Applications of Organometallic Reagents in an Approach to Taxanes starting from Glucose

Thesis submitted for the degree of
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at the University of Leicester

By

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Statement

The accompanying thesis submitted for the degree of Ph.D. entitled "Applications of Organometallic Reagents in an Approach to Taxanes starting from Glucose" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period October 1992 and September 1995.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed: S. J. Hulme Date: 4-2-98

Part of this work has been published as a communication.
The Stereoselective Alkylation of Cyclohexane-1,2-dicarboxylic acid mono-(-)-menthyl ester.
S. J. Hulme, P. R. Jenkins, J. Fawcett and D. R. Russell, *Tetrahedron Lett.*, 1994, **35**, 5501.

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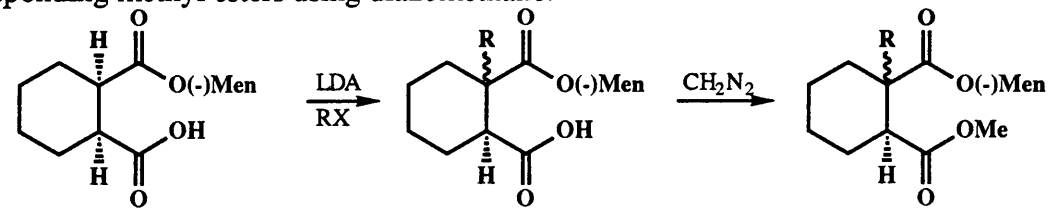
Lastly I thank Richard for all his love and for keeping me sane during the writing of this thesis.

Abstract

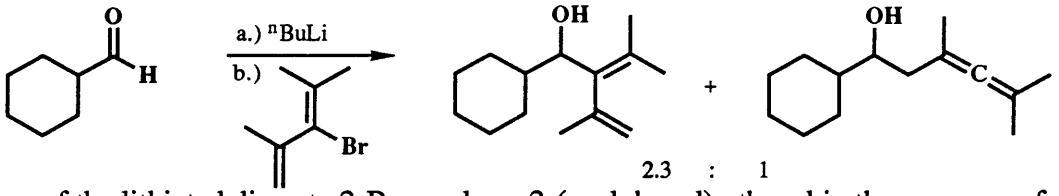
This work continues previous studies carried out by the Jenkins group to produce taxanes from glucose and is split into two projects. The first investigates alkylation of Cyclohexane-1,2-dicarboxylic acid mono(-)menthyl ester by deprotonation with LDA and treatment with a range of alkyl bromides and an iodide. The resulting crude products were converted to the corresponding methyl esters using diazomethane.



(1R, 2S) & (1S, 2S) (1R, 2S) & (1S, 2S)

In all cases both diastereoisomers were seen, but the stereoselectivity ranged from 7:1 to 32:1 depending upon the alkyl halide used. When the acid ester was treated with LDA followed by BnBr the major isomer isolated, after conversion to the methyl ester, was confirmed as the 1(R), 2(S) diastereoisomer by X-ray crystallography. The results of these stereoselctivity studies were compared to the ratios of alkylation products from treatment of cyclopentane-1,2-dicarboxylic acid mono (+) menthyl ester with various alkyl halides as described in the literature. The aim of this project was to provide a C-ring with a methyl group at C-1 of the correct stereostructure for incorporation into a taxane skeleton, this could be achieved via a radical pathway based on a C -> ABC strategy.

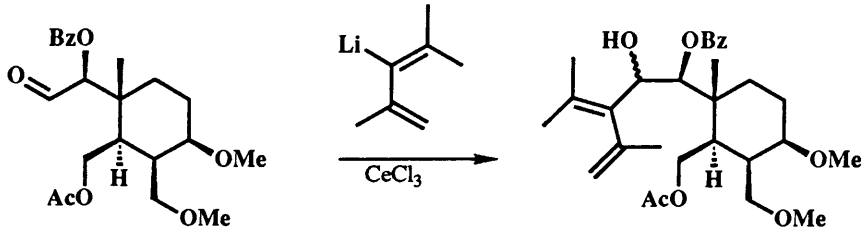
The second project investigated the addition of 3-Bromo-2,4-dimethylpenta-1,3-diene to aldehydes. The diene was first treated with ^{n}BuLi to give a lithium-halogen exchange. Reaction with cyclohexane carboxaldehyde gave a mixture of the diene alcohol and allene alcohol in the ratio of 2.3:1. Addition of the lithiated diene to a suspension of $CeCl_3$ before introduction to the aldehyde improved the ratio to >100:1. Other lanthanide (III) chlorides were also studied.



2.3 : 1

Reaction of the lithiated diene to 2-Benzoyloxy-2-(cyclohexyl)-ethanal in the presence of various lanthanide chlorides gave a mixture of both enantiomers of two diastereoisomers. The ratio of these diastereoisomers was dependent upon the nature of the lanthanide. $CeCl_3$ was found to give the highest ratio.

Using the knowledge gained from these model studies, it was attempted to add the lithiated diene in the presence of $CeCl_3$ to the aldehyde group of a highly functionalised C-ring synthesised from glucose. Successful addition was not achieved, the reasons considered for this failure were local and distant steric hindrance. Alternative protecting groups to the bulky ^{t}butyldiphenylsilyl groups were sought and regression several steps back along the route allowed the introduction of small methyl protecting groups. The protected diol was advanced to a functionalised C-ring. Treatment with the lithiated diene in a suspension of $CeCl_3$ allowed successful addition of the diene to the aldehyde. This product provided 4 of the 6 A-ring carbons and completed the top half of the B-ring.



Contents

Abbreviations

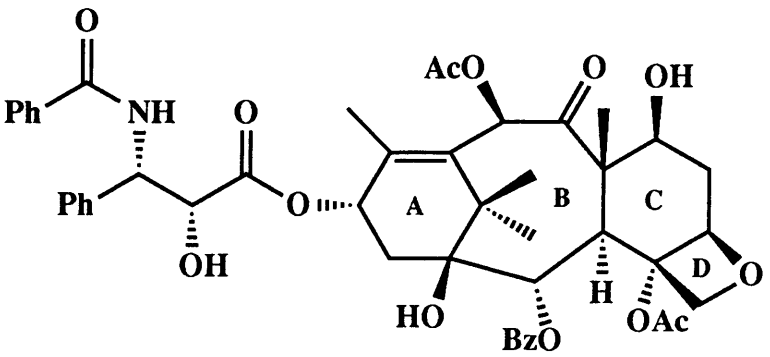
TMS	Trimethylsilyl
TES	Triethylsilyl
Bu^tPh_2Si	*tert*-Butyldiphenylsilyl
Bz	Benzoyl
THF	Tetrahydrofuran
AIBN	Azoisobutylnitrile
DMAP	4-Dimethylaminopyridine
^nBuLi	n-Butyl lithium
DMF	Dimethylformamide
DMS	Dimethyl sulphide
LDA	Lithium diisopropylamide
NBS	*N*-Bromosuccinimide
TPAP	Tetra-*n*-propylammonium perruthenate
NMO	*N*-methylmorpholine *N*-oxide
CSA	Camphor sulfonic acid
DCC	Dicyclohexylcarbodiimide
DMSO	Dimethyl sulfoxide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide

Introduction

The yew tree is a member of the order *Taxales*, family *Taxacae* and genus *Taxus*. The species of Taxus is dependent upon the habitat in which it grows, some examples are the European Yew (*Taxus baccata*), the Pacific Yew (*Taxus brevifolia*) and the Himalayan Yew (*Taxus wallichiana*).

For hundreds of years the yew has been praised for its supple, strong wood making it suitable for carving[1]. In the Middle Ages, bows and arrows were considered to be the finest if made from the wood of a Yew and a good marksman was referred to as a 'yew-man' or what is now known as a 'yeoman'. The leaves and bark contain a group of compounds called taxanes which are highly toxic and it is this set of natural products which ironically, have been discovered to possess antileukemic and antitumour properties.

The most effective anticancer agent is called Taxol™ or paclitaxel (1), this is found mainly in the bark of the pacific yew tree *Taxus brevifolia*.



(1)

In the late sixties, over 30,000 plants were tested for anti-cancer properties in a United States National Cancer Institute screening program. Two of the chemists performing these tests, Wani and Wall[2, 3] reported in 1971, "Taxol has potent antileukemic and tumour inhibitory properties and is the first compound possessing the taxane ring which has been demonstrated to have such activity." They also elucidated its

structure[2] on the basis of proton NMR and X-ray analysis following a mild base-catalysed methanolysis. Taxol™ (1) was found to be a diterpene consisting of four rings A, B, C and D, with a beta amino acid side chain. In 1979 studies by S.B Horwitz et al[4] revealed Taxol affected the microtubules of a cell and that its mode of action was unlike previously encountered anticancer agents.

Tubulin and the Formation of Microtubules.

Microtubules are used within a cell to make up its cytoskeleton and are found in the organs of movement in unicellular organisms. They are constituted from heterodimers containing 1α and 1β tubulin subunit which are proteins containing approximately 440 amino acids each. Microtubule formation[5] is initiated by the joining together of heterodimers in a head to tail fashion, this will only occur in the presence of magnesium ions, microtubule associated proteins (MAPs) and guanosine 5' triphosphate (GTP). The resulting protofilament will grow perpendicular to the axis until the structure curls round and joins its edges to give a cylindrical structure[6]. Each microtubule contains 13 protofilaments arranged in a left-handed helix with a diameter of 24nm. The grooves between the protofilaments on the outer layer are quite pronounced and are often covered with MAPs. After a certain length of time, an equilibrium between the free tubulin and microtubules exists termed the critical concentration[7]. For free tubulin this is around 1mg ml^{-1}, when the concentration is below this figure, spontaneous assembly will cease to occur. The microtubule is said to have a polarity as tubulin is constantly being lost from one end by depolymerisation and gained at the other by polymerisation often at different rates. The growing end is dubbed the 'plus' pole[8].

The Cell Cycle.

Microtubules play a crucial role during cell division by constituting the mitotic spindle. Cells are largely in a non-proliferative state known as G_0, however, if more cells are required, the low population density rapidly induces them to enter into the cell cycle in a state called G_1. This initiates the S phase where the DNA, histones and microtubule organising centres (MTOCs) are all replicated. The cells further prepare for mitosis by entering G_2 where extra tubulin is produced. Mitotic division consists of four phases, the first of these being prophase. Here two identical sister chromatids condense to form a chromosome, the cytoskeleton is simultaneously broken down into a pool of tubulin from which the mitotic spindle is constructed. The cell then enters metaphase where the chromosomes align at the equator of the spindle. During anaphase, the sister chromatids separate and move towards opposite ends of the spindle, this is aided by other microtubules which push the poles apart. Finally, in telophase, the chromatids arrive at the poles and the nuclear envelope reforms around them to give the original chromatids in the parent cell and the copied message in the daughter cell. Each cell synthesises new proteins and grows before entering into G_0 state. Normal cells do not enter proliferation when their population density is high, however, cancerous cells continue to replicate during conditions that normally induce a G_0 state, as they lack the required control mechanisms. The cell cycle for normal cells is shown in Figure 1.

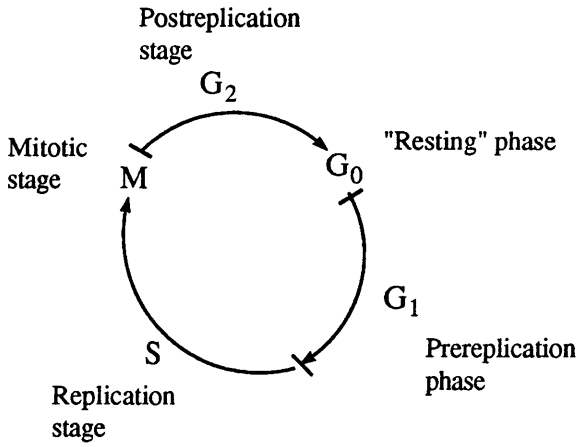
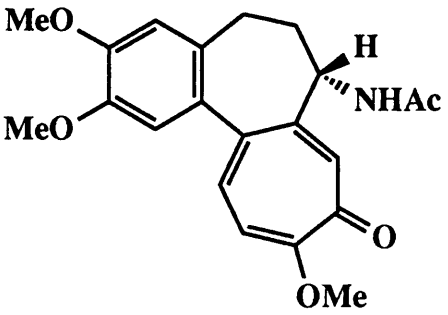


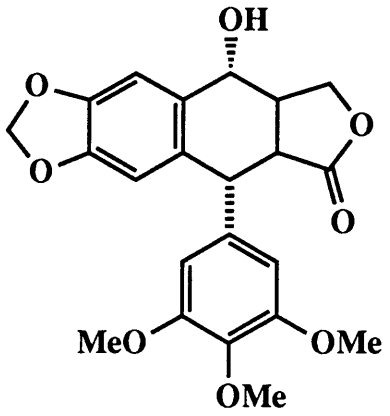
Figure 1. A cell cycle

Action of Taxol on Microtubules and Cell Division.

Most other cytotoxic anti cancer drugs effect cell division by binding to a site within the tubulin dimer that inhibits polymerisation to protofilaments, they also depolymerise microtubules and are thus known as microtubule poisons. This inhibition prevents the formation of the mitotic spindle and therefore halts cell division. Colchicine (2), podophyllotoxin (3) and nocodazole (4) are all microtubule destabilising reagents which bind to a site in the β subunit, the vinca alkaloids have a similar mode of action, but bind to a different site.



(2)



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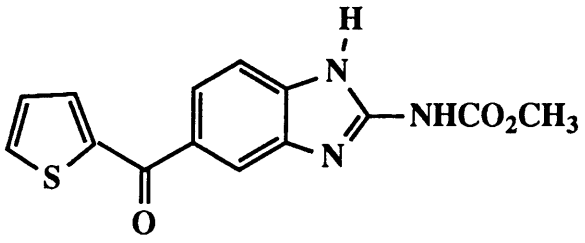


(4)

In 1979, S.B Horwitz[4] showed that Taxol™ affects the tubulin-microtubule equilibrium in a unique manner, treatment with the drug stabilises microtubules. Taxol™ decreases the induction time and critical concentration of tubulin required for polymerisation to take place and even allows microtubules to form in the absence of GTP, MAPs and magnesium ions[9]. Those formed on addition of Taxol™ have a shorter length and narrower diameter, 22nm and contain only 12 protofilaments. Horwitz carried out experiments of purified calf brain tubulin. Standard solutions in the presence and absence of Taxol were monitored for turbidity and examined by electron microscopy.

After 30 seconds, ribbons of protofilaments could be seen in the sample containing Taxol™, whereas the control only contained rings. She also proved Taxol™ had a dose-dependent affect on the lag time for assembly and that whilst normal microtubules are broken down on exposure to cooling or calcium ions, those incorporating Taxol™ did not depolymerise. The maximum effects appeared to occur when a 1:1 Taxol™ : tubulin dimer ratio was achieved[10]. The stability of these microtubules prevent the cytoskeleton of a cell from breaking down thus arresting cell division in the G_2 phase. Horwitz performed tests on HeLa cells growing at an exponential rate and showed that low doses of Taxol™ inhibit the division of these cells without affecting the DNA and protein synthesis. These results have been translated into useful anti-cancer activity.

Phase I and phase II clinical trials of Taxol™ have shown a 60% response rate with manageable side effects in the treatment of advanced recurrent ovarian cancer. These results have led the Food and Drug Administration of the United States to licence the use of Taxol™[11] as treatment for this particular cancer, it is likely that it will soon be approved for other types of cancer.

Biological Activity

A major problem of the use of Taxol™ as a drug is its high insolubility in aqueous solutions. Investigations have been carried out into the biological activity of Taxol™ and various analogues, to determine which functional groups are essential to promote the assembly of microtubules and to render the drug cytotoxic. Reviews by Kingston[12a] and Gueritte-Voegelein[12b] have summarised the effects of the various groups as shown in Figure 2.

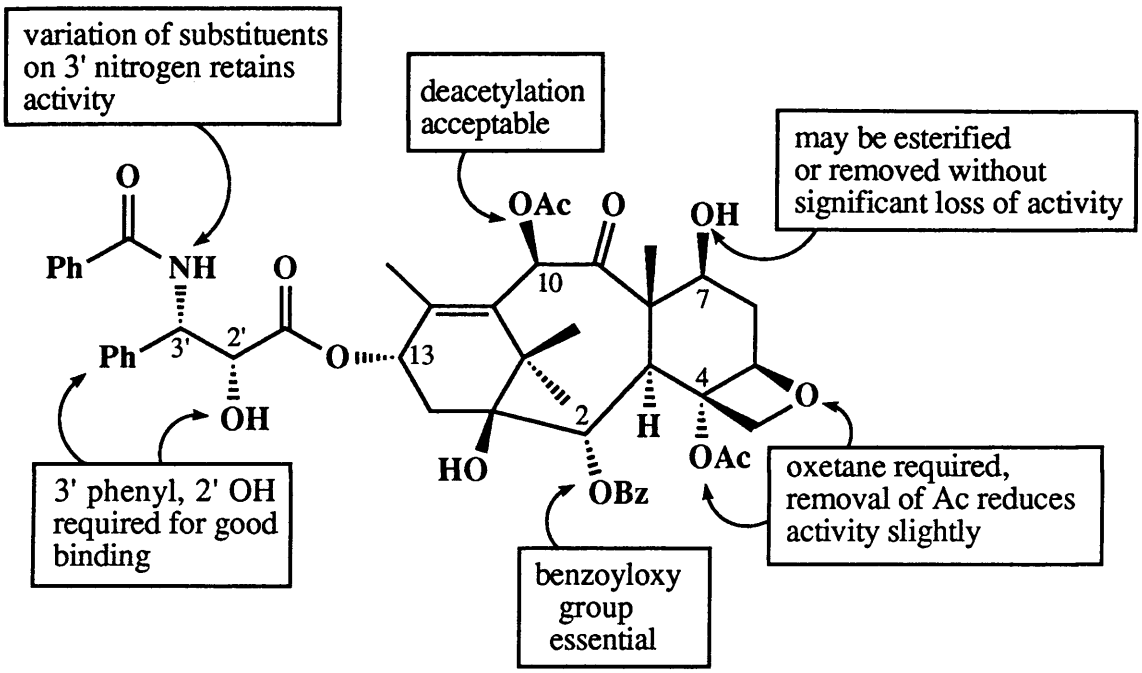
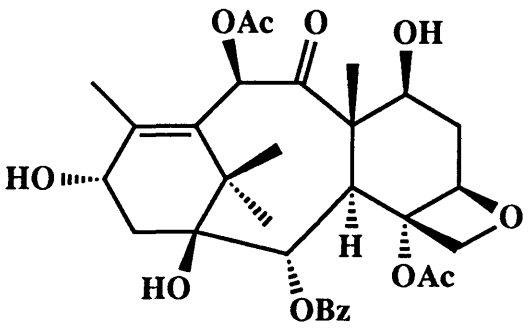
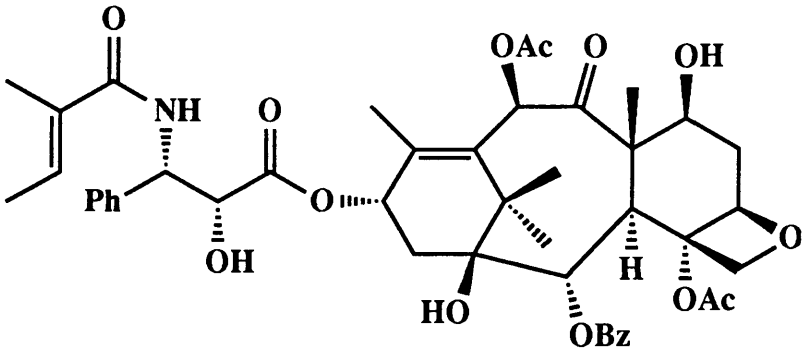


Figure 2

The need for a side chain at C-13 was demonstrated by the lack of cytotoxicity and microtubule assembly seen in Baccatin III (5). The correct length of the side chain, a hydroxyl substituent at C-2' and a phenyl group at C-3' are all essential for activity, however, variation of substituents on the nitrogen at C-3' is tolerated. An example of this is Cephalomannine (6) which has a relative cytotoxicity approaching that of Taxol™.

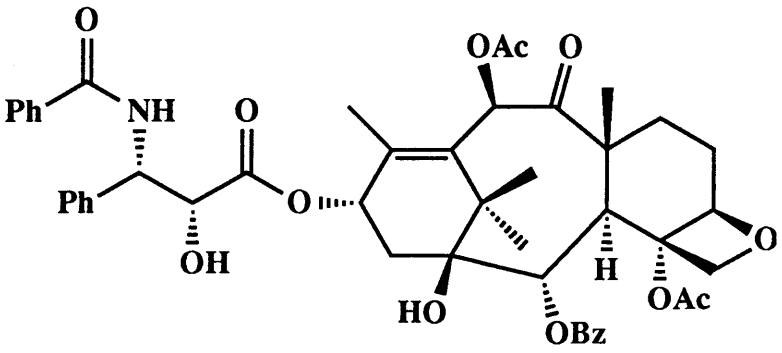


Baccatin III
(5)



Cephalomannine
(6)

Modifications across the top half of the molecule at positions 7, 8, 9 and 10 are accepted without destroying activity. Positions 7 and 10 can be used to attach polar groups to enhance solubility of the analogues. Esterification, epimerisation or deoxygenation of position 7 are allowed without significant loss of activity. Indeed, 7-desoxytaxol (7) is more active than Taxol™ in a P-388 cytotoxicity assay and comparable in a HCT116 assay. Position 10 is also not critical to tubulin binding, 10-deacetoxytaxol has been determined to have identical activity to Taxol™ in the P-388 lymphocytic leukemia cell line.



7-Desoxytaxol
(7)

Relatively minor structural changes to the bottom half of Taxol™ can have dramatic effects on the potency. Removal of the C-2 benzoyl causes a profound drop in activity and deacetylation of C-4 also causes a small reduction. These positions are required for interaction with the binding site of tubulin. 2-Debenzoyloxytaxol is much less cytotoxic than Taxol™, indicating that either benzoyl or other aryl groups are required at C-2 for activity. Various 2-aryl-2-debenzoyl analogues have been prepared, their bioactivities being dependent upon the nature of the group. Compounds containing para-substituted aromatic rings are much lower in activity, whereas those with meta-substituted rings, eg. m-chloro, m-azido, m-methoxy are sometimes more cytotoxic than Taxol™ itself. The oxetane ring is essential, Taxol™ analogues not containing the four-membered ring are inactive in both tubulin assembly and cytotoxic assays.

The C-11, C-12 double bond is required to hold the A ring conformation in a boat, this is important for interaction with microtubules to take place. A 7-protected-10-deacetylbaccatin III compound was oxidised at C-13 to give an enone, a zinc-promoted reduction in basic conditions allowed reaction with the double bond. After reduction of the C-13 ketone, the analogue was found to be much less active than 10-deacetylbaccatin III, indicating that the double bond is necessary.

These studies could prove useful in the total synthesis of analogues of Taxol™ with higher solubility for use in cancer therapy.

Whilst Taxol™ is one of the most promising antileukemic and antitumour agents, a serious problem has arisen in demand exceeding supply. Only 2g of the compound is obtained from sixty pounds of bark, which has been harvested from ten trees, this is the amount needed to treat just one patient. Once a tree has been stripped of its bark it dies and a freshly planted tree will take sixty years to reach maturity. Research teams worldwide are therefore looking for the solution by trying various approaches to obtain paclitaxel from renewable sources.

Synthetic approaches towards Taxol.

Total Synthesis.

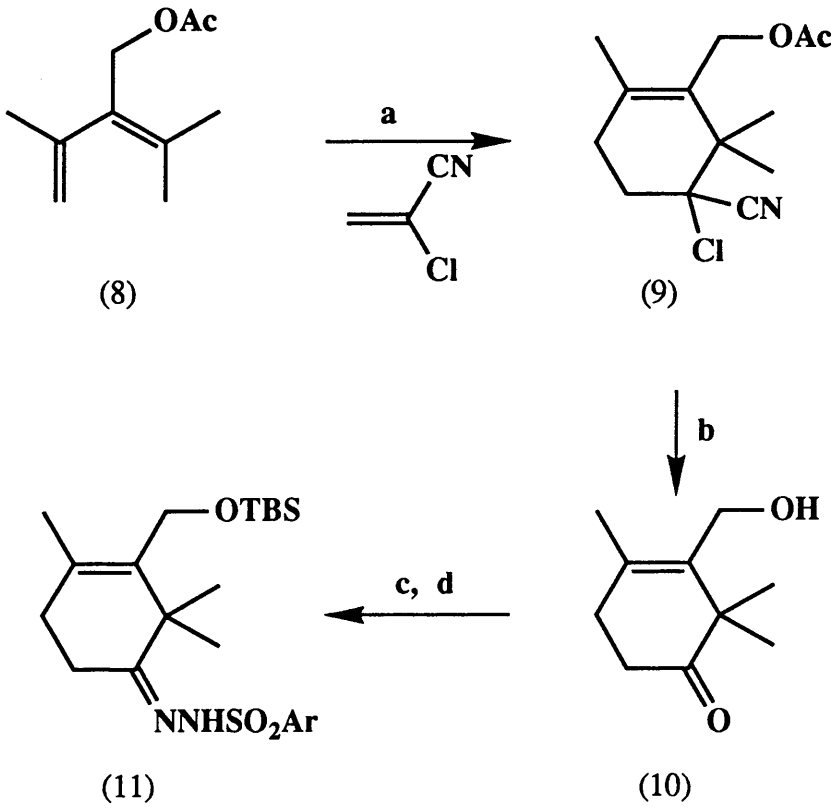
Many elegant pathways have been attempted by numerous research teams[5, 12, 13] towards the total synthesis and success has been achieved by four research teams led by Nicolaou[14b], Holton[19], Danishefsky[25b] and Wender[22b].

Nicolaou.

K.C. Nicolaou of the Scripps Institute was the first to publish the completed synthesis of Taxol™ (1) in the February 1994 edition of Nature[14a]. The approach he used was a convergent sequence in which both A and C rings were constructed separately and coupled together to complete the 8-membered B ring[14b]. Previous work indicated that the formation of the oxetane ring and attachment of the side-chain should be carried out in the final steps.

Construction of the A-ring.

A Diels-Alder cyclisation was used to furnish the achiral, cyclohexane A-ring[15a], involving a readily prepared diene (8) and 1-chloroacrylonitrile (Scheme 1). The desired regioisomer (9) was obtained and exposure to KOH in ^{t}BuOH at 70°C yielded a carbonyl group at C-1 (10). Protection of the free OH and conversion of the ketone to the corresponding hydrazone gave the required A-ring (11).

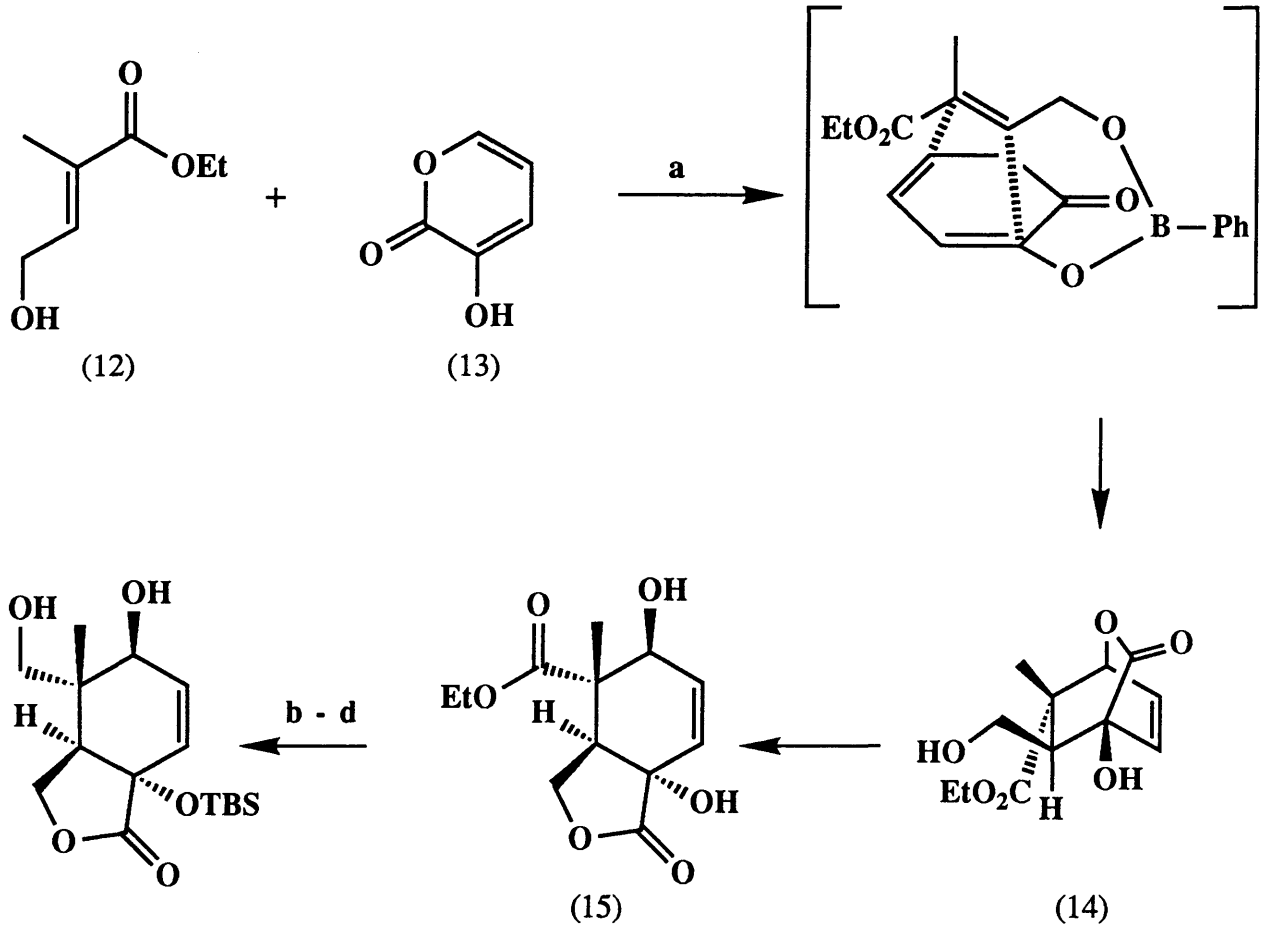


Scheme 1

a.) 1.0eq of diene, 1.5eq of CH_2=CH(CN)Cl, 130°C, 72h, 80%; b.) 6.0eq KOH, ^{t}BuOH, 70°C, 4h, 90%; c.) 1.1eq TBSCl, 1.2eq imidazole, CH_2Cl_2, 25°C, 2h; d.) 1.0eq (2,4,6-triisopropylbenzenesulphonyl) hydrazine, THF, 25°C, 2h, 88%.

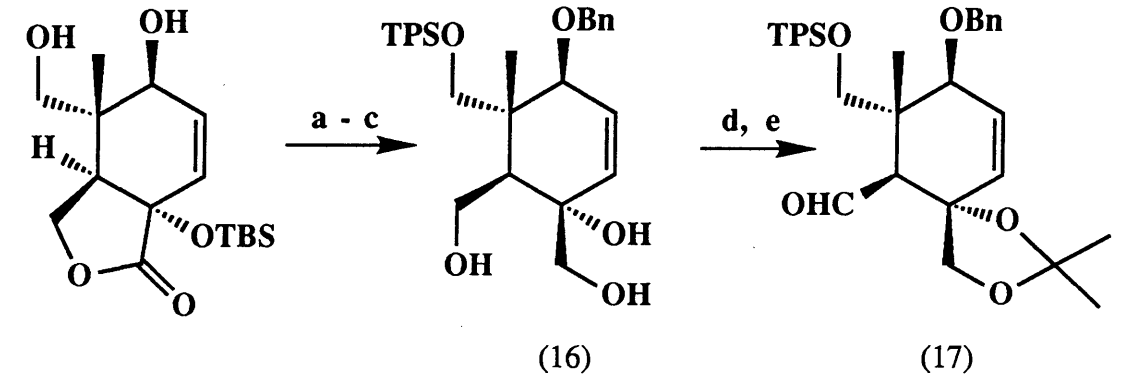
Construction of the C-ring.

Another Diels-Alder cyclisation was used to prepare the C-ring[15b]. The dienophile (12) was joined with 2-hydroxy-2-pyrone (13) in a reaction made intramolecular by the addition of phenylboronic acid. This temporarily tethers the two components together and dictates the regiochemical outcome of the cyclisation. The intermediate formed (14) (Scheme 2) quickly rearranges to give the less strained 5-membered ring (15). Protection followed by opening and reduction of the lactone (Scheme 3) gave a triol (16) which was further protected as an acetonide to complete the synthesis of the C-ring (17).



Scheme 2

a.) 1.4eq 2-hydroxy-2-pyrone, 1.4eq $PhB(OH)_2$, PhH, reflux (Dean-Stark trap), 48h, then 1.4eq 2,2-dimethyl-1,3-propanediol, 25°C, 1h, 79%; b.) 4.0eq $^tBuMe_2SiOTf$, 4.0eq 2,6-lutidine, 0.1eq DMAP, CH_2Cl_2, 0°C, 4h, 92%; c.) 1.1eq $LiAlH_4$, 0-25°C, 0.5h, 97%; d.) 0.05eq CSA, CH_2Cl_2, MeOH, 25°C, 1h, 94%.



Scheme 3

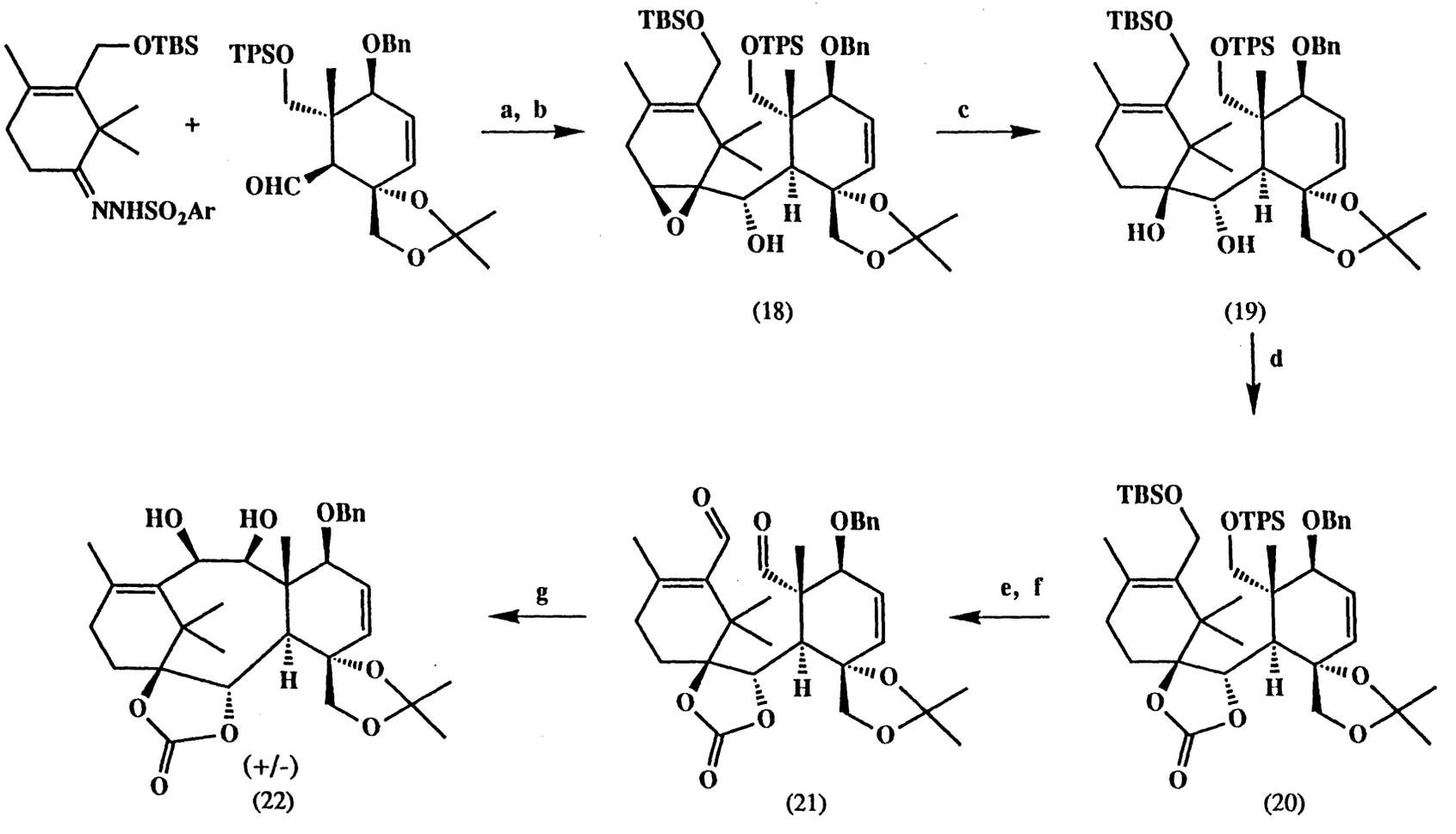
a.) 1.3eq TPSCl, 1.35eq imidazole, DMF, 25°C, 12h, 92%; b.) 1.2eq KH, 1.2eq $PhCH_2Br$, 0.04eq $^nBu_4NI$, 25°C, 1h, 88%; c.) 3eq $LiAlH_4$, Et_2O, 25°C, 12h, 80%; d.) 5eq 2,2-dimethoxypropane, 0.05eq CSA, CH_2Cl_2 : Et_2O (98:2), 25°C, 7h, 82%; e.) 0.05eq TPAP, 1.5eq NMO, CH_3CN, 25°C, 2h, 97%.

Coupling to the ABC skeleton.

The A and C-rings were coupled together[14, 15c] via a Shapiro reaction of the hydrazone with the aldehyde to yield a single diastereoisomer of the allylic alcohol. Epoxidation of the double bond afforded a single isomer (18) which was opened regiospecifically by $LiAlH_4$ to give (19). Protection of the neighbouring hydroxyl groups as a carbonate (20) allowed deprotection and oxidation to give a dialdehyde (21) (Scheme 4).

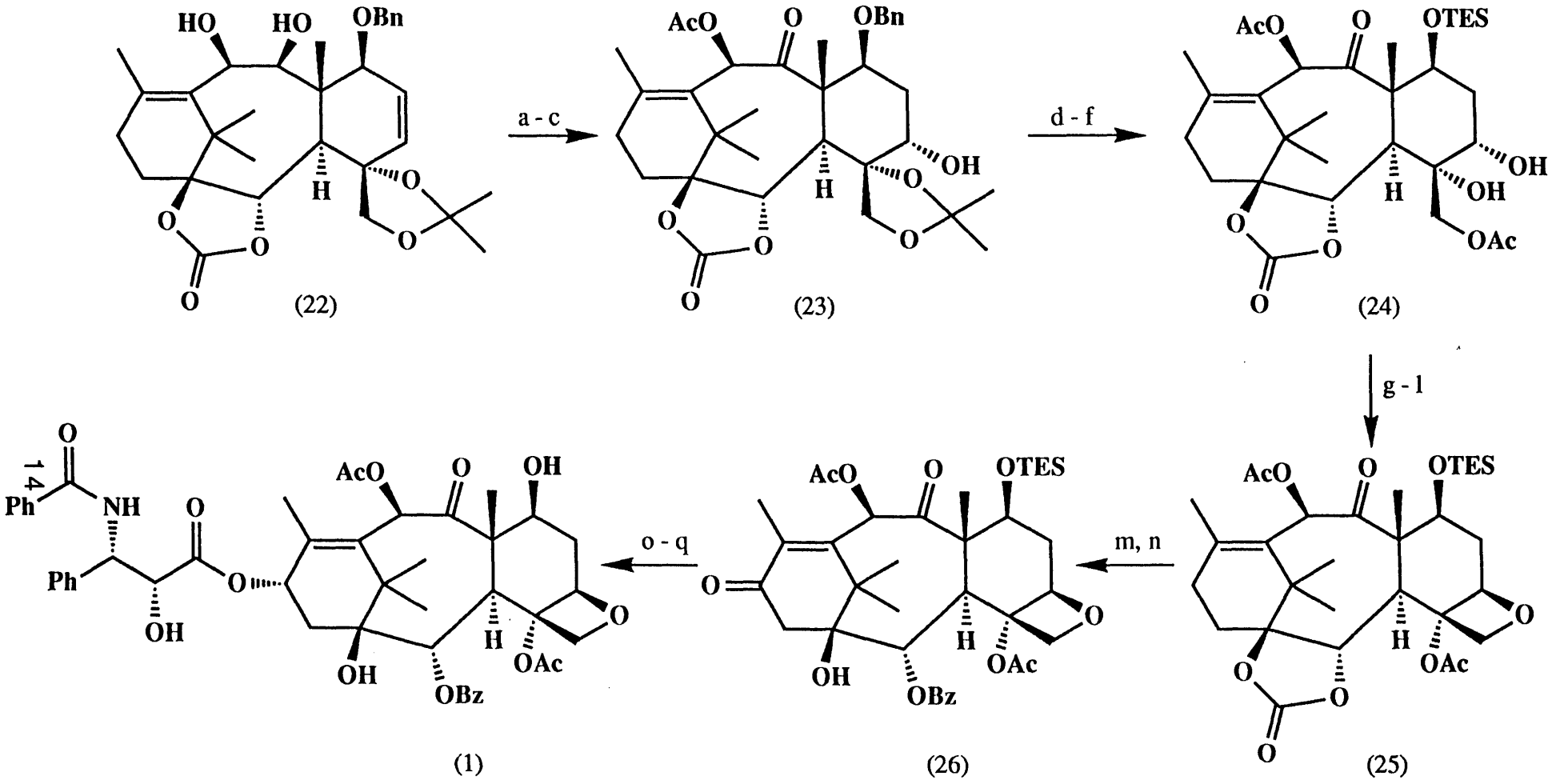
The final cyclisation to form the carbon-carbon bond between positions 9 and 10 in the taxane skeleton was achieved using a method pioneered by McMurry[16].(Scheme 5) This involved a pinacol coupling pathway give the racemic diol (22), which was resolved by separation of the camphonate esters of the C-9 hydroxyl group by chromatography. Following ester hydrolysis, selective functionalisation at C-9 and C-10 was carried out by treatment with acetic anhydride and DMAP to yield a monoacetate that was then oxidised to the ketone (23). The C-5α hydroxyl compound was obtained from a hydroboration reaction as the major regioisomer (24). The oxetane ring was installed *via* a triflate silyl ether, exposure to acidic conditions removed the silyl ether and the triflate was displaced to form the four membered ring (25). The final manipulations included oxidation of the C-13 allylic position to give enone (26) and stereoselective reduction to an allylic alcohol. The side chain was attached by treatment first with base and then with the β-lactam, removal of the TES at C-7 gave Taxol™ (1).

Although, the completion of this route was a milestone in the progress towards total synthesis, using many sophisticated and attractive steps, it is still a distance from becoming a commercially viable synthesis. The large number of steps involved give an overall yield of less than 1% of product, indicating that much more work needs to be explored in this field of total synthesis.



Scheme 4

a.) 1.1eq A-ring, 2.3eq ^{n}BuLi, THF, -78°C, 1eq C-ring, -78°C, 0.5h, 82%; b.) 0.03eq, $VO(acac)_2$, 3eq ^{t}BuOOH, PhH, 4A molecular sieves, 25°C, 14h, 87%; c.) 5.0eq $LiAlH_4$, 25°C, Et_2O, 7h, 76%; d.) 3.0eq KH, Et_2O : HMPA (3:1), 1.6eq phosgene (20% in toluene), 25°C, 0.5h, 86%; e.) 3.8eq TBAF, THF, 25°C, 14h, 80%; f.) 0.05eq TPAP, 3.0eq NMO, CH_3CN : CH_2Cl_2 (2:1), 25°C, 2h, 92%; g.)11eq $TiCl_3(DME)_{1.5}$, 26eq Zn-Cu, DME, reflux, 3h, then 70°C, then dialdehyde added over 1h, 70°C, 0.5h.

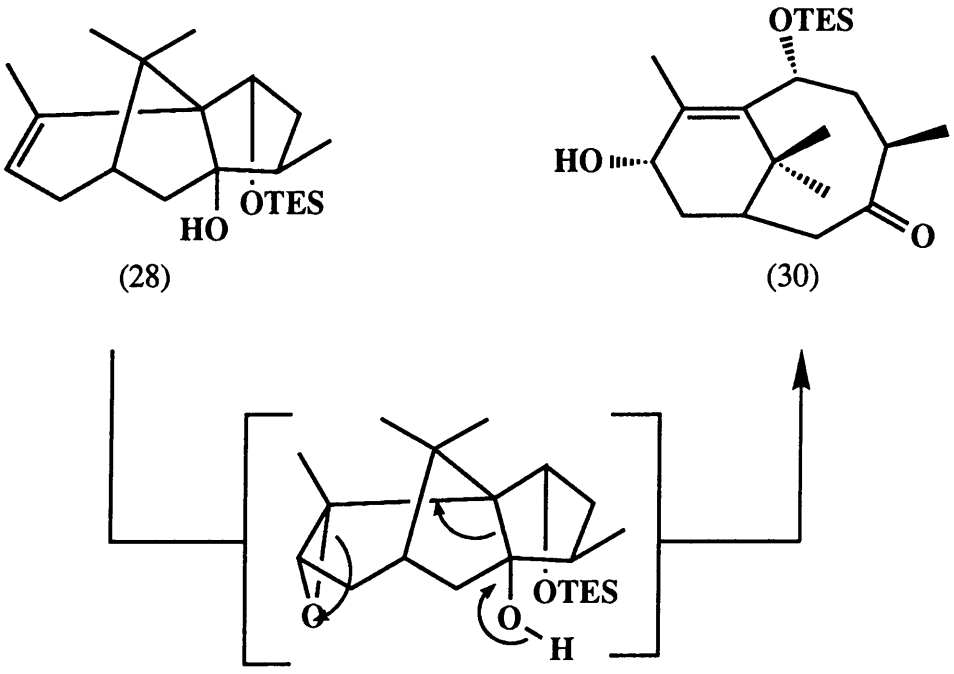


Scheme 5

a.) 1.5eq Ac_2O, 1.5eq DMAP, CH_2Cl_2, RT, 2h, 95%; b.) 0.1eq TPAP, 3.0eq NMO, CH_3CN, RT, 93%; c.) 10eq BH_3.THF, THF, 0°C, 3h, then xs H_2O_2, sat.aq. $NaHCO_3$, RT, 1h, 42% and 22% C6-OH regioisomer; d.) MeOH : cHCl (2:1), 5h, 80%; e.) 1.25eq, Ac_2O, 5eq py, 0.05eq DMAP, CH_2Cl_2, RT, 0.5h, 95%; f.) H_2, 10% $Pd(OH)_2/C$, EtOAc, RT, 0.5h, 97%; g.) 25eq TESCl, py, RT, 12h, 85%; h.) 10eq K_2CO_3, MeOH-H_2O, 0°C, 15min, 97%; i.) 10eq Me_3SiCl, 30eq py; j.) 15eq Tf_2O, 30eq $^iPr_2NEt$; k.) 0.05eq CSA, MeOH, RT, 15min, then silica gel, RT, 1h; l.) 8eq, Ac_2O, 15eq DMAP, RT, 4h, 94%; m.) 5.0eq PhLi, -78°C, 10min, 10eq Ac_2O, 5eq DMAP, 2.5h, 80%; n.) 30eq PCC, 30eq NaOAc, Celite, benzene, reflux 1h, 75%; o.) xs $NaBH_4$, MeOH, RT, 3h, 94%; p.) 3.0eq $NaN(SiMe_3)_2$, 3.5eq β-lactam, THF, 0°C, 0.5h, 86%; q.) HF.py, THF, RT, 1.25h, 80%.

Holton.

Following the success of synthesising Taxusin[17], Holton *et al* from Florida State University were the second team to complete the total synthesis of Taxol™ [19]. By retrosynthetic analysis, Holton reasoned that the taxane structure could be constructed by a C-ring closure on to a precursor already containing the bicyclo [5.3.1] skeleton (30). The key step to this synthesis was the synthesis of the AB ring system *via* fragmentation of bicyclic epoxy alcohol (29) readily available from a derivative of camphor[18] (28) (Figure 3).

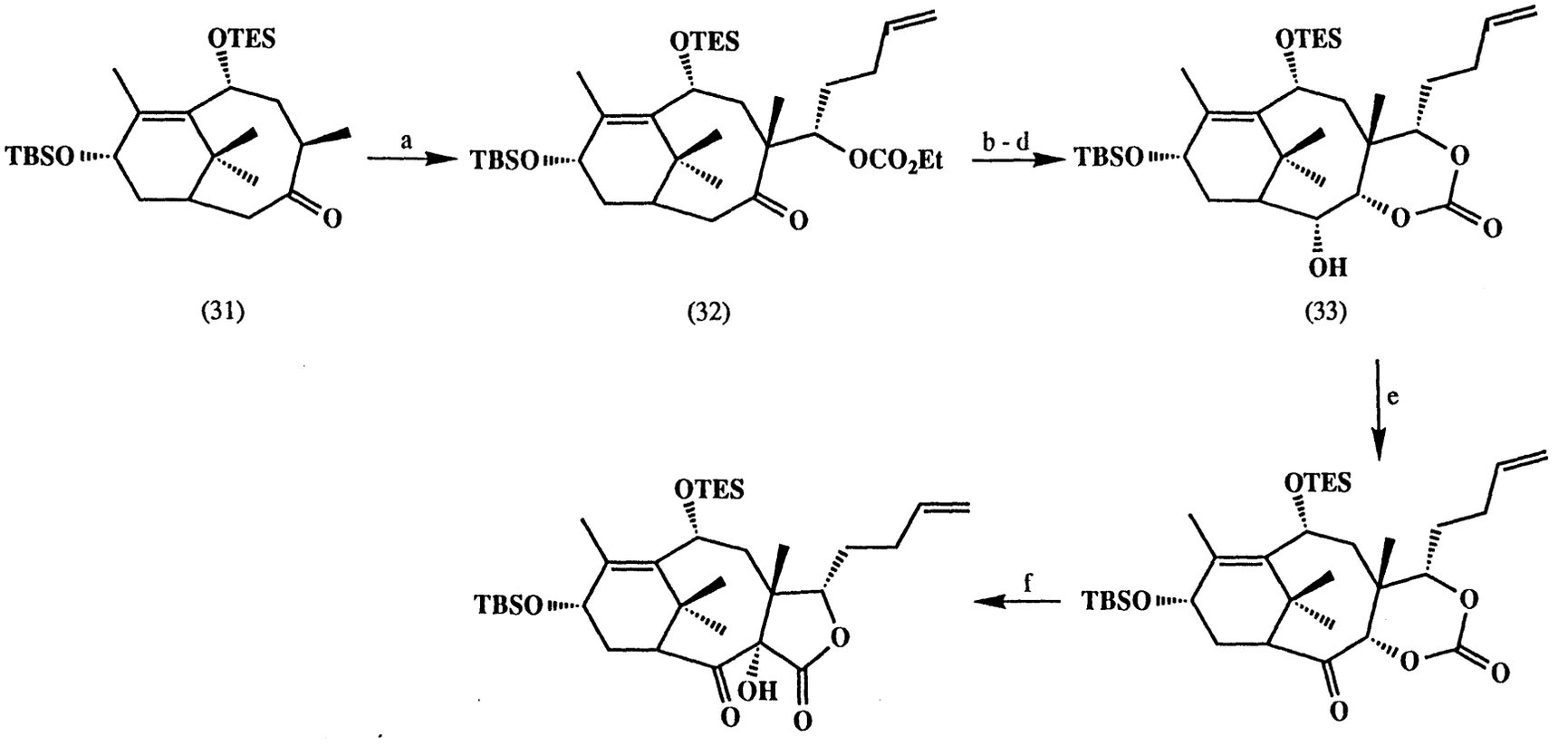


(28) (30)

(29)

Figure 3

When the OH protected AB system (31) was deprotonated and treated with 4-pentenal it underwent an aldol condensation to give the product (32) which was then protected as an ethyl carbonate. After hydroxylation at the C-2 position by treatment with LDA and (+)-camphorsulphonyl oxaziridine, the carbonyl group was then reduced and the subsequent 1,3-diol protected as a carbonate (33). Swern oxidation to give the C-2 ketone (34) was followed by treatment with LTMP to try and introduce functionality at C-1 via the enolate, however, formation of the hydroxy lactone (35) was seen. (Scheme 6)



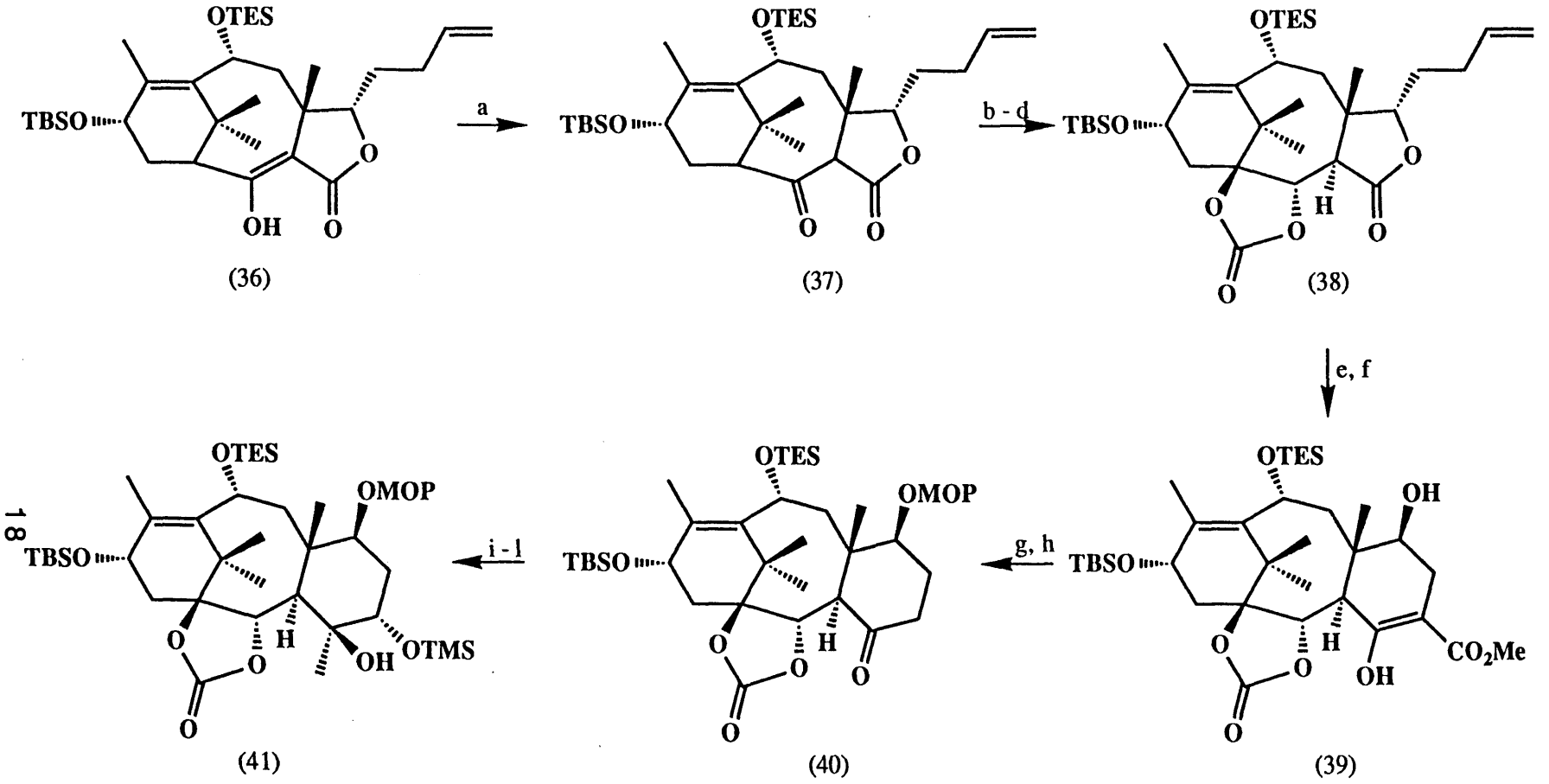
(31) (32) (33) (34) (35)

Scheme 6

a.) $(^{i}Pr)_2NH$, THF, MeMgBr, rt, 3h, then AB system, 1.5h, 4-pentenal, THF, -23°C, 1.5h, then Cl_2CO, py, -10°C, 0.5h, then EtOH, 0.5h; b.) LDA, THF, -35°C, 0.5h; c.) 20eq, Red-Al, PhMe, -78°C, 6h, 1.0eq (+)-camphorsulphonyl oxaziridine, 0.5h; d.) Cl_2CO, py, CH_2Cl_2, -78 - 25°C, 1h; e.) Swern oxidation; f.) 1.05eq LTMP, -25 - 10°C.

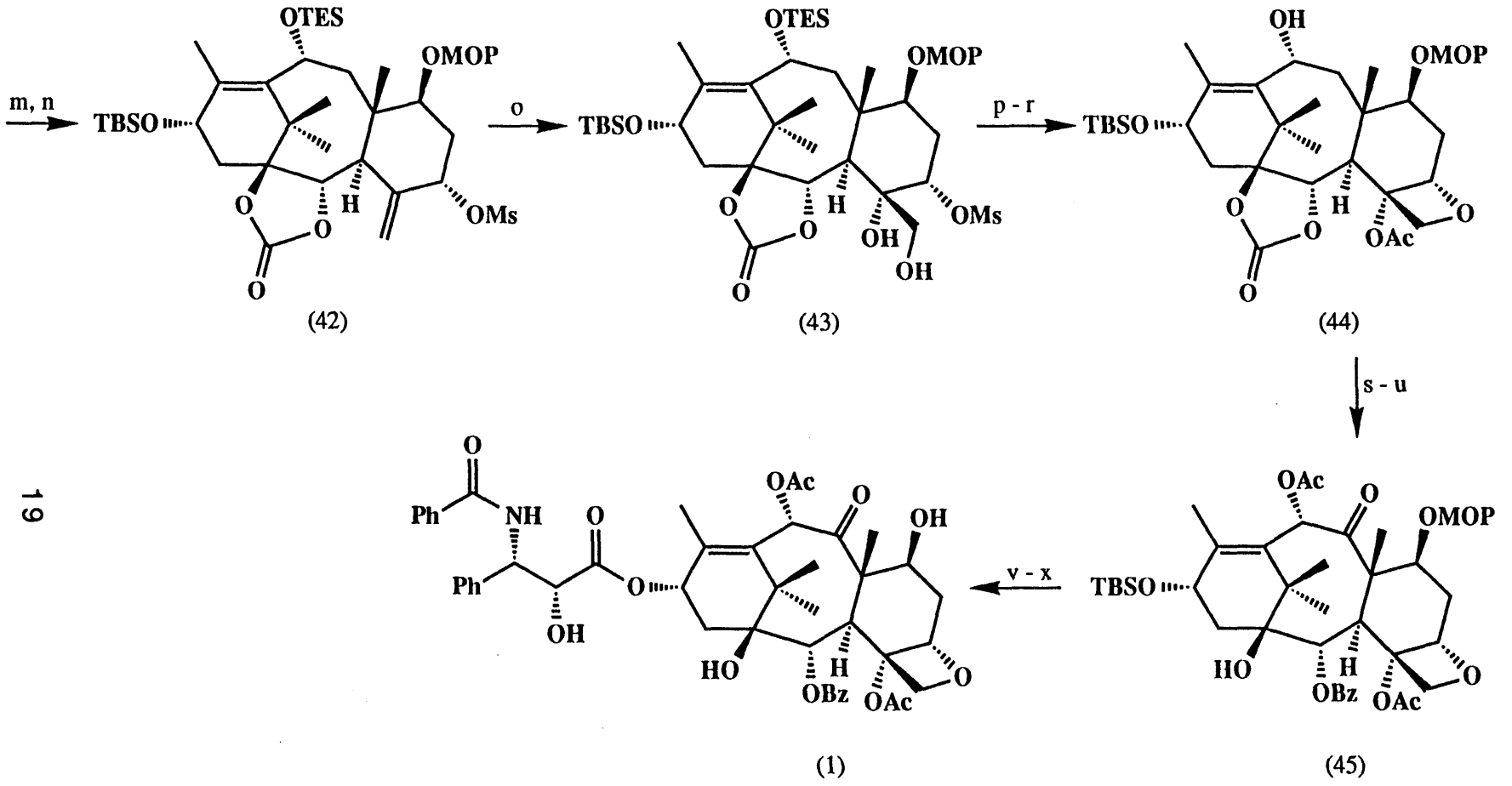
Reduction of (35) using samarium diiodide gave a stable enol (36) which after treatment with silica gel produced a 6:1 mixture of cis and trans fused lactones (37). The cis fused lactone was deprotonated at C-1 to provide an enolate which was reacted with camphorsulphonyl oxaziridine to give only the C-1β alcohol. Reduction of this compound gave the C-2α-hydroxy *trans* fused lactone which was protected as a carbonate (38). (Scheme 7)

Cleavage of the terminal double bond to the aldehyde and subsequent oxidation and esterification gave the methyl ester, which underwent a Dieckmann cyclisation to give enol ester (39). Protection of the C-7 OH with a MOP group allowed the compound to undergo decarbomethoxylation (40) (Scheme 7). A Grignard reaction followed to yield tertiary alcohol (41) and elimination using Burgess' reagent provided an allylic alcohol. The mesylate (42) was subjected to osmylation (Scheme 8) and gave diol (43), the oxetane ring was then constructed in a similar procedure as described in the Nicolaou synthesis. The C-10 TES group was removed, the carbonate treated with PhLi to furnish the C-2 benzoate and oxidation using TPAP gave a C-10 carbonyl. The enolate of this product was added to a suspension of benzeneseleninic anhydride and KO^tBu to allow oxidation of C-9. Protection as the acetate yielded (45). In the final steps, TASF removed the TBS group, the side chain was attached and the protecting group was removed to yield Taxol™ (1).



Scheme 7

a.) Silica gel; b.) 4eq LTMP, -10°C, (+/-)-camphorsulphonyl oxaziridine, -40°C; c.) Red-Al, THF, -78°C, 1.5h; d.) 10eq phosgene, py, CH_2Cl_2, -23°C, 0.5h; e.) O_3, $KMnO_4$, KH_2PO_4, then CH_2N_2; f.) LDA, THF, -78°C, 0.5h, then HOAc, THF; g.) p-TsOH, 2-methoxypropene; h.) PhSK, DMF, 86°C, 3h; i.) $EtN(^iPr)_2$, CH_2Cl_2, Bu_4NI, reflux, 32h; j.) LDA, THF, TMSCl, -78°C; k.)m-CPBA, hexane, rt, 5h; l.) MeMgBr, CH_2Cl_2, -45°C, 15h.

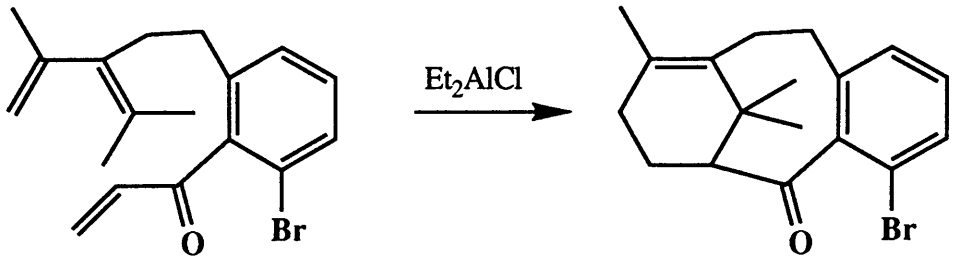


Scheme 8

m.) Burgess' reagent; n.) MsCl, py; o.) OsO_4, Et_2O, py, 0°C, 12h; p.) DBU, PhMe, 105°C, 2h; q.) Ac_2O, py, DMAP, RT, 24h; r.) HF-py complex, MeCN, 0°C, 11h; s.) 2.1eq PhLi, THF, -78°C, 10min; t.) TPAP, NMO, molecular sieves, CH_2Cl_2, RT, 15min; u.) Enolate, THF, 4eq KO^{t}Bu, -78 to 0°C, 0.5h, 8eq benzeneselenic anhydride, THF, 0°C, 40min, then Ac_2O, py, DMAP, RT, 20h; v.) TASF, THF, RT, 1h; w.) β-lactam, THF, 0°C, 1h, then HF, py, MeCN, 0°C, 1h; x.) H_2, Pd/C, EtOH, reflux, 1h.

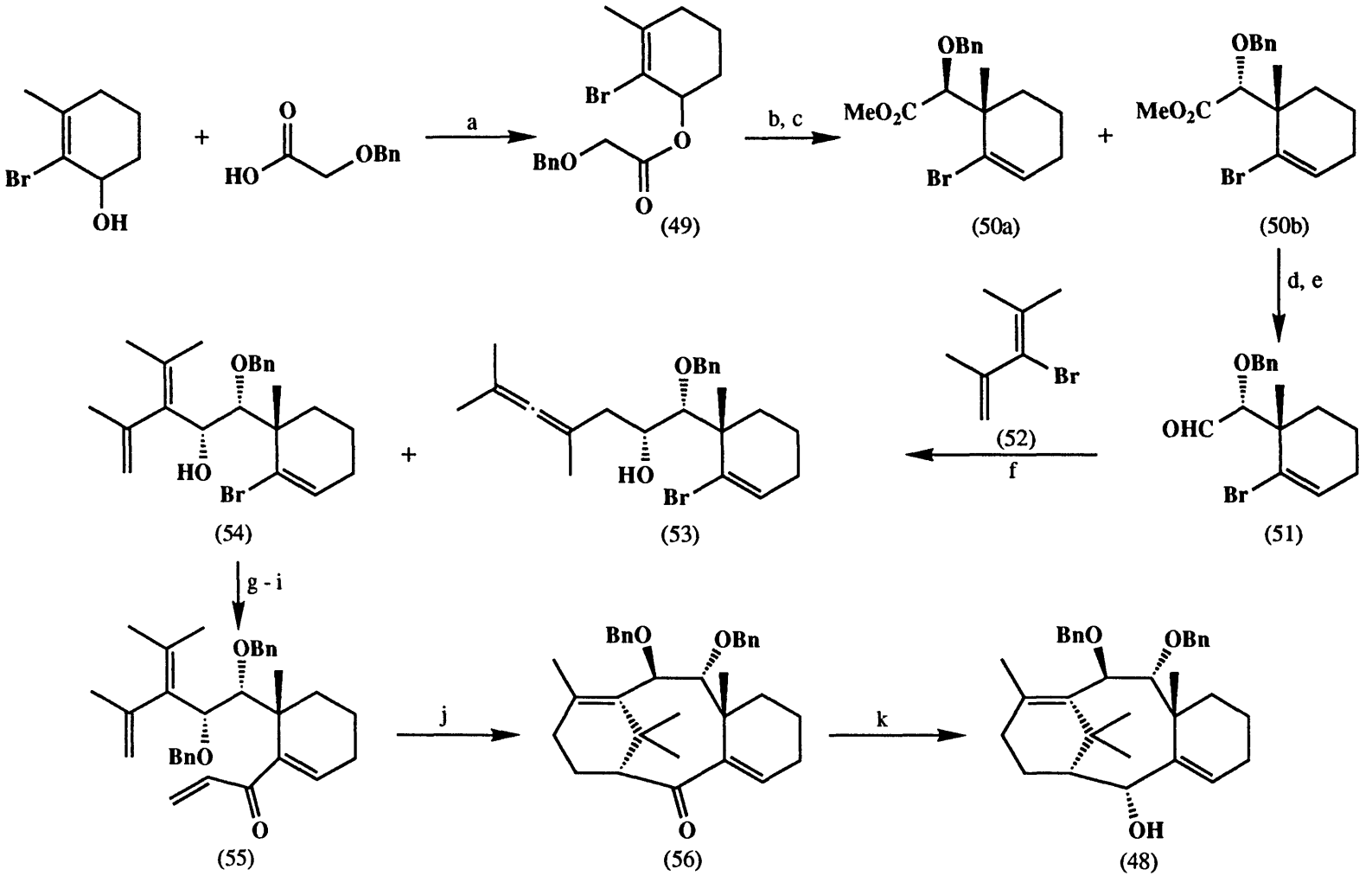
Shea.

Previous studies by Shea[20] have developed a route to taxoid structures containing aromatic C-rings (47) using intramolecular type 2 Diels-Alder cyclisations. Two atropisomers, *endo* and *exo* were obtained from these reactions, the ratio depending on whether thermal or Lewis acid conditions had been employed.



(46) (47)

More recently he has completed the synthesis of a C-1 epi-taxinine intermediate (48) which possesses the correct orientation of stereocentres found at positions 8,9 and 10[21]. This route is illustrated in Scheme 9. The allylic alcohol and carboxylic acid were coupled using DCC and DMAP to yield the ester (49). Enolisation of the carbonyl and trapping with TMSCl provided an enol ether which entered into a Claisen rearrangement on warming. Hydrolysis and esterification afforded a 3:1 mixture of diastereoisomers (50a) and (50b). Reduction to the corresponding primary alcohols allowed separation of the major isomer, which was oxidised to an aldehyde (51). The bromodiene (52) was treated with ^{t}BuLi and $CeCl_3$ presumably to produce an organocerium species which on addition to the carbonyl group afforded two products, the diene alcohol (53) and allene alcohol (54) in a ratio of 5.4:1 respectively. Both (53) and (54) were formed as single diastereomers, this was explained as a chelation controlled addition by tethering together the organometallic reagent to the α-alkoxy aldehyde. This reaction was made use of in our approach and shall be discussed further in the results and discussion section.



Scheme 9

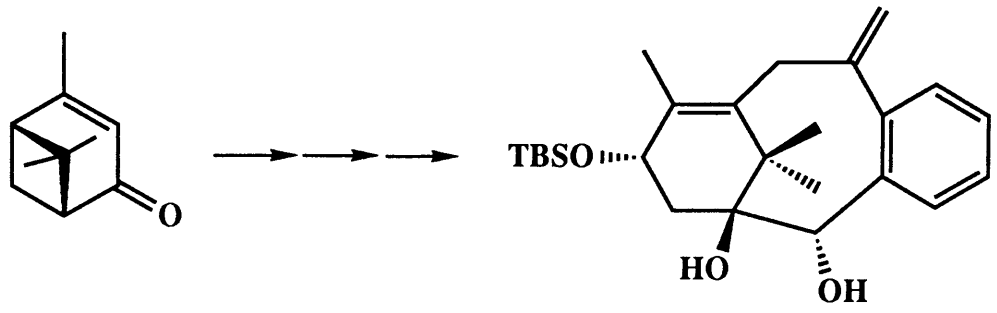
a.) DCC, DMAP, CH_2Cl_2, 85%; b.) i KHMDS, TMSCl, THF, -78 to -23°C, ii H_3O^+; c.) CH_2N_2, 67%; d.) DIBALH, 0°C, 65%; e.) $(ClCO)_2$, DMSO, NEt_3, CH_2Cl_2, 79%; f.) i ^tBuLi, 0°C, Et_2O, ii $CeCl_3$, -78°C, aldehyde; g.) BnBr, NaH, DME, 73%; h.) ^tBuLi, -78°C, then acrolein; i.) $BaMnO_4$, Celite, PhH, 48%; j.) PhMe, 205°C, 18h, 44%; DIBALH, 0°C, 73%.

The dienophile was built up by performing a lithium-halogen exchange and treating with acrolein, the resulting alcohol was oxidised to a ketone (Scheme 9). The trienone (55) was cyclised under thermal conditions and a single diastereoisomer (56) was observed after purification, whose racemic structure was proved by X-ray crystallography of the reduced product (48). It showed that the bridge was anti to the methyl group attached to C-8 *ie.* the *exo* conformation. The natural products exist in an endo conformation, bridge syn to the methyl group, therefore it was a C-1 epi taxinine derivative that had been synthesised.

Shea is currently pursuing investigations into factors affecting the stereochemistry of the Diels-Alder reaction and making C-1 epi Taxol analogues.

Wender.

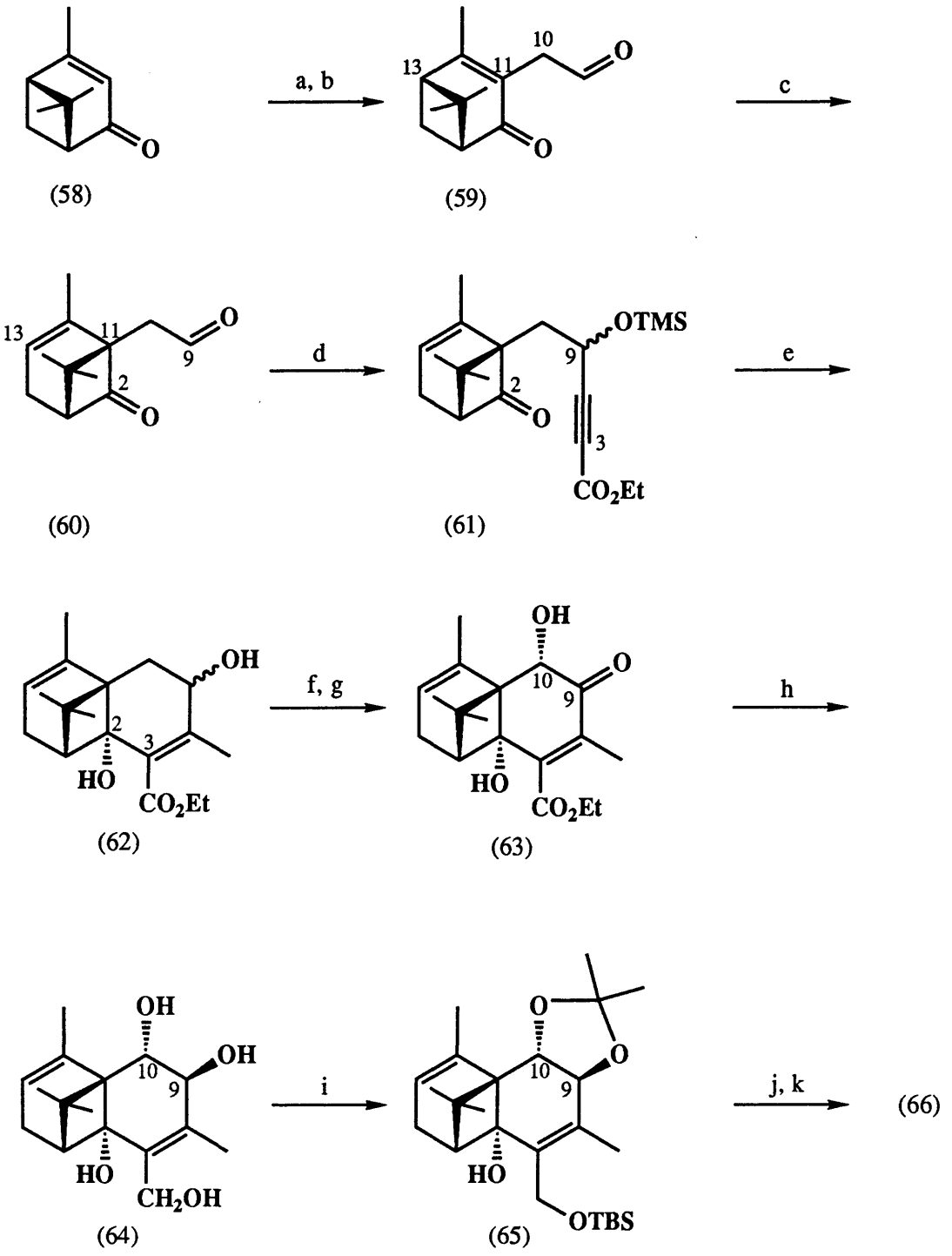
Early work by Wender describes the preparation of an aromatic C-ring taxane (57) using verbenone (58), the product from air oxidation of pinene[22a]. He reasoned that verbenone is a good starting material as it provides 10 out of the 20 carbons and the chirality of the A-ring of the taxane skeleton. Recently he has completed the total synthesis of Taxol™ from verbenone[22b].



