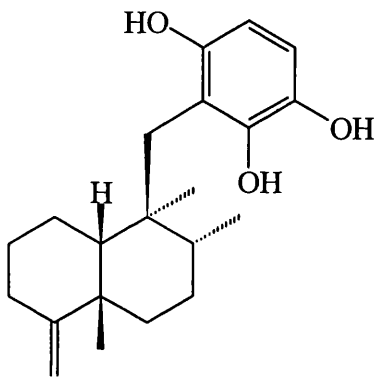
Scheme 3.1

3.2 Benzenoid Biosynthesis

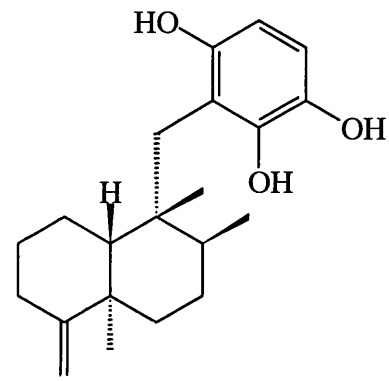
Aromatic metabolites are derived from polyketides which in turn are made from acetate. Coiling of the polyketide chain leads to intramolecular aldol or Claisen condensations, and this produces phenols. Further oxidative or alkylating process can then take place to furnish the required arene.

3.3 Biosynthetic Oxidative Dimerisation

The dibenzofuran-1,4-dione core is derivable by an enzymic or possibly nonenzymic dimerization. It is worth noting that 6'-hydroxyarenarol (**33**) has to date not been isolated; 6'-hydroxyaverol (**34**) has been isolated but Hirsh and coworkers[31] did not mention that it was unusually unstable or prone to oxidation.

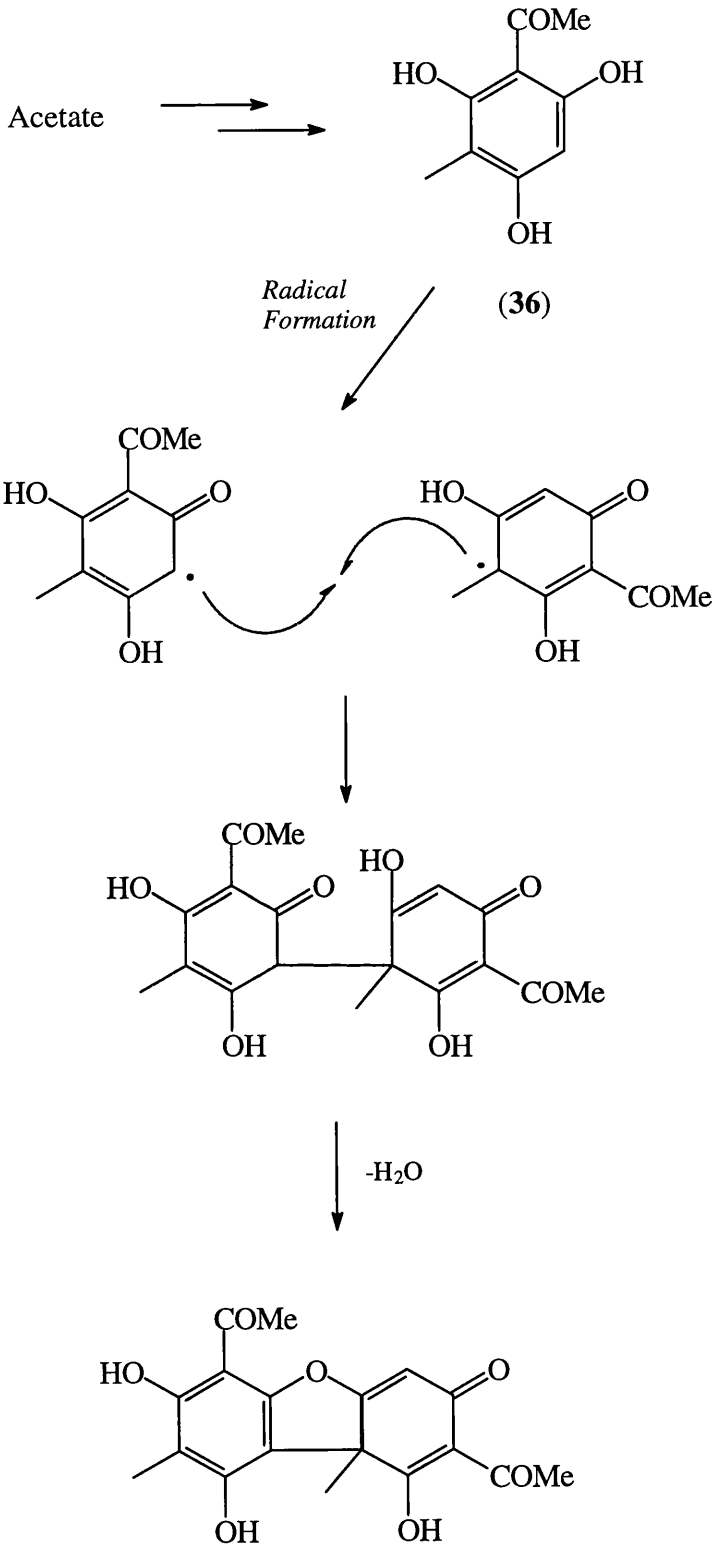


(**33**)



(**34**)

Enzymatic oxidative dimerisation would be expected to proceed in a similar manner to that of other dibenzofuranones. Usnic acid (**35**), a common lichen metabolite, provides a good example. Starting from acetate, methylphloracetophenone (**36**) is biosynthesised and then undergoes radical formation and subsequent coupling to give the natural product, Scheme 3.2.


Acetate
COMe
HO
OH
OH
Radical
Formation
(36)
COMe
HO
O
OH
HO
O
COMe
OH
COMe
HO
O
HO
O
COMe
OH
OH
-H2O
COMe
HO
O
O
COMe
OH
OH

(35)

Scheme 3.2

The enzymes responsible for most phenolic couplings are peroxidases. They have a porphyrin bound ferric ion which is also bound by the oxidising agent, either a hydroperoxy ion or a superoxide ion.

Extensive studies into the biosynthesis are required if the actual pathway is to be elucidated; that aside, the biosynthesis is essentially that of the *cis*-decalin and the dibenzofuran-1,4-dione unit.

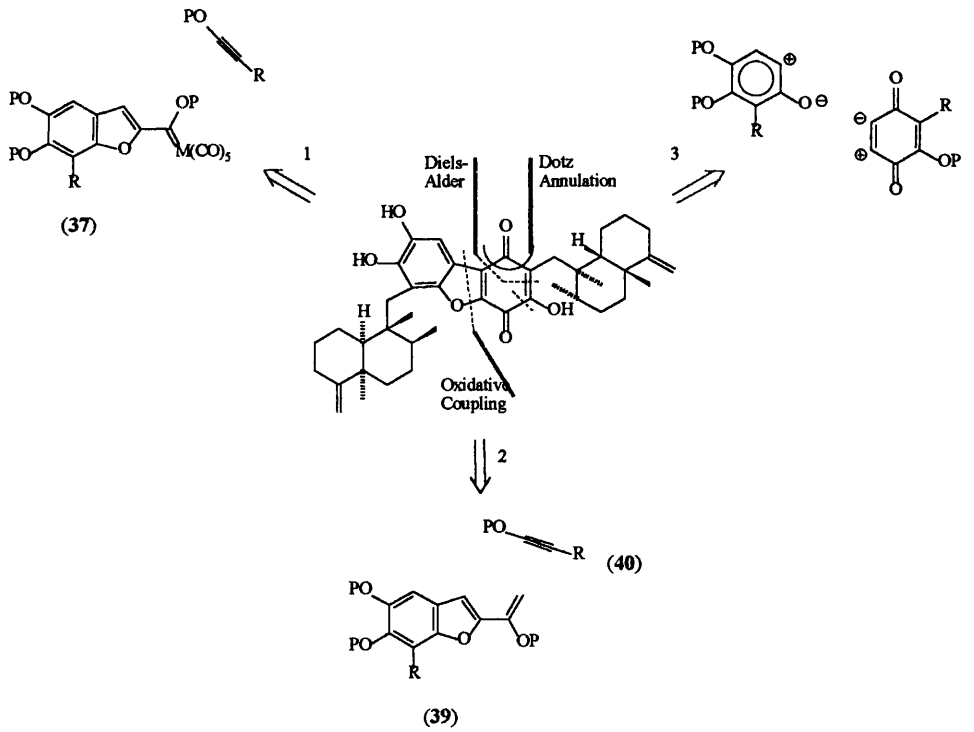
4. Retrosynthetic Analysis and Strategy

Two structural features dominate any retrosynthetic analysis of popolohuanone E:

1. **Dibenzofuran-1,4-dione** core and
2. ***cis*-Decalin** appendages.

A successful synthesis of the natural product must therefore entail the regiospecific construction of the aromatic portion and the stereospecific formation of the requisite *cis*-decalin.

4.1 Dibenzofuran-1,4-dione Analysis

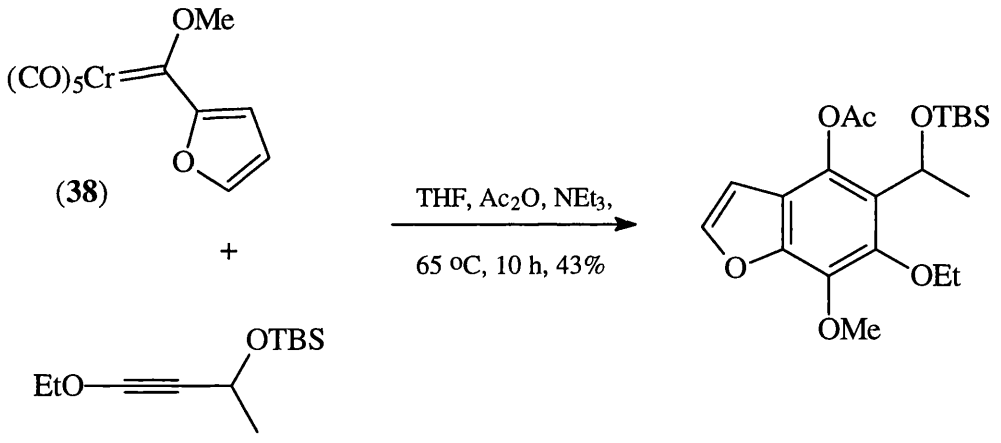


Scheme 4.1

Analysis of the dibenzofuran-1,4-dione core gives rise to many disconnections. Scheme 4.1 (R = *cis*-decalin, P = protecting group, M = metal) outlines a number of synthetically feasible routes.

4.1.1 Route 1

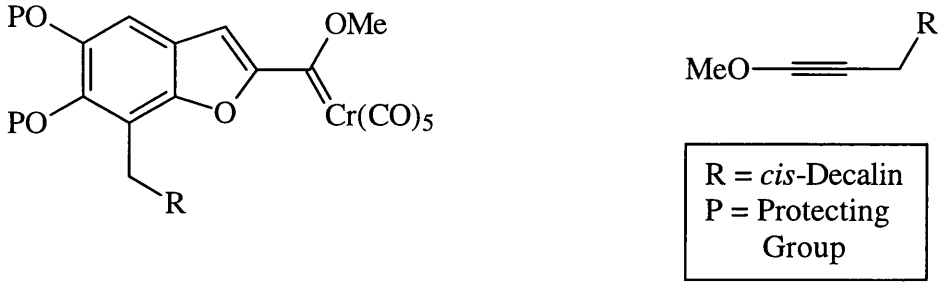
Disconnection of the C20'-21', C16'-21' and C17'-18' bonds reveals the intermediate benzofuran (**37**) which, in the forward direction, could be converted to the dibenzofuran-1,4-dione by a Dötz type annulation reaction. This would entail formation of a Fischer chromium carbene complex and reaction of this with a suitably functionalized alkyne. An example by Yamashita[32] in which the furan chromium carbene complex (**38**) was employed in the synthesis of the natural product khellin shows the applicability of this reaction; oxidative work up would yield a quinone rather than the phenol, Scheme 4.2.



Scheme 4.2

Regiospecificity predominates in favour of placing the bulkier substituent adjacent to the phenolic hydroxy group. It is known that Dötz annulation can also be carried out under sonication or dry state conditions,[33] these giving increased yield and shorter reaction times with respect to the standard thermal conditions. To access popolohuanone E *via* this methodology intermediates of the type shown in

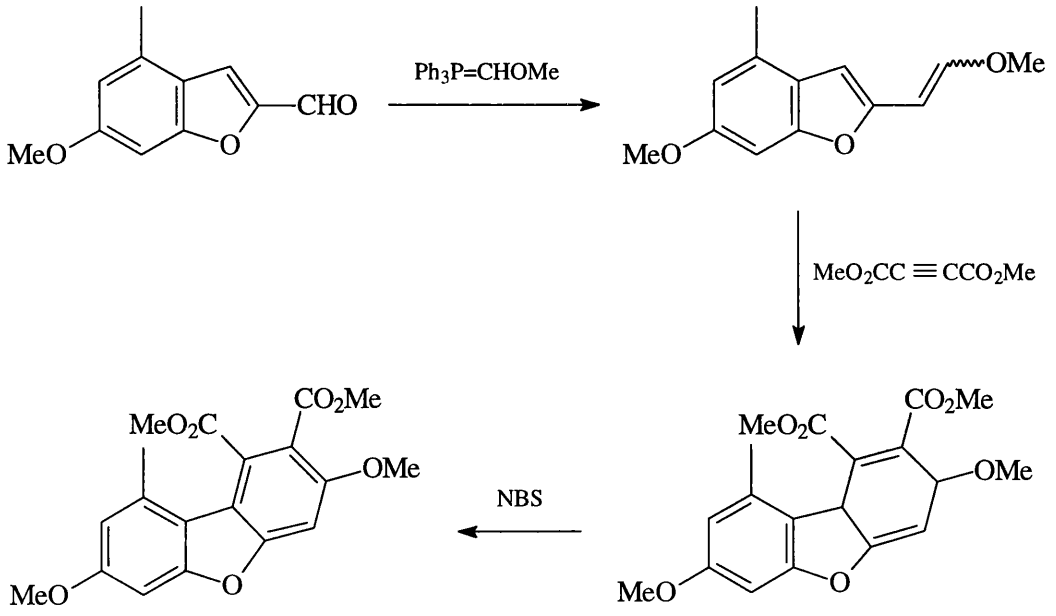
Scheme 4.3 would be required and selective oxidation of the right hand ring would have to be achieved to give the desired aromatic system.



Scheme 4.3

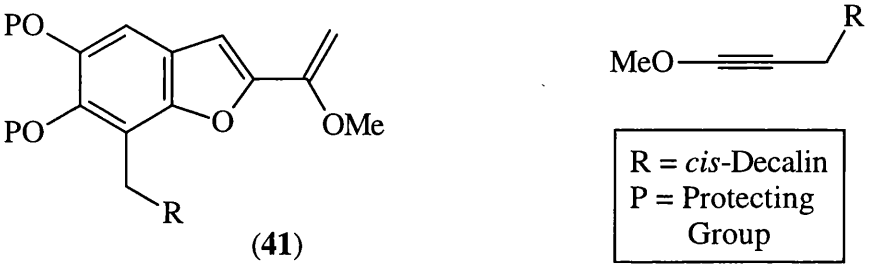
4.1.2 Route 2

Disconnection of the aromatic core across the C20'-21' and C16'-17' bonds would give rise to the two fragments (**39**) and (**40**) which synthetically could give a dibenzofuran, *via* a Diels-Alder reaction. Elix[34] has shown that 2-vinylbenzofurans can undergo [4+2] cycloadditions with dienophiles to give, after dehydrogenation, dibenzofurans, Scheme 4.4.



Scheme 4.4

Synthetically diene (**41**) and dienophiles of the type shown in Scheme 4.5 would be required if this route were to be employed in the synthesis of the aromatic core. However, the regiospecificity of addition may exclude this route and once again selective oxidation would have to be carried out.

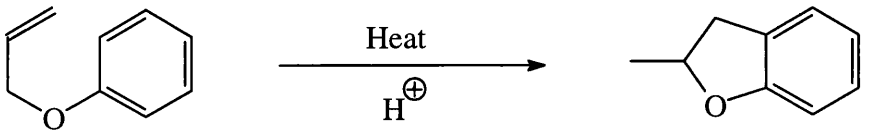


Scheme 4.5

Both of these strategies would require the synthesis of suitably functionalized benzofurans.

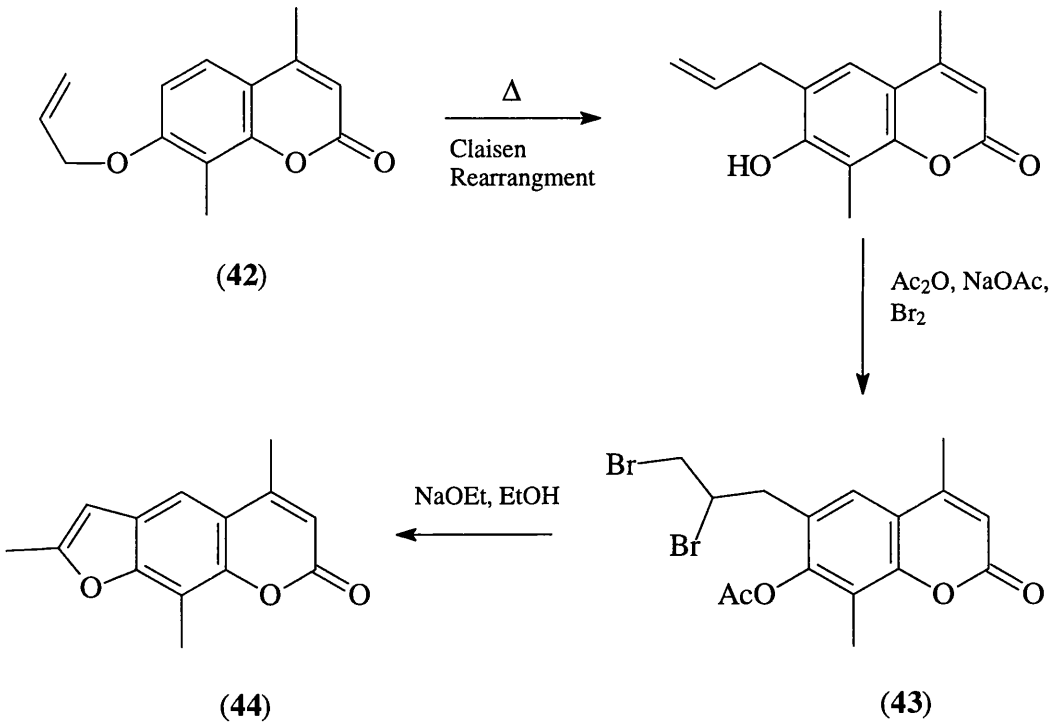
4.1.3 Synthesis of Benzofurans

The intramolecular cyclization of a suitably functionalized phenol is the most frequently employed strategy. One of the simplest examples is the rearrangement of *O*-allylphenol,[35] which on thermal cyclization, in the presence of acid, gives good yield of 2-methyldihydrobenzofuran, Scheme 4.6.



Scheme 4.6

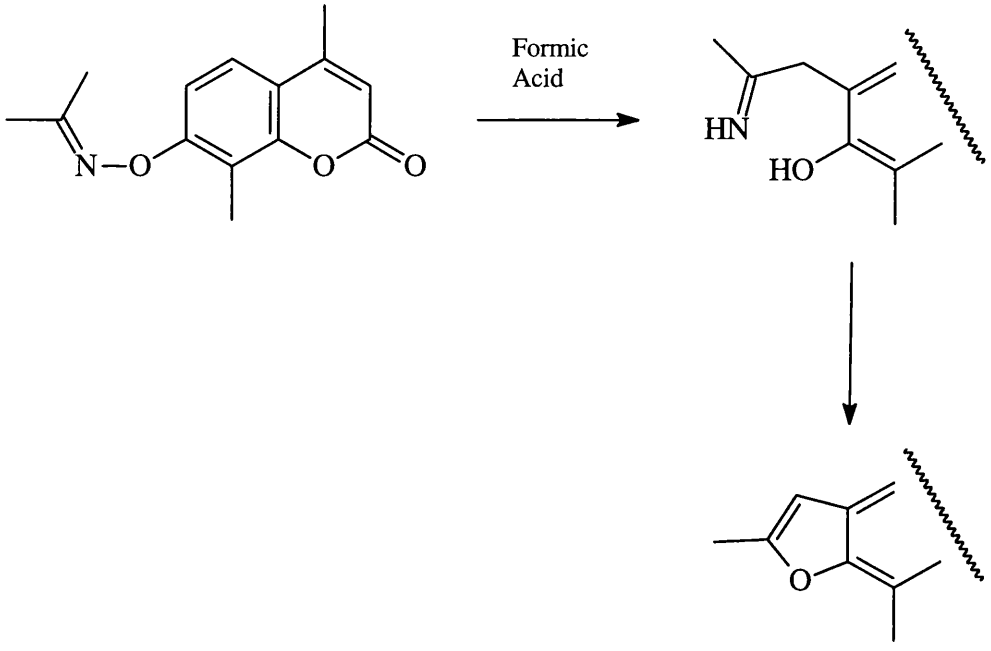
However, without the addition of acid (**42**), a precursor used in the synthesis of 5-methylpsoralens undergoes the same thermal cyclization - *via* a Claisen rearrangement - to afford an *o*-allylic phenol. Nucleophilic attack by the phenolic oxygen on an electophilic carbon in the *ortho*-side chain can then be employed[36] to bring about ring closure and introduce the furan. The ring closure in this case is effected *via* the dibromide (**43**) by a process of substitution then elimination and finally isomerisation to give 4,5',8-trimethylpsoralen (**44**), Scheme 4.7.



Scheme 4.7

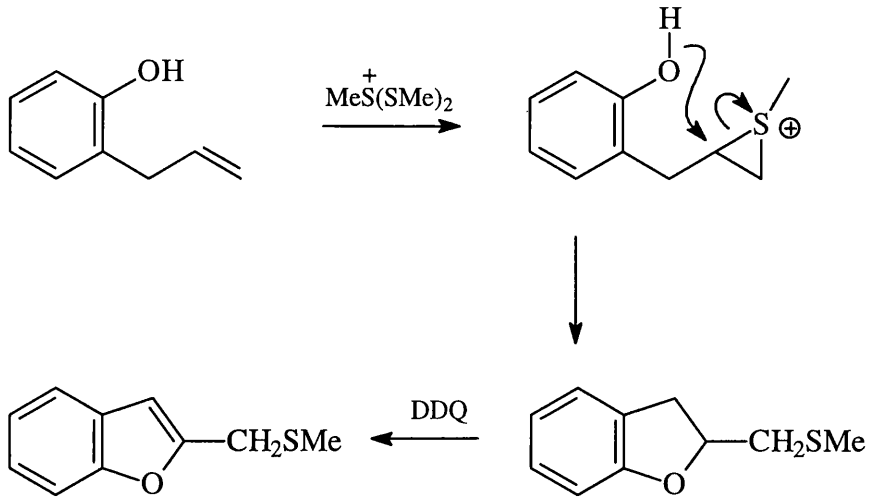
The Fischer indole[37] synthesis has also been utilised in the synthesis of benzofurans as illustrated, once again, by the synthesis of 4,5',8-trimethylpsoralen, Scheme 4.8. The O-aryloxime precursor synthesis - from hydroxycoumarin by amination with

O-(2,4-dinitrophenyl) hydroxylamine and then imine formation - is nontrivial limiting the general application of this methodology.



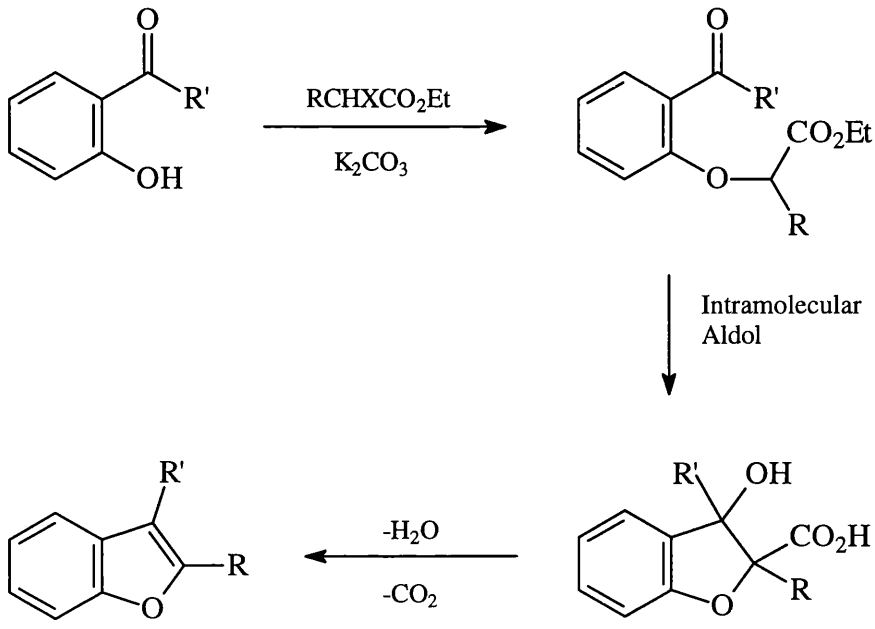
Scheme 4.8

An example by Capozzi[38] in which a thiiranium ion was used as the electrophilic precursor required for cyclization is shown in Scheme 4.9. Exposure of *o*-allylphenol to the sulfonium salt will result in attack at the double bond to give the thiiranium ion. Nucleophilic attack by the phenolic oxygen in a 5-*exotet* cyclization results in dihydrofuran formation. Dehydrogenation is achieved by exposure to DDQ.



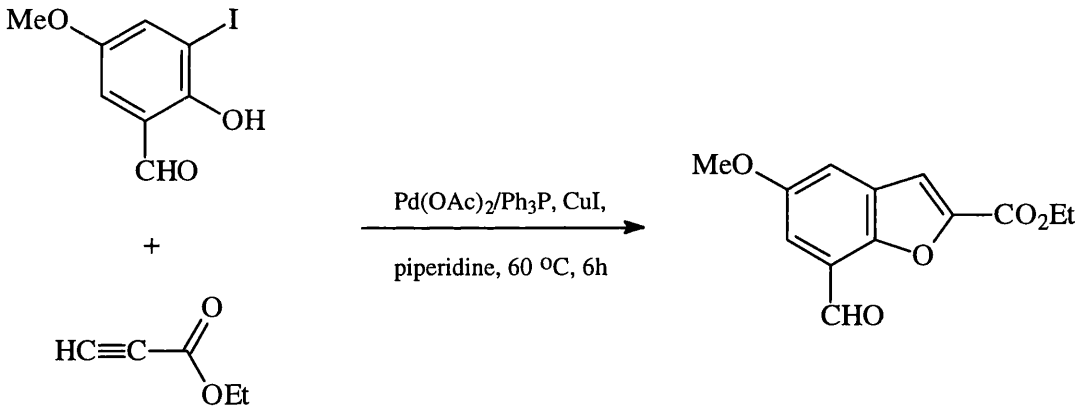
Scheme 4.9

The condensation of *o*-keto phenols with α-halogenated carbonyl compounds - in the presence of K_2CO_3 or KOH - followed by an intramolecular aldol cyclization affords, after dehydration and decarboxylation, benzofurans. The synthesis outlined in Scheme 4.10 illustrates the general applicability of this methodology.[36]



Scheme 4.10

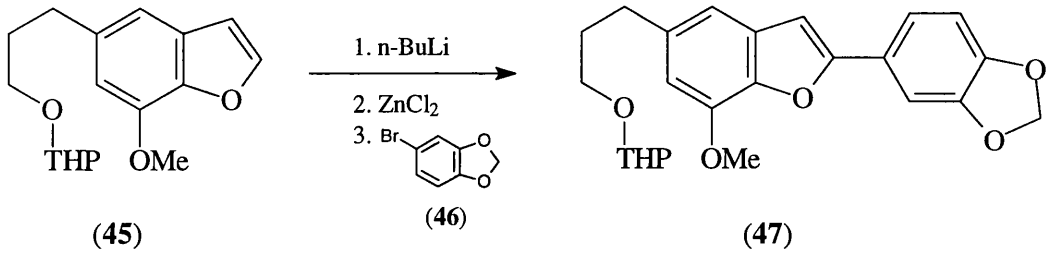
Cacchi and co-workers have developed a mild method[39] of synthesising 2-substituted benzofurans from *ortho* substituted phenols and terminal alkynes, Scheme 4.11. This is an extension to the already established method of benzofuran synthesis from the reaction of *o*-halophenols with copper(I)acetylides. Unfortunately this method requires elevated temperatures and a stoichiometric amount of the organocopper reagent is required. Cacchi utilised a palladium catalyst and CuI as cocatalyst to bring about the transformation under mild and non-stoichiometric conditions. The synthesis of 2-ethoxycarbonyl-6-methoxy-8-formylbenzofuran *via* this route is outlined in Scheme 4.11.



Scheme 4.11

It is also possible to functionalise the 2-position of benzofurans by metalation. Reaction of a benzofuran with n-BuLi forms the 2-lithiobenzofuran which can easily undergo transmetalation and thus allow transition metal mediated coupling reactions to be undertaken. Ohta and co-workers utilised this in the synthesis of egonol.[40] Reaction of benzofuran (**45**) with n-BuLi, then addition of $ZnCl_2$ gives

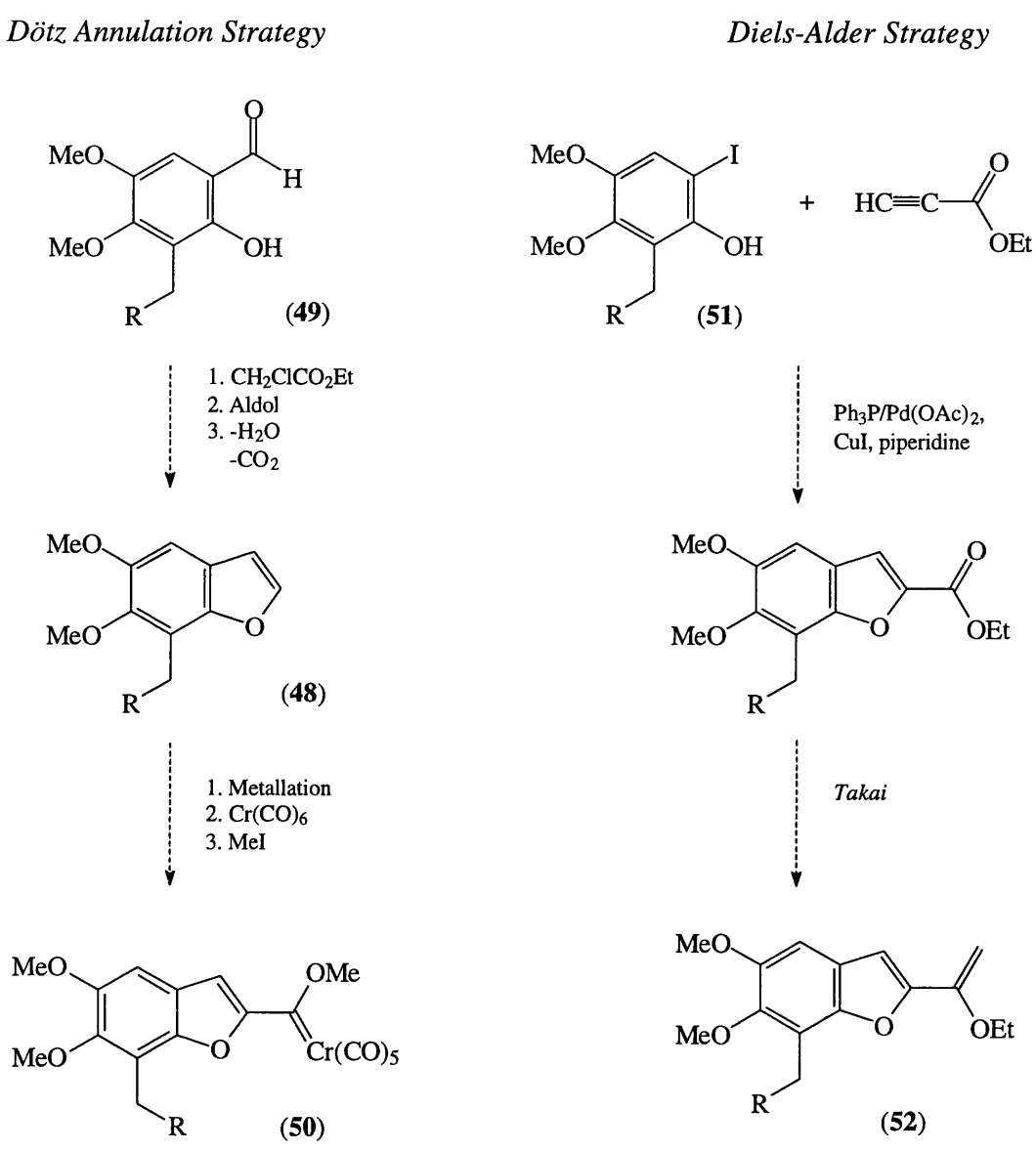
the intermediate organozinc species. In the presence of Pd(0) this couples smoothly with aryl bromide (**46**) in 75 % yield to give the THP-protected egonol (**47**), Scheme 4.12.



(**45**) (**46**) (**47**)

Scheme 4.12

An approach to the benzofurans required for the Dötz annulation and Diels-Alder cycloaddition strategies is outlined in Scheme 4.13. The chromium carbene complex could be accessed through the benzofuran (**48**). Thus in a forward direction (**48**) could be synthesised from the phenol (**49**) by aldol type annulation chemistry. Formation of the chromium carbene complex could be carried out by metalation then reaction with $Cr(CO)_6$, which after rearrangement and methylation could give precursor (**50**). Dienophile synthesis could be carried out from the phenol (**51**), by the Cacchi palladium catalyzed reaction to give a 1-carbonylated benzofuran which, by a Takai alkylidenation, could be converted into the dieneophile (**52**).

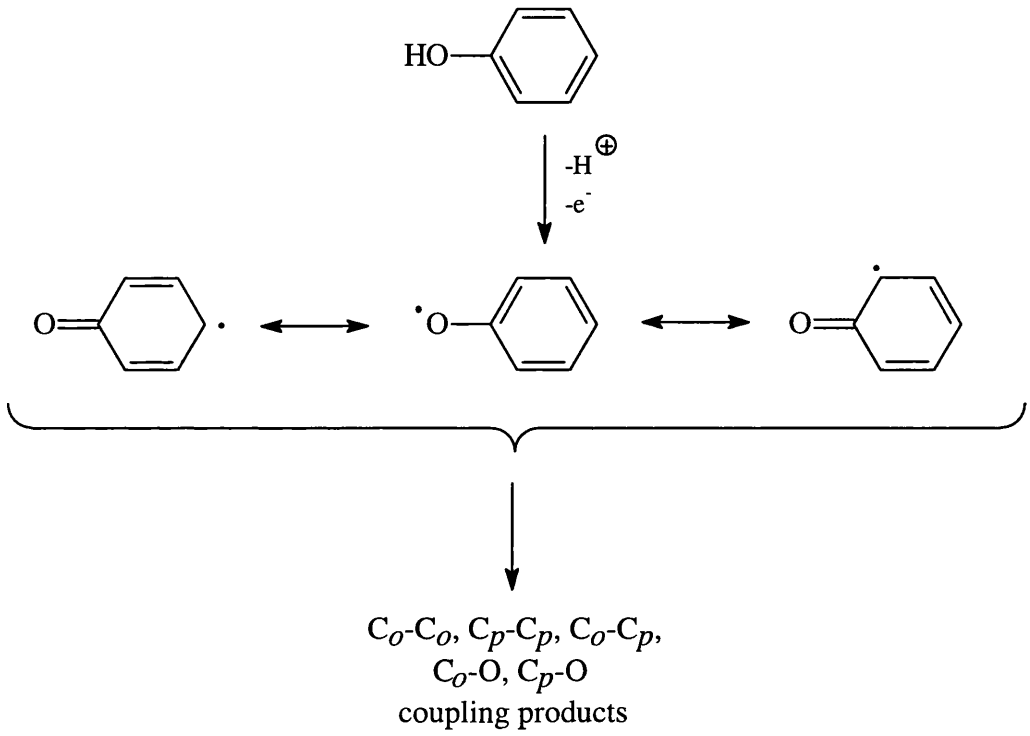


Scheme 4.13

4.1.4 Route 3

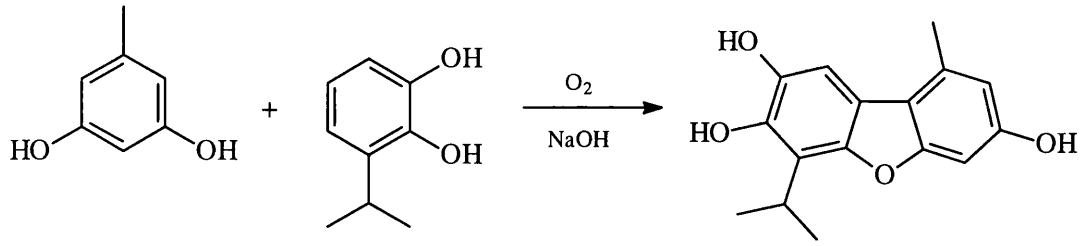
A more convergent synthesis of the aromatic core would entail disconnection across the furan ring to give a phenol and a quinone. In the forward direction it may be possible to couple two phenols either to give the required dibenzofuran-1,4-dione core or a dibenzofuran, the latter requiring selective oxidation to give the quinone. Oxidative coupling of phenols is a well documented reaction[41] in which

oxidation of a phenol with proton and electron loss gives rise to an aryloxy radical, Scheme 4.14. Five modes of dimerisation are possible, three types of C-C bond formation and two types of C-O bond formation.



