Approaches to the synthesis of bruceantin

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APPROACHES TO THE SYNTHESIS OF BRUCEANTIN

Submitted by I. A. Scruton-Evans
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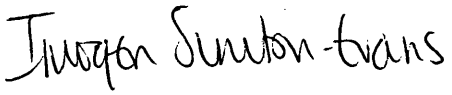
1987



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ABSTRACT

The thesis is introduced by a comprehensive review of published synthetic efforts towards bruceantin and other naturally occurring quassinoids, and covers both racemic and chiral approaches. Section 2 includes an overview of steroidal approaches to the synthesis of quassinoids, and describes the potential advantages and problems of using a steroid starting material.

Using (-)-dehydroepiandrosterone as the chiral starting material, the synthesis of a B,C-ring functionalised precursor to bruceantin, 3β,17β-diacetoxy-7β-hydroxy-11-oxoandrost-8-ene, is described. The introduction of a C-8β nitrile group, essential for the construction of the C-8 - C-13 ether linkage in bruceantin, is achieved by the use of the 'Nagata' reagent, Et_2AlCN. Modification of the C-8β nitrile resulted in the synthesis of 3β,11β-dihydroxy-5α-ergost-22-ene-8β-carboxylic acid, 8,11-lactone. Various fragmentations of the steroid D-ring are reviewed, and work aimed towards a C-14α two carbon fragment is described. A novel methodology for lactone contractions, specifically for ε→δ-lactones, is proposed, and literature reports of lactone contractions reviewed. The attempted preparation of the silylketene-O,O-acetal of 4-*t*-butyl-ε-caprolactone, and subsequent ozonolysis to give a ring contracted product is described, although the instability of both the O-trimethylsilyl and O-t-butyldimethylsilyl acetals prevented any useful transformations.

ABBREVIATIONS

The following abbreviations are used in the text:

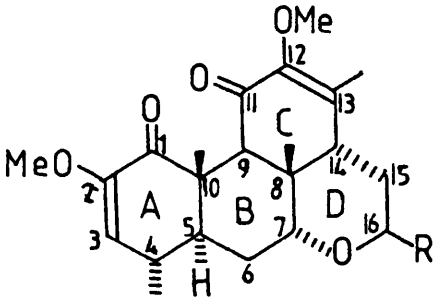
Ac	Acyl, $-COCH_3$
AIBN	Azobisisobutyronitrile
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DHP	3,4-Dihydro-2H-pyran
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMP	3,5-Dimethylpyrazole
DMSO	Dimethyl sulfoxide
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
LDA	Lithium N,N-diisopropylamide
M	Molar
M-CPBA	meta-Chloroperoxybenzoic acid
MOM	Methoxymethylene, CH_3OCH_2-
MVK	Methyl vinyl ketone
NBS	N-Bromosuccinimide
OEE	Ethoxyethyl ether
PCC	Pyridinium chlorochromate
PHT	Pyrrolidone hydrotribromide
PPTS	Pyridinium p-toluenesulfonate
p-TSOH	para-Toluene sulphonic acid
py	Pyridine
R_f	Retention factor
TBDMS	tert-Butyldimethylsilyl

THF	Tetrahydrofuran
THP	Tetrahydropyran
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMS	Trimethylsilyl

CONTENTS

INTRODUCTION

The Simaroubacae form a large botanical family of mostly pan-tropical distribution.[1] Many species of this family have been known, for over a century, to contain bitter substances collectively called "quassin". The isolation of individual constituents and elucidation of their structures was not, however, achieved until modern physical techniques of investigation were available (NMR, mass spectroscopy, circular dichroism). The first Simaroubacae constituents to be structurally confirmed were quassin (1) and its corresponding hemi-acetal, neoquassin (2) by Valenta and workers in the 1960's.[2,3]

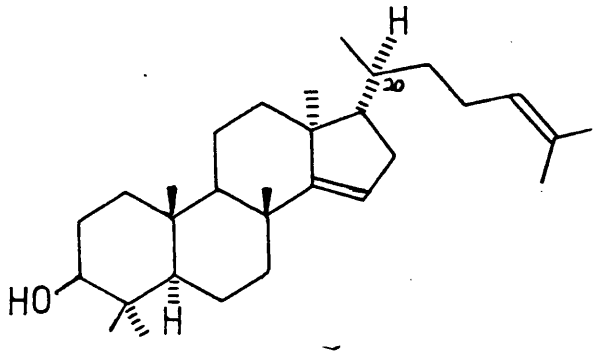


(1) R= =O

(2) R= OH / H

The Simaroubacae constituents, occurring either as esters or in the free state, are all closely related chemically, and form the bitter principles of the quassin group, called quassinoids or Simaroubolides. Most quassinoids are fundamentally C_{20} compounds and have the basic tetracyclic skeleton exhibited by quassin (1). Studies on the biogenesis of quassinoids led to the proposal that these compounds originated in a tetracyclic triterpene, such as apu-euphol, or

its 20α isomer apo-tirucallol (3).[4]



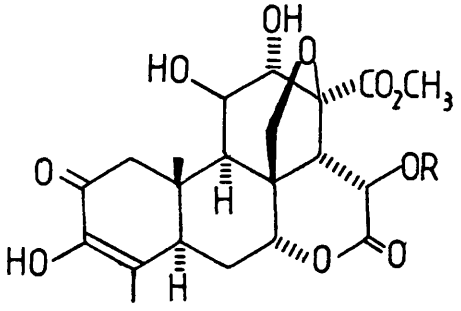
(3)

The quassinoids are heavily oxygenated lactones (δ-lactones in the C_{20}- and γ-lactones in the C_{19}-compounds) and rarely possess more than one double bond. They have varying numbers of oxygen-containing groups (eg hydroxy, esterified hydroxyl, carbonyl, methoxyl, or carboxymethyl), and in C_{20} compounds these may be found at most of the carbon atoms, although oxygenation of the methyl groups at C-4 and C-10 (numbering as for (1)) and carbons C-5 and C-9 has not yet been observed.

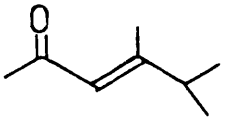
Bruceins have a C-8 hydroxymethyl group engaged in an ether function terminating at C-13. Bruceolide (4), the 'parent' compound of this group has the structure shown overleaf.

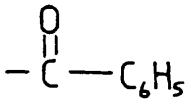
In 1973, Kupchan and Ziegler reported the isolation and

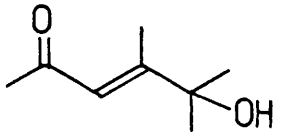
structural elucidation of two new quassinoids from *Brucea antidysenterica* Mill,[5,6] a simaroubaceous tree which is used in Ethiopia in the treatment of cancer.[7] From the alcoholic extract of stem bark, leaves, and wood of the stems, bruceantin (5) and bruceantarin (6) were obtained.



(4) R=H

(5) R= 

(6) R= 

(7) R= 

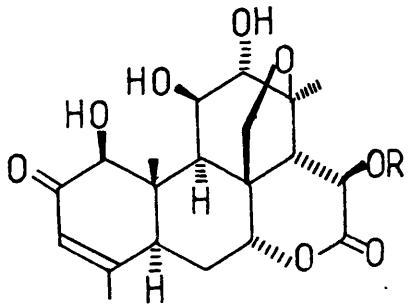
This extract showed significant *in vitro* inhibitory activity against cells derived from the human carcinoma of the nasopharynx, and against two standard animal tumours (P-388 leukaemia in mice, and Walker 256 intramuscular carcinosarcoma in rats). Bruceantin (5) also showed activity against the L-1210 lymphoid leukaemia, and two solid murine tumour systems, Lewis Lung carcinoma, and B-16 melanocarcinoma, a property not common in anti-tumour compounds.[6]

Anti-leukaemic activity of the bruceolide (4) derivatives, of which at least ten were isolated, varied greatly with the nature of the C-15 ester substituent. Bruceantin (5) and brucenatinol (7) with α,β-unsaturated esters demonstrated potent activity, whereas bruceolide (4) showed only marginal activity. Kupchan and Ziegler[6] suggest that the ester moiety may serve as a carrier group involved in processes such as transport or complex formation.

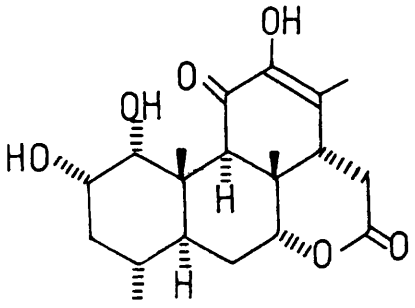
Due to the promising anti-tumour activity of bruceantin (5), and its challenging synthesis, considerable medicinal and synthetic interest in the quassinoid field was initiated. Fuchs and Pariza[8] reported, however, that preliminary results from phase-two clinical trials in humans were disappointing, with only marginal beneficial effects against a number of tumour systems, although bruceantin exhibited exceptionally low human toxicity.

They emphasised the need for a bruceantin synthesis capable of providing analogues in sufficient quantity for further clinical evaluation.

Although bruceantin (5), and the closely related quassimarin (8) have yet to be synthesised, two tetracyclic quassinoids, quassin (1)[9] and castelanolide (9)[10] have been prepared by Grieco and workers, albeit in racemic form.



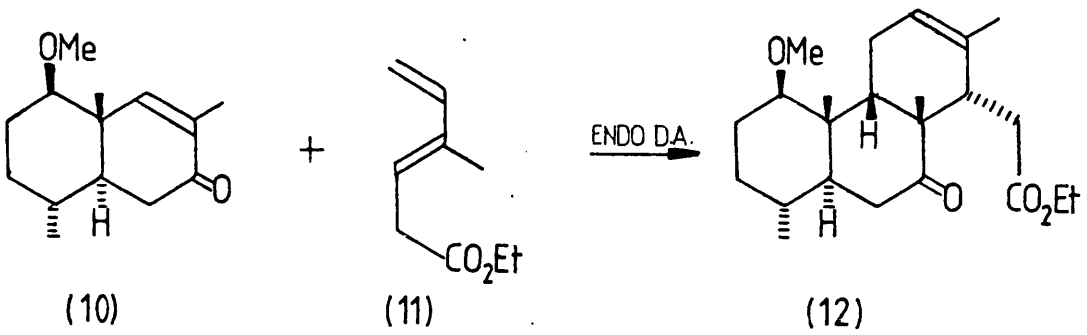
(8) R = COC(OAc)(Me)Et



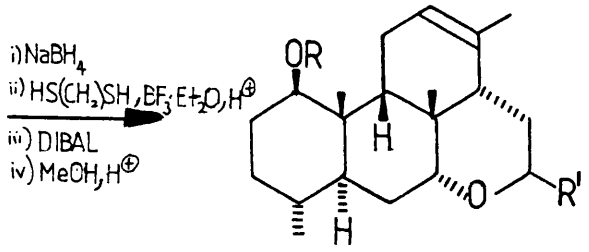
(9)

Castelanolide (9) was isolated from *Castela nicholsoni*, a simaroubaceous plant known to have anti-amoebic activity by Geissman and workers[11] in the early 1970's.

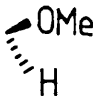
Grieco synthesised (±)-quassin and (±)-castelanolide using a Diels-Alder approach, and a common intermediate, the protected lactol (14), obtained by aluminium chloride-mediated Diels-Alder reaction of (1) with excess diene (11) (Scheme 1).



(10) (11) (12)

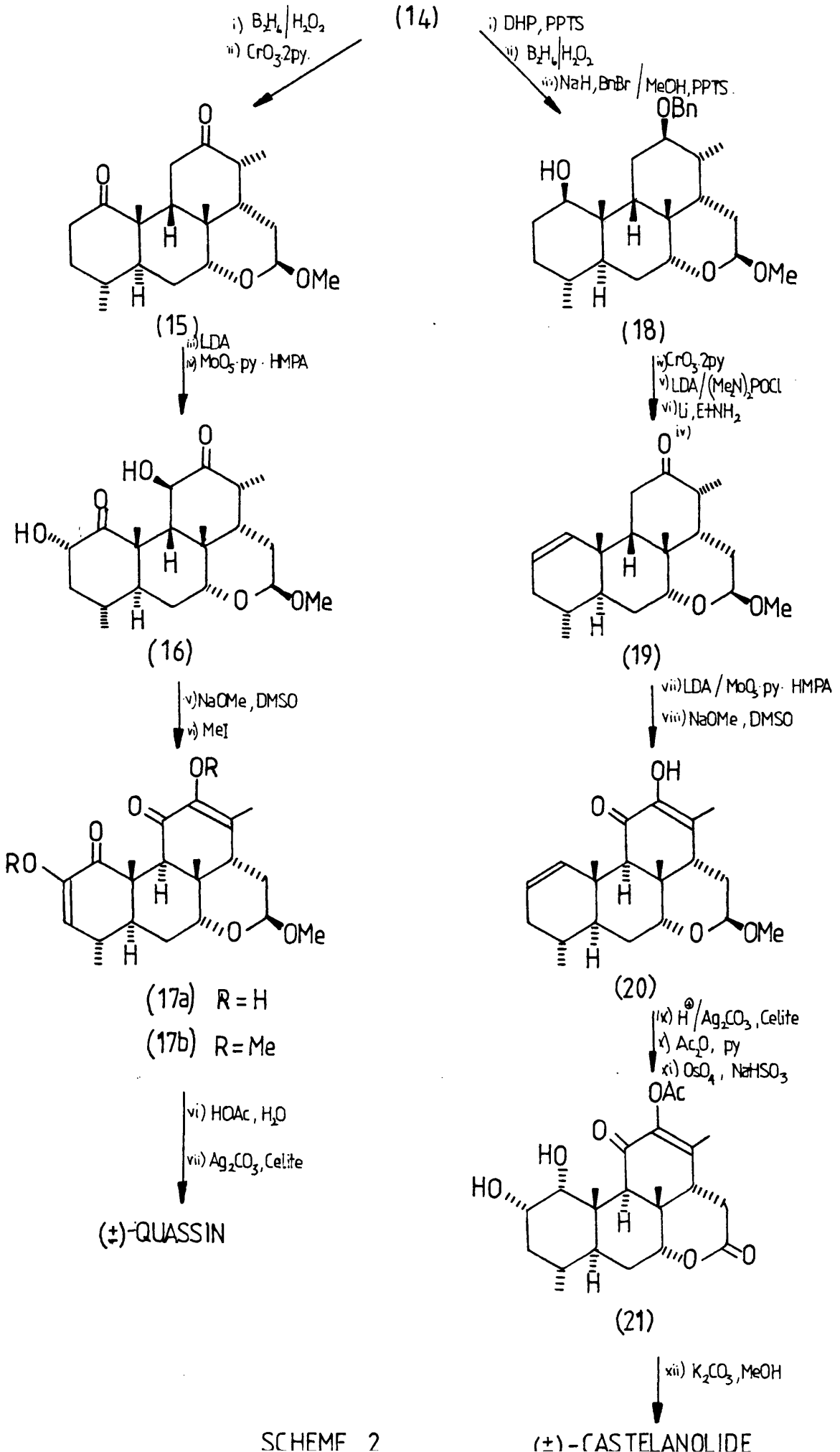


(13) R = H R' = =O

(14) R = H R' = 

SCHEME 1

With the exception of the configuration at C-9 the Diels-Alder product (12) has six of the seven stereocentres in quassin established. Only the endo adduct (12), obtained by approach of the diene (11) from the α-face of (10) was isolated, with no evidence of attack from the β-face of (10) which would give rise to 9α-and 8α-stereochemistry. This is presumably due to the presence of the methyl group at C-10 in (10) seriously interfering with approach of the diene from the β-face. That only the endo adduct (12) was obtained is perhaps surprising due to the interaction between the diene


(14)
i) B_2H_6 / H_2O_2
ii) CrO_3·2py.
(15)
iii) LDA
iv) MoO_5·py·HMPA
(16)
v) NaOMe, DMSO
vi) MeI
(17a) R = H
(17b) R = Me
vi) HOAc, H_2O
vii) Ag_2CO_3, Celite
(±)-QUASSIN
i) DHP, PPTS
ii) B_2H_6 / H_2O_2
iii) NaH, BnBr / MeOH, PPTS
(18)
iv) CrO_3·2py
v) LDA / $(Me_2N)_2POCl$
vi) Li, $EtNH_2$
(19)
vii) LDA / MoO_5·py·HMPA
viii) NaOMe, DMSO
(20)
ix) $H^{\oplus}$ / Ag_2CO_3, Celite
x) Ac_2O, py
xi) OsO_4, $NaHSO_3$
(21)
xii) K_2CO_3, MeOH
(±)-CASTELANOLIDE

SCHEME 2

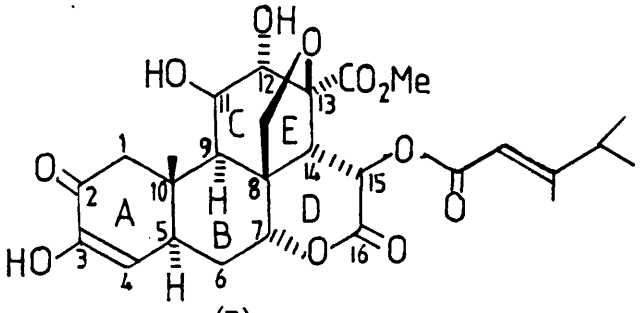
system and the C-5 proton encountered in the transition state. The presence of the cis-fused BC rings ensured hydride attack on the C-7 carbonyl from the convex face of the molecule, thereby guaranteeing the required α-configuration at C-7 in (13).

For the synthesis of (±)-quassin, the protected lactol (14) was converted to diketone (15) (hydroboration; Collins oxidation) [Scheme 2]. Oxygenation of the dianion of (15) (LDA, MoO_5,py, HMPA) gave the bis (α-hydroxy ketone) (16). The inversion of the C-9 proton was achieved by the serendipitous discovery that treatment of (16) with sodium methoxide in dimethyl sulphoxide at elevated temperature led to the bis (diosphenol) (17a), with the A- and C-ring functionalisation completed, and the correct 9α-stereochemistry established. This latter reaction is dependent upon having oxygen present, although attempts to carry out the transformation in an atmosphere of oxygen led to decomposition of the intermediate diosphenol. Methylation of (17a) gave (17b), which on selective hydrolysis of the protected lactol and oxidation (Fetizon's reagent) gave (±)-quassin (1) in 12 steps from (10), 2·9% overall yield.

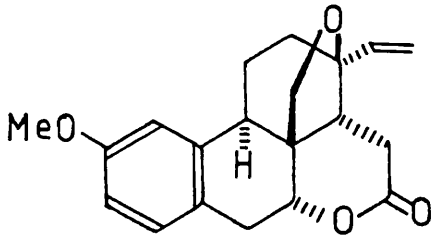
The conversion of (14) to (±)-castelanolide (9) requires oxygenation at C-11 and the use of the hydroxyl at C-1 for the vicinal glycol structure at C-1 - C-2. Protection of the C-1 hydroxyl group as its tetrahydropyranyl ether, and hydroboration of the C-12 - C-13 double bond as for (±)-quassin, followed by benzylation of C-12 hydroxyl and deprotection of C-1 gave the tetracyclic alcohol (18) (Scheme 2). Oxidation at C-1 and phosphonylation of its enolate gave the corresponding phosphorodiamidate, which, on exposure to lithium in ethylamine/THF resulted in simultaneous cleavage of the phosphorodiamidate C-O ester bond, and the benzyl group, to give a tetracyclic olefin, which on oxidation at C-12 gave (19).

Oxygenation of the enolate of (19) provided the 12β hydroxy group, and reaction with sodium methoxide and dimethyl sulfoxide as described for (±)-quassin gave the C-ring diosphenol (20), with correct 9α-stereochemistry. Deprotection and oxidation of the D-ring δ-lactone, and protection of the diosphenol unit as its acetate was followed by oxidation of the C-1 - C-2 olefinic bond with OsO_4 with subsequent mild reduction ($NaHSO_3$) of the osmate ester to give (±)-castelanolide monoacetate (21). Cleavage of the acetate-protecting group in (21) gave (±)-castelanolide in 15 steps from (18), 15·2% overall yield.

The synthesis of bruceantin (5) has attracted considerable interest and although (5) has yet to be synthesised, five pentacyclic intermediates, (22)[12] (23)[13] (24)[14a] (25)[15] (26)[16] and one tetracyclic skeleton (27)[17] have been reported as viable intermediates for quassinoid, or specifically bruceantin, synthesis.



(5)



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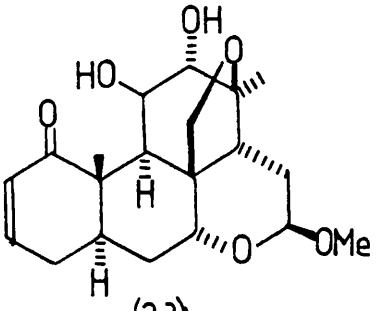

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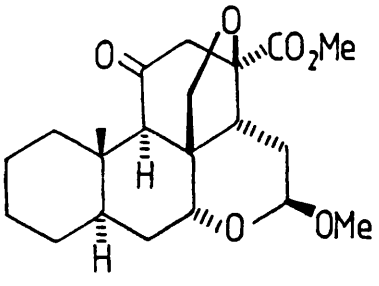

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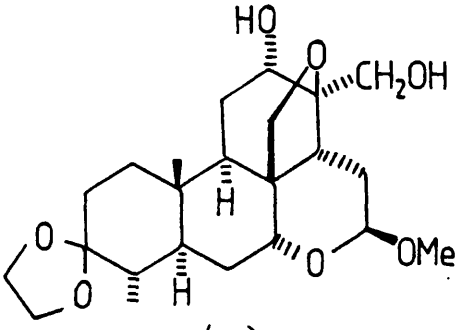

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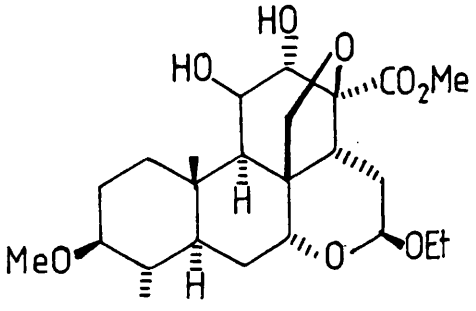

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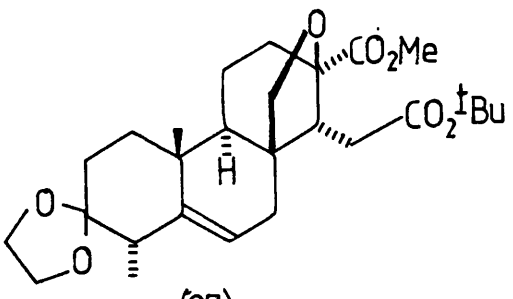


(27)

Of these intermediates, none has been synthesised in optically pure form, although Ziegler[14b] and Fukumoto[18] have addressed this problem and have reported on studies directed towards this aim.

Any approach towards the synthesis of bruceantin must concentrate on three major features:

1) The attainment of the trans-fused AB and BC ring junctions
2) The insertion of an 8β-(bruceantin numbering) substituent for E ring construction, and,
3) The correct α orientation at the C-7 and C-14 positions in the D ring lactone moiety.

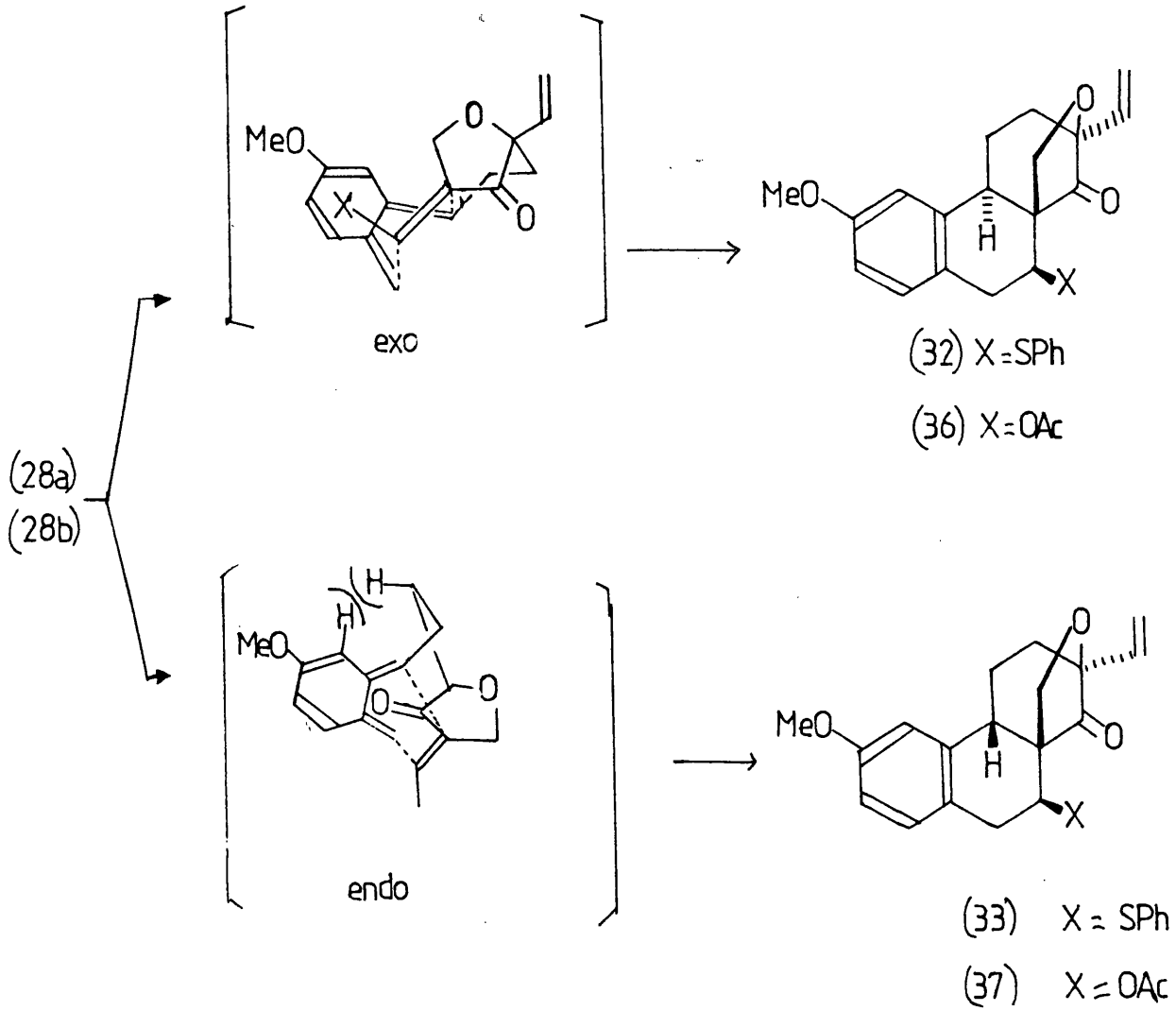
The diosphenol grouping in ring A, being very sensitive to conditions employed during the construction of the rest of the skeleton, has in general been overlooked, and interest focussed on the functionalisation of the B, C, D and E rings.

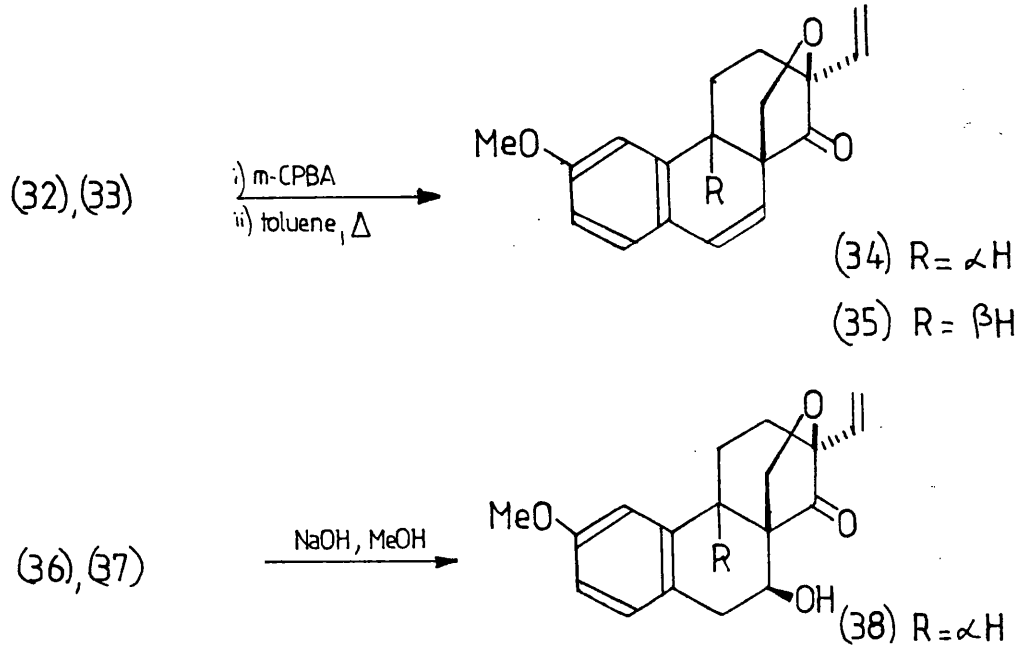
Various methods have been employed for the satisfaction of the major features listed above; eg stereoselective Diels-Alder reaction,[12] a Claisen-based rearrangement[14] and ring annelation. An overview of the synthesis of these intermediates is given, considerable details being necessary, due to the complexity of the molecules involved.

Synthesis of pentacycle (22)

Kametani *et al*[12] used a stereoselective intramolecular Diels-Alder reaction to construct the B, C and E rings of their racemic pentacyclic intermediate (22), with correct orientation of the C-8 - C-13 ether linkage and the desired 9α-configuration. The intermediate (28) was prepared from the aldehyde (29)[19] by the successive introduction of a vinyl group, a C3 unit and a dienophile (Scheme 3).

A key reaction in the conversion of (29) to (28) was the con-

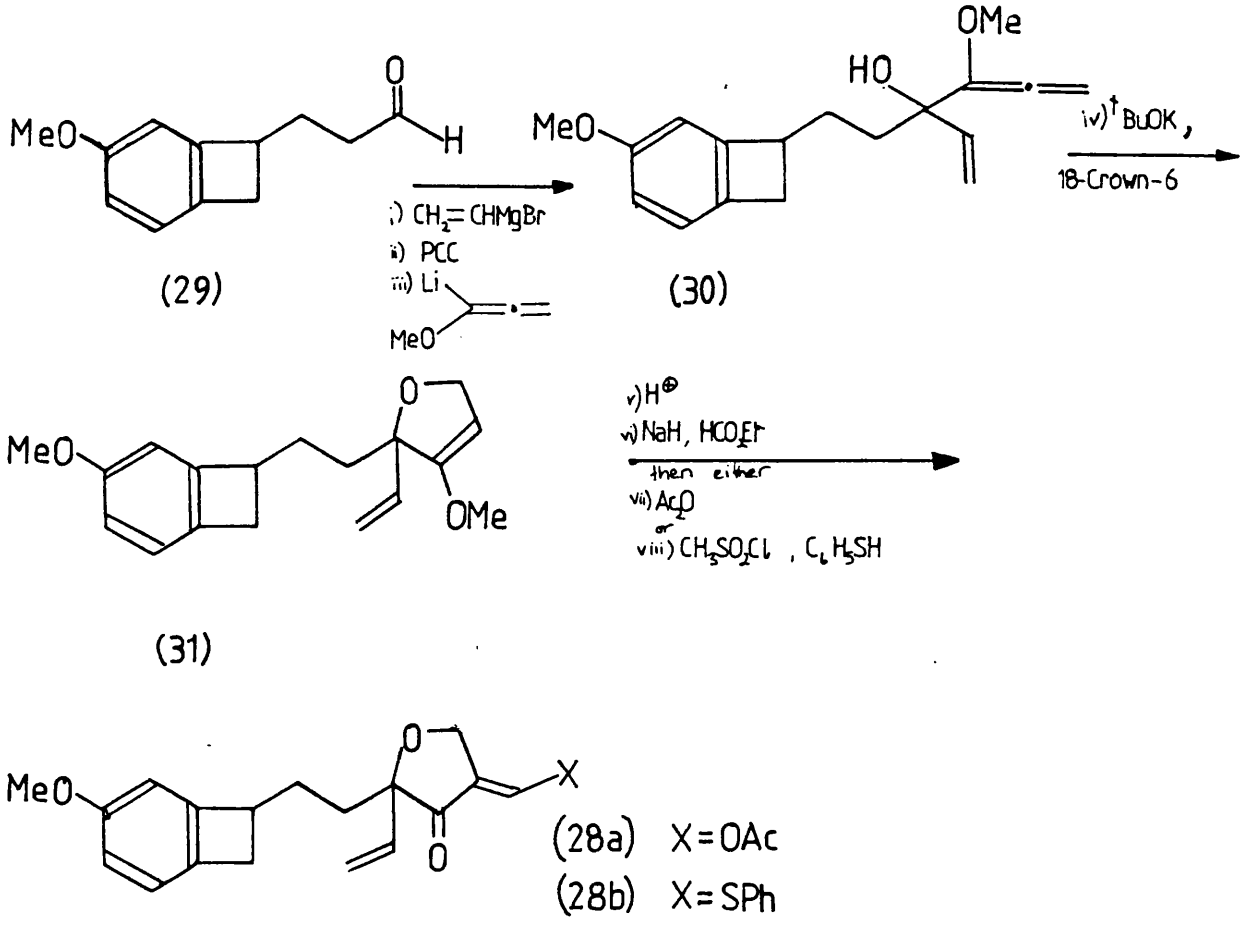

MeO
X
O
O
exo
(28a)
(28b)
MeO
H
O
O
X
(32) X=SPh
(36) X=OAc
H
H
MeO
O
O
endo
MeO
H
O
O
X
(33) X = SPh
(37) X = OAc


(32),(33)
i) m-CPBA
ii) toluene, Δ
MeO
R
O
O
(34) R = αH
(35) R = βH
(36),(37)
NaOH, MeOH
MeO
R
OH
O
O
(38) R = αH
(39) R = βH

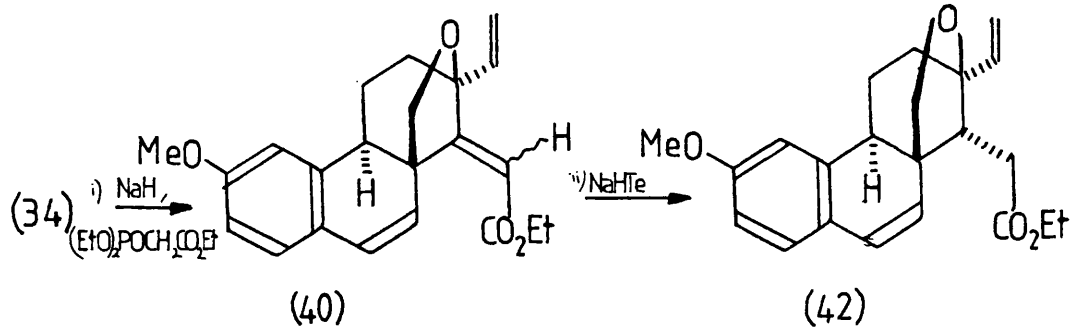
SCHEME 4

version of the alcohol (30) to the cyclised enol ether (31) by the Magnus procedure.[20] Thus reaction of the crude (30) with potassium t-butoxide in the presence of 18-crown-6 afforded (31) which was hydrolysed, without isolation, to give the corresponding ketone.

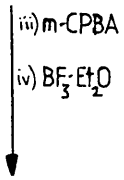
Thermolysis of (28b) (CH_2Cl_2, 180°C, 15 hours) gave an inseparable diastereomeric mixture of (32) and (33), the major isomer (32), with required 9α stereochemistry, generated from the exo-transition state. Separation was achieved by an oxidation-elimination sequence to give a 6·7 : 1 mixture of olefins (34) and (35). Similarly, thermolysis of (28a) gave a mixture of (36) and (37), separated by hydrolysis to give alcohols (38) and (39) in a 6:1 ratio (Scheme 4).

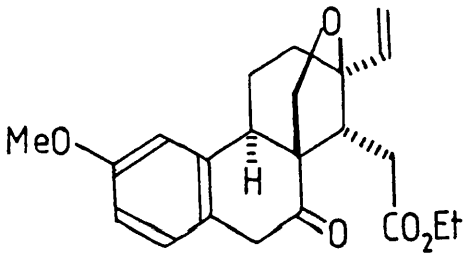


SCHEME 3

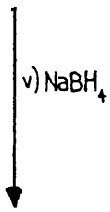


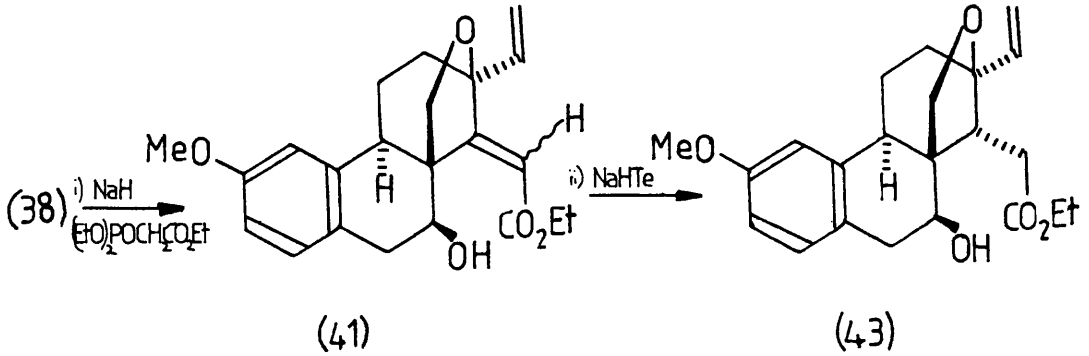
(40) (42)





(44)





(41) (43)

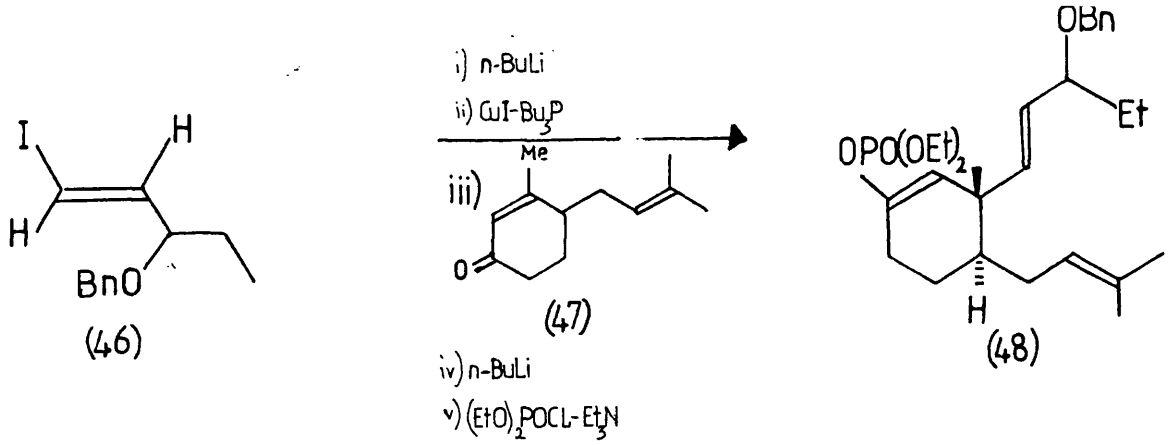
SCHEME 5

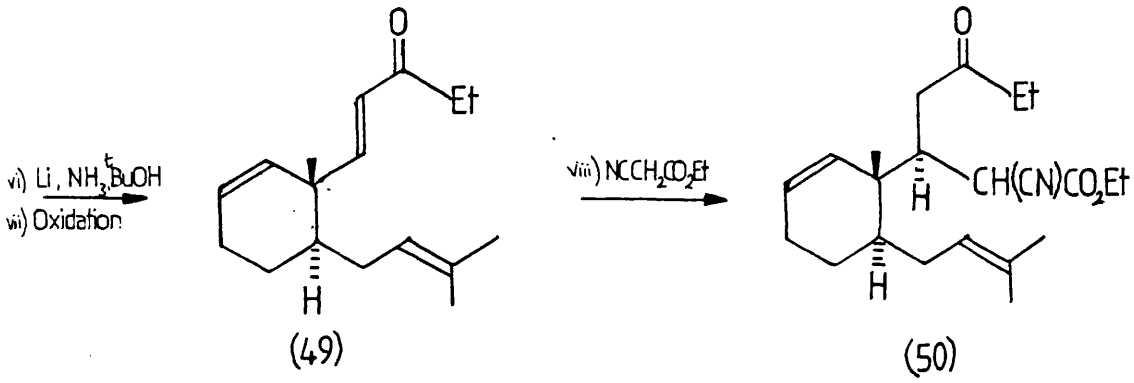
The synthesis of (22) was completed by Emmons-Horner reaction of (34) and (38) ($(EtO)_2POCH_2CO_2Et$, NaH) to give an inseparable E/Z mixture of the α,β-unsaturated esters (40) and (41), which were selectively reduced with sodium hydrotelluride to give (42) and (43) as single compounds (Scheme 5). Ester (42) was converted to (43) by epoxidation of the B-ring double bond, followed by acid-catalysed rearrangement to the keto-ester (44). Reduction of (44) afforded (43).

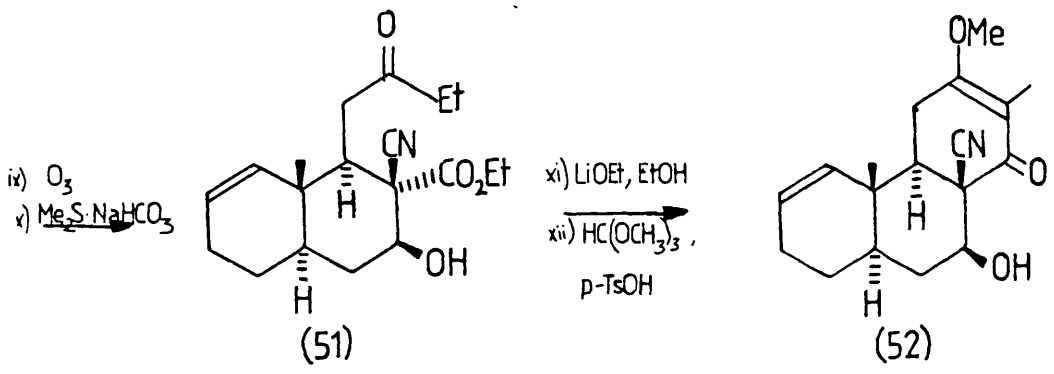
Conversion of (43) to the pentacyclic lactone (22) required selective activation of the B-ring hydroxy group in the hydroxy acid derived from (43), achieved by selective hydrolysis of the dimesylate. Acidification yielded (22), obtained in 4·5% yield, 17 steps from (29) when X=SPh, and 6·1% yield, 13 steps from (29) when X=OAc. The functionalisation of the A and C rings, and the introduction of the C-15 side chain are still required for the conversion of (22) to bruceantin (5), although as a model for studies on bruceantin, pentacycle (22) contains many of the pertinent features.

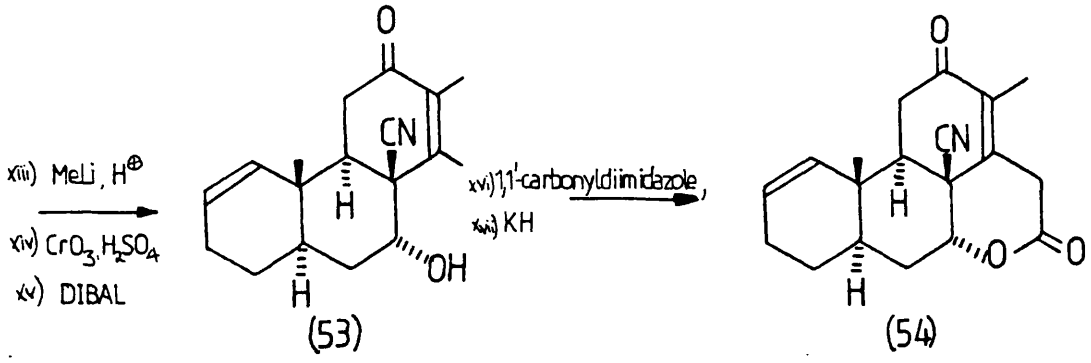
Synthesis of pentacycle (23)

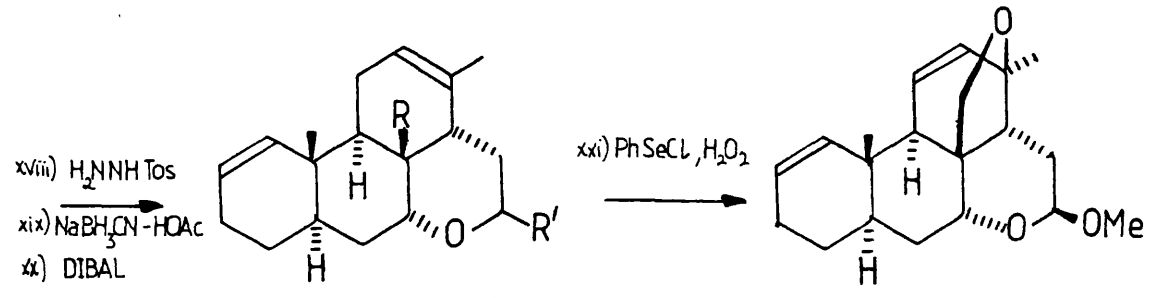
Ganem *et al*[13] synthesised a racemic pentacyclic intermediate (23), which was the result of a series of stereoselective annelations. The methodology employed allows access to both structural classes of ring C bridged ethers in quassinoids, ie C-8 - C-13 bridging as present in bruceantin (5), and also C-8 - C-11 bridging shown by eg Glaucarubolone (45b), found as a minor principle in the seeds of *Simarouba glauca*, along with glaucarubinone (45a), and glaucarubin (45c).[21,22] Glaucarubolone (45b) has also been isolated from the wood of *Castela nicholsoni*,[11] from which castelanolide (9), synthesised by Grieco was also isolated. In France, glaucarubin is sold commercially as a medicincal preparation (an amoebicide). Much of the carbon skeleton of (23) was assembled in a single conjugate addition-enolate trapping


i) n-BuLi
ii) CuI-Bu3P
iii)
iv) n-BuLi
v) (EtO)2POCl-Et3N
(46)
(47)
(48)

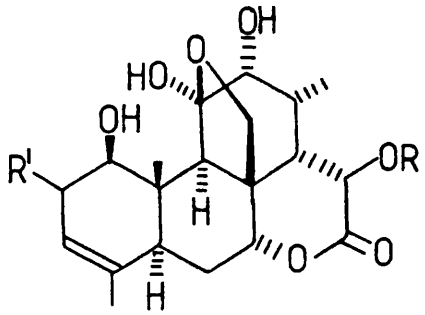

vi) Li, NH3, tBuOH
vii) Oxidation
viii) NCCH2CO2Et
(49)
(50)


ix) O3
x) Me2S·NaHCO3
xi) LiOEt, EtOH
xii) HC(OCH3)3, p-TsOH
(51)
(52)


xiii) MeLi, H⊕
xiv) CrO3, H2SO4
xv) DIBAL
xvi) 1,1'-carbonyldiimidazole,
xvii) KH
(53)
(54)

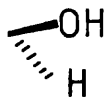

xviii) H2NNHTos
xix) NaBH3CN-HOAc
xx) DIBAL
xxi) PhSeCl, H2O2
(55) R = CN, R' = =O
(56) R = CH2OH R' = OMe
(57)

SCHEME 6



(45a) R= COC(Me)(OH)-C_2H_5 , R'= =O

(45b) R=H , R'= =O

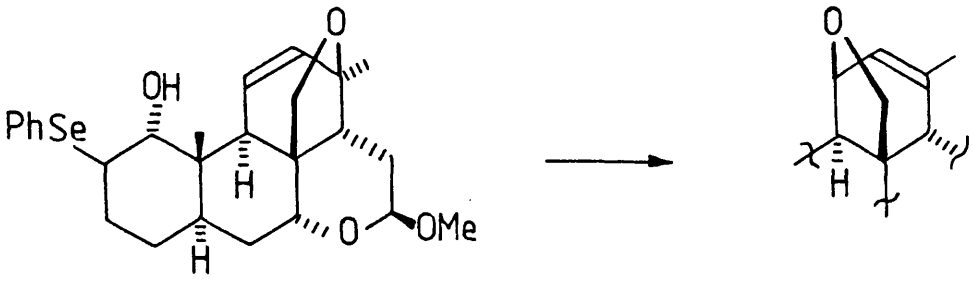
(45c) R= COC(Me)(OH)-C_2H_5 R= 

reaction, using a modification of Noyori's organo-copper based procedure.[23] Thus trans-1-iodo-3-(benzyloxy)-1-pentene (46) and 4-prenyl-3-methyl-2-cyclohexanone (47) gave the triene (48) under the conditions shown opposite (Scheme 6).