(58) (57)

The first step was to form the C10-C11 bond of the taxane skeleton by treatment of verbenone with KO^{t}Bu and prenyl bromide, selective ozonolysis provided (59) in good yield (Scheme 10). The next step was the crucial migration of the one carbon bridge from C13 to C11, this was affected by photorearrangement to give (60). The B-ring of the taxane skeleton was established by connecting a two-carbon portion to the C9 carbonyl (61), introduction of a methyl group using Me_2CuLi allowed a C3 carbanion to

be generated which formed an intramolecular bond between C2-C3 in 97% yield. The alcohol (62) was oxidised to a ketone and deprotonation with KHMDS followed by treatment with Davis' oxaziridine allowed the C10 oxygen to be introduced from the less hindered side of the enolate (63). Stereoselective reduction gave the tetraol (64) which was protected as an acetonide (65). The conformational rigidity of the tricycle was exploited by treating with m-CPBA which gave stereoselective epoxidation of the C12-C13 double bond from the α face. The 4-membered ring was highly strained and treatment with DABCO affected fragmentation of the ring to form a new 8-membered ring (66), this is illustrated in Scheme 10. The bridge and the C13 position are both in the correct orientation for taxane structures. The bridgehead hydroxyl group was introduced using KO^tBu, $P(OEt)_3$ and oxygen gas. Deprotection of the TBS group and stereoselective reduction of C2 gave the triol (67) (Scheme 11). The C3-C8 double bond was hydrogenated catalytically and oxidation provided the aldehyde (68). Homologation with $Ph_3PCHOMe$ followed by hydrolysis of the resulting enol ether and the acetonide groups gave an aldehyde. Protection of C9, oxidation of C10 and introduction of C20 using $[Me_2NCH_2]I$ and NEt_3 resulted in the enal (69). The remaining two carbons of the taxane C-ring were introduced by a Grignard reaction using allylmagnesium bromide and $ZnCl_2$, BOM protection gave the ether (70). C9 was deprotected, the cyclic carbonate was opened with PhLi to give the C2 benzoate and C9 was acylated. The acetoxyketone was transposed using the guanidinium base and ozonolysis of the monosubstituted alkene gave (71) (Scheme 11).

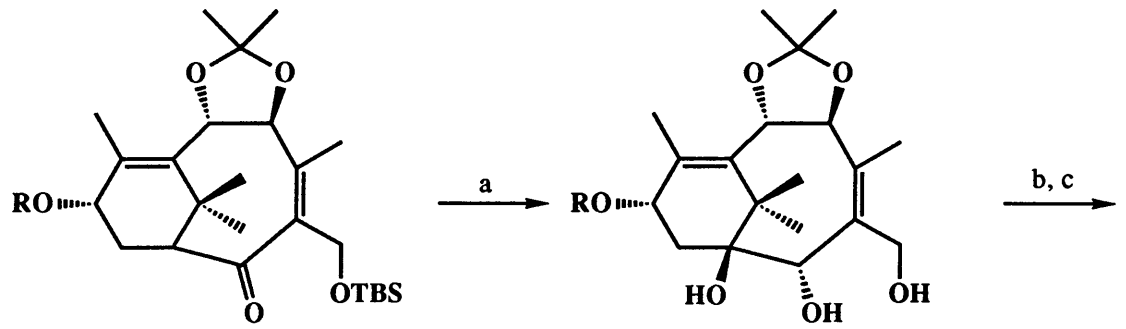


(58) (59) (60) (61) (62) (63) (64) (65)

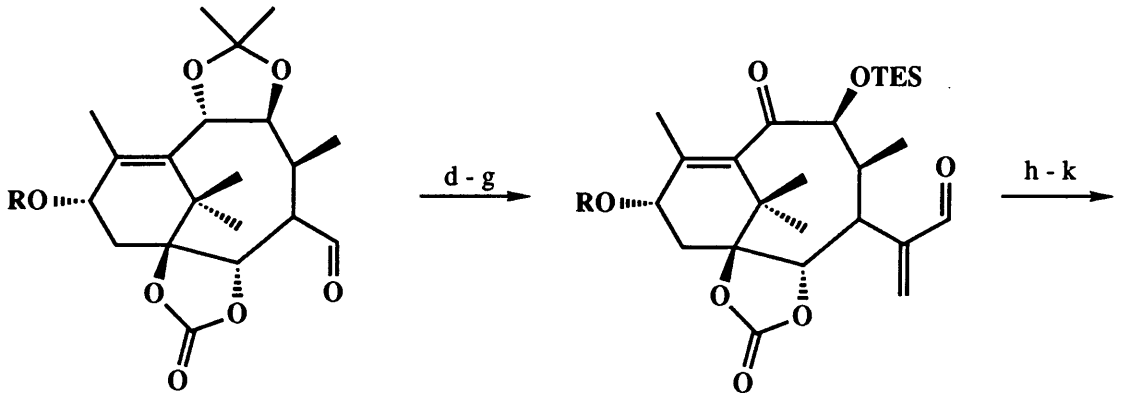
Scheme 10

a.) KO^{t}Bu, 1-bromo-3-methyl-2-butene, DME, -78°C to rt, 79% at 41% conversion; b.) O_3, CH_2Cl_2, MeOH, 85%; c.) hv, MeOH, 85%; d.) LDA, ethyl propiolate, THF, -78°C, TMSCl, 89%; e.) Me_2CuLi, Et_2O, -78°C to rt, AcOH, H_2O, 97%; f.) $RuCl_2(PPh_3)_3$, NMO, acetone, 97%; g.) KHMDS, Davis' oxaziridine, THF, -78 to -20°C, 97% at 57% conversion; h.) $LiAlH_4$, Et_2O, 74%;, i.) TBSCl, imid., PPTS, 2-methoxypropene, rt, 91%; j.) m-CPBA, Na_2CO_3, CH_2Cl_2; k.) DABCO (cat.), CH_2Cl_2, heat, TIPSOTf, 2,6-lutidine, -78°C, 85% over 2 steps.

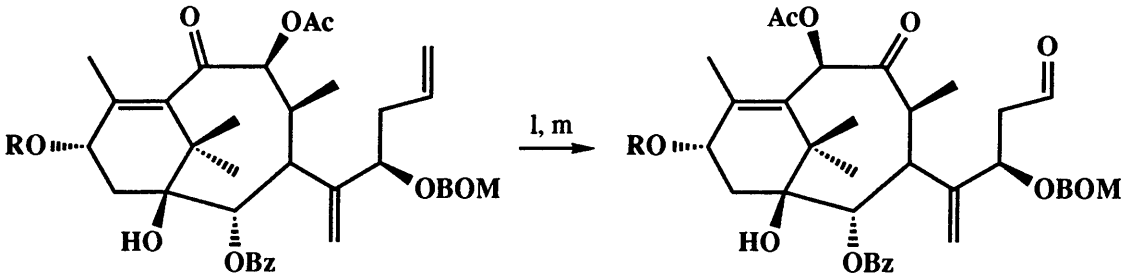
The final steps (Scheme 12) were to use an aldol cyclisation to close the C-ring and complete the taxane skeleton. Earlier opening of the C1-C2 carbonate allowed the C8 hydrogen to align with the C9 carbonyl in the B-ring and thus permit deprotonation. Introduction of 4-pyrrolidinopyridine gave (72a) and (72b) in an 11:1 ratio. Protection of (72a) using TROCCl gave (73), the BOM ether was cleaved (74), the OH was converted to the mesylate (75) and this gave the bromide (76) on reaction with LiBr. Osmylation of the double bond gave a diol, however, benzoyl migration from C2 to C20 occurred. The C1-C2 diol was therefore reprotected as the cyclic carbonate and the C20 benzoate was removed to give (77). The oxetane ring was formed by reaction with Hunig's base and acylation of C4 gave (78). deprotection and reaction of the C13 alcohol with PhLi gave (79a) and (79b) in a 2:1 ratio. The final step involved the addition of the side chain using the Ojima method to furnish Taxol^{TM} (1). This route represents the shortest reported synthesis of Taxol^{TM} (1) using an inexpensive starting material.



(66) (67)



(68) (69)

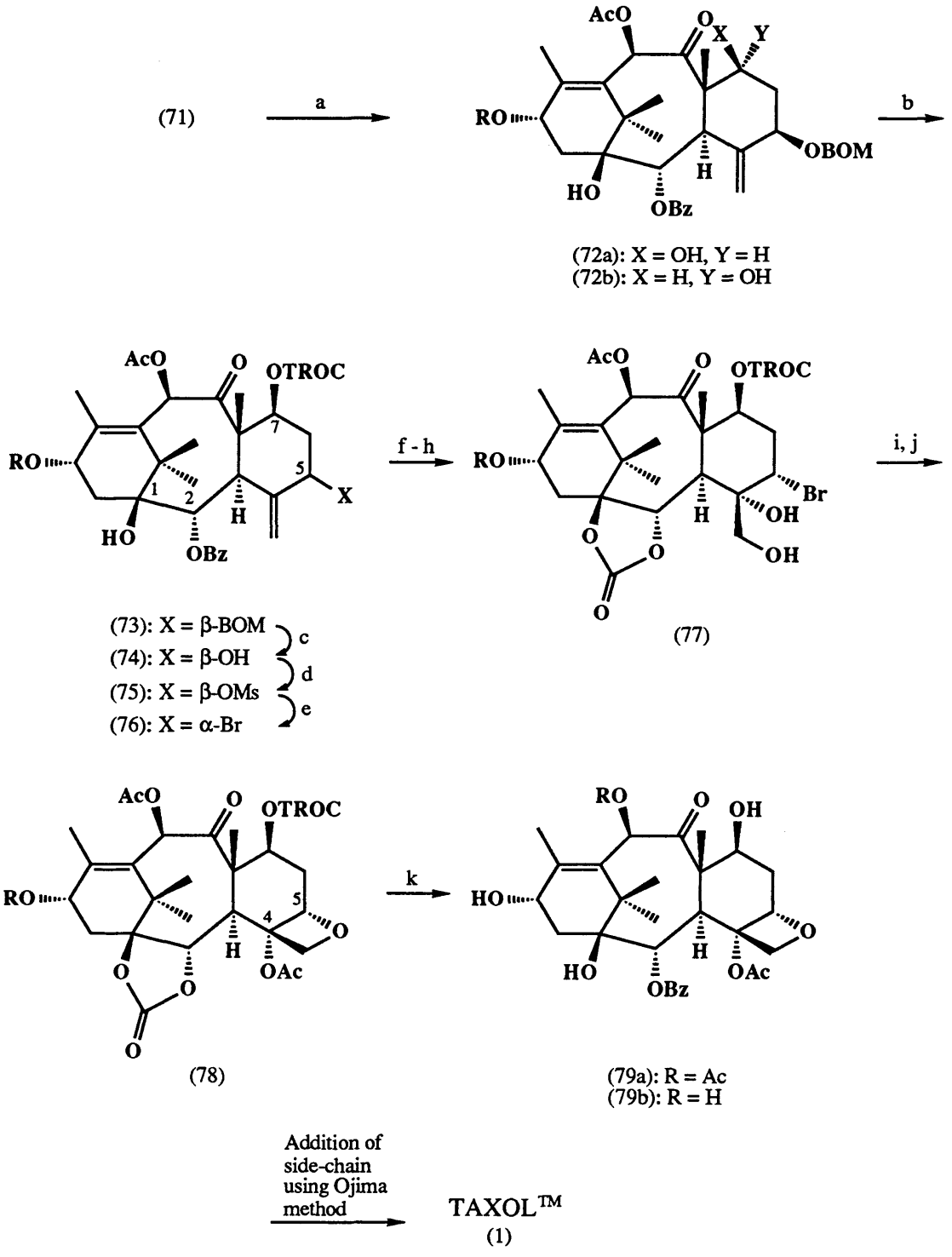


(70) (71)

R = TIPS

Scheme 11

a.) KO^{t}Bu, O_2, $P(OEt)_3$, THF, -40°C; NH_4Cl, MeOH, rt; $NaBH_4$, 91%; b.) H_2, Crabtree's catalyst, CH_2Cl_2, rt; TMSCl, py, -78°C; triphosgene, 0°C, 98%; c.) PCC, 4A molecular sieves, CH_2Cl_2, 100%; d.) $Ph_3PCHOMe$, THF, -78°C, 91%; e.) 1M HCl(aq), NaI, dioxane, 94% at 90% conversion; f.) TESCl, py, CH_2Cl_2, -30°C, 92%; g.) Dess-Martin periodinane, CH_2Cl_2; Et_3N, Eschenmoser's salt, 97%; h.) allyl-MgBr, $ZnCl_2$, THF, -78°C, 89%; i.) BOMCl, $^i Pr_2NEt$, 55°C; j.) NH_4F, MeOH, rt, 93% over two steps; k.) PhLi, THF, -78°C, Ac_2O, DMAP, py, 79%; l.) guanidinium base, CH_2Cl_2, rt, 1h, 80% at 63% conversion; m.) O_3, CH_2Cl_2, -78$_o$C; $P(OEt)_3$, 86%.

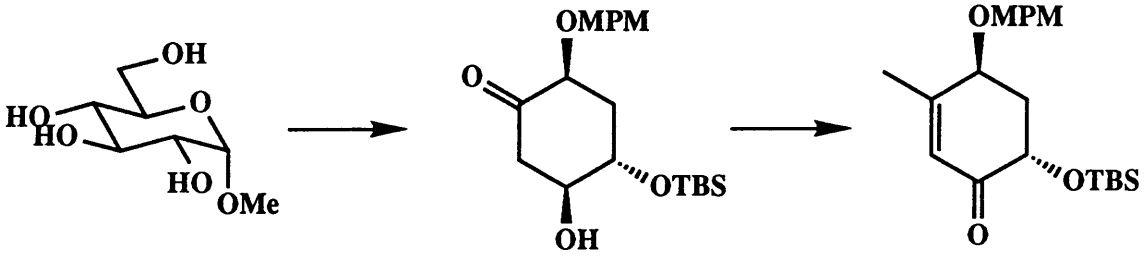


Scheme 12 (71) to (78) R = TIPS

a.) 4-pyrrolidinopyridine; b.) DMAP (xs), CH_2Cl_2; TROCCl, 62%; c.) NaI, $HCl_{(aq)}$, acetone, 97% at 67% conversion; d.) MsCl, py, DMAP, CH_2Cl_2, 83%; e.) LiBr, acetone, 79% at 94% conversion; f.) OsO_4, py, THF; $NaHSO_3$, imid., $CHCl_3$, 76% at 94% conversion; g.) triphosgene, py, CH_2Cl_2, 92%; h.) KCN, EtOH, 0°C, 76% at 89% conversion; i.) $^iPr_2NEt$, toluene, 110°C, 95% at 83% conversion; j.) Ac_2O, DMAP, 89%; k.) TASF, THF, 0°C; PhLi, -78°C, 46% (79b), 33% (79a).

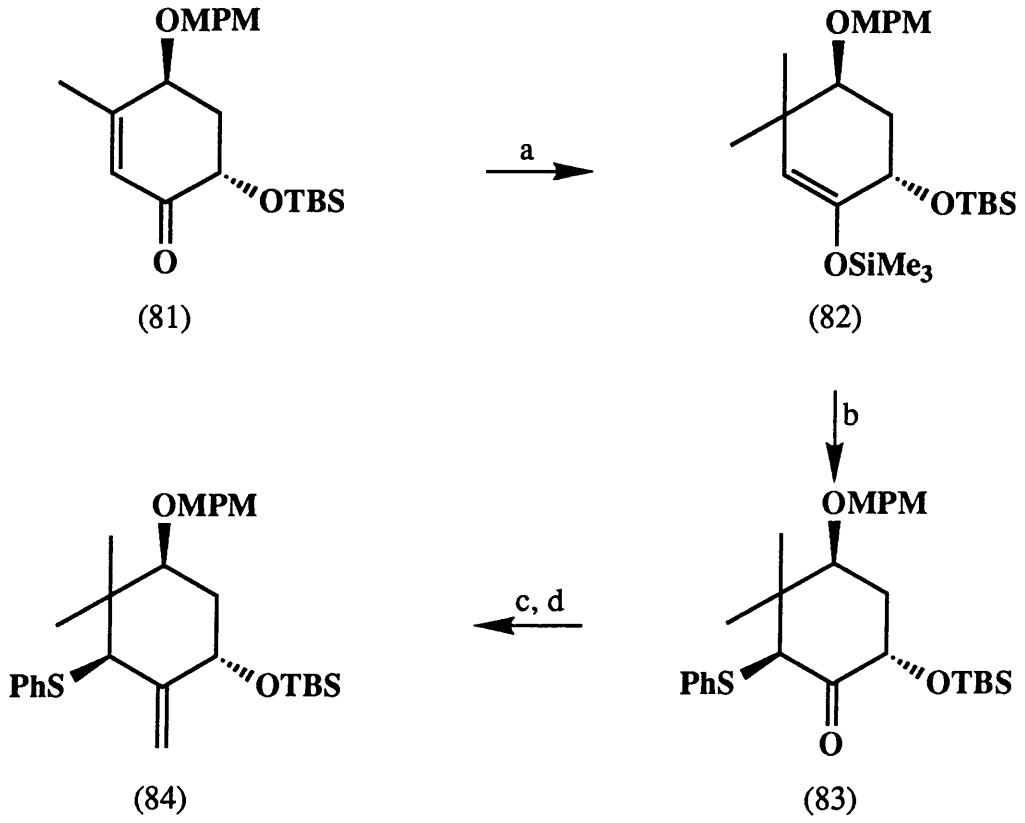
Ermolenko.

A publication by Ermolenko describes the syntheses of both A[23] (84) and C[24] (88) ring structures derived from a common intermediate. The hydroxycyclohexanone (80) was available from methylglucopyranoside using literature methods including a Ferrier rearrangement. A two-step sequence furnished the 3-substituted cyclohexenone (81) which was used as the advanced material for both routes.



(80) (81)

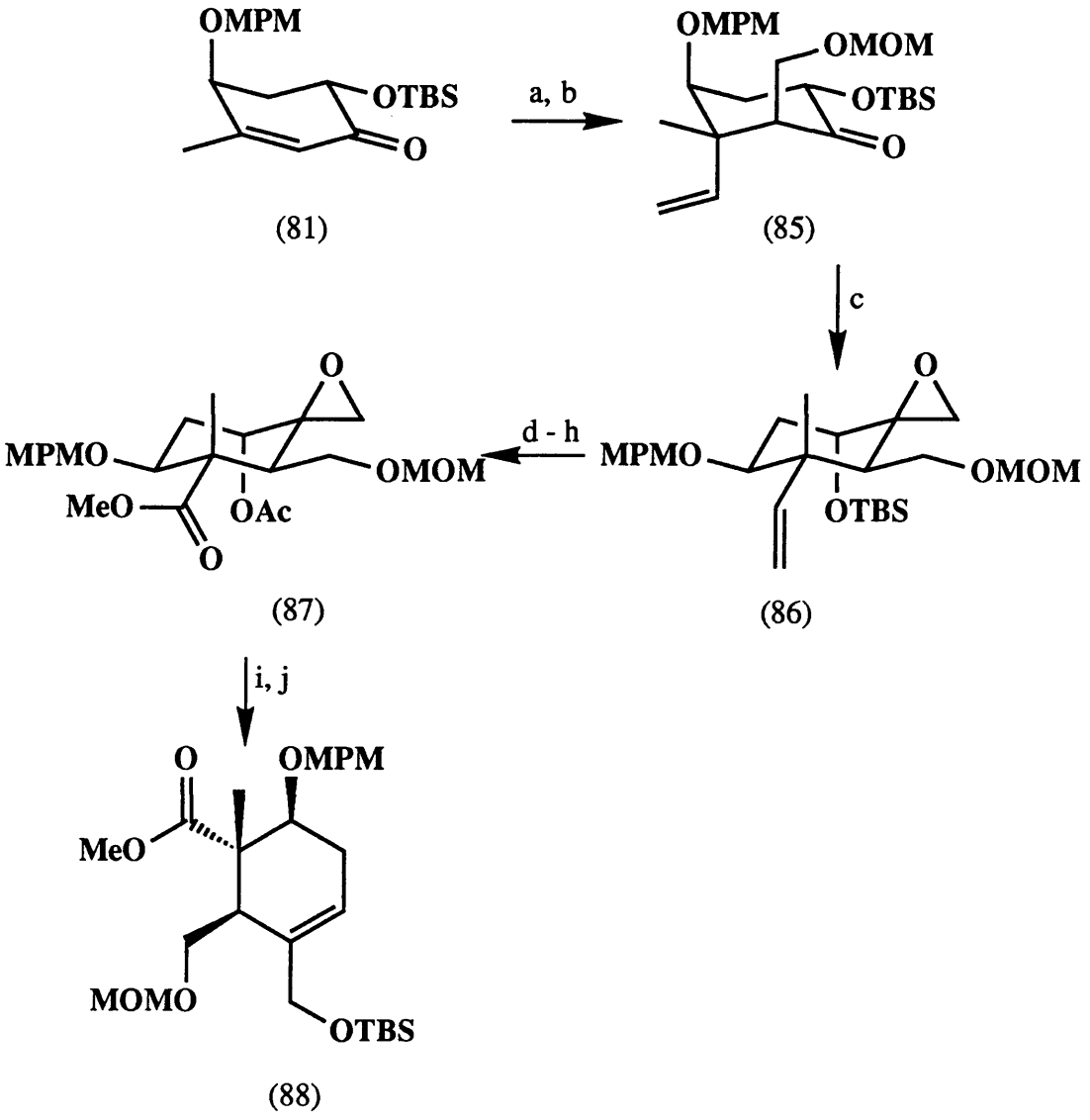
The A-ring synthesis was completed as illustrated in Scheme 13.



Scheme 13

a.) Me_2CuLi, TMSCl, Et_3N, HMPA / THF, -78°C; b.) PhSCl, Et_3N / CH_2Cl_2, RT; c.) Me_3SiCH_2MgCl, THF; d.) KH, THF.

The C-ring was constructed by introducing a vinyl group, (81) to (85), which could easily be converted to a carbonyl function (87) by ozonolysis (Scheme 14). An epoxide had earlier been installed using the Matteson epoxide synthesis (86), which would be subjected to a titanium catalysed isomerisation to yield the desired allylic alcohol. Protection of the alcohol completed the required C-ring (88).



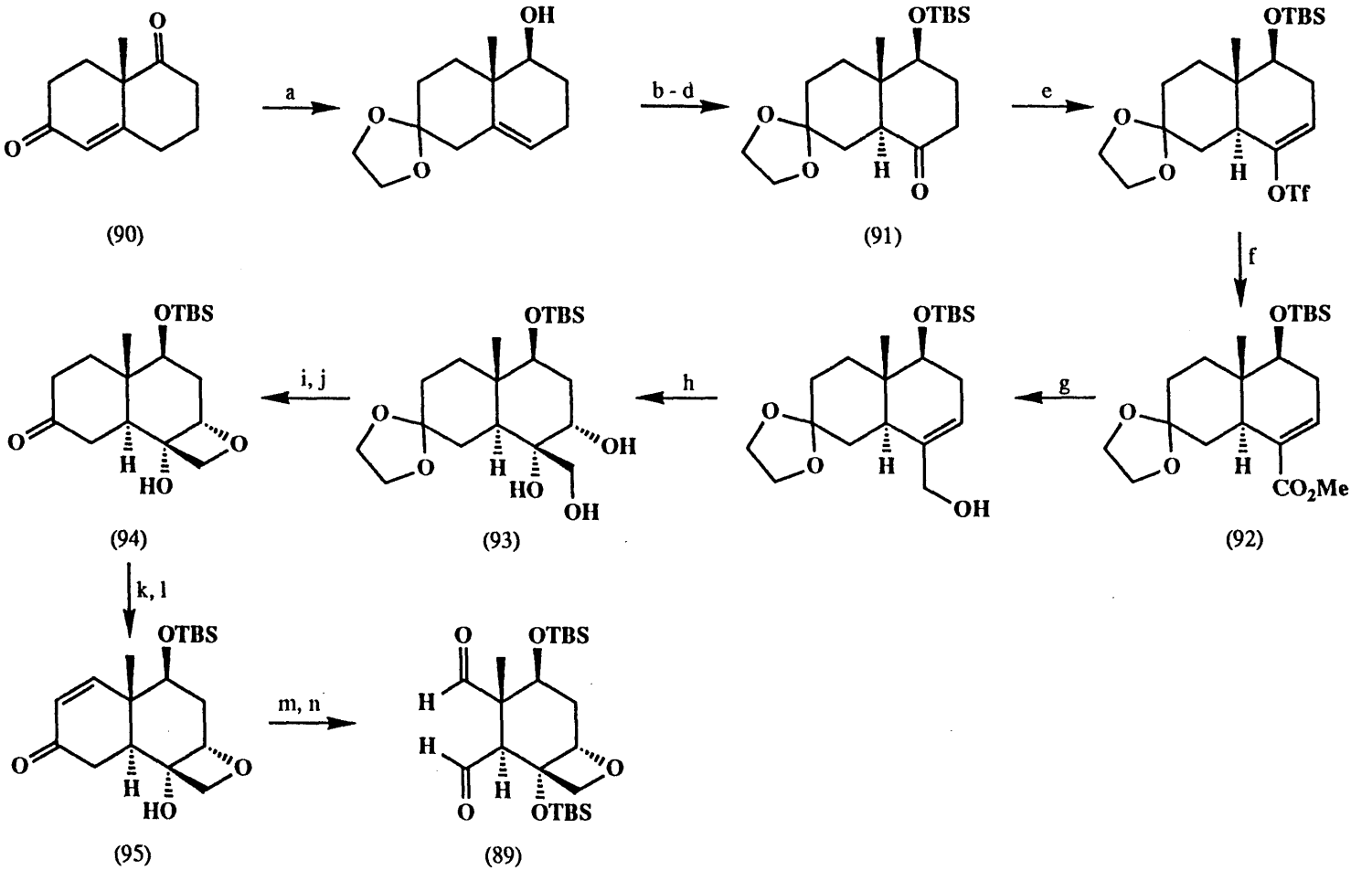
Scheme 14

a.) CH_2=CHCu(Me)(CN)Li_2, THF : Et_2O (1:3), -78°C - 0°C for 1h, then CH_2O, THF, -78°C, 0.5h; b.) MOMCl, (^iPr)$_2$NEt, RT, 12h; c.) ICH_2Cl, MeLi, THF, -78°C, 0.5h; d.) O_3, PPh_3; e.) $KMnO_4$, ^{t}BuOH, NaH_2PO_4 aq; f.) CH_2N_2; g.) Bu_4NF, THF; h.) Ac_2O, Et_3N, DMAP (cat); i.) Cp_2TiCl_2, Zn, THF, RT, 12h; j.) TBSCl, ImH, DMF.

Danishefsky.

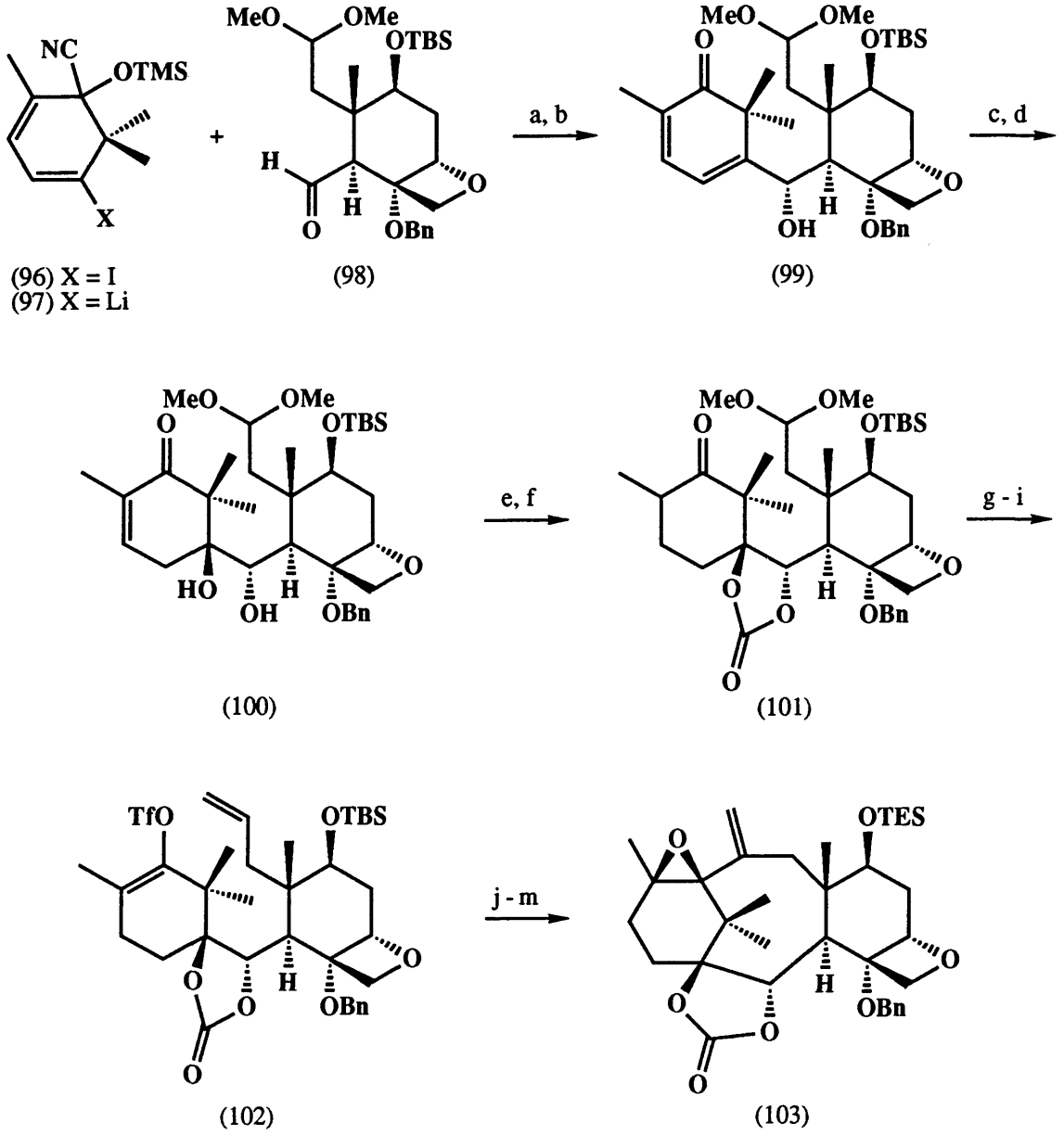
Danishefsky completed a synthesis of a functionalised CD ring (89) and pioneered the closure of the oxetane ring[25a], the strategy which was employed by Nicolaou[14] and Holton[19] in their full syntheses. Starting from the enantiomerically pure Wieland-Miescher ketone (90), (Scheme 15), the key steps involved a stereoselective hydroboration and oxidation to install a carbonyl function (91) using a route pioneered by Heathcock[25b], a carbonylation reaction mediated by palladium to achieve an ester (92) and an osmylation to yield the triol (93). Closure to the D-ring was carried out by silylation of the primary OH and conversion of the C-5 OH to a triflate, heating the product allowed desilylation and displacement of the triflate to cyclise the ring (94). Palladium acetate was used to convert the intermediate silyl enol ether to the α-β conjugated enone (95). Enolisation furnished a diene which on ozonolysis gave the final dialdehyde (89).

More recently the Danishefsky group has published the total synthesis of Taxol™ by building upon this work[25c,d]. Earlier work involved the assembly of a Cholesterol-Baccatin III hybrid[26] in which the C-ring of the baccatin is derived from one of the 6-membered rings of 5-Cholestan-3-one and the A-ring is derived from a dienyl iodide (96). This approach was used to couple the same A-ring, which was treated with BuLi to give the lithium anion (97), with a protected form (98) of the dialdehyde (89) (Scheme 16). Directed epoxidation and hydrogenation of the product (99) gave the diol (100). The diol (100) was protected as the carbonate and reduced to the ketone (101). Conversion to the vinyl triflate was followed by cleavage of the dimethylacetal group and lengthening of the chain by CH_2 using the Wittig reaction (102). The next step was the crucial closing of the B-ring. This was achieved using an intramolecular Heck vinylation reaction as employed in the synthesis of the Cholesterol-Baccatin III hybrid. To avoid later problems, the TBS protecting group was removed and the OH reprotected as a TES ether. To introduce functionality at C10, the C11-C12 double bond was converted to the



Scheme 15

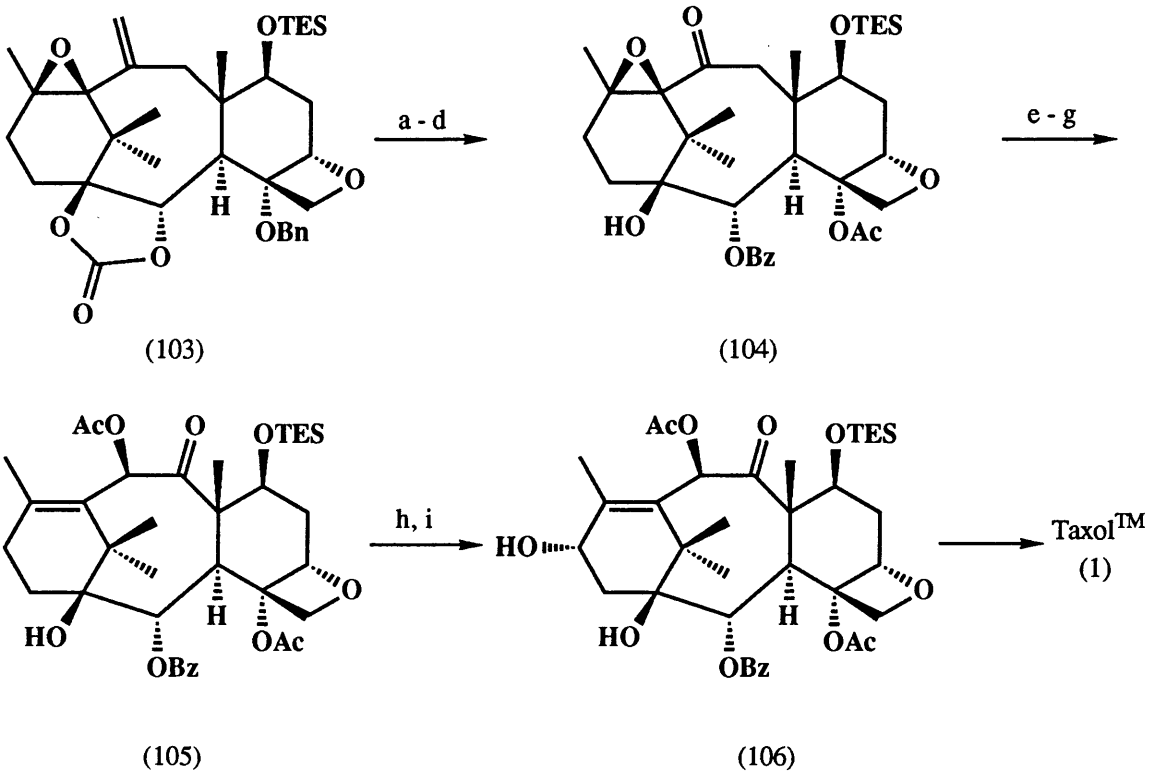
a.) Steps reference 25b; b.) TBSOTf, 2, 6-lutidine; c.) BH_3-THF, then H_2O, NaOH; d.) TPAP; e.) KHMDS, THF, -78°C, then $PhNTf_2$; f.) $Pd(OAc)_2$, PPh_3, CO, MeOH; g.) DIBAL, -78°C; h.) 5mol% OsO_4, NMMO; i.) TMSCl, py, -78°C then Tf_2O, -78°C to rt, then ethyleneglycol, 40°C, 12h; j.) collidinium tosylate, acetone, H_2O; k.) 2eq LDA, -78°C then TMSCl; l.) $Pd(OAc)_2$, then MeOH, K_2CO_3; m.) TBSCl, imid; n.) LDA, THF, -78°C then TMSCl then O_3, CH_2Cl_2, -78°C then PPh_3.



Scheme 16

a.) (96), ^{t}BuLi, THF, -78°C, then (98), 93%; b.) TBAF, THF, -78°C, 80%; c.) m-CPBA, CH_2Cl_2, rt, 80%; d.) H_2, Pd-C, -5°C, EtOH, 65%; e.) carbonyl diimidazole, NaH, DMF, 81%; f.) L-Selectride, THF, -78°C, 93%; g.) $PhNTf_2$, KHMDS, THF, -78oC, 98%; h.) PPTS, acetone, H_2O, 96%; i.) $Ph_3P{=}CH_2$, THF, -78 to 0°C, 77%; j.) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 4A molecular sieves, 90°C, 49%; k.) TBAF, THF, rt, 92%; l.) TESOTf, Et_3N, CH_2Cl_2, -78oC, 92%; m.) mCPBA, $NaHCO_3$, CH_2Cl_2, rt, 45%.

epoxide (103). The benzyl ether was exchanged for an acyl protecting group and treatment of the carbonate group with PhLi resulted in a benzoyl group at C2 (Scheme 17). Cleavage of exo-methylene group produced the ketone (104) and SmI_2 allowed deoxygenation of the oxirane. Functionality was introduced at C9 by oxidation to the ketone, the α-ketol was then subject to acylation which yielded (105). Allylic oxidation followed by reduction gave OH at C13 (106). Deprotection of the TES group gave Baccatin III (5) or Taxol™ (1) could be produced simply by following the Ojima route as described in the semi-synthesis.



(103) (104)

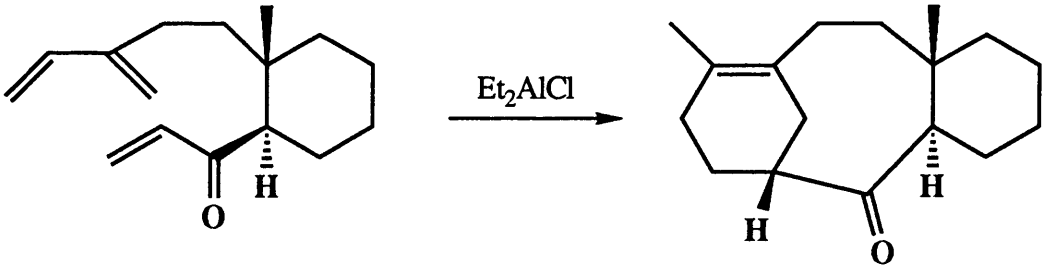
(105) (106)

Scheme 17

a.) H_2, Pd-C, EtOH, rt, 82%; b.) Ac_2O, DMAP, py, rt, 66%; c.) PhLi, THF, -78°C, 93%; d.) OsO_4, py, 105°C; $Pb(OAc)_4$, PhH, MeOH, 0°C, 61%; e.) SmI_2, Ac_2O, THF, -78°C, 92%; f.) KO^{t}Bu, $(PhSeO)_2O$, THF, -78°C; KO^{t}Bu, THF, -78$_o$C, 81%; g.) Ac_2O, DMAP, py, 76%; h.) PCC, NaOAc, PhH, reflux, 64%; i.) $NaBH_4$, MeOH, 79%.

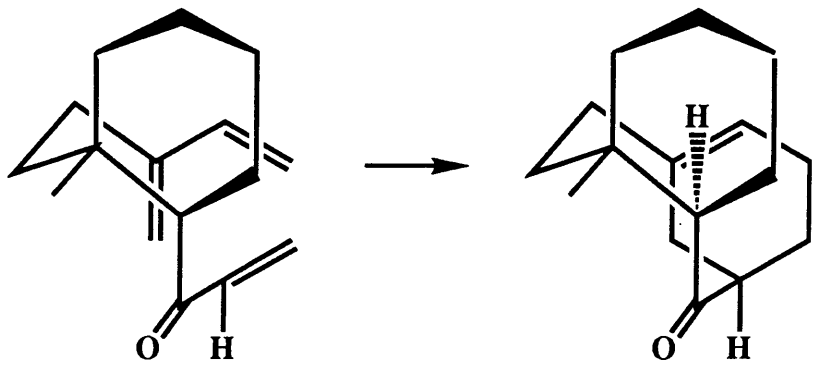
Jenkins.

The strategy employed by the Jenkins group is the construction of the ABC skeleton starting from the C-ring and performing a Diels-Alder cyclisation to simultaneously complete the A and B rings. A significant leap forward by Brown in 1986[27] saw the successful construction of the taxane skeleton (108) via such a Diels-Alder reaction in the presence of a Lewis acid.



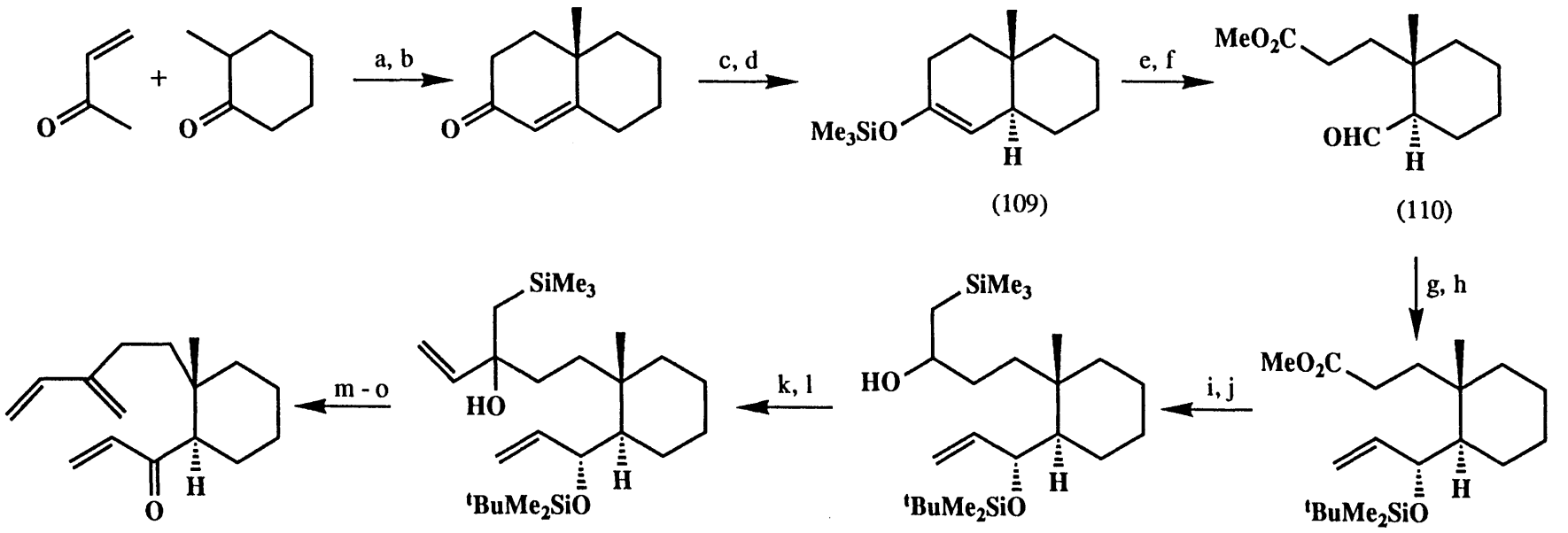
(107) (108)

A single isomer was obtained in 72% yield and X-ray crystallography proved the relative configuration at C-1 to be the same as that found in the taxane natural product Taxinine[27]. The explanation of this stereochemistry was that the Diels-Alder reaction occurs with the eight membered ring in a chair-boat conformation (107) leading to the product (108) (Figure 4). The boat-chair is presumably of lower energy than the alternative twist chair-boat.



(107) (108)

Figure 4



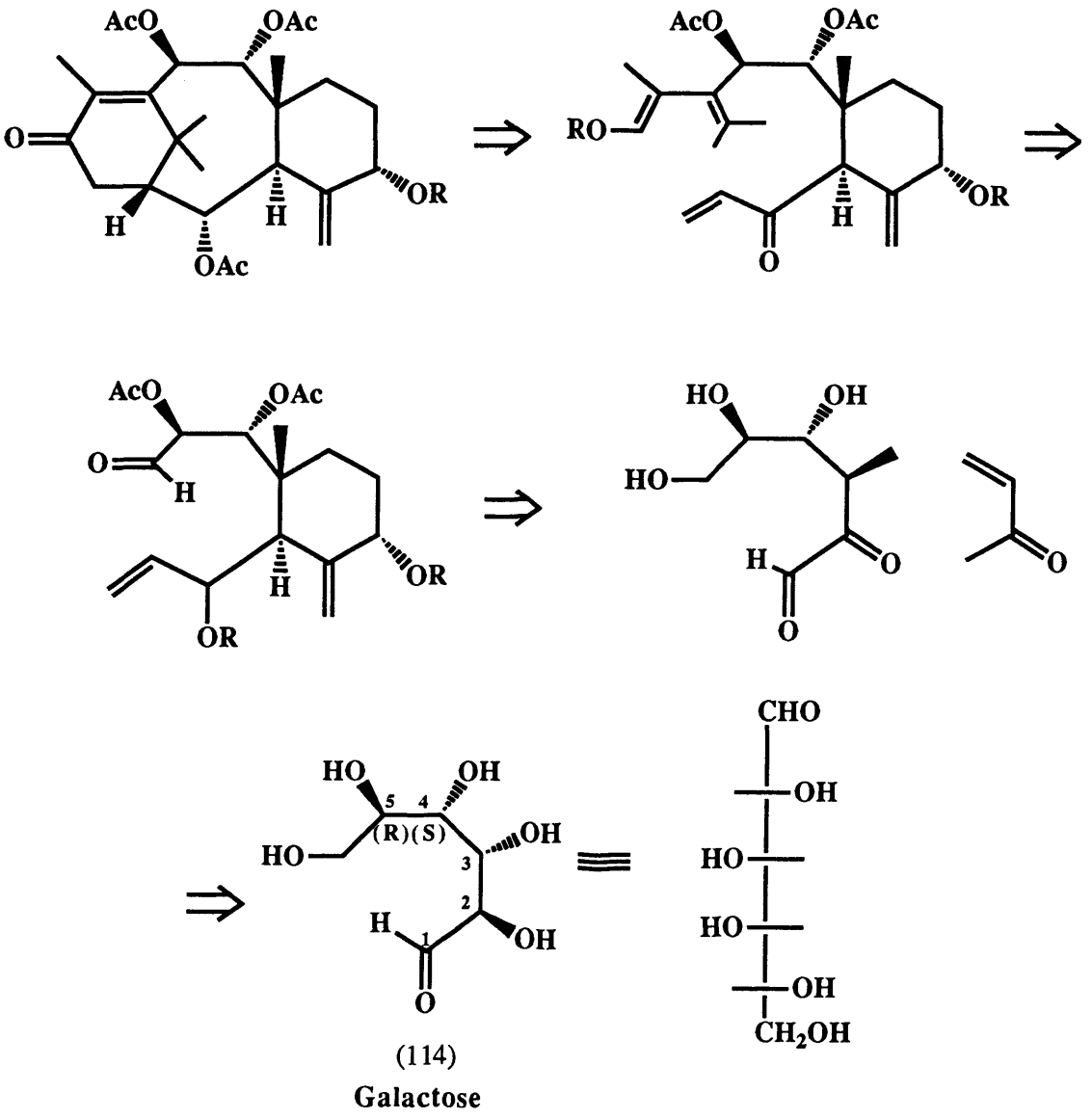
(107) (113) (112) (111) (109) (110)

Scheme 18

a.) NaOEt, -10°C, 12h; b.) KOH, H_2O, steam distillation; c.) 2.2eq Li, NH_3, THF, 15min, destroy xs Li, remove NH_3, cool to -10°C; d.) 2eq TMSCl, 2eq NH_3; e.) O_3, CH_2Cl_2, MeOH, Sudan Red III; f.) CH_2N_2; g.) 1eq CH_2=CHMgBr, THF, -78°C; h.) 1.5eq $^tBuMe_2SiOSO_2CF_3$, 2eq 2, 6-lutidine, CH_2Cl_2, rt; i.) 1eq DIBAH in hexane, PhMe, -78°C; j.) $TMSCH_2MgCl$, Et_2O, reflux, 1h; k.) 6eq CrO3, 12eq py, CH_2Cl_2, rt; l.) CH_2=CHMgBr, THF, rt, 1h; m.) MeCOOH, $MeCOONa.3H_2O$; n.) HF (15%), H_2O, MeCN, rt, 1.5h; o.) 6eq CrO3, 12eq py, CH_2Cl_2, rt, 5min.

The trienone (107) was prepared as illustrated in Scheme 18 making use of a Robinson annulation as the primary step. A regiospecific Li/NH_3 reduction of the double bond and protection as a TMS ether gave an intermediate (109), which upon ozonolysis followed by esterification gave the ester aldehyde (110). Treatment of the aldehyde with vinyl magnesium bromide furnished the dienophile portion, whilst the diene was constructed starting from the methyl ester. Reduction of the ester group to the aldehyde allowed addition of $TMSCH_2MgCl$ to give the β-hydroxysilane (112). This was oxidised to a ketone in order to introduce another double bond via vinyl magnesium bromide (113). A Peterson elimination then yielded the second double bond of the diene, leaving only desilylation and oxidation to reach the trienone (107).

The Diels-Alder was further extended to produce a more complex taxane skeleton with the vinyl methyl and gem dimethyl groups in place[28]. The diene portion was constructed on this occasion using selenium chemistry and the Diels-Alder was carried out in the presence of $BF_3.OEt_2$. The stereochemistry of the reaction was consistent with the cyclisation described above (Figure 3), again allowing the 8-membered ring in the transition state to adopt the chair-boat conformation. The next step was to introduce functionality into the rings. A retrosynthetic analysis (Scheme 19) suggested that a suitable starting material containing four chiral centres needed would be galactose (114). A Robinson annulation incorporating the 2 and 3 positions of the sugar would form the C-ring skeleton[30].

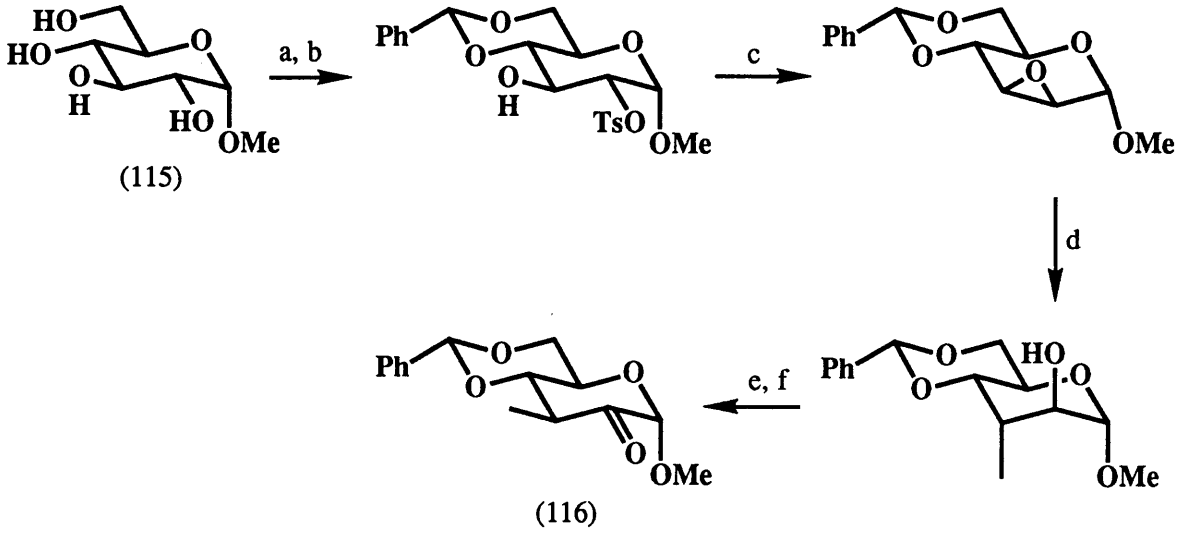


(114)

Galactose

Scheme 19

For practical reasons, the actual starting material used was methylglucopyranoside (115), this allowed us to synthesise the methyl ketone (116) illustrated using the methods pioneered by Sinay and Fraser-Reid[29] (Scheme 20).



(115)

(116)

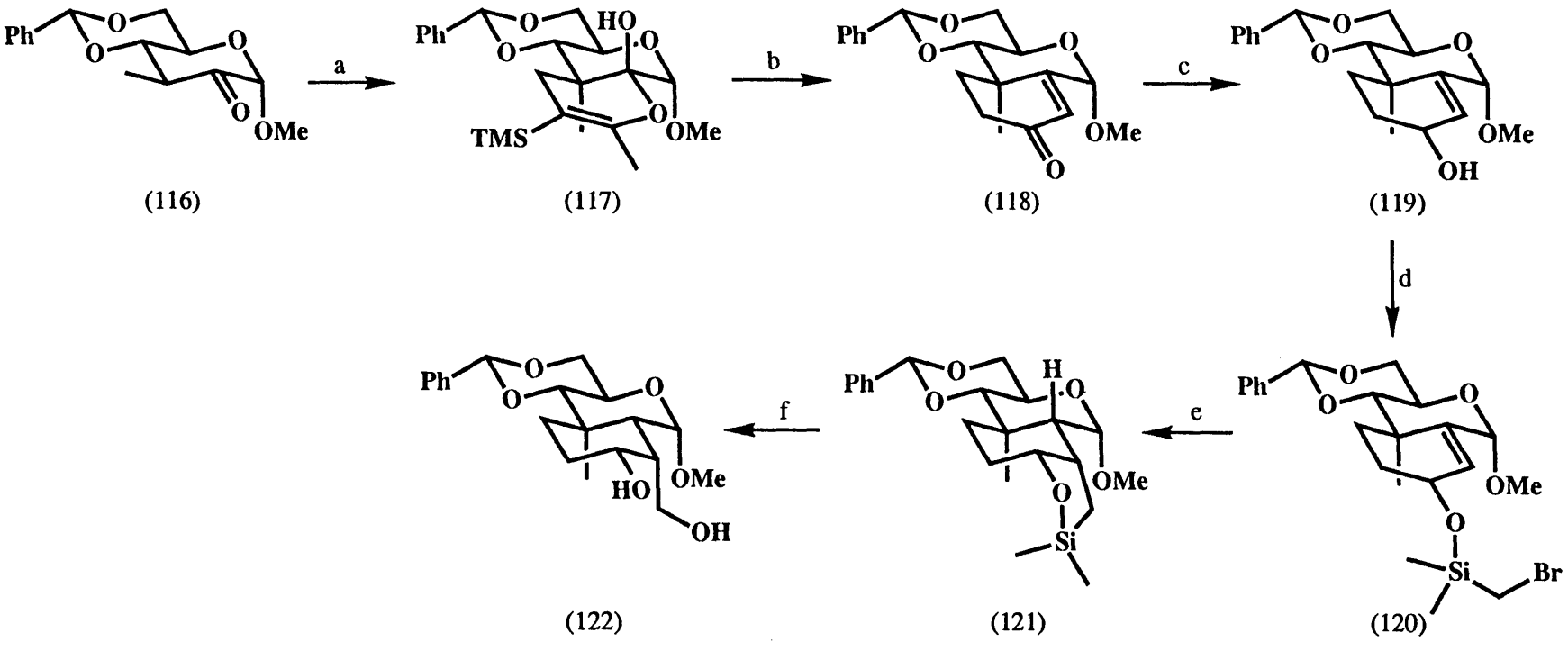
Scheme 20

a.) $PhCH(OMe)_2$, DMF, pTSA, reflux, 3h; b.) NEt_3, CH_2Cl_2, 0°C, then *p*-TsCl, 0°C to rt, 2h; c.) DMF, 0°C, NaH, 0°C to rt, 2h; d.) MeMgCl, THF, 0°C to reflux, 5h, H_2O; e.) TFAA, CH_2Cl_2, DMSO, -65°C, 1.5h, NE_{t3}, -65°C to rt; f.) DMF, NEt_3, rt, 72h.

Bonnert carried out a Robinson annulation on the carbohydrate derivative[30, 31] (Scheme 21). The enolate was reacted with 3-trimethylsilylbutenone at 0°C, an isolable intermediate was achieved (117), which on heating with KOH and MeOH gave the desired enone (118). A carbocyclic ring has been formed starting from a protected sugar, this ring will form the C-ring of our taxane skeleton. The structure was proved by nOe and an X-ray crystal structure of a later compound. These revealed that equatorial attack had occurred, which was opposite to when the enolate had been treated with deuterated iodomethane and axial attack was seen. The route was advanced by the reduction of the carbonyl using L-Selectride, this gave a 30 : 1 mixture of isomers with the equatorial OH being favoured. Further work was performed by Howarth[32], who converted the allylic alcohol (119) into an allylic (bromomethyl) silyl ether (120). Treatment of this with tributyltin chloride, sodium cyanoborohydride and AIBN generated tributyltin hydride "in situ", which removed the bromine to create a methylene radical, this was able to react with the underside of the p orbitals of the double bond and cyclise to a tetracyclic siloxane (121), this method had been pioneered by Stork[33]. *Trans* stereochemistry results

between the two 6-membered rings due to steric hindrance of the lower face to the approach of a hydrogen species and the 5-membered ring is cis-fused. Exposure to sodium carbonate and hydrogen peroxide in MeOH and THF produced a diol (122) (Scheme 21), the hydroxy and methylhydroxy of which would later be used to construct the oxetane D-ring.

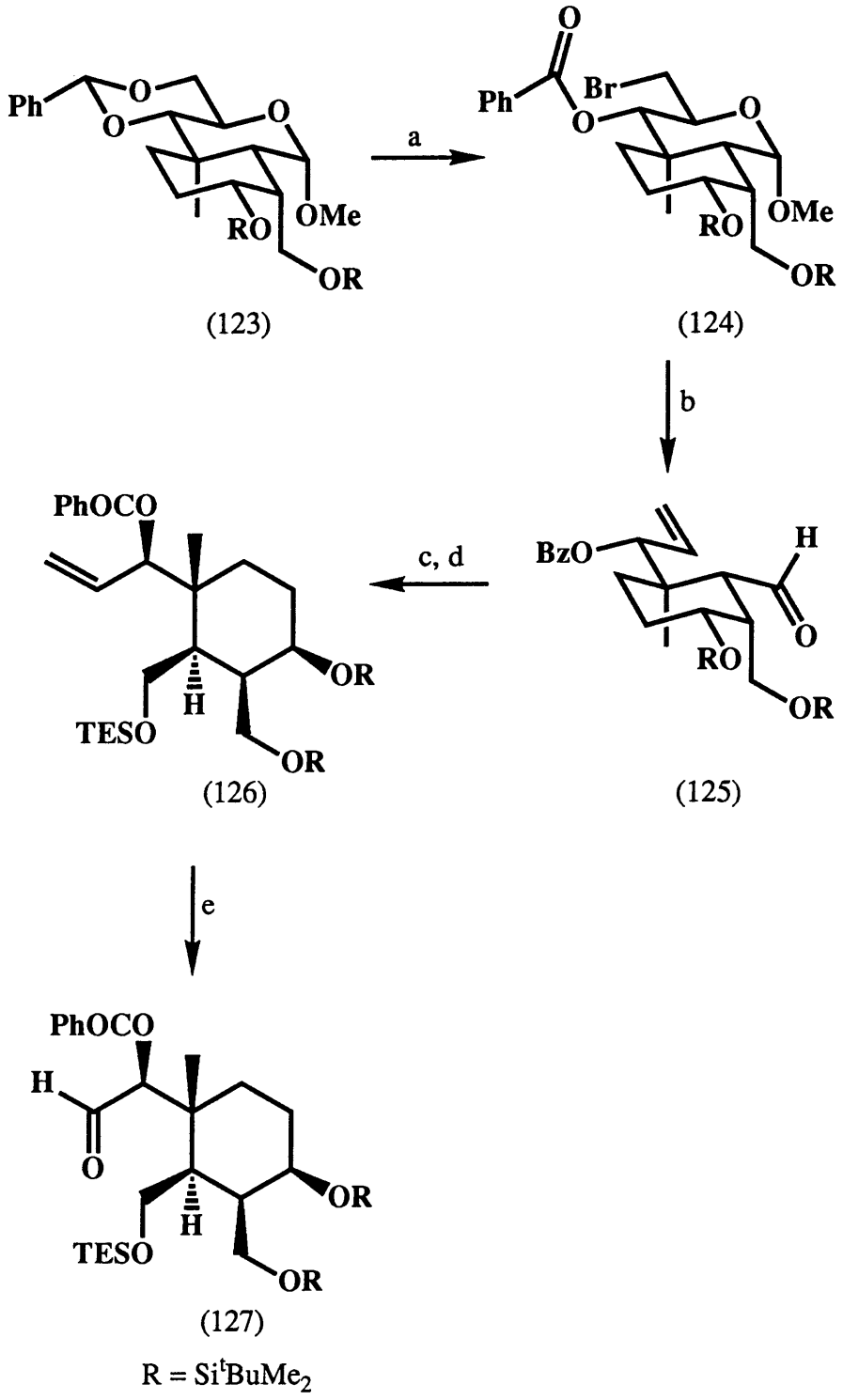
At this time, the hydroxyls were protected as diphenyltertiarybutylsilyl ethers (123), as they add bulk to the compound and are more stable than other silyl protecting groups such as TES or TBDMS (Scheme 22). The next step involved fragmentation of the benzylidene ring and after many unsuccessful attempts at hydrolysis, the solution was realised by Lawrence who used the Hanessian method[34]. Refluxing with $BaCO_3$ and NBS affected the fragmentation to give a benzoxy ester and a bromo methyl group (124). The second heterocyclic ring was opened by treatment with zinc in ^{i}PrOH, a method used by Vasella[35]. The lone pair on the zinc attacks the bromine to break the C-Br bond, simple arrow pushing can be followed to give the product (125) is achieved. Reduction of the aldehyde and protection using a TES group allowed the double bond of (126) to be cleaved by ozonolysis. We now have a highly functionalised carbocyclic C-ring[37] (127) with the stereocentres in the correct configurations and an aldehyde as a handle onto which we can introduce a diene portion.



(116) (117) (118) (119) (120) (121) (122)

Scheme 21

a.) N-lithio-2,2,6,6-tetramethylpiperidine, Et_2O, 0.5h, 0°C; 3-TMS-3-buten-2-one, 0°C, 2h; b.) 4% aq KOH, MeOH, 80°C, 6h; c.) L-Selectride, THF, -78°C, 1h; d.) $ClSiMe_2CH_2Br$, Et_3N, CH_2Cl_2, rt, 1.5h; e.) ^tBuOH, $NaBH_3CN$, Bu_3SnCl, AIBN, reflux, 3h; f.) THF, MeOH, Na_2CO_3, H_2O_2, reflux, 4h.



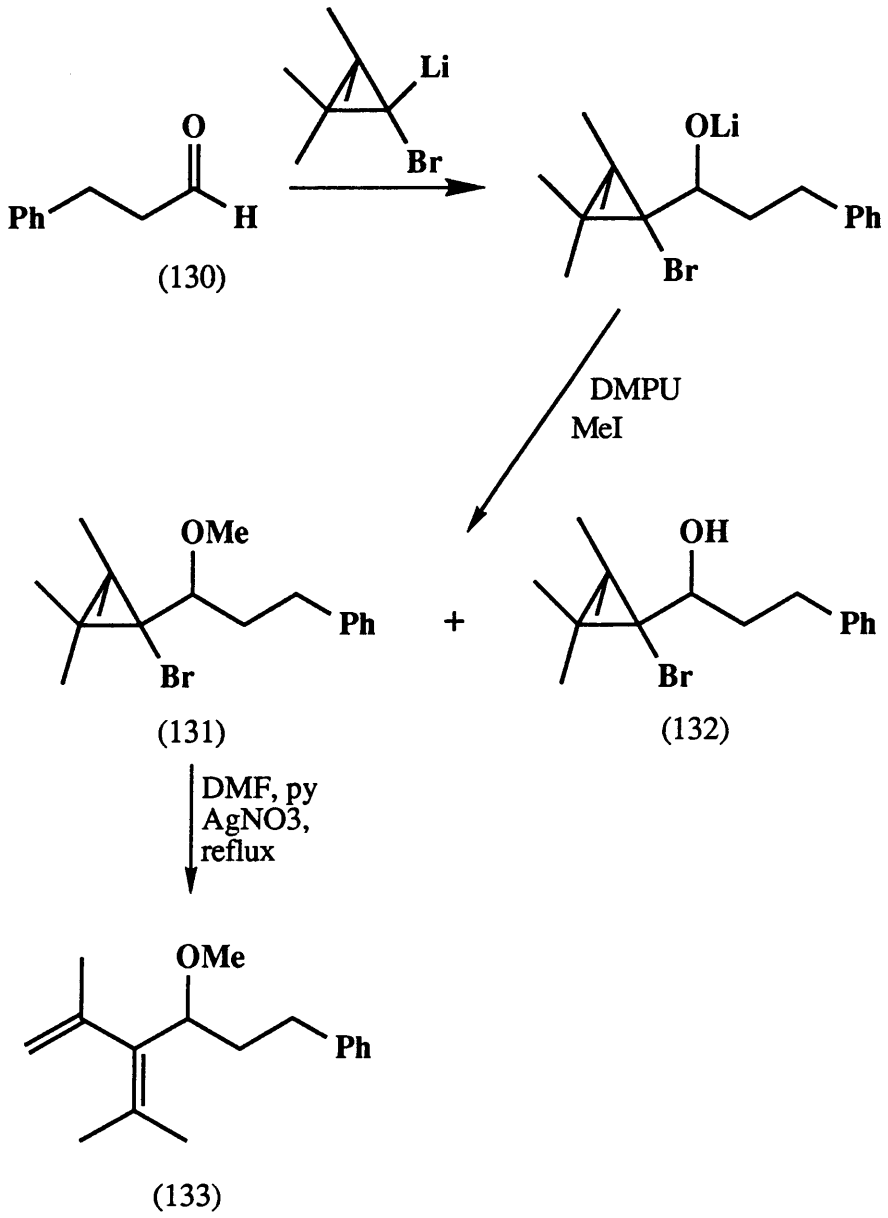
(123) (124) (125) (126) (127)

R = Si^tBuMe_2

Scheme 22

a.) NBS, $BaCO_3$, CCl_4, reflux, 3h; b.) Zn, ^iPrOH, reflux, 5h; c.) $NaBH_4$, ^iPrOH, 60°C, 15min; d.) Et_3SiCl, CH_2Cl_2, imidazole, RT, 15h; e.) O_3, CH_2Cl_2, MeOH, -78°C, then DMS.

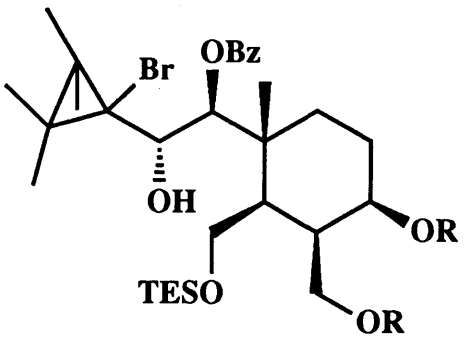
The earlier described methods of building up dienes[27, 28] cannot be used in this case as the side chain is one carbon short. Clark carried out investigations[36] to study the



(130) (131) (132) (133)

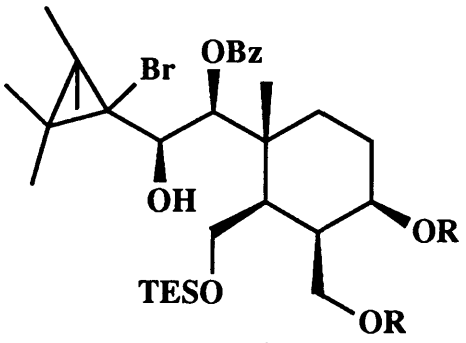
Scheme 23

However, addition of the cyclopropane to the C-ring aldehyde (127) was more difficult. The lithiated cyclopropane was treated with $CeCl_3$ to generate an organocerium species in an attempt to improve the addition reaction. It was hoped that an organocerium species would be more selective to aldehydes in the presence of esters. The two diastereomers (134a) and (134b) were achieved in 30% and 63% yields respectively[36].



Minor

(134a)

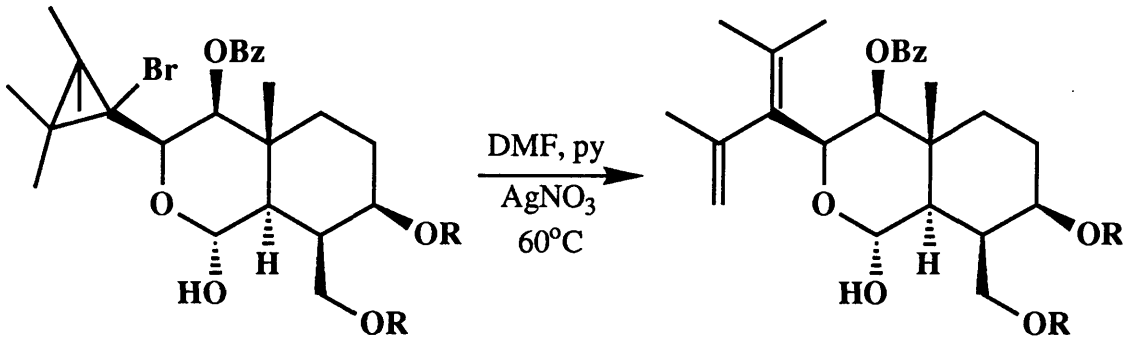


Major

(134b)

R = Si^tBuPh_2

Later it was discovered that this result was not reproducible and that on one occasion, microanalysis showed the major isomer contained chlorine rather than bromine and the minor isomer disappeared altogether. It was found that the adduct containing chlorine would not rearrange to the diene. The only bromo compound that Clark tried to rearrange was the lactol (135) and the reaction gave a quantitative yield of the desired diene (136).



(135)

R = Si^tBuMe_2

(136)

In order to achieve success in this approach, it appears that it would be necessary to find a reliable route to the bromo cyclopropane (134b). When the reaction was attempted with $CeBr_3$ instead of $CeCl_3$, no addition at all was seen.

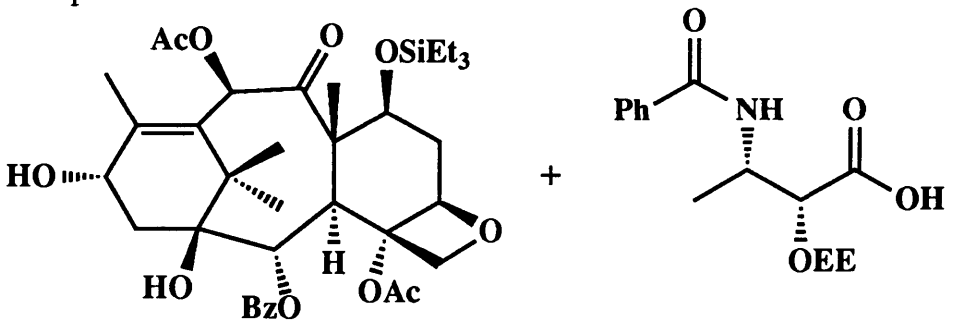
Semi-synthesis.

As these reviews of the total synthesis have shown, a commercial viable, large scale production is still far from being achieved, however, semi-synthesis has provided a short, efficient pathway that is used by Bristol-Myers-Squibb.

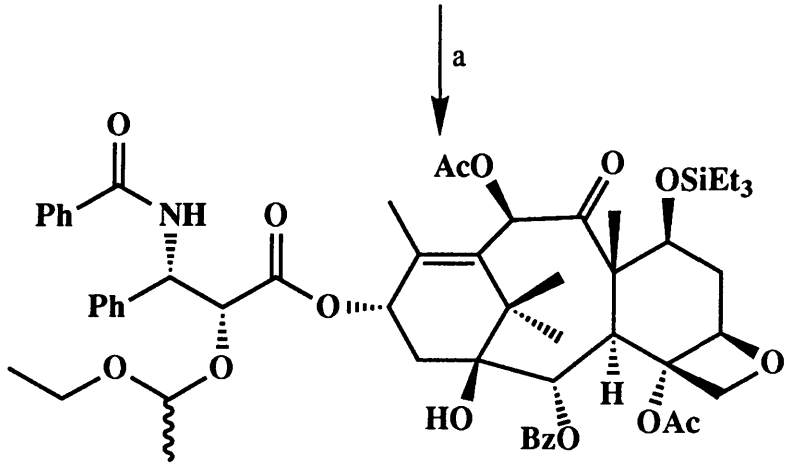
Semi-synthesis is the most viable method of manufacturing Taxol™ as 10-Deacetyl-baccatin III (5) can be isolated from the needles of *Taxus baccata* in a much higher yield than Taxol™ (1). The needles are a renewable source and therefore provide an abundance of 10-Deacetyl-baccatin III (5) which has the same structure as Taxol™ (1) but without the side-chain.

Potier and Greene.

These groups were the first to complete the semi-synthesis[38] by coupling the C-7 and C-10 protected baccatin (106) with a side chain equivalent (135) in the presence of DPC and DMAP (Scheme 24). The product (136) was converted to Taxol (1) in high yields upon acidic treatment.



(106) (135)



(136)

TAXOL

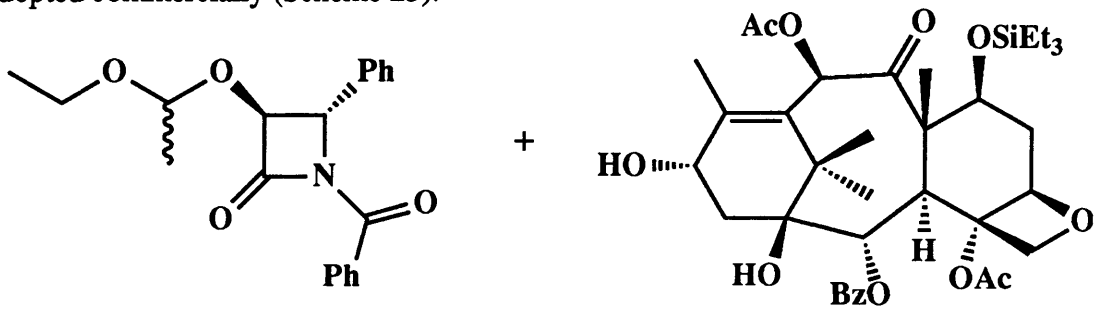
(1)

Scheme 24

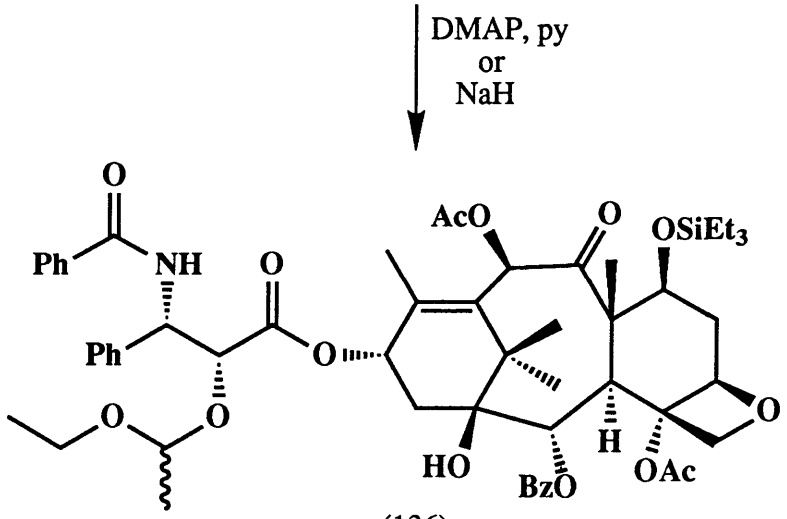
a.) DPC, DMAP, PhMe, 73°C, 100h; b.) 0.5% HCl, EtOH, H_2O, 0°C, 30h.

