New Synthetic Methods in an Approach to Taxinine

by

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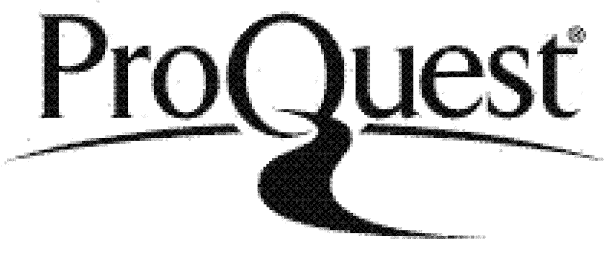

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STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "New Synthetic Methods in an Approach to Taxinine" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period October 1984 and September 1987.

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: 12th October 1987

Parts of this work have been published as communications;

The First Example of a Robinson Annulation on a Carbohydrate Derivative
R. V. Bonnert and P. R. Jenkins, J. Chem. Soc., Chem. Commun., 1987, 6.

A Silicon Directed Diene Synthesis
P. A. Brown, R. V. Bonnert, P. R. Jenkins and M. R. Selim, Tetrahedron Lett., 1987, 28, 693.

The Diels-Alder Reaction of Dienes with a Cis-1-methyl Group
R. V. Bonnert and P. R. Jenkins, Tetrahedron Lett., 1987, 28, 697.

A New Synthesis of Substituted Dienes and its Application to an Alkylated Taxane Model System
R. V. Bonnert and P. R. Jenkins, J. Chem. Soc., Chem. Commun., 1987, accepted for publication.

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NEW SYNTHETIC METHODS IN AN APPROACH TO TAXININE

by Roger Victor Bonnert

ABSTRACT

A series of studies were undertaken directed towards the synthesis of taxinine. As part of these studies the need arose for a stepwise synthesis of a highly substituted butadiene from an aldehyde. The initial approach used the Peterson elimination to control the regiochemistry in the formation of tri- and tetra-substituted dienes. The generality of this method appeared to be hampered by the basicity of 2-lithio-2-trimethylsilyl propane, which was required to undergo nucleophilic attack at an aldehyde.

A study of the Diels-Alder reactions of a 3-alkyl-2,4-penta-1,3-diene and a 3-alkyl-4-methyl-penta-1,3-diene showed the former to react more efficiently. A deuterium labelling experiment eliminated the degeneracy of this diene in a 1,5-hydrogen shift as a reason for its increased reactivity.

A more reliable route to the preparation of highly substituted butadienes was attained using the highly nucleophilic 2-lithio-2-phenylseleno-propane reagent. This route was used to prepare a triene system which underwent an intramolecular Diels-Alder reaction to enable the preparation of the taxane model compound 8,12,15,15-tetramethyltricyclo[9.3.1.$0^{3,8}$]pentadec-11-en-2-one which has the same stereochemistry and methyl group substitution as the naturally occurring taxanes.

Attempts were then made to prepare taxinine using a carbohydrate derivative. A key step in the route to taxinine involved a Robinson annulation of a carbohydrate derived ketone. Alkylations of a carbohydrate derived enolate were studied initially. The Robinson annulation was then carried out using 3-trimethylsilyl-3-buten-2-ol and the enolate derived from methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexapyranosid-2-ulose.

To Mandy and My Parents.

COMMON YEW—*TAXUS BACCATA.*

From P. Groom, "Trees and Their Life Histories", Cassell & Co., London, 1907, p.137.

LIST OF CONTENTS

ABBREVIATIONS

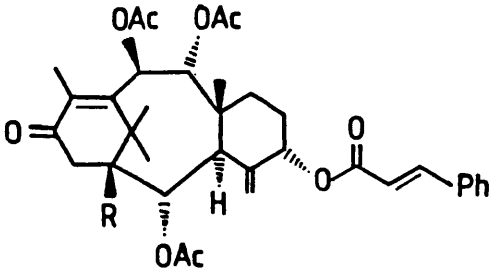
DIBAH	-	di-isobutylaluminium hydride
TMS	-	trimethylsilyl
LDMAN	-	lithium(dimethylamino)naphthalenide
DME	-	dimethoxyethane
THF	-	tetrahydrofuran
n.O.e.	-	nuclear Overhauser effect
DNP	-	dinitrophenylhydrazine
trisyl	-	2,4,6-triisopropylbenzenesulphonyl
DDQ	-	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
IMDA	-	Intramolecular Diels-Alder
LDA	-	lithium di-isopropylamide
LTMP	-	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	-	meta-chloroperbenzoic acid
HMPA	-	hexamethylphosphoramide
9-BBN	-	9-borabicyclo[3,3,1]nonane

CHAPTER 1

Introduction

1.1 INTRODUCTION

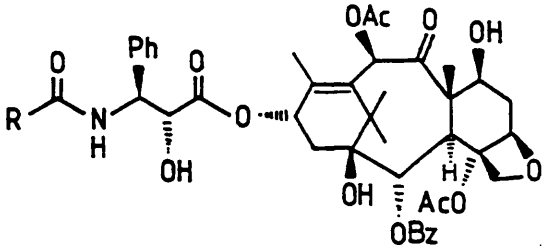
Taxine is the name used for the amorphous basic compounds contained in the European, *Taxus baccata* and Japanese, *Taxus cuspidata* yew trees, as well as other related species, *Taxaceae*[1] and are responsible for the poisonous properties of the yew tree. The product that has been isolated from these trees consists of two principal components; O-cinnamoyl-taxicin-I triacetate (1) and O-cinnamoyltaxicin-II triacetate (taxinine) (2). They are both contained within the plant as esters of β-dimethyl-



(1) R = OH
(2) R = H

amino-β-phenylpropionic acid, $Me_2NCH(Ph)\text{-}CH_2CO_2H$,[2] but are converted to cinnamates by loss of dimethylamine during isolation.[3]

Many compounds that contain the taxane 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



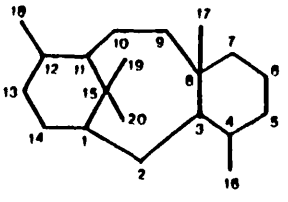
(3) R = Ph
(4) R = $CCH_3 = CHCH_3$

properties.[5,6] Taxol (3) is currently undergoing clinical trials as an anticancer chemotherapeutic agent in America and France.[7] This biological activity has spurred on an ever increasing effort to provide the total

synthesis of naturally occurring taxines and new structural analogues for further biological testing. Despite this effort none of the natural taxines have yet been synthesised.

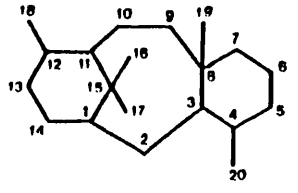
1.2 NOMENCLATURE

The literature, prior to 1964, contains a variety of numbering systems for the taxane derivatives.[4] In 1964, three laboratories recommended the name taxane for a nucleus (5) and numbered the framework accordingly.[8] In 1969, however, a different numbering scheme for the



(5)

methyl groups was introduced which resulted in both systems then being used. In 1978 IUPAC recommended the numbering system shown for the taxane skeleton (6).[9]



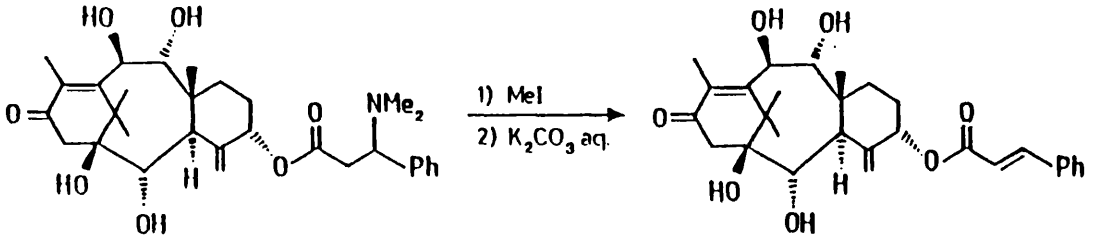
(6)

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

1.3 ISOLATION OF O-CINNAMOYLTAXICIN-I TRIACETATE (1) AND TAXININE (2)

Typical extraction methods that were employed, involved soaking the dried yew leaves in sulphuric acid for seven days.[4] The acid solution obtained was then basified and extracted with ether.[3] Winterstein and Latrides[11] showed that taxines were present in the plant as esters of

β-dimethylamino-β-phenylpropionic acid (Winterstein acid). The instability of this ester was attributed to be the reason for some of the early difficulties in the isolation.[12] Both English[13] and Japanese[14] groups chose to eliminate dimethylamine from the Winterstein ester to produce the corresponding cinnamate esters. Treatment of taxine-I (7) with methyl iodide produced "taxine methiodide" which could then be reacted with aqueous potassium carbonate to yield O-cinnamoyltaxicin-I (8).[3]



(7) (8)

The cinnamates were usually then reacted under Zemplen methanolysis conditions[15] which removed the acetate groups but left the cinnamate esters unaffected. O-cinnamoyltaxicin-I (8) could then be separated directly by crystallisation. The mother liquor was then re-acetylated and O-cinnamoyltaxicin-I triacetate (1) and taxinine (2) separated out by chromatography.[3] From 10 Kg of dried yew clippings, using the above extraction technique, it was possible to isolate approximately 40g of crude taxine. Separation of the crude taxine then produced 7.7g of O-cinnamoyltaxicin I (8), 4.4g of its triacetate (1) and 1.9g of taxinine (2).[3]

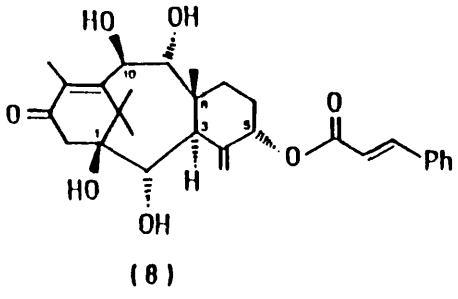
The vigorous conditions used in the isolation procedure have meant that taxine-I and taxine-II have only been isolated as their derivatives.[4] Much milder extraction procedures have been used to isolate many of the more complex taxines. Taxol (3), for example, was obtained by alcohol extraction of bark from the western yew, *Taxus brevifolia* and then

purified by successive chromatography and crystallisation.[5]

1.4 STRUCTURE DETERMINATION OF TAXININE (2)

Ever since the taxines were first isolated by Lucas[16] in 1856 the majority of the early literature concerned their structure determination. The major product isolated from the British yew, *Taxus baccata*, was O-cinnamoyltaxicin-I (8) and because of this the British groups tended to concentrate on this compound, whereas the major product from the Japanese yew, *Taxus cuspidata*, was taxinine (2) and consequently the Japanese work was centred around this compound.[12]

The molecular formulae for O-cinnamoyltaxicin-I (8) and taxinine (2) were established as $C_{29}H_{36}O_7$[13] and $C_{35}H_{42}O_9$[17] respectively. The majority of the functional groups were determined by chemical means.[12] Initial studies on O-cinnamoyltaxicin-I (8) showed that it contained four hydroxyl groups, an isolated methylene and an enone group.[13] One of the important chemical reactions of (8) was periodate oxidation which gave two fragments (9) and (10).[18] The structures of the two fragments were determined by both chemical and spectroscopic means.[19]



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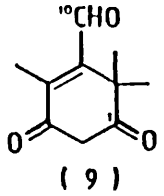
$NaIO_4$



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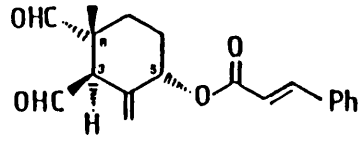
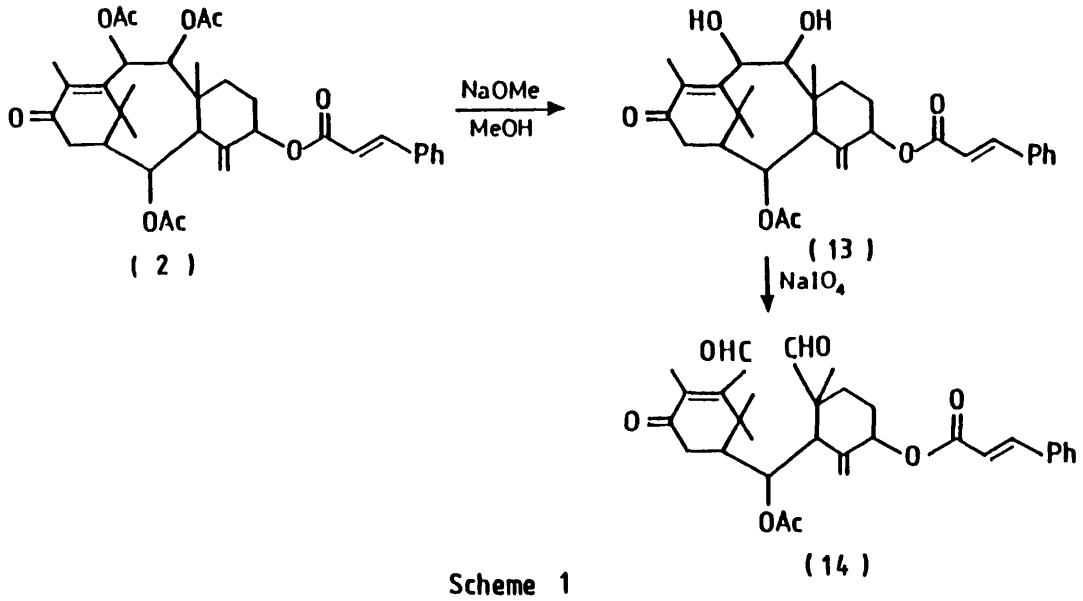


(10)

It soon became apparent that O-cinnamoyltaxicin-I triacetate (1) and taxinine (2) were structurally related. The best evidence for the similarity in structure and stereochemistry was illustrated by the

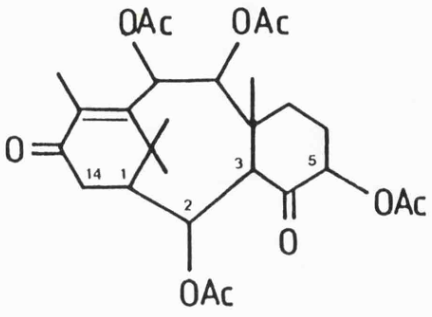
proton n.m.r., Figure 1, of oxonortaxicin-II tetra-acetate (11) and oxonortaxicin-I tetra-acetate (12).[20] The n.m.r. not only shows the similarities but also illustrates some differences in the C-1, C-2 and C-14 positions.

Chemical studies of taxinine (2) showed that it lacked the free tertiary hydroxyl group which was present in the O-cinnamoyltaxicin-I series.[21] Methanolysis of taxinine (2) led to the formation of the 2-monoacetate (13).[20] Treatment of the monoacetate (13) with periodate gave the dialdehyde (14), Scheme 1. The n.m.r. spectrum showed the aldehyde protons as singlets which implied that they were flanked by carbons bearing no hydrogens.[20]



Scheme 1

Hydrogenation of taxinine (2) using hydrogen over a platinum catalyst gave dihydrotaxicin-II β-cyclohexylpropionate triacetate (15).[20] The enone double bond proved inert to hydrogenation (and oxidation) in a similar way to O-cinnamoyltaxicin-I triacetate (1).[3] 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



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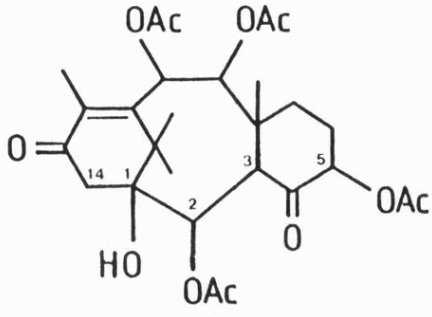

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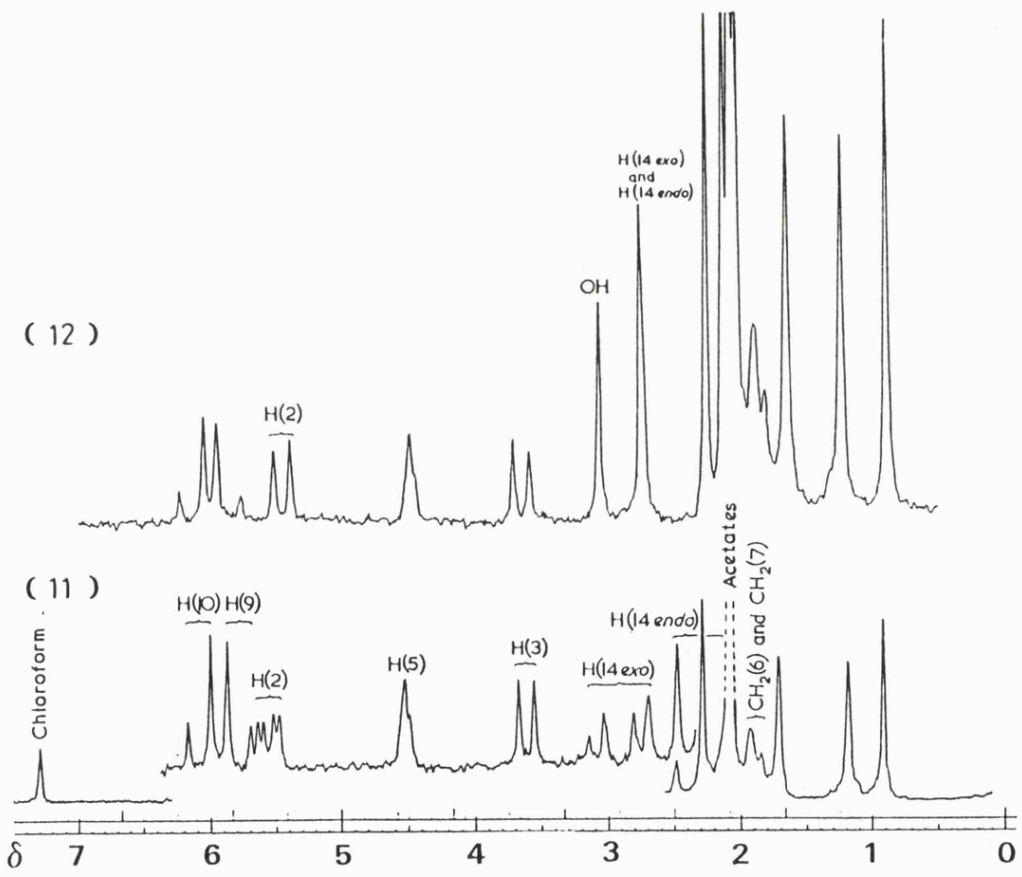
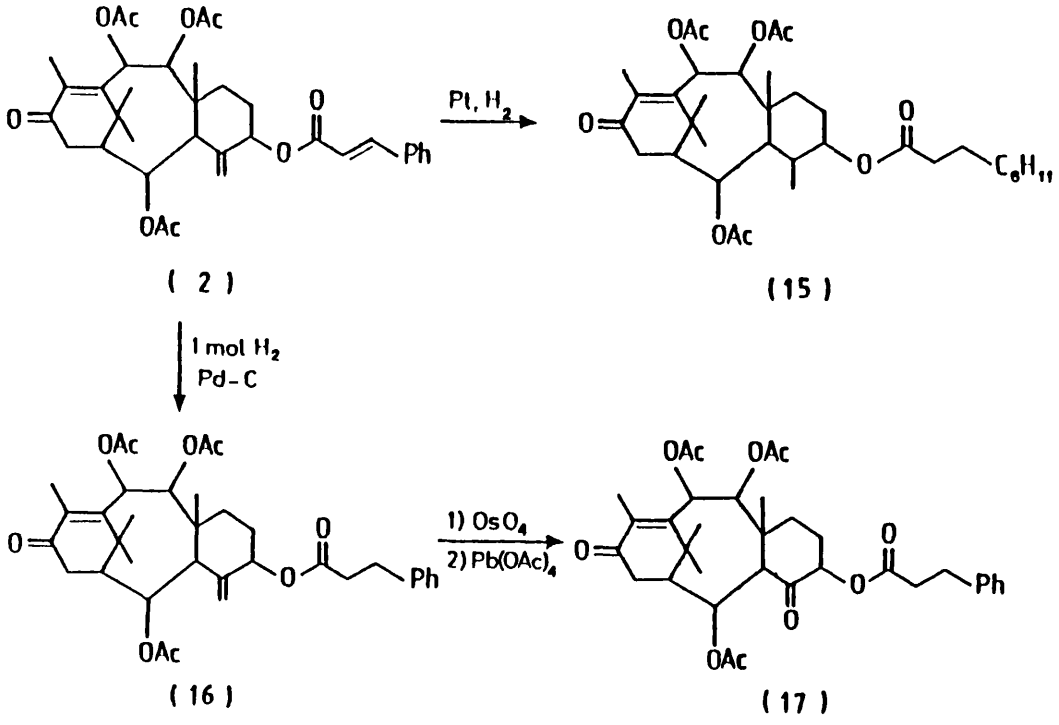


Figure 1

(16). 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 (17) and formaldehyde, Scheme 2.[20]

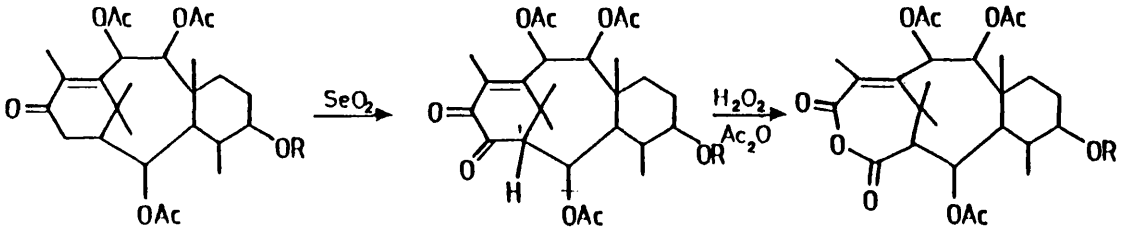


(2) (15) (16) (17)

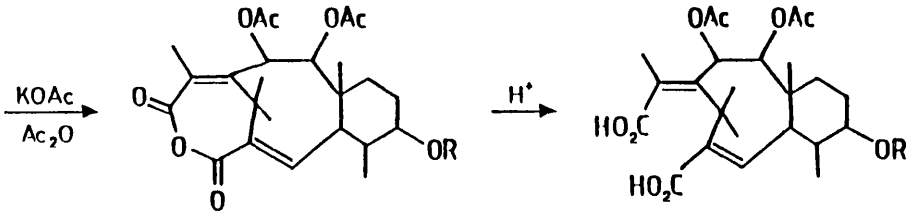
Scheme 2

Additional chemical evidence for the structure of taxinine (2) was demonstrated when tetrahydrotaxinine (18) was oxidised using selenium dioxide to provide the α diketone (19). The proton n.m.r. showed a proton corresponding to H-1 as a doublet at δ2.88. Baeyer-Villiger oxidation of (19) produced the anhydride (20). Treatment of (20) with potassium acetate and acetic anhydride furnished the anhydride (21) which on reaction with acid then gave the dicarboxylic acid (22), Scheme 3.[17]

The final piece of chemical evidence for the structure of taxinine (2) was the treatment of the 2-monoacetate (13) with alkali to provide anhydrotaxininol (23).[22]



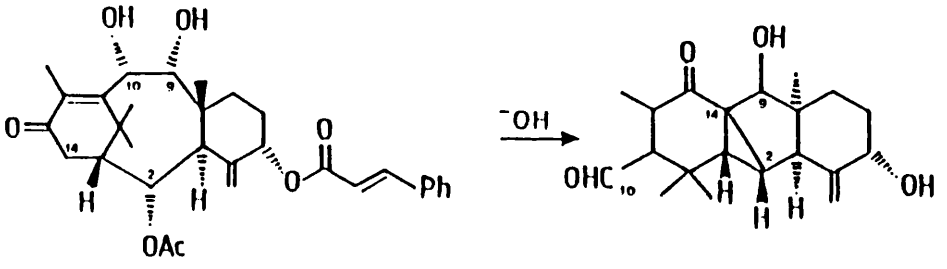
(18) (19) (20)



(21) (22)

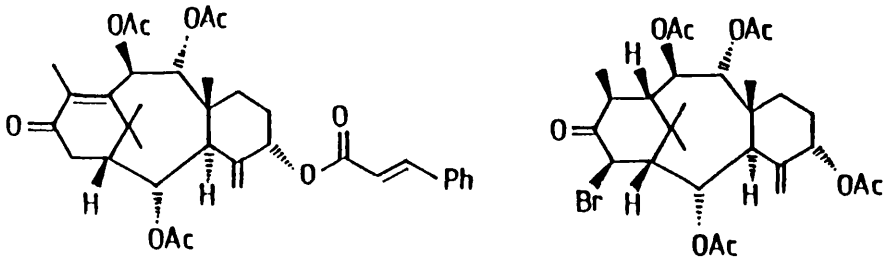
R = $COCH_2CH_2Ph$

Scheme 3



(13) (23)

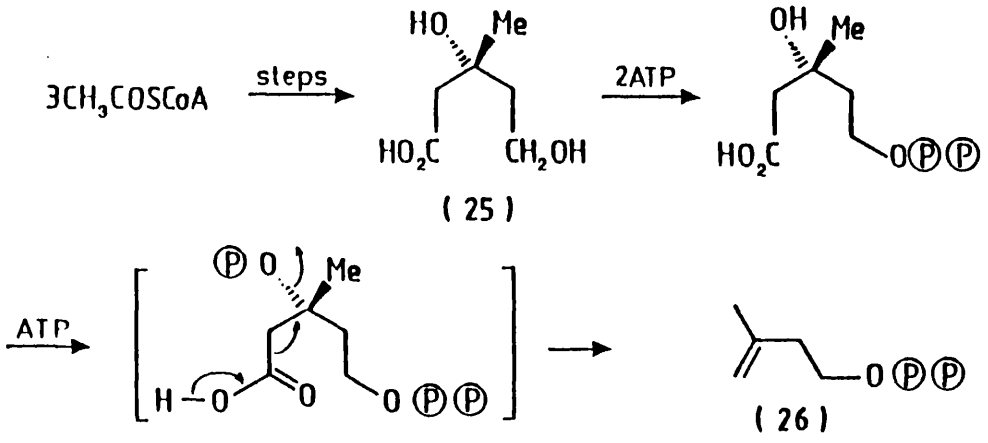
The stereochemistry of taxinine (2) was originally inferred from the coupling constants in the proton n.m.r. but this led to the wrong configuration being assigned at C-3, C-9 and C-10.[23] The relative configuration of taxinine (2) was later confirmed by X-ray analysis of 14-bromotaxinol (24).[24]



(2) (24)

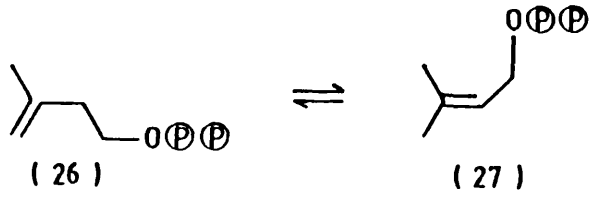
1.5 BIOSYNTHESIS

The taxane skeleton is a diterpenoid compound and, as all terpenes, originates from mevalonic acid (25) which is itself derived from three molecules of acetyl-CoA.[25] In the biosynthesis of terpenes the mevalonic acid (25) is converted to isopentenyl pyrophosphate (IPP) (26)



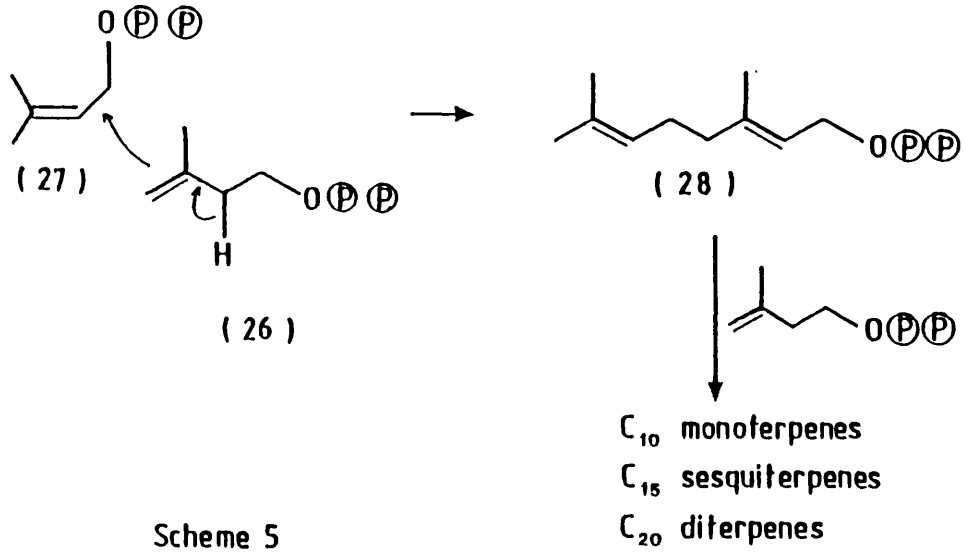
Scheme 4

by phosphorylation with ATP followed by decarboxylation, Scheme 4.[25] IPP (26) is readily isomerised to dimethylallyl pyrophosphate (DMAPP) (27).

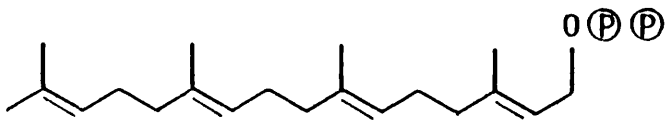


IPP (26) and DMAPP (27) can now be joined together in a head-to-tail fashion to form trans-geranyl pyrophosphate (28); the pyrophosphate group remaining on (28) enables further alkylation with IPP (26) so extending the chain in C_5 units, Scheme 5.[25]

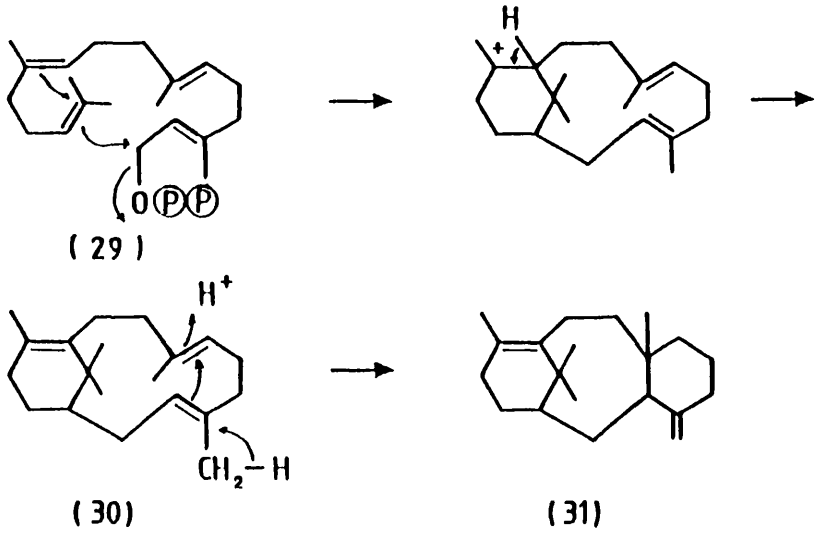
The C_{20} taxane skeleton is therefore derived from geranylgeranyl pyrophosphate (GGPP) (29). A sequence such as that outlined in Scheme 6 has been proposed for the cyclisation of GGPP (29) to the taxane skeleton (31).[26] Verticillene (30) is the putative biogenetic precursor



Scheme 5



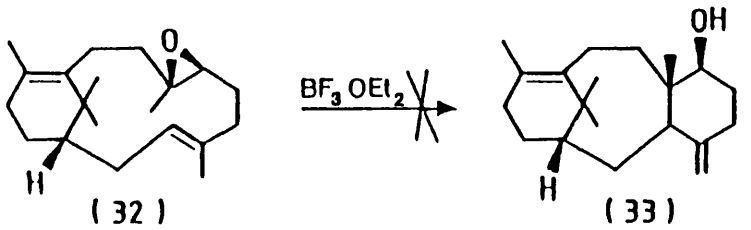
C_{20} geranylgeranyl pyrophosphate
(29)



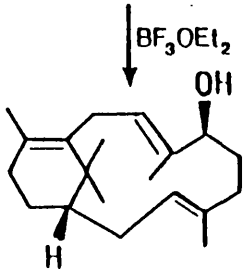
Scheme 6

of the taxane group.[27] However, it has been found that verticillene (30) failed to undergo cyclisation <u>in vitro</u> to the corresponding taxane ring.[28] Treatment of the epoxide (32) with boron trifluoride etherate

failed to produce any of the tricyclic alcohol (33) but gave the allylic alcohol (34).[28] Whilst this does not disprove the involvement



(32) (33)



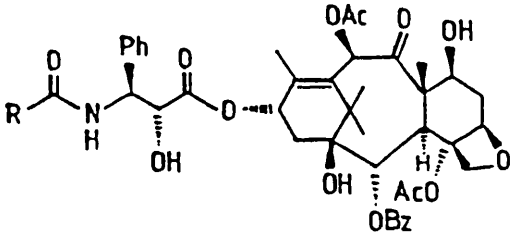
(34)

of verticillene (30) in the biosynthesis of the taxines, it does suggest a more subtle process.[28]

The considerable modification of the carbon framework (31) required to prepare any of the naturally occurring taxines, is thought to occur by oxidation of this skeleton.

1.6 BIOLOGICAL ACTIVITY

Two of the more complex taxines isolated, taxol (3)[5] and cephalomannine (4)[6] have been shown to possess antileukaemic and tumour inhibitory properties. This biological activity has invoked a consider-



(3) R = Ph
(4) R = $CCH_3 = CHCH_3$

able amount of interest in determining the mechanism for the action of taxol (3) and the functionality responsible for this activity.[29]

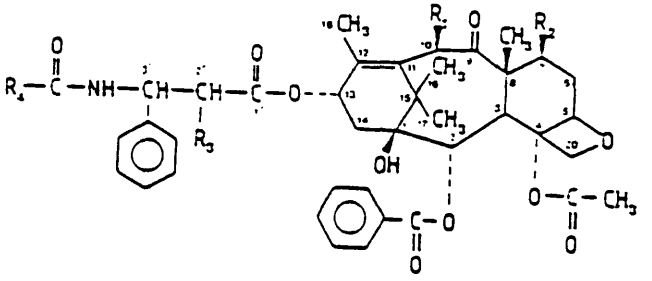
Taxol (3) was shown to inhibit cell replication in HeLa cells mainly in the mitotic phase of the cell cycle.[30] This activity has been related to the in vitro interaction with microtubule proteins.[31] Microtubules are important components of eukaryotic cells and are thought to be involved in a number of cellular functions including chromosome movement, regulation of cell form and anchorage of surface receptors in the plasma membrane.[29] Whilst other plant alkaloids, like vinblastine and colchicine prevent the assembly of tubulin, taxol (3) promotes the assembly of microtubules and inhibits the depolymerisation of tubulin.[7] This unique feature of taxol (3) has alone made it an important aid for studying the structure and function of microtubules.[32]

Preparation and use of tritium labelled taxol have shown that the drug binds specifically and reversibly to assembled microtubules in vitro and that one mole of taxol binds to one mole of tubulin dimer.[32] It has also been shown that taxol specifically effects the tubulin-microtubule system and does not bind to DNA or influence actin polymerisation.[33] Research is continuing to determine the precise mechanism of the action of taxol (3) in cells.

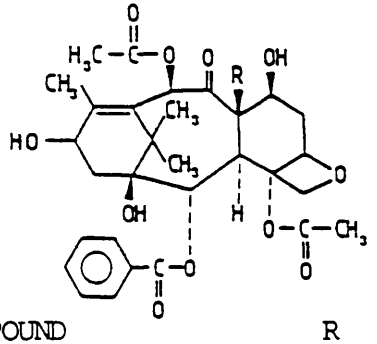
Although taxol (3) is currently undergoing clinical trials, its use in humans is severely hampered because of its insolubility in an aqueous medium.[32] In connection with this, information about the chemical structure of the drug which relates to its biological activity has been sought. This knowledge is also of use to a synthetic chemist when trying to develop a synthetic alternative to taxol (3).

Figure 2 shows some of the naturally occurring taxines and some semisynthetic derivatives that have been studied.[32] For each compound the cytotoxicity and the ability to promote microtubule assembly in vitro

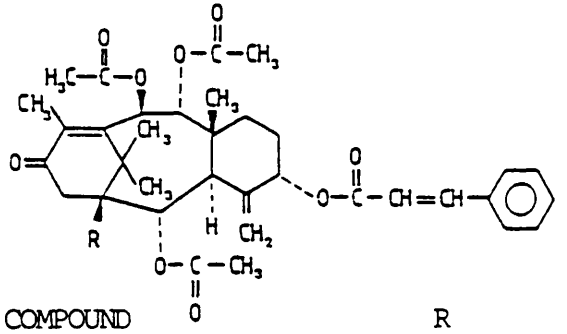
FIGURE 2



COMPOUND	R_1	R_2	R_3	R_4
(3) Taxol	$OCOCH_3$	OH	OH	
(35) 10-deacetyltaxol	OH	OH	OH	
(36) 2',7-diacetyltaxol	$OCOCH_3$	$OCOCH_3$	$OCOCH_3$	
(37) 2'-acetyltaxol	$OCOCH_3$	OH	$OCOCH_3$	
(38) 7-acetyltaxol	$OCOCH_3$	$OCOCH_3$	OH	
(39) 2',7-diacetyl, 10-deacetyltaxol	OH	$OCOCH_3$	$OCOCH_3$	
(4) Cephalomannine	$OCOCH_3$	OH	OH	$C(CH_3)=CHCH_3$
(40) 10-deacetylcephalomannine	OH	OH	OH	$C(CH_3)=CHCH_3$



COMPOUND	R
(41) Baccatin III	CH_3
(42) 19-hydroxybaccatin III	CH_2OH



COMPOUND	R
(1) O-cinnamoyltaxicin-I triacetate	OH
(2) Taxinine	H

TABLE 1

Compound	Induction of Microtubule Assembly	Relative Cytotoxicity
(3) Taxol[a]	Yes	+++++
(35) 10-deacetyltaxol[a]	Yes	+++
(36) 2',7-diacetyltaxol[a]	No	+
(37) 2'-acetyltaxol[b]	No	+++
(38) 7-acetyltaxol[b]	Yes	++++
(39) 2',7-diacetyl, 10-deacetyltaxol[a]	No	++
(4) Cephalomannine[a]	Yes	++++
(40) 10-deacetylcephalomannine[a]	Yes	++
(41) Baccatin III[a]	No	-[c]
(42) 19-hydroxybaccatin III[a]	No	-[c]
(1) O-cinnamoyltaxicin-I triacetate[a]	No	-[c]
(2) Taxinine[a]	No	-[c]

[a] *See Ref. 30;*
[b] *See Ref. 34;*
[c] *No activity at 10* μm.

were examined, the results being shown in Table 1.[32]

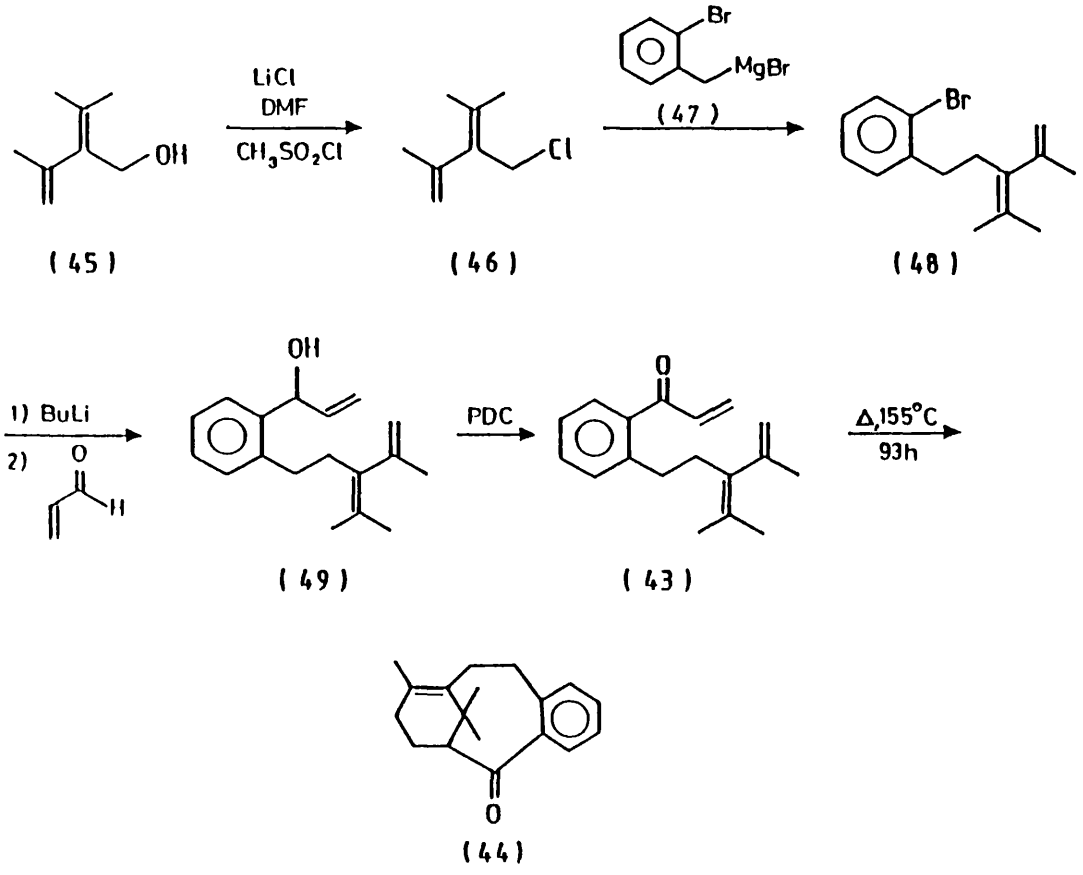
Experiments have indicated that both an intact taxane ring and an ester side chain at position C-13 are required for cytotoxicity. Changing the acetate at C-10 and the N-acyl substituent appear to have little effect on the activity. One of the key functional groups responsible for the ability of taxol (3) to cause microtubule assembly appears to be the hydroxyl function at C-2'.[34] This can be deduced from the fact that 2'-acetyltaxol (37) and 2',7-diacetyltaxol (36) do not promote microtubule assembly. However, in derivatives where the C-2' hydroxyl is free, a similar type of activity to taxol (3) is observed. From these studies[32] it is also apparent that the free hydroxyl at C-7 is not required for *in vitro* activity. The hydroxyl at C-7 could therefore be used to attach a hydrophilic group to improve solubility.[32] The potential of taxol (3) in cancer therapy has yet to be fully investigated and the results of further experimentation and clinical trials are eagerly awaited.

1.7 SYNTHETIC APPROACHES

Since 1980 there has been an ever increasing number of publications attempting the synthesis of the taxane series.[35] Despite the diversity of the approaches, none have yet succeeded in the total synthesis of a naturally occurring taxine. Due to the number of papers that have appeared only those that have completed the basic tricyclic skeleton are reviewed here.

The first synthesis to meet this criterion was reported by Shea and Davis[36] in 1983. The key step involved an intramolecular Diels-Alder reaction of the trienone (43) to produce the C-aromatic taxane skeleton (44).[36] The trienone (43) was prepared as outlined in Scheme 7. The

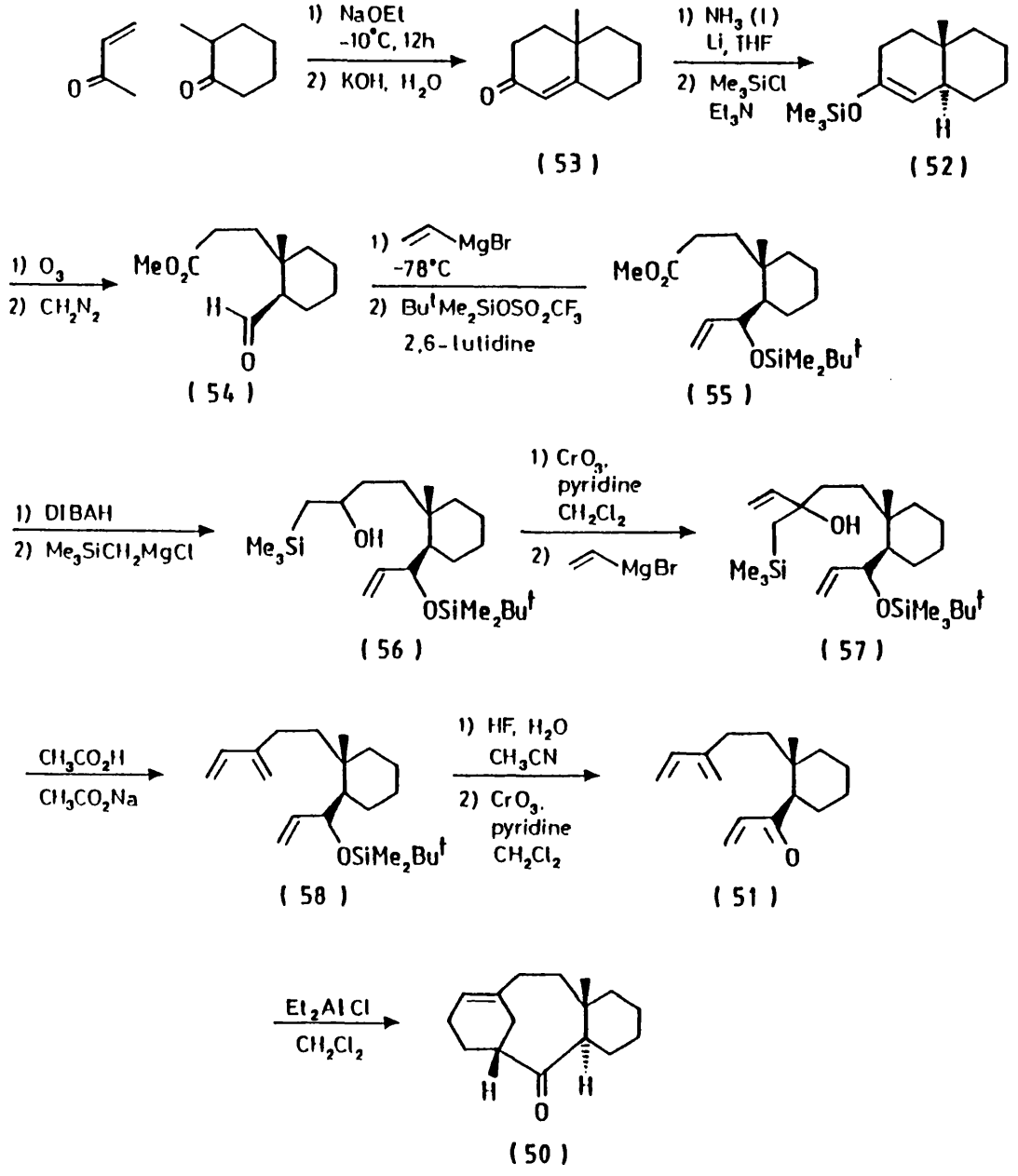
alcohol (45) was converted to the chloride (46) and reacted with the Grignard (47) to yield the diene (48). The dienophile moiety of the trienone (43) was then introduced by metallation of (48) with n-butyllithium followed by reaction with acrolein to provide the allylic alcohol (49). Oxidation of (49) furnished the trienone (43) which when heated to 155°C for 93h underwent cyclisation to form the tricyclic ketone (44).[36] Subsequently it was reported that the cyclisation could be achieved using Lewis acid catalysis under milder conditions.[37]



Scheme 7

Work carried out in this laboratory also made use of an intramolecular Diels-Alder reaction to produce the taxane skeleton (50).[38] This approach is particularly relevant as the subject of this text is a continuation of this work. The trienone (51) was constructed according

to Scheme 8.[38]



Scheme 8

The crucial trans stereochemistry of the decalin (52) was achieved by use of a lithium in ammonia reduction of the enone (53) using the method developed by Stork et al.[39] Ozonolysis of the enol ether (52) led to cleavage of the double bond and treatment with diazomethane gave the ester aldehyde (54). By performing the reaction of (54) with vinyl

Grignard at low temperature it was possible to react the aldehyde functionality in preference to the ester to produce the corresponding allylic alcohol. The alcohol functionality was then protected with a t-butyldimethylsilyl group to yield the ester (55). DIBAH reduction of the ester (55) gave the aldehyde which could then be reacted with trimethylsilylmethylmagnesium chloride to furnish the β-hydroxy silane (56). Careful Collins oxidation[40] provided the β-keto silane which was treated with vinylmagnesium bromide to yield the β-hydroxy silane (57). Peterson elimination[41] of the hydroxy silane (57) then produced the triene (58).[38]

The dienophile part of the molecule was then activated by deprotection of the alcohol functionality with hydrogen fluoride in acetonitrile followed by oxidation to give the trienone (51). The intramolecular Diels-Alder reaction was carried out using a Lewis acid catalyst to produce the tricyclic ketone (50), Scheme 8.[38]

The relative stereochemistries of C-1, C-3 and C-8 were confirmed by X-ray analysis and are the same as for the taxane natural products. The rationalisation for the stereochemistry of the cyclisation can be represented by Figure 3, where the eight-membered ring adopts the chair-boat conformation which is preferred over the alternative twist chair-boat conformation.[42]

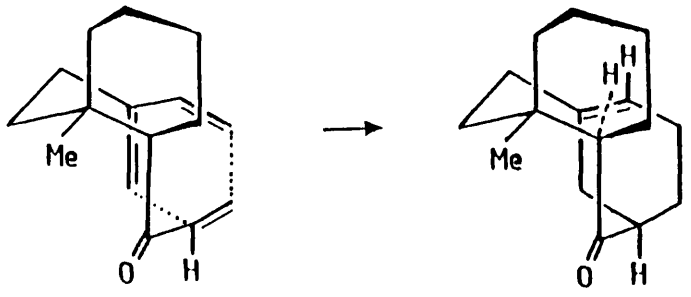
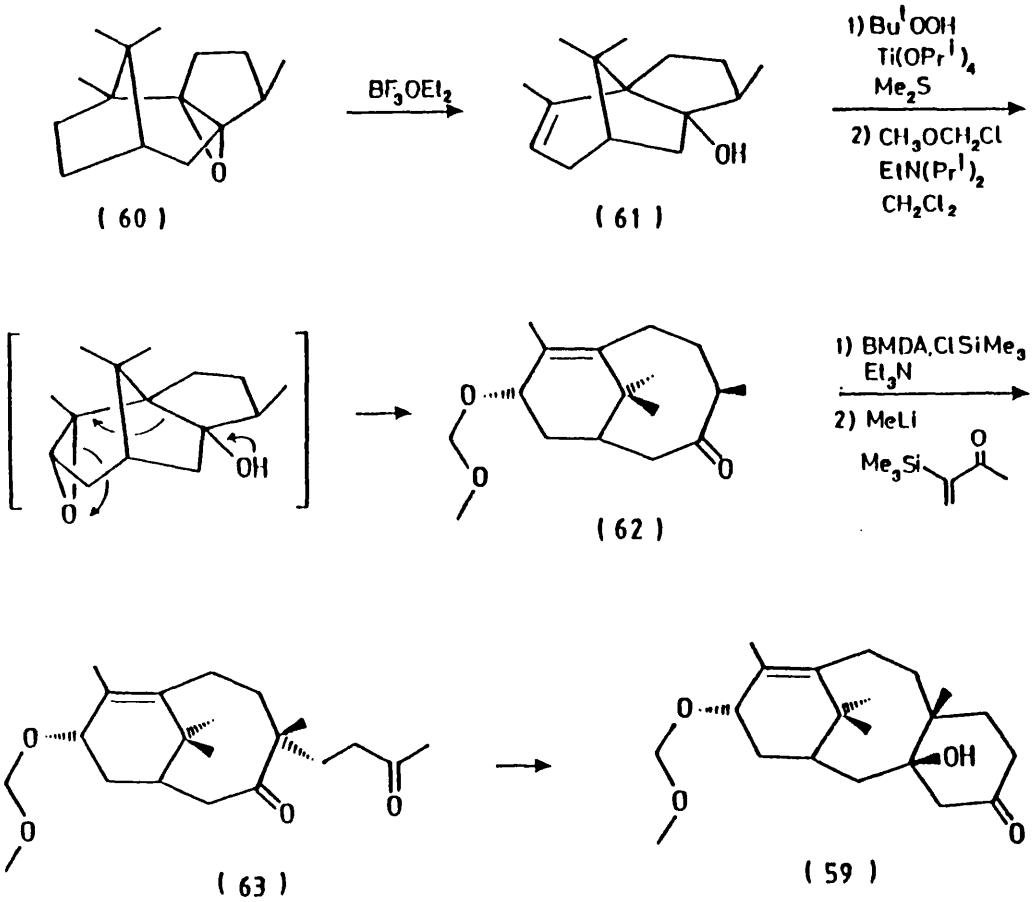


Figure 3

An alternative strategy was published by Holton[43] to produce the tricyclic alcohol (59). The sequence is outlined in Scheme 9 and used

β-patchouline oxide (60) as the starting material. The first important step in the synthesis involved the rearrangement of the alcohol (61) to form the A and B rings of the taxane skeleton. Treatment of the ketone (62) with bromomagnesium di-isopropylamide (BMDA),[44] TMS chloride and triethylamine gave exclusively the more substituted enol ether. The enolate could be regenerated by reaction with methyllithium and then reacted with 3-trimethylsilyl-3-buten-2-one to yield the diketone (63). An intramolecular aldol condensation of (63) using BMDA then gave the alcohol (59).[43]

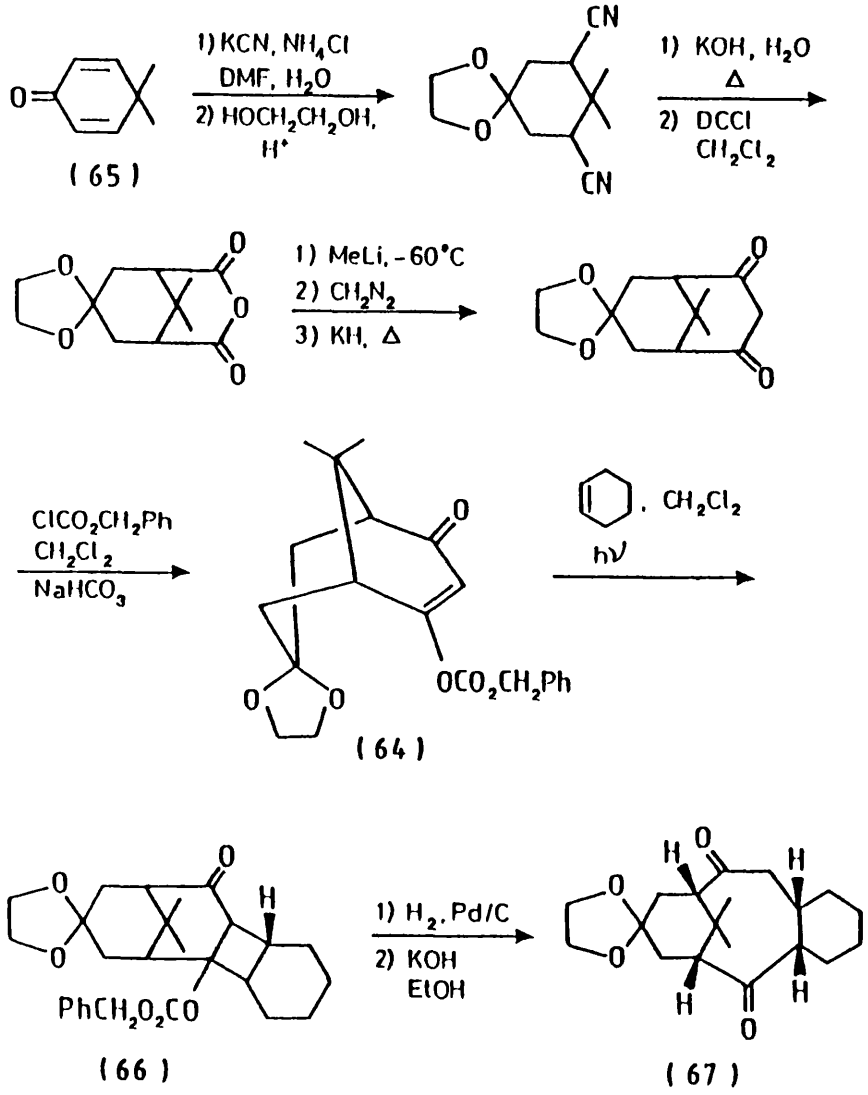


Scheme 9

This is probably one of the most advanced syntheses but the starting material (β-patchouline oxide) and possibly the rearrangement may not be very adaptable to the additional functionality that is required to

produce a complete synthesis.

A report by Neh et al.[45] used a photochemical [2+2] cycloaddition in the key step en route to forming the eight-membered ring. The enol benzoate (64) was prepared as outlined in Scheme 10 from cyclohexa-



(65) (64) (66) (67)

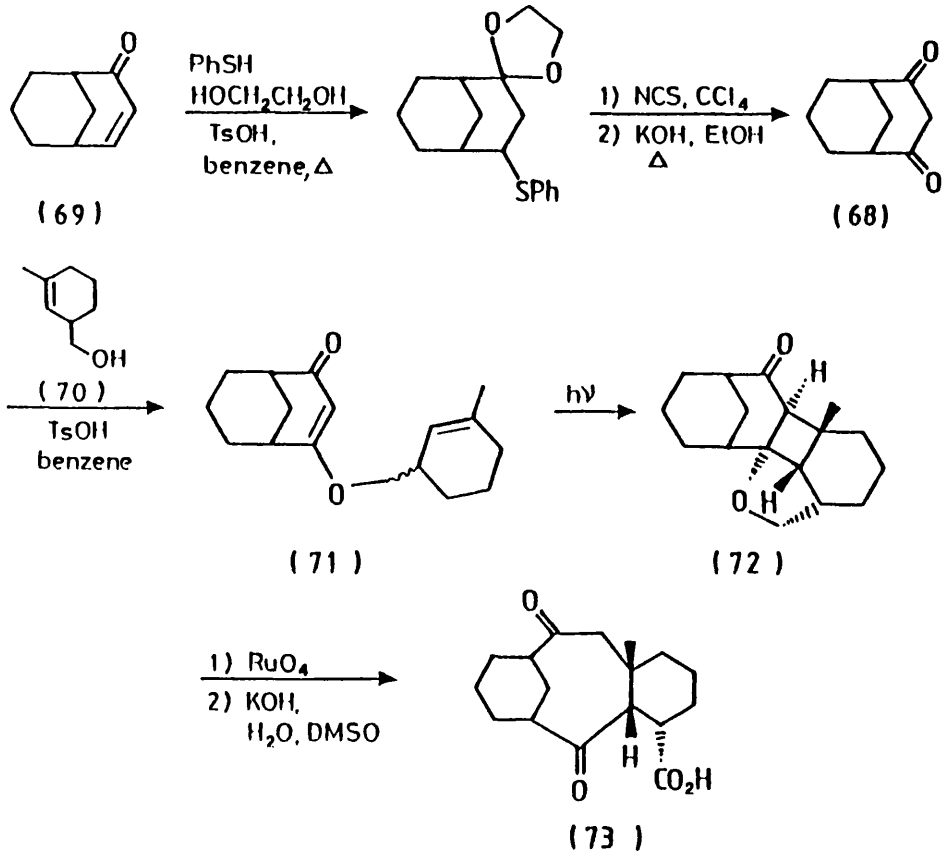
Scheme 10

dienone (65). The [2+2] cycloaddition of (64) with cyclohexene was initiated by irradiation with a mercury lamp to furnish the tetracyclic ketone (66). Hydrogenolysis of the ketone (66) led to the formation of the corresponding alcohol which, upon treatment with ethanolic potassium hydroxide solution, underwent a retroaldol reaction to give the tri-

cyclic dione (67).[45]

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.

