SYNTHESIS AND STRUCTURE–ACTIVITY RELATIONSHIPS OF RING D ALKYL 19-NORSTEROIDS

by

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Supervisor: Professor J.R. Bull

To: my Parents, Adriaan, and to Sylvia

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SUMMARY

Studies have been conducted in synthesising ring D alkyl 19-norsteroids. The aim was to investigate methods for the stereoselective introduction of alkyl groups at C(14) and C(15), for eventual conversion of the intermediates into 14- and 15-alkyl analogues of estradiol hormones.

In the first phase of this investigation, 17β-*tert*-butyldimethylsilyloxyestra-1,3,5(10),14-tetraen-16-one was synthesised as starting material for alkylation experiments. Estrone 3-methyl ether was converted into the derived 17β-hydroxy 16-ketone by standard methods. This conversion involved the introduction of a 16α-hydroxyl group by bromination–hydrolysis, followed by base-mediated rearrangement of the hydroxy ketone to the thermodynamically preferred 16-ketone. Protection of the 17β-hydroxyl group as a TBS-ether, followed by palladium acetate-mediated dehydrosilylation of the derived Δ^{15}-16-trimethylsilyloxy enol ether gave the Δ^{14}-16-ketone.

The 17β-silyloxy Δ^{14}-16-ketone resisted conjugate addition reactions, leading only to products of 1,2-alkylation. Stereoselective introduction of a 16-allyl group gave the corresponding Δ^{14}-16-allyl 16-alcohols, but these compounds showed no sigmatropic reactivity and failed to undergo anionic oxy-Cope rearrangement.

Hydride reduction of the 16-oxo group gave the corresponding Δ^{14}-16-alcohols. The stereoselectivity was dependant on the choice of reagent. The Δ^{14}-16α-alcohol underwent stereodirected cyclopropanation to give 17β-*tert*-butyldimethylsilyloxy-14,15α-methylene-estra-1,3,5(10)-trien-16α-ol. Oxidation of this compound gave the corresponding 14α,15α-methylene 16-ketone, dissolving metal reduction of which furnished the 16β-alcohol. Routine deprotection of the epimeric pair of methylene 16-alcohols gave the derived estriol analogues, which were subjected to biological evaluation. Treatment of the 14α,15α-methylene 16-ketone with lithium in liquid ammonia gave 17β-*tert*-butyldimethylsilyloxy-14-methylestra-1,3,5(10)-trien-16-one. Stereoselective reduction of the 16-oxo group gave the epimeric 14α-methyl 16-alcohols. Deprotection of these compounds at C(3) gave a second pair of estriol analogues, which were also assayed for receptor binding affinity.

In the second phase of this work, a series of 15,15-dialkylestradiol analogues was prepared. The approach entailed sequential conjugate alkylation – dehydrogenation – conjugate alkylation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one. Circular dichroism and ^{13}C NMR data for the series of 15,15-dialkyl 17-ketones are presented. Reduction of the 17-oxo group of the 15,15-dialkyl 17-ketones gave the corresponding 17β-alcohols in high yield. Routine demethylation at C(3) gave the 15,15-dialkylestradiols, which were tested for biological activity.

An extension of this investigation involved the preparation of 15,15- and 16,16-dimethyl analogues of 17a-homoestrone. Sequential conjugate methylation –

dehydrogenation of 3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one gave the corresponding 16-methyl Δ^{15}-17a-ketone, conjugate methylation of which gave 3-methoxy-16,16-dimethyl-17a-homo-estra1,3,5(10)-trien-17a-one. Reduction of the 17a-oxo group gave the epimeric 17a-alcohols, demethylation of which gave the related homoestradiol analogues.

A synthetic route to the 15,15-dimethyl 17a-ketone was attempted through ring homologation of 3-methoxy-15,15-dimethylestra-1,3,5(10)-trien-17-one. However, an approach based upon cyclopropanation of the silyl enol ether of the 15,15-dimethyl 17-ketone was unsuccessful. In an alternative approach, 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one was converted into the related 15,15-dimethyl Δ^{17}-16-ketone. Epoxidation of the Δ^{17}-bond occurred smoothly, but the derived epoxy ketone failed to undergo Wharton rearrangement, to give the desired Δ^{16}-17a-alcohol.

Binding affinity results for the estradiol and estriol analogues prepared in this study are presented. Significant estrogenicity was displayed by three of these hormones, *viz.* 15,15-dimethylestra-1,3,5(10)-triene-3,17β-diol (CF 1.5), 15,15-dimethyl-14β-estra-1,3,5(10)-triene-3,17α-diol (CF 1.0), and 14,15α-methylene-estra-1,3,5(10)-triene-3,16β,17β-triol (CF 1.0).

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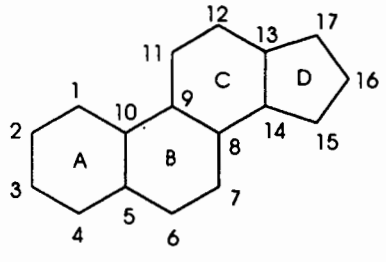
Chapter 1

INTRODUCTION

Two major constraints influence the binding of a hormone to its receptor.[1] Firstly, steric accessibility plays a crucial role in recognition. The presence of a sterically demanding group will prevent close association between the hormone and the three dimensional space presented by the receptor, and hence inhibit recognition. In the second instance, upon successful recognition, hydrogen bonding plays a major stabilising role in maintaining the hormone–receptor complex and in anchoring the relative active sites of the interacting units.

The physiological action of the hormone stems from the hormone–receptor complex and the biological activity is governed by the concentration of this hormone–receptor complex.[2] This hormone–receptor bonding is reversible, in order for the biological effect to cease, and to allow fresh stimulation.

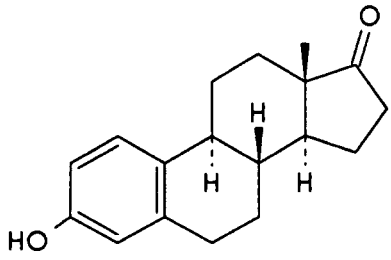
In most cases, the tetracyclic perhydrocyclopenta[a]phenanthrene nucleus **1** is a common feature in steroidal hormones of widely differing physiological activities. Although this system exhibits no biological activity of its own, the presence of polar functional groups at the extremities, unsaturation in ring A, as well as angular methyl groups in an all *trans-transoid* array of fused rings constitute the foundation of the primary sex and adrenocortical hormones. The ring system is thought to serve as a template for spatial positioning of attached polar functionalities, most typically hydroxy and oxo groups, in such a way that selective binding between the hormone and a defined receptor site is promoted.



1

Compounds with a high affinity for the estrogen receptor almost invariably contain a phenolic ring A.[3] This feature enables interaction with the estrogen receptor, and hence is accountable for estrogenicity. The most essential naturally occurring estrogenic hormones

are estrone **2**, estradiol **3** and estriol **4***, and display biological activities in the ratio 3:10:1 respectively.[3]



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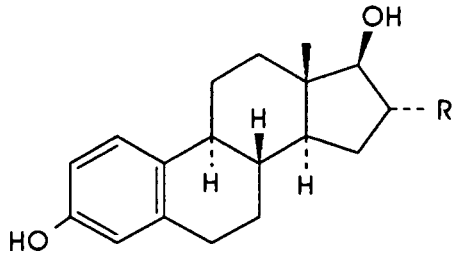
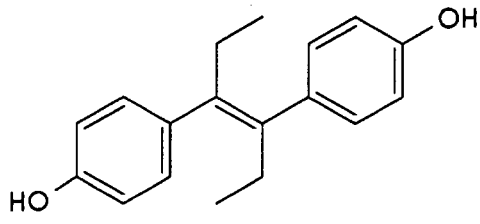


3 (R = H)
4 (R = OH)

The hydroxy group at C(3) of ring A acts as a hydrogen-bond donor, and this bond is thought to be more important than the molecular conformation in terms of binding to the estrogen receptor.[4,5] This was illustrated[3] by the estrogenicity of the non-steroidal compound diethylstilbestrol **5**, containing two phenolic rings, which emulate ring A of estradiol. Hence, for complete hormone expression, the importance of two polar groups at the extremities of the otherwise hydrophobic skeleton is defined. Removal of the 17-hydroxy group from estradiol significantly decreases binding and almost totally destroys estrogenic activity.[3] By contrast, removal of the 3-OH group virtually eliminates receptor binding, but activity is retained in proportion to the reduced degree of binding. This illustrates that 3-OH is more important to binding than 17-OH. The latter probably plays a role in stabilising the hormone–receptor complex by hydrogen bonding. Its absence may change the stability of the ring A binding interactions to the receptor.



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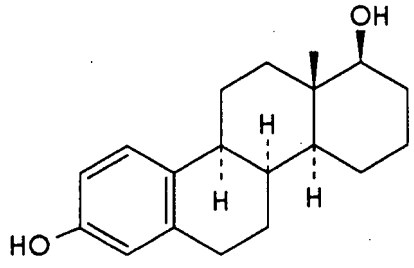
* All *trans-transoid* ring fusion as indicated. Unless otherwise specified, configuration is assumed to be 8β, 9α, 14α, and is omitted in subsequent illustrations for clarity.

Configurational changes of the parent ring system are frequently responsible for altered hormonal properties. Several 8α and 9β derivatives were shown to have biological activities similar to that of estradiol,[6] regardless of the conformational discrepancies between the steroids of natural and 'inverted' configurations. An example of such an instance is 17a-homo-8α-estra-1,3,5(10)-triene-3,17aβ-diol **6** and 3-hydroxy-9β-estra-1,3,5(10)-triene-11,17-dione **7**, which are superior in estrogenicity than their respective natural isomers. The conclusion drawn from this finding was that molecular planarity is not necessarily an essential requirement for activity.[3]



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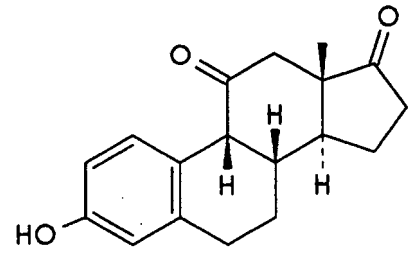

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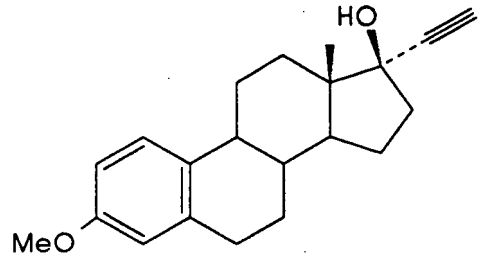
Changes in the substitution pattern are often attended by differences in binding characteristics.[6] This feature has become a useful experimental device, as it provides a basis for quantifying the influence of specific structural features upon binding sites.[2] For example, the introduction of a 17α-ethynyl group onto estradiol affords 3-methoxy-19-nor-17α-pregna-1,3,5(10)-trien-20-yn-17-ol **8**, which is *ca* 15 times more orally active than the parent hormone.[7] This potentiating influence of the ethynyl group was ascribed to the tertiary alcohol at C(17) becoming less susceptible to metabolic degradation.



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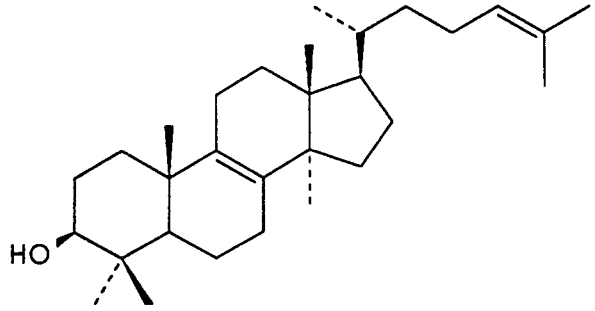
Notwithstanding numerous such successes in empirical structure–activity studies of recent times,[8,9] no general predictive principle of structure–activity has hitherto been established. Such an objective may be unattainable, but even the partial ability to quantify

additive trends in functional group modification could have enormous value for designing specific hormones.

Hydrophobic groups attached to ring D of the estrone skeleton have a strong influence on the physiological properties of these compounds.[10] An interest in 14-methyl steroids stems from early discoveries regarding the biochemical conversion of lanosterol **9** into cholesterol **10**. The introduction of a 14-alkyl group is, however, less straightforward. Degradation of lanosterol **9** has been used as a route to 14α-methyl-11-oxoprogesterone **11**, which was subsequently used towards the synthesis of 14-methylprogesterone **12** and 14-methyltestosterone **13**.[11,12] Further, base-mediated alkylation of cholest-8(14)-en-15-one **14** afforded 14-methylcholest-7-en-15-one **15**, thus establishing the biosynthetic relation between cholesterol and lanosterol (Scheme 1.1).[13]

This method of 14-alkylation was adopted by several groups (Scheme 1.2). Treatment of the 15-ketone **16** gave the derived 14β-methyl compound **17**, which was incorrectly assigned by the authors as the epimeric 14α-compound.[14] In a subsequent study, this misconception was rectified by an X-ray crystal structure.[15] Base-mediated methylation of 3-methoxy-14β-estra-1,3,5(10),8-tetraen-15-one **18** favoured 14α-alkylation and gave an epimeric mixture of 14-methyl 15-ketones **19** and **20** in the ratio of 5:1. By contrast, similar methylation of 20,20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10),trien-15-one **21** gave exclusively the 14α-methyl 15-ketone **22**. Thus, the stereochemical outcome of 14-alkylation of 15-oxo systems is dependent on $\Delta^{8(9)}$ unsaturation and is also influenced by the 17β-substitution.

Scheme 1.1



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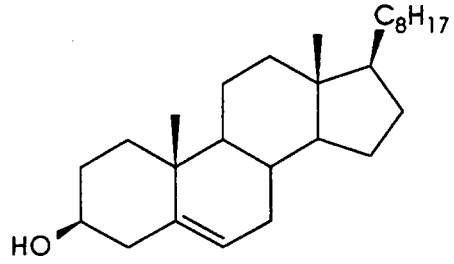

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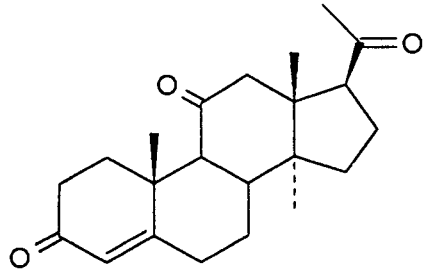

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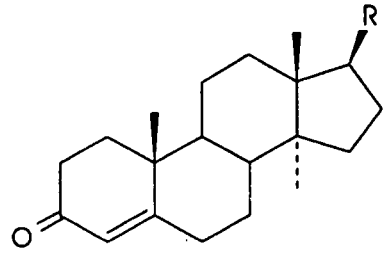
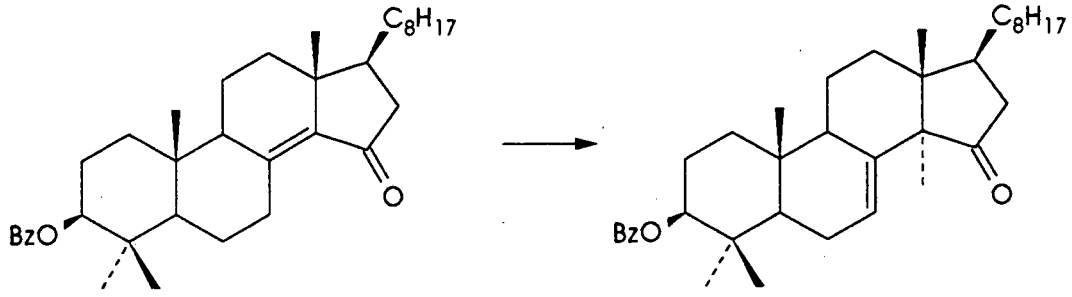
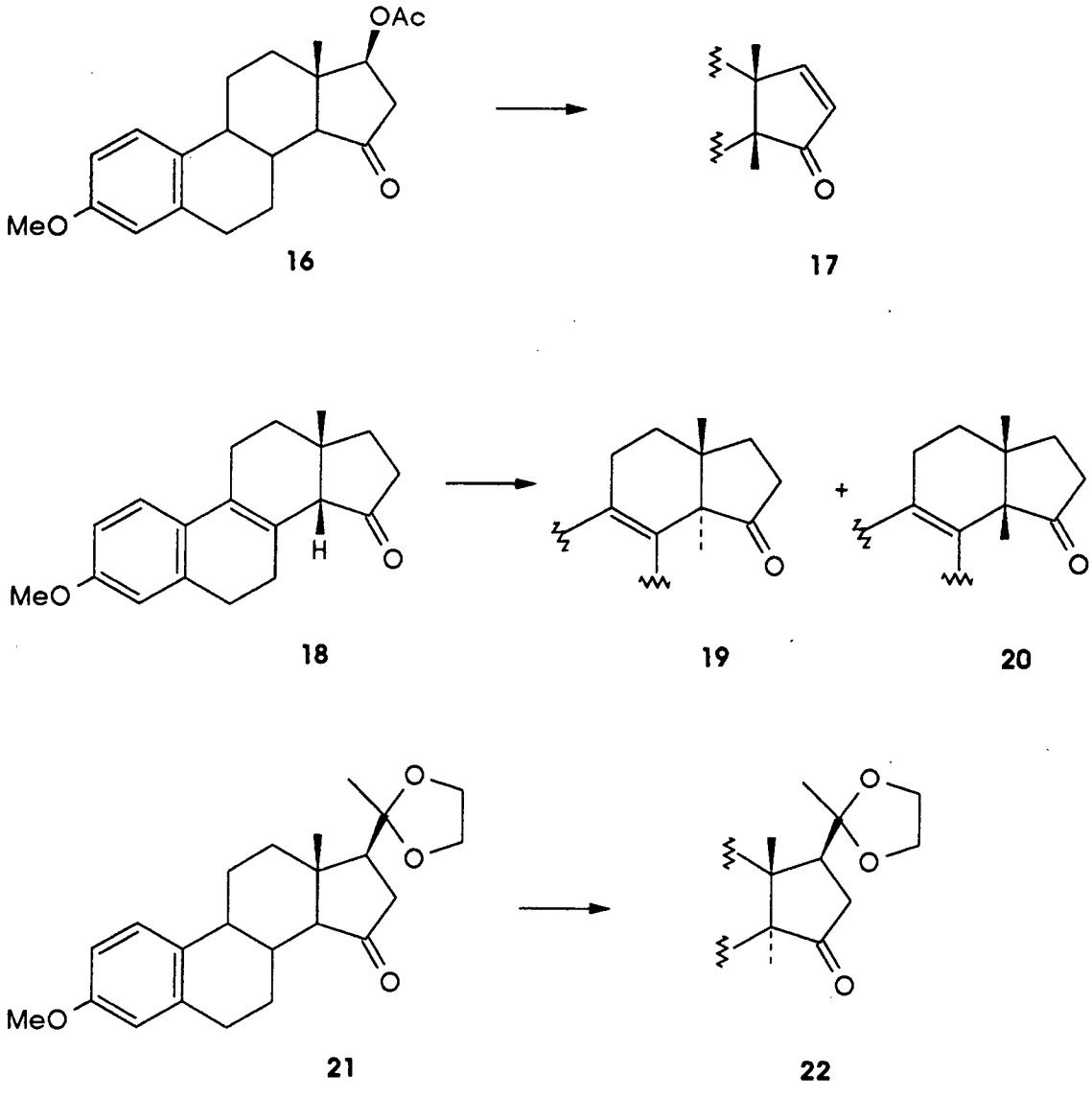


12 (R = COMe)
13 (R = OH)



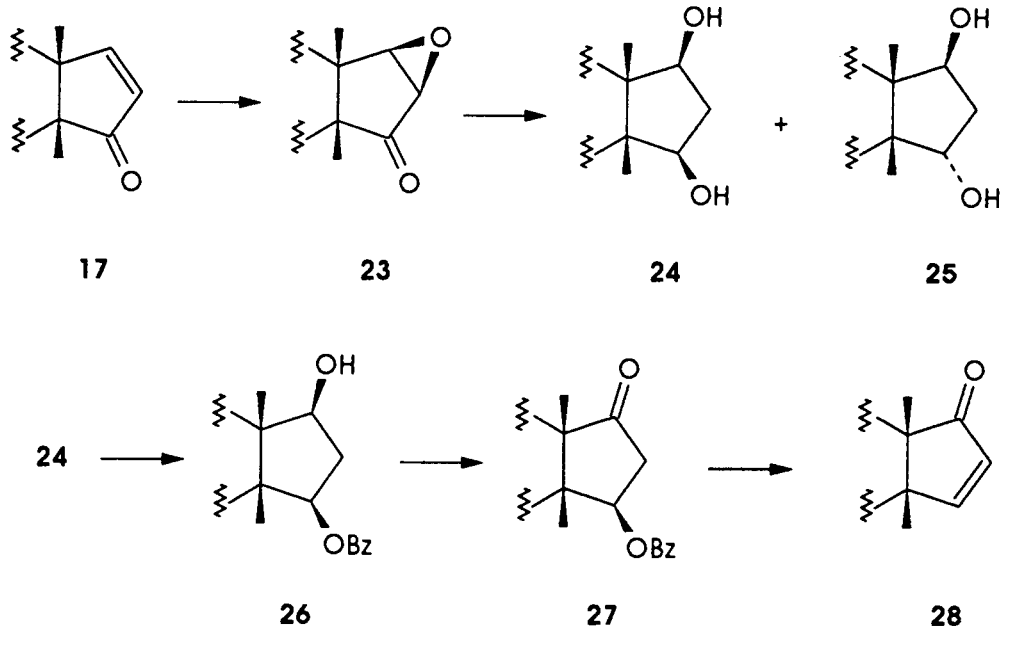
14 **15**

Scheme 1.2



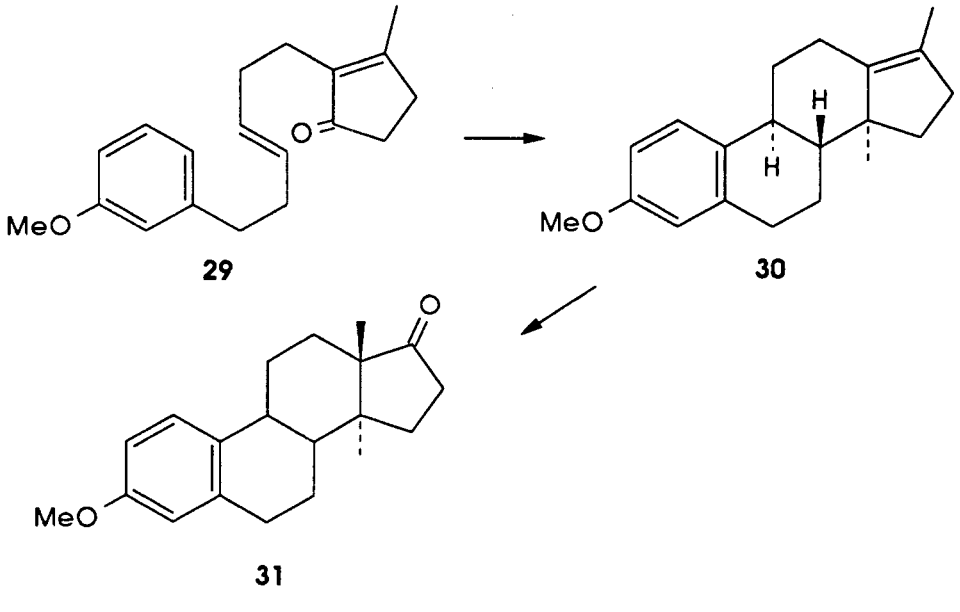
Oxygen functionality was re-introduced at C(17) of the Δ^{16}-15-ketone **17** by the sequence illustrated in Scheme 1.3.[16] Stereoselective epoxidation of **17** gave exclusively the 16β,17β epoxide **23**, lithium aluminium hydride treatment of which gave an epimeric mixture of 15β,17β- and 15α,17β-diols **24** and **25** (8.5:1). Benzoylation of the 15β,17β-diol **24** gave a complex mixture, containing mainly the 15β-benzoyloxy 17β-alcohol **26**. Oxidation of the 17β-hydroxyl group, followed by β-elimination gave 3-methoxy-14β-methylestra-1,3,5(10),15-tetraen-17-one **28**.

Scheme 1.3



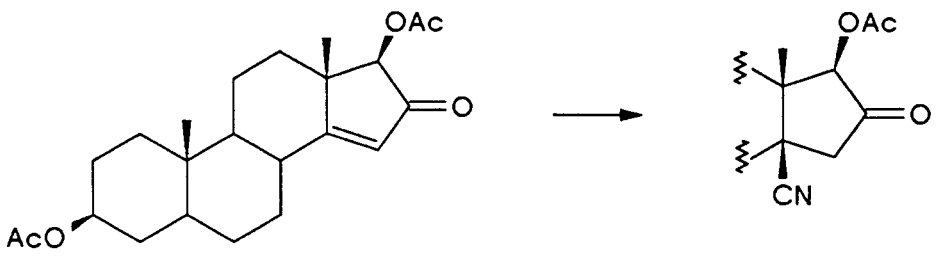
A biomimetic total synthesis of 14α-methyl 19-norsteroids was carried out by Groen and Zeelen[17] (Scheme 1.4). Treatment of the ketone **29** with methyllithium proceeded with concomitant cyclisation to give tetracyclic intermediate **30**. Subsequent conversions involved introduction of oxygen functionality at C(17) by epoxidation and rearrangement to give (*rac*)-3-methoxy-14-methylestra-1,3,5(10)-trien-17-one **31**.

Scheme 1.4



The functionalisation of C(14) by conjugate addition methodology has hitherto only been reported once. McLean[18] prepared the Δ^{14}-16-ketone **32** from dehydroepiandrosterone. Treatment of the latter with hydrogen cyanide gave the 14β-carbonitrile **33** (Scheme 1.5).

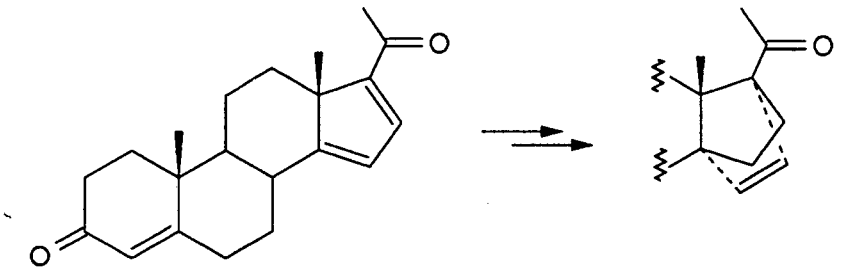
Scheme 1.5



32 **33**

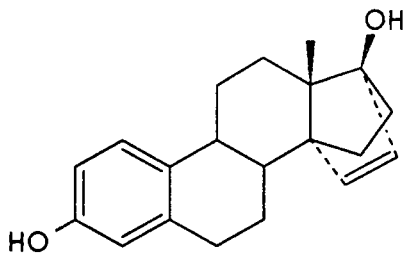
Some years ago, it was established that the introduction of a 14,17α-ethano bridge to progesterone **34** (Scheme 1.6) resulted in a decrease in hormonal activity.[19] This phenomenon was rationalised in terms of constraining the 17β-acetyl substituent of the cycloadduct **35** towards the α-side of the bridge, thereby inhibiting receptor binding ability.

Scheme 1.6



34 **35**

Subsequently, extensive work has been carried out on bridged and bridge-functionalised hormone analogues.[20] It has been discovered that bridged analogues of estradiol **36** and **37**, and estriol **38** show enhanced hormonal activity.[21]



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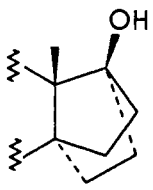

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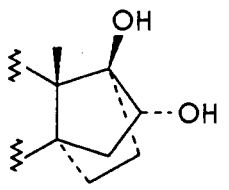
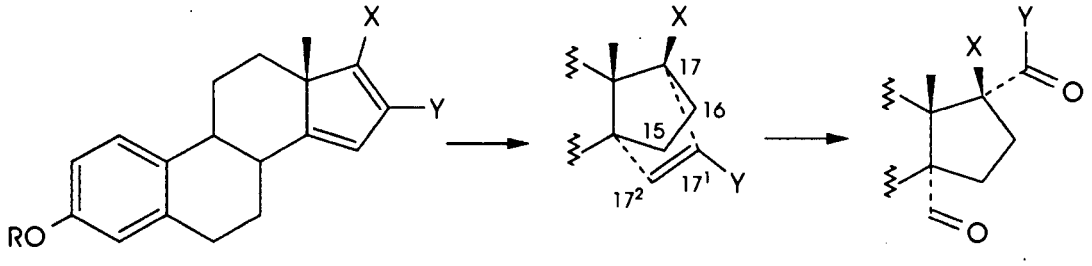


38

It has recently been shown that 14α-alkyl 19-norsteroids are conveniently attainable from a cycloaddition–oxidative cleavage route.[22] In this approach, an ethylene equivalent was reacted with a steroidal 14,16-diene **39**, followed by oxidative cleavage of the residual olefinic bond in the resultant cycloadduct **40**. In this way, ring D is restored with simultaneous functionalisation of C(14) and C(17) **41**, depending on the X,Y substitution pattern in the original diene (Scheme 1.7).

Scheme 1.7

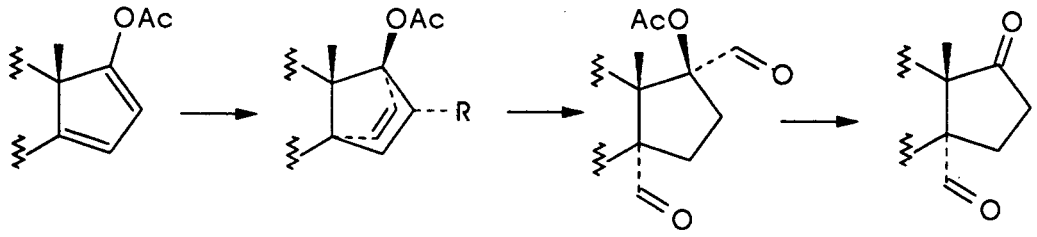


39 **40** **41**

An example of this is the cycloaddition of phenyl vinyl sulfone to the 15,17-dienyl 17-acetate **42**, which was prepared from estrone 3-methyl ether in three steps. The structure of the cycloadduct **43** was verified by subsequent conversions.[22] Removal of the sulphonyl group of **43**, followed by oxidative cleavage of the 14α,17α-bridge led to the 14α-carbaldehyde **46**. Reduction of the carbaldehyde gave the 14α-hydroxymethyl 17-ketone **47**, whereas deoxygenation gave the 14α-methyl compound **31** (Scheme 1.8).

Further elaboration of the 14α-carbaldehyde into C(14) chain homologated products were hindered by limited reactivity.[23]

Scheme 1.8

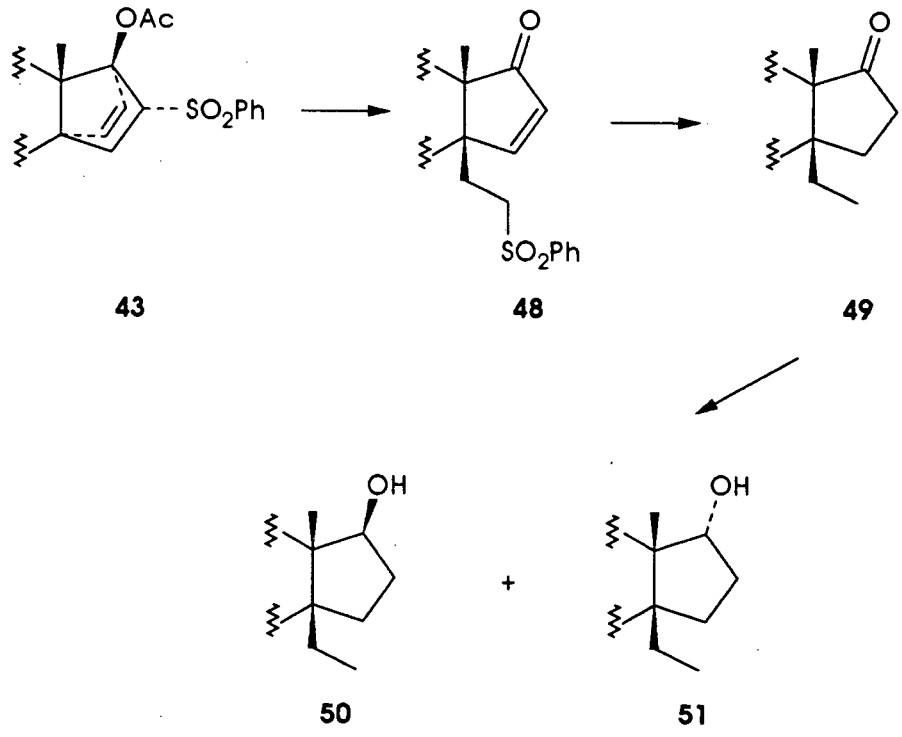


42 **43** (R = SO_2Ph) **44** (R = H) **45** **46**

31 **47**

Base treatment of the cycloadduct **43** resulted in retro-aldol cleavage of the β-bridge, to give the 14β-(2-phenylsulfonylethyl) Δ^{15}-17-ketone **48**, which was reduced to the 14β-ethyl 17-ketone **49**.[24] This compound was further elaborated into the 17α- and 17β-estradiol analogues **50** and **51**, which displayed moderate estrogenic activity (Scheme 1.9).

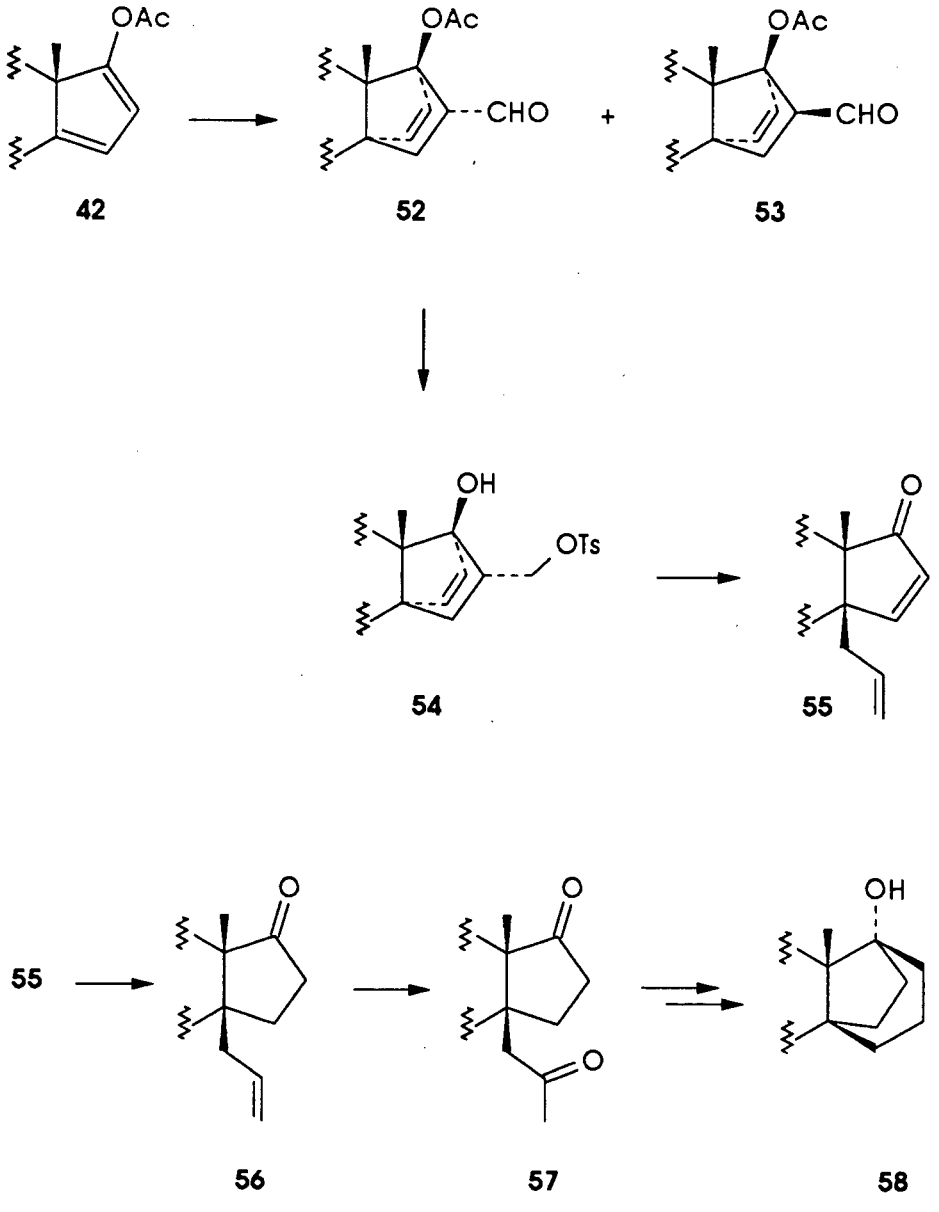
Scheme 1.9



43 **48** **49** **50** **51**

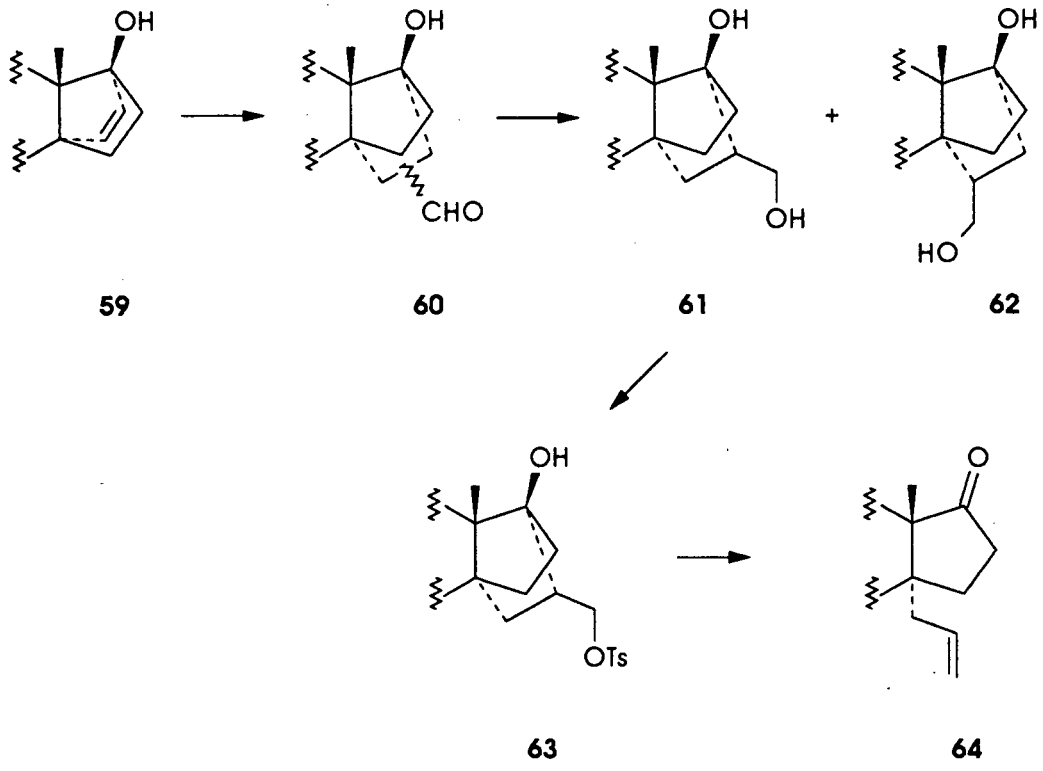
Cycloaddition of the dienyl acetate **42** with acrolein gave mainly the cycloadduct **52**,[25] accompanied by a very small amount of a minor isomer **53** in the ratio of 12:1. Reduction of the 16α-carbaldehyde group of **52**, followed by selective tosylation of the primary alcohol gave the hydroxy tosylate **54**. Base treatment of this compound effected cleavage of the β-bridge by a Wharton fragmentation to give the 14β-allyl Δ^{15}-17-ketone **55**, thereby establishing an efficient route for the introduction of a 14β-allyl group. Further elaboration of the 14β-allyl compound **55** included reduction of the Δ^{15}-bond, followed by Wacker oxidation to give the 14β-acetyl 17-ketone **57**. Aldol closure towards C(17), followed by deoxygenation and C(3)-deprotection gave the 14β,17β-propano analogue **58** of estradiol, which displayed diminished affinity for the estradiol receptor (Scheme 1.10).

Scheme 1.10



A route towards the introduction of a 14α-allyl group involved hydroformylation at the 14,17α-bridge of the cycloadduct **59**, to give a complex mixture of carbaldehydes **60**.[26] Treatment of the mixture with lithium aluminium hydride gave a separable mixture of 17^1- and 17^2-hydroxymethyl compounds **61** and **62**. Selective tosylation of **61** gave the hydroxy tosylate **63**, base-mediated Wharton fragmentation of which gave the 14α-allyl 17-ketone **57** (Scheme 1.11). However, this approach was abandoned in the light of the overall inefficiency.

