Approaches to Taxanes from Carbohydrate Precursors

by

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Statement

The accompanying thesis submitted for the degree of Ph.D entitled "Approaches to Taxanes From Carbohydrate Precursors" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period October 1987 and September 1990.

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. ..... Date 1st NOVEMBER 1990

Parts of this work have been published as a communication.

The Stereochemistry of the Stork Silyl Methylene Radical Cyclisation in an Annulated Sugar Derivative. R. V. Bonnert, M. J. Davies, J. Howarth and P. R. Jenkins, *J. Chem. Soc., Chem. Commun.*, 1990, 148.

ACKNOWLEDGEMENTS

This will be one of the few occasions where I can thank all those that have brought interest and excitement to my life. It is also a rare chance to thank those who work unrecognised behind the scenes.

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APPROACHES TO TAXANES FROM CARBOHYDRATE PRECURSORS
by Joshua Howarth

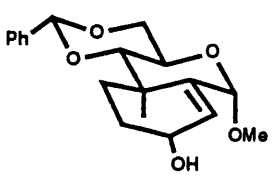
ABSTRACT

This thesis is a continuation of the work by Bonnert to produce taxanes from glucose. The application of a Stork silyl methylene radical cyclisation to the allylic alcohol (1) led to the diol (2). This has a *trans* ring junction and has introduced regiospecifically a hydroxy methylene group adjacent to an hydroxyl group. This provides the necessary stereochemistry for the B-C ring junction in taxanes. However the ring hydroxyl group has the wrong stereochemistry for taxinine. In an endeavour to correct this, the allylic alcohol (1) was inverted and the radical cyclisation performed again. This resulted though in the radical and the hydrogen atom adding *trans*, once more, despite the fact that this gave rise to the formation of two *cis* ring junctions. Therefore, this too produced the wrong stereochemistry at the B-C ring junction.

A series of studies were undertaken to assess the generality of the Robinson annulation of a carbohydrate. This study was extended to the incorporation the C-7 hydroxyl group in taxol during this annulation. A study of the C-ring functionality was performed leading to the formation of a carbohydrate oxetane. Several attempts at the production of 2-trimethyl-3-lithiobutadiene, as a synthetic building block, resulted in failure.

Following previous work at Leicester, involving the use of intramolecular Diels-Alder reactions in the synthesis of taxanes, studies were initiated to convert (2) and (3) into diene-dienophile systems. The first approach was to construct the dienophile, prior to the diene, on C-9 (C-1 carbohydrate numbering). This approach failed due to the difficulties encountered when differentially protecting several similar hydroxyl groups.

Altering our initial ideas, such that the diene is built before the dienophile, on C-6, has met though with more success. However, before attempting the construction of the diene on our intermediate (4) a model study was undertaken on a simple carbohydrate aldehyde, using a selenium directed synthesis. This was successful and so this approach has the potential for providing the means for the formation of a diene-dienophile system in our intermediate (4), and hence eventually resulting in the creation of a highly substituted taxane skeleton.



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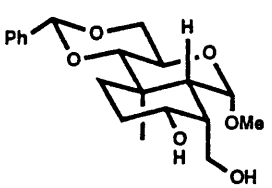

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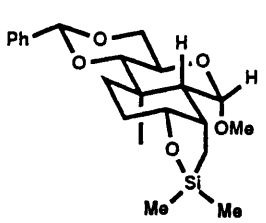

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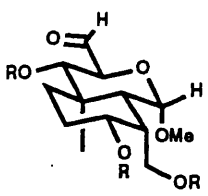

(4) R=Ac
R=Bn

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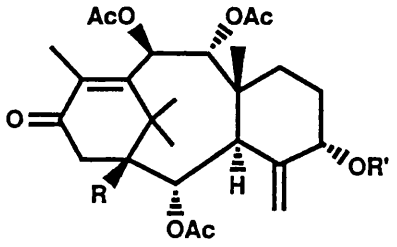
CHAPTER 1.

Introduction

1.1 INTRODUCTION

It has been known since classical times that the leaves and berries of yew trees are toxic to animals and man. The constituents of the needles and other parts of various species of yew tree are responsible for the toxic properties and are collectively known as taxines.[1] This group of amorphous basic compounds contained in the Japanese yew *Taxus cuspidata,* the European yew *Taxus baccata* and other related species *taxaceae* consists mainly of two principal isolated constituents, O-cinnamoyl taxicin-I-triacetate (1) and taxinine (2).



(1) R = OH, R' = -COCH:CHPh

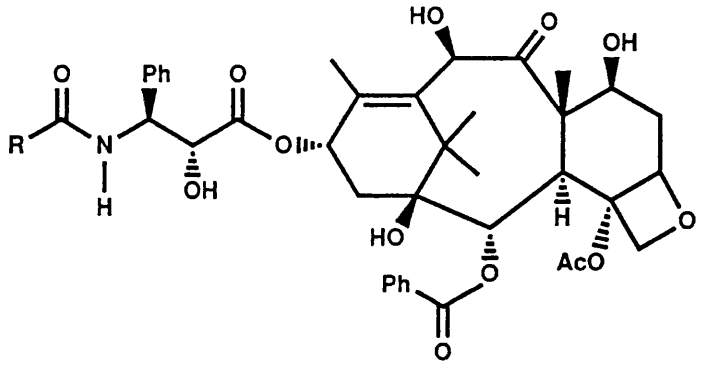
(2) R = H, R' = -COCH:CHPh

(1a) R = OH, R' = -$COCH_2CH(N(Me)_2)Ph$

(2a) R = H, R' = -$COCH_2CH(N(Me)_2)Ph$

They are both alkaloids which are contained within the plant as esters of β-dimethyl-amino-β-phenyl propanoic acid, $Me_2NCH(Ph)-CH_2CO_2H$,[2] but are converted to cinnamates by loss of dimethylamine during isolation to produce stable crystalline compounds.[3] Many compounds that contain the taxane diterpenoid skeleton have now been isolated and identified.[4]

Some of the more complex derivatives, taxol (3)[5] and cephalomannine (4)[6] show antileukaemic and tumour inhibitory properties.[5,6] Taxol (3) is undergoing extensive clinical trials[7] as an anticancer chemotherapeutic agent. This biological activity has provoked a large increase in the efforts to synthesise naturally occuring taxanes and taxane analogues.



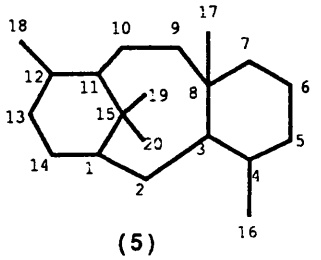
(3) R = Ph

(4) R = $-CCH_3=CHCH_3$

1.2 NOMENCLATURE

The literature prior to 1964, contains a variety of naming and numbering systems for the taxane derivatives.[4] In 1964, three laboratories recommended the name taxane for the nucleus (5) and numbered the framework accordingly.[8] In 1969, however, a different numbering scheme for the methyl groups was introduced which resulted in both systems being used. In 1978 IUPAC recommended the numbering system shown for the taxane skeleton (6).[9]

The numbering and naming systems used in this text, for all compounds are, as far as possible, in accordance with IUPAC (1978) recommendations.[10]



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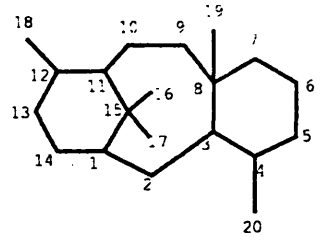
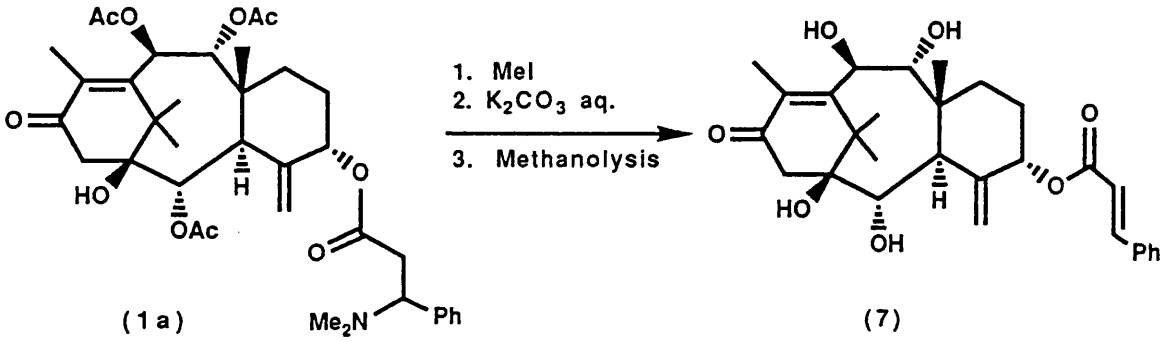


(6)

1.3 ISOLATION OF TAXANES

After first being isolated by Lucas[11] in 1856 no major advances were made on the amorphous basic fraction from *Taxus baccata* until Winterstein *et al*[12] indicated that the amorphous basic fraction or taxine was an ester of a nitrogen free polyhydroxylic compound with acetic acid and β-dimethyl amino-β-phenylpropionic acid (Winterstein's acid). Later studies by Graf[13] and then Lythgoe[3,14] demonstrated that taxine was a mixture of two major alkaloids taxin-I (1a) and taxin-II (2a) which give O-cinnamoyltaxicin-I-triacetate (1) and taxinine (2) respectively on loss of dimethylamine. Some of the early difficulties in isolation of members of the taxane family

were due to the instability of the esters of Winterstein's acid. Subsequently both English[3,14] and Japanese[15] groups employed an isolation technique whereby complete elimination of dimethylamine from Winterstein esters occurs by treating the crude taxine methiodide with potassium carbonate in cold water and isolation of the corresponding cinnamate esters.



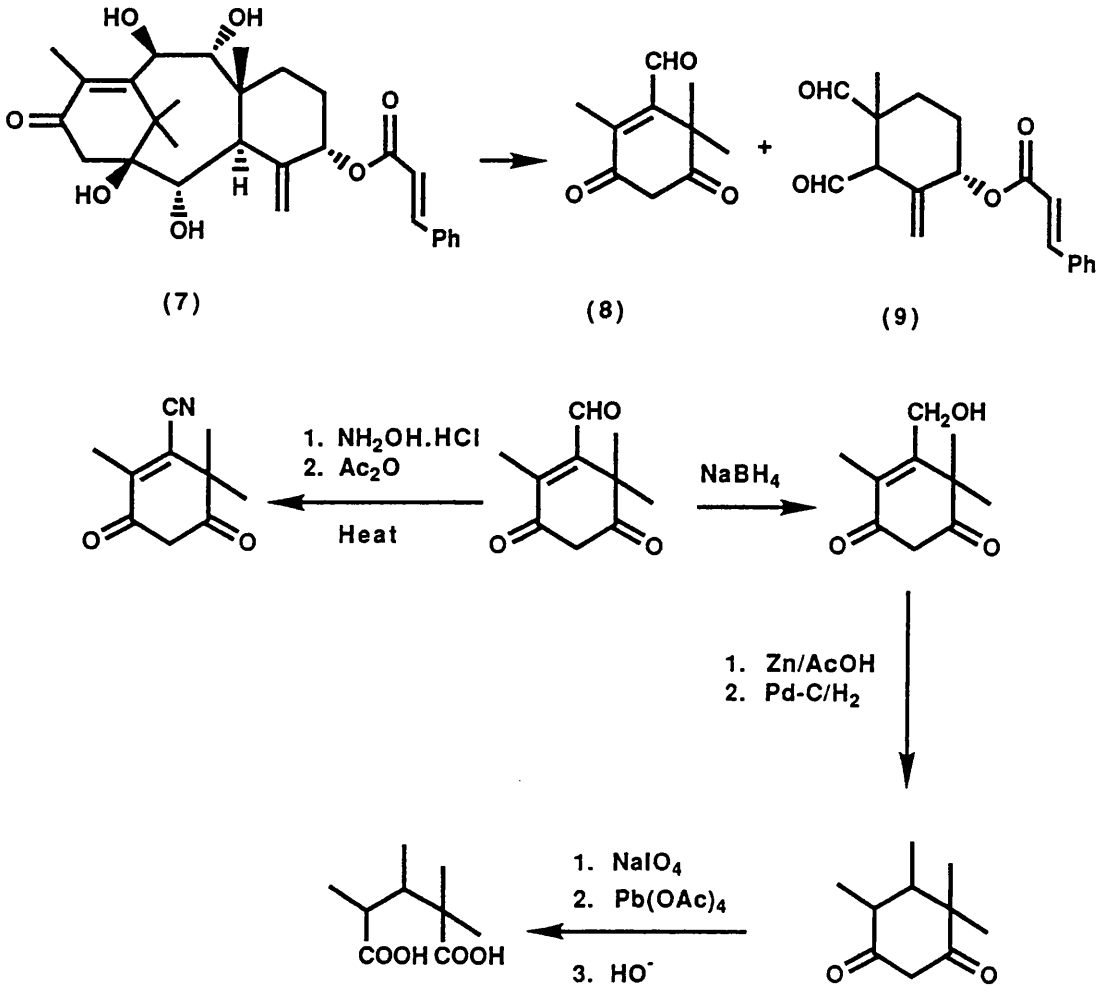
(1a) (7)

The cinnamates were usually then reacted under Zemplen methanolysis conditions[16] which removed the acetate groups but left the cinnamate esters unaffected. O-cinnamoyl taxicin-I (7) could then be readily separated by direct crystallisation. The mother liquor was then reacetylated and O-cinnamoyltaxicin triacetate (1) and taxinine (2) separated by chromatography. From ten kilograms of dried yew clippings, using the above extraction technique, it was possible to isolate approximately forty grams of crude taxine. Separation of the crude taxine afforded eight grams of O-cinnamoyl taxicin I (7), four grams of its triacetate (1) and two grams of taxinine (2).[2]

The vigorous conditions, typically involving soaking the dried yew leaves in sulphuric acid for seven days[4] followed by basification and extraction with diethyl ether, used in the extraction of taxanes means that they were only isolated as their derivatives. Much milder extraction techniques have been used to isolate many of the more complex taxanes. For example, taxol (3) was obtained by alcohol extraction of the bark of the western yew, *Taxus brevifolia* and purified by successive chromatography and crystallisation.[5] Mild extraction techniques used by Halsall[17] enabled twenty-one new polyoxygenated diterpenoids to be isolated.

1.4 STRUCTURE DETERMINATION OF THE TAXANES

The structural identification of taxin-I (1a) and its derivatives isolated from *Taxus baccata* was undertaken mainly by the English group of Lythgoe, whilst the Japanese group of Nakanishi concentrated their efforts on taxin-II (2a) and its derivatives isolated in major amounts from *Taxus cuspidata*. The molecular formulae of O-cinnamoyl taxicin-I (7) and taxinine (2) were established as $C_{29}H_{36}O_7$[13] and $C_{35}H_{42}O_9$[18] respectively. The majority of the functional groups were determined by chemical means.[19] One of the most important chemical reactions performed on (7) was periodate oxidation which gave (8) and (9).[20] The structures of the two fragments were then determined by both chemical means and spectroscopic means, as shown in Scheme 1 and Scheme 2 respectively.


HO
OH
O
HO
H
OH
O
O
Ph
(7)
CHO
O
O
(8)
+
OHC
OHC
O
O
Ph
(9)
CN
O
O
1. NH2OH.HCl
2. Ac2O
Heat
CHO
O
O
NaBH4
CH2OH
O
O
1. Zn/AcOH
2. Pd-C/H2
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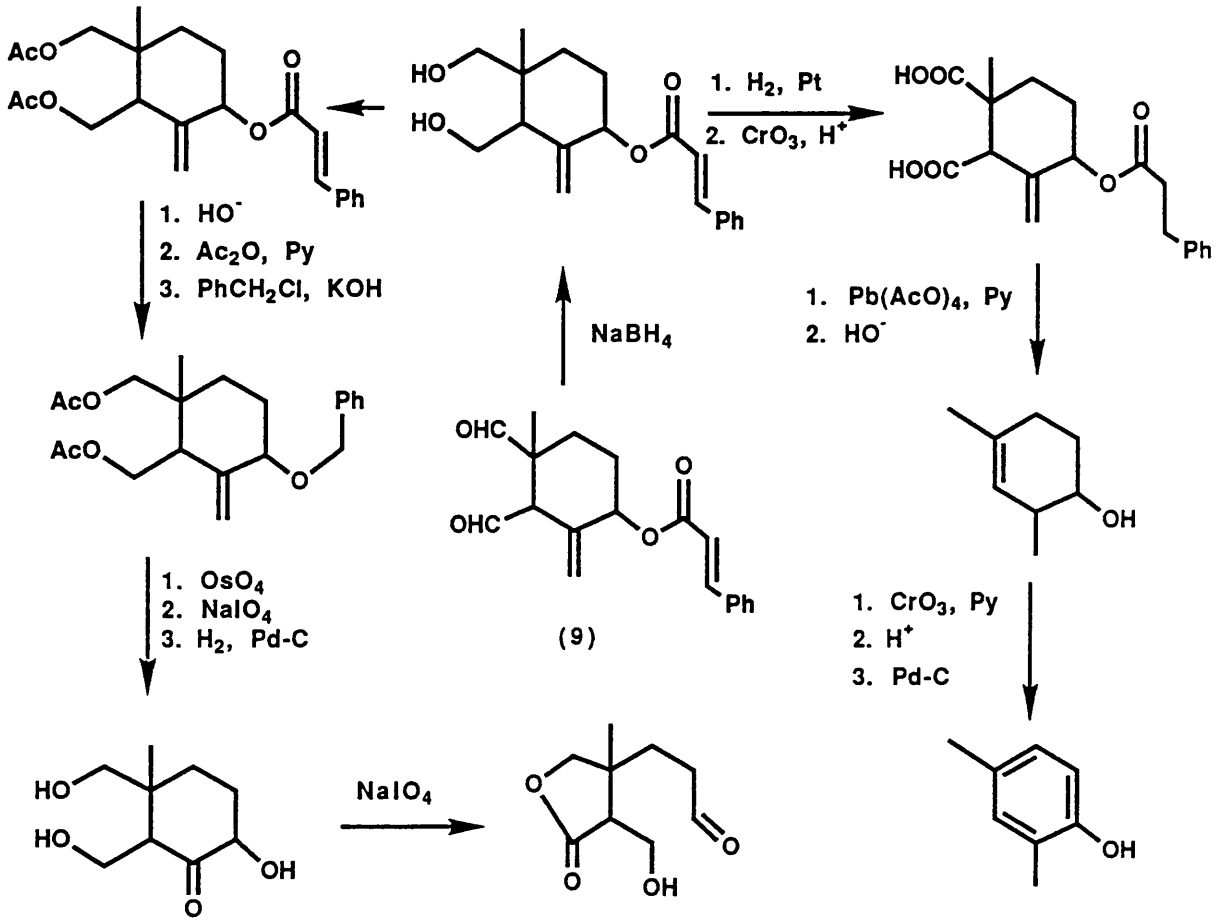
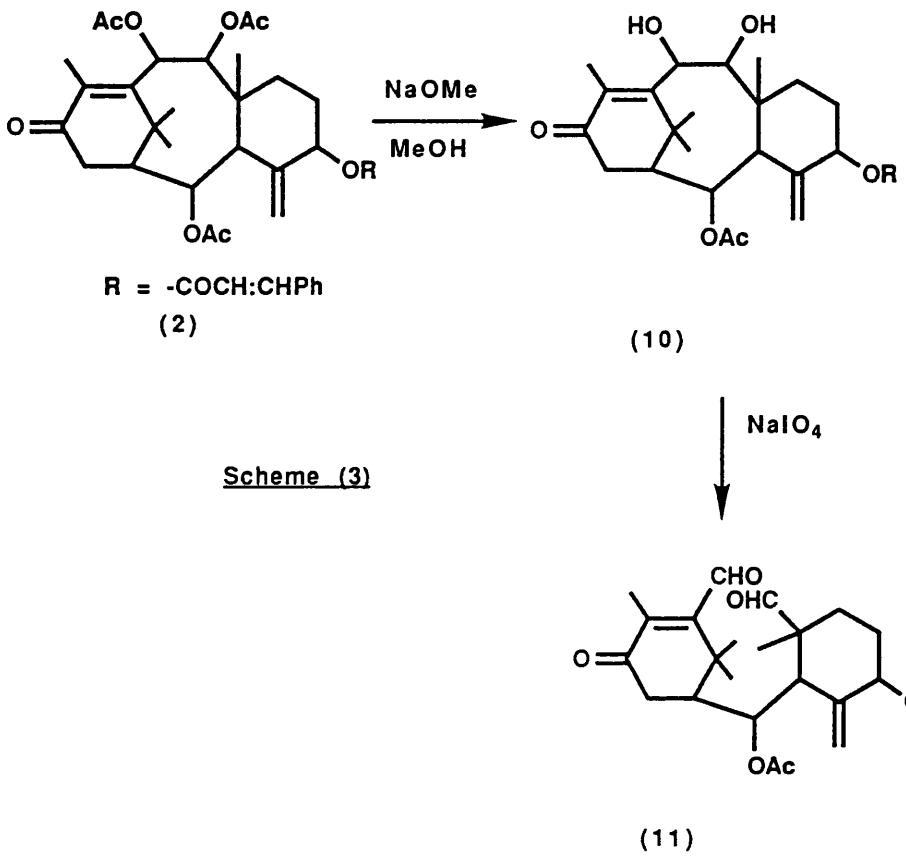
O
1. NaIO4
2. Pb(OAc)4
3. HO-
COOH COOH

Scheme 1



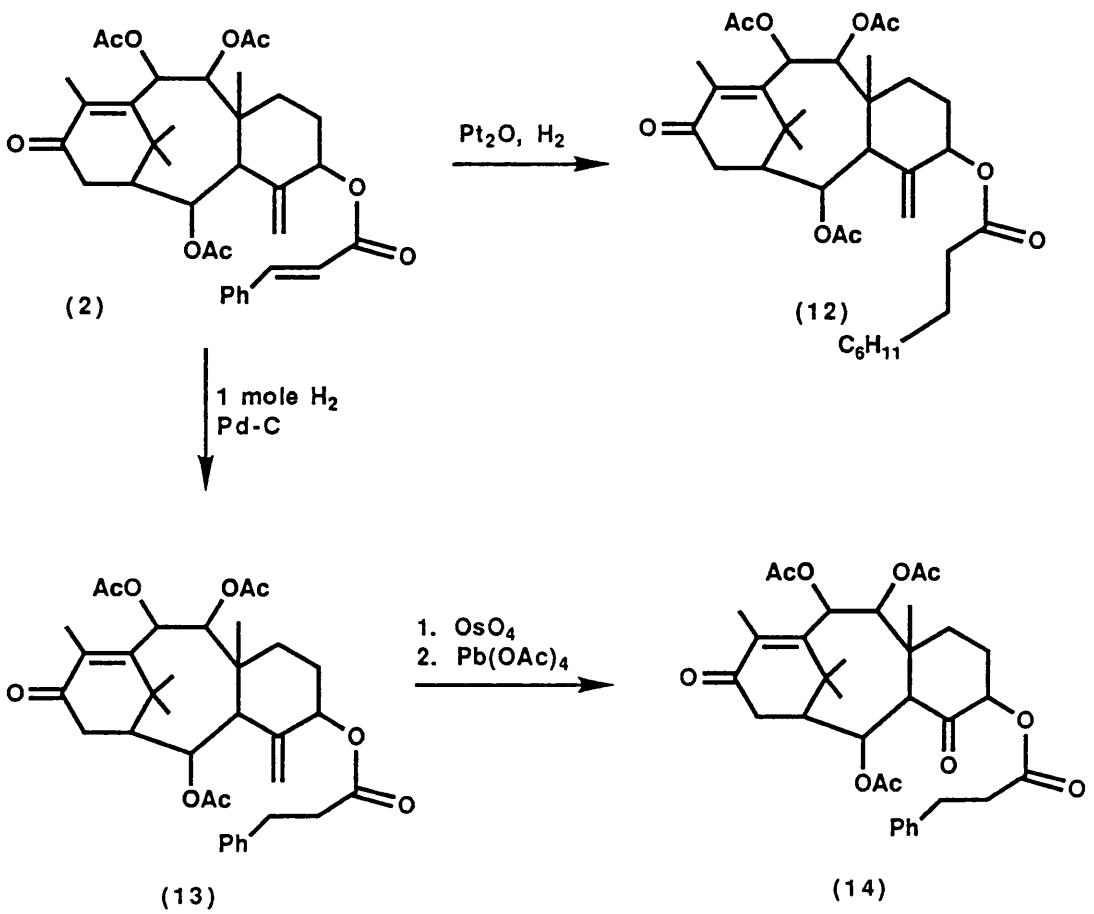
Scheme 2

It was soon apparent that O-cinnamoyl taxicin-I-triacetate (1) and taxinine (2) were structurally related. Chemical studies of taxinine (2) showed that it lacked the free tertiary hydroxyl group which was present in the O-cinnamoyl taxicin-I series.[21] Methanolysis of taxinine (2) led to the formation of the 2-monoacetate (10).[22] Treatment of the monoacetate (10) with periodate gave the dialdehyde (11), as shown in Scheme 3. The n.m.r spectrum showed the aldehyde protons as singlets which implied that they were flanked by carbons bearing no hydrogens.[22]



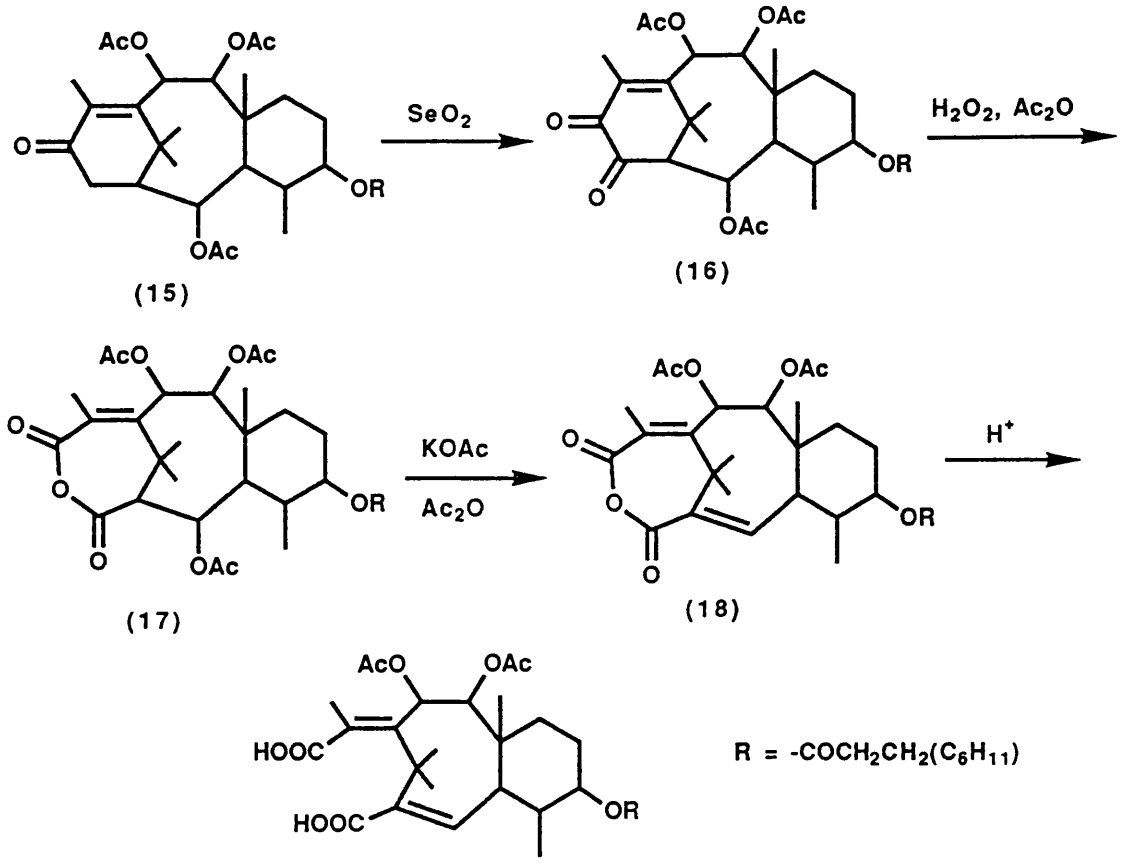
Scheme (3)

Hydrogenation of taxinine (2) over a platinum catalyst gave dihydrotaxicin-II-β-cyclohexyl propionate triacetate (12).[22] The enone double bond proved inert to hydrogenation (and oxidation) in a similar way to O-cinnamoyl taxicin-I-triacetate (1). Treatment of taxinine (2) with one mole of hydrogen and a palladium catalyst led to the hydrogenation of the cinnamate double bond to yield dihydrotaxinine (13). The exocyclic double bond could then be cleaved using osmium tetroxide to yield the corresponding diol which in turn could be reacted with lead tetraacetate to furnish the ketone (14) and formaldehyde, Scheme 4.



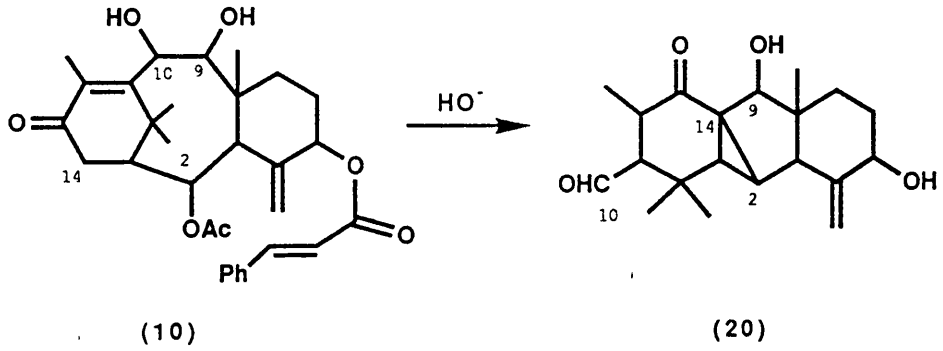
Scheme 4

Additional chemical evidence for the structure of taxinine (2) was demonstrated when tetrahydrotaxinine (15) was oxidised using selenium dioxide to provide the α-diketone (16). The proton n.m.r. showed a doublet δ2.88 at corresponding to H-1. Baeyer-Villiger oxidation of (16) produced the anhydride (17). Treatment of (17) with potassium acetate and acetic anhydride furnished the anhydride (18), which on reaction with acid gave the dicarboxylic acid (19), Scheme 5.[12]



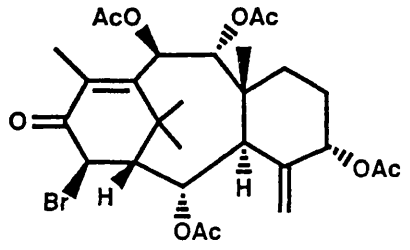
Scheme 5

The final piece of chemical evidence for the structure of taxinine (2) was the treatment of the 2-monoacetate (10) with alkali to provide anhydrotaxininol (20).[23]



The stereochemistry of taxinine (2) was originally inferred from the coupling constants in the proton n.m.r., but this led to the wrong configurations being assigned at

C-3, C-9 and C-10.[24] The relative configuration of taxinine (2) was later confirmed by X-ray analysis of 14-bromotaxinol (21).



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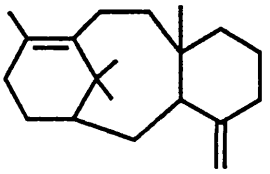


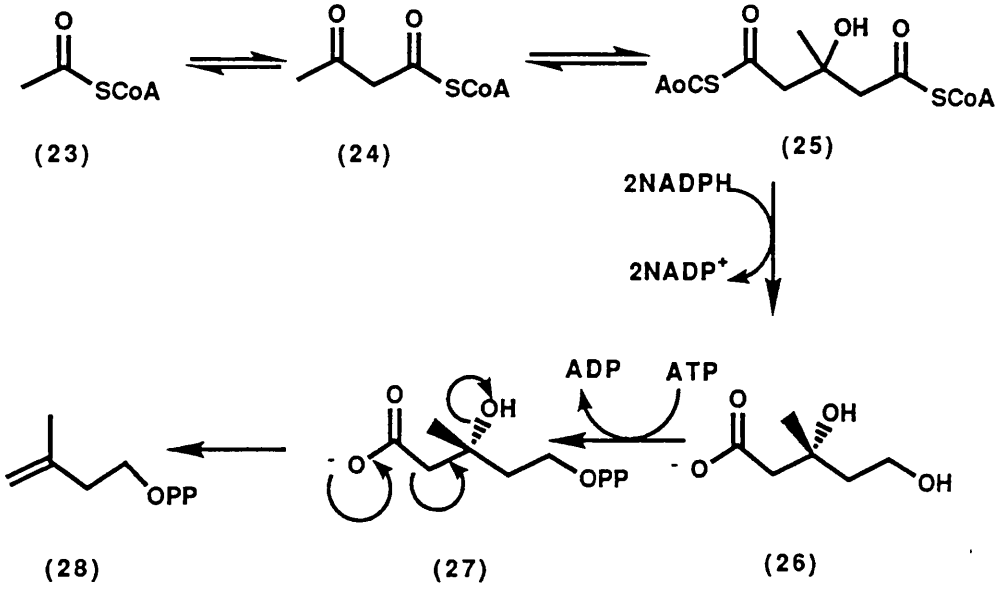
(22)

Since the structure elucidation of taxin-I (1a) and taxin -II (2a), the structures of many more related compounds have been identified.[25] The derivatives first isolated from the heartwood of *taxus baccata* by Halsall *et al*,[17] are of particular interest. In several brief communications[26] he claims to have isolated nineteen different taxane derivatives. Retrospectively the most important derivatives are the baccatins that contain the novel oxetane ring.[27] This importance is due to the biological activity of the baccatins. The structures and spectral data of some naturally occuring taxanes and their derivatives can be found in Appendix 1.

1.5 BIOSYNTHESIS

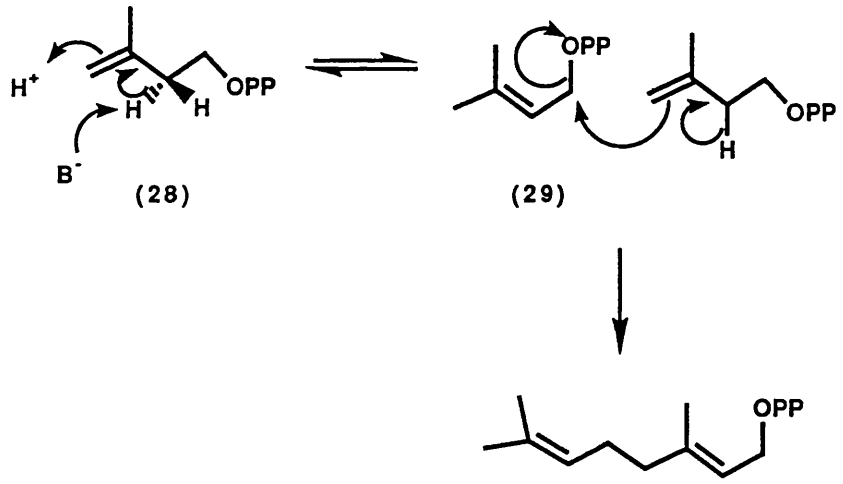
The standard C_{20} taxane skeleton (22) is a member of the terpenoid class of secondary metabolites. The biosynthesis of all terpenes has a common origin in mevalonic acid (MVA) and the isoprenoid units derived from it. The formation of MVA commences with a Claisen type condensation between two

molecules of acetyl Co-enzyme A (CoA) (23) to give acetoacetyl CoA (24)[28] (although it maybe that malonyl CoA is the chain extender as in fatty acid synthesis).[29] This then undergoes an aldol type condensation with a further molecule of acetyl CoA to yield 13-hydroxy-13-methylglutaryl CoA (25). Mevalonic acid (26) is then obtained by a two step reduction of (24) involving nicotinamide adenine dinucleotide (NADPH). Subsequently, (26) is phosphorylated by adenosine triphosphate (ATP) to give the corresponding 5-pyrophosphate (27) which is then decarboxylated with concominant dehydration to yield the isoprene building block isopentenyl pyrophosphate (IPP) (28). Consumption of one mole of ATP during dehydration suggests that the hydroxyl group is probably lost as its pyrophosphate,[28] Scheme 6.



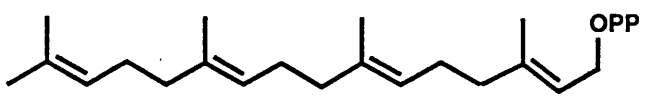
Scheme 6

The isomerisation of IPP to dimethylallyl pyrophosphate (DMAPP) (29), the other diterpenoid building block, proceeds *via* addition of a proton from the medium and abstraction of a hydrogen at C-2 by a base.[28] DMAPP is a powerful alkylating agent susceptible to nucleophilic attack at C-1 with loss of pyrophosphate, in a complex S_N1 type process. Thus IPP and DMAPP can join together in a head to tail fashion incorporating any number of C_5 units and producing an array of terpenoids most of which have the all *trans* stereochemistry, Scheme 7.

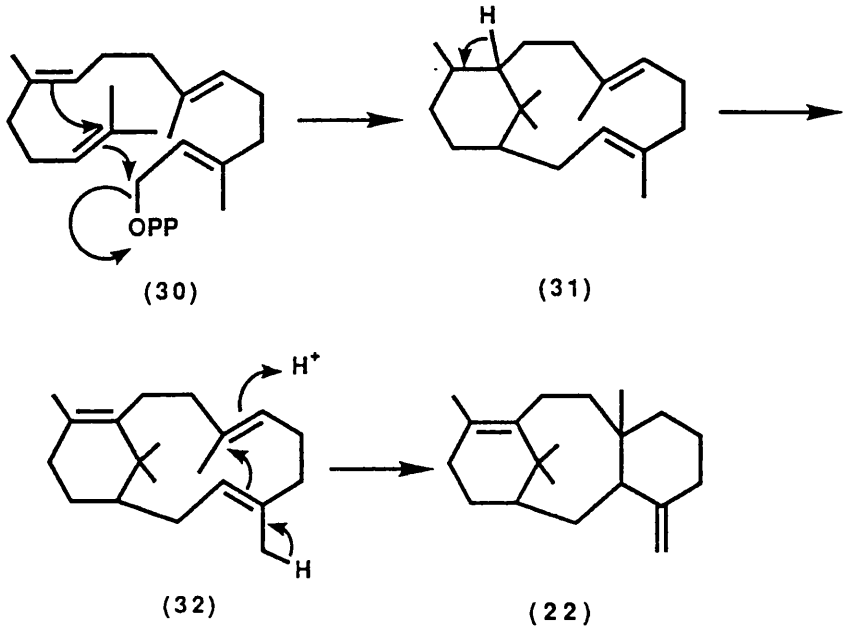


Scheme 7

The C_{20} taxane skeleton is therefore derived from the geranylgeranyl pyrophosphate (GGPP) (30). A sequence such as that outlined in Scheme 8 has been proposed for the cyclisation



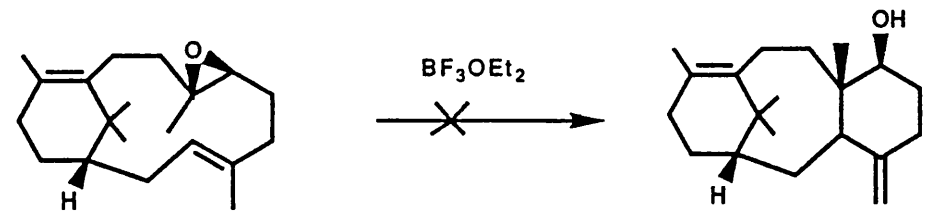
C_{20} Geranylgeranyl pyrophosphate (30)



Scheme 8

of GGPP (30) to the taxane skeleton (22). Verticillene (32) is thought to be the theoretical precursor of the taxane group.[30] However, it has been found that verticillene (32) failed to undergo cyclisation *in vitro* to form the corresponding taxane ring system.[31] Treatment of the epoxide (33) with boron trifluoride etherate failed to produce any of the tetracyclic alcohol (34) but gave the allylic alcohol (35).[31] Whilst this does not disprove the involvement of verticillene (32) in the biosynthesis, it does suggest a more subtle process.

The considerable amount of modification of the carbon framework (22) required to prepare any naturally occuring taxanes, is thought to occur by subsequent oxidation of the skeleton.



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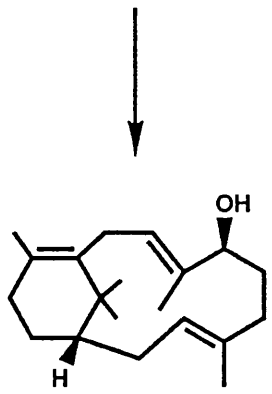
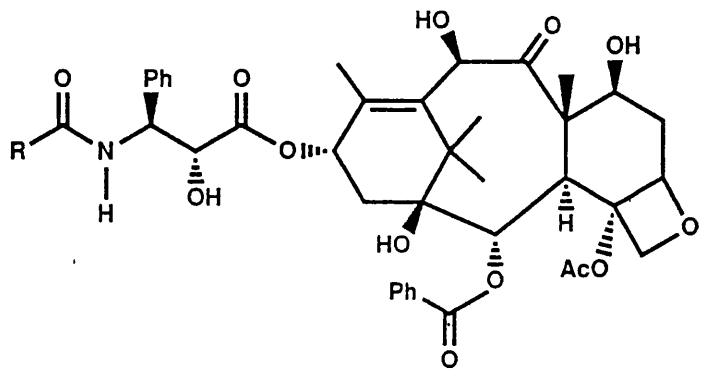


(35)

1.6 BIOLOGICAL ACTIVITY

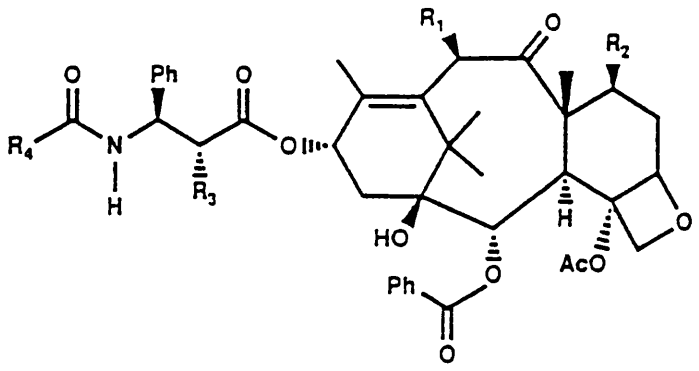
Two of the more complex taxanes isolated, taxol (3)[5] and cephalomannine (4),[6] have been shown to possess antileukemic and tumour inhibitory properties. This biological activity has invoked a considerable amount of interest in determining the mechanism for the action of taxol (3) and the functionality responsible for this activity.[32]



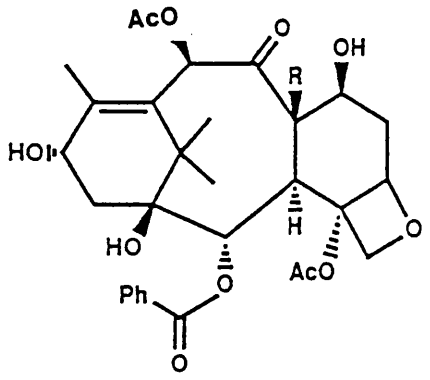
(3) R = Ph

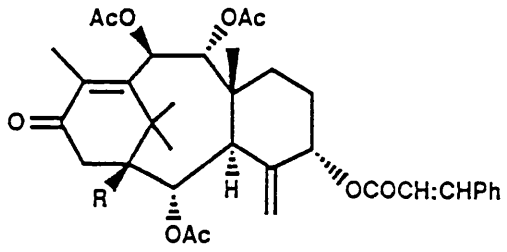
(4) R = -CCH=CHCH$_3$

Taxol is cytotoxic in a wide variety of cell culture systems[33,34,35] and blocks cell replication in HeLa cells, predominantly in the mitotic phase of the cell cycle.[36] Studies with purified microtubule protein have demonstrated that taxol promotes the assembly of tubulin into calcium stable microtubules *in vitro* in the presence or absence of GTP or microtubule-associated proteins.[37,38] Taxol binds directly to polymerised tubulin.[39,40] In addition to taxol (3), other taxanes listed in Figure 1 have been isolated from ethanolic extracts of *taxus sp.* and some , 10-deacetyltaxol (102), cephalomannine (4) and 10-deacetylcephalomannine (36) also shows cytotoxic activity comparable to taxol (3). Figure 2 tabulates the induction of microtubule assembly by the listed taxanes (3) to (2). Whilst other plant alkaloids, like vinblastine and colchicin prevent the assembly of tubulin, taxol (3) promotes the assembly of microtubules and inhibits the depolymerisation of tubulin.[6] This unique feature of taxol (3) has made it an important aid for studying the structure and function of microtubules.[42] Taxol (3) does not bind to DNA or influence actin polymerisation.[41] Although taxol (3) is currently undergoing clinical trials, its use is hampered by its insolubility in aqueous media.[43] Therefore information about the chemical structure of the drug, which relates to its biological activity, is being sought. Experiments have indicated that both an intact taxane ring and an ester side chain at position C-13 are required for cytoxicity. The hydroxyl function at C-2' seems to be required for microtubule assembly,[44] since 2'-acetyltaxol



	COMPOUND	R_1	R_2	R_3	R_4
(3)	Taxol	$OCOCH_3$	OH	OH	Ph
(38b)	10-deacetyltaxol	OH	OH	OH	Ph
(38)	2',7-diacetyltaxol	$OCOCH_3$	$OCOCH_3$	$OCOCH_3$	Ph
(38d)	7-acetyltaxol	$OCOCH_3$	$OCOCH_3$	OH	Ph
(37)	2'-acetyltaxol	$OCOCH_3$	OH	$OCOCH_3$	Ph
(38c)	2',7-diacetyl, 10-deacetyltaxol	OH	$OCOCH_3$	$OCOCH_3$	Ph
(4)	Cephalomannine	$OCOCH_3$	OH	OH	$C(CH_3)=CHCH_3$
(36)	10-deacetyl cephalomannine	OH	OH	OH	$C(CH_3)=CHCH_3$





COMPOUND	R	COMPOUND	R
(38e) Baccatin III	CH_3	(1) O-cinnamoyltaxicin-I triacetate	OH
(38b) 19-hydroxybaccatin III	CH_3OH	(2) Taxinine	H

Figure 1

COMPOUND	INDUCTION OF MICROTUBULE ASSEMBLY	RELATIVE CYTOXICITY
(3) Taxol[a]	YES	+ + + + +
(38b) 10-deacetyltaxol[a]	YES	+ + +
(38) 2',7-diacetyltaxol[a]	NO	+
(37) 2'-acetyltaxol[b]	NO	+ + +
(38d) 7'-acetyltaxol[b]	YES	+ + + +
(38c) 2',7-diacetyl, 10-deacetyl taxol[a]	NO	+ +
(4) Cephalomannine[a]	YES	+ + + +
(36) 10-deacetyl cephalomannine[a]	YES	+ +
(1) O-cinnamoyltaxicin-1 triacetate[a]	NO	C
(38b) 19-hydroxybaccatin III[a]	NO	C
(38e) Baccatin III[a]	NO	C
(2) Taxinine[a]	NO	C

a See Ref. 41
b See Ref. 44
c No activity at 10 micromols

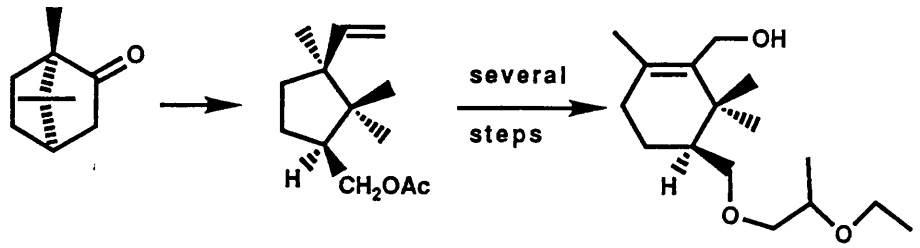
Figure 2

(37) and 2', 7-diacetyltaxol (38) do not promote microtubule assembly.

1.7 SYNTHETIC APPROACHES TO TAXANES

Since 1979 there has been an increasingly large effort in the attempt to synthesise taxanes. The effort has mainly gone into producing taxane model systems or into producing the simpler taxanes; taxucin (see Scheme 24) and taxinine (2). The assault on taxol is limited to dabbling in models containing the D-ring system, the taxol side chain or the semi-synthesis of taxol. The following review of synthetic approaches to taxanes includes many partial syntheses, and although not covered in detail, these syntheses serve as a reminder of the difficulties of involved. The syntheses in which a tricyclic structure has been achieved are covered in more detail.

In 1980 Kitagawa[45] synthesised a chiral 1, 1, 3-trimethyl cyclohexene derivative (40) as a potential key building block for the synthesis of taxane type diterpenoids, as shown in Scheme 9.



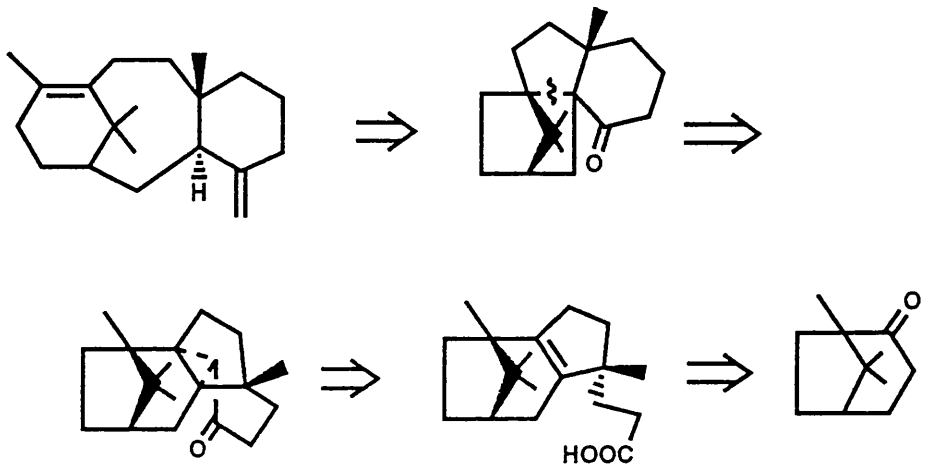
(40)

Scheme 9

The moiety (40) was prepared from D-camphor through a conversion pathway involving a novel ring enlargement

reaction of a 1, 1, 2-trimethyl cyclopentane derivative. This was the first synthesis of any taxane building block using a homochiral starting material.

Inouye carried out work[46] to produce compounds such as (41), Scheme 10, having a 5-alkyl-1, 5, 11, 11 tetramethyl tricyclo [6.2.1,$0^{2,6}$] undecane system.

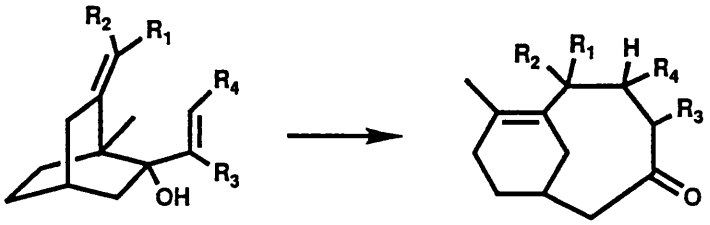


(41)

Scheme 10

The intermediate (41) was thought to be derivable from a homocamphor framework by creating a 5-membered ring on it. The target molecule proved to be elusive to Inouye and there has been no further attempt to pursue this route since 1981.

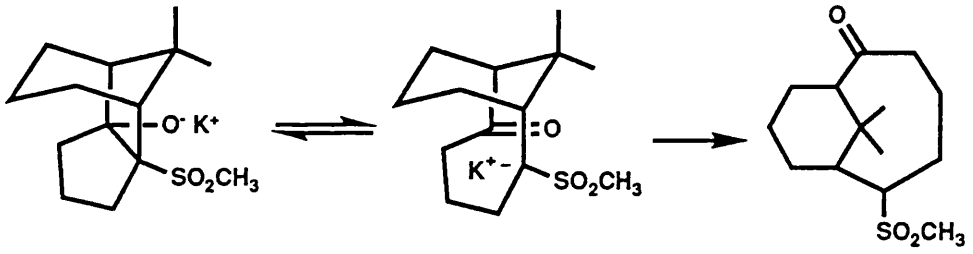
An anionic oxy-Cope rearrangement served as a key step in a novel route to the bicyclo [5.3.1] undec-7-ene ring system by White.[47] This gave the important structural element of taxane diterpenes *i.e.* (43) from (42).



(42) (43)

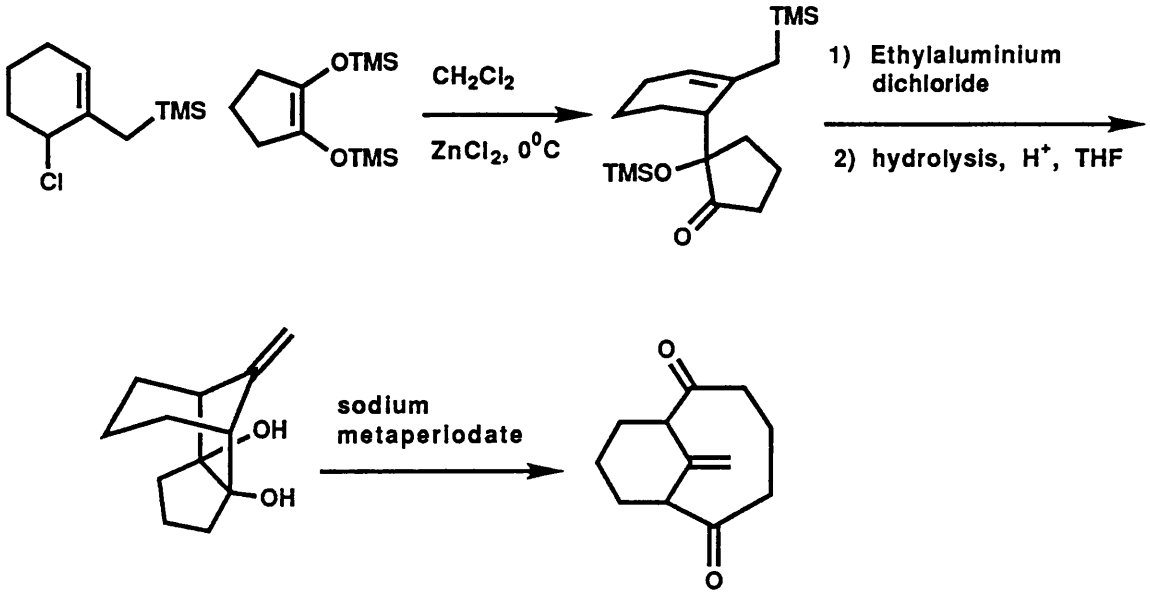
R^1, R^2, R^3 and R^4 are various alkyl chains. Further investigation into this route has been promised, but to date no further publication as to the state of the synthesis has been produced.

In the same year Trost[48] created the ring system (44) using the ability of some bifunctional reagents containing electrophilic and nucleophilic centres not to self annihilate.



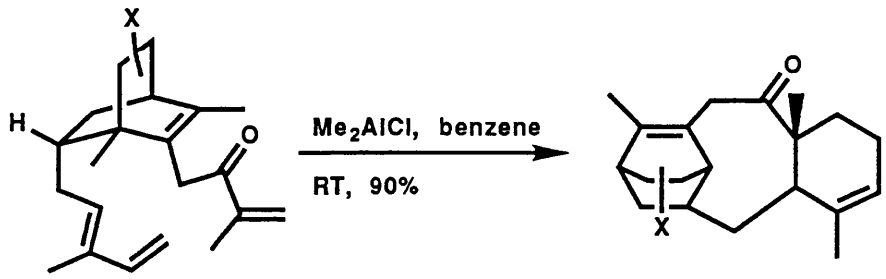
(44)

This investigation was more interested in equilibrium ratios of ion pairs than in a synthetic approach to taxanes. Trost[49] used this approach again in 1984 to produce (45).



(45)

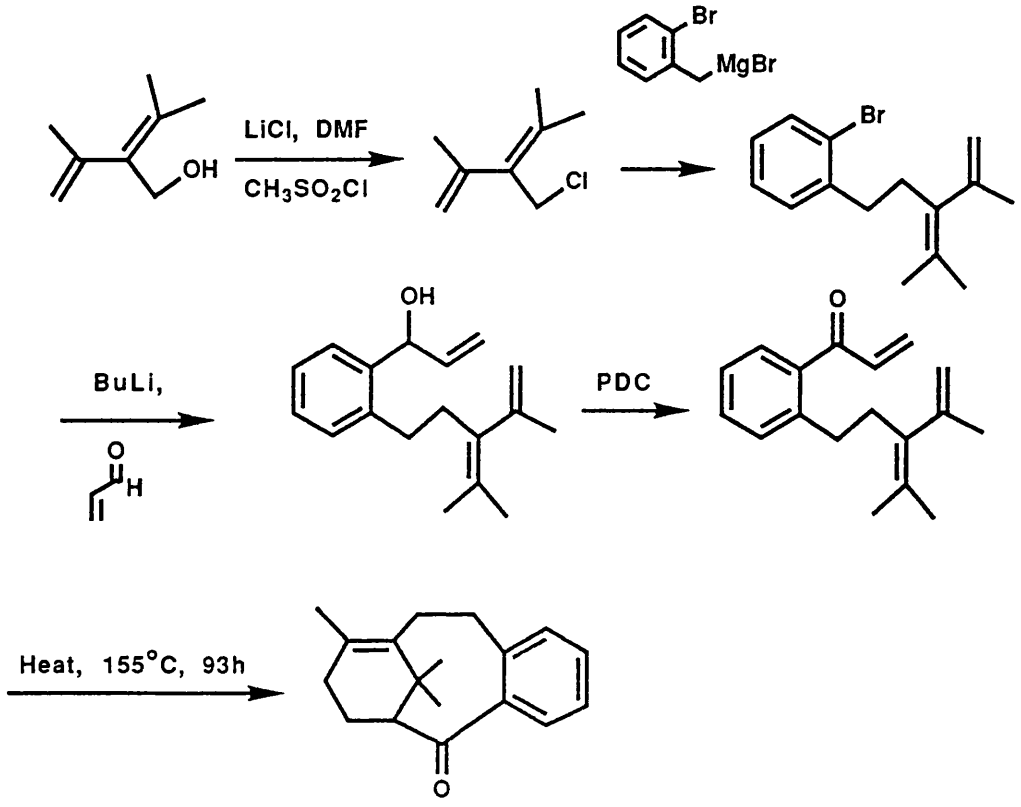
In 1983 Sakan[50] successfully carried out a single step stereocontrolled synthesis of a taxane model system.



(46)

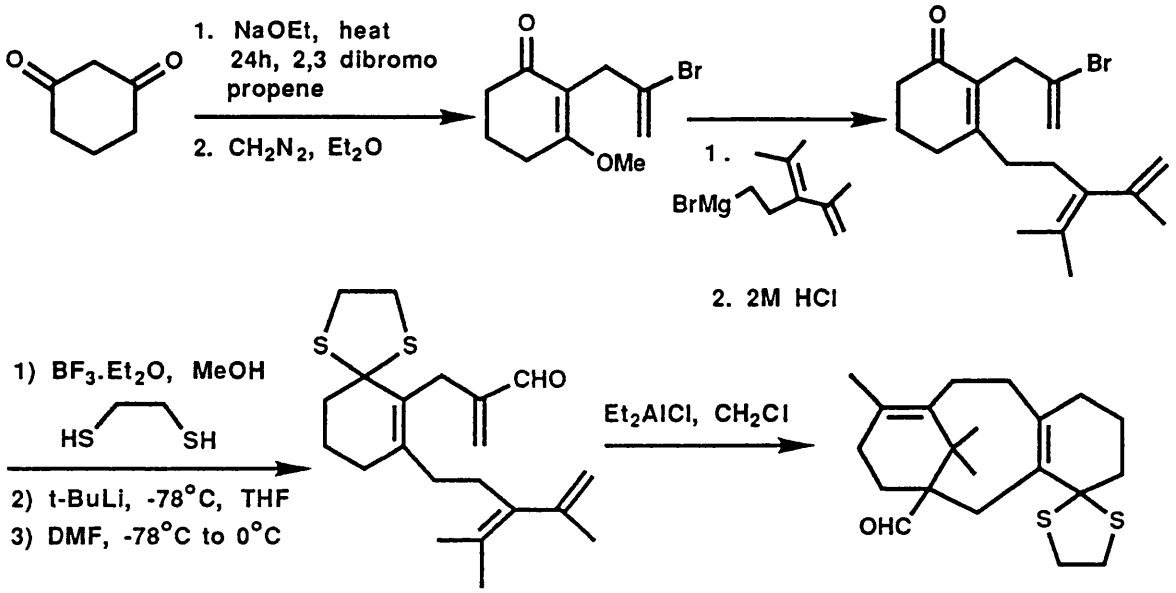
With provision of an appropriate functionality X, the bicyclo [2.2.2] octene system of (46) can be considered as synthetically equivalent to the taxane A ring. Further work is said to be continuing in an attempt to produce a total synthesis of taxinine (2) but communications as to the state of the synthesis have not as yet been forthcoming.

The first synthesis of a skeleton which bore close resemblence to that of a natural taxane was carried out by Shea and Davis.[51] The reaction pathway is outlined in Scheme 11.



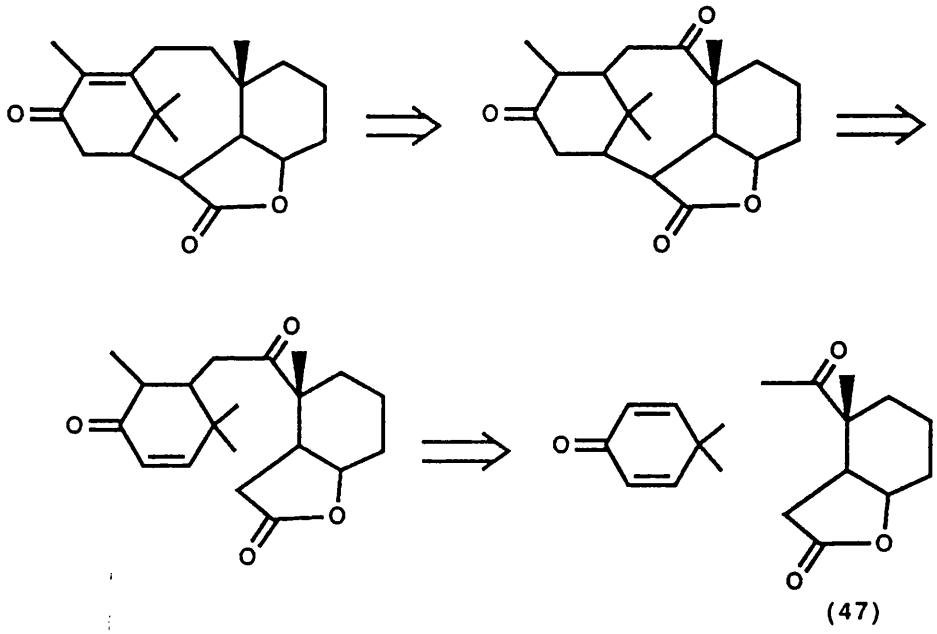
Scheme 11

Subsequently it was reported that the cyclisation could be better achieved using Lewis acid catalysis and milder reaction conditions.[52] Further work by Shea,[53] in 1988, on intramolecular Diels-Alder approaches to taxane skeletons resulted in an extremely short and simple route to taxane structure precursors. The route is detailed in Scheme 12.



Scheme 12

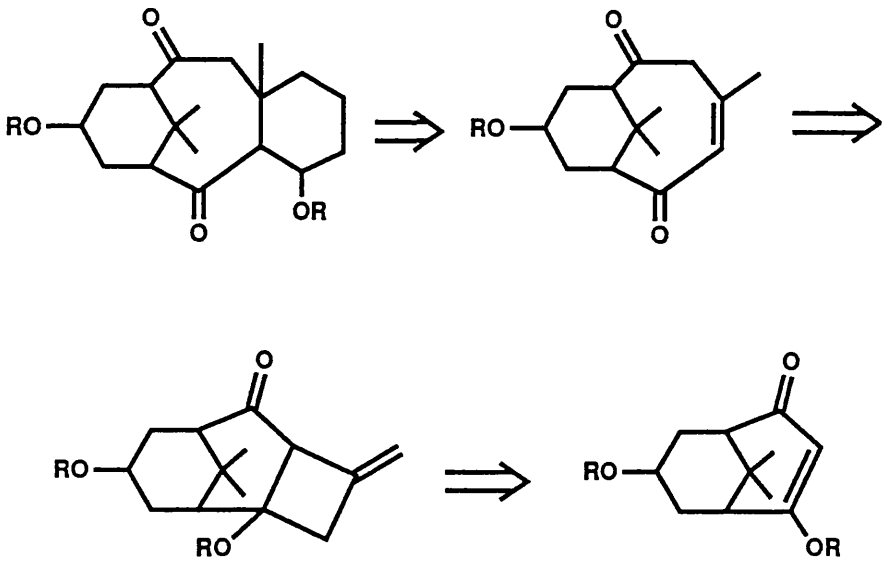
Fetizon[54] attempted to synthesise a taxane skeleton using the retrosynthetic analysis described in Scheme 13.



Scheme 13

The synthesis of the fragment (47) was successful. However several attempts to couple (47) and successfully cyclise with a second fragment failed. The approach has been

abandoned by Fetizon in favour of proposed routes published in 1986[55,56] based on a [2+2] photocyclo addition annulation procedure according to the retrosynthetic analysis detailed in Scheme 14. This route was aimed at securing a model system in which the synthesis of the functionalised C-ring of the taxane series could be explored.