A similar approach was reported subsequently by Kojima et al.[46] The formation of the eight-membered ring involved a [2+2] cycloaddition and then cleavage of the resultant six-four ring system. The major difference in this synthesis compared to the other photochemical approach[45] is that the [2+2] cycloaddition was carried out intramolecularly.



Scheme 11

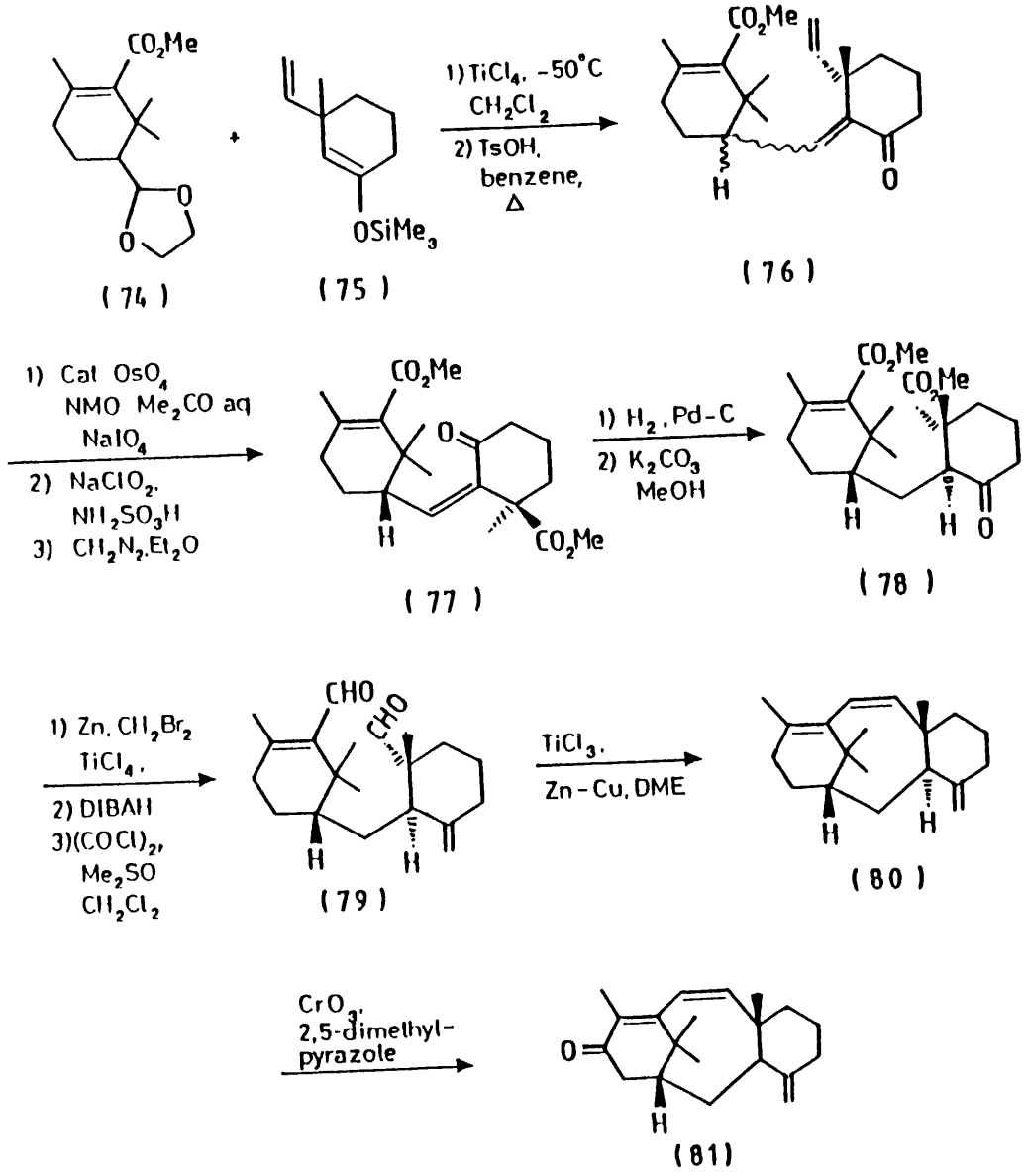
The bicyclic dione (68) was prepared according to Scheme 11 from the α,β-unsaturated ketone (69).[47] Condensation of (68) with the allylic

alcohol (70) produced the enol ether (71) as a mixture of epimers. The mixture was then irradiated with a mercury lamp to provide the cyclo-adduct (72). Only one isomer of the enol ether (71) was converted to (72); the other being recovered unchanged. A similar type of ring opening to that used previously[45] led to the tricyclic acid (73).[46]

Whilst this synthesis provides a good method of producing the tricyclic framework with some degree of functionality, it lacks the bridgehead double bond, the geminal dimethyl group and has a cis fused C ring.

A synthesis of the complete carbon framework of the taxanes was reported by Kende et al.[48] in 1986. The important steps in this synthesis involved a directed aldol condensation between the acetal (74) and the silyl enol ether (75) to yield, after the elimination of water, the enones (76), Scheme 12. The enones (76) 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 (77). Hydrogenation of (77) 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 (78). The formation of the eight-membered ring was achieved by a low valent titanium coupling reaction[49] of the dialdehyde (79) to produce the triene (80).[48] The fact that the allylic oxidation of the triene (80) with chromium trioxide and 2,5-dimethylpyrazole[50] gave the trienone (81) proved interesting since this type of oxidation could later be applied to the tricyclic skeleton prepared in Chapter 3.

This sequence provides the first total synthesis of the taxane triene with the stereochemically correct carbon framework. However, the poor stereochemical control in the formation of the enone (76) must restrict the viability of this route for further expansion.

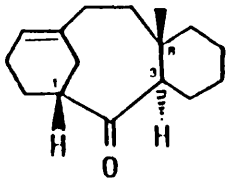

CO2Me
OSiMe3
1) TiCl4, -50°C
CH2Cl2
2) TsOH,
benzene,
Δ
(74)
(75)
(76)
1) Cat OsO4
NMO Me2CO aq
NaIO4
2) NaClO2,
NH2SO3H
3) CH2N2.Et2O
(77)
1) H2, Pd-C
2) K2CO3
MeOH
(78)
1) Zn, CH2Br2
TiCl4,
2) DIBAH
3)(COCl)2,
Me2SO
CH2Cl2
CHO
(79)
TiCl3,
Zn-Cu, DME
(80)
CrO3,
2,5-dimethyl-
pyrazole
(81)

Scheme 12

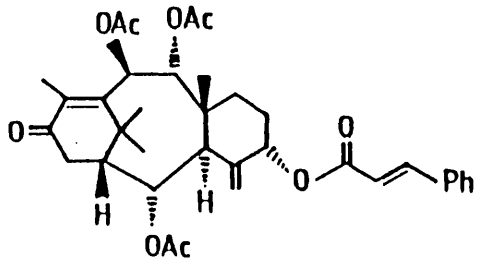
CHAPTER 2

Initial Studies in the Preparation of Highly Substituted Butadienes

The taxane model compound (50) was prepared during previous work in this laboratory.[38] Whilst it contains the tricyclic skeleton, with the correct stereochemistry at C-1, C-3 and C-8, it lacks the correct methyl group substitution found in the naturally occurring taxanes.[1] An obvious extension of this model would be to incorporate these methyl

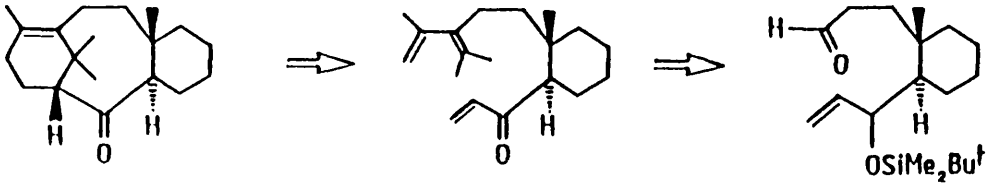


(50)



Taxinine (2)

groups. Retrosynthetic analysis of the methyl substituted model (82) suggested that it might be possible to prepare by an intramolecular Diels-Alder reaction of the trienone (83). Further disconnection of

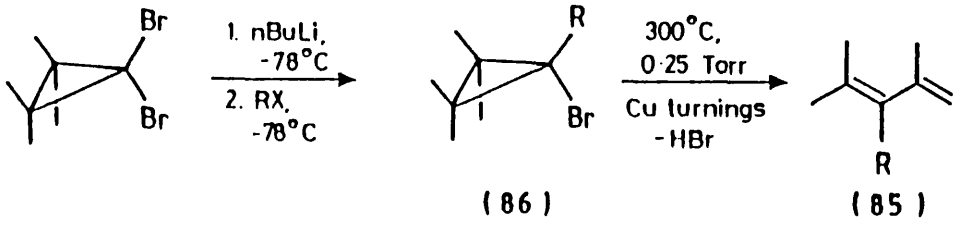


(82) (83) (84)

Scheme 13

(83) led to the known aldehyde (84).[38] One requirement for this synthesis was that the diene moiety of (83) could be constructed stepwisely from the aldehyde (84), Scheme 13.

In work carried out by Warner and Le[51] it was shown that it was possible to prepare 3-substituted-2,4-dimethyl-1,3-pentadienes (85) of the type required, Scheme 14.[51] This transformation was, however, not considered suitable since it was thought that the conditions required to open the cyclopropane ring (86) were too severe for more complicated dienes. In addition, the conversion adds one carbon to the R-chain and



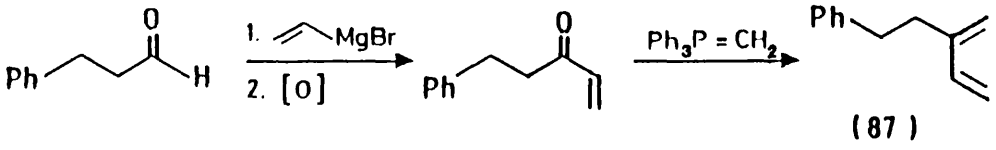
(86) (85)

Scheme 14

would, therefore, not be compatible with the existing route.[38]

Unfortunately, no suitable alternatives exist in the literature for the stepwise synthesis of highly substituted dienes from an aldehyde. Some early attempts to overcome this problem are set out below.

Initial studies were carried out using readily available commercial aldehydes as model compounds. It was thought that it might be possible to prepare the required diene using a Wittig reaction on an α,β-unsaturated ketone. Recently Danheiser et al.[52] reported the use of methylenetriphenylphosphorane to prepare the 3-substituted diene (87), Scheme 15.[52]

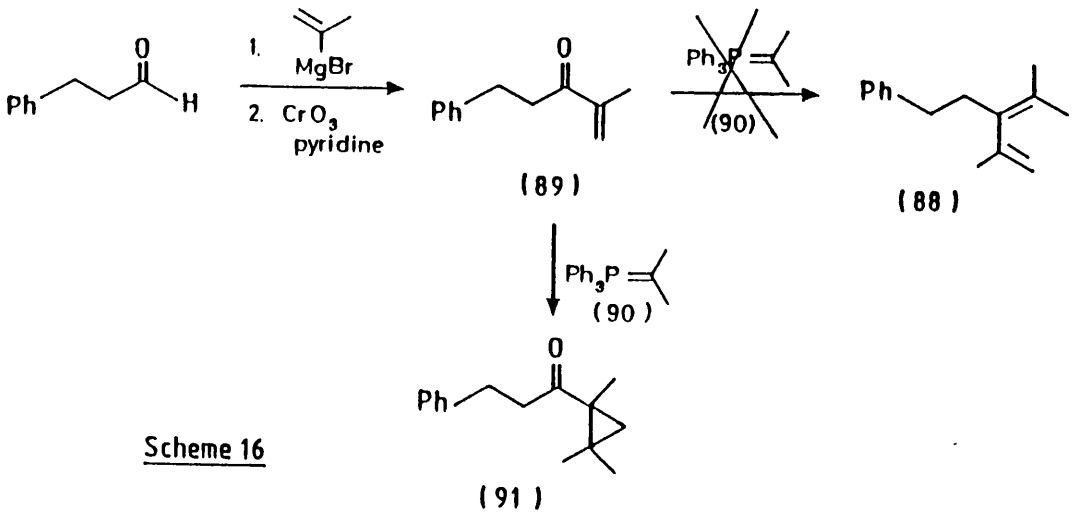


(87)

Scheme15

Scheme 16 shows the proposed route to the diene (88) using an adaptation of the existing sequence.[52] 3-Phenylpropanal was reacted with 2-propenylmagnesium bromide, prepared from 2-propenylbromide and magnesium, to yield the corresponding allylic alcohol. The allylic alcohol was then added in one portion to a Collins solution,[40] prepared in situ,[53] at room temperature. After 5 minutes the solution was filtered through a short silica column to remove the chromium residues. The product was purified by flash chromatography to provide the enone

(89) in 69% yield, Scheme 16. It was hoped that treatment of the



Scheme 16

enone (89) with isopropyltriphenylphosphorane (90), generated from isopropyltriphenylphosphonium iodide and butyllithium, would produce diene (88). However, the only products that could be isolated from the reaction were the cyclopropane (91) and triphenylphosphine.

The formation of the cyclopropane (91) presumably occurred from the 1,4-addition of the phosphorane (90) to the enone (89), probably due to the increased steric bulk of both the enone and the ylid compared to the literature example.[52] The resulting enolate (92) then cyclised eliminating triphenylphosphine to furnish the cyclopropane (91), Figure 4.

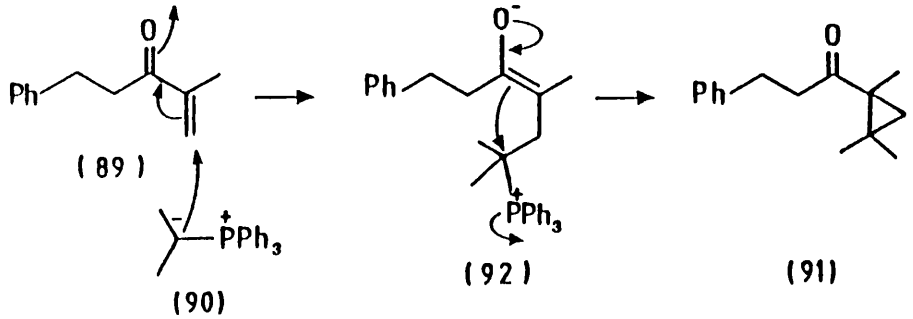
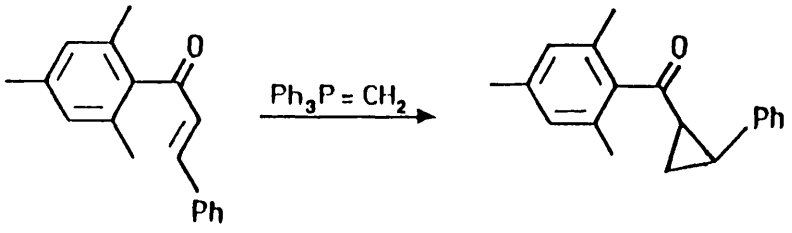


Figure 4

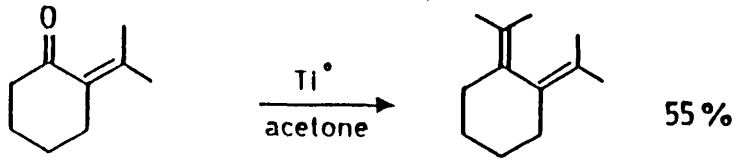
It is well known that phosphorus ylids can undergo 1,4-addition to α,β-unsaturated esters,[54] this fact being exploited in the synthesis

of chrysanthemic acid.[55] The 1,4-addition to ketones, however, appears less common[56] and is restricted to highly hindered ketones. An example is illustrated by the formation of cyclopropane (93) from the reaction of methylenetriphenylphosphorane and the α,β-unsaturated ketone (94).[57]



(94) (93)

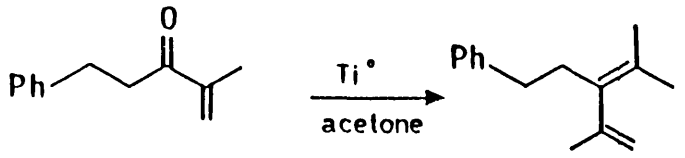
An alternative to the Wittig reaction in the construction of an olefin could be a low valent titanium coupling reaction.[49,58,59] McMurry et al. has developed the use of active titanium(0) to reductively couple two carbonyl compounds to give an olefin. Low valent titanium can also be employed in the reduction of diols to olefins.[59] The active titanium(0) is generated in situ from the reduction of titanium trichloride usually with lithium or potassium.[59] The method is most useful when two identical ketones are coupled, however, mixed couplings are possible particularly if one ketone is used in excess.[58] The viability of this method to prepare highly substituted olefins is illustrated by the reaction of the enone (95) with an excess of acetone in the presence of active titanium(0) to produce diene (96).[58]



(95) (96)

The enone (89) and acetone, in a ratio of 1:4, were reacted with titanium(0) according to the literature procedure.[58] T.l.c. showed a large number of products of which only one could be isolated cleanly. The

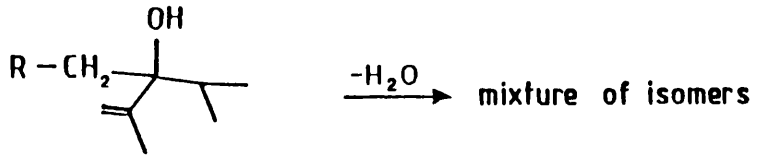
structure of this product was assigned to be that of the required diene (88) but the yield was very poor. The diene (88) was prepared



(89) (88)

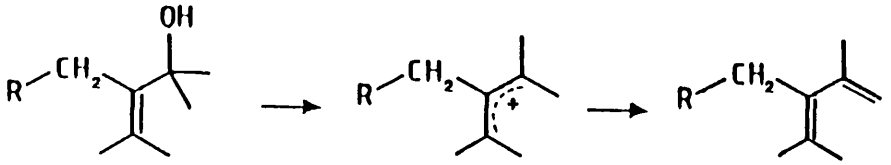
subsequently by an alternative procedure (Chapter 3) and had spectral characteristics identical to that prepared here. Despite repeating the reaction no improvement in the yield was made so this method was abandoned and an alternative sought.

The elimination of water from an intermediate of type (97) led to a mixture of regioisomers.[60] However, the elimination of water from an



(97)

intermediate of type (98) can only give one regioisomer since the resulting carbonium ion is degenerate, Scheme 17.

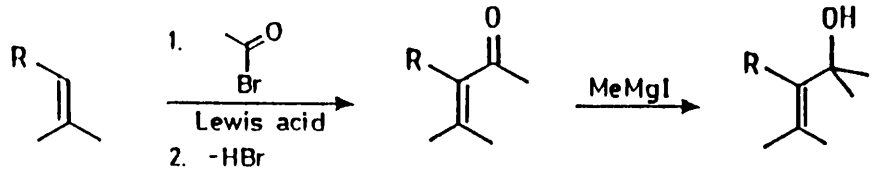


(98)

Scheme 17

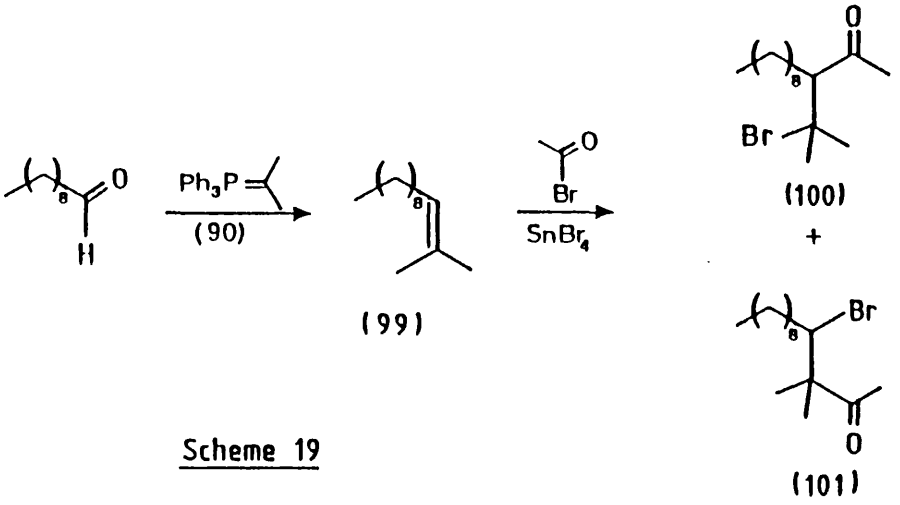
It was thought that this type of intermediate might be prepared by a Friedel-Crafts acylation of an olefin[61] with acetylbromide followed by dehydrobromination and addition of methyl Grignard, Scheme 18.

Decanal was reacted with isopropyltriphenylphosphorane (90), generated by treatment of isopropyltriphenylphosphonium iodide with



Scheme 18

butyllithium, to furnish the olefin (99) in 67% yield. When the olefin (99) was reacted with acetylbromide in the presence of tin(IV) bromide,[61] a mixture of three products was isolated. The first (46%) was thought to have arisen from the addition of hydrogen bromide across the double bond. The other two products were a result of the required Friedel-Crafts reaction but were a mixture of regioisomers in a ratio of 2:1. The two products were difficult to separate by flash chromatography and it was only possible to isolate the upper fraction pure. It would be predicted that the ketone (100) would be the major product since it is

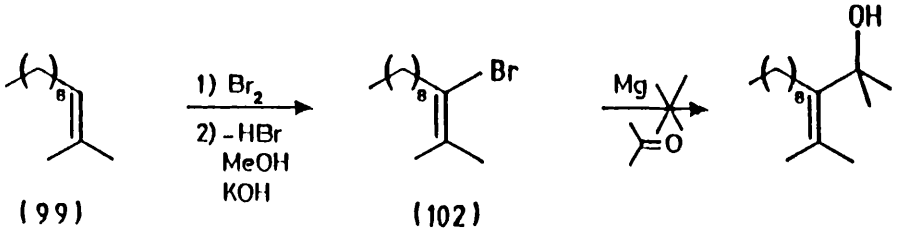


Scheme 19

formed via a tertiary carbonium ion whereas the ketone (101) is formed via a secondary carbonium ion. N.m.r. evidence also supports (100) being the major isomer, on a chemical shift basis: H-3 of the ketone (100) has an observed position of δ3.06 and a predicted position of δ2.5. For isomer (101) the predicted position for H-4 is δ4.1 and the observed δ4.88. The poor regioselectivity and a seemingly unavoidable

side reaction of the starting material led to the abandonment of this route.

An alternative idea with the same type of intermediate in mind could be envisaged if it were possible to make the vinyl Grignard of the vinyl bromide (102) and add this to acetone, as shown in Scheme 20.



(99) (102)

Scheme 20

The vinyl bromide (102) was prepared by bromination of the olefin (99) with bromine in carbon tetrachloride followed by dehydrobromination using potassium hydroxide in methanol.[62] Despite all attempts at activating the magnesium,[63] including using magnesium formed by the reduction of magnesium chloride with potassium,[64] no success was obtained in forming the Grignard of (102).

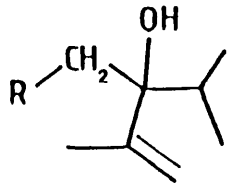
At this point it was decided to adopt a different approach using silicon chemistry to direct the regiochemistry in the formation of the diene.

CHAPTER 3

Synthesis and Diels-Alder Reactions of Highly Substituted Butadienes

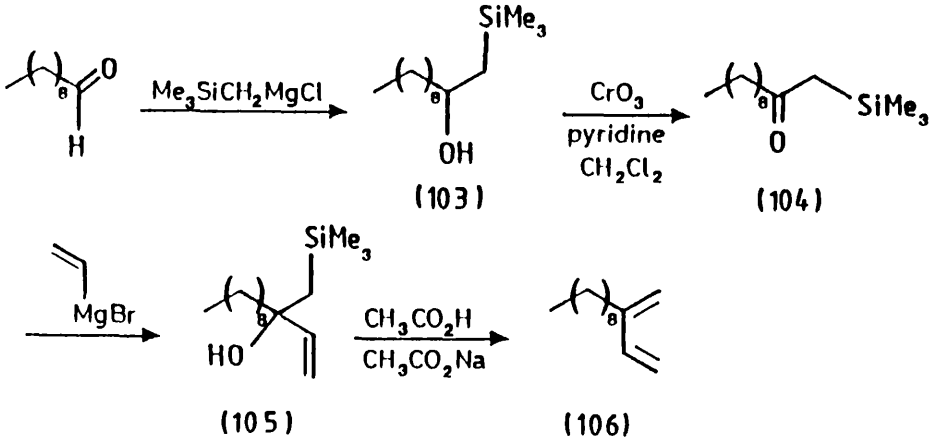
3.1 INTRODUCTION

In order to avoid the poor regiochemistry that arises from the dehydration of the species (97)[60] the inclusion of a group to control the direction of the elimination was necessary. Previous studies carried



(97)

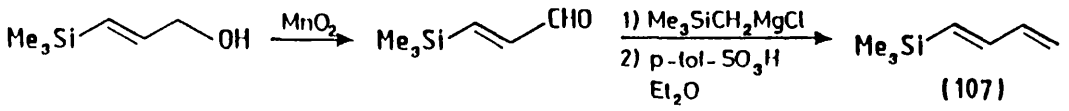
out in this laboratory[60,65] have shown the viability of using the TMS group to control the regiochemistry in the synthesis of 2-substituted 1,3-butadienes. Addition of trimethylsilylmethylmagnesium chloride to decanal produced the β-hydroxy silane (103) which was then carefully oxidised using a Collins solution,[40] prepared *in situ*,[53] to yield the β-keto silane (104). Reaction of this β-keto silane (104) with vinylmagnesium bromide gave the β-hydroxy silane (105) which upon treatment with acetic acid saturated with sodium acetate underwent a Peterson elimination[41] to provide the diene (106), Scheme 21.[60,65]



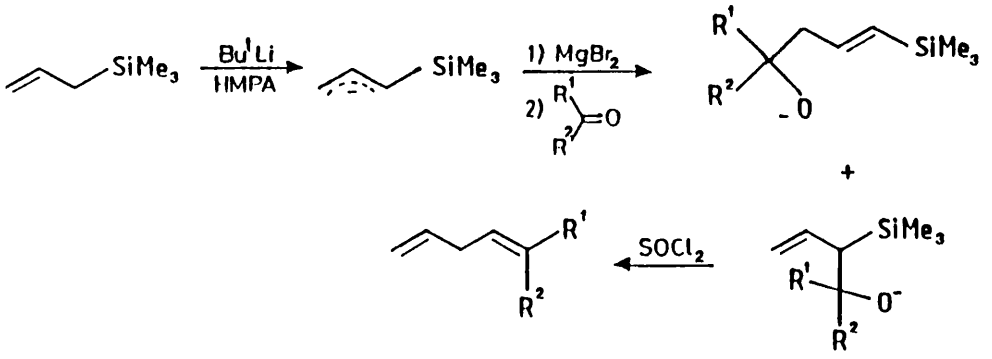
Scheme 21

Although the Peterson elimination has been used in the synthesis of 1-trimethylsilylbutadiene (107), Scheme 22,[66] and other 1-substituted

butadienes, Scheme 23,[67] the above appears to be the first example



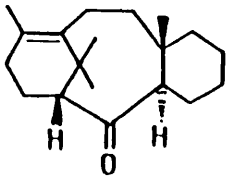
Scheme 22



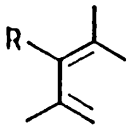
Scheme 23

where a TMS group caused double bond formation to take place in one arm of a branching carbon framework leading to a single diene.

In order to prepare the taxane model compound (82) [Chapter 2, Scheme 13] it was necessary to extend the above diene synthesis to enable the preparation of a tetra-substituted butadiene of type (108).



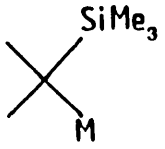
(82)



(108)

3.2 THE USE OF THE PETERSON ELIMINATION IN THE SYNTHESIS OF HIGHLY SUBSTITUTED BUTADIENES

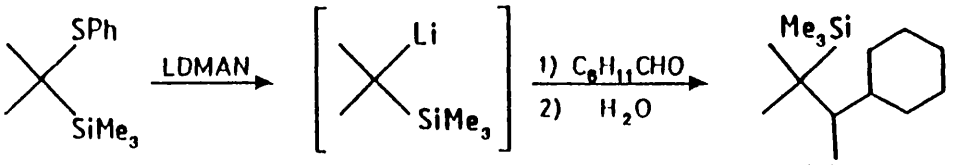
In order to extend the synthesis shown in Scheme 21 to incorporate the methyl group substitution of the diene (108) a 2-metallo-2-trimethylsilylpropane (109) was required. A search of the literature revealed



M = MgX or Li

(109)

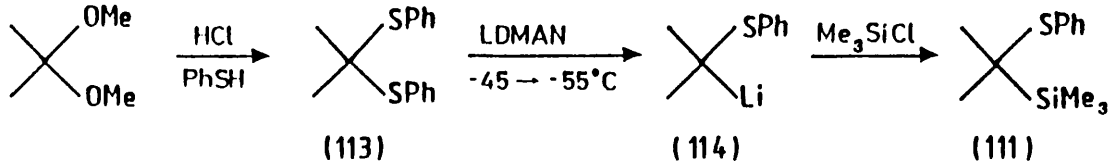
no references to the corresponding Grignard. However, the 2-lithio-2-trimethylsilylpropane (110) has been generated by reductive lithiation of the α-(phenylthio)silane (111) with lithium(dimethylamino)naphthalenide (LDMAN).[68] The α-lithiosilane (110) was then reacted with cyclohexanecarboxaldehyde to produce the β-hydroxy silane (112), Scheme 24.[68]



(111) (110) (112)

Scheme 24

2,2-Di(phenylthio)propane (113) was prepared from 2,2-dimethoxypropane and thiophenol in the presence of hydrogen chloride gas according to the literature procedure.[69] Treatment of 2,2 di(phenylthio)propane (113) with LDMAN, generated from lithium and dimethylaminonaphthalene at between -45°C and -55°C for 3h, reductively cleaved the carbon-sulphur bond to afford the 2-lithio-2-thiophenylpropane (114), which was then trapped with TMS chloride to yield the α(phenylthio)silane (111), Scheme 25.[68]



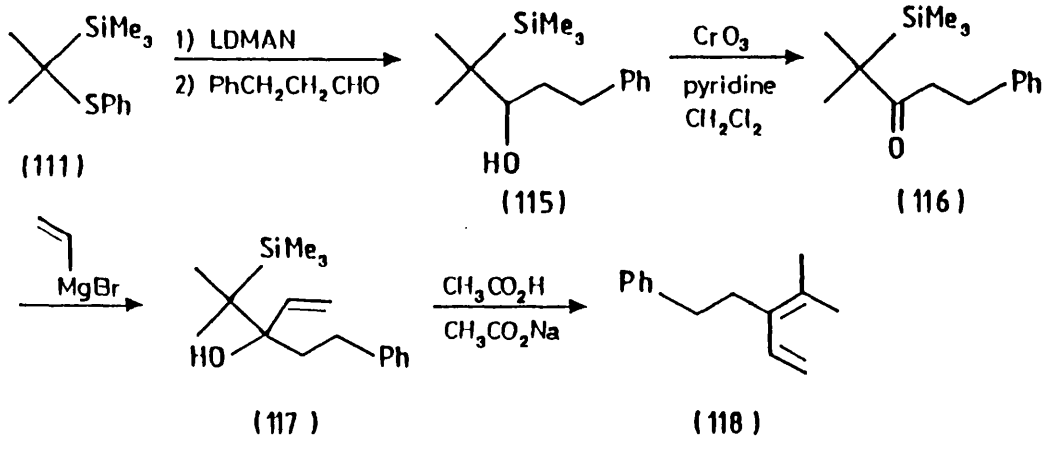
(113) (114) (111)

Scheme 25

α(Phenylthio)silane (111) was treated with a further amount of LDMAN to produce alkyl lithium (110) which was then reacted with 3-phenyl-

propanal to provide, after work-up and flash chromatography, the β-hydroxy silane (115) in moderate yield (59%), Scheme 26. Although the yield tended to vary somewhat between 15% and 59% and the product always required careful purification. The reductive lithiation provided a means of obtaining tertiary α-lithiosilanes which are not generally available by deprotonation or other exchange procedures.[68]

By using a method previously described by Hudrlik and Peterson[70] for the oxidation of β-hydroxy silanes it was possible to oxidise the β-hydroxy silane (115) without any desilation. If (115) was added to a preprepared solution of the Collins reagent,[53] the deep red colouration



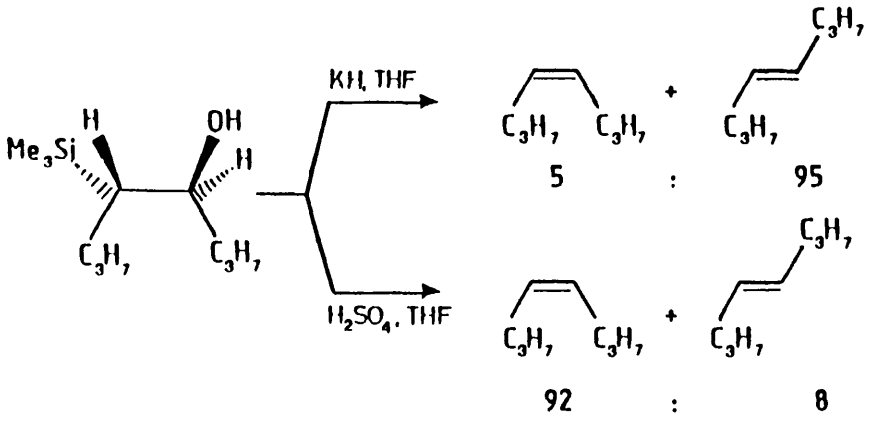
(111) (115) (116) (117) (118)

Scheme 26

was immediately discharged. The mixture was then filtered through a short silica column to produce the β-keto silane (116) in 84% yield. Treatment of the β-keto silane (116) with vinylmagnesium bromide in THF under reflux conditions for 45 minutes furnished an inseparable mixture of starting material (116) and the β-hydroxy silane (117) in a ratio of 1:9 by ^{1}H n.m.r.

The Peterson elimination[41] can be carried out under either acidic or basic conditions.[71] The different mechanisms for the two types of conditions can, with the appropriate substrate, lead to the formation of

either cis or trans olefins, Scheme 27.[72] Under acidic conditions the

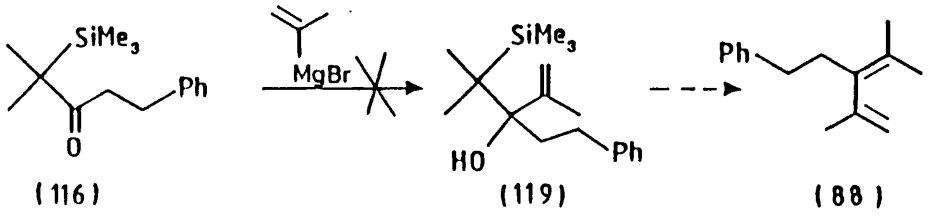


Scheme 27

elimination takes place in an anti fashion while under basic conditions a syn elimination takes place.

Using acidic conditions,[73] the crude β-hydroxy silane (117) [contaminated with 10% β-keto silane (116)] was heated with glacial acetic acid saturated with sodium acetate at 50°C for 1h. After work-up and flash chromatography the diene (118) was obtained, Scheme 26. ^{1}H and ^{13}C n.m.r. showed no evidence of any regioisomers and the sequence had been carried out in 34% overall yield from 3-phenylpropanal.

It was originally thought that by reacting the β-keto silane (116) with 2-propenylmagnesium bromide instead of vinylmagnesium bromide it would be possible to prepare the β-hydroxy silane (119), which could then be reacted under Peterson elimination conditions to produce the diene (88), Scheme 28. Treatment of the β-keto silane (116) with 2-propenylmagnesium bromide, prepared from 2-bromopropene and magnesium,

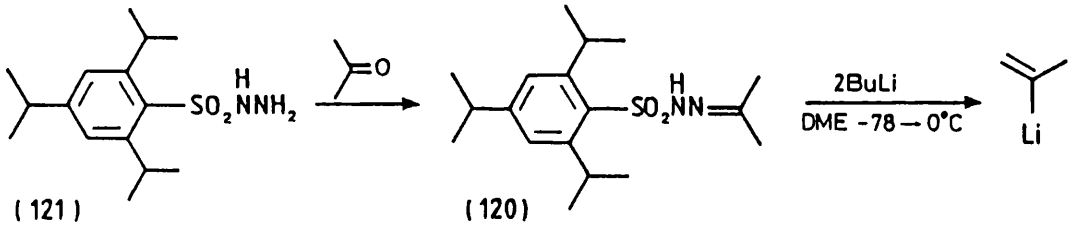


(116) (119) (88)

Scheme 28

failed to produce the β-hydroxy silane (119), even after prolonged reflux. All that was isolated from the reaction was starting material (116), together with a small amount of unidentified decomposition products. Since the β-keto silane (116) is a hindered ketone it is assumed that the increased steric bulk of the propenyl Grignard was preventing the reaction.

Propenyl lithium was an obvious alternative to the use of propenyl Grignard and it could be generated by the Shapiro reaction.[74] The trisyl hydrazone (120) was prepared from the corresponding hydrazine (121) and acetone at 0°C for ½h.[75] The reaction of hydrazone (120) with two equivalents of n-butyllithium brought about a Shapiro reaction to produce 2-propenyl lithium, Scheme 29.

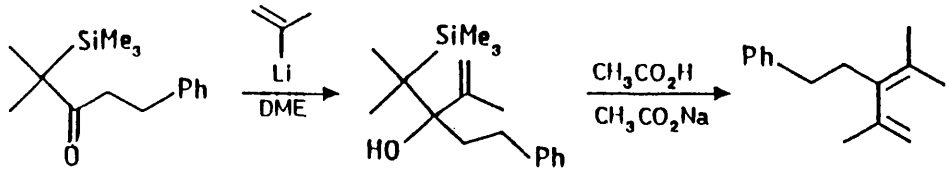


(121) (120)

Scheme 29

When the β-keto silane (116) was reacted with 2-propenyl lithium, generated by the above procedure, the β-hydroxy silane (119) was produced in 76% yield. The β-hydroxy silane (119) was then heated at 50°C for 4h in glacial acetic acid saturated with sodium acetate,[73] after work-up and flash chromatography the tetra-substituted diene (88) was isolated, Scheme 30. As in the preparation of the diene (118), n.m.r. showed no evidence that any regioisomers had been formed. The overall yield of the diene (88) was 30% from 3-phenylpropanal.

2-Lithio-2-trimethylsilylpropane (110) was prepared as before, by reductive lithiation of the α(phenylthio)silane (111) with LDMAN, and reacted separately with benzaldehyde and phenylacetaldehyde. In each

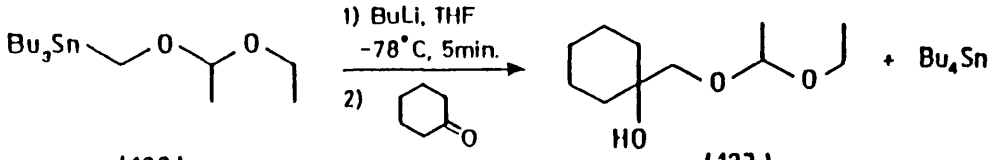


(116) (119) (88)

Scheme 30

case t.l.c. showed a large number of products of which only naphthalene, reported to arise from the decomposition of LDMAN,[76] was identified.

It was felt that in order to improve the reliability and the yield, a more efficient way of generating anion (110) was required. It is known that n-butyllithium can cleave carbon-tin bonds to produce the corresponding alkyl lithium.[77] An example of this was demonstrated by Still[78] when alkoxystannane (122) was treated with n-butyllithium and the resultant anion reacted with cyclohexanone to yield the mono-protected diol (123).[78] It was thought that this type of transmetalla-

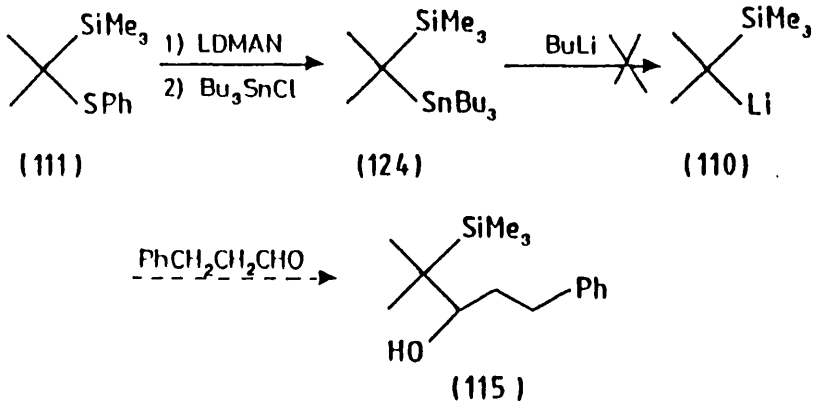


(122) (123)

tion might provide a means by which the anion (110) could be prepared in a more reliable way. It is, however, worth noting that Still[78] failed to generate a tertiary α-alkoxy anion by transmetallation of the corresponding stannane with n-butyllithium. Also (trimethylsilylmethyl)-tributyltin was found unreactive towards n-butyllithium in hexane,[79] nevertheless, it was still considered worthwhile to try the transmetallation.

2-Lithio-2-trimethylsilylpropane (110), generated in the usual way, was trapped with tributyltinchloride to produce the stannane (124). It was thought that treatment of the stannane (124) with n-butyllithium might regenerate the anion (110) which could then be reacted with 3-

phenylpropanal to yield the β-hydroxy silane (115), Scheme 31.



Scheme 31

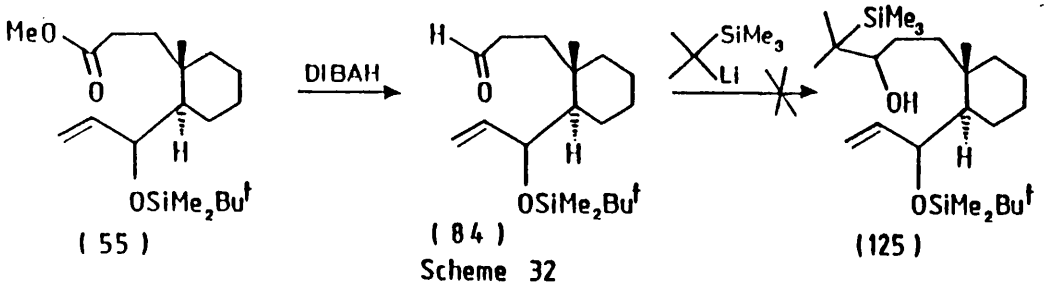
Unfortunately, attempts to produce transmetallation of (124) failed and resulted in the re-isolation of starting material (124) along with the product of n-butyllithium attack on 3-phenylpropanal. Table 2 gives a brief summary of the solvent, reaction time (to bring about the exchange) and the temperature used.

TABLE 2

Solvent	Reaction Time	Temperature	Result
THF	15 minutes	-78°C	No transmetallation
THF	"	-35°C	"
THF	1 hour	0°C	"
DME	"	0°C	"

As already stated the main aim for preparing these substituted dienes was to provide a route to the trienone (83), Scheme 13 [Chapter 2]. Despite the limited success encountered in the addition of anion (110) to aldehydes it seemed prudent to try the reaction with the aldehyde (84). If the addition was successful and produced the corresponding β-hydroxy silane (125), it should then be possible, by applying a similar sequence used to prepare the diene (88), to produce the trienone (83).

The aldehyde (84) was prepared by DIBAH reduction[80] of the ester (55).[81] 2-Lithio-2-trimethylsilylpropane (110) was prepared in the usual way, from α-(phenylthio)silane (111) and LDMAN, then reacted with the aldehyde (84), Scheme 32. T.l.c. showed a number of products and



(55) (84) (125)

Scheme 32

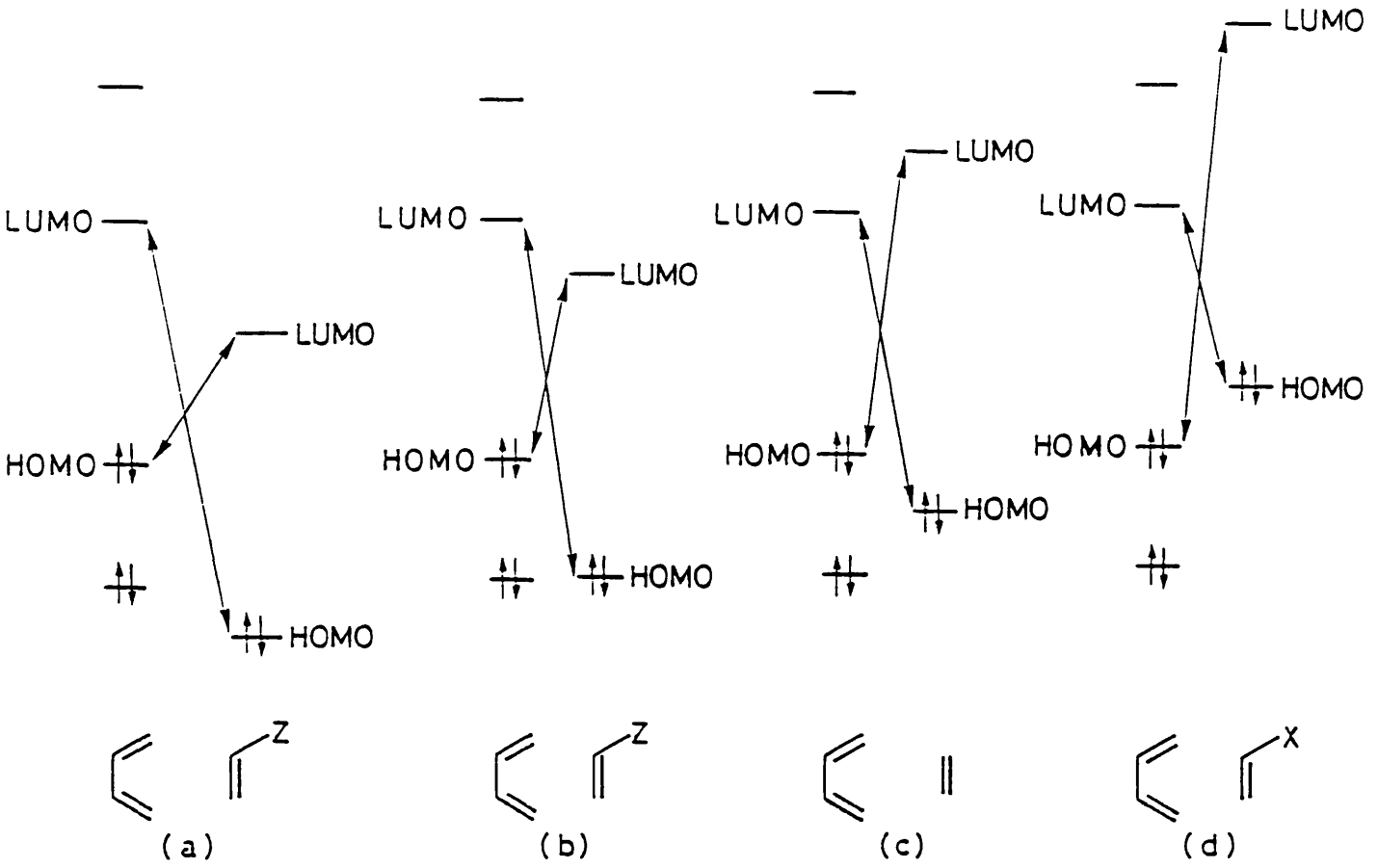
after flash chromatography the main fraction isolated showed a hydroxyl and a carbonyl absorption in the i.r. The ^{1}H n.m.r. also leads to the tentative suggestion that this product resulted from an aldol condensation of (84). This implies that the anion (110) acted as a base rather than a nucleophile to bring about this condensation.

Before trying to develop a more general method for the preparation of these highly substituted dienes, it was deemed worthwhile to undertake a study of the Diels-Alder reactions of the two dienes already prepared.

3.3 THE DIELS-ALDER REACTION

In its simplest form, the Diels-Alder reaction of butadiene and ethylene, the former contributes 4π electrons and the latter 2π electrons. From Figure 5 it can also be seen that the phases on the orbitals allow overlap from the same side of each component, i.e. suprafacially. The Diels-Alder reaction is therefore classified as a [π4s + π2s] cycloaddition.[82]

Figure 6 shows how substituents on the dienophile can vary the energy difference between the HOMO and LUMO and therefore affect



A dienophile with a Lewis acid catalyst.

A dienophile with a low-energy LUMO.

A dienophile with neither a low-energy LUMO nor a high-energy HOMO.

A dienophile with a high-energy HOMO.

Z = electron withdrawing, e.g. CHO, NO_2.
X = electron donating, e.g. OMe, NMe_2, Me.

Figure 6

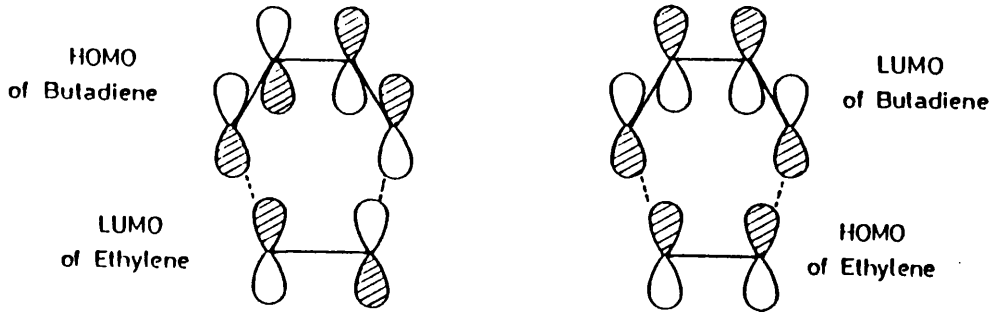


Figure 5

which interaction becomes important. A normal Diels-Alder involves an electron-deficient dienophile and an electron-rich diene, Figure 6b. The important frontier orbital interaction is between the HOMO of the diene and the LUMO of the dienophile since they are closest in energy. By using a Lewis acid it is possible to lower the energy of the LUMO (and HOMO) of the dienophile so making the energy separation between the HOMO of the diene and the LUMO of the dienophile still smaller, thereby increasing the rate of reaction, Figure 6a. In contrast, if the dienophile has an electron-donating group, Figure 6d, the most important interaction is now between the LUMO of the diene and the HOMO of the dienophile; this is then termed a reverse electron demand Diels-Alder.[82]

Substituents on the diene also effect the energies of the HOMO and LUMO of the diene. The result is similar to that observed for the dienophile in that electron-withdrawing groups lower the energies of the HOMO and LUMO. Electron-donating groups raise the energies of both the HOMO and LUMO.[82]

In the Diels-Alder reaction between maleic anhydride and cyclopentadiene there are two possible products; the endo (126) and the exo (127), which could be formed depending on the transition states, Figure 7.[83] According to Alder's endo rule, the most stable transition state is where there is *"maximum accumulation of double bonds"* and therefore the

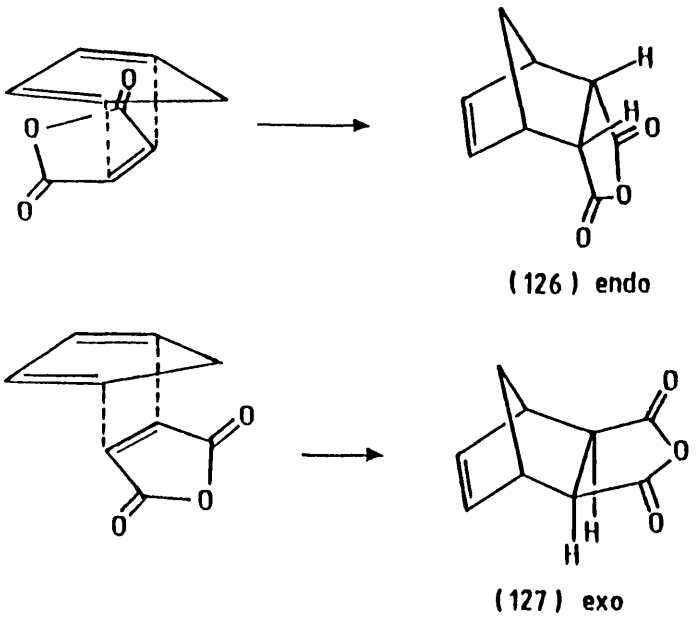


Figure 7

endo product predominates. This can be rationalised as a stabilisation of the endo transition state by a secondary orbital interaction, as shown in Figure 8, for the reaction of maleic anhydride and cyclopentadiene.[82,83]

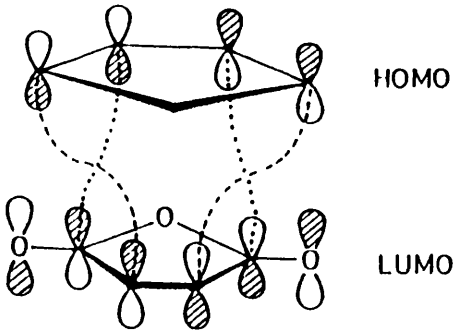
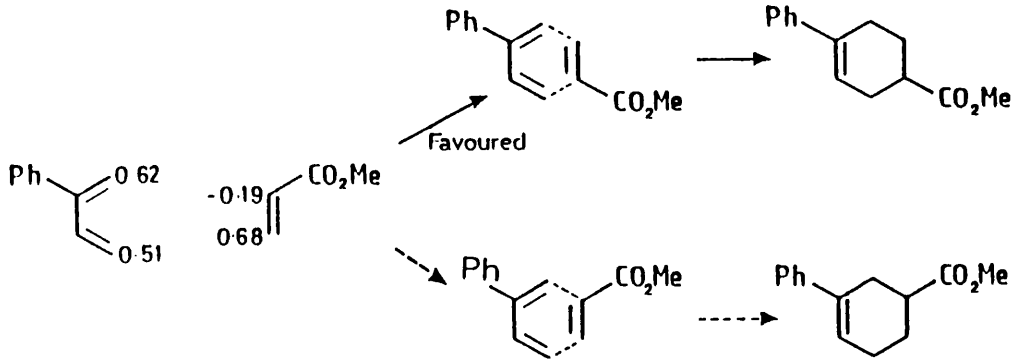


Figure 8

The regioselectivity is governed by the orbital coefficients, the atom with the larger coefficient on the dienophile interacts preferentially with the larger coefficient of the diene, Scheme 33.[82,83] Lewis acids not only affect the rate of Diels-Alder reactions, they can also alter the exo/endo selectivity and the regioselectivity since they affect

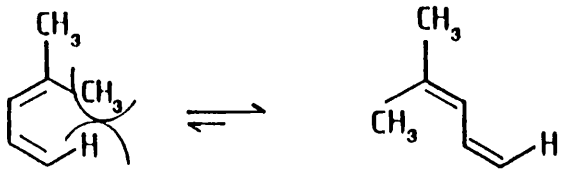


Scheme 33

the orbital coefficients.[84]

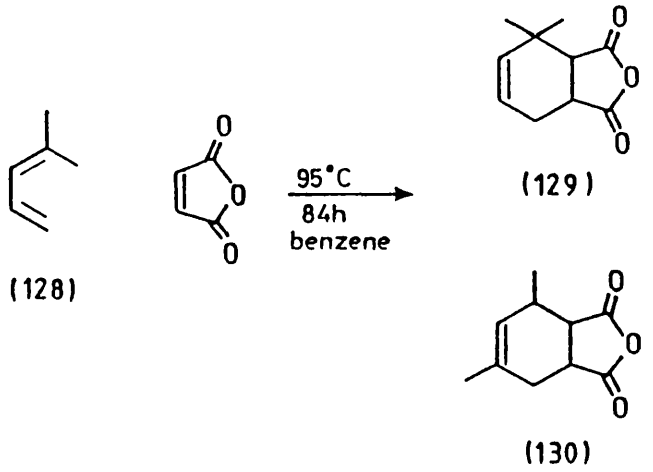
There is still a certain amount of controversy concerning the precise mechanism for the Diels-Alder reaction.[85] Evidence exists for both a concerted addition[86] in which both new bonds are formed at the same time and a two-step process involving a Zwitterion,[87] a biradical intermediate,[88] or a radical ion pair.[89] Most of the evidence for a non-concerted mechanism appears to be from special cases where the diene and/or the dienophile are highly functionalised to stabilise an intermediate radical or ion. In the majority of cases the results obtained can be best explained by a symmetry allowed one-step mechanism.[85]

It is often stated that 1,1-disubstituted butadienes are unreactive in the Diels-Alder reaction.[83,90] The reason given for this is that a bulky group in the cis 1-position sterically hinders the formation of the cisoid conformation (128a), which is required for reaction to take place, and therefore leads to this conformation being disfavoured relative to the transoid (128b).[83]



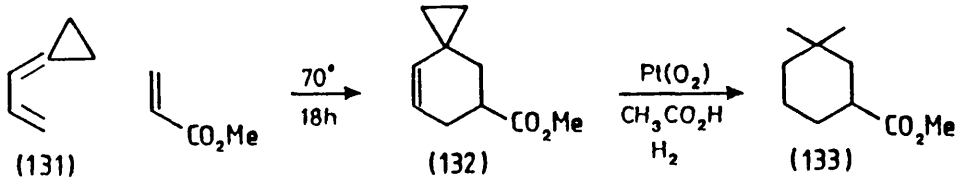
(128a) (128b)

Often when such dienes are reacted under forcing conditions an isomerization takes place before the Diels-Alder reaction thus leading to a mixture of products. An example illustrating this idea is the reaction of the 1,1-disubstituted diene (128) with maleic anhydride to produce the expected adduct (129) and the adduct (130).[91] The formation of (130) results from rearrangement of the diene (128) prior to reaction.



(128) (129) (130)

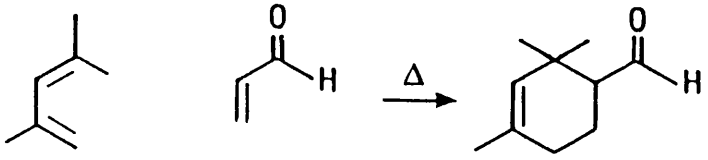
Krief and Zutterman[92] describe a way of improving the reactivity of 1,1-disubstituted dienes and avoiding problems of rearrangements by incorporating the methyl groups into a cyclopropane ring. The cyclopropane (131) was reacted with methylacrylate to give the cyclohexene (132) and then hydrogenation generated the dimethyl cyclohexane (133), Scheme 34.[92]



(131) (132) (133)

Scheme 34

Of the few examples of 1,1-disubstituted dienes undergoing Diels-Alder reactions the reaction of the diene (134) with acrolein appears to be an exception as the expected adduct (135) is produced in good

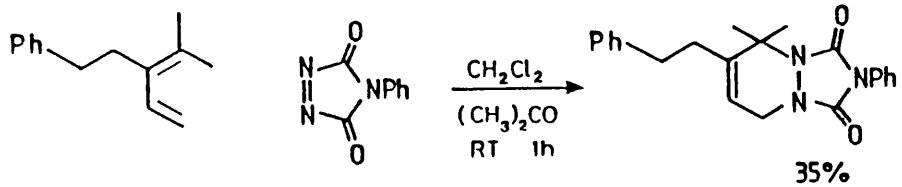


(134) (135)

yield.[93] This suggests that the methyl group at the C-3 of the butadiene fragment improves the reactivity of (134). It was thought that this fact could be investigated by studying the Diels-Alder reactions of the dienes (118) and (88).