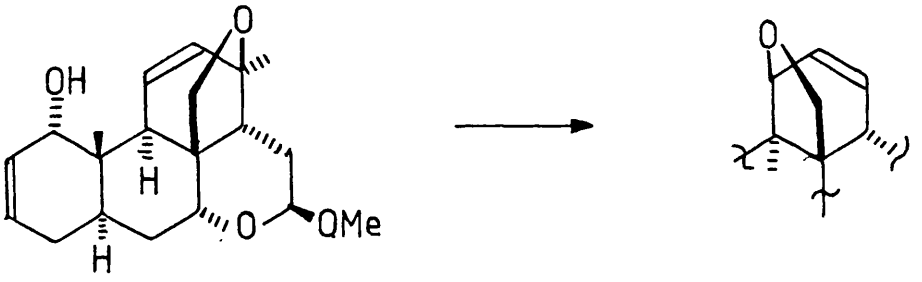
Reductive cleavage of (48) (Li, NH_3, t-BuOH) followed by oxidation gave enone (49), and stereoselective conjugate addition of ethyl cyanoacetate gave (50), with correct 9α stereochemistry and trans AB ring function.

Ozonolysis and cyclisation (Me_2S-$NaHCO_3$) of (50) gave the alcohol (51), which on cyclisation (LiOEt, EtOH) and enol etherification gave ketone (52) with the BC ring function assembled with correct 9α and 8β stereochemistry. Methyllithium addition-hydrolysis and epimerisation of the 7β-hydroxy group provided (53), which on treatment with 1,1'-carbonyldiimidazole and KH gave the tetracyclic lactone (54).

Reductive rearrangement of the tosylhydrazone of (54) gave a

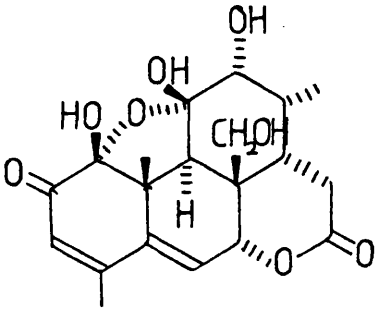


(58) (60)



(59) (61)

SCHEME 7

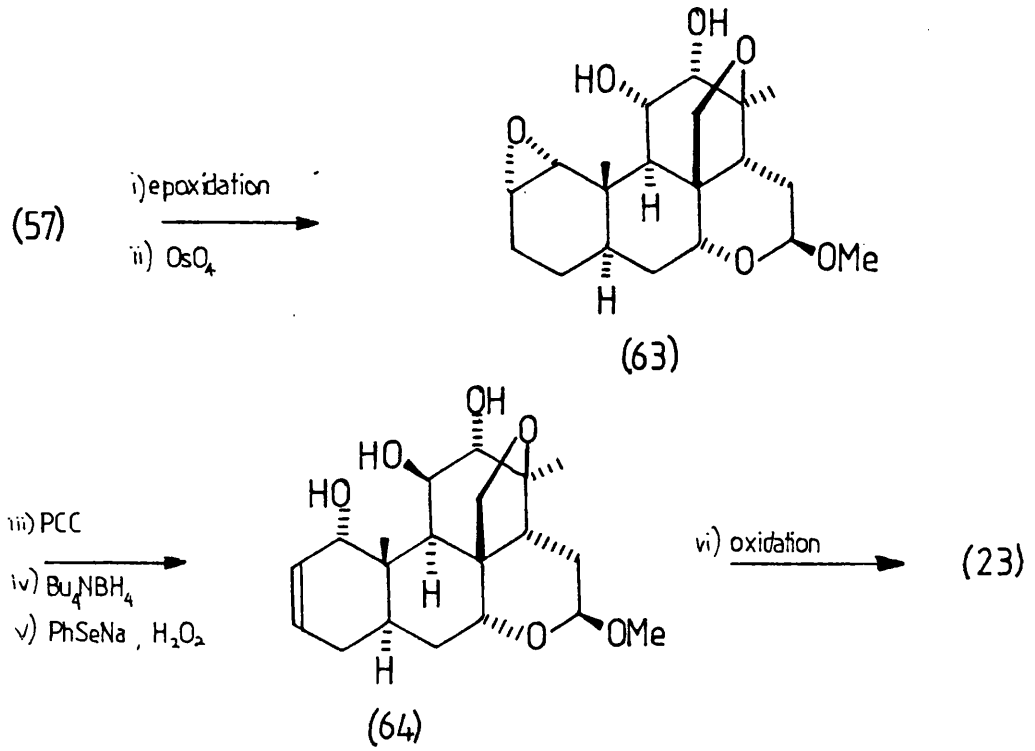


(62)

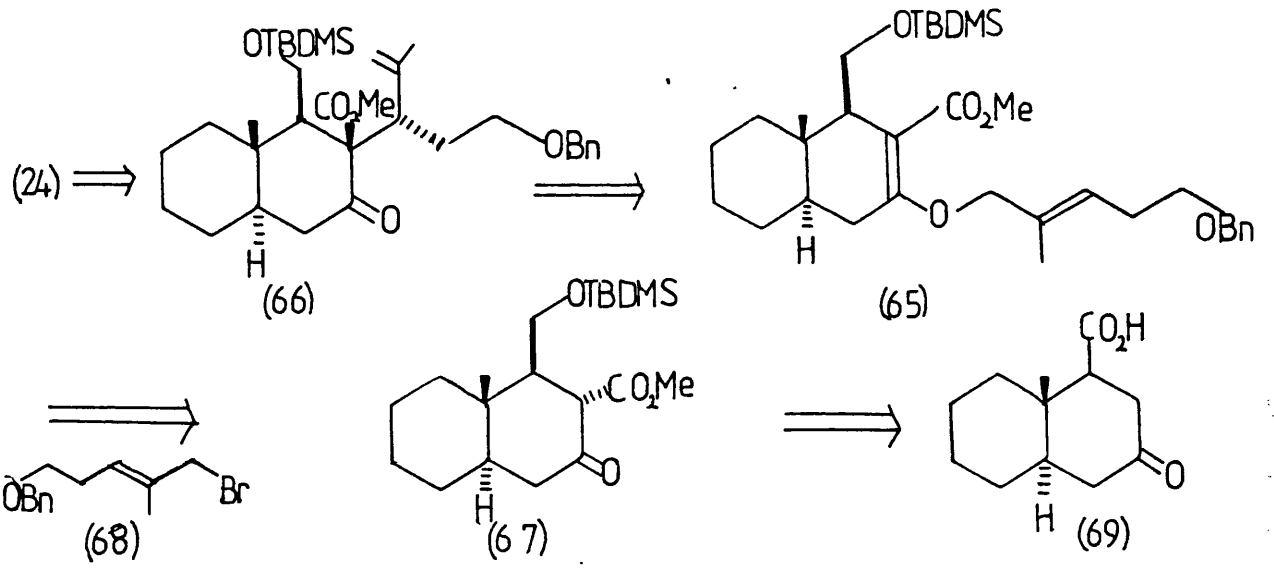
single diene (55), with correct C-14α-configuration. Stepwise reduction (DIBAL) gave alcohol (56), which on selenocyclisation and oxidative elimination gave diene (57).

Whilst diene (57) showed no tendency to rearrange, the hydroxy selenide (58) and allylic alcohol (59) isomerised to the C-11 bridged compounds (60) and (61) respectively, in quantitative yield, on standing at RT, or prolonged exposure to silica gel (Scheme 7). The failure of (57) to isomerise indicates some anchimeric assistance by the C-1 hydroxyl group, an assumption that is supported by the recent discovery of the quassinoid hemiketal karinolide (62).[24]

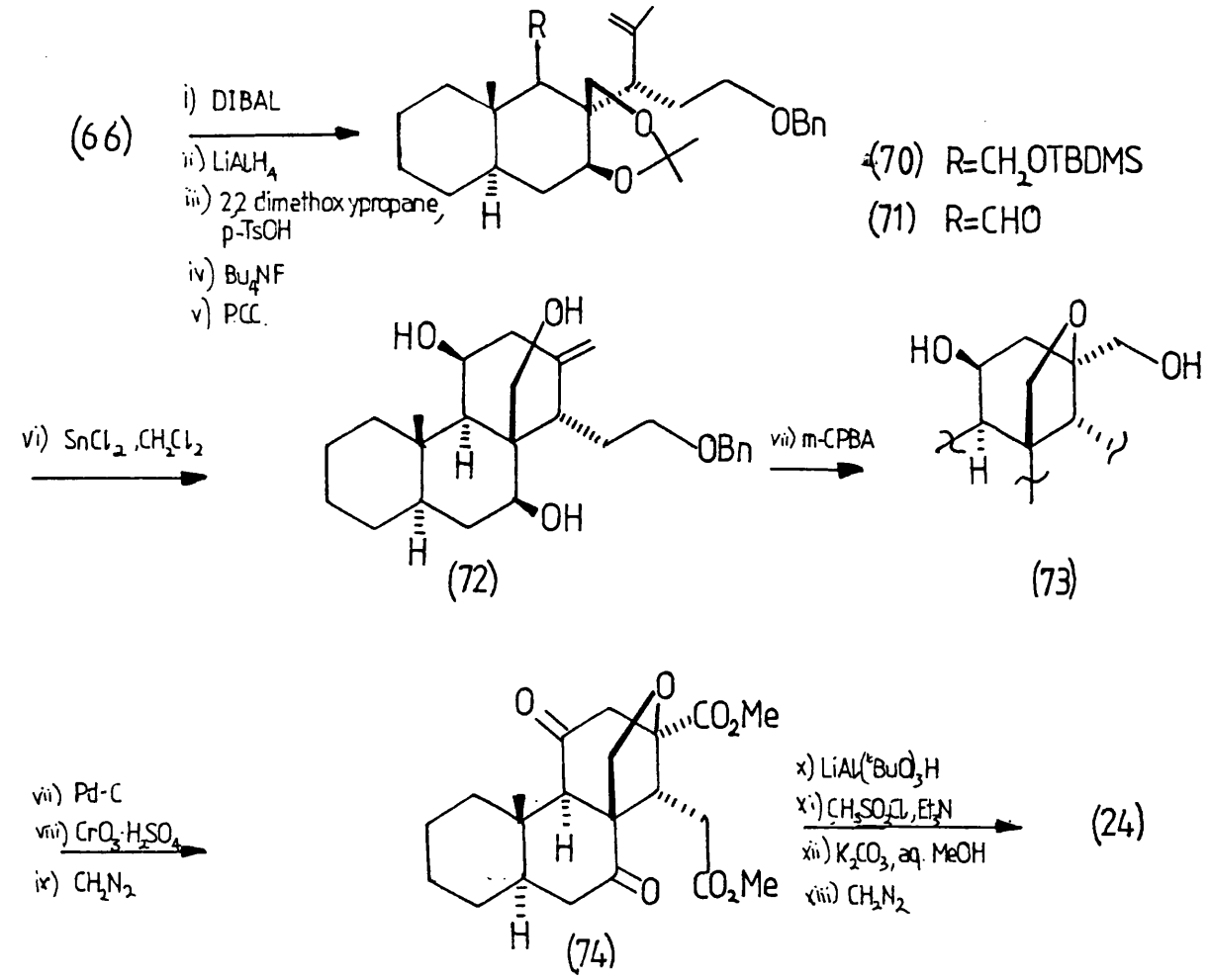
Epoxidation and osmylation of (57) gave the cis diol (63), which was selectively oxidised, reduced and isomerised to the allylic alcohol (64) (Scheme 8). Selective oxidation of the C-1 hydroxyl group gave enone (23), a potentially bioactive quassinoid, whose pharmacological properties are being investigated. Access to the C-11 bridged quassinoids has also been achieved, and these compounds, like glaucarubin (45c) may prove to be of medicinal interest.



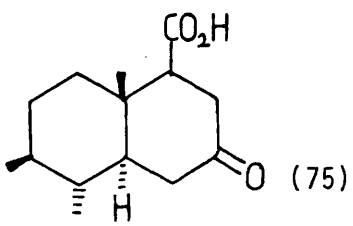
SCHEME 8



SCHEME 9



SCHEME 10



Synthesis of pentacycle (24)

A Claisen-based rearrangement constituted the key reaction in the synthesis of the pentacylic lactone (24) by Ziegler *et al.*[14a] Contrary to the traditional course of steroid and higher terpene synthesis, the issue of stereochemistry was addressed prior to the formation of the rings. Thus allyl vinyl ether (65) was rearranged to β-keto ester (66) in quantitative yield, giving a single diastereoisomer.

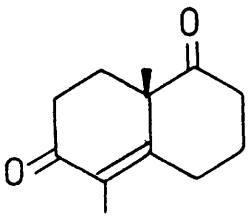
Ether (65) was synthesised in 89% yield from the reaction of the potassium enolate of (67) with allylic bromide (68), with minimal C-alkylation. β-Keto ester (67) was prepared from the keto acid (69), synthesised by the procedure of McMurry[25] (Scheme 9).

Conversion of (66) to (24) was achieved by reduction of (66) to the diol, followed by protection as the acetonide (70). Desilylation and oxidation gave aldehyde (71), which underwent a Lewis acid catalysed ene reaction to give ring-C with concomitant deprotection of the diol functionality (72). Epoxidation led directly to the tetracyclic triol (73), which was converted to diketo-diester (74). Selective reduction gave the equatorial alcohol at C-7 which gave the pentacyclic lactone (24), as shown in Scheme 10.

The use of optically active ketoacid (75) as the starting material could be applied to the synthesis of (-)-bruceantin, using the procedure described above, though C-12α and C-15β-hydroxylation and reduction of the C-11 ketone to the axial isomer as well as completion of A-ring functionalisation would still be required.[14b]

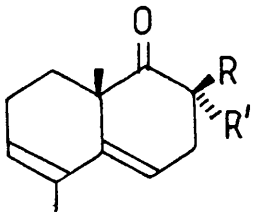
Synthesis of pentacycle (25)

Takahashi and co-workers[15] have synthesised a highly advanced intermediate (25) which has suitable functionality at various positions for synthetic elaboration towards bruceantin and its analogues.



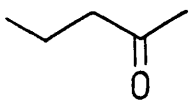
(76)

i) $(CH_2OH)_2$ - p-TsOH
ii) $NaBH_4$
iii) $H^{\oplus}$ - AcOH/MeOH
iv) $(MeO)_2CO$ - NaH - KH
v) MVK

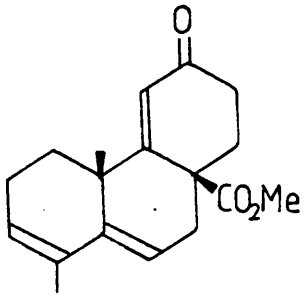


(77) R=R'=H

(78) R=CO_2Me

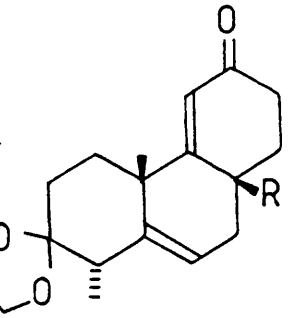
R'= 

vi) m-$MeC_6H_4CO_2H$, C_4H_9N



(79)

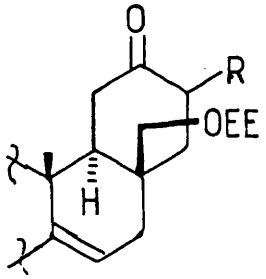
i)
vii) m-CPBA
viii) BF_3·Et_2O
i)
ix) $LiAlH_4$
x) PPTS, Me_2CO



(80) R=CO_2Me

(81) R=CH_2OH

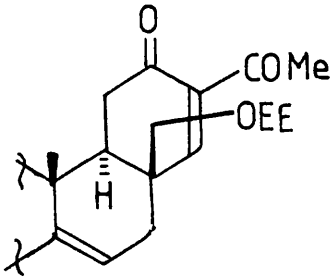
xi) CH_2=CHOEt, PPTS
xii) NaHTe
iv)



(82) R=H

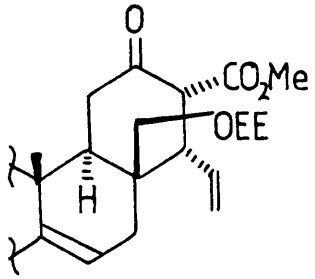
(83) R=CO_2Me

xiii) PhSeNa, H_2O_2



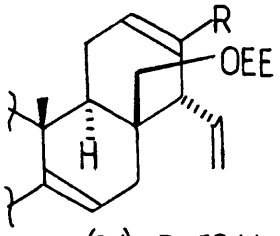
(84)

xiv) CH_2=$CHMgBr$, CuI-n Bu_3P



(85)

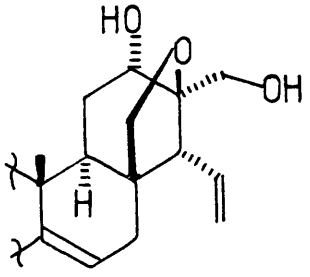
ii)
xv) CH_3SO_2Cl - Et_3N
xvi) DBU
xv) DIBAL



(86) R=CO_2Me

(87) R=CH_2OH

xvi) t-BuOOH, $Ti(OiPr)_4$
xv) PPTS, EtOH



(88)

SCHEME 11

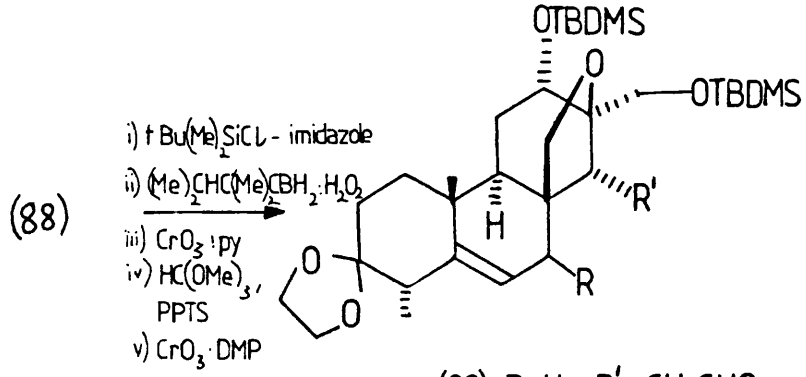
Their product (25) was prepared from dione (76) in 33 steps, 4·9% overall yield.

The monoacetal of (76) was converted to diene (77) by reduction and dehydration, and then carboxymethylation of (77) followed by reaction with methyl vinyl ether gave the Michael addition product (78). Cyclisation of (78) under forcing conditions (metatoluic acid, pyrrolidine, reflux) gave the tricyclic compound (79), with the C-8β substituent in place (Scheme 11).

Epoxidation of the A-ring of the ethylene glycol acetal of (79), followed by Lewis acid treatment gave the acetal exchange product (80). Successive reduction of the diacetal of (80) gave alcohol (81), and the saturated ketone (82) was obtained by NaHTe treatment of the α-ethoxyethyl ether of (81), attack from the α-face providing the desired C-9α-configuration. The ester (83), prepared by carboxymethylation of (82), on phenylselenylation, and oxidative elimination gave (84), which underwent smooth conjugate addition of vinylmagnesium bromide to give the desired 14α product (85).

Reduction, mesylation and elimination of (85) gave conjugated ester (86), which was reduced (DIBAL) to alcohol (87). Regio- and stereoselective epoxidation (t-BuOOH and $Ti(OiPr)_4$) of the C-ring double bond gave the α-epoxide, and treatment with pyridinium p-toluenesulfonate (PPTS) directly gave the diol (88), with concomitant formation of the crucial E-ring ether linkage.

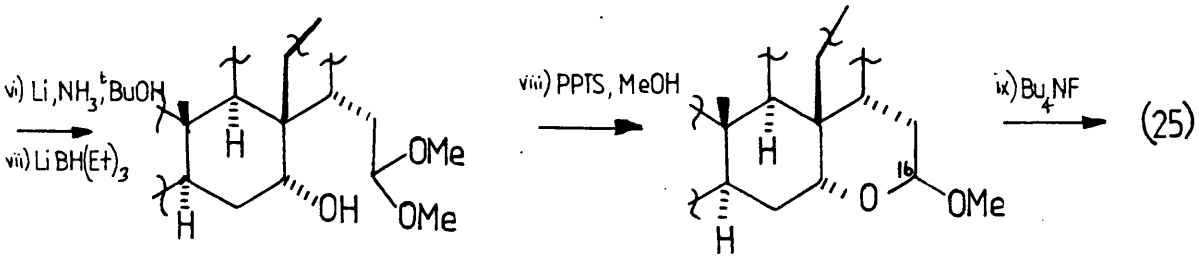
The D-ring lactone was obtained by protection of (88) as the disilyl derivative, hydroboration of the exocyclic double bond, and oxidation of the resulting alcohol to give aldehyde (89). Protection of (89) and allylic oxidation of the remaining double bond gave the enone (90), which underwent reduction to give the correct 5α-ring junction, and hydride reduction of the ketone to the α-alcohol (91).



(88)

(89) R=H, R'= CH_2CHO

(90) R=$=O$, R'=$CH_2CH(OMe)_2$



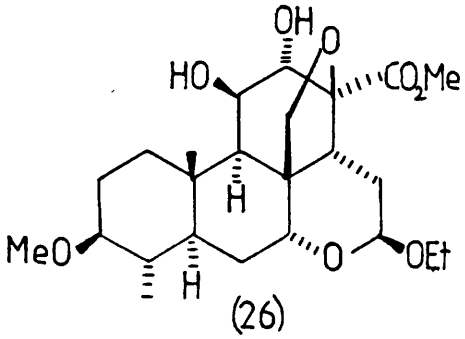
(91) (92)

SCHEME 12

The hemiacetal (92) was then obtained as a 1:1 mixture of stereoisomers at C-16 on PPTS treatment of (91), and fluoride deprotection gave diol (25) (Scheme 12).

Synthesis of pentacycle (26)

The intermediate synthesised by Fuchs,[16] the racemic pentacyclic diol (26) is very similar to Takahashi's final product (25), though Fuchs has additional functionality at C-11, and it remains only to introduce the C-15 side chain, and to complete the functionalisation of the A-ring. The tricyclic γ-silyloxy enone (93) was used as the starting compound, synthesised from 6-methoxy-α-tetralone, as shown in Scheme 13.[26]



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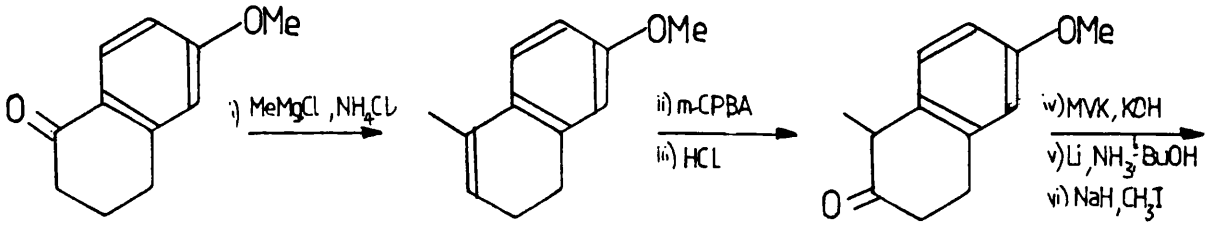
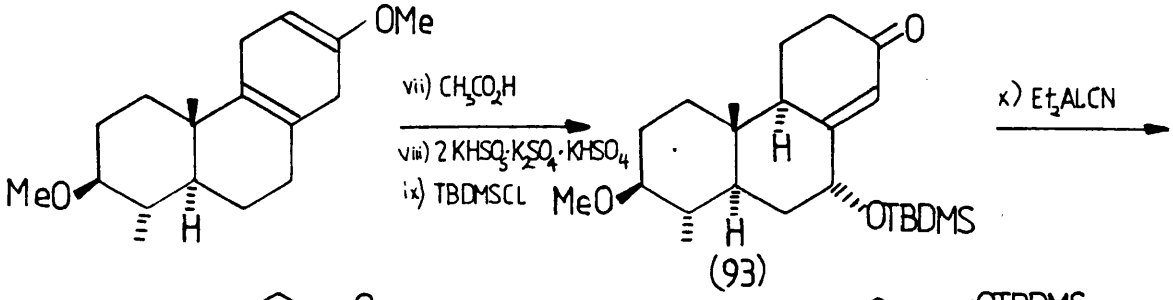
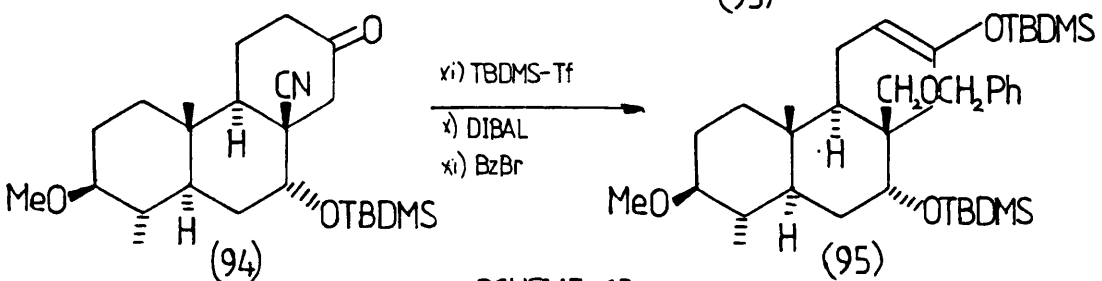


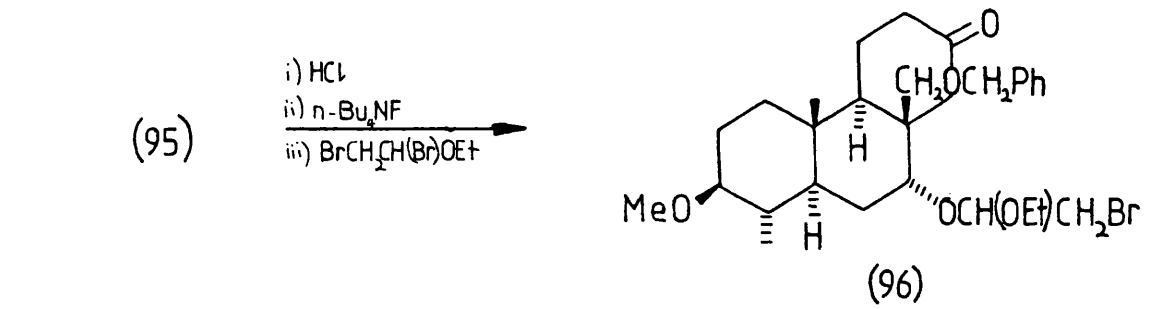


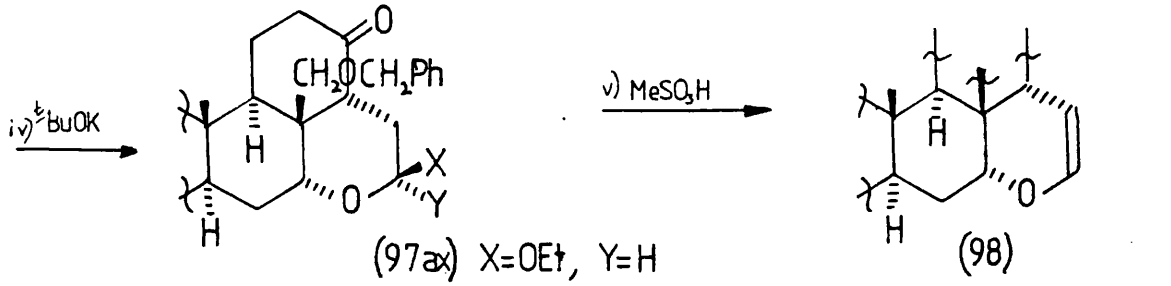
(93)

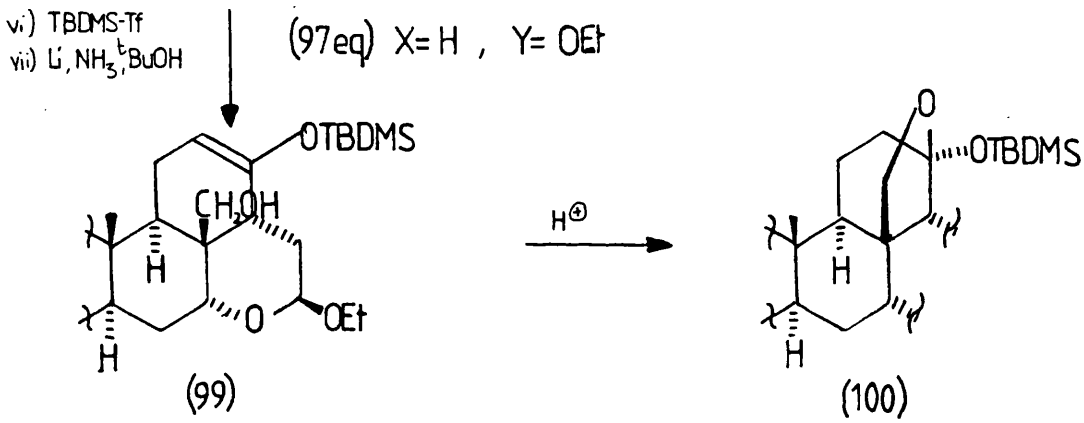


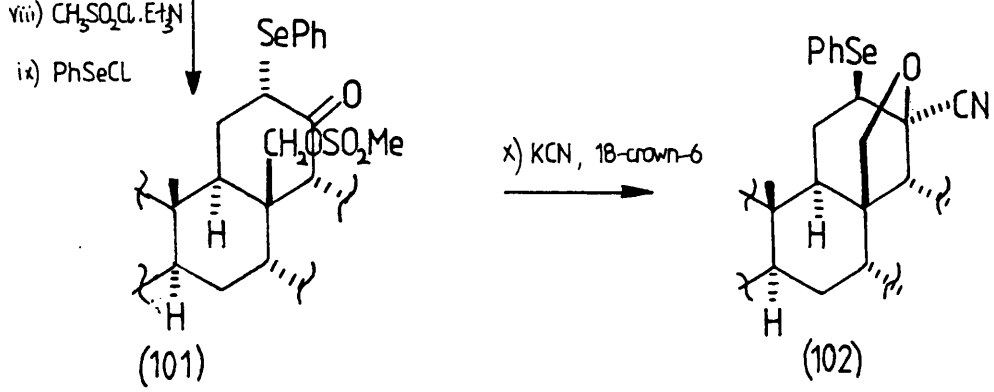
(94) (95)

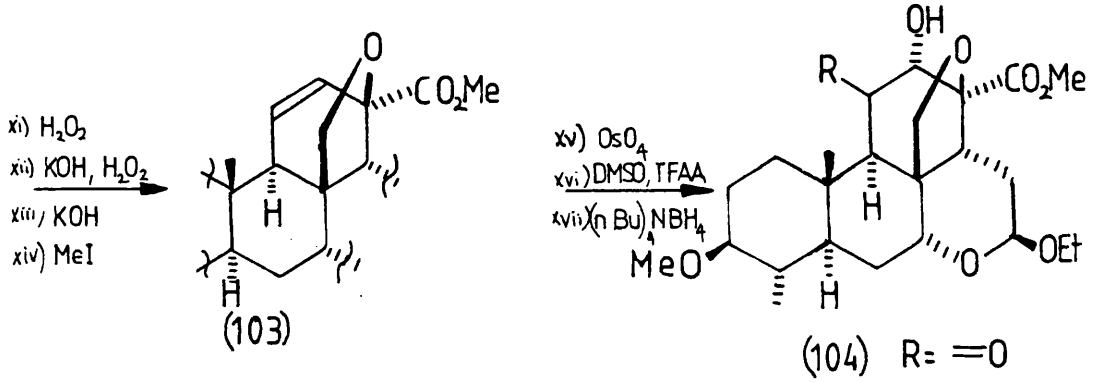
SCHEME 13


(95)
i) HCl
ii) n-Bu4NF
iii) BrCH2CH(Br)OEt
CH2OCH2Ph
MeO
OCH(OEt)CH2Br
(96)


iv) tBuOK
CH2OCH2Ph
X
Y
(97ax) X=OEt, Y=H
(97eq) X=H, Y=OEt
v) MeSO3H
(98)


vi) TBDMS-Tf
vii) Li, NH3, tBuOH
OTBDMS
CH2OH
OEt
(99)
H⊕
OTBDMS
(100)


viii) CH3SO2Cl, Et3N
ix) PhSeCl
SePh
CH2OSO2Me
(101)
x) KCN, 18-crown-6
PhSe
CN
(102)


xi) H2O2
xii) KOH, H2O2
xiii) KOH
xiv) MeI
CO2Me
(103)
xv) OsO4
xvi) DMSO, TFAA
xvii) (n Bu)4NBH4
OH
R
CO2Me
MeO
OEt
(104) R= =O
(26) R= OH H

SCHEME 14

Thus, from this series of ring annelations, a precursor with correct AB trans-fused ring junction, and C-9α-stereochemistry has been obtained. Introduction of a C-8 hydroxymethyl functionality was performed by the Nagata hydrocyanation reagent, Et_2AlCN,[62] giving the axial nitrile (94). After protection of the C-13 ketone as the TBDMS enol ether, the nitrile was reduced *via* the aldehyde to the alcohol, protected as its benzyl ether (95).

Removal of the two silyl protecting groups from (95) generated the hydroxy ketone, and the reaction of the C-7 hydroxyl with 1-ethoxy-1,2-dibromoethane afforded a 1:1 eq:ax mixture of bromoacetals (96), which gave a 3:2 mixture of cyclised acetals (97) on treatment with base (^tBuOK) (Scheme 14).

Reaction of either acetal (97 ax) or (97 eq) with $MeSO_3H$ afforded dihydropyran (98), allowing effective utilisation of the acetal mixture. Acid treatment of (98) gave (97 ax). Carbonyl protection of (97 ax) and O-benzyl cleavage gave the acid-sensitive neopentyl alcohol (99). On standing in $CDCl_3$ or contact with silica gel (99) gave the undesired pentacyclic ketal (100). However, mesylation of (99) and reaction of this with phenylselenyl chloride gave the required α-selenyl ketone (101), which on reaction with potassium cyanide and 18-crown-6 afforded the pentacyclic nitrile (102). Inversion of the centre bearing the phenylselenide group was also observed. This could have occurred either by simple cyanide-catalysed epimerisation, or *via* nucleophilic deselenylation/reselenylation with phenylselenyl cyanide generated *in situ*, but the mechanism of this epimerisation has not been established.

Selenoxide elimination from (102) and hydrolysis, saponification

and methylation of the nitrile gave the methyl ester (103). Functionalisation of the C-11 - C-12 olefin was smoothly accomplished by osmylation, to give the cis-diol, followed by Swern oxidation (in the absence of any base) to give the α-keto alcohol (104). Reduction of (104) (tetrabutylammonium borohydride) gave the trans-diol (26).

Thus (26) was synthesised from (93) in 22 steps, 5% overall yield. Unfortunately, pentacyclic compounds (103) and (26) were found to be devoid of cytotoxic activity in the KB assay at a concentration of 200-600 μg/mL.[27]

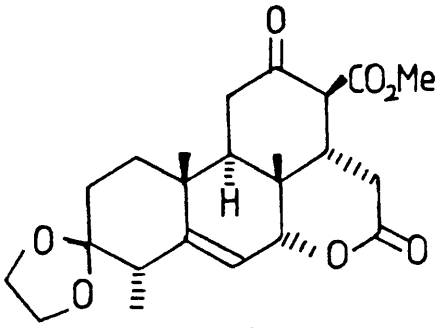
Synthesis of tetracycle (27)

Heathcock and workers have, in early studies on the synthesis of bruceantin, produced a tetracyclic lactone (105), starting from 2-methylcyclohexanone, in 11 steps, 10% overall yield.[28]

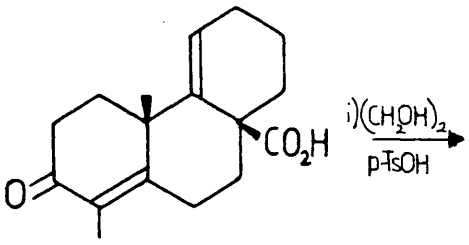
However, attempts to form the C-8 - C-11 ether linkage had proved unsuccessful, and due to these problems an approach to the alternative tetracyclic intermediate (27) was examined, where the E-ring formation precedes the D-ring lactone construction. By using a starting material already bearing functionality at the C-8 position, difficulties previously encountered in remote functionalisations were avoided. Thus the acid (106), prepared in one step from 2-carbomethoxycyclohexanone with 1-chloro-3-pentanone[8] was utilised as the starting material.

The ketal lactone (107) was prepared from (106) under standard ketalisation conditions, and hydride reduction gave the diol (108) (Scheme 15).

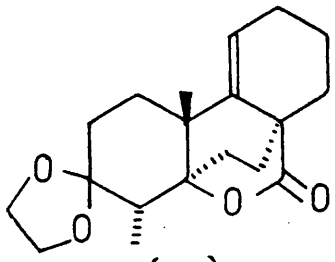
The strategy adopted by Heathcock required introduction of a double bond between C-5 and C-6 in the B-ring, for eventual elaboration of the lactone D-ring. This was achieved by protection of the primary



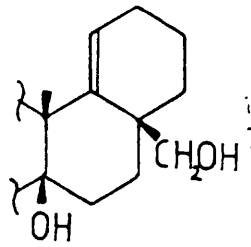
(105)



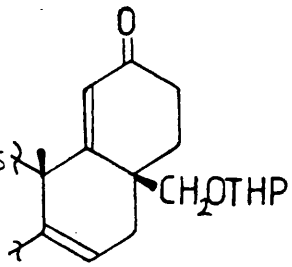
(106)



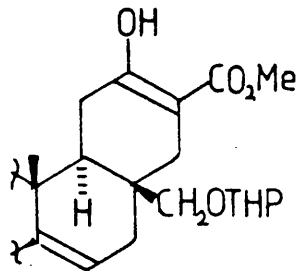
(107)



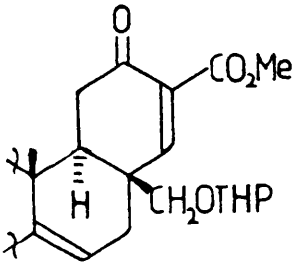
(108)



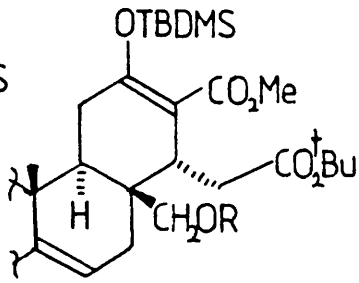
(109)



(110)

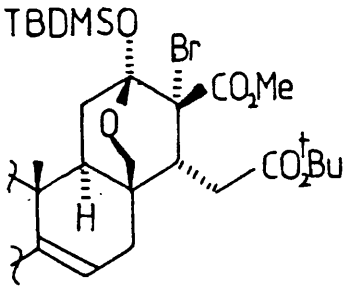


(111)

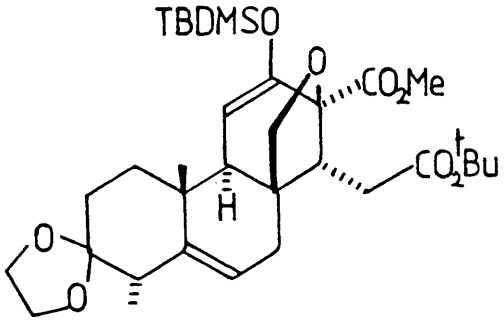


(113) R=THP

(114) R=H



(115)



(116) **SCHEME 15**

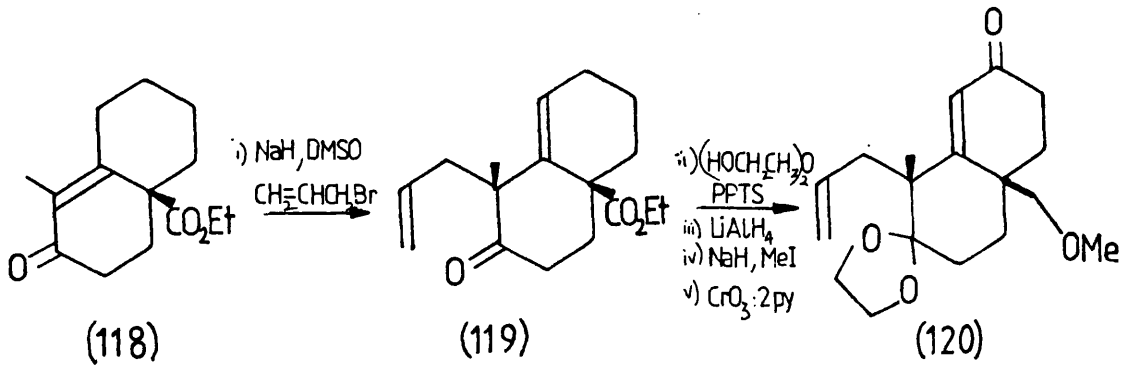
hydroxyl of (108), allylic oxidation at C-12 and dehydration of the tertiary alcohol to give dienone (109). Reduction of (109) [Li/liq.NH_3] and carboxylation using the Stiles procedure (methoxymagnesium methyl carbonate) followed by methylation gave the enolic β-keto ester (110), with the correct C-9α-stereochemistry.

The dehydrogenation of (110) to give enone (111) with the desired C-13 - C-14 double bond, was achieved by refluxing with thionyl chloride and collidine. The proposed mechanism involves sulfinylation at carbon, followed by protolytic elimination of the resulting sulfenyl chloride.

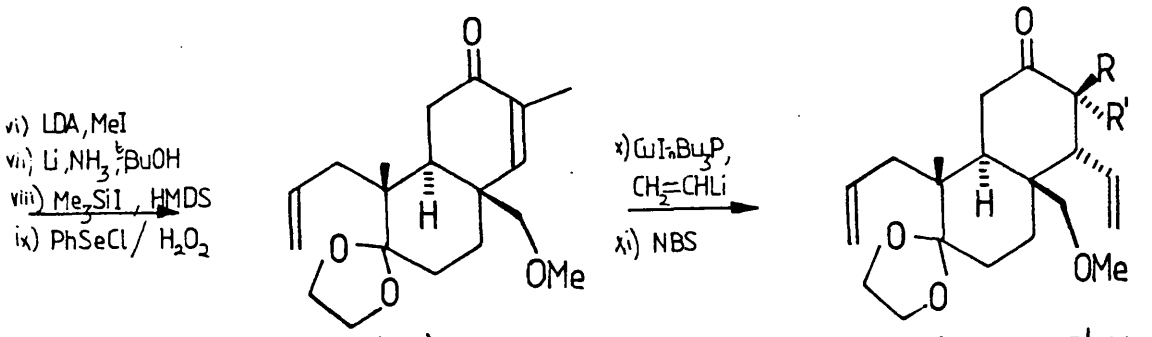
High pressure Michael addition of silyl ketene acetal (112) to enone (111) resulted in the product (113), only the one diastereoisomer, with desired C-14α-orientation being obtained. Formation of the E-ring was envisaged by displacement of a suitable leaving group from C-13, after deprotection of the THP ether in (113). Bromination of the deprotected Michael adduct (114) resulted in the formation of the tetrahydropyranyl ketal bromide (115), with no products resulting from B-ring double bond bromination being observed.

Thermal ring contraction of (115) gave the silyl enol ether (116) in quantitative yield, which was desilylated to give the final product (27) in 13 steps, 3·6% overall yield from (106). The compound (27) has the necessary C-14α-side chain, and C-5 - C-6 double bond to enable construction of the quassinoid D-ring lactone, and thus complete the pentacyclic bruceantin skeleton.

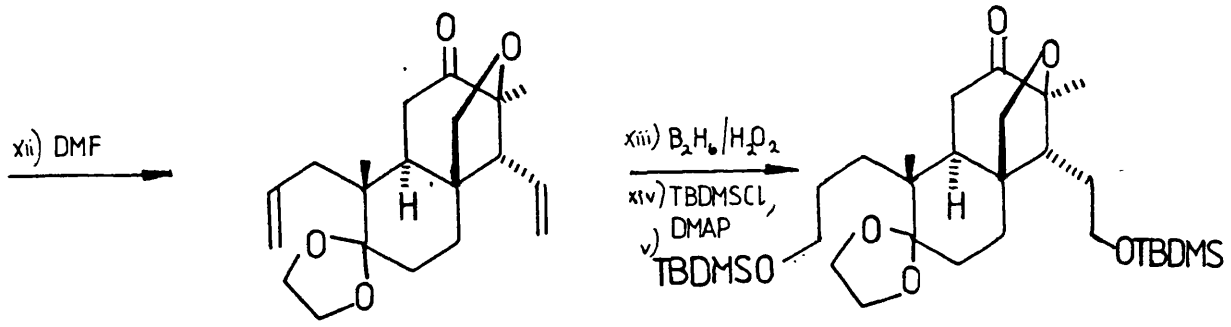
The efforts of Grieco and workers, the only group to have reported the total synthesis of any of the quassinoids, namely (±)-quassin (1) and (±)-castelanolide (9), have been concentrated on the synthesis of quassimarin (8), rather than bruceantin. They have constructed a pentacyclic carbon skeleton (117),[29,30] which has nine of



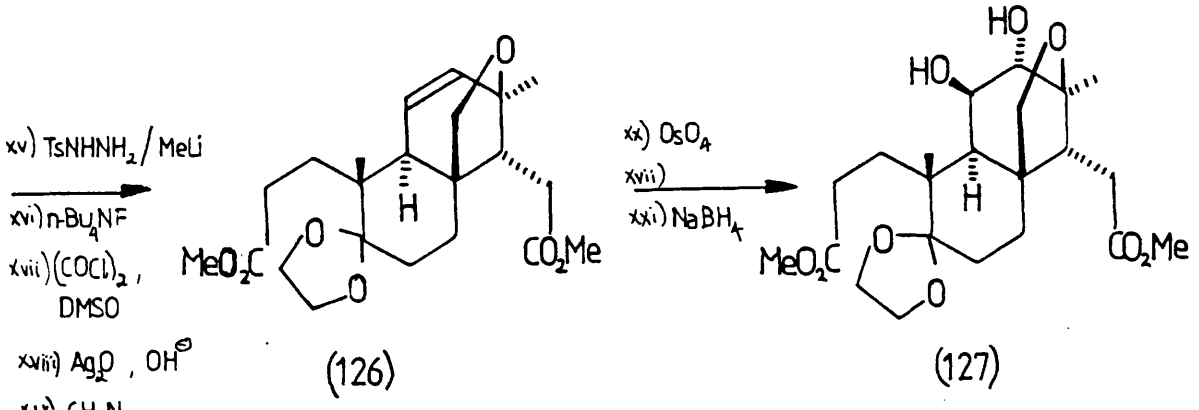
(118) (119) (120)



(121) (122) R=H, R'=Me (123) R=Me, R'=Br



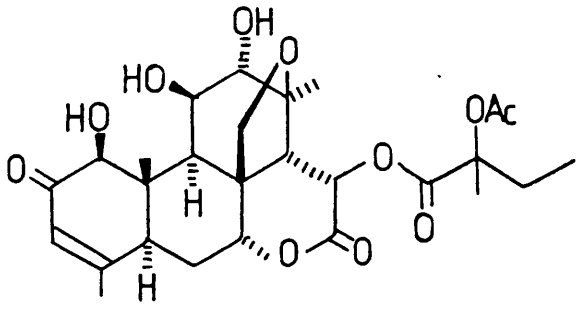
(124) (125)



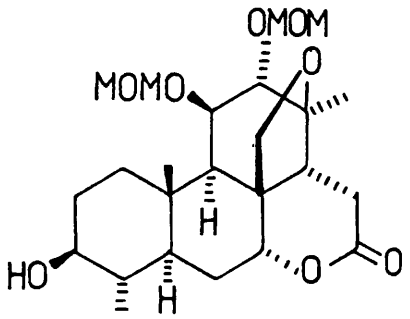
(126) (127)

SCHEME 16

the eleven stereocentres found in the framework of quassimarin. Bruceantin differs from quassimarin in the C-13 and C-15 substituents and the A-ring functionality.