Scheme 4.14

Spin density is greatest at the para position, but coupling is reversible and product ratios depend on pH, temperature, concentration and oxidant for a given phenol. The cross coupling of orcinol and isopropyl catechol,[42] Scheme 4.15, in which the major product is that shown, suggests the possibility that simple exposure of a 6'-hydroxy arenarol to a base and molecular oxygen might bring about the desired transformation. However, this type of selectivity is rare and many products often result from this type of reaction.

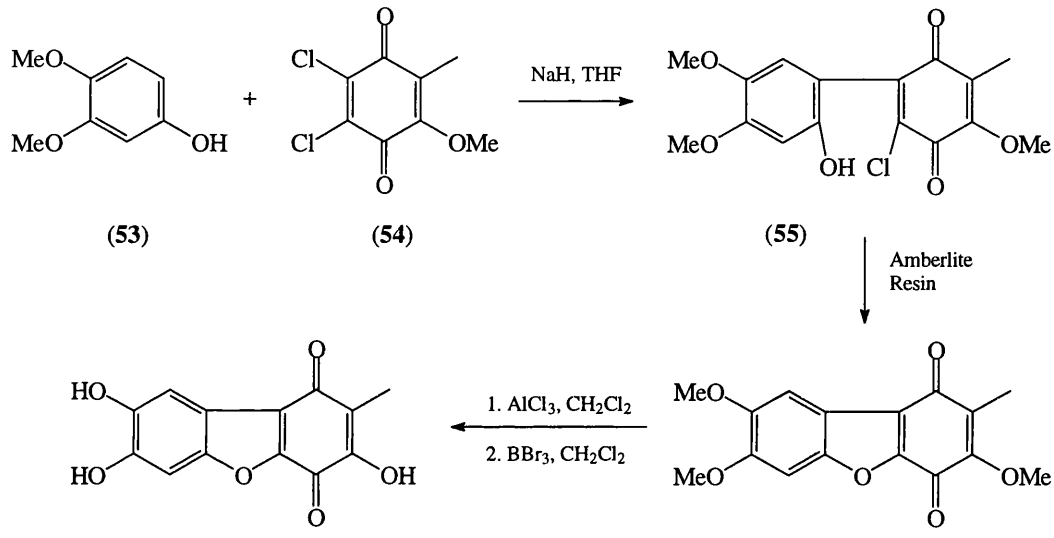


Scheme 4.15

4.1.5 Terashima's Dibenzofuran-1,4-dione Synthesis

Recently the first synthesis of the unique aromatic core, a 3,7,8-trihydroxydibenzofuran-1,4-dione, was reported by Terashima and co-workers[43] following this disconnection, Scheme 4.16. Terashima and co-workers first attempted the addition of 3,4-dimethoxyphenol (**53**) to the known 2-methyl-3-methyl-1,4-benzoquinone but unfortunately under various conditions no coupled or cyclized products were obtained. This lack of reactivity was attributed to the poor nucleophilicity of 3,4-dimethoxyphenol. Attention eventually turned to the 2,3-dichloro-1,4-benzoquinone (**54**) which was found to give the desired coupling product but did not undergo the cyclization in one step. The desired regioselective annulation was effected in a two-step process by first treatment of (**54**) with sodium hydride in THF at -78 °C followed by warming to -35 °C. This gave the C-substituted benzoquinone (**55**) as a single regioisomer in 67% yield. The regiospecificity of the reaction is due the electron-donating methoxy group at C-3 in (**53**). Studies by Terashima with 4-methoxyphenol *i.e.* without the C-3 methoxy present, produced only *O*-substituted product as a single isomer in 48% yield. Subsequent ring closure was carried out by exposure of (**55**) to Amberlite IRA-900 (hydroxide form) in chloroform at 0 °C. Thus annulation was complete in an overall yield of 63% from the phenol. It is worth noting that ring closure with

bases such as LHMDS, NaH, KH, Et_3N, pyr, DBU, K_2CO_3, and Cs_2CO_3 all gave the cyclized product but albeit in less than 20% yield. Deprotection of the hydroxyl functions was effected by treatment with aluminium chloride to give the monomethyl ether, then completed by reaction with boron tribromide to yield the desired 3,7,8-trihydroxydibenzofuran-1,4-dione.



Scheme 4.16

4.1.6 Conclusion

Utilising any of these routes simplifies the retrosynthetic analysis to that of a arenarol/arenarone like structure. The same approach to both structural types can be used as they are easily interconverted either by oxidation or reduction. Disconnection across the C15-C16 bond gives rise to two simpler fragments, one a simple protected catechol derivative, the other a suitably functionalized *cis*-decalin.

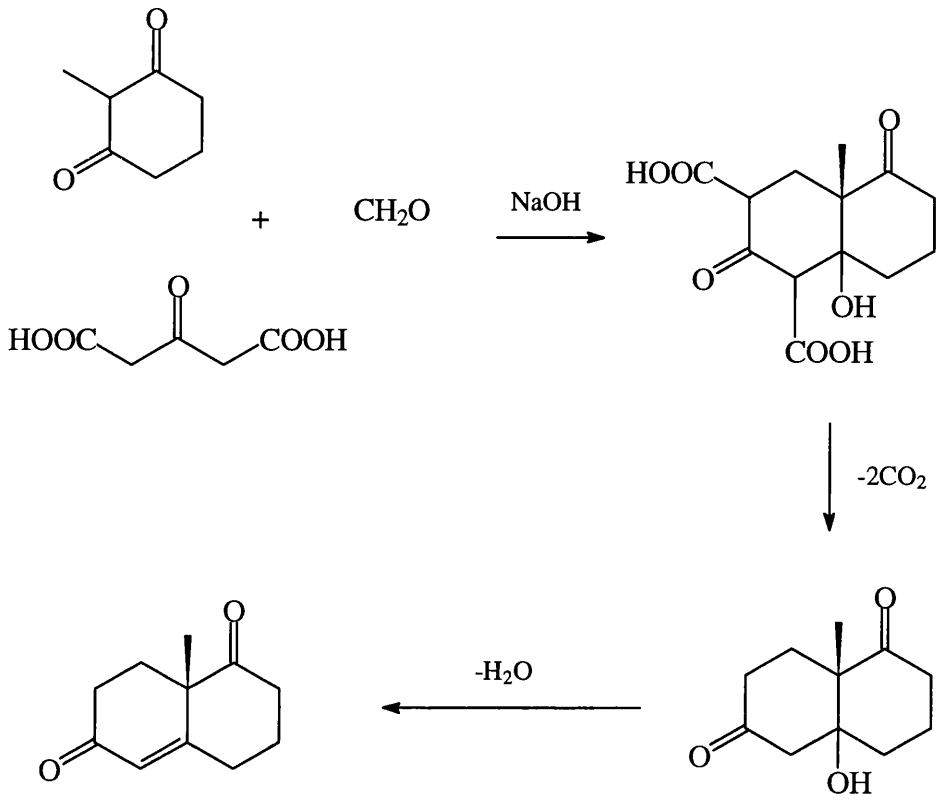
4.2 *cis*-Decalin Analysis

The decalin skeleton is an integral feature of many natural products including those of marine origin. The importance of this structural feature in natural products has resulted in the abundance of strategies that have been developed towards its synthesis. Many approaches such as Robinson annulation and Diels-Alder cycloaddition are well-established. However, many other methods, including the Heck reaction, double-Michael, tandem Michael-Claisen condensation, oxy-Cope and radical cyclizations have all been utilised in decalin synthesis. The main body of literature is concerned with *trans*-fused decalin formation; in contrast, syntheses of the *cis*-decalin skeleton are relatively sparse. This is due to the predominance of the *trans*-fused ring in natural products such as terpenoids and steroids. *cis*-Fused decalin synthesis is therefore worthy of review.

4.2.1 Synthesis of *cis*-Decalins

4.2.1.1 Robinson Annulation

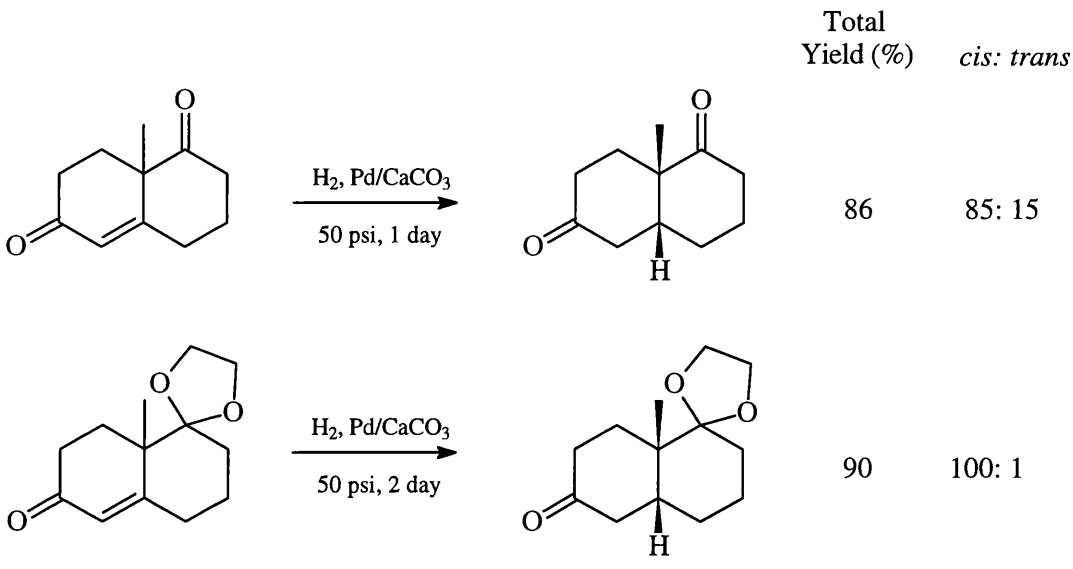
Robinson annulation is the best established synthetic route to the decalin framework and yields an enone.[44] The enone can then be elaborated to give the *cis*-decalin. The Wieland-Miescher ketone synthesis[45] acts as a general example, Scheme 4.17.



Scheme 4.17

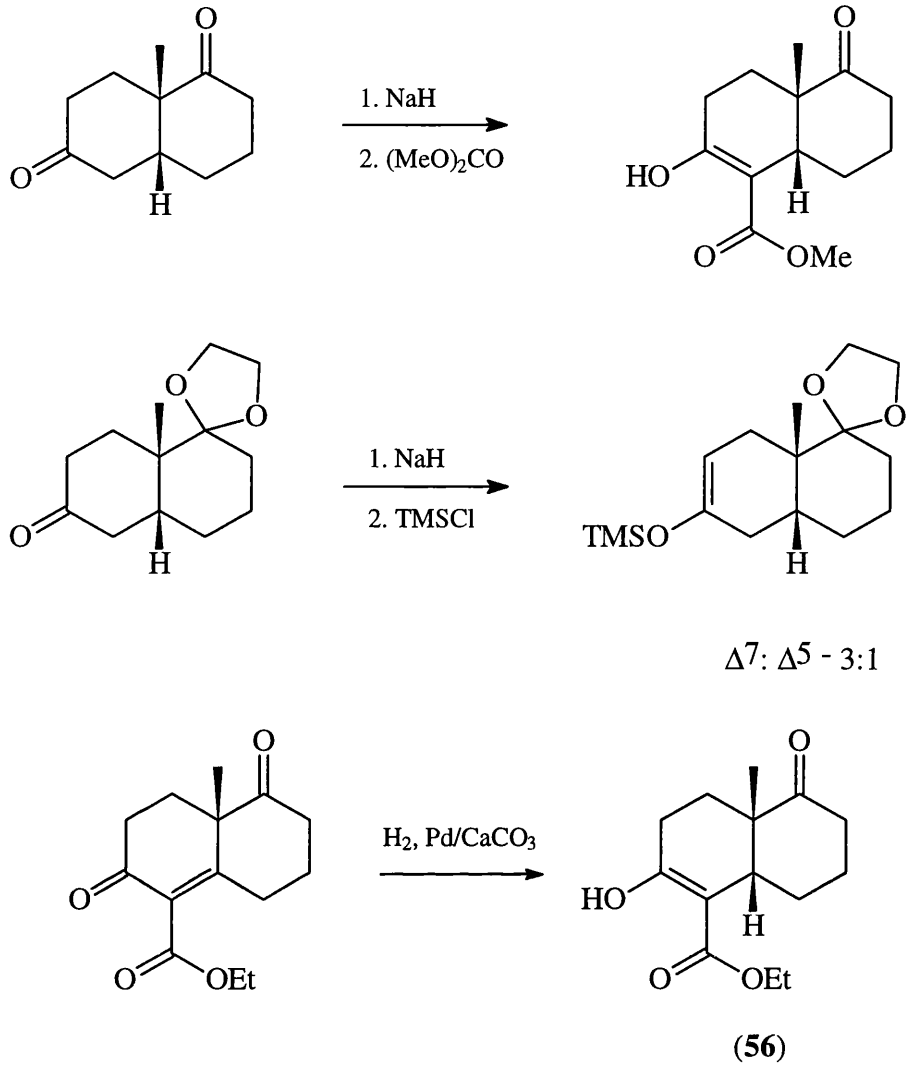
4.2.1.1.1 Hydrogenation

The problem of further manipulation to yield the *cis*-decalin has been approached in various ways. With the Wieland-Miescher ketone, hydrogenation of the olefin, using a metal catalyst, favours formation of the *cis*-fused product and also catalytic hydrogenation of the ketal protected ketone gives strong *cis* selectivity,[46] Scheme 4.18.



Scheme 4.18

Functionalisation is possible *via* enolate formation and trapping with various electrophiles. Scheme 4.19 gives an example of the selectivity possible by this method. Protection of the C-1 carbonyl as its ketal alters selectivity away from the C-5 enolate towards the C-7 enolate. This is demonstrated by formation of the silyl enol ether. Alternatively the hydrogenation of a related bicyclic enone, where the C-5 position is prefunctionalized with an ethoxycarbonyl group, is exclusive towards the *cis*-fused decalin to give (**56**) in 94% yield, Scheme 4.19.

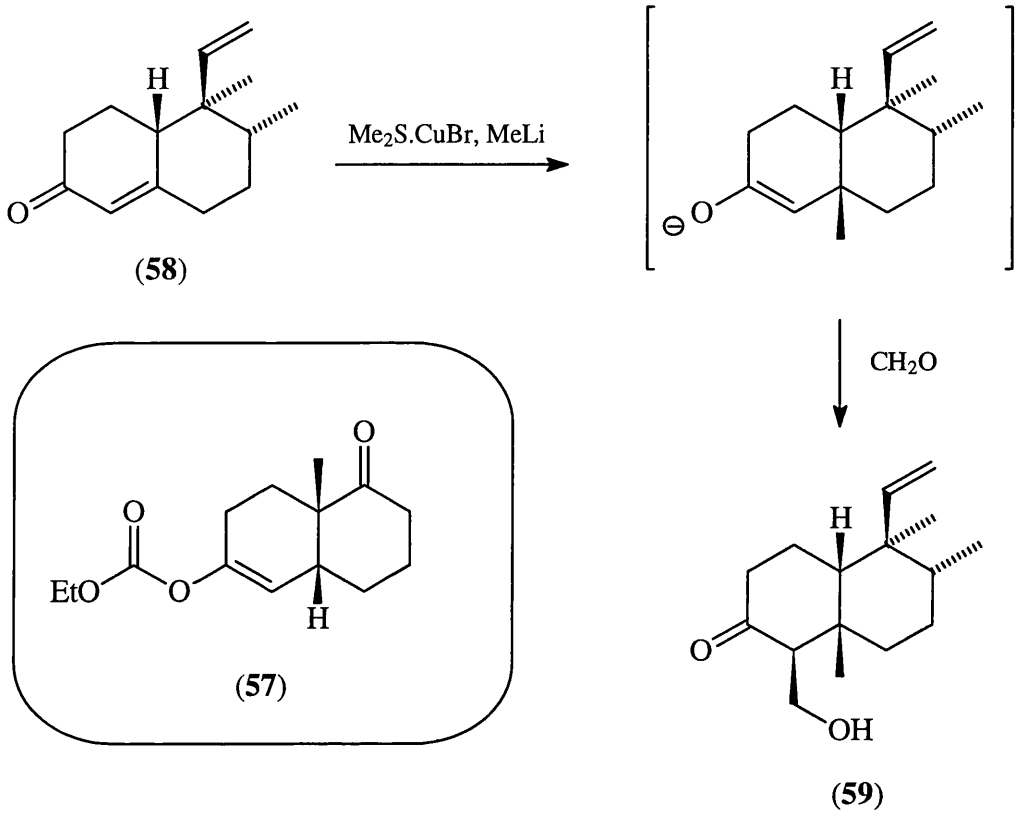


Scheme 4.19

4.2.1.1.2 Conjugate Addition

Conjugate addition of hydride[47,48] or methyl[49] cuprate reagent to the 4 position of the enone has been used to give the desired *cis*-decalin. Reaction of the Wieland-Miescher ketone with Stryker's reagent - $[(Ph_3P)CuH]_6$ - gives ketone (**57**) as a single stereoisomer, after treatment with ethyl chloroformate. Delivery of the hydride occurs from the less hindered convex side of the enone and therefore produces *cis*-fusion. Similarly, Tokoroyama has exploited this selectivity to introduce stereospecifically an angular methyl to the 4–position of enone[49] (**58**).

Reaction of (**58**) with the methyl cuprate reagent yields exclusively the *cis*-fused enolate, which is then stereospecifically trapped by formaldehyde gas to yield the *cis*-hydroxy ketone (**59**), Scheme 4.20.

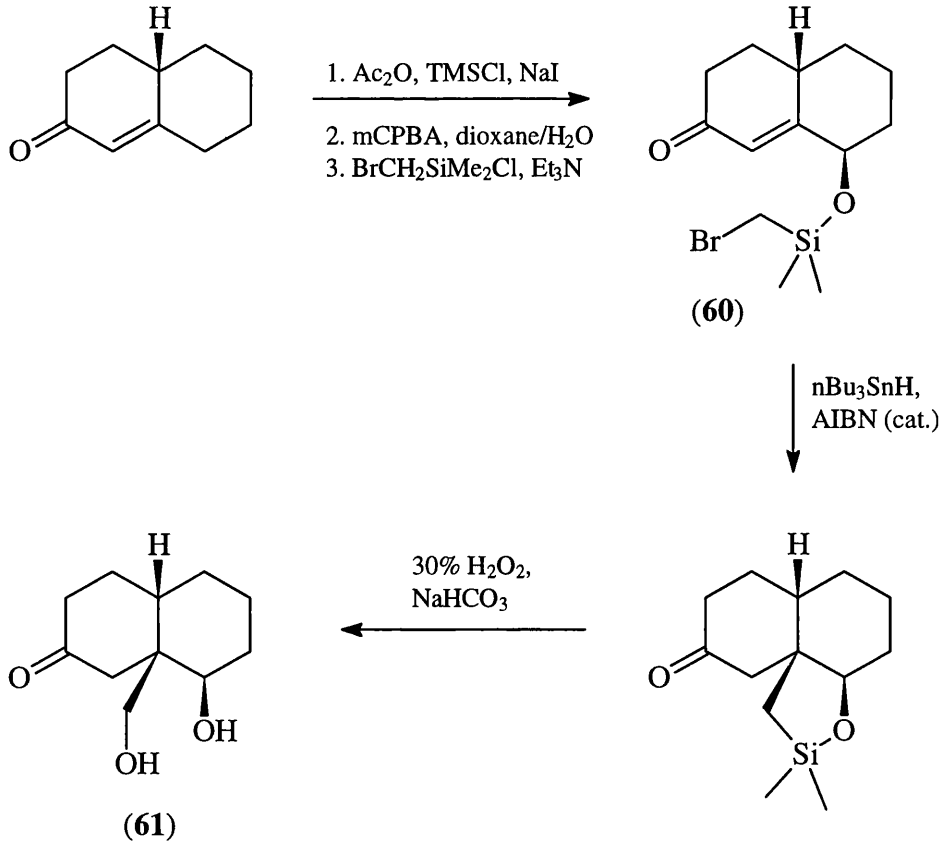


Scheme 4.20

4.2.1.1.3 Silyl Methyl Radical

An interesting and novel approach towards the problem of introducing *cis*-stereochemistry to bicyclic enones was the extension, by Lallemand,[50] of the Stork silyl methyl radical cyclization reaction.[51] Lallemand's approach introduces stereospecifically a hydroxymethyl function at the angular position of an allylic alcohol. The hydroxyl group of the allylic alcohol is utilised as an anchor to direct the reaction as depicted in Scheme 4.21. Synthesis of the desired hydroxy enone is

from the requisite bicyclic enone by dienol acetate formation then oxidation with m-CPBA. The stereochemistry of the hydroxyl group can also be inverted by the Mitsunobu protocol. Treatment of the alcohol with bromomethyl dimethylchlorosilane and triethylamine in dichloromethane gives the bromo silyl ether derivative necessary for the radical cyclization. Exposure of the bromide (**60**) to tri-n-butyltin hydride results in stereospecific cyclization and, after oxidative cleavage gives keto-diol (**61**).

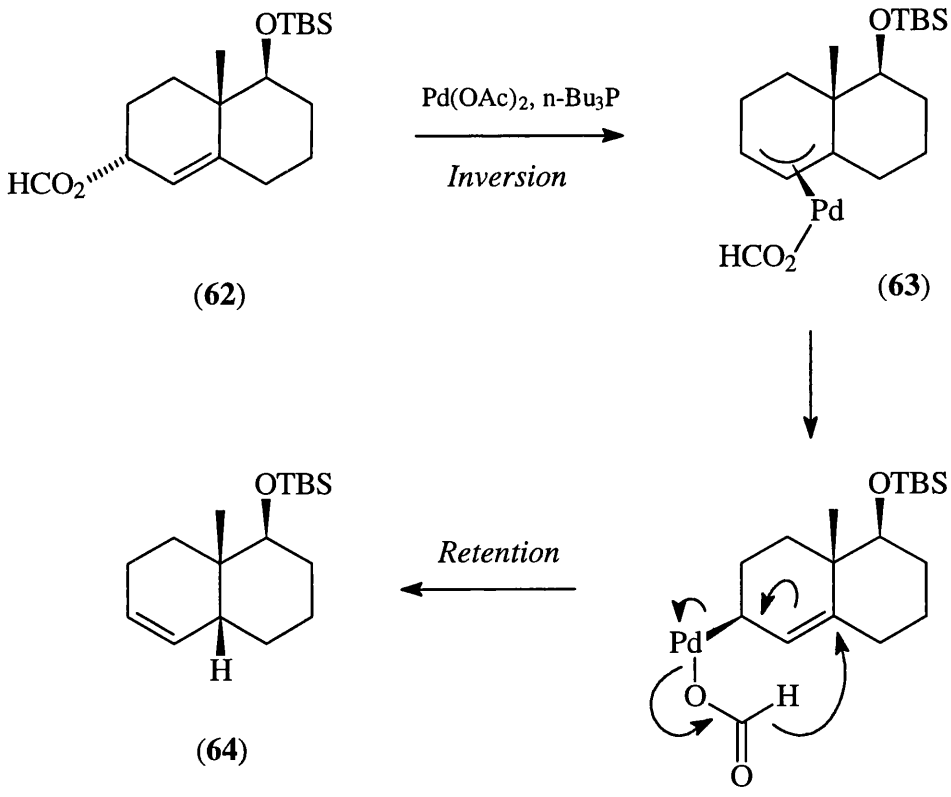


Scheme 4.21

4.2.1.1.4 Pd-Catalysed Hydrogenolysis

Palladium-catalysed regioselective and stereoselective hydrogenolysis of allylic formates has also been used to construct *cis*-fused decalin frameworks. Mandai

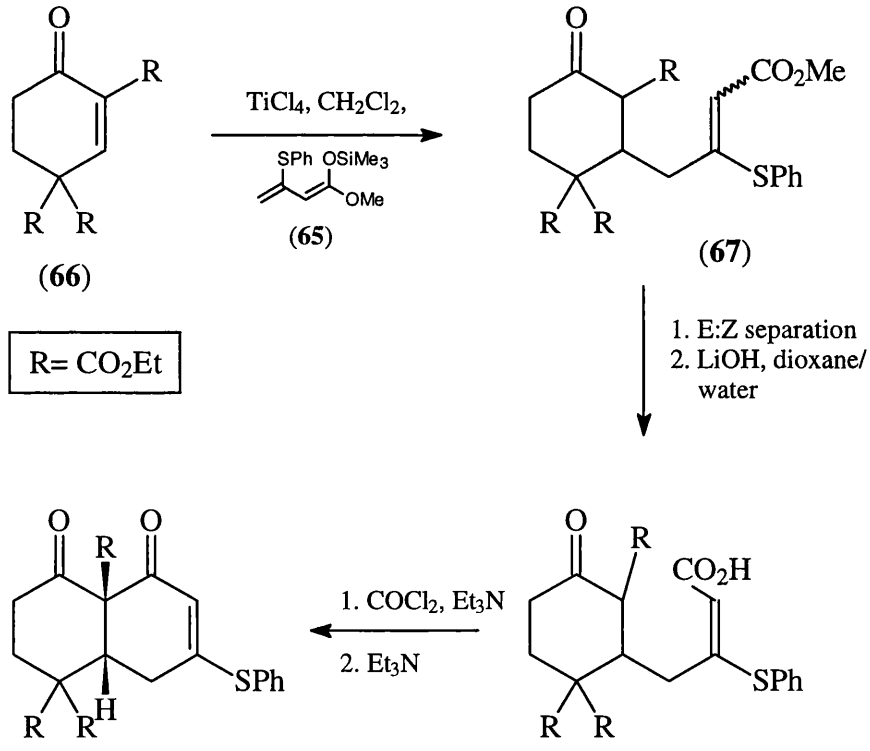
and Tsuji have shown that treatment of an allylic formate with $Pd(OAc)_2$ in the presence of n-Bu_3P affords olefins.[52] Extension of this to decalins has shown that treatment of allylic formate (**62**) under the conditions outlined in Scheme 4.22 gives rise to *cis* or *trans* decalins depending on the stereochemistry of the starting formate. The reaction proceeds initially by formation of the π-allylpalladium complex (**63**) with inversion of stereochemistry. Subsequent addition of the hard hydride nucleophile from the palladium formate to the angular carbon occurs with retention, thus overall inversion takes place to give a *cis*-decalin (**64**).



Scheme 4.22

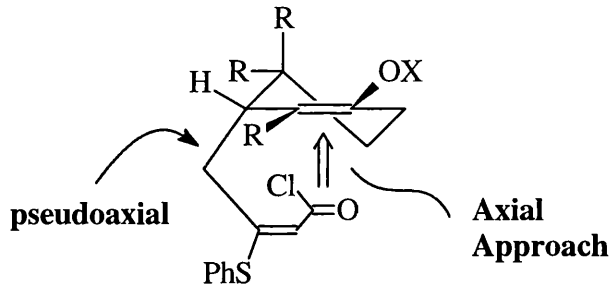
4.2.1.2 Michael-Claisen Condensation

Use of a tandem Michael-Claisen condensation to assemble the decalin structure has been extended by Chan and co-workers to give exclusively the *cis*-stereochemistry.[53] Similar methods developed by Ley and Lallemand interestingly give the opposite *trans*-stereochemistry.[54] Michael addition of silylketene acetal (**65**) to enone (**66**) gave the adduct (**67**) in 54% yield, Scheme 4.23. Hydrolysis then chlorination gave the intermediate acid chloride. The crude acid chloride was then cleanly cyclised in the presence of triethylamine to yield the *cis*-fused decalin in excellent 72% yield, as the sole stereoisomer. This highly functionalised *cis*-decalin could be converted into various intermediates required for natural product synthesis.



Scheme 4.23

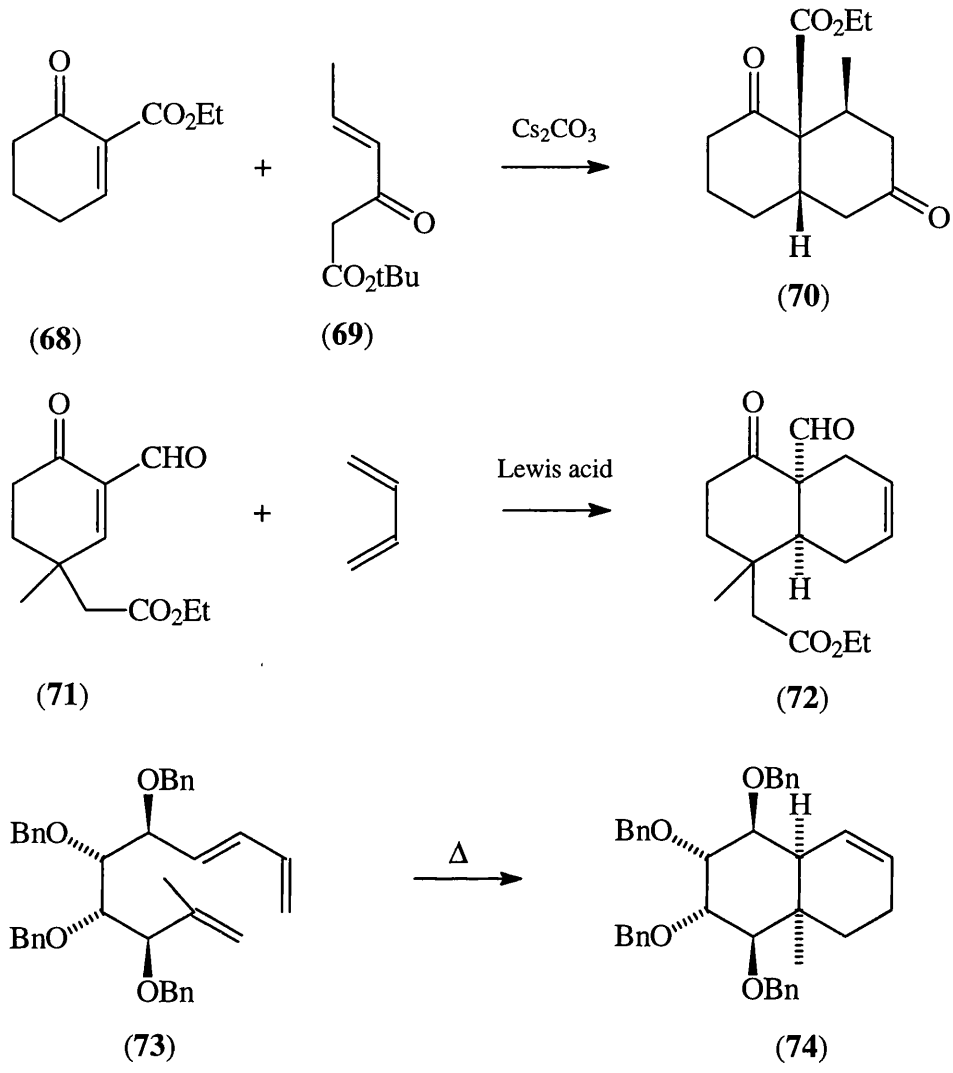
The preference for *cis*-stereochemistry has been attributed to the predominance of the stabilised enolate ion of the conformation in which the tethered electrophile adopts a pseudoaxial position, due to allylic strain considerations, Scheme 4.24. Cyclization of this conformer will occur with axial approach of the electrophile being preferred thus *cis* product geometry is obtained.



Scheme 4.24

4.2.1.3 Diels-Alder Cycloaddition

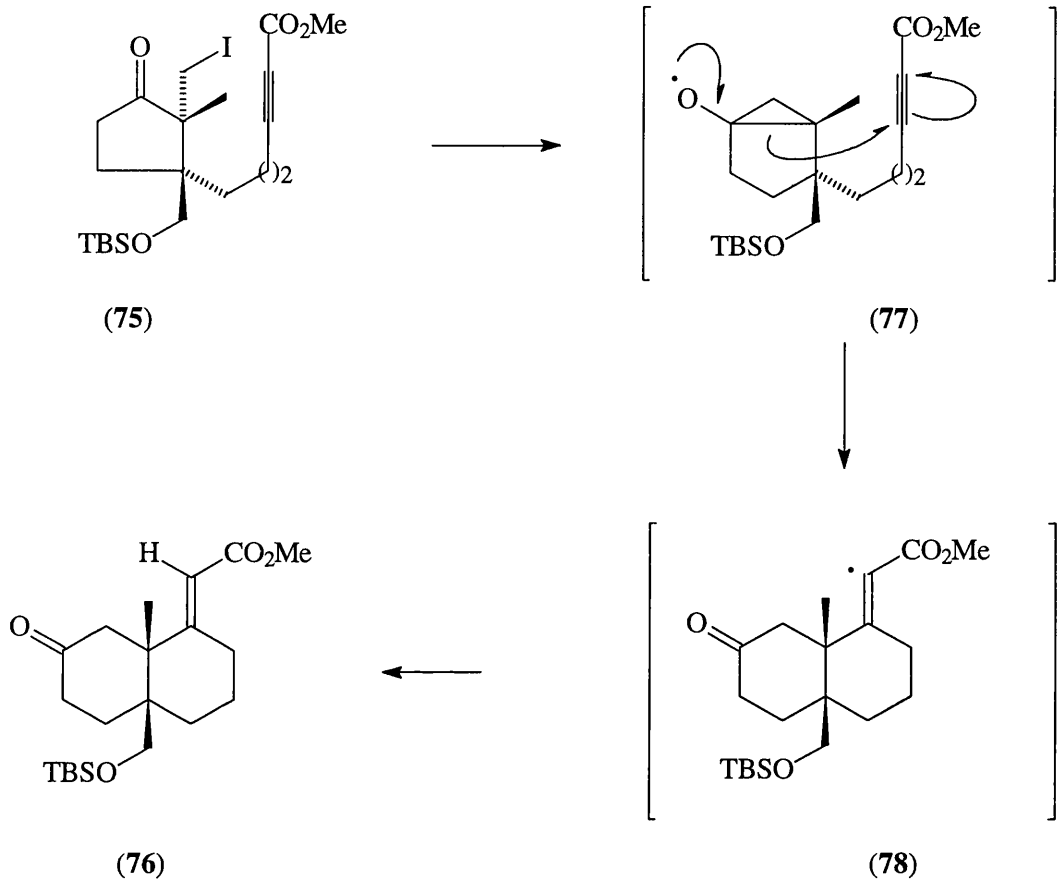
Many examples of *cis*-fused decalin syntheses using a Diels-Alder approach have been published. Delongchamps has shown that enones (**68**) and (**69**) in the presence of Cs_2CO_3 can undergo a Diels-Alder cycloaddition - by firstly enolization - to give, after hydrolysis and decarboxylation, *cis*-fused decalin[55] (**70**). Liu has also reported the use of the Diels-Alder approach as a convenient route to *cis*-decalins.[56] The Lewis acid catalysed cycloaddition of enone (**71**) and butadiene proceeds in good yield to give (**72**). Lukacs has observed high diastereoselectivity in the intramolecular Diels-Alder reaction of triene (**73**), prepared from the carbohydrate galactose.[57] Thermal intramolecular Diels-Alder cycloaddition in toluene gave (**74**) which contains an angular methyl group and *cis*-ring fusion.



Scheme 4.25

4.2.1.4 Radical Cyclization

Recently Nemoto has described a novel stereocontrolled radical route to *cis*-fused decalins.[58] Acetylenic iodide (**75**) was transformed into the *cis*-decalin (**76**) in 85% yield by exposure to tri-n-butyltin hydride, Scheme 4.26. The cyclization proceeds *via* a cyclopropyl alkoxy radical (**77**) to give the thermodynamically favoured *trans* product from the vinyl radical (**78**).