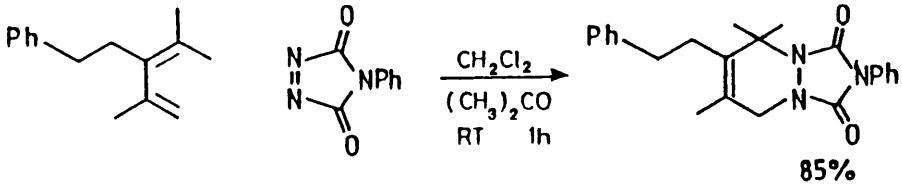
3.4 DIELS-ALDER REACTIONS WITH DIENES (118) AND (88)

Initially it was decided to try the reactions of the dienes (118) and (88) with the highly reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (136) [Cookson's dienophile].[94,95] Both the dienes (118) and (88) reacted with Cookson's dienophile at room temperature over the period of 1h. The diene (118) reacted to produce the white crystalline solid (137) in 35% yield. The diene (88) reacted in better yield (85%) to give the



(118) (136) 35% (137)

white crystalline solid (138).

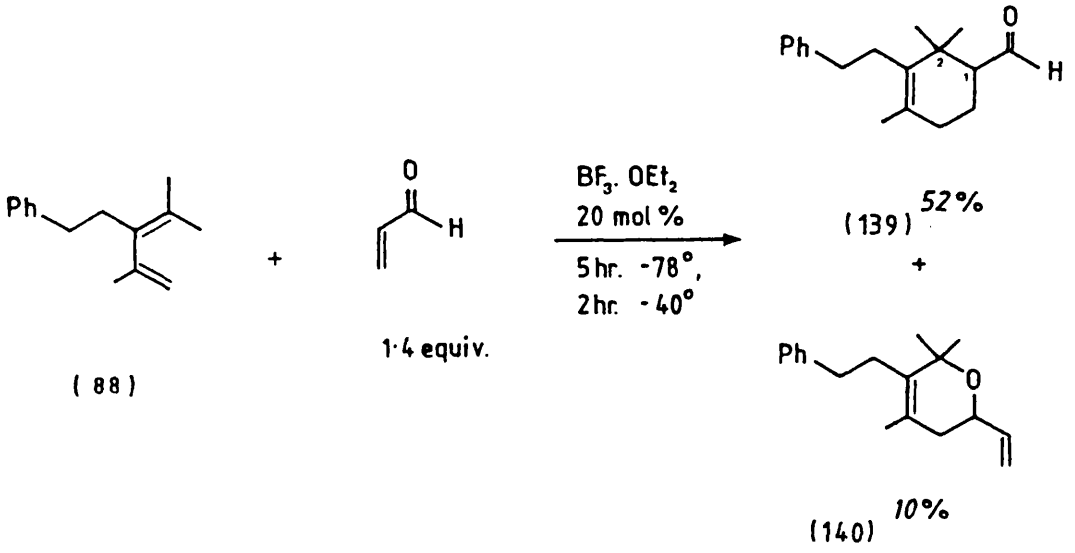


(88) (136) 85% (138)

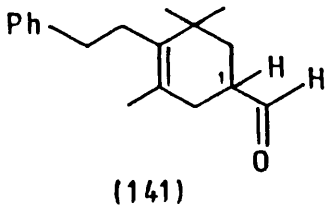
Gratified that both dienes were undergoing Diels-Alder reactions, albeit with a highly reactive dienophile, it was decided to find conditions in which they could be reacted with acrolein.

Initially the diene (88), acrolein and a small amount of hydroquinone

were heated at 130°C in toluene overnight. T.l.c., however, showed very little change, so rather than pursue the thermal reaction, Lewis acid catalysed conditions were adopted. Small scale test reactions revealed that diene (88) reacted with acrolein at -78°C in toluene with 0.2 equivalents of boron trifluoride etherate. Larger scale reactions, under the same conditions, enabled the isolation of the cyclohexene (139) in 52% yield together with the dihydropyran (140) which is derived from the aldehyde moiety acting as the dienophile.



Proof for the regiochemistry of the cyclohexene (139) was two-fold. Firstly, H-1 was identified as a doublet of triplets at δ2.13 by decoupling the aldehyde signal. The fact that it existed as a doublet of triplets suggested that the ortho-isomer (139) had been formed since H-1 would be coupled to a CH_2 and the aldehyde proton. Had the meta-isomer (141) been formed it would be expected to have a more complex signal since there would be five adjacent protons to H-1. The second



(141)

piece of evidence lay in n.O.e. experiments from the two C-2 methyl groups. Both methyls showed a n.O.e. to the aldehyde proton (4% and 5%) and both to H-1 (7% and 2.5%) thus indicating their proximity to both these protons, Figure 9. Models show that for the ortho product

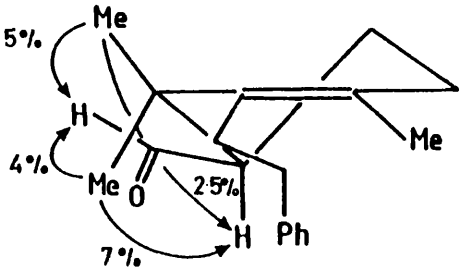
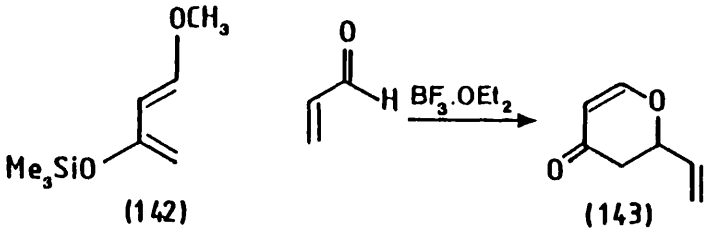


Figure 9

(139) both the aldehyde and H-1 can be close to either of the C-2 methyl groups.

It is known that acrolein itself can act as a heterodiene[96] but this type of reaction would not lead to the production of the dihydropyran (140). In a recent series of papers by Danishefsky et al.,[97] the silyloxy diene (142), under Lewis acid catalysed conditions, reacted exclusively via the carbonyl functionality in preference to the double bond moiety, with a variety of α,β-unsaturated aldehydes to furnish the pyrone (143). However, it should be noted that there is some evidence that the mechanism, under certain conditions, involves an aldol-like

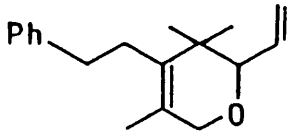


pathway rather than a pericyclic one.[97]

Certain very electrophilic carbonyls (e.g. glyoxylates and fluorinated ketones) have also been shown to undergo Diels-Alder reactions via the carbonyl functionality.[98] Although clearly there are examples of [4 + 2]

cycloadditions using heterodienophiles, they appear to be relatively uncommon.[98]

The major evidence for the structure of adduct (140), where the carbonyl moiety of acrolein had reacted as the dienophile, lay in the high resolution mass spectrum with the correct molecular ion. The high-field ^{1}H n.m.r. clearly showed the characteristic vinyl group and additional signals which could account for the remaining functionality. The regiochemistry was determined by the fact that only one signal (other than the vinyl protons) in the ^{1}H n.m.r. was shifted down-field by the oxygen which is as would be predicted for (140). If the other isomer (144) was formed it would be expected to have three deshielded protons.



(144)

The regiochemistry of the two Diels-Alder adducts (139) and (140) also fits into a pattern when looking at the predicted orbital coefficients of protonated acrolein (which can be considered as a model for Lewis acid co-ordination), Figure 10.[84] The major interaction is likely to be from the HOMO of the diene and the LUMO of the dienophile. Therefore, with reference to the LUMO of the protonated acrolein the C-1 and C-3 carbons have the larger coefficients. Since the atom with the larger coefficient on the dienophile interacts preferentially with the atom carrying the larger coefficient of the diene, it would be expected (and was found) that C-1 and C-3 of the acrolein would be bonded to the same carbon of the diene in the two adducts.

The aldehyde (139) was converted to its crystalline DNP derivative

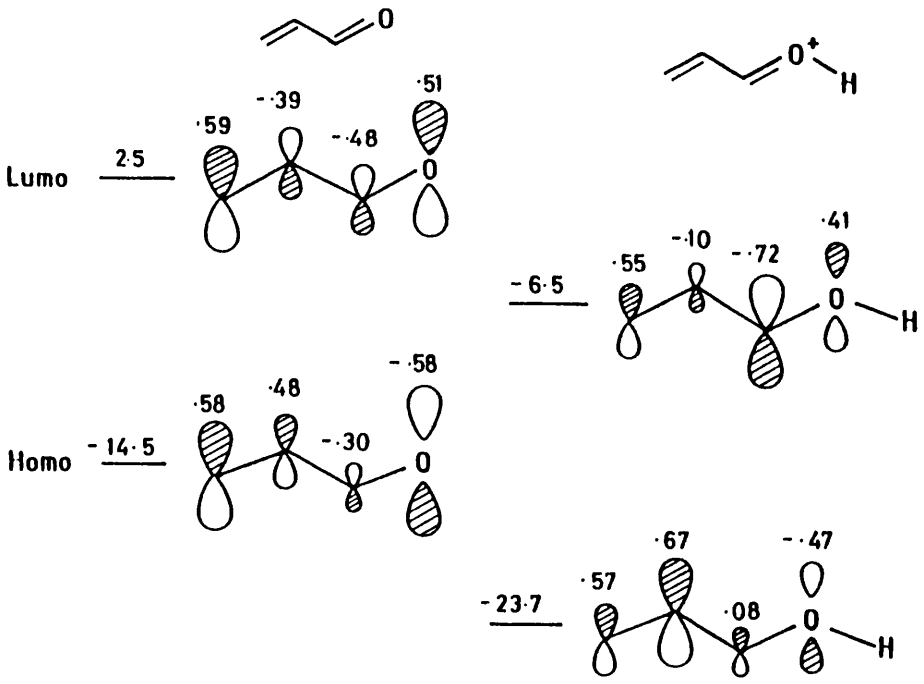
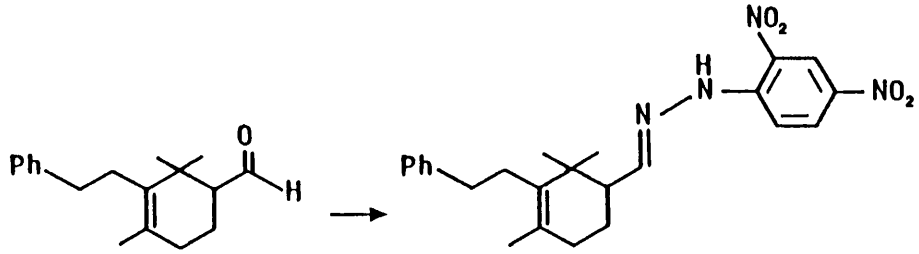


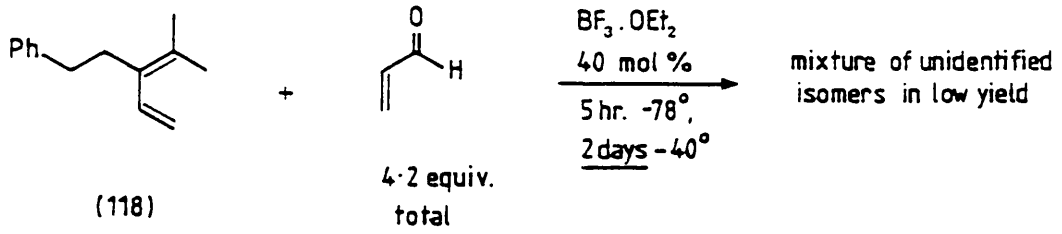
Figure 10

(145) which gave microanalytical and n.m.r. data that were consistent with the proposed structure.



The diene (118) was reacted with acrolein and 0.2 equivalents of boron trifluoride etherate at -78°C, and after 5h the t.l.c. showed only starting material. The mixture was then warmed to -35°C and after 12h t.l.c. showed some reaction had taken place, however, a large amount of the diene (118) still remained. At this point further portions of acrolein and boron trifluoride etherate were added (the same product was isolated irrespective of the second portion but in even worse yield). After an additional 7h the mixture was worked-up. T.l.c. showed some streaking and a number of faint spots that could not be isolated. It

was, however, possible to re-isolate the starting diene (118) (49%) and a main product (19%) which was one spot on t.l.c. However, high-



(118)

field ^1H n.m.r. revealed a 2:1 mixture of isomers. Characteristic signals in the ^1H n.m.r. were two aldehyde proton signals, one for each isomer, at δ9.66 and 10.00. The presence of a carbonyl was also confirmed by an i.r. showing a strong absorption at 1720 cm^{-1}. Additional features in the ^1H n.m.r. were six characteristic vinyl signals, three for each isomer, very similar to those already observed for the dihydropyran (140). Since the product appeared to be a 2:1 mixture of isomers the remaining signals in the ^1H n.m.r. were additionally complicated and other than integration and chemical shift not much more information could be obtained. However, it was clear that the product was not the expected Diels-Alder adduct or a product arising from simple rearrangement of the diene (118) prior to reaction. The product gave a molecular ion in its mass spectrum consistent with two molecules of acrolein combining with one of the diene (118). Identification of the products was made more difficult since only small amounts could be obtained due to the poor yield and insufficient quantities of the diene (118). In addition, the products showed signs of decomposition after a few days at 0°C.

It was felt that if a crystalline derivative was prepared it might be possible to separate the two isomers by recrystallisation and prove the structure unambiguously by X-ray analysis. Also, a crystalline derivative would hopefully alleviate any decomposition problems. The products were,

therefore, converted to their DNP derivatives. After one recrystallisation the ^1H n.m.r. showed that the ratio of isomers had improved to essentially one compound. However, it was not possible to obtain a crystal which was suitable for X-ray analysis. The high resolution mass spectrum of the DNP derivative confirmed a molecular formula of $C_{26}H_{30}N_4O_5$ which is consistent with one molecule of the diene (118), two molecules of acrolein and the DNP group. The high-field ^1H n.m.r. showed similar features, together with the DNP group, as the initial products except with the minor isomer absent. Despite the fact that the compound was now pure, it was still not possible to make a clear identification. The structure shown in Figure 11 is most consistent with the available evidence for the initial product and the corresponding DNP derivative. The two isomers that were originally isolated could conceivably have arisen from either regioisomers or even diastereoisomers of the structure shown. Clearly this reaction needs further investiga-

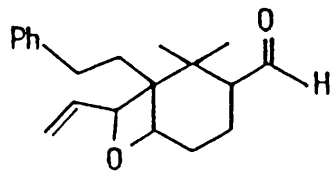


Figure 11

tion before a structure for the product can be more confidently suggested. However, examples of dienes undergoing non-concerted [2 +2] do exist in the literature[85,87] and Zwitterionic or radical intermediates are proposed.

It therefore appeared that diene (88) was more reactive and gave cleaner products than diene (118). It was thought that there were three possible reasons for this.

Firstly, the diene (88) is degenerate to a 1,5-hydrogen shift, Figure

12, therefore rearrangement would not lead to different dienes as it would with diene (118), Figure 12.

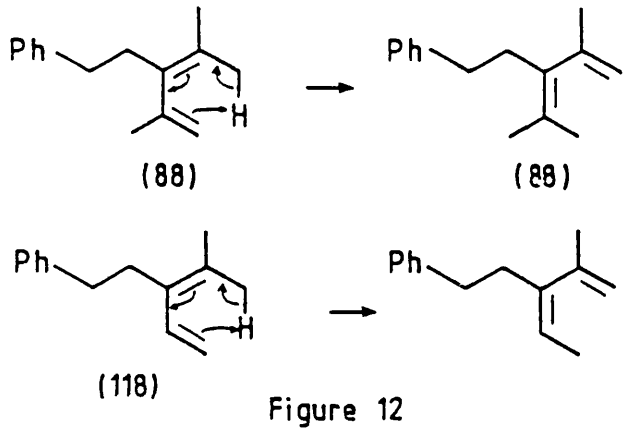
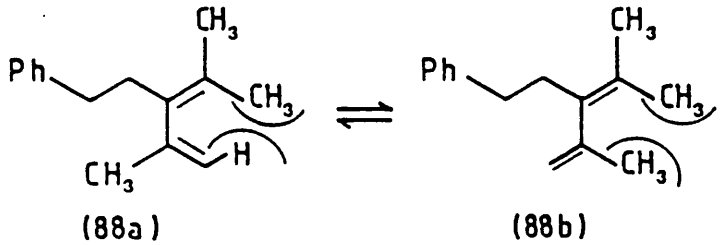


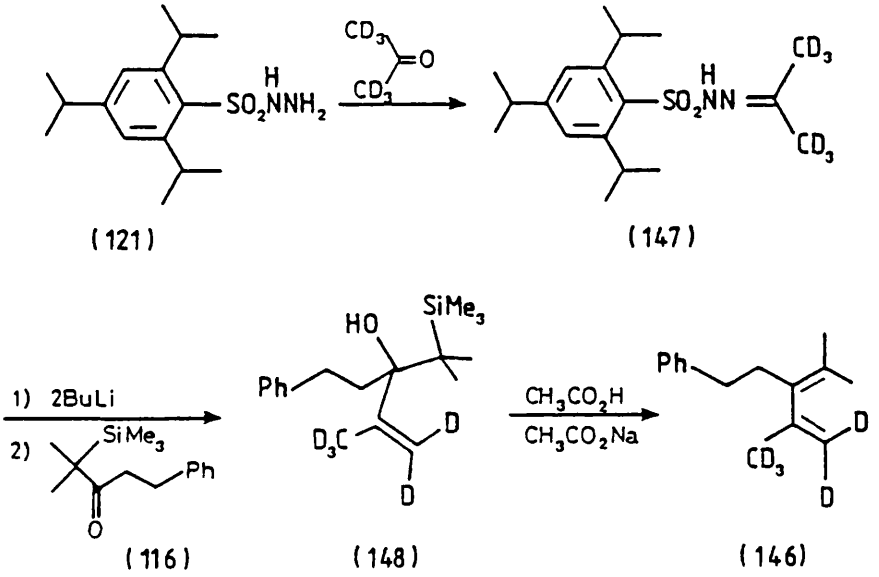
Figure 12

Secondly, the extra methyl group of the diene (88) has the effect of raising the HOMO (and LUMO) of the diene,[82] therefore decreasing the energy-gap between the HOMO of the diene and the LUMO of the dienophile. This has the effect of lowering the transition state energy and so increasing the rate of reaction relative to the diene (118) without the extra methyl group.

The third alternative is a steric argument; the reason generally given as to why geminally disubstituted dienes fail to undergo Diels-Alder reaction is that the cisoid conformation (88a) is sterically disfavoured.[83] In the diene (88) this unfavourable steric interaction with the cis-methyl group in the approximate cisoid conformation (88a) is counter-balanced by the steric interaction between the cis-methyl group and the methyl group at the C-3 position of the butadiene fragment in the approximate transoid conformation (88b).



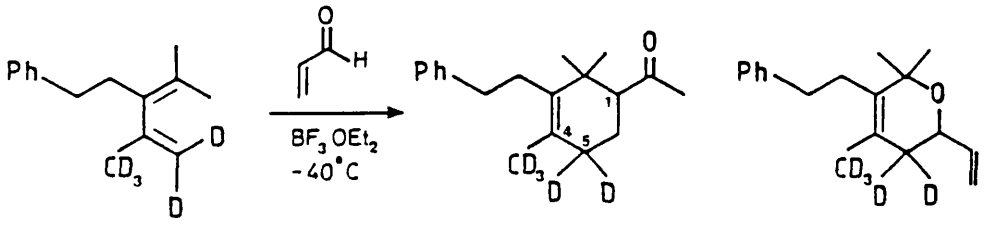
In order to rule out the possibility of a 1,5-hydrogen shift, the deuterium labelled diene (146) was prepared. The [$^2H_6$] hydrazone (147) was prepared from [$^2H_6$] acetone and the hydrazine (121). Treatment of the [$^2H_6$] hydrazone (147) with two equivalents of n-butyllithium produced [$^2H_5$] propenyl lithium which was then reacted with the β-keto silane (116) to yield the [$^2H_5$] α-hydroxy silane (148), Scheme 35. The reaction of (148) under Peterson elimination conditions[73] furnished the [$^2H_5$] diene (146). High-field ^1H and ^2H n.m.r. of the [$^2H_5$] diene (146)



Scheme 35

were consistent with specific labelling of deuterium in the positions shown. The mass spectrum indicated an average of 97% deuterium incorporation at each site.

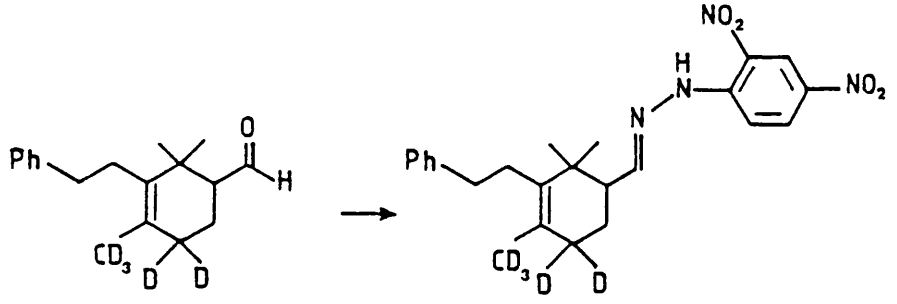
The [$^2H_5$] diene (146) was then reacted with acrolein and boron trifluoride etherate, under the same conditions as for the undeuterated case, to produce the [$^2H_5$] cyclohexene (149) and the [$^2H_5$] dihydropyran (150) in yields of 60% and 5% respectively. A small amount of unreacted [$^2H_5$] diene (146) was also re-isolated (15%), the ^1H n.m.r. of which was identical to the starting material (146).



(146) (149) (150)

Figure 13 shows the ^1H n.m.r. of both the labelled Diels-Alder adduct (149) and the unlabelled adduct (139). The ^1H n.m.r. of adduct (149) clearly shows the absence of the multiplet at δ2.03 and the singlet at δ1.74 assigned to the protons at C-5 and the methyl group at C-4 respectively in the unlabelled adduct (139). Also, the methyl groups at C-2 remain undisturbed. This result rules out the possibility of the diene (88/146) undergoing rearrangement during the Diels-Alder reaction with acrolein under boron trifluoride etherate catalysed conditions.

The $[^2H_5]$ cyclohexene (149) was also converted to its $[^2H_5]$ DNP derivative (151). The ^1H and ^2H n.m.r. were consistent with structure (151) and neither showed any signs of scrambling of the deuterium.



(149) (151)

In addition, if the $[^2H_5]$ diene (146) was heated at 100°C for 12h, no evidence for any scrambling was observed in the ^1H n.m.r. From this and the above evidence it seemed that the improved reactivity of the diene (88) with the methyl group at the C-3 position of the butadiene fragment was not a result of its degeneracy. It was not possible to

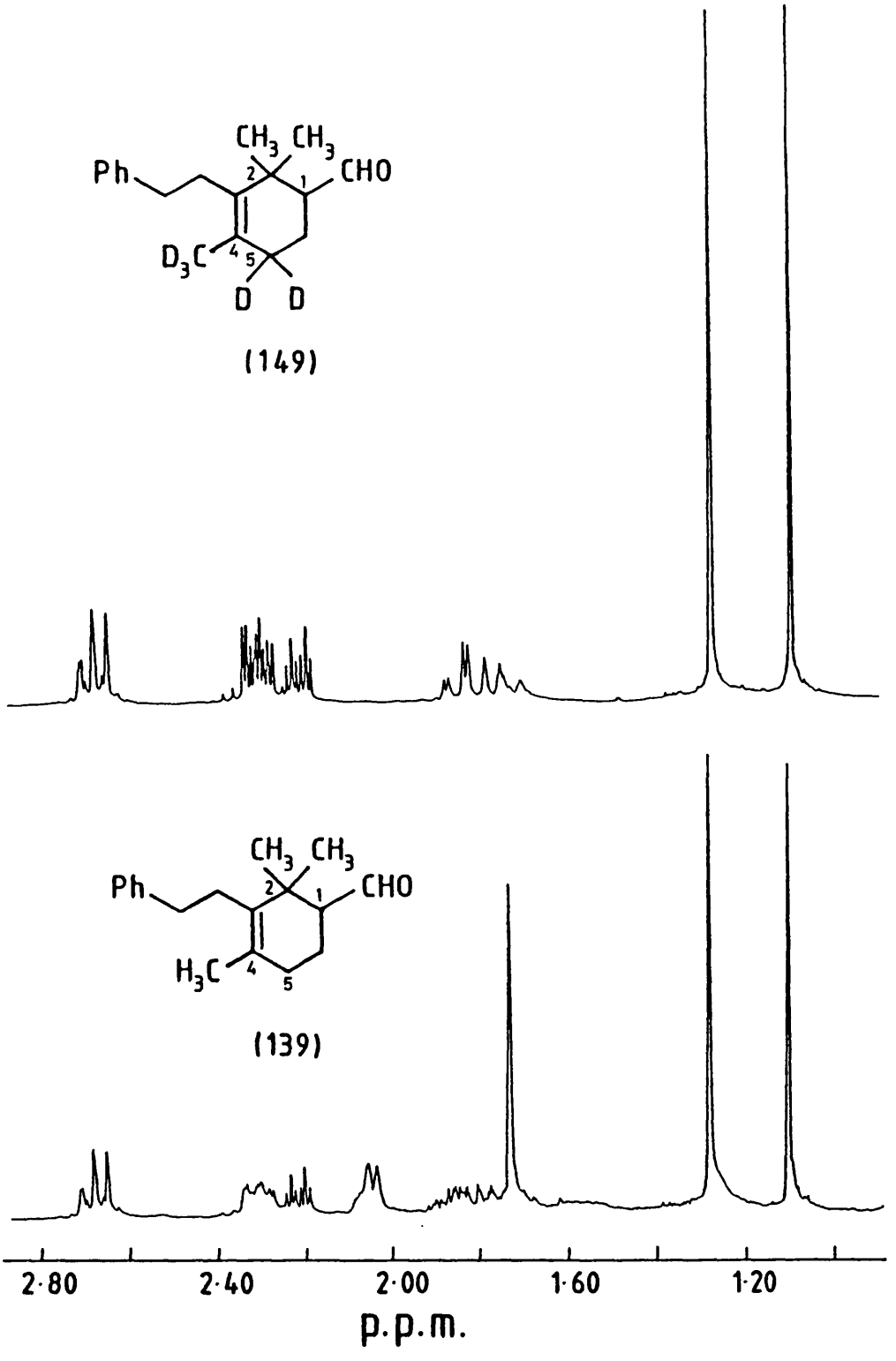


FIGURE 13

The 300 MHz ($CDCl_3$) ^1H NMR of (139) and (149).

determine whether the increased reactivity arose from electronic or steric effects or, more likely, a combination of the two. However, it was apparent that the extra methyl group of the diene (88) played an important rôle in its reactivity towards a Diels-Alder reaction.

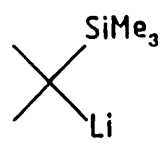
Encouraged that conditions were found whereby the diene (88) could be made to undergo Diels-Alder reactions, a more reliable route to its preparation, which could then be applied to the taxane model system, was sought making use of selenium chemistry.

CHAPTER 4

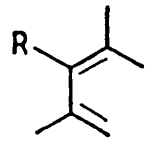
A Synthesis of Substituted Dienes and its Application to an Alkylated Taxane Model System

4.1 INTRODUCTION

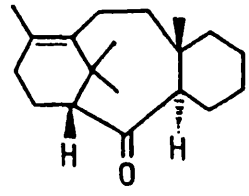
Chapter 3 describes the successful application of the Peterson elimination[41] to control the regiochemistry in the preparation of highly substituted butadienes. However, use of this method was restricted by difficulties experienced in the preparation of 2-lithio-2-trimethylsilyl propane (110) and the high basicity of this reagent. It was, therefore, necessary to develop a more reliable route to dienes of type (108) that could then be applied to the preparation of the alkylated taxane model system (82).



(110)

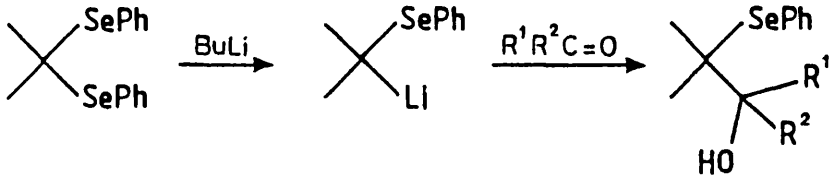


(108)



(82)

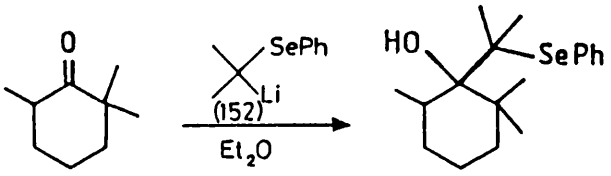
In keeping to a similar type of methodology to that used in the silicon directed diene synthesis an alternative to alkyllithium (110) was sought. The corresponding α-selenoalkyl lithium (152) appeared to be readily available from the selenoacetal (153) and n-butyllithium.[99] Addition of this anion (152) to an aldehyde or ketone results in the formation of a β-hydroxy selenide (154).[77] According to the literature



(153) (152) (154)

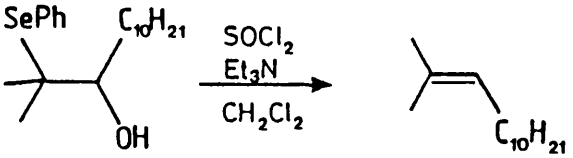
α-selenoalkyl lithiums have the advantage of being easily prepared, stable at -78°C and also highly nucleophilic.[77] This high nucleophilicity allows attack at a highly hindered ketone without competing enolisation.[100] This fact is illustrated by the reaction of 2,2,6-trimethylcyclohexanone (155) with the anion (152) to produce the β-hydroxy phenylselenide (156)

in 84% yield.[100]



(155) (156)

β-Hydroxy selenides are versatile synthetic intermediates and can be used to produce a variety of functionalised compounds; allylic alcohols,[101] α,β-unsaturated carbonyl compounds,[102] vinyl selenides,[77] epoxides,[103] alcohols[104] and olefins[105] of particular relevance to the diene synthesis is the ability of β-hydroxy selenides to be converted, with complete regiospecificity, to olefins.[105] The treatment of the β-hydroxy selenide (157) with thionyl chloride and triethylamine in dichloromethane leads to the formation of alkene (158) in 90% yield.[106] An intermediate seleniranium ion has been proposed for this transformation.[106]

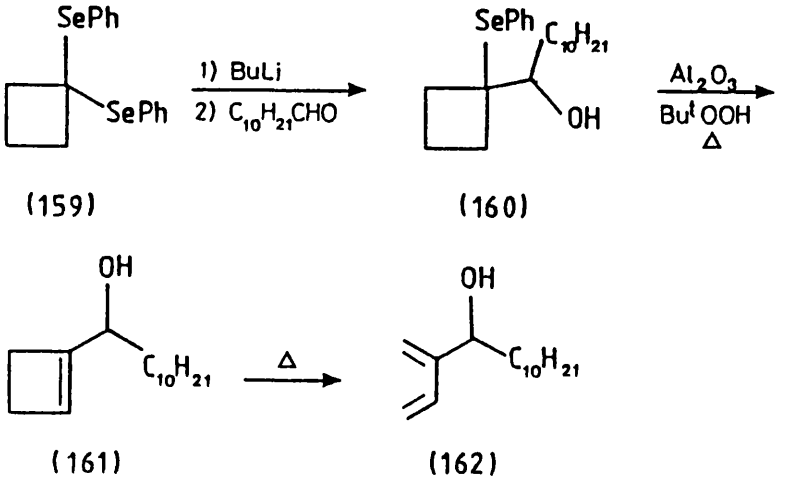


(157) (158)

Selenium chemistry has been previously utilised in the preparation of 1,3-dienes, some examples are shown below.

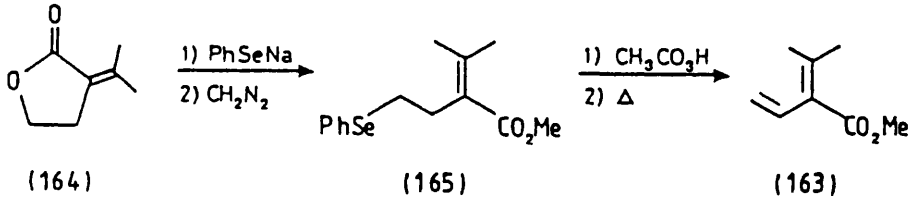
Halazy and Krief[107] prepared 2-substituted butadienes from the 1,1-bis selenocyclobutanes (159) outlined in Scheme 36. Reaction of (159) with n-butyllithium produced the corresponding α-lithioselenocyclobutane which was added to an aldehyde to yield the cyclobutyl alcohol (160). Oxidation of the selenium moiety to the selenoxide followed by elimination gave cyclobutenyl alcohol (161) which could be ring opened to furnish the 2-substituted diene (162).[107]

A later report used a selenoxide elimination to produce the diene (163),



Scheme 36

Scheme 37.[108] The reaction of α-isopropylidene-γ-butyrolactone (164) with sodium phenylselenide and subsequent esterification of the intermediate acid with diazomethane provided the ester (165). Oxidation of the selenium moiety with peracid followed by thermal elimination of the selenoxide gave the diene (163).[108]

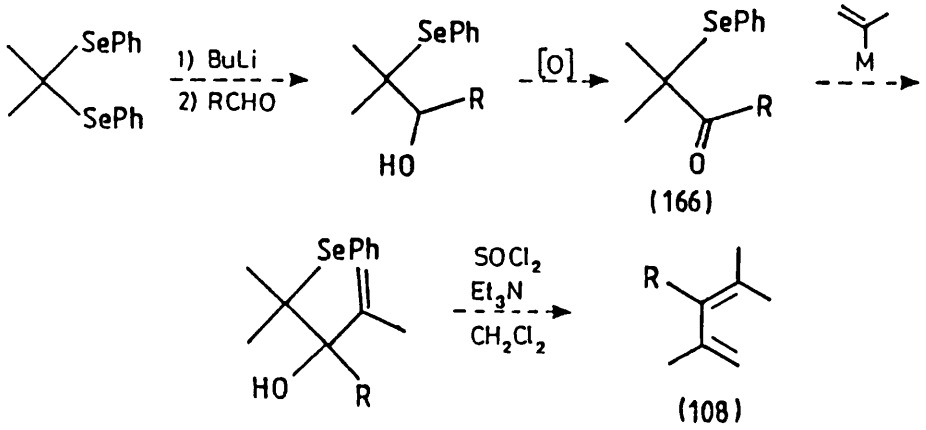


Scheme 37

4.2 SELENIUM DIRECTED DIENE SYNTHESIS

Originally it was thought that the synthesis of dienes could be achieved by substituting 2-lithio-2-phenylselenopropane (152) for 2-lithio-2-trimethylsilylpropane (110) in the sequence already developed in Chapter 3. Scheme 38 shows the proposed route to the diene (108) using the selenium moiety to control the regiochemistry of the elimination.

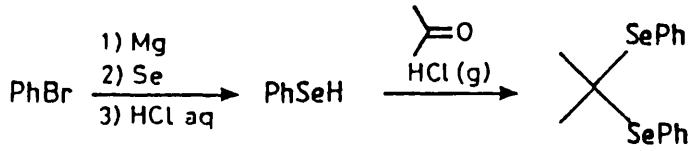
The production of β-hydroxy selenides is well precedented in the



Scheme 38

literature and it was thought that this step could be achieved without too many problems. However, the key step in the sequence is the oxidation of the alcohol functionality in the presence of the selenium moiety.[77] The following reagents have been used to oxidise an alcohol in the presence of a selenide group; the Corey-Kim,[109] Choral on alumina,[110] triphenylbismuth carbonate[111] and DDQ.[112] If the β-keto selenide (166) could be prepared the remainder of the synthesis would follow in a similar fashion to the silicon directed synthesis [Chapter 3], by addition of propenyl Grignard or propenyl lithium then elimination to yield the diene (108). The sequence was therefore initially undertaken using readily available aldehydes as model compounds.

The selenoacetal (153) was prepared according to literature procedure from acetone and selenophenol (167) in the presence of hydrogen chloride gas.[113] The product first isolated was found to contain some diphenyl diselenide derived from the oxidation of the selenophenol (167). The diphenyl diselenide was removed by flash chromatography and the seleno-acetal (153) was obtained as a pale yellow solid with the ^{1}H n.m.r. consistent with the literature.[113] The selenophenol (167) itself was prepared from phenyl Grignard and powdered black selenium, acidic work-up, then

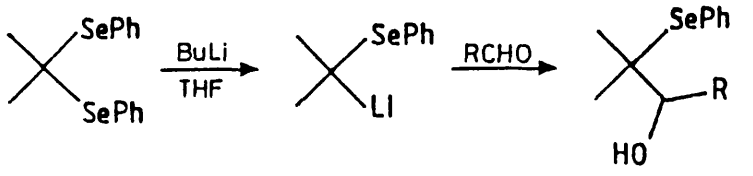


(167) (153)

Scheme 39

produced air and light-sensitive selenophenol (167), Scheme 39.[114]

Treatment of the selenoacetal (153) with n-butyllithium in THF gave the anion (152) which was reacted with three different aldehydes; benzaldehyde, 3-phenylpropanal and heptanal to provide the corresponding β-hydroxy selenides (168a,b,c), Table 3.

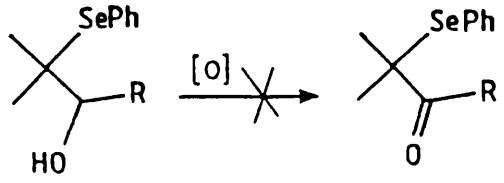


(153) (152) (168a,b,c)

TABLE 3

Aldehyde	Yield of (168)
a R = Ph	78%
b R = C_6H_{13}	92%
c R = $PhCH_2CH_2$	89%

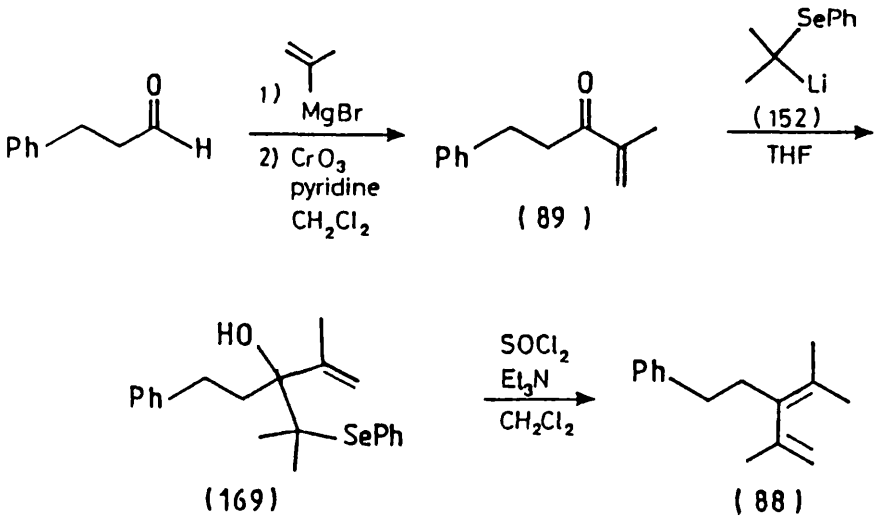
The β-hydroxy selenide (168a) was reacted with a number of different oxidising agents; Corey-Kim,[109] Swern,[115] Collins[40,53] and DDQ,[112] none of which produced the required β-keto selenide (166a). The only product which was identified was diphenyldiselenide. Treatment of the β-hydroxy selenide (168b) under Corey-Kim,[109] Swern,[115] or DDQ[112] oxidising conditions also failed to produce the corresponding β-keto selenide (166b). Finally the oxidation of (168c) again failed to produce the β-keto selenide (166c). More attention could have been directed at this oxidation since according to the literature[77] it ought to have been



(168a,b,c) (166a,b,c)

possible to oxidise these β-hydroxy selenides to β-keto selenides. However, a more thorough examination of the literature revealed that the anion (152) has a strong tendency to undergo 1,2 additions to α,β-unsaturated carbonyl compounds.[116] Therefore, by altering the order of the sequence in Scheme 38 it should be possible to avoid the necessity to carry out the oxidation with the selenium moiety present.

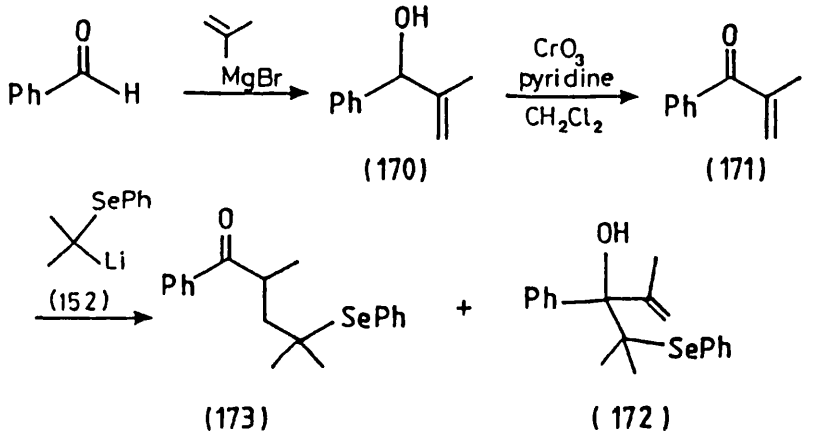
The enone (89) was prepared as previously described in Chapter 2 by addition of propenyl Grignard to 3-phenyl propanal followed by oxidation. The enone (89) was added at -78°C to a solution of 2-lithio-2-phenyl-selenopropane (152) which had been prepared from the selenoacetal (153) and n-butyllithium. The mixture was allowed to warm to room temperature over the period of 1h then worked-up. After flash chromatography the β-hydroxy selenide (169) was obtained in 73% yield. The t.l.c. of the crude product and the n.m.r. and i.r. of the purified product showed no evidence for any products arising from 1,4-addition to the enone (89). The β-hydroxy selenide (169) was reacted with thionyl chloride and triethylamine according to the method of Krief[106] for the formation of olefins from β-hydroxy selenides. After work-up and flash chromatography the diene (88) was isolated in 62% yield, Scheme 40. The n.m.r. showed no evidence that any regioisomers had been formed and the product was identical in all respects to the diene (88) obtained from the silicon directed diene synthesis [Chapter 3]. The overall yield from 3-phenyl-propanal was only 17%. It was, however, thought that this could be



Scheme 40

improved since it was the seemingly straightforward first two steps that were mainly responsible.

The sequence was then repeated using benzaldehyde as the starting material, Scheme 41. Propenyl Grignard was added to benzaldehyde to

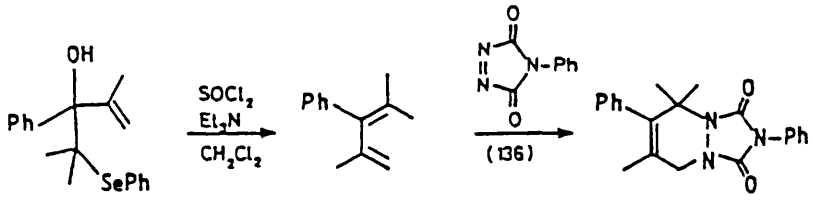


Scheme 41

produce the allylic alcohol (170). The ^1H n.m.r. and t.l.c. showed the product to be relatively pure so it was used without further purification in the next step. Collins oxidation of (170) provided the enone (171) in a much improved 70% yield from benzaldehyde. The addition of 2-lithio-2-selenophenylpropane (152) to the enone (171), however, produced both

the required β-hydroxy selenide (172) together with the ketone (173) which resulted from 1,4-addition of the anion (152) to the enone (171). The yield of (172) and (173) was 29% and 38% respectively. It is possible that either the electronic affect of the phenyl group or the increased steric bulk around the carbonyl might have caused the enone (171) to undergo Michael addition as well as 1,2-addition.

Obviously the ketone (173) was of no use in the diene synthesis but the β-hydroxy selenide (172) was reacted with thionyl chloride and triethylamine to yield the diene (174) which was further reacted with Cookson's dienophile (136)[94] to yield the crystalline derivative (175), Scheme 42. Microanalytical and spectroscopic data for the adduct (175) was consistent with the structure proposed.

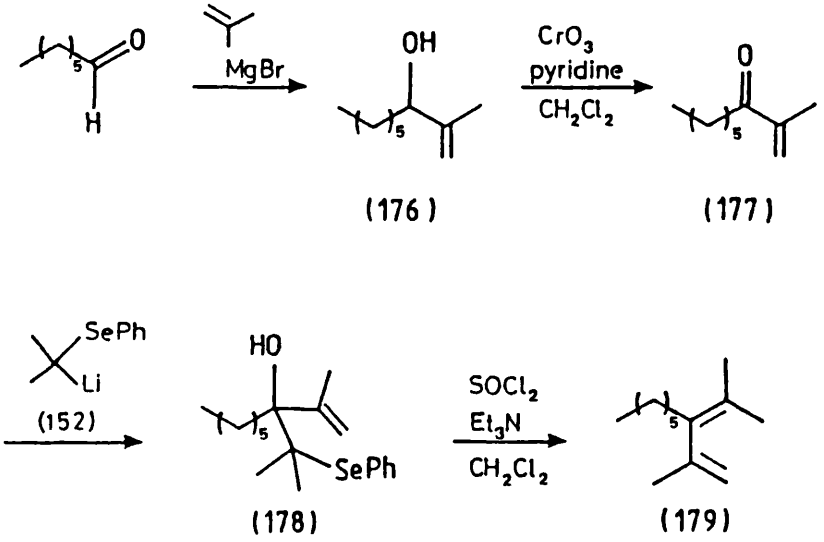


(172) (174) (175)

Scheme 42

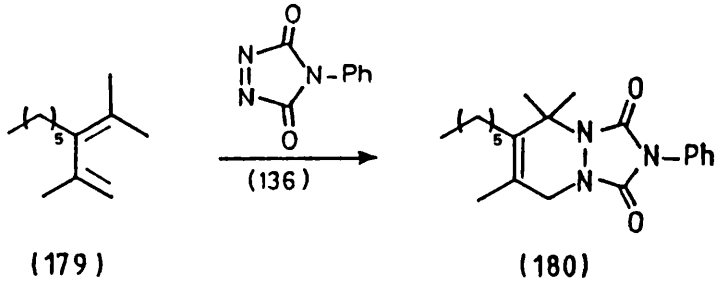
In order to investigate further the reliability of this diene synthesis another model aldehyde was used. Heptanal was added to a solution of propenyl Grignard and stirred for ½h. After work-up the allylic alcohol (176), which appeared to be pure by t.l.c. and ^{1}H n.m.r., was obtained and it was used in the next stage without further purification. Collins oxidation[53] of (176) furnished the enone (177) in 70% overall yield from heptanal. 2-Lithio-2-phenylselenopropane (152) was again prepared from the selenoacetal (153) and n-butyllithium. The anion (152) was then reacted with the enone (177) to produce the β-hydroxy selenide (178) in 86% yield, after flash chromatography. No evidence of any 1,4-addition product was observed from the t.l.c. of the

crude product or the n.m.r. and i.r. of the purified product. The elimination of both the hydroxyl and selenyl moieties using thionyl chloride and triethylamine[106] then provided the diene (179), Scheme 43. The overall yield from heptanal was now a respectable 39%.



Scheme 43

The diene (179) was reacted with Cookson's dienophile (136)[94] to produce the crystalline adduct (180). Again the microanalytical and spectroscopic data was in accord with the structure proposed for the adduct (180).



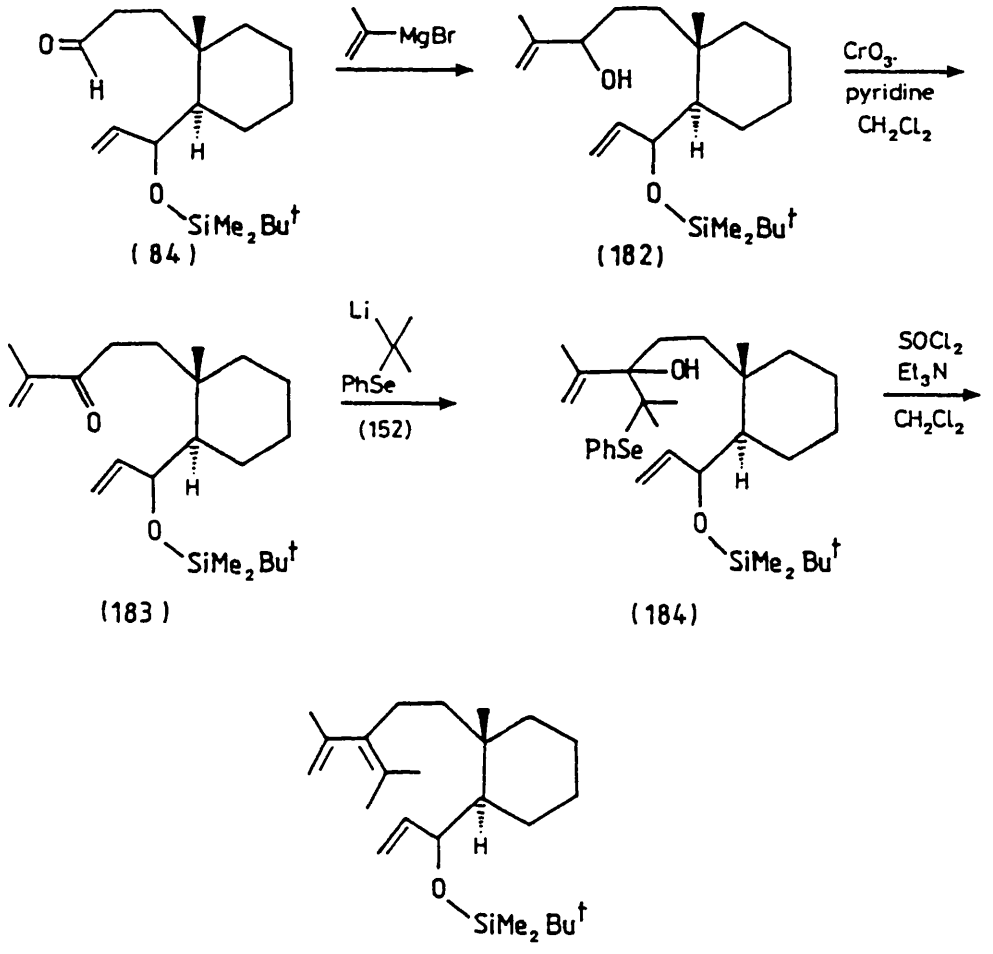
Although the conversion of a 1-hydroxy-2-methylselenobut-2-ene unit into a diene has been mentioned as unpublished results by Krief,[106] full details and specific applications to highly substituted dienes have not been reported. From the three model dienes prepared it appears that the selenium directed diene synthesis is more widely applicable than the

silicon directed route. The limiting factor appears to be the competing 1,4-addition of the selenium stabilised anion to the α,β-unsaturated ketone, this however was only observed in the enone prepared from benzaldehyde. With more confidence it was decided to extend the sequence to the alkylated taxane model system.

4.3 THE PREPARATION OF 8,12,15,15-TETRAMETHYLTRICYCLO[9.3.1.$0^{3,8}$]-PENTADECANE (82)

The conversion of the aldehyde (84) to the diene (181) was performed in a similar way to that in the model diene synthesis, Scheme 44. 2-Propenyl Grignard was added to the aldehyde (84) and after work-up and flash chromatography the allylic alcohol (182) was obtained as a colourless oil. The t.l.c. of the product showed a "dumb-bell" shaped spot which suggested that two diastereoisomers had been formed. The ^{13}C n.m.r. of the crude reaction mixture showed that the majority of the signals were duplicated which again suggested that two diastereoisomers had been formed. The ratio appeared to be approximately 1:1. There was obviously little point in further study of the diastereoisomer ratio as the new chiral centre is destroyed in the next step. Collins oxidation[53] of the allylic alcohol (182) gave the enone (183) in 74% yield. The enone (183) was then reacted with 2-lithio-2-phenylselenopropane (152) to furnish the β-hydroxy selenide (184). Presumably, (184) existed as a mixture of diastereoisomers but it was not evident from t.l.c. or 90 MHz ^{1}H n.m.r. and since the elimination removes the new chiral centre, (184) was not investigated further. Treatment of the β-hydroxy selenide (184) with thionyl chloride and triethylamine[106] then provided the diene (181), Scheme 44.

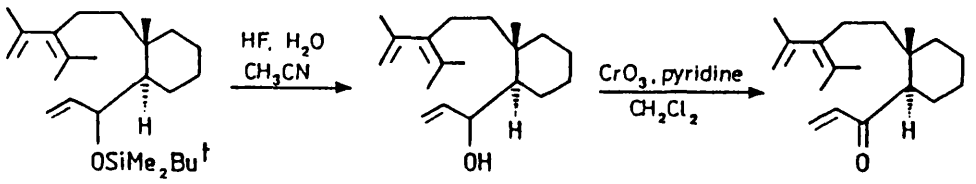
It was then necessary to activate the dienophile part of the molecule before carrying out the intramolecular Diels-Alder reaction. The depro-



Scheme 44

tection of the alcohol functionality of (181), using aqueous hydrofluoric acid and acetonitrile in glass apparatus[117] led to the allylic alcohol (185). The oxidation of this alcohol (185) using a Collins solution,[40] generated *in situ*[53] then provided the trienone (83), Scheme 45. The epimerisation of the centre next to the carbonyl in the trienone (83) was anticipated to be a possible problem. However, the high-field ^{1}H and ^{13}C n.m.r. showed no evidence for this.

The cyclisation of the trienone (83) is classified as an intramolecular ($4\pi s + 2\pi s$) cycloaddition [see Chapter 3].[82] The intramolecular Diels-Alder (IMDA) reaction has been used in the synthesis of a large

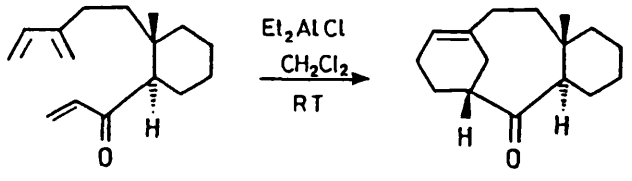


(181) (185) (83)

Scheme 45

number of natural products[118] and usually occurs with a high degree of control over the regiochemistry and stereochemistry.

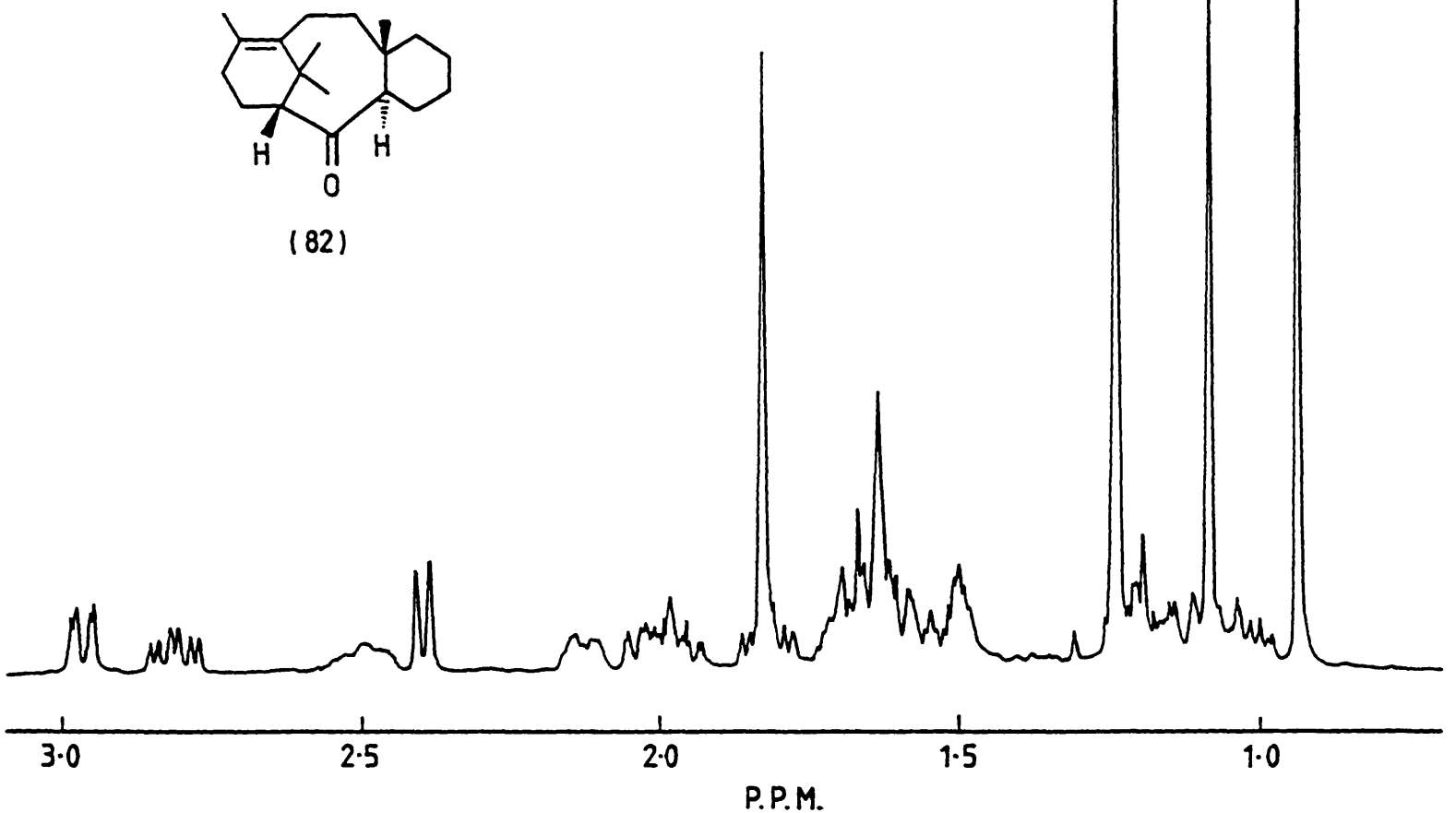
In previous studies from this laboratory[38] the cyclisation of the trienone (51) to the tricyclic ketone (50) was performed using diethylaluminium chloride as a catalyst. The IMDA reaction produced (50) with the same stereochemistry at C-1, C-3 and C-8 as the taxane natural products.