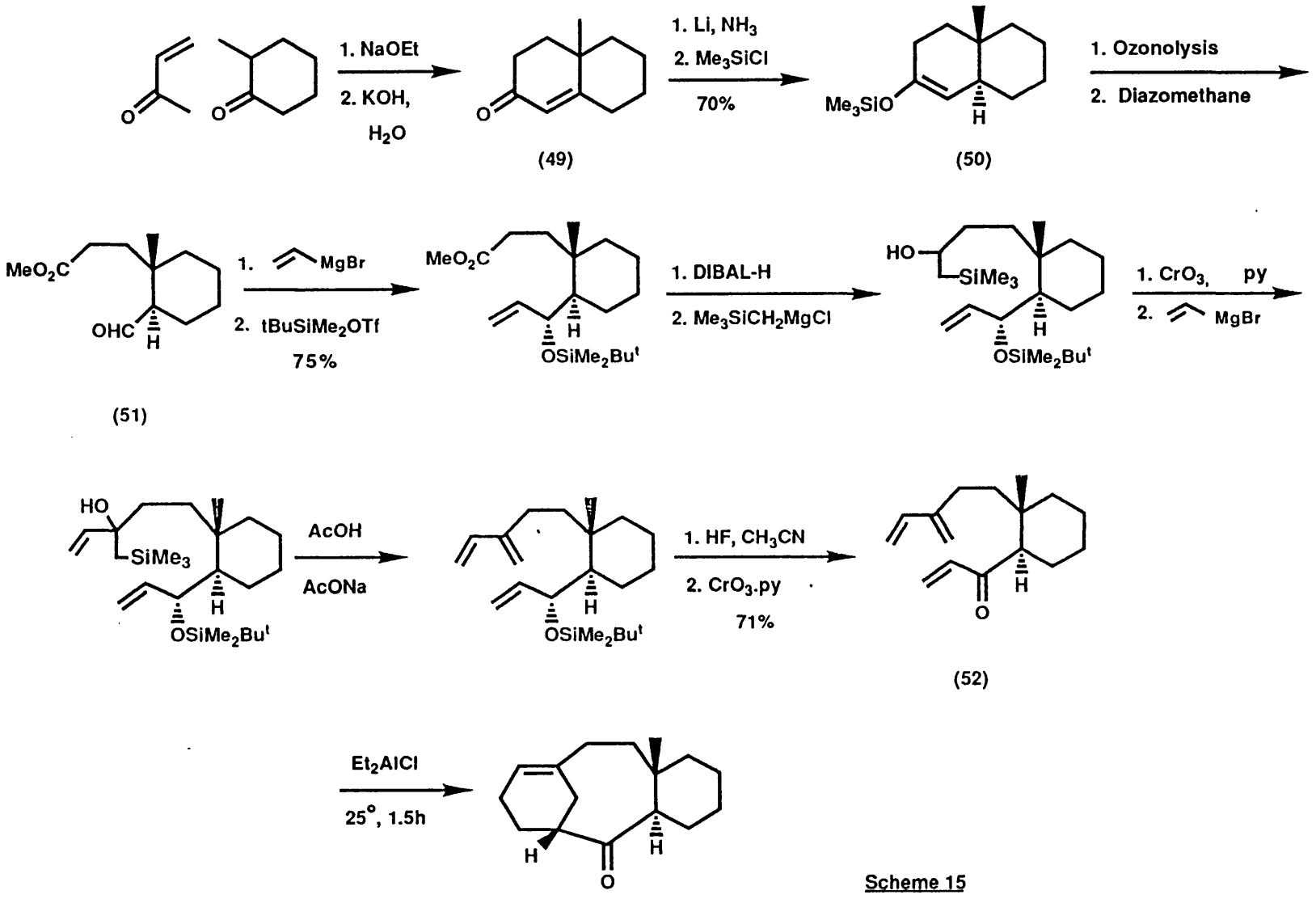


(48)

Scheme 14

The publication reports the successful synthesis of (48), but no further results concerning this route have been published to date.

Work carried out here at Leicester[57] makes use of an intramolecular Diels-Alder reaction to produce the taxane skeleton. The Diels-Alder approach is of direct relevance, as is the modified version described later (pg 42), because the work found in this thesis is a continuation of this approach. The trienone (52) was constructed according to Scheme 15. The crucial *trans* stereochemistry of decalin

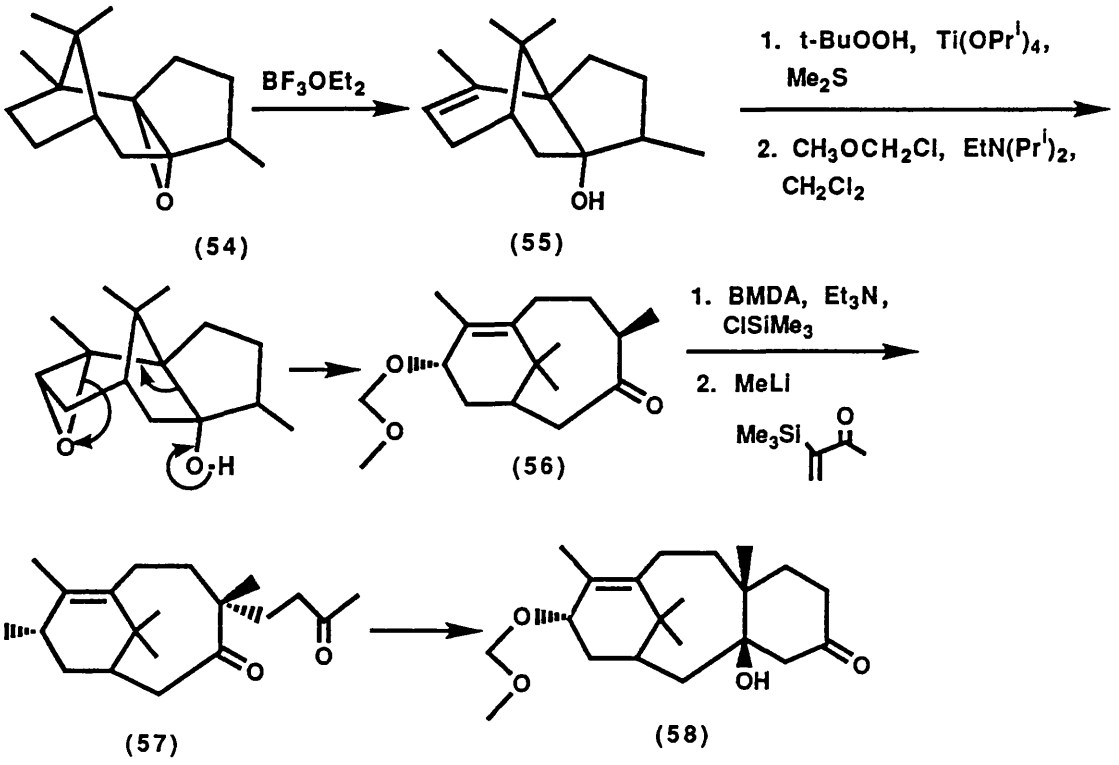

1. NaOEt
2. KOH,
H_2O
1. Li, NH_3
2. Me_3SiCl
70%
1. Ozonolysis
2. Diazomethane
(49)
(50)
MeO_2C
OHC
H
1. MgBr
2. $tBuSiMe_2OTf$
75%
$OSiMe_2Bu^t$
1. DIBAL-H
2. Me_3SiCH_2MgCl
HO
$SiMe_3$
1. CrO_3, py
2. MgBr
(51)
AcOH
AcONa
1. HF, CH_3CN
2. CrO_3.py
71%
O
(52)
Et_2AlCl
25°, 1.5h
(53)

Scheme 15

(50) was acheived by use of a lithium in ammonia reduction of the enone (49) using a method developed by Stork *et al.*[58] Ozonolysis of the enol ether (50) led to cleavage of the double bond and treatment with diazomethane gave the ester aldehyde (51). By reacting (51) with vinyl Grignard reagent at low temperature it was possible to react the aldehyde functionality in preference to the ester so producing the corresponding allylic alcohol, which was subsequently protected. The construction of the diene involved a Peterson elimination[59] leading to the trienone (52), after deprotection and oxidation of the allylic alcohol. The Diels-Alder cyclisation of (52) was successfully achieved at room temperature to give (53). The relative stereochemistries of C-1, C-3, and C-8 were confirmed by X-ray analysis and have been found to be the same as those for the taxane natural products.

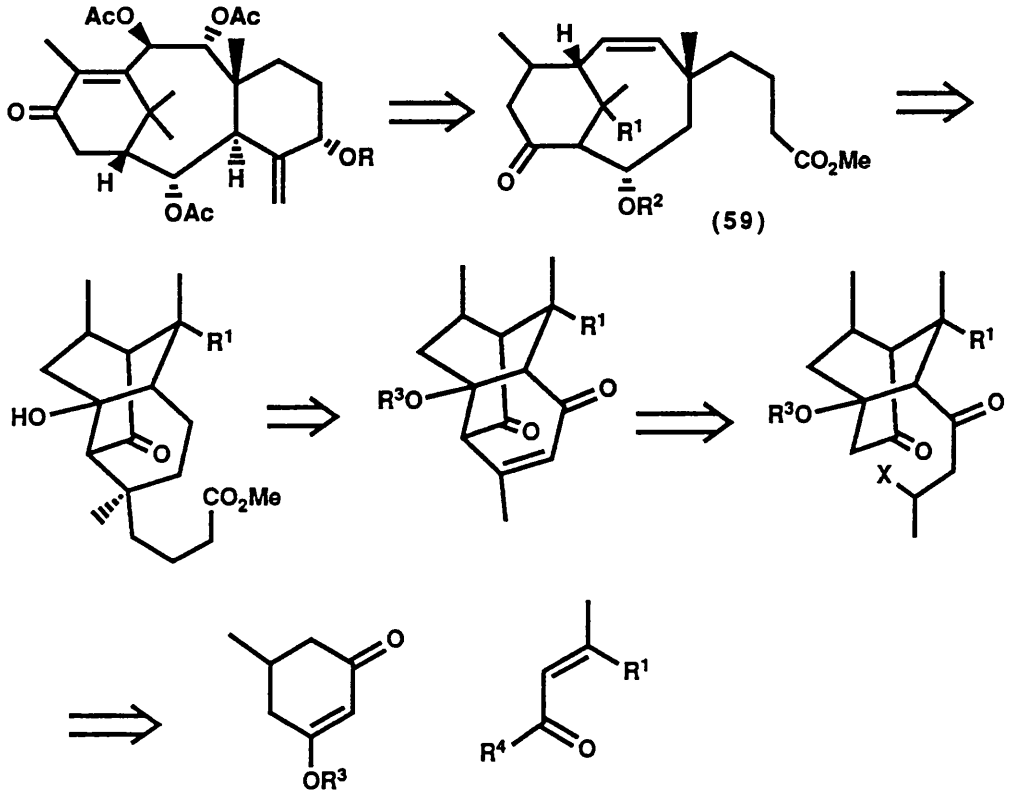
An alternative strategy published by Holton[60] produce a more advanced synthesis. This sequence gave rise to the tricyclic alcohol (58) and the route is outlined in Scheme 16. β-Patchouline oxide (54) was used as the starting material. The first important step in the synthesis involved the rearrangement of the alcohol (55) to form the A and B rings of the taxane skeleton. Treatment of the ketone (56) with bromomagnesium diisopropylamide (BMDA),[61] trimethylsilyl chloride and triethylamine gave exclusively the more substituted enol ether. The enolate could be regenerated by reaction with methyllithium and and addition of 3-trimethylsilyl-3-buten-2-one yielded the diketone

(57). An intramolecular aldol condensation of (57) using BMDA then gave the alcohol (58).



Scheme 16

Yamada[62] approached the taxane skeleton using the retro-synthetic analysis outlined in Scheme 17.

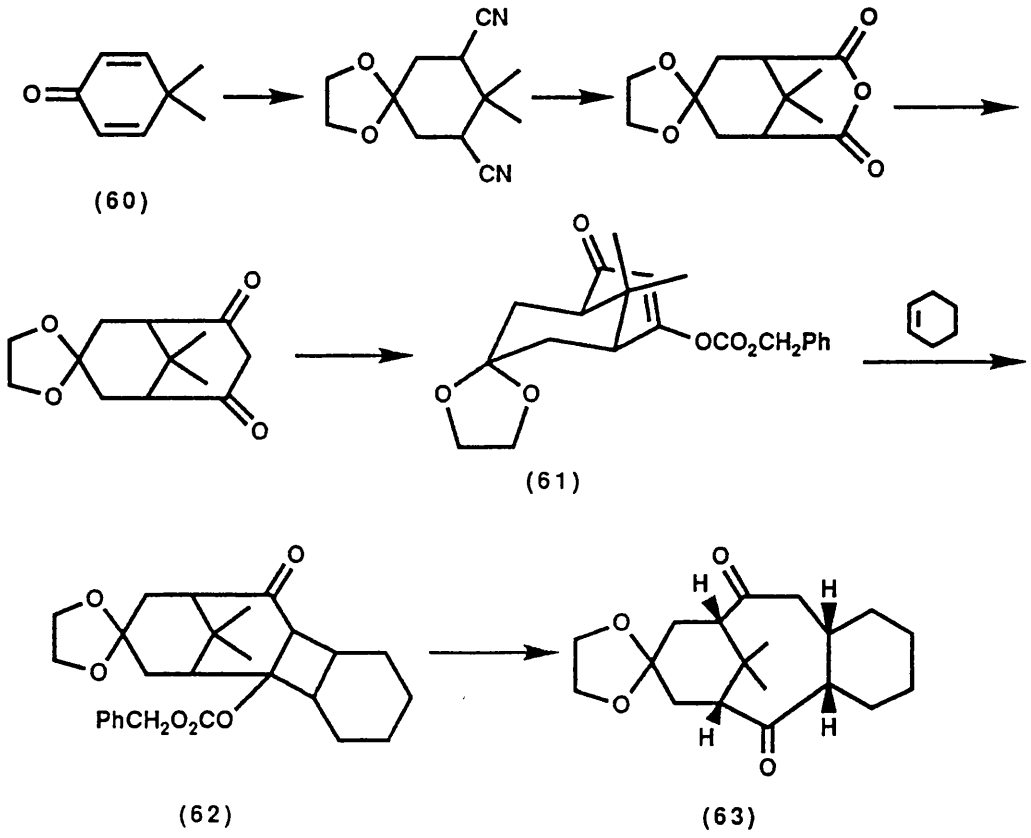


Scheme 17

This is a promising synthesis. The thirteen steps which are required to obtain (59) have not been detailed here. All the steps to (59) went in yields of 70% or more. The reaction pathway is still under developement by Yamada as a potential route to taxane molecules.

A report by Neh *et al*[63] used a photochemical [2+2] cycloaddition in the key step *en route* to forming the eight membered ring. The enol benzoate (61) was prepared as outlined in Scheme 18 from cyclohexadienone (60). The [2+2] cycloaddition of (61) with cyclohexene was initiated by irradiation with a mercury lamp and furnished the tetracyclic ketone (62). Hydrogenolysis of the tetra cyclic ketone (62) led to the formation of the

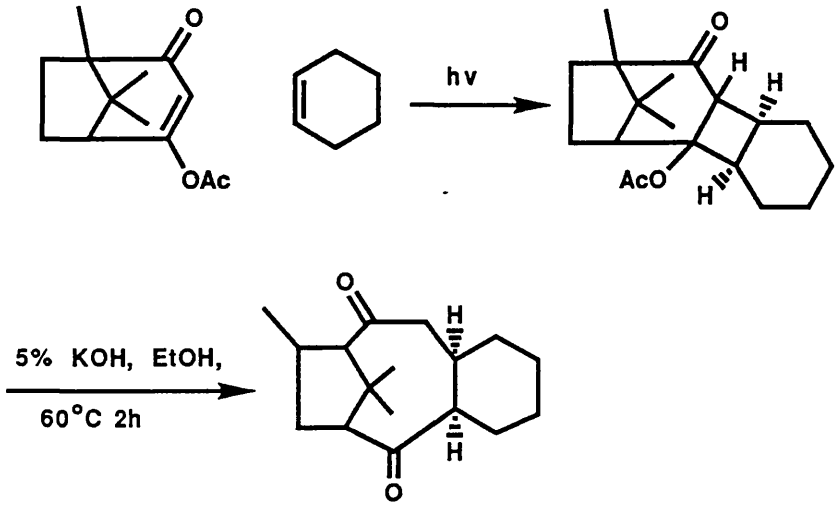
corresponding alcohol which upon treatment with ethanolic potassium hydroxide solution, underwent a retro-aldol reaction to give the tricyclic dione (63). This sequence provides a novel entry into the tricyclic taxane skeleton with a considerable amount of useful functionality in the A and B rings. However, the *cis* stereochemistry of the C ring junction is not that observed in the natural taxanes and the bridgehead double bond is absent.



Scheme 18

Berkowitz[64] applied photochemical reactions to the inter and intramolecular cycloaddition of various cyclohexenes with homocamphorquinone derivatives to generate a model for

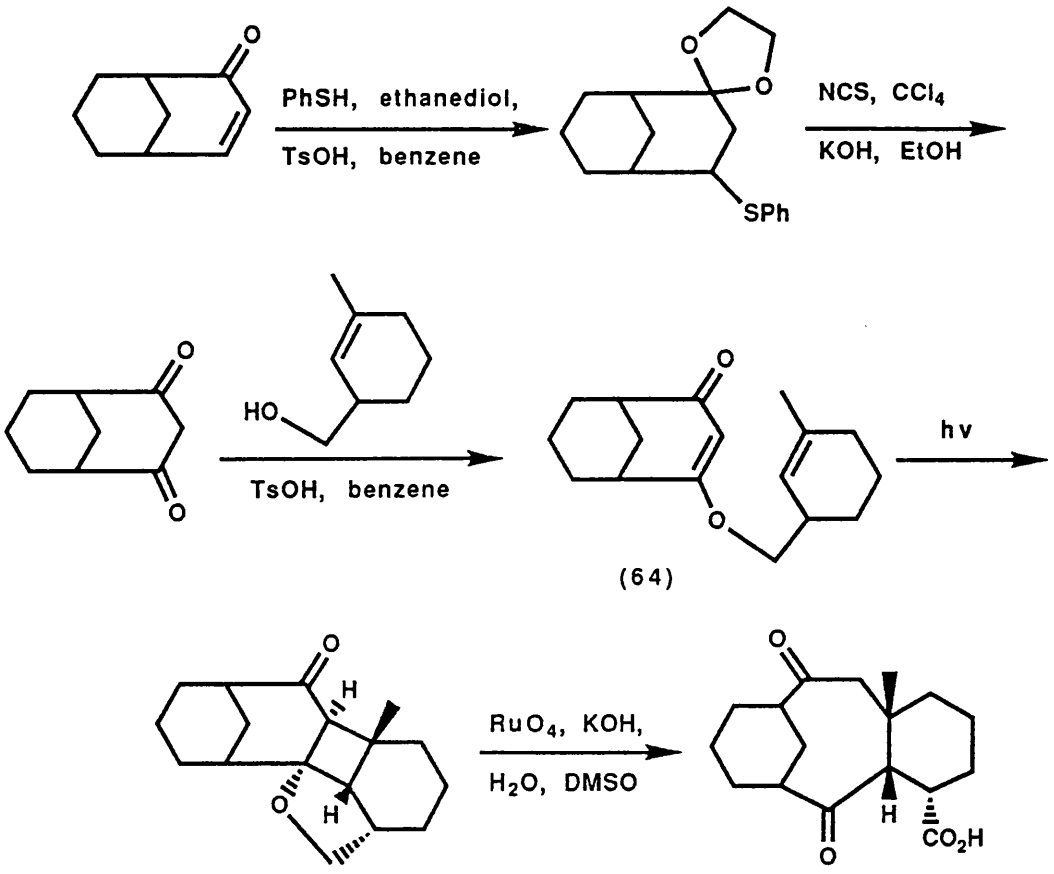
the A, B and C ring of taxanes. A summary of this approach is shown in Scheme 19.



Scheme 19

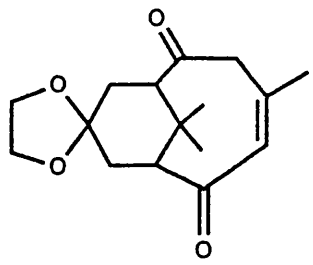
This route is not intended as a synthetic approach to taxanes.

Another intramolecular photo [2+2] cycloaddition has been reported by Kojima.[65] Photocycloaddition of a 4-(3-methyl-2-cyclohexenyl) methoxybicyclo [3.3.1] non-3-en-2-one (64) followed by oxidation with ruthenium tetroxide and alkaline hydrolysis gave 8-methytricyclo [9.3.1,$0^{3,8}$] pentadecan-2, 10-dione-4-carboxylic acid, a (±)-3, 3-trinortaxane derivative (65), as described in Scheme 20.



Scheme 20 (65)

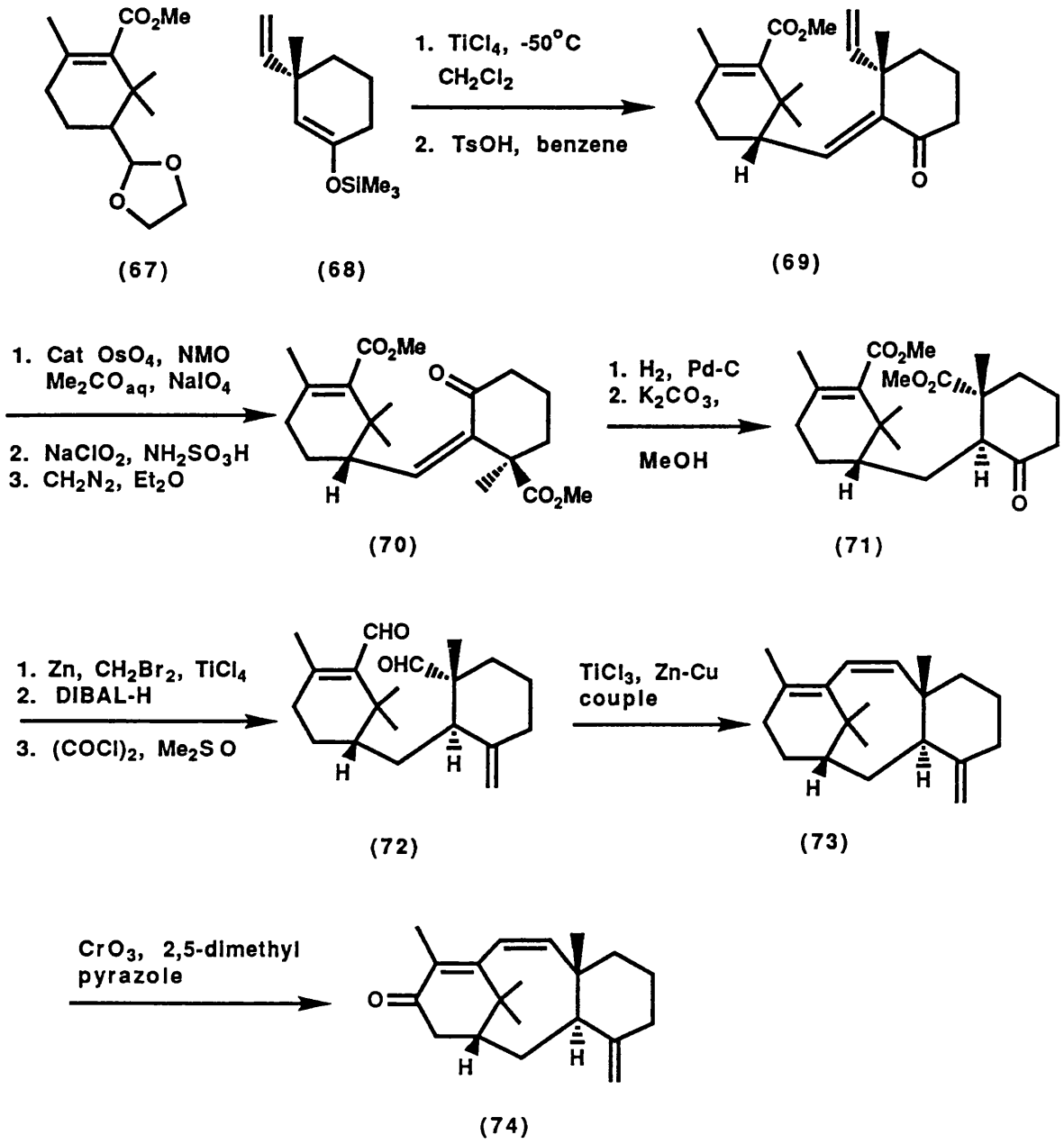
However, whilst again this type of synthesis provides a good method for producing the tricyclic framework it still gives a *cis* C-ring junction. The [2+2] photocyclisation was last applied by Blechert[66] who used it effectively to produce the A and B rings of the taxane skeleton (66).



(66)

The [2+2] photochemical cycloaddition route has not been used since 1986, which is indicative of its major flaw as a viable route to taxanes.

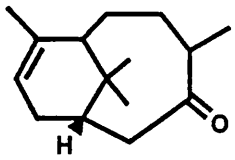
A synthesis of the complete carbon framework contained in taxanes was reported by Kende *et al.*[67] The important steps in this synthesis involved a directed aldol condensation between the acetal (67) and the silyl enol ether (68) to yield, after the elimination of water, the enones (69), Scheme 21. The enones (69) were formed as a 2:1 mixture of two Z and two E isomers which had to be separated after their transformation to the diester (70). Hydrogenation of (70) initially gave the wrong stereochemistry at C-3 (taxane numbering), but epimerisation gave a mixture of epimers in a ratio of 4:1 in favour of the desired isomer (71). The formation of the eight membered ring was achieved by a low valent titanium coupling reaction[68] of the dialdehyde (72) to produce the trienone (73).[67] The fact that the allylic oxidation of the triene (73) with chromium trioxide and 2, 5-dimethylpyrazole[69] gave the trienone (74), proved interesting since this type of oxidation could later be applied in the approach to the tricyclic skeleton being taken in this thesis. This sequence provided the first total synthesis to a taxane with stereochemically correct framework. However, poor stereochemical control in the formation of the enone (69) must restrict the viability of this route for further expansion.



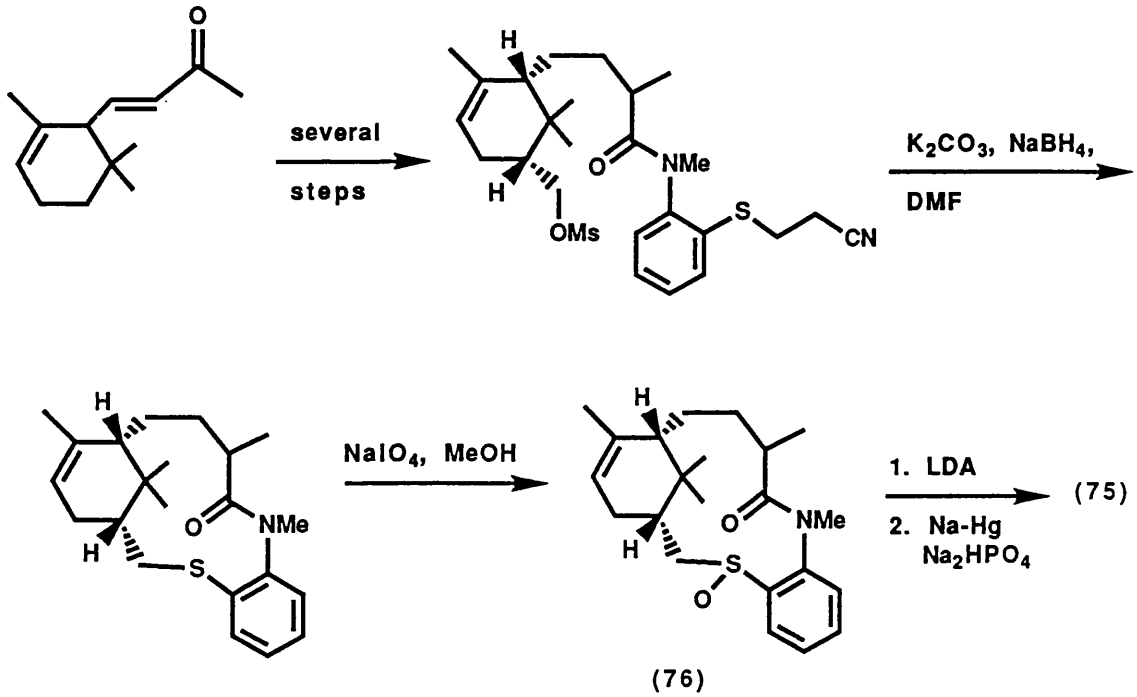
Scheme 21

Ohtsuka and Oishi[70] synthesised bicyclo [5.3.1] undecenone (75) whose structure corresponded to the A and B rings in the taxane diterpenes. The eight-membered ring was constructed by a base-induced intramolecular cyclisation of a twelve-membered lactam sulphoxide (76). They used a novel intramolecular cyclisation process which they had

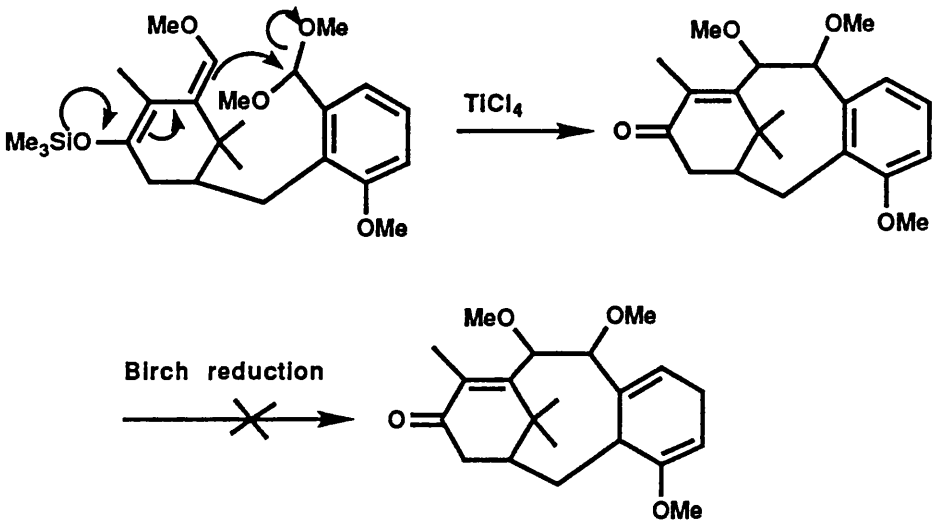
developed earlier and attempted direct closure of the eight membered ring from a suitable precursor.



(75)



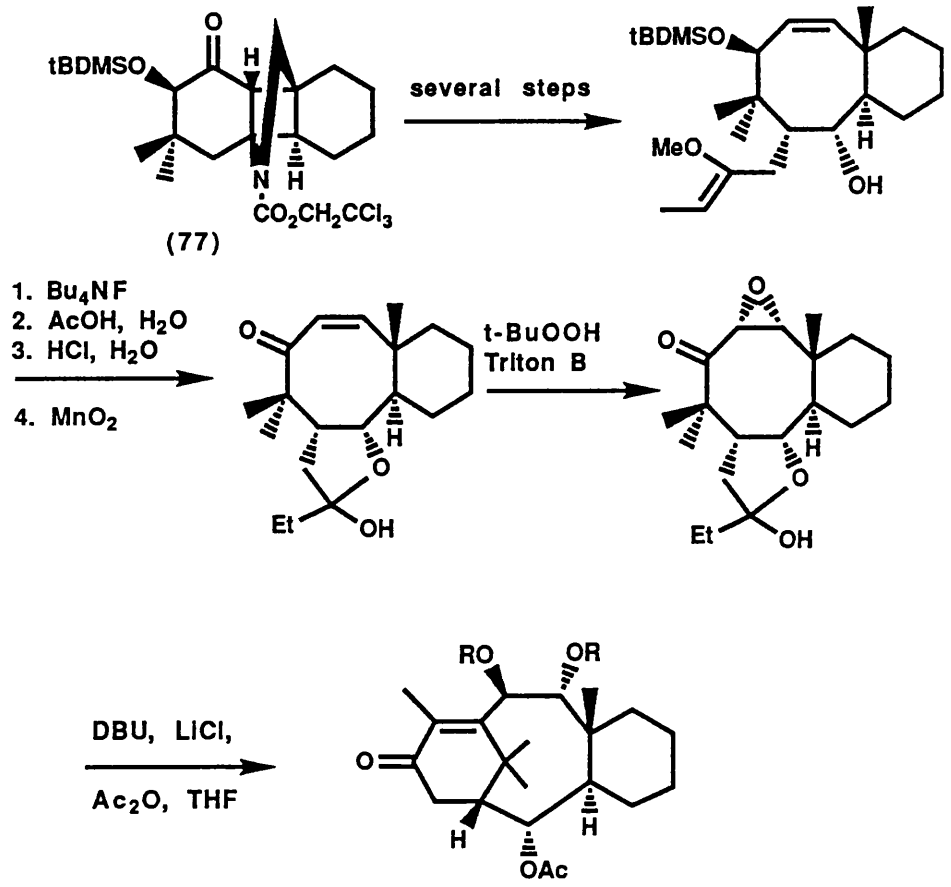
Kuwajima[71] used a silicon-accelerated organic reaction to try and achieve a taxane skeleton along the lines described in Scheme 22.



Scheme 22

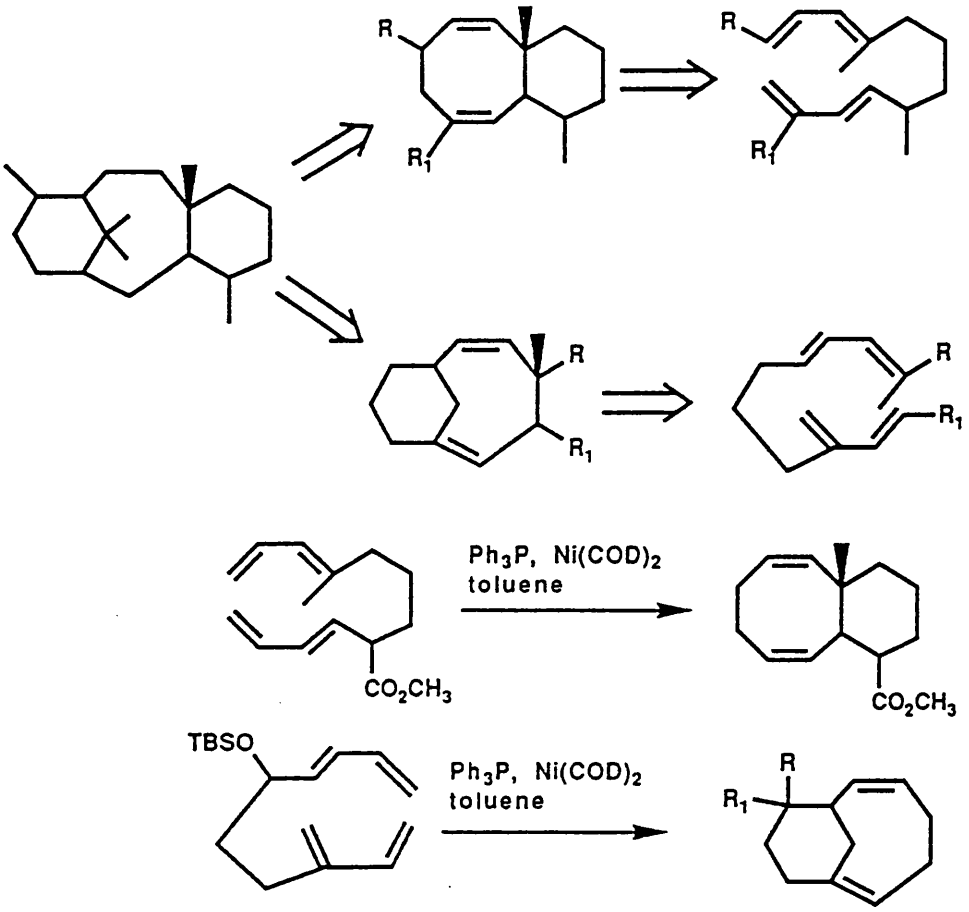
Kuwajima was unable to reduce the aromatic ring and has since abandoned the route.

Building on previous work,[72,73,74] Swindell and Patel[75] have constructed the tricyclic taxane ring structure with a fully functionalised A and B ring system as required for taxinine (2), through a series of stereoselective operations on the eight membered ring including annulation of the A ring through a novel tandem aldolisation-Payne rearrangement process starting from (77).



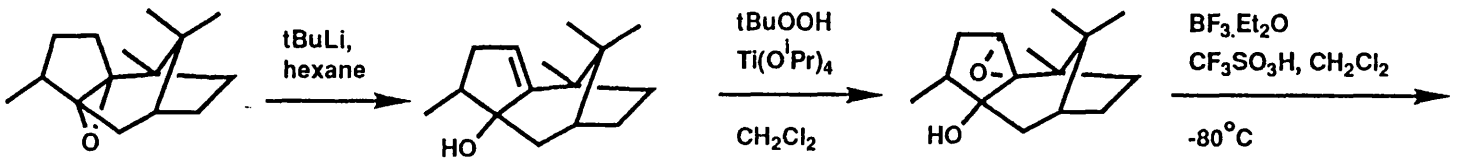
This synthesis, along with that of Taxucin by Holton,[76] is the most advanced synthesis towards taxinine to date.

A successful application of a nickel-catalysed intramolecular [4+4] cycloaddition of bis-dienes to the preparation of both the AB and BC ring systems of taxane diterpenes was carried out by Wender.[77] The cycloaddition methodology provides the basis for a general and efficient route to angularly alkyl substituted bicyclo [6.4.0] dodecanes and bicyclo [5.3.1] undecanes. The general approach is described in the Scheme 23.

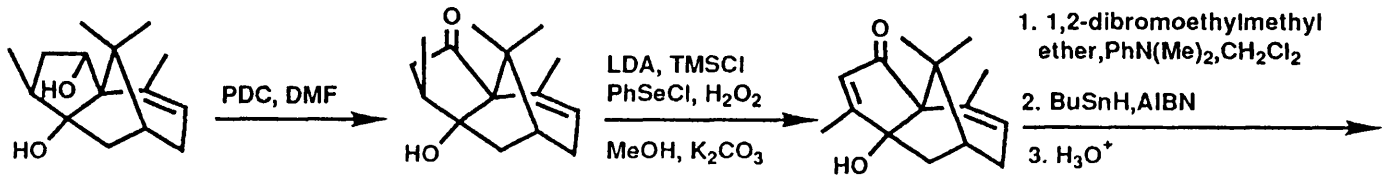


Scheme 23

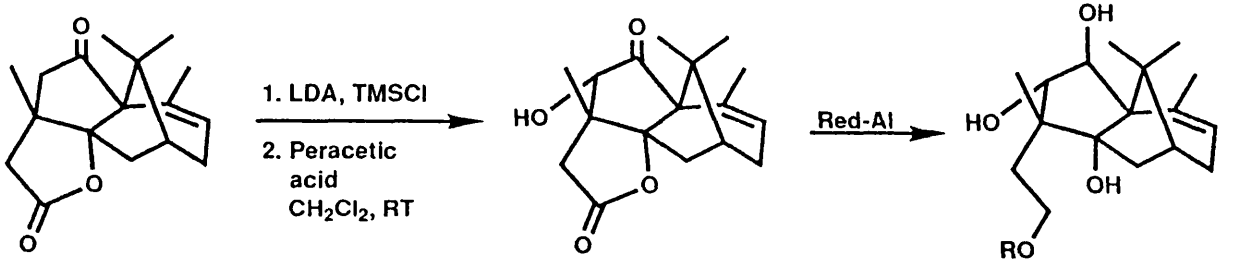
A paper published by Holton[76] in 1988 described the first total synthesis of a naturally occurring taxane, albeit the enantiomer, (-) Taxucin (94). This synthesis is described in full in Scheme 24. The approach is similar to that used by Holton[60] to synthesise a general taxane skeleton in 1984. The synthesis starts from the readily available (-) β-patchoulene oxide (79) which upon treatment with t-butyllithium gave the allylic alcohol (80). (80) Underwent epoxidation to give the diol (81). Oxidation of the diol furnished ketone (82) which was converted to enone (83). The hydroxy enone reacted with 1,2-dibromoethyl methyl ether to provide a diastereomeric mixture of bromo acetals



(79) (80)

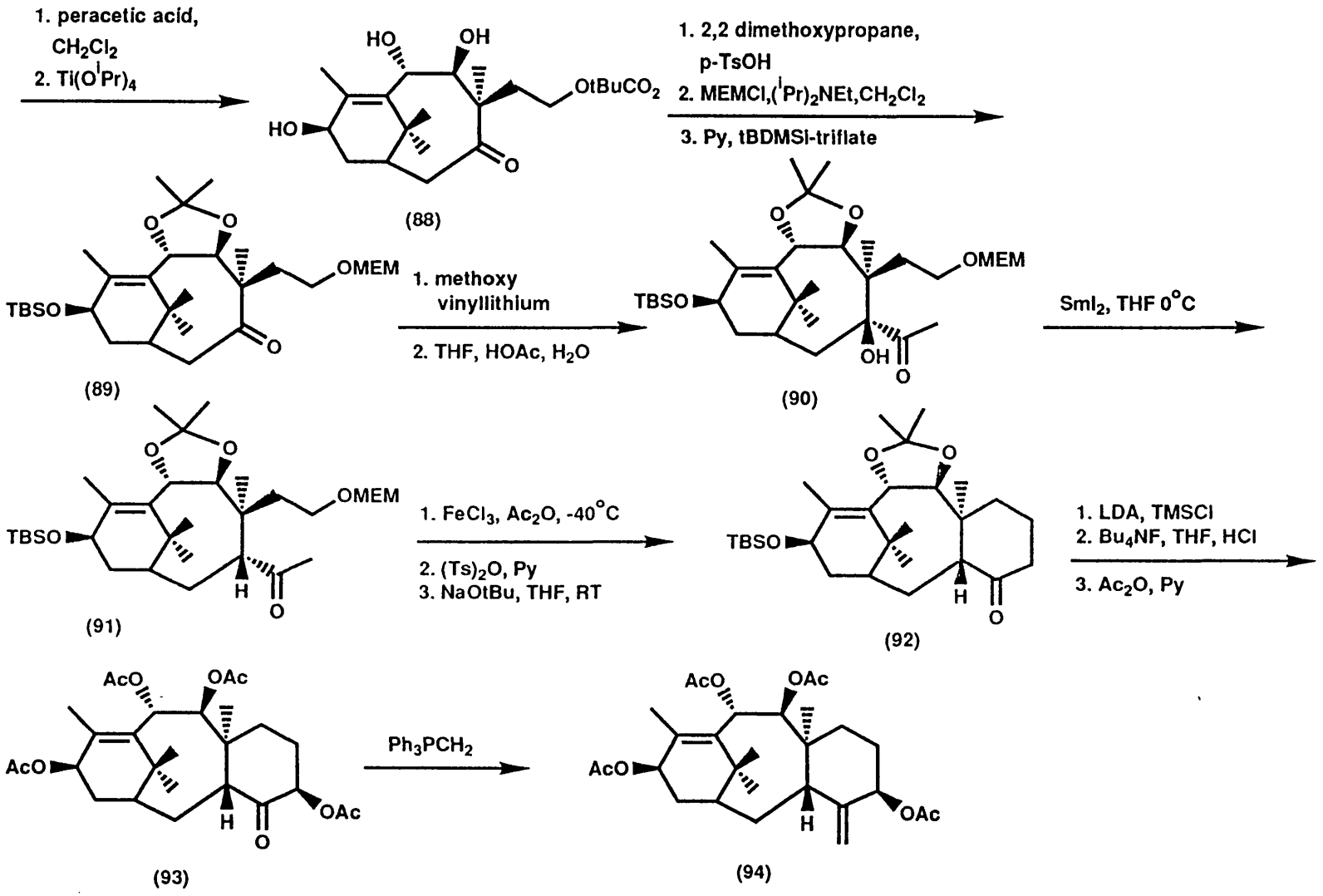


(81) (82) (83)



(84) (85)

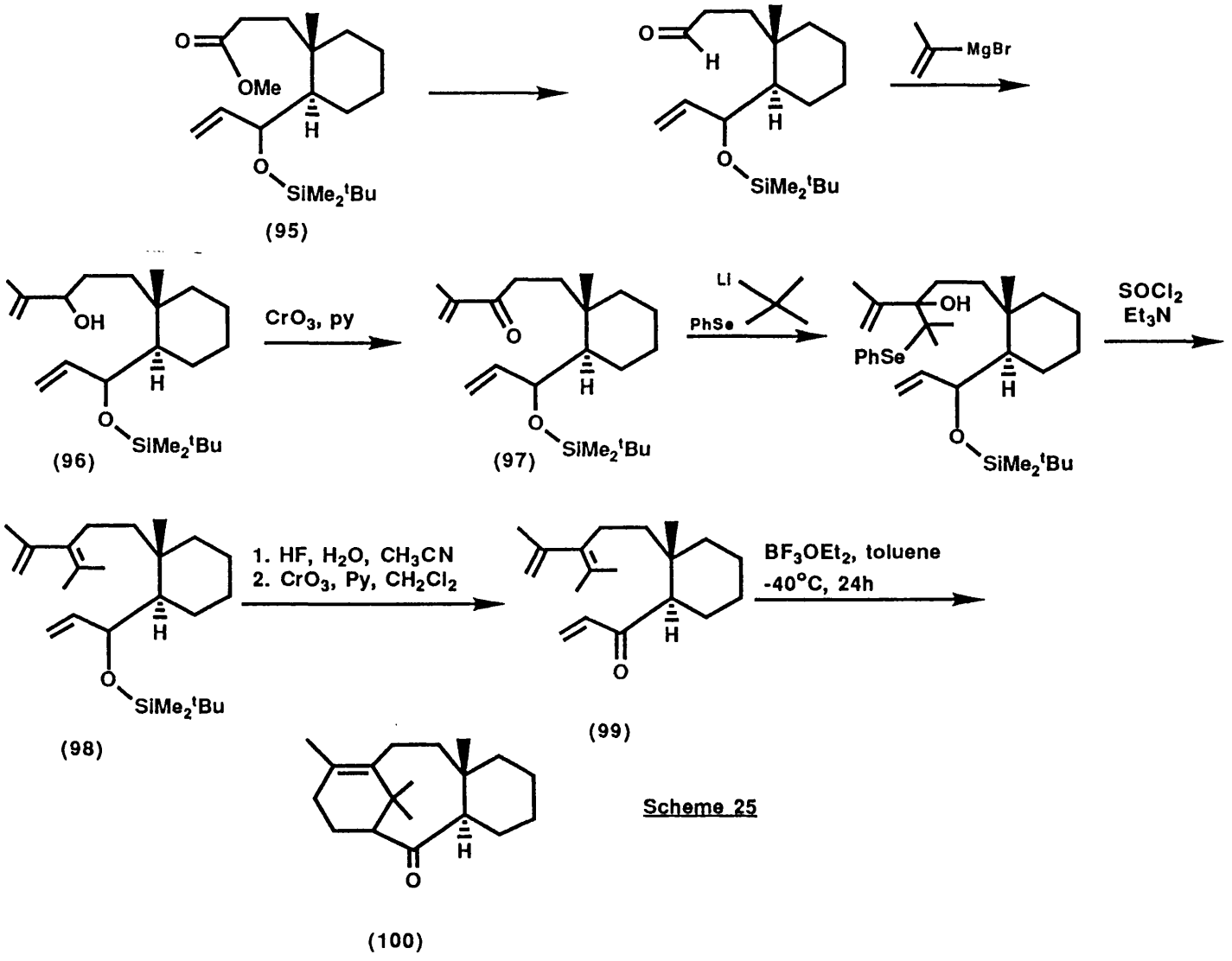
(86) R = H
(87) R = CO$_2$tBu


1. peracetic acid,
CH2Cl2
2. Ti(OiPr)4
HO
OH
OtBuCO2
HO
O
(88)
1. 2,2 dimethoxypropane,
p-TsOH
2. MEMCl,(iPr)2NEt,CH2Cl2
3. Py, tBDMSi-triflate
OMEM
TBSO
O
O
O
(89)
1. methoxy
vinyllithium
2. THF, HOAc, H2O
OMEM
TBSO
OH
O
(90)
SmI2, THF 0°C
OMEM
TBSO
H
O
(91)
1. FeCl3, Ac2O, -40°C
2. (Ts)2O, Py
3. NaOtBu, THF, RT
TBSO
H
O
(92)
1. LDA, TMSCl
2. Bu4NF, THF, HCl
3. Ac2O, Py
AcO
OAc
AcO
H
OAc
O
(93)
Ph3PCH2
AcO
OAc
AcO
H
OAc
(94)

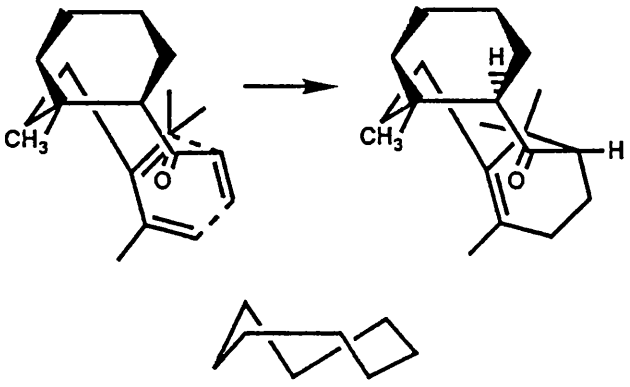
Scheme 24

which upon radical cyclisation, hydrolysis and oxidation gave the keto lactone (84). Stereospecific introduction of the C-9 and C-10 trans diol functionality was readily accomplished due to the severe steric encumberance of the β-face of (84) and (85) by the geminal methyl groups. The silyl ether of (84) reacted with peracetic acid to give the hydroxy ketone (85). Reduction of (85) gave the tetraol (86) which could be converted to the monopivalate (87) using t-BuCOCl and pyridine. (87) Could be converted to (88) using a large excess of anhydrous peracetic acid and subsequent treatment with $Ti(O^iPr)_4$. Protection of (88) provided (89). The introduction of C-4 and C-5 was accomplished by the addition of α-methoxyvinyl lithium[78] to (89) followed by *in situ* hydrolysis to give the hydroxy ketone (90). The observed stereospecificity is due to a novel directing effect exerted by the MEM ether protecting group. Subsequently the hydroxy ketone (90) was reduced to the ketone (91). A series of reactions on ketone (91) resulted in (92). Stereospecific oxidation of the silyl enol ether of (92) followed by deprotection and acetylation provided the tetraacetoxy ketone (93). Finally olefination of (93) gave the enantiomer of natural (+)-taxucin, (-)-taxucin (94). Holton states that in view of Buchi's preparation of (-) β-patchoulene oxide (79) from (+) camphor[79] and the ready avalability of (-) camphor, that this route describes a method for the naturally occurring (+) taxucin and that studies are now being directed towards the synthesis of taxol (3).

In 1989 Jenkins[80] produced a route to the taxane skeleton based on previous work.[57] This route is described in Scheme 25. Using the ester (95) produced earlier,[79] selenium-directed chemistry was used to build a diene. Addition of the propenyl Grignard reagent to the aldehyde produced on reduction of the ester (95), *i.e.* (96). Oxidation of (96) afforded (97). Reaction of $Me_2C(SePh)_2$ with n-butyllithium, following a literature procedure,[81] gave $LiCMe_2SePh$ which added to (97) in a 30 to 40% yield. Elimination was achieved using thionyl chloride to produce (98). Deprotection and oxidation followed by a low temperature Diels-Alder furnished the taxane skeleton (100). The stereochemistry of the intramolecular Diels-Alder reaction (99) to (100) is shown in Figure 3 and 4. The eight-membered ring is formed in a chair-boat conformation. N.m.r nuclear Overhauser effects were used to assign the stereochemistry of (100). The strongest evidence in favour of the structure (100) is the n.O.e. between H-3 and the C-12 methyl, Figure 5. This effect would not be present in the alternative Diels-Alder cyclisation product obtained *via* the twist chair-boat conformation shown in Figure 3.

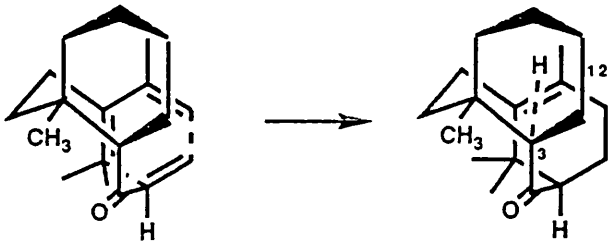

OMe
SiMe2tBu
(95)
MgBr
OH
CrO3, py
(96)
(97)
Li
PhSe
PhSe
SOCl2
Et3N
1. HF, H2O, CH3CN
2. CrO3, Py, CH2Cl2
BF3OEt2, toluene
-40°C, 24h
(98)
(99)
(100)

Scheme 25



twist chair-boat

Figure 3



boat-chair

Figure 4

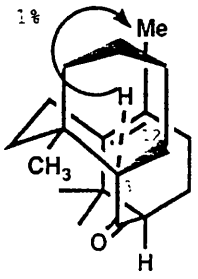
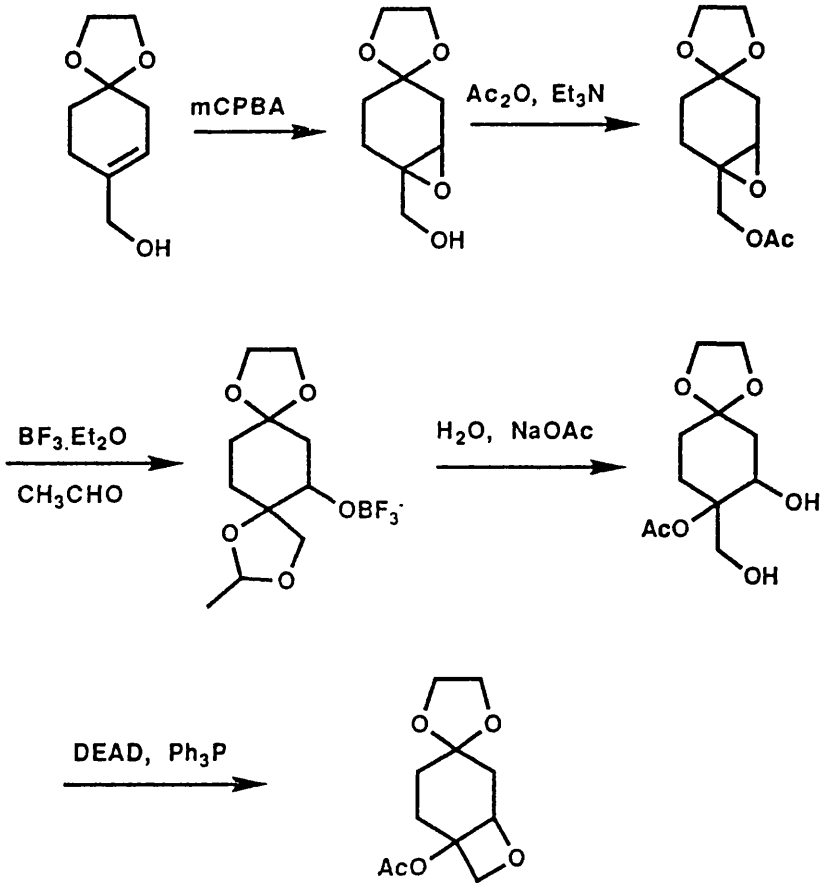


Figure 5

This work is very significant to the direction of chemistry taken in the following text, and it is the intended method for building up the diene functionality in later work.

The final discussion of synthetic approaches to taxanes involves the work of Berkowitz[82] and Greene[83] who have worked on the D-ring and side chain of taxol (3) respectively.

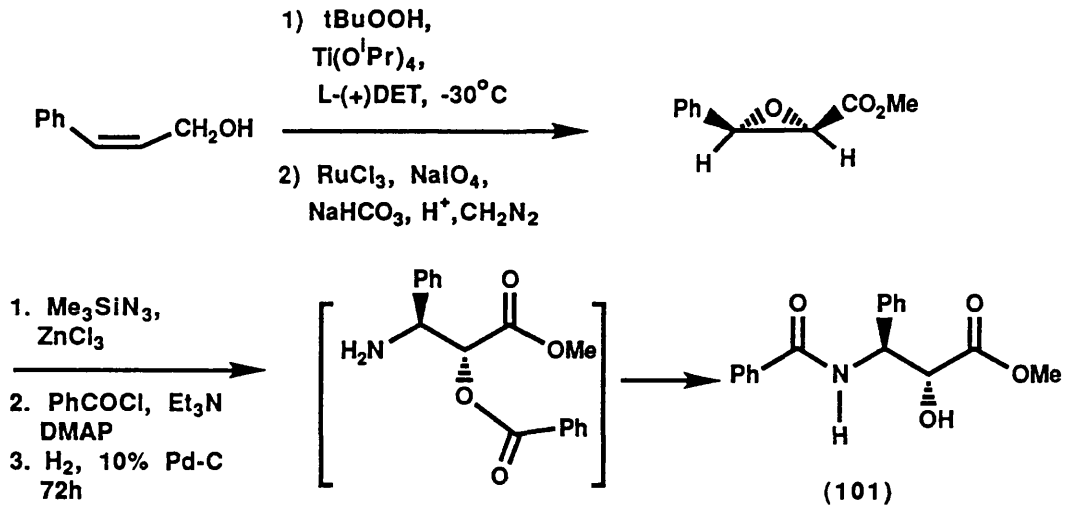
Berkowitz[82] reported a sequence of reactions applicable to the construction of the oxetane ring (D-ring) tertiary acetate grouping in taxol, using model compounds. The chemistry is described below in scheme (26).



Scheme 26

This could be applicable to later stages of the synthesis described in this thesis.

Greene[83] developed methods for the construction of the taxol side chain involving asymmetric epoxidation and a highly regioselective epoxide cleavage as the key reactions. Greene also looked into *trans* esterification of the resulting methyl esters. The chemistry is outlined in Scheme 27.



Scheme 27

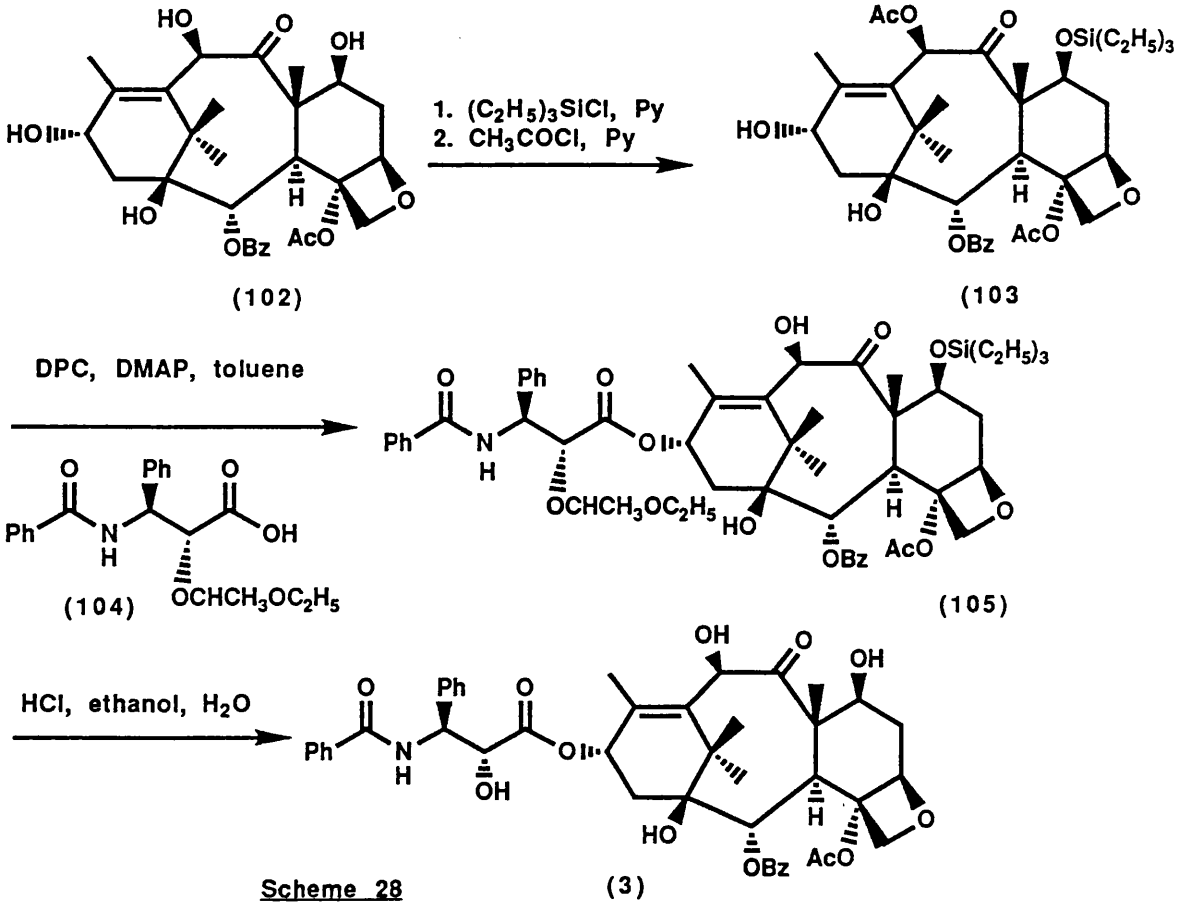
This route was later improved by Greene[84] to some degree but has not been described here.

1.8 SEMISYNTHESIS OF TAXOL DERIVATIVES

Due to its unique mode of action taxol may be the prototype for a new class of chemotherapeutic drugs. However, one of the disadvantages of taxol is associated with its limited availability from natural sources: It is impossible to extract from the very slow growing yew tree in large quantities indefinitely, and already the yew tree population in the southern hemisphere has been severely damaged. Because, to date, no synthetic pathway has been

found for taxol so it would seem reasonable to use the supply of taxane derivatives to its fullness and to use simpler taxanes, as precursors to taxol and biologically active analogues, in a taxol semisynthesis.

Work in this direction has been carried out most notably by Gueritte-Voegelein and Greene[85] who have now successfully completed a semisynthesis from 10-deacetyl baccatin III (102) which can be readily extracted in high yield from the leaves of *Taxus Baccata*.[86,87] Yew leaves are quickly regenerated. The synthesis of taxol (3) from 10-deacetyl baccatin III (102) is given in Scheme 28.



(102) (103) (104) (105) (3)

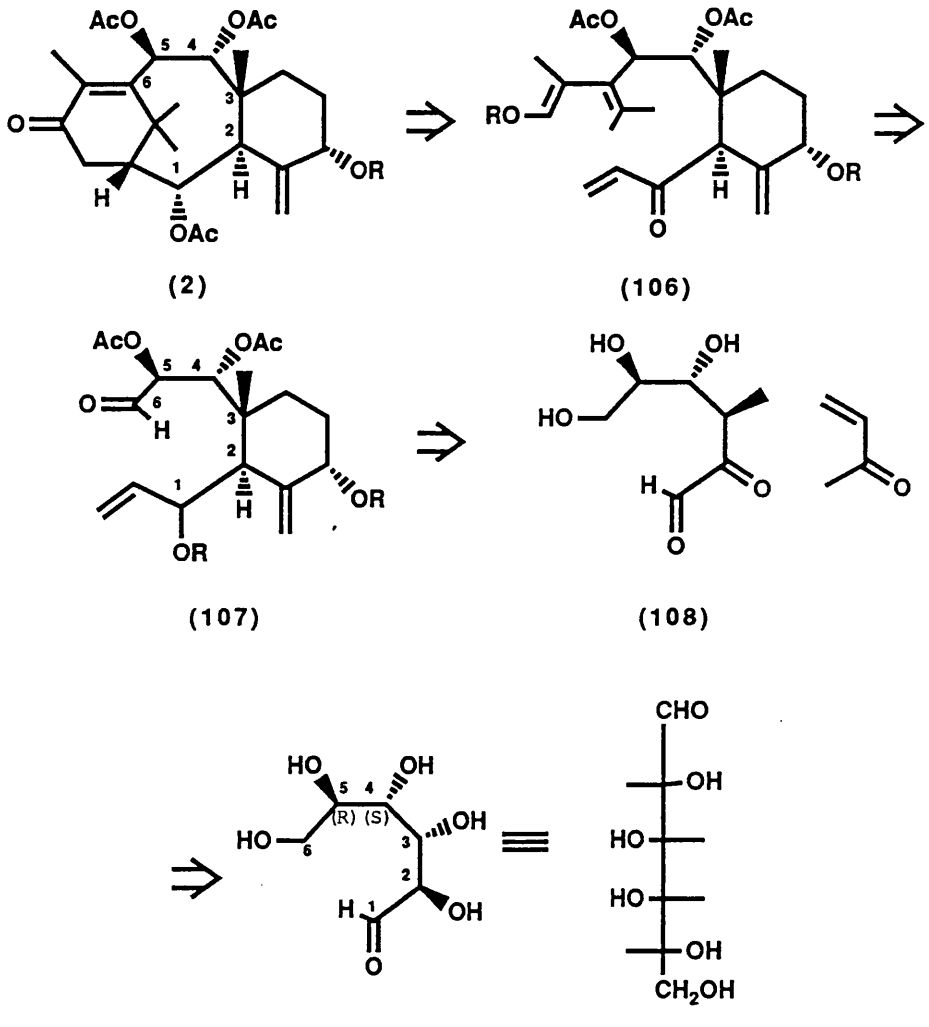
Scheme 28

CHAPTER 2.

