CYCLOADDITION-FRAGMENTATION MEDIATED PATHWAYS TO RING D MODIFIED 19-NORSTEROIDS

BY

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Thesis Presented for the Degree of
DOCTOR OF PHILOSOPHY

in the
Department of Chemistry
UNIVERSITY OF CAPE TOWN

MAY 1997

SUPERVISOR: PROFESSOR J.R. BULL

I declare that "*Cycloaddition-Fragmentation Mediated Pathways to Ring* D *Modified 19-Norsteroids*" is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signed by candidate

Eugene Stanford Sickle

ACKNOWLEDGEMENTS

I would like to thank the following people for their contribution to the preparation of this thesis:

My sincerest thanks must go to Professor James R. Bull for his support, encouragement and advice throughout the course of the work presented in this thesis;

My colleagues of the Steroid Research Group at the University of Cape Town, especially Nicholas Desmond-Smith, Judith Du Toit, Naziem George, Richard Gordon, Dr Steven Heggie, Dr Clarissa Hoadley, Dr Anwar Jardine, Pieter de Koning, Dr Michiel Loedolff, Isaac Mayeng, Dr Peter Mitchell, Camielah Mohamed, Dr Pia Mountford, Peter Ray, Anthony Seymour, Shiela Shadbolt and Anne Stevens

Postdoctoral Fellows Dr Sasha Baranovsky, Dr Jonathan Bentley, Dr Berndt Kretschman, Dr Kumar Emayan and Dr Axel Kröger for their advice;

Professor Roger Hunter, Dr David Gammon, Mr Bill Campbell and Dr Kelly Chibale for helpful discussions;

Margie Nair, Noel Hendricks, Pierro Benincasa and Dr Krassi Dimitrova for their analytical services;

Dr Anita Coetzee and Alicia Horne for the X-Ray crystal structure determination;

Schering AG (Berlin) for the binding affinity studies;

The Foundation for Research Development and Schering AG (Berlin) for financial support;

Finally I must thank my wife, parents, family and friends for their past, present and ongoing support of all my endeavours. They have made *this* possible!

SUMMARY

An efficient strategy for the synthesis of 14β-3'-oxobutyl 19-norsteroids has been developed and the intramolecular reactivity of the derived compounds has been investigated.

The approach is based on cycloaddition of methyl vinyl ketone to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate which proceeded with a high degree of regio- and stereoselectivity to give 16α-acetyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate. The cycloadduct underwent base mediated fragmentation, affording an efficient and stereocontrolled synthesis of 3-methoxy-14β-3'-oxobutylestra-1,3,5(10),15-tetraen-17-one which in turn gave 3-methoxy-5',6'-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-4'(3'*H*),17-dione *via* an intramolecular Michael reaction. Regioselective deoxygenation of the dione at C-4', followed by standard functional group modifications provided the parent 14β-perhydrobenzo[14,15]-estradiol analogues.

An alternative, more expedient, route to this novel steroidal ring system was developed which relied on an anionic oxy-Cope rearrangement as the key step. Thus methylenation of the cycloadducts derived from reaction of the dienyl acetate and selected dienophiles (acrolein and methyl vinyl ketone) gave after hydrolysis of the bridgehead ester, substrates which underwent [3,3]sigmatropic rearrangement to generate a series of 14β-perhydrobenzo[14,15]-17-ketones.

The course of the base mediated reaction of the 14β-3'-oxobutyl Δ^{15}-17-ketone was, in the presence of cerium(III) anions, altered in favour of intramolecular aldol condensation, to give 17α-hydroxy-3-methoxy-14,17β-butanoestra-1,3,5(10),15-tetraen-17^2-one.

Conjugate reduction of the 14β-3'oxobutyl Δ^{15}-17-ketone yielded the derived 14β-3'-oxobutyl 17-ketone which underwent intramolecular aldol condensation to give (16^1*R*)-16^1-hydroxy-3-methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-17-one.

The intramolecular reductive coupling of the 14β-3'-oxobutyl Δ^{15}-17-ketone and 14β-3'-oxobutyl 17-ketone was investigated. Treatment of the 14β-oxobutyl Δ^{15}-17-ketone with samarium(II) iodide proceeded *via* a ketyl-olefin coupling pathway to give a mixture of C-3' epimeric 3'-hydroxy-3'-methyl-cyclopenta[14,15]-17-ketones. Surprisingly the 14β-3'-oxobutyl 17-ketone underwent an intramolecular aldol condensation in the presence of samarium(II) iodide to give the C-16^1 epimer of the 14,16β-propano-17-ketone derived from base mediated condensation of the identical substrate.

The 14,15-fused ring diketone was identified as a suitable candidate for intramolecular reductive coupling and accordingly underwent a samarium(II) iodide mediated reductive coupling to give the highly strained ring D caged estriol analogue. As an extension of this work, with the aim of generating structural variants of these strained systems, the 16^1-hydroxy-14,16β-propano-17-ketone was subjected to a dehydration-hydroboration-oxidation sequence to give the 14,16β-propano-16^2,17-dione. The diketone underwent samarium(II) iodide mediated pinacol coupling to give an estriol analogue. In addition chemoselective methylenation of the 14,16β-propano-16^2,17-dione followed by hydroboration-oxidation of the derived 16^2-methylene-17-ketone gave the 16^2-formyl-14,16β-propano-17-ketone which underwent a stereoselective intramolecular pinacol coupling.

A preliminary investigation into the synthesis of 14β-2',5'-cyclohexanyl Δ^{1}5-17-ketone has been undertaken. Cycloaddition of *p*-benzoquinone to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate proceeded, in the presence of boron trifluoride diethyl ether complex, to give a mixture of cycloadducts derived from β-face addition of the dienophile to the steroidal 14,16-diene. The stereochemistry of the major cycloadduct was assigned as *endo*, and confirmed by its subsequent photoreactivity. Thus the major cycloadduct underwent an intramolecular [2+2] cycloaddition to generate a ring D caged dione, deoxygenation of which, at C-15^1 and C-16^1, proceeded to give an estradiol analogue.

Attempted retroaldol fragmentation of the *endo*-cycloadduct resulted in aromatisation of the benzoquinone moiety to give 3-methoxy-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-3',6',17β-triol.

The *endo*-cycloadduct was converted to the dihydro derivative *via* selective hydrogenation of the 4'-olefinic bond. L-Selectride mediated reduction of the dihydro-cycloadduct occurred exclusively at the 3'-oxo group and the chemoselectivity of the reduction process is readily rationalised in terms of approach of the bulky hydride from the sterically more accessible direction. The regioselective reduction to give the 17-acetoxy-3'-hydroxy-6'-ketone provides a substrate which serves as a possible Wharton fragmentation precursor.

The binding affinity data of the estradiol and estriol analogues synthesised during the course of this work are presented.

CONTENTS

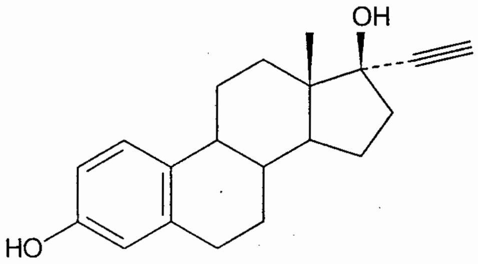
Chapter **Page**

CHAPTER 1

Introduction

The steroidal hormones play a vital role in a wide variety of essential physiological processes. Cholesterol, the adrenocorticoids and the sex hormones have similar gross structural features but each class of steroids demonstrates distinctly different biological activities. The female sex hormones that are steroids may principally be divided into two classes i.e. the estrogens and progestins. Estrogens are important substances that are responsible for the development of secondary sex characteristics in females[1] and are also implicated in the regulation of the growth and differentiation of various mammalian tissues.[2] Estrone was the first crystalline estrogen to be isolated and its discovery was rapidly followed by the identification of 2 other C-18 estrogens, i.e. 17β-estradiol and estriol.[3] Estradiol is the most potent endogenous estrogen.[1] It exhibits a high affinity for the estrogen receptor and is particularly potent when administered parenterally. Despite the high bioactivity of the endogenous estrogens these compound are only weakly active when administered orally. These substances are easily absorbed from the intestine but are degraded by micro-organisms in the gastrointestinal tract and rapidly metabolised by the liver.[4] Abnormalities in steroid hormone synthesis, metabolism and receptor interactions are implicated in numerous diseases. These include coronary atherosclerosis in pre-menopausal women, osteoporosis and other post-menopausal symptoms and in a wide variety of menstrual disturbances.[5] In addition estrogen antagonists find increasing therapeutic use in the treatment of hormone-dependent breast cancer.[6] As such the search for synthetic estrogens with enhanced oral efficacy and increased metabolic resistance remains a current and topical area of research.

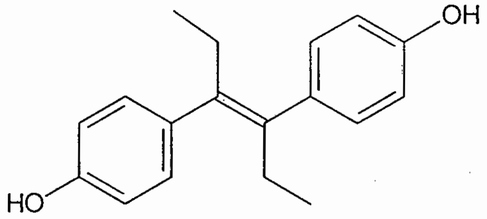
Numerous approaches to overcoming the rapid metabolism of 17β-estradiol have been developed. One strategy aimed at overcoming the rapid inactivation of estradiol is based upon stabilisation of the ring D functionality by appropriate substitution at C-17. This is exemplified by 17α-ethynyl estradiol[7] **1** a potent synthetic estrogen when taken orally. An additional example based on this strategy is the estrogen 3-cyclopentyloxy-17α-ethynylestradiol which after oral administration is absorbed and stored in the fat reserves of the body from which it is slowly released over a period of several days.[8] An alternative approach to improving metabolic stability and binding affinity is based upon introducing a range of functional groups at various positions on the steroid nucleus. In this regard substitution at C-7 and C-11 has been found to have significant influence on activity.[9] Extensive research has focused on varying both the nature and configuration of substituents at these positions. This approach, of varying the steric environment at positions identified as being important to receptor binding is a general strategy which further aims to define the boundary conditions for receptor site access.



1

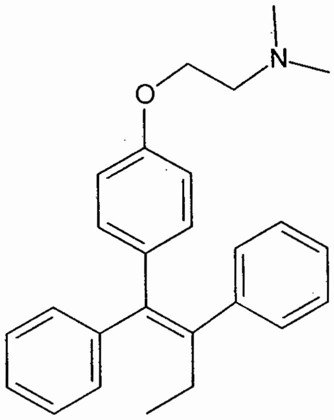
The rational design of drugs is generally based upon an understanding of the three-dimensional (3D) structure of the active sites of proteins. This allows for the design and synthesis of ligands with appropriate 3D-characteristics for improved receptor site access and accompanying induction or blocking of activity.[10] The difficulties associated with the isolation, purification and characterisation of stable steroid hormone receptor proteins results in such an approach being impractical at present. In the absence of direct evidence as to the 3D-structure of the steroid hormone receptor two complementary approaches to gaining insight into the nature of the steroid binding site have been developed. In the first instance structure prediction methods, including molecular modelling, may be used to create a 3D-model of the receptor. Secondly an analysis of the binding data for a collection of hormone analogues may lead to the identification of important structure-activity relationships.

It is generally accepted that estrogen receptor binding is primarily the result of interaction between the receptor and the steroid ring A.[11] This is supported by the fact that the steroid nucleus is not essential for estrogenic activity as exemplified by the potent non-steroidal estrogen diethylstilbestrol[12] **2** which contains two phenolic rings capable of imitating ring A of estradiol thus initiating receptor binding. However, while a phenolic ring A is essential for binding, ring D controls the activity of estrogens. It has been proposed that the conformational features and functional groups present in ring D are crucial mediators of activity.[13] This is achieved by allostery (i.e. inducing or stabilising an essential conformational state in the receptor), by influencing the aggregation state of the receptor or by participating in a direct interaction with DNA or chromatin.[13]



2

Estrogen antagonists compete for and bind to the receptor site but either lack essential ring D elements associated with initiating activity or possess additional elements which prevent this initiation. These two approaches to antagonists are exemplified by the non-steroidal estrogens[6] tamoxifen **3** and nafoaxidine **4** and more recently the steroidal derivatives ICI 164,384 **5** and ICI 182,780 **6** have been described.[14] These compounds bind to the estrogen receptor, effectively blocking estradiol binding and are completely devoid of estrogenic activity.



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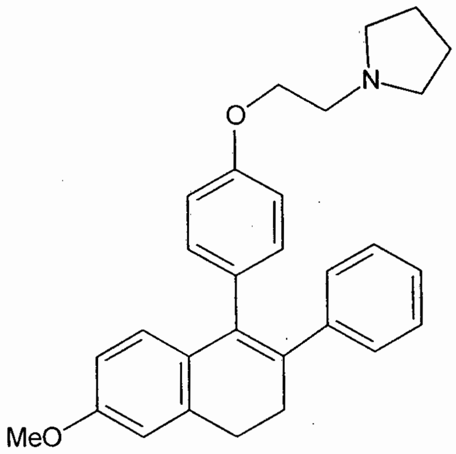

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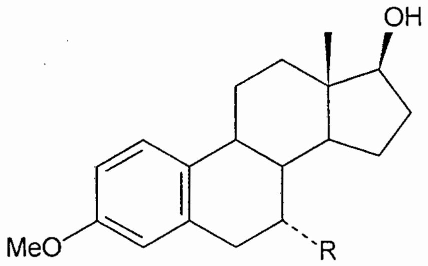
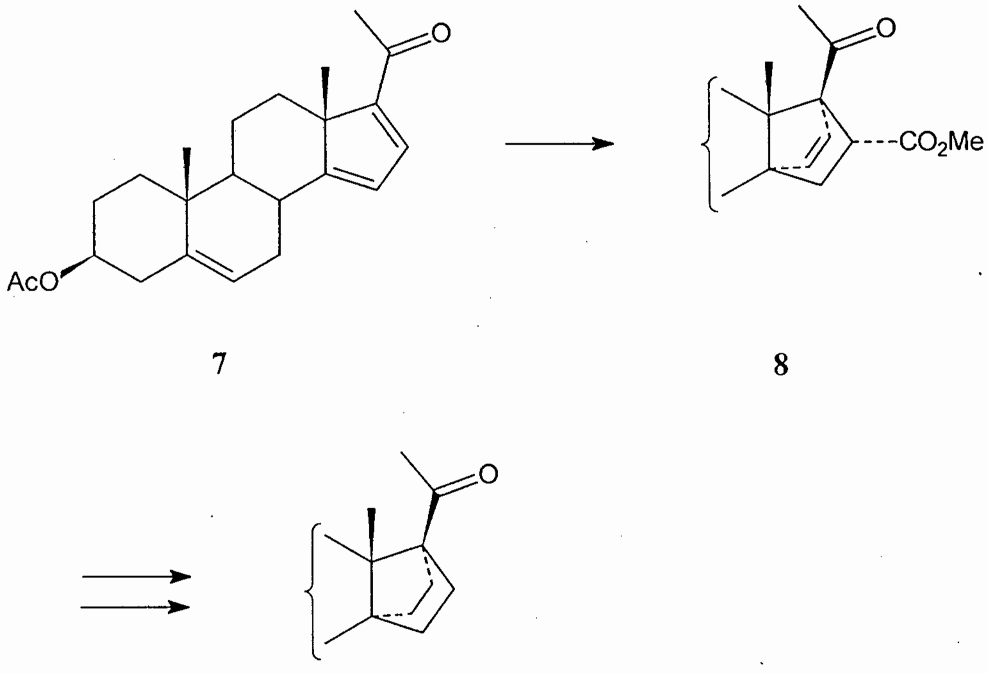


5 ICI 164,384: R = $(CH_2)_{10}CON(CH_3)(CH_2)_3CH_3$
6 ICI 182,780: R = $(CH_2)_9SO(CH_2)_3CF_2CF_3$

The importance of ring D in initiating activity in a steroid-receptor complex has resulted in the synthesis of numerous ring D modified steroid hormone analogues. The therapeutically important 17α-ethynylestradiol is just one example of a series of 17α-alkyl substituted estradiols displaying enhanced biological activity. Solo *et al.*[15] in an investigation aimed at examining the influence of 17α-substitution on biological activity, introduced a 14,17α-ethano bridge into the progesterone skeleton with the aim of restricting the conformational freedom of the 17α-alkyl substituent. The antiprogestational activity of the resultant compound **9** prompted an extensive investigation into the influence of ring D alkyl bridges on the biological activity of these steroid hormones.[16]

The synthetic approach adopted by Solo *et al.* to 14,17α-ethano bridged progesterone was based on cycloaddition of methyl acrylate to the steroidal diene 7 and subsequent transformation of the derived cycloadduct **8** (Scheme 1.1).



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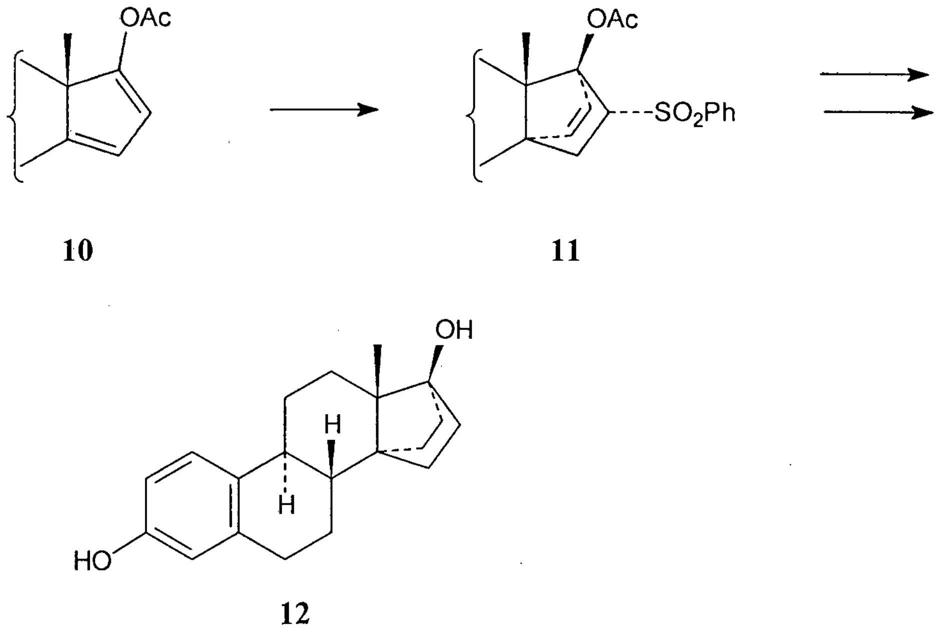
8

9

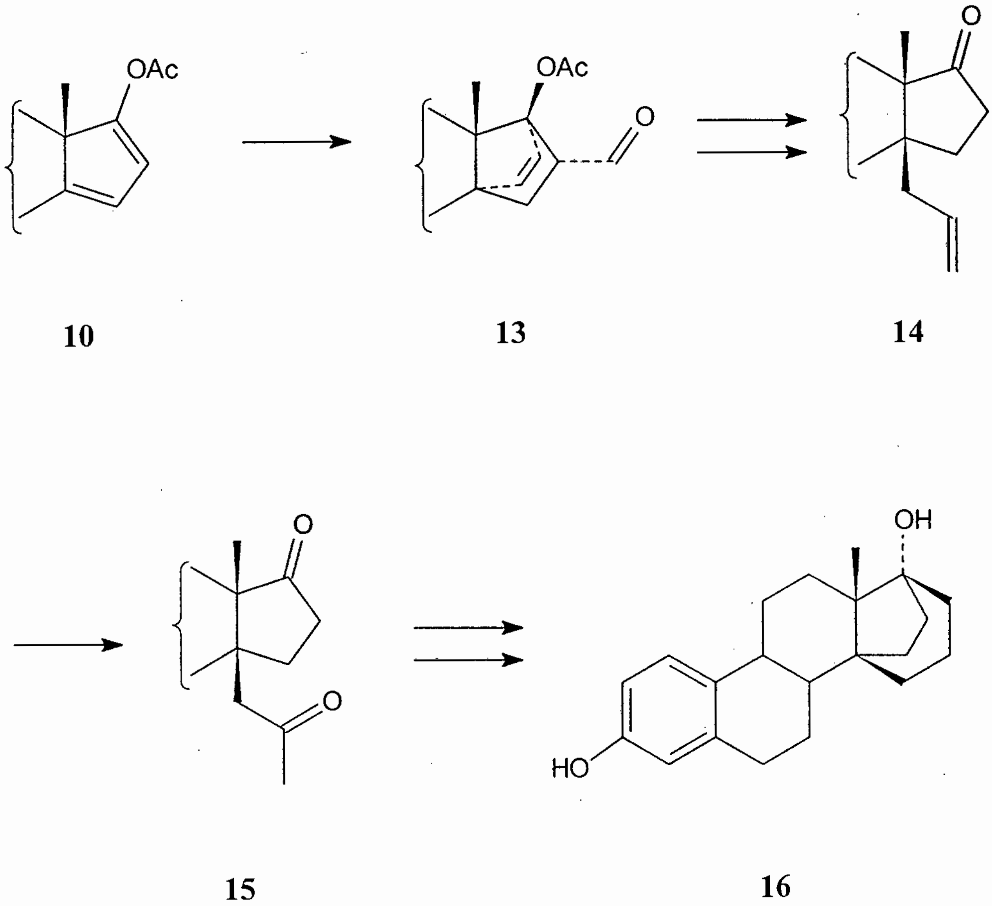
Scheme 1.1

The synthesis of a variety of ring D functionalised steroids has been based on this cycloaddition approach and this methodology has been exploited for the synthesis of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **12** (Scheme 1.2).[17] The discovery that the introduction of a two carbon bridge between positions 14 and 17 of estradiol significantly increased both the binding affinity and biological activity of **12** prompted an investigation into the structure-activity relationships of such ring D bridged compounds.[18] One aim of such an investigation is to delineate the influence of both the size and orientation of the alkyl bridge on the estrogenicity of such modified estradiol analogues.



Scheme 1.2

In accordance with this aim the synthesis of the 14β,17β-propano bridged compound **16** was undertaken.[19] Synthesis of the **16** was achieved by cycloaddition of acrolein to the dienyl acetate **10** followed by conversion of the derived cycloadduct **13** to the 14β-allyl-17-ketone **14**. Regioselective functionalisation of **14** gave the 14β-acetonyl-17-ketone **15** which underwent intramolecular aldol condensation to give, after functional group modification, 14,17β-propanoestra-1,3,5(10)-trien-3,17α-diol **16** (Scheme 1.3).

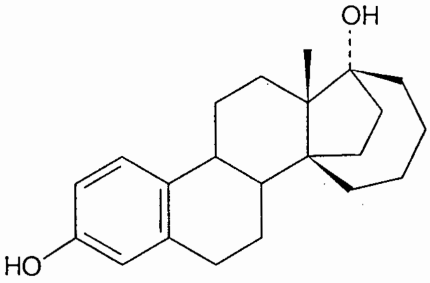


10 13 14

15 16

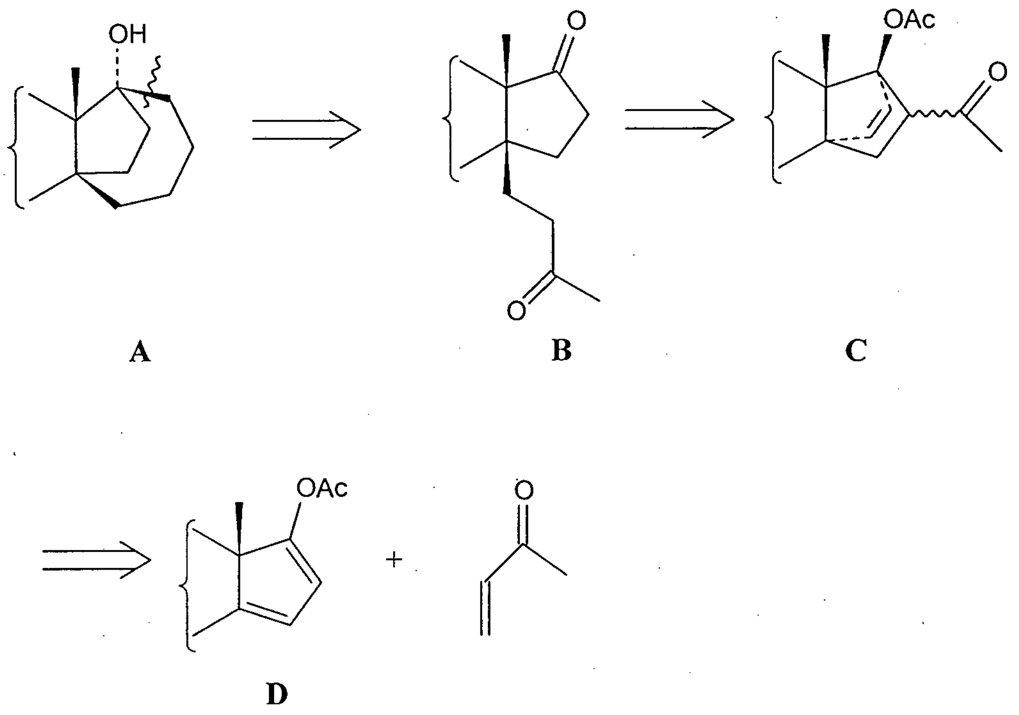
Scheme 1.3

As an extension of this work 14,17β-butanoestra-1,3,5(10)-trien-3,17α-diol **A** was identified as an important synthetic target. It was expected that the binding properties of **A** to the estradiol receptor would serve to further define the boundary conditions for estrogenic activity in this series of compounds.



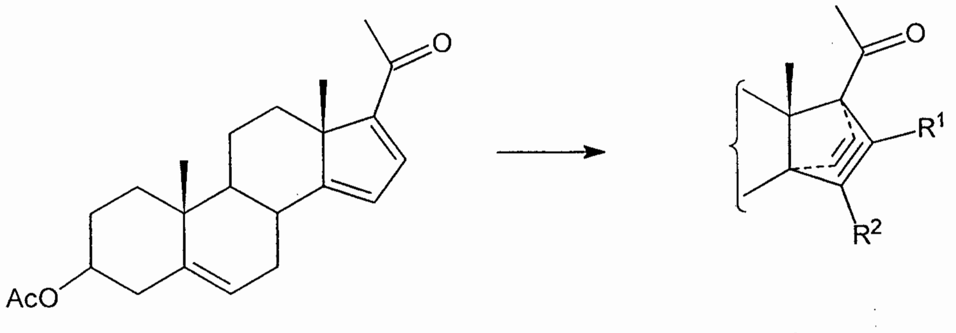
A

Retrosynthetic analysis of **A** is based upon disconnection of the butano-bridge at the point of attachment to C-17 leading to synthon **B** as depicted in Scheme 1.4. Synthon **B** could conceivably be derived, *via* a base mediated fragmentation, from the protected β-hydroxy ketone **C**. Further retrosynthetic simplification identifies **C** as a cycloadduct derived from the 14,16-diene **D** and methyl vinyl ketone.



Scheme 1.4

Significant precedent may be found for highly regio- and stereoselective cycloadditions to steroidal 14,16-dienes. Solo and Singh[20] demonstrated that the reaction of 3β-acetoxy-20-keto-5,14,16-pregnatriene **7** with a series of dienophiles (hexafluorobutyne, dimethyl acetylenedicarboxylate and methyl propiolate) proceeded with a high degree of regio- and stereoselectivity giving almost exclusively products (**17** - **19**) derived from β-face addition (Scheme 1.5).

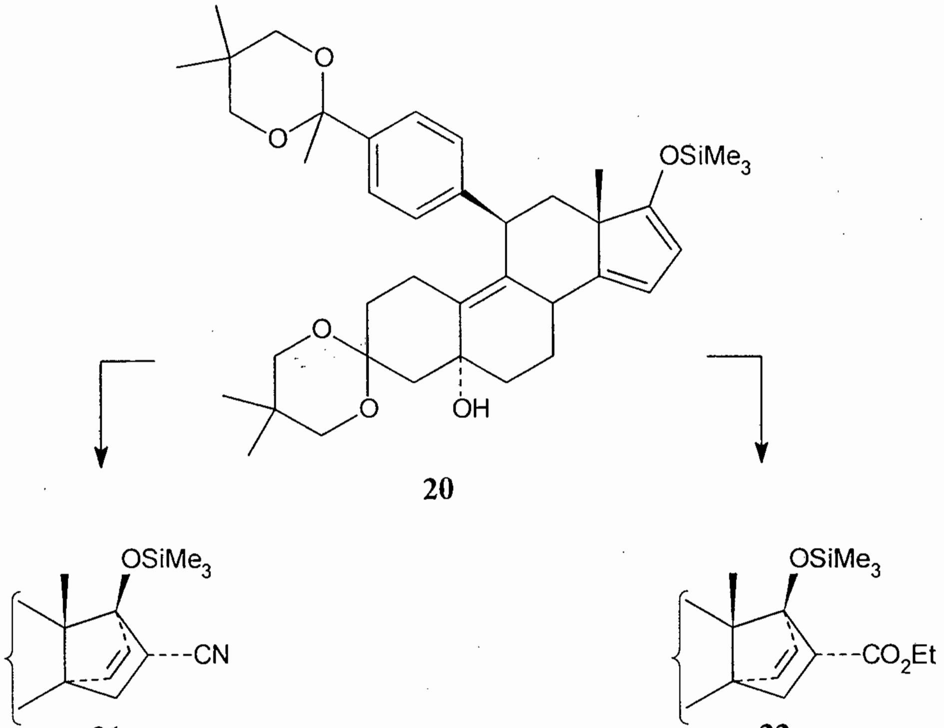


7

17: $R^1 = R^2 = CF_3$
18: $R^1 = R^2 = CO_2Me$
19: $R^1 = CO_2Me$, $R^2 = H$

Scheme 1.5

This high degree of selectivity has been exploited by Scholz *et al.*[21] for the synthesis of progesterone antagonists. The key step in the synthesis is a stereo- and regioselective cycloaddition of methyl acrylate and acrylonitrile to the diene **20** to give the cycloadducts **21** and **22** respectively (Scheme 1.6).



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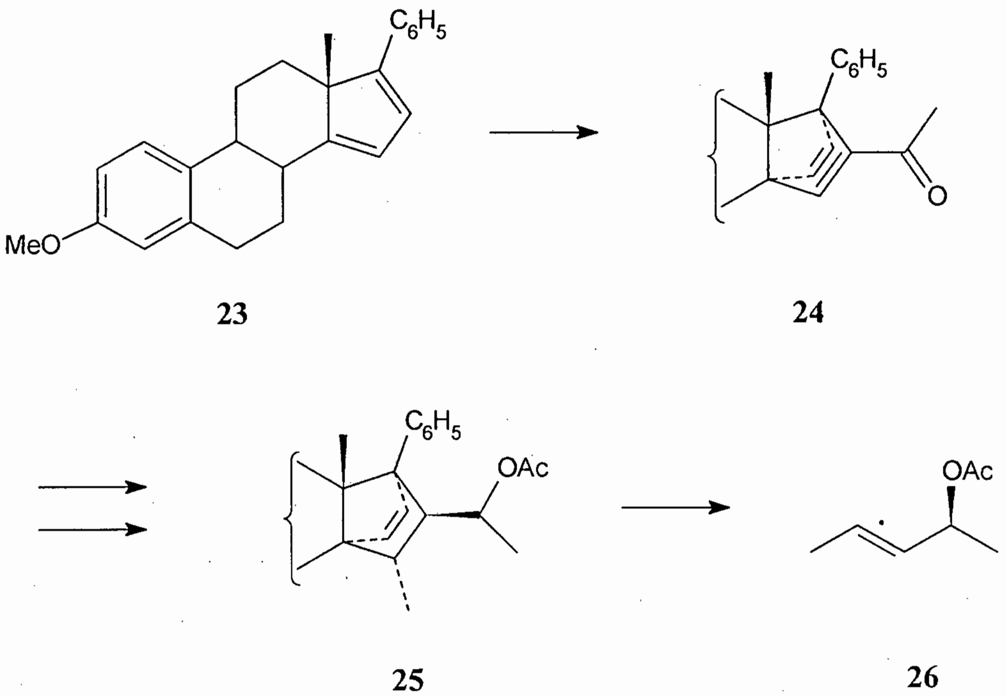
21

22

Scheme 1.6

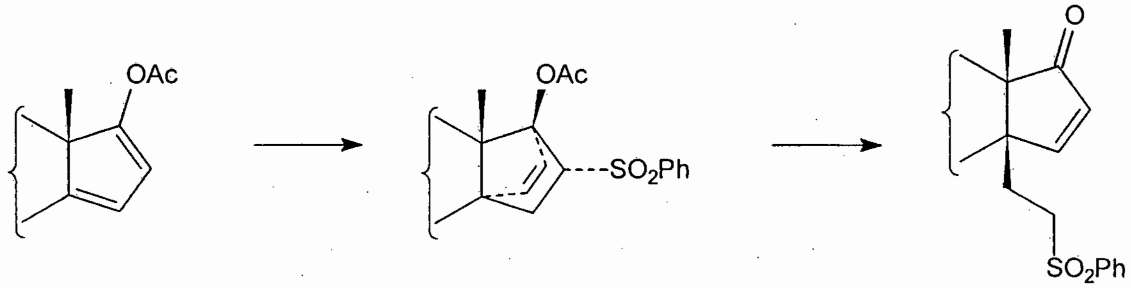
Furthermore Winterfeldt *et al.*[22] have developed a synthesis of enantiomerically pure compounds using steroidal dienes as chiral templates. The strategy is exemplified in Scheme 1.7 and is based upon cycloaddition to the diene **23** followed by diastereoselective transformation of the derived cycloadduct **24**. Thermal retro Diels-Alder reaction of **25** regenerates the diene **23** and expels enantiomerically pure **26**.



23 **24** **25** **26**

Scheme 1.7

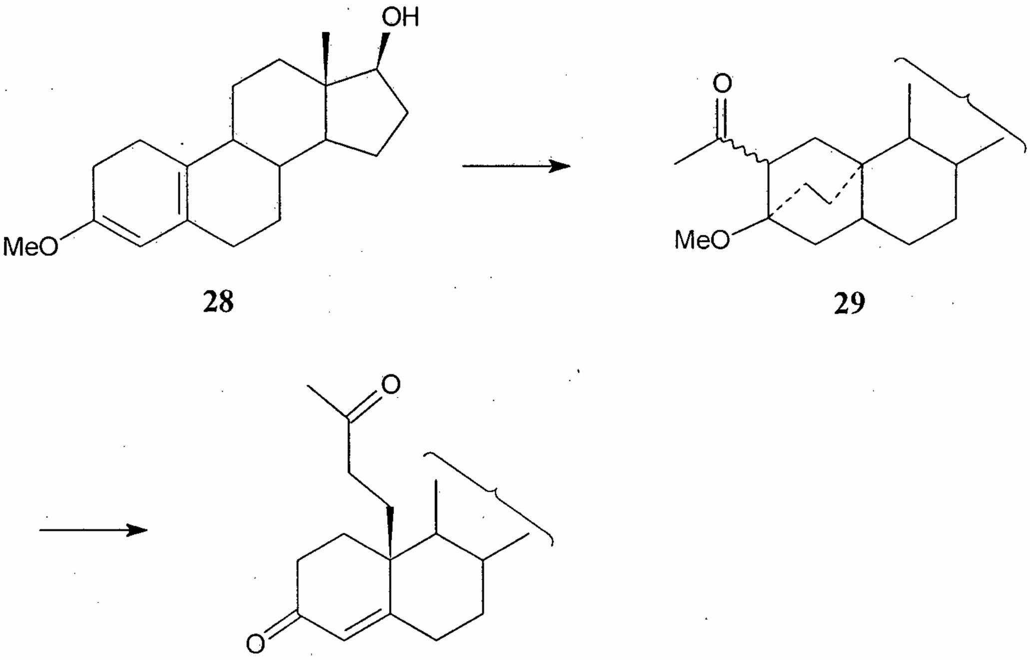
It is thus expected that cycloaddition of methyl vinyl ketone to the diene **D** should proceed with a high degree of regio- and stereoselectivity to give the cycloadduct **C**. The synthesis of **B** is dependent on fragmentation of **C** and the feasibility of this process has been demonstrated by Bull *et al.*[17] in the synthesis of 14β-2'-phenylsulfonylethyl Δ^{15}-17-ketone **27** (Scheme 1.9). Cycloaddition of phenyl vinyl sulfone to the 14,16-diene **10** followed by base mediated fragmentation of the derived cycloadduct **11** gave **27** in 87% overall yield.



10 **11** **27**

Scheme 1.8

In addition Birch and McKague[23], in the synthesis of C-19 substituted testosterone derivatives, prepared the cycloadduct **29** from Diels-Alder reaction of methyl vinyl ketone with the 1,5(10)-diene **28**. The derived cycloadduct underwent a facile acid mediated fragmentation to yield the 10β-3'-oxobutyl Δ^4-3-ketone **30** (Scheme 1.9).

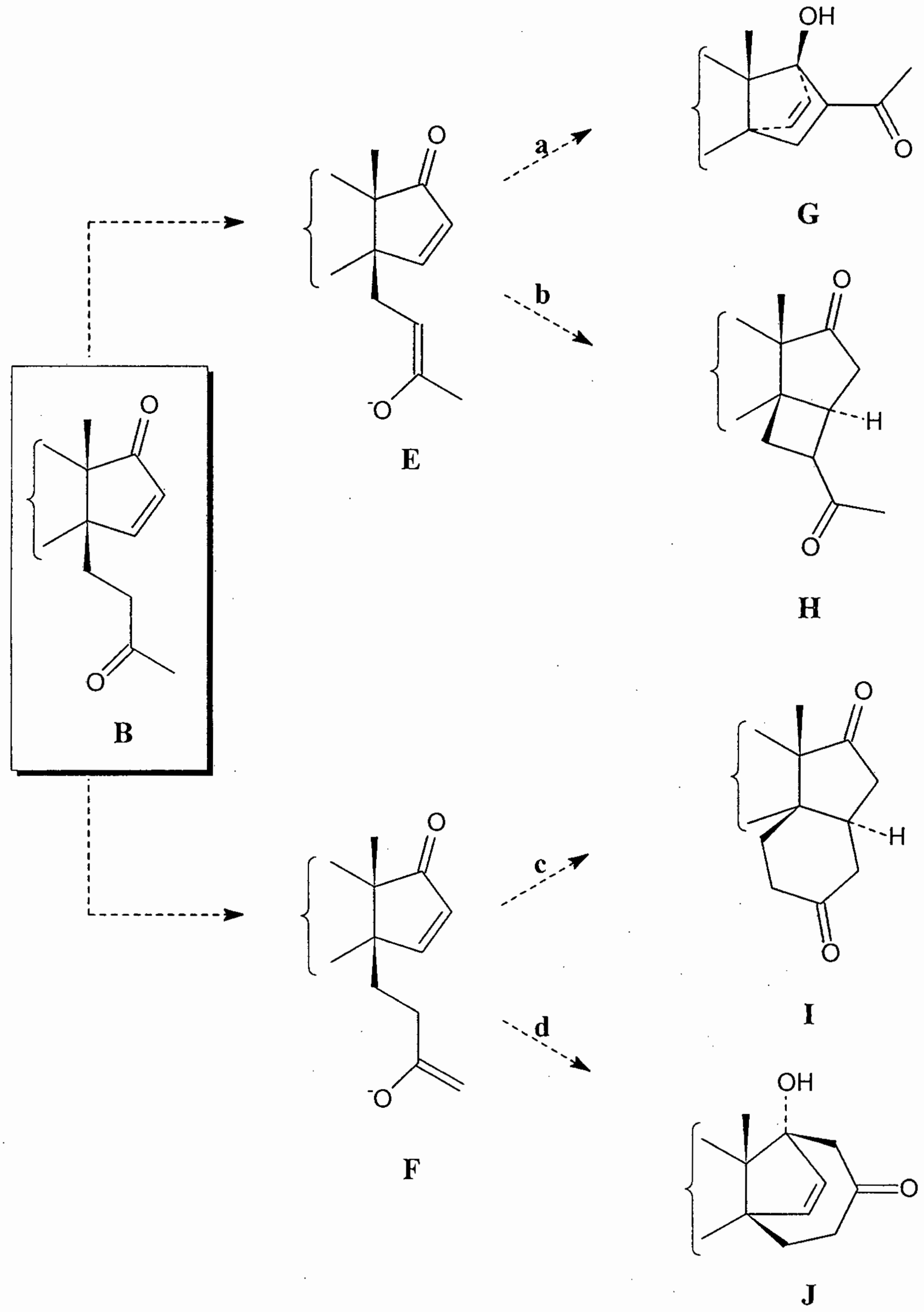


28 **29** **30**

Scheme 1.9

The diene of choice was the readily available 3-methoxyestra-1,3,5(10),14,16-tetraen-17-yl acetate **10** which is synthesised in three steps from estrone 3-methyl ether.[17] The diene synthesis is based upon bromination of estrone 3-methyl ether followed by dehydrobromination to give a mixture of Δ^{14}- and Δ^{15}-17-ketones. Enol-acetylation of this mixture produces the dienyl acetate **10** in 66% overall yield.
Assuming the cycloaddition to methyl vinyl ketone[24] proceeded with the predicted stereo- and regioselectivity, the resultant 1,3 disposition of the bridgehead ester and the 16^1-ketone in the cycloadduct, suggests that cleavage of the bridgehead ester, would generate an alkoxide which is perfectly set up for fragmentation to the 14β-substituted enone **B**.

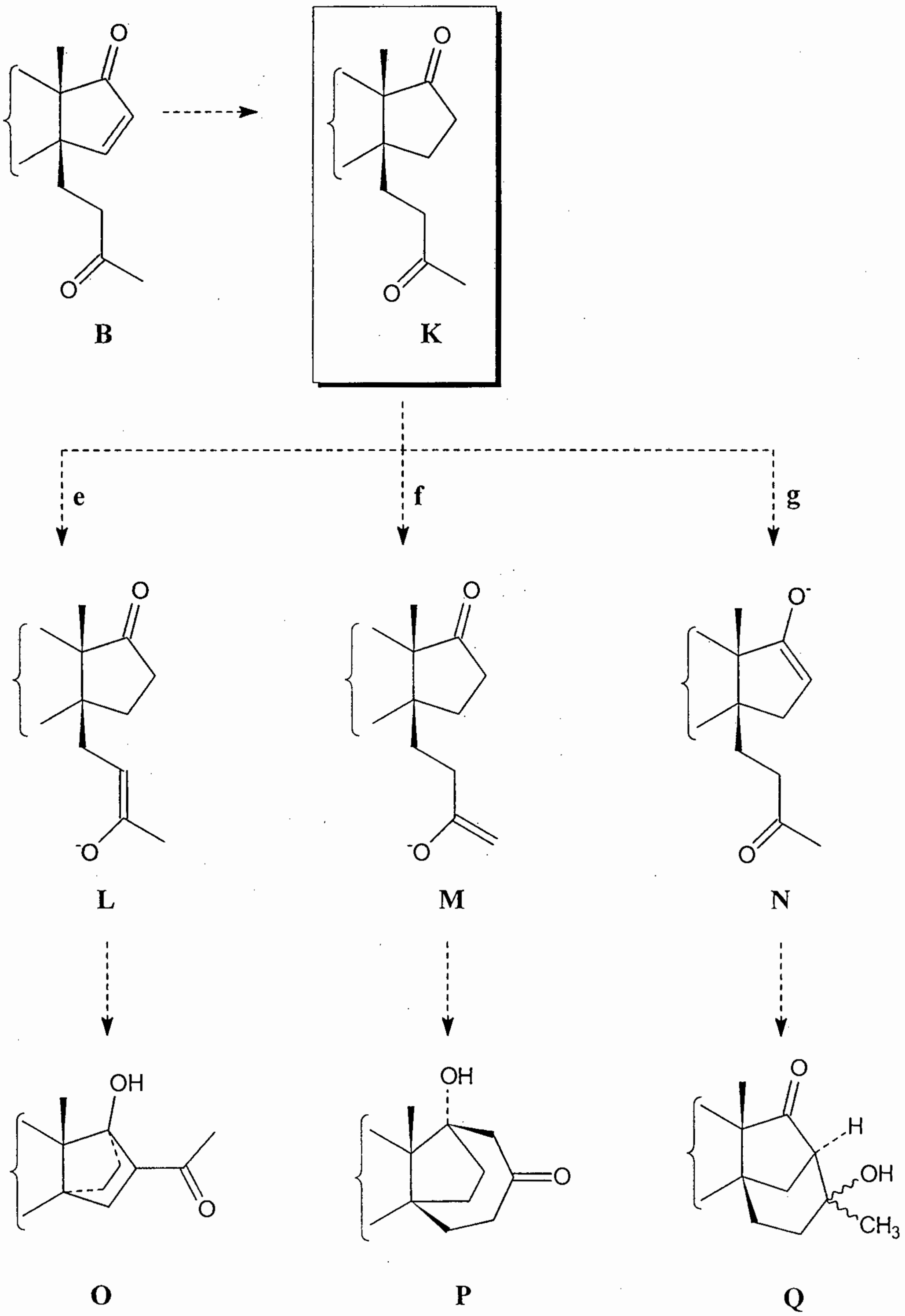
The successful synthesis of the target compound **A** is dependant on the effective transannular condensation of the 14β-functionalised Δ^{15}-17-ketone **B**. At this point it was recognised that the four possible reaction pathways were open to enolates derived from intermediate (**B**) (Scheme 1.10). Pathway **a** is simply a reversal of the fragmentation process and was not expected to be a competitive process. Pathway **b** was considered to be unlikely given the inherent strain accompanying the formation of cyclobutanoid rings.[25] The two remaining pathways are both considered to be possible options. Both pathways proceed through the intermediacy of enolate **F** which can undergo intramolecular Michael reaction, to yield the perhydro-15αH-benzo[14,15]-14β-4',17-dione **I**, or intramolecular aldol closure yielding the 14,17β-butano compound **J**.



Scheme 1.10 Possible Intramolecular Condensation Pathways for the 14β-3'-Oxobutyl Δ^{15}-17-ketone **B**

If competing Michael addition precluded the formation of the desired bridged compound an alternative strategy was proposed. It was envisaged that reduction of the olefinic bond of the 14β-oxobutyl Δ^{15}-17-ketone **B** would produce the 14β-3'-oxobutyl 17-ketone **K** thereby excluding the intramolecular Michael reaction. Compound **K** has three reaction pathways available to it (Scheme 1.11). Path **e** , leading to the 14,17-ethano bridged compound **O** *via* the enolate **L**, is not expected to compete for reasons discussed above. The outcome of the reaction is thus dependent on which of the remaining two pathways is followed. Path **f** invokes enolisation of the 3'-oxo group, generating the enolate **M**, which will, after aldol condensation, produce the 14,17β-butano bridged compound **P**. Alternatively the formation of the enolate **N** (path **g**) will lead to the aldol product **Q**.

A successful transannular cyclisation to give the 14β,17β-butano bridged compound would provide a substrate which could be converted *via* standard functional group modification, to an estradiol analogue suitable for biological evaluation.



Scheme 1.11 Possible Intramolecular Condensation Pathways for the 14β-3'-Oxobutyl 17-ketone **K**

CHAPTER 2

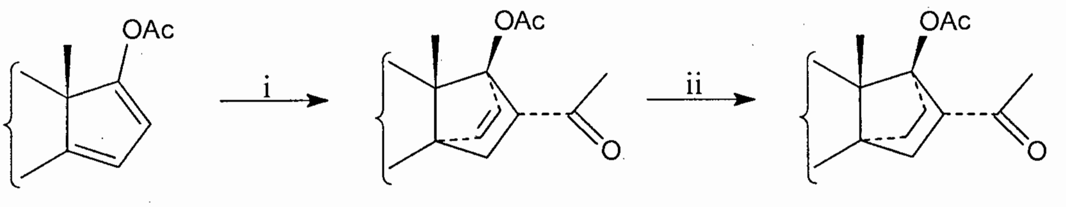
Synthesis and Intramolecular Reactions of 3-Methoxy-14β-3'-oxobutylestra-1,3,5(10),15-tetraen-17-one

2.1 Synthesis and Base Mediated Intramolecular Reactions of the 14β-3'-Oxobutyl Δ^{15}-17-Ketone 34

Initially the cycloaddition was performed between 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **10** and methyl vinyl ketone in dry benzene in a sealed tube at 125°C for 32 h and provided the cycloadduct **32** in 74% yield (Scheme 2.1).

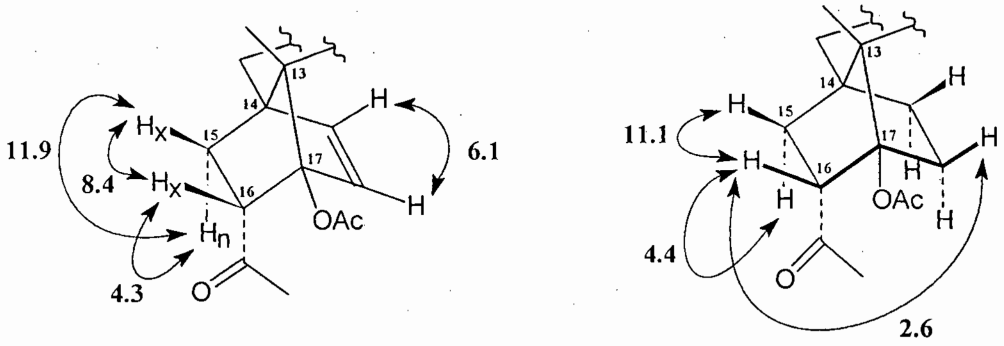
Mass spectral, microanalytical and NMR spectral data were consistent with the assigned structure of the cycloadduct. The essential features of the ^{1}H NMR spectrum are summarised in Figure 2.1. The signal for 16β-H resonated at δ 3.40 (dd, *J* 8.4 and 4.3 Hz), the splitting pattern compatible with one large *exo-exo* coupling, between 16β-H and 15β-H, and a smaller *exo-endo* coupling between 16β-H and 15α-H .[26]

The stereoselectivity of the process could not be inferred from the available evidence though it was expected that, in accordance with frontier molecular orbital principles[27], the process should be *endo*-selective. Further evidence in support of *endo*-cycloaddition was derived from catalytic hydrogenation of the cycloadduct which proceeded smoothly to give the 17^1,17^2-dihydro compound **33** (Scheme 2.1). The outstanding feature of the ^{1}H NMR spectrum of **33** was a multiplet at δ 3.34 assigned to 16β-H. This signal displayed a large vicinal coupling (*J* 11.1 Hz) in addition to a four-bond W-coupling (*J* 2.6 Hz) with 17^1-H_x (Figure 2.1).This long-range coupling can only arise if the 16-substituent adopts an *endo*-orientation. The value of the long-range coupling constant is consistent with data reported for 2-*endo*-substituted bicyclo[2.2.1]heptanes.[26] In the light of considerable evidence in support of favoured β-face addition to steroidal 14,16-dienes, as discussed in Chapter 1, it is reasonable to assume that the dienophile added to the β-face of the diene.



10 **32** **33**

Scheme 2.1 *Reagents and Conditions*: (i) CH_2=CHCOMe, $BF_3 \cdot OEt_2$, toluene or THF; (ii) H_2, Pd on C, EtOAc



32 **33**

Figure 2.1

Coupling Constants for Ring D Protons for the Cycloadduct **32** and the Dihydro Derivative **33**

Purification of the product was complicated by the presence of a minor unidentified contaminant which formed under these reaction conditions. Since the cycloadduct **32** is a primary intermediate in the proposed reaction sequence the need for an efficient and clean procedure for large scale preparation necessitated further experimentation.

While [4+2] cycloadditions are thermally allowed, in accordance with the Woodward and Hoffmann rules[28], it has been found that numerous Diels-Alder reactions are catalysed by both Bronsted and Lewis acids.[29] It is generally believed that protonation or complexation of the dienophile occurs leading to a significant lowering of the LUMO energy of the dienophile according to frontier molecular orbital theory. This lowering in energy ultimately leads to acceleration and enhanced selectivity observed for

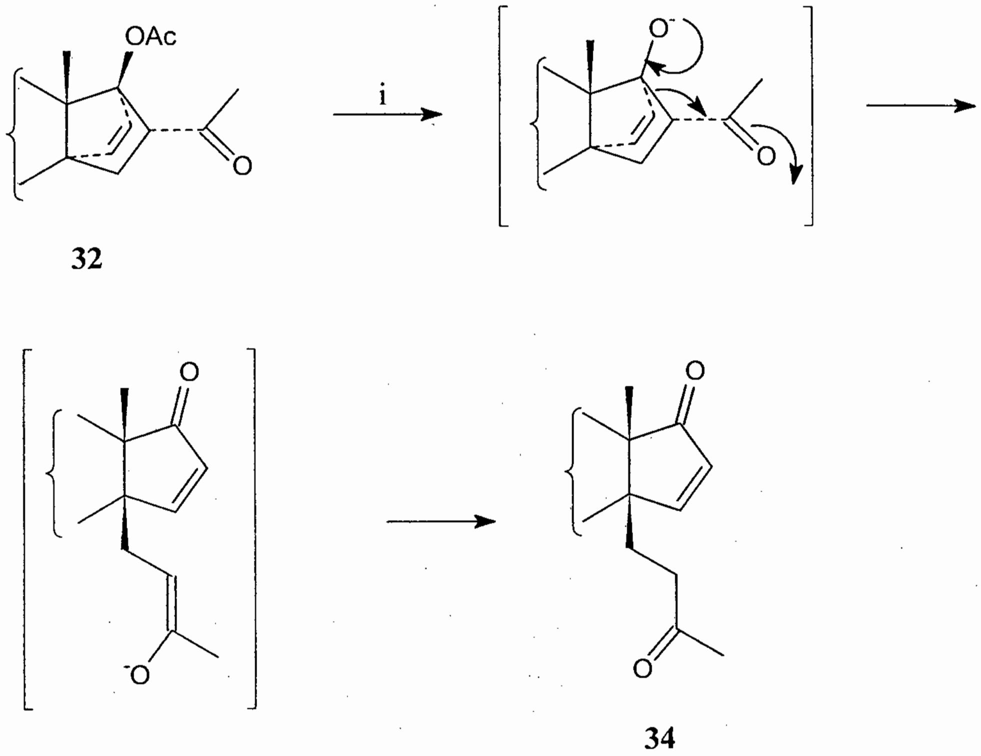
$HOMO_{diene}$-$LUMO_{dienophile}$ controlled cycloadditions.[28, 30]

The catalysed reaction between the diene **10** and methyl vinyl ketone in dry benzene at 0°C in the presence of boron trifluoride diethyl ether complex yielded after 8h the cycloadduct **32** in 74% yield. Once again the formation of **32** was accompanied by the presence of contaminating by-products.

In the last few years several experimental and theoretical works dealing with the effect of solvent on the regio- and stereochemical outcome of the intermolecular Diels Alder reaction have been published[31,32] and the topic has formed part of a review.[29] It was decided to determine whether a variation of solvent would result in improved yields and a cleaner reaction which would obviate the need for large scale chromatography at the purification stage. It has been found[31] that significant rate enhancement and the improvement of *endo*/*exo* selectivity can be achieved on conducting cycloadditions in more solvophobic[33] solvents.

Thus the cycloaddition was performed between the dienyl acetate **10** and methyl vinyl ketone at 0°C in dry tetrahydrofuran. The reaction was conducted in the presence of catalytic boron trifluoride diethyl ether complex and gave exclusively the cycloadduct **32** in 94% yield. In addition the reaction time decreased from 8 h in benzene to 3 h in tetrahydrofuran. The lack of contaminants associated with the catalysed reaction in tetrahydrofuran led to this being the method of choice for large scale preparation of **32**.

Although the properties of **32** and **33** failed to yield evidence in support of the assigned regiochemistry of cycloaddition, it is apparent that confirmation of the regioselectivity would be found in a successful retroaldol reaction. In the event, treatment of the cycloadduct **32** with methanolic potassium hydroxide (1 M) at 24°C for 2.5 h gave the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** in 93% yield (Scheme 2.2). The product displayed spectroscopic and analytical properties consistent with the assigned structure. The 16-H resonated at δ 6.20 (*J* 5.8 Hz) while its coupling partner 15-H resonated at δ 7.33.

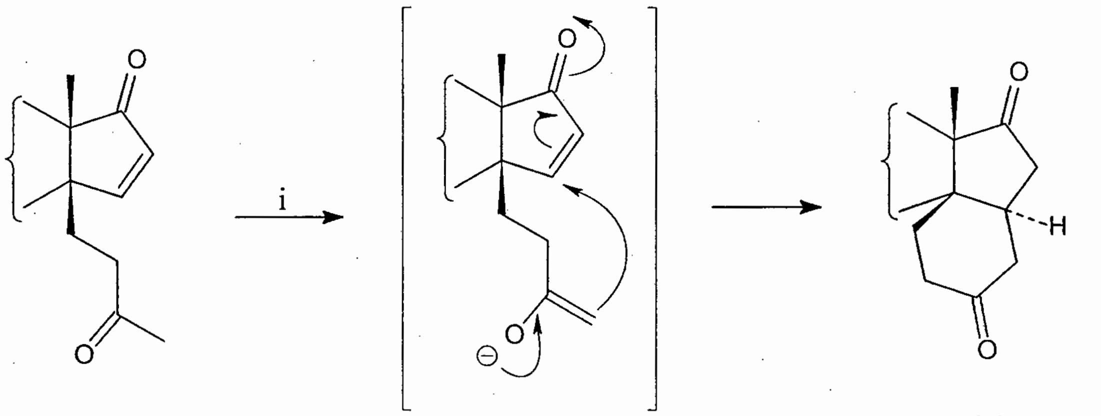


Scheme 2.2. *Reagents and Conditions*: (i) KOH, MeOH, 24°C

Two resonances in the ^{13}C NMR spectrum, at δ 207.5 and 213.8 were assigned to C-3' and C-17 respectively. The IR spectrum of the compound displayed a broad peak centred at 1709 cm^{-1} assigned to the carbonyl absorption.

The product must arise *via* cleavage of the bridgehead ester followed by fragmentation of the 16,17-bond and results in stereospecific introduction of a 14β-substituent while restoring the oxo-functionality at the C-17 (Scheme 2.2).

The 14β-3'-oxobutyl Δ^{15}-17-ketone **34** was heated under reflux in the presence of methanolic potassium hydroxide (0.03 M) for 4h and gave a single product **35** in 94% yield (Scheme 2.3). Analytical data were consistent with the assigned structure the novelty of which prompted a thorough investigation of its spectroscopic properties in order to probe the conformational properties of this new ring system and to facilitate structural assignments of derived compounds.



34 **35**

Scheme 2.3 *Reagents and Conditions*: (i) KOH, MeOH, Δ

It was possible to fully assign the 400 MHz ^{1}H NMR spectrum (Figure 2.2) of the diketone **35** with the aid of COSY (Figure 2.3), HETCOR, DEPT and ^{13}C data . While the ^{1}H NMR spectrum, run in deuteriochloroform, allowed for the assignment of all the key protons in ring D and the 14,15β-fused ring, overlapping signals precluded a more extensive assignment of the ring B and ring C protons. The assignment of these protons was crucial to establishing the effect, if any, of the additional fused ring on the conformation of these rings. In order to achieve greater dispersion of signals of the ^{1}H NMR spectrum, it was run in the strongly coordinating solvent deuteriopyridine and allowed for a more complete assignment of all the proton resonances. These ^{1}H NMR data are summarised in Table 2.1

It is evident from the data in Table 2.1 that no significant changes in either the chemical shift or the values of the coupling constants were observed on changing solvents from deuteriochloroform to deuteriopyridine. This is somewhat surprising as it is well established that solvents with large anisotropy effects such as deuteriopyridine cause significant signal shifts in molecules with polar functional groups and that such effects diminish with distance from such functional groups.[34] It was therefore particularly gratifying that, on changing solvents, the signals associated with the ring C protons displayed greater dispersion and allowed for their full assignment.