(51) (50)

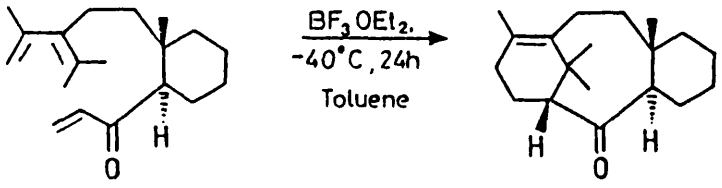
Small scale test reactions using diisobutylaluminium chloride to catalyse the IMDA reaction of the trienone (83) failed to produce an identifiable product. The t.l.c. of the products formed in the reaction showed a considerable amount of streaking and a heavy base line spot. Attention was turned to boron trifluoride etherate as the catalyst since this Lewis acid had been used to promote the Diels-Alder reaction between diene (88) and acrolein in Chapter 3. After a number of test reactions it appeared from t.l.c. that a new product was being formed in the reaction of trienone (83) and boron trifluoride etherate at -40°C for 24h. Scaling up the reaction enabled the isolation of the tricyclic ketone (82) as a colourless oil in 58% yield. The high field ^1H [Figure 14]

FIGURE 14 - ^{1}H n.m.r. of the tricyclic ketone (82).



(82)

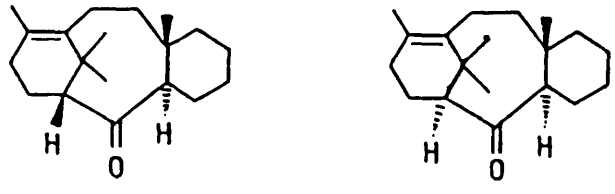
and ^{13}C n.m.r., together with other spectroscopic evidence was in accord with the cyclised product. The overall yield of the sequence from the



(83) (82)

aldehyde (84) to the tricyclic ketone (82) was a respectable 13%.

There are two possible diastereoisomers that could have been formed in the cyclisation of (83); the required product (82) and (186) which has the wrong configuration at C-1 compared to the natural taxanes. The



(82) (186)

stereochemistry of the product from the IMDA reaction of the trienone (83) was assigned to be that shown for structure (82). The main evidence for this lies with extensive n.m.r. studies performed on the tricyclic product. The majority of the proton signals in the ^1H n.m.r. were assigned with the help of a COSY spectra, Figure 15. Having assigned the proton resonances, extensive n.O.e. studies were then carried out and some of the results are shown in Figure 16. By examination of models of the two possible isomers it was apparent that these n.O.e. results could only be explained for the structure (82). Probably the most important n.O.e. observed was that between the proton at C-3 and the methyl group at C-12 which would be expected for the structure (82) but not for the structure (186).

The stereochemical outcome of the cyclisation can also be predicted theoretically. Calculations, together with X-ray and n.m.r. work have

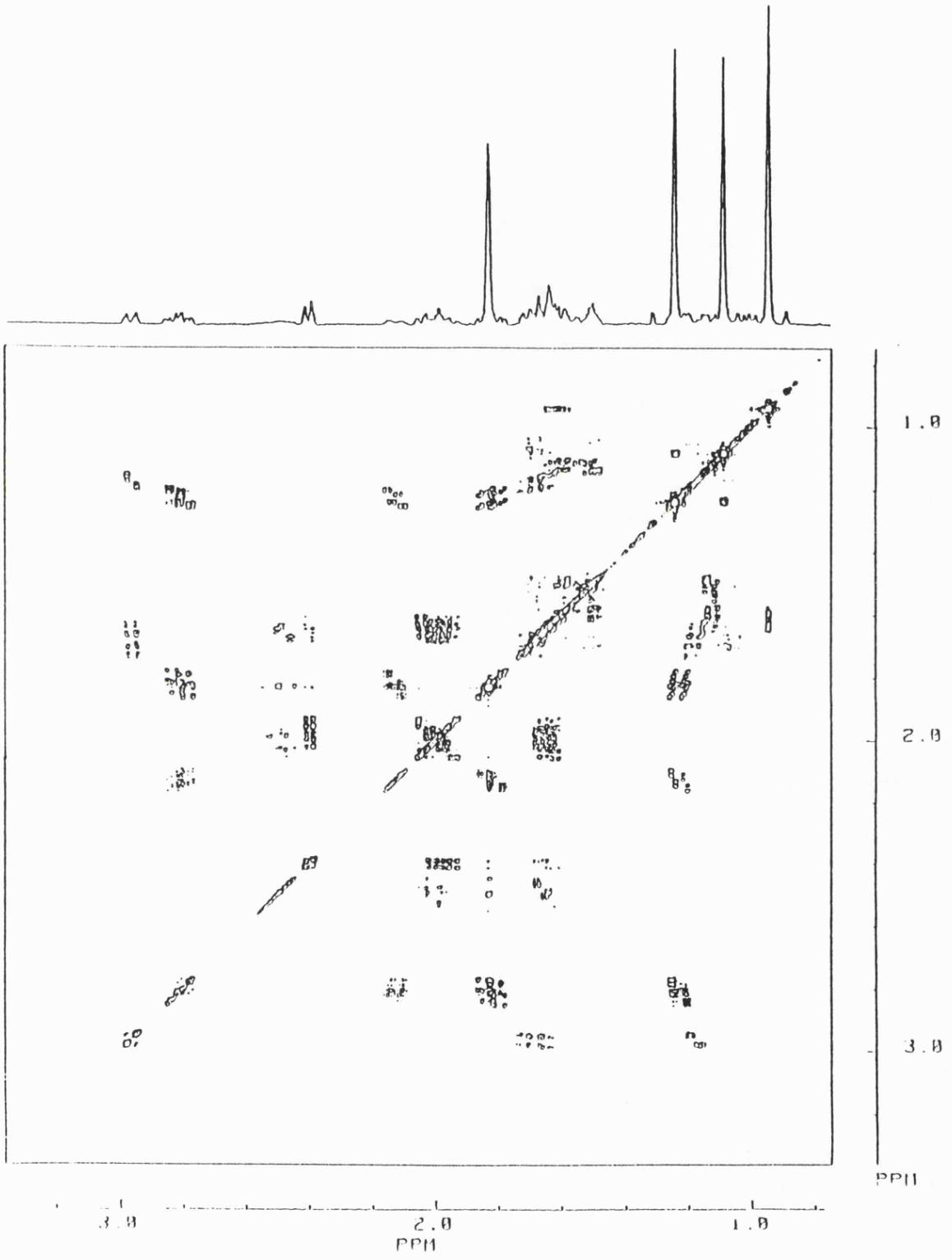


FIGURE 15

COSY spectra of the tricyclic ketone (82).

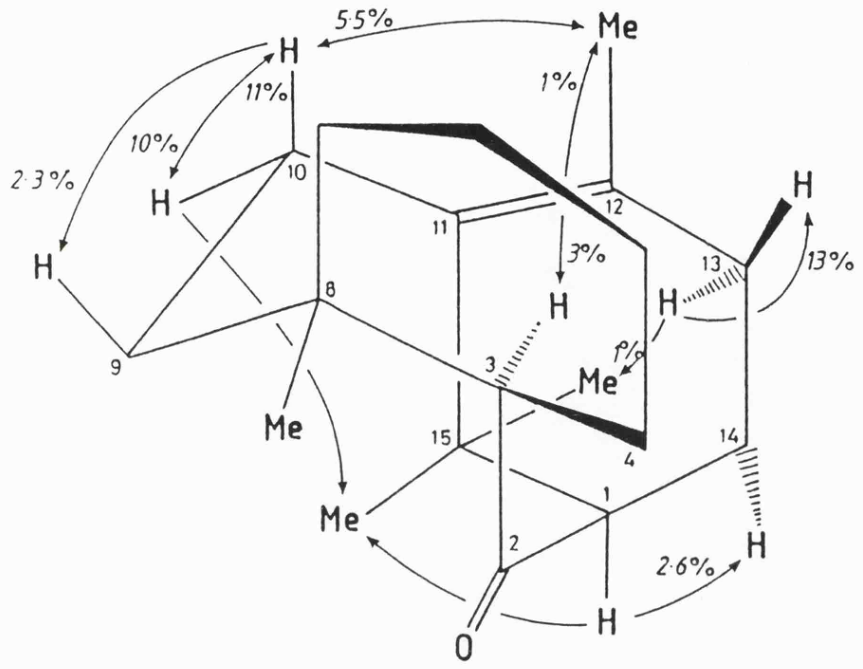
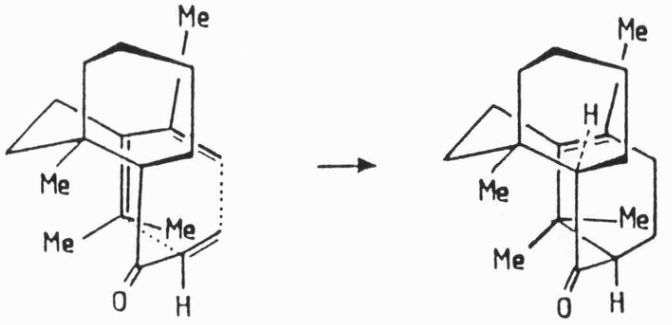


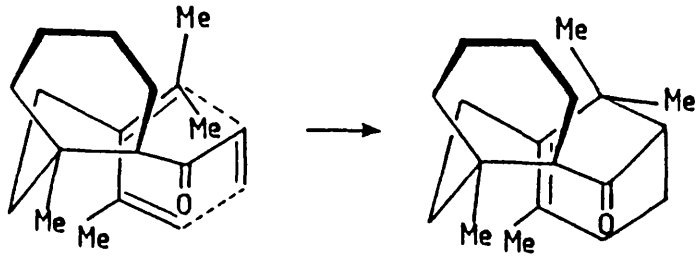
Figure 16

shown that in simple cyclo-octanes the chair-boat conformation is preferred over the twist chair-boat conformation by approximately 2 kcal/mol.[42] This fact and by analogy with the cyclisation of trienone (51),[38] it would be predicted that the IMDA reaction would take place via the preferred chair-boat conformation, Figure 17, rather than via the twist chair-boat conformation, Figure 18. From models the inclusion of the methyl groups did not appear to add any serious steric interaction in the chair-boat transition state, whereas the twist chair-boat transi-



(82) chair-boat

Figure 17



(186) twist chair-boat

Figure 18

tion state does not seem to accommodate these methyls as well.

Hence, by the use of selenium chemistry to control the regiochemistry in the formation of highly substituted butadienes, it has been possible to prepare the tricyclic ketone (82) with the same carbon framework and stereochemistry as the naturally occurring taxanes. Attention was turned next to the preparation of taxinine (2) complete with all its oxygen functionality.

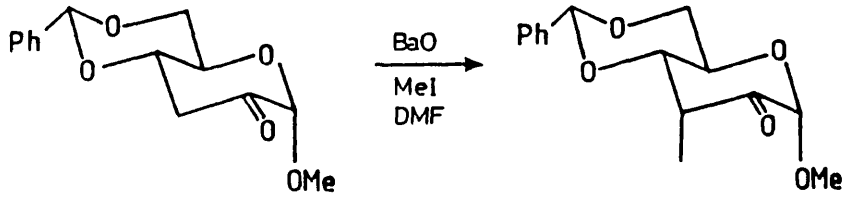
CHAPTER 5

The Use of Carbohydrate Precursors in the Synthesis of Taxinine (2)

5.1 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. A key step in the route to taxinine (2) (Scheme 48) is the Robinson annulation[119] which involves the Michael addition of an enolate to an α,β-unsaturated ketone then subsequent cyclisation. Set out below is a brief review of the existing work on carbohydrate derived enolates.

Examination of the literature revealed that sugar enolates had not been studied extensively. The first example of an α-methylation of a sugar ketone was reported by Butterworth et al.[120] This used barium oxide to deprotonate the carbohydrate ketone (187) which was then methylated with methyl iodide to produce the ketone (188).[120]

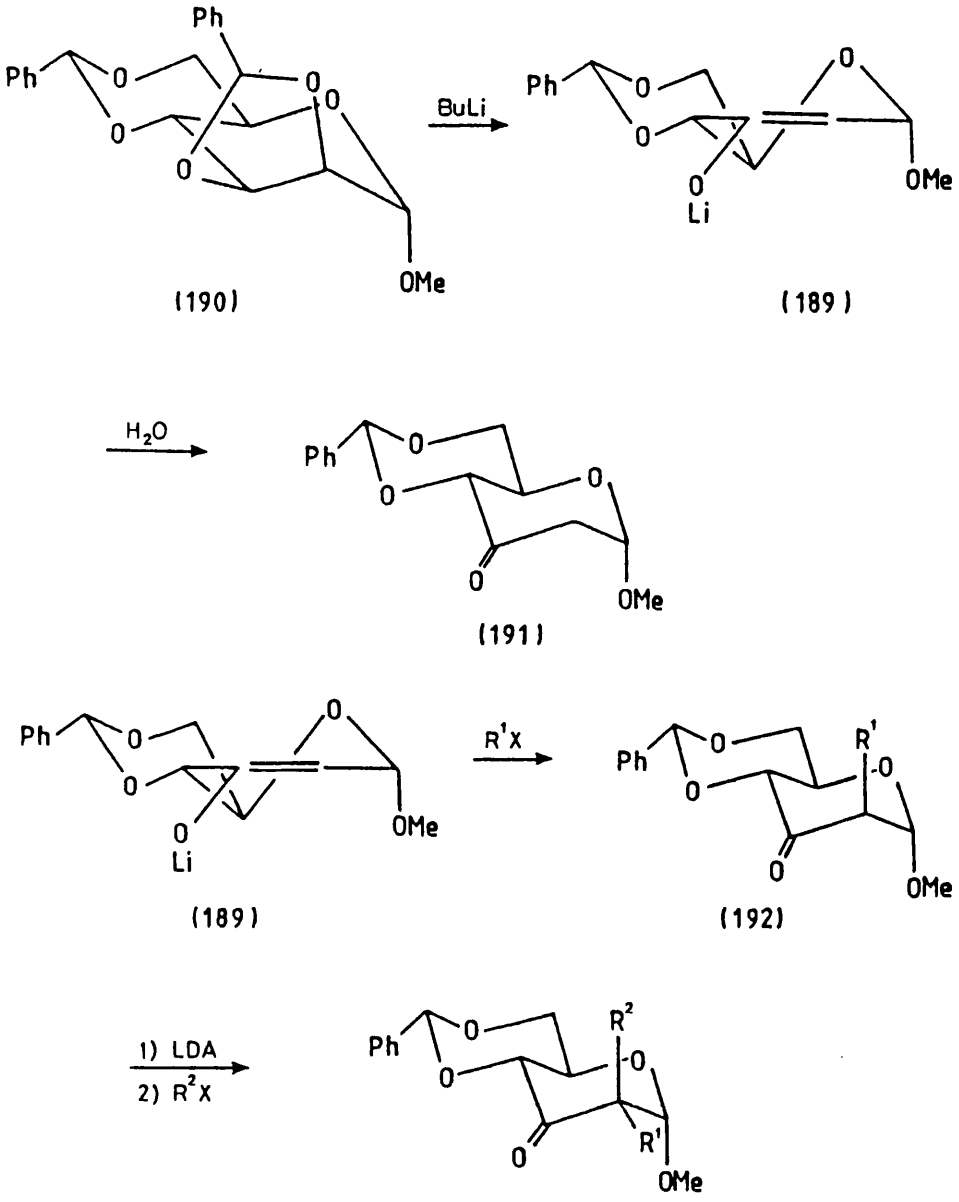


(187) (188)

Subsequently Klemer and Rodmeyer,[121] and Horton and Weckerle[122] demonstrated that the lithium enolate (189) was generated by the reaction of dibenzylidene protected sugar (190) with n-butyllithium. After work-up the ketone (191) was produced in 70% yield.

More recently Chapleur[123] utilised the enolate (189) generated by similar means and reacted it with a number of electrophiles which gave alkylated derivatives of the type (192). Treatment of the ketone (192) with lithium di-isopropylamide (LDA) generated an enolate and enabled further alkylation with a second electrophile. Spectroscopic evidence suggested that the second group was in an axial position, Scheme 46.[123]

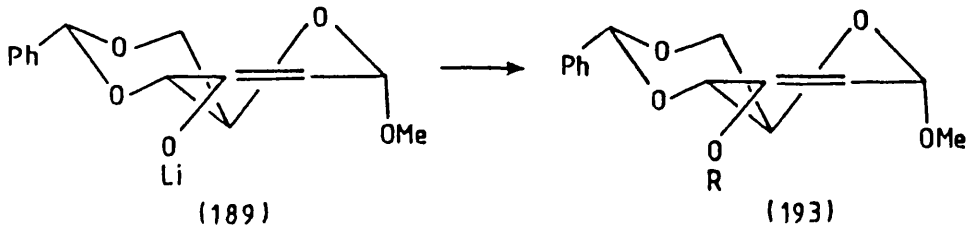
Shortly after this work was published Fraser-Reid and Tsang[124] also



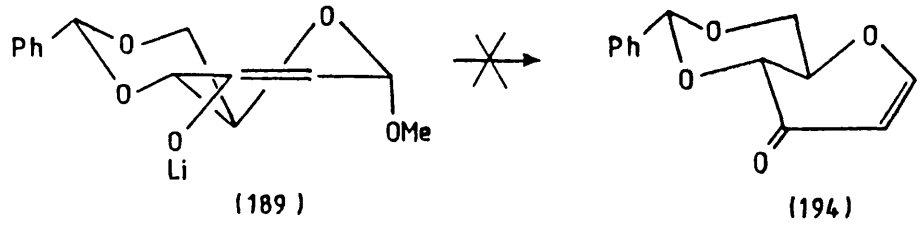
Scheme 46

used the enolate (189) generated as above or by deprotonation of the ketone (191) with lithium hexamethyldisilazide. The resulting enolate (189) reacted, with methyl chloroformate or chloromethyl methyl ether, via oxygen to yield the enol ether (193). With a number of other acylating agents no reaction was observed.[124]

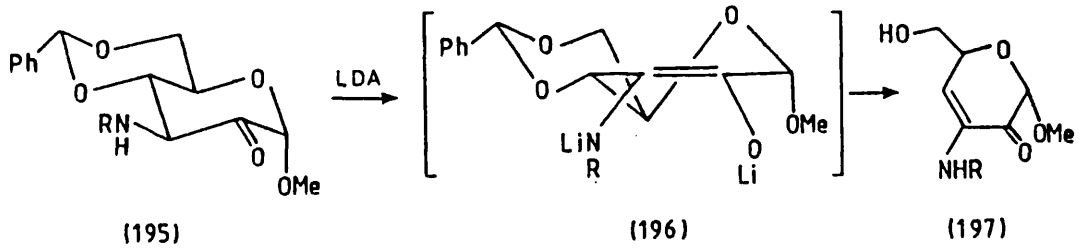
It is worth noting that β-elimination products were not reported in



any of the above cases.[120-124] The elimination of methoxide from the enolate (189) to give the enone (194) would be an example of a β-elimination.

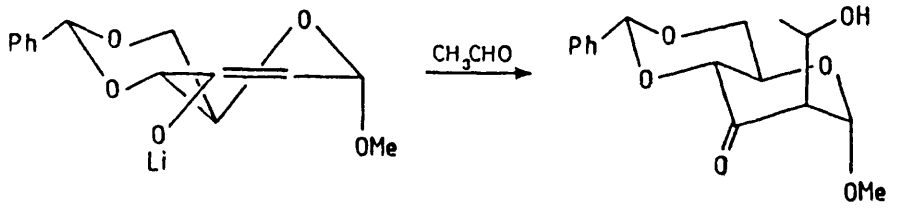


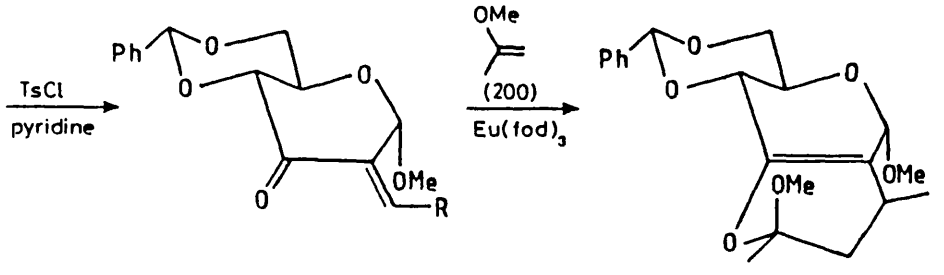
In a recent series of papers by Klemer et al.,[125] carbohydrate enolates were prepared from the corresponding ketone using LDA, then alkylated with methyl iodide. Alkylation took place on carbon and/or oxygen depending on the nature of the enolate and on the reaction conditions used. In these studies β-elimination of the enolate is sometimes observed as the major product. For example, the deprotonation of the ketone (195) using LDA in THF results in the enolate (196) which then undergoes preferential β-elimination to give the α,β-unsaturated ketone (197) as the major product.[126]



In a recent development[127] the carbohydrate enolate (189), prepared from dibenzylidene protected sugar (190), was reacted with acetaldehyde to give the aldol product (198). Treatment of this with methanesulphonyl-

chloride in pyridine gave α,β-unsaturated ketone (199). This ketone (199) could then be reacted in a reverse electron demand hetero Diels-Alder reaction with the enol ether (200), in the presence of $Eu(fod)_3$,[128] to produce the dihydropyran (201). This sequence was carried out with complete control over stereospecificity and creation of the new chiral centres, Scheme 47.[127]





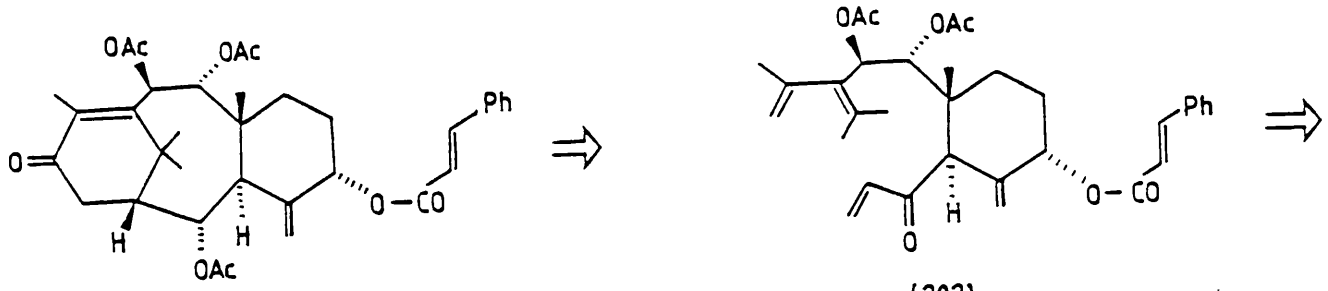
fod = 1,1,1,2,2,3,3 - heptafluoro-7,7-dimethyloctane-4,6-dionate

Scheme 47

Fraser-Reid et al. had already shown the viability of the Diels-Alder reaction using sugar enones to produce cyclohexeno pyranosides.[129] It was hoped that the proposed Robinson annulation would provide a complementary method for the preparation of highly functionalised cyclohexenones.

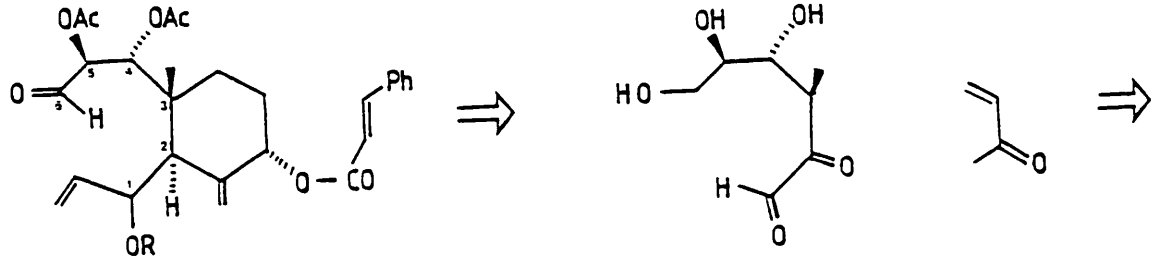
5.2 INITIAL STUDIES USING β-METHYLGALACTOPYRANOSIDE (207)

Having been successful in the synthesis of model taxane ring system (82) [Chapter 4] the next goal was the synthesis of taxinine (2) with all its functionality. The retrosynthetic analysis in Scheme 48 illustrates

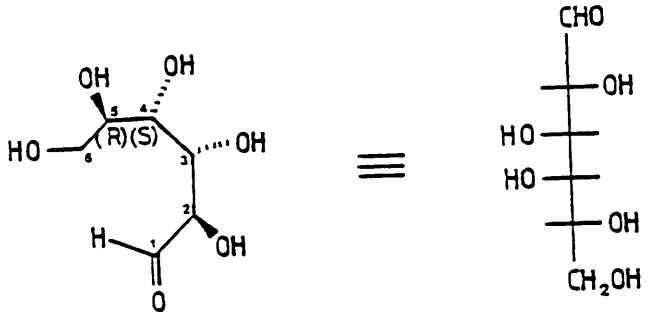


(2) (202)

Diene synthesis

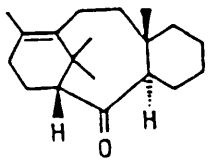


(203) (204)

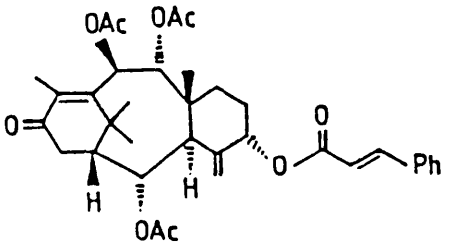


Galactose

Scheme 48



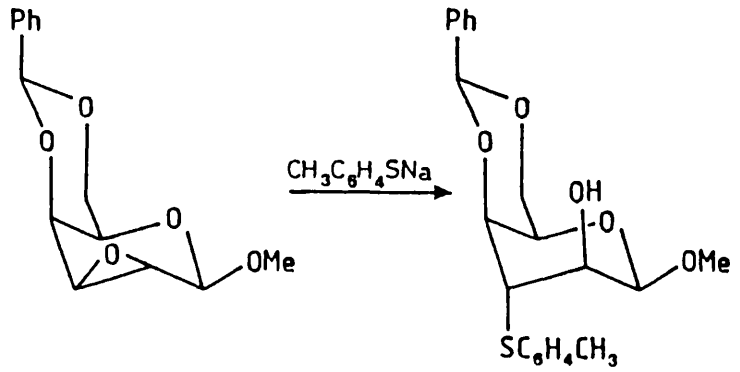
(82)



Taxinine (2)

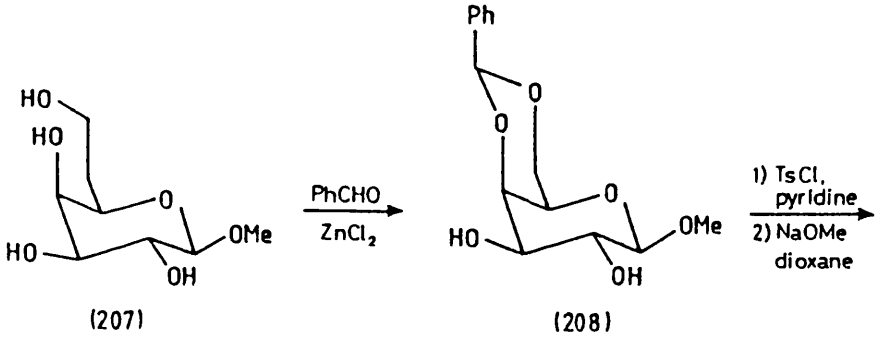
the proposed strategy for the construction of taxinine (2). The sequence continues to use the intramolecular Diels-Alder approach. It was hoped that the additional functionality could be accommodated by the cyclisation conditions used in the formation of (82). It was thought that the diene (202) could be constructed from the aldehyde (203) using the selenium directed diene synthesis developed in Chapter 4. Inserting arbitrary numbers to structure (203) suggested that carbons 1-6 could be available from a carbohydrate precursor. Construction of the cyclohexane ring by a Robinson annulation[119] led back to structure (204) which, in turn, could be derived from an aldohexose. Galactose has the required configuration for C-4 and C-5 and it was therefore considered as a practical starting material.

One of the problems during the early stages in the proposed route was the introduction of a methyl group at C-3 of the sugar. This process was known to be well documented in the glucose series and involved the opening of an epoxide with methyl magnesium chloride.[130] The equivalent sequence for galactose is known as far as the epoxide (205).[131] This epoxide has been opened by a range of nucleophiles[131,132] but apparently not organometallic reagents. The epoxide (205) has been reacted with p-thiocresolate to give the diaxially opened alcohol (206).[133] The talo epoxide (205) was required since diaxial opening would give the methyl functionality in the C-3 position and oxygen in the C-2 position. It was thought that the precursor to the Robinson annulation could be

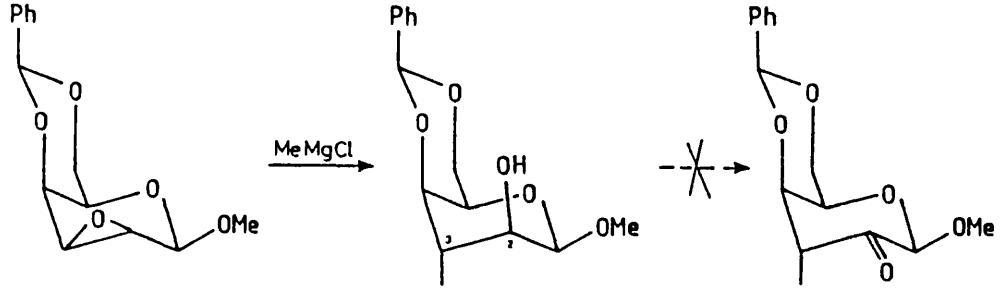


(205) (206)

prepared as outlined in Scheme 49.



(207) (208)



(205) (209) (210)

Scheme 49

Hence, commercially available β-galactopyranoside (207) was reacted with benzaldehyde in the presence of zinc chloride, according to literature,[134] to yield the benzylidene protected β-galactopyranoside (208). The anhydro-β-taloside (205) was then prepared via the ditosylate according to Frahn[131] without contamination with the anhydro-β-guloside. It was for this reason that the β-galactopyranoside (207) was chosen for

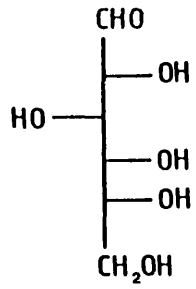
the starting material rather than the cheaper α-galactopyranoside which gives a mixture of the anhydro-α-gulo and α-talo pyranosides.[131]

The next stage required the opening of the epoxide (205) with methyl Grignard. Following a similar procedure as described for the opening of a glucose derived epoxide,[130] the anhydro-β-taloside (205) was refluxed with a ten-fold excess of methylmagnesium chloride in ether. After 1 week t.l.c. showed the disappearance of starting material. The mixture was then worked-up and the β-idoside (209) was isolated in poor yield (45%), together with two additional unidentified products which were not separable from each other by flash chromatography. Micro-analytical data and spectroscopic evidence was in accord with the structure proposed for (209). The small coupling constants in the ^1H n.m.r. for H-2, H-3 and H-4 were consistent with diaxial opening of the epoxide (205).

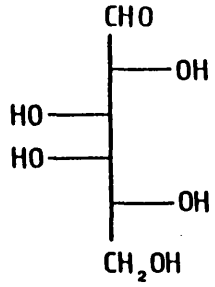
Attempts to oxidise (209) by a Swern oxidation,[115] using conditions described by Yoshimura *et al.*[135] for the general oxidation of carbohydrate alcohols, failed and only starting material (209) was recovered despite increasing the reaction time from ½h to 3h. Owing to the poor yield in the preparation of (209) and the reluctance of it to undergo oxidation to the ketone (210), it was felt more advantageous to pursue the more precedented glucose route.[130]

5.3 THE PREPARATION OF THE GLUCOSE DERIVED KETONE (213)

Glucose differs from galactose by having the opposite configuration at the C-4 hydroxyl. Referring back to the retrosynthetic analysis, Scheme 48, C-4 of the carbohydrate will ultimately be position C-9 in taxinine (2). Hence, the use of glucose throughout the synthesis would lead to C-9 having the wrong configuration. There exists, however, the

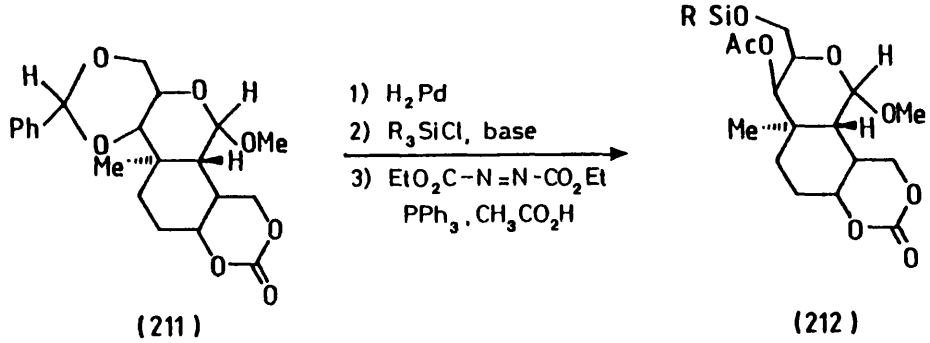


Glucose



Galactose

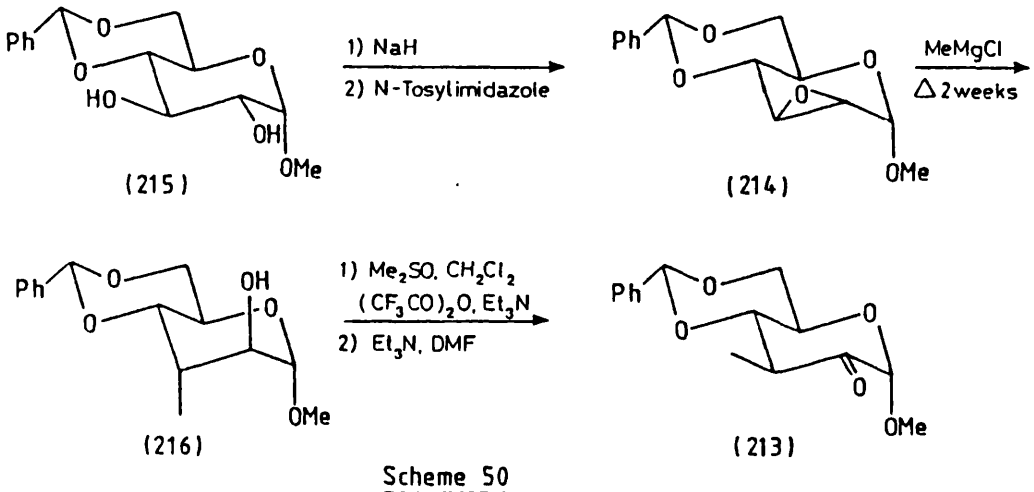
opportunity to correct this problem at a stage soon after the Robinson annulation. This could be achieved by inverting the C-4 hydroxyl configuration by means of the Mitsunobu reaction.[136] For example, the inversion could be carried out on an intermediate of type (211). The first step would be the deprotection of the benzylidene group with hydrogen on palladium then selective protection of the primary alcohol functionality. Finally, treatment with diethyl azodicarboxylate, triphenylphosphine and acetic acid[136] would cause inversion at C-4 to produce the carbohydrate derivative (212).



(211)

(212)

The approach using the glucose precursor was similar to that initiated in the galactose series but had literature precedent for the preparation of the α-arabino ulose (213), Scheme 50.[130] The anhydro-α-mannoside (214) was prepared according to the literature by treatment of the benzylidene protected α-methyl pyranoside (215) with sodium hydride and N-p-tolylsulphonylimidazole.[137] The preparation of N-p-tolylsulphonylimidazole was achieved by the reaction of p-tolylsulphonylchloride with



Scheme 50

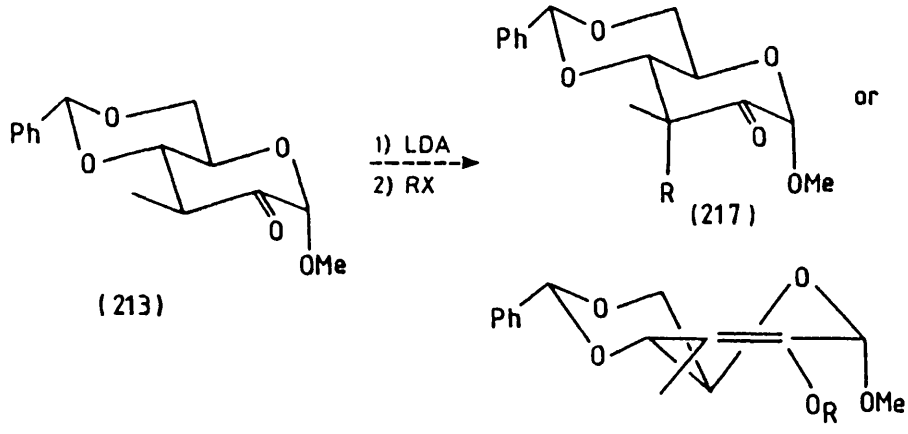
imidazole.[137] Using the above procedure it was possible to prepare exclusively the anhydro-α-mannoside (214) since tosylation takes place solely on the C-2 hydroxyl.[137]

The epoxide (214) can be opened by a number of organometallic nucleophiles; alkyl Grignards,[138] alkyl lithiums[139] and dimethyl cuprates.[140] The best method appeared to be that of Pougny and Sinay[130] and, indeed, when the epoxide (214) was reacted with sixteen equivalents of methylmagnesium chloride in ether under reflux for 2 weeks, the α-altroside (216) was formed in an essentially quantitative yield. The crude α-altroside (216) was oxidised using trifluoroacetic anhydride, dimethylsulphoxide and triethylamine to give a ketone with the methyl group initially in an axial position.[130,135] Treatment of the initial product with triethylamine in dimethylformamide cause epimerisation of the axial methyl group to the conformationally preferred ketone (213) with an equatorial methyl group. Hence, α-arabino ulose (213) was produced as a white crystalline solid.[130]

5.4 ENOLATE REACTIONS OF THE KETONE (213)

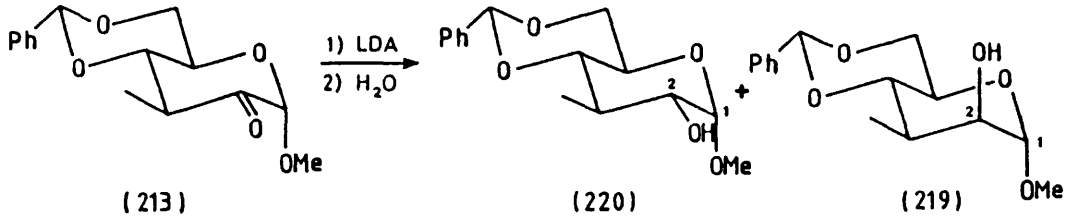
The reactions of carbohydrate derived enolates have not been explored widely [see Introduction 5.1] chiefly because of their instability and

tendency to undergo β-elimination.[123,126] It was therefore considered worthwhile investigating some simple alkylations of the enolate derived from the ketone (213) before attempting the Robinson annulation. The alkylation of the enolate could take place on carbon to give the ketone (217) or on oxygen to give the enol ether (218).



(213) (217) (218)

Initial studies were directed at enolising the ketone (213) using LDA and trapping the resultant enolate with TMS chloride. Confusion arose initially since the product isolated contained the TMS group as shown by a signal in its ^{1}H n.m.r. However, when (213) was treated with LDA and then quenched with water, rather than starting material being recovered, a mixture of the axial and equatorial alcohols (219) and (220) was obtained, via a reduction of the carbonyl group by the LDA. The two isomers were inseparable by t.l.c. but by ^{1}H n.m.r. were in a ratio of 4:1. The major product was assigned to be the one with the equatorial

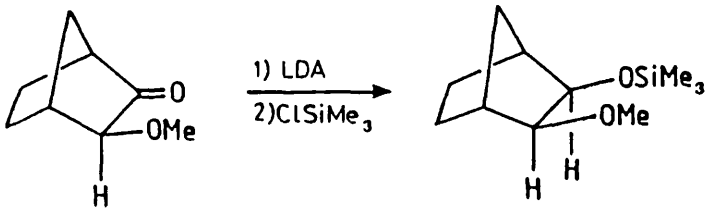


(213) (220) (219)

hydroxyl (220) on the basis of larger coupling constants between H-1 and H-2 (3.7 Hz) in the ^{1}H n.m.r. The coupling constant between H-1 and H-2

in (219) was only 1.4 Hz. It seems likely therefore, that the product isolated when trapping the "enolate" with TMS chloride was in fact the siloxy ether rather than the TMS enol ether.

Initial surprise at this result gave way at the discovery of a literature precedent which exists for the reduction of enolisable α-halo and α-methoxy ketones, together with non-enolisable ketones by LDA.[141] The reaction of bicycloheptan-2-one (221) with LDA followed by TMS chloride gave, exclusively, the siloxy ether (222).[141] In previous



(221) (222)

work[123,125,126] on carbohydrate enolates generated by the use of LDA, no problems of reduction appear to have been encountered. The mechanism is considered to be a nitrogen analogue of the Meerwein-Ponndorf-Verley reduction, Figure 19. For this reduction to take place, the amide base

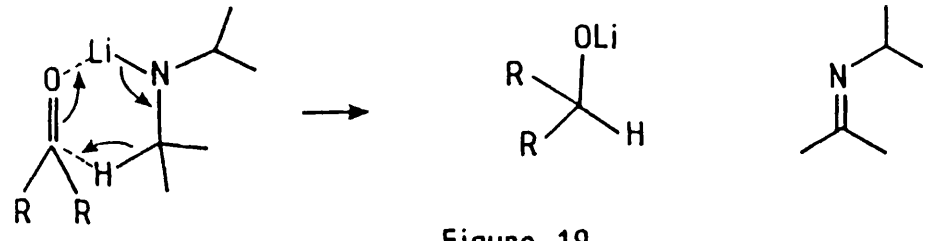
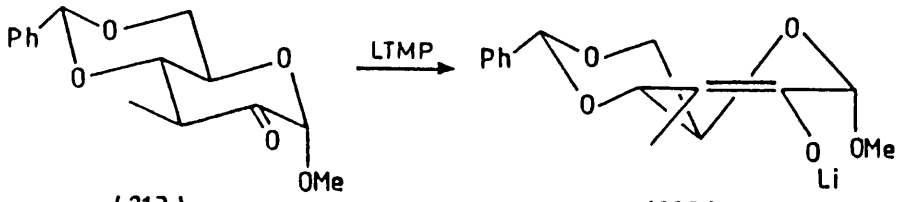


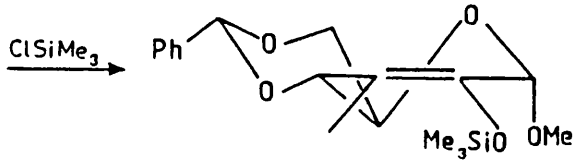
Figure 19

must have an α-hydrogen, so it was considered to be possible to overcome this problem by the use of either lithium hexamethyldisilazide or lithium 2,2,6,6-tetramethylpiperidide (LTMP) as the base.

Extensive work revealed that the ketone (213) could be deprotonated with LTMP in ether; the enolate (223) was then trapped with TMS chloride to furnish the enol ether (224). It was also found that the enol ether (224) could be prepared if the ketone (213) was subjected to the same



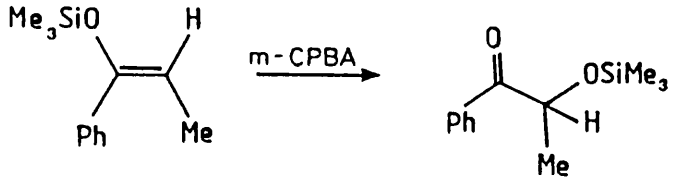
(213) (223)



(224)

conditions used for its epimerisation, Scheme 50, but in the presence of TMS chloride.

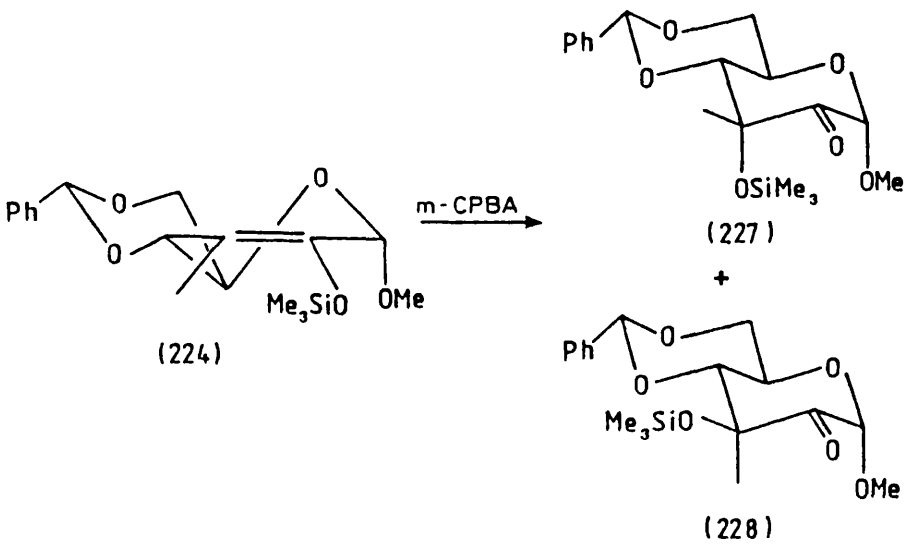
An interesting digression, at this point, was considered concerning the reaction of the enol ether (224) with m-CPBA. TMS enol ethers are known to react with m-CPBA to give protected α-hydroxy ketones.[142] An example is shown by the reaction of the silyl enol ether (225) with m-CPBA to yield the α-siloxy ketone (226).[143] This transformation would



(225) (226)

be of use in carbohydrate chemistry as it would add additional functionality but maintain a differentiation between the hydroxyl groups.

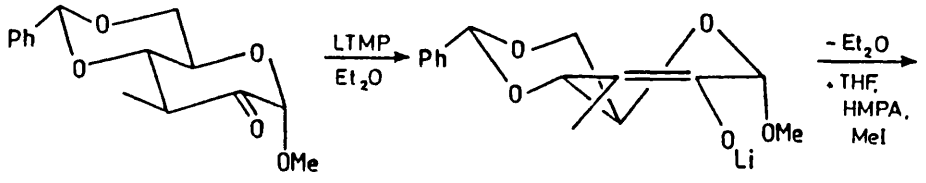
When the TMS enol ether (224) was treated with m-CPBA, in dichloromethane, the product was isolated as one spot by t.l.c. but ^{1}H n.m.r. showed it to be a mixture of isomers in a ratio of 6:1. ^{1}H n.m.r. was in accord with the expected siloxy ketones (227) and (228) but from the evidence available it was not possible to determine which isomer was the major one. On steric grounds it might be expected that the β-face would be preferentially attacked producing the corresponding siloxy ketone (228).



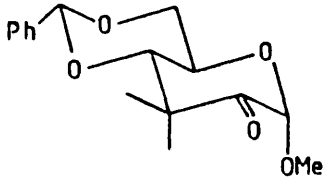
(224) (227) + (228)

Obviously more work could have been carried out to determine the configuration of the products and possible improvement of the ratio but as a digression, it was not considered to be of crucial relevance, so attention was directed back to the enolate (223).

If the enolate (223) was generated by use of LTMP in ether and an excess of methyliodide added, the enolate remained unreactive, even at room temperature. The addition of TMS chloride to the same solution resulted in the trapping of the enolate (223) to form the enol ether (224). It was therefore apparent that the enolate was being formed; it was not decomposing but did not react under these conditions. After considerable experimentation it was found that removal of the ether as the solvent from the enolate solution, by means of a vacuum pump, and replacing it by THF, followed by the addition of excess methyl iodide (7 equivalents) and HMPA (½ equivalent) resulted in the enolate (223) being alkylated on carbon to give the dialkyl carbohydrate (229) in respectable yield (57%). Solvent studies showed that it was better to generate the enolate (223) in ether then change the solvent to THF rather than try to form the enolate (223) directly in THF.

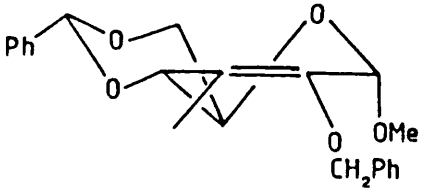


(213) (223)



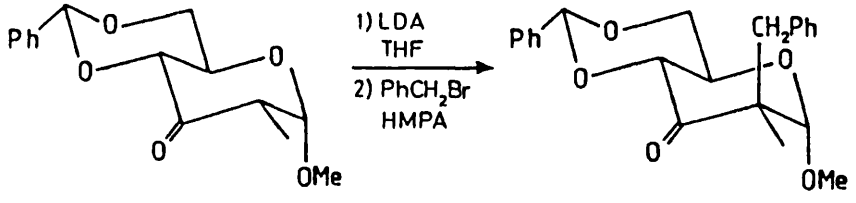
(229)

Under similar conditions the enolate (223) reacted with benzyl bromide to produce, after work-up, a crystalline solid with n.m.r. and i.r. data consistent with the O-alkylated product (230). The O-alkyla-



(230)

tion appeared to contradict the C-alkylation observed by Chapleur[123] when the ketone (231) was treated with LDA then alkylated with benzyl bromide to give the dialkylketone (232). There appears no obvious explanation

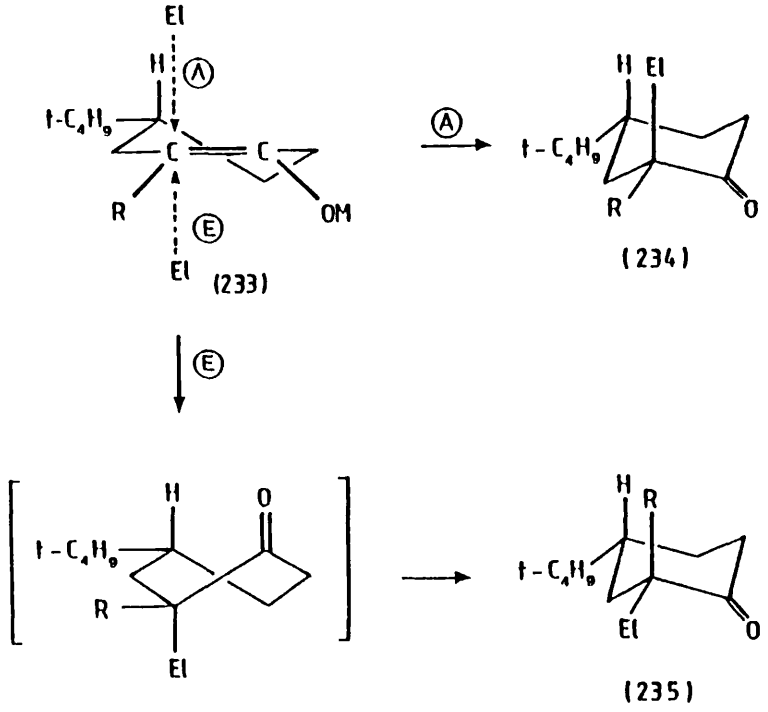


(231) (232)

as to why this difference occurs, as both reactions used THF as the solvent and both had HMPA as a cosolvent (HMPA accelerates the rate of alkylation but also promotes O-alkylation[144]).

In order to prove whether the new methyl group in the ketone (229) had an equatorial or axial orientation the enolate (223) was alkylated

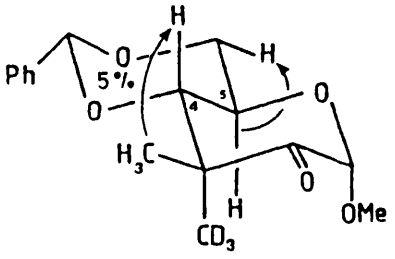
with [$^2H_3$] methyl iodide. ^1H n.m.r. revealed the absence of the signal at δ1.33 which corresponds to one of the methyl groups. This indicated that only one of the two alternatives had been formed. Scheme 51[145] shows how electrophilic attack can occur on the two faces of the cyclohexane enolate (233). The product (234), with the electrophile in an axial position, arises via a postulated chair-like transition state which is presumed to be preferred to the boat-like transition state which leads to the ketone (235) with the electrophile in an equatorial



Scheme 51

position.[145] It was therefore predicted that the product from the alkylation of the enolate (223) with [$^2H_3$] methyl iodide would have the [$^2H_3$] methyl group in an axial position, Figure 20. N.O.e. were observed between the methyl at δ1.25 and H-4 at δ3.54 (5%) and between H-5 at δ4.28 and H-6 eq. at 4.41, Figure 20, crucially no n.O.e. was measured from the methyl signal at δ1.25 and H-5. This evidence strongly supports the predicted product (236) which results from axial attack of the

enolate (223).

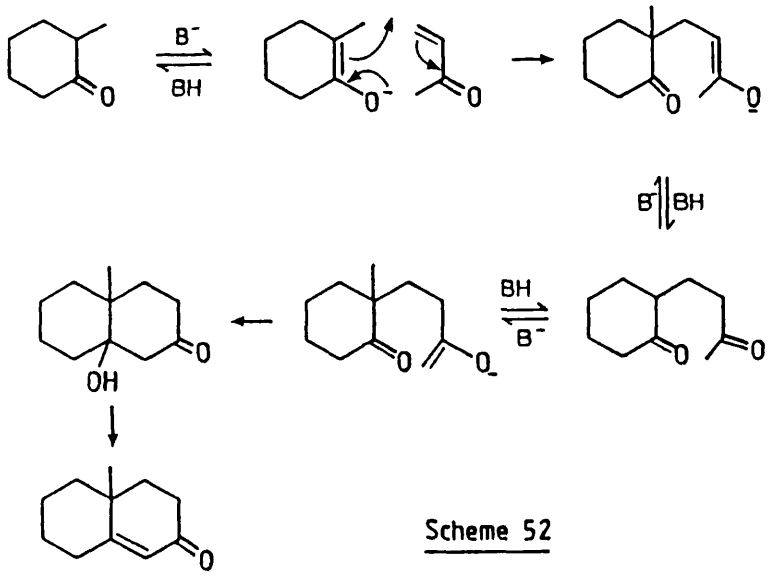


(236)

Figure 20

5.5 THE ROBINSON ANNULATION OF A CARBOHYDRATE DERIVATIVE

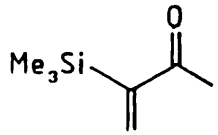
Confident that LTMP provided a reliable method for generation of enolate (223), attention was turned to the Robinson annulation. The original Robinson annulation[119] involves a base-catalysed Michael addition of a ketone to methyl vinyl ketone followed by acid or base-catalysed aldol condensation, Scheme 52.[146] There are two major problems



Scheme 52

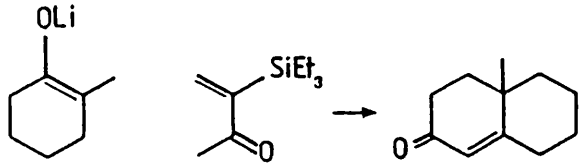
with methyl vinyl ketone; firstly its tendency to polymerise, especially in the presence of strongly basic enolates. This problem was largely overcome by the generation of methyl vinyl ketone *in situ*.[146] The second problem stems from the fact that the generation of the methyl vinyl ketone *in situ* relies on an equilibrium process and cannot therefore be used for

regiospecifically generated enolates. Both problems were simultaneously and independently surmounted by Stork et al.[147] and by Boeckman,[148] by the use of the α-silyl enone (237). The silyl group in the enone (237)



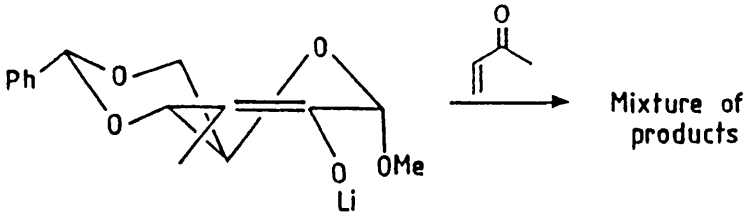
(237)

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.[146] The use of the silyl enone (237) in the Robinson annulation is illustrated by the reaction of the enolate (238) with the enone (239) to produce the decenone (53).[147] Yields of cyclised product using this method are typically over 60%.



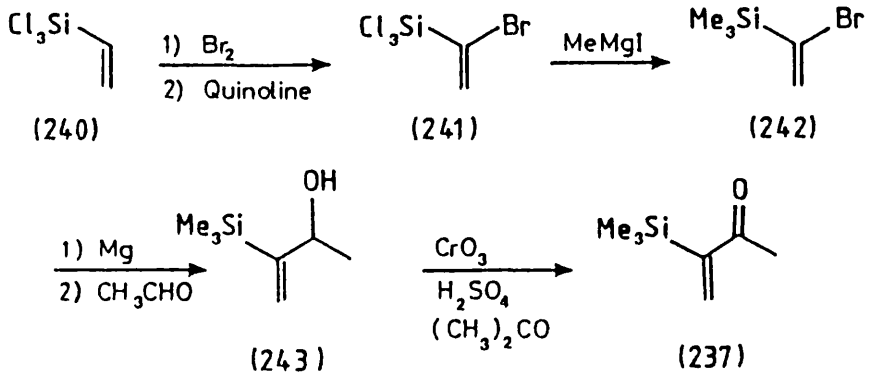
(238) (239) (53) 70%

Before preparing the α-silyl enone (237) it was thought that it was worthwhile to try the reaction of the enolate (223) with methyl vinyl ketone. T.l.c. of the product showed a large number of spots and so this was not pursued any further.