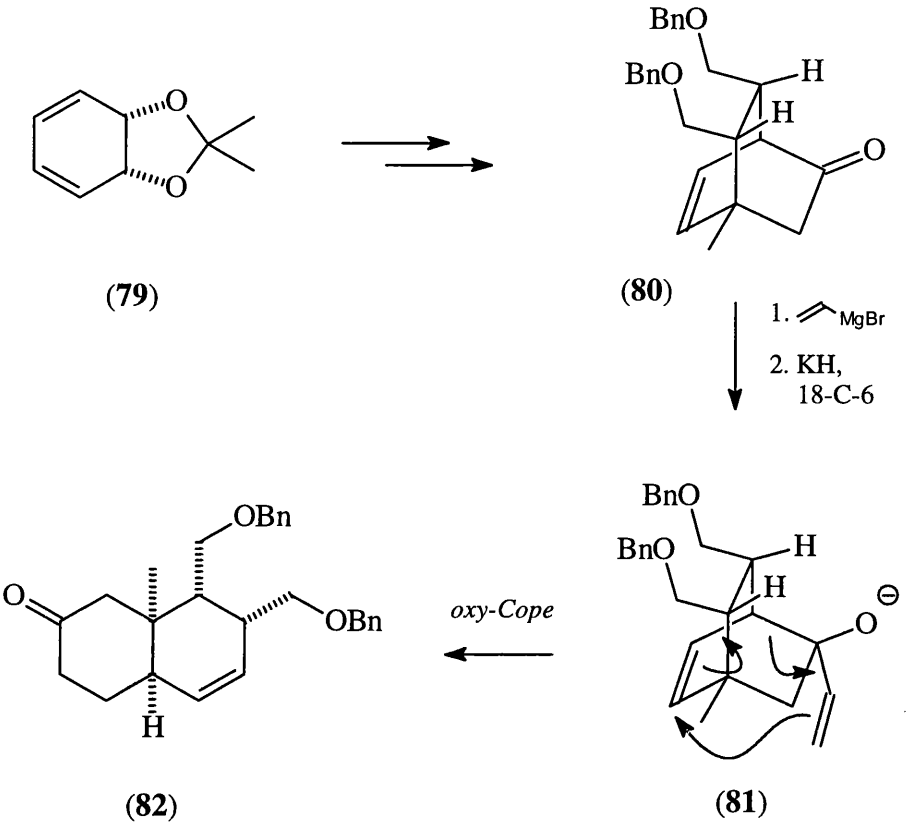


Scheme 4.26

4.2.1.5 Oxy-Cope Rearrangement

Anionic oxy-Cope rearrangements have also been utilised in the efficient stereospecific synthesis of highly functionalized *cis*-decalins. Banwell[59] and Liao[60] have independently established a route to *cis*-decalins from 2-vinyl bicyclo[2.2.2]octenes using the anionic oxy-Cope rearrangement as the key step. An example from Banwell's work (Scheme 4.27) starts from the readily prepared protected diol (**79**) and by a sequence involving a Diels-Alder cycloaddition of maleic anhydride with the acetonide then reduction and protection-deprotection gives a [2.2.2]bicyclooctane. Oxidation, acetylation and reduction with SmI_2 in

acetic acid gives the ketone (**80**). Nucleophilic attack by vinyl magnesium bromide gives the key allyl alcohol required for rearrangment. Under standard anionic oxy-Cope conditions (**81**) rearranges to the *cis*-decalin (**82**) in 80% yield.

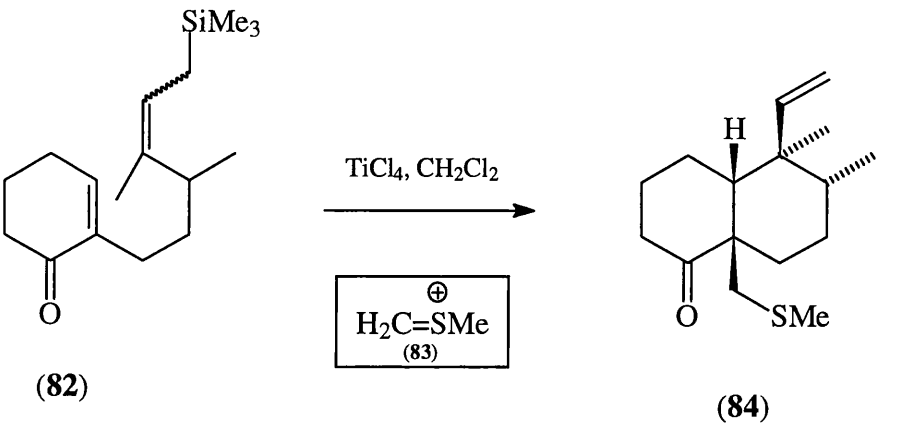


Scheme 4.27

4.2.1.6 Hosomi-Sakurai Reaction

Tokoroyama has also established a route to the *cis*-decalin framework by an intramolecular Hosomi-Sakurai reaction.[61] The Hosomi-Sakurai reaction involves the Michael addition of an allylsilane to an enone under Lewis acid catalysed conditions.[62] Tokoroyama has used this methodology to show that the cyclization of (**82**) proceeds with remarkable diastereoselectivity, in the presence of $TiCl_4$ and HMPA, to yield an intermediate enolate anion. Subsequent trapping of this enolate anion is stereospecific and attack of the electrophile (**83**) - formed from reaction of

$TiCl_4$ with $ClCH_2SMe$ - occurs only from the convex side of the titanium enolate to give the *cis*-decalin (**84**), Scheme 4.28.

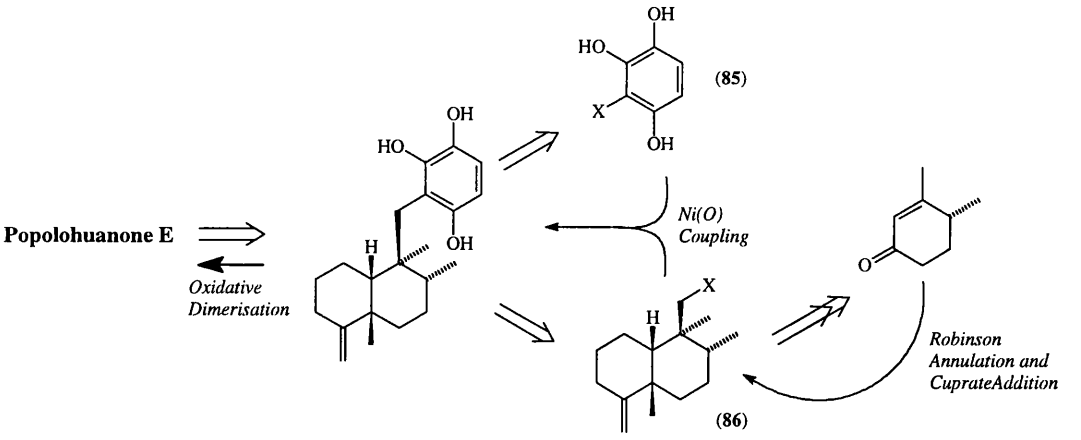


(**82**) (**84**)

Scheme 4.28

4.3 Conclusion - First Generation Strategy

Analysis of popolohuanone E gives rise to a wide variety of possible synthetic routes; however, the inital approach chosen was by the most convergent envisaged. This was to disconnect across the furan ring to give the monomeric 6'-hydroxy arenarol and to further disconnect this precursor to a *cis*-decalin (**86**) and the aryl halide (**85**), Scheme 4.27. This route should not only give access to popolohuanone E but provide a general synthetic route to all the related marine natural products. Preparation of the decalin fragment was envisaged initially *via* a modification of Tokoroyama's route *via* the bicyclic enone (**58**). It was hoped that this would give rapid access to the *cis*-decalin fragment (**86**). The bicyclic enone was to be synthesised from 3,4-dimethylcyclohex-2-enone and then *cis*-decalin formation by stereospecific cuprate addition and enolate trapping.

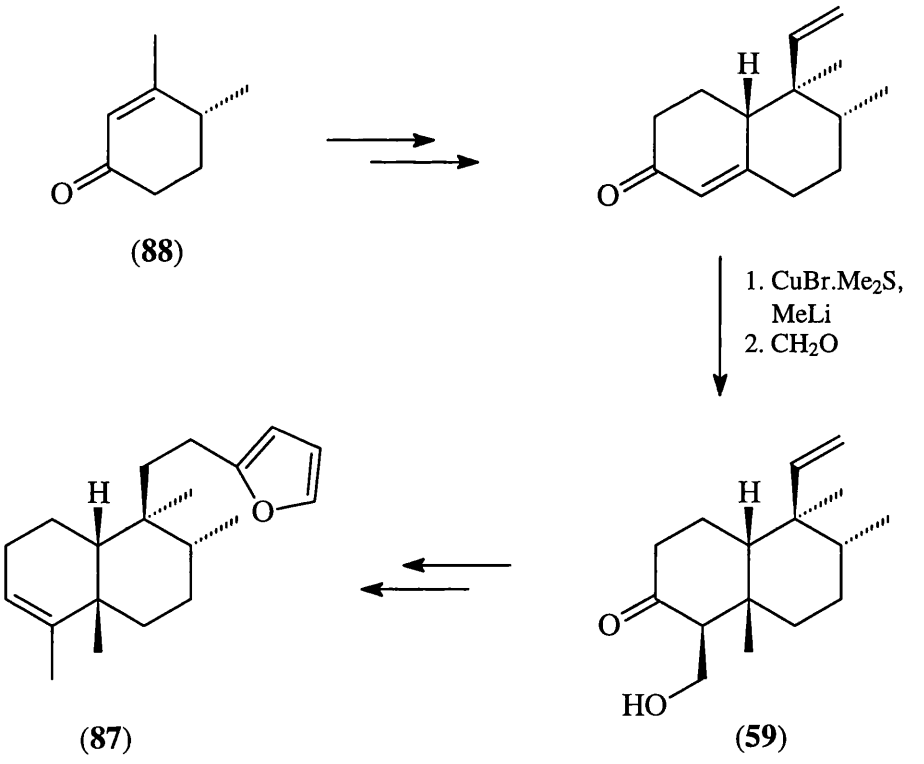


Scheme 4.27

Further manipulation would hopefully give a suitably functionalized decalin to enable coupling to the aryl halide (**85**). The reaction was initially envisaged by a nickel(0) mediated cross-coupling reaction between the neopentyl halide and the *o,o'*-disubstituted aryl halide, Scheme 4.27.

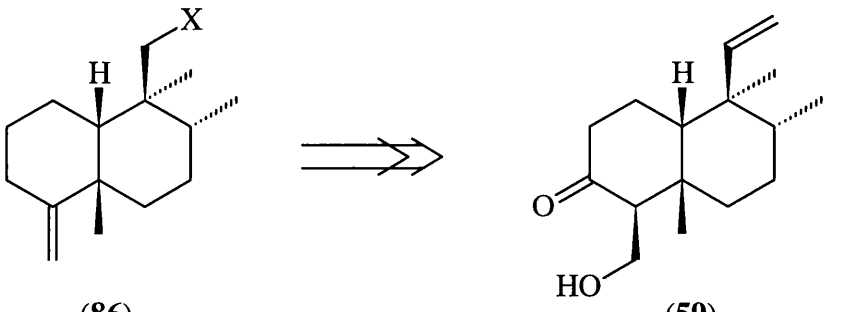
5. First Generation Decalin Synthesis

Straightforward utilisation of Tokoroyama's synthesis of the *cis*-clerodane diterpenoid[63] (**87**) was chosen as the basis of the initial route to fragment (**86**). Starting from 3,4-dimethylcyclohex-2-enone (**88**) and by a sequence that included two stereospecific cuprate additions and a Robinson annulation the intermediate *cis*-decalin (**59**) was synthesised. Further elaboration converted this useful decalin into the clerodane (**87**), Scheme 5.1.



Scheme 5.1

Therefore following this route to known decalin (**59**) and subsequent manipulation of the functional groups should give rapid access to coupling fragment (**86**), Scheme 5.2.

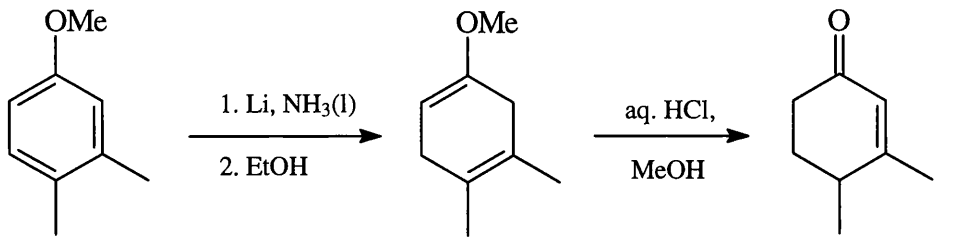


(86) (59)

Scheme 5.2

5.1 Synthesis of Bicyclic Enone (94)

3,4-Dimethylcyclohex-2-enone (**88**) was obtained from the corresponding 3,4-dimethylanisole by Birch reduction[64] with lithium in liquid ammonia to give the intermediate enol ether (**89**). Hydrolysis and double bond migration gave the desired enone (**88**) in 52 % yield after distillation, Scheme 5.3. All spectroscopic data were in accordance with the literature. The methyl singlet and doublet at δ 1.96 and 1.20 respectively in the proton NMR spectrum and the presence of the olefinic signal at δ 5.82 were evidence for the exclusive isolation of the α,β-enone.

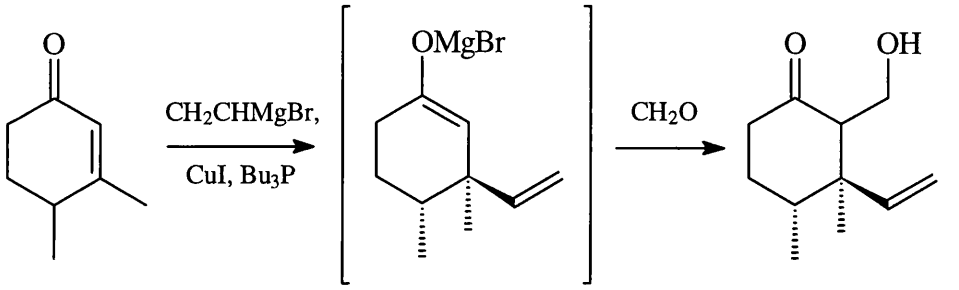


(89) (88)

Scheme 5.3

To obtain the desired *cis* relationship of the two methyl groups, conjugate addition to 3,4-dimethylcyclohex-2-en-1-one (**88**) was carried out according to the

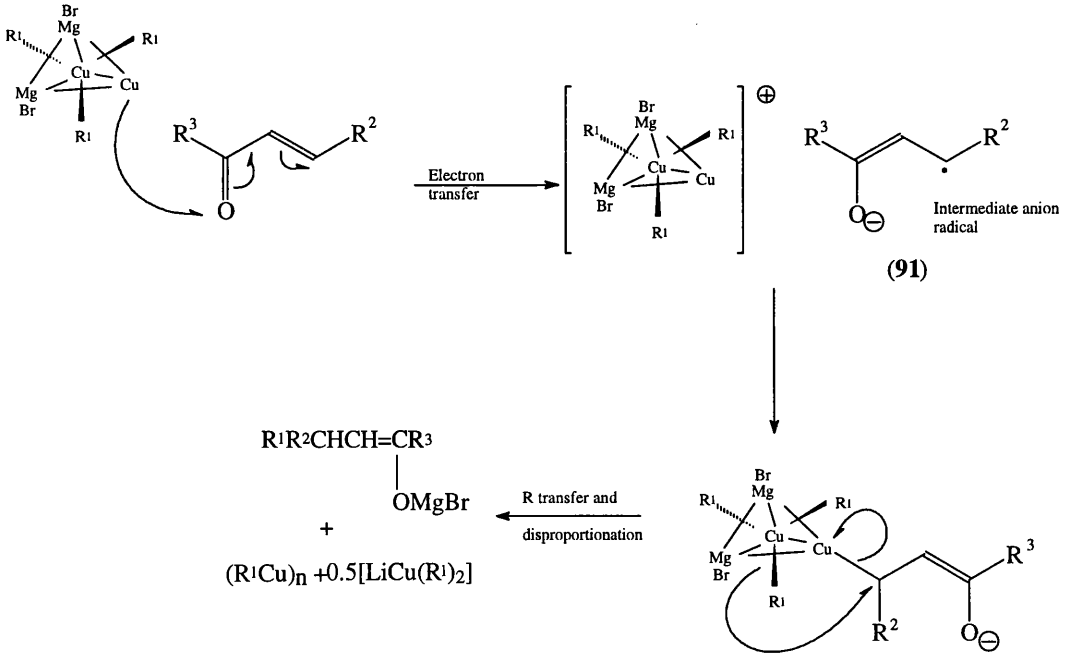
procedure of Ziegler.[65] Addition of the vinyl cuprate reagent - vinylmagnesium bromide-CuI-tri-n-butylphosphine complex - to the enone proceeds with 100% stereoselectivity, that is only the isomer with the *cis* related methyl groups is formed, Scheme 5.4.



(88) **(90)**

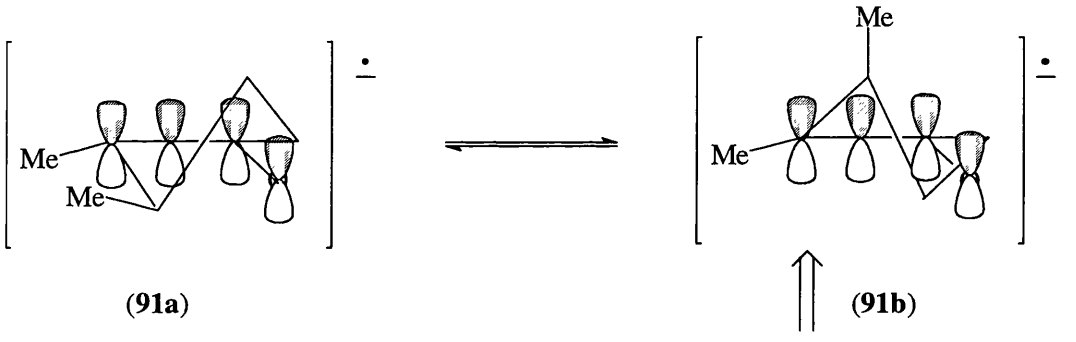
Scheme 5.4

To understand the selectivity, the mechanism of the conjugate addition has to be considered. It is thought that the mechanism proceeds *via* the electron transfer process outlined in Scheme 5.5.



Scheme 5.5

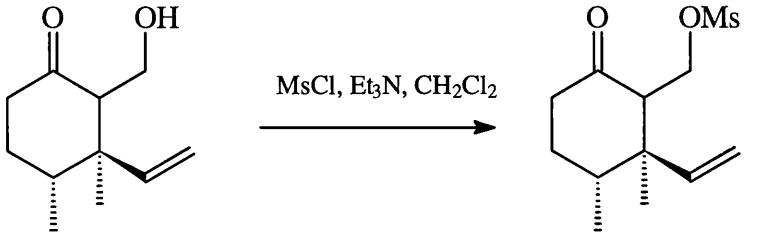
The conformation adopted by the intermediate radical anion (**91**) is the decisive factor. Scheme 5.6 shows two possible conformations; the axial conformation of the 4-methyl group is favoured, to avoid 1,2-interactions with the 3-methyl group. In this conformation there are no flagpole interactions across the ring because of the substantial sp^2 hybridisation of the three carbon atoms shown. Finally, trapping of the enolate anion with formaldehyde gas gave a diastereomeric mixture of the alcohols (**90**), Scheme 5.4.



(**91a**) (**91b**)

Scheme 5.6

Mesylation of the alcohol by reaction with MsCl, in the presence of Et_3N and with dichloromethane as solvent, proceeded smoothly in preparation for substitution with the anion of methyl acetoacetate, Scheme 5.7.

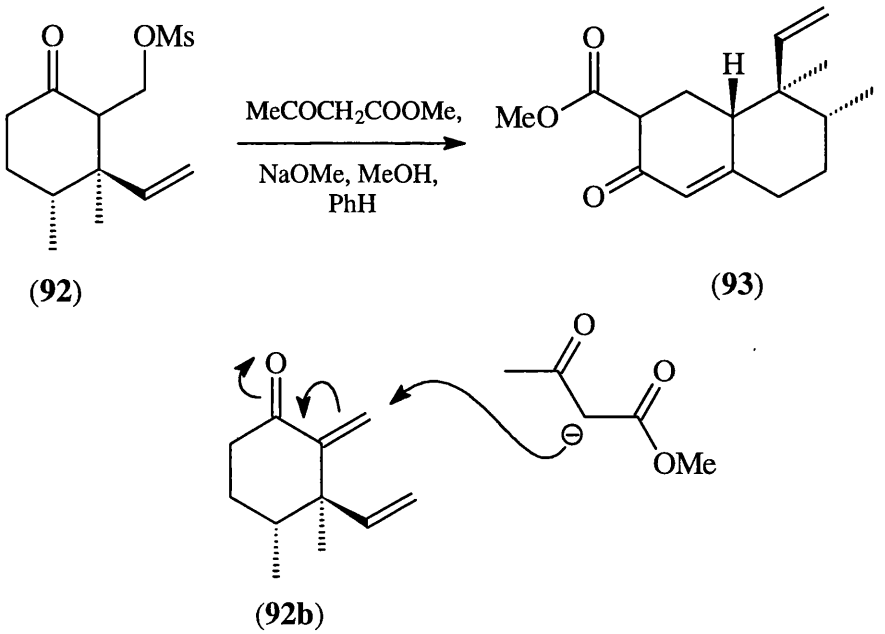


(**90**) (**92**)

Scheme 5.7

Purification of the unstable mesylate (**92**) was required before proceeding with the next reaction as this greatly affected the yield. Chromatography gave the mesylate in >98% yield. All spectroscopic data were in accordance with the literature values with the methanesulfonyl protons resonating at δ 3.02 in the proton NMR spectrum.

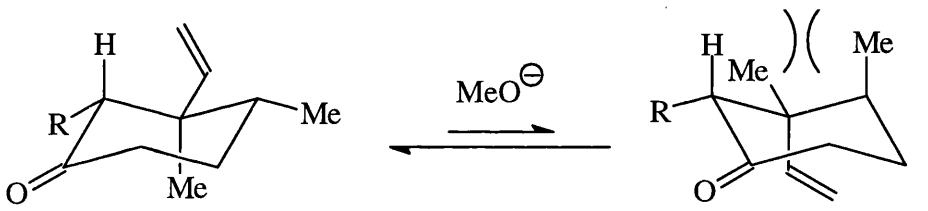
Reaction of the mesylate with methyl acetoacetate in sodium methoxide gave enone (**93**), Scheme 5.8. Under the reaction conditions, deprotonation of methyl acetoacetate will occur to give the resonance stabilised anion, Scheme 5.8. Mechanistically an S_N2 displacement of the mesylate leaving group would give the desired intermediate (**92a**). However, the reaction conditions could also lead to elimination of methane sulfonic acid to form the enone (**92b**). Michael addition of the anion of methyl acetoacetate to this enone would also give the desired intermediate.



Scheme 5.8

Subsequent ring closure by a Robinson type annulation occurred under the same conditions and afforded the bicyclic enone (**93**).

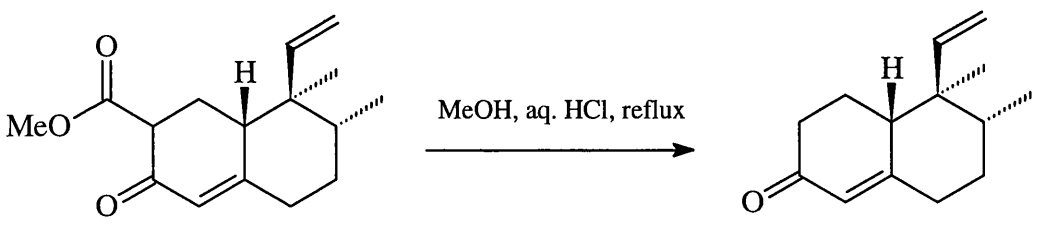
The stereoselectivity of the ring closure, that is the *anti* relationship of the C-4a proton and the C-6 methyl, has been attributed to thermodynamic control. The *anti* relationship is thermodynamically favoured over the *syn* due to the 1,3-diaxial interaction between the C-4a proton and the C-6 methyl. The intermediate (**92a**) must undergo rapid epimerisation to place the largest substituent (R = $-CH_2CH(COMe)COOMe$) axial prior to ring closure, Scheme 5.9.



(**92a**)

Scheme 5.9

The bicyclic enone (**93**) was then heated at reflux in methanolic HCl, without prior purification, to bring about hydrolysis and decarboxylation and furnish the enone (**94**), Scheme 5.10.



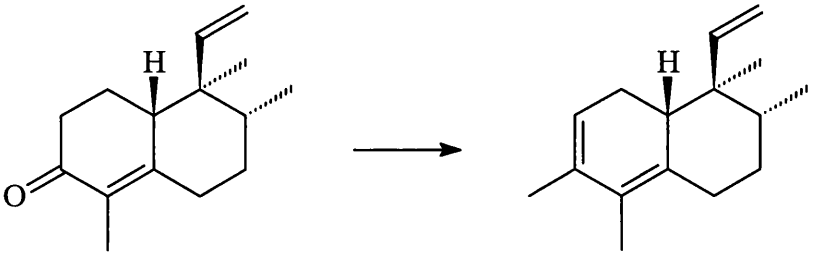
(**93**) (**94**)

Scheme 5.10

An approximate yield of 10% of the deconjugated product was also obtained in accordance with literature results; this was readily removed by silica gel chromatography. All spectroscopic data were in accordance with the literature and only one diastereoisomer was obtained.

5.2 Conjugate Addition/Alkylation

Tokoroyama's method of introducing *cis* ring fusion entails the conjugate addition of a methyl nucleophile to the 4-position of a bicyclic enone. Tokoroyama utilised this procedure in the synthesis of various clerodane natural products; however, some problems were encountered. Initially conjugate addition to the enone (**95**) was attempted but unfortunately under all conditions except that of House, the desired 1,4-addition product was elusive. Even under House's conditions[66] a yield of <10% was obtained; however the result was not always reproducible. In most cases the product was that of 1,2-addition.

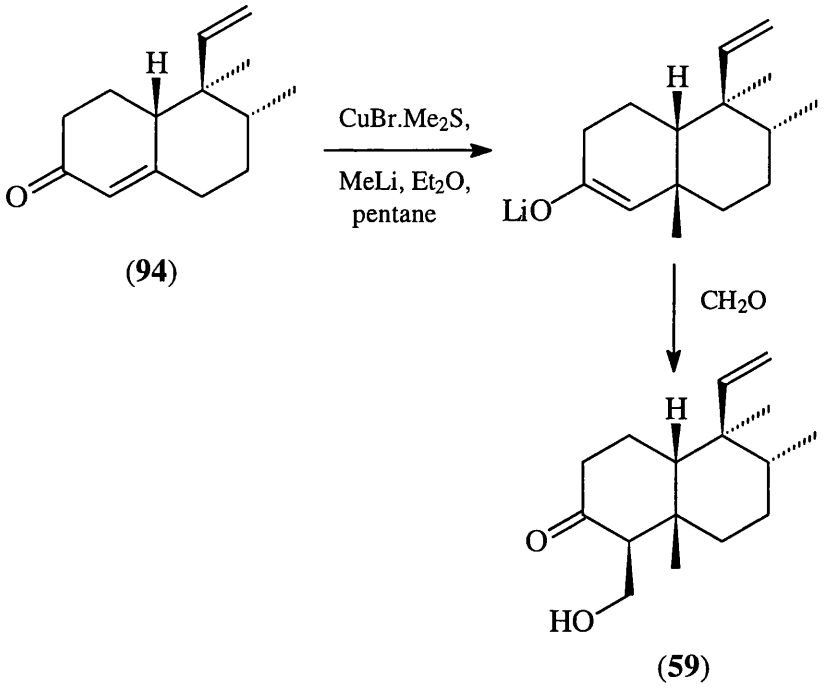


(**95**) (**96**)

Scheme 5.11

Attempts to improve the yield by the addition of Lewis acids proved futile and mainly resulted in the formation of the diene (**96**), by 1,2-addition and subsequent elimination. Interestingly the use of TMSCl as an additive did give the desired product, albeit in poor yield (~18%). Tokoroyama has reasoned, using House's

concept of electron transfer,[67] that the reduction potential of enone (**95**) can be estimated to be -2.2 V. The threshold for addition to occur, according to House, is -2.4 V, thus this system is not very susceptible towards conjugate addition. Subsequent attention was turned to the use of the more reactive enone (**94**), which underwent conjugate addition using Me_2S.CuBr-MeLi and could be alkylated by trapping the resultant enolate anion with formaldehyde, Scheme 5.12.

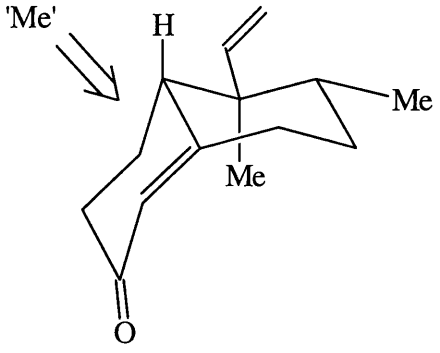


(**94**)

(**59**)

Scheme 5.12

Addition occurs from the convex side of the Δ^4-octalone system; this is the less sterically demanding approach. Hence, the angular methyl is placed on the same side as the C-4a proton. In this case it is worth noting that approach to the opposite side of the enone is also blocked by the axial methyl on C-5, Scheme 5.13.



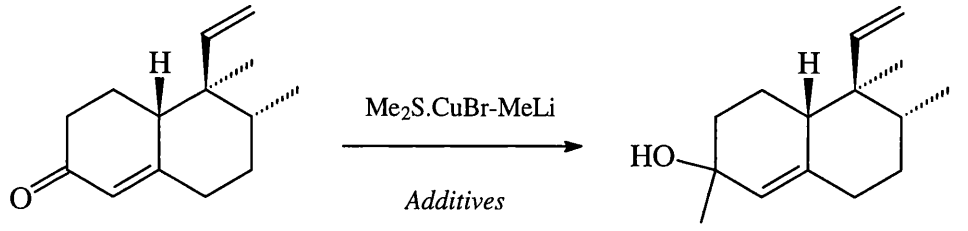
(**94**)

Scheme 5.13

Conjugate addition to enone (**94**) following Tokoroyama's conditions unfortunately gave a low yield of 1,4-adduct after stereospecific trapping of the enolate with gaseous formaldehyde. Only the convex face of the intermediate enolate is accessible by the electrophile. After much experimentation it was found that the yield could be increased by using recrystallised $Me_2S.CuBr$ and increasing the reaction time from 1½ hrs to 4 hrs. A maximum yield of 33 % of (**59**) was obtainable. Once again all spectroscopic data were in accordance with Tokoroyama's literature values with the angular methyl signal, a singlet, resonating at δ 27.5 in the ^{13}C NMR spectrum. The diastereotopic hydroxymethyl protons gave the expected double doublets at δ 3.85 and δ 3.58. The commercially available $Me_2S.CuBr$ was inferior to the recrystallised material in all experiments carried out. Interestingly, addition of copper wire, following a report by Fuchs,[68] to the reaction using the non-purified material gave comparable results to that of the freshly recrystallised complex.

The inconsistency and low yield of this reaction prompted further investigation of the conjugate addition. Addition using dimethylcopper lithium[69] or

$Me_2Cu(CN)Li$[70] was attempted but only starting material was recovered in both cases. Attention was then turned to the use of additives[71] ($TiCl_4$, TMSCl and $BF_3.Et_2O$) with the $Me_2S.CuBr$-MeLi system, but unfortunately the results were similar to those reported by Tokoroyama using enone (**95**), only 1,2-addition being observed even with TMSCl, Scheme 5.14.

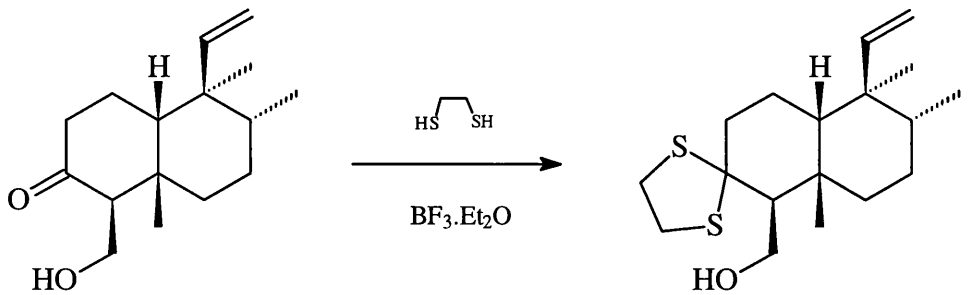


(**94**) (**94a**)

Scheme 5.14

5.3 Deoxygenation

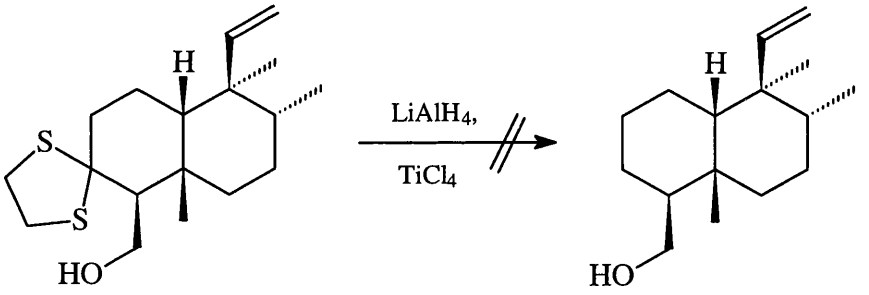
Albeit on a small scale, further elaboration of the *cis*-decalin (**59**) was attempted in order to obtain the desired decalin for popolohuanone E synthesis. Removal of the carbonyl function was attempted initially by formation of the dithioketal (**97**) and then reduction by exposure to Raney nickel.



(**59**) (**97**)

Scheme 5.15

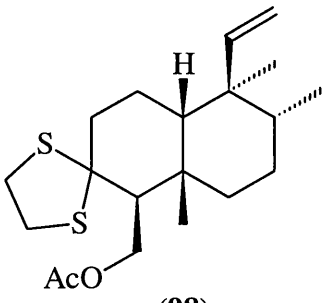
Standard Lewis acid catalysed conditions[72] were used to furnish the dithioketal in disappointing 19 % yield after purification by silica gel chromatography, Scheme 5.15. The absence of a carbonyl signal in the ^{13}C NMR spectrum coupled with the presence of the quaternary carbon at δ 73.2 supported the thioketal structure. Further disappointment arose when reductive removal of the ketal was attempted. Under standard reaction conditions[73] and with addition of large quantities of Raney nickel and extended reaction times only starting material was recovered. Reduction of (**97**) using $TiCl_4$ and $LiAlH_4$ following a procedure by Mukaiyama[74] was then attempted. Once again the desired reaction did not take place with only an inseparable mixture of organic compounds being recovered, Scheme 5.16.



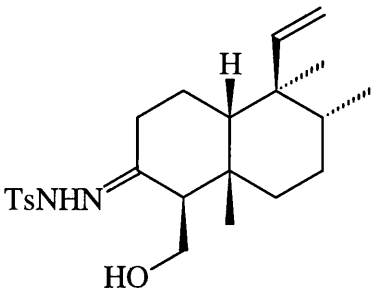
(**97**)

Scheme 5.16

Using the Huang-Minlon modification[75] of the Wolff-Kishner reaction only an inseparable mixture of organic compounds was obtained. After conversion of the hydroxyl function to an acetate (Ac_2O, py, DMAP), to give (**98**), again reduction with Raney nickel was attempted. Starting material was again returned. Reduction may be possible using a more active grade of Raney nickel; however an alternative method was sought due to the poor yield of thioketal formation.



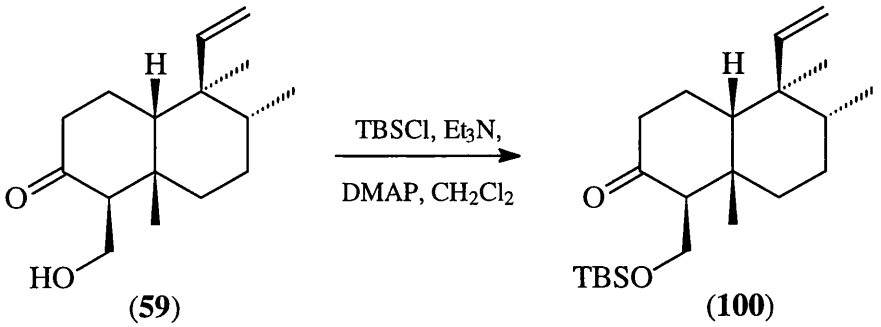
(**98**)



(**99**)

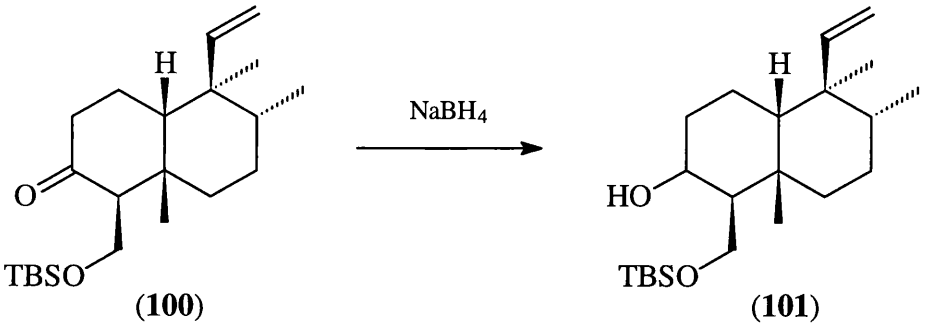
A now common method of carbonyl to methylene transformation is the reduction of an intermediate tosylhydrazone using $NaCNBH_3$. Following the procedure of Caglioti[76] the formation and subsequent reduction of the tosylhydrazone (**99**) was first attempted in DMF and sulfolane as co-solvents. Unfortunately, this did not yield the desired product and recovery of either the tosylhydrazone (**99**) or the ketoalcohol (**59**) proved difficult.

Protection of the primary alcohol as its TBS ether[77] was then carried out. Reaction of (**59**) with TBSCl and Et_3N in dichloromethane, with a catalytic amount of DMAP present, gave the TBS protected ketoalcohol (**100**), Scheme 5.17. IR spectroscopy confirmed the absence of the hydroxyl function and proton and ^{13}C NMR spectroscopy supported the expected structure.