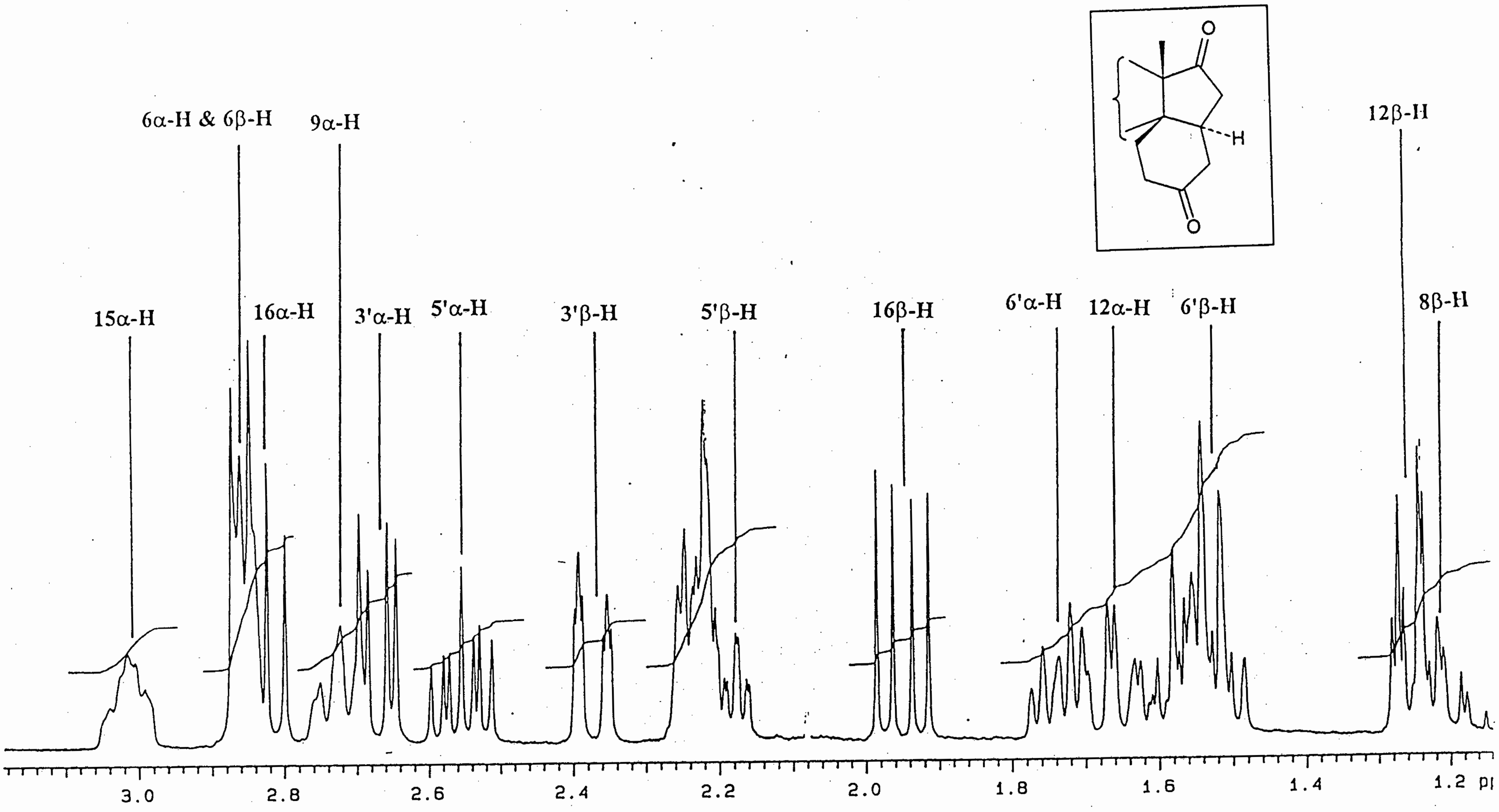


Figure 2.2
Highfield Region of ^{1}H NMR Spectrum of Diketone 35

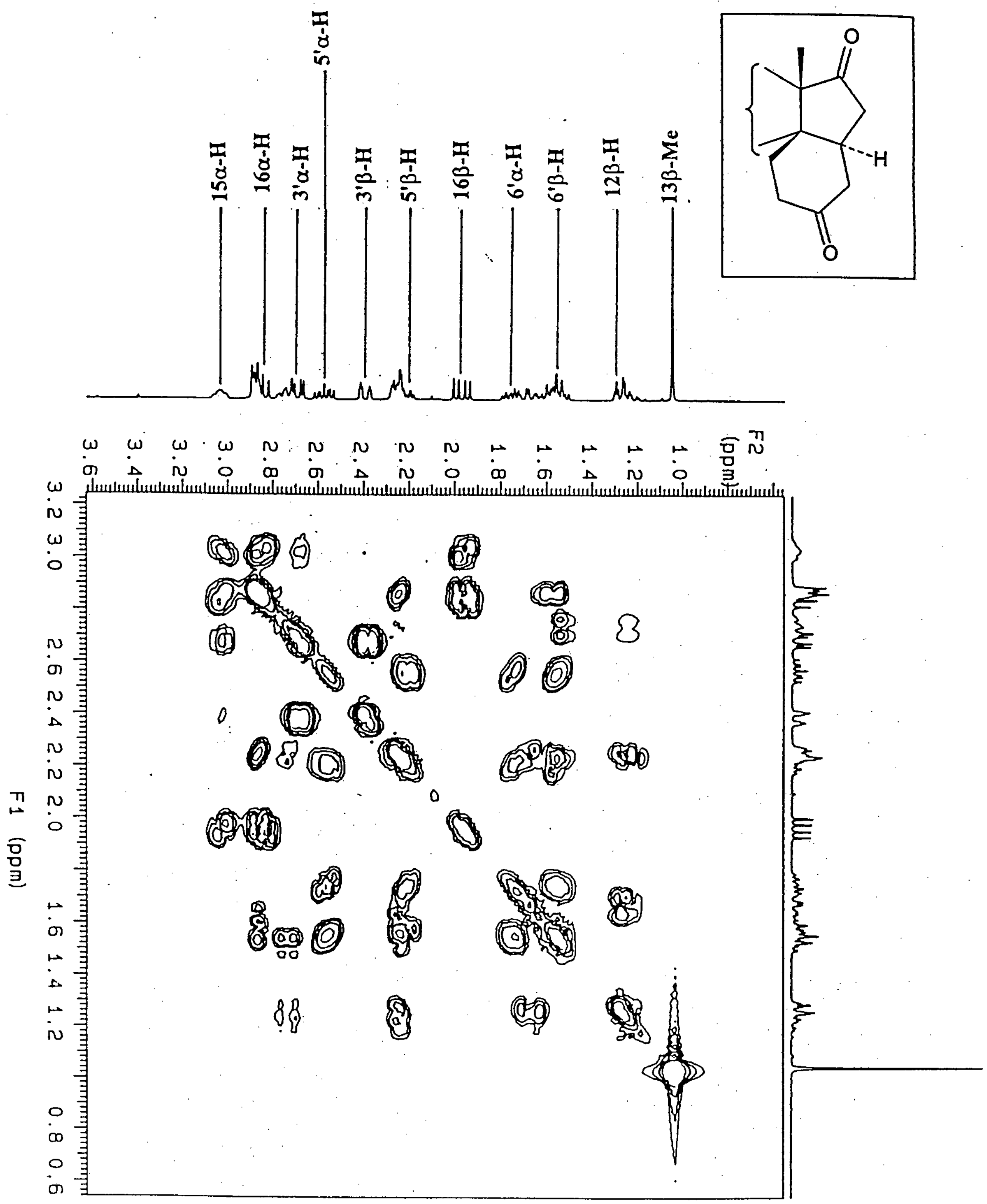


Figure **2.3**
Highfield Region of COSY Spectrum of 4',17-Dione **35**

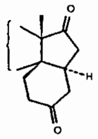
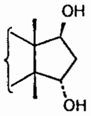
Table 2.1 Ring D and Ring E ^{1}H NMR Assignments* for Diketone **35**

Proton	Chemical Shift ($CDCl_3$)		Coupling Constant	Chemical Shift (C_5D_5N)		Coupling Constant
15α-H	3.20	m		3.20	m	
16α-H	2.86	dd	19.9 and 10.2	2.85	dd	19.4 and 10.1
16β-H	1.79	dd	19.9 and 9.0	1.95	dd	19.4 and 9.0
3'α-H	2.67	dd	15.9 and 5.0	2.67	dd	15.7 and 5.1
3'β-H	2.39	ddd	15.9, 2.1 and 1.7	2.37	ddd	15.7, 2.4 and 1.9
5'α-H	2.55	ddd	17.1, 9.6 and 6.7	2.55	ddd	16.9, 10.1 and 6.6
5'β-H	2.18	dtd	17.1, 6.4, 6.0 and 1.7	2.18	dtd	16.9, 2 x 6.1 and 1.9
6'α-H	1.99	ddd	15.4, 6.7 and 6.4	1.73	ddd	15.2, 6.6 and 6.1
6'β-H	1.70	ddd	15.4, 9.6 and 6.0	1.57	ddd	15.2, 10.1 and 6.1

*Chemical shift values in ppm and Coupling Constants in Hz

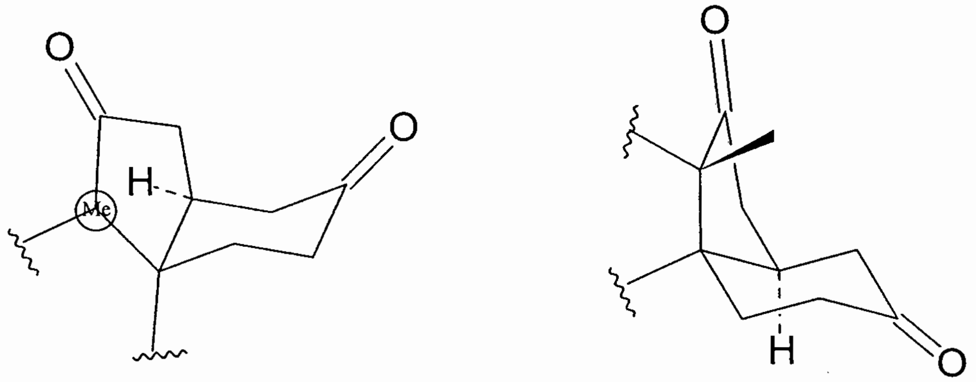
The coupling constants for the ring C protons are listed in Table 2.2 along with the corresponding coupling data for the 14β-methyl-15α,17β-diol **37**[35] and the average magnitude of the proton-proton coupling constants for 14β-methyl steroids having ring C in a chair conformation.[36]

Table 2.2 Coupling Constants (J) for Ring C Protons*

Coupling Protons	 **35**	 **37**	$J_{average}$
8β,9α	11.1	11.8	11.4
9α,11α	4.0	4.0	3.5
9α,11β	11.1	12.2	11.5
11α,12α	4.0	4.2	3.5
11α,12β	3.2	3.3	3.5
11β,12α	14.4	12.8	13.5
11β,12β	3.2	3.3	3.5

* J-values in Hz

The ^{1}H NMR coupling data for ring E protons reported in Table 2.1 are consistent with this ring adopting a chair conformation. Two unique ring E chair conformations are possible and are illustrated in Figure 2.4. The first conformation **A** has ring E in a $_{14}C^{4'}$ chair[37] while maintaining ring C in a $_9C^{13}$ chair. The second option, conformation **B**, has ring E in a $^{14}C_{4'}$ chair. An examination of molecular models indicates that in order for ring E to adopt this conformation ring C must adopt an obligatory $B_{9,13}$ boat enforced on it *via* conformational transmission. An examination of the ring C proton-proton coupling data (Table 2.2) indicates no significant deviations from the values expected for a ring C chair thereby excluding **B** as a possible conformer. It may thus be concluded that **A** (Figure 2.4) is the preferred conformer of **35**.



A

RING C
$^{9}C_{13}$ CHAIR

B

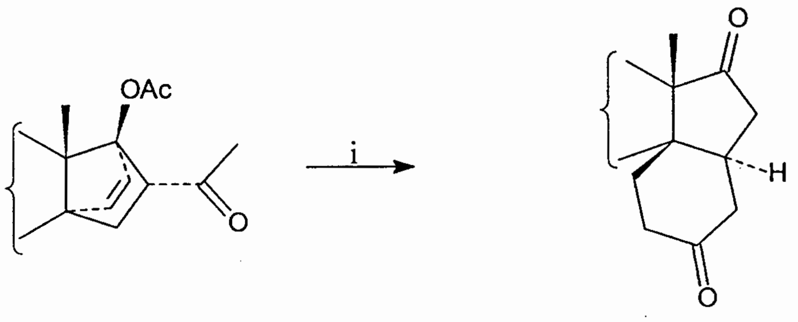
RING C
$B_{9,13}$ BOAT

Figure 2.4

Ring E Chair Conformations of Diketone **35**

The preferred mode of cyclisation of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34**, favouring intramolecular Michael addition rather than aldol condensation, is unsurprising. The regiochemical outcome of the addition is essentially governed by steric factors and by the relative stabilities of the 1,2- and 1,4-adducts.[38] In the first instance the angular methyl group at C-13 effectively shields the carbonyl group at C-17 favouring initial attack at C-15. Secondly, while both Michael and aldol reactions are formally reversible, 1,4-adducts are generally considered to be more stable to reversal[39], and any 1,2-adducts that may form are subject to retroaldol fragmentation to yield the starting enolate which may then undergo Michael addition. The combined effect of these factors is the resultant accumulation of the 14,15-fused ring diketone **35**

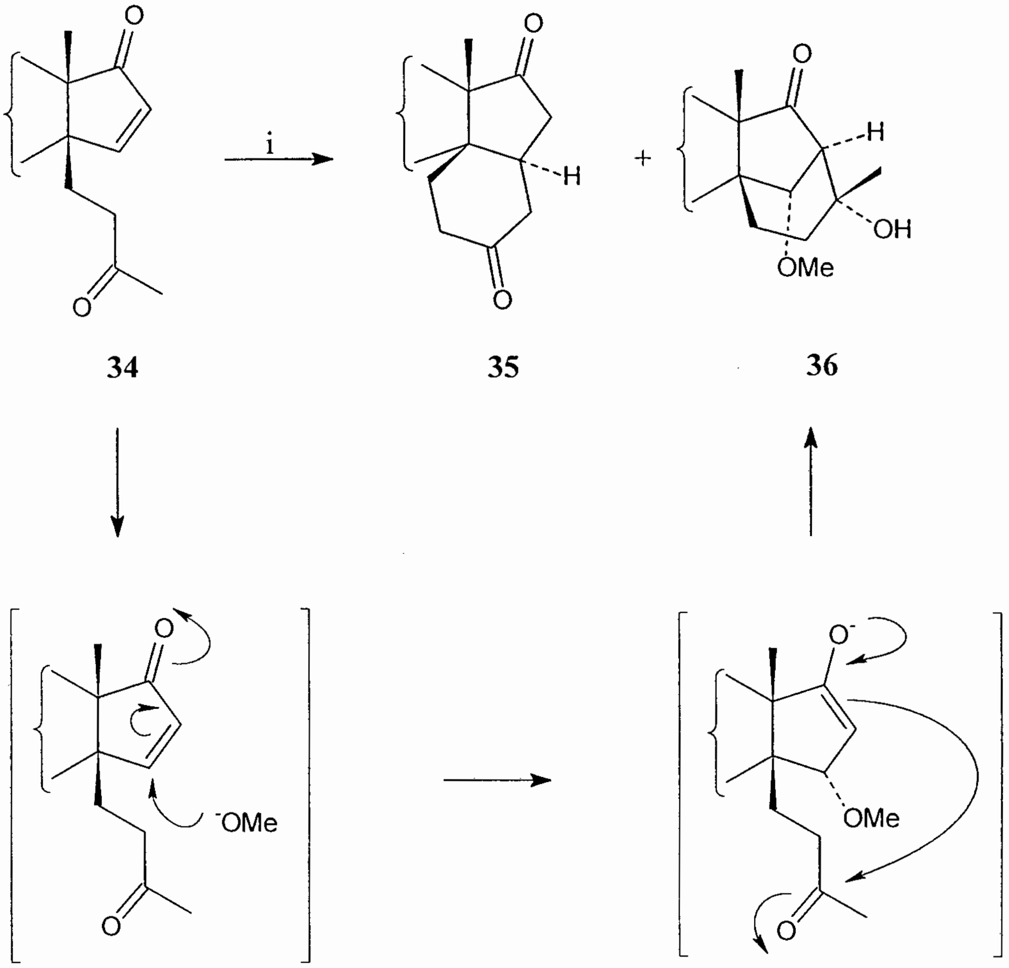
Since the diketone **35** was formed from the cycloadduct *via* the intermediacy of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** it was logical to presuppose that the diketone should be directly accessible from the cycloadduct in a one-pot procedure. Treatment of the cycloadduct with potassium hydroxide (0.05 M) in refluxing methanol for 4.5 h gave the diketone **35** in 95% yield (Scheme 2.4).



32 **35**

Scheme 2.4 *Reagents and Conditions*: (i) KOH, MeOH, Δ

It was found that the conversion of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** to the diketone **35** was sensitive to the concentration of the base used. Initial experiments, using 0.03 M potassium hydroxide in methanol, at 24°C, gave the diketone **35** as the only product and no side reaction was observed. Subsequent experiments conducted in the presence of methanolic potassium hydroxide (1 M) gave the diketone **35** in reduced yield (74%) and an additional product formulated as 15α-methoxy-14,16β-propano-17-ketone **36** in 4% yield (Scheme 2.5). The structure of this compound was assigned by analysis of its ^{1}H NMR spectrum with the aid of COSY, HETCOR, DEPT and ^{13}C spectra.



Scheme 2.5 *Reagents and Conditions*: (i) KOH, MeOH, Δ

Two peaks in the ^{13}C spectrum at δ 55.2 and 56.2 were characteristic of, and assigned to the 3- and 15α-OMe carbons. Crosspeaks, in the HETCOR, to two singlets (each integrating for three protons) at δ 3.39 and 2.89 are consistent with the expected chemical shift for methyl ethers. The hydroxyl bearing C-16^1 resonated at δ 73.5 while the 17-carbonyl carbon resonated at δ 221.9. The pattern of signals associated with 16α-H and 15β-H was distinctive and unambiguously fixed the configuration of the C-15 substituent. The signal for 16α-H, at δ 2.38 appeared as a doublet (*J* 1.4 Hz). A crosspeak in the COSY spectrum to 16^2-H_x, partially obscured by 8β-H and 16^2-H_n, arises from a four-bond W-coupling. The 15β-H resonated at δ 4.06 as a singlet, serving to confirm its orthogonality to 16α-H (Figure 2.5).

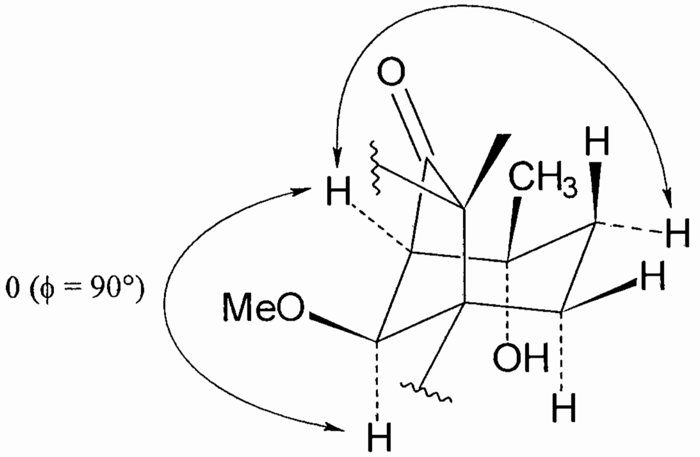
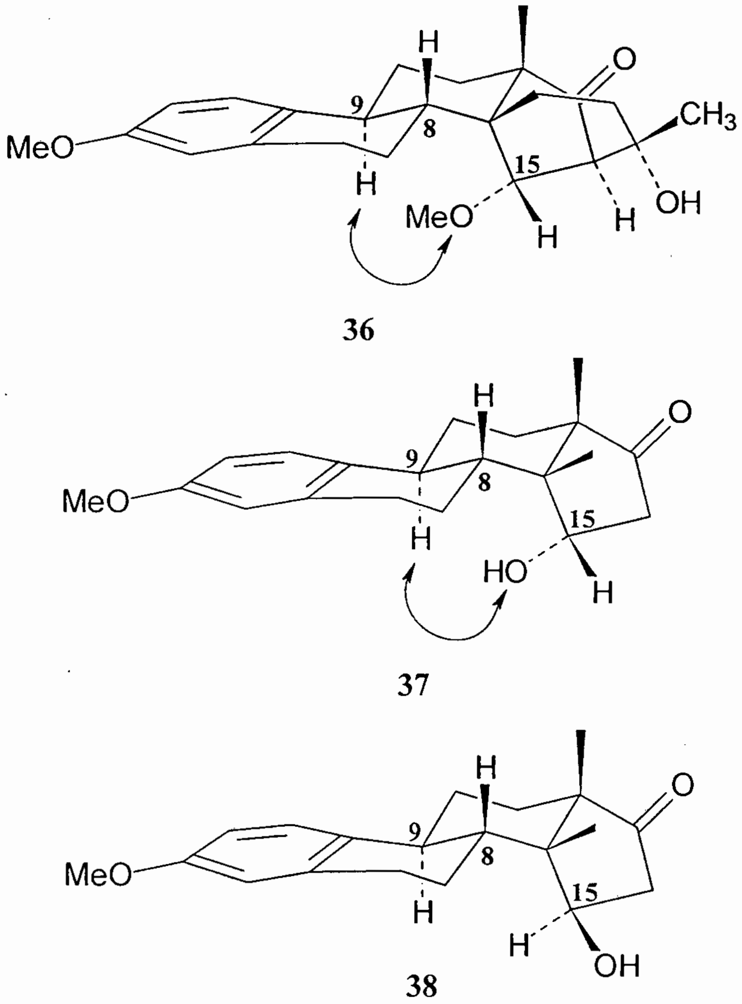


Figure 2.5

Selected ^{1}H NMR *J*-values (in Hz) for 15α-Methoxy 17-Ketone **36**

Further evidence in support of the structural assignment was obtained by noting the significant downfield shift of the signal assigned to 9α-H. The change in chemical shift from δ 2.4-2.9, the range typical for 14β-substituted 19-norsteroids[40], to δ 3.23 may be ascribed to the deshielding influence of the proximal 15α-oxygen substituent (Figure 2.6). This shift is in agreement with that found by Sefton[35] who observed a shift in the signal assigned to the 9α-H to δ 3.12 for the 14β-methyl-15α,17β-diol **37,** from δ 2.61 for the 14β-methyl-15β,17β-diol **38**.



36

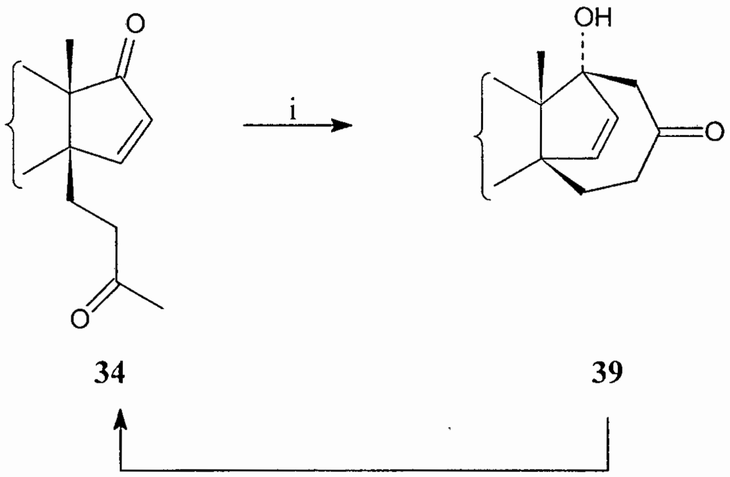
37

38

Figure 2.6

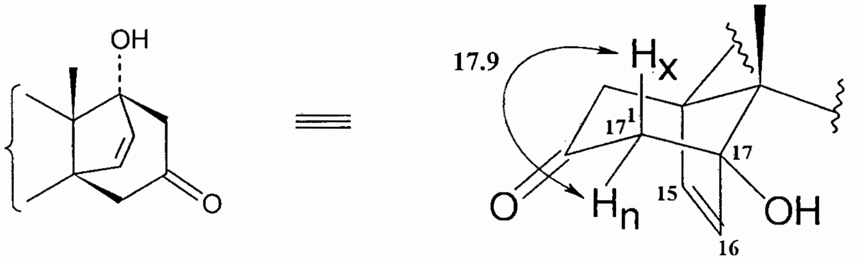
The assigned product must arise from conjugate addition of methoxide to the Δ^{15}-17-ketone **34** followed by intramolecular capture of the intermediate enolate (Scheme 2.5).
It has been reported that conjugate addition of alkoxides to Δ^{15}-17-ketones gave 15β-substituted products exclusively.[41, 42, 43] Nevertheless the presence of a 14β-alkyl substituent is expected to have a profound influence on the stereoselectivity of the conjugate addition. A substituent at C-4 of a cyclopent-2-en-1-one generally screens the face from which it protrudes and conjugate addition usually, and often exclusively, occurs from the opposite face.[44] In this instance the attack by methoxide occurs exclusively *anti* to the 14β-3'-oxobutyl substituent.

It was of interest to determine whether the cyclisation of **34** could be influenced in favour of an intramolecular aldol condensation which would afford the Δ^{15}-14,17β-butanoestradiol **39**. It is well known that organocerium reagents, generated *in situ* by transmetalation of organolithiums or organomagnesiums, react with α,β-unsaturated systems to give 1,2-addition products with high regioselectivity.[45, 46] A cerium mediated cyclisation protocol was expected to suppress Michael reactivity in favour of aldol condensation. Treatment of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** with lithium hexamethyldisilazane in the presence of cerium(III) chloride at -50°C gave starting material **34** and a product formulated as the 17α-hydroxy-14,17β-butano-17^{2}-ketone **39** (Scheme 2.6). The IR spectrum of **39** was consistent with the assigned structure revealing a carbonyl absorption band at 1702 cm^{-1} and a hydroxyl absorption band at 3567 cm^{-1}. Unfortunately the 14,17β-butano bridged **39** compound readily underwent a retroaldol reaction to give the starting 14β-3'-oxobutyl Δ^{15}-17-ketone **34**.



Scheme 2.6 *Reagents and Conditions*: (i) LiHMDS, CeCl$_3$, THF, -50°C

When the ^{1}H and ^{13}C NMR spectra were recorded they displayed resonances for both the product **39** and the starting 14β-3'-oxobutyl Δ^{15}-17-ketone **34**. The resonances arising from **34** were assigned by comparison with data obtained for the pure compound. The remaining resonances were consistent with a product formulated as a 14,17β-butano-estradiol **39**. In particular a set of AB doublets at δ 2.54 and 2.62 (*J* 16.9 Hz) were assigned to the 17^{1}α-H and 17^{1}β-H. These chemical shift and *J* values compare favourably with those reported[47] for the analogous β-hydroxy ketone **40** (Figure 2.7). In addition resonances at δ 5.69 and 5.82 (each a doublet with *J* 6.7 Hz were assigned to 15-H and 16-H. The product was found to be difficult to handle and this route, while indicating that access to the desired compound was possible, was not pursued further.

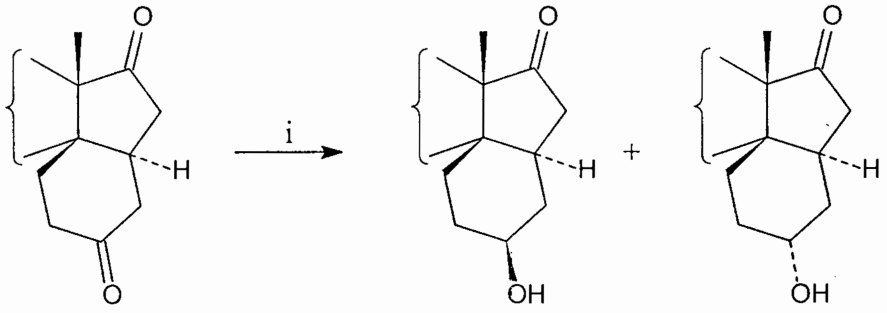


40

Figure 2.7

17^1-Proton Geminal Coupling Constant (in Hz) for Hydroxy-Ketone **40**

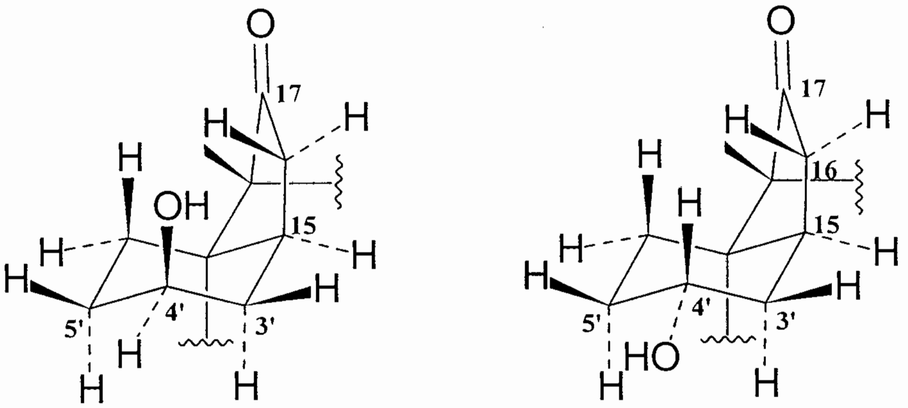
The availability of the diketone **35** presented an opportunity to explore the reactivity of this compound with the view to gaining insights into the chemistry of this structurally novel steroid. The prospect of preparing new hormone analogues based upon this structure, and comparing the binding affinities with analogous estradiols, was an added incentive. An initial examination of chemoselective reactivity of the diketone **35** was performed. Treatment of **35** with sodium borohydride in tetrahydrofuran-methanol at 0°C for 10 min gave a mixture of epimeric hydroxy-ketones **41** and **42** in 60 and 30% yield respectively (Scheme 2.7).



35 **41** **42**

Scheme 2.7 *Reagents and Conditions* (i) $NaBH_4$, MeOH-THF, 0°C

The IR spectra of the products **41** (ν_{max} 1721 cm^{-1}) and **42** (ν_{max} 1727 cm^{-1}) supported the presence of a cyclopentanone moiety and hence it was concluded that reduction had taken place chemoselectively at the 4'-position. The isomers were readily differentiated with the aid of ^{1}H NMR spectroscopy. Thus the major isomer **41** displayed a signal at δ 4.22 (quint., *J* 4 x 3.4 Hz) uniquely assigned to the presence of an axial hydroxy group in a cyclohexanoid chair conformation. The comparable signal of the minor isomer **42**, appeared at δ 3.88 (tt, *J* 2 x 11.3 and 2 x 5.0 Hz) in support of the corresponding equatorial orientation of the substituent (Figure 2.8).



41 **42**

Figure 2.8

Conformational Representation of 4'-Hydroxy 17-Ketones **41** and **42**

The stereochemical outcome of the reduction may be explained as follows.

While the stereoselectivity of the reduction of aldehydes and ketones has been the object of in-depth mechanistic and theoretical studies it is generally accepted for simple rigid cyclic ketones stereoelectronic control favours axial approach of the hydride leading to equatorial alcohols.[48] It would thus be expected that, solely on the basis of stereoelectronic considerations, the formation of the 4'α-alcohol **42** should be favoured. However, it is evident from examination of the steric environment at C-4' that stereoelectronically favoured β-face approach by hydride is sterically impeded by the elements of ring D, in particular the 1,3-removed axial C-15–C-16 bond, leading to predominant approach from the α-face leading mainly to the axial 4'β-hydroxy product **41**. (Figure 2.9).

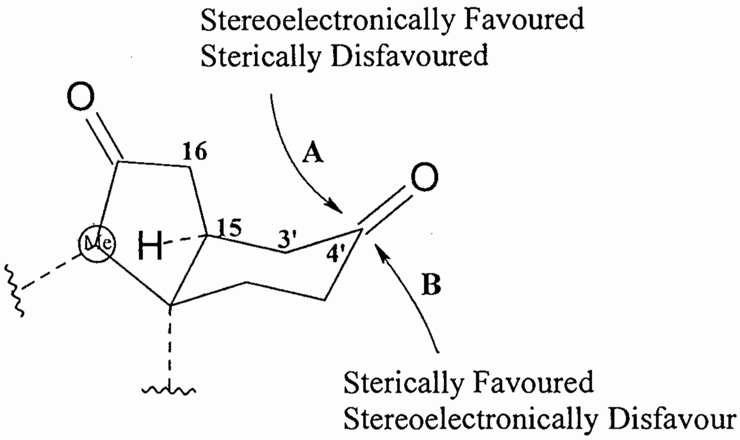


Figure 2.9

Hydride Approach to 4'-Oxo Group of Diketone **35**

It has been shown, for the diketone **35**, that ring C and ring E adopt chair conformations. In order to confirm this and gain further insight into the conformational properties of the novel ring system a single-crystal structure determination of the 4'β-alcohol **41** was performed. The compound crystallises in two distinct forms, distinguishable from each other by the trivial difference in the orientation of the substituent at C-3. The conformational properties of rings B, C, D and E are identical. Specifically ring C and ring E adopt chair conformations and the 4'β-substituent is clearly in an axial position (Figure 2.10).

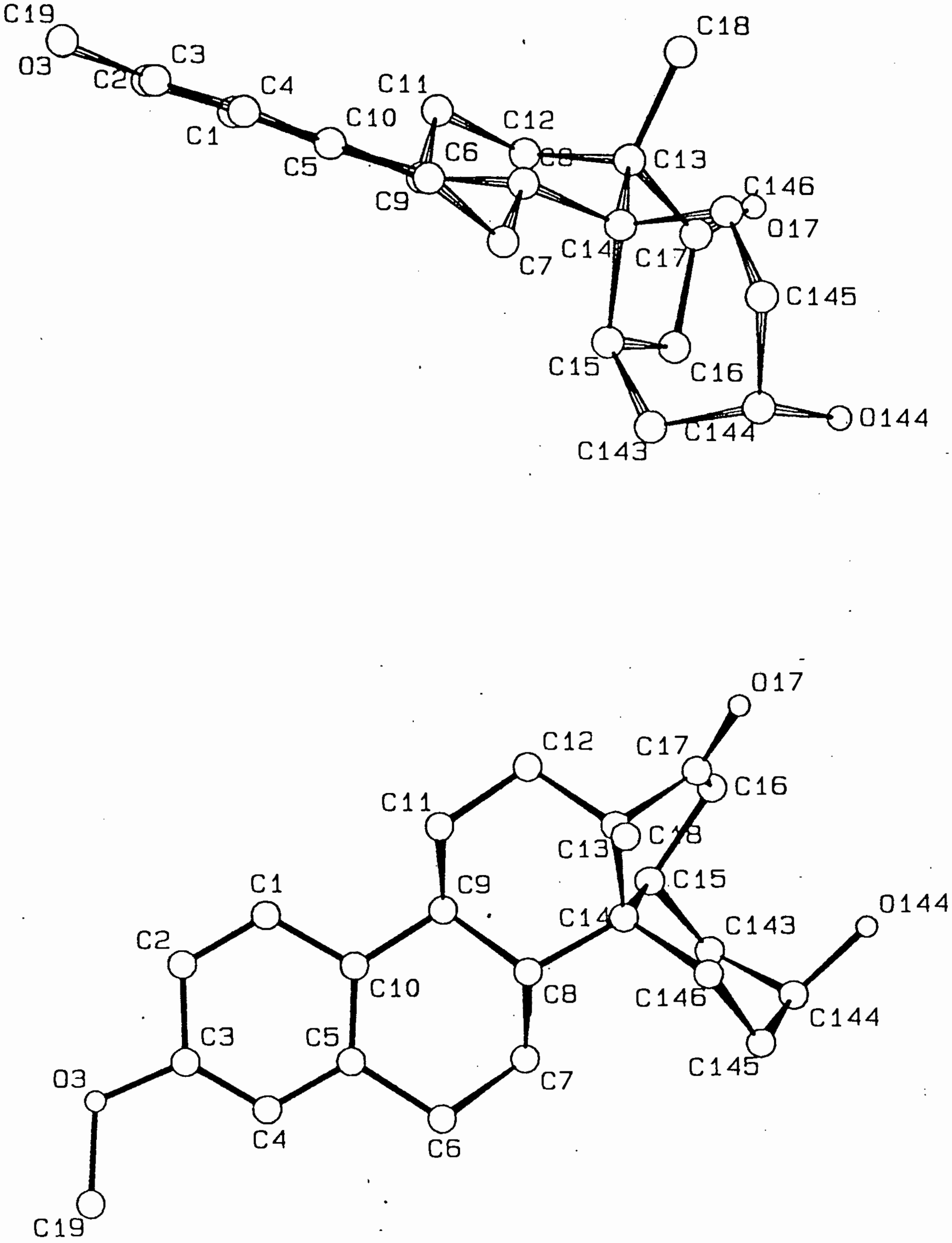


Figure 2.10
Crystal Structure of 4'β-Hydroxy 17-Ketone **41**

The chemoselective reduction of the diketone **35**, leading to the hydroxy-ketones **41** and **42** confirmed the feasibility of conducting a selective deoxygenation of the 4'-oxo functionality. Of the methods available for the reduction of carbonyl groups to their fully saturated analogues the formation of cyclic s,s-dithioacetals[1][*] followed by reduction with Raney nickel has several advantages. These include the fact that the cyclic s,s-dithioacetals are hydrolytically stable and the conditions for their removal are both highly specific and mild.[50] Treatment of the diketone **35** in dichloromethane with 1,2-ethanedithiol and catalytic boron trifluoride diethyl ether complex gave after 30 min at 24°C the 4',4'-ethylenedithio-17-ketone **43** in 98% yield (Scheme 2.8).

Spectroscopic evidence confirmed that chemoselective dithioacetalisation of the 4'-oxo group had occurred. A sharp band in the IR spectrum of the product at 1727 cm^{-1} was indicative of the fact that the 17-ketone functionality was preserved. This was supported by a single carbonyl resonance, in the ^{13}C NMR spectrum, at δ 220.8, characteristic of, and assigned to C-17. The 4'-carbon resonated at δ 65.1 in accordance with expectations. The ^{1}H NMR spectrum was unremarkable except for a multiplet at δ 3.20-3.40 (integrating for four protons) assigned to the ethylenedithio-moiety.

Desulfurisation of the dithioacetal **43** proceeded in ethanol at 50°C yielding the ketone **44** in 90% yield after 1 h (Scheme 2.8). Spectroscopic and analytical evidence confirmed that desulfurisation had occurred. The ^{13}C NMR spectrum of the product displayed the diagnostic resonance at δ 221.7 assigned to C-17 indicating that the 17-oxo functionality had been preserved throughout the deoxygenation sequence.

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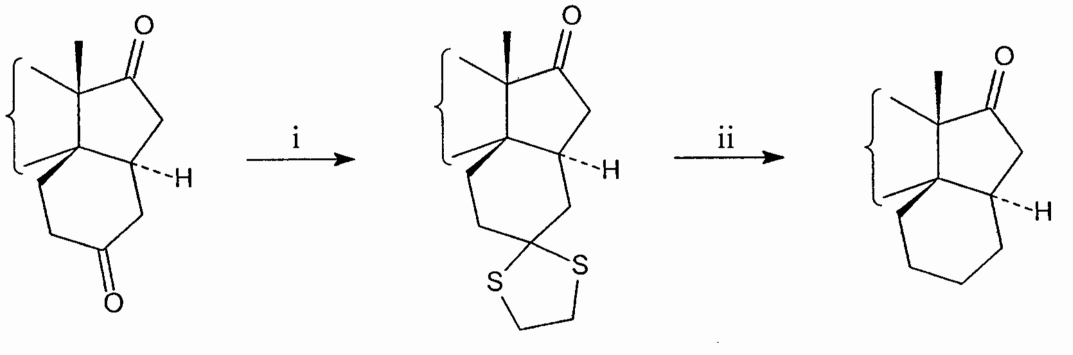
[1]

[*] The term 'ketal' has been re-introduced by IUPAC[49], however the term acetal is used thoughout this document.



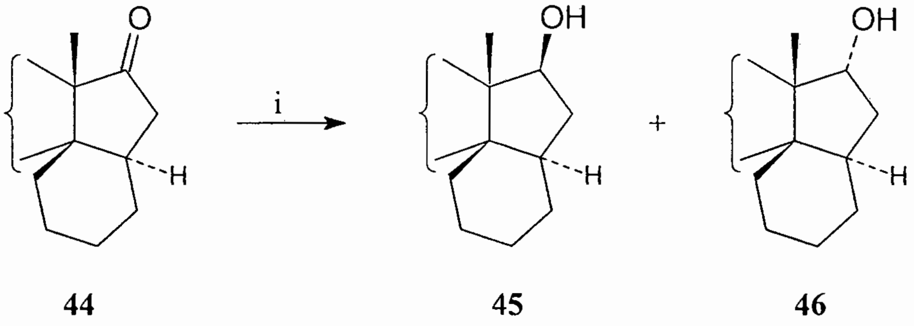
35 **43** **44**

Scheme 2.8 *Reagents and Conditions*: (i) ethanedithiol, $BF_3{\cdot}OEt_2$; (ii) Raney Nickel, ethanol, 50°C

In order to convert the ketone **44** into estradiol analogues for biological evaluation two steps remained. Firstly the 17-oxo group had to be reduced to the corresponding 17α- and 17β-alcohols and secondly deprotection at C-3 had to be performed.

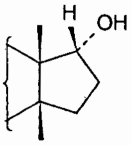
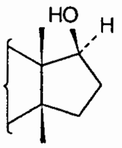
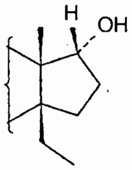
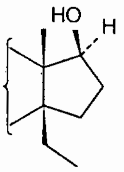
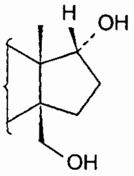
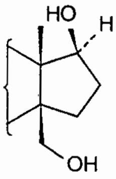
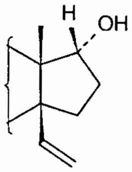
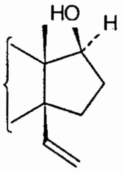
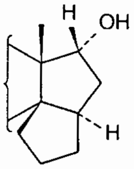
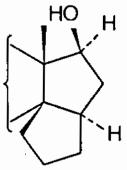
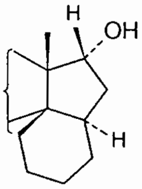
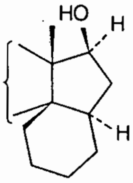
Treatment of the ketone **44** with lithium aluminium hydride in tetrahydrofuran gave, after chromatography, the alcohols **45** and **46** in 49 and 31% yield respectively (Scheme 2.9). While lithium aluminium hydride mediated reduction of 3-methoxy-14β-estra-1,3,5(10)-trien-17-one[51] and its 14β-hydroxy derivative[52] gave exclusively 17α-alcohols, the reduction of 14β-alkyl 17-ketones tend to give 1:1 mixtures of 17β- and 17α-alcohols indicative of the increased steric impedance, to preferred β-face approach of the hydride, by 14β-substitution.[53] In line with expectations a preponderance of the 17β-alcohol was found indicative of the increased steric bulk, associated with the 14,15β-fused ring, favouring attack from the α-face. The assigned structures were confirmed by both the multiplicity and chemical shift of 17-H in the ^{1}H NMR spectra of the products. A survey of the literature reveals that clear trends exist in both chemical shift and multiplicity of signals associated with 17-carbinol protons in 14β-alkyl substituted 17-alcohols. The data are summarised in Table 2.3. It is evident that 17α-protons resonate at significantly lower frequencies than their 17β-counterparts. In addition the signals associated with 17α-protons are characterised by one large (~7-8 Hz) and one smaller (~1-3 Hz) coupling while the signals associated with 17β-protons are characterised by two large (~7-9 Hz) couplings (see Table 2.3 for examples).

Thus the ^{1}H NMR spectrum of the major isomer **45** exhibited a doublet of doublets at δ 3.62 with coupling constants of *J* 6.4 and 5.2 Hz, and was assigned to 17α-H. By contrast the ^{1}H NMR spectrum of the minor isomer **46** exhibited a triplet at δ 4.14 with coupling constants *J* 2 x 8.6 Hz assigned to 17β-H. The chemical shift and coupling patterns of these protons are consistent with the data presented in Table 2.3 and unambiguously define the configuration at C-17.



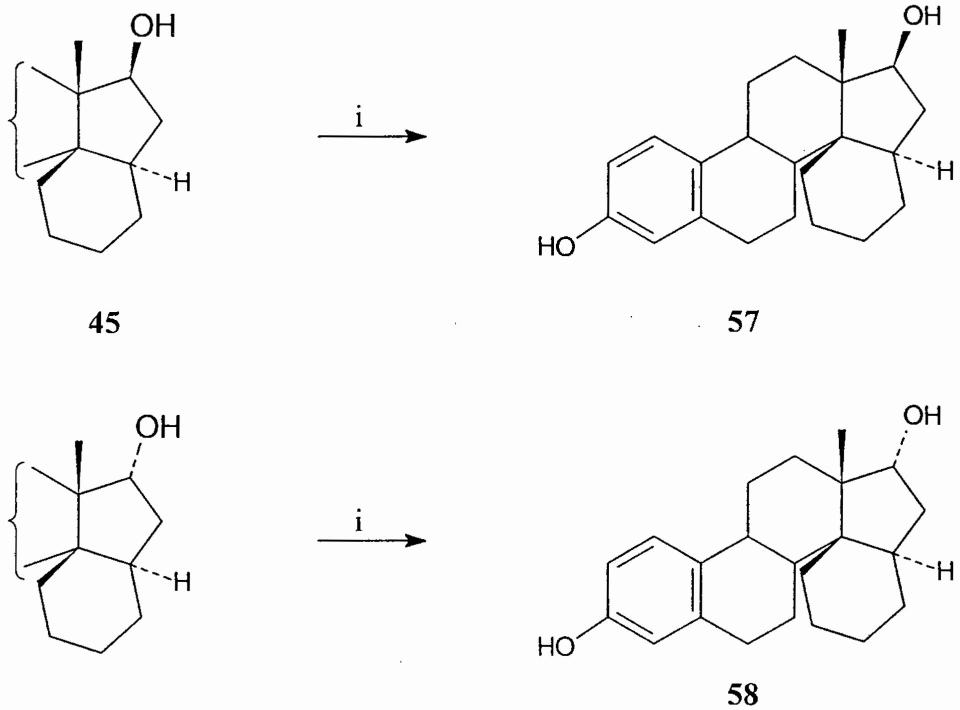
Scheme 2.9 *Reagents and Conditions*: (i) LAH, THF

Table 2.3 Comparison of Carbinol Proton Chemical Shift Values and Coupling Constants for 14β-Substituted 17-Alcohols*

17β-Protons		17α-Protons		Reference
 47	4.17 *J* 9.3 and 7.7	 48	3.75 *J* 7.9 and 2.9	35
 49	4.17 *J* 9.0 and 7.5	 50	3.70 *J* 8.0 and 3.4	54
 51	4.20 *J* 2 x 8.5	 52	3.70 *J* 8.6 and 1.6	55
 53	3.93 *J* 2 x 9.6	 54	3.57 *J* 7.4 and 1.3	55
 55	3.93 *J* 9.5 and 8.9	 56	3.70 *J* 7.0 and 1.1	47
 46	4.14 2 x 8.6	 45	3.62 6.4 and 3.2	

* Chemical shift values in ppm and *J* values in Hz

Standard deprotection of the 3-methyl ethers with di-isobutylaluminium hydride[56] (DIBAH) in refluxing toluene gave the estradiol analogues **57** and **58** in good yield (Scheme 2.10). These compounds were submitted for biological evaluation.



45 **57**

46 **58**

Scheme 2.10 *Reagents and Conditions*: (i) DIBAH, toluene, Δ

2.2 Oxy-Cope Routes to Perhydrobenzo[14,15]-14β-estradiols

The structural novelty of the perhydro-15αH-benzo[14,15]-14β-estradiols **57** and **58** prompted an investigation into alternative routes to structural variants of this fused-ring system. It was recognised that perhydroindenes are readily accessible *via* a [3,3]-sigmatropic rearrangement of a vinyl-bicyclo[2.2.1]heptene. Formally this rearrangement is known as the Cope rearrangement,[57] discovered in 1940 by Arthur C. Cope. It comprises the thermal [3,3]-sigmatropic rearrangement of 1,5 dienes to isomeric 1,5-dienes (Figure 2.11). The early history of the reaction is characterised by infrequent use until Berson and Jones,[58] in 1964, discovered that substitution of a hydroxy-group at positions 3 or 4 of the 1,5-diene resulted, after rearrangement, in an enol which underwent irreversible protonation leading to δ,ε-unsaturated carbonyl compounds. The derived product has two different functional groups which may be selectively manipulated for further synthetic purposes (Figure 2.11).

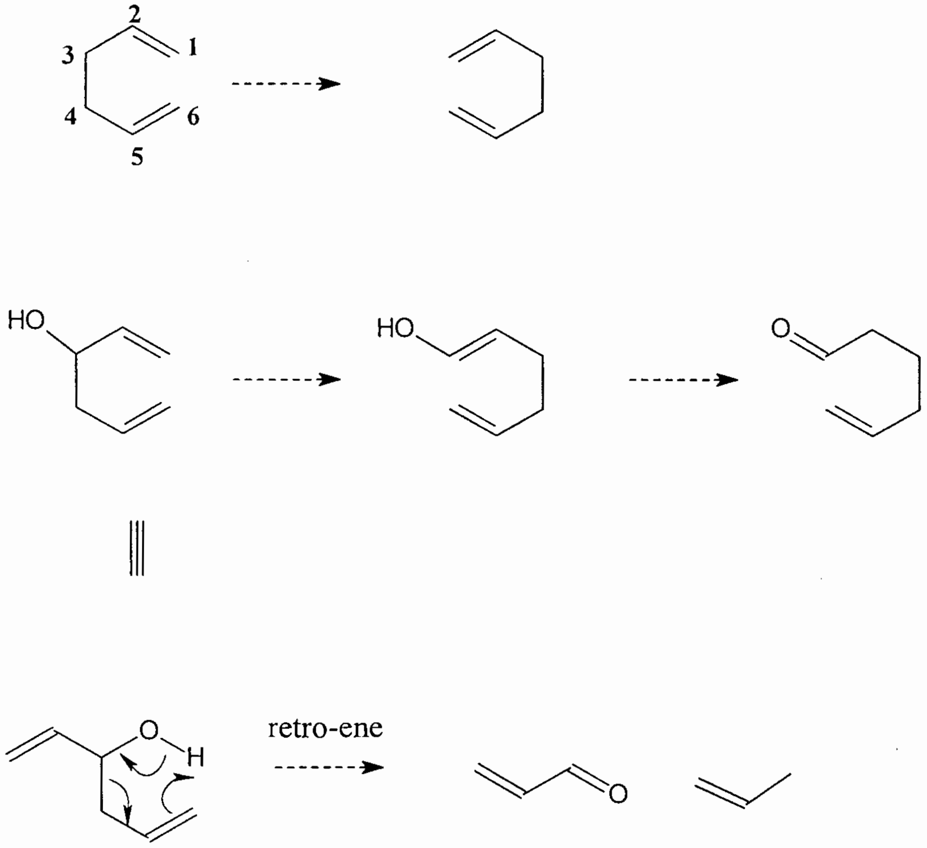
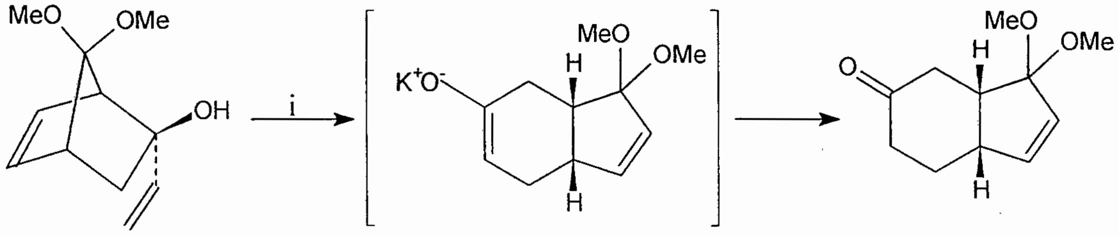


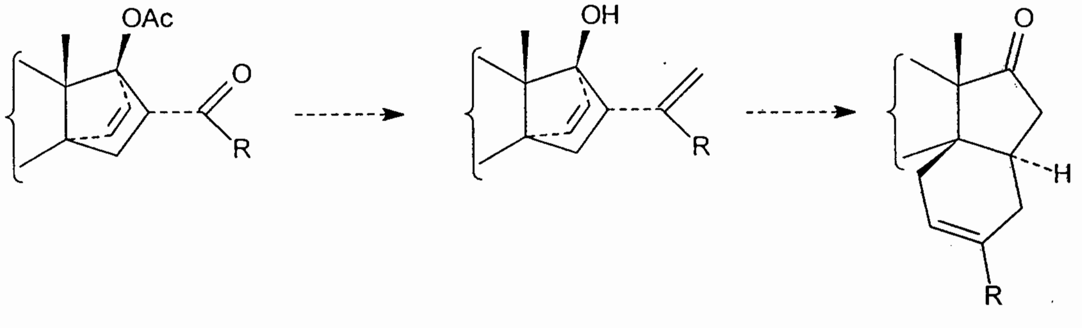
Figure 2.11

The principle drawback of the oxy-Cope rearrangement is competing fragmentation of the substrate *via* a thermal retro-ene reaction. In 1975 Evans and Golob[59] reported that remarkable rate enhancements of oxy-Cope rearrangements occurred when using the alkoxide derived from the allylic hydroxy group rather than the neutral alcohol. Formation of the alkoxide is most commonly achieved using potassium hydride. In 1978 Jung and Hudspeth were the first to demonstrate the feasibility of anionic oxy-Cope rearrangement of substituted bicyclo[2.2.1]hept-5-en-2-ols (Scheme 2.11).[60]



Scheme 2.11 *Reagents and Conditions*: (i) KH, THF, 25°C

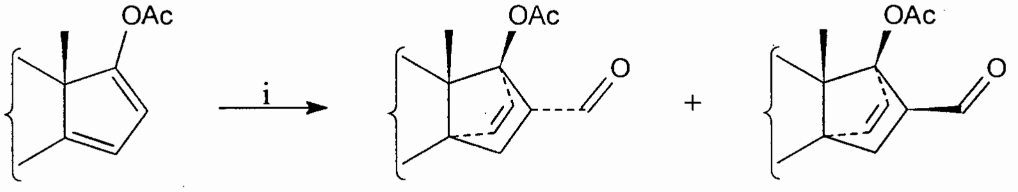
The rearrangement is permitted as long as the vinyl moiety is *endo*. It was anticipated that the inherent *endo*-stereoselection accompanying cycloaddition to steroidal 14,16-dienes could be exploited to gain access to oxy-Cope substrates. Methylenation of the 16^1-oxo functionality present in the cycloadducts **A**, derived from cycloaddition between the dienyl acetate and α,β-unsaturated dienophiles such as methyl vinyl ketone and acrolein would lead directly to 1,5-diene systems **B** which meet all the requirements for anionic assisted oxy-Cope rearrangement to perhydro-15αH-benzo[14,15]-17-ketones **C** (Scheme 2.12).



A **B** **C**

Scheme 2.12 R = H or Me

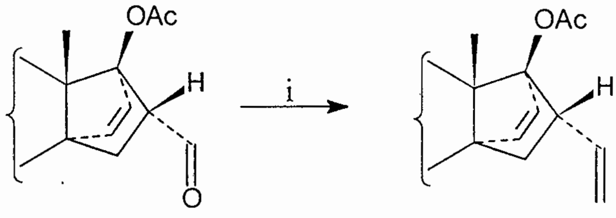
The cycloaddition of acrolein to 3-methoxy-estra-1,3,5(10),14,16-pentaen-17-yl acetate **10** has been reported.[61] The reported reaction was conducted in toluene with Lewis acid catalysis and gave the cycloadduct **59** accompanied by a small amount (~2%) of the 16β-carbaldehyde **60** (Scheme 2.13). In line with the success achieved in varying the solvent in which the cycloaddition between methyl vinyl ketone and the dienyl acetate **10** was conducted, leading to cleaner reaction, the reaction with acrolein was conducted as described in the literature but tetrahydrofuran was used in place of toluene. The cycloadduct **59** was obtained in 86% yield overall as the only product.



10 **59** **60**

Scheme 2.13 *Reagents and Conditions*: (i) acrolein, $BF_3 \cdot OEt_2$, toluene or THF

Treatment of the cycloadduct **59** with the phosphorane derived from reaction of methyltriphenylphosphonium iodide with t-butyllithium gave, after 2 h at 25°C, a product formulated as the 16α-vinyl 17-acetate **61** in 82% yield (Scheme 2.14). Analytical and spectroscopic data were in accordance with the proposed structure. The ^{13}C NMR spectrum displayed four distinctive signals in the olefinic region of the spectrum. Signals at δ 115.5(t) and 139.9(d) were assigned to C-16^2 and C-16^1 respectively while signals at δ 131.3 and 131.5 were assigned to C-17^1 and C-17^2 by analogy. The ^{1}H NMR spectrum displayed the requisite signals for all the ring D and olefinic protons. The data are summarised in Figure 2.12. The outstanding feature of the ^{1}H NMR data are the signals assigned to the methylene protons. In addition to the vicinal and geminal coupling constants the signal for each methylene proton was further split by a small coupling of 0.8 Hz. This was assigned to a long-range allylic coupling to 16β-H. The reciprocal splitting of the signal assigned to 16β-H, at δ 3.01, could not be detected although a broadening of the signal lines was evident. This allylic coupling was confirmed by examination of the COSY spectrum of the derived 17-alcohol **62** which clearly depicts a crosspeak between16β-H and the methylene protons.



59 **61**

Scheme 2.14 *Reagents and Conditions*: (i) $(Ph)_3PCH_2^+Li^-$

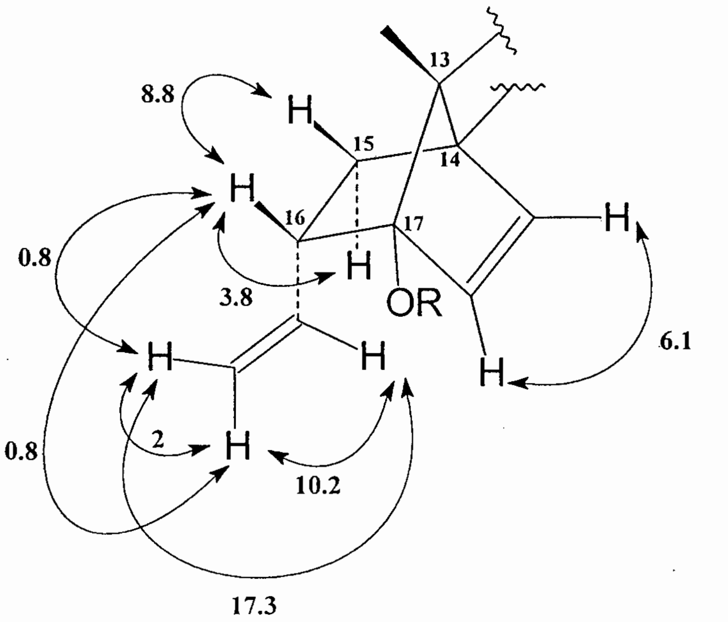


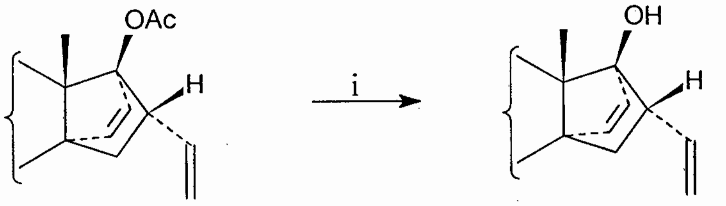
Figure 2.12

Selected ^{1}H NMR Data for 16α-Vinyl-14,17α-etheno-17β-acetate **61**

(*J* values in Hz)

In an attempt to improve the yield of the reaction the methylenation was repeated using the titanium mediated protocol with dibromomethane in the presence of zinc powder. This methylenation procedure is reported to have several advantages over the Wittig reaction in that the carbonyl group of esters is unreactive under these conditions and the reagent is not subject to the same steric constraints commonly associated with methylenetriphenylphosphorane.[62] However, treatment of the cycloadduct **59** with the reagent, preformed from dibromomethane and zinc powder, in the presence of titanium tetrachloride gave **61** in a reduced yield of 71%.

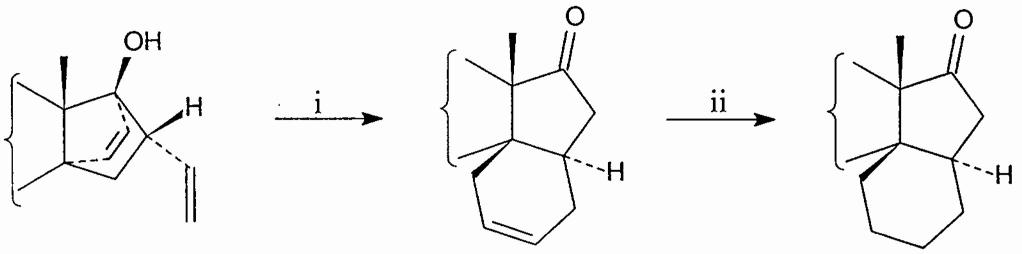
Treatment of the 17-acetate **61** with lithium aluminium hydride in tetrahydrofuran afforded the 17-alcohol **62** (Scheme 2.15). The ^{1}H NMR spectrum of the hydroxy-diene **62** is in many respects similar to that of the acetoxy-diene **61** and will not be discussed in detail.



61 **62**

Scheme 2.15 *Reagents and Conditions*: (i) LAH, THF

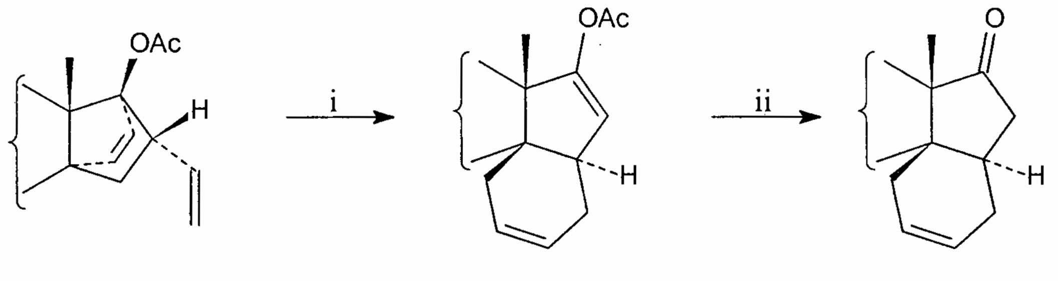
Treatment of the 16α-vinyl-14α,17α-etheno-17-alcohol **62** with potassium hydride in refluxing tetrahydrofuran gave, after 1 h, the olefinic-ketone **63** in 87% yield (Scheme 2.16). The IR spectrum of the product displayed the distinctive C-17 carbonyl absorption band at 1724 cm^{-1}. The resonance at δ 221.5 in the ^{13}C NMR spectrum confirmed the presence of a carbonyl carbon, while resonances at δ 123.5 and 127.6 were assigned to C-4' and C-5'. The ^{1}H NMR spectrum displayed characteristic olefinic resonances at δ 5.64 and 5.81 assigned to 4'-H and 5'-H. The complexity of the signals, due in part to multiple opportunities for long-range coupling, precluded the full assignment of their coupling patterns. The 15α-H resonated at δ 2.96 as a multiplet displaying non-first order characteristics. The 16β-H resonated at δ 2.58 with couplings to 15α-H (*J* 11.3 Hz) and to 16α-H (*J* 19.2 Hz). It's geminal coupling partner, 16α-H, resonated at δ 2.58 with vicinal coupling constant of 8.3 Hz. Irrefutable proof of the assigned structure was obtained by hydrogenation of **63** in the presence of palladium on carbon to give the previously synthesised perhydro-15αH-benzo[14,15]-14β-17-ketone **44** (Scheme 2.16).



62 **63** **44**

Scheme 2.16 *Reagents and Conditions*: (i) KH, THF, Δ, 1 h ; (ii) H$_2$, Pd on C, EtOAc

The thermal [3,3]-sigmatropic rearrangement of **61** was investigated. Accordingly **61** was heated in toluene in a sealed tube at 150°C for 48 h and underwent Cope rearrangement to give the enol acetate **64** in 67% yield accompanied by uncharacterised decomposed material (Scheme 2.17). The ^{1}H NMR spectrum displayed multiplets at δ 5.34 and 5.57 assigned to 4'-H and 5'-H. In addition a doublet at δ 4.84 (*J* 5.7 Hz) was assigned to 16-H, the chemical shift and multiplicity appropriate for the olefinic proton of an enol-acetate moiety. Further evidence in support of the assigned structure was obtained by hydrolysis of **64** by treatment with potassium hydroxide (0.1 M) in methanol to give **63** (Scheme 2.17).

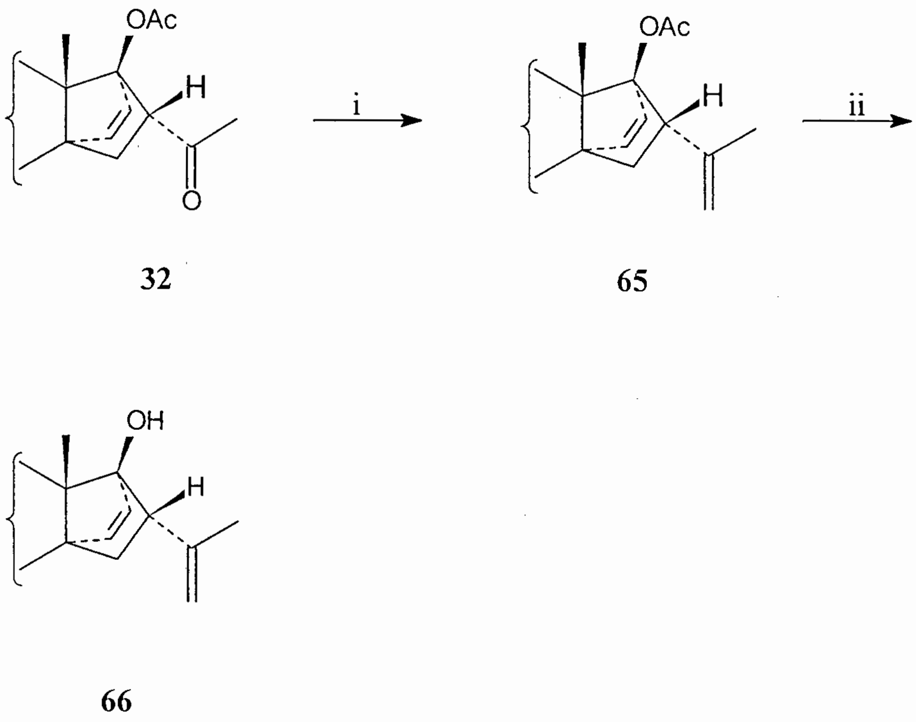


61 **64** **63**

Scheme 2.17 *Reagents and Conditions*: (i) Δ, toluene; (ii) KOH, MeOH

Overall the synthesis outlined above constitutes an expedient route to **44** eliminating the need for chemoselective deoxygenation of the diketone **35**.