(8)

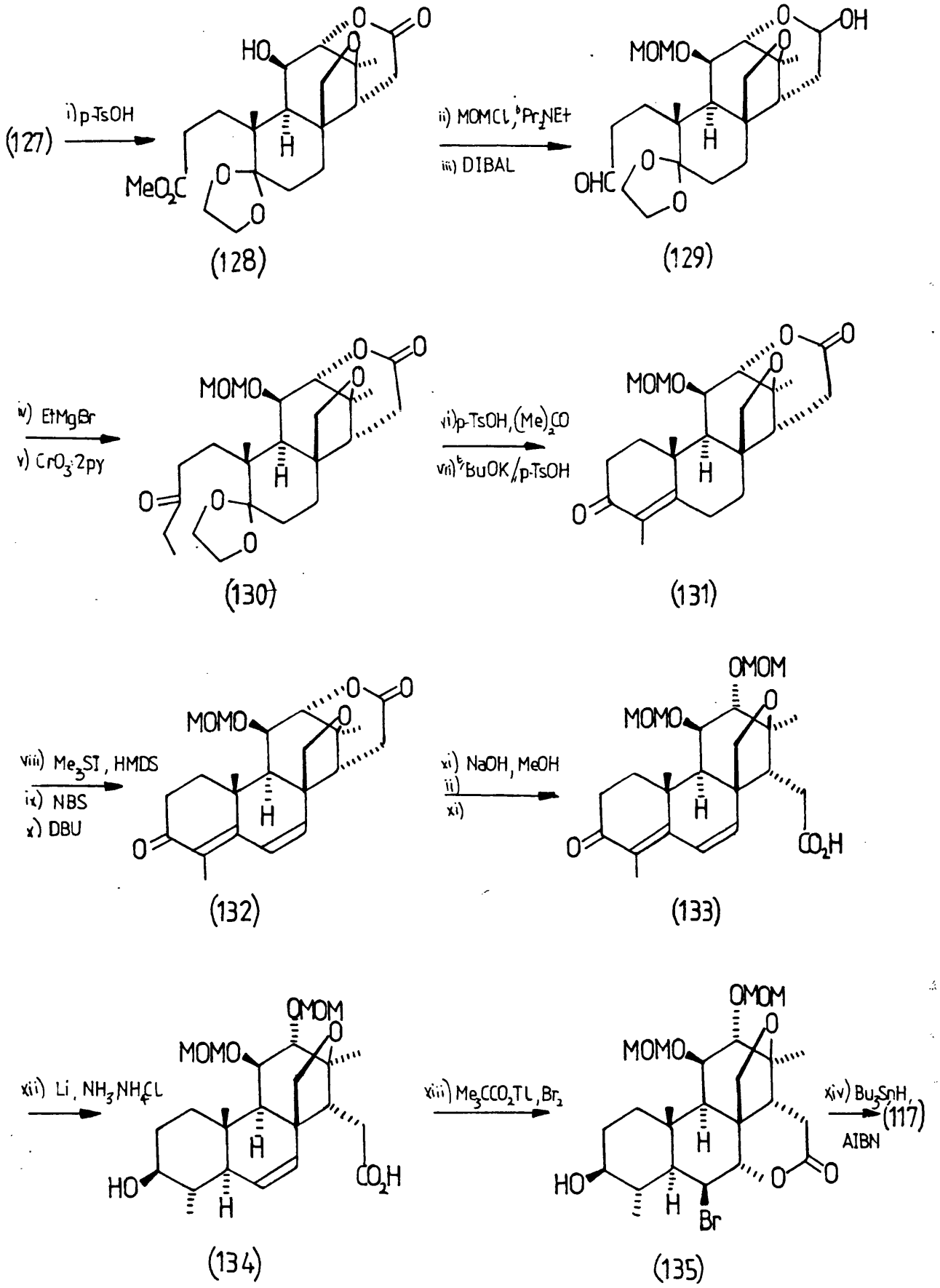


(117)

The strategy involved a BC → BCE → ABCE → ABCDE ring approach. Using the known octalone (118) as the starting material, the ketone (119) was prepared by alkylation with allyl bromide. Acetalisation, reduction and protection of the alcohol as its methyl ether, followed by allylic oxidation gave octalone (120) (Scheme 16).

Alkylation of (120) and subsequent conjugate reduction established the trans relationship between the B and C rings, and introduction of a double bond in the C-13 - C-14 position was achieved by selenylation of the thermodynamic trimethylsilylenol ether, with oxidation and loss of benzeneselenic acid to give (121).

1,4-addition of vinyl-cuprate to the α-face of the molecule


(127)
i) p-TsOH
HO
MeO2C
(128)
ii) MOMCl, iPr2NEt
iii) DIBAL
MOMO
OHC
OH
(129)
iv) EtMgBr
v) CrO3·2py
MOMO
(130)
vi) p-TsOH, (Me)2CO
vii) tBuOK // p-TsOH
MOMO
(131)
viii) Me3SI, HMDS
ix) NBS
x) DBU
MOMO
(132)
xi) NaOH, MeOH
ii)
xii)
OMOM
MOMO
CO2H
(133)
xii) Li, NH3, NH4Cl
OMOM
MOMO
HO
CO2H
(134)
xiii) Me3CCO2Tl, Br2
OMOM
MOMO
HO
Br
(135)
xiv) Bu3SnH, AIBN
(117)

SCHEME 17

provided (122), with the two carbon unit needed for D-ring construction in place. The elaboration of the C-8 - C-13 epoxymethano bridge was accomplished by heating the bromide (123), derived from (122), in DMF at 140°C to give the tricyclic ketone (124).

Conversion of (124) to ketone (125) was smoothly accomplished (B_2H_6/H_2O_2, $^tBuMe_2SiCl$, $CrO_3.2py$), and the tosylhydrazone of (125) upon treatment with excess methyllithium and subsequent deprotection and oxidation gave diester (126).

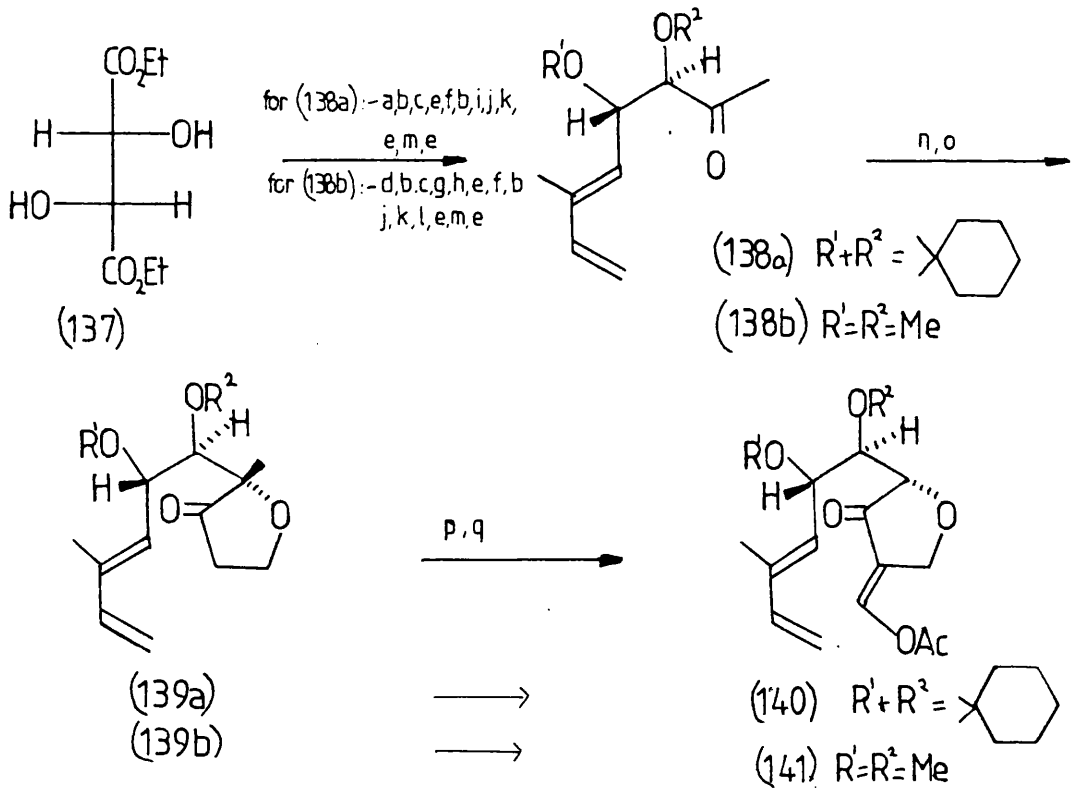
Osmium tetraoxide treatment of (126) generated the cis-diol which was selectively oxidised and reduced to give the BCE tricyclic diol (127).

Lactonisation of (127) allows differentiation between the two ester units, since only the C-12 - C-14 lactone (128) is obtained (Scheme 17). Protection of the C-11 hydroxy group as the MOM-ether, followed by DIBAL reduction afforded the aldehyde-lactol (129), which on addition of EtMgBr and subsequent Collins oxidation gave the keto lactone (130).

Deacetalisation of (130) followed by aldol condensation and dehydration gave pentacyclic enone (131). Introduction of a C-6 - C-7 double bond, for construction of the D-ring lactone was achieved by bromination of the thermodynamic silyl dienol ether of (131), followed by dehydrobromination, to give dienone (132).

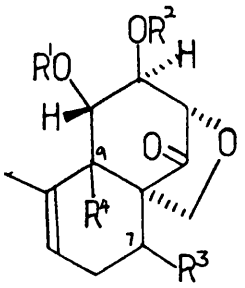
Ring opening of lactone (132) and protection of the 12α-hydroxy group gave carboxylic acid (133). Reduction of (133) [Li/liq.NH_3] gave the tetracyclic alkene (134), with only a small amount of the undesired $\Delta^{5,6}$-isomer. Treatment of (134) with thallium pivalate and bromine gave (135) and subsequent reductive debromination gave the final product (117).

All of the efforts aimed at the synthesis of bruceantin and/or



a) cyclohexanone, p-TsOH, PhH b) $LiAlH_4$, THF c) BnBr, NaH, DME d) MeI, NaH, Et_2O e) Swern ox. f) $Ph_3P{=}C(Me)CO_2Me$. PhH g) $(^tBu)(Me)_2SiCl$, imidazole, CH_2Cl_2 h) Li, liq.NH_3 i) NaH, THF then Li, liq.NH_3 j) MnO_2, CH_2Cl_2 k) $Ph_3\overset{+}{P}MeB\overset{-}{r}$, ^nBuLi, THF l) $^nBu_4NF$ m) MeLi, Et_2O n) α-methoxy-allene, ^nBuLi, $MgBr_2$, THF o) ^tBuOK, ^tBuOH then HCl p) HCO_2Et, NaH, DME q) Ac_2O, py., DMAP, CH_2Cl_2

SCHEME 18



(140) ⟶

(142) $R'+R^2=$, $R^3=\alpha OAc$, $R^4=\alpha H$

(143) $R'+R^2=$, $R^3=\beta OAc$, $R^4=\beta H$

(141) ⟶

(144) $R'=R^2=Me$, $R^3=\alpha OH$, $R^4=\alpha H$

(145) $R'=R^2=Me$, $R^3=\alpha OH$ $R^4=\beta H$

(146) $R'=R^2=Me$, $R^3=\alpha OSOMe$, $R^4=\alpha H$

SCHEME 19

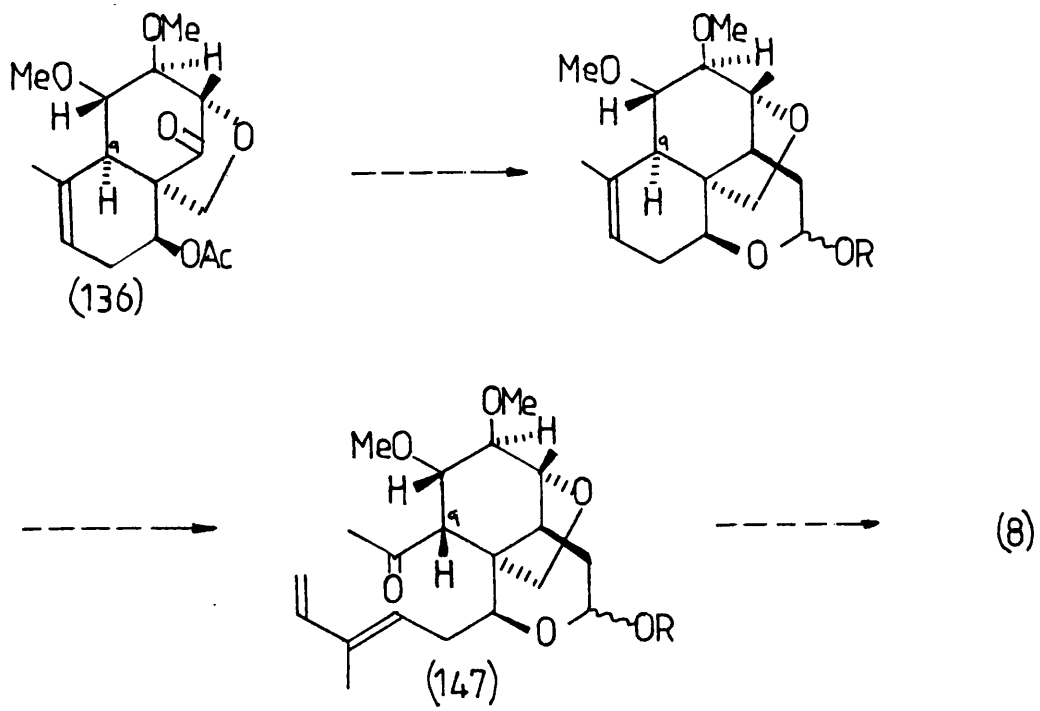
other quassinoid targets have therefore resulted in advanced intermediates with the ABCD & E-skeleton either fully constructed or suitable functionality included for their completion. However, the C-15 side chain has yet to be included, as has the diosphenol unit present in ring A. Another important factor has been the absence of a chiral approach, although Ziegler has addressed this problem.[14b] Fukumoto amd Kametani, as well as synthesising the highly functionalised intermediate (22) have also prepared a tricyclic synthon (136) in optically active form, aimed towards the total synthesis of (-) quassimarin (8).[18] From an economical point of view, the starting material used was L-(+)-diethyl tartrate (137), which would finally be transformed into the enantiomer of natural quassimarin.

An extension of the methodology used in the construction of (22), ie, an intramolecular Diels-Alder reaction, was utilised. Two trienes, a "rigid" one (140) and a flexible one (141) were synthesised from (137) in order to compare the stereoselectivity of the Diels-Alder reaction. Scheme 18 details the sequence of reactions used to construct (140) and (141).

The key-stereoselective construction of the dihydrofuranone moiety in (139) was achieved *via* Mg^{2+}-ion controlled addition of α-methoxyallene to the α,β-dialkoxy ketones (138a) and (138b). Thermolysis of triene (140) (xylene sol^{n}, 180°C, 53 hrs) followed by basic hydrolysis of the resulting acetate gave two isomeric alcohols in 18% and 7% yield, which were independently converted to the acetates (142) and (143) respectively. The major adduct was (142), obtained *via* an endo transition state (Scheme 19).

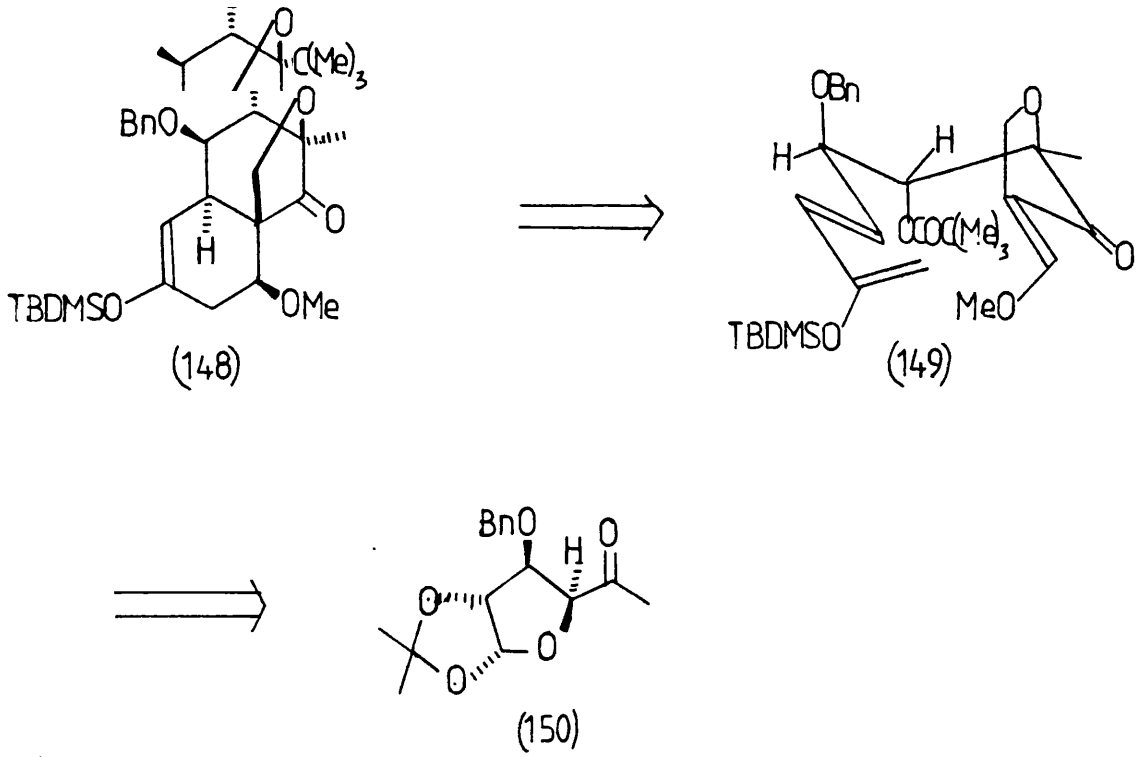
Thermolysis of (141) (toluene, 150°C, 1 hr) gave the alcohol (144) after hydrolysis, along with a trace amount of (145), in a ratio of >30:1 in 85% yield.

Thus both trienes underwent intramolecular Diels-Alder reaction in a highly endoselective manner. Inversion of the configuration of the C-7 in (144) was achieved by mesylation, (146) and treatment with cesium acetate in 18-crown-6 to give the inverted acetate (136). For the eventual synthesis of (+)-quassimarin, the methyl ketone function in (147) should allow epimerisation at C-9 (Scheme 20).



SCHEME 20

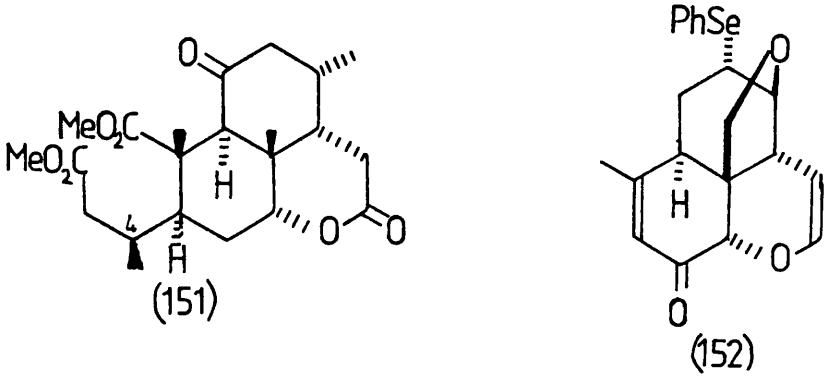
Another approach to the synthesis of (-)-quassimarin has been reported by Schlessinger and Springer.[31] Based upon an exo-selective intramolecular Diels-Alder reaction, they have prepared the chiral tricyclic adduct (148) in 10 steps, 24% overall yield from the methyl ketone (150) (Scheme 21). The Diels-Alder precursor (149) underwent Lewis acid catalysed cyclisation in an exo-mode to give exclusively (148).



SCHEME 21

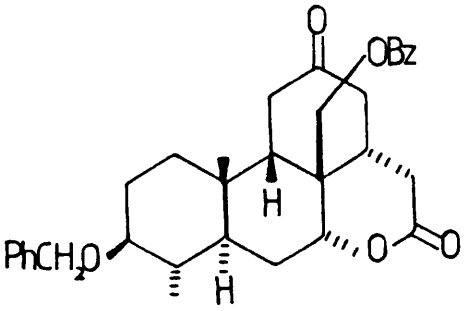
Mention should also be made of the efforts of other workers who have contributed to advances in the synthetic quassinoids field. Valenta and workers[32] have synthesised (151), a ring A seco-derivative of quassin (1). Six of the seven chiral centres of quassin are established in (151), the seventh, C-4, having the incorrect configuration. It is known that quassin derivatives undergo equilibration at C-4 to give compounds with the equatorial (alpha) methyl group.

Vinogradoff and Stevens[33] efforts have been aimed towards bruceantin, and they have synthesised racemic (152) *via* a BC → BCE → BCED strategy.

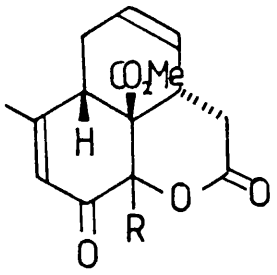


Weller and Stirchak[34] synthesised two BCD-ring tricyclic quassinoid analogues (153) and (154), both of which possess incorrect C-9 stereochemistry, and are readily equilibrated (DBU, THF) to a 2/1 ratio of (153)/(154).

Watt *et al.*, using a Diels-Alder addition of a dienophile incorporating the AB rings to a diene comprising a C-ring progenitor, succeeded in obtaining an ABCD ring intermediate (155), with suitable functionality for elaboration of the E-ring in place. Again, the C-9 stereochemistry requires inversion.



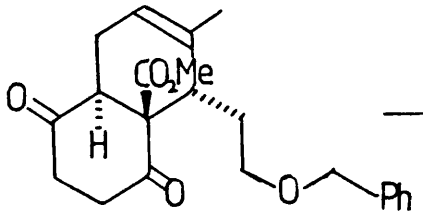
(155)



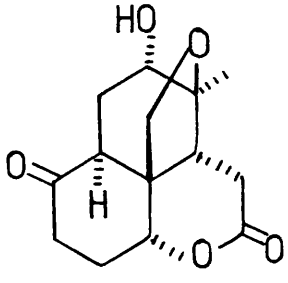
(153) R=αH

(154) R=βH

The tetracyclic BCDE ring system (157) was synthesised by Kraus[35] as a precursor to quassimarin. Using a Diels-Alder reaction of an *in situ* generated quinone the functionalised BC ring precursor (156) was prepared, which was converted in 10 steps, 29% overall yield to (157).



(156)

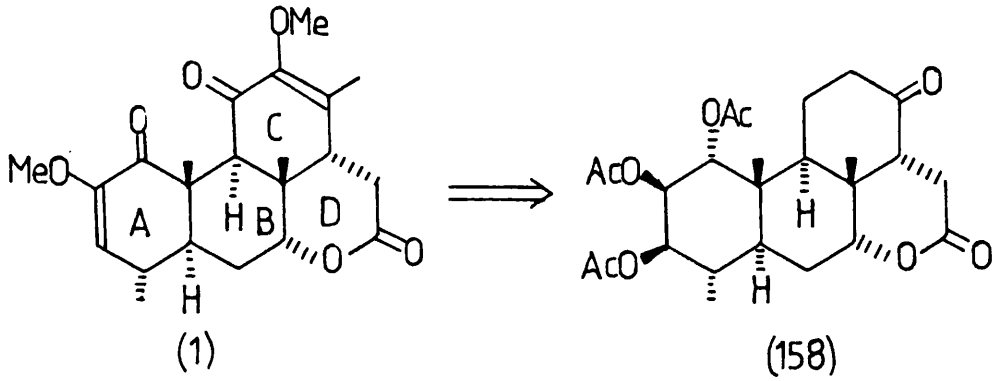


(157)

DISCUSSION

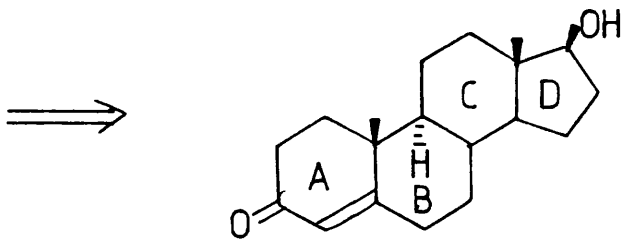
An approach to the synthesis of bruceantin or other quassinoids using a steroid starting material offers several advantages over conventional total synthesis. The stereochemistry of the A, B and C ring junctions in quassinoids is present in the basic steroid nucleus, and by functionalisation and selective degradation of the nucleus, it should be possible to form the pentacyclic bruceantin skeleton. By the use of an optically pure steroid, chirality of the steroid will be retained, and the problems of racemic products, as in Grieco's synthesis of (±)-quassin,[9] would be avoided. Intermediates obtained from a steroid approach could be tested for anti-tumour activity at various stages in the synthesis, thus enabling more to be learnt about the potent activity of these quassinoids.

Graf and Pfenninger have synthesised lactone (158), a key intermediate in the synthesis of quassin (1) in 28 steps, 0·004% overall yield, starting from testosterone (159).[36]



(1)

(158)



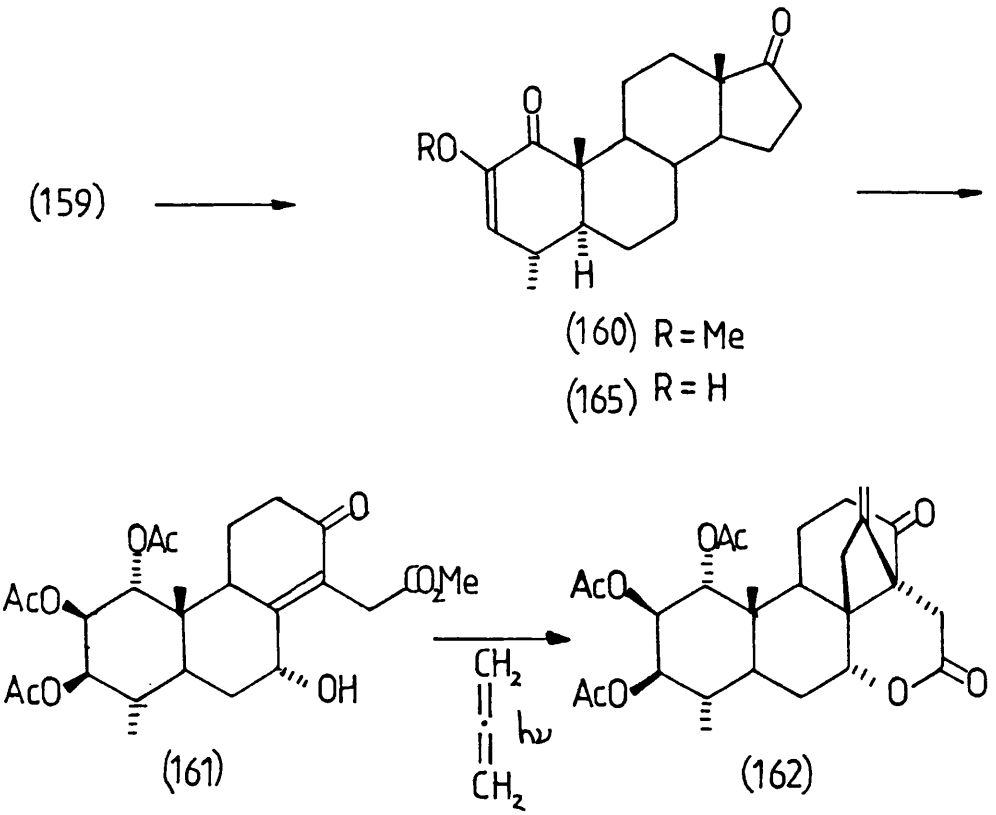
(159)

The strategy employed involved

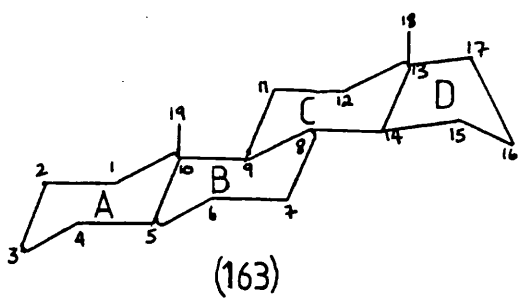
a) the functionalisation of the A ring of testosterone to give the quassin A ring structure (160), although this was found to be too sensitive to carry through the synthesis, and a less advanced functionalisation was utilised.

b) fragmentation of the D ring of testosterone and functionalisation of the C-7 position (steroid numbering, see (163)), to give the key intermediate (161), and

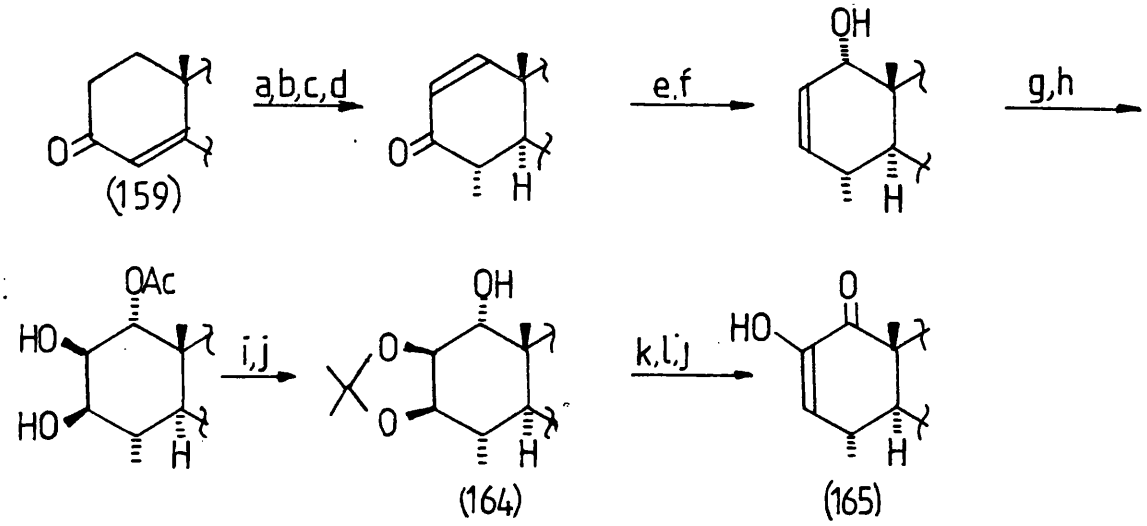
c) the photochemical [2+2]-cycloaddition of allene to the enone functionality of (161) to give (162) (Scheme 22).



SCHEME 22



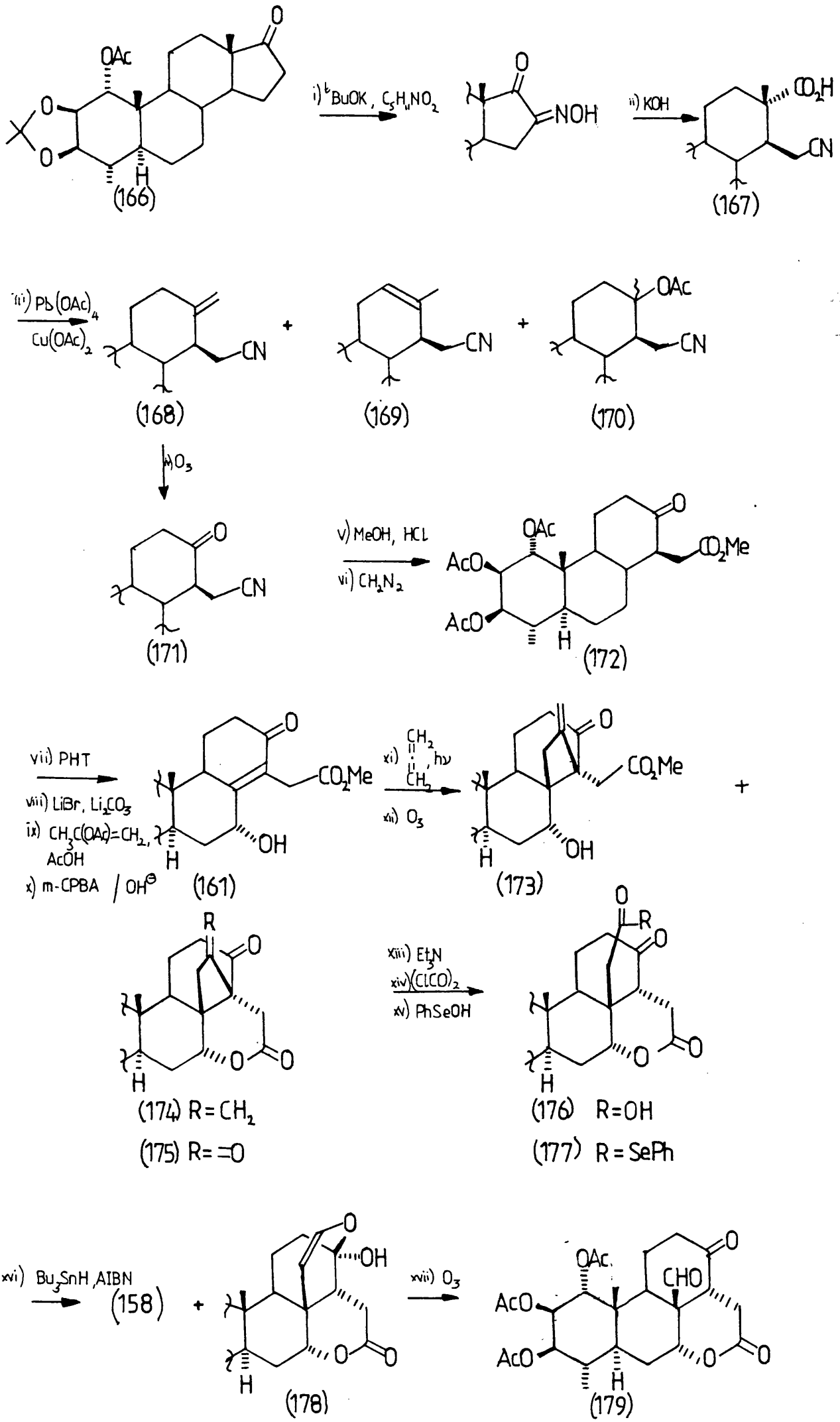
This strategy would also be applicable to the synthesis of bruceantin, although the author's immediate target was quassin. The synthesis of (165) was achieved by a series of reactions shown in Scheme 23.



SCHEME 23

(a) Li/Liq.NH_3, (b) MeI, (c) HBr, (d) LiBr/Li_2CO_3, (e) H_2O_2, base, (f) H_2NNH_2, (g) Ac_2O, (h) OsO_4, (i) NaOH, MeOH, (j) p-TsOH, acetone, Δ (k) PCC, (l) $HClO_4$.

The feasibility of this approach having been demonstrated, the acetylated form of (164) was used for the D-ring fragmentations, since (165) was too sensitive to withstand conditions required for future manipulations of the steroid D-ring. In order to obtain a two carbon fragment at C-14, which, when epimerised, would serve to construct the D-ring lactone moiety of quassin, fragmentation was required between C-16 and C-17 (steroid numbering). This was achieved by condensation of ketone (166) with pentyl nitrite and potassium t-butoxide, to give the oxime group at C-16. Treatment with KOH gave the 16,17-secosteroid-17-acid (167), which on oxidative fragmentation


(166)
i) tBuOK, C5H11NO2
ii) KOH
(167)
iii) Pb(OAc)4
Cu(OAc)2
(168)
(169)
(170)
iv) O3
(171)
v) MeOH, HCl
vi) CH2N2
(172)
vii) PHT
viii) LiBr, Li2CO3
ix) CH3C(OAc)=CH2, AcOH
x) m-CPBA / OH⊖
(161)
xi) CH2, hν, CH2
xii) O3
(173)
(174) R = CH2
(175) R = =O
xiii) Et3N
xiv) (ClCO)2
xv) PhSeOH
(176) R = OH
(177) R = SePh
xvi) Bu3SnH, AIBN
(158)
(178)
xvii) O3
(179)

SCHEME 24

(lead (IV) acetate, and copper (II) acetate), gave a mixture of the exocyclic olefin (168), the $\Delta^{12,13}$-olefin (169), and the substitution product (170). Ozonolysis of (168) gave (171), which was converted to (172) by standard procedures (Scheme 24).

Conversion of (172) to the required 7α-hydroxy-$\Delta^{8(14)}$-enone (161) was accomplished by

i) bromination at the C-14 position

ii) dehydrobromination to give the $\Delta^{8(14)}$- enone, and

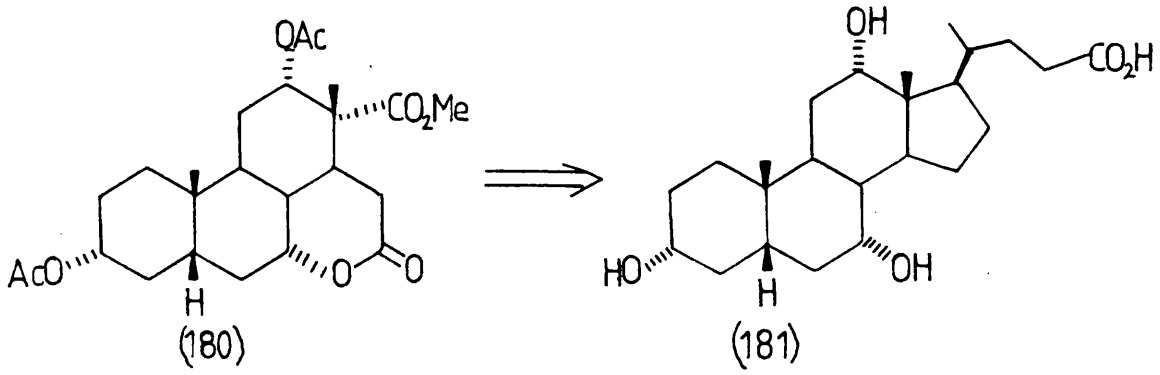
iii) reaction with acetic acid-isopropenylacetate to give the $\Delta^{7,13(14)}$- diene. Epoxidation and base-promoted opening served to insert the 7α-hydroxy group present in (161).

Photochemical addition of allene to the $\Delta^{8(14)}$ double bond served to introduce the 8β-substituent, giving the required β,β-configuration of the resulting cyclobutane ring, (173) (Scheme 24). Lactone formation between the C-14α fragment and the 7α-hydroxy group occurred under the reaction conditions to give (174), confirming the face selectivity of the allene addition. Ozonolysis of (174) gave the unstable diketone (175), which gave (176) on reaction with base. Conversion to the phenylselenylester (177) (*via* the acyl chloride), and degradation of (177) with AIBN initiated reaction with tributyltinhydride, gave a mixture of the two products; the desired 8β-methyl compound (158), and the alkenyl half acetal (178). Ozonolysis of (178) produced (179), a useful intermediate for bruceantin.

Thus a chiral intermediate (158) was prepared, which has all of the chiral centres of quassin in place, and requires only functionalisation of the C-ring, and modification of the A-ring, the methodology for which has already been demonstrated (see Scheme 23).

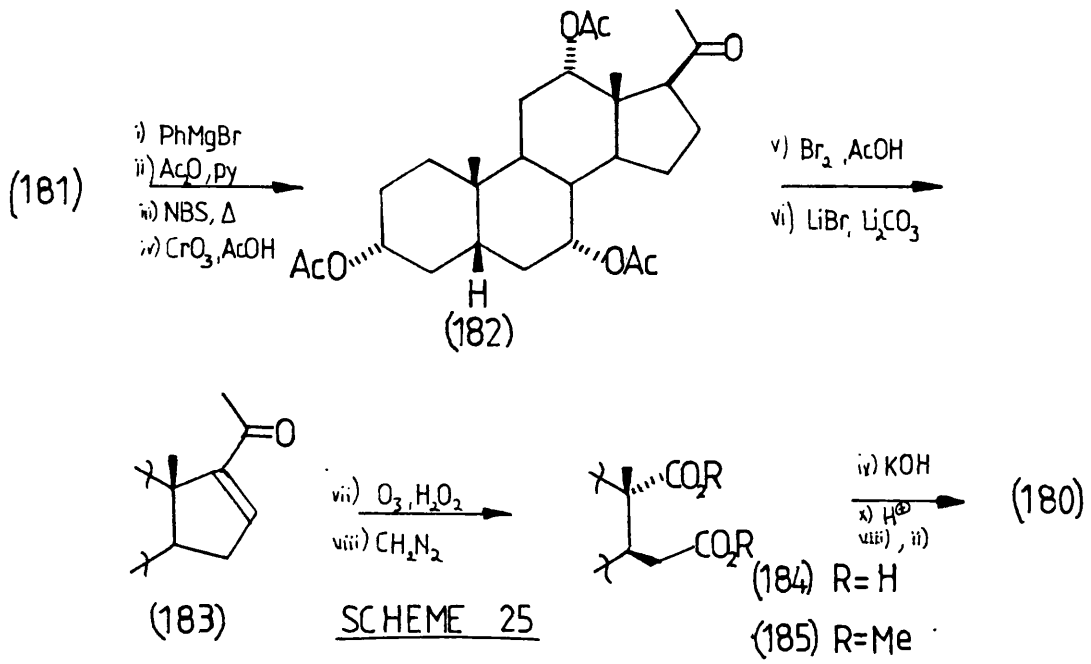
Dias and workers have also reported several studies towards the synthesis of quassinoids, using a steroidal starting material. Their

early work[37] concentrated on the preparation of a tetracyclic skeleton (180), with correct quassinoid stereochemistry at the C-7 position, although the C-14 and C-5 orientations are not those required. Methyl cholate (181) was used as the starting material.



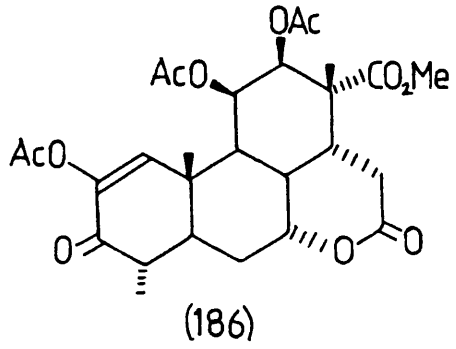
(180) (181)

Barbier-Wieland C-17 side-chain degradation of (181) gave the ketone (182), which by bromination-dehydrobromination was converted to the enone (183) (Scheme 25). Ozonolysis of (183) with oxidative work-up gave the D-seco-diacid (184). The diester (185) was lactonized to give (180), postulated to have rings A and C in chair conformation, and B and D in boat conformation.



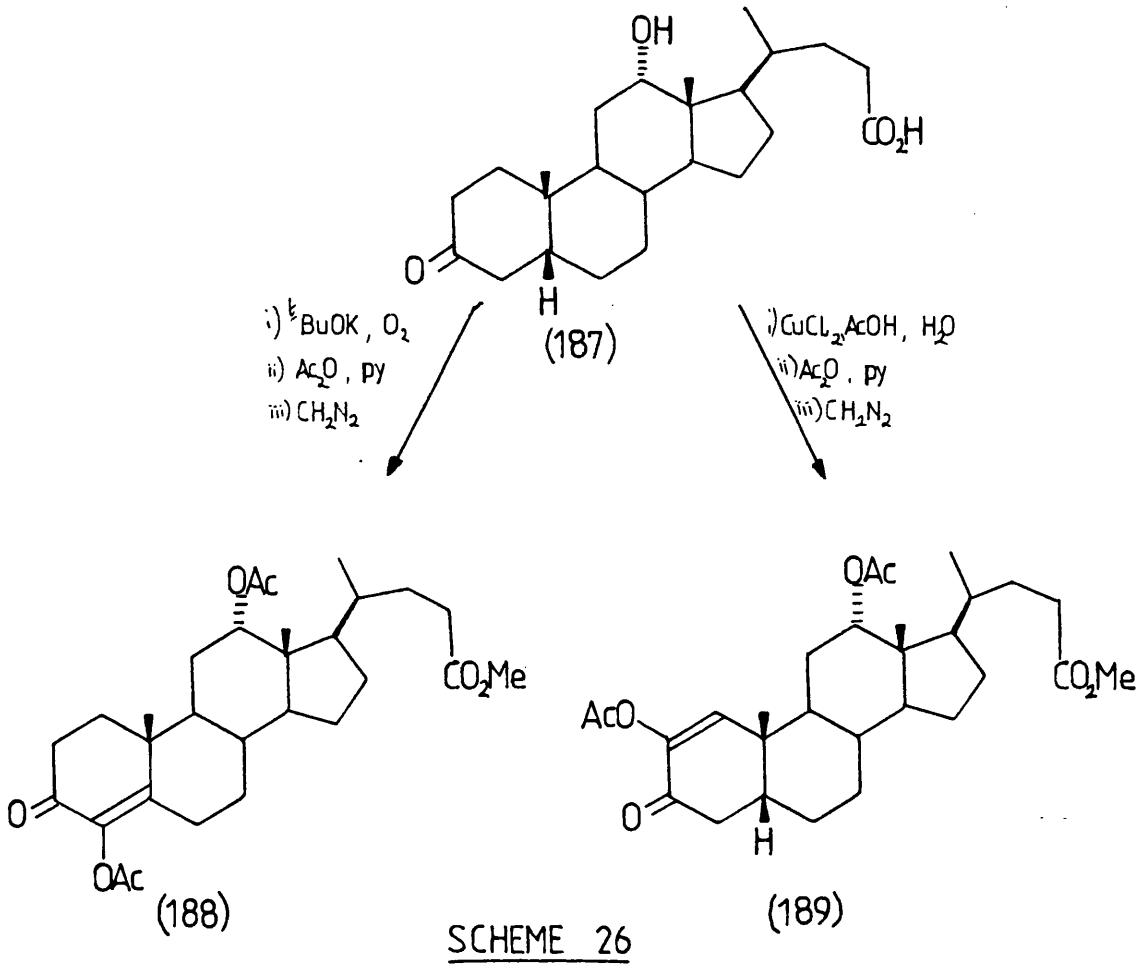
SCHEME 25

In response to reports that the inhibition of P-388 leukaemia in mice by quassinoids is attributable to their A-ring diosphenol system,[38] Dias also studied formation of the A-ring acetate found in the triacetate of bruceosin (186).[37]



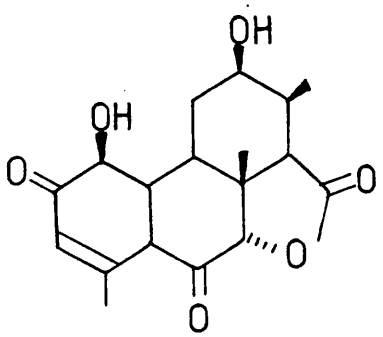
(186)

Deoxycholic acid (187) was converted to the two isomeric A-ring diosphenol acetate derivatives. The 4-acetoxy-3-oxo-Δ^4-steroid (188) was obtained by treatment of (187) with base and oxygen, whilst the 2-acetoxy-3-oxo-Δ^2-steroid (189) resulted from reaction of (187) with cupric chloride (Scheme 26).



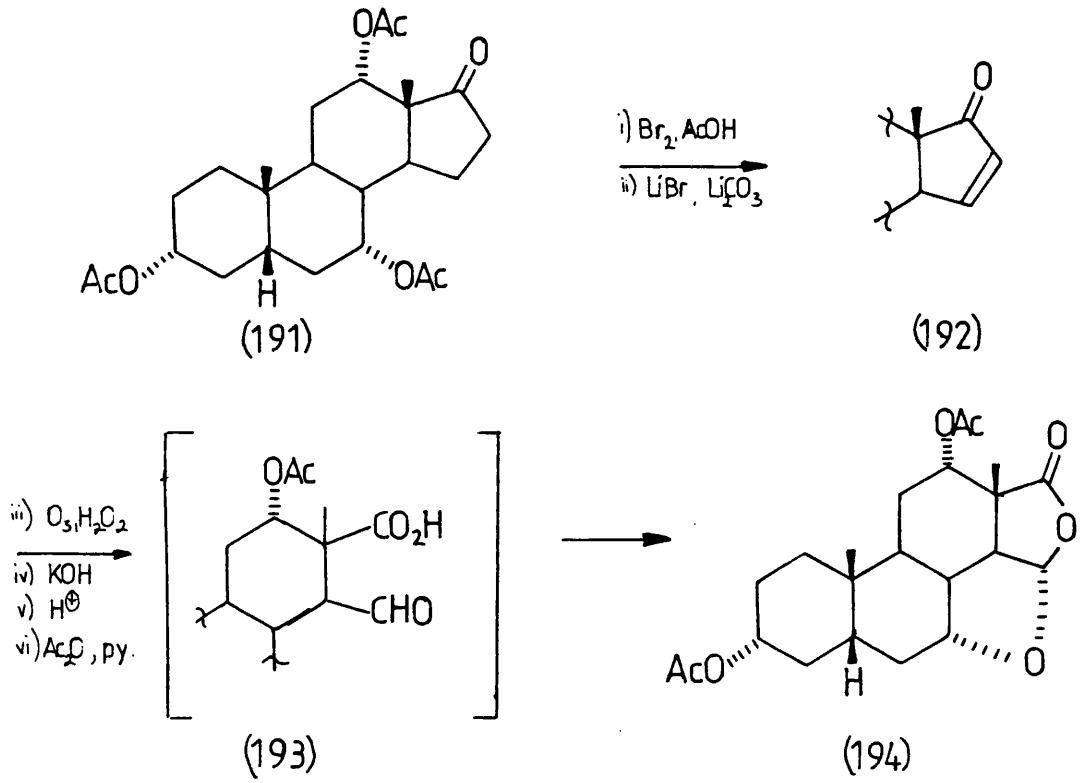
SCHEME 26

Dias' most recent publication on the quassinoids focussed on the D-γ-lactone quassinoid, eurycomalactone (190).[39] This Simaroubacae was isolated from *Eurycoma longifolia* Jack, a bush indigenous to regions of Vietnam, by Thoi and Suong in 1968.[40] Its bark has been widely used in Vietnamese pharmacopaeia.



(190)

Bromination and dehydrobromination of (191), (a by-product from over oxidation during the side-chain degradation of (181)) gave enone (192), which on ozonolysis and oxidative work-up gave (194), *via* the intermediate (193) (Scheme 27). Oxidation of the aldehyde moiety in (193) to an acid, followed by cyclisation to the 7α-hydroxy group should provide the γ-lactone present in (190), and further studies are continuing.