(**59**) (**100**)

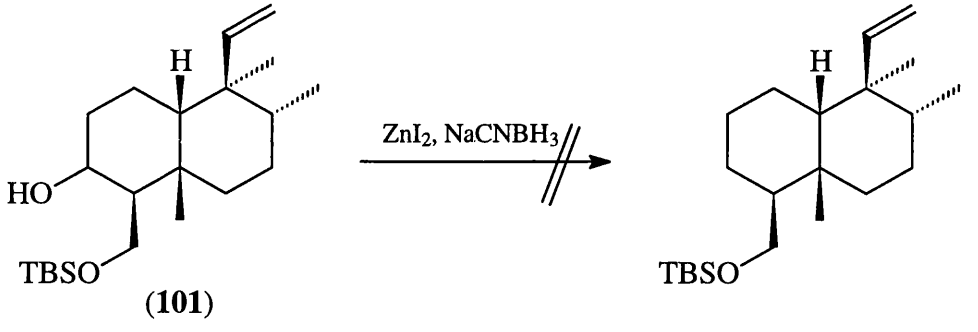
Scheme 5.17



(**100**) (**101**)

Scheme 5.18

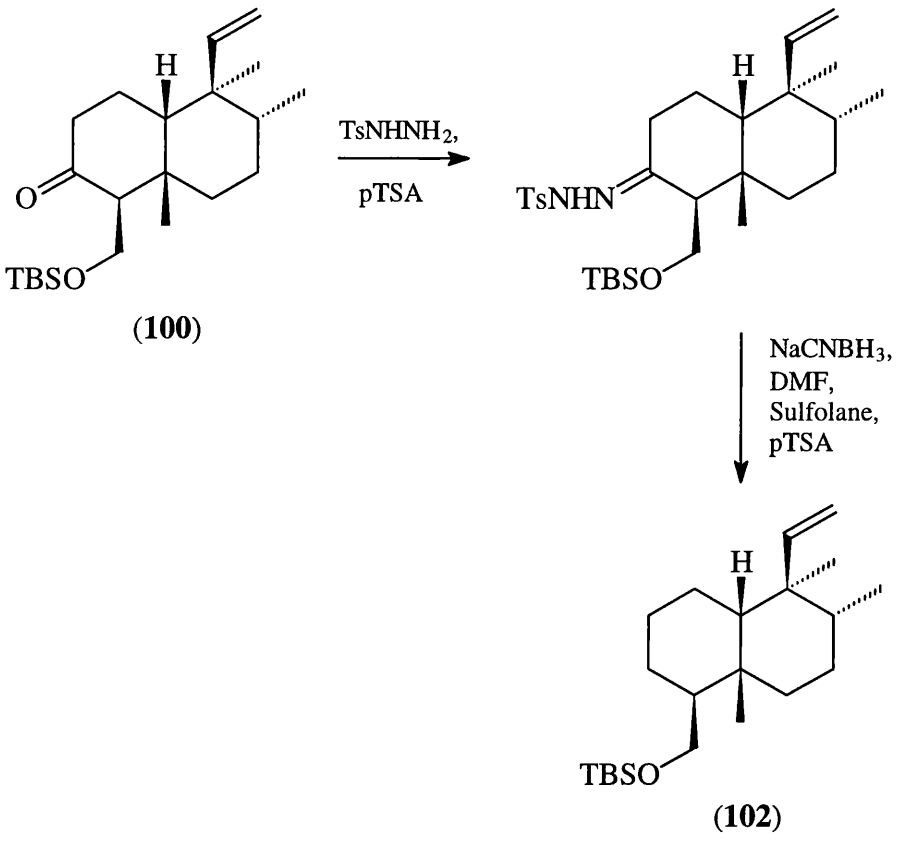
Exposure of (**100**) to $NaBH_4$ gave quantitatively the secondary alcohol (**101**), Scheme 3.18. Further reduction was unsuccessful using ZnI_2 and $NaCNBH_3$,[78] returning starting material, Scheme 5.19.



(**101**)

Scheme 5.19

Reduction of the TBS ether (**100**) was successful by tosylhydrazone formation in ethanol and then reduction, with $NaCNBH_3$ in a DMF-sulfolane co-solvent system.[79] Exposure of (**100**) to tosylhydrazine and a catalytic amount of pTSA in refluxing ethanol gave the tosylhydrazone derivative. After removal of the ethanol and exposure to $NaCNBH_3$ for 12 hrs at 80 °C the protected alcohol (**102**) was finally obtained, Scheme 5.20.



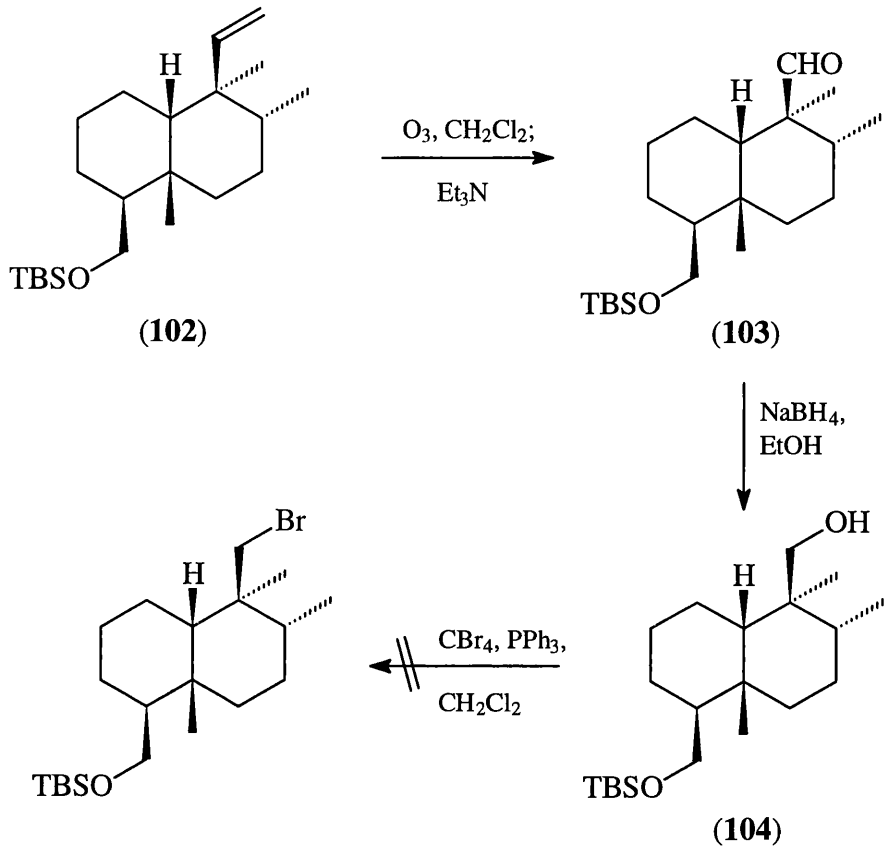
(100)

(102)

Scheme 5.20

The yield for this two step process was however low. Difficulty in extracting the product from the polar solvent may have been a reason for the poor recovery when the reaction was attempted prior to protection of the alcohol as its TBS ether. However, the added lipophilicity of the TBS group should have overcome this seemingly minor problem.

With the carbon framework of the decalin fragment constructed unmasking of the vinyl group to give the halide was carried out by a straightforward procedure outlined in Scheme 5.21.

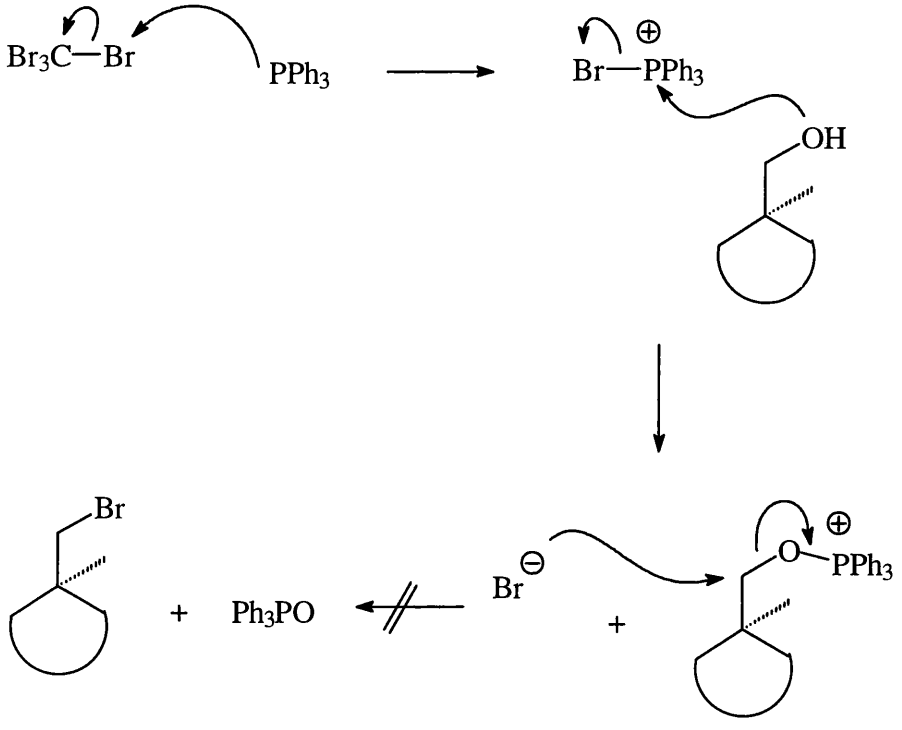


Scheme 5.21

Ozonolysis of the vinyl group in dichloromethane then reduction of the ozonide with Et_3N gave the aldehyde (**103**). The absence of the vinyl signals and the appearance of signals at δ 9.06 and δ 207.1 in, respectively, the proton NMR and ^{13}C NMR spectra confirmed the presence of the aldehyde group. Subsequent reduction with $NaBH_4$ in ethanol gave the monoprotected diol (**104**).

Conversion of the alcohol (**104**) to a halide suitable for the cross-coupling was now required. With the other hydroxyl function protected as its TBS ether a non-acidic halogenation procedure was required. The transformation was attempted using a CBr_4 - PPh_3 bromination;[80] unfortunately none of the desired halide was formed, Scheme 5.21. The difficulty in brominating by this method may be

attributed to the steric nature of both the alcohol and the reagent. The mechanism of the reaction is outlined in Scheme 5.22. Initially the formation of the active phosphonium salt takes place, then the alcohol is activated by reaction with this species *via* an S_N2 attack by the hydroxyl on the phosphorus displacing bromide ion. Attack by the neopentyl alcohol on such a species may be difficult due to steric crowding. After activation S_N2 attack at the neopentyl carbon by bromide, displacing triphenyl phosphine oxide, should occur. However, S_N2 displacement at a neopentyl centre is known to be sterically demanding and therefore it is more likely that substitution by bromide is not occurring.

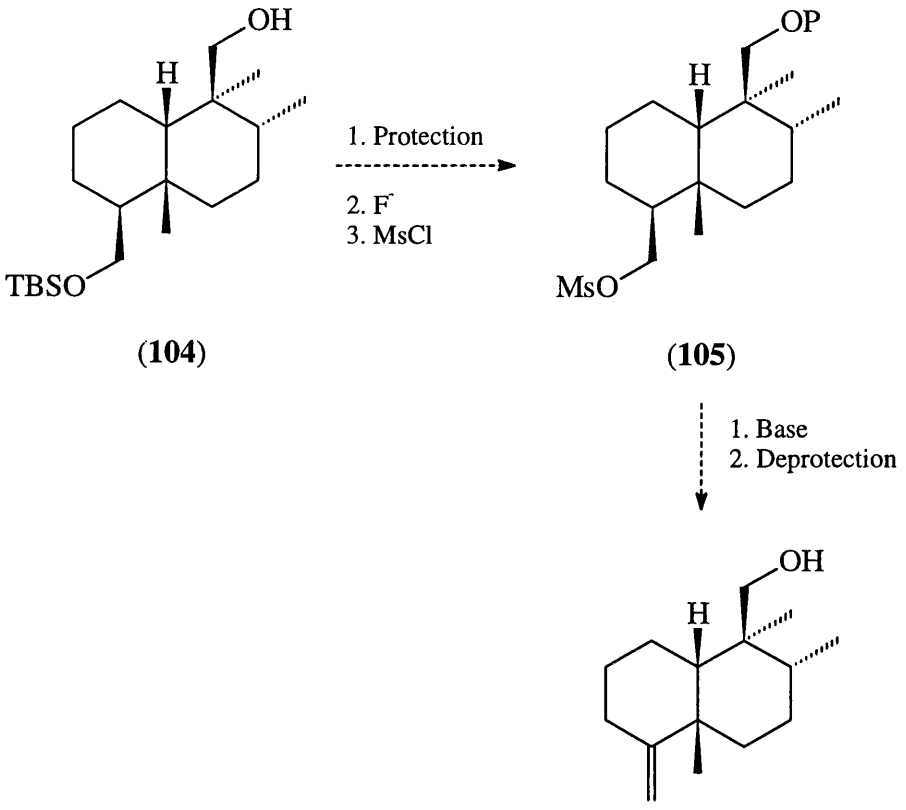


Scheme 5.22

5.4 Future Work

Further work to improve the yield of methyl cuprate addition and the deoxygenation procedure is essential if this route is to be successfully employed in total synthesis. Another method of halogenation will also need to found.

Protection of the neopentyl alcohol then silyl removal and mesylation would hopefully give (**105**). Elimination and removal of the hydroxyl protection would allow for further studies into the halogenation of the neopentyl carbon, without the restrictions imposed by the TBS group, Scheme 5.23.



(**104**) (**105**)

Scheme 5.23

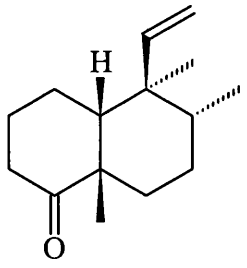
6. Second Generation Decalin Synthesis

6.1 Introduction

The poor yield and unreliability of the initial decalin synthesis from 3,4-dimethyl-cyclohex-2-enone (**88**), *via* Robinson annulation and conjugate addition, prompted the development of a second route. The inherent difficulties in the first synthesis were:-

1. Conjugate Addition to the bicyclic enone
2. Deoxygenation of the carbonyl function

A synthesis was sought which did not rely on either of these reactions but gave rapid access to the carbon framework of the decalin with minimal superfluous functionality. Once again work by Tokoroyama,[61] in which the appropriately functionalized decalin (**106**), Scheme 6.1 (see also Scheme 4.28), was synthesised *via* an intramolecular Hosomi-Sakurai reaction, was followed.

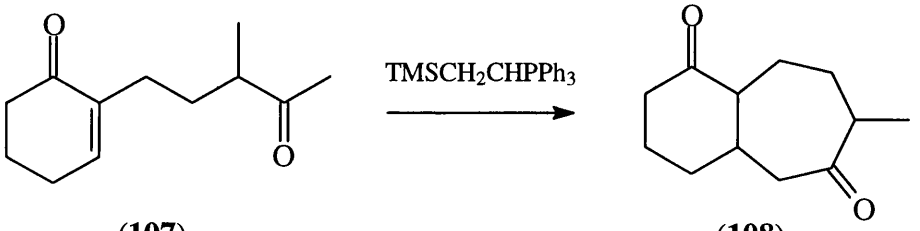


(106)

Scheme 6.1

Initially Tokoroyama approached the monocyclic precursor of the decalin *via* a Wittig reaction from the diketone (**107**), Scheme 6.2. Rather than the desired allyl silane Tokoroyama recovered only the bicyclic diketone (**108**) from the reaction.

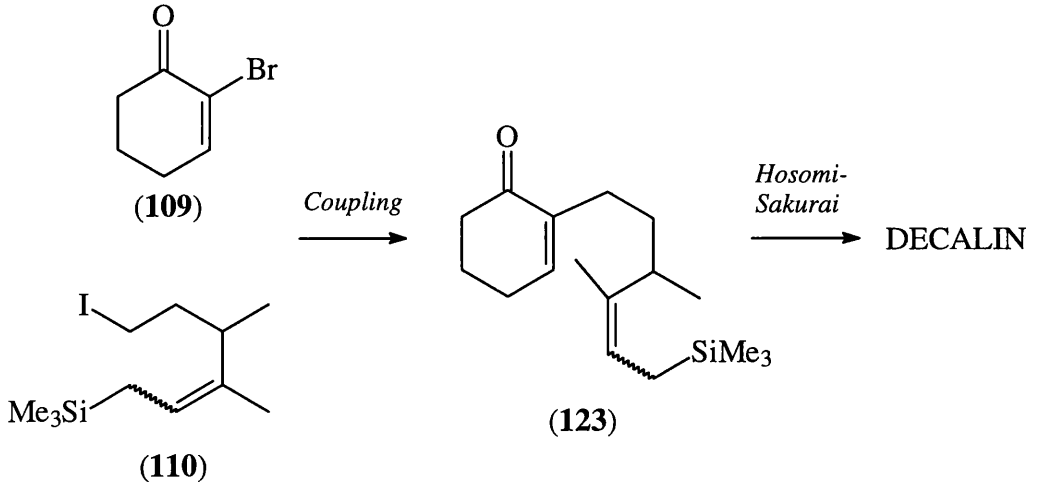
Presumably the Wittig reagent in this instance is acting as a base to facilitate the ring closure and allow for 1,4-addition to the enone to occur. This route having proven futile, the direct coupling of the allylsilane side chain to the cyclohexenone ring was then carried out.



(107) **(108)**

Scheme 6.2

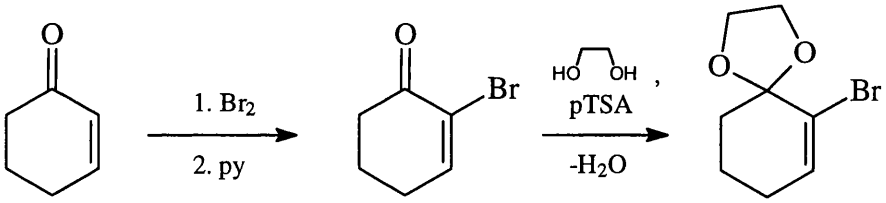
Tokoroyama's synthesis began from 2-bromocyclohex-2-enone (**109**) and the iodoallylsilane (**110**) by a coupling reaction and then Hosomi-Sakurai cyclisation in the presence of $TiCl_4$, Scheme 6.3. The iodoallylsilane was synthesised from commercially available tiglic aldehyde *via* a Claisen rearrangement.[81]



Scheme 6.3

6.2 Synthesis of Bromocyclohexene (111)

The synthesis of the protected bromocyclohexenone (**111**) was carried out according to Smith's uneventful three step protocol.[82] Bromination of cyclohexenone using liquid bromine in CCl_4 and subsequent dehydrobromination using pyridine gave the bromoenone in a good yield of 74 %. Use of pyridine was essential as Et_3N resulted in aromatization. Ketalization was carried out using a standard Dean-Stark apparatus with ethylene glycol and pTSA in benzene, Scheme 6.4. The structures of both compounds were supported by standard spectroscopic methods; both compounds gave the expected bromine isotope signals in the H.R.M.S.

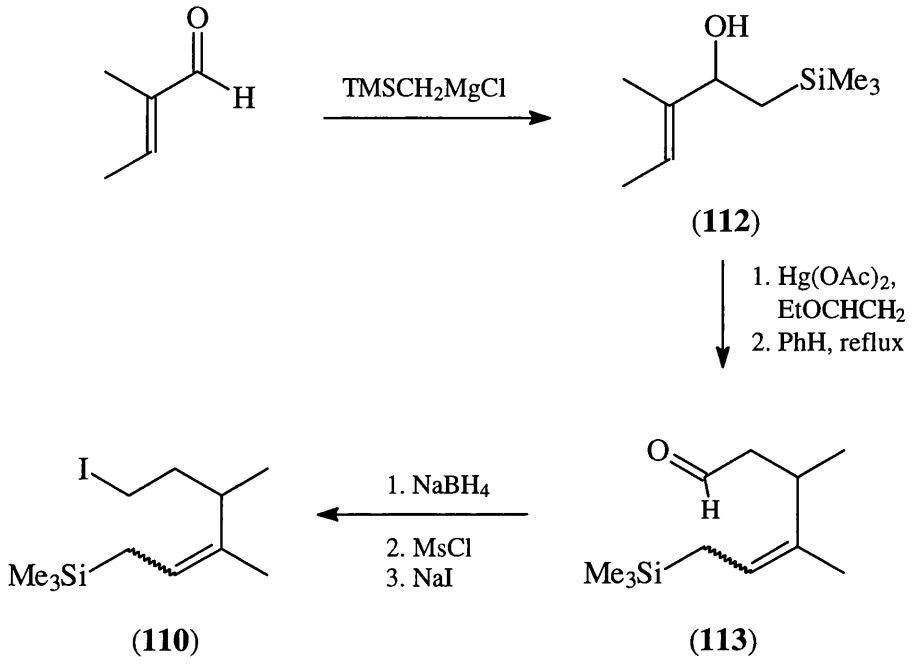


(**109**) (**111**)

Scheme 6.4

6.3 Synthesis of Iodoallylsilane (110)

Tokoroyama's approach to the iodoallylsilane (**110**), following Wilson's procedure,[81] proved rather more troublesome. Synthesis of the side chain began from tiglic aldehyde by reaction with the Grignard reagent formed from chloromethyltrimethylsilane.

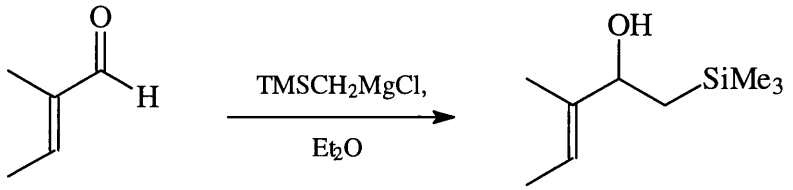


Scheme 6.5

This gave the β–hydroxysilane (**112**) which was converted to the vinyl ether under standard conditions ($Hg(OAc)_2$ and ethyl vinyl ether).[83] Subsequent Claisen rearrangement gave the aldehyde (**113**) which could be reduced and then converted to the iodide (**110**), Scheme 6.5.

6.3.1 Synthesis of Amide (116)

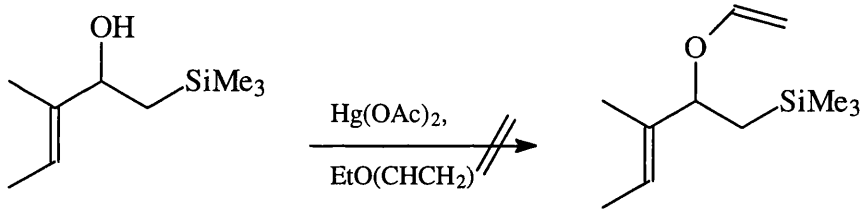
Repetition of this procedure proved difficult. Formation of the Grignard reagent from chloromethyltrimethylsilane was performed according to Peterson's procedure.[84]



(**112**)

Scheme 6.6

Exposure of the β–hydroxysilane (**112**) to $Hg(OAc)_2$ in ethyl vinyl ether gave only an uncharacterizable mixture of organic compounds, Scheme 6.7.



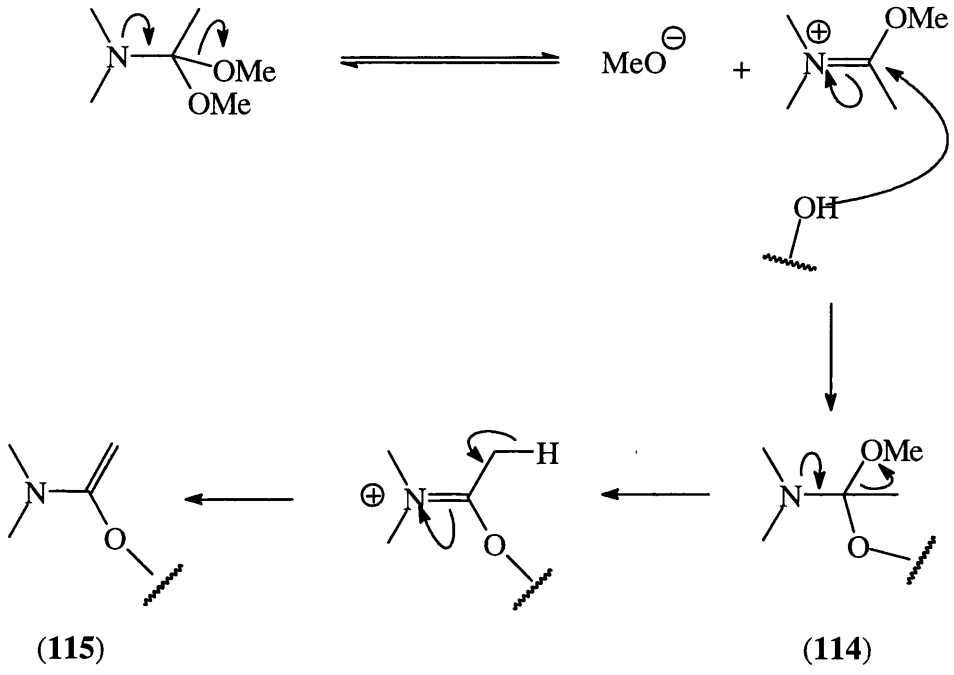
(**112**)

Scheme 6.7

Alterations to the reaction time, temperature and order of addition as well as careful reagent purification all proved futile.

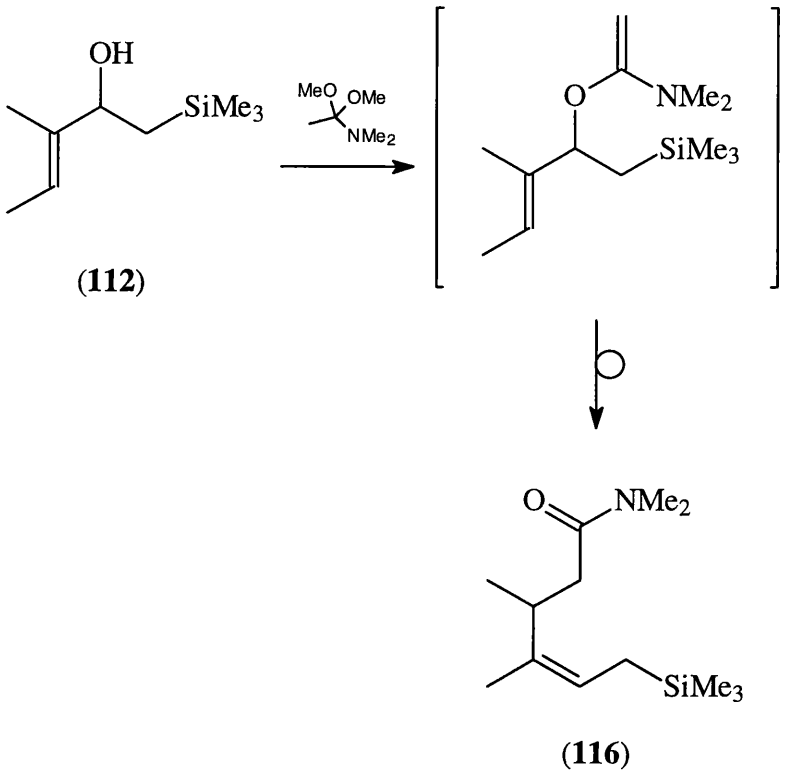
The problem was overcome by reverting to the use of an Eschenmoser-Claisen rearrangement[85] to bring about the 2-carbon homologation of the tiglyl unit. Eschenmoser first reported, in 1979, that the reaction of N,N-dimethylacetamide dimethyl acetal with an allylic alcohol gives, after rearrangement, an amide. The reaction proceeds firstly by the elimination of methoxide from the acetal, then nucleophilic attack by the hydroxyl to give intermediate N,O,O-orthoester (**114**). Elimination of methanol from this molecule *via* the two step process in Scheme 6.8

gives the ketene N,O-acetal (**115**). A Claisen type rearrangement then gives an amide. Carrying out the reaction under the standard conditions - in refluxing benzene - results in a one-pot conversation of an alcohol to an amide.



Scheme 6.8

Exposure of β–hydroxysilane (**112**) to N,N-dimethylacetamide dimethylacetal, in refluxing benzene for 10 hrs, gave after standard work-up the amide (**116**) in an excellent 77 % yield, Scheme 6.9.



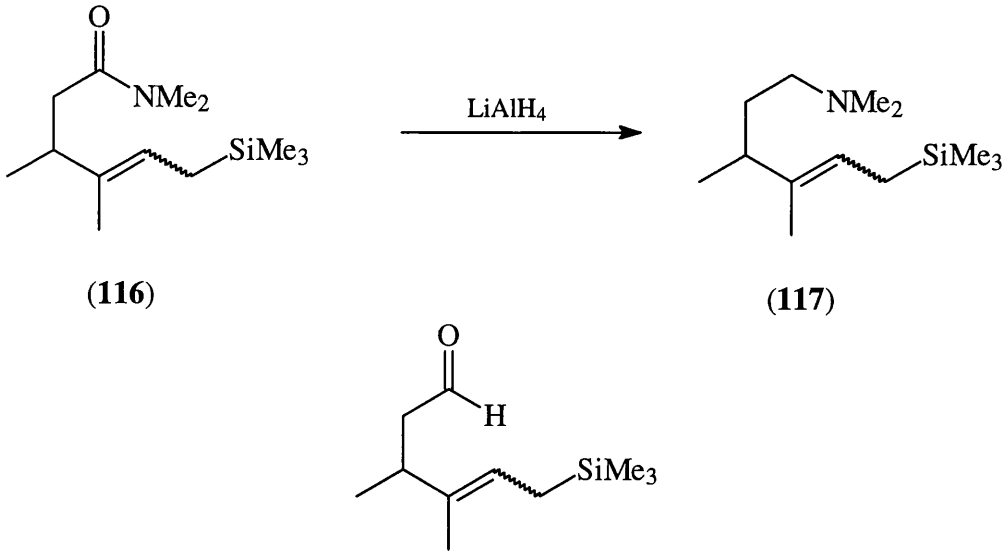
(**112**)

(**116**)

Scheme 6.9

6.1.2.2 Amide Reduction

Conversion of the amide (**116**) to the iodide (**110**) required prior reduction. It is possible to reduce amides with $LiAlH_4$ if the reducing agent is present in excess.[86] Therefore, reduction was attempted by careful reaction of the amide with $LiAlH_4$. Unfortunately the reaction is not consistent and although it was possible to obtain aldehyde (**113**) by this method the reaction mainly yielded amine (**117**).

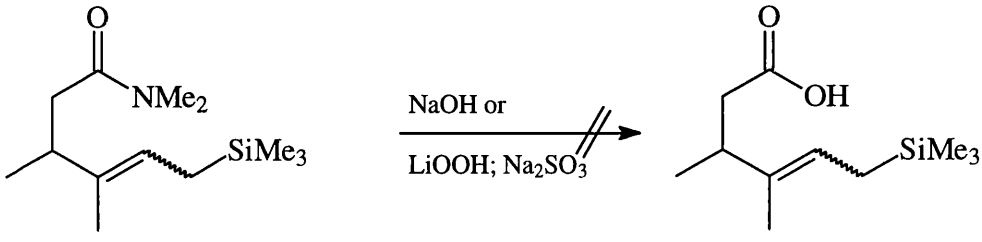


(**116**) (**117**)

(**113**)

Scheme 6.10

Other reducing agents were tried; however, none of these gave satisfactory reduction. Attention was then turned to hydrolysing the amide to give the corresponding carboxylic acid (**118**) which in turn could be reduced.



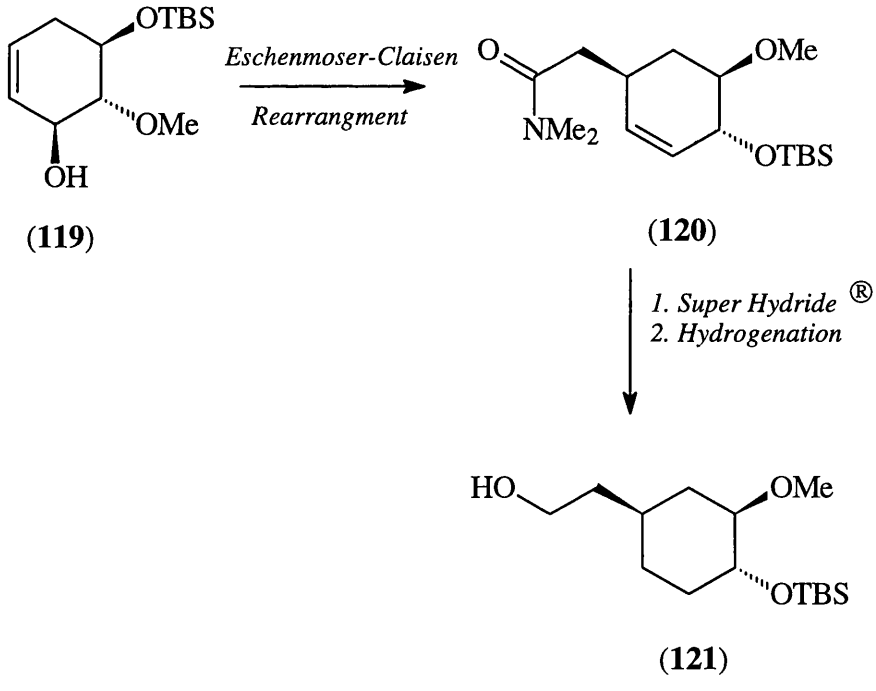
(**118**) (**116**)

Scheme 6.11

Disappointingly no hydrolysis was possible using either sodium hydroxide solution in an organic solvent[87] and/or a phase transfer catalyst or by using lithium peroxide solution in THF.[88] The stubborn nature of the N,N-dimethyl amide is well documented[89] although these results are still surprising. A high percentage of

amide was always recovered and no trace of acid was detected even with a reaction time of 3 days.

During the synthesis of Rapamycin,[90] Nicolaou and coworkers utilised the Eschenmoser-Claisen rearrangement for the stereospecific conversion of allylic alcohol (**119**) to the primary alcohol (**121**). Treatment of (**119**) with N,N-dimethylacetamide dimethylacetal in xylenes gave the amide (**120**) which was then smoothly reduced to the alcohol using Super Hydride®. Reduction of the double bond then gave (**121**).

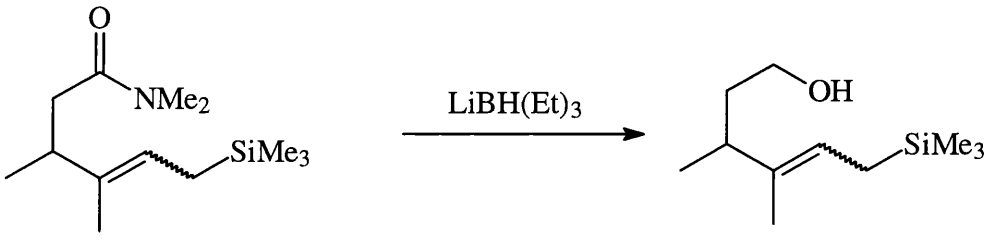


(**119**) (**120**) (**121**)

Scheme 6.12

Exposure of amide (**116**) to Super Hydride® at 0 °C gratifyingly gave, after silica gel chromatography, the desired alcohol (**122**) in 80 % yield, Scheme 6.13. The alcohol stretching frequency at 3358 cm^{-1} in the I.R. and the appearance of the

diastereotopic methylene protons at δ 3.72-3.53 in the proton NMR spectrum confirmed the presence of the alcohol.

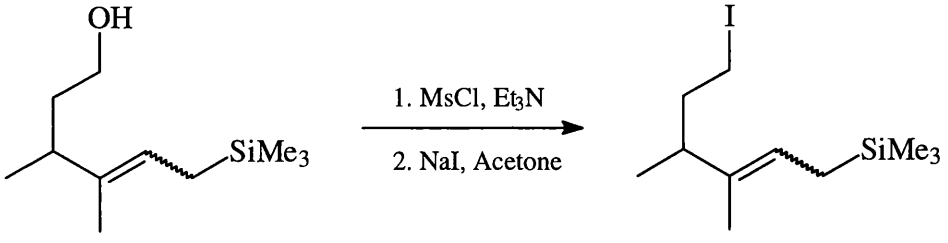


(116) **(122)**

Scheme 6.13

6.3.3 Iodination of Allylsilane (122)

Conversion to the iodide was carried out by firstly mesylation of the alcohol (MsCl, Et_3N, CH_2Cl_2) and then nucleophilic displacement of the leaving group by iodide, using NaI in refluxing acetone.[91] This gave, after purification, the iodide in a good yield of 84 % from the alcohol (**122**). The absence of a triplet at δ 61.8 in the ^{13}C NMR spectrum and the presence of a triplet at δ 38.3 confirmed the conversion of the alcohol to the iodide. The presence of the molecular ion in the H.R.M.S. confirmed the molecular formula.