Scheme 1.11



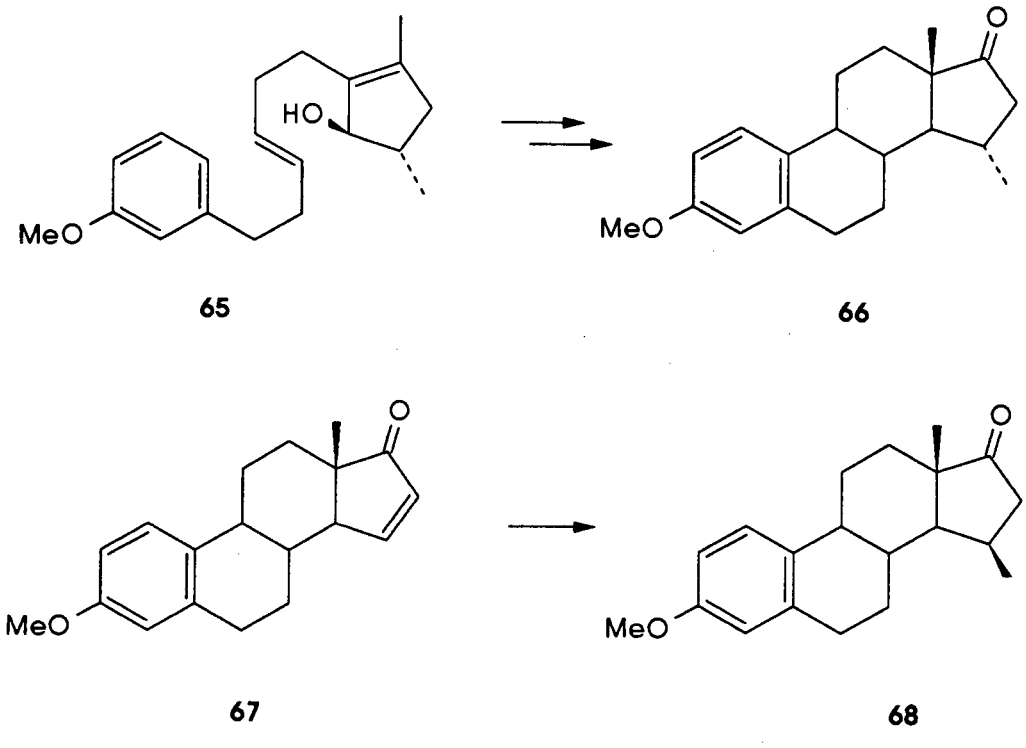
59 **60** **61** **62**

63 **64**

To summarise the foregoing overview, direct introduction of 14-alkyl groups by alkylation of 15-ketones gives mixtures of 14-alkyl products, depending on the substrate. Conjugate alkylation–fragmentation methods are particularly efficient towards the preparation of 14α-alkyl intermediates, but subsequent elaboration is impeded by diminished reactivity in that region. This methodology also readily gave access to functionalised 14β-alkyl intermediates. However, no efficient method exists for the stereocontrolled introduction of functionalised 14α-alkyl groups.

The stereospecific introduction of 15-alkyl and other functional groups has also received some attention in the literature. Groen and Zeelen[27] synthesised (*rac*)-3-methoxy-15α-estra-1,3,5(10)-trien-17β-ol **66** by biomimetic cyclisation of the polyene **65** (Scheme 1.12). This product was compared to the epimeric 15β-methyl 17-ketone **68** obtained from conjugate methylation[28] of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **67**, in order to establish the configuration at C(15).

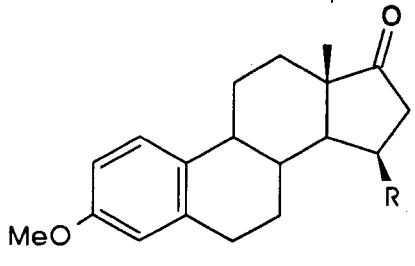
Scheme 1.12



65 **66**

67 **68**

Stereoselectivity during conjugate addition onto Δ^{15}-17-ketones has been widely documented. Reports in the early literature revealed that Michael addition of alkoxides,[29,30] sulfides[31] and cyanides[30] gave exclusively products of 15β-substitution **69**. The configurational assignments were supported by optical rotatory dispersion and ^{1}H NMR arguments.

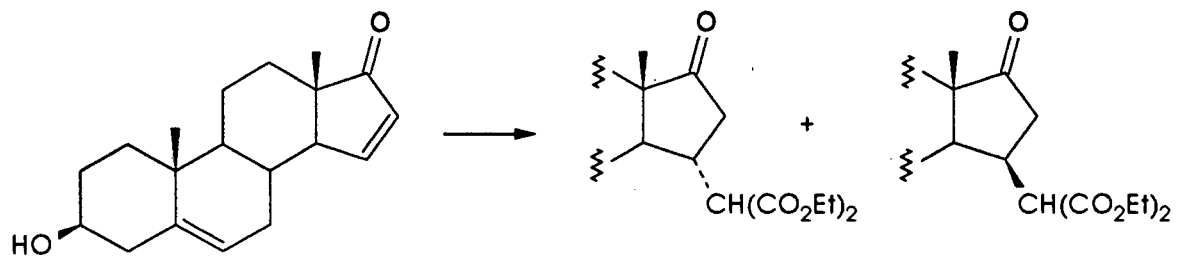


69 R = OBn, OMe, CN, $S(CH_2)_2CO_2Me$

However, in contrast to the above results, it was reported by Condom and co-workers[32] that Michael addition of diethyl malonate to the enone **70** gave exclusively 15α-carboxymethyl-3β-hydroxyandrost-5-en-17-one **71**. Subsequently, Miyake[33] reported that this conjugate addition reaction gave an equimolar mixture of 15α- and 15β-bis(ethoxycarbonyl)-methyl 17-ketones **71** and **72**. Loss of selectivity was explained in

terms of thermodynamic control. Rapid equilibration between the 15β-compound **72** and the starting material **70** led to the accumulation of the thermodynamically favoured 15α-epimer **71** (Scheme 1.13).

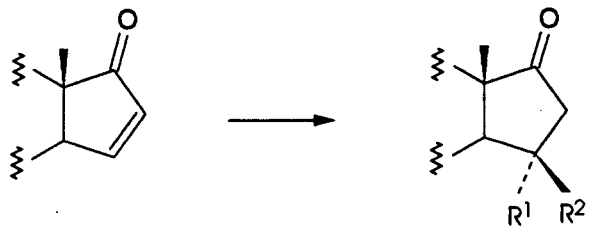
Scheme 1.13



70 **71** **72**

A further report on loss of stereoselectivity during conjugate alkylation was published by Labrie (Scheme 1.14).[34] In this instance, the copper(I)-catalysed addition of chain-extended Grignard reagents to the Δ^{15}-17-kerone **67** was reported to proceed mainly via a 15α-pathway. No interpretation of the observed stereoselectivity was given. Comparison of the chemical shift of the 13β-methyl groups was used as a basis for configurational assignments.

Scheme 1.14



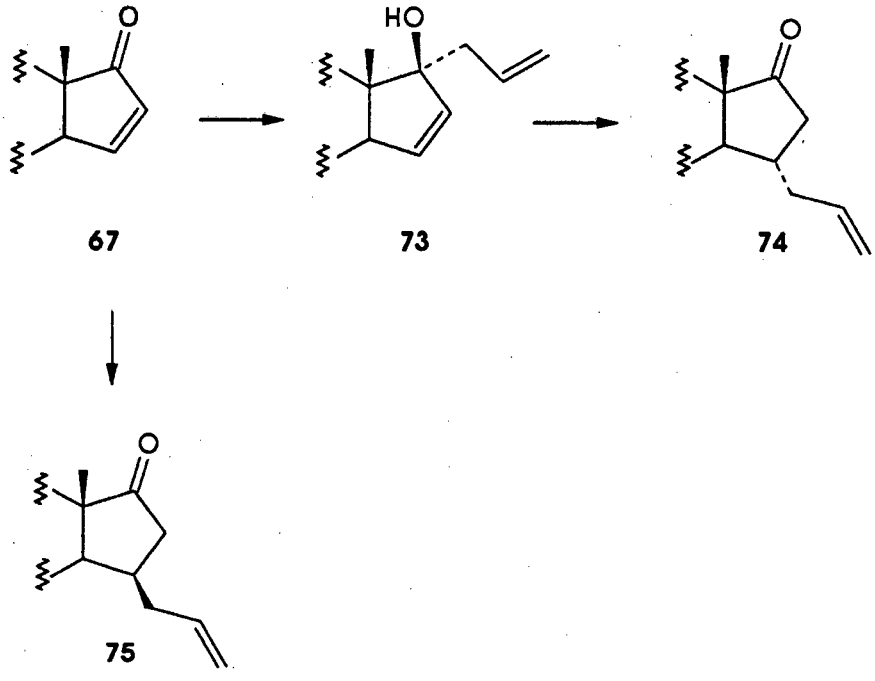
67

$R^1 = (CH_2)_nOTHP$; $R^2 = H$ (85%)
$R^1 = H$; $R^2 = (CH_2)_nOTHP$ (15%)
(n = 9 or 11)

This reported modest π-face differentiation encouraged Künzer[35] to further investigate stereochemical 15-alkylation (Scheme 1.15). In the first instance, the strong inclination of C/D ring trans-fused steroidal C(17) ketones to react with organometallic reagents at the α-face, i.e. anti to the angular 13β-methyl group, was exploited. Reaction of the Δ^{15}-17-ketone **67** with allylmagnesium chloride gave a single tertiary alcohol **73**. This

substrate contained all the required elements for an anion-accelerated oxy Cope rearrangement. Exposure of **73** to strongly basic conditions at 20 °C smoothly effected the desired suprafacial [3,3]-sigmatropic shift to give the 15α-allyl 17-ketone **74**. By contrast, when the enone **67** was treated with allylmagnesium bromide in the presence of copper(I) iodide and chlorotrimethylsilane, exclusively the 15β-allyl compound **75** was obtained. The assignment of stereochemistry at C(15) in compound **74** was verified by the coupling $J_{8\beta,15\beta}$ 10.8 Hz, which is indicative of an anti-periplanar arrangement of 14α- and 15β-H, thus an obligatory 15α-allyl group. For the epimer **75**, the configuration was assigned by exclusion.

Scheme 1.15



Chapter 2

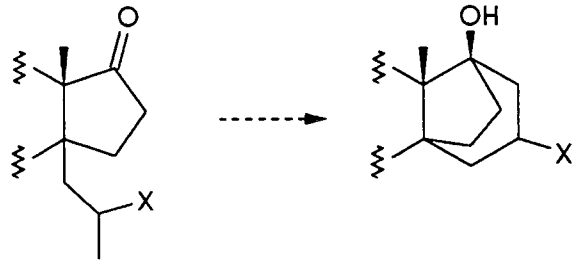
STEREODIRECTED APPROACHES TO THE SYNTHESIS OF 14-ALKYL 19-NORSTEROIDS

2.1 General Objectives

The introduction of alkyl groups onto C(14) of the steroid nucleus by 14-alkylation of 15-ketones, and by a cycloaddition – fragmentation approach has been discussed in the previous chapter. It was mentioned that the former route favoured products of 14β-alkylation, and further, that the scope was restricted by the need for subsequent functional group manipulation. On the other hand, the cycloaddition approach was particularly effective as a route to 14β-allyl compounds, as well as toward the introduction of a 14α-formyl group. The latter, however, was restricted in application for further elaboration.

The scope therefore exists for the stereocontrolled introduction of functionalised C(14)-alkyl groups by methods independent of the above routes. Access to these compounds was required as substrates for further intramolecular reaction, ultimately leading to ring D bridged hormone analogues, as illustrated in Scheme 2.1.

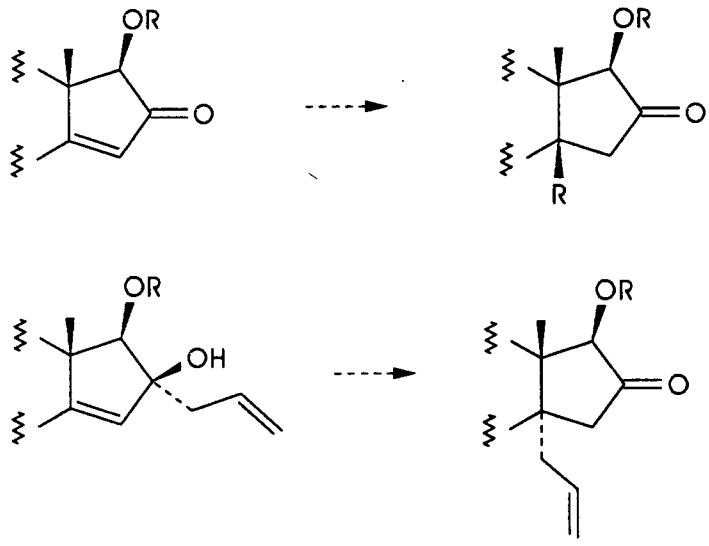
Scheme 2.1



Of particular interest was use of the Δ^{14}-16-functionality in achieving the desired alkylation (Scheme 2.2). Conjugate alkylation of a Δ^{14}-16-ketone conceptually is the most direct route. However, in the light of analogous transformations on analogously unsaturated hydrindane systems (see later), the expectation was products of 14β-alkylation.

Alternatively, the use of the C(16)-functionality to direct 14-alkylation by a sigmatropic process was considered. Stereocontrolled introduction of an allyl group at C(16) would give a Δ^{14}-16-allyl 16-alcohol, which contains a hydroxy dienyl system for an oxy-Cope rearrangement. For illustrative purposes, Scheme 2.2 indicates only the 16α-pathway.

Scheme 2.2



The initial aim of this investigation was therefore to prepare a suitable Δ^{14}-16-ketone as starting material. It seemed logical to leave the C(17) oxygen functionality in place, thereby eliminating the need for subsequent re-oxygenation to generate hormonal activity. Further, with suitable oxygen functionality in position at C(16), stereodirected alkylation at C(14) would give access to 14-alkyl estriol derivatives.

2.2 Synthesis of 16,17-Difunctionalised 3-Methoxyestra-1,3,5(10),14-tetraenes

In accordance with the requirements for the starting material for this investigation, a suitable intermediate was identified as 17β-*tert*-butyldimethylsilyloxy-3-methoxyestra-1,3,5(10),14-tetraen-16-one (Figure 2.3). A bulky silyl ether was used as protecting group for the C(17) hydroxyl group, in order to differentiate C(16) and C(17)-oxygen functionalities during the various interconversions.

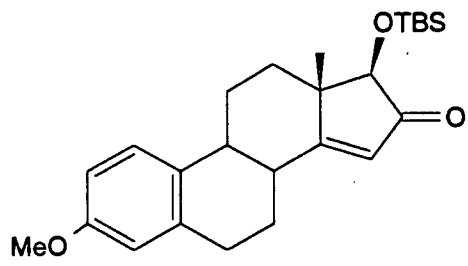
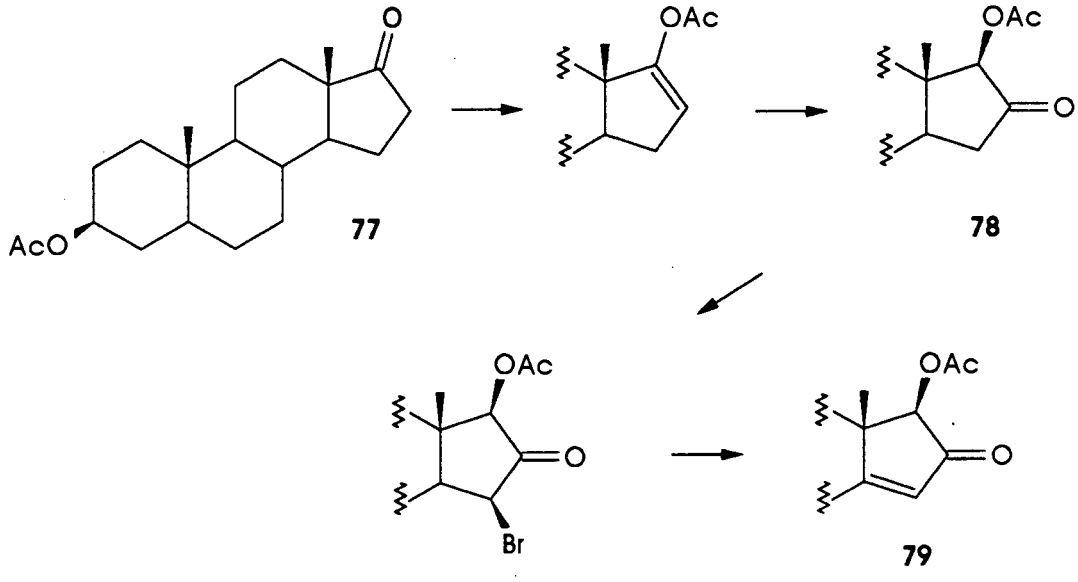


Figure 2.3: 17β-*tert*-butyldimethylsilyloxy Δ^{14}-16-ketone

In the early literature, a route to an androstane-based 17β-acetoxy Δ^{14}-16-ketone **79** has been published by McLean.[18] Enol acetylation – epoxidation of the ketone **77** gave the α,β-unsaturated ketone **79** (Scheme 2.4). The overall yield for this sequential transformation amounted to *ca* 30%.

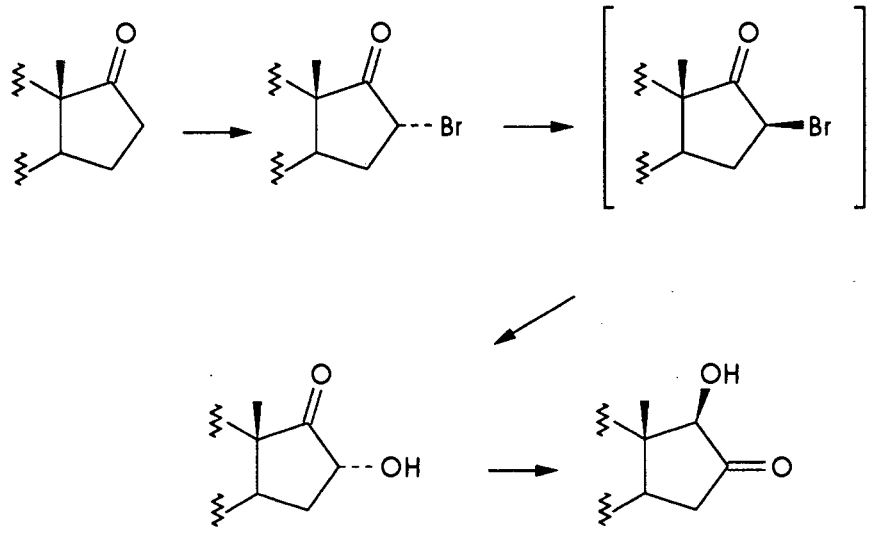
Scheme 2.4



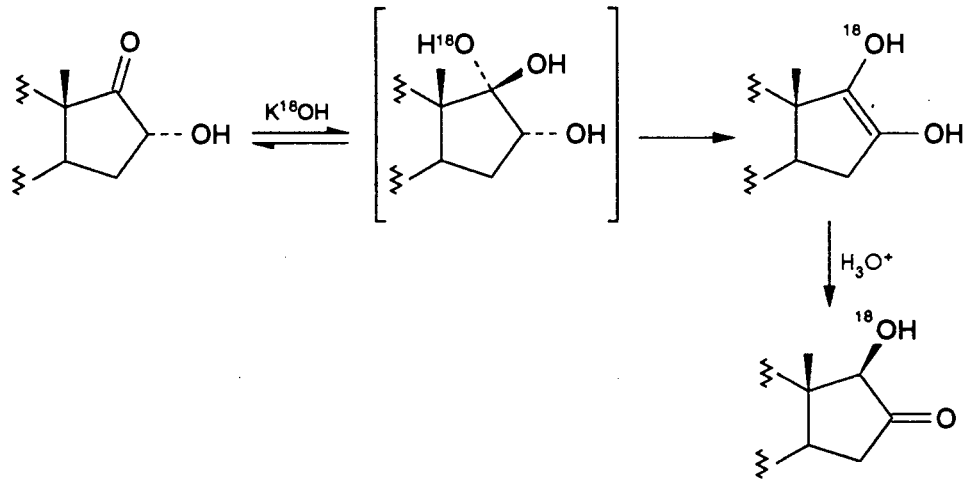
An alternative and more efficient process for the introduction of oxygen at C(16) onto a steroidal ring D was based on a bromination – hydrolysis pathway.[36] In the literature, this route was adopted as the method of choice for the stereospecific synthesis of 16α-hydroxy 17-oxo steroids.[36,37] Subsequent treatment with aqueous base resulted in equilibration to the thermodynamically preferred 17β-hydroxy 16-ketones (Scheme 2.5). It was pointed out[38] that this S_N2-displacment of bromide was preceded by inversion of the 16α-bromide into the 16-epimer. Hydrolysis of a 16α-bromo 17-ketone gives a 16α-hydroxy compound, i.e. an overall retention of C(16)-configuration.

Some controversy exists regarding the exact nature of this α-hydroxy ketone rearrangement. An initial concept based on simple enolisation – protonation[36] was discarded on the basis of mass-spectroscopic analysis of ^{18}O-labelled substrates.[38] From the latter investigation, a pathway involving hydration – dehydration (Scheme 2.6) was postulated on the grounds of the semi-quantitative incorporation of the labelled oxygen at C(17).

Scheme 2.5



Scheme 2.6

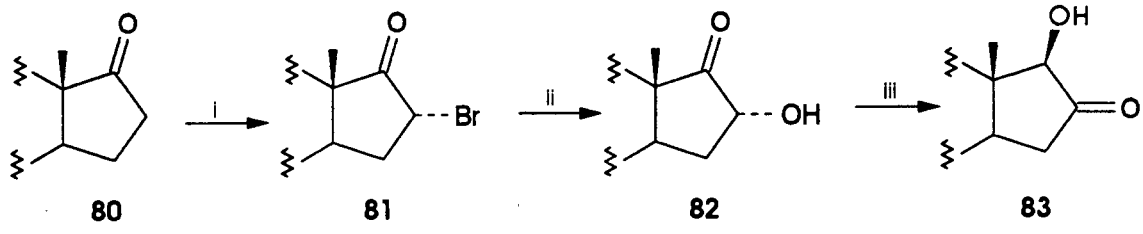


However, this mechanism was challanged by Gros,[37] who followed the reaction progress by ^{13}C NMR spectroscopy and failed to obtain convincing evidence for the intermediacy of any triol or enediolate species. No alternative proposal was made.

For the present purpose, bromination of estrone 3-methyl ether **80** with copper(II) bromide in refluxing methanol gave the 16α-bromo 17-ketone **81**[36] (Scheme 2.7), alkaline hydrolysis of which yielded 16α-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one **82**.[39] Equilibration of the 16α-hydroxy 17-ketone **82** in the presence of aqueous sodium hydroxide gave 17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-16-one **83**.[36] The intermediates

81–83 showed exact correspondence in analytical data to those published.[36,39] Based on estrone 3-methyl ether **80**, the overall conversion into the 17β-hydroxy 16-ketone **83** was 77%. This efficiency is clearly superior to, for example, the epoxidation route used by McLean.[18]

Scheme 2.7



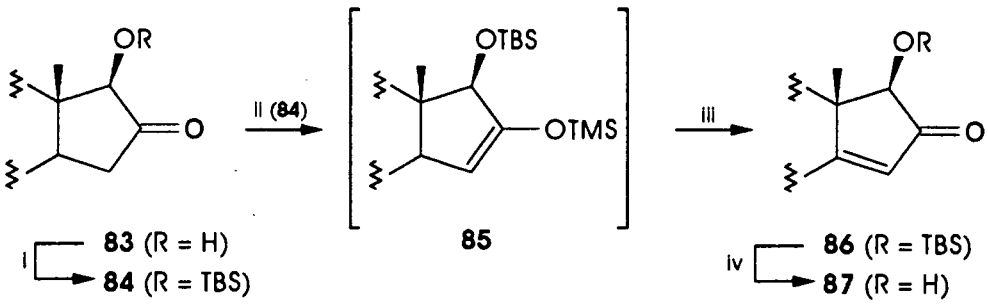
i, $CuBr_2$, MeOH-C_6H_6; ii, aq KOH, DMF; iii, aq NaOH, MeOH-C_6H_6

Protection of the 17β-hydroxy group of **83** was carried out with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF,[40] to give the 17β-TBS ether **84** (Scheme 2.8). In the mass spectrum of **84**, a base peak at M^+ - 57 was observed, which corresponded to loss of the *tert*-butyl group. This is a common feature of the mass spectra of *tert*-butyldimethylsilyloxy alcohols.[41,42] Therefore in this work, molecular ions of all TBS-ethers are reported as observed, i.e. M^+ - 57.

With the 17-protected 16-ketone **84** in hand, the Δ^{14}-unsaturation was readily introduced through dehydrosilylation[43] of the trimethylsilyl enol ether **85** with palladium acetate in refluxing acetonitrile (Scheme 2.8). The yield for this two step conversion was 81%, which is clearly superior over the bromination – elimination route described by McLean.[18] From spectroscopic data, the presence of the Δ^{14}-16-ketone in **86** was verified. An infrared spectrum showed a conjugated carbonyl stretching frequency at ν_{max} 1709 cm^{-1}, whereas the vinylic 15-H resonated at δ 5.84 (s) in the ^1H NMR spectrum.

To gain access also to the parent 17β-alcohol, the TBS-ether **86** was converted into 3-methoxy-17β-hydroxyestra-1,3,5(10),14-tetraen-16-one **87** by reacting with tetrabutylammonium fluoride in tetrahydrofuran.[40] Loss of the silyl group in **86** was confirmed by the microanalytical data, as well as by a molecular ion *m/z* 298. In the ^1H NMR spectrum, the 17β-hydroxy proton was observed as an D_2O-exchangable signal at δ 2.86.

Scheme 2.8



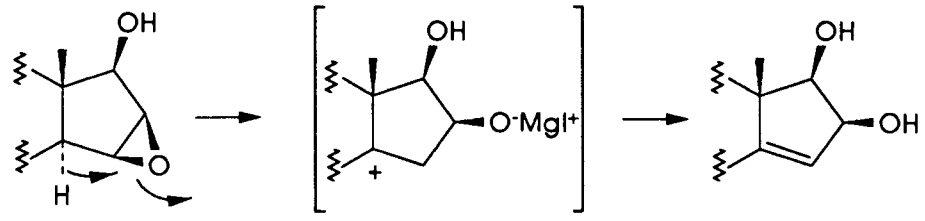
I, TBSCl, ImH, DMF; II, LDA-TMSCl, -78 °C
III, $Pd(OAc)_2$, MeCN, Δ; IV, Bu_4NF, THF

The overall yield for the conversion of estrone 3-methyl ether **80** into the 17β-silyloxy Δ^{14}-16-ketone **86** was *ca* 73%. This procedure was amenable to large-scale preparation, since all the intermediate products were formed in good yield and chromatographic purification was only required after the final step.

To gain access to the related Δ^{14}-16-alcohols, the 16-oxo group of the enone **86** was reduced with a series of hydrides. These allylic alcohols were required for correlation purposes with products of 1,2-alkylation of the enone **86** (see later).

Both 16-epimers of the estrone derived Δ^{14}-16,17β-diols have been described in the literature. It was reported[44] that treatment of the 15β,16β-epoxy 17β-alcohol **88** with methylmagnesium iodide gave 3-methoxyestra-1,3,5(10),14-tetraen-16β,17β-diol **90** in 55% yield. This reaction is probably a result of the Lewis-acidic Grignard reagent. Thus, a 1,2-hydride shift gave a tertiary carbocation intermediate **89**, collapse of which gave the allylic alcohol **90** (Scheme 2.9).

Scheme 2.9

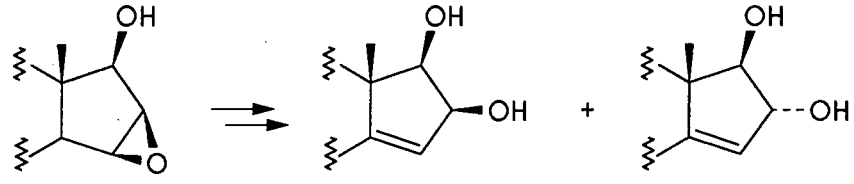


88 89 90

It was further reported[45] that treatment of the epoxy alcohol **88** with acetic anhydride followed by hydrolysis of the products gave the Δ^{15}-16β,17β-diol **90** (17%), as well as a hitherto unknown allylic alcohol, namely 3-methoxyestra-1,3,5(10),14-tetraen-16α,17β-diol

91 (30%) (Scheme 2.10). The diols **90** and **91** were differentiated by the lower OH-stretching frequency for the *syn*-diol, as caused by hydrogen bonding. Further structural evidence was offered by ^1H chemical shift arguments. Oxygen functionality in the 16β-orientation exerted a greater deshielding effect on the 13β-methyl group than for the epimeric 16α-compound, thereby providing a basis for relating spectral infromation to the C(16)-configuration.

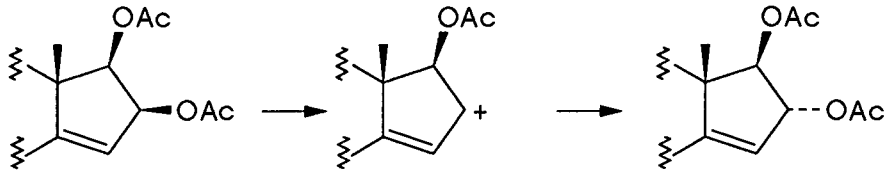
Scheme 2.10



88 **90** **91**

A simple mechanism for the epimerisation was offered, which invoked the intermediacy of an allylic carbocation (Scheme 2.11). The exact requirements, as well as the generality for this inversion remained ambiguous from the article.[45]

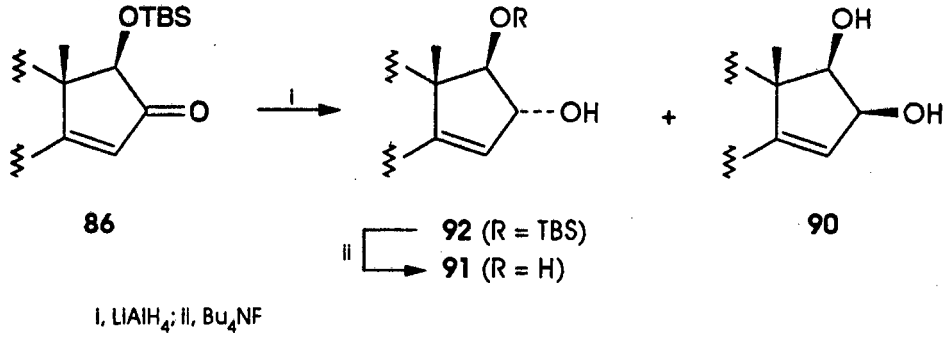
Scheme 2.11



In the present study, 1,2-reduction of the Δ^{14}-16-ketone **86** was carried out with lithium aluminium hydride (LAH) in tetrahydrofuran at 0 °C for 1 h (Scheme 2.12). A readily separable 2:1 mixture of allylic alcohols was obtained, comprising 17β-*tert*-butyldimethylsilyloxy-3-methoxyestra-1,3,5(10),14-tetraen-16α-ol **92** (61%) and the known 16β,17β-diol[44] **90** (30%). Spectroscopic characteristics supported the assignments (see later). In order to convert the 16α-alcohol **92** into the known parent diol[45] for comparison, the silyl ether of **92** was cleaved with tetrabutylammonium fluoride in tetrahydrofuran to give the highly insoluble 3-methoxyestra-1,3,5(10),14-tetraene-16α,17β-diol **91**.[45] Desilylation of the 17β-silyloxy 16β-alcohol occurred during the reaction course. It is reasonable to assume that this side reaction is effected by intramolecular hydrogen delivery, facilitated by close proximity of the $-[OAlH_3]^-$ group in the intermediate. Hydrolysis of

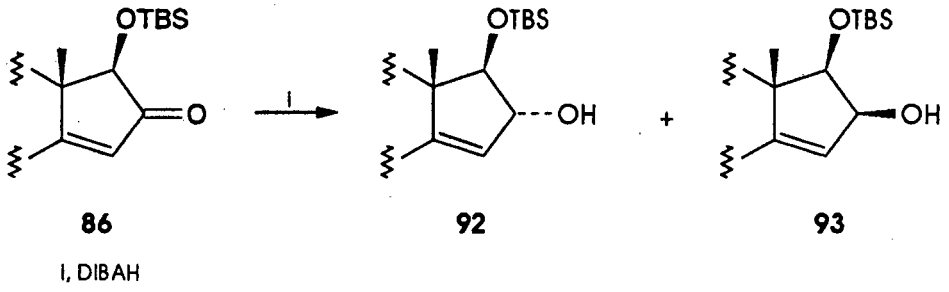
exclusively the *syn* diol served as additional configurational evidence, as a *trans*-disposed 16α-alkoxide would not be able to exert an analogous intramolecular bond-weakening influence on the 17β-O–Si bond.

Scheme 2.12



Reduction of the 16-oxo functionality of the enone **86** with a sterically more demanding hydride than LAH gave practically no change in the distribution of 16-epimers. Treatment of **86** with diisobutylaluminium hydride (DIBAH) in tetrahydrofuran gave allylic alcohols **92** and **93** (Scheme 2.13). Careful chromatography revealed a *ca* 2:1 preference in favour of the 16α-alcohol **92**.

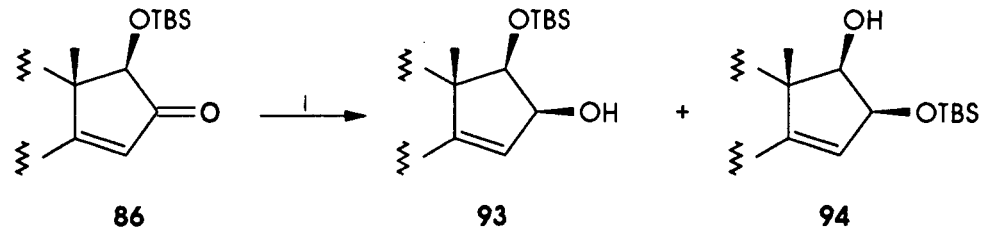
Scheme 2.13



In this instance, no desilylation of the 17β-silyloxy 16β-alcohol **93** occurred. As opposed to LAH, the reduced basicity of DIBAH was insufficient to assist the 16β-alkoxide in intramolecular O–Si bond cleavage.

A complete reversal in selectivity of 16-oxo reduction was achieved with a highly hindered hydride. Thus, treating the enone **86** with lithium tri-*sec*-butylborohydride (L-Selectride®) resulted in exclusive reagent entry from the α-side, giving the 17β-silyloxy Δ^{14}-16β-alcohol **93** (90%). As a by-product, 16β-*tert*-butyldimethylsilyloxy-3-methoxyestra-1,3,5(10),14-tetraen-17β-ol **94** was isolated in 5% yield (Scheme 2.14).

Scheme 2.14

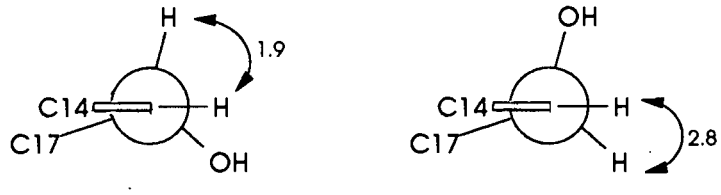


86 **93** **94**

I, L-Selectride

Allylic alcohols **92** and **93** were confidently assigned by comparison of analytical data to those published.[44,45] The influence of a 16-hydroxyl group *syn* or *anti* to the 13β-methyl group was reflected by the relative chemical shift of the latter, as remarked on by Ponsold.[45] For the Δ^{14}-16β-alcohol **93**, the 13β-Me resonance appeared at δ 1.09, which is at a lower field relative to that of the 16-epimer **92** (δ 1.02). Similarly, in the ^{13}C NMR spectrum, the C(18) resonance of the 16β-alcohol **93** (δ_C 20.3) was deshielded by the *syn* 16β-OH in comparison to the analogous signal for the 16α-epimer (δ_C 18.7).

An additional pointer to the C(16)-configurations of the 16-alcohols **92** and **93** is the magnitude of the coupling $J_{15,16}$. For the 16α-alcohol **92**, near orthogonality between the pseudo-axial 16β-H and the 15-proton causes a diminished coupling of J 1.9 Hz. However, the 16-epimer **93** has the 16α-proton in a pseudo-equatorial orientation, and hence a larger coupling of $J_{15,16\alpha}$ 2.8 Hz. These couplings are illustrated in Figure 2.15 on a Newman projection along the C(15)–C(16) bond.



92 **93**

Figure 2.15: $J_{15,16}$ coupling for the Δ^{14}-16-alcohols **92** and **93**

A remarkable feature of the ^1H NMR spectrum of the Δ^{14}-16α-alcohol **92** is the presence of a five-bond or 'homo-allylic' coupling $J_{8\beta,16\beta}$ 3.2 Hz. Although rare, this type of coupling is known to occur between protons separated by an olefinic bond flanked on either side by two single bonds, i.e. for the system *H*-C-C=C-C-*H*.[46] It is closely related to the

more common four-bond allylic coupling, in that similar geometric prerequisites dictate the appearance. Orthogonality of both coupling partners to the olefinic plane maximises the coupling magnitude, which typically ranges J 1.9–3.5 Hz for cyclic systems.[46] From a molecular model, this orientation is uniquely compatable with the 16α-alcohol **92**. A Newman projection of the latter along the C(15)–C(14) bond is illustrated in Figure 2.16.

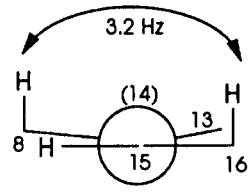


Figure 2.16: Homo-allylic coupling in Δ^{14}-16α-alcohol **92**, projected along C(14)–C(15)

The coupling connectivites for the Δ^{14}-16-alcohols **92** and **93** are illustrated in Figure 2.17. Orthogonality between 8β- and 15-H causes an allylic coupling of *ca J* 1.9 Hz. Owing to the synclinal arrangement between the 17α- and 16-protons, the couplings $J_{16\alpha,17\alpha}$ and $J_{16\beta,17\alpha}$ were virtually equal, thereby precluding the extraction of any configurational information.

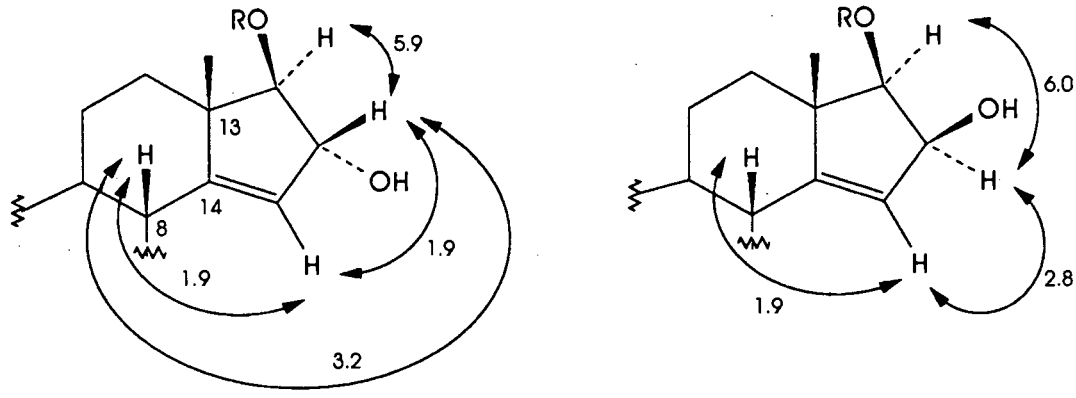
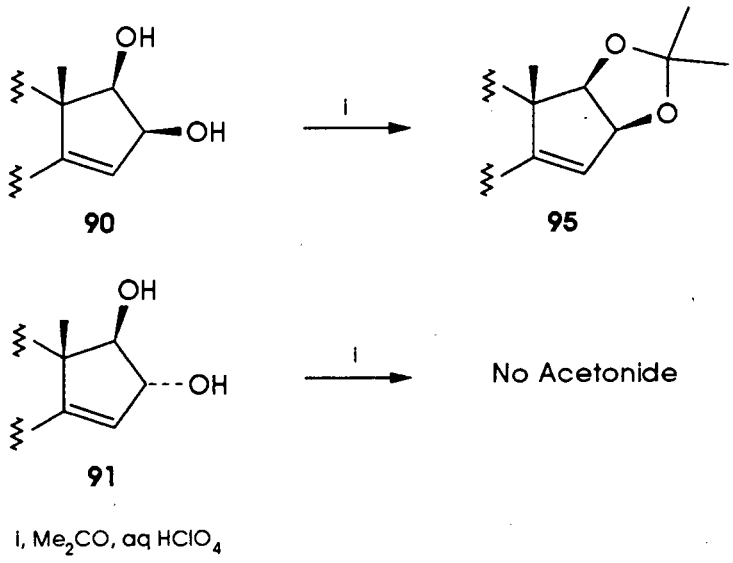


Figure 2.17: Coupling connectivities in the Δ^{14}-16-alcohols **92** and **93**

Chemical support in favour of the assigned structures was obtained from the parent diols **90** and **91**, by exposing each to the conditions of acetonide formation (Scheme 2.18). Thus, the 16β,17β-diol **90** was readily converted into the derived acetonide **95** in the presence of acetone – perchloric acid. A molecular ion *m/z* 340, as well as the presence of two additonal methyl resonances (δ 1.37 and 1.46) in the ^{1}H NMR spectrum confirmed the

assignment. By contrast, the 16α,17β-diol **91** failed to react after an extended period of 3 days. This combination of chemical and spectroscopic evidence firmly corroborate the structures assigned to the allylic alcohols **92** and **93**.