SCHEME 27

The starting material for our approach was (-)-dehydroepiandrosterone (195), a readily available optically pure steroid. Starting with (195), three distinct initial approaches are possible, namely:

a) functionalisation of the A-ring,

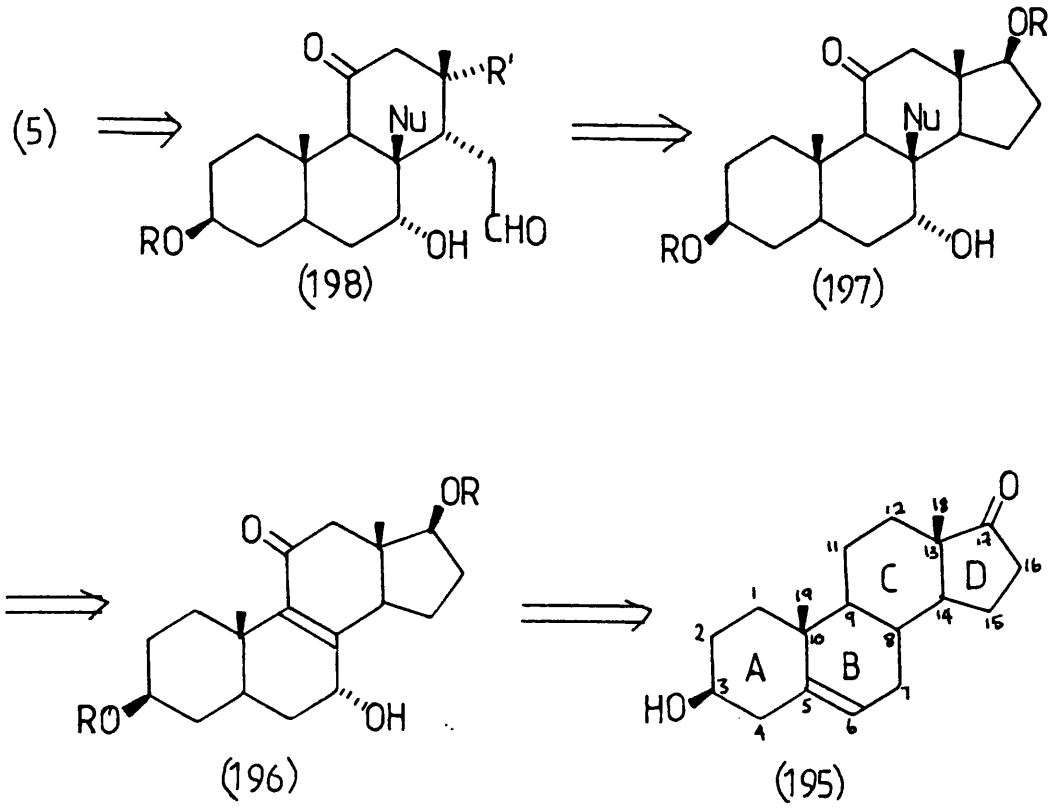
b) functionalisation of the B- and C-rings, with formation of the quaternary centre at C-8 (steroid numbering, see (195)), followed by D-ring fragmentation, or

c) fragmenting the D-ring first.

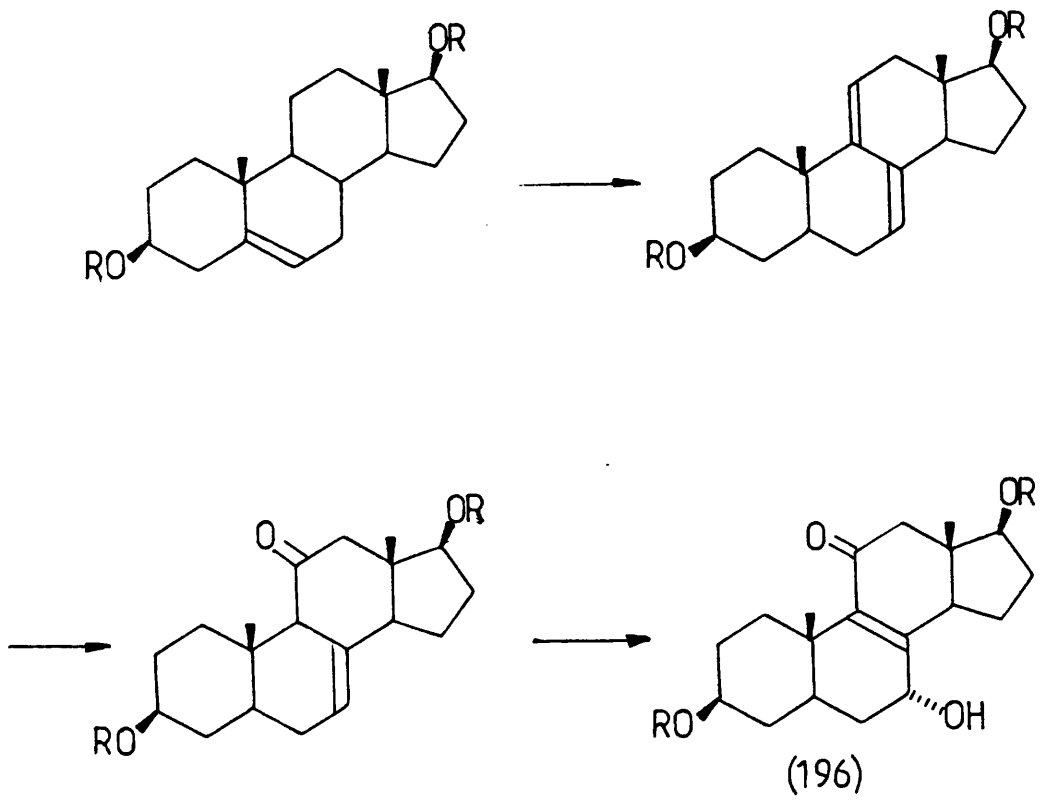
Whichever approach is used, two of the key steps will be

i) Introduction of the β-substituent at C-8, a very hindered position in steroids, due to the two blocking methyl groups at C-18 and C-19, and

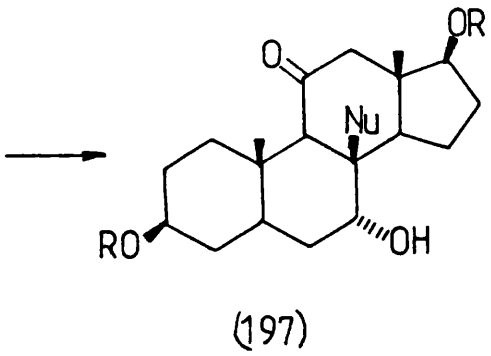
ii) epimerisation of the C-14 position, after D-ring fragmentation, so that the D-ring lactone in bruceantin can be set up with correct stereochemistry (Scheme 28).



SCHEME 28



(196)



(197)

SCHEME 29

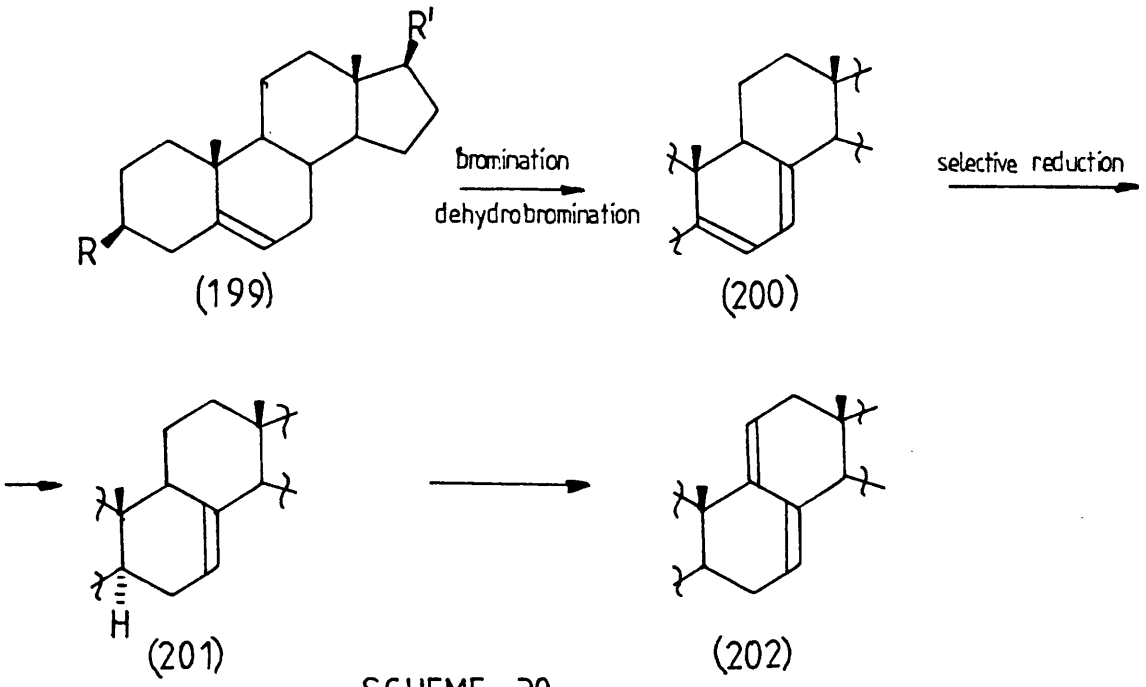
The initial approach pursued was (b), whereby functionalisation of the 7-, 8- and 11- positions would be attained, the C-8β substituent serving as a precursor for the formation of the E-ring ether moiety present in bruceantin. Possible groups providing this 'handle' are methyl or a nitrile, the latter having precedent for introduction at the required position. In order to functionalise the 7- and 11-positions in (195), a series of manipulations must be carried out on the B and C-rings, methods for which are well documented in the early steroid literature. Thus starting from (195), a useful target for the first stage of the synthesis would be (197), obtained *via* (196). Subsequent D-ring fragmentation, with loss of a carbon atom, and epimerisation at C-14 would provide (198), which, on lactonisation would give a tetracyclic skeleton, with functionality for the C-8 - C-13 ether linkage in bruceantin in place.

The A ring in bruceantin is relatively unstable, and sensitive to forcing conditions, and for this reason it was felt that, providing a suitable functionality was retained in ring A, these transformations could be best achieved after formation of the basic tetracyclic skeleton.

A proposed schematic approach to intermediate (197) is shown opposite in Scheme 29.

FUNCTIONALISATION OF THE B-AND C-RINGS

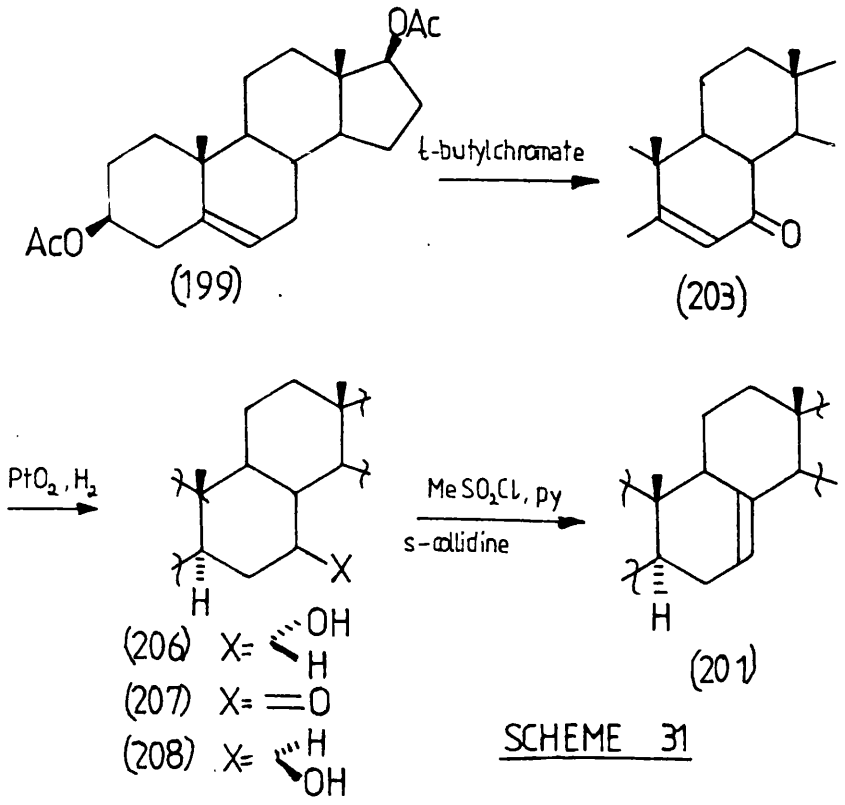
The $\Delta^{7,9(11)}$-diene (202) can be synthesised from (199) by several routes, one of which involves formation of the $\Delta^{5,7}$-diene (200), and selective reduction of the Δ^{5}-bond to give the Δ^{7}-ene (201), as shown in Scheme 30.[41,42]



SCHEME 30

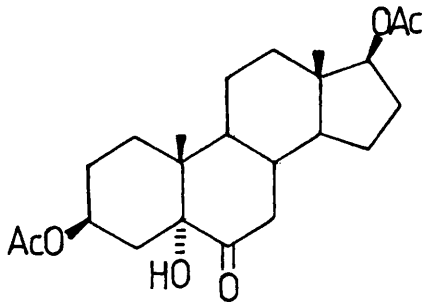
Dehydroepiandrosterone (195) was acetylated (Ac_2O, Δ), to give ((199), R=OAc, R'=O) in 97% yield. Attempted bromination with N-bromosuccinimide/hν gave only very low yields (10%) of the required 7α-bromo compound, despite literature reports of 61% yield.[41] Elimination of this bromide with either s-collidine[43] or trimethyl-phosphite[44] gave a colourless solid which decomposed rapidly on storage, even at low temperature. Isomerisation of the $\Delta^{5,7}$ diene[45] and/or oxidation was thought to be the cause of this decomposition, and due to this instability, an alternative route to the Δ^{7}-ene (201) was

developed. The method of Heusler and Wettstein,[46] shown in Scheme 31 was employed.

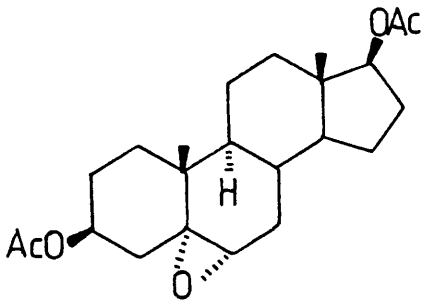


SCHEME 31

Dehydroepiandrosterone (195) was reduced ($NaBH_4$/EtOH) to give the 3,17-dihydroxy compound, then acetylated (Ac_2O, Δ) to give ((199), R=R'=OAc) in 65% overall yield. Oxidation of (199) (CrO_3, *t*-butanol) gave (203) in 60% yield. Two other compounds (204) and (205) were also isolated from this reaction in ≈5% yield each. Heusler[46] also isolated 3β,17β-diacetoxy-5α-oxy-6-ketoandrostane (204), though their assignment is based on UV and IR data only.

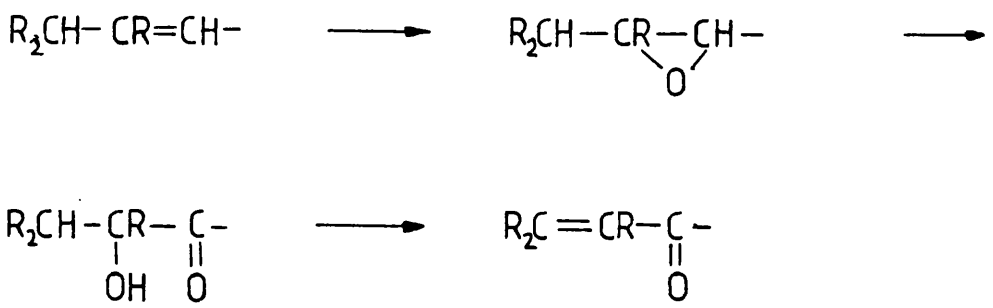


(204)



(205)

Our assignment of structure (204) was based on ^{1}H NMR, and 2D COSY, these spectra being consistent with (204), although it was difficult to unambiguously assign the stereochemistry at the C-5 centre. The structure of epoxide (205) was assigned on the basis of 2D COSY, where the 6β-proton, a doublet at δ 3·08 (J=2·3 Hz) was seen to be coupled to the 7β-and 7α-protons. N.O.e. spectra, with irradiation at H-9, showed no enhancement of H-6, confirming its β-orientation. The formation of (204) and (205) in chromic acid oxidations has been reported by Fieser,[47] where they postulate the following sequence of oxidation.

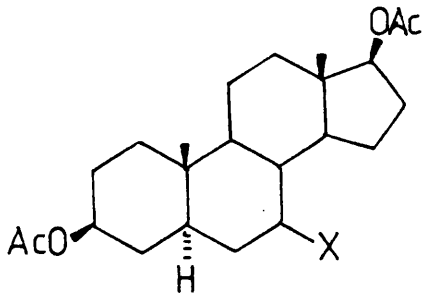


They state, however, that epoxides such as (205) are very rarely isolated under these conditions, due to their sensitivity to chromic acid. Attempts to convert (205) to (204) under the reaction conditions were unsuccessful, probably due to the difficulty in obtaining the

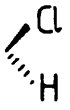
exact conditions required on a small scale.

Hydrogenation of enone (203) (H_2/PtO_2), gave the 7α-alcohol (206), *via* the ketone (207). Heusler[46] reports the formation of the 7β-alcohol (208) under the reaction conditions, but in our hands only the 7α-alcohol was isolated, in 67% yield. On a large scale (>10 g), the ketone (207) could be isolated, but on smaller scales, hydrogenation continued through to the alcohol. On prolonged reaction time, a third compound was obtained, with similar polarity (tlc) to (206) which was assumed to be the 7β-alcohol (208). That the main product (206) was the 7α-alcohol (axial), was confirmed by NMR where the signal due to the C-7 equatorial proton showed no large axial-axial coupling constants, the couplings being of small magnitude (J=4·0 and 2·8 Hz).

Also isolated from this hydrogenation was the totally reduced compound (209), in 2% yield.



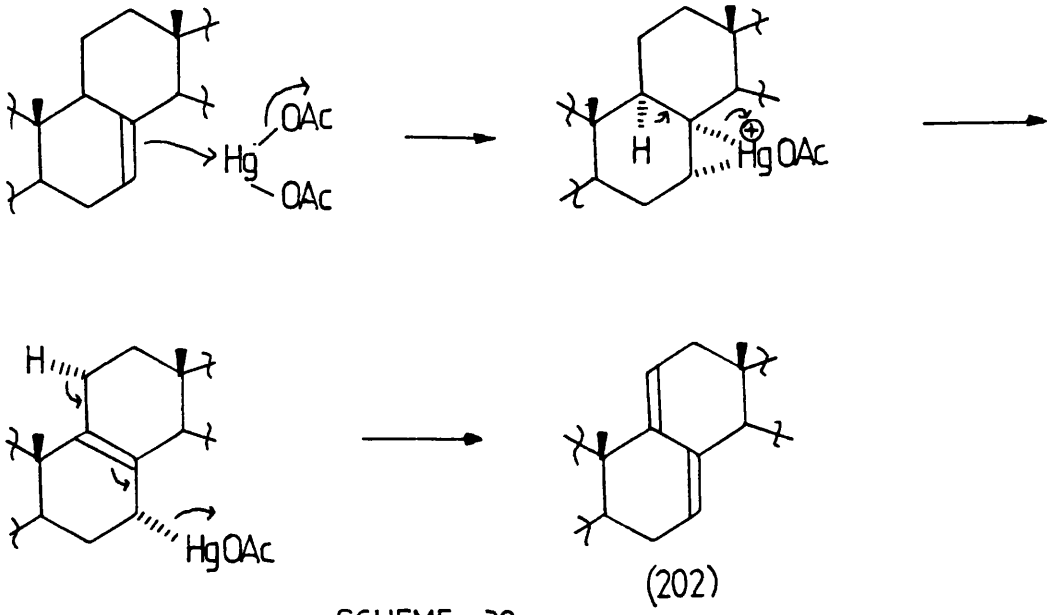
(209) X = H_2

(210) X = 

Mesylation of (206) proceeded smoothly, but on heating with s-collidine in toluene at reflux for 12 hours to give (201), the conditions employed by Heusler,[46] considerable amounts of a by-product, tentatively assigned structure (210), were isolated (≈20%). It was found that reflux for 6 hours provided the Δ^7-ene (201) in fairly good yield (55% from (206)), with only trace amounts of (210).

At this stage, repetition of literature work had proved successful, yields obtained being similar to those reported, although several

by-products had also been isolated and characterised. The next stage involved mercuric acetate oxidation of Δ^{7}-ene (201) to the $\Delta^{7,9(11)}$ diene ((202), R=R'=OAc). The proposed mechanism is shown in Scheme 32.



(202)

SCHEME 32

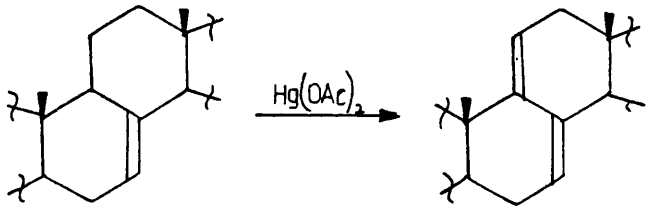
This reaction has been reported to proceed smoothly in 95% ethanol to give the diene (202) in 46% yield.[46] However, in our hands, considerable difficulties were encountered in trying to repeat the yield obtained in this report. On attempting this reaction, a u.v. active spot was observed by t.l.c., which was coincident with the starting Δ^{7}-ene. Separation of this mixture using various solvent systems was unsuccessful. It was assumed that the u.v. activity was due to the diene, but the extent of reaction was obviously difficult to follow. The literature[46] quotes a melting point for the diene very close to the Δ^{7}-ene (127-125°C and 131-133°C respectively), and by repeated recrystallisation of the reaction product, a small sample (≤5% yield) of diene of reasonable purity was obtained, which was

characterised by usual methods. Recovery of the Δ^7-ene (201) was very low (≈30%). In an attempt to improve this reaction, mercury (II) trifluoroacetate was used in place of mercury (II) acetate, with trifluoroacetic acid, and although the reaction appeared to be considerably faster, the extent of reaction was again difficult to judge, and several more products were observed. HPLC was used to monitor the reaction, but, again, purification of the product was difficult. The problems encountered at this stage necessitated optimisation of the different parameters involved (molar excess of $Hg(OAc)_2$, temperature, reaction time). Since ultra violet absorption data for the diene was available in the literature,[46] quantitative u.v. spectroscopy was used to determine the percentage diene in the product, the time at which each reaction was worked up being judged by the u.v. intensity of the product on t.l.c. The Δ^7-ene (201) does not absorb in the region of the diene absorption (235, 242 and 250 nm), allowing the intensity of the peaks obtained to be directly related, using the log ε value for each peak, to the concentration of diene in the product mixture. These calculations showed that, in an exact repetition of the literature procedure, as little as 5% diene was present in the final mixture. Optimisation through parameter changes produced no increase on 5% (202) : 95% (201).

At this stage, it was discovered that another group[48] had had very similar problems with this oxidation, and had found that the use of 95% ethanol prepared from absolute ethanol diluted with 5% water, instead of commercially available 95% ethanol, dramatically increased the rate of reaction. Recrystallisation of the $Hg(OAc)_2$ from glacial acetic acid had also proved helpful. It was proposed that the methanol found in commercial 95% ethanol in some way inhibited the reaction, although the exact reason is not known. Table 1 shows the

results of sample reactions carried out in the series, and it can be seen that just by the change of solvent suggested, a four-fold increase in % diene is obtained. Comparison of experiments 4 and 5 shows that addition of a 4·6 molar excess of $Hg(OAc)_2$ over 140 hours in 2 x 2·3 molar additions results in a greater conversion to diene than the addition of 4·6 molar excess over 70 hours. Heating (experiment 6) does not improve the yield of this oxidation.

TABLE 1

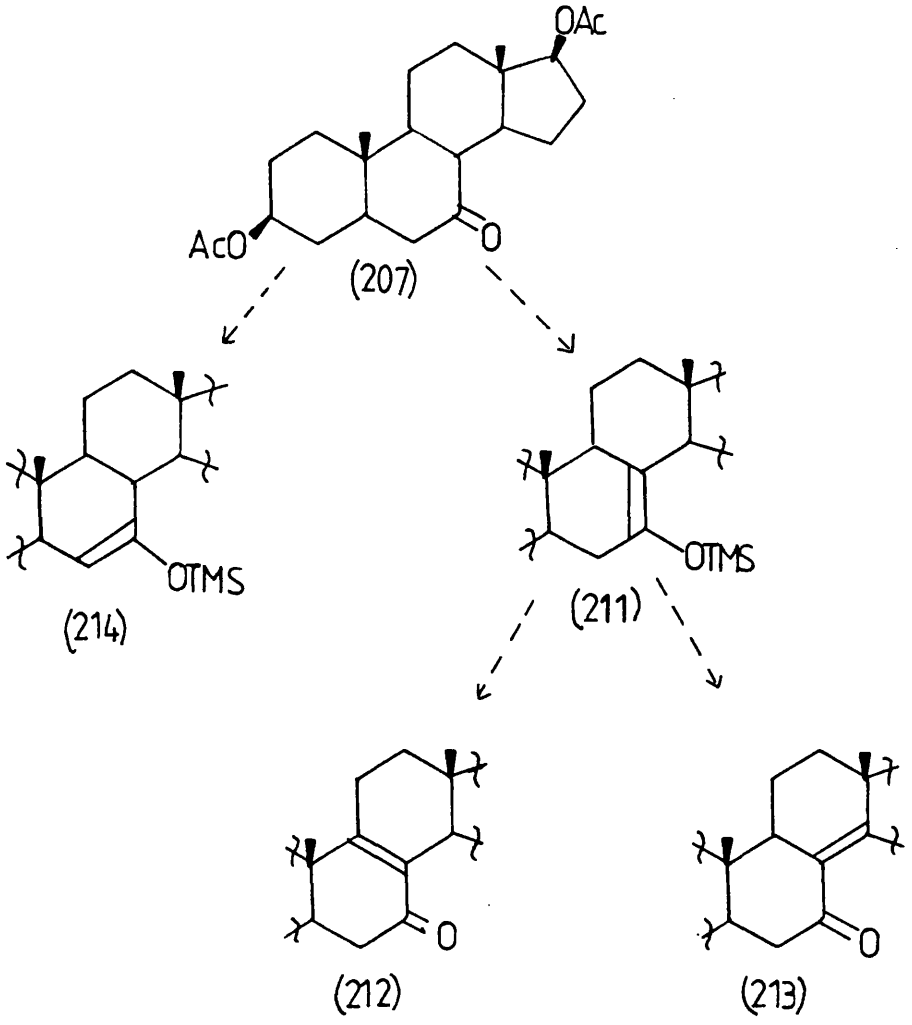


(201) (202)

	Conditions of Reaction	Scale of Reaction (Wt ene)	% Yield	% Diene in Product (by UV)
1	2·3 molar xs unrecrystallised $Hg(OAc)_2$. Commercial 95% EtOH, 65 hr reaction time	250 mg	46%	<5%
2	As for 1, but recrystallised $Hg(OAc)_2$. 60 hr reaction time	50 mg	52%	<5%
3	2·3 molar xs unrecrystallised $Hg(OAc)_2$. Diluted absolute ethanol. 80 hr reaction time	150 mg	70%	20%
4	2·3 molar xs recrystallised $Hg(OAc)_2$. Diluted absolute ethanol. 70 hr reaction time THEN 2·3 molar xs recrystallised $Hg(OAc)_2$ added. 70 hr extra reaction time	100 mg	50%	60%
5	4·6 molar xs recrystallised $Hg(OAc)_2$. Diluted absolute ethanol. 70 hr reaction time	200 mg	50%	22%
6	As for exp't 4, but heated at 40°C for 36 hr after addition of second quantity of $Hg(OAc)_2$	250 mg	50%	40%

Improvement on 50% total yield could not be obtained, and with a maximum of 60% diene conversion, this corresponds to only a 30% yield of diene (202) from (201). However, separation and recovery of (201) can be achieved at the next stage, and this was recycled.

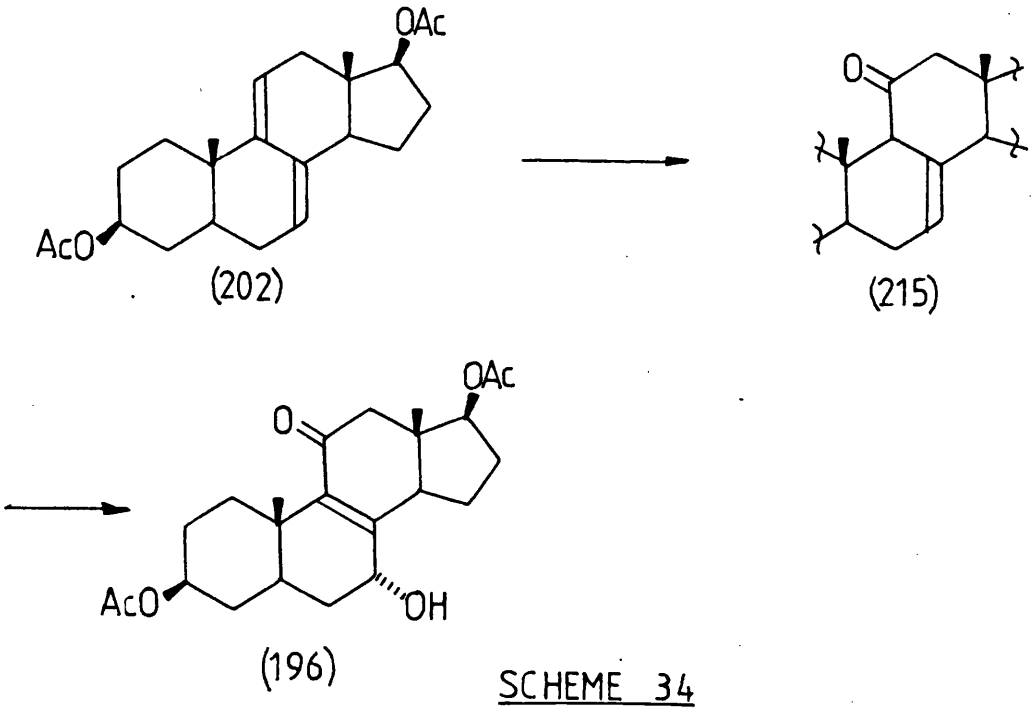
As a possible means of avoiding this low-yielding ene → diene conversion, we attempted to prepare the enone (212) *via* the trimethylsilyl enol ether (211), using the ketone (207) as the starting material (Scheme 33).



SCHEME 33

By analogy to a simple cyclohexanone system, it might be reasonable to assume that (211) would be the thermodynamically preferred silyl enol ether. Preparation of (211) was attempted using

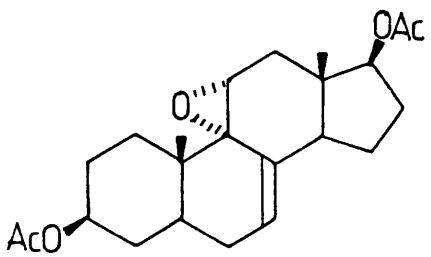
triethylamine and chlorotrimethylsilane. Reaction of (211) should have produced either (212) or (213), since the 9α- and 14α-hydrogens in the steroid nucleus are of similar accessibility towards oxidation. If obtained, enone (212) would have allowed functionalisation of the C-11 position, avoiding the $\Delta^{7,9(11)}$ diene. However, preparation of (211) was not successful, and unchanged ketone was recovered in quantitative yield. Attempts to prepare (214) using LDA at -78°C followed by enolate trapping were also unsuccessful. Thus the low yielding method for synthesising (202) was accepted, and further reactions carried out on this molecule. The sequence envisaged to give (196) is as shown in Scheme 34.



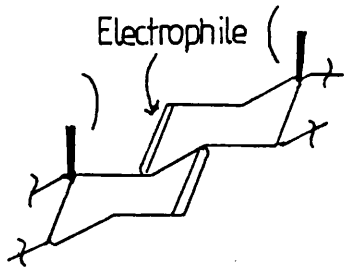
SCHEME 34

The β,γ-unsaturated ketone (215) has been prepared from (202) *via* the 9α,11α-epoxide (216).[49,50,51] It has been shown that the Δ^7 and $\Delta^{7,9(11)}$ bonds have different reactivity towards peracids, and thus selective epoxidation can be achieved. With aromatic peracids the

9,11-epoxide is formed, and (216) was obtained from the diene (202) in 69% yield using monophthalic peracid.[52] Separation of the Δ^7-ene (201) present in the diene as an impurity can also be effected at this stage, and thus material can be recycled. The α-epoxide is formed exclusively, presumably due to the hindrance to β-attack by the axial C-18 and C-19 methyl groups (217).

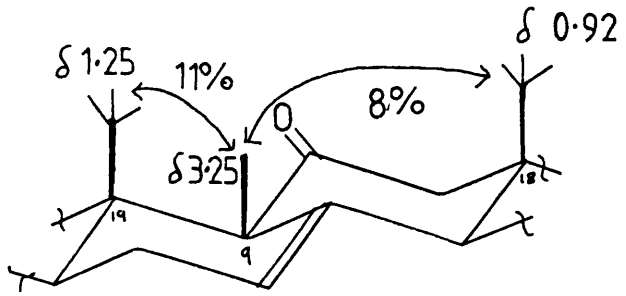


(216)

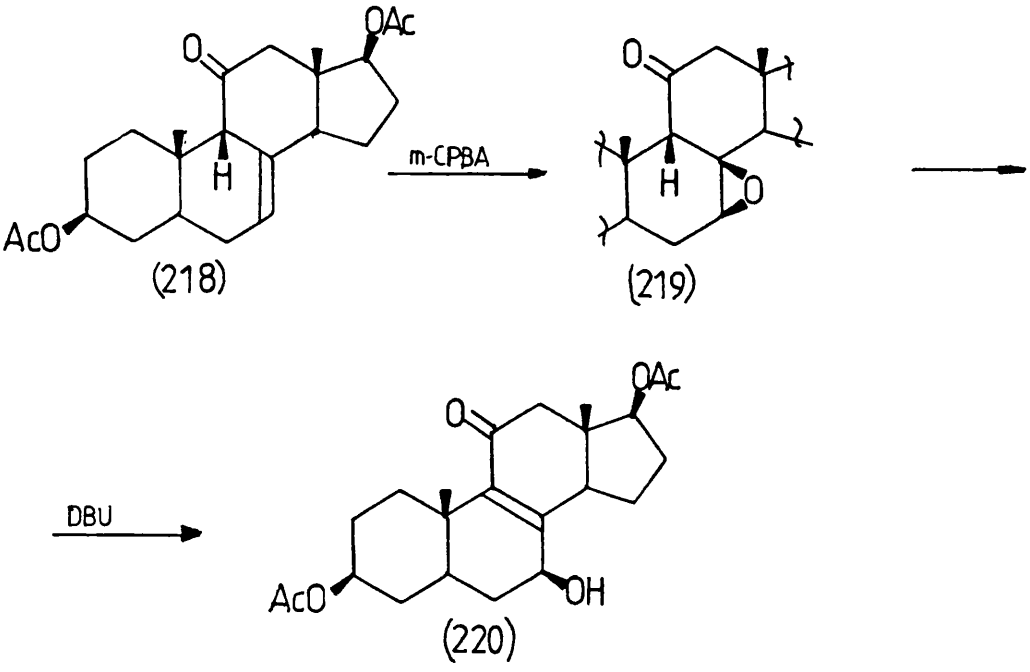


(217)

The α-orientation of the epoxide was assigned by ^{1}H NMR, the 11β proton resonance appearing as a doublet at δ 3·25 (J=5·3 Hz). Treatment of (216) with $BF_3.Et_2O$ gave the β,γ-unsaturated ketone (218) in 55% yield, with inversion of the natural configuration of the C-9 proton.[49,53] In performing this experiment, care must be taken not to isomerise the double bond to give the α,β-unsaturated ketone. By careful monitoring of the reaction (t.l.c.) this unwanted product can be avoided. The β-orientation of the C-9 proton was confirmed by ^{1}H NMR n.O.e. experiments, when irradiation of the 9-H signal at δ 3·25 led to enhancements of the C-19 and C-18 methyl signals of 11% and 8% respectively.



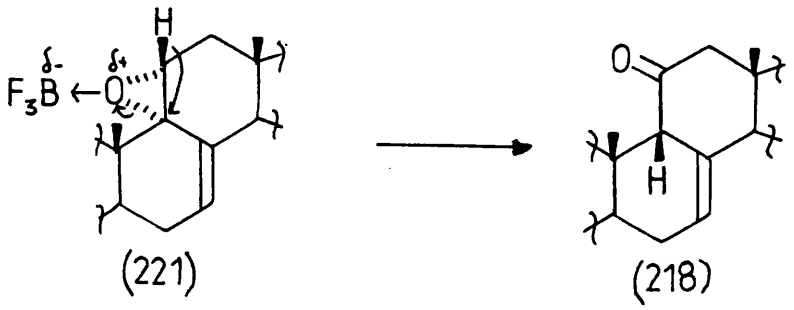
Oxidation of the Δ^{7}- bond in (218) with m-CPBA gave the 7β-epoxide (219), with attack from the least hindered face.[49] The keto-epoxide (219) was unstable to purification, and the crude product was treated with base (DBU) to give the keto-alcohol (220), the C-7 epimer of (196), in 48% overall yield from (218) (Scheme 35).



SCHEME 35

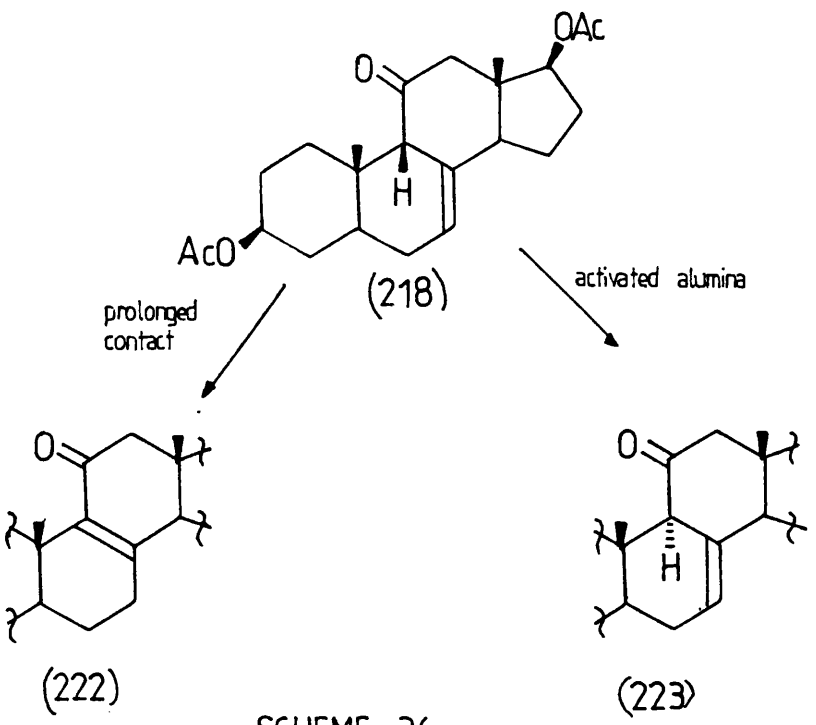
If epoxide (219) was left in contact with m-CPBA for extended periods, the epoxide opened to give (220) without the need for base.

The unnatural β-configuration of the C-9 proton in (218) has been explained by Bladon[54] as arising from movement of the 11β proton along the β-face of the molecule to C-9. Thus co-ordination of the boron trifluoride with the epoxide group gives (221), which is followed by movement of the C-9 oxygen bonding electrons onto the electron-deficient oxygen atom, with simultaneous movement of the 11β-proton to C-9: ie, the ring opening and migration of hydrogen is concerted.



(221) (218)

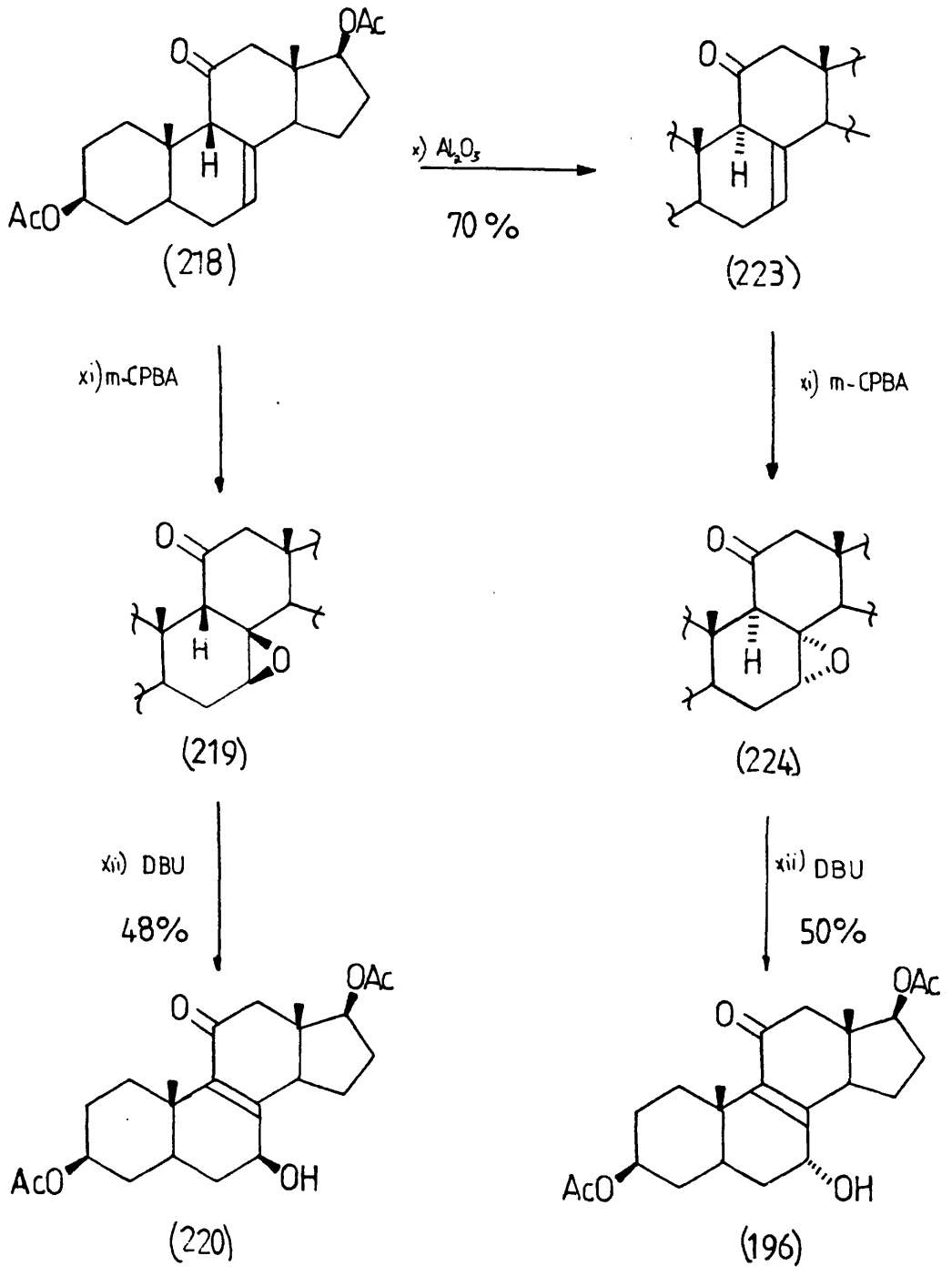
Hydroxy-enone (220) provides a useful model for introduction of the 8β-substituent, but the 7-hydroxyl group required for eventual lactonisation onto the fragmented D ring (see (198)) must be of α-orientation. As the 9β-proton in (218) determines the face of attack by m-CPBA, inversion of this proton should lead to α-epoxidation at the Δ^7 bond, and hence the 7α-hydroxy group required. This inversion has been reported to occur by simply filtering a benzene solution of (218) through activated alumina.[52,54] In our hands this inversion proceeded smoothly, although over-exposure to the alumina resulted in isomerisation of (218) to the α,β-unsaturated ketone (222) (Scheme 36).



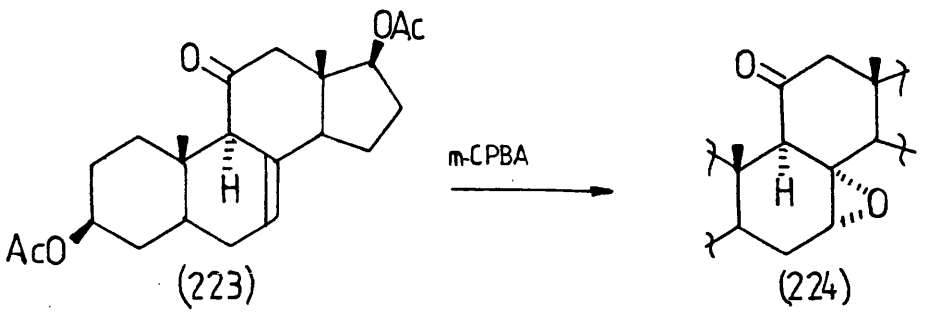
SCHEME 36

Thus (223) was obtained in 70% yield, the reaction being monitored by ^{1}H NMR, when the diminishment of the conspicuous 9β-proton resonance at δ 3·25 can be seen. Interestingly, the 3α-proton signal moved upfield, and the 17α-signal downfield, inverting their relative positions.

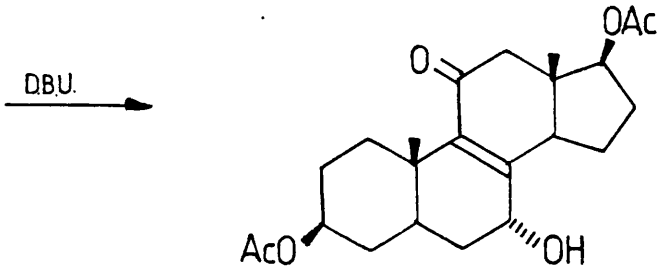
Epoxidation of (223) with m-CPBA gave keto-epoxide (224), which, without purification, underwent base promoted opening to give (196) in 50% overall yield from (223) (Scheme 37).


OAc
O
H
AcO
(218)
x) Al_2O_3
70 %
(223)
xi) m-CPBA
xi) m-CPBA
(219)
(224)
xii) DBU
48%
xii) DBU
50%
OAc
OH
(220)
(196)

SCHEME 39



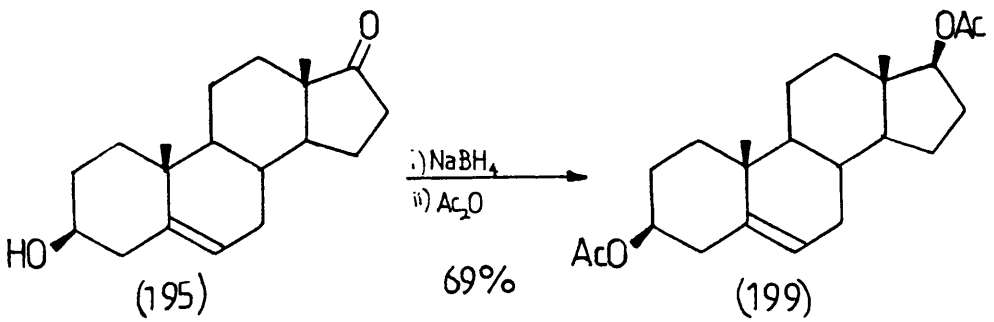
(223) (224)



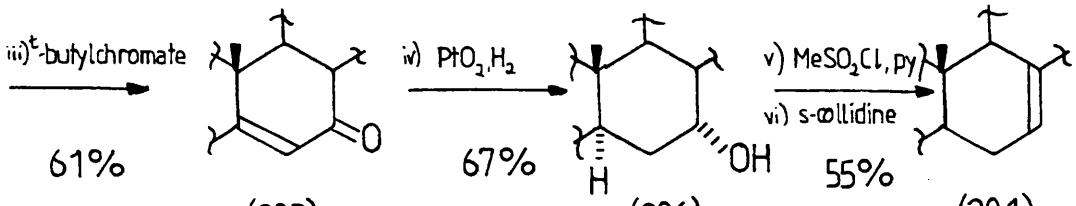
(196)

SCHEME 37

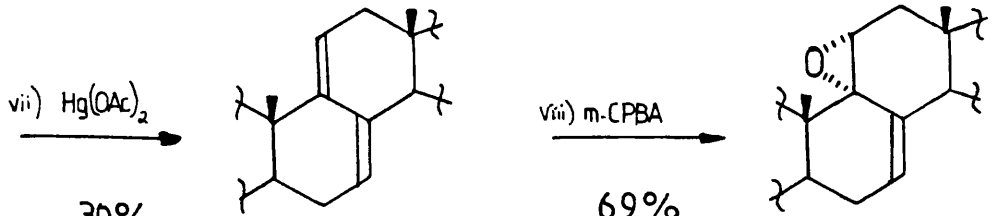
Thus (196) was synthesised from (-)-dehydroepiandrosterone (195) in 12 steps, 0·6% overall yield, and (220) from (195) in 11 steps, 0·8% overall yield, summarised in Schemes 38 and 39. The initial goal of functionalisation of the B and C-rings has thus been achieved, with suitable functionality for introduction of an 8β-substituent, and the 7α-hydroxy group in position.