An extension of the work described above was to examine the oxy-Cope reactivity of the 1,5-diene derived from the methyl vinyl ketone cycloadduct **32**. To this end the cycloadduct was treated with the slurry derived from prior reaction of dibromomethane with titanium tetrachloride in the presence of zinc powder, to give the 16α-isopropenyl-14,17α-etheno-17-acetate **65** in 77% yield (Scheme 2.18). Treatment of the 17-acetate **65** with lithium aluminium hydride in tetrahydrofuran gave after 20 min the 16α-isopropenyl-14,17α-etheno-17β-alcohol **66** with analytical and spectroscopic data consistent with the assigned structure. Selected ^{1}H NMR data for **66** are presented in Figure 2.13. The noteworthy features of the ^{1}H NMR spectrum are the appearance of the two resonances at δ 4.64 and 4.80 assigned to 16^2-H$_{cis}$ and 16^2-H$_{trans}$ respectively. The signal for 16^2-H$_{cis}$ was split by a geminal coupling of 4.1 Hz and an allylic coupling (J 3 x 1.8 Hz) to the 16^1-methyl group. By contrast the signal for 16^2-H_{trans}, in addition to the geminal coupling, was further split by a smaller allylic coupling (J 3 x 0.8 Hz) to the 16^1-methyl group (Figure 2.13). The splitting pattern of these signals was consistent with the respective assignments which were based on the fact that allylic couplings between methylene protons and an olefinic methyl substituent are maximised for protons in a *cis*-relationship to the methyl substituent.[63]



32

65

66

Scheme 2.18 *Reagents and Conditions*: (i) CH_2Br_2-Zn, $TiCl_4$, CH_2Cl_2; (ii) LAH, THF

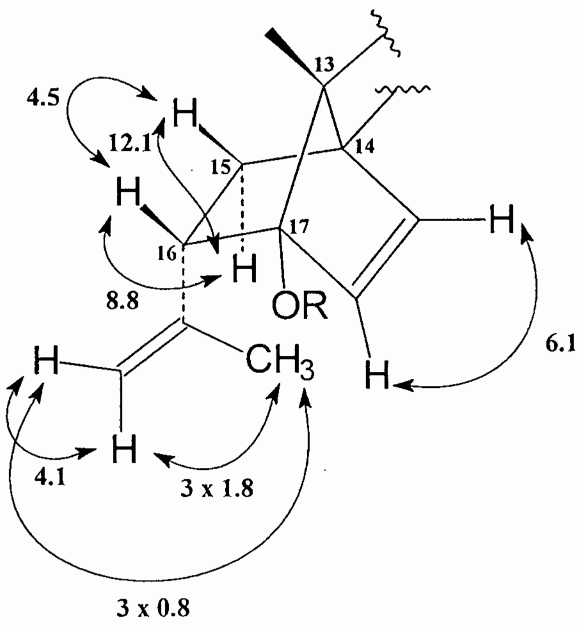
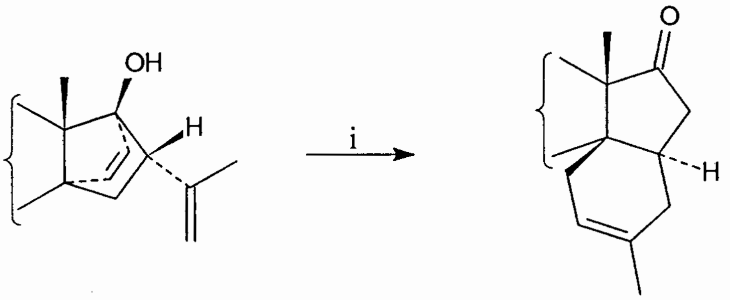


Figure 2.13

Selected Coupling Constants for 16α-Isopropenyl-14,17α-etheno-17β-alcohol **66**

(*J* values in Hz)

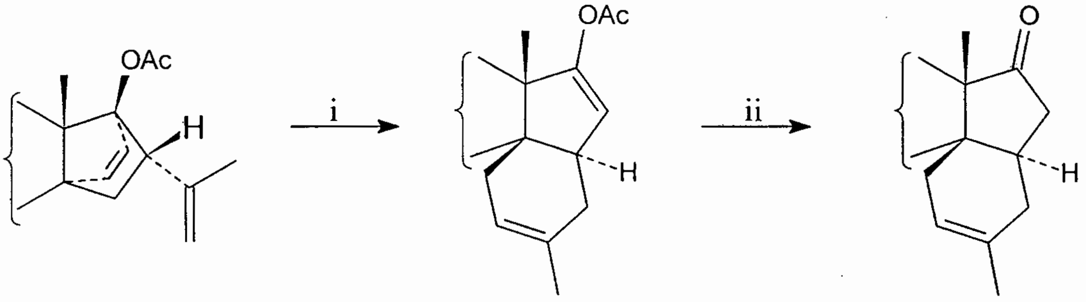
The 1,5-diene **66** underwent oxy-Cope rearrangement upon treatment with potassium hydride in refluxing tetrahydrofuran to give, after 2 h, **67** in 82% yield (Scheme 2.19). The ^{1}H NMR spectrum of **67** displayed a broad singlet integrating for 3 H's assigned to the 4'-methyl, the broadening of the signal a consequence of long-range coupling to 5'-H. The 5'-H resonated as a multiplet at δ 5.49. The 15α-H resonated at δ 2.95, the value of the chemical shift diagnostic for 15α-H's in this series of 14,15-fused ring compounds. The complexity of the signal precluded a full assignment of the all the couplings. The 16β-H resonated at δ 2.00 with large geminal coupling (*J* 19.0 Hz) and smaller vicinal coupling of 11.4 Hz while 16α-H resonated at δ 2.58 (*J* 19.0 and 8.3 Hz).



66 **67**

Scheme 2.19 *Reagents and Conditions*: (i) KH, THF, Δ, 1 h

In accordance with the foregoing thermal Cope rearrangement of **61** to give the enol-acetate **64**, the analogous 17-acetoxy compound **65** underwent [3,3]-sigmatropic rearrangement when heated in toluene to give **68** with analytical and spectroscopic data consistent with the assigned structure (Scheme 2.20). The reaction was characterised by prolonged reaction time (56 h), a reduced yield (64%) and accompanied by considerable decomposition of starting material. Hydrolysis of the enol-acetate **68** proceeded readily in the presence of potassium hydroxide (0.1 M) in methanol at 24°C to give the olefinic-ketone **67** (Scheme 2.20).



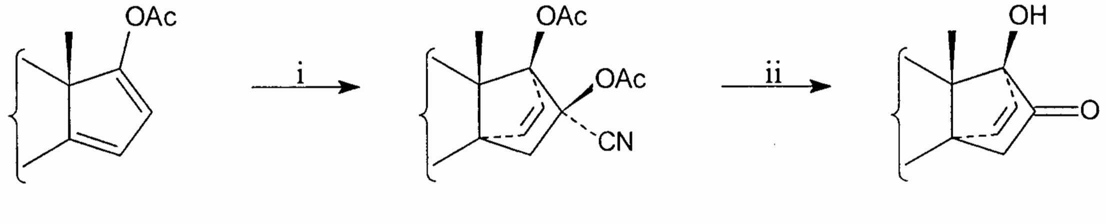
65 **68** **67**

Scheme 2.20 *Reagents and Conditions*: (i) Δ, toluene; (ii) KOH, MeOH

The foregoing discussion has demonstrated the feasibility of using the *endo*-substituted cycloadducts derived from cycloaddition to the dienyl acetate **10**, to gain access to substrates which readily undergo both thermal and anionic assisted oxy-Cope rearrangement to perhydro-15αH-benzo[14,15]-17-ketones. In order to further explore the scope and limitations of this methodology, the synthesis of an additional oxy-Cope substrate was undertaken with the view to examining rearrangements to this novel ring system.

The most common route to *endo*-substituted bicyclo[2.2.1]hept-5-enes involves Grignard addition to bicyclo[2.2.1]hept-5-en-2-ones, giving alcohols which serve as oxy-Cope substrates. While Grignard addition may give rise to diastereomeric mixtures of products ample precedent exists[57] for highly diastereoselective additions to unsaturated 7,7-disubstituted norbornanones due to the *endo*-face of the bicyclic ring system being more accessible than the *exo*-face. The result of this diastereoselection is that the major product of such additions is the one with the vinyl group *endo*, a prerequisite for oxy-Cope rearrangement.

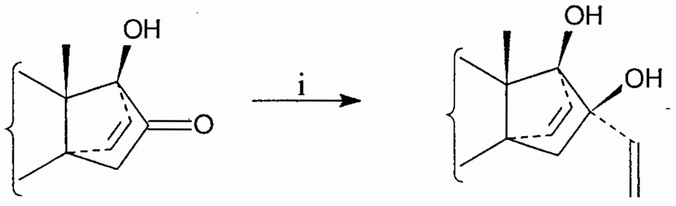
The synthesis of the bicyclic hydroxy-ketone **70** was undertaken as it is well suited for Grignard addition of vinylmagnesium bromide followed by potassium hydride mediated oxy-Cope rearrangement to give the desired ring system. The bicyclic hydroxy-ketone **70** was synthesised according to a literature procedure, from the dienyl acetate **10** in 68% overall yield (Scheme 2.21).[64] This two step procedure involves cycloaddition of 2-acetoxyacrylonitrile to the dienyl acetate **10** followed by base treatment of the derived cycloadduct **69** in dimethyl sulfoxide-tetrahydrofuran.



10 **69** **70**

Scheme 2.21 *Reagents and Conditions*: (i) 2-acetoxyacrylonitrile; (ii) KOH, DMSO, THF

Grignard addition of vinylmagnesium bromide to the hydroxy-ketone **70** afforded the 16α-vinyl-16β,17β-diol **71** in 83% yield (Scheme 2.22). Spectroscopic and analytical evidence are consistent with the addition of the vinyl moiety. The ^{1}H NMR spectrum displayed the requisite signal for the olefinic protons with coupling patterns in accordance with expectations (Figure 2.14). There is no direct evidence for the assignment of the vinyl group as *endo*, however the subsequent reactivity of the product **71** provides unequivocal proof as to the proposed stereochemistry since only the 16α-vinyl-16β,17β-diol is expected to undergo oxy-Cope rearrangement.



70 **71**

Scheme 2.22 *Reagents and Conditions*: (i) vinyl magnesium bromide

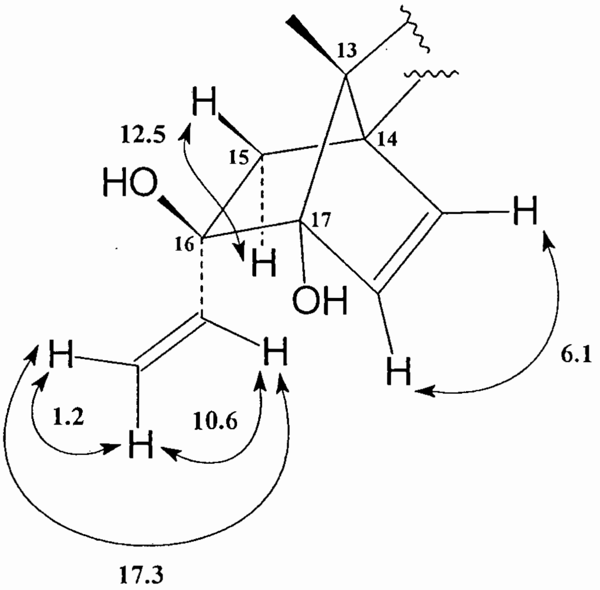
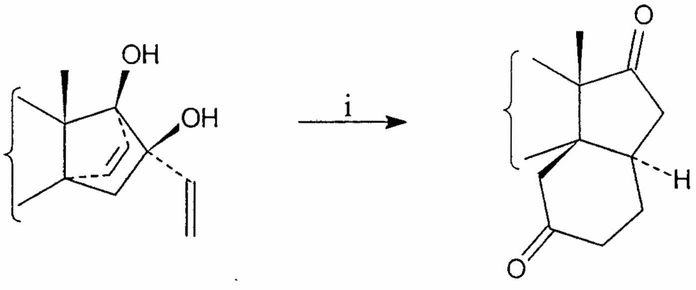


Figure 2.14

Ring D ^{1}H NMR Coupling Data for 16α-Vinyl-14,17α-etheno-16β,17β-diol **71**

(*J* values in Hz)

Treatment of the diol **71** with potassium hydride in tetrahydrofuran at -78°C gave, after 15 min., the diketone **72** in 78% yield (Scheme 2.23). The structure of the product was assigned with the aid of the ^{1}H and ^{13}C NMR spectra. The ^{13}C NMR spectrum displayed characteristic peaks at δ 211.4 and 219.4 assigned to C-5'- and C-17. In the ^{1}H NMR spectrum 16β-H and 16α-H resonated at δ 1.61 and δ 2.78. The 16β-H resonated as a double doublet with a geminal coupling of 19.7 Hz and a vicinal coupling to 15α-H of 10.3 Hz. The signal for its geminal coupling partner was further split by a vicinal coupling of 9.9 Hz. The 15α-H resonated at δ 3.09, slightly upfield from the corresponding proton in the ^{1}H NMR spectrum of the isomeric diketone **35**, which resonated at δ 3.20 ppm (Table 2.4). The signal was split with couplings of 10.3, 9.9, 5.0 and 2.4 Hz.



71 **72**

Scheme 2.22 *Reagents and Conditions*: (i) KH, THF, -78°C

Table 2.4 ^{1}H NMR Data* for Ring D Protons for Diketones **35** & **72**

Proton	**35**		**72**	
	δ	*J*	δ	*J*
15α-H	3.20	m	3.09	10.3, 9.9, 5.0 and 2.4
16α-H	2.86	19.9 & 10.2	2.78	19.7 & 9.9
16β-H	1.79	19.9 & 9.0	1.61	19.7 & 10.3

* Chemical shift values in ppm and *J* values in Hz

It was noted that the diol **71** underwent significantly faster [3,3]-sigmatropic rearrangement at a much lower temperature when compared to the analogous alcohols **62** and **66** (Table 2.5). This rate enhancement may be attributed to the "double potentiation" for oxy-Cope rearrangement present in **71**. As has been noted the presence of a hydroxy-group at either position 3 or 4 of a 1,5-diene system has been found to significantly increase the rate of rearrangement. The diol **71** has hydroxy-groups at both positions 3 and 4 (C-16 and C-17) of the 1,5-diene system and consequently undergoes a highly facile oxy-Cope rearrangement when compared to **62** and **66** which have a single potentiating group at C-17. The methodology developed here may be further exploited to provide facile entry to perhydro-15αH-benzo[14,15]-estradiols.

Table 2.5 Reaction Conditions for Anionic oxy-Cope Rearrangements

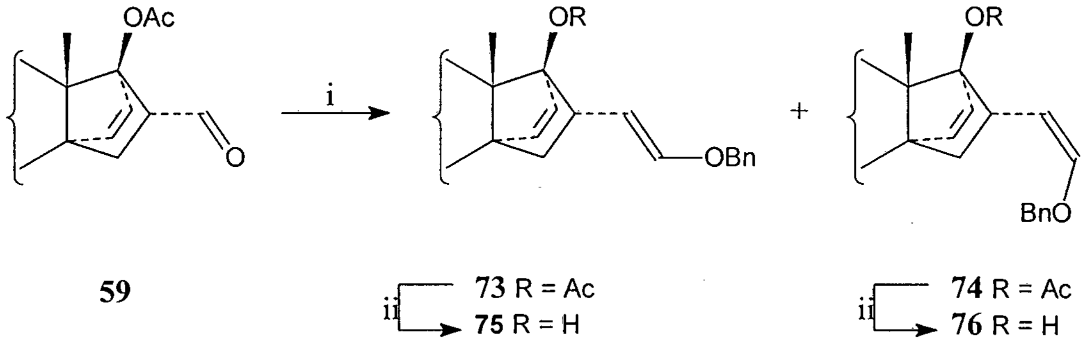
Compound	**Temp.** (°C)	**Time** (min)	**Product**	**Yield** (%)
62	reflux	60	**63**	87
66	reflux	120	**67**	82
71	-78	15	**72**	78

The final phase the work directed at developing an efficient and versatile synthesis of perhydro-15αH-benzo[14,15]-estradiols entailed examining the anionic oxy-Cope rearrangement of 16α-vinyl-14,17α-etheno bridged 17-alcohols substituted at the β-carbon of the vinyl moiety. It was expected that the anionic oxy-Cope rearrangement of such species would provide products substituted at the 3'-position of the newly formed six-membered ring. The initial approach entailed examining the [3,3]sigmatropic rearrangement of substrates possessing a benzyloxy substituent at the terminus of the vinyl group. The benzyloxy group was chosen given the ease with which it is converted to the corresponding hydroxy functionality which may be further exploited for the synthesis of structural variants of this ring system.

It was of also of interest to determine whether the configuration of the vinyl ether moiety (*cis* or *trans*) would be transferred during an anionic oxy-Cope process to the product resulting in the stereospecific introduction of the 3'-substituent.

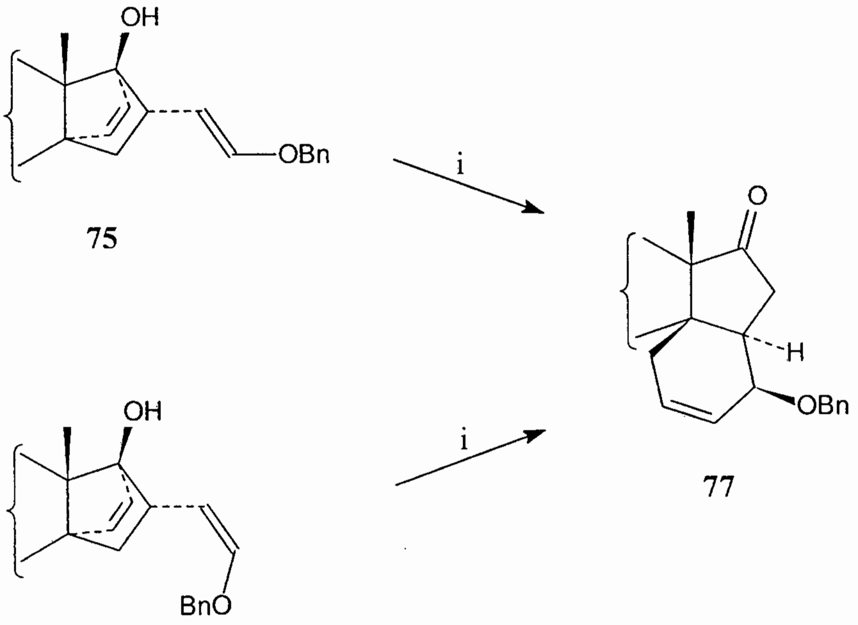
Reaction of the cycloadduct **59** with benzyloxymethyltriphenyl phosphorane proceeded in refluxing tetrahydrofuran to give, after 1 h, a mixture of the *trans* and *cis* vinyl ethers **73** and **74** in 25 and 61% yield respectively (Scheme 2.24). The products were readily separable and the structural assignments confirmed by spectral and analytical data. The configurational assignments of the vinyl moieties were inferred from the proton coupling data. In particular the 16^1-H–16^2-H coupling constant (*J* 12.5 Hz) for **73** confirms the *trans* relationship of the protons while the corresponding value (*J* 6.2 Hz) for **74** is consistent with a *cis* relationship between the coupling partners.

The esters **73** and **74** were converted into the corresponding 17-hydroxy compounds **75** and **76** respectively by treatment with lithium aluminium hydride in tetrahydrofuran at 0°C.



Scheme 2.24 *Reagents and Conditions*: (i) (Ph$_3$)PCH$_2$OBnCl, t-BuLi, THF, (ii) LAH, THF, 0°C

The hydroxy diene **75** reacted in the presence of potassium hydride in refluxing tetrahydrofuran to give after 1h the 3'β-benzyloxy 17-ketone **77** in 79% yield (Scheme 2.25). Surprisingly treatment of the isomeric hydroxy diene **76** under similar conditions proceeded to give after 3 h the identical product **77** in 67% yield. Selective irradiation of the benzyloxymethylene protons resulted in an enhancement of both the signals assigned to 16β- and 16α-H confirming the configurational assignment at C-3'



75

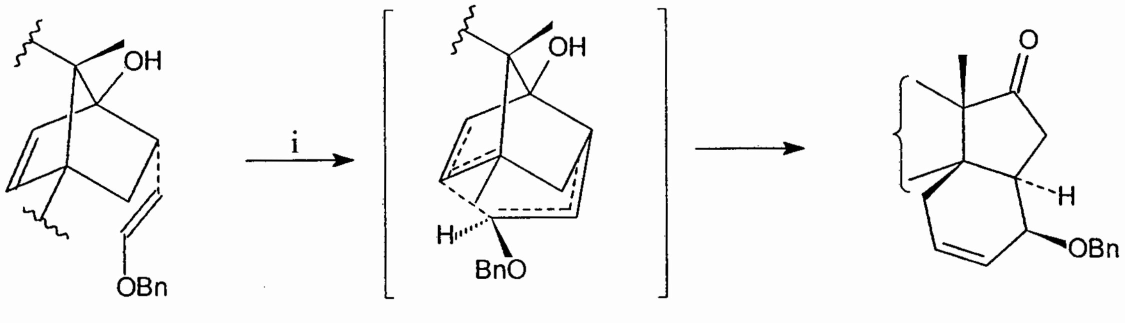
77

76

Scheme 2.25 *Reagents and Conditions*: (i) KH, THF, Δ

Paquette *et al.*[65] have proposed that the anionic oxy-Cope rearrangement of vinylbicyclo[2.2.1]hept-5-en-2-ols may proceed *via* two alternative pathways. In the first instance a concerted process may operate through a requisite boat transition state.[66] Secondly a stepwise path may be followed in which bond breaking results in the formation of a diradical species[67] followed by recombination to give the observed products.

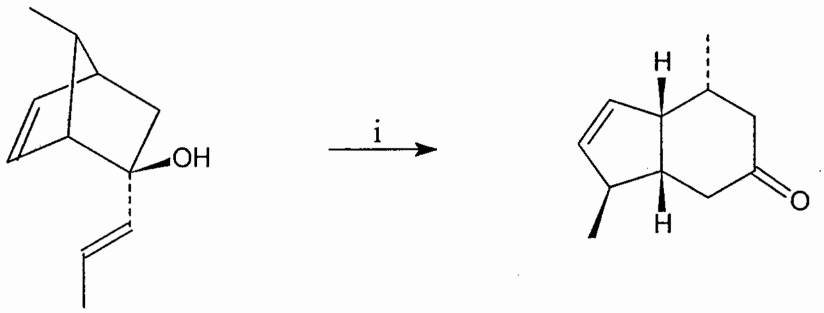
The stereochemical outcome of the *trans* isomer **75** is thus readily rationalised in terms of a concerted [3.3]sigmatropic rearrangement proceeding through a boat transition state in which the benzyloxy substituent at the β-carbon of the vinyl moiety may be accommodated in an preferred orientation away from the rest of the molecule (Scheme 2.26).



75 **77**

Scheme 2.26 *Reagents and Conditions*: (i) KH, THF, Δ, 1h

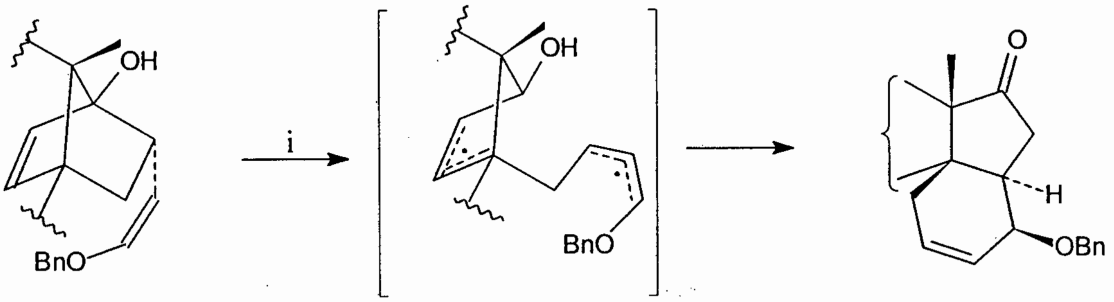
This is consistent with the finding of Fleming and Terrett[68] that the anionic oxy-Cope rearrangement of the vinylbicyclo[2.2.1]hept-5-en-2-ol **78** proceeded to generate the bicyclo[4.3.0]non-3-one **79** with stereospecific introduction of the methyl substituent at C-5 (Scheme 2.27).



78 **79**

Scheme 2.27 *Reagents and Conditions*: (i) KH, THF

The failure of the *cis* isomer **76** to give the expected 3'α-benzyloxy 17-ketone suggests that the reaction for this isomer does not proceed *via* a concerted process. This may be explained by considering that in a concerted process which proceeds via a boat transition state the sterically demanding benzyloxy substituent experiences significant buttressing by the elements of ring B. The nett result is that a boat transition state is no longer accessible and a stepwise diradical process gains greater prominence (Scheme 2.28). This may explain the prolonged reaction time and decreased yield when compared to the reaction of the *trans* isomer **75**.



76 **77**

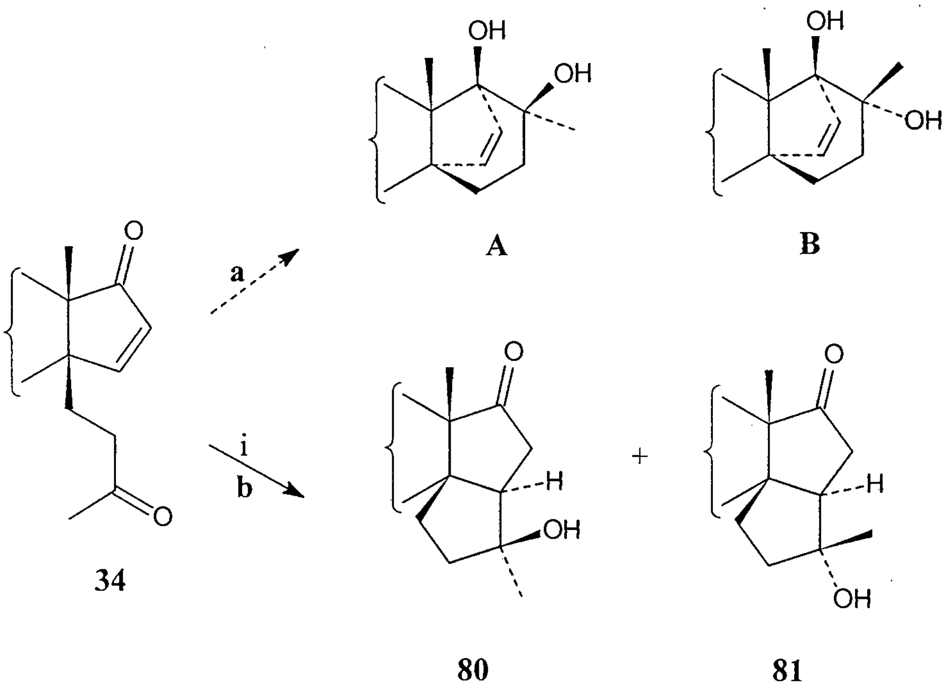
Scheme 2.28 *Reagents and Conditions*: (i) KH, THF, Δ, 3 h

The synthesis of the 3'-benzyloxy $\Delta^{4'}$-17-ketone **77** outlines a general approach to 3'-substituted variants of perhydro-15αH-benzo[14,15] 17-ketones. Further work in this area will seek to exploit these compounds for the synthesis of additional estradiol analogues based on this ring system.

2.3 Intramolecular Reductive Coupling of the 14β-3'-Oxobutyl Δ^{15}-17-Ketone 34

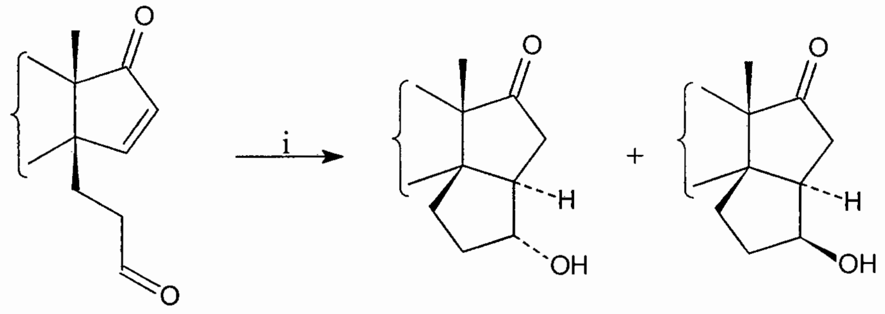
The intramolecular reductive coupling of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** was investigated with the aim of determining which of two possible modes of intramolecular cyclization are realised. The first involves intramolecular pinacol coupling[71] giving rise to the olefinic diols (path a, **A** and **B**) while the second is a vinylogous reductive coupling[73] between the 14^3-oxo group and the ring D enone producing the hydroxy-ketones **80** and **81** (Scheme 2.29).

The emergence, over the last decade, of samarium(II) iodide as a powerful single electron reducing agent[45] prompted us to attempt the intramolecular reductive coupling using this versatile reagent. Kagan and co-workers published a convenient synthesis of this reagent and outlined its general reactivity with common functional groups.[69] This inspired an extraordinary number of subsequent studies which focused on the utility of samarium(II) iodide as a reducing and reductive coupling agent in selective organic synthesis.[70] In the latter category the pinacol reaction has been extensively studied and samarium(II) iodide has become one of the methods of choice for the synthesis of 1,2-diols *via* the reductive coupling of dicarbonyl compounds.[71] This method is complementary to McMurry's well established titanium mediated pinacol coupling reaction .[72]



Scheme 2.29 *Reagents and Conditions*: (i) SmI_2, THF, -78°C

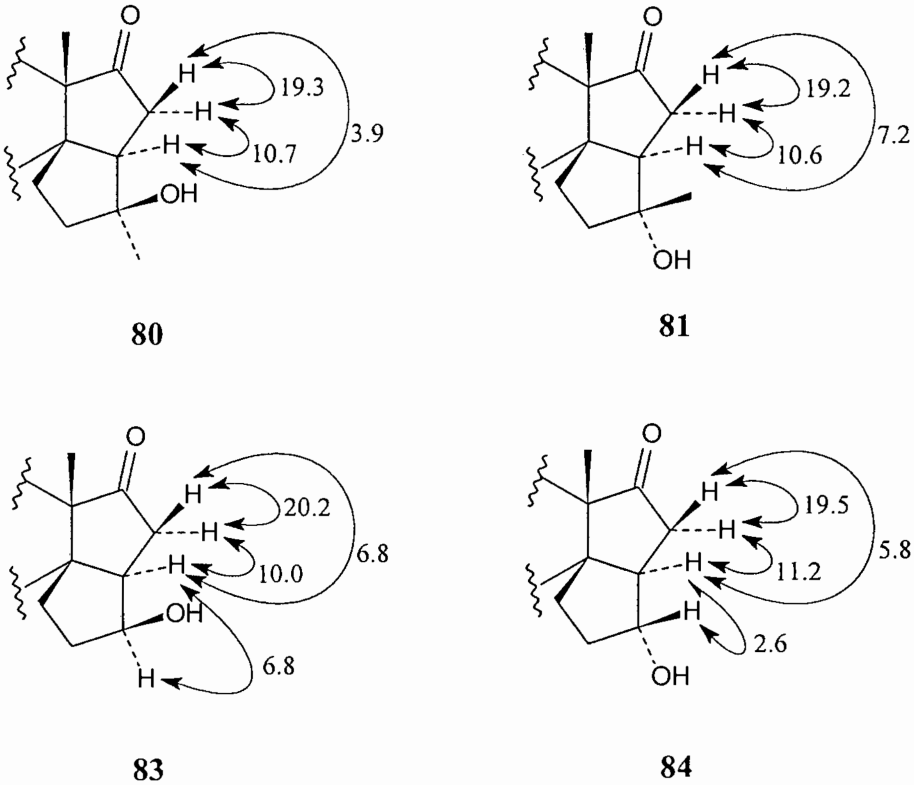
Treatment of the 14β-3'-oxobutyl Δ^{15}-17-ketone with two equivalents of samarium(II) iodide at -78°C gave after 30 min two products identified as the epimeric 3'-hydroxy-17-ketones (**80,** 36 %) and (**81,** 62 %) (Scheme 2.29). In related work the attempted pinacol coupling of the formylethyl-enone **82** using a titanium mediated protocol led to the exclusive formation of the epimeric 3'-hydroxy-17-ketones **83** (26 %) and **84** (60 %) (Scheme 2.30).[47]



82 **83** **84**

Scheme 2.30 *Reagents and Conditions*: (i) $TiCl_3.(DME)_{1.5}$, Zn-Cu, DME, 0-5°C

The structure of the products followed directly from NMR data. The characteristics for the 15α-H,16α-H and 15α-H,16β-H interactions are consistent for these epimers and are consistent with the proton coupling data reported for the analogous compounds **83** and **84** (Figure 2.16).[47]



80 **81**

83 **84**

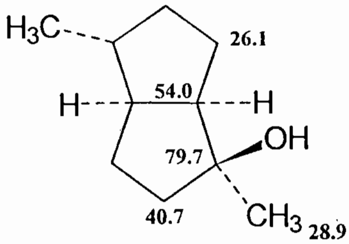
Figure 2.16

^1H NMR Data for 3'-Hydroxy-17-Ketones **80-84**

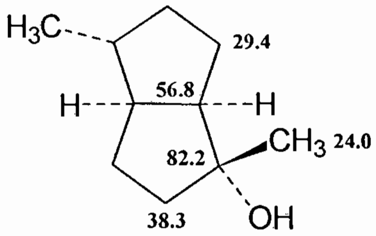
(*J* values in Hz)

Selective irradiation of the 3'β-methyl group in **81** results in enhancement of the signal assigned to 16β-H, whereas a similar irradiation of the 3'α-methyl group in **80** failed to reveal any nOe in ring D. This is readily interpreted in terms of favourable proximity of the nOe partners in **81** imposed by the *cis*-fusion of the diquinonoid moiety.

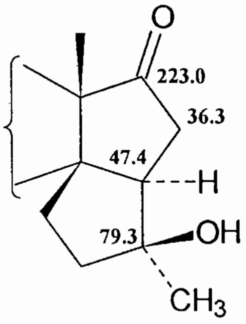
The ^{13}C NMR data also served to confirm the structural assignments and confirmed the configurational assignment at C-3'. It is well known that the introduction of a second methyl group γ to the methyl of methylcyclohexane results in an upfield shift of the methyl group by 2.5 ppm.[74] This effect is representative of a general phenomenon which accompanies gauche like butane interactions and is known as the γ-gauche effect. The introduction of a γ-substituent causes a perturbation of the carbon-hydrogen bond involved causing the charge density to drift towards carbon with a resultant expansion of the bonding orbitals on carbon. This in turn increases the shielding at carbon and the net effect is an upfield shift of the corresponding carbon resonance.[75] It has been established that shifts due to the introduction of γ-oxygen also occur and are quite general. In addition these shifts due to γ-oxygen are generally larger than observed with the introduction of γ-carbon.[74] The chemical shift of the resonance assigned to C-16 for **80** experiences a upfield shift in relation to the corresponding signal for **81** under the influence of the γ-gauche hydroxyl group. A similar shift is observed for the analogous bicyclo[3.3.0]octanes[76] **85** and **86** with the chemical shift of C-8 experiencing a upfield shift of 3.3 ppm under the influence of the hydroxyl group (Figure 2.17). In addition the position of the C-17 resonance reflects the hydrogen bonding capacity of the epimers. It has been shown that intramolecular hydrogen bonds increase the positive charge on the carbonyl carbon resulting in a deshielding and consequent downfield shift of the carbonyl carbon resonance relative to the non-hydrogen bonded isomer.[75] The carbonyl carbon resonates at δ 220.3 for **81** while the corresponding resonance for **80** resonates downfield at δ 223.0 under the influence of hydrogen bonding between the 3'β-hydroxyl and 17-oxo groups.



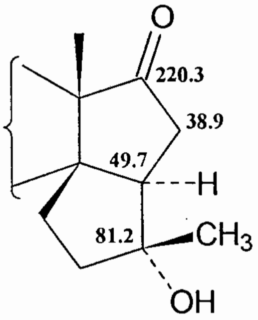
85



86



80



81

Figure 2.17

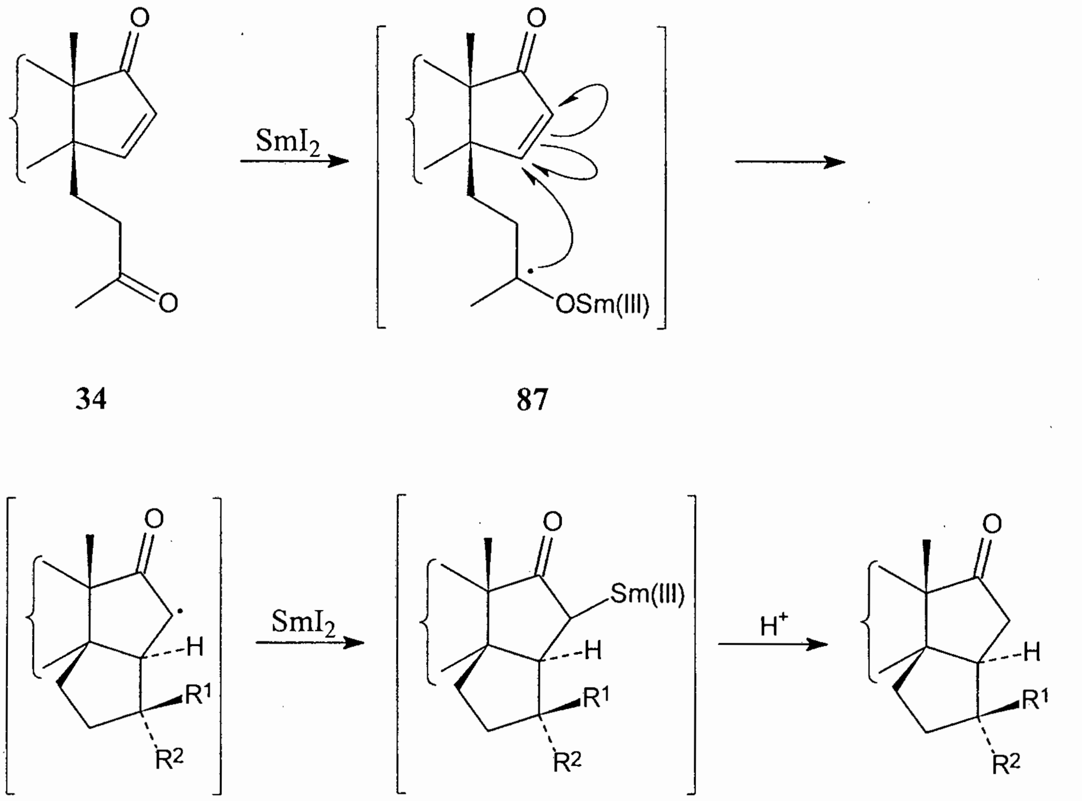
Selected ^{13}C NMR Data for Hydroxy-Ketones **80** and **81**

and Bicyclic Alcohols **85** and **86**

(δ values in ppm)

Both intramolecular and intermolecular ketyl-olefin coupling reactions are known. While couplings between ketyl radicals and unactivated olefins have been reported the reaction is promoted by coupling to olefins in conjugation with electron withdrawing groups.[77] The nucleophilic ketyl radicals will add to a wide variety of acceptors including α,β-unsaturated esters and nitriles, styrene, vinyl acetates and allylic acetates. The intramolecular version of the reaction will tolerate a wider range of acceptors than the intermolecular version.[78] Surprisingly only one report was found in the literature of an intramolecular coupling to an α,β-unsaturated ketone.[79] While the formation of five- and six-membered rings are generally favoured the synthesis of seven- and eight-membered rings using this methodology has been reported.[80]

Molander and Kenny[81] have studied this reaction extensively and have postulated a mechanism which is readily applied to the reductive coupling of the 14β-3'-oxobutyl Δ^{15}-17-ketone investigated in this study (Scheme 2.31). The reaction proceeds *via* initial samarium(II) iodide mediated reduction of the 4'-oxo group generating a ketyl radical **87.** Addition of this ketyl radical to the α,β-unsaturated ketone occurs thereby generating a 16-methylene radical **88** which is reduced by a second equivalent of samarium(II) iodide. This results in the formation of a transient organosamarium intermediate **89**. The sequence is terminated by protonation of the organosamarium intermediate.



34 **87**

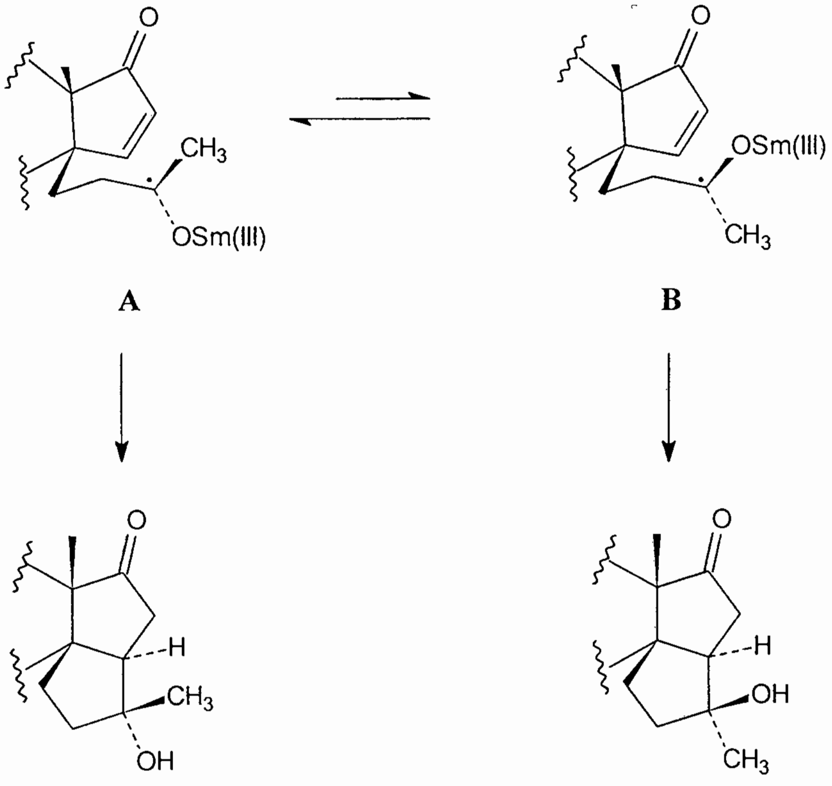
88 **89**

80: $R^1 = OH; R^2 = CH_3$
81: $R^1 = CH_3; R^2 = OH$

Scheme 2.31

The stereoselectivity of samarium(II) iodide mediated radical cyclisations has been investigated.[82] The observed stereoselectivity may be rationalised as follows:

ketyl-olefin couplings proceed through a chair-like transition state in which the favoured conformation **A** is that with the ketone substituent (in this case the 3'-methyl group) nearly eclipsed with the developing methylene radical centre (Scheme 2.32). This favoured *trans* relationship between the π-system and the ketyl oxygen has precedent and is electronic in nature.[83, 84] This conformation will lead to **81**, the major product. As the steric bulk of the ketone substituent increases the alternative conformation **B** becomes increasingly significant as it relieves steric repulsion between the substituent and the olefin, leading to formation of the minor isomer **80**. The stereochemical outcome of the reaction is thus a compromise between stereoelectronic factors favouring **81** and steric factors favouring **80**.



A **B**

81 **80**

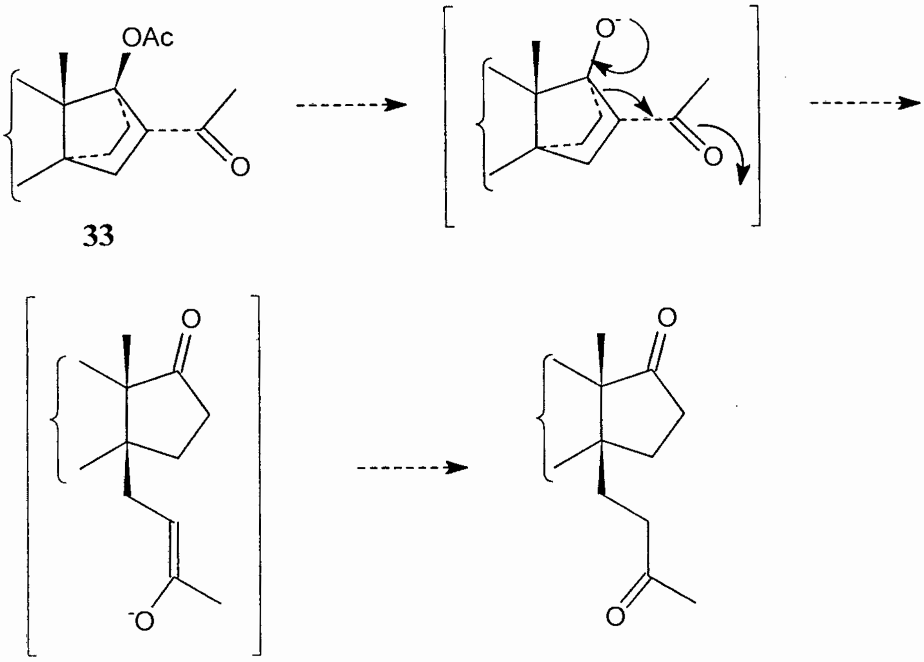
Scheme 2.32

CHAPTER 3

Synthesis and Intramolecular Reactions of 3-Methoxy-14β-3'-oxobutyl-estra-1,3,5(10)-triene-17-one

3.1 Synthesis and Base Mediated Intramolecular Reactions of the 14β-3'-Oxobutyl 17-Ketone 90

In the preceding chapter it has been demonstrated that the14β-3'-oxobutyl Δ^{15}-17-ketone **34** underwent intramolecular Michael addition in preference to transannular aldol condensation. The course of the reaction could be altered in favour of aldol condensation by treatment of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** with lithium hexamethyldisilazane in the presence of cerium(III) chloride to give the desired 14,17β-butano compound **39** but the reaction was not considered to be synthetically useful given the attendant difficulty in handling the product. This prompted an investigation into the intramolecular reactivity of the derived 14β-3'-oxobutyl 17-ketone **90** (Scheme 3.1) which has no intramolecular Michael reaction pathway available to it. The various cyclisation options available to **90** have been covered in Chapter 1. The availability of the dihydro-cycloadduct **33** suggested that this would serve as a suitable precursor to the desired 14β-3'-oxobutyl 17-ketone **90**. It was envisaged that base mediated cleavage of the bridgehead ester of **90** followed by fragmentation of the 16,17-bond and protonation of the resultant enolate would lead directly to **90**. (Scheme 3.1).

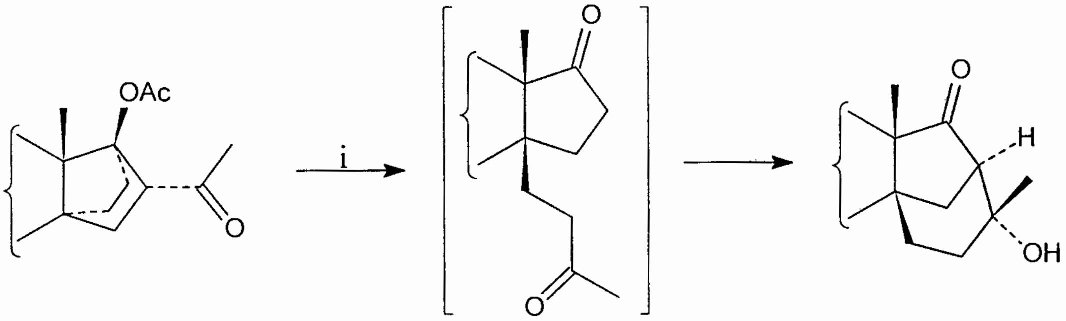


33

90

Scheme 3.1

The dihydro-cycloadduct **90** was treated with potassium hydroxide (1 M) in methanol at 0°C and afforded, after 1.5 h, the hydroxy-ketone **91** in almost quantitative yield (Scheme 3.2).



33 **90** **91**

Scheme 3.2 *Reagents and Conditions*: (i) KOH, MeOH, 0°C

The structural assignment followed from an analysis of the spectroscopic properties of the product. The IR spectrum displayed two peaks at 3597 and 1726 cm^{-1} assigned to the hydroxyl and carbonyl absorption bands respectively. All the ring D and 14,16-bridge protons in the ^{1}H NMR spectrum of **91** (Figure 3.1) were assigned with aid of COSY, HETCOR and DEPT spectra. The ^{13}C-NMR spectrum displayed diagnostic singlets at δ 71.0 and 221.3 assigned to C-16^1 and C-17. Of the three highfield doublets in the ^{13}C-NMR spectrum two, at δ 37.3 and 42.6 were assigned to C-8 and C-9 by analogy.[40] The remaining doublet at δ 57.2 was assigned to C-16. A crosspeak in the HETCOR located the signal assigned to 16α-H at δ 2.41 (*J* 5.6 and 2.2 Hz). The magnitude of the larger coupling is consistent with the synclinal relationship between 16α-H and 15α-H with a dihedral angle of ~30°. The smaller coupling is the result of a four-bond W-coupling with 16^2-H$_x$ (Figure 3.2). The 16α-H and 15β-H are orthogonal to each other and as such do not couple. The location of the corresponding coupling partners served to confirm this assignment. Thus a crosspeak in the COSY from 16α-H allowed for the unambiguous assignment of 15α-H which resonated at δ 2.04. Besides the geminal coupling constant (*J* 12.2 Hz) the signal was further split by the coupling to 16α-H (*J* 5.6 Hz) and a four-bond W-coupling (*J* 3.1 Hz) to 16^3-H$_n$ (Figure 3.2). Its geminal coupling partner, 15β-H, resonated at δ 2.18 (*J* 12.2) as a doublet. The lack of additional coupling served to confirm its orthogonal relationship to 16α-H.

The long range coupling between 16α-H and 16^2-H$_x$ allowed for the location of the signal assigned to 16^2-H$_x$. This proton resonated as a quartet of triplets at δ 1.58. The signal displayed a large geminal coupling (*J* 15.0 Hz) and a smaller vicinal coupling to the 16^3-H$_x$. The signal was further split by two smaller couplings of similar magnitude (*J* 2.0 Hz) corresponding to the vicinal coupling to the 16^3-H$_n$ and the long-range coupling to 16α-H. The 16^2-H$_n$ resonated at δ 1.33 (*J* 15.0, 13.5 and 5.8 Hz). Crosspeaks in the COSY spectrum confirmed the couplings to 16^2-H$_x$, 16^3-H$_x$ and 16^3-H$_n$ respectively. The 16^3-H$_x$ resonated as a triplet of doublets with large couplings (*J* 2 x 13.5 Hz) assigned to a geminal coupling and vicinal coupling to 16^2-H$_n$. A smaller coupling (*J* 5.9 Hz) was assigned to the coupling to 16^2-H$_x$. Finally 16^3-H$_n$ resonated at δ 1.26.

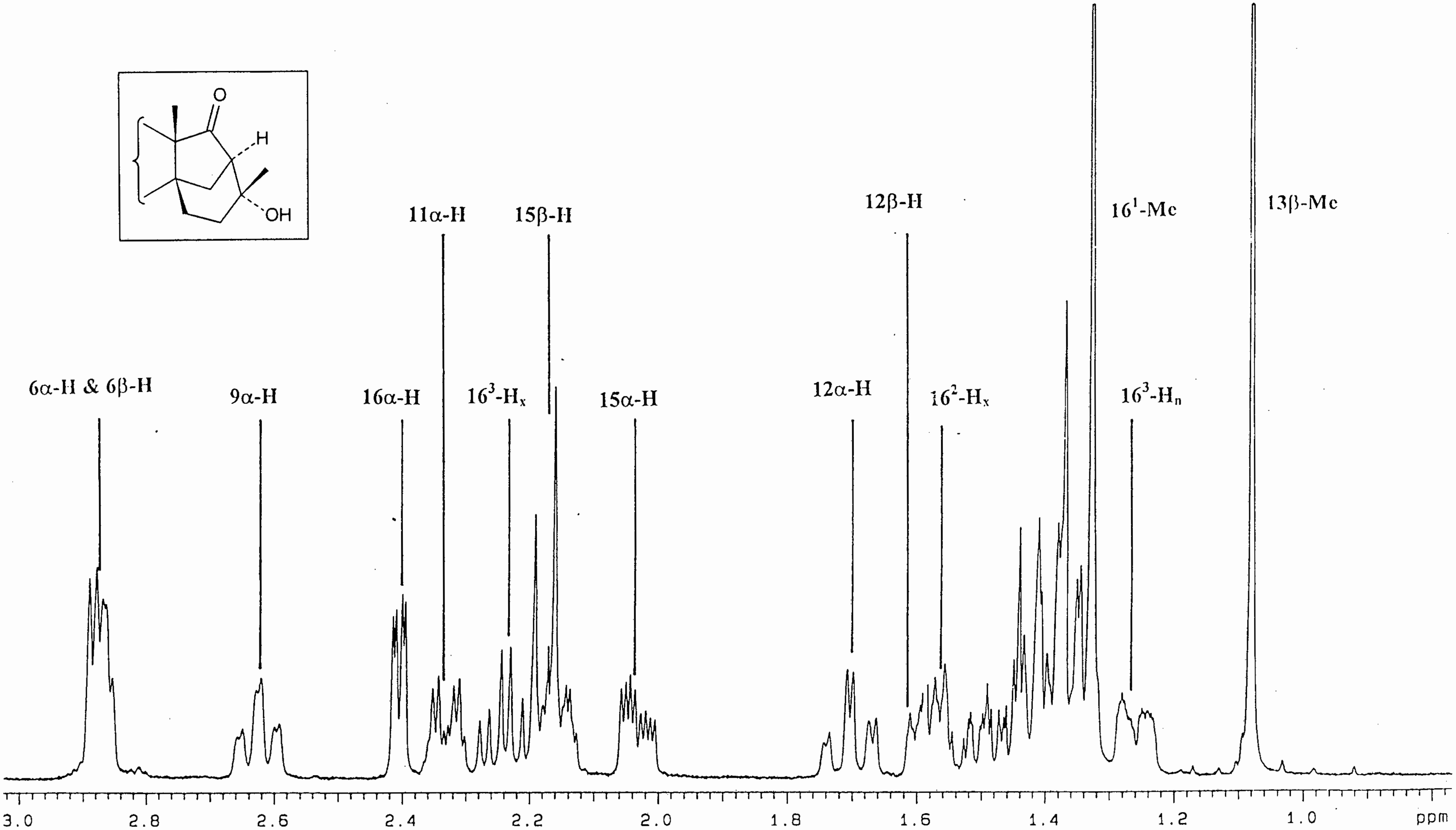
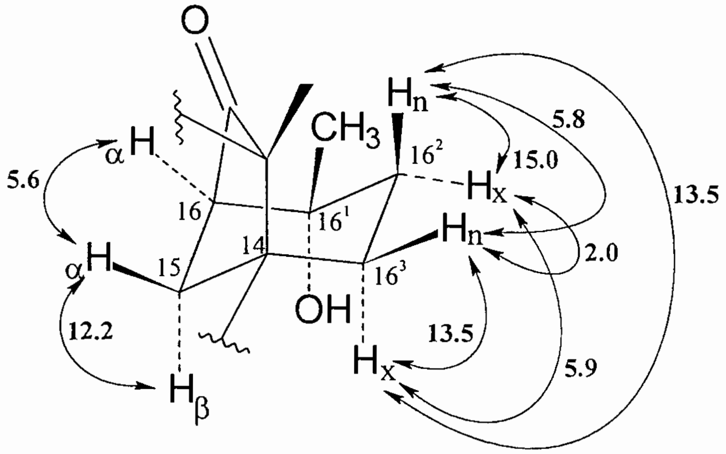
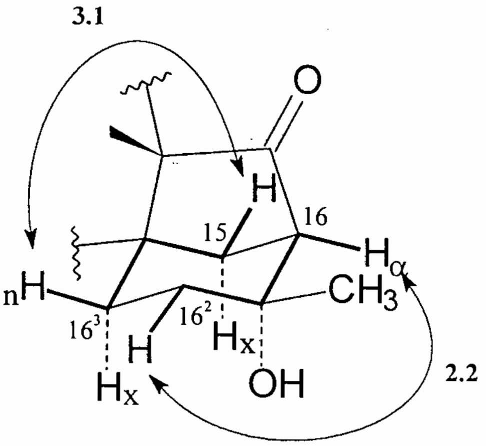


Figure **3.1**
Highfield Region of ^{1}H NMR Spectrum of Hydroxy Ketone **91**

The configuration at C-16^1 was assigned with the aid of a difference nOe study of **91**. Selective irradiation of the signal at δ 1.08, assigned to the 13β-methyl group, resulted in an enhancement of the signal assigned to the C-16^1 methyl group. As expected the selective irradiation of the C-16^1 methyl group resulted in the enhancement of the 13β-methyl group. The product must arise from cleavage of the bridgehead ester followed by retroaldol reaction leading to the intermediate oxobutyl ketone **90** which then undergoes enolisation of the 17-oxo group followed by intramolecular aldol condensation to give the thermodynamically favoured[85] 14,16β-propano bridged compound **91** (Scheme 3.2).



Geminal and Vicinal Coupling Constants

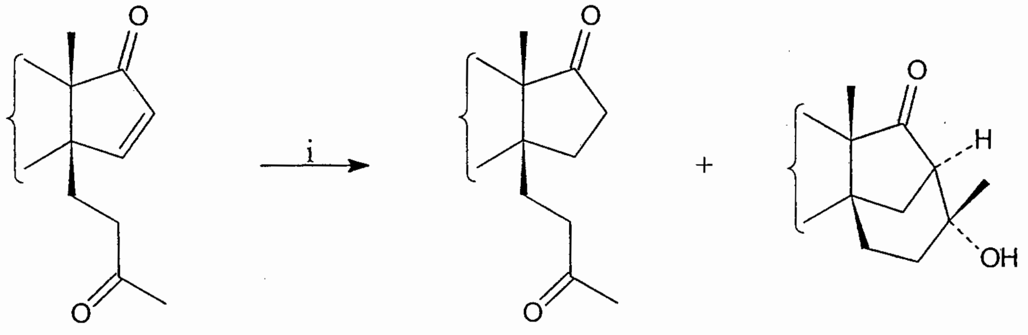


Long-range Coupling Constants

Figure 3.2

Selected ^{1}H NMR Data for 16^1-Hydroxy-17-Ketone **91**

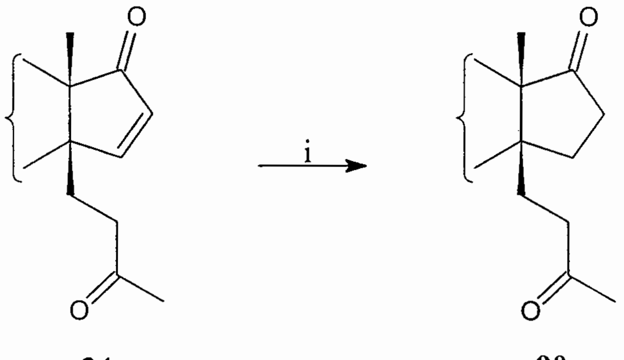
An alternative approach to the desired 14β-3'-oxobutyl 17-ketone **90** necessitated catalytic hydrogenation of the 14β-oxobutyl Δ^{15}-17-ketone **34**. Generally the hydrogenation of α,β-unsaturated carbonyl compounds in the presence of catalytic palladium on carbon proceeds readily with little or no reduction of the carbonyl functionality.[86] Hydrogenation of **34** in the presence of palladium on carbon gave a mixture of the desired hydrogenated product **90** and a second product which was identified as the hydroxy-ketone **91** (Scheme 3.3). Overlapping signals in the ^{1}H NMR spectrum of the 14β-3'-oxobutyl 17-ketone **90** precluded a full assignment of the proton signals. Nevertheless the assigned structure was confirmed by mass and ^{13}C NMR spectral data. In particular the ^{13}C-NMR spectrum displayed diagnostic signals at δ 207.7 and 222.0 assigned to C-3' and C-17. The formation of the cyclised product could not be prevented and therefore alternative reductive pathways to the desired 14β-3'-oxobutyl 17-ketone **90** were investigated.



34 **90** **91**

Scheme 3.3 *Reagents and Conditions*: (i) H_2, Pd on C, EtOAc

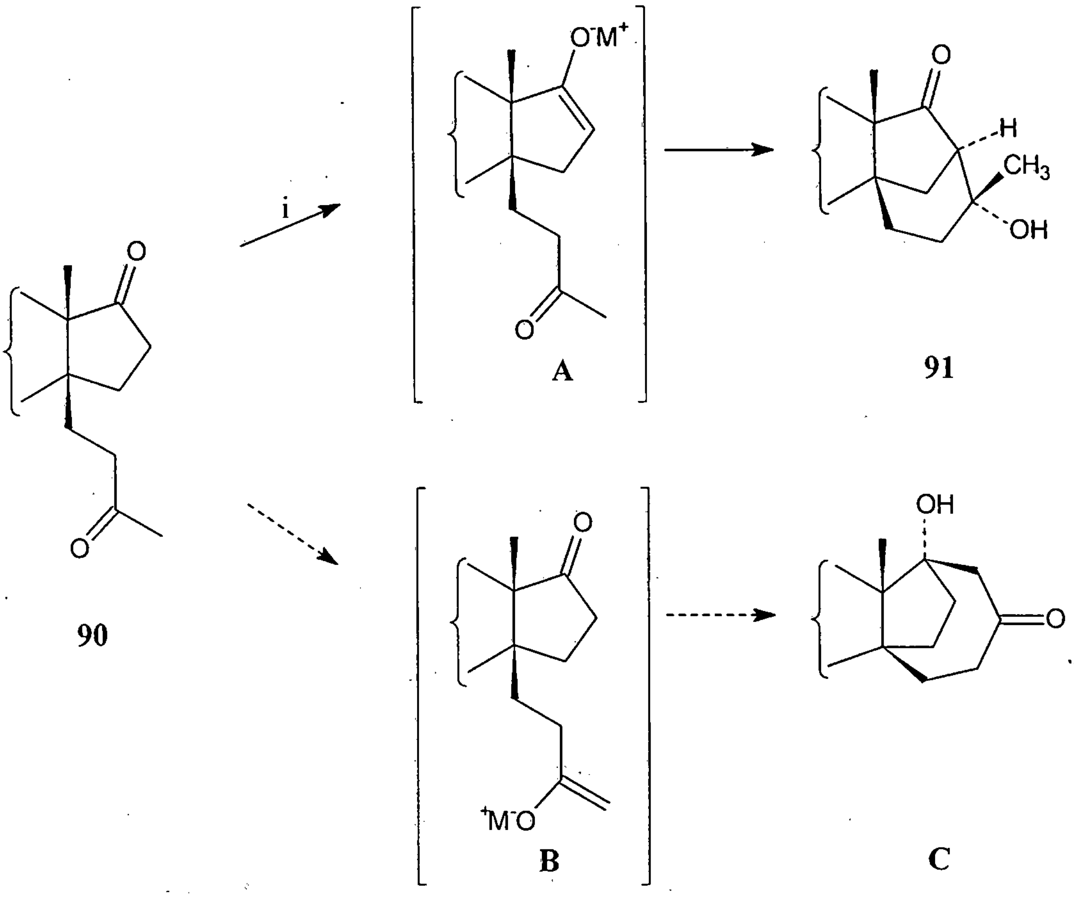
The selective reduction of double bonds of α,β-unsaturated systems may be achieved by a number of methods. Of the available methods, the reduction using the copper hydride hexamer, $[(Ph_3P)CuH]_6$, developed by Stryker *et al.*[87] seemed to be highly suited to our needs. It has been reported that for base sensitive substrates undesirable side reactions may be eliminated by careful control of the reaction conditions.[87] Nevertheless attempted conjugate reduction of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34**, using triphenylphosphine copper hydride hexamer in both stoichiometric[87, 88] and catalytic[89] reduction protocols, failed to produce any of the desired ketone **90**. Only unreacted starting material was recovered in each experiment. These results, while disappointing, are not unusual for sterically demanding substrates which have been found to be resistant to reduction using this procedure.[89] The successful reduction of an analogous 14β-substituted Δ^{15}-17-ketone[47] has been accomplished using methodology reported by Tsuda *et al.*[90] While the reduction of α,β-unsaturated systems with DIBAH generally takes place at the carbonyl group it has been found that a change in selectivity may be brought about by the addition of hexamethylphosphoric triamide (HMPA). Tsuda found that the reactivity of the DIBAH/HMPA mixture was dramatically enhanced by the addition of a catalytic amount of methylcopper. The selective reduction of a series of α,β-unsaturated systems was achieved without any evidence of 1,2-reduction. The addition of methylcopper, prepared *in situ* from methyllithium and copper(I) iodide, was crucial to the successful outcome of the reaction. Thus treatment of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** with DIBAH, in the presence of methylcopper, in tetrahydrofuran with HMPA as co-solvent gave the ketone **90** in 84% yield (Scheme 3.4). No evidence of side-reactions was observed.



Scheme 3.4 *Reagents and Conditions*: (i) DIBAH, MeCu, HMPA, THF

Having found a synthetically useful route to **90**, an investigation of its aldol reactivity was undertaken. The 14β-3'-oxobutyl 17-ketone **90** upon treatment with methanolic potassium hydroxide (1 M) in tetrahydrofuran at 24°C underwent efficient intramolecular aldol condensation to give the hydroxy-ketone **91** in 85% yield (Scheme 3.5). In an experiment designed to investigate the influence of the nature of the base on the course of the reaction

90 was treated with lithium hexamethyldisilazane in tetrahydrofuran at -78°C to give **91** as the only reaction product.