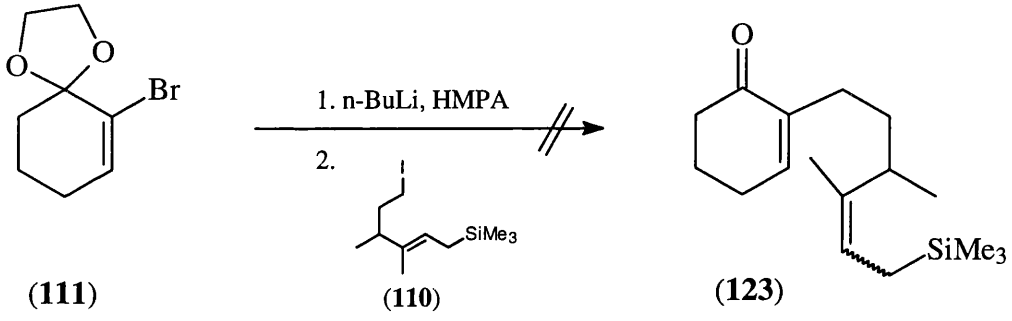


(122) **(110)**

Scheme 6.14

6.4 Coupling of Iodide (110) and Bromide (111)

Coupling of the iodide (**110**) to the vinyl bromide (**111**) was attempted by lithium-halogen exchange of the bromide with n-BuLi then reaction of this with the iodide, Scheme 6.15. Following the procedure of Millon[92] none of the expected product was obtained and due to time constraints further exploration of this reaction was not possible.



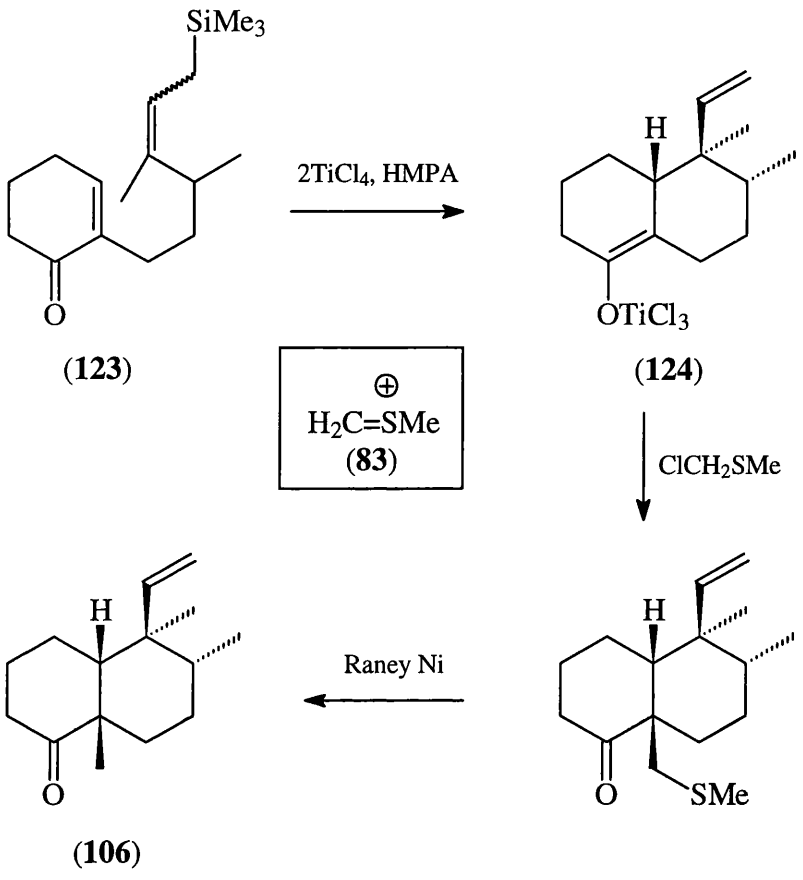
(**111**) (**110**) (**123**)

Scheme 6.15

6.5 Future Work

Completing the decalin (**85**) synthesis *via* this route would require the optimisation of the iodoallylsilane synthesis and successful coupling to the vinyl bromide. Tokoroyama coupled the two halides together as explained previously; however, it may be possible, in the light of the result in section 6.4, to improve this by using a nickel or palladium catalysed cross-coupling reaction (see Chapter 7).

Tokoroyama completed the synthesis by deprotection of the ketone using aqueous oxalic acid to give the enone (**123**). Exposure of the enone to $TiCl_4$ in the presence of chloromethyl methylsulfide resulted in an intramolecular Hosomi-Sakurai reaction to give stereospecifically the titanium enolate (**124**).

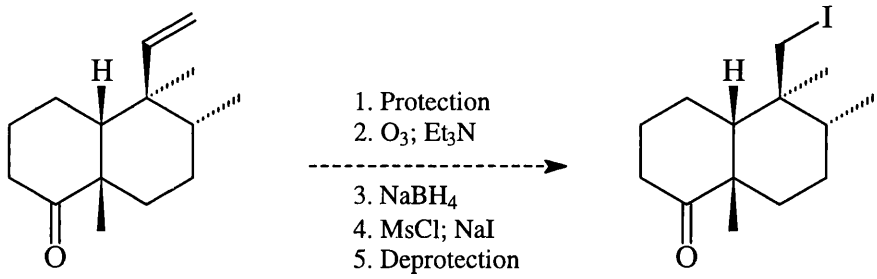


Scheme 6.16

Stereospecific trapping of this enolate in high yield was possible using the strong electrophile (**83**), formed from the action of $TiCl_4$ on the chloromethyl methylsulfide. As with the conjugate addition of nucleophiles to enones, discussed in Chapter 5.2, the attack of the electrophile is from the convex side of the molecule. Tokoroyama then converted the reduced *cis*-decalin (**106**) into naturally occurring clerodane diterpenoids.

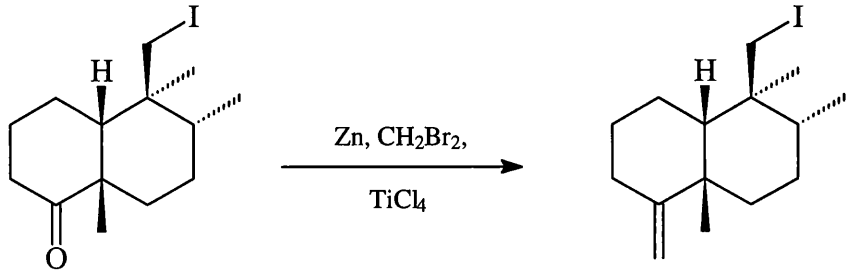
Transformation of the decalin (**106**) obtained by Tokoroyama from this route into a suitable coupling partner would require functionalization of the vinyl group and conversion of the ketone into an exocyclic methylene. As with the first generation

synthesis, ozonolysis and then reduction of the aldehyde would give an alcohol. Transformation into a halide should be possible following Wiemer's procedure of mesylation and then substitution with iodide as used in the synthesis of arenarol, Scheme 6.17.



Scheme 6.17

The carbonyl to methylene interconversion should be possible by the use of Nysted's alkenylidation conditions.[93] Wiemer, during the synthesis of arenarol,[23] attempted this transformation using a Wittig reagent and Tebbe's reagent, but found the ketone unreactive to either. Use of Nysted's conditions - Zn, CH_2Br_2, $TiCl_4$ - gave the olefin in good yield, Scheme 6.18.

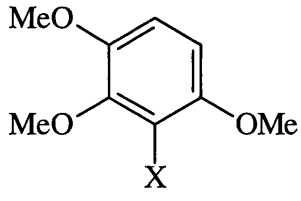


Scheme 6.18

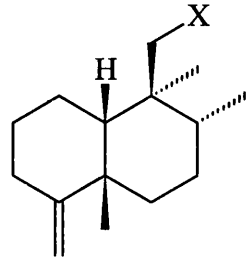
7. Cross Coupling - Model Studies

7.1 Introduction

Model studies to optimise the conditions for coupling of fragments (**85**) and (**86**) were undertaken using a simplified system. Cross coupling between sp^3 and sp^2 carbon centres has been widely used since the 1970's when it was first reported that iron, nickel, palladium and copper catalysts were extremely effective for the cross coupling of Grignard reagents with organic halides.[94] The reactions utilising nickel and palladium are now commonplace for carrying out this type of carbon-carbon bond formation due to their high efficiency.



(**86**)



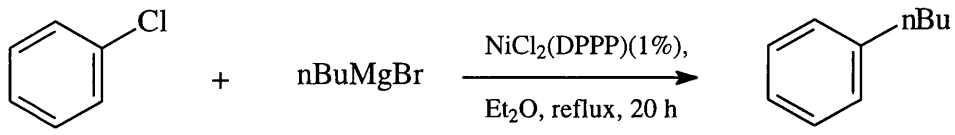
(**85**)

X = I, Br or Cl

Scheme 7.1

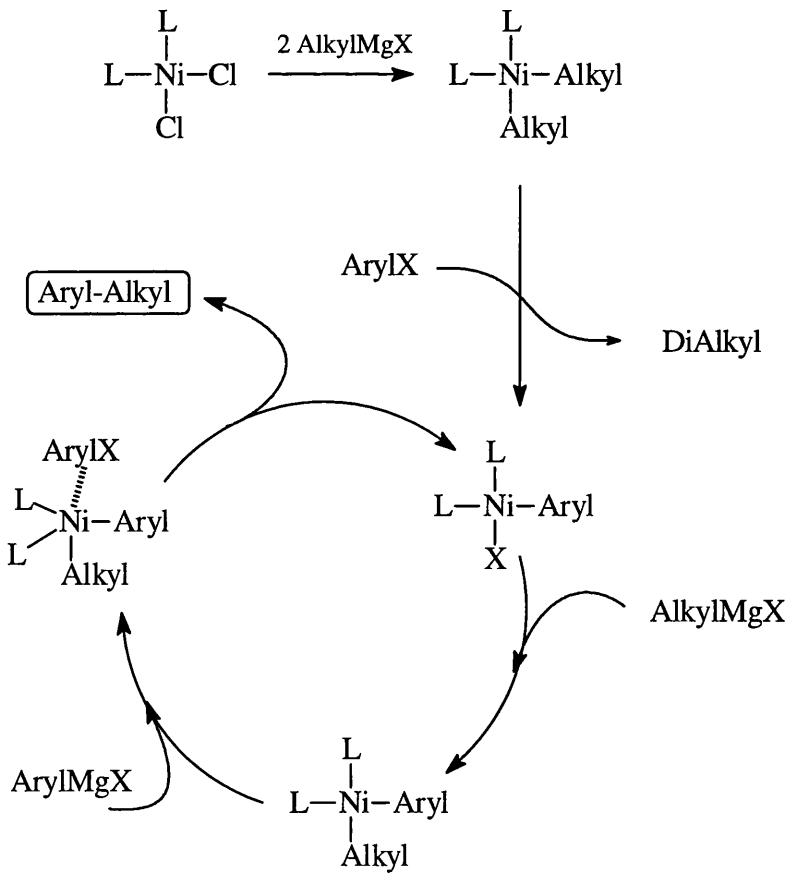
The coupling fragments required for popolohuanone E are a primary alkyl halide (**85**) and an aromatic halide (**86**), Scheme 7.1. The coupling of aromatic halides and primary alkyl Grignard reagents is most commonly carried out using the method reported by Tamao and Kumada where a nickel catalyst bearing two phosphine ligands has become standard.[95] An example from Tamao's work, Scheme 7.2, shows the efficient coupling of chlorobenzene to butylmagnesium

bromide in an excellent yield of 98 %. It is believed that the reaction proceeds by the mechanism outlined in Scheme 7.3.



Scheme 7.2

Initial reduction of the catalyst by the addition of two equivalents of the Grignard reagent forms a dialkyl nickel species.



Scheme 7.3

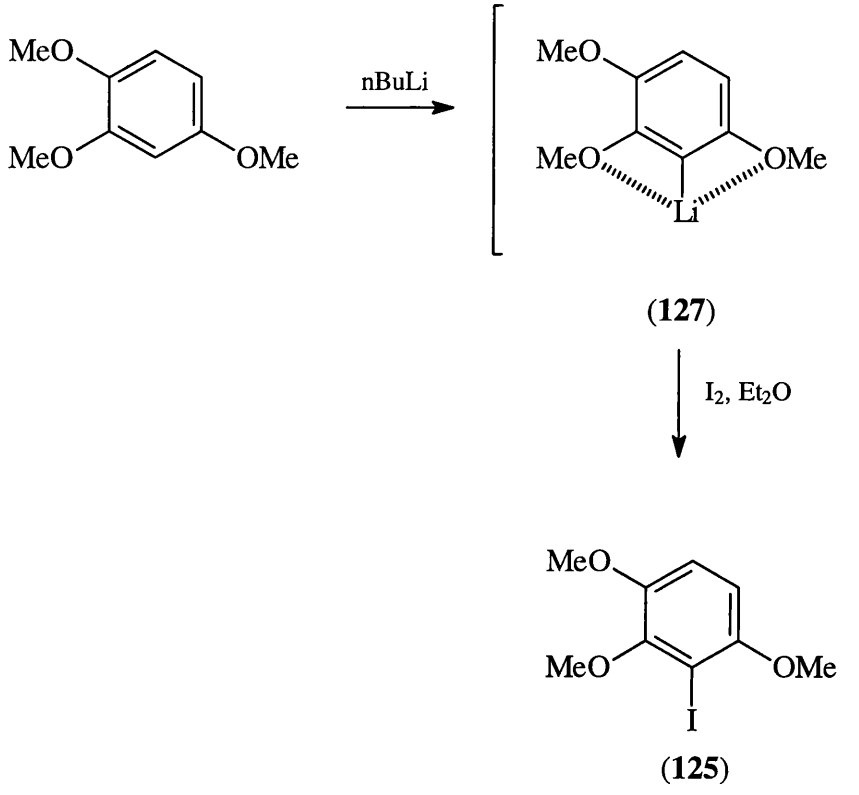
Addition of one mole of aryl halide releases the alkyl ligands and gives rise to the catalytic nickel species. Reaction with a further mole of the alkyl Grignard reagent displaces the halide. Further addition of one more mole of Grignard reagent gives the pentacoordinate intermediate which, after coupling and thus decomplexation, gives the desired coupled product and returns the active catalyst. The nature of the ligands affects the reactivity of the catalyst; however, $NiCl_2$(DPPP) has so far been found to be the most reactive and generally applicable. The order of reactivity of the aryl halides is ArI > ArBr > ArCl >> ArF. Generally, electron-withdrawing substituents on the aromatic ring accelerate the coupling; methoxy substituents, however, also seem to be activating.

Side products are commonplace when using the more reactive halides (I and Br) and hindered aromatic halides are usually stubborn towards coupling. 1-Iodo-2,3,6-trimethoxybenzene (**125**) and cyclohexylmagnesium bromide (**126**) were chosen for initial model studies, the reactivity of the aryl iodide being offset by the hindered *o,o'*-disubstituted ring.

7.2 Use of Nickel Catalyst in Model Studies

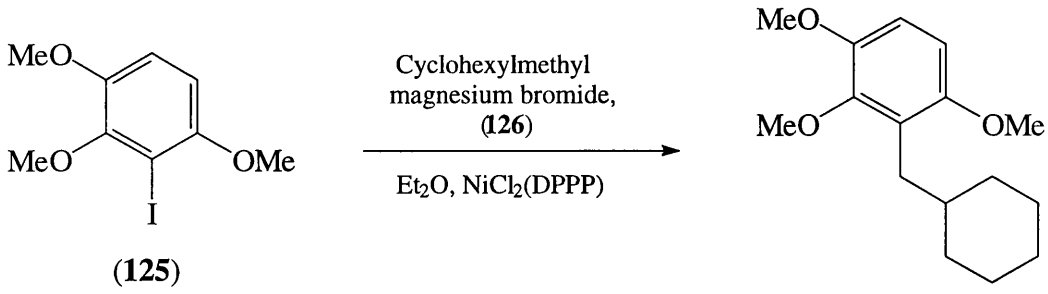
1-Iodo-2,3,6-trimethoxybenzene can be synthesised[96] expediently from the commercially available 1,2,4-trimethoxybenzene. Reaction of 1,2,4-trimethoxybenzene with n-BuLi gave the intermediate organolithium species (**127**), Scheme 7.4. Further reaction with a solution of iodine in ether gave iodide (**125**) in 70% yield, after recrystallisation. The regiospecificity of this reaction is attributed to the stabilisation of the organolithium intermediate by the ortho

substituents.[97] Hence the thermodynamically favoured isomer is that shown in Scheme 7.4.



Scheme 7.4

Following Tamao's procedure the coupling reaction was first attempted by formation of the Grignard reagent (**126**) and addition of this to a suspension of $NiCl_2$(DPPP) and (**125**) in ether. After a reaction time of 22 hrs at room temperature only a very poor yield - 6 % - of the coupled product was obtained, Scheme 7.5. The reaction was repeated varying the reaction time, temperature and the solvent; however, no improvement on this result was possible. Changing the catalyst to $NiCl_2$(DPPE) unfortunately did not produce any coupled material.

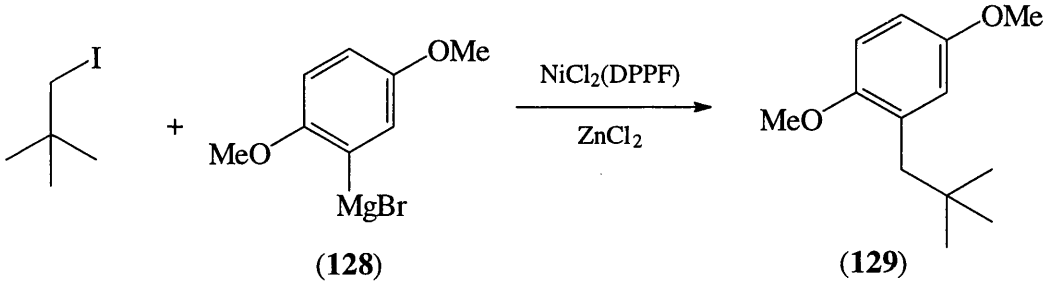


(125)

Scheme 7.5

7.3 Synthesis of $NiCl_2$(DPPF)

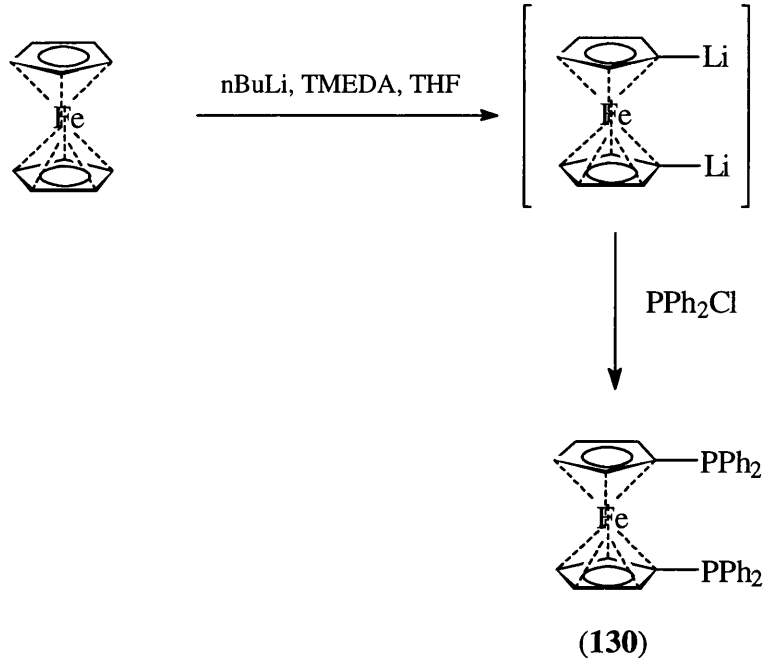
Disappointing as these results were, it is not unusual with this chemistry to find some catalysts to be very efficient for certain coupling reactions while others are ineffective.



(128) (129)

Scheme 7.6

For the reactive bromobenzene, $NiCl_2$(DPPF) is reported to be the best catalyst - by reducing side reactions - and has been proven to be the most efficient for bringing about neopentyl cross-couplings according to Scott.[23a] Scheme 7.6

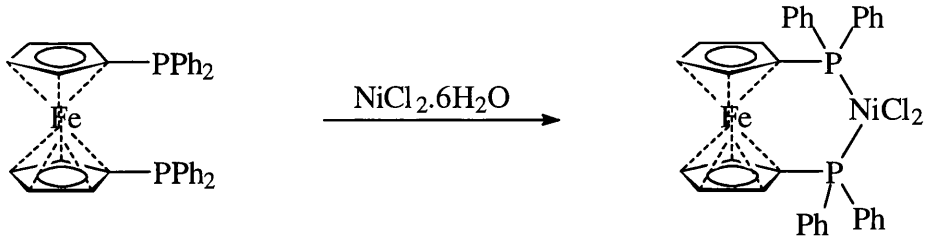


(**130**)

Scheme 7.7

provides an example[98] where neopentyl iodide is efficently cross-coupled with aryl Grignard reagent (**128**) to give (**129**) in 84 % yield.

Synthesis of the catalyst was carried out according to the literature procedure.[99] Reaction of ferrocene with nBuLi gave dilithioferrocene and subsequent reaction in hexane with two equivalents of chlorodiphenylphosphine gave the ligand (**130**) as an orange precipitate;[99] after recrystallisation a total yield of 51 % was obtained, Scheme 7.7. Straightforward addition of a hot butanol solution of the ligand to a hot butanol solution of $NiCl_2$ resulted in the crystallisation of the complex (**131**) as dark green analytically pure needles, Scheme 7.8. The model reactions using this catalyst were not undertaken as other work took precedence.



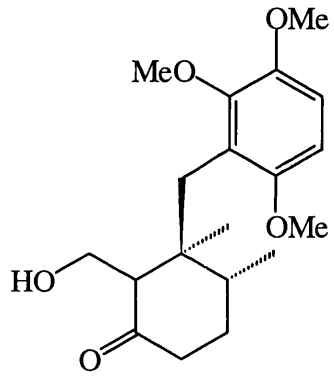
(**130**) (**131**)

Scheme 7.8

8. Benzylic Cuprate Addition

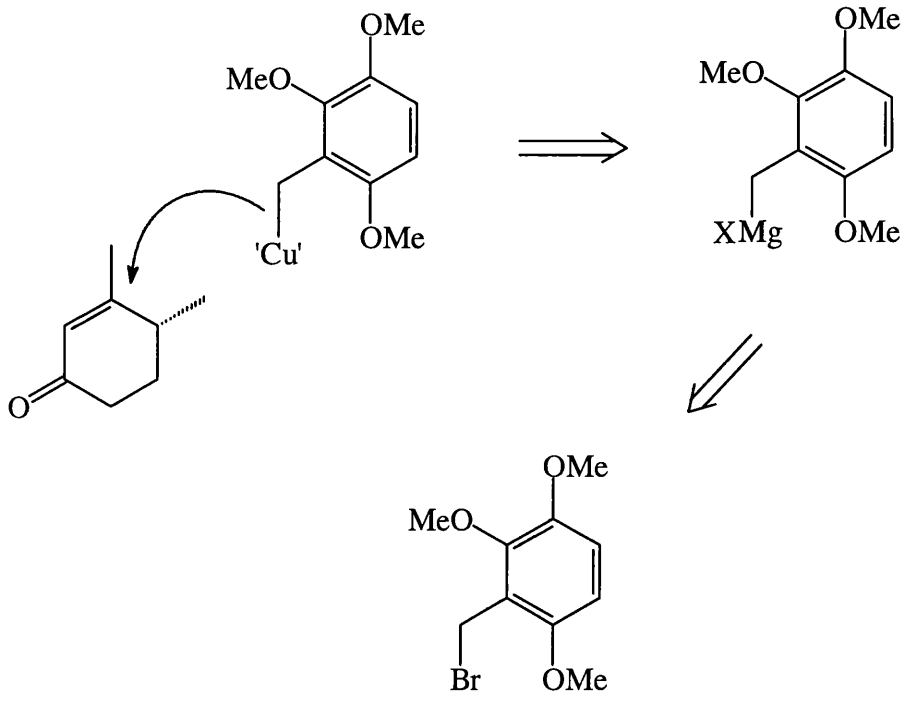
8.1 Analysis

The foreseeable difficulties in coupling the aryl iodide to the halo decalin led to attempts to circumvent this reaction completely. In an extension of the first generation decalin synthesis, it was assumed that if a vinyl cuprate could be stereospecifically added to an enone then the addition of the appropriate benzylic cuprate should furnish the intermediate alcohol (**132**) with the arene portion intact.



(132)

This approach requires the formation of the trimethoxybenzyl cuprate which in turn could be derived from the benzyl bromide (**133**), Scheme 8.1. Literature reports[100] suggest that the formation of Grignard or organolithium reagents using electron rich benzylic halides can be troublesome, resulting in extensive Wurtz coupling or substitution.

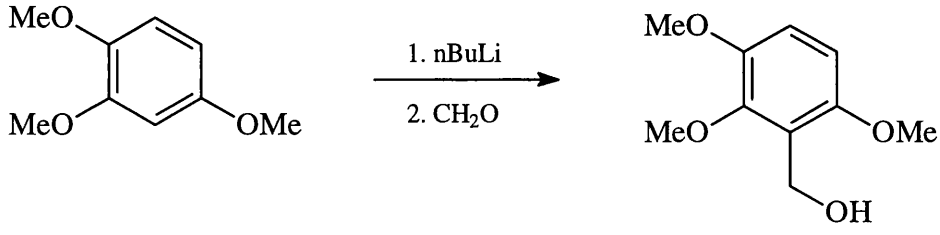


(**133**)

Scheme 8.1

8.2 Synthesis of 2,3,6-Trimethoxybenzyl bromide

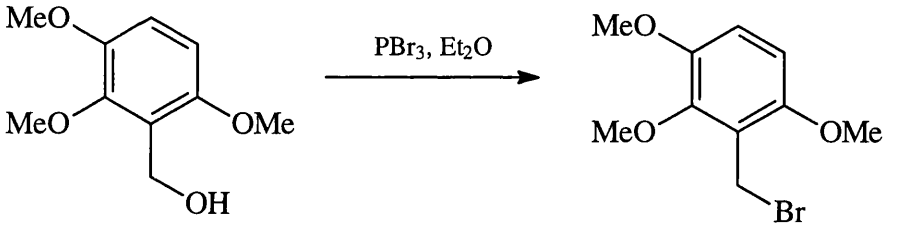
Synthesis of the bromide was approached *via* procedures already undertaken in this study. The bromide was made by *ortho* lithiation then reaction with formaldehyde and then subsequent bromination of the alcohol (**134**), Scheme 8.2. Reaction of 1,2,4-trimethoxybenzene with n-BuLi was carried out as before, to give the intermediate organolithium reagent (**127**).



(**134**)

Scheme 8.2

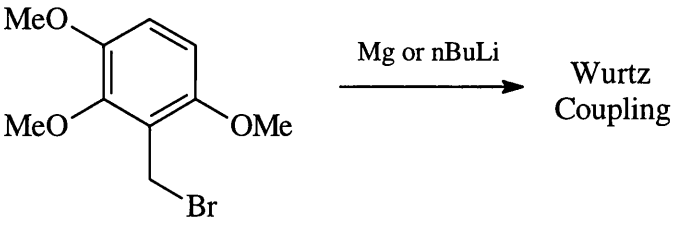
It was found that the addition of paraformaldehyde, rather than introduction of formaldehyde gas, to a solution of (**127**) resulted in a good yield of the desired benzylic alcohol (**134**) without the inconvenience that the latter procedure causes. Recrystallisation of the alcohol gave a good yield (70 %) of white crystals which gave a characteristic broad hydroxyl stretch at 3592 cm^{-1} in the I.R. spectrum. A pair of doublets at δ 6.80 and 6.58, *J* 9 Hz, provided proof that the substitution pattern was the expected 1,2,3,4-arene. Bromination was carried out by reaction of the alcohol with PBr_3 in ether at 0 °C over 15 mins, Scheme 8.3.



(**134**) (**133**)

Scheme 8.3

Silica gel chromatography then gave the bromide (**133**) as a soft white solid which exhibited the characteristic bromine isotope ratios in the H.R.M.S. All other data were consistent with the expected structure.



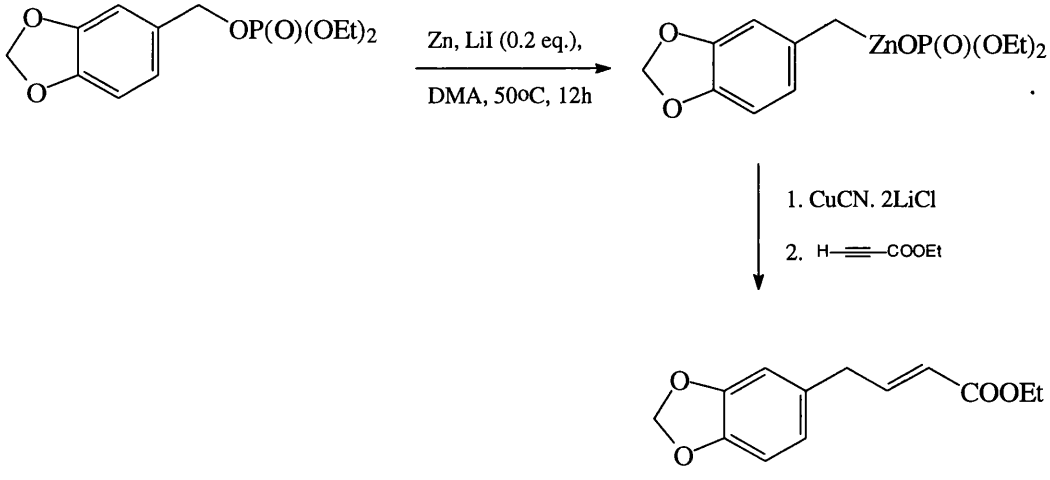
(**133**)

Scheme 8.4

All attempts to form either the Grignard reagent or the organolithium species resulted in the expected Wurtz coupling, Scheme 8.4.

8.3 Preparation of Benzylic Copper Reagent

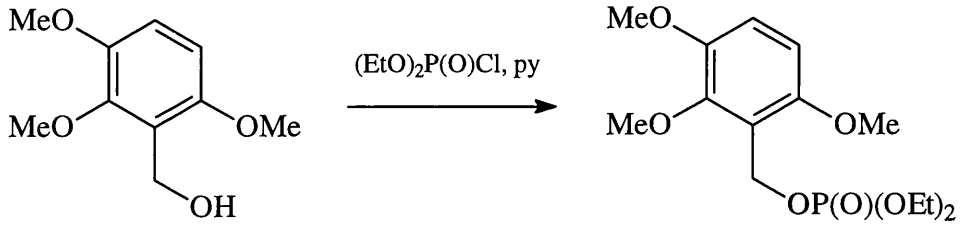
Work by Knochel[101] suggested an expedient solution, preparation of the corresponding benzylic zinc reagent and subsequent transmetallation to give the cuprate. The insertion of zinc into organic halides has been known for some time. However, Knochel has shown that organometallic reagents from reactive allylic and benzylic halides which would normally undergo Wurtz coupling, can be successfully accessed from the corresponding phosphate or sulfonate. After transmetallation to the corresponding copper reagent with CuCN.2LiCl, the addition of electrophiles such as Michael acceptors affords the desired adducts, Scheme 8.5. Extension of this methodology required the synthesis of the phosophate (**135**).



Scheme 8.5

8.3.1 *Via* Benzylic Phosphate

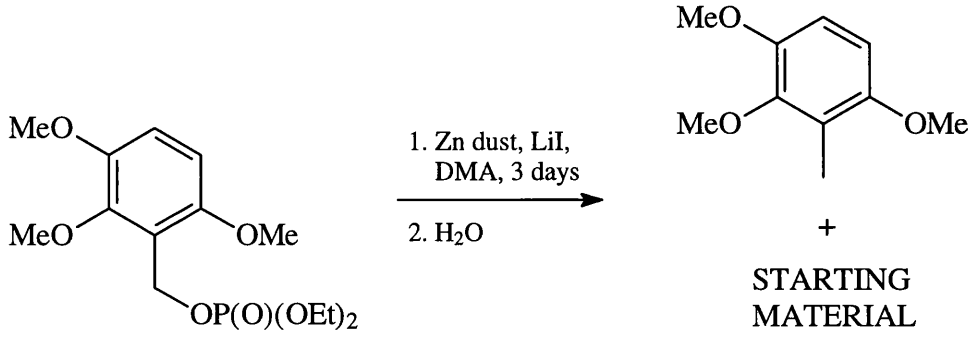
Reaction of chlorodiethyl phosphate with benzylic alcohol (**134**) in pyridine was carried out at 0 °C for 4 hrs and gave (**135**). The proton NMR spectrum showed a characteristic phosphorus coupling of 5.2 Hz to the benzylic protons and a coupling of 14.7 Hz to the ethoxy methylene protons.



(**134**) (**135**)

Scheme 8.6

Following Knochel's procedure, the zinc reagent was made by addition of the phosphate to a suspension of activated zinc dust in DMA containing LiI. Due to poor initial results this reaction was studied to determine if the zinc species was forming. Analysis of the reaction after 12 hrs, 1 day and 3 days indicated that the reaction did not go to completion.

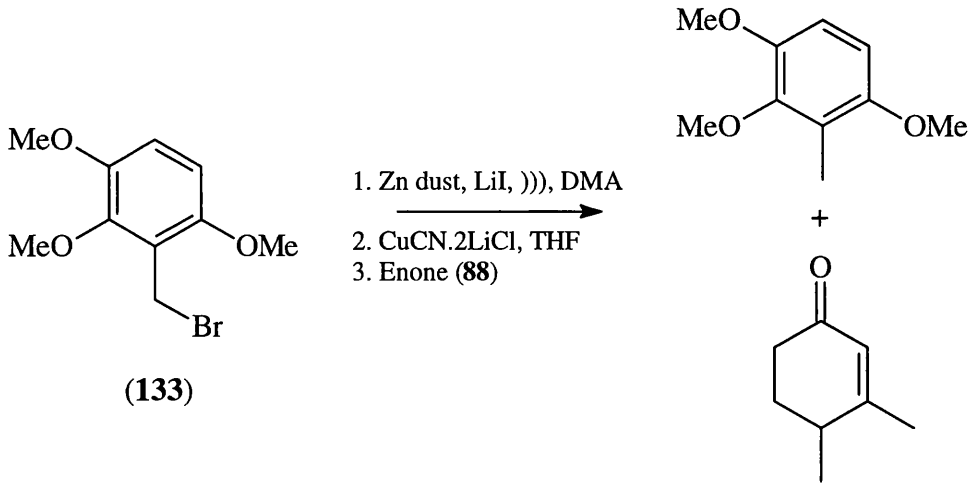


Scheme 8.7

Further alteration to the reaction conditions did not produce complete conversion. Transmetallation to the copper reagent was done, none the less, by addition of the organozinc solution to a solution of CuCN.2LiCl in THF at -40 °C. Addition of 3,4-dimethylcyclohex-2-enone (**88**) to this solution, after work-up, gave no adduct but returned (**88**), phosphate (**135**) and 2,3,6-trimethoxytoluene.

8.3.2 *Via* Benzylic Bromide

As the phosphate was not reactive enough towards zinc insertion the reaction was repeated using the benzylic bromide (**133**), rather than the phosphate. Under the thermal conditions reported by Knochel the reaction did not go to completion. Sonication, however brought about the desired conversion as analysis of the reaction mixture after hydrolysis indicated only the presence of 2,3,6-trimethoxytoluene.



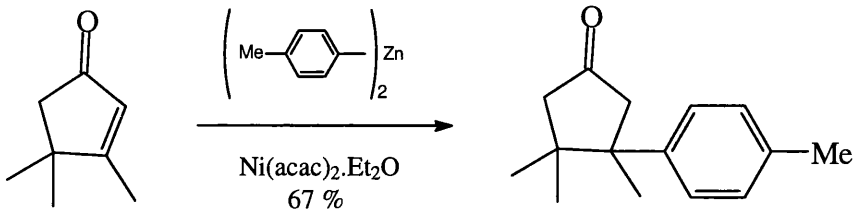
(**133**)

Scheme 8.8

Once again transmetallation was carried out according to the literature and exposure of the mixture to (**88**) disappointingly gave no adduct, Scheme 8.8. The reaction was repeated using cyclohexenone to determine if addition was being hindered by the extra bulk of the methyl substituents. This reaction did not produce any 1,4 adduct. If the transmetallation was unsuccessful the organozinc reagent may be expected to add 1,2 or 1,4 to the enone but only enone (**88**) and 2,3,6-trimethoxytoluene were isolated from the reaction.

8.4 Future Work

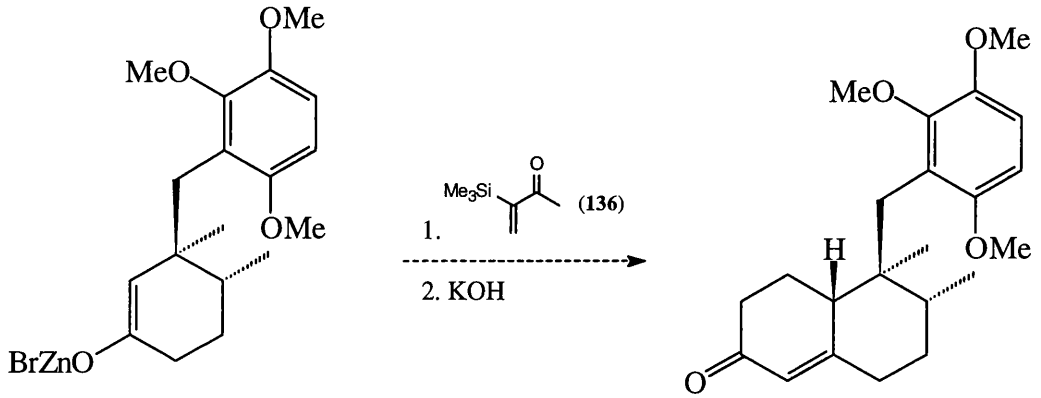
Work into the direct 1,4-addition of the organozinc reagent to the enone (**88**) is required. An example of the use of a nickel promoted alkylation at the hindered terminus of an enone is shown in Scheme 8.9. In this case a diaryl zinc reagent was used.