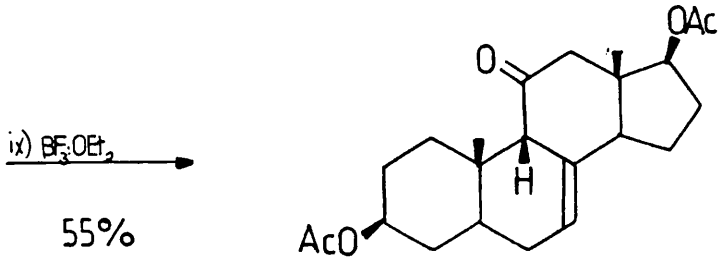
(195) (199)



(203) (206) (201)



(202) (216)

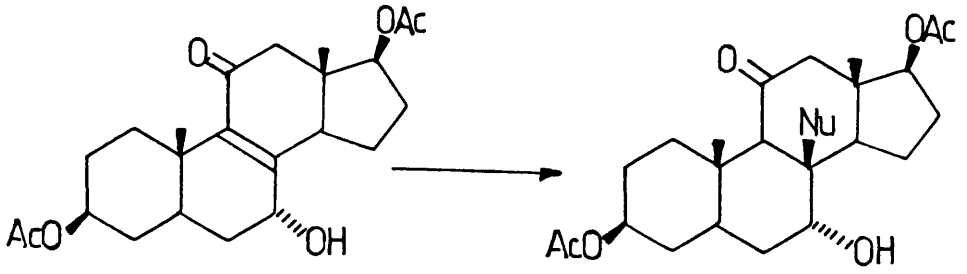


(218)

SCHEME 38

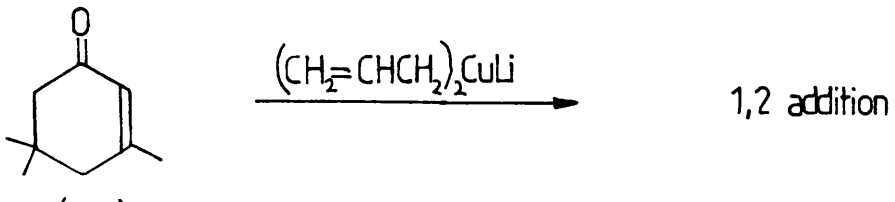
INTRODUCTION OF A C-8β-SUBSTITUENT

As described earlier, one of the key reactions in the attainment of a suitable bruceantin skeleton is the introduction of a β-orientated group into the C-8 position of enone (196).



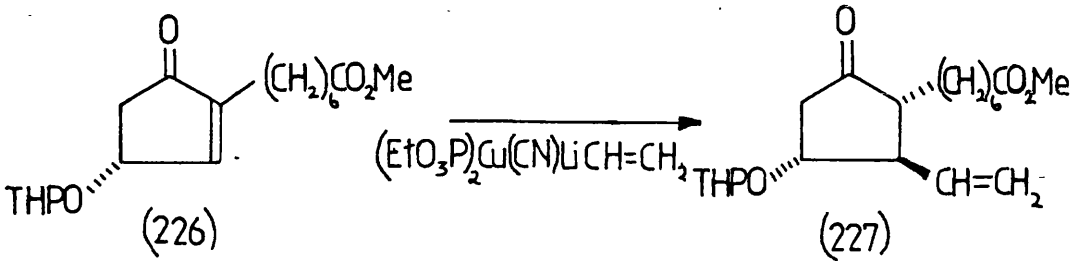
(196) (197)

Conjugate additions to α,β-unsaturated carbonyl compounds can be carried out in a number of ways. House[55] details the use of organocopper reagents, R_2CuLi, where R can be alkyl, aryl or alkenyl, for 1,4-addition to a number of substrates. In an unhindered cyclohexenone system, the group R is introduced predominantly from the direction that will give a cyclohexanone with an axial substituent. With more hindered cyclic enones, the nucleophile R is usually added from the less hindered side of the enone. House[56] reported the 1,4-addition of $(CH_2{=}CHCH_2)_2CuLi$ to cyclohexenone, whereas with the more hindered compound (225), 1,2-addition took place.

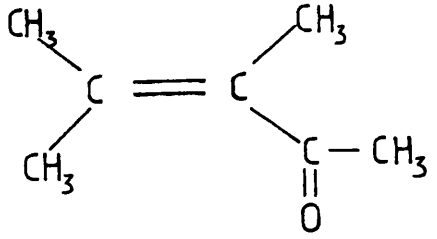


(225)

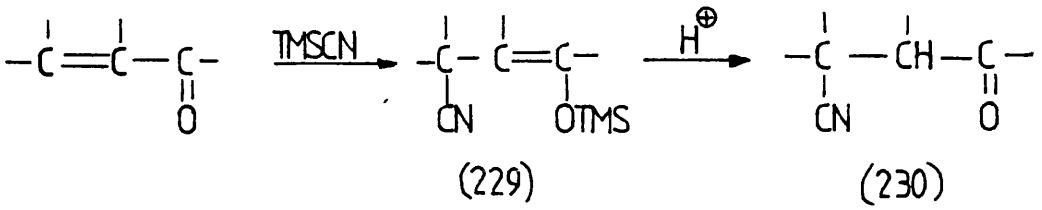
Alvarez *et al*[57] observed 1,4-addition to enone (226), using bis(triethylphosphite)copper (I) cyanide vinyllithium, with approach of the nucleophile from the less hindered side to give (227).



A combination of an organocuprate and Lewis acid have been found to be useful for conjugate additions to an α,β-unsaturated ketone or ester, where the double bond is sterically crowded. Thus 1,4-addition was observed with the β,β,α-trisubstituted enone (228) with $BuCu.BF_3$, whereas with Bu_2CuLi, only 1,2-addition took place.[58]

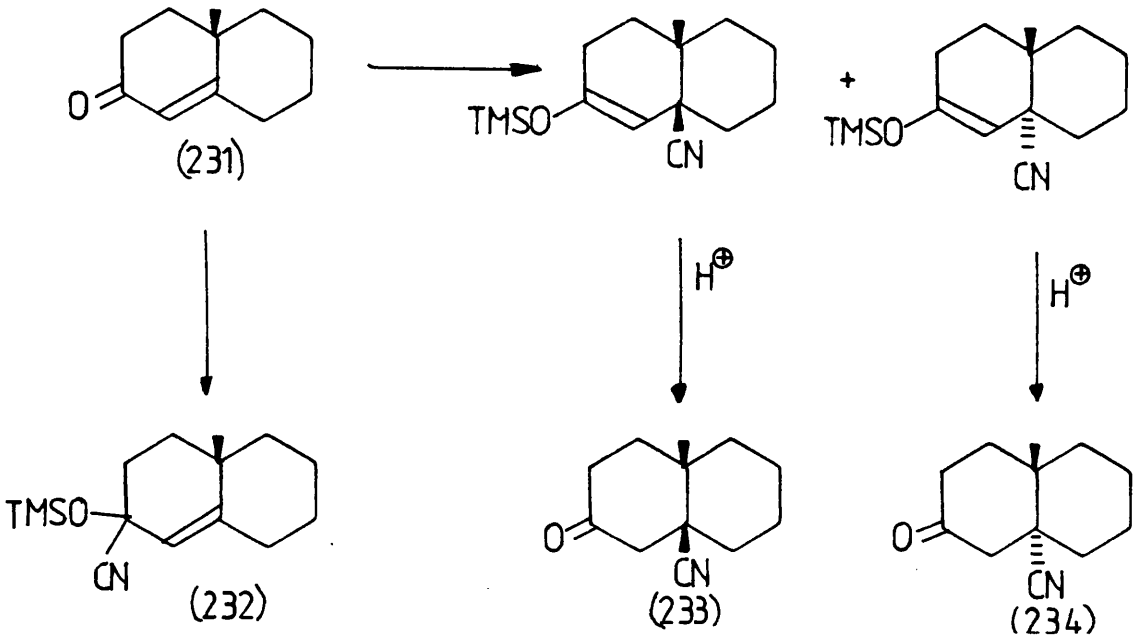


Another method for conjugate addition involves the triethylaluminium-mediated reaction of cyanotrimethylsilane to an α,β-unsaturated ketone, to give the β-cyanotrimethylsilyl enol ether (229), which on hydrolysis yields the β-substituted ketone (230).[59] Selective 1,2-addition to enones has been reported with cyanotrimethylsilane alone.[60]



(229) (230)

In a cyclic system, such as 6-methylbicyclo[4.4.0]dec-1-en-3-one, (231), variation of reaction time and solvents gave either 1,2-addition (232) or 1,4-addition (233) and (234). The reaction is kinetically controlled in toluene (cis/trans = 233/234 = 95:5) and thermodynamically controlled in THF at reflux (233/234 = 55/45). Decreased reaction time at room temperature gave exclusively (232) (Scheme 40).



(231) (232) (233) (234)

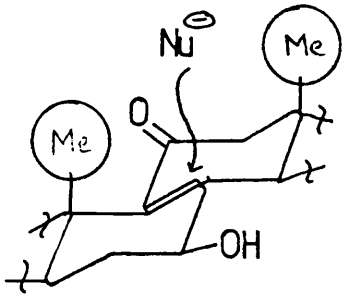
SCHEME 40

Samson and Vandewalle[61] reported conjugate addition of -CN, using diethylaluminium cyanide, Et_2AlCN, with TMSCl/pyridine work-up of the initially formed aluminium enolate to give β-substituted silyl

enol ethers in good yield. With Δ^4-3-cholestenone, the trans:cis isomer ratio at C-5 was 65:35 after 5 minutes, but 1:9 after prolonged reaction time (3 hours).

Hydrogen cyanide and an alkyl aluminium (R_3Al-HCN), or an alkylaluminium cyanide (R_2AlCN), are highly efficient reagents for conjugate addition of cyanide to α,β-unsaturated ketones.[62,63] The mechanism of the reaction of these two reagents with enones was shown by Nagata to be different.[63b] The R_3Al-HCN method is catalytic with respect to R_3Al, with little initial 1,2-addition, whereas R_2AlCN is solvent dependent, with an equivalent amount of reagent required. Furthermore, the initial stage does involve rapid and predominantly reversible 1,2-addition. Diethylaluminium cyanide was shown to be the superior reagent, and Nagata has demonstrated its efficiency with numerous cyclic enones.

In the case of enone (220), the synthesis of which has been described earlier, the introduction of a nucleophile into the C-8β position has to contend with severe steric problems, due to the C-18 and C-19 methyl groups, as shown below.

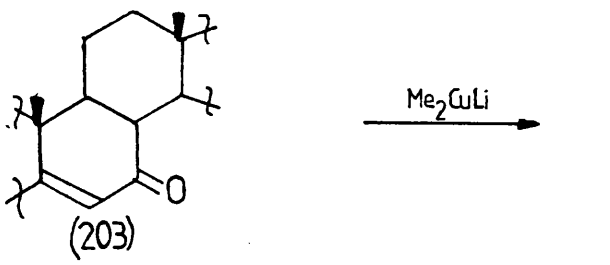


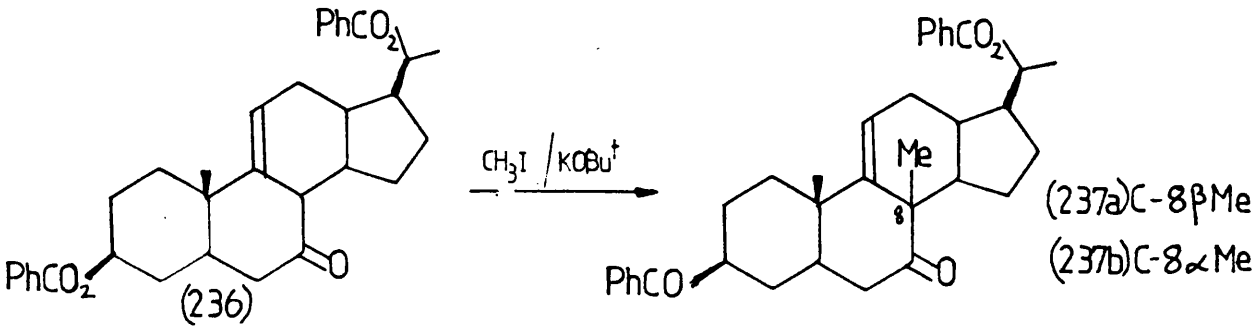
(220)

Any group introduced into this position must be compatible with eventual transformation into the C-8 - C-13 ether linkage present in bruceantin. For this reason, a methyl or nitrile substituent was

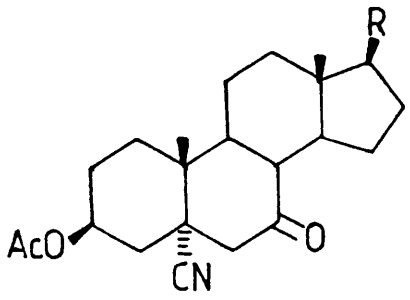
considered suitable. Conjugate addition of $-CH_3$ using an organocuprate reagent was considered, although our model studies on enone (203) gave only the 1,2-addition product (235). The stereochemistry at C-7 is unconfirmed, but the failure of 1,4-addition to the relatively unhindered C-5 position did not bode well for introduction at the hindered C-8 position.

Amiard *et al* claimed that the 8β-methylpregnane derivative (237a) was obtained in 35% yield by methylation of the $\Delta^{9(11)}$-7-keto-steroid (236) with methyl iodide, but their assignment of the newly introduced methyl group at C-8, based on circular dichroism data, was proved to be incorrect, and was later revised as C-8α (237b).[64,65]

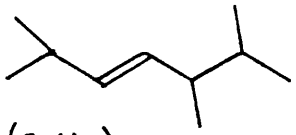




Attention was thus focussed on the Nagata reagent, Et_2AlCN, which has been shown to add conjugatively to enones, even in the case of Δ^8-11-keto steroids.[63c] The Δ^5-enone (203) was again used as a model compound, and although initial handling problems were encountered with the highly viscous Et_2AlCN/toluene solution, a 67% yield of the addition product (238) was obtained, with 30% recovery of unreacted starting material. Nagata claims a 93% yield of (239), using $HCN\text{-}AlEt_3$.[63c]

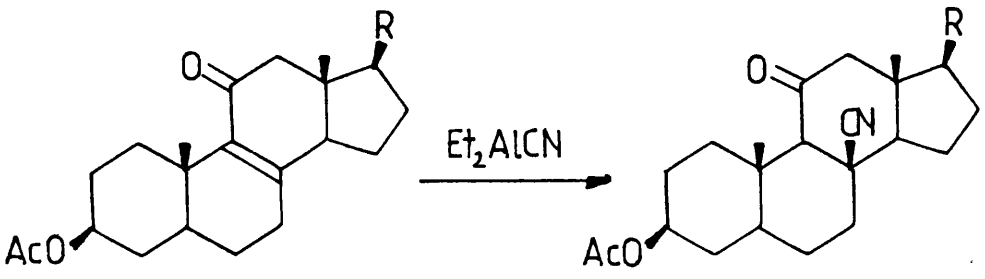


(238) R = OAc

(239) R = 

(C_9H_{17})

A Δ^8-11-keto steroid was required to test the introduction into the C-8 position. As previously explained, prolonged contact of the β,γ-unsaturated ketone (218) with BF_3:etherate leads to isomerism to give (222) in good yield. However, treatment of (218) in ether with a few drops of concentrated sulphuric acid gave a cleaner quantitative conversion. Thus (222) was treated with Et_2AlCN, according to Nagata's procedure,[62] to give (240) in 60% yield, with 30% recovery of starting material. We also obtained a 68% yield of (242) from (241). Nagata obtained an 86% yield for this reaction (241 → 242).[66]

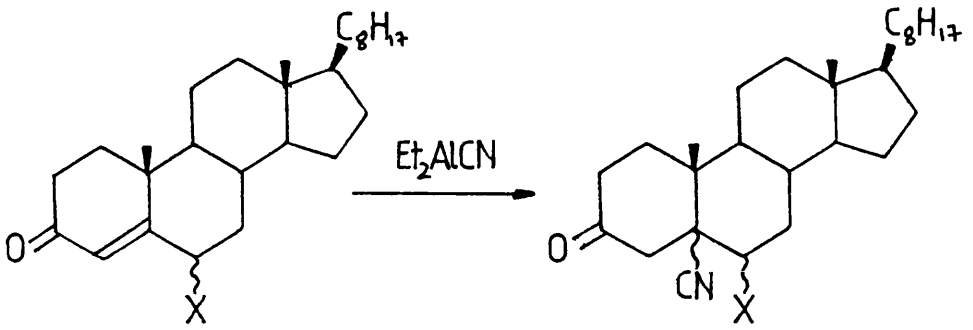


(222) R = OAc

(240) R = OAc

(241) R = C_9H_{17}

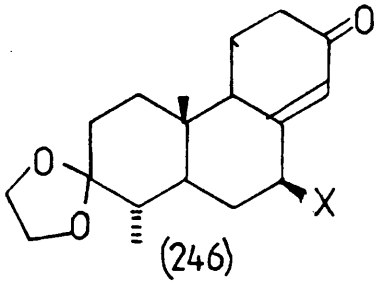
(242) R = C_9H_{17}



	rel. rate	trans	cis
X = H	1·0	67	18
X = β OAc (244)	0·016	15	24
X = α OAc (245)	0·013	25	31

SCHEME 41

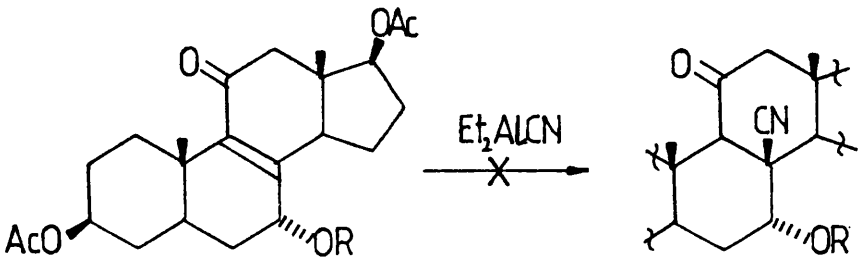
Fuchs, in his work on bruceantin, also observed a retardation and lack of cis/trans selectivity, when using Et_2AlCN with a C-7 substituent (246, X = OTBDMS *vs* X = H).[67]



(246)

However, in our hands, addition to (220) took place very rapidly to give a 90% yield of (243), characterised by classical techniques, and single crystal X-ray analysis, which proved the β-orientation of the nitrile (see Appendix). Attempts to extend this reaction to the 7α-hydroxy compound (196) proved unsuccessful, starting material being recovered even with prolonged reaction times, higher temperature,

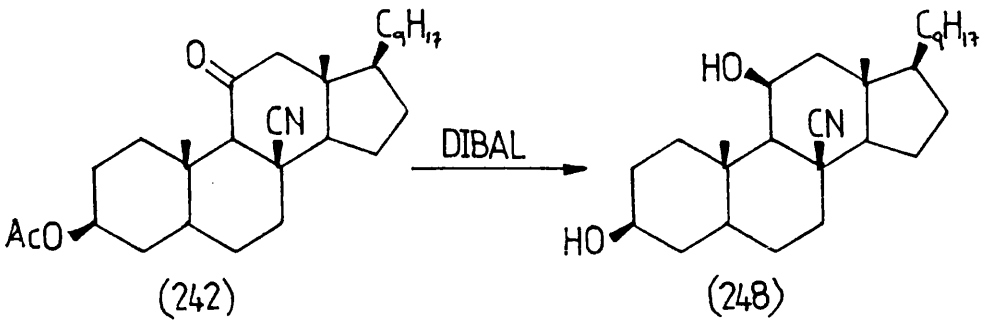
and the use of an excess of Et_2AlCN.



(196) R=H
(247) R=Ac

This result may be rationalised by invoking reagent approach control. The co-ordination of the 7β-hydroxy oxygen to the aluminium species could aid delivery from the β-face, whereas the α-hydroxy could conversely inhibit β-delivery by a similar co-ordination. Acetylation at the C-7 position (247) led to no reaction, the oxygen still being too basic with respect to the Lewis acid to aid delivery.

With compounds (240), (242) and (243) in hand, modification of the nitrile group was envisaged, by reduction to either the aldehyde or the primary alcohol. Numerous methods are known for reducing a nitrile to an aldehyde.[68] DIBAL is perhaps the most commonly used reagent,[69] but on reaction of (242) with DIBAL at 0°C, only the C-11 ketone was reduced with cleavage of the C-3 acetoxy group to give diol (248). Increase in temperature (20 → 80°C) led to no further reaction.



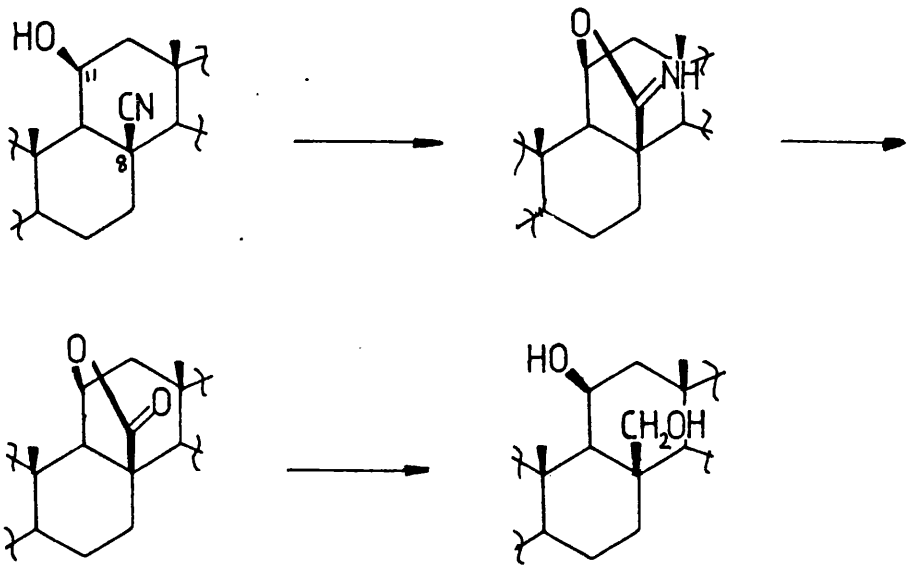
(242) (248)

Lithium aluminium hydride has been used to reduce nitriles in the C-5α and C-5β steroid positions.[70] The same group have also claimed to reduce the 8β-nitrile group with $LiAlH_4$, though no experimental details were provided.[71] In our hands, diol (248) was again obtained. Moist Raney Nickel in formic acid at elevated temperatures is claimed by Staskun to be a good reagent for reduction of hindered nitriles to aldehydes, although no steroid examples were examined.[72] No reaction was observed with (242) using this reagent, unreacted starting material being recovered. Similarly, reaction with orthophosphoric acid and Raney Nickel was unsuccessful.[73]

The use of lithium diisobutylaluminium hydride ($LiAlH_2$ $(i\text{-}Bu)_2$) for the reduction of the 8β-nitrile to the imine has been reported,[71] but all attempts to prepare this reagent from lithium hydride and DIBAL failed, with only a viscous oil obtained, rather than a crystalline solid.[74] Reaction of this oil (242) again gave the diol (248). Lithium triethoxyaluminate hydride ($LiAlH(OC_2H_5)_3$) only reduced the C-11 carbonyl group.[75]

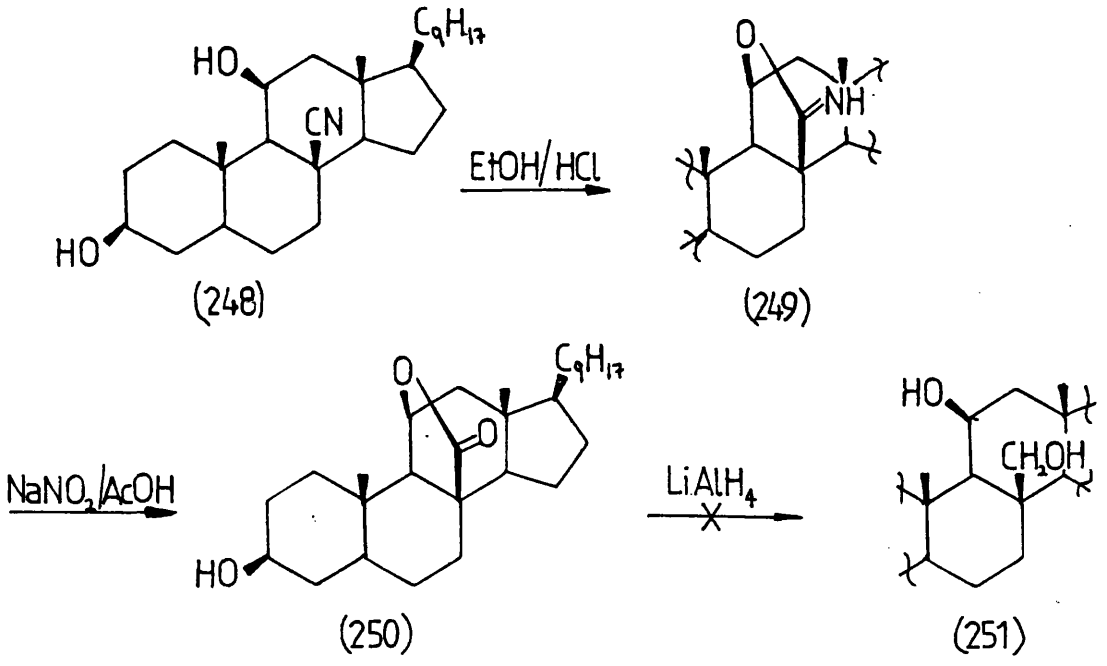
Due to the lack of success in modifying the nitrile group, presumably due to its extreme steric hindrance, we decided to utilise its proximity to the C-11β-hydroxy group in (248) to perform an intramolecular cyclisation. Thus a sequence such as that shown in Scheme

42 could lead to modification of the nitrile.[66]



SCHEME 42

Literature conditions, though not given in detail, are acidic reflux for imino-ether formation, nitrous acid treatment to convert to the δ-lactone, and $LiAlH_4$ reduction to give the diol.[76] Despite initial problems of isolation, the imino-ether (249) was prepared in 76% yield from (248). Conversion to the lactone (250) required heating (249) in an excess of sodium nitrite and acetic acid, the product (250) showing an IR absorption consistent with a 5-membered lactone ring (ν_{max} 1760 cm^{-1}) (Scheme 43).



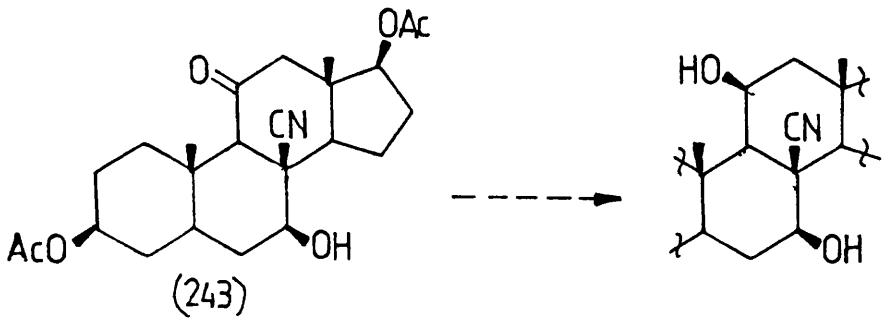
SCHEME 43

Attempts to reduce (250) to the triol (251) with $LiAlH_4$ at room temperature or reflux led only to starting material being isolated. All attempts at varying temperature and prolonged reaction time proved unsuccessful.

However, with the C-8 - C-11 lactone (250) available, this conveniently 'protects' the 8β-substituent, so that when D-ring fragmentation takes place, with removal of the blocking C-18 methyl group, modification of the lactone to give the primary alcohol at C-8 should prove straightforward. Attention was focussed on repeating the intramolecular lactone synthesis on (243), with the C-7β-hydroxy group in position. However, attempts to reduce the C-11 ketone to give the β-alcohol were unsuccessful. Table 2 details the reagents used, and products obtained.

The major problem was that any product obtained by reduction of the C-11 position, with, in certain cases, concomitant cleavage of the acetate groups, would lead to a tetra-hydroxy compound, a very

TABLE 2



ENTRY	REAGENT	CONDITIONS	RESULTS
1	$NaBH_4$/EtOH	0°C → R.T. Overnight	Starting material only recovered
2	$NaBH_4$/MeOH	R.T. Overnight	Starting material only recovered
3	$NaBH_4$/MeOH	Reflux (~14 hours)	Complex mixture obtained, unidentifiable by IR and NMR
4	$LiAlH_4$/Ether/THF	R.T. → reflux	Very polar product obtained, unidentifiable by IR and NMR
5	DIBAL	R.T. → heating	Complex mixture by t.l.c.
6	DIBORANE	R.T. 3 hours	Very polar product seen by t.l.c.

polar moiety, and unsatisfactory recovery of material was evident. To assist isolation, in entries 4 and 5, acidification of all aqueous extracts was performed, to destroy any possible aluminium complexes, and exhaustive extraction employed, but no identifiable material was obtained. Attempted hydroboration (entry 6) produced a very polar compound (t.l.c.), but isolation was unsuccessful. Thus the C-8 - C-11 imino-ether of (243) could not be formed and the sequence

illustrated in Scheme 42 was not applicable to the 7β-hydroxy-8-cyano-steroids.

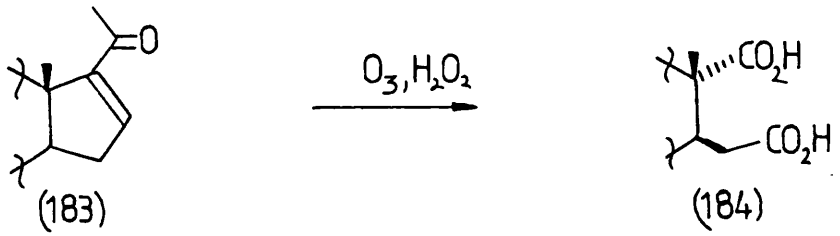
SUMMARY

The functionalisation of the C-7 and C-11 positions had been achieved, as had the introduction of at β-substituent at C-8. Confirmation of the β-orientation had been made by X-ray analysis, and by intramolecular imino-ether and subsequent lactone formation with the C-11β-hydroxy group. The C-7β-hydroxy group prevented reduction of the C-11 ketone in (243), and the C-7α hydroxy prevented reaction with the 'Nagata' reagent in (196).

Therefore, although the target molecule (243) had been prepared, subsequent useful transformations were limited, and it was decided that attention should be diverted to the D-ring fragmentation. Several of the problems encountered should be solved by the relief of steric crowding resulting from this fragmentation. The reactions established in the B- and C-ring functionalisation could then be incorporated into a suitably functionalised D-ring fragmented product.

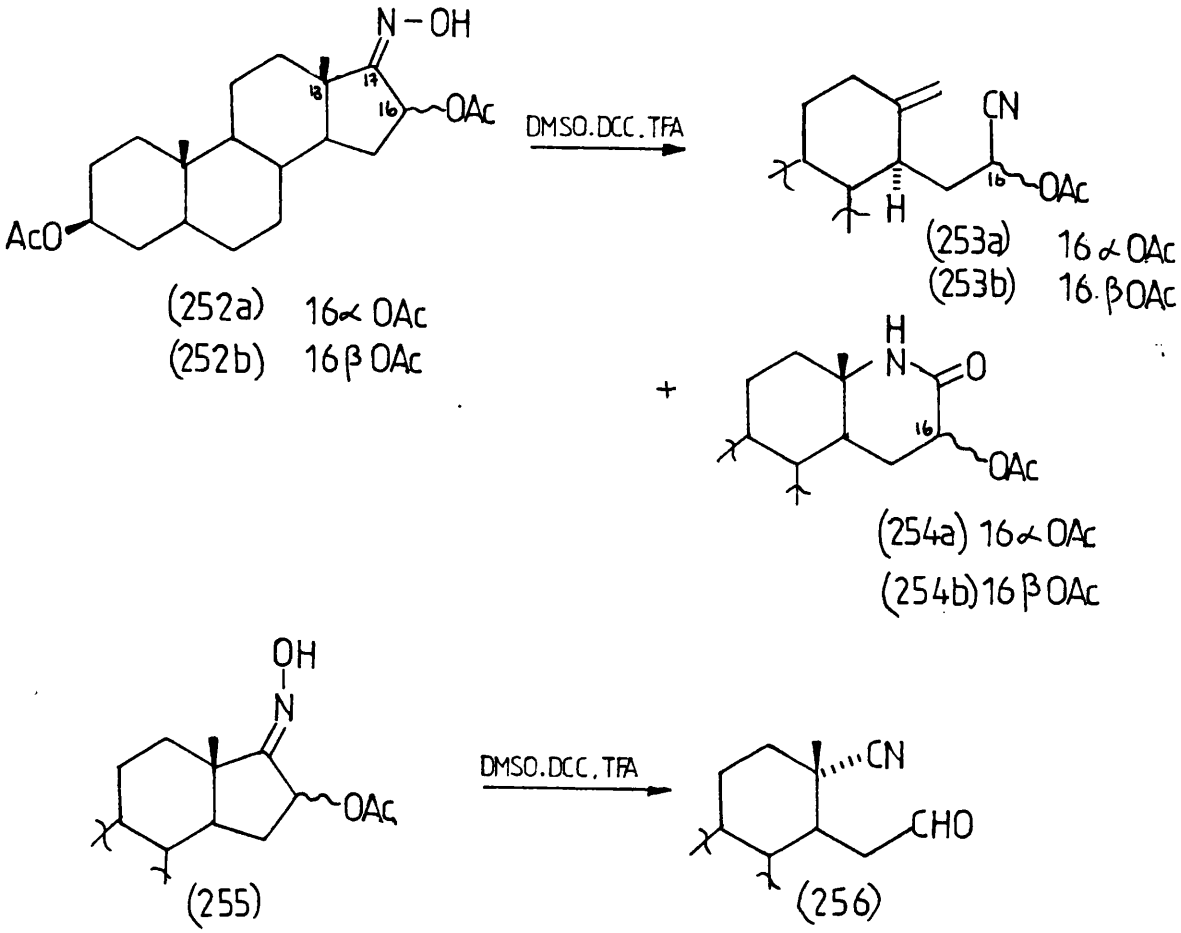
D-RING FRAGMENTATION

The D-ring cleavage of steroids has been reported by several groups. Dias, in his work towards the synthesis of eurycomalactone and the quassinoid skeleton described earlier,[37] cleaved the D-ring enone (183) with ozone, to give the diacid (184).



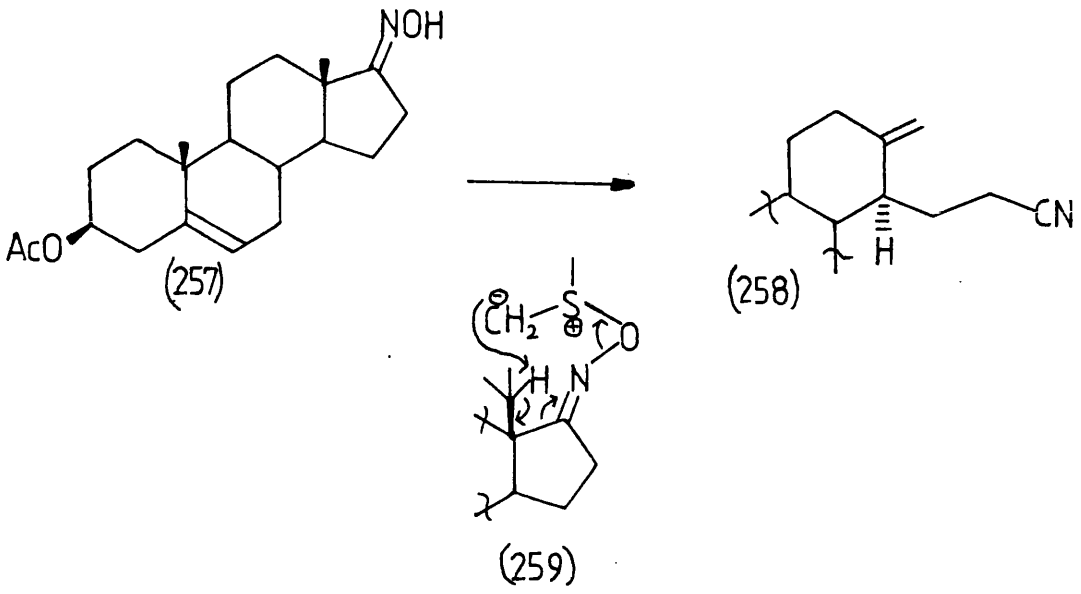
(183) (184)

The fragmented D-ring then served to form the δ-lactone ring present in quassinoids, although the stereochemistry at C-14 is not that required. Graf and Pfenninger also studied D-ring fragmentations, the oxidative fragmentation with lead (IV) acetate and copper (II) acetate described on page 29, as well as the 'abnormal' Beckmann fragmentation.[36,77] The Beckmann fragmentation, pioneered by Moffat,[78] gives rise to the seco-nitrile, as well as a low yield of the 'normal' Beckmann lactams. Thus Graf and Pfenninger reported that oxime (252) in its Z form, gave the C-13 - C-17 fragmented seco-nitriles (253a and 253b) with the lactams (254a and 254b). The E-isomer (255) gave exclusively the C-16 - C-17 fragmentation product (256)[77] (Scheme 44).



SCHEME 44

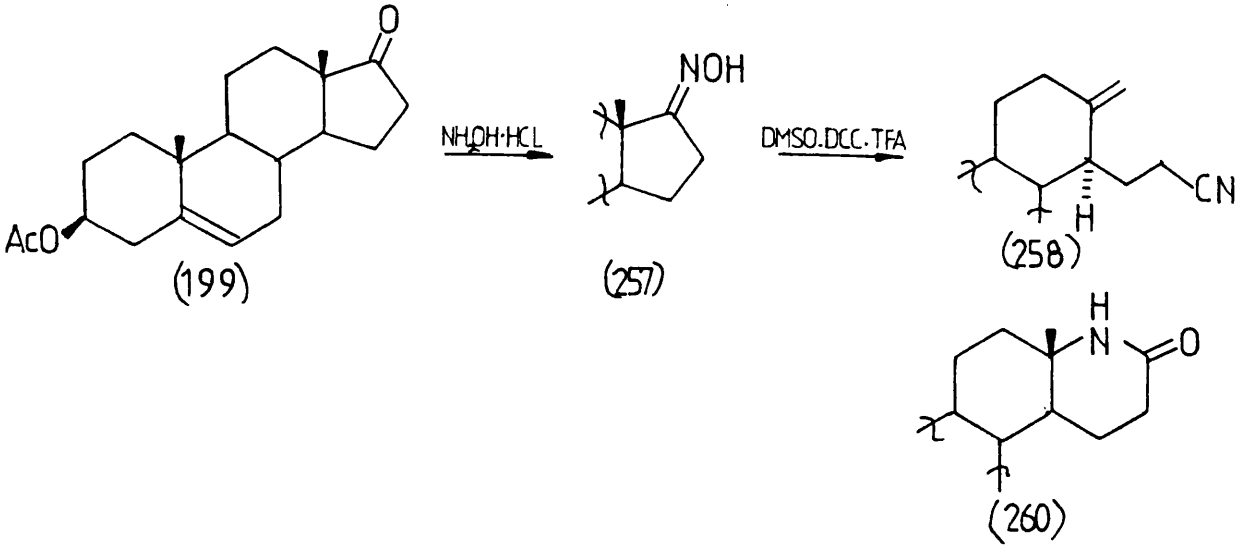
Moffat prepared the seco-nitrile (258) in 61% yield by fragmentation of (257) under the same conditions employed above.[78] A cyclic fragmentation mechanism (259) was proposed to rationalise this result.



However, Whiting, under the same conditions, obtained only 35% of seco-nitrile (258), the 'normal' lactam being the major product.[79] In case this discrepancy was caused by the stereoisomeric composition of the oxime (257), the E and Z isomers were separated. Using the literature procedure[78] for the preparation of the oxime from the C-17 ketone (hydroxylamine hydrochloride, pyridine, EtOH, Δ), the Z isomer was present in <1%. If a cyclic mechanism such as (259) is operating, the Z-geometry should aid this, although Pfenninger and Graf could not obtain the nitrile (258) from the Z oxime of (257).[77] It therefore seems likely that a cyclic mechanism is not operating, but that the E-isomer can adopt a suitable geometry for a concerted fragmentation. Chapman and Pinhey[80] also report the formation of the seco-nitrile from a D-ring oxime, with 52% nitrile, 40% lactam the best yield obtained.

The use of this Beckmann fragmentation provides access to a C-14 fragment which, on suitable modification, would lead to a δ-lactone on reaction at the C-7α position. The stereochemistry at

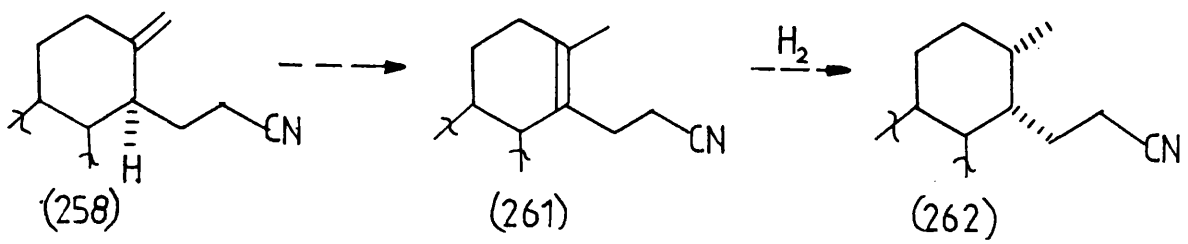
C-14 would need to be inverted, but as the α- configuration is the most stable, this should not be a problem. Thus, from dehydroepiandrosterone acetate (199), the oxime (257) was prepared in 87% yield under standard conditions.[78] Fragmentation, according to the procedure of Moffat,[78] gave 42% of the seco-nitrile (258), and 23% of the lactam (260). The exocyclic vinyl proton resonances in (258) were clearly seen as two singlets at δ 4·8 and δ 4·5 (Scheme 45).



(199) (257) (258) (260)

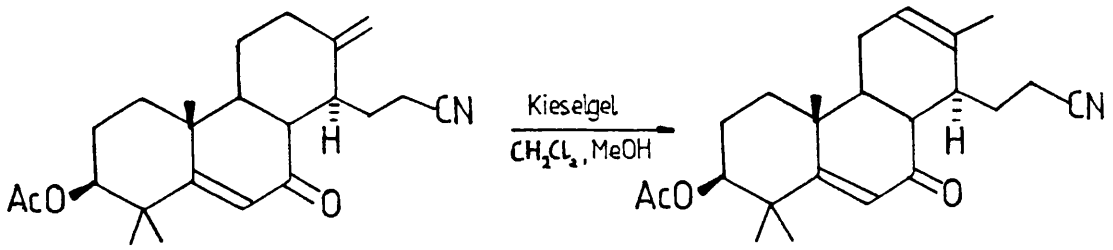
SCHEME 45

Our initial aim was to isomerise the exocyclic double bond in (258) to the internal tetrasubstituted $\Delta^{13,14}$-olefin (261), which, on hydrogenation from the top (β) face, would effect net epimerisation of the C-14 centre to give the α-nitrile fragment (262).



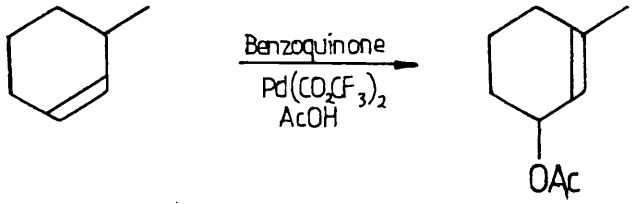
(258) (261) (262)

Barton used rhodium chloride to catalyse the isomerisation of various unsaturated substrates,[81] but in our hands, treatment of the seco-nitrile (258) ($RhCl_3.3H_2O$, Δ, EtOH/$CHCl_3$) led to a u.v. active product (t.l.c.), which, on isolation, gave a very low yield of a yellow oil, characterisation of which was not possible due to decomposition. Isomerisation of the Δ^5-bond to give a diene ($\Delta^{5,7}$, $\Delta^{7,13(14)}$ or $\Delta^{6,8(14)}$) was the probable cause of failure. Iodine/hν treatment of (258) gave no reaction.[82] Attempts to isomerise the double bond to the $\Delta^{12,13}$-position also proved fruitless, despite Schlatter and Graf's reported success in isomerising (263) to (264) on silica gel in dichloromethane/methanol.[83]



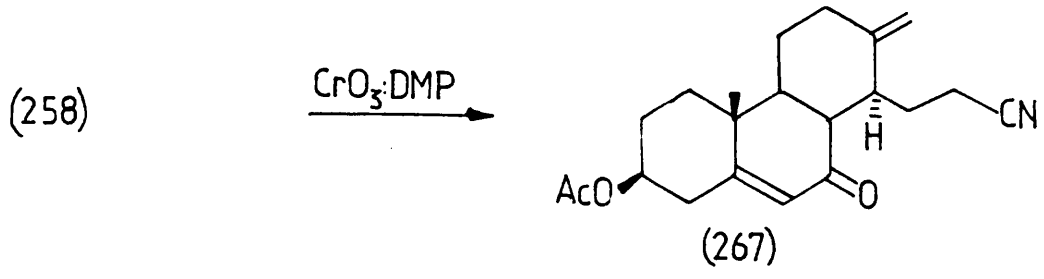
(263) (264)

It was thought that allylic oxidation at C-12 might be accompanied by internal isomerisation of the $\Delta^{13,17}$-double bond. McMurry reports the use of catalytic palladium (II) trifluoroacetate and a co-oxidant to convert olefins into allylic acetates, with, in certain cases, allylically isomeric products being obtained, as in the conversion of (265) to (266).[84]



(265) (266)

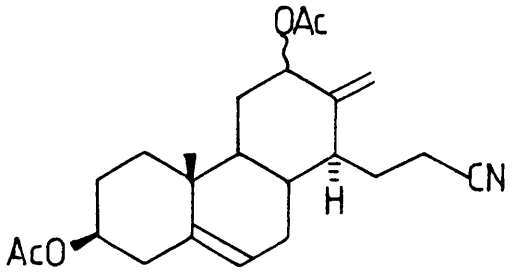
With seco-nitrile (258), there are two possible sites for oxidation, the C-12 and C-7 positions. Reaction with $Pd(CO_2CF_3)_2$ and benzoquinone, as described by McMurry, gave no reaction at either position, at room temperature or elevated temperatures. A combination of chromium trioxide and 3,5-dimethylpyrazole has been extensively used for allylic oxidations.[85] Using an excess of these reagents, seco-nitrile (258) gave 56% recovery of unreacted starting material, and 38% yield of a u.v. active product, the spectral data of which was consistent with structure (267). Thus only the C-7 position has been attacked. The same product (267) was obtained in 34% yield on oxidation with t-butyl chromate.[46]



(267)

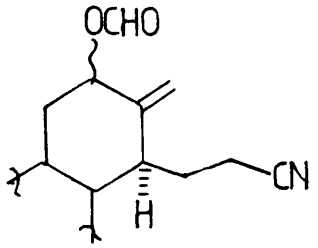
Selenium dioxide has been widely used for allylic oxidation of olefins, giving allylic alcohols, α,β-unsaturated carbonyl compounds, or a mixture of the two, depending on experimental conditions employed.[86] Reaction of (258) with SeO_2 (benzene, acetic acid,

H_2O, Δ), gave an unstable yellow oil. Spectral data indicated a hydroxyl group at C-12, but oxidation with pyridiniumchlorochromate in order to simplify the spectra gave a u.v. active product which decomposed on purification. This reaction was repeated, with direct acetylation of the oil produced, in order to give a more stable product. The product, assigned structure (268), was isolated in low yield (15%), but this also decomposed on standing.

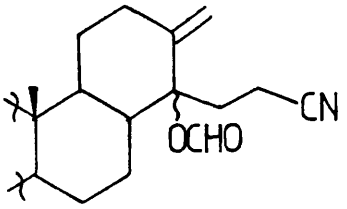
(258) $\xrightarrow[Ac_2O]{SeO_2}$ 

(268)

Thus oxidation at the C-12 position had been achieved, shown by the appearance of a multiplet at δ 5·5 (12-H), and a sharp singlet at δ 2·0 ($-COCH_3$), but the exocyclic double bond had not isomerised, (2 singlets at δ 5·1 and 5·3). When this reaction was repeated using selenium dioxide in formic acid, at a lower temperature (55°C), instead of the expected product (269), oxidation took place at C-14 to give (270), in 35% yield. ^{13}C NMR confirmed the tertiary centre at C-14, but the reasons for this selectivity are not clear.

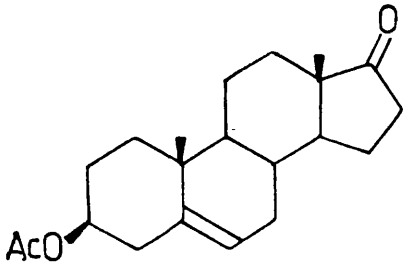


(269)



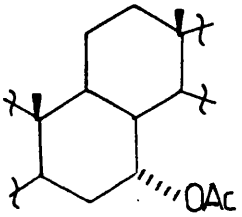
(270)

The 7α-acetate (271), prepared *via* the sequence shown in Scheme 46 was subjected to the same conditions (SeO_2, formic acid). The presence of the bulky substituent at C-7 did not hinder the reaction at C-14, and (272) was obtained in 44% yield. An attempt to establish the stereochemistry at C-14 was unsuccessful.