Introduction of the taxane B-C ring junction stereochemistry

2.1 INTRODUCTION

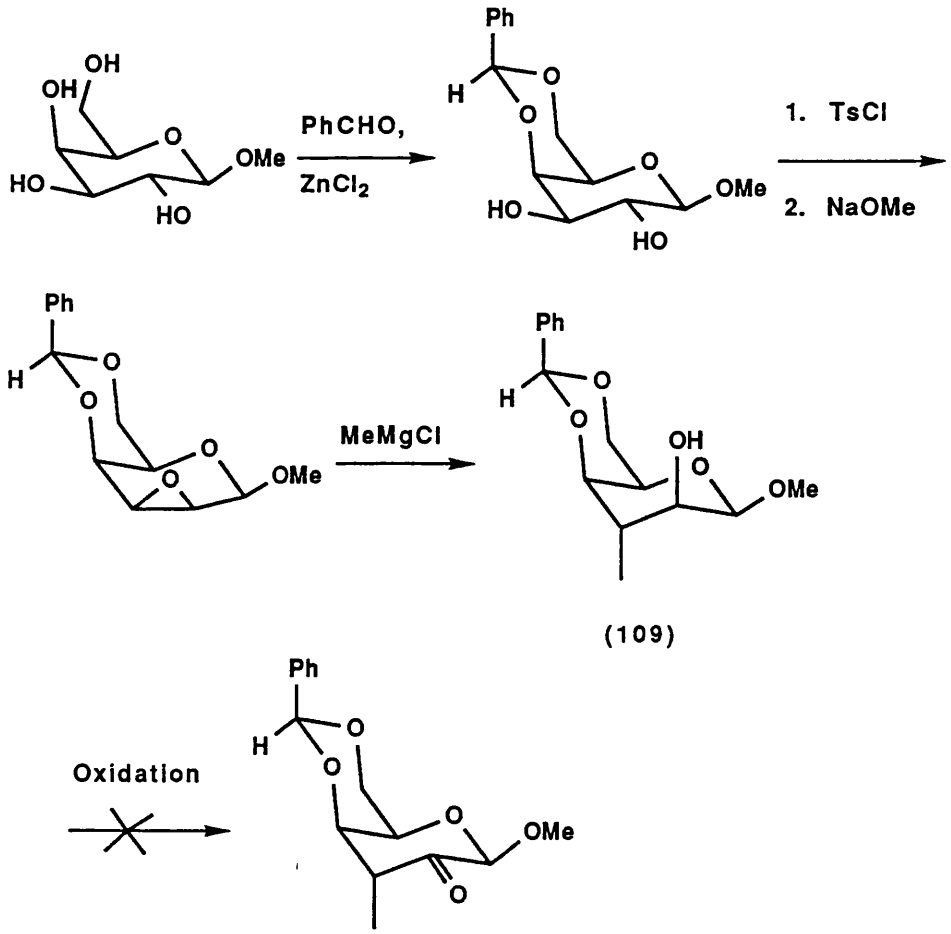
The high degree of oxygenation in the taxane group of natural products[1] suggested that a carbohydrate might be useful as a precursor in the total synthesis. An outline of the retrosynthetic pathway is shown in Scheme 29.



Scheme 29

This sequence continues to use the intramolecular Diels-Alder approach, which was developed in previous model studies.[57,80] It was thought that the diene (106) could be constructed from the aldehyde (107) using the selenium or

silicon directed syntheses[88,89] which had been studied earlier. On further inspection of taxinine (2) and the aldehyde (107) it was decided that it was the carbons 1-6 which could originate from the carbohydrate precursor. Construction of the cyclohexane ring by a Robinson annulation[90] led back to the structure (108) which in turn, could be derived from an aldohexose. As galactose has the required configuration for C-4 and C-5 and it was considered to be a practical starting material.

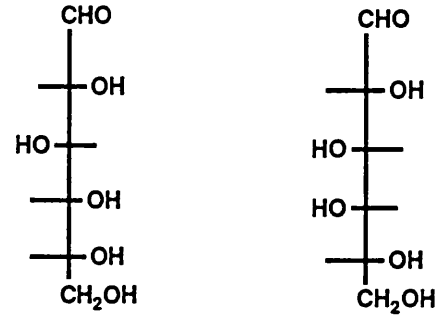


Scheme 30

However, previous work by Bonnert[91] shown in Scheme 30 showed that galactose was not a useful starting material for two reasons. Firstly, attempts to oxidise the alcohol (109) to the ketone (110) using a Swern oxidation,[92] with the conditions described by Yoshimura *et al.*[93] for the general oxidation of carbohydrate alcohols, failed and only starting material (109) was recovered. Further attempts to oxidise (109) using alternative dimethyl sulphoxide oxidations,[94] chromium trioxide and pyridine in dichloromethane[95] and ruthenium tetroxide in tetrachloromethane[96] also failed. Secondly, the yield achieved for the preparation of the alcohol (109) was poor. For these reasons it was felt that it would be more advantageous to pursue the more precedented glucose route[97] as this had already been fully developed by Pougny and Sinay[97] for a route to carbohydrate methyl ketones.

2.2 PREPARATION OF THE GLUCOSE DERIVED KETONE (118)

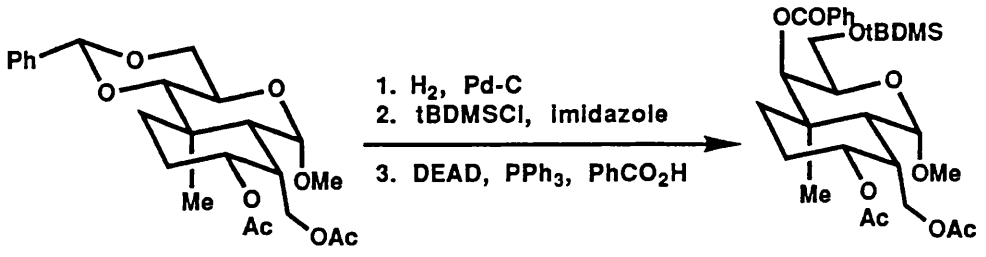
Glucose differs from galactose by having the opposite configuration at the C-4 hydroxyl group. Referring back to the retrosynthetic analysis, Scheme 29, C-4 of the carbohydrate will ultimately be C-9 in taxinine (2). Hence,



Glucose Galactose

the use of glucose throughout the synthesis would lead to C-9 having the wrong configuration in the final product.

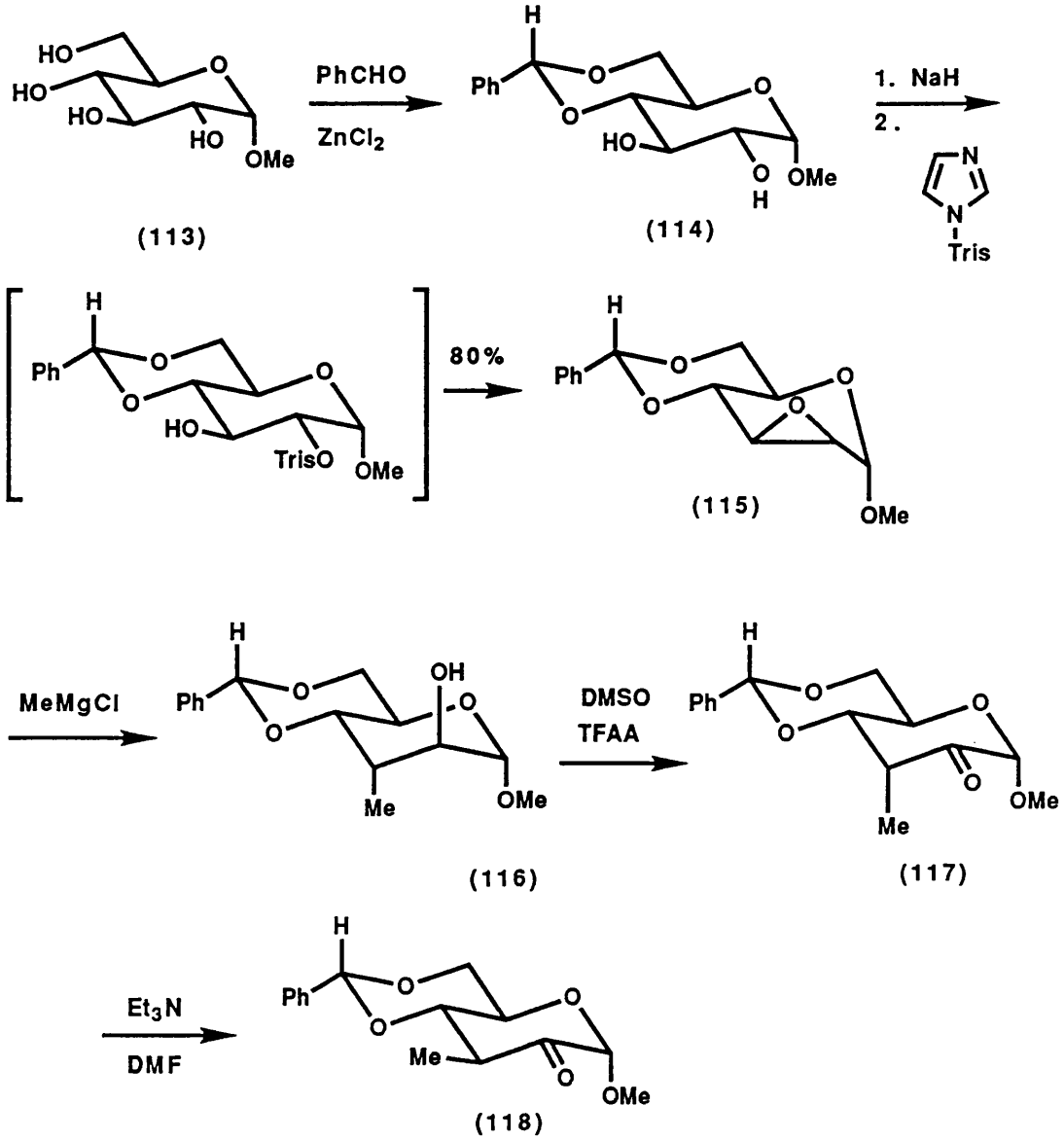
There exists, however, the opportunity to correct this problem at a stage soon after the Robinson annulation. This could be achieved by inverting the C-4 hydroxyl configuration by means of a Mitsunobu reaction.[98] For example, the inversion could be performed on an intermediate of the type (111). Before (111) could be subjected to an inversion reaction, the benzylidene group would have to be removed and the primary alcohol function selectively protected. Finally the treatment with diethyl azodicarboxylate, triphenyl



(111) (112)

phosphine and benzoic acid,[98] would perhaps cause inversion of the C-4 hydroxyl to produce the carbohydrate derivative (112).

The approach undertaken for the glucose precursor is similar to that initiated for the galactose series but, as already stated, had literature precedent for the preparation of the α-arabinoulose (118), Scheme 31.[97]



Scheme 31

Anhydro-α-mannoside (115) was prepared with a slight modification of the literature procedure.[99] Treatment of the benzylidene protected α-methyl pyranoside (114) with sodium hydride and N-triisopropylbenzene sulphonyl imidazole instead of N-p-tolylsulphonyl imidazole as in the literature,[99] results in a higher yield of (115), 70-80% as opposed to 39%. The preparation of N-triisopropylbenzene sulphonyl imidazole

was achieved using the same procedure as for the preparation of N-p-tolylsulphonyl imidazole.[99] From the above procedure it was possible to prepare exclusively the anhydro-α-mannoside (115), since the triisopropyl benzene sulphonation takes place only on the C-2 hydroxyl group.[99]

The epoxide (115) can be opened by a number of organometallic nucleophiles; alkyl Grignards reagents,[100] alkyllithiums[101] and dimethylcuprates.[102] The best method in this case was that used by Pougny and Sinay.[97] When the epoxide (115) was reacted with ten equivalents of methylmagnesium chloride in ether under reflux for ten days, the α-altroside (116) was formed in essentially quantitative yield. We have now modified this such that the ring opening of the epoxide (115) can be performed in a matter of hours, by using a slurry of the epoxide (115) in tetrahydrofuran and adding the methyl Grignard reagent to it.

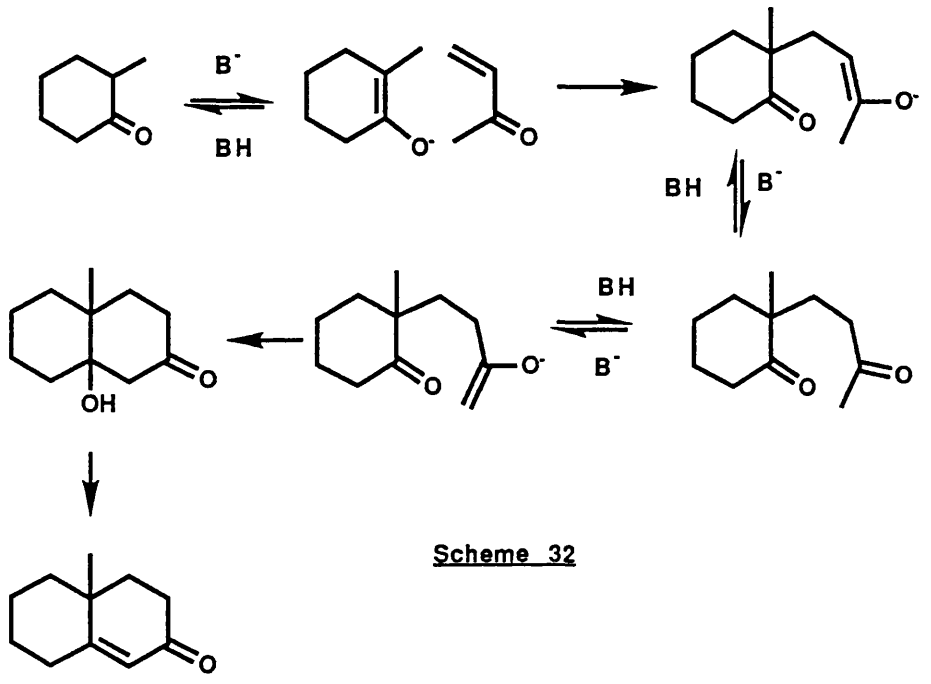
The crude α-altroside (116) was oxidised using trifluoro-acetic anhydride, dimethylsulphoxide and triethylamine to give a ketone with the methyl group initially in an axial position.[93,97] Treatment of this initial product (117) with triethylamine in dimethylformamide causes epimerisation of the axial methyl group to the conformationally preferred ketone (118) with an equatorial methyl group *via* enolisation of the ketone (117). Hence, α-arabinoulose (118) was produced as a white crystalline solid.[97]

2.3 THE ROBINSON ANNULATION OF THE CARBOHYDRATE (118)

Extensive work by Bonnert,[91] produced conditions for the first reported example of a Robinson annulation of a

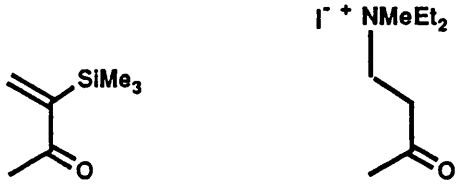
carbohydrate derivative.[103] The original Robinson annulation involves a base-catalysed Michael addition of a ketone to methyl vinyl ketone, followed by acid or base catalysed aldol condensation, Scheme 32.[104]

There are two major problems with methyl vinyl ketone.



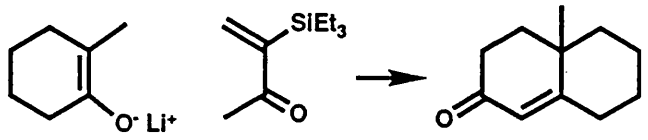
Scheme 32

Firstly, its tendency to polymerise especially in the presence of strongly basic enolates. This problem was largely overcome by the generation of methyl vinyl ketone *in situ*[104] from (120). The second problem stems from the fact that the generation of the methyl vinyl ketone *in situ* relies on an equilibrium process and can not therefore be used for regiospecifically generated enolates. Both problems were simultaneously and independently surmounted by Stork *et al*[105] and Boeckman,[106] by the use of the α-silyl enone (119).



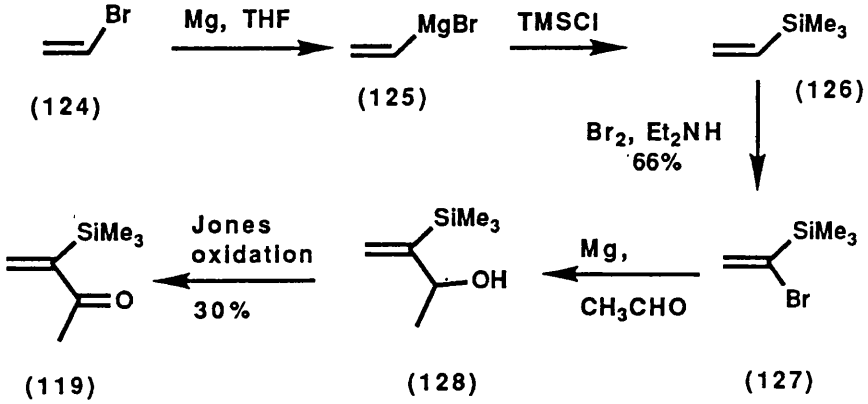
(119) (120)

The silyl group in the enone (119) stabilises the initial negative charge formed by the addition of the enolate ion to the enone. It also provides a large steric bulk which slows down anionic polymerisation.[104] The use of the silyl enone (119) in the Robinson annulation is illustrated by the reaction of the enolate (121) with the



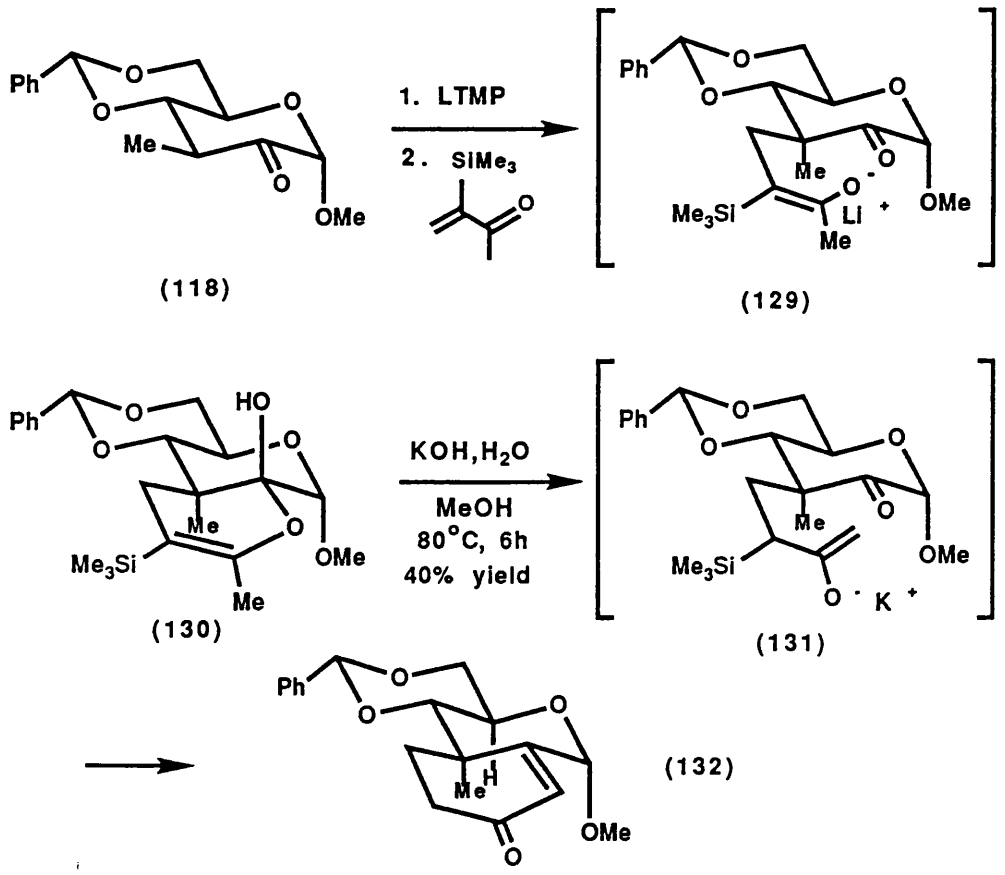
(121) (122) (123)

enone (122) to produce the decenone (123).[105] Yields of the cyclised product using this method are typically over 60%. The α-silyl enone was prepared according to the literature procedure, Scheme 33.[107]



Scheme 33

The Robinson annulation of the carbohydrate ketone (118) was carried out according to the procedure of Bonnert.[91,103] The enolate was produced using lithium tetramethyl piperidine (LTMP) in diethyl ether. The silyl enone (119) was added at -78°C and subsequently the mixture was allowed to warm slowly to room temperature followed by continued stirring for one hour. The reaction is believed to proceed according to Scheme 34 to give the enone (132) as an oil.

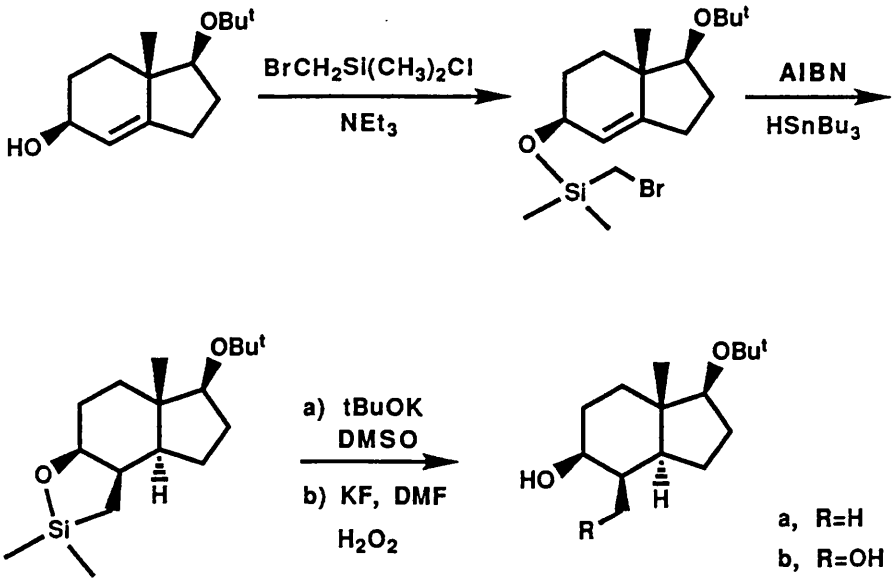


Scheme 34

Extensive n.O.e experiments[103] determined the stereochemistry at the C-1 (C-3 carbohydrate numbering) position. The configuration of the C-1 centre in enone (132) is the same as that required for C-8 in taxanes.

2.4 THE REDUCTION OF THE KETONE (132)

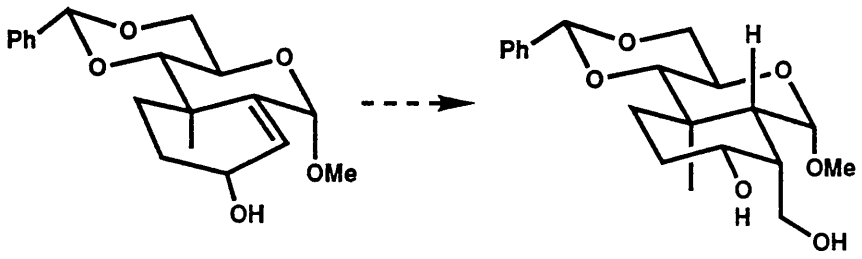
With a reliable route to the enone (132), albeit that the yield is only around 30 to 40%, the next stage in the synthesis of taxinine (2), Scheme 29, required the reduction of the carbon-carbon double bond to give specifically a *trans* ring junction as required for the B-C ring junction of taxinine (2). At the same time it is important to introduce the functionality that is required to produce the taxinine (2) C-ring functionality, regiospecifically. Stork and Sofia[108] published a procedure using an allylic alcohol rather than an enone which gives specifically a *trans* ring junction, Scheme 35.



Scheme 35

This led to the regiospecific introduction of a hydroxyl methylene group adjacent to the hydroxyl group. It was also stereochemically *cis* to it and the addition of a hydrogen to the double bond occurred on the opposite face to the hydroxyl

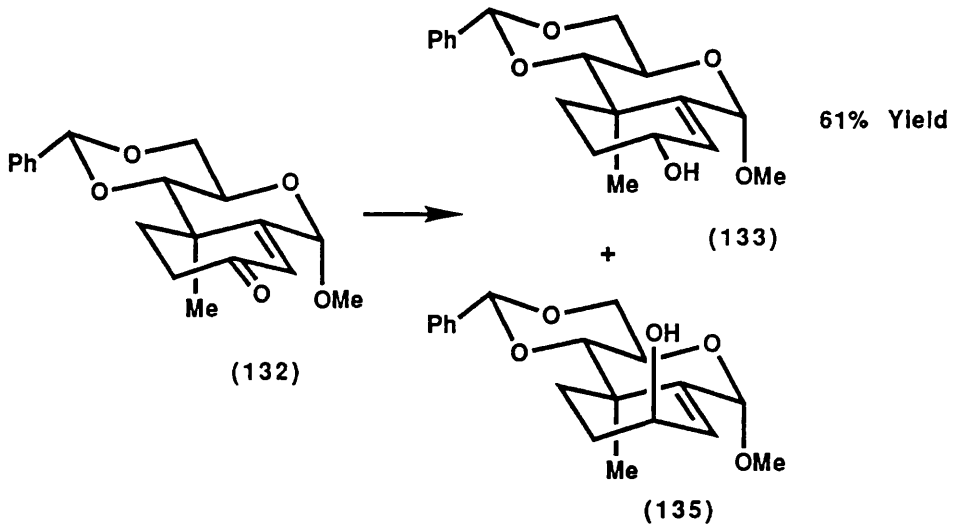
group. The application of Stork and Sofia's procedure[108] to the allylic alcohol (133), derived from the Robinson



(133) (134)

annulation product (132), would lead directly to the diol (134).

Bonnert[91] tried three sterically hindered reducing agents to effect the reduction of the enone (132); Diisobutyl aluminium hydride (DIBAL-H)[109], 9-borobicyclo [3.3.1] nonane (9BBN)[110]



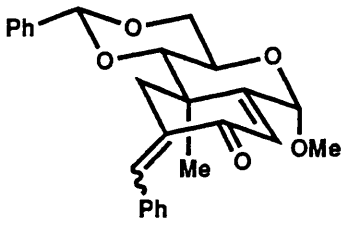
(132) (135)

	Equatorial	: Axial
DIBAL	3.4	: 1
9-BBN	5	: 1
L-Selectride	30	: 1

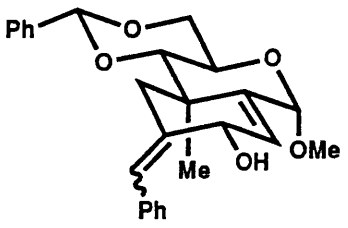
and L-selectride.[111] The reduction of the enone (132) with these reducing agents produced a mixture of epimers at the hydroxyl position. However the reduction of enone (132) with L-selectride gave the allylic alcohols (133) and (135) in a ratio of 30:1 respectively. After one recrystallisation from 60-80°C petroleum ether, only the major product (133) is observed by ^{1}H n.m.r. An X-ray crystal structure of the allylic alcohol (133), obtained by Bonnert,[91] showed conclusively that the configuration at the C-1 centre was the same as that required for C-8 in the taxanes.

Although the route to the enone (132) was reliable, the yields of this reaction were low, at best 40% and usually around 30%. Therefore it was considered worthwhile to explore the conditions required for the second carbon-carbon bond formation step of the Robinson annulation, since the initial Michael addition step occurred to give the hemiacetal (130), in yields of up to 80%, it must be at the second stage of the synthesis that the yield loss takes place. The initial attempt to increase the yield of enone (132) met with no success, but it is still being explored as this key step must be improved in order to achieve a viable synthetic route. However, during this exploration, we looked at the effect of changing the addition of aqueous potassium hydroxide followed by heating to 60°C, to just adding methanol and utilising the base already present in the reaction mixture to effect the cyclisation on leaving it overnight. Although this actually led to a decrease in yield, it did provide an interesting novel compound. We could deduce from the proton n.m.r that there were two phenyl

groups present in this compound compared to the one expected for the enone (132). It was also observed that there were two types of vinylic protons present in the molecule; a singlet at δ6.08 and a doublet (J=2.4Hz) at δ7.71. The C-13 proton signals had also disappeared. Infrared spectroscopy confirmed the presence of an α,β-unsaturated carbonyl. We therefore propose (136) as the structure of our novel compound. This fits the carbon n.m.r data, mass spectroscopy and elemental analysis data. It would appear from the n.m.r data that there is a single isomer formed, however, we have not determined whether it is the E or Z isomer.



(136)

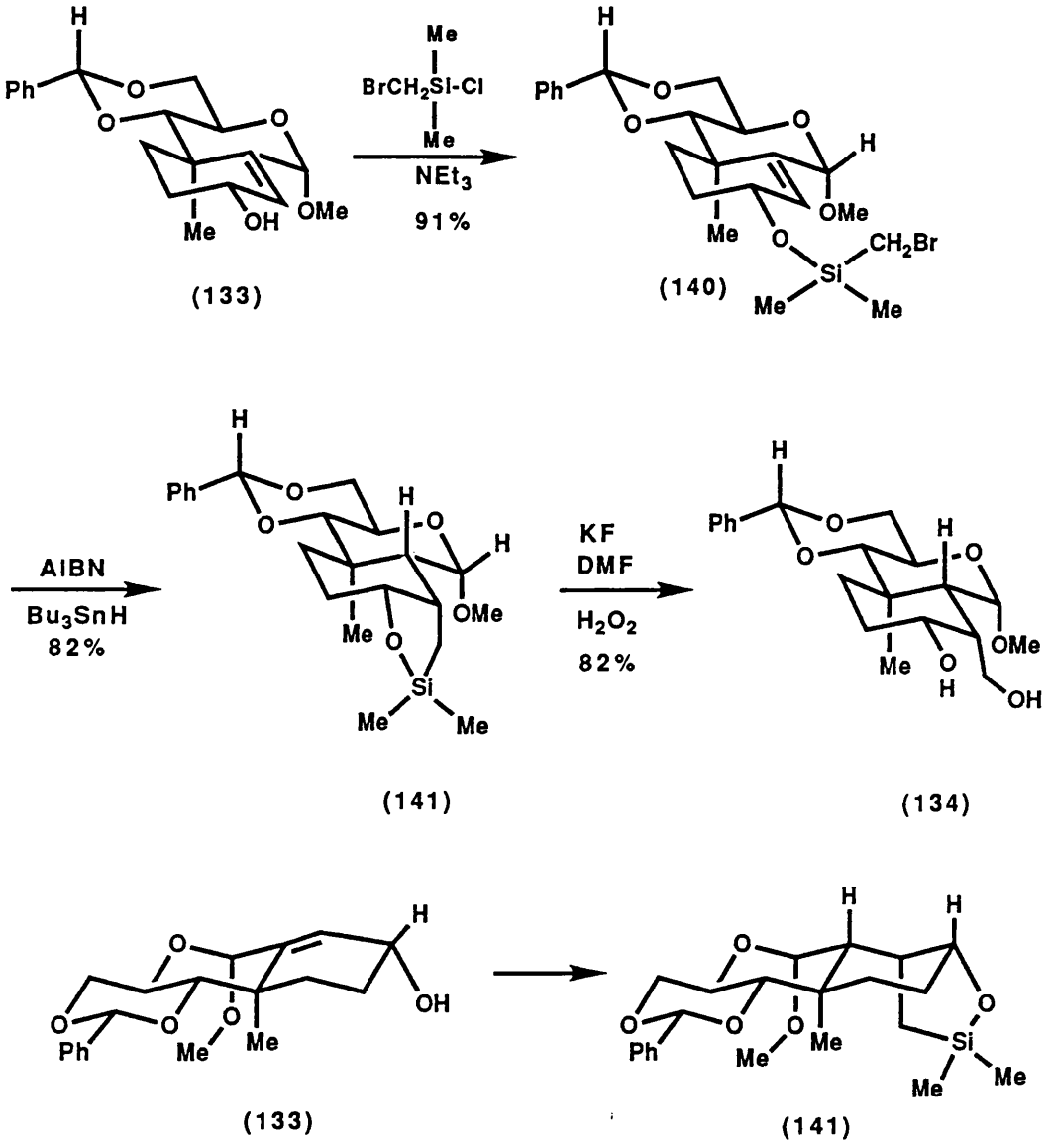


(137)

By producing (136), which almost co-elutes with the enone (132), we found it difficult to obtain either (132) or (136) totally pure. On reduction of the mixture with L-selectride, the alcohol (137) was produced and could be obtained as a crystalline white solid. Neither of the compounds (136) or (137) have any immediate use in the synthesis of taxanes. They might however have a use in producing analogues of taxanes or even in the placement of the C-7 hydroxyl group when the route is extended to taxol at a later date.

2.5 THE STORK SILYL METHYLENE RADICAL CYCLISATION OF (133)

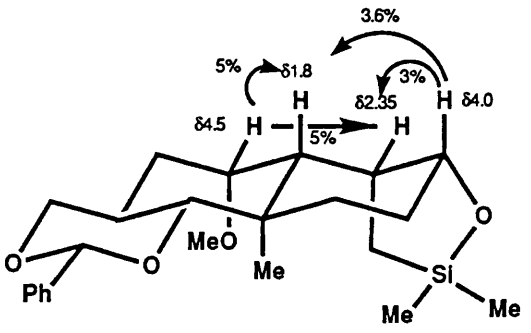
Having obtained the enol (133), in high purity, we were now in a position to apply the Stork silyl methylene radical cyclisation[108] procedure given in Scheme 35 to enol (133), Scheme 36.



Scheme 36

Reaction of (bromomethyl)chlorodimethyl silane[108] produced the silyl ether (140) which subsequently underwent a radical cyclisation on treatment with tributyltin hydride to give the

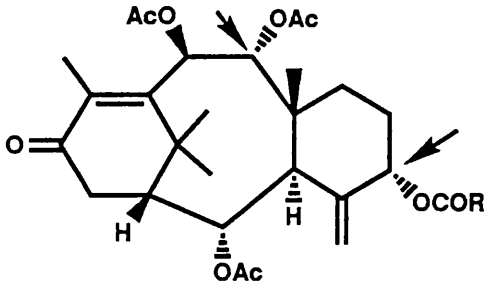
tetracyclic structure (141) as a white crystalline solid. The proton n.m.r spectrum and observed n.O.e experiments, which are summarised in Figure 6, were entirely consistent with the above structure. We found that δ1.80 (H-10) showed a n.O.e with δ4.50 (H-9) of 5.2% and with δ4.00 (H-15) of 3.6%; δ2.35 (H-11) showed a n.O.e with δ4.00 (H-15) of 3.1% and with δ4.50 (H-9) of 5.2%; δ4.00 (H-15) showed a n.O.e with δ2.35 (H-11) of 3.1% and with δ1.80 (H-10) of 3.6% and finally δ4.50 (H-9) showed a n.O.e with δ1.80 (H-10) of 5.2% and δ2.35 (H-11) of 5.2%. The carbon n.m.r data, mass spectroscopy and elemental analysis fit perfectly with the assigned structure of (141).



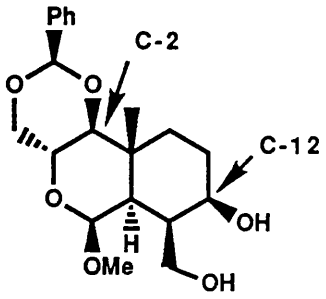
(141) Figure 6

Treatment with potassium fluoride and hydrogen peroxide produced the diol (134) in an 82% yield. These results are entirely in accord with the expectations from the literature.[108] Although n.O.e experiments have been carried out to prove the structure of (141), attempts are being made to carry out an X-ray analysis on (141) for absolute confirmation of its structure. Comparison of taxinine (2) and the diol (134) shows that the stereochemistry of the C-12

hydroxyl grouping in (134) has the opposite stereochemistry to that required for taxinine (2), along with the fact that the C-2 centre has the incorrect stereochemistry for reasons already given.



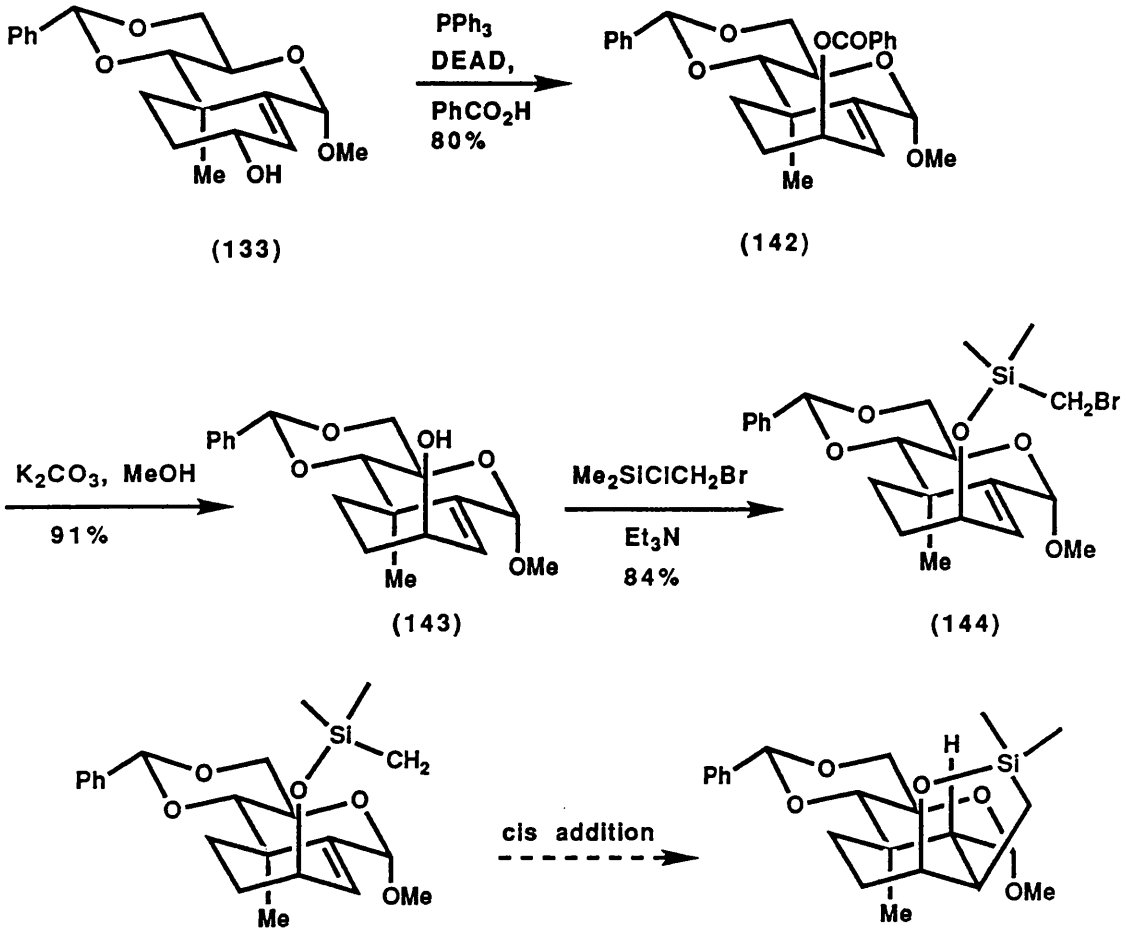
(2)



(134)

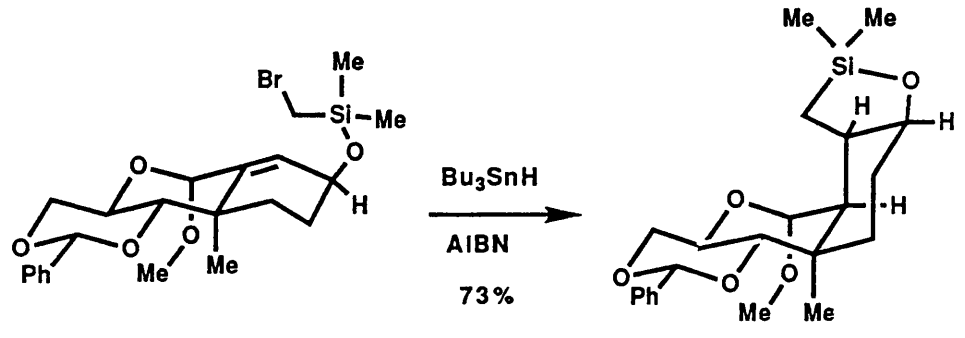
2.6 THE STORK RADICAL CYCLISATION OF THE (133) EPIMER (143)

One way to achieve the correct stereochemistry at C-12 would be to invert the enol (133) and for it to undergo a *cis* radical cylisation. In all the published examples of the Stork silyl methylene radical cyclisation a *trans* addition across the olefin was observed. We felt that the enol (133) provided a further test of this stereochemical preference in that the all *trans* stereochemistry of the tricyclic system (143) might force the reaction to occur by *cis* addition. Scheme 37 describes the inversion of the 12(R) allylic alcohol (133) *via* the ester (142) to the 12(S) allylic alcohol (143). Conversion to the silyl ether proceeded under normal conditions to give the β-bromosilane (144). Radical



Scheme 37

cyclisation occurred, on treatment with tributyltin hydride, to produce the tetracyclic structure (145) as a crystalline white solid. The radical and hydrogen atom have again added



trans despite the fact that this results in the formation of two *cis* ring junctions. A crystal of the tetracyclic compound (145), which was suitable for an X-ray crystal

analysis, was obtained and the result of the X-ray structure is shown in Figure 7. This confirms the stereochemistry of the tetracyclic molecule (145). Since the stereochemistry of the C-10, C-1 ring junction is *cis*, the tetracyclic structure (145) has no use in the synthesis of taxinine (2). However we have proved that the Stork radical cyclisation reaction occurs with the *trans* stereochemistry in two epimeric sugar derivatives, despite the fact that this leads to the doubly *cis* fused tetracyclic molecule (145).

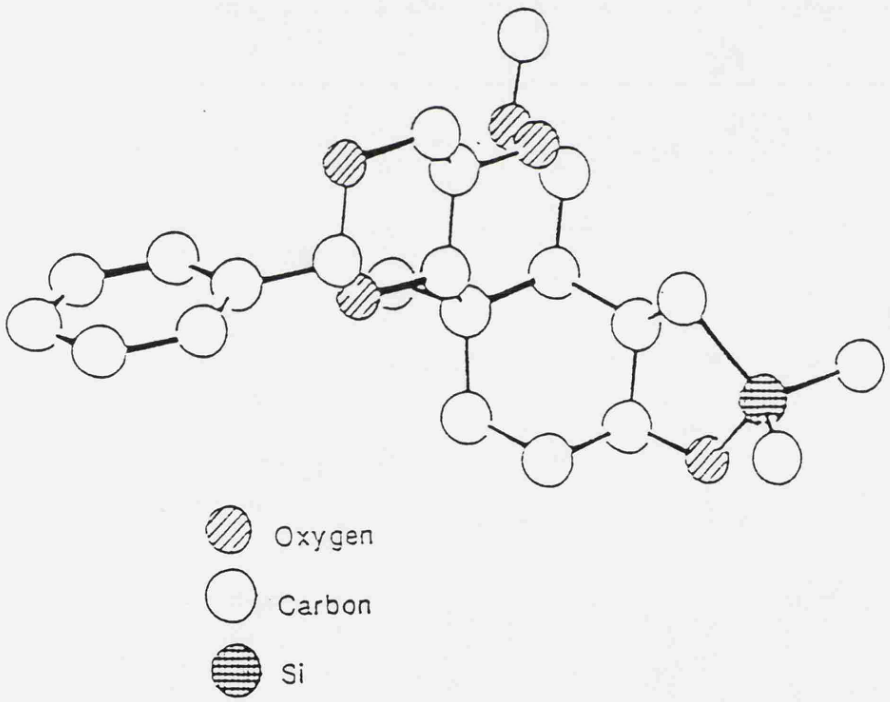
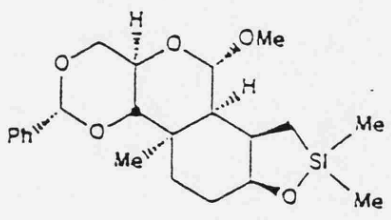


Figure 7



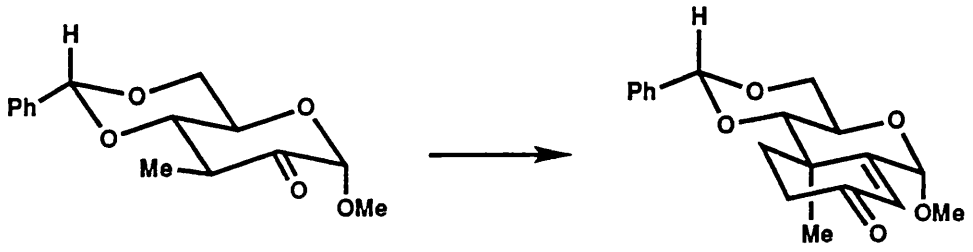
(145)

CHAPTER 3.

Investigations into Robinson annulations, taxane C-ring functionality and 3-lithiobutadienes

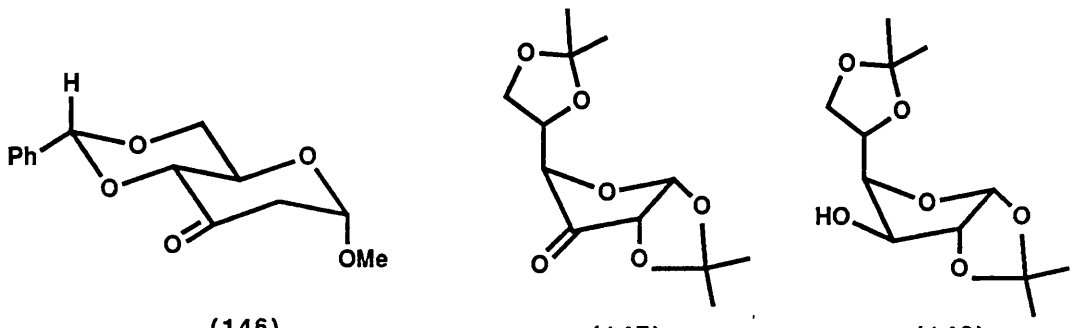
3.1 INTRODUCTION

As discussed in chapter two the first Robinson annulation of a carbohydrate ketone was carried out by Bonnert.[103] The exact conditions used to achieve the annulation of the ketone (118) required enormous investigation by Bonnert, to obtain an optimised yield of 40% for the enone (132). Thus we considered it worthwhile to study the Robinson annulation of other keto sugars in order to determine whether the reaction was generally applicable.



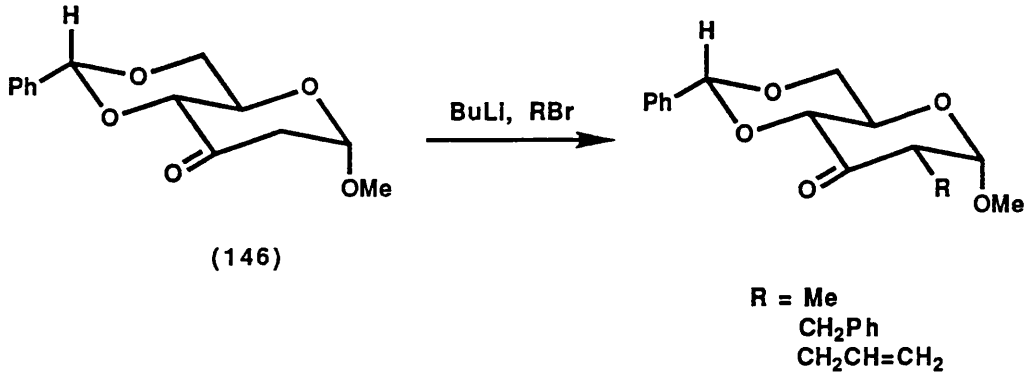
(118) (132)

Several carbohydrate ketones are readily available, of which (146) and (147) are just two examples.



(146) (147) (148)

It was thought that the ketones (146) and (147) would be suitable for Robinson annulations. The ketone (146) already had literature precedence for enolate reactions, as shown by Fraser-Reid[112] (below), and ketone (147) could be



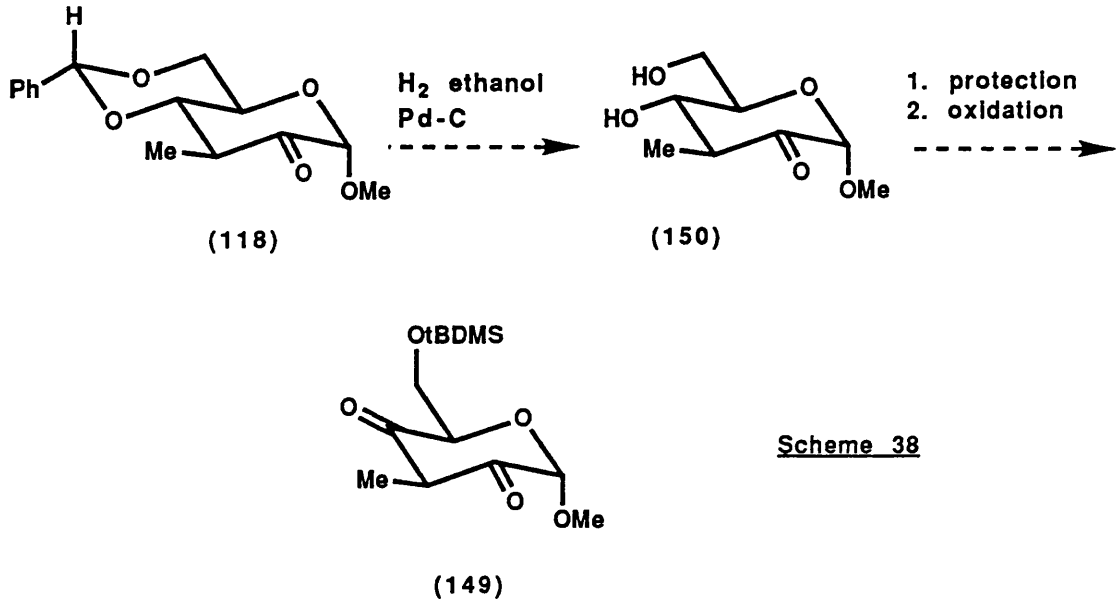
(146)

R = Me
CH_2Ph
$CH_2CH=CH_2$

obtained in large quantities from 1, 2; 5, 6 diisopropylidene-α-D-glucofuranose (148). We also considered the Robinson annulation of the diketone (149) (Scheme 38), since it would perhaps be possible to synthesise from materials we already had from the taxane synthetic studies. It would be interesting to see if there was any selection between the C-2 and C-4 carbonyl groups and the stereochemistry of the resulting product.

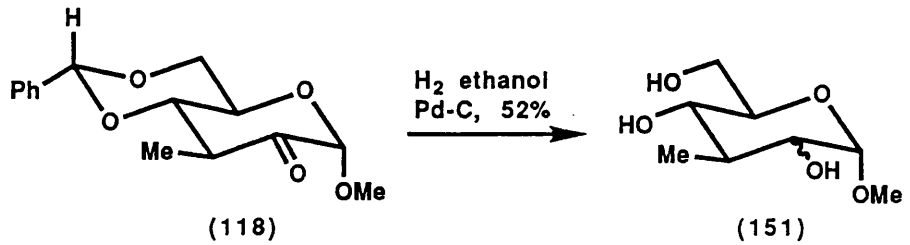
3.2 ATTEMPTS AT SYNTHESISING THE DIKETONE (149)

We planned to synthesise the diketone (149) by firstly removing the benzylidene acetal grouping from (118), with hydrogenation over palladium on charcoal, to give the diol (150), followed by protection of the primary alcohol and oxidation of the secondary alcohol, according to Scheme 38.



Scheme 38

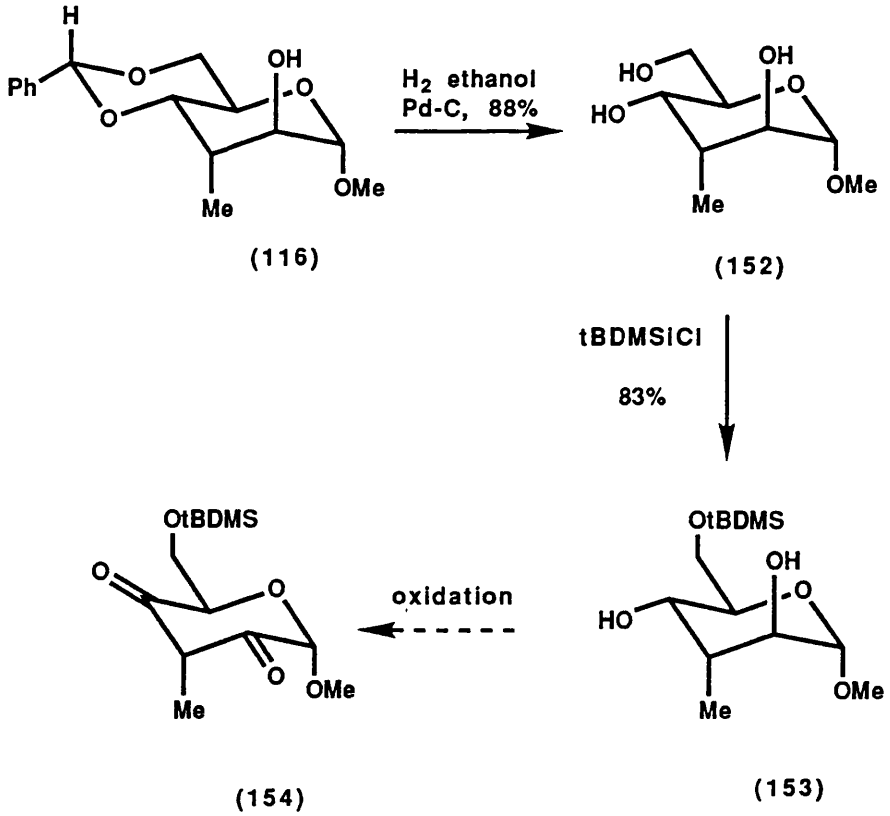
However, it was found that removal of the benzylidene group with palladium on charcoal and hydrogen did not result in (150) Instead the triol (151) was obtained as shown in Scheme 39.



Scheme 39

We could have tried p-toluenesulphonic acid in methanol[124] here as well, remove the benzylidene group from the ketone (118), but we had already found that it was possible to obtain the diol (153) from the alcohol (116), according to the Scheme 40. Removal of the benzylidene group followed by protection of the primary alcohol gave the diol (153) which could either undergo stepwise or simultaneous

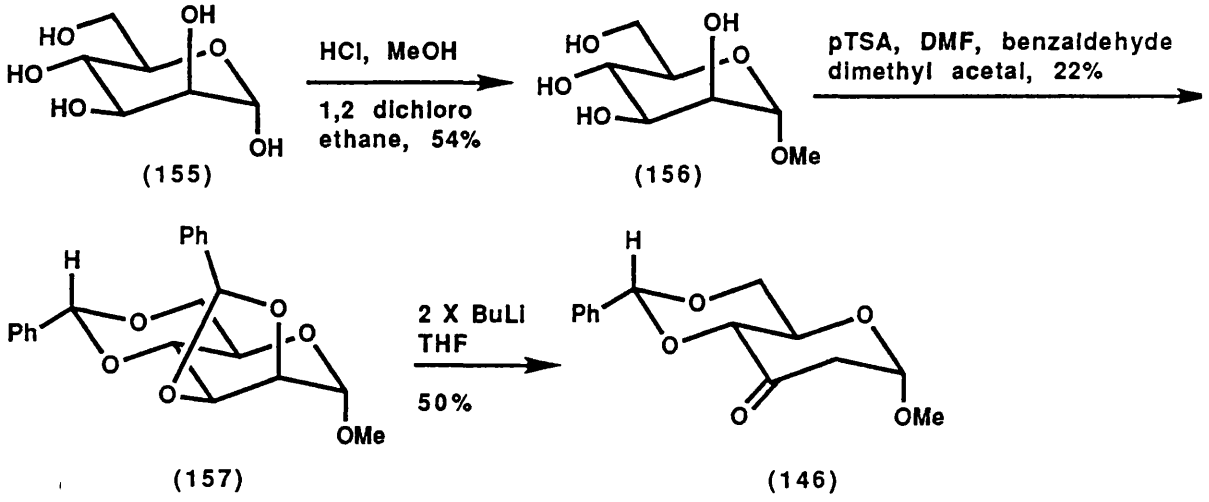
oxidation of the two secondary alcohols to give the diketone (154). This methodology could have similarly been applied to (151), but this was considered an unnecessary use of the ketone (118) at this stage. However, the diol could not be oxidised to give the diketone (154), which is epimeric with diketone (149) at the C-3 methyl, by any of the standard carbohydrate oxidation methods.[113] We therefore resorted to the removal of the benzylidene group from the ketone (118) using p-toluenesulphonic acid in methanol[124] as previously suggested. Unfortunately this resulted in a mixture of products from which it was not apparent that any diol (150) had been formed.



Scheme 40

3.3 ATTEMPT AT ANNULATING THE KETONES (146) AND (147)

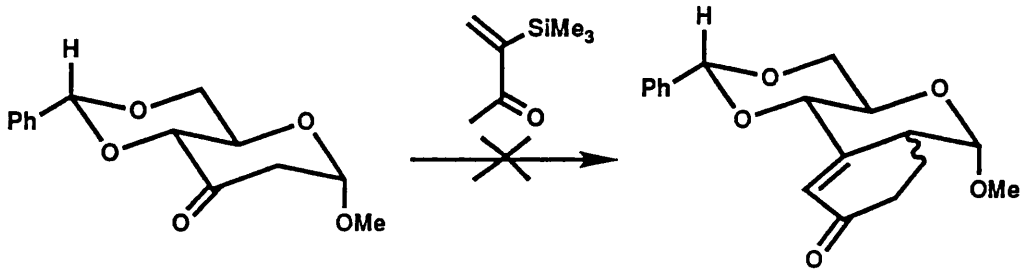
We turned our attention to the other carbohydrate ketone (146). 4, 6-O-Benzyliden-2-deoxy-α-D-erythro-hexo pyranosid-3-ulose (146) can be prepared on a large scale according to Scheme 41. The synthesis begins by methylation of the anomeric position in D-mannose (155), using 1, 2-dichloroethane and acidified methanol, to give (156). Subsequent protection of the 2, 3 and 4, 6-hydroxyl groups by benzylidene acetals is achieved by reaction of (156) with p-toluenesulphonic acid and benzaldehyde dimethyl acetal in dimethylformamide. This acetal exchange reaction leads to the formation of (157). The 2, 3-benzylidene acetal of (157) then eliminates to give the ketone (146) on addition of two equivalents of n-butyllitium.



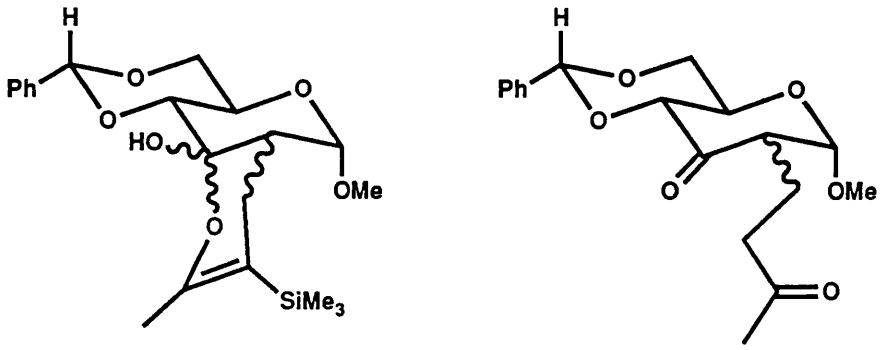
Scheme 41

Numerous attempts to obtain the annulation product (158) by reaction of the ketone (146) with 3-trimethyl-3-butene-2-one (119) failed. The resulting brown tars consisted of

many products by t.l.c, which even as mixtures, showed by proton n.m.r no evidence of the tricyclic product (158). Similarly attempts to isolate the Michael addition product (159), from the first stage of the reaction, did not give any compounds which could be identified by proton n.m.r as the expected product, the hemiacetal (159) or the diketone (160). Only starting material could be recovered from the reaction.

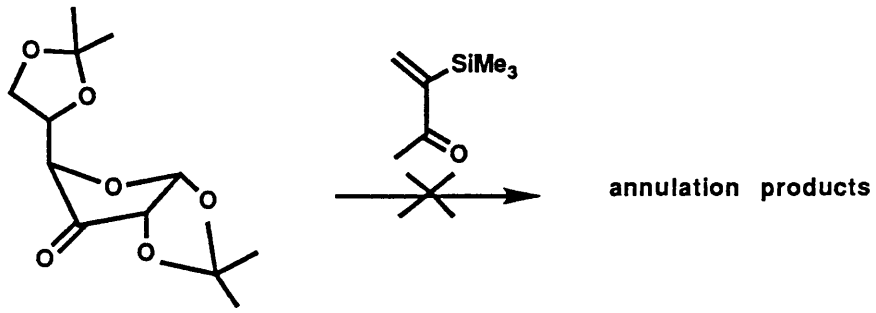


(146) (158)



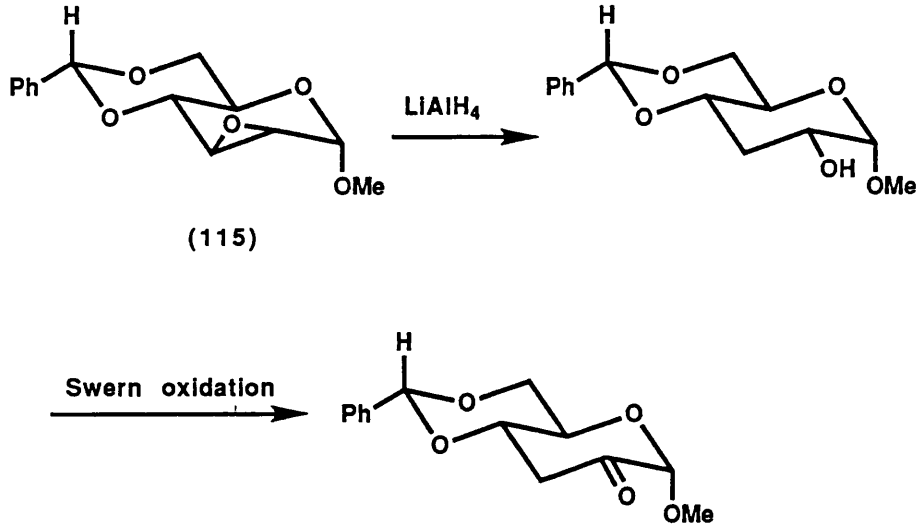
(159) (160)

Unfortunately the same result was found with the other keto carbohydrate (147). Perhaps the carbohydrate ketones



(147)

(146), (147), (149) and (154) were slightly too ambitious as starting materials for the reaction. We are continuing the study of Robinson annulation of carbohydrates using the ketone (161). (161) is readily available as shown by Scheme 42.[114] (161) is closely related to the ketone (118) and therefore should meet with more success.



Scheme 42

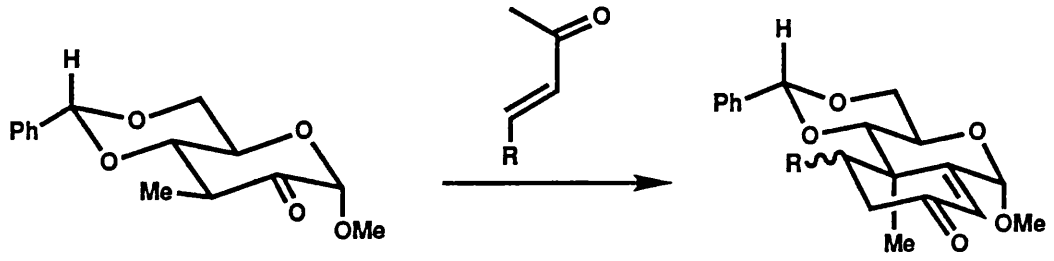
(115)

(161)

3.4 VARIATION OF THE α,β-UNSATURATED KETONE

Having had no success in changing the carbohydrate ketone substrate in the Robinson annulation reaction we thought that it might be possible to vary the α-β-unsaturated

ketone instead, in order to give the C-7 hydroxyl functionality which is found in taxol (3), Scheme 43.

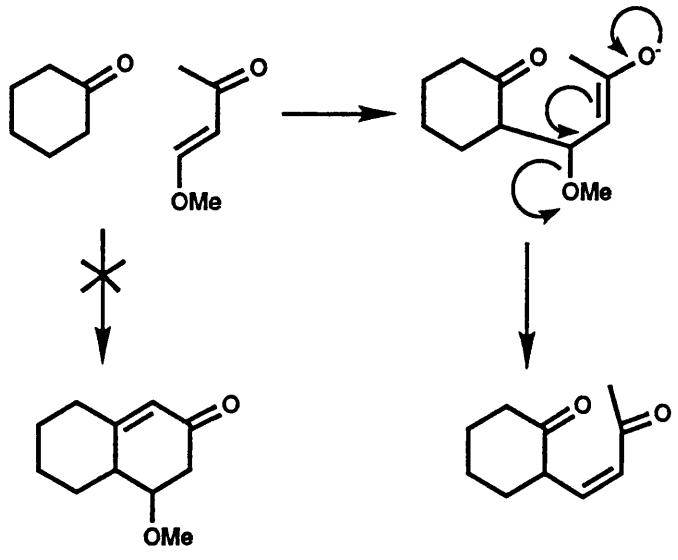


(118) (162)

Scheme 43

R is a functional group which could be easily converted to a hydroxyl group when so desired.

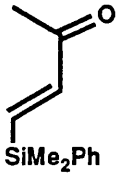
Our initial idea was to use *trans*-4-methoxy-3-buten-2-one, which is readily available. However a survey of the literature[115] showed that the methoxy group would be lost to form an α-β-unsaturated adduct (163) during the first stage of the Robinson annulation, and hence the desired product would not be obtained, Scheme 44.