Holton and Ojima.

Holton[39] and Ojima[40] both achieved success in joining a protected derivative of Baccatin III (106) with an optically active β lactam (137). This procedure has been adopted commercially (Scheme 25).



(137) (106)



(136)

TAXOL

(1)

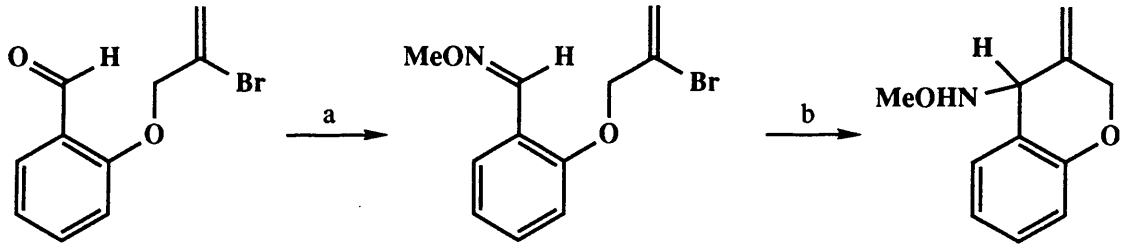
Scheme 25

Chapter 2

Proposed construction of the taxane skeleton using a radical cyclisation.

Radical Additions to Oxime Ethers.

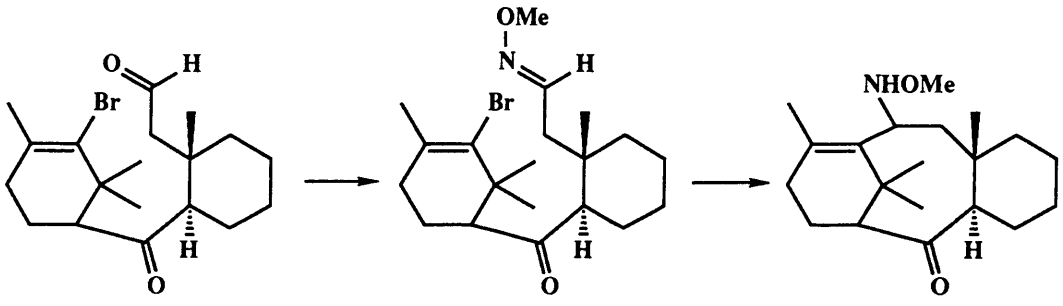
During the first twelve months of my research, a project was undertaken investigating a new approach to the construction of the taxane skeleton. In previous years, Booth had carried out investigations into intramolecular additions of vinyl and aryl radicals to oxime ethers. Five, six and seven membered bicyclic and tricyclic ring systems could be constructed from these reactions[41].



(138) (139) (140)

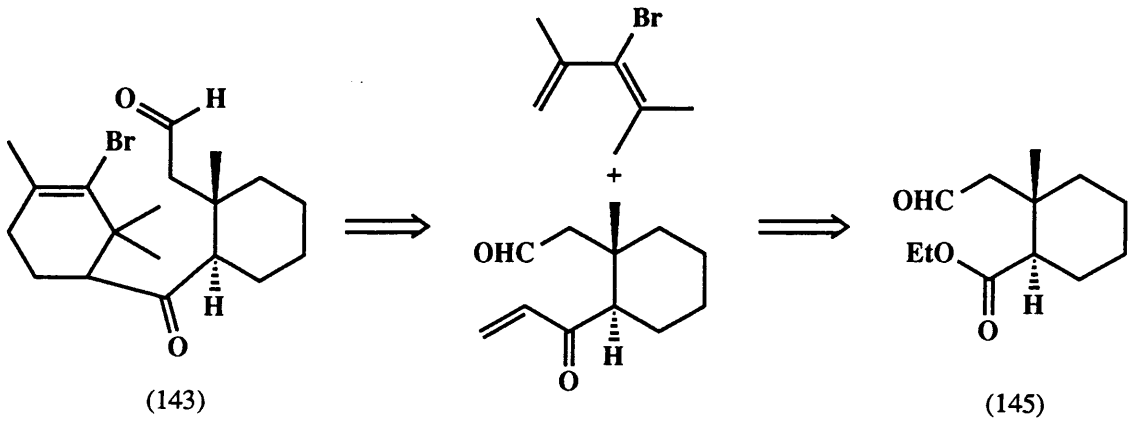
) $MeONH_2.HCl$, py, RT; b.) Bu_3SnH, AIBN, PhH, reflux.

Addition of a benzene solution of AIBN via a syringe pump to a solution of the oxime ether (139) and Bu_3SnH in benzene allowed cyclisation to the methoxyamine (140) in good yields. The efficiency of these reactions appears to lie in the high stability of the alkoxyl aminyl radical (R^1-O-N-R^2). One possible explanation is the stabilising effect of the aminyl radical by a lone pair on the adjacent oxygen due to the overlap of the sp^3 orbital and the p orbital containing the single electron and the electron donating properties of the oxygen lone pair.



(141) (142)

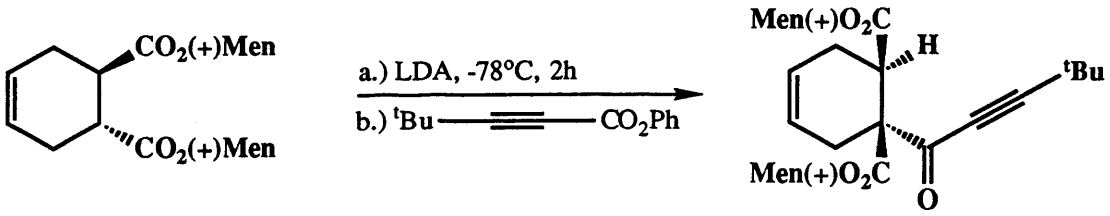
It was intended to construct the tricyclic taxane skeleton (142) from the oxime ether (141) using this method. An intramolecular cyclisation of a vinyl radical onto an oxime ether acceptor would be employed to complete the B-ring. Formation of seven membered rings had been achieved in modest yields[41b] and it was hoped to extend the method to the synthesis of an eight membered ring. This approach starts from the C ring synthon (145) to be the first to be prepared. Introduction of a vinyl group will create a dienophile (144), this could then enter into an intermolecular Diels-Alder cyclisation with the bromodiene to give the A ring (143).



(143) (144) (145)

Stereoselective alkylations of the C ring.

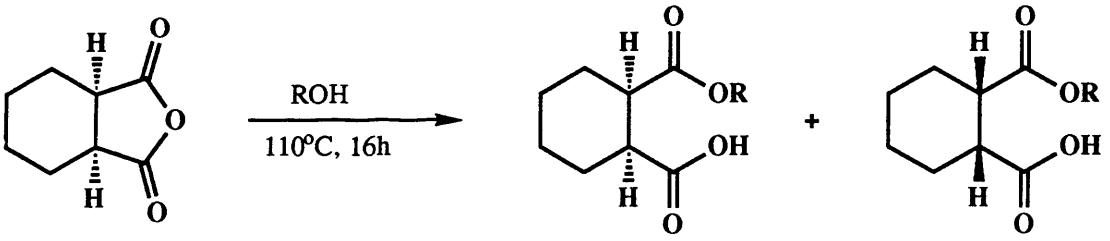
The first step towards the ABC skeleton was to synthesise a homochiral 1-methyl, cyclohexane-1,2-dicarbonyl derivative with the configuration of the quaternary carbon the same as the C-ring of the natural taxanes. The route we used involved alkylation of a cyclohexane-1,2-dicarboxylic acid, mono-ester[42]. The nearest published results were by E.J Corey and W.-g. Su[43] in which (R,R)-trans-4-cyclohexene-1,2-dicarboxylic acid, dimenthyl ester (146) was deprotonated using LDA and reacted with one equivalent of phenyl-3-^{t}butylpropiolate to yield a Claisen product (147).



(146) (147)

This reaction occurred stereospecifically from the least hindered face of the enolate to yield the cis diester product.

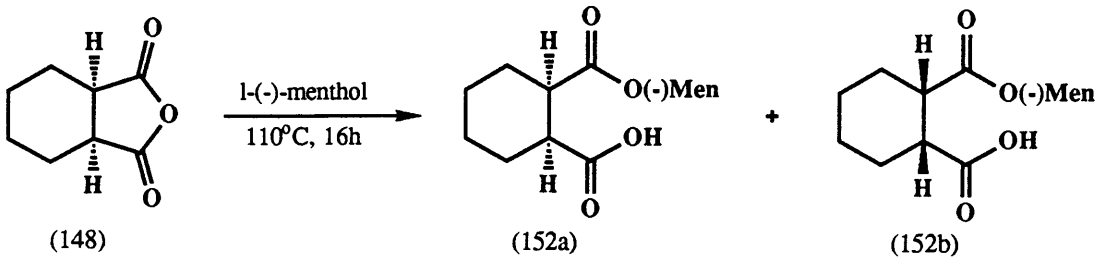
For our purposes the starting material used in the synthesis of a cyclohexane-1,2-dicarboxylic acid, mono-ester was *cis*-cyclohexane-1,2-dicarboxylic anhydride (148). Following a literature procedure[44], treatment with various alcohols, at high temperatures in a sealed vial, opened the anhydride ring to yield the corresponding acid-esters (149-151). The symmetrical anhydride afforded racemic products (149-151 a and b) in each case, as the lone pair of the alcohol oxygen can attack equally at either carbonyl group.



(149a)	R = $CH_3(CH_2)_7$-	(149b)
(150a)	R = $PhCH_2$-	(150b)
(151a)	R = Me-	(151b)

The octyl (149) and benzyl[45] (150) esters were both isolated as oils and the methyl ester[46] (151) was obtained as a powdery solid which would not crystallise. It was surmised that treatment of the cyclic anhydride with a single enantiomer of menthol would furnish two diastereoisomers (152a and b), rather than enantiomers and thus allow separation. The solid anhydride (148) and l-(-)-menthol were melted together in a sealed tube and heated at 110°C overnight, the crude product was obtained as a colourless brittle solid on cooling. The ratio of diastereoisomers was measured from the ^1H NMR of the menthyl, methyl diester, prepared by treatment of the crude product (152) with diazomethane. This was found to be 2.39 : 1 by measuring the integrations of the two

separate methoxy peaks, which were well separated using highfield NMR. Six recrystallisations from petroleum ether followed by methylation gave a product in 6% overall yield with a single methoxy signal in the ^1H NMR. The absolute configuration of the chiral centres in the enantiomerically pure compound (152a) was determined from an X-ray crystal analysis and shown to be the 1(R), 2(S) isomer.



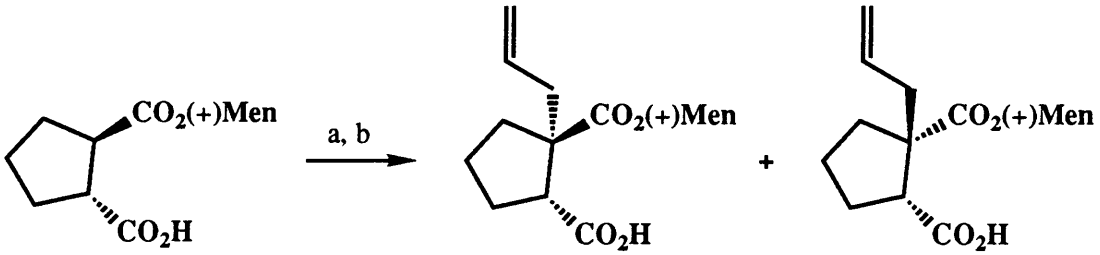
(148) (152a) (152b)

2.39 : 1

6 recrystallisations

>100 : 1

The next step was to stereospecifically introduce an alkyl group at the C-1 position. It was found in the literature that Yamada et al[47] had reported the contrasteric alkylation of a cyclopentane-1,2-dicarboxylic acid, mono-(+)-menthyl ester (153) to give the acid esters (154) and (155).



(153) (154) contrasteric alkylation (155) normal alkylation

) LDA, THF, -25°C, 1h; b.) CH_2=$CHCH_2Cl$, -25 to +25°C, 3.7h, 96%.

The starting material was prepared by the partial hydrolysis of dimenthyl (1R, 2R) cyclopentane-1,2-dicarboxylate. This had been synthesised from the direct coupling of dimenthyl succinate with 1,3-dibromopropane according to the Yamamoto[48] procedure. The ester enolate was generated using LDA and alkylation with allyl chloride afforded a 4.9 : 1 mixture of diastereoisomeric esters[47a], the predominant isomer (154) being as a

result of attack from the most sterically hindered face of the enolate. This was described as contrasteric alkylation. Yamada investigated the stereochemical outcome of further alkylations in which various methallyl halides, allyl halides and allyl tosylates were used. It was discovered that reactions with methallyl and allyl tosylates or chlorides proceeded to give largely the contrasteric isomer, whereas treatment with the bromides and allyl iodide yielded predominantly normal alkylation products. The formation of contrasteric products increased with the hardness of the leaving group in the alkylating reagent, the order being OTs > Cl > Br > I. This pattern is in accordance with the ability of the leaving groups to complex to a lithium cation. Chlorine and tosylate are hard leaving groups which co-ordinate tightly to the lithium counter-ion of the carboxylate group next to the enolate. This strong association causes the alkylation from the same side as the carboxylate group to occur to a larger degree (Figure 1).

With bromine and iodine, the co-ordination is weaker and attack will prefer to occur trans to the carboxylate on steric grounds. The introduction of the cation-complexing agent HMPA into the reaction mixture interfered with the association of the halide to the lithium counter-ion and subsequently reduced the amount of contrasteric alkylation in all cases. Further evidence to support these theories was provided by treating the sodium and potassium enolates with various allyl halides. The proportion of contrasteric attack was reduced each time, due to the Na and K cations having a lower affinity for halide ions.

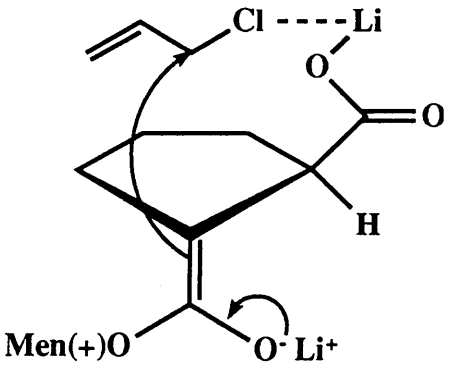
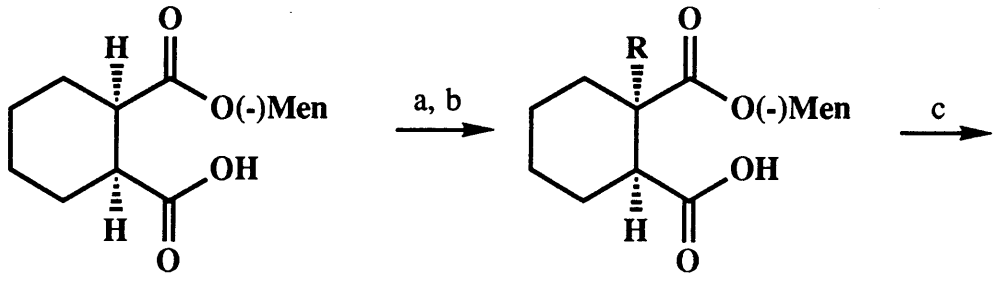


Figure 1

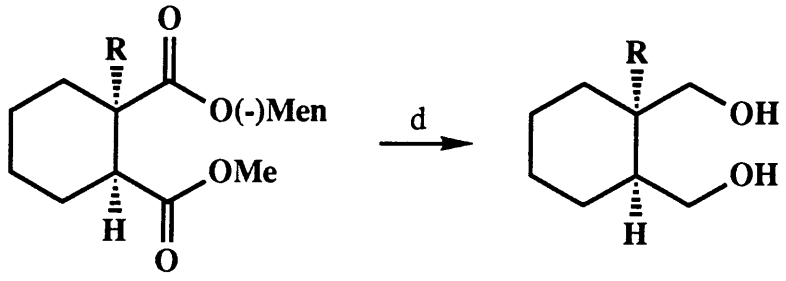
Similar studies were performed on the cyclohexane derivative using a variety of alkylating reagents[42]. 1(R), 2(S)-Cyclohexane-1,2-dicarboxylic acid, 1-menthyl ester

(152a) was exposed to 2.4 equivalents of freshly prepared LDA[49]. One equivalent deprotonated the carboxylic acid group and the second removed the proton adjacent to the ester function to generate the ester enolate. Treatment with different electrophiles at -25°C resulted in a mixture of diastereoisomers in all cases. The reaction times varied between 2 and 72 hours depending on the reagent used. Yields of 37-75% were achieved and no unreacted starting material was seen. The results are summarised in table 1. In the reaction scheme only the major isomer is shown, it is assumed that the configurations of (156a,c-f) are analogous to (156b), the structure of which was proved by X-ray crystallography (Figure 2).



(152a)

(156a) R = Me
(156b) R = Bn
(156c) R = $CH_2CH{=}CH_2$
(156d) R = $CH_2CH{=}CH_2$
(156e) R = $CH_2CH{=}CMe_2$
(156f) R = $CH_2CH{=}CHPh$

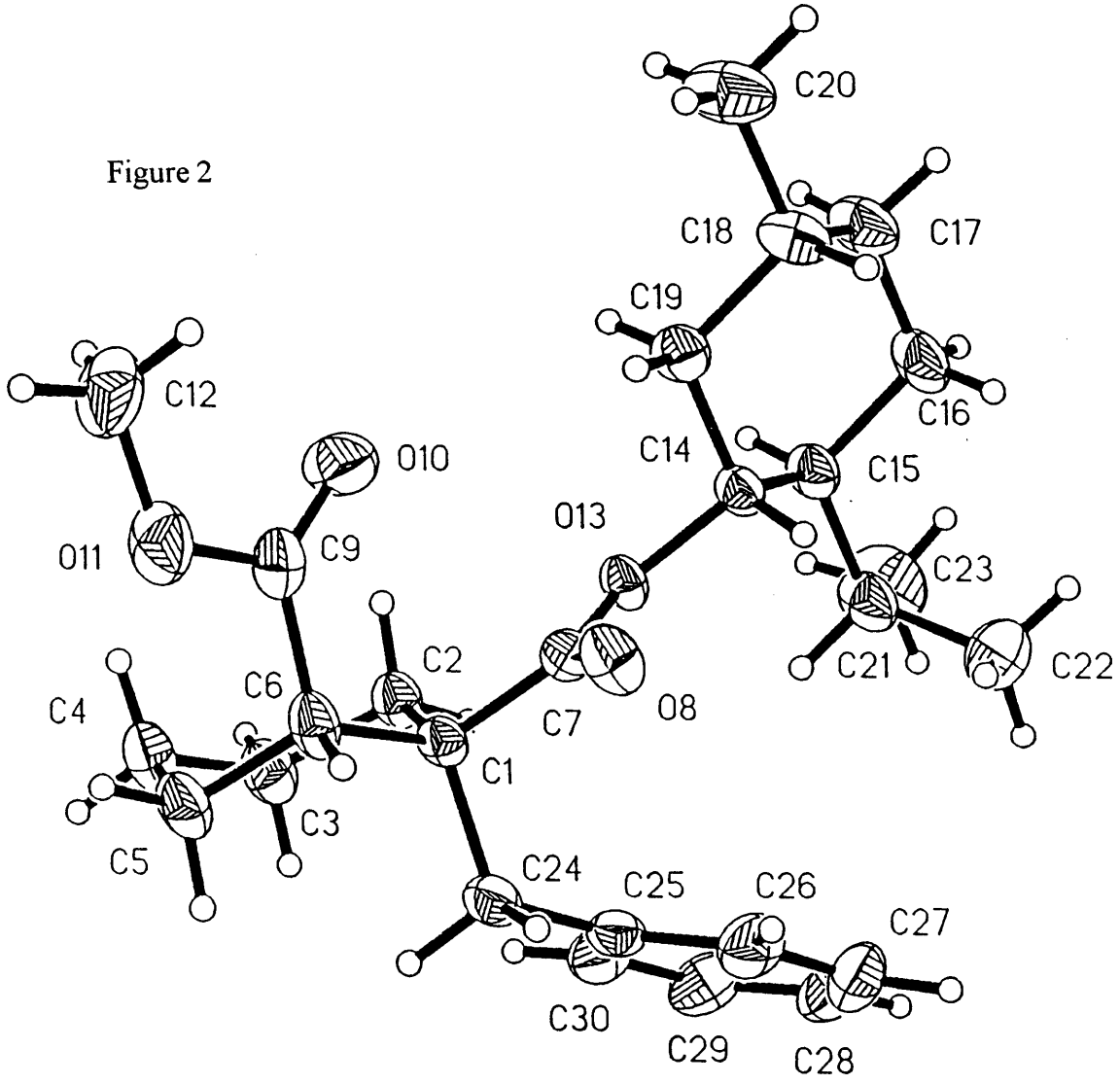


(157a-f)

(158a-f)

) LDA, THF, -25°C, 0.5h; b.) RX see Table 1; c.) CH_2N_2, Et_2O, 0°C, 0.5h, 93-100%; d.) 1M $LiAlH_4$ in THF, 25°C, 1h, 74-91%.

Figure 2


C20
C18
C17
C19
C12
C16
O10
C14
C15
O13
O11
C9
C23
C2
C21
C22
C6
C4
C7
O8
C1
C3
C5
C24
C25
C26
C27
C30
C29
C28

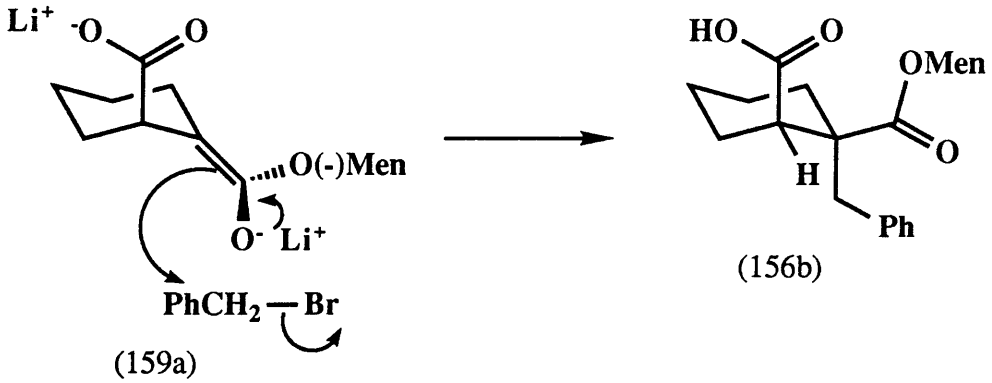
Product	Electrophile	Time (h)	Temp (°C)	Yield (%) Crude acid	Yield (%) Crude diester	Diastereoisomer ratio GC	NMR
(130a)	MeI	2	-25	91	91	11.1:1	10.7:1
(130b)	BnBr	16	-25	>100	94	7.2:1	7.6:1
(130c)	CH_2=$CHCH_2Br$	16	-25	>100	85	26.8:1	27.9:1
(130d)	CH_2=$CHCH_2Cl$	5	-25 to +25	93	80	13.2:1	13.7:1
(130e)	Me_2C=$CHCH_2Br$	16	-25	93	89	-	13.4:1
(130f)	PhCH=$CHCH_2Br$	72	-25 to +25	>100	100	-	32.5:1

Table 1

Each crude product was converted quantitatively to the methyl ester by reaction with diazomethane via a 1,3 dipolar cycloaddition. The diastereoisomer ratio was measured from the methoxy signal in the ^1H NMR spectrum of the crude methyl esters (157a-f). There were two clearly separate methoxy peaks in the highfield NMR which were integrated accurately. Measurements taken by GC of the diesters (157a - 157d) were in good agreement to the ^1H NMR results. The products (157e) and (157f) were not volatile enough to allow GC readings.

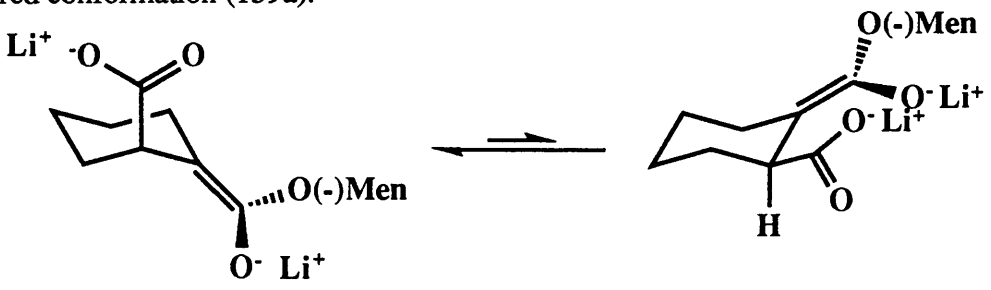
The results show alkylations with selectivities ranging from 7:1 for (157a) to 32:1 for (157f). Compound (157b) made by attack of the enolate on benzyl bromide and further reaction with CH_2N_2 was isolated as a yellow solid. This was recrystallised from EtOH to yield white crystals. Proton NMR showed that the signals for the minor isomer were no longer visible. This diastereomerically and enantiomerically pure sample was sent for X-ray analysis (Figure 2). As the configuration of the (-)-menthyl group was known, it was possible to determine the absolute configuration of chiral centres at positions 1 and 2.

Alkylation at the C-1 position has created a centre with the S configuration and that at C-2 has been unaffected by the reaction. Interestingly, both the methyl ester and the benzyl group are axial with the menthyl ester equatorial. A suggestion for the mechanism of alkylation is shown by axial attack from the least hindered face of the enolate dianion (159a) leading to the acid (156b) after protonation, the structure of (156b) being consistent with the X-ray analysis of the methyl ester (157b).



(159a) (156b)

This conformation of the dianion (159a) is favoured over the alternative flipped chair (159b) due to a factor called A-strain between the equatorial acid anion and the ester enolate. We would therefore expect the equilibrium to be on the side of the sterically less hindered conformation (159a).

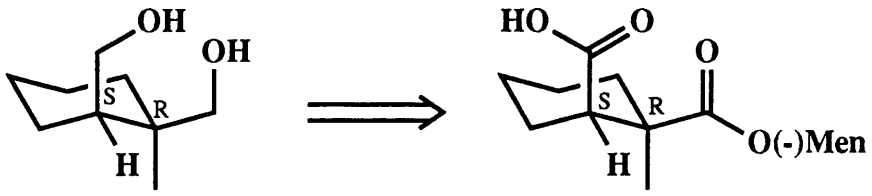


(159a) (159b)

From the mechanism of attack on BnBr, it can be noted that normal alkylation is predominant, that is the enolate attacks from the less sterically hindered face. The preference for axial attack in the preferred conformation (159a) seems to be the most important factor and all the alkylations occur in an axial fashion on the opposite face to the axial acid anion. There is little evidence of the contrasteric alkylation observed in the cyclopentane examples of Yamada[47]. The explanation of this may be that the more flexible conformation of the five-membered ring allows the weak association shown in Figure 1 to become more important than the simple steric preference of conformation (159a). However, comparison of the reaction of enolate with allyl bromide and allyl chloride, showed that although in both cases, (156c) and (156d), normal alkylation was prevalent, the proportion of normal attack was seen to decrease from 26.8:1 to 13.2:1 on changing the leaving group from Br to Cl. This suggests that Yamada's theories[47] may have correct and that a small amount of tethering of the carboxylate to the allyl chloride could still be occurring, however, it should also be noted that reaction with allyl bromide was performed at -25°C, but the reaction with allyl chloride was started at -25°C and allowed to warm to +25°C and it may be this temperature difference which is effecting the ratios.

The acid esters (156a-f) were reduced to the substituted 1,2-bismethanol derivatives[50] (158a-f) in quantitative yields. Both 1(R),2(S)-1-methyl (cis)-1,2-bishydroxymethylcyclohexane, $[\alpha]_D$= +23.4° and 1(S),2(S)-1-methyl (trans)-1,2-

bishydroxymethylcyclohexane, $[\alpha]_D$= +1.2° are known. The observed rotation of the crude diol (158a) is $[\alpha]_D$= +21.4°, which is consistent with an 11:1 mixture of cis and trans diols respectively. The major (*cis*) isomer is illustrated, this provides further proof that the major attack has occurred from the face opposite the carboxylate.

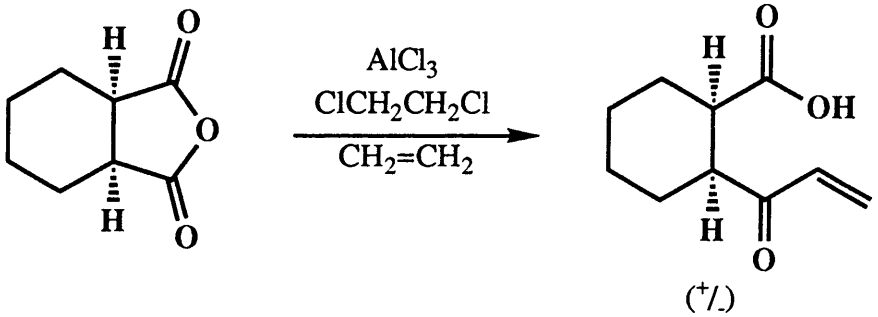


(158a) (156a)

The configuration of the quaternary centre is therefore the same as the C-8 position in taxinine and other taxane natural products. However, epimerisation of the carbon bearing the methyl ester will be necessary to equate to the C-3 position.

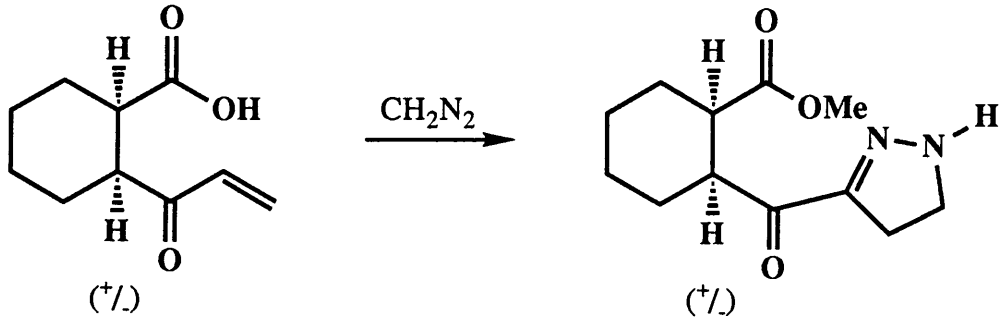
Synthesis of the dienophile.

The next step required a vinyl group to be coupled to the methyl ester to create a dienophile. Preliminary investigations were carried out on cis-cyclohexane-1,2-dicarboxylic anhydride (148). It was attempted to open the cyclic anhydride using vinylmagnesium bromide, but this was unsuccessful. A literature procedure[51] showed that enone (160) could be prepared by adding the anhydride to a suspension of anhydrous $AlCl_3$ in dichloroethane and bubbling in ethylene for 4.5 hours. The reaction is an electrophilic substitution on ethylene.



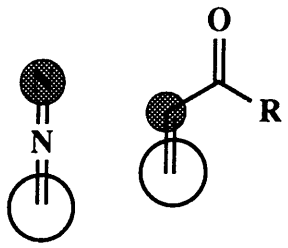
(148) (160)

It was imperative that the anhydrous $AlCl_3$ is of good quality and that dry solvents were used. $AlCl_3$ produces $Al(OH)_3$ on exposure to moisture and this would react with the anhydride to produce only cis-cyclohexane-1,2-dicarboxylic acid. The $AlCl_3$ acts as a Lewis acid to increase the polarity of the C=O bond, the Π electrons of the ethylene can then attack the carbonyl carbon. The product was obtained in modest yield (58%) as a yellow oil which could be crystallised from Et_2O-hexane to give a white crystalline solid of melting point 90-93°C. This compound decomposes rapidly unless it is stored at fairly low temperatures, therefore it was attempted to create a more stable derivative by converting the acid group into a methyl ester. However, this reaction was accompanied by a regioselective 1,3-dipolar cycloaddition of the double bond with excess CH_2N_2 to yield compound (161).



(160) (161)

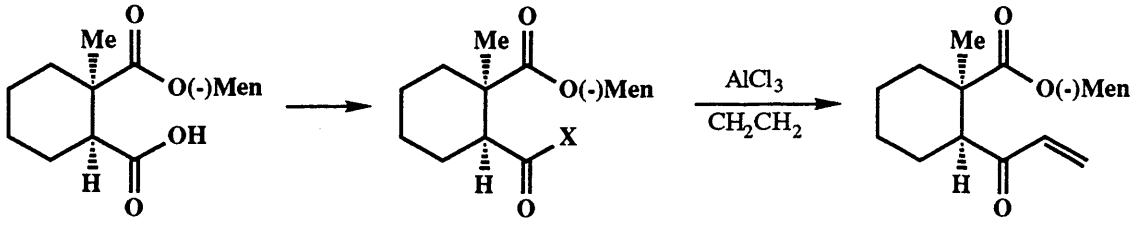
The regiochemistry can be explained using the Frontier Orbital Theory[52]. The smallest energy separation is for the reaction between the HOMO of diazomethane and the LUMO of the conjugated olefin (160). The coefficients show that the orientation will be that of the carbon end of the dipole bonded to the β-carbon of the α,β unsaturated ketone (Figure 2).



HOMO LUMO

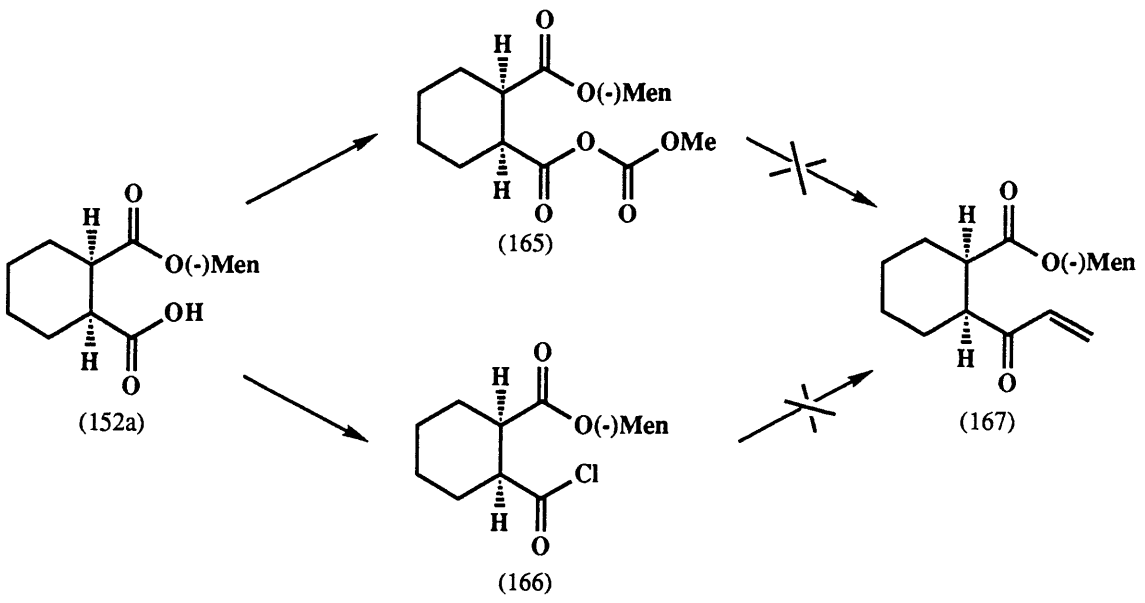
Figure 2.

It was hoped that conversion of the carboxylic acid group of 1-methyl cyclohexane-1,2-dicarboxylic acid, 1-menthyl ester (156a) into an acid chloride (162) or an anhydride (163) followed by treatment with $AlCl_3$ and ethylene would allow the Friedel-Crafts reaction to an enone (164).



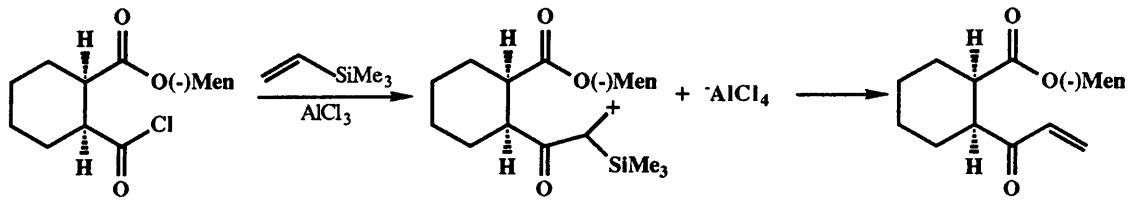
(156a) (162) X = Cl (163) X = OCO_2Me (164)

Investigations were initially carried out on the commercially available, enantiomerically pure cyclohexane-1,2-dicarboxylic acid, mono-menthyl ester (152a). A mixed anhydride (165) was synthesised by reaction of the acid-ester with $ClCO_2Me$ in the presence of di-isopropylethylamine in quantitative yield[53]. The acid chloride (166) was furnished in a modest yield of 59% by treatment of the acid moiety with oxalyl chloride and DMF. Several attempts of the reaction of both the mixed anhydride (165) and the acid chloride (166) with ethylene and $AlCl_3$ failed and only the acid-ester (152a) was recovered.



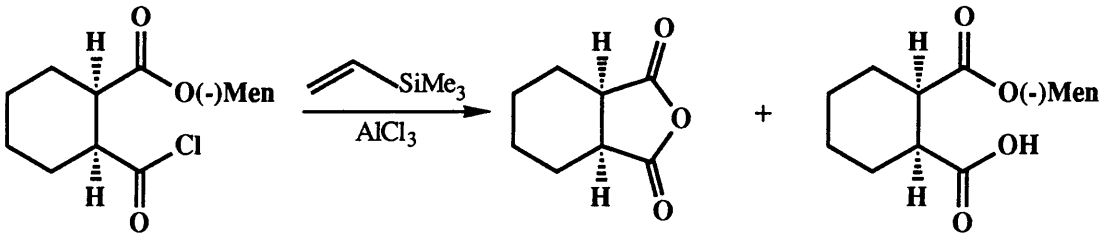
(152a) (165) (166) (167)

Further investigations to make an enone from the acid chloride and anhydride included reaction with vinyltrimethylsilane in the presence of $AlCl_3$. It was thought that the double bond may be more reactive, as the silyl group would stabilise the β-positive charge formed in the intermediate (168). Attack by a chloride anion on the silicon would the remove the TMS group and form the double bond to give (169).



(166) (168) (169)

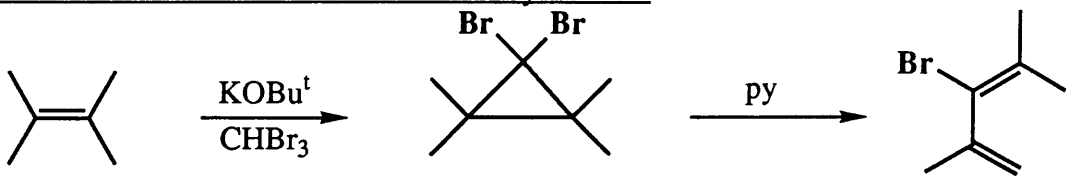
Both reactions yielded cis-cyclohexane-1,2-dicarboxylic anhydride (148) as the major product with small amounts of the acid ester (152a). The $AlCl_3$ Lewis acid could have co-ordinated with the Cl pulling it away from the carbonyl group and leaving a formal positive charge on the carbon. The lone pair on the oxygen of water used in the work-up could then have attacked the carbonyl carbon to yield the two undesired products.



(166) (148) (152a)

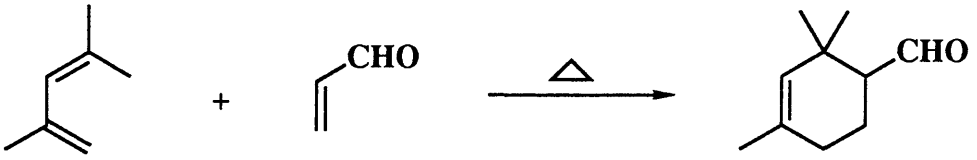
Alternative methods of introducing a vinyl moiety need to be studied, for example, reaction with vinyl lithium or lithium acetylide ethylenediamine complex. Once a suitable route has been found, the next reaction will be the intermolecular Diels-Alder cyclisation.

Control of the Intermolecular Diels-Alder Cyclisation.

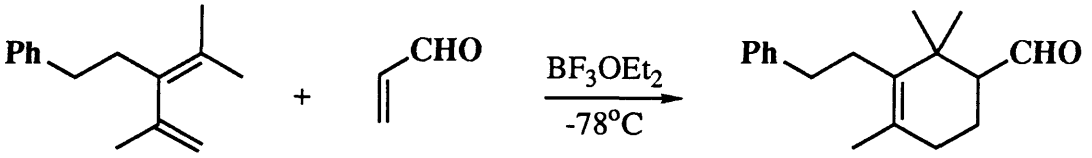


(170) (171) (172)

3-Bromo-2,4-dimethylpenta-1,3-diene (172) is a particularly stable diene due to the three methyl substituents. It was readily prepared in 55% yield following a literature procedure[55] by reaction of the double bond of 1,3-dimethylbut-2-ene (171) with a carbene to give 1,1-dibromo-2,2,3,3-tetramethyl cyclopropane (169) which was opened to the diene by elimination of HBr using pyridine. An important consideration in the Diels-Alder reaction of unsymmetrically substituted dienes is regiochemistry. The following two reactions has been studied in previous work by the group[54].

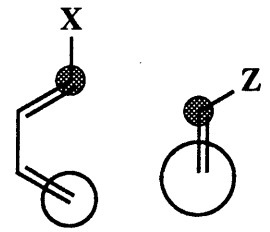


(173)



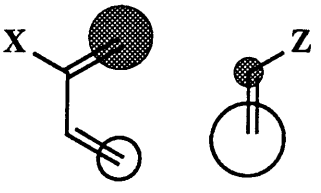
(174)

The isomers obtained (173) and (174) were those expected according to Frontier Orbital Theory[52]. A C-1 substituted diene will react with the dienophile to give the ortho adduct as the major isomer (Figure 3), whereas a C-2 substituted diene will give an adduct in which the CHO is meta to the alkyl substituent (Figure 4).



HOMO LUMO

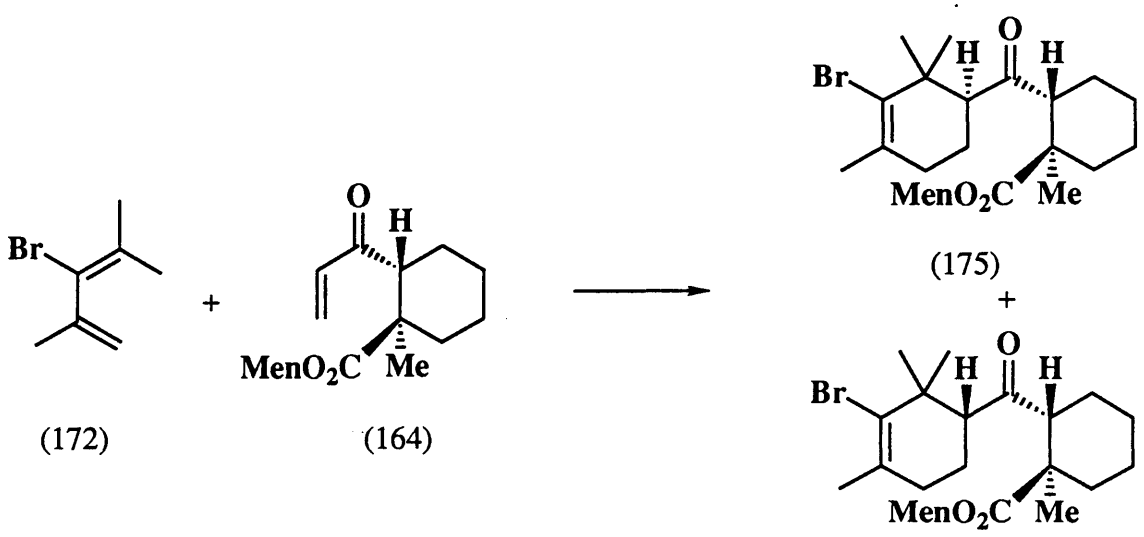
Figure 3



HOMO LUMO

Figure 4

From the above results, it can be predicted that the major isomer from the reaction of the diene (172) with the enone (164) will be as illustrated.



(172) (164) (175) (176)

Despite this regio control, it is likely that a small amount of the opposite regioisomer will still be obtained. As the product contains one new chiral centre created from the reaction, this approach would therefore give a mixture of two diastereoisomeric products (175) and (176).

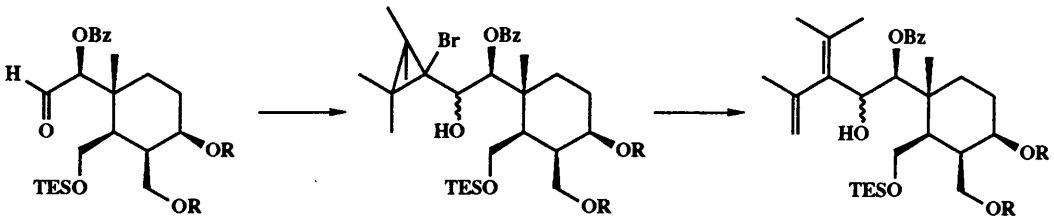
Further work in this thesis describes investigations carried out as part of the main group venture as described in Chapter 1. The new project was more challenging and had already been developed much further. This route uses a highly functionalised C ring[38] (127) and the aim was to complete the taxane skeleton using a regio and stereo-controlled intramolecular Diels-Alder reaction.

Chapter 3

The use of Lanthanide Halides in the Addition of a Diene to the C-Ring.

Introduction.

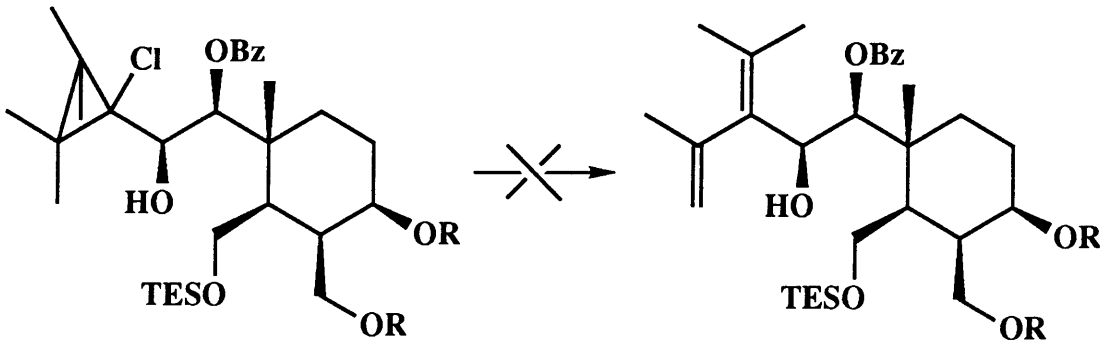
The most advanced results of Clark's work[36] are summarised in the introduction and below. A highly functionalised C-ring synthon has been efficiently synthesised using two fragmentations followed by functional group interconversion[37]. The next objective was to add a diene unit to aldehyde (121), which would be most efficiently achieved by addition of the anion of bromotetramethylcyclopropane as described in the introduction. This reaction proved to be difficult, however, with the aid of $CeCl_3$, addition was achieved to give a 2:1 mixture of diastereoisomers (134a and b). Subsequent attempts to repeat this reaction under the same conditions caused exchange of the bromine atom with cerium chloride leading to the chloro-cyclopropane (177).



(127) (134b) 1S, 2S = 63% (134a) 1S, 2R = 30% (129)

R = Si^tBuPh_2

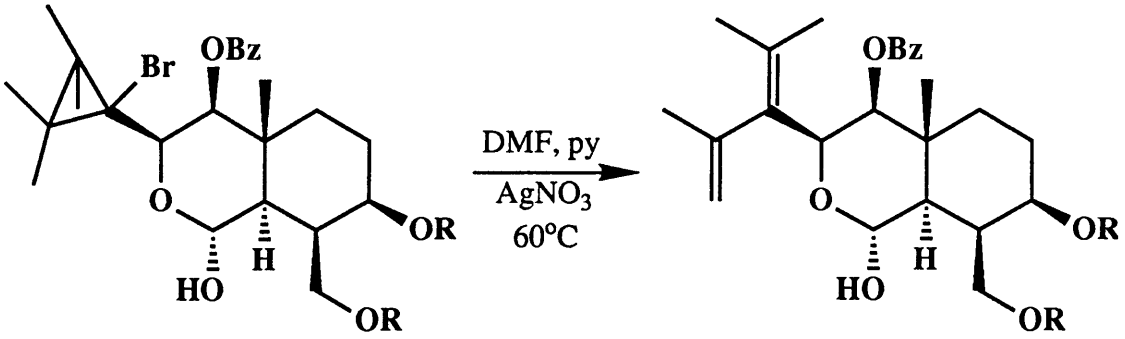
Attempts to rearrange this product (177) to the diene (129) using $AgNO_3$, pyridine and DMF failed and only starting material was recovered.



(177) (129)

R = Si^tBuPh_2

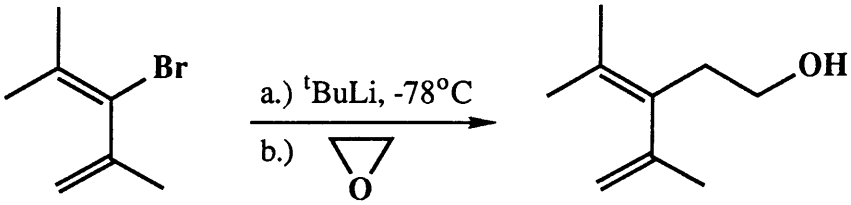
However, rearrangement to the diene (136) was achieved in quantitative yield with the lactol (135) obtained from cyclisation of the major diastereoisomer of the bromocyclopropane adduct (134b).



(135) R = Si^tBuPh_2 (136)

Addition of the Bromodiene (172) to Model Aldehydes.

As the introduction of the cyclopropane group had proved difficult, it was decided to try the coupling of the aldehyde (127) to the bromodiene (172) directly. Despite previous reports in the literature of these types of reactions being complicated by the formation of inseparable allenes, it was felt that the metallated diene may be less hindered and therefore add to the aldehyde more efficiently than it's bromocyclopropane precursor. Work published by Shea et al[20] showed successful addition of the same bromodiene (172) to ethylene oxide to give an alcohol (178). In this work, the bromodiene (172) was firstly treated with ^{t}BuLi to give the anion by lithium-halogen exchange, which then opened the epoxide by an S_N2 displacement.

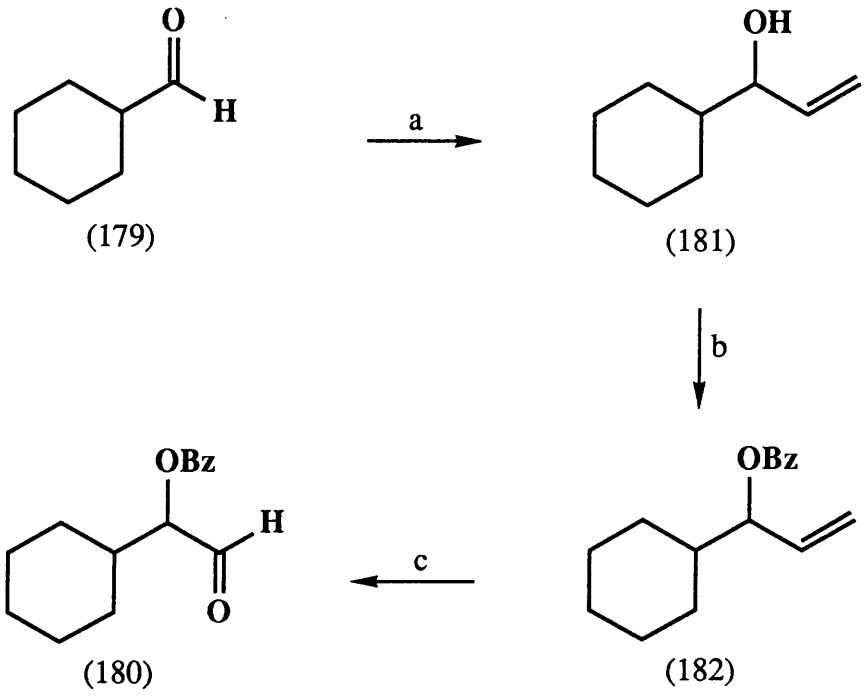


(52) (151)

Another advantage to following this route was the facile preparation of the bromodiene according to literature procedures[55] as described in Chapter 2. Provided the product

was kept at < 4°C, it could be stored for several weeks without any decomposition being visible by NMR.

Preliminary studies were performed using two model aldehydes, one being cyclohexane carboxaldehyde (179). The second model (180) was slightly closer to the real C-ring in that it contained a two carbon side chain, with a carbon bearing a benzoxyl group adjacent to the aldehyde. A three step synthesis (Scheme 26) involving a Grignard addition gave (181), protection gave (182) and ozonolysis furnished the racemic product (180). In the first step it was essential that the aldehyde was added dropwise to a cooled solution of the Grignard reagent to prevent polymerisation from occuring.

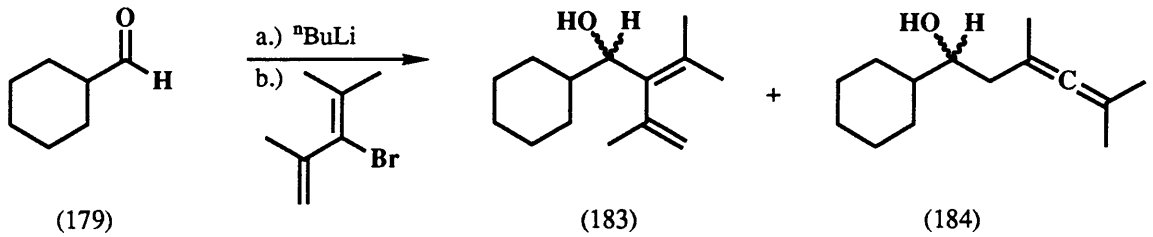


Scheme 26

) 1.1eq CH_2=CHMgBr, THF, 0°C, 45 min, 49%; b.) 5eq Bz_2O, 11.5eq DMAP, 40eq NEt_3, CH_2Cl_2, RT, 1h, 81%; c.) 1.2eq MeOH, 4eq py, CH_2Cl_2, -78°C, O_3, 80 min, then 5eq DMS, -78°C, 10 min, 83%.

The first reaction tested was the addition of the lithiated diene to cyclohexane carboxaldehyde (179) for 3 hours at -78°C. The lithium-halogen exchange was brought about by the treatment of the bromodiene (172) in THF with ^{n}BuLi at -78°C for 0.75 hours. T.L.C. showed a series of faint spots and a major one which was isolated in 64% yield by flash column chromatography. NMR indicated that the sample actually

contained two products, these were found to be the diene alcohol (183) and the allene alcohol (184).



(179) (183) (184)

2.3 : 1

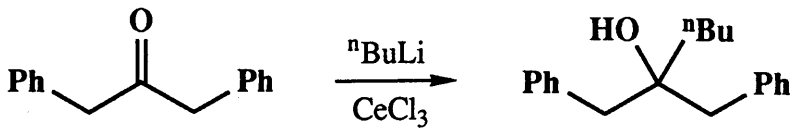
64%

The ratio of these two products was calculated from the integration of the proton on the carbon bearing the hydroxyl group in the proton NMR spectrum. These had a different chemical shift and first order signal in each case. The CH peak for the diene alcohol was a doublet with J = 9.7 Hz at δ 4.16 and that in the allene was depicted as a ddd at δ 3.48. A ratio of 2.3:1 was measured using the NMR of a crude sample, this figure was reproducible when the reaction was repeated. Signals in the ^{13}C NMR also corroborated that the diene alcohol was the major isomer.

Although the formation of comparable amounts of diene (183) and allene alcohol (184) was disappointing, it was encouraging that some addition of the diene had been achieved and in a combined yield of 64%. The first change of variable that was considered was the metal cation. It was hoped that by using an alternative to lithium, a more favourable ratio and improved yield would be obtained.

Cerium and Lanthanide (III) Reagents.

The lanthanides[56] belong to the 4-f set of elements in the periodic table and have a stable oxidation state of +3. Commercially available lanthanides occur as the hydrated chlorides eg. $CeCl_3.7H_2O$, $PrCl_3.6H_2O$ which can be dehydrated to give $CeCl_3$ or $PrCl_3$. Imamoto et al reported many carbon-carbon bond forming reactions in high yields using cerium chemistry[57], one example is the addition of an ^nBu group to (185) to give the tertiary alcohol (186).

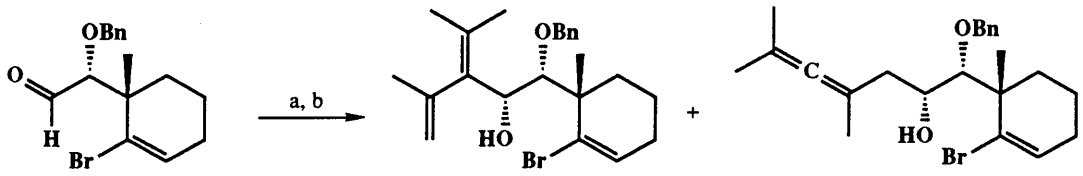


(185) (186)

96%

Organocerium (III) reagents are generated by transmetallation between organolithium compounds and anhydrous $CeCl_3$ or CeI_3. Cerium reagents exhibit a strong oxophilic character which allows them to react like as a Lewis Acid. They react cleanly at -65 to -78°C and can be considered to be like Grignard reagents, but they do not undergo the side reactions of enolisation or reduction, sometimes found when using a Grignard, these advantages arise from the low basicity of organolanthanides. The strong affinity of trivalent cerium for oxygen atoms can aid in the activation of oxygenated organic functions, indeed it is this oxophilicity which allows only 1, 2 addition to an α,β unsaturated carbonyl, discouraging 1, 4 attack.

Several factors affected the decision to try the addition of the bromodiene as an organocerium (III) to the model aldehydes, one being that cerium (III) chloride heptahydrate is commercially available at moderate prices and can therefore be used in stoichiometric amounts. Shea et al[21] had reported the addition of the same diene portion to an aldehyde (51) by treatment with the dienylcerium reagent. An inseparable mixture of dienyl alcohol (53) and allenyl alcohol (54) was isolated in a ratio of 5.4:1 respectively, this was an improvement on our 2.3:1 figure.



(51) (53) (54)

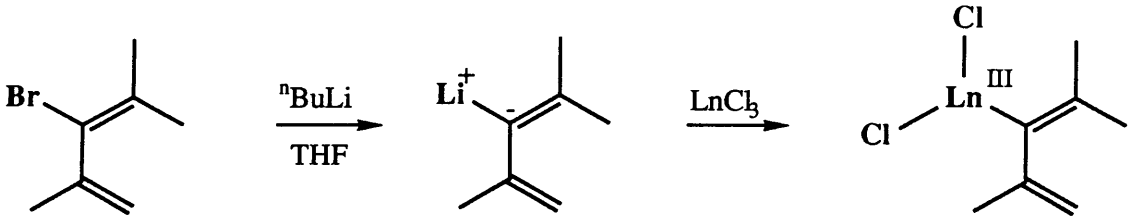
Scheme 27

a.) ^{t}BuLi, (52), THF; b.) $CeCl_3$, then aldehyde (51), THF, -78°C.

Cerium species will also react preferentially with aldehydes in the presence of esters[58], it was hoped that this would prevent complications on addition to our second model (180) which contains a benzoxy group.

Lanthanide Mediated Additions to our Models.

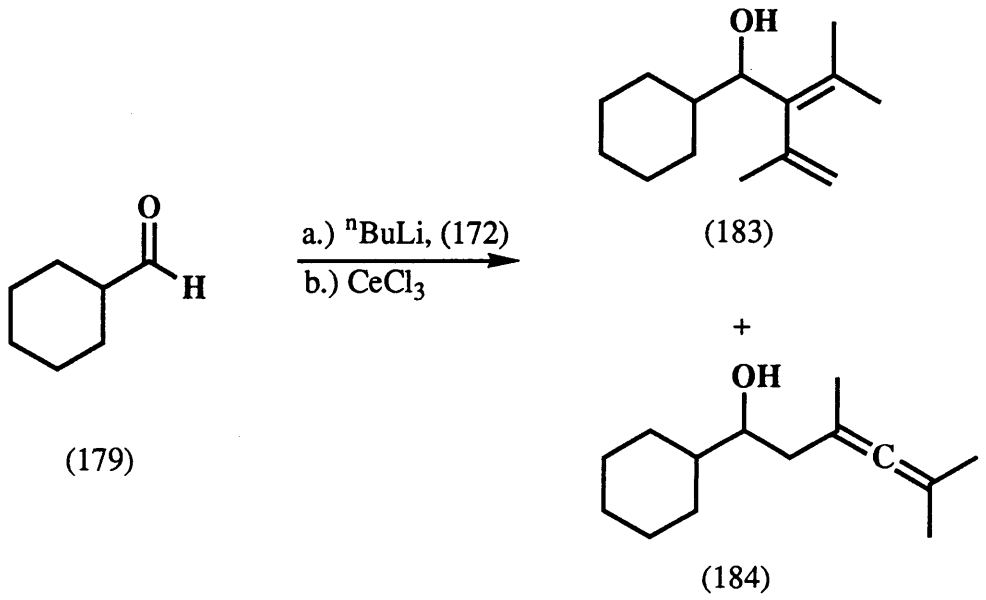
Coupling of the diene to cyclohexane carboxaldehyde (179) using treatment with cerium and various other lanthanide chlorides was attempted (Scheme 29). To generate the organolanthanide species (188), the lithiated diene anion (187) was created by lithium-halogen exchange and added to a suspension of $LnCl_3$[57-59] and THF (Scheme 28). Formation of the metallated nucleophile was indicated by the appearance of deep colours in each case, red / brown for organocerium, green for organopraseodynium and orange for organolanthanum.



(172) (187) (188)

Scheme 28

Each reaction was performed at -78°C and stirred for 3 hours once the aldehyde had been added. Leaving reactions for further lengths of time did not enhance the yields. The results are summarised in table 3-1.



Scheme 29

Metallating reagent	Yield	Diene : Allene ratio*
1.3eq ^{n}BuLi	64%	2.28 : 1
1.3eq ^{n}BuLi / $CeCl_3$	55%	>100 : 1
1.3eq ^{n}BuLi / $LaCl_3$	40%	2.40 : 1
1.3eq ^{n}BuLi / $YbCl_3$	28%	2.32 : 1
1.3eq ^{n}BuLi / $TbCl_3$	No reaction	

Table 3-1

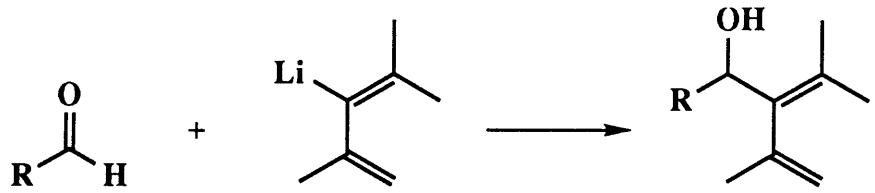
**The ratios were measured by integration of the proton adjacent to the hydroxyl group in the ^{1}H NMR.*

Clearly treatment with $CeCl_3$ favours the reaction to give the dienyl alcohol (183) in 55% yield. No allene alcohol (184) was visible in either the ^{1}H or ^{13}C NMR spectra. All lanthanides have a strong affinity for oxygen and it was expected that they would co-ordinate to the carbonyl oxygen and encourage attack of the diene moiety. It was therefore surprising to find that the introduction of alternative lanthanides gave lower yields than with no lanthanides or no reaction at all. The low reactivity of $YbCl_3$ and $TbCl_3$ can be explained by their position in the periodic table. A lanthanide contraction

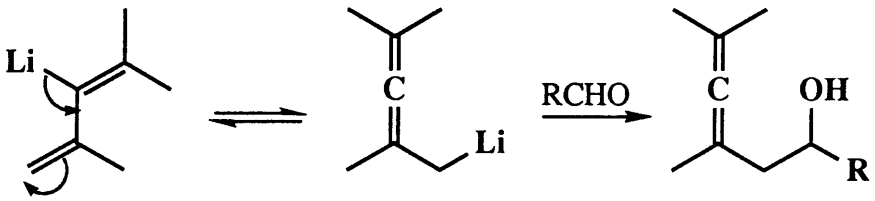
is seen on progressing across the row, therefore Tb^{3+} and Yb^{3+} have smaller radii than the earlier lanthanides. The trihalides are quite salt-like and the tendency towards hydrolysis increases with decreasing radius. The oxidation state 2+ of Yb can be achieved easily by reduction of the trihalide, for example with an electropositive metal such as lithium. Under the reaction conditions it is possible that Yb 2+ is formed by electron transfer from the dienyl anion. This willingness to give the 2+ oxidation state is strongly linked to the creation of a full 4f shell.

Possible Explanation of Diene : Allene Ratio with change of Lanthanide Metal.

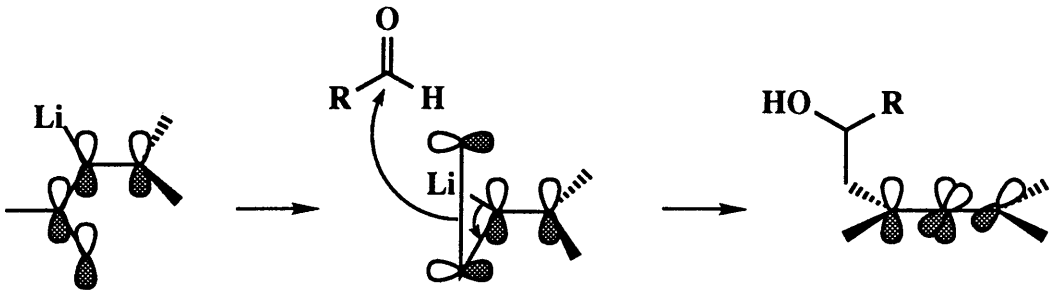
In trying to arrive at an explanation of these results, we first have to understand how the diene and allene products arise in the reaction. The diene product could be formed simply by direct reaction of the carbon metal bond on the electrophile.



One way in which the allenyl alcohol (184) could form is by rearrangement of the metallated diene (187) to the allene before its reaction with the electrophile.

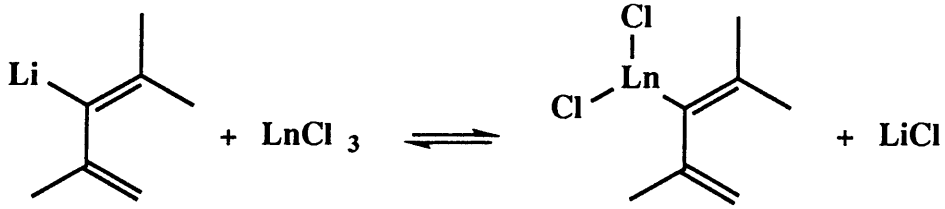


However, the energy barrier of conversion of the diene anion to the allene anion is relatively large, this is due to the pair of electrons in the diene anion (187) being in an sp^2 hybridised orbital perpendicular to the p orbitals of the neighbouring double bond. To allow overlap and subsequent rearrangement to the allene, the C-C bond must rotate and the resonance energy of the diene will be lost.



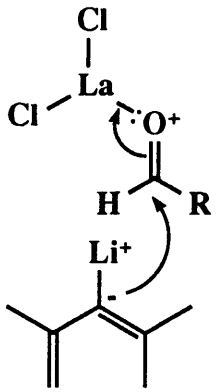
conjugated diene | transition state with perpendicular double bonds | allenyl alcohol

The reaction of the lithiodiene (187) with lanthanide chloride and addition to a carbonyl group is a Lewis Acid initiated event and each metal has different Lewis acid properties. This postulation can be used in a suggestion of why the diene : allene ratios may vary with different metals. It is possible that an equilibrium may be set up as shown and that the proportion of the two Lewis Acids in the reaction mixture will depend on the metal.

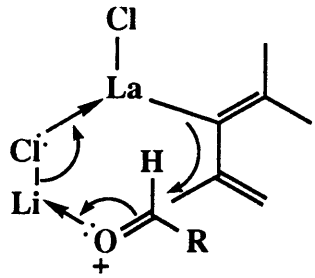


(187) | Lewis acid | (188) Lewis acid

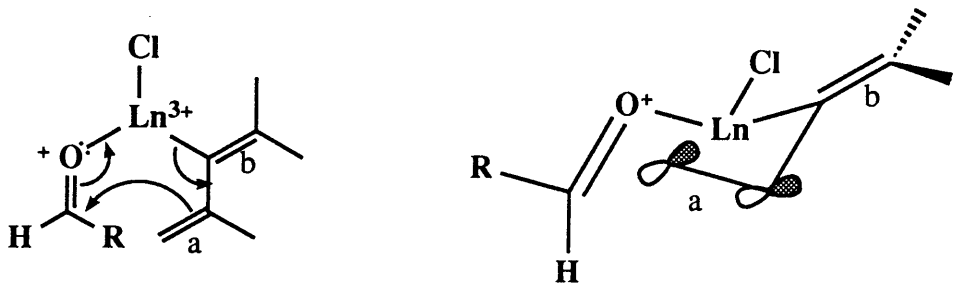
Let us take the reaction using $LaCl_3$ as an example where both dienyl (183) and allenyl alcohol (184) are formed. We propose a mechanism for the formation of the dienyl alcohol (183) using the left hand side of the equilibrium. The carbonyl oxygen could co-ordinate to the $CeCl_3$ and the diene addition would take place through an intermolecular pathway.



Alternatively, the reaction could be proceeding through the species on the right of the equilibrium via an intramolecular pathway. This may involve co-ordination of the carbonyl oxygen lone pair to the lithium of LiCl, a lone pair on the chlorine could then attach to the metal to give a six-membered transition state.

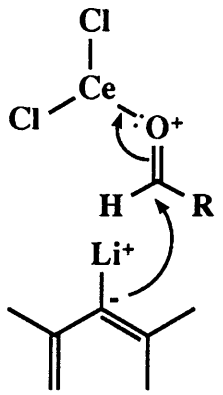


When the allenyl alcohol (184) forms, we propose that the aldehyde co-ordinates to the metal of the right-hand Lewis acid (188) and that the reaction occurs via a six-membered transition state, which may be compared with a [3, 3] sigmatropic rearrangement.



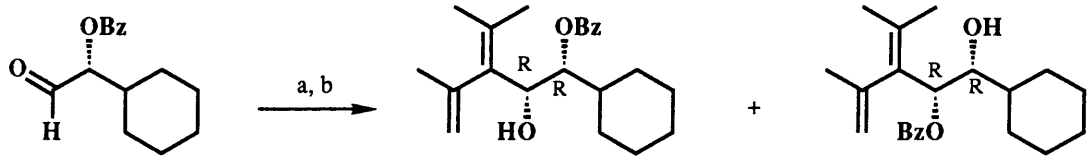
In the chair conformation, the double bond (a) moves out of conjugation with double bond (b) to become co-planar with the Ln-C bond. This facilitates the loss of diene resonance energy to form the perpendicular allene arrangement.

The lack of allenyl alcohol in the reaction using $CeCl_3$ may be explained by the different Lewis acid properties of $CeCl_3$ and $CeCl_2$.diene. In this case, $CeCl_3$ must be the more reactive Lewis acid and the dienyl alcohol therefore forms by direct addition of the diene to the aldehyde which is co-ordinated to $CeCl_3$.



The organocerium species on the right of the equilibrium is less reactive, therefore formation of the allenyl alcohol by the chair-like transition state is less likely to occur and the dienyl alcohol is the major product.

The studies were now extended to the other closer model aldehyde (180). Several initial attempts to perform the reaction resulted in only starting material being recovered before it was discovered that the number of equivalents of bromodiene, $^{n}BuLi$ and lanthanide chloride needed to be doubled to 2.6. Reactions were complete after 3 hours at -78°C and two major separable spots were seen on the T.L.C. plate. Flash column chromatography allowed separation of the two compounds which were subsequently characterised as products (189a) and (189b) (Scheme 30).

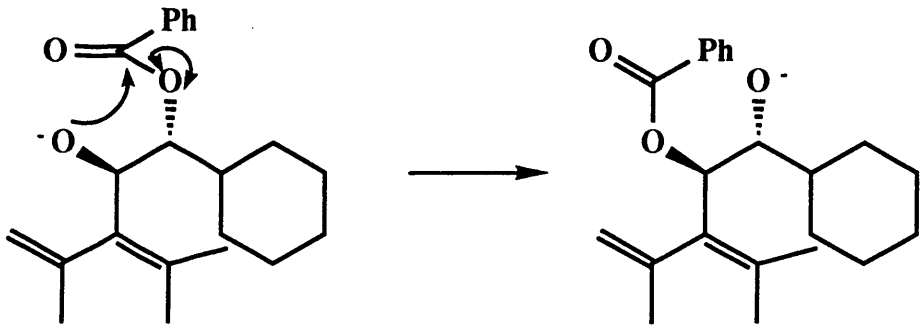


(+/-) (180) (+SS) (189a) (+SS) (189b)

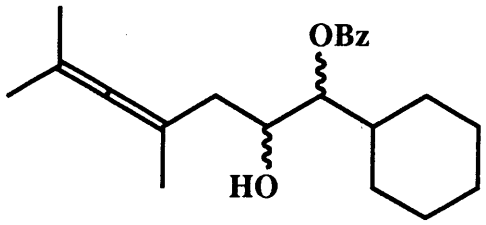
Scheme 30

a.) 2.86eq $^{n}BuLi$, 2.6eq (52), -78°C, 1h; b.) $CeCl_3$, -78°C, 1h, then aldehyde (153), -78°C, 3h.

Only one racemic diastereoisomer was produced therefore it is most likely to be the product of addition to the least hindered side of the chelated conformation, (189a) was assumed to be the major product. The full explanation of the assignment of (189a) as the major product is explained in the next section. The minor product (189b) is the result of benzoyl migration taking place during the reaction. The diene adds to the aldehyde group to give the expected intermediate, however, the anion then rearranges via a 5 membered ring transition state as shown below to give an alternative anion which on protonation yields the product (189b).



In certain reactions a trace amount of the allenyl alcohol (190) was isolated with (189b) as an inseparable mixture of products, this was dependant on the lanthanide chloride used (Table 3-2).