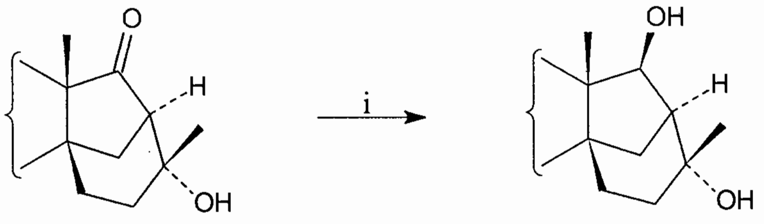


Scheme 3.5 *Reagents and Conditions*: (i) KOH-MeOH, THF, 24°C or LiHMDS, THF, -78°C

The preferred mode of cyclisation of **90**, to give **91** rather than the 14β,17β-butano bridge compound **C** (Scheme 3.5) may be attributed to the ease of formation of the two enolates **A** and **B** and their subsequent relative reactivity. The formation of **91** under both conditions of thermodynamic and kinetic control requires the intermediacy of A, though under the strongly basic conditions employed it is reasonable to assume that the formation of **B** occurs, at least in competition with the formation of **A**. It is evident that **A** undergoes a highly favourable 6-enol*exo*-trig cyclisation[91] to give **91**. The fate of **B** is less certain in that it either does not undergo the less favourable 7-enol*exo*-trig cyclisation leading to **C**, or if **C** is formed it is subject to rapid retroaldol reaction to give starting material. Allinger *et al* have found that transannular strain is particularly severe for medium-ring (7-9) cycloalkanes.[25] The presence of this strain in **C** will serve to effectively drive the retroaldol reaction. The nett effect of these factors is the resultant accumulation of the stable hydroxy-ketone **91**.

At this point in the work it became evident from the binding affinity data for the 14,17β-propano-14β-estra-1,3,5(10)-trien-3,17α-diol that increasing the size of the β-face bridge significantly attenuates biological activity when compared to the 14,17β-etheno analogue. In line with this finding the synthesis of the analogous 14,17β-butano 3,17α-diol was not further pursued.

It has been shown in Chapter 2 that hydride reduction of 14β-alkyl 17-ketones gave mixtures of 17β- and 17α-alcohols in contrast to the reduction of 3-methoxy-14β-estra-1,3,5(10)-trien-17-one which gave exclusively the 17α-alcohol. It was expected that hydride reduction of **91** should proceed with enhanced stereoselectivity given that the approach of hydride from the β-face is impeded by the presence of the 14,16β-propano bridge. Treatment of the hydroxy-ketone **91** with lithium aluminium hydride in tetrahydrofuran gave a single product which was assigned the structure **92** (Scheme 3.6).



91 **92**

Scheme 3.6 *Reagents and Conditions*: (i) LAH, THF, 24°C

The IR spectrum of the product displayed a broad band centred at 3400 cm^{-1} assigned to the hydroxyl stretching frequency. The ^{1}H NMR spectrum displayed a self-consistent set of signals for the ring D protons. The 17α-H resonated at δ 3.99 as a doublet (*J* 6.8 Hz), the signal split by a coupling to 16α-H. The magnitude of the coupling constant is consistent with assigned stereochemistry at C-17. An examination of molecular models indicates that the alternative isomer has 17β-H and 16α-H in an orthogonal relationship thus expecting a smaller coupling constant (Figure 3.3). The 16α-H, resonating at δ 1.60, displayed two couplings in addition to the vicinal coupling to 17α-H. The larger coupling constant (*J* 7.3 Hz) arose from the coupling between 16α-H and 15α-H and the signal was further split by a small long range coupling (*J* 2.8 Hz) between 16α-H and 16^2-H_x similar to that observed for the hydroxy-ketone **91**. The 15α-H resonated at δ 2.07 (*J* 12.7 and 7.3 Hz) the signal displaying one large vicinal coupling (12.7 Hz) and a smaller vicinal coupling (7.3 Hz) to 16α-H. As with the hydroxy-ketone **91** 16α-H of **92** did not couple to 15β-H which resonated as a doublet at δ 1.98 (*J* 12.7 Hz).

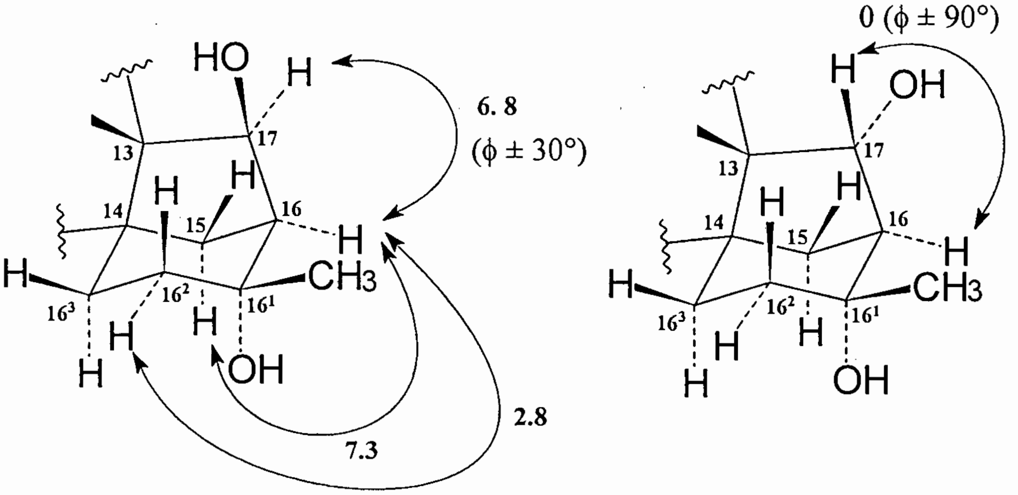
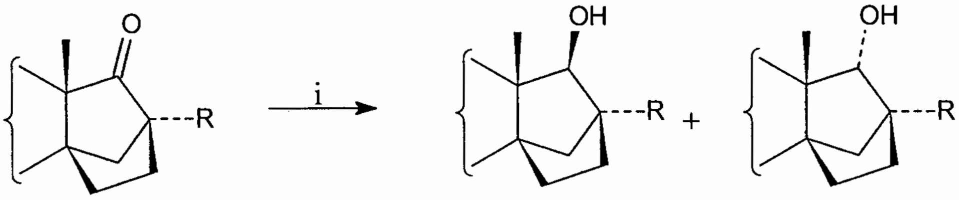


Figure 3.3

Coupling Constants for 16α- and 17α-Protons for 16^1,17β-Diol **92**

(*J* values in Hz)

The stereoselectivity of this process may be attributed to the 14,16β-propano bridge which effectively shields the β-face from attack by hydride leading to the exclusive formation of the observed product. The hydride reduction of 3-methoxy-14,16β-ethanoestra-1,3,5(10)-trien-17-one **93** has been investigated and found to proceed *via* preferred approach of hydride from the sterically less demanding α-face to give, as a major isomer, the 17β-alcohols **94** and **96** (Scheme 3.7).[92]



93

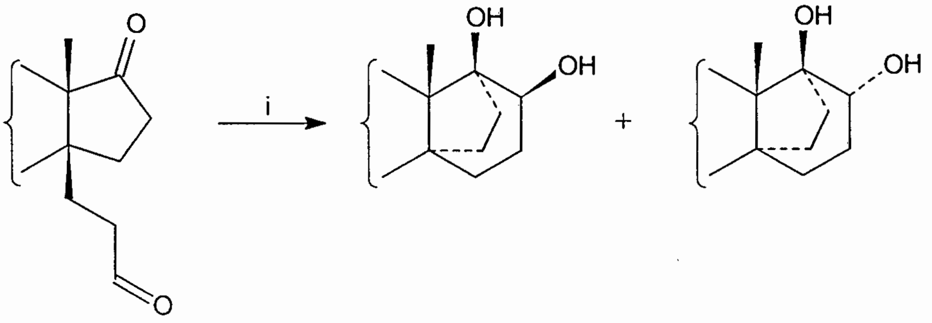
R = H **94** (90%) **95** (7%)

R=Me **96** (75%) **97** (14%)

Scheme 3.7 *Reagents and Conditions*: (i) $NaBH_4$, EtOH, 50°C

3.2 Intramolecular Reductive Coupling of the 14β-3'-Oxobutyl 17-Ketone 90

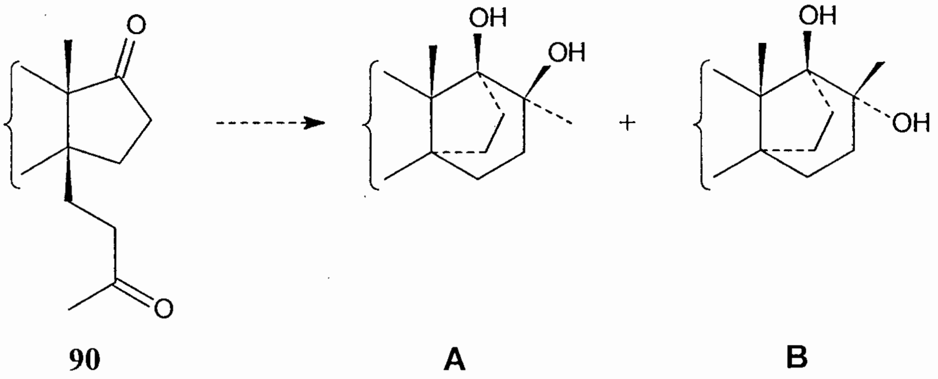
It has recently been shown[19] that intramolecular reductive coupling of the 14β-formylethyl 17-ketone **98** mediated by the McMurray reagent[72] results in the formation of the 14,17β-propano 16,17-diols **99** and **100** (Scheme 3.8). The product distribution strongly favours the latter isomer and was explained in terms of a transition state in which approximately colinear alignment of the interacting centres is stereoelectronically appropriate, and unimpeded by steric interactions.



98 **99** **100**

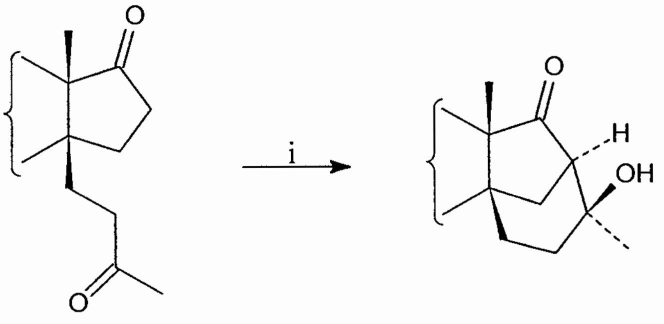
Scheme 3.8 *Reagents and Conditions*: (i) $TiCl_3(DME)_{1.5}$, DME, 20°C, 3 h

It was of interest to ascertain whether the 14β-3'-oxobutyl 17-ketone **90** would undergo intramolecular reductive coupling (Scheme 3.9), since the acetyl methyl group would be expected to experience steric interaction with the 13β-methyl group during the bond-forming process in a similar transition state. The resultant compounds **A** and **B** further serve to provide additional insights into the structure-activity relationships in 14,17β-alkano bridged compounds.



Scheme 3.9

Treatment of the 14β-3'-oxobutyl 17-ketone **90** with 2 equivalents of samarium(II) iodide in tetrahydrofuran at 0°C gave a single product in 87% yield (Scheme 3.10). Analytical data indicated that the product was isomeric with starting material thus excluding any of the expected reductive coupling products. The infrared spectrum displayed absorption bands at 3530 cm^{-1} and 1726 cm^{-1} suggesting the presence of both a hydroxyl and carbonyl group. On the basis of spectroscopic evidence the isolated product was assigned the structure **101.** The 16α–H, 15α-H and 15β-H displayed a self-consistent array of signals (Table 3.1).



90 **101**

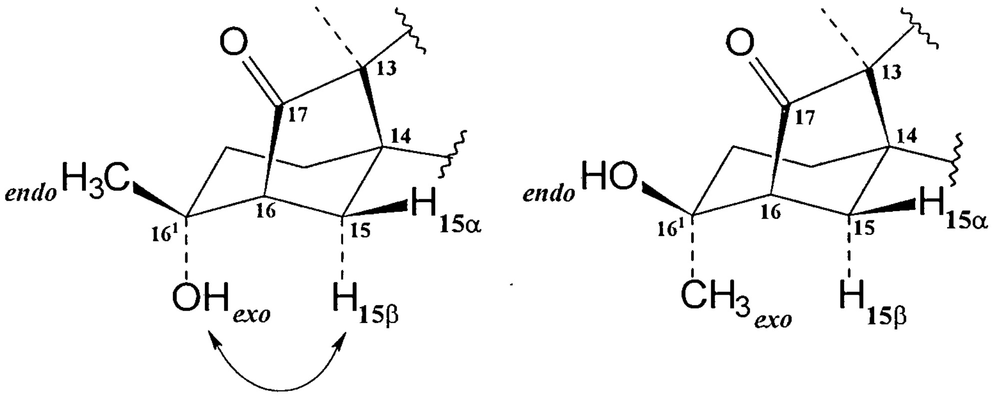
Scheme 3.10 *Reagents and Conditions*: (i) SmI_2 (2 equivalents), THF, 24°C

The configuration at C-16^1 was assigned with the aid of a difference nOe experiment. Thus the 16^1-methyl group of **101** was irradiated with a resultant enhancement of the signal assigned to 15β-H. In addition to the nOe data, direct comparison of the spectral properties of the **91** and **101** provided secondary evidence which served to confirm the assignments. A comparison of the ^{1}H NMR spectra reveals a significant upfield shift in the signal for 15β-H from δ 2.18 for **91** to δ 1.62 for **101** (Table 3.1). This change in chemical shift ($\Delta\delta$ = 0.56 ppm) is a reflection of the influence of the hydroxyl group. In **91** 15β-H and the 16^1-hydroxyl group are in a 1,3-diaxial relationship (Figure 3.4). It is well known that axial hydroxy groups introduce large positive increments for γ-axial protons.[93] The absence of such a 1,3-diaxial relationship for **101** results in the relative upfield shift of the resonance assigned to 15β-H.

Table 3.1 ^{1}H NMR Data* for Ring D Protons of 16^1-Hydroxy-17-Ketones **91** and **101**

Proton	**91**	**101**
15α	2.04	2.24
	12.2, 5.6 and 3.1 Hz	12.8, 6.2 and 3.2 Hz
15β	2.18	1.62
	12.2 Hz	12.8 Hz
16α	2.41	2.38
	5.6 and 2.2 Hz	6.2 and 1.8 Hz

* Chemical shift values in ppm and *J*-values in Hz



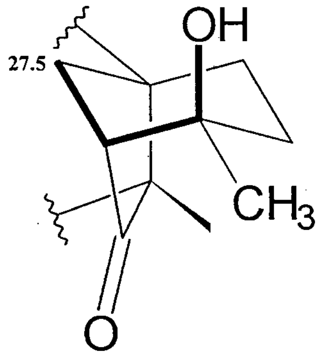
92 **101**

Figure 3.4

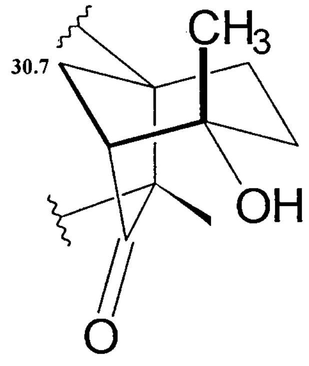
Spatial Relationship Between 15β-H and 16^1-OH Group for the C-16^1 Epimeric 16^1-Hydroxy-17-ketones **92** and **101**

An examination of the ^{13}C-NMR data revealed chemical shift differences consistent with the proposed structures. The resonances associated with C-15 for both **91** and **101** were unambiguously assigned with the aid of HETCOR experiments. A comparison of the chemical shift data indicates that C-15 resonates at a higher frequency (δ 30.7) for **101** than the corresponding carbon in **91** (δ 27.5) (Table 3.2). This upfield shift of 3.2 ppm, on going from **101** to **91**, is indicative of the γ-gauche relationship between C-15 and the C-16^1-hydroxyl group in the latter compound **A** and **B**, Figure 3.5). This effect is mirrored in the substituted bicyclo[3.2.1]octanes (Figure 3.5).[94] An examination of the ^{13}C NMR data shows a downfield shift, from δ 29.3 (for **102** to 36.1 for **103**, of 6.8 ppm for C-8 of the pair of epimeric alcohols.

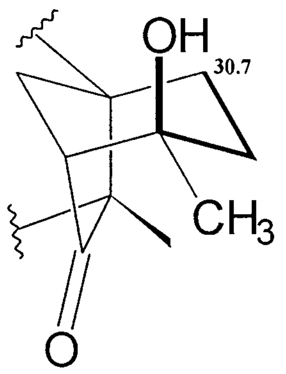
A similar trend is observed for the resonances assigned to C-16^3. The signal for **91** resonates at δ 30.7 while the corresponding resonance for **101** resonates at δ 36.1. This downfield shift can be attributed to the influence of the γ-gauche hydroxyl group which causes C-16^3 to resonate at a lower frequency for **91** (**C** and **D**, Figure 3.5). Once again this is supported by ^{13}C NMR data for the substituted bicyclo[3.2.1]octanes **102** and **103** which displays an analogous trend.



A

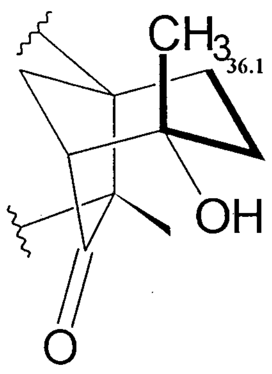


B



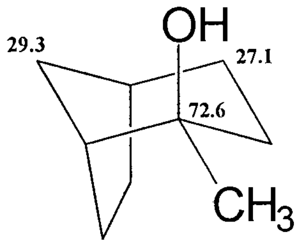
C

92

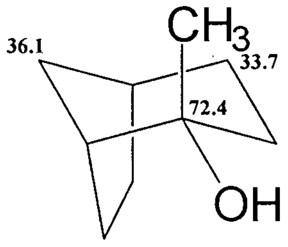


D

101



102



103

Figure 3.5

γ-Gauche Relationships in 16^1-Hydroxy-17-ketones **92** & **101** and Alcohols **102** & **103**

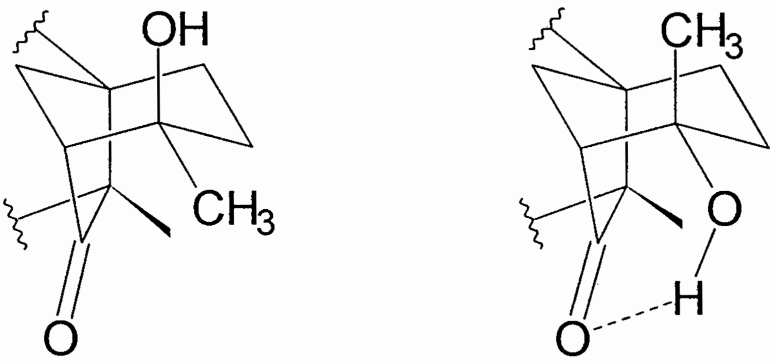
(δ values in ppm)

Table 4.2 ^{13}C NMR Data* for 16^1-Hydroxy-17-ketones **91** and **101**

Carbon	**91**	**101**
1	126.6	126.6
2	111.7	111.8
3	157.6	157.6
4	113.5	113.5
5	137.9	137.7
6	30.7	30.6
7	23.6	23.5
8	42.6	42.0
9	37.3	37.4
10	131.4	132.1
11	26.2	26.0
12	31.7	30.8
13	42.6	45.9
14	49.2	49.7
15	**27.5**	**30.7**
16	57.2	56.6
17	**221.3**	**224.4**
18	15.2	13.8
3-OMe	55.2	55.2
16^1	**71.0**	**72.5**
16^2	34.1	29.8
16^3	**30.7**	**36.1**
16^1-CH_3	28.2	25.1

* δ values in ppm

An examination of molecular models of both **91** and **101** suggests that the latter compound is a potential candidate for intramolecular hydrogen bonding based on the proximity of the 16^1-hydroxyl group to the 17-oxo functionality. A comparison of the C-17 resonances indicates that such a shift is indeed observed (Table 4.2). The signal for C-17 resonates at δ 221.3 for **91** and shifts, due to intramolecular hydrogen bonding , to δ 224.4 for **101** (Figure 3.6).

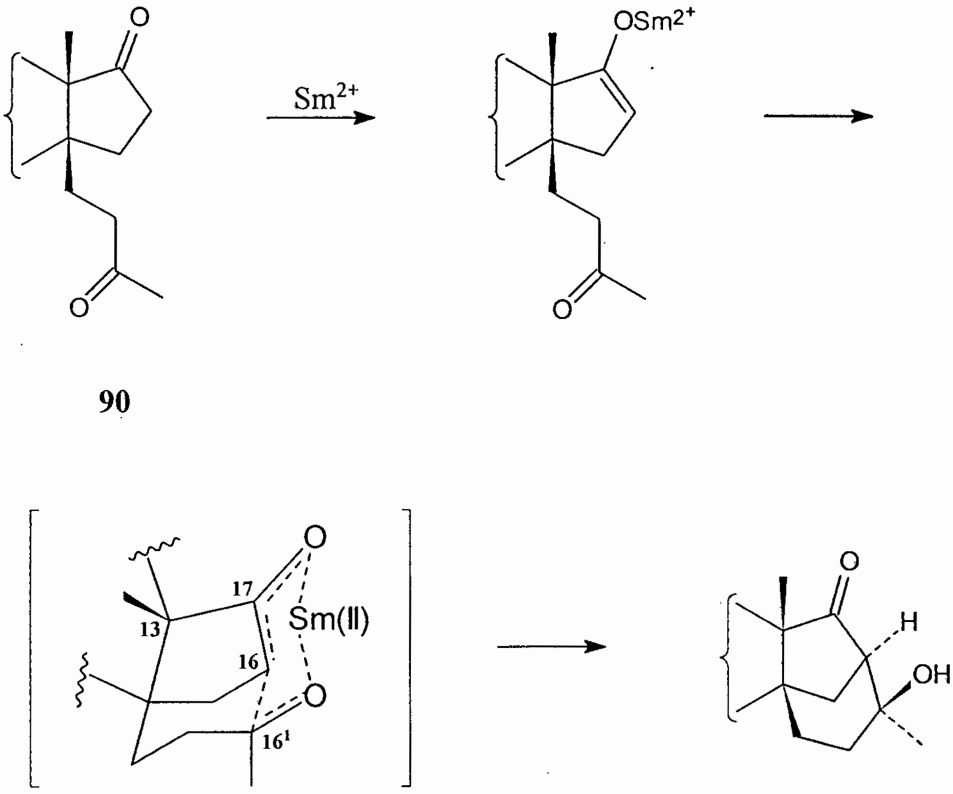


92 **101**

Figure 3.6

Intramolecular Hydrogen Bonding in 16^1-Hydroxy-17-ketones **92** and **101**

The unexpected outcome of the attempted reductive coupling process may be attributed to the adventitious enolisation of the 17-oxo group of **90** followed by intramolecular aldol condensation to give the observed product **101**. It is notable that the stereoselectivity of this samarium(II) iodide mediated process is reversed when compared to the base mediated intramolecular aldol condensation of the 14β-3'-oxobutyl 17-ketone to give **91**. It is proposed that this reversal in stereoselectivity may be rationalised in terms of initial formation of a samarium enolate, and that condensation occurs *via* a six-membered transition state in which the strongly oxophilic samarium anion[95] coordinates the 3'-oxo group during the bond-forming process (Scheme 3.11).

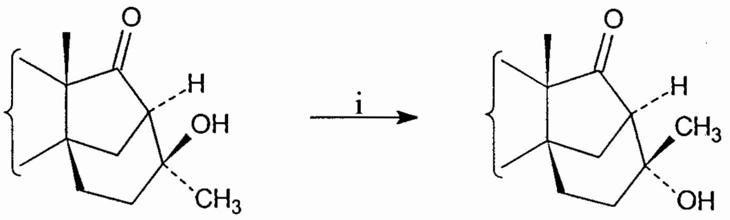


90

101

Scheme 3.11 Postulated transition state leading to the formation of aldol reaction product **101**

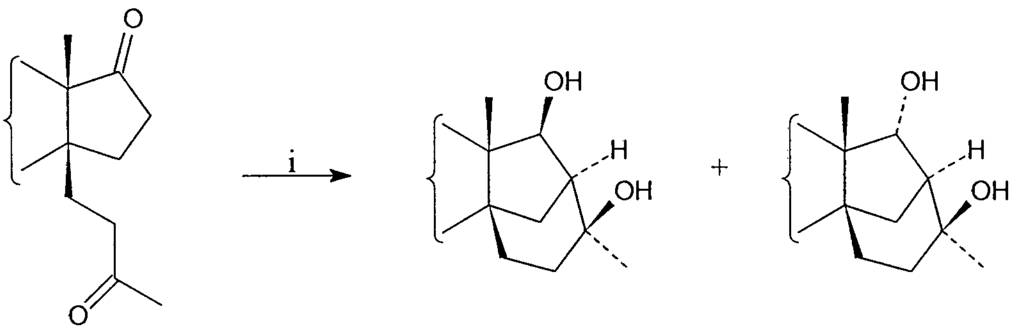
The β-hydroxy-ketones **101** should, in the presence of alkali, be in equilibrium with the open form which can be expected to undergo intramolecular aldol closure to the isomer **91**. Treatment of **101** with methanolic potassium hydroxide (1 M) at 24°C for 5 h gave the epimeric hydroxy-ketone **91** in 80% yield (Scheme 3.12).



101 **91**

Scheme 3.12 *Reagents and Conditions*: (i) KOH, MeOH

It is generally accepted that samarium(II) iodide mediated pinacol couplings are favoured, above alternative reductive processes (e.g. simple reduction of the oxo group), at elevated temperatures'[96, 97] Accordingly, in order to investigate whether **90** could be persuaded to undergo reductive coupling rather than intramolecular aldol condensation at elevated temperature the 14β-3'-oxobutyl 17-ketone **90** was treated with two equivalents of samarium(II) iodide in refluxing tetrahydrofuran for 4.5 h. The reaction proceeded to give the hydroxy-ketone **101** in 79 % yield, the temperature having no influence on the outcome of the reaction. The reaction was repeated using an excess of samarium(II) iodide and resulted in the formation of the epimeric diols **104** and **105** (Scheme 3.13). The structural assignments, of both compounds followed directly from an analysis of their NMR spectra.



90 **104** **106**

Scheme 3.13 *Reagents and Conditions*: (i) SmI$_2$ (excess), THF, Δ, 4.5 h

The stereochemistry at C-17 was unambiguously assigned by examination of the signals assigned to 17-H (Table 3.3). Thus 17α-H for **104** resonated at δ 4.11 as a doublet (after D$_2$O exchange). The magnitude of the vicinal coupling constant (*J* 6.8 Hz) was indicative of the synclinal relationship between 17α-H and 16α-H. By comparison 17β-H of **105** resonated at δ 4.15 as a singlet. The absence of any vicinal coupling is consistent with the mutual orthogonal relationship between 17β-H and 16α-H (Figure 3.7). The relative chemical shifts of the 15α-protons served to confirm the stereochemical assignment at C-17. The signal for 15α-H of the 17β-alcohol **104** resonated at δ 1.74 while the corresponding signal for the 17α-alcohol **105** resonated at δ 2.09. This downfield shift of

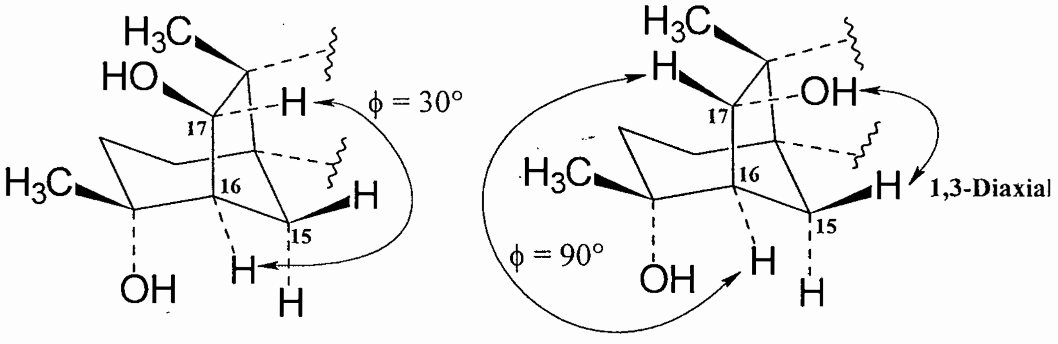
0.35 ppm is as a consequence of the 1, 3-pseudodiaxial relationship between the 17α-hydroxy group and 15α-H across the five-membered ring (Figure 3.7). As has been noted before such downfield shifts are well documented.[93]

Table 3.3 ^{1}H NMR Data* for Ring D Protons for Diols **104** and **105**

H	104	105
15α-H	1.74, ddd	2.09, ddd
	12.7, 5.7 and 3.3	12.4, 6.4 and 3.1
15β-H	1.37, d	1.23, d
	12.7	12.4
16α-H	2.30, ddd	1.78, d
	6.8, 5.7 and 1.8	6.0
17-H**	4.11, d	4.15, s
	6.8	

* ^{1}H NMR data reported as chemical shift (in ppm), multiplicity and *J* values (in Hz)

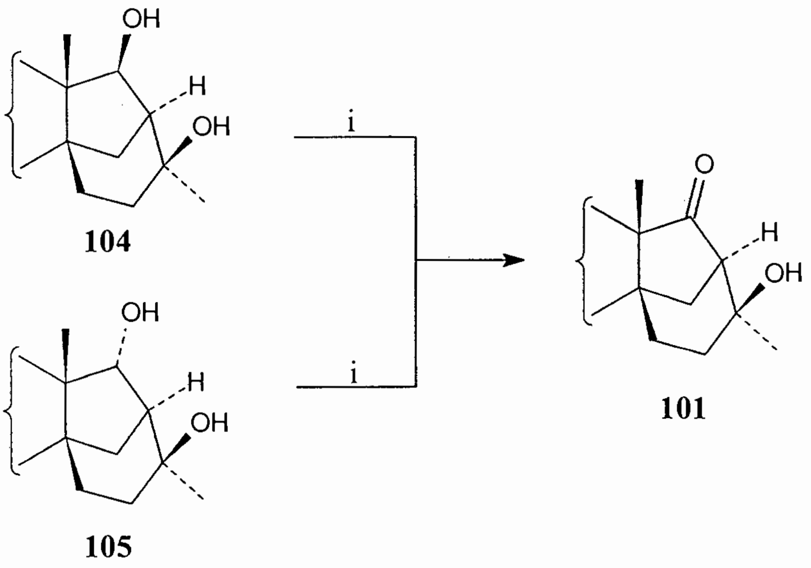
**After D_2O exchange

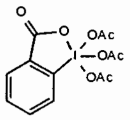


104 **105**

Figure 3.7

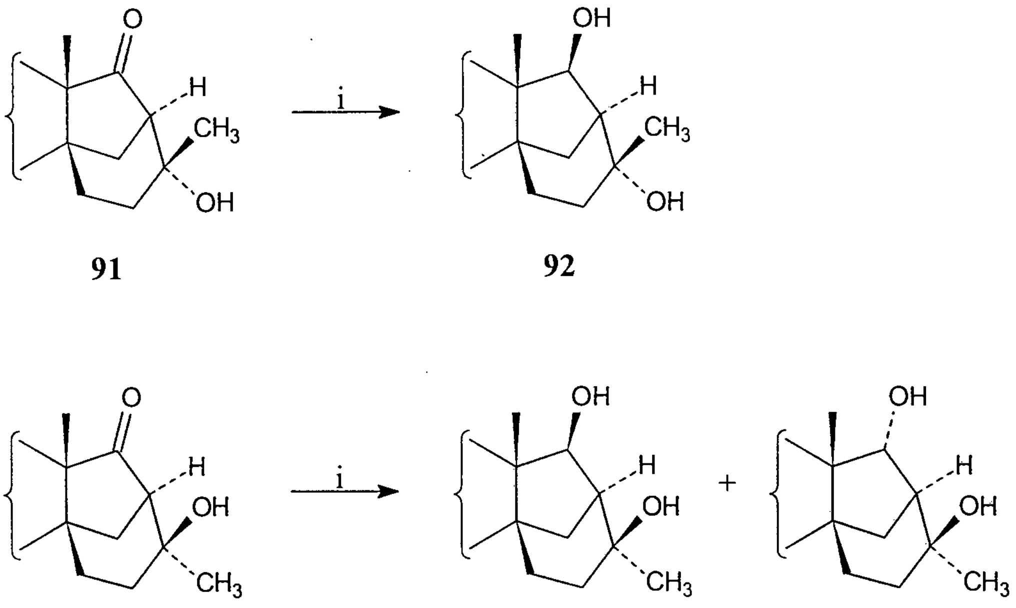
Dess Martin oxidation[98] of each of the diols **104** and **105** gave the hydroxy-ketone **101** (Scheme 3.14). This confirmed that the configuration at C-16[1] for **104** and **105** is identical to that of **101**.



Scheme 3.14 *Reagents and Conditions:* (i)  , CH_2Cl_2

In light of the highly stereoselective hydride mediated reduction of the hydroxy-ketone **91**, to give the diol **92** as the exclusive product, the stereochemical outcome of the samarium(II) iodide mediated cyclisation-reduction process is remarkable. It is reasonable to propose that the configuration at C-16[1] has a determining influence on the stereochemical outcome of the reduction process. In order to test this proposal the samarium(II) iodide mediated reduction of the epimeric hydroxy-ketones **91** and **101** was investigated.

In the first instance treatment of the hydroxy-ketone **91**, derived from aldol reaction of the 14β-3'-oxobutyl 17-ketone **90**, with samarium(II) iodide in the presence tertiary butyl alcohol[70] gave a single product identified as the diol **92** (Scheme 3.15). The stereochemical outcome of this reaction is identical to that obtained from simple hydride reduction of **91** which also proceeded to give exclusively the diol **92**. By contrast reduction of the hydroxy-ketone **101**, under identical conditions, gave the mixture of diols **104** and **105** in similar proportions to that isolated from the initial reaction (Scheme 3.15). Since the hydroxy-ketones **91** and **101** only differ at one stereogenic centre the difference in the stereochemical outcome of these reductions must be attributed to the influence of the remote hydroxyl group at C-16[1].



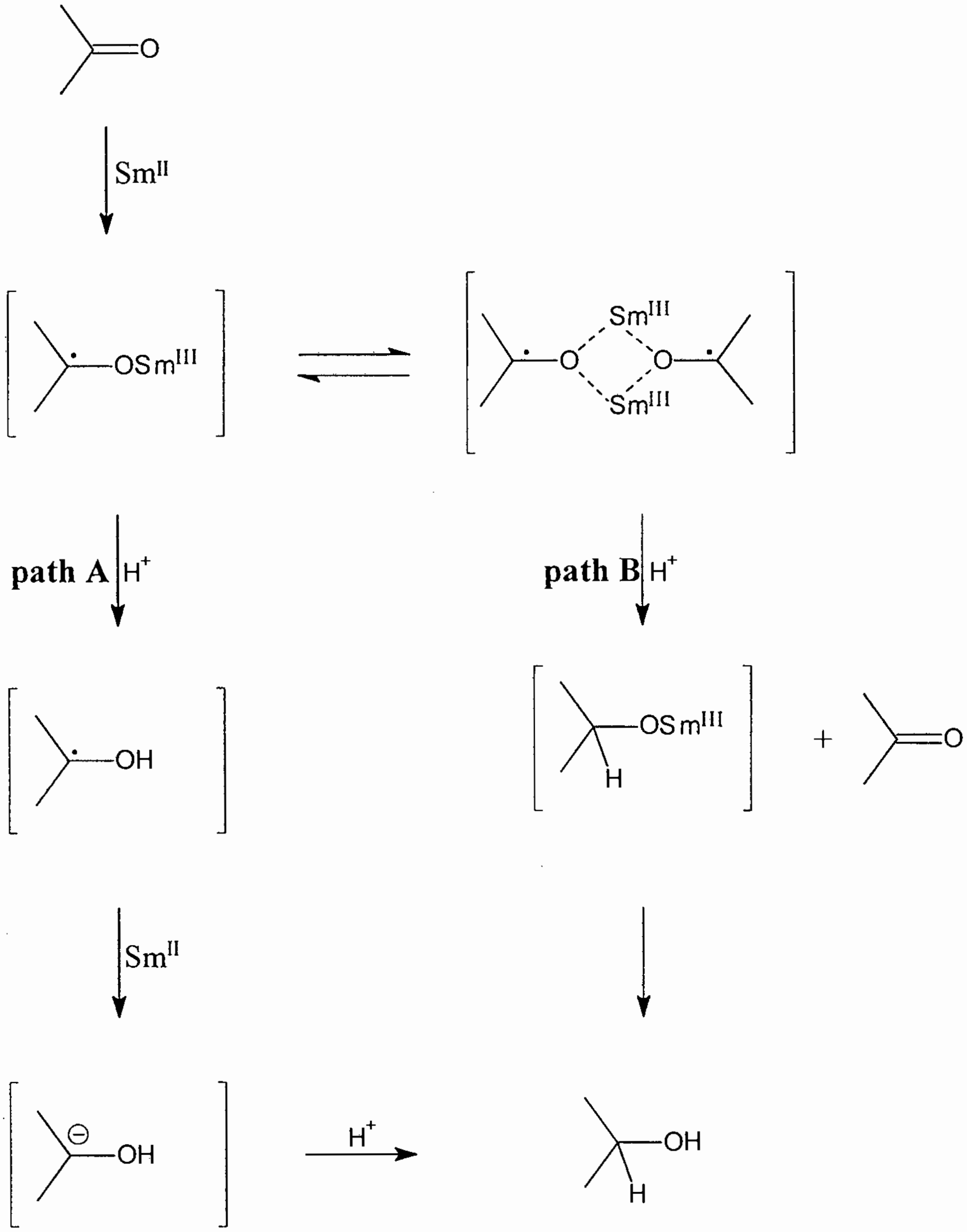
91 **92**

101 **104** **104**

Scheme 3.15 *Reagents and Conditions*: (i) SmI_2, t-BuOH, Δ

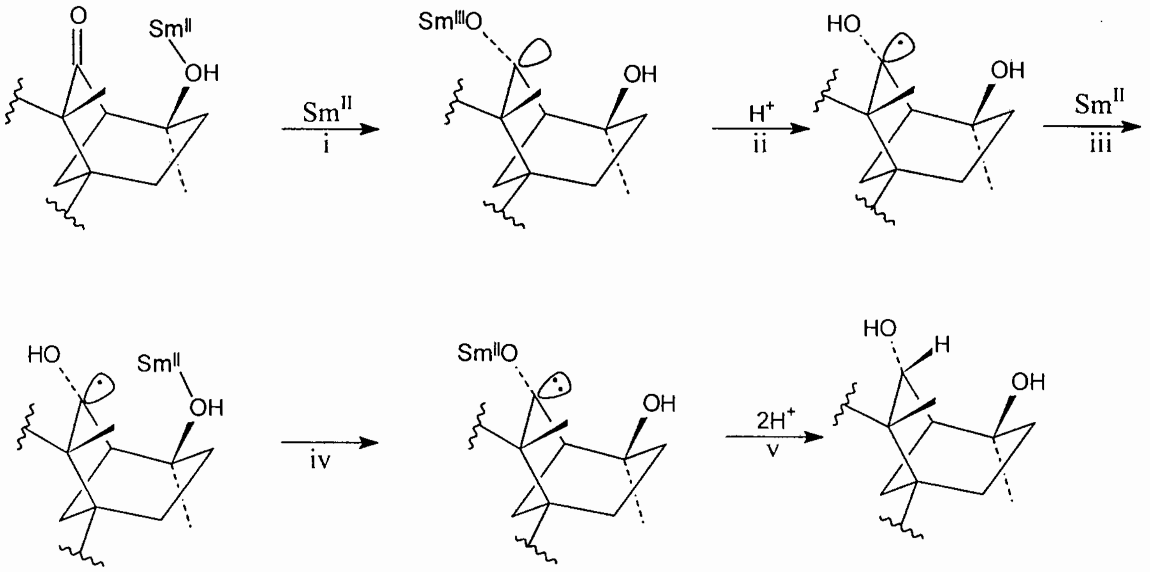
While the scope and mechanism of dissolving metal and Bouveault-Blanc reductions of aldehydes and ketones are reasonably well understood,[99] those associated with samarium(II) iodide reductions are not clearly delineated.[70] Molander[70] has suggested that similar general mechanistic and stereochemical considerations apply to samarium(II) iodide reductions of aldehydes and ketones as those that apply to other single electron transfer protocols (Scheme 3.16).

Thus it is generally accepted that single electron transfer to the ketone generates a ketyl radical anion. It is believed that such anions can exist in dimeric or even polymeric forms. In the presence of a proton donor the ketyl radical anion (or the Sm(III) aggregate) has two alternative pathways available. The first pathway (path A) invokes reversible protonation of the ketyl to provide a carbinol radical. A second electron transfer generates a hydroxyalkyl carbanion that is protonated to afford the observed alcohol. The alternative pathway (path B) involves rapid disproportionation of the dimers to give a molecule of alcohol and a molecule of ketone.



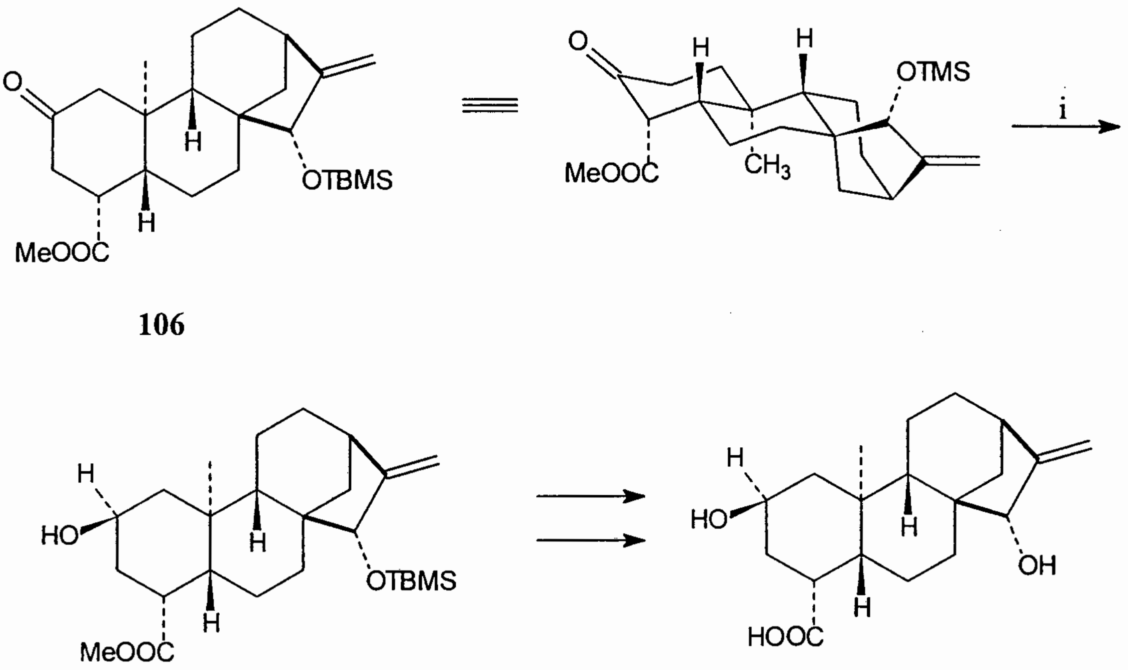
Scheme 3.16 Literature mechanism for SmI$_2$ reduction of carbonyl compounds[70]

It is well known that samarium(III) anions are oxophilic[95] and that stabilization of Sm^{2+} species by coordination is a strong driving force in reduction processes.[100] The above mechanistic considerations can be used to explain the stereochemical outcome of the reduction process. In the absence of a coordinating group the hydroxy-ketone **91** undergoes reduction which parallels that observed for bicyclo[2.2.1]heptan-2-ones.[101] Rautenstrauch examined the dissolving metal reduction of a series of bicyclo[2.2.1]heptan-2-ones and the empirical finding was that in every case the *endo*-alcohol predominated. The dramatic change in the stereochemical outcome of the reduction of the isomeric hydroxy-ketone **101** may be rationalised in terms of co-ordination of the Sm^{3+} anion to the remote hydroxyl group. If pathway **A** (Scheme 3.16) is invoked the stereochemical outcome of the reduction will be controlled by the second electron transfer process (Scheme 3.17). Coordination of the samarium anion to the 16^1-hydroxyl group will ensure that the second electron is delivered from the β-face (step iv, Scheme 3.17)) generating a hydroxyalkyl carbanion. Houk and Wu have postulated that once such hydroxyalkyl carbanions are formed they are protonated before inversion occurs.[102] Protonation of the carbanion (step v) would thus occur from the β-face giving, as observed, the α-alcohol. The nett effect of this process is that the resultant hydroxy-group adopts an orientation, in the product, *anti* to the co-ordinating centre.



Scheme 3.17

Corey *et al.*[103] have used this principle of directed samarium(II) iodide mediated ketone reduction in the synthesis of the diterpenoid atractyligenin **108** (Scheme 3.18). In this case the methoxycarbonyl group acts as a coordinating centre ensuring that the hydroxyl group, in the product, is orientated "*anti*" to it.



106

107

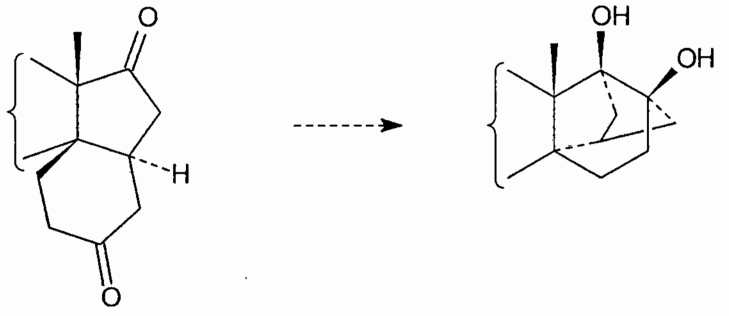
108 Atractyligenin

Scheme 3.18 *Reagents and Conditions*: (i) SmI$_2$, THF, H$_2$O

CHAPTER 4

Synthesis of Ring D Caged Estriol Analogues

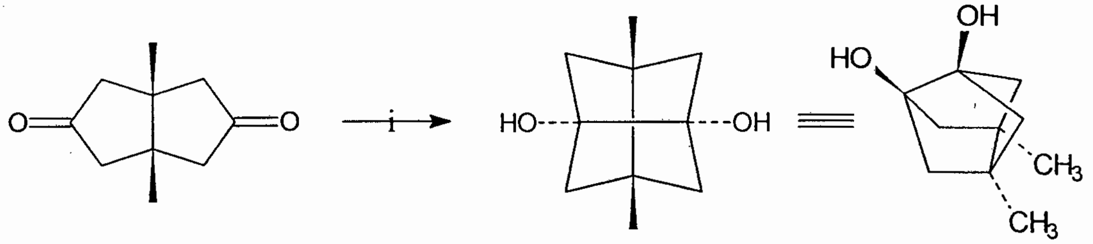
The intramolecular Michael reaction of the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** provided access to the fused-ring diketone **35**, the structure of which was considered to be amenable to intramolecular pinacol coupling to generate a new caged-ring system **A** (Scheme 4.1). This cage-compound, while maintaining the 14,17-ethano bridge moiety, which is known to enhance biological activity, has additional bridging elements in place affording the opportunity to probe the influence of steric congestion on the α-face on biological activity when compared to estradiol and estriol. The evaluation of these compounds will further define the spatial constraints associated with oral estrogenicity and will contribute to mapping the limits of binding-affinity associated with ring D.



35 **A**

Scheme 4.1

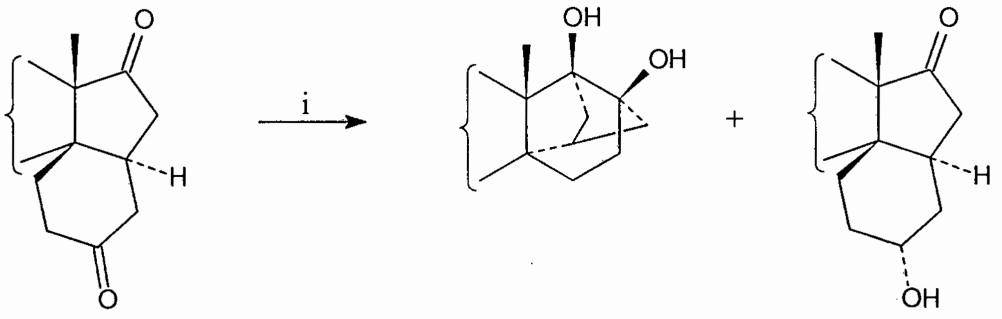
The feasibility of achieving intramolecular pinacol coupling of **35** was demonstrated in a recent report by Hoffmann *et al.*[104, 105] in which the synthesis of the highly strained functionalised tricyclo[3.3.0.0^{2,7}]octan-1,5-diol **111** *via* samarium(II) iodide mediated pinacol coupling of the bicyclic diketone **110** (Scheme 4.2). This report indicated that highly strained cage-compounds are readily accessible from bicyclic precursors using this methodology.



110 **111**

Scheme 4.2 *Reagents and Conditions:* (i) SmI_2, THF, Δ

Treatment of the diketone **35** with samarium(II) iodide in refluxing tetrahydrofuran gave, after 2 h, the diol **112** in 82% yield accompanied by a small amount (11%) of the 4'-hydroxy-17-ketone **42** (Scheme 4.3). Mass spectral and microanalytical data were consistent with the assigned structure. In addition the IR spectrum displayed a broad band centred at 3480 cm^{-1} assigned to the hydroxyl absorption. The ^{13}C NMR spectrum displayed characteristic resonances for hydroxy-bearing carbons at δ 78.2 and 83.2.



ii: **35** 3-OMe → **117** 3-OH

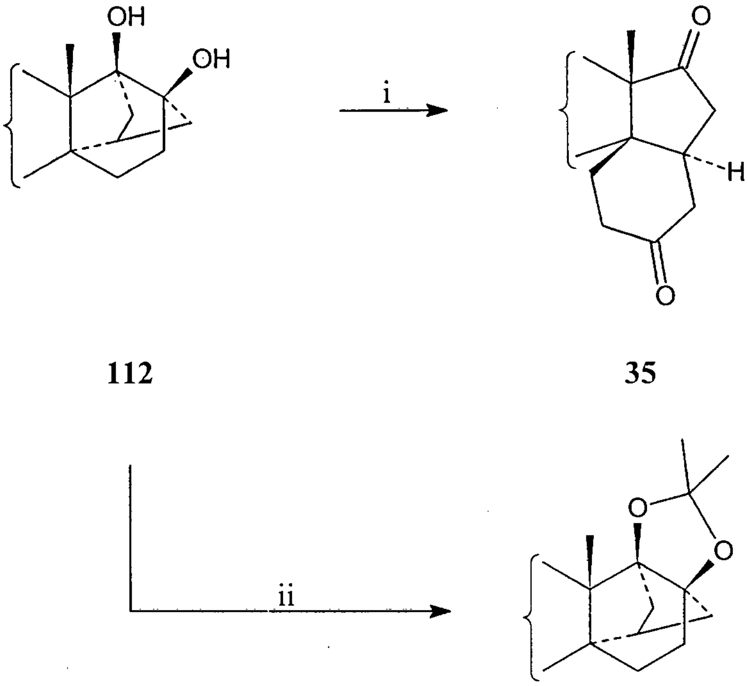
iii: **118** 3-OH → **112** 3-OMe

iii: **119** 3-OH → **42** 3-OMe

Scheme 4.3 *Reagents and Conditions*: (i) SmI_2, THF; (ii) TMSCl, NaI, acetonitrile, (iii) dimethyl sulfate, K_2CO_3

Although the ^1H NMR spectrum revealed little direct information in support of the assigned structure, this was readily demonstrated by appropriate chemical transformations which reveal the presence of a vicinal diol moiety in the product. Thus, treatment of **112** with sodium periodate in aqueous ethanol at 20°C proceeded readily to give the diketone

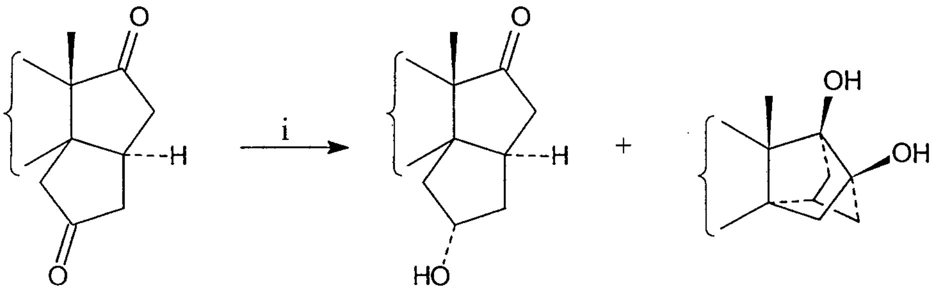
35. Similarly the reaction of **112** with acetone in the presence of catalytic sulfuric acid resulted in the formation of the corresponding acetonide **113** in 81% yield (Scheme 4.4).



112 **35** **113**

Scheme 4.4 *Reagents and Conditions*: (i) $NaIO_4$; (ii) acetone, H_2SO_4

The synthesis of an analogous ring D caged estriol **116**, from the diketone **114** has been achieved with moderate success,[47] the low yield (8 %) of coupled diol **116** indicative of the increased strain associated with the additional fusion to the steroid nucleus (Scheme 4.5).

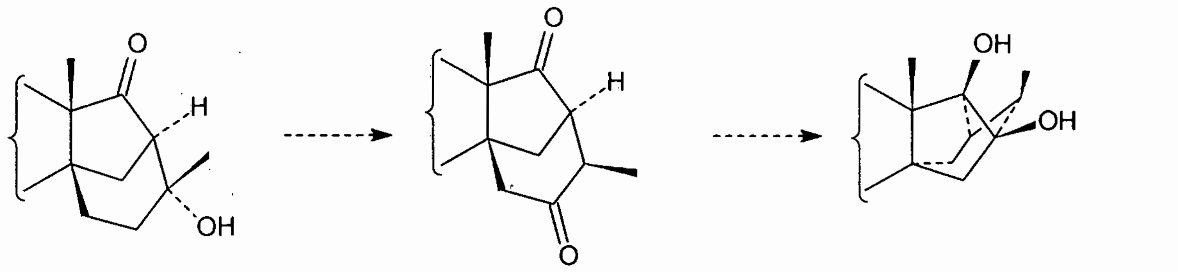


114 **115** **116**

Scheme 4.5 *Reagents and Conditions*: (i) SmI_2, THF, Δ

Inexplicably the attempted formation of the estriol analogues through treatment of the diol **112** with DIBAH in refluxing toluene was unsuccessful and an alternative approach was developed, whereby the diketone **35** was deprotected at C-3 prior to reductive coupling. Treatment of the diketone **35** was with iodotrimethylsilane[107], generated *in situ* from chlorotrimethylsilane and sodium iodide, in acetonitrile and gave the 3-hydroxy-4',17-diketone **117** which underwent efficient samarium(II) iodide mediated closure to give the desired product **118** accompanied by a small amount (~ 11%) of the 3,4'-dihydroxy-17-ketone **119** (Scheme 4.3). The mass spectral and microanalytical data of the products were consistent with the assigned structures. Although the polarity and attendant insolubility of the product precluded full NMR assignment verification of the assigned structures was obtained by treatment of the triol **118** with dimethyl sulfate and potassium carbonate for 24 h to give the 3-methoxy-17β,17aβ-diol **112** with analytical and spectroscopic properties identical to that of an authentic sample (Scheme 4.3).

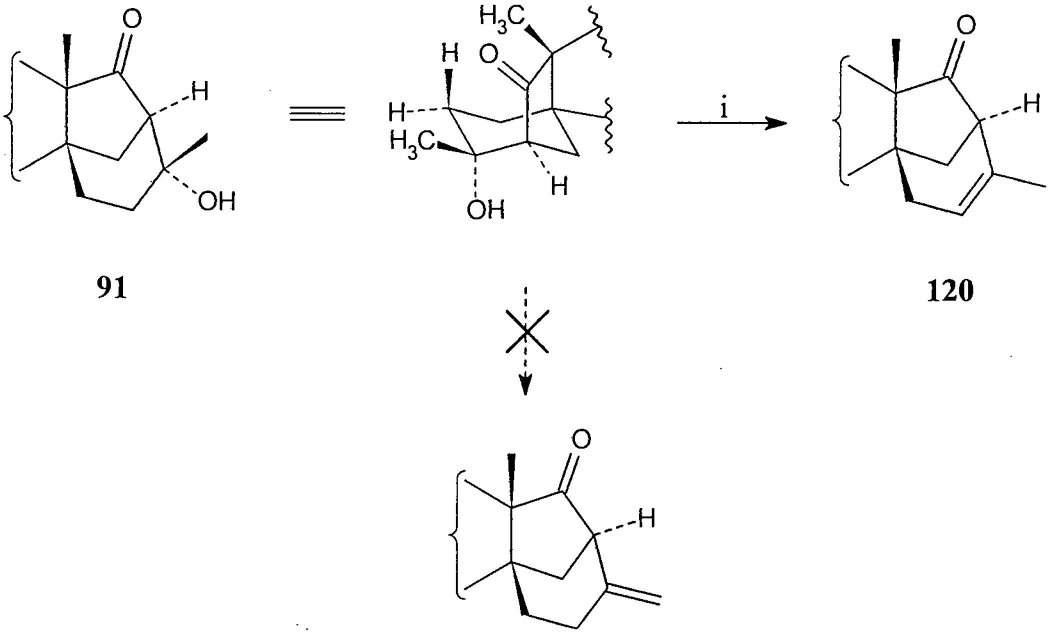
An extension of the foregoing investigation into novel ring D caged analogues of estriol was suggested by the availability of the 14β,16β-propano compound **91**. It was envisaged that the introduction of a 16^2-oxo group into the bridged structure would provide a substrate **A** for intramolecular pinacol coupling between C-17 and C-16^2, to give a further structural variant of estriol **B** having a highly congested α-surface of ring D (Scheme 4.6).



91 **A** **B**

Scheme 4.6

A synthetic plan was developed which entailed a dehydration-hydroboration-oxidation sequence to give the diketone **A** for intramolecular reductive coupling to give the diol **B** . It was recognised that in theory dehydration of the hydroxy-ketone **91** could give rise to two products arising from endo- and exocyclic elimination. Nevertheless it was expected that given the favourable *anti*-periplanar alignment of the 16^1-hydroxy group and 16^2-H_n (Scheme 4.7), elimination to give the *endo*cyclic olefin should at least occur in competition with that giving rise to the exocyclic isomer. Gratifyingly treatment of the 16^1-hydroxy-17-ketone **91** with thionyl chloride in dry pyridine gave the olefinic-ketone **120** in 93% yield. (Scheme 4.7).



91

120

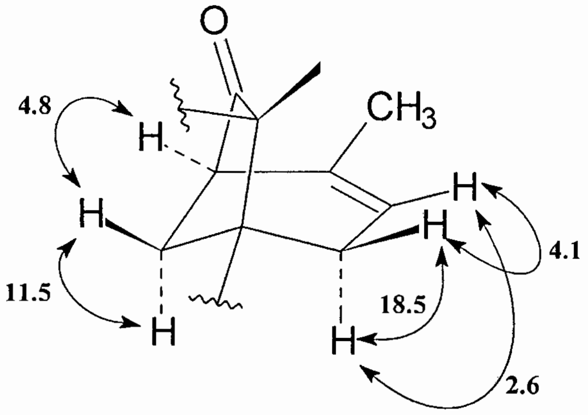
Scheme 4.7 *Reagents and Conditions:* (i) $SOCl_2$, pyridine 24°C

The assigned structure followed directly from the analytical and spectral data. In particular the regioselectivity of the dehydration was confirmed by the presence of one resonance in the downfield region of the ^1H NMR spectrum for a single olefinic proton. The ^1H NMR spectrum (Figure 4.1) displayed a self-consistent array of signals for the ring D and 14,16-bridge protons and these were fully assigned with the aid of DEPT, COSY (Figure 4.2) and HETCOR spectra. Selected coupling data are presented in Figure 4.3 and Table 4.1.