(223)

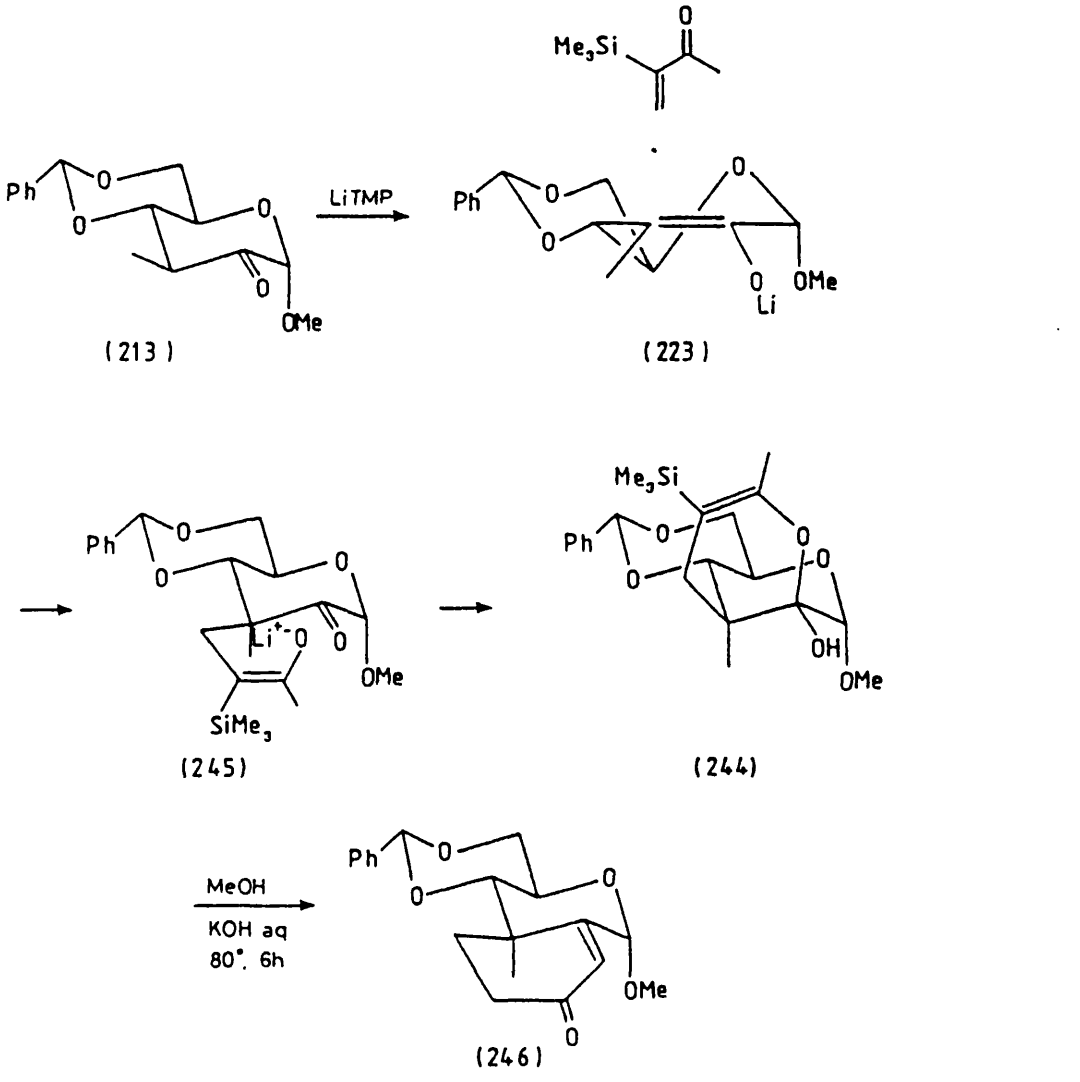
The α-silyl enone (237) was prepared according to literature procedures, Scheme 53.[145,150] Trichlorovinyl silane (240) was brominated with bromine in carbon tetrachloride followed by dehydrobromination with



Scheme 53

quinoline to give the vinyl silane (241). Reaction of (241) with three equivalents of methylmagnesium iodide furnished the bromovinyl trimethylsilane (242).[149] Reaction of the Grignard of (242) with acetaldehyde gave the butenol (243) and this crude reaction mixture was then oxidised to produce the α-silyl enone (237) which had i.r. and ^{1}H n.m.r. spectra in accordance with the literature.[150]

The enolate (223) was generated in the usual way in ether as the solvent and, rather than change to THF, the enolate solution was merely concentrated by removing approximately half the ether volume. The silyl enone (237) was added, at -78°C and then the mixture slowly allowed to warm to room temperature, followed by continued stirring for 1h. After work-up and flash chromatography (on some occasions it was found unnecessary to purify) an intermediate (244) was isolated. This initial product gave spectra consistent with Michael addition of the enolate (223) to the enone (237) followed by O-cyclisation of the resulting enolate (245) back onto the carbonyl of the original sugar ketone, Scheme 54. At this stage it was not known whether axial or equatorial attack had taken place but from high-field n.m.r. it appeared that only one isomer had been formed. Reaction of (244) with 4% aqueous potassium hydroxide in methanol for 6h,

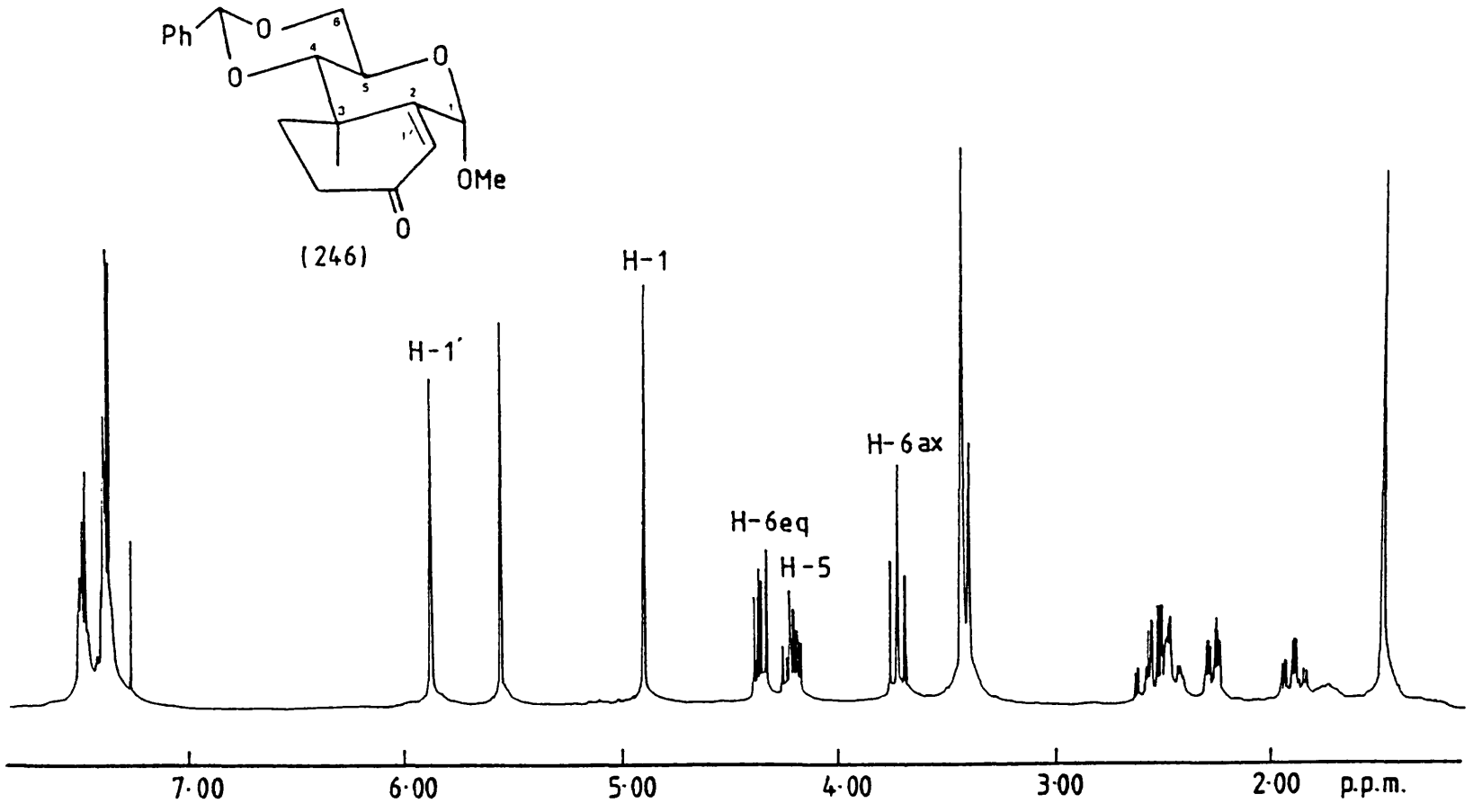


(213) (223) (245) (244) (246)

Scheme 54

at 80°C, furnished the Robinson annulation product (246) in 58% overall yield from (213). Despite attempts to crystallise (246) it remained a waxy oil, which made it necessary to determine the stereochemistry at C-3 using n.m.r. techniques. The high-field ^{1}H [Figure 21] and ^{13}C n.m.r. together with other spectroscopic evidence was in accord with the product (246). The stereochemistry at the C-3 position was determined by n.O.e. experiments, Figure 22 shows the results of these n.O.e. studies. The important n.O.e. observed between H-5 and the C-3 methyl group suggested that the two were axial and that the new ring was in an equatorial position. This configuration of the C-3 centre in the enone

FIGURE 21 - ^{1}H n.m.r. of enone (246).



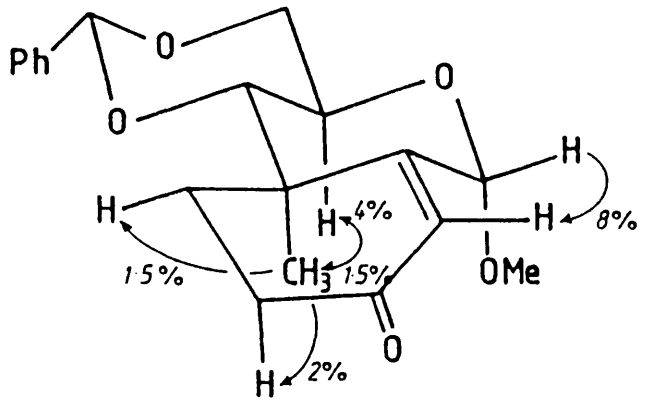


Figure 22

(246) is the same as is required for C-8 in taxinine (2). The stereochemistry of the enone (246) was later confirmed by an X-ray crystal structure of a derivative of this compound, Figure 23 and Appendix 1.

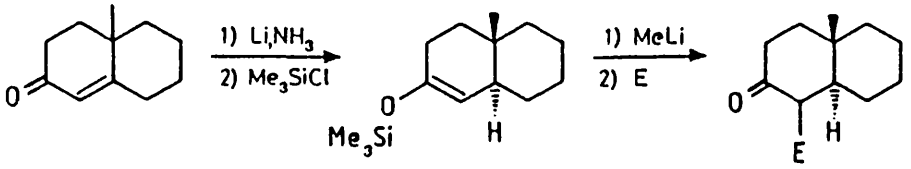
It therefore appeared that the enone (246) resulted from equatorial attack of the α-silyl enone (237) to the enolate (223). The equatorial attack leading to the Robinson annulation product was the opposite to that observed for the methylation with [$^2H_3$] methyl iodide, Figure 20. A possible reason for this could be that the reaction of the enolate (223) with methyl iodide cannot be reversible whereas it is possible that in the case of the α-silyl enone (237) the reaction may be reversible and so lead to a thermodynamic product. Also the two reactions were carried out in different solvent and it is possible that changes in the degree of association and aggregation of the enolate (223) might influence the stereochemistry,[151] although it seems unlikely that this would have such a pronounced effect.

5.6 FURTHER REACTIONS OF THE ENONE (246)

With a reliable route to the enone (246), the next stage in the synthesis of taxinine (2), Scheme 48, required reduction of the double bond to give specifically a trans ring junction and to regiospecifically

introduce functionality which could be converted to an exocyclic methylene.

Stork et al.[39] has studied the lithium in ammonia reduction of the octalone (53).[39] This method regiospecifically generates the enolate which can be trapped with TMS chloride to give the enol ether (52). The enolate can then be regenerated with methyllithium and reacted with the required electrophile, Scheme 55.[39] Initial small scale attempts at

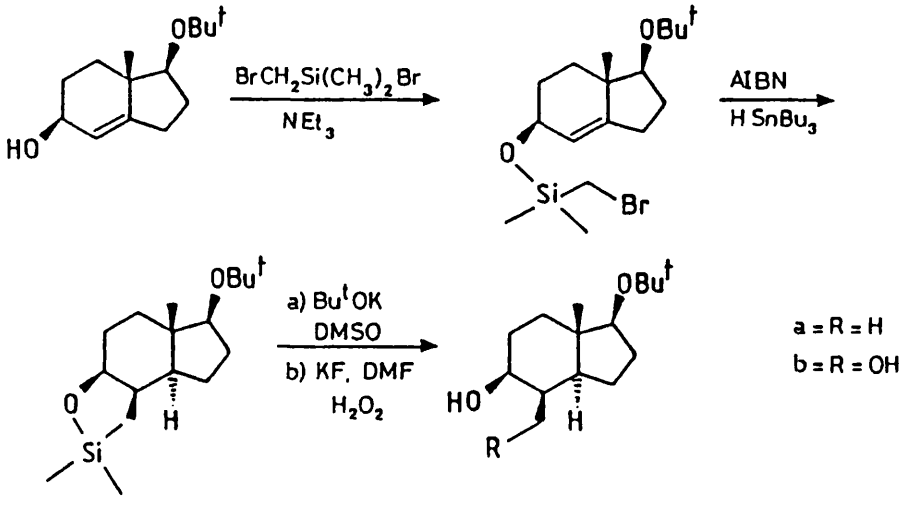


(53) (52)

Scheme 55

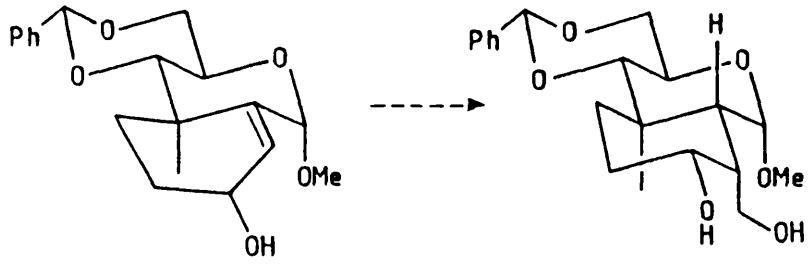
reacting the enone (246) with lithium in ammonia followed by trapping of the enolate with TMS chloride proved unsuccessful and no identifiable products could be isolated. The lithium in ammonia conditions used can also remove the benzylidene protecting group so this may account for some of the problems encountered here.

Recently Stork and Sofia[152] published a more satisfactory procedure to perform a similar conversion but using an allylic alcohol rather than an enone, Scheme 56. This leads to the regiospecific introduction of a



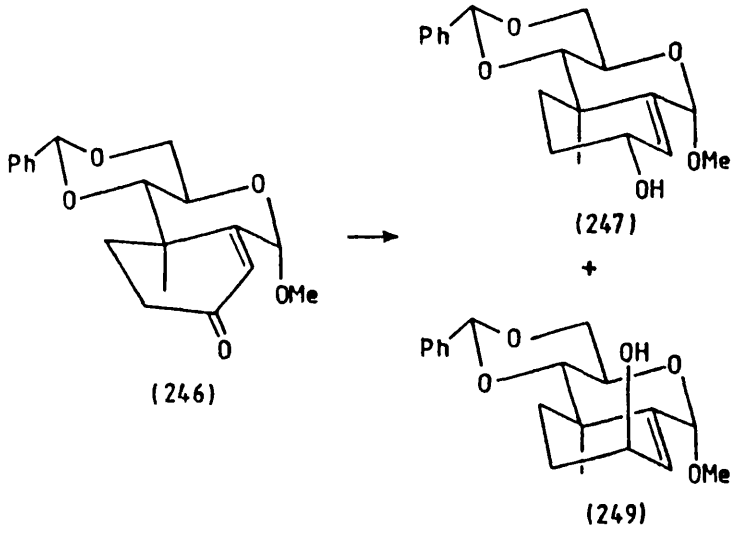
Scheme 56

methyl group adjacent to the hydroxyl group and stereochemically cis to it and the addition of a hydrogen to the double bond but on the opposite face to the hydroxyl group. The application of this procedure to the allylic alcohol (247), derived from the Robinson annulation product (246), would lead directly to the diol (248).



(247) (248)

It was considered possible that the allylic alcohol (247) could be prepared by reduction of the enone (246). Obviously the reducing agent could attack from either the α or β face but models seemed to show that the α-face was more sterically hindered by the axial methyl and methoxy groups. Three hindered reducing agents were tried; diisobutylaluminium hydride (DIBAH),[80] 9-borabicyclo[3.3.1]nonane (9-BBN)[153] and L-selectride.[154] The treatment of the enone (246) with DIBAH, at -78°C,



resulted in the reduction of the ketone functionality to yield the allylic alcohols (247) and (249). The high-field ^{1}H n.m.r. showed the

product to be a mixture of epimers at the hydroxyl position in a ratio of 3.4:1. The reduction using 9-BBN improved the ratio of (247):(249) to 5:1 but the best result was obtained using L-selectride in THF, at -78°C, where the ratio was approximately 30:1. It was possible to crystallise the product from the selectride reduction and after one recrystallisation from 60-80 petroleum ether the ^{1}H n.m.r. showed only the major product. A crystal of the allylic alcohol (247), which was suitable for an X-ray crystal structure was obtained and the result of the X-ray structure is shown in Figure 23 [see also Appendix 1]. The X-ray structure confirms that the alcohol functionality is on the required α-face. The result also confirms the stereochemistry of the Robinson annulation product (246) to be that already predicted from the n.m.r. studies.

Unfortunately at this exciting stage time elapsed and it was not possible to carry out the reductive hydroxymethylenation.[152] Should this reductive hydroxymethylenation be successful the product (248) could, after a deprotection, reprotection sequence, incorporating an inversion of configuration at C-4 and C-2', be converted to the aldehyde (250). By making use of the selenium directed diene synthesis in a similar type of conversion as that already used in Chapter 4, it ought to be possible to produce the Diels-Alder precursor (251). It is predicted that the intramolecular Diels-Alder reaction would then proceed to produce the tricyclic ketone (252) as a single isomer and hence virtually complete the total synthesis of taxinine (2), Scheme 57.

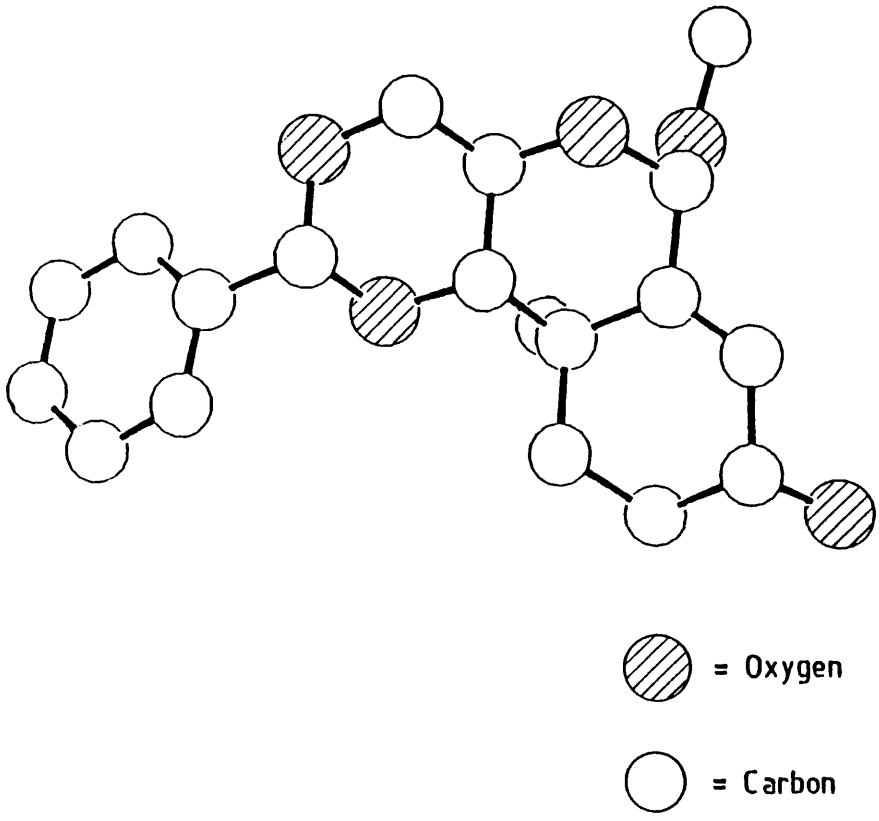
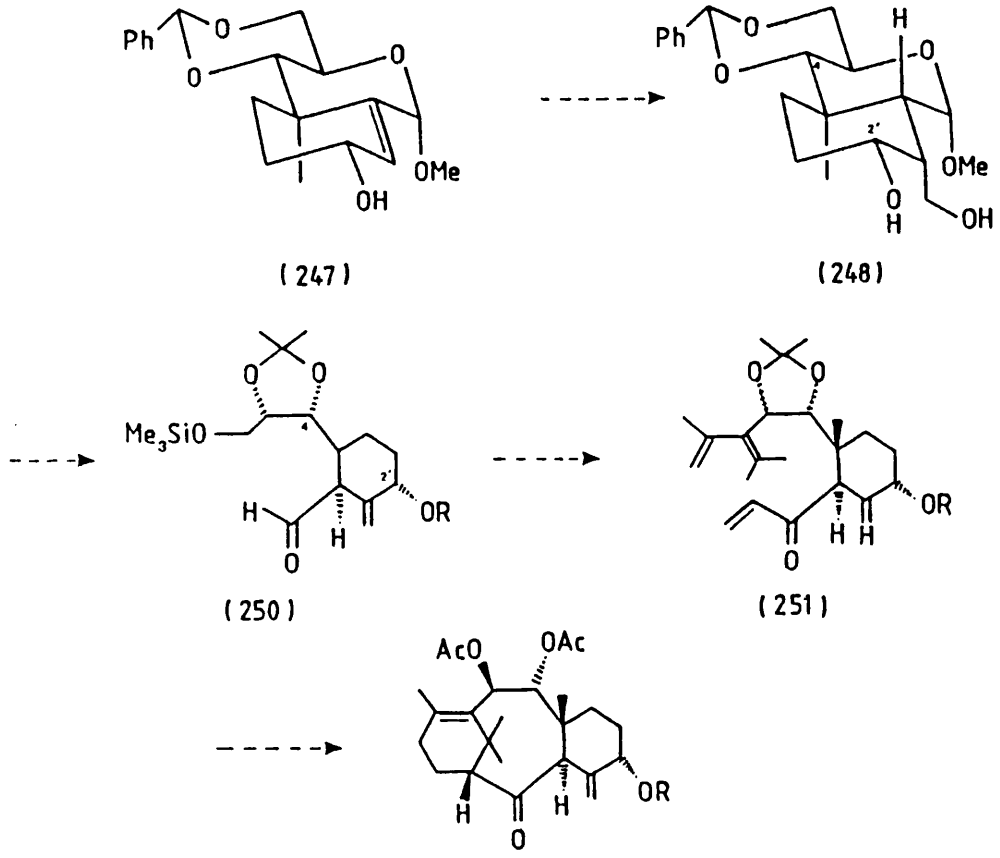


FIGURE 23

X-Ray Crystal Structure of Allylic Alcohol (247)



(247) (248) (250) (251)

Scheme 57

EXPERIMENTAL

EXPERIMENTAL

All 90 MHz ^{1}H n.m.r. spectra were recorded on a Varian EM-390 spectrometer. High-field ^{1}H n.m.r. (300 MHz) and ^{13}C n.m.r. (75 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. ^{1}H n.m.r. (400 MHz) and ^{13}C n.m.r. (100 MHz) spectra were recorded using the high-field n.m.r. service at the University of Warwick. The ^{31}P n.m.r. (24 MHz) spectra were recorded on a Jeol JNM-FX-60 spectrometer. 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 and ultra-violet spectra on a Shimadzu UV-240 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.*[†] using silica gel manufactured by Merck & Co., Kiesel 60, 230-400 mesh (ASTM). Purifications by chromatotron were performed using model 7924T and Merck & Co. Kieselgel 60 PF254 silica plates. T.l.c. was conducted on precoated aluminium sheets (60-254) with a 0.2 mm layer thickness, manufactured by Merck & Co.

The concentration of the n-butyllithium was determined by back titration with 0.1 M hydrochloric acid from solutions in dibromoethane and water using phenolphthalein as an indicator.

Petroleum ether refers to the 40-60°C fraction and all petroleum ether and ethyl acetate was distilled prior to use. THF, DME, toluene and

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[†] W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.

dioxane were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether and was distilled from $LiAlH_4$. Dichloromethane, triethylamine, dimethylsulphoxide and pyridine were distilled from powdered calcium hydride and trimethylsilylchloride was distilled immediately prior to use from tributylamine. Methanol and ethanol were distilled from magnesium and iodine.

Superscripts in the experimental text refer to notes at the end of the experiment and not to the main references.

Preparation of 2-methyl-5-phenyl-1-penten-3-ol (253)[1]

(253)

2-Bromopropene (0.89 g, 7.4 mmol) in THF (9 ml) was added to magnesium turnings (0.18 g, 7.5 mmol) in THF (1 ml), under nitrogen, at such a rate so as to maintain a gentle reflux. After the addition the mixture was refluxed for a further 1h then cooled in ice and 3-phenylpropanal (1 g, 7.4 mmol) was slowly added in THF (5 ml). After a further ½h the mixture was poured into a saturated aqueous solution of NH_4Cl (75 ml) and extracted with ether (3 × 50 ml). The extracts were combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (7:1 petroleum ether-ether) 2-methyl-5-phenyl-1-penten-3-ol (253)[1] was obtained as a colourless oil (0.7 g, 53%).

R_f 0.35 (7:1 petroleum ether-ether);

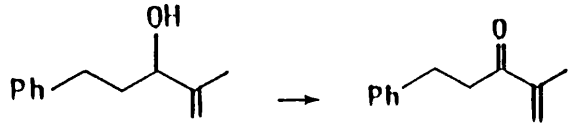
ν_{max} (film) 3400brs(OH), 3080m, 3060m, 3025m, 2945s, 2860m, 1650w, 1604m, 1495m, 1450s, 1060brs, 1030s, 900s, 700s;

δ_H (90 MHz; $CDCl_3$) 1.5 (1H, s, OH), 1.72 (3H, s, Me-2) overlapping 1.7-1.95 (2H, m, H-4), 2.58-2.76 (2H, m, H-5), 4.05 (1H, t, J = 6Hz, H-3), 4.85 (1H, brs, H-1), 4.93 (1H, brs, H-1), 7.18 (5H, s, $C_6\underline{H}_5$).

Notes

1. Known compound see Ref. 155.

Preparation of 2-methyl-5-phenyl-1-penten-3-one (89)[1]



(253) (89)

Chromium trioxide[2] (2.39 g, 23.9 mmol) was added to a stirred solution of pyridine (3.86 ml, 47.7 mmol) in dichloromethane (60 ml) under nitrogen. Rapid stirring was continued for ½h at room temperature to produce a deep red solution.[3] 2-Methyl-5-phenyl-1-penten-3-ol (253) (0.7 g, 4.0 mmol) in dichloromethane (5 ml) was added in one portion, the solution immediately turned brown. After approximately 5 min. the mixture was filtered through a short silica column and the chromium residues washed with ether (2 × 75 ml). The solvent was removed in vacuo and after flash chromatography (20:1 petroleum ether-ether) 2-methyl-5-phenyl-1-penten-3-one (89)[1] was obtained as a colourless oil (0.48 g, 69%).

R_f 0.40 (20:1 petroleum ether-ether);

ν_{max} (film) 3080w, 3060w, 3020m, 2950m, 2920m, 1675s(C=O), 1630m, 1602w, 1490m, 1450s, 1410m, 1368m, 1312w, 1090m, 1070m, 1030m, 935m, 750m, 700s;

δ_H (90 MHz; $CDCl_3$) 1.83 (3H, s, CH_3), 2.90 (4H, s), 5.68 (1H, s, H-1), 5.87 (1H, s, H-1), 7.15 (5H, s, $C_6\underline{H}_5$);

m/z 174 (M^+, 90), 159(20), 105(30), 111(20), 91(80), 69(90), 41(100).

Notes

1. Known compound see Ref. 156.
2. Dried over P_2O_5 at 60°C under vacuum overnight.
3. See Ref. 53.

Preparation of Isopropyltriphenylphosphonium Iodide (254)[1]

Triphenylphosphine[2] (31 g, 118 mmol) and isopropyl iodide (21 g, 124 mmol) were heated together at 100°C for 20h according to the literature. The resultant solid was recrystallised from ethanol to yield isopropyltriphenylphosphonium iodide (254)[1] (40.5 g, 79%).

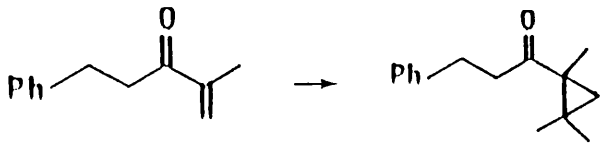
δ_H (90 MHz, $CDCl_3$) 1.3 (6H, dd, J = 21, 7 Hz), 4.8-5.25 (1H, m), 7.39-8.15 (15H, m, 3 × $C_6\underline{H}_5$);

δ_p (24 MHz, $CDCl_3$) 31.87.

Notes

1. Literature procedure see Ref. 157.
2. Recrystallised from 60-80 petroleum ether immediately prior to use.

Preparation of 1-3'-phenyl-1'-propanone-1,2,2-trimethylcyclopropane (91)



(89) (91)

n-Butyllithium[1] (1.3 ml, 3.24 mmol) was added dropwise to a stirred solution of isopropyltriphenylphosphonium iodide (254) (1.4 g, 3.24 mmol) in dry THF (40 ml), at room temperature, under nitrogen. After a further 2h 2-methyl-5-phenyl-2-penten-3-one (89) (0.54 g, 3.08 mmol) was added to the deep red coloured solution and the mixture refluxed for 1h. The solution was quenched with water and the aqueous phase extracted with ether (3 × 50 ml).[2] The combined ether extracts were dried ($MgSO_4$) and the solvent removed <u>in vacuo</u>. After flash chromatography (20:1 petroleum ether-ether) and Kugelröhr distillation (b.p. 120°C at 1 mmHg) 1-3'-phenyl-1'-propanone-1,2,2-trimethylcyclopropane (91) was obtained

as a colourless oil (0.3 g, 45%).

R_f 0.6 (20:1 petroleum ether-ether);

$C_{15}H_{20}O$ requires C 83.29%, H 9.32%, N 0.00%,

found C 83.21%, H 9.28%, N 0.00%;

ν_{max} (film) 3090m, 3065s, 3030s, 3000s, 2950s, 1690s(C=O), 1608s, 1495s, 1455s, 1410s, 1393s, 1230m, 1190m, 1115s, 1000s, 800s, 750s, 700s;

δ_H (300 MHz; $CDCl_3$) 0.31 (1H, d, J = 4.3 Hz, H-3), 0.89 (3H, s, CH_3), 1.15 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.46 (1H, d, J = 4.3 Hz, H-3), 2.59-2.97 (4H, m), 7.1-7.3 (5H, m, $C_6\underline{H}_5$);

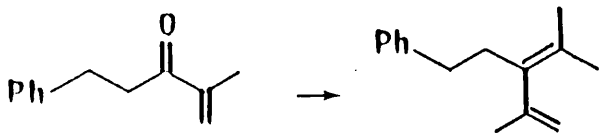
δ_C (75 MHz; $CDCl_3$) 16.84(q), 20.55(q), 21.43(q), 25.79(s, C-2), 26.11(t), 29.84(t), 36.00(s, C-1), 42.51(t), 125.83(d), 128.25(d), 128.28(d), 141.50(s), 209.20(s);

m/z 216 (M^+, 60), 200(10), 173(40), 125(70), 105(70), 91(100), 83(50).

Notes

1. n-Butyllithium was 2.4 M by titration.
2. A white solid insoluble in ether was extracted into dichloromethane and found to be recovered (254), δ_p 31.6.

Preparation of 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88)



(89) (88)

Lithium (1.1 g, 150 mmol) was added to a stirred slurry of anhydrous titanium trichloride (6.8 g, 43 mmol) in dry DME (60 ml) under argon, at room temperature. The mixture was refluxed for 1h then cooled and a mixture of 2-methyl-5-phenyl-1-penten-3-one (89) (0.95 g, 5.5 mmol) and acetone (1.6 g, 27 mmol) was added in DME (4 ml). The mixture was

stirred at room temperature for 2h then refluxed for 20h. After the mixture had been allowed to cool it was filtered and the residue washed with ether (2 × 50 ml). The solvent was removed in vacuo and after flash chromatography[1] (petroleum ether) 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88)[2] was obtained as a colourless oil (15 mg, 1%).

R_f 0.5 (petroleum ether);

ν_{max} (film) 3070w, 3020m, 2960s, 2920s, 2880s, 1630w, 1603w, 1495m, 1450s, 1370m, 1260w, 1170w, 895m, 750m, 698s;

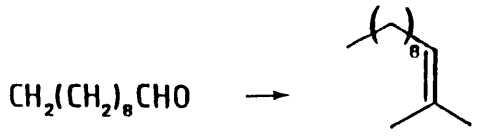
δ_H (300 MHz; $CDCl_3$) 1.62 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.80 (3H, dd, J = 1.5, 0.9 Hz, CH_3), 2.33-2.41 (2H, m), 2.57-2.66 (2H, m), 4.62 (1H, dq, J = 2.7, 0.9 Hz, H-1), 4.98 (1H, dq, J = 2.7, 1.5 Hz, H-1), 7.14-7.31 (7H should be 5H, m, $C_6\underline{H}_5$);

m/z 200 (M^+, 10), 109(30), 91(30), 67(20), 55(20), 40(100).

Notes

1. A large number of polar unidentified products were also formed.
2. The diene (88) was further characterised when prepared by alternative means, see p.120.

Preparation of 2-methyl-2-dodecene (99)



(99)

Decanal (1.8 g, 11.5 mmol) was added to isopropyltriphenylphosphorane (90) in THF (50 ml) which had been generated from isopropyltriphenylphosphonium iodide (254) (5 g, 11.6 mmol) and n-butyllithium[1] (4.6 ml, 11.5 mmol) see preparation of (91). A white precipitate of triphenylphosphine oxide was deposited and after 2h at room temperature the

mixture was poured into water and extracted with ether (3 × 75 ml). Each extract was washed with saturated brine solution (30 ml) then combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (petroleum ether) and Kugelröhr distillation (b.p. 110°C at 18 mmHg) 1-methyl-2-dodecene (99) was obtained as a colourless oil (1.39 g, 67%).

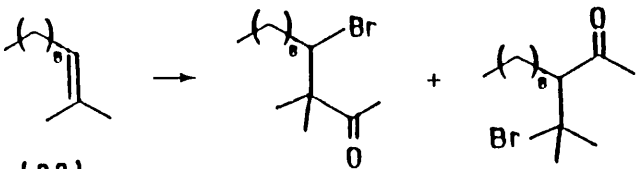
R_f 0.92 (petroleum ether);

ν_{max} (film) 2960s, 2920s, 2850s, 2725w, 1468m, 1455m, 1375m, 830w, 720w; δ_H (90 MHz; $CDCl_3$) 0.88 (3H, brs, CH_3), 1.24 (14H, brs), 1.57 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.75-2.1 (2H, m), 5.1 (1H, brt, J = 7 Hz); m/z 182 (M^+, 10) 111(10), 98(20), 83(20), 69(100), 56(80).

Notes

1. n-Butyllithium was 2.5 M by titration.

The reaction of 2-methyl-2-dodecene (99) and acetyl bromide in the presence of tin(IV) bromide



(99) (101) (100)

Acetyl bromide[1] (0.11 ml, 1.45 mmol) was added to a stirred solution of tin(IV) bromide (1.22 g, 2.78 mmol) in dry dichloromethane (20 ml) under nitrogen at -78°C. 2-Methyl-2-dodecene (99) (0.27 g, 1.48 mmol) was added in dichloromethane (5 ml) to the stirred solution then the mixture left for 12h at -40°C. The mixture was poured into water and neutralised with solid sodium bicarbonate. The aqueous layer was then extracted with ether (2 × 100 ml) and the extracts washed with a saturated brine solution (50 ml). The combined organic extract was dried ($MgSO_4$)

and the solvent removed in vacuo. After purification by flash chromatography (20:1 petroleum ether-ether) 2-bromo-2-methyldodecane (255)[2] (0.285 g, 46%), 3-(1'-bromo-1'-methylethyl)-2-dodecanone (100) (34 mg, 6%) and 4-bromo-3,3-dimethyl-2-tridecanone (101) contaminated with (100)[3] (156 mg, 25%) were obtained.

(255)

R_f 0.70 (petroleum ether);

ν_{max} (film) 2960s, 2920s, 2850s, 1468s, 1385m, 1370s, 1260w, 1148m, 1105m, 820w, 720m;

δ_H (90 MHz; $CDCl_3$) 0.73-0.98 (3H, m, CH_3), 1.1-1.58 (18H, m), 1.72 (6H, s, $2 \times CH_3$).

m/z 182 (M^+ -81, 15), 154(5), 126(5), 111(5), 98(10), 83(15), 69(100).

(100)

R_f 0.38 (20:1 petroleum ether-ether);

ν_{max} (film) 2960s, 2930s, 2855s, 1715s(C=O), 1460s, 1390m, 1375s, 1358s, 1220m, 1180m, 1155m, 1125m, 1110s, 820w, 722w;

δ_H (300 MHz; $CDCl_3$) 0.88 (3H, brt, J = 7 Hz, CH_3), 1.26 (16H, brs), 1.80 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.29 (3H, s, H-1), 3.06 (1H, dd, J = 11.3, 2.9 Hz, H-3);

δ_C (75 MHz; $CDCl_3$) 14.03(q), 22.64(t), 28.19(t), 29.24(t), 29.36(t), 29.49(t), 29.67(t), 30.35(t), 31.86(t), 31.92(q), 32.37(q), 33.85(q), 64.67(d, C-3), 66.65(s, C-1'), 210.18(s);

m/z 224 (M^+ -81, 5), 219(10), 181(5), 166(15), 97(100).

(101) contaminated with (100)

ν_{max} (film) 3075w, 2925s, 2855s, 1715s(C=O), 1643m, 1468s, 1390m, 1370s, 1355s, 1220m, 1155m, 1105s, 910m, 898m, 735s;

δ_H (90 MHz; $CDCl_3$) 0.68-0.92 (3H, m, both isomers superimposed), 1.25

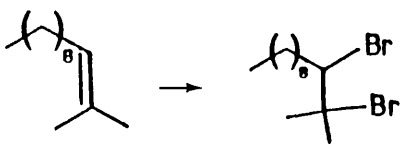
(16H(16H, brs, both isomers superimposed), 1.56 (6H of (101), s, $2 \times CH_3$), 1.781.78 (6H of (100), s, $2 \times CH_3$), 2.03 (3H of (101), s, H-1), 2.24 (3H of (100(100), s, H-1), 3.0 (1H of (100), dd, J = 11, 3 Hz, H-3), 4.88 (1H of (101(101), brs, H-4);

m/z m/z 224 (M^+ -81, 5), 219(20), 181(5), 166(60), 111(50), 98(100).

NoteNotes

1. A1. Acetyl bromide was distilled from N,N-dimethylaniline under n nitrogen.
2. A2. A tentative assignment from the available evidence.
3. R3. Ratio of crude product was about 2:1 (100):(101).

PrepPreparation of 2,3-dibromo-2-methyldodecane (256)



(99) (256)

B Bromine (0.7 g, 4.38 mmol) in carbon tetrachloride (2 ml) was added to ato a stirred solution of 2-methyl-2-dodecene (99) (0.63 g, 3.47 mmol) in cin carbon tetrachloride (5 ml) at room temperature, under nitrogen, untiuntil a faint red colouration remained. The mixture was stirred for an addiadditional ½h then poured into water and washed with a saturated aqueous solusolution of sodium thiosulphate. The carbon tetrachloride layer was driedried ($MgSO_4$) and the solvent removed in vacuo to yield as a crude prodproduct 2,3-dibromo-2-methyldodecane (256) (1.12 g, 94%).

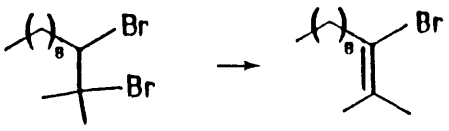
R R_f 0.83 (petroleum ether);

ν_{max} ν_{max} (film) 2955s, 2920s, 2850s, 1468m, 1455m, 1385m, 1370m, 1098s, 720w720w;

δ_H (δ_H (90 MHz; $CDCl_3$) 0.75-0.98 (3H, m, CH_3), 1.26 (14H, brs), 1.78 (3H, s,

CH_3), 1.94 (3H, s, CH_3), 2.0-2.50 (2H, m), 4.12 (1H, dd, J = 10, 2 Hz, H-3).

Preparation of 3-bromo-2-methyl-2-dodecene (102)



(256) (102)

Powdered potassium hydroxide (1g, 17.9 mmol) was added to 2,3-dibromo-2-methyldodecane (256) (1.1 g, 3.22 mmol) in methanol (5 ml). The mixture was stirred at 85°C under nitrogen for 15 min., after which time t.l.c. showed no starting material so the mixture was poured into water and extracted with ether (3 × 100 ml). Each extract was washed with a saturated brine solution then combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (petroleum ether) 3-bromo-2-methyl-2-dodecene (102) was obtained as a colourless oil (0.749 g, 89%).

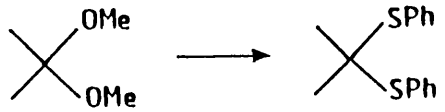
R_f 0.94 (petroleum ether);

ν_{max} (film) 2955s, 2920s, 2850s, 1655w, 1465m, 1378w, 1222w, 1133w, 1112w, 1098w, 720w;

δ_H (90 MHz; $CDCl_3$) 0.77-1.0 (3H, m, CH_3), 1.28 (12H, brs), 1.36-1.65 (2H, m), 1.75 (3H, s, CH_3), 1.85 (3H, s, CH_3), 2.48 (2H, brt, J = 7.5 Hz, H-4);

m/z 262, 260 (M^+, 15) 180(5), 149(10), 124(5), 110(10), 69(100).

Preparation of 2,2-Di(phenylthio)propane (113)[1]



(113)

Dry HCl(g)[2] was passed through a stirred mixture of 2,2-dimethoxypropane (18 ml, 146 mmol) and thiophenol (30 ml, 293 mmol) for 1h at room temperature. On standing a white crystalline solid formed which was recrystallised from ethanol to yield 2,2-di(phenylthio)propane (113) (26.5 g, 70%), m.p. 55-56°C (lit.[1] m.p. 56°C).

δ_H (90 MHz; $CDCl_3$) 1.5 (6H, s, geminal CH_3), 7.1-7.75 (10H, m, $C_6\underline{H}_5$).

Notes

1. Literature procedure, see Refs. 68 and 69.
2. HCl(g) was dried by passing through H_2SO_4(c).

Preparation of 2-phenylthio-2-trimethylsilylpropane (111)[1]

(113) (111)

Lithium wire[2] (0.4 g, 58 mmol) was added to dry THF (50 ml) under argon in a 2-neck flask. The mixture was cooled to between -45 and -55°C, followed by dropwise addition of 1-dimethylaminonaphthalene (8.69 g, 51 mmol). After about 10 min. a dark green colour appeared indicating the formation of lithium dimethylaminonaphthalenide (LDMAN), and after a further 3.5h with rapid stirring at between -45 and -55°C the LDMAN was fully formed. The dark green solution was cooled to -78°C and 2,2-di(phenylthio)propane (113) (5.51 g, 21 mmol) was added in THF (10 ml).

After 15 min., freshly distilled trimethylsilylchloride[3] (2.5 g, 23 mmol) was added and within 1 min. the following standard work-up procedure for reductive lithiations was performed. The reaction was quenched with excess water at -78°C. The solvent was removed under reduced pressure and the residue taken up in ether (250 ml). The ether extract was washed twice with 1 M sodium hydroxide (2 × 100 ml), twice with 1 M sulphuric acid (2 × 100 ml) and finally with saturated aqueous sodium bicarbonate (100 ml). The organic extract was dried ($MgSO_4$) and the ether removed in vacuo. After flash chromatography (petroleum ether) 2-phenylthio-2-trimethylsilylpropane (111)[1] was obtained as a colourless oil (3.86 g, 81%).

R_f 0.35 (petroleum ether);

ν_{max} (film) 3080m, 3060m, 2960s, 2860m, 1580w, 1478m, 1440m, 1360m, 1300w, 1260m, 1250s, 1102m, 1025m, 895m, 840brs, 750s, 705s, 695s;

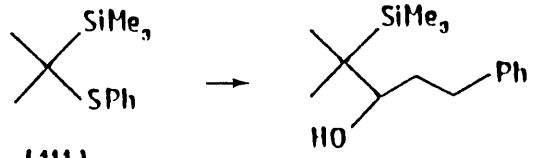
δ_H (90 MHz; $CDCl_3$)[4] 0.0 (9H, s, $SiMe_3$), 1.0 (6H, s, geminal CH_3), 7.05-7.4 (5H, m, $C_6\underline{H}_5$);

m/z 226 (M^+, 60), 151(80), 147(60), 77(100), 73(90).

Notes

1. Literature procedure, see Ref. 68.
2. Squeezed through press immediately prior to use.
3. Distilled from tributylamine under nitrogen.
4. No $SiMe_4$ used as internal standard.

Preparation of 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanol (115)



(111) (115)

LDMAN (18 mmol) was generated as described previously [see preparation of (111)] in THF (40 ml). 2-Phenylthio-2-trimethylsilylpropane (111) (1.7 g, 7.6 mmol) was added in THF (6 ml), at -78°C, and stirred for 15 min. 3-Phenylpropanal (1 g, 7.5 mmol) was added in THF (5 ml) and stirring continued for 2 min. at -78°C. After standard work-up the solvent was removed in vacuo and the residual oil purified by flash chromatography (9:1 petroleum ether-ether) to yield 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanol (115) as a colourless oil (1.1 g, 59%).

R_f 0.3 (9:1 petroleum ether-ether);

$C_{15}H_{26}OSi$ requires C 71.93%, H 10.46%, N 0.00%,

found C 71.91%, H 10.26%, N 0.00%;

ν_{max} (film) 3600br(OH), 3480m, 3080w, 3060m, 3025m, 2960s, 2900s, 2860s, 1605m, 1498m, 1465m, 1455s, 1405m, 1395m, 1365m, 1250s, 1030m, 950m, 840s, 750s, 700s;

δ_H (300 MHz; $CDCl_3$)[1] 0.004 (9H, s, $Si(CH_3)_3$), 0.85 (3H, s, CH_3), 0.89 (3H, s, CH_3), 1.37 (1H, brs, OH), 1.63 (1H, dddd, J = 13.9, 10.4, 9.7, 5.1 Hz, H-4), 1.84 (1H, dddd, J = 13.9, 10.0, 6.7, 1.8 Hz, H-4), 2.62 (1H, ddd, J = 13.6, 9.7, 6.7 Hz, H-5), 2.91 (1H, ddd, J = 13.6, 10.0, 5.1 Hz, H-5), 3.52 (1H, brd, J = 10.7 Hz, H-3), 7.15-7.33 (5H, m, $C_6\underline{H}_5$);

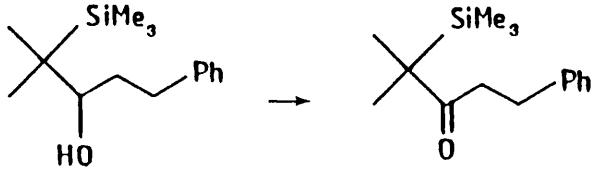
δ_C (75 MHz; $CDCl_3$) -2.56(q, $Si(CH_3)_3$), 18.86(q), 20.09(q), 26.23(s, C-2), 33.43(t), 34.20(t), 78.01(d, C-3), 125.74(d), 128.34(d), 128.39(d), 142.32(s);

m/z 232 (M^+ -18, 10), 165(45), 91(50), 73(100), 69(100).

Notes

1. Pyrazine was used as an internal standard and set to δ8.6.

Preparation of 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanone (116)



(115) (116)

Chromium trioxide[1] (2.69 g, 27 mmol) was added to a stirred solution of pyridine (4.25 g, 54 mmol) in dichloromethane (60 ml) under nitrogen. Rapid stirring was continued for ½h at room temperature to produce a deep red solution.[2] 2-Methyl-5-phenyl-2-trimethylsilyl-3-pentanol (115) (1.12 g, 4.5 mmol), in dichloromethane (10 ml), was added in one portion. The solution immediately turned brown. After 1 min. the mixture was filtered rapidly through a short silica column and the chromium residues washed with ether (2 × 75 ml). The solvent was removed in vacuo to yield, after flash chromatography, (20:1 petroleum ether-ether) 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanone (116) as a colourless oil (0.937 g, 84%).

R_f 0.6 (9:1 petroleum ether-ether);

ν_{max} (film) 3090w, 3060m, 3025m, 2960s, 2900m, 2870m, 1680s(C=O), 1585w, 1498m, 1470s, 1455s, 1385m, 1253s, 995m, 840s, 753s, 700s;

δ_H (300 MHz; $CDCl_3$)[3] -0.001 (9H, s, $Si(CH_3)_3$), 1.22 (6H, s, geminal CH_3), 2.72-2.67 (2H, m), 2.84-2.89 (2H, m), 7.18-7.30 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) -3.74(q, $Si(CH_3)_3$), 20.38(q), 30.13(t), 42.02(t), 42.12(s, C-2), 125.89(d), 128.35(d), 128.51(d), 141.81(s), 213.59(s, C-3).

m/z 248 (M^+, 20), 205(10), 157(10), 105(20), 91(100), 73(40);

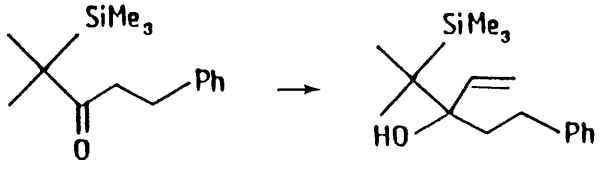
$C_{15}H_{24}OSi$ requires 248.1596,

found 248.1597.

Notes

1. Dried over P_2O_5 at 60°C, under vacuum overnight.
2. See Ref. 53.
3. Pyrazine was used as an internal standard and set to δ8.6.

Preparation of 4-methyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (117)



(116) (117)

Vinylmagnesium bromide[1] (6 ml, 6 mmol) was added to a stirred solution of 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanone (116) (0.99 g, 4 mmol) in THF (15 ml). After 20 min. at room temperature the mixture was refluxed for a further 45 min. then poured into saturated aqueous NH_4Cl solution (100 ml). The mixture was extracted with ether (2 × 100 ml) and each extract washed with saturated brine (50 ml), then dried ($MgSO_4$). The solvent was removed in vacuo to yield a yellow oil (1.089 g). T.l.c. (9:1 petroleum ether-ether) showed essentially one spot; ^1H n.m.r. however revealed a mixture of starting material (116) and 4-methyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (117) in a ratio of approximately 1:9.

R_f 0.54 (9:1 petroleum ether-ether);

ν_{max} (film) 3500brw(OH), 3085m, 3060m, 3030m, 2950s, 2870m, 1675w(C=O), 1608w, 1500m, 1470m, 1455m, 1410m, 1250s, 1000m, 920m, 840s, 760s, 700s;

δ_H (90 MHz; $CDCl_3$) 0.0 (1H, s, starting material), 0.1 (9H, s, $Si(CH_3)_3$),

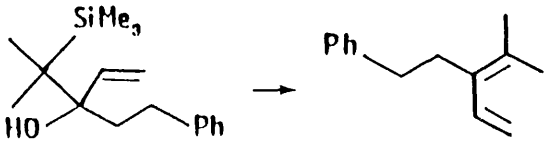
0.95 (6H, s, CH_3), 1.2 (0.8H, s, starting material), 1.3-3.1 (7H should be 5H, m), 5.18 (1H, dd, $J_{1,2\,cis} = 11$, $J_{1,1} = 2$ Hz, H-1), 5.2 (1H, dd, $J_{1,2\,trans} = 18$, $J_{1,1} = 2$ Hz, H-1), 5.91 (1H, dd, $J_{2,1\,trans} = 18$, $J_{2,1\,cis} = 11$ Hz, H-2), 7.17 (5H, s, $C_6\underline{H}_5$);

m/z 259 ($M^+ - 18$), 186(25), 143(25), 95(90), 91(85), 73(100).

Notes

1. 1 M solution in THF obtained from Aldrich.

Preparation of 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118)



(117) (118)

4-Methyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (117)[1] (1.04 g, 3.8 mmol) was stirred with acetic acid (5 ml), saturated with sodium acetate, at 50°C[2] for 1h. T.l.c. showed the disappearance of the starting material (117) and the mixture was poured into water (100 ml) and neutralised with solid sodium bicarbonate. The aqueous layer was extracted with ether (3 x 50 ml) and the extracts were combined and dried ($MgSO_4$). The ether was then removed in vacuo. After flash chromatography (petroleum ether) and Kugelröhr distillation (100°C at 1 mmHg) 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118) was obtained as a colourless oil (0.513 g, 73% and 34% overall from 3-phenylpropanal).

R_f 0.33 (petroleum ether);

$C_{14}H_{18}$ requires C 90.26%, H 9.74%, N 0.00%,

found C 89.99%, H 9.77%, N 0.00%.

ν_{max} (film) 3090s, 3060m, 3025s, 2925s, 2880s, 1635s, 1608m, 1498s,

1455s, 1415m, 1375m, 1170m, 1075w, 1030m, 990s, 895s, 750s, 700s;

δ_H (300 MHz; $CDCl_3$) 1.70 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.50-2.68 (4H, m), 5.01 (1H, d, $J_{1,2\ cis}$ = 11.0 Hz, H-1), 5.20 (1H, d, $J_{1,2\ trans}$ = 17.4 Hz, H-1), 6.76 (1H, dd, $J_{2,1\ trans}$ = 17.4, $J_{2,1\ cis}$ = 11.0 Hz, H-2), 7.14-7.29 (5H, m, $C_6\underline{H}_5$);

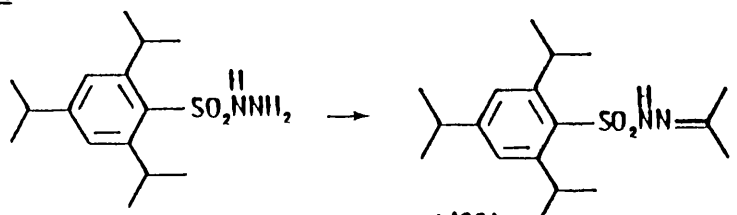
δ_C (75 MHz; $CDCl_3$) 20.24(q), 21.3(q), 30.17(t), 35.08(t), 110.83(t, C-1), 125.69(d), 128.34(d), 130.84(s), 132.05(s), 132.51(d, C-2), 142.65(s);

m/z 186 (M^+, 90), 171(70), 143(60), 95(100), 91(90), 67(60), 40(100).

Notes

1. The crude β-hydroxysilane (117) was used directly from the previous reaction and was contaminated with some β-keto silane (116).
2. Method described by Hudrlik and Peterson, see Ref. 73.

Preparation of Propan-2-one-2',4',6'-triisopropylbenzenesulphonylhydrazone (120)[1]



(121) (120)

Acetone (40 ml, 0.87 mol) was added to 2,4,6-triisopropylbenzenesulphonylhydrazine (121) (5 g, 16.8 mmol) under nitrogen, at 0°C. When the hydrazine had been consumed the excess acetone was removed <u>in vacuo</u> to leave a white solid. The solid was recrystallised from petroleum ether (80-100) to yield propan-2-one-2',4',6'-triisopropylbenzenesulphonylhydrazone (120)[1] (4.74 g, 84%), m.p. 135-137°C, (lit.[1] m.p. 130-132°C).

R_f 0.48 (dichloromethane);

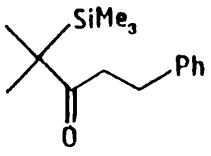
δ_H (90 MHz; $CDCl_3$) 1.25 (18H, d, J = 7.5 Hz, $-CH(C\underline{H}_3)_2$), 1.75 (3H, s,

CH_3), 1.85 (3H, s, CH_3), 2.85 (1H, quintet, J = 7.5 Hz, para -C<u>H</u>$(CH_3)_2$), 4.2 (2H, quintet, J = 7.5 Hz, ortho -C<u>H</u>$(CH_3)_2$), 7.09 (2H, s).

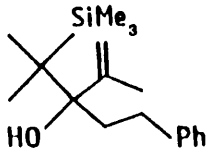
Notes

1. Literature procedure, see Ref. 75.

Preparation of 2,4-dimethyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (119)



(116)



(119)

n-Butyllithium[1] (2.96 ml, 7.1 mmol) was added to a stirred solution of propan-2-one-2',4',6'-triisopropylbenzenesulphonylhydrazone (120) (1.2 g, 3.55 mmol) at -78°C, in DME (10 ml), under nitrogen. The yellow solution was allowed to warm to 0°C for 15 min., during which time bubbles of nitrogen were evolved. The mixture was recooled to -78°C and 2-methyl-5-phenyl-2-trimethylsilyl-3-pentanone (116) (0.85 g, 3.55 mmol) was added in DME (5 ml) and after 10 min. at -78°C the solution was allowed to warm slowly to room temperature, then poured into saturated aqueous NH_4Cl solution. The aqueous solution was extracted with ether (3 × 75 ml), the extracts combined and dried ($MgSO_4$). The ether was removed <u>in vacuo</u> and after flash chromatography (20:1 petroleum ether-ether) <u>2,4-dimethyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (119)</u> was obtained as a colourless oil (0.78 g, 76%).

R_f 0.74 (20:1 petroleum ether ether);

$C_{18}H_{30}OSi$ requires C 74.42%, H 10.41%, N 0.00%,

found C 74.68%, H 10.39%, N 0.00%.

ν_{max} (film) 3610brm(OH), 3090m, 3080m, 3020m, 2960s, 1630w, 1605m, 1495m, 1455m, 1248s, 1050m, 1030m, 995m, 960m, 900s, 840brs, 750s, 700s;

δ_H (300 MHz; $CDCl_3$)[2] 0.09 (9H, s, $Si(C\underline{H}_3)_3$), 0.94 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.66 (1H, s, OH), 1.88 (3H, dd, J = 1.4, 0.6 Hz, 2-CH_3), 1.95-2.12 (2H, m), 2.38 (1H, ddd, J = 13.5, 11.3, 4.8 Hz, H-2'), 2.63 (1H, ddd, J = 13.5, 11.3, 6.3 Hz, H-2'), 4.98 (1H, brs), 5.07 (1H, s with fine coupling), 7.16-7.33 (5H, m, $C_6\underline{H}_5$);

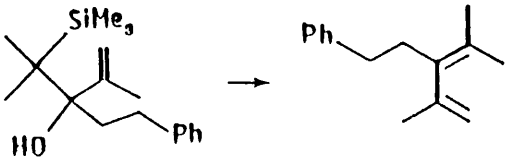
δ_C (75 MHz; $CDCl_3$) -0.17(q, $Si(CH_3)_3$), 20.80(q), 21.30(q), 22.66(q), 30.12(t), 31.03(s, C-4), 37.94(t), 83.44(s, C-3), 112.8(t, C-1), 125.69 (d), 128.36(d), 128.41(d), 142.80(s), 148.56(s);

m/z 272 (M^+ -18, 10), 200(30), 181(40), 109(100), 96(60), 73(80), 75(85), 67(60).

Notes

1. n-Butyllithium was 2.4 M by titration.
2. Pyrazine was used as an internal standard and set at δ8.6.

Preparation of 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88)



(119) (88)

2,4-Dimethyl-3-2'-phenylethyl-4-trimethylsilyl-1-penten-3-ol (119) (0.7 g, 2.4 mmol) was stirred with acetic acid (5 ml) saturated with sodium acetate at 50°C for 4h.[1] The reaction was then worked-up as in the preparation of (118). After flash chromatography (petroleum ether) and Kugelröhr distillation (120°C at 0.5 mmHg) 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88) was obtained as a colourless oil (0.406 g, 84%

and 30% overall from 3-phenylpropanal).

R_f 0.6 (petroleum ether);

$C_{15}H_{20}$ requires C 89.94%, H 10.06%, N 0.00%,

found C 90.07%, H 10.14%, N 0.00%;

λ_{max} (CH_3CN) 235 (ε 2050 $dm^3\ mol^{-1}\ cm^{-1}$);

ν_{max} (film) 3080m, 3060m, 3030m, 2920s, 2880s, 1632m, 1605m, 1496m, 1453s, 1372m, 1125w, 1060w, 895s, 750m, 700s;

δ_H (300 MHz; $CDCl_3$) 1.61 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.80 (3H, dd, J = 1.5, 0.9 Hz, CH_3), 2.32-2.41 (2H, m), 2.58-2.66 (2H, m), 4.63 (1H, dq, J = 2.8, 0.9 Hz, H-1), 4.98 (1H, dq, J = 2.8, 1.5 Hz, H-1), 7.10-7.28 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 19.51(q), 21.74(q), 22.74(q), 33.36(t), 34.81(t), 113.4(t, C-1), 125.59(d + s), 128.19(d), 128.34(d), 135.94(s), 142.62(s), 146.33(s);

m/z 200 (M^+, 70), 157(5), 109(100), 96(80), 91(60), 81(70), 67(90), 55(50).