(190)

Although the yields are low, the mass balance is recovered as starting material. When $CeCl_3$ was used in the reaction no allenyl alcohol (190) was detectable in the proton or ^{13}C NMR spectra and reactions using $LaCl_3$ or $PrCl_3$ showed only a trace amount by

NMR. We need to explain the almost exclusive formation of diene in the reaction of aldehyde (180), while allene was formed in the reaction of (172) with cyclohexane carboxaldehyde (179). One suggestion is that the ester oxygen of the benzoxy group in (180) co-ordinates to the metal, along with the carbonyl oxygen of the aldehyde group to give a five membered chelate ring (Figure 3-1). The diene is also attached to the chelated metal, however, the diene CH_2 group is too far away from the carbonyl carbon to allow formation of the allene. The dienyl alcohol forms readily by intermolecular attack. Extra support for this theory comes from the fact that 2.6 equivalents of the organocerium species are needed for the reaction to occur, the first equivalent is necessary to co-ordinate to the bidentate ligand, the second can then add to the carbonyl group intermolecularly.

Reagent	**Yield**	**Ratio (189a) : (189b)**	**Allene**
2.6eq ^{n}BuLi / $CeCl_3$	38%	3.91 : 1	None
2.6eq ^{n}BuLi / $LaCl_3$	27%	2.15 : 1	Trace
2.6eq ^{n}BuLi / $PrCl_3$	37%	3.06 : 1	Trace

Table 3-2

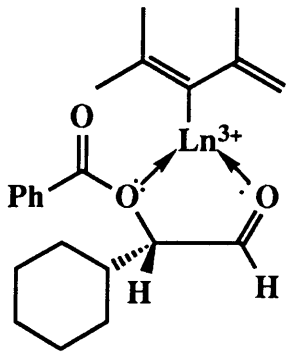


Figure 3-1

The ratio of products (189a) to (189b) was measured from the vinylic protons in the ^{1}H NMR of the crude mixture at δ 4.82 and 5.20ppm for (189a) and 4.70 and 5.16ppm for (189b). The results are illustrated in table 3-2. The ratio varies depending on the lanthanide chloride employed, this is probably due to small energy changes in the

chelation model effecting the extent of co-ordination. If the co-ordination is strong as with $CeCl_3$, then the proportion of free anions, which are produced when the aldehyde is not coordinated to a lanthanide metal and the lithiodiene attacks the carbonyl directly, is reduced and fewer molecules can undergo benzoyl migration by the mechanism described on Page 77.

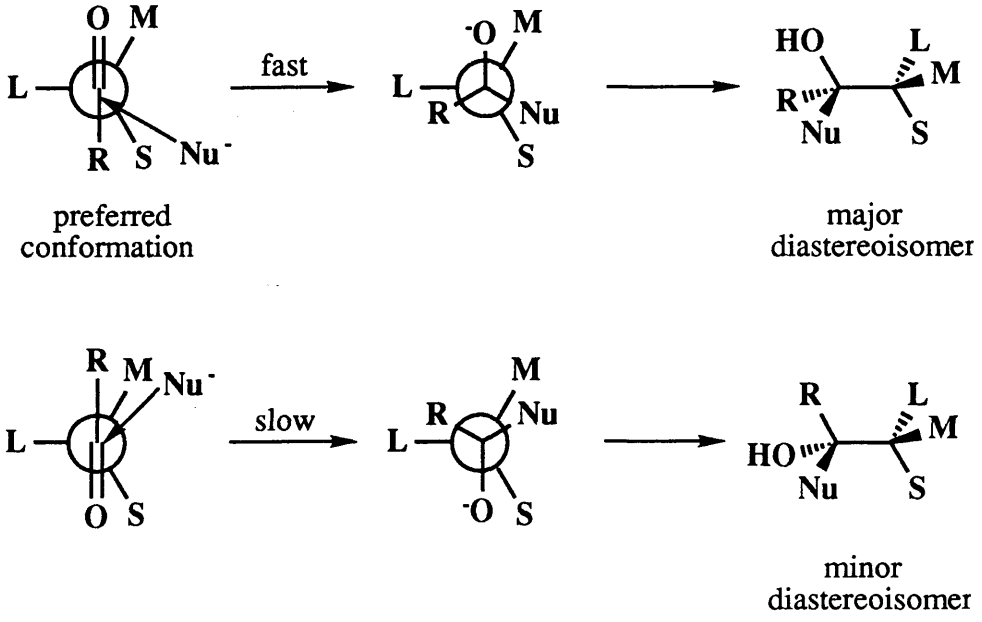
A racemic mixture of only a single diastereoisiomer is seen for each of the products (189a) and (189b). The starting material (180) contains one chiral centre of which 50% is the R configuration and 50 % the S configuration, it is expected that the diene could attack from either face of the aldehyde to give enantiomers of both diastereoisomers, however attack is seen from one face only of each enantiomer to give a single diastereoisomer. Diastereoselectivity was also observed when Shea et al[21] added the diene to an aldehyde to give the (R, R), (S, S) diastereoisomer. Without a crystal structure to confirm the relative configuration it is difficult to state which diastereoisomer we have obtained, however it is assumed that it is also the (R, R), (S, S) isomer that has been isolated in the above series of reactions.

Elucidation of the Diastereoselectivity using Felkin-Anh models.

Assumptions of the favoured conformations were based primarily on the Felkin-Anh[60] steric model (Figure 3-2). The molecule adopts a conformation in which the three groups on the α-carbon are staggered relative to the carbonyl. The most reactive conformation places the carbonyl oxygen between the large and the medium groups. In the case of compound (180), the large group represents the cyclohexane ring, the medium group is the benzoxy and the small group is the hydrogen.

The nucleophile will approach the aldehyde group at an angle of 109° to the plane of the carbonyl, this is known as the Burgi-Dunitz trajectory. The two faces of the carbonyl are diastereotopic and nucleophilic attack will be preferred on the face away from the bulky cyclohexane ring to give the major diastereoisomer. The minor diastereoisomer is achieved when the opposite face of the carbonyl is attacked. For this to be allowed the aldehyde group must be rotated through 180° placing the carbonyl oxygen between

the small and large groups. As the nucleophile approaches along the Burgi-Dunitz trajectory, it will experience steric hindrance by interaction with the medium substituent. Attack of this conformation is slower and will result in the minor isomer.



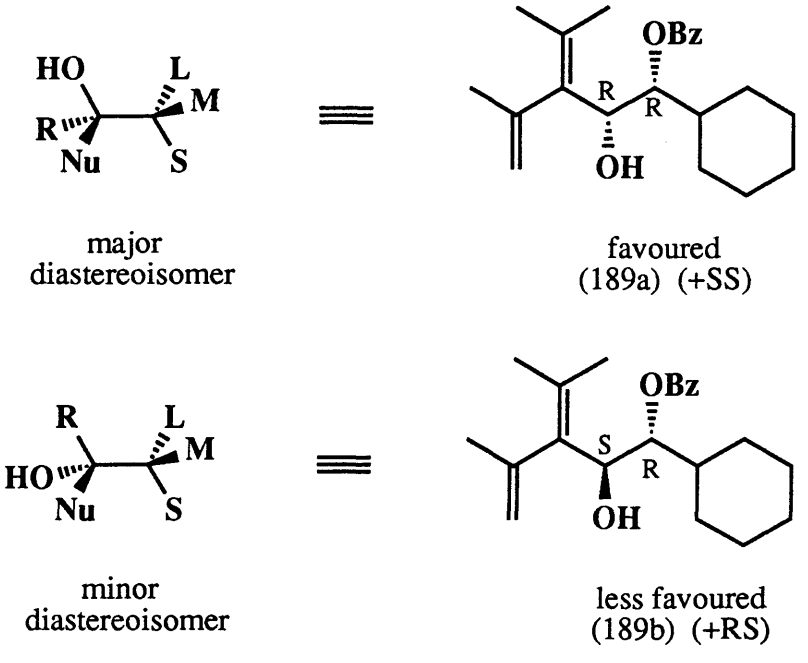


Figure 3-2

The preferred conformation can be modified slightly to take into account the Felkin-Anh chelation control model (Figure 3-3). The benzoxy group on the α-carbon can use a lone pair on the ether oxygen to co-ordinate to the organometallic reagent. The aldehyde oxygen is also co-ordinated to the metal through one of its lone pairs.

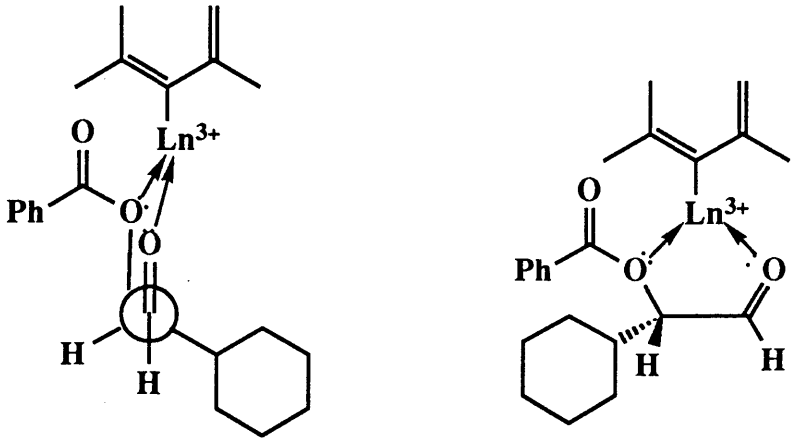
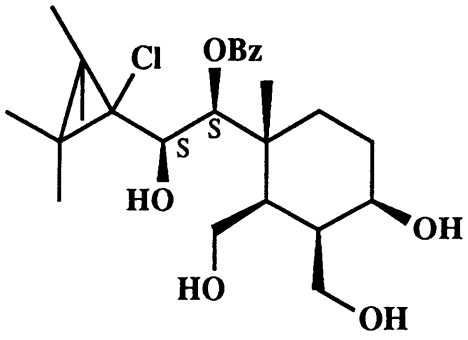


Figure 3-3

The aldehyde carbonyl, the co-ordinating substituent on the α-carbon and the metal are all held in the same plane as a five membered chelate ring. As the benzoxy group is equivalent to a medium sized group, the nucleophile will attack intermolecularly and preferentially from the less hindered side, adjacent to the α-hydrogen. The small change in ratio on utilising different lanthanides could be due to a small energy change in the chelation model, as the extent of co-ordination may vary according to the metal. The same stereocontrol was noted by Shea[21] in the addition of the bromodiene (172) to a similar model (51). The aldehyde oxygen and the ester oxygen are temporarily tethered together to hold the carbonyl group in such an orientation that attack from only one face is permitted.

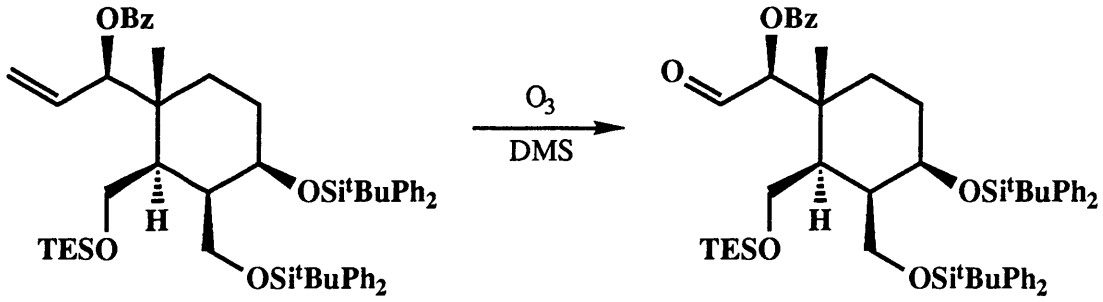
Further evidence in helping predict the relative configuration of the major isomer came from X-ray analysis of a deprotected version of the major diastereoisomer from cyclopropane addition to the C-ring aldehyde prepared by Clark[36]. The crystal structure showed the compound (191) to have the SS absolute configuration, this is in accordance with the predicted relative isomer for the model aldehyde.



(191)

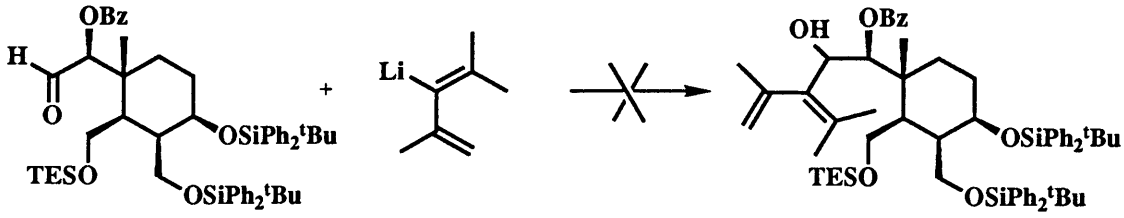
Attempts to add the Diene to the C-Ring.

Addition of the 1,1,3-tetramethylbutadiene unit to the highly functionalised C-ring was to be performed by generating the organocerium (III) species. Ozonolysis of the olefin (126) to yield the aldehyde (127) proceeded smoothly via a 1,3 dipolar cycloaddition and the product could be used crude provided that the sample had been kept under oil-pump vacuum for an hour prior to its use. The olefin (126) is more stable than the aldehyde (127), therefore the latter was freshly prepared before the diene addition.



(126) (127)

In the first reaction, the conditions used were the same as in the second model studies, 2.6 equivalents of ^{n}BuLi, bromodiene and $CeCl_3$ were reacted and then added to the aldehyde. After 2.5 hours at -78°C no reaction had occurred. The suspension was kept at -78°C for 24 hours, but only starting material was detected. The reaction was repeated several times using larger amounts of the organocerium, up to 14 equivalents and long reaction times of up to 72 hours. Despite, these alterations no addition product (129) was seen and only starting material was recovered.



(127) (187) (129)

It was suspected that the aldehyde group was experiencing steric hindrance preventing the approach of the diene anion. There are two possibilities that could affect the carbonyl (Figure 3-4), the first is local steric hindrance caused by the OBz group and the second is remote hindrance by the bulky silyl protecting groups.

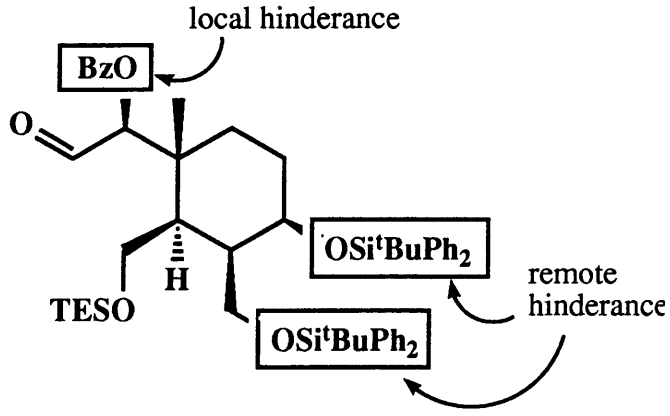
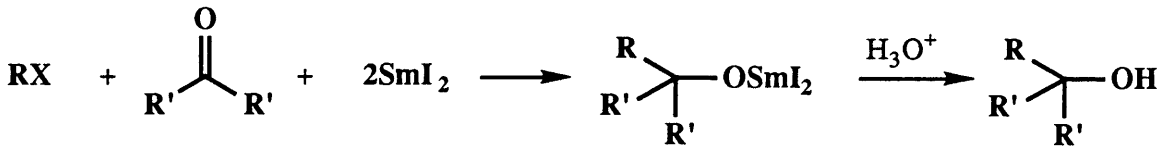


Figure 3-4

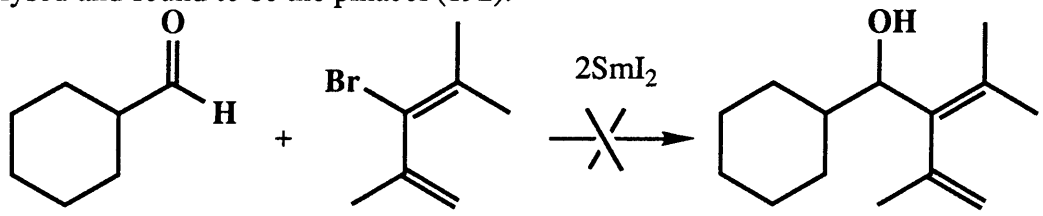
Preliminary Investigations into an Alternative Approach using SmI_2.

Further studies into the lanthanide mediated delivery of the diene moiety to the aldehyde carbonyl included the use of the divalent species SmI_2. The dipositive oxidation state is easily attained with samarium due to its half filled 4f subshell. Samarium diiodide has been shown to act as a one electron donor in Barbier-like reactions[56]. Electron transfer to a p orbital of the carbonyl double bond gives a radical anion intermediate, the R-X bond cleaves homolytically and the p orbital of the R· radical containing one electron overlaps with the p orbital of the radical anion of the carbonyl compound which also contains one electron, rehybridisation of the orbitals then gives an sp^3 quaternary centre. Hydrolysis on work-up of the reaction mixture

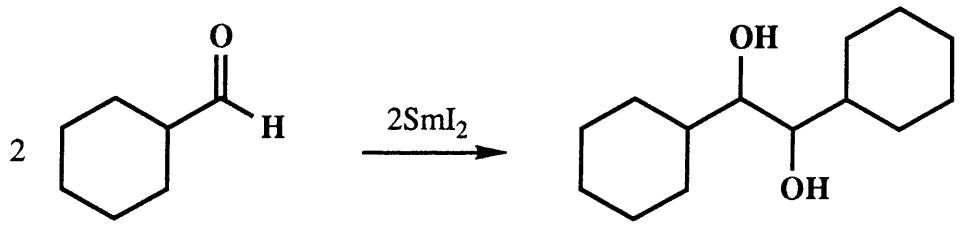
gives the secondary or tertiary alcohol depending on the carbonyl compound being an aldehyde or a ketone.



Clean reactions between alkyl halides and carbonyls do not occur, however, allyl and benzyl halides give good yields of addition to aldehydes in just a few minutes. Ester groups contained within the starting materials are compatible with the reaction. The yellow colour of Sm^{3+} signifies that the reaction is complete. It was hoped that addition of the bromodiene (172) to the aldehyde (127) in the presence of SmI_2 would afford the product (129). Initial attempts used cyclohexane carboxaldehyde (179), however, the only product obtained after 5 hours was a colourless solid which was analysed and found to be the pinacol (192).



(179) (172) (183)



(179) (192)

Pinacols form when two RCHO radical anions add together (Figure 3-5). The same result was achieved with the other model aldehyde (180), only a pinacol was formed (193).

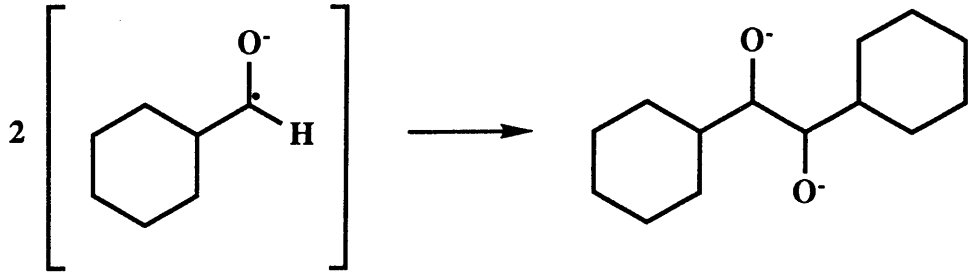
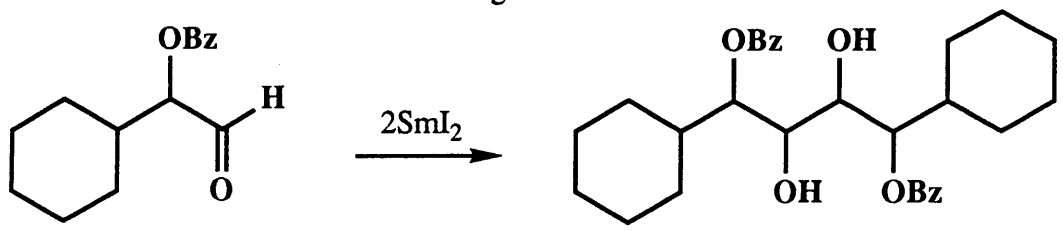
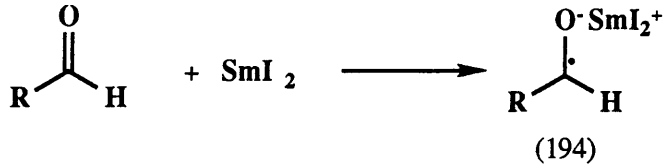


Figure 3-5

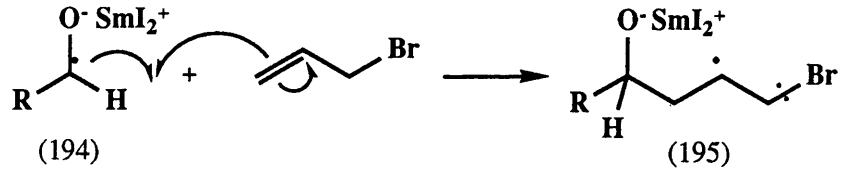


(180) (193)

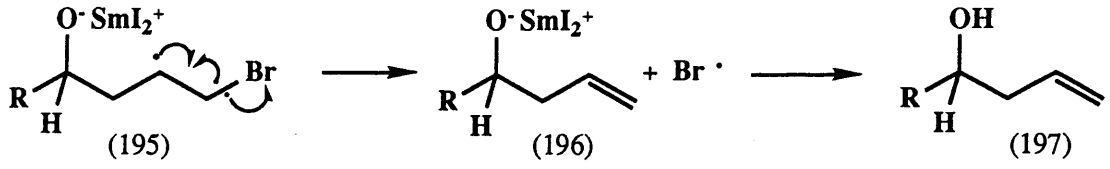
On studying the reaction mechanism of the addition of an aldehyde radical anion to allyl bromide (Figure 3-6), it became apparent as to why the bromodiene (172) would not add to either of the aldehydes.



(194)



(194) (195)



(195) (196) (197)

Figure 3-6

The samarium diiodide reacts with the aldehyde to form a radical anion in the initiation step. In the propagation step, an electron in a p orbital of the double bond of allyl bromide pairs with the single electron in a p orbital of the radical anion (194) by overlap

of the orbitals to form a carbon-carbon bond, the second electron from the double bond will be located in the other p orbital as an intermediate radical (195). The C-Br bond will cleave homolytically to generate a bromine radical and the other electron will be located in a p orbital on the terminal carbon, this p orbital will overlap with the p orbital on the neighbouring carbon to form a double bond. Protonation of the intermediate (196) on work-up gives the final product (197). For the above mechanism to work efficiently the SmI_2 must be freshly prepared as traces of HI form rapidly which will prevent a radical pathway.

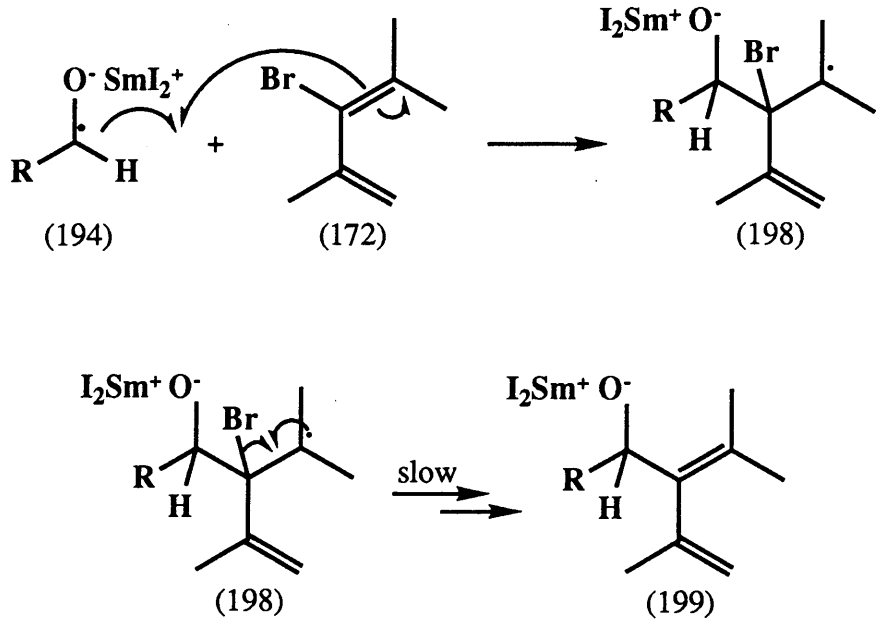


Figure 3-7

However, in the case of the bromodiene (172), the formation of the pinacol is preferred to an addition reaction to give the dienyl alcohols. It is proposed that the most substituted double bond may attack the radical anion to form a new carbon- carbon bond, the other electron will be in the p orbital of the most highly substituted carbon between the two methyl groups (Figure 3-7). This intermediate radical (198) has a neighbouring quaternary centre and is much more hindered than the intermediate (195) seen in the reaction with allyl bromide, where the radical is adjacent to a CH_2 group. The C-Br bond must rotate to be parallel to the p orbital containing the radical in order that the final diene will be conjugated and therefore formation of the double bond to

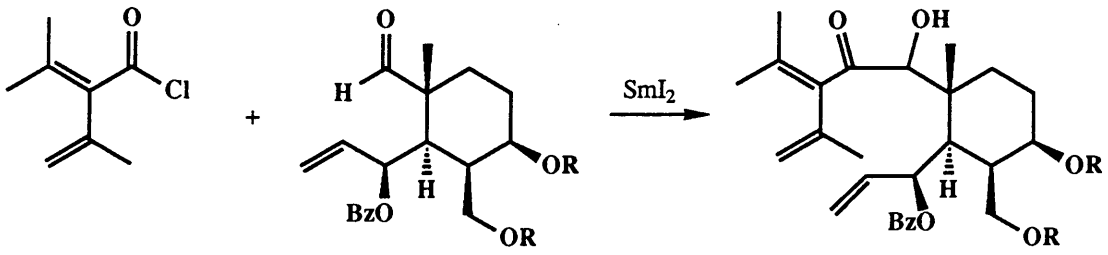
give the diene (199) may be slower. It is likely that the disubstituted double bond may also attack the radical anion in a competing reaction to give a secondary radical which on cleavage of the C-Br bond would result in the undesired allene product. The competing dimerisation of the radical anions was faster than both of these pathways resulting in only the pinacol being isolated.

However, there is a variation of the SmI_2 work which has yet to be tested. It has been reported that SmI_2 reacts with acid chlorides to give an acylsamarium[61] intermediate, this can be trapped by nucleophilic aldehyde and ketone to give an α-ketol. These type of additions are very fast and would react more rapidly than the time taken to form the pinacol.

$$RCOCl + SmI_2 \longrightarrow RCOCl^{-}SmI_2^{+} \longrightarrow RCO^{\cdot} + SmI_2Cl$$

$$RCOCl + \begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!\!=O + SmI_2 \xrightarrow[THF]{25^{\circ}C} \xrightarrow{H_3O^+} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{OH}{|}}{\overset{\overset{R^1}{|}}{C}}-R^2$$

One way of adapting this to our work would be to use the acid chloride (200) and the aldehyde (201) to synthesise the α-hydroxy ketone (202), this product could also be achieved by refluxing the carboxylic esters of (200) and (201) with Na in xylene, this is known as an acyloin condensation.



(200) (201) (202)

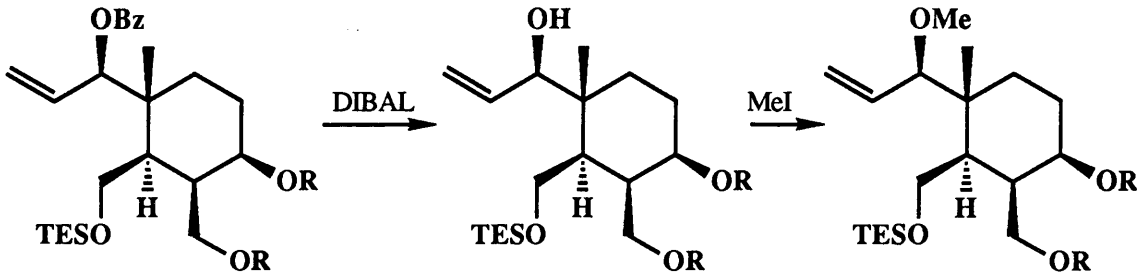
The acid chloride (200) could be prepared via the carboxylic ester which has been synthesised by the method outlined below and the possibility of making the alternative C-ring (201) was investigated by Wood.

Chapter 4

Construction of a Less Hindered C-Ring Synthon using Alternative Protecting Groups.

Changing the Local Steric Hindrance.

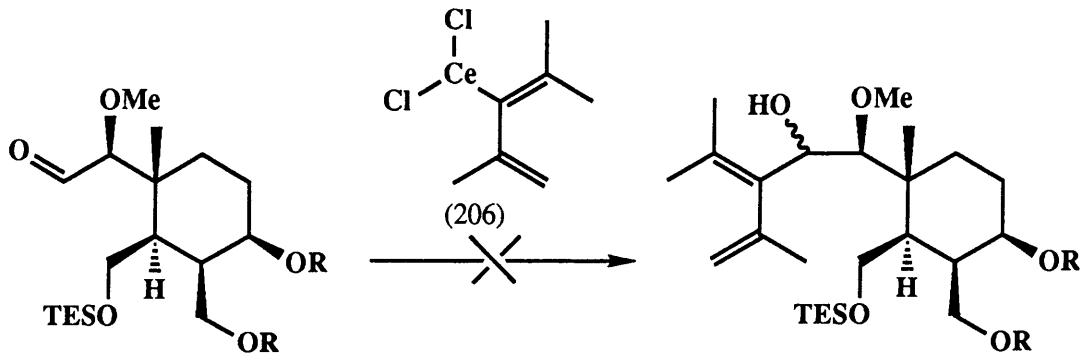
It was suggested in Chapter 3 (Figure 3-4) that the reaction of the aldehyde (127) with the lithiodiene (187) in the presence of $CeCl_3$ was being hampered due to steric factors. Local steric hindrance caused by the benzoate group is one possibility and this idea was investigated by Simons. The studies involved removal of the C-1 benzoate group of the olefin (126) and replacement with a smaller group. The benzoate was removed by treatment with DIBAL to yield the alcohol (203) and treatment with methyl iodide, sodium hydride and DMPU afforded the methyl ether (204).



(126) (203) (204)

R = $SiPh_2{}^tBu$

Ozonolysis of (204) gave an aldehyde (205) almost quantitatively which was used as a C-ring synthon. However, coupling of the cerium diene (206) to the carbonyl group was unsuccessful and the expected product (207) was not acquired.



(205) R = $SiPh_2{}^tBu$ (207)

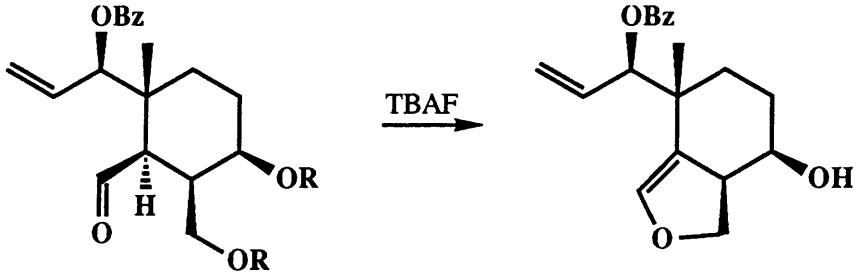
This result suggests that local hindrance is not the major steric factor affecting the addition of the metallated diene to the aldehyde.

Changing the Remote Steric Hindrance.

Investigations were pursued into the possibility of remote hindrance by the bulky t-butyldiphenylsilyl (TBPS) protecting group. The aim was to remove the TBPS groups at C-3' and C-4' and reprotect the alcohol functions either individually with smaller groups or together using a cyclic protecting group.

Deprotection of the Silyl Ether Groups using Fluorine Reagents.

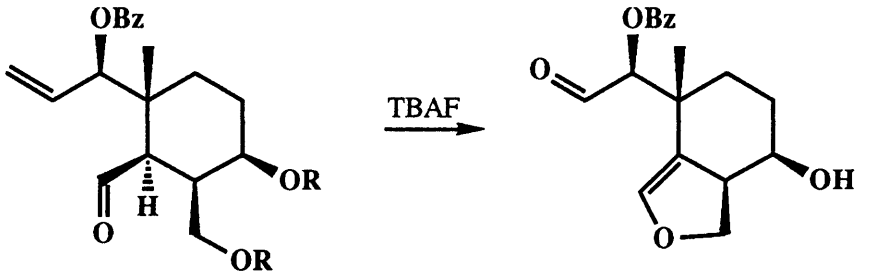
Removal of the TBPS groups of the C-ring synthon (127) was achieved using TBAF in THF, however, this method also removed the smaller TES group to give the triol (208). This would cause problems later in the selective protection of the C-3' and C-4' OH over the C-2' hydroxymethyl.



(125) (209)

R = $SiPh_2{}^tBu$

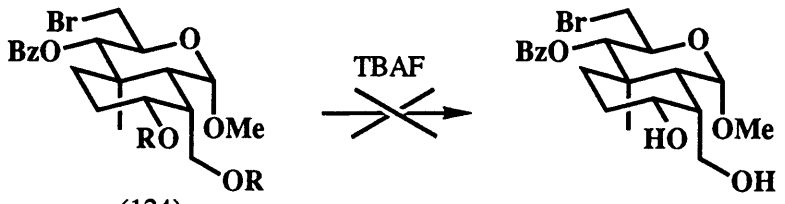
Simons treated the product (125), obtained from the Vasella[35] fragmentation step, with TBAF in THF. A single compound was isolated, however, the ^1H NMR lacked an aldehyde signal and the product was believed to be compound (209) obtained via a lactol.



(125) (209)

R = $SiPh_2{}^tBu$

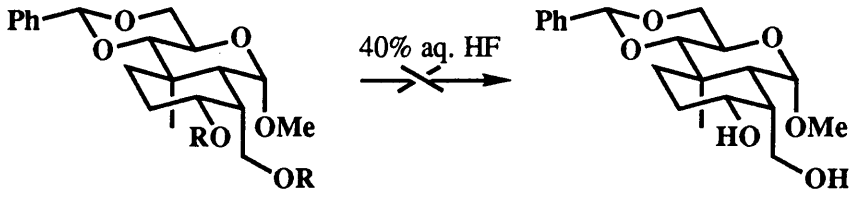
Deprotection of the pre-Vasella compound (124) was attempted, but treatment with TBAF resulted in only starting material being recovered.



(124)

R = $SiPh_2{}^tBu$

Stronger conditions were employed to deprotect the tricyclic compound (123) using 40% aqueous HF, however, this reagent decomposed the starting material to a thick black tar which was difficult to purify and characterise.



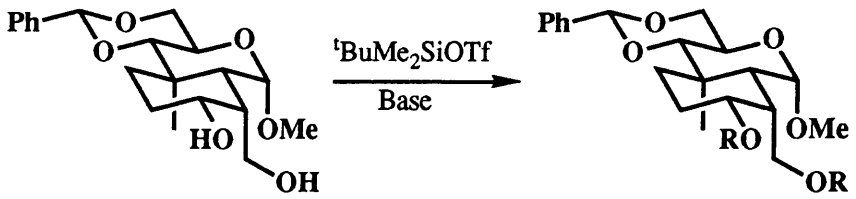
(123) (122)

R = $SiPh_2{}^tBu$

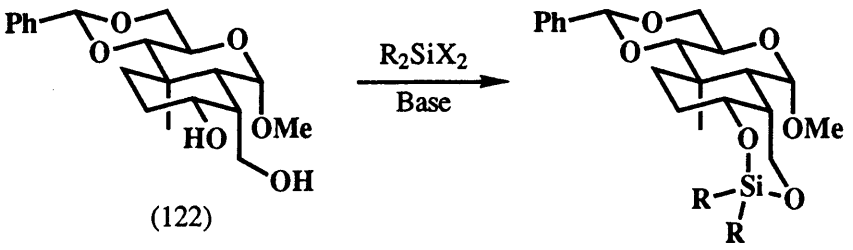
As none of the above reactions had proceeded smoothly, it was necessary to go back five steps from the C-ring synthon and introduce new protecting groups on to the diol (122).

Protection of the Diol as Alternative Silyl Ethers.

Three silyl protected diols (210), (211) and (212) were readily prepared. Simons synthesised compounds (210) and (211) by treatment of the diol (122) with t-butyldimethylsilyltrifluoromethanesulphonate and t-dibutylsilylbis(trifluoromethane sulphonate) respectively. The second cyclic silyl ether (212) was prepared by reaction of the diol with dichlorodiphenylsilane.



(122) (210) R = $^tBuMe_2Si$

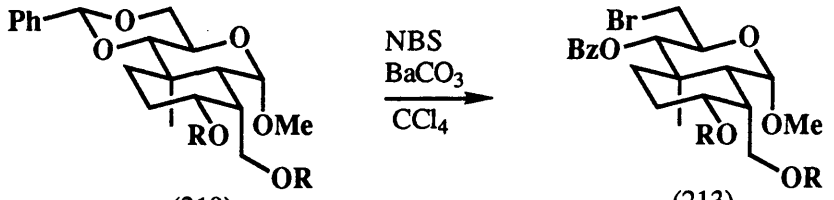


(122)

X = Cl or Tf

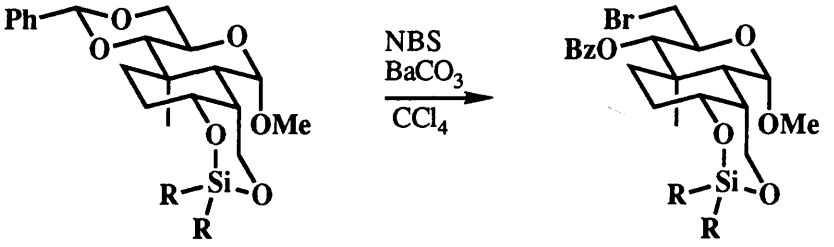
(211) R = ^{t}Bu
(212) R = Ph

Problems arose in the next reaction which was a fragmentation step affected by NBS. The bromo compounds (213), (214) and (215) were achieved in very low yields with several other byproducts were seen on the T.L.C. plates.



(210)
R = $SiMe_2{}^tBu$

(213)
R = $SiMe_2{}^tBu$
28%



(211) R = ^{t}Bu
(212) R = Ph

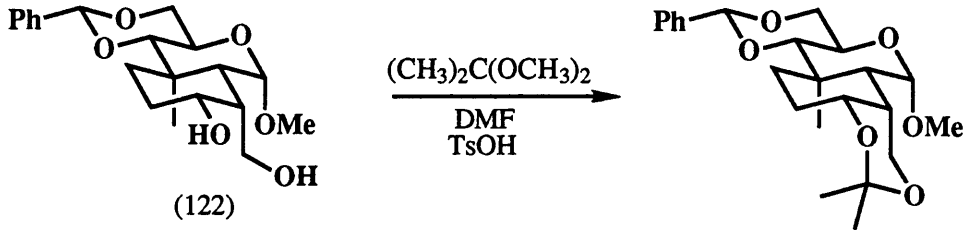
(214) R = ^{t}Bu 30%
(215) R = Ph 20%

This indicates that a more robust protecting group is required to withstand the rigorous NBS conditions.

Protection of the Diol as an Acetal.

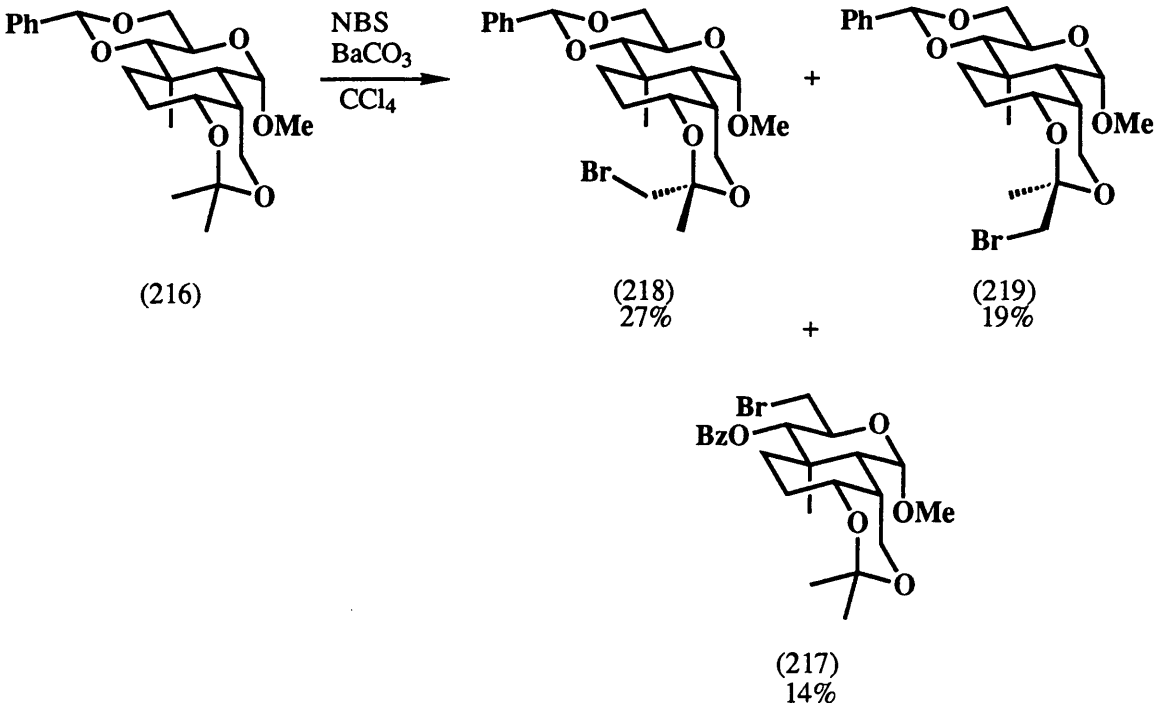
It was decided to continue with the theme of a cyclic protecting group, as it was thought that this may help in reducing steric hindrance of the C-ring synthon aldehyde group and controlling the conformation of the C-ring. A cyclic acetal would tie the hydroxyl and hydroxymethyl groups together and hold them in a rigid conformation, this

would prevent the carbocyclic ring from flipping. The diol (212) was successfully protected as the acetonide[62] (216) using 2, 2-dimethoxypropane and TsOH in a yield of 67%.

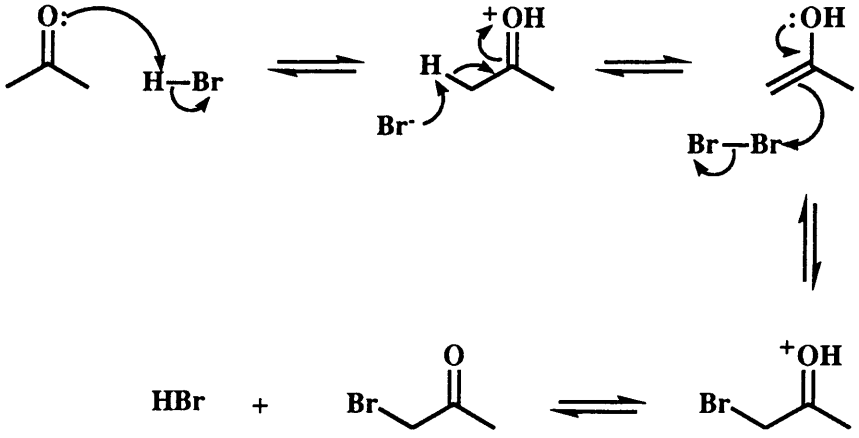


(216)

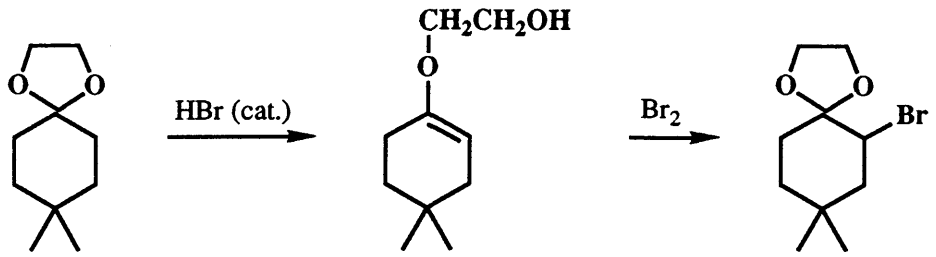
The opening of the benzylidene ring by bromination with NBS resulted in three compounds being isolated. The desired product (217) was obtained as the minor compound in a yield of 14%. The two other products (218) and (219) were isomers formed by the reaction of a methyl group of the acetal with NBS to give a bromomethyl. They were isolated in yields of 27% and 19% and peaks in the ^{1}H and ^{13}C NMR spectra showed that (218) was the major isomer. The signal for the CH_2Br group in this compound is further downfield in the ^{13}C NMR than for the other isomer and the singlet for the adjacent methyl is further upfield. This would be expected for (218) as the phenyl group will affect only the CH_2 group and shift the signal downfield, whereas in isomer (219), it would be the methyl that experiences a deshielding effect.



Ketones and aldehydes can be halogenated at the α-carbon position by reaction with bromine in acidic solution. The mechanism shown below involves the formation of an enol and its attack on molecular bromine to give an intermediate, which on deprotonation yields the α-halogenated product.



The bromination of ketals occurs by a similar mechanism. In the literature procedure shown below, a catalytic amount of acid generated in the reaction mixture opens the ketal ring to form an enol ether. The double bond is brominated whilst the ring is simultaneously reformed to give the α-brominated ketal.

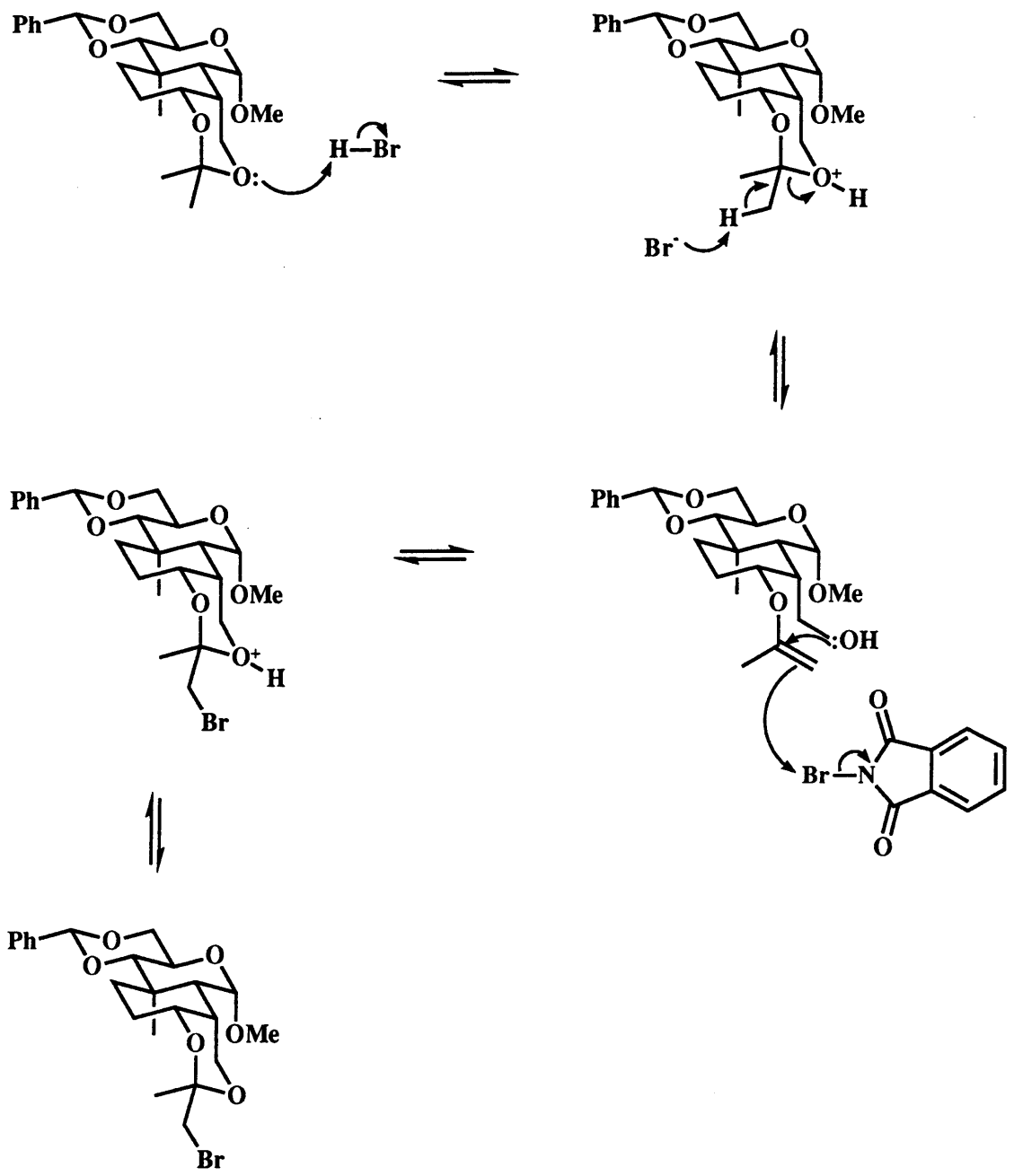


It is thought that a similar mechanism may be occurring with the acetal group of (216) (Scheme 31). A small amount of HBr will be present within the reaction mixture which will protonate an oxygen of the acetal. The bromide anion could act as a base and remove an α-acidic hydrogen to generate a double bond. The N-Br bond of NBS is polarised such that the Br bears a slight positive charge, the oxygen of the hydroxyl group could then cyclise as the double bond simultaneously attacks a NBS molecule at the α-position or the double bond could attack a molecule of bromine which will also be present within the reaction mixture. Loss of the proton co-ordinated to the oxygen would yield the α-brominated product. The C-O bond next to the double bond can rotate freely, thereby allowing cyclisation to either face of the quaternary carbon to give both products (218) or (219).

Protection of the Diol as an Ether.

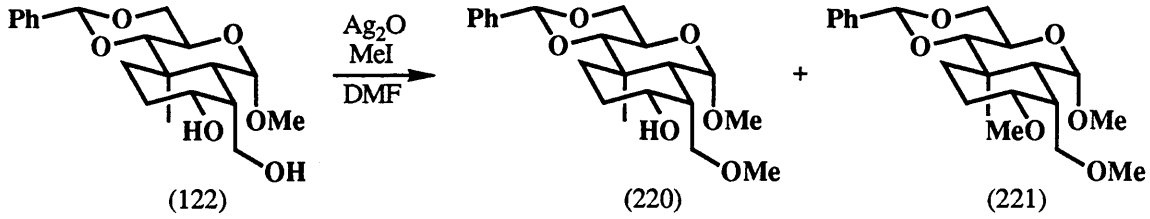
An alternative protecting group needed to be found which does not contain any α-hydrogens and the next approach was to protect the OH functions as methyl ethers. Whilst it was realised that methyl groups would be difficult to remove later in the route, it was thought that this small group would dramatically reduce remote steric hindrance of the aldehyde in the C-ring synthon. The methyl protected product would hopefully allow the addition of the diene portion to the carbonyl group, the introduction of a dienophile and ultimately the completion of the Diels-Alder cyclisation to produce a chiral taxoid from glucose.

The first synthesis of the dimethyl ether (221) involved treatment of the diol (122), dissolved in DMF, with silver oxide and MeI. The reaction mixture was stirred at room temperature for 24 hours, however, the major product isolated in a yield of 63%



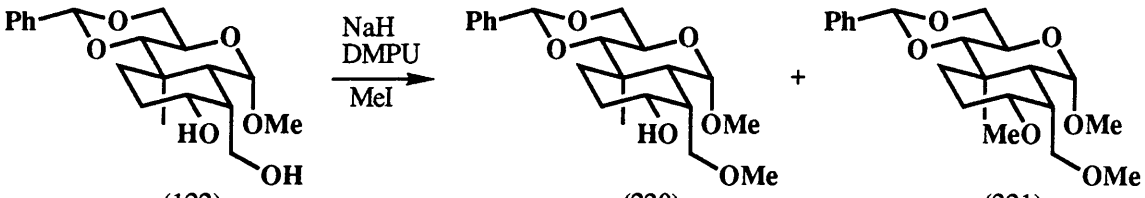
Scheme 31

was the monomethylated compound (220), in which only the primary hydroxyl had been converted to its methyl ether. The desired dimethylated product (221) was also acquired, but only in a yield of 13%. From these yields it could be seen that an alternative preparation must be sought.



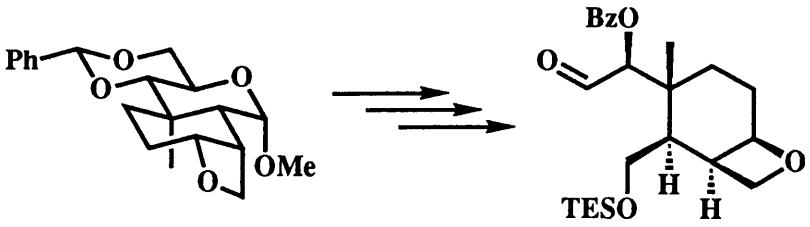
(122) (220) (221)

A much higher proportion of the dimethylated compound (221) was achieved when the diol was deprotonated by stirring with NaH and DMPU at room temperature for 1 hour, followed by the introduction of MeI into the mixture. The optimum yields of the two products were 66% of (221) and 18% of (220). Another advantage to this reaction is that it is possible to isolate the monomethylated compound (220) and further treat with the same conditions to afford more dimethylated product, thereby increasing the overall yield.



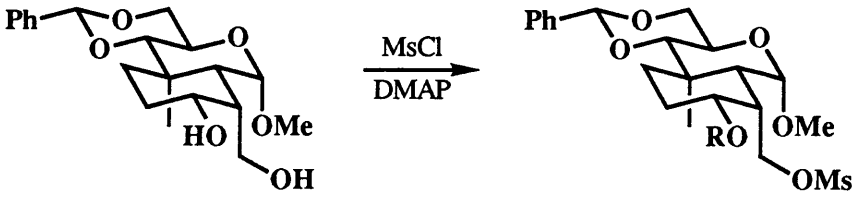
(122) (220) 18% (221) 66%

As the ultimate aim was to construct an oxetane ring on the C-ring of the final taxane skeleton, it was thought that introducing the D-ring at this stage would be more efficient, as this would prevent the need for a protecting group. If the oxetane (222) was able to withstand the subsequent reactions, it would be possible to progress to a CD ring synthon (223) with the oxetane ring already in place.



(222) (223)

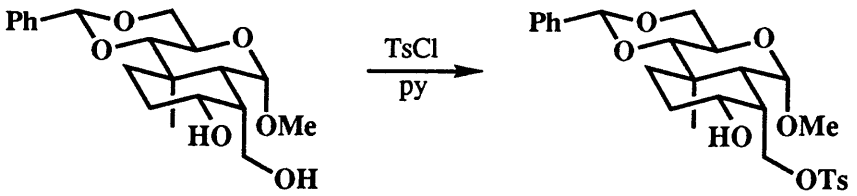
To construct the oxetane ring, the aim was to convert the primary hydroxyl into a good leaving group, deprotonation of the secondary OH would then cyclise on to the CH_2 group simultaneously displacing the good leaving group by an S_N2 mechanism. The diol was treated with DMAP and mesyl chloride at 0°C to synthesise the monomesylate[15a] (225), after one hour the major compound isolated was the dimesylate (224) in a yield of 40%. The monomesylate (225) was obtained in a low yield of 25% and the mass balance was unreacted starting material.



(122)

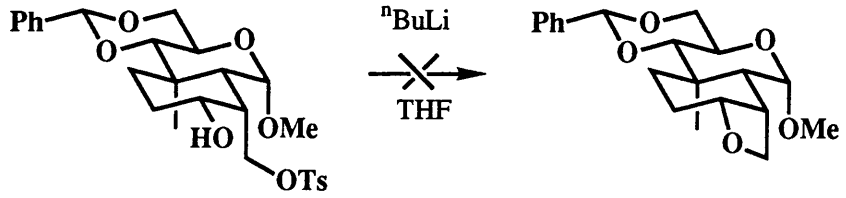
(224) R = Ms 40%
(225) R = H 25%

Shorter reaction times did not reduce the proportion of dimesylated compound, it was thus decided to use TsCl as this may be more selective for the primary hydroxyl due to its larger size. The diol was reacted with TsCl and pyridine in dry CH_2Cl_2 at room temperature for 43 hours. The tosylate (226) was achieved in 35% and 47% of unreacted starting material was recovered. Increasing the reaction times did not improve yields and also allowed the formation of 5% of ditosylate. It was necessary to recycle the starting material and react it again to obtain a second batch of the required product.

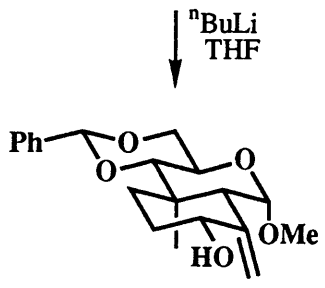


(122) (226)

The tosylate (226) was refluxed with ^{n}BuLi in THF to deprotonate the hydroxyl group and cyclise to the oxetane ring. A product was isolated as a white solid in 61% yield, however, a signal in the ^{13}C NMR spectrum (Figure 4-1) representing a quaternary centre at δ146.3 indictated that the oxetane (227) had not been formed. From its position, it was suspected that this peak was due to a quaternary centre which was part of a double bond. Also, a CH_2 signal at δ106.4 could be another carbon making up half of a double bond, as it is further downfield than anticipated for the CH_2 of an oxetane ring. Further evidence was provided by the infra-red spectrum which revealed a peak at 1650cm^{-1}, this probably represents a double bond, a sharp signal at 3600cm^{-1} also indictates that the product contains a free hydroxyl group. The mass spectrum showed a molecular ion of mass 346, which is the same as that expected for the oxetane ring product. From these spectra and the ^{1}H NMR, it was suspected that deprotonation at C-7 may have occurred which would allow elimination of the tosylate group to yield the product (227) containing a double bond with a quaternary carbon at one end and a CH_2 group at the other.

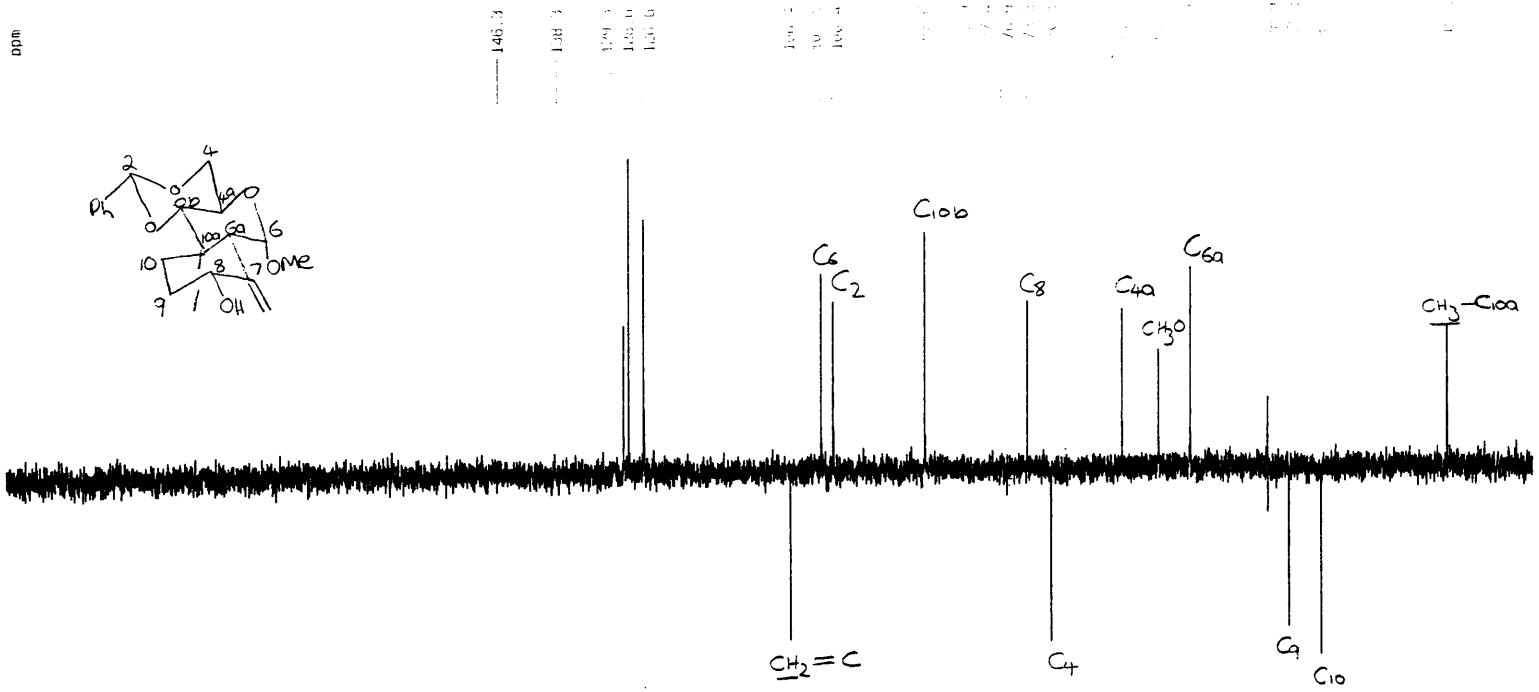


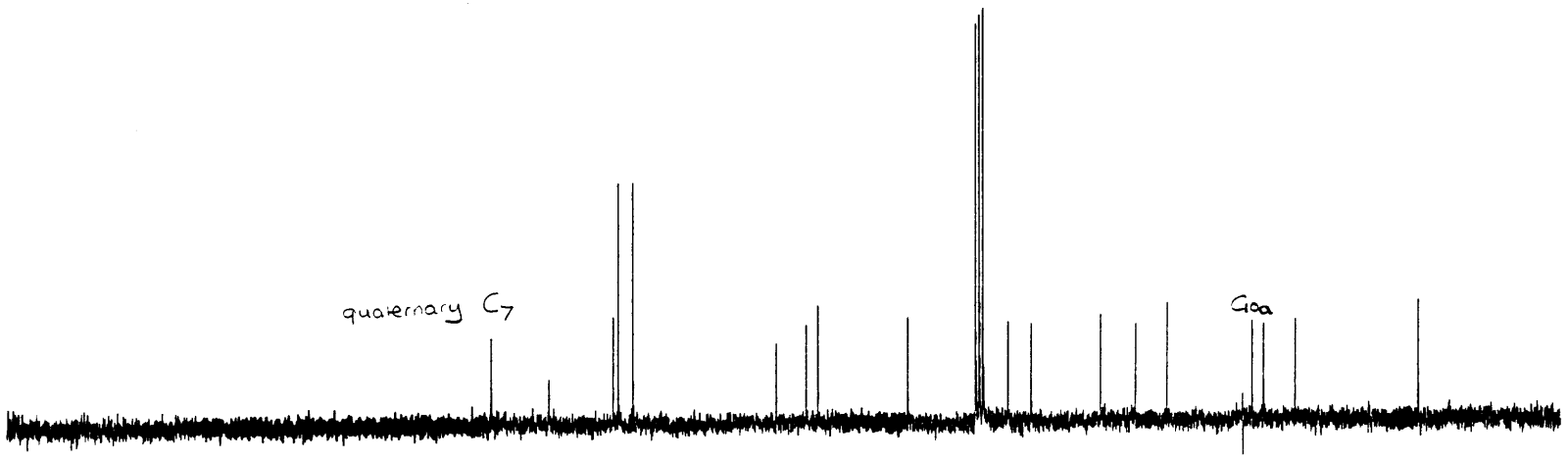
(226) (222)



(227)

This structure was confirmed by X-ray crystallography (Figure 4-2), the crystals were not of high enough quality to pinpoint co-ordinates of the hydrogen atoms, but the analysis did allow a picture of the carbon and oxygen framework to be obtained.





Current Data Parameters

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PROCNO	1

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RG	16384
NUCLEUS	13C
D12	0.0000200 sec
DL6	18.00 dB
D1	1.0000000 sec
P31	100.60 usec
D11	0.0300000 sec
DL5	18.00 dB
P1	7.00 usec
DE	35.00 usec
SFO1	62.9015337 MHz
SWH	20000.00 Hz
TD	65536
NS	256
DS	2

F2 - Processing parameters

SI	32768
SF	62.8959294 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	30.00 cm
F1P	215.000 ppm
F1	13522.63 Hz
F2P	-5.000 ppm
F2	-314.48 Hz
PPMCM	7.33333 ppm/cm
HZCM	461.23682 Hz/cm

Figure 4-1

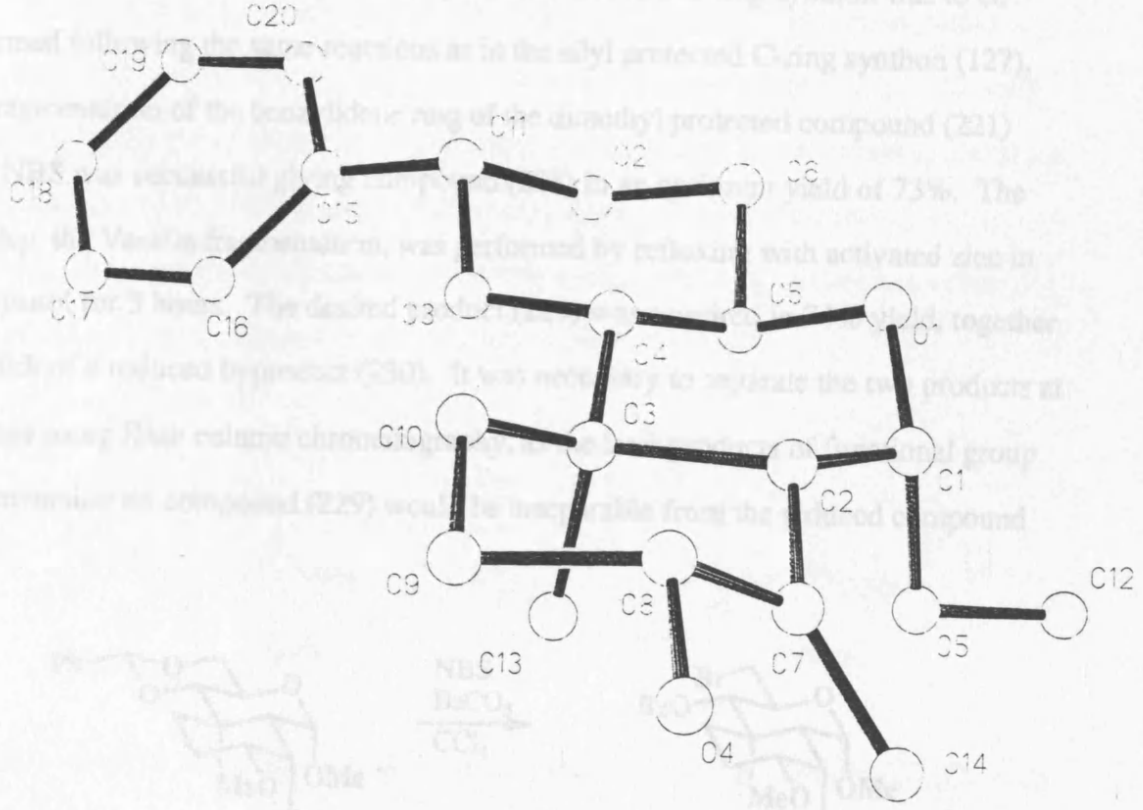
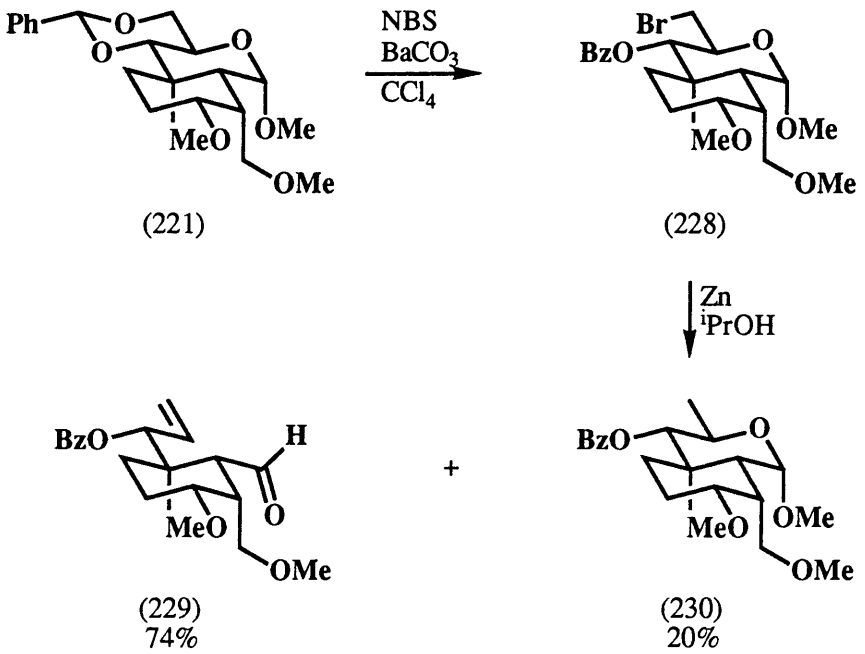

C20
C19
C18
C17
C16
C15
C11
C12
C6
C5
C1
C4
C3
C2
C10
C9
C8
C7
C13
C14
O4
O5
O3
C12

Figure 4-2

The product (227) was subjected to the conditions of the benzylidene fragmentation, but T.L.C. showed several spots which were decomposition products.

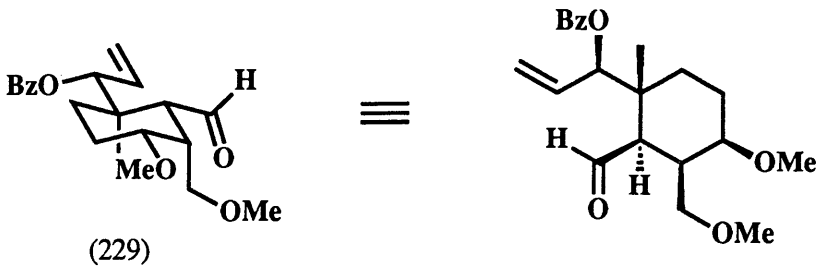
Synthesis of a Methyl Protected C-Ring Synthon.

The conversion of the protected product (221) to a C-ring synthon was to be performed following the same reactions as in the silyl protected C-ring synthon (127). The fragmentation of the benzylidene ring of the dimethyl protected compound (221) using NBS was successful giving compound (228) in an optimum yield of 73%. The next step, the Vasella fragmentation, was performed by refluxing with activated zinc in isopropanol for 3 hours. The desired product (229) was acquired in 74% yield, together with 20% of a reduced byproduct (230). It was necessary to separate the two products at this stage using flash column chromatography, as the later products of functional group interconversion on compound (229) would be inseparable from the reduced compound (230).



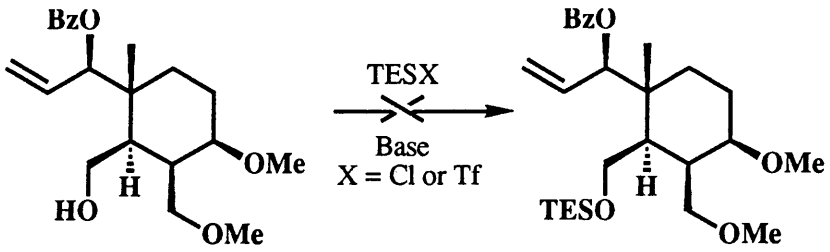
(221) (228)

(229) 74% (230) 20%



(229)

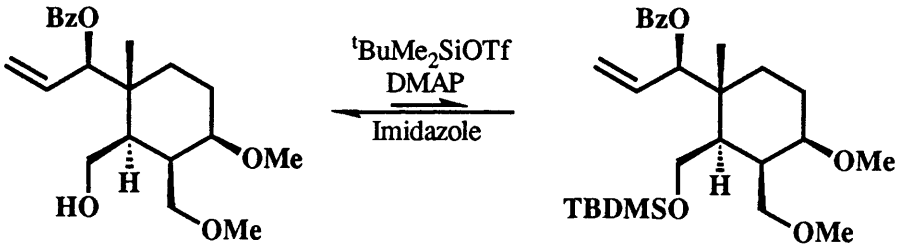
The reduction of the aldehyde group of (229) to the alcohol (231) proceeded smoothly in high yields using $NaBH_4$, but problems were encountered in the following step where the OH group needed to be protected as a silyl ether. As attempts to introduce a triethylsilyl group had failed using the standard reagents of imidazole and triethylsilylchloride, further efforts were made by trying triethylsilyltriflate and other bases including DMAP, pyridine and a mixture of NaH and DMPU.



(231) (232)

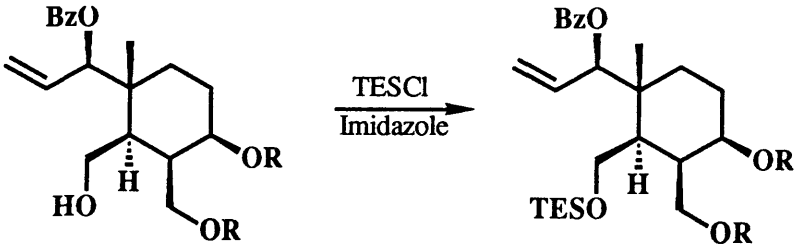
However, all these reactions showed only starting material (231) by T.L.C., even after reaction times of 24 hours. It was thought that the triethylsilyl group of compound (232) would be extremely labile and that after protection of the OH, the silyl group would be immediately hydrolysed to return to the starting material (231). It was anticipated that the problem may be solved by using a bulkier silyl protecting group which would be less labile. The reagent chosen was t-butyldimethylsilyltriflate, this was introduced to the reaction mixture after the alcohol had been treated with 2.0 equivalents of imidazole and 0.16 equivalents of DMAP at -10°C. After 50 minutes, T.L.C. showed the reaction had proceeded to approximately 50%. The mixture was stirred for another 25 minutes after which time the reaction did not appear to have progressed any further, but a T.L.C. of the reaction mixture taken after a further one hour showed only starting material again, indicating that the silyl group had been hydrolysed. The reaction was repeated and stopped after 50 minutes when it had reached approximately 50% conversion, but on

quenching the mixture the silyl group was again hydrolysed and only starting material was isolated.



(199) (201)

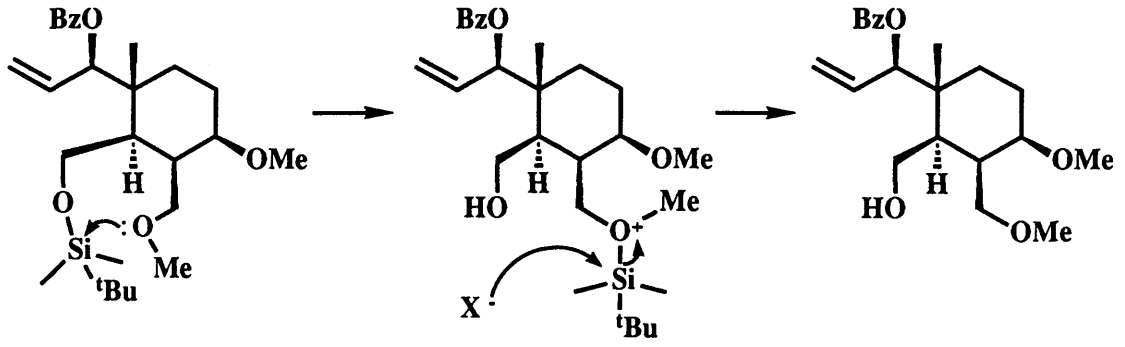
It was deduced that hydrolysis of the silyl ethers must be linked to the presence of the methyl protecting groups as this phenomenon was not seen for the equivalent alcohol (125) which contained bulky silyl protecting groups. Protection of (125) using a TES group gave compound (126) which was highly stable.