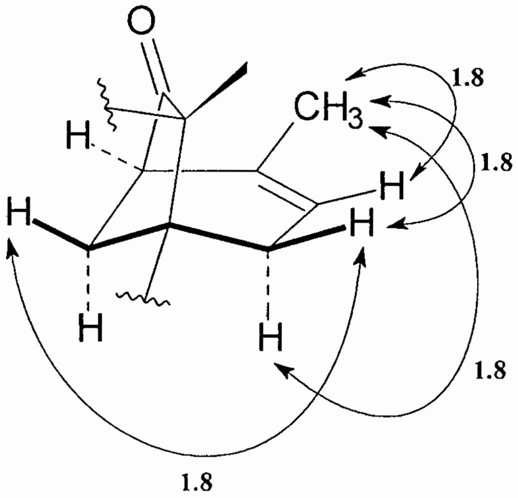
Table 4.1 Selected ^{1}H NMR Data* for Olefinic-ketone **120**

H	δ	Mult.	*J*
15α-H	2.11	ddd	11.5, 4.8 and 1.8
15β-H	1.60	d	11.5
16α-H	2.72	d	4.8
16^2-H	5.37	ddd	4.1, 2.6 and 1.8
16^3-H$_x$	2.58	ddd	18.5, 2.6 and 1.8
16^3-H$_n$	1.83	qt	18.5, 4.1 and 2 x 1.8
16^1-CH$_3$	1.74		3 x 1.8

* δ values in ppm and *J* values in Hz



Geminal and Vicinal Coupling Constants



Long-range Coupling Constants

Figure 4.3

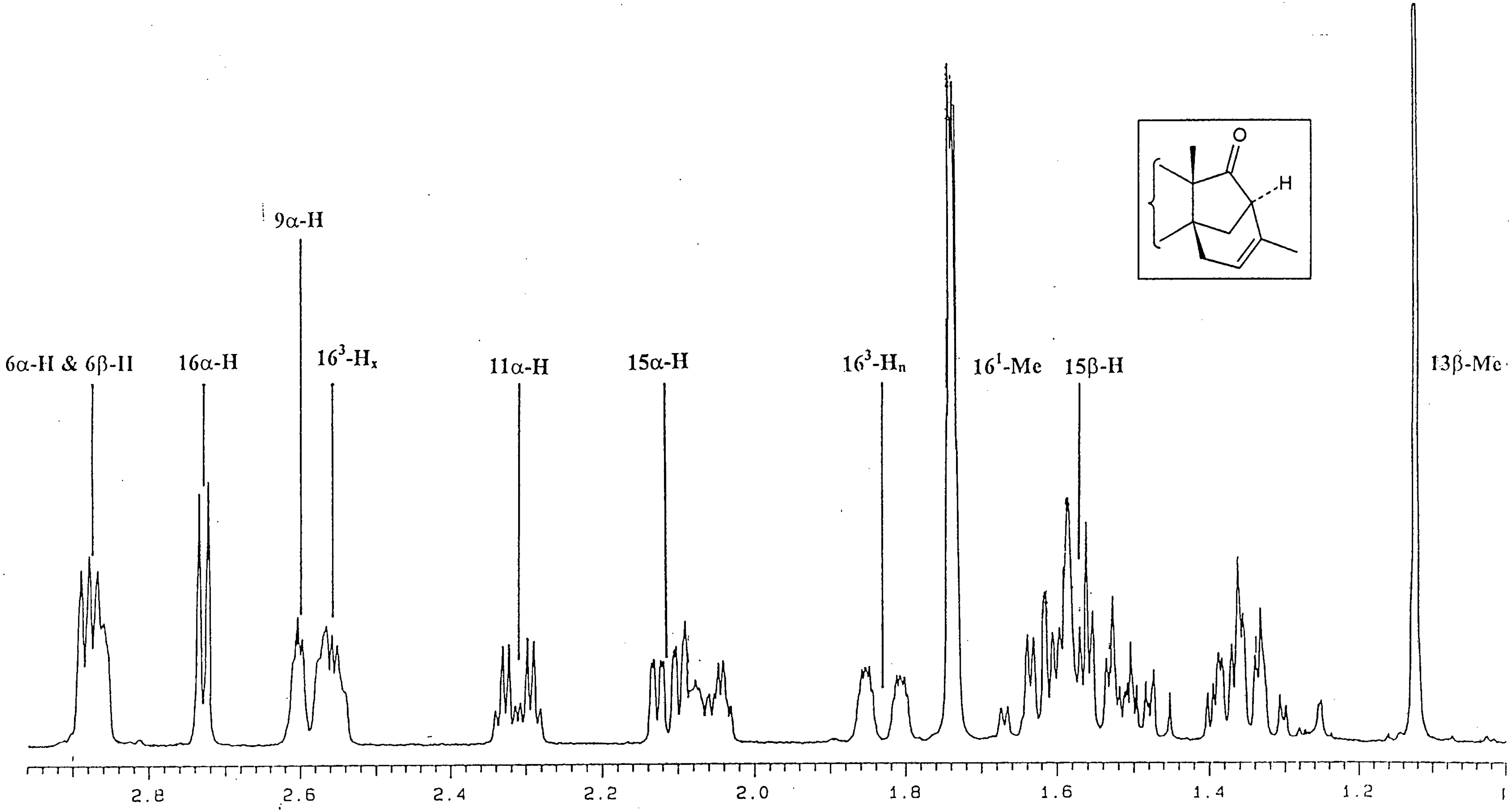


Figure **4.1**
Highfield Region of ^{1}H NMR Spectrum of Olefinic Ketone **120**

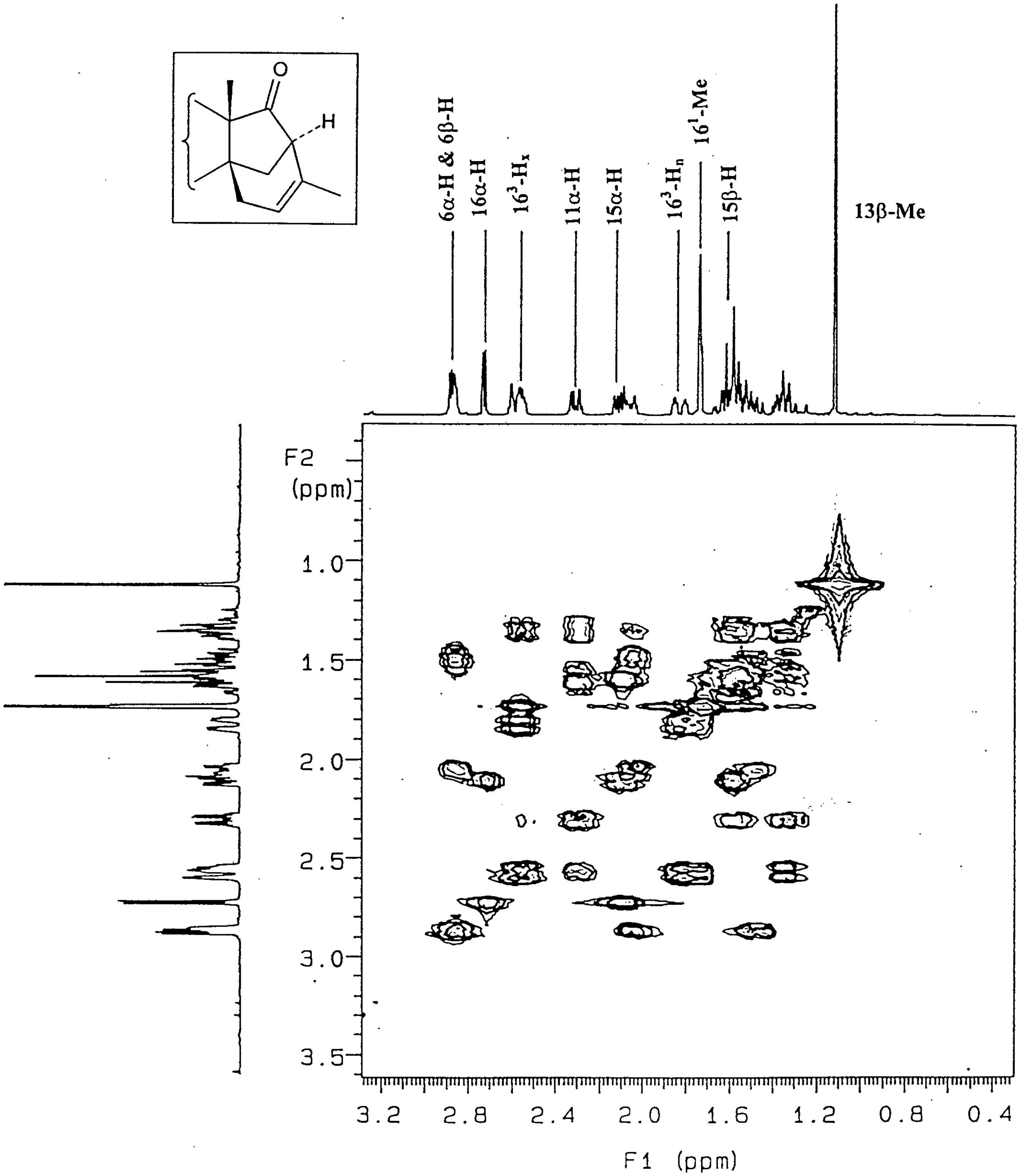


Figure **4.2**
Highfield Region of COSY Spectrum of Olefinic Ketone **120**

The next step in the reaction sequence involved hydroboration of the olefinic bond. Treatment of the **120** with borane-dimethyl sulfide in tetrahydrofuran followed by oxidative work-up gave a single product **121** in 79% yield with analytical data consistent with a hydroboration product (Scheme 4.8). It is well known[106] that hydroboration occurs preferentially from the less hindered face of a facially disymmetric olefin. An examination of molecular models indicated that hydroboration of the olefinic-ketone **120** should occur preferentially from the *exo*-face given that the requisite reagent trajectory associated with approach from the *endo*-face is subject to severe steric crowding by the 14,16-two carbon bridge and the appended 13β-methyl group (Figure 4.4). By contrast approach from the *exo*-face is relatively unhindered.

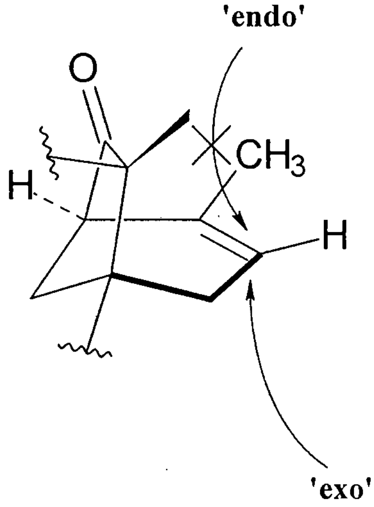
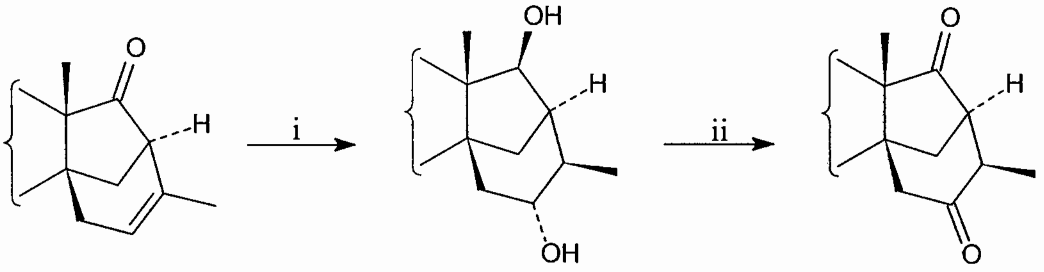


Figure 4.4

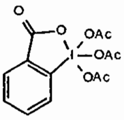
Expected Stereoselectivity for Hydroboration of the Olefinic-Ketone **120**

The product was thus assigned the structure **121** based on the above considerations and ^1H NMR data were consistent with the assigned structure. The configurational assignment at C-17 was confirmed by the coupling patterns of the 17α-H which resonated at δ 4.01 as a doublet (*J* 7.1 Hz) indicative of it's synclinal relationship to the 16α-H. It has previously been demonstrated that 17β-H of 14,16β-propano bridged 17α-alcohols does not couple to 16α-H. The 16^2-H_n resonated as a ddd with three very similar couplings (*J* 8.7, 7.8 and 6.1 Hz). While this coupling pattern does not unambiguously define the stereochemistry at

C-16, nOe studies of the diketone **122** derived from oxidation of the diol **121** provided irrefutable evidence that the hydroboration had occurred from the less hindered *exo*-face.



120 **121** **122**

Scheme 4.8 *Reagents and Conditions*: (i) BH_3-Me_2S then H_2O_2, NaOH; (ii) 

, CH_2Cl_2

Dess Martin oxidation of the diol **121** gave the 16^2,17-dione **122** in 92% yield (Scheme 4.8). The ^{1}H NMR spectrum (Figure 4.5) of **122** was well dispersed and was fully assigned with the aid of COSY (Figure 4.6) and HETCOR spectra. The signals assigned to 16α-H, 16^1-H_x, 15α-H and 15β-H formed a self-consistent pattern (Figure 4.7). Thus the 16^1-methyl protons resonated at δ 1.10 as a doublet (*J* 6.6 Hz). A crosspeak in the COSY spectrum allowed for the location of 16^1-H_x at δ 2.52 (*J* 3 x 6.6 and 3.8 Hz). The smaller geminal coupling constant is consistent with the synclinal relationship between the 16^1-H_x and 16α-H. The 16α-H resonated at δ 2.72 (*J* 5.7 and 3.8) with larger vicinal coupling to the 15α-H. The 16α-H and 15β-H did not couple. The 15α-H was located using the COSY spectrum and resonated at δ 2.32 (*J* 15.6 and 3.8 Hz). This allowed for the location of the 15β-H, confirmed by locating the corresponding ^{13}C resonance using the HETCOR spectrum. The ^{1}H NMR spectrum displayed a distinctive doublet at δ 1.89 (*J* 12.5 Hz) which was assigned to the 16^3-H_n. A crosspeak in the COSY spectrum allowed for the location of the 16^3-H_x at δ 2.56.

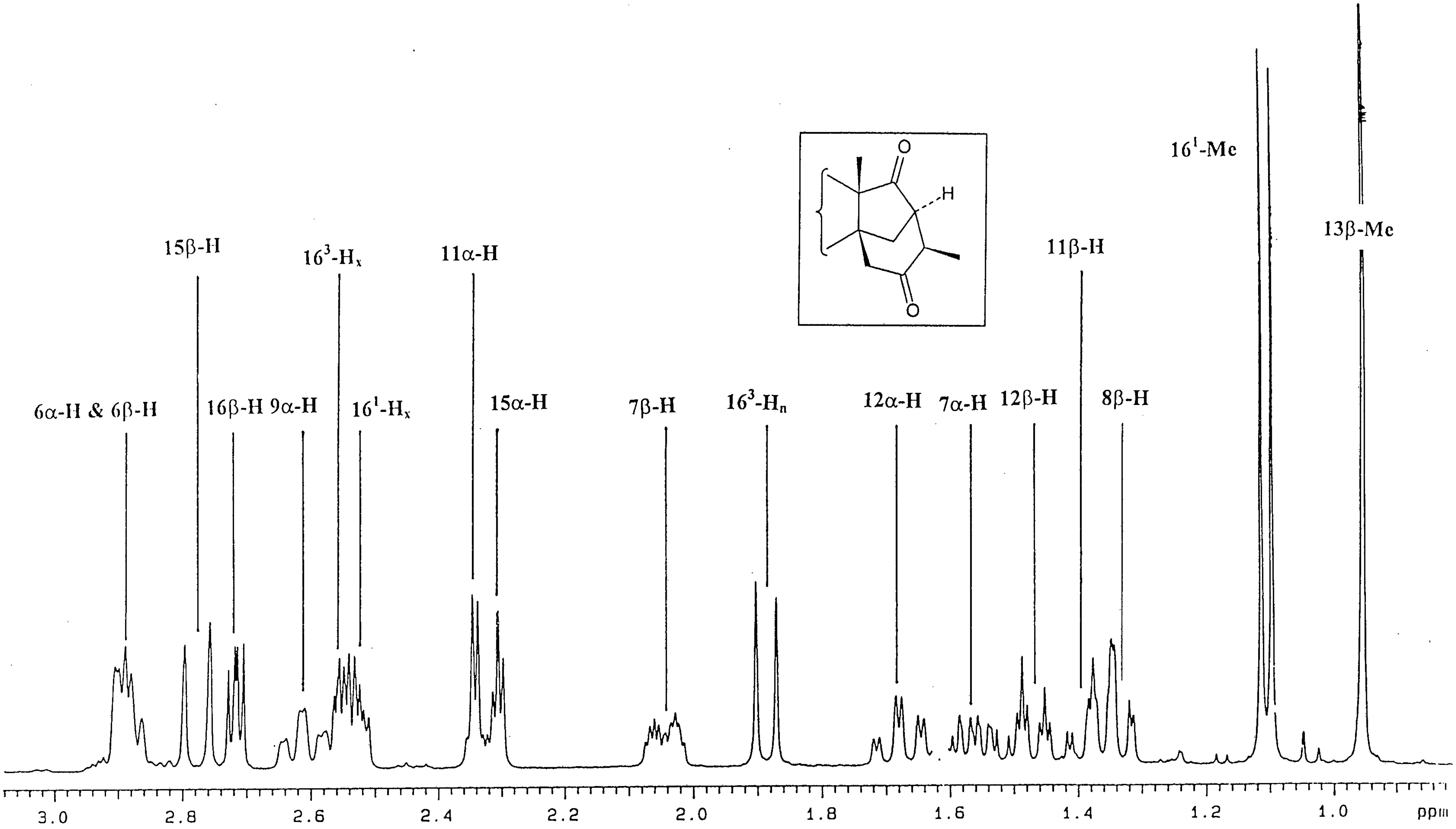


Figure **4.5**
Highfield Region of ^{1}H NMR Spectrum of 16^2,17-Dione **122**

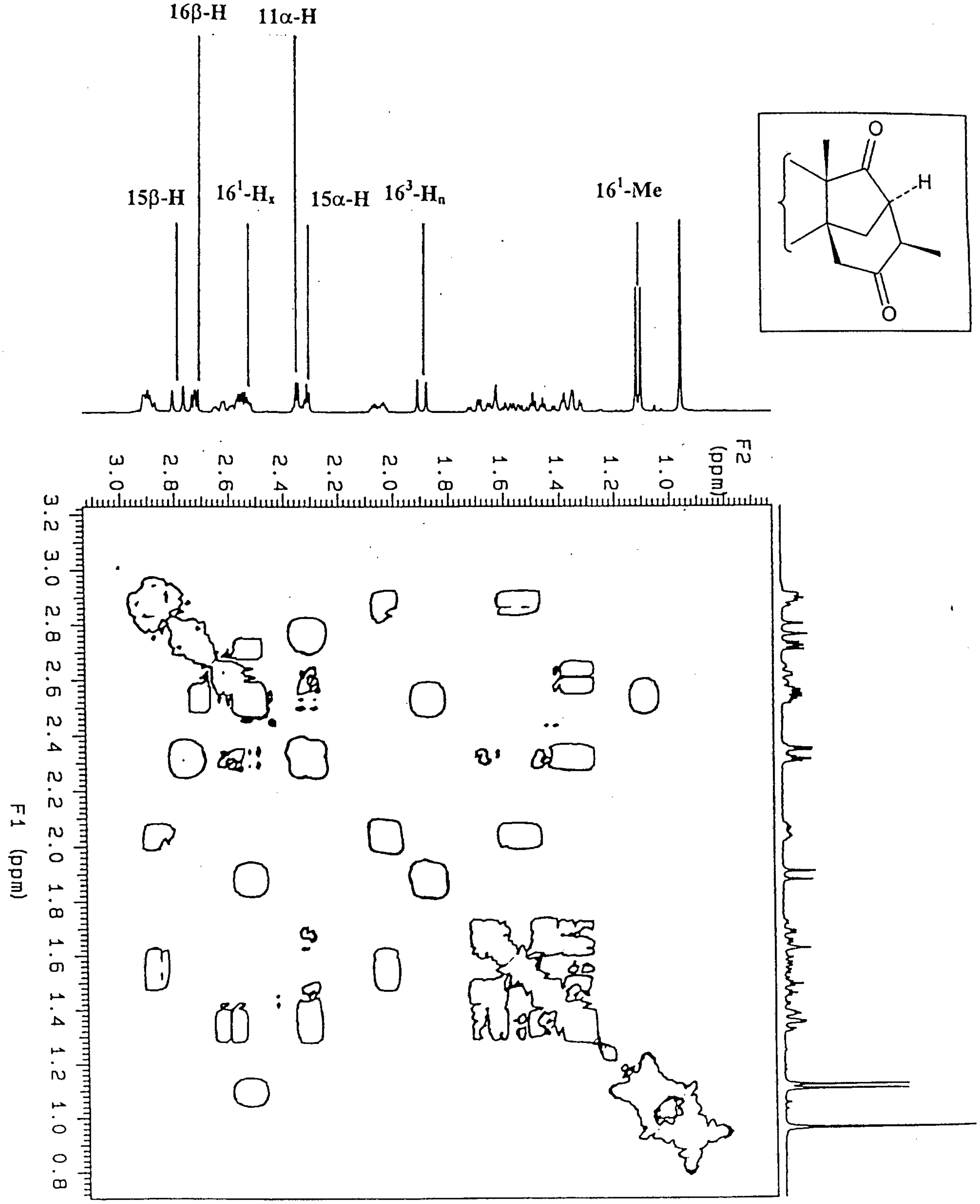


Figure **4.6**
Highfield Region of COSY Spectrum of 16^2,17-Dione **122**

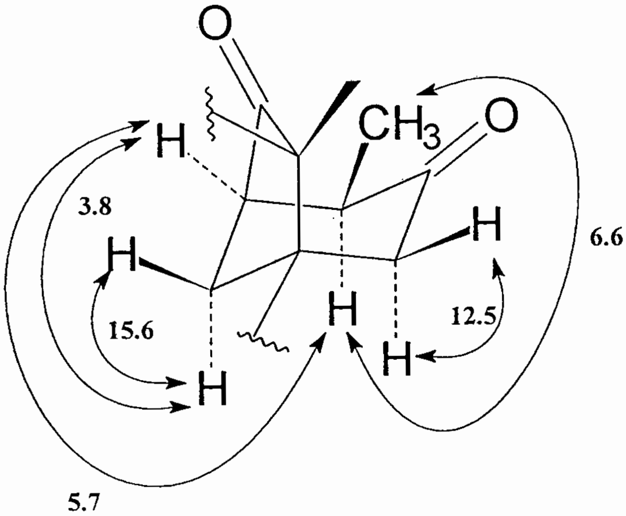
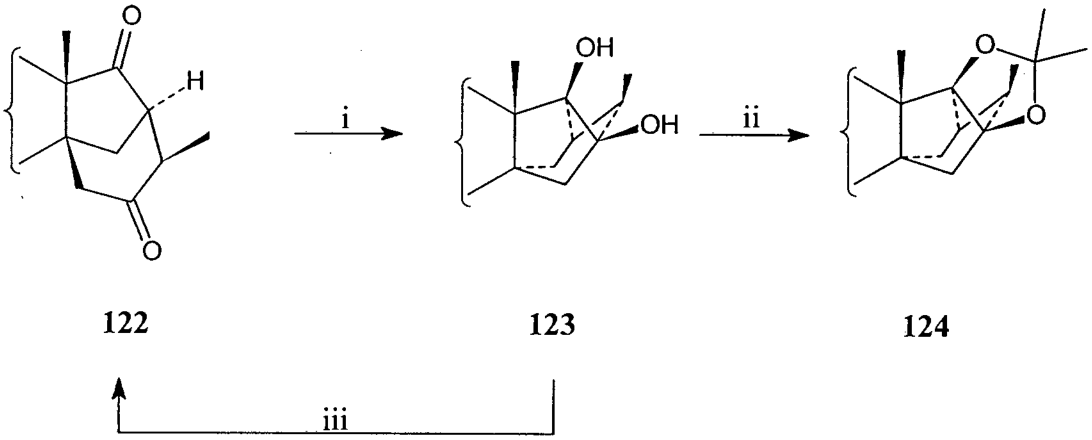


Figure 4.7

Selected Coupling Constants for 16^2,17-Dione **122**

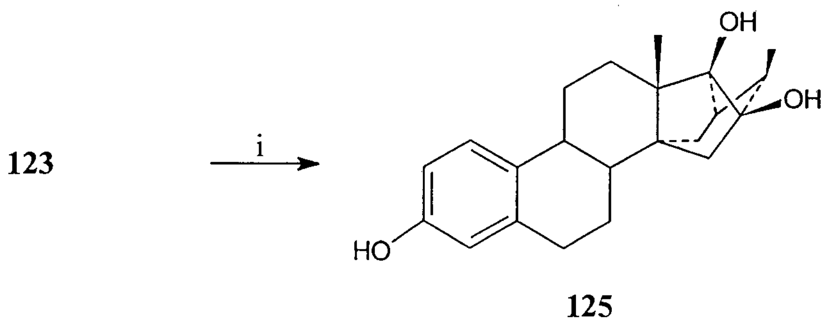
(*J* values in Hz)

Selective irradiation of 16^1-H_X resulted in the enhancement of the resonances assigned 15β-H and 16^3-H_X. These protons are both in 1,3-diaxial relationships with the 16^1-H_X and the experiment served to confirm the assigned stereochemistry at C-16^1. Furthermore this verifies the fact that, as anticipated, the delivery of borane, in the hydroboration-oxidation sequence occurred exclusively from the *exo*-face resulting in the formation of the diol **121**. Treatment of the diketone **122** with samarium(II) iodide in refluxing tetrahydrofuran gave the diol **123** in 78% yield (Scheme 4.9). Overlapping signals precluded a full assignment of the key resonances in the ^{1}H NMR spectrum of the **123**. Nevertheless analytical, IR and ^{13}C NMR data were consistent with the assigned structure. The IR spectrum displayed a characteristic broad band at 3560 cm^{-1} assigned to the hydroxyl absorption. The presence of hydroxyl bearing carbons was confirmed by resonances at δ 74.5 and 93.6 assigned to C-17 and C-16. The absence in the ^{1}H NMR spectrum, of any resonances characteristic of protons α to an hydroxyl group ruled out the simple reduction of the carbonyl groups to the corresponding alcohols. The presence of the vicinal diol moiety was confirmed by cleavage with sodium periodate to give the diketone **122** and by conversion of **123** into the corresponding acetonide **124** (Scheme 4.9).



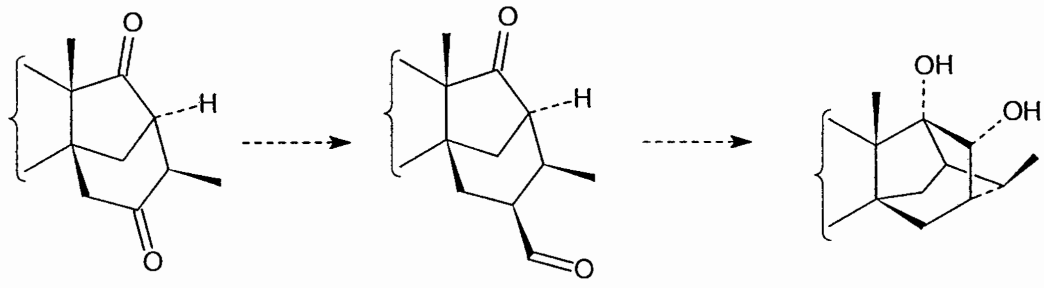
Scheme 4.9 *Reagents and Conditions*: (i) SmI_2; (ii) H_2SO_4, acetone; (iii) $NaIO_4$

In contrast to the diol **112** which was resistant to DIBAH mediated deprotection of the 3-methyl ether, the diol **123** underwent smooth demethylation, in the presence of DIBAH, to yield the triol **125** in 78% yield (Scheme 4.10). Analytical and mass spectral data were consistent with the assigned structure and the product was subjected to biological evaluation.



Scheme 4.10 *Reagents and Conditions:* (i) DIBAH, toluene, Δ

The availability of the diketone **122** suggested that a chemoselective one-carbon homologation at C-16^{2}, leading to the 16^{2}-formyl 17-ketone **A** would provide an additional substrate for intramolecular pinacol coupling to the estriol analogue **B** (Scheme 4.11).

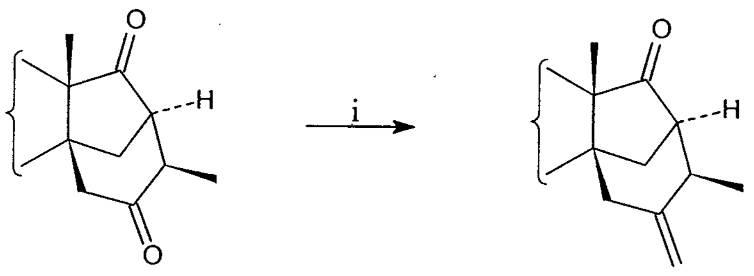


122 **A** **B**

Scheme 4.11

A synthetic plan was devised which relied upon chemoselective methylenation of the 16^{2}-oxo group of **122** followed by stereoselective hydroboration of the resultant olefinic-ketone which after oxidation should yield the 16^{2}-formyl 17-ketone **A** .

Treatment of the diketone **122** with the phosphorane derived from pre-treatment of methyltriphenylphosphonium iodide with t-butyllithium in tetrahydrofuran at 0°C proceeded to give a single product formulated as the 16^{2}-methylene 17-ketone **126** (Scheme 4.12). Mass spectral and micro-analytical data were consistent with mono-methylenation and the chemoselectivity was confirmed by spectroscopic data. In particular the ^{1}H NMR spectrum (selected data summarised in Table 4.2) revealed a long-range allylic coupling between the 16^{2}-methylene protons and 16^{3}-H_X and 16^{1}-H_X. The ^{13}C NMR data were confirmatory revealing a characteristic carbonyl resonance at δ 221.3 assigned to C-17. The chemoselectivity of the process may be attributed to steric impedance associated with approach to C-17 by the 13β-methyl group.



122 **126**

Scheme 4.12 *Reagents and Conditions*: (i) Ph_3PCH_2I, t-BuLi, THF

Treatment of the olefinic ketone **126** with borane-dimethyl sulfide in tetrahydrofuran at 24°C for 3.5 h followed by oxidation with alkaline hydrogen peroxide gave the diol **127** in 78% yield (Scheme 4.13). The regioselectivity of the hydroboration is in line with expectations and was confirmed by the presence, in the ^{1}H NMR spectrum of the product, a 2 proton multiplet at δ 3.54-3.63 assigned to the 16^2-hydroxymethyl protons. The configurational assignment at C-16^2 is based on an examination of molecular models which suggest that reagent approach from the *endo*-face is severely restricted by the 14,17β-ethano bridge and the appended 13β-methyl group. By contrast approach from the *exo*-face is unimpeded and was expected to be favoured (Figure 4.8). While the ^{1}H NMR spectrum of **127** revealed no direct evidence in support of the assigned configuration at C-16^2 the stereoselectivity of the process was confirmed by the subsequent reactivity of the derived 16^2-formyl 17-ketone **128**.

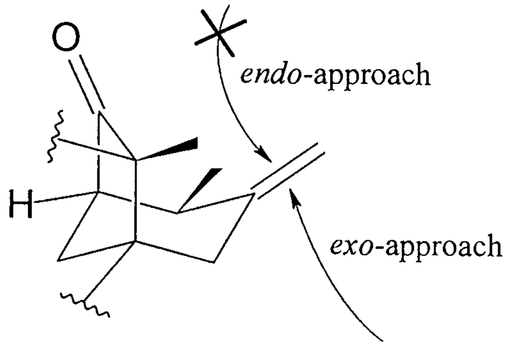
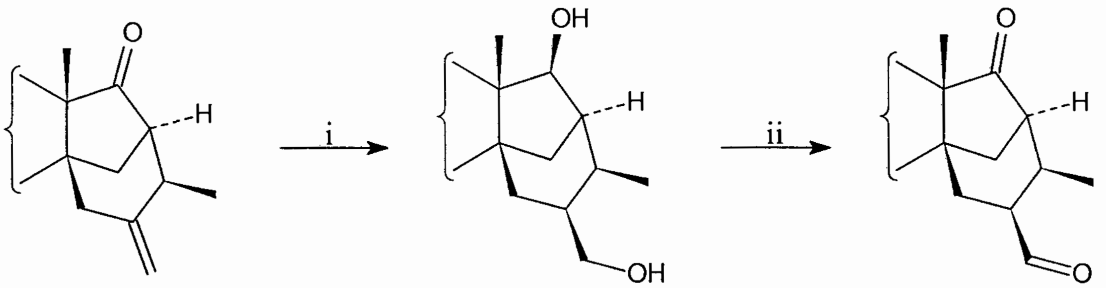


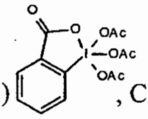
Figure 4.8

Expected Stereoselectivity for Hydroboration of the 16^2-Methylene-17-ketone **126**

Dess Martin oxidation of **127** proceeded at 24°C in dichloromethane to give the 16^2-formyl 17-ketone **128** in 96% yield with analytical and spectroscopic data consistent with the assigned structure (Scheme 4.13). The configurational assignment at C-16^2 was confirmed by examination of the ^{1}H NMR data (Table 4.2). While the signal for the 16^2-H_x was obscured by the multiplet assigned to 6α-H and 6β-H, the resonance assigned to 16α-H resonated at δ 2.67. The signal was split by two vicinal couplings (*J* 2x5.8 Hz) to 15α-H and 16^1-H_x and a four bond W-coupling to 16^2-H_x. This long-range coupling can only be accommodated if the 16^2-formyl group is orientated *endo* (Figure 4.9).



126 **127** **128**

Scheme 4.13 *Reagents and Conditions*: (i) BH_3-Me_2S then H_2O_2, NaOH; (ii) 

, CH_2Cl_2

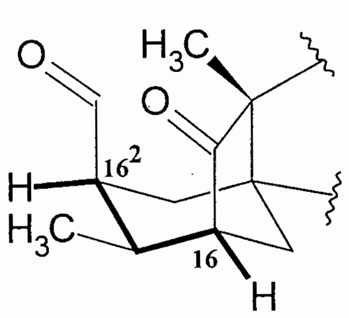


Figure 4.9

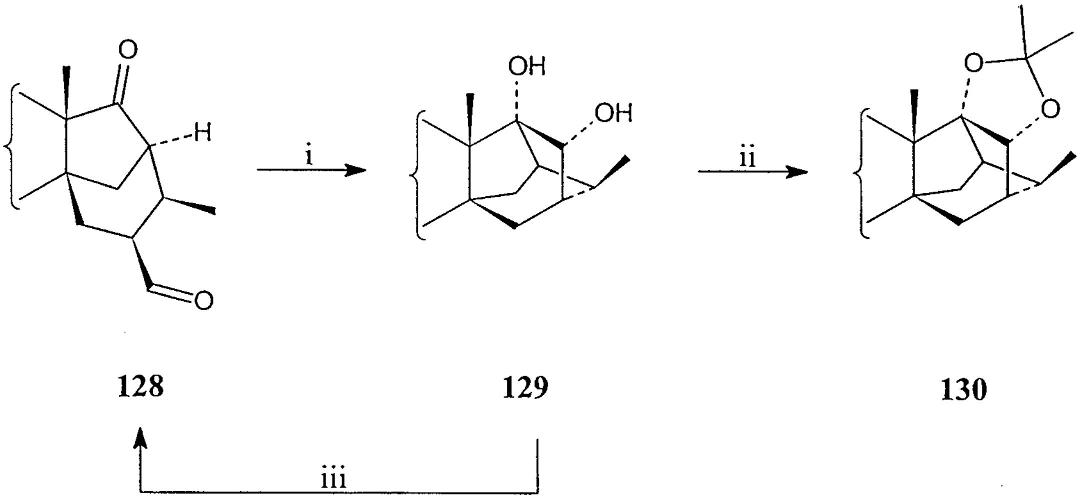
Origin of Diagnostic W-coupling in 16^2-Formyl-17-ketone **128**

Table 4.2 Selected ^{1}H NMR data* for **126** and **128**

Proton	**126**	**128**
15α-H	2.51, dd, 15.4 & 3.9	2.31, ddd, 12.7, 5.58 & 2.7
15β-H	2.12, d, 15.4	1.62, d, 12.7
16α-H	2.63, dd, 6.1 & 3.9	2.67, ddd, 2x5.8 & 2.1
16^1-Me$_n$	1.23, d, 6.8	1.27, d, 6.7
16^3-H$_x$	2.37, dd, 19.1 & 1.5	2.21, dd, 17.2 & 6.5
16^3-H$_n$	1.98, d, 19.1	2.04, ddd, 17.2, 5.8 & 2.7
16^2=CH$_2$	4.75, m	—
16^2-CHO$_n$	—	9.73, d, 1.9
16^2-H$_x$	—	2.91 (obscured m)

* Data reported as chemical shift (ppm), multiplicity and *J* values (Hz)

The 16^2-formyl 17-ketone **128** underwent efficient intramolecular pinacol coupling mediated by samarium(II) iodide in refluxing tetrahydrofuran to give the diol **129** (Scheme 4.14). The presence of the vicinal diol moiety was confirmed by conversion of **129** into the corresponding acetonide **130**. In addition the diol underwent efficient oxidative cleavage mediated by sodium periodate in ethanol to give the starting 16^2-formyl 17-ketone **128**. The ^{1}H NMR spectrum of **129** displayed a doublet at δ 4.17 assigned to 17β-H (*J* 6.36 Hz), the coupling magnitude and multiplicity appropriate for one synclinal neighbour.



128 **129** **130**

Scheme 4.14 *Reagents and Conditions*: (i) SmI$_2$, THF; (ii) acetone, H$_2$SO$_4$; (iii) NaIO$_4$, EtOH

The stereochemical outcome of the intramolecular reductive coupling is rationalised in terms of approach of the 16^2-formyl group which presents the *si*-face to the 17-oxo group. This preferred approach is favoured in that it relieves the sterically unfavourable interaction between the 16^2-formyl oxo and 13β-methyl groups in the less-favoured orientation in which the *re*-face of the formyl group is presented to the 17-oxo moiety (Figure 4.10). These results are consistent with those reported for the analogous pinacol coupling of the 14β-formylethyl 17-ketone **131** leading to **132** (53%) and **133** (4%) (Scheme 4.15).[19]

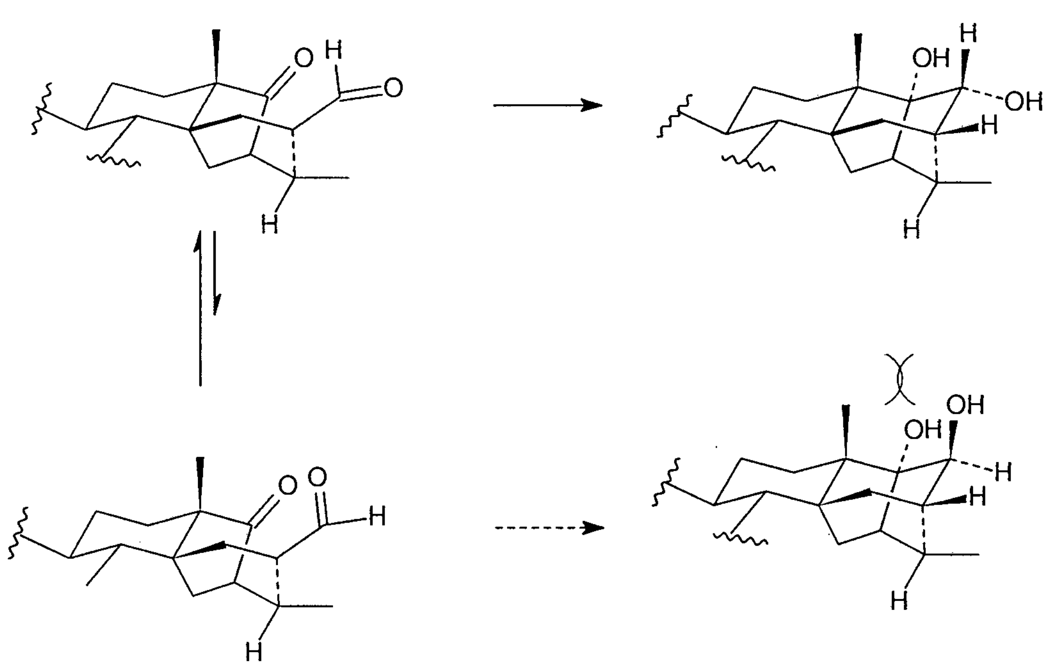
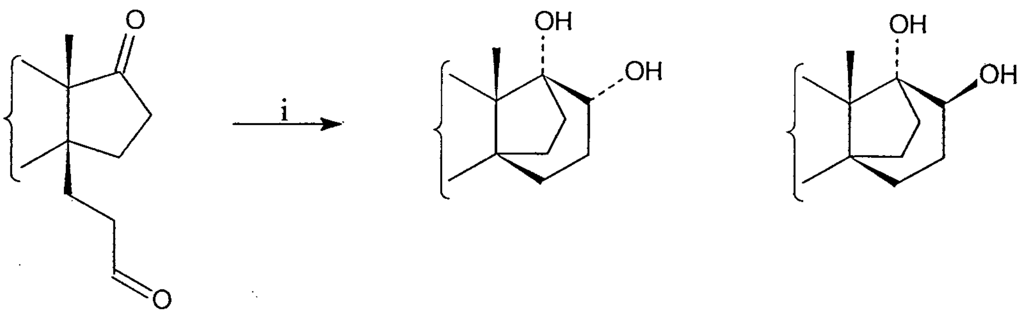


Figure 4.6

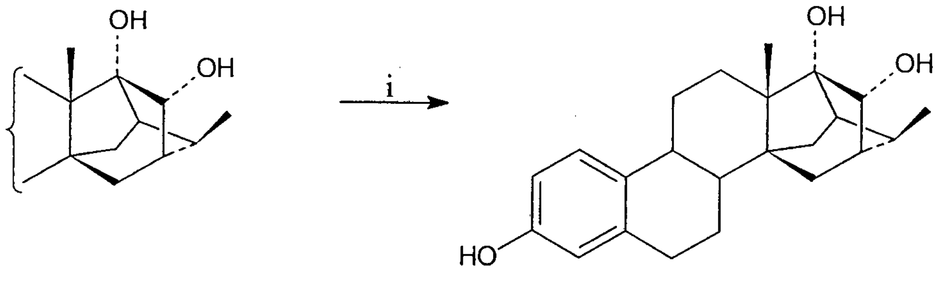
Influence of Rotameric Preference at C-16^2 upon the Stereoselctivity of the Reductive Coupling of the Dioxo-compound **128**



131 **132** **133**

Scheme 4.15 *Reagents and Conditions:* (i) $TiCl_3 \cdot DME_{1.5}$, Zn-Cu, DME, 20°C

The diol **129** underwent deprotection at C-3 upon treatment with DIBAH in refluxing toluene to give the triol **134** (Scheme 4.16).



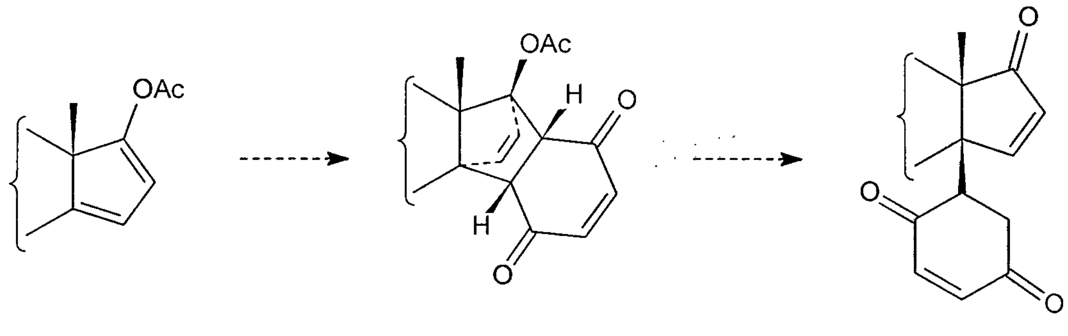
129 **134**

Scheme 4.16 *Reagents and Conditions:* (i) DIBAH, toluene, Δ

CHAPTER 5

Approaches to the Synthesis of 14β-2',5'-Dioxocyclohexanyl Δ^{15}-17-Ketones

In Chapter 2 it was demonstrated that the 14β-3'-oxobutyl Δ^{15}-17-ketone **34** served as a substrate for intramolecular Michael reaction to yield, after functional group modification, the perhydro-15αH-benzo[14,15]-estradiols **57** and **58**. As an extension of this work, with the aim of generating more elaborate 14β,15β-fused ring compounds, approaches to the synthesis of the 14β-2',5'-dioxocyclohexanyl Δ^{15}-17-ketone **B** were investigated (Scheme 5.1). This species incorporates the structural motif of the 14β-3'-oxobutyl-Δ^{15}-17-ketone in a more elaborate functionalised ring option and it's synthesis was of interest to serve as an intermediate for the investigation of secondary intramolecular reactions. It was expected that a cycloadduct **A** derived from the reaction of the dienyl acetate **10** with *p*-benzoquinone would provide an intermediate for retroaldol fragmentation similar to that of the methyl vinyl ketone cycloadduct **32**.



10 **A** **B**

Scheme 5.1

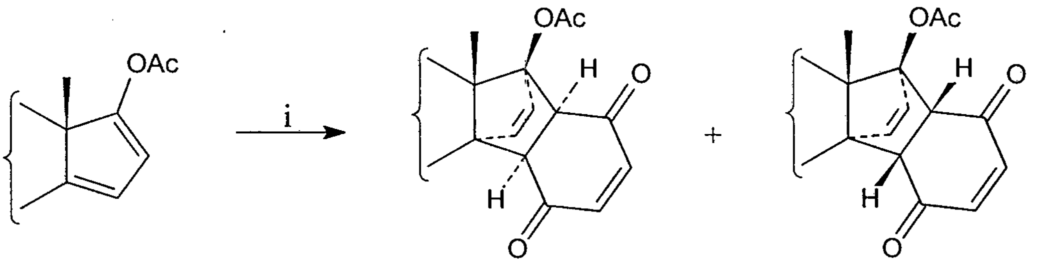
The cycloaddition between the dienyl acetate **10** and *p*-benzoquinone was conducted in dry toluene at 0°C in the presence of boron trifluoride diethyl ether complex to give after 30 min. a two-component mixture of products. The products were readily separated and assigned as the *exo*- and *endo*-cycloadducts **137** (7%) and **138** (72%) respectively (Scheme 5.2). The structural assignments followed directly from analytical and spectral data. Selected ^{1}H NMR data for **137** and **138** are summarised in Table 5.1. The assignment of the signals for the 15- and 16-protons is based on the expected influence of the 17-acetoxy group on their relative chemical shifts. The 16-protons are in a relatively more electron rich environment when compared to the 15-protons and are thus expected to resonate downfield from these protons.

The full assignment of the signals in **137** was restricted by the coincidental chemical shift equivalence of the signals for 17^1-H and 17^2-H and for 4'-H and 5'-H. The signal for the former AB pair was assigned to the two proton singlet at δ 6.12 while that of the latter appeared as a two proton singlet at δ 6.64. In order to separate these signals the ^{1}H NMR spectrum was recorded in deuteriobenzene and gratifyingly the signals for the protons in question displayed a greater dispersion. Thus 17^1-H and 17^2-H resonated as a set of doublets (*J* 5.8 Hz) at δ 5.64 and 5.81 while 4'-H and 5'-H also resonated as a set of doublets (*J* 10.3 Hz) at δ 5.93 and 6.02.

Table 5.1 Selected ^{1}H NMR Data* for **137** and **138**

Proton	**137** ($CDCl_3$)	**137** (C_6D_6)	**138** ($CDCl_3$)
15-H	3.86	3.08	3.38
	1H, d, 8.2	1H, d, 8.4	1H, d, 8.1
16-H	4.39	4.16	3.65
	1H, d, 8.2	1H, d, 8.4	1H, d, 8.1
17^1-H & 17^2-H	6.12	5.64 and 5.81	6.04 and 6.42
	2H, s	each 1H, d, 5.8	each 1H, d, 6.1
4'-H & 5'-H	6.64	5.93 and 6.02	6.57 and 6.63
	2H, s	each 1H, d, 10.3	each 1H, d, 10.3

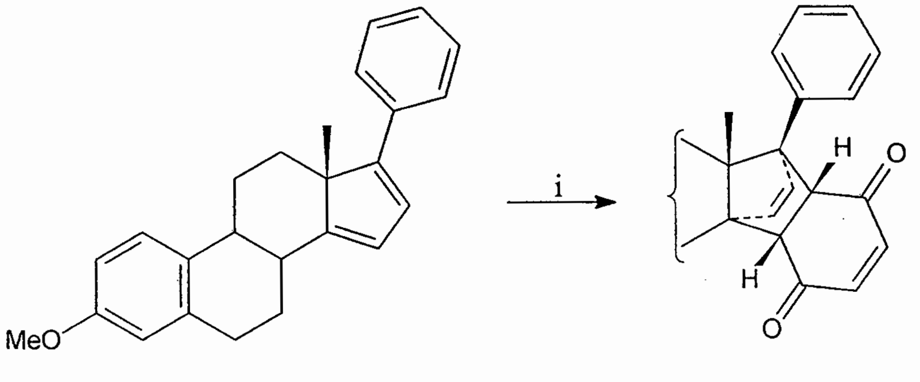
* Data reported as chemical shift (in ppm), integration, multiplicity and J values (in Hz)



10 **137** **138**

Scheme 5.2 *Reagents and Conditions*: (i) *p*-benzoquinone, BF$_3$-OEt$_2$, toluene, 0°C

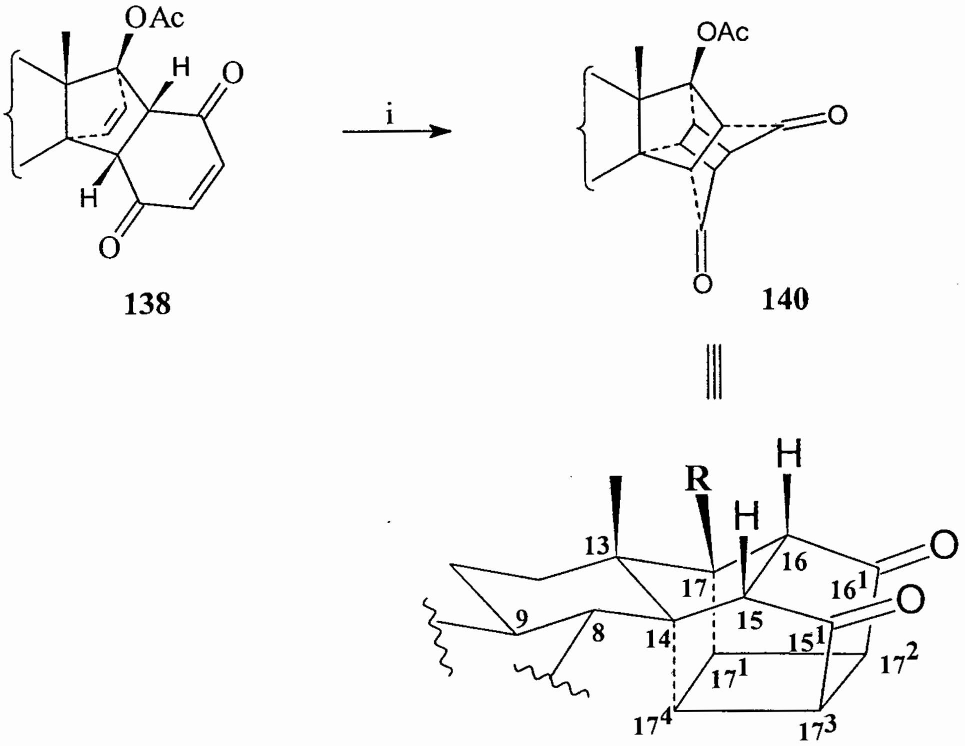
The data presented above, while consistent with the structural assignments, do not confirm the stereoselectivity of the cycloaddition. The symmetrical nature of the dienophile dictates that only four isomers are possible arising from *exo*- and *endo*-addition to the α- and β-face of the diene. On the basis of the well documented β-face selective addition of dienophiles to steroidal 14,16-dienes (see Chapter 1) it can be confidently assumed that the α-face adducts may be excluded. In addition Winterfeldt *et al.*[108] have demonstrated that the cycloaddition of *p*-benzoquinone to the analogous steroidal 14,16-diene **23** occurs *via* exclusive β-face addition to give the cycloadduct **139** (Scheme 5.3). It is well documented [109, 110] that the reaction between *p*-benzoquinone and cyclopentadiene gives rise to the *cis-endo* cycloadduct and the assignment of the structure of the major product **138** is thus based on β-face *endo*-addition of *p*-benzoquinone to the dienyl acetate **10**. The stereochemistry of the major cycloadduct **138** was confirmed by it's subsequent photoreactivity. Assuming β-face addition, the only possible structure for the minor product **137** must be that arising from *exo*-addition of the dienophile.



23 **139**

Scheme 5.3 *Reagents and Conditions*: (i) *p*-benzoquinone, CH_2Cl_2, 6.5 kbar

It was discovered that the major cycloadduct **138** is unstable and readily underwent intramolecular [2+2] cycloaddition in the presence of sunlight to give the steroidal caged-dione **140** in quantitative yield (Scheme 5.4). By contrast the minor cycloadduct **137** did not undergo photochemically mediated intramolecular reaction confirming the foregoing configurational assignment of the two cycloaddition products. The intramolecular [2+2] cycloaddition of adducts of *p*-benzoquinone and cyclopentadiene is well documented in the literature with the first reports of this work published by Cookson *et al.*[111] The expected absence of olefinic proton signals in the ^{1}H NMR spectrum of **140** was accompanied by the appearance of resonances characteristic of cyclobutanoid protons in pentacyclo[5.4.0.0^{2,6}.0^{8,9}]undecan-8,11-diones[112, 113] in the upfield region of the spectrum. The 15β-H resonated at δ 3.10 with a large vicinal coupling (*J* 10.3 Hz) to the 16β-H and two smaller long-range W-couplings (*J* 2.4 Hz) to 17^3-H and 17^4-H. Similarly 16β-H resonated at δ 3.21 with large vicinal coupling (*J* 10.3 Hz) and two smaller long-range W-couplings (*J* 2.6 Hz) to 17^1-H and 17^2-H. A complex multiplet centred at δ 3.44 and integrating for three protons was assigned to the resonances associated with 17^1-H, 17^2-H and 17^3-H. The remaining cyclobutane proton, 17^4-H, resonated as a multiplet at δ 2.98.



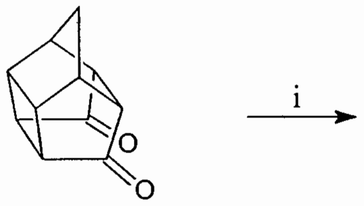
138

140

Scheme 5.4 *Reagents and Conditions*: (i) hv, CH_2Cl_2

It was recognised that deoxygenation of the caged dione **140** at C-15^1 and C-16^1 would provide a ring D caged estradiol analogue. This compound would further extend the understanding of the influence of α-face congestion on the biological activity in this series of strained ring D caged analogues of estriol and estradiol.

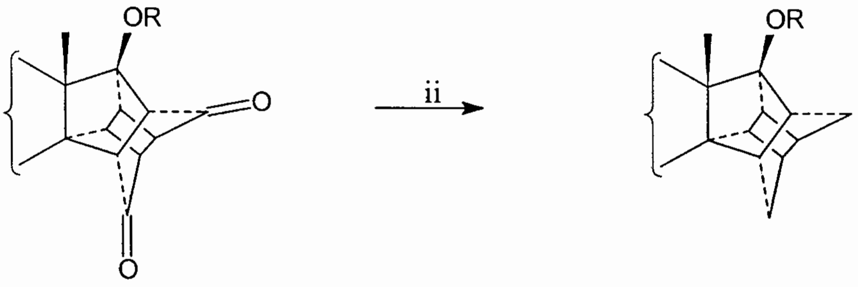
Marchand and Allen[114] have reported the three step synthesis of the caged hydrocarbon **142** from cyclopentadiene and *p*-benzoquinone (Scheme 5.5). The final step in the synthesis involved Wolff-Kishner reduction of the pentacyclo[5.4.0.0^{2,6}.0^{5,9}]undecan-8,11-dione **141** to yield the hydrocarbon **142** in 59% yield.



141 **142**

Scheme 5.5 *Reagents and Conditions*: N_2H_2, NaOH, Δ

It was expected that the ring D caged dione **140** was amenable to a similar deoxygenation process. To this end the 17-acetate **140** was treated with potassium carbonate in ethanol at 5°C for 6 h to give the $15^1,16^1$-dioxo-17-alcohol **143** in 81 % yield. Treatment of **143** with hydrazine hydrate in diethylene glycol for 12 h at 24°C followed by heating of the mixture in the presence of potassium hydroxide for 2 h gave the ring D caged 17-alcohol **144** in 78 % yield (Scheme 5.6) with analytical and spectroscopic data consistent with the assigned structure. The insolubility of the product in common organic solvents precluded an examination of it's NMR properties. Consequently the alcohol **144** was converted into the 17-acetate **145** under standard conditions. The 400 MHz ^1H NMR spectrum displayed a 4 proton multiplet at δ 2.65 to 2.83 characteristic of resonances associated with the cyclobutane protons in pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanes.[112] The ^{13}C data were consistent with the assigned structure.

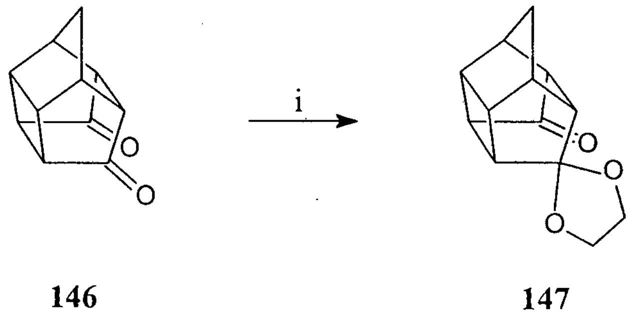


i: **140** R = Ac → **143** R = H

iii: **144** R = H → **145** R = Ac

Scheme 5.6 *Reagents and Conditions*: (i) K_2CO_3, ethanol; (ii) N_2H_2, NaOH, diethylene glycol; (iii) acetic anhydride, pyridine, DMAP

An alternative deoxygenation strategy was explored based upon a dithioacetalisation-desulfurisation sequence. It was expected that bis-dithioacetalisation of the dione **140** would not be readily achieved given the severe steric constraints which obtain after the initial dithioacetalisation step. Furthermore Eaton *et al.*[115] have demonstrated that treatment of pentacyclo[5.4.0.$0^{2,6}$.$0^{5,9}$]undecan-8,11-dione **146** with ethylene glycol in the presence of *p*-toluenesulfonic acid in refluxing benzene for 5 h yields only the monoacetal **147** (87%) (Scheme 5.7) and no evidence of the bis-acetal was detected.

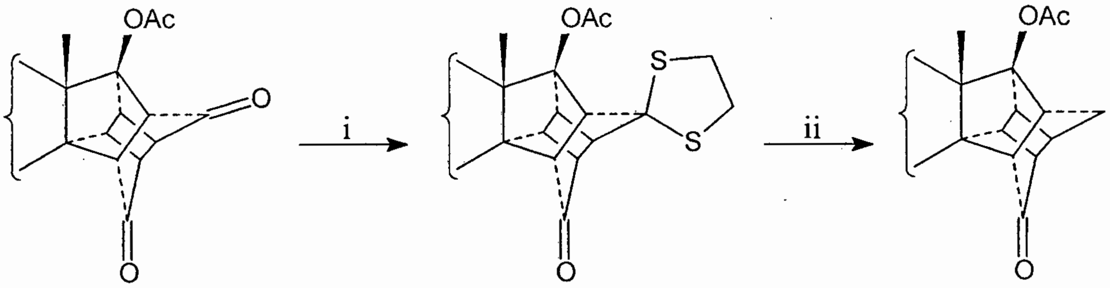


Scheme 5.7 *Reagents and Conditions*: $(CH_2OH)_2$, TsOH, benzene, Δ

It thus stood to reason that dithioacetalisation followed by desulfurisation should lead to a 17-acetoxy-ketone which could be subjected to a second dithioacetalisation-desulfurisation sequence leading to a ring D caged-17-acetate which upon deprotection at C-17 would provide the previously synthesised alcohol **144**.

Treatment of **140** with ethanedithiol in the presence of catalytic boron-trifluoride diethyl ether complex at 0°C for 1h proceeded uneventfully to give the thioacetal **148** in 86 % yield (Scheme 5.8). Mass spectral and microanalytical data were consistent with monothioacetalisation. The IR spectrum of the compound displayed characteristic resonances at 1676 and 1727 cm^{-1} assigned to the 15^1- and 17-acetoxy-carbonyl absorption bands respectively. The ^1H NMR spectrum of the product displayed the characteristic 4 proton multiplet centred at δ 3.25 assigned to the thioacetal protons. The 15β-H resonated at 3.40 ppm. The ^{13}C NMR spectrum revealed two carbonyl carbon resonances at δ 170.2 and 217.6 assigned to the 17-acetoxy and C-15^1 oxo groups

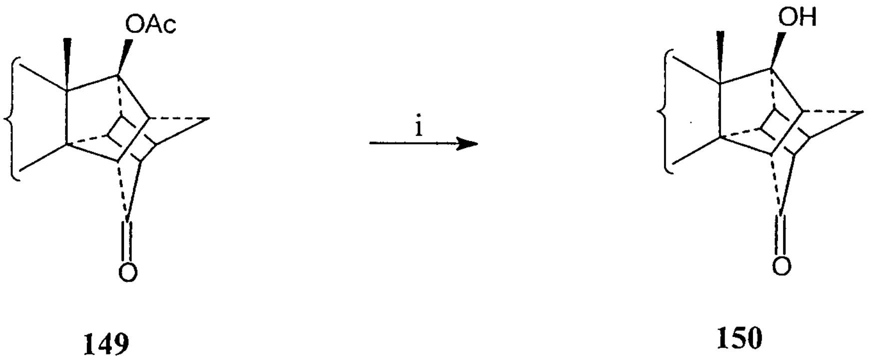
The dithioacetal **148** underwent desulfurisation in the presence of Raney nickel in refluxing ethanol to give, after 3 h, the 15^1-oxo-17-acetate **149** in 91 % yield (Scheme 5.8). ^{13}C and ^1H NMR data were in agreement with the gross structural assignment. The ^{13}C NMR spectrum displayed a resonance at δ 212.8, assigned to C-15^1. The ^1H NMR spectrum revealed a 4 proton multiplet at δ 3.17-3.29 characteristic of and assigned to 17^1-H, 17^2-H, 17^3-H and 17^4-H. The chemical shift value is consistent with data reported in the literature for four-membered ring protons of pentacyclo[$5.4.0.0^{2,6}.0^{3,10}.0^{5,9}$]undecanes. The 15β-H resonated at δ 3.59. IR data supported the structural assignment with resonances at 1678 and 1728 cm^{-1} assigned to the carbonyl absorption bands.



140 **148** **149**

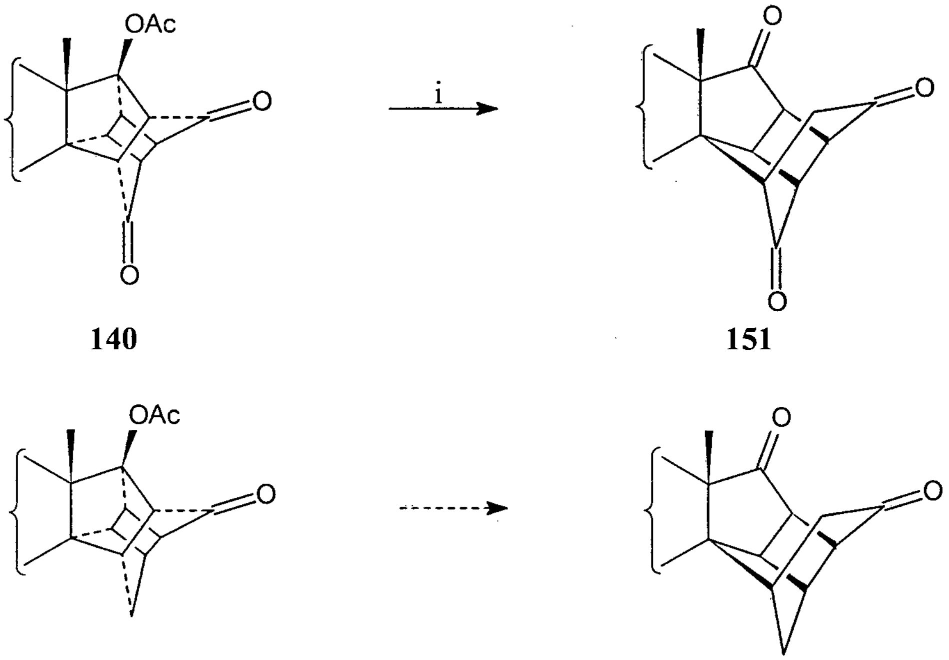
Scheme 5.8 *Reagents and Conditions*: (i) $(SHCH_2)_2$, BF_3-OEt_2; (ii) Raney Ni, ethanol, Δ

The spectroscopic data did not provide an indication as to the chemoselectivity of the process and secondary evidence in support of the assigned structure was sought. To this end the 17-acetoxy-15^1-ketone **149** was treated with methanolic potassium hydroxide first at 24°C then in refluxing methanol and gave the 17-hydroxy 15^1-ketone **150** as the sole product (Scheme 5.9). Analytical data clearly indicated that hydrolysis had occurred and this was confirmed by a broad resonance at 3547 cm^{-1}, assigned to the 17-hydroxy absorption band, in the IR spectrum of the product. ^{13}C NMR data were consistent with the assigned structure with resonances at δ 86.7, assigned to C-17, and at δ 214.4, assigned to C-15^1.



Scheme 5.9 *Reagents and Conditions*: (i) KOH, MeOH

It was expected that had the chemoselectivity of the thioacetalisation-desulfurisation sequence been different to that indicated in Scheme 5.9, the alternate 17-acetoxy-16^1-ketone **A** would be expected to undergo retroaldol fragmentation to yield the diketone **B** (Scheme 5.10). This expectation is based upon the successful retroaldol fragmentation of the primary [2+2] cycloadduct **140**. Treatment of **140** with methanolic potassium hydroxide for 6 h at 24°C proceeded to give the triketone **151** (Scheme 5.10). The assigned structure was readily confirmed by characteristic ^{13}C NMR data. In particular three distinct signals at δ 204, 209 and 221 ppm clearly indicate the presence of three carbonyl carbons in accordance with expectations. The failure of **149** to undergo any reaction, except simple hydrolysis, indicates that the chemoselectivity of the dithioacetalistion step is such as to invoke reagent attack at C-16^1, leading to **148**.

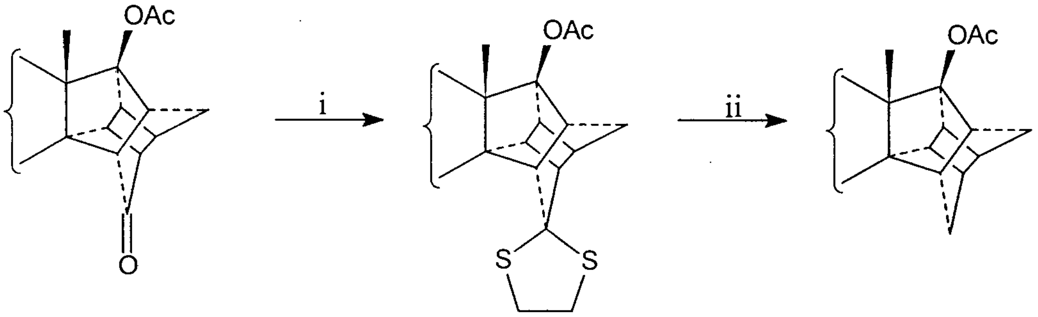


140 **151**

A **B**

Scheme 5.10 *Reagents and Conditions*: KOH, MeOH

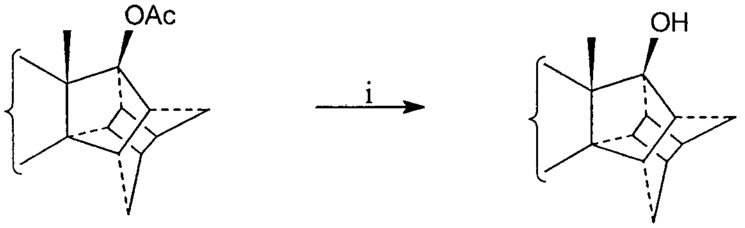
The 17-acetoxy-15^1-ketone **149** was subjected to second dithioacetalisation-desulfurisation sequence which proceeded uneventfully to give **145** with analytical and spectroscopic data consistent with that of the product derived from Wolff-Kishner deoxygenation of the hydroxy-dione **143** (Scheme 5.11)



149 **152** **145**

Scheme 5.11 *Reagents and Conditions*: (i) $(SHCH_2)_2$, BF_3-OEt_2; (ii) Raney Ni, ethanol, Δ

Treatment of **145** with potassium carbonate in ethanol at 24°C for 5h resulted in deprotection at C-17 to give the 17-alcohol **144**. Treatment of the 3-methoxy-17-alcohol **144** with DIBAH in refluxing toluene for 57 h gave $17^1,17^4$-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butano-estra-1,3,5(10)-triene-3,17β-diol **153** in 86% yield (Scheme 5.12). The compound was subjected to biological evaluation.