Scheme 2.18

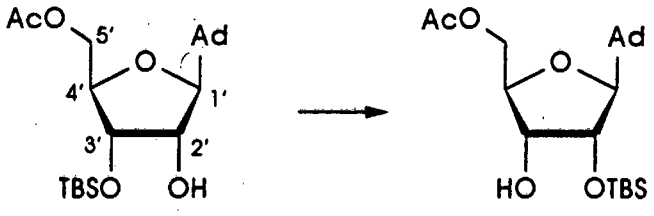


The outcome of selectivities of hydride reductions of the enone **86** was rationalised by considering reagent – substrate steric interactions. The approach of sterically demanding L-Selectride *syn* to the 13β-methyl group was precluded by a 1,3-diaxial interaction. This type of steric interaction did, however, not impede β-face approach by the smaller hydrides, i.e. LAH and even DIBAH. A mixture of 16β-alcohols resulted.

During the reduction of the enone **86** with L-Selectride, formation of a by-product **94** in which the silyl group migrated onto the 16β-alkoxide diminished the effective yield of **93** (Scheme 2.14). However, by performing the reaction at -40 °C and by using a method of low temperature reverse quench, loss of material by this route was limited to *ca* 5%.

This type of anion-assisted 1,4-silyl group migration has been established in the literature. The intramolecular transfer of a silyl group from oxygen and nitrogen atoms onto nucleophilic carbons[47] and oxygen[48] centres are documented.[49] Isomeric 2′- and 3′-*O*-TBS ribonucleosides **96** and **97** (Scheme 2.19) were also reported to undergo interconversion during attempted selective *O*-silylation.[50] From a kinetic study, it was established that this process is base-catalysed, whereas even trace amounts of acid severely inhibited the rate.[50] From this finding, it is clear that an alkoxy species is involved in the silyl transfer.

Scheme 2.19

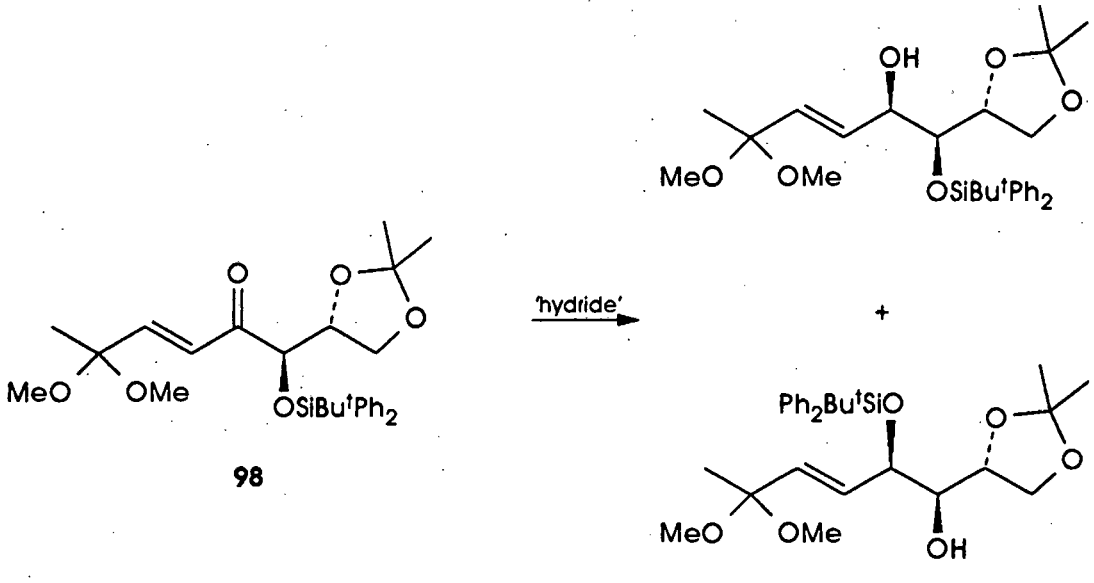


96 **97**

Ad = adenin-9-yl

Only a single report of silyl group transfer during the carbonyl group reduction in an α-silyloxy enone system was found. It has been reported by Jurczak and co-workers[51] that the *tert*-butyldiphenylsilyl group (TBDPS) migrated during hydride reduction of the α,β-unsaturated ketone **98** (Scheme 2.20). Their finding was that reactions carried out with lithium aluminium hydride and sodium borohydride gave mixtures of monosilylated diols. DIBAH on the other hand, gave virtually none of the silicon-migrated compound.

Scheme 2.20



98

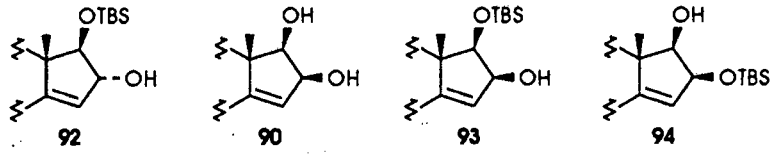
Based on these reports, the silyl transfer observed during the reduction of the 17β-silyloxy Δ^{14}-16-ketone **86** was rationalised. With lithium aluminium hydride as reducing agent, hydrogenolysis of the 17β-OTBS ether prevented silyl migration. Similar to the report by Jurczak,[51] no silyl transfer was noted in the reduction with DIBAH. This was probably due to a bonding interaction between the hydride-based aluminium and the newly formed

16β-alkoxide, which reduced the nucleophilicity of the latter. By contrast, when L-Selectride was used as reducing agent, the 16β-oxy-anion was unhindered in initiating the silyl transfer.

In summary, the observed product distributions for hydride reduction of the Δ^{14}-16-ketone **86** are shown in Table 2.1.

Table 2.1: Selectivities in hydride reduction of the Δ^{14}-16-ketone **86**

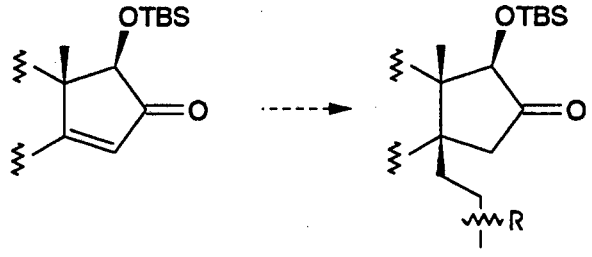
	Product Distribution	
Hydride	16α-OH	16β-OH
$LiAlH_4$	**92** (61%)	**90** (30%)
DIBAH	**92** (60%)	**93** (28%)
L-Selectride	-	**93** (90%) + **94** (5%)



2.3 Conjugate and Sigmatropic reactivity of the Δ^{14}-Intermediates

The principles governing conjugate alkylation of α,β-unsaturated carbonyl compounds with organocuprates[52] and organosilanes[53] are well known. For the purpose of this study, it was of particular interest to investigate the scope for regio and stereodirected introduction of a functionalised three-carbon chain at C(14) by this approach. For illustrative purposes, only the 14β-isomer is indicated in Scheme 2.21.

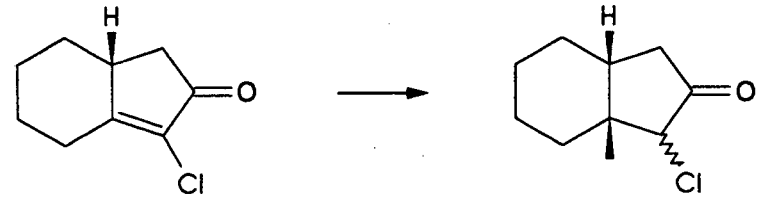
Scheme 2.21



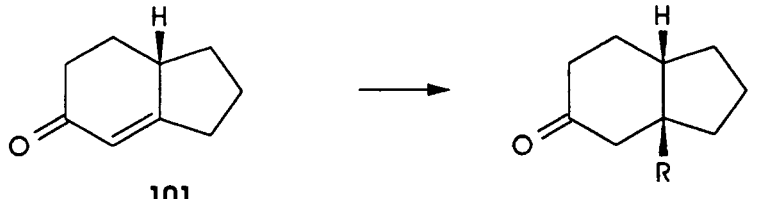
Conjugate alkylations to the ring-junction position of hydrindenone systems by organocuprates have been reported to give mainly products with a *cis*-fused ring system. The enone **99** reacted with an excess amount of lithium dimethylcuprate to give the methyl ketone **100** in a 60% yield.[54] The stereochemistry of the chloro group was not given. Similarly, as indicated in Scheme 2.22, conjugate addition of a methyl group or functionalised alkyl chains to the enone **101** proceeded successfully.[55]

In recent years, allylsilanes in combination with Lewis acid catalysis became an attractive reagent to perform conjugate allylation reactions. It was shown that this methodology may be used for the stereoselective introduction of an allyl group at the ring junction of $\Delta^{1(9)}$-2-octalone **102** (Scheme 2.23).[56] This method proved superior to the equivalent transformation involving organocuprate chemistry; both in terms of the absence of an elaborate reagent generation protocol, as well as the improved general reactivity of the reagent.

Scheme 2.22



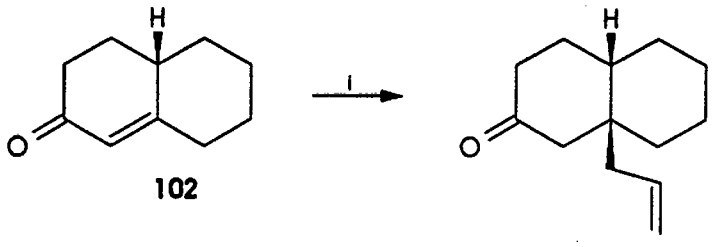
99 **100**



101

R = Me, $[Me_3SiC(=CH_2)]_2CuLi$, or
(*E*)-$(Me_3SiCH=CH)_2CuLi$

Scheme 2.23



102

I, CH_2=$CHCH_2SiMe_3$, Bu_4NF, DMF

Optimisation of the conditions for conjugate addition of allyltrimethylsilane was found in the work by Majetich.[57] It was reported that fluoride ion, as obtained from anhydrous tetrabutylammonium fluoride (TBAF), provided a superior catalyst in generating the allyl anion. These conditions were adopted for the present study. Thus, a solution of the Δ^{14}-16-ketone **86** in dry DMF and freshly distilled allyltrimethylsilane were added to an anhydrous solution of TBAF in tetrahydrofuran. However, after 2 h using temperatures of up to 80 °C, no reaction, apart from partial 17-deprotection was noted.

Several repititions of this reaction with rirgorous care to exclude adventitious moisture failed to achieve the desired result. In the light of this apparent lack of reactivity of the enone **86**, it seemed necessary to explore the general conjugate reactivity of the Δ^{14}-16-ketone toward carbon nucleophiles. As an initial experiment, a conjugate addition reaction with lithium dimethylcuprate was carried out. It was decided to follow the method described by Alexakis,[58] where the addition of chlorotrimethylsilane was shown to significantly accelerate the rate of reaction.*

Thus, the enone **86** was treated with lithium dimethylcuprate – chlorotrimethylsilane.[58] After 50 min over the temperature range -78 to 0 °C, the reaction was complete by TLC monitoring. A single product was isolated, but the spectroscopic properties were incompatible with the expected product of conjugate methylation. The infrared spectrum indicated the absence of a carbonyl stretching frequency. The ^{1}H NMR spectrum indicated a signal for the vinylic 15-proton, thus non-reaction of the Δ^{14}-bond. As a result, the product was formulated as a compound of 1,2-methylation, i.e. 17β-*tert*-butyldimethylsilyloxy-3-methoxy-16α-methylestra-1,3,5(10),14-tetraen-16β-ol **103** (81%) (Scheme 2.24). The C(16) configuration was assigned by ^{1}H and ^{13}C chemical shifts of the 13β-methyl group (δ_H 1.10 and δ_C 18.4), which were very similar to that of the Δ^{14}-16β-alcohol **93** (see Tables 2.2 and 2.3).

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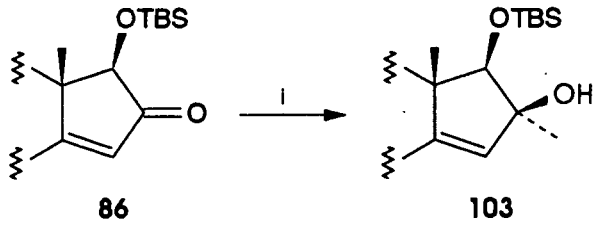
* Conjugate alkylation by the reagent combination organocuprate – chlorotrimethylsilane was originally described by A. Alexakis, G. Cahiez and J.F. Normant, *Tetrahedron Lett.*, 1980, **36**, 2305.

Scheme 2.24

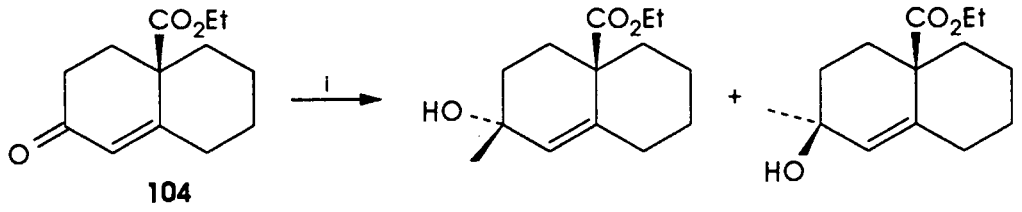


86 **103**

i, Me_2CuLi-TMSCl

Organocuprate 1,2 alkylation is not unknown and often occurs during attempted conjugate alkylation at a ring-junction position.[59] An example of such a reaction on a substituted octalone system **104** is indicated in Scheme 2.25.[60] In this instance, deactivation of the olefinic bond by the ring junction ester group is probably the cause of the lack of conjugate reactivity.

Scheme 2.25



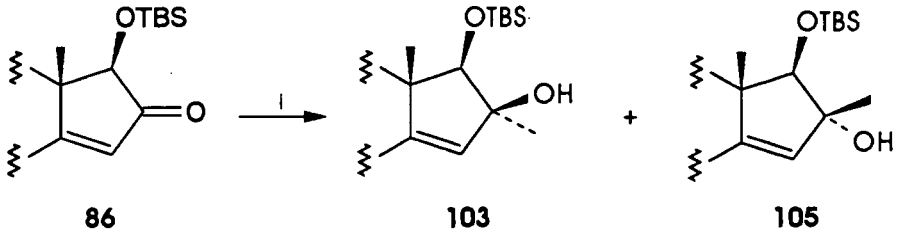
104

i, Me_2CuLi

In a further conjugate alkylation experiment, the enone **86** was reacted with methylmagnesium iodide in the presence of copper(I) iodide (Scheme 2.26). As for the analogous organocuprate reaction, only 1,2-alkylation took place. Further, an epimeric mixture of 16-alcohols, with a 2:1 preference of the 16α-methyl compound **103** was obtained. Deliberate 1,2-alkylation of the enone **86** with methylmagnesium iodide, i.e. in the absence of copper(I)-catalysis, produced an identical result (Scheme 2.26).

A comparison of the ^1H and ^{13}C data of the 16-methyl epimers **103** and **105** (see Tables 2.2 and 2.3) to those of the Δ^{14}-16-alcohols **92** and **93** revealed analogous trends as a basis for configurational assignments.

Scheme 2.26

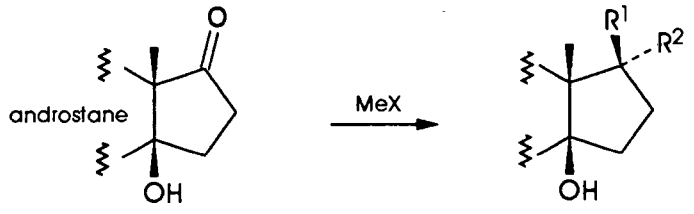


86 **103** **105**

i, MeMgI-CuI or MeMgI

The observed selectivities in 1,2-alkylations of **86** were rationalised by considering reagent–substrate interactions. Various models have been developed to predict the outcome of 1,n-asymmetric inductions.[61-63] In cyclic carbonyl compounds, conformational transition states are clearly limited by the rigidity of the system. The possibility of reagent chelation to the carbonyl function and a neighbouring α- or β-removed group becomes the predominant factor in stereoselective nucleophilic addition.[64] Reagent 'chelatability' is often exploited, as exemplified in the work of Fetizon and co-workers (Scheme 2.27).[65] In their work, 14β-hydroxy androstanes underwent stereoselective C(17) functionalisation, depending on the choice of organolithium or Grignard reagents.[65]

Scheme 2.27



X = Li : R^1 = OH, R^2 = Me
X = MgBr : R^1 = Me, R^2 = OH

Considering the present case, when the enone **86** was treated with lithium dimethylcuprate, chelation of the reagent to the 16- and 17β-oxygen functions rendered the β-face sterically inaccessible to further reagent approach. Exclusively the α-face was subjected to nucleophilic attack, thus reinforcing the Cram selectivity to give the 16α-methyl 16β-alcohol **103** (Figure 2.28). This argument was supported by an alkylation experiment carried out with methyllithium, which also gave exclusively the 16α-methyl alcohol **103**. In the case of Grignard addition, the magnesium was incapable of coordinating to the 17β-silyloxy group. The weaker chelation abilities of both the reagent-based

magnesium,[66] as well as the non-chelating 17β-silyloxy group[67] prevented this type of association. Selectivity in this case was based on the non-chelated Cram model, leading to a 2:1 preference of α-approach to give **103** and **105**.

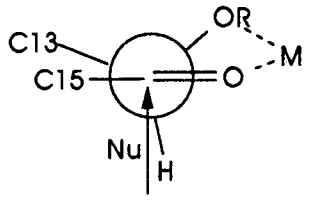
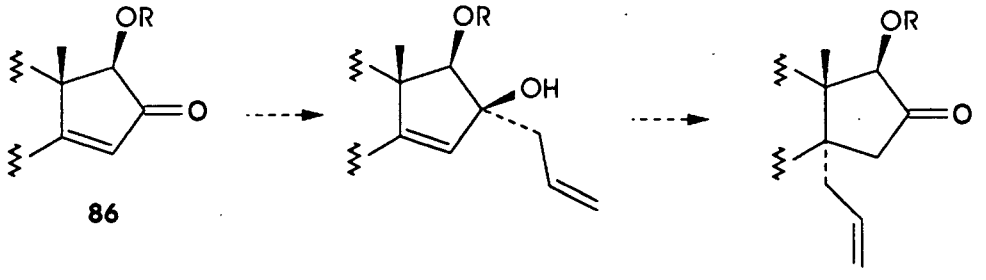


Figure 2.28: Reagent chelation onto the Δ^{14}-16-ketone

The apparent lack of conjugate reactivity of the enone **86**, as opposed to the ease of undergoing 1,2-alkylation led to exploring the scope for achieving the desired stereoselective C(14) alkylation by means of a sigmatropic [3,3] rearrangement. Conversion of **86** into the derived 16-allyl alcohols would give the corresponding 1,5-dienes as intermediates for oxy-Cope transformations. For illustrative purposes, only the route by 16α-alkylation is shown in Scheme 2.29.

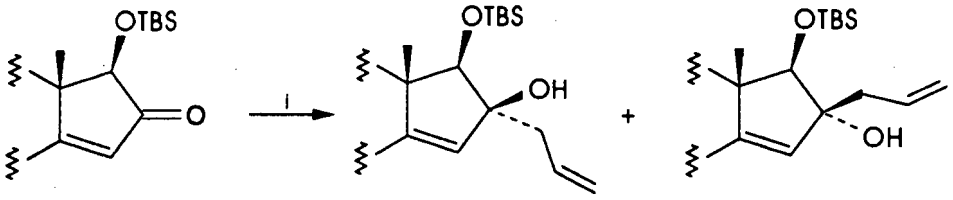
Scheme 2.29



86

Treating the enone **86** with allylmagnesium chloride gave a separable mixture of allyl alcohols **106** (54%) and **107** (36%) (Scheme 2.30). Spectroscopic data of the compounds were compatible to products of 1,2-allylation. The infrared spectra indicated the absence of a carbonyl group, whereas a ^{1}H NMR spectrum showed a resonance for the vinylic 15-proton (δ *ca* 5.2). The C(16)-configurations were assigned from NMR data by analogy to the Δ^{14}-16-alcohols **92** and **93** (see Tables 2.2 and 2.3).

Scheme 2.30



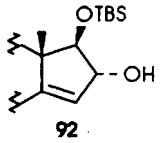
86 **106** **107**

I, CH_2=$CHCH_2MgCl$

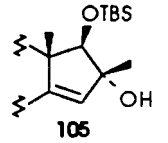
Proton NMR data for ring D signals of the series of Δ^{14}-16-alcohols are listed in Table 2.2 and clearly reveals the deshielding effect of a *syn* 16β-OH group on the chemical shift position of the 13β-Me resonance. The splitting in the 15-H resonances reflects the allylic coupling $J_{8\beta,15}$ 1.4 and 1.9 Hz. The vicinal couplings $J_{15,16}$, as well as the coupling characteristics of the 16-protons for the Δ^{14}-16α-alcohol **92** and its 16-epimer **93** were discussed previously, and it was shown that these couplings were indicative of the C(16)-configurations.

Table 2.2: Key ^{1}H NMR data for Δ^{14}-16-alcohols

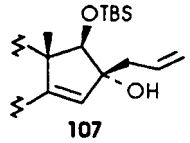
	Signal			
Compound	13β-Me	15-H	16-H	17α-H
92	1.02 (s)	2.49 (t, 1.9)	4.59 (ddd, 5.9, 3.2 and 1.9)	3.71 (d, 5.9)
105	0.91 (s)	5.15 (d, 1.9)	-	3.74 (s)
107	1.03 (s)	5.17 (obsc.)	-	3.93 (s)
93	1.09 (s)	5.59 (dd, 2.8 and 1.9)	4.29 (dd, 6.0 and 2.8)	3.38 (d, 6.0)
103	1.10 (s)	5.40 (d, 1.4)	-	3.57 (s)
106	1.09 (s)	5.43 (d, 1.4)	-	3.63 (s)



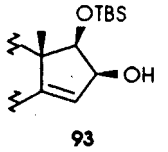
92



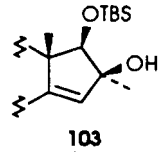
105



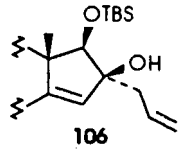
107



93



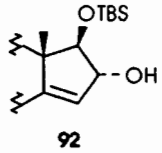
103



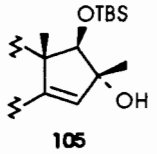
106

Table 2.3: ^{13}C NMR data for Δ^{14}-16-alcohols

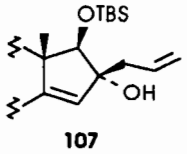
	Compound					
	16α-OH			16β-OH		
Signal	**92**	**105**	**107**	**93**	**103**	**106**
C-1	126.7	126.1	126.7	126.8	126.1	126.8
C-2	111.8	111.8	111.8	111.9	111.8	111.9
C-3	157.6	157.6	157.6	157.7	157.6	157.9
C-4	113.8	113.8	113.8	113.8	113.7	113.9
C-5	137.9	137.8	137.8	137.9	137.9	137.7
C-6	29.8	29.8	29.8	29.9	29.8	29.8
C-7	25.0	25.2	27.2	25.2	25.1	27.9
C-8	38.8	38.6	38.7	39.2	38.8	39.2
C-9	43.2	43.4	42.2	43.6	43.4	43.7
C-10	131.9	131.9	131.9	131.7	131.9	131.8
C-11	27.2	27.2	25.2	27.2	27.2	25.9
C-12	39.7	40.8	40.9	40.1	40.3	39.3
C-13	47.7	48.0	47.8	47.7	48.6	48.1
C-14	153.7	151.8	152.5	158.3	155.0	157.7
C-15	119.2	124.1	122.3	118.4	123.1	120.8
C-16	82.4	83.8	84.4	73.9	78.2	80.6
C-17	91.8	91.8	91.3	82.4	87.3	83.2
C-18	18.7	18.4	18.6	20.9	19.8	21.6
3-OMe	55.2	55.2	55.2	55.2	55.2	55.2
16-Me	-	23.8	-	-	27.3	-
C-1′	-	-	43.4	-	-	44.0
C-2′	-	-	134.4	-	-	133.7
C-3′	-	-	118.7	-	-	118.9



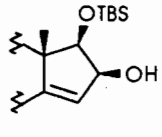
92



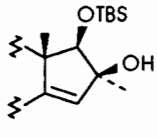
105



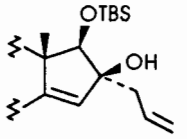
107



93



103

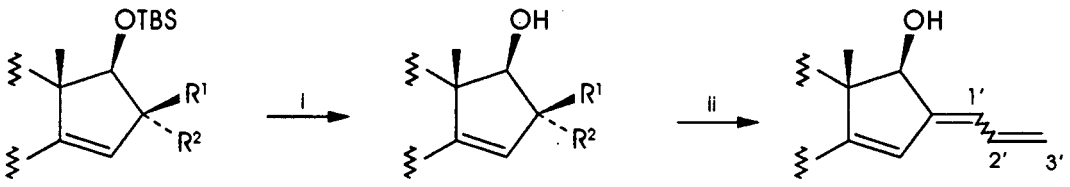


106

The ^{13}C NMR data for the Δ^{14}-16-alcohols are tabulated in Table 2.3 and revealed self-consistency in C(1)–C(13). The configuration at C(16) had a uniform influence on chemical shifts of both C(16) and C(17). Similarly, the effect of the 16-hydroxy group *syn* or *anti* to the 13β-methyl group was clearly demonstrated in the trend in chemical shift of C(18).

An attempt to establish the diastereoselectivity of 1,2-allylation was based on selective acetonide formation of the *syn* diol derived from **106**. Therefore **106** and **107** were smoothly converted into their respective diols **108** and **109**. However, treatment of each under the very mild acetonide-forming conditions of acetone in the presence of anhydrous copper(II) sulfate gave a common product of dehydration, formulated from spectroscopic data as the triene **110** (Scheme 2.31).

Scheme 2.31



106 (R^1 = OH, R^2 = allyl)
107 (R^1 = allyl, R^2 = OH)

108 (R^1 = OH, R^2 = allyl)
109 (R^1 = allyl, R^2 = OH)

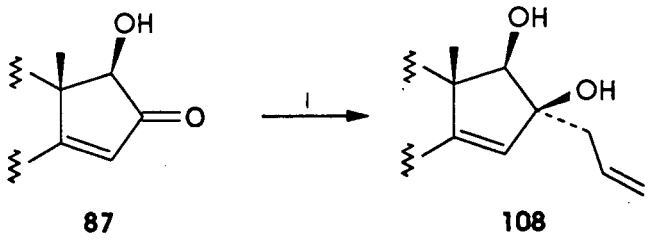
110

i, Bu_4NF; ii, Me_2CO, anh. $CuSO_4$

It was not possible to establish the C(16)–C(1′) double bond geometry from NMR data. A COSY plot was used to verify the coupling connectivities of the exocyclic dienyl substituent. The 1′-proton (δ 5.81, dd, *J* 11.6 and 1.3 Hz), experienced allylic coupling $J_{1',17\alpha}$ 1.3 Hz to the 17α-proton and vicinal coupling $J_{2',3'}$ 11.6 Hz. For the terminal 3′-protons, a geminal coupling of *J* 1.9 Hz, as well as the expected *cis* $J_{1',2'}$ 10.1 Hz and *trans* $J_{1',2'}$ 16.8 Hz were observed. The magnitudes of vicinal couplings 1′–2′ and 3′–2′ were reconciled with the splitting observed for the 2′-proton (δ 6.59, ddd, *J* 16.8, 11.6 and 10.1 Hz).

For the purpose of gaining supportive evidence regarding the influence of the 17β-silyloxy group on the stereoselectivity of 1,2-alkylation, the 17β-hydroxy Δ^{14}-16-ketone **87** was treated with allylmagnesium chloride to give a single product. From the previous data, this product was assigned as the *syn*-diol **108** (Scheme 2.32). This finding upholds the previously drawn conclusion about magnesium chelation to a free 17β-hydroxy group only,[67] as reflected by the exclusive α-face approach.

Scheme 2.32



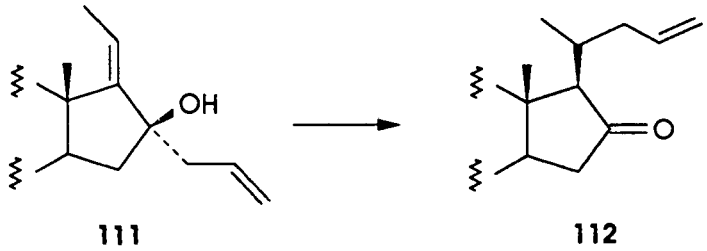
87 108

I, CH_2=$CHCH_2MgCl$

With the epimeric 16-hydroxy Δ^{14}-16-allyl alcohols **106** and **107** in hand, the next step in the synthetic approach was to investigate methods for effecting the desired Cope transformations. This type of suprafacial-suprafacial [3,3] sigmatropic rearrangement has been well researched and continuous investigations increasingly define the scope and utility of the process.[68] These rearrangements may be achieved thermally, but substantial rate accelerations were reported by the anionic oxy-Cope variant, which involved conversion of the 3-hydroxy 1,5-dienyl system into the corresponding lithium or potassium alkoxide.[68] An 'electron push' by the oxy-anion attached to the migrating σ-bond is thought to be the cause of this rate enhancement. By contrast to the classical Cope reaction, the overall effect of carbon-carbon bond migration is irreversible. A further virtue of the anionic version is the ability of the reaction to proceed at lower temperatures; thereby making this transformation more tolerant of sensitive functional groups.

A successful anionic oxy-Cope tranformation involving a steroidal 16-ketone is found in the work of Koreeda.[69] Treatment of the diene **111** with potassium hydride in refluxing dioxane gave the C(20)-homologated compound **112** (Scheme 2.33).

Scheme 2.33

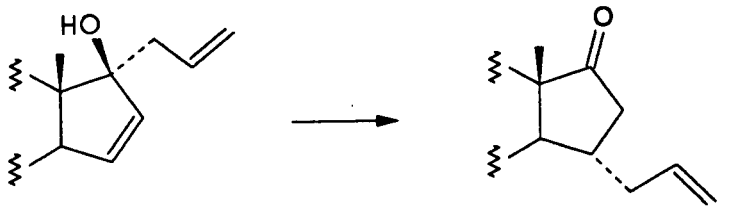


111 112

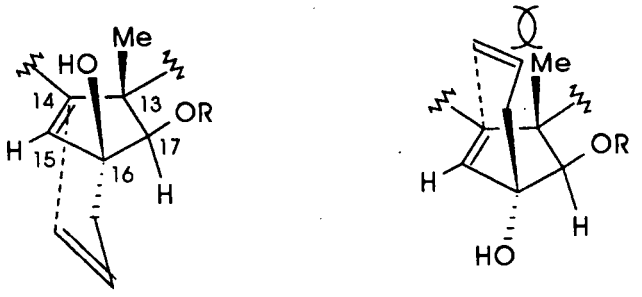
The necessity for the dienyl moiety to adopt a boat or a chair-like conformation[68] often limits the applicability of this transformation to rigid cyclopentanoid systems containing an endocyclic portion of the diene. However, it was recently shown that Δ^{15}-17α-

allyl 17β-alcohols of the type indicated in Scheme 2.34 readily rearranged under strongly basic conditions.[35]

Scheme 2.34



A molecular model of the Δ^{14}-16α-allyl 16β-alcohol **106** revealed the ability to adopt a chair-like transition state (Figure 2.35). However, owing to the pseudo-equatorial disposition of the 16α-allyl group, close proximity between the allyl terminus and C(14) is not possible. For the 16-epimer **107**, the pseudo-axial 16β-allyl group places the allyl terminus much closer to C(14) in a chair-like conformation (Figure 2.35). However, steric interactions between the angular 13β-Me and the 16β-allyl group were expected to limit the probability of this transition state.



106 **107**

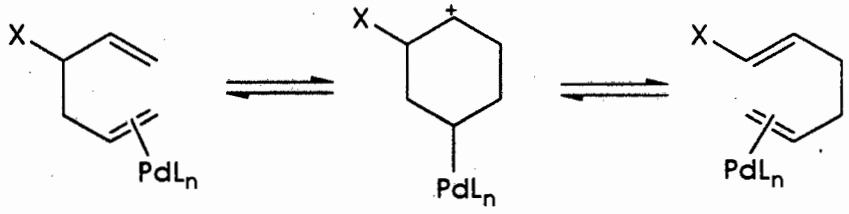
Figure 2.35: Chair-like conformations for the Δ^{14}-16-allyl alcohols **106** and **107**

In a rearrangement experiment, the alkoxide of **106** was generated at -78 °C in tetrahydrofuran with potassium hexamethyldisilazide (KHMDS). A small amount of 18-crown-6 was added. The complexation of the crown ether to the potassium cation was reported to generate a more reactive 'naked' oxy-anion.[68] The mixture was slowly warmed to 20 °C, but without any consumption of the starting material.

Several modifications were made to the reaction conditions for both epimeric 16-alcohols **106** and **107** (see experimental section), but all without success. As a possible

alternative to the anionic oxy-Cope rearrangement, an experiment with transition metal catalysis of this transformation was carried out. Numerous reports were published in the recent literature conserning mercury(II) and especially palladium(II)-catalysed [3,3]-sigmatropic processes.[70] Current mechanistic understanding of this catalysed Cope rearrangement is based on a cyclisation-induced process, in which the rate determining step involves cyclisation of the Pd^{II}–alkene complex to form a cyclohexyl cation intermediate.[71] Elimination of the metal yields the observed product (Scheme 2.36).

Scheme 2.36

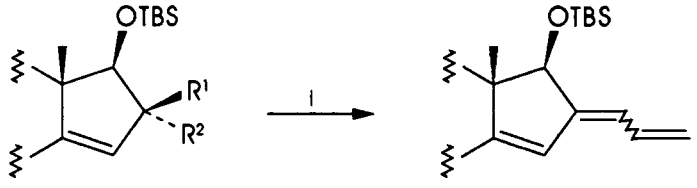


In a publication by Bluthe[72] it was reported that the palladium-catalysed equivalent of an anionic oxy-Cope transformation proceeded smoothly (Scheme 2.37).

Scheme 2.37

From this analogy, involving a hydroxy dienyl system, the scope for a similar transformation relating to the present case was explored. It was chosen to explore this reaction with bis(acetonitrile)palladium chloride as discussed in the review article.[70] Reacting the 16α-allyl alcohol **106** in tetrahydrofuran with 0.5 mol equiv. of the palladium salt for 15 min at 20 °C gave a dark red solution. However, rather than the expected product of allyl migration, the reaction product was identified as a product of dehydration **113** (Scheme 2.38). A similar result was obtained with the epimer **107**.

Scheme 2.38



106 (R^1 = OH, R^2 = allyl) **113**
107 (R^1 = allyl, R^2 = OH)

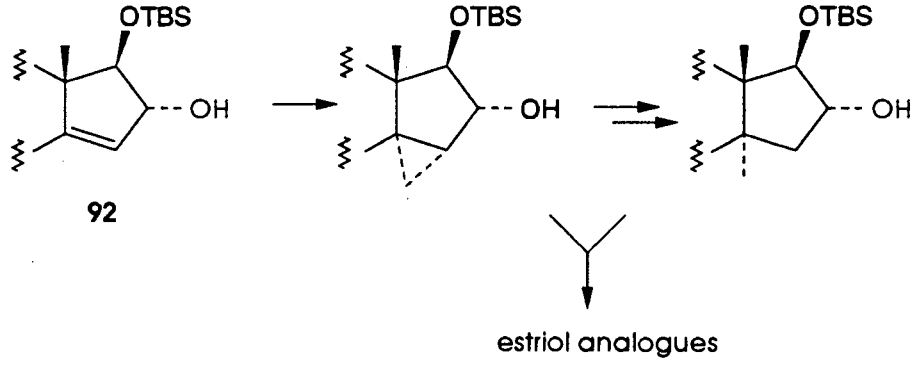
I, $(MeCN)_2PdCl_2$

This result once again demonstrated the strong inclination of the tertiary allyl alcohol for undergoing dehydration. Given the difficulties associated with adopting a reactive transition state for sigmatropic reactivity, elimination of the doubly allylic disposed tertiary 16-hydroxy group into conjugation is perhaps not surprising. No literature analogy was found, and it was therefore concluded that this dehydration tendency is a specific feature of the system under study.

2.4 Stereodirected Cyclopropanation of the Δ^{14}-16-Alcohols

With Δ^{14}-16-alcohols **92** and **93** obtained from successful 1,2 reduction of the enone **86** (Scheme 2.13), the aim was to carry out a stereodirected cyclopropanation of the Δ^{14}-bond and to prepare the 14,15-methylene analogues of estriol. Manipulation of the cyclopropyl intermediate resulting in eventual cleavage of the 2′,3′-bond was expected to lead the way to 14-methyl estriol analogues. This conceptual approach is indicated in Scheme 2.39. For illustrative purposes, only the Δ^{14}-16α-alcohol **92** is indicated.

Scheme 2.39



There is a substantial amount of literature on cyclopropanation of olefins, covering a diversity of cyclopropanation reagents.[73] For the current purpose, the investigation was concentrated on the use of Simmons-Smith reagents only, i.e. diiodomethane and an activated zinc species to generate the carbene source.[74] Reported carbene sources include halomethyllithiums, diazomethane and polyhalomethanes, but the Simmons-Smith intermediates are known to have more controlled reactivity, thereby yielding fewer side reactions.[73]

Originally, the Simmons-Smith reagent was generated from diiodomethane and a zinc-copper couple. It is known that the copper plays no role other than to activate the zinc surface for reaction.[75] Mechanistic aspects of the cyclopropanation reaction are not fully understood. However, it is generally regarded that an α-iodomethyl species is a key intermediate in the sequence of events leading to carbon-carbon bond formation.

$$CH_2I_2 + Zn(Cu) \rightarrow ICH_2ZnI + (Cu)$$

The improvement involving a zinc-silver couple seemed more appropriate to this study, given that it has been successfully applied in the steroid field.[76] Other carbene generators include the use of triethylaluminium[77] or a samarium-mercury couple, but perhaps the most important improvement was the modification proposed by Furukawa,[78] involving the use of diethylzinc with diiodomethane. Advantages of this modification over organozinc methodology include rapid formation of the cyclopropanating reagent under mild conditions, compatability with a broader range of substrates and the optional use of non-coordinating solvents.[79] A drawback of this organometallic reagent is, however, the highly pyrophoric nature.

A feature of the Simmons-Smith reaction that is often exploited is the stereodirecting ability of heteroatoms. An occurrence commonly observed in allylic as well as homoallylic alcohols is cyclopropanation at the olefinic plane *syn* to the hydroxyl function. This process, as indicated in Figure 2.40, involves the intermediacy of a cyclic transition state, in which coordination of the Simmons-Smith reagent occurs to the heteroatom and the *syn* olefinic face.[80]

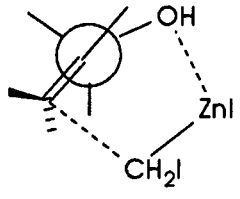
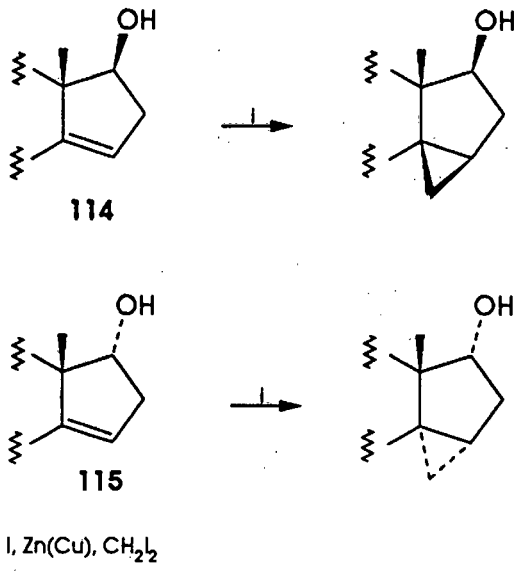


Figure 2.40: Transition state for stereodirected cyclopropanation

Stereodirected Δ^{14} cyclopropanation reactions have been documented in the recent literature. Ponsold[76] reported on the efficient stereodirected homo-allylic cyclopropanation of Δ^{14}-17α- and 17β-alcohols **113** and **114** (Scheme 2.41) with a zinc-copper couple and diiodomethane.

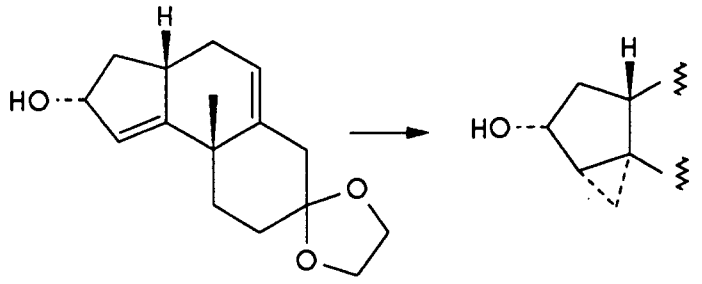
Scheme 2.41



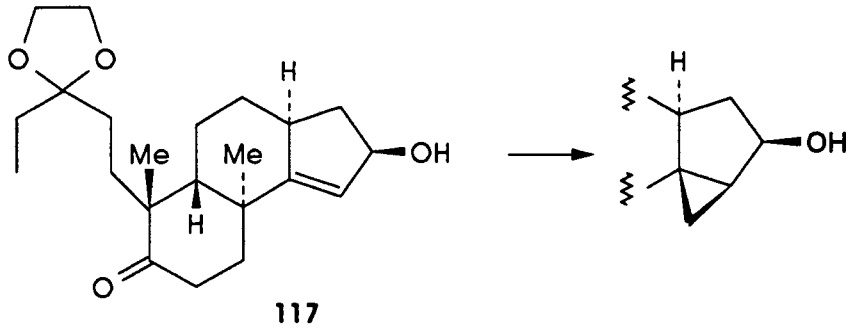
A report by Corey[81] illustrated cyclopropanation of the Δ^{14}-16β-alcohol **116** (Scheme 2.42) with the Simmons-Smith reagent. The pseudo-axial hydroxyl group very effectively directed the reagent onto the α-face. Similarly, Saxton[82] performed an analogous reaction on the tricyclic allylic alcohol **117**. In this instance, the reagent was directed by a pseudo-equatorial hydroxyl group.