(97a) (98)

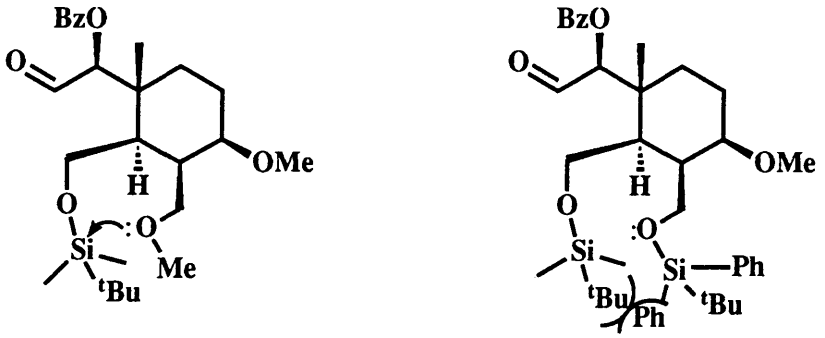
R = Si^{t}BuPh$_2$

One possible suggestion for the mechanism of hydrolysis is illustrated below. The lone pair on the oxygen of the nearby methoxy group could attack the silyl group and cause the Si-O bond to break by an S_N2 displacement. The chloride or triflate anion would then attack the silicon faster than the carbon of the methyl group to give back the starting material.



(233) (234) (231)

The chloride or triflate anion would be more likely to attack the second species (234) rather than (233) as the oxygen bears a positive charge thereby weakening the Si-O bond. This mechanism therefore necessitates the involvement of the neighbouring OMe group and can lead us to an explanation of why (126) is much more stable. In the case of compound (233), the methoxy group is small and the oxygen can approach the silicon without much hindrance (Figure 4-3), however, in (126) the bulky TBDPS protecting group will be subject to much more steric hindrance if the oxygen tries to approach the neighbouring silicon of the TES or TBDMS group. The hydrolysis of (126) is thus less likely to take place.

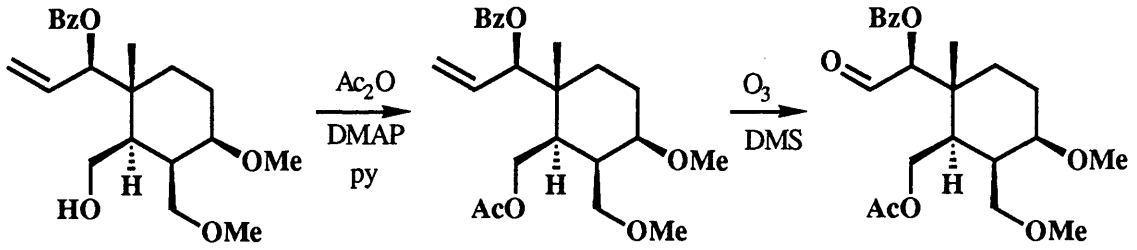


(233) (126)

Figure 4-3

Protecting the alcohol as an acetate provided a solution to the problem, the acetyl was introduced by reaction with Ac_2O in the presence of DMAP and pyridine. The yield was optimised to give 82% of the product (235), which upon ozonolysis in a 1.56M solution of MeOH in dichloromethane cleaved the double bond cleanly to afford an

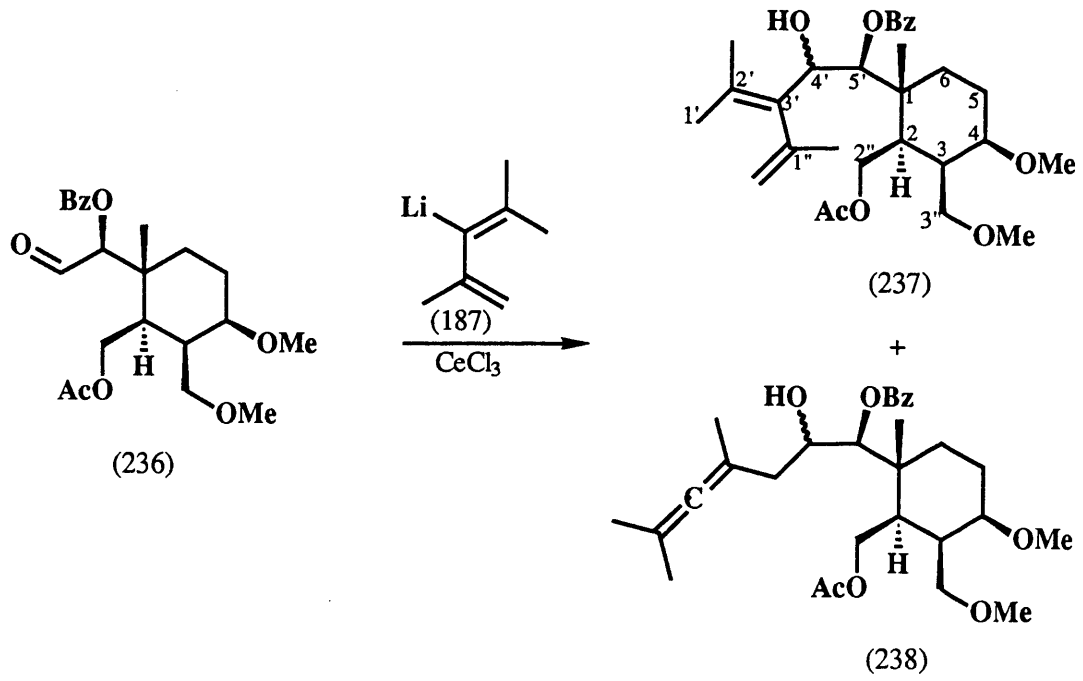
aldehyde (236) quantitatively. This was the C-ring synthon required to test the diene addition.



(231) (235) (236)

Diene Addition to the C-Ring Synthon (236).

The addition of the diene moiety to the carbonyl group of the C-ring synthon was carried out using the same conditions as described in Chapter 3. The bromodiene (172) was converted to the lithiodiene (187) by lithium-halogen exchange using ^{n}BuLi, treatment with $CeCl_3$ then generated an organocerium species[57-59]. The aldehyde (236) was introduced at -78°C and after 90 minutes the T.L.C indicated that no starting material was remaining. After an aqueous work-up, T.L.C. showed a series of small spots and two larger ones. The minor products were either uncharacterisable decomposition products or too small to be isolated. However, the two larger spots could be separated after purification by a minimum of two silica gel columns in yields of 40% and 17%. The major product was found to contain a single diastereoisomer of the desired dienyl alcohol product (237). The minor product was found to be a mixture of the opposite diastereoisomer of the dienyl alcohol (237) and a small amount of one diastereoisomer of the allenyl alcohol (238).

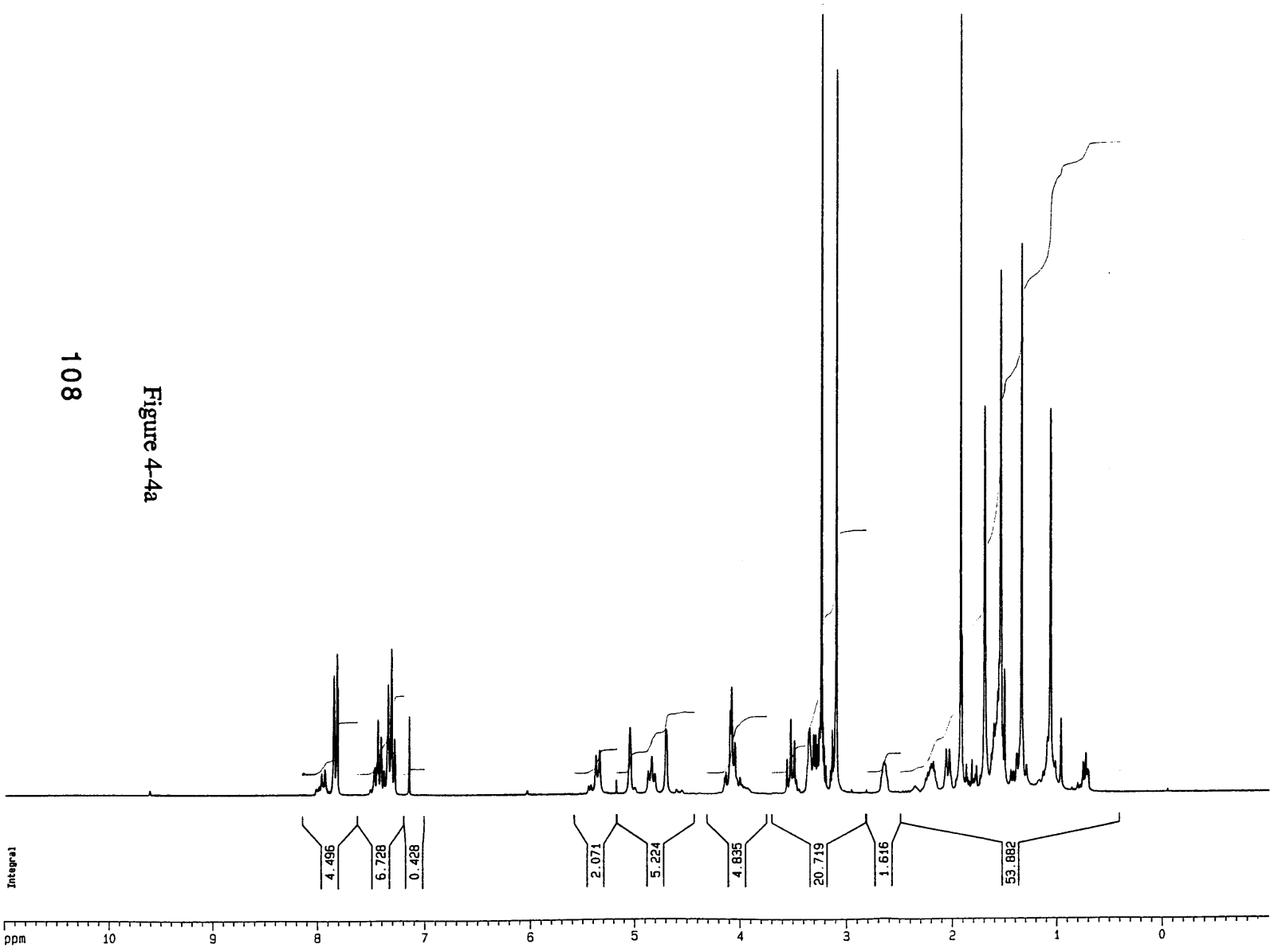


The structure of the major product (237) was elucidated using ^{1}H and ^{13}C NMR and a ^{1}H-^{1}H COSY correlation, the spectra can be seen in Figures 4-4a, 4-4b and 4-5. The numbering system employed in the assignment of the peaks is shown in structure (237). The methyl peaks on the diene can be seen clearly as singlets with an integration of 3H each at δ1.47, 1.67 and 1.82. The protons of the CH_2 group within the diene are seen separately as two singlets at δ4.83 and 5.17, the COSY correlation shows a weak coupling between these signals and the methyl group attached to C-1". The protons of C-1' and the methyl on C-2' are too far away to couple to the diene CH_2 group, but the COSY spectrum indicates that they couple weakly to each other. The broad triplet at δ4.96 representing H-4' is likely to be a broad doublet of doublets, as the proton couples both to H-5', which is shown as a doublet at δ5.48, and to the OH group at δ2.17 with similar coupling constants. The COSY correlation confirms the reciprocal coupling of each of these groups to the proton on C-4'. Further analysis of the structure is provided by the infra-red spectrum which shows a broad signal at 3500cm^{-1} representing the OH group, it is difficult to see any peaks due to the diene double bonds as these will be obscured by the signals from the phenyl ring within the benzoate group. The mass spectrum revealed a molecular ion of mass 502 which is expected for the structure (237).

SPECIAL NOTE

THIS ITEM IS BOUND IN SUCH A MANNER AND WHILE EVERY EFFORT HAS BEEN MADE TO REPRODUCE THE CENTRES, FORCE WOULD RESULT IN DAMAGE

Figure 4-4a



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PROCNO	1

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FIDRES	0.157307 Hz
DW	97.0 usec
RG	512
NUCLEUS	1H
D1	1.0000000 sec
P1	10.0 usec
DE	138.6 usec
SF01	250.1343021 MHz
SWH	5154.64 Hz
TD	32768
NS	16
DS	2

F2 - Processing parameters

SI	16384
SF	250.1328812 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	30.00 cm
F1P	11.000 ppm
F1	2751.46 Hz
F2P	-1.000 ppm
F2	-250.13 Hz
PPMCM	0.40000 ppm/cm
HZCM	100.05315 Hz/cm

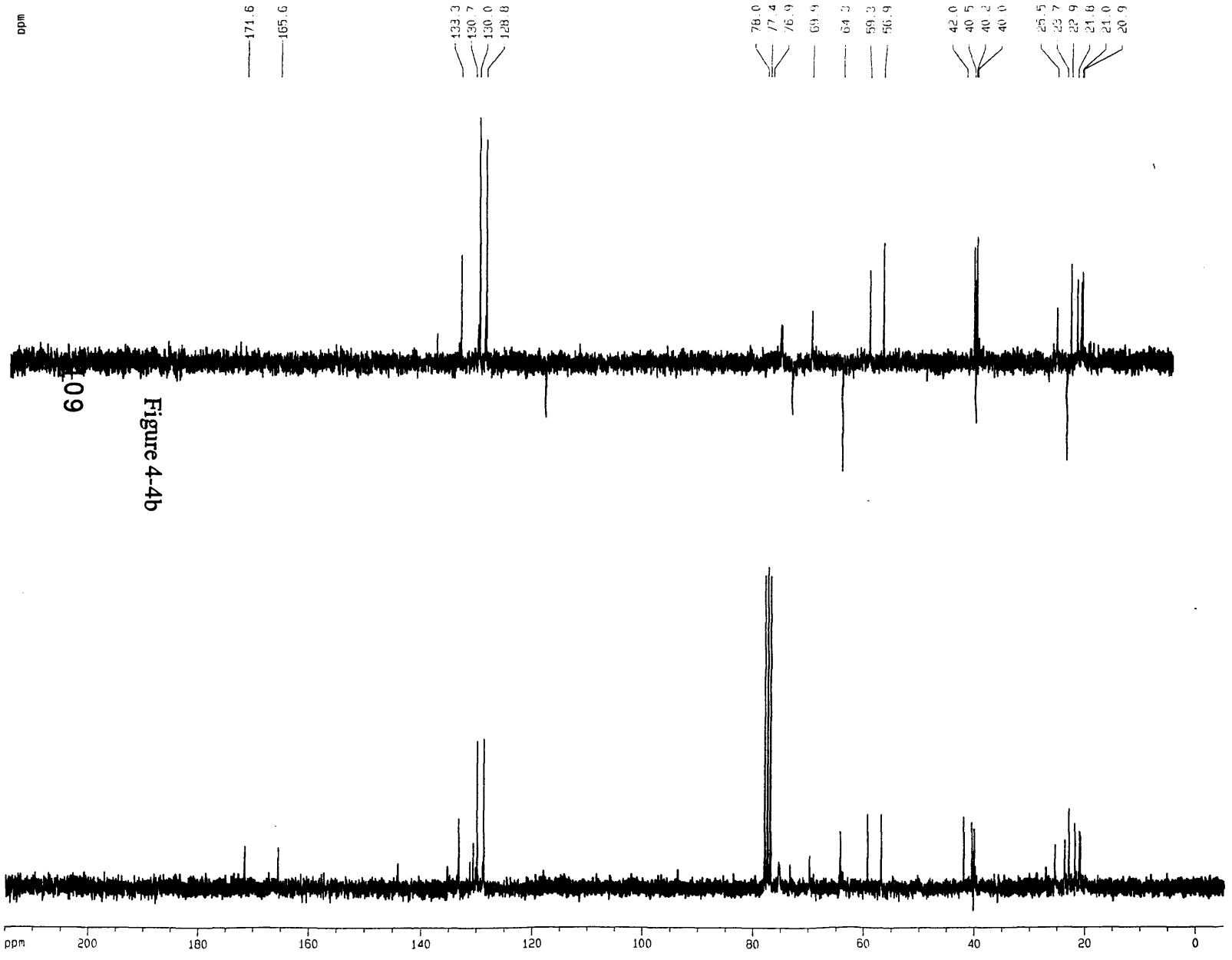

Figure 4-4b

Current Data Parameters

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PROCNO	1

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Time	14.38
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SOLVENT	CDCl3
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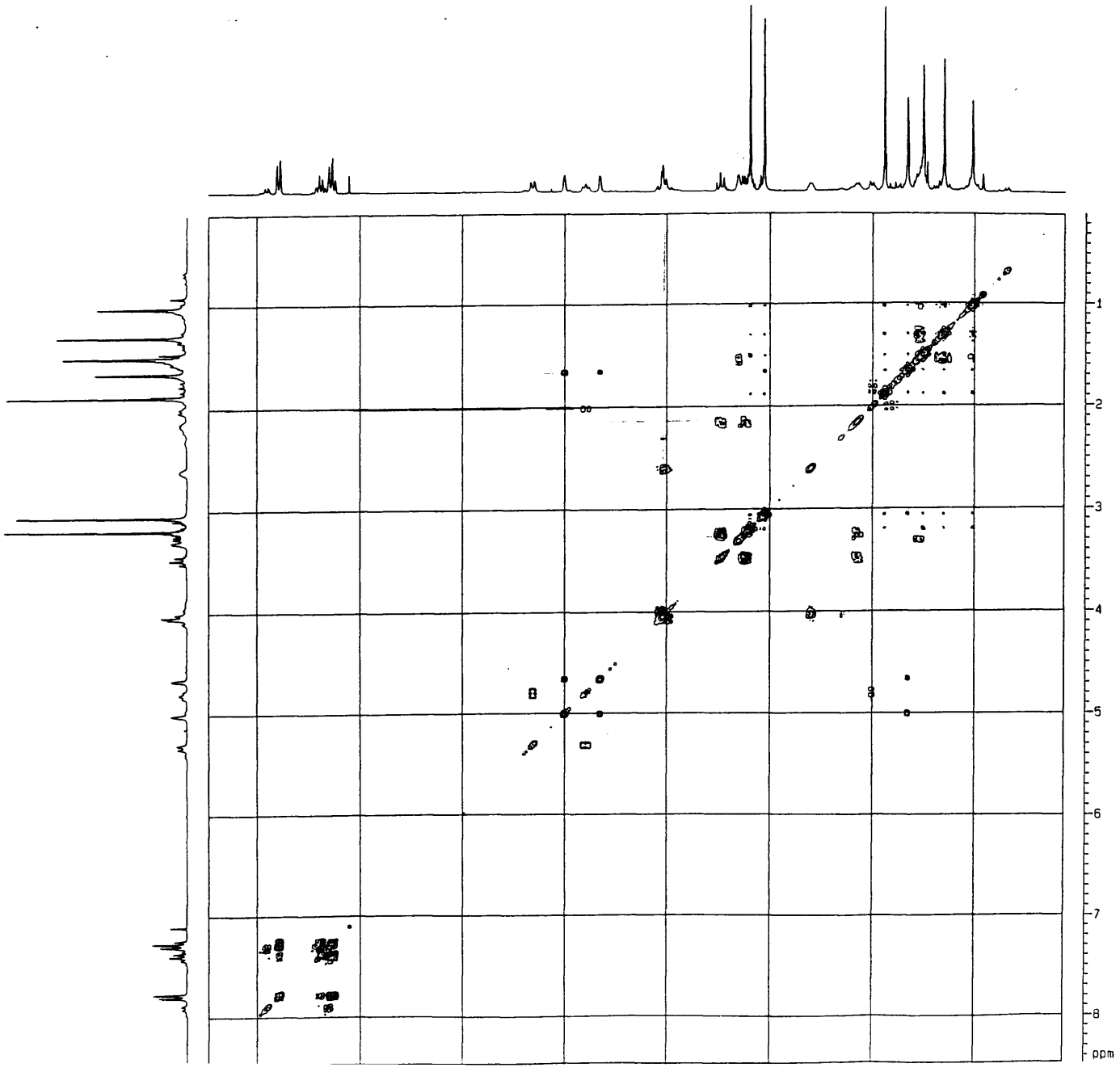
FIDRES	0.305176 Hz
DW	25.0 usec
RG	32768
NUCLEUS	13C
D12	0.0000200 sec
DL6	18.00 dB
D1	1.0000000 sec
P31	100.0 usec
D11	0.0300000 sec
DL5	18.00 dB
P1	7.0 usec
DE	35.7 usec
SF01	62.9015337 MHz
SWH	20000.00 Hz
TD	65536
NS	256
DS	2

F2 - Processing parameters

SI	32768
SF	62.8959294 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	30.00 cm
F1P	215.000 ppm
F1	13522.63 Hz
F2P	-5.000 ppm
F2	-314.48 Hz
PPMCM	7.33333 ppm/cm
HZCM	461.23682 Hz/cm



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PROCNO	1

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FIDRES	1.021509 Hz
DW	239.0 usec
RG	360
NUCLEUS	1H
D1	1.9098890 sec
P1	10.0 usec
D0	0.0000030 sec
DE	278.6 usec
SFO1	250.1339667 MHz
SWH	2092.05 Hz
TD	2048
NS	8
DS	4
IN0	0.0004780 sec

F1 - Acquisition parameters

ND0	1
TD	256
SFO1	250.134 MHz
FIDRES	8.17071 Hz
SW	8.364 ppm

F2 - Processing parameters

SI	1024
SF	250.1328931 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

F1 - Processing parameters

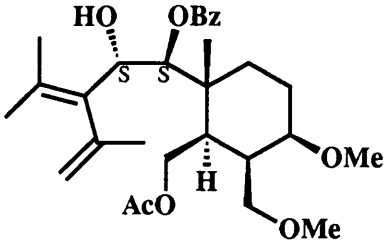
SI	1024
MC2	QF
SF	250.1328931 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	20.00 cm
CX1	20.00 cm
F2PLO	8.474 ppm
F2LO	2119.55 Hz
F2PHI	0.110 ppm
F2HI	27.51 Hz
F1PLO	8.474 ppm
F1LO	2119.55 Hz
F1PHI	0.110 ppm
F1HI	27.51 Hz
F2PPMCM	0.41819 ppm/cm
F2HZCM	104.60206 Hz/cm
F1PPMCM	0.41819 ppm/cm
F1HZCM	104.60206 Hz/cm

Figure 45

The product (237) was isolated as an oil and crystallisation was extremely difficult, therefore it was not possible to gain any data by X-ray analysis. It is thus difficult to state the absolute stereochemistry of the major diastereoisomer, but it can be predicted from the Felkin-Anh[60] models in Chapter 3 (Figure 3-2) that the S,S diastereoisomer (237a) will be favoured.

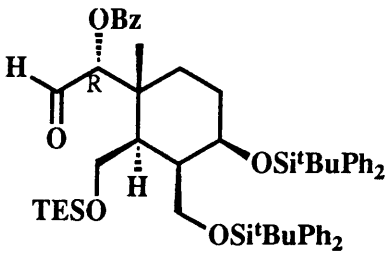


(237a)

The success of this reaction was a milestone in the route towards the taxane skeleton. The top half of the B ring and four out of the six carbons of the A ring had now been incorporated.

Molecular Modelling Studies of a C-Ring Synthon.

A molecular modelling study of the C ring synthon (127) containing the bulky t-butyldiphenylsilyl protecting groups was carried out by Simons and Sutcliffe. The aim of these investigations was to find the lowest energy conformation and study the probable approach of a nucleophile to the aldehyde. The minimum energy conformation is shown in Figure 4-6. However, the compound that had been modelled was infact a diastereoisomer of (127) in which the carbon bearing the benzoate group was of the R configuration (127a).



(127a)

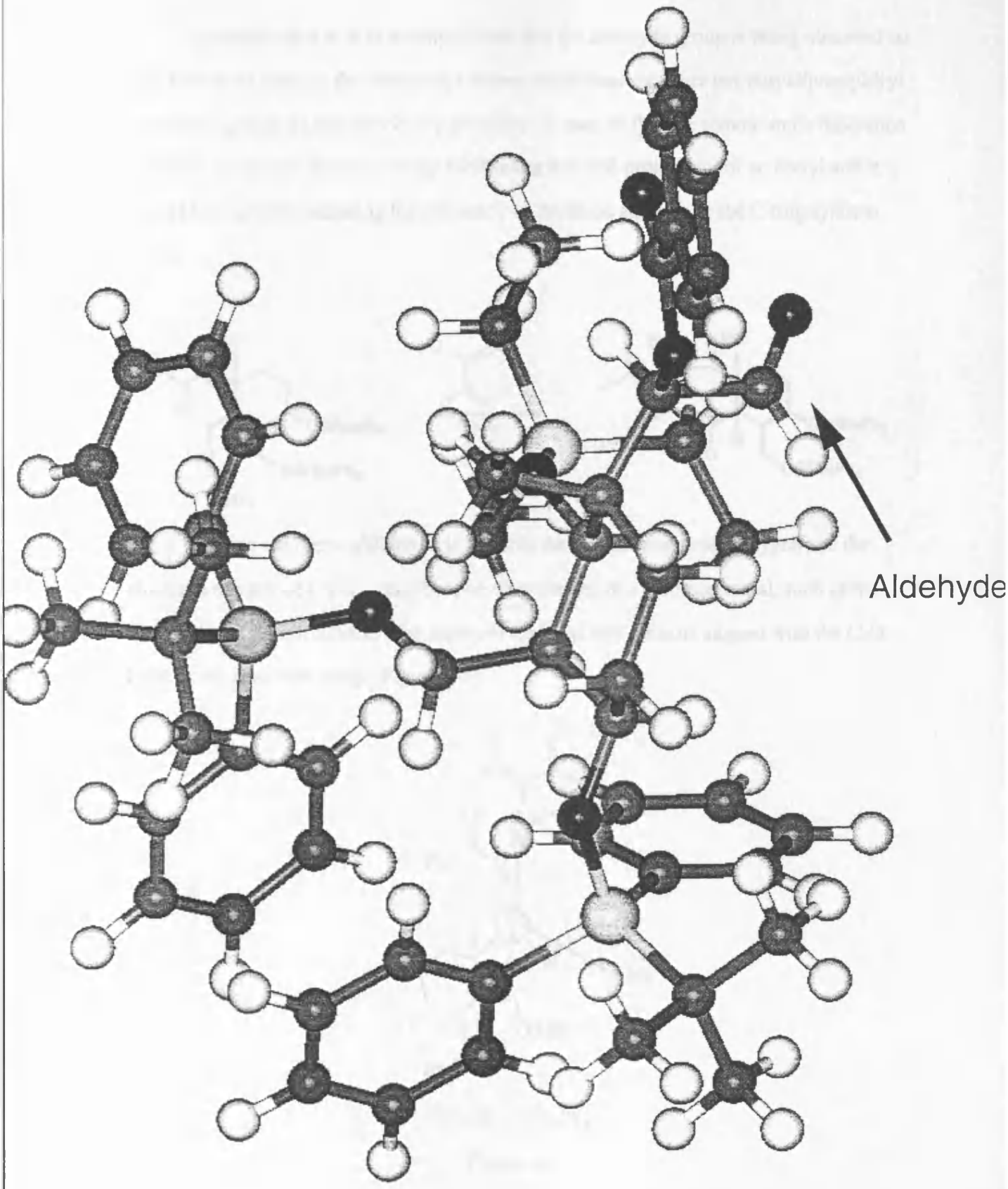
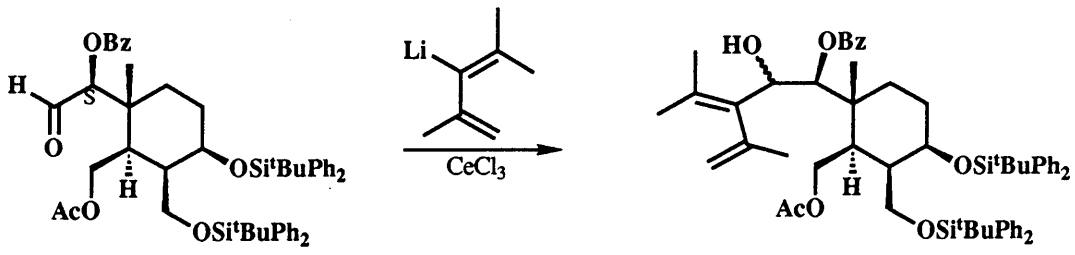


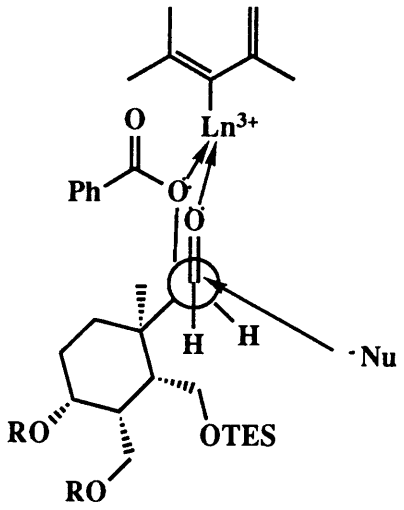
Figure 4-6

From figure 4-6, it is worthy of note that the aldehyde group is being obscured on one face by an ethyl of the triethylsilyl moiety rather than the other tert-butyldiphenylsilyl protecting groups as was previously predicted. It may be that the remote steric hindrance problem could have been solved by substituting the TES protection for an acetyl and it would be worth investigating the efficiency of the diene addition to the C ring synthon (239).



(239) ?

During the diene addition, it is possible that the benzoate ester oxygen and the aldehyde oxygen of (127a) could both be co-ordinated to a common metal, such as the cerium, by chelation control. The aldehyde carbonyl will become aligned with the C-O bond in the benzoate group (Figure 4-7).



(127a) R = Si^{t}BuPh$_2$

Figure 4-7

In figure 4-6 we can visualise that the diene unit would prefer to attack from behind and parallel to the C-H bond, as in figure 4-7, this would avoid any steric hindrance with the cyclohexane ring and result in the R,R diastereomer being the major isomer. As the C-2 of our C ring synthon (236) has an S configuration, we can predict that the S,S diastereoisomer of the diene addition product (237a) will be preferred.

Chapter 5

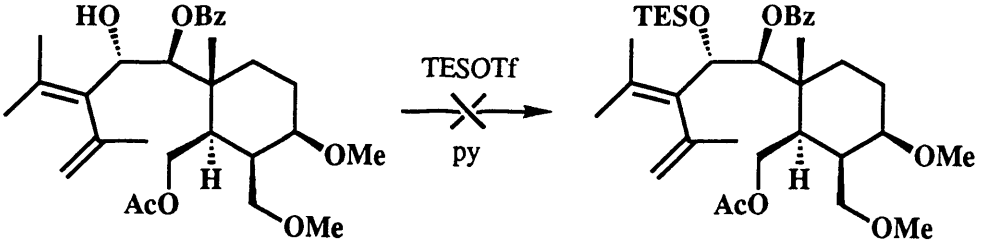
Further Progress towards a Cyclic Taxoid.

Repeating the Diene Addition to the C-Ring Synthon (236).

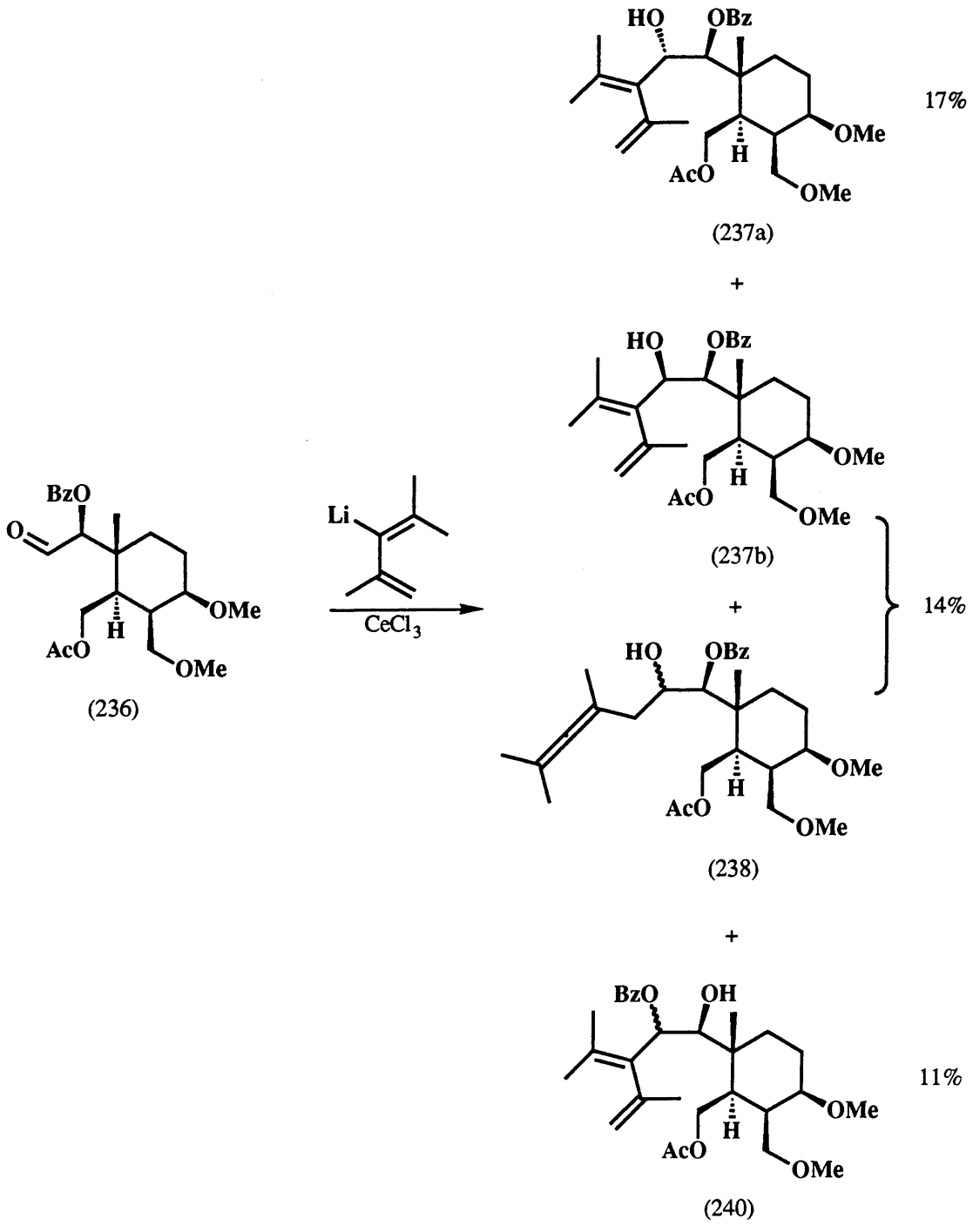
Initial attempts to reproduce the results of the diene addition reported in Chapter 4 were unsuccessful and only the starting material (236) was recovered. It was discovered that it is crucial to use a fresh bottle of cerium (III) chloride heptahydrate and to dry it thoroughly at 140°C under vacuum for 2 hours, heating for longer periods of time will cause decomposition and the reaction will fail. It is also essential to use freshly opened ^{n}BuLi or a bottle that has been sealed efficiently and stored at <4°C. On one occasion, only 17% of the major diastereoisomer (237a) was isolated along with 14% of a sample containing the opposite diastereoisomer (237b) and allenyl alcohol (238). However, a further compound in a yield of 11% was also obtained after column chromatography and this was elucidated to have the structure (240) in which the original product (237a) had undergone benzoyl migration. The same type of rearrangement was seen earlier in chapter 3 giving product (189b), the mechanism for the migration will be as illustrated for the previous aldehyde.

Further manipulations of the Diene Addition Product.

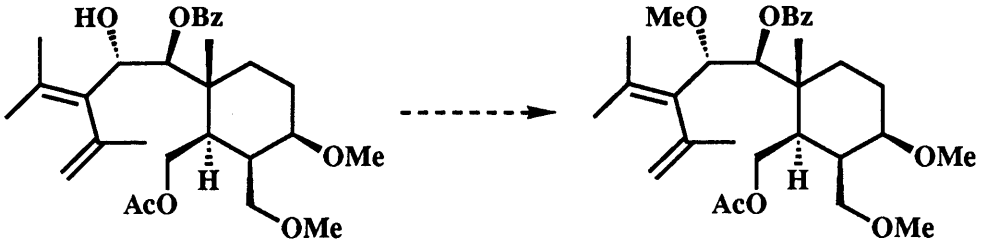
As the minor diastereoisomer of the dienyl alcohol (237b) was inseparable from the allenyl alcohol (238), the next few reactions were performed on the major diastereoisomer (237a). The first step was to find a suitable protecting group for the secondary hydroxyl function. Triethylsilyl was selected as the first candidate, as this would be easy to selectively remove at a later stage. Unfortunately, reaction of the dienyl alcohol with triethylsilyltriflate in pyridine overnight at room temperature afforded only recovered starting material.



(237a) (241)

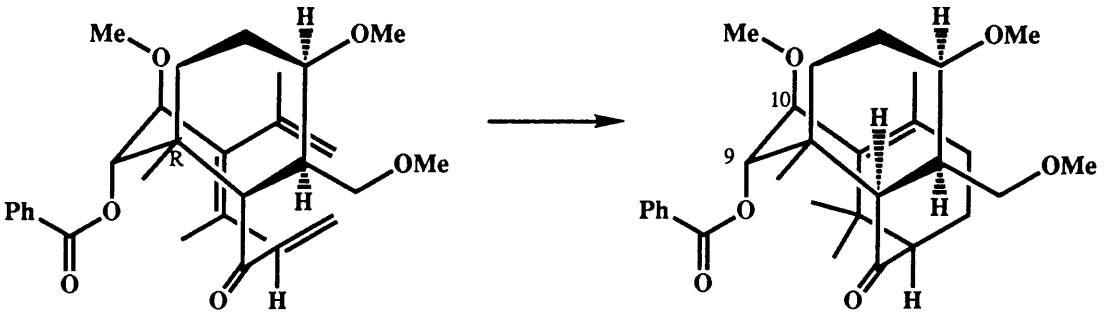

HO
OBz
OMe
H
AcO
OMe
17%
(237a)
+
HO
OBz
OMe
H
AcO
OMe
(237b)
+
14%
HO
OBz
OMe
H
AcO
OMe
(238)
+
BzO
OH
OMe
H
AcO
OMe
11%
(240)
BzO
O
OMe
H
AcO
OMe
(236)
Li
CeCl3

The second possibility was to protect the hydroxyl group as a methyl ether (242).



(237a) (242)

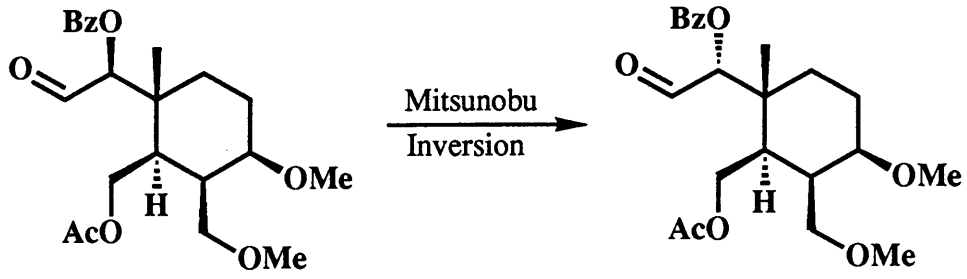
A small group at this position would be necessary in the final Diels-Alder cyclisation of (243) to (244). The trienone (243) needs to adopt a conformation such that the eight-membered ring in the transition state will have a chair-boat conformation. This will be facilitated if the group at C-9 and C-10 are both small. These groups will both be axial and thus experience 1,3 diaxial interactions, therefore keeping the bulk of these groups to a minimum will reduce the steric interactions and increase the chances of the trienone adopting the correct conformation.



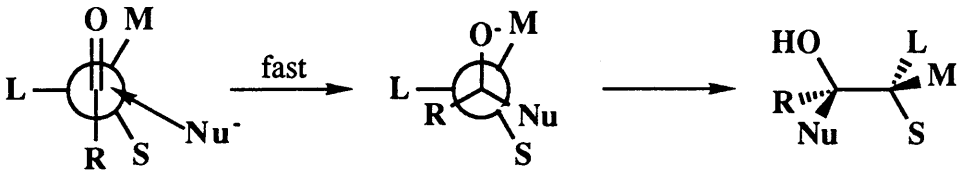
(243) (244)

The chances of a successful Diels-Alder cyclisation occurring would be greatly increased if both the benzoate group and methyl groups were in the equatorial position. In the minor diastereoisomer (237b) the methoxyl group would already be in the equatorial position, therefore if it were possible to invert the benzoate group, 1,3 diaxial strain would be avoided and the trienone would have a much higher ability to adopt the required chair-boat conformation. However, as the minor isomer is inseparable from the allenyl alcohol (238) a different approach must be sought.

This could be achieved by changing the stereostructure of the benzoate group in the C-ring aldehyde prior to diene addition using a Mitsunobu inversion.

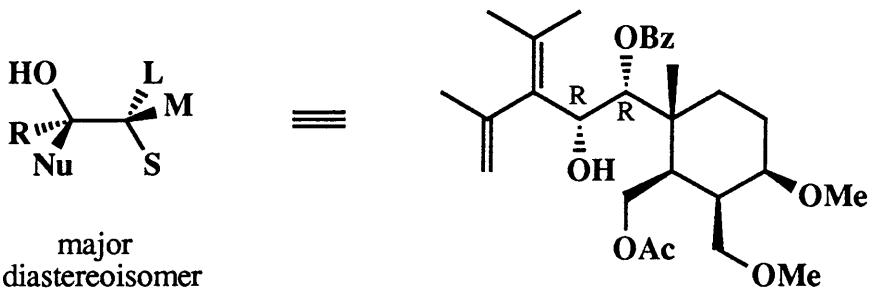


Addition of the diene portion to the aldehyde group using the same method as described in Chapter 4 would yield the required (R, R) diastereoisomer of (237) as the major product. This has been predicted using the same Felkin-Anh assumptions as before, where addition will occur from the opposite face of the aldehyde group.



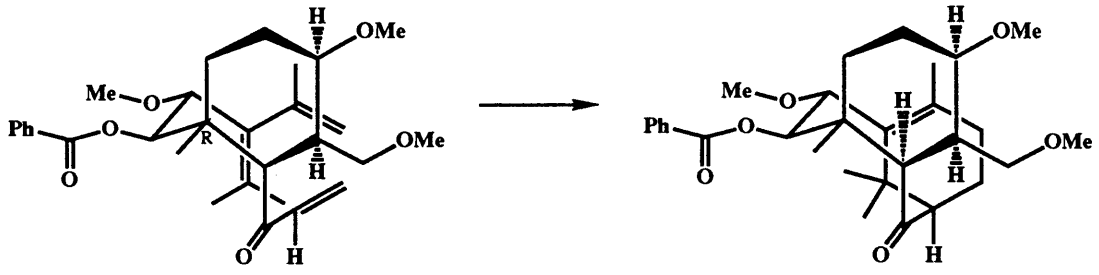
preferred conformation

major diastereoisomer



major diastereoisomer

Following protection of the hydroxyl as a methyl ether and the introduction of a dienophile, it would be possible for the resulting trienone to adopt the chair-boat conformation with groups C-9 and C-10 in the equatorial position. This should facilitate the cyclisation via the 8-membered ring transition state to give the final product (244a).

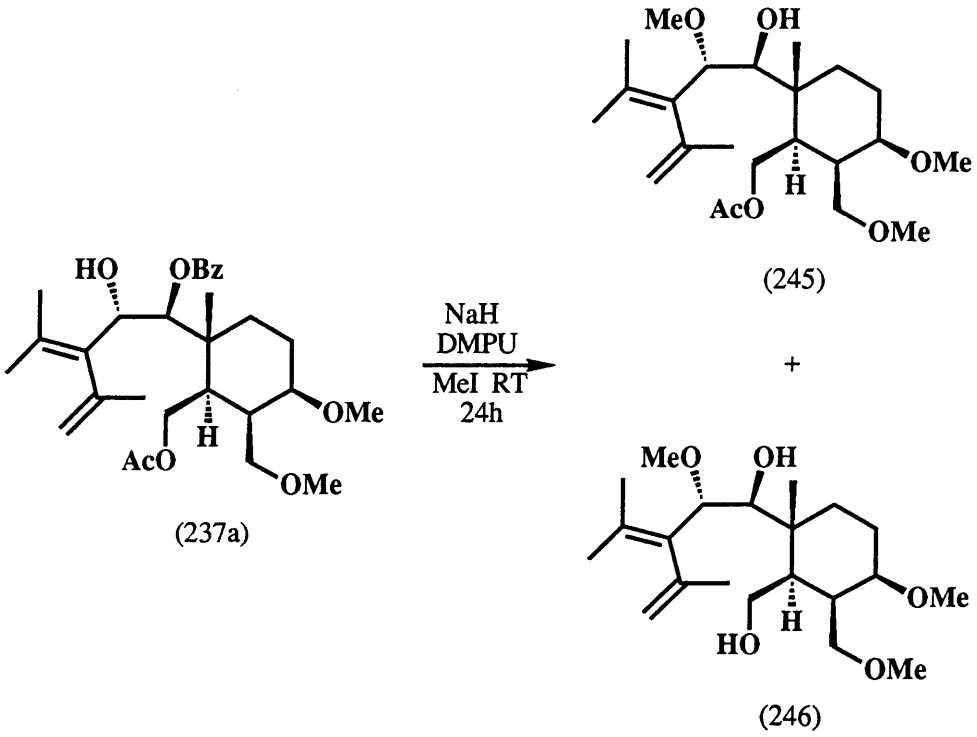


(243a) (244a)

As there was insufficient time to try the inversion and repeat the diene addition, the route was continued using the major product (237a) to investigate the possibility of protecting the hydroxyl as a methyl ether.

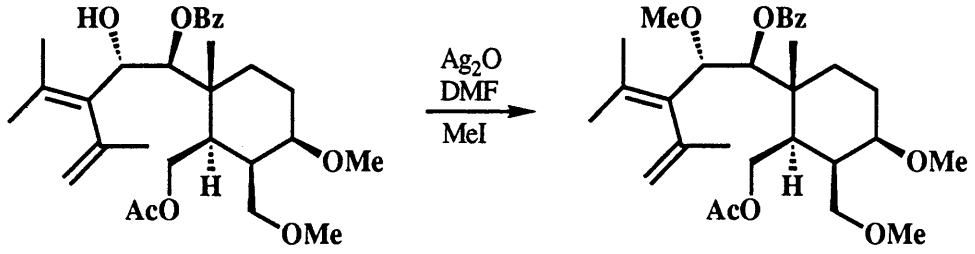
Protection of the hydroxyl function.

The dienyl alcohol (237a) was deprotonated using NaH and DMPU and treated with MeI for 2.5 hours to give the product (242) in 37% yield. The reaction was repeated and left to stir overnight in the hope of improving the yield, but the compound isolated in 45% yield was a mixture of the two products (245) and (246). The major product was (245) in which the benzoate ester had been hydrolysed and the minor compound (246) resulted from hydrolysis of both ester groups.



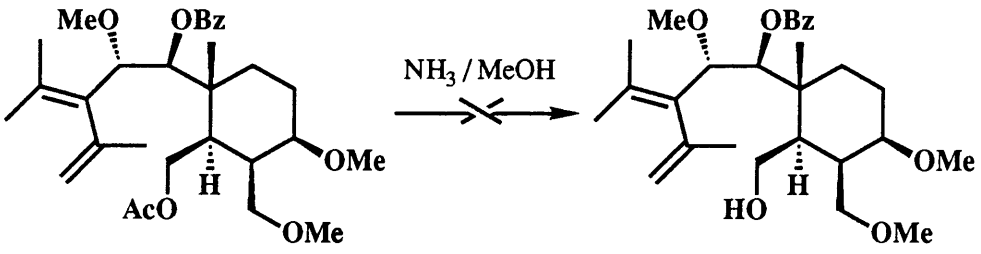
(237a) (245) (246)

An alternative method of introducing the methyl group was tried using the milder reagents of silver oxide and MeI in DMF. A T.L.C. taken after the mixture had been stirred for 16 hours showed < 10% conversion to the product (242) which was difficult to isolate by column chromatography as the reaction had been performed on < 10mg.



(237a) (242) < 10%

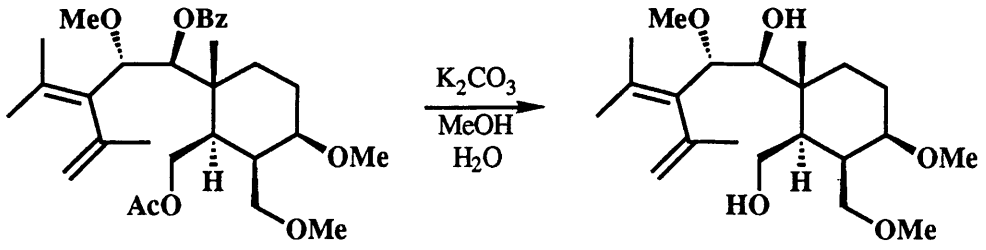
It was therefore necessary to return to the reaction employing NaH, DMPU and MeI and quench the mixture after just 2 hours. Despite the low yields, it was possible to attain a reasonable purity of (242) and continue the next reaction sequence. The aim of the following step in the route was to selectively remove the acetyl group in the presence of a benzoate ester, this would furnish a hydroxymethyl (247) which on oxidation to an aldehyde group would provide a handle onto which the dienophile portion could be introduced. It was hoped that by suspending the starting material (242) in a 50% solution of methanolic ammonia and stirring at room temperature the hydroxymethyl product (247) would be obtained, but after 24 hours only starting material was present in the mixture.



(242) (247)

Hydrolysis of the acetyl group was tried using potassium carbonate dissolved in methanol and water. This reaction proceeded slowly showing only starting material after 1 and 3 hour intervals, but on stirring the reaction mixture for 16 hours, a product was

isolated which was suspected to be the diol (246) where both ester groups had been hydrolysed.



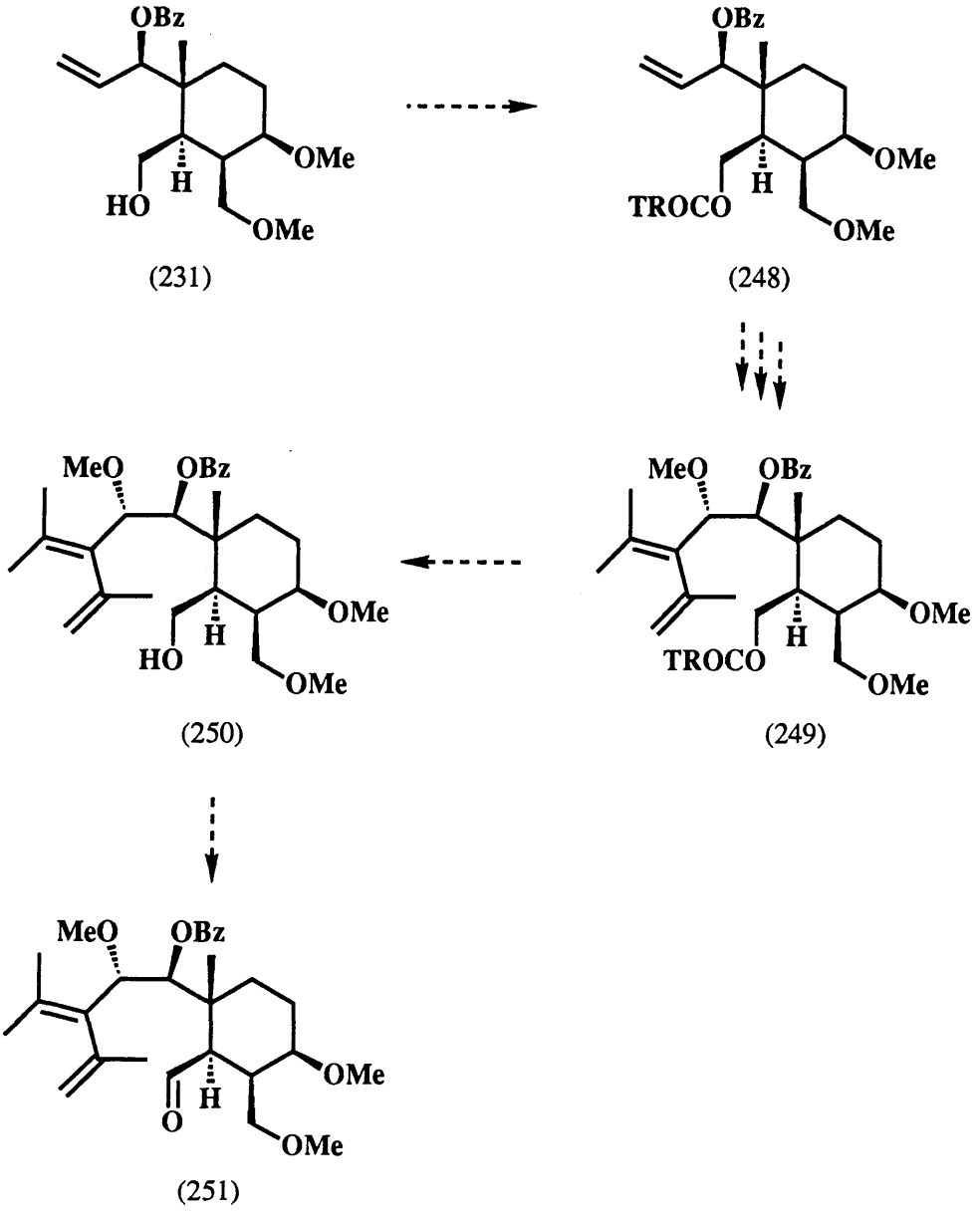
(242) (246)

The protected alcohol (242) was also treated with NaOMe in dry methanol and CH_2Cl_2 at 0°C for 19 hours. It is believed that this reaction resulted in the same diol (246) being obtained. At this stage, the reactions were being carried out on a scale of <8mg and the yields of products were approximately 2mg, it was therefore difficult to elucidate and characterise fully the structure of (246). The ^1H NMR would suggest the structure illustrated and the mass spectrum indicates a molecular mass of 338, this could be due to the loss of MeOH on heating to give the ion $[M\text{-}MeOH]^+$. It was at this point that the supply of advanced intermediates was exhausted and time elapsed, these factors prevented further investigation of this route.

Further Aims within The Research Group.

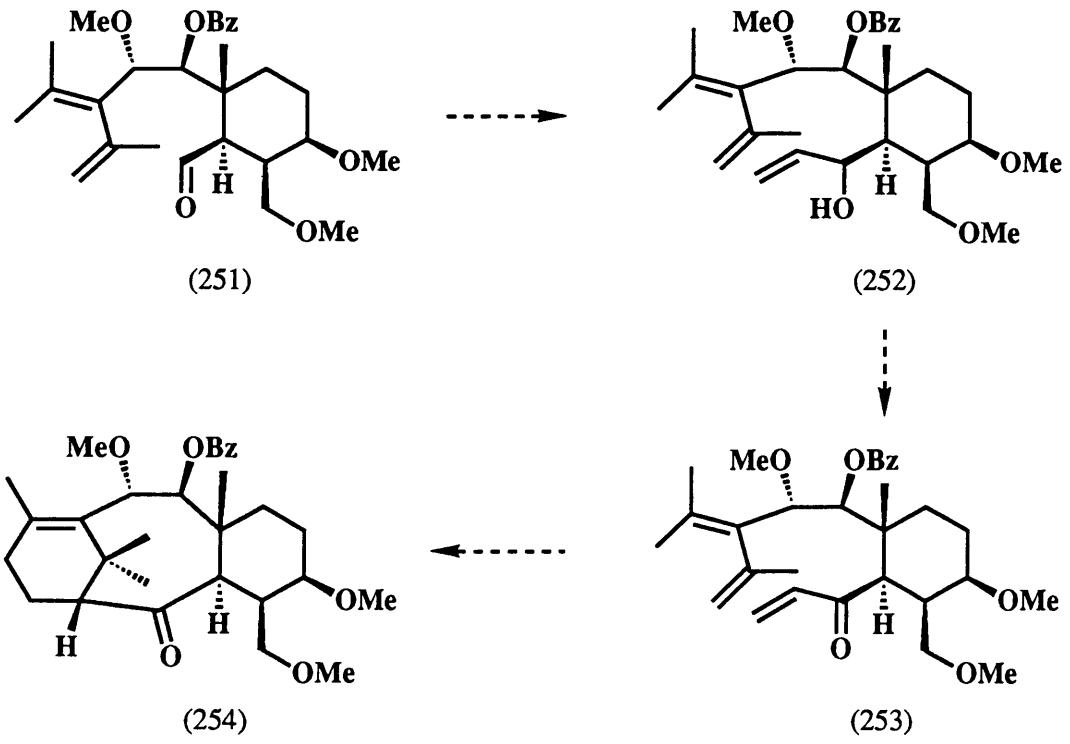
To resolve the problems experienced in the selective hydrolysis of the acetate, it would be necessary to protect with an alternative group before the ozonolysis reaction. One suitable candidate may be a trichloroethoxycarbonyl (TROC) group, which could be introduced using trichloroethylcarbonylchloride and pyridine to give (248). After the protection of the dienyl alcohol as a methyl ether (249), the TROC group could be cleaved by β-elimination under the mild conditions of zinc and acetic acid to give a hydroxymethyl (250) without affecting the benzoate ester. Oxidation of the primary hydroxyl will yield an aldehyde (251). Another alternative would be protect the alcohol as a chloroacetate, the electron withdrawing effect of the Cl would stabilise the carboxyl thereby discouraging hydrolysis. However, the size of the protecting group would be

similar to the acetate, whereas a TROC group would be bulkier and may lead to steric hindrance of the aldehyde as predicted by molecular modelling in Chapter 4.

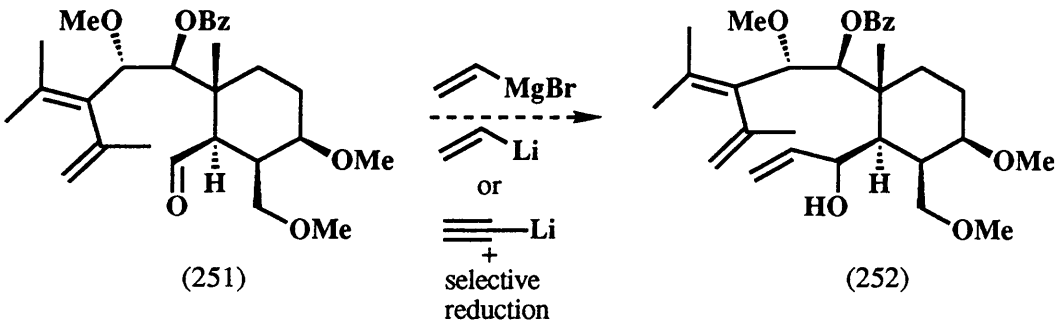


Introduction of the Dienophile.

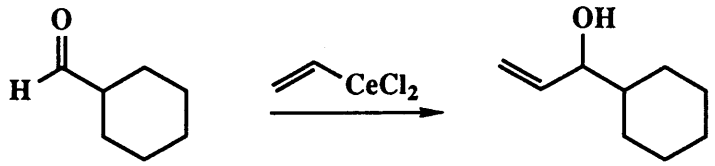
The remaining three steps to a chiral taxane skeleton are the addition of a vinyl group to the aldehyde to give an trienol (252), oxidation to the trienone (243) and Diels-Alder cyclisation to the tricyclic product[27, 28] (244).



There are a number of possible reagents that could be used to introduce a vinyl group which will form part of the dienophile side chain, including vinyl magnesium bromide, vinyl lithium and ethynyl lithium. If the lithium reagents prove to be too basic, cerium (III) chloride could be added to the reaction mixture to generate and organocerium species as in the diene addition.

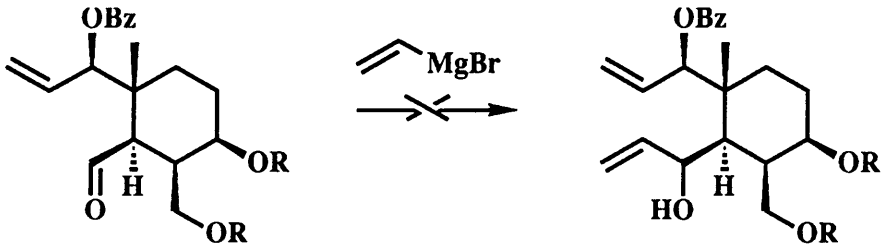


Reactions of these reagents on the model cyclohexane carboxaldehyde (179) were carried out by Boa. The cerium reagent gave the required product (181) in 50% yield, accompanied by another unidentified byproduct. Using vinyl lithium gave the cleanest reaction, but it was difficult to separate the product from the tetraphenyltin residues. These were formed as a byproduct of the reaction of tetravinyltin and phenyl lithium used to generate the vinyl lithium.



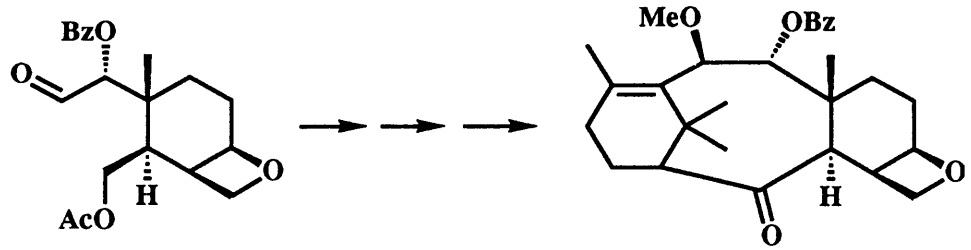
(179) (181)

It is likely that the reaction of the aldehyde group of (219) will be slow due to steric factors. The reaction of the aldehyde (255) with vinyl magnesium bromide was unsuccessful probably owing to steric reasons. A 3-D picture of the starting material was obtained by molecular modelling (Figure 5-1) and it can be seen that a nucleophile approaching along the Burgi-Dunitz trajectory would be hindered. The carbonyl group in the aldehyde (251) is likely to be even more obscured by the diene portion.



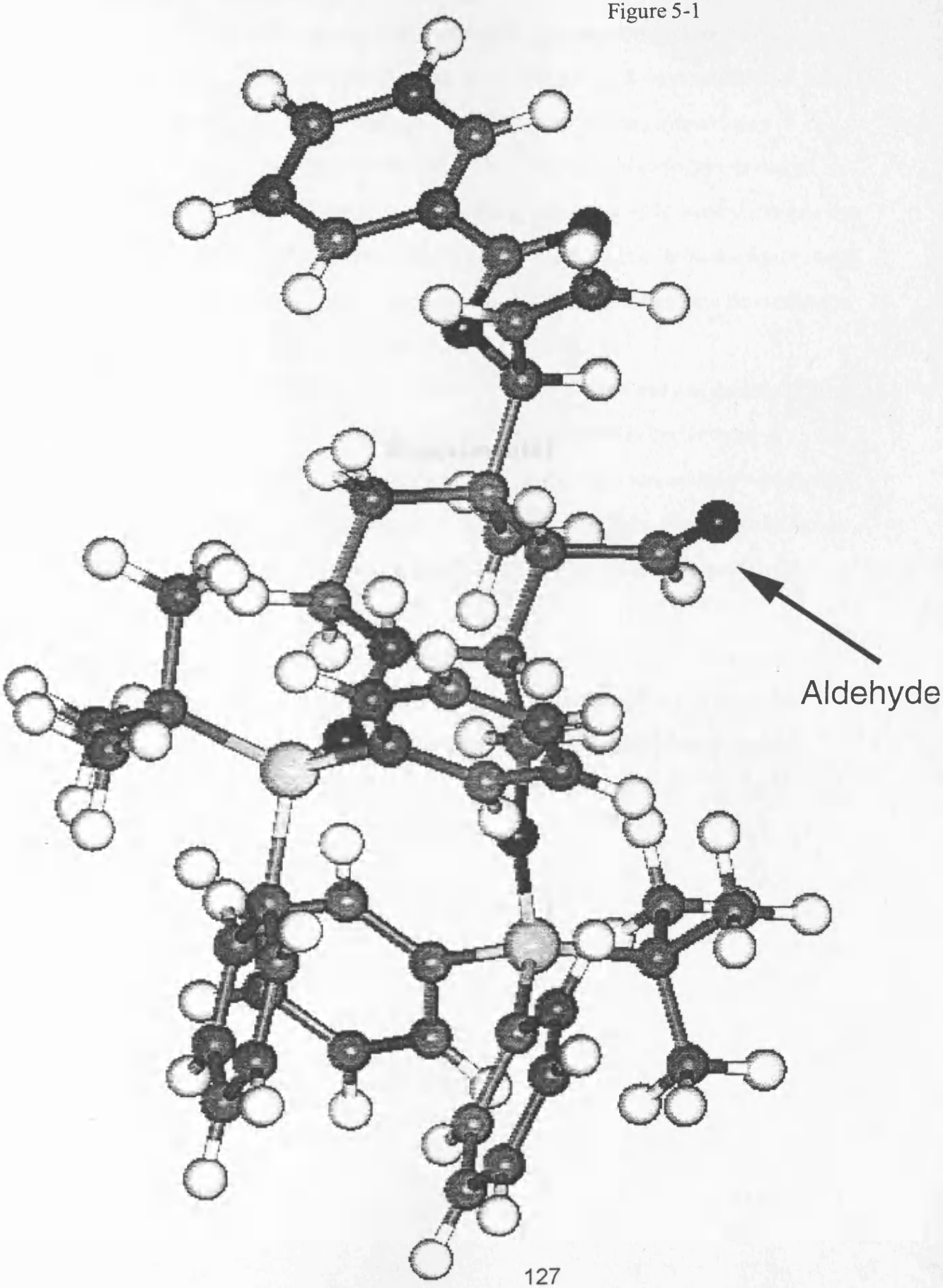
(255) R = Si^tBuPh_2 (256)

Cerium reagents are much more efficient at adding to hindered carbonyl groups, therefore treating vinyl lithium with $CeCl_3$ may improve the yields. If the trienone (243) was obtained successfully, the final cyclisation to the taxoid skeleton may be possible. Further work for the group could then include seeking methods of introducing the oxetane ring prior to the diene addition to give a CD ring (257). Advancing through the steps of Mitsunobu inversion, diene addition, protection, dienophile addition and cyclisation would result in a functionalised 4-ring taxoid structure (258) which would be a milestone for the group.



(257) (258)

Figure 5-1



Experimental

Experimental Introduction.

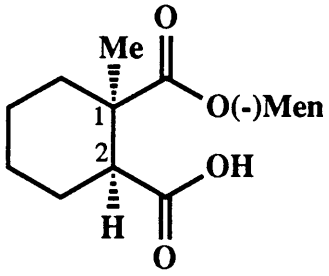
90MHz ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer. High-field ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-300 or ARX-250 spectrometers. *J* values are given in Hz. Mass spectra and accurate mass determinations were recorded at either the SERC Mass Spectrometry Service at the University College of Swansea or at the University of Leicester. Elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. Infra-red spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Melting points were determined on a Kofler hotstage and are uncorrected.

Light petroleum refers to the 40 - 60°C boiling fraction and was distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone. Diethyl ether was distilled from $LiAlH_4$. Dichloromethane was distilled from calcium hydride. Methanol was distilled from KOH pellets. Carbon tetrachloride was dried over 4A molecular sieves which had previously been dried in an oven at 100°C.

Flash chromatography was carried out according to Still et al. using silica gel manufactured by Merck & Co., Kiesel 60, 230 - 400 mesh (ASTM). T.L.C. was conducted on precoated aluminium sheets (60-254) with a 0.2mm layer thickness, manufactured by Merck & Co.

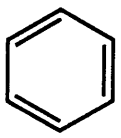
Nomenclature.

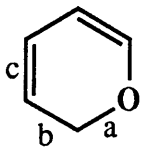
a) The compounds obtained by stereoselective alkylation are based on the cyclohexane ring with the two carboxylic acid groups occupying positions 1 and 2. Esterification of one of the carboxylic acid groups is named as the carboxylic acid ester at position 1. As substitution at the α-position can only occur adjacent to the ester group, it is position 1 which bears this group at the quaternary centre. The following compound is therefore named as **1-Methyl-cyclohexane-1,2-dicarboxylic acid, 1-mono-menthyl ester**.



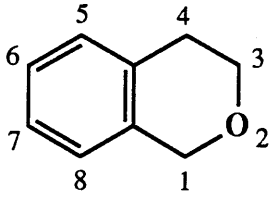
b) The fusion names were obtained following the IUPAC rules and verified from examples within the IUPAC nomenclature text and in Chemical Abstracts.

1) The fusion of benzene and 2H - pyran

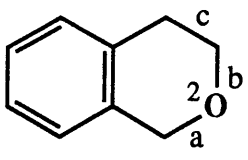


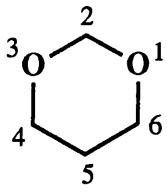


gives 1H - benzo[c]pyran

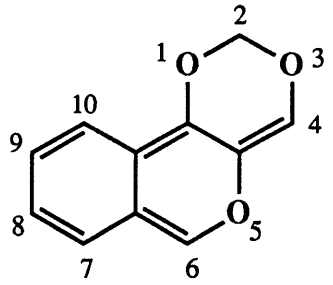


2) The fusion of 1,3 - dioxan with 1H - benzo[c]pyran



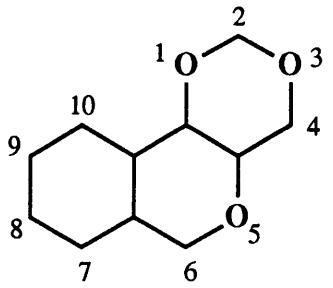


gives 1,3 - dioxino[5,4-c][2]benzopyran

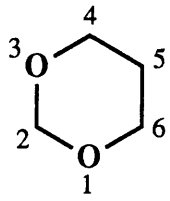


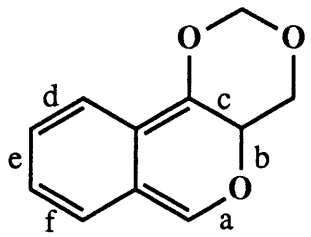
The fully saturated compound is named as follows;

4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b - Decahydro - 1,3 - dioxino[5,4-c][2]benzopyran.

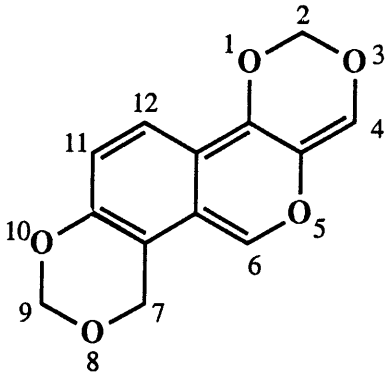


3) The fusion of a second 1,3 - dioxan with 1,3 - dioxino[5,4-c][2]benzopyran



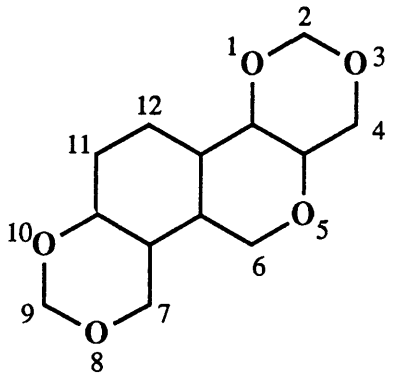


gives bis - 1,3 - dioxino[5,4-c][4,5-f][2]benzopyran

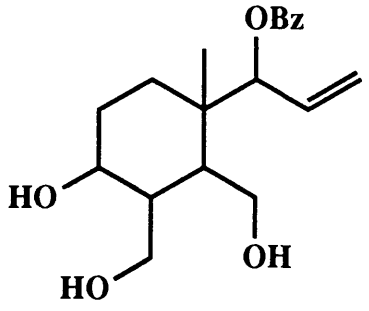


The fully saturated compound is named as follows;

4, 4a, 6, 6a, 6b, 10a, 11, 12, 12a, 12b - Decahydro - bis - 1,3 - dioxino[5,4-c] [4,5-f][2]benzopyran.

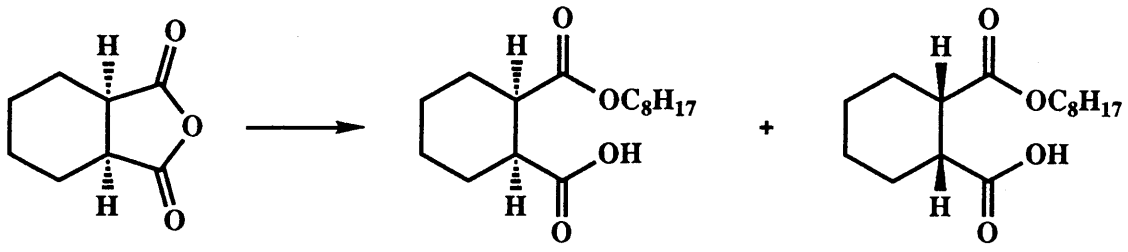


c) The nomenclature of the series of cyclohexane compounds after the Vasella reaction takes the alkyl chain as the stem with the cyclohexane ring and benzoate ester as substituents. Although, alternative, better systems may exist, this method of naming the monocyclic products was used previously in J. Clark's thesis[36] and therefore allows easy comparison of NMR assignments. A computer program (Beaker) also concurred that the name of the compound shown below was **1-(4'-Hydroxy-2',3'-bis-hydroxymethyl-1'-methyl-cyclohexyl)-2-propenyl benzoate.**



Cyclohexane-1,2-dicarboxylic acid, 1-mono-octyl ester. (149)

Literature reference: *Org. Synth.*, Coll. Vol. I, 410.



(149a) (149b)

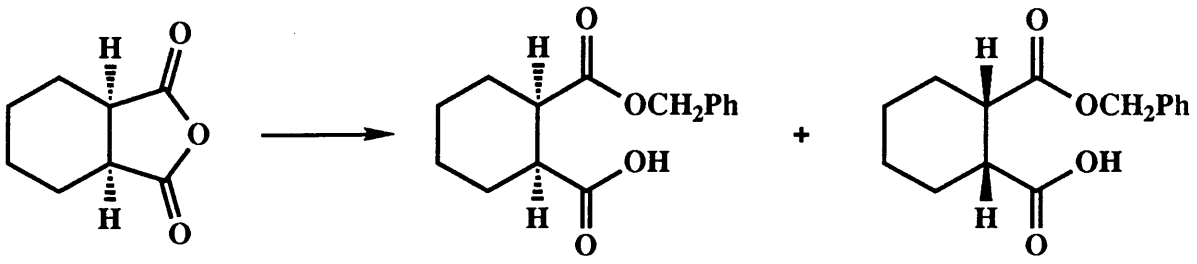
Cyclohexane dicarboxylic anhydride (2.41g, 15.62mmol, 1eq) and octanol (2.03g, 15.62mmol, 1eq) were heated in a sealed vial for 18 hours at 110 - 115°C with magnetic stirring. The reaction mixture was cooled to room temperature and added to a solution of sodium carbonate (2.34g, 21.84mmol in 125ml of water) with shaking. 0.1M Dilute hydrochloric acid (40ml) was added and the aqueous solution extracted with 100ml dichloromethane three times. The organic phase was dried ($MgSO_4$) and evaporated to afford the title compound as a pale yellow oil (3.35g, 75%).