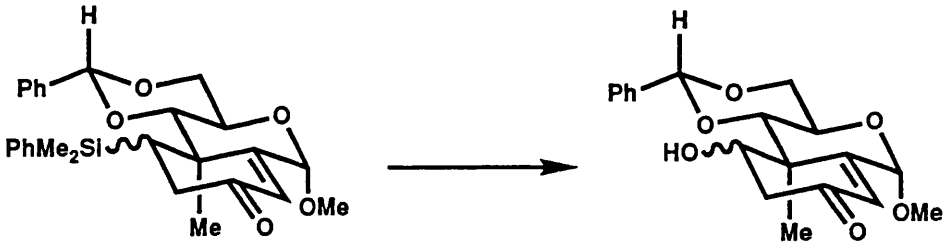
(163)

Scheme 44

It has been well documented that compounds containing the functionality $Ph(CH_3)_2Si$- can be seen as masked alcohols, since the silyl group can be converted to a hydroxyl group by oxidative reactions.[58] Thus it would seem reasonable that if we could produce 4-(phenyldimethylsilyl)-3-buten-2-one (164) and find conditions such that it would undergo a



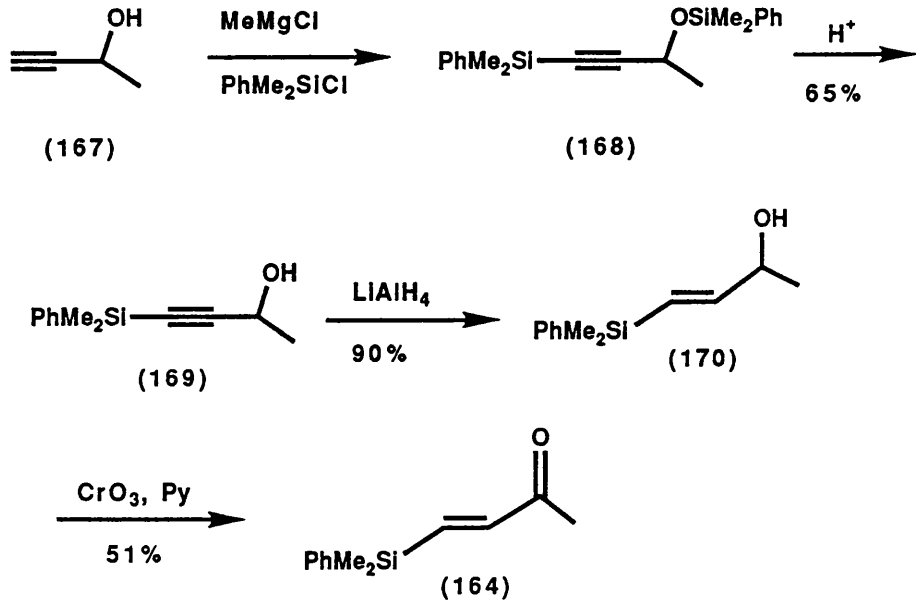
(164)



(165) (166)

Robinson annulation with the carbohydrate ketone (118) we could obtain (165), (R = $Si(CH_3)_2Ph$), and hence (166), (R = OH). A synthetic route was therefore devised to obtain the butene-2-one (164) and it is given in Scheme 45.

The readily available 1-butyne-3-ol (167) was refluxed with two equivalents of methyl magnesium chloride, to produce the dianion,[116] and chlorophenyldimethyl silane was added. This led to the disilane (168) which, on refluxing with acetic acid, gave the alcohol (169). Reduction of the alkyne to the alkene, followed by oxidation with chromium trioxide and pyridine in dichloromethane, led to the desired enone (164).



Scheme 45

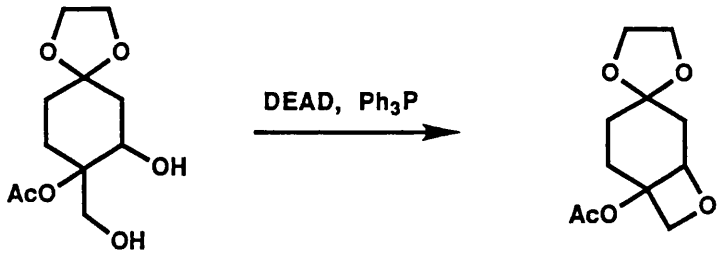
Attempts to obtain the tricyclic product (165), (R = $Si(CH_3)_2Ph$), using the enone (164) failed, with only starting material being recovered. Retrospectively this is not all that surprising due to the numerous problems associated with vinyl ketone Robinson annulations. In fact we have, by producing a C-4 silyl group on our Michael acceptor, destabilised the initial negative charge formed on addition of the enolate to the enone. Also the steric bulk of the silyl group may prevent attack of the enolate of ketone (118) on the enone (164).

This idea, for now, has been abandoned as a viable method for producing the C-7 hydroxyl group in taxol. However, if the present synthetic stratagy towards taxinine is to be extended to the synthesis of taxol, this problem of producing the C-7 hydroxyl function whilst performing the

Robinson annulation, must be overcome since formation of the C-7 hydroxyl group later on in the synthetic pathway may involve many extra steps.

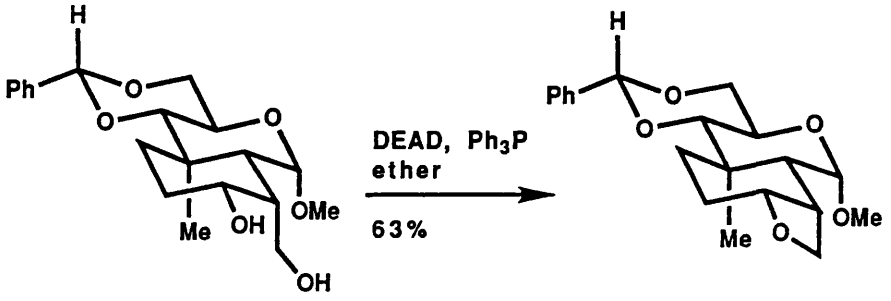
3.5 INVESTIGATIONS INTO THE FUNCTIONALISATION OF THE C-RING OF THE TAXANES

Whilst looking at the more detailed functionality of taxol (3), we thought that we should gain some appreciation of the difficulties in placing an oxetane D-ring into the synthetic route and, at the same time, investigate methods for forming the exocyclic double bond as found in taxinine (2). It was noted in the introduction that the complete oxetane system of taxol has been achieved on a model compound by Berkowitz[82] from a diol.



As this route for the production of oxetanes is well documented, we decided to apply it to our compounds. Thus we performed a Mitsunobu[98] reaction on our diol (134), Scheme 46. On stirring the diol (134) in diethyl ether with diethylazodicarboxylate (DEAD) and triphenyl phosphine, the oxetane (171) was formed. The proton n.m.r showed the expected signals[117] for the oxetane methylene group, C-12. The structure was consistent with the carbon and proton n.m.r. data, the mass spectroscopy and elemental

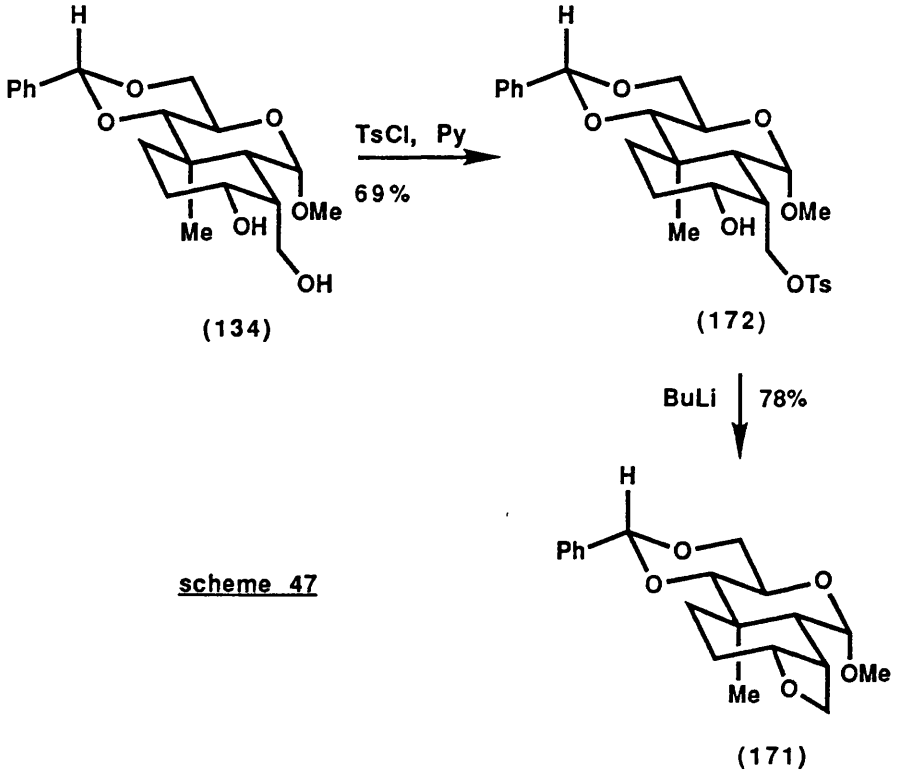
analysis. For interest the oxetane (171) was tested for activity in mouse cancer tumours, however no activity was observed.



(134) (171)

Scheme 46

It was found that the oxetane (171) could also be prepared by the method of Moulines,[118] which is described in Scheme 47.



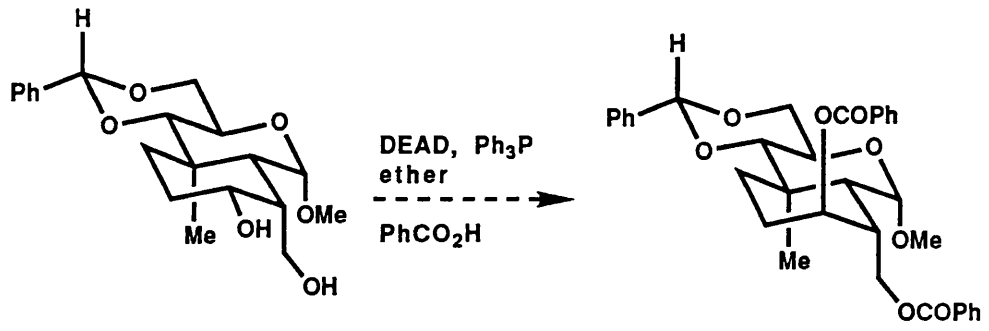
(134) (172) (171)

scheme 47

Here, the diol is firstly converted into the mono-tosylate (172) under standard conditions. The tosylate is then attacked by the hydroxy anion, when n-butyllithium is added to give the oxetane (171) in 78% yield.

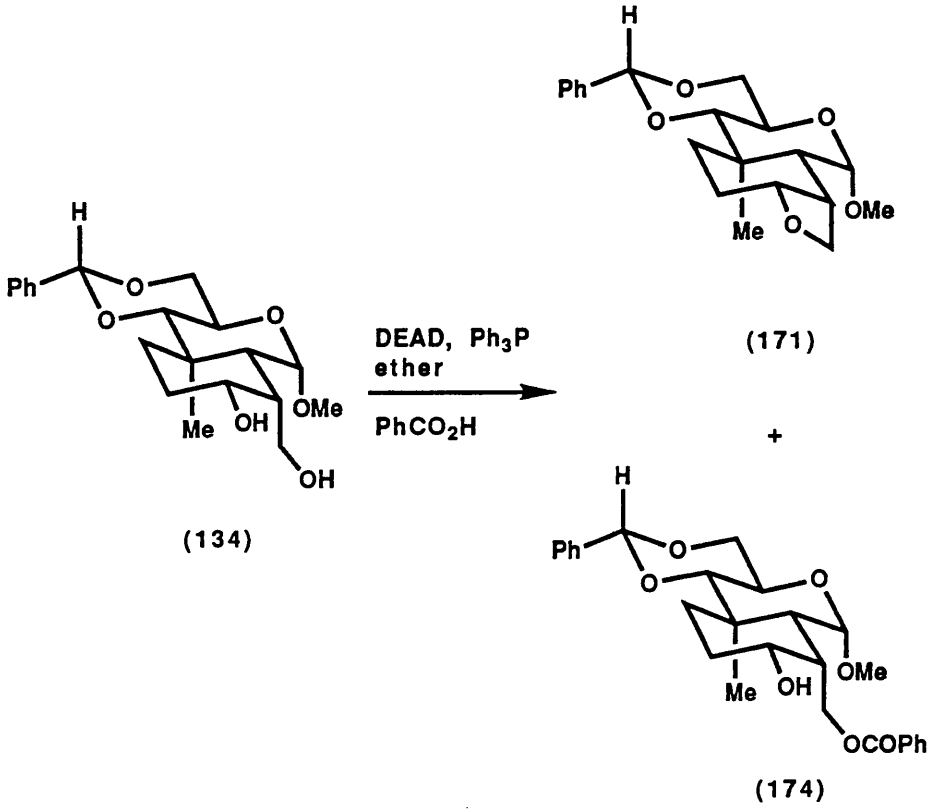
It has also been well documented that the Mitsunobu reaction is an excellent method for the inversion of hydroxyl functions *via* formation of an ester. We had already used this reaction in the synthesis seen in chapter two. Now there is still the problem in the route that the secondary hydroxyl group in the diol (134) has the wrong configuration to the hydroxyl group in taxinine (2). It might be possible for this to be corrected by the Mitsunobu reaction.

Reaction of the diol (134) with two equivalents of tri-phenylphosphine, DEAD and benzoic acid, did not, however,

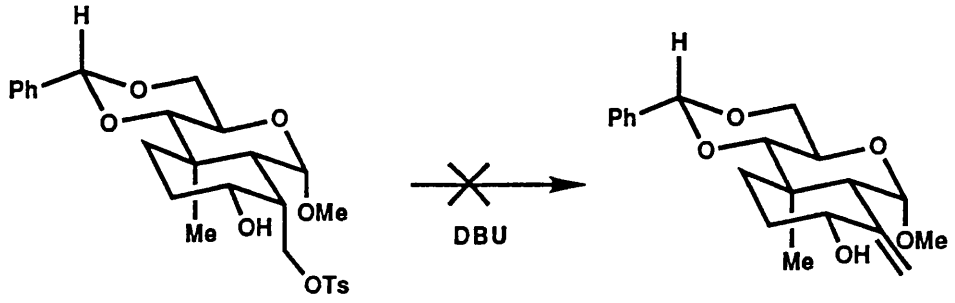


(134) (173)

result in the inversion of the secondary hydroxyl group to give the diester (173), but in a mixture of the oxetane (171) and the benzoate ester (174).

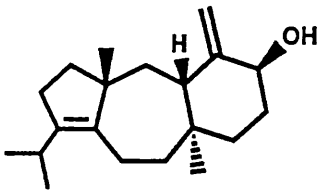


The elimination of the tosylate group from (172) would result in the exocyclic double bond in taxinine (2) being formed. Only one attempt at this elimination was made because we felt that construction of the taxane ring system was becoming the paramount objective. 1, 8-Diazobicyclo [5.4.0] undec-7-ene (DBU) has been used as a base to effect eliminations.[119] Thus we tried eliminate the tosylate group with DBU to give the alkene (175). The reaction however was unsuccessful and only starting material was recovered, tosylate (172).



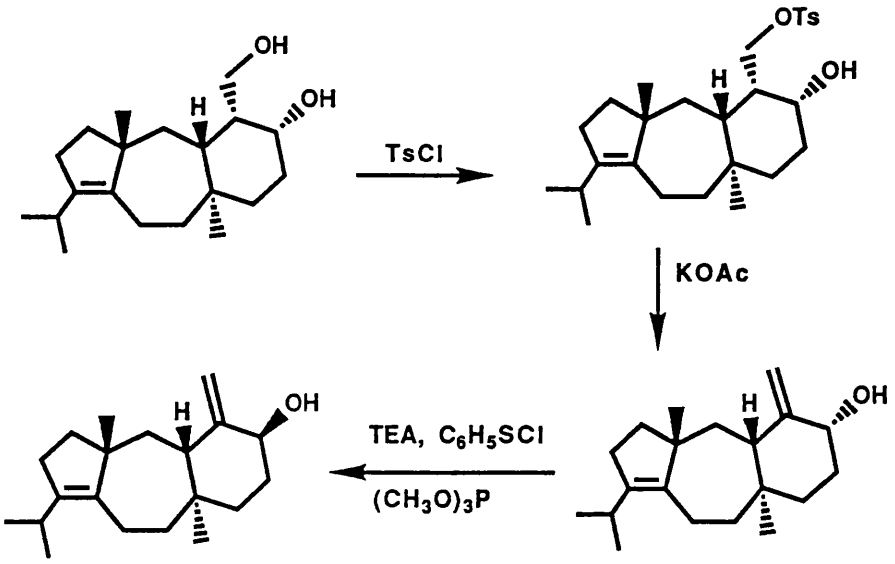
(172) (175)

Since our work on trying to form the exocyclic double bond, a paper has been published by Nemeth and Majetich[120] on a direct synthesis of 14-deoxyisoamijiol (176).



(176)

The six membered ring of (176) has the same functionality as that found in the taxinine (2) C-ring. Nemeth and Majetich's synthesis of this functionality, Scheme 48, can be applied directly to our diol system (134).

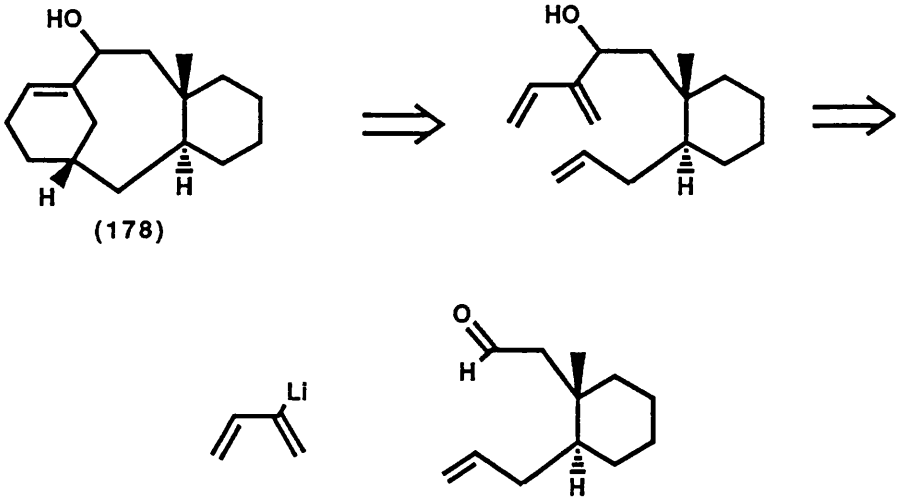


Scheme 48

Thus we feel confident that construction of the C-ring functionality for taxinine (2) can be achieved once the taxane skeleton has been synthesised.

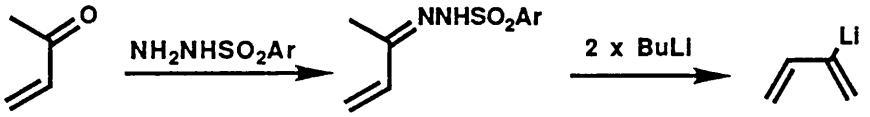
3.6 ATTEMPTS AT PREPARATION OF 3-LITHIO-2-TRIMETHYLSILYL BUTADIENE

The final part of this chapter is concerned with chemistry that is only vaguely connected with the synthesis of taxanes, in so much as the idea arose from Brown's investigations[121] into the use of 2-lithiobutadienes, which was one of the key steps in a stratagey to produce the taxane skeleton (178), Scheme 49.



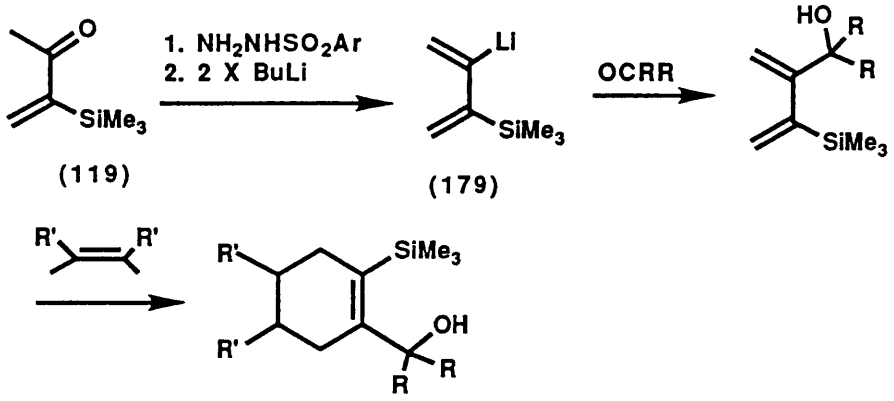
Scheme 49

The 2-lithiobutadiene was formed using the Shapiro reaction.[122]

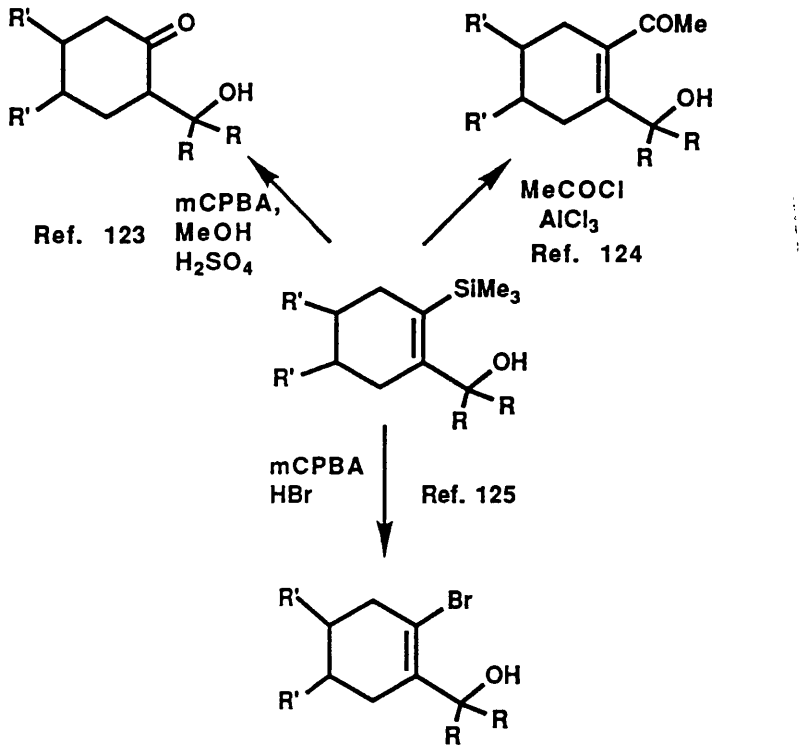


Ar = $C_6H_5Pr^i$-2,4,6

Since the reactions of vinylsilanes are so wide and varied, it was thought that some interesting chemistry might arise if 3-trimethylsilyl-3-butene-2-one (119) could be converted to 3-lithio-2-trimethylsilyl butadiene (179). This could then be added to electrophiles, possibly chiral, and the products could then undergo Diels-Alder reactions followed by some vinyl silane chemistry, Schemes 50 and 51.

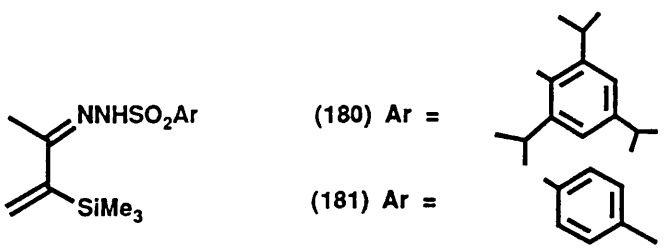


Scheme 50



Scheme 51

Both the compounds (180) and (181) were prepared, although in each case the yields were low, *c.a.* 25%.



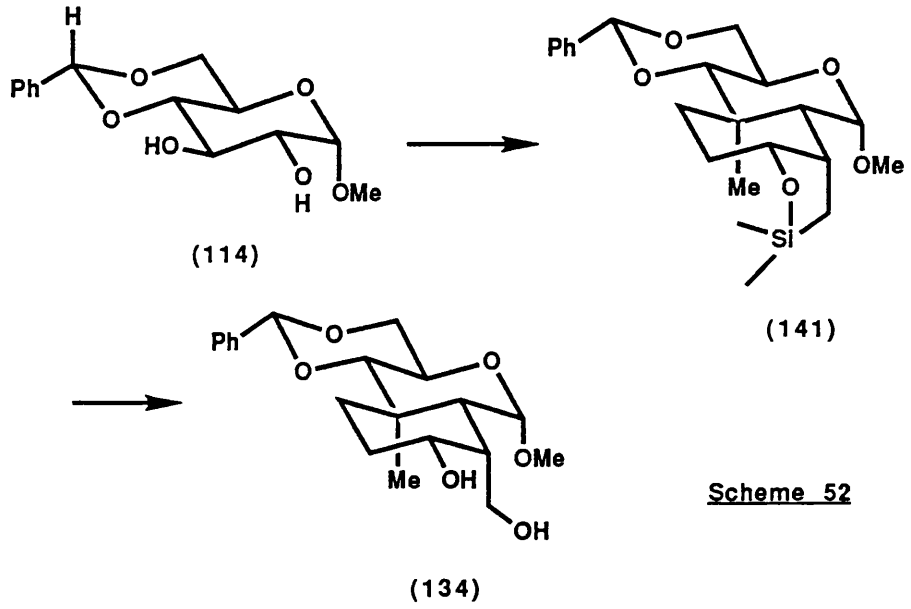
However, even after trying a wide range of solvent and temperature systems, neither (180) nor (181) could be made to undergo elimination in order to give the required butadiene anion (179).

CHAPTER 4.

Approaches for construction of the dienophile before the diene

4.1 INTRODUCTION

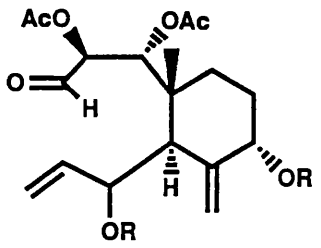
In chapter two the successful development of the carbohydrate (114) into the more advanced intermediates, the tetracyclic structure (141) and the diol (134), was described, Scheme 52.



Scheme 52

The next stage in the synthesis of taxinine (2) involves the conversion of one or both of these intermediates, which are essentially modified carbohydrates, into cyclohexane derivatives. The cyclohexane must contain the functionality required to build up a diene,[88,89] as in Schemes 15 and 25, (chapter one), by using a silicon- or selenium-assisted elimination. The cyclohexane obtained from (134) or (141) must also have the necessary functionality to allow construction of the dienophile in order to carry out the intramolecular Diels-Alder reaction. This would result in the formation of the desired taxane skeleton.

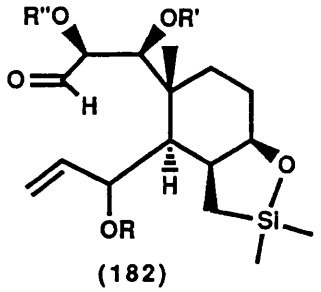
The initial retrosynthetic analysis, Scheme 29, led to the intermediate aldehyde (107). Therefore, this chapter consists of our attempts to produce an intermediate with this structure and functionality.



(107)

4.2 APPROACHES USING THE TETRACYCLIC STRUCTURE (141)

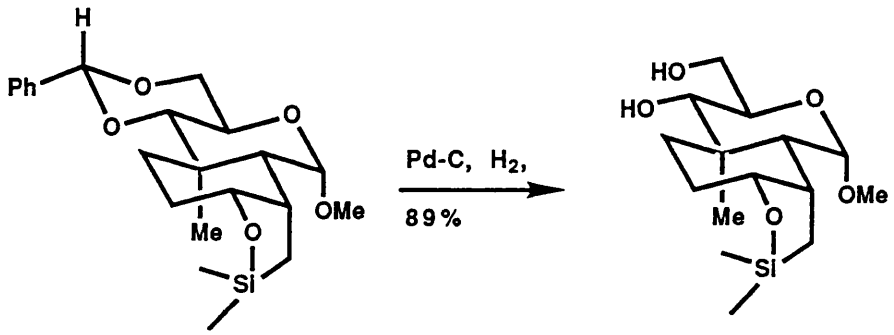
We felt that the dimethylsilaoxapentane ring system could possibly be used as a masked diol system. This would mean that the step for reprotecting the diol would not be needed. For this reason our modified target molecule became the aldehyde (182), where R, R' and R'' are suitable protecting groups.



(182)

With functional group interconversion of the dimethylsilaoxapentane ring to an exocyclic double bond and a hydroxyl group, by the method of Nemeth[120] we would have access to an intermediate similar to the aldehyde (107).

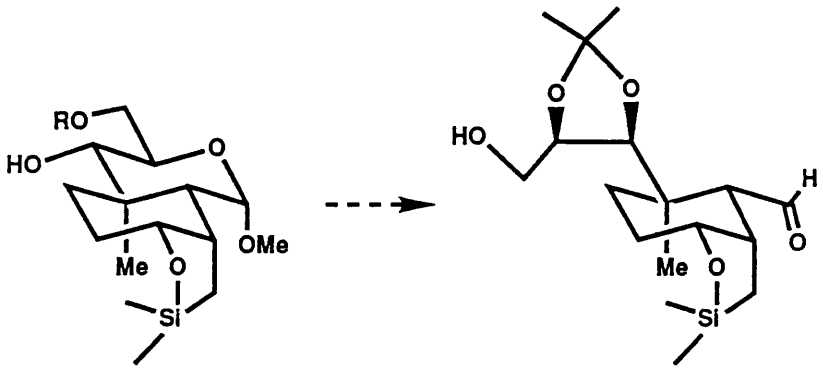
The initial steps towards achieving our target molecule (182) involved the investigation of the conditions necessary to selectively remove the benzylidene acetal in preference to cleaving the pyranoside acetal, hence resulting in the diol (183). A search of the literature gave two possibilities.



(141) (183)

The first method involved the use of p-toluenesulphonic acid in methanol,[126] and the second removed the acetal by reductive cleavage using hydrogen and palladium hydroxide on carbon in methanol.[127] Although both methods worked, we found that 5% palladium on carbon worked as well as palladium hydroxide on carbon and gave quantitative yields of the diol (183). This has been used to remove benzylidene acetals on different systems but never from carbohydrates.[128] The use of p-toluenesulphonic acid did not give as clean a reaction as the catalytic method and the products needed to be purified further by chromatography. This introduced a new problem, which was to become a crucial factor in deciding the fate of this route. The dimethylsilaoxapentane ring system was found to be unstable on silica.

Our plan, for the next step in the synthesis, was initially to protect the primary hydroxyl group in the diol (183). The pyranoside acetal could then be simultaneously opened and the C-2 and C-3 hydroxyl groups protected with an acetonide, as described in Scheme 53.



R = tBDMS (184) Yield 63%
R = OAc (185) Yield 58%

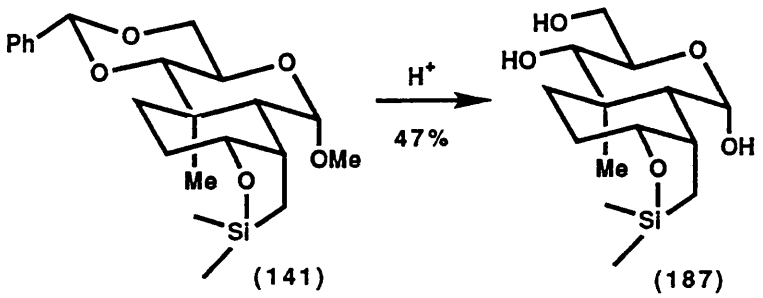
(186)

Scheme 53

To effect this reaction, the primary hydroxyl protected silyl ether (184), or acetate (185), was treated with acetone in the presence of a wide range of Lewis acid catalysts (aluminium chloride, boron trifluoride etherate and titanium tetra- chloride) as well as p-toluenesulphonic acid. However, at no stage of this investigation was there any indication of a moiety such as (186), either by t.l.c, n.m.r or mass spectrometry.

Literature precedent[129] implied that we would have to convert the pyranoside acetal into a hemiacetal if we were to have any success in reaching our target molecule (182). It was possible to convert the tetracyclic structure (141) directly into the hemiacetal (187) under strong acidic

conditions, such as refluxing with 1 molar aqueous sulphuric acid.

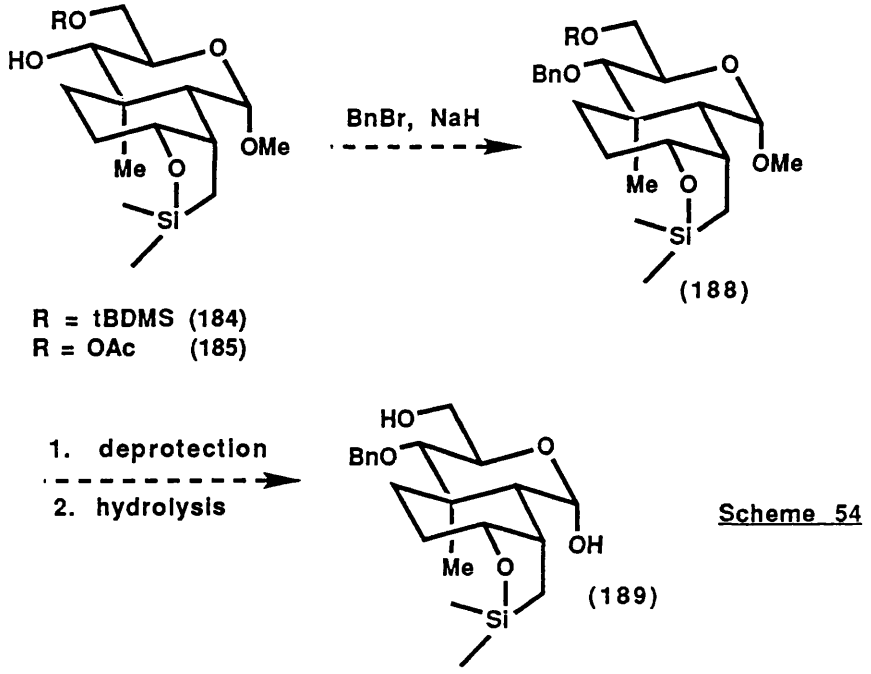


(141) (187)

The hemiacetal (187) cannot undergo differential protection of the primary hydroxyl group and the hydroxyl group at C-2 to leave the hemiacetal functionality free of protection, as the hemiacetal always reacts fastest with any protecting group.[130] We tried subjecting the tert-butyldimethylsilyl (t-BDMS) protected molecule (184) to the same conditions used for the conversion of (141) to the hemiacetal (187). However, even with careful monitoring of the rection, the t-BDMS group was removed during the course of the reaction to give, once again, the hemiacetal (187). However, it was considered possible for the ester (185) to be treated with an 80% acetic acid solution to cleave the acetal[131] and still retain the acetate protecting group. In fact this was not possible and t.l.c of this reaction showed numerous spots, presumably containing a mixture of the combinations of acetate protected hemiacetal (187), and so this route was pursued no further.

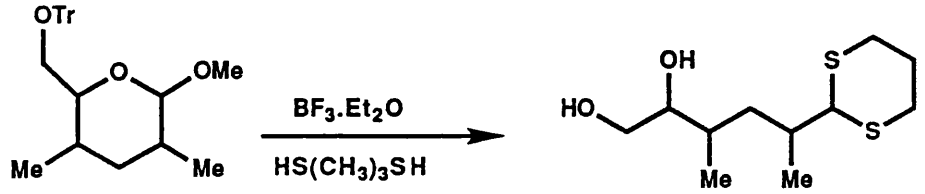
We wondered if it would be possible to avoid the loss of the silyl protecting group in the silylether (184) and the need for simultaneous protection of the C-2 and C-3

hydroxyl groups, as in Scheme 53, by using either of the mono protected molecules (184) or (185), and then protecting the C-2 hydroxyl group with a more inert protecting group such as a benzyl[132] or methyl ether[133] type group. Subsequent deprotection of the primary hydroxyl and hydrolysis of the pyranoside acetal (188) would provide the monohydroxyl hemiacetal (189), Scheme 54.

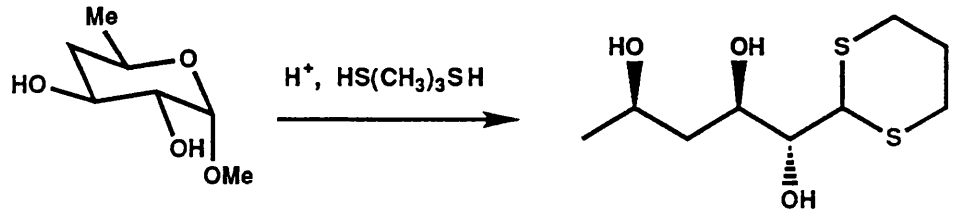


Scheme 54

Conversion of acetals or hemiacetals to dithanes has been well covered in the literature. Sum and Weiler[134] opened the carbohydrate (190) to give (191) by using 1, 3-propanedithiol and boron trifluoride etherate. This reaction can also be carried out using alternative acid conditions as reported by Redlich.[135]

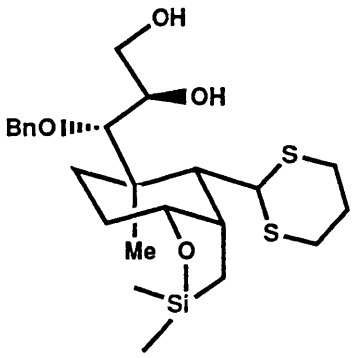


(190) (191)

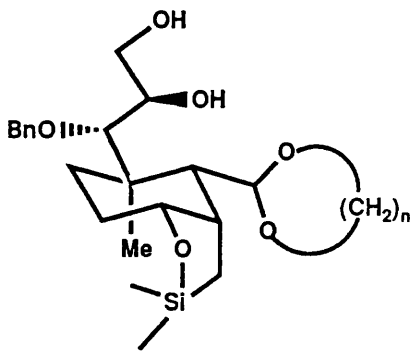


(192) (193)

The synthesis of (189) would give us the possibility of converting the hemiacetal function to the dithiane (194) or possibly to an alternative acetal such as (195).



(194)

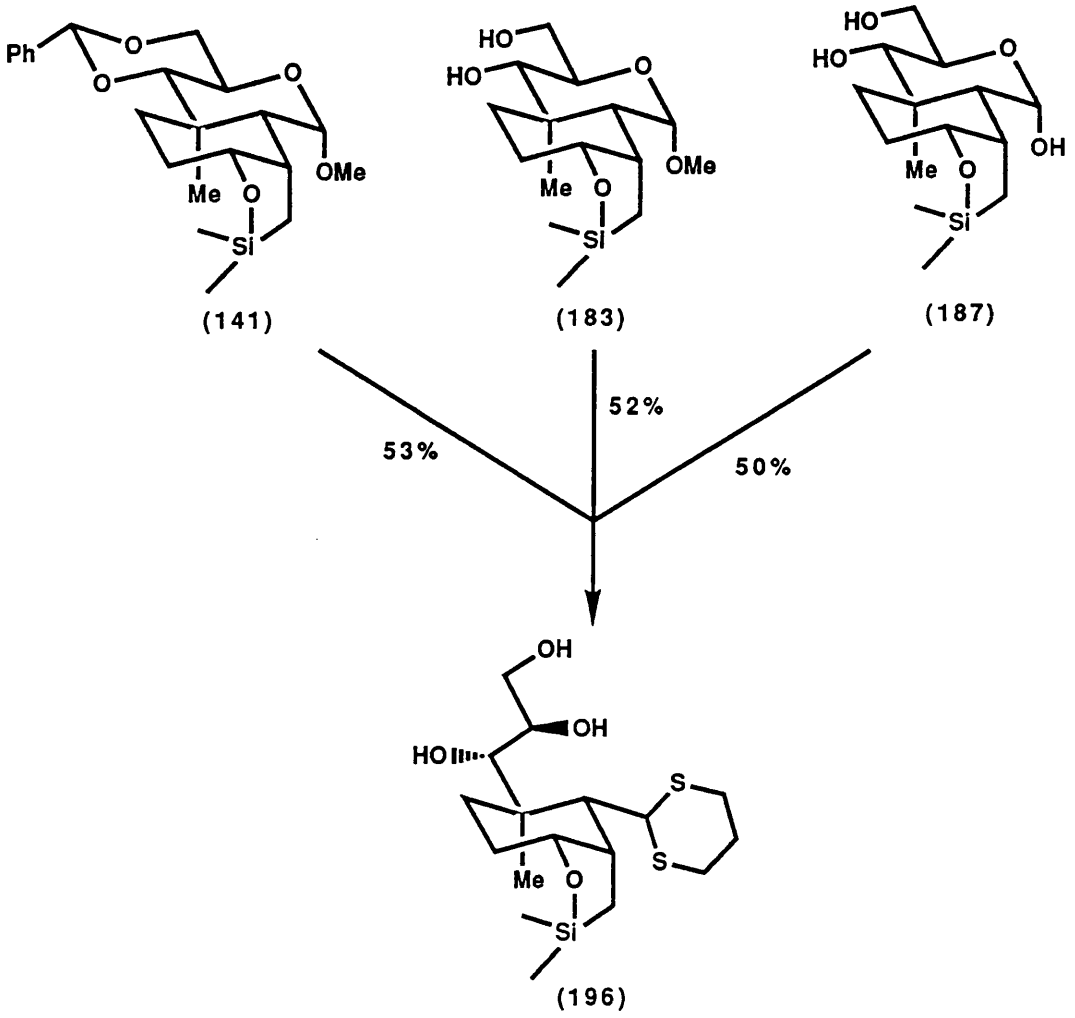


(195) n = 2 or 3

Compounds such as (194) or (195) would lead smoothly to the target aldehyde (182).

Unfortunately, we could not protect the C-2 hydroxyl of (184) as the benzyl or methyl ether, because the dimethylsilaoxapentane ring appeared to be attacked by the hydride reagent, used to attach the benzyl group, thus producing a black tar. However, it was possible to take

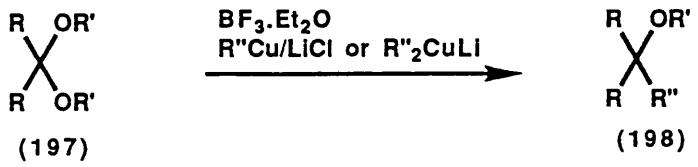
the compounds (141), (183) and (187), and convert them to the dithiane (196), using 1, 3- propanedithiol and boron trifluoride etherate at room temperature.



The cyclohexane (196) was the first breakthrough in our attempt to convert the initial advanced intermediate (141) into a molecule that no longer contained a pyranoside ring. Although this was an achievement to us, the dithiane (196) was of no use in furthering the synthesis of taxinine (2) for two reasons. Firstly attempts to selectively protect the primary hydroxyl function failed, resulting in a probable mixture of the C-2, C-3 and C-4 protected hydroxyl

groups, when protection by acetate or tert-butyldimethylsilyl chloride (t-BDMS-Cl) were attempted. It was not possible to separate the mixture by chromatography. Secondly the yields of the dithiane (196) were never greater than 53% and this could only be achieved by careful monitoring of the reaction. It would appear that the dimethylsilaoxapentane ring was also being attacked by the boron trifluoride etherate. As this approach to aldehyde (182) was becoming impracticable, so we sought a different method for the acetal ring opening.

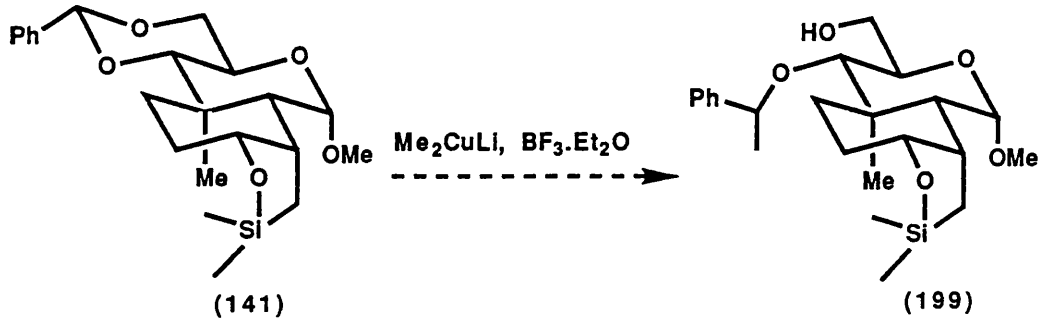
It has been shown by Alexakis[137] that acetals are cleaved by reaction with organocopper reagents in the presence of borontrifluoride etherate, to afford the product of substitution of one alkoxy group, Scheme 55.



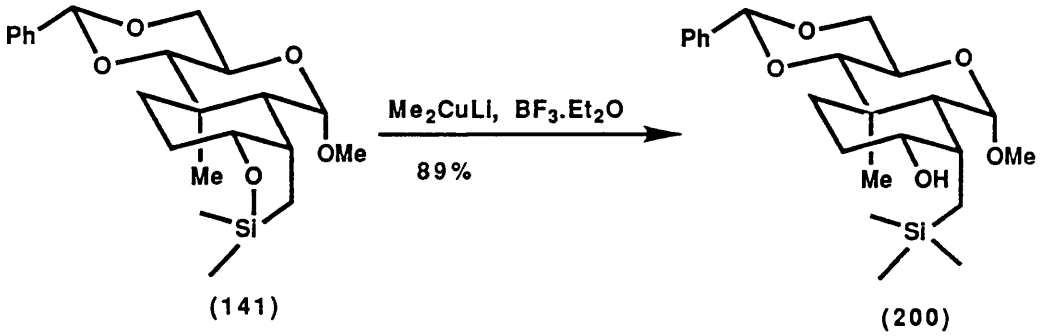
Scheme 55

The reaction is quite fast, even at low temperatures, and organocuprates, are more reactive than organocopper reagents. If this reaction could be applied to the tetracyclic product (141), using the simple organocuprate Me_2CuLi, then there is a possibility that we could regioselectively cleave the benzylidene acetal, without affecting the pyranoside acetal, to give a methyl benzyl ether on the C-2 hydroxyl group. This would achieve the

protection order necessary for the production of aldehyde (182).

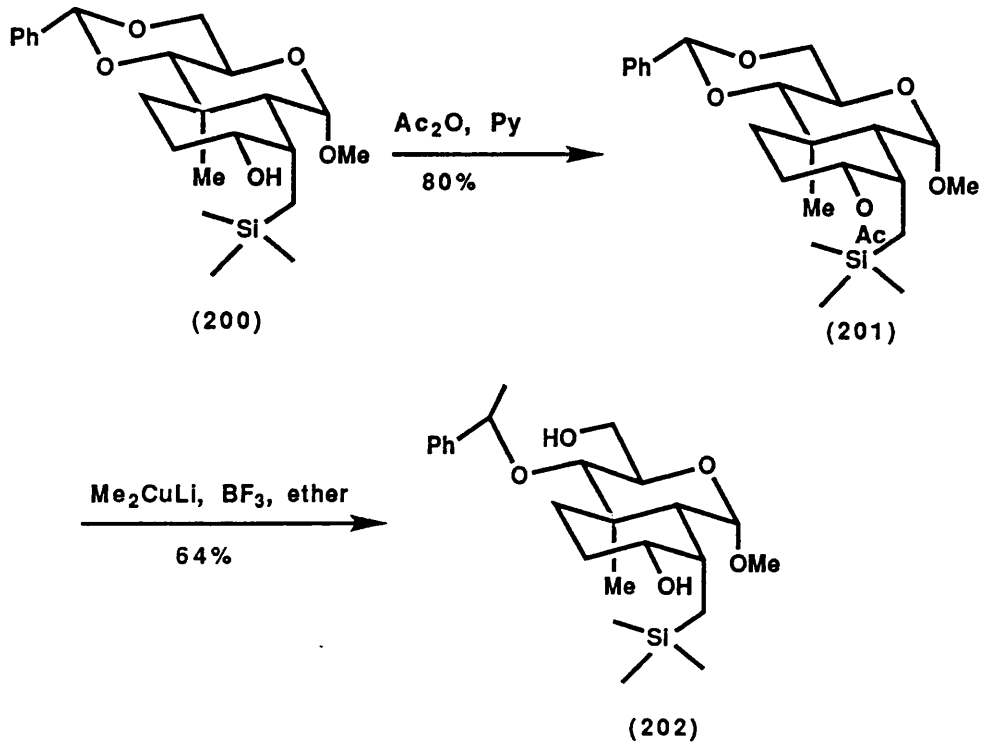


This opening of acetals with organocopper reagents is performed with a 1:1 stoichiometric amount of the reactants. When it was applied to the tetracyclic molecule (141), the outcome was that the dimethylsilaoxapentane ring was cleaved to give the secondary alcohol (200), and not the desired product (199).



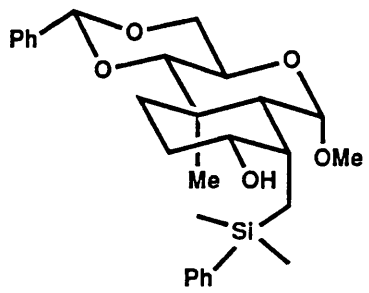
However, we still needed to know the regioselectivity of these organocopper or cuprate reagents on our system (141). Thus the tricyclic molecule (200) was protected at the hydroxyl group to give the acetate ester (201). We hoped that at low temperature the acetate would not be cleaved by

the organometallic reagent. Subsequent addition of a one molar



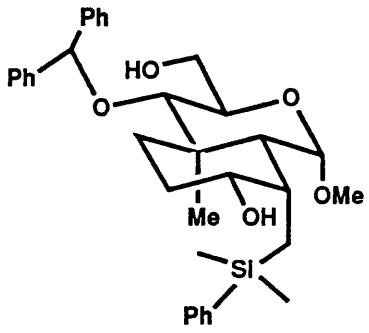
equivalent of Me_2CuLi to the ester (201) at -50°C led to a mixture of a diol , the alcohol (200) and starting material. Addition of two molar equivalents of Me_2CuLi to the ester (201) gave a diol in 64% yield. It was observed that the diol obtained had a methylene group with a carbon n.m.r shift of δ62.36. From carbon shift n.m.r data tables[138] we know that a methylene group bonded to an ether at oxygen has a shift of δ71.00. We also know that a methylene group bonded to a free hydroxyl group has a shift of δ63.00. The three other methylene groups in the diol have shifts of δ39.00 and higher. We can therefore deduce that the diol has the structure shown, (202). Thus the reaction has the desired regioselectivity.

These compounds, (200), (201) and (202) are of little use because the trimethylsilyl group cannot be converted to any useful functionality. Therefore we thought that it was unnecessary to carry out an X-ray crystal analysis on (202) to confirm the regioselectivity of the reaction. However this pathway could possibly be modified to produce the alcohol (203). We could convert the phenylsilyl group into a hydroxyl function[58] provided that we could make phenyl-copper or



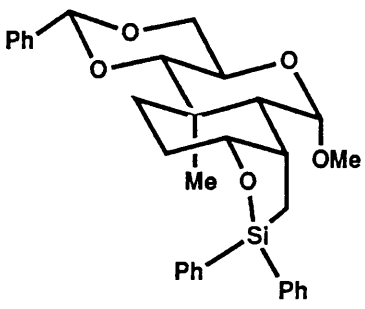
(203)

cuprate reagents add in the same way as the Me_2CuLi. The addition of phenylcopper, lithium chloride and boron trifluoride to the tetracyclic (141) resulted in a mixture of products along with starting material, according to t.l.c. Several attempts to obtain a much cleaner reaction were not successful. However, we feel from crude n.m.r spectra and mass spectrometry of the mixture, that the diol (204) was not formed.



(204)

This pathway has not been fully explored as possible route to the target molecule (107). Due to the continuing difficulties posed though, by the tendency of the dimethylsilaoxapentane ring to partially disintegrate on flash chromatography, especially if the products of the reactions have lower R_f values than the starting material, that it would be prudent to discontinue using (141) as a masked diol and to seek alternative paths. One such path would perhaps be to form the diphenyl analogue of (141), (205) as this would perhaps have more stability. Research by Lawrence[139] failed to



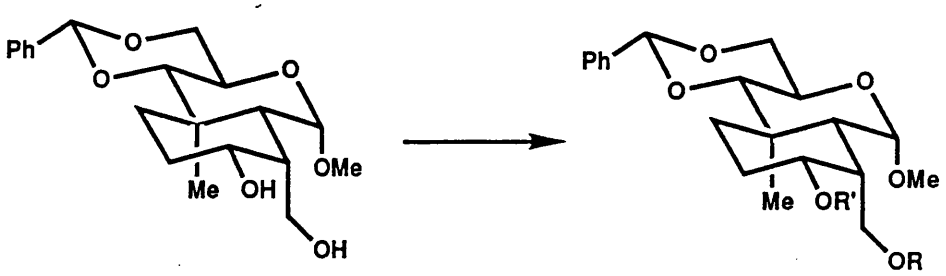
(205)

produce the diphenyl analogue of dimethyl (bromomethyl) chlorosilane, necessary for the radical cyclisation reaction and so we turned our attention to the use of the

diol (134) as our starting intermediate for our approach to the aldehyde (107).

4.3 APPROACHES USING THE DIOL (134)

It was decided to start by looking at viable protecting groups for all the hydroxyl groups within the diol (134).



(134)

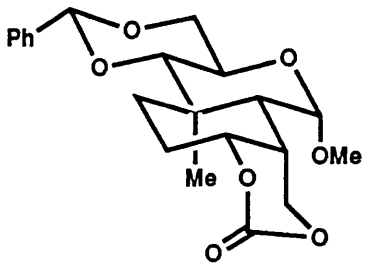
The fundamental requirements for the protecting groups, R and R', depends upon the path chosen to obtain an intermediate equivalent to the aldehyde (182). Firstly, R and R' must not be removed under the conditions used to remove the benzylidene group, *i.e* hydrogenation or acid hydrolysis. This is probably the most important criterion. Secondly, they must be stable, if possible, to boron trifluoride etherate. Thirdly, they must not be open to attack by alkyl metals, since the diene synthesis involves the use of these reagents. Lastly they must be able to be selectively removed from the molecule at later stages in the synthesis. Therefore, from this, it should be appreciated that with such a molecule where there is a potential for five hydroxyl groups, some of which are in very similar environments, and an aldehyde functionality it is almost impossible to meet these requirements even with

the vast selection of protection groups available. It should also be noted that, at this particular stage, the priority lay with creating a general taxane ring system from glucose and not with producing a synthesis to one specific taxane. Thus, studies of the removal of one particular ester, for example, in favour of another or the removal of one specific silyl ether in preference to another, were not of major importance here. Hence, for our purpose, protection of the hydroxyl group can be classified into several distinct groups.

Firstly, there are the ethers, which contain protection such as benzyl, MOM, MEM and THP groups.[140] The MOM, MEM and THP groups are stable to mild acidic conditions, but they tend to be cleaved by strong acids and boron trifluoride etherate. The benzyl and methyl ethers require hydrogenation, sodium in liquid ammonia or vigorous acid conditions to remove them.

Secondly, there are the silyl ethers. These are usually stable to mild acidic conditions, with the exception of TMS, and to hydrogenation. They usually require fluoride ions or strong acid conditions to remove them, although other methods have been reported.[140,141] Thirdly, there are the esters,[140] which is a fairly diverse family. There are numerous methods for their formation but most esters are unstable to acidic conditions. However, they appear to be stable to boron trifluoride etherate. Fourthly, there is the group of carbonates. However, like esters, these are cleaved under basic conditions. They are though, generally stable to acid with the exception of alkyl isobutyl

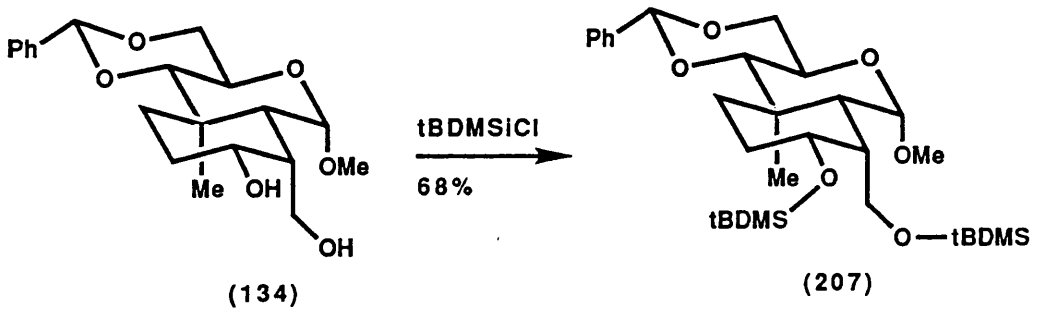
carbonates.[142] The last group contains the acetals. These could not be used as two acetal functions were already present and a third would only make the problem worse. Initially, it was decided to use the carbonate protecting group. Attempts at making the carbonate (206) though, using N',N'-carbonyl diimidazole under reflux for five days,[143] were



(206)

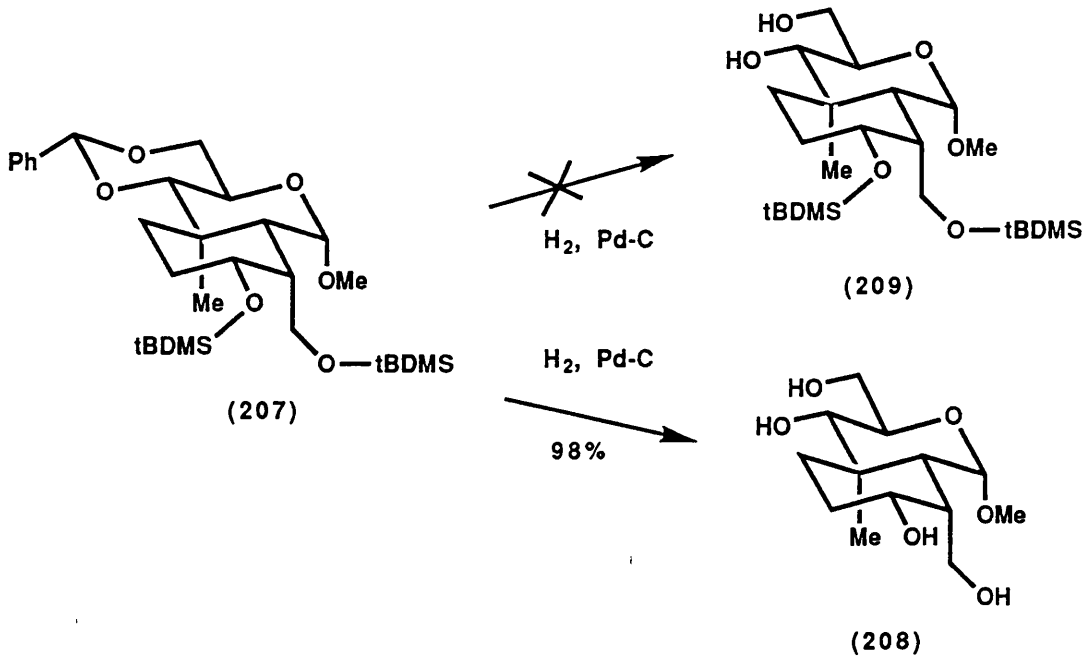
unsuccessful. Also, we suspected that, though the carbonate function would be stable to acid, it would be removed in some of the steps later on in the synthesis. Therefore, this route was ruled out.

We chose the dimethyltertiarybutyl silyl group as our next form of hydroxyl group protection. It has the ability to withstand fairly vigorous conditions including, according to literature precedence,[140] hydrogenation. The diol (134) was reacted with two equivalents of dimethyltertiarybutyl silylchloride to produce the silyl ether (207).



(134) (207)

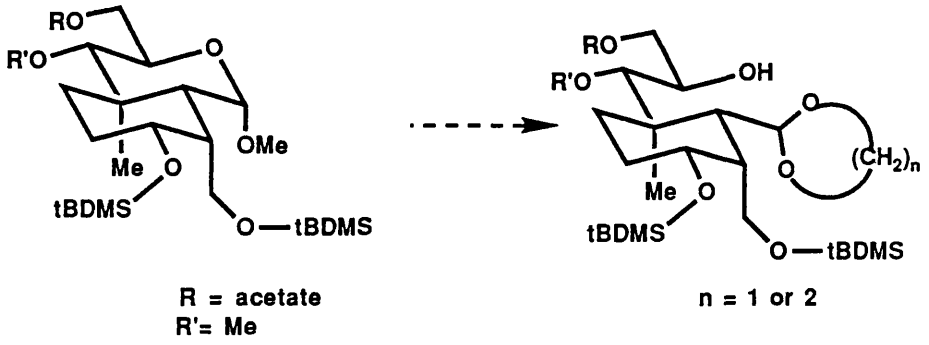
It was known that boron trifluoride etherate could remove a t-BDMS group,[140] but we could possibly use the method of Redlich[135] to produce the dithiane. However, an unexpected result was obtained, when the silyl ether (207) was subjected to identical hydrogenation conditions to those used in the formation of the diol (183). Hydrogenation removed both t-BDMS groups to give the tetraol (208) and none of the diol (209) was obtained.



(207) (209) (208)

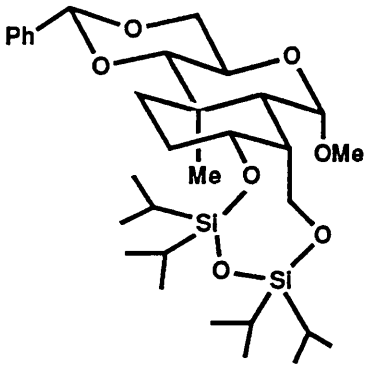
We found that gently refluxing (207) with 2M sulphuric acid removed the t-BDMS and benzylidene acetal groups. We therefore concluded that silyl ether (207) would not

survive the conditions necessary to construct a dithiane, and felt that it was unnecessary to try p-toluene sulphonic acid in an attempt to obtain diol (209). Therefore, we were now in a position where we could not use hydrogenation or boron trifluoride etherate in our attempt to convert our intermediates into cyclohexanes. We could not even form alternative acetals of the pyranoside acetal, as in Scheme 56, using tosic acid and various glycols. Thus, we decided that it was time to change our strategy.

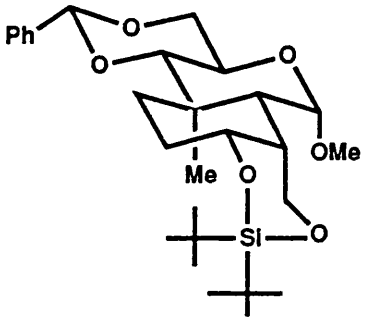


Scheme 56

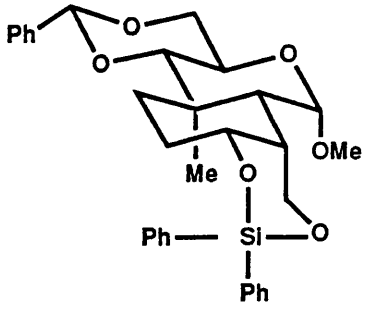
However, before this approach was completely abandoned, some alternative silyl protecting groups for the diol (134) were tried. Most of this work was covered by Davies.[144] The three compounds (210), (211) and (212) were prepared.



(210)



(211)



(212)

All of these compounds were subjected to the conditions applied to (207). They were all found to be unstable and so this part of the work was concluded.

CHAPTER 5.

Approaches for construction of the diene before the dienophile

5.1 INTRODUCTION

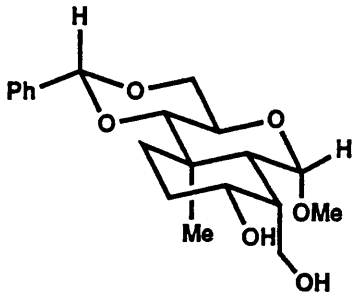
From the work covered in chapter four, it appeared that a route to the desired intermediate aldehyde (107) was not going to be achieved using that strategy. The synthetic pathway comprising of selective protection of the hydroxyl groups in the diol (134) followed by removal of the benzylidene function, differential protection of the resulting free hydroxyl groups and ring opening of the pyranoside acetal, proved to be too difficult. We were attempting to follow the same methodology as described by Bonnert in his synthesis of the taxane skeleton (99) (Schemes 15 and 25). This therefore required the exposure of the C-9 (C-1 carbohydrate numbering) aldehyde function during the synthesis in order to facilitate subsequent attack by a vinyl Grignard reagent. Hence incorporation of the dienophile would occur before the construction of the diene.

However, it occurred to us that it should be possible to construct the diene prior to the dienophile, since the pyranoside acetal can be considered as a protecting group for a hydroxyl group and an aldehyde function. Thus, removal of the benzylidene group and producton of an aldehyde function on the exposed primary hydroxyl group would enable construction of the diene.

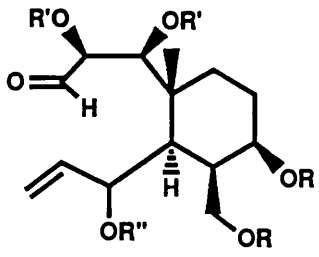
5.2 PREPARATION OF THE ADVANCED INTERMEDIATE, ALDEHYDE (229)

We initiated a search for the best intermediate in order to develop our new strategy of building up the diene

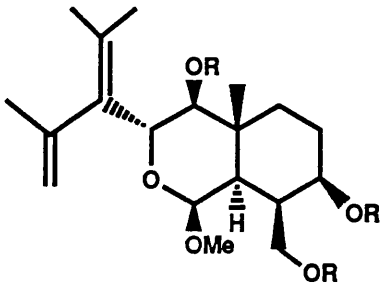
functionality on the C-6 (carbohydrate numbering) carbon atom of the protected diol (134) (see Scheme 57). Therefore our target molecule now changed from being the aldehyde (182) to the diene (213), where R, R' and R" are suitable protecting groups.