In the present study, a cyclopropanation reaction of the Δ^{14}-16α-alcohol **92** was carried out with a zinc-silver couple[83] and diiodomethane (Scheme 2.43). Commercially available zinc dust was reacted with a solution of silver(I) acetate in glacial acetic acid. Immediate metal exchange was noted and the black bimetallic couple was subsequently treated with an excess (*ca* 15 mol) of diiodomethane to generate the carbenoid species, followed by a solution of the Δ^{14}-16α-alcohol **92** in dry diethyl ether. After 30 min of reflux, an aqueous work-up gave 17β-*tert*-butyldimethylsilyloxy-3-methoxy-14,15α-methylene-estra-1,3,5(10)-trien-16α-ol **118** in a yield of 77%. The use of diethylzinc[78] as carbenoid generator and performing the reaction in benzene drastically improved the conversion of the allylic alcohol **92** into the cyclopropyl compound **118** to 94%. This finding is consistent with the literature reports[79] on the yield enhancement brought about by non-coordinating solvents. Seen in this perspective, the use of bimetallic couples was discarded. The extreme pyrophoricity of diethylzinc, however, demanded care.

Scheme 2.42

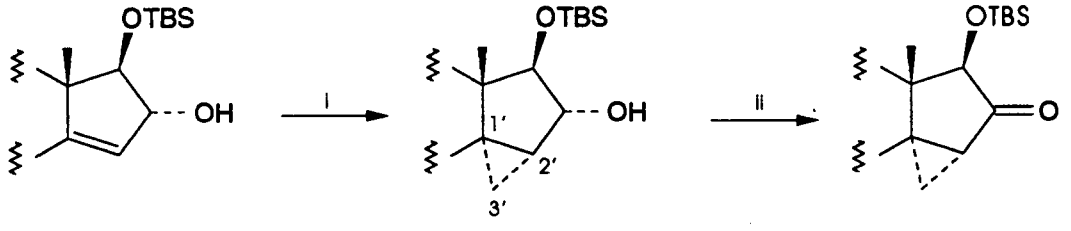


116



117

Scheme 2.43



92 118 119

I, Zn(Ag) or Et_2Zn, CH_2I_2; II, Dess-Martin Periodinane

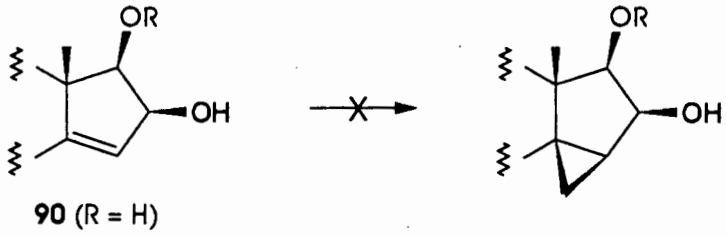
Spectroscopic characteristics of the cyclopropyl alcohol **118** were in agreement with the overall assigned structure. The two high-field AB-signals for 3′-H_{exo} (δ 0.36, dd, *J* 7.8 and 5.5 Hz) and 3′-H_{endo} (δ 0.64, dd, *J* 5.5 and 2.9 Hz) were clearly visible. These were differentiated by the characteristic larger exo–vicinal coupling constant (*J* 7.8 *vs* 2.9 Hz in **41**) in a cyclopropyl system.[46] From a COSY plot, the 2′-H (δ 1.68, ddd, *J* 7.8, 4.2 and 2.9 Hz) was identified through the coupling connectivities to the 3′-protons and the coupling $J_{2',16\beta}$ 4.2 Hz (See Figure 2.46). No definite evidence in support of the assigned

stereochemistry of cyclopropanation existed at this stage. However, chemical and spectroscopic correlation techniques proved the assignment to be correct (see later).

Oxidation of the 14α,15α-methylene 16α-alcohol **118** to the 16-ketone **119** was initially carried out under Swern conditions, but Dess-Martin periodinane[84] became the reagent of choice (Scheme 2.43). The yield of the 14α,15α-methylene 16-ketone **119** was comparable under both sets of conditions and neither of the methods required chromatographic purification of the ketone, but the periodinane reaction offered the distinct advantage of ease of monitoring of the reaction progress. From the ^{1}H NMR spectrum of the ketone **119**, the 2′-proton (δ 2.00, dd, *J* 8.3 and 2.1 Hz) was clearly visible as a result of deshielding by the 16-ketone.

To perform the analogous stereodirected cyclopropanation on the Δ^{14}-16β-alcohol **93**, a solution of the latter in dry benzene was reacted with diethylzinc – diiodomethane. However, the starting material was recovered. In a second attempt, the reaction was repeated in refluxing toluene to obtain the same non-reactivity. To investigate the possible steric influence of the 17β-silyl ether, the Δ^{14}-16β,17β-diol **90** was exposed to the conditions shown to achieve cyclopropanation. At refluxing temperature, no reaction was noted and the starting material was recovered quantitatively.

Scheme 2.44



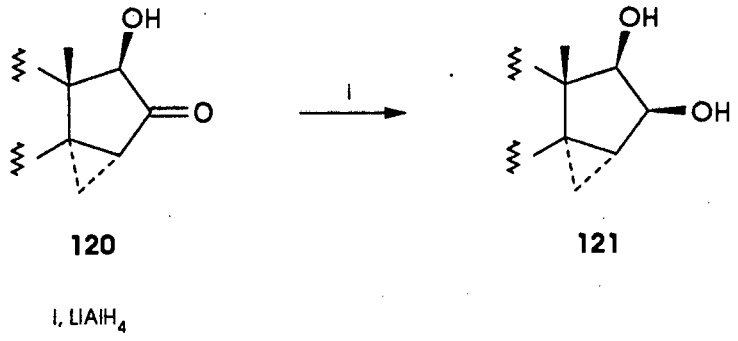
90 (R = H)
93 (R = TBS)

These failures of the Δ^{14}-16β-alcohol to react under the conditions known to effect cyclopropanation in the 16α-series were rather surprising. Impedance of reactivity caused by steric bulk at C(17) may be excluded, in the light of the non-reactivity of the 17β-hydroxy Δ^{14}-16β-alcohol **90**. It was therefore reasoned that steric interactions between the axial 13β-methyl group and the pseudo-axial 16β-hydroxy group completely deactivated the reactivity towards directed cyclopropanation.

Carbonyl group reduction of the 14α,15α-methylene 16-ketone **120** with hydride reagents was expected to give the derived 16β-alcohol. Hydride entry was reasoned to favour the α-side, owing to obstruction of the β-side by reagent chelation to the 16-carbonyl and 17β-hydroxyl groups. A close analogy exists between the present case and the reduction of 17β-hydroxy 16-ketones, which was shown to lead predominantely to *syn*-diols.[85,86]

Together with the primary cyclopropanation product **118**, the 16-hydroxy epimers derived from the ketone **120** constitute the 3-methyl ether precursors of the desired estriols. Thus, treatment of the ketone **120** with lithium aluminium hydride gave 3-methoxy-14,15α-methylene-estra-1,3,5(10)-triene-16β,17β-diol **121** in 90% yield (Scheme 2.45).

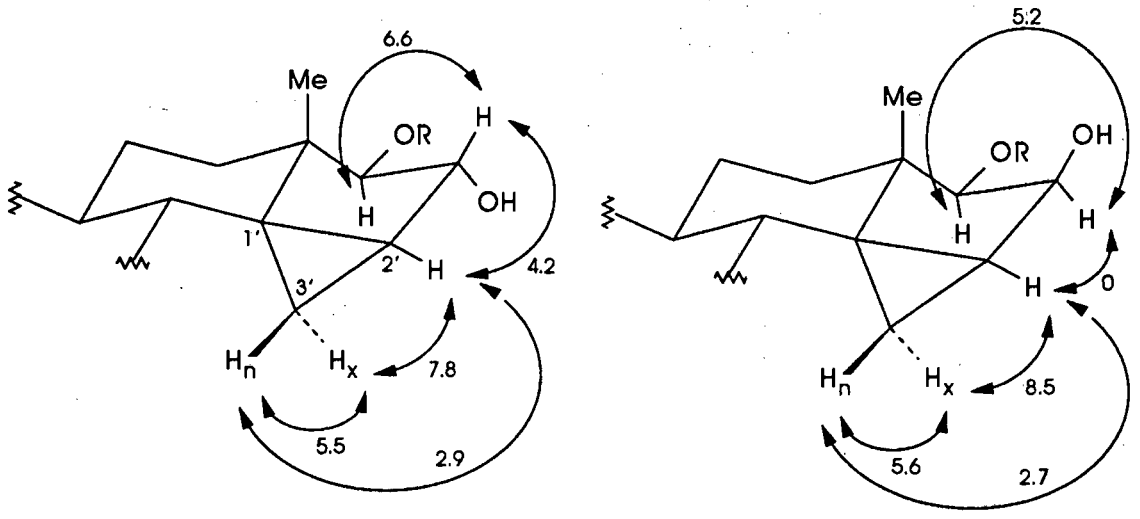
Scheme 2.45



120 **121**

I, $LiAlH_4$

The C(16) configuration of the 14α,15α-methylene 16β-alcohol **121** could be clearly assigned from ^1H NMR data. A molecular model of **121** indicated orthogonality between 15β- and 16α-H, and indeed, no scalar coupling was observed between these protons. The 15β-H only experienced coupling to the neighbouring 3'-H_2 (J 8.5 and 2.7 Hz). By contrast, the 16-epimer **118** had an additional coupling for 15β-H of $J_{15\beta,16\beta}$ 4.2 Hz. The proton–proton coupling for the 14,15α-methylene 16-alcohols **118** and **121** are illustrated in Figure 2.46. A COSY plot of the 14,15a-methylene 16b,17b-diol **121** in indicated in Figure 2.47.



118 **121**

Figure 2.46: Proton couplings in the 14α,15α-methylene 16-alcohols **118** and **121**

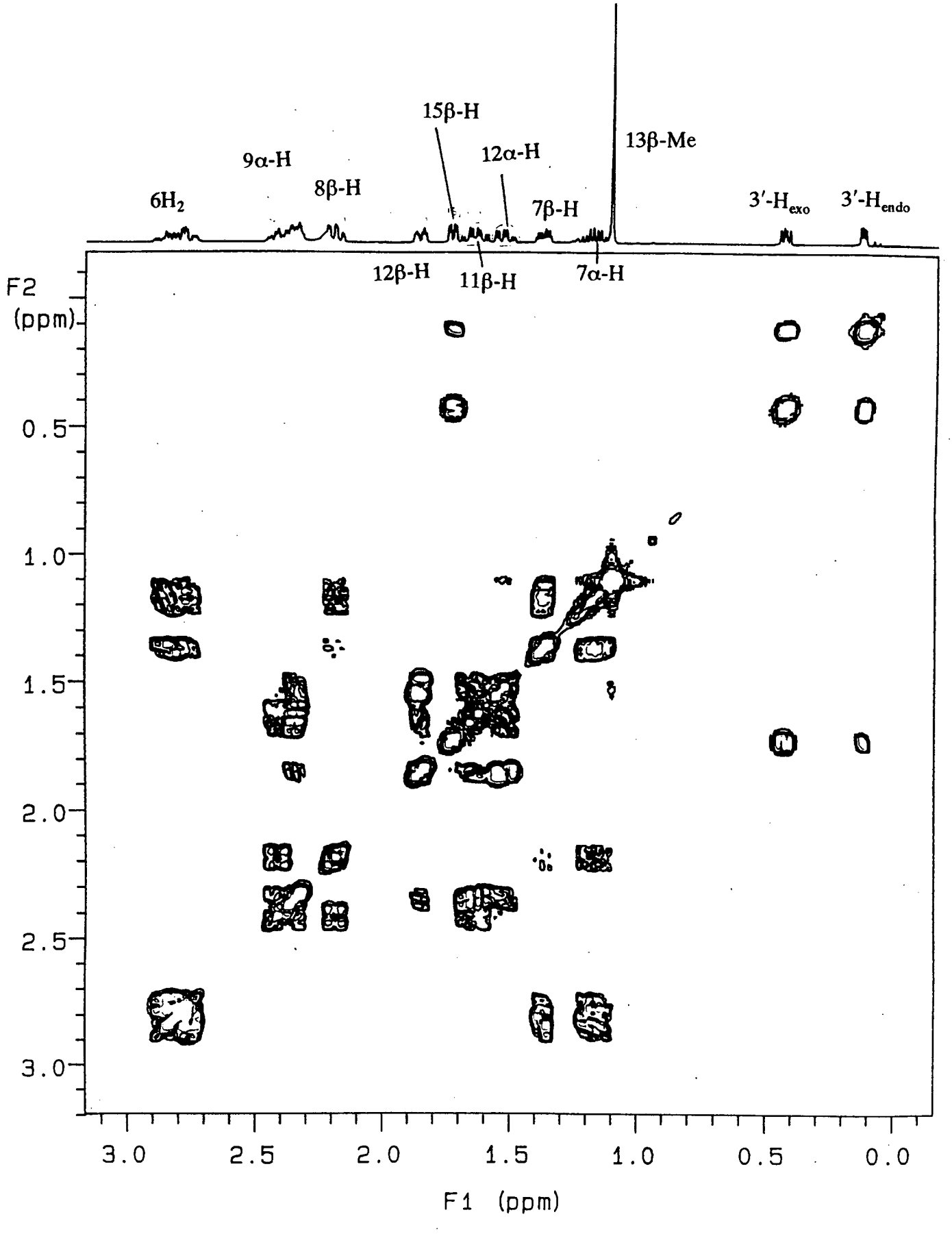
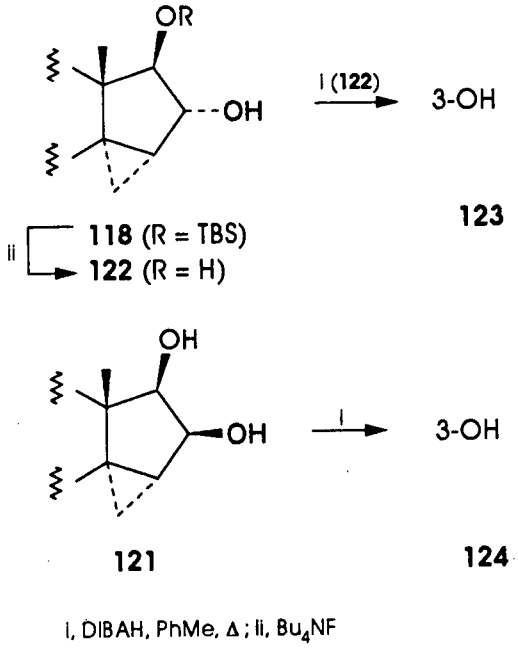


Figure 2.47: COSY plot showing high-field region of 14,15α-methylene 16β,17β-diol **121**

Treatment of the 17β-silyloxy 14,15α-methylene 16α-alcohol **118** with tetrabutylammonium fluoride gave the parent 16α,17β-diol **122**. Demethylation of the epimeric 16-alcohols **121** and **122** with diisobutyl aluminium hydride[87] (DIBAH) (5–10 mol) in refluxing toluene gave the estriol analogues **123** and **124** (Scheme 2.48), which were subjected to biological evaluation (see Chapter 4).

Scheme 2.48

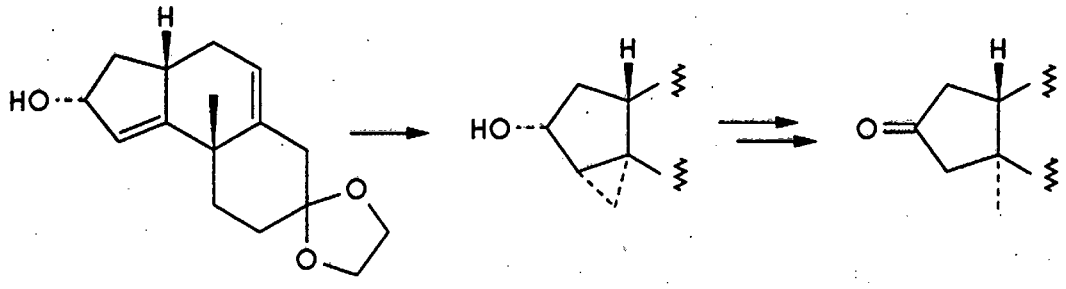


i, DIBAH, PhMe, Δ ; ii, Bu_4NF

With the 14,15α-methylene 16-ketone **119** in hand, the conceived route to 14-methyl analogues of estriol is shown in Scheme 2.39. The key step involved reductive cleavage of the 2′,3′-cyclopropyl bond of **119** to give the derived 14-methyl 16-ketone. Stereoselective reduction of the 16-oxo group was expected to give the epimeric 16-alcohols.

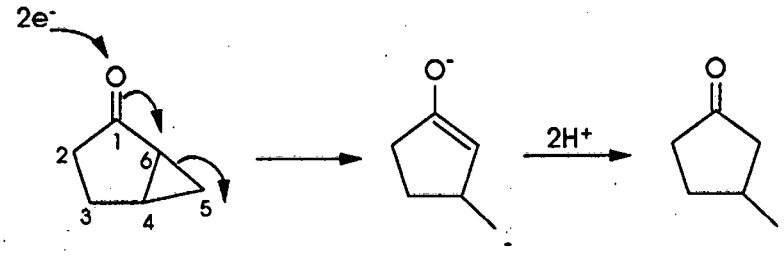
It is known that bicyclo[3.1.0]hexan-1-ones undergo cleavage of the exocyclic cyclopropyl bond under conditions of dissolving metal reduction.[81,82] This type of methodology is often used for the introduction of 'angular' methyl groups in fused ring systems. Saxton and co-workers[82] commented on the difficulties associated with attempted direct angular alkylation in the synthesis of the C/D ring system of paspalicine, and adopted a cyclopropanation–fragmentation route (Scheme 2.49) as their method of choice.

Scheme 2.49



Mechanistically, the process involves electron flow into the carbonyl oxygen to give a dianion. As illustrated below for a cyclopentanoid model, protonation upon work-up then yields a β-methyl ketone.

Scheme 2.50

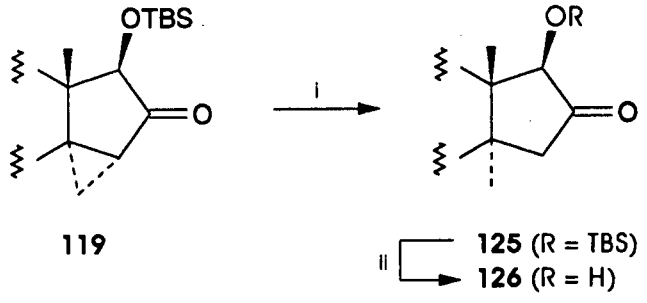


Reduction of 16-ketones with metal hydrides have been shown[88] to give mainly the related 16β-alcohols (*ca* 8:1). This stereoselectivity corresponds to reagent approach from the α-face, thereby eliminating 1,3-interactions with the angular 13β-methyl group. The presence of a 17β-hydroxy group amplifies this stereoselectivity by a chelation involving the reagent, 17β-OH and the 16-oxo group, as predicted by Felkin and Anh models.[62,63] By contrast, when the analogous reduction is carried out under conditions of dissolving metal in liquid ammonia, the selectivity is reversed, to give mainly the product of thermodynamic control, i.e. a 16α-alcohol.[89]

In the present study, a solution of the methylene ketone **119** in tetrahydrofuran was treated with an excess of lithium (*ca* 10 mol) in liquid ammonia at -78 °C to give the 14α-methyl 16-ketone **125** as shown in Scheme 2.51. The reaction was quenched with solid ammonium chloride under strictly aprotic conditions to prevent side reactions involving the the aromatic ring A. A ^{1}H NMR spectrum of **125** clearly indicated cleavage of the 2′,3′-bond, in that the cyclopropyl resonances were replaced by a methyl signal for 14α-Me (δ 1.09, s), as well as the expected AB doublets for the 15-methylene protons (δ 2.01 and

2.12, *J* 18.0 Hz). The 17β-silyloxy group of **125** was readily hydrolysed with tetrabutylammonium fluoride in tetrahydrofuran, to give the parent 17β-alcohol **126**.

Scheme 2.51

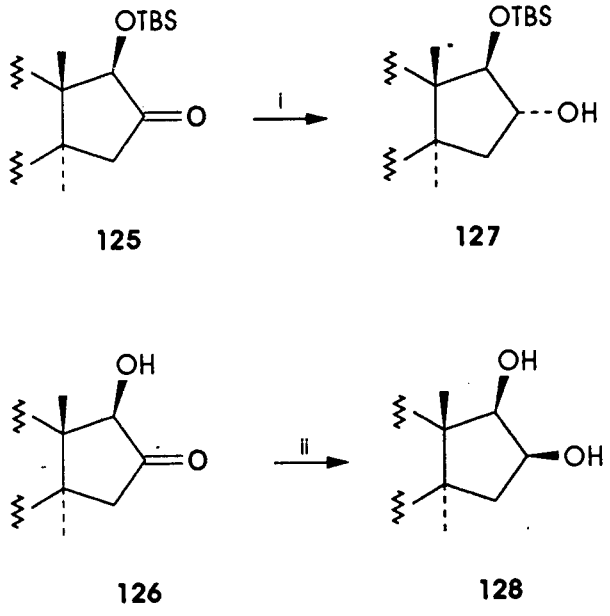


i, Li-NH_3; ii, Bu_4NF

Treatment of the 14α-methyl 16-ketone **125** with lithium in liquid ammonia gave exclusively the thermodynamically favoured 16α-alcohol **127** in 76% yield. By contrast, reaction of the 16-ketone **126** with lithium aluminium hydride gave exclusively the 16β,17β-diol **128** (Scheme 2.52), in analogy to the literature result.[85] Thus, steric shielding of the 16-carbonyl group by the combined effects of the 1,3-disposed axial 13β-methyl group, as well as reagent chelation to the 16- and 17β-oxygen functionalities outweighed any steric influence by the other 1,3-disposed axial methyl group, namely the 14α-Me. Hydride entry was therefore obliged to occur from the α-face, leading to the 16β-alcohol **49** in 83% yield.

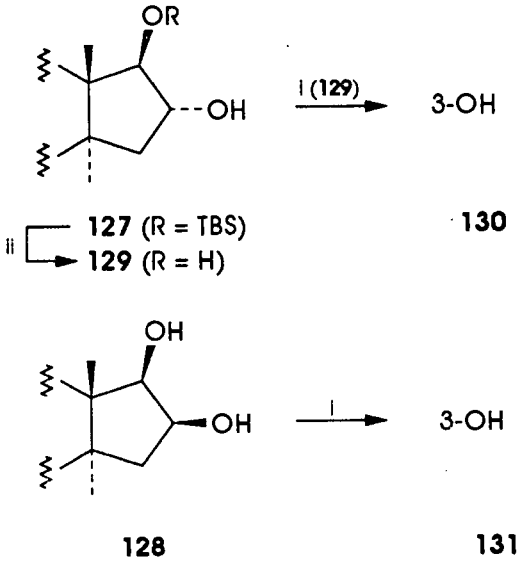
Desilylation of the silyl ether **127** with tetrabutylammonium fluoride to give the parent 16α,17β-diol **129** followed by 3-demethylation with DIBAH[87] in refluxing toluene to give 14-methylestra-1,3,5(10),triene-3,16α,17β-triol **130** occurred in 62% overall yield (Scheme 2.53). Similarly, demethylation of the 16β,17β-diol **128** gave the 16-epimeric triol **131** (91%). These estriol analogues were subjected to biological evaluation (see Chapter 4).

Scheme 2.52



i, Li-NH_3; ii, $LiAlH_4$

Scheme 2.53



i, DIBAH, PhMe, Δ ; ii, Bu_4NF

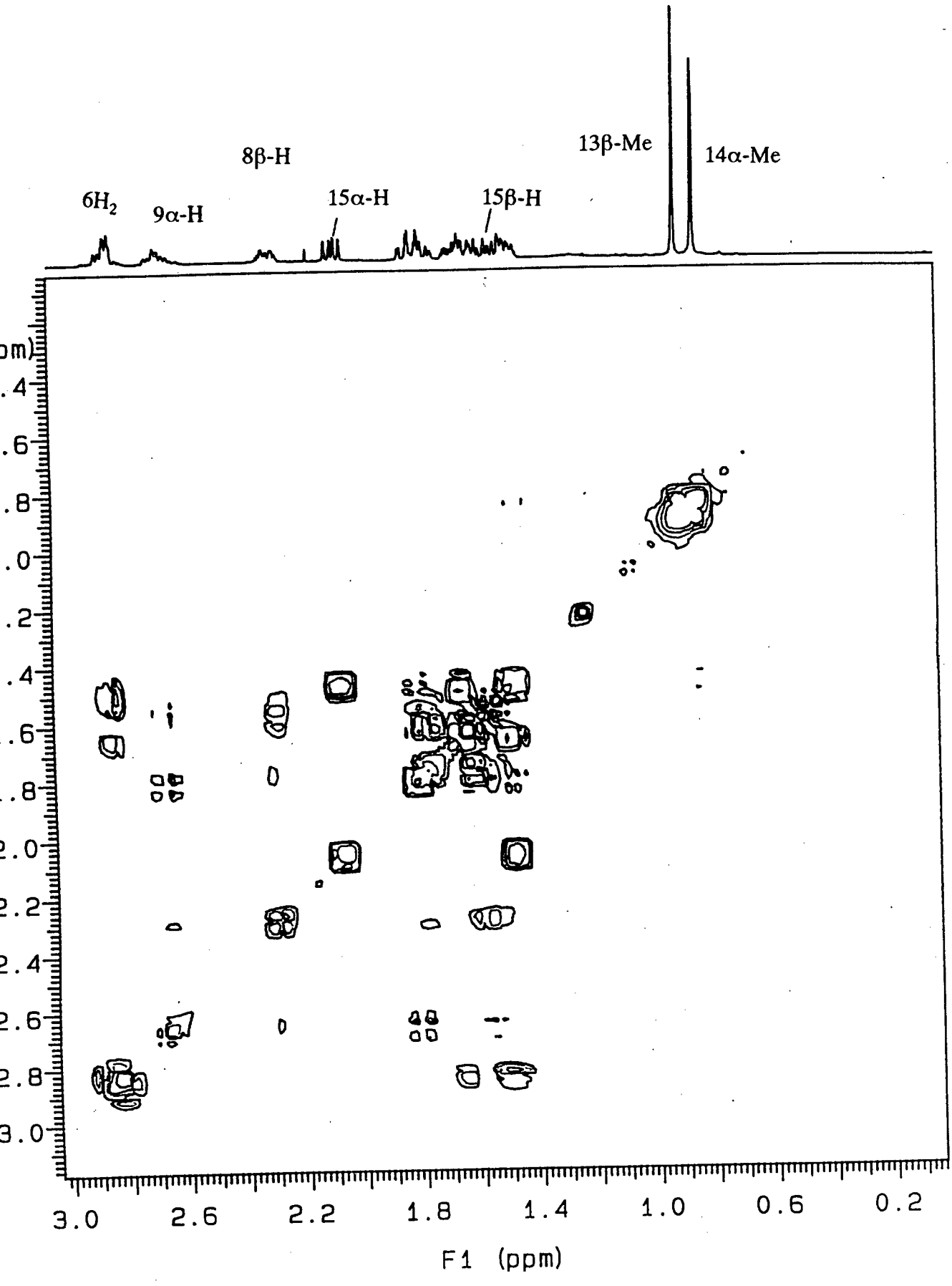


Figure 2.54: High-field region of COSY plot of 14-methyl 16β,17β-diol **128**

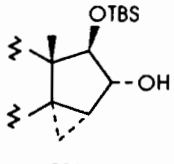
Signals for the ring D protons of the 14α,15α-methylene 16-alcohols **118** and **121**, as well as those of the 14α-methyl 16-alcohols **127** and **128** are listed in Table 2.4. Extraction of configurational information from the coupling $J_{15\beta,16}$ for the methylene compounds **118** and **121** was discussed previously. An immediate pointer to the C(16) configurations of the 14-methyl 16-alcohols **127** and **128** was obtained from coupling patterns. Ponsold and co-workers[90] have published on the utility of the coupling $J_{16,17}$ for establishing the C(16) configuration. For an epimeric pair of 16,17β-diols, this coupling was reported as $J_{16\beta,17\alpha}$ 6 Hz for a 16α,17β-diol and $J_{16\alpha,17\alpha}$ 7.5 Hz for the analogous *syn*-diol. The coupling patterns for the 14-methyl 16,17β-diols **127** and **128** listed in Table 2.4 clearly agree with the published values.[90] Another distinguishing feature of the 16β,17β-diol **127** is the equivalent couplings $J_{15\alpha,16\alpha}$ and $J_{16\alpha,17\alpha}$ 7.5 Hz. As a consequence, the signal for the 16α-proton appears as a triplet of doublets.

The ^{13}C NMR data for the 16-alcohols **118**, **121**, **127**, and **128** are listed in Table 2.5. The C(16) configuration had a consistent influence on the chemical shifts of C(16), C(17) and C(18), analogous to the trend observed for the Δ^{14}-16-alcohols (see Table 2.2). For the 14α-methyl 16-alcohols **127** and **128**, both the 13β- and 14α-methyl groups in turn responded to the deshielding effect of a *syn* 16-hydroxyl group.

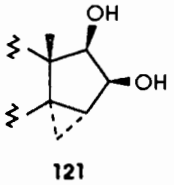
Table 2.4: Key ^1H NMR data for 14,15α-methylene and 14-methyl 16-alcohols

	Signal[a]				
Compound	13β-Me	15α-H	15β-H	16-H	17α-H
118	1.00 (s)	-	1.68 (ddd, 7.8, 4.2 and 2.9)	4.12 (dd, 6.6 and 4.2)	3.21 (d, 6.6)
121	1.12 (s)	-	1.73 (dd, 8.5 and 2.7)	3.46 (d, 5.2)	4.09 (d, 5.2)
127	1.09 (s)	1.36 (dd, 13.2 and 1.5)	2.07 (dd, 13.2 and 9.3)	4.15 (ddd, (9.3, 4.7 and 1.5)	4.00 (d, 4.7)
128	0.95 (s)	2.15 (dd, 12.7 and 7.5)	1.59 (dd, (12.7 and 5.6)	4.39 (td, 7.5 and 5.6)	4.00 (d, 7.5)

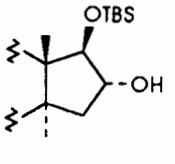
[a]Given as $\delta_H(J/Hz)$



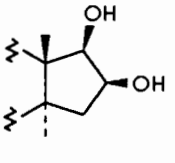
118



121



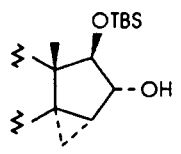
127



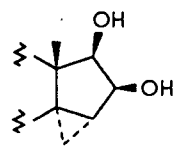
128

Table 2.5: ^{13}C NMR Data for 14,15α-methylene and 14-methyl 16-alcohols

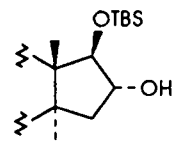
	Compound			
Signal	**118**	**121**	**127**	**128**
C-1	126.8	126.9	126.7	126.8
C-2	111.8	111.7	111.6	111.6
C-3	157.4	157.4	157.3	157.3
C-4	113.7	113.7	113.7	113.7
C-5	137.9	137.8	137.9	137.7
C-6	30.1	30.1	30.8	30.7
C-7	23.8	23.6	24.2	24.3
C-8	36.8	37.2	36.7	36.7
C-9	42.9	43.0	42.6	42.3
C-10	132.8	132.7	134.0	133.7
C-11	27.1	27.1	26.1	26.2
C-12	33.6	34.2	29.7	30.2
C-13	42.5	42.2	44.4	42.6
C-14	36.4	39.6	47.5	45.8
C-15	22.6	23.9	43.5	43.6
C-16	79.3	74.6	80.1	70.1
C-17	82.8	77.8	86.7	76.9
C-18	16.2	17.0	16.4	17.2
3-OMe	55.2	55.2	55.2	55.2
C-3′	5.3	6.6	-	-
14-Me	-	-	15.1	14.1



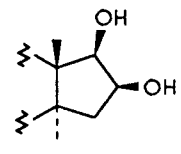
118



121



127



128

To gain further support for the C(14)-configuration of the 14α-methyl 16-ketone **125**, a chiroptical investigation was carried out. Kirk systematised the circular dichroistic data, based on the $n \rightarrow \pi^*$ transition of the various classes of hexahydroindanones as found in steroidal skeletons.[91] These data were particularly analysed for the influence of methyl substituents in the vicinity of the carbonyl chromophore and the

ring junction. Further examination of the data showed that the observed Δε for a ring system could be related directly to the length of a particular coplanar 'zig-zag' of carbon-carbon bonds in a polycyclic structure. The zig-zag bonds for a steroidal 16-ketone are shown in Figure 2.55

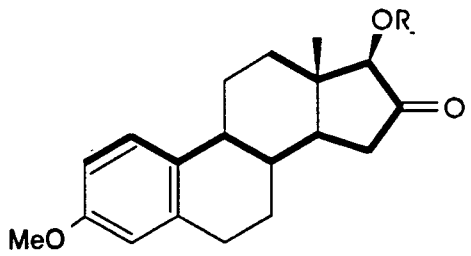


Figure 2.55: Coplanar bonds in a steroidal 16-ketone

For the class of hexahydroindan-2-ones, as represented by the steroidal C and D rings, Kirk[91] described the cyclopentanoid ring to be in a 'twist' conformation. The horizontal plain is defined by C(15), C(17), and the carbonyl-bearing C(16). Carbon atoms C(13) and C(14) are at the rear of the ring and are disposed at opposite sides of the horizontal plane. An exact description holds for the *cis*-fused hexahydroindan-2-one. Octant drawings of this pair of ring systems, projected down the O=C-axis are indicated in Figure 2.56.

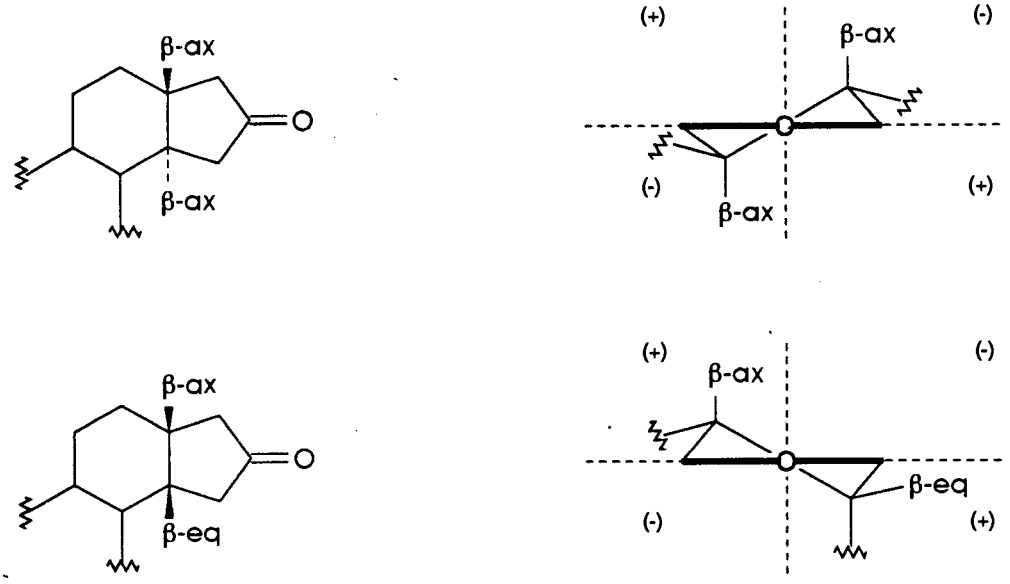


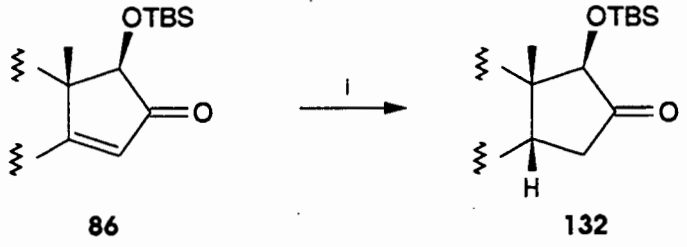
Figure 2.56: Octant projections for steroidal 16-ketones

For both of these fused ring systems, the twist of the cyclopentane ring was suggested as the dominant factor causing the chiroptical behaviour.[91] The *trans* fused system typically shows an octant consignate, i.e. negative $\Delta\varepsilon_{max}$ in the range of -6.0 to -5.0.[92] Methyl substitution at the bridge head positions produces an octant-consignate effect $\Delta\Delta\varepsilon$ *ca* 1, usually only if both positions are substituted. The *cis* fused ring shows consignate values $\Delta\varepsilon_{max}$ *ca* 3.3,[92] with a small octant-consignate contribution when both β-axial and β-equatorial methyl groups are present. Hence, an immediate pointer to the stereochemistry of ring fusion in elaborated hexahydroindan-2-one systems is the opposite signs of the Cotton effect.

In the present work, comparison of the Cotton effect (CE) of 16-ketones with known 14α- and 14β-configurations to that of the 14-methyl 16-ketone **125**, the configuration of the latter would be verified. An intermediate from an aforementioned route, namely, the 17β-silyloxy 16-ketone **84** (Scheme 2.8), would serve as a chiroptical standard with the 14α-configuration. Access to the 14β-epimer was envisaged through conjugate reduction of the Δ^{14}-16-ketone **86**.

Thus, treatment of the enone **86** with lithium in liquid ammonia – tetrahydrofuran under strictly aprotic conditions gave 17β-*tert*-butyldimethylsilyloxy-14β-estra-1,3,5(10)-trien-16-one **132** (Scheme 2.57).

Scheme 2.57



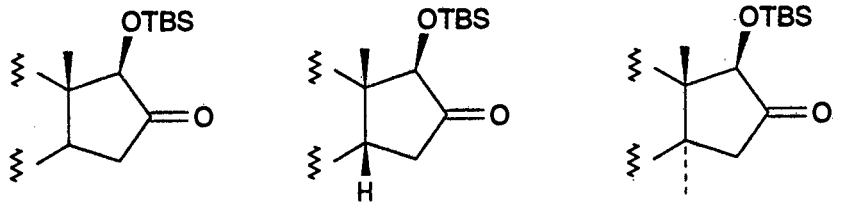
86 **132**

i, Li-NH_3

The ^{1}H NMR spectrum of **132** clearly indicated the 14β-configuration by the coupling $J_{8\beta,14\beta}$ 4.3 Hz. This coupling magnitude requires a near-gauche orientation of the coupling partners, necessitating the 14β-configuration.

The Cotton effects for the 16-ketones **84**, **125** and **132** were determined and are illustrated in Figure 2.58. Whereas the ketone of natural 14α-configuration **84** showed a Cotton effect $\Delta\varepsilon_{max}$ -5.50 (303 nm), the 14-epimer **125** indicated complete inversion of this effect with $\Delta\varepsilon_{max}$ +3.31 (318 nm). The sign of the Cotton effect of the 14-methyl 16-ketone **132** [$\Delta\varepsilon_{max}$ -6.30 (309 nm)] gave the immediate verification of the assigned structure for this compound. The octant-consignate effect[91] of two axial β-removed methyl groups as

described above is indicated. For the hypothetical case of opposite C(14) configuration, the expectation would have been an oppositely signed $\Delta\varepsilon_{max}$, with a small (*ca* $\Delta\Delta\varepsilon$ 0.5) contribution from the axial 14β-methyl group in the presence of the equatorial 13β-Me,[92] i.e. $\Delta\varepsilon_{max}$ *ca* +3.8.

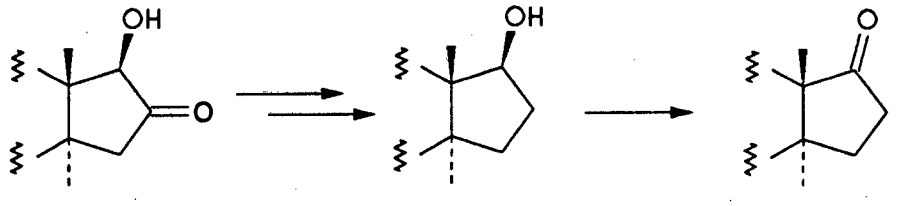


	84	125	132
$\Delta\varepsilon_{max}$ (λ/nm)			
	-5.50	+3.31	-6.30
	(303)	(318)	(309)

Figure 2.58: Circular dichroism data for 16-ketones

With the 14-methyl 17β-hydroxy 16-ketone **126** in hand, the opportunity presented itself to perform a correlation with a known compound, namely 3-methoxy-14-methylestra-1,3,5(10)-trien-17-one **133**.[22] The adopted strategy was deoxygenation at C(16), followed by deprotection and oxidation up to the 17-ketone (Scheme 2.59).