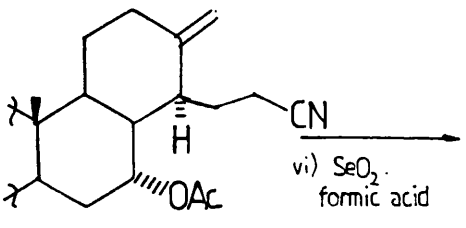


(199)

i) CrO_3, ^{t}Butanol
ii) PtO_2. H_2
iii) Ac_2O

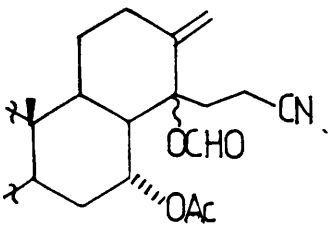


iv) $NH_2OH \cdot HCl$
v) DMSO. DCC. TFA



(271)

vi) SeO_2. formic acid

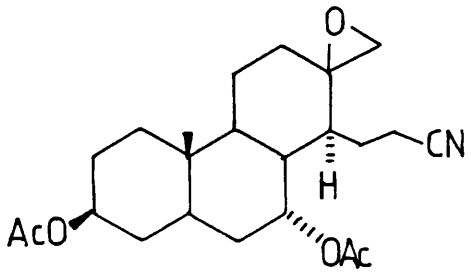


(272)

SCHEME 46

Thus reactions carried out on the fragmented D-ring did not lead to isomerisation of the exocyclic double bond, the transformation required to enable epimerisation at C-14, nor did these experiments give useful functionalisation of the C-12 position, since products isolated were too unstable.

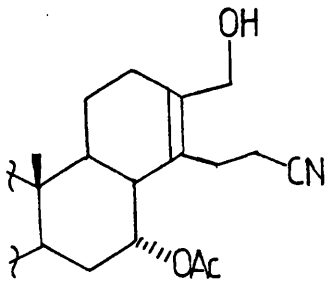
A different approach to obtaining the $\Delta^{13,14}$-bond was therefore required. Epoxidation of the exocyclic double bond in D-ring fragmented steroids has been reported using m-CPBA.[80] In our hands, a 70% yield of epoxide (273) was isolated on reaction of (271) under these conditions.

(271) $\xrightarrow{\text{m-CPBA}}$ 

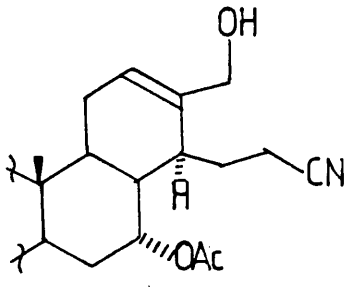
(273)

Chapman and Pinhey reported a 6:4 mixture of C-13 epimers, but the ^{1}H NMR spectrum of (273) showed the presence of only one methyl peak (δ 0·8, singlet), indicating a single isomer. The stereochemistry of the epoxide was not assigned.

There are various methods known for the conversion of epoxides to allylic alcohols.[87] Epoxide (273) could give either (274) or (275), the former being the required isomer.

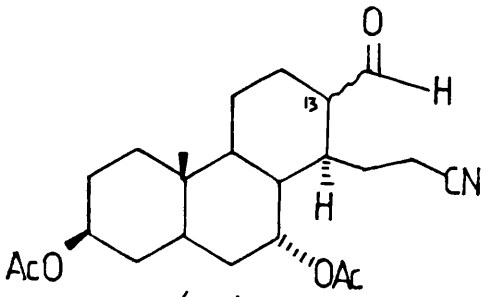


(274)



(275)

Reaction of (273) with DBU or lithium diisopropylamide gave unreacted starting material,[87] and sodium phenylselenide with hydrogen peroxide gave mainly unreacted (273), with several other products visible by t.l.c.[88] Lithium diethylamide[89] gave a complex mixture of at least seven compounds by t.l.c. as did methylmagnesium bromide and N-cyclohexylisopropylamine.[90] However, treatment of epoxide (273) with BF_3.etherate gave (276) as a 3:2 mixtures of epimers at C-13 (two aldehyde signals at δ 9·6 and 9·7).[80]



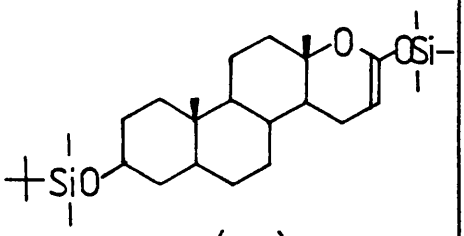
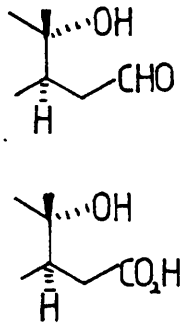
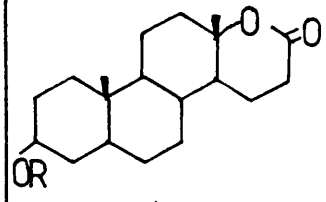
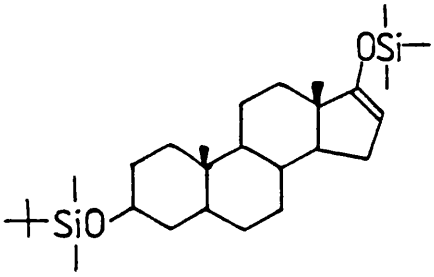
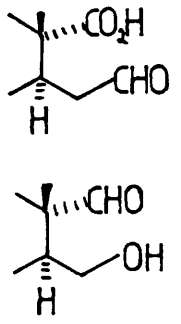
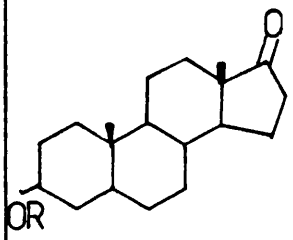
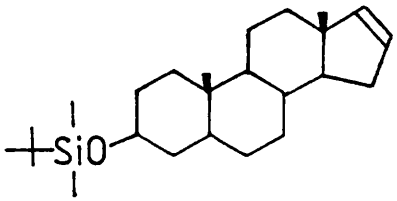
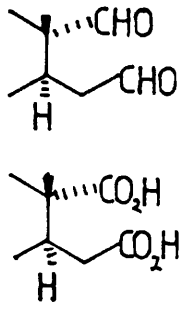
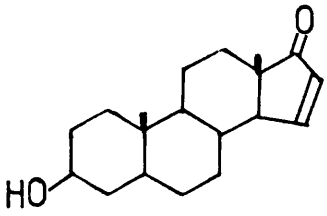
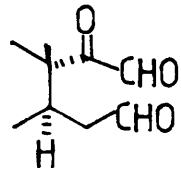
(276)

Attempts to achieve the epimerisation of C-14, or functionalisation of the C-ring using the methodology described above had therefore failed.

Additional work carried out by Dr Keith Motion at Bath University on the D-ring had met with limited succes. A brief coverage of his work is described below. Initial attempts to

TABLE 3

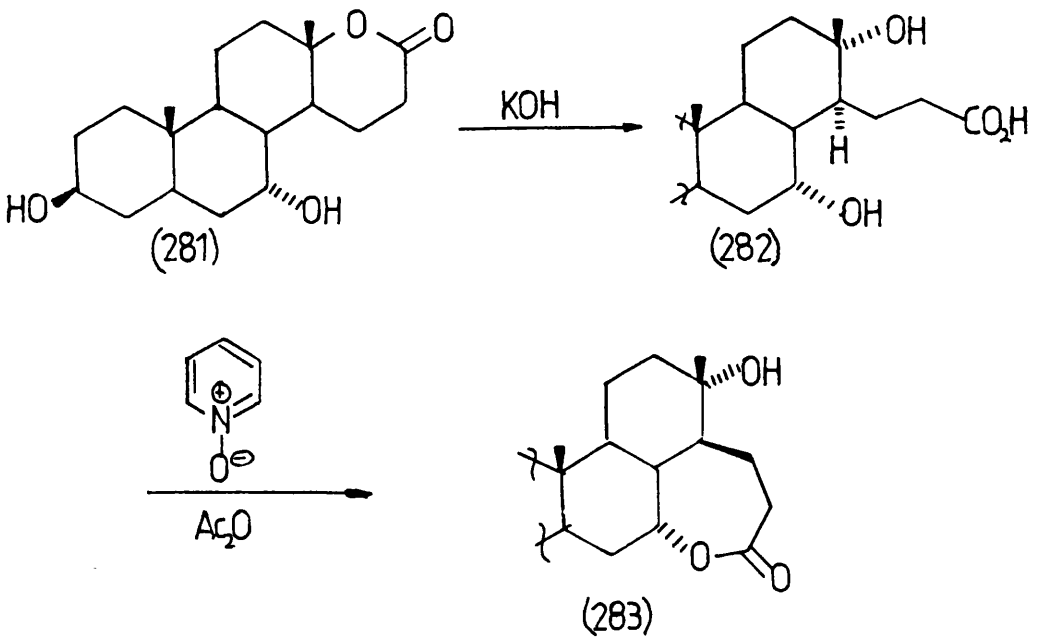
OZONOLYSIS ATTEMPTS

SUBSTRATE	PRODUCT REQUIRED	CONDITIONS	ACTUAL PRODUCT
 (277)		a) $CHCl_3$, -15°C Me_2S b) EtOAc, -72°C H_2O_2	 R=H or Si
 (278)		a) $CHCl_3$, -5°C Me_2S b) THF, -25°C Me_2S c) $CHCl_3$, -5°C H_2|Pd-C	 R=H or Si
 (279)		a) MeOH, -25°C Me_2S b) MeOH, -25°C H_2O_2	Starting material
 (280)		a) $CHCl_3$, -10°C Me_2S b) AcOH, R.T. Me_2S	Starting material

ozonolyse various D-ring functionalised compounds in order to obtain a two carbon C-14 fragment, suitable for δ-lactone formation with a C-7α-hydroxy group, were unsuccessful, as shown in Table 3.

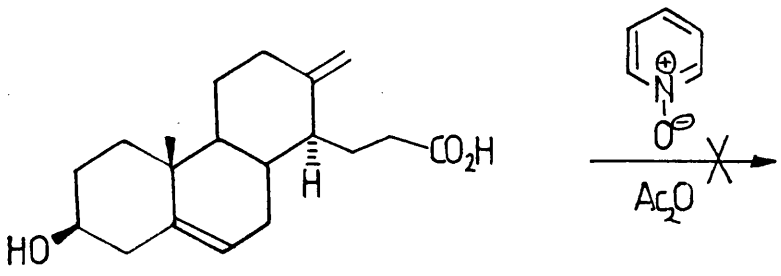
The failure of substrate (279) to react at all was attributed to the close proximity of the angular methyl group hindering the approach of the ozone. However, the use of (280), with the olefin in the C-15 - C-16 position also led to no reaction.

Attempts to decarboxylate the acid (282) (obtained by hydrolysis of lactone (281)) with pyridine-N-oxide failed, the only product isolated being the seven-membered lactone (283) in <10% yield[91] (Scheme 47).



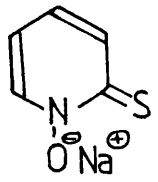
SCHEME 47

Hydroxy acid (284) obtained by hydrolysis of seco-nitrile (258) gave only products derived from the mixed anhydride of the acid, with no decarboxylated compounds observed.



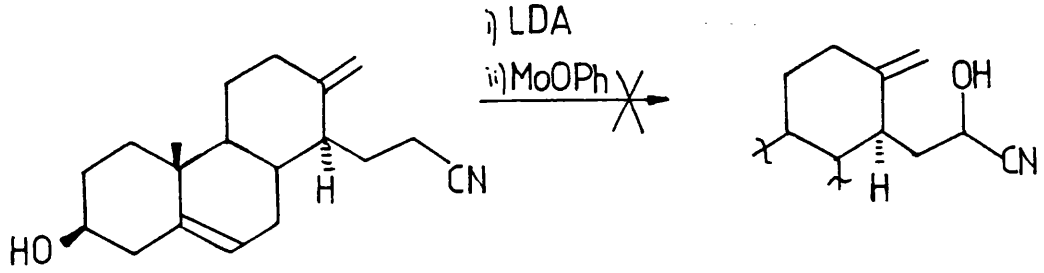
(284)

Attempts to produce the C-14 aldehyde using the Hunsdiecker/ Kornblum sequence (silver salt, bromine, DMSO/base),[92] the Barton modification of this sequence, using the pyridine thione salt (285),[93] and the thallium (1) salt method introduced by McKillop[94] all proved unsuccessful.



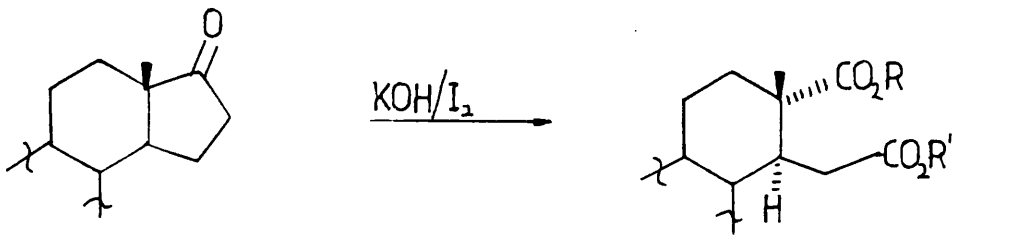
(285)

The reaction of seco-nitrile (286) with the MoOPh reagent (molybdenum pentoxide, HMPA, pyridine),[95] in an attempt to generate the cyano-hydrin (287) also failed.

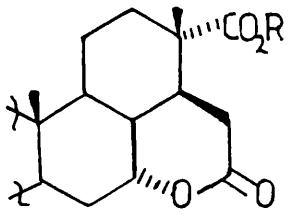


(286) (287)

The most successful cleavage reactions investigated were those of the parent D-ring ketone, which on reaction with hypoiodite (KOH, I_2) gave diacid, diester or a mixture, depending on the solvent used.[96] Thus compounds of the type (288) could be obtained, which are two carbon fragments, with correct oxidation state at the terminus for lactone formation (Scheme 48).



(288) (a) R=R'= H
(b) R=R'=Me
(c) R=H, R'=Me

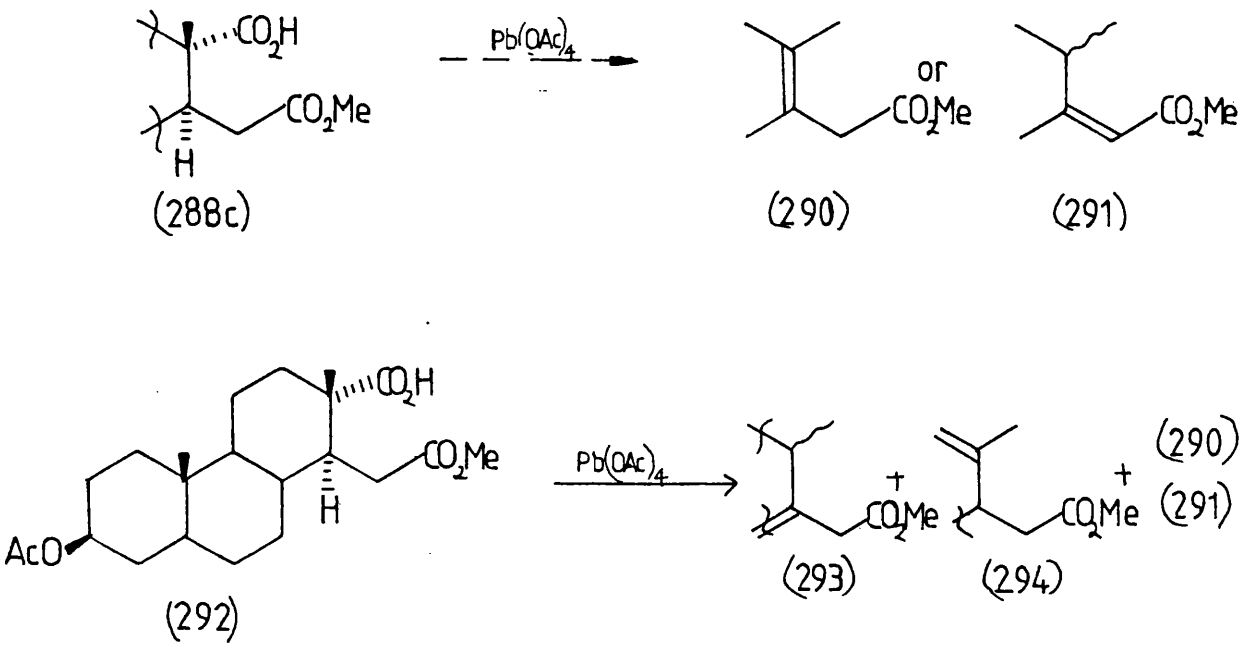


(289)

SCHEME 48

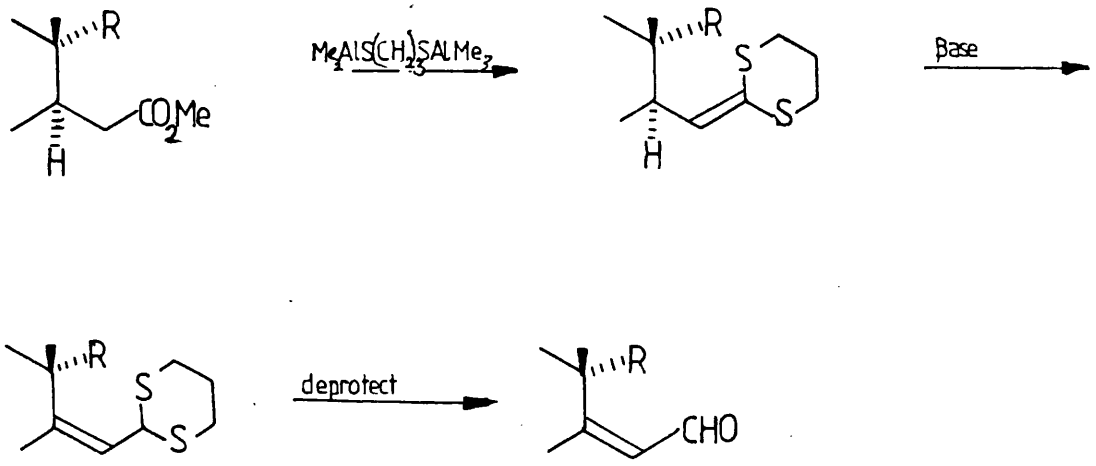
However, attempts to form a lactone such as (289) with the "wrong" stereochemistry at C-14 were unsuccessful.

Attention was then focussed on the epimerisation of C-14, so that this lactonisation could take place. The mixed product (288c) was used to attempt to form an olefinic species such as (290) or (291), both of which would have been useful for epimerisation, since hydrogenation of this double bond should take place from the top face to give the C-14α-fragment.



However, the saturated acid (292) gave an inseparable mixture of products, thought to be (290), (291), (293) and (294), which on hydrogenation also gave an intractable mixture.

Attempts to prepare the α,β-unsaturated ester from (288b) (LDA, PhSeSePh,[97] or SeO_2/AcOH/t-Butanol)[98] also failed, mixtures being obtained. The ketene dithiane rearrangement chemistry of Corey,[99] outlined below in Scheme 49, was considered as a means of producing an α,β-unsaturated species.



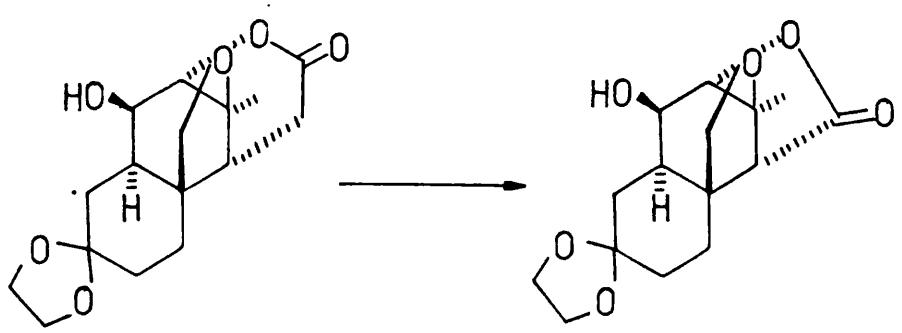
SCHEME 49

However, the diester (288b) was too hindered for dithiane formation. Thus, although a two carbon fragment could be obtained from D-ring cleavages, epimerisation of the C-14 position was not successful.

LACTONE CONTRACTION

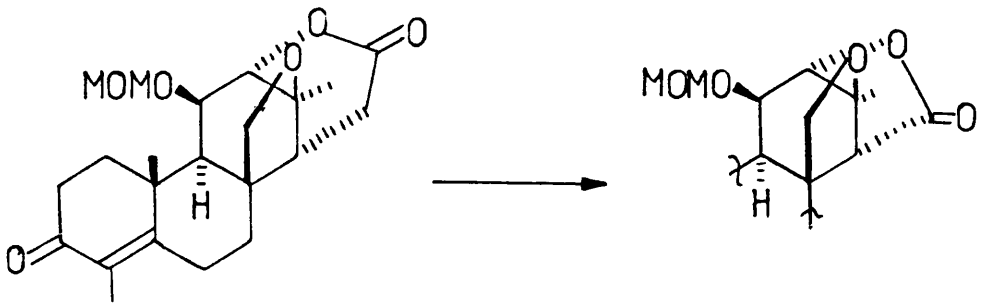
Due to the difficulties encountered in removing a carbon atom from the C-14-D-ring fragment in (284), so as to give a δ-lactone, rather than an ε-lactone, a methodology for lactone ring contraction was required. Reports of these contractions in the literature are sparse, those available being very specific for certain additional functionalities.

Grieco,[100] in his work on quassinoids, described a novel copper (II) mediated ring contraction of δ- to γ-lactones, but this was only general within the framework of quassinoids possessing the C-8 - C-13 ether linkage. Thus (295) was converted to (296) by bubbling oxygen through a solution of (295) in methanol, in the presence of $Cu(OAc)_2$, pyridine and diisopropylethylamine (Hunig's base).

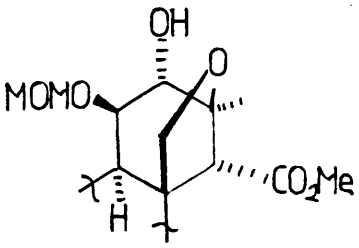


(295) (296)

Pyridine and $Cu(OAc)_2$ were found to be essential for this reaction to occur. Hunig's base could be replaced by triethylamine, but the reaction was substantially slower. During the conversion of (297) to (298), if the reaction is terminated after only a few hours, appreciable amounts of the hydroxy ester (299) can be isolated. The enone system remained intact throughout the reaction.

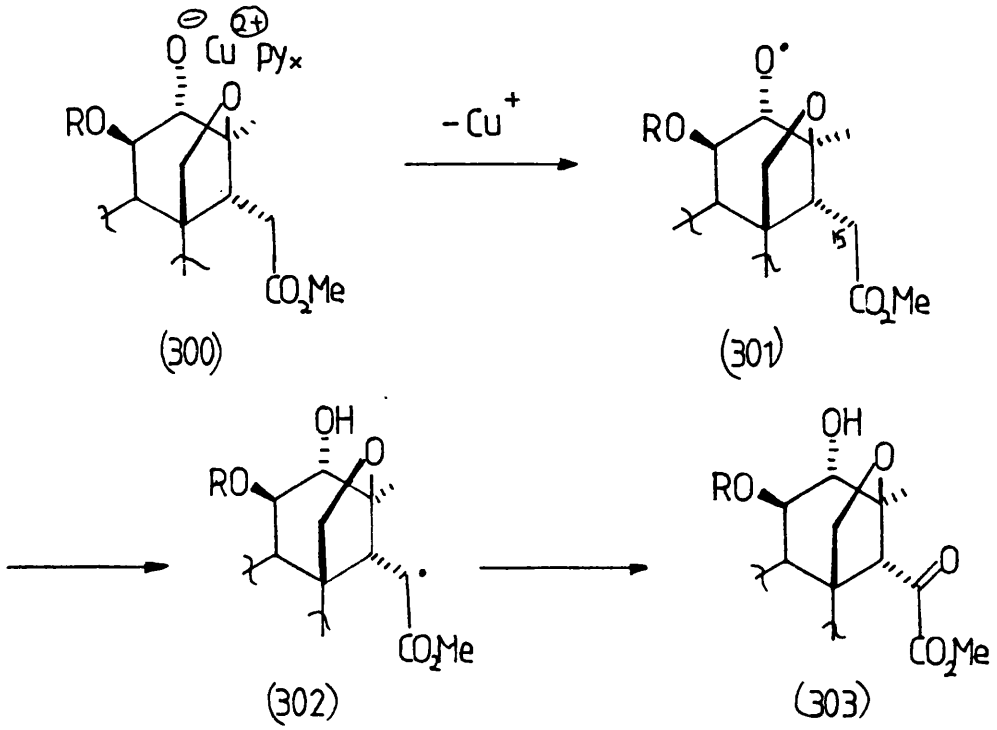


(297) (298)



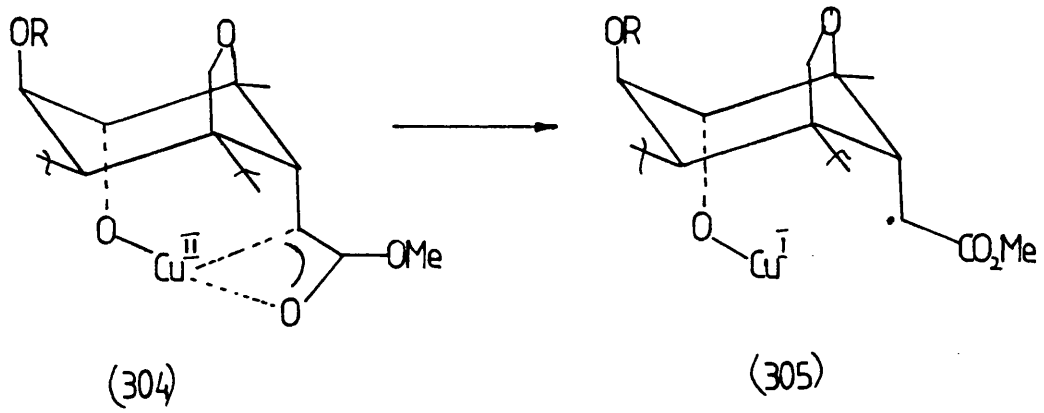
(299)

In an attempt to probe the generality of this reaction, several simple lactones, e.g. δ-valerolactone, caprolactone, and some polycyclic lactones were subjected to the reaction conditions. No ring contracted products were detected, only products derived from methanolysis being isolated. Thus Grieco concluded that a stringent requirement for reaction to occur was a 1,3-axial-axial relationship between the hydroxyl group at C-12, and a methyl acetate unit at C-14. If the C-12 hydroxyl is protected, no reaction occurs. These results were rationalised by proposing initial methanolysis, followed by complexation of the C-12 hydroxyl with copper (II) and pyridine, and subsequent electron transfer, ((300)→(301)), Scheme 49. Hydrogen atom abstraction from C-15 in intermediate (301) provides access to (302), which presumably gives rise to the α-oxo-ester (303).

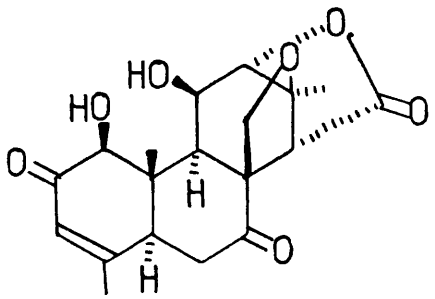


SCHEME 49

Another mechanism could involve formation of a copper (II) enolate, *via* base catalysis, followed by electron transfer ((304) → (305)).

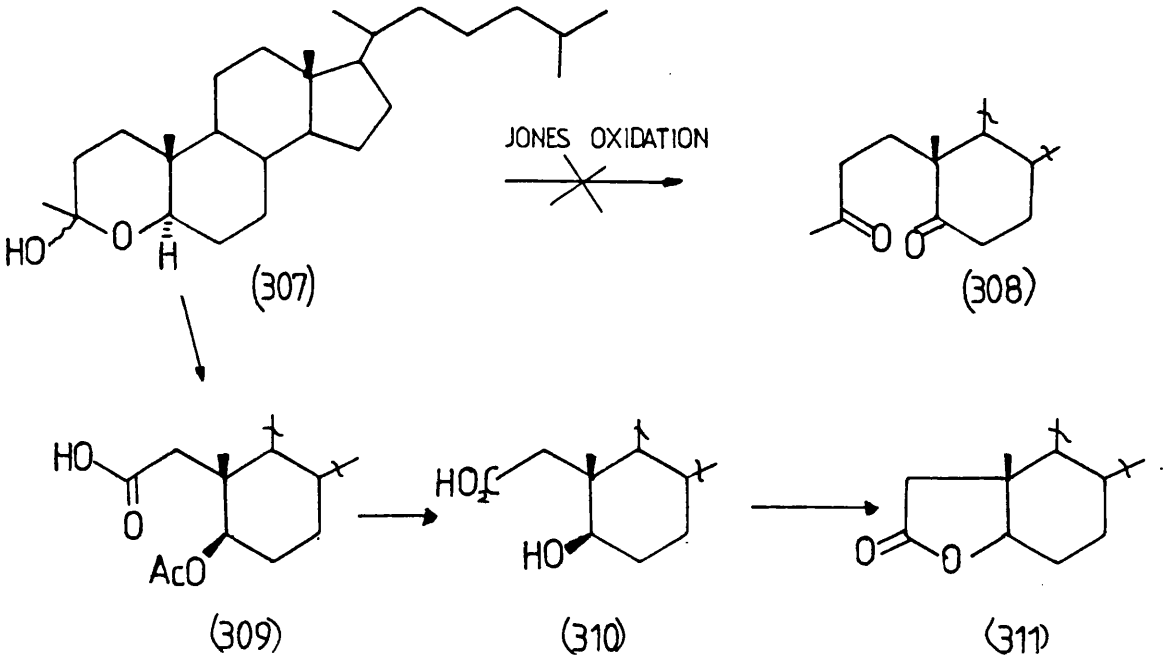


This δ → γ-lactone conversion provides a unique entry into samaderine B (306), and related natural products.[101]



(306)

Uusvuori *et al.*[102] have reported the anomalous Jones oxidation of cyclic hemiacetals as a method for ring contraction of polycyclic δ-lactones to γ-lactones. When attempting the Jones oxidation of hemiacetal (307) to the diketone (308), a 90% yield of acetoxy acid (309) was obtained. The structure of (309) was confirmed by hydrolysis to the hydroxy acid (310), and lactonisation to (311).

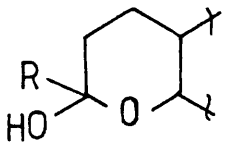


(307) (308)

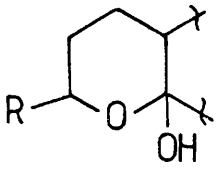
(309) (310) (311)

The authors prepared other type A hemiacetals, and found that this anomalous Jones oxidation is a useful reaction for C-C cleavage of hydroxy ketones which exist in the hemiacetal form. With type B cyclic

hemiacetals, normal Jones oxidation to diketones are known, but some C-C bond cleavage and macrocyclic keto lactone formation is observed.



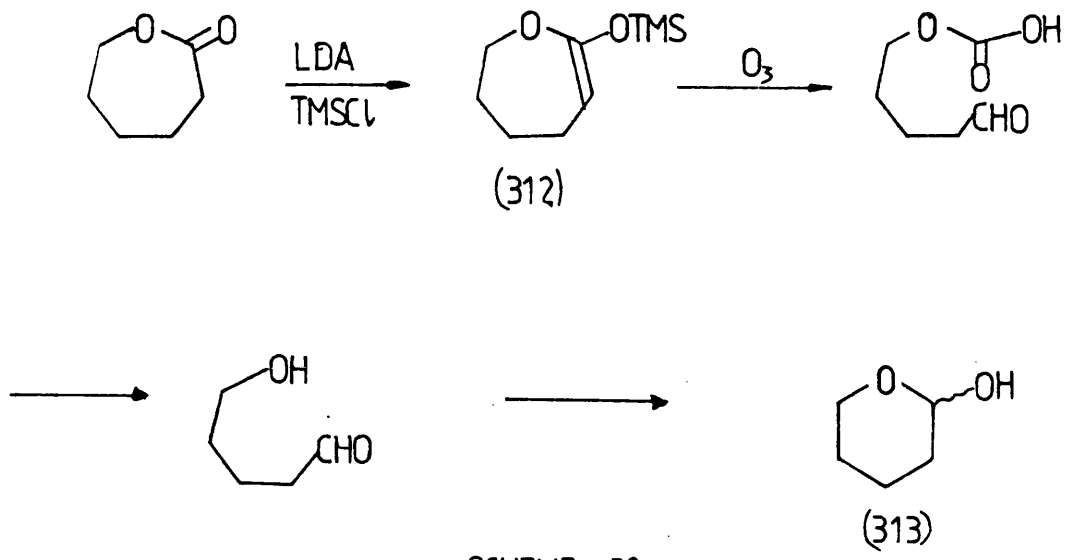
TYPE A



TYPE B

Apparently, the anomolous Jones oxidation will occur if the hydroxy ketone exists in a cyclic hemiacetal tautomer, and they suggest that an enol ether intermediate is involved in the oxidation, *via* the preferred endocyclic double bond formation. Thus, in cases where the hemiacetal tautomer prevails, the overall sequence constitutes a 3-step route for the ring contraction of polycyclic δ-lactones, with an unsubstituted α-carbon, to the corresponding γ-lactone.

Our work on lactone contractions concentrated on an ε→δ-lactone conversion, using the most general methodology possible. The initial strategy envisaged the formation of the trialkylsilyl ketene acetal of a simple lactone (312), and ozonolysis to give the carbonic acid, which on decarboxylation and recyclisation would give the ring contracted hemiacetal (313) (Scheme 50).



SCHEME 50

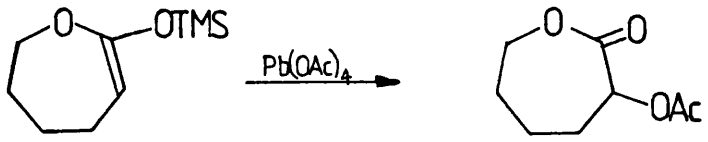
The reaction of ketone enolates with alkylating or silylating reagents can be used to prepare O-alkyl or O-silyl vinyl ethers. The analogous reaction of ester enolates would produce O-silyl or O-alkyl ketene acetals. Hauser[103] was the first to treat sodium ester enolates with trimethylchlorosilane (TMSCl), and he formulated the product as a C-silylated one. Later, Rochow,[104] using TMSCl and sodio ethyl acetate found both C- and O-alkylated products (22·3 and 13·7% respectively).

$$^{\ominus}CH_2CO_2Et + TMSCl \longrightarrow TMSCH_2CO_2Et + CH_2{=}C(OEt)(OTMS)$$

Rathke and Sullivan[105] have reported the synthesis of O-silyl ketene acetals. Lithium ester enolates, prepared from the ester and lithium-N-isopropylcyclohexylamide, were reacted with a variety of silylating and alkylating reagents. Reaction of lithio ethyl acetate with alkylating agents gave only C-alkylated products, yields ranging

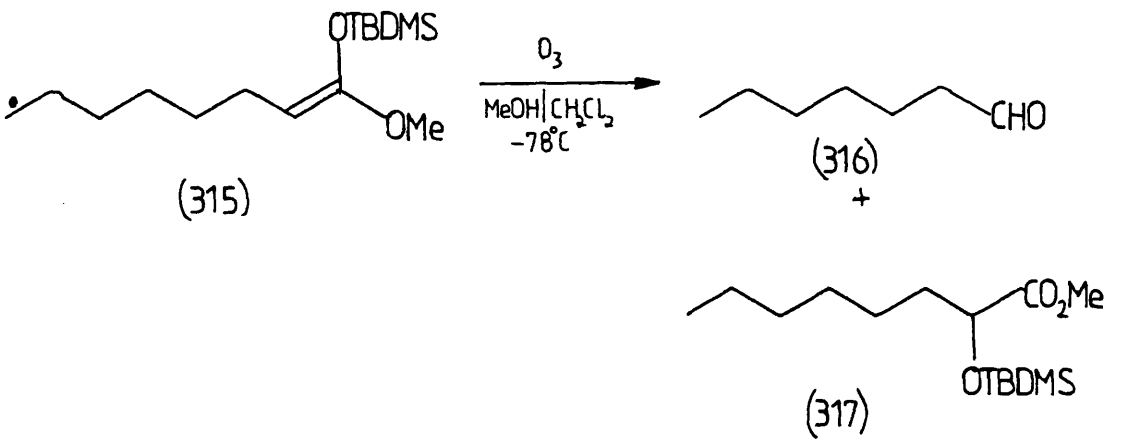
from 40% with iodomethane, to nearly quantitative with more reactive reagents. Similar behaviour was observed with the lithium enolates of ethyl hexanoate, and ethyl isobutyrate. Addition of TMSCl to lithio methyl acetate gave a mixture of O-silylated and C-silylated products. Results obtained showed that substitution on the alcohol portion of the ester favours C-silylation, whereas substitution on the α-carbon favours O-silylation.[105]

C-Silylated esters are quite stable to acid, and are readily isolated by acid extraction. The O-silyl derivatives are much more sensitive to acid hydrolysis, and also undergo thermal decomposition at relatively low temperatures, and attempts to separate the amine by vacuum distillation are generally unsuccessful. However, *t*-butyldimethylchlorosilane (TBDMSCl), as well as a greater tendency to furnish O-silylated products, also gives O-*t*-butyldimethyl ketene acetals, which are much more tolerant to cold aqueous acetic acid extraction, although distillation still results in extensive decomposition.[105] Rubottom[106] has prepared alkyl trimethylsilyl ketene acetals from esters and lactones using lithium diisopropylamide and TMSCl. Oxidation with lead tetra-acetate gave α-acetoxy lactones, (314).



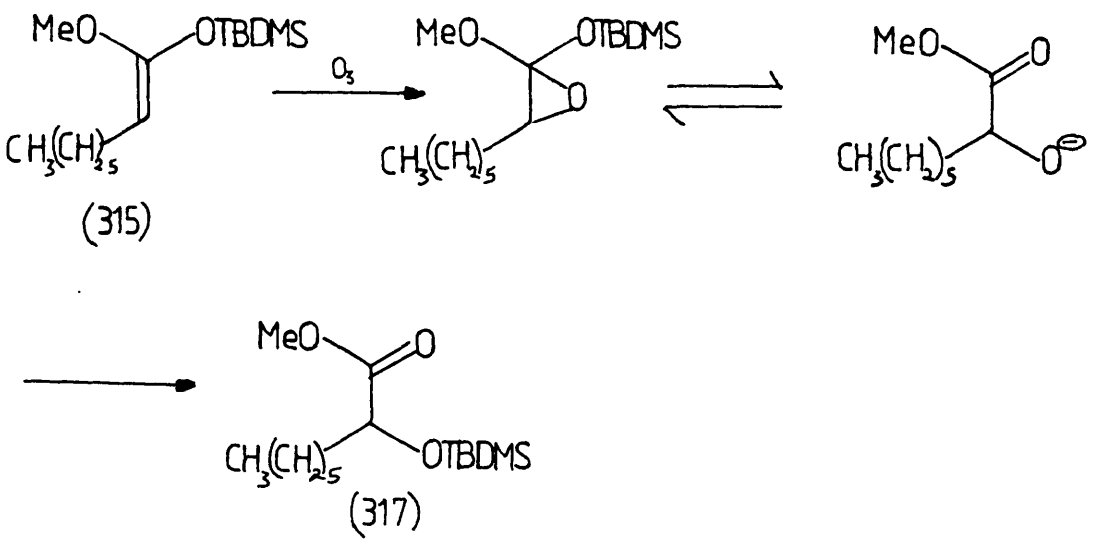
(314)

Thus O-silyl ketene acetals can be prepared, although their isolation presents problems. The ozonolysis of a straight chain ketene acetal has been reported. The TBDMS-ketene acetal (315) was ozonolysed in a mixture of dichloromethane and methanol to give (316) and (317) in 50% yield respectively.[107]



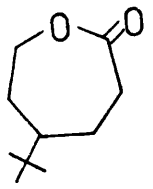
(315) (316) + (317)

The abnormal product (317) can be formulated as arising due to an intermediate oxirane, as shown below.



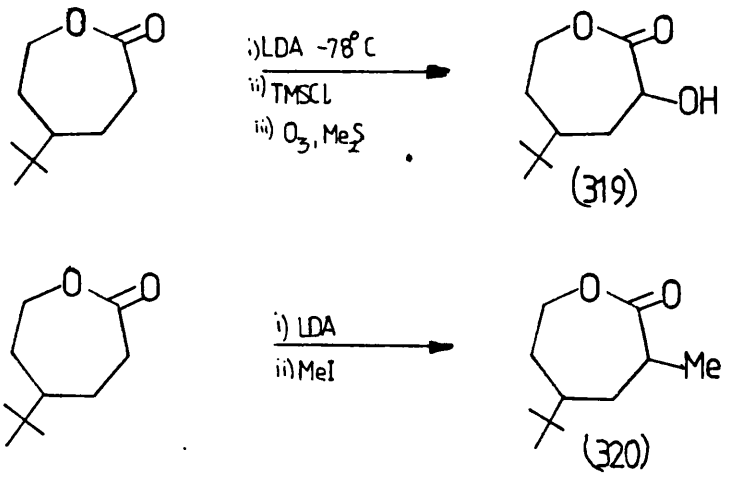
(315) (317)

Our proposed strategy for lactone contraction thus appears to be feasible:- O-silyl ketene acetals can be prepared and ozonolysis is possible. The lactone chosen for model studies was γ-*t*-butyl-ε-caprolactone (318), a readily handled crystalline solid, prepared in 51% yield by Baeyer-Villiger oxidation of 4-*t*-butylcyclohexanone.[108]



(318)

Initial attempts to prepare the O-silyl ketene acetal of (318), using lithium diisopropylamide and TMSCl were unsuccessful, unreacted starting material being recovered. However, the crude reaction mixture did show a trimethyl signal by ^1H NMR, and the absence of the methylene next to the carbonyl, indicating that reaction had occurred. On bulb to bulb distillation, however, the starting lactone was obtained. As the problem seemed to be one of isolation, the reaction was repeated, with direct ozonolysis of the crude reaction mixture. Ozonolysis in methanol and dichloromethane at -78°C, with reductive work up (Me_2S) gave unreacted (318), identical to the starting material. Repeating the reaction with dichloromethane only as the solvent gave a crystalline product in 30% yield, identified as the α-hydroxy lactone (319). This product could have been formed *via* the mechanism suggested for formation of (317), confirming formation of the O-silyl ketene acetal. A blank experiment involving ozonolysis of lactone (318) gave only unreacted starting material. To ensure that the initial anion of the lactone was being produced, (318) was treated with lithium diisopropylamide and iodomethane. The α-methylated product (320) was indeed produced, albeit in low yield.



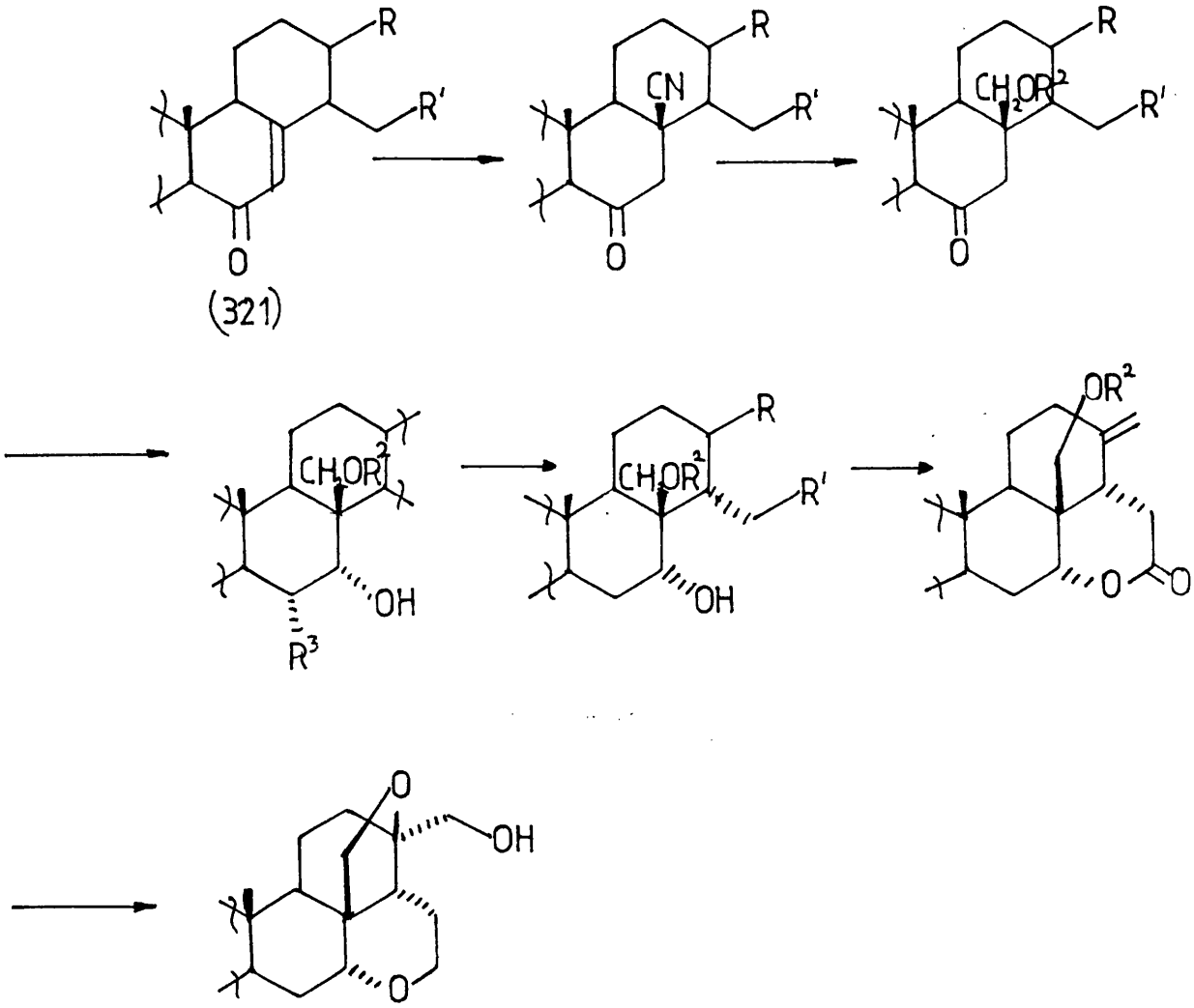
TBDMS derivatives of alcohols and ketones are reported to be much less sensitive to hydrolysis than the corresponding TMS derivatives.[105] THF solutions of lithium ester enolates are, however, inert to TBDMSCl at -78°C. A sluggish reaction occurs on warming to room temperature, but is accompanied by considerable Claisen condensation. Satisfactory results have been obtained using solvent mixtures containing hexamethylphosphoramide (HMPA).[105] Repeating the reaction of (318) with lithium N-isopropylcyclohexylamide and TBDMSCl with HMPA gave a complex mixture, which by GC/mass spec. showed no peak attributable to a silylated product. Ozonolysis gave a multi-component mixture, from which some starting lactone was recovered. Numerous experiments which involved varying the amine (cyclohexylamine, diisopropylamine), temperature of formation of the anion (-78°C→0°C), reaction time and ozonolysis solvent furnished no identifiable products.

Attempts to prepare the enol acetate of (318) as possibly being more stable than the O-TMS ketene acetal gave a yellow oil, which by ^1H NMR showed no vinyl proton or methyl signal, and by GC showed starting lactone and at least five other peaks.

Thus attempts at what appeared in theory to be a feasible

procedure for lactone contraction, for general use, and specifically for the D-ring in quassinoids proved unsuccessful in practice, only the α-hydroxy lactone (319) being obtained.