(134)

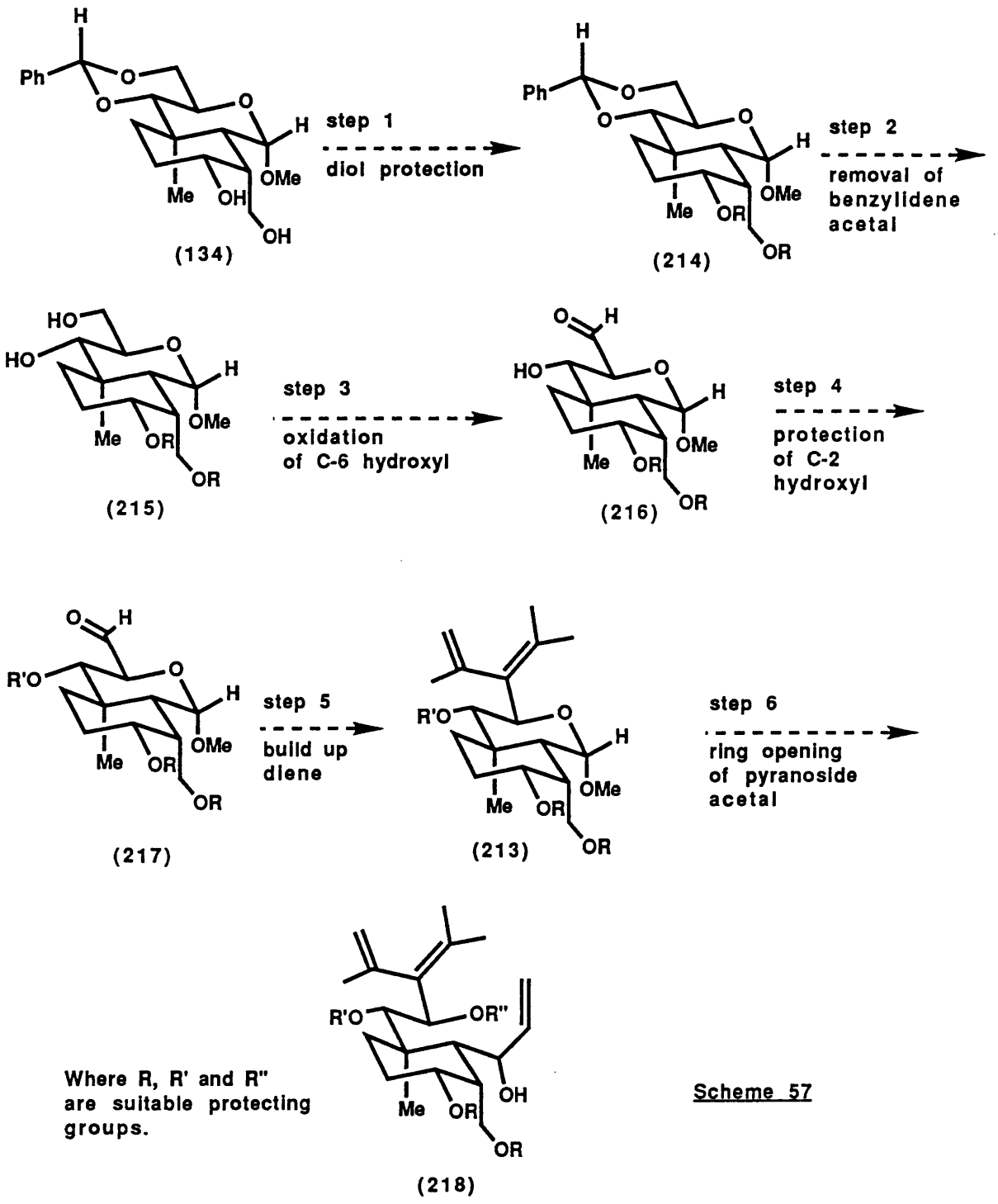


(182)



(213)

It was already known that it was possible to selectively protect the diol (134) with several different groups. The new synthetic pathway is outlined in Scheme 57.

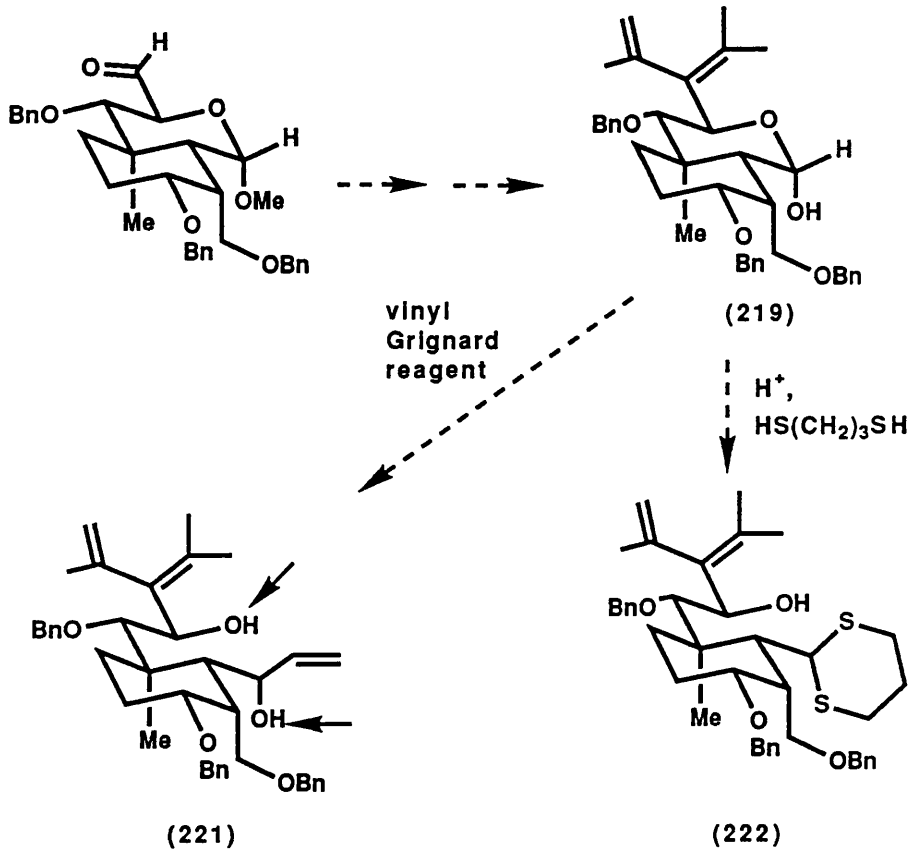


Scheme 57

We proposed to protect the hydroxyl groups in (134) to give (214), from which the benzylidene acetal could then be removed. Subsequent oxidation of the primary hydroxyl group, and protection of the secondary hydroxyl group would lead to the aldehyde (217). We could then build up the

diene, by using the methods developed by Bonnert[80] or Brown,[57] to give (213) which is our new target molecule. Removal of the pyranoside acetal to give the dithiane of (213), protection of the C-2 hydroxyl group, deprotection of the dithiane and attack on the unmasked aldehyde, would result in the enol (218) finally being formed. This product is only two steps away from a taxane.

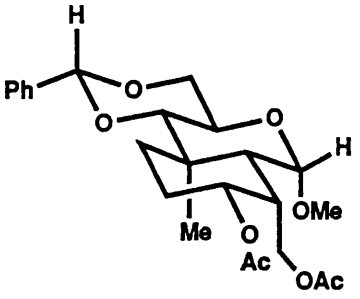
The use of silicon protecting groups in step one, was ruled out as they had already proved to be unstable to the reaction conditions required to produce (218). This left a choice between an ether or an ester protecting group for the hydroxyl groups in the diol (134). The use of a benzyl ether as a protecting group, would lead to the diene (219). This product (219) would require the use of acid hydrolysis for the opening of the pyranoside acetal or preparation of a dithiane (222) without the use of boron trifluoride etherate. Also a direct attack of a vinyl Grignard reagent on this compound (219) will result in the formation of a product (221), where selective protection and oxidation of two allylic hydroxyl groups (arrowed), in chemically equivalent positions, would be required, Scheme 58.



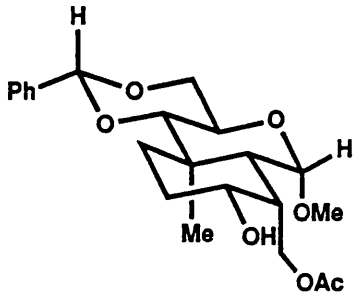
Scheme 58

The use of ester protecting groups poses a problem with subsequent reactions as they require organometallic reagents, Scheme 25, which could also attack the ester function. However, this problem could be overcome by using low temperature reaction conditions.

Therefore, initially, we opted for the acetate ester as the best protecting group for the diol (134). Since it is stable to boron trifluoride etherate.[145] Hence, reaction of the diol (134) with acetic anhydride and pyridine, at room temperature, produced the desired diacetate (223) in a 62% yield with the monoacetate (224) in a 21% yield.

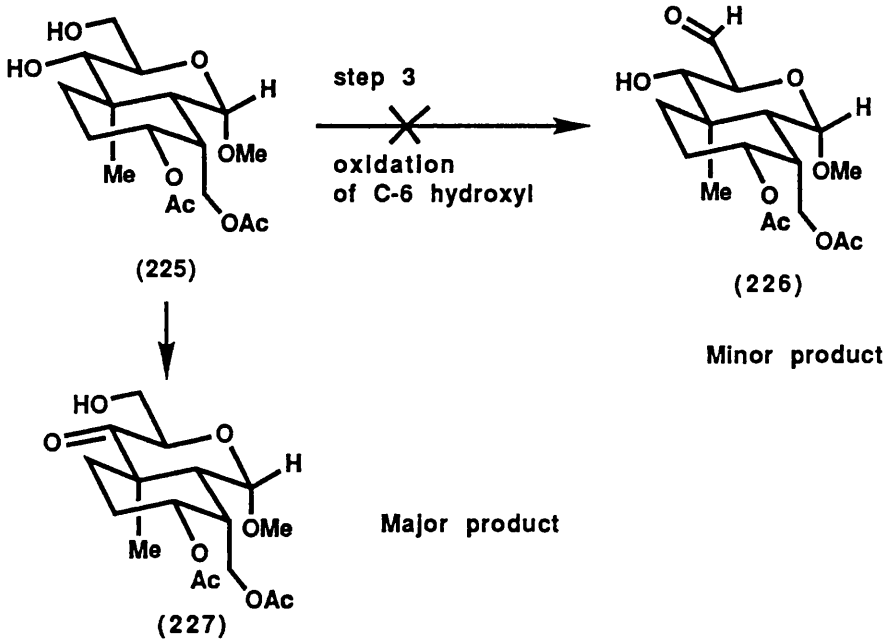


(223)



(224)

Hydrogenation of (223) over palladium on carbon, produced the diol (225), with no complications in a 95% yield. The next step involved the oxidation of the primary hydroxyl group in the presence of the secondary hydroxyl group, to give the aldehyde (226).

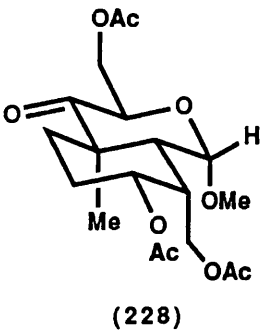


From the large number of methods available, for the oxidation of hydroxyl groups to aldehydes, none of those tried would oxidise the primary hydroxyl group in favour of the secondary to give (226) as the major product (see Table 1). All the acidic oxidising agents were excluded due to

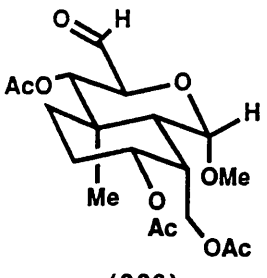
the high sensitivity of the acetate and the acetal functionalities in the diol (225) to acids. Various dimethylsulphoxide oxidation conditions were tried,[94] together with chromium trioxide and pyridine in dichloromethane,[95] ruthenium tetraoxide[96] and Fetizon's reagent.[146] The ketone (227) co-eluted with the aldehyde (226), on flash chromatography, so the quantity of each formed had to be estimated from their acetate derivatives. Thus, on treating the mixture of aldehyde (226) and ketone (227) acetic anhydride and pyridine, the keto acetate (228) and the aldehyde acetate (229) were formed.

Oxidising reagent	Percentage of carbonyl	
	(228)	(229)
$DMSO/(CF_3CO)_2O$	26	21
CrO_3/py	58	13
RuO_4/CCl_4	25	26
Ag_2CO_3/silica	-	-

Table 1



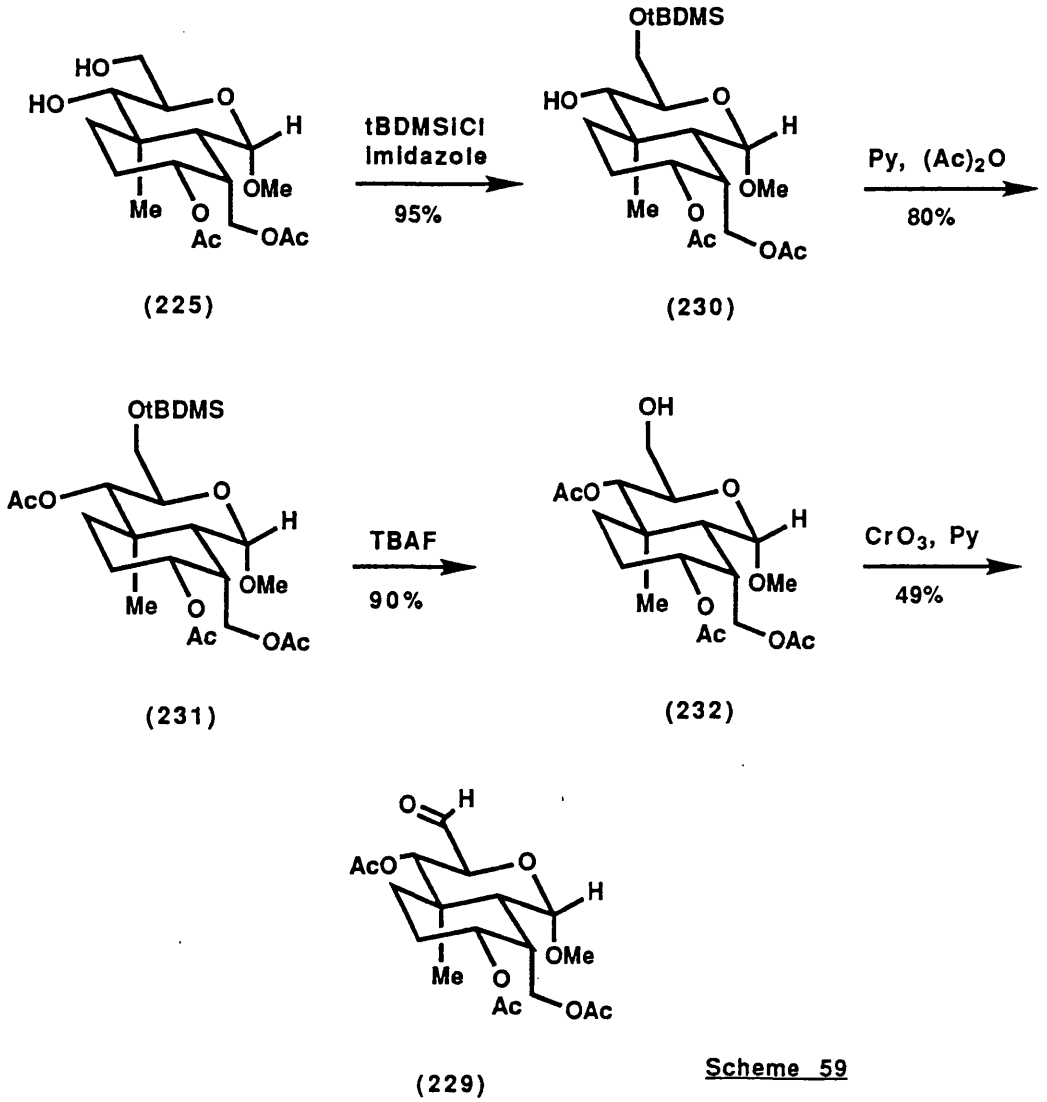
(228)



(229)

These were now separable by flash chromatography. The aldehyde (229) was the target molecule for step four, if R' = R (Scheme 57). However, this method for producion it was not very satisfactory, and so it was decided to investigate a longer but hopefully more productive route. This route is outlined in Scheme 59.

Firstly, the diol (225) was mono-protected, using dimethyltertiarybutylsilyl chloride to give the alcohol (230). This was then subjected to standard acetylation conditions to give the triacetate (231).

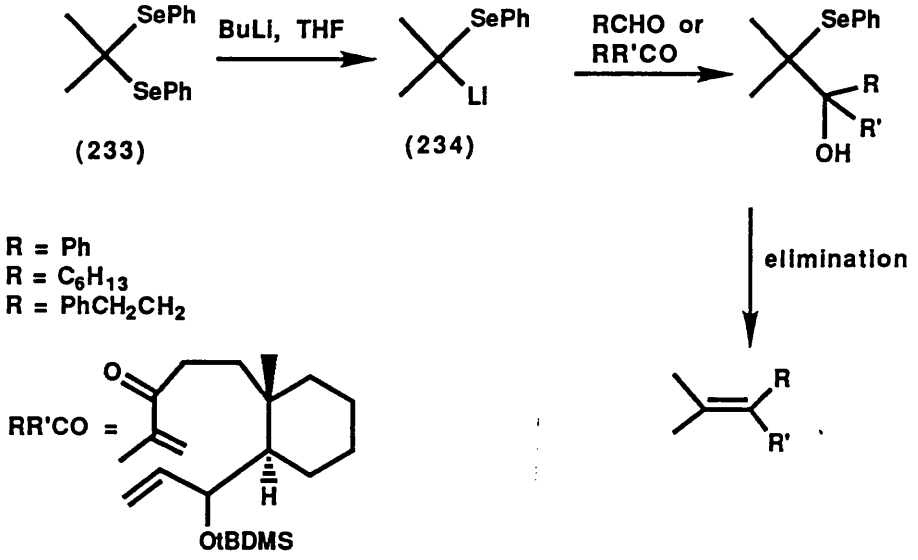


(225) (230) (231) (232) (229)

Scheme 59

Once the silyl group had been removed, using tetrabutyl ammonium fluoride (TBAF),[147] the resulting primary alcohol could be oxidised to the aldehyde (229) using pyridinium dichromate or by a Swern oxidation. We had therefore managed to produce an advanced intermediate onto which the diene moiety could now be constructed by using the selenium- or silicon-directed synthesis.

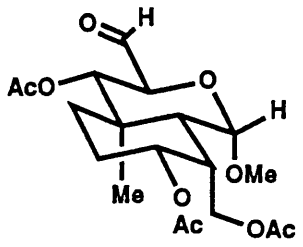
However, it was felt that the model systems studied by Brown[57] and Bonnert[80,88] in order to construct the diene by either a silicon- or selenium-assisted route, were too simple to justify an immediate attempt at building up the diene on our intermediate aldehyde (229). The aldehydes investigated by Bonnert are shown in Scheme 60. There is very little steric hindrance present in these substrates and there is



Scheme 60

no other oxygen functionality apart from the carbonyl. However, within our precursor (229) the large amount of

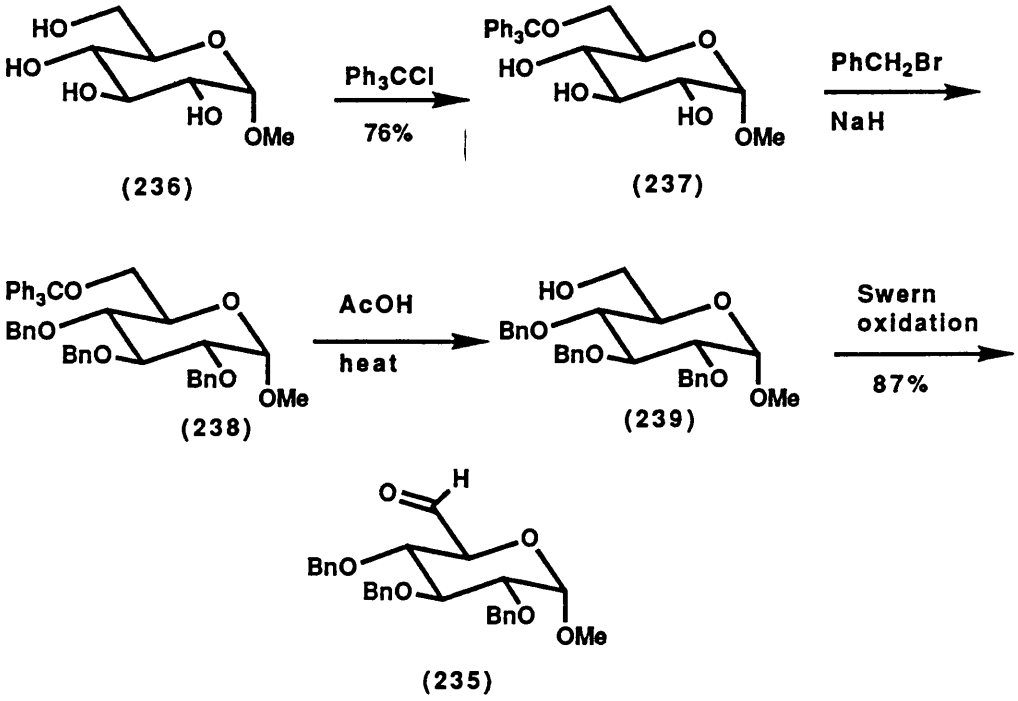
oxygen functionality may affect its reaction with the organometallic reagents and the steric bulk is greater around the aldehyde function. Thus, it was decided that further model studies were warranted on the selenium directed diene synthesis, using a carbohydrate aldehyde, before applying it to our compound (229).



(229)

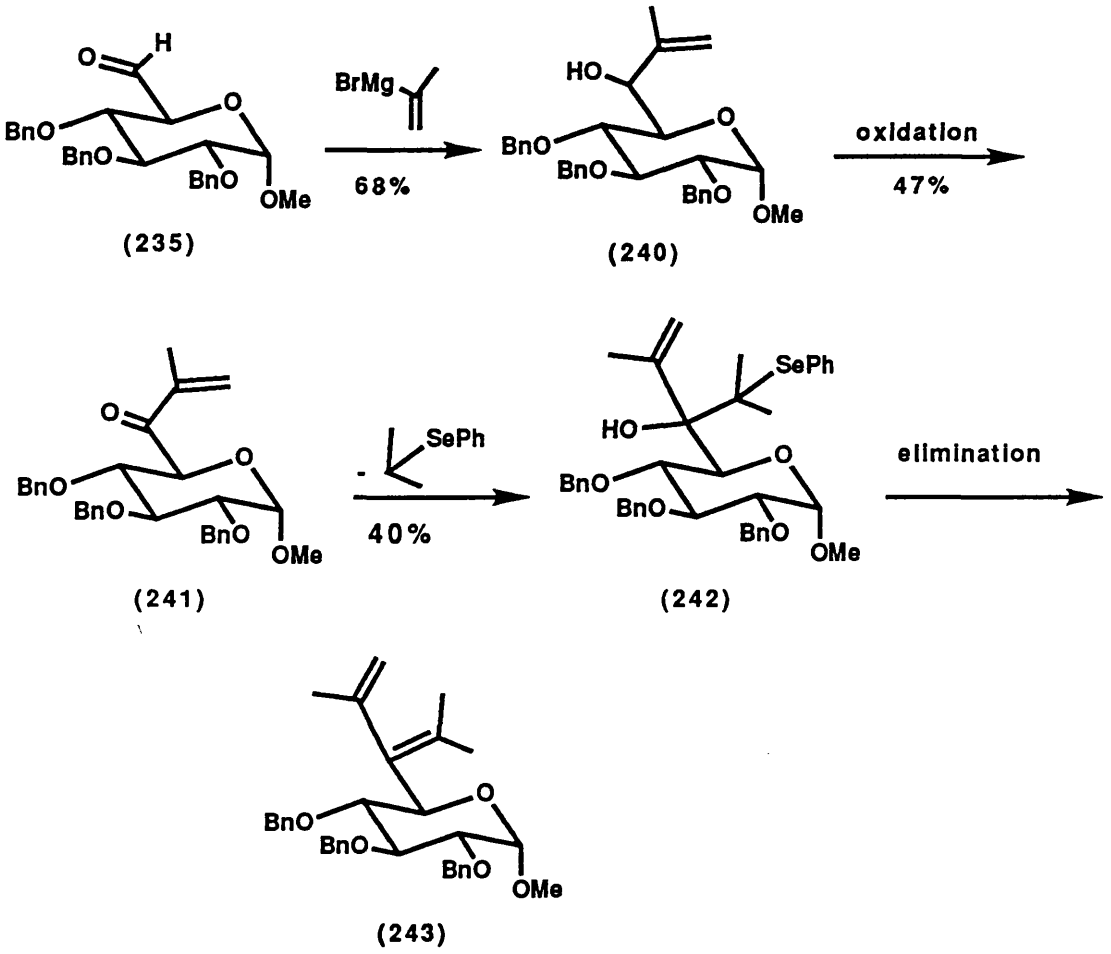
5.3 A MODEL STUDY FOR THE CONSTRUCTION OF HIGHLY SUBSTITUTED DIENES ON COMPLEX ALDEHYDES

The most readily accessible cabohydrate aldehyde, available in large quantities is the aldehyde (235), which could be made by the simple route[148,149] shown in Scheme 61.



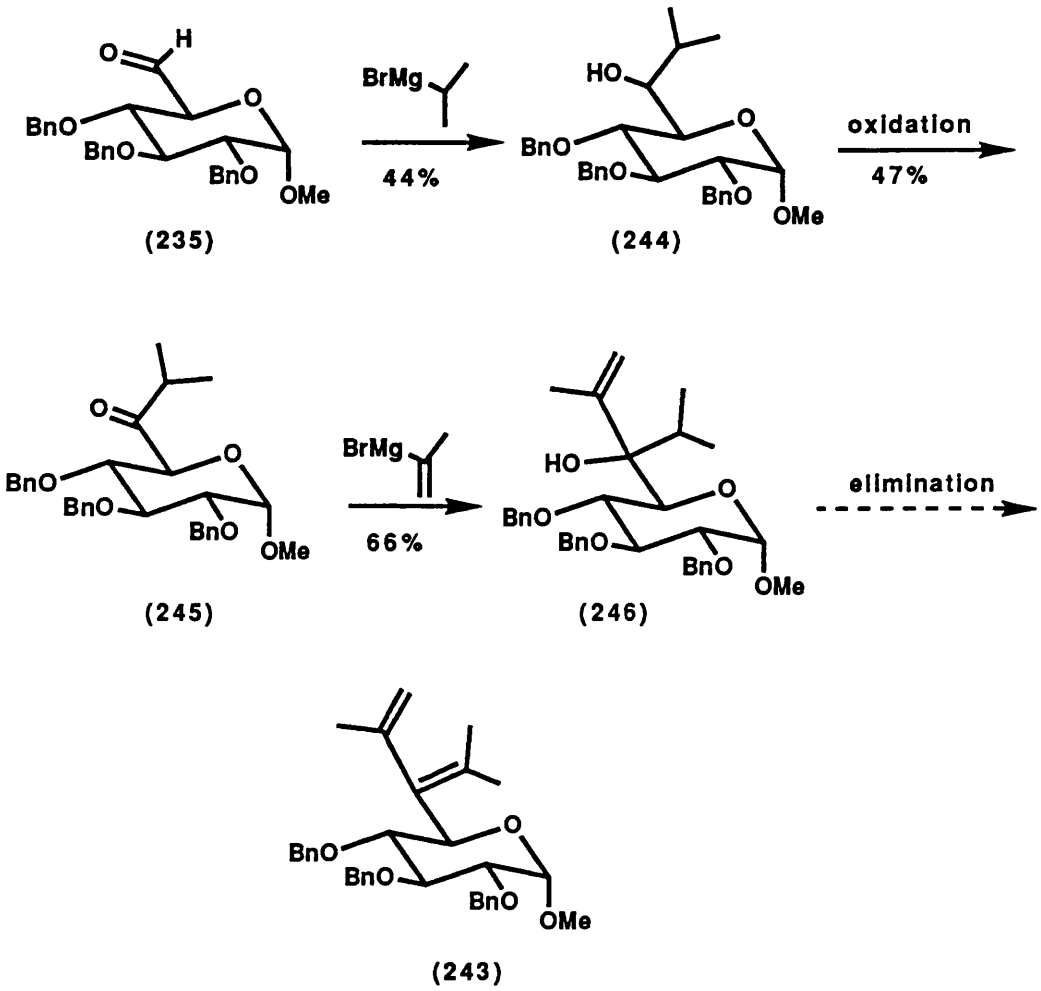
Scheme 61

Although the advanced intermediate (229) contained acetate functions, possible side reactions involving the attack of organometallic reagents onto the acetate groups could occur, making the investigation of the diene synthesis very complicated. Since it was the construction of the diene which was of upmost importance, it was decided to replace the acetate functions with benzyl ethers in our model. The effect of the acetates on the reaction could be determined later. The pathway, shown in Scheme 62, outlines the methodology choosen for the formation of the diene (243) from the aldehyde (235).



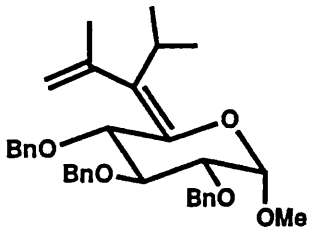
Scheme 62

The conversion of the aldehyde (235) into the enone (241) occurred efficiently. However, due to the fact that this route would be greatly simplified, and the risk arising from the use of toxic selenium eliminated, if an alternative step for the creation of the diene could be found, it was considered worthwhile to study another reaction which did not contain the selenium reagent, Scheme 63.

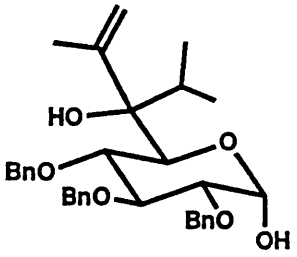


Scheme 63

Previous work, here at Leicester,[150] showed that it was possible to produce a diene by an elimination of a hydroxyl group using p-toluenesulphonic acid as a catalyst. This elimination would result in the formation of two possible dienes, that of the desired diene (243) and the alternative diene (247).



(247)

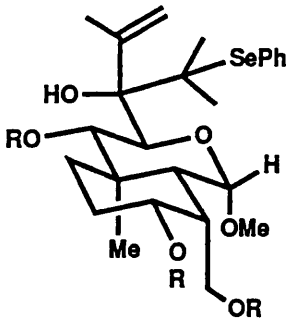


(248)

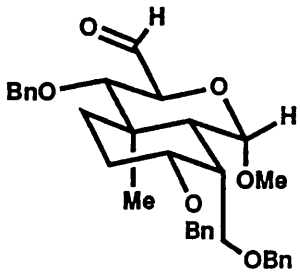
However, it was found that the hemiacetal (248) obtained, by the loss of the anomeric methyl group, only and that neither of the expected elimination products were received. Thus, we had to resort to the original selenium route. Addition of the 2-lithio-2-(phenylseleno)propane to the enone (241) occurred in consistent yields of 40%. This low yield is disappointing but not unexpected since 1, 4-addition, as well as the 1,2- addition, to the enone (241) was obviously likely. A 1:1 mixture of the 1, 2- and 1, 4-addition products was observed. This problem of 1, 4 addition might be reduced by using cerium reagents.[152]

The next step involves the elimination of the hydroxyl selenium functionality to give the diene. Several methods have been reported for this type of elimination. For example thionyl chloride[153] and triethylamine in dichloromethane at room temperature; p-toluene sulphonic acid[154] in refluxing pentane; phosphorous triodide[155] and triethylamine in dichloromethane; $HClO_4$[154] in ether and finally trifluoroacetic anhydride[154] and triethylamine in dichloromethane. All these reactions were tried, but unfortunately none appeared to result in the formation of the diene (243) by proton n.m.r.

Recently, extensive research by Lawrence[139] has shown that the diene (243) can be produced in a reasonable yield using phosphorous trichloride in dichloromethane with triethylamine under reflux. It is felt that these conditions could now induce elimination in both the structurally related selenyl alcohol (250) and its acetate analogue (251), which would result in the application of this scheme to the advanced intermediate (229).

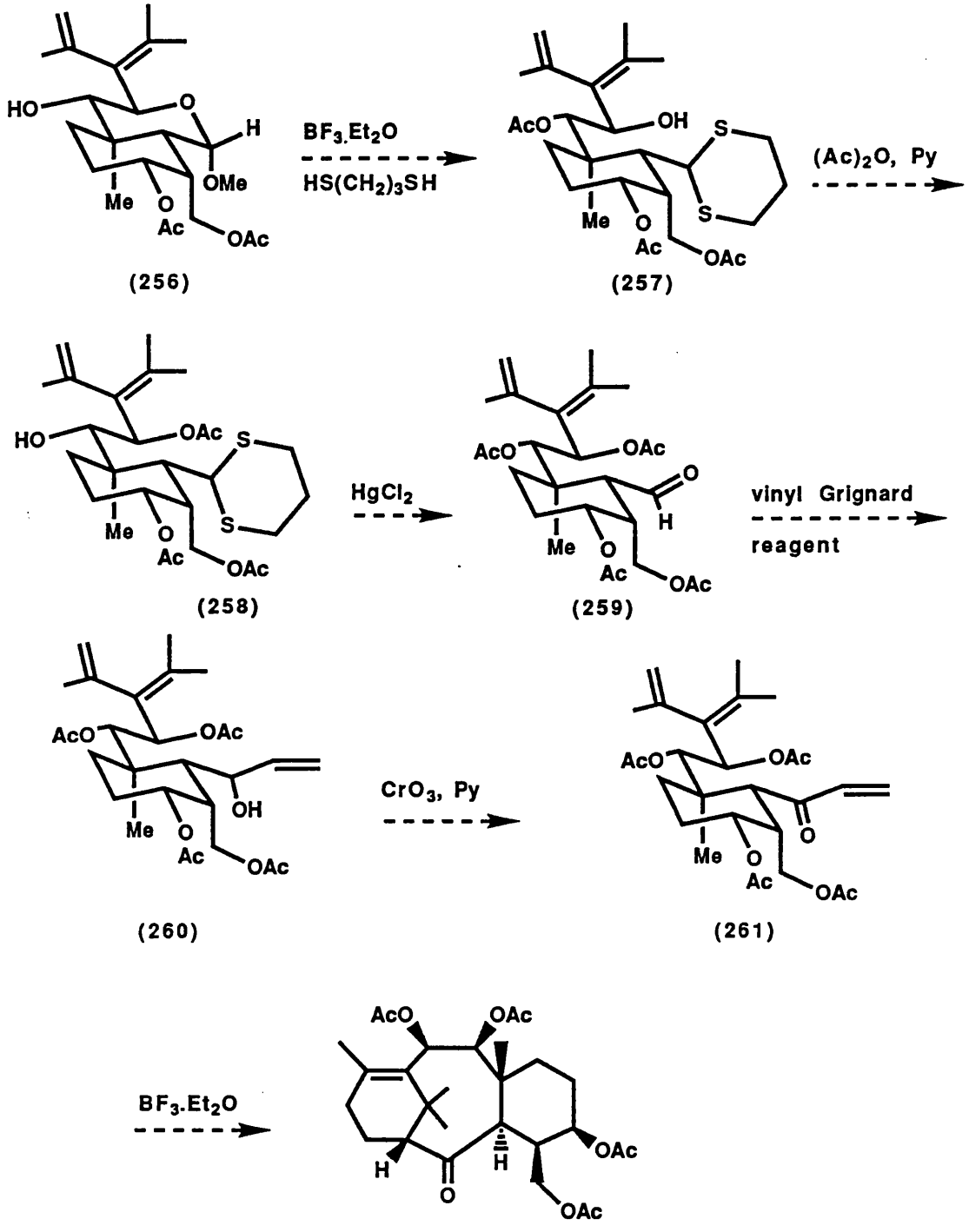


R = Bn (250)
R = Ac (251)



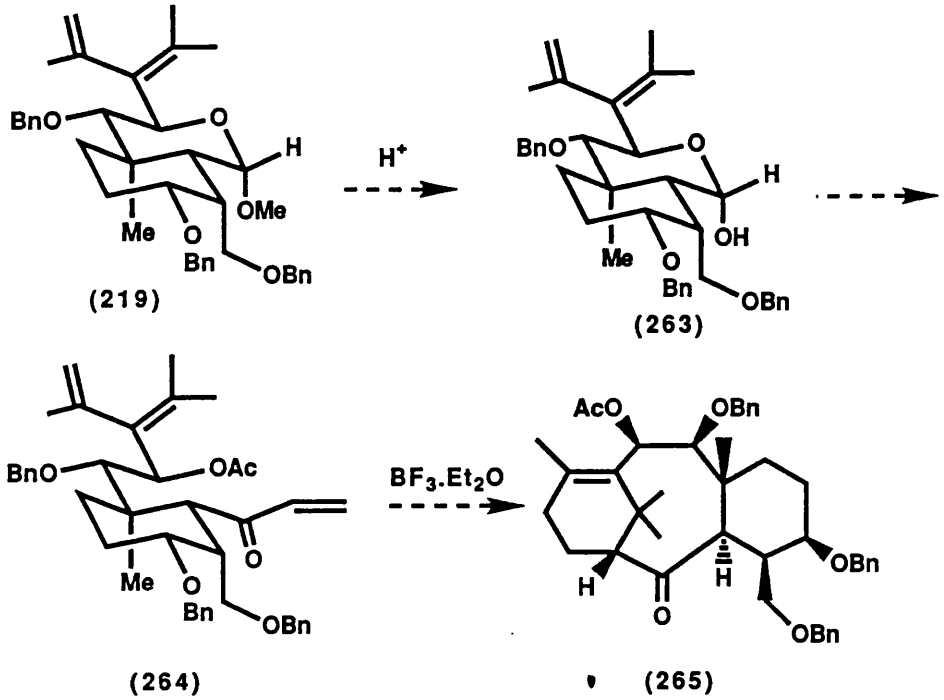
(252)

Unfortunately, at this point it was necessary to draw the investigations to a close. It is hoped that construction of the diene on the aldehyde (229) or on the aldehyde (252) will be successful, so allowing one of the two routes given in Schemes 64 and 65 to be followed thus leading ultimately to the taxane skeleton.



(256) (257) (258) (259) (260) (261)

Scheme 64


BnO
O
H
OMe
Me
O
Bn
OBn
(219)
H+
BnO
O
H
OH
Me
O
Bn
OBn
(263)
BnO
OAc
O
Me
O
Bn
OBn
(264)
BF3.Et2O
AcO
OBn
H
H
O
OBn
OBn
(265)

Scheme 65

CHAPTER 6.

Experimental

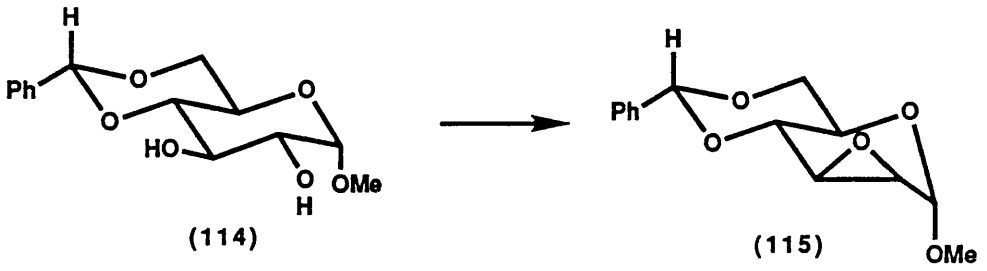
EXPERIMENTAL

All 90 MHz proton n.m.r spectra were recorded on a Varian EM-390 spectrometer. High-field proton n.m.r. (300MHz) and carbon n.m.r. (75MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. Proton n.m.r. (400MHz, n.O.e experiments) spectra were recorded using the highfield n.m.r. service at the University of Warwick. Accurate mass measurements were made at the SERC mass spectrometry centre, University College of Swansea and standard mass spectra were recorded on a Micromass 16B spectrometer. Elemental analysis was carried out by CHN Analysis, Wigston, Leicester or Butterworth Laboratories, Teddington, Middlesex. Infra-red spectra were recorded on a Perkin-Elmer 298 spectrometer. Melting points were determined on a Kofler hotstage and are uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*[155] using silica gel manufactured by Merck & Co., Kiesel 60, 230-400 mesh (ASTM). T.l.c. was conducted on pre-coated aluminium sheets (60-254) with a 0.2 mm layer thickness, manufactured by Merck & Co.

Petroleum ether refers to the 40-60°C fraction and all petroleum ether and ethyl acetate was distilled prior to use. THF, DME and toluene were distilled from sodium metal in the presence of benzophenone. Diethyl ether was distilled from $LiAlH_4$. Dichloromethane, triethylamine, dimethylsulphoxide and pyridine were distilled from powdered calcium hydride. Methanol and ethanol were distilled from magnesium and iodine.

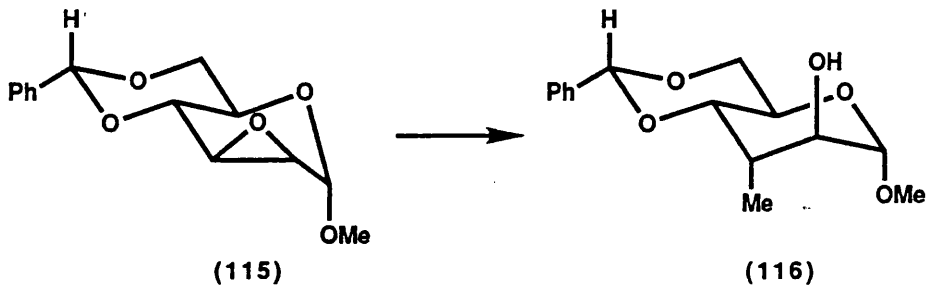
Preparation of Methyl 2, 3-anhydro-4, 6-O-benzyliden-α-D-mannopyranoside (115).[99]



Methyl 4, 6-O-benzyliden-α-D-glucopyranoside (114) (20.00g, 0.07 mol.) was reacted with sodium hydride (80% dispersion, 4.27g, 0.15 mol.) and triisopropylbenzene sulphonyl imidazole (23.60g, 0.08 mol.) in dry dimethylformamide (300ml) according to literature procedure.[99] After work-up and purification by sublimation (120°C at 0.2mmHg) the title compound (115) was obtained as a white crystalline solid (15.00g, 80%), m.p. 145-147°C (lit.[99] m.p. 145-147°C).

$[\alpha]_D^{20}$ = +103° (1.0 in chloroform), lit.[99] $[\alpha]_D^{15}$ = +107° (1.6 in chloroform).

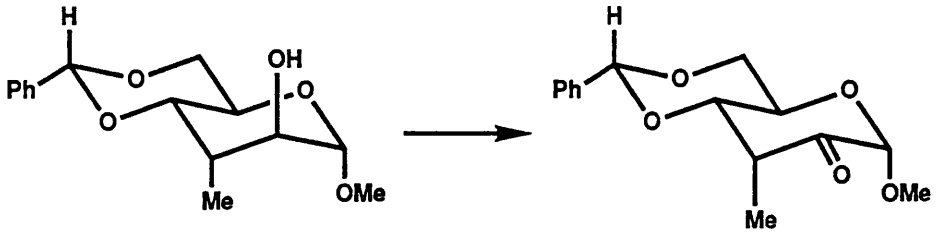
Preparation of methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-altropyranoside (116).[97]



Methyl magnesium chloride (250ml, 0.75 mol.) and methyl 2,3-anhydro-4, 6-O-benzyliden-α-D-mannopyranoside (115) (22.55g, 0.08 mol) were refluxed under nitrogen for two weeks according to the literature procedure. After work-up the title compound (116) was obtained as a white solid (26.76g, 0.10 mol.) which was used in the next stage without further purification.

R_f 0.44 (1:1 petroleum ether-ethyl acetate)
δ_H (90MHz; $CDCl_3$) 1.23 (3H, d, J=7.5Hz, $C\underline{H}_3$), 2.1 (1H, brs, OH), 2.35 (1H, brm, H-3), 3.38 (3H, s, $OC\underline{H}_3$), 3.65-4.40 (5H, m), 4.57 (1H, s, H-1), 5.60 (1H, s), 7.27-7.57 (5H, m, $C_6\underline{H}_5$).

Preparation of methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-ribohexopyranosid-2-ulose (117).[97]



(116) (117)

Trifluoroacetic anhydride (26.72g, 0.13 mol.) in dry dichloromethane (10ml) was added dropwise, under nitrogen, over 10min., to a cooled solution (-65°C) of dimethyl sulphoxide (13.28g, 0.17 mol.) in dichloromethane (100ml). The mixture was stirred for a further 10 min. at -65°C then methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-altro

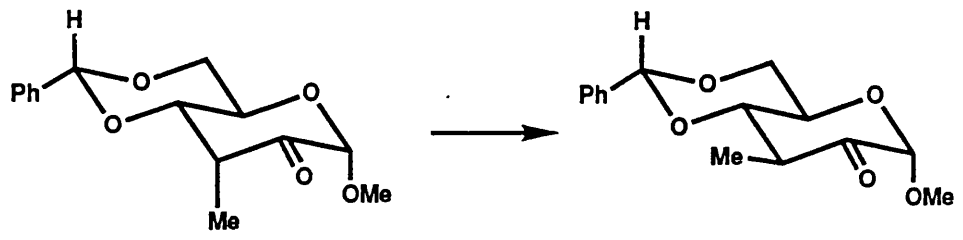
pyranoside (116) (23.80g, 0.09 mol.) in dichloromethane (150ml) was added slowly keeping the mixture at -65°C. After an additional 45 min. at -65°C triethylamine (35ml, 0.50 mol.) was added and the solution was allowed to warm to r.t. The reaction mixture was diluted with diethyl ether (300ml) then washed with 1M HCl (300ml), saturated aqueous solution of sodium hydrogen carbonate (3 X 100ml) and finally with a saturated sodium chloride solution (100ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual crude oil, the title compound (117) (26.00g), was used in the next stage without further purification.

A small quantity of crude (117) was purified by flash chromatography (9:1 petroleum ether-ethyl acetate) to give (117) as a colourless oil.

R_f 0.30 (9:1 petroleum ether-ethyl acetate)

δ_H (90MHz; $CDCl_3$) 1.32 (3H, d, J=7Hz, $C\underline{H}_3$), 2.82-3.16 (1H, m, H-3), 3.39 (3H, s, $OC\underline{H}_3$), 3.55-4.48 (4H, m), 4.53 (1H, s, H-1), 5.49 (1H,s), 7.22-7.5 (5H, m, $C_6\underline{H}_5$).

Preparation of methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-arabinohexopyranosid-2-ulose (118).[97]



(117) (118)

Crude methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-ribo-hexopyranosid-2-ulose (117) (26.00g, 0.09 mol.) was stirred with triethylamine (35ml, 0.25 mol.) in dimethylformamide (200ml) at r.t. for 36h. After work-up and recrystallisation from petroleum ether (60-80°C) the title compound (118) was obtained as a white solid (16.00g, 63%), m.p. 124-126°C (lit.[97] m.p. 125.5-126°C).

$[\alpha]_D^{20}$ = +60° (0.57 in chloroform), lit.[97] $[\alpha]_D^{20}$ = +56° (0.77 in chloroform).

Preparation of 1-(bromovinyl)trimethylsilane (127).[107]

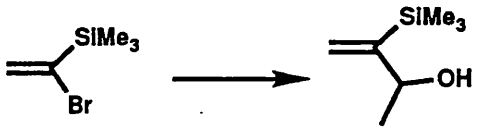
(126) (127)

Vinyltrimethylsilane (126) (50.00g, 0.50 mol.) was cooled to -78°C and bromine (88.00g, 0.55 mol.) was added dropwise over *c.a* 1h. The mixture was then warmed to r.t. Diethylamine (300ml, 2.97 mol.) was then added with continued stirring. After the addition was complete the reaction mixture was refluxed for 12h. The precipitate of diethylamine hydrobromide was filtered off and washed with diethyl ether (3 X 300ml). The diethyl ether filtrate was then washed with 100ml portions of 10% hydrochloric acid until the aqueous layer remained acidic, then with water (100ml) and saturated aqueous sodium chloride (200ml). The

organic layer was then dried ($MgSO_4$), concentrated *in vacuo*, and distilled under reduced pressure (120 mmHg, b.p.72-75°C), through a 20cm Vigreux column to give the title compound (127) (60.00g, 66%).

δ_H (90MHz; $CDCl_3$) 0.21 (9H, s, $Si(C\underline{H}_3)_3$), 6.18 (1H, d, J=2Hz), 6.28 (1H, d, J=2Hz).

Preparation of 3-trimethylsilyl-3-buten-2-ol (128).[107]

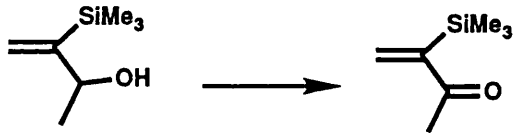


(127) (128)

A flask was charged with magnesium turnings (11.39g, 0.47 mol.) in tetrahydrofuran (50ml) and 1,2 dibromoethane (2g) was added to initiate the formation of the Grignard reagent. Then a solution of 1-(bromovinyl)trimethylsilane (127) (60.00g, 0.33 mol.) in tetrahydrofuran (75ml) was added dropwise maintaining a gentle reflux. After the addition was completed the reaction mixture was heated to reflux for a further 1h. Then freshly distilled acetaldehyde (30.00g, 0.68 mol.) was added carefully. After this addition the reaction mixture was refluxed for a further 1h. Then approximately 100ml of distillate were collected. The reaction mixture was then cooled (0°C) and 100ml Of diethyl ether were added. It was then hydrolysed by enough saturated ammonium chloride solution to dissolve

the thick sticky precipitate. The salts were filtered off and washed with diethyl ether (200ml), and the aqueous layer was extracted with diethyl ether (3 X 100ml). The combined organics were dried ($MgSO_4$) and concentrated by distillation to give the crude title compound (128) (55-60g) as a liquid which was used in the next step without further purification.

Preparation of 3-trimethyl-3-buten-2-one (119).[107]

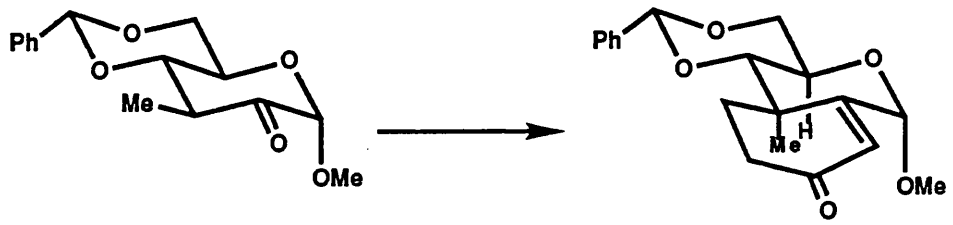


(128) (119)

To a stirred solution of crude 3-trimethylsilyl-3-buten-2-ol (128) (55.00g, 0.38 mol.) in acetone (100ml) an aqueous solution of chromic acid and sulphuric acid[107] was added dropwise. After completion of the addition isopropyl alcohol was added until a green end point was reached. The reaction mixture was then poured into diethyl ether (450ml) and saturated aqueous sodium chloride solution (300ml) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (5 X 150ml). The combined organic extracts were dried ($MgSO_4$) and distilled to give the title compound (119) (16.00g, 30%).

δ_H (90MHz; $CDCl_3$) 0.12 (9H, s, $Si(C\underline{H}_3)_3$), 2.25 (3H, s, H-1), 6.31 (1H, d, J=2Hz, H-4), 6.47 (1H, d, J=2Hz, H-4).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S)-1-methyl-9-methoxy-4-phenyl, 3, 5, 8, trioxatricyclo [8.4.0.$0^{2,7}$] tetradec-10(11)-en-12-one (132).[91,103]



(118) (132)

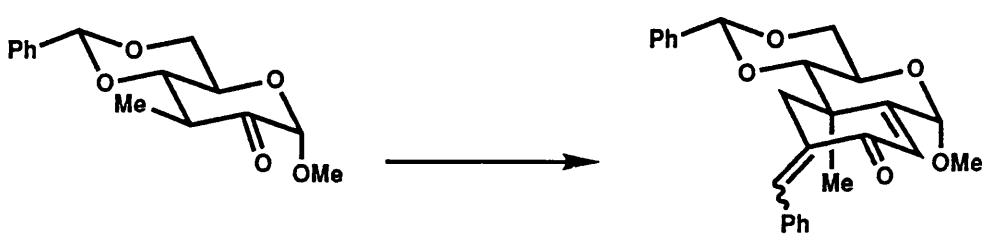
Lithium 2, 2, 6, 6-tetramethylpiperidine (LTMP) (0.011 mol.) was prepared from tetramethylpiperidine (1.661g, 0.012 mol.) and n-butyllithium (4.32ml, 0.011 mol.) in diethyl ether (30ml) at 0°C, under nitrogen, for 1h. Methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (118) (3.002g, 0.011 mol.) in diethyl ether (30ml) was then added to the stirred solution of LTMP at 0°C. After 1h the enolate solution was concentrated by removing approximately half the solvent by means of a vacuum pump. 3-Trimethylsilyl-3-buten-2-one (119) (2.147g, 0.015 mol.) was then added to the stirred enolate solution at -78°C. The mixture was then allowed to warm up to r.t. and stirring continued for a further 1h. The mixture was poured into water (100ml) and extracted with diethyl ether (3 X 150ml). Each extract was washed with saturated aqueous sodium chloride solution (50ml) and the combined organic extracts were dried ($MgSO_4$). The diethyl ether was removed *in vacuo* to yield a thick oil. The viscous oil was heated at 80°C with 10% sodium methoxide solution in

methanol. The methanol was then removed *in vacuo* and the residue extracted with diethyl ether (3 X 150ml). The diethyl ether extract was washed with aqueous sodium chloride solution and dried ($MgSO_4$). After removal of the solvent and flash chromatography (8:2 petroleum ether-ethyl acetate) the title compound (132) was obtained as a viscous oil (1.52g, 41%).

R_f 0.44 (8:2 petroleum ether-ethyl acetate)

δ_H (300MHz; $CDCl_3$) 1.48 (3H, s), 1.87 (1H, brdt, J=14.0, 5.0Hz, H-14), 2.25 (1H, ddd, J=13.5, 5.0, 2.6Hz, H-14), 2.43 (1H, dddd, J=17.5, 5.0, 2.6, 0.8Hz, H-13), 2.55 (1H, ddd, J=17.5, 14.6, 5.0Hz, H-13), 3.38-3.41 (1H, d) overlapping 3.41 (3H,s), 3.71 (1H, t, J=10.2Hz, H-6_{ax}), 4.19 (1H, dt, J=9.8, 5.2Hz, H-7), 4.34 (1H, dd, J=10.2, 5.2Hz, H-6_{eq}), 4.89 (1H, s, H-9), 5.54 (1H, s), 5.86 (1H, s), 7.32-7.51 (5H, m, $C_6\underline{H}_5$).

Data for (136) 1(R), 2(S), 4(S), 7(R), 9(S)-13-phenyl methylen-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0.$0^{2,7}$] tetradec-10(11),13-dien-12-one.



(118) (136)

R_f 0.44 (8:2 petroleum ether-ethyl acetate)

$[\alpha]_D^{20}$ = -37° (8.0 in chloroform)

$C_{26}H_{26}O_5$ Requires C 74.62% H 6.26% N 0.00%

Found C 74.62% H 6.36% N 0.00%

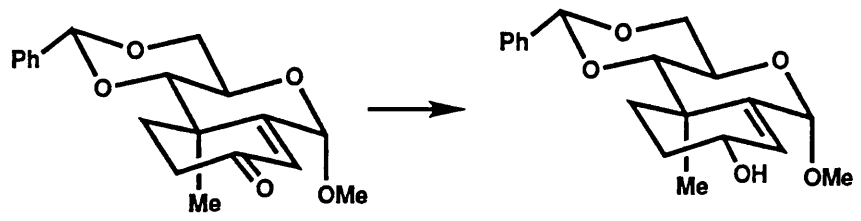
ν_{max} (CH_2Cl_2) 2950s, 1730m, 1650m(C=O), 1600m, 1450s, 1375s.

δ_H (300MHz; $CDCl_3$) 1.35 (3H, s, $C\underline{H}_3$), 2.60 (1H, dd, J=14.7, 2.4Hz, H-14), 3.41 (3H, s, $OC\underline{H}_3$), 3.50 (1H, d, J=14.7, H-14) overlapping 3.55 (1H, d, J=10.1 H-2), 3.74 (1H, t, J=10.1, H-6_{ax}), 4.15 (1H, dt, J=10.2, 5.4Hz, H-7), 4.33 (1H, dd, J=10.2, 5.4Hz, H-6_{eq}), 4.97 (1H, s, H-9), 5.57 (1H, s, C<u>H</u>Ph), 6.08 (1H, s, H-11), 7.30 (10H, m, 2x$C_6\underline{H}_5$), 7.71 (1H, d, J=2.4Hz, C=C<u>H</u>).

δ_C (75MHz; $CDCl_3$) 18.87(q), 38.73(t), 39.36(s), 55.25(q), 59.58(d), 69.20(t), 84.62(d), 100.91(d), 101.57(d), 126.06(d), 128.03(d), 128.09(d), 128.38(d), 128.47(d), 128.91(d), 129.56(d), 131.70(s), 135.09(s), 137.10(d), 137.32(s), 157.24(s), 188.02(s).

m/z 418(m^+)(100), 387(20), 311(5), 269(20), 240(70), 225(30), 209(20), 181(40), 165(30).

<u>Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-ol (133).</u>[91]

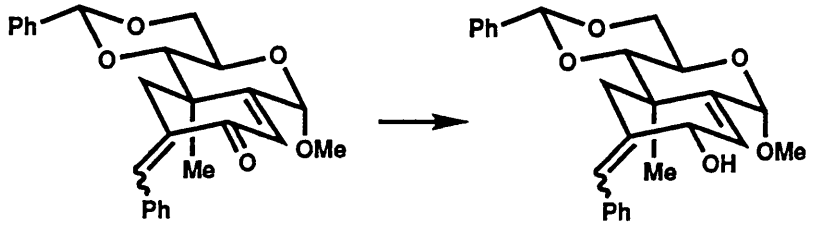


(132) (133)

L-selectride (5.42ml, 5.42×10^{-3} mol.) was added to a stirred solution of 1(R), 2(S), 4(S), 7(R), 9(S)-1-methyl-9-methoxy-4-phenyl, 3, 5, 8, trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-one (132) (1.78g, 5.42×10^{-3} mol.) in dry tetrahydrofuran (30ml) at -78°C under nitrogen. After 1.5h, when t.l.c. showed no starting material, 2M sodium hydroxide (3.34ml) and 30% hydrogen peroxide (1.5ml) were added and the mixture stirred for 1h at r.t. The aqueous layer was then extracted with diethyl ether (3 X 150ml) and the combined organic extracts were washed with aqueous saturated sodium chloride and dried ($MgSO_4$). The residual oil, after removal of solvent, was purified by flash chromatography (1:1 petroleum ether-ethyl acetate) to yield the title compound (133) as a white crystalline solid (1.12g, 61%), m.p. 125-126°C, (lit.[91] m.p. 125-126°C).

δ_H (300MHz; $CDCl_3$) 1.40 (3H, s, $C\underline{H}_3$) overlapping 1.40-1.52 (1H, m) overlapping 1.56 (1H, tdd, J=14.3, 9.5, 2.5Hz), 1.73 (1H, brs, OH), 1.89-1.97 (1H, m), 2.01-2.09 (1H, m), 3.27 (1H, d, J=9.5Hz, H-2), 3.38 (3H, s, $OC\underline{H}_3$), 3.68 (1H, t, J=10.2Hz, H-6_{ax}), 4.12 (1H, dt, J=9.7, 5.0Hz, H-7), 4.23 (1H, brt, J=5Hz, H-12), 4.30 (1H, dd, J=10.2, 5.0Hz, H-6_{eq}), 4.78 (1H, s, H-9), 5.51 (1H, s), 5.72 (1H, s with some fine splitting, H-11), 7.31-7.49 (5H, m, $C_6\underline{H}_5$).

Spectroscopic data for the side product 1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-13 phenylmethylen-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11),13-dien-12-ol (137).



(136) (137)

m.p. 155-157°C

R_f 0.55 (diethyl ether)

$[\alpha]_D^{20}$ = +87° (3.3 in chloroform)

$C_{26}H_{28}O_5$ Requires C 74.26% H 6.71% N 0.00%

Found C 74.18% H 6.74% N 0.00%

ν_{max} (CH_2Cl_2) 3550m (OH), 2900s, 1425w, 1350m, 1150m, 1050s

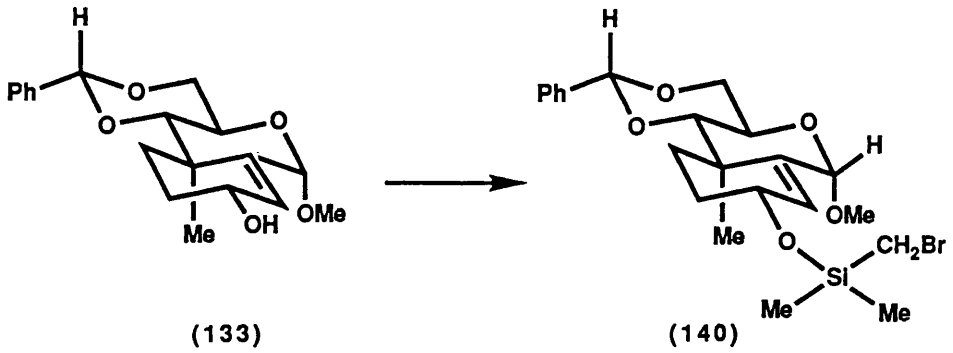
δ_H (300MHz; $CDCl_3$) 1.27 (3H, s, CH_3), 1.65 (1H, brs, OH), 1.80 (1H, brd, J=9.8Hz, H-14), 2.10 (1H, brd, J=9.8Hz, H-14), 3.15 (1H, d, J=10.1Hz, H-4), 3.33 (3H, s, OCH_3), 3.67 (1H, t, J=10.1Hz, H-6_{ax}), 4.05 (1H, dt, J=10.2, 5.3Hz, H-7), 4.30 (1H, dd, J=10.2, 5.3Hz, H-6_{eq}), 4.80 (1H, brd, J=4.6Hz, H-12) overlapping 4.82 (1H, s, H-9), 5.51 (1H, s, CHPh), 5.81 (1H, d, H-11), 6.82 (1H, brs, C=CHPh), 7.15-7.42 (10H, m, 2xC_6H_5).

δ_C (75MHz; $CDCl_3$) 19.51(q), 37.12(t), 41.00(s), 55.11(q), 60.12(d), 69.52(t), 69.55(d), 85.67(d), 101.57(d), 102.83(d), 124.10(d), 126.01(d), 126.33(d), 128.12(d),

128.17(d), 128.51(d), 128.86(d), 130.85(d). 137.00(s), 137.09(s), 137.51(s), 140,54(s).

m/z 420(m^+)(15), 419(39), 403(100), 389(35), 373(10), 283(63), 267(43), 253(46), 121(29).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-dimethyl(bromomethyl) silylether (140).



(133) (140)

1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-ol (133) (1.871g, 5.62×10^{-3} mol.) was stirred under nitrogen in dry dichloromethane with (bromomethyl)chloro dimethyl silane (1.055g, 5.6×10^{-3} mol.) and a catalytic amount of DMAP (0.095g, 7.8×10^{-4} mol). Triethylamine (8ml) was added dropwise over 5min. After 1.5h the solvent was removed *in vacuo* to yield a sticky residue. The residue was purified by flash chromatography (diethyl ether) to yield the title compound (140) (2.480g, 91%) as a clear oil.

R_f 0.75 (diethyl ether)

$[\alpha]_D^{20}$ = +4.5° (10.0 in methanol)

ν_{max} (film) 2900s, 1450m, 1375m, 1250m, 1100s, 850s, 700m

δ_H (300MHz; $CDCl_3$) 0.35 (6H, $Si(C\underline{H}_3)_2$), 1.46 (3H, s, $C\underline{H}_3$) overlapping 1.48 (1H, brm, H-13), 1.74 (1H, brm, H-13), 1.97 (2H, brm, H-14), 2.47 (2H, s, $C\underline{H}_2Br$), 3.30 (1H, d, J=10.0Hz, H-2), 3.45 (3H, s, $OC\underline{H}_3$), 3.72 (1H, t, J=10.1Hz, $H\text{-}6_{ax}$), 4.15 (1H, dt, J=10.1, 5.1Hz, H-7), 4.35 (1H, dd, J=10.1, 5.1Hz, $H\text{-}6_{eq}$) overlapping with 4.45 (1H, ddd, J=9.3, 8.1, 3.5Hz, H-12), 4.80 (1H, s, H-9), 5.57 (1H, s, $C\underline{H}Ph$), 5.69 (1H, brs, H-11), 7.40-7.60 (5H, m, $C_6\underline{H}_5$)

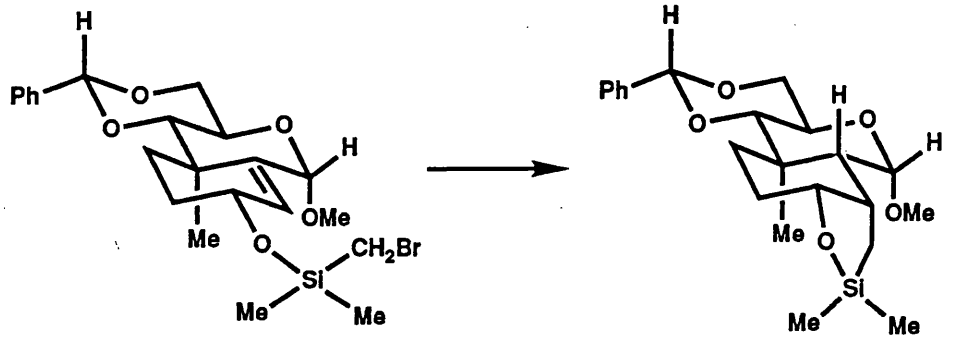
δ_C (75MHz; $CDCl_3$) -2.42(q), 16.21(t), 18.87(q), 28.13(t), 34.38(q), 37.18(s), 54.86(q), 60.33(d), 68.56(d),69.59(t), 86.83(d), 101.48(d), 103.28(d), 126.10(d), 128.11(d), 128.83(d), 131.86(d), 137.77(s), 138.75(s).

m/z 481/482 (m^+)(20), 430(50), 380(75), 330(95), 318(65), 280(100), 150(75), 92(70).