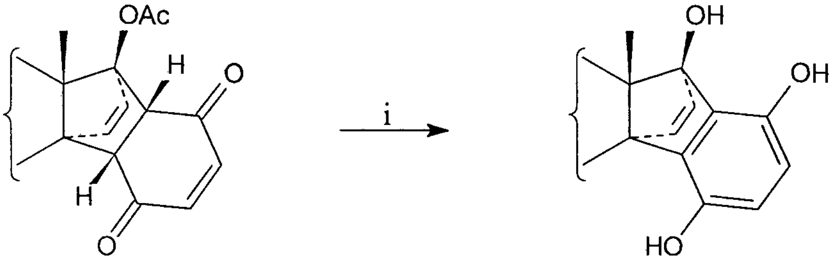
145

144 3-OMe

153 3-OH

Scheme 5.12 *Reagents and Conditions*: (i) K_2CO_3, EtOH; (ii) DIBAH, toluene, Δ

The successful retroaldol fragmentation of the caged-dione **140** encouraged the expectation that the cycloadduct **138** or a suitable derivative thereof, would undergo fragmentation to give the desired 14β-2',5'-dioxocyclohexanyl Δ^{15}-17-ketone. To this end the cycloadduct **138** was treated with methanolic potassium hydroxide (1 M) at 0° C and gave after 30 min a product formulated as 3-methoxybenzo[15,16]-14α,17α-ethenoestra-1,3,5(10)-triene-3',6',17β-triol **154** in 76% yield (Scheme 5.13).



138

154

Scheme 5.13 *Reagents and Conditions*: (i) KOH in MeOH, 0°C

Analytical and spectroscopic data fully supported the assigned structure. An examination of the ^{13}C NMR data revealed 7 resonances in the high-field region (0 - 50 ppm) of the spectrum assigned to C-6, C-7, C-8, C-9, C-11, C-12 and C-18. The absence of additional resonances associated with ring-D and the [15,16]-fused ring indicated that aromatisation had occurred. The low-field region of the ^{13}C NMR spectrum displayed the usual resonances for the aromatic ring A carbons plus additional resonances associated with the new aromatic ring. Resonances at δ 144. 3 and 146.5 (each s) are characteristic of phenolic carbons[116] and were assigned to C-3' and C-6'. Singlets at δ 133.7 and 135.2 were assigned to C-15 and C-16 while doublets at δ 140.3 and 140.5 were assigned to C-4' and C-5'. The ^{1}H NMR data served to confirm the structural assignment. The highfield region of the ^{1}H NMR spectrum of **154** (Figure 5.1) was striking in that it revealed a well dispersed set of signals for all the protons associated with ring B and ring C. An analysis of the spectrum allowed for the full assignment of all the chemical shift and coupling constants of these protons (Table 4.2). The low-field region of the ^{1}H NMR spectrum displayed the requisite signals for the 14α,17α-etheno bridge at δ 6.50 and 6.56 (*J* 8.7 Hz). In addition a four proton multiplet at δ 6.76-6.82 was assigned to 2-H, 4-H, 4'-H and 5'-H. It is of interest to note the significant downfield shift of the resonance assigned to 7β-H from δ 2.10 - 2.20, the typical range for 14β-alkyl steroids[35], to δ 3.27. This shift may be ascribed to the influence of the proximate 6'-hydroxyl group which exerts a through-space electronic influence on 7β-H.

Table 4.2 ^{1}H NMR Data* for Ring B and Ring C Protons for **154**

Proton	δ	**Multiplicity**	*J*
6α	2.96	ddd	16.6, 5.3 and 2.9
6β	3.16	ddd	16.6, 11.3 and 5.6
7β	3.27	dddd	12.3, 5.6, 2 x 2.9
7α	1.88	dddd	12.3, 11.3, 10.7 and 5.3
8β	2.16	ddd	10.7, 10.2 and 2.3
9α	2.62	ddd	13.1, 10.2 and 3.6
11α	2.31	dddd	13.1, 3 x 3.6
11β	1.48	dddd	2 x 13.1, 12.6 and 3.6
12α	2.44	ddd	2 x 12.6 and 3.6
12β	1.58	ddd	12.6 and 2 x 3.6

* δ values in ppm and *J* values in Hz

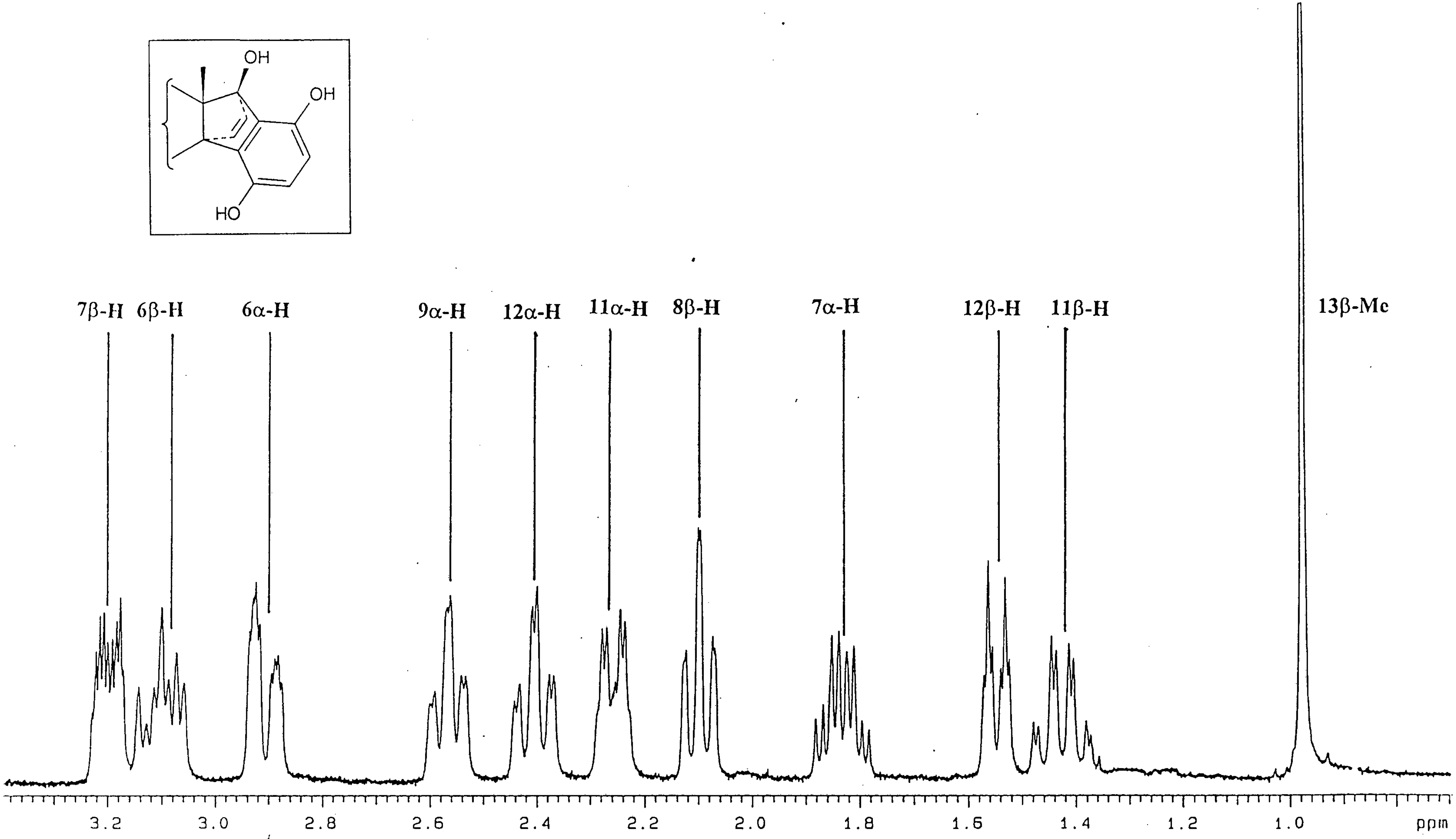
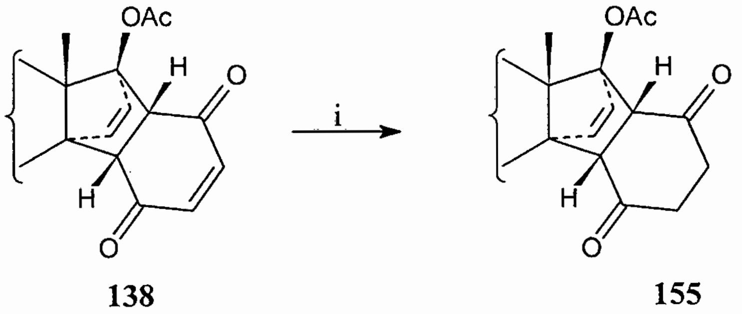


Figure **5.1**
Highfield Region of ^{1}H NMR Spectrum of **154**

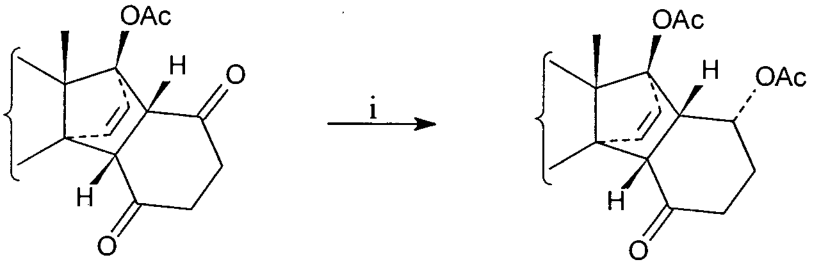
The aromatisation of the cycloadduct **138** under these conditions is not surprising given the facility with which the analogous adduct derived from cycloaddition of *p*-benzoquinone and cyclopentadiene undergoes aromatisation under both basic and acidic conditions.[117, 118] It is facilitated by the presence of the 4'-olefinic bond and an investigation into the scope for retroaldol fragmentation of the derived dihydro-cycloadduct was undertaken. Molecular models of the cycloadduct **138** indicated that the olefinic bond of the cyclohexen-dione moiety is more accessible than that of the 14α,17α-etheno bridge and should be amenable to selective reduction. The cycloadduct **138** was hydrogenated at 24°C in ethyl acetate in the presence of catalytic palladium on carbon to give after 2.5 h the dihydro-cycloadduct **155** arising from selective hydrogenation of the 4'-olefinic bond with analytical and spectroscopic data consistent with the assigned structure (Scheme 5.14). Treatment of **155** with potassium hydroxide in methanol at varying temperatures (0°C, 24°C and reflux) resulted in each instance in the formation of complex mixtures of products and it was not envisaged that this approach was suited to achieving the desired synthetic target.



Scheme 5.14 *Reagents and Conditions*: (i) H_2, Pd on C, EtOAc

From the foregoing discussion it may be concluded that 14β-2',5'-dioxocyclohexanyl Δ^{15}-17-ketones are not directly accessible *via* retroaldol fragmentation of the *p*-benzoquinone cycloadduct **138** or the derived dihydro compound **155** and an alternative synthetic plan was proposed which involved chemoselective differentiation of the two-carbonyl moieties of **155**. It was envisaged that if the chemoselective reduction of one of the carbonyl moieties could be achieved, there was scope for exploiting the remaining functionality with the aim of producing a suitable fragmentation precursor. The approach is based on hydride mediated reduction of the diketone **155** and L-Selectride was chosen as the hydride source given that its steric bulk should enhance the chemoselectivity of the process.

Treatment of the 3',5'-dioxo-17-acetate **155** with L-Selectride in dry toluene at -78°C for 3 h gave a 1:1 mixture of two compounds which proved difficult to separate and handle. It soon became evident that even after partial separation of the mixture, the individual components readily interconverted in solution giving once again the original two component mixture. A possible explanation for the formation of this interconvertible two component mixture is that *trans* esterification[119] was occurring catalysed by traces of acid or base. The intramolecular *trans*-esterification of steroidal hydroxy-acetates has precedent and was found to occur readily upon hydride reduction of the cycloadduct derived from reaction between that dienyl acetate **10** and acrolein.[47] In order to confirm that *trans*-esterification was giving rise to the two-component mixture, acetylisation of the crude reaction material, under standard conditions, gave a single product formulated as the 6'-oxo-3',17-diacetate **156** (Scheme 5.15).



155 **156**

Scheme 5.15 *Reagents and Conditions*: (i) L-Selectride, toluene then acetic anhydride, pyridine, DMAP

The analytical and spectral data confirmed the general structural features of **156**. The ^{13}C NMR spectrum revealed resonances at δ 67.1 and 93.7 assigned to C-3' and C-17 while the resonance at δ 209.4 was assigned to C-6'. The ^{1}H NMR spectrum displayed a characteristic resonance at δ 5.28 assigned to 3'β-H. The signal appeared as a triplet of doublets with two large couplings (*J* 4.3 Hz) to 16β-H and 4'β-H and a smaller coupling (*J*

1.6 Hz) to 4'α-H. The 16β-H resonated at δ 3.28, the signal split by vicinal couplings to 3'β-H (*J* 4.3 Hz) and 15β-H (*J* 11.3 Hz). The 15β-H resonated at δ 2.98. The assigned diastereoselectivity of the reduction is based upon ample precedent which exists in the literature for exclusive delivery of hydride from the less hindered *exo*-face of the dione-moiety in related systems.[120, 121]

The chemoselectivity of the reduction process was confirmed with the aid of a long-range HETCOR experiment. In the first instance a crosspeak between the 13β-methyl group and the singlet in the ^{13}C NMR spectrum at δ 62.2 ppm allowed for the assignment of the C-13 resonance. The singlet at δ 57.5 was assigned to C-14 on the basis of a crosspeak between it and the resonances assigned to 17^1-H and 17^2-H. Having unambiguously located the resonances assigned to C-13 and C-14 a crosspeak in the long-range HETCOR spectrum between the doublet at δ 2.98 and C-14 confirmed its assignment as the 15β-H.

The chemoselectivity of the process may be ascribed to the preferred boat-like conformation of the 1,4-cyclohexanedione moiety of related adducts. In particular it has been shown that of the two possible boat conformations that the *endo*-monoadduct, of *p*-benzoquinone and cyclopentadiene, may adopt, the preferred conformation is that in which the carbonyl-oxygen's are orientated away from each other in what has been referred to as the 'open' form.[122] As such the preferred conformation of **155** is the "open" form (Figure 5.2) and the chemoselectivity of the reduction process may be rationalised in terms of the relative ease of approach to the respective carbonyl groups. It is expected that the elements of ring B account for significantly greater shielding of the 6'-oxo group than the corresponding 17-acetate functionality does for the 3'-oxo group (Figure 5.2).

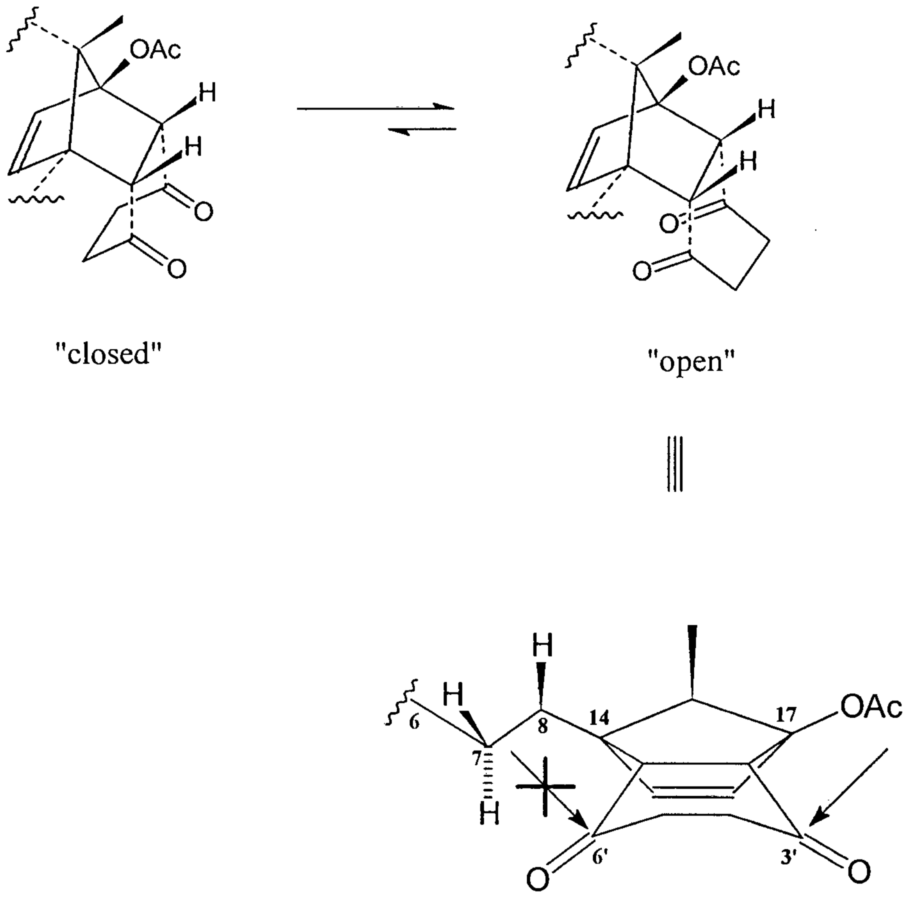
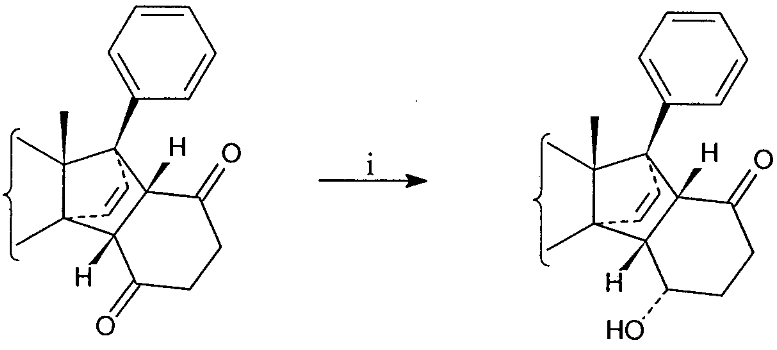


Figure 5.2

Alternative Boat Conformations of 17-Acetoxy-3',6,-dione **155**

This argument is consistent with results published by Winterfeldt *et al.*[108, 121] in which it is demonstrated that treatment of the dihydro-cycloadduct **157** with L-Selectride results in chemoselective reduction of the 6'-oxo group to give the 6'α-hydroxy-3'-ketone **158** (Scheme 5.16). The chemoselectivity of this process has been ascribed to the typical boat-like conformation of the cyclohexandione moiety and the resultant steric hindrance of the 3'-carbonyl group by the phenyl substituent at C-17.[121]



157 **158**

Scheme 5.16 *Reagents and Conditions*: (i) L-Selectride, toluene, -78°C

Conclusions

This chapter has documented the synthesis of **156** and it is envisaged that this substrate is amenable to further transformations to the desired target 14β-cyclohexyl Δ^{15}-17-ketone. In particular deprotection of the diacetate should yield a diol which should undergo selective tosylation to yield a 17-hydroxy-3'-tosylate, a possible Wharton fragmentation[123] substrate. In addition the synthesis of the highly strained ring D caged estradiol analogue **153** has been presented.

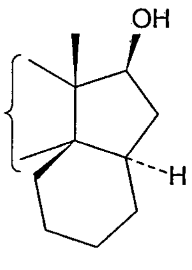
CHAPTER 6

Binding Affinity Studies

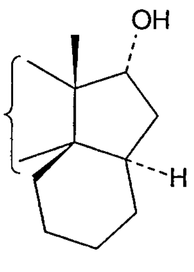
Binding affinities, of the estradiol and estriol analogues synthesised throughout the course of this work, were measured by the method of competitive binding.[125] This technique requires addition of both a radioactively labelled reference compound and the test substance to the receptor protein. Both reference and test hormone compete for receptor site occupancy. The affinity of the test substance towards the receptor is expressed as a **competition factor** (CF). This is defined as the ratio of the concentration of the test sample to that of the reference substance required for 50% competition. By definition the reference substance, in this case estradiol, has a CF = 1. Hormone analogues with competition factors less than or equal to 1 are thus considered to be highly competitive.

14β-Perhydro-15α-benzo[14,15]-estradiols

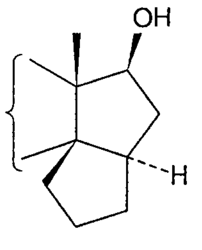
The 14β,15β-butano fused ring estradiol analogues **57** and **58** displayed relatively high binding affinities for the estradiol receptor. This is consistent with data reported for other 14β,15β-fused ring estradiols[47, 126] and indicates that 14β,15β-ring fusion does not significantly attenuate binding affinity (Figure 6.1).



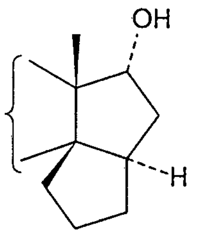
57
CF 1.5



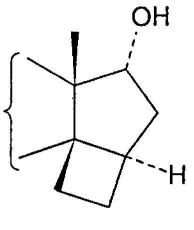
58
CF 14



CF 1.3



CF 7.4

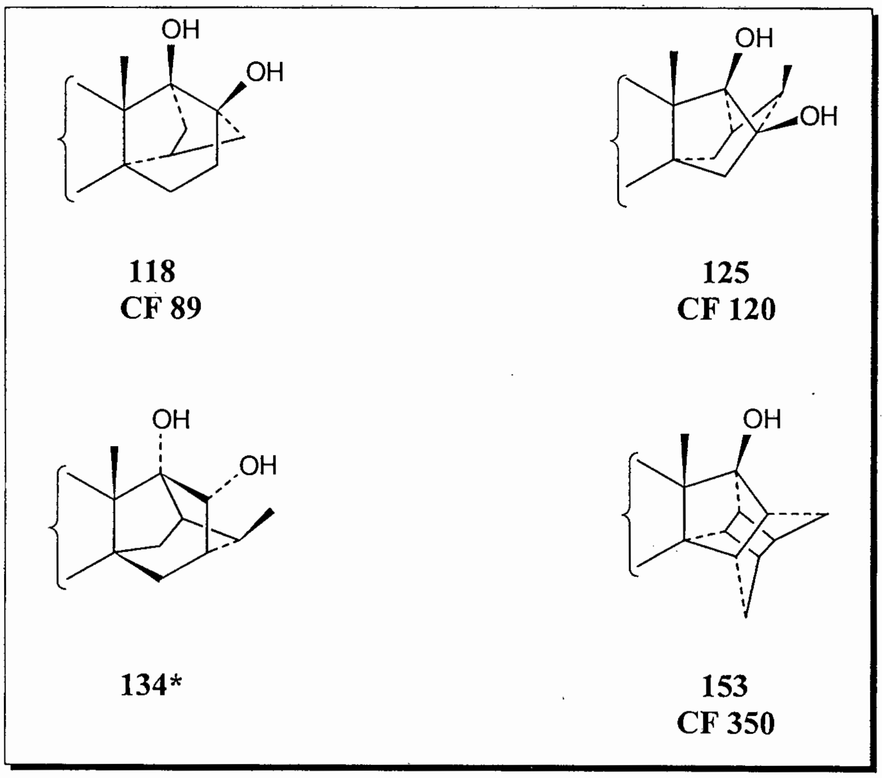


CF 20

Figure 6.1
Binding Affinity Data for Ring D Fused Compounds

Ring D Caged Compounds

It is clear from the binding affinity data for ring D caged compounds (Figure 6.2) that steric congestion on the α-face is a negative feature which effectively serves to impede access to the receptor. In particular compounds **125** and **153** while retaining the 14,17α-etheno bridge moiety, a feature which is known to enhance activity, have additional bridging elements in place with a resultant decrease in binding affinity. These results are important in defining the boundary conditions for receptor site access in ring D modified hormone analogues.



118
CF 89

125
CF 120

134*

153
CF 350

Figure 6.2

Binding Affinity Data for Ring D Caged Compounds

(* Data not available at present)

CHAPTER 7

EXPERIMENTAL

7.1 General

Reactions were monitored by thin layer chromatography using Merck F_{254} aluminum-backed precoated silica gel plates. Upon development the plates were viewed under ultra-violet light (where appropriate) and then sprayed with a 1% solution of cerium sulphate in 3M sufuric acid followed by baking at 200°C. Column chromatography was performed using Merck Kieselgel 60: 70-230 mesh for gravity columns and 230-400 mesh for flash chromatography. Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using chloroform solutions unless otherwise stated. Infrared spectra were recorded as chloroform solutions on a Perkin-Elmer 983 spectrometer. ^1H NMR spectra were recorded on a Varian VXR-200 instrument at 200 MHz or a Varian Unity spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Varian VXR-200 instrument at 50 MHz or a Varian Unity spectrometer at 100 MHz

All spectra were recorded in deuteriochloroform, unless otherwise stated, using $CHCl_3$, δ 7.24, as internal standard. All chemical shifts are reported in ppm. Elemental analyses were performed using a Heraues CHN-rapid combustion analyser. Mass spectra were recorded on a VG micromass 16F mass spectrometer operating at 70eV with an accelerating volatge of 4 kV.

Commonly used solvents were purified as follows:

Tetrahydrofuran - dried over sodium and then distilled from sodium and benzopheneone under an atmosphere of argon prior to use.

Benzene and toluene: distilled from sodium and stored over sodium wire.

Pyridine: distilled from potassium hydroxide and stored over potassium hydroxide pellets.

Preparation of Samarium(II) Iodide: Samarium(II) Iodide was prepared according to the method described by Kagan and Namy:[69]

Samarium powder (300 mg, ~40 mesh, 99.9%) was placed in a 3-neck flask fitted with a nitrogen inlet, a condenser and a pressure compensated dropping funnel. Diiodoethane (282 mg, 1 mmol) and tetrahydrofuran (10 ml) were added to the dropping funnel and the resultant mixture added to the samarium powder slowly with vigorous stirring. The solution was then heated at reflux for 30 min to give an intense blue 1 M solution of samarium(II) iodide.

7.2 Experimental

16α-Acetyl-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 32

(a) Boron trifluoride-diethyl ether (0.1 cm^3, 0.82 cm^3) was added to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate **10** (648 mg, 2 mmol) and methyl vinyl ketone (0.9 cm^3, 10.8 mmol) in dry tetrahydrofuran (15 cm^3) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 3 h, then ice-water added and the mixture was extracted with ethyl acetate. The combined extracts were washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude residue (756 mg) was chromatographed on silica gel (65 g) with ethyl acetate-hexane (3:7) as eluent to give **32** (740 mg, 94%), m.p. 141-142°C (from acetone-methanol); $[\alpha]_D$ +78° (*c*.1.1); ν_{max}/cm^{-1} 1729 (CO); δ_H(400 MHz) 0.98(3H, s, 13β-Me), 1.13(1H, ddd, *J* 13.3, 3.6 and 2.9 Hz, 12β-H), 1.36(1H, ddd, *J* 2 x 11.6 and 2.6 Hz, 8β-H), 1.38(1H, dddd, *J* 2 x 13.3, 11.6 and 3.6 Hz, 11β-H), 1.62(1H, dd, *J* 11.9 and 8.4 Hz, 15β-H), 1.74(1H, dd, *J* 11.9 and 4.3 Hz, 15α-H), 2.13 and 2.16(each 3H, s, 17β-OAc and 16^1-Me), 2.20(1H, dddd, *J* 13.3, 4.4, 3.8 and 2.9 Hz, 11α-H), 2.30(1H, ddd, *J* 2 x 13.3 and 4.4 Hz, 12α-H), 2.48(1H, ddd, *J* 2 x 11.6 and 3.8 Hz, 9α-H) 3.40(1H, dd, *J* 8.4 and 4.3 Hz, 16β-H), 3.77(3H, s, 3-OMe), 6.04 and 6.14(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.18(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 14.9(q, C-18), 21.6(q, 16^1-Me), 23.8(t, C-7), 27.2(t, C-11), 29.5(t, C-12), 30.2(t, C-6), 30.4(q, 17-OCO*Me*), 30.6(t, C-15), 39.4(d, C-8), 40.2(d, C-9), 55.3(d, C-16), 55.4(q, 3-OMe), 61.8 and 61.9(each s, C-13 and C-14), 95.9(s, C-17), 111.8(d, C-2), 113.8(d, C-4), 127.1(d, C-1), 129.9 and 132.3(each d, C-17^1 and C-17^2), 132.4(s, C-10), 137.9(s, C-5), 157.5(s, C-3), 169.8(s, 17-O*C*OMe) and 207.6(s, C-16^1); (Found: C, 76.1; H, 7.9%; M^+, 394; $C_{25}H_{30}O_4$ requires C, 76.1; H 7.7%; *M*, 394).

(b) The reaction was conducted as before on the dienyl acetate **10** (624 mg, 2 mmol) using dry benzene (15 cm^3) in place of tetrahydrofuran, and worked up, after 8h, as described in the foregoing experiment. The solid residue (603 mg) was chromatographed on silica gel (65g) with ethyl acetate-hexane (3:7) as eluent to give an unidentified product (4 mg) followed by **32** (580 mg, 74%).

(c) A solution of the dienyl acetate **10** (200 mg, 0.62 mmol) and methyl vinyl ketone (0.25 cm^3, 3 mmol) in dry benzene (2 cm^3) was purged with nitrogen and heated in a sealed tube at 125°C (oil bath) for 32 h. The cooled reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue (339 mg) was chromatographed on silica gel (40 g) with ethyl acetate-hexane (3:7) as eluent to give two unidentified products (4.6 and 3.2 mg) followed by **32** (193 mg, 74%).

16α-Acetyl-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate 33

The 14α,17α-etheno compound **32** (192 mg, 0.48 mmol) in ethyl acetate (10 cm^3) at 24°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%, 50 mg). After 3 h the mixture was filtered, and the filtrate evaporated under reduced pressure to give a crude residue (195 mg). Filtration through silica gel (10 g) using toluene as eluent gave **33** (191 mg, 100%), m.p. 163-164°C (from acetone-methanol); $[\alpha]_D$ +37° (*c* 1.2); ν_{max} /cm^{-1} 1728 (OAc) and 1705 (CO); δ_H(200 MHz) 1.0(3H, s, 13β-Me), 2.07(1H, s, 17β–OAc), 2.17(3H, s, 16α-COMe), 3.34(1H, ddd, *J* 11.1, 4.4 and 2.6 Hz, 16β-H), 3.76(3H, s, 3-OMe), 6.61(1H, d, *J* 2.7 Hz, 4-H), 6.70(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.2(1H, d, *J* 8.5 Hz, 1-H); δ_C(50 MHz) 14.1(C-18), 21.8(16α-CO*Me*), 55.0(C-16), 55.2(3-OMe), 92.5(C-17), 111.6(C-2), 113.8(C-4), 126.5(C-1), 132.9(C-10), 137.8(C-5), 157.5(C-3), 170.3(17-OCOMe), 209.4(C-16^1); (Found: C, 75.5; H, 8.0%; M$^+$, 396; $C_{25}H_{32}O_4$ requires C, 75.7; H, 8.1%; *M*, 396)

3-Methoxy-14β-3'-oxobutylestra-1,3,5(10),15-tetraen-17-one 34

The cycloadduct **32** (1.94 g, 4.93 mmol) was suspended in methanolic M-potassium hydroxide (10 cm^3, 10 mmol) and the suspension stirred at 24°C for 2.5 h. Saturated aqueous ammonium chloride was added and the mixture extracted with ethyl acetate. The combined organic phase was washed with brine and water, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.87 g) which was chromatographed on silica gel (100 g) using toluene as eluent to give **34** (1.61 mg, 93%), m.p. 114-116°C (from acetone-methanol); $[\alpha]_D$ +123° (*c* 1.1); ν_{max}/cm^{-1} 1627 (C:C) and 1709br (CO); δ_H(200 MHz) 1.07(3H, s, 13β-Me), 2.13(3H, s, 3'-Me), 2.80(2H, m, 6α- and 6β-H), 3.76(3H, s, 3-OMe), 6.20(1H, d, *J* 5.8 Hz, 16-H), 6.59(1H, d, 2.8 Hz, 4-H), 6.70(1H, dd, 8.7 and 2.8 Hz, 2-H), 7.08(1H, d, 8.7 Hz, 1-H) and 7.33(1H, d, 5.8 Hz, 15-H); δ_C(50 MHz) 19.7(C-18), 24.7(3'-Me), 27.4(C-11), 27.6(C-7), 30.3(C-6), 30.9(C-1'), 32.5(C-12), 36.4(C-2'), 39.0(C-8), 42.2(C-9), 51.7 and 54.0(C-13 and C-14), 55.2(3-OMe), 112.2(C-2), 113.2(C-4), 127.8(C-1), 131.3(C-15), 132.6(C-10), 137.2(C-5), 157.5(C-3), 164.6(C-16), 207.5(C-3') and 213.8(C-17); (Found: C, 78.4; H, 8.3%; M$^+$, 352; $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352).

3-Methoxy-5',6'-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-4'(3'*H*),17-dione 35

(a) The 14β-3'-oxobutyl Δ^{15}-17-ketone **34** (1.32 g, 3.75 mmol) was dissolved in methanol (20 cm^3) and methanolic potassium hydroxide (0.1 M, 10 cm^3) was added. The resultant mixture was heated under reflux for 4 h then cooled to 24°C and saturated aqueous ammonium chloride added. The mixture was extracted with ethyl acetate, the combined extracts washed with brine and water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude residue (1.26 g) was chromatographed on silica gel (50 g) using ethyl acetate-toluene (3:7) as eluent to give **35** (1.24 g, 94%), m.p. 86-88°C (from methanol-diethyl ether); $[\alpha]_D$ +76° (*c* 1.2); ν_{max}/cm^{-1} 1701 (4'CO) and 1724(17CO);

δ_H(400 MHz) 1.06(3H, s, 13β-Me),1.70(1H, ddd, *J* 15.4, 9.6 and 6.0 Hz, 6'β-H), 1.79(1H, dd, 19.9 and 9.0 Hz, 16β-H), 1.99(1H, dtd, *J* 15.4, 6.7, 6.4 and 1.4 Hz, 6'α-H), 2.18(1H, dtd, *J* 17.1, 6.4, 6.0 and 1.7 Hz, 5'β-H), 2.39(1H, ddd, *J* 15.9, 2.1 and 1.7 Hz, 3'β-H), 2.55(1H, ddd, *J* 17.1, 9.6 and 6.7 Hz, 5'α-H), 2.67(1H, dd, *J* 15.9 and 5.0 Hz, 3'α-H), 2.86(1H, dd, *J* 19.9 and 10.2 Hz, 16α-H), 2.92(2H, m, 6α- and 6β-H), 3.20(1H, m, 15α-H), 3.78(3H, s, 3-OMe), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.68(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23(1H, d, *J* 8.6 Hz, 1-H); δ_H(400 MHz, pyridine-d5) 1.02(3H, s, 13β-Me), 1.20(1H, td, *J* 2 x 13.0 and 3.5 Hz, 8β-H), 1.25(1H, dt, *J* 14.1 and 2 x 3.2 Hz, 12β-H), 1.57(1H, ddd, *J* 15.2, 10.1 and 6.1 Hz, 6'β-H), 1.67(1H, td, *J* 14.4, 14.1 and 4.0 Hz, 12α-H), 1.73(1H, dt, *J* 15.2, 6.6 and 6.1 Hz, 6'α-H), 1.95(1H, dd, *J* 19.4 and 9.0 Hz, 16β-H), 2.18(1H, dtd, *J* 16.9, 2 x 6.1 and 1.9 Hz, 5'β-H), 2.37(1H, ddd, *J* 15.7, 2.4 and 1.9 Hz, 3'β-H), 2.55(1H, ddd, *J* 16.9, 10.1 and 6.6 Hz, 5'α-H), 2.67(1H, dd, *J* 15.7 and 5.1 Hz, 3'α-H), 2.73(1H, ddd, *J* 13.0, 11.1 and 4.0 Hz, 9α-H), 2.84(2H, m, 6α- and 6β-H), 2.85(1H, dd, *J* 19.4 and 10.1 Hz, 16α-H), 3.20(1H, m, 15α-H), 3.74(3H, s, 3-OMe), 6.81(1H, d, *J* 2.7 Hz, 4-H), 6.96(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.32(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 14.8(q, C-18), 26.6(t, C-11), 27.1(t, C-7), 31.0(t, C-6'), 31.7(t, C-6), 32.5(d, C-15), 32.9(t, C-12), 38.4(d, C-8), 38.9(t, C-5'), 40.7(t, C-16), 43.2(t, C-3'), 44.5(s, C-13), 45.8(d, C-9), 55.2(s, C-14), 56.1(q, 3-OMe), 112.3(d, C-2), 113.3(d, C-4), 127.5(d, C-1), 131.4(s, C-10), 137.1(s, C-5), 157.7(s, C-3), 211.7(s, C-4') and 218.9(s, C-17); (Found: C, 78.5; H, 8.1%; M^+, 352; $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352).

(b) The cycloadduct **32** (2 g, 5.1 mmol) was suspended in methanol (10 cm^3) and methanolic M-potassium hydroxide (11 cm^3) added. The resultant mixture was heated under reflux for 4.5 h until all starting material had been consumed (TLC), then cooled to 24°C. Saturated aqueous ammonium chloride was added and the product (1.97 g) isolated by extraction with ethyl acetate and purified by filtration through silica gel (100g) with ethyl acetate-toluene (3:7) as eluent to give **35** (1.88 mg, 94%).

(c) The 14β-3'-oxobutyl Δ^{15}-17-ketone **34** (400 mg, 1.14 mmol) was dissolved in methanol (5 cm^3) and methanolic M-potassium hydroxide (5 cm^3) was added. The resultant mixture was heated under reflux for 2.5 h then cooled to 21°C and saturated aqueous ammonium chloride added. The mixture was extracted with ethyl acetate, the combined extracts washed with brine and water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude residue (407 mg) was chromatographed on silica gel (44 g) using ethyl acetate-toluene (3:7) as eluent to give **35** (296 mg, 74 %) followed by (16^1S)-16^1-*hydroxy*-3,15α-*dimethoxy*-16^1-*methyl*-14,16β-*propano*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **36** (18 mg, 4%), m.p. 123-124°C (from ethyl acetate-hexane); $[\alpha]_D$ +83° (*c*. 1.1); ν_{max}/cm^{-1} 3611 (OH) and 1725 (CO); δ_H(400 MHz) 1.09(3H, s, 13β-Me), 1.35(3H, s, 16^1-Me), 2.54(1H, d, *J* 1.8 Hz, 16α-H), 3.16(1H, td, *J* 2 x 11.8 and 3.7 Hz, 9α-H), 3.22(3H, s, 15α-OMe), 3.78(3H, s, 3-OMe), 4.19(1H, s, 15β-H), 6.68(1H, d, *J* 2.8 Hz, 4-H), 6.75(1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.10(1H, d, *J* 8.5 Hz, 1-H); δ_H(400 MHz, C_6D_6) 0.88(1H, ddd, *J* 13.9, 5.5 and 1.8 Hz, 16^3-H_n), 1.00(3H, s, 13β-Me), 1.06 - 1.17(3H, m, 8β-H, 16^2-H_n and 16^2-H_x), 1.14(3H, s, 16^1-Me), 1,24(1H, qd, *J* 3 x 13.0 and 3.4 Hz, 11β-H), 1.55(1H, dt, *J* 13.0 and 2 x 3.4 Hz, 12β-H), 1.57(1H, qd, *J* 12.5, 11.5, 11.0 and 6.7 Hz, 7α-H), 1.90(1H, dq, *J* 12.5 and 3 x 3.4 Hz, 7β-H), 1.93(1H, ddd, *J* 13.9, 11.8 and 7.5 Hz, 16^3-H_x), 2.14(1H, dq, *J* 13.0 3.8, 3.7 and 3.4 Hz, 11α-H), 2.38(1H, d, *J* 1.4 Hz, 16α-H), 2.41(1H, td, *J* 2 x 13.0 and 3.8 Hz, 12α-H), 2.68 - 2.74(2H, m, 6α- and 6β-H), 2.89(3H, s, 15α-OMe) 3.23(1H, td, *J* 2 x 13.0 and 3.7 Hz, 9α-H), 3.39(3H, s, 3-OMe), 4.06(1H, s, 15β-H), 6.70(1H, d, *J* 2.8 Hz, 4-H), 6.75(1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.10(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 17.5(q, C-18), 23.6(t, C-7), 25.4(t, C-11), 28.4(q, C-16^1β-Me), 30.7(t, C-6), 30.8(t, C-16^3), 33.1(t, C-12), 34.1(t, C-16^2), 38.4(d, C-9), 43.4(d, C-8), 48.4 and 49.2(each s, C-13 and C-14), 55.2(q, 3-OMe), 56.2(q, C15α-OMe), 62.3(d, C-16), 73.5(s, C-16^1) 85.5(d, C-15), 111.4(d, C-2), 113.6(d, C-2) 125.9(d, C-1), 134.2(s, C-10), 137.7(s, C-5), 157.4(s, C-3) and 221.9(s, C-17); (Found: C, 74.8; H, 8.2%; M^+, 384; $C_{24}H_{32}O_4$ requires C, 75.0; H, 8.4%; *M*, 384).

17α-Hydroxy-3-methoxy-14,17β-butanoestra-1,3,5(10),15-tetraen-17^2-one 39

Cerium(III) chloride heptahydrate (300 mg, 0.81 mmol) was dried under vacuum at 150°C for 2 h, then cooled under nitrogen to 24°C and tetrahydrofuran (5 cm^3) was added. The 14β-3'-oxobutyl Δ^{15}-17-ketone **34** (130 mg, 0.37 mmol) in tetrahydrofuran (8 cm^3) was added and the mixture cooled to -78°C. A solution of lithium hexamethyldisilazane [formed by the addition of n-butyllithium (0.3 cm^3, 1.6 M, 0.38 mmol) to hexamethyldisilazide (0.15 cm^3, 0.72 mmol) in tetrahydrofuran (10 cm^3) at -78°C, followed by stirring for 30 min at 0°C], also cooled to -78°C, was added and the mixture was stirred at -78°C for 1 h. Saturated aqueous ammonium chloride was added followed by extraction into ethyl acetate. The combined organic phase was washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the crude material (119 mg) on silica gel (15 g) using ethyl acetate-toluene (7:13) as eluent gave starting material **34** (67 mg, 49%) followed by **39** (50 mg, 38%) ν_{max}/cm^{-1} 1702 (CO) and 3567 (OH) δ_H (200 MHz, **34** & **39**) 1.06(13β-Me), 2.54 and 2.62(each 1H, d, *J* 16.9 Hz, 17^{1}α- and 17^{1}β-H), 3.76(3-OMe), 5.69 and 5.82(each 1H, d, *J* 6.7 Hz, 15- and 16-H), 6.60(1H, d, *J* 2.7 Hz, 4-H), 6.71(1H, dd, *J* 8.8 and 2.7 Hz) and 7.10(1H, d, *J* 8.7 Hz, 1-H), δ_C (50 MHz, **34** & **39**) 20.6(C-18), 55.2(2-OMe), 71.5(C-17), 112-3(C-2), 113.2(C-4), 128.0(C-1), 131.2 and 131.4(C-15 and C-16), 132.9(C-10), 137.2(C-5), 157.4(C-3) and 214.2(C-17^2); (Found M$^+$, 352; $C_{23}H_{28}O_3$ requires *M*, 352).

Hydride Reduction of the 4',17-Dione 35

Sodium borohydride (28 mg, 0.74 mmol) was added slowly to a stirred solution of the diketone **35** (252 mg, 0.72 mmol) in tetrahydrofuran-methanol (3:1, 12 cm^3) at 0°C under nitrogen. After 10 min at 0°C the reaction was complete (TLC). Saturated aqueous ammonium chloride was added and the mixture maintained at 0°C until effervescence ceased. The mixture was then extracted with ethyl acetate and the combined extracts washed with saturated aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (242 mg). The crude material was chromatographed on silica gel (25 g) using ethyl acetate-toluene (1:5) as eluent to give 4'β-*hydroxy*-3-*methoxy*-3',4',5',6'-*tetrahydro*-15αH-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* **41** (153 mg, 60%), m.p. 80-82°C (from acetone); $[\alpha]_D$ +45° (*c*. 1.0); ν_{max}/cm^{-1} 3606 (OH) and 1721 (CO); δ_H(400 MHz) 1.01(3H, s, 13β-Me), 2.76(1H, dd, *J* 19.2 and 10.4 Hz, 16α-H), 3.18(1H, dd, *J* 19.2 and 7.5 Hz, 16β-H), 3.32(1H, m, 15α-H), 3.77(3H, s, 3-OMe), 4.22(1H, q, 4 x 3.4 Hz, 4'α-H), 6.60(1H, d, *J* 2.9 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.9 Hz, 2-H) and 7.21(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 14.3(q, C-18), 27.3, 27.4 and 27.5(each t, C-7, C-11 and C-6'), 29.2(d, C-15), 31.8(t, C-6), 32.1, 32.5 and 32.6(each t, C-12, C-3' and C-5'), 38.3(d, C-8), 40.7(t, C-16), 44.2(s, C-13 or C-14), 46.6(d, C-9), 55.2(q, 3-OMe), 57.0(s, C-14 or C-13), 66.0(d, C-4'), 112.1(d, C-2), 113.1(d, C-4), 127.7(d, C-1), 132.1(s, C-10), 137.3(s, C-5), 157.4(s, C-3) and 220.1(s, C-17); (Found: C, 77.7; H, 8.4%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354) followed by 4'α-*hydroxy*-3-*methoxy*-3',4',5',6'-*tetrahydro*-15α-H-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* **42** (77 mg, 30%), m.p. 104-105°C (from acetone); $[\alpha]_D$ 53° (*c*.1.2); ν_{max}/cm^{-1} 3603 (OH) and 1727 (CO); δ_H(400 MHz) 0.98(3H, s, 13β-Me), 2.20(1H, dd, *J* 19.9 and 8.8 Hz, 16β-H), 2.75(1H, dd, 19.9 and 10.6 Hz, 16α-H), 3.07(1H, m, 15α-H), 3.78(3H, s, 3-OMe), 3.88(1H, tt, *J* 2 x 11.3 and 2 x 5.0 Hz, 4'β-H), 6.55(1H, d, *J* 2.4 Hz, 4-H), 6.68(1H, dd, *J* 8.8 and 2.4 Hz, 2-H) and 7.16(1H, d, *J* 8.8 Hz, 1-H); δ_C(100 MHz, $CDCl_3$)14.1(q, C-18), 27.7 and 27.9(each t, C-7 and C-11), 31.6(d, C-15), 31.8(t, C-6), 32.4(t, C-6'), 32.7(t, C-12); 34.4 and 37.7(each t, C-3' and C-5'), 38.0(d, C-8), 38.6(t, C-16), 43.7(s, C-13 or C-14), 46.5(d, C-9), 55.2(q, 3-OMe), 57.3(s, C-14 or C-13), 65.5(d, C-4'), 112.3(d, C-2), 113.1(d, C-4), 127.7(d, C-1), 131.8(s, C-10), 137.4(s, C-5), 157.5(s, C-3) and 220.5(s, C-17); (Found: C, 77.9; H, 8.3%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

4',4'-Ethylenedithio-3-methoxy-5',6'-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 43

A solution of the diketone **35** (120 mg, 0.34 mmol) in dichloromethane (2 cm^3) was cooled to 0°C and ethanedithiol (0.4 cm^3, 4.8 mmol) was added followed by boron trifluoride-diethyl ether (0.2 cm^3, 4.7 mmol). The solution was stirred at 24°C for 30 min, then water added and the resultant mixture poured into aqueous sodium hydrogen carbonate. The mixture was extracted with chloroform and the combined extracts washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a crystalline residue (158 mg). Recrystallisation of this crude material gave pure **43** (142 mg, 98%), m.p. 242-244°C (from chloroform-methanol); $[\alpha]_D$ +32° (*c*.0.97); ν_{max}/cm^{-1} 1727 (CO); δ_H(200 MHz) 1.02(3H, s, 13β-Me), 3.20 - 3.40(2H, m, -SCH_2CH_2S-), 3.77(3H, s, 3-OMe), 6.60(1H, d, *J* 2.9 Hz, 4-H), 6.72(1H, dd, *J* 8.7 and 2.9 Hz, 2-H) and 7.18(1H, d, *J* 8.7 Hz, 1-H); δ_C(50 MHz) 16.0(C13β-Me), 56.1(3-OMe), 65.1(C-4'), 112.2(C-2), 113.1(C-4), 127.7(C-1), 132.2(C-10), 137.3(C-5), 157.5(C-3), 220.8(C-17); (Found: C, 70.2; H, 7.5; S, 14.6%; M^+, 428; $C_{25}H_{32}S_2O_2$ requires C, 70.1; H, 7.5; S, 15.0%; *M*, 428).

3-Methoxy-3',4',5',6'-tetrahydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 44

Raney nickel (Aldrich, W2, 0.5g) was washed (4x) with absolute ethanol, the ethanol decanted and the nickel suspended in further ethanol (2 cm^3). A solution of the thioacetal **43** (158 mg, 0.36 mmol) in ethanol (2ml) was added and the resultant mixture heated with stirring at 50°C for 1 h. The mixture was allowed to cool to 24°C and chloroform (3ml) was added. The mixture was filtered through Celite and the Celite washed repeatedly with chloroform. The filtrate was evaporated to dryness under reduced pressure to give a solid residue (131 mg). Recrystallisation of the crude material (134 mg) gave **44** (112 mg, 90%), m.p. 137-138°C (from acetone-ethanol); $[\alpha]_D$ +23° (*c*.1.1); ν_{max}/cm^{-1} 1728 (CO); δ_H(200 MHz) 0.89(3H, s, 13β-Me), 3.70(3H, s, 3-OMe), 6.54(1H, d, *J* 2.8 Hz, 4-H), 6.66(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.15(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz); 13.7(q, C13β-Me), 30.4(d, C-15), 37.9(d, C-9), 44.1(s, C-14), 46.7(d, C-8), 55.2(q, 3-OMe), 57.7(s, C-13), 112.1(d, C-2), 113.2(d, C-4), 127.7(d, C-1), 132.1(s, C-10), 137.5(s, C-5), 157.4(s, C-3) and 221.7(s, C-17); (Found: C, 81.7; H, 8.7%; M$^+$, 338; $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338).

Hydride reduction of the 17-Ketone 44

Lithium aluminium hydride (100 mg, 2.7 mmol) was added slowly to a stirred solution of the ketone **44** (300 mg, 0.89 mmol) in tetrahydrofuran at 0°C under nitrogen, then the mixture was stirred at 24°C for 10 min. Water was added dropwise to the solution until the evolution of hydrogen ceased and chloroform added to the resultant precipitate. The mixture was filtered and the precipitate washed repeatedly with chloroform. The total filtrate was extracted with chloroform, the organic phase washed with water and dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude material (236 mg) was chromatographed on silica gel (30 g) using ethyl acetate-toluene (2:8) as eluent to give 3-*methoxy*-3',4',5',6'-*tetrahydro*-15αH-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17β-*ol* **45** (135 mg, 49 %), m.p. 136-137°C (from ethyl acetate-methanol); $[\alpha]_D$ +77° (*c*.1.2); ν_{max} /cm^{-1} 3578 (OH); δ_H(200 MHz) 1.05(3H, s, 13β-Me), 3.62(1H, dd, *J* 6.4 and 5.2 Hz, 17α-H), 3.77(3H, s, 3-OMe), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.22(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 15.1(C13β-Me), 27.4(C-7), 28.3(C-11), 39.7(C-15), 44.8(C-9), 48.4(C-8), 51.1(C-14), 55.2(3-OMe), 66.0(C-13), 82.3(C-17), 112.1(C-2), 112.9(C-4), 127.7(C-1), 132.6(C-10), 137.5(C-5) and 157.3(C-3); (Found: C, 81.4; H, 9.2%; M$^+$, 340; $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; *M*, 340) followed by 3-*methoxy*-3',4',5',6'-*tetrahydro*-15αH-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17α-*ol* **46** (86 mg, 31%), m.p. 144-145°C (from dichloromethane-methanol); $[\alpha]_D$ +56°(*c*.1.0); ν_{max} /cm^{-1} 3566 (OH); δ_H(200 MHz) 0.96(3H, s, 13β-Me), 4.14(1H, dd, *J* 2 x 8.6 Hz, 17β-H), 3.77(3H, s, 3-OMe), 6.59(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.24(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 17.3(C13β-Me), 27.2(C-7), 27.7(C-11), 39.3(C-15), 44.1(C-9), 48.3(C-8), 48.4(C-14), 55.2(3-OMe), 66.3(C-13), 78.4(C-17), 112.0(C-2), 112.9(C-4), 127.7(C-1), 132.5(C-10), 137.4(C-5) and 157.3(C-3); (Found: C, 81.2; H, 9.6%; M$^+$, 340; $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; *M*, 340).

Deprotection of the 3-Methyl Ethers 45 and 46

(a) Di-isobutylaluminium hydride (1.2 M solution in toluene, 1.5 cm^3, 1.8 mmol) was added to a stirred solution of the alcohol **45** (100 mg, 0.29 mmol) in dry toluene (10 cm^3) and the mixture was refluxed under nitrogen for 48 h. The mixture was cooled to 24°C and hydrochloric acid (10%, 10 cm^3) added. The aqueous layer was extracted with chloroform, the combined organic phase washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crystalline residue (81 mg). Recrystallisation from acetone-methanol gave 3',4',5',6'-*tetrahydro*-15αH-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-3,17β-*diol* **57** (72 mg, 75%); m.p. 179-181°C; $[\alpha]_D$ +82° (*c*.1.1); (Found: C, 80.8; H, 9.5%; M^+, 326; $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

(b) Di-isobutylaluminium hydride (1.2 M solution in toluene, 1.5 cm^3, 1.8 mmol) was added to a stirred solution of the alcohol **46** (100 mg, 0.29 mmol) in dry toluene (10 cm^3) and the mixture was refluxed under nitrogen for 48 h. The mixture was cooled to 24°C and hydrochloric acid (10%, 10 cm^3) added. The aqueous layer was extracted with chloroform, the combined organic phase washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crystalline residue (79 mg). Recrystallisation from acetone-methanol gave 3',4',5',6'-*tetrahydro*-15αH-*benzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-3,17α-*diol* **58** (69 mg, 72%); m.p. 196-198°C; $[\alpha]_D$ +49°(*c*.1.1); (Found: C, 81.0; H, 9.4%; M^+, 326; $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

17β-Acetoxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16α-carbaldehyde 59

Boron trifluoride-diethyl ether (0.15 cm^3, 1.23 mmol) was added to the dienyl acetate **10** (2 g, 6.2 mmol) and acrolein (1 cm^3, 14.8 mmol) in dry tetrahydrofuran (22 cm^3) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 5 h, then ice-water added and the mixture was extracted with ethyl acetate. The combined extracts were washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure to yield a crystalline residue (2.1 g). The material was crystallised from ethyl acetate-hexane and gave **59** (1.74 g, 74 %), m.p. 173-176°C (lit.[61] 173-175°C); $[\alpha]_D$ +102° (*c*.1.0); ν_{max}/cm^{-1} 1730 (OAc); (Found: C, 75.7; H, 7.4%; M$^+$, 380; $C_{24}H_{28}O_4$ requires; C, 75.8; H 7.4%; M, 380). The mother liquor material (290 mg) was chromatographed on silica gel (30 g) with ethyl acetate-toluene (1:19) as eluent and gave further 16α-carbaldehyde **59** (277 mg, 12%).

3-Methoxy-14,17α-etheno-16α-vinylestra-1,3,5(10)-trien-17β-yl-acetate 61

(a) t-Butyllithium (0.7 cm^3, 1.7 M) was added to a suspension of methyltriphenylphosphonium iodide (485 mg, 1.2 mmol) in tetrahydrofuran (5 cm^3) cooled to 0°C. The mixture was stirred at this temperature for 1 h. The cycloadduct **59** (300 mg, 0.79 mmol) in dry tetrahydrofuran (3 cm^3) was added to the orange solution and the mixture stirred at 25°C for 2 h. The mixture was diluted with water (10 cm^3) and extracted with ethyl acetate. The combined extracts were washed with dilute hydrochloric acid (10 cm^3, 0.1 M), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a crude residue (275 mg). Flash chromatography on silica gel (30 g) using ethyl acetate-toluene (1:19) as eluent gave **61** (245 mg, 82%), m.p.147-150°C (from acetone-methanol); $[\alpha]_D$ +176° (*c*. 1.0); ν_{max}/cm^{-1} 1734 (OAc); δ_H(400 MHz) 0.95(3H, s, 13β-Me), 1.12(1H, dd, *J* 11.9 and 3.8 Hz, 15β-H), 1.16(1H, ddd, *J* 13.5, 4.3 and 2.7 Hz, 12β-H), 1.26(1H, qd, *J* 2x13.5, 11.6 and 4.3 Hz, 11β-H), 1.38(1H, td, *J* 2x11.6 and 2.5 Hz, 8β-H), 1.62 and 1.82(each 1H, each m, 7α- and 7β-H), 2.08(3H, s, 17-OAc), 2.21(1H, dddd, *J* 13.5, 4.4, 3.0 and 2.7 Hz, 11α-H), 2.30(1H, tdd, *J* 2x13.5, 4.4 and 0.93 Hz, 12α-H), 2.50(1H, td, *J* 2x11.6 and 3.0 Hz, 9α-H), 2.83-2.90(2H, m, 6α- and 6β-H), 3.01(1H, ddd, *J* 8.8, 8.3 and 3.8 Hz, 16β-H), 3.77(3H, s, 3-OMe), 4.98(1H, ddd, *J* 10.2, 2.0 and 0.8 Hz, 16^2-H_{cis}), 5.04(1H, ddd, *J* 17.1, 2.0 and 0.8 Hz, 16^2-H_{trans}), 5.60(1H, ddd, *J* 17.1, 10.2 and 8.3 Hz, 16^1-H), 6.03 and 6.25(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.20(1H, d, *J* 8.5 Hz, 1-H); δ_C(100MHz) 14.6(q, C-18), 21.6(q, 17-OCO*Me*), 23.7(d, C-7), 27.2(d, C-11), 29.7(d, C-12), 30.2(d, C-6), 34.7(t, C-15), 39.5 and 40.0(each d, C-8 and C-9), 46.9(d, C-16), 55.2(q, 3-OMe), 55.5 and 60.5(each s, C-13 and C-14), 96.3(s, C-17), 111.7(d, C-2), 113.7(d, C-4), 115.5(t, C-16^2), 127.1(d, C-1), 131.3 and 131.5(each d, C-17^1 and C-17^2), 132.5(s, C-10), 137.9(s, C-5), 139.9(d, C-16^1), 157.4(s, C-3) and 170.3(s, 17-O*C*OMe); (Found: C, 79,3; H, 7.8%; M$^+$, 378; $C_{25}H_{30}O_3$ requires C, 79.3; H, 7.9%; *M*, 378).

(b) To a stirred suspension of methyltriphenylphosphonium iodide (170 mg, 0.42 mmol) in tetrahydrofuran (2 cm^3), cooled to -78°C, was added n-butyllithium (1.4 M, 0.3 cm^3). The mixture was allowed to warm to 0°C and then stirred for 4 h at that temperature. The cycloadduct **59** (100 mg, 0.26 mmol) in tetrahydrofuran (2 cm^3) was added to the orange solution and the mixture stirred at 0°C for 4 h. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture warmed to 25°C. The mixture was extracted with chloroform and the combined organic phase washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (89 mg). This residue was dissolved in pyridine (2 cm^3), and acetic anhydride (0.3 cm^3) and 4-(dimethylammino)pyridine (5 mg, 0.04 mmol) added. The mixture was stirred at 25°C for 3 h, then poured into water and the product isolated by extraction with chloroform to give crystalline material (81 mg) which was chromatographed on silica gel (10 g). Elution with ethyl acetate-toluene (1:9) gave **61** (63 mg, 63%).

(c) Dibromethane (0.06 cm^3, 0.86 mmol) was added to a stirred suspension of zinc powder (20 mg, 0.3 mmol) in dry tetrahydrofuran (3 cm^3) under nitrogen. The mixture was cooled to -40°C (dry ice/acetone bath) and titanium tetrachloride (0.08 cm^3, 0.73 mmol) was added dropwise over 15 min. The mixture was stirred at 5°C for 2 h and then dichloromethane (5 cm^3) was added to the dark grey slurry. The cycloadduct **59** (200 mg, 0.53 mmol) in dichloromethane (2 cm^3) was added and the resultant mixture stirred at 24°C for 1.5 h. The mixture was diluted with pentane (10 cm^3) and a saturated aqueous solution of sodium hydrogen carbonate was added slowly until effervescence ceased. The organic phase was separated and the resultant aqueous phase extracted with dichloromethane. The combined organic phase was washed successively with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and the crude residue (167 mg) chromatographed on silica gel (20 g) using ethyl acetate-toluene (1:9) as eluent affording **61** (156 mg, 71%).

3-Methoxy-14,17α-etheno-16α-vinylestra-1,3,5(10)-trien-17β-ol 62

Lithium aluminium hydride (106 mg, 2.7 mmol) was added to the acetoxy-diene **61** (250 mg, 0.66 mmol) in dry tetrahydrofuran (10 cm^3) at 0°C under nitrogen, then the mixture stirred at 25°C for 20min. Aqueous sodium sulfate was added to the solution at 0°C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture stirred for 30 min, then filtered through layers of magnesium sulfate and Celite in a sintered glass funnel. The filter pad was washed with chloroform and the solvent removed under reduced pressure to give **62** (182 mg, 82%), m.p. 237-239°C (from ethyl acetate-hexane); $[\alpha]_D$ +156° (*c.* 1.0); ν_{max}/cm^{-1} 3430 (OH); δ_H(400 MHz) 0.95(3H, s, 13β-Me), 1.17(1H, dd, *J* 12.2 and 4.0 Hz, 15β-H), 1.23(1H, ddd, *J* 12.9, 4.3 and 2.7 Hz, 12β-H), 1.35(1H, obsc. m, 11β-H), 1.40(1H, td, *J* 2x11.6 and 2.9 Hz, 8β-H), 1.62 and 1.82(each 1H, each m, 7α- and 7β-H), 1.94(1H, dd, *J* 12.2 and 8.5 Hz, 15α-H), 2.10(1H, td, *J* 2x12.9 and 4.3 Hz, 12α-H), 2.24(1H, m, 11α-H), 2.48(1H, td, *J* 2x11.6 and 4.2 Hz, 9α-H), 2.75(1H, ddd, *J* 8.8, 8.5 and 4.0 Hz, 16β-H), 2.83-2.90(2H, m, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 5.02(1H, ddd, *J* 10.1, 2.0 and 0.7 Hz, 16^2-H(cis)), 5.12(1H, ddd, *J* 17.1, 2.0 and 1.0 Hz, 16^2-H(trans)), 5.60(1H, ddd, *J* 17.1, 10.1 and 8.8 Hz, 16^1-H), 5.80 and 6.08(each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.63(1H, d, *J* 2.7 Hz, 4-H), 6.72(1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.22(1H, d, *J* 8.7 Hz, 1-H); δ_C(100 MHz) 14.2(C-18), 23.8(C-7), 27.1(C-11), 27.6(C-12), 30.3(C-6), 36.2(C-15), 39.5 and 40.3(C-8 and C-9), 49.0(C-16), 55.2(3-OMe), 56.5 and 59.2(C-13 and C-14), 92.3(C-17), 111.7(C-2), 113.8(C-4), 116.1(C-16^2), 127.0(C-1), 132.6(C-10), 133.9 and 134.3(C-17^1 and C-17^2), 137.9(C-5), 140.5(C-16^1) and 157.4(C-3); (Found: C, 82.3; H, 8.3%; M$^+$ 336; $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336).