Notes

1. Method described by Hudrlik and Peterson, see Ref. 73.

Preparation of 2-tributyltin-2-trimethylsilylpropane (124)

(111) (124)

2-Phenylthio-2-trimethylsilylpropane (111) (1 g, 4.46 mmol) was treated with LDMAN (11 mmol) prepared in the usual way.[1] Tributyltinchloride (1.21 ml, 4.44 mmol) in THF (3 ml) was added at -78°C and the solution stirred for 15 min. After standard work-up, the product was purified by

chromatography (petroleum ether) to yield 2-tributyltin-2-trimethylsilylpropane (124) as a colourless oil (1.138 g, 63%).

R_f solvent front (petroleum ether);

ν_{max} (film) 2960s, 2920s, 2875s, 2845s, 1455m, 1378m, 1260m, 1248s, 1075m, 960w, 880s, 830s, 750s, 680s;

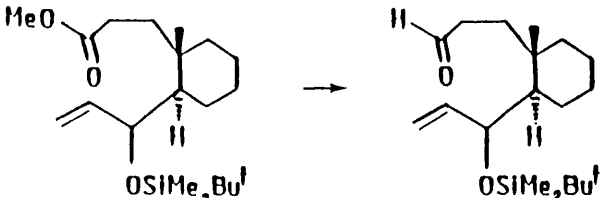
δ_H (90 MHz; $CDCl_3$) -0.09 (9H, s, $Si(CH_3)_3$), 0.7-1.7 (33H, m);

m/z 406 (M^+), 392(1), 347(5), 289(100), 236(80), 179(60), 135(10).

Notes

1. See preparation of (111).

Preparation of trans-3-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}propionaldehyde (84)[1]



DIBAH[2] (4.24 ml, 4.24 mmol) was added dropwise to a solution of methyl trans-3-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}propionate (55)[3] (1.5 g, 4.24 mmol) in toluene (60 ml), at -78°C, under nitrogen. After the disappearance of starting material on t.l.c. the reaction was quenched with 1 M HCl (200 ml) and extracted with ether (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography (20:1 petroleum ether-ether) to yield trans-3-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}propionaldehyde (84)[1] as a colourless oil (0.79 g, 58%).

R_f 0.31 (20:1 petroleum ether-ether);

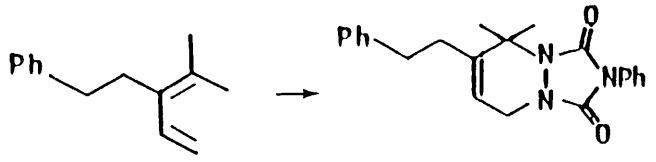
ν_{max} (film) 2930s, 2860s, 2825s, 2718s, 1725s(C=O), 1640w, 1470m, 1460s, 1455m, 1405w, 1360w, 1255s, 1160w, 1125m, 1095s, 1080m, 1022m, 1006m, 995s, 922s, 840s, 815m, 775s;

δ_H (90 MHz; $CDCl_3$) 0.0 (3H, s, CH_3-Si), 0.2 (3H, s, CH_3-Si), 0.9 (9H, s, -C(CH_3)$_3$), 0.95 (3H, s, CH_3), 1.1-1.9 (11H, m), 2.15-2.55 (2H, m), 4.33 (1H, brd, J = 7 Hz, H-1"), 4.94-5.20 (2H, m), 5.72-6.20 (1H, m), 9.75-9.85 (1H, m).

Notes

1. Literature procedure, see Ref. 38.
2. 1 M solution in toluene obtained from Aldrich.
3. Prepared by Dr. P. A. Brown who kindly left this compound after completing his work.

Preparation of 2,2-dimethyl-8-phenyl-3-2'-phenylethyl-1,6,8-triazo-[4,3,0]bicyclonon-3-ene-7,9-dione (137)



(118) (137)

4-Phenyl-1,2,4-triazoline-3,5-dione (136)[1] (0.124 g, 0.71 mmol) in acetone (1 ml) was added to a solution of 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118) (0.12 g, 0.65 mmol) in dichloromethane (1 ml), at room temperature. The bright red colouration slowly faded and after 1h the solvent was removed in vacuo to give a white solid. The solid was re-crystallised from methanol to yield 2,2-dimethyl-8-phenyl-3-2'-phenyl-ethyl-1,6,8-triazo[4,3,0]bicyclonon-3-ene-7,9-dione (137) (75 mg, 32%), m.p. 139-139.5°C.

$C_{22}H_{23}N_3O_2$ requires C 73.11%, H 6.41%, N 11.63%,

found C 73.04%, H 6.38%, N 11.68%.

ν_{max} (nujol mull) 1770m, 1710s, 1600w, 1415s, 1270m, 1220w, 835w, 770m, 735m, 712m;

δ_H (300 MHz; $CDCl_3$) 1.65 (6H, s, CH_3), 2.3-2.39 (2H, m), 2.83 (2H, t, J = 8.1 Hz), 4.09-4.14 (2H, m, H-5), 5.59-5.65 (1H, m, H-4), 7.18-7.56 (11H should be 10, m, $C_6\underline{H}_5$);

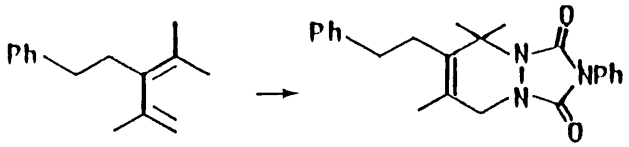
δ_C (75 MHz; $CDCl_3$) 22.85(q), 31.52(t), 34.99(t), 43.22(t, C-5), 62.57 (s, C-2), 113.76(d, C-4), 125.51(d), 126.20(d), 127.89(d), 128.25(d), 128.48(d), 128.93(d), 131.39(s, C-3), 141.09(s), 141.74(s), 152.41(s, C=O), 152.48(s, C=O);

m/z 362 (M^+, 100), 346(80), 268(30), 227(60), 198(20), 185(20), 91(70).

Notes

1. Prepared according to literature, see Ref. 95 also see Ref. 94.

Preparation of 8-phenyl-3-2'-phenylethyl-2,2,4-trimethyl-1,6,8-triazo-[4,3,0]bicyclonon-3-ene-7,9-dione (138)



(88) (138)

4-Phenyl-1,2,4-triazoline-3,5-dione (136)[1] (0.104 g, 0.59 mmol) in acetone (1 ml) was added to a solution of 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88) (0.108 g, 0.54 mmol) in dichloromethane (1 ml), at room temperature. After 1h the solvent was removed in vacuo and the resulting white solid recrystallised from methanol to yield 8-phenyl-3-2'-phenylethyl-2,2,4-trimethyl-1,6,8-triazo[4,3,0]bicyclonon-3-ene-

7,8-dione (138) (0.173 g, 85%) m.p. 136-137°C.

$C_{23}H_{25}N_3O_2$ requires C 73.58%, H 6.71%, N 11.19%,

found C 73.31%, H 6.71%, N 11.13%.

ν_{max} (nujol mull) 1770m, 1710s, 1600w, 1410s, 1390m, 1365m, 1280m, 770m, 750w, 740m, 710m, 700m, 690m;

δ_H (300 MHz; $CDCl_3$) 1.67 (6H, s, CH_3), 1.83 (3H, s, CH_3), 2.30-2.41 (2H, m), 2.70-2.78 (2H, m), 3.97 (2H, s, H-5), 7.17-7.56 (10H, m, $C_6\underline{H}_5$);

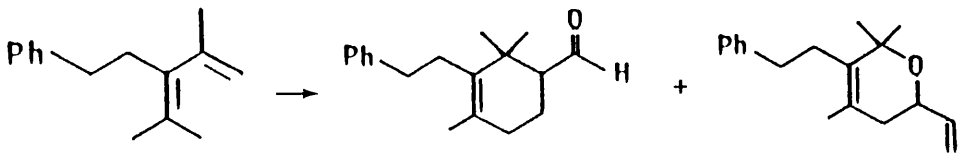
δ_C (75 MHz; $CDCl_3$) 16.94(q), 23.21(q), 30.49(t), 35.98(t), 47.08(t), 62.56(s, C-2), 121.59(s), 125.50(d), 126.24(d), 127.92(d), 128.04(d), 128.58(d), 128.97(d), 131.30(s), 134.42(s), 141.47(s), 152.32(s, C=O), 152.36(s, C=O);

m/z 375 (M^+, 60), 360(90), 282(20), 241(30), 213(20), 91(100).

Notes

1. Prepared according to literature, see Ref. 95 also see Ref. 94.

Preparation of 3-2'-phenylethyl-2,2,4-trimethyl-3-cyclohexene-1-carbaldehyde (139) and 5,6-dihydro-3-2'-phenylethyl-2,2,4-trimethyl-6-vinyl-2H-pyran (140)



(88) (139) (140)

Acrolein (50 ul, 0.74 mmol) was added to 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88) (0.106 g, 0.54 mmol) in toluene (1 ml). The mixture was cooled to -78°C and boron trifluoride etherate (14 ul, 0.11 mmol) added. After stirring for 5h at -78°C and 2h at -40°C, t.l.c. showed no starting material and the reaction was quenched with water and extracted with ether (3 × 20 ml). The extracts were washed with saturated

brine, combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (20:1 petroleum ether-ether) 3-2'-phenylethyl-2,2,4-trimethyl-3-cyclohexene-1-carbaldehyde (139) and 5,6-dihydro-3-2'-phenylethyl-2,2,4-trimethyl-6-vinyl-2H-pyran (140) were obtained as colourless oils (70 mg, 52%) and (14 mg, 10%) respectively.

139

R_f 0.44 (20:1 petroleum ether-ether);

ν_{max} (film) 3090w, 3060w, 3020m, 2940s, 2730w, 1720s(C=O), 1605w, 1495m, 1470m, 1452m, 1385w, 1368m, 1030m, 750m, 700s;

δ_H (400 MHz; $CDCl_3$) 1.01 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.66-1.82 (2H, m, H-6), 1.93-2.0 (2H, m, H-5), 2.13 (1H, dt, J = 10.2, 3.2 Hz, H-1), 2.17-2.29 (2H, m, H-1'), 2.53-2.65 (2H, m, H-2'), 7.07-7.23 (5H, m, $C_6\underline{H}_5$), 9.78 (1H, d, J = 3.2 Hz, -C$\underline{H}$O);

m/z 256 (M^+, 1), 227(5), 137(20), 135(20), 133(20), 105(20), 91(60), 74(60), 59(100);

1.01 (CH_3) shows a n.O.e. to 2.13 (H-1, 7%), 2.17-2.29 (3%), 2.53-2.65 (2%) and 9.78 (C$\underline{H}$O, 4%);

1.20 (CH_3) shows a n.O.e. to 2.13 (H-1, 2.4%), 2.17-2.29 (3%), 2.53-2.65 (1.5%) and 9.78 (C$\underline{H}$O, 5%).

140

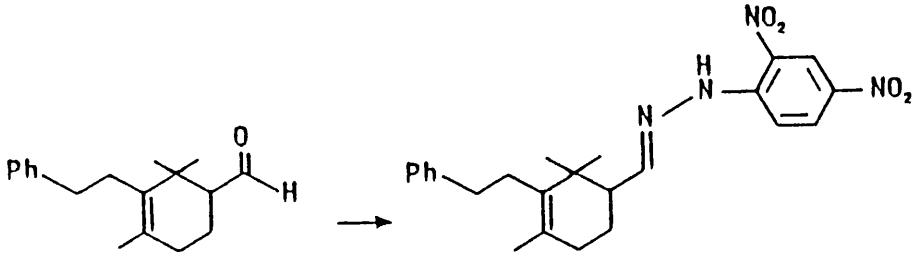
R_f 0.55 (20:1 petroleum ether-ether);

δ_H (300 MHz; $CDCl_3$) 1.33 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.66-1.88 (5H, m), 2.06-2.32 (3H should be 2H, m), 2.6-2.76 (2H, m), 4.13-4.22 (1H, m, H-6), 5.14 (1H, ddd, J_{cis} = 10.5, J = 1.7, 1.2 Hz, CH=C$\underline{H}_2$), 5.27 (1H, dt, J_{trans} = 17.3, J = 1.5 Hz, -CH=C$\underline{H}_2$), 5.92 (1H, ddd, J_{trans} = 17.3, J_{cis} = 10.5, J = 5.9 Hz, -C$\underline{H}$=CH_2), 7.16-7.34 (5H, m, $C_6\underline{H}_5$);

$C_{18}H_{24}O$ requires 256.1827,

found 256.1840.

Preparation of 1-(methanal-2,4-dinitrophenylhydrazone)-3-2'-phenylethyl-2,2,4-trimethyl-3-cyclohexene (145)



(139) (145)

2,4-Dinitrophenylhydrazine (48 mg, 0.24 mmol) was dissolved in ethanol (2 ml) and concentrated HCl (100 ul).[1] The solution was then added to 3-2'-phenylethyl-2,2,4-trimethyl-3-cyclohexene-1-carbaldehyde (139) (58 mg, 0.23 mmol) and the mixture warmed for 10 min. On cooling a yellow solid precipitated out which was then collected by filtration and recrystallised twice from ethanol to give 1-(methanal-2,4-dinitrophenylhydrazone)-3-2'-phenylethyl-2,2,4-trimethyl-3-cyclohexene (145) as flaky yellow crystals (41 mg, 42%) m.p. 165-166.5°C.

$C_{24}H_{28}N_4O_4$ requires C 66.04%, H 6.47%, N 12.84%,

found C 65.84%, H 6.51%, N 12.83%.

ν_{max} (nujol mull) 3270w(N-H), 1610w, 1580w, 1330m, 1305m, 1260w, 1210w, 1140w, 920w;

δ_H (300 MHz; $CDCl_3$) 1.05 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.77 (3H, s, CH_3), 1.79-1.97 (2H, m), 2.01-2.18 (2H, m), 2.27-2.39 (2H, m), 2.48 (1H, ddd, J = 10, 7.3, 3.2 Hz, H-1), 2.62-2.77 (2H, m), 7.14-7.34 (5H, m, $C_6\underline{H}_5$), 7.59 (1H, d, J = 7.3 Hz, -C$\underline{H}$=N-), 7.95 (1H, d, J = 9.6 Hz), 8.29 (1H, dd, J = 9.6, 2.6 Hz), 9.10 (1H, d, J = 2.6 Hz), 11.04 (1H, brs, N-$\underline{H}$);

m/z 436 (M^+, 1), 253(10), 174(20), 162(60), 133(40), 121(40), 105(90), 91(100), 81(30).

Notes

1. See Vogel "Textbook of Practical Organic Chemistry", 4th. Ed., Longman, 1978, p.1111.

The reaction of acrolein and 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118)

Acrolein (42 ul, 0.63 mmol) was added to a solution of 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118) (83 mg, 0.45 mmol) in toluene (1 ml). The mixture was cooled to -78°C and boron trifluoride etherate (11 ul, 0.09 mmol) added. After 5h at -78°C t.l.c. showed no reaction so the mixture was allowed to warm to -35°C for 12h. T.l.c. again showed a large amount of starting material so further amounts of acrolein[1] (42 ul, 0.63 mmol) and boron trifluoride etherate (11 ul, 0.09 mmol) were added, and the mixture kept at -35°C for a further 7h. The mixture was then worked-up as in the preparation of (139). The solvent was removed in vacuo and the residual oil was purified by flash chromatography[2] (10:1 petroleum ether-ether) to yield recovered starting material (118) (41 mg) and a main product[3] (26 mg).

R_f 0.36 (10:1 petroleum ether-ether);

ν_{max} (CH_2Cl_2) 3025w, 2930s, 2860m, 1720s(C=O), 1602w, 1495w, 1450m, 1135w, 1060s, 990m, 935m, 855w;

δ_H (300 MHz; $CDCl_3$)[4] 1.54-1.88 (10H, m), 2.05 (1H, dq, J = 12.9, 3.6 Hz), 2.28-2.48 (3H, m), 2.55-2.67 (1H, m), 2.74-2.88 (1H, m), 4.07 (0.7H ≡ 1H of major isomer, dd, J = 10.1, 6.3 Hz), 4.32-4.41 (1H, m), 4.48 (0.3H ≡ 1H of minor isomer, dd, J = 11.4, 2.7 Hz), 5.22 (0.7H ≡ 1H of major isomer, ddd, J_{cis} = 10.5, J = 1.5, 1 Hz, -CH=C$\underline{H}_{cis}H_{trans}$), 5.28 (0.3H ≡ 1H of minor isomer, dt, J_{cis} = 10.9, J = 1.8 Hz, -CH=C$\underline{H}_{cis}H_{trans}$), 5.36 (0.7H ≡ 1H of major isomer, dt, J_{trans} = 17.2, J = 1.4 Hz, -CH=C$H_{cis}\underline{H}_{trans}$), 5.45 (0.3H ≡ 1H of minor isomer, dt, J_{trans} = 17.4, J = 1.8 Hz, -CH=C$H_{cis}\underline{H}_{trans}$), 5.94 (0.7H ≡ 1H of major isomer, ddd, J_{trans} = 17.2, J_{cis} = 10.5, J = 6.4 Hz, -C$\underline{H}$=CH_2), 6.06 (0.3H ≡ 1H of minor isomer, ddd, J_{trans} = 17.4, J_{cis} = 10.9, J = 4.1 Hz, -C$\underline{H}$=CH_2), 7.14-7.32 (5H, m, C_6H_5), 9.66 (0.6H ≡ 1H of major

isomer, d, J = 2.6 Hz, -CHO), 10.00 (0.2H ≡ 1H of minor isomer, dd, J = 1.7, 1.2 Hz, -CHO);

m/z 298 (M^+, 12), 280(6), 251(4), 242(4), 207(17), 166(17), 160(15), 138(10), 107(28), 90(100).

Notes

1. It was assumed that the initial acrolein would have decomposed by this time. The same product was isolated irrespective of the second portion of acrolein and boron trifluoride but in worse yield.
2. T.l.c. showed some streaking and a number of faint spots that could not be isolated.
3. The product isolated was one spot on t.l.c. but was a mixture of isomers (ratio 2:1) see discussion page 49 for a possible structure.
4. For the integration 1H was taken to be one of the vinyl protons of both isomers combined.

The formation of the hydrazone of the product from the reaction of 4-methyl-3-2'-phenylethyl-1,3-pentadiene (118) and acrolein

The aldehydes isolated in the previous experiment (34 mg, 0.11 mmol) were reacted with 2,4-dinitrophenylhydrazine (23 mg, 0.12 mmol) as in the preparation of (145). The orange solid obtained was recrystallised from methanol to yield the crystalline derivative of one of the aldehydes (19 mg, 35%) m.p. 177-179°C.

δ_H (300 MHz; $CDCl_3$) 1.55-1.96 (12H should be 10H, m), 2.13 (1H, dq, J = 13.1, 3.6 Hz), 2.38-2.54 (3H, m), 2.58-2.71 (1H, m), 2.77-2.90 (1H, m), 3.94 (1H, dd, J = 9.9, 6.6 Hz), 4.43 (1H, dd, J = 10.1, 3.6 Hz), 5.24 (1H, d with some further fine splitting, J_{cis} = 10.5 Hz, -CH=CH$_{cis}$H$_{trans}$), 5.37 (1H, d with some further fine splitting, J_{trans} = 17.2 Hz, -CH=CH$_{cis}$ H$_{trans}$), 5.93 (1H, ddd, J_{trans} = 17.2, J_{cis} = 10.5, J = 6.6 Hz, -CH=CH$_2$),

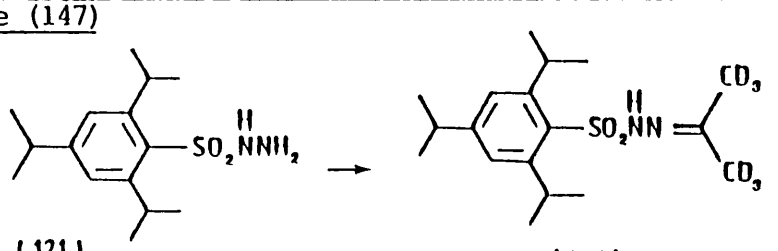
7.16-7.33 (6H should be 5H, m, $C_6\underline{H}_5$), 7.42 (1H, d, J = 5.8 Hz), 7.93 (1H, d, J = 9.6 Hz), 8.31 (1H, dd, J = 9.6, 2.6 Hz), 9.11 (1H, d, J = 2.6 Hz), 11.02 (1H, brs, N-$\underline{H}$);

m/z 478 (M^+), 422(25), 287(4), 331(5), 240(4), 236(4), 186(100), 171(31), 144(43), 118(20);

$C_{26}H_{30}N_4O_5$ requires 478.2216,

found 478.2220.

Preparation of [$^2H_6$]Propan-2-one-2',4',6'-triisopropylbenzenesulphonylhydrazone (147)



(121) (147)

[$^2H_6$] Acetone[1] (10 g, 156 mmol) was added to 2,4,6-triisopropylbenzenesulphonylhydrazine (121) (2 g, 6.7 mmol) under nitrogen, at 0°C. When the hydrazine had been consumed the excess acetone was removed in vacuo to yield [$^2H_6$]propan-2-one-2',4',6'-triisopropylbenzenesulphonylhydrazone (147) as a white crystalline solid (1.62 g, 70%).

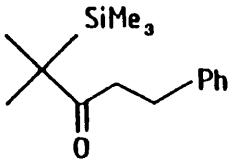
δ_H (90 MHz; $CDCl_3$) 1.25 (18H, d, J = 7.5 Hz), 2.85 (1H, quintet, J = 7.5 Hz), 4.2 (2H, quintet, J = 7.5 Hz), 7.1 (2H, s);

m/z 345 (M^+, 5), 282(50), 267(100), 252(25), 233(20), 203(70), 175(40).

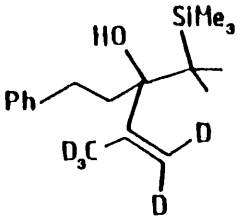
Notes

1. 99.5% deuterium enrichment obtained from Aldrich.

Preparation of 2-[$^2H_3$]Methyl-4-methyl-3-2'-phenylethyl-4-trimethylsilyl-1,1-[$^2H_2$]-1-penten-3-ol (148)



(116)



(148)

2-Methyl-5-phenyl-2-trimethylsilyl-3-pentanone (116) (0.4 g, 1.6 mmol) was treated with [$^2H_5$]propenyl lithium generated from [$^2H_6$]propan-2-one-2',4',6'-triisopropylsulphonylhydrazone (147) (0.56 g, 1.61 mmol) and n-butyllithium[1] (1.65 ml, 3.2 mmol) as in the preparation of (119). The reaction was worked up and after flash chromatography (20:1 petroleum ether-ether) 2-[$^2H_3$]methyl-4-methyl-3-2'-phenylethyl-4-trimethylsilyl-1,1-[$^2H_2$]-1-penten-3-ol (148) was obtained as a colourless oil (0.164 g, 34%).

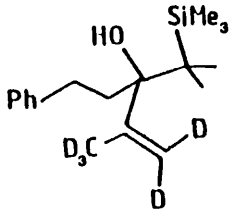
R_f 0.64 (20:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.1 (8H should be 9H, s, $-Si(CH_3)_3$), 0.94 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.65 (1H, s, OH), 1.87-2.86 (4H, m), 7.21 (5H, s, $C_6\underline{H}_5$).

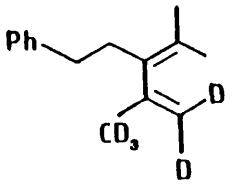
Notes

1. n-Butyllithium was 1.95 M by titration.

Preparation of 2-[$^2H_3$]Methyl-4-methyl-3-2'-phenylethyl-1,1-[$^2H_2$]-1,3-pentadiene (146)



(148)'



(146)

2-[$^2H_3$]Methyl-4-methyl-3-2'-phenylethyl-4-trimethylsilyl-1,1-[$^2H_2$]-1-penten-3-ol (148) (160 mg, 0.54 mmol) was heated at 50°C in acetic acid saturated with sodium acetate.[1] After 4h t.l.c. showed no starting material so the mixture was poured into water and worked up as in the preparation of (88). After flash chromatography (petroleum ether) 2-[$^2H_3$]methyl-4-methyl-3-2'-phenylethyl-1,1-[$^2H_2$]-1,3-pentadiene (146) was obtained as a colourless oil (72 mg, 65%).

R_f 0.6 (petroleum ether);

δ_H (300 MHz; $CDCl_3$) 1.61 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.33-2.39 (2H, m), 2.59-2.64 (2H, m), 7.13-7.29 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 19.54(q), 21.75(q), 33.36(t), 34.80(t), 125.60(d), 125.64(s), 128.21(d), 128.36(d), 135.88(s), 142.67(s), 146.10(s);

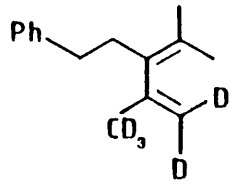
δ^2_H (300 MHz; $CHCl_3$)[2] 1.86(brs), 4.76(brs), 5.12(brs);

m/z 205 (M^+, 60), 188(5), 114(100), 99(55), 91(95), 83(20), 69(50).

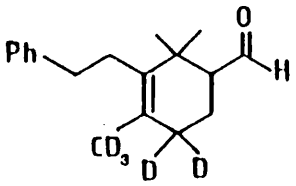
Notes

1. Method described by Hudrlik and Peterson, see Ref. 73.
2. $CDCl_3$ set at δ7.3.

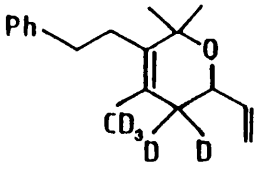
Preparation of 2,2-dimethyl-4-[$^2H_3$]methyl-3-2'-phenylethyl-5,5-[$^2H_2$]-3-cyclohexene-1-carbaldehyde (149) and 5,6-dihydro-2,2-dimethyl-4-[$^2H_3$]methyl-3-2'-phenylethyl-6-vinyl-5,5-[$^2H_2$]-2H-pyran (150)



(146)



(149)



(150)

2-[$^2H_3$]Methyl-4-methyl-3-2'-phenylethyl-1,1-[$^2H_2$]-1,3-pentadiene (146) (70 mg, 0.34 mmol), acrolein (32 ul, 0.48 mmol) and boron trifluoride etherate (9 ul, 0.07 mmol) were reacted together at -40°C in toluene (0.7 ml) as in the preparation of (139) and (140). The reaction was worked up after 12h and after flash chromatography (20:1 petroleum ether-ether) starting material (146),[1] 2,2-dimethyl-4-[$^2H_3$]methyl-3-2'-phenylethyl-5,5-[$^2H_2$]-3-cyclohexene-1-carbaldehyde (149) and 5,6-dihydro-2,2-dimethyl-4-[$^2H_3$]methyl-3-2'-phenylethyl-6-vinyl-5,5-[$^2H_2$]-2H-pyran (150) were obtained (13 mg, 15%), (53 mg, 60%) and (4 mg, 5%) respectively.

149

R_f 0.45 (20:1 petroleum ether-ether);

δ_H (300 MHz; $CDCl_3$) 1.10 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.68-1.88 (2H, m), 2.21 (1H, dt, J = 10.1, 3.3 Hz, H-1), 2.27-2.34 (2H, m), 2.62-2.71 (2H, m), 7.16-7.33 (5H, m, $C_6\underline{H}_5$), 9.86 (1H, d, J = 3.3 Hz, $C\underline{H}O$).

150

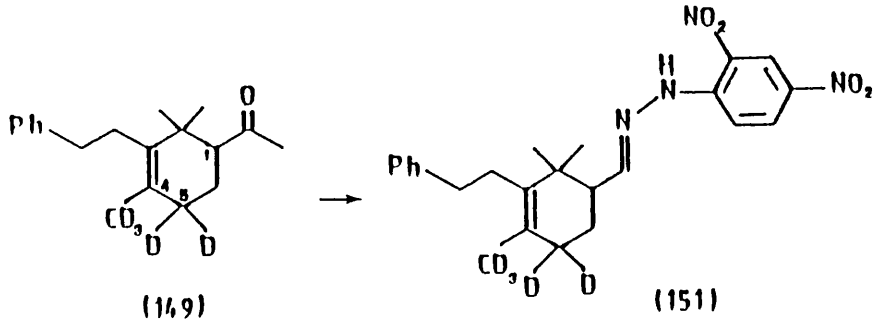
R_f 0.53 (20:1 petroleum ether-ether);

δ_H (300 MHz; $CDCl_3$) 1.33 (3H, s, CH_3), 1.36 (3H, s, CH_3), 2.22-2.33 (2H, m), 2.61-2.75 (2H, m), 4.16 (1H, brd, J = 5.8 Hz), 5.13 (1H, ddd, J_{cis} = 10.5, J = 1.6, 1.2 Hz, -CH=C$\underline{H}_{cis}H_{trans}$), 5.27 (1H, dt, J_{trans} = 17.3, J = 1.6 Hz, -CH=C$H_{cis}\underline{H}_{trans}$), 5.92 (1H, ddd, J_{trans} = 17.3, J_{cis} = 10.5, J = 5.8 Hz, -C$\underline{H}$=CH_2), 7.17-7.34 (7H should be 5H, m, $C_6\underline{H}_5$).

Notes

1. 300 MHz ^1H n.m.r. of recovered starting material (146) was identical to that prepared previously.

Preparation of 1-(methanal-2,4-dinitrophenylhydrazone)-2,2-dimethyl-4-[$^2H_3$]-methyl-3-2'-phenylethyl-5,5-[$^2H_2$]-3-cyclohexene (151)



(149) (151)

The dinitrophenylhydrazone derivative was prepared as in the preparation of (145) using 2,2-dimethyl-4-[$^2H_3$]-methyl-3-2'-phenylethyl-5,5-[$^2H_2$]-3-cyclohexene-1-carbaldehyde (149) (52 mg, 0.2 mmol) and 2,4-dinitrophenylhydrazine (40 mg, 0.2 mmol) in ethanol (2 ml). After recrystallisation from ethanol 1-(methanal-2,4-dinitrophenylhydrazone)-2,2-dimethyl-4-[$^2H_3$]-methyl-3-2'-phenylethyl-5,5-[$^2H_2$]-3-cyclohexene (151) was obtained as a yellow solid (13 mg, 15%).

δ_H (300 MHz; $CDCl_3$) 1.04 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.77 (1H, dd, J = 13.2, 9.7 Hz, H-6_{ax}), 1.91 (1H, dd, J = 13.2, 3.2 Hz, H-6_{eq}), 2.27-2.38 (2H, m), 2.48 (1H, ddd, J = 9.7, 7.3, 3.2 Hz, H-1), 2.63-2.74 (2H, m), 7.18-7.34 (5H, m, $C_6\underline{H}_5$), 7.57 (1H, d, J = 7.3 Hz), 7.96 (1H, d, J = 9.6 Hz), 8.30 (1H, dd, J = 9.6, 2.6 Hz), 9.12 (1H, d, J = 2.6 Hz), 11.04 (1H, brs, N-H);

δ^2_H (300 MHz; $CHCl_3$) 1.77(s), 2.11(brs);

m/z 441 (M^+, 15), 422(5), 407(10), 350(15), 316(10), 279(5), 259(20), 205(20), 167(20), 105(100).

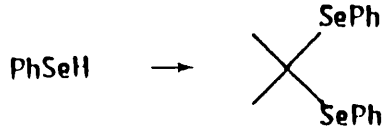
Preparation of Selenophenol (167)[1]

Phenylmagnesium bromide (0.3 mol) was prepared in the usual way from bromobenzene (31.6 ml, 0.3 mol) and magnesium (7.2 g, 0.3 mol) in ether (300 ml). Dry powdered black selenium (22.75 g, 0.29 mol) was then added. After work-up and distillation selenophenol (167)[1] was obtained as a colourless oil (32.9 g, 73%) b.pt. 62-64°C at 15 mmHg, (lit.[2] b.pt. 72-75°C at 15 mmHg).

Notes

1. Literature procedure, see Ref. 114.
2. See Ref. 113.

Preparation of 2,2-Bis(phenylseleno)propane (153)[1]



(167) (153)

Hydrogen chloride gas was passed through a mixture of selenophenol (167) (32.8 g, 0.21 mol) and acetone (7.7 ml, 0.104 mol) for ½h at 0°C. After work-up and flash chromatography[2] (petroleum ether) 2,2-bis(phenylseleno)propane (153)[1] was obtained as a pale yellow solid (9.6 g, 26%[2]).

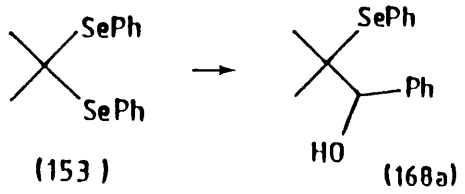
R_f 0.25 (petroleum ether);

δ_H (90 MHz; $CDCl_3$) 1.70 (6H, s, CH_3), 7.1-7.8 (10H, m, $C_6\underline{H}_5$).

Notes

1. Literature procedure, see Ref. 113.
2. 25 g of crude product was divided into two portions for flash chromatography and only one half columned.

Preparation of 2-methyl-1-phenyl-2-phenylseleno-1-propanol (168a)



(153) (168a)

n-Butyllithium[1] (136 ul, 0.29 mmol) was added to a stirred solution of 2,2-bis(phenylseleno)propane (153) (0.1 g, 0.29 mmol) in THF (1 ml), at -78°C, under nitrogen. After ½h at -78°C, a solution of benzaldehyde[2] (29 ul, 0.29 mmol) in THF (½ ml) was added and stirring continued for a further 1h at -78°C. The mixture was then allowed to warm to room temperature and then quenched with water. The aqueous layer was extracted with ether (3 × 20 ml) and each extract washed with a saturated brine solution (10 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo. After flash chromatography (5:1 petroleum ether-ether) 2-methyl-1-phenyl-2-phenylseleno-1-propanol (168a) was obtained as a white solid (67 mg, 78%).

R_f 0.37 (5:1 petroleum ether-ether);

ν_{max} (CH_2Cl_2) 3480brm(OH), 3030w, 2965m, 2930m, 2870m, 1603w, 1490w, 1478m, 1452m, 1385s, 1365m, 1325m, 1185s, 1112s, 1050s, 1020m, 1000m, 840brm;

δ_H (300 MHz; $CDCl_3$) 1.24 (3H, s, CH_3), 1.30 (3H, s, CH_3), 3.41 (1H, brs, OH), 4.43 (1H, s, H-1), 7.25 (5H, s), 7.26-7.42 (3H, m), 7.66-7.69 (2H, m);

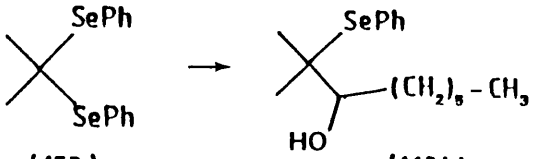
δ_C (75 MHz; $CDCl_3$) 21.49(q), 27.82(q), 55.38(s, C-2), 78.14(d, C-1), 126.39(s), 127.53(d), 127.59(d), 127.98(d), 128.94(d), 129.03(d), 137.95(s), 138.07(d).

Notes

1. n-Butyllithium was 2.4 M by titration.

2. The benzaldehyde was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) then distilled prior to use.

Preparation of 2-methyl-2-phenylseleno-3-nonanol (168b)



(153) (168b)

Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (2.82 mmol) and heptanal[1] (0.38 ml, 2.82 mmol) in THF (15 ml) were reacted together at -78°C for 1h. After work-up and flash chromatography (5:1 petroleum ether-ether) 2-methyl-2-phenylseleno-3-nonanol (168b) was obtained as a pale yellow oil (0.816 g, 92%).

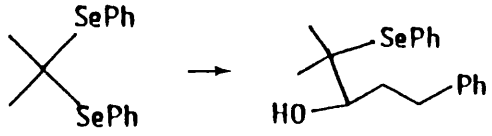
R_f 0.54 (5:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.88 (3H, brs, CH_3), 1.15-1.60 (16H, m), 2.58 (1H, brs, OH), 3.20-3.40 (1H, m, H-3), 7.20-7.70 (5H, m, $C_6\underline{H}_5$).

Notes

1. The heptanal was distilled prior to use.

Preparations of 2-methyl-5-phenyl-2-phenylseleno-3-pentanol (168c)



(153) (168c)

Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (0.28 mmol) and 3-phenylpropanal[1] (37 ul,

0.28 mmol) in THF (2 ml) were reacted together at -78°C for 1h. After work-up and flash chromatography (5:1 petroleum ether-ether) 2-methyl-5-phenyl-2-phenylseleno-3-pentanol (168c) was obtained as a colourless oil (84 mg, 89%).

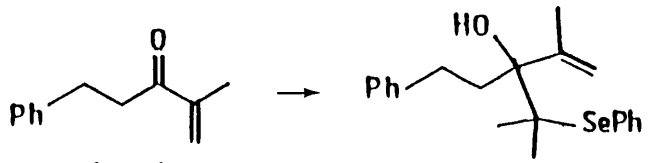
R_f 0.5 (5:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 1.25 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.52-1.85 (2H, m, H-4), 2.38-3.11 (3H, m), 3.20-3.45 (1H, m, H-3), 7.10-7.60 (10H, m, $C_6\underline{H}_5$).

Notes

1. 3-Phenylpropanal was distilled prior to use.

Preparation of 2,4-dimethyl-3-2'-phenylethyl-4-phenylseleno-1-penten-3-ol (169)



(89) (169)

Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (1.15 mmol) and 2-methyl-5-phenyl-1-penten-3-one (89) (0.2 g, 1.15 mmol) were reacted together in THF (5 ml) at -78°C for 1h then at room temperature for 1h. After work-up [as for (168a)] and flash chromatography (20:1 petroleum ether-ether) 2,4-dimethyl-3-2'-phenylethyl-4-phenylseleno-1-penten-3-ol (169) was obtained as a colourless oil (0.313 g, 73%).

R_f 0.33 (20:1 petroleum ether-ether);

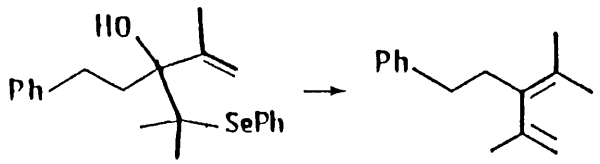
ν_{max} (film) 3480brm, 3060s, 3025s, 2965s, 2870s, 1625m, 1605m, 1580m, 1498m, 1475m, 1455s, 1438s, 1380s, 1120s, 1022m, 1000m, 905m, 740s, 695s;

δ_H (300 MHz; $CDCl_3$) 1.37 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.91 (3H, d, J = 0.6 Hz), 2.07-2.19 (2H, m, H-1'), 2.48 (1H, ddd, J = 13.7, 9.4, 6.8 Hz, H-2'), 2.71 (1H, s, OH), 2.80 (1H, ddd, J = 13.7, 9.5, 7.8 Hz, H-2'), 5.08 (1H, s, H-1), 5.18 (1H, m, H-1), 7.14-7.33 (8H, m), 7.58-7.64 (2H, m);

δ_C (75 MHz; $CDCl_3$) 22.69(q), 26.87(q), 27.01(q), 30.27(t, C-1'), 38.33 (t, C-2'), 60.93(s, C-4), 81.85(s, C-3), 114.92(t, C-1), 125.61(d), 127.92(s), 128.28(d), 128.34(d), 128.65(d), 138.46(d), 142.75(s), 145.20(s);

m/z 355 (M^+ -18), 312(5), 217(15), 199(14), 157(12), 154(11), 133(17), 111(15), 105(67), 91(100).

Preparation of 2,4-dimethyl-3-2'-phenylethyl-1,3-pentadiene (88)



(169) (88)

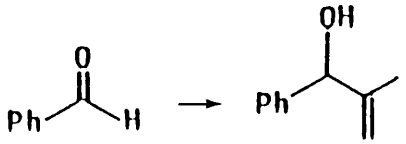
Thionyl chloride[1] (42 ul, 0.58 mmol) in dichloromethane (2 ml) was added to a stirred mixture of 2,4-dimethyl-3-2'-phenylethyl-4-phenyl-seleno-1-penten-3-ol (169) (0.108 g, 0.29 mmol) and triethylamine (0.282 ml, 2 mmol) in dichloromethane (2 ml) under nitrogen, at room temperature.[2] The reaction was monitored by t.l.c. and after 2h no starting material remained. The reaction was then poured into water (10 ml), extracted with ether (2 × 20 ml), washed with HCl 1 M (10 ml) and finally saturated brine solution (10 ml). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. After purification by a "chromatotron" (petroleum ether) 2,4-dimethyl-3-2'-phenylethyl-1,3-

pentadiene (88) was obtained as a colourless oil (36 mg, 62%).[3]

Notes

1. Freshly distilled from linseed oil.
2. Method described by Rémion and Krief, see Ref. 106.
3. Identical in spectral properties to that prepared previously.

Preparation of 2-methyl-1-phenyl-2-propen-1-ol (170)[1]



(170)

Propenyl Grignard was prepared as in the preparation of (253) from magnesium turnings (1.25 g, 50 mmol) and 2-bromopropene (3.3 ml, 37 mmol) in THF (40 ml). To the Grignard solution was added benzaldehyde[2] (3 ml, 30 mmol) in THF (10 ml). After work-up a crude yield of 2-methyl-1-phenyl-2-propen-1-ol (170) was isolated (4.22 g, 95%).[3]

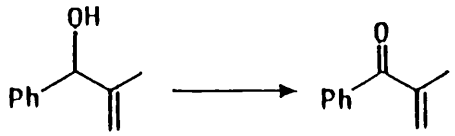
R_f 0.29 (10:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 1.55 (3H, s, CH_3), 2.10 (1H, s, OH), 4.90 (1H, s), 5.10 (1H, s), 5.15 (1H, s), 7.28 (5H, s, $C_6\underline{H}_5$).

Notes

1. Known compound, see Ref. 158.
2. Washed with aqueous sodium bicarbonate, dried ($MgSO_4$) then distilled prior to use.
3. Used without further purification in the next stage.

Preparation of 2-methyl-1-phenyl-2-penten-1-one (171)[1]



(170) (171)

Using the same procedure as for the preparation of (89) a solution of 2-methyl-1-phenyl-2-propen-1-ol (170)[2] (4.22 g, 28.5 mmol) in dichloromethane (40 ml) was oxidised with a preformed solution of chromium trioxide[3] (17.1 g, 0.171 mol) and pyridine (27 g, 0.34 mol) in dichloromethane (400 ml).[4] After standard work-up and flash chromatography (20:1 petroleum ether-ether) 2-methyl-1-phenyl-2-penten-1-one (171)[1] was obtained as a colourless oil (2.93 g, 70%).

R_f 0.39 (20:1 petroleum ether-ether);

ν_{max} (film) 3080m, 3060m, 2980m, 2960m, 2925m, 1660s(C=O), 1600m, 1588m, 1448s, 1400w, 1372w, 1330s, 1200s, 1177s, 1075w, 900s, 750s, 710s;

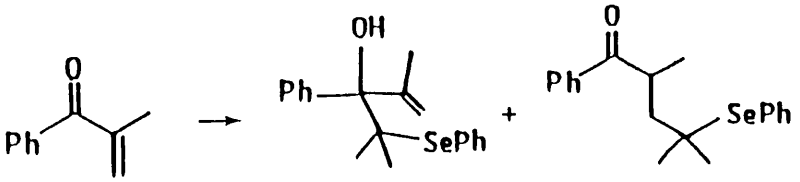
δ_H (90 MHz; $CDCl_3$) 2.02 (3H, s, CH_3), 5.58 (1H, s, H-3), 5.86 (1H, s, H-3), 7.25-7.75 (5H, m, $C_6\underline{H}_5$);

m/z 146 (M^+, 26), 118(23), 105(100), 77(70).

Notes

1. Known compound, see Ref. 158.
2. Obtained crude from the previous reaction.
3. Dried over P_2O_5 at 60°C under vacuum overnight.
4. Method described by Ratcliffe and Rodehorst, see Ref. 53.

Preparation of 2,4-dimethyl-3-phenyl-4-phenylseleno-1-penten-3-ol (172) and 2,4-dimethyl-1-phenyl-4-phenylseleno-1-pentanone (173)



(171) (172) (173)

Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (2.06 mmol) and 2-methyl-1-phenyl-2-penten-1-one (171) (0.3 g, 2.05 mmol) were reacted together in THF (6 ml) at -78°C for 1h then at room temperature for 1h. After work-up [as for (168a)] and flash chromatography (20:1 petroleum ether-ether) 2,4-dimethyl-3-phenyl-4-phenylseleno-1-penten-3-ol (172) and 2,4-dimethyl-1-phenyl-4-phenylseleno-1-pentanone (173) were obtained as a pale yellow solid (0.21 g, 29%) m.p. 66-70°C, and a pale yellow oil (0.27 g, 38%) respectively.

172

R_f 0.59 (20:1 petroleum ether-ether);

ν_{max} (nujol mull) 3480w(OH), 1338m, 1163m, 1118m, 1038s, 995w, 912m, 900m, 762s, 745s, 710m, 696s;

δ_H (300 MHz; $CDCl_3$) 1.03 (3H, s, CH_3), 1.61 (3H, m, CH_3), 1.67 (3H, s, CH_3), 3.34 (1H, s, OH), 5.22 (1H, m, H-1), 5.73 (1H, s, H-1), 7.20-7.66 (10H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 21.71(q), 28.11(q), 29.22(q), 58.71(s, C-4), 83.64(s, C-3), 113.64(t, C-1), 126.96(d), 127.05(d), 127.95(d), 128.49(s), 128.68(d), 138.31(d), 139.30(s), 146.85(s);

m/z 346 (M^+, 1), 344 (M^+), 314(4), 312(2), 234(5), 232(2), 199(30), 197(13), 189(26), 147(25), 129(25), 119(34), 105(100).

173

R_f 0.47 (20:1 petroleum ether-ether);

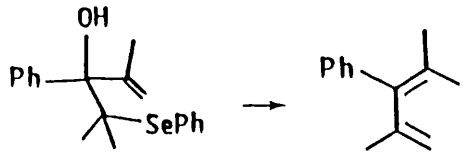
ν_{max} (film) 3060m, 2970s, 2930s, 2875m, 1680s(C=O), 1600m, 1580m, 1450s, 1365m, 1255m, 1215m, 1115m, 1022m, 1001m, 975s, 795m, 740s;

δ_H (300 MHz; $CDCl_3$) 1.17 (6H, s and d overlapping, J = 7.2 Hz, CH_3), 1.38 (3H, s, CH_3), 1.56 (1H, dd, J_{33} = 14.8, J = 2.2 Hz, H-3), 2.50 (1H, dd, J_{33} = 14.8, J = 8.8 Hz, H-3), 3.94-4.04 (1H, m, H-2), 7.21-7.63 (8H, m), 8.02-8.06 (2H, m);

δ_C (75 MHz; $CDCl_3$) 20.48(q), 29.29(q), 31.67(q), 38.12(d, C-2), 45.51 (t, C-3), 48.17(s, C-4), 127.66(s), 128.31(d), 128.45(d), 128.56(d), 128.59(d), 132.83(d), 136.31(s), 138.04(d), 203.81(s, C=O);

m/z 346 (M^+, 2), 344 (M^+, 1), 314(4), 312(2), 234(4), 232(2), 189(39), 171(23), 105(100).

Preparation of 2,4-dimethyl-3-phenyl-1,3-pentadiene (174)



(172) (174)

Using the same procedure[1] as for the preparation of (88) (on page 139) a solution of 2,4-dimethyl-3-phenyl-4-phenylseleno-1-penten-3-ol (172) (0.195 g, 0.57 mmol) was treated with thionyl chloride[2] (82 ul, 1.13 mmol) and triethylamine (550 ul, 3.96 mmol) in dichloromethane (6 ml). After work-up and purification by "chromatotron" (petroleum ether) 2,4-dimethyl-3-phenyl-1,3-pentadiene (174) was isolated as a colourless oil (64 mg, 66%).

R_f 0.65 (petroleum ether);

ν_{max} (film) 3075s, 2980s, 2970s, 2910s, 2855s, 2720w, 1630m, 1600m, 1490s, 1440s, 1370s, 1205w, 1090m, 1070m, 1002w, 987w, 895s, 763s, 700s;

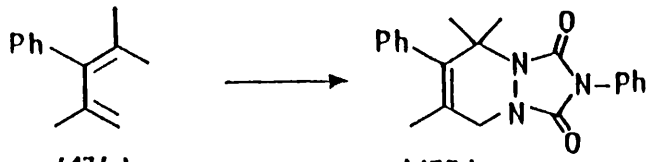
δ_H (300 MHz; $CDCl_3$) 1.63-1.64 (6H, m, CH_3), 1.87 (3H, s, CH_3), 4.84-4.85 (1H, m, H-1), 5.02-5.03 (1H, m, H-1), 7.14-7.3 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 21.66(q), 22.02(q), 22.63(q), 114.05(t, C-1), 126.12(d), 127.78(d), 128.42(s), 129.21(d), 139.10(s), 141.41(s).

Notes

1. Method described by Rémion and Krief, see Ref. 106.
2. Distilled from linseed oil.

Preparation of 3,8-diphenyl-2,2,4-trimethyl-1,6,8-triazo[4,3,0]bicyclo-non-3-ene-7,4-dione (175)



(174) (175)

4-Phenyl-1,2,4-triazoline-3,5-dione (136)[1] (16 mg, 87 umol) in acetone (250 ul) was added to a solution of 2,4-dimethyl-3-phenyl-1,3-pentadiene (174) (15 mg, 87 umol) in dichloromethane (250 ul) at room temperature. After 1h the solvent was removed in vacuo and the resulting white solid recrystallised twice from methanol to yield 3,8 diphenyl-2,2,4-trimethyl-1,6,8-triazo[4,3,0]bicyclonon-3-ene-7,9-dione (175) as a white crystalline solid (21 mg, 69%), m.p. 153-5°C.

$C_{21}H_{21}N_3O_2$ requires C 72.60%, H 6.09%, N 12.09%,

found C 72.38%, H 6.11%, N 12.00%.

ν_{max} (nujol mull) 1770m, 1710s(C=O), 1598w, 1503m, 1283m, 1248w, 1138m, 840w, 798w, 760m, 742s, 720m, 700m, 693m;

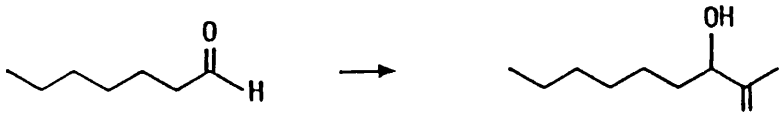
δ_H (90 MHz; $CDCl_3$) 1.43 (3H, s, CH_3), 1.54 (6H, s, CH_3), 4.08 (2H, s, H-5), 6.95-7.52 (10H, m, $C_6\underline{H}_5$);

m/z 347 (M^+, 75), 332(100), 213(54), 198(27), 171(29), 157(16), 143(20), 129(38).

Notes

1. Prepared according to literature, see Ref. 95 also see Ref. 94.

Preparation of 2-methyl-1-nonen-3-ol (176)[1]



(176)

Propenyl Grignard was prepared as in the preparation of (253) from magnesium turnings (0.81 g, 34 mmol) and 2-bromopropene (2.4 ml, 27 mmol) in THF (20 ml). To the Grignard solution was added heptanal[2] (3 ml, 22 mmol) in THF (20 ml). After ½h at room temperature the mixture was worked-up in the usual way to yield 2-methyl-1-nonen-3-ol (176)[3] as a pale yellow oil (3.47 g, 99%).

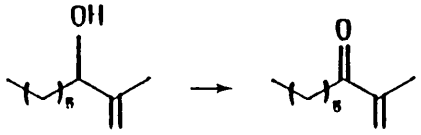
R_f 0.40 (10:1 petroleum ether-ether);

δ_H (90 MHz; $CDCl_3$) 0.74-0.93 (3H, m, CH_3), 1.13-1.53 (10H, m), 1.68 (3H, s, CH_3), 1.75 (1H, s, OH), 4.0 (1H, brt, J = 6 Hz, H-3), 4.76 (1H, s with some fine splitting, H-1), 4.88 (1H, brs, H-1).

Notes

1. Literature procedure, see Ref. 159.
2. Distilled prior to use.
3. Used without further purification in the next stage.

Preparation of 2-methyl-1-nonen-3-one (177)[1]



(176) (177)

Using the same procedure as for the preparation of (89) a solution of 2-methyl-1-nonen-3-ol (176)[2] (3.47 g, 22 mmol) in dichloromethane (30 ml) was oxidised with a preformed solution of chromium trioxide[3] (13.3 g, 133 mmol) and pyridine (21.5 ml, 266 mmol) in dichloromethane (300 ml).[4] After standard work-up and flash chromatography (20:1 petroleum ether-ether) 2-methyl-1-nonen-3-one (177)[1] was obtained as a colourless oil (2.4 g, 70%).

R_f 0.61 (20:1 petroleum ether-ether);

ν_{max} (film) 3095w, 2940brs, 2860s, 1675s(C=O), 1630s, 1450s, 1410m, 1370m, 1125m, 1070s, 980w, 930s, 725w;

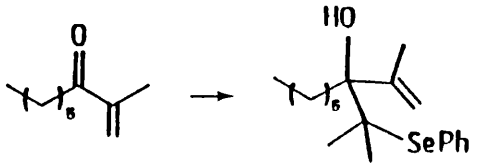
δ_H (90 MHz; $CDCl_3$) 0.80-1.0 (3H, m, CH_3), 1.23-1.70 (8H, m), 1.88 (3H, s, CH_3), 2.68 (2H, t, J = 7.5 Hz, H-4), 5.75 (1H, s, H-1), 5.95 (1H, s, H-1);

m/z 154 (M^+, 10), 111(15), 105(18), 84(80), 69(100).

Notes

1. Known compound, see Ref. 160.
2. Obtained crude from the previous reaction.
3. Dried over P_2O_5 at 60°C under vacuum overnight.
4. Method described by Ratcliffe and Rodehorst, see Ref. 53.

Preparation of 2,4-dimethyl-3-hexyl-4-phenylseleno-1-penten-3-ol (178)



(177) (178)

Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (3.24 mmol) and 2-methyl-1-nonen-3-one (177) (0.5 g, 3.24 mmol) were reacted together in THF (14 ml) at -78°C for 1h then at room temperature for 1h. After work-up and flash chromatography (20:1 petroleum ether-ether) 2,4-dimethyl-3-hexyl-4-phenylseleno-1-penten-3-ol (178) was obtained as a pale yellow oil (0.988 g, 86%).

R_f 0.58 (20:1 petroleum ether-ether);

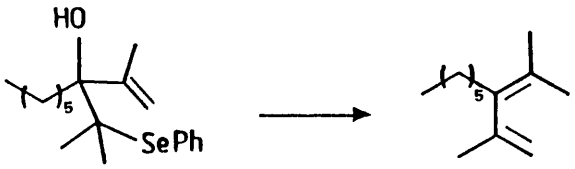
ν_{max} (film) 3480brm(OH), 3060w, 2955s, 2920s, 2855m, 1578w, 1460m, 1435m, 1378m, 1110m, 1065w, 1020m, 1000w, 900m, 740s, 693s;

δ_H (300 MHz; $CDCl_3$) 0.86-0.92 (3H, m, CH_3), 1.24-1.33 (8H, brs), 1.36 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.78-1.87 (5H, m), 2.49 (1H, s, OH), 5.0 (1H, s, H-1), 5.08 (1H, m, H-1), 7.22-7.38 (3H, m), 7.63-7.67 (2H, m);

δ_C (75 MHz; $CDCl_3$) 14.01(q), 22.59(t and q overlapping), 23.59(t), 26.92(q), 27.07(q), 29.77(t), 31.80(t), 35.91(t), 60.66(s, C-4), 81.97 (s, C-3), 114.47(t, C-1), 128.19(s), 128.52(d), 138.49(d), 145.56(s);

m/z 354 (M^+, 1), 352 (M^+), 311(2), 214(31), 212(15), 197(11), 182(11), 158(100), 113(28).

Preparation of 2,4-dimethyl-3-hexyl-1,3-pentadiene (179)



(178) (179)

Using the same procedure[1] as for the preparation of (88) (on page 139) a solution of 2,4-dimethyl-3-hexyl-4-phenylseleno-1-penten-3-ol (178) (0.4 g, 1.13 mmol) was treated with thionyl chloride[2] (165 ul, 2.27 mmol) and triethylamine (1.1 ml, 7.93 mmol) in dichloromethane (15 ml). After work-up and purification by "chromatotron" (petroleum ether) and Kugelröhr distillation (50°C at 15 mmHg) 2,4-dimethyl-3-hexyl-1,3-pentadiene (179) was isolated as a colourless oil (0.132 g, 65%).

R_f 0.7 (petroleum ether);

$C_{13}H_{24}$ requires C 86.59%, H 13.41%, N 0.00%,

found C 86.44%, H 13.22%, N <0.2%.

λ_{max} (CH_3CN) 236 (ε 1910 $dm^3\ mol^{-1}\ cm^{-1}$);

ν_{max} (film) 3080w, 2980s, 2925s, 2860s, 1632w, 1450brm, 1370m, 1135w, 895s;

δ_H (300 MHz; $CDCl_3$) 0.88 (3H, brt, J = 6.7 Hz), 1.27 (8H, brs), 1.66 (6H, s, CH_3), 2.75 (3H, dd, J = 1.5, 0.9 Hz, $-CH_3$), 2.06 (2H, brt, J = 7.4 Hz), 4.53 (1H, dq, J = 2.8, 0.9 Hz, H-1), 4.90 (1H, dq, J = 2.8, 1.5 Hz, H-1);

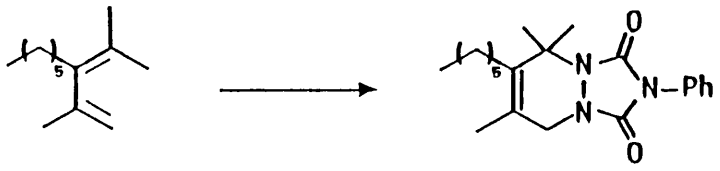
δ_C (75 MHz; $CDCl_3$) 14.10(q), 19.62(q), 21.72(q), 22.74(t and q overlapping), 28.67(t), 29.35(t), 31.19(t), 31.91(t), 112.72(t, C-1), 124.52 (s), 137.03(s), 146.81(s);

m/z 180 (M^+, 21), 165(16), 137(28), 123(17), 109(42), 95(60), 81(100), 66(65).

Notes

1. Method described by Rémion and Krief, see Ref. 106.
2. Distilled from linseed oil.

Preparation of 3-hexyl-8-phenyl-2,2,4-trimethyl-1,6,8-triazo[4,3,0]-bicyclonon-3-ene-7,9-dione (180)



(179) (180)

4-Phenyl-1,2,4-triazoline-3,5-dione (136)[1] (79 mg, 0.44 mmol) in acetone (1 ml) was added to a solution of 2,4-dimethyl-3-hexyl-1,3-pentadiene (179) (80 mg, 0.44 mmol) in dichloromethane (1 ml) at room temperature. After 1h the solvent was removed in vacuo and the resulting white solid recrystallised twice from methanol to give 3-hexyl-8-phenyl-2,2,4-trimethyl-1,6,8-triazo[4,3,0]bicyclonon-3-ene-7,9-dione (180) as a white crystalline solid (96 mg, 70%), m.p. 88°C.