$C_{22}H_{30}BrO_5Si$ $[m\text{-}H^+]$ Requires 481.1073

Found 481.1088

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0,$0^{2,7}$,$0^{11,15}$] heptadecane (141).



(140) (141)

1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-dimethyl(bromomethyl)silyl ether (140) (1.485g, 3.07×10^{-3} mol.) was stirred under nitrogen in dry benzene (20ml) with AIBN (0.025g, 7.5×10^{-5} mol.). Tributyltin hydride (1.342g, 4.6×10^{-3} mol.) was added dropwise over 30min. whilst the reaction mixture was refluxing. After 2h the benzene was removed *in vacuo*. Petroleum ether was added and the solution was left to stand at 4°C for 24h. The resulting white crystals were filtered to give (1.008g, 82%) of the title compound (141), m.p. 155-157°C.

$[\alpha]_D^{20}$ = +15.2° (6.3 in methanol)

$C_{22}H_{32}O_5Si$ Requires C 65.31% H 7.97% N 0.00%

Found C 65.24% H 8.00% N 0.00%

ν_{max} (CH_2Cl_2) 2950s, 1450w, 1375m, 1200w, 1130m, 1050s, 850s.

δ_H (300MHz; $CDCl_3$) 0.21 (3H, s, $SiC\underline{H}_3$), 0.33 (3H, s, $SiC\underline{H}_3$), 0.96 (1H, dd, J=15.2, 7.8Hz, H-12), 1.14 (1H, t, J=15.2Hz, H-12), 1.16 (1H, brdm, H-17), 1.45 (3H, s, $C\underline{H}_3$), 1.47 (1H, m, H-16), 1.86 (3H, m, H-10, H-16, H-17), 2.39 (1H, m, H-11), 3.21 (1H, d, J=9.4Hz, H-2), 3.44 (3H, s, $OC\underline{H}_3$), 3.72 (1H, t, J=10.2Hz, H-6_{ax}), 4.05 (1H, m, H-15), overlapping 4.07 (1H, dt, J=9.6, 5.0Hz, H-7), 4.29 (1H, dd, J=10.2, 5.0Hz, H-6_{eq}), 4.51 (1H, d, J=3.0Hz, H-9), 5.56 (1H, s, $C\underline{H}Ph$), 7.35-7.53 (5H, m, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) 0.22(q), 1.51(q), 13.47(t), 15.83(q), 27.41(t), 35.84(t), 36.12(s), 39.90(d), 47.18(d), 55.15(q), 60.73(d), 69.77(t), 79.29(d), 87.93(d), 101.28(d), 103.08(d), 126.11(d), 128.11(d), 128.77(s), 137.97(s).

m/z 404(m^+)(11), 256(69), 224(46), 195(28), 149(59), 121(70), 105(82)

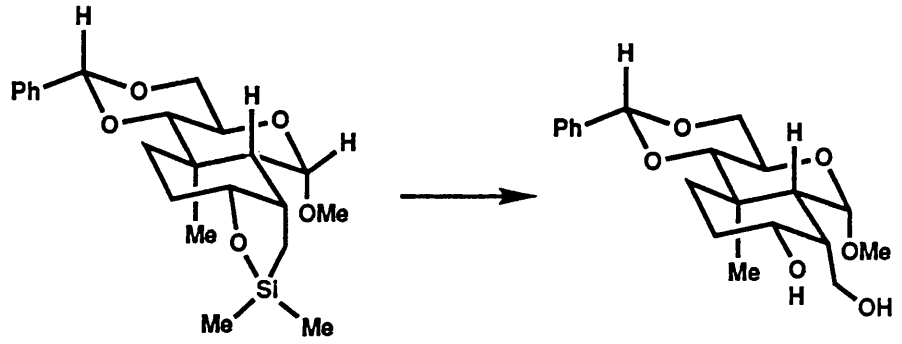
1.80 (H-10) shows a n.O.e to 4.50 (H-9; 5.2%) and 4.00 (H-15; 3.6%).

2.35 (H-11) shows a n.O.e to 4.00 (H-15; 3.1%) and 4.5 (H-9; 5.2%).

4.00 (H-15) shows a n.O.e to 2.35 (H-11; 3.1%) and 1.8 (H-10; 3.6%).

4.50 (H-9) shows n.O.e to 1.8 (H-10; 5.2%) and 2.35 (H-11; 5.2%).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S),12(R)-1-hydroxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134).



(141) (134)

1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-Trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0,$0^{2,7}$,$0^{11,15}$] heptadecane (141) (1.026g, 2.54×10^{-3} mol.) was stirred in dimethylformamide (30ml) with potassium fluoride (0.442g, 7.62×10^{-3} mol.). To this reaction mixture 30% hydrogen peroxide (2.5ml) was added dropwise. After stirring for 24h, water (60ml) was added. The aqueous layer was extracted with diethyl ether (3 X 100ml) and the combined organics were washed with aqueous saturated sodium chloride and dried ($MgSO_4$). After removal of solvent *in vacuo*, the residual oil was purified by flash chromatography (ethyl acetate) and recrystallisation (petroleum ether-ethyl acetate) to give the title compound (134) as a white solid (0.64g, 69%), m.p. 146-148°C.

R_f 0.34 (ethyl acetate)

$[\alpha]_D^{20}$ = +26° (0.8 in methanol)

$C_{20}H_{28}O_6$ Requires C 65.91% H 7.74% N 0.00%

Found C 65.61% H 7.75% N 0.00%

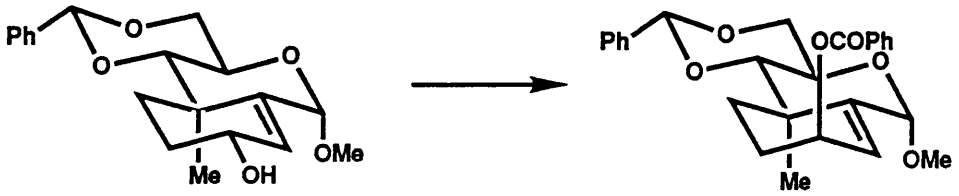
ν_{max} (CH_2Cl_2) 3450s (OH), 2900s, 1450m, 1350s, 1125m, 1100s, 1025s.

δ_H (300MHz; $CDCl_3$) 1.50 (1H, brt, J=10.1, 5.1Hz, H-14) overlapping 1.20 (3H, s, C<u>H</u>$_3$), 1.69 (3H, brm, H-13, H-13, H-10), 1.87 (1H, dt, J=13.3, 6.7Hz, H-14), 2.31 (1H, brm, H-11), 3.15 (1H, d, J=9.5, H-2), 3.35 (3H, s, OC<u>H</u>$_3$), 3.49 (2H, brs, OH), 3.65 (1H, t, J=10Hz, H-6_{ax}), 3.85 (1H, brm, H-12), 3.95 (1H, dt, J=10.0, 5.2Hz, H-7), 4.02 (1H, brt, J=9.8Hz, C<u>H</u>OH), 4.20 (1H, dd, J=10.0, 5.2Hz, H-6_{eq}) overlapping 4.19 (1H, brm, C<u>H</u>OH), 4.6 (1H, d, J=4.5Hz, H-9), 5.50 (1H, s, C<u>H</u>Ph), 7.30-7.50 (5H, m, C_6<u>H</u>$_5$).

δ_C (75MHz; $CDCl_3$) 15.64(q), 26.65(t), 35.71(s), 36.76(t), 44.90(d), 47.75(d), 55.06(q), 60.19(t), 60.28(d), 69.53(t), 74.57(d), 87.69(d), 101.31(d), 102.57(d), 126.07(d), 128.10(d), 128.82(d), 137.76(s).

m/z 364(m^+)(5), 185(18), 165(64), 159(48), 119(36), 105(100).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0.$0^{2,7}$] tetradec-10(11)-en-12-benzoate (142).



(133) (142)

A solution of 1(R), 2(S), 4(S), 7(R), 9(S), 12(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxa tricyclo [8.4.0.$0^{2,7}$] tetradec-10(11)-en-12-ol (133) (0.300g, 9.02×10^{-4} mol.) and triphenylphosphine (0.237g, 9.03×10^{-4} mol.) in dry diethylether (10ml) was added dropwise to a solution of benzoic acid (0.110g, 9.02×10^{-3} mol.) and diethylazo dicarboxylate (0.157g, 9.04×10^{-4} mol.) in dry diethyl ether (5ml). A white precipitate of triphenylphosphine oxide quickly appeared. After stirring the mixture for 3h, the precipitate was filtered off. The filtrate was evaporated *in vacuo*. The residual sticky oil was purified by flash chromatography (4:5:1 diethyl ether-petroleum ether-methanol) to yield the title compound (142) as a white solid (0.312g, 80%), m.p. 47-55°C.

R_f 0.64 (4:5:1 diethyl ether-petroleum ether-methanol)

$[\alpha]_D^{20} = -112°$ (1.6 in methanol)

$C_{26}H_{28}O_6$ Requires C 71.54% H 6.46% N 0.00%

Found C 71.44% H 6.48% N 0.00%

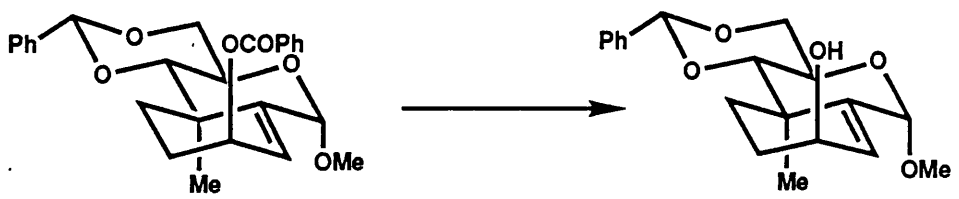
ν_{max} (CH_2Cl_2) 3040m, 2940m, 2820m, 1705m (C=O), 1600w, 1450w, 1375w, 1275m, 1235w.

δ_H (300MHz; $CDCl_3$) 1.37 (3H, s, $C\underline{H}_3$), 1.75-1.85 (1H, brm, H-14), 1.90-2.05 (3H, brm, H-14, H-13, H-13), 3.40 (1H, d, J=9.5Hz, H-2) overlapping with 3.41 (3H, s, $OC\underline{H}_3$), 3.71 (1H, t, J=10.1Hz, H-6_{ax}), 4.18 (1H,dt, J=9.9, 5.2Hz, H-7), 4.32 (1H, dd, J=10.1, 5.2Hz, H-6_{eq}), 4.83 (1H, s, H-9), 5.5 (1H, brm, H-12), 5.56 (1H, s, $\underline{H}$CPh), 5.96 (1H, d, J=4.6Hz, H-11), 7.30-8.15 (10H, m, 2x$C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) 14.41(q), 17.67(q), 24.44(t), 30.99(t), 37.35(s), 55.02(q), 60.24(d), 66.58(d), 69.54(t), 86.40(d), 101.57(d), 103.09(d), 125.14(d), 126.14(d), 128.18(d), 128.30(d), 128.40(d), 129.60(d), 130.12(d), 132.92(d), 133.56(s), 143.36(s), 165.96(s).

m/z 436(m^+)(5), 405(24), 404(64), 287(30), 137(20), 136(80), 121(67), 105(86), 104(100).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-ol (143).



(142) (143)

1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxy tricyclo [8.4.0.$0^{2,7}$] tetradec-10(11)-en-12-benzoate (142) (0.835g, $2.5x10^{-3}$ mol.) was stirred under nitrogen in dry methanol (50ml), with anhydrous potassium carbonate (0.30g, $2.2x10^{-3}$ mol.) for 3.5h. The methanol was then removed *in vacuo* and the solid was extracted with diethyl ether (2 X 150ml) and filtered. The solvent was removed *in vacuo* to leave an oily residue. This was then purified by flash chromatography (4:5:1 diethyl ether-petroleum ether-methanol) to give the title compound (143) as an thick oil (0.581g, 91%).

R_f 0.38 (4:5:1 diethyl ether-petroleum ether-methanol)

$[\alpha]_D^{20}$ = +18° (3.2 in methanol)

$C_{19}H_{24}O_5$ Requires C 68.65% H 7.28% N 0.00%

Found C 68.38% H 7.30% N 0.00%

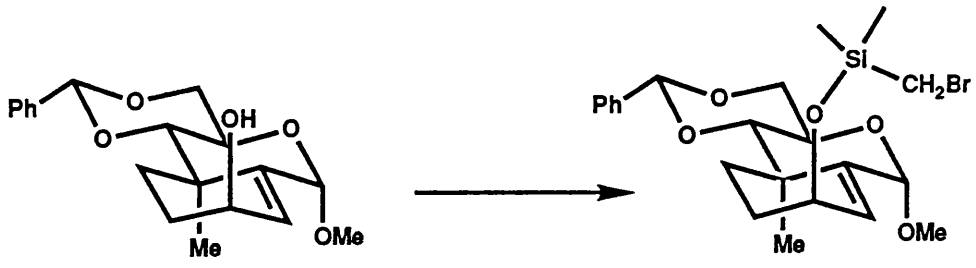
ν_{max} (CH_2Cl_2) 3600m (OH), 3940m, 3850m, 1450m, 1360s 1050s

δ_H (300MHz; $CDCl_3$) 1.32 (3H, s, CH_3), 1.62-1.70 (1H, brm, H-14), 1.75-1.90 (2H, brm, H-14, H-13), 1.97 (1H, brs, H-13), 3.37 (1H, d, J=9.5Hz, H-14), 3.39 (3H, s, $OC\underline{H}_3$), 3.68 (1H, t, J=10.1Hz, H-6_{ax}), 4.11 (1H, dt, J=9.6, 5.4Hz, H-7), 4.15 (1H, brm, H-12), 4.30 (1H, dd, J=10.05, 5.4Hz, H-6_{eq}), 4.81 (1H, s, H-9), 5.53 (1H, s, $\underline{H}CPh$), 5.84 (1H, d, J=4.4Hz, H-11), 7.34-7.49 (5H, m, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) 17.78(q), 27.23(t), 30.06(t), 37.28(s), 54.86(q), 60.16(d), 63.11(d), 69.50(t), 86.28(d), 101.48(d), 103.21(d), 126.08(d), 128.10(d), 128.83(d), 128.89(d), 137.70(s), 140.96(s).

m/z 332(m^+)(10), 302(28), 301(87), 165(37), 154(24), 151(30), 149(41), 138(33), 105(100)

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-dimethyl(bromomethyl) silylether (144).



(143) (144)

1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-ol (143) (0.581g, 1.747×10^{-3} mol.) was stirred under nitrogen in dry dichloromethane with (bromomethyl)chloro dimethylsilane (0.360g, 1.747×10^{-3} mol.) and a catalytic amount of DMAP (0.040g, 3.8×10^{-4} mol.). Triethylamine (2.5ml) was added dropwise over 5min. after 1.5h the solvent and the excess triethylamine were removed *in vacuo* to yield a sticky residue. The residue was purified by flash chromatography (diethyl ether) to yield the pure title compound (144) (0.708g, 84%) as a clear oil.

R_f 0.75 (diethyl ether)

$[\alpha]_D^{20}$ = +6° (6.0 in chloroform)

ν_{max} (film) 2900s, 1450m, 1380m, 1100s, 850s.

δ_H (300MHz; $CDCl_3$) 0.32 (6H, $Si(C\underline{H}_3)_2$), 1.34 (3H, s, $C\underline{H}_3$), 1.70-1.90 (4H, brm, H-14, H-14, H-13, H-13), 2.52 (2H, s, $C\underline{H}_2Br$), 3.41 (3H, s, $OC\underline{H}_3$) overlapping 3.41 (1H, d, J=9.5Hz, H-2), 3.72 (1H, t, J=10.1Hz, H-6_{ax}), 4.12 (1H, dt, J=10.1, 5.0Hz, H-7), 4.27 (1H, brm, H-12) overlapping with 4.32 (1H, dd, J=10.1, 5.0Hz, H-6_{eq}), 4.83 (1H, s, H-9), 5.56 (1H, s, C<u>H</u>Ph), 5.77 (1H, d, 4.6Hz, H-11), 7.30-7.55 (5H, m, $C_6\underline{H}_5$).

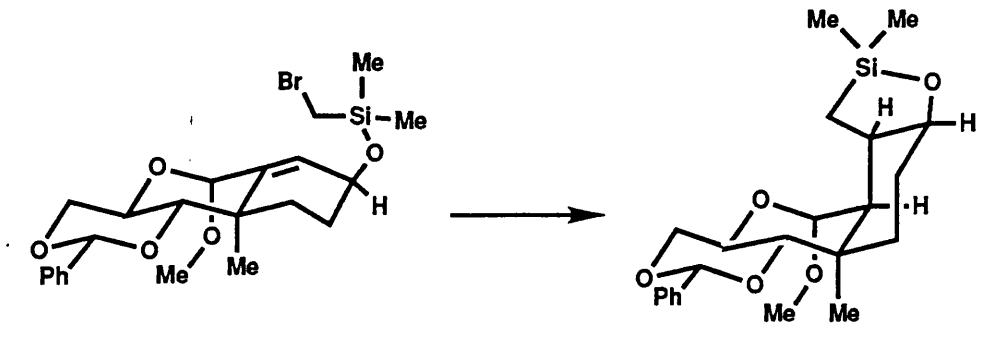
δ_C (75MHz; $CDCl_3$) -2.38(q), 16.31(t), 18.00(q), 27.92(t), 30.08(t), 37.20(s), 54.89(q), 60.30(d), 64.58(d), 69.58(t), 85.94(d), 101.50(d), 103.36(d), 126.13(d), 128.14(d), 128.84(d), 129.35(d), 137.85(s), 140.30(s).

m/z 484(m^+)(5), 453(27), 452(37), 149(30), 115(21), 107(20), 105(61)

$C_{22}H_{30}BrOSi$ [m-H^+] Requires 483.0926

Found 483.0928

<u>Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(R), 11(R), 15(S)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0,$0^{2,7}$,$0^{11,15}$] heptadecane (145).</u>



(144) (145)

1(R), 2(S), 4(S), 7(R), 9(S), 12(S)-1-Methyl-9-methoxy-4-phenyl-3, 5, 8-trioxy tricyclo [8.4.0,$0^{2,7}$] tetradec-10(11)-en-12-dimethyl(bromomethyl)silyl ether (144) (0.249g, $4,24x10^{-4}$ mol.) was stirred under nitrogen in dry benzene (20ml) with AIBN (0.010g, $6.36x10^{-4}$ mol.). Tributyltin hydride (0.171ml, $6.1x10^{-4}$ mol.) was added dropwise over 10min. whilst the reaction mixture was refluxing. After 3h the benzene was removed *in vacuo*. The residue was purified by flash chromatography (1:1 diethyl ether-petroleum ether) and recrystallisation from hexane to give the title compound (145), as a white crystalline solid (0.114g, 73%), m.p. 142-145°C.

R_f 0.32 (1:1 diethyl ether-petroleum ether)

$[\alpha]_D^{20}$ = +7.6° (5.0 in methanol)

$C_{22}H_{32}O_5Si$ Requires C 65.31% H 7.97% N 0.00%

Found C 65.26% H 7.97% N 0.00%

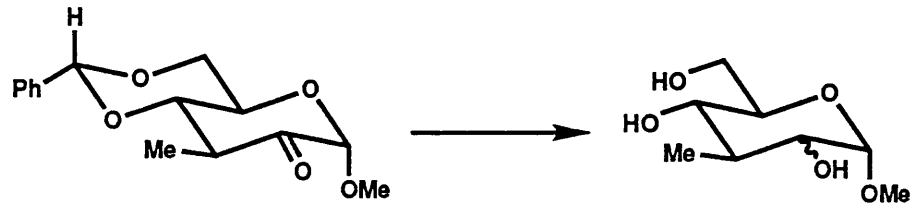
ν_{max} (CH_2Cl_2) 3080s, 2950s, 1440s, 1255s, 1075m, 1025m, 900m

δ_H (300MHz; $CDCl_3$) 0.02 (3H, s, $SiC\underline{H}_3$), 0.06 (3H, s, $SiCH_3$), 0.90 (2H, brm, H-12), 1.10 (1H, brdt, J=10.1, 5.0Hz, H-17), 1.37 (1H, brm, H-17) overlapping with 1.32 (3H, s, $C\underline{H}_3$), 1.65 (1H, brm, H-16), 2.05 (1H, dt, J=13.4, 3.5Hz, H-16), 2.07 (1H, brs, H-10), 2.40 (1H, brm, H-11), 3.41 (3H, s, $OC\underline{H}_3$), 3.77 (1H, t, J=10.1Hz, H-6_{ax}), 3.88 (1H, d, J=10.0Hz, H-2), 4.00 (1H, dt, J=10.1, 5.0Hz, H-5) overlapping with 4.05 (1H, m, H-15), 4.30 (1H, dd, J=10.1, 5.1Hz, H-6_{eq}), 4.55 (1H, s, H-9), 5.59 (1H, s, C$\underline{H}$Ph) 7.30-7.50 (5H, m, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) 0.01(q), 1.30(q), 15.06(t), 24.87(q), 26.38(q), 32.21(t), 34.61(s), 41.09(d), 47.93(d), 54.95(q), 60.34(d), 70.01(t), 78.12(d), 78.91(d), 101.98(d), 103.21(d), 126.01(d), 128.21(d), 129.00(d), 138.08(s).
m/z 404(m^+)(5), 373(15), 372(17), 313(18), 256(31), 255(100), 223(34), 195(17), 149(35).

A crystal which was suitable for X-ray analysis was obtained for crystal data, see Appendix 2.

Reaction of methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-arabinohexopyranosid-2-ulose (118) with palladium on carbon and hydrogen.



(118) (151)

Methyl 4, 6-O-benzyliden-3-deoxy-3-C-methyl-α-D-arabino hexopyranosid-2-ulose (118) (0.50g, $1.75x10^{-3}$ mol.) was shaken with 5% palladium on carbon (0.50g) in ethanol (50ml) under hydrogen at atmospheric pressure for 2.5h. The catalyst was filtered off and the solvent was removed *in vacuo* to yield a sticky oil. After purification by flash chromatography (2:2:1 diethyl ether-petroleum ether-methanol) a clear oil containing the carbohydrate (151) (0.24g, 72%) was obtained.

R_f 0.30 (2:2:1 diethyl ether-petroleum ether-methanol)

$[\alpha]_D^{20}$ = +182° (0.28 chloroform)

ν_{max} 3300s (OH), 2950m, 1375w, 1250s, 1100s.

δ_H (300MHz; CD_3OD) 1.12 (3H, d, J=9.5Hz, $C\underline{H}_3$), 1.81 (1H, m, H-3), 3.02 (1H, t, J=11.2Hz, H-6), 3.17 (1H, dd, J=10.0, 5.2Hz, H-2), 3.42 (3H, s, $OC\underline{H}_3$), 3.51 (1H, m, H-5), 3.65 (1H, dd, J=11.2, 6.0Hz, H-4), 3.81 (1H, dd, J=11.2, 3.2Hz, H-6), 4.57 (1H, d, J=5.2Hz, H-1).

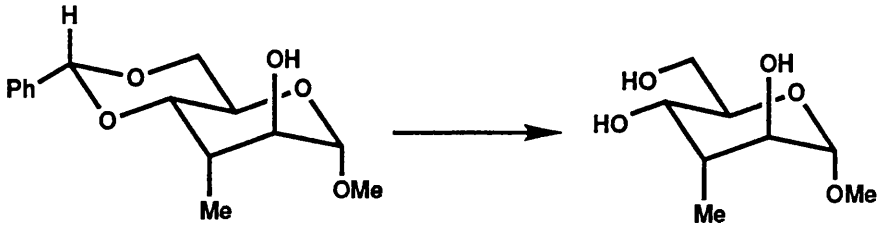
δ_C (75MHz; CD_3OD) 14.53(q), 40.21(d), 55.20(q), 63.12(t), 71.56(d), 73.85(d), 74.01(d), 100.50(d).

m/z 196(m^+)(very weak), 161(21), 142(64), 113(72), 100(26).

$C_8H_{20}NO_5$ $[m+NH_4^+]$ Requires 210.1340

Found 210.1336

Preparation of 3-deoxy-3-C-methyl-α-D-mannopyranoside (152).



(116) (152)

4, 6-O-Benzyliden-3-deoxy-3-C-methyl-α-D-altropyranoside (116) (0.50g, $1.78x10^{-3}$ mol.) was shaken with 5% palladium on carbon (0.50g) in ethanol (50ml) under hydrogen at atmospheric pressure for 2.5h. The catalyst was filtered off and the solvent was removed *in vacuo* to yield a sticky

oil. After purification by chromatography (2:2:1 diethyl ether-petroleum ether-methanol) the title compound (152) was obtained (0.30g, 88%) as a glass.

R_f 0.32 (2:2:1 diethyl ether-petroleum ether-methanol)

$[\alpha]_D^{20}$ = +72° (10.0 in methanol)

ν_{max} ($CHCl_3$) 3400s (OH), 1450m, 1200w, 1100s, 850w

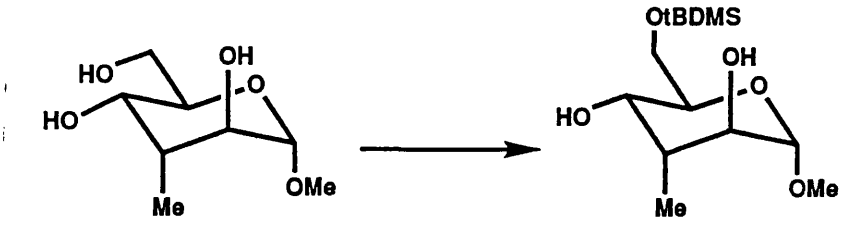
δ_H (300MHz; $CDCl_3$) 1.10 (3H, d, J=10.3Hz, $C\underline{H}_3$), 2.15 (1H, brm, H-3), 3.20 (3H, s, $OC\underline{H}_3$), 3.56 (1H, dd, J=10.0, 4.1Hz, H-2), 3.80 (4H, complex mutiplet, H-4, H-5, H-6) overlapping with 3.75 (3H, brs, OH), 4.51 (1H, d, J=4.1Hz, H-1).

δ_C (75MHz; $CDCl_3$) 10.05(q), 38.11(d), 55.20(q), 61.52(t), 69.78(d), 70.00(d), 72.61(d), 102.01(d).

m/z 210($m+NH_4^+$) (30), 178(28), 124(5), 52(18).

$C_8H_{20}NO_5$ $[m+NH_4^+]$	Requires	210.1340
	Found	210.1345

<u>Preparation of 6-O-(tert-butyldimethylsiloxy)-3-deoxy-3-C-methyl-α-D-mannopyranoside (153).</u>



(152) (153)

3-Deoxy-3-C-methyl-α-D-mannopyranoside (152) (0.190g, 9.89×10^{-3} mol.) was stirred in dry dichloromethane (10ml)

with chloro-tert-butyldimethylsilane (0.156g, 9.89×10^{-3} mol.) and 2, 6-lutidine (0.212g, 2.0×10^{-3} mol.) for 36h under nitrogen, then dichloromethane (30ml) was added and the mixture was washed with water (2 X 100ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a sticky glass. After purification by flash chromatography (2:2:1 diethyl ether-petroleum ether-methanol), the title compound (153) (0.251g, 83%) was obtained as a sticky oil.

R_f 0.62 (2:2:1 diethyl ether-petroleum ether-methanol)

$[\alpha]_D^{20} = +71^\circ$ (6.0 in methanol)

ν_{max} (CH_2Cl_2) 3325m (OH), 2900s, 1375m, 1250s, 1200s, 1100m.

δ_H (300MHz; $CDCl_3$) 0.05 (6H, s, $Si(C\underline{H}_3)_2$), 0.85 (9H, s, $C(C\underline{H}_3)_3$), 1.06 (3H, d, J=9.6Hz, $C\underline{H}_3$), 2.01 (1H, brm, H-3), 3.17 (2H, brs, OH), 3.35 (3H, s, $OC\underline{H}_3$), 3.51 1H, dd, J=9.4, 3.8Hz, H-2), 3.75 (4H, complex mutiplet, H-4, H-5, H-6), 4.45 (1H, d, J=3.8Hz, H-1).

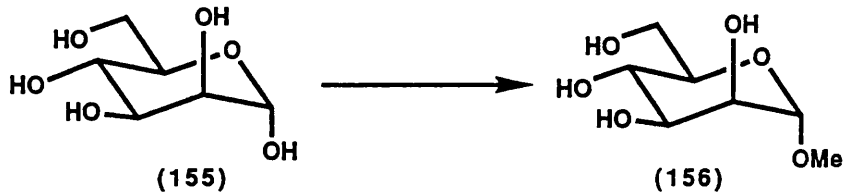
δ_C (75MHz; $CDCl_3$) -5.00(q), 11.21(q), 25.72(q), 37.12(d), 55.23(q), 64.85(t), 68.97(d), 71.82(d), 71.91(d), 102.35(d).

m/z 306(m^+)(5), 217(50), 199(13), 171(10), 131(53), 101(62).

$C_{14}H_{30}O_5Si$ Requires 306.1862

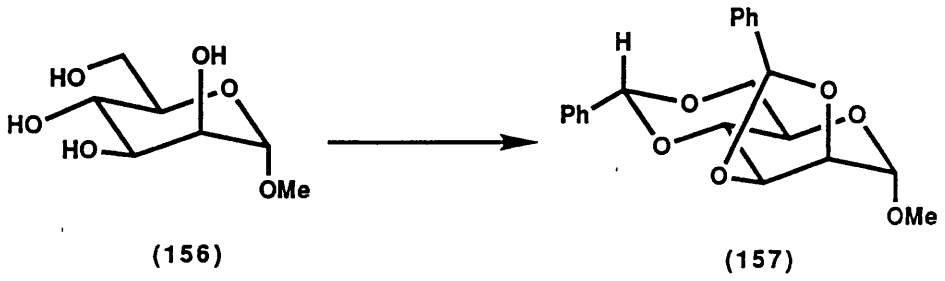
Found 306.1869

Preparation of methyl α-D-mannopyranoside (156).[112]



Crystalline D-mannose (155) (100.00g, 0.55 mol.), in 3% acidified methanol solution (100ml) and 1, 2-dichloroethane (200ml) was refluxed for 4h. During the 4h a solid mass formed in the solution, this subsequently dissapeared. After cooling overnight a solid precipitated and was filtered off, washed with cold methanol until the washings were clear, then with diethyl ether (200ml) and dried. The crude solid was then recrystallised from ethanol to yield the title compound (156) (59.10g, 54%), m.p. 189-190°C (lit.[112] m.p. 191-192°C).

Preparation of methyl 2, 3; 4, 6-di-O-benzyliden-α-D-manno pyranoside (157).[112]

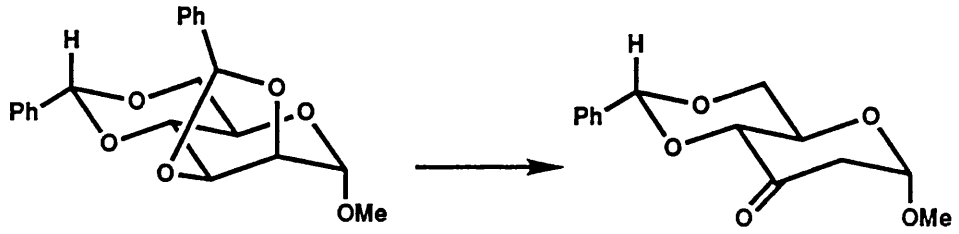


A mixture of methyl α-D-mannopyranoside (156) (50.00g, 0.25 mol.), benzaldehyde dimethyl acetal (92.00g, 0.60 mol.) and

anhydrous p-toluenesulphonic acid (1.00g) in dimethyl formamide (300ml) was heated for 3h at 65°C. The mixture was poured into ice water containing sodium hydogen carbonate (30.00g). The resultant precipitate was filtered off and dried over phosphorous pentoxide. On recrystallisation from *iso*-propylalcohol the title compound (157) was obtained (20.23g, 22%), m.p. 176-177°C, (lit.[112] m.p. 174-178°C).

δ_H (90MHz; $CDCl_3$) 3.32 (3H, s, $OC\underline{H}_3$), 3.9-4.6 (6H, m), 4.95 (1H, s), 6.25 (1H, s), 7.15-7.60 (10H, m, $2xC_6\underline{H}_5$).

Preparation of 4, 6-O-benzyliden-2-deoxy-α-D-erythro hexopyranosid-3-ulose (146).[112]

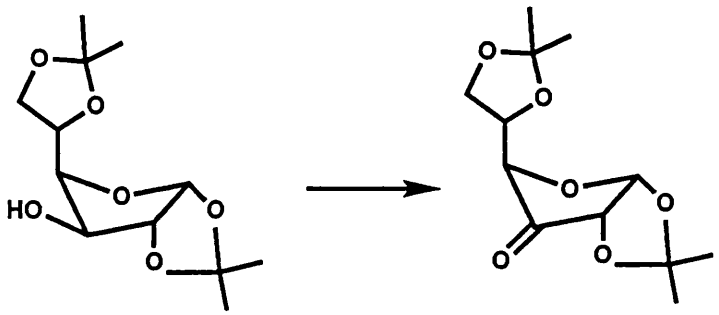


(157) (146)

A solution of methyl 2, 3; 4, 6-di-O-benzyliden-α-D-manno pyranoside (157) (0.740g, $2.0x10^{-4}$ mol.) in tetrahydrofuran (2ml) under nitrogen was cooled to -40°C. Butyllithium in hexane (0.16ml, $4x10^{-4}$ mol.) was added. After 0.5h, during which the colour of the reaction changed from yellow to red, the solution was poured into ice-water (2ml) containing ammonium chloride (0.5g). The tetrahydrofuran was removed *in vacuo*. The aqueous slurry was cooled and

the precipitate was filtered off to yield, on recrystallisation from ethanol, the title compound (146) (0.240g, 50%), m.p. 170-171°C (lit.[112] m.p. 170-171°C).

Preparation of 1, 2; 5, 6-di-O-isopropyliden-α-D-ribohexo furanos-3-ulose (147).[113]

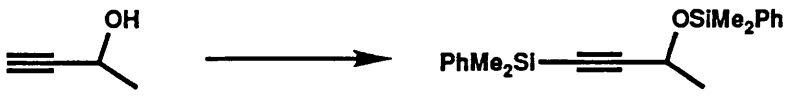


(148) (147)

1, 2; 5, 6-Di-O-isopropylidene-α-D-glucofuranose (148) (2.60g, 0.01 mol.) was dissolved in a mixture of dimethyl sulphoxide (30ml) and acetic anhydride (20ml). After 24h at r.t. the solvent was distilled off at 40°C, 0.2mmHg, to yield a syrupy residue. The syrup was purified by column chromatography (1:1 petroleum ether-diethyl ether) to yield the title compound (147) (2.46g, 95%) as a white solid, m.p. 107-109°C (lit[113]. m.p. 108-112°C).

R_f 0.52 (1:1 petroleum ether-diethyl ether)

Preparation of 1-(phenyldimethylsilyl)-3-phenyldimethyl siloxy)but-1-yne (168).

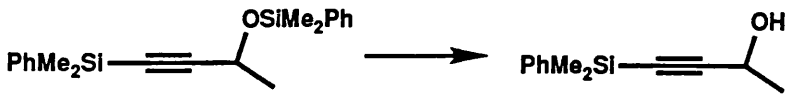


(167) (168)

But-1-yne-3-ol (167) (5.71ml, 0.073 mol.) was stirred in dry tetrahydrofuran under nitrogen at -5°C. Methylmagnesium chloride (49ml, 0.160 mol.) was added dropwise over 20min. The reaction was the refluxed for 1h. After cooling to r.t. phenyldimethylchlorosilane (25.00g, 0.145 mol.) was added dropwise, the reaction mixture was then refluxed for a further 1h. The resulting white precipitate was filtered off and the tetrahydrofuran was removed *in vacuo* to give a pale yellow oil (22.78g, 93%). The crude 1-(phenyldimethylsilyl)-3-phenyldimethyl siloxy) but-1-yne (168) was used directly in the next stage without further purification.

δ_H (90MHz; $CDCl_3$) 0.40 (12H, s, 3xSi($C\underline{H}_3$)$_2$), 1.61 (3H, d, J=6.7Hz, $C\underline{H}_3$), 4.51 (1H, q, J=6.7Hz, $C\underline{H}OH$), 7.50 (12H, m, 2x$C_6\underline{H}_5$).

Preparation of 1-phenyldimethyl but-1-yne-3-ol (169).



(168) (169)

The crude 1-(phenyldimethylsilyl)-3-phenyldimethylsiloxy) but-1-yne (168) (23.0g, 0.07 mol.) was refluxed in 50% aqueous acetic acid (150ml) for 2.5h. After cooling diethyl ether (100ml) was added, the solution was then neutralised with an aqueous saturated solution of sodium hydrogen carbonate and extracted with diethyl ether (3 X 100ml). The combined organic extracts were dried ($MgSO_4$) and after removal of solvent *in vacuo* the crude title compound (169) was purified by flash chromatography (7:3 petroleum ether-diethyl ether) to yield a pale yellow oil (9.12g, 65%), b.p. 120-126°C at 70.0mmHg.

R_f 0.6 (7:3 petroleum ether-diethyl ether)

ν_{max} (film) 3330s (OH), 3000m, 2150m, 1420m, 1250m, 1110s, 800s.

δ_H (300MHz; $CDCl_3$) 0.48 (6H, s, $Si(C\underline{H}_3)_2$), 1.53 (3H, d, J=6.6Hz, CH_3), 2.19 (1H, brs, OH), 4.60 (1H, brm, C<u>H</u>OH), 7.55 (5H, m, $C_6\underline{H}_5$).

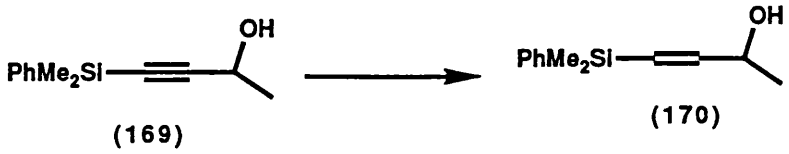
δ_C (75MHz; $CDCl_3$) -0.96(q), 24.19(q), 58.73(d), 86.38(s), 109.39(s), 127.84(d), 129.41(d), 133.54(d), 136.65(s).

m/z 222(mNH_4^+)(100), 206(20), 189(5), 178(10), 152(30), 144(30), 91(60).

$C_{12}H_{20}NOSi$ $[m+NH_4^+]$ Requires 222.1313

Found 222.1314

Preparation of 1-phenyl dimetylsilylbut-1-en-3-ol (170).



(169) (170)

A slurry of lithium aluminium hydride (0.150g, 3.92×10^{-3} mol.) in dry tetrahydrofuran (5ml) was prepared under nitrogen. To this slurry 1-phenyldimethylsilylbut-1-yne-3-ol (169) (0.200g, 9.8×10^{-4}mol.) in tetrahydrofuran was added dropwise. The reaction mixture was refluxed under nitrogen for 5h. The excess lithium aluminium hydride was destroyed by the addition of water saturated diethyl ether. Magnesium sulphate was then added to the solution. After 2h the solids were removed and the solvent removed *in vacuo* and the residual oil distilled (132-137°C at 25mmHg) to give the title compound (170) (0.180g, 90%).

R_f 0.29 (8:2 petroleum ether-diethyl ether)

ν_{max} (film) 3350s (OH), 3000s, 1600m, 1425m, 1250s, 1100s, 1050s, 875s.

δ_H (300MHz; $CDCl_3$) 0.47 (6H, s, $Si(CH_3)_2$), 1.35 (3H, d, J=6.5Hz, CH_3), 2.39 (1H, brs, OH), 4.38 (1H, m, C<u>H</u>OH), 6.06 (1H, dd, J=18.7, 1.3Hz, SiC<u>H</u>=C), 6.26 (1H, dd, J=18.7, 4.9Hz, C=C<u>H</u>CHOH), 7.55 (5H, m, C_6H_5).

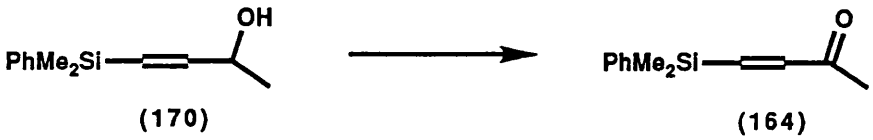
δ_C (75MHz; $CDCl_3$), -2.66(q), 22.82(q), 70.15(d), 125.65(d), 127.66(d), 128.86(d), 133.66(d), 138(s), 151.42(d).

m/z 224(mNH_4^+)(10), 206(90), 189(100), 179(10), 152(50), 122(30), 91(80).

$C_{12}H_{20}NSi$ [$m-H_2O+NH_4^+$] Requires 206.1363

Found 206.1365

Preparation of 4-phenyl dimethylsilylbut-3-en-2-one (164).



(170) (164)

To chromium trioxide (3.50g, 0.04 mol.) in dry dichloro methane (50ml), pyridine (5.61g, 0.071 mol.) was added, the solution was then stirred for 1h under nitrogen at r.t., after which a solution of 1-phenyl dimethylsilylbut-1-en-3-ol (170) (2.00g, $5.9x10^{-3}$ mol.) was added in dichloromethane (5ml). The reaction mixture was stirred for a further 1h at r.t. The chromium salts were then filtered off through a short silica column and the solvent removed *in vacuo* and after purification by flash chromatography (8:2 petroleum ether-diethyl ether) the title compound (164) (1.01g, 51%) was obtained as a pale yellow oil, b.p. 110-119°C at 80mmHg.

R_f 0.45 (8:2 petroleum ether-diethyl ether)

ν_{max} (film) 3000s, 1685s (C=O), 1425m, 1350m, 1250m, 1100m, 825s.

δ_H (300MHz; $CDCl_3$) 0.50 (6H, s, $Si(CH_3)_2$), 2.33 (3H, s, CH_3), 6.55 (1H, d, J=19.2Hz), 7.18 (1H, d, J=19.2Hz), 7.50 (5H, m, C_6H_5).

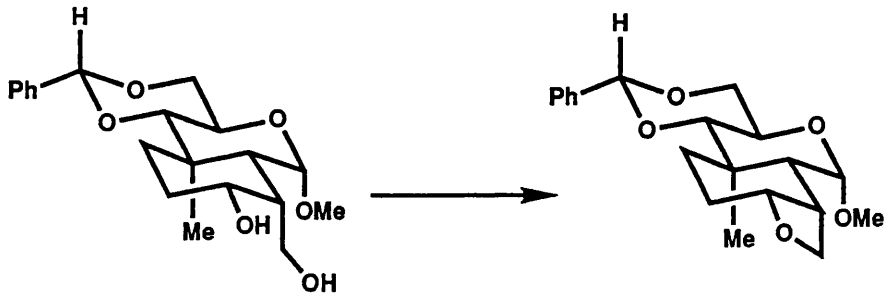
δ_C (75MHz; $CDCl_3$) -3.21(q), 26.30(q), 127.71(d), 129.51(d), 132.91(s), 133.74(d), 144.07(d), 145.41(d), 198.40(s).

m/z 205(mNH_4^+)(100), 189(50), 166(5), 152(10), 127(30), 91(30).

$C_{12}H_{17}OSi$ [mH^+] Requires 205.1048

Found 205.1049

Reaction of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S),12(R)-1-hydroxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) with triphenylphosphine and diethylazodicarboxylate.



(134) (171)

A solution of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-1-hydroxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) (0.42g, 1.15×10^{-3} mol.) and triphenylphosphine (0.33g, 1.26×10^{-3} mol.) in dry diethyl ether (10ml) was added dropwise to a solution of diethylazodicarboxylate (0.21g, 1.26×10^{-3}mol) in dry diethyl ether. A white precipitate of triphenylphosphine oxide appeared. When the reaction had gone to completion by t.l.c. after 3h, the precipitate was

filtered off. The filtrate was evaporated *in vacuo.* The residual sticky oil was purified by flash chromatography (ethyl acetate) to yield 1(R), 2(S), 4(S), 7(R), 9(s), 10(S), 11(S), 14(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8, 13-tetraoxatetracyclo [8.6.0,$0^{2,7}$,$0^{11,14}$] hexadecane (171) (0.25g, 63%), m.p. 130-132°C

R_f 0.33 (ethyl acetate)

$[\alpha]_D^{20}$ = +9° (0.7 in methanol)

$C_{20}H_{26}O_5$ Requires C 69.34% H 7.56% N 0.00%

Found C 68.98% H 7.51% N 0.00%

ν_{max} (CH_2Cl_2) 2950s, 1450s, 1375s, 1100w, 1050w.

δ_H (300MHz; $CDCl_3$) 1.12 (3H, s, $C\underline{H}_3$), 1.29 (1H, brm, H-16), 1.48 (1H, brm, H-16), 1.94 (1H, m, H-15) overlapping 1.98 (1H, m, H-10), 2.11 (1H, brm, H-11) overlapping 2.15 (1H, brm, H-15), 3.32 (1H, d, J=9.4Hz, H-2), 3.39 (3H, s, $OC\underline{H}_3$), 3.71 (1H, t, J=10.1Hz, H-6_{ax}), 3.93 (1H, brm, H-14), 4.26 (1H, dt, J=9.8, 4.8Hz, H-7), 4.27 (1H, dd, J=10.1, 4.8Hz, H-6_{eq}), 4.68 (1H, d, J=2.8Hz, H-9), 5.10 (1H, brd, J=1.4Hz, H-12), 5.24 (1H, brd, J=1.4Hz, H-12), 5.52 (1H, s, $C\underline{H}$Ph), 7.41 (5H, m, $C_6\underline{H}_5$).

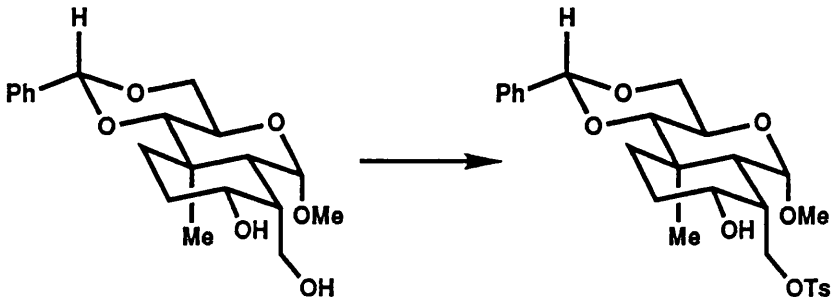
δ_C (75MHz; $CDCl_3$) 14.41(q), 31.94(t), 36.53(t), 38.10(s), 50.14(d), 54.52(q), 59.57(d), 69.31(t), 72.48(d), 86.92(d), 99.65(d), 101.29(d), 105.60(t), 125.73(d), 127.60(d), 128.49(d), 137.55(s), 145.52(s).

m/z 347(mH^+)(100), 332(5), 315(20), 226(15), 209(40), 121(60).

$C_{20}H_{27}O_5$ [$m+H^+$] Requires 347.1858

Found 347.1858

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-tosylmethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (172).



(134) (172)

1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-Hydroxy methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) (0.231g, 6.34×10^{-4} mol.) was dissolved in dry dichloromethane (30ml), to this solution pyridine (0.200ml, 2.5×10^{-3} mol.) and p-toluene sulphonylchloride (0.133g, 7.0×10^{-4} mol.) was added. The mixture was stirred under nitrogen for 48h. After removal of solvent *in vacuo* and purification by flash chromatography (ethyl acetate) the title compound (172) (0.228g, 69%) was obtained as a white solid, m.p. 67-69°C.

R_f 0.60 (ethyl acetate)

$[\alpha]_D^{20}$ = +10° (0.42 in methanol)

$C_{27}H_{34}O_8S$ Requires C 62.25% H 6.61% N 0.00%

Found C 62.25% H 6.62% N 0.00%

ν_{max} (CH_2Cl_2) 3600m (OH), 3000s, 1600w, 1510m, 1475m.

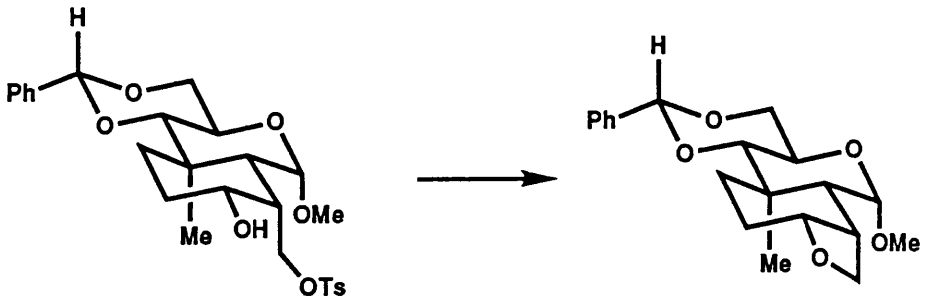
δ_H (300MHz; $CDCl_3$) 0.94 (1H, m, H-14), 1.06 (3H, s, $C\underline{H}_3$), 1.22 (1H, m, H-14) overlapping 1.32 (1H, m, H-13), 1.69

(1H, t, J=3.4Hz, H-10), 1.77 (1H, m, H-13), 2.42 (3H, s, $PhC\underline{H}_3$) overlapping 2.45 (1H, brm, H-11), 3.14 (1H, d, J=9.4Hz, H-2), 3.23 (3H, s, $OC\underline{H}_3$), 3.64 (1H, t, J=10.2Hz, $H\text{-}6_{ax}$), 3.74 (1H, brm, H-12), 3.91 (1H, dt, J=9.8, 4.9Hz, H-7), 4.21 (1H, dd, J=4.9, 10.2Hz, $H\text{-}6_{eq}$) overlapping 4.25 (1H, dd, J=8.7, 6.6Hz, C<u>H</u>OTs), 4.53 (1H, d, J=3.0Hz, H-9), 4.91 (1H, dd, J=8.7, 1.4Hz, C<u>H</u>OTs), 5.50 (1H, s, C<u>H</u>Ph), 7.60 (9H, m, $C_6\underline{H}_5$, $C_6\underline{H}_4$).

δ_C (75MHz; $CDCl_3$) 15.23(q), 21.58(q), 25.90(t), 35.58(t), 36.26(s), 43.02(d), 46.66(d), 55.24(q), 60.26(d), 67.74(t), 69.50(t), 71.87(d), 87.28(d), 101.29(d), 102.22(d), 126.07(d), 127.83(d), 128.09(d), 128.80(d), 129.73(d), 133.33(s), 137.78(s), 144.50(s).

m/z 348(m^+-OTs)(10), 314(21), 301(36), 296(65), 195(15), 173(100).

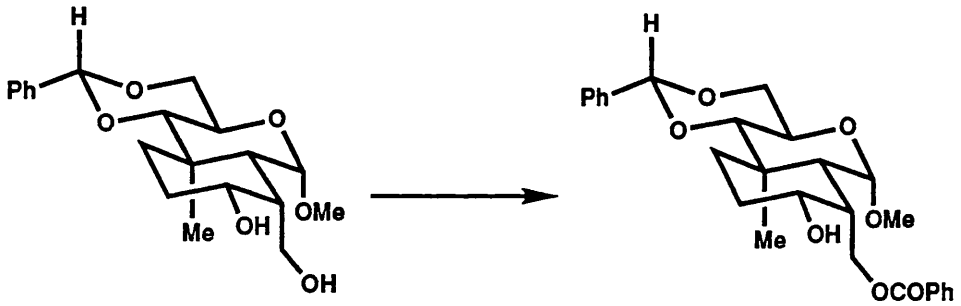
<u>Preparation of 1(R), 2(S), 4(S), 7(R), 9(s), 10(S), 11(S), 14(R)-1-methyl-9-methoxy-4-phenyl-3, 5, 8, 13-tetraoxatetracyclo [8.6.0,$0^{2,7}$,$0^{11,14}$] hexadecane (171)</u>.



To a solution of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-tosylmethyl-1-methyl-9-methoxy-4-phenyl-3, 5,

8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (172) (0.228g, $4.4x10^{-4}$ mol.) in dry tetrahydrofuran at r.t. under nitrogen, butyllithium in hexane (0.48ml, $4.8x10^{-4}$ mol.) was added. The reaction mixture was refluxed for 1h until t.l.c. showed no starting material to be present. The reaction was quenched with water and extracted with diethyl ether (3 X 15ml). The combined organic extracts were dried ($MgSO_4$). After removal of solvent the crude product was purified by flash chromatography (ethyl acetate) to yield the title compound (171) (0.12g, 78%).

Reaction of (134) with triphenylphosphine, DEAD and benzoic acid.



(134) (174)

A solution of (134) (0.200g, $5.5x10^{-4}$ mol.) and triphenylphosphine (0.300g, $1.14x10^{-3}$ mol.) in dry diethyl ether (2.0ml) was added dropwise to a solution of benzoic acid (0.134g, $1.1x10^{-3}$ mol.) and diethylazodicarboxylate (0.200ml, $1.14x10^{-3}$ mol.) in dry diethyl ether (2.0ml). A white precipitate of triphenyl phosphine oxide appeared. After 2h the precipitate was filtered off. The filtrate was evaporated *in vacuo*. The residual oil was purified by

flash chromatography to yield 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-benzoylmethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (174) (0.191g, 80%) and the oxetane (171) (0.035g, 15%).

Data for (174)

R_f 0.5 (ethyl acetate)

$[\alpha]_D^{20}$ = +20° (1.6 in chloroform)

ν_{max} (CH_2Cl_2) 3450s (OH), 3000s, 1700s, 1600w, 1450m, 1275s

δ_H (300MHz; $CDCl_3$) 1.19 (1H, m, H-14), 1.28 (3H, s, C$\underline{H}_3$), 1.80 (3H, m, H-13, H-13, H-14), 2.50 (1H, brm, H-10), 2.62 (1H, brs, OH), 3.21 (1H, d, J=9.6Hz, H-2), 3.42 (3H, s, OC$\underline{H}_3$), 3.68 (1H, t, J=10.1Hz, H-6_{ax}) overlapping 3.78 (1H, m, H-12), 4.00 (1H, dt, J=9.8, 5.0Hz, H-7), 4.25 (1H, dd, J=10.1, 5.0Hz, H-6_{eq}), 4.60 (1H, dd, J=10.2, 5.2Hz, H-11), 4.67 (1H, d, J=2.6Hz, H-9), 5.18 (1H, dd, J=10.2, 2.3Hz, H-11), 5.57 (1H, s, C$\underline{H}$Ph), 7.20-8.10 (10H, m, 2x$C_6\underline{H}_5$).

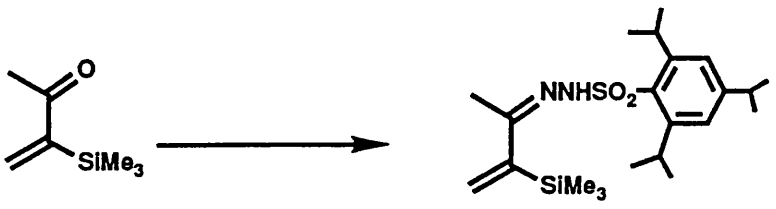
δ_C (75MHz; $CDCl_3$) 15.57(q), 26.68(t), 35.92(s), 36.62(t), 43.15(d), 47.33(d), 55.55(q), 60.44(d), 62.04(t), 69.64(t), 72.97(d), 87.63(d), 101.39(d), 102.71(d), 126.11(d), 128.14(d), 128.37(d), 128.85(d), 129.46(d), 130.30(s), 132.95(d), 137.83(s), 166.68(s).

m/z 468(m^+)(2), 454(5), 437(100), 419(10), 331(50), 315(40), 287(10), 209(10).

$C_{26}H_{29}O_6$ [m-OMe^+] Requires 437.1960

Found 437.1964

Preparation of N'-but-(3-trimethylsilane)-3-en-2-ylidene hydrazono-2, 4, 6-triisopropylbenzene sulphonhydrazide (180).



(119) (180)

Triisopropylbenzene sulphonylhydrazine (0.50g, 1.67×10^{-3} mol.) was stirred in a 1:8 ratio with 3-trimethylsilyl-3-butene-2-one (119) (2.0ml, 0.013 mol.) at 0°C under nitrogen for 2h. The excess enone (119) was removed *in vacuo* and the remaining pale yellow residue was triturated with cold hexane (10ml) to produce a solid which was filtered off. After washing with further amounts of hexane (2 X 10ml) and recrystallisation from petroleum ether (60-80°C) the title compound (180) (0.29g, 42%) was obtained as a pale yellow solid, m.p. 155-156°C.

$C_{18}H_{38}N_2O_2S$ Requires C 62.51% H 9.06% N 6.63%

Found C 62.63% H 9.04% N 6.64%

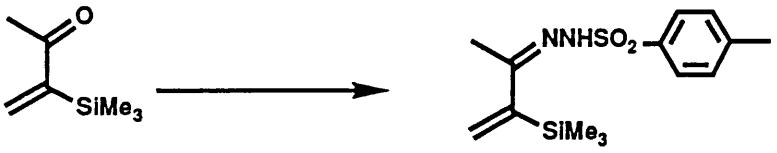
ν_{max} (nujol mull) 3230w (NH), 1600w, 1450s, 1365m.

δ_H (90MHz; $CDCl_3$) 0.21 (9H, s, $Si(CH_3)_3$), 1.24 (18H, d, J=11.4Hz, 3x$CH(C\underline{H}_3)_2$), 1.83 (3H, s, CH_3), 2.85 (1H, m, p-$C\underline{H}(CH_3)_2$), 4.21 (2H, m, o-$C\underline{H}(CH_3)_2$), 5.62 (1H, d, J=4.2Hz), 5.91 (1H, d, J=4.2Hz), 7.10 (2H, s).

δ_C (300MHz; $CDCl_3$) -0.23(q), 11.26(q), 14.82(q), 15.91(q), 34.34(q), 35.72(d), 129.21(d), 132.13(d), 140.10(s), 149.11(s), 150.12(s), 151.23(s), 157.39(s).

m/z 423($m+H^+$)(30), 341(10), 300(10), 155(100).

Preparation of N'-but-(3-trimethylsilane)-en-2-ylidene hydrazono tolylsulphonyl hydrazide (181).



(119) (181)

Tolylsulphonylhydrazine (0.85g, $3.45x10^{-3}$ mol.) was stirred in a 1:8 ratio with 3-trimethylsilyl-3-buten-2-one (119) (3.86g, 0.027 mol.) at 0°C under nitrogen for 2h. The excess enone (119) was removed *in vacuo* and the remaining yellow solid was washed with hexane. After recrystallisation from hexane the title compound (181) (0.240g, 28%) was obtained as a pale yellow solid, m.p. 124-126°C.

$C_{14}H_{22}N_2O_2SiS$ Requires C 54.15% H 7.14% N 9.02%

Found C 53.84% H 7.11% N 8.57%

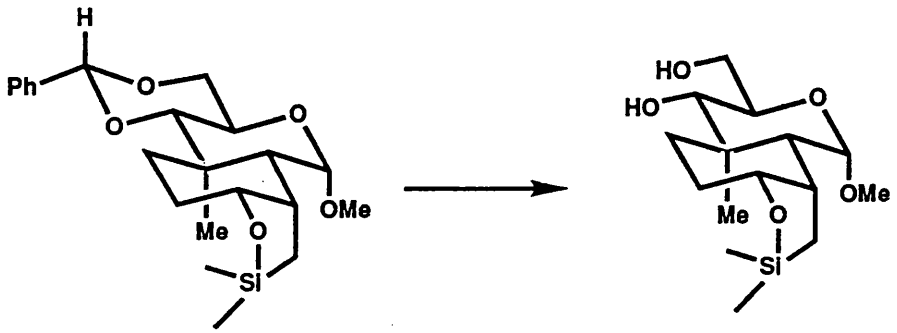
ν_{max}(nujol mull) 3210m (NH), 2950s, 1600w, 1455m, 1350m, 1300w, 1250w, 1150m.

δ_H (300MHz; $CDCl_3$) 0.00 (9H, s, $Si(CH_3)_3$), 1.92 (3H, s, CH_3), 2.45 (3H, s, CH_3), 5.71 (1H, d, J=4.21Hz), 5.97 (1H, d, J=4.21Hz), 7.3-7.85 (4H, $NHC_6\underline{H}_4CH_3$).

δ_C (75MHz; $CDCl_3$) -0.50(q), 11.25(q), 21.80(q), 128.13(d), 128.95(t), 129.41(d), 135.51(s), 144,10(s), 150.25(s), 156.72(s).

m/z 310(m^+)(4), 293(31), 244(10), 229(17), 198(20).

Preparation of 1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-Hydroxymethyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0.$0^{4,8}$] dodecan-2-ol (183).



(141) (183)

To a solution of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0.$0^{2,7}$.$0^{11,15}$] heptadecane (141) (0.583g, $1.45x10^{-3}$ mol.)in methanol (30ml) 5% palladium on carbon (0.60g) was added after premoistening with methanol. The flask was sealed and purged with hydrogen. The flask was then shaken vigorously for 3.5h with the reaction mixture still under hydrogen at atmospheric pressure. The catalyst was then filtered of through celite. The solvent was removed *in vacuo* to yield the title compound (183) (0.408g, 89%) as a white crystalline solid on recrystallisation from petroleum ether and diethyl ether, m.p. 143-144°C.

R_f 0.30 (ethyl acetate)

$[\alpha]_D^{20}$ = +5.3° (1.3 in methanol)

$C_{15}H_{28}O_5Si$ Requires C 56.93% H 8.92% N 0.00%

Found C 57.01% H 8.90 N 0.00%

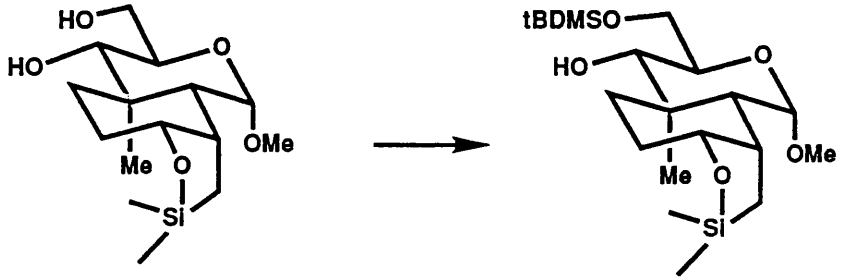
ν_{max} (CH_2Cl_2) 3400s (OH), 2950s, 1550m, 1400w, 1250m, 1125w, 1025s.

δ_H (300MHz; $CDCl_3$) 0.13 (3H, s, $SiC\underline{H}_3$), 0.25 (3H, s, $SiC\underline{H}_3$), 1.00 (3H, complex multiplet, H-2, $C\underline{H}_2Si$), 1.25 (3H, s, $C\underline{H}_3$) overlapping 1.32 (1H, m, H-2), 1.75 (3H, complex multiplet, H-3, H-9), 2.30 (1H, brm, H-8), 3.20 (1H, brm, H-12) overlapping 3.21 (1H, brs, OH), 3.26 (3H, s, $OC\underline{H}_3$), 3.55 (1H, d, J=8.6Hz, H-13), 3,72 (2H, brm, $C\underline{H}_2OH$) overlapping 3.74 (1H, brs, OH), 3.92 (1H, brm, H-4), 4.46 (1H, d, J=5.1Hz, H-10).

δ_C (75MHz; $CDCl_3$) 0.07(q), 1.35(q), 13.42(t), 14.79(q), 27.34(t), 36.22(t), 36.89(s), 39.47(d), 46.50(d), 54.91(q), 63.05(t), 69.25(d), 76.75(d), 79.26(d), 102.63(d).

m/z 283(m^+-OMe)(8), 256(16), 255(65), 223(36), 183(27), 167(20), 127(46).

Preparation of 1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-tert butyldimethylsiloxy methyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-ol (184).



(183) (184)

1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-Hydroxymethyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-ol (183) (0.35g, 1.15×10^{-3} mol.) was stirred under nitrogen in dichloromethane (3ml) with imidazole (0.17g 2.5×10^{-3} mol.). To this stirred solution tertbutyldimethylchlorosilane (0.195g, 1.27×10^{-3} mol.) was added dropwise in a solution of dichloromethane (1ml). The reaction mixture was stirred for 24h after which water (2ml) was added. The aqueous layer was separated from the organic layer and was further extracted with dichloromethane (3 X 10ml) then the combined organics were washed with aqueous saturated sodium chloride and dried ($MgSO_4$). After removal of solvent, flash chromatography (ethyl acetate) and recrystallisation (1:1 diethyl ether-petroleum ether), the title compound (184) was obtained as a white crystalline solid, m.p. 105-106°C.

R_f 0.44 (ethyl acetate)

$[\alpha]_D^{20}$ = +11° (6.4 in methanol)

$C_{20}H_{42}O_5Si_2$ Requires C 58.56% H 9.83% N 0.00%

Found C 58.84% H 9.78% N 0.00%

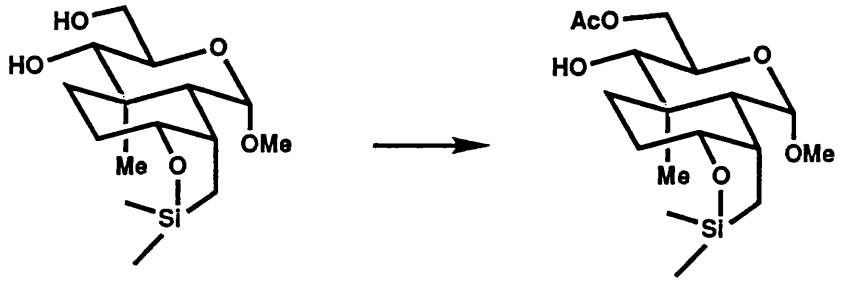
ν_{max} (CH_2Cl_2) 3450s (OH), 2925s, 1475m, 1350m, 1200w, 1050s, 850s.