3-Methoxy-3'*H*,6'*H*,15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 63

Potassium hydride (35% suspension in mineral oil, 97 mg, 0.85 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in tetrahydrofuran (3 cm^3). A solution of the diene **62** (160 mg, 0.48 mmol) in tetrahydrofuran (3 cm^3) was added and the resulting mixture heated at reflux for 1 h. The mixture was cooled and the reaction quenched by the slow addition of ethanol (10 cm^3) and water. The resultant solution was extracted with ethyl acetate, the combined organic phase washed with water, dried (Mg SO_4) and the solvent removed under reduced pressure. The crude residue (149 mg) was chromatographed on silica gel (20 g) using ethyl acetate-toluene (2:8) as eluent to give **63** (140 mg, 87%), m.p. 176-178°C (from ethyl acetate-hexane); $[\alpha]_D$ +213° (*c.* 1.1); ν_{max}/cm^{-1} 1724 (CO); δ_H(400 MHz) 1.03(3H, s, 13β-Me), 2.00(1H, dd, *J* 19.2 and 11.3 Hz, 16α-H), 2.58(1H, dd, *J* 19.2 and 8.3 Hz, 16β-H), 2.76-2.80(2H, m, 6α- and 6β-H), 2.88(1H, td, *J* 11.6x2 and 4.0 Hz, 9α-H), 2.96(1H, m, 15α-H), 3.78(3H, s, 3-OMe), 5.64(1H, m, 4'-H), 5.81(1H, m, 5'-H) 6.60(1H, d, *J* 2.7 Hz, 4-H), 6.74(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.22(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 13.9(q, C13β-Me), 23.8(t, C-11), 27.2(t, C-7), 27.9(t, C-12), 29.8(d, C-15), 30.5(t, C-6), 31.9(t, C-6'), 32.3(t, C-3'), 36.6(d, C-8), 41.8(t, C-16), 43.7(s, C-14), 46.1(d, C-9), 55.2(q, 3-OMe), 56.1(s, C-13), 112.1(d, C-2), 113.4(d, C-4), 127.1(d, C-1), 123.5 and 127.6(each d, C-4' and C-5'), 132.0(s, C-10), 137.9(s, C-5), 157.4(s, C-3), 221.5(s, C-17); (Found: C, 82,1; H, 8.4%; M^+, 336; $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.3%; *M*, 336).

Hydrogenation of the Olefinic Ketone 63

The olefinic-ketone **63** (22 mg, 0.07 mmol) in ethyl acetate (5 cm^3) at 24°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%, 5 mg). After 3 h the mixture was filtered, and the filtrate evaporated under reduced pressure to give a crude residue (19 mg). Filtration through silica gel (2 g) using toluene as eluent gave **44** (18 mg, 81%) which was identical to authentic reference material (m.p., mixed m.p., mass and infrared spectra).

3-Methoxy-3'*H*,6'*H*,15αH-benzo[14,15]-14β-estra-1,3,5(10),16-tetraen-17-yl acetate 64

A solution of the acetoxy-diene **61** (85 mg, 0.22 mmol) in dry toluene (5 cm^3) was purged with nitrogen and then heated in a sealed tube at 150°C (oil bath) for 48 h. The cooled reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The resultant residue (61 mg) was chromatographed on silica gel (7 g) using ethyl acetate-toluene (1:9) as eluent to give **64** (57 mg, 67%), m.p. 163-164°C (from ethyl acetate-hexane); $[\alpha]_D$ +278° (*c*. 1.0); ν_{max}/cm^{-1} 1729 (CO); δ_H(400 MHz) 1.08(3H, s, 13β-Me), 2.12(3H, s, 17-OCO*Me*), 2.76-2.80(2H, m, 6α- and 6β-H), 3.02(1H, m, 15α-H), 3.77(3H, s, 3-OMe), 4.84(1H, d, *J* 5.7 Hz, 16-H), 5.34 and 5.57(each 1H, m, 4'-H and 5'-H), 6.62(1H, d, *J* 2.7 Hz, 4-H), 6.71(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.19(1H, d, *J* 8.5 Hz, 1-H); (Found: C, 79,5; H, 7.9%; M^+, 378; $C_{25}H_{30}O_3$ requires C, 79.3; H, 8.0; *M*, 378).

Hydrolysis of the Enol Acetate 64

The enol acetate **64** (20 mg, 0.05 mmol) was suspended in methanol (3 cm^3) and potasium hydroxide (0.1 M solution in methanol, 1 cm^3) was added. The mixture was stirred at 24°C for 30 min., then saturated aqueous ammonium chloride added. Standard work-up followed by filtration of the crude product (18 mg) through silica gel (2 g) using toluene as eluent gave **63** (15 mg, 84 %)

3-Methoxy-14,17α-etheno-16α-isopropenylestra-1,3,5(10)-trien-17β-yl acetate 65

Dibromoethane (0.1 cm^3., 1.43 mmol) was added to a stirred suspension of zinc powder (130 mg, 2 mmol) in tetrahydrofuran (5 cm^3) under nitrogen. The mixture was cooled to -40°C (dry ice/acetone bath) and titanium tetrachloride (0.15 cm^3, 1.4 mmol) was added dropwise over 15 min. The mixture was stirred at 5°C for 2 h and then dichloromethane (5 cm^3) was added to the dark grey slurry. The cycloadduct **32** (394 mg, 1.0 mmol) in dichloromethane (5 cm^3) was added and the resultant mixture stirred at 24°C for 1.5 h. The mixture was diluted with pentane (10 cm^3) and a saturated aqueous solution of sodium hydrogen carbonate was added slowly until effervescence ceased. The organic phase was separated and the resultant aqueous phase extracted with dichloromethane. The combined organic phase was washed successively with sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and the crude residue (374 mg) chromatographed on silica gel (40 g) using ethyl acetate-toluene (1:9) as eluent affording **65** (303 mg, 77%), m.p. 167-169°C (from acetone-methanol); $[\alpha]_D$ +209° (*c*.1.0); ν_{max}/cm^{-1} 1728 (OAc); δ_H(400 MHz) 0.97(3H, s, 13β-Me), 1.13(1H, dt, *J* 13.4 and 2x3.2 Hz, 12β-H), 1.26(1H, obsc. m, 11β-H), 1.33(1H, dd, *J* 12.1 and 4.5 Hz, 15β-H), 1.39(1H, td, *J* 2x11.5 and 2.6 Hz, 8β-H), 1.76(3H, s, 16^1-Me), 1.78(1H, dd, *J* 12.1 and 8.8 Hz, 15α-H), 2.09(3H, s, 17-OAc), 2.23(1H, dddd, *J* 13.4, 2x3.7 and 3.2 Hz, 11α-H), 2.36(1H, td, 2x13.4 and 3.7 Hz, 12α-H), 2.50(1H, td, 2x11.5 and 3.7 Hz, 9α-H), 2.85-2.90(2H, m, 6α- and 6β-H), 3.08(1H, dd, *J* 8.8 and 4.5 Hz, 16β-H), 3.77(3H, s, 3-OMe), 4.64(1H, dq, *J* 4.1 and 3x1.8 Hz, 16^2-H$_{cis}$), 4.80(1H, dq, *J* 4.1 and 3x0.8 Hz, 16^2-H$_{trans}$), 5.96 and 6.18(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H's), 6.64(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.22(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 14.8(C-18), 21.7(17-OCO*Me*), 23.7(C-7), 24.1(16^1-Me), 27.3(C-11), 30.0(C-12), 30.2(C-6), 33.0(C-15), 39.5 and 40.0(C-8 and C-9), 47.4(C-16), 55.1(C-13), 55.2(3-OMe), 61.3(C-14), 96.7(C-17), 111.7(C-2), 112.2(C-16^2), 113.7(C-4), 127.1(C-1), 130.3 and 131.3(C-17^1 and C-17^2), 132.6(C-10), 137.9(C-5), 145.2(C-16^2), 157.4(C-3), 169.9(17-O*C*OMe); (Found: C, 79.4; H, 8.2%; M$^+$ 392; $C_{26}H_{32}O_3$ requires C, 79.6; H, 8.2%; *M*, 392).

3-Methoxy-14,17α-etheno-16α-isopropenylestra-1,3,5(10)-trien-17β-ol 66

Lithium aluminium hydride (70mg, 1.7mmol) was added to the acetoxy-diene **65** (170 mg, 0.43 mmol) in dry tetrahydrofuran (7 cm^3) at 0°C under nitrogen, then the mixture stirred at 25°C for 20 min. Aqueous sodium sulfate was added to the solution at 0°C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture stirred for 30 min, then filtered through layers of magnesium sulfate and Celite in a sintered glass funnel. The filter pad was washed with chloroform and the solvent removed under reduced pressure to give **66** (116 mg, 77%), m.p. 217-220°C (from acetone-methanol); $[\alpha]_D$ +197° (*c.* 1.1); ν_{max}/cm^{-1} 3475 (OH); δ_H(200 MHz) 1.01(3H, s, 13β-Me), 1.25(1H, dd, *J* 12.7 and 4.6 Hz, 15β-H), 1.81(3H, br s, 16^1-Me), 1.83(1H, dd, *J* 12.7 and 8.5 Hz, 15α-H), 3.05(1H, dd, 8.5 and 4.6 Hz, 16β-H), 3.77(3H, s, 3-OMe), 4.56 and 4.73(each 1H, m, 16^1- and 16^2-H), 6.61 and 6.71(each 1H, d, *J* 8.4 Hz, 17^1- and 17^2-H), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.22(1H, d, *J* 8.6 Hz, 1-H); δ_C(50MHz) 15.3(C-18), 23.9(C-7), 24.8(16^1-Me), 27.1(C-11), 30.2(C-12), 30.6(C-6), 35.2(C-15), 39.6 and 41.7(C-8 and C-9), 48.0(C-16), 54.2(C-13), 55.2(3-OMe), 61.5(C-14), 87.2(C-17), 111.6(C-2), 113.4(C-4), 114.7(C-16^2), 127.3(C-1), 130.8 and 131.5(C-17^1 and C-17^2), 132.5(C-10), 137.4(C-5), 148.2(C-16^2) and 157.4(C-3); (Found: C, 82.2; H, 8.4%; M$^+$, 350; $C_{24}H_{30}O_2$ requires C, 82.2; H, 8.6%; *M*, 350).

3-Methoxy-4'-methyl-3'*H*,6'*H*-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 67

Potassium hydride dispersion (35% suspension in mineral oil, 64 mg , 0.56 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in tetrahydrofuran (3 cm^3). A solution of the diene **66** (110 mg, 0.31 mmol) in tetrahydrofuran (2 cm^3) was added and the resulting mixture heated at reflux for 2 h. The mixture was cooled and the reaction quenched by the slow addition of ethanol (10 cm^3) and water. The resultant solution was extracted with ethyl acetate, the combined organic phase washed with water, dried (Mg SO_4) and the solvent removed under reduced pressure. The crude residue (98 mg) was chromatographed on silica gel (10 g) using ethyl acetate-toluene (2:8) as eluent to give **67** (90 mg, 82%), m.p. 211-214°C (from ethyl acetate); $[\alpha]_D$ +284° (*c.* 0.8); ν_{max}/cm^{-1} 1725 (CO); δ_H(400MHz) 1.02(3H, s, 13β-Me), 1.33(3H, broad s, 4'-Me), 2.00(1H, dd, *J* 19.0 and 11.4 Hz, 16α-H), 2.58(1H, dd, *J* 19.0 and 8.3 Hz, 16β-H), 2.88(1H, td, *J* 11.8x2 and 3.6 Hz, 9α-H), 2.95(1H, m, 15α-H), 3.77(3H, s, 3-OMe), 5.49(1H, m, 5'-H), 6.60(1H, d, *J* 2.8 Hz, 4-H), 6.74(1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21(1H, d, *J* 8.7 Hz, 1-H); (Found: C, 82,4; H, 8.8%; M$^+$, 350; $C_{24}H_{30}O_2$ requires C, 82.2; H, 8.6%; *M*, 350).

3-Methoxy-4'-methyl-3'*H*,6'*H*,15αH-benzo[14,15]-14β-estra-1,3,5(10),16-tetraen-17β-yl acetate 68

A solution of the acetoxy-diene **65** (67 mg, 0.17 mmol) in dry toluene (6 cm^3) was purged with nitrogen and then heated in a sealed tube at 150°C (oil bath) for 56 h. The cooled reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The resultant residue (45 mg) was chromatographed on silica gel (5 g) using ethyl acetate-toluene (1:9) as eluent to give **68** (42 mg, 64%), m.p. 147-149°C (from ethyl acetate-hexane); $[\alpha]_D$ +306° (*c*. 0.9); ν_{max}/cm^{-1} 1728 (CO); δ_H(400 MHz) 1.12(3H, s, 13β-Me), 2.09(3H, s, 17-OCO*Me*), 2.72-2.81(2H, m, 6α- and 6β-H), 3.11(1H, m, 15α-H), 3.78(3H, s, 3-OMe), 4.69(1H, d, *J* 6.1 Hz, 16-H), 5.65 and 5.74(each 1H, m, 4'-H and 5'-H), 6.61(1H, d, *J* 2.7 Hz, 4-H), 6.73(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.19(1H, d, *J* 8.5 Hz, 1-H); (Found: C, 79.8; H, 8.3%; M^+ 392; $C_{26}H_{32}O_3$ requires C, 79.6; H, 8.2%; *M*, 392).

Hydrolysis of the Enol Acetate 68

The enol acetate **68** (23 mg, 0.06 mmol) was suspended in methanol (3 cm^3) and potassium hydroxide (0.1 M solution in methanol, 0.8 cm^3) was added. The mixture was stirred at 24°C for 30 min., then saturated aqueous ammonium chloride added. Standard work-up followed by filtration of the crude product (20 mg) through silica gel (2 g) using toluene as eluent gave **67** (18 mg, 87 %)

16β,17β-Diacetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-16α-carbonitrile 69

A solution of the dienyl acetate **10** (972 mg, 3.0 mmol), 2-acetoxyacrylonitrile (0.5 cm^3, 4.7 mmol) and hydroquinone (50 mg) in anhydrous toluene (5 cm^3) was heated in a sealed tube under nitrogen at 150°C. Further aliquots of 2-acetoxyacrylonitrile (each 0.2 cm^3, 1.8 mmol) were added after 48 and 96 h. After a total reaction time of 144 h the mixture was allowed to cool, filtered through Celite and evaporated under reduced pressure to yield a crude residue (1.1 g). Chromatography of this residue on silica gel (100 g) using toluene as eluent gave starting material **10** (175 mg, 18%) followed by **69** (1.04 g, 80%) m.p. 142-145°C (lit.[64] 140-145°C); $[\alpha]_D$ +163° (*c* 1.0); (Found: C, 71.5; H, 6.6; N, 3.1%; M^+ ,435; $C_{26}H_{29}NO_5$ requires C, 71.7; H, 6.7; N, 3.2%; *M*, 435).

17β-Hydroxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16-one 70

Aqueous M-potassium hydroxide (4 cm^3) was added to a solution of the cycloadduct **69** (500 mg, 1.15 mmol) in dimethyl sulfoxide (10 cm^3) and tetrahydrofuran (10 cm^3) cooled to 0°C. The solution was allowed to warm 23°C and stirred at that temperature for 24 h. Saturated aqueous ammonium chloride was added to the reaction mixture followed by extraction with chloroform. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography of the crude residue (339 mg) on silica gel (30 g), using ethyl acetate-toluene (1:9) as eluent, gave **70** (316 mg, 85%), m.p. 154-158°C (lit.[64] 154-158°C); $[\alpha]_D$ +435° (*c* 1.0); (Found: C, 77.9; H, 7.4%; M^+, 324; $C_{21}H_{24}O_3$ requires C, 77.8; H, 7.5%; *M*, 324).

3-Methoxy-16α-vinyl-14,17α-ethenoestra-1,3,5(10)-trien-16β,17β-diol 71

The hydroxy-ketone **70** (212 mg, 0.65 mmol) was added to a solution of vinyl magnesium bromide [prepared from vinyl bromide (0.1 cm^3, 0.93 mmol) and magnesium turnings (24 mg, 1 mmol)] in tetrahydrofuran (10 cm^3) and the resultant mixture stirred at 24°C for 3 h. Saturated aqueous sodium hydrogen carbonate was added, the mixture stirred for 15 min, then extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a solid residue (198 mg). Flash chromatography on silica gel (20 g) using ethyl acetate-toluene (3:7) as eluent gave **71** (193 mg, 83%), m.p. 182-184°C (from chloroform-methanol); $[\alpha]_D$ +213° (*c*.0.9); ν_{max}/cm^{-1} 3460br (OH); δ_H(400 MHz) 1.19(3H, s, 13β-Me), 1.84 and 1.95(each 1H, d, *J* 12.5 Hz, 15α- and 15β-H), 2.50(1H, td, *J* 11.6x2 and 3.4 Hz, 9α-H), 2.78-2.90(2H, m, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 5.11(1H, dd, *J* 10.6 and 1.2 Hz, 16^2-H(cis)), 5.25(1H, dd, *J* 17.3 and 1.2 Hz, 16^2-H(trans)), 5.87 and 5.99(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 5.97(1H, dd, 17.3 and 10.6 Hz, 16^1-H), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 15.7(C-18), 24.0(C-7), 26.7(C-11), 28.7(C-12), 30.1(C-6), 38.8(C-15), 39.9(C-8), 41.8(C-9), 55.2(3-OMe), 55.8(C-13), 60.7(C-14), 82.2(C-16), 92.7(C-17), 111.7(C-2), 113.6(C-4), 113.7(C-16^2), 127.0(C-1), 132.6(C-10), 134.7 and 135.8(C-17^1 and C-17^2), 137.8(C-5), 143.9(C-16^1), 157.4(C-3); Found: C, 78.1; H, 8.6%; M^+, 354; $C_{23}H_{28}O_3$ requires C, 77.9; H, 8.6%; *M*, 354).

3-Methoxy-3',4'-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-5'(6'H),17-dione 72

Potassium hydride dispersion (35% suspension in mineral oil, 45 mg, 0.4 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in tetrahydrofuran (5 cm^3). A solution of the diene **71** (130 mg, 0.37 mmol) in tetrahydrofuran (3 cm^3) was added to the suspension, cooled to -78°C, and the resulting mixture stirred at that temperature for 15 min. The reaction was quenched by the slow addition of ethanol and the mixture was allowed to warm to 24°C. Water was added and the resultant solution was extracted with ethyl acetate, the combined organic phase washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the crude residue (113 mg) on silica gel (10g) using ethyl acetate-toluene (2:8) as eluent gave **72** (105 mg, 78%), m.p. 106-109°C (from methanol-diisopropyl ether); $[\alpha]_D$ +267°; ν_{max}/cm^{-1} 1698 and 1725 (CO); δ_H(400 MHz) 0.98(3H, s, 13β-Me), 1.61(1H, dd, *J* 19.7 and 10.3 Hz, 16β-H), 1.94(1H, d, *J* 15.5 Hz, 6'α-H), 2.20(1H, dd, *J* 15.5 and 1.7 Hz, 6'β-H), 2.78(1H, d, *J* 19.7 and 9.9 Hz, 16α-H), 3.09(1H, dddd, *J* 10.3, 9.7, 5.0 and 2.4 Hz, 15α-H), 3.77(3H, s, 3-OMe), 6.60(1H, d, *J* 2.8 Hz, 4-H), 6.74(1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.20(1H, d, *J* 8.7 Hz, 1-H); δ_C(50 MHz) 13.9(C13β-Me), 26.1(C-11), 26.2(C-3'), 27.4(C-7), 30.0(C-6), 31.5(C-12), 31.7(C-4'), 34.9(C-15), 38.1(C-8), 46.2(C-9), 48.7(C-6'), 52.0(C-13), 55.2(3-OMe), 55.8(C-14), 112.4(C-2), 113.3(C-4), 127.2(C-1), 131.2(C-10), 137.4(C-5), 157.6(C-3), 211.4(C-5') and 219.4(C-17); (Found: C, 78.4; H, 8.0%; M$^+$, 352; $C_{23}H_{28}O_3$ requires C, 78.7; H, 8.0%; *M*, 352).

3-Methoxy-14,17α-etheno-16^2-benzyloxy-16α-vinylestra-1,3,5(10)-trien-17β-yl acetate

t-Butyllithium (0.8 cm^3, 1.7 M) was added to a suspension of benzyloxytriphenylphosphonium chloride (585 mg, 1.4 mmol) in tetrahydrofuran (12 cm^3) cooled to 0°C. The mixture was stirred at this temperature for 1 h. The cycloadduct **59** (380 mg, 1 mmol) in dry tetrahydrofuran (8 cm^3) was added to the orange solution and the mixture stirred at 25°C for 3 h. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with dilute hydrochloric acid (0.1 M), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a crude residue (487 mg). Flash chromatography on silica gel (50 g) using ethyl acetate-toluene (1:19) as eluent gave *(16^{2}E)-3-methoxy-*14,17*α-etheno-*16^2-*benzyloxy-*16*α-vinylestra-*1,3,5(10)*-trien-*17*β-yl acetate* **73** (121 mg, 25%), m.p.213-215°C (from acetone-methanol); $[\alpha]_D$ +307° (*c*. 1.2); ν_{max}/cm^{-1} 1734 (OAc); δ_H(400 MHz) 0.93(3H, s, 13β-Me), 1.02(1H, dd, *J* 11.9 and 3.6 Hz, 15β-H), 1.13(1H, dt, *J* 13.4 and 2x3.1 Hz, 12β-H), 1.26(1H, qd, *J* 2x13.4, 11.6 and 3.1 Hz, 11β-H), 1.37(1H, td, *J* 2x11.6 and 2.4 Hz, 8β-H), 1.63 and 1.80(each 1H, each m, 7α- and 7β-H), 1.88(1H, dd, *J* 11.9 and 8.8 Hz, 15α-H), 2.05(3H, s, 17-OCO*Me*), 2.20(1H, dddd, *J* 13.4, 4.2 and 2x3.1 Hz, 11α-H), 2.32(1H, tdd, *J* 2x13.4 and 4.2 Hz, 12α-H), 2.51(1H, td, *J* 2x11.6 and 3.1 Hz, 9α-H), 2.82-2.88(3H, m, 16β-, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 4.61(1H, dd, *J* 12.5 and 9.4 Hz, 16^1-H), 4.71(1H, s, O*CH*$_2$), 6.03 and 6.21(each 1H, d, *J* 6.3 Hz, 17^1- and 17^2-H), 6.38(1H, d, *J* 12.5, 16^2-H), 6.64(1H, d, *J* 2.7 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.22(1H, d, *J* 8.6 Hz, 1-H) and 7.29-7.40(5H, m, OCH_2*Ph*); δ_C(100 MHz) 14.5(q, C-18), 21.6(q, 17-OCO*Me*), 23.7(d, C-7), 27.2(d, C-11), 29.9(d, C-12), 30.2(d, C-6), 35.9(t, C-15), 39.4 and 40.0(each d, C-8 and C-9), 41.7(d, C-16), 55.2(q, 3-OMe), 55.2 and 60.3(each s, C-13 and C-14), 71.1(t, OCH_2), 96.1(s, C-17), 106.4(d, C-16^1), 111.7(d, C-2), 113.7(d, C-4), 127.1(d, C-1), 127.5(d, 2xC-2"), 127.8(d, C-4'), 128.4(d, 2xC-3"), 131.1 and 131.7(each d, C-17^1 and C-17^2), 132.6(s, C-10), 137.9(s, C-5), 146.6(d, C-16^2)157.4(s, C-3) and 170.3(s, 17-OCOMe); followed by (16^{2}Z)-3-*methoxy*-14,17α-*etheno*-16^2-*benzyloxy*-16α-*vinylestra*-1,3,5(10)-*trien*-17β-*yl acetate* **74** (296 mg, 61%), m.p.231-232°C (from acetone-methanol); $[\alpha]_D$ +267° (*c.* 1.1); ν_{max}/cm^{-1} 1731 (OAc) δ_H(400 MHz) 0.76(1H, dd, *J* 11.7 and 3.8 Hz, 15β-H), 1.0(3H, s, 13β-Me), 1.60 and 1.78(each 1H, each m, 7α- and 7β-H), 1.97(1H, dd, *J* 11.7 and 8.9 Hz, 15α-H), 2.04(3H, s, 17-OCO*Me*), 2.82-2.90(2H, m, 6α- and 6β-H), 3.60(1H, ddd, *J* 2x8.9 and 3.8 Hz, 16β-H), 3.77(3H, s, 3-OMe), 4.25(1H, dd, *J* 8.9 and 6.2 Hz, 16^1-H), 4.70(1H, s, O*CH$_2$*), 6.01(1H, d, *J* 6.2, 16^2-H), 6.08 and 6.33(each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.20(1H, d, *J* 8.6 Hz, 1-H) and 7.28-7.30(5H, m, OCH$_2$*Ph*); δ_C(100 MHz) 14.7(q, C-18), 21.7(q, 17-OCO*Me*), 23.7(d, C-7), 27.2(d, C-11), 29.9(d, C-12), 30.3(d, C-6), 36.7(t, C-15), 37.8(d, C-16), 39.5 and 40.0(each d, C-8 and C-9), 55.2(q, 3-OMe), 55.4 and 60.5(each s, C-13 and C-14), 73.6(t, OCH$_2$), 96.6(s, C-17), 109.4(d, C-16^1), 111.7(d, C-2), 113.7(d, C-4), 127.1(d, C-1), 127.2(d, 2xC-2"), 127.5(d, C-4'), 128.4(d, 2xC-3"), 131.6 and 131.7(each d, C-17^1 and C-17^2), 132.6(s, C-10), 137.9(s, C-5), 145.4(d, C-16^2), 157.4(s, C-3) and 170.5(s, 17-OCOMe); (Found: C, 79,6; H, 7.3%; M$^+$, 484; $C_{32}H_{36}O_4$ requires C, 79.3; H, 7.4; *M*, 484)

(16^2*E*)-3-Methoxy-14,17α-etheno-16^2-benzyloxy-16α-vinylestra-1,3,5(10)-trien-17β-ol 75

Lithium aluminium hydride (15 mg, 0.4 mmol) was added to the acetoxy-diene **73** (100 mg, 0.21 mmol) in dry tetrahydrofuran (5 cm^3) at 0°C under nitrogen, then the mixture stirred at 25°C for 20 min. Aqueous sodium sulfate was added to the solution at 0°C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture stirred for 30 min, then filtered through layers of magnesium sulfate and Celite in a sintered glass funnel. The filter pad was washed with chloroform and the solvent removed under reduced pressure to give **75** (79 mg, 85%), m.p. 254-255°C (from ethyl acetate-hexane);

$[\alpha]_D$ +311° (*c.* 1.0); ν_{max}/cm^{-1} 3467 (OH); δ_H(400 MHz) 0.92(3H, s, 13β-Me), 1.06(1H, dd, *J* 12.1 and 3.8 Hz, 15β-H), 1.95(1H, dd, *J* 12.1 and 8.6 Hz, 15α-H), 2.59(1H, ddd, *J* 9.9, 8.6 and 3.8 Hz, 16β-H), 2.82-2.88(2H, 6α- and 6β-H), 3.77(3H, s, 3-OMe), 4.59(1H, dd, *J* 12.5 and 9.9 Hz, 16^1-H), 4.71(1H, s, O*CH*$_2$), 5.78 and 6.07(each 1H, d, *J* 6.0 Hz, 17^1- and 17^2-H), 6.46(1H, d, *J* 12.5, 16^2-H), 6.62(1H, d, *J* 2.7 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.7 Hz, 2-H), 7.20(1H, d, *J* 8.6 Hz, 1-H) and 7.29-7.40(5H, m, OCH$_2$*Ph*); (Found: C, 81.6; H, 7.8%; M$^+$ 442; $C_{30}H_{34}O_3$ requires C, 81.4; H, 7.7%: *M*, 442).

(16^2*Z*)-3-Methoxy-14,17α-etheno-16^2-benzyloxy-16α-vinylestra-1,3,5(10)-trien-17β-ol 76

Lithium aluminium hydride (20 mg, 0.5 mmol) was added to the acetoxy-diene **74** (200 mg, 0.42 mmol) in dry tetrahydrofuran (8 cm^3) at 0°C under nitrogen, then the mixture stirred at 25°C for 35 min. Aqueous sodium sulfate was added to the solution at 0°C until a white precipitate formed. Diethyl ether (10 cm^3) was added and the mixture stirred for 30 min, then filtered through layers of magnesium sulfate and Celite in a sintered glass funnel. The filter pad was washed with chloroform and the solvent removed under reduced pressure to give **76** (150 mg, 81%), m.p. 217-219°C (from ethyl acetate-hexane); $[\alpha]_D$ +212° (*c.* 1.1); ν_{max}/cm^{-1} 3478 (OH); δ_H(400 MHz) 0.97(3H, s, 13β-Me), 1.03(1H, dd, *J* 11.9 and 3.8 Hz, 15β-H), 2.01(1H, dd, *J* 11.9 and 8.2 Hz, 15α-H), 2.82-2.91(2H, m, 6α- and 6β-H), 3.32(1H, dddd, *J* 2x8.2, 3.8 and 1.5 Hz, 16β-H), 3.77(3H, s, 3-OMe), 4.20(1H, dd, *J* 8.2 and 6.2 Hz, 16^1-H), 4.82(1H, s, O*CH*$_2$), 5.86 and 6.0(each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.09(1H, dd, *J* 6.2 and 1.5 Hz, 16^2-H), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.20(1H, d, *J* 8.6 Hz, 1-H) and 7.26-7.30(5H, m, OCH$_2$*Ph*); (Found: C, 81.4; H, 7.9%; M$^+$ 442; $C_{30}H_{34}O_3$ requires C, 81.4; H, 7.7%: *M*, 442).

3-Methoxy-6'*H*,15αH-3'β-benzyloxybenzo[14,15]-14β-estra-1,3,5(10)-trien-17-one 77

(a) Potassium hydride (35% suspension in mineral oil, 30 mg, 0.26 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in tetrahydrofuran (4 cm^3). A solution of (16^2*E*)-3-*methoxy*-14,17α-*etheno*-16^2-*benzyloxy*-16α-*vinylestra*-1,3,5(10)-*trien*-17β-*ol* **75** (60 mg, 0.14 mmol) in tetrahydrofuran (5 cm^3) was added and the resulting mixture heated at reflux for 1 h. The mixture was cooled and the reaction quenched by the slow addition of ethanol (10 cm^3) and water. The resultant solution was extracted with ethyl acetate, the combined organic phase washed with water, dried (Mg SO_4) and the solvent removed under reduced pressure. The crude residue (57 mg) was chromatographed on silica gel (10 g) using ethyl acetate-toluene (1:9) as eluent to give **77** (49 mg, 79%), m.p. 256-258°C (from chloroform-hexane); $[\alpha]_D$ +356° (*c*. 0.9); ν_{max}/cm^{-1} 1727 (CO); δ_H(400 MHz) 1.04(3H, s, 13β-Me), 2.26(1H, dd, *J* 19.8 and 11.2 Hz, 16α-H), 2.60(1H, dd, *J* 19.8 and 8.3 Hz, 16β-H), 2.72-2.90(2H, m, 6α- and 6β-H), 3.24(1H, m, 15α-H), 3.78(3H, s, 3-OMe), 4.32(1H, m, 3'α-H), 5.72(1H, m, 4'-H), 5.84(1H, m, 5'-H) 6.61(1H, d, *J* 2.7 Hz, 4-H), 6.75(1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.22(1H, d, *J* 8.5 Hz, 1-H) and 7.28-7.35(5H, m, OCH_2*Ph*); (Found: C, 81.4; H, 7.9%; M^+ 442; $C_{30}H_{34}O_3$ requires C, 81.4; H, 7.7%: *M*, 442).

(b) Potassium hydride (35% suspension in mineral oil, 40 mg, 0.35 mmol) was washed with pentane to remove the oil, then dried by the passage of nitrogen over the hydride and finally suspended in tetrahydrofuran (4 cm^3). A solution of (16^2*Z*)-3-*methoxy*-14,17α-*etheno*-16^2-*benzyloxy*-16α-*vinylestra*-1,3,5(10)-*trien*-17β-*ol* **76** (110 mg, 0.25 mmol) in tetrahydrofuran (6 cm^3) was added and the resulting mixture heated at reflux for 3 h. The mixture was cooled and the reaction quenched by the slow addition of ethanol (10 cm^3) and water. The resultant solution was extracted with ethyl acetate, the combined organic phase washed with water, dried (Mg SO_4) and the solvent removed under reduced pressure. The crude residue (98 mg) was chromatographed on silica gel (20 g) using ethyl acetate-toluene (1:9) as eluent to give 77 (74 mg, 67%)

Reductive Coupling of the 14β-3'-Oxobutyl Δ^{15}-17-Ketone 34

Samarium diiodide (12 cm^3 of a 0.1 M solution, 1.2 mmol) was added to a solution of **34** (178 mg, 0.51 mmol) in tetrahydrofuran (15 cm^3) cooled to -78°C. The mixture was stirred at that temperature for 30 min, then allowed to warm to 20°C and neutralised by the addition of hydrochloric acid (0.1 M, 10 cm^3). The mixture was extracted with chloroform. The combined organic phase was washed with hydrochloric acid, sodium thiosulfate, saturated aqueous sodium hydrogen carbonate and water, then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (171 mg) which was chromatographed on silica gel (18 g) using ethyl acetate-toluene (3:5) as eluent to give 3'β-*hydroxy*-3'α-*methyl*-3-*methoxy*-4',5'-*dihydro*-3'*H*,15α*H*-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* **80** (64 mg, 36%), m.p. 167-170°C (from acetone-methanol); $[\alpha]_D$ -6.6° (*c*.1.3); ν_{max}/cm^{-1} 3537 (OH) and 1727 (CO); δ_H(400 MHz, C_6D_6) 0.86(3H, s, 3'α-Me), 1.17(3H, s, 13β-Me), 1.82(1H, dd, *J* 10.7 and 3.9 Hz, 15α-H), 2.01(1H, dd, *J* 19.3 and 10.7 Hz, 16α-H), 2.49(1H, dd, 19.3 and 3.9 Hz, 16β-H), 2.27(2H, m, 6α- and 6β-H), 3.37(3H, s, 3-OMe), 6.63(1H, d, *J* 2.8Hz, 4-H), 6.70(1H, dd, *J* 8.5 and 2.8Hz, 2-H) and 6.90(1H, d, *J* 8.5Hz, 1-H); δ_C(100 MHz, C_6D_6) 23.6(t, C-7), 23.8(q, 3'α-Me), 26.9(q, C-18), 28.8(t, C-11), 30.9(t, C-5'), 31.0(t, C-6), 32.3(t, C-12), 34.4(d, C-9), 36.3(t, C-16), 42.9(t, C-4'), 45.3(d, C-8), 47.4(d, C-15), 52.2(s, C-14), 54.5(q, 3-OMe), 57.2(s, C-13), 79.3(s, C-3'), 112.6(d, C-2), 113.1(d, C-4), 128.8(d, C-1), 134.4(s, C-10), 137.0(s, C-5), 157.6(s, C-3), 223.0(s, C-17); (Found: C, 77.7; H, 8.2%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354) followed by 3'α-*hydroxy*-3'β-*methyl*-3-*methoxy*-4',5'-*dihydro*-3'*H*,15α*H*-*cyclopenta*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* **81** (111 mg, 62%), m.p. 143-145°C (from acetone-methanol); $[\alpha]_D$ -26.5° (*c*. 0.98); ν_{max}/cm^{-1} 3564 (OH) and 1728 (CO); δ_H(400 MHz, C_6D_6) 0.94(3H, s, 3'β-Me), 1.01(3H, s, 13β-Me), 1.75(1H, dd, *J* 19.2 and 7.2Hz, 16β-H), 2.03(1H, dd, *J* 10.6 and 7.2Hz, 15α-H), 2.42(1H, dd, *J* 19.2 and 10.6Hz, 16β-H), 3.42(3H, s, 3-OMe), 6.68(1H, d, *J* 2.8Hz, 4-H), 6.85(1H, dd, *J* 8.4 and 2.8Hz, 2-H) and 7.14(1H, d, *J* 8.4Hz, 1-H); δ_C(100 MHz, C_6D_6) 16.9(q, C-18), 26.1(t, C-7), 27.8(q, 3'β-Me), 29.5(t, C-11), 32.6(t, C-12), 33.0(t, C-6), 33.4(t, C-5'), 38.8(d, C-9), 38.9(t, C-16), 40.4(t, C-8), 45.0(d, C-8), 49.7(d, C-15), 54.8(s, C-14), 55.0(q, 3-OMe), 59.0(s, C-13), 81.2(s, C-3'), 112.8(d, C-2), 113.5(d, C-4), 128.5(d, C-1), 132.9(s, C-10), 138.6(s, C-5), 157.2(s, C-3), 220.3(s, C-17); (Found: C, 77.9; H, 8.8%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

(16^1*R*)-16^1-Hydroxy-3-methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-17-one 91

The 14α,17α-ethano compound **33** (100 mg, 0.25 mmol) was suspended in methanolic potassium hydroxide (1 M, 2.5 cm^3, 2.5 mmol) and the mixture was stirred at 0°C. After 1.5 h the reaction was complete (TLC), and saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, the combined extracts washed with brine and water, then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue (100 mg) was filtered through silica gel (10 g) using toluene as eluent to give **91** (99 mg, 99%), m.p. 195-197°C (from acetone-methanol); $[\alpha]_D$ -78° (*c*. 1.1); ν_{max}/cm^{-1} 3597 (OH) and 1726 (CO); δ_H(400 MHz) 1.08(3H, s, 13β-Me), 1.26(1H, dddd, *J* 13.6, 5.8, 3.1 and 2.0 Hz, 16^3-H_n), 1.33(3H, s, 16^1-Me), 1.33(1H, ddd, *J* 15.0, 13.6 and 5.8 Hz, 16^2-H_n), 1.58(1H, qt, *J* 15.0, 5.9 and 2 x 2.0 Hz, 16^2-H_x), 2.04(1H, ddd, *J* 12.2, 5.6 and 3.1 Hz, 15α-H), 2.18(1H, d, *J* 12.2 Hz, 15β-H), 2.24(1H, td, *J* 2 x 13.6 and 5.9 Hz, 16^3-H_x), 2.41(1H, dd, *J* 5.6 and 2.2 Hz, 16α-H), 2.62(1H, td, 2 x 11.9 and 3.6 Hz, 9α-H), 3.20-3.51(2H, m, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 6.64(1H, d, *J* 2.8 Hz, 4-H), 6.73(1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.22(1H, d, *J* 8.5 Hz, 1-H); δ_C(50 MHz) 15.2(q, C-18), 23.6(t, C-7), 26.2(t, C-11), 27.5(t, C-15), 28.2(q, 16^1-Me), 29.3(t, C-16^3), 30.7(t, C-6), 31.7(t, C-12), 34.1(t, C-16^2), 37.3(d, C-9), 42.6(d, C-8), 45.3 and 49.2(each s, C-13 and C-14), 55.2(q, 3-OMe), 57.2(d, C-16), 71.0(s, C-16^1), 111.7(d, C-2), 113.5(d, C-4), 126.6(d, C-1), 131.4(s, C-10), 137.9(s, C-5), 157.6(s, C-3) and 221.3(s, C-17); (Found: C, 77.8; H, 8.6%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

Hydrogenation of the 14β-3'-Oxobutyl Δ^{15}-17-Ketone 34

The 14β-3'-oxobutyl Δ^{15}-17-ketone **34** (100 mg, 0.28 mmol) in ethyl acetate (8 cm^3) at 24°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%, 30 mg). After 90 min the mixture was filtered, and the filtrate evaporated under reduced pressure to give a crude residue (532 mg). Flash chromatography of this residue on silica gel (55 g) using ethyl acetate-toluene (1:9) as eluent gave 3-*methoxy*-14β-3'-*oxobutylestra*-1,3,5(10)-*trien*-17-*one* **90** (61 mg, 61%), m.p. 147-149°C (from acetone-methanol); $[\alpha]_D$ -47° (*c*.0.9); ν_{max}/cm^{-1} 1727 (CO); δ_H(200 MHz) 1.04(3H, s, 13β-Me), 2.13(3H, s, 3'-Me), 2.82-2.92(2H, m, 6α- and 6β-H), 3.79(3H, s, 3-OMe), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.67(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.21(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 15.6(q, C-18), 23.5(t, C-11), 25.4(t, C-7), 25.6(t, C-15), 30.2(q, C-4'), 30.4(t, C-6), 31.2(t, C-1'), 33.0(t, C-12), 33.5(t, C-16), 37.9(d, C-8), 39.3(t, C-2'), 41.8(d, C-9), 45.9(s, C-13), 52.6(s, C-14), 55.2(q, 3-OMe), 111.7(d, C-2), 113.5(d, C-4), 126.4(d, C-1), 132.1(s, C-10), 137.6(s, C-5), 157.6(s, C-3), 207.7(s, C-3') and 222.0(s, C-17); (Found: C, 77.7; H, 8.6%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354) followed by **91** (31 mg, 31%).

Conjugate Reduction of the 14β-3'-Oxobutyl 17-Ketone 34

Methyllithium (0.14 cm^3 of 5% solution in ether, 0.3 mmol) was added to a stirred suspension of copper(I) iodide (57 mg, 0.3 mmol) in dry tetrahydrofuran (5 cm^3) at 0°C under nitrogen. The suspension of methylcopper was cooled to -78°C and hexamethylphosphoric triamide (2 cm^3, 11.4 mmol) and di-isobutylaluminium hydride (0.3 cm^3 of 1.2 M solution in toluene, 4 mmol) were added successively. The mixture was stirred at -78°C for 30 min, then enone **34** (352 mg, 1 mmol) in dry tetrahydrofuran (2 cm^3) was added. The mixture was stirred at -78°C for 1.5 h, then M-hydrochloric acid (5 cm^3) was added and the mixture was extracted with chloroform. The extract was washed with M-hydrochloric acid, aqueuos sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (310 mg). Filtration through silica gel (30 g) with toluene yielded **90** (296 mg, 84%).

Base Treatment of the 14β-3'-Oxobutyl 17-Ketone 90

(a) The 14β-3'-oxobutyl 17-ketone **90** (100 mg, 0.28 mmol) was suspended in methanolic M-potassium hydroxide (10 cm^3, 10 mmol) and the mixture was stirred at 24°C. After 2.25 h the reaction was complete (TLC), and saturated aqueous ammonium chloride was added. The mixture was extracted with chloroform, the combined extracts washed with brine and water, then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue (89 mg) was filtered through silica gel (10 g) using ethyl acetate-hexane (3:7) as eluent to give **91** (85 mg, 85%).

(b) A solution of the 14β-3'-oxobutyl 17-ketone **90** (118 mg, 0.33 mmol) in tetrahydrofuran (5 cm^3) was added to lithium hexamethyldisilazane [from hexamethyldisilazane (0.1 cm^3, 0.4 mmol) and n-BuLi (1.6 M, 0.25 cm^3), stirred at 0°C for 30 min.] in tetrahydrofuran (10 cm^3) at -78°C and the resultant mixture stirred at that temperature for 1 h. Saturated aqueous ammonium chloride was added and the mixture extracted with chloroform. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a crude residue (99 mg). Chromatography on silica gel (10 g) using ethyl acetate-hexane as eluent gave **91** (96 mg, 81%).

(16^1*R*)-3-Methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-16^1,17β-diol 92

Lithium aluminium hydride (100 mg) was added to a solution of the hydroxy-ketone **91** (100 mg, 0.28 mmol) in tetrahydrofuran (3 cm^3) and the mixture stirred at 21°C for 20min. Water (10 cm^3) was added slowly followed by chloroform (10 cm^3) and the resulting mixture filtered under suction through Celite. The Celite was washed well with chloroform and the filtrate extracted with chloroform. The combined organic phase was washed with water (10 cm^3), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (97 mg). Chromatography on silica gel (10g) using ethyl acetate-toluene (1:1) eluent gave **92** (93 mg, 92%), m.p. 226-227°C (from acetone); ν_{max}/cm^{-1} 3400br (OH);

δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.12(1H, tdd, *J* 13.3, 3.6x2 and 2.8 Hz, 16^2-H$_x$), 1.24(1H, td, *J* 11.4x2 and 2.4 Hz, 8β-H), 1.42(3H, s, 16^1-Me), 1.60(1H, ddd, *J* 7.3, 6.8 and 2.8 Hz, 16α-H), 1.98(1H, d, *J* 12.7 Hz, 15β-H), 2.07(1H, dd, *J* 12.7 and 7.3 Hz, 15α-H), 2.46(1H, td, *J* 11.4x2 and 2.1 Hz, 9α-H), 2.78-2.84(2H, m, 6α- and 6β-H), 3.76(3H, s, 3-OMe), 3.99(1H, d, *J* 6.8 Hz, 17α-H), 6.61(1H, d, *J* 2.7 Hz, 4-H), 6.70(1H, dd, *J* 2.7 and 8.6 Hz, 2-H) and 7.2(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz); 15.7(q, C-18), 25.3(t, C-7), 27.6(t, C-11), 28.9(t, C-16^3), 29.9(t, C-6), 31.2(t, C-12), 31.3(q, 16^1-Me), 33.5(t, C-16^2), 38.3(d, C-9), 41.9(t, C-15), 42.9(s, C-13), 44.9(d, C-8), 46.0(s, C-14), 50.2(d, C-16), 55.2(q, 3-OMe), 72.0(s, C-16^1), 83.6(d, C-17), 111.6(d, C-2), 113.4(d, C-4), 126.7(d, C-1), 133.2(s, C-10), 138.2(s, C-5), 157.4(s, C-3); (Found C, 77.6; H, 8.9%; M$^+$, 356; $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.1%; *M*, 356).

Reductive Coupling of the 14β-3'-Oxobutyl 17-Ketone 90

(a) Samarium diiodide (10 cm^3 of a 0.1M solution, 1 mmol) was added to a solution of **90** (150 mg, 0.42 mmol) in tetrahydrofuran (5 cm^3) cooled to -78°C. The mixture was stirred at -78°C for 6 h, allowed to warm to 20°C and neutralised by the addition of hydrochloric acid (0.1 M, 10 cm^3). The mixture was extracted with chloroform. The combined organic phase was washed with hydrochloric acid (0.1 M), saturated aqueous sodium hydrogen carbonate, sodium thiosulfate and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (129 mg) which was chromatographed on silica gel (12g) using ethyl acetate-toluene (2:8) as eluent to give (16^1*S*)-16^1-*hydroxy*-3-*methoxy*-16^1-*methyl*-14,16β-*propanoestra*-1,3,5(10)-*trien*-17-*one* **101** (130 mg, 87%), m.p. 132-134°C (from ethyl acetate-methanol); ν_{max}/cm^{-1} 3530 (OH), 1718 (CO); δ_H (400 MHz) 1.08(3H, s, 13β-Me), 1.34(3H, s, 16^1-Me) 1.62(1H, d, *J* 12.8 Hz, 15β-H), 2.24(1H, ddd, *J* 12.8, 6.2 and 3.2 Hz, 15α-H), 2.38(1H, dd, *J* 6.2 and 1.8 Hz, 16α-H), 2.60(1H, td, *J* 2x11.3 and 3.5 Hz, 9α-H), 2.84-2.89(2H, m, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.20(1H, d, *J* 8.6 Hz, 1-H); δC (100 MHz) 13.8(q, C-18), 23.5(t, C-7), 25.1(q, 16^1-Me), 26.0(t, C-11), 29.8(t, C-16^3), 30.6(t, C-6), 30.7(t, C-15), 30.8(t, C-12), 36.1(t, C-16^2), 37.4(d, C-9), 41.95(d, C-8), 45.9(s, C-13), 49.7(s, C-14), 55.2(q, 3-OMe), 56.6(d, C-16), 72.5(s, C-16^1), 111.8(d, C-2), 113.5(d, C-4), 126.6(d, C-1), 132.1(s, C-10), 137.7(s, C-5), 157.6(s, C-3), 224.4(s, C-17); (Found C, 77.9; H, 8.5%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 78.0; H, 8.5%; *M*, 354).

(b) Samarium diiodide (6 cm^3 of a 0.1 M solution, 0.6 mmol) was added to a solution of **90** (100 mg, 0.28 mmol) in tetrahydrofuran (5 cm^3). The mixture was heated under reflux for 4.5 h, cooled to 20°C and neutralised by the addition of hydrochloric acid (0.1 M, 10 cm^3). The mixture was extracted with chloroform. The combined organic phase was washed with hydrochloric acid (0.1 M), aqueous sodium hydrogen carbonate, sodium thiosulfate and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (82 mg) which was chromatographed on silica gel (10 g) using ethyl acetate-toluene (2:8) as eluent to give **101** (79 mg, 79%).

(c) Samarium diiodide (24 cm^3 of a 0.1M solution, 2.4 mmol) was added to a solution of **90** (200 mg, 0.56 mmol) in tetrahydrofuran (5 cm^3). The mixture was heated under reflux for 4.5 h, cooled to 20°C and neutralised by the addition of hydrochloric acid (0.1 M, 10 cm^3). The mixture was extracted with chloroform. The combined organic phase was washed with hydrochloric acid (0.1 M), aqueous sodium hydrogen carbonate, sodium thiosulfate and water and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a residue (187 mg) which was chromatographed on silica gel (20 g) using ethyl acetate-toluene (3:2) as eluent to give (16^1*S*)-3-*methoxy*-16^1-*methyl*-14,16β-*propanoestra*-1,3,5(10)-*trien*-16^1,17β-*diol* **104** (26 mg, 13%) m.p. 184-186°C (from acetone-methanol); ν_{max}/cm^{-1} 3400br (OH); δ_H (400 MHz) 1.03(3H, s, 13β-Me), 1.27(3H, s, 16^1-Me), 1.37(1H, d, *J* 12.7 Hz, 15β-H), 1.74(1H, ddd, *J* 12.7, 5.7 and 3.3 Hz, 15α-H), 2.30(1H, dd, 6.8, 5.7 and 1.8 Hz, 16α-H), 2.40(1H, td, 2x11.4 and 3.3 Hz, 9α-H), 2.80-2.85(2H, m, 6α- and 6β-H), 3.77(3H, s, 3-OMe), 4.11(1H, d, *J* 6.8 Hz, 17α-H), 6.61(1H, d, *J* 2.7 Hz, 4-H), 6.7(1H, dd, *J* 2.7 and 8.6 Hz, 2-H) and 7.2(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz); 14.9(C-18), 25.2(C-7), 27.5(C-11), 29.7(16^1-Me), 31.0(C-6), 31.1(C-12), 35.0(C-16^2), 38.5(C-9), 41.5(C-15), 42.8(C-13), 44.4(C-8), 46.8(C-14), 49.3(C-16), 55.2(3-OMe), 74.4(C-16^1), 86.0(C-17), 111.7(C-2), 113.4(C-4), 126.7(C-1), 133.0(C-10), 138.0(C-5), 157.5(C-3);

(Found C, 77,6; H, 9.4%; M$^+$, 356; $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.1%; *M*, 356) followed by (16^1*S*)-3-*methoxy*-16^1-*methyl*-14,16β-*propanoestra*-1,3,5(10)-*trien*-16^1,17α-*diol* **105** (137 mg, 68%) m.p. 197-198°C (from acetone-methanol); ν_{max}/cm^{-1} 3400br (OH); δ_H (400 MHz) 1.08 (3H, s, 13β-Me), 1.23(1H, d, *J* 12.4 Hz, 15β-H), 1.31(3H, s, 16^1-Me), 1.44(1H, ddd, *J* 14.1, 6.6 and 3.6 Hz, 12β-H), 1.78(1H, d, 6.0 Hz, 16α-H), 2.00(1H, td, *J* 2x14.1 and 3.6 Hz, 12α-H), 2.09(1H, ddd, *J* 12.4, 6.4 and 3.1 Hz, 15α-H), 2.29(1H, dq, *J* 13.1 and 3x3.6 Hz, 11α-H), 2.46(1H, td, *J* 2x11.6 and 3.6 Hz, 9α-H), 2.80(2H, m, 6α- and 6β-H), 3.76(3H, s, 3-OMe), 4.15(1H, s, 17β-H), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 2.8 and 8.6 Hz, 2-H) and 7.24(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz); 19.0(q, C-18), 25.5(t, C-7), 26.9(t, C-11), 27.2(q, 16^1-Me), 30.5(t, C-16^3), 30.8(t, C-12), 31.0(t, C-6), 31.2(t, C-15), 34.9(t, C-16^2), 38.2(d, C-9), 43.6(d, C-8), 45.5(s, C-13), 48.4(s, C-14), 55.2(q, 3-OMe), 56.5(d, C-16), 72.4(s, C-16^1), 81.6(d, C-17), 111.6(d, C-2), 113.4(d, C-4), 126.9(d, C-1), 133.2(s, C-10), 138.0(s, C-5), 157.4(s, C-3); (Found C, 77.8; H, 9.2%; M$^+$, 356; $C_{23}H_{32}O_3$ requires C, 77,5; H, 9.1%; *M*, 356)

Isomerisation of Hydroxy Ketone 101

The hydoxy-ketone **101** (10 mg, 0.03 mmol) was suspended in methanol (2 cm^3) and methanolic potassium hydroxide (1 M, 2 cm^3) was added. The mixture was stirred at 20°C for 5 h, saturated aqueous ammonium chloride (3 cm^3) added and the mixture extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield a residue (10 mg). Crystallisation of the product from chloroform-methanol gave pure (16^{1}R)-hydroxy-3-methoxy-(16^1)-methyl-14,16β–propanoestra-1,3,5(10)-trien-17-one **91** which was identical to authentic reference material (m.p., mixed m.p., mass and infrared spectra).

Oxidation of the Diol 104

To the diol **104** (52 mg, 0.14 mmol) in dry dichloromethane (5 cm^3) was added periodinane (650 mg, 1.6 mmol) and the suspension was stirred at 20°C for 2 h. Diethyl ether (10 cm^3) was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) containing solid sodium thiosulfate (1 g). The mixture was stirred for 15 min until all the solid material had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried ($MgSO_4$) and evaporated to dryness to give a solid residue (47 mg). Recrystallisation of this residue from chloroform-methanol gave **101** (42 mg 79%),

Oxidation of the Diol 105

To the diol **105** (80 mg, 0.22 mmol) in dry dichloromethane (10 cm^3) was added periodinane (1 g, 2.4 mmol) and the suspension was stirred at 20°C for 2 h. Diethyl ether (10 cm^3) was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) containing solid sodium thiosulfate (1 g). The mixture was stirred for 15 min until all the solid material had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (20 cm^3) and water (20 cm^3), dried ($MgSO_4$) and evaporated to dryness to give a solid residue (79 mg). Recrystallisation of this residue from chloroform-methanol gave **101** (69 mg 85%).

Samarium(II) Iodide Mediated Reduction of the Hydroxy Ketone 91

The hydroxy-ketone **91** (60 mg, 0.17 mmol) was dissolved in tetrahydrofuran (5 cm^3) and to this solution t-butanol (0.1 cm^3) and then samarium(II) iodide (4 cm^3 of a 0.1 M solution, 0.4 mmol) were added. The mixture was heated under reflux for 1 h, cooled to 24°C, then hydrochloric acid (0.1 M, 10 cm^3) was added and the mixture extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium thiosulfate, water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressue. The crude material (57 mg) was chromatographed on silica gel (6 g) using ethyl acetate-toluene (2:3) as eluent to give **92** (50 mg, 82%) which was identical to authentic reference material (m.p., mixed m.p., mass and infrared spectra).

Samarium(II) Iodide Mediated Reduction of the Hydroxy Ketone 101

The hydroxy-ketone **101** (100 mg, 0.28 mmol) was dissolved in tetrahydrofuran (5 cm^3) and to this solution t-butyl alcohol (0.1 cm^3) and then samarium(II) iodide (6 cm^3 of a 0.1 M solution, 0.6 mmol) were added. The mixture was heated under reflux for 1 h, cooled to 24°C, then hydrochloric acid (0.1 M, 10 cm^3) was added and the mixture extracted with ethyl-acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium thiosulfate, water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material (86 mg) was chromatographed on silica gel (10 g) using ethyl acetate-toluene (3:2) as eluent to give **104** (15 mg, 15%) followed by **105** (66 mg, 65%) both compounds identical to authentic reference material (m.p., mixed m.p., mass and infrared spectra).

Hydride Mediated Reduction of the Hydroxy Ketone 101

Lithium aluminium hydride (10 mg, 26 mmol) was added to a solution of the hydroxy-ketone **101** (30 mg, 0.08 mmol) in tetrahydrofuran (3 cm^3) and the mixture stirred at 21°C for 20 min. Water was added slowly followed by chloroform and the resulting mixture filtered under suction through Celite. The Celite was washed well with chloroform and the filtrate extracted with chloroform. The combined organic phase was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a residue (26 mg). Chromatography on silica gel (5 g) using ethyl acetate-toluene (1:1) eluent gave (16^1*S*)-3-*methoxy*-16^1-*methyl*-14,16β-*propanoestra*-1,3,5(10)-*trien*-16^1,17β-*diol* **104** (23 mg, 79%)

(17a^2*R*)-3-Methoxy-17α,17a^2-methano-14,17aα-ethano-17a-homoestra-1,3,5(10)-trien-17β,17aβ-diol 112

Samarium(II) iodide (6 cm^3 of a 0.1 M solution in tetrahydrofuran, 0.6 mmol) was added dropwise to a solution of the diketone **35** (100 mg, 0.28 mmol) in tetrahydrofuran (5 cm^3). The resultant mixture was heated under reflux for 2 h, cooled to 24°C, neutralised by the addition of hydrochloric acid (0.1 M) and extracted with ethyl acetate. The combined extracts were washed with saturated aqueuos sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated to dryness to give a residue (112 mg). Chromatography on silica gel (15 g) using ethyl acetate-hexane (1:1) as eluent gave **112** (83 mg, 82%), m.p. 198-200°C (from ethyl acetate-hexane); $[\alpha]_D$ +43° (*c.* 1.1); ν_{max}/cm^{-1} 3480 (OH); δ_H(200 MHz) 1.15(3H, s, 13β-Me), 2.60(1H, dt, *J* 10.3 and 2x3.3 Hz, 12β-H), 2.66-2.76(2H, m, 6α- and 6β-H), 3.70(3H, s, 3-OMe), 6.53(1H, d, *J* 2.8 Hz, 4-H), 6.66(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.17(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 19.8(C-18), 23.7(C-7), 29.1(C-11), 31.0(C-6), 31.1(C-12), 32.9(C-15), 34.5 and 37.1(C-17a^1 and C-17a^2), 38.2(C-9), 45.5(C-14), 46.1(C-17^1), 47.6(C-13), 48.4(C-16), 55.2(3-OMe), 78.2 and 83.2(C-17 and C-17a), 111.9(C-2), 113.4(C-4), 127.9(C-1), 132.4(C-10), 138.4(C-5) and 157.3(C-3); (Found: C, 77.9; H, 8.6%; M$^+$, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354) followed by **42** (11 mg, 11%).

Oxidative Cleavage of the Diol 112

The diol **112** (20 mg, 0.06 mmol) was suspended in ethanol (2 cm^3) and sodium periodate (20 mg, 0.09 mmol) was added with stirring. The suspension was stirred at 25°C for 1.5 h, then water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant residue (17 mg) was filtered through silica gel (2 g) using toluene as eluent to give pure **35** (14 mg, 75%) which was identical to an authentic sample (m.p., mixed m.p., $[\alpha]_D$ and mass spectrum).

($17a^2$*R*)-17β,17aβ-Isopropylidenedioxy-3-methoxy-17α,$17a^2$-methano-14,17aα-ethano-17a-homoestra-1,3,5(10)-triene 113

Sulfuric acid (0.3 cm^3, 1.0 M) was added to a solution of the diol **112** (50 mg, 0.14 mmol) in acetone (2 cm^3) and the mixture stirred for 10 min at 24°C. Standard work-up (chloroform) gave a residue (47 mg). Flash chromatography on silica gel (5 g) using ethyl acetate-toluene (2:5) as eluent gave **113** (45 mg, 81%), m.p. 168-171°C (from acetone-methanol); $[\alpha]_D$ +24° (*c*. 1.0); δ_H(200 MHz) 1.26(3H, s, 13β-Me), 1.48 and 1.53(each 3H, s, C*Me*$_2$), 2.72-2.81(2H, m, 6α- and 6β-H), 3.76(3H, s, 3-OMe), 6.59(1H, d, *J* 2.7 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 20.1(C-18), 23.8(C-7), 29.2(C-11), 29.6 and 29.9(C*Me*$_2$), 31.1(C-6), 31.4(C-12), 33.7(C-15), 37.0 and 37.5(C-$17a^1$ and C-$17a^2$), 38.1(C-9), 42.6(C-8), 45.9(C-14), 46.0(C-13), 46.1(C-17^1), 47.5(C-16), 55.2(3-OMe), 89.9 and 93.2(C-17 and C-17a), 111.9(C-2, 113.4(C-4), 115.1(*C*Me$_2$), 128.0(C-1), 132.4(C-10), 138.3(C-5) and 157.3(C-3); (Found: C, 79.4; H, 8.8%; M^+, 394; $C_{26}H_{34}O_3$ requires C, 79.2; H, 8.7%; *M*, 394).

3-Hydroxy-5',6'-dihydro-15αH-benzo[14,15]-14β-estra-1,3,5(10)-trien-4'(3'H),17-dione 117

Chlorotrimethylsilane (0.3 cm^3, 2.84 mmol) was added to a suspension of sodium iodide (430 mg, 2.87 mmol) in acetonitrile (2 cm^3). The diketone **35** (100 mg, 0.28 mmol) in acetonitrile (2 cm^3) was added to the bright orange solution and the mixture heated under reflux for 7 h. After the reaction was judged to be complete (TLC) the mixture was cooled to 25°C, water added and mixture extracted with chloroform. The combined organic phase was washed with sodium thiosulfate, water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the residue (92 mg) on silica gel (10 g) using ethyl acetate-toluene (3:7) as eluent gave **117** (86 mg, 89%), m.p. 112-114°C (from acetone-methanol); $[\alpha]_D$ +57° (*c*. 0.8); ν_{max}/cm^{-1} 3570 (OH) and 1727br (CO); δ_H(200 MHz) 1.0(3H, s, 13β-Me), 1.80(1H, dd, *J* 19.7 and 8.8 Hz, 16β-H), 2.84(1H, dd, *J* 19.7 and 10.4 Hz, 16α-H), 3.16(1H, m, 15α-H), 6.52(1H, d, *J* 2.6 Hz, 4-H), 6.61(1H, dd, *J*

8.4 and 2.6 Hz, 2-H) and 7.15(1H, d, *J* 8.4 Hz, 1-H); δ_C(50 MHz) 14.8(C-18), 26.5(C-11), 27.0(C-7), 30.9(C-6'), 31.4(C-6), 32.4(C-15), 32.9(C-12), 38.3(C-8), 38.8(C-5'), 40.6(C-16), 43.1(C-3'), 44.5(C-13), 45.7(C-9), 56.0(C-14), 113.4(C-2), 114.9(C-4), 127.6(C-1), 131.2(C-10), 137.3(C-5), 153.7(C-3), 211.9(C-4'), 219.1(C-17); (Found: C, 77.8; H, 7.6%; M^+, 338; $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%; *M*, 338).