$C_{21}H_{29}O_2N_3$ requires C 70.96%, H 8.22%, N 11.82%,

found C 71.13%, H 8.30%, N 11.97%.

ν_{max} (nujol mull) 1770m, 1710s, 1600w, 1505m, 1490m, 1420s, 1280m, 1200w, 1145m, 1110w, 840w, 810w, 760s, 750s, 690s, 650m;

δ_H (300 MHz; $CDCl_3$) 0.91 (3H, brt, J = 7 Hz, CH_3), 1.28-1.50 (8H, m), 1.62 (6H, s, CH_3), 1.76 (3H, s, CH_3), 2.01-2.07 (2H, m), 3.94 (2H, s, H-5), 7.26-7.53 (5H, m, $C_6\underline{H}_5$);

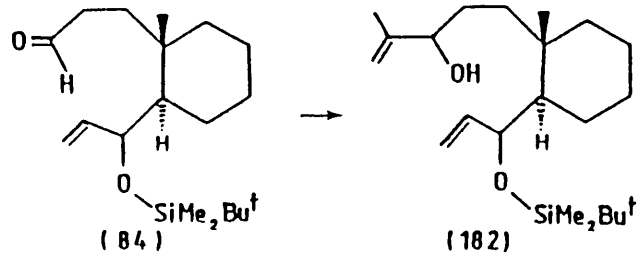
δ_C (75 MHz; $CDCl_3$) 13.96(q), 16.75(q), 22.57(t), 23.10(q), 28.29(t), 29.90(t), 31.42(t), 46.98(t, C-5), 62.49(s, C-2), 120.36(s), 125.42(d), 127.78(d), 128.86(d), 131.32(s), 135.31(s), 152.24(s), 152.30(s);

m/z 355 (M^+, 40), 340(100), 270(5), 221(41), 193(28), 179(27), 151(11), 123(27), 119(37), 109(38).

Notes

1. Prepared according to literature, see Ref. 95 also see Ref. 94.

Preparation of trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-ol (182)



(84) (182)

Propenyl Grignard was prepared as in the preparation of (253) from magnesium turnings (62 mg, 2.6 mmol) and 2-bromopropene (0.21 ml, 2.4 mmol) in THF (3 ml). To the Grignard solution was added trans-3-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}propionaldehyde (84) (0.7 g, 2.2 mmol) in THF (10 ml) and the mixture stirred for ½h at room temperature. After usual work-up and purification by flash chromatography (4:1 petroleum ether-ether) trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-ol (182) was obtained as a colourless oil (0.54 g, 68%).[1]

R_f 0.30 and 0.34 (4:1 petroleum ether-ether);

ν_{max} (film) 3350brm(OH), 3075w, 2930s, 2860s, 1650w, 1470m, 1462m, 1360m, 1252s, 1095s, 1078s, 1020s, 920s, 900m, 840s, 775s;

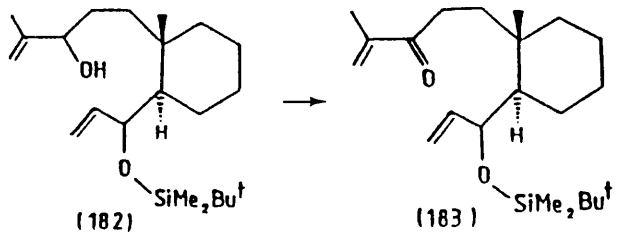
δ_H (90 MHz; $CDCl_3$)[2] -0.05 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.93 (3H, s, CH_3), 1.05-1.65 (14H, m, 6 x CH_2, H-2' and OH), 1.73 (3H, s, CH_3), 4.0 (1H, brs, H-3), 4.32 (1H, brd, J = 7.5 Hz, H-1"), 4.81-5.15 (4H, m), 5.91 (1H, ddd, J = 17.5, 9.6, 7.0 Hz, H-2");

m/z 348 (M^+ -18), 333(1), 309(2), 291(2), 239(12), 217(5), 171(100), 135(17), 131(16), 115(27), 109(21).

Notes

1. Crude ^{13}C n.m.r. shows diastereoisomer ratio to be approximately 1:1.
2. $CHCl_3$ signal set to δ7.3.

Preparation of trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-one (183)



Using the same procedure as for the preparation of (89) a solution of trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-ol (182) (0.52 g, 1.42 mmol) in dichloromethane (10 ml) was oxidised with a preformed solution of chromium trioxide[1] (0.85 g, 8.5 mmol) and pyridine (1.38 ml, 17 mmol) in dichloromethane (15 ml).[2] After standard work-up and flash chromatography (20:1 petroleum ether-ether) trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-one (183) was obtained as a colourless oil (0.383 g, 74%).

R_f 0.42 (20:1 petroleum ether-ether);

ν_{max} (film) 2925s, 2855s, 1678s(C=O), 1633w, 1460m, 1370m, 1252s, 1094s, 1020m, 1005m, 995m, 922s, 888s, 775s;

δ_H (300 MHz; $CDCl_3$)[3] -0.03 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.94 (3H, s, CH_3), 1.05-1.78 (15H should be 11H, m, 5 x CH_2 and H-2'), 1.87 (3H, dd, J = 1.5, 0.9 Hz, CH_3), 2.59-2.65 (2H, m, H-4), 4.34 (1H, d, J = 7.2 Hz, H-1"), 4.96 (1H, ddd, $J_{3",2"cis}$ = 10.3, $J_{3",3"}$ = 1.7, J = 0.9 Hz, H-3"), 5.03 (1H, ddd, $J_{3",2"trans}$ = 17.3, $J_{3",3"}$ = 1.7, J = 1.1 Hz, H-3"), 5.74 (1H, m, H-1), 5.88 (1H, ddd, $J_{2",3"trans}$ = 17.3, $J_{2",3"cis}$ = 10.3, $J_{2",1"}$ = 7.2 Hz, H-2"), 5.94 (1H, m, H-1);

δ_C (75 MHz; $CDCl_3$) -4.52(q), -3.07(q), 17.78(q), 18.13(s, $SiC(CH_3)_3$), 20.50(q), 21.11(t), 22.14(t), 26.02(q, $SiC(CH_3)_3$), 26.67(t), 31.68(t), 35.75(s, C-1'), 37.17(t), 38.62(t), 50.93(d, C-2'), 72.82(d, C-1"),

113.32(t), 124.10(t), 142.85(d), 144.58(s, C-2), 202.82(s, C-3);

m/z 364 (M^+), 307(23), 339(5), 171(100), 115(28), 109(23), 105(10);

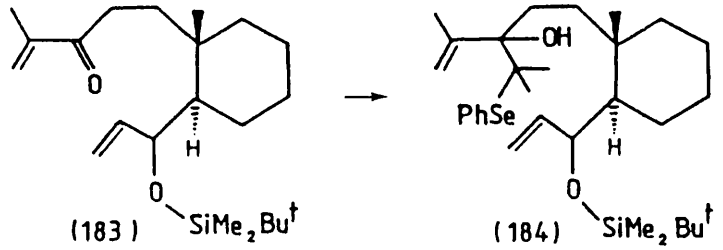
$C_{22}H_{40}O_2Si$ requires 365.2876,

found 365.2878.[4]

Notes

1. Dried over P_2O_5 at 60°C under vacuum overnight.
2. Method described by Ratcliffe and Rodehorst, see Ref. 53.
3. $CHCl_3$ signal set at δ7.3.
4. Chemical ionisation conditions used which showed $(M+H)^+$ molecular ion.

Preparation of trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-3-(1'"-methyl-1'"-phenylselenoethyl)-2-methyl-pent-1-en-3-ol (184)



Using the same procedure as for the preparation of (168a), 2-lithio-2-phenylselenopropane (152) (1.05 mmol) and trans 5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-2-methyl-pent-1-en-3-one (183) (0.38 g, 1.04 mmol) were reacted together in THF (10 ml) at -78°C for 1h and then at room temperature for 1h. After work-up and flash chromatography (20:1 petroleum ether-ether) trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-3-(1'"-methyl-1'"-phenyl-selenoethyl)-2-methyl-pent-1-en-3-ol (184) was obtained as a colourless oil (0.503 g, 85%).

R_f 0.63 (20:1 petroleum ether-ether);

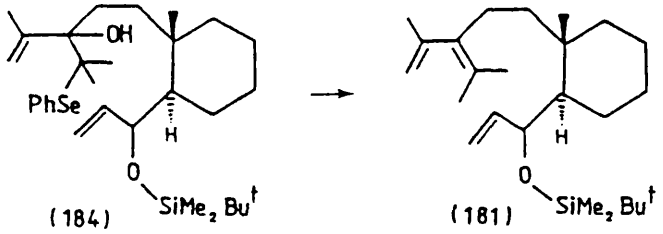
ν_{max} (film) 3480brw(OH), 3070w, 2930s, 2855s, 1635w, 1580w, 1461s, 1438s,

1380s, 1251s, 1120s, 1095s, 1078s, 1022s, 1005s, 920s, 838s, 774s, 740s, 695s;

δ_H (90 MHz; $CDCl_3$) -0.04 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, s, CH_3), 1.03-1.73 (19H, m, $6 \times CH_2$, $2 \times CH_3$ and H-2'), 1.83 (3H, s, CH_3), 2.44 (1H, brs, OH), 4.3 (1H, brt, J = 6.5 Hz, H-1"), 4.83-5.23 (4H, m), 5.61-6.11 (1H, m, H-2'), 7.13-7.68 (5H, m, $C_6\underline{H}_5$);

m/z 546 (M^+ -18), 544 (M^+ -18), 388(3), 349(15), 314(22), 312(18), 220(15), 205(52), 171(100), 157(45).

Preparation of trans-2-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1-methyl-1-[4'-methyl-3'-(1"'-methylethenyl)pent-3'-enyl]cyclohexane (181)



Using the same procedure as for the preparation of (88) (on page 139) a solution of trans-5-{2'-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1'-methylcyclohexyl}-3-(1"'-methyl-1"'-phenylselenoethyl)-2-methyl-pent-1-en-3-ol (184) (0.214 g, 0.38 mmol) was treated with thionyl chloride[1] (0.38 ml, 0.76 mmol) and triethylamine (0.365 ml, 2.66 mmol) in dichloromethane (4 ml).[2] After work-up and flash chromatography (petroleum ether) trans-2-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1-methyl-1-[4'-methyl-3'-(1"'-methylethenyl)pent-3-enyl]cyclohexane (181) was isolated as a colourless oil (80 mg, 54%).

R_f 0.78 (petroleum ether);

ν_{max} (film) 3075m, 2920brs, 1633m, 1470s, 1460s, 1445s, 1371s, 1360m, 1253s, 1094s, 1020s, 1005s, 994s, 920s, 895s, 838s, 775s, 680m;

δ_H (300 MHz; $CDCl_3$)[1] -0.03 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.92 (3H, s, CH_3), 1.03-1.57 (13H should be 11H, m, 5 × CH_2 and H-2), 1.66 (6H, s, CH_3), 1.76 (3H, dd, J = 1.4, 0.9 Hz, CH_3), 1.86-2.09 (2H, m, H-2'), 4.36 (1H, brd, J = 7.2 Hz, H-1"), 4.55-4.56 (1H, m, H-2"'), 4.89-4.91 (1H, m, H-2"'), 4.96 (1H, ddd, $J_{3",2"cis}$ = 10.3, $J_{3",3"}$ = 1.7, J = 0.9 Hz, H-3"), 5.03 (1H, ddd, $J_{3",2"trans}$ = 17.3, $J_{3",3"}$ = 1.7, J = 1.1 Hz, H-3"), 5.89 (1H, ddd, $J_{2",3"trans}$ = 17.3, $J_{2",3"cis}$ = 10.3, $J_{2",1"}$ = 7.2 Hz, H-2");

δ_C (75 MHz; $CDCl_3$) -4.58(q), -3.01(q), 18.15(q, $SiC(CH_3)_3$), 19.47(q), 20.76, 21.11, 21.72, 22.26, 22.87, 24.80(t), 26.09(q, $SiC(CH_3)_3$), 26.84(t), 35.85(s, C-1), 38.60(t), 41.03(t), 50.22(d, C-2), 72.70(d, C-1"), 112.73(t), 113.08(t), 124.37(s), 137.14(s), 143.11(d, C-2"), 146.88(s);

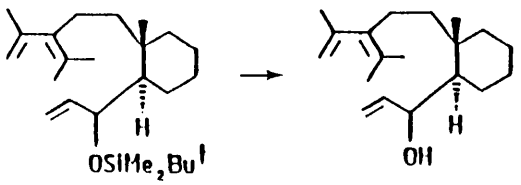
$C_{25}H_{46}OSi$ requires 390.3318,

found 390.3313.

Notes

1. $CHCl_3$ signal set to δ7.3.

Preparation of trans-1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)-pent-3"-enyl]cyclohexyl}-prop-2-en-1-ol (185)



(181) (185)

A solution of 40% aqueous hydrofluoric acid (0.88 ml) was added via an Eppendorf syringe to a stirred solution of trans-2-[1"-(dimethyl-t-butylsiloxy)prop-2"-enyl]-1-methyl-1-[4'-methyl-3'-(1"'-methylethenyl)-

pent-3'-enyl]cyclohexane (181) (0.164 g, 0.42 mmol) in acetonitrile (5 ml) in a glass round-bottomed flask.[1] The reaction was monitored by t.l.c. and after 6h at room temperature the starting material had disappeared. The mixture was poured into water (2 ml), then neutralised with solid sodium bicarbonate and extracted with ether (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and then the solvent removed *in vacuo* to yield trans-1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)pent-3"-enyl]cyclohexyl}-prop-2-en-1-ol (185) as an oil (0.115 g, 99%) which was used without further purification.

R_f 0.47 (5:1 petroleum ether-ether);

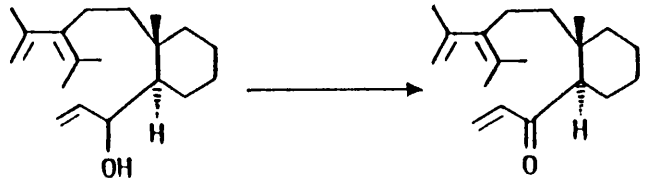
ν_{max} (film) 3400brs(OH), 3070m, 2920brs, 1630m, 1442s, 1370m, 1218w, 1120m, 985m, 920s, 892s, 760s, 735s;

δ_H (90 MHz; $CDCl_3$) 1.0 (3H, s, CH_3), 1.12-1.58 (10H, m), 1.61 (6H, s, CH_3), 1.72 (3H, s, CH_3), 1.6-2.2 (overlapping with CH_3, 4H, m), 4.33-4.57 (2H, m), 4.81-5.28 (3H, m), 5.83 (1H, ddd, $J_{2,3\,trans} = 16$, $J_{2,3\,cis} = 10$, $J_{2,1} = 6$ Hz, H-2).

Notes

1. Method described by Newton *et al.*, see Ref. 117.

Preparation of trans-1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)-pent-3"-enyl]cyclohexyl}-prop-2-en-1-one (83)



(185) (83)

Chromium trioxide[1] (0.239 g, 2.39 mmol) was added to a stirred solution of pyridine (386 ul, 4.78 mmol) in dry dichloromethane (6 ml) at

room temperature. The stirring was continued for a further 30 min. then trans 1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)pent-3"-enyl]-cyclohexyl}-prop-2-en-1-ol (185)[2] (110 mg, 0.4 mmol) in dichloromethane (1 ml) was added.[3] After 5 min. the mixture was filtered through a short silica column and the chromium residues were washed with ether (3 × 30 ml). The solvent was removed in vacuo and the residue purified by "chromatatron" (40:1 petroleum ether-ether) to give trans-1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)pent-3"-enyl]cyclohexyl}-prop-2-en-1-one (83) as a colourless oil (108 mg, 99%).

R_f 0.39 (20:1 petroleum ether-ether);

ν_{max} (film) 3075w, 2925s, 2860s, 1680s, 1672s, 1630m, 1608s, 1465m, 1445s, 1398s, 1370m, 1150w, 1083m, 983m, 965m, 895s, 758s;

δ_H (300 MHz; $CDCl_3$) 1.00 (3H, s, CH_3), 1.21-1.32 (4H, m), 1.45-1.78 (6H, m) overlapping with 1.62 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.72 (3H, dd, J = 1.4, 0.9 Hz, CH_3), 1.92-2.12 (2H, m, H-2"), 2.66 (1H, dd, $J_{1',6'ax}$ = 11.0, $J_{1',6'eq}$ = 3.7 Hz, H-1'), 4.49 (1H, dq, $J_{2''',2'''}$ = 2.8, J = 0.9 Hz, H-2"'), 4.86 (1H, dq, $J_{2''',2'''}$ = 2.8, J = 1.4 Hz, H-2"'), 5.65 (1H, dd, $J_{3,2cis}$ = 10.4, $J_{3,3}$ = 1.5 Hz, H-3), 6.17 (1H, dd, $J_{3,2trans}$ = 17.4, $J_{3,3}$ = 1.5 Hz, H-3), 6.40 (1H, dd, $J_{2,3trans}$ = 17.4, $J_{2,3cis}$ = 10.4 Hz, H-2);

δ_C (75 MHz; $CDCl_3$) 19.16(q), 19.36(q), 21.54(t), 21.65(q), 22.70(q), 24.85(t), 25.01(t), 25.27(t), 36.12(s, C-2'), 37.32(t), 41.75(t), 54.86 (d, C-1'), 112.89(t), 124.53(s), 126.70(t), 136.61(s), 137.53(d, C-2), 146.40(s), 203.60(s, C-1);

$C_{19}H_{30}O$ requires 274.2297,

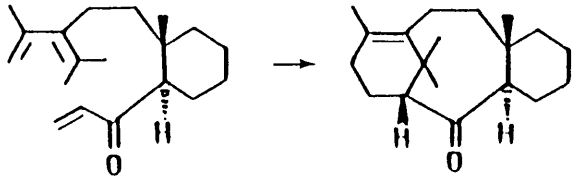
found 274.2294.

Notes

1. Dried over P_2O_5 at 60°C under vacuum overnight.

2. Used directly from previous step without purification.
3. Method described by Ratcliffe and Rodehorst, see Ref. 53.

Preparation of (1R/S,3R/S,8S/R)-8,12,15,15-tetramethyltricyclo[9.3.1.$0^{3,8}$]-pentadec-11-en-2-one (82)



(83) (82)

Boron trifluoride etherate (18 ul, 0.15 mmol) was added to a stirred solution of trans-1-{2'-methyl-2'-[4"-methyl-3"-(1"'-methylethenyl)pent-3"-enyl]cyclohexyl}-prop-2-en-1-one (83) (40 mg, 0.146 mmol) in toluene (1 ml) at -40°C. After 24h, t.l.c. showed no starting material and so the mixture was poured into water (5 ml) and extracted with ether (3 × 10 ml). The organic extracts were combined and dried ($MgSO_4$). The solvent was removed under reduced pressure and after purification by "chromatotron" (40:1 petroleum ether-ether) (1R/S,3R/S,8S/R)-8,12,15,15-tetramethyltricyclo[9.3.1.$0^{3,8}$]pentadec-11-ene-2-one (82) was obtained as a colourless oil (23 mg, 58%).

R_f 0.33 (20:1 petroleum ether-ether);

ν_{max} (CH_2Cl_2) 2930s, 2850m, 1678s(C=O), 1460m, 1390w, 1380m, 1368m, 1270w, 1244m, 1218m, 948w, 800brm;

δ_H (400 MHz; $CDCl_3$) 0.94 (3H, s, 8-$C\underline{H}_3$), 0.98-1.21 (4H, m), 1.08 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.47-1.74 (6H, m), 1.82 (1H, ddd, J = 15.5, 12.7, 5.5 Hz, H-9β) overlapping 1.83 (3H, m, CH_3), 1.97 (1H, dddd, J = 15.4, 11.3, 8.6, 2.4 Hz, H-14β), overlapping 2.02 (1H, ddd, J = 18.3, 10.1, 2.4 Hz, H-13α), 2.09-2.17 (1H, m, H-10β), 2.40 (1H, d, J = 8.6 Hz, H-1), 2.44-2.59 (1H, m, H-13β), 2.81 (1H, ddd, J = 14.2, 12.7, 5.6 Hz, H-10α), 2.96

(1H, dd, J = 12.2, 3.0 Hz, H-3);

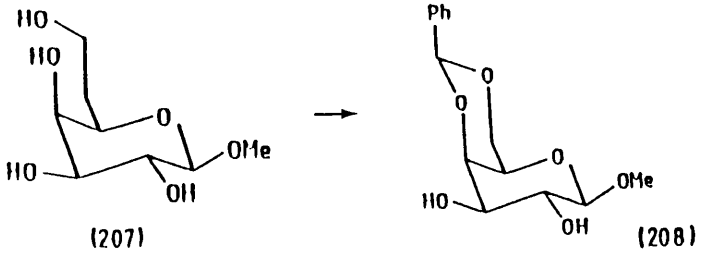
δ_C (100 MHz; $CDCl_3$) 18.95(t), 21.81(t), 22.09(q), 22.17(q), 25.17(t), 26.02(q), 26.18(t), 26.39(t), 29.16(t), 29.69(q), 38.09(s), 38.78(s), 39.47(t), 41.08(t), 50.83(d), 62.79(d), 130.23(s), 137.68(s), 218.95(s);

$C_{19}H_{30}O$ requires 274.2297,

found 274.2288.

2.96 (H-3) shows a n.O.e. to 1.83 (12-CH_3, 1%), 2.81 (H-10α) shows a n.O.e. to 2.09-2.17 (H-10β, 10%), 1.83 (12-CH_3), 1.82 (H-9β), 2.44-2.59 (H-13β) shows a n.O.e. to 2.02 (H-13α, 13%), 1.08 (1%), 2.40 (H-1) shows a n.O.e. to 1.97 (H-14β, 2.6%), 1.24 (15-CH_3), 1.08 (15-CH_3), 2.09-2.17 (H-10β) shows a n.O.e. to 2.81 (H-10α, 11%), 1.24 (15-CH_3), 1.83 (12-CH_3) shows a n.O.e. to 2.96 (H-3, 3%), 2.81 (H-10α, 5.5%), 1.24 (15-CH_3) shows a n.O.e. to 2.40 (H-1, 3.5%), 2.09-2.17 (H-10β, 5%), 1.08 (15-CH_3), 0.94 (8-CH_3), 1.08 (15-CH_3) shows a n.O.e. to 2.96 (H-3), 2.44-2.59 (H-13β), 2.4 (H-1), 1.24 (15-CH_3).

Preparation of methyl 4,6-O-benzylidene-β-D-galactopyranoside (208)[1]



(207) (208)

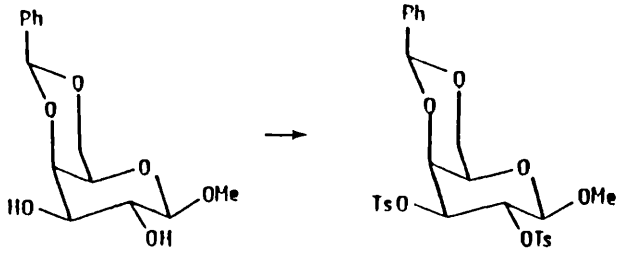
Methyl β-D-galactopyranoside (207) (25 g, 0.129 mol) was reacted with benzaldehyde[2] (65 ml, 0.644 mol) and anhydrous zinc chloride[3] (19.3 g, 0.142 mol) for 36h according to literature procedures. After work-up and recrystallisation from ethanol methyl 4,6-O-benzylidene-β-D-galacto-pyranoside (208) was obtained as a white crystalline solid (20 g, 55%), m.p. 198-199°C (lit.[1] m.p. 198-200°C).

$[\alpha]_D^{20}$ = -33° (1.96 in $CHCl_3$), lit.[1] $[\alpha]_D^{20}$ = -35.5° (2 in $CHCl_3$).

Notes

1. Literature procedure, see Ref. 134.
2. Washed with aqueous sodium bicarbonate, dried ($MgSO_4$) then distilled prior to use.
3. Dried over P_2O_5 under vacuum overnight.

Preparation of methyl 4,6-O-benzylidene-2,3-di-O-tosyl-β-D-galactopyranoside (257)[1]



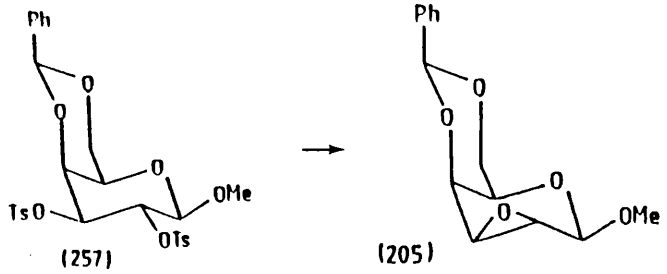
(208) (257)

Methyl 4,6-O-benzylidene-β-D-galactopyranoside (208) (20 g, 71 mmol) in pyridine (52 ml) was reacted with p-toluensulphonyl chloride[2] (40.5 g, 0.212 mol) in chloroform (80 ml) according to the literature.[1] After work-up and recrystallisation from chloroform/petroleum ether methyl 4,6-O-benzylidene-2,3-di-O-tosyl-β-D-galactopyranoside (251)[1] was obtained as a white crystalline solid (40.4 g, 96%), m.p. 167-170°C (lit.[1] m.p. 171-172°C).

Notes

1. Literature procedure, see Ref. 131.
2. p-Toluensulphonyl chloride was recrystallised from petroleum ether prior to use.

Preparation of methyl 2,3-anhydro-4,6-O-benzylidene-β-D-talopyranoside (205)[1]



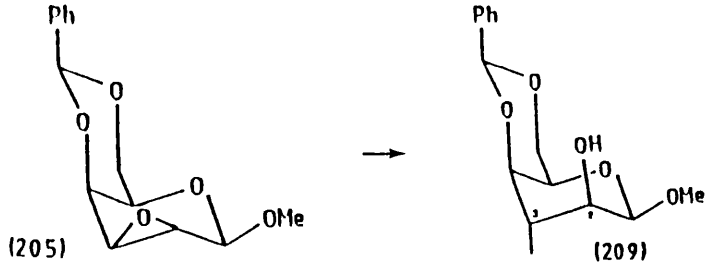
Methyl 4,6-O-benzylidene-2,3-di-O-tosyl-β-D-galactopyranoside (257) (10g, 16.9 mmol) was reacted with sodium methoxide (3M, 30 ml) in dioxan[2] (160 ml) according to the literature procedure. After work-up and recrystallisation from methanol methyl 2,3-anhydro-4,6-O-benzylidene-β-D-talopyranoside (205)[1] was obtained as a white crystalline solid (3.08 g, 69%), m.p. 245-249°C (lit.[1] m.p. 248-250°C).

$[\alpha]_D^{20}$ = -143° (0.43 in pyridine), lit.[1] $[\alpha]_D^{22}$ = -143° (0.4 in pyridine).

Notes

1. Literature procedure, see Ref. 131.
2. Dried and distilled from sodium and benzophenone.

Preparation of methyl 4,6-O-3-deoxy-3-C-methyl-β-D-idopyranoside (209)



Methyl magnesium chloride[1] (5 ml, 15.2 mmol) was added to methyl-2,3-anhydro-4,6-O-benzylidene-β-D-talopyranoside (205) (0.4 g, 1.52 mmol) in dry ether (60 ml) and the mixture refluxed for 1 week under argon. The mixture was then quenched with a saturated aqueous solution of NH_4Cl (50 ml) and the aqueous phase extracted with ether (3 × 100 ml). The

combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The resultant oil was purified by flash chromatography to produce methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-β-D-idopyranoside (209) and two unidentified products (0.15 g). The methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-β-D-pyranoside (209) was recrystallised from diisopropylether to produce a white crystalline solid (0.19 g, 45%), m.p. 135-137°C.

$[\alpha]_D$ = -95° (0.68 in $CHCl_3$);

R_f 0.5 (5:4.5:0.5 petroleum ether-ethyl acetate-methanol);

$C_{15}H_{20}O_5$ requires C 64.27%, H 7.19%, N 0.00%,

found C 64.46%, H 7.33%, N 0.2%.

ν_{max} (CH_2Cl_2) 3500m, 3480m, 2820s, 2755s, 1460s, 1375m, 1325w, 1210m, 1155m, 1140s, 1055s, 1010s, 900w, 860w, 765m, 700m;

δ_H (300 MHz; $CDCl_3$) 1.49 (3H, d, J = 7.8 Hz), 2.42 (1H, qt, J = 7.8, 1.8 Hz, H-3), 3.40 (1H, d, J = 11.1 Hz, OH), 3.46 (1H, d with some additional splitting, J = 11.1 Hz, H-2), 3.58 (3H, s, OCH_3), 3.61-3.64 (1H, m), 3.73-3.76 (1H, m), 4.04 (1H, dd, J = 12.8, 2.3 Hz, H-6), 4.35 (1H, dd, J = 12.8, 2.1 Hz, H-6), 4.52 (1H, d, J = 1 Hz, H-1), 5.46 (1H, s), 7.28-7.52 (5H, m, $C_6\underline{H}_5$);

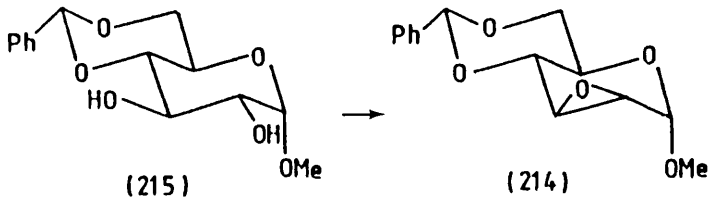
δ_C (75 MHz; $CDCl_3$) 13.68(q), 38.78(d), 56.63(q), 66.22(d), 69.51(t), 69.80(d), 76.31(d), 99.58(d), 101.08(d), 125.79(d), 127.89(d), 128.70(d), 137.36(s);

m/z 280 (M^+, 5), 262(10), 248(10), 190(5), 142(10), 131(25), 107(100).

Notes

1. Obtained as a 3M solution in THF from Aldrich.

Preparation of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (214)[1]



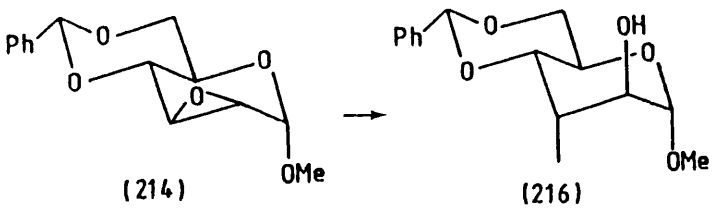
Methyl 4,6-O-benzylidene-α-D-glucopyranoside (215) (11.28g, 40 mmol) was reacted with sodium hydride (80% dispersion, 2.52 g, 84 mmol) and N-p-tolylsulphonylimidazole[2] (9.76 g, 44 mmol) in dry dimethylformamide[3] (400 ml) according to literature procedure.[1] After work-up and purification by sublimation (120°C at 0.2 mmHg) methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (214)[1] was obtained as a white crystalline solid (4.14 g, 39%), m.p. 145-146°C (lit.[1] m.p. 145-147°C).

$[\alpha]_D^{20}$ = 103 (1 in $CHCl_3$), lit.[1] $[\alpha]_D^{15}$ = +107 (1.6 in $CHCl_3$).

Notes

1. Literature procedure, see Ref. 137.
2. Prepared from imidazole and p-tolylsulphonyl chloride, see Ref. 137.
3. Dried over 3Å molecular sieves then distilled.

Preparation of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-altro-pyranoside (216)[1]



Methylmagnesium chloride[2] (58 ml, 0.174 mol) and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (214) (3.5 g, 13.3 mmol) were refluxed under argon for two weeks according to the literature procedure.[1]

After work-up methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-altropyranoside (216) was obtained as a white solid (3.67 g, 99%) which was used in the next stage without further purification.

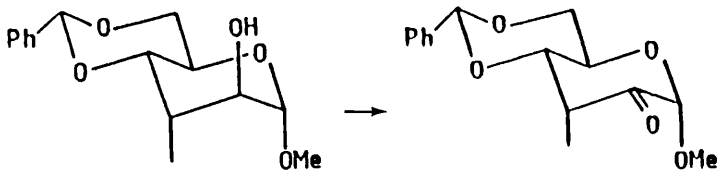
R_f 0.43 (1:1 petroleum ether-ethyl acetate);

δ_H (90 MHz; $CDCl_3$) 1.23 (3H, d, J = 7.5 Hz, CH_3), 2.1 (1H, brs, OH), 2.35 (1H, brm, H-3), 3.38 (3H, s, OCH_3), 3.65-4.40 (5H, m), 4.57 (1H, s, H-1), 5.60 (1H, s), 7.27-7.57 (5H, m, $C_6\underline{H}_5$).

Notes

1. Literature procedure, see Ref. 130.
2. 3M solution in THF from Aldrich.

Preparation of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-ribo-hexopyranosid-2-ulose (258)[1]



(216) (258)

Trifluoroacetic anhydride (2.75 ml, 19.7 mmol) in dry dichloromethane (7 ml) was added dropwise, under nitrogen, over 10 min., to a cooled solution (-65°C) of dimethylsulphoxide[2] (1.86 ml, 26.2 mmol) in dichloromethane (26 ml). The mixture was stirred for a further 10 min. at -65°C then methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-altropyranoside (216)[3] (3.67 g, 13.1 mmol) in dichloromethane (30 ml) was slowly added keeping the mixture at -65°C. After an additional 45 min. at -65°C triethylamine (5.29 ml, 38 mmol) was added and the solution allowed to warm to room temperature. The reaction mixture was diluted with ether (500 ml) then washed with 1M HCl (2 × 100 ml), a saturated aqueous solution of sodium bicarbonate (2 × 100 ml) and finally with a saturated brine

solution (100 ml). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The residual oil was purified by flash chromatography (9:1 petroleum ether-ethyl acetate) to give methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-ribo-hexopyranosid-2-ulose (258)[1] as a colourless oil (3.2 g, 88%).

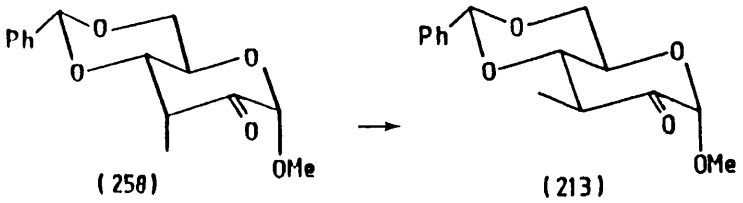
R_f 0.30 (9:1 petroleum ether-ethyl acetate);

δ_H (90 MHz; $CDCl_3$) 1.32 (3H, d, J = 7 Hz, CH_3), 2.82-3.16 (1H, m, H-3), 3.39 (3H, s, OCH_3), 3.55-4.48 (4H, m), 4.53 (1H, s, H-1), 5.49 (1H, s), 7.22-7.5 (5H, m, C_6H_5).

Notes

1. Literature procedure, see Ref. 130.
2. Dried and distilled from calcium hydride.
3. Used directly from previous stage without further purification.

Preparation of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213)[1]



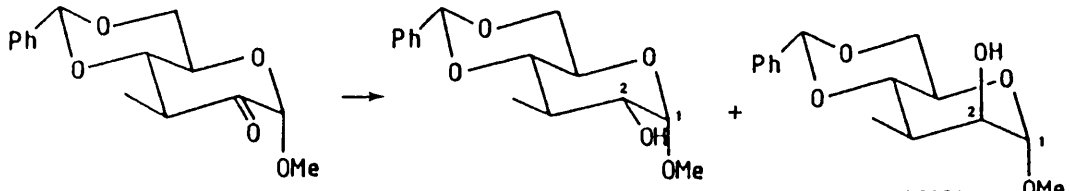
Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-ribo-hexopyranosid-2-ulose (258) (3.2 g, 11.5 mmol) was stirred with triethylamine (3.8 g, 216 mmol) in dimethyl formamide[2] (13 ml) at room temperature for 36h. After work-up and recrystallisation from petroleum ether (60-80) methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) was obtained as a white crystalline solid (2.6 g, 81%), m.p. 124-126°C (lit.[1] m.p. 125.5-126°C).

$[\alpha]_D^{20}$ = 60° (0.57 in $CHCl_3$), lit.[1] $[\alpha]_D$ = 56° (0.77 in $CHCl_3$).

Notes

1. Literature procedure, see Ref. 130.
2. Dried over molecular sieves then distilled.

Treatment of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) with LDA



(213) (220) (219)

LDA (0.385 mmol) was prepared from di-isopropylamine (60 ul, 0.423 mmol) and n-butyllithium[1] (200 ul, 0.385 mmol) in dry ether (1 ml), under nitrogen, at 0°C for ½h. Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (107 mg, 0.385 mmol) was added in ether (2 ml) to the stirred LDA solution at -78°C. The mixture was allowed to warm to room temperature then quenched with water (10 ml). The aqueous phase was extracted with ether (3 × 20 ml) and each extract was washed with a saturated brine solution (10 ml). The combined organic extracts were dried ($MgSO_4$) then the solvent removed in vacuo. After flash chromatography (1:1 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-glucopyranoside (220) and methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-mannopyranoside (219) were obtained in a ratio of (4:1) (65 mg, 60%).

R_f 0.37 (1:1 petroleum ether-ethyl acetate);

ν_{max} (nujol mull) 3340m(OH), 1305w, 1220w, 1200w, 1183w, 1150m, 1125s, 1075s, 1008s, 960m, 920w, 748s, 725m, 698s;

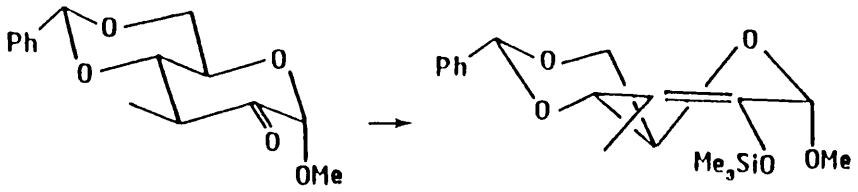
δ_H (300 MHz; $CDCl_3$) 1.11 (3H, d, J = 6.8 Hz, CH_3 (219)), 1.17 (3H, d, J = 6.4 Hz, CH_3 (220)), 1.90-2.06 (2H, m, H-3 (220) and OH), 2.14-2.26 (1H,

m, H-3 (219)), 3.14 (1H, dd, J = 10.5, 8.9 Hz, H-4 (220)), 3.33 (1H, vbrm, H-2), 3.40 (3H, s, OCH_3 (219)), 3.45 (3H, s, OCH_3 (220)), 3.58 (1H, dd, J = 10.4, 9 Hz, H-4 (219)), 3.67 (1H, t, J = 10.4 Hz, H-6_{ax} (220)), 3.72-3.84 (1H, m, H-5 (219) and (220)), 4.25 (1H, (219) and (220) overlapping, (220) dd, J = 9.5, 4.1 Hz, H-6_{eq}), 4.57 (1H, d, J = 1.4 Hz, H-1 (219)), 4.67 (1H, d, J = 3.7 Hz, H-1 (220)), 5.49 (1H, s, (220)), 5.53 (1H, s, (219)), 7.31-7.50 (5H, m, $C_6\underline{H}_5$ (219) and (220)).

Notes

1. n-Butyllithium was 1.93 M by titration.

Preparation of methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (224)



(213) (224)

LITMP (0.72 mmol) was prepared from tetramethylpiperidine (133 ul, 0.79 mmol) and n-butyllithium[1] (400 ul, 0.72 mmol) in ether (2 ml) at 0°C, under nitrogen for 1h. Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (0.2 g, 0.72 mmol) in ether (2 ml) was added to the stirred LITMP solution at 0°C. After a further 1h at 0°C trimethylsilylchloride[2] (0.27 ml, 2.16 mmol) was added and the mixture stirred for 1h at room temperature. The mixture was then poured into water and extracted with ether (2 × 50 ml). Each extract was washed with a saturated brine solution, combined then dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (8:1 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-

methyl-α-D-erythro-hex-2-enopyranoside (224) was obtained as a colourless oil (0.18 g, 71%).

$[\alpha]_D^{20}$ = 69.6° (0.8 in $CHCl_3$);

R_f 0.67 (8:1 petroleum ether-ethyl acetate);

δ_H (300 MHz; $CDCl_3$)[3] 0.23 (9H, s, $Si(CH_3)_3$), 1.71 (3H, t, J = 1.2 Hz, CH_3), 3.45 (3H, s, OCH_3), 3.81 (1H, dd, J = 10.3, 9.8 Hz, H-6_{ax}), 3.94 (1H, dt, J = 9.1, 4.3 Hz, H-5), 4.12 (1H, d with some fine splitting, J = 8.8 Hz, H-4), 4.30 (1H, dd, J = 9.8, 4.3 Hz, H-6_{eq}), 4.61 (1H, s with some fine splitting, H-1), 5.58 (1H, s), 7.33-7.54 (5H, m, $C_6\underline{H}_5$);

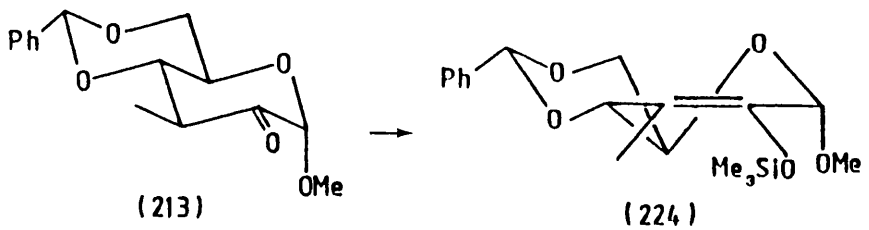
δ_C (75 MHz; $CDCl_3$) 0.51(q, $Si(\underline{C}H_3)_3$), 9.37(q), 55.63(q), 64.39(d), 69.05 (t), 77.80(d), 97.78(d), 101.49(d), 115.55(s), 126.13(d), 128.08(d), 128.76(d), 137.67(s), 142.15(s);

m/z 350 (M^+, 15), 335(5), 319(6), 244(7), 202(13), 200(12), 174(49), 149(33), 105(32), 92(33), 73(100).

Notes

1. n-Butyllithium was 1.8 M by titration.
2. Distilled from tributylamine immediately prior to use.
3. $CHCl_3$ signal set to δ7.3.

An alternative preparation of methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (224)



(213) (224)

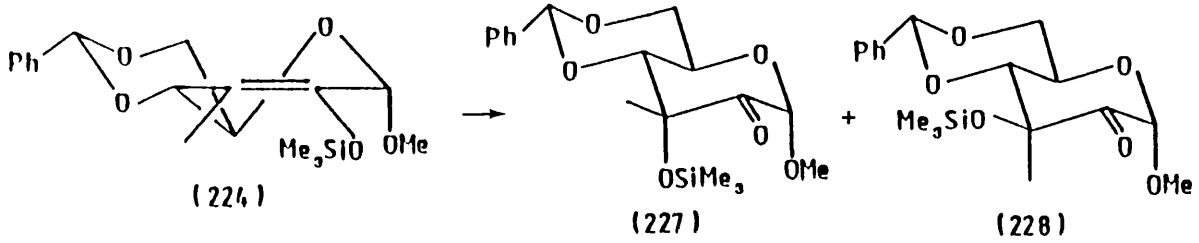
Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (0.234 g, 0.84 mmol) was stirred with triethylamine (281 ul, 2.02 mmol) and freshly distilled trimethylsilylchloride[1] (320 ul, 2.53

mmol) in dimethyl formamide[2] (3 ml) under nitrogen for 36h. The mixture was then poured into water (30 ml) and extracted with ether (3 × 50 ml). Each extract was washed with a saturated brine solution (30 ml), combined then dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (8:1 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (224)[3] was obtained as a colourless oil (0.257 g, 87%).

Notes

1. Distilled from tributylamine immediately prior to use.
2. Dried over molecular sieves then distilled.
3. Identical spectroscopic properties as (224) isolated in the previous experiment.

The reaction of methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (224) with m-CPBA



m-CPBA (23 mg, 0.13 mmol) was added to a solution of methyl 4,6-O-benzylidene-3-deoxy-2-O-trimethylsilyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (224) (38 mg, 0.109 mmol) in dichloromethane (1 ml) at 0°C, under nitrogen. After 1h t.l.c. showed no starting material and so the solution was filtered through a short alumina column and washed through with an additional amount of dichloromethane (5 ml). The solvent was removed in vacuo and after flash chromatography (10:1 petroleum ether-ethyl acetate) a colourless oil, (227) and (228),[1] was obtained as a mixture of isomers (6:1 by ^1H n.m.r.), (18 mg, 45%).

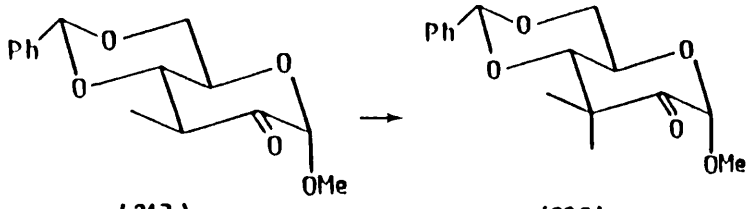
R_f 0.44 (10:1 petroleum ether-ethyl acetate);

δ_H (300 MHz; $CDCl_3$) 0.22 (9H, s, $Si(CH_3)_3$, minor isomer), 0.23 (9H, s, $Si(CH_3)_3$, major isomer), 1.46 (3H, s, CH_3, major isomer), 1.47 (3H, s, minor isomer), 3.47 (3H, s, OCH_3, minor isomer), 3.48 (3H, s, OCH_3, major isomer), 3.58 (1H, d, J = 9.7 Hz, H-4, major isomer), 3.63 (1H, d, J = 9.7 Hz, H-4, minor isomer), 3.67 (1H, t, J = 10.2 Hz, H-6_{ax}, minor isomer), 3.71 (1H, t, J = 10.2 Hz, H-6_{ax}, major isomer), 3.87 (1H both isomers overlapping, major isomer dt, J = 9.7, 4.5 Hz, H-5), 4.22 and 4.21 both isomers overlapping (1H, both dd, J = 10.1, 4.5 Hz, major, J = 10.2, 4.5 Hz, minor, H-6_{eq}), 4.74 (1H, s, H-1, major isomer), 4.84 (1H, s, H-1, minor isomer), 5.51 (1H, s, both isomers), 7.35-7.50 (5H, m, $C_6\underline{H}_5$, both isomers).

Notes

1. The structure is tentatively assigned to be (227) and (228).

Preparation of methyl 4,6-O-benzylidene-3-deoxy-3,3-C-dimethyl-α-D-erythro-hexopyranosid-2-ulose (229)



(213) (229)

LITMP (0.72 mmol) was prepared from tetramethylpiperidine (133 ul, 0.79 mmol) and n-butyllithium[1] (0.4 ml, 0.72 mmol) in ether (2 ml) at 0°C, under nitrogen, for 1h. A solution of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (0.2 g, 0.72 mmol) in ether (2 ml) was added to the stirred LITMP solution at 0°C and after a further 1h at 0°C the ether solvent was removed, by means of a

vacuum pump, whilst maintaining a nitrogen atmosphere. THF (1 ml) was then added, with stirring, followed by iodomethane (314 ul, 5.03 mmol) and HMPA (63 ul, 0.36 mmol). The mixture was stirred for 4h at room temperature, then the mixture was poured into water (20 ml) and extracted with ether (3 × 50 ml). Each extract was washed with a saturated brine solution (20 ml) then combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (10:1 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-3-deoxy-3,3-C-dimethyl-α-D-erythro-hexopyranosid-2-ulose (229) was obtained as a colourless oil (120 mg, 57%).

[α] = 16.3 (3.5 in EtOH);

R_f 0.48 (8:1 petroleum ether-ethyl acetate);

$C_{16}H_{20}O_5$ requires C 65.74%, H 6.90%, N 0.00%,

found C 65.71%, H 6.96%, N 0.00%;[2]

ν_{max} (film) 3100w, 3065m, 3040m, 2980s, 2960s, 2860brs, 1730s(C=O), 1610w, 1500m, 1460s, 1405s, 1380s, 1368s, 1330s, 1310s, 1292s, 1220s, 1150s, 1110s, 1048s, 995s, 920m, 750s, 700s;

δ_H (300 MHz; $CDCl_3$) 1.25 (3H, s, CH_3), 1.33 (3H, s, CH_3), 3.44 (3H, s, OCH_3), 3.52 (1H, d, J = 9.6 Hz, H-4), 3.73 (1H, t, J = 10.1 Hz, H-6_{ax}), 4.27 (1H, dt, J = 9.7, 5.2 Hz, H-5), 4.39 (1H, dd, J = 10.1, 5.2 Hz, H-6_{eq}), 4.59 (1H, s, H-1), 5.51 (1H, s), 7.3-7.52 (5H, m, $C_6\underline{H}_5$);

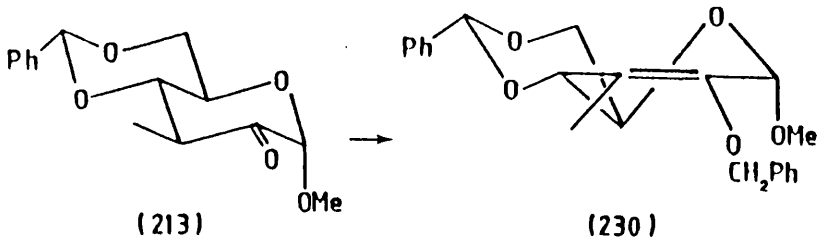
δ_C (75 MHz; $CDCl_3$) 18.89(q), 20.72(q), 48.18(s, C-3), 55.96(q, O-$\underline{C}H_3$), 59.89(d), 69.16(dd, C-6), 83.44(d), 101.19(d), 101.29(d), 126.05(d), 128.10(d), 128.93(d), 137.3(s), 203.85(s, C-2);

m/z 292 (M^+), 264(3), 204(3), 190(3), 148(93), 135(8), 120(20), 107(37), 105(44), 98(100).

Notes

1. n-Butyllithium was 1.8 M by titration.
2. Sample for analysis was distilled by Kugelröhr (220°C at 0.1 mmHg).

Preparation of methyl 4,6-O-benzylidene-3-deoxy-2-O-benzyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (230)



(213) (230)

LTMP (0.72 mmol) was prepared from tetramethylpiperidine (133 ul, 0.79 mmol) and n-butyllithium[1] (304 ul, 0.72 mmol) in dry ether (2 ml) at 0°C, under nitrogen, for 1h. A solution of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (0.2 g, 0.72 mmol) in ether (2 ml) was added to the stirred LTMP solution. After a further 1h at 0°C the ether solvent was removed, by means of a vacuum pump, whilst maintaining a nitrogen atmosphere. THF (1 ml) was then added, with stirring, followed by benzylbromide (600 ul, 5.04 mmol) and HMPA (63 ul, 0.36 mmol). The mixture was stirred for 3h at room temperature then poured into water (20 ml) and extracted with ether (3 × 50 ml). Each extract was washed with a saturated brine solution (20 ml) then combined and dried ($MgSO_4$). The solvent was removed in vacuo and after flash chromatography (10:1 petroleum ether-ethyl acetate) and recrystallisation (isopropylether) methyl 4,6-O-benzylidene-3-deoxy-2-O-benzyl-3-C-methyl-α-D-erythro-hex-2-enopyranoside (230) was obtained as a white crystalline solid (142 mg, 54%), m.p. 125-127°C.

$[\alpha]_D$ = 24.6° (2.4 in $CHCl_3$);

R_f 0.63 (7:1 petroleum ether-ethyl acetate);

$C_{22}H_{24}O_5$ requires C 71.72%, H 6.57%, N 0.00%,

found C 71.38%, H 6.61%, N 0.01%;

ν_{max} (CH_2Cl_2) 3040w, 2940m, 2920m, 2870m, 2835w, 1680w, 1500w, 1455m, 1395m, 1360w, 1325w, 1218m, 1195m, 1165m, 1090s, 1060s, 1038s, 1010s, 965m, 920w;

δ_H (300 MHz; $CDCl_3$) 1.77 (3H, t, J = 1.2 Hz, CH_3), 3.47 (3H, s, OCH_3), 3.80 (1H, t, J = 10.0 Hz, H-6_{ax}), 3.96 (1H, dt, J = 10.0, 4.4 Hz, H-5), 4.09 (1H, d with some fine splitting, J ≈ 9 Hz, H-4), 4.30 (1H, dd, J = 10.0, 4.4 Hz, H-6_{eq}), 4.83 (1H, s, H-1) overlapping, 4.81 (1H, d, J = 11.5 Hz), 4.89 (1H, d, J = 11.5 Hz), 5.56 (1H, s), 7.28-7.52 (10H, m, $C_6\underline{H}_5$);

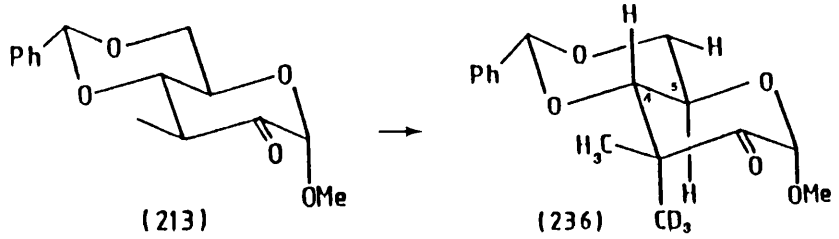
δ_C (75 MHz; $CDCl_3$) 9.27(q), 55.55(q, OCH_3), 64.03(d), 68.96(t), 73.26(t), 77.45(d), 96.94(d), 101.58(d), 120.42(s), 126.06(d), 127.46(d), 127.67(d), 128.02(d), 128.23(d), 128.75(d), 137.46(s), 137.51(s), 145.95(s);

m/z 368 (M^+, 2), 338(5), 337(5), 277(5), 246(6), 224(53), 202(13), 174(26), 159(17), 105(81), 91(100).

Notes

1. n-Butyllithium was 2.4 M by titration.

Preparation of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-C-[$^2H_3$]-methyl-α-D-erythro-hexopyranosid-2-ulose (236)



(213) (236)

Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (0.1 g, 0.36 mmol) was treated with LTMP (0.4 mmol) as in

the preparation of (229). The enolate was then alkylated with [$^2H_3$]-iodomethane[1] (160 ul, 2.5 mmol) in THF (½ ml) with HMPA (33 ul, 0.18 mmol) as a co-solvent. After work-up [as for (229)] and flash chromatography (10:1 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-C-[$^2H_3$]-methyl-α-D-erythro-hexopyranosid-2-ulose (236) was obtained as a colourless oil (52 mg, 49%).

R_f 0.5 (8:1 petroleum ether-ethyl acetate);

δ_H (400 MHz; $CDCl_3$) 1.25 (3H, s), 3.46 (3H, s, OCH_3), 3.54 (1H, d, J = 9.6 Hz, H-4), 3.72 (1H, t, J = 10.3 Hz, H-6_{ax}), 4.28 (1H, dt, J = 9.7, 5.2 Hz, H-5), 4.41 (1H, dd, J = 10.3, 5.2 Hz, H-6_{eq}), 4.60 (1H, s, H-1), 5.53 (1H, s), 7.34-7.50 (5H, m, $C_6\underline{H}_5$);

m/z 295 (M^+, 1), 267(2), 207(4), 151(100), 120(19), 119(20), 105(67), 101(98);

5.53 shows a n.O.e. to 3.54 (H-4, 8.6%), and to 3.72 (H-6_{ax}, 4%);

4.60 (H-1) show a n.O.e. to 3.49 (OCH_3, 1.3%);

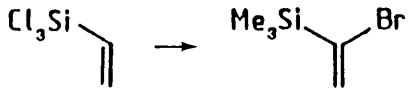
1.25 (CH_3) shows a n.O.e. to 3.54 (H-4, 5%);

4.28 (H-5) shows n.O.e. to 4.41 (H-6_{eq}).

Notes

1. Obtained from Aldrich as 99% [$^2H_3$]iodomethane.

Preparation of 1-(bromovinyl)trimethylsilane (242)[1]



(240) (242)

A solution of bromine (79.9 g, 0.5 mol) in carbon tetrachloride (100 ml) was added dropwise, under nitrogen, over 1½h to a stirred solution of vinyltrichlorosilane (240) (63.6 ml, 0.5 mol) in carbon tetrachloride

(500 ml) illuminated with a daylight lamp. The red solution was stirred for an additional 1h and then the solvent was removed under reduced pressure.

Quinoline (76.7 ml, 0.65 mol) was then added dropwise to the solvent free mixture, under nitrogen, and after 30 min. a yellow precipitate formed. The reaction mixture was then diluted with dry ether (200 ml) and filtered under nitrogen. The ether was distilled off at atmospheric pressure and then 1-(bromovinyl)trichlorosilane (241)[2] was distilled off, b.p. 65-75°C at 50 mmHg (lit.[1] b.p. 70-71° at 53 mmHg).

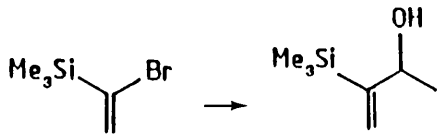
Methylmagnesium iodide (1.5 mol) prepared from iodomethane (93 ml, 1.5 mol) and magnesium (37g, 1.52 mol) in ether (1.5 dm^3) was added dropwise to a solution of 1-(bromovinyl)trichlorosilane (241) in ether (500 cm^3), under nitrogen, at a rate so as to maintain a steady reflux. After the addition the mixture was refluxed for a further 5h and then poured into water (2 dm^3). The aqueous phase was extracted with ether (1 dm^3) and then dried ($MgSO_4$). The ether was distilled off at atmospheric pressure through a 30 cm Vigreux column and finally 1-(bromovinyl)-trimethylsilane (242)[1] was obtained as a liquid (21.19 g, 24%), b.p. 48-53°C at 56 mmHg (lit.[1] b.p. 56.7°C at 67 mmHg).

δ_H (90 MHz; $CDCl_3$) 0.21 (9H, s, $Si(CH_3)_3$), 6.18 (1H, d, J = 2 Hz), 6.28 (1H, d, J = 2 Hz).

Notes

1. Literature procedure, see Ref. 149.
2. Air sensitive compound.

Preparation of 3-trimethylsilyl-3-buten-2-ol (243)[1]



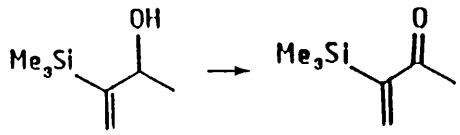
(242) (243)

1-(Bromovinyl)trimethylsilane (242) (21 g, 0.117 mol) in dry THF (30 ml) was slowly added to magnesium turnings (3.94 g, 0.164 mol) in THF (20 ml), under nitrogen, at such a rate so as to maintain a gentle reflux. After the addition, the mixture was refluxed for an additional 1h and then acetaldehyde[2] (13.1 ml, 0.235 mol) in THF (10 ml) was added dropwise to the stirred solution. After the addition the mixture was refluxed for a further 1h. The majority of the THF was then distilled off at atmospheric pressure, and the residue was then diluted with ether (100 ml) and hydrolysed with saturated aqueous NH_4Cl solution (30 ml). The aqueous layer was then extracted with ether (3 × 100 ml) and each extract washed with a saturated brine solution (50 ml). The combined ether extracts were dried ($MgSO_4$) and the ether removed by distillation at atmospheric pressure to give a crude yield of 3-trimethylsilyl-3-buten-2-ol (243)[1] which was used directly in the next stage.