Scheme 8.9

If successful trapping of the enolate (**137**) could be done as before with formaldehyde or with enone[103] (**136**) which would give, after basic work up, the bicyclic enone (**138**), Scheme 8.10. Conversion of (**138**) into the monomeric unit could be done using the troublesome conjugate addition/alkylation procedure.

Alternatively the angular substituent could be introduced by Lallemand's extension of the Stork silyl methyl radical cyclization (see section 4.2.1.1.3).



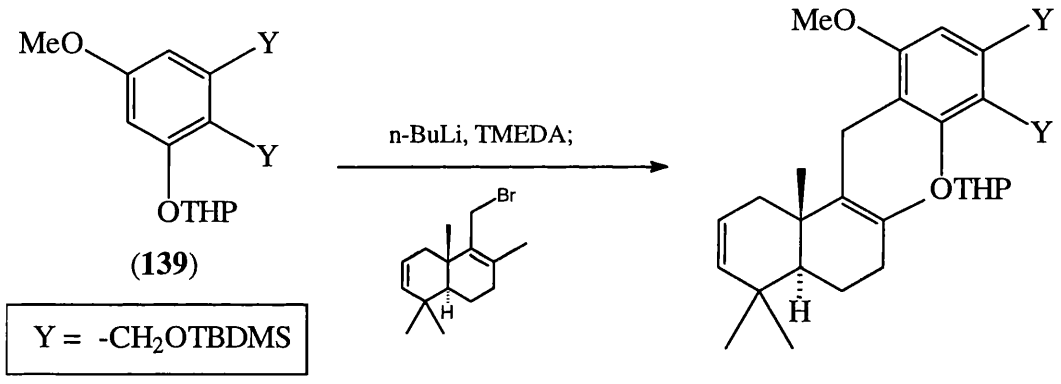
(137) (138)

Scheme 8.10

9. Alternative Coupling Strategies

9.1.1 Addition to Aldehyde

Reports by McMurray[104] and Chackalamannil[105] where the addition of an aryllithium reagent to a decalin bearing an allylic bromide or a formyl group respectively prompted investigation of a non-catalysed reaction using aldehyde (**103**). During the synthesis of K-19 McMurray formed the benzylic bond by addition of the anion of (**139**) to an allylic bromide in a yield of 54 %, Scheme 9.1.

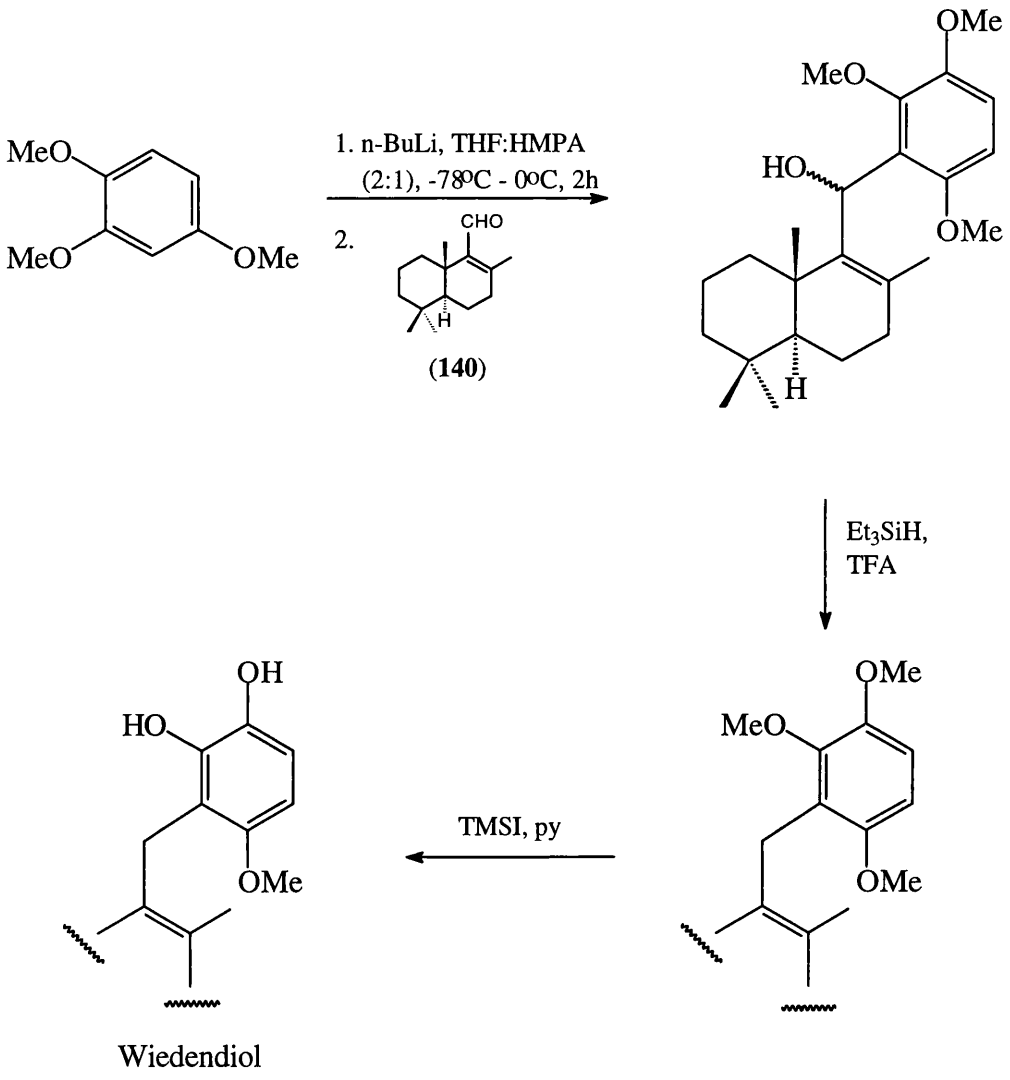


Scheme 9.1

More encouraging was the report by Chackalamannil that the anion of 1,2,4-trimethoxybenzene could be added to enal (**140**) in moderate yield. This reaction was utilised in the total synthesis of the natural product wiedendiol-A, Scheme 9.2.

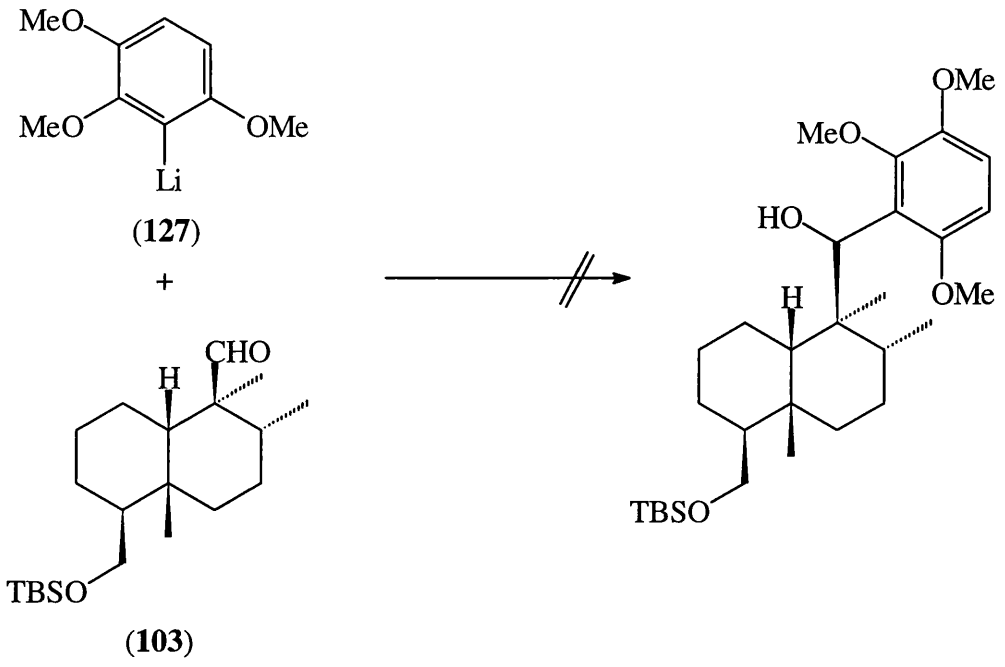
Preparation of the anion (**127**) was carried out at -78 to 0 °C in the presence of TMEDA according to the report by Chackalamannil. Addition of aldehyde (**103**), made *via* the Robinson annulation protocol, in THF and HMPA was then carried out. The reaction was monitored by TLC but even after warming to 25 °C no

reaction took place, Scheme 9.3. Although initial studies proved to be unsuccessful addition to the aldehyde (**103**) requires further investigation. Simply raising the temperature may be all that is required to promote addition.



Wiedendiol

Scheme 9.2

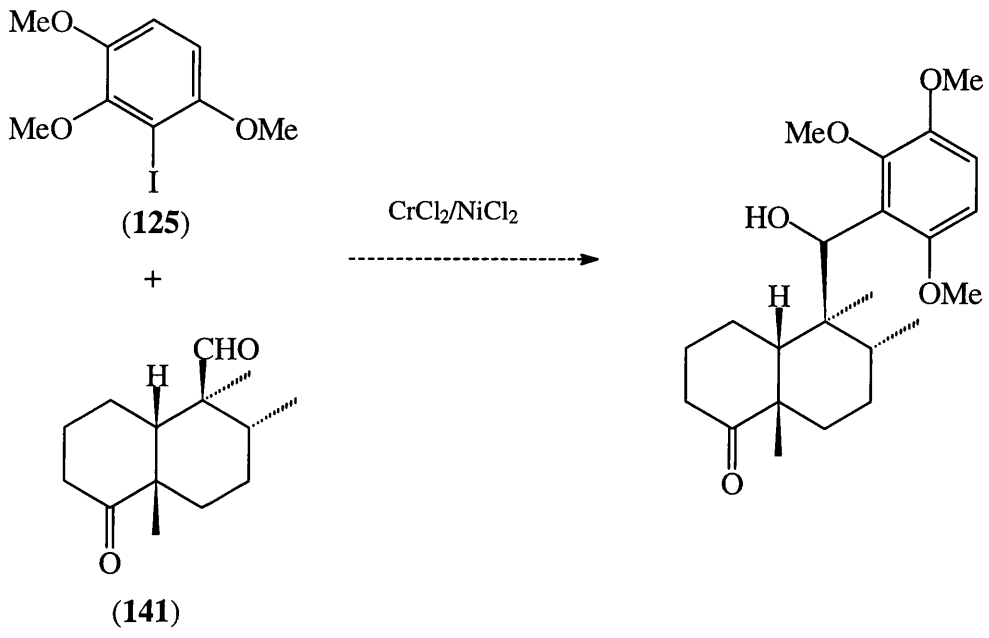


Scheme 9.3

9.1.2 $CrCl_2/NiCl_2$ Catalysed Coupling

$CrCl_2/NiCl_2$ catalysed addition of iodide (**125**) to aldehyde (**141**) is another alternative to the cross-coupling approach, Scheme 9.4. This method would also allow reaction of the aldehyde (**141**) without prior protection or interconversion of the ketone. Section 1.2.1 discusses the use of this reaction in natural product synthesis.

Completion of the decalin synthesis using any of the aldehyde addition methods would require reduction of the benzylic alcohol produced. This can be carried out in a variety of ways. In the synthesis of wiedendiol-A reduction was carried out using TFA and Et_3SiH, Scheme 9.2.



Scheme 9.4

10. Conclusion

Realisation of a total synthesis of popolohuanone E will require further development of strategies towards the decalin portion and further studies into the coupling of the arene and decalin fragments. A synthesis of the aldehyde (**103**) has been achieved, although in poor yield. With the publication of a successful synthesis of the core dibenzofuran-1,4-dione by Terashima, a formal synthesis of the natural product requires only the addition of the arene to (**103**) and minor manipulation.

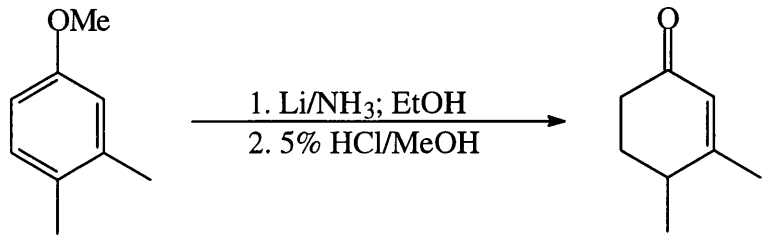
Experimental

General

Infra red spectra were obtained on a Perkin Elmer 580 spectrophotometer in the form stated. Nuclear magnetic resonance spectra were recorded with a Bruker AM200-SY or a WP200-SY spectrometer operating at 200 MHz (δ_H) and 50 MHz (δ_C). The multiplicities of the ^{13}C NMR spectra were determined using DEPT spectra with pulse angles of $\phi = 90^0$ and $\phi = 135^0$. Spectra were recorded for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal standard with the exception of silyl containing compounds which were recorded with no internal standard. Mass spectra were obtained with an A. E. I. MS 902 spectrometer. Elemental analyses were obtained with a Carlo-Erba 1106 elemental analyser.

Tetrahydrofuran and diethyl ether were dried by distillation from sodium, containing benzophenone, under nitrogen prior to use. Dichloromethane was dried by distillation from phosphorus pentoxide. Methanol was dried by distillation from clean, dry magnesium turnings and iodine. DMA and HMPA were dried by distillation from calcium hydride. Tetrahydrofuran and diethyl ether are referred to throughout as THF and ether repectively. All organic solutions were dried over anhydrous magnesium sulphate and filtered before concentration unless otherwise stated. All chemicals were purchased from the Aldrich Chemical Company Ltd.

3,4-Dimethylcyclohex-2-enone[64]



A 2-L, 3-necked, round-bottomed flask equipped with a magnetic stirring bar, a stopper, and a dry ice/acetone condenser, fitted with a $CaCl_2$ drying tube, was charged with 3,4-dimethylanisole (50g; 0.37 mol) and dry ether (170 mL). To this flask was added liquid ammonia (700 mL), carefully to avoid excess evaporation. After the addition was complete, Li wire (14g; 2 mol/atom) was added in small pieces, with stirring, over 10 mins to avoid excess boiling of the NH_3. Once the addition was complete the reaction mixture was stirred for a further 15 mins before the careful dropwise addition of anhydrous EtOH (116g; 2.52 mol). When the dark blue colour disappeared the ammonia was evaporated. Ether (100 mL) and water (100 mL) were added and the product extracted with ether (3 x 100 mL). After concentration *in vacuo* the remaining organic material was placed in a 500 mL round-bottomed flask containing a magnetic stirring bar. To this flask was added 5% HCl (100 mL) and methanol (200 mL) and the mixture stirred overnight. After evaporation of the methanol the water layer was extracted with ether (3 x 100 mL). The combined organic layer was then washed with water (100 mL), followed by saturated brine (100 mL), and then dried. After concentration *in vacuo,*

purification by distillation gave *3,4-dimethylcyclohex-2-enone* as a colourless liquid (15.8g; 0.13 mol; 51%), bp 81-83 °C/25mmHg (lit.[64] 60-62 °C/4.5-5.0mmHg).

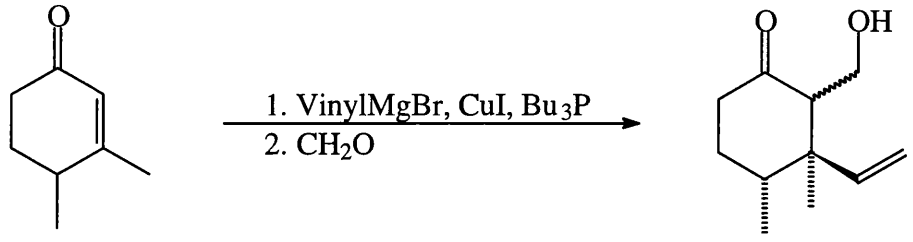
υ_{max} 2963, 1672, 1649 and 860 cm^{-1}.

δ_H(200 MHz) 5.82 (1H, bs, CC<u>H</u>), 2.78-2.06 (3H, m, CC<u>H</u>$_2$ and C<u>H</u>Me), 1.96 (3H, s, C<u>Me</u>), 1.84-1.71 (2H, m, CHC<u>H</u>$_2$), 1.20 (3H, d, *J* 7.1, CH<u>Me</u>).

δ_C(50 MHz) 199.6 (s), 166.6 (s), 126.2 (d), 34.5 (t), 34.3 (d), 30.2 (t), 22.6 (q), 17.6 (q).

Found: M^+, 124.0891. $C_8H_{12}O$ requires *M*, 124.0888.

(±)-2-Hydroxymethyl-3α,4α-dimethyl-3β-vinylcyclohexan-1-one[49]



(**88**) (**90**)

A 2 L, 3-necked, round-bottomed flask equipped with a mechanical stirrer, a rubber septum inlet, and a nitrogen balloon was charged with cuprous iodide (28.5g; 0.15 mol) and anhydrous ether (300 mL). To this stirred suspension, held at 0 °C, was added dropwise tri-n-butylphosphine (37.5 mL; 0.15 mol) using a syringe. After the addition was complete the mixture was stirred at room temperature until a clear solution resulted. To this solution was added 0.1M vinylmagnesium bromide solution in THF (300 mL; 0.3 mol), dropwise *via* cannula, at -78 °C during 1.5 hrs. The reaction mixture was then stirred for a further 30 mins at -78 °C. To the vinylcuprate solution thus formed was added, dropwise, a solution of *3,4-dimethylcyclohex-2-enone* (14.7g; 0.12 mol) in anhydrous THF (60 mL) at -78 °C over 1 hr and the temperature was then allowed to rise to -40 °C during 2 hrs. An excess of formaldehyde gas - made by the pyrolysis of paraformaldehyde at ~180 °C - was then introduced by means of a nitrogen flow over 2

hrs. The reaction mixture was then added to saturated aqueous NH_4Cl (500 mL) containing ice. The organic layer was separated, and the aqueous layer extracted with ether (3 x 250 mL). The combined organic layer was washed with saturated aqueous NH_4Cl (200 mL), followed by saturated aqueous $NaHCO_3$ (200 mL), and finally with saturated brine (200 mL). After drying and concentration *in vacuo* the residue was chromatographed on a column of silica gel (2:1 pentanes-EtOAc). Evaporation of the solvent gave the *title compound* as a golden oil (12.71g; 59%; 2:1 mixture of diastereomers).

NB: Proton and carbon NMR data are for major diastereomer only.

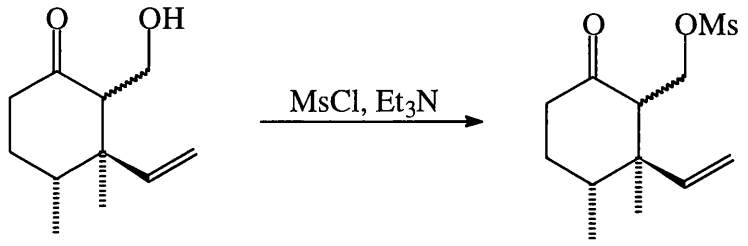
$\upsilon_{max}(CHCl_3)$ 3578, 2974, 1700, 1638, 1090, 782 and 732 cm^{-1}.

δ_H(200 MHz) 5.76 (1H, dd, *J* 10.7 and 16.0, $CH_2C\underline{H}$), 5.06 (1H, dd, *J* 1.0 and 10.7, CHCH$\underline{H}$), 4.92 (1H, dd, *J* 1.0 and 16.0, CHC$\underline{H}$H), 3.91 (1H, dd, *J* 9.3 and 11.2, C$\underline{H}$HOH), 3.43 (1H, m, CH$\underline{H}$OH), 2.77 (1H, br s, O$\underline{H}$), 2.55-1.63 (6H, m, $CC\underline{H_2}C\underline{H_2}C\underline{H}CC\underline{H}$), 1.09 (3H, s, C$\underline{Me}$), 1.09 (3H, d, *J* 6.8, CH$\underline{Me}$).

δ_C(50 MHz) 214.9 (s), 143.5 (d), 113.9 (t), 59.7 (t), 59.1 (d), 45.8 (s), 37.8 (t), 37.6 (d), 29.3 (t), 20.7 (q), 15.1 (q).

Found: M^+, 182.1302. $C_{11}H_{18}O_2$ requires *M*, 182.1307.

(±)-2-Mesyloxymethyl-3α,4α-dimethyl-3β-vinylcyclohexan-1-one[49]



(**90**) (**92**)

A 500 mL, 3-necked, round-bottomed flask equipped with a magnetic stirring bar, N_2 balloon, rubber septum inlet, and a stopper was charged with *hydroxy-ketone* (**90**) (15g; 82.4 mmol), anhydrous dichloromethane (230 mL), and dry Et_3N (16.8 mL; 12.2 mmol). To this stirred mixture, held at -10-0 °C, was added dropwise, *via* syringe, a solution of methanesulfonyl chloride (11.0g; 95.7 mmol) in anhydrous dichloromethane (115 mL), over 30 mins. The mixture was then allowed to stir at 0 °C for a further 1 hr before being poured onto ice-water (250 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic layer was then washed successively with 2M HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and saturated brine (2 x 100 mL). The solution was then dried and carefully concentrated *in vacuo* - with only gentle heating to avoid decomposition. Chromatography on a column of silica gel (99:1 CH_2Cl_2-MeOH) gave the unstable *mesylate* as a clear oil (16.82g; 64.7 mmol; 98%; 3:1 mixture of diastereomers).

NB: Proton and carbon NMR data are for major diastereomer only.

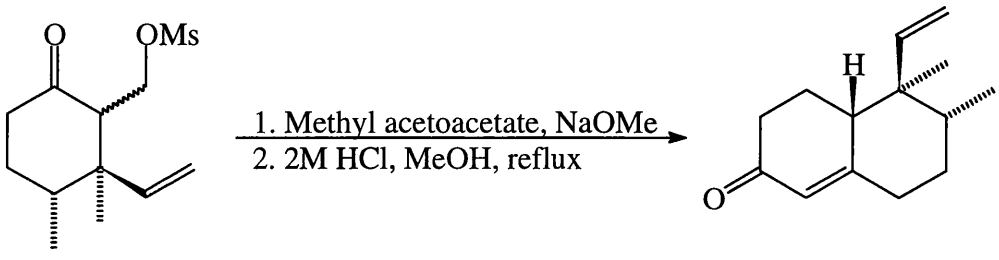
$\upsilon_{max}(CHCl_3)$ 2969, 1715, 1357, 1175 and 959 cm^{-1}.

δ_H(200 MHz) 5.65 (1H, dd, *J* 10.9 and 17.4, $CH_2C\underline{H}$), 5.09 (1H, dd, *J* 0.7 and 10.9, CHCH$\underline{H}$), 4.99 (1H, dd, *J* 0.7 and 17.4, CHC$\underline{H}$H), 4.57 (1H, dd, *J* 8.8 and 10.1, C$\underline{H}$HOH), 4.12 (1H, dd, *J* 3.5 and 10.1, CH$\underline{H}$OH), 3.02 (3H, s, $SO_2\underline{Me}$), 2.74-1.58 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}CC\underline{H}$), 1.15 (3H, s, C$\underline{Me}$), 1.09 (3H, d, *J* 6.7, CH$\underline{Me}$).

δ_C(50 MHz) 221.4 (s), 141.9 (d), 115.1 (t), 66.2 (t), 55.4 (d), 46.5 (s), 37.8 (d), 37.6 (t), 37.1 (q), 29.1 (t), 21.0 (q), 14.9 (q).

Found: M^+, 260.1086. $C_{12}H_{20}O_4S$ requires *M*, 260.1082.

(±)-4,4aβ,5,6,7,8-Hexahydro-5α,6α-dimethyl-5β-vinyl-2(3*H*)-naphthalenone[49]



(**92**) (**96**)

A 1 L, 3-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum inlet, N_2 balloon, and a stopper was charged with methyl acetoacetate (16.3 mL; 152 mmol), dry benzene (65 mL) and anhydrous methanol (60 mL). To this solution was added, *via* cannula, sodium methoxide solution - from sodium (8.15g; 0.35 mol/atoms) and anhydrous methanol (410 mL) - with stirring at room temperature. Following this, the dropwise addition of *mesylate* (**92**) (16.82g; 64.7 mmol) dissolved in dry benzene (110 mL) was done *via* syringe, over 30 mins. After the mixture was allowed to react at room temperature for 3.5 hrs with stirring, the reaction was quenched by the addition of 2M HCl (250 mL). After the evaporation of the methanol *in vacuo* the crude product was obtained by extraction with ether (5 x 200 mL). After evaporation of the solvent the crude organic material was dissolved in methanol (165 mL) and treated with 2M HCl (110 mL) under refluxing for 5 hrs. The methanol was then removed *in vacuo* and the resultant mixture extracted with ether (3 x 100 mL) and the combined organic layer washed with saturated aqueous $NaHCO_3$ (100 mL), followed by saturated

brine (100 mL). The solution was then dried and concentrated *in vacuo*. Purification, of the resultant crude product, by chromatography on a column of silica gel (6:1 pentanes-ether) gave the *title compound* as golden oil (8.38 g; 41.1 mmol; 63%).

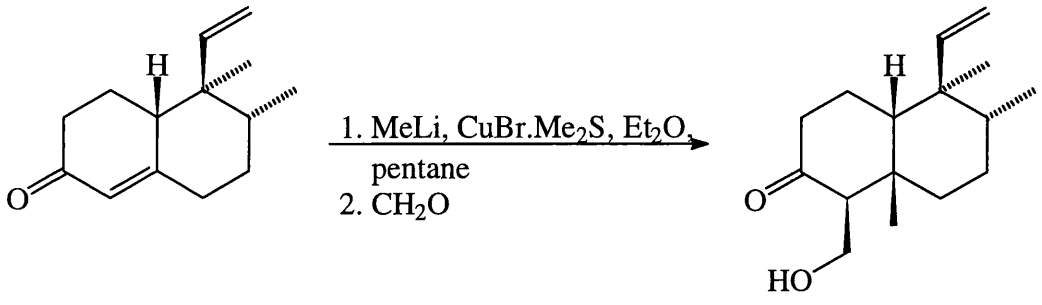
$\upsilon_{max}(CHCl_3)$ 2960, 1666 and 1258 cm^{-1}.

δ_H(200 MHz) 5.91 (1H, t, *J* 1.9, C<u>H</u>CO), 5.59 (1H, dd, *J* 10.7 and 17.4, C<u>H</u>CH_2), 5.17 (1H, dd, *J* 1.2 and 10.7, CHCH<u>H</u>), 5.0 (1H, dd, *J* 1.2 and 17.4, CHC<u>H</u>H), 2.44-1.12 (10H, m), 0.8 (3H, d, *J* 6.4, CH<u>Me</u>), 0.79 (3H, s, C<u>Me</u>).

δ_C(50 MHz) 199.8 (s), 164.6 (s), 146.3 (d), 126.0 (d), 114.1 (t), 46.5 (s), 46.2 (d), 40.0 (d), 36.5 (t), 35.3 (t), 29.6 (t), 22.1 (t), 16.3 (q), 10.3 (q).

Found: M^+, 204.1514. $C_{14}H_{20}O$ requires *M*, 204.1514.

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-1β-hydroxymethyl-5,6,8aβ-trimethyl-5β-vinyl-2(1*H*)-naphthalenone[49]



(**94**) (**59**)

A 250 mL, 3-necked, round-bottomed flask equipped with a magnetic stirring bar, N_2 balloon, rubber septum inlet, and a stopper was charged with copper(I)bromide-dimethylsulfide complex (3.02g; 14.7 mmol) and anhydrous ether (12 mL). To this stirred suspension was added 1.4M MeLi solution in THF (17.7 mL; 24.8 mmol) at O °C over 20 mins. Dry pentane (40 mL) was then added to the colourless clear solution to precipitate white solids. The mixture was then cooled to -25 °C and *bicyclic enone* (**94**) (1g; 4.9 mmol), dissolved in anhydrous ether (5 mL), was added dropwise with stirring over 30 mins. The yellow coloured suspension was stirred at this temperature for a further 4 hrs, followed by the introduction of formaldehyde gas by means of an N_2 flow for 30 mins, at -10 °C. The mixture was then allowed to warm to 0 °C when it was poured onto saturated aqueous NH_4Cl (100 mL). Insoluble material was removed by filtration and the filtrate extracted with ether (3 x 30 mL). The combined organic layer was washed successively with saturated aqueous NH_4Cl (20 mL), saturated aqueous

$NaHCO_3$ (30 mL), and saturated brine (30 mL). Drying and concentration *in vacuo* gave the crude product, which was purified by chromatography on a column of silica gel (4:1 pentanes-EtOAc), to give the *title compound* as a golden oil (330mg; 1.32 mmol; 27%).

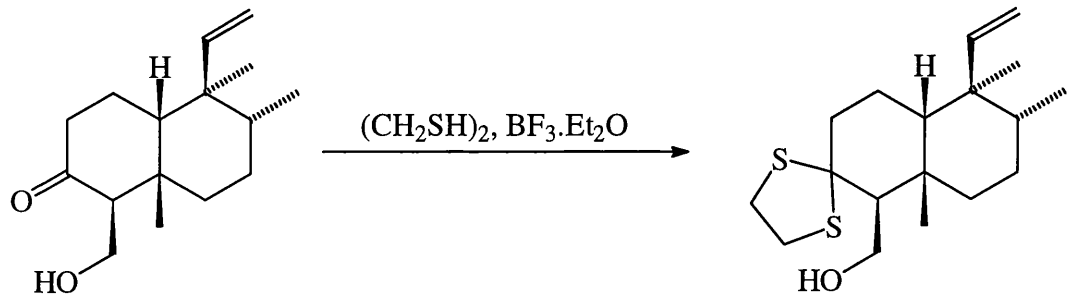
$\upsilon_{max}(CHCl_3)$ 3564, 2966, 1692 and 1634 cm^{-1}.

δ_H(200 MHz) 5.38 (1H, dd, *J* 10.7 and 17.3, $CH_2C\underline{H}$-), 5.07 (1h, dd, *J* 1.3 and 10.7, $CH\underline{H}CH$-), 4.93 (1H, dd, *J* 1.3 and 17.3, $C\underline{H}HCH$-), 3.85 (1H, dd, *J* 8.9 and 11.3, $CH\underline{H}OH$), 3.58 (1H,dd, *J* 3.4 and 11.3, $C\underline{H}HOH$), 2.97 (1H, dd, *J* 3.4 and 8.9, $COC\underline{H}$), 2.80 (1H, br s, $O\underline{H}$), 2.46-1.17 (10H, m), 1.12 (3H, s, $C\underline{Me}$), 0.81 (3H, s, $C\underline{Me}$), 0.72 (3H, d, *J* 6.2, $CH\underline{Me}$).

δ_C(50 MHz) 217.2 (s), 149.8 (d), 113.5 (t), 58.5 (t), 54.3 (d), 49.2 (d), 45.4 (s), 41.3 (d), 40.6 (s), 39.8 (t), 36.8 (t), 27.5 (q), 25.8 (t), 22.1 (t), 16.6 (q), 14.0 (q).

Found: M^+, 250.1925. $C_{16}H_{26}O_2$ requires *M*, 250.1933.

(±)-1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-hydroxymethyl-2-spirodithiaethane-5,6,8aβ-trimethyl-5β-vinyl-naphthalene



(**59**) (**97**)

A 25 mL, 2-necked, round-bottomed flask equipped with magnetic stirring bar, a rubber septum inlet, and a N_2 balloon was charged with *hydroxy-ketone* (**59**) (500mg; 2 mmol), dry dichloromethane (10 mL), and ethane-1,2-dithiol (0.25 mL; 3 mmol). To this solution was added boron trifluoride etherate (0.1 mL; 12.7 mmol) dropwise, with stirring. The solution was stirred at room temperature for 14 hrs and 5% NaOH solution (2.5 mL) was then added. The organic layer was separated and the aqueous layer washed with dichloromethane (3 x 10 mL). The combined organic layer was then washed with water (5 mL) and brine (5 mL), dried and the solvent removed *in vacuo*. Chromatography on a column of silica gel (5:1 n-hexane-ether) gave the *title compound* as a white solid (122 mg; 0.37 mmol, 19 %), m.p. 124-126 °C.

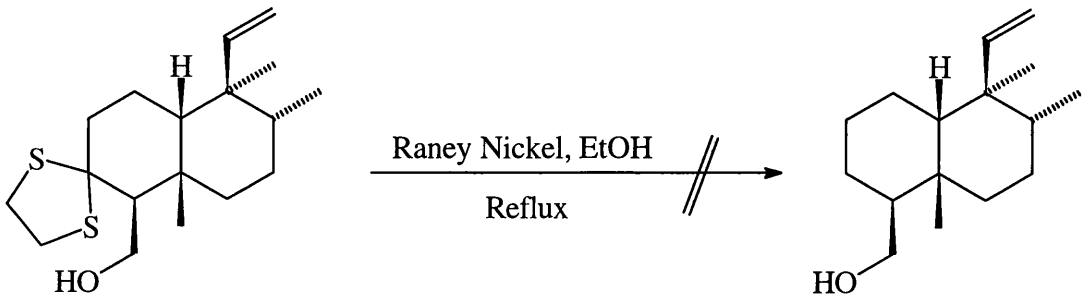
$\upsilon_{max}(CHCl_3)$ 3616, 2926 and 1633 cm^{-1}.

δ_H(200 MHz) 5.18 (1H, dd, *J* 10.7 and 17.3, -C<u>H</u>CH_2), 4.83 (1H, dd, *J* 1.4 and 10.7, -CHCH<u>H</u>), 4.68 (1H, dd, *J* 1.4 and 17.3, -CHC<u>H</u>H), 3.82 (1H, dd, *J* 3.1 and 12.1, CH<u>H</u>OH), 3.57 (1H, br d, *J* 12.1, C<u>H</u>HOH), 3.16-2.90 (4H, m, ($C\underline{H_2}S)_2C$), 2.24-1.08 (11H, m), 0.83 (6H, s, C<u>Me</u> x2), 0.51 (3H, d, *J* 6.3, CH<u>Me</u>).

δ_C(50 MHz) 150.4 (d), 112.7 (t), 73.2 (s), 63.2 (t), 51.7 (d), 48.2 (d), 45.4 (s), 44.5 (t), 41.7 (d), 40.2 (t), 39.3 (t), 38.4 (s), 37.9 (t), 28.5 (q), 26.1 (t), 21.5 (t), 16.7 (q), 15.4 (q).

Found: M^+, 326.1738. $C_{18}H_{30}OS_2$ requires *M*, 326.1738.

Attempted Reduction of the Dithioketal (97)

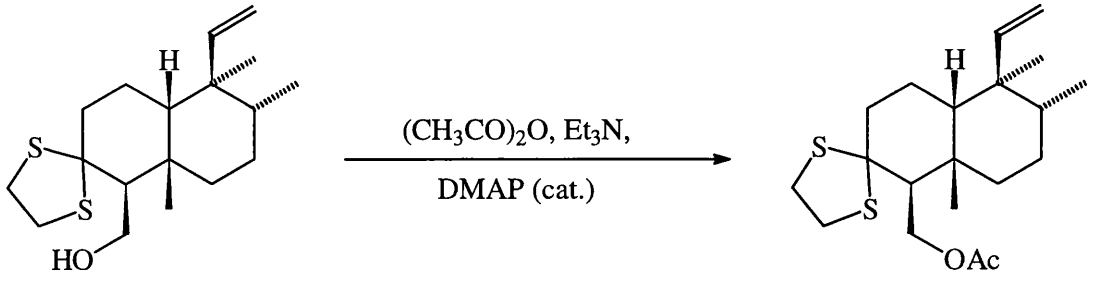


(**97**)

A 10 mL round bottomed flask, equipped with a reflux condenser and SiO_2 drying tube, was charged with *thioketal* (**97**) (460mg; 1.41 mmol) in absolute ethanol (2 mL) and Raney nickel (~ 2 g). The mixture was then heated under reflux for 72 hrs. After cooling the solids were removed by filtration through a pad of Celite 531, which was washed with hot ethanol (2 x 2 mL). After evaporation of the filtrate *in vacuo* the crude material was purified by chromatography on a column of silica gel (3:1 n-hexane-EtOAc), to afford the starting material as a white solid (281 mg; 0.86 mmol; 61%).

Spectroscopic data identical in all respects to that of starting material.

(±)-1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-acetoxymethyl-2-spirodithiaethane-5,6,8aβ-trimethyl-5β-vinyl-naphthalene



(**97**) (**98**)

A 10 mL round bottomed flask, equipped with stirring bar, rubber septum inlet and an N_2 balloon, was charged with *hydroxy-thioketal* (**97**) (207 mg; 0.63 mmol) in dichloromethane (10 mL), acetic anhydride (0.13 mL; 1.32 mmol), anhydrous Et_3N (0.13 ml; 0.95 mmol) and DMAP (5 mg). The mixture was then stirred at 25 °C for 48 hrs before water (15 mL) was added. The water layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layer was then washed with water (5 mL) and brine (10 mL). Evaporation of the solvent *in vacuo* gave the *title compound* as a white solid (171 mg; 0.46 mmol; 73 %), m.p. 108-110 °C.