CONCLUSION



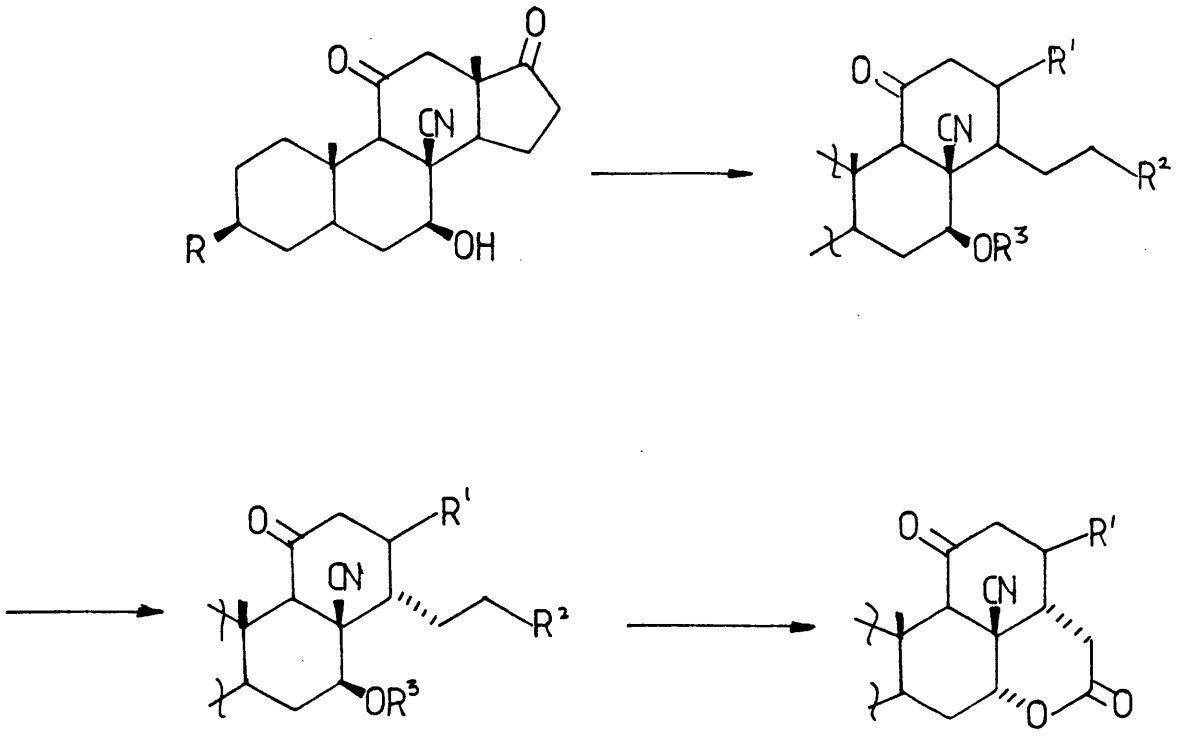
SCHEME 51

CONCLUSION

A B,C-ring functionalised precursor to bruceantin has been synthesised, with correct 8β functionality inserted. A C-7α hydroxy group prevented reaction with Et_2AlCN at the C-8 position, although a 7β-hydroxy-11-keto-8β nitrile steroid (243) was synthesised. Difficulties encountered in reduction of the nitrile were attributed to the steric encumbrance by the C-18 and C-19 methyl groups. However, use was made of the C-8β nitrile's proximity to the C-11β hydroxy group, and a C-8 - C-11 lactone bridge was constructed on a C-7 unsubstituted steroid (250). The presence of a C-7β hydroxy group prevented reduction of the C-11 ketone in (243), and thus lactone construction was not possible. All attempts to produce a D-ring fragmented product with a C-14α two carbon fragment were unsuccessful, and useful functionalisation of the C-ring was prevented by the instability of products obtained by allylic oxidation at C-12 (eg (268)).

An ε→δ-lactone contraction methodology using ozonolysis of lactone derived trialkylsilyl ketene, O,O-acetals was not successful, with only an α-substituted product being isolated (319). The failure of this methodology was attributed to the instability of the trialkylsilyl derivatives, and complex mixtures were obtained on ozonolysis.

A different approach, ie introduction of a C-8β substituent after D-ring fragmentation could be researched in further work on this project. A schematic approach is shown opposite in Scheme 51. An attempt at introducing an 8β substituent into a $\Delta^{7,8}$ enone has been reported as unsuccessful in a D-ring intact steroid,[66] but the fragmentation of the D-ring should allow unhindered attack by a nucleophile at C-8. Modification of the nitrile should be straight-



SCHEME 52

forward, and a C-7α hydroxy group could be introduced either by reduction of the C-6 ketone, elimination to a $\Delta^{5,6}$ intermediate, allylic oxidation and reduction, or elimination to a $\Delta^{6,7}$ intermediate, and OsO_4 oxidation, which should give the 6α,7α-diol from attack from the less hindered face. If a two carbon fragment with correct α-stereochemistry could be produced at C-14, lactonisation should be straightforward and the C-8 - C-13 ether linkage could be constructed by epoxidation of an exocyclic C-13 - C-17 double bond, (as for (273)), and intramolecular epoxide opening by the C-8β substituent. Preliminary attempts at preparing an intermediate such as (321) have been made, but results were not encouraging.

D-Ring fragmentation on a C-8β substituted steroid could also be investigated (Scheme 52). A three carbon unit at C-14, with correct α-stereochemistry, and correct oxidation state at the terminus, could be used to displace a suitably activated group at the C-7β position, thus providing the δ-lactone required. Modification of the nitrile and construction of the C-8 - C-13 ether linkage could then be achieved as suggested in Scheme 51.

As illustrated by the numerous synthetic efforts in the quassinoid field, their synthesis has to date proved to be long and problematic. The work presented in this thesis could be used as a guideline to the successes and failures of a steroidal approach.

EXPERIMENTAL

Instrumentation and Experimental Techniques

Infrared (IR) spectra were recorded in the range 4000-600 cm^{-1} using Perkin-Elmer 197 and 1310 grating spectrophotometers, with 0·05 mm polystyrene film as a calibration reference (1601·4 cm^{-1} absorption) and peaks are reported in wavenumbers (cm^{-1}). Spectra of samples were taken in $CHCl_3$ or $CHBr_3$ solution, or Nujol mulls.

Routine mass spectra from both electron ionisation (E.I.) and chemical ionisation (C.I., reagent gas isobutane), and high resolution accurate mass determinations were recorded with a VG Analytical 7070E instrument with a VG 2000 data system at an ionising potential of 70 eV. Unless otherwise stated, mass spectra data is from E.I. Where possible, the molecular ion peak ($M^{+\cdot}$) is indicated, as are all sizeable fragmentations with intensities.

Proton magnetic resonance (^1H NMR) spectra were recorded at 60 MHz on Hitachi Perkin-Elmer high resolution R-24B and Varian Anaspect EM-360 spectrometers, on JEOL 100 MHz, 250 MHz and 270 MHz, and Bruker 400 MHz spectrometers, using the SERC facility at Warwick University. ^{13}C NMR spectra were determined with a JEOL FX90Q or GNM GX FT 270 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, and are expressed in parts per million (δ) downfield from internal tetramethylsilane. 2D COSY spectra were performed at Warwick University. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp), and are uncorrected. Elemental microanalyses were carried out using the Carlo Erba 1106 Elemental Analyser.

For experimental procedures of a general nature, a complete general description is given and subsequent details for actual

examples include quantities of reagent, yield, and characterisation details.

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light, and developing with a 7% (w/v) methanol solution of dodecamolybdophosphoric acid (PMA) followed by warming of the t.l.c. plate.

Preparative thin layer chromatography (PLC) was carried out using 20 x 20 cm glass plates coated with a 1 mm layer of silica gel 60 F_{254} s (Merck) with a concentrating zone 4 x 20 cm.

Unless otherwise stated, petroleum refers to petroleum spirit boiling point range 60-80°C. This was distilled before use as an eluent in column chromatography.

Medium pressure flash column chromatography was routinely employed using Kieselgel 60 and 60 H silica gel (Merck) for reaction component separations. A pressure gradient was developed using a small, commercially available hand bellows (Gallenkamp). In all cases, columns were prepared in petroleum and chromatography was carried out with petroleum as the initial eluent, then eluting with ethyl acetate-petroleum mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column, or applied as a solution in toluene.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was re-distilled immediately prior to use.

Glassware used for low temperature alkylation reactions was baked in an oven at 120°C for *ca.* 12 h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirring bars were, however, additionally flame dried under dry nitrogen.

In all experiments, the excess solvent was evaporated with a Büchi rotary evaporator by using water aspirator reduced pressure, at room temperature to avoid unnecessary heating. All yields quoted are of purified products, and are uncorrected unless otherwise stated.

All other general reagents and solvents were purified when required, and where necessary, dried, using the methods described by D.D. Perrin, W. Armarego and D.R. Perrin in 'Purification of Laboratory Chemicals', 2nd Edn., Pergamon Press, Oxford, 1980. $[\alpha]_D^{20}$ values were recorded on a Perkin-Elmer 141 Polarimeter, using a 10 mm cell, so that

$$[\alpha]_D^{20} = \frac{\text{observed rotation x 100}}{0{\cdot}001 \text{ x concentration}}$$

where concentration is quoted in g/100 ml of solvent.

3β,17β-Diacetoxyandrost-5-ene ((199), R=R'=OAc) To a solution of dehydroepiandrosterone (195) (15 g, 50 mmol) in absolute ethanol (200 ml) stirred at 0°C was added portionwise $NaBH_4$ (1·9 g, 50 mmol). The mixture was stirred for 1 h, then the solvent removed *in vacuo* to give a colourless solid, which was dissolved in water (50 ml) and EtOAc (100 ml). The organic extract was washed with saturated aqueous NaCl (30 ml), dried ($MgSO_4$), and evaporated to give 3β,17β-dihdroxy-androst-5-ene (13·7 g, 94%) as a colourless solid, m.p. 174-176°C from methanol (lit.,[109] 175-178°C). Without purification, this was dissolved in Ac_2O (200 ml), and heated at reflux for 1 h. The mixture was poured onto ice, stirred for 1 h, and the resulting colourless precipitate filtered off, dissolved in CH_2Cl_2 (100 ml), dried ($MgSO_4$), and evaporated to give ((199) R=R'=OAc), (12·1 g, 69%) as colourless plates, m.p. 157-158°C from methanol [lit.,[110] 157·5 - 158°C (methanol)].

3β,17β-Diacetoxyandrost-5-ene-7-one (203) To a solution of 3β,17β-diacetoxyandrost-5-ene (199), (22·7 g, 60·7 mmol) in CCl_4 (120 ml) at reflux was added dropwise a solution of *t*-butyl chromate (from *t*-butanol (95 ml) and CrO_3 (37 g) in CCl_4 (100 ml)[46]), Ac_2O (20 ml) and AcOH (50 ml). The mixture was stirred at reflux for 9 h, cooled in an ice-bath, and oxalic acid (60 g) in water (100 ml) cautiously added. When addition was complete, the mixture was allowed to warm to room temperature, and stirred for a further 2 h. The green mixture was then filtered through a Celite pad, and the aqueous layer extracted with CCl_4 (3 x 100 ml). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (300 ml), water (300 ml), saturated aqueous NaCl (100 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a pale green solid, recrystallised from benzene-petroleum

ether to give enone (203) (12·07 g) as colourless needles. Flash chromatography of the mother liquors (1:2 EtOAc : petroleum ether) gave a further 2·3 g of (203); Total yield (14·37 g, 61%), m.p. 210-212°C from benzene-petroleum ether, (lit.,[46] 216-219°C (ether)); $[\alpha]_D^{20}$ -123° (c 1·18 in $CHCl_3$), [lit.,[46] -125° (c 1·24 in ($CHCl_3$)]; R_f 0·42 (SiO_2, 3:7 EtOAc : petroleum ether); ν_{max} ($CHCl_3$) 1720 and 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·80 (3H, s, 18-CH_3), 1·13 - 2·56 (17H, m), 1·20 (3H, s, 19 -CH_3), 2·03 (3H, s, -$OCOCH_3$), 2·04 (3H, s, -$OCOCH_3$), 4·64 (1H, dd, J 7·3, 9·3 Hz, 17-H), 4·70 (1H, m, 3-H), 5·70 (1H, d, J 1·7 Hz, 6-H); $^m/z$ 328 (100%), 187 (30), 161 (35), 43 (70).

Flash chromatography of the mother liquors gave two other compounds,

i) 3β,17β-Diacetoxy-5α-hydroxyandrost-6-one (204), (1·18 g, 5%) as colourless plates, m.p. 229-230°C from benzene-petroleum ether, [lit.,[46] 232-234°C (benzene-petroleum ether)]; $[\alpha]_D^{20}$ -69° (c 1·58 in $CHCl_3$), [lit.,[46] -62° (c 1·54 in $CHCl_3$)]; R_f 0·35 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 406·2347. Calc. for $C_{23}H_{34}O_6$: M, 406·2356); ν_{max} ($CHCl_3$) 3400 and 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·76 (3H, s, 18-CH_3), 0·81 (3H, s, 19-CH_3), 1·22 - 2·22 (18H, m), 2·00 (3H, s, -$OCOCH_3$), 2·03 (3H, s, -$OCOCH_3$), 2·37 (1H, s, 5-OH), 2·72 (1H, t, J 12·7 Hz, 7α-H), 4·61 (1H, dd, J 7·7, 9·2 Hz, 17-H), 5·02 (1H, m, 3-H); $^m/z$ 406 (M^+, 7%), 346 (80). For 2D COSY Spectrum, see Appendix.

ii) 3β,17β-Diacetoxy-5α,6α-epoxyandrostane (205), (1·36 g, 6%) as colourless crystals, m.p. 159-160°C from petroleum ether (lit.,[111] 165-166°C); $[\alpha]_D^{20}$ -75° (c 1·54 in $CHCl_3$), [lit.,[111] -71° (c 1·43 in $CHCl_3$)]; R_f 0·59 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 390·2402. Calc. for $C_{23}H_{34}O_5$: M, 390·2406); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·62 (1H, m, 9α-H), 0·75 (3H, s, 18-CH_3), 0·81 -

2·22 (18H, m), 1·00 (3H, s, 19-CH_3), 2·02 (6H, s, 2 x -$OCOCH_3$), 3·08 (1H, d, J 2·3 Hz, 6β-H), 4·55 (1H, dd, J 7·4, 9·2 Hz, 17-H), 4·75 (1H, m, 3-H); $^m/z$ 390 (M^+, 10%), 330 (60); n.O.e. expt.; irradiation of the 9α-H signal at δ0·62 resulted in no change in intensity of the signal at δ3·08 (H-6), confirming the α-orientation of the epoxide. For 2D COSY Spectrum, see Appendix.

3β,17β-Diacetoxy-7α-hydroxyandrostane (206), To a solution of enone (203), (5·0 g) in AcOH (25 ml) was added PtO_2 (*ca* 100 mg, dried at 200°C under vacuum). The vessel was evacuated at the water-pump for 5 min, and then exposed to an atmosphere of H_2. After stirring for 22 h at room temperature, the reaction mixture was filtered, and the solvent removed *in vacuo* to give a colourless oil, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) 3β,17β-Diacetoxyandrostane (209), (0·48 g, 10%) as colourless plates, m.p. 121-122°C from methanol [lit.,[112] 128-129°C (ethanol)]; R_f 0·82 (SiO_2, 3:7 EtOAc : petroleum ether).

Continued elution (3:7 EtOAc : petroleum ether) gave

ii) title compound (206), (3·38 g, 67%) as colourless needles, m.p. 184-185°C from ether [lit.,[46] 184·5 - 186°C (ether)]; $[\alpha]_D^{20}$ -13·5° (c 1·44 in $CHCl_3$) [lit.,[46] $-15^o \pm 4^o$ (c 1·454 in $CHCl_3$)]; R_f 0·32 (SiO_2, 3:7 EtOAc : petroleum ether); ν_{max} ($CHCl_3$) 3400 and 1720 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·76 (3H, s, 18-CH_3), 0·81 (3H, s, 19-CH_3), 1·08 - 2·20 (21H, m), 1·99 (3H, s, -$OCOCH_3$), 2·02 (3H, s, -$OCOCH_3$), 3·81 (1H, m, 7-H), 4·60 (1H, dd, J 7·7, 9·2 Hz, 17-H), 4·69 (1H, m, 3-H); $^m/z$ 374 (M^+-H_2O, 5%), 314 (80), 254 (35), 43 (100).

Small quantities of 3β,17β-diacetoxyandrosta-7-one (207) were isolated on a large scale (>20 g) reaction, m.p. 194-195°C from methanol [lit.,[46] 192-193°C (methanol)].

3β,17β-Diacetoxyandrost-7-ene (201) To a solution of alcohol (206) (2·81 g, 7 mmol) in pyridine (9 ml) at -15°C was slowly added CH_3SO_2Cl (2·2 ml) in pyridine (5 ml). The mixture was stirred at room temperature for 24 h, diluted with Et_2O (20 ml), and washed with water (20 ml), 2N H_2SO_4 (10 ml), water (20 ml), saturated aqueous $NaHCO_3$ (10 ml), and then dried ($MgSO_4$). Evaporation of the solvent gave a reddish-brown solid, 3β,17β-diacetoxy-7α-mesyloxy-androstane (2·86 g, 85%); m.p. 127-128°C from methanol [lit.,[46] 121-123°C (methanol)]. Elimination of this mesylate was effected by heating at reflux in a mixture of toluene (9 ml) and s-collidine (9 ml) for 7 h. The reaction mixture was diluted with Et_2O (20 ml), washed with 1N H_2SO_4 (10 ml), saturated aqueous $NaHCO_3$ (20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a colourless oil, which crystallised on cooling in methanol to give colourless needles of (201), (1·45 g, 55% from (206)); m.p. 126-127°C from methanol [lit.,[46] 127-128°C (methanol)]; R_f 0·71 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 374·2450. Calc. for $C_{23}H_{34}O_4$: M, 374·2457); ν_{max} (Nujol) 1720 cm^{-1}; δ_H (100 MHz, $CDCl_3$) 0·70 - 1·81 (19H, m), 0·82 (3H, s, 18-CH_3), 1·20 (3H, s, 19-CH_3), 2·00 (6H, s, 2 x -$OCOCH_3$), 4·12 (1H, m, 17-H), 4·60 (1H, m, 3-H), 5·19 (1H, s, 7-H); $^m/z$ 374 (M^+, 20%), 314 (60), 254 (30), 43 (100).

Also isolated on prolonged reaction time (>12 h) were small quantities of 3β,17β-diacetoxy-7β-chloroandrostane (210), m.p. 158-159°C (hexane) [lit.,[46] 160-161°C (hexane)].

3β,17β-Diacetoxyandrost-7,9(11)-diene (202), To a solution of (201), (2·6 g, 7 mmol) in 95% ethanol (35 ml, prepared from absolute ethanol and 5% water) was added $Hg(OAc)_2$ (5·12 g, 16·1 mmol, recrystallised

from AcOH) in AcOH (52 ml). The mixture was stirred under N_2 at room temperature for 3 days. $Hg(OAc)_2$ (5·12 g, 16·1 mmol) was then added, and the mixture stirred for a further 3 days. The yellow reaction mixture was then filtered, and the yellow solid washed copiously with Et_2O. The filtrate was washed with water (10 x 20 ml), and the aqueous extracts re-extracted with Et_2O (2 x 30 ml). All organic extracts were combined, and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil, subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give a pale yellow oil, which solidified on trituration with cold petroleum ether, yielding 1·61 g of colourless crystals, m.p. 112-114°C, a mixture of (201) and (202). Repeated recrystallisation afforded a small sample of pure (202); m.p. 130-131°C (methanol) [lit.,[46] 131-132·5°C (methanol)]; R_f 0·72 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 372·2279. Calc. for $C_{23}H_{32}O_4$: M, 372·2300); ν_{max} (Nujol) 1720 cm^{-1}; λ_{max} 235, 242 and 250 nm; δ_H (400 MHz, $CDCl_3$) 0·63 (3H, s, 18-CH_3), 0·95 (3H, s, 19-CH_3), 1·01 - 2·35 (16H, m), 2·02 (3H, s, -$OCOCH_3$), 2·06 (3H, s, -$OCOCH_3$), 4·56 (1H, dd, J 7·8, 9·2 Hz, 17-H), 4·65 (1H, m, 3-H), 5·19 (1H, dd, J 2·4, 5·1 Hz, 7-H), 5·37 (1H, m, 11-H); $^m/z$ 372 (M^+, 20%), 312 (20), 252 (30), 43 (100).

Routinely, the pure diene (202) was not isolated. The reaction was monitored by quantitative UV, the percentage of diene in the mixture being calculated from the extinction coefficients for the maxima at 235 and 242 nm (log ε = 4·14 and 4·18 respectively). The crude ene (201)/diene (202) mixture was then used in the next stage (see Discussion).

3β,17β-Diacetoxy-9-11α-epoxyandrost-7-ene (216), To a solution of the (201)/(202) mixture (3·33 g, 5·4 mmol (202)) in dry Et_2O (20 ml) was added an ethereal monophthalicperacid solution[113] (17·1 ml, 0·321M, 5·5 mmol). This was left to stand for 4 days at 5°C. The mixture was then washed with saturated aqueous $NaHCO_3$ (20 ml), and the organic layer dried ($MgSO_4$). Evaporation of the solvent gave a colourless solid, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted 3β,17β-diacetoxyandrost-7-ene (201), (1·29 g, 39% from the starting mixture); m.p. 126-127°C from methanol [lit.,[46] 127-128°C (methanol)],

ii) Title compound (216), (1·43 g, 69% from available diene) as colourless plates, m.p. 151-152°C from ether [lit.,[52] 152-153·5°C (ether)]; R_f 0·44 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 388·2247. Calc. for $C_{23}H_{32}O_5$: M, 388·2250); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 0·80 (3H, s, 18-CH_3), 1·00 (3H, s, 19-CH_3), 1·05 - 2·40 (16H, m), 2·02 (3H, s, -$OCOCH_3$), 2·04 (3H, s, -$OCOCH_3$), 3·25 (1H, d, J 5·3 Hz, 11-H), 4·60 - 4·80 (2H, m, 3-H and 17-H), 5·64 (1H, m, 7-H); $^m/z$ 388 (M^+, 35%), 300 (75), 43 (100).

3β,17β-Diacetoxy-9β-androst-7-ene-11-one (218) To a solution of epoxide (216) in ether (10 ml) was added $BF_3.OEt_2$ (4 drops). The mixture was allowed to stand at room temperature for 21 h, and then washed with saturated aqueous $NaHCO_3$ (5 ml) and the organic layer dried ($MgSO_4$). Evaporation of the solvent gave (218), (0·82 g, 55%) as colourless needles, m.p. 144-146°C from ether [lit.,[49] 146-149°C (ether)]; $[\alpha]_D^{20}$ -170° (c 0·916 in $CHCl_3$) [lit.,[49] -175° (c 0·940 in $CHCl_3$)]; R_f 0·51 (SiO_2, 3:7 EtOAc : petroleum ether); Found: M^+, 388·2245. Calc. for $C_{23}H_{32}O_5$: M, 388·2250; ν_{max} ($CHCl_3$) 1720 cm^{-1};

δ_H (400 MHz, $CDCl_3$), 0·92 (3H, s, 18-CH_3), 1·25 (3H, s, 19-CH_3), 1·30 - 2·60 (16H, m), 2·00 (3H, s, -$OCOCH_3$), 2·04 (3H, s, -$OCOCH_3$), 3·27 (1H, m, 9β-H), 4·63 (1H, dd, J 7·2, 9·5 Hz, 17-H), 4·76 (1H, m, 3-H), 5·56 (1H, m, 7-H); $^m/z$ 380 (M^+, 9%), 328 (30), 43 (100); n.O.e. expt. irradiation of the 9-H signal at δ3·27 gave enhancements in intensity of the signals at δ0·92 and δ1·25 (18-CH_3 and 19-CH_3) of 8 and 11% respectively, confirming the β-orientation of the C-9 proton.

3β,17β-Diacetoxy-7β-hydroxyandrost-8-ene-11-one (220), To a solution of (218) (52 mg, 0·13 mmol) in CH_2Cl_2 (10 ml) at 0°C was added dropwise a solution of m-CPBA (26·6 mg, 0·15 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at 0°C for 7 h and then washed with saturated aqueous $NaHCO_3$ (10 ml) and saturated aqueous NaCl (10 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated to give a colourless solid, 3β,17β-diacetoxy-7,8β-epoxyandrost-11-one (219), m.p. 127-129°C from methanol. Without purification, (219) was dissolved in CH_2Cl_2 (3 ml), and DBU (2 drops) added. The mixture was allowed to stand at room temperature for 2 h, and the solvent then evaporated to give a colourless solid, which was subjected to flash chromatography (3:7 EtOAc : petroleum ether) to give (220) (26 mg, 48% from (218)), as colourless plates, m.p. 198-201°C (decomp) from EtOAc-petroleum ether ; R_f 0·13 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 404·2174. Calc. for $C_{23}H_{32}O_6$: M, 404·2197); ν_{max} ($CHBr_3$) 3420, 1720 and 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·85-2·75 (16H, m), 0·89 (3H, s, 18-CH_3), 1·24 (3H, s, 19-CH_3), 2·01 (3H, s, -$OCOCH_3$), 2·04 (3H, s, -$OCOCH_3$), 4·64 (1H, t, J 6·7 Hz, 7-H), 4·40 (1H, br, s, 7-OH), 4·64 (1H, m, 3-H), 4·83 (1H, dd, J 6·9, 9·3 Hz, 17-H); $^m/z$ 404 (M^+, 10%), 316 (50), 43 (100).

3β,17β-Diacetoxyandrost-7-ene-11-one (223), A solution of (218) (830 mg, 2·14 mmol) in benzene : petroleum ether (7 ml, 1:1) was rapidly adsorbed onto a column of activated alumina[50] (5 x 1 cm). The column was immediately eluted with benzene (10 ml) and pyridine (0·1 ml), and the eluent passed rapidly through the column once more. The eluent was then evaporated to give (223) (581 mg, 70%) as colourless plates, m.p. 154-155°C from ether; R_f 0·51 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 388·2241. Calc. for $C_{23}H_{32}O_5$: M, 388·2250); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·61 (3H, s, 18-CH_3), 0·97 (3H, s, 19-CH_3), 1·06-2·82 (17H, m), 2·02 (3H, s, -$OCOCH_3$), 2·04 (3H, s, -$OCOCH_3$), 4·68 (1H, m, 3-H), 4·82 (1H, dd, J 7·5, 9·3 Hz, 17-H), 5·35 (1H, m, 7-H); $^m/z$ 388 (M^+, 100%), 328 (80).

3β,17β-Diacetoxy-7α-hydroxyandrost-8-ene-11-one (196), A solution of (223) (43 mg, 0·11 mmol) in CH_2Cl_2 (10 ml) at 0°C was reacted with m-CPBA (24 mg, 0·13 mmol) in CH_2Cl_2 (2 ml), and further with DBU (2 drops) as described for the preparation of (220). The title compound was obtained in 54% yield as colourless needles, m.p. 213-215°C (decomp); R_f 0·14 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 404·2211. Calc. for $C_{23}H_{32}O_6$: M, 404·2197); ν_{max} ($CHCl_3$) 3420, 1720 and 1660 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·79 (3H, s, 18-CH_3), 1·09 (3H, s, 19-CH_3), 1·21-2·95 (17-H, m), 2·03 (3H, s, -$OCOCH_3$), 2·05 (3H, s, -$OCOCH_3$), 4·20 (1H, d, J 3·8 Hz, 7-H), 4·72 (1H, m, 3-H), 4·90 (1H, dd, J 7·1, 9·2 Hz, 17-H); $^m/z$ 404 (M^+, 35%), 316 (35), 43 (100).

3β,17β-Diacetoxy-7-hydroxy-7-methylandrost-5-ene (235), To a stirred slurry of CuI (0·38 g, 2 mmol) in ether (10 ml) at 0°C was added MeLi (2·86 ml, 1·4M, 4 mmol) dropwise. The colourless solution obtained was stirred for a further 10 min at 0°C, and then enone (203) (0·38 g, 1 mmol) added in one portion. The yellow mixture was stirred at 0°C for 45 min and then at room temperature for 3 h. After dilution with Et_2O (20 ml), the organic layer was washed with saturated aqueous NH_4Cl (20 ml), water (20 ml) and saturated aqueous NaCl (15 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a colourless solid, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted starting material (203) (100 mg, 26%)

ii) Title compound (235), (46 mg, 11%) as a colourless foam; R_f 0·32 (3:7 EtOAc : petroleum ether); (Found: C, 71·4; H, 9·1%. $C_{24}H_{36}O_5$ requires C, 71·26; H, 8·97%); ν_{max} ($CHBr_3$) 3590 and 1720 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0·82 (3H, s, 18-CH_3), 1·12 (3H, s, 19-CH_3), 1·20 (3H, s, 7-CH_3), 1·25-2·40 (18H, m), 2·03 (6H, s, 2 x -$OCOCH_3$), 4·60 (2H, m, 3-H and 17-H), 5·20 (1H, s, 6-H); δ_C ($CDCl_3$) 171·00 (acetate carbonyl), 170·21 (acetate carbonyl), 139·00 (C-5), 131·92 (C-6), 82·16 (C-3), 73·15 (C-17), 72·56 (C-7); $^m/_z$ 344 (50%), 329 (100).

3β,17β-Diacetoxy-5-cyanoandrosta-7-one (238) To a solution of the enone (203) (400 mg, 1·03 mmol) in benzene (9 ml) under an atmosphere of N_2 was added dropwise Et_2AlCN (3·0 ml, 1·8M in toluene, 5·4 mmol).[62] The mixture was stirred for a further 3½ h, and then poured onto 2N NaOH/ice (10 ml), and extracted with CH_2Cl_2 (2 x 25 ml). The organic layers were then combined, washed with water (10 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a colourless solid, which

was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted starting material (203), (120 mg, 30%).

ii) Title compound (238) (286 mg, 67%) as colourless needles, m.p. 236-237°C from ethanol-water; R_f 0·24 (SiO_2, 3:7 EtOAc : petroleum ether); (Found C, 69·8; H, 8·2; N, 3·2%. $C_{24}H_{33}NO_5$ requires C, 69·37; H, 8·00; N, 3·37%); ν_{max} (Nujol) 2240 and 1730 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0·80 (3H, s, 18-CH_3), 1·26 (3H, s, 19-CH_3), 1·40-2·70 (19H, m), 2·03 (6H, s, 2 x $OCOCH_3$), 4·63 (1H, t, J 7·5 Hz, 17-H), 5·13 (1H, m, 3-H); δ_C ($CDCl_3$) 205·1 (C-7), 170·7 (acetate carbonyl), 169·6 (acetate carbonyl), 120·4 (nitrile), 81·4 (C-3), 78·1 (C-17); $^m/_z$ 415 (M^+, 20%), 355 (70), 328 (30).

3β,17β-Diacetoxyandrost-8-ene-11-one (222), To a solution of (218) (116 mg) in Et_2O (5 ml) was added 1 ml of a solution of conc. H_2SO_4 (1 ml) in Et_2O (25 ml). The reaction mixture was kept in the dark for 4½ h and then quenched with saturated aqueous $NaHCO_3$ (5 ml), and the organic extract washed with saturated aqueous NaCl (5 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a colourless oil, which was subjected to preparative t.l.c. to give the title compound (222) (114 mg, 98%) as colourless needles, m.p. 173-174°C from methanol [lit.,[49] 172-173°C (methanol)].

3β,17β-Diacetoxy-8β-cyanoandrosta-11-one (240), To a solution of enone (222) (50 mg, 0·13 mmol) in benzene (2 ml) and toluene (1 ml) at 0°C, under an atmosphere of N_2 was added dropwise Et_2AlCN (0·43 ml, 1·8M in toluene, 0·78 mmol). The mixture was stirred for 1½ h at 0°C, and then worked up as for (238), to give a colourless solid, which was subjected to flash chromatography (1:9 EtOAc : petroleum

ether) to give

i) Unreacted starting enone (222), (9·5 mg, 19%).

ii) Title compound (240), (30·2 mg, 60%) as colourless needles, m.p. 217-218°C from ethanol-water; R_f 0·13 (SiO_2, 3:7 EtOAc : petroleum ether); (Found C, 69·1, H, 8·1; N, 3·3%. $C_{24}H_{33}NO_5$ requires C, 69·37; H, 8·00; N, 3·37%); ν_{max} (Nujol) 2236, 1738 and 1720 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0·7-2·35 (17H, m), 1·10 (3H, s, 18-CH_3), 1·42 (3H, s, 19-CH_3), 2·02 (3H, s, -$OCOCH_3$), 2·06 (3H, s, -$OCOCH_3$), 2·40 (2H, s, 12-H), 4·65 (1H, m, 3-H), 4·78 (1H, t, J 7·5 Hz, 17-H); $^m/z$ 415 (M^+, 3%), 355 (70), 295 (20), 43 (100).

3β-Acetoxy-8β-cyano-11-oxo-5α-ergost-22-ene (242) To a solution of 3β-Acetoxy-11-oxo-5α,8,22-ergostadiene (241)[144] (227 mg, 0·5 mmol) in benzene (6 ml) and toluene (3 ml) at 0°C under an atmosphere of N_2 was added dropwise Et_2AlCN (1·67 ml, 1·8M in toluene, 3 mmol). The mixture was stirred for 2¼ h at 0°C, and then worked up as for (238), to give a colourless solid, subjected to flash chromatography (1:19 EtOAc : petroleum ether) to give

i) Unreacted starting enone (241) (35 mg, 15%).

ii) Title compound (242), (164 mg, 68%), as colourless needles, m.p. 214-217°C from ethanol-water [lit.,[115] 218-220°C (chloroform-methanol)]; $[\alpha]_D^{20}$ + 32° (c 0·68 in $CHCl_3$), [lit.,[115] $[\alpha]_D^{23}$ + 38·9°]; R_f 0·68 (SiO_2, 3:7 EtOAc : petroleum ether); (Found C, 77·2; H, 9·9; N, 2·9%. $C_{31}H_{47}NO_3$ requires C, 77·29; H, 9·83; N, 2·91%); ν_{max} (Nujol) 2236, 1735 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·7-2·3 (33H, m), 1·02 (3H, s, 18-CH_3), 1·41 (3H, s, 19-CH_3), 2·02 (3H, s, -$OCOCH_3$), 2·34 (1H, d, J 12·5 Hz, 12-H), 2·59 (1H, d, J 12·5 Hz, 12-H), 4·68 (1H, m, 3-H), 5·21 (2H, m, 22-H and 23-H); $^m/z$ 481 (M^+, 100%), 454 (14), 438 (70).

8β-cyano-3β,11β-dihydroxy-5α-ergost-22-ene (248) To a solution of (242) (50 mg, 0·10 mmol) in benzene (3 ml) at 0°C was added dropwise DIBAL (0·27 ml, 1·5M, 0·42 mmol). After stirring at 0°C for 1 h, the mixture was poured into ice-cold 1N HCl (5 ml), and extracted with EtOAc (2 x 10 ml). The organic extracts were combined, washed with water (5 ml), saturated aqueous NaCl (5 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a colourless solid, which was subjected to flash chromatography to give the title diol (248), (32 mg, 70%), m.p. 213-215°C from methanol [lit.,[116] 214-216°C]; R_f 0·41 (SiO_2, 1:1 EtOAc : petroleum ether); (Found C, 79·1; H, 10·5; N, 3·0%. $C_{29}H_{47}NO_2$ requires C, 78·86; H, 10·72; N, 3·17%); ν_{max} ($CHCl_3$) 3600, 3400 and 2220 cm^{-1}; δ_H (400 MHz, $CDCl_3$), 0·61-2·20 (37H, m), 0·99 (3H, s, 18-CH_3), 1·42 (3H, s, 19-CH_3), 3·56 (1H, m, 3-H), 4·43 (1H, d, J 2·8 Hz, 11-H), 5·20 (2H, m, 22-H and 23-H); $^m/z$ 441 (M^+, 62), 398 (47), 298 (100), 280 (55).

3β,17β-Diacetoxy-8β-cyano-7β-hydroxyandrosta-11-one (243), To a solution of enone (220) (5 mg, 0·012 mmol) in benzene (2 ml) and toluene (1 ml) at 0°C under an atmosphere of N_2 was added dropwise Et_2AlCN (0·1 ml, 1·8M in toluene, 0·18 mmol). The mixture was stirred at 0°C for 45 min and then worked up as for (238), to give a colourless solid, which was subjected to flash chromatography to give the title compound (243), (4·9 mg, 92%) as colourless needles m.p. 288-289°C (decomp) from ethanol-water; R_f 0·15 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 431·2301. Calc. for $C_{24}H_{33}NO_6$: M, 431·2305); ν_{max} (Nujol) 3560, 2240 and 1720 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0·70-2·40 (18H, m), 1·10 (3H, s, 18-CH_3), 1·40 (3H, s, 19-CH_3), 2·03 (3H, s, -$OCOCH_3$),.2·06 (3H, s, -$OCOCH_3$), 3·62 (1H, m, 7-H), 4·64 (1H,

m, 3-H), 4·78 (1H, t, J 7·5 Hz, 17-H); $^{m}/z$ 431 (M^+, 4%), 388 (4), 371 (50), 327 (30). For X-ray data, see Appendix.

3β,11β-Dihydroxy-5α-ergost-22-ene-8β-carboxamidic acid, 8,11-lactone (249) To a solution of (248) (54 mg, 0·12 mmol) in absolute EtOH (25 ml) was added conc. HCl (2·5 ml). The mixture was refluxed under an atmosphere of N_2 for 2 h, and then diluted with EtOAc (10 ml), and the organic layer washed with saturated aqueous $NaHCO_3$ (5 ml), water (5 ml), saturated aqueous NaCl (5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a colourless oil, which was subjected to flash chromatography (8:2 EtOAc : petroleum ether) to give

i) Unreacted starting diol (248), (9 mg, 16%).

ii) Title compound (249), (41 mg, 76%), as colourless needles, m.p. 145-147°C from methanol (lit.,[117] 170·5 - 171·5°C); R_f 0·20 (SiO_2, EtOAc); (Found C, 78·7; H, 10·6; N, 3·3%. $C_{29}H_{47}NO_2$ requires C, 78·85; H, 10·73; N, 3·17%); ν_{max} (Nujol) 3600, 2400 and 1685 cm^{-1}; δ_H (270 MHz, $CDCl_3$), 0·70-2·31 (37H, m), 0·80 (3H, s, 18-CH_3), 0·94 (3H, s, 19-CH_3), 3·60 (1H, m, 3-H), 4·54 (1H, d, J 5 Hz, 11-H), 5·10 (2H, m, 22-H and 23-H); $^{m}/z$ 441 (M^+, 20%), 396 (30), 296 (40), 69 (100), 55 (100).

3β,11β-Dihydroxy-5α-ergost-22-ene-8β-carboxylic acid, 8,11-lactone (250) To a solution of (249), (30 mg, 0·06 mmol) in dioxane (3 ml) was added $NaNO_2$ (81 mg) in water (0·5 ml) under an atmosphere of N_2. To this mixture was added dropwise a solution of AcOH (0·72 ml) in dioxane (1·46 ml). After stirring at room temperature for 30 min, the temperature was raised to 55°C, and $NaNO_2$ (81 mg) in water (0·5 ml) added followed by dropwise addition of AcOH (0·72 ml) in dioxane (1·46 ml). The mixture was heated at 55°C for a further 4 h, and then

diluted with EtOAc (10 ml), the organic layer washed with water (5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a colourless solid, which was subjected to flash chromatography (3:7 EtOAc : petroleum ether) to give title lactone (250) (27 mg, 90%) as colourless needles, m.p. 264·3-267·3 (decomp) from methanol; R_f 0·8 (SiO_2, EtOAc); (Found: M^+, 442·3394. Calc. for $C_{29}H_{46}O_3$: M, 442·3446); ν_{max} ($CHCl_3$) 3600 and 1760 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·73-2·20 (36H, m); 0·79 (3H, s, 18-CH_3), 0·90 (3H, s, 19-CH_3), 3·57 (1H, m, 3-H), 4·61 (1H, d, J 4·7 Hz, 11-H), 5·20 (2H, m, 22-H and 23-H); $^m/z$ 442 (M^+, 20), 315 (35), 271 (30), 69 (100), 55 (100).

D-RING FRAGMENTATIONS

3β-Acetoxyandrost-5-en-17-one ((199), R = OAc, R' = = O) Obtained by acetylation of dehydroepiandrosterone (195) (Ac_2O, Δ), as colourless needles (98% yield) m.p. 168-170°C from ethyl acetate [lit.,[118] 165-167°C (dichloromethane-methanol).

3β-Acetoxyandrost-5-en-17-oxime (257) Ketone (199) (2·0 g), hydroxylamine hydrochloride (2·0 g) and pyridine (2 ml) were heated at reflux in ethanol (45 ml) for 45 min. The solvent was removed *in vacuo*, and the resulting solid extracted with Et_2O (50 ml), washed with water (30 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a yellow solid, which was recrystallised from methanol to give the title oxime (257) (1·83 g, 87%) as pale yellow crystals, m.p. 165-167°C from methanol [lit.,[119] 162-163°C (dilute methanol)].

3β-Acetoxy-13,17-secoandrosta-5,13(18)diene-17-nitrile (258) To a solution of oxime (257) (0·98 g, 2·8 mmol) in dry benzene (6 ml) and DMSO (6 ml) at 0°C under an atmosphere of N_2 was added dicyclohexylcarbodiimide (0·66 g) and trifluoroacetic acid (0·2 ml).[78] The mixture was stirred at room temperature for 3 days, and then poured onto water (30 ml). After extraction with Et_2O (50 ml) and water (30 ml), the organic extract was washed with saturated aqueous $NaHCO_3$ (30 ml), water (30 ml), and then dried ($MgSO_4$). Evaporation of the solvent was followed by flash chromatography (1:4 EtOAc : petroleum ether) to give

i) Title seco-nitrile (258) (0·4 g, 43%) as colourless crystals m.p. 101-102°C from methanol [lit.,[79] 104-105°C]; R_f 0·45 (SiO_2, 3:7 EtOAc : petroleum ether); ν_{max} (Nujol) 2240 and 1720 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·75-2·51 (19H, m), 0·91 (3H, s, 19-CH_3), 2·01 (3H, s, -OCOCH_3), 4·48 (1H, s, 18-H), 4·58 (1H, m, 3-H), 4·81 (1H, s, 18-H), 5·36 (1H, t, J 4·5 Hz, 6-H). Continued elution with 1:1 EtOAc : petroleum ether gave

ii) 3β-Acetoxy-17a-aza-D-homoandrost-5-en-17-one (260) (0·22 g, 23%) as colourless crystals, m.p. 291-292°C from methanol [lit.,[78] 292-293°C]; R_f 0·21 (SiO_2, 3:7 EtOAc : petroleum ether); ν_{max} (Nujol) 3320 and 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·94 (3H, s, 19-CH_3), 1·09 (3H, s, 18-CH_3), 2·01 (3H, s, -OCOCH_3), 2·54-2·62 (2H, m, 16-H), 4·57 (1H, m, 3-H), 5·36 (1H, m, H-6), 7·49 (1H, br, -NH).

iii) Unreacted starting material, (0·2 g, 20%).

3β-Acetoxy-13,17-secoandrosta-5,13(18)diene-7-one-17-nitrile (267) Prepared from seco-nitrile (258), either by reaction with t-butylchromate[46] (see (203)), or by reaction with CrO_3-DMP[85] - To a

solution of CrO_3 (364 mg, 3·64 mmol, dried under vacuum over P_2O_5) in CH_2Cl_2 (10 ml) at -20°C was added 3,5-dimethylpyrazole (350 mg, 3·66 mmol) in one portion. Stirring was continued for 15 min at -20°C, and then the seco-nitrile (50 mg, 0·152 mmol) added. After 4 h at -20°C, NaOH (5 ml, 5N) was added, and the mixture stirred at 0°C for 1 h. The organic layer was then separated, washed with dilute HCl (10 ml), water (10 ml), and saturated aqueous NaCl (10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a colourless solid, subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted starting material (26 mg, 52%).

ii) Title enone (267), (20 mg, 38%) as colourless needles, m.p. 100-102°C from ethyl acetate-petroleum ether; R_f 0·22 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: C, 73·9; H, 8·1; N, 4·3%. $C_{21}H_{27}NO_3$ requires C, 73·87; H, 7·97; N, 4·10%); ν_{max} ($CHCl_3$) 2240, 1720 and 1660 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·8-2·65 (17H, m), 1·15 (3H, s, 19-CH_3), 2·05 (3H, s, -OCOCH_3), 4·65-4·78 (2H, m, 3-H and 18-H), 4·90 (1H, s, 18-H), 5·78 (1H, d, J 1·7 Hz, 6-H); $^m/z$ (CI) 342 ($M^+ + 1$, 1%), 282 (100).

3β,12-Diacetoxy-13,17-secoandrosta-5,13(18)diene-17-nitrile (268) To a solution of seco-nitrile (258) (106 mg, 0·323 mmol) in benzene (2 ml) was added SeO_2 (120 mg, 1·08 mmol) in AcOH (2 ml) and water (0·05 ml). The mixture was heated at 85°C for 1 h, and the solvent then evaporated to give a yellow oil, which was dissolved in Et_2O (10 ml), the organic layer washed with water (5 ml) and saturated aqueous NaCl (5 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil, which was dissolved in Ac_2O (10 ml) and pyridine (0·5 ml), and a few crystals of 4-dimethylaminopyridine added. After

stirring for 1 h at room temperature, the solvent was evaporated, and the residue dissolved in Et_2O (10 ml), washed with water (2 x 5 ml), saturated aqueous NaCl (5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil, subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give an unstable yellow oil, assigned as the title compound (268), (18·5 mg, 15%); R_f 0·49 (SiO_2, 1:1 EtOAc : petroleum ether); ν_{max} ($CHCl_3$) 2240 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·81-2·70 (17H, m), 0·98 (3H, s, 19-CH_3), 2·03 (3H, s, -OCOCH_3), 2·09 (3H, s, -OCOCH_3), 4·62 (1H, m, 3-H), 5·08 (1H, s, 18-H), 5·32 (1H, s, 18-H), 5·44 (1H, t, J 2·3 Hz, 6-H), 5·61 (1H, t, J 3·1 Hz, 12-H); $^m/z$ and CHN analysis data were not possible, due to the instability of the compound.

3β-Acetoxy-13,17-secoandrosta-5,13(18)diene-17-nitrile-14-formate (270)

To a solution of seco-nitrile (258) (200 mg, 0·61 mmol) in formic acid (10 ml) was added SeO_2 (135 mg, 1·22 mmol), and the mixture heated at 55°C for 6 min. The reaction was then diluted with water (5 ml), extracted with Et_2O (20 ml), and the organic extract washed with water (5 ml), saturated aqueous $NaHCO_3$ (10 ml), saturated aqueous NaCl (5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give the title formate (270), (80 mg, 35%) as colourless crystals, m.p. 94·1-94·9°C from petroleum ether; R_f 0·47 (SiO_2, 3:7 EtOAc : petroleum ether), (Found: C, 71·1; H, 7·7; N, 3·9%. $C_{22}H_{29}NO_4$ requires C, 71·13; H, 7·87, N, 3·77%); ν_{max} ($CHCl_3$) 2240 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·78 (3H, s, 19-CH_3), 1·10-2·80 (18H, m), 2·02 (3H, s, -OCOCH_3), 4·63-4·76 (3H, m, 2 x 18-H and 3-H), 5·43 (1H, t, J 2·4 Hz, 6-H), 8·07 (1H, s, -OCHO); δ_C ($CDCl_3$, D.E.P.T.), *quat.* 160·95 (acetate carbonyl), 140·42 (C-5), 136·74 (C-13), 130·15

(C-14), 119·01 (C-17), 37·24 (C-10); *CH* 170·50 (formate carbonyl), 121·65, 73·70, 48·12, 34·16; *CH_2* 63·57, 37·59, 36·52, 31·18, 29·15, 27·39, 24·53, 21·79, 16·67; *CH_3* 21·39 (-$OCOCH_3$) 18·43 (C-19); $^m/z$ 311 (M^+-CH_3CO_2H, 20%), 265 (90), 211 (100).

3β-Acetoxyandrost-5-ene-7,17-dione Prepared by t-butylchromate oxidation of 3β-Acetoxyandrost-5-ene-17-one ((199), R=OAc, R'=O) (see (203)) in 63% yield, colourless needles m.p. 177-181°C from methanol [lit.,[118] 179-182°C (methanol)].

3β,7α-Diacetoxyandrost-17-one Prepared by hydrogenation over PtO_2 of 3β-Acetoxyandrost-5-ene-7,17-dione (see (206)) to give 3β-Acetoxy-7α-hydroxyandrost-17-one (70%) as colourless crystals, m.p. 165-168°C from methanol, followed by acetylation (Ac_2O, Δ), to give title ketone (80% yield) as colourless crystals, m.p. 165-166°C from methanol; (Found C, 70·5; H, 8·7%. $C_{23}H_{34}O_5$ requires C, 70·75, H, 8·77%); ν_{max} ($CHCl_3$), 1720 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0·84 (3H, s, 18-CH_3), 0·85 (3H, s, 19-CH_3), 0·88-2·46 (20H, m), 2·02 (3H, s, -$OCOCH_3$), 2·07 (3H, s, -$OCOCH_3$), 4·71 (1H, m, 3-H), 5·07 (1H, m, 7-H); $^m/z$ 390 (M^+, 2%), 330 (72), 270 (38), 43 (100).