ν_{max} (film)/cm^{-1} 3600-2300 (s, OH), 2920 (s), 2855 (s), 1730 (s, C=O), 1700 (s, C=O), 1450 (s), 1300 (s), 1255 (s), 1220 (s), 1180 (s), 1130 (s), 1030 (s).

δ_H (90MHz; $CDCl_3$) 0.85 (3H, m), 1.07 - 2.43 (20H, m), 2.80 (2H, m, 1-H, 2-H), 4.02 (2H, t, J = 6.8, $\underline{CH_2}$-OCOR), 9.75 (1H, brs, OH).

Cyclohexane-1,2-dicarboxylic acid, 1-mono-benzyl ester. (150)

Literature reference: *Org. Synth.*, Coll. Vol. I, 410.



(150a) (150b)

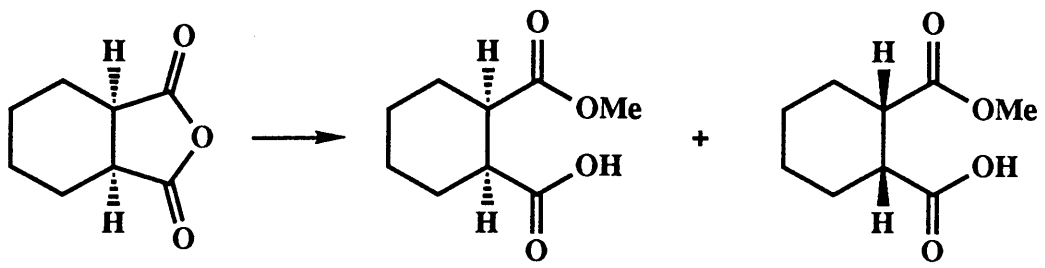
Cyclohexane dicarboxylic anhydride (2.09g, 13.57mmol) and benzyl alcohol (1.47g, 13.57mmol) were heated in a sealed vial for 18 hours at 110 - 115°C with magnetic stirring. The reaction mixture was cooled to room temperature and added to a solution of sodium carbonate (2.04g in 109ml of water) with shaking. 0.1M dilute HCl (32ml) was added and the aqueous solution was extracted three times with 100ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to afford the title compound as a colourless oil (2.92g, 82%).

ν_{max} (film)/cm^{-1} 3600-2300 (s, OH), 2940 (s), 2860 (s), 1730 (s, C=O), 1700 (s, C=O), 1450 (s), 1255 (s), 1210 (s), 1170 (s), 1125 (s), 1025 (s), 730 (s), 695 (s).

δ_H (90MHz; $CDCl_3$) 1.17 - 2.50 (8H, m, 3eq-H, 3ax-H, 4eq-H, 4ax-H, 5eq-H, 5ax-H, 6eq-H, 6ax-H), 2.88 (2H, m, 1-H, 2-H), 5.12 (2H, s, $\underline{CH_2}$Ph), 7.30 (5H, s, PhH), 9.47 (1H, brs, OH).

Cyclohexane-1,2-dicarboxylic acid, 1-mono-methyl ester. (151)

Literature reference: *Org. Synth.*, Coll. Vol. I, 410.



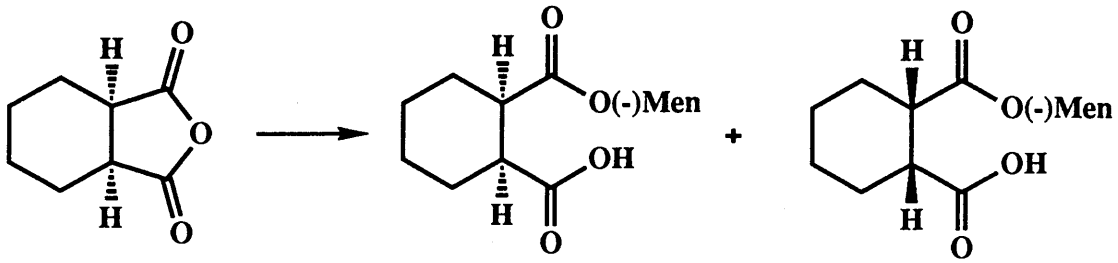
(151a) (151b)

Cyclohexane dicarboxylic anhydride (3.03g, 19.63mmol) and methanol (0.79ml, 19.63mmol) were heated in a sealed vial for 18 hours at 110 - 115°C with magnetic stirring. The reaction mixture was cooled to room temperature and added to a solution of sodium carbonate (2.94g in 157ml of water) with shaking. 0.1M dilute HCl (32ml) was added and the aqueous solution was extracted three times with 100ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to afford the title compound as a yellow oil which solidified on cooling. The white solid was filtered, ground with a mortar and pestle in water, filtered again and dried over P_2O_5 *in vacuo* to give the title compound (2.92g, 82%).

ν_{max} (Nujol mull)/cm^{-1} 3600-2300 (s, OH), 2920 (s), 2850 (s), 1730 (s, C=O), 1700 (s, C=O), 1310 (s), 1210 (s), 1180 (s), 1130 (s).

δ_H (90MHz; $CDCl_3$) 0.90 - 2.27 (8H, m, 3eq-H, 3ax-H, 4eq-H, 4ax-H, 5eq-H, 5ax-H, 6eq-H, 6eq-H), 2.82 (2H, m, 1-H, 2-H), 3.61 (3H, s, CH_3, OMe), 9.03 (1H, brs, OH).

Cyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester. (152a).



2.39 : 1

6 recrystallisations

>100 : 1

l-(-)-Menthol (3.000g, 19.20mmol, 1eq) and *cis*-cyclohexane-1,2-dicarboxylic anhydride (122) (2.959g, 19.20mmol, 1eq) were heated together in a sealed vial for 16 hours at 110°C. The mixture was cooled to room temperature and the sticky, colourless solid was dissolved in 100ml petrol (60-80°C) with heating. On cooling the solution, white crystals of the product (152) were obtained, which were filtered off and washed with 50ml cold light petroleum. The solid was recrystallised six times until the melting point remained constant, to afford a yield of 0.353g (6%).

M.p. = 102 - 104°C.

$[\alpha]_D$ = -44.70° (c 1.35 $CHCl_3$).

Found: C, 69.8; H, 9.9. $C_{18}H_{30}O_4$ requires C, 69.6; H, 9.7%.

ν_{max} (CH_2Cl_2)/cm^{-1} 3500-2400 (br, OH), 2950 (s), 2875 (s), 1730 (s, C=O ester), 1710 (s, C=O acid), 1450 (s), 1380 (s), 1185 (s), 1030 (s).

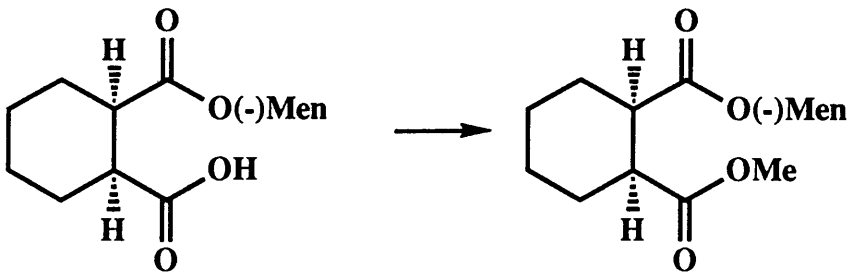
δ_H (300MHz; $CDCl_3$) 0.73 (3H, d, *J* = 7.0, MeCH(Me)C2'), 0.90 (6H, d, *J* = 7.0, MeCH(Me)C2' & C5'-Me), 1.03 - 2.50 (17H, m, $7CH_2$ & 3CH, 3ax-H, 3eq-H, 4ax-H,

4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 6'ax-H, 6'eq-H, $(CH_3)_2$-CH, 2'-H, 5'-H), 2.63 - 3.10 (2H, m, 1-H, 2-H), 4.70 (1H, ddd, J = 10.5, 10.5, 4.5, H1'-H), 8.43 - 9.23 (1H, s, CO_2H).

δ_C (75.5MHz; $CDCl_3$) 15.87 (CH_3), 20.62 (CH_3), 21.84 (CH_3), Me_2CHC2' & C5'-Me, 23.11 (CH_2), 23.34 (CH_2), 25.75 (CH_2), 25.92 (CH, Me_2CH), 26.32 (CH_2), 31.20 (CH, C-5'), 34.12 (CH_2), 40.48 (CH_2), 42.32 (CH, C-2'), 42.43 (CH, C-2), 46.75 (CH, C-1), 74.18 (CH, C-1'), 172.88 (C, C=O), 180.34 (C, C=O).

m/z (EI^+) 310 (M^+, 1%), 295 ([M-Me]$^+$, 0.4), 173 (35), 172 (15), 155 ([M-Men]$^+$, 91), 139 (20), 138 (100), 123 (22), 97 (19), 95 (39), 81 (59), 55 (14).

Cyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester.



(152a)

The acid-ester (152a) (0.621g, 0.002mol, 1eq) dissolved in ether (15ml) was treated with diazomethane generated from Diazald (1.670g, 7.68mmol, 3.84eq) and aqueous KOH (5g in 8ml) at 0°C. The yellow mixture was stirred for 30 minutes and then treated with glacial acetic acid until no more N_2 was evolved and the solution turned colourless. The ether was evaporated off and the residue dissolved in 20ml dichloromethane. The organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. The di-ester was obtained as a colourless oil in a yield of 0.628g (97%).

$[\alpha]_D$ = -51.91° (c 1.40 in $CHCl_3$, 17°C).

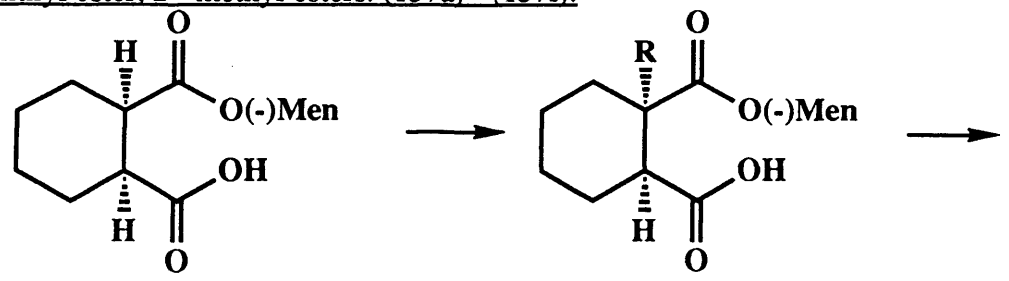
ν_{max} (CH_2Cl_2)/cm^{-1} 2940 (s), 2860 (s), 1730 (s, C=O), 1440 (s), 1360 (s), 1110 (s), 1030 (s), 965 (s).

δ_H (300MHz; $CDCl_3$) 0.76 (3H, d, *J* = 7.0, MeCH(Me)C2'), 0.90 (3H, d, *J* = 7.1, MeCH(Me)C2'), 0.91 (3H, d, *J* = 6.5, C5'-Me), 0.85 - 1.13 (4H, m, 4ax-H, 4eq-H, 5ax-H, 5eq-H), 1.33 - 1.58 (6H, m, 3ax-H, 3eq-H, 6ax-H, 6eq-H, 4'ax-H, 4'eq-H), 1.65 - 1.93 (4H, m, 3'ax-H, 3'eq-H, 6'ax-H, 6'eq-H), 1.96 - 2.11 (3H, m, $(CH_3)_2$-CH, 2'-H, 5'-H), 2.79 (1H, dt, *J* = 7.8, 4.4, 2-H), 2.86 (1H, dt, *J* = 7.0, 4.5, 1-H), 3.66 (3H, s, OMe), 4.69 (1H, ddd, *J* = 10.9, 10.9, 4.4, 1'-H).

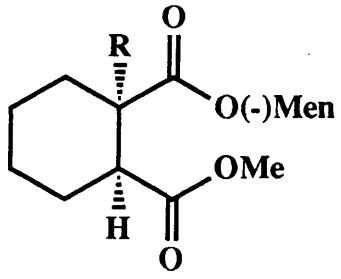
δ_C (75.5MHz; $CDCl_3$) 16.16 (CH_3), 20.82 (CH_3), 22.03 (CH_3), $\underline{Me_2}CHC2'$& C5'-$\underline{Me}$, 23.39 (CH_2), 23.65 (CH_2), 23.94 (CH_2), 26.09 (CH, $Me_2\underline{CH}$), 26.15 (CH_2), 26.50 (CH_2), 31.37 (CH, C-5'), 34.29 (CH_2), 40.82 (CH_2), 42.48 (CH, C-2'), 42.81 (CH, C-2), 46.95 (CH), 51.43 (CH_3, OMe), 74.11 (CH, C-1'), 173.12 (C, C=O), 174.03 (C, C=O).

m/z (EI^+) 324 (M^+, 1%), 187 (46), 169 ([M-OMen]$^+$, 100), 155 (38), 138 (47), 123 (12), 109 (18), 95 (23), 84 (89), 55 (10).

Synthesis of 1 - Substituted - cyclohexane - 1, 2 - dicarboxylic acid, 1 - (1'*R*, 2'*S*, 5'*R*) - menthyl ester, 2 - methyl esters. (157a) - (157f).



(152a) (156a-f)



(157a-f)

(a) R = Me
(b) R = Bn
(c) R = $CH_2CH{=}CH_2$
(d) R = $CH_2CH{=}CH_2$
(e) R = $CH_2CH{=}CMe_2$
(f) R = $CH_2CH{=}CHPh$

1-Methylcyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester. (157a).

A solution of LDA was prepared by adding ^{n}BuLi (1.6M) (5.2ml, 8.504mmol, 2.59eq) to a solution of di-isopropylamine (1.2ml, 8.504mmol, 2.64eq) in dry THF (5ml) at -25°C and stirring for 0.5 hours. To the LDA was added a solution of the mono-menthyl ester (152a) (1.000g, 3.22mmol, 1eq) in THF (4ml), the mixture was stirred for 1 hour at -25°C. MeI (0.6ml, 9.66mmol, 3eq) was introduced to the reaction and the mixture stirred for a further 2.5 hours. The solution was warmed to room temperature, diluted with 14ml 2M HCl and extracted three times with 50ml diethyl ether. The organic phase was washed three times with 50ml saturated brine, dried ($MgSO_4$) and evaporated. A brown oil (156a) was obtained in a yield of 0.949g (91%). 0.939g of the crude sample was converted to the methyl ester by reacting with diazomethane generated from Diazald (1.670g) at 0°C. Excess diazomethane was destroyed by the addition of six drops of glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous

$NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude methyl ester (157a) was obtained in a yield of 0.898g (91%). The product was purified by column chromatography using 5 : 1 hexane : diethyl ether to give the title compound (157a) as a yellow oil in a yield of 0.656g (60%, over the 2 steps).

$[\alpha]_D$ = -34.61° (c 1.00 in $CHCl_3$, 20°C).

Found: C, 70.94; H, 10.03. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.13%.

ν_{max} (CH_2Cl_2)/cm^{-1}; 2980 (s), 2870 (s), 1725 (s, C=O), 1450 (s), 1190 (s).

δ_H (300MHz; $CDCl_3$) 0.75 (3H, d, *J* = 6.9, CH_3, MeCH(Me)-C2'), 0.89 (6H, d, *J* = 6.8, $2CH_3$, MeCH(Me)-C2' & C5'-Me), 1.31 (3H, s, CH_3, C1-Me), 1.18 -1.52 (8H, m, $4CH_2$, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 1.64 - 1.69 (3H, m, CH_2 & CH, 4'ax-H, 4'eq-H, $(Me)_2$-CH-C2'), 1.82 -2.02 (5H, m, $2CH_2$ & CH, 3'ax-H, 3'eq-H, 6'ax-H, 6'eq-H, 5'-H), 2.14 (1H, m, CH, 2'-H), 2.59 (1H, t, J = 5.8, CH, 2-H), 3.65 (3H, s, OMe), 4.65 (1H, ddd, *J* = 10.8, 10.9, 4.3, CH, 1'-H).

δ_C (75.5MHz; $CDCl_3$) 15.73 (CH_3, Me), 20.78 (CH_3, Me), 21.89 (CH_3, Me), Me_2CH-C2' & C5'-Me, 21.69 (CH_2), 22.91 (CH_2), 23.31 (CH_2), 24.91 (CH_3, C1-Me), 25.14 (CH_2), 25.68 (CH, $(Me)_2$CH-), 31.20 (CH, C-5'), {33.20 (CH_2), 34.17 (CH_2), 40.42 (CH_2), C-3', C-4' & C-6'}, 44.16 (C, C-1), 46.81 (CH, C-2'), 48.25 (CH, C-2), 51.21 (CH_3, OMe), 73.86 (CH, C-1'), 176.84 (C, C=O), 179.46 (C, C=O).

m/z (EI^+) 338 (2.2%, M^+), 201 (65), 183 (70, M^+- OMen), 169 (32), 155 (51), 138 (43), 123 (26), 95 (100), 83 (65), 69 (24), 55 (33) (Found: M^+, 338.24572. ($C_{20}H_{34}O_4$) requires *M*, 338.24570).

1-(Prop-2"-enyl) Cyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester. (157c) & (157d).

Method 1 (157c).

To a solution of (152a) (0.500g, 1.61mmol, 1eq) in THF (1.5ml) was added a solution of LDA in THF (4ml) prepared from $^{i}Pr_2NH$ (0.6ml, 4.25mmol, 2.64eq) and $^{n}BuLi$ (2.6ml, 4.17mmol, 2.59eq) at -25°C. The solution was stirred at -25°C for 1 hour. Allyl bromide (0.42ml, 4.83mmol, 3eq) was then introduced and the mixture was kept at -25°C for 16 hours. The reaction was quenched with 7ml 2M HCl , extracted three times with 20ml ether, washed three times with 20ml saturated brine, dried ($MgSO_4$) and evaporated. The crude yellow oil (156c) was obtained in a yield of 0.584g (>100%). This was treated with diazomethane, generated from Diazald (1.670g), at 0°C. Excess diazomethane was destroyed by the addition of six drops of glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude methyl ester (157c) was obtained in a yield of 0.500g (85%, over 2 steps). The material was purified by column chromatography using 10:1 light petroleum : ethyl acetate to give the title compound (157c) (0.440g, 75%, over 2 steps).

Method 2 (157d).

To a solution of (126a) (1.000g, 3.22mmol, 1eq) in THF (3ml) was added a solution of LDA in THF (8ml) prepared from $^{i}Pr_2NH$ (1.2ml, 8.50mmol, 2.64eq) and $^{n}BuLi$ (5.2ml, 8.34mmol, 2.59eq) at -25°C. The solution was stirred at -25°C for 1 hour. Allyl chloride (0.80ml, 9.66mmol, 3eq) was then introduced and the mixture was warmed to room temperature and stirred for 4 hours. The reaction was quenched with 14ml 2M HCl, extracted three times with 40ml ether, washed three times with 40ml saturated brine, dried ($MgSO_4$) and evaporated. The crude yellow oil (156d) was obtained in a yield of 0.931g (93%). This was treated with diazomethane, generated from Diazald (1.670g), at 0°C. Excess diazomethane was destroyed by the addition of

six drops of glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude methyl ester (157d) was obtained in a yield of 0.940g (80%, over 2 steps), this was purified by column chromatography using 30:1 light petroleum : diethyl ether to give the title compound (157d) (0.682g, 58%).

$[\alpha]_D$ = -89.27° (c 0.15 in $CHCl_3$, 19°C).

Found: C, 72.9; H, 10.3. $C_{22}H_{36}O_4$ requires C, 72.5; H, 10.0%.

ν_{max} (CH_2Cl_2)/cm^{-1} 2980 (s), 2860 (s), 1720 (s, C=O), 1455 (s), 1080 (s).

δ_H (300MHz; $CDCl_3$) 0.76 (3H, d, J = 6.9, CH_3, Me-CH(Me)-C2'), 0.91 (3H, d, J = 7.1, CH_3, Me-CH(Me)-C2'), 0.92 (3H, d, J = 6.5, CH_3, C5'-Me), 0.81 - 1.13 (2H, m, CH_2, 4ax-H, 4eq-H), 1.29 - 2.18 (15H, m, 6CH_2 & 3CH, 3ax-H, 3eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 6'ax-H, 6'eq-H, $(CH_3)_2$CH, 2'-H, 5'-H), 2.42 (1H, dd, J_{gem} = 14.0, ^3J = 7.7, 1"-H'), 2.58 (1H, dd, J_{gem} = 14.0, ^3J = 7.1, 1"-H"), 2.76 (1H, t, J = 5.2, 2-H), 3.68 (3H, s, OMe), 4.67 (1H, ddd, J = 10.9, 10.8, 4.3, 1'-H), 5.08 (1H, m, J_{trans} = 2.0, 3"Z-H), 5.13 (1H, d, J_{cis} = 1.1, 3"*E*-H), 5.74 (1H, m, ^3J = 7.4, J_{trans} = 2.0, J_{cis} = 1.2, 2"-H).

δ_C (75.5MHz; $CDCl_3$) 15.70 (CH_3, Me), 21.00 (CH_3, Me), 22.04 (CH_3, Me) Me_2CHC2' & C5'-Me, 21.38 (CH_2), 22.82 (CH_2), 24.97 (CH_2), 25.55 (CH, Me_2CH), 28.91 (2CH_2), 31.34 (CH, C-5'), {34.27 (2CH_2), 40.21 (CH_2), 40.68 (CH_2, C-1", C-3', C-4', C-6'}, 45.79 (CH, C-2), 46.90 (CH, C-2'), 47.13 (C, C-1), 51.38 (CH_3, OMe), 74.32 (CH, C-1'), 118.38 (CH_2, C-3"), 133.16 (CH, C-2"), 174.32 (C, C=O), 175.21 (C, C=O).

m/z (EI^+) 364 (M^+, 1.4%), 322 (2.5), 263 (1.9), 227 (58), 226 (100), 209 (46), 181 (64), 166 (26), 149 (21), 139 (28), 121 (68), 83 (65), 69 (28), 55 (41). (Found: M^+, 364.26127. ($C_{22}H_{36}O_4$) requires *M*, 364.26134).

1-Benzyl-cyclohexane-1,2-dicarboxylic acid -1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester, (157b).

To a solution of (152a) (1.000g, 3.22mmol, 1eq) in THF (3ml) was added a solution of LDA in THF (7.4ml) prepared from $^iPr_2NH$ (1.2ml, 8.50mmol, 2.64eq) and ^nBuLi (5.2ml, 8.34mmol, 2.59eq) at -25°C. The solution was stirred at -25°C for 1 hour. Benzyl bromide (1.15ml, 9.66mmol, 3eq) was then introduced and the mixture kept at -20°C for 16 hours. The reaction was quenched with 14ml 2M HCl, extracted three times with 40ml ether, washed three times with 40ml saturated brine, dried ($MgSO_4$) and evaporated. Excess $PhCH_2Br$ was removed by distillation at 80°C / 4mmHg using Kugelruhr apparatus. The crude brown oil (156b) (1.373g, >100%) was treated with diazomethane, generated from Diazald (1.670g), at 0°C. Excess diazomethane was destroyed by the addition of six drops glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$, dried and evaporated. The crude methyl ester (157b) was obtained as a yellow solid in a yield of 1.251g (94%, over 2 steps), this was recrystallised from EtOH to afford the title compound (157b) as a white crystalline solid (0.748g, 56%).

M.p.110 - 112°C.

$[\alpha]_D$ = -35.22° (c 0.18 in $CHCl_3$, 20°C)

Found: C, 75.32; H 9.48. $C_{26}H_{38}O_4$ requires C, 75.32; H, 9.24%.

δ_H (300MHz; $CDCl_3$) 0.73 (3H, d, J = 6.9, CH_3, Me-CH(Me)-C2'), 0.85 (3H, d, J = 7.0, CH_3, Me-CH(Me)-C2'), 0.93 (3H, d, J = 6.6, CH_3, C5'-Me), 1.25 - 2.19 (17H, m, $7CH_2$ & 3CH, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 6'ax-H, 6'eq-H, $(CH_3)_2CH$, 2'-H, 5'-H), 2.60 (1H, t, J = 6.1, CH, 2-H), 3.01 (1H, d, J_{gem} = 13.5, C1-CH'H"Ph), 3.30 (1H, d, J_{gem} = 13.5, C1-CH'H"Ph), 3.72 (3H, s, OMe), 4.66 (1H, ddd, J = 10.8, 10.8, 4.4, CH, 1'-H), 7.17 - 7.31 (5H, m, Ph).

δ_C (75.5MHz; $CDCl_3$) 15.81 (CH_3), 20.92 (CH_3), 21.93 (CH_3), Me_2CH-C2' & C5'-Me, 21.77 (CH_2), 22.81 (CH_2), 23.22 (CH_2), 25.35 (CH, Me_2CH), 25.41 (CH_2), 30.23 (CH_2), 31.21 (CH, C-5'), 34.11 (CH_2), 40.49 (CH_2), 41.76 (CH_2, CH_2Ph), 45.92 (CH, C-2'), 46.75 (CH, C-2), 48.88 (C, C-1), 51.32 (CH_3, OMe), 74.45 (CH, C-1'), 126.37 (CH, Ph), 127.85 (CH, Ph), 130.48 (CH, Ph), 136.78 (C, Ph), 174.22 (C, C=O), 174.90 (C, C=O).

m/z (EI^+) 414 (M^+, 21%), 276 (51), 244 (20), 230 (100 [$M-CO_2$(-)Men]$^+$), 199 (21), 171 (21), 139 (8), 91 (44, $PhCH_2^+$), 55 (8). (Found: M^+, 414.27702. $C_{26}H_{38}O_4$ requires *M*, 414.27699).

1-(3"-Methyl-but-2"-enyl) cyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester. (157e).

To a solution of (152a) (0.500g, 1.61mmol, 1eq) in THF (3ml) was added a solution of LDA in THF (4ml) prepared from $^iPr_2NH$ (0.6ml, 4.25mmol, 2.64eq) and ^nBuLi (2.6ml, 4.17mmol, 2.59eq) at -25°C. The solution was stirred at -25°C for 1 hour. Prenyl bromide (0.95g, 4.83mmol, 3eq) was then introduced and the mixture was kept at -25°C for 72 hours. The reaction was quenched with 7ml 2M HCl, extracted three times with 20ml ether, washed three times with 20ml saturated brine, dried ($MgSO_4$) and evaporated. Excess prenyl bromide was removed by distillation at 60°C / 60mmHg using Kugelruhr apparatus. The crude oil (156e) was obtained in a yield of 0.568g

(93%). This was treated with diazomethane, generated from Diazald (1.670g), at 0°C. Excess diazomethane was destroyed by the addition of six drops of glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude methyl ester (157e) was obtained in a yield of 0.560g (89%, over 2 steps), this was purified by column chromatography using 10:1 light petroleum : diethyl ether to give the title compound (157e) as a colourless oil (0.359g, 61%). The product was further purified by distillation using Kugelruhr apparatus at 180°C / 1mmHg to give 0.336g (53%) of the methyl ester.

B.p. = 180°C / 1mmHg.

$[\alpha]_D$ = -38.04 (c 1.33 in $CHCl_3$, 20°C).

(Found: C, 73.74; H, 10.11. $C_{24}H_{40}O_4$ requires C, 73.43; H, 10.27%.

ν_{max} (CH_2Cl_2)/cm^{-1} 2950 (s), 2870 (s, C-H), 1735 (s, C=O), 1450 (s), 1370 (s), 1230 (s), 1180 (s), 1070 (s), 1040 (s), 965 (s).

δ_H (300MHz; $CDCl_3$) 0.74 (3H, d, J = 6.9, CH_3, Me-CH(Me)-C2'), 0.89 (3H, d, J = 7.0, CH_3, Me-CH(Me)-C2'), 0.89 (3H, d, J = 6.5, CH_3, C5'-Me), 0.83 - 1.11 (4H, m, $2CH_2$, 4ax-H, 4eq-H, 5ax-H, 5eq-H), 1.32 - 1.55 (5H, m, 3ax-H, 3eq-H, 4'ax-H, 4'eq-H & Me_2CH), 1.57 - 1.76 (4H, m, $2CH_2$, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H), 1.61 (3H, s, CH_3, 4"-H), 1.69 (3H, s, CH_3, Me-C3"), 1.77 - 2.17 (4H, m, 6'ax-H, 6'eq-H, 2'-H & 5'-H), 2.37 (1H, dd, J_{gem} = 14.5, ^3J = 7.6, 1"-H'), 2.46 (1H, dd, J_{gem} = 14.5, ^3J = 7.1, 1"-H"), 2.75 (1H, t, J = 5.2, 2-H), 3.65 (3H, s, OMe), 4.65 (1H, ddd, J = 10.8, 10.8, 4.3, 1'-H), 5.06 (1H, dd, ^3J = 7.3, 7.3, 2"-H).

δ_C (75.5MHz; $CDCl_3$) 15.78 (CH_3, Me), 18.12 (CH_3, Me), 21.05 (CH_3), Me_2CH-C2' & C5'-Me, 21.65 (CH_2), 22.06 (CH_3, C-4"), 22.71 (CH_2), 22.88 (CH_2), 25.25 (CH_2), 25.60 (CH, Me_2CH), 26.04 (CH_3, C3"-Me), 28.98 (CH_2, C-1"), 31.33 (CH,

C-5'), {34.30 (CH_2), 34.36 (CH_2), 40.64 (CH_2), C-3', C-4', C-6'}, 46.05 (CH, C-2), 46.90 (CH, C-2'), 47.62 (C, C-1), 51.35 (CH_3, OMe), 74.18 (CH, C-1'), 118.98 (CH, C-2''), 134.31 (C, C-3''), 174.51 (C, C=O), 175.65 (C, C=O).

m/z (EI^+) 392 (M^+, 7.0%), 254 (30), 208 (100), 194 (34), 149 (18), 83 (15), 69 (18), 55 (97).

(Found: M^+, 392.29297. $C_{24}H_{40}O_4$ requires *M*, 392.29264).

1-(3''-Phenyl-prop-2''-enyl) Cyclohexane-1,2-dicarboxylic acid, 1-(1'*R*, 2'*S*, 5'*R*)-menthyl ester, 2-methyl ester. (157f).

To a solution of (152a) (0.500g, 1.61mmol, 1eq) in THF (3ml) was added a solution of LDA in THF (4ml) prepared from $^iPr_2NH$ (0.6ml, 4.25mmol, 2.64eq) and ^nBuLi (2.6ml, 4.17mmol, 2.59eq) at -25°C. The solution was stirred at -25°C for 1 hour. Cinnamyl bromide (0.95g, 4.83mmol, 3eq) was then introduced and the mixture was warmed to room temperature and stirred for 72 hours. The reaction was quenched with 7ml 2M HCl, extracted three times with 20ml ether, washed three times with 20ml saturated brine, dried ($MgSO_4$) and evaporated. Excess cinnamyl bromide was removed by distillation at 60°C / 4mmHg using Kugelruhr apparatus. The crude thick, orange oil (156f) was obtained in a yield of 0.972g (>100%). This was treated with diazomethane, generated from Diazald (1.670g), at 0°C. Excess diazomethane was destroyed by the addition of six drops of glacial acetic acid, the organic layer was washed three times with 20ml saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude methyl ester (157f) was obtained in a yield of 0.706g (100%, over 2 steps). This was recrystallised from EtOH to give the title compound (157f) (0.264g, 37%) as a pale yellow solid.

M.p. 92 - 94.5°C.

$[\alpha]_D$ = -34.70 (c 1.35 in $CHCl_3$, 19°C).

Found: C, 75.96; H, 9.29%. $C_{28}H_{40}O_4$ requires C, 76.33; H, 9.15%.

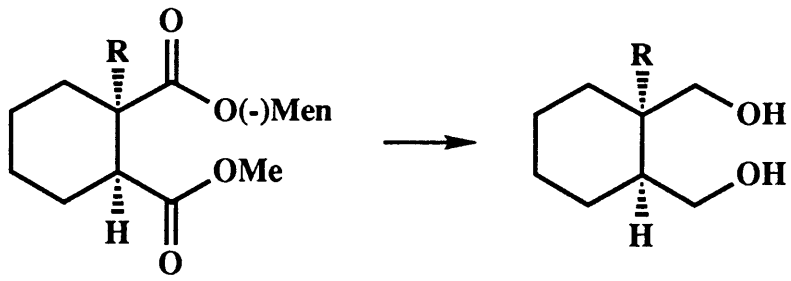
ν_{max} (CH_2Cl_2)/cm^{-1} 2960 (s), 2880 (s, C-H), 1735 (s, C=O), 1720 (s, C=O), 1670 (w, C=C), 1450 (s), 1250 (s), 1195 (s), 1150 (s), 995 (s).

δ_H (300MHz; $CDCl_3$) 0.71 (3H, d, J = 6.9, CH_3, Me-CH(Me)-C2'), 0.84 (3H, d, J = 7.0, CH_3, Me-CH(Me)-C2'), 0.87 (3H, d, J = 6.5, CH_3, C5'-Me), 0.90 - 1.09 (2H, m, CH_2, 4ax-H, 4eq-H), 1.26 - 1.75 (10H, m, $5CH_2$, 3ax-H, 3eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H), 1.82 - 2.21 (5H, m, CH_2 & 3CH, 6'ax-H, 6'eq-H, $(Me)_2$-CH, 5'-H, 2'-H), 2.56 (1H, dd, J_{gem} = 14.0, ^3J = 7.1, 1"-H'), 2.69 (1H, dd, J_{gem} = 14.0, ^3J = 7.1, 1"-H"), 2.77 (1H, t, J = 5.5, 2-H), 3.66 (3H, s, OMe), 4.69 (1H, ddd, J = 10.9, 10.8, 4.3, 1'-H), 6.13 (1H, ddd, J_{trans} = 15.6, ^3J = 7.5, 2"-H), 6.42 (1H, d, J_{trans} = 15.7, 3"-H), 7.17 - 7.43 (5H, m, Ph).

δ_C (75.5MHz; $CDCl_3$); δ 15.66 (CH_3, Me), 20.99 (CH_3, Me), 22.03 (CH_3, Me), Me_2CH-C2' & C5'-Me, 21.51 (CH_2), 22.84 (CH_2), 25.12 ($2CH_2$), 25.64 (CH, Me_2CH), 29.33 (CH_2), 31.36 (CH, C-5'), 34.26 (CH_2), 39.69 (CH_2, C-1"), 40.83 (CH_2, C-6'), 46.09 (CH, C-2), 46.88 (CH, C-2'), 47.76 (C, C-1), 51.44 (CH_3, OMe), 74.42 (CH, C-1'), 124.86 (CH, C-2"), 126.15 (2CH, Ph), 127.19 (CH, C-3"), 128.42 (2CH, Ph), 133.32 (CH, Ph), 137.169 (C, Ph), 174.33 (C, C=O), 175.28 (C, C=O).

m/z (EI^+) 440 (M^+, 10%), 302 (37), 270 (18), 256 (100), 242 (23), 197 (16), 117 (48), 91 (11), 83 (16), 55 (12).
(Found: M^+, 440.29206. $C_{28}H_{40}O_4$ requires *M*, 440.29264).

Synthesis of 1-Substituted-1,2-dihydroxymethanes. (158a) - (158f).



(157a-f) (158a-f)

(a) R = Me
(b) R = Bn
(c) R = $CH_2CH=CH_2$
(d) R = $CH_2CH=CH_2$
(e) R = $CH_2CH=CMe_2$
(f) R = $CH_2CH=CHPh$

1-Methyl-cyclohexane-1,2-dihydroxymethane. (158a).

Literature reference: *J. Org. Chem.*, 1967, **32**, 3919.

To a solution of the di-ester (157a) (0.607g, 1.793mmol, 1eq) in dry THF (13.3ml) was added 1M $LiAlH_4$ in THF (5.31ml, 5.313mmol, 2.96eq), the mixture was stirred for 1 hour at room temperature. Sodium fluoride (2.310g, 0.055mol, 30.74eq) was added to the reaction and the suspension was stirred for 10 minutes at room temperature. The flask was cooled in ice and the reaction quenched with a mixture of H_2O-THF (1:9) (10ml). After stirring the suspension at room temperature for 10 minutes, it was filtered through a pad of Celite. The residue was washed with 30ml ether and the filtrate was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography using 1:1 light petroleum : diethyl ether to separate the product (158a) from the menthol generated in the reaction. The product was obtained as a colourless oil which was distilled using Kugelrohr apparatus at 111°C / 1mm Hg to yield the title compound (158a) as a low melting point solid 0.260g (92%).

M.p. 17 -18°C (No literature value).

$[\alpha]_D$ = +21.41 (*c* 1.35 in MeOH, 20°C).

Found: C, 68.21; H, 11.43. $C_9H_{18}O_2$ requires C, 68.31; H, 11.47%.

ν_{max} (Nujol mull)/cm^{-1} 3500 - 3100 (br, OH), 2920 (Nujol), 2860 (Nujol), 1465 (s), 1360 (Nujol), 1050 (s, C-O), 1100 - 990 (m, C-C stretch).

δ_H (300MHz; $CDCl_3$) 1.02 (3H, s, CH_3, C1-Me), 1.04 - 1.74 (9H, m, $4CH_2$ & CH, 2-H, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 3.14 (1H, d, J_{gem} = 11.3, C1-CH'H"OH), 3.57 (1H, dd, J_{gem} = 11.3, ^3J = 4.8, C2-CH'H"OH), 3.79 (1H, dd, J_{gem} = 11.3, ^3J = 2.3, C2-CH'H"OH), 3.86 (1H, d, J_{gem} = 11.3, C1-CH'H"OH), 4.47 (2H, s, 2OH).

δ_C (75.5MHz; $CDCl_3$) 21.79 (CH_2), 24.39 (CH_3, C1-Me), 25.46 (CH_2), 25.76 (CH_2), 37.24 (C, C-1), 37.43 (CH_2), 46.63 (CH, C-2), 62.93 (CH_2, CH_2OH), 66.17 (CH_2, CH_2OH).

m/z (EI+) 158 (M^+, 0.1%), 140 ([M-H_2O]+, 2.4), 125 (4), 110 (100), 109 (96), 95 (29), 82 (16.5), 81 (36), 67 (49), 55 (28) (Found: M^+, 158.13074. $C_9H_{18}O_2$ requires *M*, 158.13067).

1-(-Prop-2'-enyl)-cyclohexane-1,2-dihydroxymethane. (158c).

To a solution of the di-ester (157c) (0.311g, 0.852mmol, 1eq) in dry THF (6.3ml) was added 1M $LiAlH_4$ in THF (2.52ml, 2.521mmol, 2.96eq), the mixture was stirred for 1 hour at room temperature. Sodium fluoride (1.100g, 0.026mol, 30.74eq) was added to the reaction and the suspension was stirred for 10 minutes at room temperature. The flask was cooled in ice and the reaction quenched with a mixture of H_2O-THF (1:9)

(4.8ml). After stirring the suspension at room temperature for 10 minutes, it was filtered through a pad of Celite. The residue was washed with 20ml ether and the filtrate was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography using 1:1 light petroleum : diethyl ether to separate the product (158c) from the menthol generated in the reaction. A white solid was obtained in a yield of 0.116g (74%). The material was recrystallised from light petroleum to give the title compound (158c) as a crystalline solid 0.091g (58%).

M.p. 57 - 58.5°C.

B.p. 169°C / 1mmHg.

$[\alpha]_D$ = + 12.73 (*c* 1.51 in MeOH, 20°C).

Found: C, 71.49; H, 11.13. $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94%.

ν_{max} (Nujol mull)/cm^{-1} 3440 - 3090 (br, OH), 3070 (C-H), 2930 (Nujol), 2860 (Nujol), 1640 (w, C=C), 1460 (Nujol), 1380 (Nujol), 1050 (s, C-O), 1020 (s, C-C), 980 - 915 (s, C-H).

δ_H (300MHz; CD_3OD) 1.19 - 1.71 (9H, m, $4CH_2$ & CH, 2-H, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 2.21 (1H, dd, J_{gem} = 13.9, ^3J = 7.9, 1'-H'), 2.28 (1H, dd, J_{gem} = 13.9, ^3J = 7.5, 1'-H''), 3.37 (1H, d, J_{gem} = 11.4, C1-C<u>H</u>'H''OH), 3.57 (1H, dd, J_{gem} = 11.1, ^3J = 5.35, C2-C<u>H</u>'H''OH), 3.66 (1H, d, J_{gem} = 11.4, C1-CH'<u>H</u>''OH), 3.66 (1H, dd, J_{gem} = 11.4, ^3J = 2.15, C2-CH'<u>H</u>''OH), 4.87 (2H, s, 2OH), 5.04 (1H, d, J_{trans} = 4.1, 3'-H'), 5.08 (1H, s, CH, 3'-H''), 5.88 (1H, m, ^3J = 7.7, ^3J = 7.8, J = 4.0, 2'-H).

δ_C (75.5MHz, CD_3OD) {22.75 (CH_2), 26.24 (CH_2), 26.75 (CH_2), 33.79 (CH_2), C-3, C-4, C-5 & C-6} 41.07 (C, C-1), 41.25 (CH_2, C-1'), 45.83 (CH, C-2), 63.09 (CH_2, CH_2OH), 64.63 (CH_2, CH_2OH), 117.88 (CH_2, C-3'), 135.72 (CH, C-2').

m/z (CI^+) 202 ($[M+NH_4]^+$, 42%), 185 (MH^+, 100), 167 (32), 149 (4), 125 (4). (Found: M^+, 184.14636. $C_{11}H_{20}O_2$ requires *M*, 184.14632).

1-Benzyl-cyclohexane-1,2-dihydroxymethane. (158b).

To a solution of the di-ester (157b) (0.300g, 0.724mmol, 1eq) in dry THF (5.4ml) was added 1M $LiAlH_4$ in THF (2.14ml, 2.142mmol, 2.96eq), the mixture was stirred for 1 hour at room temperature. Sodium fluoride (0.940g, 0.022mol, 30.74eq) was added to the reaction and the suspension was stirred for 10 minutes at room temperature. The flask was cooled in ice and the reaction quenched with a mixture of H_2O-THF (1:9) (4.0ml). After stirring the suspension at room temperature for 10 minutes, it was filtered through a pad of Celite. The residue was washed with 20ml ether and the filtrate was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography using 1:1 light petroleum : diethyl ether to separate the product (158b) from the menthol generated in the reaction. The product was obtained as a white solid, 0.125g (73%) which was recrystallised from light petroleum and diethyl ether to give the title compound (158b) as a white crystalline solid, 0.084g, (50%).

M.p. 91.5 - 93°C.

$[\alpha]_D$ = +22.89 (*c* 1.33 in MeOH, 22°C).

Found: C, 76.88; H, 9.54. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%.

ν_{max} (CH_2Cl_2)/cm^{-1} 3600, (s, free OH), 3500-3140 (br, H-bonded OH), 2920 (s), 2860 (s), 1600 (w), 1490 (w), 1450 (w C=C), 1050 (s), 1025 (s, C-O), 975 (s).

δ_H (300MHz; $CDCl_3$) 1.20 - 1.40 (4H, m, $2CH_2$, 4ax-H, 4eq-H, 5ax-H, 5eq-H), 1.52 - 1.85 (5H, m, $2CH_2$ & CH, 3ax-H, 3eq-H, 6ax-H, 6eq-H, 2-H), 2.55 (1H, d, J_{gem} = 13.0, C<u>H</u>'H"Ph), 3.19 (1H, d, J_{gem} = 13.0, CH'<u>H</u>"Ph), 3.22 (1H, d, J_{gem} = 11.5, C1-C<u>H</u>'H"OH), 3.40 - 4.00 (2H, brs, 2OH), 3.73 (1H, dd, J_{gem} = 11.3, ^3J = 4.7, C2-CH'<u>H</u>"OH), 3.87 (1H, d, J_{gem} = 11.6, C1-CH'<u>H</u>"OH), 4.08 (1H, dd, J_{gem} = 11.2, ^3J = 1.8, C2-CH'<u>H</u>"OH), 7.20 - 7.32 (5H, m, Ph).

δC (75.5MHz; $CDCl_3$, 313K) {21.58 (CH_2), 25.58 (CH_2), 25.62 (CH_2), 33.46 (CH_2), C-3, C-4, C-5 & C-6}, 40.84 (CH, C-2), 41.43 (CH_2, CH_2-Ph), 41.70 (C, C-1), 63.04 (CH_2, CH_2-OH), 63.37 (CH_2, CH_2OH), 125.71 (CH, Ph), 127.59 (2CH, Ph), 130.73 (2CH, Ph), 138.13 (C, Ph).

m/z (CI^+) 252 ($[M+NH_4]^+$, 17.5%), 235 (MH^+, 100), 215 ($[M-H_2O]^+$, 24), 125 (12.5), 91 ($PhCH_2^+$, 11). (Found: M^+, 234.16204. $C_{15}H_{22}O_2$ requires *M*, 234.16197).

<u>1-(3'-Phenyl-prop-2'-enyl) cyclohexane-1,2-dihydroxymethane. (158f).</u>

To a solution of the di-ester (157f) (0.497g, 1.128mmol, 1eq) in dry THF (8.4ml) was added 1M $LiAlH_4$ in THF (3.341ml, 3.338mmol, 2.96eq), the mixture was stirred for 1 hour at room temperature. Sodium fluoride (1.460g, 0.035mol, 30.74eq) was added to the reaction and the suspension was stirred for 10 minutes at room temperature. The flask was cooled in ice and the reaction quenched with a mixture of H_2O-THF (1:9) (6.3ml). After stirring the suspension at room temperature for 10 minutes, it was filtered through a pad of Celite. The residue was washed with 20ml ether and the filtrate was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography using 1:1 light petroleum : diethyl ether to separate the product (158f)

from the menthol generated in the reaction. The product was obtained as a colourless oil which was distilled using Kugelrohr apparatus at 227°C / 1mm Hg to yield the title compound (158f) as a white solid, 0.209g (71%).

M.p. 66 - 69°C.

$[\alpha]_D$ = +14.91 (*c* 1.32 in MeOH, 20°C).

ν_{max} (CH_2Cl_2)/cm^{-1} 3610 (s, free OH), 3500-3150 (br, H-bonded OH), 3030 (m, C=C-H), 1600 (s), 1490 (m), 1470 (m), 1450 (m, aromatic C=C), 1130 - 1010 (br, C-C), 1030 (s, C-O), 970 (C=C-H bending).

δ_H (300MHz; CD_3OD) 1.26 - 1.71 (9H, m, $4CH_2$ & CH, 2-H, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 2.33 (1H, dd, J_{gem} = 13.8, ^3J = 7.2, 1'-H'), 2.44 (1H, dd, J_{gem} = 13.9, ^3J = 7.0, 1'-H''), 3.42 (1H, d, J_{gem} = 11.4, C1CH'H''OH), 3.50 (2H, brs, 2OH), 3.62 (1H, dd, J_{gem} = 11.1, ^3J = 5.2, C2CH'H''OH), 3.70 (1H, d, J_{gem} = 11.4, C1CH'H''OH), 3.71 (1H, dd, J_{gem} = 11.1, ^3J = 3.3, C2CH'H''OH), 6.33 (1H, dt, J_{trans} = 15.7, ^3J = 7.3, 2'-H), 6.43 (1H, d, J_{trans} = 15.8, 3'-H), 7.13 - 7.37 (5H, m, Ph).

δ_C (75.5MHz; CD_3OD) {22.79 (CH_2), 26.28 (CH_2), 26.71 (CH_2), 34.04 (CH_2), C-3, C-4, C-5, C-6}, 40.34 (CH_2, C-1'), 41.65 (C, C-1), 46.09 (CH, C-2), 63.18 (CH_2, CH_2OH), 64.73 (CH_2, CH_2OH), 126.91 (2CH, Ph), 127.41 (CH, C-2'), 127.60 (CH, C-3'), 129.37 (2CH, Ph), 133.95 (CH, Ph), 139.10 (C, Ph).

m/z (EI+) 260 (M^+, 9%), 242 ([M-H_2O]$^+$, 51), 229 (81), 211 (22), 130 (38), 125 (40), 107 (48), 95 (39), 81 (48), 79 (40), 67 (22), 55 (30). (Found: M^+, 260.11759. $C_{17}H_{24}O_2$ requires *M*, 260.17762).

1-(3'-Methyl-but-2'-enyl) cyclohexane-1,2-dihydroxymethane. (158e).

To a solution of the di-ester (157e) (0.278g, 0.732mmol, 1eq) in dry THF (5.4ml) was added 1M $LiAlH_4$ in THF (2.2ml, 2.166mmol, 2.96eq), the mixture was stirred for 1 hour at room temperature. Sodium fluoride (0.940g, 0.022mol, 30.74eq) was added to the reaction and the suspension was stirred for 10 minutes at room temperature. The flask was cooled in ice and the reaction quenched with a mixture of H_2O-THF (1:9) (4.1ml). After stirring the suspension at room temperature for 10 minutes, it was filtered through a pad of Celite. The residue was washed with 20ml ether and the filtrate was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography using 1:1 light petroleum : diethyl ether to separate the product (158e) from the menthol generated in the reaction. The product was obtained as a yellow oil which was distilled at 200°C / 1mm Hg using Kugelrohr apparatus to give the title compound (158e) as a colourless oil, 0.124g (80%).

$[\alpha]_D$ = +18.45 (*c* 1.39 in MeOH, 17°C).

ν_{max} (CH_2Cl_2)/cm^{-1} 3610 (s, free OH), 3500 - 3100 (br, H-bonded OH), 1670 (w, C=C), 1090 (s), 1030 (s, C-O), 1060 - 1000 (br, C-C), 975 (s).

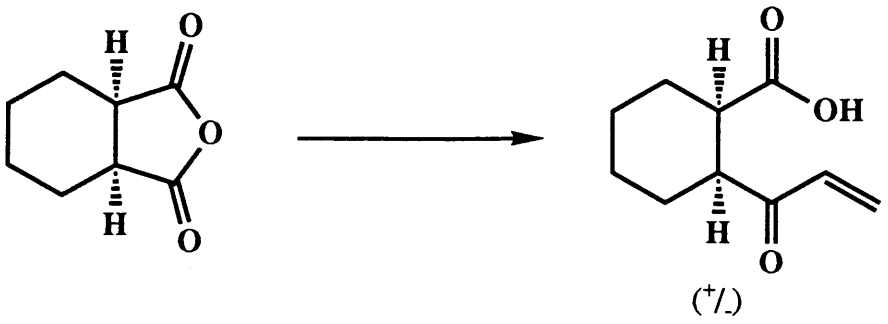
δ_H (300MHz; $CDCl_3$) 1.17 - 1.80 (9H, m, $4CH_2$ & CH, 2-H, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 1.65 (3H, s, CH_3, 4'-H), 1.73 (3H, s, CH_3, Me-C3'), 2.14 (1H, dd, J_{gem} = 14.5, ^3J = 7.8, 1'-H'), 2.21 (1H, dd, J_{gem} = 14.5, ^3J = 8.0, 1'-H''), 3.36 (1H, d, J_{gem} = 11.3, C1-CH'H''OH), 3.40 - 3.45 (2H, s, 2OH), 3.56 (1H, dd, J_{gem} = 11.1, ^3J = 5.1, C2-CH'H''OH), 3.65 (1H, d, J_{gem} = 11.4, C1-CH'H''OH), 3.68 (1H, dd, J_{gem} = 11.1, ^3J = 3.3, C2-CH'H''OH), 5.23 (1H, dd, *J* = 7.7, 7.8, 2'-H).

δ_C (75.5MHz; $CDCl_3$) 18.17 (CH_3, C-4'), (22.88 (CH_2), 26.38 (CH_2), C-4 & C-5) 26.40 (CH_3, Me-C3'), (26.93 (CH_2), 33.96 (CH_2), C-3 & C-6), 34.86 (CH_2, C-1'), 41.95 (C, C-1), 45.83 (CH, C-2), 63.33 (CH_2, CH_2OH), 64.83 (CH_2, CH_2OH), 121.09 (CH, C-2'), 134.22 (C, C-3').

m/z (EI^+) 212 (M^+, 2.3%), 194 ($[M-H_2O]^+$, 70), 181 (25), 163 (43), 125 (52), 107 (86), 95 (95), 81 (100), 69 (74), 55 (69). (Found: M^+, 212.17745. $C_{13}H_{24}O_2$ requires *M*, 212.17762.

Cis - 2 - (Prop - 2' - en - 1' - onyl) cyclohexane - 1 - carboxylic acid. (160).

Literature reference : *J. Med. Chem.*, 1982, **25**, 257.



(148) (160)

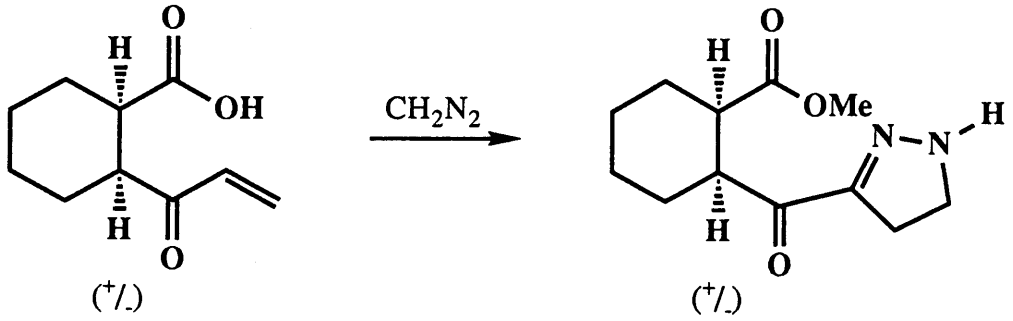
To a vigorously stirred suspension of anhydrous $AlCl_3$ (0.87g, 6.49mmol, 2eq) in 1,2-dichloroethane (15ml) was added *cis*-1,2-cyclohexane dicarboxylic acid (0.50g, 3.24mmol, 1eq) in 1,2-dichloroethane (5ml). Ethylene was bubbled through the reaction mixture for 3.5 hours and the solution was poured into 5% HCl (12ml). Extraction of the mixture three times with diethyl ether (30ml) and evaporation of the organic layer gave a brown residue. This was treated with 10% aqueous K_2CO_3 solution (4ml) and heated on a steam bath for 30 minutes. The cooled aqueous solution was extracted three times with diethyl ether (30ml), acidified using 1M HCl and extracted again with three portions of diethyl ether (30ml). The organic phase was dried ($MgSO_4$) and evaporated to afford the title compound (160) as a white solid (0.34g, 58%).

M.p. = 90 - 92°C (Literature value 90-93°C).

ν_{max} (CH_2Cl_2)/cm^{-1} 3540-2300 (s, OH), 2940 (s), 2860 (s), 1700 (s, C=O), 1615 (s, C=C), 1450 (s), 1400 (s), 1220 (m), 1085 (m), 980 (m), 910 (s).

δ_H (90MHz; $CDCl_3$) 0.90 - 2.42 (8H, m, 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 2.62 (1H, m, 1-H), 3.07 (1H, m, 2-H), 5.63 (1H, dd, J = 10.0, 2.3, 3'*E*-H), 6.17 (1H, dd, J = 16.5, 2.3, 3'Z-H), 6.40 (1H, dd, J = 16.5, 10.0, 2'-H), 10.20 (1H, brs, OH).

Cis - 2 - (Oxo - 1' - (5', 6' - dihydro - 3', 4' - diazolyl) methyl) cyclohexane carboxylic acid, 1 - methyl ester. (161).



(160) (161)

To a solution of *cis*-2-(1-oxo-2-propenyl) cyclohexane carboxylic acid (160) (0.34g, 1.866mmol) in dichloromethane (10ml) at 0°C was added a solution of diazomethane in diethyl ether (15ml), generated from Diazald (1.67g, 7.66mmol), KOH (5g), water (8ml) and ethanol (10ml). The reaction was stirred for 15 minutes and then treated with glacial acetic acid until no more N_2 evolved. The solution was evaporated to dryness, dissolved in 20ml diethyl ether and washed three times with saturated $NaHCO_3$ (20ml). The organic phase was dried ($MgSO_4$) and evaporated to afford the title compound (161) as a yellow oil (0.69g, 79%). The crude material was distilled at 170°C / 4mm Hg using Kugelrohr apparatus to give a pale yellow oil (0.21g, 50%).

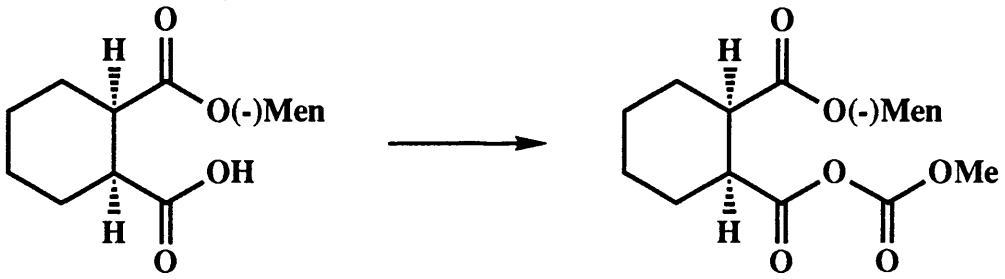
ν_{max} (CH_2Cl_2)/cm^{-1} 3400 (w, NH), 2940 (s), 2860 (s), 1730 (s, C=O), 1660 (s, C=N), 1550 (m), 1440 (m), 1200 (s, C-O), 910 (s).

δ_H (300MHz; $CDCl_3$) 1.39 - 1.59 (4H, m, 4eq-H, 4ax-H, 5eq-H, H5ax-H), {1.72 - 1.90 (2H, m), 1.92 - 2.03 (1H, m), 2.06, 2.16 (1H, m), 3eq-H, 3ax-H, 6eq-H, H6ax-H}, 2.76 (1H, dt, *J* = 4.5, 7.3, 1-H), 2.85 (1H, dt, *J* = 4.5, 7.3, 2-H), 2.95 (1H, dd, *J* = 6.8, 4'-H), 3.65 (3H, s, CH_3, OMe), 3.73 (1H, t, *J* = 6.9, 6'-H'), 3.75 (1H, t, *J* = 6.9, 6'-H''), overlapping 3.75 (2H, m, 5'-H', 5'-H'').

δ_C (75.5MHz; $CDCl_3$) 23.5, 23.7, 25.4, 26.2 (CH_2, C-3, C-4, C-5, C-6), 38.5 (CH_2, C-6'), 42.5 (CH, C-1), 42.9 (CH_2, C-5'), 49.6 (CH, C-2), 51.6 (CH_3, OMe), 135.9 (C, C-2'), 174.1 (C, COOR), 208.3 (C, C=O).

m/z (EI^+) 238 (M^+, 16.6%), 205 (10), 169 (20), 168 (10), 140 (25), 109 (25), 108 (18), 97 (53), 95 (16), 82 (18), 81 (100), 69 (22), 67 (21) (Found: M^+, 238.13153. $C_{12}H_{18}N_2O_3$ requires *M*, 238.13174).

Cyclohexane - 1,2 - dicarboxylic acid, 1 - (1'*R*, 2'*S*, 5'*R*) - methyl ester, 2 - methoxycarbonyl anhydride. (165).



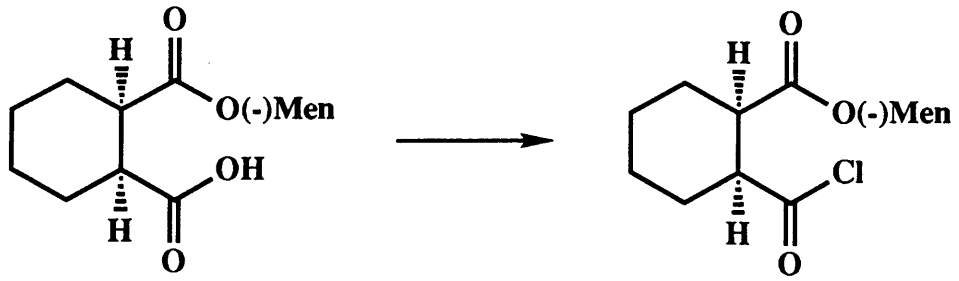
(152a) (165)

A solution of $ClCO_2Me$ (0.16ml, 2.082mmol, 1.3eq) in dry, distilled CH_2Cl_2 (2.4ml) was added to a solution of the mono-menthyl ester (0.501g, 1.614mmol, 1.0eq) in CH_2Cl_2 (9.5ml). The mixture was cooled to -6°C and $^iPr_2NEt$ (0.313g, 2.421mmol, 1.5eq) in CH_2Cl_2 (4.75ml) was added dropwise. After stirring for 30 minutes at -4 to -6°C, the reaction mixture was washed with water (15ml), saturated brine (15ml) and water (15ml). The organic phase was separated, dried ($MgSO_4$) and evaporated to yield the mixed anhydride (165) as a pale yellow oil (0.533g, 86%).

ν_{max} (CH_2Cl_2)/cm^{-1} 2960 (s), 2870 (s), 1820 (s, C=O anhydride), 1765 (s, C=O anhydride), 1730 (s, C=O ester), 1450 (s), 1370 (s), 1250 (s), 1195 (s), 1105 (s), 1080 (s), 995 (s)

δ_H (300MHz; $CDCl_3$) 0.72 (3H, d, *J* = 6.9, MeCH(Me)C2'), 0.87 (3H, d, *J* = 6.9, MeCH(Me)C2'), 0.89 (3H, d, *J* = 6.4, C5'-Me), {0.77 - 1.21 (3H, m), 1.33 - 2.05 (14H, m), 3ax-H, 3eq-H, 4ax-H, 4eq-H, 5ax-H, 5eq-H, 6ax-H, 6eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 6'ax-H, 6'eq-H, $(CH_3)_2CH$, 2'-H, 5'-H}, 2.83 (2H, m, 1-H & 2-H), 3.73 (3H, s, OMe), 4.68 (1H, ddd, *J* = 10.8, 10.8, 4.3, 1'-H)

Cyclohexane - 1 - carboxylic acid, (1'R, 2'S, 5'R) - methyl ester, 2 - carbonyl chloride. (166).



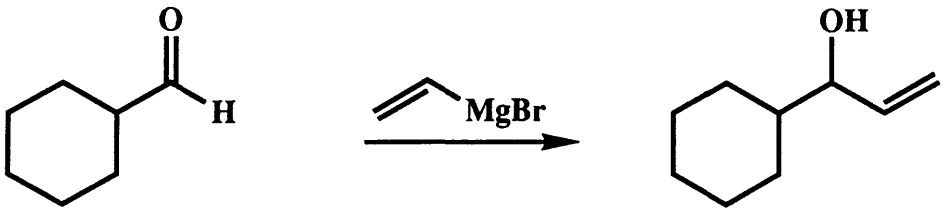
(152a) (166)

Oxalyl chloride (0.133ml, 1.530mmol, 4.75eq) was added to a solution of the acid ester (152a) (0.100g, 0.322mmol, 1eq) and dry DMF (0.025ml, 0.322mmol, 1eq) in hexane (4ml) at room temperature. The reaction mixture was stirred for 1 hour. A white precipitate formed which was removed by filtration. The filtrate was evaporated to dryness to afford the acid chloride (166) (0.063g, 59%) as a pale yellow oil.

ν_{max} (CH_2Cl_2)/cm^{-1} 2930 (s), 2860 (s), 1800 (s, C=O acid chloride), 1720 (s, C=O ester), 1450 (s), 1260 (s), 1190 (s), 1125(m), 1035 (m), 970 (s), 950 (s), 845 (s)

3 - (Cyclohexyl) - 3 - hydroxyl - prop - 1 - ene. (181).

Literature reference: A.N. Boa, Post-doctoral report, University of Leicester, 1995.



(179) (181) (+ / -)

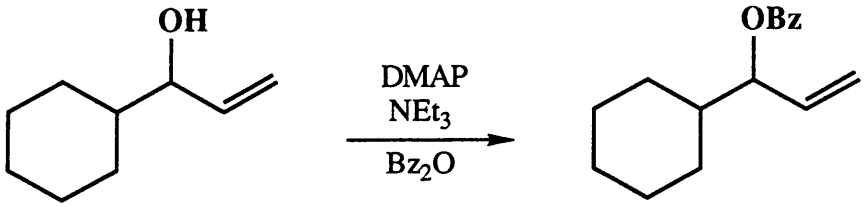
Cyclohexane carboxaldehyde (2.05g, 18.0mmol, 1eq) in dry, freshly distilled THF (10ml) was added dropwise to a solution of vinyl magnesium bromide (20.1ml, 20.0mmol, 1.1eq) in THF (5ml) at 0°C with stirring. Once the addition was complete, the reaction was quenched with 1M HCl (40ml). The reaction mixture was extracted three times with diethyl ether (40ml), the organic phases were combined and washed three times with 40ml saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated to dryness. The crude material was purified using column chromatography with diethyl ether - light petroleum (1:10, v/v) to afford the title compound (181) (1.23g, 49%).

δ_H (300MHz; $CDCl_3$) 0.94 - 1.32 (4H, m, $2CH_2$, 3'ax-H, 3'eq-H, 5'ax-H, 5'eq-H), 1.42 (1H, m, J = 6.2, 1'-H), 1.65 - 1.89 (6H, m, 2'ax-H, 2'eq-H, 4'ax-H, 4'eq-H, 6'ax-H, 6'eq-H), 3.86 (1H, brt, J = 6.4, 3-H), 5.15 (1H, ddd, J_{cis} = 10.4, ^4J = 1.4, J_{gem} = 1.4, 1*Z*-H), 5.21 (1H, ddd, J_{trans} = 17.2, ^4J = 1.5, J_{gem} = 1.5, 1*E*-H), 5.87 (1H, ddd, J_{trans} = 17.1, J_{cis} = 10.4, ^3J = 6.7, 2-H).

δ_C (75.5MHz; $CDCl_3$) {25.93 (CH_2), 25.99 (CH_2), 26.36 (CH_2), 28.20 (CH_2), 28.59 (CH_2), C-2', C-3', C-4', C-5', C-6'}, 43.30 (CH, C-1'), 77.59 (CH, C-3), 115.27 (CH_2, C-1), 139.62 (CH, C-2).

3 - Benzoyloxy - 3 - (cyclohexyl) - prop - 1 - ene. (182).

Literature reference: A.N. Boa, Post-doctoral report, University of Leicester, 1995.



(181)
(+/-)

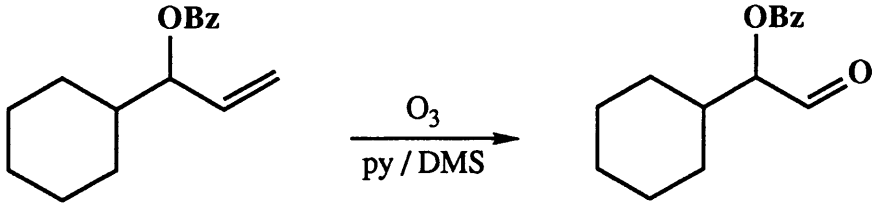
(182)
(+/-)

Benzoic anhydride (8.35g, 36.91mmol, 5eq) and DMAP (10.37g, 84.89mmol, 11.5eq) was added to 1-cyclohexane-prop-2-enol (1.04g, 7.38mmol, 1eq). The flask was fitted with a nitrogen filled balloon and NEt_3 (41.1ml, 29.53mmol, 40eq) and CH_2Cl_2 (9.3ml) were added. The reaction mixture was stirred at room temperature for 1.5 hours and quenched by adding water (3ml) and stirring for 10 minutes. Dichloromethane was used to extract the product, the organic phase was washed with water, dried ($MgSO_4$) and evaporated. The crude material was purified by column chromatography using a gradient of diethyl ether - light petroleum (0:100, 1:50, 1:20, 1:10, v/v) as the eluent to afford the product (182) (1.45g, 80%) as a colourless oil.

δ_H (90MHz; $CDCl_3$) 0.85 - 1.97 (11H, m, 2'ax-H, 2'eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 5'ax-H, 5'eq-H, 6'ax-H, 6eq'-H & 1'-H), 5.26 (3H, m, 3-H, 1*E*-H & 1*Z*-H), 5.88 (1H, ddd, J_{trans} = 16.5, J_{cis} = 9.9, ^3J = 6.9, 2-H), 7.47 (3H, m, Ph-H), 8.03 (2H, d, J = 7.0, Ph-H).

2 - Benzoyloxy - 2 - (Cyclohexyl) - ethanal. (180).

Literature reference: A.N. Boa, Post-doctoral report, University of Leicester, 1995.



(155)
(+ / -)

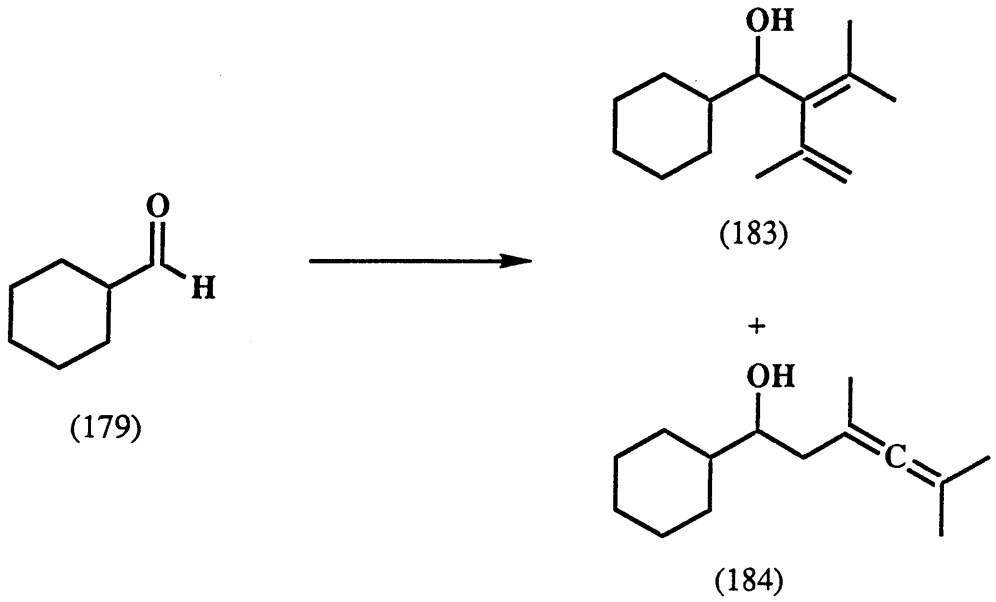
(153)
(+ / -)

Methanol (62µl, 1.53mmol, 1.2eq) and pyridine (0.41ml, 5.08mmol, 4eq) were added to a solution of the olefin (0.31g, 1.27mmol, 1eq) in dichloromethane (10.3ml). The mixture was cooled to -78°C and treated with ozone for 80 minutes. Nitrogen was then bubbled through the solution for 10 minutes and DMS (0.47ml, 6.36mmol, 5eq) was added. The reaction mixture was allowed to warm to room temperature and poured into water (20ml). The product was extracted three times using dichloromethane (20ml) and the organic phases were dried ($MgSO_4$) and evaporated. The crude material was purified using column chromatography with diethyl ether - light petroleum (1:10, v/v) to afford the aldehyde (180) (0.26g, 83%) as a colourless oil.

δ_H (300MHz; $CDCl_3$) {1.17 - 1.46 (5H, m), 1.67 - 1.83 (5H, m), 2'ax-H, 2'eq-H, 3'ax-H, 3'eq-H, 4'ax-H, 4'eq-H, 5'ax-H, 5'eq-H, 6'ax-H, 6'eq-H}, 2.10 (1H, m, 1'-H), 5.07 (1H, dd, J = 4.7, 1.0, 2-H), 7.48 (2H, t, J = 7.5, meta Ph-H), 7.60 (1H, t, J = 7.4, para Ph-H), 8.10 (2H, d, J = 7.7, ortho Ph-H), 9.65 (1H, d, J = 1.0, 1-H).

δ_C (75.5MHz; $CDCl_3$) 25.9 ($2CH_2$), 26.0 (CH_2), 27.7 (CH_2), 29.2 (CH_2), C-2', C-3', C-4', C-5', C-6', 38.8 (C-1'), 82.4 (C-2), 128.5 (2CH, Ph), 129.3 (C, Ph), 129.8 (2CH, Ph), 133.4 (CH, Ph), 166.1 (C=O), 198.9 (C-1).

2 - Methyl - 3 - (1'- cyclohexyl) - hydroxymethyl - 4 - methyl penta - 1, 3 - diene. (183).



Method 1.

The lithiated diene was generated 'in situ' by adding 1.6M ^{n}BuLi (0.8ml, 1.275mmol, 1.43eq) to the bromodiene (172) (0.203g, 1.159mmol, 1.3eq) in THF (1.8ml) and stirring for 0.75 hours at -78°C. Cyclohexane carboxaldehyde (0.100g, 0.892mmol, 1eq) in THF (1.8ml) was introduced and the reaction mixture was stirred for 3 hours at -78°C. The reaction was quenched by adding saturated NH_4Cl solution (4ml) dropwise.The product was extracted three times with dichloromethane (8ml), the organic phase was separated, dried ($MgSO_4$) and evaporated to afford the crude product (0.186g, 100%). Column chromatography with diethyl ether-light petroleum (1:20, v/v) was used to purify the crude material and provide an inseparable mixture (0.119g, 64%) of (183) and (184) in a ratio of 2.28:1 respectively.

Method 2.

Cerium(III) chloride heptahydrate (0.480g, 1.3mmol, 1.3eq) was dried at 140°C *in vacuo* for 2 hours, the anhydrous solid was then cooled and placed under an atmosphere of nitrogen. Dry, distilled THF (5ml) was introduced and the suspension was placed in an ultra-sound bath for 1 hour[59], the mixture was then cooled to -78°C. In a separate

flask, 1.6M ^{n}BuLi (1.0ml, 1.6mmol, 1.6eq) was added to a solution of the bromodiene (172) (0.259g, 1.48mmol, 1.48eq) in THF (2ml) at -78°C and stirred for 0.75 hours to generate the lithiated diene 'in situ'. The resulting yellow solution was added to the suspension of cerium chloride and stirred for 1 hour at -78°C. A deep red/brown colour was observed immediately on addition of the lithiated diene. Cyclohexane carboxaldehyde (0.12ml, 1mmol, 1eq) in THF (2ml) was introduced at -78°C and the reaction mixture was stirred for 3 hours. The reaction was quenched by adding saturated NH_4Cl solution (5ml) dropwise and the product was extracted three times with dichloromethane (10ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by column chromatography using diethyl ether - light petroleum (1:5, v/v) to afford (183) (0.114g, 55%) as a white crystalline solid.

Method 3.

$LaCl_3.7H_2O$ (0.430g, 1.159mmol, 1.3eq) was dried for 16 hours at 120°C. The anhydrous solid was dissolved in THF (4ml) and placed in an ultra-sound bath for 1 hour[59]. 1.6M ^{n}BuLi (0.8ml, 1.275mmol, 1.43eq) was added to the bromodiene (172) (0.203g, 1.159mmol, 1.3eq) at -78°C in THF (2ml) and the solution was stirred for 0.75 hours. The resulting solution of lithiated diene was added to the suspension of $LaCl_3$ and a bright yellow colour was observed. After stirring for 1 hour at -78°C, cyclohexane carboxaldehyde (0.100g, 0.89mmol, 1eq) in THF (2ml) was added, the reaction mixture turned white in colour immediately after addition. The mixture was stirred for 3 hours and the reaction was quenched by adding saturated NH_4Cl solution (4ml) dropwise. The product was extracted three times with dichloromethane (8ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the crude material (0.0942g, 51%) as a colourless oil. Purification by column chromatography using diethyl ether-light petroleum (1:5, v/v) afforded an inseparable mixture (0.074g, 40%) of (183) and (184) in a ratio of 2.40:1 respectively as a white crystalline solid.