(17a²*R*)-17α,17a²-Methano-14,17aα-ethano-17a-homoestra-1,3,5(10)-trien-3,17β,17aβ-triol 118

Samarium(II) iodide (13 cm³ of a 0.1 M solution in tetrahydrofuran, 1.3 mmol) was added dropwise to a solution of the diketone **117** (200 mg, 0.59 mmol) in tetrahydrofuran (8 cm³). The resultant mixture was heated under reflux for 2 h, cooled to 24°C, neutralised by the addition of hydrochloric acid (10 cm³, 0.1 M) and extracted with ethyl acetate. The combined extracts were washed with aqueuos saturated sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated to dryness to give a residue (198 mg). Chromatography on silica gel (25g) using ethyl acetate-hexane (1:1) as eluent gave **118** (157 mg, 78%); m.p. 203-204°C (from acetone-methanol); $[\alpha]_D$ +29°; ν_{max}/cm^{-1} 3490 (OH); (Found: C, 77.5; H, 8.1%; M^+, 340; $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340) followed by 3,4'α-*dihydroxy*-15αH-*tetrahydrobenzo*[14,15]-14β-*estra*-1,3,5(10)-*trien*-17-*one* **119** (11 mg, 11%); m.p. 156-158°C (from acetone); $[\alpha]_D$ +47° (c. 1.1, pyridine); ν_{max}/cm^{-1} 3556br (OH) and 1726 (CO); (Found: C, 77.5; H, 8.1%; M^+, 340; $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

Methylation of the Triol 118

The triol **118** (10 mg, 0.03 mmol) was added to a stirred suspension of dimethyl sulfate (10.5 mmol) and potassium carbonate (100 mg, 0.72 mmol) and the mixture stirred at 23°C for 24 h. Aqueous ammonia (25%, 0.1 cm³) was added and the solution filtered through celite. Standard work-up (chloroform) followed by flash chromatography of the crude material (10 mg) on silica gel (1 g) using toluene as eluent gave **112** (8 mg, 76%) which was shown to be identical to an authentic sample (m.p., mixed m.p., mass spectrum).

3-Methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10),16^1-tetraen-17-one 120

Thionyl chloride (0.26 cm^3, 3.6 mmol) was added to a stirred solution of the hydoxy-ketone **91** (850 mg, 2.4 mmol) in dry pyridine (30 cm^3) cooled to 0°C. The solution was allowed to warm up to 23°C, was stirred for 0.5 h, then poured into ice/water and extracted with ethyl acetate. The combined organic phase was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Recrystallisation of the resulting residue (803 mg) gave pure **120** (750 mg, 93%) m.p. 136-138°C (from acetone-methanol); $[\alpha]_D$ +67° (*c* 0.9); ν_{max}/cm^{-1} 1725 (CO); δ_H (400 MHz) 1.13(3H, s, 13β-Me), 1.60(1H, d, *J* 11.5 Hz, 15β-H), 1.74(3H, q, *J* 3x1.8 Hz, 16^1-Me), 1.83((1H, ddt, *J* 18.5, 4.1 and 2x1.8 Hz, 16^3-H$_n$), 2.11(1H, ddd, 11.5, 4.8 and 1.8 Hz, 15α-H), 2.22(1H, dq, *J* 13.0 and 3x3.5, 11α-H), 2.58(1H, ddd, 18.5, 2.6 and 1.8 Hz, 16^3-H$_x$), 2.72(1H, d, *J* 4.8 Hz, 16α-H), 2.84-2.90(2H, m, 6α- and 6β-H), 3.78(3H, s, 3-OMe), 5.37(1H, ddd, *J* 4.1, 2.6 and 1.8 Hz, 16^2-H), 6.64(1H, d, *J* 2.8 Hz, 4-H), 6.73(1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.22(1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz); 18.0(q, C–18), 21.9(q, 16^1-Me), 24.7(t, C-7), 25.7(t, C-11), 29.8(t, C-15), 30.8(t, C-6), 32.4(t, C-12), 33.4(t, C-16^3), 38.4(d, C-8), 42.8(d, C-9), 44.6(s, C-13), 49.7(s, C-14), 51.7(d, C-16), 55.2(q, 3-OMe), 111.6(d, C-2), 113.6(d, C-4), 122.3(d, C-16^2), 126.5(d, C-1), 132.6(s, C-10), 134.3(s, C-16^1), 137.9(s, C-5), 157.6(s, C-3), 213.0(s, C-17); (Found C, 82.2; H, 8.2%; M$^+$, 336; $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.4%; *M*, 336).

(16^1*R*, 16^2*R*)-3-Methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-16^2,17β-diol 121

A solution of the enone **120** (72 mg, 0.21 mmol) in tetrahydrofuran (3 cm^3) was cooled to 0°C and boron-dimethyl sulfide (0.1 cm^3, 1 mmol) was added. The mixture was allowed to warm up to 24°C and was stirred at that temperature for 4h. Aqueous sodium hydroxide (5%, 10 cm^3) was added slowly followed by hydrogen peroxide (30%, 10 cm^3). The mixture was stirred for 12 h, water added and the mixture extracted with chloroform. The combined organic phase was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield a solid residue (75 mg). The residue was chromatographed on silica gel (10g) using ethyl acetate-toluene (4:6) as eluent to give **121** (60 mg, 79%) m.p. 213-215°C; $[\alpha]_D$ +54° (*c* 0.9); ν_{max}/cm^{-1} 3670br (OH); δ_H (400 MHz) 0.98(3H, s, 13β-Me), 1.22(1H, d, *J* 11.7 Hz, 15α-H), 1.25(3H, d, *J* 6.8 Hz, 16^1-Me_n), 1.90(1H, dd, *J* 11.7 and 5.2 Hz, 15α-H), 2.30(1H, ddd, *J* 7.1, 5.2 and 1.9 Hz, 16α-H), 2.45(1H, td, *J* 11.6x2 and 3.4 Hz, 9α-H), 2.80-2.86(2H, m, 6α- and 6β-H), 3.77(3H, s, 3-OMe), 4.01(1H, d, *J* 7.1 Hz, 17α-H), 4.15(1H, ddd, *J* 8.7, 7.8 and 6.6 Hz, 16^2-H_n), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.20(1H, d, *J* 8.7 Hz, 1-H); δ_C (50 MHz); 14.6(C-18), 18.2(16^1-Me), 25.1(C-7), 27.4(C-11), 31.1(C-6), 36.1(C), 38.3(C-9), 41.1(C), 43.5(C-9), 44.2(C-15), 44.5(C), 44.6(C), 45.9(C), 48.7(C-13), 55.2(3-OMe), 71.2(C-16^2), 85.6(C-17), 111.7(C-2), 113.4(C-4), 126.7(C-1), 132.0(C-10), 138.1(C-5), 157.5(C-3); (Found C, 77.8; H, 8.5%; M^+, 356; $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.0%; *M*, 356).

(16^1*R*)-3-Methoxy-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-16^2,17-dione 122

To the diol **121** (180 mg, 0.5 mmol) in dry dichloromethane (20 cm^3) was added periodinane (2.1 g, 5 mmol) and the suspension was stirred at 23°C for 1 h. Diethyl ether (30 cm^3) was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) containing solid sodium thiosulfate (2 g). The mixture was stirred for 15 min until all the solid material had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated to dryness to give a solid residue (176 mg). Chromatography on silica gel (20 g) using ethyl acetate-toluene (1:4) as eluent gave **122** (164 mg, 92%) m.p. 167-168°C (from chloroform-methanol); $[\alpha]_D$ +27° (*c* 1.2); ν_{max}/cm^{-1} 1705 and 1727 (CO); δ_H (400 MHz) 0.95(3H, s, 13β-Me), 1.10(3H, d, *J* 6.6 Hz, 16^1-Me_n), 1.35(1H, td, *J* 2x11.8 and 2.8 Hz, 8β-H), 1.40(1H, dddd, *J* 14.1, 13.2, 11.8 and 3.5 Hz, 11β-H), 1.48(1H, dt, *J* 14.1 and 2x3.5 Hz, 12β-H), 1.56(1H, m, 7α-H), 1.68(1H, td, 2x14.1 and 3.5 Hz, 12α-H), 1.89(1H, d, *J* 12. Hz, 16^{3}-H$_{n}$), 2.04(1H, m, 7β-H), 2.32(1H, dd, *J* 15.6 and 3.8 Hz, 15α-H), 2.36(1H, dq, *J* 13.2 and 3x3.5 Hz, 11α-H), 2.52(1H, qd, *J* 3x6.6 and 5.7 Hz, 16^{1}-H$_{x}$), 2.56(1H, d, *J* 12.5 Hz, 16^{3}-H$_{x}$), 2.62(1H, td, *J* 2x11.8 and 2.8 Hz, 9α-H), 2.72(1H, dd, *J* 5.7 and 3.8 Hz, 16α-H), 2.78(1H, d, *J* 15.6 Hz, 15β-H), 2.86-2.92(2H, m, 6α- and 6β-H), 3.77(3H, s, 3-OMe), 6.63(1H, d, *J* 2.7 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.20(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 12.0(q, 16^{1}-Me), 14.8(q, C13β-Me), 23.9(t, C-7), 25.8(t, C-11), 30.5(t, C-6), 31.9(t, C-12), 33.7(t, C-16^{3}), 37.8(d, C-9), 42.0(d, C-8), 48.8(s, C-13), 50.4(d, C-16^{1}), 50.6(t, C-15), 51.5(d, C-16), 51.6(s, C-14), 55.2(q, 3-OMe), 111.8(d, C-2), 113.5(d, C-4), 126.5(d, C-1), 131.6(s, C-10), 137.4(s, C-5), 157.7(s, C-3), 210.5(s, C-16^{2}), 218.6(s, C-17); (Found C, 78.3; H, 7.9%; M^{+}, 352; $C_{23}H_{28}O_3$ requires C, 78.4; H, 8.0%; *M*, 352).

(16^{1}*R*, 17^{1}*R*)-3-Methoxy-16^{1}-methyl-16α,17^{1}-methano-14,17α-ethanoestra-1,3,5(10)-trien-16β,17β-diol 123

Samarium(II) iodide (10 cm^{3} of a 0.1 M solution in tetrahydrofuran, 1 mmol) was added to a solution of the diketone **122** (150 mg, 0.43 mmol) in tetrahydrofuran (5 cm^{3}). The mixture was refluxed for 0.5 h, cooled to 23°C and neutralised with hydrochloric acid (0.1M). The mixture was extracted with chloroform, the combined organic phase was washed with aqueous sodium hydrogen carbonate, sodium thiosulfate and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a residue (147 mg). Chromatography on silica gel (15 g) using ethyl acetate-toluene (1:1) as eluent to gave **123** (118 mg, 78%) m.p. 222-224°C (from chloroform-hexane); $[\alpha]_D$ -35° (*c* 1.1); ν_{max}/cm^{-1} 3560 (OH); δ_H (200 MHz) 0.9(3H, s, 13β-Me), 1.26(3H, d, *J* 7.2 Hz, 16^{1}-Me), 2.84-2.92(2H, m, 6α- and 6β-H), 3.76(3H, s, 3-OMe), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.71(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 13.8 and 14.1(each q, C-18 and 16^{1}-Me), 24.4(t, C-7), 25.8(t, C-11), 27.1(t, C), 30.3(t, C-6), 35.4(t, C), 37.3(d, C), 37.5(d, C), 39.3(d, C-8), 46.7(t, C), 47.5(s, C-13), 49.5(d, C-9), 50.0(s, C-14), 55.2(q, 3-OMe), 74.5(s, C-17), 93.6(s, C-16), 111.6(d, C-2), 113.8(d, C-4), 126.5(d, C-1), 133.2(s, C-10), 137.8(s, C-5), 157.7(s, C-3); (Found C, 78.0; H, 8.8%; M^+, 354; $C_{23}H_{30}O_3$ requires C, 77.9; H, 8.5%; *M*, 354).

Oxidative Cleavage of the Diol 123

The diol **123** (22 mg, 0.06 mmol) was suspended in ethanol (4 cm^3) and sodium periodate (20 mg, 0.09 mmol) was added with stirring. The suspension was stirred at 25°C for 2 h, then water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant residue (20 mg) was filtered through silica gel (2 g) using toluene as eluent to give pure **122** (17 mg, 78%) which was identical to an authentic sample (m.p., mixed m.p., $[\alpha]_D$ and mass spectrum).

(16^1*R*, 17^1*R*)-16β,17β-Isopropylidenedioxy-3-methoxy-16^1-methyl-16α,17^1-methano-14,17α-ethanoestra-1,3,5(10)-triene 124

Sulfuric acid (0.3 cm^3, 1.0 M) was added to a solution of the diol **123** (41 mg, 0.11 mmol) in acetone (2 cm^3) and the mixture stirred for 10 min at 24°C. Standard work-up (chloroform) gave a residue (34 mg). Flash chromatography on silica gel (5 g) using ethyl acetate-toluene (2:5) as eluent gave **124** (27 mg, 62%), m.p. 217-220°C (from acetone-methanol); $[\alpha]_D$ +54° (*c*. 1.0); δ_H(200 MHz) 0.98(3H, s, 13β-Me), 1.17(3H, s, 161-Me), 1.37 and 1.49(each 3H, s, C*Me*$_2$), 3.77(3H, s, 3-OMe), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.24(1H, d, *J* 8.6 Hz, 1-H); (Found: C, 79.3; H, 8.7%; M^+, 394; $C_{26}H_{34}O_3$ requires C, 79.2; H, 8.6%; *M*, 394).

(16^1R, 17^1R)-16^1-Methyl-16α,17^1-methano-14,17α-ethanoestra-1,3,5(10)-trien-3,16β,17β-diol 125

Di-isobutylaluminium hydride (1.2 M solution in toluene, 1 cm^3) was added to a stirred solution of the diol **123** (55 mg, 0.16 mmol) in dry toluene (12 cm^3) and the mixture was refluxed under nitrogen for 56 h. The mixture was cooled to 24°C and M-hydrochloric acid (10 cm^3) added. The aqueous layer was extracted with chloroform, the combined organic phase washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crystalline residue (46 mg). Recrystallisation from acetone-methanol gave **125** (41 mg, 78 %); m.p. 210-213°C; $[\alpha]_D$ +116° (*c*.1.1); (Found: C, 77.6; H, 8.7 %; M^+, 340; $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3 %; *M*, 340).

(16^1R)-3-Methoxy-16^1-methyl-16^2-methylene-14,16β-propanoestra-1,3,5(10)-trien-17-one 126

t-Butyllithium (1.7 M, 0.5 cm^3) was added to a suspension of methyltriphenyl-phosphonium iodide (343 mg, 0.85 mmol) in tetrahydrofuran (7 cm^3) cooled to 0°C. The mixture was stirred at this temperature for 1.5 h. The diketone **122** (250 mg, 0.71 mmol) in dry tetrahydrofuran (3ml) was added to the orange solution and the mixture stirred at 25°C for 3 h. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with dilute hydrochloric acid (0.1M, 10 cm^3), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a oily crude residue (387 mg). Flash chromatography on silica gel (40 g) using ethyl acetate-toluene (1:19) as eluent gave the 16^2-methylene 17-ketone **126** (209 mg, 84%), m.p.151-153°C (from acetone-methanol); $[\alpha]_D$ +76° (*c*. 1.0); ν_{max}/cm^{-1} 1729 (CO); δ_H(400 MHz) 0.97(3H, s, 13β-Me), 1.23(3H, d, *J* 6.8 Hz, 16^1-Me_x), 1.98(1H, d, *J* 19.1 Hz, 16^3-H_n), 2.12(1H, d, *J* 15.4 Hz, 15β-H), 2.37(1H, dd, *J* 19.1 and 1.5 Hz, 16^3-H_x), 2.43(1H, m, 16^1-H_x), 2.51(1H, dd, *J* 15.4 and 3.9 Hz, 15α-H), 2.63(1H, dd, *J* 6.1 and 3.9 Hz, 16α-H), 2.85-2.91(2H, m, 6α- and 6β-H), 3.77(3H, s, 3-OMe), 4.75(2H, m 16^2=CH_2), 6.64(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and

7.21(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 14.9(q, C-18), 19.7q, C-16^1), 23.8(d, C-7), 25.7(d, C-11), 29.6(d, C-12), 30.6(d, C-6), 36.8(t, C-16^3), 40.1 and 40.4(each d, C-8 and C-9), 48.7(t, C-15), 50.1(d, C-16^1), 52.4(d, C-16), 55.2(q, 3-OMe), 55.5 and 55.9(each s, C-13 and C-14), 107.4(t, 16^2=*C*H_2), 111.4(d, C-2), 113.9(d, C-4), 127.0(d, C-1), 132.8(s, C-10), 137.9(s, C-5), 157.4(s, C-3) 160.1(s, C-16^2) and 221,3(s, C-17); (Found: C, 82,3; H, 8.9%; M^+, 350; $C_{24}H_{30}O_2$ requires; C, 82.3; H, 8.6; *M*, 350).

(16^1*R*, 16^2*S*)-3-Methoxy-16^2-hydroxymethyl-16^1-methyl-14,16β-propanoestra-1,3,5(10)-trien-17β-ol 127

A solution of the 16^2-methylene 17-ketone **126** (186 mg, 0.53 mmol) in tetrahydrofuran (4 cm^3) was cooled to 0°C and borane-dimethyl sulfide (0.1 cm^3, 1mmol) was added. The mixture was allowed to warm to 24°C and was stirred at that temperature for 3.5 h. Aqueous sodium hydroxide (5%, 10 cm^3) was added slowly followed by hydrogen peroxide (30%, 10 cm^3). The mixture was stirred overnight, water added and then the mixture extracted with chloroform. The combined organic phase was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield a solid residue (175 mg) which was chromatographed on silica gel (20 g) using ethyl acetate-toluene (2:3) as eluent to give the diol **127** (153 mg, 78 %) m.p. 204 -206°C (from acetone-methanol); $[\alpha]_D$ +145° (*c* 0.8); ν_{max}/cm^{-1} 3670br (OH); δ_H (400 MHz) 1.04(3H, s, 13β-Me), 1.17(1H, d, *J* 14.7 Hz, 15β-H), 1.31(3H, d, *J* 6.8 Hz, 16^1-Me), 2.03(1H, dd, *J* 14.7 and 5.8 Hz, 15α-H), 2.36(1H, ddd, *J* 7.5, 5.8 and 1.7 Hz, 16α-H), 3.54-3.63(2H, m, 16^2-C*H_2*OH), 3.77(3H, s, 3-OMe), 4.03(1H, d, *J* 7.8 Hz, 17α-H), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.21(1H, d, *J* 8.7 Hz, 1-H); (Found C, 77.9; H, 9.5 %; M^+, 370; $C_{24}H_{34}O_3$ requires C, 77.8; H, 9.2 %; *M*, 370).

(16^1*R*, 16^2*S*)-3-Methoxy-16^1-methyl-16^2-formyl-14β,16β-propanoestra-1,3,5(10)-trien-17-one 128

To the diol **127** (150 mg, 0.4 mmol) in dry dichloromethane (18 cm^3) was added periodinane (2.1g, 5mmol) and the suspension was stirred at 23°C for 1 h. Diethyl ether (30 cm^3) was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate containing solid sodium thiosulfate (2 g). The mixture was stirred for 15 min until all the solid material had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated to dryness to give a solid residue (150 mg) which was chromatographed on silica gel (14 g) using ethyl acetate-toluene (1:4) as eluent to give **128** (143 mg, 96%), m.p. 162-164°C (from ethyl acetate-hexane); $[\alpha]_D$ +127° (*c* 0.9); ν_{max}/cm^{-1} 1708 and 1727 (CO); 1.12(1H, d, *J* 12.7 Hz, 15β-H), 1.19(3H, s, 13β-Me), 1.27(3H, d, *J* 6.7Hz, 16^1-Me), 1.74(1H, dd, *J* 17.2, 5.8 nad 2.7 Hz, 16^3-H_n), 2.01(1H, ddd, *J* 12.7, 5.8 and 2.7 Hz, 15α-H), 2.21(1H, dd, *J* 17.2 and 6.5 Hz, 16^3-H_x), 2.67(1H, ddd, *J* 2x5.8 and 2.1 Hz, 16α-H), 2.82-2.99(3H, m, 6α-, 6β- and 16^2-H_x), 3.77(3H, s, 3-OMe), 6.60(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.40(1H, d, *J* 8.6 Hz, 1-H) and 9.73(1H, d, *J* 1.9 Hz, 16^2-C*H*O); δ_C(100MHz) 14.8(q, C-18), 19.6(q, C16^1-Me), 23.8(t, C-7), 27.1(t, C-11), 27.9(t, C-15), 30.6(t, C-6), 32.0(t, C-12), 36.8(t, C-16^3), 37.8(d, C-9), 43.4(d, C-8), 46.7(s, C-13), 47.8(d, C-16^1), 49.4(d, C-14), 55.2(q, 3-OMe), 55.8(d, C-16^2), 58.1(d, C-16), 111.6(d, C-2), 113.7(d, C-4), 126.6(d, C-1), 132.5(s, C-10), 137.8(s, C-5), 157.6(s, C-3), 201.4(d, 16^2-*C*HO), and 221.5(s, C-17); (Found: C, 78.5; H, 8.1%; M^+, 366; $C_{24}H_{30}O_3$ requires C, 78.7; H, 8.3%; *M*, 366).

(16^1*S*, $17a^1$*R*)-3-Methoxy-16α, $17a^1$-methano-16^1-methyl-14,17aα-ethano-17a-homoestra-1,3,5(10)-trien-17β,17aβ-diol 129

Samarium(II) iodide (7 cm^3 of a 0.1 M solution in tetrahydrofuran, 0.7 mmol) was added to a solution of the formyl-ketone **128** (112 mg, 0.31 mmol) in tetrahydrofuran (5 cm^3). The mixture was heated under refluxed for 1 h, cooled to 23°C and neutralised with hydrochloric acid (0.1 M). The mixture was extracted with chloroform, the combined organic phase was washed with aqueous sodium hydrogen carbonate, sodium thiosulfate and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a resdue (98 mg). Chromatography on silica gel (10g) using ethyl acetate-toluene (1:1) as eluent to give **129** (92 mg, 81%) m.p. 234-235°C (from chloroform-methanol); $[\alpha]_D$ -125° (*c* 1.1); ν_{max}/cm^{-1} 3567 (OH); δ_H (400 MHz) 1.02(3H, s, 13β-Me), 1.22(3H, d, *J* 7.0 Hz, 16^1-Me), 3.77(3H, s, 3-OMe), 4.17(1H, d, *J* 6.36 Hz, 17α-H), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.03(1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 13.9 and 14.7(each q, C-18 and 16^1-Me), 24.7(C-7), 26.0(C-11), 27.2(C-12), 30.3(C-6), 34.3(C-17^2), 36.8(C-15), 37.7(C-17^1), 38.2(C-16), 38.4(C-16^1), 39.8(C-8), 47.2(C-13), 49.9(C-9), 50.7(C-14), 55.2(3-OMe), 73.7(C-17), 91.8(C-17a), 111.7(C-2), 113.7(C-4), 126.6(C-1), 133.4(C-10), 137.6(C-5) and 157.3(C-3); (Found C, 78.4; H, 8.5%; M^+, 368; $C_{24}H_{32}O_3$ requires C, 78.2; H, 8.8%; *M*, 368).

Oxidative Cleavage of the Diol 129

The diol **129** (12 mg, 0.03 mmol) was suspended in ethanol (2 cm^3) and sodium periodate (10 mg, 0.05 mmol) was added with stirring. The suspension was stirred at 25°C for 1 h, then water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant residue (10 mg) was filtered through silica gel (2 g) using toluene as eluent to give pure **128** (8 mg, 73%) which was identical to an authentic sample (m.p., mixed m.p., $[\alpha]_D$ and mass spectrum).

(16^1*S*, 17a^1*R*)-17β,17aβ-Isopropylidenedioxy-3-methoxy-16α,17a^1-methano-16^1-methyl-14,17aα-ethano-17a-homoestra-1,3,5(10)-triene 130

Sulfuric acid (0.1 cm^3, 1.0 M) was added to a solution of the diol **129** (13 mg, 0.04 mmol) in acetone (2 cm^3) and the mixture stirred for 10 min at 24°C. Standard work-up (chloroform) gave a residue (13 mg). Flash chromatography on silica gel (5 g) using ethyl acetate-toluene (1:4) as eluent gave **130** (11 mg, 76%), m.p. 177-179°C (from acetone-methanol); $[\alpha]_D$ -362° (*c*. 0.8); δ_H(200 MHz) 1.09(3H, s, 13β-Me), 1.21(3H, s, 16^1-Me), 1.51 and 1.54(each 3H, s, C*Me*$_2$), 3.78(3H, s, 3-OMe), 6.57(1H, d, *J* 2.9 Hz, 4-H), 6.74(1H, dd, *J* 8.5 and 2.9 Hz, 2-H) and 7.13(1H, d, *J* 8.5 Hz, 1-H); (Found: C, 79.6; H, 8.6%; M$^+$, 408; $C_{27}H_{36}O_3$ requires C, 79.4; H, 8.9%; *M*, 408).

(16^1*S*,17a^1*R*)-16α, 17a^1-Methano-16^1-methyl-14,17aα-ethano-17a-homoestra-1,3,5(10)-trien-3,17β,17aβ-triol 134

Di-isobutylaluminium hydride (1.2 M solution in toluene, 1 cm^3) was added to a stirred solution of the diol **129** (47 mg, 0.13 mmol) in dry toluene (8 cm^3) and the mixture was refluxed under nitrogen for 24 h. The mixture was cooled to 24°C and M-hydrochloric acid added. The aqueous layer was extracted with chloroform, the combined organic phase washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crystalline residue (39 mg). Recrystallisation from acetone-methanol gave **134** (36 mg, 77%); m.p. 214-215°C; $[\alpha]_D$ +156° (*c*.1.0); (Found: C, 77.9; H, 8.6 %; M$^+$, 354; $C_{23}H_3O_3$ requires; C, 77.9; H, 8.5 %; *M*, 354).

Cycloaddition of the Dienyl Acetate 10 with *p*-Benzoquinone

Boron trifluoride-diethyl ether (0.05 cm^3, 0.41 mmol) was added to the dienyl acetate **10** (972 mg, 3 mmol) and *p*-benzoquinone (486 mg, 4.5 mmol) in dry toluene (20 cm^3) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 0.5 h, then ice-water added and the mixture was extracted with ethyl acetate. The combined extracts were washed successively with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the crude residue (1.05 g) on silica gel (70 g) with ethyl acetate-toluene (3:7) as eluent gave 3-*methoxy*-3',6'-dioxo-15α*H*,16α*H*-*benzo*[15,16]-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-yl acetate **137** (91 mg, 7%), m.p. 177-179°C (from acetone-methanol); $[\alpha]_D$ -62° (*c* 0.9); ν_{max}/cm^{-1} 1653, 1712 and 1723 (CO); δ_H(400 MHz) 0.97(3H, s, 13β-Me), 1.66(1H, ddd, *J* 14.3, 4.7 and 2.5 Hz, 12β-H), 1.88(1H, dt, *J* 11.8x2 and 2.3 Hz, 8β-H), 2.18(3H, s, 17β-OCOC*H*$_3$), 3.78(3H, s, 3-OMe), 3.86 and 4.39(each 1H, d, *J* 8.2 Hz, 15α- and 16α-H), 6.12(2H, s, 17^1- and 17^2-H), 6.57(2H, s, 4'- and 5'-H), 6.64(1H, d, *J* 2.8 Hz, 4-H), 6.74(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.23(1H, d, *J* 8.6 Hz, 1-H); δ_H(400 MHz, C_6D_6) 0.98(3H, s, 13β-Me), 1.89(3H, s, 17-OCOC*H*$_3$), 3.08(1H, d, *J* 8.4 Hz, 15α-H), 3.40(3H, s, 3-OMe), 4.16(1H, d, *J* 8.4 Hz, 16α-H), 5.64 and 5.81(each 1H, d, *J* 5.8 Hz, 17^1- and 17^2-H), 6.00 and 6.02(each 1H, d, *J* 10.3 Hz, 4'- and 5'-H), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.84(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.16(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 15.2(q, C-18), 21.8(q, 17-OCO*C*H$_3$), 24.6(t, C-7), 27.4(t, C-11), 30.5(t, C-12), 31.4(t, C-6), 37.3 and 38.8(each d, C-15 and C-16), 45.2 and 49.2(each d, C-8 and C-9), 55.2(q, 3-OMe), 62.9 and 63.0(each s, C-13 and C-14), 97.2(s, C-17), 111.9(d, C-2), 113.7(d, C-4), 127.3(d, C-1), 132.0(s, C-10), 132.9 and 135.1(each d, C-17^1 and C-17^2), 138.2(s, C-5), 140.7 and 143.6(each d, C-4' and C-5'), 157.5(s, C-3), 170.3(s, 17-O*C*OCH$_3$) and 197.9 and 199.0(each s, C-3' and C-6'); (Found: C, 74.8; H, 6.6%; M$^+$, 432; $C_{27}H_{28}O_5$ requires C, 75.0; H 6.5%; *M*, 432) followed by 3-*methoxy*-3',6'-*dioxo*-15β*H*,16β*H*-*benzo*[15,16]-14,17α-*ethenoestra*-1,3,5(10)-*trien*-17β-*yl acetate* **138** (933 mg, 72%), m.p. 145-148°C (from acetone-methanol); $[\alpha]_D$ -114° (*c* 0.8); ν_{max}/cm^{-1} 1656, 1698 and 1728 (CO); δ_H(400 MHz) 1.05(3H, s, 13β-Me), 2.17(3H, s, 17β-OCOCH$_3$), 3.38(1H, d, *J* 8.1 Hz, 15β-H), 3.65(1H, d, *J* 8.1 Hz, 16β-H), 3.78(3H, s, 3-OMe), 6.04 and 6.42(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.57 and 6.63(each 1H, d, *J* 10.3 Hz, 4'- and 5'-H), 6.62(1H, d, *J* 2.9 Hz, 4-H), 6.70(1H, dd, *J* 8.7 and 2.9 Hz, 2-H) and 7.18(1H, d, *J* 8.6 Hz, 1-H); δ_C(100 MHz) 14.9(q, C-18), 21.3(q, 17-OCOCH$_3$), 25.0(t, C-7), 27.6(t, C-11), 30.6(t, C-6), 31.5(t, C-12), 37.3 and 39.1(each d, C-15 and C-16), 44.9 and 49.0(each d, C-8 and C-9), 55.2(q, 3-OMe), 62.5 and 62.6(each s, C-13 and C-14), 97.0(s, C-17), 112.3(d, C-2), 113.8(d, C-4), 127.1(d, C-1), 132.1(s, C-10), 133.0 and 134.9(each d, C-17^1 and C-17^2), 138.2(s, C-5), 140.1 and 142.9(each d, C-4' and C-5'), 158.1(s, C-3), 169.5(s, 17-$OCOCH_3$) and 197.0 and 197.8(each s, C-3' and C-6'); (Found: C, 75.3; H, 6.5%; M^+, 432; $C_{27}H_{28}O_5$ requires C, 75.0; H 6.5%; *M*, 432)

3-Methoxy-15^1,16^1-dioxo-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17β-yl acetate 140

The cycloadduct **138** (478 mg, 1.1 mmol) was dissolved in dichloromethane (20 cm^3) and the solution allowed to stand in sunlight for 6 h. The solvent was evaporated under reduced pressure to yield pure **140** (478 mg, 100%); m.p. 232-233°C (from ethyl acetate-hexane); $[\alpha]_D$ -207° (*c* 1.2); ν_{max}/cm^{-1} 1709, 1725 and 1742 (CO); δ_H(400 MHz, C_5D_5N) 1.08(3H, s, 13β-Me), 1.95(3H, s, 17-$OCOCH_3$), 2.53(1H, td, *J* 11.0x2 and 4.5 Hz, 9α-H), 2.60-2.75(2H, m, 6α- and 6β-H), 2.98(1H, m, 17^4-H), 3.10(1H, dt, *J* 10.3 and 2x2.4 Hz, 15β-H), 3.21(1H, dt, *J* 10.3 and 2x2.6 Hz, 16β-H), 3.38-3.50(3H, m, 17^1, -17^2- and 17^3-H), 3.71(3H, s, 3-OMe), 6.72(1H, d, *J* 2.6 Hz, 4-H), 6.93(1H, dd, *J* 8.8 and 2.6 Hz, 2-H) and 7.28(1H, d, *J* 8.8 Hz, 1-H); δ_C(100 MHz, C_5D_5N) 16.8(q, C-18), 20.3(q, 17-$OCOCH_3$), 24.8(t, C-7), 25.9(t, C-11), 26.3(t, C-12), 29.6(t, C-6), 38.0(d, C-15), 38.9(d, C-16), 39.0(d, C-8), 42.6(d, C-9), 45.6 and 48.6(each d, C-17^1 and C-17^4), 53.7(s, C-13), 55.2(q, 3-OMe), 56.0(s, C-14), 57.8 and 59.8(each d, C-17^2 and C-17^3), 95.6(s, C-17), 112.5(d, C-2), 113.9(d, C-4), 127.3(d, C-1), 131.9(s, C-10), 137.4(s, C-5), 158.3(s, C-3), 171.6(s, 17-$OCOCH_3$), 208.8 and 212.7(C-15^1 and C-16^1); (Found: C, 74.7; H, 6.3%; M^+, 432; $C_{27}H_{28}O_5$ requires C, 75.0; H, 6.5%; *M*, 432).

17β-Hydroxy-3-methoxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-15^1,16^1-dione 143

Potassium carbonate (52 mg, 0.38 mmol) was added to a solution of the diketone **140** (136 mg, 0.31 mmol) in tetrahydrofuran (6 cm^3) cooled to 5°C. The solution was stirred at 5°C for 6 h then saturated aqueous ammonium chloride added and the mixture extracted with chloroform. The combined extracts were washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue (112 mg) was chromatographed on silica gel (10g) using ethyl acetate-toluene (3:7) as eluent to give **143** (98 mg, 81 %); m.p. 212-213°C (from chloroform-methanol); [α]$_D$ -237° (*c* 1.0); ν_{max}/cm^{-1} 1718, 1737 (CO) and 3467br (OH); δ_H(400 MHz, C_5D_5N) 1.08(3H, s, 13β-Me), 2.43(1H, td, *J* 2x11.0 and 4.5 Hz, 9α-H), 2.45-2.61(2H, m, 6α- and 6β-H), 3.11(1H, dt, *J* 10.7 and 2x1.6 Hz, 15β-H), 3.24(1H, dt, *J* 10.7 and 2x1.8 Hz, 16β-H), 3.36-3.48(3H, m, 17^1, -17^2-, 17^3- and 17^4-H), 3.77(3H, s, 3-OMe), 6.72(1H, d, *J* 2.6 Hz, 4-H), 6.93(1H, dd, *J* 8.8 and 2.6 Hz, 2-H) and 7.28(1H, d, *J* 8.8 Hz, 1-H); δ_C(100MHz, C_5D_5N) 16.8(q, C-18), 22.8, 23.9, 25.6 and 26.7(each t, C-7, C-11, C-12 and C-6), 38.7 and 38.9(each d, C-15 and C-16), 39.8 and 42.7(each d, C-8 and C-9), 48.6 and 48.9(each d, C-17^1 and C-17^4), 53.7(s, C-13), 55.2(q, 3-OMe), 56.0(s, C-14), 57.1 and 59.3(each d, C-17^2 and C-17^3), 83.6(s, C-17), 112.4(d, C-2), 113.2(d, C-4), 127.8(d, C-1), 132.5(s, C-10), 138.4(s, C-5), 157.3(s, C-3), 211.7 and 212.4(each s, C-15^1 and C-16^1); (Found: C, 76.7; H, 6.5%; M$^+$, 390; $C_{25}H_{26}O_4$ requires C, 76.9; H, 6.7%; *M*, 390).

3-Methoxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17β-ol 144

Hydrazine hydrate (95%, 2 cm^3) was added to a solution of the diketone **143** (92 mg, 0.23 mmol) in diethylene glycol (10 cm^3) and the mixture stirred at 24°C for 12 h. Sodium hydroxide (25 mg, 0.63 mmol) was added and the mixture heated at 140-150°C for 2h. The cooled reaction mixture was extracted with chloroform, the combined extracts washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crystalline residue (66 mg) was recrystallised from chloroform to give **144** (65 mg, 78 %), m.p. 243-246°C; [α]$_D$ -267° (*c* 0.8, pyridine); (Found: C, 82.8; H, 8.6%; M$^+$, 362; $C_{25}H_{30}O_2$ requires C, 82.8; H, 8.3%; *M*, 362).

3-Methoxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17βyl acetate 145

The alcohol **144** (20 mg, 0.06 mmol) was dissolved in pyridine (2 cm^3) and acetic anhydride (0.5 cm^3, 5.3 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.05 mmol) added. The mixture was stirred for 13 h, then water added and stirring continued for 30 min. Standard work-up (ethyl acetate) gave crude material (25 mg) which was chromatographed on silica gel (4g) using ethyl acetate-toluene (1:9) as eluent to give **145** (23 mg, 95 %), m.p. 200-201°C (from acetone-methanol); [α]$_D$ -345° (*c* 1.0); ν_{max}/cm^{-1} 1723 (CO); δ_H(400 MHz) 1.03(3H, s, 13β-Me), 2.07(3H, s, 17-OCOCH$_3$), 2.65-2.83(2H, m, 6α- and 6β-H), 3.19-3.32(4H, m, 17^1-, 17^2-, 17^3- and 17^4-H), 3.77(3H, s, 3-OMe), 6.62(1H, d, *J* 2.8 Hz, 4-H), 6.74(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.11(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz); 18.7(C-18), 21.6(17-OCO*C*H$_3$), 23.4(C-7), 24.6(C-11), 25.9 and 26.7(C-3' and C-6'), 29.6(C-6), 32.7(C-12), 36.2, 37.9, 41.2(C-8), 47.8(C-9), 49.9, 50.7(C-13), 51.8(C-14), 52.8, 53.4, 55.2(3-OMe), 57.0, 97.5(C-17), 112.1(C-2), 113.6(C-4), 127.3(C-1), 130.5(C-10), 137.1(C-5), 157.8(C-3) and 170.5(17-O*C*OCH$_3$); (Found: C, 80.0; H, 7.9%; M$^+$, 404; $C_{27}H_{32}O_3$ requires C, 80.2; H, 8.0%; *M*, 404).

16^1,16^1-Ethylenedithio-3-methoxy-15^1-oxo-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17β-yl acetate 148

A solution of the diketone **140** (250 mg, 0.58 mmol) in dichloromethane (2 cm^3) was cooled to 0°C and ethanedithiol (0.1 cm^3, 1.2 mmol) was added followed by boron trifluoride-diethyl ether (0.05 cm^3, 1.1 mmol). The solution was stirred at 0°C for 1h, then water added and the resultant mixture poured into aqueuos sodium hydrogen carbonate. The mixture was extracted with chloroform and the combined extracts washed with aqueuos sodium hydrogen carbonate and water, dried (MgSO$_4$), and the solvent removed under reduced pressure to yield a crystalline residue (258 mg). Flash chromatography on silica gel (20 g) using ethyl acetate-toluene (1:4) gave **148** (265 mg, 86%), m.p. 225-228°C (from chloroform-methanol); [α]$_D$ -232° (*c* 0.9); ν_{max}/cm^{-1} 1709 and 1727 (CO);

δ_H(200 MHz) 1.07(3H, s, 13β-Me), 2.11(3H, s, 17-$OCOCH_3$), 2.71-2.80(2H, m, 6α- and 6β-H), 3.11-3.26(3H, obsc. m, 17^1, -17^2- , 17^3- and 17^4-H), 3.25(4H, obsc. m, -SCH_2CH_2S-), 3.48(1H, dt, *J* 10.8 and 2x2.1 Hz, 15β-H), 3.75(3H, s, 3-OMe), 6.56(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.16(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz) 17.2(C-18), 22.4(17-$OCOCH_3$), 23.8(C-7), 26.1(C-11), 29.5(C-6), 35.2(C-12), 37.5, 38.0(C-8), 39.1, 39.3, 42.7(C-9), 45.1, 55.3(C-13), 53.4, 54.1(C-14), 55.2(3-OMe), 56.3 62.3 and 73.4(S-*C*-*C*-S), 99.7(C-17), 111.9(C-2), 113.4(C-4), 126.8(C-1), 131.5(C-10), 137.2(C-5), 157.6(C-3), 170.2(17-$OCOCH_3$), and 217.6(C-15^1); (Found: C, 68.5; H, 6.5; S, 12.2%; M$^+$, 508; $C_{29}H_{32}O_4S_2$ requires C, 68.5; H, 6.3; S, 12.6%; *M*, 508).

3-Methoxy--15^1-oxo-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17β-yl acetate 149

Raney nickel (Aldrich, W2, 0.5g) was washed (4x) with absolute ethanol, the ethanol decanted and the nickel suspended in further ethanol (2 cm^3). A solution of the thioketal **148** (217 mg, 0.0.43 mmol) in ethanol (5 cm^3) was added and the resultant mixture heated with stirring at 50°C for 3 h. The mixture was allowed to cool to 24°C and chloroform (3 cm^3) was added. The mixture was filtered through Celite and the Celite washed repeatedly with chloroform. The filtrate was evaporated to dryness under reduced pressure to give a solid residue (179 mg). Recrystallisation of the crude material gave **149** (162 mg, 91%), m.p. 178-179°C (from acetone-methanol); $[\alpha]_D$ -123° (*c* 1.1); ν_{max}/cm^{-1} 1711, 1728 (CO); δ_H(400 MHz) 0.97(3H, s, 13β-Me), 2.07(3H, s, 17-$OCOCH_3$), 2.74-2.82(2H, m, 6α- and 6β-H), 3.17-3.29(4H, m, 17^1-, 17^2-, 17^3- and 17^4-H), 3.59(1H, dt, *J* 8.1 and 2x2.1 Hz, 15β-H), 3.76(3H, s, 3-OMe), 6.58(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.21(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz); 18.1(C-18), 22.4(17-$OCOCH_3$), 23.6(C-7), 25.9(C-11), 26.7(C-3'), 28.1(C-12), 29.9(C-6), 38.7, 39.7(C-8), 42.2(C-9), 48.2, 49.4, 49.8(C-13), 50.9(C-14), 52.6, 54.9, 55.2(3-OMe), 56.5, 98.5(C-17), 112.1(C-2), 113.3(C-4), 127.3(C-1), 131.0(C-10), 137.3(C-5), 157.6(C-3), 170.6(17-$OCOCH_3$) and 212.8(C-15^1); (Found: C, 77.4; H, 7.2%; M$^+$, 418; $C_{27}H_{30}O_4$ requires C, 77.5; H, 7.2%; *M*, 418).

17β-hydroxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-15^1-one 150

Methanolic potassium hydroxide (5 cm^3, 0.5 M) was added to a solution of the 17-acetoxy-15^1-ketone **149** (57 mg, 0.14 mmol) in tetrahydrofuran (5 cm^3) and the mixture stirred at 24°C for 2 h. The mixture was then heated under reflux for 2.5 h, cooled and saturated sodium hydrogen carbonate added. The mixture was extracted with chloroform, the combined extracts washed with water and brine, dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material was filtered through silica gel (5 g) using toluene as eluent to give **150** (46 mg, 89 %), m.p. 197-198°C (from acetone-methanol); [α]$_D$ -145° (*c* 1.0); ν_{max}/cm^{-1} 1678 (CO) and 3547 (OH) δ$_H$(400 MHz) 1.03(3H, s, 13β-Me), 2.67-2.88(2H, m, 6α- and 6β-H), 3.21-3.36(4H, m, 17^1-, 17^2-, 17^3- and 17^4-H), 3.72(3H, s, 3-OMe), 3.48(1H, dt, *J* 9.3 and 2x1.9 Hz, 15β-H), 6.63(1H, d, *J* 2.8 Hz, 4-H), 6.72(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.24(1H, d, *J* 8.6 Hz, 1-H); δ$_C$(50 MHz); 19.2(C-18) 24.7(C-7), 25.8(C-11), 25.6, 28.4, 30.7, 38.7, 38.8, 43.1, 47.6, 49.7, 50.1(C-13), 50.9(C-14), 54.1, 54.8, 55.2(3-O*Me*), 57.8, 86.7(C-17), 112.5(C-2), 113.5C-4), 127.2(C-1), 132.8(C-10), 136.9(C-5), 157.3(C-3) and 214.2(C-15^1); (Found: C, 79.5; H, 7.5%; M$^+$, 376; C$_{25}$H$_{28}$O$_3$ requires C, 79.8; H, 7.5%; M, 376).

3-Methoxy-16,17-seco-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-triene-15^1,16^1,17-trione 151

Methanolic potassium hydroxide (1 cm^3, 0.5 M) was added to a solution of the 17-acetoxy-15^1,16^1-diketone **140** (48 mg, 0.11 mmol) in tetrahydrofuran (3 cm^3) and the mixture stirred at 24°C for 5 h. The mixture was extracted with chloroform, the combined extracts washed with water and brine, dried (MgSO$_4$) and the solvent removed under reduced pressure. The crude material (46 mg) was chromatographed on silica gel (5 g) using ethyl acetate-toluene (3:7) as eluent to give **151** (33 mg, 77 %), m.p. 221-224°C (from acetone-methanol); [α]$_D$ -98° (*c* 1.1); ν_{max}/cm^{-1} 1705br (CO) and 1729 (CO) δ$_H$(400 MHz, C$_5$D$_5$N) 1.07(3H, s, 13β-Me), 2.63-2.74(2H, m, 6α- and 6β-H), 2.86(1H, dd, *J* 17.2 and 2.3 Hz, 16α-H), 2.94-3.08(4H, m, 17^1-, 17^2-, 17^3- and 17^4-H), 3.17(1H, dd, *J* 8.7 and 2.3 Hz, 15β-H), 3.26(1H, dd, *J* 17.2 and 8.7 Hz, 16β-H)), 3.74(3H, s, 3-OMe), 6.61(1H, d, *J* 2.8 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.21(1H, d, *J* 8.6 Hz, 1-H); δ_C(50 MHz); 19.8(C-18) 24.6, 24.5, 26.5, 28.9, 31.3, 36.0, 39.8, 43.9 ,49.7, 50.1, 50.9, 54.8, 55.2(3-O*Me*), 57.8, 112.5(C-2), 113.5C-4), 127.2(C-1), 132.8(C-10), 136.9(C-5), 157.3(C-3) and 204, 209 and 214.2(C-15^1, C-16^1 and C-17); (Found: M^+, 390; $C_{25}H_{26}O_4$ requires M, 390).

15^1,15^1-Ethylenedithio-3-methoxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17βyl acetate 152

A solution of the ketone **149** (150 mg, 0.36 mmol) in dichloromethane (2 cm^3) was cooled to 0°C and ethanedithiol (0.1 cm^3, 1.2 mmol) was added followed by boron trifluoride-diethyl ether (0.05 cm^3, 1.1 mmol). The solution was stirred at 24°C for 4h, then water added and the resultant mixture poured into aqueous sodium hydrogen carbonate. The mixture was extracted with chloroform and the combined extracts washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and the solvent removed under reduced pressure to yield a crystalline residue (184 mg). Flash chromatography on silica gel (20g) using ethyl acetate-toluene (3:7) gave thioketal **152** (167 mg, 94%), m.p. 231-233°C (from chloroform-methanol); $[\alpha]_D$ -198° (*c* 1.3); ν_{max}/cm^{-1} 1657 (CO); δ_H(200 MHz) 1.03(3H, s, 13β-Me), 2.17(3H, s, 17-$OCOCH_3$), 2.71-2.79(2H, m, 6α- and 6β-H), 3.13-3.28(4H, obsc. m, 17^1-, 17^2- 17^3- and 17^4-H), 3.25(4H, m, -SCH_2CH_2S-), 3.77(3H, s, 3-OMe), 6.60(1H, d, *J* 2.6 Hz, 4-H), 6.73(1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.20(1H, d, *J* 8.6 Hz, 1-H); (Found: C, 70.7; H, 6.7; S, 12.7%; M^+, 494; $C_{29}H_{34}O_3S_2$ requires C, 70.4; H, 6.9; S, 13.0%; *M*, 494).

Desulfurisation of the Thioacetal 152

Raney nickel (Aldrich, W2, 0.5g) was washed (4x) with absolute ethanol, the ethanol decanted and the nickel suspended in further ethanol (2 cm^3). A solution of the thioketal

152 (135 mg, 0.27 mmol) in ethanol (5 cm^3) was added and the resultant mixture heated with stirring at 50°C for 2 h. The mixture was allowed to cool to 24°C and chloroform (3 cm^3) was added. The mixture was filtered through Celite and the Celite washed repeatedly with chloroform. The filtrate was evaporated to dryness under reduced pressure to give a solid residue (102 mg). Recrystallisation of the crude material gave 3-methoxy-17^1,17^4-cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-17β–yl acetate **145** (98 mg, 89%) with analytical and spectroscopic data identical to that of an authentic sample.

Hydrolysis of the 17-Acetoxy-Caged Compound 145

The ester **145** (80 mg, 0.2 mmol) was added to a suspension of potassium carbonate (60 mg, 0.23 mmol) in ethanol (3 cm^3) and the mixture stirred at 24°C for 5 h. Water was added and the mixture extracted with chloroform, then the combined extracts washed with water and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crystalline residue (70 mg) was recrystallised from chloroform to give 3-*methoxy*-17^1,17^4-*cyclo*-15α,17^3;16α,17^2-bismethano-14,17α-*butano-estra*-1,3,5(10)-*trien*-17β-*ol* **144** (65 mg, 90%) identical to an authentic sample.

17^1,17^4-Cyclo-15α,17^3;16α,17^2-bismethano-14,17α-butanoestra-1,3,5(10)-trien-3,17β-diol 153

Di-isobutylaluminium hydride (1.2 M solution in toluene, 1 cm^3, 1.2 mmol) was added to a stirred solution of the alcohol **144** (55 mg, 0.15 mmol) in dry toluene (10 cm^3) and the mixture was refluxed under nitrogen for 57 h. The mixture was cooled to 24°C and 10%-hydrochloric acid (20 cm^3) added. The aqueous layer was extracted with chloroform, the combined organic phase washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crystalline residue (49 mg). Recrystallisation from acetone gave

153 (45 mg, 86%); m.p. 239-240°C; $[\alpha]_D$ -198°(*c* 0.9, pyridine); (Found: C, 82.5; H, 8.3%; M^+, 348; $C_{24}H_{28}O_2$ requires C, 82.7; H, 8.1%; *M*, 348).

3-Methoxy-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-3',6',17β-triol 154

The cycloadduct **138** (86 mg, 0.2 mmol) was dissolved in tetrahydrofuran (5 cm^3) and the mixture cooled to 0°C. Methanolic potassium hydroxide (1 M, 0.25 cm^3) was added and the mixture stirred at 0°C for 0.5 h. Saturated aqueous ammonium chloride was added, the mixture was allowed to warm to 24°C and then extracted with chloroform. The combined organic phase was washed with water and brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material (76 mg) was chromatographed on silica gel (8 g) using ethyl acetate-toluene (2:3) as eluent to give **154** (59 mg, 76 %), m.p. 242-244°C decomp. (from acetone); $[\alpha]_D$ +246° (*c* 0.9; pyridine); ν_{max}/cm^{-1} 3570 br (OH); δ_H(400 MHz) 1.04(3H, s, 13β-Me), 1.48(1H, dddd, *J* 2 x 13.1, 12.6 and 3.6 Hz, 11β-H), 1.58(1H, ddd, *J* 12.6, 2 x 3.6 Hz, 12β-H), 1.88(1H, dddd, *J* 12.3, 11.3, 10.7 and 5.3 Hz, 7α-H), 2.16(1H, ddd, *J* 10.7, 10.2 and 2.3 Hz, 8β-H), 2.31(1H, dddd, *J* 13.1 and 3 x 3.6 Hz, 11α-H), 2.44(1H, ddd, *J* 2 x 12.6 and 3.6 Hz, 12α-H), 2.62(1H, ddd, *J* 13.1, 10.2 and 3.6 Hz, 9α-H), 2.96(1H, ddd, *J* 16.6, 5.3 and 2.9 Hz, 6α-H), 3.16(1H, ddd, *J* 16.6, 11.3 and 5.6 Hz, 6β-H), 3.27(1H, dddd, *J* 12.3, 5.6, 2 x 2.9 Hz, 7α-H), 3.79(3H, s, 3-OMe), 6.50 and 6.56(each 1H, d, *J* 8.7 Hz, 17^1- and 17^2-H), 6.76-6.82(4H, m, 2-, 4-, 4'- and 5'-H), and 7.28(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 16.5(q, C-18), 25.6(t, C-11), 27.9(t, C-7), 28.0(t, C-12), 30.6(t, C-6), 36.8(d, C-8), 41.7(d, C-9), 55.3(q, 3-OMe), 66.1(s, C-13), 82.3(s, C-14), 96.1(s, C-17), 111.4(d, C-2), 113.8(d, C-4), 114.9 and 116.1(each d, C-17^1 and C-17^2), 126.4(d, C-1), 132.9(s, C-10), 133.7 and 135.2(each s, C-15 and C-16), 138.9(s, C-5), 140.3 and 140.5(each d, C-4' and C-5'), 144.3 and 146.5(each s, C-3' and C-6') and 157.6(s, C-3); (Found C, 76.8; H, 6.7 %; M^+, 390; $C_{25}H_{26}O_4$ requires C, 76.9; H, 6.7 %; *M*, 390).

3-Methoxy-3'(4'*H*),6'(5'*H*)-dioxo-15β*H*,16β*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate 155

The cycloadduct **138** (128 mg, 0.29 mmol) in ethyl acetate (10 cm^3) at 24°C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%, 25 mg). After 2.5 h the mixture was filtered through Celite, and the filtrate evaporated under reduced pressure to give a crude residue (125 mg). Filtration through silica gel (10 g) using toluene as eluent gave **155** (119 mg, 94%), m.p. 178-179°C (from acetone-methanol); $[\alpha]_D$ -235° (*c* 1.1); ν_{max}/cm^{-1} 1687, 1705 and 1729 (CO); δ_H(400MHz) 1.01(3H, s, 13β-Me), 2.16(1H, s, 17β–$OCOCH_3$), 2.32(1H, d, *J* 9.8 Hz, 15β-H), 3.66(1H, *J* 9.8 Hz, 16β-Me), 3.77(3H, s, 3-OMe), 6.25 and 6.58(each 1H, d, *J* 6.1 Hz, 17^1- and 17^2-H), 6.62(1H, d, *J* 2.7 Hz, 4-H), 6.71(1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.2(1H, d, *J* 8.5 Hz, 1-H); δ_C(100 MHz) 16.0(q, C-18), 21.7(q, 17-$OCOCH_3$), 24.3(t, C-7), 26.7(t, C-11), 28.6(t,C-12), 30.1(t, C-6), 38.1 and 39.6(each t, C-4' and C-5'), 40.0(d, C-8), 40.9(d, C-9), 55.2(q, 3-OMe), 56.2 and 56.5(each d, C-15 and C-16), 60.6 and 62.8(each s, C-13 and C-14), 95.5(s, C-17), 111.9(d, C-2), 113.4(d, C-4), 127.0(d, C-1), 131.6(d, C-17^1), 131.8(s, C-10), 134.8(d, C-17^2), 157.5(s, C-3), 170.2(s, 17-$OCOCH_3$) and 206.8 and 211.0(each s, C-3' and C-6'); (Found: C, 74.8; H, 7.0%; M$^+$, 434; $C_{27}H_{30}O_5$ requires C, 74.6; H, 6.9%; *M*, 434).

3-Methoxy-6'(5'*H*)-oxo-15β*H*,16β*H*-benzo[15,16]-14,17α-ethenoestra-1,3,5(10)-trien-17β,3'α-diyl diacetate 156

The diketone **155** (200 mg, 0.46 mmol) was dissolved in dry toluene (20 cm^3), then the solution cooled to -78°C and L-Selectride (0.5 cm^3 of a 1.0 M solution in tetrahydrofuran, 0.5 mmol) added. The mixture was stirred at -78°C for 3 h, then saturated aqueous ammonium chloride added and the mixture was allowed to warm to 24°C. Aqueous sodium hydoxide (5%, 10 cm^3) was added slowly followed by hydrogen peroxide (30%, 10 cm^3), the mixture stirred for 0.5 h and then extracted with dichloromethane. The combined organic phase was washed with saturated sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude material

(181 mg) was dissolved in pyridine (3 cm^3) and aceatic anhydride (0.5 cm^3, 5.3 mmol) and 4-(Dimethylamino)pyridine (12 mg, 0.1 mmol) added. The mixture was stirred for 11 h, then water added and stirring continued for 30 min. Standard work-up (ethyl acetate) gave crude material (180 mg) which was chromatographed on silica gel (20g) using ethyl acetate-toluene (1:9) as eluent to give **156** (173 mg, 79%), m.p. 176-177°C (from ethyl acetate-hexane); $[\alpha]_D$ -267° (*c* 1.1); ν_{max}/cm^{-1} 1708 and 1724 (CO); δ_H(400 MHz) 1.01(3H, s, 13β-Me), 1.11(1H, ddd, *J* 13.2, 4.3 and 2.4 Hz, 12β-H), 1.28(1H, tdd, *J* 13.3x2, 11.6 and 4.3 Hz, 11β-H), 1.45(1H, td, *J* 11.6x2 and 2.7 Hz, 8β-H), 1.98 and 2.08(each 3H, s, 17- and 3'-OCOCH$_3$), 2.60(1H, td, *J* 11.6x2 and 4.8 Hz, 9α-H), 2.98(1H, d, *J* 11.3 Hz, 15β-H), 3.28(1H, dd, *J* 11.3 and 4.3 Hz, 16β-H), 3.77(3H, s, 3-OMe), 5.28(1H, td, *J* 4.3x2 and 1.6 Hz, 3'-H), 6.19(2H, s, 17^1- and 17^2-H), 6.61(1H, d, *J* 2.5 Hz, 4-H), 6.70(1H, dd, *J* 8.6 and 2.5 Hz, 2-H) and 7.21(1H, d, *J* 8.6 Hz, 1-H); δ_C(100MHz) 15.4(q, C-18), 21.3 and 21.5(each q, 17- and C3'-OCOCH$_3$), 25.9(t, C-4'), 26.4(t, C-7), 27.9(t, C-11), 28.1(t, C-12), 30.7(t, C-6), 34.8(t, C-5'), 40.2 and 40.3(each d, C-8 and C-9), 50.0(d, C-16), 55.1(d, C-15), 55.2(q, 3-OMe), 57.5 and 62.2(each s, C-13 and C-14), 67.1(d, C-3'), 93.7(s, C-17), 111.9(d, C-2), 113.4(d, C-4), 127.5(d, C-1), 130.6 and 131.6(each d, C-17^1 and C-17^2), 132.1(s, C-10), 139.0(s, C-5), 157.4(s, C-3), 169.9 and 170.1(each s, C-17- and C3'-OCOCH$_3$) and 209.4(s, C-6'); (Found: C, 72.8; H, 7.3%; M$^+$, 478; $C_{29}H_{34}O_6$ requires C, 72.8, H, 7.2%; *M*, 478).

7.3 Crystal Structure Determination[#]

A single crystal of diffraction quality was mounted on a glass fibre. X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer, using graphite monochromated Mo Kα radiation (l = 0.7107 nm) and the ω - 2θ scan mode. The unit cell was refined using the setting angles of 24 reflections in the θ range 16 - 17°. Three reference reflections were monitored periodically for intensity and orientation control. A Lorentz-polarisation correction was applied to the data.

All non-hydrogen atoms were found by direct methods using SHELX-86.[127] The structure was refined using SHELX-93.[128] Hydrogen atoms were placed in geometrically calculated positions and refined with a common temperature factor for chemically equivalent groups. The hydroxyl hydrogens could not be located in the electron density map, and were omitted from the final model. All atoms were refined with isotropic temperature factors. The structure refined to a final R-value of 0.0797 for 1957 reflections with $I > 2\sigma(I)$.

The hydroxy-ketone **41** crystallised in the orthorhombic crystal system, in the space group $P2_12_12_1$, with Z=8. This implies that two whole molecules constitute the assymetric unit, both located in general positions. The molecular structures of the two molecules have been designated **41**(**A**) and **41**(**B**)

Details of the data collection and refinement are given in Table 1.

Atomic coordinates are given in Tables 2 and 3.

[#] Crystal structure determination kindly performed by Dr A Coetzee

Table 1: Crystal Data for 4'β-Hydroxy-3-methoxy-3',4',5',6'-tetrahydro-15αH-benzo[14,15]-estra-1,3,5(10)-trien-17-one 41

Empirical Formula	$C_{23}H_{30}O_3$
Formula Weight	354.47
Temperature	293(2) K
Crystal System	Orthorhombic
Space Group	$P2_12_12_1$
Unit Cell Dimensions (Å)	a = 12.355(2)
	b = 15.885(2)
	c = 19.355(3)
Volume (Å^3)	3798(1)
Z	8
Density (g.cm^3) (calculated)	1.240
Absorption Coefficient (nm^{-1})	0.080
F(000)	1536
Theta Range	1.66 to 24.98 deg.
Index Range	$0 \leq h \leq 14$, $0 \leq k \leq 18$, $0 \leq l \leq 22$
Reflections Collected	3730
Reflections with $I > 2\sigma > (I)$	1957
Refinement Method	Full-matrix least-squares on F^2
Data / Restraints / Parameters	3730 / 0 / 259
Goodness-of-fit on F2	0.998
Final R indices [$I > 2\sigma > (I)$]	R1 = 0.0739, wR2 = 0.1969
R indices (all data)	R1 = 0.1892, wR2 = 0.2543
Absolute Structure Parameters	-3(5)
Extinction Coefficient	0.003(1)

Table 2: Fractional Atomic Coordinates and Thermal Parameters (Å) for 41(A)

Atom	*x/a*	*y/b*	*z/c*	*Uequiv.*
C1A	-0.27627	0.89638	0.98897	0.05113
C2A	-0.37868	0.88468	1.01620	0.05316
C3A	-0.46263	0.85932	0.97266	0.06087
C4A	-0.44762	0.84689	0.90460	0.06008
C5A	-0.34604	0.85838	0.87635	0.04354
C6A	-0.33250	0.84328	0.79793	0.05872
C7A	-0.22748	0.88361	0.77045	0.05887
C8A	-0.13376	0.85633	0.81405	0.04257
C9A	-0.14550	0.89462	0.88754	0.04122
C10A	-0.25868	0.88112	0.91567	0.04579
C11A	-0.05825	0.86170	0.93421	0.05486
C12A	0.05525	0.88361	0.90662	0.06470
C13A	0.07204	0.84614	0.83343	0.04817
C14A	-0.01888	0.87361	0.78046	0.04468
C15A	0.00575	0.97008	0.76748	0.05528
C16A	0.13523	0.97843	0.77513	0.07074
C17A	0.16569	0.89546	0.80496	0.05665
C18A	-0.03055	1.00216	0.69547	0.05476
C19A	-0.00037	0.94917	0.63512	0.06014
C20A	-0.04209	0.85801	0.64559	0.06014
C21A	-0.00112	0.82221	0.71408	0.05102
C22A	0.09629	0.75240	0.83732	0.06941
C23A	-0.65434	0.82118	0.96738	0.09445
O3A	-0.56050	0.84910	1.00841	0.07498
O17A	0.26206	0.87582	0.81431	0.08133
O19A	0.11533	0.95166	0.62505	0.06775

Table 3: Fractional Atomic Coordinates and Thermal Parameters (Å) for 41(B)

Atom	*x/a*	*y/b*	*z/c*	*U*equiv.
C1B	-0.11711	1.01476	0.12776	0.04701
C2B	-0.10021	1.05937	0.06642	0.05540
C3B	0.00311	1.04874	0.03615	0.04387
C4B	0.08381	1.00054	0.06573	0.05447
C5B	0.05958	0.95895	0.12960	0.04041
C6B	0.15063	0.90952	0.16344	0.05556
C7B	0.13632	0.90454	0.23992	0.04953
C8B	0.02300	0.86731	0.25908	0.03762
C9B	-0.06422	0.92731	0.23083	0.03856
C10B	-0.04184	0.96582	0.15957	0.04310
C11B	-0.17472	0.87966	0.23342	0.05280
C12B	-0.20104	0.85954	0.30615	0.05731
C13B	-0.10993	0.80543	0.34535	0.04241
C14B	0.00307	0.84483	0.33687	0.03856
C15B	0.00241	0.91889	0.38818	0.03801
C16B	-0.07180	0.88869	0.44832	0.04829
C17B	-0.13553	0.81904	0.41981	0.05427
C18B	0.11242	0.94989	0.41460	0.05536
C19B	0.19050	0.88069	0.43850	0.05356
C20B	0.19678	0.80971	0.38722	0.05404
C21B	0.08637	0.77679	0.36216	0.04876
C22B	-0.12414	0.71175	0.32128	0.06585
C23B	-0.04227	1.14106	-0.05920	0.07713
O3B	0.03355	1.08699	-0.02573	0.07205
O17B	-0.19866	0.77470	0.45375	0.08414
O19B	0.15451	0.85150	0.50500	0.02303

CHAPTER 8

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