Scheme 2.59

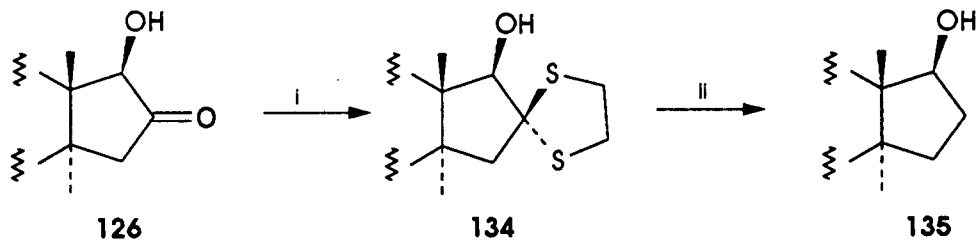


126 **133**

The method of choice for achieving the desired reduction at C(16) was that of thioketalisation-desulfurisation. Thus, conversion of the 16-ketone **126** into the derived dithioketal **134** was routinely carried out in glacial acetic acid with ethylene dithiol and *p*-toluene sulfonic acid (Scheme 2.60). A lengthy reaction gave after 24 h the desired product in 65% yield. The infrared spectrum indicated absence of a carbonyl stretching frequency and the ^{1}H NMR spectrum showed the thioketal methylene protons as two multiplets (δ 3.18

and 3.31, respectively). Further, the microanalytical data confirmed the incorporation of sulfur.

Scheme 2.60



126 **134** **135**

i, $(CH_2SH)_2$, glac. HOAc; ii, Ni_2B

Raney nickel is the conventional reagent for desulfurisation reactions. However, the frequent need for lengthy reaction times as well as uncertainties in the reactivity of the reagent has prompted an investigation into the scope for an alternative thiophile. The use of nickel boride as a desulfurisation reagent was first reported by Truce and co-workers.[93] A recent publication[94] on the utility of the reagent on a variety of substrates led to the adaptation of this methodology for the present work.

Thus, nickel boride was prepared *in situ* by slow, portionwise addition of an excess of sodium borohydride to a solution of the dithioketal **134** and nickel chloride hexahydrate in ethanol – tetrahydrofuran at 0 °C.[94] After 18 h at 20 °C, the desulfurisation was complete to yield the 14-methyl 17β-alcohol **135** in an acceptable 82% conversion (Scheme 2.60). The mass spectrum showed the expected molecular ion at *m/z* 300 and the ^1H NMR spectrum indicated the AB-signal for the 17α-proton (δ 4.13, dd, *J* 9.2 and 6.6 Hz), as expected for the 17β-alcohol **135**.

At this point, useful spectroscopic correlations between **135** and literature compounds could be made. Bischofberger and Bull[95] prepared the (+)-14β-methyl 17β-alcohol **136** by partial synthesis, whereas work by Groen and Zeelen[17] led to the total synthesis of the (±)-14-methyl 17β-alcohol **137** (Scheme 2.61).

Scheme 2.61

136 (±) **137**

A comparison of three distinctive ring D ^{1}H NMR signals is shown in Table 2.6. Close agreement in the data for **135** and the compound **137** is noted, thereby giving confidence in the assignment.

Table 2.6: Comparison of ring D ^{1}H NMR signals for 14-methyl 17β-alcohols

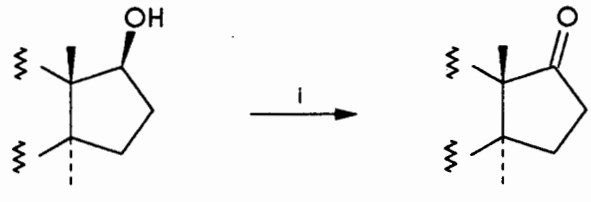
	Signal[a]		
Compound	13β-Me	14-Me	17α-H
135 (14α-Me)	0.89	0.88	4.13
136 (14β-Me)[b]	1.00	1.13	3.75
137 ±(14α-Me)[b]	0.89	0.89	4.16

[a]Given as δ_H

[b]See Scheme 2.61

Oxidation of the 17β-alcohol **135** up to the 17-ketone was carried out with Dess-Martin periodinane[84] and proceeded smoothly at 20 °C to give the 17-ketone **133** in 81% yield (Scheme 2.62). Comparing the melting point, optical rotation and 200 MHz ^{1}H NMR data of **133** to the known compound[22] once again closely agreed and confirmed the identity of the two compounds.

Scheme 2.62



135 **133**

I, Dess-Martin Periodinane

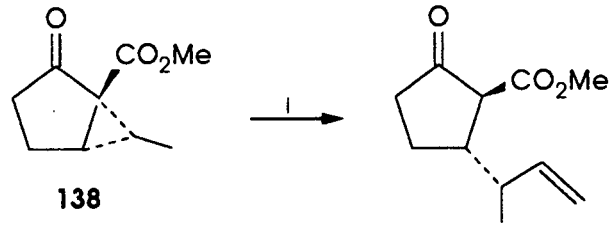
The above pair of correlative techniques clearly supports the assignment of the 14-methyl 16-ketone **132**. Seen in the context of the earlier explicit verification of the C(16)-configuration of the Δ^{14}-16-alcohol **92**, the assumptions about directed cyclopropanation on this allylic alcohol as indicated in Scheme 2.43 were clearly valid.

2.5 Reactivity of the 14,15α-Methylene 16-Ketone 119

In an attempt to further the synthetic objectives toward stereoselective C(14)-alkylation, the cyclopropyl ketone **119** was reacted with a selection of nucleophiles. The aim was to open the cyclopropyl ring, with concomitant functionalisation of the cyclopropyl residue.

It is known that organocuprate reagents add to α,β-cyclopropyl ketones in a 1,5-sense (i.e. 'homo-Michael' addition).[96] The reactivity of the electrophilic cyclopropyl ring usually relies on double activation by being in conjugation with two electron withdrawing groups, as shown for the cyclopentanoid compound **138** in Scheme 2.63.

Scheme 2.63

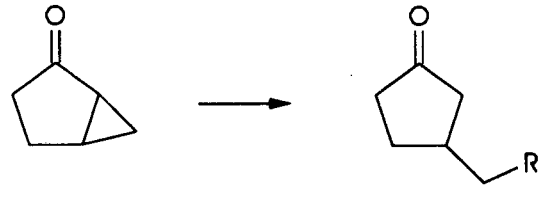


138

i, $(CH_2=CH)_2CuLi$

It has, however, also been shown that mono-activated systems do react with Lewis acid-modified organocuprate reagents[97] (Scheme 2.64). The increased nucleophilicity of the Lewis acid – organocuprate combination compensates for the diminished electrophilicity of the substrate.

Scheme 2.64

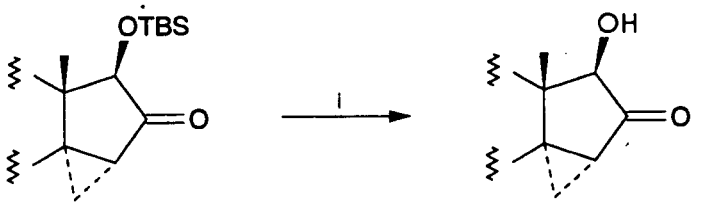


Other forms of ring opening – trapping reactions include the use of trimethylsilyl iodide, which gives γ-iodo ketones.[98,99] Sulfonic acids are also known to react under mild conditions to give the related γ-sulfonates. Further elaboration of these γ-functionalised intermediates usually proceed *via* a dissociative pathway with carbon nucleophiles.

To explore the scope for these types of transformations in the current study, the 14α,15α-methylene 16-ketone **119** was reacted with lithium dimethylcuprate – boron trifluoride-diethyl ether. However, during a reaction course of 90 min, over a temperature range of -78 to 0 °C, no reaction of the starting material was detected by TLC monitoring. It was concluded that the nucleophilicity of the cuprate-Lewis acid combination was insufficient to react with the mono-activated cyclopropyl system.

In a second attempted functionalisation of the cyclopropyl ring, the 14α,15α-methylene 16-ketone **119** was reacted with trimethylsilyl iodide at 0 °C for 30 min. However, the reaction was hydrolysis of the 17β-silyl ether by the Lewis acidic reagent (Scheme 2.65). Prolonged exposure failed to achieve any futher reaction.

Scheme 2.65

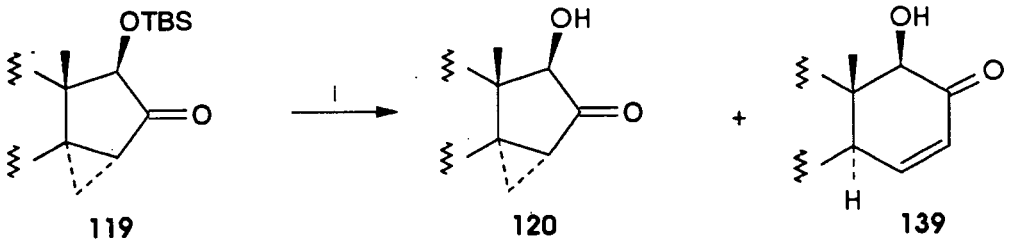


119 **120**

i, TMSCl, NaI

In a third attempt, the ketone **119** was reacted with *p*-toluene sulfonic acid in the hope to obtain the related 14-tosyloxymethyl compound. After an exposure of the material to the acid in refluxing benzene for 15 min, two products were isolated (Scheme 2.66). The minor product was identified as the 17-desilylated ketone **120** (28%), whereas the major reaction product (77%) was formulated as 17aβ-hydroxy-3-methoxy-17a-homoestra-1,3,5(10),15-tetraen-17-one **139**.

Scheme 2.66



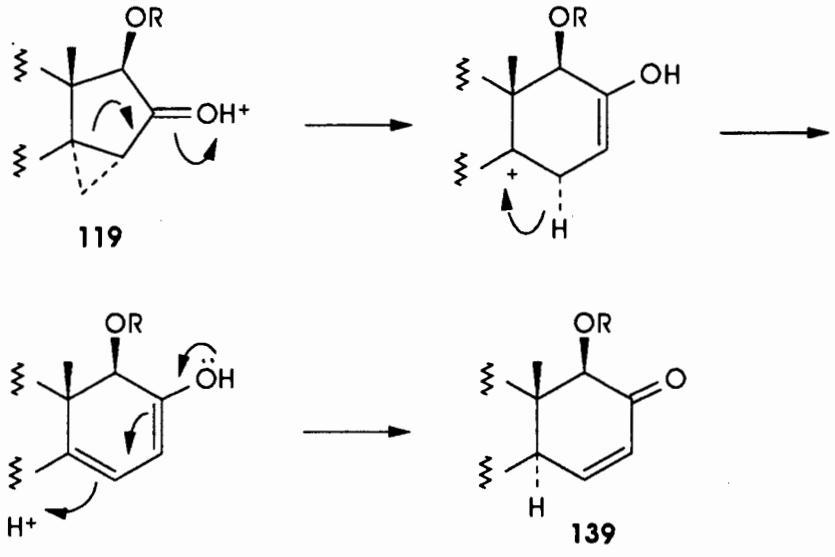
119 **120** **139**

i, *p*-TsOH

The infrared spectrum of **139** showed a carbonyl stretching frequency ν_{max} 1676 cm^{-1}, characteristic of a conjugated cyclohexenone system. From the ^1H NMR spectrum, a disubstituted olefinic bond was indicated by two vinylic signals for 15-H (δ 6.34, dd, *J* 10.2 and 1.8 Hz), and the 16-proton (δ 5.94, dd, *J* 10.2 and 3.2 Hz). The small magnitude of the vicinal coupling $J_{14\alpha,15}$ 1.8 Hz was ascribed to the near-orthogonal orientation between the coupling partners, as indicated by a molecular model. A COSY plot verified the allylic coupling $J_{14\alpha,16}$ 3.2 Hz. Support for the 14α-configuration was obtained from the coupling pattern of the 14-proton (δ 1.62, ddd, *J* 11.4, 3.2 and 1.8 Hz). The magnitude of $J_{8\beta,14}$ 11.4 Hz is indicative of an anti-periplanar arrangement and, therefore, requires the 14α-configuration.

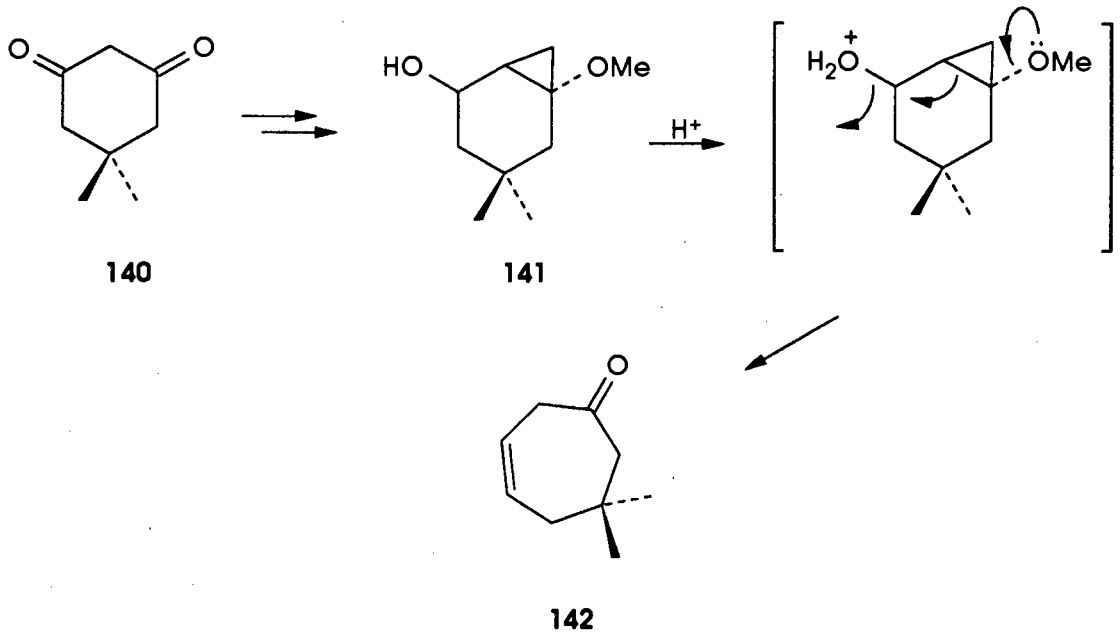
Mechanistically, formation of this product was described as following from protonation at the carbonyl oxygen of **119**, followed by cleavage of the 1′,2′ cyclopropyl bond. Rearrangement of the tertiary carbocation to give a dienyl system, followed by eventual protonation yields the D-homo enone **139** as indicated in Scheme 2.67.

Scheme 2.67



Although no immediate analogy for this type of acid-catalysed ring homologation of an α,β-cyclopropyl ketone was found, similar reactions of cyclopropyl systems are not unknown in the literature.[100] For example, Wenkert and co-workers converted dimedone **140** (Scheme 2.68) into the derived methoxy cyclopropyl alcohol **141**, followed by acid treatement to give a β,γ-unsaturated cycloheptenone **142**.[101] In this instance, ring-expansion occurred to quench the secondary carbocation that formed upon protonation and elimination of the hydroxyl group.

Scheme 2.68



140 141 142

In the light of the non-reactivity of the 14,15α-methylene 16-ketone **119** towards nucleophilic addition, and the propensity of the compound to undergo ring homologation under mildly acidic conditions, the approach of C(14)-alkylation by cyclopropanation - fragmentation – trapping was abandoned. The successful preparation of 14α-methyl compounds, including the alternative route to 14-methyl estrone, as well as the partial synthesis of four estriol analogues satisfied the exploitability of the cyclopropanation approach to 14- and 15-functionalised 19-norsteroids.

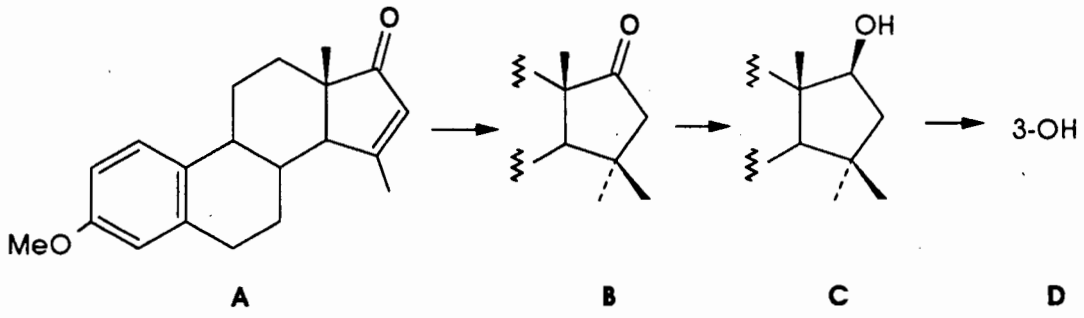
Chapter 3

SYNTHESIS OF RING D *gem*-DIALKYL 19-NORSTEROIDS

3.1 General Objectives

The introduction of 15-alkyl groups into the steroid nucleus has been well documented,[27,28,33-35] and the topic was discussed in Chapter 1 of this thesis. Surprisingly however, no work has been conducted on the structure-activity effects of geminal 15,15-dialkylation. As a consequence, it was aimed in this investigation to prepare, in the first instance, the 15,15-dimethyl analogue of estradiol and to determine the binding affinity of this modified hormone toward the estradiol receptor. The conceptual approach is shown in Scheme 3.1. A successful route to the synthesis of 3-methoxy-15-methylestra-1,3,5(10),15-tetraen-17-one **A** has been established in a separate study.[102] In the present investigation, conjugate methylation of the enone **A** was expected to give a 15,15-dimethyl 17-ketone **B** as key intermediate. Reduction of the 17-oxo group to give the 17β-alcohol **C**, followed by demethylation at C(3) was expected to yield the targeted hormone analogue **D**.

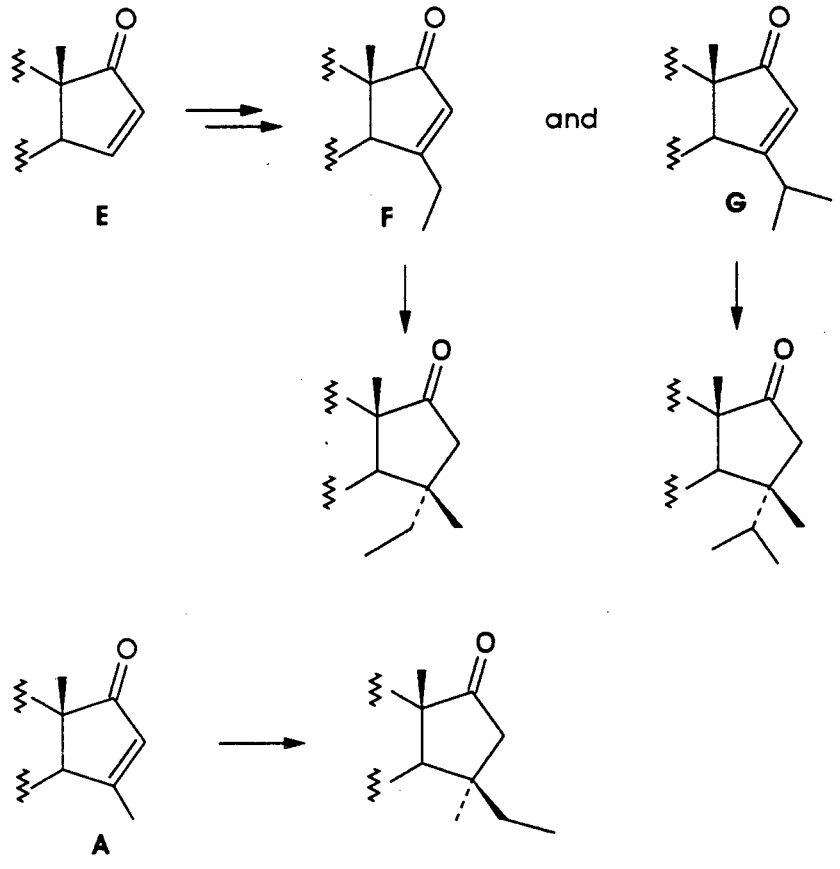
Scheme 3.1



A further aspect of this investigation was to determine the structure-activity relation associated with α- and β-face chain homologation or branching (i.e. Me → Et → *i*-Pr). By adjusting the alkyl substitution pattern at C(15), it would become possible to evaluate the extent to which steric bulk in this region can be accommodated during the receptor – substrate interaction. The approach adopted towards this synthetic objective was an extension of the successful route to the 15,15-dimethyl 17-ketone **B**. Thus, conjugate addition of an ethyl or isopropyl group onto the enone **E**, followed by dehydrogention was expected to give the corresponding 15-alkyl Δ^{15}-17-ketones **F** and **G** (Scheme 3.2). Conjugate methylation of these intermediates was argued to lead to stereodefined 15,15-dialkyl 17-ketones. Analogously, conjugate ethylation of the 15-methyl Δ^{15}-17-ketone **A**

was expected to give an epimeric 15-ethyl 15-methyl 17-ketone. Ample precedent exists for high stereoselectivity during conjugate addition to steroidal Δ^{15}-17-ketones, as was discussed in Chapter 1.

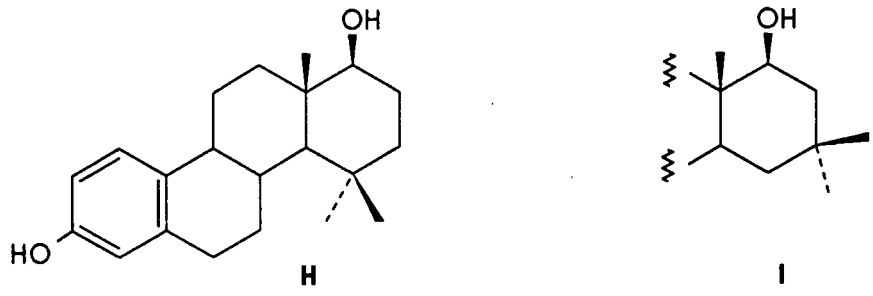
Scheme 3.2



The synthetic objectives towards 15,15-dialkyl substitution were adapted to include 15,15-dimethyl and 16,16-dimethyl analogues of 17a-homoestradiol (**H** and **I**, Scheme 3.3). Hereby, the effect of steric impedance on either the α- or β-faces of ring D as a possible inhibiting influence on metabolic degradation may be investigated.

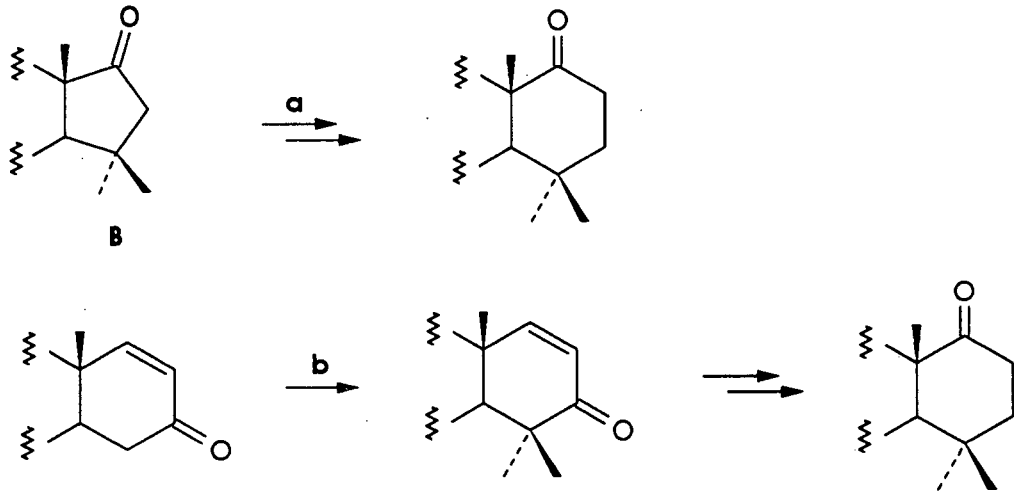
The presence of a 15β-methyl group in **H** would be expected to mimic the steric role of the same group at the β-face in **D**. Analogously, the axial 16α-methyl group in **I** would contribute a similar steric impedance on the α-face.

Scheme 3.3



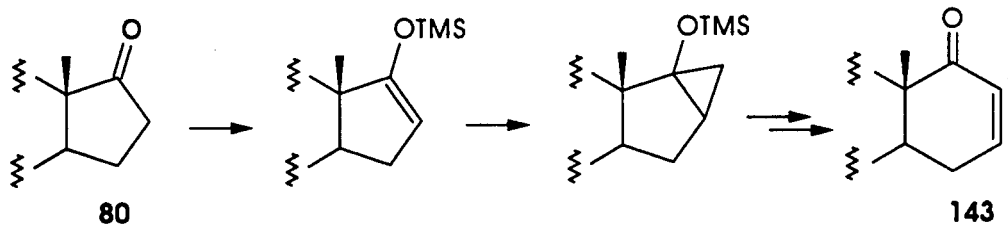
Two conceptual routes to the 15,15-dimethyl analogues of 17a-homoestradiol were considered. In the first, it was reasoned that ring expansion of the 15,15-dimethyl 17-ketone **B** would allow direct access to the target compound (Scheme 3.4, route **a**). An alternative, less direct route would involve 15,15-dimethylation of an appropriately functionalised 17a-homo precursor, followed by functional group transposition (Scheme 3.4, route **b**).

Scheme 3.4



A reaction sequence analogous to that depicted in route **a** was recently optimised by Mountford,[103] in which estrone 3-methyl ether **80** was homologated to give 3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one **144**.[107] This conversion involved an enolisation – trapping – cyclopropanation pathway, followed by iron(III) chloride ring expansion[104] (Scheme 3.5). By analogy, it was expected that a similar conversion would be possible on the 15,15-dimethyl 17-ketone **B**.

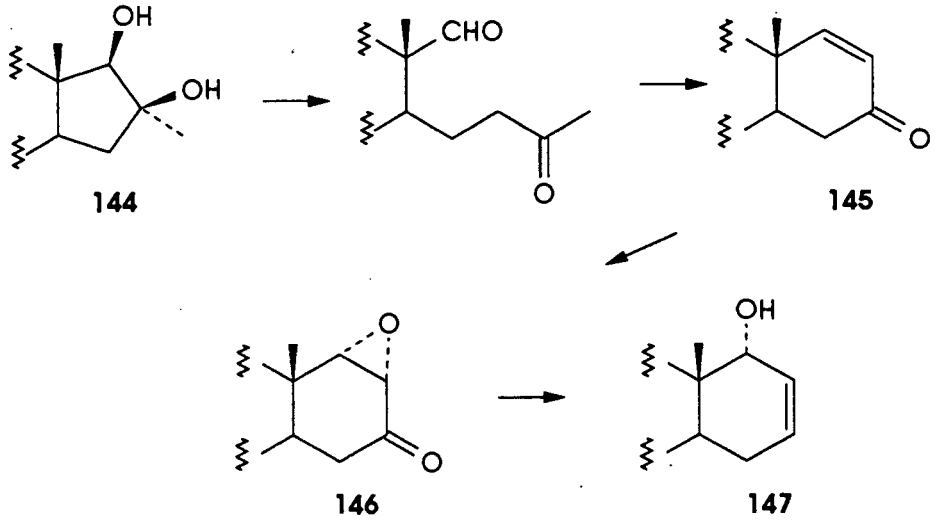
Scheme 3.5



80 **143**

The D-homo enone starting material indicated in route **b** of Scheme 3.4 is known in the patent literature[105] and was recently prepared[106] in a separate investigation from 3-methoxy-16α-methylestra-1,3,5(10),triene-16β,17β-diol **144**. It was shown that oxidative cleavage of the diol **144**, followed by base-mediated aldol closure gave 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one **145**. It was further shown[106] that the enone **145** readily underwent epoxidation to **146** and Wharton rearrangement to give the Δ^{16}-17aα-alcohol **147** (Scheme 3.6). Adaptation of this method was expected to lead to oxygen transposition as indicated as route **b** in Scheme 3.4.

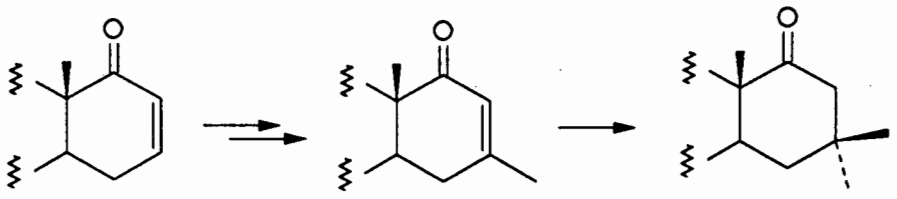
Scheme 3.6



144 **145** **146** **147**

Access to the 16,16-dimethyl analogue of 17a-homoestradiol was envisaged through sequential conjugate methylation – dehydrogenation of the known[107] Δ^{16}-17a-homo 17a-ketone **143**, followed by a second conjugate methylation (Scheme 3.7).

Scheme 3.7



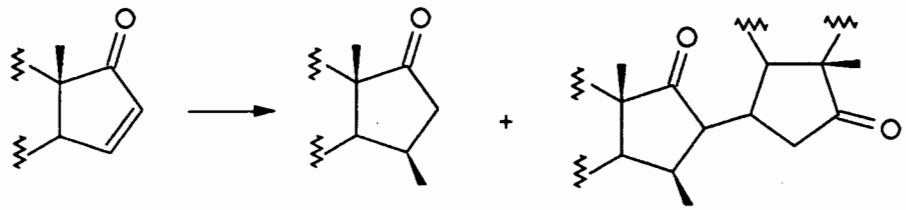
143

3.2 Synthesis and Properties of 15,15-Dialkylestradiols

3.2.1 Synthesis of 15,15-dialkyl compounds. The key intermediate in the synthetic route to 15,15-dimethylestradiol, namely 3-methoxy-15-methylestra-1,3,5(10),15-tetraen-17-one **158**, has been successfully prepared in a previous study.[102] The following overview briefly describes the optimised reaction conditions, as well as alternatives considered during the synthetic approach.*

Thus, conjugate methylation of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **148** was carried out with lithium dimethylcuprate, to give the known[28] 15β-methyl 17-ketone **149** in a 60% yield (Scheme 3.8). The spectroscopic properties of the 15β-methyl 17-ketone were compatible with the assigned structure, in that a 3-proton doublet (δ 1.16, *J* 7.4 Hz) was observed for the 15β-methyl group in the 400 MHz ^{1}H NMR spectrum. It was not possible to clearly extract the signal for the 15α-proton, but a COSY plot verified the assignment of the coupling $J_{14\alpha,15\alpha}$ 6.8 Hz. This requires a near-gauche relationship between the 14α- and 15-protons, therefore an obligatory β-configuration for the 15-methyl group. Further support in favour of the assigned configuration was obtained from spectroscopic evidence of a derived product (see later).

Scheme 3.8

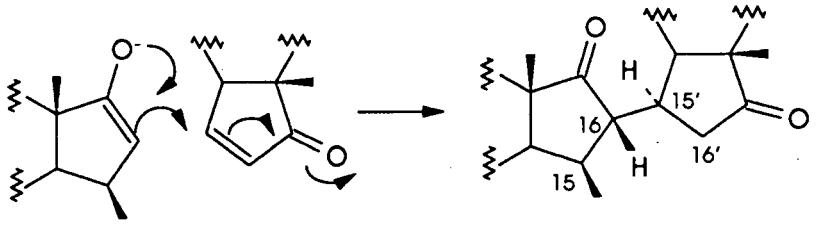


148 149 150

* Aspects of this work will appear in *J. Chem. Soc., Perkin Trans I*

A non-crystalline by-product (*ca* 30%) from the above reaction displayed mass and spectral properties consistent with a bisteroid structure, formulated as 3-methoxy-16α-[3-methoxy-17-oxoestra-1,3,5(10)-trien-15β-yl]-15β-methylestra-1,3,5(10)-trien-17-one **150** (30%). Thus, a molecular ion at *m/z* 580 suggested a methyl bisteroidal diketone. Furthermore, ^{13}C signals originating from ring D carbons appeared in duplicate, whereas the remainder of the signals overlapped, giving peaks of double intensity. It was thought that this by-product arose by a competitive Michael-type condensation, involving the lithium enolate of **149** and the unreacted enone **148** (Scheme 3.9).

Scheme 3.9

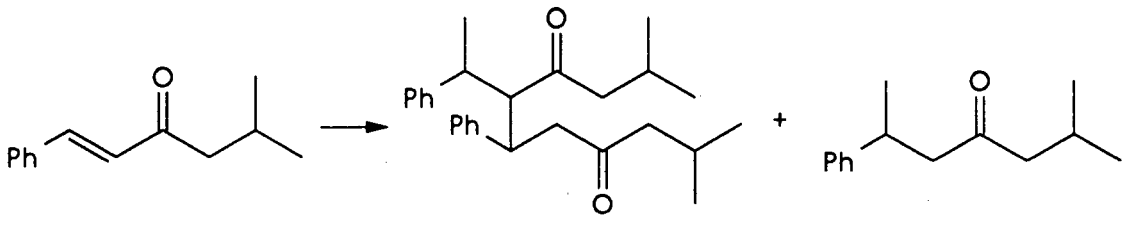


150

No irrefutable proof of the stereochemical assignment of the C(16)–C(15′) bond as indicated in Scheme 3.9 was offered. It was, however, assumed that conjugate addition of the steroidal enolate of **149** to the Δ^{15}-17-ketone **148** would form a 15β-bond with the latter compound, and at the same time, be obliged to react from the sterically less impeded α-face at C(16).

A literature search revealed that only one analogous reaction has been reported to date. From the lithium dimethylcuprate conjugate alkylation of styryl isobutyl ketone **151**, Blanch and co-workers[108] reported the isolation of a secondary reaction product (Scheme 3.10). The structure of their by-product was elucidated as 2,10-dimethyl-6-phenyl-5-(1-phenyl)ethylundecane-4,8-dione **152** (60%).

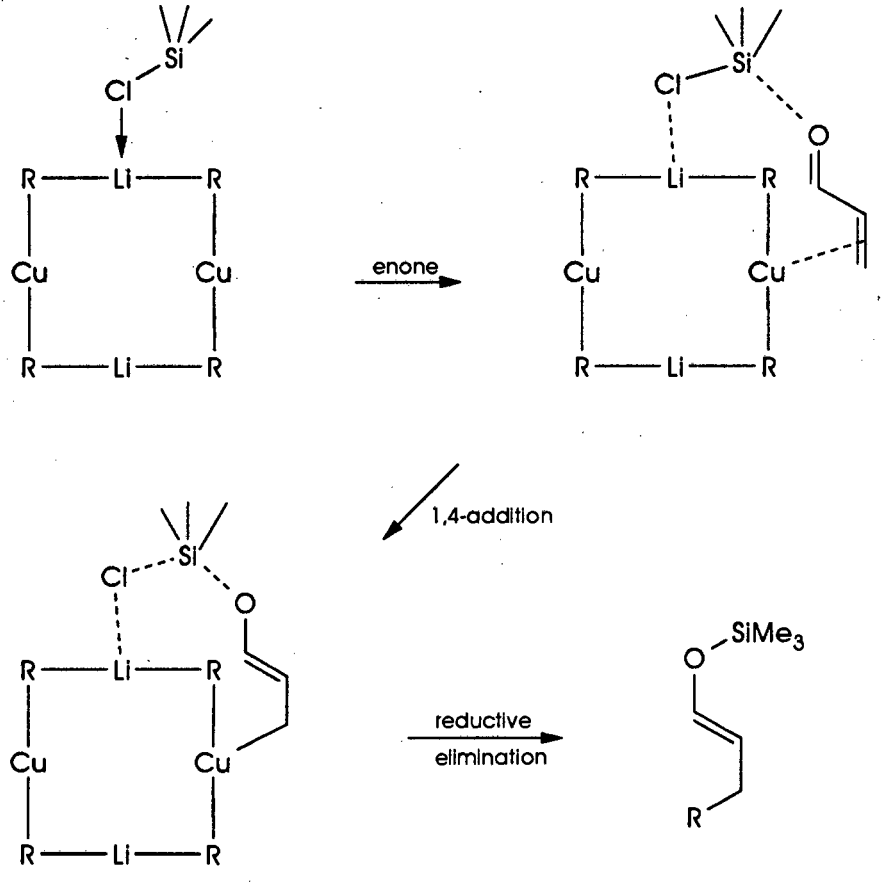
Scheme 3.10



151 **152** (60%) **153** (30%)

Optimisation of the conjugate methylation of the Δ^{15}-17-ketone **148** was based upon reports by Alexakis[58] and Johnson.[109] In their work, a method was proposed in which addition of the substrate to the cuprate was preceded by an addition of chlorotrimethylsilane (TMSCl).* Trapping of the enolate from conjugate alkylation therefore occurs as it is generated, and not during work-up, as is more conventional. The former idea was founded upon evidence that reaction between an organocuprate and TMSCl is very slow at low temperatures.[110] A low-temperature (-80 °C) ^{7}Li NMR experiment by Lipshutz[111] revealed that TMSCl acts as a Lewis base toward the cuprate, with a Cl–Li interaction playing the major role. This association was established by the change in chemical shift of the Li-signal of $\Delta\delta$ 0.13, introduced by the addition of 1 molar equivalent of TMSCl. Given that ^{7}Li NMR spectroscopy merely ranges *ca* 4 ppm, this increment was regarded as a significant change in chemical shift. A proposed sequence of events for TMSCl-accelerated 1,4-addition is indicated in Scheme 3.11.

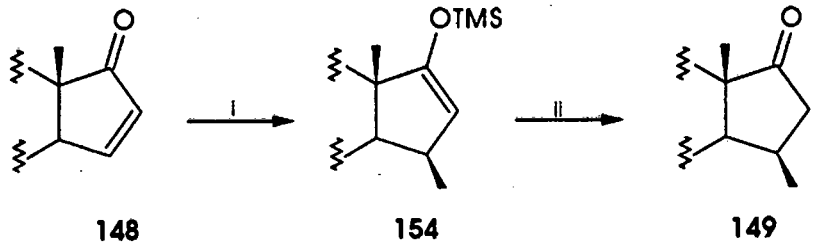
Scheme 3.11



* See footnote on page 31.

In a conjugate methylation experiment of the enone **148** with lithium dimethylcuprate – TMSCl at -78 °C (Scheme 3.12), the silyl enol ether **154** was isolated as as an only product. The latter could be isolated, but was not fully characterised. Hydrolysis of the silyl ether **154** gave the 15β-methyl 17-ketone **149** (92%).

Scheme 3.12

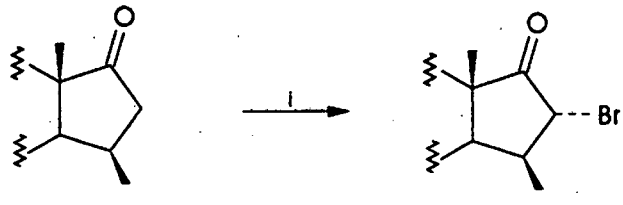


148 **154** **149**

I, Me_2CuLi-TMSCl; ii, HCl

With the 15β-methyl 17-ketone **149** in hand, methods for the introduction of Δ^{15}-unsaturation were investigated. Initially, a bromination – dehydrobromination route was examined. Treatment of **149** with copper(II) bromide in refluxing methanolic benzene gave a single product, namely 16α-bromo-3-methoxy-15β-methylestra-1,3,5(10)-trien-17-one **155**, in 82% yield.

Scheme 3.13



149 **155**

I, $CuBr_2$, MeOH-C_6H_6

This 16α-bromo ketone **155** displayed ^1H NMR spectral features uniquely compatible with the assigned structure, thereby imparting additional support in favour of the 15β-methyl assignment. The equivalent coupling of the 15-proton (δ 2.75, d quint, *J* 4 x 7.8 and 1.8 Hz) to both the 15-methyl group and the 14α-proton as verified by a COSY plot, requires a *syn* relationship between 14α- and 15-H, and, necessarily, a 15β-methyl group. Further, the coupling $J_{15,16}$ 1.8 Hz requires near-orthogonality of the 15- and 16-protons, a configuration only attainable through 16α-bromination. Inversion of the stereochemistry at

either or both of C(15) and C(16) would have led to significant differences in the observed couplings. A perspective view of ring D is shown in Figure 3.14.

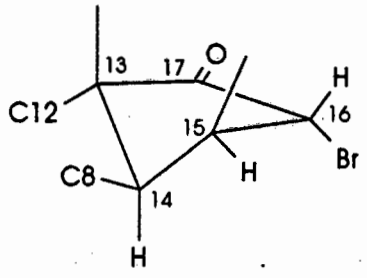
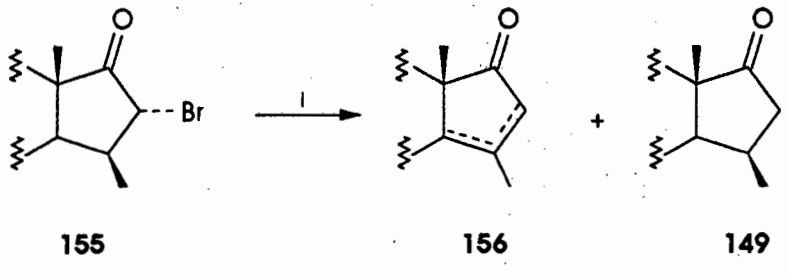


Figure 3.14: Substitution pattern in 16α-bromo 15β-methyl 17-ketone **155**

Owing to the unfavourable *syn* orientation between 15α-H and the 16α-Br, the dehydrobromination of the 16α-bromo ketone **155** with lithium carbonate and lithium bromide in refluxing dimethylformamide proceeded slowly and inefficiently (Scheme 3.15), and gave an inseperable mixture of Δ^{14} and Δ^{15}-17-ketones **156** (54%), as well as some debrominated material, i.e. the 15β-methyl 17-ketone **149** (23%).