3β,7α-Diacetoxyandrostan-17-oxime Prepared by reaction of 3β,7α-diacetoxyandrost-17-one with hydroxylamine hydrochloride and pyridine (see (257)) (94% yield), m.p. 171-173°C from methanol; (Found, C, 68·3; H, 8·6; N, 3·4%. $C_{23}H_{35}NO_5$ requires C, 68·12; H, 8·70; N, 3·45%); ν_{max} ($CHCl_3$) 3580, 3340 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·82 (3H, s, 18-CH_3), 0·86 (3H, s, 19-CH_3), 1·07-1·95 (18H, m), 1·99 (3H, s, -$OCOCH_3$), 2·03 (3H, s, -$OCOCH_3$), 2·47 (2H, m, 16-CH_2), 4·67 (1H, m, 3-H), 4·95 (1H, d, J 2·6 Hz, 7-H), 8·60 (1H, s, -OH); $^m/z$ (CI) 406 (M^+ + 1, 10%),

373 (30), 328 (40), 80 (100).

3β,7α-Diacetoxy-13,17-secoandrosta-13(18)-ene-17-nitrile (271) To a solution of 3β,7α-diacetoxyandtrostan-17-oxime (2·9 g, 7·2 mmol) in dry benzene (17 ml) and DMSO (17 ml) was added dicyclohexylcarbodiimide (4·75 g) and the mixture cooled to 0°C. Trifluoroacetic acid (0·7 ml) was added dropwise, and the mixture stirred at room temperature for 3 days. Work up was as for (258), to give seco-nitrile (271) (1·01 g, 36%) as a colourless foam, which resisted all attempts at crystallisation; R_f 0·45 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 387·2412. Calc. for $C_{23}H_{33}NO_4$: M, 387·2409); ν_{max} (Nujol), 2240 and 1730 cm^{-1}; δ_H (270 MHz, $CDCl_3$), 0·72 (3H, s, 19-CH_3), 1·02-2·40 (20H, m), 1·99 (3H, s, -$OCOCH_3$), 2·03 (3H, s, -$OCOCH_3$), 4·48 (1H, s, 18-H), 4·62 (1H, m, 3-H), 4·81 (1H, s, 18-H), 5·18 (1H, m, 7-H); $^m/z$ 387 (M^+, 10%), 327 (35), 261 (65), 55 (100).

3β,7α-Diacetoxy-13,17-secoandrosta-13(18)-ene-17-nitrile-14-formate (272) To a solution of seco-nitrile (271) (50 mg, 0·13 mmol) in formic acid (5 ml) was added SeO_2 (28·7 mg, 0·26 mmol). The mixture was heated at 50°C for 5 min, and then diluted with water (5 ml), and extracted with Et_2O (2 x 10 ml). The organic layer was washed with water (2 x 5 ml), saturated aqueous $NaHCO_3$ (5 ml), saturated aqueous NaCl (5 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil, which was subjected to flash chromatography (1:4 EtOAc : petroleum ether) to give a colourless foam, tentatively assigned as seco-nitrile (242) (24·5 mg, 44%) which resisted attempts at crystallisation, R_f 0·3 (SiO_2, 3:7 EtOAc : petroleum ether); (Found C, 66·4; H, 7·8; N, 3·4%. $C_{24}H_{33}NO_6$ requires C, 66·80; H, 7·71; N, 3·25%); ν_{max} ($CHCl_3$) 2240 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·79 (3H, s, 19-CH_3), 1·21-2·83 (19H, m), 2·01 (6H, s, 2 x -$OCOCH_3$), 4·60-4·80

(3H, m, 2 x 18-H and 3-H), 5·24 (1H, d, J 2·6 Hz, 7-H), 8·05 (1H, s, -OCHO); δ_C ($CDCl_3$, D.E.P.T.), *quat* 160·93 (acetate carbonyl), 160·57 (acetate carbonyl), 136·44 (C-13), 131·23 (C-14), 120·61 (C-17), 37·10 (C-10); $^m/z$ (CI) 386 (50), 326 (25), 266 (100).

3β,7α-Diacetoxy-13,17-secoandrost-13,18-epoxy-17-nitrile (273) To a solution of seco-nitrile (271) (46 mg, 0·12 mmol) in $CHCl_3$ (5 ml) at 0°C was added m-CPBA (22·6 mg, 0·13 mmol), and the mixture stored at -5°C for 23 h, then diluted with $CHCl_3$ (10 ml), the organic layer washed with saturated aqueous $NaHCO_3$ (10 ml) and saturated aqueous NaCl (5 ml), and dried ($MgSO_4$). Removal of the solvent gave a colourless oil, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted starting seco-nitrile (271) (10·6 mg, 23%).

ii) Title epoxide (273) (32·5 mg, 68%) as a colourless foam which resisted attempts at crystallisation, R_f 0·28 (SiO_2, 3:7 EtOAc : petroleum ether); (Found: M^+, 403·2336. Calc. for $C_{23}H_{33}NO_5$: M, 403·2356); ν_{max} ($CHCl_3$) 2240 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$), 0·83 (3H, s, 19-CH_3), 1·23-2·40 (20H, m), 2·03 (3H, s, -$OCOCH_3$), 2·13 (3H, s, -$OCOCH_3$), 2·59 (1H, d, J 3·6 Hz, 18-H), 2·82 (1H, d, J 3·5 Hz, 18-H), 4·74 (1H, m, 3-H), 5·20 (1H, d, J 2·6 Hz, 7-H); $^m/z$ 403 (M^+, 5%), 343 (30), 283 (25).

3β,7α-Diacetoxy-13,17-secoandrost-13-formyl-17-nitrile (276) To a solution of epoxide (273) (15 mg) in Et_2O (2 ml) was added $BF_3.OEt_2$ (4 drops). The mixture was kept in the dark at room temperature for 16 h, and the solvent then evaporated to give a pale yellow oil, subjected to flash chromatography (1:4 EtOAc : petroleum ether) to give

i) Unreacted starting epoxide (273) (5 mg, 33%).

ii) Title aldehyde (276) (7·8 mg, 52%) (3:2 mixture of epimers at C-13), as a colourless oil, R_f 0·3 (SiO_2 1:1 EtOAc : petroleum ether); ν_{max} ($CHCl_3$) 2240 and 1720 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·76 ($\frac{3}{2}$ H, s, 19-CH_3), 0·80 ($\frac{3}{2}$ H, s, 19-CH_3), 1·01-2·40 (21H, m), 2·01 (3H, s, -OCOCH_3), 2·12 (3H, s, -OCOCH_3), 4·70 (1H, m, 3-H), 5·14 (1H, m, 7-H), 9·55 ($\frac{1}{2}$H, d, J 3·7 Hz, CHO), 9·73 ($\frac{1}{2}$H, s, CHO); $^m/z$ and CHN data were not possible due to the instability of the compound.

LACTONE CONTRACTIONS

γ-*t*-butyl-ξ-Caprolactone (318) To a solution of 4-*t*-butylcyclohexanone (3 g, 19·4 mmol) in CH_2Cl_2 (50 ml) was added slowly a solution of m-CPBA (3·3 g, 19·4 mmol) in CH_2Cl_2 (10 ml). After stirring for 13 h at room temperature, the mixture was diluted with CH_2Cl_2 (30 ml), and the organic layer washed with saturated aqueous $NaHCO_3$ (2 x 20 ml), saturated aqueous NaCl (30 ml) and dried ($MgSO_4$). Removal of the solvent gave a colourless solid, the title lactone (318), (1·78 g, 54%) as colourless needles, m.p. 56·6 - 57·3°C from n-heptane [lit.,[108] 57·5 - 58·5°C (n-heptane)].

γ-*tert*-butyl-α-hydroxy-ξ-Caprolactone (319) To a solution of diisopropylamine (0·99 ml, 7·1 mmol) in THF (10 ml) at -15°C under an atmosphere of N_2 was added dropwise n-BuLi (4·04 ml, 1·6M, 6·46 mmol). The mixture was stirred for 10 min, and then cooled to -78°C. The lactone (318) (1·0 g, 5·7 mmol) in THF (1 ml) was added dropwise, and the mixture stirred at -78°C for 30 min, and

then TMSCl (2·5 ml, 19·8 mmol) added in one portion. The mixture was allowed to warm to room temperature, and stirred for a further 3 h. The solvents were removed *in vacuo*, pentane (10 ml) added, and the suspension filtered through a cotton-wool plug. Removal of the solvent from the eluent gave a yellow oil, which, without purification, was used in the next stage.

The yellow oil was dissolved in CH_2Cl_2 (15 ml) and ozonised using a Welsbach Ozonator, at -78°C. After 45 min, when the blue colouration persisted, the solution was flushed with N_2, Me_2S (1·5 ml) was added, and the reaction mixture allowed to warm to room temperature, and stirred for a further 2 h. Removal of the solvents *in vacuo* gave a yellow oil, which was dissolved in EtOAc (20 ml), and the organic layer washed with water (10 ml), saturated aqueous NaCl (10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale-yellow solid, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) Unreacted starting lactone (318) (0·56 g, 56%)

ii) title α-hydroxy lactone (319) (0·28 g, 30%) as colourless crystals, m.p. 110·1 - 111·9°C from EtOAc-petroleum ether; R_f 0·52 (SiO_2 , 3:7 EtOAc : petroleum ether); (Found C, 64·4; H, 9·8%. $C_{10}H_{18}O_3$ requires C, 64·49, H, 9·74%); ν_{max} ($CHCl_3$) 3520 and 1740 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·89 (9H, s, $-C(CH_3)_3$), 1·12-2·2 (6H, m, 2 x $-CH_2$, -CH and -OH), 4·14-4·24 (1H, m, -CHOCO-), 4·40-4·49 (1H, m, -CHOCO-), 4·70-4·74 (1H, m, -C*H*-OH); $^m/z$ (CI) 187 ($M^+ + 1$, 100%).

γ-*tert*-butyl-α-methyl-ε-Caprolactone (320) To a solution of diisopropylamine (0·18 ml, 1·29 mmol) in THF (4 ml) at 0°C under an atmosphere of N_2 was added dropwise n-BuLi (0·92 ml, 1·4M, 1·29 mmol). The mixture was stirred at 0°C for 10 min, and then cooled to -78°C.

The lactone (318) (200 mg, 1·18 mmol) in THF (1 ml) was added dropwise, and stirring continued for 20 min. MeI (1 ml) was then added in one portion, and the mixture stirred for a further 45 min at -45°C. Removal of the solvents *in vacuo* gave a colourless oil, which was subjected to flash chromatography (1:9 EtOAc : petroleum ether) to give

i) title α-methyl lactone (319) (34 mg, 16%) as colourless crystals, m.p. 94·3 - 95·6°C from EtOAc-petroleum ether; R_f 0·55 (SiO_2, 3:7 EtOAc : petroleum ether), (Found C, 71·6; H, 11·0%. $C_{11}H_{20}O_2$ requires C, 71·70; H, 10·94%); ν_{max} ($CHCl_3$) 1730 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0·87 ($\frac{9}{2}$ H, s, $-C(CH_3)_3$) 0·88 ($\frac{9}{2}$ H, s, $-C(CH_3)_3$), 1·20 ($\frac{3}{2}$ H, s, $-CH_3$), 1·23 ($\frac{3}{2}$ H, s, $-CH_3$), 1·25-1·56 (3H, m, $-CH_2$ and -CH), 1·73-1·78 (1H, m, $-CH_2$), 1·99-2·06 (1H, m, $-CH_2$), 2·63-2·72 (1H, m, -CHCOO-), 4·16-4·36 (2H, m, $-CH_2OCO$); $^m/z$ (CI) 185 ($M^+ + 1$, 100%), 129 (17), 86 (17).

A general procedure for the attempted preparation of γ-*tert*-butyl-O-TBDMS-ε-caprolactone is given below.[105]

To a solution of n-BuLi (3·87 ml, 1·6M, 6·2 mmol) in THF (6 ml) at 0°C under an atmosphere of N_2 was added dropwise N-isopropylcyclohexylamine (1·02 ml, 6·2 mmol). The mixture was stirred for 10 min, and cooled to -78°C. The lactone (318) (1 g, 5·9 mmol) in THF (1 ml) was added dropwise, and stirring continued for 10 min. HMPA (0·6 ml) was then added, followed by a solution of TBDMSCl (0·93 g, 6·2 mmol) in pentane (2 ml) in one portion. The reaction mixture was allowed to warm to 0°C, and after 15 min, AcOH (6 ml, 1M solution in water) added. The organic layer was separated, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a yellow oil, which showed no peak attributable to a silylated product by GC/mass spec. or Glpc.

Ozonolysis of this oil according to the procedure for (324)

gave a multi-component mixture from which some starting lactone (322) (0·21 g, 21%) was recovered.

Variation of the amine (cyclohexylamine, diisopropylamine), temperature of formation of the anion (-78°C → 0°C), reaction time (10 min - 1 h) and ozonolysis solvent (CH_2Cl_2, MeOH-CH_2Cl_2) gave no identifiable products.

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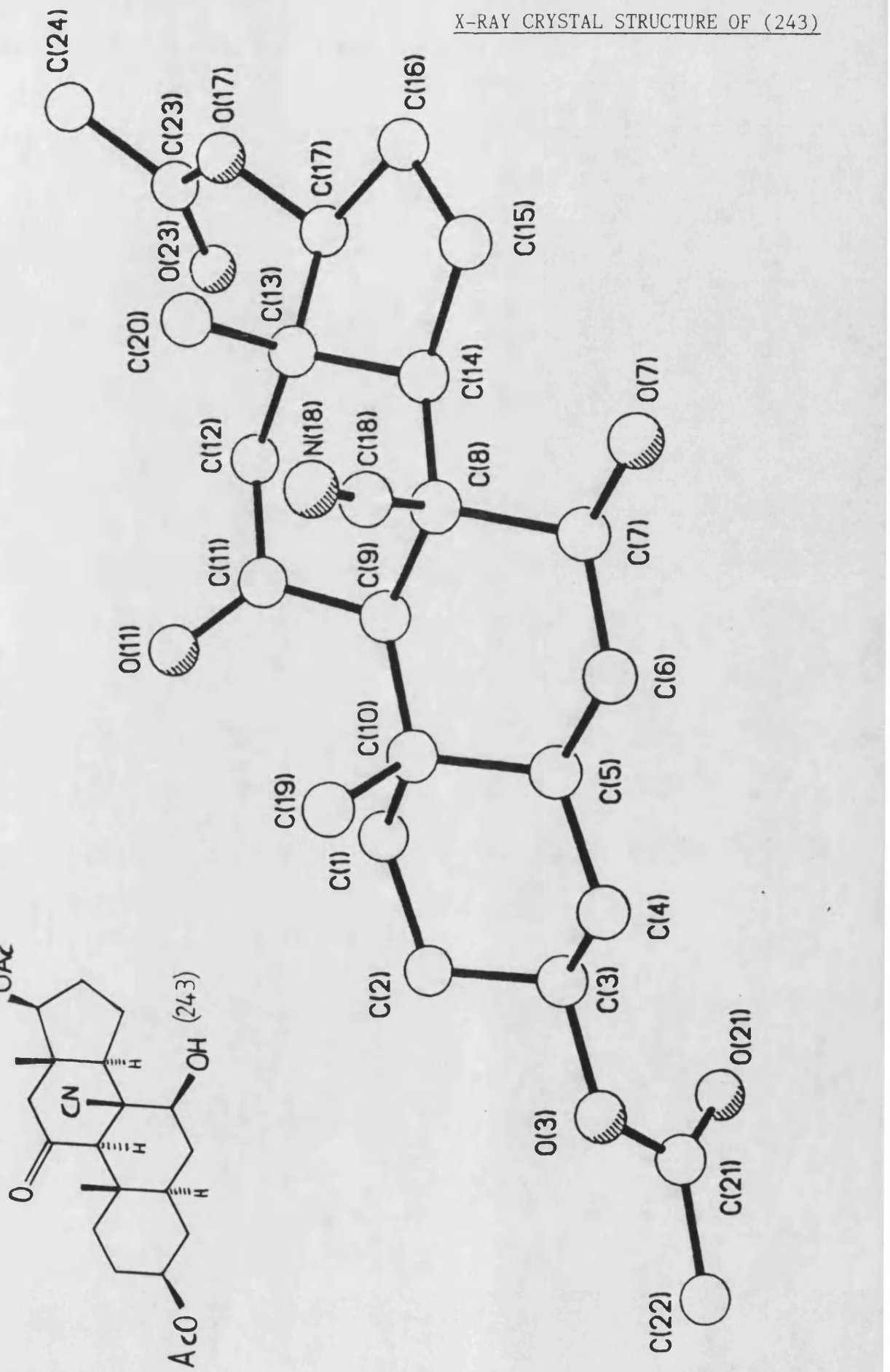
APPENDIX

X-RAY CRYSTAL STRUCTURE OF (243)



X-RAY DATA

INFO ALL LPT

SYMCODES FOR GR65365X

55501.	.00000 +X	.00000 +Y	.00000 +Z
55502.	.50000 -X	.00000 -Y	.50000 +Z
55503.	.50000 +X	.50000 -Y	.00000 -Z
55504.	.00000 -X	.50000 +Y	.50000 -Z

A= 6.489(2) B= 12.535(8) C= 29.384(17) ALPHA= 90.00 BETA= 90.00 GAMMA= 90.00

ATOM	TYPE	X	Y	Z	SOF	U11	U22	U33	U23	U13	U12
C1	1	.06890	1.13379	.91070	1.00000	.07084	.07794	.05830	-.01675	.00844	.00380
H1A	2	-.06344	1.11671	.89804	1.00000	.09897					
H1B	2	.11963	1.19829	.89710	1.00000	.09997					
C2	1	.04548	1.15204	.96158	1.00000	.06917	.16505	.05323	-.01636	.00203	-.00668
H2A	2	-.05722	1.20597	.96643	1.00000	.13498					
H2B	2	.17538	1.17627	.97331	1.00000	.13498					
C3	1	-.01308	1.05485	.98681	1.00000	.07515	.10740	.04082	-.03166	.00723	-.01506
H3	2	-.14801	1.03579	.97616	1.00000	.09027					
O3	3	-.01678	1.07568	1.03548	1.00000	.06536	.22862	.04729	-.01999	.00389	-.03038
C4	1	.13918	.96153	.97829	1.00000	.06931	.09536	.04949	.00469	-.00038	-.00603
H4A	2	.08890	.89818	.99291	1.00000	.07652					
H4B	2	.27278	.97905	.99017	1.00000	.07652					
C5	1	.15248	.94446	.92723	1.00000	.05539	.06881	.04906	-.00725	-.00861	.00056
H5	2	.01152	.93419	.91833	1.00000	.06249					
C6	1	.27585	.84133	.91467	1.00000	.07487	.06944	.05141	.00760	-.00958	-.01015
H6A	2	.22816	.78320	.93315	1.00000	.08182					
H6B	2	.41925	.85389	.92065	1.00000	.08182					
C7	1	.25023	.81309	.86528	1.00000	.05501	.06105	.04755	.00372	-.00669	.00218
H7	2	.10720	.79832	.85980	1.00000	.06254					
O7	3	.36575	.71966	.85509	1.00000	.06026	.06132	.06753	.00044	-.01282	.00658
H7O	2	.24546	.67807	.84553	1.00000	.06272					
C8	1	.31251	.90708	.83276	1.00000	.03431	.04135	.05073	-.00366	-.00221	-.00533
C9	1	.20527	1.01437	.84903	1.00000	.03923	.05850	.05052	.00052	.00100	-.00890
H9	2	.05867	1.00410	.84863	1.00000	.05916					
C10	1	.22621	1.03980	.89975	1.00000	.04301	.06606	.05035	-.00543	.00007	-.00162
C11	1	.23867	1.09992	.81487	1.00000	.05500	.04307	.06111	-.01712	.01172	-.01238
O11	3	.31304	1.18623	.82382	1.00000	.10504	.07429	.07043	-.01200	.01904	-.02638
C12	1	.16278	1.07738	.76661	1.00000	.06633	.05393	.04855	-.00869	.01007	.00444
H12A	2	.19622	1.13624	.74706	1.00000	.06579					
H12B	2	.01614	1.06727	.76704	1.00000	.06579					
C13	1	.26702	.97686	.74947	1.00000	.04656	.04177	.04983	.00754	.00529	-.00411
C14	1	.23501	.88270	.78352	1.00000	.03659	.04675	.05019	-.00203	-.00038	-.00082
H14	2	.09559	.86938	.79285	1.00000	.05175					
C15	1	.30297	.78554	.75712	1.00000	.05511	.05579	.06079	.00467	.00252	.00145
H15A	2	.44938	.77620	.75959	1.00000	.05993					
H15B	2	.23438	.72274	.76808	1.00000	.05993					
C16	1	.23953	.80985	.70672	1.00000	.07417	.07009	.05175	-.00293	.00686	.00478
H16A	2	.13232	.76237	.69690	1.00000	.07802					
H16B	2	.35605	.80317	.68679	1.00000	.07802					
C17	1	.16274	.92478	.70790	1.00000	.06670	.04362	.04740	-.00228	.01094	.00871
H17	2	.01610	.93152	.71112	1.00000	.06272					
O17	3	.21636	.97553	.66465	1.00000	.06910	.05515	.05089	.00063	.00321	.00898
C18	1	.54016	.91084	.83443	1.00000	.05347	.04418	.05452	-.00526	-.00497	-.00595
N18	4	.71588	.91008	.83509	1.00000	.04085	.10246	.09227	-.00566	-.01047	-.00045
C19	1	.44990	1.07498	.91352	1.00000	.04709	.13867	.05696	-.02192	-.00377	-.02011
H19A	2	.48253	1.13566	.89495	1.00000	.09657					
H19B	2	.54334	1.01779	.90668	1.00000	.09657					
H19C	2	.46252	1.09396	.94505	1.00000	.09657					
C20	1	.49479	1.00272	.73848	1.00000	.06182	.08389	.05455	.00855	.00320	-.00953
H20A	2	.54685	.93791	.72542	1.00000	.07068					
H20B	2	.56660	1.01746	.76635	1.00000	.07068					
H20C	2	.51545	1.06051	.71754	1.00000	.07068					
C21	1	-.17945	1.06208	1.05822	1.00000	.08881	.09609	.06379	.00874	.00455	-.00811
O21	3	-.33350	1.03570	1.04047	1.00000	.11572	.42332	.09423	-.05523	.03191	-.10553
C22	1	-.16078	1.09195	1.10689	1.00000	.11390	.06857	.05832	-.00167	.01321	.01041
H22A	2	-.29571	1.11548	1.11574	1.00000	.09376					
H22B	2	-.06289	1.14790	1.11234	1.00000	.09376					
H22C	2	-.12347	1.03014	1.12434	1.00000	.09376					
C23	1	.09995	1.05407	.64946	1.00000	.06392	.07114	.05408	-.00155	-.00187	-.00108
O23	3	-.04847	1.08756	.67151	1.00000	.07895	.10661	.06486	.01544	.00693	.02711
C24	1	.17777	1.09920	.60531	1.00000	.09042	.08700	.05014	.01948	-.00222	-.00249
H24A	2	.05718	1.10856	.58682	1.00000	.09987					
H24B	2	.28726	1.07045	.58707	1.00000	.09987					
H24C	2	.21930	1.16682	.61758	1.00000	.09987					

TORSALL LPT

DIHEDRAL ANGLES OF TYPE 1

C10	C1	C2	C3	-54.7
C2	C1	C10	C5	52.9
C2	C1	C10	C9	169.1
C2	C1	C10	C19	-68.0
C1	C2	C3	O3	175.5
C1	C2	C3	C4	55.2
C2	C3	O3	C21	121.0
C4	C3	O3	C21	-116.2
C2	C3	C4	C5	-54.8
O3	C3	C4	C5	-176.6
C3	O3	C21	O21	-2.5
C3	O3	C21	C22	-177.1
C3	C4	C5	C6	-171.4
C3	C4	C5	C10	59.4
C4	C5	C6	C7	168.1
C10	C5	C6	C7	-60.6
C4	C5	C10	C1	-58.1
C4	C5	C10	C9	-173.0
C4	C5	C10	C19	61.1
C6	C5	C10	C1	172.3
C6	C5	C10	C9	57.4
C6	C5	C10	C19	-68.5
C5	C6	C7	O7	179.5
C5	C6	C7	C8	55.7
C6	C7	C8	C9	-48.9
C6	C7	C8	C14	-166.9
C6	C7	C8	C18	73.7
O7	C7	C8	C9	-172.2
O7	C7	C8	C14	69.8
O7	C7	C8	C18	-49.6
C7	C8	C9	C10	48.7
C7	C8	C9	C11	-171.9
C14	C8	C9	C10	167.9
C14	C8	C9	C11	-52.7
C18	C8	C9	C10	-68.7
C18	C8	C9	C11	70.7
C7	C8	C14	C13	173.5
C7	C8	C14	C15	-59.9
C9	C8	C14	C13	54.1
C9	C8	C14	C15	-179.3
C18	C8	C14	C13	-70.9
C18	C8	C14	C15	55.7
C7	C8	C18	N18	61.7
C9	C8	C18	N18	-178.2
C14	C8	C18	N18	-56.7
C8	C9	C10	C1	-167.5
C8	C9	C10	C5	-53.4
C8	C9	C10	C19	71.9
C11	C9	C10	C1	57.2
C11	C9	C10	C5	171.3
C11	C9	C10	C19	-63.4
C8	C9	C11	O11	-125.6
C8	C9	C11	C12	57.7
C10	C9	C11	O11	11.8
C10	C9	C11	C12	-164.8
C9	C11	C12	C13	-57.7
O11	C11	C12	C13	125.5
C11	C12	C13	C14	53.6
C11	C12	C13	C17	162.8
C11	C12	C13	C20	-73.5
C12	C13	C14	C8	-56.7
C12	C13	C14	C15	167.5
C17	C13	C14	C8	-176.8
C17	C13	C14	C15	47.4
C20	C13	C14	C8	67.0
C20	C13	C14	C15	-68.8
C12	C13	C17	C16	-160.6
C12	C13	C17	O17	80.7
C14	C13	C17	C16	-43.5
C14	C13	C17	O17	-162.2
C20	C13	C17	C16	76.4
C20	C13	C17	O17	-42.3
C8	C14	C15	C16	-164.7
C13	C14	C15	C16	-34.0
C14	C15	C16	C17	6.3
C15	C16	C17	C13	24.1
C15	C16	C17	O17	146.3
C13	C17	O17	C23	-90.8
C16	C17	O17	C23	151.9
C17	O17	C23	O23	2.3
C17	O17	C23	C24	178.7

DIHEDRAL ANGLES OF TYPE 2

C2	C3	O3	C4	-122.9
C2	C3	C4	O3	121.8
C4	C5	C6	C10	-131.4
C4	C5	C10	C6	129.6
C6	C7	O7	C8	-124.8
C6	C7	C8	O7	123.3
C7	C8	C9	C14	-119.2
C7	C8	C9	C18	117.4
C14	C8	C9	C18	-123.4
C7	C8	C14	C9	119.4
C7	C8	C14	C18	-115.6
C9	C8	C14	C18	125.0
C7	C8	C18	C9	-120.1
C7	C8	C18	C14	118.3
C9	C8	C18	C14	-121.5
C8	C9	C10	C11	135.3
C8	C9	C11	C10	-137.5
C1	C10	C19	C5	117.1
C1	C10	C19	C9	-119.3
C5	C10	C19	C9	123.6
C9	C11	O11	C12	-176.6
C9	C11	C12	O11	176.8
C12	C13	C14	C17	120.1
C12	C13	C14	C20	-123.7
C17	C13	C14	C20	116.2
C12	C13	C17	C14	-117.1
C12	C13	C17	C20	123.0
C14	C13	C17	C20	-119.8
C12	C13	C20	C14	124.8
C12	C13	C20	C17	-126.5
C14	C13	C20	C17	108.7
C8	C14	C15	C13	-130.8
C13	C17	O17	C16	117.4
O3	C21	O21	C22	-174.0
O3	C21	C22	O21	174.3
O17	C23	O23	C24	176.0
O17	C23	C24	O23	-176.3

DIHEDRAL ANGLES OF TYPE 3

C5	C1	C10	C9	116.2
C5	C1	C10	C19	-120.9
C9	C1	C10	C19	122.9
O3	C2	C3	C4	-120.2
O21	O3	C21	C22	-174.6
C6	C4	C5	C10	-129.2
C1	C5	C10	C9	-114.9
C1	C5	C10	C19	119.2
C9	C5	C10	C19	-125.9
O7	C6	C7	C8	-123.8
C9	C7	C8	C14	-118.1
C9	C7	C8	C18	122.6
C14	C7	C8	C18	-119.3
C10	C8	C9	C11	139.4
C13	C8	C14	C15	126.6
C1	C9	C10	C5	114.1
C1	C9	C10	C19	-120.6
C5	C9	C10	C19	125.3
O11	C9	C11	C12	-176.7
C14	C12	C13	C17	109.2
C14	C12	C13	C20	-127.1
C17	C12	C13	C20	123.7
C8	C13	C14	C15	-135.8
C16	C13	C17	O17	-118.7
C13	C16	C17	O17	122.1
O23	O17	C23	C24	176.5

BANG 07 H70 LPT

BOND LENGTHS AND ANGLES FOR

07	C7	1.422		
07	H70	.980	94.5	
07	023'	2.755	99.3	4.9
			C7	H70
H70	07	.980		
H70	023'	1.781	172.5	
			07	

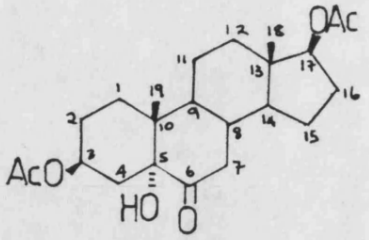
TABLE 2. Bond lengths (A)

C(1)-C(2)	1.520(10)	C(1)-C(10)	1.592(11)
C(2)-C(3)	1.476(13)	C(3)-O(3)	1.454(8)
C(3)-C(4)	1.551(12)	O(3)-C(21)	1.261(11)
C(4)-C(5)	1.518(9)	C(5)-C(6)	1.565(10)
C(5)-C(10)	1.520(10)	C(6)-C(7)	1.503(9)
C(7)-O(7)	1.422(9)	C(7)-C(8)	1.570(9)
C(8)-C(9)	1.588(9)	C(8)-C(14)	1.562(9)
C(8)-C(18)	1.479(9)	C(9)-C(10)	1.530(9)
C(9)-C(11)	1.485(9)	C(10)-C(19)	1.570(10)
C(11)-O(11)	1.213(8)	C(11)-C(12)	1.528(9)
C(12)-C(13)	1.516(9)	C(13)-C(14)	1.561(9)
C(13)-C(17)	1.541(9)	C(13)-C(20)	1.547(10)
C(14)-C(15)	1.510(9)	C(15)-C(16)	1.567(9)
C(16)-C(17)	1.525(10)	C(17)-O(17)	1.463(8)
O(17)-C(23)	1.319(9)	C(18)-N(18)	1.140(9)
C(21)-O(21)	1.175(13)	C(21)-C(22)	1.483(11)
C(23)-O(23)	1.234(10)	C(23)-C(24)	1.503(11)

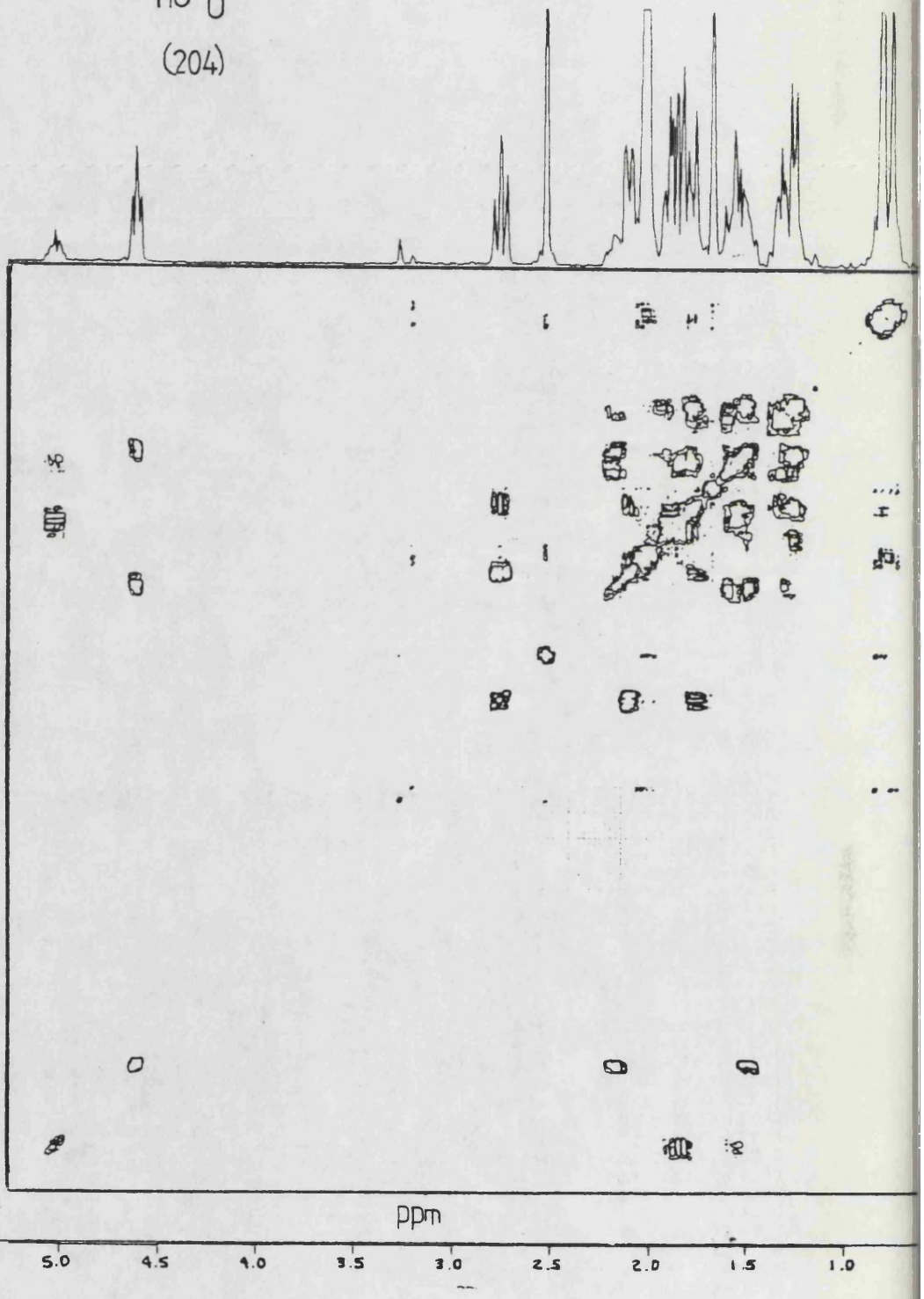
TABLE 3. Bond angles (deg.)

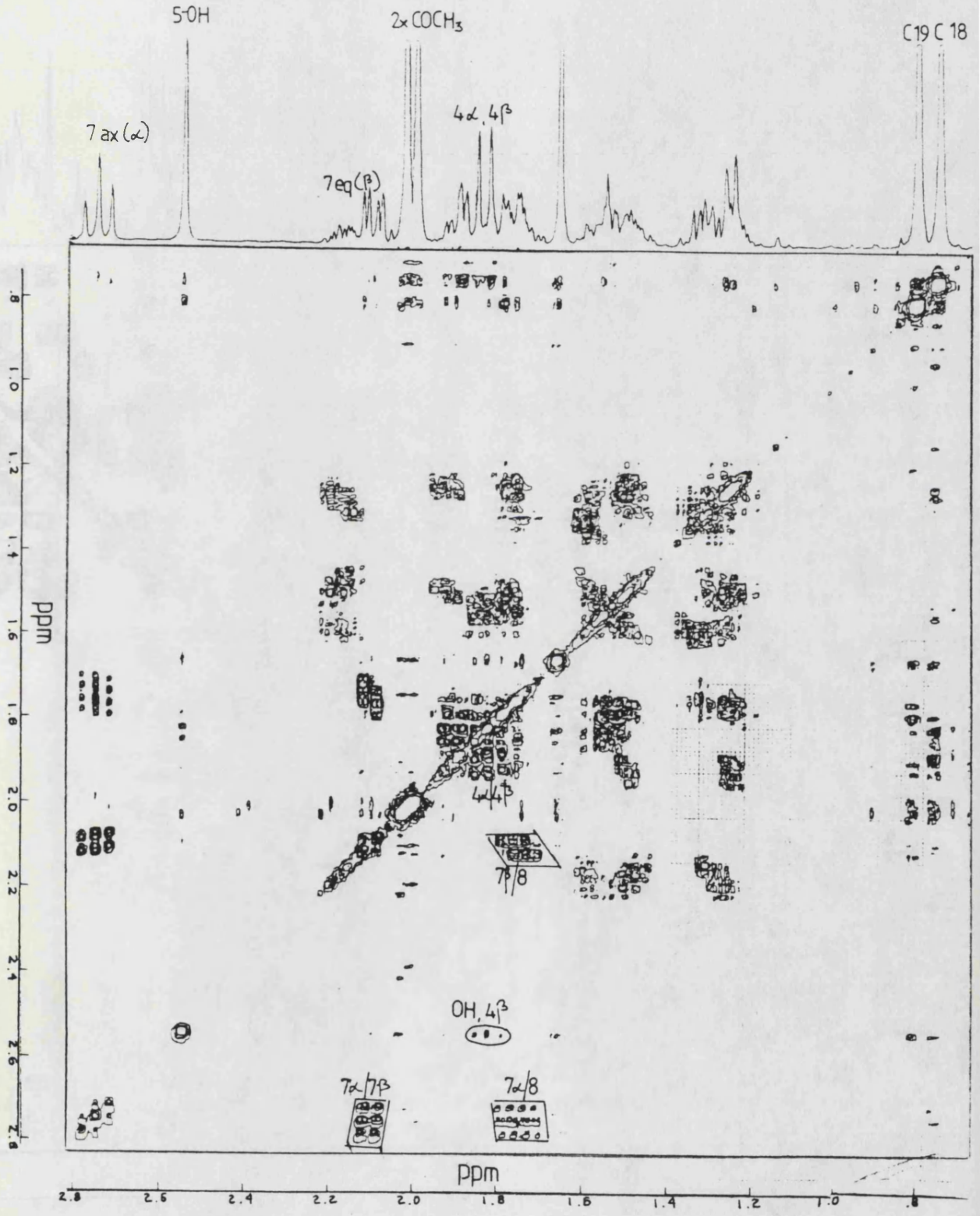
C(2)-C(1)-C(10)	112.0(6)	C(1)-C(2)-C(3)	113.3(8)
C(2)-C(3)-O(3)	110.5(7)	C(2)-C(3)-C(4)	112.2(7)
O(3)-C(3)-C(4)	107.7(6)	C(3)-O(3)-C(21)	120.7(7)
C(3)-C(4)-C(5)	107.6(6)	C(4)-C(5)-C(6)	112.3(6)
C(4)-C(5)-C(10)	115.6(6)	C(6)-C(5)-C(10)	111.3(6)
C(5)-C(6)-C(7)	111.5(6)	C(6)-C(7)-O(7)	109.8(6)
C(6)-C(7)-C(8)	112.5(6)	O(7)-C(7)-C(8)	110.7(5)
C(7)-C(8)-C(9)	109.8(5)	C(7)-C(8)-C(14)	109.5(5)
C(9)-C(8)-C(14)	107.7(5)	C(7)-C(8)-C(18)	105.1(5)
C(9)-C(8)-C(18)	113.6(5)	C(14)-C(8)-C(18)	111.0(5)
C(8)-C(9)-C(10)	115.5(5)	C(8)-C(9)-C(11)	110.1(5)
C(10)-C(9)-C(11)	119.7(6)	C(1)-C(10)-C(5)	105.8(6)
C(1)-C(10)-C(9)	107.1(5)	C(5)-C(10)-C(9)	109.0(6)
C(1)-C(10)-C(19)	109.4(6)	C(5)-C(10)-C(19)	112.0(6)
C(9)-C(10)-C(19)	113.1(6)	C(9)-C(11)-O(11)	123.8(6)
C(9)-C(11)-C(12)	116.5(6)	O(11)-C(11)-C(12)	119.6(6)
C(11)-C(12)-C(13)	108.6(6)	C(12)-C(13)-C(14)	110.8(5)
C(12)-C(13)-C(17)	114.8(6)	C(14)-C(13)-C(17)	97.4(5)
C(12)-C(13)-C(20)	108.7(6)	C(14)-C(13)-C(20)	114.8(6)
C(17)-C(13)-C(20)	110.1(5)	C(8)-C(14)-C(13)	113.8(5)
C(8)-C(14)-C(15)	122.7(5)	C(13)-C(14)-C(15)	104.0(5)
C(14)-C(15)-C(16)	104.6(5)	C(15)-C(16)-C(17)	104.4(5)
C(13)-C(17)-C(16)	105.9(5)	C(13)-C(17)-O(17)	113.6(5)
C(16)-C(17)-O(17)	108.3(5)	C(17)-O(17)-C(23)	118.8(6)
C(8)-C(18)-N(18)	177.5(7)	O(3)-C(21)-O(21)	121.0(8)
O(3)-C(21)-C(22)	114.1(8)	O(21)-C(21)-C(22)	124.6(9)
O(17)-C(23)-O(23)	121.5(7)	O(17)-C(23)-C(24)	112.4(7)
O(23)-C(23)-C(24)	126.0(7)		

2D COSY SPECTRUM OF (204)

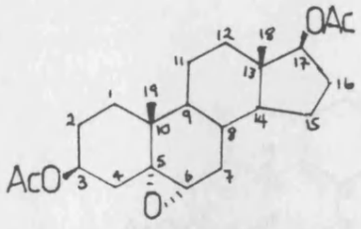


(204)

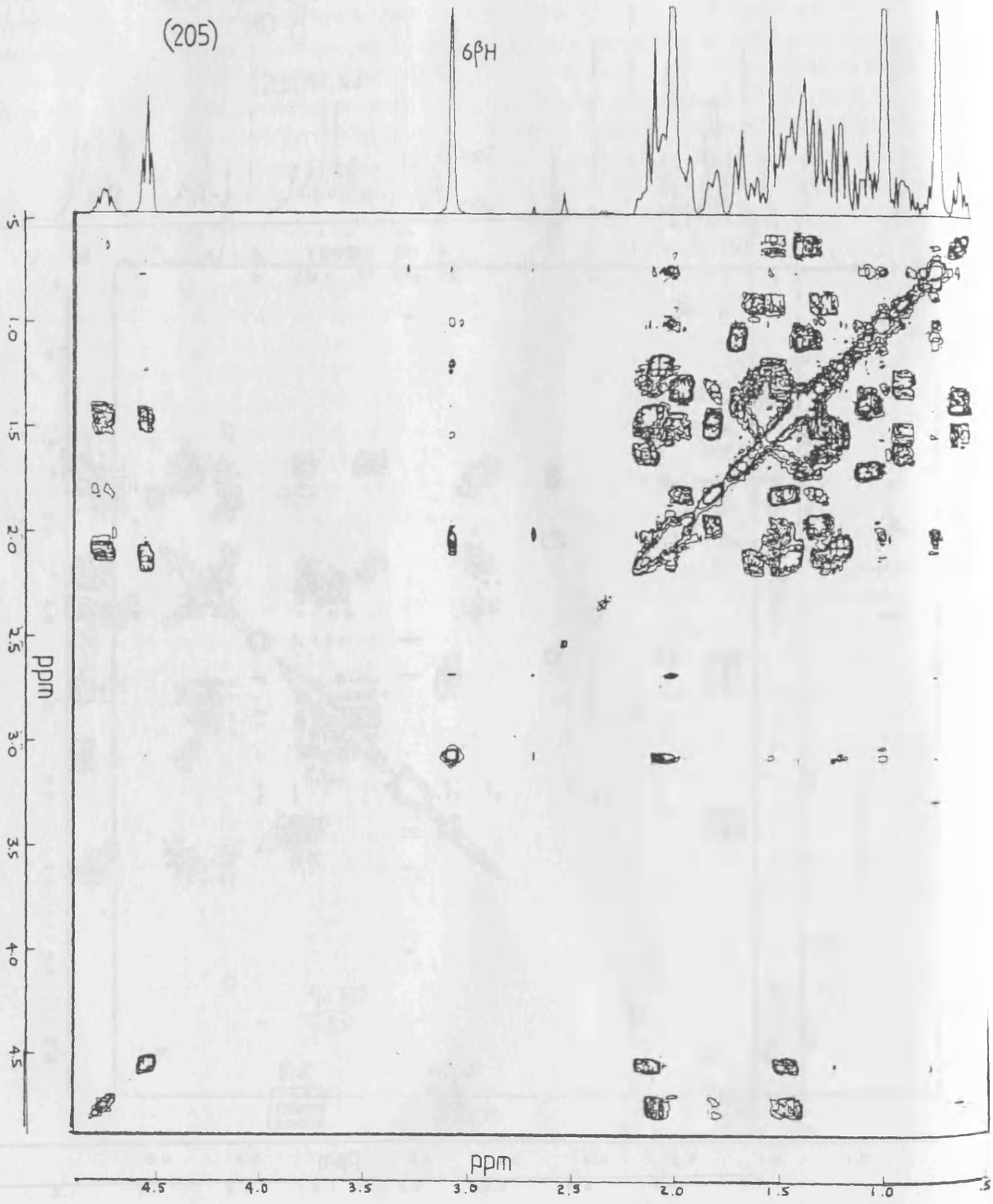


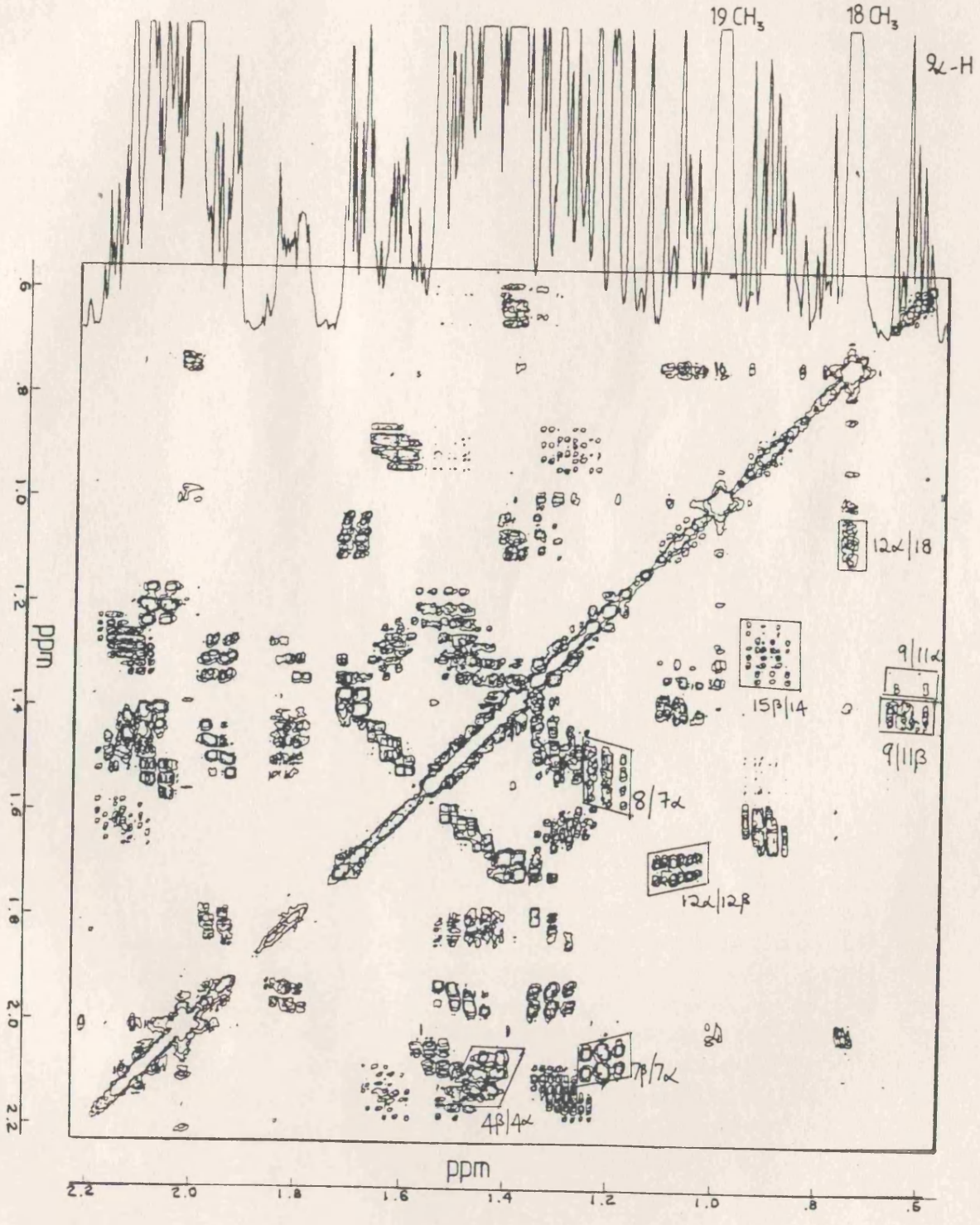

5-OH
2x COCH3
C19 C 18
7 ax (α)
7eq (β)
4α, 4β
4α/4β
7β/8
OH, 4β
7α/7β
7α/8
ppm
ppm

2D COSY SPECTRUM OF (205)



(205)




19 CH3
18 CH3
2α-H
12α|18
9|11α
15β|14
9|11β
8|7α
12α|12β
7β|7α
4β|4α
ppm
ppm
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6