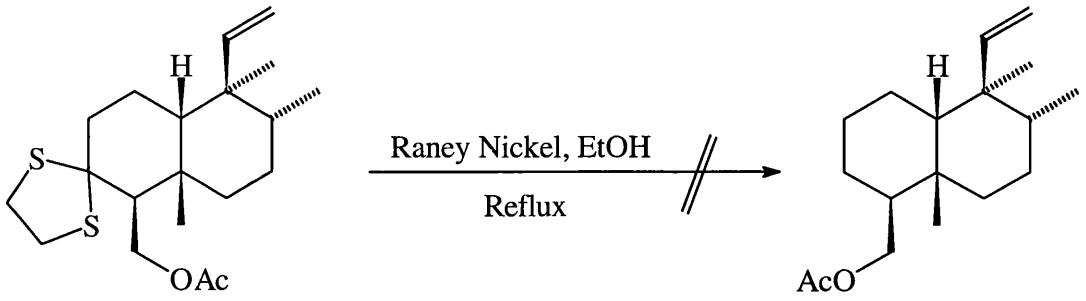
υ_{max}(KBr) 2965, 1736 and 1633 cm^{-1}.

δ_H(200 MHz) 5.41 (1H, dd, *J* 10.7 and 17.3, -C<u>H</u>CH$_2$), 5.07 (1H, dd, *J* 1.3 and 10.7, -CHCH<u>H</u>), 4.92 (1H, dd, *J* 1.3 and 17.3, -CHC<u>H</u>H), 4.40 (1H, br d, *J* 11.9, CH<u>H</u>OAc), 4.15 (1H, dd, *J* 5.7 and 11.9, C<u>H</u>HOAc), 3.30-3.08 (4H, m, (C<u>H</u>$_2$S)$_2$C), 2.68 (11H, m), 2.05 (3H, s, <u>Me</u>COO), 1.12 (3H, s, C<u>Me</u>),1.08 (3H, s, C<u>Me</u>), 0.75 (3H, d, *J* 6.1).

δ_C(50 MHz) 170.8 (s), 150.3 (d), 112.8 (t), 72.1 (s), 65.4 (t), 48.0 (d), 46.9 (d), 45.3 (s), 44.4 (t), 41.6 (d), 40.2 (t), 39.6 (t), 38.4 (s), 38.1 (q), 25.8 (t), 21.2 (q), 21.2 (t), 16.7 (q), 15.4 (q).

Found: M^+, 368.1818. $C_{20}H_{32}O_2S_2$ requires *M*, 368.1844.

Attempted Reduction of the Acetoxy-dithioketal

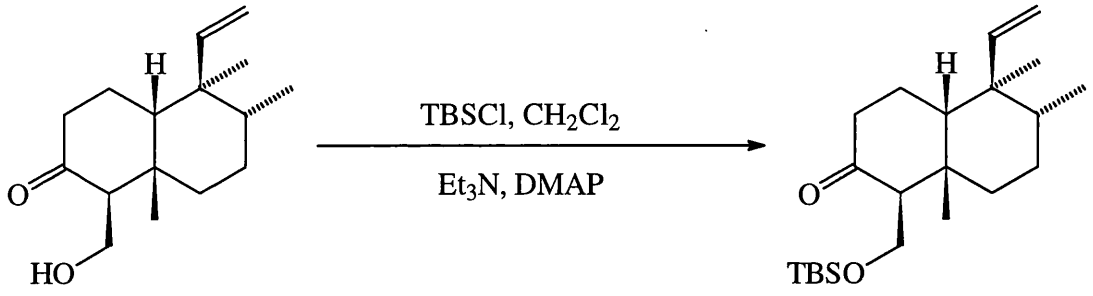


(**98**)

A 5 mL round bottomed flask, equipped with a reflux condenser and SiO_2 drying tube, was charged with *acetoxy-dithioketal* (**98**) (171 mg; 0.46 mmol), absolute ethanol (1 mL) and Raney nickel (~ 1 g). The mixture was then refluxed for 4 hrs. After cooling the solids are removed by filtration through a pad of Celite 531, which was washed with hot ethanol (2 x 2 mL). Evaporation of the filtrate *in vacuo* returned starting material (108 mg, 0.29 mmol, 63 %).

Spectroscopic data identical in all respects to that of starting material.

(±)-3,4,4aβ,5,6,7,8,8a-Octahydro-1β-t-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl-5β-vinyl-2(1*H*)-naphthalenone



(**59**) (**100**)

A 10 mL 2-necked round bottomed flask, equipped with a rubber septum inlet, magnetic stirring bar and a N_2 balloon, was charged with TBSCl (0.76 g, 5.05 mmol), Et_3N (0.56 g, 5.54 mmol), anhydrous dichloromethane (8 mL) and DMAP (15 mg). To this stirred solution held at 0 °C was added, dropwise, a solution of *ketoalcohol* (**59**) (1.10 g, 4.38 mmol) in anhydrous dichloromethane (7.5 mL). The solution was then stirred at room temperature for a further 10 hrs before dilution with dichloromethane (25 mL) and the addition of water (25 mL). The organic layer was then separated and the water layer washed with dichloromethane (3 x 10 mL). The combined organic layers were then washed with 0.5 M HCl (2 x 10 mL), and brine (10 mL) before being dried and concentrated *in vacuo*. The crude product was then purified by chromatography on a

column of silica gel (5:1 pentanes-EtOAc) to give the *TBS ether* (**100**) as a golden oil (1.46 g, 4.01 mmol, 92 %).

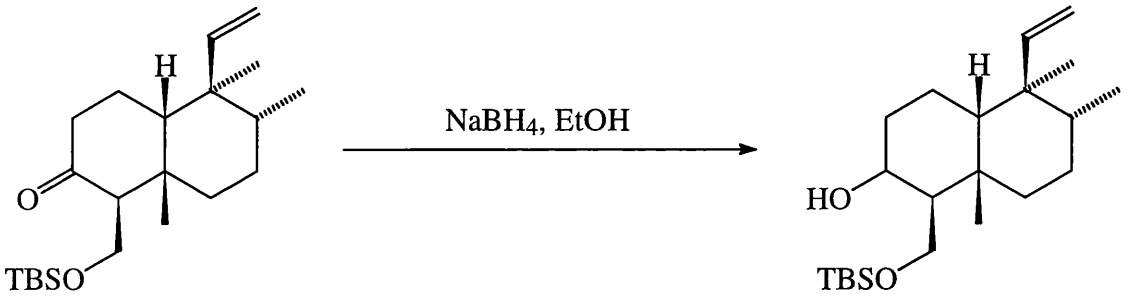
υ_{max}(neat) 2925, 1725, 1460, 1255cm^{-1}.

δ_H(200 MHz) 5.36 (1H, dd, *J* 10.7 and 17.4, -C<u>H</u>CH$_2$), 4.98 (1H, dd, *J* 1.5 and 10.7, -CHCH<u>H</u>), 4.84 (1H, dd, *J* 1.5 and 17.4, -CHC<u>H</u>H), 3.73 (1H, dd, *J* 4.6 and 10.0, -CH<u>H</u>OSi), 3.21 (1H, dd, *J* 7.5 and 10.0, -C<u>H</u>HOSi), 2.37-0.85 (11H, m), 0.99 (3H, s, C<u>Me</u>), 0.87 (3H, s, C<u>Me</u>), 0.85 (9H, s, SiC<u>tBu</u>), 0.66 (3H, d, *J* 6.5, CH<u>Me</u>), 0.00 (6H, s, Si<u>Me$_2$</u>).

δ_C(50 MHz) 213.5 (s), 150.1 (d), 113.2 (t), 58.3 (t), 55.6 (d), 49.2 (d), 45.5 (s), 41.5 (s), 41.1 (d), 40.0 (t), 37.7 (t), 27.1 (q), 26.4 (t), 25.8 (q), 25.7 (s), 22.6 (t), 16.7 (q), 13.8 (q), 13.8 (q), -5.5 (q).

Found: M^+, 364.2806. $C_{22}H_{40}O_2Si$ requires *M*, 364.2798.

(±)-1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-t-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl-5β-vinyl-2-naphthol



(**100**) (**101**)

A 25 mL round bottomed flask, equipped with an N_2 balloon and a magnetic stirring bar, was charged with *ketone* (**100**) (190 mg, 0.52 mmol) and absolute ethanol (10 mL). To this solution was added $NaBH_4$ (100mg, 2.63 mmol), portion wise, with stirring. The solution was then stirred for 10 hrs and the ethanol removed *in vacuo*. After the addition of saturated aqueous NH_4Cl (2 mL) and ether (2 mL) the organic layer was separated. The water layer was then extracted with ether (3 x 2 mL) and the combined organic layers washed with brine (2 mL). After drying and concentration the *alcohol* (**101**) was obtained as a soft white solid (173 mg, 0.47 mmol, 91 %), m.p. 36-39 °C.

υ_{max}(neat) 3460, 2930, 2859, 1632, 1462, 1257 cm^{-1}.

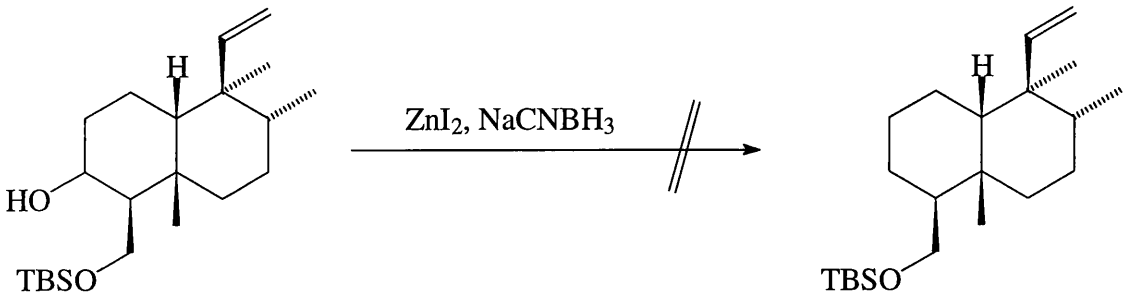
δ_H(200 MHz) 5.42 (1H, dd, *J* 10.8 and 17.4, -C<u>H</u>=CH_2), 5.03 (1H, dd, *J* 1.4 and 10.8, CH=CH<u>H</u>), 4.89 (1H, dd, *J* 1.4 and 17.4, CH=C<u>H</u>H), 4.31(1H, br s,

CHOH), 4.01 (1H, dd, *J* 5.4 and 10.5, CHHOSi), 3.84 (1H, dd, *J* 4.5 and 10.5, CHHOSi), 3.15 (1H, br s, -OH), 2.01-1.07 (11H, m), 1.27 (3H, s, CMe), 0.97 (3H, s, CMe), 0.89 (9H, s, SitBu), 0.71 (3H, d, *J* 6.2, CHMe), 0.00 (6H, s, $SiMe_2$).

δ_C(50 MHz) 151.0 (d), 112.3 (t), 70.1 (d), 63.3 (t), 50.1 (d), 45.5 (s), 41.9 (d), 41.7 (d), 39.0 (t), 35.8 (s), 30.5 (t), 30.3 (q), 26.1 (t), 25.9 (q), 18.0 (s), 17.6 (t), 16.8 (q), 15.0 (q), -5.6 (q).

Found: M^+, 366.2992. $C_{22}H_{42}O_2Si$ requires *M*, 366.2954.

Attempted Reduction of Alcohol (101)

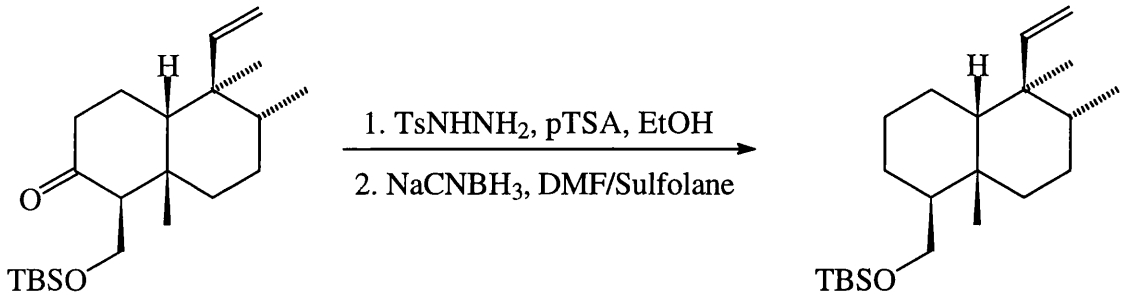


(**101**) (**102**)

To a 10 mL round bottomed flask, equipped with a magnetic stirring bar and an N_2 balloon, and charged with *alcohol* (**101**) (168 mg, 0.46 mmol) and dichloromethane (5 mL) was added ZnI_2 (176 mg, 0.55 mmol) in small portions over 5 min. To this stirred suspension was then added $NaCNBH_3$ (35 mg, 0.55 mmol) in small portions over 5 min. The mixture was then stirred at room temperature for 4 hrs before the addition of water (25 mL) and dichloromethane (25 mL). The water layer was separated and washed with dichloromethane (3 x 5 mL). The combined organic layer was extracted with brine (10 mL), dried and concentrated *in vacuo* to give starting *alcohol* as a white solid (161 mg).

Spectroscopic data were identical in all respects to that of starting material.

(±)-2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-t-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl-5β-vinyl-naphthalene



(**100**) (**102**)

A stirred mixture of *ketone* (**100**) (252 mg, 0.692 mmol), p-toluenesulfonylhydrazine (154 mg, 0.83 mmol), pTSA (15 mg) in dry ethanol (2 mL) was heated at reflux for 1.5 hrs in a 5 mL round-bottomed flask. After cooling the ethanol was carefully removed *in vacuo* before the addition of dry DMF (1 mL) and sulfolane (1 mL). To this solution, held under N_2, was added $NaCNBH_3$ (2.76 mL, 2.76 mmol, 1M soln. in THF) and the mixture was then heated under reflux for 18hrs before the addition of water (2 mL). The resultant solution was extracted with hexane (10 x 3 mL). The combined organic layer was then washed with water (10 x 2 mL) before being dried and concentrated. The crude product was then purified by chromatography on a column of silica gel (hexane) to give the *olefin* (**102**) as a golden oil (153 mg, 0.437 mmol, 63 %).

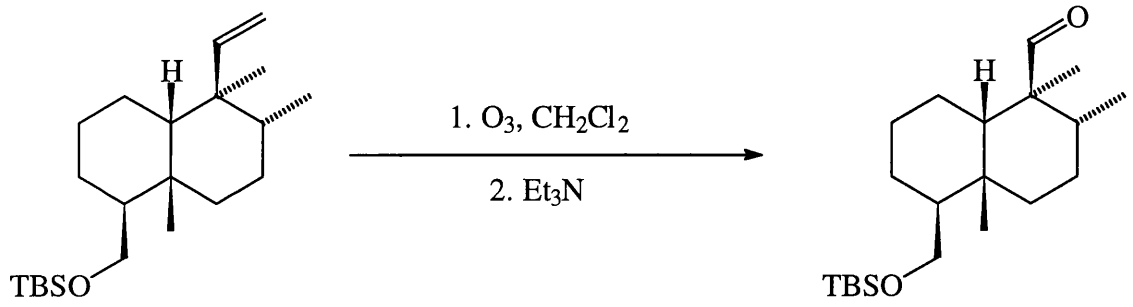
υ_{max}(neat) 2954, 1634, 1456, 1380, 1072 and 838 cm^{-1}.

δ_H(200 MHz) 5.36 (1H, dd, *J* 10.7 and 17.3, -C<u>H</u>CH_2), 4.98 (1H, dd, *J* 1.5 and 10.7, -CHCH<u>H</u>), 4.84 (1H, dd, *J* 1.5 and 17.3, -CHC<u>H</u>H), 3.74 (1H, dd, *J* 4.6 and 10.0, -C<u>H</u>HOSi), 3.21 (1H, dd, *J* 7.5 and 10.0, -CH<u>H</u>OSi), 1.96-0.94 (13H, m), 0.99 (3H, s, C<u>Me</u>), 0.89 (3H, s, C<u>Me</u>), 0.87 (9H, s, SiC<u>tBu</u>), 0.68 (3H, d, *J* 6.5), 0.00 (6H, s, Si<u>Me_2</u>).

δ_C(50 MHz) 151.2 (d), 112.2 (t), 64.8 (t), 50.2 (d), 45.7 (s), 41.7 (d), 39.6 (d), 38.0 (t), 35.9 (s), 25.9 (q), 25.7 (t), 25.6 (q), 24.5 (t), 23.1 (t), 21.6 (t), 18.2 (s), 16.8 (q), 15.4 (q), -5.4 (q).

Found: M^+, 350.2990. $C_{22}H_{42}OSi$ requires *M*, 350.3005.

(±)-2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-t-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl -5β-formyl-naphthalene



(**102**) (**103**)

A 50 mL round bottomed flask was charged with *olefin* (**102**) (183 mg, 0.52 mmol) and dry dichloromethane (25 mL). Dry ozone was then bubbled through the solution, held at -78 °C, for 30 mins before purging the flask with N_2. Dry Et_3N (1 mL) was then added and the solution was allowed to warm to room temperature and allowed to stand overnight. Water (10 mL) was added and the organic layer separated before extracting the water layer with dichloromethane (3 x 5 mL). The combined organic layers were then washed with 2M HCl (2 x 5 mL) and brine (5 mL). Drying and concentration *in vacuo* afforded *aldehyde* (**103**) as a clear oil (179 mg, 50 mmol, 96 %).

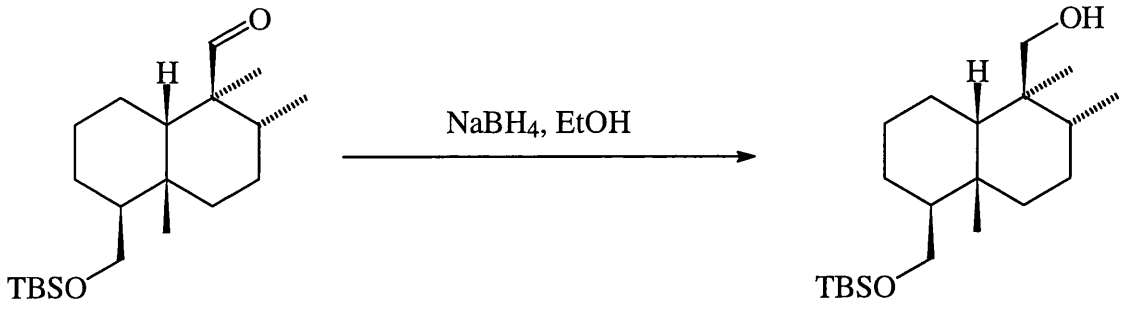
υ_{max}(neat) 2928, 1726, 1471, 1360, 1253, 1062 cm^{-1}.

δ_H(200 MHz) 9.06 (1H, s, CHO), 3.70 (1H, dd, *J* 4.8 and 10.0, CHHOSi), 3.23 (1H, dd, 6.9 and 10.0), 2.11-1.13 (14H, m), 1.09 (3H, s, CMe), 0.94 (3H, s, CMe), 0.85 (9H, s, SiCtBu), 0.67 (3H, d, *J* 6.7, CHMe), 0.00 (6H, s, SiMe).

δ_C(50 MHz) 207.1 (d), 64.6 (t), 55.1 (d), 39.7 (d), 37.5 (t), 36.0 (d), 34.9 (s), 25.9 (q), 25.2 (q), 25.1 (t), 24.2 (t), 22.7 (t), 22.4 (t), 18.2 (s), 16.9 (q), 13.0 (q), -5.4 (q).

Found: MH^+, 353.2909. $C_{21}H_{40}O_2Si$ requires *MH*, 353.2876.

(±)-2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β-t-butyldimethylsilyloxymethyl-5,6,8aβ-trimethyl-5β-hydroxymethyl-naphthalene



(**103**) (**104**)

A 25 mL round bottomed flask equipped with an N_2 balloon and a magnetic stirring bar was charged with *aldehyde* (**103**) (179 mg, 0.50 mmol) and absolute ethanol (10 mL). To this solution was added $NaBH_4$ (76 mg, 2 mmol), portion wise, under stirring. The solution was stirred for 10 hrs and the ethanol removed *in vacuo*. After the addition of saturated aqueous NH_4Cl (25 mL) the organic layer was separated. The water layer was then extracted with ether (3 x 10 mL), and the combined organic layers washed with brine (10 mL), dried and concentrated *in vacuo*. Purification by chromatography on a column of silica gel (6:1 pentanes-EtOAc) afforded the *title compound* as a clear oil (128 mg, 0.36 mmol, 72 %).

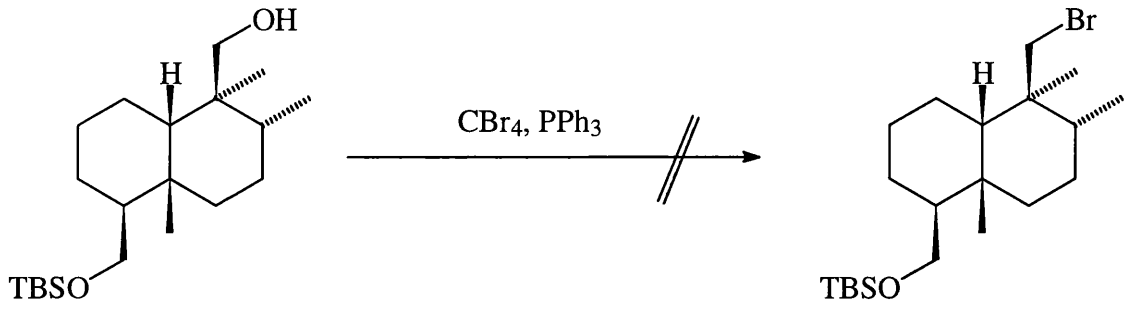
υ_{max}(neat) 3596, 2926, 1357, 1229, 1067 cm^{-1}.

δ_H(200 MHz) 3.73 (1H, dd, *J* 4.5 and 9.9, C<u>H</u>HOSi), 3.42 (1H, d, *J* 11.6, C<u>H</u>HOH), 3.24 (1H, d, *J* 11.6, CH<u>H</u>OH), 3.21 (1H, dd, *J* 7.8 and 9.9, CH<u>H</u>OSi), 2.21 (1H, br s, O<u>H</u>), 2.00-1.04 (13H, m), 0.89 (3H, s, C<u>Me</u>), 0.85 (9H, s, SiC<u>tBu</u>), 0.78 (3H, d, *J* 6.2, CH<u>Me</u>), 0.77 (3H, s, C<u>Me</u>), 0.00 (6H, s, Si<u>Me</u>$_2$).

δ_C(50 MHz) 66.2 (t), 64.7 (t), 43.6 (d), 42.2 (s), 39.8 (d), 37.9 (t), 36.3 (s), 35.5 (d), 26.2 (t), 25.9 (q), 25.5 (q), 24.4 (t), 23.1 (t), 20.7 (t), 18.2 (s), 16.6 (q), 16.1 (q), -5.4 (q).

Found: M^+, 354.2961. $C_{21}H_{42}O_2Si$ requires *M*, 354.2954.

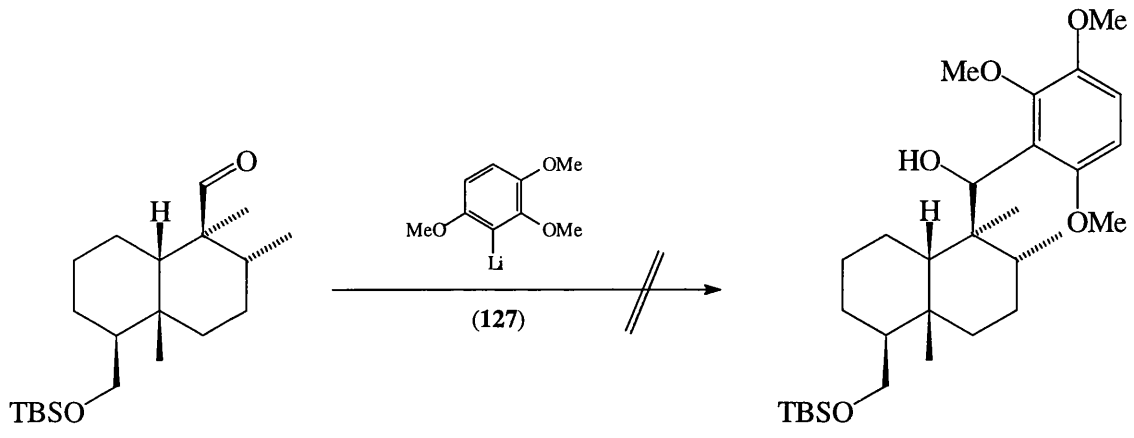
Attempted Bromination of Alcohol (104)



(**104**)

To a 10 mL flask equipped with a magnetic stirring bar was added *alcohol* (**104**) (52 mg, 0.15 mmol) and dry pyridine (3 mL). This mixture was then cooled to O °C before the addition of Ph_3P (79 mg, 0.3 mmol). Still at 0 °C, CBr_4 (50 mg, 0.15 mmol) was added in small portions before the flask was flushed with N_2 and then sealed. The stirred mixture was warmed to 60 °C for 4hrs before being allowed to cool. Methanol (0.25 mL) was then added to quench the reaction. After the addition of water (1 mL) and hexane (2 mL) the aqueous layer was separated and extracted with hexane (3 x 2 mL). The combined organic layer was then washed with aqueous $CuSO_4$ (2 mL), brine (2 mL) and dried. After concentration *in vacuo* the Ph_3P was removed by chromatography on a column of silica gel (6:1 pentanes-EtOAc). Concentration returned starting material (45 mg, 0.13 mmol).

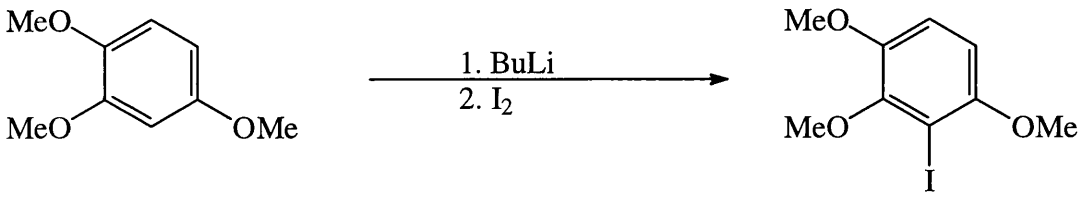
Attempted Addition of 1-Lithio-2,4,6-trimethoxy-benzene to Aldehyde (103)



(**103**)

To 10 mL round bottomed flask with side arm, equipped with a magnetic stirring bar, rubber septum inlet and N_2 balloon, was added 1,2,4-trimethoxybenzene (33.6mg, 0.2 mmol), anhydrous THF (1 mL) and TMEDA (0.5 mL). To this stirred solution, held at -78 °C, was added 1.45 M nBuLi solution in hexanes (138µl, 0.2 mmol). The resulting solution was warmed to 0 and stirred for 2 hrs before the addition of a solution of *aldehyde* (**103**) (46 mg, 0.13mmol) in anhydrous THF (0.5 mL) at -78 °C. The solution was allowed to warm to room temperature and then stirred for a further 3 hrs before the addition of water (1 mL). The THF was then removed *in vacuo* before extraction of the aqueous layer with ether (3 x 5 mL). The combined organic layer was then washed with brine (3 mL), dried and then concentrated *in vacuo*. Analysis - ^{1}H NMR and TLC - of the crude organic material (81 mg) indicated only the presence of starting *aldehyde* (**103**) and 1,2,4-trimethoxybenzene.

1-Iodo-2,3,6-trimethoxybenzene[96]



(**125**)

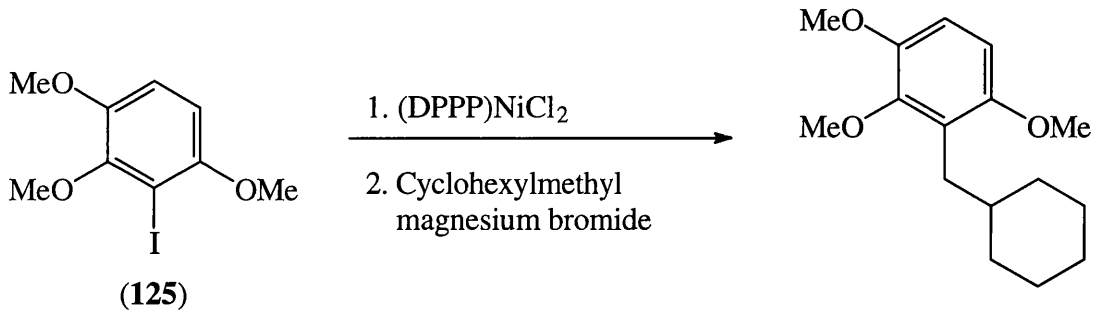
To a 250 mL 3-necked round bottomed flask equipped, with a reflux condenser, rubber septum inlet, stopper, N_2 balloon and magnetic stirring bar, was added a solution of 1,2,4-trimethoxybenzene (5g, 29.8 mmol) and anhydrous ether (50 mL). To this solution, at reflux, was added 1.55 M nBuLi solution in hexanes (23.0 mL, 33.4 mmol) dropwise over 20 mins. Heating, at reflux, was continued for a further 2hrs before cooling the solution to 0 °C. Iodine (9.1g, 35.2 mmol) in anhydrous ether (50 mL) was added dropwise over 45mins until an orange/yellow colour was observed due to excess iodine. The reaction was quenched immediately with saturated aqueous Na_2SO_3 (10 mL) and the organic layer separated. The organic layer was then washed with saturated aqueous Na_2SO_3 (50 mL), dried and concentrated *in vacuo*. The resultant white solid was washed with ethanol (3 x 5 mL) to give the *title compound* as white crystals (6.12g, 20.8 mmol, 70 %), m.p. 107-108 °C (lit.[96] 107-108 °C).

δ_H(200 MHz) 6.87 (1H, d, *J* 8.9, Ar<u>H</u>), 6.55 (1H, d, *J* 8.9, Ar<u>H</u>), 3.85 (3H, s, O<u>Me</u>), 3.83 (6H, s, 2 x O<u>Me</u>).

δ_C(50 MHz) 153.2 (s), 150.1 (s), 147.2 (s), 113.0 (d), 105.9 (d), 85.5 (s), 60.4 (q), 56.6 (q), 56.6 (q).

Found: M^+, 293.9751. $C_9H_{11}O_3I$ requires *M*, 293.9752.

2,3,4-Trimethoxybenzylcyclohexane



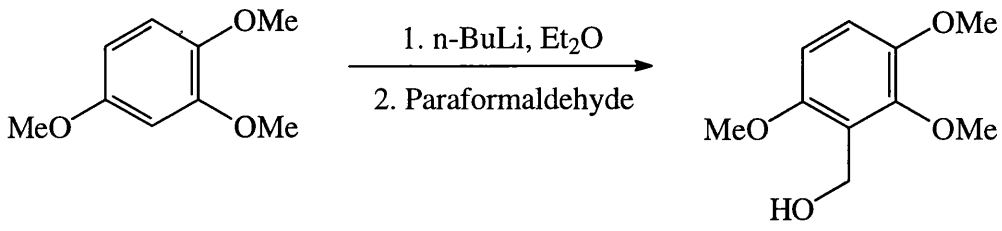
(**125**)

A 50 mL 2-necked round bottomed flask, was equipped with a rubber septum inlet, magnetic stirring bar, reflux condenser and a N_2 balloon. To this flask was added $Ni(DPPP)Cl_2$ (30.52 mg, 0.06 mmol), 1-iodo-2,3,6-trimethoxybenzene (2g, 6.8 mmol) and anhydrous ether. To this stirred suspension was added dropwise a ~0.6 M solution of bromomethylcyclohexane (5 mL) - from magnesium (0.26 g, 10.83 mmol) and cyclohexylmethyl bromide (1.44 g, 8.14 mmol) - over 20 mins. The mixture was heated under reflux for a further 22 hrs before being hydrolysed by the addition of 0.5M HCl (0.5 mL), under cooling in an ice-bath. The organic layer was then separated and the water layer extracted with ether (3 x 2 mL) and the combined organic layers washed with brine (2 mL), dried and concentrated *in vacuo.* Purification by chromatography on a column of silica gel (6:1 hexane-EtOAc) afforded the impure *title compound*, an oil (70 mg, 0.24 mmol, 6 %).

δ_H(200 MHz) 6.76 (1H, d, *J* 8.9, ArH), 6.53 (1H, d, *J* 8.9, ArH), 3.78 (3H, s, -OMe), 3.77 (3H, s, -OMe), 3.75 (3H, s, -OMe), 2.52 (3H, d, *J* 4.8, arCH_2-), 1.85-0.79 (11H, m, Chexyl).

L.R.M.S. 264 (100%), 181 (87), 166 (52), 91 (14).

2,3,6- Trimethoxybenzyl alcohol



(134)

To a 100 mL round bottomed flask with side arm, fitted with a N_2 balloon and a rubber septum inlet, was added a solution of 1,2,4-trimethoxybenzene (5 g, 30 mmol) in anhydrous ether (20 mL). To this solution held at -78 °C was added dropwise a solution of 2 M n-butyllithium in hexanes (16.4 mL, 33 mmol) over 20 mins. This solution was stirred at room temperature for 2 hrs before the addition of paraformaldehyde (3 g). The resulting mixture was then stirred at room temperature for 10 hrs before being poured onto iced saturated aqueous NH_4Cl (20 mL). The organic layer was separated and the aqueous layer washed with ether (3 x 10 mL). The combined organic layer was then extracted with brine (10 mL) and dried. Concentration *in vacuo* gave a white solid which was recrystallised (hexane-ether) to give the *title compound* (4.1 g, 21 mmol, 70 %), m.p. 65-66 °C.

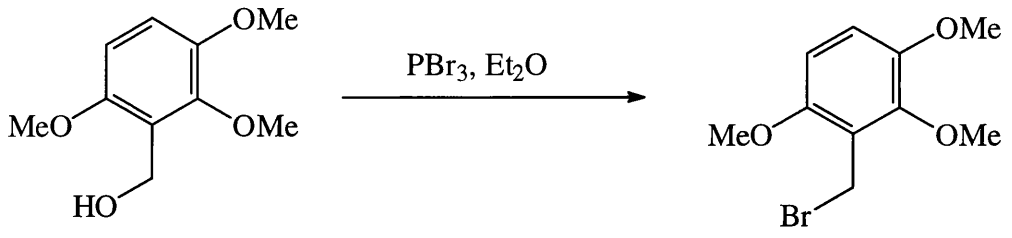
$\upsilon_{max}(CHCl_3)$ 3592, 1490, 1258 and 1100 cm^{-1}.

δ_H(200 MHz) 6.80 (1H, d, *J* 9.0, ArH), 6.58 (1H, d, *J* 9.0, ArH), 4.76 (2H, br s, -CH_2OH), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.80 (3H, s, Ome), 2.74 (1H, br s, OH).

δ_C(50 MHz) 152.2 (s), 147.9 (s), 147.0 (s), 123.3 (s), 111.9 (d), 105.5 (d), 61.4 (q), 56.2 (q), 55.8 (q), 55.3 (t).

Found: M^+, 198.0889. $C_{10}H_{14}O_4$ requires *M*, 198.0892.

2,5,6- Trimethoxybenzyl bromide



(**134**) (**133**)

To a 2-necked round bottomed flask, fitted with a magnetic stirring bar and an N_2 balloon, was added a solution of *alcohol* (**134**) (840 mg, 4.24 mmol) in anhydrous ether (8 mL). To this solution held at O °C was added a solution of PBr_3 (0.20 mL) in anhydrous ether (3 mL) dropwise over 5 mins. Stirring was continued at 0 °C for a further 15 mins before quenching with methanol (1 mL). After the addition of water (3 mL) the organic layer was separated and the aqueous layer extracted with ether (3 x 3 mL). The combined organic layers were then washed with brine (3 mL) before being dried and concentrated *in vacuo*. The crude product was purified by recrystalisation (hexane-EtOAc) to give the *title compound* as a white solid (920 mg, 3.52 mmol, 83 %), m.p. 31-32 °C.

$\upsilon_{max}(CHCl_3)$ 1482, 1238 and 1046 cm^{-1}.

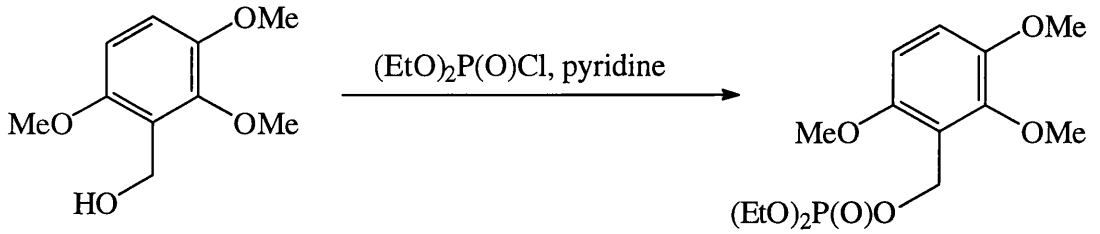
δ_H(200 MHz) 6.83 (1H, d, *J* 9.0, ArH), 6.55 (1H, d, *J* 9.0, ArH), 4.66 (2H, s, -CH_2Br), 3.99 (3H, s, OMe), 3.83 (3H, s, OMe), 3.80 (3H, s, OMe).