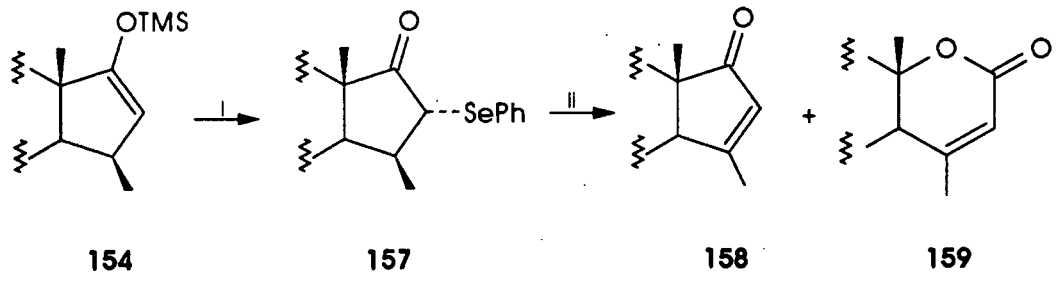
Scheme 3.15



I, LiBr, Li_2CO_3, DMF, Δ

As a more practical alternative, a *syn*-elimination route involving a 16-phenylselenoxide intermediate was considered. Conversion of the enol silyl ether **154** into the 16α-phenylselenide **157** (Scheme 3.16) proceeded in 80% yield. This labile compound was not fully characterised, but a mass spectrum displayed a base peak *m/z* 453, which was consistent with the expected molecular ion. Further, a 200 MHz ^{1}H NMR spectrum indicated a similarity in the coupling pattern for the 16-proton in **157** (δ 3.84, d, *J* 1.9 Hz) relative to that of the 16α-bromo 15β-methyl 17-ketone **155** (δ 4.37, d, *J* 1.8 Hz). Therefore, it was inferred that the phenylselenenyl group in **157** was present on the α-face of the ring, in a configuration suitable for *syn* elimination.

Scheme 3.16



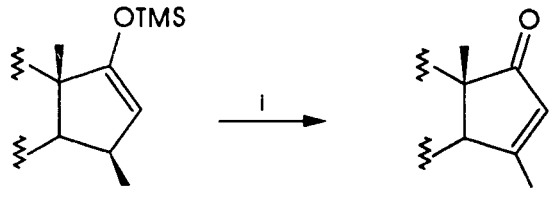
154 **157** **158** **159**

I, $PhSeCl$, $BF_3.Et_2O$; II, H_2O_2

Oxidation with hydrogen peroxide occurred within 1.5 h with concomitant thermolysis at 20 °C to give a mixture of two products (Scheme 3.16). The secondary product was identified as the desired 15-methyl Δ^{15}-17-ketone **158** (40%), whereas the main reaction product (45%) was formulated as 3-methoxy-15-methyl-17a-oxa-17a-homoestra-1,3,5(10),15-tetraen-17-one **159**. A competing Baeyer-Villiger oxidation of the enone **158** was argued to give rise to this lactone. This assignment was based on spectral evidence, as well as literature analogy.[112] In the latter instance, it was shown that treatment of estrone 3-methyl ether with phenylselenenyl chloride, followed by oxidative elimination gave exclusively the related unsaturated δ-lactone.

A third and most efficient route to the 15-methyl Δ^{15}-17-ketone **17** made direct use of the silyl enol ether **154** (Scheme 3.17). Thus, reaction of **154** with palladium(II) acetate in refluxing acetonitrile[43] achieved dehydrosilylation to give the desired enone **158** in 82% yield.

Scheme 3.17



154 **158**

I, $Pd(OAc)_2$, MeCN, Δ

A 200 MHz ^1H NMR spectrum of **158** clearly indicated a trisubstituted olefinic bond by a signal in the vinylic region for the 16-proton (δ 5.77, s). The signal for the 15-methyl group appeared at δ 2.25 as a singlet.

To conclude this concise overview, it is almost redundant to emphasise the superiority of this latter synthetic approach to the 15-methyl Δ^{15}-17-ketone **158**. The 'one pot' conjugate methylation – enolate silylation gave an optimum yield of 15β-methylated material and eliminated the need for a separate deprotonation – trapping step to generate the silyl enol ether. Further, the 15-methyl Δ^{15}-17-ketone **158** was obtained as an exclusive product under relatively mild reaction conditions.

In the present investigation, introduction of the geminal 15-methyl group onto the 15-methyl Δ^{15}-17-ketone **158** was carried out with lithium dimethylcuprate in the presence of boron trifluoride–diethyl ether ($BF_3.Et_2O$).[113] This modification in the reagent was made to overcome any possible steric hindrance of the 15-methyl group on the desired reaction outcome. The influence of the $BF_3.Et_2O$ on the events leading ultimately to carbon-carbon bond formation is described in the following discussion.

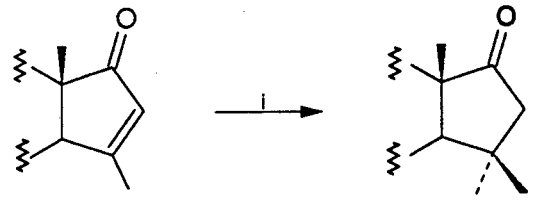
It has been recognised for some time that conjugate alkylation reactions could be enhanced by the addition of Lewis acids, prior to introduction of the substrate.[114,115] The presumed effect of the additive was that of substrate activation via complexation to the oxygen of an α,β-unsaturated carbonyl system. However, it recently came to light that this assumption may represent only a partial truth. In a composition study on the effects of boron trifluoride–diethyl ether ($BF_3.Et_2O$) on lower order organocuprates (i.e. R_2CuLi), Lipshutz and co-workers have reported on a two-fold role of the Lewis acid.[113] In addition to substrate activation, $BF_3.Et_2O$ served to modify the structure of the cuprate reagent itself, affording a more reactive, modified cuprate-Lewis acid combination. Upon ^1H NMR examination of Me_2CuLi, containing two equivalents of $BF_3.Et_2O$ at -80 °C, the immediate appearance of three new signals, over and above the expected signal at δ -1.5[116] was observed. These new peaks were rationalised in terms of the actual 'sequestration' of MeLi by $BF_3.Et_2O$ from the dimeric Me_2CuLi (i.e. $Me_4Cu_2Li_2$), hence

$$(Me_2CuLi)_2 + BF_3.Et_2O \rightarrow MeLi.BF_3 + Me_3Cu_2Li + Et_2O$$

The ratio of the singlet at δ -0.35 to that at δ -1.31 was *ca* 1:2, as expected for Me_3Cu_2Li, which contains magnetically nonequivalent methyl groups. Over a period of 1.5 h, further build-up of Me_2Cu_2Li and $MeLi.BF_3$ occurred at the expense of Me_2CuLi, to a total of *ca* 80% of the total mixture. All of these changes occurred *before* substrate introduction, and these findings uphold the assumption that modification of the original cuprate by the Lewis acid had taken place. In the presence of $BF_3.Et_2O$, the major contributor towards product formation, for the case of lower order organocuprates, therefore has to by Me_3Cu_2Li.

Thus, treatment of the 15-methyl Δ^{15}-17-ketone **158** with lithium dimethylcuprate and $BF_3.Et_2O$ gave the 15,15-dimethyl 17-ketone **160** in 70% yield (Scheme 3.18). A 400 MHz ^1H NMR spectrum of **160** revealed the expected features associated with a 15,15-dimethyl substituted 17-ketone. The geminal methyl groups resonated at δ 1.28 and 1.29 respectively, and the signals for the 16-protons were clearly visible at δ 2.09 (d, *J* 19.4, 16α-H) and δ 2.61 (d, *J* 19.4, 16β-H). In addition, the signal for the 14α-proton was easily identified as an isolated doublet at δ 1.47 (d, *J* 10.9 Hz). A COSY plot is illustrated in Figure 3.19.

Scheme 3.18



158 **160**

i, Me_2CuLi, $BF_3.Et_2O$

During the conjugate methylation of the 15-methyl Δ^{15}-17-ketone **158**, none of the dimerisation product, as reported to occur during the conjugate methylation of the Δ^{15}-17-ketone **148** (Scheme 3.8), was observed. This is not surprising, as the steric environment brought about by geminal methyl substitution at C(15) precluded the condensation leading to the formation of bisteroidal material.

With the 15,15-dimethyl 17-ketone **160** in hand, the 17-oxo group was reduced with lithium aluminium hydride at 0 °C in tetrahydrofuran to give exclusively the corresponding 17β-alcohol **161** in 85% yield (Scheme 3.20). The C(17)-configuration was assigned from the appearance of the 17-proton (δ 3.71, dd, *J* 10.2 and 7.9 Hz) in the ^1H NMR spectrum. For the 17α-alcohol, the expected couping pattern for the 17β-proton would resemble that of a triplet, with near-equivalent couplings to the vicinal 16-protons. These characteristic splitting patterns of the 17-proton are a well-established probe into the configuration of 17-alcohols.[117] Demethylation at C(3) of **161** was routinely carried out with diisobutylaluminium hydride (DIBAH) in refluxing toluene[87] and gave 15,15-dimethylestra-1,3,5(10)-triene-3,17β-diol **162** in 90% yield (Scheme 3.20).

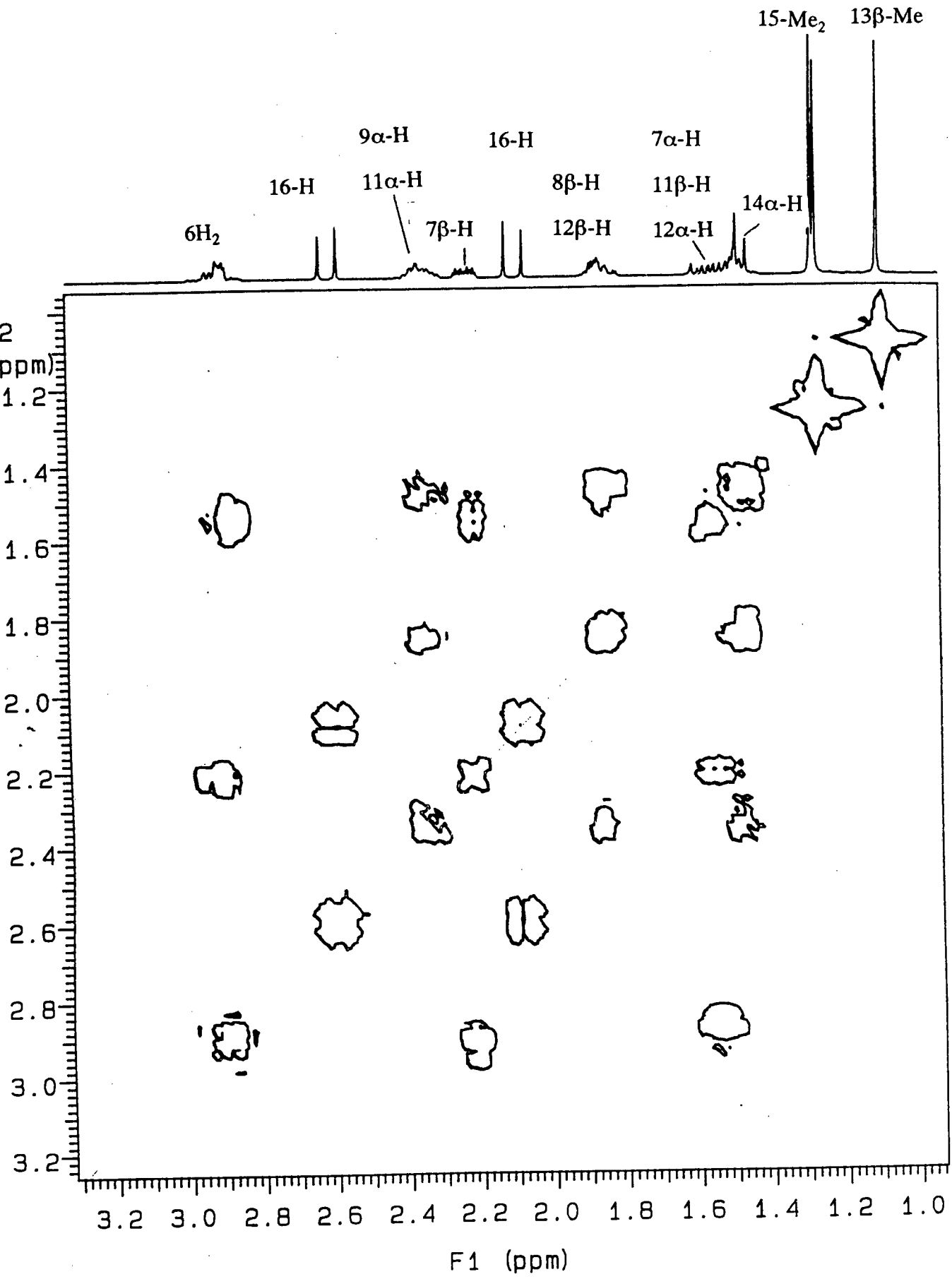
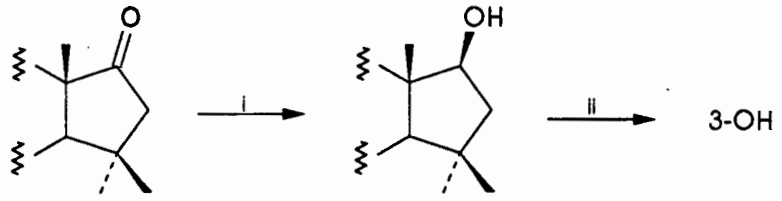


Figure 3.19: COSY plot of 15,15-dimethyl 17-ketone **160**

Scheme 3.20



160 **161** **162**

i, $LiAlH_4$; ii, DIBAH

Biological evaluation of this hormone analogue revealed both high competitive binding to the estradiol receptor, as well as high oral estrogenicity. To investigate the structure–activity implications of this finding, further 15,15-dialkyl estradiol analogues were prepared in order to evaluate the influence of α- and β-face chain homologation or branching (i.e. Me → Et → *i*-Pr) upon receptor binding affinity.

The introduction of chain extended alkyl groups to the Δ^{15}-17-ketone **148** through conjugate alkylation by organocuprate methodology was impractical, owing to difficulties in the handling of the precursor alkyllithium reagents. Therefore, copper-catalysed Grignard reagents were utilised to achieve the desired 1,4-alkylation. Although this type of reagent combination is well documented in the review literature,[115] no definite report exists on the solution composition of the Grignard reagent – copper salt combination. As a consequence, the nature of the active reagent is rather speculative at this stage. A composition study[118] on equimolar amounts of copper(I) iodide and methylmagnesium bromide in tetrahydrofuran at -85 °C afforded a heterogeneous solution, with *ca* one third of the copper salt in solution. A ^{1}H NMR experiment carried out at -85 °C revealed the formation of Me_3CuMg, as shown below.

$$CuBr + 3\ MeMgBr \rightarrow Me_3CuMg + 2\ MgBr_2$$

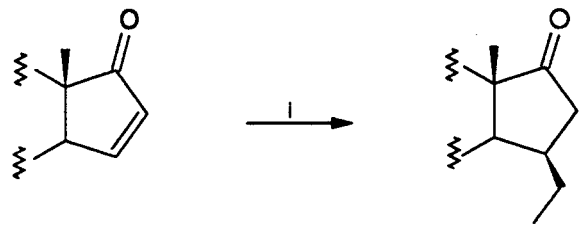
Adding a three fold excess of Grignard reagent and warming of the solution to -30 °C gave more of the magnesium cuprate species, as all of the copper salt dissolved. It was further reported that over a period of time in the temperature range -60 to -40 °C, other copper complexes, like MeCu, Me_6Cu_4Mg and Me_8Cu_6Mg were formed.

The identity of these organocopper complexes was found to be dependent on the extent of copper bromide solvation, and each exhibited a different stability profile.[118] Therefore, the assumption was made that carbon-carbon bond formation in a copper-

catalysed Grignard conjugate alkylation reaction possibly proceeds via an organomagnesium cuprate species, the nature of which is dictated by the relative amounts of Grignard reagent and copper salt.

In the present study, the Δ^{15}-17-ketone **148** was reacted at 20 °C in tetrahydrofuran with ethylmagnesium bromide in the presence of a catalytic amount (*ca* 10 mol %) of copper(I) iodide. A single product, formulated as 15β-ethyl-3-methoxyestra-1,3,5(10)-trien-17-one **163** (Scheme 3.21) was isolated in 87% yield. Chromatographic purification was not required and a single recrystallisation gave material of analytical purity.

Scheme 3.21



148 **163**

I, EtMgI, CuI

The ^{1}H NMR spectrum of the 15β-ethyl 17-ketone **163** clearly indicated the presence of the ethyl group. A triplet was observed for 15-CH_2*Me* (δ 0.95, t, *J* 7.5 Hz), whereas the diastereotopic 15-C*H*$_2$Me protons resonated at δ 1.34 and 1.65 respectively. Owing to the complexity in the coupling patterns of these protons to their respective five neighbours (i.e. geminal to each other and vicinal to the 15-proton and CH_2*Me*-protons), clear interpretation of the signals was not possible. The 16-protons resonated as doublets of doublets at δ 2.37, *J* 19.4 and 2.5, 16β-H), and δ 2.43 (*J* 19.4 and 7.8, 16α-H). Unfortunately, the signal for the 14α-proton is obscured. An assessment of the C(15)-configuration through the coupling $J_{14\alpha,15}$ was therefore not possible. However, the magnitude of the coupling $J_{15,16\beta}$ 2.5 Hz indicates near orthogonality, therefore a 15α-proton. This requirement translates into a 15β-orientation for the 15-ethyl group. Hence, copper-catalysed conjugate ethylation of the Δ^{15}-17-ketone with ethylmagnesium bromide gave the expected product of 15β-alkylation.

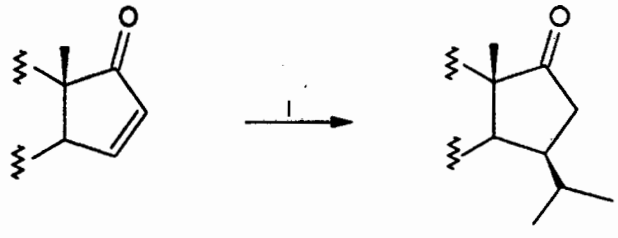
In a similar conjugate alkylation experiment, the Δ^{15}-17-ketone **148** was reacted with isopropylmagnesium bromide and copper(I) iodide. However, the 15β-isopropyl 17-ketone **164** was isolated in a very low yield and significant amounts of starting material was recovered (*ca* 80%). Almost complete heterogeneity in the reaction medium was noted.

These difficulties were overcome by applying the methodology by Nakamura and co-workers.[119] It was reported that copper(I) iodide – dimethyl sulfide (CuI.SMe_2) showed

greater medium tolerance, especially in the presence of hexamethylphosphoric triamide (HMPA) as co-solvent. The latter was also reported to impart improved solubility to the copper species involved in carbon-carbon bond formation (see previous discussion). Further, the addition of chlorotrimethylsilane to the reagent *during the reaction course* was shown to significantly accelerate the reaction rate. A possible explanation of the latter phenomenon was offered in terms of substrate activation by coordination to the oxygen of the carbonyl group. With this reagent combination, successful conjugate addition of Grignard reagents was reported[119] to occur at low temperatures (i.e. 0 °C, or less).

In the present case, a solution of the Δ^{15}-17-ketone **148** in tetrahydrofuran and chlorotrimethylsilane was added to a reagent mixture of isopropylmagnesium bromide – $CuI.SMe_2$ – HMPA in diethyl ether at 0 °C (Scheme 3.22). Complete homogeneity in the reaction medium was noted, and the yield of the 15β-isopropyl 17-ketone **164** was significantly increased to 88%.

Scheme 3.22



148 **164**

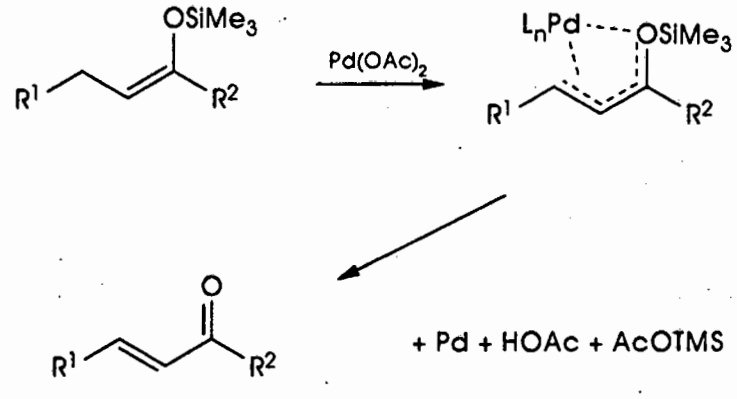
i, *i*-PrMgBr, $CuI.SMe_2$, TMSCl

In the ^{1}H NMR spectrum of **164**, the methyl resonances of the isopropyl group were clearly visible at δ 0.96 and 1.10 (each d, *J* 6.4 Hz). The pair of 16-protons resonated at δ 2.38 (dd, *J* 19.2 and 3.1 Hz, 16β-H) and δ 2.44 (dd, *J* 19.2 and 7.0 Hz, 16α-H). The magnitude of the coupling $J_{15,16\beta}$ 3.1 Hz is comparable to the analogous coupling in the 15β-ethyl 17-ketone **163** ($J_{15,16\beta}$ 2.5 Hz). Further, coupling $J_{8\alpha,15}$ for the 15β-isopropyl compound **164** (*J* 6.0 Hz) is very similar to that of the 15β-methyl 17-ketone **149** (*J* 6.8 Hz). This requires a near-gauche orientation between the 14α- and 15-protons, which, in turn, indicates an obligatory 15β-alkyl group.

With the 15β-ethyl and 15β-isopropyl 17-ketones **163** and **164** in hand, the next step in the synthetic scheme was to introduce the Δ^{15}-unsaturation. From the earlier work conducted on the 15β-methyl compound, the superiority of a palladium-mediated dehydrosilylation[43] route was clearly evident. The mechanism of this dehydrosilylation reaction is thought to involve an oxo-π-allylpalladium(II) complex[120] and the entire process

can be seen as the reverse of transition metal-induced 1,4-addition of hydrosilanes to α,β-unsaturated carbonyl compounds[121] (Scheme 3.23). The reaction is stoichiometric with respect to palladium acetate, but the introduction of benzoquinone, to regenerate an active Pd^{II} species, has been reported to diminish the requirement to 0.5 mol. equiv. $Pd(OAc)_2$. All attempts by Saegusa and co-workers[43] to generate a catalytic cycle by increasing the amount of benzoquinone at the expense of the palladium salt failed.

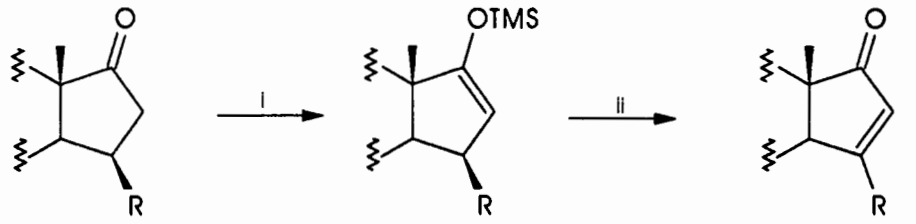
Scheme 3.23



Thus, the 15β-ethyl 17-ketone **163** was converted into the derived silyl enol ether **165** in the standard way by low-temperature deprotonation with lithium diisopropylamide and trapping with chlorotrimethylsilane (Scheme 3.24). Neither purification, nor characterisation of the silyl enol ether **165** was performed, and the total crude product was treated with palladium(II) acetate in refluxing acetonitrile (Scheme 3.24). Chromatography of the reaction product gave 15-ethyl-3-methoxyestra-1,3,5(10),15-tetraen-17-one **167** in 85% yield. An infrared spectrum of this enone showed a carbonyl stretching frequency at ν_{max} 1689 cm^{-1}, indicative of an α,β-unsaturated carbonyl group. The ^1H NMR spectrum of **167** showed similar features to that of the 15-methyl Δ^{15}-17-ketone **158**, in that a signal in the vinylic region was observed for the olefinic 16-proton as a broad singlet (δ 5.79). Resolution enhancement techniques failed to resolve the fine structure. The 15-CH_2*Me*-protons resonated at δ 1.20 (t, *J* 2 x 7.6 Hz) and the diastereotopic 15-CH_2Me-protons were observed as a two-proton multiplet (δ 2.35–2.46).

Similar treatment of the 15β-isopropyl 17-ketone **164** gave 15-isopropyl-3-methoxyestra-1,3,5(10)-15-tetraen-17-one **168** in 85% yield (Scheme 3.24).

Scheme 3.24



163 (R = Et)
164 (R = Pr^i)

165 (R = Et)
166 (R = Pr^i)

167 (R = Et)
168 (R = Pr^i)

I, LDA-TMSCl; II, $Pd(OAc)_2$, MeCN, Δ

The ^{1}H NMR spectrum of **168** showed the vinylic 16-proton at δ 5.80 (dd, *J* 2.7 and 1.2 Hz). From a COSY, plot these connectivities were identified as four-bond couplings to the allylic neighbours, thus $J_{14\alpha,16}$ 2.7 and $J_{15\text{-}CH\text{Me}Me,16}$ 1.2 Hz, respectively. The orthogonality required for allylic coupling between the 8α- and 16-protons was clearly evident from a molecular model. It was inferred that reduction in the rotational mobility of the sterically demanding isopropyl group causes the 15-C*H*Me$_2$ and 16-protons to reside in an orthogonal orientation. This phenomenon is not observed in the analogous ethyl and methyl compounds, owing to higher rotational freedom of these alkyl groups. Free rotation, in these instances, causes the 16-H resonances to appear as broad singlets. The apparent rotational preferences of the various 15-alkyl groups are discussed later.

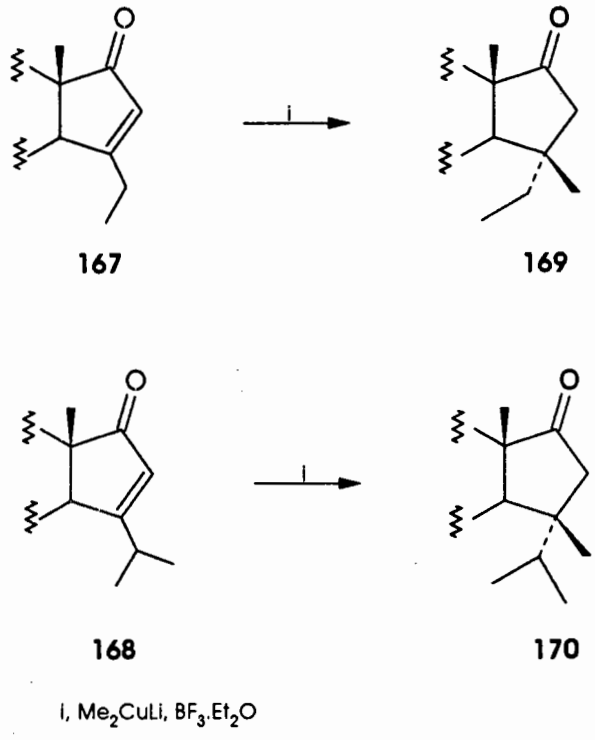
With the 15-ethyl- and 15-isopropyl Δ^{15}-17-ketones **167** and **168** in hand, the next step in the synthetic plan was to perform conjugate methylations on these enones. The precedent of β-face reagent entry was expected to lead to 15α-ethyl 15β-methyl- and 15α-isopropyl 15β-methyl 17-ketones. Similarly, conjugate ethylation of the 15-methyl Δ^{15}-17-ketone **158** was expected to yield an epimeric compound, i.e. a 15α-methyl 15β-ethyl 17-ketone. Finally, conjugate ethylation of the 15-ethyl Δ^{15}-17-ketone **167** was expected to give a 15,15-diethyl 17-ketone.

Thus, reaction of the 15-ethyl Δ^{15}-17-ketone **167** with lithium dimethylcuprate and boron trifluoride – diethyl ether gave 15α-ethyl-3-methoxy-15β-methylestra-1,3,5(10)-trien-17-one **169** in 81% yield. In a similar fashion, 15α-isopropyl-3-methoxy-15β-methylestra-1,3,5(10)-trien-17-one **170** was prepared in an 86% conversion (Scheme 3.25). Both of these reactions gave single, highly crystalline products. No suggestion of diastereomeric mixtures was evident from the narrow melting point ranges.

The ^{1}H NMR spectra of **169** and **170** clearly showed the singlet resonances of the newly introduced 15β-methyl groups at δ 1.25 and 1.32, respectively. These were differentiated from the angular 13β-methyl groups by comparison of chemical shift values.

For the 15α-ethyl 15β-methyl 17-ketone **169**, the diastereotopic 15α-C*H*$_2$Me-protons resonated at δ 1.36 and 1.76 (each dq, *J* 14.8 and 3 x 7.4 Hz), whereas the signal for 15β-CH$_2$*Me* appeared at δ 0.89 (t, *J* 7.4 Hz). The 15β-CH*Me*$_2$ protons of the 15α-isopropyl 15β-methyl 17-ketone **170** gave a pair of three-proton doublets at δ 0.87 and 0.89 (*J* 6.7 Hz), which in turn coupled to the 15β-C*H*Me$_2$ proton, to give a seven-line splitting at δ 1.94 (sept, *J* 6 x 6.7 Hz). Remaining signals originating from ring D protons for both of the above pair of 15,15-dialkyl 17-ketones comprised those of the 14α-proton (δ 1.49, d, *J* 10.1 Hz), and the AB-multiplets for the 16α-H (δ *ca* 2.2, d, *J* 19.4 Hz) and 16β-H (δ *ca* 2.3, d, *J* 19.4 Hz). These are consistent with those observed for the 15,15-dimethyl 17-ketone **160**, as indicated in Table 3.1.

Scheme 3.25



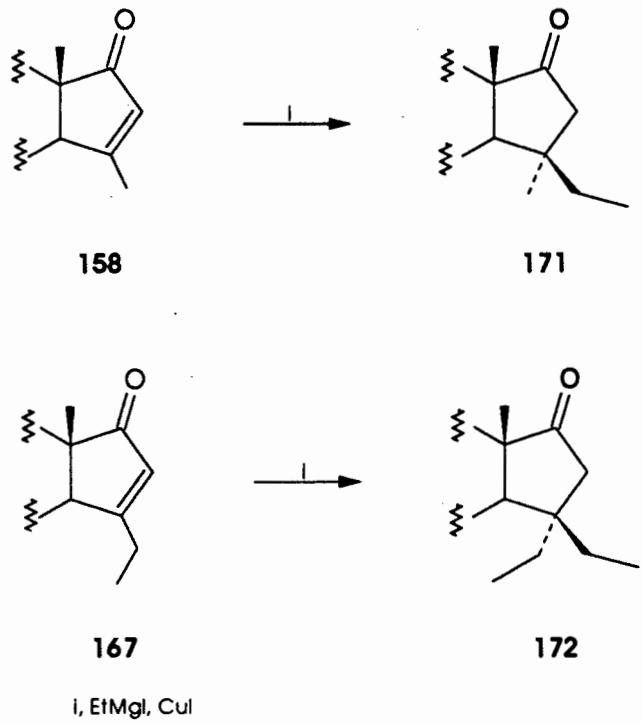
Reacting the 15-methyl Δ^{15}-17-ketone **158** with ethylmagnesium iodide and copper(I) iodide gave 15β-ethyl-3-methoxy-15α-methylestra-1,3,5(10)-trien-17-one **171** in a yield of 84% (Scheme 3.26). A similar experiment on the 15-ethyl Δ^{15}-17-ketone **167** gave the derived 15,15-diethyl 17-ketone **172** (90%).

The 15β-ethyl 15α-methyl 17-ketone **171** displayed ^{1}H NMR spectral properties essentially identical to those of the 15-epimer **169**. Convincing evidence in favour of the assignments of the pair of epimeric 15-ethyl 15-methyl 17-ketones **169** and **171** was obtained by comparison of the NOESY spectra. The 15α-ethyl 15β-methyl 17-ketone **169**

showed cross-peaks for 16β-H↔15β-Me and for 16α-H↔15α-CH_2*Me*. By contrast, the 15α-methyl 15β-ethyl compound **171** showed cross-peaks for 13β-Me↔15β-CH_2*Me* and 16α-H↔15α-Me. These NOE interactions can only arise through *syn*-relationships between the interacting protons.

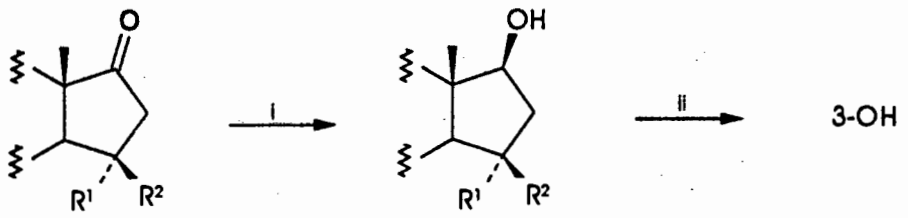
For the 15,15-diethyl compound **172**, the 15α- and 15β-CH_2*Me* protons resonated at δ 0.87 and 0.93 respectively (each t, *J* 7.4 Hz). Signal overlap precluded the clear extraction of the four CH_2Me-resonances, which were observed as multiplets, centered at δ 1.42, 1.55, 1.65, and 1.76 respectively.

Scheme 3.26



With the series of 15,15-dialkyl 17-ketones **169–172** in hand, reduction of the 17-oxo group was carried out with lithium aluminium hydride (LAH), to obtain the corresponding 15,15-dialkyl 17β-alcohols **173–176** in high yield (Scheme 3.27). The ^{1}H NMR spectra of these alcohols revealed coupling patterns of the 17α-proton (δ *ca* 3.6, dd, *J ca* 9 and 8 Hz) similar to those of the 15,15-dimethyl 17β-alcohol **161** (δ 3.71, dd, *J* 10.2 and 7.9 Hz). Therefore, it was concluded that reduction of the 17-oxo group with LAH for the series of 15,15-dialkyl 17-ketones **173–176** proceeded with high stereoselectivity. This result is unsurprising, since the pseudo-equatorial 15α-alkyl groups were not expected to influence the course of hydride approach on the α-face at C(17). Additional steric shielding resulting from the presence of the pseudo-axial 15β-alkyl groups can only amplify the pre-existing stereoselectivity of reduction of steroidal 17-ketones.

Scheme 3.27



169 (R^1 = Et, R^2 = Me)	**173** (R^1 = Et, R^2 = Me)	**177** (R^1 = Et, R^2 = Me)
170 (R^1 = Pr^i, R^2 = Me)	**174** (R^1 = Pr^i, R^2 = Me)	**178** (R^1 = Pr^i, R^2 = Me)
171 (R^1 = Me, R^2 = Et)	**175** (R^1 = Me, R^2 = Et)	**179** (R^1 = Me, R^2 = Et)
172 (R^1, R^2 = Et)	**176** (R^1, R^2 = Et)	**180** (R^1, R^2 = Et)

I, $LiAlH_4$, THF, 0 °C; II, DIBAH, PhMe, Δ

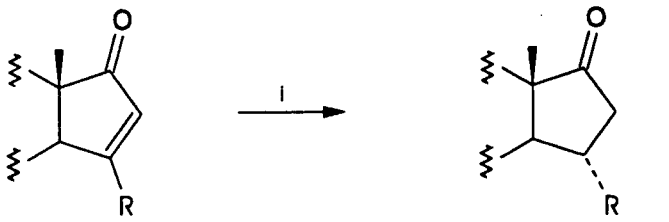
Demethylation of the 17β-alcohol 3-methyl ethers with diisobutylaluminium hydride (DIBAH) in refluxing toluene[87] gave the corresponding 15,15-dialkylestradiols **177–180** in high yield (Scheme 3.27). Biological evaluation of these analogues revealed much reduced estrogenicity, compared to the 15,15-dimethyl analogue **162**. The structure-activity implications are discussed in Chapter 4.

3.2.2 Spectroscopic Properties of 15-Alkyl 17-Ketones. The use of ^{13}C NMR and circular dichroism spectra as a method for obtaining further stereochemical information about the series of 15-alkyl 17-ketones was investigated. For a complete evaluation, access was required to the 15-epimers of the 15β-alkyl 17-ketones prepared in this work. Starting from the 15-alkyl Δ^{15}-17-ketones **158**, **167** and **168**, the most direct route to the corresponding 15α-alkyl compounds was perceived through stereoselective reduction of the Δ^{15}-bond. Accordingly, catalytic hydrogenation (10% Pd on charcoal, 3 atm. H_2) was carried out, but failed to give any stereocontrol. Inseparable mixtures of 15-epimers were obtained, as evidenced by the NMR spectra. By contrast, treatment of the 15-alkyl Δ^{15}-17-ketones with lithium in liquid ammonia–tetrahydrofuran (Scheme 3.28) gave the corresponding 15α-alkyl 17-ketones **181–183** in *ca* 75% yield. Protonation of the enolates derived from the 15-alkyl enones occurred from the β-side, leading to the thermodynamically favoured 15α-alkyl compounds, with the 15-alkyl groups projecting away from the angular 13β-methyl group.

The ^1H NMR signals originating from the 15α-alkyl groups for **181–183** were similar to those observed for the corresponding 15-epimers **149**, **163** and **164**. An outstanding feature in support of the 15α-alkyl configuration is the presence of a large $J_{14\alpha,15\beta}$ *ca* 10.8 Hz. This is indicative of an antiperiplanar relationship between the 14α- and 15β-protons, necessitating a 15α-alkyl group. This finding is in agreement with the results published by Künzer[35] for 15α- and 15β-alkyl 17-ketones. A selection of ^1H NMR data for

the 15-alkyl 17-ketones is presented in Table 3.1, and shows a self-consistent pattern in chemical shift and coupling values in support of all the configurational assignments. For the 15-monoalkyl 17-ketones, the orientation of the 15-alkyl group had a consistent influence on the angular 13β-methyl group. Also, the relation between $J_{14\alpha,15}$ and the C(15)-configuration as described previously is clearly illustrated in the table.