δ_H (300MHz; $CDCl_3$) 0.14 (6H, s, $Si(C\underline{H}_3)_2$), 0.18 (3H, s, $SiC\underline{H}_3$), 0.30 (3H, s, $SiC\underline{H}_3$), 0.94 (9H, s, $SiC(C\underline{H}_3)_3$) overlapping 1.04 (1H, dd, J=11.1, 5.3Hz, H-7) overlapping 1.08 (1H, t, J=11.1Hz, H-7), 1.33 (3H, s, $C\underline{H}_3$) overlapping 1.40 (1H, m, H-2), 1.71 (1H, t, J=3.1Hz, H-9), 1.85 (3H, brm, H-3, H-2), 2.35 (1H, brm, H-8), 3.24 (1H, d, J=9.0Hz, H-13), 3.33 (1H, brs, OH), 3.38 (3H, s, $OC\underline{H}_3$), 3.80 (2H, complex multiplet, H-12, C<u>H</u>OH), 3.91 (1H, m, C<u>H</u>OH), 4.00 (1H, brm, H-4), 4.51 (1H, d, J=3.1Hz, H-10).

δ_C (75MHz; $CDCl_3$) -5.53(q), 0.19(q), 1.46(q), 13.61(t), 15.05(q), 18.22(s), 25.86(q), 27.56(t), 36.26(t), 36.91(s), 39.70(d), 46.38(d), 54.99(q), 66.44(t), 67.73(d), 79.43(d), 80.81(d), 102,77(d).

m/z No m^+ found, 342(90), 323(12), 249(50), 223(32), 195(31), 175(45).

Preparation of 1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-acetoxymethyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-ol (185).



(183) (185)

1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-Hydroxymethyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-ol (183) (0.35g, 1.15×10^{-3} mol.) was stirred under nitrogen in pyridine (2.0ml, 0.036 mol.). To this stirred solution acetic anhydride (0.11ml, 1.26×10^{-3} mol.) was added dropwise. The reaction mixture was stirred for 48h after which the solvent was removed *in vacuo*. Water (5ml) and diethyl ether (6ml) were added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 X 10ml). The combined organics were washed with aqueous saturated sodium chloride and dried (Na_2SO_4). After removal of solvent and flash chromotagraphy (ethyl acetate) the title compound (185) (0.238g, 58%) was obtained as a glass.

R_f 0.55 (ethyl acetate)

$[\alpha]_D^{20}$ = +215° (5.4 in methanol)

ν_{max} (CH_2Cl_2) 3500s (OH), 2900s, 1725s (C=O), 1450m, 1375s, 1200s, 1125m, 1000s, 850s.

δ_H (300MHz; $CDCl_3$) 0.15 (3H, s, $SiC\underline{H}_3$), 0.27 (3H, s, $SiC\underline{H}_3$), 0.90 (1H, dd, J=11.0, 5.4Hz, H-7) overlapping 1,07 (1H, t, J=11.0Hz, H-7), 1.28 (3H, s, $C\underline{H}_3$) overlapping 1.32 (1H, m, H-2), 1.6 (1H, brm, H-9), 1.80 (3H, complex mutiplet, 2xH-3, H-2), 2.17 (3H, s, $COC\underline{H}_3$), 2.31 (1H, brm, H-8), 3.05 (1H, d, J=10.1Hz, H-13), 3.37 (3H, s, $OC\underline{H}_3$), 3.89 (1H, brm, CHOAc), 4.01 (1H, brm, H-2), 4.23 (1H, dd, J=13.1, 2.2Hz, H-12), 4.51 (1H, dd, J=13.1, 4.1Hz, CHOAc), 4.57 (1H, d, J=3.4Hz, H-10).

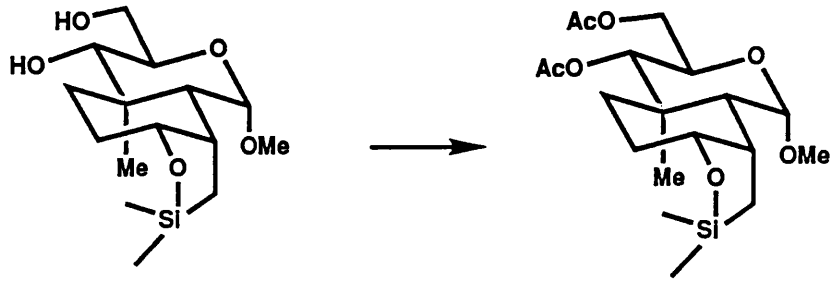
δ_C (75MHz; $CDCl_3$) 0.08(q), 1.36(q), 13.44(t), 14.64(q), 20.80(q), 27.38(t), 36.32(t), 36.93(s), 39.47(d), 46.45(d), 54.94(q), 64.52(t), 68.31(d), 75.70(d), 79.18(d), 102.72(d), 171.90(s).

m/z 359($m+H^+$)(10), 344(50), 327(100), 302(5), 285(30), 255(10), 182(10), 128(10).

$C_{17}H_{31}O_6Si$ [$m+H^+$] Requires 359.1889

Found 359.1890

Data for the diacetate 1(R), 4(R), 8(S), 9(S), 10(S), 12(R), 13(S)-12-acetoxymethyl-10-methoxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-acetate.



(183)

R_f 0.71 (ethyl acetate)

$[\alpha]_D^{20}$ = +67° (8.2 in chloroform)

ν_{max} (CH_2Cl_2) 2910s, 1730s (C=O), 1450m, 1360m, 1250s, 1020s, 830s.

δ_H (300MHz; $CDCl_3$) 0.16 (3H, s, $SiCH_3$), 0.27 (3H, s, $SiCH_3$), 0.91 (1H, dd, J=11.0, 5.4Hz, H-7) overlapping 1.08 (1H, t, J=11.0Hz, H-7), 1.30 (3H, s, CH_3) overlapping 1.31 (1H, m, H-2), 1.58 (1H, brm, H-9), 1.80 (3H, m, H-3, H-2), 2.05 (3H, s, $COCH_3$), 2.10 (3H, s, $COCH_3$), 2.30 (1H, brm, H-8), 3.11 (1H, d, J=10.1Hz, H-13), 3.43 (3H, s, OCH_3), 3.89 (1H, brm, CHOAc), 4.01 (1H, brm, H-4), 4.21 (1H, dd, J=13.2, 2.2Hz, H-12), 4.61 (1H, dd, J=13.1, 4.1Hz, CHOAc), 4.57 (1H, d, J=3.4Hz, H-10).

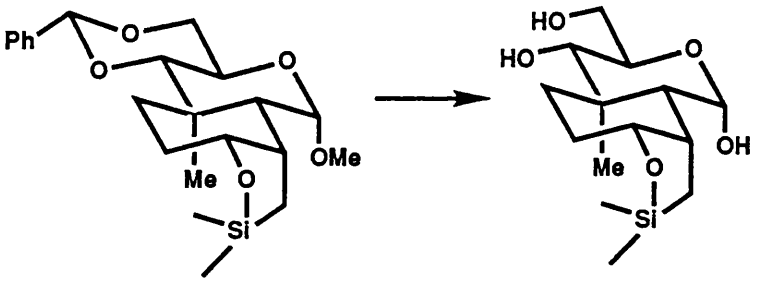
δ_C (75MHz; $CDCl_3$) 0.08(q), 1.38(q), 13.38(t), 15.59(q), 20.66(q), 20.73(q), 27.13(t), 36.04(q), 37.14(s), 39.33(d), 46.32(d), 55.08(q), 63.11(t), 65.72(d), 66.12(d), 78.80(d), 102.61(d), 169.88(s), 170.74(s).

m/z 418(mNH_4^+)(10), 401(5), 386(25), 369(100), 309(5), 249(20).

$C_{19}H_{36}NO_7Si$ [$m+NH_4^+$] Requires 418.2259

Found 418.2261

Preparation of 1(R), 4(R), 8(S), 9(S), 12(R), 13(S)-12-hydroxymethyl-10-hydroxy-1, 6, 6-trimethyl-5, 11-dioxa-6-silatricyclo [7.4.0,$0^{4,8}$] dodecan-2-ol (187).



(141) (187)

1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0.$0^{2,7}$.$0^{11,15}$] heptadecane (141) (1.025g, $2.5x10^{-3}$ mol.) was dissolved in dioxane (30ml) and a 2.5% aqueous solution of sulphuric acid (20ml) was added. The solution was refluxed for 6h until t.l.c. showed no remaining starting material. The solution was cooled and neutralised with sodium hydrogen carbonate, filtered and the solvents removed *in vacuo* to leave a white solid which was extracted with methanol (50ml). Removal of the methanol *in vacuo* and flash chromatography (diethyl ether-10% methanol) left a sticky glass of the title compound (187) (0.354g, 47%).

R_f 0.41 (diethyl ether-10% methanol)

$[\alpha]_D^{20}$ = +26° (1.6 in methanol)

ν_{max} (nujol mull) 3300s (OH), 2900s, 1700s, 1650s, 1400s, 1250s, 1050s.

δ_H (300MHz; CD_3OD) 0.16 (3H, s, $SiC\underline{H}_3$), 0.22 (3H, s, $SiC\underline{H}_3$), 0.61 (1H, dd, J=11.2, 5.4Hz, H-7), 0.72 (1H, t, J=11.2Hz, H-7), 1.11 (1H, brt, J=10.1, 5.0Hz, H-2), 1.26 (3H, s, CH_3), 1.49 (1H, t, J=2.8Hz, H-9), 1.71 (3H, brm, H-3, H-2), 2.32 (1H, brm, H-8), 3.16 (1H, d, J=10.5Hz, H-13), 3.58 (2H, brm, $C\underline{H}_2OH$, OH), 3.70 (4H, complex multiplet, $C\underline{H}_2OH$, H-12, H-4, OH), 5.08 (1H, d, J=2.8Hz, H-10).

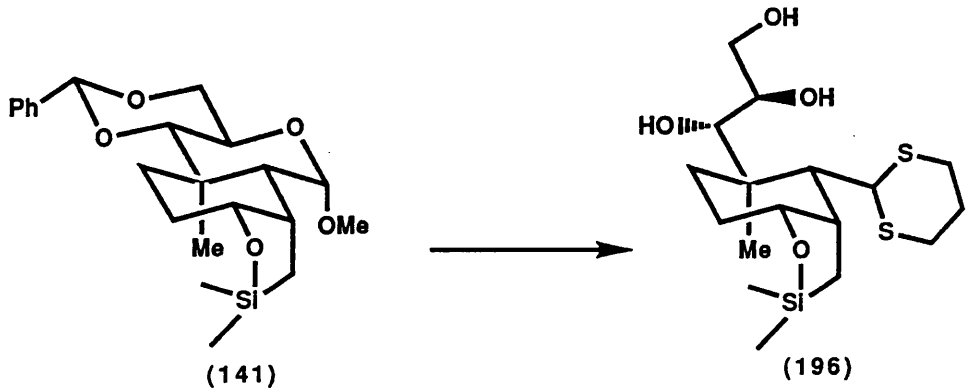
δ_C (75MHz; CD_3OD) 0.21(q), 1.32(q), 17.51(t), 22.52(q), 29.23(t), 30.01(t), 33.10(d), 38.98(s), 48.53(d), 64.48(t), 66.05(d), 74.00(d), 78.49(d), 98.21(d).

m/z 300(m^+)(20), 285(100), 267(10), 237(15), 193(25), 179(18), 149(30), 119(31), 105(35).

$C_{14}H_{26}NaO_5Si$ [$m+Na^+$ (FAB)] Requires 325.1447

Found 325.1447

Preparation of 5-(1", 3"-dithiane)-(1', 2', 3'-propane triol)-4, 8, 8-trimethyl [4.3.0] octadecane (196).



1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-Trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0.$0^{2,7}$.$0^{11,15}$] heptadecane (141) (0.239g, $5.9x10^{-4}$ mol.) was stirred under nitrogen in dichloromethane (3ml) with 1, 3-propanedithiol (0.160ml, $1.47x10^{-3}$ mol.). To this solution borontrifluoride etherate (0.070ml, $6x10^{-4}$ mol.) was added. After 5h at r.t. the solvent was removed *in vacuo* and the resulting residue was purified by flash chromatography (ethyl acetate-5% methanol) to yield the title compound (196) (0.122g, 53%) as a white glass.

R_f 0.41 (ethyl acetate-5% methanol)

$[\alpha]_D^{20}$ = +23° (6.6 in methanol)

ν_{max} (nujol mull) 3350s (OH), 2875s, 1450s, 1375s, 1250w, 1025m, 800m.

δ_H (300MHz; CD_3OD) 0.34 (3H, s, $SiC\underline{H}_3$), 0.47 (3H, s, $SiC\underline{H}_3$), 1.16 (1H, t, J=7.1Hz, H-7), 1.21 (1H, dd, J=7.1,

5.1Hz, H-7), 1.30 (1H. ddd, J=10.1, 5.0Hz, H-3) overlapping 1.32 (2H, m, H-5") overlapping 1.34 (3H, s, $C\underline{H}_3$) overlapping 1.39 (1H, m, H-3), 1.62 (1H, brm, H-2), 1.80 (1H, dd, J=10.2, 4.8Hz, H-5), 2.00 (1H, m, H-2), 2.20 (1H, t, J=6.3Hz, H-4"), 2.55 1H, m, H-1), 2.61 (1H, t, J=6.4Hz, H-6"), 3.05 (2H, m, H-4", H-6"), 3.25 (1H, d, J=9.7Hz, H-1'), 3.67 (1H, m, H-3') overlapping (1H, brd, J=10.2Hz, H-2"), 3.80 (1H, m, H-2')' 3.97 (1H, dd, J=10.3, 2.1Hz, H-3'), 4.20 (1H, m, H-1').

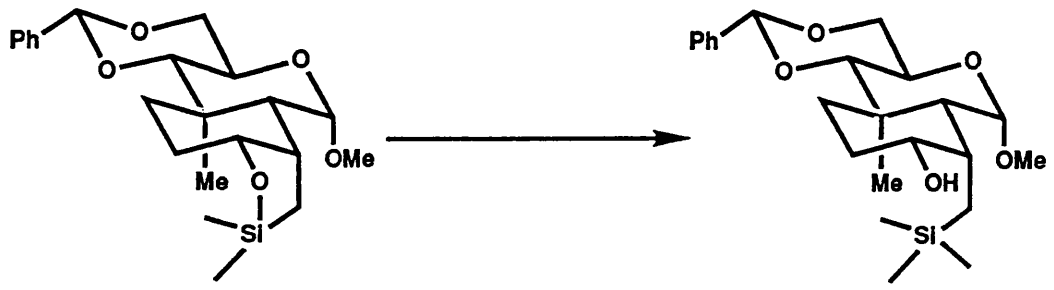
δ_C (75MHz; CD_3OD) 0.01(q), 1.97(q), 11.81(t), 14.02(q), 24.21(t), 28.51(t), 29.15(t), 35.33(t), 36.00(t), 40.98(d), 49.11(d), 64.30(t), 76.56(d), 79.02(d), 80.89(d), 83.41(d).

m/z 392(m^+)(3), 341 (5), 317(15), 302(10), 285(100), 267(10), 225(10), 183(10), 92(10).

$C_{17}H_{36}NO_4S_2Si$ [$m+NH_4^+$] Requires 410.1853

Found 410.1855

Reaction of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0.$0^{2,7}$.$0^{11,15}$] heptadecane (141) with MeCuLi.



(141) (200)

To a stirred suspension of $CuBrMe_2S$ (0.208g, $1.01x10^{-3}$ mol.) in diethyl ether (5ml) under nitrogen, methyllithium (1.44ml, $2.02x10^{-3}$ mol.) was added at -50°C. After stirring for 10min at -35°C a clear solution was obtained. Then 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 15(R)-1, 13, 13-trimethyl-9-methoxy-4-phenyl-3, 5, 8, 14-tetraoxa-13-silatetracyclo [8.7.0.$0^{2,7}$.$0^{11,15}$] heptadecane (141) (0.321g, $1.01x10^{-3}$ mol.) in diethyl ether (3ml) was added at -50°C and the mixture cooled to -78°C whereupon a solution of borontrifluoride etherate (0.12ml, $1.01x10^{-3}$ mol.) in diethyl ether (2ml) was slowly added. The temperature was allowed to rise to -30°C and the reaction mixture was stirred for 30min. The reaction was quenched at -40°C with aqueous ammonium chloride solution (30ml) and extracted with diethyl ether (3 x 30ml), the organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a crude residue. After flash chromatography

(1:1 diethyl ether-petroleum ether) and recrystallisation from petroleum ether 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-(trimethylsila)methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (200) (0.377g, 89%) was obtained as a white solid, m.p. 105-106°C.

R_f 0.44 (1:1 diethyl ether-petroleum ether)

$[\alpha]_D^{20}$ = +20° (11.6 in methanol)

ν_{max} (CH_2Cl_2) 3600s (OH), 2950s, 1450s, 1350s, 1325s, 1050s, 1000s, 850s.

δ_H (300MHz; $CDCl_3$) 0.08 (9H, s, Si($C\underline{H}_3$)$_3$) overlapping 0.09 (1H, m, $C\underline{H}Si$), 0.57 (1H, dd, J=15.1, 7.5Hz, $C\underline{H}Si$), 1.15 (1H, dt, J=13.7, 3.3Hz, H-14), 1.42 (3H, s, $C\underline{H}_3$), 1.50 (1H, dd, J=12.7, 3.3Hz, H-14), 1.60 (1H, m, H-13), 1.65 (1H, t, J=3.2Hz, H-10), 1.92 (1H, brdt, J=13.7, 3.1Hz, H-13), 2.25 (1H, brm, H-11), 3.20 (1H, d, J=9,5Hz, H-2), 3.38 (3H, s, $OC\underline{H}_3$), 3.65 (1H, m, H-12), 3.75 (1H, t, J=10.1Hz, H-6_{ax}), 4.00(1H, dt, J=10.1, 5.0Hz, H-7), 4.31 (1H, dd, J=10.1, 5.0Hz, H-6_{eq}), 4.51 (1H, d, J=3.2Hz, H-9), 5.55 (1H, s, $C\underline{H}$Ph), 7.30-7.58 (5H, m, $C_6\underline{H}_5$).

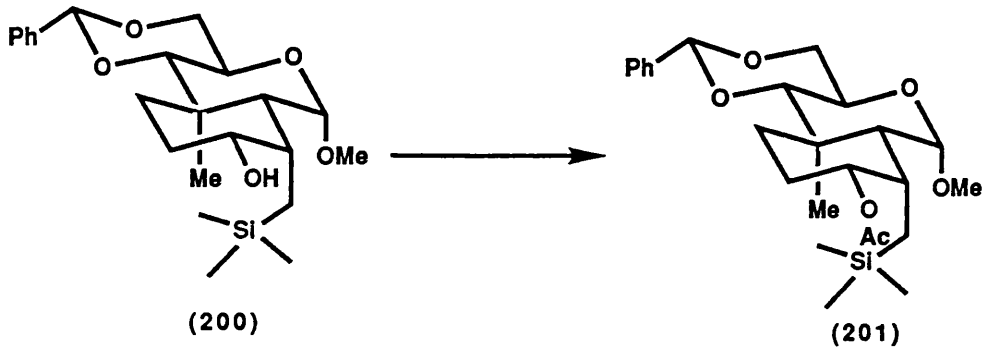
δ_C (75MHz; $CDCl_3$) -0.95(q), 11.05(t), 16.16(q), 25.55(t), 36.07(s), 37.09(d), 37.15(t), 48.32(d), 54.58(q), 60.10(d), 69.54(t), 73.83(d), 87.99(d), 101.09(d), 103.18(d), 125.99(d), 127.95(d), 128.60(s), 137.86(s).

m/z 421(m+H^+)(30), 389(15), 193(20), 149(32), 121(100), 90(31).

$C_{23}H_{37}O_5Si$ [m+H^+] Requires 421.2436

Found 421.2410

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-(trimethylsila)methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-acetate (201).



1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-(Trimethylsila)methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (200) (0.377g, $8.9x10^{-4}$ mol.) was stirred under nitrogen in pyridine (3.0ml, 0.037 mol). To this stirred solution acetic anhydride (0.33ml, $3.56x10^{-3}$ mol.) was added dropwise. The reaction mixture was stirred for 48h after which the solvent was removed *in vacuo*. Water (5.0ml) and diethyl ether (10.0ml) were added. The organic layer was separated and the aqueous layer was further extracted with diethyl ether (3 X 10ml). The combined organics were washed with aqueous saturated sodium chloride (10ml) and dried (Na_2SO_4). After removal of solvent and flash chromatography (ethyl acetate) the title compound (201) (0.328g, 80%) was obtained as a white solid, m.p. 84-86°C.

R_f 0.59 (ethyl acetate)

$[\alpha]_D^{20}$ = +28° (6.7 in methanol)

ν_{max} (CH_2Cl_2) 2950s, 1720s (C=O), 1450w, 1375s, 1250m, 1130s, 1075s, 850s.

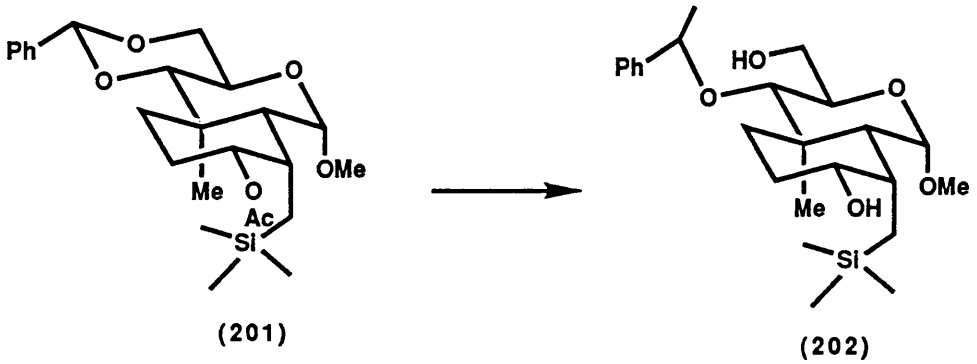
δ_H (300MHz; $CDCl_3$) 0.33 (9H, s, $Si(C\underline{H}_3)_3$) overlapping 0.04 (1H, m, $SiC\underline{H}$), 0.67 (1H, dd, J=15.1, 6.9Hz, $SiC\underline{H}$), 1.27 (1H, dt, J=13.6, 3.4Hz, H-14), 1.44 (3H, s, $C\underline{H}_3$), 1.52 (1H, dd, 12.9, 2.9Hz, H-14), 1.71 (1H, m, H-13) overlapping 1.75 (1H, t, J=3.2Hz, H-10), 1.91 (1H, brm, H-13), 2.08 (3H, s, $COC\underline{H}_3$), 2.35 (1H, brm, H-11), 3.20 (1H, d, J=9.5Hz, H-2), 3.36 (3H, s, $OC\underline{H}_3$), 3.72 (1H, t, J=10.1Hz, H-6_{ax}), 4.00 (1H, dt, J=10.1, 5.0Hz, H-7), 4.30 (1H, d, J=3.2Hz, H-9), 4.85 (1H, dt, J=11.9, 4.7Hz, H-12), 5.55 (1H, s, $C\underline{H}Ph$), 7.30-7.60 (5H, m, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) 0.93(q), 11.68(t), 16.33(q), 21.71(q), 22.51(t), 34.58(d), 36.29(s), 37.02(t), 48.41(d), 54.60(q), 60.22(d), 69.60(t), 76.63(d), 87.88(d), 101.23(d), 102.89(d), 126.07(d), 128.07(d), 128.72(d), 137.91(s), 170.43(s).

m/z 463($m+H^+$)(10), 387(30), 371(10), 298(10), 249(20), 193(10), 175(30), 149(80), 121(90), 73(100).

$C_{25}H_{39}O_6Si$ [$m+H^+$]	Requires	463.2525
	Found	463.2516

Preparation of 1(R), 2(R), 3(R), 5(S), 6(S), 7(S), 8(R)-3-hydroxymethyl-5-methoxy-1-methyl-2-(phenylmethyl)methylen-7-(trimethylsila)methyl-4-oxabicyclo [4.4.0] decan-8-ol (202).



(201) (202)

To a stirred suspension of $CuBrMe_2S$ (0.346g, $1.68x10^{-3}$ mol.) in diethylether (5ml) under nitrogen, methyllithium (2.40ml, $3.36x10^{-3}$ mol.) was added at -50°C. After stirring for 10min at -35°C a clear solution was obtained. Then 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-(trimethylsila) methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-acetate (201) (0.388g, $8.39x10^{-4}$ mol.) in diethyl ether (3ml) was added at -50°C and the mixture cooled to -78°C whereupon a solution of boron trifluoride etherate (0.206ml, $1.68x10^{-3}$ mol.) in diethyl ether (2ml) was slowly added. The temperature was allowed to rise to -30°C and the reaction mixture was stirred for 30min. The reaction was quenched at -40°C with aqueous ammonium chloride solution (30ml) and extracted with diethyl ether (3 X 35ml), the organics were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give

a crude residue. After flash chromatography (1:1 diethyl ether-petroleum ether) and recrystallisation from petroleum ether the title compound (202) (0.234g, 64%) was obtained as a powder, m.p. 61-62°C.

R_f 0.25 (1:1 diethyl ether-petroleum ether)

$[\alpha]_D^{20}$ = +89° (15.5 in chloroform)

$C_{24}H_{40}O_5Si$ Requires C 66.01% H 9.23% N 0.00%

Found C 65.99% H 9.49% N 0.00%

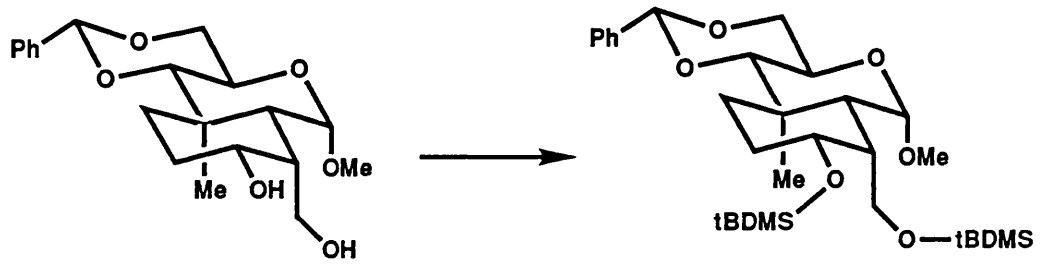
ν_{max} (CH_2Cl_2) 3500s (OH), 2950s, 1600w, 1450m, 1360, 1200m, 1050s, 850s

δ_H (300MHz; $CDCl_3$) 0.03 (9H, s, $Si(C\underline{H}_3)_3$) overlapping 0.04 (1H, m, $SiC\underline{H}$), 0.52 (1H, dd, J=15.0, 6.8Hz, $SiC\underline{H}$), 0.95 (1H, m, H-10), 1.35 (3H, s, $C\underline{H}_3$), 1.47 (3H, d, J=6.3Hz, $PhCHC\underline{H}_3$), 1.56 (1H, t, J=3.1, H-6), 1,85 (2H, brm, H-9, H-10), 1,94 (1H, dt, J=12.6, 3.0Hz, H-9), 2.25 (1H, brm, H-7), 3.06 (1H, d, J=10.1Hz, H-2), 3.25 (3H, s, $OC\underline{H}_3$) overlapping 3.30 (1H, m, $C\underline{H}OH$), 3.45 (1H, d, J=11.7, 2.3Hz, H-3), 3.65 (2H, brm, $C\underline{H}OH$, H-8), 4.43 (1H, d, J=3.1Hz, H-5), 4.60 (1H, q, J=6.5Hz, $PhC\underline{H}CH_3$), 7.35 (5H, brs, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) -0.99(q), 11.10(t), 16.14(q), 23.24(q), 25.90(t), 37.01(d), 38.46(t), 39.01(s), 48.16(d), 54.33(q), 62.36(t), 68.82(d), 73.85(d), 78.43(d), 81.92(d), 102.78(d), 126.28(d), 127.53(d), 128.27(d), 143.55(s).

m/z 437(mH^+) (10), 422(20), 405(40), 391(40), 318(30), 301(25), 283(100), 267(10), 105(30)

Preparation of the di-tertbutyldimethylsilyl ether of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-1-Hydroxy methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (207).



1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-1-Hydroxy methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) (0.322g, 8.8×10^{-4} mol.) was stirred under nitrogen in dichloromethane (10ml) with imidazole (0.318g, 2.11×10^{-3} mol.). To this stirred solution tert-butyldimethylchlorosilane (0.318g, 2.11×10^{-3} mol.) was added dropwise in a solution of dichloromethane (5ml). The reaction mixture was stirred for 48h after which water (10ml) was added. The aqueous layer was separated from the organic layer and was further extracted with dichloromethane (2 X 25ml) then the combined organics were washed with aqueous saturated sodium chloride solution (10ml) and dried ($MgSO_4$). After removal of the solvent and flash chromatography (ethyl acetate) and recrystallisation from hexane the title compound (207) (0.359g, 68%) was obtained as a white crystalline solid, m.p. 150-152°C.

R_f 0.69 (ethyl acetate)

$[\alpha]_D^{20}$ = +28° (0.6 in methanol)

$C_{32}H_{56}O_6Si_2$ Requires C 64.82% H 9.52% N 0.00%

Found C 64.69% H 9.49% N 0.00%

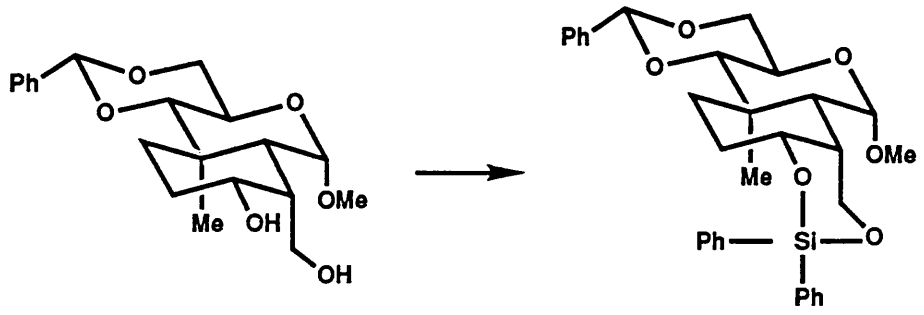
ν_{max} (CH_2Cl_2) 2900s, 1460w, 1350w, 1050s, 850s.

δ_H (300MHz; $CDCl_3$) 0.10 (6H, s, $Si(C\underline{H}_3)_2$), 0.11 (6H, s, $Si(C\underline{H}_3)_2$), 0.94 (18H, brs, $SiC(C\underline{H}_3)_3$), 1.21 (3H, s, $C\underline{H}_3$), 1.61 (2H, m, H-14, H-13), 1.70 (1H, t, J=2.8Hz, H-10), 1.85 (1H, dt, J=15.1, 3.1Hz, H-13), 2.10 (1H, brm, H-11), 3.22 (1H, d, J=9.5Hz, H-2), 3.40 (3H, s, $OC\underline{H}_3$), 3.70 (1H, brm, H-12) overlapping 3.72 (1H, t, J=10.1Hz, $H\text{-}6_{ax}$), 3.83 (1H, dd, J=9.0, 4.3Hz, $C\underline{H}OSi$), 4.00 (1H, dt, J=10.1, 5.0Hz, H-7), 4.20 (1H, dd, J=9.0, 2.4Hz, $C\underline{H}OSi$), 4.31 (1H, dd, J=10.1, 5.1Hz, $H\text{-}6_{eq}$) 4.65 (1H, d, J=2.8Hz, H-9), 5.51 (1H, s, $C\underline{H}Ph$), 7.30-7.50 (5H, m, $C_6\underline{H}_5$).

δ_C (75MHz; $CDCl_3$) -5.32(q), -5.12(q), -4.72(q), -4.44(q), 15.40(q), 18.41(q), 18.42(s), 26.12(q), 26.18(q), 28.27(t), 36.02(s), 37.08(t), 47.74(d), 48.04(d), 55.39(q), 58.54(t), 60.28(d), 69.82(t), 73.67(d), 88.20(d), 101.39(d), 103(d), 126.13(d), 128.14(d), 128.79(d), 138.04(s).

m/z 561 (m^+-OMe)(50), 455(10), 429(100), 355(5), 329(10), 121(40).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 16(R)-1-methyl-9-methoxy-4, 14, 14-triphenyl-3, 5, 8, 13, 15-pentaoxa-14-silatetracyclo [8.8.$0^{2,7}$,$0^{11,16}$] octadecane (212).



(134) (212)

1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S),12(R)-1-hydroxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxa tricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) (0.210g, 5.76×10^{-4} mol.) was stirred in triethylamine (2ml) under nitrogen. To the reaction mixture dichlorodiphenyl silane (0.150g, 5.94×10^{-4} mol.) was added dropwise over 10min. After 48h the triethylamine was removed *in vacuo* and water was added (10ml). The aqueous layer was extracted with diethyl ether (3 X 20ml). The organic layers were combined and washed with saturated aqueous sodium chloride and dried (Na_2SO_4). After removal of the solvent the residual oil was purified by flash chromatography (ethyl acetate) to give the title compound (212) (0.209g, 67%) as a white solid m.p. 131-133°C.

R_f 0.72 (ethyl acetate)

$[\alpha]_D^{20}$ = +56° (6.3 in chloroform)

ν_{max} (CH_2Cl_2) 2900s, 1450w, 1375m, 1075s, 800m.

δ_H (300MHz; $CDCl_3$) 1.13 (1H, brdt, J=14.2, 3.9Hz, H-18) overlapping 1.2 (3H, s, C<u>H</u>$_3$), 1.75 (1H, t, J=4.0Hz, H-10), 1.85 (2H, m, H-17, H-18), 1.95 (1H, m, H-17), 2.73 (1H, brm, H-11), 3.15 (1H, d, J=10.6Hz, H-2), 3.35 (3H, s, OC<u>H</u>$_3$), 3.66 (1H, t, J=10.2Hz, H-6_{ax}), 3.90 (1H, dt, J=10.2, 5.1Hz, H-7), 4.23 (1H, dd, J=10.1, 5.1Hz, H-6_{eq}) overlapping 4.23 (1H, brm, H-16), 4.44 (1H, t, J=15.0Hz, CH_2OH), 4.53 (1H, dd, J=7.6, 4.4Hz, CH_2OH), 4.62 (1H, d, J=4.0Hz, H-9), 5.50 (1H, s, C<u>H</u>Ph), 7.25-7.70 (15H, m, 3xC_6<u>H</u>$_5$).

δ_C (75MHz; $CDCl_3$) 16.00(q), 26.91(t), 35.69(s), 36.58(t), 43.64(d), 48.19(d), 55.10(q), 60.46(d), 61.79(t), 69.58(t), 76.76(d), 87.62(d), 101.32(d), 102.48(d), 126.09(d), 127.81(d), 127.86(d), 128.13(d), 128.83(d), 130.37(d), 130.49(d), 134.11(s), 134.30(s), 134.43(d), 134.47(d), 137.83(s).

m/z 545(mH^+)(25), 513(40), 439(52), 407(55), 279(25), 216(20), 121(100).

$C_{32}H_{37}O_6Si$ [$m+H^+$] Requires 545.2357

Found 545.2360

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-3, 7-dihydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decan-2,8-diol (208).

(207) (208)

To a solution of the di tertbutyldimethylsilyl ether of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-1-hydroxy methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (207) (0.359g, 6.06×10^{-4} mol.) in methanol (30ml) 5% palladium on carbon (0.41g) was added after premoistening with methanol. The flask was sealed and purged with hydrogen. The flask was then shaken vigorously for 2.5h with the reaction mixture still under hydrogen at atmospheric pressure. The catalyst was the filtered off through celite. The solvent was removed *in vacuo* to yield the title compound (208) (0.16g, 98%) as a white crystalline solid, m.p. 155-156°C.

R_f 0.30 (ethyl acetate-5% methanol)

$[\alpha]_D^{20} = 23.5°$ (6.0 in chloroform)

$C_{13}H_{24}O_6$ Requires C 56.52% H 8.75% N 0.00%

Found C 56.32% H 8.75% N 0.00%

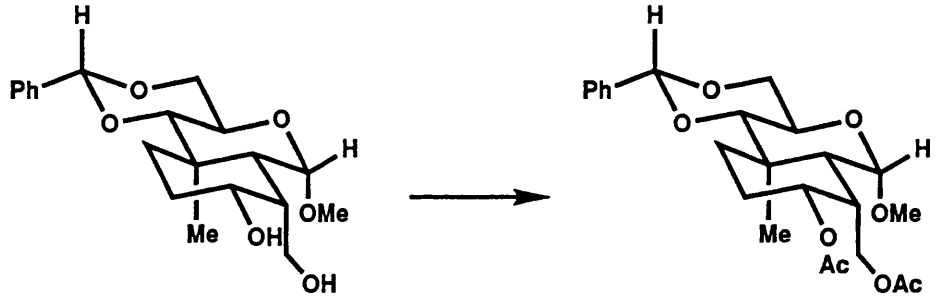
ν_{max} (nujol mull) 3300s (OH), 2920s, 1450s, 1375m, 1125m.

δ_H (300MHz; CD_3OD) 1.25 (3H, s, $C\underline{H}_3$) overlapping 1.27 (1H, brm, H-10), 1.90 (4H, complex multiplet, H-10, H-9, H-7), 2.43 (1H, brm, H-6), 3.27 (1H, d, J=12.2Hz, H-2), 3.58 (3H, s, $OC\underline{H}_3$), 3.83 (2H, m, $C\underline{H}_2OH$), 3.96 (2H, m, $C\underline{H}_2OH$), 4.55 (1H, dd, J=10.1, 9.2Hz, H-3), 4.39 (1H, dd, J=10.0, 3.4Hz, H-8), 4.80 (1H, d, J=3.9Hz, H-1).

δ_C (75MHz; CD_3OD) 15.81(q), 27.94(t), 38.96(s), 38.36(t), 46.62(d), 48.90(d), 55.48(q), 61.40(t), 63.87(t), 71.55(d), 75.46(d), 77.77(d), 104.02(d).

m/z 276(m^+)(5), 213(15), 167(37), 153(26), 149(78), 109(62).

Preparation of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-acetoxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-acetate (223).



1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S),12(R)-1-hydroxy methyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-ol (134) (1.505g, 4.13×10^{-3} mol.) was dissolved in pyridine (2.0ml) to which acetic anhydride (0.505g, 4.95×10^{-3} mol.) was added under nitrogen with stirring. The reaction mixture was left stirring for 48h

after which the excess pyridine and acetic anhydride were removed *in vacuo* to leave a crude oil. After flash chromatography (ethyl acetate) the title compound (223) (1.15g, 62%) was obtained as a glass. The monoacetate (224) was also obtained as a glass (0.362g, 21%).

Data for diacetate (223).

R_f 0.5 (ethyl acetate)

$[\alpha]_D^{20}$ = +57° (4.3 in chloroform)

ν_{max} (CH_2Cl_2) 2950s, 2850s, 1725s (C=O), 1450m, 1375s, 1216s, 1100s

δ_H (300MHz; $CDCl_3$) 0.92 (1H, m, H-14), 1.18 (1H, m, H-14) overlapping 1.21 (3H, s, C$\underline{H}_3$), 1.73 (2H, m, H-13, H-13), 1.97 (1H, m, H-10) overlapping 1.97 (3H, s, COC$\underline{H}_3$) and 1.99 (3H, s, COC$\underline{H}_3$), 2.61 (1H, m, H-11), 3.19 (1H, d, J=9.5Hz, H-2), 3.38 (3H, s, OC$\underline{H}_3$), 3.67 (1H, t, J=10.2Hz, H-6_{ax}), 3.96 (1H, dt, J=9.8, 5.0Hz, H-7), 4.19 (1H, dd, J=11.1, 7.6Hz, C$\underline{H}$OAc) overlapping 4.24 (1H, dd, J=10.2, 5.0Hz, H-6_{eq}), 4.60 (1H, d, J=3.1Hz, H-9), 4.73 (1H, m, J=11.6, 5.3Hz, H-12), 4.96 (1H, brd, J=11.1Hz, C$\underline{H}$OAc), 5.51 (1H, s, C$\underline{H}$Ph), 7.40 (5H, m, $C_6\underline{H}_5$).

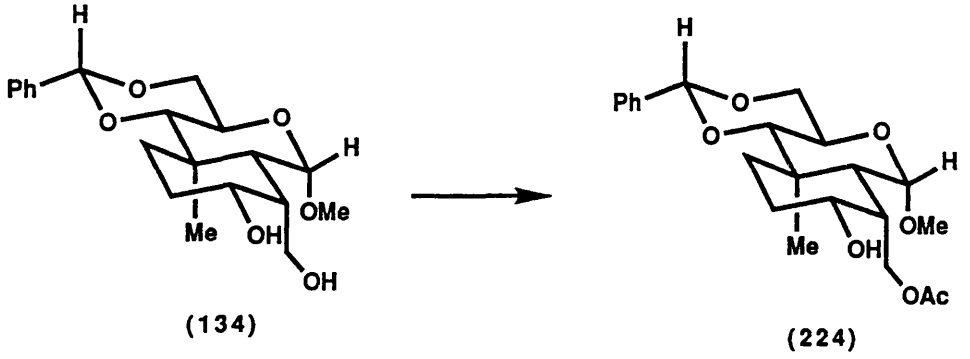
δ_C (75MHz; $CDCl_3$) 15.28(q), 20.97(q), 21.17(q), 23.01(t), 35.74(s), 36.50(t), 38.95(d), 46.80(d), 55.34(q), 60.21(d), 61.46(t), 69.54(t), 74.28(d), 87.39(d), 101.35(d), 102.31(d), 126.07(d), 128.09(d), 128.80(d), 137.77(s), 170.33(s), 170.44(s).

m/z 449(mH^+)(40), 434(45), 417(40), 357(15), 343(20), 311(40), 239(20), 165(20), 121(100).

$C_{24}H_{33}O_8$ [m+H^+] Requires 449.2171

Found 449.2175

Data for monoacetate, 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-acetoxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0.$0^{2,7}$] tetradecan-12-ol (224).



R_f 0.38 (ethyl acetate)

$[\alpha]_D^{20}$ = +19° (1.08 in chloroform)

ν_{max} ($CHCl_3$) 3525m (OH), 2975s, 1720s, 1600w, 1600w, 1390s, 1240s, 1125s, 1050s.

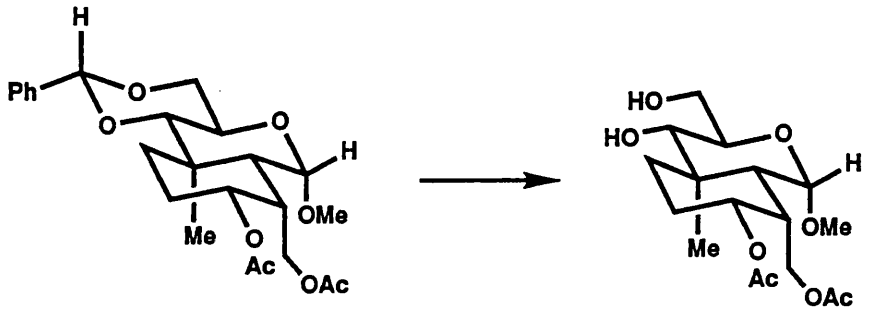
δ_H (300MHz; $CDCl_3$) 1.11 (1H, m, H-14) overlapping 1.20 (3H, s, C<u>H</u>$_3$) overlapping 1.25 (1H, m, H-14), 1.72 (2H, m, H-13, H-13) overlapping 1.81 (1H, brm, H-10), 2.05 (3H,s, COC<u>H</u>$_3$), 2.31 (1H, brs, OH, 2.40 (1H, brm, H-11), 3.19 (1H, d, J=9.5Hz, H-2), 3.40 (3H, s, OC<u>H</u>$_3$), 3.67 (1H, t, J=10.2Hz, H-6_{ax}) overlapping 3.72 (1H, m, H-12), 3.96 (1H, dt, J=9.8, 5.0Hz, H-7), 4.24 (1H, dd, J=10.2, 5.0Hz, H-6_{eq}), 4.35 (1H, dd, J=11.2, 7.6Hz, C<u>H</u>OAc), 4.61 (1H, d, J=3.0Hz, H-9), 4.90 (1H, dd, J=11.2, 2.0Hz, C<u>H</u>OAc), 5.50 (1H, s, C<u>H</u>Ph), 7.40 (5H, m, C_6<u>H</u>$_5$).

δ_C (75MHz; $CDCl_3$) 15.46(q), 21.18(q), 26.56(t), 35.81(s), 36.61(t), 42.81(d), 47.29(d), 55.40(q), 60.36(d), 61.54(t), 69.59(t), 72.96(d), 87.60(d), 101.35(d), 102.63(d), 126.07(d), 128.11(d), 128.81(d), 137.80(s), 171.00(s)

m/z 406(m^+)(4), 376(50), 315(20), 269(20), 225(100), 209(10), 165(100).

$C_{22}H_{31}O_7$	$[m+H^+]$	Requires	407.2070
		Found	407.2070

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-7-acetoxymethyl-3-hydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decan-2-ol (225).



(223) (225)

To a stirred solution of 1(R), 2(S), 4(S), 7(R), 9(S), 10(S), 11(S), 12(R)-11-acetoxymethyl-1-methyl-9-methoxy-4-phenyl-3, 5, 8-trioxatricyclo [8.4.0,$0^{2,7}$] tetradecan-12-acetate (223) (1.15g, 2.56×10^{-3} mol.) in methanol (50ml) 5% palladium on carbon (0.41g) was added after premoistening with methanol. The flask was sealed and purged with hydrogen. The flask was then shaken vigorously for 3h with the reaction mixture still under hydrogen at atmospheric pressure. The catalyst was the filtered off through celite. The solvent was removed *in vacuo* to yield the title compound (225) (0.88g, 95%) as a white glass.

R_f 0.30 (ethyl acetate)

$[\alpha]_D^{20} = +58°$ (8.0 in chloroform)

ν_{max} (CH_2Cl_2) 3400s (OH), 2950s, 1710s (C=O), 1450m, 1375m, 1250m, 1050m.

δ_H (300MHz; $CDCl_3$) 1.07 (3H, s, $C\underline{H}_3$) overlapping 1.11 (1H, m, H-10), 1.67 (2H, m, H-9, H-10) overlapping 1.85 (1H, m, H-9), 1.99 (3H, s, $COC\underline{H}_3$), 2.02 (3H, s, $COC\underline{H}_3$) overlapping 2.04 (1H, m, H-6), 2.57 (1H, brm, H-7), 3.05 (1H, brs, OH), 3.26 (1H, d, J=9.8Hz, H-2), 3.35 (3H, s, $OC\underline{H}_3$) overlapping 3.40 (1H, dd, J=10.7, 7.8Hz, C<u>H</u>OAc), 4.58 (1H, d, J=2.9Hz, H-5), 4.70 (1H, m, J=11.4, 5.3Hz, H-8), 4.95 (1H, d, J=10.7Hz, C<u>H</u>OAc).

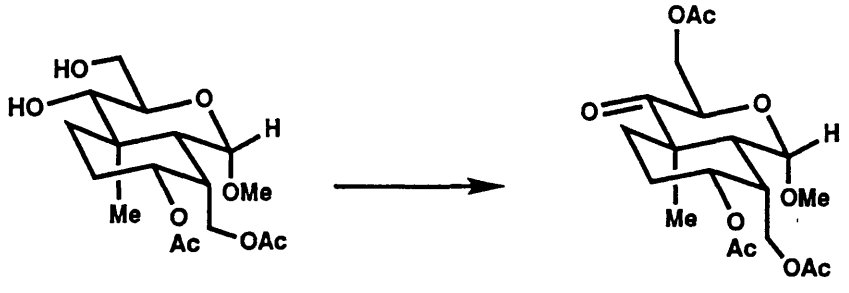
δ_C (75MHz; $CDCl_3$) 14.43(q), 20.88(q), 21.09(q), 23.02(t), 36.58(t), 36.88(s), 38.65(d), 46.31(d), 55.10(q), 61.50(t), 62.82(t), 68.80(t), 74.30(d), 76.23(d), 101.97(d), 170.41(s), 170.53(s).

m/z 378(mNH_4^+)(30), 346(100), 329(70), 269(70), 218(20), 167(10).

$C_{17}H_{32}NO_8$ $[m+NH_4^+]$ Requires 378.2127

Found 378.2128

<u>Preparation of 1(R), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-3-acetoxymethyl-7-acetoxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decan-2-one (228).</u>



(225) (228)

To chromium trioxide (0.557g, $5,57x10^{-3}$ mol.) in dry dichloromethane (10ml), pyridine (0.88ml, 0.011 mol.) was

added. The solution was stirred for 1h under nitrogen at r.t after which a solution of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-7-acetoxymethyl-3-hydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decan-2-ol (225) (0.350g, $9.29x10^{-4}$ mol.) in dichloromethane (5ml) was added. The reaction mixture was stirred for a further 2h at r.t. The chromium salts were filtered off through silica and the solvent removed *in vacuo* to yield a crude oil which could not be purified to give either the ketone (227) or the aldehyde (226) pure. The crude oil was dissolved in pyridine (2ml) and acetic anhydride (0,50ml, $4.9x10^{-3}$ mol.) was added. The solution was stirred under nitrogen for 48h, after which the solvent was removed *in vacuo* to yield a crude oil. The oil was purified by flash chromatography (ethyl acetate) to yield the title compound (228) (0.217g, 58%) as a glass and the aldehyde (229) (0.051g, 13%) as a thick oil.

R_f 0.7 (ethyl acetate)

$[\alpha]_D^{20}$ = +22° (7.0 in $CHCl_3$)

ν_{max} (CH_2Cl_2) 2955s, 1720s (C=O), 1450s, 1375s, 1225s 1150s.

δ_H (300MHz; $CDCl_3$) 1.33 (3H, s, $C\underline{H}_3$), 1.51 (1H, m, H-10), 1.81 (2H, brm, H-9, H-10), 2.01 (3H, s, $COC\underline{H}_3$), 2.03 (3H, s, $COC\underline{H}_3$) overlapping 2.04 (1H, m, H-9) overlapping 2.07 (3H, s, $COC\underline{H}_3$), 2.20 (1H, m, H-6, 2.67 (1H, brm, H-7), 3.51 (3H, s, $OC\underline{H}_3$), 4.15 (1H, dd, J=12.1, 6.9Hz, H-8), 4.27 (1H, dd, J=11.9, 6.3Hz, C<u>H</u>OAc), 4.50 (1H, dd, J=11.9, 3.4Hz, C<u>H</u>OAc), 4.65 (1H, dd, J=6.3, 3.4Hz, H-3) overlapping 4.65

(1H, m, CHOAc), 4.81 (1H, d, J=2.8Hz, H-5), 5.02 (1H, d, J=11.2Hz, CHOAc).

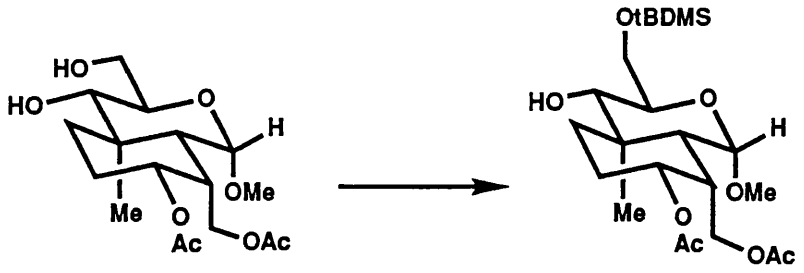
δ_C (75MHz; $CDCl_3$) 20.73(q), 20.87(q), 21.06(q), 21.21(q), 22.81(t), 31.74(t), 39.03(d), 46.05(s), 47.09(d), 55.83(q), 60.97(t), 62.27(t), 69.37(d), 73.21(d), 101.71(d), 170.19(s), 170.40(s), 170.55(s), 207.83(s).

m/z 418(mNH_4^+)(80), 386(100), 369(20), 309(100), 210(50), 150(30), 118(15).

$C_{19}H_{32}NO_9$ $[m+NH_4^+]$ Requires 418.2076

Found 418.2077

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-7-acetoxymethyl-5-methoxy-1-methyl-3-(tertbutyldimethylsila)methyl-4-oxabicyclo [4.4.0] decan-2-ol (230).



(225) (230)

1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-7-acetoxymethyl-3-hydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decan-2-ol (225) (2.294g, 8.82×10^{-3} mol.) was stirred under nitrogen in dichloromethane (20ml) with imidazole (1.30g, 0.019 mol.). To this stirred solution tertbutyldimethylchlorosilane (1.463g, 9.66×10^{-3} mol.) was added dropwise in a solution of dichloromethane

(5ml). The reaction mixture was stirred for 30h after which water (20ml) was added. The aqueous layer was separated from the organic layer and was further extracted with dichloromethane (3 X 30ml) then the combined organics were washed with aqueous saturated sodium chloride solution (20ml) and dried ($MgSO_4$). After removal of solvent and flash chromatography (ethyl acetate) the title compound (230) (3.97, 95%) was obtained as a thick oil.

R_f 0.7 (ethyl acetate)

$[\alpha]_D^{20}$ = +26° (20.0 in chloroform)

ν_{max} (CH_2Cl_2) 3500s (OH), 2900s, 1730 (C=O), 1455m, 1370m, 1250s, 1050s, 843s.

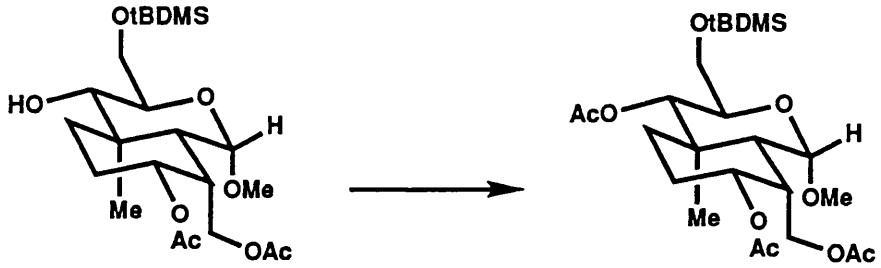
δ_H (300MHz; $CDCl_3$) 0.09 (6H, s, $Si(C\underline{H}_3)_2$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 1.11 (3H, s, $C\underline{H}_3$) overlapping 1.15 (1H, m, H-10), 1.68 (2H, m, H-9, H-10), 1.91 (1H, m, H-9), 1.98 (3H, s, $COC\underline{H}_3$), 2.02 (3H, s, $COC\underline{H}_3$) overlapping 2.02 (1H, m, H-6), 2.58 (1H, brm, H-7), 3.26 (1H, d, J=9.8Hz, H-2), 3.33 (3H, s, $OC\underline{H}_3$) overlapping 3.40 (1H, brs, OH), 3.70 (1H, m, H-3), 3.81 (2H, brm, $C\underline{H}_2OSi$), 4.11 (1H, dd, J=10.6, 7.8Hz, $C\underline{H}OAc$), 4.58 (1H, d, J=2.9Hz, H-5), 4.72 (1H, m, J=11.4, 5.3Hz, H-8), 4.92 (1H, d, J=10.6Hz, $C\underline{H}OAc$).

δ_C (75MHz; $CDCl_3$) -3.97(q), 14.59(q), 18.10(s), 20.90(q), 21.10(q), 23.07(t), 25.74(q), 36.46(s), 36.84(t), 38.69(d), 46.05(d), 55.02(q), 61.57(t), 65.92(t), 67.23(d), 74.35(d), 79.89(d), 101.84(d), 170.31(s), 170.43(s).

m/z 475(mH^+)(5), 460(60), 443(100), 383(30), 346(10), 315(30), 194(20).

$C_{24}H_{43}O_8Si$	[m+H$^+$]	Requires	475.2727
		Found	475.2727

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-2-acetoxy-8-acetoxy-7-acetoxymethyl-3-tertbutyldimethylsila) methyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decane (231).



(230) (231)

To stirred solution of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-8-acetoxy-7-acetoxymethyl-5-methoxy-1-methyl-3-(tertbutyldimethylsila)methyl-4-oxabicyclo [4.4.0] decan-2-ol (230) (3.97g, 8.38×10^{-3} mol.) in pyridine (5ml) under nitrogen, acetic anhydride (2ml, 0.02 mol.) was added. The reaction mixture was left stirring for 48h and then the excess pyridine and acetic anhydride was removed *in vacuo*. The resulting crude oil was purified by flash chromatography (ethyl acetate) to yield the title compound (231) (3.42g, 80%) as a glass.

R_f 0.9 (ethyl acetate)

$[\alpha]_D^{20} = +13^\circ$ (1.0 in chloroform)

ν_{max} (CH_2Cl_2) 2930s, 1740s (C=O), 1455m, 1365s, 1260s, 1160s, 1075s.

δ_H (300MHz; $CDCl_3$) 0.06 (3H, s, $SiC\underline{H}_3$), 0.07 (3H, s, $SiC\underline{H}_3$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 1.14 (3H, s, $C\underline{H}_3$), 1.27 (1H, m, H-10), 1,49 (1H, dt, J=13.5, 3.3Hz, H-10), 1.71 (2H, m, 2xH-9), 1.82 (1H, t, J=3.7Hz, H-6), 2.01 (3H, $COC\underline{H}_3$), 2.02 (3H, s, $COC\underline{H}_3$), 2.06 (3H, s, $COC\underline{H}_3$), 2.64 (1H, brm, H-7), 3.38 (3H, s, $OC\underline{H}_3$), 3.61 (1H, d, J=4.3Hz, H-2), 3.87 (1H, dt, J=10.3, 4.3Hz, H-3), 4.17 (1H, dd, J=11.1, 7.9Hz, C<u>H</u>OAc), 4.61 (2H, d, J=10.3Hz, $C\underline{H}_2OSi$) overlapping 4.63 (1H, d, J=2.6Hz, H-5), 4.71 (1H, m, H-8), 4.97 (1H, d, J=11.1Hz, C<u>H</u>OAc).

δ_C (75MHz; $CDCl_3$) -4.13(q), -4.08(q), 15.51(q), 18.30(s), 20.79(q), 20.98(q), 21.15(q), 22.93(t), 25.86(q), 36.83(s), 36.93(t), 38.54(d), 46.37(d), 55.62(q), 61.49(t), 63.42(t), 68.48(d), 74.00(d), 76.33(d), 101.51(d), 169.89(s), 170.20(s), 170.48(s).

m/z 517(mH^+)(20), 502(20), 485(100), 425(5).

$C_{25}H_{45}O_9Si$ [$m+H^+$] Requires 517,2832

Found 517.2833

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-2-acetoxy-8-acetoxy-7-acetoxymethyl-3-hydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decane (232).

(231) (232)

To a solution of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-2-acetoxy-8-acetoxy-7-acetoxymethyl-3-tertbutyldimethylsila) methyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decane (231) (3.15g, 6.11×10^{-3} mol.) in tetrahydrofuran (20ml), tetrabutylammonium fluoride (4.71g, 0.018 mol.) was added. The mixture was stirred at r.t. for 2h, after which the solvent was removed *in vacuo*. To the resulting waxy solid diethyl ether (1oml) and water (20ml) were added. The aqueous layer was extracted with diethyl ether (3 X 30ml) and the combined organic extracts dried (Na_2SO_4). The solvent was removed *in vacuo* to yield an oil which was purified by flash chromatography (ethyl acetate) to give the title compound (232) (2.213g, 90%) as a waxy solid.

R_f 0.73 (ethyl acetate)

$[\alpha]_D^{20} = +48^o$ (9.2 in chloroform)

ν_{max} (CH_2Cl_2) 3500s (OH), 2965s, 1720s (C=O), 1450s, 1355s, 1300s, 1180s, 1100s, 750s.

δ_H (300MHz; $CDCl_3$) 1.08 (3H, s, $C\underline{H}_3$) overlapping 1.14 (1H, m, H-10), 1.72 (2H, m, H-9, H-10), 1.91 (1H, m, H-9), 1.99 (3H, s, $COC\underline{H}_3$), 2.02 (3H, s, $COC\underline{H}_3$) overlapping 2.05 (1H, brm, H-6) overlapping 2.12 (3H, s, $COC\underline{H}_3$), 2.58 (1H, brm, H-7), 3.09 (1H, d, J=9.8Hz, H-2), 3.23 (1H, brs, OH), 3.37 (3H, s, $C\underline{H}_3$), 3.83 (1H, brm, H-3), 4.16 (1H, dd, J=11.5, 8.3Hz, C<u>H</u>OH), 4.24 (1H, dd, J=10.9, 1.9Hz, C<u>H</u>OAc), 4.44 (1H, dd, J=12.0, 4.5Hz, C<u>H</u>OH), 4.61 (1H, d, J=2.9Hz, H-5), 4.69 (1H, m, J=11.4, 5.3Hz, H-8), 4.93 (1H, d, J=10.9Hz, C<u>H</u>OAc).

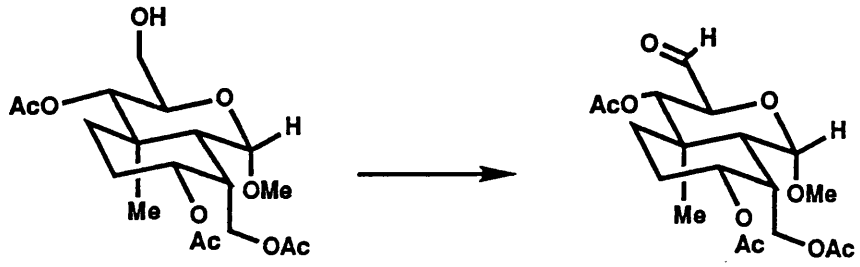
δ_C (75MHz; $CDCl_3$) 14.07(q), 20.52(q), 20.63(q), 20.83(q), 22.80(t), 36.43(t), 36.70(s), 38.38(d), 46.00(d), 54.85(q), 61.22(t), 64.15(t), 67.50(d), 74.00(d), 75.11(d), 101.74(d), 170.10(s), 170.24(s), 171.45(s).

m/z 403(mH^+)(2), 489(20), 488(100), 371(30), 311(30).

$C_{18}H_{27}O_8$ [$m-OMe^+$] Requires 371.1700

Found 371.1706

Preparation of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-2-acetoxy-8-acetoxy-7-acetoxymethyl-3-formylmethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decane (229).



(232) (229)

To chromium trioxide (2.25g, 0.22 mol.) in dry dichloromethane (20ml), pyridine (3.50ml, 0.44 mol.) was added. The solution was stirred for 1h under nitrogen at r.t. after which a solution of 1(R), 2(S), 3(R), 5(S), 6(S), 7(S), 8(R)-2-acetoxy-8-acetoxy-7-acetoxymethyl-3-hydroxymethyl-5-methoxy-1-methyl-4-oxabicyclo [4.4.0] decane (232) (1.51g, 3.75×10^{-3} mol.) was added in dichloromethane (20ml). The reaction mixture was stirred for a further 2h at r.t. The chromium salts were then filtered off through silica and the solvent removed *in vacuo* to yield a crude oil. After flash chromatography (ethyl acetate) the title compound (229) (0.71, 49%) was obtained as a thick oil.

R_f 0.51 (ethyl acetate)

$[\alpha]_D^{20} = +87^\circ$ (16.6 in chloroform)

δ_H (300MHz; $CDCl_3$) 1.17 (3H, s, $C\underline{H}_3$), 1.23 (1H, m, H-10), 1.60 (1H, m, H-10), 1.72 (2H, m, 2xH-9), 1.87 (1H, m, H-6), 2.00 (3H, s, $COC\underline{H}_3$), 2.03 (3H, s, $COC\underline{H}_3$), 2.06 (3H, s, $COC\underline{H}_3$), 2.62 (1H, brm, H-7), 3.39 (1H, d, J=8.9Hz, H-2), 3.41 (3H, s, $OC\underline{H}_3$), 4.10 (1H, m, H-3), 4.70 (3H, m, H-5, $C\underline{H}_2OAc$), 4.95 (1H, brm, H-8), 9.53 (1H, d, J=2.2Hz, $C\underline{H}C=O$).

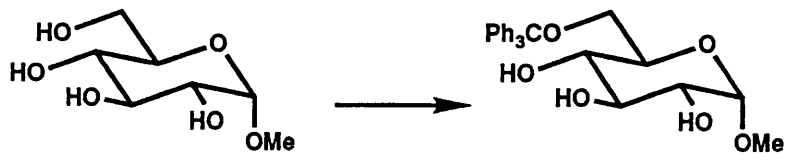
δ_C (75MHz; $CDCl_3$) 15.23(q), 20.40(q), 20.71(q), 20.91(q), 22.67(t), 36.28(t), 36.41(s), 45.74(d), 55.59(q), 60.94(t), 71.32(d), 73.48(d), 74.32(d), 101.59(d), 169.98(s), 170.02(s), 170.26(s), 198.27(d).

m/z 418(mNH_4^+)(45), 404(10), 386(100), 369(20), 341(10), 309(50), 260(10).

$C_{19}H_{32}NO_9$ $[m+NH_4]^+$ Requires 418.2077

Found 418.2077

Preparation of methyl-6-O-tritylglucopyranoside (237).[148]



(236) (237)

Methylglucopyranoside (236) (23.20g, 0.12 mol.) was stirred in dimethylformamide (150ml) at r.t. with DMAP (1.00g, $8.14x10^{-3}$ mol.) and trityl chloride (36.80g, 0.13 mol.). Triethylamine (30ml) was then added and the reaction mixture stirred for 4h at r.t. and a further 18h at 45°C.

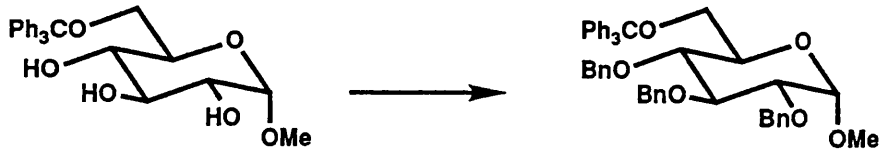
Water (100ml) was added and the solution extracted with diethyl ether (3 X 200ml) to give the crude title compound (237) (40.00g, 76%).