δ_C(50 MHz) 152.0 (s), 148.3 (s), 146.9 (s), 120.9 (s), 113.2 (d), 105.7 (d), 60.9 (q), 56.3 (q), 56.1 (q), 23.1 (t).

Found: M^+, 262.0040. $C_{10}H_{13}O_3{}^{81}Br$ requires *M*, 262.0028.

M^+, 260.0036. $C_{10}H_{13}O_3{}^{79}Br$ requires *M*, 260.0048.

Diethoxy-2,3,6-trimethoxybenzyl phosphite



(**134**) (**135**)

A 10 mL flask, fitted with a magnetic stirring bar and N_2 balloon, was charged with *benzylic alcohol* (**134**) (500 mg, 3.33 mmol), chlorodiethylphosphate (604 mg, 3.50 mmol) and dry pyridine (538 µl, 6.67 mmol). The resulting solution was then stirred, at 0 °C, for 3 hrs before the addition of 0.5M HCl (0.5 mL) and ether (10 mL). The organic layer was then separated and washed with aqueous $CuSO_4$ (3 x 5mL), dried and concentrated *in vacuo* to give *benzylic phosphate* (**135**) as a clear oil (1.05g, 3.14 mmol, 94 %).

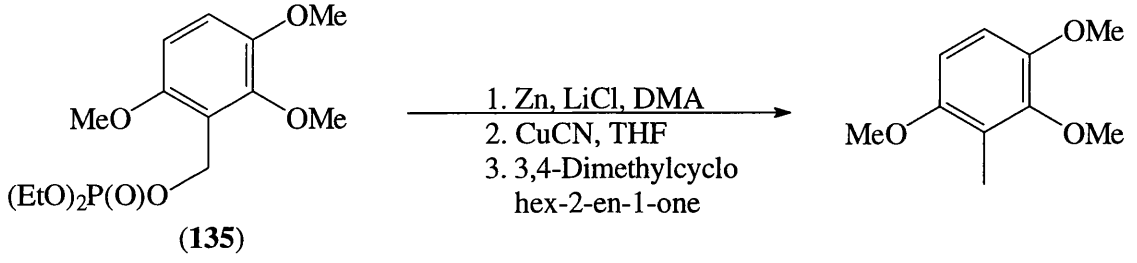
υ_{max}(neat) 2983, 2941, 2909, 1492, 1466, 1261, 1111, 1028 cm^{-1}.

δ_H(200 MHz) 6.78 (1H, d, *J* 9.0, ArH), 6.49 (1H, d, *J* 9.0, ArH), 5.07 (2H, d, $J(^{31}P)$ 5.2, $ArCH_2OP$), 4.02 (4H, dt, *J* (^{31}P) 14.7 and (^{1}H) 7.2, $P(O)CH_2$), 3.79 (3H, s, OMe), 3.72 (3H, s, OMe), 3.69 (3H, s, OMe), 1.24 (6H, dt, *J* (^{31}P) 2.1 and (^{1}H) 7.2, $P(O)CH_2CH_3$).

δ_C(50 MHz) 152.6 (s), 149.6 (s), 146.7 (s), 117.4 (s), 113.6 (d), 105.5 (d), 65.0 (t), 63.4 (t), 61.4 (q), 58.6 (t), 55.8 (q), 15.8 (q).

Found: M^+, 334.1193. $C_{14}H_{23}O_7P$ requires *M*, 334.1181.

Attempted Transmetalation and Conjugate Addition of Aryl Zinc Reagent



(**135**)

To a 5 mL round bottomed flask with side arm, equipped with a rubber septum inlet, reflux condenser and N_2 balloon, was added zinc powder (294 mg, 4.5 mmol) and DMA (1.2 mL). To this stirred suspension was added 1,2-dibromoethane (30 µl) and TMSCl (15 µl) to activate the zinc. To this mixture, held at ~55 °C, was added *phosphate* (**135**) (500 mg, 1.5 mmol) and LiI (39 mg, 0.3 mmol) and the mixture stirred at this temperature for 24 hrs. After cooling to room temperature and allowing the zinc to settle the liquid was added dropwise *via* syringe to a solution of CuCN (0.12 g, 1.35 mmol) and LiCl (0.114 g, 2.7 mmol) in anhydrous THF (0.6 mL) at -40 °C. Still at -40 °C 3,4-dimethylcyclohex-2-en-1-one (130 mg, 1.05 mmol) was added. The solution was allowed to warm to 0 °C before being stirred at ~ -20 °C for 13 hrs. Saturated aqueous NH_4Cl (1 mL) and ether (1 mL) were added and the mixture filtered through a pad of Celite 531. The aqueous layer was separated and extracted with ether (3 x 5 mL) and then the combined organic layer washed with brine (5 x 5 mL) to remove the DMA. Drying and concentration *in vacuo* afforded crude organic material (0.158 mg) which

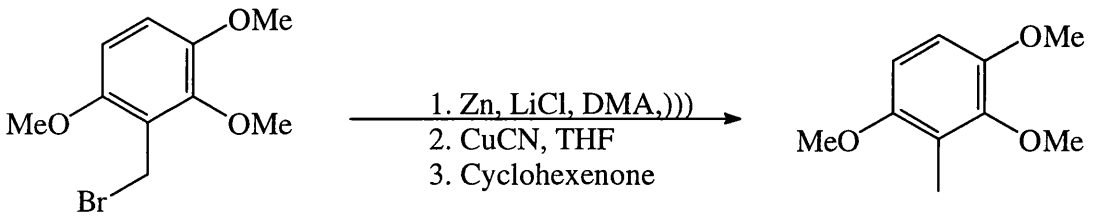
was purified by TLC (4:1 hexane-EtOAc) to give *2,3,6-trimethoxytoluene* (30 mg, 0.16 mmol), an oil (lit.[106] bp 145-147 °C/14 mm), as the only product.

δ_H(200 MHz) 6.70 (1H, d, *J* 8.9, ArH), 6.54 (1H, d, *J* 8.9, ArH), 3.82 (3H, s, OMe), 3.79 (3H, s, OMe), 3.78 (3H, s,OMe), 2.16 (3H, s, ArMe).

δ_C(50 MHz) 152.3 (s), 148.2 (s), 147.1 (s), 121.1 (s), 109.1 (d), 105.1 (d), 60.3 (q), 56.1 (q), 55.8 (q), 8.9 (q).

Found: M^+, 182.0938. $C_{10}H_{14}O_3$ requires *M*, 182.0943.

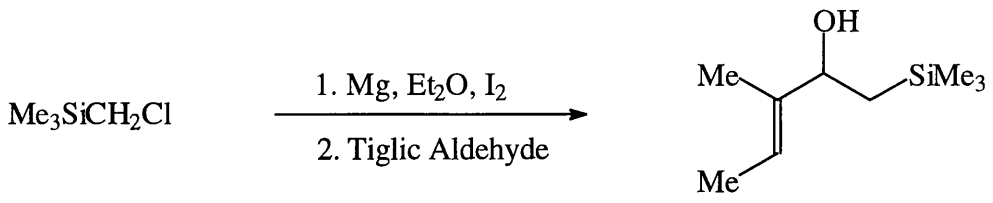
Alkyl Zinc Formation by Sonication



(**133**)

To a 5 mL round bottomed flask with side arm, equipped with a rubber septum inlet, reflux condenser and N_2 balloon, was added zinc powder (294 mg, 4.5 mmol) and DMA (1.2 mL). To this stirred suspension was added 1,2-dibromoethane (30 µl) and TMSCl (15 µl) and after a further 5 mins *bromide* (**133**) (, 1.5 mmol). The mixture was then placed in a sonic bath, held at ~ 30 °C for 20 mins. After allowing the zinc to settle the liquid was added dropwise *via* syringe to a solution of CuCN (0.12 g, 1.35 mmol) and LiCl (0.114 g, 2.7 mmol) in anhydrous THF (0.6 mL) at -40 °C. Still at -40 °C, cyclohexenone (130 mg, 1.05 mmol) was added. The solution was allowed to warm to 0 °C before being stirred at ~ -20 °C for 13 hrs. Saturated aqueous NH_4Cl (1 mL) and ether (1 mL) were added and the mixture filtered through a pad of Celite 531. The aqueous layer was separated and extracted with ether (3 x 5 mL) and then the combined organic layer washed with brine (5 x 5 mL) to remove the DMA. Drying and concentration *in vacuo* afforded crude organic material (0.158 mg) which was purified by TLC (4:1 hexane-EtOAc) to give *2,3,6-trimethoxytoluene* (30 mg, mmol) and cyclohex-2-en-1-one as the only products.

1-Trimethylsilyl-3-methyl-pent-3-en-2-ol[81]



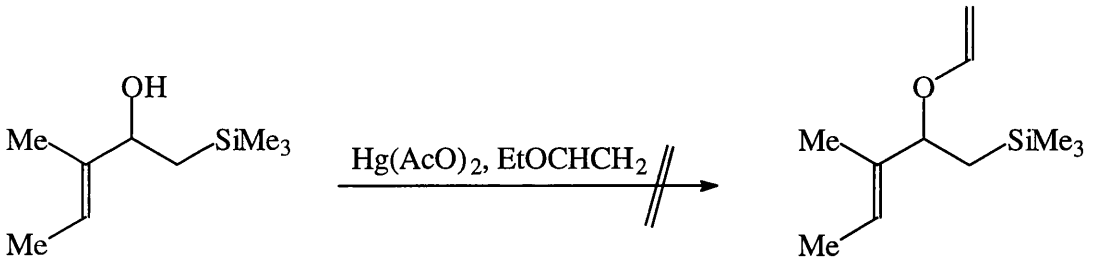
(**112**)

To a flame dried 25 mL 2-necked round bottomed flask, equipped with a reflux condenser, magnetic stirring bar and N_2 balloon, charged with fresh dry Mg turnings (110 mg, 4.78 mmol/atom) was added anhydrous ether (5 mL) and iodine (1 crystal). To this mixture was added dropwise - with gentle heating - a solution of chloromethyltrimethylsilane (500 mg, 4.44 mmol) in anhydrous ether (5 mL). After initiation had taken place the solution was heated under gentle reflux for 1hr before being cooled to 0 °C. Tiglic aldehyde (343 mg, 4.08 mmol) in ether (4 mL) was then added dropwise and the mixture stirred at 0 °C for 15 mins. Water (10 mL) was then added and the organic layer separated. The aqueous layer was then extracted with ether (3 x 10 mL) and the combined organic layers then washed with brine (10 mL). Drying and concentration *in vacuo* gave the *title compound* as a clear oil (670 mg, 3.90 mmol, 95 %).

δ_H(200 MHz) 5.50 (1H, m, C=C<u>H</u>), 4.22 (1H, t, *J* 7.6, C<u>H</u>OH), 1.60 (3H, s, C<u>Me</u>), 1.59 (3H, d, *J* 4.8, CH<u>Me</u>), 0.97 (2H, d, *J* 7.6, C<u>H</u>$_2$SiMe$_3$), 0.00 (9H, s,Si<u>Me</u>$_3$).
(3H, d, *J* 4.8, CH<u>Me</u>), 0.97 (2H, d, *J* 7.6, C<u>H</u>$_2$SiMe$_3$), 0.00 (9H, s,Si<u>Me</u>$_3$).

δ_C(50 MHz) 137.8 (s), 118.5 (d), 74.6 (d), 22.3 (t), 11.4 (q), 8.6 (q), -2.9 (q).

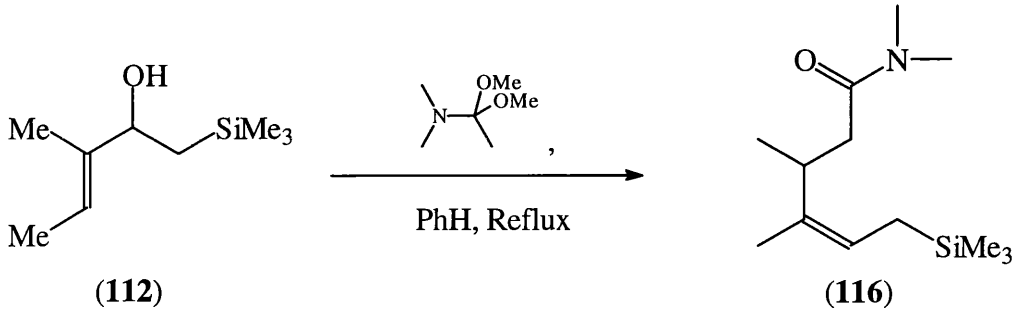
Attempted Ether Exchange with $Hg(OAc)_2$[81]



(**112**)

To 10 mL flask equipped with a magnetic stirring bar, N_2 balloon and reflux condenser was added β-*hydroxysilane* (**112**) (699 mg, 4 mmol) and ethyl vinyl ether (2.88 mL, 40 mmol). To this solution at reflux was added $Hg(OAc)_2$ (59 mg, 0.19 mmol) portion wise over 1.5 hrs. The mixture was then heated under reflux for a further 6 hrs before cooling to 0 °C and the addition of 10% aqueous Na_2CO_3 (2 mL). Stirring was continued for 1 hr before the organic layer was separated. The aqueous layer was then extracted with ether (3 x 5 mL) and the combined organic layer washed with brine (5 mL). Drying and concentration *in vacuo* gave an inseparable mixture of compounds which were not characterisable by standard methods.

N,N-Dimethyl-3,4-dimethyl-6-trimethylsilyl-hex-4-enamide



(**112**) (**116**)

To 25 mL flask fitted with a magnetic stirring bar, reflux condenser and an N_2 balloon was added β-*hydroxysilane* (**112**) (670 mg, 3.90 mmol) and dry benzene (8 mL). To this solution was added N,N-dimethylacetamide dimethylacetal (1.23 mL, 1.12g, 8.44 mmol). The flask was then flushed with N_2 and the mixture was heated under reflux for 10 hrs. After cooling, water (5 mL) was added and the organic layer separated. The aqueous layer was extracted with ether (3 x 5 mL) and the combined organic layers washed with brine (10 mL). After drying and concentration *in vacuo* the crude material was purified by chromatography on a column of silica gel (3:1 hexane-EtOAc) to give the *amide* (**116**) as a golden oil (721 mg, 2.99 mmol, 77 %).

υ_{max}(neat) 2954, 1648, 1653, 1457 and 1246 cm^{-1}.

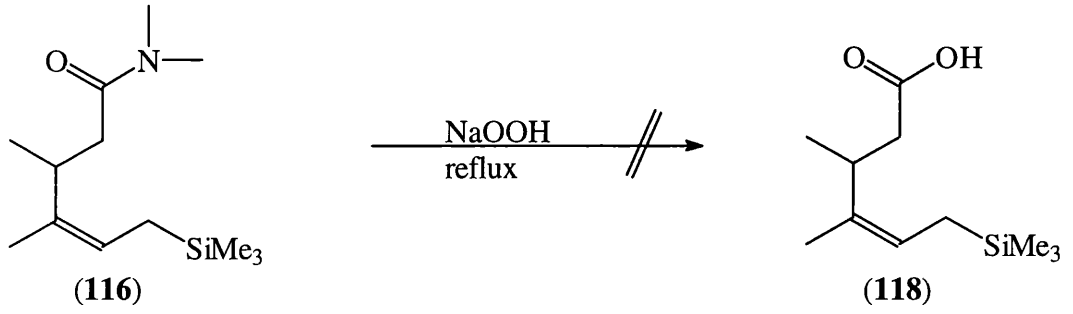
δ_H(200 MHz) 5.23 (1H, br t, *J* 8.5, C=C<u>H</u>), 3.00 (3H, s, N<u>Me</u>), 2.92 (3H, s, N<u>Me</u>), 2.66 (1H, m, C<u>H</u>), 2.42 (1H, dd, *J* 5.9 and 14.5), 2.22 (1H, dd, *J* 8.0 and

14.5), 1.53 (3H, d, *J* 1.1), 1.37 (2H, d, *J* 8.6), 1.03 (3H, d, *J* 6.8), 0.00 (9H, s, Si$\underline{Me}_3$).

δ_C(50 MHz) 172.4 (s), 135.7 (s), 119.6 (d), 39.4 (d), 39.2 (t), 37.4 (q), 35.3 (q), 35.3 (q), 19.5 (q), 18.3 (t), 13.1 (q), -1.9 (q).

Found: M^+, 241.1866. $C_{13}H_{27}NOSi$ requires *M*, 241.1862.

Attempted Hydrolysis of Amide (116)



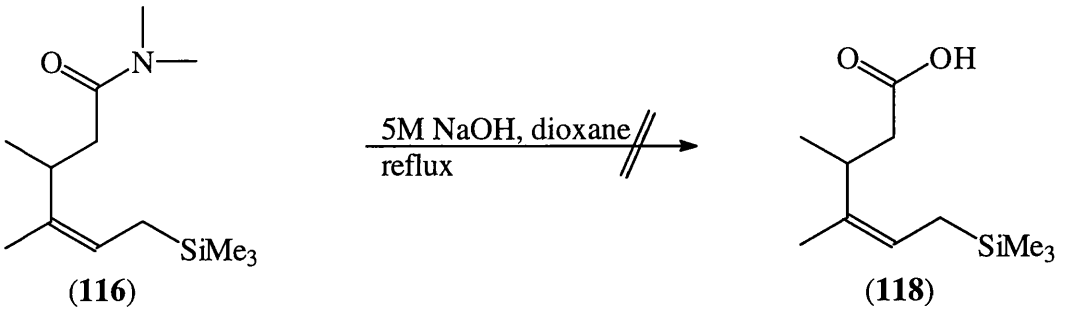
(**116**) (**118**)

A 10 mL round bottomed flask with side arm, equipped with a magnetic stirring bar, rubber septum inlet, N_2 balloon and reflux condenser, was charged with *amide* (**116**) (100 mg, 0.47 mmol), NaOH (53 mg, 1.33mmol), THF (1.66 mL) and distilled water (1.25 mL). To this stirred solution was added 30% H_2O_2 (0.17 mL) and the solution heated under reflux for 12 hrs. After cooling, Na_2SO_3 (0.2 g, mmol) in distilled water (1 mL) was added and the mixture acidified to pH 1 using 5M HCl. The mixture was then extracted with EtOAc (3 x 5 mL) and the combined organic layer washed with brine (5 mL), dried and concentrated *in vacuo* to give starting *amide* (50.7 mg, 0.27 mmol).

The reaction repeated using LiOOH in place of NaOOH also gave no hydrolysis product.

Spectroscopic data were identical in all respects to that of starting material.

Attempted Hydrolysis of Amide (116)

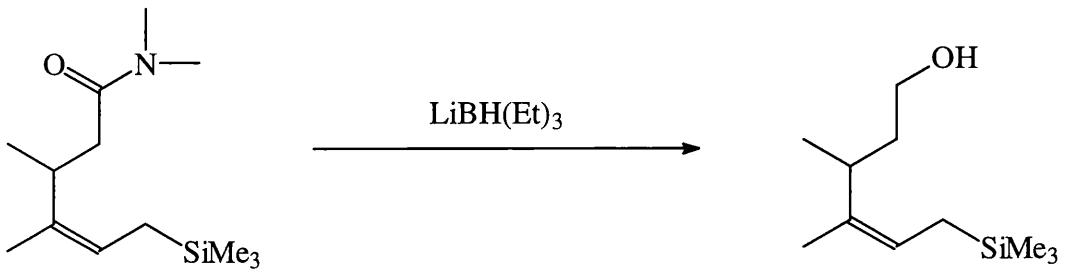


(**116**) (**118**)

A 25 mL round bottomed flask, equipped with a magnetic stirring bar and reflux condenser, was charged with *amide* (**116**) (200 mg, 0.93 mmol), 2.5 M aqueous NaOH solution (7 mL), dioxane (5 mL) and tetrabutylammonium bromide (30 mg). The solution was then heated under reflux for 24 hrs. After cooling the mixture was acidified to pH 1 using 5M HCl. The mixture was then extracted with EtOAc (3 x 5 mL) and the combined organic layer washed with brine (5 x 5 mL), dried and concentrated *in vacuo* to give starting *amide* (180 mg, 0.84 mmol).

Spectroscopic data were identical in all respects to that of starting material.

3,4-Dimethyl-6-trimethylsilylhex-4-en-1-ol[61]



(**116**) (**122**)

To a 25 mL, round bottomed, flask equipped with side arm and fitted with a N_2 balloon and a rubber septum inlet was added a solution of *amide* (**116**) (500 mg, 2.07 mmol) in anyhdrous THF (20 mL). To this solution held at 0 °C was added dropwise a 1M solution of lithium triethylborohydride in ether (6.24 mL, 6.24 mmol) over 20 mins. This solution was stirred at room temperature for 4 hrs before being quenched by the addition of water (5 mL) and ether (20 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 10 mL). The combined organic layer was then washed with brine (10 mL) and dried. Purification by chromatography on a column of silica gel (4:1 hexane-EtOAc) gave the *title compound* (372 mg, 1.86 mmol, 90 %) as a clear oil.

υ_{max}(neat) 3358, 2956, 1655, 1247 and 855 cm^{-1}.

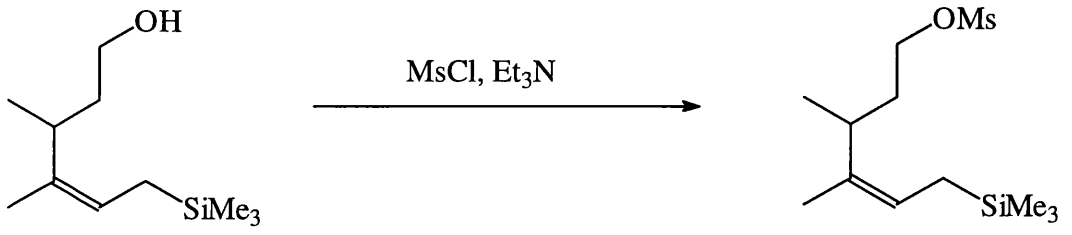
δ_H(200 MHz) 5.28-5.24 (1H, m, -C=C<u>H</u>), 3.72-3.53 (2H, m, -C<u>H</u>$_2$OH), 2.32-2.17 (1H, m, -C<u>H</u>Me), 1.68-1.51 (2H, m, -C<u>H</u>$_2$CH$_2$OH), 1.46 (3H, br s, C=C<u>Me</u>),

1.37 (3H, br d, *J* 8.4, CH<u>Me</u>), 0.98 (2H, d, *J* 6.9, -C<u>H</u>$_2$SiMe$_3$), 0.04 (9H, s, Si<u>Me</u>$_3$).

δ_C(50 MHz) 136.5 (s), 120.5 (d), 61.8 (t), 39.9 (d), 37.3 (d), 19.9 (q), 11.5 (q) and -2.1 (q).

Found: M^+, 200.1603. $C_{11}H_{24}OSi$ requires *M*, 200.1596.

1-Mesyloxy- -3,4-dimethyl-6-trimethylsilylhex-4-ene[61]



(**122**)

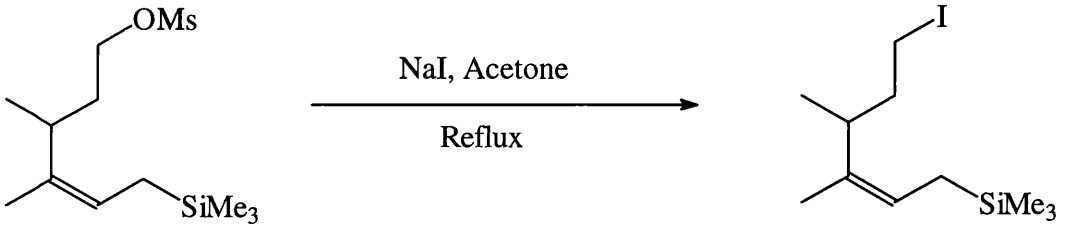
A 25 mL round bottomed flask with side arm was equipped with a rubber septum inlet, magnetic stirring bar and a N_2 balloon. The flask was charged with *alcohol* (**122**) (225 mg, 1.13 mmol), dry Et_3N (0.3 mL) and anhydrous dichloromethane (5 mL) before being cooled to 0 °C. Following this methanesulfonyl chloride (200 µl, 300 mg, 2.62 mmol) in anhydrous dichloromethane (3 mL) was added dropwise over 10 mins. Stirring was continued at this temperature for 1 hr before the mixture was poured onto iced water (10 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layer washed with 1M HCl (2 x 3 mL) and saturated brine (3 mL). The solution was then dried and carefully concentrated *in vacuo*. Chromatography on a column of silica gel (5:1 hex-EtOAc) gave the unstable *mesylate* as a clear oil (201 mg, 0.72 mmol, 65%).

δ_H(200 MHz) 5.27 (1H, br t, *J* 8.5, C=C<u>H</u>), 4.24-4.05 (2H, m, C<u>H</u>$_2$OMs), 2.99 (3H, s, OSO$_2$<u>Me</u>), 2.36-2.22 (1H, m, CH=CC<u>H</u>), 1.86-1.70 (2H, m, C<u>H</u>$_2$COMs), 1.48 (3H, s, CH=C<u>Me</u>), 1.41 (2H, d, *J* 8.6, C<u>H</u>$_2$Si), 1.03 (3H, d, *J* 6.9, CH=CC<u>Me</u>), 0.00 (9H, s, Si<u>Me</u>$_3$).

δ_C(50 MHz) 134.2 (s), 121.4 (d), 69.1 (t), 39.3 (d), 37.2 (q), 33.7 (t), 20.0 (q), 18.4 (t), 11.9 (q), -1.7 (q).

Found: M^+, 278.1380. $C_{12}H_{26}O_3SiS$ requires *M*, 278.1372.

1-Iodo-3,4-dimethyl-6-trimethylsilylhex-4-ene[61]



(**110**)

A 5 mL round bottomed flask equipped with a reflux condener and N_2 balloon was charged with *mesylate* (150 mg, 0.54 mmol), NaI (150 mg, 1 mmol) and dry acetone (1.5 mL). The mixture was then heated under reflux for 9 hrs then allowed to cool to room temperature. After removal of the solids by filtration the acetone was removed *in vacuo* and ether (5 mL) added. The ether was then washed with dilute aqueous sodium thiosulfate (2 x 2 mL), water (2 mL) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave the *iodide* (**110**) as a clear spectroscopically pure oil (144 mg, 0.46 mmol, 84 %).

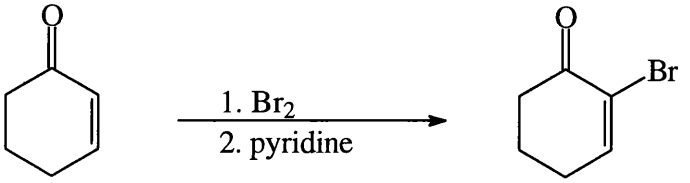
δ_H(200 MHz) 5.30 (1H, br t, *J* 7.9, C=C<u>H</u>), 3.22-3.11 (1H, m, CH<u>H</u>I), 3.06-2.94 (1H, m, C<u>H</u>HI), 2.34-2.23 (1H, m, CH=CC<u>H</u>), 1.88-1.73 (2H, m,

$C\underline{H}_2CH_2I$), 1.50 (3H, s, CH=C$\underline{Me}$), 1.01 (3H, d, *J* 6.9, CH=CC$\underline{Me}$), 0.86 (2H, d, *J* 3.3, $C\underline{H}_2Si$), 0.00 (9H, s, $Si\underline{Me}_3$).

δ_C(50 MHz) 133.9 (s), 121.6 (d), 43.6 (d), 38.3 (t), 19.5 (q), 18.5 (t), 11.5 (q), 6.0 (t), -1.7 (q).

Found: M^+, 310.0597. $C_{11}H_{23}SiI$ requires *M*, 310.0613.

2-Bromo-2-cyclohexen-1-one[82]



(**109**)

To a 25 mL, 2-necked, round bottomed flask equipped with a magnetic stirring bar, rubber septum inlet and N_2 balloon was added *cyclohex-2-en-1-one* (1 g, 10.4 mmol) and dry CCl_4 (10 mL). To this solution, held at 0 °C, was added, dropwise, bromine (0.59 mL, 1.83 g, 11.4 mmol) with stirring, over 5 mins. The mixture was stirred at this temperature for a further 10 mins before the dropwise addition of anhydrous pyridine (4 mL). The mixture was then warmed to room temerature and stirred for a further 2 hrs. After this the pyridine hydrobromide was filtered off and the cake was washed with CCl_4 (5 x 5 mL) . The filtrate was then washed with aqueous $CuSO_4$ (3 x 5mL) and the organic layer dried and concentrated *in vacuo*. The crude material was recrystallised from hex:ether at -20 °C to give the *title compound* as a white solid (1.34 g, 7.66 mmol, 74%), m.p. 74-76 °C (lit.[107] 75-76 °C).

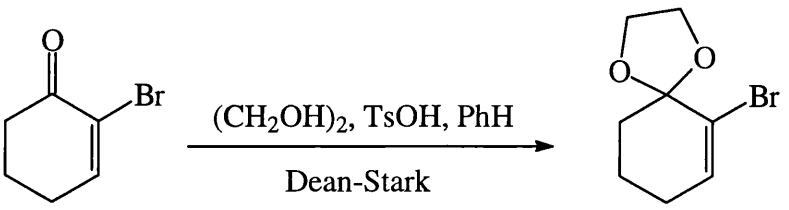
δ_H(200 MHz) 7.45 (1H, t, *J* 4.4), 2.67-2.60 (2H, m), 2.52-2.44 (2H, m), 2.15-2.02 (2H, m).

δ_C(50 MHz) 191.2 (s), 151.5 (d), 123.6 (s), 38.3 (t), 28.3 (t), 22.6 (t).

Found: M^+, 175.9666. $C_6H_7O^{81}Br$ requires *M*, 175.9660.

M^+, 173.9671. $C_6H_7O^{79}Br$ requires *M*, 173.9680.

1-Spirodioxyethane-2-bromohex-2-ene[82]



(**109**) (**111**)

A Dean and Stark water separator was charged with *bromide* (**109**) (1.34g, 7.66 mmol), ethylene glycol (0.52g, 8.42 mmol), benzene (10 mL) and TsOH (15 mg). The resultant emulsion was heated under reflux for 10 hrs before being allowed to cool. Water (5 mL) was added and the organic layer separated. The aqueous layer was then extracted with hexane (3 x 5 mL) and the organic layers combined and washed with water (5 x 5 mL). After drying and concentration *in vacuo* the crude material was purified by chromatography on a column of silica gel (6:1-3:1 hexane-ether), to give the *title compound* as a soft white solid (1.05g, 4.79 mmol, 63 %), m.p. 45-47 °C (lit.[108] bp 60 °C/ 5mm).

υ_{max}(neat) 2950, 1438, 1317, 1257, 1176 cm^{-1}.

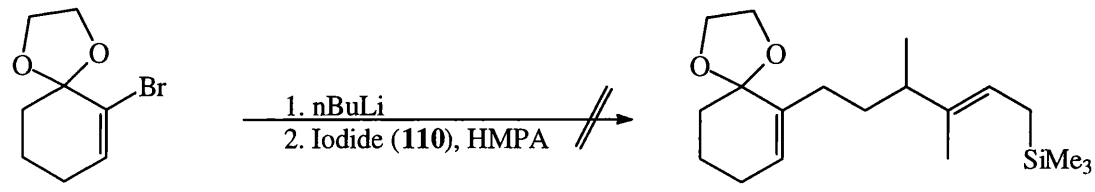
δ_H(200 MHz) 6.24 (1H, t, *J* 4.6, C=C<u>H</u>), 4.19-3.88 (4H, m, C(OC<u>H</u>$_2$)$_2$), 2.40-1.75 (6H, m).

δ_C(50 MHz) 134.1 (d), 122.8 (s), 103.8 (s), 63.9 (t), 33.7 (t), 25.6 (t), 18.5 (t).

Found: M^+, 219.9925. $C_8H_{11}O_2{}^{81}Br$ requires *M*, 219.9923.

M^+, 217.9933. $C_8H_{11}O_2{}^{79}Br$ requires *M*, 217.9943.

Attempted Coupling of Iodide (110) and Bromide (111)

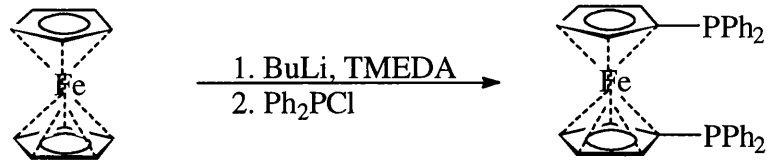


(**111**)

To a 10 mL round bottomed flask with side arm, equipped with a rubber septum inlet and magnetic stirring bar, was added *bromide* (**111**) (88 mg, 0.4 mmol) in anhydrous THF (4 mL). To this stirred solution, held at -78 °C, was added dropwise a 1.33M solution of n-butyllithium in hexanes (0.75 mL, 0.4 mmol). The reaction mixture was then stirred at this temperature for a further 30 mins before the dropwise addition of *iodide* (**110**) (100 mg, 0.32 mmol) in dry HMPA (2 mL), over 10 mins. The reaction mixture was then allowed to warm to room temperature and stirred for 6 hrs after which saturated aqueous NH_4Cl (2 mL) was added. The mixture was then extracted with hexane (10 x 2 mL) and the combined organic layer then washed with water (10 x 2 mL). After drying over anhydrous Na_2SO_4 and concentration *in vacuo* the crude material was purified by TLC to return *iodide* (**111**) (11 mg) as the only characterizable compound.

Spectroscopic data identical in all respects to that of starting material.

Ferrocene-1,1'-bis(diphenylphosphine)[99]



(130)

To a 250mL 3-necked round bottomed flask fitted with a reflux condenser, magnetic stirring bar, rubber septum inlet and a N_2 balloon, charged with ferrocene (2g, 10.8 mmol) and dry hexane (64 mL), was added TMEDA (2.6g 3.38 mmol). To this stirred solution was added, dropwise, a 1.4 M solution of n-butyllithium in hexanes (15.7 mL, 22 mmol). The solution was stirred for 4.5 hrs at room temperature and then a solution of chlorodiphenylphosphine (4.1 mL, 5g, 22.8 mmol) in hexane (4.3 mL) was added dropwise over 20 mins. The reaction was then stirred for a further 2 hrs before being quenched by the addition of water (4.3 mL). The supernatant hexane layer was decanted from the brownish-orange soild and the solid was then washed with water (3 x 11 mL). The solid was then dissolved in dioxane (22 mL). Cooling of this dioxane solution gave the *title compound* as orange crystals (2.32 g, 4.19 mmol, 39 %), m.p. 183-184 °C (lit.[109] 181-183 °C). Concentration of the mother liquor gave a second crop of slightly less pure product (0.72 g, 1.30 mmol, 12 %).

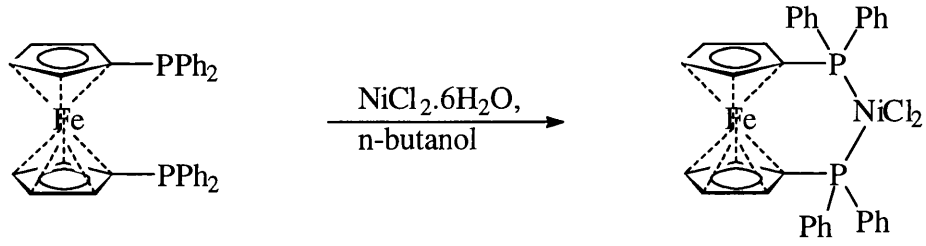
υ_{max}(nujol) 1462, 1377, 722 and 442 cm^{-1}.

δ_H(200 MHz) 7.29 (20H, m), 4.31 (4H, t, *J* 1.6, Cp), 4.06 (4H, ABq, *J* 1.8 and 3.6, Cp).

δ_C(50 MHz) 138.8 (s), 133.6 (d), 133.2 (d), 128.5 (d), 128.2 (d), 128.0 (d), 76.5 (s), 73.9 (d), 73.6 (d), 72.5 (d), 72.4 (d).

L.R.M.S. 554 (M^+, 100%), 477 (28), 369 (16), 292 (13), 171 (42).

Ferrocene-1,1'-bis(diphenylphosphino) nickel (II) chloride[99]



(**130**) (**131**)

To a solution of *ferrocene-1,1'-bis(diphenylphosphine)* (1g, 1.8 mmol) in hot 1-butanol (69 mL) was added a solution of hydrated nickel (II) chloride (0.43g, 1.8 mmol) in hot 1-butanol (26 mL). On cooling of this solution the *title compound* crystallised and was collected by filtration. The solid was then washed with 1-butanol (2 x 5 mL), pentane (3 x 5 mL) and then air dried to give the *title compound* as analytically pure green crystals (576mg, 0.84 mmol, 47 %) m.p. 278 °C (dec.), (lit.[110] 283-284 °C).

Found: C 59.65, H 4.07, Cl 10.42, P 9.11. $C_{34}H_{28}FeP_2NiCl_2$ requires C 59.69, H 4.09, Cl 10.39, P 9.07.

υ_{max}(nujol) 1462, 1377 and 459 cm^{-1}.

L.R.M.S. 554 (M^+, 100%), 477 (34), 369 (17), 292 (14), 226 (15), 171 (42).

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