Scheme 3.28



158 (R = Me)
167 (R = Et)
168 (R = Pr^i)

181 (R = Me)
182 (R = Et)
183 (R = Pr^i)

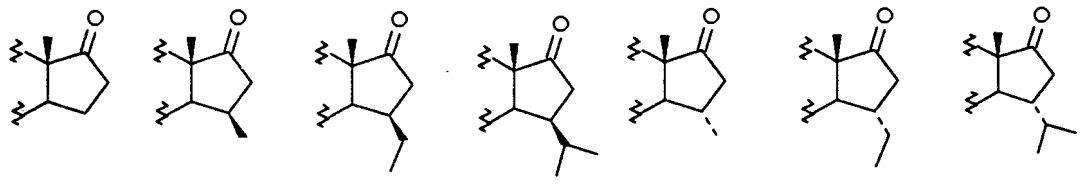
i, Li-NH_3

Table 3.1 Selected ^{1}H NMR data for 15-alkylated 17-ketones

	Signal			
Compound	13β-Me	14α-H	16α-H	16β-H
149 15β-Me	1.07	1.68 (dd, 11.3, 6.8)	2.51 obsc.	2.30 obsc.
163 15β-Et	1.02	1.73 (m)	2.43 (dd, 19.4, 7.8)	2.37 (dd, 19.4, 2.5)
164 15β-Pr^i	1.08	1.77 (dd, 11.8, 6.0)	2.44 (dd, 19.2, 7.0)	2.38 (dd, 19.2, 3.1)
181 15α-Me	0.95	1.22 (t, 2 x 10.8)	1.73 (dd, 19.3, 8.4)	2.77 (dd, 19.3, 8.7)
182 15α-Et	0.97	1.29 (t, 2 x 10.7)	1.79 (dd, 19.4, 7.9)	2.78 (dd, 19.4, 8.8)
183 15α-Pr^i	0.97	1.45 (t, 2 x 10.8)	1.95 (dd, 18.5, 7.7)	2.42 (dd, 18.5, 8.5)
160 15,15-Me_2	1.10	1.47 (d, 10.9)	2.09 (d, 19.4)	2.61 (d, 19.4)
169 15α-Et				
15β-Me	1.12	1.48 (d, 11.0)	2.18 (d, 19.4)	2.44 (d, 19.4)
170 15α-Pr^i				
15β-Me	1.13	1.49 (d, 10.1)	2.20 (d, 19.4)	2.26 (d, 19.4)
171 15α-Me				
15β-Et	1.09	1.49 (d, 10.1)	1.87 (d, 19.3)	2.80 (d, 19.3)
172 15,15-Et_2	1.10	1.49 (d, 10.1)	1.95 (d, 19.6)	2.64 (d, 19.6)

Table 3.2: ^{13}C NMR data for 15-alkyl 17-ketones

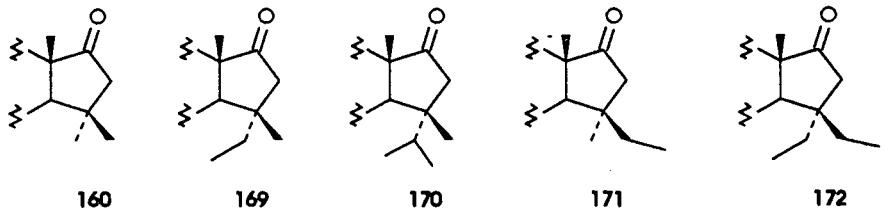
	Compound						
Signal	**80**	**149**	**163**	**164**	**181**	**182**	**183**
C-1	126.9	126.0	126.0	126.0	126.7	126.8	126.8
C-2	113.5	111.4	111.4	111.4	111.7	111.8	111.7
C-3	155.8	157.7	157.7	157.7	157.5	157.5	157.5
C-4	115.9	113.9	113.9	113.9	113.5	113.5	113.5
C-5	138.2	137.8	137.8	137.9	137.4	137.4	137.4
C-6	30.2	29.5	29.5	29.5	29.8	29.9	30.1
C-7	27.4	26.8	26.8	28.2	26.5	27.8	27.4
C-8	39.8	36.0	36.0	32.3	39.6	37.8	39.9
C-9	45.0	44.5	44.6	45.0	44.2	44.2	44.4
C-10	131.9	132.5	132.4	132.4	131.9	131.9	132.0
C-11	26.4	25.6	25.6	25.4	27.7	26.5	26.4
C-12	32.5	34.1	34.0	34.8	31.7	31.6	31.8
C-13	48.3	47.5	47.1	46.5	50.8	50.3	50.1
C-14	51.1	52.3	52.9	55.5	57.2	54.5	50.6
C-15	22.2	27.7	36.5	45.5	30.8	39.7	41.7
C-16	35.9	44.8	42.2	42.4	47.5	42.7	35.7
C-17	219.3	221.3	221.4	220.8	220.1	220.2	220.1
C-18	13.9	17.9	17.8	17.4	15.8	15.7	15.6
3-OMe	55.2	55.2	55.2	55.2	55.2	55.2	55.2
15-Me	-	17.0	-	-	22.0	-	-
15-CH_2Me	-	-	23.8	-	-	30.0	-
15-CH_2*Me*	-	-	13.9	-	-	12.4	-
15-$CHMe_2$	-	-	-	38.0	-	-	28.5
15-$CHMe_2$	-	-	-	21.8	-	-	14.9
				24.3			27.7



80 149 163 164 181 182 183

Table 3.3: ^{13}C NMR data for 15,15-dialkyl 17-ketones

	Compound				
Signal	**160**	**169**	**170**	**171**	**172**
C-1	126.4	126.5	126.5	126.4	126.4
C-2	111.6	111.6	111.6	111.6	111.6
C-3	157.6	157.6	157.6	157.6	157.6
C-4	113.6	113.6	113.6	113.6	113.6
C-5	137.4	137.4	137.4	137.4	137.4
C-6	29.8	29.9	30.0	29.8	29.9
C-7	28.2	28.3	27.8	28.6	27.8
C-8	37.5	37.8	37.7	37.3	37.5
C-9	44.9	44.9	45.0	45.1	45.0
C-10	132.2	132.2	132.3	132.3	132.3
C-11	26.0	26.1	26.1	27.4	25.9
C-12	34.2	34.2	34.5	34.4	34.3
C-13	50.2	50.0	49.9	49.8	49.5
C-14	58.4	56.6	51.6	59.8	52.6
C-15	35.5	38.9	41.5	39.4	42.1
C-16	53.6	49.8	44.6	48.9	44.7
C-17	221.4	220.4	220.3	220.3	220.5
C-18	17.9	18.2	17.8	18.3	18.3
3-OMe	55.2	55.2	55.2	55.2	55.2
15-Me	24.5	30.3	23.0	30.3	-
	34.6				
15-CH_2Me	-	21.8	-	25.9	28.1
					32.7
15-CH_2*Me*	-	9.4	-	9.0	9.1 (x2)
15-*C*HMe_2	-	-	36.9	-	-
15-CH*Me_2*	-	-	18.4	-	-
			18.8		



160 169 170 171 172

The ^{13}C NMR data for the 15-alkyl 17-ketones and for the 15,15-dialkyl 17-ketones are listed in Table 3.2 and Table 3.3, respectively. General self-consistency among the chemical shift values was evident, and so were the trends associated with C(15)-substitution.[122] The data were inspected particularly for γ-shifts related to C(15)-substitution, and this analysis gave insight into the apparent rotameric preferences of the ethyl and isopropyl groups. Thus, measured relative to estrone 3-methyl ether, the 15β-methyl 17-ketone **149** shows γ-gauche (γ_g) shielding in C(8) and C(13) of $\Delta\delta_C$ -3.8 and -0.8, respectively. The diminished influence shielding of the quaternary C(13) is in line with established expectations. The steric component of the γ_g effect is exemplified for C(8) in the 15α-methyl 17-ketone **181**. It is known[123] that proton-proton repulsion of γ-separated hydrogen-bearing carbon atoms causes additional shielding through polarisation of the C–H bonds towards the carbon atoms. In the case represented by the 15α-methyl compound **181**, the γ-anti (γ_a) orientation of the 15α-Me gave a diminished shielding of C(8) of $\Delta\delta_C$ -0.2. This evidence also served as additional support in favour of the assigned C(15) configurations.

Relative to the 15β-methyl 17-ketone **149**, chain homologation produced a γ_g shielding of $\Delta\delta_C$ -2.6 of C(16) in the 15β-ethyl 17-ketone **163**. The γ-removed C(14) of **163** experienced a *downfield* shift of $\Delta\delta_C$ +0.6. This was rationalised in terms of the absence of a steric component between the 14α- and 15β-CH_2*Me* protons, to contribute to the expected deshielding. For the epimeric 15α-ethyl 17-ketone **182**, similar γ_g effects were observed for C(16) ($\Delta\delta_C$ -4.8) and C(14) ($\Delta\delta_C$ -2.7). The observed response in C(14) only toward 15α-alkyl substitution is analogous to the effect described above for C(8) in the epimeric 15-methyl 17-ketones **149** and **181**, and lends additional confidence to the C(15) assignments.

For the 15-ethyl 17-ketones **163** and **182**, the ethyl groups are expected to adopt certain preferred rotameric conformations. The rotameric possibilities not involving eclipsing of σ-bonds are illustrated for the pair of ketones in Figure 3.29 as conformational drawings, as well as Newman projections along the 15^1,15-bond.

Clearly on steric grounds alone, the rotamer **163a** for the 15β-ethyl compound is a resonable expectation. By adopting this orientation, only one gauche interaction with C(16) is experienced. The remaining rotamers involve steric interactions with ring elements and the 13β-methyl group, which would have been reflected in the ^{13}C chemical shift values of, for instance, C(7), C(8) and C(18). Analogously, rotamer **182a** of the 15α-ethyl 17-ketone experiences only one gauche interaction between 15α-CH_2*Me* and C(16). The rotamer **182b** is considered as improbable, owing to the diaxial interaction between 14α-H and 15α-CH_2*Me*, whereas rotamer **182c** would cause a steric interaction between C(7), and the 15α-ethyl group.

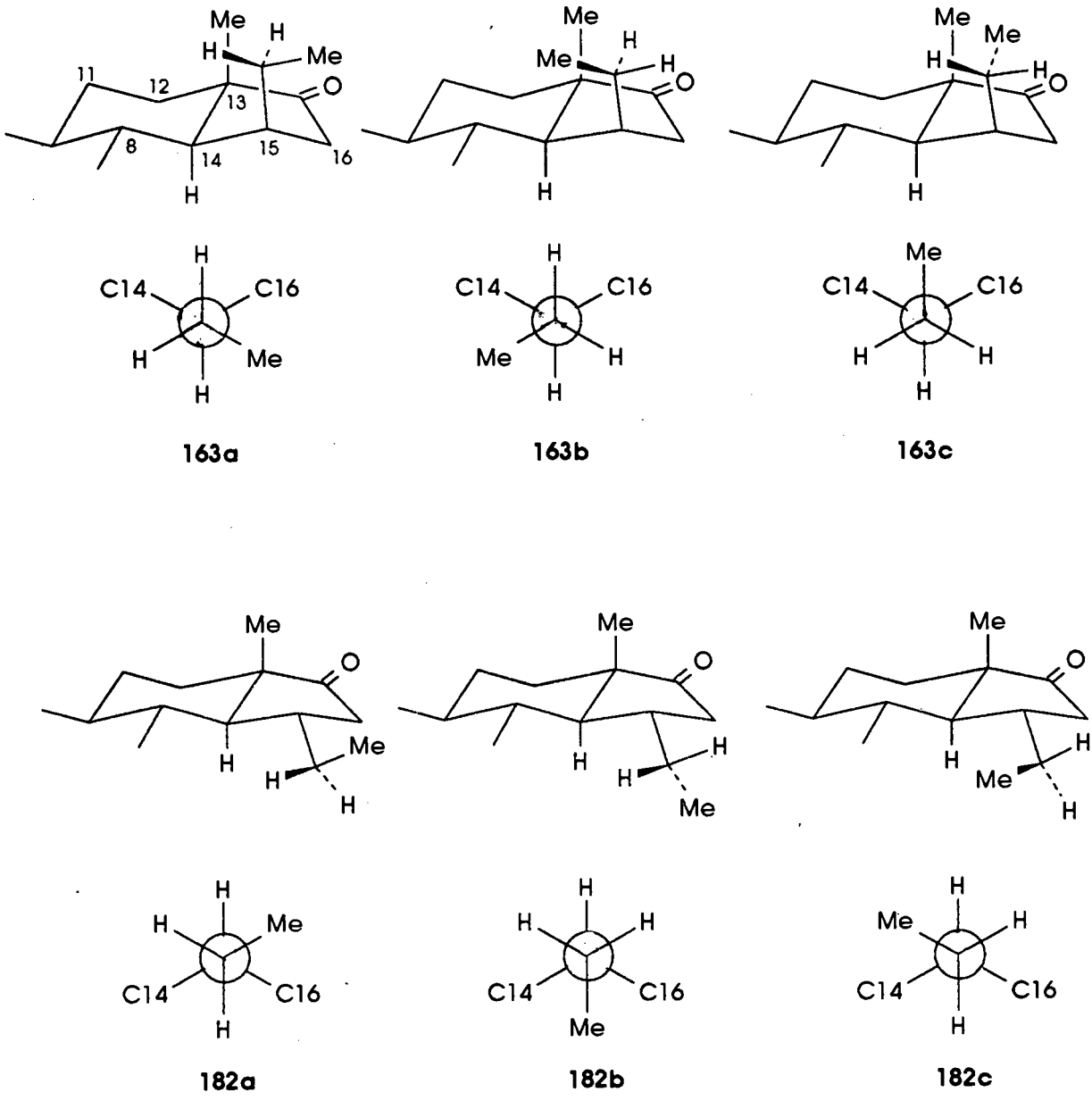


Figure 3.29: Rotameric conformations for the 15-ethyl 17-ketones

Chain branching by the introduction of a 15β-isopropyl group in **164** had an uncertain effect on the γ-removed carbon atoms. Both C(14) and C(16) experienced a *downfield* shift of $\Delta\delta_C$ +2.6 and +0.2, respectively. By contrast, the substitution effect for the 15α-isopropyl 17-ketone **183** was much clearer. Both C(14) ($\Delta\delta_C$ -3.9) and C(16) ($\Delta\delta_C$ -7.0) displayed the expected shielding. The possible rotameric conformations for the isopropyl groups in **164** and **183** are indicated in Figure 3.30. Newman projections are along the 15^1,15-bond.

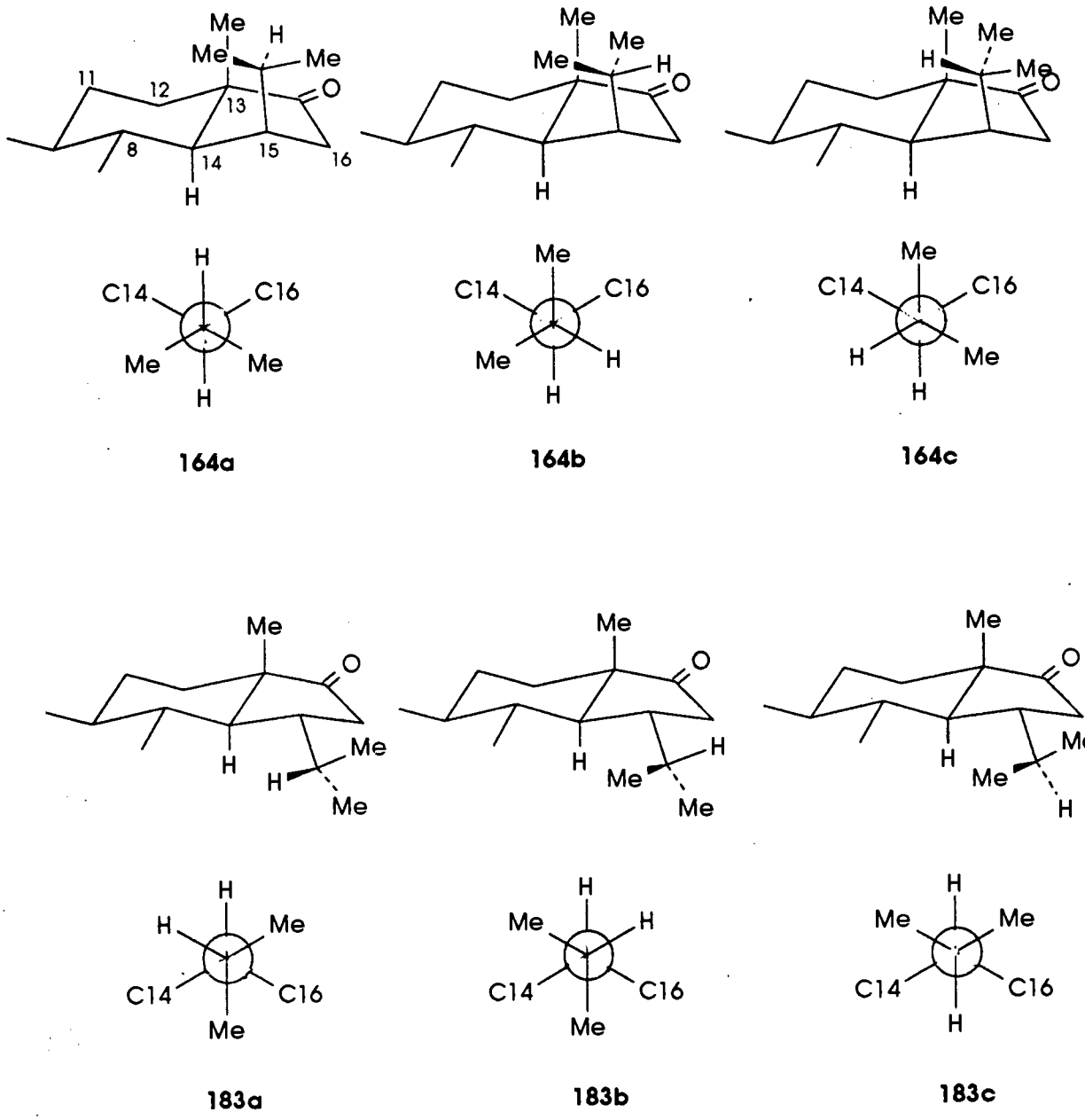


Figure 3.30: Rotameric conformations for the 15-isopropyl 17-ketones

For the 15β-isopropyl compound, rotamer **164a** is the only plausible conformation, since **164b** and **164c** both involve steric interactions between the 13β-Me and 15β-CH*Me*$_2$ groups. Further, a shielding of $\Delta\delta_C$ -3.7 is observed for C(8), originating from an obligatory steric interaction with a methyl group on the 15β-isopropyl substituent. In the case of the 15α-isopropyl compound **183**, rotamer **183a** arguably is the preferred conformation. This orientation of the 15α-isopropyl group causes both of the methyl groups to experience a gauche interaction with C(16), which in turn is reflected in the increased shielding in C(16) of $\Delta\delta_C$ -7.0. Rotamers **183b** and **183c** are considered as improbable, in that only a single γ_g

interaction between a methyl group on the isopropyl substituent and C(16) would have resulted in a diminished substitution shift of the latter. By comparing Figures 3.29 and 3.30, it is evident that branching does not cause a severe change in the rotameric preferences of the 15-alkyl groups.

A similar analysis was carried out for the 15,15-dialkyl 17-ketones. Relative to estrone 3-methyl ether, the ^{13}C chemical shift values for C(8) and C(13) of the 15,15-dimethyl 17-ketone **160** displayed shifts of $\Delta\delta_C$ -2.3 and +1.9, respectively. The effect of geminal substitution at a γ-position relative to the quaternary C(13) was uncertain, but C(8) displayed a γ_g shielding. The predicted chemical shift values for these carbon atoms, derived from the increments obtained from the 15α- and 15β-methyl 17-ketones **181** and **149**, amounted to δ -4.0 and +1.7 for C(8) and C(13), respectively. This was not considered as a very good fit, and these deviations point to the uncertainties associated with estimation of chemical shift values in complex molecules.

For the 15α-ethyl 15β-methyl 17-ketone **169**, comparisons were made relative to the 15,15-dimethyl comound **160**. Thus, chain extension at the α-face caused γ-shielding at C(14) ($\Delta\delta_C$ -1.8) and C(16) ($\Delta\delta_C$ -3.8). Some uncertainty exists regarding the rotameric preference of the 15α-ethyl group, in that the gauche interaction with the 15β-methyl might necessitate the adoption of an orientation to minimise this effect. A plausible alternative involves diaxial interaction with the 14α-proton, and it might be argued that this interaction is preferred. The exact scenario was not evident from ^{13}C NMR data. A Newman projection along the 15^1,15-bond of these two rotamers is indicated in Figure 3.31.

Figure 3.31: Newman projection along the 15^1,15-bond for the 15α-ethyl 15β-methyl 17-ketone **169**

Chain branching in 15α-isopropyl 15β-methyl 17-ketone **170** caused virtually an equal amount of shielding in the γ-removed carbon atoms. Shifts for C(14) and C(16) amounted to $\Delta\delta_C$ -5.0 and -5.2, respectively. This similarity in shielding points to a rotameric conformation in which each of C(14) and C(16) experiences a single γ_g-interaction by the methyl groups on the 15α-isopropyl group. In addition, the 15β-methyl group experiences a shielding of $\Delta\delta_C$ -7.3 relative to the 15α-ethyl 15β-methyl compound **169**, which is indicative of a summed γ_g-interaction by the isopropyl group. Thus, it is argued that

the rotameric preference of the 15α-isopropyl group changes upon 15β-methyl substitution. A Newman projection of this conformation is indicated in Figure 3.32.

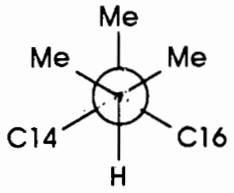


Figure 3.32: Newman projection along 15¹,15-bond for 15α-isopropyl 17-ketone **170**

For the case represented by the 15β-ethyl 15α-methyl 17-ketone **171**, chain extension on the β-face caused C(14) to experience *deshielding* of $\Delta\delta_C$ +1.4. By contrast, C(16) showed a *shielding* of $\Delta\delta_C$ -4.7, as caused by the γ_g-interaction with the 15β-ethyl group. These observations followed the established trend observed for chain homologation in the 15β-monoalkyl series, and gives confidence to the assigned C(15)-configurations for the 15-ethyl 15-methyl 17-ketones **169** and **171**. Each of the three possible rotamers of for the 15β-ethyl group involves a gauche interaction with the 15α-methyl group. Therefore, it is reasonable to assume that the adopted rotamer will minimise steric interactions with the ring elements, as illustrated for the 15β-ethyl 17-ketone **163**. No change in rotameric preference therefore occurred upon 15α-methylation. Figure 3.33 illustrates the assigned rotameric conformation for **171**.

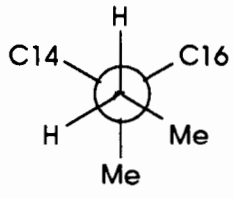


Figure 3.33: Rotameric preference for 15β-ethyl 15α-methyl 17-ketone **171**. Newman projection along 15¹,15-bond.

Gathering chemical shift information regarding the preferred orientations of the ethyl groups in the 15,15-diethyl 17-ketone **172** proved less trivial. However, based on steric arguments, it is reasonable to assume that the 15β-ethyl group will adopt an orientation similar to those for the 15β-ethyl and 15β-ethyl 15α-methyl 17-ketones **163** and **171**. The 15α-ethyl group, similarly, will be obliged to adopt an orientation away from the 15β-substitution, thereby engaging in a diaxial interaction with the 14α-proton. Two Newman projections of this conformation are indicated in Figure 3.34. The illustration on the left

hand side represents a view along the 15¹α,15 bond, whereas the second drawing indicates a view along the 15¹β,15 bond.

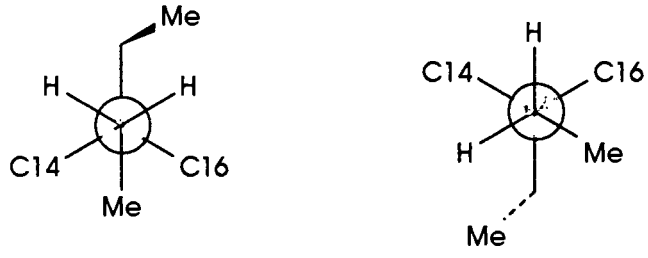


Figure 3.34: Orientation of 15-ethyl groups in **172**.
Newman projections along 15¹,15-bonds.

Therefore in summary, although the preferred rotamers for the 15-ethyl and 15-isopropyl 17-ketones **163** and **164** were reasonably clear, some degree of uncertainty existed in the case of disubstitution. For the 15α-ethyl 15β-methyl 17-ketone **169**, two possible orientations of the ethyl group were argued. In the case of the 15α-isopropyl 15β-methyl 17-ketone **170**, the isopropyl group was argued to change orientation upon 15β-methylation. The orientation of a 15β-ethyl group was shown not to be effected by the introduction of a 15α-methyl group, as exemplified for the 15β-ethyl 15α-methyl 17-ketone **171**. Finally, it was argued on steric grounds alone that the ethyl groups of the 15,15-diethyl 17-ketone **173** could adopt only one orientation in which interactions with ring elements and substituents were minimised.

3.2.3 Circular Dichroism Examination of 15-Alkyl 17-Ketones. An examination of the CD properties of the 15-alkyl and 15,15-dialkyl 17-ketones was also undertaken, in search of a diagnostic trends in further support of the configurational assignments. The CD properties of the class of substituted hexahydroindan-1-ones represented by the steroidal C/D ring system have been evaluated in the work of Kirk.[91] An analysis of the CD data (Table 3.4) for the 15-substituted ketones revealed certain trends for the different 15-alkyl groups on the Cotton effect for the 17-oxo group. Thus, the negative increment for the 15β-methyl 17-ketone **149** (ΔΔε -0.59) is in agreement with the predicted magnitude of an octant-dissignate contribution by a 1,3-removed axial methyl group. The 15β-ethyl group in **163** also causes octant-dissignate behaviour, but the effect is diminished. In contrast, the increment for the 15β-isopropyl 17-ketone **164** is strongly octant-consignate. The diastereomeric 15α-alkyl 17-ketones **181–183** all display octant-consignate, i.e. negative increments. For the 15α-isopropyl group, this effect is accentuated. Octant projections along the O=C-bond for these 15-alkyl 17-ketones are illustrated in Figure 3.35, indicating the alkyl substituents in the appropriate octants (i.e. positive or negative).

Table 3.4: CD data for the 15-alkyl and 15,15-dialkyl 17-ketones

Compound	Δε (λ_{max}/nm)	Substituent Effect (ΔΔε)	
		Observed[a]	Calculated[b]
149 15β-Me	+2.83(295)	-0.59	
163 15β-Et	+3.22(294)	-0.20	
164 15β-Pr^i	+4.69(296)	+1.27	
181 15α-Me	+2.70(295)	-0.72	
182 15α-Et	+2.94(292)	-0.48	
183 15α-Pr^i	+1.70(293)	-1.72	
160 15,15-Me_2	+2.08(295)	-1.34	-1.31
169 15α-Et 15β-Me	+2.18(294)	-1.24	-1.07
170 15α-Pr^i 15β-Me	+1.85(293)	-1.57	-2.31
171 15β-Et 15α-Me	+2.30(294)	-1.12	-0.92
172 15,15-Et_2	+2.99(293)	-0.43	-0.68

[a]Derived by taking the difference from Δε +3.42 (296 nm)[91] for estrone 3-methyl ether.
[b]Derived by adding observed ΔΔε values for individual monoalkyl compounds.

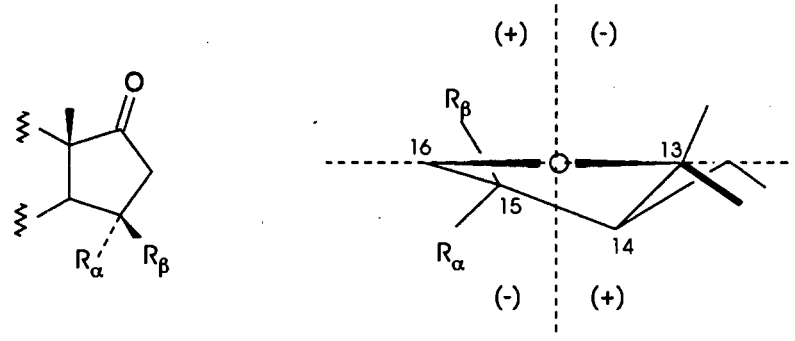
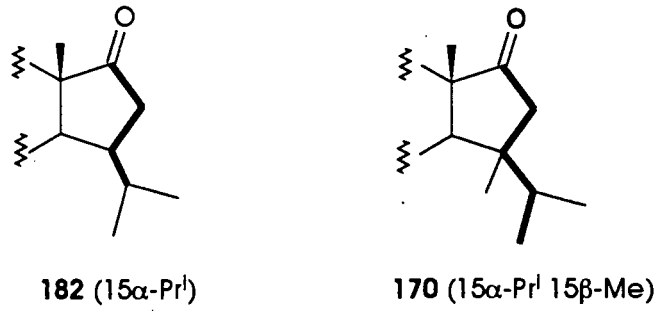


Figure 3.35: Octant projections of 15-alkyl 17-ketones

The summed increments for the appropriate pair of 15-alkyl 17-ketones were compared with those observed for the actual 15,15-dialkyl 17-ketones (Table 3.4). Good agreement between the predicted and actual values was obtained for the 15,15-dimethyl 17-ketone **160**. Similarly, for the epimeric 15-ethyl 15-methyl 17-ketones **169** and **171**, the calculated $\Delta\varepsilon_{max}$ values fell within reasonable agreement (ΔΔε *ca* 0.2). However, for the 15α-isopropyl 15β-methyl compound **170**, a significant discrepancy of ΔΔε 0.74 was observed. This phenomenon was rationalised in terms of the change in rotameric preference

data. By adopting a different orientation, the branching in the 15α-isopropyl group contributes to the 'primary zig-zag bonds',[91] thereby increasing the octant-consignate (i.e. negative in this instance) contribution to the Cotton effect. These extra 'zig-zag' bonds are indicated in Figure 3.36 by solid lines.



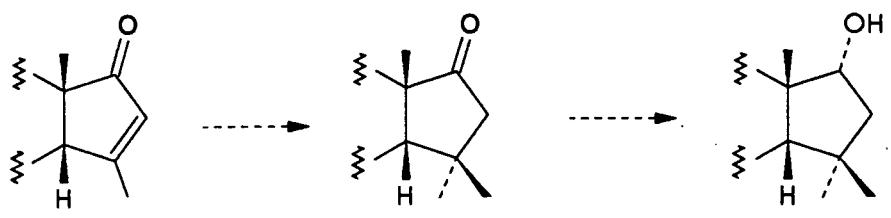
182 (15α-Pr^i) **170** (15α-Pr^i 15β-Me)

Figure 3.36: Extension of zig-zag bonds by 15α-isopropyl group

3.3 Synthesis of 15,15-dimethyl-14β-estra-1,3,5(10),triene-3,17α-diol

Owing to the high *in vivo* activity of 3-methoxy-15,15-dimethylestra-1,3,5(10)-triene-3,17β-diol **162**, an extension of this investigation involved an evaluation of the influence of configurational inversion at C(14) on the biological activity. Conjugate alkylation of 3-methoxy-15-methyl-14β-estra-1,3,5(10),15-tetraen-17-one **184**[124] was expected to give access to the 15,15-dimethyl 17-ketone, as indicated in Scheme 3.37. Reduction of the carbonyl group was expected to give the 17α-alcohol.[65] It was reported that steroidal 17-ketones in the 14β-series underwent hydride reduction of the carbonyl group to give mainly products of β-face reagent approach, i.e. 17α-alcohols.

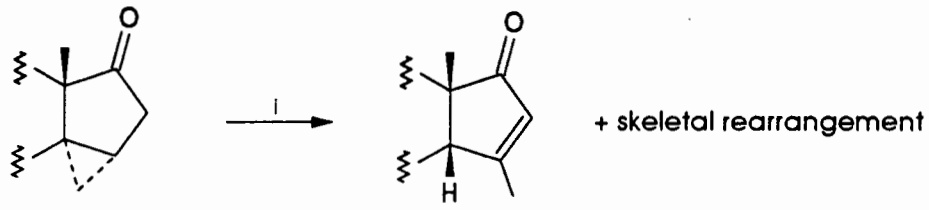
Scheme 3.37



184

A route to 3-methoxy-15-methyl-14β-estra-1,3,5(10),15-tetraen-17-one **184** has been established[124] through acid treatment of a 3-methoxy-14,15α-methylene-estra-1,3,5(10)-trien-17-one **185**, to give a complex mixture containing ring D-homologated products of skeletal rearrangement, as well as **184** (Scheme 3.38). A very diagnostic feature of the ^{1}H NMR spectrum of **184** is the signal obtained from the 14β-proton. An isolated doublet at δ 2.75 (*J* 5.1 Hz) was reported, obtained from the near-gauche orientation relative to 8β-H.

Scheme 3.38

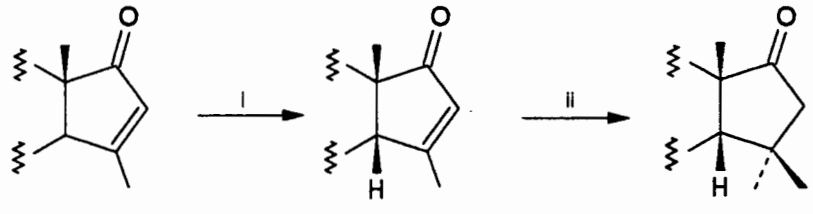


185 **184** (40%)

i, *p*-TsOH

In this study, access to **184** was obtained through an alternative route, which involved treatment of the 15-methyl Δ^{15}-17-ketone **158** with toluene-*p*-sulfonic acid (TsOH) in refluxing benzene. The conversion proceeded efficiently, to give **184** in 96% yield (Scheme 3.39). Characterisation was performed by comparison of ring D ^{1}H NMR signals to that published in the literature.[124] Thus, the signal from the vinylic 16-proton was observed as a singlet at δ 5.98. The methyl groups resonated at δ 1.12 (13β-Me) and 2.17 (15-Me) respectively, and the 14β-proton was observed as the reported doublet at δ 2.72 (d. *J* 5.1 Hz).

Scheme 3.39



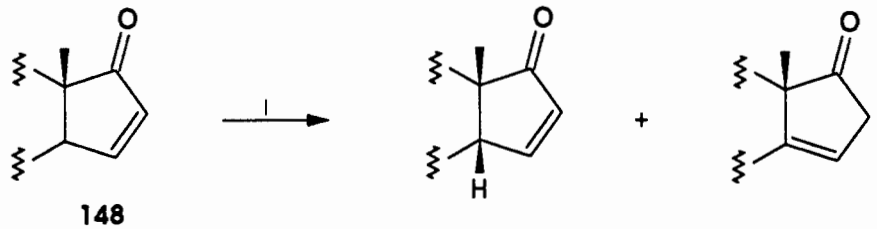
158 **184** **186**

i, *p*-TsOH, C_6H_6, Δ; ii, Me_2CuLi-TMSCl, then H^+

This acid-mediated epimerisation at the γ-position of an α,β-unsaturated ketone is reminiscent of early work carried out by Johnson.[125] It was reported that treatment of 3-

methoxyestra-1,3,5(10),15-tetraen-17-one **148** with TsOH gave a mixture (1:2.5) of 14β-estrone 3-methyl ether, as well as the β,γ-unsaturated enone (Scheme 3.40).

Scheme 3.40



148

I, *p*-TsOH

In the present investigation, conjugate methylation of **184** was achieved with lithium dimethylcuprate, to give the 15,15-dimethyl 17-ketone **186** (Scheme 3.39). The ^{1}H NMR spectrum of this compound displayed the expected features; the 14β-configuration was clearly discernible through the coupling $J_{8\beta,14\beta}$ 4.7 Hz, while the geminal methyl groups resonated at δ 1.27 and 1.33 repectively. Coalescence in chemical shift of the 16-protons caused the signal to appear as a two-proton singlet at δ 2.29. Configurational inversion was also evident from a ^{13}C NMR spectrum. A γ_g-interaction between C(9) and C(15) led to a shielding of $\Delta\delta_C$ -8.4 in C(9), relative to the 15,15-dimethyl 17-ketone **160** in the 14α-series. A COSY plot of the 15,15-dimethyl 17-ketone **186** is indicated in Figure 3.41.

Reduction of the 17-oxo group of **186** was carried out with lithium aluminium hydride, to give the 17α-alcohol **187** (Scheme 3.42). For clearer spectroscopic signals, **187** was converted into the related 17-acetate **188**. The C(17)-configuration was verified from the ^{1}H NMR signal of the 17-proton, in that the characteristic coupling pattern for a 17β-proton in the 14β-series was observed at δ 4.83 (dd, *J* 9.9 and 8.2 Hz). Demethylation of the 3-methyl ether **187** was routinely carried out with DIBAH in refluxing toluene,[87] to give 15-15-dimethyl-14β-estra-1,3,5(10)-triene-3,17α-diol **189** (Scheme 3.42) in good yield. Biological evaluation of this analogue revealed competitive binding affinity to the estradiol receptor similar to that of the natural hormone (see Chapter 4).

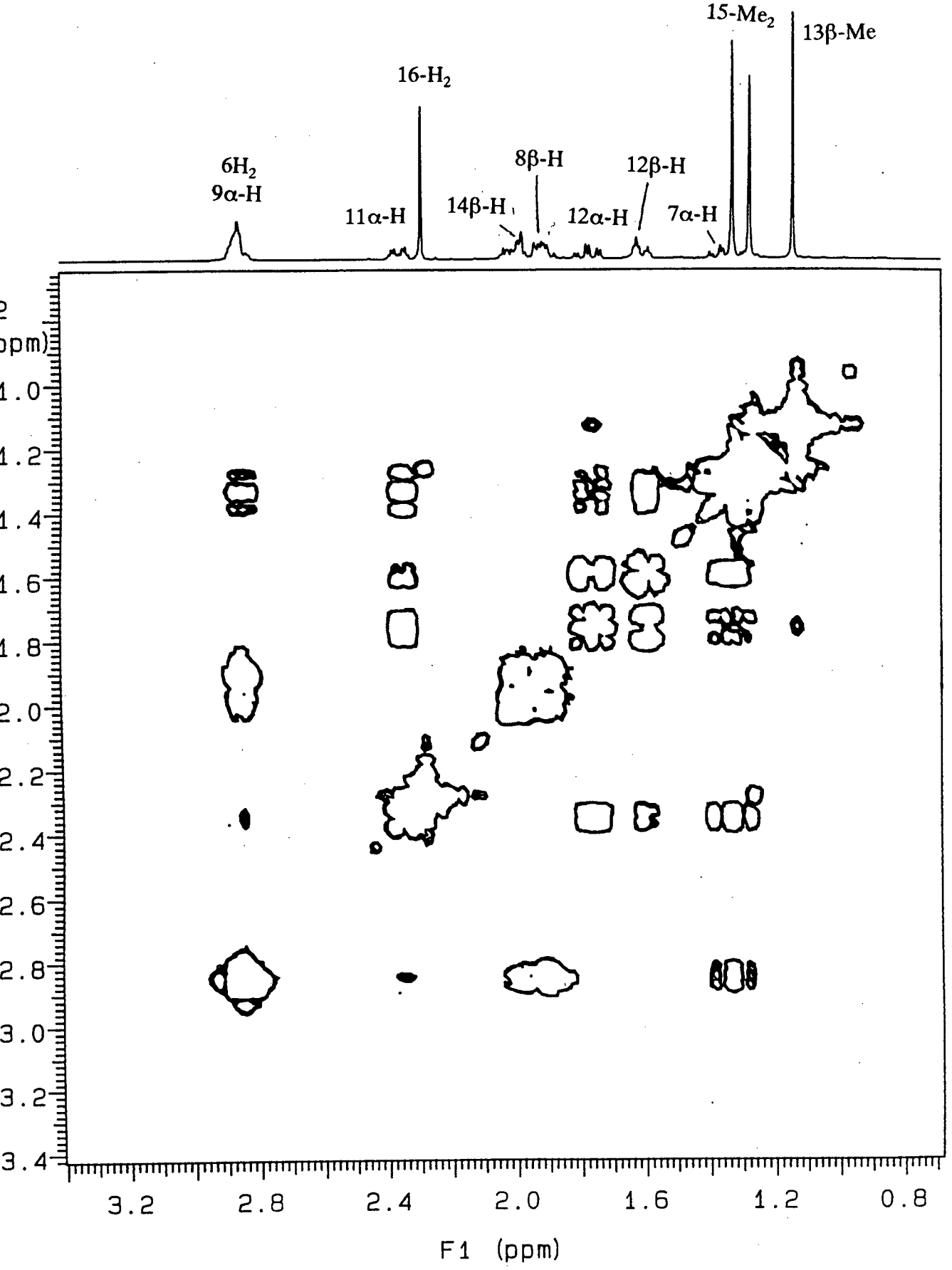
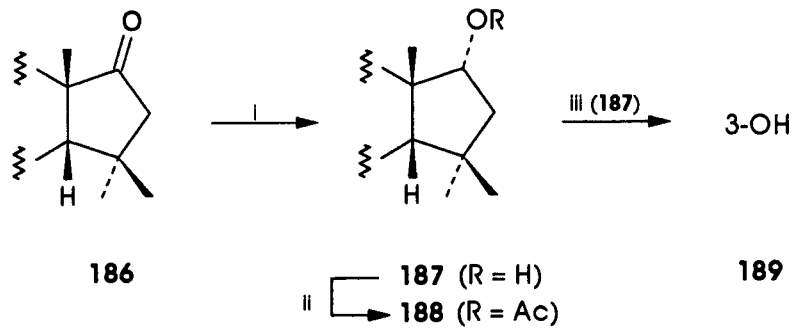


Figure 3.41: COSY plot of 15,15-dimethyl 17-ketone **186**

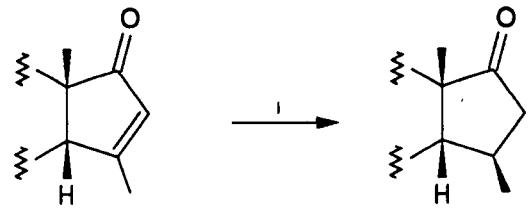
Scheme 3.42



i, $LiAlH_4$, THF, 0 °C; ii, Ac_2O, Py; iii, DIBAH, PhMe, Δ

In order to investigate the influence of 15-mono *vs* dimethylation upon ^{13}C chemical shift and circular dichroism observations, access to least one epimer in the 15-methyl 17-ketone series was required. Catalytic hydrogenation with 5% palladium on activated charcoal of the enone **184** gave, by NMR analysis, an inseparable mixture of 15-diastereomers. Reduction with lithium in liquid ammonia gave, by contrast, exclusively 15β-methyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one **190** in a yield of 78% (Scheme 3.43). Protonation of the enolate of **184** occurred from the α-side, thus giving the thermodynamically favoured 15β-methyl compound **190**, with the 15β-methyl group projecting away from the concave side of the C/D ring system.

Scheme 3.43



I, $Li\text{-}NH_3$

The C(15)-configuration was confidently assigned from the appearance of the 14β-proton (δ 1.65, dd, *J* 11.1 and 2.4 Hz) in the ^1H NMR spectrum. A COSY plot verified the coupling $J_{8\beta,14\beta}$ 2.4 Hz, as well as the coupling $J_{14\beta,15}$ 11.1 Hz. The anti periplanar orientation required for the latter coupling is attainable only for a 15α-proton, thus an obligatory 15β-methyl group. Other discernible ring D resonances comprised the 15β-

methyl group (δ 1.11, d, *J* 6.3 Hz), as well as 16α-H (δ 1.85, dd, *J* 19.2 and 9.5 Hz) and 16β-H (δ 2.77, dd, *J* 19.2 and 8.4 Hz). It was not possible to clearly extract coupling information for the 15α-proton, and this signal is therefore reported as a multiplet ranging δ 2.39–2.51. The γ_g-interaction between C(9) and C(15) brought about by the 14β-configuration was evidenced by a shielding of C(9) by $\Delta\delta_C$ -7.4, relative to the 15β-methyl 17-ketone **149** from the 14α-series.