Notes

1. Literature procedure, see Ref. 150.
2. Freshly distilled prior to use.

Preparation of 3-trimethylsilyl-3-buten-2-one (237)[1]



(243) (237)

An aqueous solution (33 ml) containing chromic acid and sulphuric acid[2] was added to a solution of the crude 3-trimethylsilyl-3-buten-2-ol (243) (22 g) in acetone (20 ml) at 0°C. After the addition, isopropylalcohol was added until the mixture turned green, indicating consumption of the excess oxidising agent. The solution was then poured into water (100 ml) and extracted with ether (3 × 100 ml). The ether extracts were washed with a saturated brine solution (50 ml), then combined and dried ($MgSO_4$). The ether was distilled off at atmospheric pressure through a 30 cm Vigreux column then continued distillation under reduced pressure gave 3-trimethylsilyl-3-buten-2-one (237)[1] as a colourless liquid (4.79 g, 29%), b.p. 85-90°C at 75 mmHg, (lit.[1] b.p. 98-103°C at 100 mmHg).

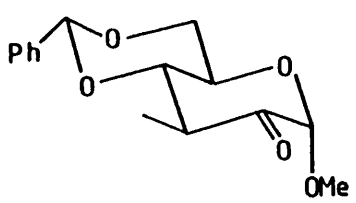
ν_{max} (film) 3060w, 2960s, 2900m, 1725m, 1660s, 1400s, 1352s, 1270s, 1235s, 1105w, 970s, 860s, 840s, 765m, 695m, 645m;

δ_H (90 MHz; $CDCl_3$) 0.12 (9H, s, $Si(CH_3)_3$), 2.25 (3H, s, H-1), 6.13 (1H, d, J = 2 Hz, H-4), 6.47 (1H, d, J = 2 Hz, H-4).

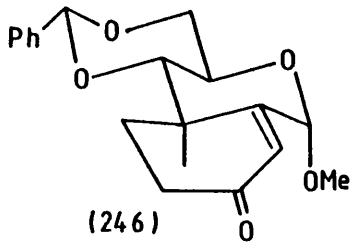
Notes

1. Literature procedure, see Ref. 150.
2. Oxidising reagent was prepared as described by Ref. 161.

Preparation of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246)



(213)



(246)

LTMP (4.14 mmol) was prepared from tetramethylpiperidine (0.767 ml, 4.55 mmol) and n-butyllithium[1] (1.82 ml, 4.14 mmol) in ether (12 ml) as in the preparation of (229). Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-arabino-hexopyranosid-2-ulose (213) (1.15 g, 4.13 mmol) in ether (12 ml) was then added to the stirred LTMP solution at 0°C. After a further 1h the enolate solution was concentrated by removing approximately half the ether solvent by means of a vacuum pump. 3-Trimethylsilyl-3-buten-2-one (237) (0.82 g, 5.79 mmol) was then added to the stirred enolate solution at -78°C. The mixture was then allowed to warm to room temperature and stirring continued for 1h. The mixture was then poured into water (100 ml) and extracted with ether (3 × 150 ml). Each extract was washed with a saturated brine solution (100 ml) and then dried ($MgSO_4$). The ether was removed in vacuo and after flash chromatography (8:2 petroleum ether-ethyl acetate) a viscous oil was obtained with the following spectral properties.[2]

R_f 0.49 (8:2 petroleum ether-ethyl acetate);

δ_H (300 MHz; $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 1.20 (3H, s, CH_3), 1.83 (s with some fine splitting, CH_3), 1.89 (1H, dq, J = 16.7, 2.3 Hz), 2.08 (1H, brd, J = 16.7 Hz), 3.14 (1H, s), 3.42 (3H, s), 3.46 (1H, d, J = 9.6 Hz, H-4), 3.68 (1H, t, J = 10.0 Hz, H-6_{ax}), 3.91 (1H, dt, J = 10.0, 4.9 Hz, H-5), 4.26 (1H, dd, J = 10.0, 4.9 Hz, H-6_{eq}), 4.42 (1H, s, H-1), 5.40 (1H, s), 7.27-7.42 (5H, m, C_6H_5);

δ_C (75 MHz; $CDCl_3$) 0.34(q), 16.79(q), 20.00(q), 28.47(t), 37.01(s), 55.84(q), 60.04(d), 69.33(t), 77.27(d), 94.88(s), 97.94(s), 101.47(d), 102.85(d), 125.97(d), 128.10(d), 128.76(d), 137.74(s), 150.15(s); m/z 420 (M^+, 2), 389(1), 350(3), 277(3), 204(10), 149(100), 105(18).

The viscous oil was heated at 80° for 6h in methanol (18 ml) containing a 4% aqueous solution of potassium hydroxide (1.9 ml, 1.36 mmol). The methanol was then removed in vacuo and the residue extracted with ether (250 ml). The ether extract was washed with a saturated brine solution (2 × 100 ml) and dried ($MgSO_4$). The ether was removed in vacuo and after flash chromatography (8:2 petroleum ether-ethyl acetate) methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) was obtained as a viscous oil (0.79 g, 58%).

$[\alpha] = -38°$ (3.3 in $CHCl_3$);

R_f 0.44 (7:3 petroleum ether-ethyl acetate);

$C_{19}H_{22}O_5$ requires C 69.07%, H 6.71%, N 0.00%,

found C 68.98%, H 6.65%, N 0.00%.

ν_{max} (CH_2Cl_2) 3020w, 2940m, 2870m, 1685s(C=O), 1470m, 1453m, 1400m, 1390m, 1378m, 1335w, 1232m, 1218m, 1155s, 1125s, 1110s, 1095s, 1076s, 1050s, 1035s, 993m, 970s, 910w, 880m;

δ_H (300 MHz; $CDCl_3$) 1.48 (3H, s), 1.87 (1H, brdt, J = 14, 5 Hz, H-$4'_{ax}$), 2.25 (1H, ddd, J = 13.5, 5.0, 2.6 Hz, H-$4'_{eq}$), 2.43 (1H, dddd, J = 17.5 5.0, 2.6, 0.8 Hz, H-$3'_{eq}$), 2.55 (1H, ddd, J = 17.5, 14.6, 5.0 Hz, H-$3'_{ax}$), 3.38-3.41 (1H, d) overlapping 3.41 (3H, s), 3.71 (1H, t, J = 10.2 Hz, H-6_{ax}), 4.19 (1H, dt, J = 9.8, 5.2 Hz, H-5), 4.34 (1H, dd, J = 10.2, 5.2 Hz, H-6_{eq}), 4.89 (1H, s, H-1), 5.54 (1H, s), 5.86 (1H, s), 7.32-7.51 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 16.60(q), 33.53(t), 34.61(t), 37.81(s), 55.16(q), 59.71(d), 69.13(dd), 85.32(d), 101.47(d), 125.96(d), 127.15(d), 128.04 (d), 128.87(d), 137.27(s), 157.95(s), 198.56(s);

m/z 330 (M^+, 5), 299(3), 240(1), 181(42), 152(100), 121(31), 105(19), 91(25);

1.48 shows a n.O.e. to 2.25 (H-$4'_{eq}$, 1.5%), 2.55 (H-$3'_{ax}$, 2%), 4.19 (H-5, 4%);

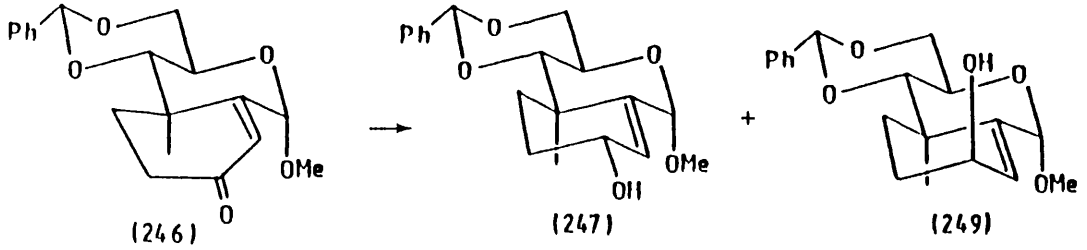
4.19 (H-5) shows a n.O.e. to 1.48 (1.5%);

4.89 (H-1) shows a n.O.e. to 5.86 (H-1, 8%).

Notes

1. n-Butyllithium was 2.3 M by titration.
2. On some occasions the intermediate was not purified but used directly in the next stage.

Reduction of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) with DIBAH



DIBAH[1] (116 ul, 0.106 mmol) was added dropwise to a stirred solution of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) (35 mg, 0.106 mmol) in toluene (1 ml) at -78°C under nitrogen. After 2h the mixture was quenched with a saturated NH_4Cl solution (10 ml) and 1M HCl (½ ml). The mixture was extracted with ether (3 × 10 ml) and each extract washed with a saturated brine solution (10 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo. After flash chromatography (1:1 petroleum

ether-ethyl acetate) methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-ol)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (247) and (249) was obtained as a mixture of epimers at C-2' in a ratio of 3.4:1.

R_f 0.38 (1:1 petroleum ether-ethyl acetate);

ν_{max} (film) 3440brm(OH), 3110w, 3065m, 3040s, 2970s, 1460s, 1395m, 1320w, 1280w, 1158m, 1120m, 1100m, 1070s, 1040s, 990s, 955s, 925w, 870m, 750m, 700s;

δ_H (300 MHz; $CDCl_3$) 1.32 (3H, s, CH_3 (249)), 1.40 (3H, s, CH_3 (247)), 1.44-1.67 (3H, m, (247) and (249)), 1.88-1.97 (1H, m, (247) and (248)), 2.00-2.11 (1H, m, (247) and (249)), 3.27 (1H, d, J = 9.5 Hz, H-4 (247)), 3.37 (1H, d, H-4 (249)) overlapping 3.38 (3H, s, OCH_3 (247)), 3.39 (3H, s, OCH_3 (249)), 3.67 (1H, t, J = 10.2 Hz, H-6_{ax} (247)), 3.68 (1H, t, J = 10.1 Hz, H-6_{ax} (249)), 4.11 (1H, dt, J = 9.7, 5.4 Hz, H-5 (247) and (249)), 4.17-4.33 (2H, m, H-6_{eq} and H-2' (247) and (249)), 4.77 (1H, s, H-1 (247)), 4.79 (1H, s, H-1 (249)), 5.51 (1H, s, (247)), 5.53 (1H, s, (249)), 5.72 (1H, s with some fine splitting, H-1' (247)), 5.84 (1H, brd, J = 4.4 Hz, H-1' (249)), 7.34-7.49 (5H, m, $C_6\underline{H}_5$ (247) and (249)).

Notes

1. 1M solution in toluene from Aldrich.

Reduction of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) with 9-Borabicyclo[3,3,1]-nonane (9-BBN)

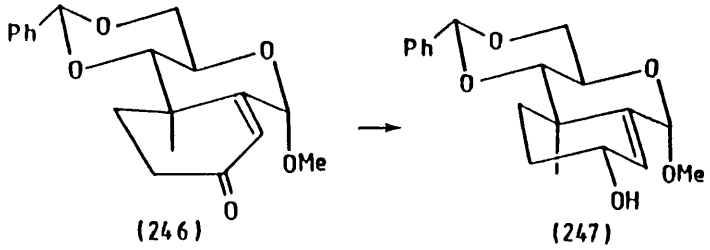
9-BBN[1] (395 ul, 0.197 mmol) was added to a stirred solution of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) (62 mg, 0.188 mmol) in THF (½ ml) under nitrogen at 0°C. After 2h, methanol (100 ul) was added (to destroy the excess 9-BBN) followed by 2M sodium hydroxide (108 ul, 0.217 mmol) and 30% hydrogen

peroxide (42 ul, 0.4 mmol). The mixture was then stirred for an additional 1h at room temperature. The aqueous phase was extracted with ether (3 × 10 ml) and each extract washed with a saturated brine solution (10 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The residual oil was purified by flash chromatography (1:1 petroleum ether-ethyl acetate) to give methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-ol)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (247) and (249) as a mixture of epimers at C-2' in a ratio of 5:1[2] (39 mg, 63%).

Notes

1. 0.5 M solution in THF.
2. High field ^1H n.m.r. was identical to that obtained in the previous reaction using DIBAH with only the ratio of (247) to (249) varying.

Reduction of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) with L-selectride



L-Selectride[1] (203 ul, 0.203 mmol) was added to a stirred solution of methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-one)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (246) (67 mg, 0.203 mmol) in THF (1 ml) at -78°C under nitrogen. After 1½h, when t.l.c. showed no starting material, 2M sodium hydroxide (122 ul, 0.24 mmol) and 30% hydrogen peroxide (55 ul, 0.487 mmol) were added and the mixture stirred for 1h at room temperature. The aqueous layer was then extracted with ether (3 × 10 ml) and each extract washed with a saturated brine solution (10 ml). The combined

extracts were dried ($MgSO_4$) and the solvent removed in vacuo. The residual oil was purified by flash chromatography (1:1 petroleum ether-ethyl acetate)[2] and recrystallisation (60-80 petroleum ether) to yield methyl 4,6-O-benzylidene-2,3-C-(2-buten-2'-ol)-3-deoxy-3-C-methyl-α-D-arabino-hexopyranoside (247) as a white crystalline solid[3] (55 mg, 82%), m.p. 125-126°C.

$[\alpha]_D^{20}$ = 8° (1.5 in EtOH);

$C_{19}H_{24}O_5$ requires C 68.66%, H 7.28%, N 0.00%,

found C 68.88%, H 7.37%, N 0.00%;

R_f 0.4 (1:1 petroleum ether-ethyl acetate);

ν_{max} (nujol mull) 3440brm(OH), 1320m, 1280w, 1198w, 1168m, 1120m, 1100s, 1070s, 1042s, 1030s, 990s, 955s, 870m, 750m, 700s;

δ_H (300 MHz; $CDCl_3$) 1.40 (3H, s, CH_3) overlapping 1.4-1.52 (1H, m) overlapping 1.56 (1H, tdd, J = 14.3, 9.5, 2.5 Hz), 1.73 (1H, brs, OH), 1.89-1.97 (1H, m), 2.01-2.09 (1H, m), 3.27 (1H, d, J = 9.5 Hz, H-4), 3.38 (3H, s, OCH_3), 3.68 (1H, t, J = 10.2 Hz, H-6_{ax}), 4.12 (1H, dt, J = 9.7, 5.0 Hz, H-5), 4.23 (1H, brt, J = 5 Hz, H-2'), 4.30 (1H, dd, J = 10.2, 5.0 Hz, H-6_{eq}), 4.78 (1H, s, H-1), 5.51 (1H, s), 5.72 (1H, s with some fine splitting, H-1'), 7.31-7.49 (5H, m, $C_6\underline{H}_5$);

δ_C (75 MHz; $CDCl_3$) 18.98(q), 28.29(t), 34.37(t), 37.33(s, C-3), 54.87(q, OCH_3), 60.42(q), 67.41(d), 69.59(t, C-6), 86.74(d), 101.53(d), 103.27(d), 126.13(d), 128.14(d), 128.87(d), 131.73(d), 137.79(s), 139.33(s).

Notes

1. L-Selectride was obtained from Aldrich as a 1M solution in THF.
2. The ratio of (247) to (248) after chromatography was approximately 30:1.
3. A crystal which was suitable for X-ray analysis was obtained for crystal data, see Appendix 1.

APPENDIX

X-RAY CRYSTAL STRUCTURE DATA FOR THE ALLYLIC ALCOHOL (247)

Crystal Data $C_{19}H_{24}O_5$, M = 332.39, Orthorhombic, Space Group $P2_12_12_1$

$\underline{a}$ = 10.053(1), $\underline{b}$ = 28.748(2), $\underline{c}$ = 6.079(16)Å,

U = 1753.4 Å^3, Z = 4, μ = 0.54 cm^{-1}, λ(Mo-Kα) = 0.7107 Å, F(000) = 712.0

dx = 1.259 g cm^{-3}.

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 3182 unique reflections with $2\theta < 52°$ and (+h, ±k, +l) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite monochromated Mo-Kα radiation using an omega-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1180 reflections with $I>3\sigma(I)$.

The structure was solved using the TREF option of SHELXS 84*. All subsequent calculations were carried out using the computer program SHELX-76**.

Hydrogen atoms were included in calculated positions (C-H = 1.08 Å). All non-hydrogen atoms were refined as anisotropic.

Final cycles of refinement employed a weighting parameter g(.00054) $\{w = 1/[\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices $R\{ = \Sigma|(|Fo|-|Fc|)|/\Sigma|Fo|\}$ 0.062 and $Rw\{ = [\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{\frac{1}{2}}\}$ 0.059. The final difference Fourier map was featureless and an analysis of the weighting scheme over |Fo| and $\sin\theta/\lambda$ was satisfactory.

The geometry of the molecule is shown in Figure . Final atomic positional and thermal parameters and lists of |Fo| and |Fc| values have been deposited as supplementary material with the editor from whom copies are available on request.

Acknowledgements - Leicester University Computer Centre who provided support and facilities for X-ray single crystal calculations and G. M.

Sheldrick for the use of SHELXS.

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

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

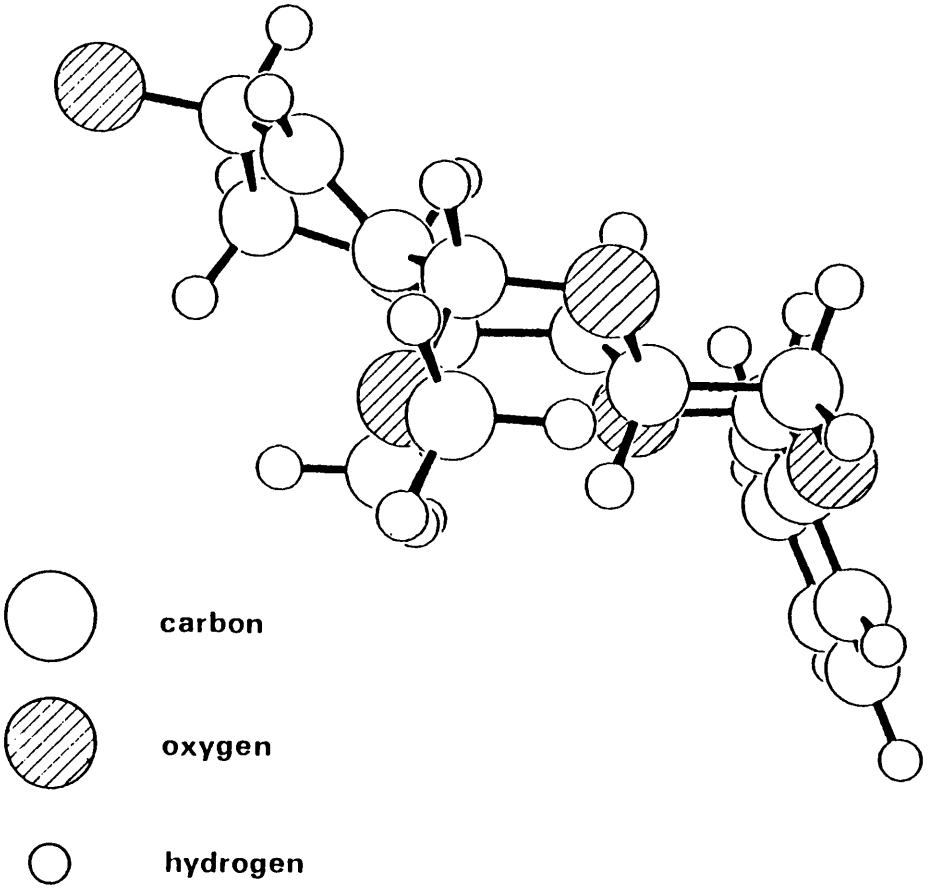


FIGURE 24

X-Ray Crystal Structure of Allylic Alcohol (247)

TABLE 4

Fractional atomic co-ordinates for Allyl alcohol (247) $C_{19}H_{24}O_5$

Atom	x	y	z
C(1)	0.0112(7)	0.03520(25)	1.2254(16)
C(2)	-0.1159(7)	0.05972(23)	1.1531(14)
C(3)	-0.1026(7)	0.09973(24)	0.9925(14)
C(4)	0.0141(6)	0.12938(24)	1.0761(16)
C(5)	0.1396(7)	0.10049(26)	1.1080(18)
C(6)	0.2505(7)	0.13216(28)	1.1819(18)
C(7)	-0.2305(7)	0.04719(22)	1.2368(14)
C(8)	-0.3619(7)	0.07041(24)	1.1946(15)
C(9)	-0.3570(7)	0.10063(23)	0.9938(17)
C(10)	-0.2280(6)	0.12930(23)	1.0044(17)
C(11)	0.1440(8)	0.19456(25)	1.0058(19)
C(12)	0.1547(7)	-0.02708(25)	1.1441(18)
C(13)	-0.0777(8)	0.08393(23)	0.7592(14)
C(14)	0.1586(6)	0.23329(18)	0.8449(11)
C(15)	0.2634(6)	0.23506(18)	0.6945(11)
C(16)	0.2633(6)	0.26852(18)	0.5281(11)
C(17)	0.1584(6)	0.30018(18)	0.5121(11)
C(18)	0.0536(6)	0.29839(18)	0.6625(11)
C(19)	0.0537(6)	0.26495(18)	0.8289(11)
H(1)	-0.0101(7)	0.01649(25)	1.3754(16)
H(4)	-0.0139(6)	0.14345(24)	1.2342(16)
H(5)	0.1667(7)	0.08335(26)	0.9564(18)
H(7)	-0.2306(7)	0.01753(22)	1.3461(14)
H(8)	-0.3822(7)	0.09194(24)	1.3363(15)
H(11)	0.1213(8)	0.20753(25)	1.1683(19)
H(15)	0.3446(6)	0.21057(18)	0.7069(11)
H(16)	0.3445(6)	0.26990(18)	0.4117(11)
H(17)	0.1584(6)	0.32607(18)	0.3833(11)
H(18)	-0.0276(6)	0.32289(18)	0.6501(11)
H(19)	-0.0274(6)	0.26355(18)	0.9453(11)
H(61)	0.3426(7)	0.11281(28)	1.1896(18)
H(62)	0.2276(7)	0.14603(28)	1.3426(18)
H(91)	-0.3574(7)	0.07931(23)	0.8475(17)
H(92)	-0.4421(7)	0.12363(23)	0.9915(17)
H(101)	-0.2270(6)	0.14847(23)	1.1572(17)
H(102)	-0.2273(6)	0.15339(23)	0.8680(17)
H(121)	0.1835(7)	-0.05100(25)	1.0156(18)
H(122)	0.1176(7)	-0.04641(25)	1.2836(18)
H(123)	0.2400(7)	-0.00672(25)	1.1936(18)
H(131)	0.0115(8)	0.06299(23)	0.7538(14)
H(132)	-0.0656(8)	0.11396(23)	0.6542(14)
H(133)	-0.1613(8)	0.06352(23)	0.7028(14)
O(1)	0.0398(5)	0.16628(15)	0.9260(10)
O(2)	0.2636(5)	0.16951(17)	1.0279(13)
O(3)	0.1150(5)	0.06744(18)	1.2744(10)
O(4)	0.0521(5)	0.00339(16)	1.0635(10)
O(5)	-0.4668(4)	0.03687(16)	1.1696(10)

TABLE 5

Atomic thermal parameters (×10**4) for Allyl alcohol (247) $C_{19}H_{24}O_5$

Atom	U or U11	U22	U33	U23	U13	U12
C(1)	481(46)	497(43)	595(68)	-94(52)	-36(48)	-31(41)
C(2)	440(44)	447(46)	502(60)	-65(43)	-39(48)	-13(39)
C(3)	278(39)	548(47)	575(65)	48(48)	-13(49)	-54(37)
C(4)	486(46)	474(40)	463(59)	35(50)	0(45)	4(41)
C(5)	451(49)	577(50)	676(74)	70(56)	45(54)	17(42)
C(6)	469(48)	711(52)	1002(85)	98(65)	-45(60)	-48(50)
C(7)	537(46)	366(40)	484(57)	57(41)	-36(52)	-18(39)
C(8)	458(49)	480(44)	664(68)	53(54)	16(50)	-2(41)
C(9)	444(49)	498(45)	975(90)	153(55)	88(61)	28(39)
C(10)	438(42)	492(39)	937(82)	176(53)	-20(57)	-28(41)
C(11)	551(52)	614(50)	882(80)	-139(59)	119(58)	-200(48)
C(12)	630(55)	668(51)	1082(93)	-52(60)	28(60)	264(47)
C(13)	663(56)	557(48)	469(62)	-4(43)	20(57)	-168(41)
C(14)	510(51)	510(48)	981(85)	-51(59)	90(60)	-192(48)
C(15)	696(63)	629(54)	1215(97)	-65(62)	220(78)	39(53)
C(16)	832(72)	936(66)	1105(105)	55(77)	372(83)	110(67)
C(17)	1046(77)	605(57)	1017(97)	30(59)	92(82)	-180(59)
C(18)	636(58)	660(59)	1043(90)	92(61)	151(73)	-119(47)
C(19)	525(50)	505(47)	1172(92)	43(61)	105(67)	-107(46)
O(1)	475(31)	514(29)	685(44)	62(33)	17(35)	-88(27)
O(2)	387(34)	716(36)	1392(68)	165(44)	-24(42)	-121(30)
O(3)	477(31)	592(33)	806(48)	-11(36)	-179(36)	41(28)
O(4)	608(33)	574(29)	664(42)	-51(34)	-18(37)	181(29)
O(5)	458(30)	663(31)	763(48)	-16(33)	-23(33)	-134(29)

All Hydrogen atoms were included in calculated positions with a fixed isotropic thermal parameter U = .05

TABLE 6

Bond lengths (Å) for Allyl alcohol (247) $C_{19}H_{24}O_5$

C(4)-O(1)	1.422(8)	C(11)-O(1)	1.411(8)
C(6)-O(2)	1.430(10)	C(11)-O(2)	1.406(8)
C(1)-O(3)	1.426(7)	C(5)-O(3)	1.409(9)
C(1)-O(4)	1.404(9)	C(12)-O(4)	1.438(7)
C(8)-O(5)	1.436(7)	H(1)-C(1)	1.080(0)
C(2)-C(1)	1.523(9)	C(3)-C(2)	1.514(10)
C(7)-C(2)	1.309(8)	C(4)-C(3)	1.535(9)
C(10)-C(3)	1.521(8)	C(13)-C(3)	1.510(10)
H(4)-C(4)	1.080(0)	C(5)-C(4)	1.521(8)
H(5)-C(5)	1.080(0)	C(6)-C(5)	1.507(9)
H(61)-C(6)	1.080(0)	H(62)-C(6)	1.080(0)
H(7)-C(7)	1.080(0)	C(8)-C(7)	1.500(8)
H(8)-C(8)	1.080(0)	C(9)-C(8)	1.499(11)
H(91)-C(9)	1.080(0)	H(92)-C(9)	1.080(0)
C(10)-C(9)	1.536(8)	H(101)-C(10)	1.080(0)
H(102)-C(10)	1.080(0)	H(11)-C(11)	1.080(0)
C(14)-C(11)	1.489(10)	H(121)-C(12)	1.080(0)
H(122)-C(12)	1.080(0)	H(123)-C(12)	1.080(0)
H(131)-C(13)	1.080(0)	H(132)-C(13)	1.080(0)
H(133)-C(13)	1.080(0)	C(15)-C(14)	1.395(0)
C(19)-C(14)	1.395(0)	C(16)-C(15)	1.395(0)
H(15)-C(15)	1.080(0)	C(17)-C(16)	1.395(0)
H(16)-C(16)	1.080(0)	C(18)-C(17)	1.395(0)
H(17)-C(17)	1.080(0)	C(19)-C(18)	1.395(0)
H(18)-C(18)	1.080(0)	H(19)-C(19)	1.080(0)

TABLE 7

Bond Angles (Å) for Allyl alcohol (247) $C_{19}H_{24}O_5$

C(11)-O(1)-C(4)	110.1(7)	C(11)-O(2)-C(6)	111.6(6)
C(5)-O(3)-C(1)	114.5(6)	C(12)-O(4)-C(1)	111.5(6)
O(4)-C(1)-O(3)	110.8(6)	H(1)-C(1)-O(3)	107.0(5)
H(1)-C(1)-O(4)	109.0(4)	C(2)-C(1)-O(3)	111.9(5)
C(2)-C(1)-O(4)	110.1(6)	C(2)-C(1)-H(1)	107.9(5)
C(3)-C(2)-C(1)	117.6(7)	C(7)-C(2)-C(1)	119.8(7)
C(7)-C(2)-C(3)	122.5(6)	C(4)-C(3)-C(2)	106.0(7)
C(10)-C(3)-C(2)	108.7(6)	C(10)-C(3)-C(4)	107.8(5)
C(13)-C(3)-C(2)	113.1(6)	C(13)-C(3)-C(4)	110.6(6)
C(13)-C(3)-C(10)	110.4(7)	C(3)-C(4)-O(1)	109.9(7)
H(4)-C(4)-O(1)	109.8(4)	H(4)-C(4)-C(3)	107.7(4)
C(5)-C(4)-O(1)	109.8(6)	C(5)-C(4)-C(3)	111.8(5)
C(5)-C(4)-H(4)	107.8(5)	C(4)-C(5)-O(3)	108.3(6)
H(5)-C(5)-O(3)	110.5(4)	H(5)-C(5)-C(4)	110.4(5)
C(6)-C(5)-O(3)	108.8(8)	C(6)-C(5)-C(4)	108.7(6)
C(6)-C(5)-H(5)	110.0(5)	C(5)-C(6)-O(2)	109.0(7)
H(61)-C(6)-O(2)	109.6(4)	H(61)-C(6)-C(5)	109.6(4)
H(62)-C(6)-O(2)	109.6(5)	H(62)-C(6)-C(5)	109.6(5)
H(62)-C(6)-H(61)	109.5(0)	H(7)-C(7)-C(2)	117.2(4)
C(8)-C(7)-C(2)	125.7(7)	C(8)-C(7)-H(7)	117.1(4)
C(7)-C(8)-O(5)	111.4(5)	H(8)-C(8)-O(5)	109.2(4)
H(8)-C(8)-C(7)	106.5(4)	C(9)-C(8)-O(5)	109.0(6)
C(9)-C(8)-C(7)	111.6(7)	C(9)-C(8)-H(8)	108.9(4)
H(91)-C(9)-C(8)	110.0(4)	H(92)-C(9)-C(8)	109.8(4)
H(92)-C(9)-H(91)	109.5(0)	C(10)-C(9)-C(8)	107.7(7)
C(10)-C(9)-H(91)	110.0(5)	C(10)-C(9)-H(92)	109.9(3)
C(9)-C(10)-C(3)	113.4(5)	H(101)-C(10)-C(3)	108.5(5)
H(101)-C(10)-C(9)	108.5(5)	H(102)-C(10)-C(3)	108.4(4)
H(102)-C(10)-C(9)	108.5(5)	H(102)-C(10)-H(101)	109.5(0)
O(2)-C(11)-O(1)	111.8(6)	H(11)-C(11)-O(1)	110.8(5)

TABLE 7 *(Continued)* ....

H(11)-C(11)-O(2)	105.6(5)	C(14)-C(11)-O(1)	106.1(7)
C(14)-C(11)-O(2)	111.2(6)	C(14)-C(11)-H(11)	111.3(4)
H(121)-C(12)-O(4)	109.5(4)	H(122)-C(12)-O(4)	109.5(4)
H(122)-C(12)-H(121)	109.5(0)	H(123)-C(12)-O(4)	109.5(4)
H(123)-C(12)-H(121)	109.5(0)	H(123)-C(12)-H(122)	109.5(0)
H(131)-C(13)-C(3)	109.5(4)	H(132)-C(13)-C(3)	109.5(4)
H(132)-C(13)-H(131)	109.5(0)	H(133)-C(13)-C(3)	109.5(4)
H(133)-C(13)-H(131)	109.5(0)	H(133)-C(13)-H(132)	109.5(0)
C(15)-C(14)-C(11)	122.1(4)	C(19)-C(14)-C(11)	117.3(4)
C(19)-C(14)-C(15)	120.0(0)	C(16)-C(15)-C(14)	120.0(0)
H(15)-C(15)-C(14)	120.0(0)	H(15)-C(15)-C(16)	120.0(0)
C(17)-C(16)-C(15)	120.0(0)	H(16)-C(16)-C(15)	120.0(0)
H(16)-C(16)-C(17)	120.0(0)	C(18)-C(17)-C(16)	120.0(0)
H(17)-C(17)-C(16)	120.0(0)	H(17)-C(17)-C(18)	120.0(0)
C(19)-C(18)-C(17)	120.0(0)	H(18)-C(18)-C(17)	120.0(0)
H(18)-C(18)-C(19)	120.0(0)	C(18)-C(19)-C(14)	120.0(0)
H(19)-C(19)-C(14)	120.0(0)	H(19)-C(19)-C(18)	120.0(0)

TABLE 8

Non-bonded Contacts (Å) for Allyl alcohol (247) $C_{19}H_{24}O_5$

O(2)...O(1)	2.333	C(3)...O(1)	2.421
H(4)...O(1)	2.057	C(5)...O(1)	2.408
C(6)...O(1)	2.803	H(11)...O(1)	2.060
C(14)...O(1)	2.318	C(4)...O(2)	2.774
C(5)...O(2)	2.392	H(61)...O(2)	2.061
H(62)...O(2)	2.061	H(11)...O(2)	1.991
C(14)...O(2)	2.389	C(15)...O(2)	2.767
O(4)...O(3)	2.330	H(1)...O(3)	2.025
C(2)...O(3)	2.443	C(4)...O(3)	2.377
H(5)...O(3)	2.053	C(6)...O(3)	2.372
H(1)...O(4)	2.031	C(2)...O(4)	2.400
H(121)...O(4)	2.066	H(122)...O(4)	2.066
H(123)...O(4)	2.066	C(7)...O(5)	2.426
H(8)...O(5)	2.062	C(9)...O(5)	2.390
H(1)...O(5)	2.367	2, -1.0000, 0.0000, 0.0000	
C(3)...C(1)	2.597	C(4)...C(1)	2.854
C(5)...C(1)	2.385	C(7)...C(1)	2.453
C(12)...C(1)	2.349	C(2)...H(1)	2.120
C(4)...C(2)	2.434	C(5)...C(2)	2.833
H(7)...C(2)	2.043	C(8)...C(2)	2.502
C(9)...C(2)	2.860	C(10)...C(2)	2.466
C(13)...C(2)	2.523	H(4)...C(3)	2.128
C(5)...C(3)	2.531	C(7)...C(3)	2.477
C(9)...C(3)	2.555	H(101)...C(3)	2.127
H(102)...C(3)	2.125	H(131)...C(3)	2.129
H(132)...C(3)	2.129	H(133)...C(3)	2.129
H(5)...C(4)	2.151	C(6)...C(4)	2.461
C(10)...C(4)	2.469	C(11)...C(4)	2.322
C(13)...C(4)	2.503	C(5)...H(4)	2.118
H(61)...C(5)	2.128	H(62)...C(5)	2.128

TABLE 8 *(Continued)* ....

C(11)...C(5)	2.773	C(6)...H(5)	2.134
C(11)...C(6)	2.346	H(62)...H(61)	1.764
H(8)...C(7)	2.083	C(9)...C(7)	2.481
C(10)...C(7)	2.750	C(8)...H(7)	2.212
H(91)...C(8)	2.126	H(92)...C(8)	2.124
C(10)...C(8)	2.451	C(9)...H(8)	2.112
H(101)...C(9)	2.140	H(102)...C(9)	2.140
H(92)...H(91)	1.764	C(10)...H(91)	2.159
C(10)...H(92)	2.158	C(13)...C(10)	2.489
H(17)...H(102)	2.000	3, 0.0000, 0.0000,	1.0000
H(102)...H(101)	1.764	C(15)...C(11)	2.524
C(19)...C(11)	2.463	C(14)...H(11)	2.134
H(122)...H(121)	1.764	H(123)...H(121)	1.764
H(123)...H(122)	1.764	H(132)...H(131)	1.764
H(133)...H(131)	1.764	H(133)...H(132)	1.764
C(16)...C(14)	2.416	C(17)...C(14)	2.790
C(18)...C(14)	2.416	H(15)...C(14)	2.149
H(19)...C(14)	2.149	C(17)...C(15)	2.416
C(18)...C(15)	2.790	C(19)...C(15)	2.416
H(16)...C(15)	2.149	C(18)...C(16)	2.416
C(19)...C(16)	2.790	H(15)...C(16)	2.149
H(17)...C(16)	2.149	C(19)...C(17)	2.416
H(16)...C(17)	2.149	H(18)...C(17)	2.149
H(17)...C(18)	2.149	H(19)...C(18)	2.149
H(18)...C(19)	2.149		

REFERENCES

REFERENCES

1. K. Nakanishi, T. Goto, S. Itô, S. Natori and S. Nozoe (Eds), "Natural Product Chemistry", Academic Press, New York, 1974, Vol. 1, p.281.
2. E. Winterstein and A. Guyer, Z. Physiol. Chem., 1923, 128, 175.
3. J. N. Baxter, B. Lythgoe, B. Scales, R. M. Scrowston and S. Trippett, J. Chem. Soc., 1962, 2964.
4. R. W. Miller, J. Nat. Prods., 1980, 43, 425.
5. M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon and A. T. McPhail, J. Am. Chem. Soc., 1971, 93, 2325.
6. R. G. Powell, R. W. Miller and C. R. Smith, J. Chem. Soc., Chem. Commun., 1979, 102.
7. F. Guéritte-Voegelein, V. Sénilh, B. David, D. Guénard and P. Potier, Tetrahedron, 1986, 42, 4451.
8. B. Lythgoe, K. Nakanishi and S. Uyeo, Proc. Chem. Soc., 1964, 301.
9. IUPAC Commission on Nomenclature of Organic Chemistry, Eur. J. Biochem., 1978, 86, 1.
10. IUPAC Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H, Pergamon, Oxford, 1979.
11. E. Winterstein and D. Iatrides, Z. Physiol. Chem., 1921, 117, 240.
12. B. Lythgoe in "The Alkaloids", ed. R. H. E. Manske, Academic Press, New York, 1968, Vol. X, p.597.
13. J. N. Baxter, B. Lythgoe, B. Scales, S. Trippett and B. K. Blount, Proc. Chem. Soc., 1958, 9.
14. T. Takahashi, K. Ueda, R. Oishi and K. Minamoto, Chem. and Pharm. Bull. (Tokyo), 1958, 6, 728;
H. Kondo and J. Taga, Ann. Rept. Itsuu Lab., 1958, 9, 67 and 71.
15. G. Zemplén and A. Kunz, Chem. Ber., 1923, 56, 1705.
16. H. Lucas, Arch. Pharm., 1856, 95, 145.
17. M. Kurono, Y. Nakadaira, S. Onuma, K. Sasaki and K. Nakanishi, Tetrahedron Lett., 1963, 2153.
18. B. W. Langley, B. Lythgoe, B. Scales, R. M. Scrowston, S. Trippett and D. Wray, J. Chem. Soc., 1962, 2972.
19. J. W. Harrison and B. Lythgoe, J. Chem. Soc. (C), 1966, 1932.
20. M. Dukes, D. H. Eyre, J. W. Harrison, R. M. Scrowston and B. Lythgoe, J. Chem. Soc. (C), 1967, 448.
21. D. H. Eyre, J. W. Harrison, R. M. Scrowston and B. Lythgoe, Proc. Chem. Soc., 1963, 271.
22. J. Taga, Chem. and Pharm. Bull. (Tokyo), 1960, 8, 934;
Y. Yamamoto, S. Uyeo and K. Ueda, ibid., 1964, 12, 386.
23. M. Kurono, Y. Maki, K. Nakanishi, M. Ohashi, K. Ueda, S. Uyeo, M. C. Woods and Y. Yamamoto, Tetrahedron Lett., 1965, 1917.

24. M. Shiro, T. Sato, H. Koyama, Y. Maki, K. Nakanishi and S. Uyeo, Chem. Commun., 1966, 97.

25. J. M. Tedder, A. Nechvatal, A. W. Murry and J. Carnduff, "Basic Organic Chemistry", Wiley, London, 1977, Part 4, p.217.

26. J. W. Harrison, R. M. Scrowston and B. Lythgoe, J. Chem. Soc. (C), 1966, 1933.

27. C. B. Jackson and G. Pattenden, Tetrahedron Lett., 1985, 26, 3393.

28. M. J. Begley, C. B. Jackson and G. Pattenden, Tetrahedron Lett., 1985, 26, 3397.

29. J. J. Manfredi and S. B. Horwitz, Pharmac. Ther., 1984, 25, 83.

30. J. Parness, D. G. I. Kingston, R. G. Powell, C. Harracksingh and S. B. Horwitz, Biochem. Biophys. Res. Commun., 1982, 105, 1082.

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

32. S. B. Horwitz, L. Lothstein, J. J. Manfredi, W. Mellado, J. Parness, S. N. Roy, P. B. Schiff, L. Sorbara and R. Zeheb, Ann. N.Y. Acad. Sci., 1986, 466, 733.

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

34. W. Mellado, N. F. Magri, D. G. I. Kingston, R. Garcia-Arenas, G. A. Orr and S. B. Horwitz, Biochem. Biophys. Res. Commun., 1984, 124, 329.

35. T. Kato, H. Takayanagi, T. Suzuki and T. Uyehara, Tetrahedron Lett., 1978, 1201;
A. S. Kende, M. Benechie, D. P. Curran, P. Fludzinski, W. Swenson and J. Clardy, ibid., 1979, 4513;
I. Kitigawa, H. Shibuya, H. Fujioka, A. Kejiwara, S. Tsujii, Y. Yamamoto and A. Takagi, Chem. Lett., 1980, 1001;
Y. Inouye, C. Fukaya and H. Kakisawa, Bull. Chem. Soc. Jpn., 1981, 54, 1117;
B. M. Trost and H. Hiemstra, J. Am. Chem. Soc., 1982, 104, 886;
S. F. Martin, J. B. White and R. Wagner, J. Org. Chem., 1982, 47, 3190;
K. Sakan and B. M. Craven, J. Am. Chem. Soc., 1983, 105, 3732;
Y. Ohtsuka and T. Oishi, Heterocycles, 1984, 21, 371;
G. R. Clark, J. Lin and M. Nikaido, Tetrahedron Lett., 1984, 25, 2645;
R. Z. Andriamialisoa, M. Fétizon, I. Hanna, C. Pascard and T. Prange, Tetrahedron, 1984, 40, 4285;
B. M. Trost and M. J. Fray, Tetrahedron Lett., 1984, 25, 4605;
H. Nagaoka, K. Ohsawa, T. Takata and Y. Yamada, ibid., 1984, 25, 5389;
W. F. Berkowitz, J. Perumattam and A. Amaresekara, ibid., 1985, 26, 3665;
Y. Ohtsuka and T. Oishi, ibid., 1986, 27, 203;
M. Fétizon, I. Hanna and R. Zeghdoudi, Synth. Commun., 1986, 16, 1;
B. M. Trost and H. Hiemstra, Tetrahedron, 1986, 42, 3323;
H. Cervantes, D. Do Khac, M. Fétizon, F. Guir, J. C. Beloeil, J. Y. Lallemand and T. Prange, Tetrahedron, 1986, 42, 3491;
R. Kaczmarek and S. Blechert, Tetrahedron Lett., 1986, 27, 2845;
J. D. Winkler, J. P. Hey and S. D. Darling, ibid., 1986, 27, 5959;

J. D. Winkler, J. P. Hey and P. G. Williard, J. Am. Chem. Soc., 1986, 108, 6425;
C. S. Swindell and S. J. de Solms, Tetrahedron Lett., 1984, 25, 3801;
W. F. Berkowitz and A. S. Amarasekara, ibid., 1985, 26, 3663;
C. S. Swindell and S. F. Britcher, J. Org. Chem., 1986, 51, 793;
C. S. Swindell, B. P. Patel, S. J. de Solms and J. P. Springer, ibid., 1987, 52, 2346;
P. A. Wender and M. L. Snapper, Tetrahedron Lett., 1987, 28, 2221;
L. Pettersson, T. Frejd and G. Magnusson, Tetrahedron Lett., 1987, 28, 2753.

36. K. J. Shea and P. D. Davis, Angew. Chem. Int. Ed. Engl., 1983, 22, 419; also see K. J. Shea, J. W. Gilman, C. D. Haffner and T. K. Dougherty, J. Am. Chem. Soc., 1986, 108, 4953.

37. K. J. Shea and J. W. Gilman, Tetrahedron Lett., 1983, 24, 657.

38. P. A. Brown and P. R. Jenkins, J. Chem. Soc., Perkin Trans. 1, 1986, 1303.

39. G. Stork, P. Rosen and N. L. Goldman, J. Am. Chem. Soc., 1961, 83, 2965;
G. Stork and J. d'Angelo, J. Am. Chem. Soc., 1974, 96, 7114.

40. J. C. Collins, W. W. Hess and F. J. Frank, Tetrahedron Lett., 1968, 3363.

41. D. J. Peterson, J. Org. Chem., 1968, 33, 780.

42. J. B. Hendrickson, J. Am. Chem. Soc., 1967, 89, 7036 and 7043;
N. L. Allinger, M. T. Tribble and M. R. Miller, Tetrahedron, 1972, 28, 1173.

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

44. M. E. Krafft and R. A. Holton, Tetrahedron Lett., 1983, 24, 1345.

45. H. Neh, S. Bleckert, W. Schnick and M. Jansen, Angew. Chem. Int. Ed. Engl., 1984, 23, 905.

46. T. Kojima, Y. Inouye and H. Kakisawa, Chem. Lett., 1985, 323.

47. J. P. Schaefer, J. C. Lark, C. A. Flegal and L. M. Honig, J. Org. Chem., 1967, 32, 1372.

48. A. S. Kende, S. Johnson, P. Sanfilippo, J. C. Hodges and L. N. Jungheim, J. Am. Chem. Soc., 1986, 108, 3513.

49. J. E. McMurry, Acc. Chem. Res., 1983, 16, 405.

50. W. G. Salmond, M. A. Barta and J. C. Havens, J. Org. Chem., 1978, 43, 2057.

51. P. M. Warner and D. Le, Synth. Commun., 1984, 14, 1341.

52. R. L. Danheiser, J. J. Bronson and K. Okano, J. Am. Chem. Soc., 1985, 107, 4579.

53. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 1970, 35, 4000.

54. P. A. Grieco and R. S. Finkelhor, Tetrahedron Lett., 1972, 3781;
W. G. Dauben and A. P. Kozikowski, Tetrahedron Lett., 1973, 3711.

55. M. J. Devos, L. Hevesi, P. Bayet and A. Krief, Tetrahedron Lett., 1976, 3911.

56. J. I. G. Cadogan, "Organophosphorus Reagents in Organic Synthesis", Academic Press, London, 1979, p.218.

57. J. P. Freeman, Chem. and Ind., 1959, 1254.

58. J. E. McMurry and L. R. Krepski, J. Org. Chem., 1976, 41, 3929.

59. J. E. McMurry and M. P. Fleming, J. Org. Chem., 1976, 41, 896.

60. P. A. Brown, Ph.D. Thesis, University of Leicester, 1984.

61. J. K. Groves, Chem. Soc. Rev., 1972, 1, 73;
F. H. Cottee, B. P. Straughan, C. J. Timmons, W. F. Forbes and R. Shilton, J. Chem. Soc. (B), 1967, 1146.

62. A. Wohl, Chem. Ber., 1919, 52, 51.

63. Y-H. Lai, Synthesis, 1981, 585.

64. R. D. Rieke, S. E. Bales, P. M. Hudnall and G. S. Poindexter, Org. Synth., 1979, 59, 85.

65. M. R. Selim, Ph.D. Thesis, University of Leicester, 1987.

66. M. J. Carter and I. Fleming, J. Chem. Soc., Chem. Commun., 1976, 679.

67. P. W. K. Lau and T. H. Chan, Tetrahedron Lett., 1978, 2383.

68. T. Cohen, J. P. Sherbine, J. R. Matz, R. R. Hutchins, B. M. McHenry and P. R. Willey, J. Am. Chem. Soc., 1984, 106, 3245.

69. E. Campaigne and J. R. Leal, J. Am. Chem. Soc., 1954, 76, 1272.

70. P. F. Hudrlik and D. Peterson, Tetrahedron Lett., 1974, 1133; see also Ref. 53.

71. D. J. Ager, Synthesis, 1984, 384.

72. P. F. Hudrlik and D. Peterson, J. Am. Chem. Soc., 1975, 97, 1464.

73. P. F. Hudrlik and D. Peterson, Tetrahedron Lett., 1972, 1785.

74. R. H. Shapiro and M. J. Heath, J. Am. Chem. Soc., 1967, 89, 5734.

75. A. R. Chamberlin and F. T. Bond, Synthesis, 1979, 44.

76. T. Cohen and J. R. Matz, Synth. Commun., 1980, 10, 311.

77. A. Krief, Tetrahedron, 1980, 36, 2531.

78. W. C. Still, J. Am. Chem. Soc., 1978, 100, 1481.

79. D. J. Peterson, Organometal. Chem. Rev. A, 1972, 7, 295.

80. E. Winterfeldt, Synthesis, 1975, 617.

81. Prepared by Dr. P. A. Brown who kindly left this compound after completing his work.

82. I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976.

83. W. Carruthers, "Some Modern Methods of Organic Synthesis", Cambridge University Press, London, 1978, 2nd. Edn.

84. K. N. Houk and R. W. Strozier, J. Am. Chem. Soc., 1973, 95, 4094.

85. J. Sauer, Angew. Chem. Int. Ed. Engl., 1967, 6, 16;

J. Sauer and R. Sustmann, Angew. Chem. Int. Ed. Engl., 1980, 19, 779;
M. J. S. Dewar and A. B. Pierini, J. Am. Chem. Soc., 1984, 106, 203;
M. J. S. Dewar, ibid., 1984, 106, 209.

86. R. B. Woodward and R. Hoffmann, Angew. Chem. Int. Ed. Engl., 1969, 8, 781; also see Ref. 82.

87. R. Gompper, Angew. Chem. Int. Ed. Engl., 1969, 8, 312;
J. Drexler, R. Lindermayer, M. A. Hassen and J. Sauer, Tetrahedron Lett., 1985, 26, 2559.

88. L. K. Montgomery, K. Schueller and P. D. Bartlett, J. Am. Chem. Soc., 1964, 86, 622.

89. M. Dern, H-G. Korth, G. Kopp and R. Sustmann, Angew. Chem. Int. Ed. Engl., 1985, 24, 337.

90. Y. S. Kulkarni and B. B. Snider, Org. Prep. Proced. Int., 1986, 18, 7;
H. J. Reich and E. K. Eisenhart, J. Org. Chem., 1984, 49, 5282.

91. I. Ichikizaki and A. Arai, Bull. Chem. Soc. Jpn., 1964, 37, 432.

92. F. Zutterman and A. Krief, J. Org. Chem., 1983, 48, 1135.

93. N. P. Sopov, Zh. Org. Chim., 1968, 1, 446;
O. N. Jitkow and M. T. Bogert, J. Am. Chem. Soc., 1941, 63, 1979.

94. R. C. Cookson, S. S. H. Gilani and I. D. R. Stevens, J. Chem. Soc. (C), 1967, 1905.

95. R. C. Cookson, S. S. Gupte, I. D. R. Stevens and C. T. Watts, Org. Synth., 1971, 51, 121.

96. G. Desimoni and G. Tacconi, Chem. Rev., 1975, 75, 651.

97. S. Danishefsky and J. F. Kerwin, J. Org. Chem., 1982, 42, 3183;
S. J. Danishefsky, E. Larson, D. Askin and N. Kato, J. Am. Chem. Soc., 1985, 107, 1246.

98. S. M. Weinreb and R. R. Staib, Tetrahedron, 1982, 38, 3087.

99. W. Dumont, P. Bayet and A. Krief, Angew. Chem. Int. Ed. Engl., 1974, 13, 804;
D. Seebach and A. K. Beck, ibid., 806; also see Ref. 77.

100. D. Labar and A. Krief, J. Chem. Soc., Chem. Commun., 1982, 564.

101. D. Seebach, N. Meyer and A. K. Beck, Liebigs Ann. Chem., 1977, 846;
D. Labar, L. Hevesi, W. Dumont and A. Krief, Tetrahedron Lett., 1978, 1141.

102. J. Lucchetti and A. Krief, C.R. Acad. Sc. Paris (C), 1979, 288, 537.

103. W. Dumont and A. Krief, Angew. Chem. Int. Ed. Engl., 1975, 14, 350;
D. Van Ende, W. Dumont and A. Krief, ibid., 700.

104. D. L. J. Clive, G. Chittattu and C. K. Wong, J. Chem. Soc., Chem. Commun., 1978, 41;
K. C. Nicolaou, S. P. Seitz, W. J. Sipio and J. F. Blount, J. Am. Chem. Soc., 1979, 101, 3884; see also Ref. 77.

105. H. J. Reich and F. Chow, J. Chem. Soc., Chem. Commun., 1975, 790; S. Halazy and A. Krief, J. Chem. Soc., Chem. Commun., 1979, 1136.

106. J. Rémion and A. Krief, Tetrahedron Lett., 1976, 3743.

107. S. Halazy and A. Krief, Tetrahedron Lett., 1980, 21, 1997.

108. G. Fráter and J. Wenger, Helv. Chim. Acta, 1984, 67, 1702.

109. E. J. Corey and C. U. Kim, J. Am. Chem. Soc., 1972, 94, 7586; also see Ref. 112.

110. G. H. Posner and M. J. Chapdelaine, Tetrahedron Lett., 1977, 3227.

111. D. H. R. Barton, D. J. Lester, W. B. Motherwell and M. T. B. Papoula, J. Chem. Soc., Chem. Commun., 1980, 246.

112. R. Baudat and M. Petrzilka, Helv. Chim. Acta, 1979, 62, 1406.

113. M. Clarembeau, A. Cravador, W. Dumont, L. Hevesi, A. Krief, J. Lucchetti and D. Van Ende, Tetrahedron, 1985, 41, 4793.

114. D. G. Foster, Org. Synth., Vol. 3, 771.

115. T. M. Santosusso and D. Swern, Tetrahedron Lett., 1968, 4261.

116. D. Van Ende and A. Krief, Tetrahedron Lett., 1976, 457.

117. R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly and S. M. Roberts, Tetrahedron Lett., 1979, 3981.

118. G. Brieger and J. N. Bennett, Chem. Rev., 1980, 80, 63; A. G. Fallis, Can. J. Chem., 1984, 62, 183.

119. E. C. du Feu, F. J. McQuillin and R. Robinson, J. Chem. Soc., 1937, 53.

120. R. F. Butterworth, W. G. Overend and N. R. Williams, Tetrahedron Lett., 1968, 3239.

121. A. Klemer and G. Rodmeyer, Chem. Ber., 1974, 107, 2612.

122. D. Horton and W. Weckerle, Carbohydr. Res., 1975, 44, 227.

123. Y. Chapleur, J. Chem. Soc., Chem. Commun., 1983, 141.

124. R. Tsang and B. Fraser-Reid, J. Chem. Soc., Chem. Commun., 1984, 60.

125. A. Klemer and H. Beermann, J. Carbohydr. Chem., 1983, 2, 457; A. Klemer and H. Thiemeyer, Liebig Ann. Chem., 1984, 1094; A. Klemer and H. Stegt, J. Carbohydr. Chem., 1985, 4, 205.

126. A. Klemer and H. Wilbers, Liebigs Ann. Chem., 1985, 2328.

127. Y. Chapleur and M. N. Euvrard, J. Chem. Soc., Chem. Commun., 1987, 884.

128. M. Bednarski and S. Danishefsky, J. Am. Chem. Soc., 1983, 105, 3716.

129. J. L. Primeau, R. C. Anderson and B. Fraser-Reid, J. Am. Chem. Soc., 1983, 105, 5874.

130. J. R. Pougny and P. Sinay, J. Chem. Res. (M), 1982, 0186.

131. J. L. Frahn, Aust. J. Chem., 1980, 33, 1021; E. Sorkin and T. Reichstein, Helv. Chim. Acta, 1945, 28, 1.

132. S. Hanessian and T. H. Haskell, J. Org. Chem., 1965, 30, 1080.

133. V. Heřmánková, A. Zobáňová and J. Jarý, Collect. Czech. Chem. Commun., 1971, 36, 303.

134. Vogel's "Textbook of Practical Organic Chemistry", Longman, New York, 1978, 4th. Edn., p.469.

135. J. Yoshimura, K. Sato and H. Hashimoto, Chem. Lett., 1977, 1327.

136. O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Jpn., 1971, 44, 3427;
O. Mitsunobu, Synthesis, 1981, 1.

137. D. R. Hicks and B. Fraser-Reid, Synthesis, 1974, 203.

138. I. D. Inch and G. J. Lewis, Carbohydr. Res., 1970, 15, 1.

139. A. A. J. Feast, W. G. Overend and N. R. Williams, J. Chem. Soc., 1965, 7378.

140. D. R. Hicks, R. Ambrose and B. Fraser-Reid, Tetrahedron Lett., 1973, 2507.

141. C. Kowalski, X. Creary, A. J. Rollin and M. C. Burke, J. Org. Chem., 1978, 43, 2601.

142. A. G. Brook and D. M. Macrae, J. Organomet. Chem., 1974, 77, C19.

143. A. Hassner, R. H. Reuss and H. W. Pinnick, J. Org. Chem., 1975, 40, 3427.

144. W. J. Le Noble and H. F. Morris, J. Org. Chem., 1969, 34, 1969.

145. J. D. Morrison (Ed), "Asymmetric Synthesis", Academic Press, New York, 1984, Vol. 3, p.25.

146. M. E. Jung, Tetrahedron, 1976, 32, 3.

147. G. Stork and B. Ganem, J. Am. Chem. Soc., 1973, 95, 6152;
G. Stork and J. Singh, ibid., 1974, 96, 6181.

148. R. K. Boeckman, J. Am. Chem. Soc., 1973, 95, 6867;
R. K. Boeckman, ibid., 1974, 96, 6179.

149. T. H. Chan, W. Mychajlowskij, B. S. Ong and D. N. Harpp, J. Org. Chem., 1978, 43, 1526.

150. R. K. Boeckman, D. M. Blum, B. Ganem and N. Halvey, Org. Synth., 1978, 58, 152.

151. H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Philippines, 1972, 2nd. Edn., p.589.

152. G. Stork and M. J. Sofia, J. Am. Chem. Soc., 1986, 108, 6826.

153. S. Krishnamurthy and H. C. Brown, J. Org. Chem., 1975, 40, 1864;
H. C. Brown, S. Krishnamurthy and N. M. Yoon, ibid., 1976, 41, 1778.

154. H. C. Brown and S. Krishnamurthy, J. Am. Chem. Soc., 1972, 94, 7159;
E. J. Corey, K. B. Becker and R. K. Varma, ibid., 1972, 94, 8616;
J. M. Fortunato and B. Ganem, J. Org. Chem., 1976, 41, 2194.

155. T. Inoue, T. Uchimaru and T. Mukaiyama, Chem. Lett., 1977, 1215.

156. U. Hertenstein, S. Hünig and M. Öller, Synthesis, 1976, 416.

157. G. Wittig and D. Wittenberg, Liebigs Ann. Chem., 1957, 606, 1.

158. H. J. Reich, S. K. Shah and F. Chow, J. Am. Chem. Soc., 1979, 101, 6648.

159. J. A. Katzenellenbogen and K. J. Christy, J. Org. Chem., 1974, 39, 3315.

160. R. B. Miller and B. F. Smith, Tetrahedron Lett., 1973, 5037.

161. J. Meinwald, J. Crandall and W. E. Hymans, Org. Synth., 1973, 5, 866.