Method 4.

$YbCl_3.6H_2O$ (0.337g, 0.869mmol, 1.62eq) was dried for 16 hours at 120°C. The anhydrous solid was dissolved in THF (3ml) and placed in an ultra-sound bath for 1 hour[59]. 1.6M ^nBuLi (0.48ml, 0.765mmol, 1.43eq) was added to the bromodiene (172) (0.120g, 0.695mmol, 1.3eq) at -78°C in dry THF (2ml) and the solution was stirred for 0.75 hours. The resulting solution of lithiated diene was added to the suspension of $YbCl_3$ in THF. After stirring for 1 hour at -78°C, cyclohexane carboxaldehyde (0.060g, 0.535mmol, 1eq) in THF (2ml) was added, the mixture was stirred for 16 hours and the reaction was quenched by adding saturated aqueous NH_4Cl solution (2.5ml) dropwise. The product was extracted three times with dichloromethane (5ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the crude material as a colourless oil. Purification by column chromatography using diethyl ether-light petroleum (1:5, v/v) afforded an inseparable mixture (0.031g, 28%) of (183) and (184) in a ratio of 2.32:1 respectively as a white crystalline solid.

Data for 2 - Methyl - 3 - (1'- cyclohexyl) - hydroxymethyl - 4 - methyl - penta - 1, 3 - diene. (183).

ν_{max} (CH_2Cl_2)/cm^{-1} 3500 - 3100 (br, s, OH), 2920 (s), 2850 (s), 1630 (br, m, C=C), 1450 (s), 1375 (s), 1080 (m), 1000 (s), 890 (s).

δ_H (300MHz; $CDCl_3$) 0.77-1.03 (2H, m, 3"-H' & 5"-H'), 1.06-1.27 (2H, m, 4"-H' & OH), 1.35 (1H, dtt, J = 11.3, 10.0, 3.2, 4"-H"), 1.52-1.80 (6H, m, 2"-H', 2"-H", 6"-H', 6"-H", 3"-H", 5"-H"), 1.68 (3H, s, Me-C4), 1.70 (3H, s, CH_3, 5-H), 1.86 (3H, dd, J = 1.4, 0.9, Me-C2), 2.14 (1H, brd, J = 13.4, 1"-H), 4.16 (1H, brd, J = 9.7, 1'-H), 4.63 (1H, dq, J = 2.6, 0.9, 1-Ha), 5.11 (1H, dq, J = 2.6, 1.4, 1-Hb).

δ_C (75.5MHz; $CDCl_3$) {19.5 (CH_3), 22.0 (CH_3), 25.3 (CH_3), C-5, C4-Me, C2-Me}, {25.9 ($2CH_2$), 26.5 (CH_2), 29.4 (CH_2), 30.0 (CH_2), C-2", C-3", C-4", C-5", C-6"},

42.6 (CH, C-1''), 74.8 (CH, C-1'), 115.2 (CH_2, C-1), {128.7 (C), 136.6 (C), 144.0 (C), C-2, C-3, C-4}.

Data for 6 - (Cyclohexyl) - 2, 4 - dimethyl - 6 - hydroxy - 1, 2 - hexadiene. (184).

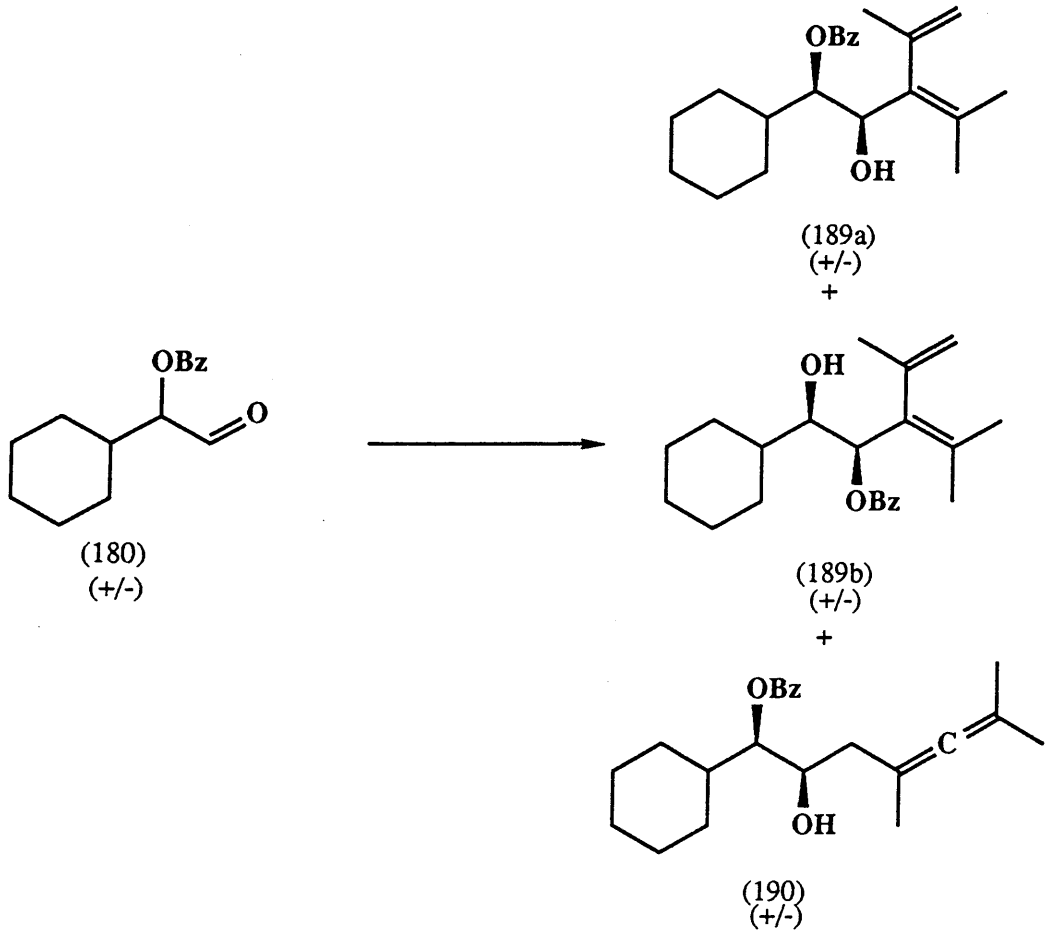
The two compounds (183) and (184) were inseparable therefore any data obtained for (184) has been assigned from spectra of the mixture. Method 1 desribed above gave the product (183) as a single compound, therefore by comparing spectra of this isolated compound with spectra from the mixture, the data below for (184) was deduced. The ^{13}C NMR for compound (184) gave entirely separate, defined peaks from those of (183) thus a full ^{13}C NMR spectra was achieved, the allene C being particularly distinct at δ199.05. The ^{1}H NMR of the mixture gave only a limited amount of information for (184) as the cyclohexane, methyl attached to C-4 and OH peaks were masked by those of (183). However, the 6-H peak of the allene was clearly defined which aided in deducing the ratios of (183):(184) for each method described above. The infrared spectra of the mixture of (183) and (184) was comparable to that of pure compound (183).

δH (300MHz; $CDCl_3$) 1.66 (6H, s, $2CH_3$, Me-C2 & 1-H), 1.96 (1H, d, J = 9.3, 5-H'), 2.01 (1H, d, J = 9.3, 5-H''), 3.46 (1H, ddd, J = 9.3, 9.3, 9.0, 6-H).

δ_C (250MHz; $CDCl_3$) {19.61 (CH_3), 20.64 (CH_3), 20.95 (CH_3), C-1, C2-Me & C4-Me}, {26.13 (CH_2), 26.27 (CH_2), 26.36 (CH_2), 27.91 (CH_2), 29.11 (CH_2), C-2', C-3', C-4', C-5', C-6'}, 39.41 (CH_2, C-5), 42.85 (CH, C-6), 73.33 (CH, C-1'), {94.25 (C), 94.60 (C), C-2 & C-4}, 199.05 (C, C-3).

5 - Benzoyloxy - 5 - (cyclohexyl) - 3 - (1' - methylethenyl) - pent - 2 - en - 4 - ol.

(189a).



Method 1.

$CeCl_3.7H_2O$ (0.197g, 0.527mmol, 2.6eq) was dried for 16 hours at 120°C under vacuum, dry, freshly distilled THF (1.5ml) was added and the reaction flask placed in an ultra-sound bath for 1 hour[59]. The suspension was cooled to -78°C.

The lithiated diene was generated 'in situ' by the addition of $^{n}BuLi$ (0.36ml, 0.580mmol, 2.86eq) to the bromodiene (172) (0.092g, 0.527mmol, 2.6eq) in 2ml THF at -78°C. The solution was stirred for 0.75 hours and added to the suspension of $CeCl_3$. A red/brown colour was instantly noticed and the reaction mixture was stirred for 1 hour. The aldehyde (180) (0.050g, 0.203mmol, 1eq) dissolved in 2ml THF was introduced and the reaction stirred for 3 hours. It was quenched with saturated 2ml NH_4Cl solution and the product extracted three times with 4ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to give the crude material (0.086g, >100%). This was purified by column chromatography with diethyl ether-light petroleum (1:20, v/v) to

afford two separate compounds (189a) as a white solid (0.021g, 30%) and (189b) as a white solid (0.005g, 8%).

Method 2.

$LaCl_3.7H_2O$ (0.196g, 0.527mmol, 2.6eq) was dried for 16 hours at 120°C under vacuum, dry, freshly distilled THF (1.5ml) was added and the reaction flask placed in an ultra-sound bath for 1 hour[59]. The suspension was cooled to -78°C.
The lithiated diene was generated 'in situ' by the addition of ^nBuLi (0.36ml, 0.580mmol, 2.86mmol) to the bromodiene (172) (0.092g, 0.527mmol, 2.6eq) in 2ml THF at -78°C. The solution was stirred for 0.75 hours and added to the suspension of $LaCl_3$. An orange colour was instantly noticed and the reaction mixture was stirred for 1 hour. The aldehyde (180) (0.050g, 0.203mmol, 1eq) dissolved in 2ml THF was introduced and the reaction stirred for 2.5 hours, the suspension had turned pale yellow. It was quenched with 2ml saturated NH_4Cl solution and the product extracted three times with 4ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to give the crude material (0.064g, 91%). This was purified by column chromatography with diethyl ether-light petroleum (1:20, v/v) to afford (189a) as a white solid (0.013g, 18%) and an inseparable mixture of (189b) and the allene (190) (0.006g, 9%) as a white solid.

Method 3.

$PrCl_3.6H_2O$ (0.188g, 0.527mmol, 2.6eq) was dried for 16 hours at 120°C under vacuum, dry, freshly distilled THF (1.5ml) was added and the reaction flask placed in an ultra-sound bath for 1 hour[59]. The suspension was cooled to -78°C.
The lithiated diene was generated 'in situ' by the addition of ^nBuLi (0.36ml, 0.580mmol, 2.86mmol) to the bromodiene (172) (0.092g, 0.527mmol, 2.6eq) in 2ml THF at -78°C. The solution was stirred for 0.75 hours and added to the suspension of $PrCl_3$. A green colour was instantly noticed and the reaction mixture was stirred for 1 hour. The aldehyde (180) (0.050g, 0.203mmol, 1eq) in 2ml THF was introduced and the reaction stirred for 2.5 hours, the suspension had turned bright yellow. It was quenched with

2ml saturated aqueous NH_4Cl solution and the product extracted three times with 4ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to give the crude material (0.064g, 91%). This was purified by column chromatography with diethyl ether-light petroleum (1:20, v/v) to afford (189a) as a white solid (0.020g, 28%) and an inseparable mixture of (189b) and the allene (190) (0.006g, 9%) as a white solid.

Data for 5 - Benzoyloxy - 5 - (cyclohexyl) - 3 - (1' - methylethenyl) - pent - 2 - en - 4 - ol. (189a).

δ_H (300MHz; $CDCl_3$) 1.11-1.19 (2H, m), 1.26-1.41 (3H, m), 3"-H', 3"-H", 4"-H', 5"-H', 5"-H", 1.57 (3H, s, Me-C2), 1.66-1.90 (5H, m, 2"-H', 2"-H", 4"-H", 6"-H', 6"-H"), 1.71 (3H, s, CH_3, 1-H), 1.90 (3H, s, Me-C1'), 2.03 (2H, brd, J = 9.0, 1"-H & OH), 4.82 (1H, s, 2'-H'), 4.89 (1H, dd, J = 8.1, 9.2, 4-H), 5.07 (1H, dd, J = 2.4, 9.5, 5-H), 5.20 (1H, s, 2'-H"), 7.47 (2H, t, Ph-H), 7.58 (1H, t, Ph-H), 8.02 (2H, d, Ph-H).

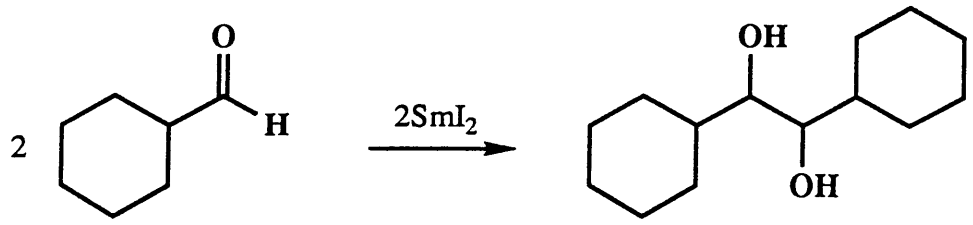
δ_C (75.5MHz; $CDCl_3$) {20.03 (CH_3, Me), 22.29 (CH_3, Me), 25.29 (CH_3, Me), Me-C2, C-1, Me-C1'}, 26.03 (CH_2), 26.31 (CH_2), 26.47 (CH_2), 26.51 (CH_2), 30.75 (CH_2), C-2", C-3", C-4", C-5", C-6", 39.11 (CH, C-1"), 67.93 (CH, C-4), 78.43 (CH, C-5), 116.76 (CH_2, C-2'), 128.28 (2CH, Ph), 129.58 (2CH, Ph), 130.41 (C, Ph), 132.73 (CH, Ph), 130.73 (C, C=C), 134.4 (C, C=C), 143.59 (C, C=C), C-3, C-2, C-1', 165.54 (C, C=O).

Data for 4 - Benzoyloxy - 5 - (cyclohexyl) - 3 - (1' - methylethenyl) - pent - 2 - en - 5 - ol. (189b).

δ_H (300MHz; $CDCl_3$) 0.90 (1H, m, 4"-H'), 1.13-1.38 (4H, m, 3"-H', 3"-H", 5"-H' & 5"-H"), 1.45 (1H, ddt, J = 12.0, 11.7, 3.4, 4"-H"), 1.54-1.65 (4H, m, 2"-H', 2"-H", 6"-H' & 6"-H"), 1.80 (3H, s, Me-C2), 1.87 (3H, s, Me-C1'), overlapping 1.73-1.87 (2H, m, 1"-H & OH), 2.00 (3H, s, CH_3, 1-H), 3.79 (1H, brd, J = 9.7, 5-H), 4.70 (1H, s, 2'-H'), 5.16 (1H, s, 2'-H"), 6.04 (1H, d, J = 9.5, 4-H), 7.49 (2H, t, Ph-H), 7.61 (1H, t, Ph-H), 8.07 (2H, d, Ph-H).

1,2-Ethanediol-1,2-dicyclohexane. (192).

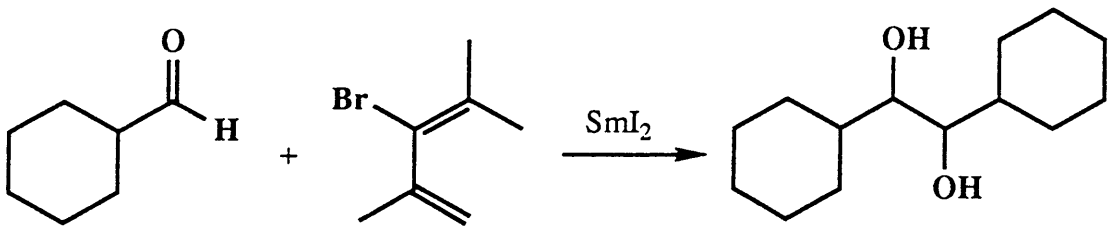
Literature reference: *Tetrahedron*, 1986, **42**, 6573; *Tetrahedron Lett.*, 1982, **23**, 3497.



(179) (192)

To a 0.1M solution of SmI_2 in THF (10ml, 1mmol, 1eq) was added cyclohexane carboxaldehyde (0.1122g, 1mmol, 1eq) in dry, freshly distilled THF (3ml), the mixture was stirred at room temperature for 23 hours. A colour change from blue to green to yellow was observed. The yellow colour indicated the end of the oxidation. The solution was hydrolysed with 0.1M HCl (20ml) and extracted three times with 20ml dichloromethane. The organic layers were combined, washed twice with 30ml saturated aqueous NaCl solution, dried ($MgSO_4$) and evaporated to afford a white solid which was recrystallised from light petroleum - chloroform to afford the pinacol (192) as a white, crystalline solid (0.0915g, 81%), melting point 148-150°C.

Method 2.



(179) (172) (192)

To a 0.1M solution of SmI_2 in THF (20ml, 2mmol, 1eq) was added the bromodiene (172) (0.1751g, 1mmol, 1eq) in dry, freshly distilled THF (2ml). Cyclohexane carboxaldehyde (0.1122g, 1mmol, 1eq) in dry THF (3ml) was introduced dropwise and

the reaction mixture was stirred under N_2 at room temperature. After 5 hours, the solution had turned green and a yellow precipitate was seen on the wall of the flask. The reaction was quenched with 0.1M HCl (20ml) and extracted three times with 20ml dichloromethane. The organic phase was washed twice with 30ml saturated aqueous NaCl solution, dried ($MgSO_4$) and evaporated to give a white solid (0.1186g). The crude product was recrystallised from light petroleum - chloroform to afford the pinacol (192) as a white, crystalline solid (0.0563g, 50%).

M.p. = 148.5 - 150°C (A mixed m.p. 148 - 150°C, showed the product from both methods to be the same compound).

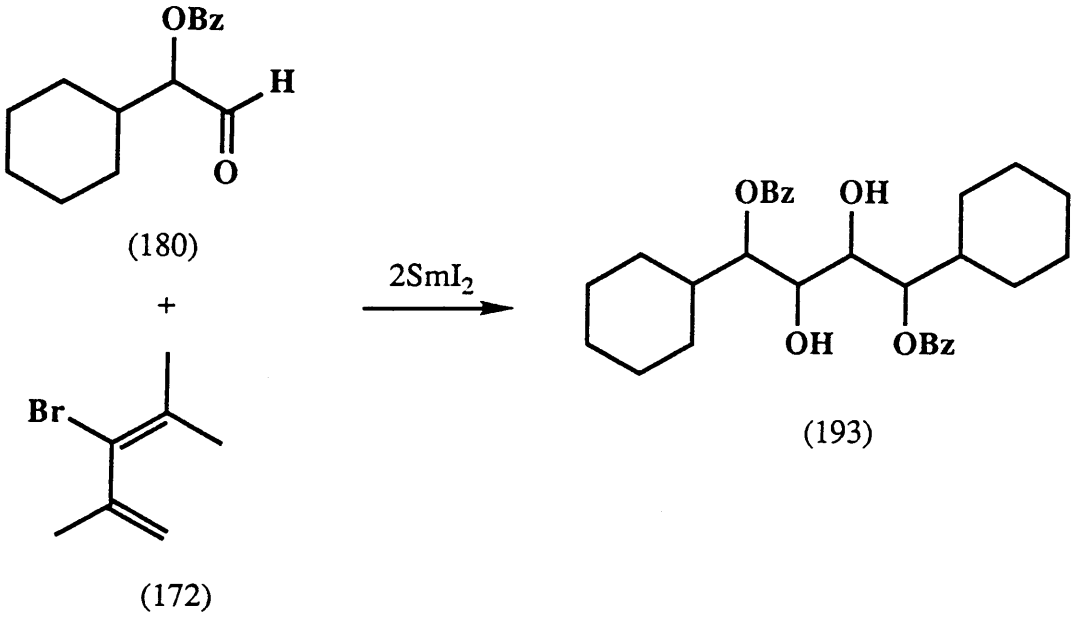
$[\alpha]_D$ = -18.80° (*c* 0.35 in $CHCl_3$, 19°C).

δ_H (90MHz; $CDCl_3$) 0.73 - 1.97 (24H, brm, $2C_6H_{11}$ & 2OH), 3.30 (2H, brt, *J* = 5.0, 1-H & 2-H)

δ_C (75.5MHz; CD_3OD) {27.2 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 30.0 (CH_2), 30.6 (CH_2), C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5", C-6"} 41.3 (CH, C-1' & C-1"), 76.0 (CH, C-1 & C-2)

m/z (EI^+) 226 (M^+, 2.7%), 209 ($[M-OH]^+$, 2.0), 198 (2), 143 ($[M-C_6H_{11}]^+$, 59), 113 (77), 95 (100), 81 (52), 67 (46), 55 (66)

1, 4 - Dibenzoyl - 2, 3 - butanediol - 1, 4 - dicyclohexane. (193).

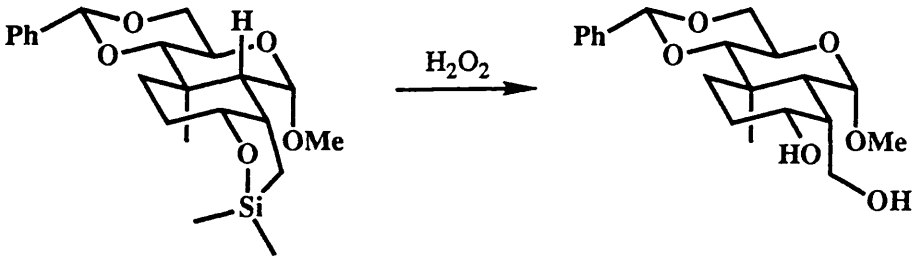


To a solution of 0.1M SmI_2 in THF (4.30ml, 0.43mmol, 2eq) under N_2 was added bromodiene (172) (0.038g, 0.215mmol, 1eq) in THF (0.5ml). On addition of the aldehyde (0.053g, 0.215mmol, 1eq) in THF (0.5ml), the solution immediately changed colour from blue to yellow. The reaction mixture was quenched with 0.1M HCl (10ml) and extracted three times with 10ml diethyl ether. The organic layer was washed three times with 15ml saturated brine, dried ($MgSO_4$) and evaporated. The crude material was purified by column chromatography with diethyl ether-light petroleum (1:5, v/v) to afford the pinacol (193) (0.029g, 54%) as a colourless oil.

δ_H (90MHz; $CDCl_3$) 0.60 - 1.17 (24H, brm, $2C_6H_{11}$ & 2OH), 3.33 (4H, m, 1-H, 2-H, 3-H, 4-H), 7.42 (6H, m, Ph-H), 7.95 (4H, m, Ph-H)

(2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*)-4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b-Decahydro -7-hydroxymethyl-6-methoxy-10a-methyl-2-phenyl-1,3-dioxino[5,4-a]benzopyran-8-ol (122).

Literature reference: J. Clark, PhD thesis, 1993, Leicester University.



To a solution of the siloxane (1.830g, 4.357mmol, 1eq) in THF (10ml) and MeOH (10ml) was added Na_2CO_3 (0.554g, 5.228mmol, 1.2eq) and a 30% w/v solution of H_2O_2 (2.23ml, 21.784mmol, 5eq). The reaction mixture was refluxed with stirring for 3 hours and cooled to room temperature. The solution was filtered through cotton wool and the filtrate was evaporated to half it's volume. 10ml Saturated brine solution was added to the solution and the product was extracted three times with 20ml ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography using 550ml diethyl ether followed by 700ml ethyl acetate as the eluents. The diol (122) was obtained as a white solid in a yield of 0.954g (60%).

Melting point = 138-140°C

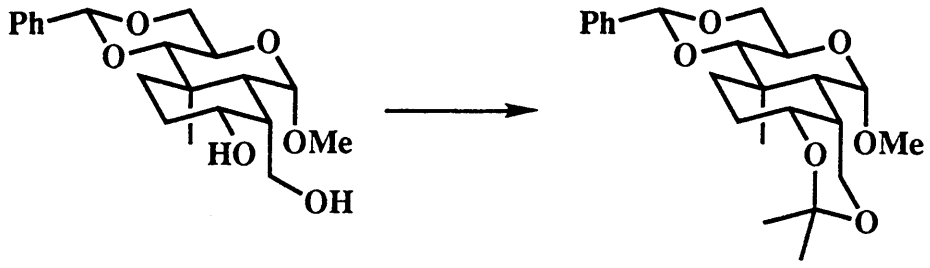
$[\alpha]_D$ =19.05° (*c* 0.20 in $CHCl_3$, 21°C).

δ_H (250MHz; $CDCl_3$) 1.16 (3H, s, Me-C10a), 1.24 (1H, m, 10-H'), 1.68 (3H, m, 9-H, 6a-H), 1.84 (1H, dt, *J* = 13.1, 3.4, 10-H''), 2.31 (1H, brm, 7-H), 3.14 (1H, d, *J* = 9.5, 10b-H), 3.33 (3H, s, OMe), 3.64 (1H, t, *J* = 10.2, 4ax-H), 3.81 (1H, m, 8-H), 3.92 (1H, ddd, *J* = 9.8, 9.8, 5.0, 4a-H), 4.04 (1H, t, *J* = 9.0, CH'H''OH), 4.20 (1H,

brm, CH'H''OH), 4.24 (1H, dd, J = 10.2, 5.0, 4eq-H), 4.58 (1H, d, J = 3.2, 6-H), 5.50 (1H, s, 2-H), 7.26-7.78 (5H, m, Ph-H)

δ_C (69.2MHz; $CDCl_3$) 16.1 (CH_3, C10a-Me), 27.2 (CH_2, C-10), 36.2 (C, C-10a), 37.2 (CH_2, C-9), 45.4 (CH, C-7), 48.2 (CH, C-6a), 55.6 (CH_3, OMe), 60.7 (CH_2, CH_2OH), 60.7 (CH, C-4a), 70.0 (CH_2, C-4), 75.2 (CH, C-8), 88.1 (CH, C-10b), 101.8 (CH, C-2), 103.0 (CH, C-6), 126.5 (2CH, Ph), 128.6 (2CH, Ph), 129.3 (CH, Ph), 138.2 (C, Ph).

(4a*R*, 6*S*, 6b*R*, 10a*R*, 12a*R*, 12b*S*)-4, 4a, 6, 6a, 6b, 10a, 11, 12, 12a, 12b - Decahydro - 9 - dimethyl - 6 - methoxy - 12a - methyl - 2- phenyl - bis - 1, 3 - dioxino [5, 4-c], [4, 5-f], [2] benzopyran. (216).



(122) (216)

To a solution of the diol (122) (0.880g, 2.417mmol, 1eq) in DMF (7.5ml) was added p-TsOH (6mg, 0.031mmol, 0.013eq) and 2,2-dimethoxypropane (0.565ml, 4.592mmol, 1.9eq). The reaction mixture was stirred at room temperature for 24 hours and then quenched with 7.5ml water. The product was extracted thee times with 10ml dichloromethane, dried ($MgSO_4$) and evaporated. The crude oil was purified by column chromatography using diethyl ether -light petroleum (1:1, v/v) to give the title compound (216) as a white foam in a yield of 0.657g (67%).

Melting point = 46 - 49°C

$[\alpha]_D$ = +59.44° (c 0.047 in CH_2Cl_2, 22°C).

Found: C, 68.1; H, 7.8. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%.

ν_{max} (CH_2Cl_2)/cm^{-1} 2940 (m), 2900 (m), 1455 (m), 1370 (s), 1245 (m), 1195 (m), 1140 (s, C-O), 1080 (s, C-O), 1050 (s), 980 (s)

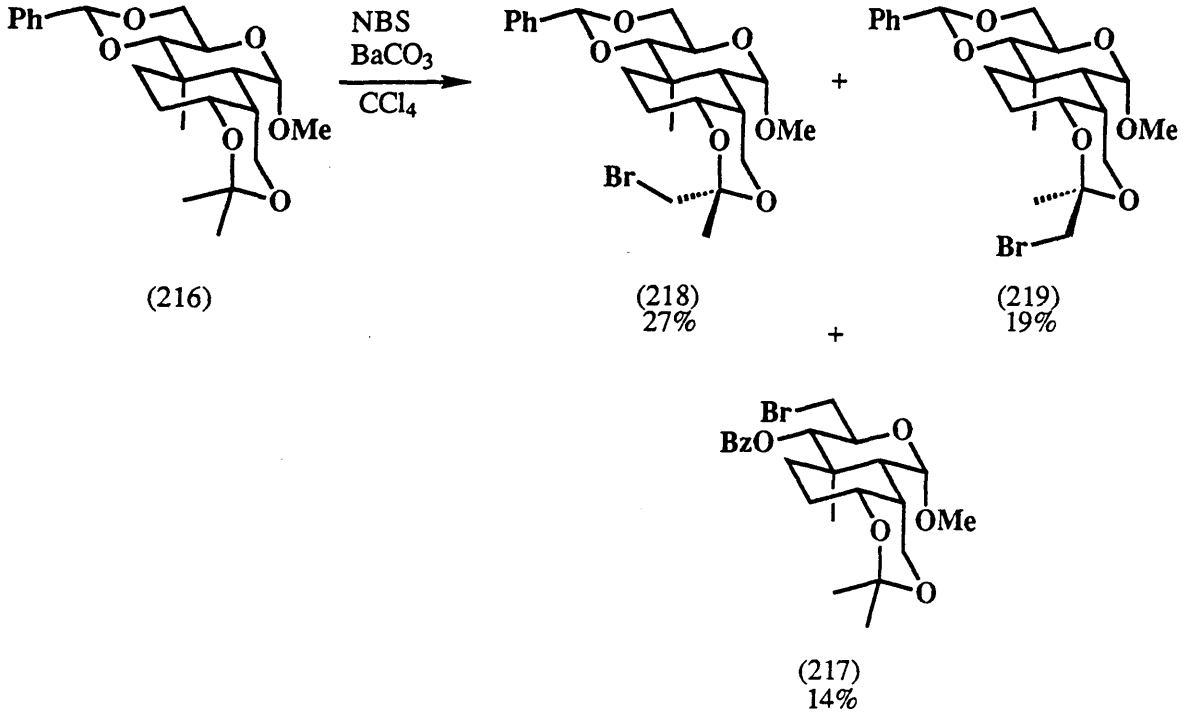
δH (250MHz; $CDCl_3$) 0.99 (1H, ddt, *J* = 13.3, 4.6, 3.2, 11eq-H), 1.29 (3H, s, Me-C12a), 1.32 (3H, s, CH_3, Me-C9), 1.42 (3H, s, CH_3, Me-C9), 1.62 (1H, dd, *J* = 4.2,

3.4, 6a-H), 1.74 (1H, dt, J = 13.3, 4.6, 12ax-H), 1.84 (1H, dt, J = 13.3, 3.6, 12eq-H), 2.08 (1H, ddt, J = 12.9, 4.6, 3.4, 11ax-H), 2.42 (1H, ddt, J= 10.9, 5.4, 3.4, 6b-H), 3.12 (1H, d, J = 9.5, 12b-H), 3.28 (3H, s, OMe), 3.60 (1H, t, J = 10.2, 4ax-H), 3.80 (1H, m, 10a-H), 3.89 (2H, m, 4a-H & 7-H'), 4.16 (1H, d, J = 11.7, 7-H''), 4.18 (1H, dd, J = 10.1, 4.8, 4eq-H), 4.50 (1H, d, J = 3.0, 6-H), 5.45 (1H, s, 2-H), 7.29 (3H, m, Ph-H), 7.40 (2H, m, Ph-H).

δ_C (62.9MHz; $CDCl_3$) 16.48 (CH_3, C12a-Me), 26.39 (CH_2, C-12), 26.74 (CH_3, Me-C9), 30.33 (CH_3, Me-C9), 36.09 (C, C-12a), 36.58 (CH_2, C-11), 36.97 (CH, C-6b), 48.21 (CH, C-6a), 55.55 (CH_3, OMe), 59.99 (CH_2, C-7), 61.05 (CH, C4a), 70.07 (CH_2, C4), 73.86 (CH, C-10a), 87.83 (CH, C-12b), 98.28 (C, C-9), 101.80 (CH, C-2), 102.88 (CH, C-6), 126.56 (2CH, Ph), 128.62 (2CH, Ph), 129.32 (CH, Ph), 138.28 (C, Ph).

m/z (EI^+) 389 ($[M-CH_3]^+$, 100%), 373 ($[M-OMe]^+$, 1.5), 329 (15), 149 (21), 105 (13), 91 ($PhCH_2^+$, 13), 77 (Ph^+, 4) (Found: M^+, 404.21974. $C_{23}H_{32}O_6$ requires M, 404.219874).

(4a*R*, 4b*R*, 5*S*, 7*S*, 8*S*, 8a*R*, 10a*R*) - 4, 4a, 4b, 5, 7, 8, 9, 10, 10a - Decahydro - 8 - benzoyl - 7 - bromomethyl - 2 - dimethyl - 5 - methoxy -8a - methyl - 1, 3 - dioxino [4,5-f] [2] benzopyran.(217).



The acetonide (216) (0.142g, 0.353mmol, 1eq) was dissolved in dry CCl_4 (8ml) to which $BaCO_3$ (0.383g, 1.939mmol, 5.5eq) and NBS (0.075g, 0.423mmol, 1.2eq) was added. The mixture was refluxed for 2.5 hours and cooled to room temperature. The suspension was filtered through cotton wool to remove the $BaCO_3$, the filtrate was washed twice with 8ml water, dried ($MgSO_4$) and evaporated to give a white foam. The crude material was purified by column chromatography using 3:1 light petroleum : diethyl ether. The first compound to elute off the cloumn was the desired product (217) in a yield of 0.024g (14%), the next was the brominated acetal (218) in a yield of 0.458g (27%) and the final product was the alternative brominated acetal (219) in a yield of 0.327g (19%).

Data for (4a*R*, 4b*R*, 5*S*, 7*S*, 8*S*, 8a*R*, 10a*R*) - 4, 4a, 4b, 5, 7, 8, 9, 10, 10a - Decahydro - 8 - benzoyl - 7 - bromomethyl - 2 - dimethyl - 5 - methoxy - 8a - methyl - 1, 3 - dioxino [4,5-f] [2] benzopyran. (217).

δ_C (69.2MHz; $CDCl_3$) 16.70 (CH_3, C8a-Me), 16.83 (CH_3,C2-Me), 24.52 (CH_3, C2-Me), 26.37 (CH_2, C-9), 33.45 (CH_2, C7-CH_2Br), 35.85 (CH, C-4a), 36.82 (C, C-8a), 37.80 (CH_2, C-10), 47.47 (CH, C-4b), 55.74 (CH_3, OMe), 60.10 (CH_2, C-4), 68.30 (CH, C-7), 73.62 (CH, C-11), 78.90 (CH, C-8), 98.02 (C, C-2), 102.24 (CH, C-5), 129.06 (CH, Ph), 129.62 (C, Ph), 130.18 (CH, Ph), 134.02 (CH, Ph), 165.93 (C, C=O).

Data for (4a*R*, 6*S*, 6b*R*, 9*S*, 10a*R*, 12a*R*, 12b*S*)-4, 4a, 6, 6a, 6b, 10a, 11, 12, 12a, 12b - Decahydro - 9 - bromomethyl - 6 - methoxy - 9 - methyl - 12a - methyl - 2- phenyl - bis - 1, 3 - dioxino [5, 4-c], [4, 5-f], [2] benzopyran. (218).

δ_H (250MHz; $CDCl_3$) 1.34 (3H, s, CH_3, Me-C9), 1.53 (3H, s, CH_3, Me-C10a), 1.70 (1H, dd, J = 4.3, 3.3, 6a-H), {1.02 - 1.13 (1H, m), 1.59 (1H, m), 1.88 - 2.10 (2H, m), 11ax-H, 11eq-H, 12ax-H, 12eq-H}, 2.54 (1H, m, 6b-H), 3.18 (1H, d, J = 9.5, 12b-H), 3.35 (3H, s, OMe), 3.49 (1H, d, J_{gem} = 10.8, C9-CH'H"Br), 3.53 (1H, d, J_{gem} = 10.9, C9-CH'H"Br), 3.67 (1H, dd, J = 10.2, 10.2, 4ax-H), 3.92 - 4.08 (3H, m, 10a-H, 4a-H & 7-H'), 4.16 - 4.34 (2H, m, 4eq-H & 7-H"), 4.57 (1H, d, J=3.0, 6-H), 5.52 (1H, s, 2-H), 7.36 (3H, m, Ph), 7.47 (2H, m, Ph).

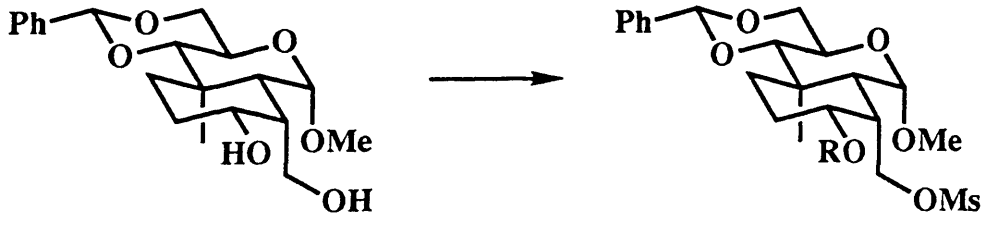
δ_C (69.2MHz; $CDCl_3$) 16.38 (CH_3, C12a-Me), 26.51 (CH_3, C9-Me), 26.51 (CH_2, C-12), 36.04 (C, C-12a), 36.29 (CH_2, C-11), 36.42 (CH, C-6b), 37.72 (CH_2, C9-CH_2Br), 47.89 (CH, C-6a), 55.57 (CH_3, OMe), 60.55 (CH_2, C-7), 61.04 (CH, C-4a), 70.03 (CH_2, C-4), 73.70 (CH, C-10a), 87.67 (CH, C-12b), 97.78 (C, C-9), 101.83 (CH, C-2), 102.68 (CH, C-6), 126.58 (2CH, Ph), 128.64 (2CH, Ph), 129.36 (CH, Ph), 138.20 (C, Ph).

m/z (CI^+) 482/484 (M^+, 1.4%), 467/469 ($[M-CH_3]^+$, 7.5), 451/453 ($[M-OMe]^+$, 1.5), 389 ($[M-CH_2Br]^+$, 100), 329 (16), 165 (13), 149 (32), 105 ($PhCO^+$, 41), 91 (30), 55 (10) (Found: M^+, 482.13042. $C_{23}H_{31}O_6{}^{79}Br$ requires 482.13040).

Data for (4a*R*, 6*S*, 6b*R*, 9*R*, 10a*R*, 12a*R*, 12b*S*)-4, 4a, 6, 6a, 6b, 10a, 11, 12, 12a, 12b - Decahydro - 9 - bromomethyl - 6 - methoxy - 9 - methyl - 12a - methyl - 2- phenyl - bis - 1, 3 - dioxino [5, 4-c], [4, 5-f], [2] benzopyran. (219).

δ_C (69.2MHz; $CDCl_3$) 16.30 (CH_3, C12a-Me), 24.42 (CH_3, C9-Me), 26.51 (CH_2, C-12), 36.10 (CH, C-6b), 36.37 (C, C-12a), 36.47 (CH_2, C-11), 39.75 (CH_2, C9-CH_2Br), 48.05 (CH, C-6a), 55.59 (CH_3, OMe), 60.23 (CH_2, C-7), 61.03 (CH, C-4a), 70.03 (CH_2, C-4), 74.20 (CH, C-10a), 87.69 (CH, C-12b), 97.24 (C, C-9), 101.81 (CH, C-2), 102.71 (CH, C-6), 126.56 (2CH, Ph), 128.64 (2CH, Ph), 129.35 (CH, Ph), 138.23 (C, Ph).

(2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*) - 4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b - Decahydro - 7 - mesyloxymethyl - 6 - methoxy - 10a - methyl - 2 - phenyl - 1, 3 - dioxino [5, 4 - c] benzopyran - 8 - ol. (225).



(122) (224) R = Ms (225) R = H

The diol (122) (25mg, 0.069mmol, 1eq) and DMAP (17mg, 0.137mmol, 2eq) were dissolved in dichloromethane (0.5ml), the solution was placed under N_2 and cooled to 0°C. Mesyl chloride (6.5µl, 0.082mmol, 1.2eq) was added and the reaction mixture was stirred for 1 hour at room temperature. A white precipitate was seen immediately after the addition of the mesyl chloride. An aqueous work-up gave a crude sample which

on purification by flash column chromatography furnished two products. The first compound to elute off the column was the dimesylate (224) in a yield of 14mg (40%) and the second product was the monomesylate (225) in a yield of 8mg (25%).

Data for (2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*) - 4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b - Decahydro - 8 - mesyloxy - 7 - mesyloxymethyl - 6 - methoxy - 10a - methyl - 2 - phenyl - 1, 3 - dioxino [5, 4 - c] benzopyran. (224).

δ_H (250MHz; $CDCl_3$) 1.12 (3H, s, C10a-C$\underline{H_3}$), 1.76 (1H, d, *J* = 3.5, 6a-H), 1.78 - 1.98 (4H, brm, 10ax-H, 10eq-H, 9ax-H, 9eq-H), 2.70 (1H, brm, 7-H), 2.97 (3H, s, $\underline{Me}$-SO_3-), 3.01 (3H, s, $\underline{Me}$-SO_3-), 3.12 (1H, d, *J* = 9.5, 10b-H), 3.36 (3H, s, OMe), 3.62 (1H, dd, *J* = 10.2, 10.2, 4ax-H), 3.89 (1H, ddd, *J* = 5.0, 9.8, 9.7, 4a-H), 4.20 (1H, dd, *J* = 10.2, 5.0, 4eq-H), 4.33 (1H, dd, *J* = 10.2, 7.0, C$\underline{H}$'H''OMs), 4.59 (1H, d, *J* = 3.1, 6-H), 4.71 (1H, m, 8-H), 5.14 (1H, d, *J* = 10.1, CH'$\underline{H}$''OMs), 5.46 (1H, s, 2-H), 7.33 (5H, m, Ph).

δ_C (62.9MHz; $CDCl_3$) 15.6 (C10a-$\underline{C}H_3$), 25.1 (CH_2, C-10), 35.9 (CH_2, C-9), 36.7 (CH_3, Me-SO_3-), 37.7 (CH_3, Me-SO_3-), 39.2 (C, C-10a), 42.0 (CH, C-7), 47.2 (CH, C-6a), 55.9 (CH_3, OMe), 60.7 (CH, C-4a), 66.6 (CH_2, $\underline{C}H_2$OMs), 69.8 (CH_2, C-4), 80.5 (CH, C-8), 87.2 (CH, C-10b), 101.9 (CH, C-2), 102.1 (CH, C-6), 126.5 (2CH, Ph), 128.7 (2CH, Ph), 129.5 (CH, Ph), 137.2 (C, Ph).

m/z (EI^+) 520 (M^+, 0.2%), 360 (11.6), 300 (6.3), 171 (26.3), 139 (46.9), 127 (28.5), 105 ($PhCO^+$, 100). Found: M+, 520.14356. $C_{22}H_{32}O_{10}S_2$ requires *M*, 520.14367.

Data for (2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*) - 4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b - Decahydro - 7 - mesyloxymethyl - 6 - methoxy - 10a - methyl - 2 - phenyl - 1, 3 - dioxino [5, 4 - c] benzopyran - 8 - ol. (225).

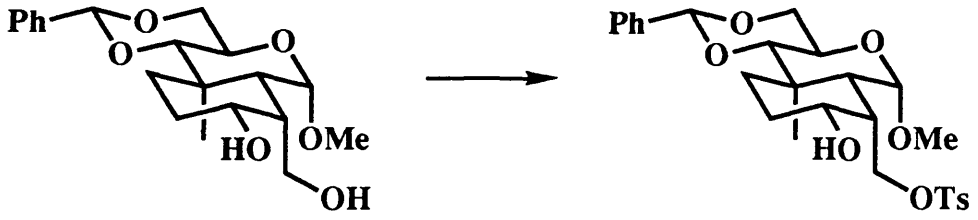
$[\alpha]_D$ = -127.33° (*c* 0.047 in $CHCl_3$, 20°C).

δ_H (250MHz; $CDCl_3$) 1.09 (3H, s, C10a-C$\underline{H_3}$), 1.18 (1H, brs, OH), 1.36 - 1.98 (4H, m, 10ax-H, 10eq-H, 9ax-H, 9eq-H), overlapping 1.70 (1H, dd, *J* = 3.4, 6a-H), 2.40 (1H, m, 7-H), 2.96 (3H, s, CH_3, Me-SO_3-), 3.13 (1H, d, *J* = 9.5, 10b-H), 3.36 (3H, s, OMe), 3.61 (1H, dd, *J* = 10.2, 10.2, 4ax-H), 3.76 (1H, m, 8-H), 3.90 (1H, ddd, *J* = 9.8, 9.8, 4.9, 4a-H), 4.20 (1H, dd, *J* = 10.2, 5.0, 4eq-H), 4.36 (1H, dd, *J* = 10.0, 6.6, C$\underline{H}$'H''OMs), 4.58 (1H, d, *J* = 3.1, 6-H), 5.08 (1H, dd, *J* = 9.9, 1.2, CH'$\underline{H}$''OMs), 5.45 (1H, s, 2-H), 7.29 (3H, m, Ph), 7.39 (2H, m, Ph).

δ_C (62.9MHz; $CDCl_3$) 15.71 (CH_3, C10a-$\underline{Me}$), 26.43 (CH_2, C-10), 36.07 (CH_2, C-9), 36.43 (C, C10a), 37.68 (CH_3, $\underline{Me}SO_3R$), 43.57 (CH, C-7), 47.14 (CH, C-6a), 55.71 (CH_3, OMe), 61.07 (CH, C-4a), 67.50 (CH_2, $\underline{C}H_2OMs$), 69.29 (CH_2, C-4), 72.50 (CH, C-10b), 87.43 (CH, C-8), 101.79 (CH, C-2), 102.62 (CH, C-6), 126.61 (2CH, Ph), 128.75 (2CH, Ph), 129.76 (CH, Ph), 137.86 (C, Ph).

m/z (EI^+) 442 (M^+, 0.6%), 346 (M^+-MsOH, 3), 261 (11.9), 16.5 (27), 149 (27), 105 (72), 91 ($PhCH_2^+$, 28), 84 (100), 77 (Ph^+, 50), 51 (45).

(2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*) - 4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b - Decahydro - 6 - methoxy - 10a - methyl - 2 - phenyl - 7 - tosyloxymethyl - 1, 3 - dioxino [5, 4 - c] benzopyran - 8 - ol. (226).



(122) (226)

The diol (122) (0.025g, 0.069mmol, 1eq) and p-TsCl (0.014g, 0.076mmol, 1.1eq) were placed in a flask which was fitted with a N_2 filled balloon. Dichloromethane (2ml) was added and then pyridine (0.022ml, 0.0275mmol, 4eq), the reaction mixture was stirred at room temperature for 43 hours. The reaction was quenched by adding 2ml water and the product was extracted three times with 2ml dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was purified by flash coulmn chromatography using ethyl acetate as the eluent. Two compounds were isolated, the mono-tosylate (226) in a yield of 0.012g (35%) and 0.012g (47%) of unreacted starting material.

M.p. = 65-68°C

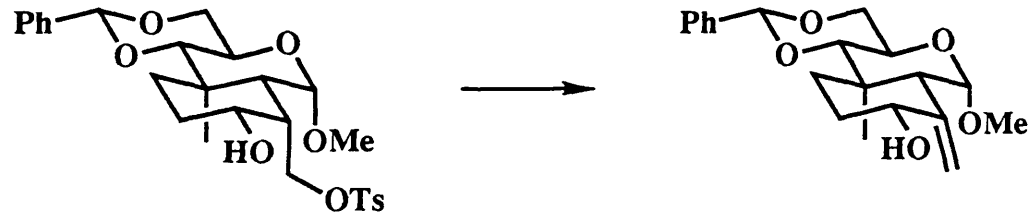
$[\alpha]_D$ = -230.17° (*c* 0.026 in $CHCl_3$, 21°C).

ν_{max} (CH_2Cl_2)/cm^{-1} 3920 (s), 3600 (s, OH), 1600 (m, aromatic ring), 1500 (s), 1360 (s), 1175 (s), 1080 (s), 1045 (s), 1030 (s), 950 (s)

δ_H (250MHz; $CDCl_3$) 1.02 (3H, s, Me-C10a), 1.08 - 1.50 (2H, m, 9-H), 1.64 - 1.88 (2H, m, 10-H), 2.40 (3H, s, Me-C_6H_4-SO_3-), 2.40 (1H, m, 7-H), 3.10 (1H, d, *J* = 9.5, 10b-H), 3.32 (3H, s, OMe), 3.59 (1H, dd, *J* = 10.2, 4ax-H), 3.71 (1H, m, 8-H), 3.84 (1H, ddd, *J* = 9.7, 9.8, 5.0, 4a-H), 4.18 (2H, m, 4eq-H & CH'H"OTs), 4.50 (1H, d, *J* = 2.9, 6-H), 4.89 (1H, d, *J* = 8.9, CH'H"OTs), 5.44 (1H, s, 2-H), 7.30 (4H, m, Ph-H), 7.38 (2H, m, Ph-H), 7.76 (4H, m, Ph-H)

δ_C NMR (69.2MHz; $CDCl_3$) 15.7 (CH_3, C10a-Me), 22.1 (CH_3, CH_3-Ar), 26.3 (CH_2, C-10), 36.0 (CH_2, C-9), 36.7 (C, C-10a), 43.6 (CH, C-7), 47.2 (CH, C-6a), 55.8 (CH_3, OMe), 60.7 (CH, C-4a), 68.1 (CH_2, CH_2OMs), 70.0 (CH_2, C-4), 72.6 (CH, C-10b), 87.7 (CH, C-8), 101.8 (CH, C-2), 102.7 (CH, C-6), 126.5 (2CH, Ph), 128.3 (2CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 130.2 (2CH, Ar), 133.6 (2CH, Ar), 138.2 (C, Ph), 145.1 (C, Ar)

(2*R*, 4a*R*, 6*S*, 6a*R*, 8*R*, 10a*R*, 10b*S*) - 4, 4a, 6, 6a, 8, 9, 10, 10a, 10b - Nonahydro - 6 - methoxy - 10a - methyl - 7 - methylene - 2 - phenyl - 1, 3 - dioxino [5, 4 - c] benzopyran - 8 - ol. (227).



(226) (227)

The tosylate (226) (0.042g, 0.0820mmol, 1eq) was dissolved in THF (5ml) and placed under N_2. 1.6M ^nBuLi (56µl, 0.090mmol, 1.1eq) was added and the mixture was refluxed for 1 hour. The reaction was quenched with 5ml water, extracted three times with 5ml ether, dried ($MgSO_4$) and evaporated. The product was purified by column chromatography using 1:1 diethyl ether : light petroleum to give (227) as a white solid in a yield of 0.0173g (61%).

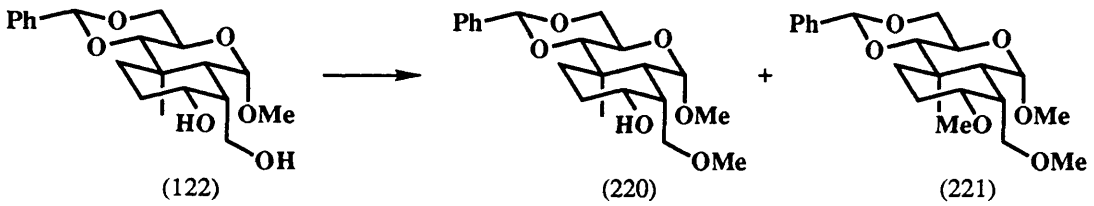
ν_{max} (CH_2Cl_2)/cm^{-1} 3600 (s, free OH), 3040 (m), 2930 (s), 2860 (s), 1650 (w, C=C), 1450 (s), 1370 (s), 1110 (s), 1080 (s), 1040 (s), 985 (s).

δ_H (250MHz; $CDCl_3$) 1.07 (3H, s, CH_3, C10a-Me), 1.18 - 1.64 (3H, m, CH_2 & CH, 10ax-H, 10eq-H, 6a-H), 1.89 - 2.00 (2H, m, CH_2, 9ax-H, 9eq-H), 2.13 (1H, brs, OH), 3.28 (1H, d, J = 9.5, 10b-H), 3.35 (3H, s, OMe), 3.67 (1H, dd, ^3J = 10.1, J_{gem} = 10.1, 4ax-H), 3.95 (1H, ddd, J = 4.9, 10.1, 9.7, 4a-H), overlapping 3.95 (1H, m, 8-H), 4.22 (1H, dd, J_{gem} = 10.1, ^3J = 4.9, 4eq-H), 4.64 (1H, d, J = 2.9, 6-H), 5.06 (1H, d, J_{gem} = 1.3, C7=CH'H"), 5.19 (1H, d, J_{gem} = 1.3, C7=CH'H"), 5.48 (1H, s, 2-H), 7.30 (3H, m, Ph), 7.41 (2H, m, ortho-Ph)

δ_C (62.9MHz; $CDCl_3$) 15.1 (CH_3, C10a-Me), 32.7 (CH_2, C-10), 37.2 (CH_2, C-9), 38.9 (C, C-10a), 50.9 (CH, C-6a), 55.3 (CH_3, OMe), 60.3 (CH, C-4a), 70.1 (CH_2, C-4), 73.3 (CH, C-8), 87.6 (CH, C-10b), 100.4 (CH, C-2), 102.1 (CH, C-6), 106.4 (CH_2, C=CH_2), 126.6 (2CH, Ph), 128.6 (2CH, Ph), 129.3 (CH, Ph), 138.3 (C, Ph), 146.3 (C, C=CH_2, C-7)

m/z (EI^+) 346 (M^+, 7%), 314 (M^+-MeOH, 6), 271 (14), 240 (M^+-PhCHO, 6.5), 197 (32), 165 (65), 149 (39.5), 137 (25), 119 (51), 105 ($PhCO^+$, 100). Found: M^+, 346.11793. $C_{20}H_{26}O_5$ requires *M*, 346.17801.

(2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*)-4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b-Decahydro-6, 8-dimethoxy-7-methoxymethyl-10a-methyl-2-phenyl-1,3-dioxo[5,4-c]benzopyran. (221).



(122) (220) (221)

Method 1.

A solution of the diol (122) (0.096g, 0.265mmol, 1eq) in DMF (1.7ml) was treated with Ag_2O (0.245g, 1.058mmol, 4eq) and MeI (0.10ml, 1.587mmol, 6eq) at room temperature. The reaction mixture was stirred for 16 hours and then filtered through a sinter funnel to remove the insoluble salts. The residues were washed with 5ml DMF and the filtrate was concentrated under reduced pressure. The residue was dissolved in 5ml chloroform, filtered again and washed twice with 5ml water. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography using diethyl ether - light petroleum (3:1, v/v) to give two compounds, the mono-methylated product (220) in a yield of 0.063g (63%) and the dimethylated product (221) in a yield of 0.132g (13%) .

Method 2.

The diol (122) (1.058g, 2.905mmol, 1eq) was dissolved in THF (10ml) and added dropwise to a suspension of 80% NaH (0.209g, 6.973mmol, 2.4eq) and DMPU (0.843ml, 6.973mmol, 2.4eq) in THF (3ml). The mixture was stirred at room temperature for 1 hour, MeI (0.724ml, 11.622mmol, 4eq) was then added and the reaction stirred for a further 16 hours. The reaction was quenched with 10ml water, extracted three times with 15ml diethyl ether and the organic layer dried ($MgSO_4$) and evaporated. The crude yellow oil was purified by flash column chromatography using diethyl ether - light petroleum (3:1, v/v) to give (220) as a white solid in a yield of 0.151g (14%) and (221) as a white solid in a yield of 0.719g (63%).

Data for (2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*)-4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b-Decahydro-6-methoxy-7-methoxymethyl-10a-methyl-2-phenyl-1,3-dioxo[5,4-c]benzopyran-8-ol. (220).

M.p. = 147 - 149°C.

$[\alpha]_D$ = -12.11° (*c* 0.11 in $CHCl_3$, 20°C).

Found: C, 66.7; H, 7.9. $C_{21}H_{30}O_6$ requires C, 66.5; H, 8.0%.

δ_H (250MHz; $CDCl_3$) 1.15 (3H, s, C10a-Me), 1.35 - 1.88 (4H, m, 10ax-H, 10eq-H, 9ax-H, 9eq-H), overlapping 1.60 (1H, dd, *J* = 3.2, 6a-H), 2.34 (1H, m, 7-H), 3.09 (1H, d, *J* = 9.5, 10b-H), 3.30 (3H, s, OMe), 3.31 (3H, s, OMe), overlapping 3.31 (2H, m, CH_2OMe), 3.59 (1H, dd, *J* = 10.2, 10.2, 4ax-H), 3.85 (2H, m, 4a-H & OH), 4.05 (1H, m, 8-H), 4.17 (1H, dd, *J* = 10.1, 5.0, 4eq-H), 4.55 (1H, d, *J* = 2.9, 6-H), 5.44 (1H, s, 2-H), 7.27 (3H, m, Ph), 7.39 (2H, m, Ph).

δ_C (69.2MHz; $CDCl_3$) 16.1 (CH_3, C10a-Me), 23.0 (CH_2, C-10), 36.5 (C, C-10a), 37.2 (CH_2, C-9), 43.9 (CH, C-7), 48.4 (CH, C-6a), 55.5 (CH_3, OMe), 56.8 (CH_3, OMe), 60.6 (CH_2, CH_2OMe), 60.7 (CH, C-4a), 70.0 (CH_2, C-4'), 84.2 (CH, C-8), 88.2 (CH, C-10b), 101.8 (CH, C-2), 103.0 (CH, C-6), 126.6 (2CH, Ph), 128.6 (2CH, Ph), 129.3 (CH, Ph), 138.3 (C, Ph).

m/z (EI^+) 378 (M^+, 4.5%), 267 (13), 222 (100), 188 (46), 171 (37), 139 (18.5), 124 (56), 109 (42), 88 (25). Found: M^+, 378.20426. $C_{21}H_{30}O_6$ requires *M*, 378.20422.

Data for (2*R*, 4a*R*, 6*S*, 6a*R*, 7*R*, 8*R*, 10a*R*, 10b*S*)-4, 4a, 6, 6a, 7, 8, 9, 10, 10a, 10b-Decahydro-6, 8-dimethoxy-7-methoxymethyl-10a-methyl-2-phenyl-1,3-dioxo[5,4-c]benzopyran. (221).

M.p. = 110-113°C

$[\alpha]_D$ = -64.31° (*c* 0.068 in $CHCl_3$, 20°C).

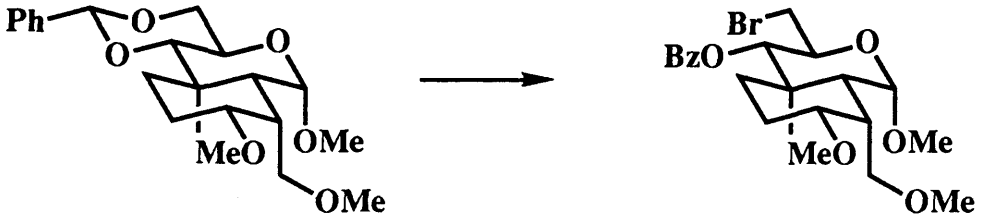
Found: C, 67.52; H 8.22. $C_{22}H_{32}O_6$ requires C, 67.32; H, 8.22%

δ_H (250MHz; $CDCl_3$) 1.11 (3H, s, CH_3, Me-C10b), 1.11 - 1.97 (4H, m, 9ax-H, 9eq-H, 10ax-H, 10eq-H), 1.59 (1H, t, *J* = 3.4, 6a-H), 2.30 (1H, m, 7-H), 3.11 (1H, d, *J* = 9.5, 10b-H), 3.24 (3H, s, Me, OMe), 3.32 (1H, m, CH'H"OMe), 3.32 (3H, s, Me, OMe), 3.33 (3H, s, Me, OMe), 3.44 (1H, dd, *J* = 8.9, 4.6, CH'H"OMe), 3.61 (1H, t, *J* = 10.2, 4ax-H), 3.91 (2H, m, 4a-H & 8-H), 4.19 (1H, dd, *J* = 10.2, 5.0, 4eq-H), 4.57 (1H, d, *J* = 3.0, 6-H), 5.49 (1H, s, 2-H), 7.27 (3H, m, Ph-H), 7.40 (2H, m, Ph-H).

δ_C (62.9MHz; $CDCl_3$) 15.8 (CH_3, Me-C10a), 25.1 (CH_2, C-10), 36.7 (C, C-10a), 37.2 (CH_2, C-9), 41.0 (CH, C-7), 47.4 (CH, C-6a), 55.8 (CH_3, OMe), 56.6 (CH_3, OMe), 58.7 (CH_3, OMe), 60.8 (CH, C-4a), 69.2 (CH_2, CH_2OMe), 70.1 (CH_2, C-4), 81.8 (CH, C-10b), 88.3 (CH, C-8), 101.1 (CH, C-2), 103.6 (CH, C-6), 126.5 (2CH, Ph-H), 128.6 (2CH, Ph-H), 129.3 (CH, Ph-H), 138.3 (C, Ph).

m/z (EI^+) 392 (M^+, 0.7%), 378 (M-CH_2^+, 0.9), 361 (M-OMe^+, 67), 179 (19), 149 (39), 127 (100), 101 (82), 91 (40), 75 (33) (Found: M^+, 392.21974. $C_{22}H_{32}O_6$ requires *M*, 392.21987).

(1*S*, 3*S*, 4*S*, 7*R*, 8*R*, 8a*R*) - 3, 4, 4a, 5, 6, 7, 8, 8a - Octahydro - 3 - bromomethyl - 1, 7 - dimethoxy - 8 - methoxymethyl - 4a methyl - 1H - benzo [c] pyranyl - 4 - benzoate. (228).



(221) (228)

The protected diol (221) (0.270g, 0.688mmol, 1eq) was dissolved in dry CCl_4 (21ml), $BaCO_3$ (0.746g, 3.781mmol, 5.5eq) and NBS (0.147g, 0.825mmol, 1.2eq) was added and the mixture was refluxed for 3 hours. The reaction was cooled to room temperature, quenched with 20ml water and the product extracted three times with 15ml dichloromethane. The crude product was purified by flash column chromatography using diethyl ether - light petroleum (1:1, v/v) to give a colourless oil (228) in a yield of 0.237g (73%).

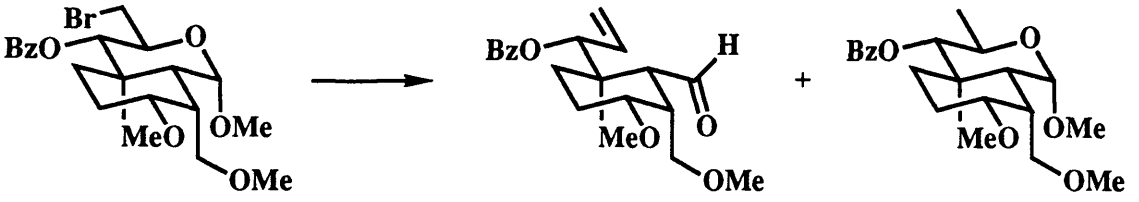
ν_{max} (CH_2Cl_2)/cm^{-1} 2930 (s), 2890 (s), 2860 (s), 1720 (s, C=O), 1420 (w), 1105 (s), 1070 (s), 1045 (s), 1030 (s), 980 (s).

δ_H (250MHz; $CDCl_3$) 1.24 (3H, s, C4a-Me), {0.87 (1H, m), 1.19 - 1.50 (2H, m), 1.72 (1H, m), 5-H, 6-H}, 1.78 (1H, dd, *J* = 3.5, 3.5, 8a-H), 2.44 (1H, brm, 8-H), 3.21 (1H, dt, *J* = 5.1, 10.8, 7-H), 3.32 (3H, s, OMe), 3.39 (3H, s, OMe), 3.49 (3H, s, OMe), overlapping 3.36 - 3.53 (3H, m, CH_2Br & CH'H"OMe), 3.96 (1H, dd, *J* = 2.1, 8.8, CH'H"OMe), 4.23 (1H, ddd, *J* = 10.0, 7.5, 2.5, 3-H), 4.77 (1H, d, *J* = 3.0, 1-H), 4.85 (1H, d, *J* = 10.0, 4-H), 7.47 (2H, m, Ph-H), 7.61 (1H, m, Ph-H), 8.04 (2H, m, Ph-H).

δ_C (62.9MHz; $CDCl_3$) 16.1 (CH_3, C4a-Me), 24.9 (CH_2, C-5), 33.6 (CH_2, CH_2Br), 37.4 (CH_2, C-6), 38.4 (C, C4a), 40.5 (CH, C-8), 47.0 (CH, C-8a), 55.9 (CH_3, OMe), 56.6 (CH_3, OMe), 58.8 (CH_3, OMe), 68.0 (CH, C-3), 69.1 (CH_2, CH_2OMe), 79.4 (CH, C-7), 81.4 (CH, C-4), 103.1 (CH, C-1), 129.0 (2CH, Ph), 130.1 (2CH, Ph), 133.9 (CH, Ph), 166.0 (C, C=O).

m/z (EI^+) 438/440 ($[M-MeOH]^+$, 99%), 406/408 ($[M-2MeOH]^+$, 14), 359 (10), 297 (18), 237 (12), 205 (9), 127 (80), 105 ($PhCO^+$, 57), 101 (37), 77 (Ph^+, 6) (Found $[M-MeOH]^+$, 438.10416. $C_{21}H_{27}O_5{}^{79}Br$ requires 438.10419).

(1'*R*, 2'*R*, 3 *R*, 3'*R*, 4'*R*) - 3 - {2' - Formyl - 4' - methoxy - 3' - methoxymethyl - 1' - methyl - cyclohexyl} - prop - 1 - enyl - 3 - benzoate. (229).



(228) (229) (230)

Zinc powder (16.180g, 0.2474mol, 130eq) was activated by washing twice with 50ml 2M HCl and once with 500ml water, 250ml iso-propanol and 250ml diethyl ether. The activated zinc was added to a solution of (228) (0.897g, 1.903mmol, 1eq) in iso-propanol (88ml) and water (10ml). The mixture was refluxed for 3 hours then allowed to cool to room temperature. The zinc was filtered off through a glass sinter and washed with 50ml diethyl ether which was added to the filtrate. The filtrate was evaporated to dryness. The residue was taken up in 50ml dichloromethane and washed three times with 50ml water. The crude colourless oil was purified by flash column chromatography eluting with light petroleum: diethyl ether (2:1, v/v) until the first product had been collected, then light petroleum: diethyl ether (1:1, v/v). The first compound to elute off the column was the aldehyde (229) in a yield of 0.519g (76%), this was obtained as a white solid. The second compound was the reduced byproduct (230) in a yield of 0.138g (18%) as a colourless oil.

Data for (1'*R*, 2'*R*, 3 *R*, 3'*R*, 4'*R*) - 3 - {2' - Formyl - 4' - methoxy - 3' - methoxymethyl - 1' - methyl - cyclohexyl} - prop - 1 - enyl - 3 - benzoate. (229).

M.p. = 77-79°C

Found: C, 70.1; H, 7.8. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%.

δ_H (250MHz; $CDCl_3$) 1.11 (3H, s, C1'-Me), 1.62-1.98 (4H, m, $2CH_2$, 6'-H & 5'-H), 2.24 (1H, m, CH, 3'-H), 2.32 (1H, t, *J* = 4.43Hz, 2'-H), 3.22 (1H, dd, *J* = 9.41, 5.75Hz, 3"-Ha), 3.30 (3H, s, CH_3, OMe), 3.33 (3H, s, CH_3, OMe), overlapping 3.33 (1H, m, 3"-Hb), 3.63 (1H, brm, CH, 4'-H), 5.39 (2H, m, 1*E*-H & 1*Z*-H), 5.84 (2H, m, 2-H & 3-H), 7.47 (2H, m, meta Ph-H), 7.59 (1H, m, para Ph-H), 8.07 (2H, m, ortho Ph-H), 9.81 (1H, d, *J* = 5.05Hz, CHO).

δ_C (62.9MHz; $CDCl_3$) 20.9 (CH_3, Me-C1'), 23.4 (CH_2, C-6'), 26.1 (CH_2, C-5'), 38.3 (C, C-1'), 40.5 (CH, C-3'), 53.9 (CH, C-2'), 57.1 (CH_3, OMe), 59.3 (CH_3, OMe), 72.2 (CH_2, C3'CH_2OMe), 74.5 (CH, C-4'), 75.1 (CH, C-3), 121.1 (CH_2, C-1), 128.9 (2CH, Ph), 130.0 (2CH, Ph), 130.5 (C, Ph), 132.5 (CH, C-2), 133.6 (CH, Ph), 165.9 (C, ester C=O), 205.1 (CH, aldehyde C=O).

m/z (CI^+) 378 ($[M+NH_4]^+$, 9.7%), 361 (MH^+, 100), 239 ($[M-OBz]^+$, 65), 171 (31), 139 (47), 107 (51), 105 ($PhCO^+$, 53), 77 (Ph^+, 16), 55 (12).

Data for (1*S*, 3*R*, 4*S*, 7*R*, 8*R*, 8a*R*) - 3, 4, 4a, 5, 6, 7, 8, 8a - Octahydro - 1, 7 - dimethoxy - 3, 4a - dimethyl - 8 - methoxymethyl - 1*H* - benzo [c] pyranyl - 4 - benzoate. (230).

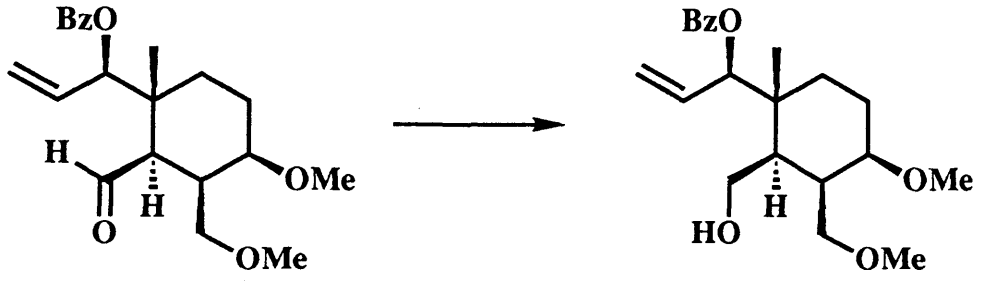
$[\alpha]_D$ = 155.87° (*c* 0.26 in $CHCl_3$, 20°C).

δ_H (250MHz; $CDCl_3$) 1.16 (3H, d, *J* = 6.2, C3-Me), 1.21 (3H, s, C4a-Me), {1.26 - 1.50 (3H, m), 1.63 -1.72 (1H, m), 5ax-H, 5eq-H, 6ax-H, 6eq-H}, 1.75 (1H, dd, *J* = 3.5, 3.5, 8a-H), 2.42 (1H, brm, 8-H), 3.21 (1H, dt, *J* = 5.1, 10.7, 7-H), 3.32 (3H, s, OMe), 3.39 (3H, s, OMe), 3.43 (3H, s, OMe), 3.50 (1H, dd, *J* = 4.7, 8.9, CH'H"OMe), 3.99 (1H, dd, *J* =8.9, 2.1, CH'H"OMe), 4.13 (1H, dq, *J* = 10.0, 6.2, 3-H), 4.66 (1H, d, *J* = 3.0, 1-H), 4.72 (1H, d, *J* = 10.0, 4-H), 7.46 (3H, m, Ph), 8.04 (2H, m, Ph).

δ_C (62.9MHz; $CDCl_3$) 16.0 (CH_3, C4a-Me), 18.2 (CH_3, C-3), 24.9 (CH_2, C-5), 37.5 (CH_2, C-6), 38.0 (C, C-4a), 40.6 (CH, C-8), 47.2 (CH, C-8a), 55.7 (CH_3, OMe), 56.6 (CH_3, OMe), 58.7 (CH_3, OMe), 63.9 (CH, C-3), 69.2 (CH_2, CH_2OMe), 81.6 (CH, C-7), 82.4 (CH, C-4), 103.1 (CH, C-1), 128.9 (CH, Ph), 130.1 (CH, Ph), 130.3 (C, Ph), 133.6 (CH, Ph), 166.4 (C, C=O).

m/z (CI^+) 393 (MH^+, 3.7%), 378 (5), 361 ($[M-OMe]^+$, 100), 127 (17), 105 ($PhCO^+$, 24).

(1'*R*, 2'*R*, 3 *R*, 3'*R*, 4'*R*) - 3 - {2' - Hydroxymethyl - 4' - methoxy - 3' - methoxymethyl - 1' - methyl - cyclohexyl} - prop - 1 - enyl - 3 - benzoate. (231).



(229) (231)

The aldehyde (229) (0.135g, 0.373mmol, 1eq) was dissolved in iso-propanol (4ml) and $NaBH_4$ (0.057g, 1.494mmol, 4eq) added to the solution followed by water (6-8 drops). The reaction mixture was stirred for 24 hours at room temperature. The iso-propanol was evaporated off under water pump vacuum, the residue dissolved in 5ml dichloromethane and washed three times with 5ml water. The organic layer was dried ($MgSO_4$) and evaporated to give an oil which on purification by column chromatography using diethyl ether - light petroleum (1:1, v/v) yielded 0.127g (92%) of the alcohol (231).

$[\alpha]_D$ = -38.71° (*c* 0.25 in $CHCl_3$, 20°C).

ν_{max} (CH_2Cl_2)/cm^{-1} 3600 (br m, OH), 3020 (m), 2960 (s), 2925 (s), 2820 (s), 1730 (s, C=O), 1650 (w, C=C), 1450 (s), 1370 (s), 1275 (s), 1240 (s), 1110(s), 1090 (s), 1000 (s), 900 (s).

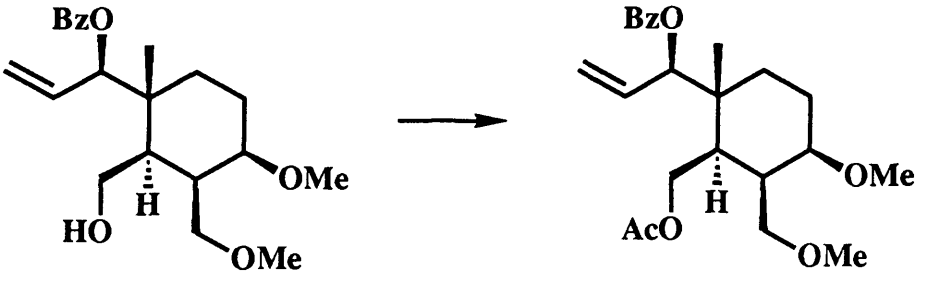
δ_H (250MHz; $CDCl_3$) 1.25 (3H, s, $C\underline{H_3}$-C1'), 1.32 - 1.89 (4H, brm, $2CH_2$, 5'-H & 6'-H), 2.13 - 2.47 (2H, m, 2'-H, 3'-H), 3.35 (3H, s, OMe), 3.37 (3H, s, OMe), 3.41 (1H, m, 3"-Ha), 3.51-3.59 (3H, m, 3"-Hb & $C\underline{H_2}OH$), 3.71 (1H, m, H-4'), 4.55 (1H, brs, OH), 5.32 (1H, d, J_{cis} = 10.3, 1*Z*-H), 5.40 (1H, d, J_{trans} = 16.8, 1*E*-H), 5.90

(1H, ddd, J_{trans} = 16.7, J_{cis} = 10.0, J = 7.3, 2-H), 5.82 (1H, d, J = 7.6, 3-H), 7.45 (2H, m, Ph-H), 7.57 (1H, m, Ph-H), 8.06 (2H, m, Ph-H).