R_f 0.5 (diethyl ether)

δ_H (300MHz; $CDCl_3$) 2.80 (3H, brs, OH), 3.31 (1H, brm) overlapping 3.40 (3H, s, $OC\underline{H}_3$), 3.60 (3H, brm), 4.10 (2H, m), 4.70 (1H, d, J=2.4Hz, H-1), 7.10-7.50 (15H, m, $3xC_6\underline{H}_5$)

δ_C (75MHz; $CDCl_3$) 18.05(q), 54.81(q), 57.89(t), 70.54(d), 71.01(d), 71.90(d), 74.25(d), 86.50(s), 99.14(d), 126.81(d), 127.62(d), 128.59(d), 143.87(s).

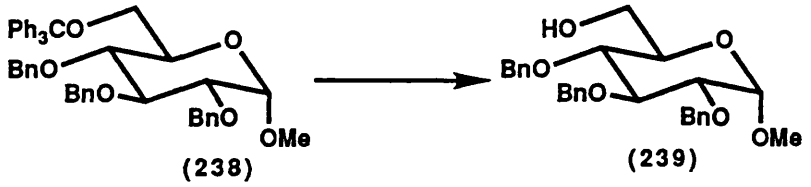
Preparation of methyl-6-O-trityl-2, 3, 4-O-tribenzyl glucopyranoside[149,132] (238).



(237) (238)

Methyl-6-O-tritylglucopyranoside (237) (20.00g, 0.045 mol.) was dissolved in benzyl chloride (300ml). To this solution sodium hydride (80% in paraffin oil) (19.00g, 0.66 mol.) was added carefully. The reaction mixture was then heated to 150°C for 3.5h under nitrogen with stirring. The excess benzyl chloride was distilled off and crude residue of the title compound (238) (25.23g) was used directly in the next step.

Preparation of methyl-2, 3, 4-O-tribenzylglucopyranoside[150] (239).



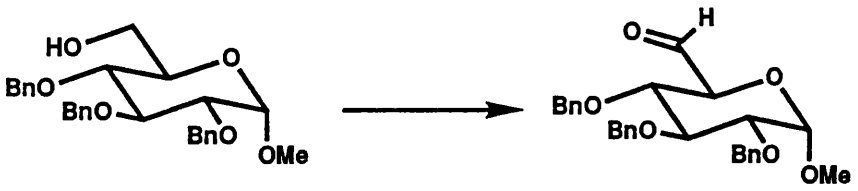
(238) (239)

The crude methyl-6-O-trityl-2, 3, 4-O-tribenzylgluco pyranoside (238) (25.23g) was heated at 50°C in acetic acid (85% aqueous solution) for 3.5h. The aqueous acetic acid was then removed *in vacuo* to a residue to which water (100ml) and diethyl ether (100ml) were added. The aqueous layer was extracted with diethyl ether (3 X 150ml) and the combined organics were washed with sodium hydrogen carbonate (100ml) and aqueous saturated sodium chloride solution (100ml). After drying ($MgSO_4$) and removal of solvent *in vacuo* the title compound (239) (18.00g) was obtained as a gummy solid.

δ_H (300MHz; $CDCl_3$) 1.70 (1H, brs, OH), 3.35 (3H, s, $OC\underline{H}_3$), 3.50 (1H, dd, J=9.66, 3.61Hz, H-4), 3.52 (1H, d, J=9.20Hz, H-2), 3.70 (3H, brm, 2xH-6, H-5), 4.00 (1H, t, J=9.2Hz, H-3), 4.55-5.00 (7H, m, $3xC\underline{H}_2Ph$, H-1).

δ_C (75MHz; $CDCl_3$) 55.15(q), 61.86(t), 70.67(d), 74.99(t), 75.70(t), 77.43(d), 80.00(d), 81.93(d), 98.16(d), 127.54(d), 127.80(d), 127.89(d), 127.96(d), 128.05(d), 128.34(d), 128.41(d), 138.12(s), 138.72(s).

Preparation of methyl-6-aldo-2, 3, 4-tribenzylgluco pyranoside-(235).



(239) (235)

Oxalyl chloride (0.18ml, $1.98x10^{-3}$ mol.) was dissolved in dry dichloromethane (4ml) at -60°C with stirring under nitrogen. Dimethylsulphoxide (2.36ml, 0.030 mol.) in dichloromethane (2ml) was then added and the reaction mixture was stirred for 10min. Then methyl-2, 3, 4-tribenzylglucopyranoside (239) (1.02g, $2.5x10^{-3}$ mol.) in dichloromethane (1ml) was then added. After a further 40min. at -60°C, triethylamine (1.26ml, 0.012 mol.) was added and the reaction allowed to warm to r.t. Water (20ml) was added and the solution extracted with diethyl ether (3 X 30ml). The combined organic extracts were dried ($MgSO_4$) and after removal of the solvent *in vacuo* and flash chromatography (ethyl acetate) the title compound (235) (0.87g, 87%) was obtained as a thick oil.

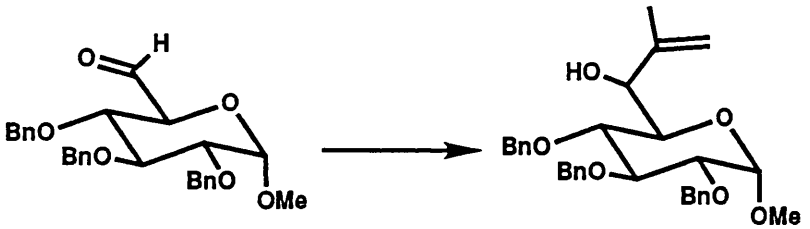
R_f 0.52 (ethyl acetate)

δ_H (300MHz; $CDCl_3$) 3.35 (3H, s, $OC\underline{H}_3$) overlapping 3.36 (1H, brm), 3.51 (2H, brm), 4.10 (1H, M), 4.51-5.01 (7H, m, $3xC\underline{H}_2Ph$, H-1), 7.25 (15H, m, $3xC_6\underline{H}_5$), 9.10 (1H, s, $C\underline{H}O$).

δ_C (75MHz; $CDCl_3$) 55.55(q), 73.29(t), 74.04(t), 74.65(t), 75.66(d), 77.60(d), 79.23(d), 81.53(d), 98.17(d),

127.57(d), 127.75(d), 127.84(d), 127.90(d), 127.95(d), 128.29(d), 137.39(s), 137.72(s), 138.32(s), 197.27(d).

Preparation of 6-C-(propen-2'-yl) methyl 2, 3, 4-O-tribenzyl glucopyranoside (240).



(235) (240)

To magnesium (0.87g, 0.036 mol.) in dry diethyl ether (25ml), 1, 2-dibromoethane (0.10ml) was added to initiate the Grignard reaction, then 2-bromopropene (3.96g, 0.038 mol.) was added dropwise in diethyl ether (20ml) over 20min, after which the reaction was refluxed for 1h and then cooled. Methyl-6-aldo-2, 3, 4-tribenzyl glucopyranoside (235) (5.00g, 0.011 mol.) was then added in ether (40ml) over 10min. The reaction was refluxed for 1h, cooled and water (50ml) was added. The aqueous layer was then extracted with diethyl ether (3 X 50ml) and the combined organic extracts were dried ($MgSO_4$). After removal of solvent *in vacuo* the resulting sticky oil was purified by flash chromatography (1:1 petroleum ether-diethyl ether) to give the title compound (240) (3.40g, 68%) as a thick oil.

R_f = 0.31 (1:1 petroleum ether-diethyl ether)

$[\alpha]_D^{20}$ = +16° (3.6 in chloroform)

ν_{max} (film) 3350m (OH), 2900s, 1500w, 1450m, 1350m, 1050s, 900m.

δ_H (300MHz; $CDCl_3$) 1.74 (3H, s, $C\underline{H}_3C=C$), 3.30 (3H, s, $OC\underline{H}_3$), 3.37 (1H, s, $C\underline{H}OH$), 3.49 (1H, dd, J=9.6, 3.4Hz, H-2), 3.70 (2H, m, H-5, H-3), 4.00 (1H, t, J=9.6Hz, H-4), 4.28 (1H, brs, OH), 4.54 (1H, d, J=3.4Hz, H-1), 4.60-5.05 (8H, m, $C\underline{H}_2Ph$, $C\underline{H}_2=C$), 7.30 (15H, m, $3xC_6\underline{H}_5$).

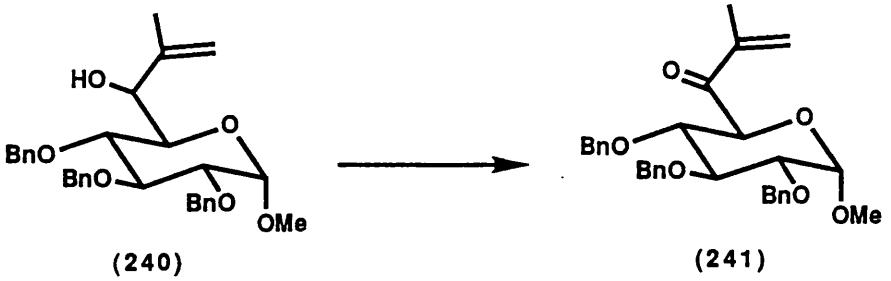
δ_C (75MHz; $CDCl_3$) 19.41(q), 55.29(q), 71.02(d), 71.88(d), 73.36(t), 75.08(t), 75.65(t), 77.75(d), 79.77(d), 82.06(d), 98.32(d), 110.84(t), 127.49(d), 127.65(d), 127.80(d), 127.84(d), 127.95(d), 128.02(d), 128.29(d), 128.34(d), 128.37(d), 138.06(s), 138.24(s), 138.70(s), 144.95(s).

m/z 522(mNH_4^+)(100), 490(70), 473(15), 372(15), 198(15), 108(100), 91(65).

$C_{31}H_{40}NO_6$ $[m+NH_4^+]$ Requires 522.2855

Found 522.2856

Preparation of 6-C-(propen-2'-yl) methyl 6-C-keto-2, 3, 4-tribenzylglucopyranoside (241).



(240) (241)

To chromium trioxide (4.40g, 0.044 mol.) in dry dichloromethane (30ml), pyridine (7.81ml, 0.088 mol.) was added. The solution was stirred for 1h under nitrogen at

r.t. after which a solution of 6-C-(propen-2'-yl) methyl 2, 3, 4-O-tribenzyl glucopyranoside (240) (3.74g, $7.43x10^{-3}$ mol.) in dichloromethane (20ml) was added. The reaction mixture was stirred for 2h until there was no change in t.l.c. The chromium salts were filtered off through silica and the solvent was removed *in vacuo* to yield a crude oil. After flash chromatography (1:1 petroleum ether-diethyl ether) the title compound (241) (1.60g, 47%) was obtained as an oil.

R_f 0.46 (1:1 petroleum ether-diethyl ether)

$[\alpha]_D^{20}$ = +93.75° (0.32 in chloroform)

ν_{max} (film) 3000s, 1690s (C=O), 1500(s), 1450s, 1350s, 1200m, 1000s.

δ_H (300MHz; $CDCl_3$) 1.91 (3H, s, $C\underline{H}_3C$=C), 3.42 (3H, s, $OC\underline{H}_3$), 3.55 (1H, dd, J=9.6, 3.6Hz, H-2), 3.85 (1H, t, J=9.4Hz, H-3), 4.05 (1H, t, J=9.4Hz, H-4), 4.48-5.00 (7H, m, $C\underline{H}_2Ph$, H-5) overlapping 4.55 (1H, d, J=3.6Hz, H-1), 5.91 (1H, brs, C$\underline{H}$=C), 6.10 (1H, brs, C$\underline{H}$=C), 7.30 (15H, m, $3xC_6\underline{H}_5$).

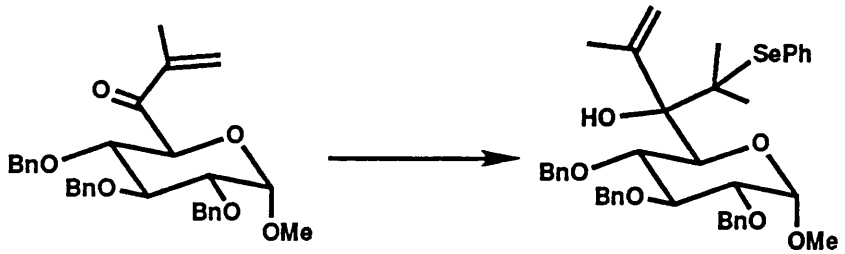
δ_C (75MHz; $CDCl_3$) 17.78(q), 56.11(q), 68.14(d), 73.63(t), 75.01(t), 75.79(t), 79.29(d), 79.47(d), 81.62(d), 99.34(d), 127.20(t), 127.56(d), 127.78(d), 127.84(d), 127.94(d), 128.11(d), 128.20(d), 128.32(d), 128.44(d), 137.97(s), 138.03(s), 138.63(s), 144.03(s), 197.02(s).

m/z 520(mNH_4^+)(100), 503(5), 471(60), 395(5), 305(5), 179(10), 108(50).

$C_{31}H_{38}NO_6$ $[m+NH_4^+]$ Requires 520.2699

Found 520.2699

Preparation of 6-C-(propen-2'-yl)-6-C-(2"-(phenylseleno) *iso*-propyl) methyl 2, 3, 4-tribenzyl glucopyranoside (242).



(241) (242)

n-Butyllithium (0.800ml, $1.2x10^{-3}$ mol.) was added to a stirred solution of 2,2-bis(phenylseleno)propane (0.400g, $1.13x10^{-3}$ mol) in tetrahydrofuran (1.0ml) at -78°C under nitrogen. After 30min at -78°C, a solution of 6-C-(propen-2'-yl) methyl 2, 3, 4-O-tribenzyl glucopyranoside (240) (0.150g, $2.98x10^{-4}$ mol.) in tetrahydrofuran (1,0ml) was added and stirring continued for a further 1h at -78°C. The mixture was then allowed to warm to r.t. and then quenched with water (10ml). The aqueous layer was extracted with diethyl ether (3 X 20ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. After flash chromatography (1:1 petroleum ether-diethyl ether) the title compound (242) (0.056g, 28%) was obtained as an oil.

R_f 0.76 (1:1 petroleum ether-diethyl ether)

$[\alpha]_D^{20}$ = +24° (1.52 in chloroform)

ν_{max} (film) 3400m (OH), 2910s, 1500w, 1450m, 1350m, 1060s, 900m.

δ_H (300MHz; $CDCl_3$) 0.93 (3H, s, $C\underline{H}_3C=C$), 1.72 (3H, s, $C\underline{H}_3CSePh$), 1.85 (3H, s, $C\underline{H}_3CSePh$), 3.51 (1H, dd, J=9.9, 3.8Hz, H-3), 3.62 (3H, s, $OC\underline{H}_3$), 3.75 (1H, brt, J=3.9Hz, H-2), 4.06 (1H, t, J=9.9Hz, H-4), 4.39 (1H, d, J=9.9Hz, H-5), 4.50-5.00 (9H, m, $3xC\underline{H}_2Ph$, H-1 and $C\underline{H}_2=C$), 5.35 (1H, brs, OH), 7.30 (25H, m, $5xC_6\underline{H}_5$).

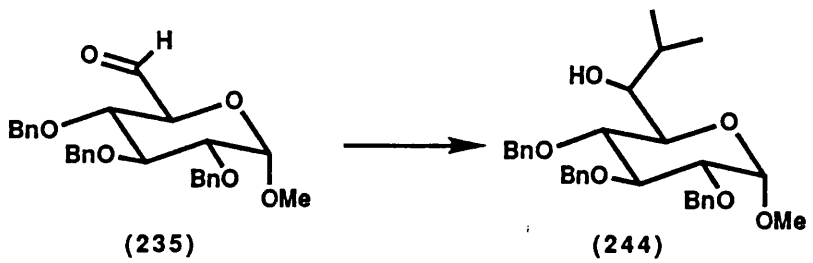
δ_C (75MHz; $CDCl_3$) 23.35(q), 27.34(q), 58.17(q), 73.25(t), 73.31(s), 73.55(t), 75.60(t), 77.66(d), 79.82(d), 80.12(s), 82.59(d), 98.36(d), 113.86(t), 126.76(d), 126.83(d), 127.36(d), 127.76(d), 127.82(d), 127.92(d), 128.21(d), 128.41(d), 128.46(d), 129.86(s), 138.24(d), 138.68(s), 139.31(s).

m/z 720(mNH_4^+)(20), 671(70), 562(50), 513(40), 490(20), 199(50), 108(100).

$C_{40}H_{50}NO_6Se$ $[m+NH_4^+]$ Requires 720.2800

Found 720.2803

Preparation of 6-C-(*iso*-propyl) methyl 2, 3, 4-tribenzyl glucopyranoside (244).



(235) (244)

To a stirred solution of Methyl-6-aldo-2, 3, 4-tribenzyl glucopyranoside (235) (2.00g, $4.33x10^{-3}$ mol.) in dry tetrahydrofuran (5.0ml) isopropylmagnesium bromide (17.00ml, 0.017 mol.) was added under nitrogen. The

reaction mixture was heated under reflux for 30min. and then cooled, quenched with water (10ml) and extracted with diethyl ether (3 X 75ml). The combined organics were dried ($MgSO_4$) and after removal of solvent *in vacuo* the crude residue was purified by flash chromatography (ethyl acetate) to yield the title compound (244) (0.95g, 44%) as a sticky oil.

R_f 0.75 (ethyl acetate)

$[\alpha]_D^{20}$ = +12.83° (11.3 1n chloroform)

ν_{max} (film) 3575m (OH), 2900s, 1450s, 1355s, 1050s, 910m, 700m.

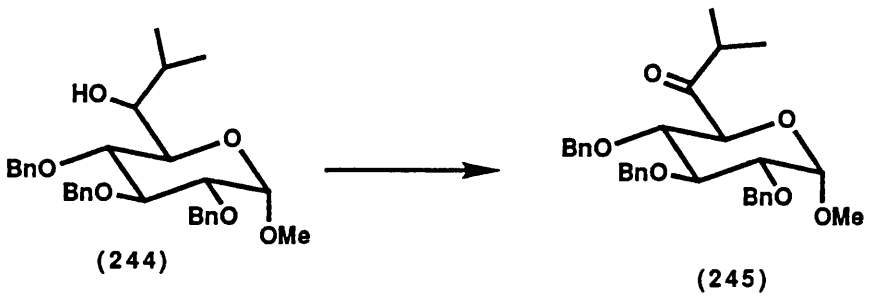
δ_H (300MHz; $CDCl_3$) 0.83 (3H, d, J=6.6Hz, $C\underline{H}_3$), 0.98 (3H, d, J=6.6Hz, $C\underline{H}_3$), 1.71 (1H, brs, OH), 1.82 (1H, m, $C\underline{H}(CH_3)_2$), 3.35 (3H, s, $OC\underline{H}_3$) overlapping (1H, m, $C\underline{H}OHCHCH_3$), 3.46 (1H, dd, J=9.7, 3.6Hz, H-2), 3.70 (2H, m, H-3, H-4), 4.00 (1H, J=9.2, H-5), 4.54 (1H, d, J=3.6Hz, H-1), 4.60-5.00 (6H, m, $3xC\underline{H}_2Ph$), 7.30 (15H, m, $3xC_6H_5$).

δ_C (75MHz; $CDCl_3$) 19.11(q), 19.41(q), 30.66(d), 55.46(q), 69.73(d), 73.13(t), 74.09(d), 74.85(t), 75.42(t), 77.61(d), 79.66(d), 81.74(d), 98.34(d), 127.25(d), 127.38(d), 127.54(d), 127.62(d), 127.77(d), 128.08(d), 128.16(d), 137.95(s), 138.20(s), 138.58(s).

m/z 524(mNH_4^+)(100), 492(100), 475(5), 402(5), 383(5), 312(15), 243(30), 198(5), 179(s), 108(100).

$C_{31}H_{42}NO_6$	$[m+NH_4^+]$	Requires	524.3080
		Found	524.3012

Preparation of 6-C-(*iso*-propyl)-6-keto 2, 3, 4-tribenzyl glucopyranoside (245).



(244) (245)

To chromium trioxide (0.646g, 6.46×10^{-3} mol.) in dry dichloromethane (15ml), pyridine (0.5ml, 0.0129 mol.) was added. The solution was stirred for 1h under nitrogen at r.t. after which a solution of 6-C-(*iso*-propyl) methyl 2, 3, 4-tribenzyl glucopyranoside (244) (0.5g, 1.07×10^{-3} mol.) in dichloromethane (15ml) was added. The reaction mixture was stirred for 1h until there was no change in t.l.c. The chromium salts were filtered off through silica and the solvent was removed *in vacuo* to yield a crude oil. After flash chromatography (1:1 petroleum ether-diethyl ether) the title compound (245) (0.250g, 47%) was obtained as an oil.

R_f 0.51 (1:1 petroleum ether-diethyl ether)

$[\alpha]_D^{20}$ = +70.58° (0.4 in chloroform)

ν_{max} (film) 3000s, 1720s (C=O), 1450m, 1300m, 1110s, 700s.

δ_H (300MHz; $CDCl_3$) 1.06 (3H, d, J=6.9Hz, $C\underline{H}_3$), 1.10 (3H, d, J-6.9Hz, $C\underline{H}_3$), 2.85 (1H, q, J=6.9Hz, $C\underline{H}(CH_3)_2$), 3.39 (3H, s, $OC\underline{H}_3$), 3.55 (1H, dd, J=9.7, 3.6Hz, H-2), 3.74 (1H, t, J=9.8Hz, H-3), 4.02 (1H, t, J=9.8Hz, H-4), 4.32 (1H, d,

t, J=9.8Hz, H-3), 4.02 (1H, t, J=9.8Hz, H-4), 4.32 (1H, d, J=9.8Hz, H-5), 4.51-5.00 (7H, m, 3x$C\underline{H}_2Ph$, H-1), 7.20 (15H, m, 3x$C_6\underline{H}_5$).

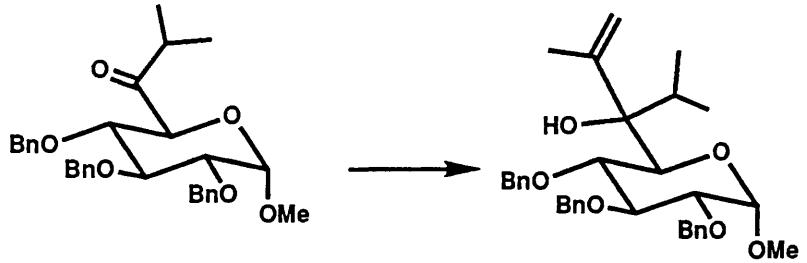
δ_C (75MHz; $CDCl_3$) 17.61(q), 17.37(q), 39.67(d), 55.44(q), 71.03(t), 73.25(d), 75.48(t), 77.59(t), 78.81(d), 79.29(d), 81.46(d), 98.65(d), 127.32(d), 127.38(d), 127.69(d), 127.82(d), 128.02(d), 128.08(d), 137.71(s), 137.77(s), 138.35(s).

m/z 522(mNH_4^+)(100), 490(50), 473(55), 414(5), 382(5), 365(s), 310(5), 274(5), 108(70).

$C_{31}H_{40}NO_6$ $[m+NH_4^+]$ Requires 522.2852

Found 522.2856

Preparation of 6-C-(propen-2'-yl)-6-C-(*iso*-propyl) methyl 2, 3, 4-tribenzyl glucopyranoside (246).



(245) (246)

To magnesium (0.016g, $6.60x10^{-4}$ mol.) in dry tetrahydrofuran (0.5ml), 2-bromopropene (0.080g, $6.60x10^{-4}$ mol.) was added. The Grignard reagent was refluxed for 1h, after which 6-C-(*iso*-propyl)-6-keto 2, 3, 4-tribenzyl gluco pyranoside (245) (0.100g, $2.2x10^{-4}$ mol.) in tetrahydrofuran (0.5ml) was added. The reaction was heated under reflux

for a further 1h after which it was cooled, quenched with water (1ml) and extracted with diethyl ether (3 X 5ml). The combined organics were dried ($MgSO_4$) and after removal of the solvent *in vacuo* the crude oil was purified by flash chromatography (1:1 petroleum ether-diethyl ether) to give the title compound (246) (0.079g, 66%)as an oil.

R_f 0.32 (1:1 petroleum ether- diethyl ether)

$[\alpha]_D^{20}$ = +29° (0.96 in chloroform)

ν_{max} (film) 3500m (OH), 3000s, 1450m, 1350m, 1050s, 900m.

δ_H (300MHz; $CDCl_3$) 0.73 (3H, d, J=6.9Hz, $C\underline{H}_3$), 0.98 (3H, d, J=6.9Hz, $C\underline{H}_3$), 1.65 (1H. brs, OH), 1.74 (3H, s, $C\underline{H}_3C=C$), 2.95 (1H, brm, $C\underline{H}(CH_3)_2$), 3.49 (3H, s, $OC\underline{H}_3$) overlapping 3.51 (2H, m, H-2, H-3), 4.00 (2H, m, H-4, H-5), 4.50-4.80 (6H, m, $3xC\underline{H}_2Ph$), 5.10 (3H, m, $C\underline{H}_2=C$, H-1), 7.30 (15H, m, $3xC_6\underline{H}_5$).

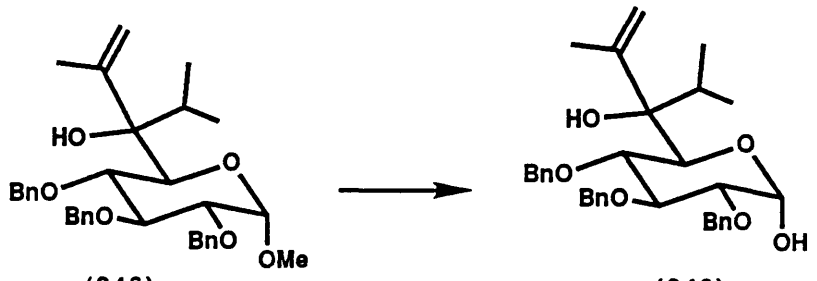
δ_C (75MHz; $CDCl_3$) 15.90(q), 16.51(q), 20.26(q), 28.80(d), 57.24(q), 71.53(d), 73.29(t), 74.42(t), 75.44(t), 80.49(d), 80.51(d), 80.56(s), 82.18(d), 98.35(d), 113.00(t), 127.52(d), 127.57(d), 127.75(d), 127.79(d), 127.85(d), 128.33(d), 128.38(d), 128.45(d), 137.44(s), 137.94(s), 138.19(s), 148.10(s).

m/z 564(mNH_4^+)(10), 532(100), 407(20), 299(10), 227(5), 187(s), 108(100).

$C_{34}H_{46}NO_6$ $[m+NH_4^+]$ Requires 564.3322

Found 564.3325

Reaction of 6-C-(*iso*-propyl)-6-keto 2, 3, 4-tribenzyl glucopyranoside (245) with tosic acid.



(246) (248)

A solution of 6-C-(*iso*-propyl)-6-keto 2, 3, 4-tribenzyl glucopyranoside (245) (0.080g, 1.46×10^{-4} mol.) in dry, degassed benzene (20ml) with tosic acid (0.008g, 4.20×10^{-5} mol.) was heated to 80°C for 1h under nitrogen, after which the solvent was removed *in vacuo* to leave a black tar. After flash chromatography (8:2 petroleum ether-diethyl ether) the hemiacetal 6-C-(propen-2'-yl)-6-C-(*iso*-propyl) 2, 3, 4-tribenzyl glucopyranoside (248) (0.035g, 47%) was isolated as a pale thick oil.

R_f 0.32 (8:2 petroleum ether-diethyl ether)

$[\alpha]_D^{20} = +6°$ (4.0 in chloroform)

ν_{max} (CH_2Cl_2) 3500m (OH), 3000s, 1720m (C=O), 1450s, 1365s, 1110s, 700s.

δ_H (300MHz; $CDCl_3$) 0.82 (3H, d, J=7.0Hz, $CHC\underline{H}_3$), 0.89 (3H, d, J=7.0Hz, $CHC\underline{H}_3$), 1.77 (3H, s, $C=CC\underline{H}_3$), 2.09 (1H, quin, J=7.0Hz $C\underline{H}(CH_3)_2$), 3.40 (1H, t, J=2.4Hz, H-2), 3.76 (2H, brs, H-3, H-4), 4.40-4.80 (7H, m, $3xC\underline{H}_2Ph$, H-5), 5.02 (1H, brs, $C=C\underline{H}$), 5.40 (1H, s, $C=C\underline{H}$), 7.30 (15H, m, $3xC_6\underline{H}_5$).

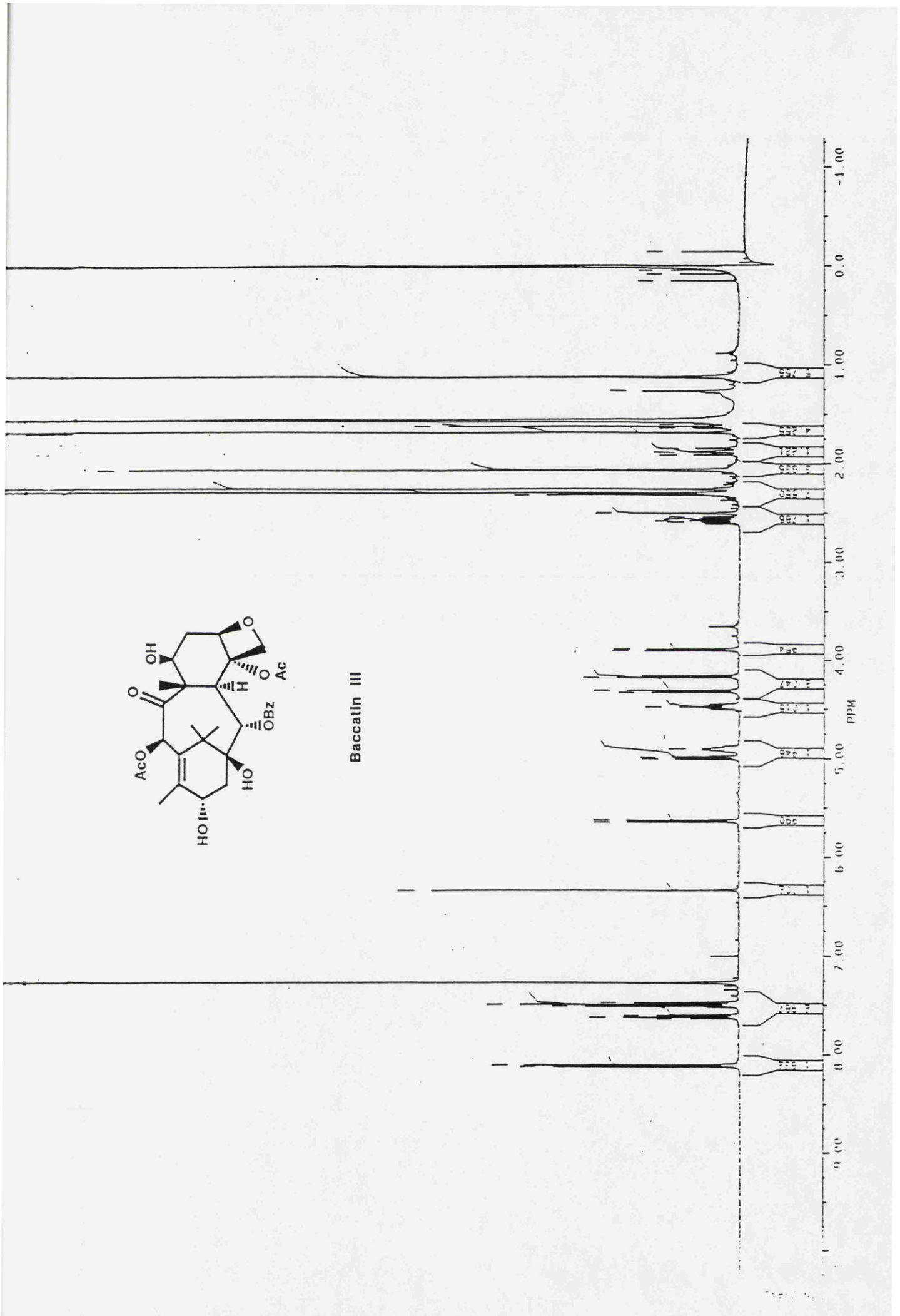
δ_C (75MHz; $CDCl_3$) 18.28(q), 18.38(q), 22.06(q), 32.86(d), 71.56(t), 72.05 (t), 72.86(t), 76.09(d), 81.53(d), 81.59(d), 82.68(d), 89.34(s), 100.71(d), 112.23(t), 127.57(d), 127.68(d), 127.77(d), 128.30(d), 128.36(d), 137.89(s), 138.30(s), 138.28(s), 145.49(d).

m/z 532($m-H_2O+NH_4^+$)(100), 442(5), 407(5), 317(5), 253(10), 194(20), 108(20).

$C_{33}H_{42}O_5N$ [$m-H_2O+NH_4^+$] Requires 532.3063

Found 532.3067

APPENDIX 1.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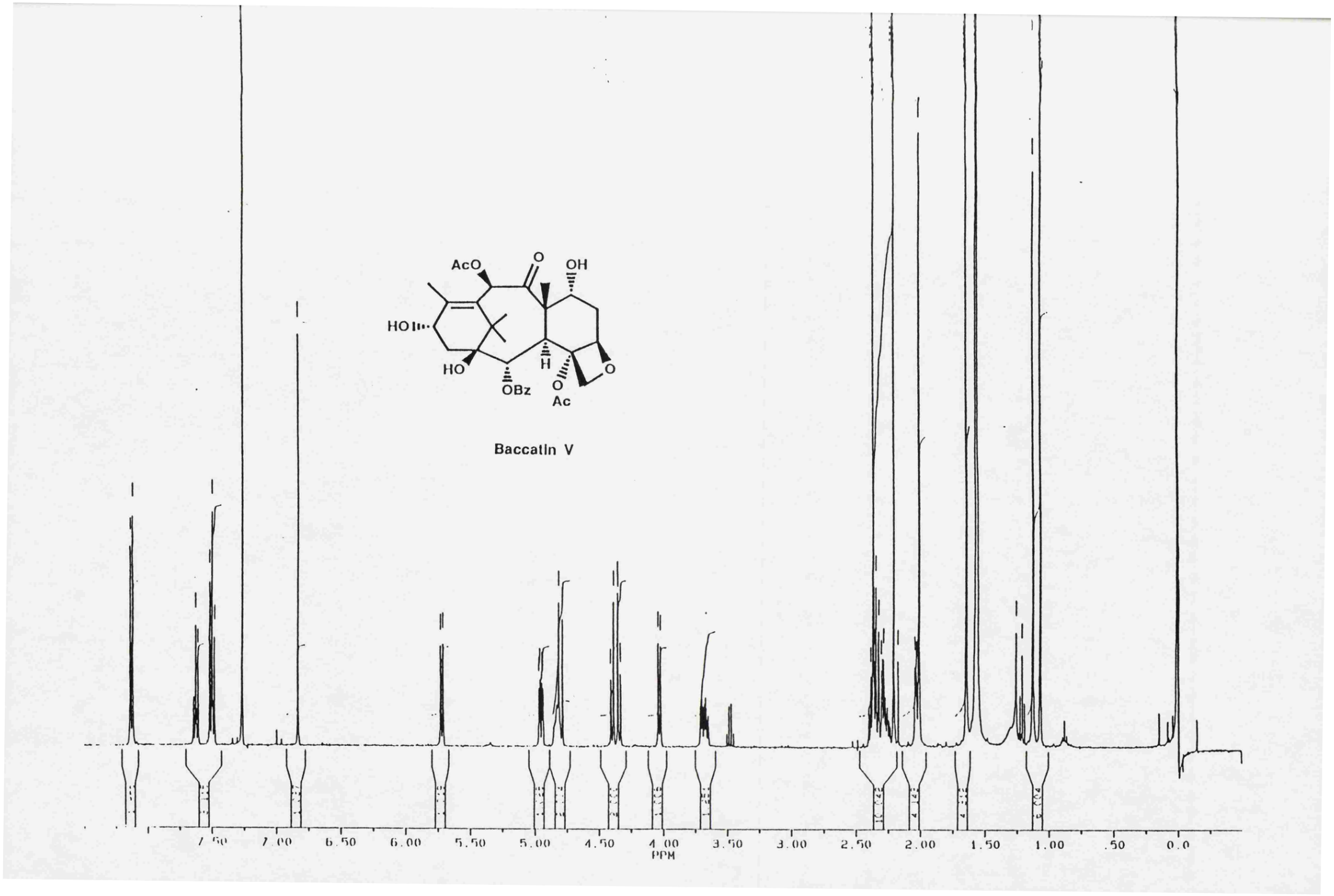
O
Ac
H
OBz
AcO
HO
HO
PPM


AcO
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HO
HO
H
O
O
OBz
O
Ac
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7.00
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6.00
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5.00
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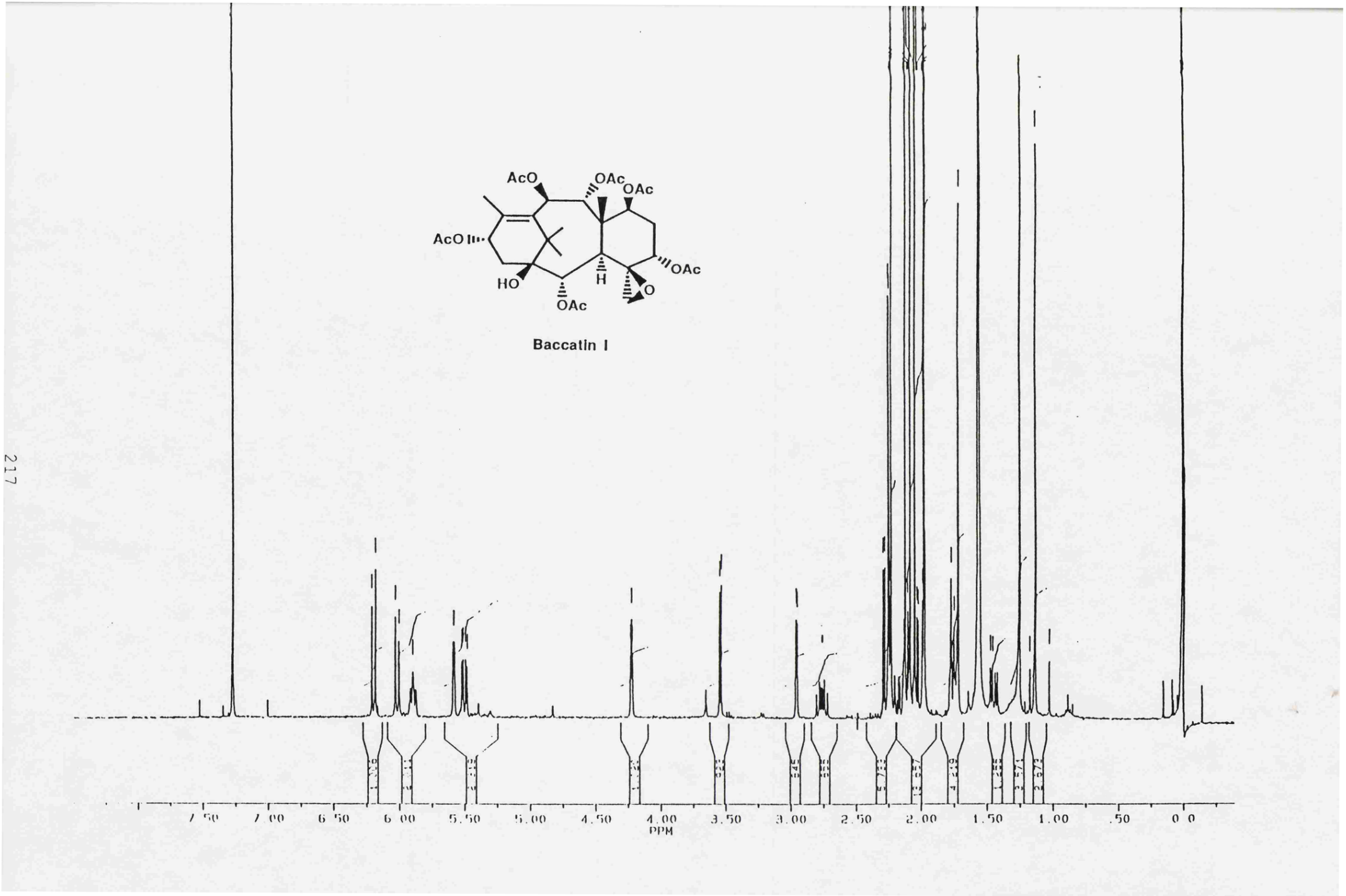
2.00
1.50
1.00
.50
0.0
PPM

Baccatin V


AcO
OAc
OAc
AcO
OAc
HO
H
O
OAc
Baccatin I
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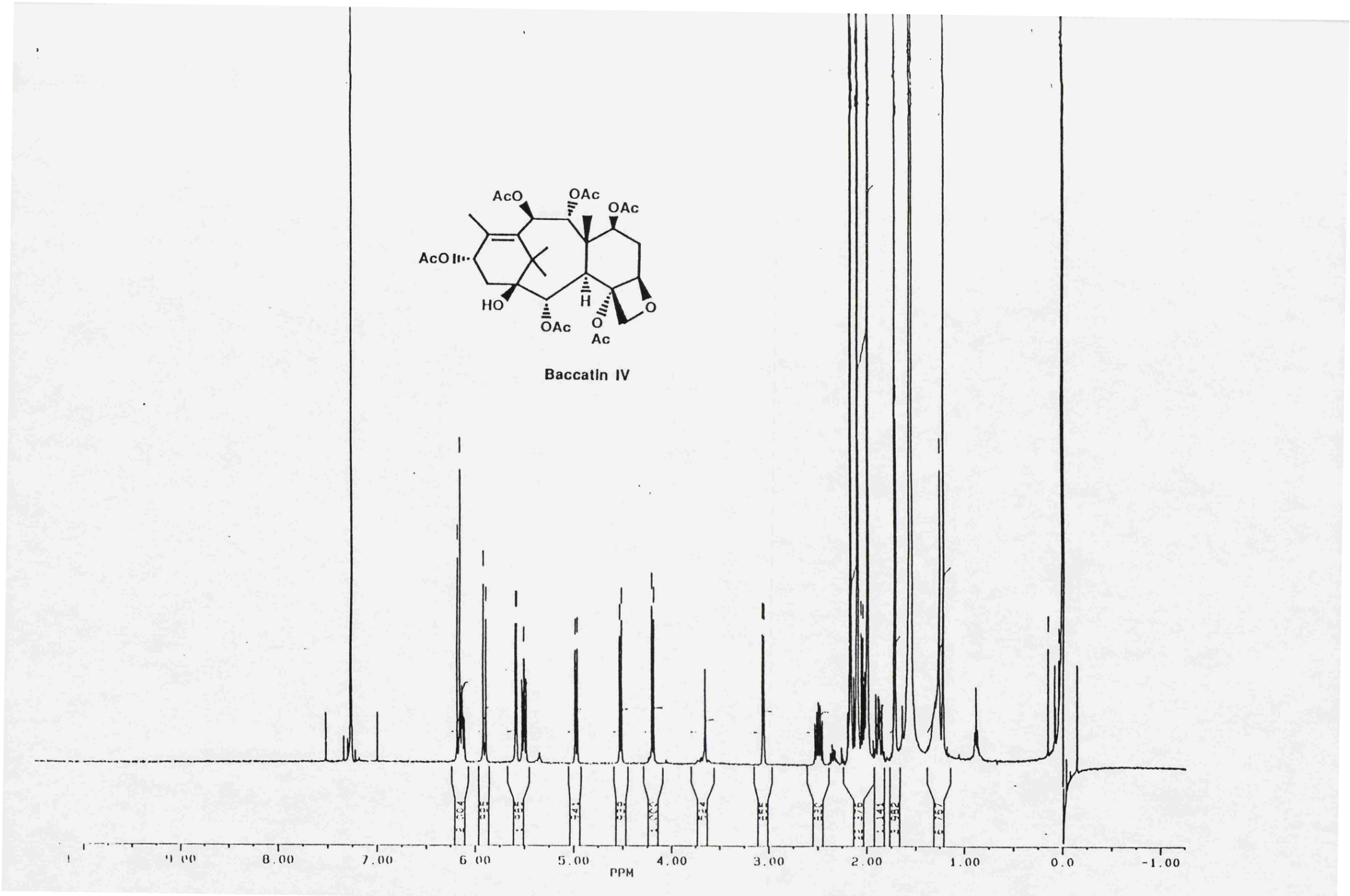
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM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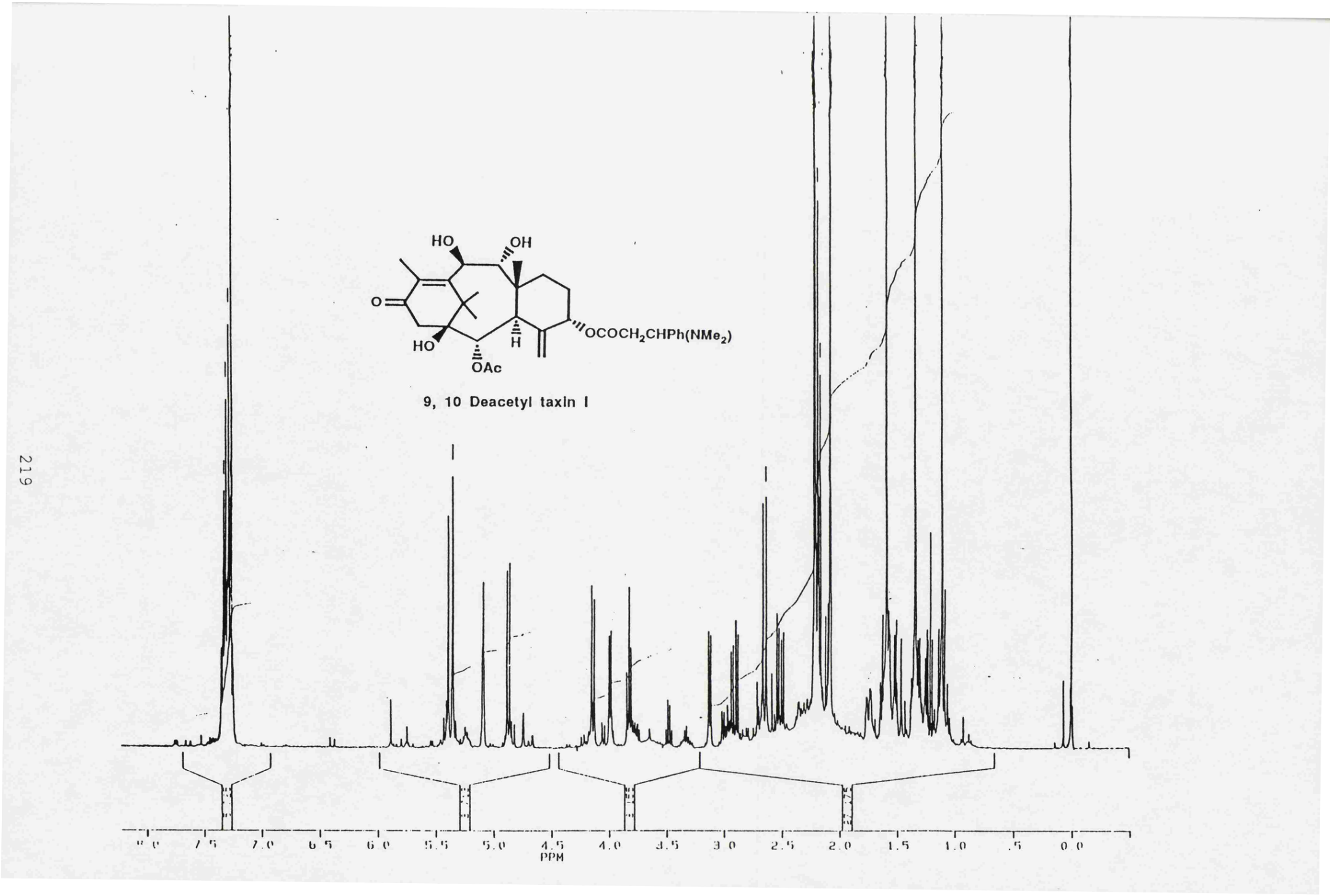
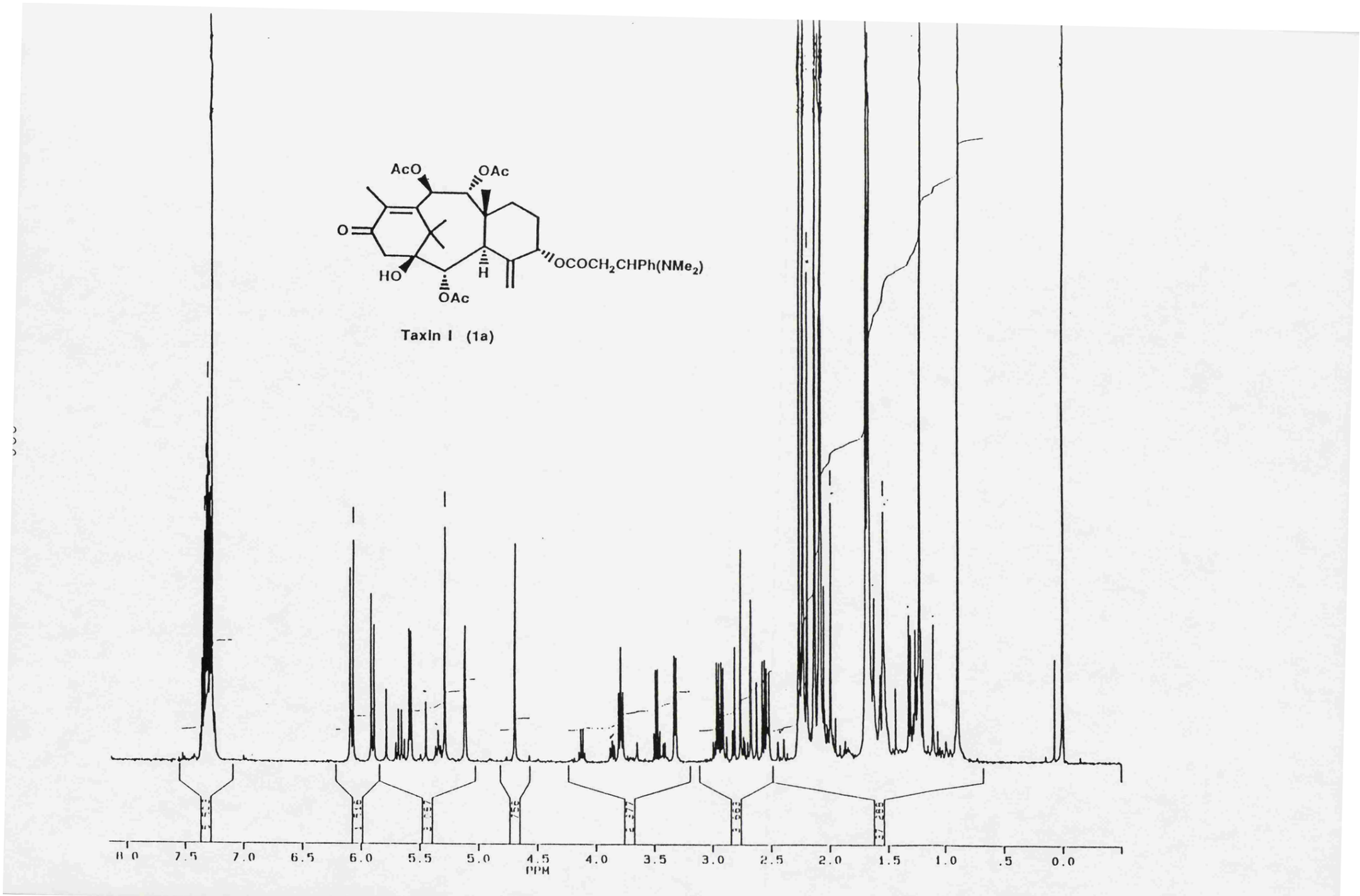
OAc
AcO
HO
OAc
H
O
O
Ac
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
-1.00
PPM

Baccatin IV



9, 10 Deacetyl taxin I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OAc
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HO
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OAc
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Taxln I (1a)
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7.5
7.0
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

APPENDIX 2.

X-RAY CRYSTAL STRUCTURE DATA FOR THE TETRACYCLIC STORK RADICAL CYCLISATION PRODUCT (145)

Crystal Data $C_{22}H_{32}O_5Si$, M = 404, Orthorhombic, Space Group $P2_12_12$, a = 18.851, b = 15.767, c = 7.547A, U = 2243.1A^3, Z = 4, μ = 0.96 cm^{-1}, λ(Mo-K_α) = 0.7107A, F(000) = 872.0

The unit cell parameters were determined from an oscillation photograph for the rotation axis c, and from refined positional data of zero layer reflections for a and b. The intensities of 1553 unique reflections with 2 theta < 52° and (+h, ±K, +l) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite monochromated Mo-K_α radiation using an omega-scan technique. 824 reflections had $I>3\sigma(I)$.

The structure was solved using SHELXS 84*. All subsequent calculations were carried out using the computer program SHELX-76**. All non-hydrogen atoms were refined as anisotropic.

The final residual indices were $R\{ = \Sigma|(|Fo|-|Fc|)|/\Sigma|Fo|\}$ =0.085 and R_w $\{=[\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{0.5}\}$ =0.085. The geometry of the molecule is shown in Figure 8. Final atomic positional and thermal parameters are given in following tables.

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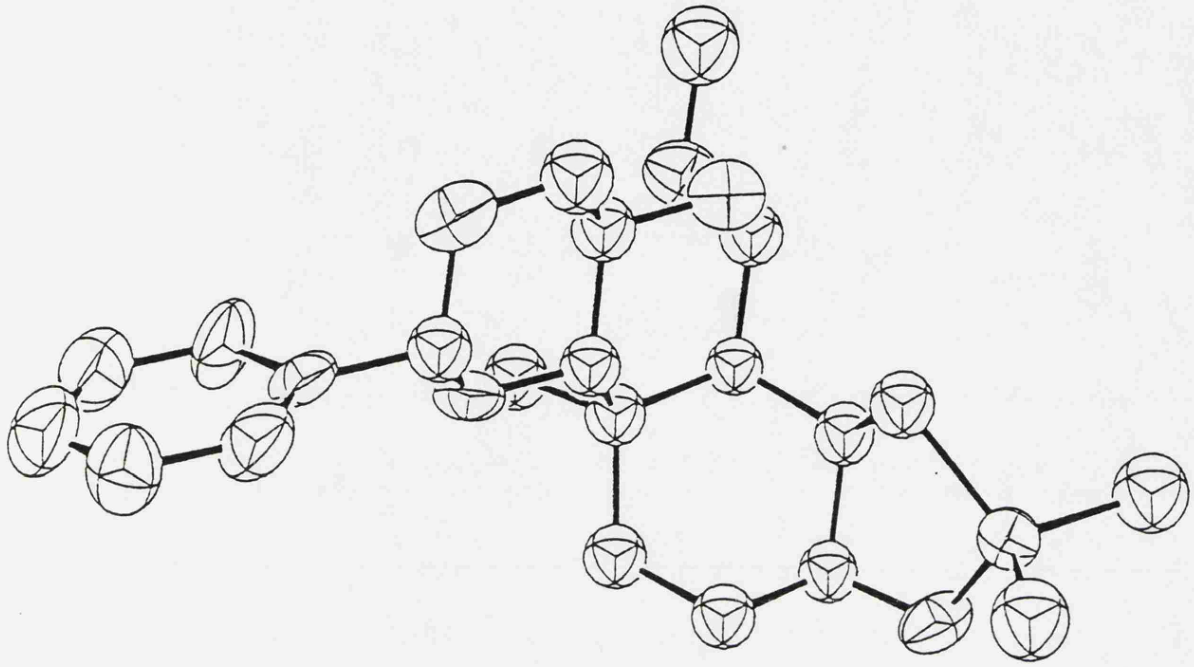
*G. M. Sheldrick SHELX 84. Private communication.

**G. M. Sheldrick SHELX 76. Program for crystal structure determination. University of Cambridge, 1976.



X-Ray Crystal Structure of Tetracyclic (145) (ORTEP)

Figure 8

Table of Fractional Atom Coordinates

ATOM	X	Y	Z
Si	0.08375(27)	0.1763(3)	0.2552(9)
O(21)	0.1738(6)	-0.2518(8)	-0.0253(21)
O(22)	0.1357(5)	-0.1448(6)	-0.2221(19)
O(31)	0.2537(6)	-0.0545(7)	0.1161(19)
O(32)	0.3380(6)	-0.0016(8)	-0.0838(19)
O(51)	0.0741(6)	0.2076(7)	0.0505(19)
C(1)	0.0959(7)	-0.2827(7)	-0.2690(18)
C(2)	0.0312(7)	-0.3251(7)	-0.2545(18)
C(3)	0.0114(7)	-0.3842(7)	-0.3827(18)
C(4)	0.0562(7)	-0.4009(7)	-0.5256(18)
C(5)	0.1209(7)	-0.3585(7)	-0.5402(18)
C(6)	0.1407(7)	-0.2994(7)	-0.4119(18)
C(21)	0.1154(9)	-0.2193(11)	-0.1204(27)
C(22)	0.2026(9)	-0.1950(12)	0.098(3)
C(23)	0.2270(9)	-0.1154(11)	-0.0135(28)
C(24)	0.1634(8)	-0.0800(10)	-0.1064(26)
C(31)	0.1840(8)	-0.0022(10)	-0.2142(25)
C(32)	0.2243(8)	0.0624(10)	-0.0931(26)
C(33)	0.2799(9)	0.0197(11)	0.0219(27)
C(34)	0.3972(11)	-0.0361(13)	0.021(3)
C(35)	0.2312(9)	-0.0294(10)	-0.3760(28)
C(41)	0.1156(8)	0.0412(10)	-0.2979(25)
C(42)	0.0686(8)	0.0893(10)	-0.1639(26)
C(43)	0.1140(9)	0.1588(10)	-0.0815(28)
C(44)	0.1774(9)	0.1206(10)	0.0253(28)
C(51)	0.1490(9)	0.0866(11)	0.2064(27)
C(61)	0.1272(10)	0.2620(12)	0.387(3)
C(62)	-0.0042(10)	0.1402(12)	0.351(3)

Table of Bond Lengths (A)

O(51)-Si	1.632(15)	C(51)-Si	1.911(17)
C(61)-Si	1.868(22)	C(62)-Si	1.896(21)
C(21)-O(21)	1.410(20)	C(22)-O(21)	1.400(22)
C(21)-O(22)	1.454(19)	C(24)-O(22)	1.442(20)
C(23)-O(31)	1.460(21)	C(33)-O(31)	1.455(19)
C(33)-O(32)	1.397(20)	C(34)-O(32)	1.470(24)
C(43)-O(51)	1.466(22)	C(2)-C(1)	1.395(0)
C(6)-C(1)	1.395(0)	C(21)-C(1)	1.547(21)
C(3)-C(2)	1.395(0)	C(4)-C(3)	1.395(0)
C(5)-C(4)	1.395(0)	C(6)-C(5)	1.395(0)
C(23)-C(22)	1.579(24)	C(24)-C(23	1.497(22)
C(31)-C(24)	1.523(22)	C(32)-C(44)	1.566(23)
C(35)-C(31)	1.571(25)	C(41)-C(31)	1.589(21)
C(33)-C(32)	1.517(22)	C(44)-C(32)	1.556(24)
C(42)-C(41)	1.545(24)	C(43)-C(42)	1.523(22)
C(44)-C(43)	1.563(23)	C(51)-C(44)	1.563(26)

Table of Bond Angles

C(51)-Si-O(51)	96.5(8)	C(61)-Si-O(51)	109.7(9)
C(61)-Si-C(51)	110.9(8)	C(62)-Si-O(51)	110.7(9)
C(62)-Si-C(51)	114.4(8)	C(62)-Si-C(61)	113.4(10)
C(22)-O(21)-C(21)	114.0(14)	C(24)-O(22)-C(21)	110.3(14)
C(33)-O(31)-C(23)	108.6(15)	C(34)-O(32)-C(33)	112.2(15)
C(43)-O(51)-Si	115.3(10)	C(6)-C(1)-C(2)	120.0(0)
C(21)-C(1)-C(2)	117.4(8)	C(21)-C(1)-C(6)	122.6(8)
C(3)-C(2)-C(1)	120.0(0)	C(4)-C(3)-C(2)	120.0(0)
C(5)-C(4)-C(3)	120.0(0)	C(6)-C(5)-C(4)	120.0(0)
C(5)-C(6)-C(1)	120.0(0)	O(22)-C(21)-O(21)	110.9(13)
C(1)-C(21)-O(21)	108.6(13)	C(1)-C(21)-O(22)	101.6(14)
C(23)-C(22)-O(21)	105.6(16)	C(22)-C(23)-O(31)	105.5(16)
C(24)-C(23)-O(31)	110.2(13)	C(24)-C(23)-C(22)	108.1(14)
C(23)-C(24)-O(22)	108.0(13)	C(31)-C(24)-O(22)	109.8(15)
C(31)-C(24)-C(23)	110.2(13)	C(32)-C(31)-C(24)	109.6(16)
C(35)-C(31)-C(24)	109.8(13)	C(35)-C(31)-C(32)	110.9(13)
C(41)-C(31)-C(24)	110.7(12)	C(41)-C(31)-C(32)	110.3(13)
C(41)-C(31)-C(35)	105.5(15)	C(33)-C(32)-C(31)	112.4(13)
C(44)-C(32)-C(31)	116.3(13)	C(44)-C(32)-C(33)	109.0(17)
O(32)-C(33)-O(31)	110.6(13)	C(32)-C(33)-O(31)	113.7(13)
C(32)-C(33)-O(32)	108.7(16)	C(42)-C(41)-C(31)	114.6(16)
C(43)-C(42)-C(41)	107.3(14)	C(42)-C(43)-O(51)	111.5(14)
C(44)-C(43)-O(51)	104.1(16)	C(44)-C(43)-C(42)	111.4(13)
C(43)-C(44)-C(32)	111.5(17)	C(51)-C(44)-C(32)	119.7(14)
C(51)-C(44)-C(43)	108.7(14)	C(44)-C(51)-Si	97.8(11)

Table Of Non-bonded Contacts (A)

C(43)...Si	2.619	C(44)...Si	2.627
O(22)...O(21)	2.360	C(1)...O(21)	2.403
C(23)...O(21)	2.376	C(24)...O(21)	2.784
C(1)...O(22)	2.327	C(6)...O(22)	2.829
C(22)...O(22)	2.836	C(23)...O(22)	2.378
C(31)...O(22)	2.426	C(35)...O(22)	2.810
C(41)...O(22)	3.012	O(32)...O(31)	2.344
C(22)...O(31)	2.420	C(24)...O(31)	2.425
C(31)...O(31)	2.936	C(32)...O(31)	2.488
C(34)...O(31)	2.815	C(23)...O(32)	2.806
C(32)...O(32)	2.369	C(35)...O(32)	3.019
C(42)...O(51)	2.471	C(44)...O(51)	2.390
C(51)...O(51)	2.649	C(61)...O(51)	2.864
C(62)...O(51)	2.907	C(3)...C(1)	2.416
C(4)...C(1)	2.790	C(5)...C(1)	2.416
C(4)...C(2)	2.416	C(5)...C(2)	2.790
C(6)...C(2)	2.416	C(21)...C(2)	2.515
C(5)...C(3)	2.416	C(6)...C(3)	2.790
C(6)...C(4)	2.416	C(21)...C(6)	2.582
C(22)...C(21)	2.358	C(23)...C(21)	2.786
C(24)...C(21)	2.377	C(24)...C(22)	2.491
C(31)...C(23)	2.477	C(32)...C(23)	2.867
C(33)...C(23)	2.367	C(35)...C(23)	3.054
C(32)...C(24)	2.524	C(33)...C(24)	2.870
C(35)...C(24)	2.532	C(41)...C(24)	2.560
C(33)...C(31)	2.562	C(42)...C(31)	2.638
C(43)...C(31)	3.030	C(44)...C(31)	2.651
C(35)...C(32)	2.583	C(41)...C(32)	2.589
C(42)...C(32)	3.015	C(43)...C(32)	2.578
C(51)...C(32)	2.696	C(34)...C(33)	2.380
C(44)...C(33)	2.502	C(51)...C(33)	3.023
C(41)...C(35)	2.516	C(43)...C(41)	2.471
C(44)...C(41)	2.979	C(44)...C(42)	2.548
C(51)...C(43)	2.540		

Table of Thermal Parameters

Atom	U or U11	U22	U33	U23	U13	U12
Si	667(32)	653(30)	504(35)	9(34)	-92(34)	121(29)
O(21)	611(81)	576(72)	924(123)	96(80)	34(83)	88(68)
O(22)	378(63)	550(66)	741(100)	44(75)	-152(70)	39(50)
O(31)	589(77)	680(84)	674(103)	121(79)	49(75)	-13(61)
O(32)	406(65)	894(88)	797(111)	54(90)	-13(75)	-63(66)
O(51)	689(81)	564(74)	791(110)	92(70)	9(76)	228(67)
C(1)	447(104)	327(78)	856(157)	56(111)	-59(132)	99(83)
C(2)	669(125)	451(100)	1076(176)	-107(152)	27(159)	56(99)
C(3)	712(140)	668(143)	858(180)	-93(142)	98(146)	-151(120)
C(4)	792(154)	507(127)	1411(266)	-279(146)	-43(169)	-45(120)
C(5)	766(151)	828(157)	1282(241)	-428(168)	-65(166)	145(132)
C(6)	614(131)	832(160)	1116(218)	-471(156)	296(146)	103(118)
C(21)	513(47)					
C(22)	642(57)					
C(23)	547(50)					
C(24)	475(45)					
C(31)	521(47)					
C(32)	463(45)					
C(33)	558(51)					
C(34)	862(68)					
C(35)	621(53)					
C(41)	570(51)					
C(42)	552(50)					
C(43)	531(49)					
C(44)	541(50)					
C(51)	593(52)					
C(61)	807(63)					
C(62)	789(63)					

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