δ_C (62.9MHz; $CDCl_3$) 19.8 (CH_3, C1'-Me), 23.2 (CH_2, C-6'), 27.0 (CH_2, C-5'), 39.1 (CH, C-2'), 39.9 (C, C-1'), 40.5 (CH, C-3'), 57.0 (CH_3, OMe), 59.2 (CH_2, CH_2OH), 59.3 (CH_3, OMe), 72.9 (CH_2, CH_2-OMe), 75.0 (CH, C-4'), 76.4 (CH, C-1), 120.6 (CH_2, C-3), 128.8 (2CH, Ph), 130.0 (2CH, Ph), 130.8 (C, Ph), 133.4 (CH, C-2), 133.5 (CH, Ph), 166.1 (C, C=O).

m/z (EI^+) 362 (M^+, 0.1%), 300 (M^+-$(OMe)_2$, 1.1), 201 (M^+-CH_2=CHCHOBz, 46.7), 171 (54.4), 139 (45.3), 105 ($PhCO^+$, 97.9), 107 (100), 77 (Ph^+, 37.1), 51 (92.9). Found: M^+, 362.20916. $C_{21}H_{30}O_5$ requires *M*, 362.20930.

(1'*R*, 2'*R*, 3 *R*, 3'*R*, 4'*R*) - 3 - {2' - Acetoxymethyl - 4'- methoxy - 3' - methoxymethyl - 1' - methyl - cyclohexyl} - prop - 1 - enyl - 3 - benzoate. (235).



(231) (235)

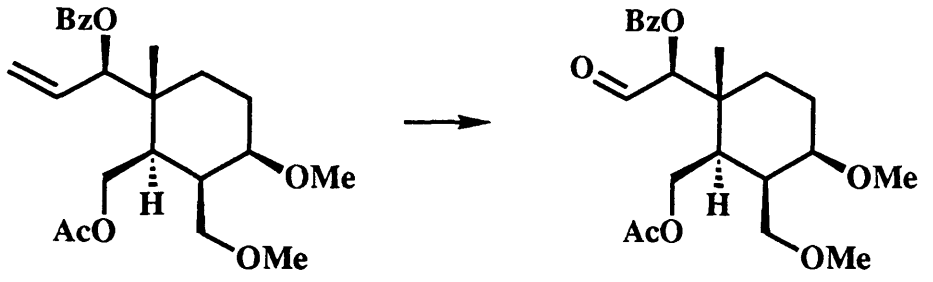
The alcohol (231) (0.388g, 1.070mmol, 1eq) and DMAP (0.013g, 0.107mmol, 0.1eq) were dissolved in pyridine (19ml) and acetic anhydride (0.20ml, 2.140mmol, 2eq) was added dropwise at room temperature under N_2. The reaction mixture was stirred under these conditions for 19 hours. It was quenched with 6 drops of ethanol and diluted with 20ml dichloromethane. The organic phase was washed twice with 20ml saturated aqueous $NaHCO_3$ solution and once with 20ml water before being dried ($MgSO_4$) and evaporated to give the crude product as a yellow oil. Purification by flash column chromatography, using light petroleum : diethyl ether (3:1, v/v) as the eluent gave the product (235) as a colourless oil in a yield of 0.408g (94%).

δ_H (250MHz; $CDCl_3$) 1.00 (3H, s, CH_3, Me-C1'), 1.18-1.89 (4H, m, $2CH_2$, 5'-H & 6'-H), 1.95 (3H, s, CH_3-CO_2R), 3.17 (3H, s, CH_3, OMe), 3.28 (3H, s, CH_3, OMe), 3.230 - 3.41 (4H, m, 2'-H, 3'-H, 3"-Ha, 3"-Hb), 3.53 (1H, t, J = 8.25Hz, 4'-H), 4.07 (1H, dd, J_{gem} = 12.57, ^3J = 7.07Hz, 2"-Ha), 4.16 (1H, dd, J_{gem} = 12.58, ^3J = 3.18Hz, 2"-Hb), 5.27 (1H, dd, J_{cis} = 10.00, J_{gem} = 1.11Hz, 1*E*-H), 5.35 (1H, dd, J_{trans} = 16.19, J_{gem} = 1.25Hz, 1Z-H), 5.86 (2H, m, 2-H & 3-H), 7.39 (2H, m, Ph-H), 7.52 (1H, m, Ph-H), 7.99 (2H, m, Ph-H).

δ_C (250MHz; $CDCl_3$) 18.9 (Me-C1'), 20.3 (Me-OAc), 22.0 ($2CH_2$, C-6' & C-5'), 38.1 (CH, C-2'), 38.9 (C, C-1'), 39.4 (CH, C-3'), 55.5 (CH_3, OMe), 57.9 (CH_3, OMe), 62.3 (CH_2, C2'CH_2OAc), 71.6 (CH_2, C3'CH_2OMe), 75.5 (CH, C-4'), 76.0 (CH, C-3), 119.0 (CH_2, C-1), 127.4 (2CH, Ph-H), 128.6 (2CH, Ph-H), 129.4 (C, Ph), 131.6 (CH, C-2), 132.0 (CH, Ph-H), 164.5 (C=O, Bz), 170.1 (C=O, Ac).

m/z (CI^+) 422 ($[M+NH_4]^+$, 20.0%), 405 (MH^+, 8.5), 391 (14), 345 ($[M-OAc]^+$, 37), 283 ($[M-OBz]^+$, 64), 243 (38), 190 (46), 151 (40), 119 (81), 105 ($PhCO^+$, 100), 86 (45), 77 (Ph^+, 34) (Found: MH^+, 405.22771. $C_{23}H_{33}O_6$ requires *M*, 405.22771).

(2*S*, 1'*R*, 2'*R*, 3'*R*, 4'*R*) - 2 - {2' - Acetoxymethyl - 4' - methoxy - 3' - methoxymethyl - 1' - methyl - cyclohexyl} - 2 - benzoyl - ethanal. (236).



(235) (236)

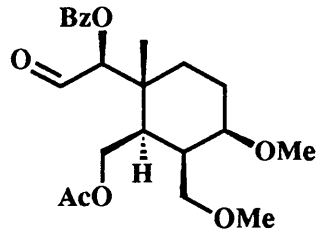
To a solution of the olefin (235) (0.1019g, 0.252mmol, 1eq) in dichloromethane (14ml) was added a 1.56M solution (194µl, 0.302mmol, 1.2eq) of MeOH in dichloromethane. Pyridine (82µl, 1.008mmol, 4eq) was introduced and the solution was cooled to -78°C whilst bubbling N_2 through for 10 minutes. Ozone was bubbled through the mixture for 40 minutes, followed by N_2 for 10 minutes before adding 0.2ml dimethylsulphide to quench the reaction. The reaction was allowed to warm to room temperature, 10ml water was added and the product extracted three times with 15ml dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated to give the product as a colourless oil in a yield of 0.1025g (100%). The product (236) was used crude for the next step.

ν_{max} (CH_2Cl_2)/cm^{-1} 2970 (s), 2930 (s), 2820 (s), 1720 (s, C=O), 1450 (s), 1370 (s), 1315 (m), 1275 (s), 1240 (s), 1110(s), 1090 (s), 1025 (m), 730 (s).

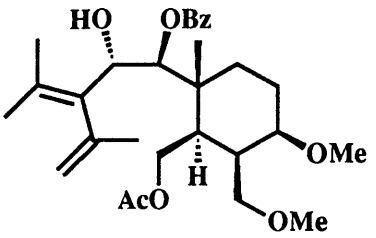
δ_H (250MHz; $CDCl_3$) 1.13 (3H, s, Me-C1'), 1.21 - 1.85 (4H, m, $2CH_2$, 5'-H & 6'-H), 1.98 (3H, s, CH_3CO_2R), 2.34 (2H, m, 2'-H & 3'-H), (3H, s, CH_3, OMe), (3H, s, CH_3, Me), 3.47 (1H, dd, J = 9.12, 5.35Hz, 3"-Ha), 3.47 (1H, m, 4'-H), 3.63 (1H, dd, J = 9.13, 7.87Hz, 3"-Hb), 4.14 (1H, dd, J_{gem} = 13.06, ^3J = 7.09, 2"-Ha), 4.24 (1H, dd, J_{gem} = 12.90, ^3J = 2.67, 2"-Hb), 5.44 (1H, brs, 1-H), 7.55 (3H, m, Ph-H), 8.10 (2H, m, Ph-H), 9.73 (1H, d, J = 1.26Hz, 2-H).

δ_C (62.9MHz; $CDCl_3$) 21.1 (CH_3, Me-C1'), 21.6 (CH_3, Me-CO_2R), 23.7 (CH_2, C-6'), 26.5 (CH_2, C-5'), 40.1 (CH, C-2'), 40.2 (CH, C-3'), 41.4 (C, C-1'), 57.0 (CH_3, OMe), 59.3 (CH_3, OMe), 63.2 (CH_2, C2'CH_2OAc), 72.6 (CH_2, C3'CH_2OMe), 75.2 (CH, C-4'), 78.8 (CH, C-1), 129.0 (2CH, Ph-H), 129.5 (C, Ph), 130.2 (2CH, Ph-H), 134.1 (CH, Ph-H), 166.4 (C=O, Bz), 171.4 (C=O, Ac), 200.0 (CH, C-2, CHO).

1 - (1*R*, 2*R*, 3*R*, 4*R*, 4'*S*, 5'*S*) - [5'- Benzoyl - 4' - hydroxy - 2' - methyl - 3' - (1" - methylethenyl) - pent-2'-enyl] - 2 - Acetoxymethyl - 4 - methoxy - 3 - methoxymethyl - 1 - methyl - cyclohexane. (237).

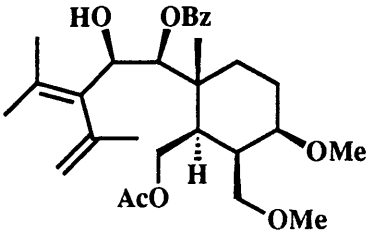


(236)



(237a)

+



(237b)

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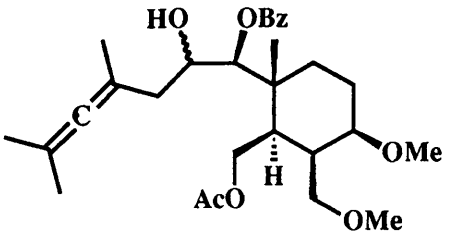

(238)

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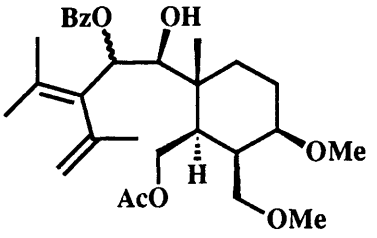


(240)

Cerium(III) chloride heptahydrate (1.305g, 3.503mmol, 13.89eq) was dried under vacuum at 140°C for 2 hours, dry, freshly distilled THF (8ml) was added and the suspension placed in an ultra-sound bath for 1 hour.

The bromodiene (172) (0.613g, 3.503mmol, 13.89eq) in dry, freshly distilled THF (6.5ml) was treated with 1.6M ^{n}BuLi (1.98ml, 3.175mmol, 12.59eq) at -78°C for 1 hour to generate the lithiated diene 'in situ'. The solution was transferred to the suspension of $CeCl_3$ at -78°C and the brown/red mixture was stirred for a further 1 hour. The aldehyde (236) (0.103g, 0.252mmol, 1eq) in THF (4ml) was introduced and the reaction stirred for 1.5 hours at -78°C.

Water (10ml) was used to quench the reaction and the flask was warmed up to room temperature. The mixture was extracted three times with 20ml dichloromethane, dried ($MgSO_4$) and evaporated to afford the crude material. This was purified by column chromatography using a gradient of light petroleum-diethyl ether (20:1 to 1:1, v/v) to yield two products, the first was the major diastereoisomer (237a) (0.051g, 40%) and the second was a mixture of the minor diastereoisomer (237b) and the allenyl alcohol (238) (0.022g, 17%).

On subsequent attempts to repeat this reaction, smaller yields were obtained. The best result achieved used $CeCl_3.7H_2O$ (1.611g, 4.324mmol, 11eq), bromodiene (0.757g, 4.324mmol, 11eq), 1.6M ^{n}BuLi (2.45ml, 3.920mmol, 10eq) and the aldehyde (0.16g, 0.394mmol, 1eq) employing the same method as above. Column chromatography as above yielded three products, (237a) (0.033g, 17%), a mixture of (205b) and (206) (0.028g, 14%) and the benzoyl migration product (240) (0.022g, 11%).

Data for 1 - (1*R*, 2*R*, 3*R*, 4*R*, 4'*S*, 5'*S*) - [5'- Benzoyl - 4' - hydroxy - 2' - methyl - 3' - (1" - methylethenyl) - pent-2'-enyl] - 2 - Acetoxymethyl - 4 - methoxy - 3 - methoxymethyl - 1 - methyl - cyclohexane. (237).

ν_{max} (CH_2Cl_2)/cm^{-1} 3525 (br, s, OH), 3030 (m), 2920 (s), 1720 (s, C=O), 1650 (m, C=C), 1600 (m, C=C), 1450 (s), 1365 (s), 1235 (s), 1100 (s, C-O), 1020 (s), 890 (m).

δ_H (250MHz; $CDCl_3$) 1.18 (3H, s, CH_3, C1-Me), 1.47 (3H, s, CH_3), 1.67 (3H, s, CH_3), Me-C2', 1'-H, 1.41 - 1.76 (4H, m, $2CH_2$, 5ax-H, 5eq-H, 6ax-H, 6eq-H), 1.82 (3H, s, CH_3, C1"-Me), 2.05 (3H, s, CH_3, $MeCO_2R$), 2.17 (1H, d, J = 7.9, OH), 2.32 (1H, m, 3-H), 2.77 (1H, m, 2-H), 3.22 (3H, s, CH_3, OMe), 3.36 (3H, s, CH_3, OMe), 3.40 (1H, dd, J = 9.1, 5.0, 3'''-Ha), 3.47 (1H, m, H-4), 3.65 (1H, dd, J = 8.8, 8.8, 3'''-Hb), 4.15 (1H, d, J_{gem} = 12.9, 2'''-Ha), 4.24 (1H, dd, J_{gem} = 12.9, J = 3.2, 2'''-Hb), 4.83 (1H, s, 2"*E*-H), 4.96 (1H, brt, J = 8.0, 4'-H), 5.17 (1H, s, 2"*Z*-H), 5.48 (1H, d, J = 8.5, 5'-H), 7.44 (2H, m, Ph), 7.56 (1H, m, para-Ph), 7.97 (2H, m, Ph)

δ_C (69.2MHz; $CDCl_3$) 20.90 (CH_3, C1-Me), 21.03 (CH_3, Me-CO_2R), 21.83 (CH_3), 22.94 (CH_3), C-1', C2'-Me, 23.72 ($2CH_2$, C-5, C-6), 25.49 (CH_3, C1"-Me), 40.03 (CH, C-2), 40.50 (CH, C-3), 42.0 (C, C-1), 56.90 (CH_3, OMe), 59.33 (CH_3, OMe), 64.33 (CH_2, CH_2OAc), 69.85 (CH, C-4'), 73.36 (CH_2, CH_2OMe), 75.26 (CH, C-4), 75.41 (CH, C-5'), 118.01 (CH_2, C-2"), 128.77 (2CH, Ph), 129.95 (2CH, Ph), 130.67 (C, Ph), 133.29 (CH, Ph), {131.21 (C, C=C), 135.30 (C, C=C), 144.11 (C, C=C) C-2', C-3', C-1"}, 165.56 (C, C=O, Bz), 171.52 (C, C=O, Ac)

m/z (EI^+) 502 (M^+, 1.6%), 378 (10), 318 (4), 286 (6), 224 (5), 164 (10), 119 (19), 105 ($PhCO^+$, 100), 77 (Ph^+,9), 55 (11). (Found; M^+, 502.29306. $C_{29}H_{42}O_7$ requires *M*, 502.29303).

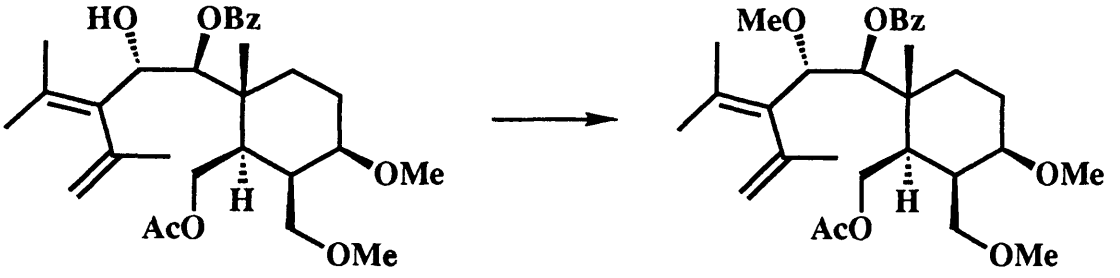
Data for 1 - (1*R*, 2*R*, 3*R*, 4*R*, 4'*S*, 5'*S*) - [4' - Benzoyl - 5' - hydroxy - 2' - methyl - 3 - (1" - methylethenyl) -pent - 2'-enyl] - 2 - Acetoxymethyl - 4 - methoxy - 3 - methoxymethyl - 1- methyl - cyclohexane. (240).

δ_H (250MHz; $CDCl_3$) 1.12 (3H, s, CH_3, Me-C1), 1.32 (1H, m), 1.60 (2H, m), 1.94 (1H, m), 5ax-H, 5eq-H, 6ax-H, 6eq-H, 1.54 (3H, s, CH_3), 1.70 (3H, s, CH_3), Me-C2' & 1'-H, 1.73 (3H, s, CH_3, Me-C1"), 2.05 (3H, s, CH_3, $MeCO_2R$), 2.15 (1H, m, OH), 2.26 (1H, m, 3-H), 3.23 (3H, s, Me, OMe), 3.26 (1H, m, 2-H), 3.34 (3H, s, Me, OMe), 3.42 (1H, dd, *J* = 9.0, 5.5, 3'''-Ha), 3.42 (1H, m, 4-H), 3.61 (1H, dd, *J* = 9.1, 7.2, 3'''-Hb), 4.19 (1H, d, *J* = 12.3, 2'''-Ha), 4.27 (1H, dd, *J* = 12.6, 3.8, 2'''-Hb), 4.68 (1H, s, 2"*E*-H), 4.91 (1H, d, *J* = 6.6, 5'-H), 4.99 (1H, s, 2"*Z*-H), 5.66 (1H, s, 4'-H), 7.47 (2H, t, *J* = 7.6, Ph-H), 7.59 (1H, t, *J* = 7.3, Ph-H), 8.07 (2H, t, *J* = 7.7, Ph-H)

δ_C (69.2MHz; $CDCl_3$) 20.8 (CH_3, Me-C1), 21.8 (CH_3, MeOCOR), 23.3 ($2CH_3$, Me-C2' & C-1'), 23.9 ($2CH_2$, C-5 & C-6), 24.9 (CH_3, Me-C1"), 40.3 (CH, C-2), 41.1 (2CH, C-5' & C-3), 41.7 (C, C-1), 56.9 (CH_3, OMe), 59.3 (CH_3, OMe), 63.3 (CH_2, CH_2OAc), 69.8 (2CH, C-4' & C-4), 75.2 (CH_2, CH_2OMe), 116.8 (CH_2, C-2"), 128.9 (2CH, Ph-H), 130.1 (C, Ph), 130.1 (2CH, Ph-H), 130.6 (C, C-1"), 133.4 (CH, Ph-H), 137.0 (C, C-2'), 144.8 (C, C-3'), 166.2 (C, C=O), 171.6 (C, C=O)

m/z (EI^+) 502 (M^+, 0.2%), 378 (14), 318 (6), 286 (13), 213 (14), 164 (15), 151 (15), 149 (12), 137 (26), 132 (23), 125 (30), 121 (36), 119 (41), 107 (24), 105 ($PhCO^+$, 100) (Found: M^+, 502.29307. $C_{29}H_{42}O_7$ requires *M*, 502.29303).

1 - (1*R*, 2*R*, 3*R*, 4*R*, 4'S, 5'S) - [5' - Benzoyl - 4' - methoxy - 2' - methyl - 3' - (1" - methylethenyl) - pent-2'-enyl] 2 - acetoxymethyl - 4 - methoxy - 3 - methoxymethyl - 1 - methyl - cyclohexane. (242).



(237a) (242)

A solution of the alcohol (237a) (0.0309g, 0.0615mmol, 1eq) in dry, freshly distilled THF (0.5ml) was added to a suspension of 80% NaH (0.0022g, 0.0738mmol, 1.2eq) and DMPU (0.009ml, 0.0738mmol, 1.2eq) in dry THF (0.5ml). The reaction mixture was stirred for 1 hour. MeI (0.006ml, 0.0922mmol, 1.5eq) was added and the solution stirred for 2.5 hours. The reaction was quenched with 0.5ml water and extracted three times with 1.5ml diethyl ether. The organic phase was separated, dried ($MgSO_4$) and evaporated. The crude material was purified by column chromatography with diethyl ether-light petroleum (1:2, v/v) to afford the protected alcohol (242) (0.0116g, 37%) as a colourless oil.

ν_{max} (CH_2Cl_2)/cm^{-1} 3060 (w), 2900 (s), 1720 (s, C=O), 1630 (w, C=C), 1435 (s), 1360 (s), 1230 (s), 1085 (s), 1020 (s), 890 (s)

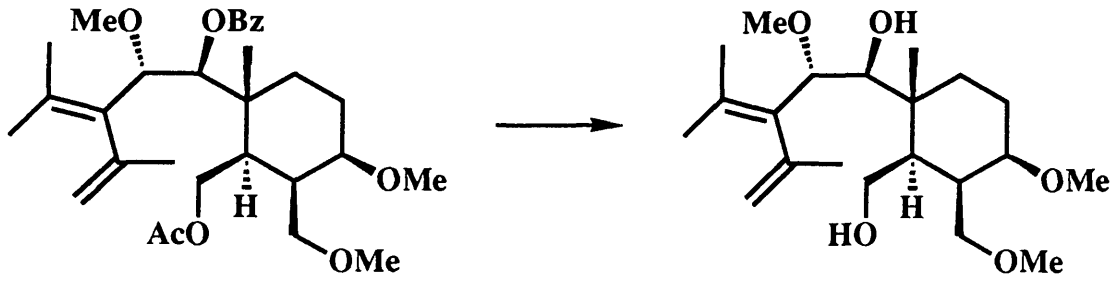
δ_H (250MHz; $CDCl_3$) 0.84 (3H, s, CH_3, Me-C1), 1.06 - 1.92 (4H, m, 5-H & 6-H), overlapping 1.71 (3H, s, CH_3), 1.76 (3H, s, CH_3), Me-C2' & H-1', 1.83 (3H, s, CH_3, Me-C1"), 2.02 (3H, s, CH_3, $MeCO_2R$), 2.65 (1H, m, 3-H), 2.76 (1H, d, *J* = 5.0, 2-H), 3.22 (1H, d, *J* = 3.2, 4'-H), 3.27 (3H, s, CH_3, OMe), 3.33 (6H, s, $2CH_3$, OMe), 3.37 (1H, m, 4-H), 3.59 (1H, m, 3'"-Ha), 3.68 (1H, t, *J* = 9.0, 3'"-Hb), 4.09 (1H, dd, *J* = 12.3, 7.2, 2'"-Ha), 4.22 (1H, dd, *J* = 12.3, 3.8, 2'"-Hb), 4.53 (1H, s, 2"*E*-

H), 4.98 (1H, s, 2"Z-H), 5.30 (1H, d, J = 3.0, 5'-H), 7.42 (2H, m, Ph-H), 7.56 (1H, m, Ph), 7.94 (2H, m, Ph)

δ_C (62.9MHz; $CDCl_3$) 19.8 (CH_3, Me-C1), 21.7 (CH_3, CH_3CO_2R), 22.7 ($2CH_3$, Me-C2' & C-1'), 23.8 (CH_2, C-6), 24.2 (CH_2, C-5), 24.5 (CH_3, CH_3-C1"), 36.3 (C, C-1), 40.3 (CH, C-2), 43.9 (CH, C-3), 53.0 (Me, MeO-C4'), 56.8 (Me, OMe), 59.2 (Me, OMe), 63.8 (CH_2, CH_2OAc), 65.1 (CH, C-4'), 72.5 (CH_2, CH_2OMe), 76.4 (CH, C-4), 76.7 (CH, C-5'), 115.3 (CH_2, C-2"), 128.7 (2CH, Ph), 130.0 (2CH, Ph), 130.5 (C, Ph), 133.1 (CH, Ph), {134.6 (C, C=C), 138.0 (C, C=C), 143.1 (C, C=C), C-1", C-2', C-3'}, 155.7 (C=O, Bz), 171.5 (C=O, Ac)

m/z (EI^+) 516 (M^+, 1.8%), 380 (1), 243 (3), 205 (11), 168 (6), 151 (16), 139 (100), 119 (35), 105 (48), 91 (17), 84 (23), 71 (16), 55 (16)

1 - (1*R*, 2*R*, 3*R*, 4*R*, 4'S, 5'S) - [5' - Hydroxy - 4' - methoxy - 2' - methyl - 3' - (1" - methylethenyl) - pent-2'-enyl] - 2 - hydroxymethyl - 4 - methoxy - 3 - methoxymethyl - 1 - methyl - cyclohexane. (246).



(242) (246)

Method 1.

The benzoyl ester (242) (0.0082g, 0.0159mmol, 1eq) was dissolved in a mixture of methanol (0.87ml) and dry dichloromethane (0.174ml) and cooled to 0°C. NaOMe (0.0028g, 0.0516mmol, 3.25eq) was added and the reaction mixture stirred for 2.25 hours. The solution was warmed to room temperature and stirred for a further 16.75 hours. The reaction was quenched with 0.1M HCl (0.52ml) and evaporated to dryness to give a residue which was dissolved in 2ml dichloromethane and washed twice with 2ml water. The organic phase was dried ($MgSO_4$) and evaporated to give a yellow oil. The crude product was purified by column chromatography (diethyl ether-light petroleum, 1:4 v/v) to afford the diol (246) (0.0020g, 34%) as a colourless oil.

Method 2.

The benzoyl ester (242) (0.008g, 0.0155mmol, 1eq) dissolved in methanol (0.2ml) was treated with K_2CO_3 (0.002g, 0.0155mmol, 1eq) and two drops of distilled water. The reaction mixture was stirred at room temperature for 19 hours and evaporated to dryness. The residue was dissolved in 2ml dichloromethane, washed twice with 2ml water, dried ($MgSO_4$) and evaporated. The crude material was purified by column chromatography

(diethyl ether-light petroleum, 1:3 v/v) to afford the diol (246) (0.0025g, 44%) as a pale yellow oil.

δ_H (250MHz; $CDCl_3$) 1.08 (3H, s, Me-C1), 1.49 - 1.62 (6H, m, $2CH_2$ & 2OH, C-5 & C-6), 1.75 (3H, s, CH_3), 1.82 (3H, s, CH_3), Me-C2' & 1'-H, 1.90 (3H, s, CH_3, Me-C1"), 1.97 (1H, dt, J = 6.6, 3.5, 2-H), 2.39 (1H, m, 3-H), 3.13 (1H, brdd, J = 9.8, 2.2, 5'-H), 3.26 (1H, m, 4-H), 3.29 (6H, s, $2CH_3$, 2OMe), 3.36 (3H, s, CH_3, OMe), 3.45 (1H, dd, J = 6.6, 2.2, 2'''-Ha), 3.50 (1H, t, J = 6.9, 2'''-Hb), 3.62 (1H, dd, J = 11.6, 3.8, 3'''-Ha), 3.90 (1H, d, J = 11.5, 11.5, 3'''-Hb), 4.32 (1H, d, J = 9.8, 4'-H), 4.61 (1H, s, 2"*E*-H), 5.10 (1H, s, 2"*Z*-H).

References

1. a.) R.C. Hosie, *Native Trees of Canada*, Queen's Printer for Canada, Ottowa, 7th edition, 1969; b.) H. Hartzell Jr., *The Yew Tree A Thousand Whispers*, Hulogosi, Eugene. OR, USA, 1991.

2. M.C. Wani, H.C. Taylor, M.E. Wall, P.Coggan and A.T. McPhail, *J. Am. Chem. Soc.*, 1971, **93**, 2325.

3. H.L. Max, *Taxane Research Journal*, 1995, **1**, 22.

4. P.B.Schiff, J. Fant and S.B. Horwitz, *Nature*, 1979, **277**, 665.

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

6. D.L. Purich and D. Kristofferson, *Adv. Protein Chem.*, 1984, **36**, 133.

7. P. Dustin, *Microtubules*, Springer Verlag, Berlin, 2nd edition, 1984.

8. a.) L.T. Haimo, *Methods Cell Biol.*, 1982, **24**, 189; b.) P.R. Burton and R.H. Himes, *J. Cell Biol.*, 1978, **77**, 120; c.) E.-M. Mandelkow and E. Mandelkow, *J. Mol. Biol.*, 1979, **129**, 135.

9. P.B. Schiff and S.B. Horwitz, *Biochemistry*, 1981, **20**, 3247.

10. J. Parness and S.B. Horwitz, *J. Cell Biol.*, 1981, **91**, 479.

11. G.A. Cordell, *Chemistry & Industry*, 1993, No21, 841.

12. a.) F. Gueritte-Voelgelein, D. Guenard, F. Lavelle, M.-T. LeGoff, L. Mangatal and P. Potier, *J. Med. Chem.*, 1991, **34**, 992; b.) D.G.I. Kingston, *Pharma. Ther.*, 1991, **52**, 1.

13. A.N. Boa, P.R.Jenkins and N.J. Lawrence, *Recent Progress in the synthesis of taxanes*, Contempory Organic Chemistry, R.S.C., 1994, 47.

14. a.) ; K.C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P.G. Nantermet, R.K. Guy, C.F.

Claiborne, J. Renaud, E.A. Couladouros, K. Paulvannan and E.J. Sorensen, *Nature*, 1994, **367**, 630; b.) K.C. Nicolaou, P.G. Nantermet, E. A. Couladouros, R.K.Guy, H. Ueno and E.J. Sorensen, *J. Am. Chem. Soc.*, 1995, **117**, 624.

15. a.) K.C. Nicolaou, C.-K. Hwang, E.J. Sorenson and C.F. Clairborne, *J. Chem. Soc., Chem. Commun.*, 1992, 1117; b.) K.C. Nicolaou, C.-K. Hwang, E.J. Sorenson and C.F. Clairborne, *J. Chem. Soc., Chem. Commun.*, 1992, 1118; c.) K.C. Nicolaou, Z. Yang, E.J. Sorenson and M. Nakada, *J. Chem. Soc., Chem. Commun.*, 1993, 1024.

16. a.) J.E. McMurry, *Chem. Rev.*, 1989, **89**, 1513; b.) J.E. McMurry, *Acc. Chem. Res.*, 1983, **16**, 405.

17. R.A. Holton, R.R. Juo, H.B. Kim, A.D. Williams, S. Harusawa, R.E. Lowenthal and S. Yogai, *J. Am. Chem. Soc.*, 1988, **110**, 6558.

18. R.A. Holton, *J. Am. Chem. Soc.*, 1984, **106**, 5731.

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

20. a.) K.J. Shea and S. Wise, *J. Am. Chem. Soc.*, 1978, **100**, 6519; b.) R.W. Jackson, R.G. Higby and K.J. Shea, *Tetrahedron Lett.*, 1992, **33**, 4695; c.) R. W. Jackson, R.G. Higby, J.W. Gilman and K.J. Shea, *Tetrahedron*, 1992, **48**, 7013.

21. R.W. Jackson and K.J. Shea, *Tetrahedron Lett.*, 1994, **35**, 1317.

22. a.) P.A. Wender and T.P. Mucciaro, *J. Am. Chem. Soc.*, 1992, **114**, 5878; b.) P.A. Wender, N.F. Badham, T.E. Glass, C. Granicher, J.B. Houze, J. Janichen, D. Lee, D.G. Marquess, P.L.McGrane, W. Meng, T.P. Mucciaro, M. Muhlebach, M.G. Natchus, H. Paulsen, D.B. Rawlins, J. Satofsky, A.J. Shuker, J.C. Sutton, R.E. Taylor and K. Tomooka, *J. Am. Chem. Soc.*, 1997, **119**, 2755; *J. Am. Chem. Soc.*, 1997, **119**, 2757.

23. M.S. Ermolenko, T. Shekharam, G. Lukacs and P. Potier, *Tetrahedron Lett.*, 1995, **36**, 2461.

24. M.S. Ermolenko, G. Lukacs and P.Potier, *Tetrahedron Lett.*, 1995, **36**, 2465.

25. a.) T.V. Magee, W.G. Bornmann, R.C.A. Isaacs and S.J. Danishefsky, *J. Org. Chem.*, 1992, **57**, 3274; b.) C.H. Heathcock and R. Ratcliffe, J. Am. Chem. Soc., 1971, 93, 1746; c.) S.J. Danishefsky, J.J. Masters, W.B. Young, J.T. Link, L.B. Snyder, T.V. Magee, D.K. Jung, R.C.A. Isaacs, W.G. Bornmann, C.A. Alaimo, C.A. Coburn and M. J. Di Grandi, *J. Am. Chem. Soc.*, 1996, **118**, 2843; d.) J.J. Masters, J.T. Link, L.B. Snyder, W.B. Young and S.J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1723.

26. J.J. Masters, D.K. Jung and S.J. Danishefsky, L.B. Snyder, T.K. Park, R.C.A. Isaacs, C.A. Alaimo and W.B. Young, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 452.

27. a.) P.A. Brown, P.R. Jenkins, J. Fawcett and D.R. Russell, *J. Chem. Soc., Chem. Commun.*, 1984, 253; b.) P.A. Brown and P.R. Jenkins, *J. Chem. Soc., Perkin Trans. I*, 1986, 1303.

28. a.) R.V. Bonnert and P.R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1987, 1540; b.) R.V. Bonnert and P.R. Jenkins, *J. Chem. Soc., Perkin Trans. I*, 1989, 413.

29. a.) J.R. Pougny and P. Sinay, *J. Chem. Res.* (M), 1982, 0186; b.) D.R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 1975, **53**, 2017; c.) D.R. Hicks and B. Fraser-Reid, *Synthesis*, 1974, 203.

30. a.) R.V. Bonnert, J. Howarth, P.R. Jenkins and N.J. Lawrence, *J. Chem. Soc., Perkin Trans. I*, 1991, 1225; b.) R.V. Bonnert and P.R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1987, 6.

31. R.V. Bonnert, *New Synthetic Methods in an approach to Taxinine*, PhD Thesis, Leicester University, 1987.

32. a.) R.V. Bonnert, M.J. Davies, J. Howarth and P.R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1990, 148; b.) R.V. Bonnert, M.J. Davies, J. Howart, P.R. Jenkins and N.J. Lawrence, *J. Chem. Soc., Perkin Trans. I*, 1992, 27.

33. a.) G. Stork and M.J. Sofia, *J. Am. Chem. Soc.*, 1986, **108**, 6826; b.) G. Stork and M.E. Reynolds, *J. Am. Chem. Soc.*, 1988, **110**, 6911; c.) G. Stork and M. Kahn, *J . Am. Chem. Soc.*, 1985, **107**, 500.

34. S. Hanessian and N.R. Plessas, *J. Org. Chem.*, 1969, **34**, 1035.

35. A. Vasella and B. Bernet, *Helv. Chim. Acta*, 1979, **62**, 1990.

36. J. Clark, *New Synthetic Methods towards the synthesis of taxanes*, PhD Thesis, Leicester University, 1995.

37. A.N. Boa, J. Clark, P.R. Jenkins and N.J. Lawrence, *J. Chem. Soc., Chem. Commun.*, 1993, 151.

38. a.) J.N. Denis, A.E. Greene, D. Guenard, F. Gueritte-Voegelein, L. Mangatal and P.Potier, *J. Am. Chem. Soc.*, 1988, **110**, 5917; b.) M. Colin, D. Guenard, F. Gueritte-Voegelein and P. Potier, *Eur. Pat. Appl.*, EP 253738A1, 20 Jan., 1988; c.) J.-N. Denis, A. Greene, D. Guenard and F. Gueritte-Voegelein, *Eur. Pat. Appl.*, EP 336840A1, 5 Apr., 1989.

39. R.A. Holton, *Eur. Pat. Appl.*, EP 400497A1, 30 May, 1990; *Chem. Abstr.*, 114, P164568q.

40. I. Ojima, I. Habus, M. Zhao, G.I. Georg and L.R. Jayasinghe, *J. Org. Chem.*, 1991, **56**, 1681.

41. a.) S.E. Booth, P.R. Jenkins and C.J. Swain, *J. Chem. Soc., Chem. Commun.*, 1991, 1248; b.) S.E. Booth, P.R. Jenkins, C.J. Swain and J.B. Sweeney, *J. Chem. Soc., Perkin Trans I*, 1994, 3499.

42. S.J. Hulme, P.R. Jenkins, J. Fawcett and D.R. Russell, *Tetrahedron Lett.*, 1994, **35**, 5501.

43. E.J. Corey and W.-g. Su, *Tetrahedron Lett.*, 1988, **29**, 3423.

44. J. Kenyon, *Organic Syntheses*, Coll. Vol. I, 410.

45. M. Shimizu, K. Matsukawa and T. Fujisawa, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2128.

46. S. Hagishita and K. Kuriyama, *J. Chem Soc., Perkin Trans II*, 1974, 686.

47. a.) H. Kigoshi, Y. Imamura, K. Yoshikawa, H. Niwa and K. Yamada, *Tetrahedron Lett.*, 1991, **32**, 4541; b.) H. Kigoshi, Y. Imamura, K. Mizuta, H. Niwa and K. Yamada, *J. Am. Chem. Soc.*, 1993, **115**, 3056.

48. A. Misumi, K. Iwanaga, K. Furuta and H. Yamamoto, J. *Am. Chem. Soc.*, 1985, **107**, 3343.

49. Y. Chapleur, *J. Chem. Soc., Chem. Commun.*, 1983, 141.

50. J.J. Bloomfield and S.L. Lee, *J. Org. Chem.*, 1967, **32**, 3919.

51. M.E. Condon, E.W. Petrillo Jr., D.E. Ryono, J.A. Reid, R. Neubeck, J.E. Heikes, E.F. Sabo, K.A. Losee, D.W. Cushman and M.A. Ondetti, *J. Med. Chem.*, 1982, **25**, 250.

52. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.

53. K.M. Tebata and M.S. Kibara, *Tetrahedron Lett.*, 1981, **37**, 709.

54. R.V. Bonnert and P.R. Jenkins, *Tetrahedron Lett.*, 1987, **28**, 697.

55. S.R. Sandler, *Org. Synth.*, 1977, **56**, 32; *J. Org. Chem.*, 1963, **28**, 703.

56. a.) H.B. Kagan and J.L. Namy, *Tetrahedron*, 1986, **42**, 6573; b.) J. Souppe, J.L. Namy and H.B. Kagan, *Tetrahedron Lett.*, 1982, **23**, 3497.

57. T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904.

58. a.) T. Imamoto, N. Takiyama, K. Natamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392; b.) T. Imamoto, *Pure & Appl. Chem.*, 1990, **62**, 747.

59. N. Greeves and L. Lyford, *Tetrahedron Lett.*, 1992, **33**, 4759.

60. M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, No18, 2199.

61. J. Souppe, J.L. Namy and H.B. Kagan, *Tetrahedron Lett.*, 1984, **25**, 2869.

62. M.E. Evans, *Carbohyd. Res.*, 1967, **3**, 453.

63. A.N. Boa, Post-doctoral report, University of Leicester, 1995.

Appendix

STRUCTURE DETERMINATION SUMMARY

Crystal Data

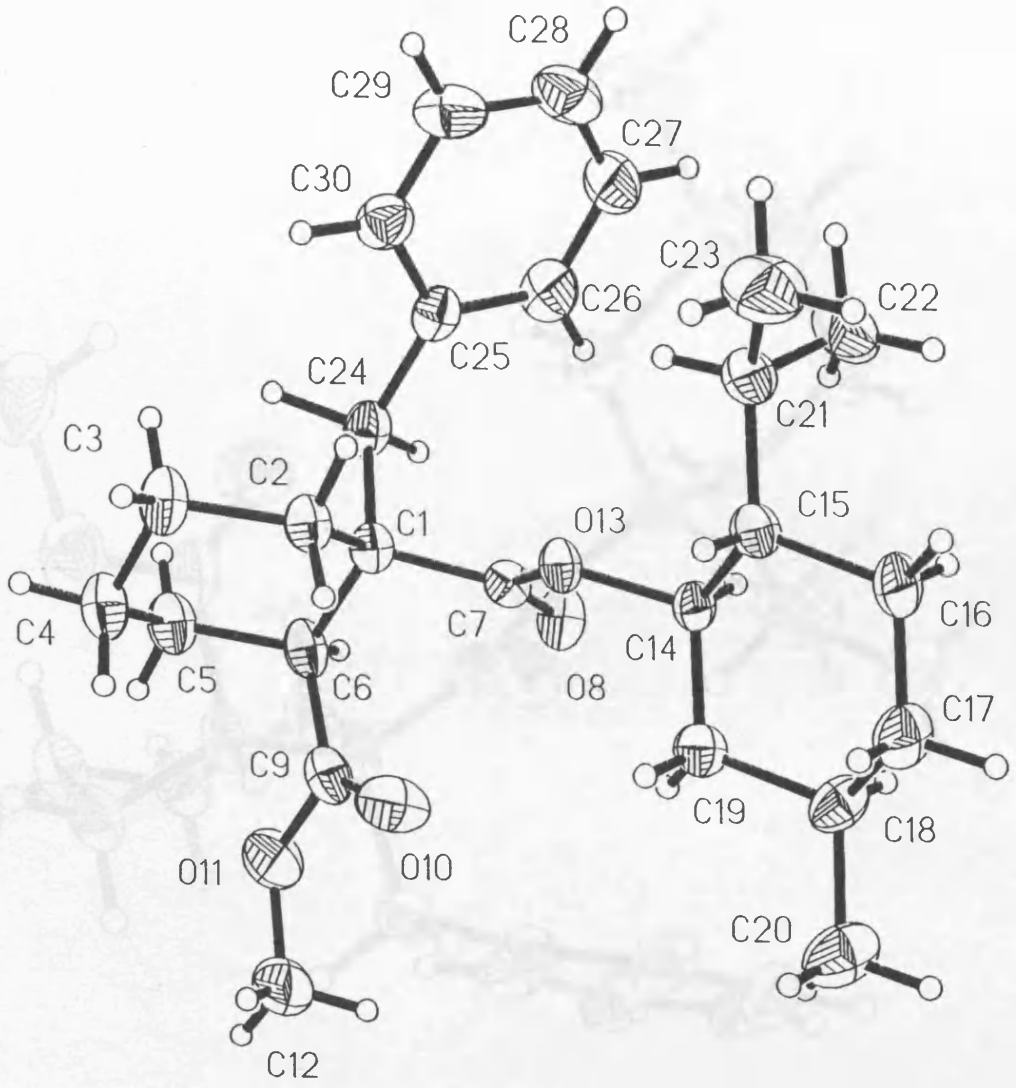
Empirical Formula	$C_{26} H_{38} O_4$
Color; Habit	Colourless Hexagonal Prism
Crystal size (mm)	0.76 x 0.26 x 0.26
Crystal System	Orthorhombic
Space Group	$P2_12_12_1$
Unit Cell Dimensions	$\underline{a}$ = 7.7240(10) Å
	$\underline{b}$ = 16.9200(10) Å
	$\underline{c}$ = 18.4760(10) Å
Volume	2414.7(3) $Å^3$
Z	4
Formula weight	414.6
Density(calc.)	1.140 Mg/m^3
Absorption Coefficient	0.075 mm^{-1}
F(000)	904

Data Collection

Diffractometer Used	Siemens P4
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	293
Monochromator	Highly oriented graphite crystal
2θ Range	4.0 to 52.0°
Scan Type	ω
Scan Speed	Variable; 3.00 to 30.00°/min. in ω
Scan Range (ω)	0.60°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25% of total scan time
Standard Reflections	3 measured every 100 reflections
Index Ranges	$-1 \leq h \leq 9$, $-20 \leq k \leq 20$ $-22 \leq l \leq 22$
Reflections Collected	5242
Independent Reflections	2931 (R_{int} = 2.81%)
Observed Reflections	2100 ($F > 4.0\sigma(F)$)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL PLUS (PC Version)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Absolute Structure	η = 4(4)
Extinction Correction	χ = 0.0030(4), where $F^* = F\ [\ 1 + 0.002\chi F^2/\sin(2\theta)\ ]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0015F^2$
Number of Parameters Refined	273
Final R Indices (obs. data)	R = 4.66 %, wR = 6.00 %
R Indices (all data)	R = 6.71 %, wR = 6.77 %
Goodness-of-Fit	1.09
Largest and Mean Δ/σ	0.013, 0.002
Data-to-Parameter Ratio	7.7:1
Largest Difference Peak	0.17 $e\text{Å}^{-3}$
Largest Difference Hole	-0.19 $e\text{Å}^{-3}$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C4
C7
C16
C14
C5
C6
O8
C17
C9
C19
C18
O10
O11
C20
C12

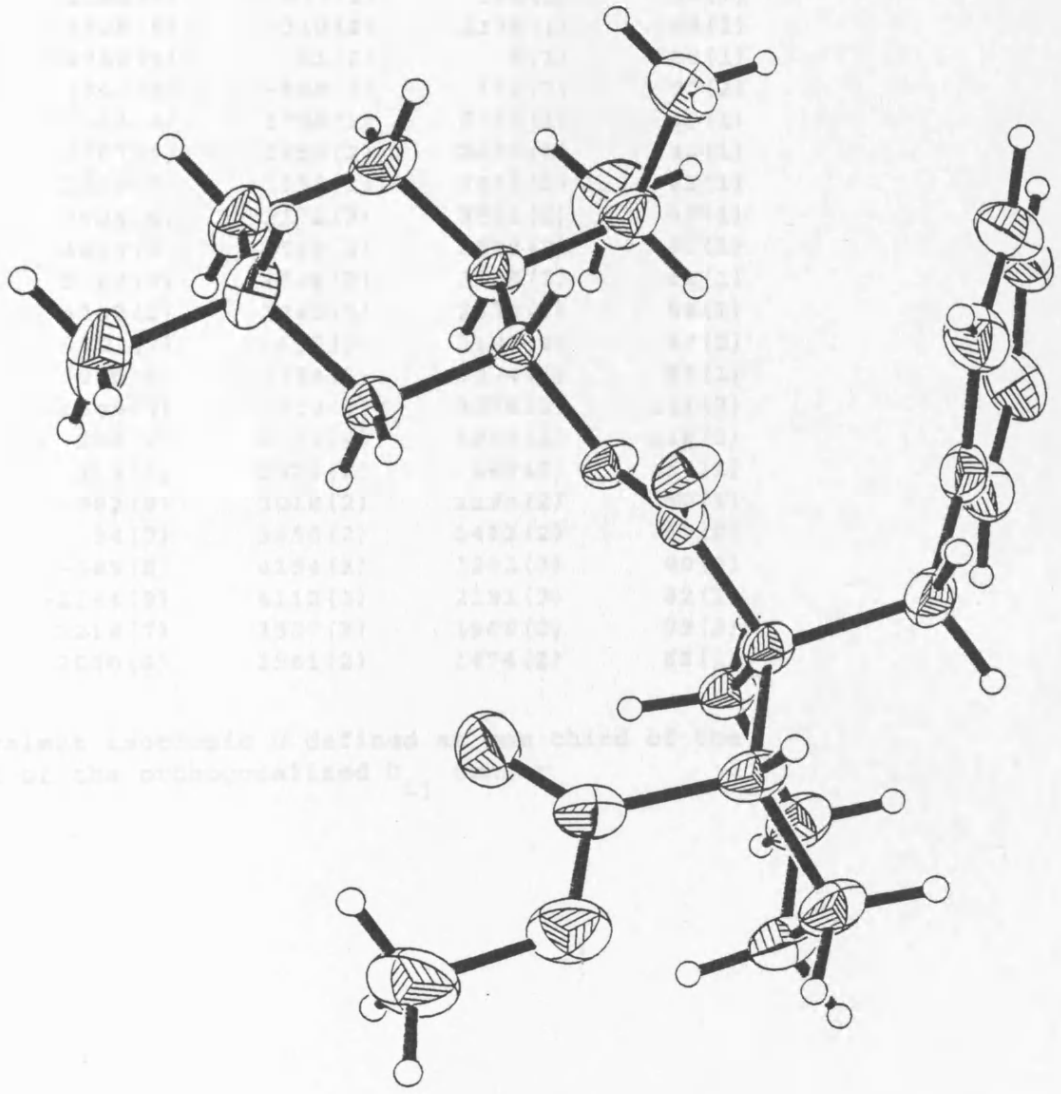

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	451(5)	1638(2)	950(2)	41(1)
C(2)	-943(5)	1155(2)	1350(2)	49(1)
C(3)	-2349(6)	831(2)	839(2)	63(1)
C(4)	-1581(6)	375(2)	207(2)	66(1)
C(5)	-249(6)	866(2)	-201(2)	62(1)
C(6)	1174(6)	1159(2)	303(2)	51(1)
C(7)	1959(5)	1887(2)	1429(2)	42(1)
O(8)	3257(4)	2180(2)	1193(1)	58(1)
C(9)	2285(6)	477(2)	564(2)	56(1)
O(10)	2636(5)	310(2)	1176(1)	83(1)
O(11)	2916(5)	61(2)	6(1)	80(1)
C(12)	3943(7)	-608(3)	172(3)	90(2)
O(13)	1643(3)	1780(1)	2135(1)	43(1)
C(14)	3067(5)	1958(2)	2632(1)	42(1)
C(15)	2238(5)	2099(2)	3372(2)	51(1)
C(16)	3688(6)	2172(3)	3938(2)	69(1)
C(17)	4897(7)	1469(3)	3938(2)	70(1)
C(18)	5727(5)	1348(2)	3206(2)	61(1)
C(19)	4302(5)	1269(2)	2634(2)	54(1)
C(20)	6921(7)	635(3)	3197(2)	87(2)
C(21)	980(6)	2798(3)	3374(2)	69(1)
C(22)	1849(9)	3602(3)	3375(3)	111(3)
C(23)	-290(9)	2736(4)	4009(2)	116(2)
C(24)	-315(6)	2429(2)	642(2)	52(1)
C(25)	-983(5)	3018(2)	1194(2)	50(1)
C(26)	34(7)	3650(2)	1412(2)	69(2)
C(27)	-589(8)	4194(3)	1902(3)	80(2)
C(28)	-2184(9)	4112(3)	2191(3)	82(2)
C(29)	-3218(7)	3507(3)	1966(2)	79(2)
C(30)	-2630(6)	2961(2)	1474(2)	62(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.540	(5)	C(1)-C(6)	1.549	(4)
C(1)-C(7)	1.523	(5)	C(1)-C(24)	1.569	(4)
C(2)-C(3)	1.540	(5)	C(3)-C(4)	1.520	(5)
C(4)-C(5)	1.523	(6)	C(5)-C(6)	1.523	(6)
C(6)-C(9)	1.517	(5)	C(7)-O(8)	1.200	(5)
C(7)-O(13)	1.339	(3)	C(9)-O(10)	1.196	(4)
C(9)-O(11)	1.339	(5)	O(11)-C(12)	1.416	(6)
O(13)-C(14)	1.464	(4)	C(14)-C(15)	1.529	(4)
C(14)-C(19)	1.506	(5)	C(15)-C(16)	1.537	(5)
C(15)-C(21)	1.530	(6)	C(16)-C(17)	1.512	(6)
C(17)-C(18)	1.511	(5)	C(18)-C(19)	1.532	(5)
C(18)-C(20)	1.519	(7)	C(21)-C(22)	1.517	(7)
C(21)-C(23)	1.534	(7)	C(24)-C(25)	1.517	(5)
C(25)-C(26)	1.387	(6)	C(25)-C(30)	1.376	(6)
C(26)-C(27)	1.378	(6)	C(27)-C(28)	1.350	(9)
C(28)-C(29)	1.363	(7)	C(29)-C(30)	1.374	(6)

Table 3. Bond angles (°)

C(2)-C(1)-C(6)	110.2(3)	C(2)-C(1)-C(7)	113.7(2)
C(6)-C(1)-C(7)	108.5(3)	C(2)-C(1)-C(24)	111.3(3)
C(6)-C(1)-C(24)	107.6(2)	C(7)-C(1)-C(24)	105.3(3)
C(1)-C(2)-C(3)	112.8(3)	C(2)-C(3)-C(4)	112.1(4)
C(3)-C(4)-C(5)	111.5(3)	C(4)-C(5)-C(6)	111.2(3)
C(1)-C(6)-C(5)	112.5(3)	C(1)-C(6)-C(9)	110.9(2)
C(5)-C(6)-C(9)	110.8(3)	C(1)-C(7)-O(8)	122.8(3)
C(1)-C(7)-O(13)	112.9(3)	O(8)-C(7)-O(13)	124.3(3)
C(6)-C(9)-O(10)	127.5(3)	C(6)-C(9)-O(11)	111.2(3)
O(10)-C(9)-O(11)	121.3(4)	C(9)-O(11)-C(12)	117.3(3)
C(7)-O(13)-C(14)	116.5(3)	O(13)-C(14)-C(15)	106.2(3)
O(13)-C(14)-C(19)	108.5(2)	C(15)-C(14)-C(19)	112.5(2)
C(14)-C(15)-C(16)	108.4(3)	C(14)-C(15)-C(21)	112.8(3)
C(16)-C(15)-C(21)	113.5(3)	C(15)-C(16)-C(17)	112.8(3)
C(16)-C(17)-C(18)	111.6(3)	C(17)-C(18)-C(19)	109.0(3)
C(17)-C(18)-C(20)	112.1(3)	C(19)-C(18)-C(20)	111.0(3)
C(14)-C(19)-C(18)	112.9(3)	C(15)-C(21)-C(22)	114.3(4)
C(15)-C(21)-C(23)	110.8(4)	C(22)-C(21)-C(23)	110.1(4)
C(1)-C(24)-C(25)	116.4(2)	C(24)-C(25)-C(26)	120.6(4)
C(24)-C(25)-C(30)	121.4(3)	C(26)-C(25)-C(30)	118.0(3)
C(25)-C(26)-C(27)	120.6(5)	C(26)-C(27)-C(28)	120.6(5)
C(27)-C(28)-C(29)	119.5(5)	C(28)-C(29)-C(30)	120.9(5)
C(25)-C(30)-C(29)	120.4(4)		

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	49(2)	45(2)	29(1)	-5(2)	0(2)	6(1)
C(2)	55(2)	53(2)	39(2)	-10(2)	0(2)	1(1)
C(3)	62(3)	72(2)	54(2)	-22(2)	-4(2)	2(2)
C(4)	71(3)	74(2)	52(2)	-19(3)	-6(2)	-9(2)
C(5)	76(3)	75(2)	35(2)	-9(3)	-4(2)	-5(2)
C(6)	64(3)	58(2)	32(1)	-19(2)	5(2)	-3(1)
C(7)	52(2)	43(2)	31(1)	0(2)	3(2)	3(1)
O(8)	59(2)	76(2)	40(1)	-20(2)	3(1)	8(1)
C(9)	64(3)	56(2)	48(2)	-12(2)	7(2)	-9(2)
O(10)	119(3)	80(2)	50(1)	35(2)	3(2)	3(1)
O(11)	89(2)	91(2)	61(1)	9(2)	10(2)	-26(2)
C(12)	71(3)	89(3)	110(4)	12(3)	8(3)	-41(3)
O(13)	49(1)	51(1)	28(1)	-10(1)	0(1)	-1(1)
C(14)	47(2)	47(2)	32(1)	-1(2)	-5(2)	-1(1)
C(15)	59(2)	60(2)	34(2)	5(2)	-1(2)	-6(1)
C(16)	79(3)	90(3)	37(2)	6(3)	-14(2)	-17(2)
C(17)	77(3)	94(3)	40(2)	13(3)	-10(2)	5(2)
C(18)	54(3)	79(2)	50(2)	9(3)	-3(2)	16(2)
C(19)	63(3)	58(2)	40(2)	6(2)	1(2)	0(2)
C(20)	85(4)	117(4)	57(2)	32(4)	4(3)	21(2)
C(21)	73(3)	87(3)	47(2)	22(3)	-10(2)	-23(2)
C(22)	143(6)	71(3)	118(4)	34(4)	-35(4)	-31(3)
C(23)	105(4)	157(5)	86(3)	44(5)	15(4)	-35(3)
C(24)	58(2)	54(2)	45(2)	-4(2)	-9(2)	10(1)
C(25)	53(2)	48(2)	49(2)	-3(2)	-9(2)	15(2)
C(26)	67(3)	57(2)	85(3)	-13(3)	0(3)	14(2)
C(27)	89(4)	46(2)	105(4)	-6(3)	-13(4)	-6(2)
C(28)	110(5)	52(2)	84(3)	18(3)	1(4)	0(2)
C(29)	73(3)	63(2)	101(3)	14(3)	19(3)	10(2)
C(30)	56(3)	56(2)	75(3)	3(2)	-2(2)	7(2)

The anisotropic displacement exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

Table 5. H-Atom coordinates ($x10^{-}$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(2A)	-1470	1485	1711	80
H(2B)	-398	721	1594	80
H(3A)	-3040	1263	665	80
H(3B)	-3092	483	1108	80
H(4A)	-2497	242	-122	80
H(4B)	-1071	-110	375	80
H(5A)	-792	1310	-431	80
H(5B)	264	545	-571	80
H(6A)	1913	1503	28	80
H(12A)	4340	-852	-267	80
H(12B)	4920	-446	456	80
H(12C)	3263	-980	442	80
H(14A)	3653	2428	2476	80
H(15A)	1588	1632	3489	80
H(16A)	3181	2226	4410	80
H(16B)	4343	2643	3841	80
H(17A)	5798	1556	4288	80
H(17B)	4269	1005	4081	80
H(18A)	6403	1807	3092	80
H(19A)	4830	1230	2165	80
H(19B)	3661	791	2716	80
H(20A)	7794	698	3563	80
H(20B)	6273	161	3290	80
H(20C)	7462	598	2731	80
H(21A)	305	2760	2939	80
H(22A)	976	4006	3374	80
H(22B)	2555	3655	3799	80
H'22C)	2558	3655	2951	80
H(23A)	-1079	3174	4003	80
H(23B)	-928	2251	3972	80
H(23C)	353	2739	4454	80
H(24B)	-1533	2270	342	80
H(24A)	777	2773	404	80
H(26A)	1191	3705	1229	80
H(27A)	108	4642	2033	80
H(28A)	-2590	4470	2556	80
H(29A)	-4370	3457	2156	80
H(30A)	-3382	2540	1322	80

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
2	0	0	553	655	6	6	11	0	21	22	-21	-5	3	1	73	77	4	6	8	1	127	120	4	6	14	1	14	8	-14
4	0	0	220	233	5	7	11	0	64	52	7	-4	3	1	146	138	4	7	8	1	42	39	9	-5	15	1	14	20	-14
6	0	0	10	7	-10	0	12	0	207	212	4	-3	3	1	71	77	3	8	8	1	13	10	-13	-4	15	1	44	51	-11
8	0	0	36	45	-10	1	12	0	148	154	2	-2	3	1	128	136	3	-8	9	1	14	14	-14	-3	15	1	57	56	8
1	1	0	909	911	11	2	12	0	120	116	4	-1	3	1	1036	1037	7	-7	9	1	76	84	7	-2	15	1	13	12	-13
2	1	0	23	35	-9	3	12	0	31	31	-13	0	3	1	721	726	5	-6	9	1	13	28	-13	-1	15	1	122	129	3
3	1	0	188	181	3	4	12	0	72	81	6	1	3	1	1035	1037	17	-5	9	1	264	259	7	0	15	1	64	64	4
4	1	0	245	230	5	5	12	0	28	14	-17	2	3	1	132	135	3	-4	9	1	23	20	-17	1	15	1	122	129	3
5	1	0	99	90	3	6	12	0	52	60	9	3	3	1	71	76	3	-3	9	1	115	117	3	2	15	1	13	12	-13
6	1	0	10	10	-7	7	12	0	14	31	-14	4	3	1	145	138	3	-2	9	1	289	300	8	3	15	1	48	56	10
7	1	0	19	6	-10	1	13	0	116	122	5	5	3	1	82	77	4	-1	9	1	77	78	2	4	15	1	35	51	-16
8	1	0	22	29	-11	2	13	0	20	12	-20	6	3	1	59	49	5	0	9	1	43	38	3	5	15	1	14	20	-14
9	1	0	13	7	-9	3	13	0	73	65	6	7	3	1	47	54	8	1	9	1	75	78	2	-5	16	1	26	19	-26
0	2	0	844	819	9	4	13	0	40	27	9	8	3	1	44	48	10	2	9	1	292	300	7	-4	16	1	47	52	11
1	2	0	347	359	4	5	13	0	45	35	10	-8	4	1	54	78	9	3	9	1	111	117	3	-3	16	1	56	53	8
2	2	0	332	323	6	6	13	0	51	48	9	-7	4	1	43	55	10	4	9	1	34	21	-9	-2	16	1	13	12	-13
3	2	0	16	5	-16	0	14	0	125	127	3	-6	4	1	146	150	4	5	9	1	246	259	6	-1	16	1	16	11	-7
5	2	0	115	118	4	1	14	0	69	66	5	-5	4	1	86	84	4	6	9	1	24	28	-24	0	16	1	127	128	3
6	2	0	37	14	8	2	14	0	13	3	-13	-4	4	1	154	158	4	7	9	1	84	84	6	1	16	1	14	11	-7
7	2	0	58	42	6	3	14	0	79	82	6	-2	4	1	262	255	6	8	9	1	30	14	-16	2	16	1	14	12	-14
8	2	0	680	699	4	4	14	0	50	44	8	-1	4	1	354	355	4	-7	10	1	51	53	9	3	16	1	61	53	8
1	3	0	305	299	5	5	14	0	14	11	-14	0	4	1	329	330	3	-6	10	1	101	105	5	4	16	1	48	52	10
2	3	0	96	125	3	6	14	0	28	10	-20	1	4	1	354	355	4	-5	10	1	42	43	10	5	16	1	14	19	-14
3	3	0	105	109	3	1	15	0	36	44	8	2	4	1	266	256	6	-4	10	1	56	58	6	-4	17	1	76	78	7
4	3	0	187	205	5	2	15	0	50	46	8	3	4	1	413	399	6	-3	10	1	114	114	4	-3	17	1	22	39	-22
5	3	0	69	67	5	3	15	0	51	45	8	4	4	1	138	158	4	-2	10	1	68	69	5	-2	17	1	33	38	-17
6	3	0	139	149	4	4	15	0	81	74	6	5	4	1	83	84	4	-1	10	1	138	139	5	-1	17	1	26	35	-8
7	3	0	14	36	-14	5	15	0	14	5	-14	6	4	1	154	150	5	0	10	1	49	43	3	0	17	1	24	15	-8
8	3	0	309	326	3	0	16	0	16	12	-12	7	4	1	59	54	6	1	10	1	137	139	2	1	17	1	38	35	7
0	4	0	508	522	3	1	16	0	174	181	5	8	4	1	72	79	6	2	10	1	72	69	4	2	17	1	50	37	8
1	4	0	140	139	3	2	16	0	23	34	-23	-8	5	1	13	10	-13	3	10	1	113	114	4	3	17	1	29	39	-29
3	4	0	62	62	4	3	16	0	22	22	-22	-7	5	1	95	99	5	4	10	1	67	59	5	4	17	1	82	78	7
4	4	0	175	181	5	4	16	0	34	43	-17	-6	5	1	43	42	7	5	10	1	41	43	9	-3	18	1	22	7	-22
5	4	0	40	36	7	5	16	0	33	11	-16	-5	5	1	29	40	-10	6	10	1	97	105	5	-2	18	1	22	37	-22
6	4	0	64	61	6	1	17	0	34	34	8	-3	5	1	101	97	3	7	10	1	42	53	-11	-1	18	1	15	10	-8
7	4	0	30	15	-14	2	17	0	14	32	-14	-1	5	1	163	169	5	-7	11	1	14	35	-14	0	18	1	69	69	4
8	4	0	1288	1239	10	3	17	0	38	36	-13	0	5	1	271	248	3	-6	11	1	39	45	-12	1	18	1	14	10	-7
1	5	0	613	586	6	4	17	0	69	63	8	1	5	1	162	168	2	-5	11	1	41	43	-11	2	18	1	21	37	-21
2	5	0	505	506	7	0	18	0	96	92	4	2	5	1	334	332	6	-4	11	1	123	123	4	3	18	1	31	7	-20
3	5	0	172	168	5	1	18	0	20	14	-8	3	5	1	87	97	4	-3	11	1	77	81	5	-2	19	1	39	39	-14
4	5	0	47	58	6	2	18	0	50	16	9	4	5	1	257	251	6	-2	11	1	291	293	8	-1	19	1	30	27	-9
5	5	0	117	123	4	3	18	0	48	33	9	5	5	1	29	39	-11	-1	11	1	201	210	4	0	19	1	16	34	-8
6	5	0	40	48	-11	1	19	0	24	27	-8	6	5	1	20	42	-20	0	11	1	152	161	3	1	19	1	33	27	8
7	5	0	87	95	6	2	19	0	39	33	-15	7	5	1	104	99	4	1	11	1	198	210	3	2	19	1	43	39	-13
8	5	0	68	68	4	0	20	0	15	5	-10	8	5	1	13	10	-13	2	11	1	276	293	8	-1	20	1	20	16	-9
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1	6	0	303	289	6	1	0	1	437	463	4	-7	6	1	47	53	8	4	11	1	122	123	4	1	20	1	16	16	-10
2	6	0	59	63	4	2	0	1	599	615	5	-6	6	1	234	243	5	5	11	1	45	43	9	0	0	2	57	56	1
4	6	0	152	150	4	3	0	1	149	151	8	-5	6	1	80	100	5	6	11	1	31	45	-17	1	0	2	287	320	3
5	6	0	103	117	5	4	0	1	18	30	-8	-4	6	1	153	150	4	7	11	1	33	35	-16	2	0	2	356	372	5
6	6	0	45	34	8	5	0	1	29	37	6	-2	6	1	802	771	6	-7	12	1	28	38	-28	3	0	2	206	202	5
7	6	0	55	39	7	6	0	1	37	39	6	-1	6	1	248	238	5	-6	12	1	43	57	-12	4	0	2	92	84	3
8	6	0	438	413	4	7	0	1	15	12	-10	0	6	1	394	400	5	-5	12	1	45	47	10	5	0	2	81	84	3
1	7	0	328	307	7	8	0	1	35	35	-14	1	6	1	252	239	4	-4	12	1	35	29	-11	6	0	2	25	19	-13
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Observed and calculated structure factors for [illegible]

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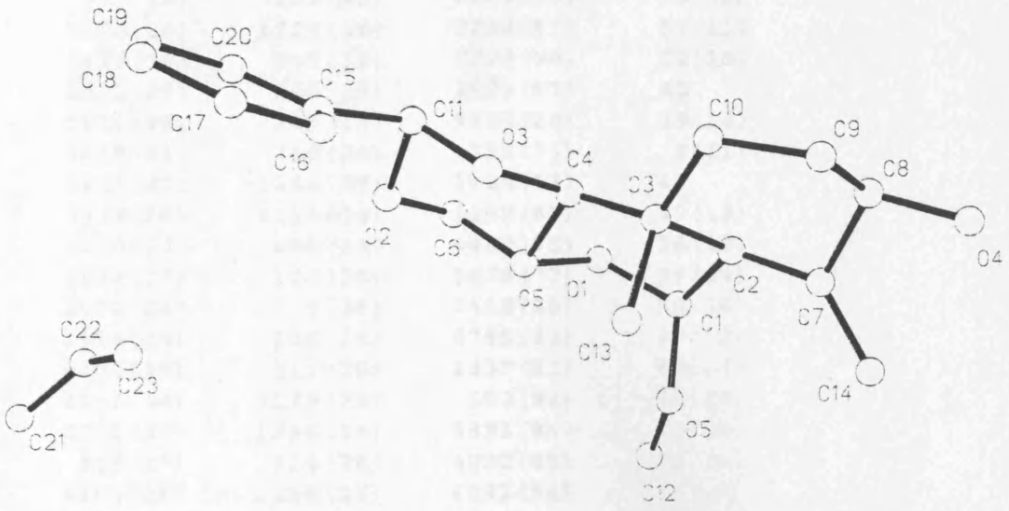
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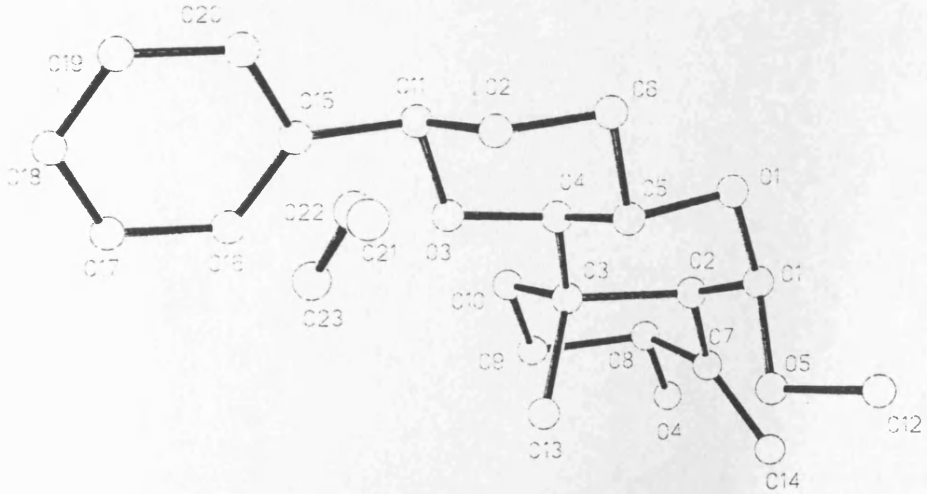
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C2
C1
C23
C10
C9
C8
C7
O5
C12
C13
O4
C14

Table 1. Atomic coordinates (x10^4) and equivalent isotropic displacement coefficients ($Å^2$x10^3)

	x	y	z	U(eq)
O(1)	3260(20)	900(19)	1499	61(12)
O(2)	4975(18)	1337(17)	3305(65)	60(11)
O(3)	4294(18)	964(18)	5489(62)	61(12)
O(4)	831(20)	-222(21)	6494(65)	70(12)
O(5)	2228(18)	1725(18)	2258(67)	51(11)
C(1)	2459(30)	945(32)	2029(90)	72(19)
C(2)	2322(27)	506(24)	3689(87)	40
C(3)	2931(26)	749(27)	5324(80)	39(16)
C(4)	3655(21)	712(20)	4333(73)	9(11)
C(5)	3817(27)	1266(25)	2684(73)	40
C(6)	4553(26)	1124(26)	1902(82)	40(15)
C(7)	1610(28)	484(24)	4442(75)	26(13)
C(8)	1520(27)	-108(26)	5878(77)	39(14)
C(9)	2072(28)	5(26)	7415(80)	50(16)
C(10)	2914(25)	136(24)	6783(83)	37(12)
C(11)	5051(29)	811(28)	4837(81)	60(16)
C(12)	2111(34)	2129(33)	553(93)	95(24)
C(13)	2771(25)	1586(25)	5893(84)	41(15)
C(14)	925(27)	914(26)	4052(85)	41(15)
C(15)	5604(26)	1188(26)	6083(88)	103(25)
C(16)	5381	1483	7692	189(40)
C(17)	5921	1715	8901	187(38)
C(18)	6684	1652	8500	178(36)
C(19)	6907	1357	6890	101(24)
C(20)	6367	1125	5682	67(19)
C(21)	6030(75)	3440(71)	4466(188)	177(51)
C(23)	6802(62)	4075(58)	2186(140)	84(40)
C(22)	6298(104)	3527(114)	2565(250)	301(101)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

O(1)-C(1)	1.482	(64)	O(1)-C(5)	1.492	(57)
O(2)-C(6)	1.362	(72)	O(2)-C(11)	1.506	(72)
O(3)-C(4)	1.508	(59)	O(3)-C(11)	1.461	(63)
O(4)-C(8)	1.328	(62)	O(5)-C(1)	1.457	(66)
O(5)-C(12)	1.503	(83)	C(1)-C(2)	1.510	(89)
C(2)-C(3)	1.709	(80)	C(2)-C(7)	1.392	(73)
C(3)-C(4)	1.494	(66)	C(3)-C(10)	1.559	(78)
C(3)-C(13)	1.578	(67)	C(4)-C(5)	1.626	(71)
C(5)-C(6)	1.461	(70)	C(7)-C(8)	1.529	(74)
C(7)-C(14)	1.468	(69)	C(8)-C(9)	1.545	(78)
C(9)-C(10)	1.590	(69)	C(11)-C(15)	1.524	(78)
C(21)-C(22)	1.537	(237)	C(23)-C(22)	1.356	(227)

Table 3. Bond angles (°)

C(1)-O(1)-C(5)	116.6(34)	C(6)-O(2)-C(11)	119.2(36)
C(4)-O(3)-C(11)	116.0(41)	C(1)-O(5)-C(12)	112.9(48)
O(1)-C(1)-O(5)	110.8(40)	O(1)-C(1)-C(2)	110.9(42)
O(5)-C(1)-C(2)	110.2(49)	C(1)-C(2)-C(3)	112.4(39)
C(1)-C(2)-C(7)	120.6(46)	C(3)-C(2)-C(7)	106.3(48)
C(2)-C(3)-C(4)	99.4(43)	C(2)-C(3)-C(10)	109.6(37)
C(4)-C(3)-C(10)	110.4(38)	C(2)-C(3)-C(13)	109.0(37)
C(4)-C(3)-C(13)	109.7(37)	C(10)-C(3)-C(13)	117.3(48)
O(3)-C(4)-C(3)	109.8(43)	O(3)-C(4)-C(5)	98.1(31)
C(3)-C(4)-C(5)	121.3(36)	O(1)-C(5)-C(4)	95.1(31)
O(1)-C(5)-C(6)	105.7(41)	C(4)-C(5)-C(6)	111.8(38)
O(2)-C(6)-C(5)	97.0(44)	C(2)-C(7)-C(8)	114.2(42)
C(2)-C(7)-C(14)	131.0(49)	C(8)-C(7)-C(14)	114.7(44)
O(4)-C(8)-C(7)	117.1(43)	O(4)-C(8)-C(9)	109.6(48)
C(7)-C(8)-C(9)	112.9(40)	C(8)-C(9)-C(10)	112.7(47)
C(3)-C(10)-C(9)	109.7(38)	O(2)-C(11)-O(3)	93.8(36)
O(2)-C(11)-C(15)	105.7(39)	O(3)-C(11)-C(15)	107.4(44)
C(11)-C(15)-C(16)	122.2(30)	C(11)-C(15)-C(20)	117.0(29)
C(21)-C(22)-C(23)	118.6(154)		