Comparison of the circular dichroism data for ketones **186** and **190** clearly demonstrated the influence of methyl substitution at a position 1,3-removed from the carbonyl chromophore. Thus, the 15β-methyl 17-ketone **190** displayed $\Delta\varepsilon_{max}$ +1.90 (284 nm), whereas the spectrum for the 15,15-dimethyl compound **186** had an absorbance maximum at $\Delta\varepsilon_{max}$ +2.80 (287 nm). A typical Cotton effect for a 14β-H 17-ketone amounts to *ca* 1.0.[92] Therefore, the observed octant-consignate contribution of the 15β-methyl group (ΔΔε +0.8) is in agreement with the expected increment of ΔΔε +0.8.[91] Similarly, for the case of disubstitution, the octant dissignate contribution of the axial 15α-methyl group (ΔΔε 0.9) approximates the reported value of ΔΔε 0.6.[92] An octant projection of the carbonyl chromophore along the O=C bond is illustrated in Figure 3.44.

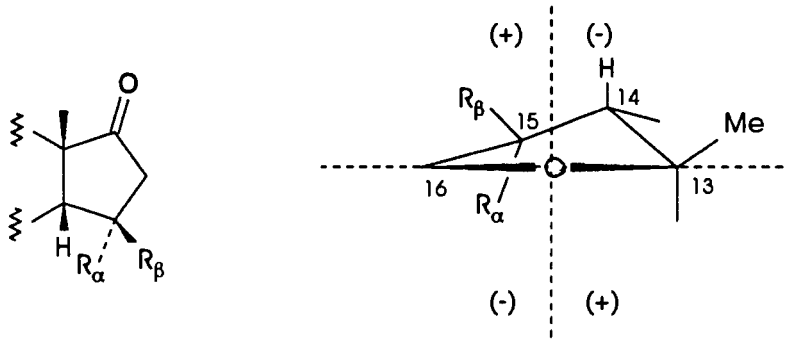
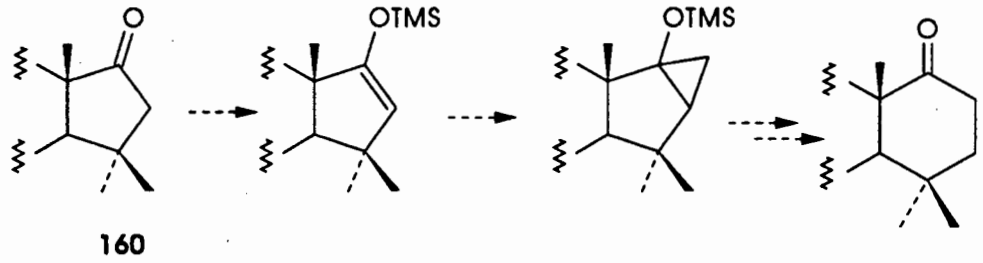


Figure 3.44: Octant projection of 14β-H 17-ketones

3.4 Synthetic Approaches to 15,15-Dimethyl-17a-homoestradiols

As set out in Chapter 3.1, this part of the investigation was aimed at synthesising the 15,15-dimethyl analogue of 17a-homoestradiol. The first approach was founded on a cyclopropanation – ring expansion reaction sequence (Scheme 3.45) on the 15,15-dimethyl 17-ketone **160**.

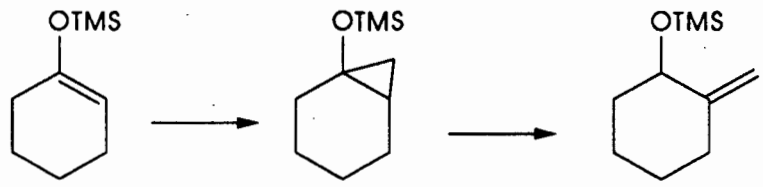
Scheme 3.45



160

The use of diethylzinc[78] to initiate a Simmons-Smith[74] reaction with diiodomethane has found application on a range of substrates, including silyl enol ethers.[126] A dependency on solvent and reagent concentration is also documented.[127] The use of hydrocarbon solvents, like pentane or hexane, was shown to improve the reaction yield by coagulating any free zinc iodide, which forms as a reaction by-product. Polar solvents, like ethers or even benzene, were reported[127] to have a tendency to coordinate to the zinc salt. This interaction then in turn facilitates the interference by the Lewis acidic zinc iodide with the expected reaction outcome. An example is found in the work by Murai,[127] where it was reported that zinc iodide promoted rearrangement of 1-silyloxy bicyclo[5.1.0]heptane **191** to yield the corresponding exocyclic methylene compound (Scheme 3.46). It was further reported by Murai[127] that adding the methylenating reagent (i.e. diiodomethane) to a concentrated solution of the substrate and diethylzinc achieved a similar rearrangement. In this instance, an explanation was offered in terms of a concentration related forced close association between the forming product and unreacted diethylzinc.

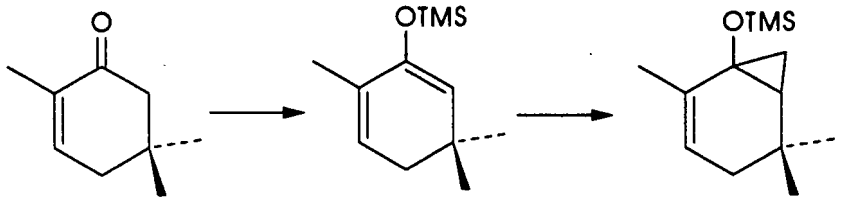
Scheme 3.46



191

With regard to the steric influence of alkyl groups in the vicinity of the cyclopropanation site, a case was found in the early literature that reported on the efficient cyclopropanation of 1-trimethylsilyloxy-3,5,5-trimethyl-2,6-cyclohexene **192**[128] (Scheme 3.47). The geminal dimethyl substitution exerted no steric constraint.

Scheme 3.47

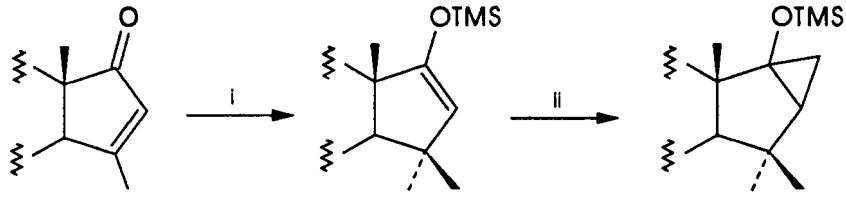


192

In the present case, severe difficulty was experienced in achieving the desired cyclopropanation in an acceptable yield. Treatment of the silyl enol ether **193** with diethylzinc and diiodomethane in benzene for 72 h gave a very modest yield of the desired cyclopropyl compound **194** (32%), accompanied by the 15,15-dimethyl 17-ketone **160** (50%) (Scheme 3.48). Monitoring of the reaction progress by TLC revealed that hydrolysis of the starting material started occurring after *ca* 24 h. Therefore, the hydrolysis product formed ***during*** the reaction course, and not during the aqueous work-up.

A ^{1}H NMR spectrum of **194** displayed the essential features: The 3′-cyclopropyl protons resonated as doublets of doublets in the expected high-field region at δ 0.70 (*J* 9.3 and 6.3, 3′-H_{exo}) and δ 0.85 (*J* 6.3 and 3.9, 3′-H_{endo}), whereas the signal for the trimethylsilyloxy group was clearly visible as a nine-proton singlet at δ 0.15. These resonances are consistent with data reported for the analogous reaction on estrone 3-methyl ether.[103] Other signals comprised the 16-proton resonance (δ 1.24, dd, *J* 9.3 and 3.9 Hz), which resonated as a doublet of doublets by coupling to the 3′-cyclopropyl protons. The geminal 15-methyl groups had resonances at δ 1.17 and 1.19. No definitive proof of the stereochemistry of cyclopropanation could be found from the spectroscopic data. It is, however, reasonable to assume that reagent entry occurred from the α-side of the molecule, owing to the steric shielding of the β-side by the axial 13β- and pseudo-axial 15β-methyl groups.

Scheme 3.48



158 **193** **194**

i, Me_2CuLi-TMSCl; ii, Et_2Zn, CH_2I_2

In an attempt to improve the conversion of **193** into the cyclopropyl compound **194**, the reaction was performed at elevated temperatures. This only promoted the hydrolysis reaction, which by TLC-monitoring was evidenced to commence after *ca* 12 h. The yield of cyclopropyl compound **194** remained essentially unchanged at 29%.

Other modifications in the reaction conditions included performing the reaction in pentane and under dilute reagent concentrations. Both of these adaptations were in accordance with the recommendations by Murai[127] (see previous discussion). However, no significant improvement in the reaction yield was observed. The conclusion drawn was that the geminal 15-methyl groups diminish the cyclopropanation reactivity of the compound. A possible explanation is offered in terms of the steric demands of this substitution, regardless of the close analogy found in a cyclohexanoid system.[128]

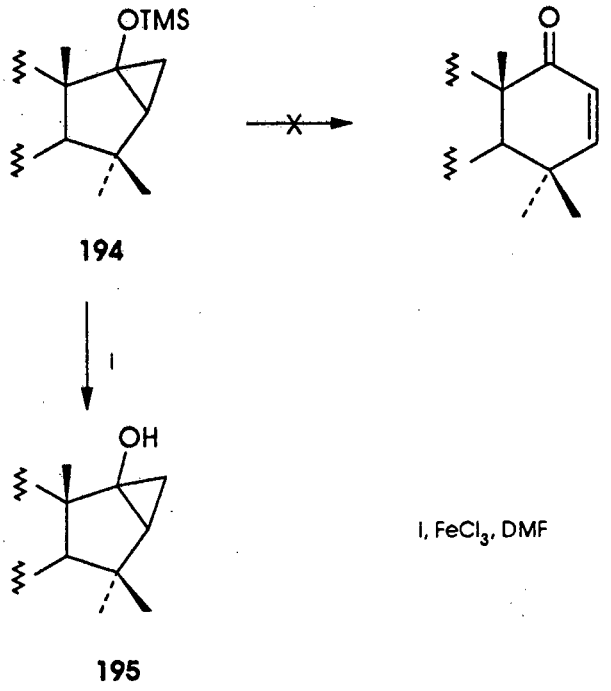
Despite a yield of **194** of *ca* 32%, the material was committed to the ring expansion step. Iron(III) chloride is known to homologate this type of silyloxy cyclopropyl system[104] by regioselective fragmentation of the internal cyclopropyl bond (i.e. 16,17 in this instance). It is believed that the regiochemistry is due to the radical nature of the reaction, but in is uncertain whether a metal homoenolate is involved. The observed product corresponds to a β-chloro expanded ketone which, either spontaneously or under mildly alkaline conditions (e.g. sodium acetate in methanol) eliminates HCl to give the enone.[104]

However, reaction of **194** with anhydrous $FeCl_3$ in DMF–pyridine failed to afford the desired 17a-homo compound. Instead, hydrolysis of the silyloxy group occurred, giving the 17-cyclopropyl alcohol **195** (Scheme 3.49). Several repetitions of this reaction, using chromatographed material and thoroughly purified reagents had no effect on the outcome.

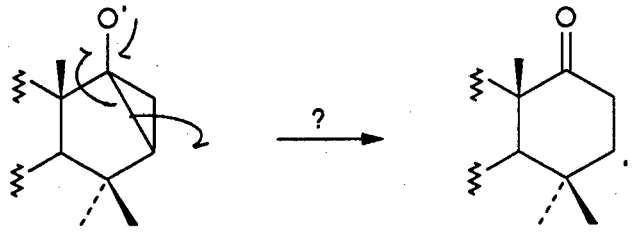
The failure of the 15,15-dimethyl compound **194** to react under conditions known to achieve ring expansion posed was indeed unexpected. Considering the mechanism of this ring homologation, the first step involves generation of the *O*-radical (Scheme 3.50).[104] If the radical is either not generated, or, immediately quenched upon formation, the subsequent rearrangement would not proceed. It is, however, unlikely that the steric requirements of the 15-geminal methyl groups play any significant role in either impeding the reactivity of the O–Si-bond towards radical formation, or the subsequent rearrangement. This reasoning is admittedly speculative, in that no analogy was found in an extensive literature survey.

In the light of the poor conversion of the silyl enol ether **193** into the cyclopropyl compound **194** as well as the complete lack of reactivity of the latter toward ring homologation, this route was abandoned.

Scheme 3.49



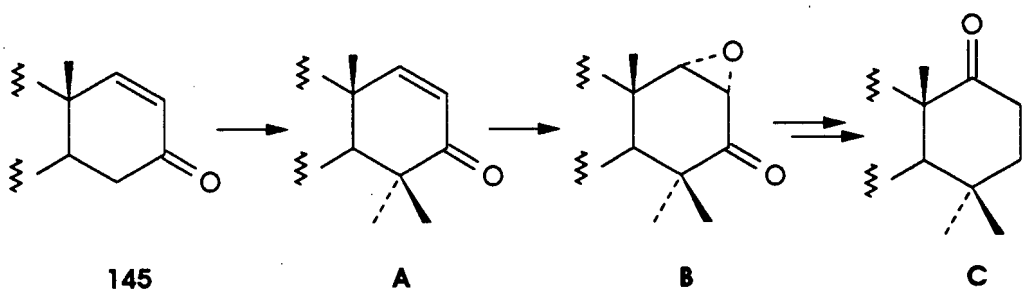
Scheme 3.50



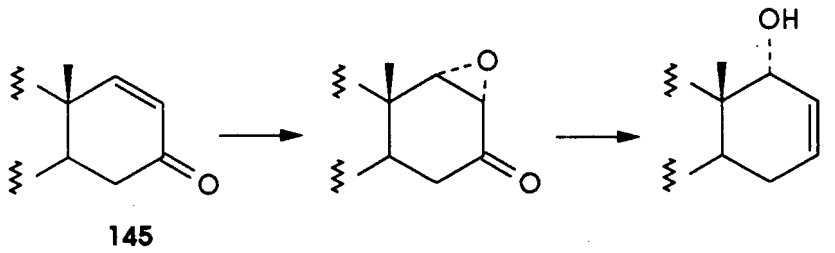
As an alternative route, it was reasoned that 15,15-dimethylation of 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-16-one **145**,[105] followed by epoxidation of the Δ^{17}-bond and subsequent Wharton rearrangement[129] of the epoxyketone **B** would lend access to the desired 15,15-dimethyl 17a-oxygenated system **C** (Scheme 3.51).

Several reports of the successful Wharton rearrangement of cyclic α,β-epoxyketones appeared in the recent literature.[130] The main application of this reaction is to effect a 1,3-transposition of carbonyl functionality. It was also shown[106] that the Δ^{17}-17a-homo-16-ketone **145** readily underwent epoxidation and Wharton rearrangement to give the derived Δ^{16}-17a-homo-17aα-alcohol (Scheme 3.52). This product also confirmed the stereochemistry of epoxidation. A clear analogy exists to the present case, and it was hoped that this reaction may be adapted to the 15,15-dimethyl analogue of **145**.

Scheme 3.51

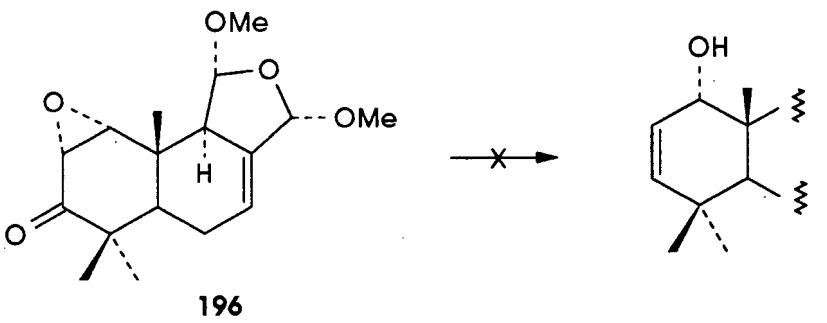


Scheme 3.52



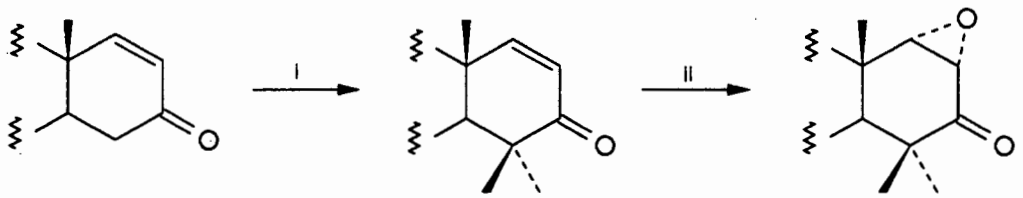
An application of the Wharton rearrangement by Tada and co-workers[131] on a triterpenoid compound **196** however proved to be unsuccessful (Scheme 3.53). This lack of reactivity towards formation of the hydrazone was ascribed to the steric demands of the geminal methyl groups. It was further reported[131] that the desired transformation was achieved by reduction of the epoxyketone with lithium aluminium hydride to give a mixture of 1,3-diols. Selective acetylation of the equatorial 3β-hydroxy group followed by Collins oxidation of the 1α-OH and elimination of acetic acid gave the desired product.

Scheme 3.53



In the present investigation, reaction of Δ^{17}-17a-homo-16-ketone **145** with freshly prepared potassium *tert*-butoxide and excess (*ca* 10 mol) iodomethane gave 3-methoxy-15,15-dimethyl-17a-homoestra-1,3,5(10),17-tetraen-16-one **197** (80%) (Scheme 3.54). In the ^{1}H-NMR spectrum, the 15-geminal methyl groups resonated at δ 1.31 and 1.33 respectively. Difference in chemical shift between the axial and equatorial 15-methyl groups was evident from the ^{13}C NMR spectrum. Resonances from the methyl groups were observed at δ 22.0 and 31.7, the former being the axial 15α-Me experiencing shielding through a steric interaction with the angular 13β-Me group.

Scheme 3.54



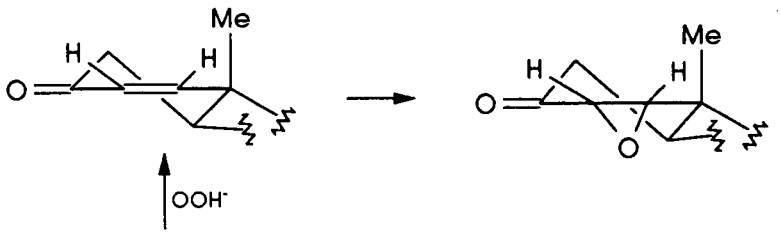
145 **197** **198**

I, Bu^{t}OK, MeI; II, H_2O_2-NaOH

The 15,15-dimethyl Δ^{17}-17a-homo-16-ketone **197** was reacted with alkaline hydrogen peroxide in methanol to give the 15,15-dimethyl 17α,17aα-epoxy-16-ketone **198** (90%). The mass spectrum of **198** shows a molecular ion of *m/z* 340, confirming introduction of an additional oxygen. In the ^{1}H-NMR spectrum, the 17- and 17a-protons resonated at δ 3.26 and 3.50 (each d, *J* 4.7 Hz) respectively. This is a typical chemical shift for oxirane methine protons. It was not possible to offer definitive evidence for the stereochemistry of epoxidation. However, it is reasonable to assume that initially, addition of the OOH$^-$-nucleophile occurred at C(17a) from the α-face of the molecule, thereby forming a stereoelectronically preferred axial bond. Reaction of the resultant enolate with the C(17a)-oxygen is then obliged to occur from the α-side as well, leading to a 17α,17aα-epoxide, as indicated in Scheme 3.55.

Treatment of the epoxyketone **198** with hydrazine hydrate at refluxing temperature led only to the recovery of starting material. Repeating the experiment with increasing amounts of the reagent had no effect either. This failure is reminiscencent of the work conducted by Tada in that lack of reactivity with respect to hydrazone formation is observed for similarly substituted epoxyketones. Their reported reductive opening of the epoxyketone was, however, not attempted in this work, owing to scarcity of material.

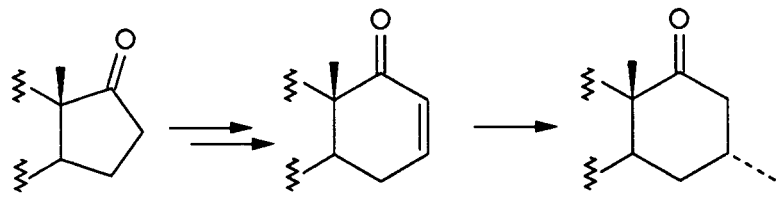
Scheme 3.55



3.5 Synthesis of 16,16-Dimethyl-17a-homoestradiols

As already elaborated, access was required to 3-methoxy-16,16-dimethyl-17a-homoestra-1,3,5(10)-trien-17a-one to investigate the influence of the 16-dimethyl substitution on the biological activity of the related 17a-homoestradiol. It was recently published[103] that the Δ^{16}-17a-homo-17a-ketone **143** was conveniently attainable through ring expansion of estrone 3-methyl ether **80**. It was also shown[103] that conjugate methylation of this enone gave the 16α-methyl compound **199** in good yield (Scheme 3.56).

Scheme 3.56



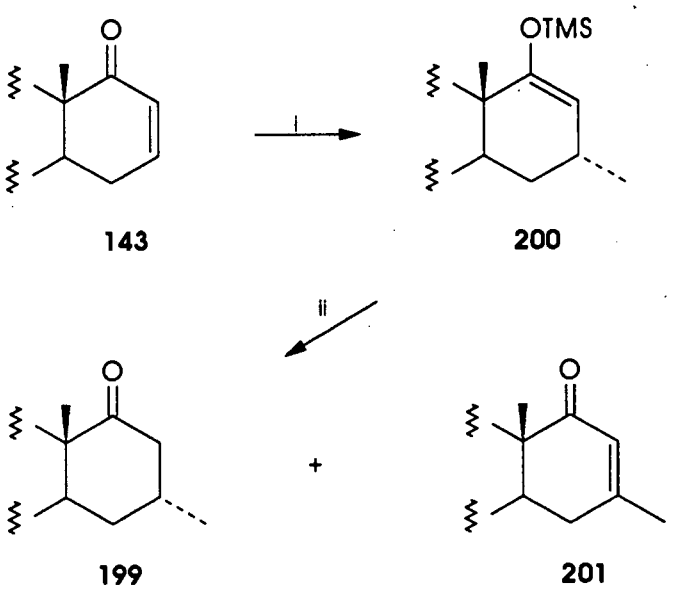
80 **143** **199**

A conceptual approach to the 16,16-dimethyl 17a-homo-17a-ketone involved sequential conjugate methylation – dehydrogenation – conjugate methylation of the 17a-homo-enone **143**, analogous to the successful route that was described in Chapter 3.2. Initially, a dehydrosilylation pathway[43] was proposed for the introduction of the Δ^{16}-bond. Conjugate methylation on the enone **143** was carried out with lithium dimethylcuprate – chlorotrimethylsilane[58] to give the 16α-methyl Δ^{17}-enol silyl ether **200** (92%) (Scheme 3.57). The intention of this modification was to obtain direct access to the silyl enol ether **200**, thereby eliminating the need for an additional deprotonation-trapping step. The ^{1}H NMR spectrum of **200** indicated the features expected from the modified ring D, i.e.

a 16α-methyl group (δ 1.00, d, *J* 7.0 Hz), the olefinic 17-proton (δ 4.58, *J* 4.6 Hz) and the 17a-trimethylsilyloxy group (δ 0.20, s).

Dehydrosilylation of **200** with palladium acetate in refluxing acetonitrile effected only a very poor conversion into the desired 3-methoxy-16-methyl-17a-homoestra-1,3,5(10),16-tetraen-17a-one **201** (21%). The main reaction product was the 16α-methyl 17a-ketone **199**[103] (70%), obtained from hydrolysis of the starting material (Scheme 3.57). TLC monitoring of the reaction course indicated that this destruction of the silyl enol ether **200** commenced after *ca* 8 h. Steric interactions between the pseudo-axial 13β- and 16α-methyl groups, and the approaching palladium reagent apparently limit the reactivity of this compound toward dehydrosilylation.

Scheme 3.57



i, Me_2CuLi-TMSCl; ii, $Pd(OAc)_2$, MeCN, Δ

The spectroscopic features of the 16-methyl Δ^{16}-17a-ketone **201** were in agreement with those expected for the cyclohexenoid moiety of ring D. The infrared spectrum indicated a carbonyl stretching frequency of ν_{max} 1658, typical of a six-membered α,β-unsaturated ketone. In the ^{1}H-NMR spectrum, the vinylic 16-methyl group resonated at δ 1.95 (d, *J* 2.0 Hz) and a trisubstituted olefinic bond was confirmed by a single resonance in the vinylic region (δ 2.06, quint, *J* 2.0 Hz). The fine structures of the 16-Me and 17-H signals were assigned with the aid of a COSY plot, which verified the couplings $J_{16\text{-Me},17}$ and $J_{15\beta,17}$. This type of four-bond allylic coupling is well documented and the appearance is dictated by mutual orthogonality of the coupling partners.[46] A molecular model of the 16-methyl Δ^{16}-17a-ketone **201** revealed the required geometric condition for the 15β- and 17-protons,

whereas momentary orthogonality can clearly be envisaged between the free-rotating 16-methyl group and the 17-proton (Figure 3.58). Equivalent coupling of the 17-proton to these allylic neighbours gives rise to the observed five-line signal.

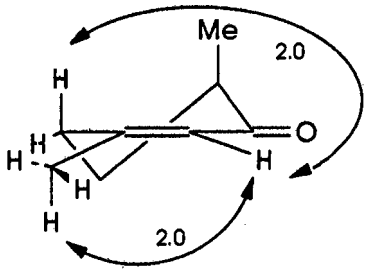
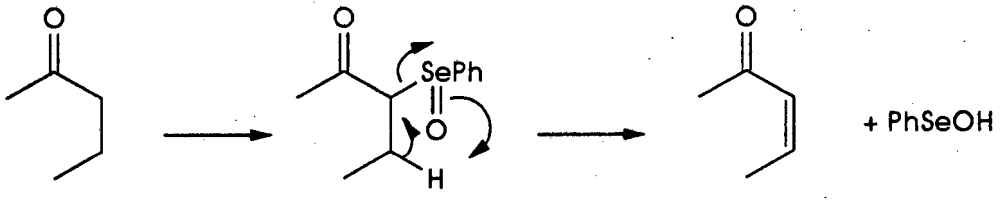


Figure 3.58 Orthogonality between allylic protons in **64**

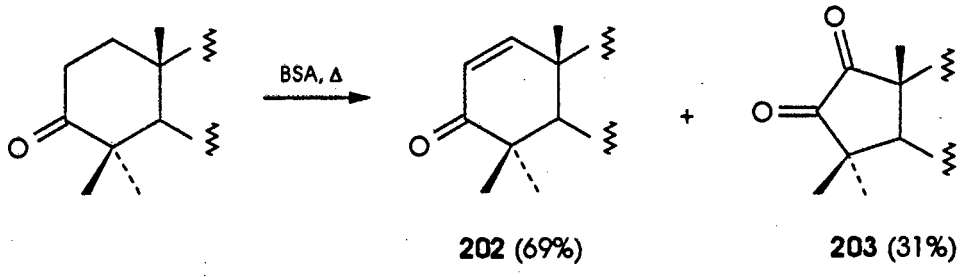
The poor conversion of the silyl enol ether **200** into the enone **201** prompted an investigation into an alternative way for introduction of the olefinic bond. Numerous cases are known in which α-phenylselenenyl ketones are converted into their corresponding α,β-unsaturated carbonyl compounds (Scheme 3.59).[132] This involves oxidation of the selenenyl substituent up to the selenoxide level, followed by *syn* elimination of phenylselenenic acid.

Scheme 3.59



The sigmatropic [2,3]-thermolysis of the selenoxide occurs entirely in the *syn* mode. By using benzeneselenenic anhydride (BSA) as selenylating reagent, the selenium is delivered in the appropriate oxidation state.[132] Hereby, the intermediacy of an oxidative step may be eliminated. A typical BSA-mediated dehydrogenation of a ketone into the derived α,β-unsaturated enone entails treatment the ketone with BSA in a refluxing solvent to achieve α-substitution with concomitant elimination of phenylselenenic acid and generation of the enone. A word of caution has been issued regarding the application of this methodology in in the steroid and triterpenoid fields. Barton[133] commented on the formation of ring-contracted diketones obtained from prolonged, high temperature exposure of the material, as indicated in Scheme 3.60.

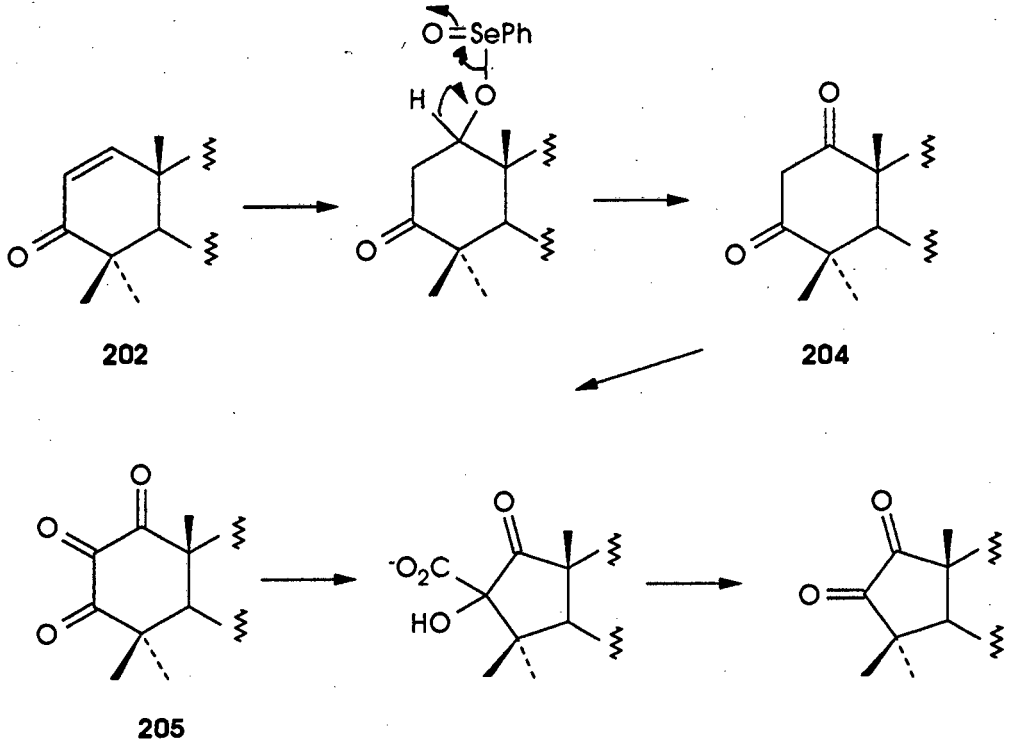
Scheme 3.60



202 (69%) **203** (31%)

Formation of the diketone **203** was explained by Barton[133] in terms of disproportionation of excess BSA to give a phenylseleninic anion ($PhSeO_2^-$). Conjugate addition of $PhSeO_2^-$ to the enone **202**, followed by elimination of phenylselenenic acid (PhSeOH) gave a 1,3-diketone **204**. Enolisation towards C(2) rendered this position reactive for a similar course of events occurs to yield a 1,2,3-triketone **205**. Contraction of the ring through a benzilic acid-type rearrangement, followed by decarboxylation gave the isolated product (Scheme 3.61).

Scheme 3.61

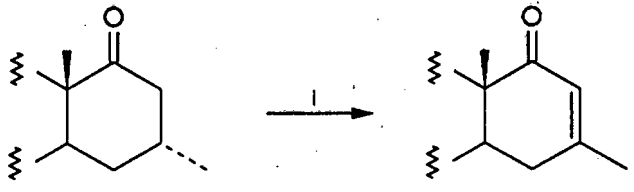


202 **204**

205

In the present work, dehydrogenation of the 16α-methyl 17a-ketone **199** was achieved with BSA (1 mol) in toluene at 80 °C (Scheme 3.62). By performing the reaction in toluene at a moderate temperature of 80 °C, the yield of **201** amounted to 60%. This is a three-fold improvement over the dehydrosilylation approach. Careful chromatography using a gradient elution technique was required to separate the selenium artefacts from the 16-methyl Δ^{16}-17a-homo-17a-ketone **201**.

Scheme 3.62

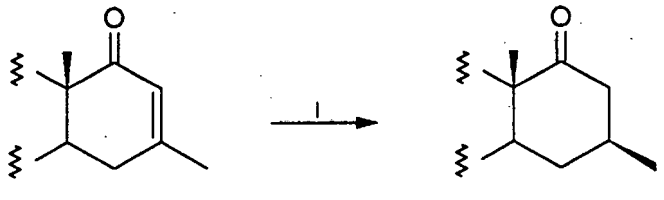


199 **201**

I, BSA, PhMe, Δ

To gain access to the 16β-methyl 17a-ketone **202** for complete spectroscopic comparitive studies, the 16-methyl Δ^{16}-17a-ketone **201** was reduced with lithium in liquid ammonia to give **206** (80%) (Scheme 3.63). Selectivity is explained in terms of axial protonation of the intermediate carbanion, to give an equatorial 16-methyl group.

Scheme 3.63



201 **206**

I, Li-NH_3

From the ^{1}H-NMR spectra of ketones **199** and **206**, the 17α- and 17β-protons were distinguished by the chemical shift differences between axial and equatorial protons adjacent to a carbonyl group. The equatorial 17α-H is co-planar with the carbonyl group, and therefore experiences less deshielding relative to the out of plane axial 17β-H. Further, the 17α-protons experience four-bond *W*-couplings $J_{15\alpha,17\alpha}$ 1.1–1.8 Hz. The appearance of the 17α-proton of **199** and **206** clearly supported the C(16)-assignments. For the 16β-methyl

17a-ketone **206**, the coupling $J_{16\alpha,17\beta}$ 13.8 is indicative of an antiperiplanar arrangement, thereby confirming a 16β-methyl group. By contrast, the 16α-methyl 17a-ketone **199** has the analogous coupling $J_{16\beta,17\beta}$ 4.7 Hz, requiring a near-gauche orientation between the coupling partners, and therefore, an axial 16α-methyl group. These coupling features are illustrated in Figure 3.64.

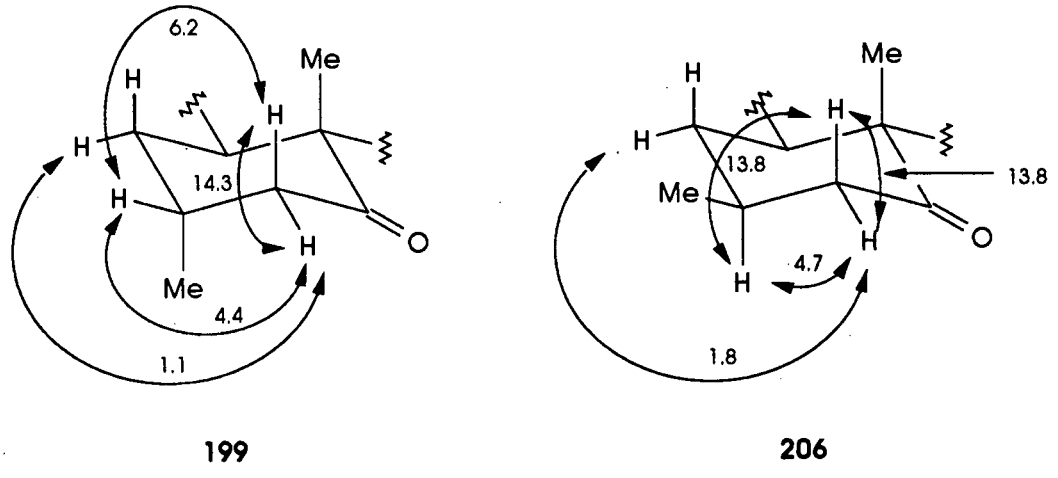
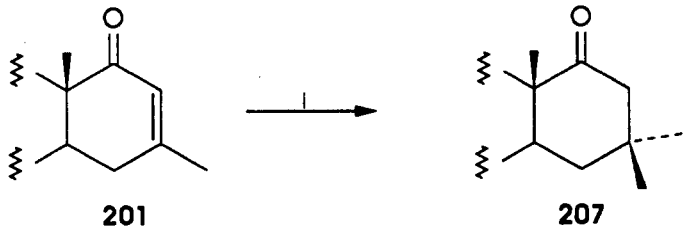


Figure 3.64: Coupling characteristics for 16-methyl 17a-ketones **199** and **206**

With the 16-methyl Δ^{16}-17a-ketone **201** in hand, the next step in the synthetic scheme was to introduce the geminal 16-methyl group. Reaction with lithium dimethylcuprate – chlorotrimethylsilane[58], followed by hydrolytic work-up proceeded in high yield to give 3-methoxy-16,16-dimethyl-17a-homoestra-1,3,5(10)-trien-17a-one **207** (88%) (Scheme 3.65).

Scheme 3.65

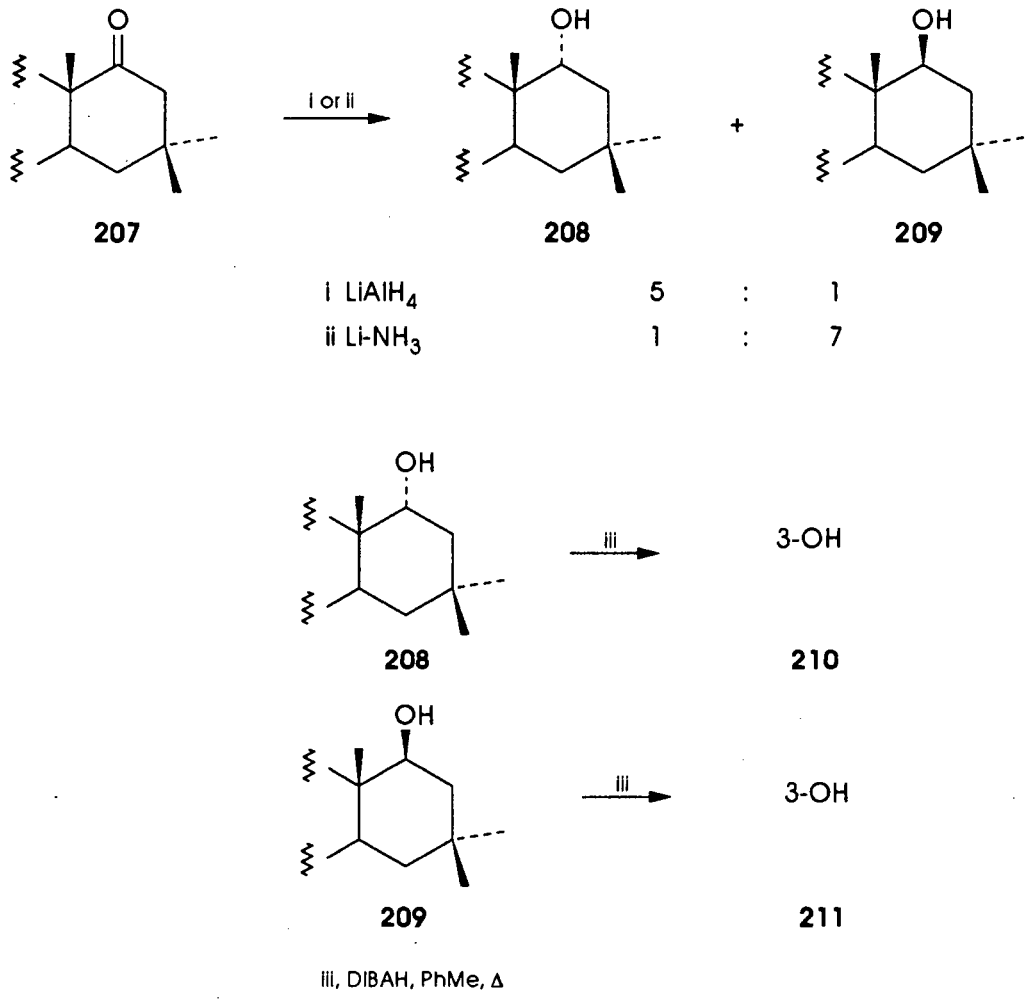


In the ^{1}H-NMR spectrum of the 16,16-dimethyl compound **207**, the 16-Me_2 protons were assigned to resonances at δ 0.9 and 1.08. The 17α-proton experienced a *W*-coupling to

15α-H ($J_{15\alpha,17\alpha}$ 1.9 Hz). Unfortunately, signal overlap prevented the clear extraction of clear couping patterns for 15-H_2. A COSY plot is indicated in Figure 3.67.

Reduction of the 17a-oxo group of **207** was carried out with lithium aluminium hydride in tetrahydrofuran at 0 °C to give a separable 5:1 mixture in favour of the 17aα-alcohol **208**. In a second experiment, the reduction was performed with lithium in liquid ammonia. Reversal of stereoselectivity was noted, with a 7:1 preference of the 17aβ-alcohol **209** (Scheme 3.66). From a 200 MHz NMR spectrum, the 17a-configurations of the alcohols **208** and **209** were clearly visible. The axial 17aα-H (δ 3.45, dd, *J* 11.2 and 5.2 Hz) of **72** showed a strong trans-diaxial coupling $J_{17\beta,17a\alpha}$ 11.2 Hz, whereas the 17a-diastereomer **73** displayed a syn-coupling $J_{17\beta,17a\beta}$ 3.1 Hz.

Scheme 3.66



The above diastereoselectivities are in close accordance with the results published for the analogous reactions on 3,3,6-trimethylcyclohexane.[134] It was reported that steric interaction from the axial 1,3-removed methyl group (16α-Me in **207**) inhibited the

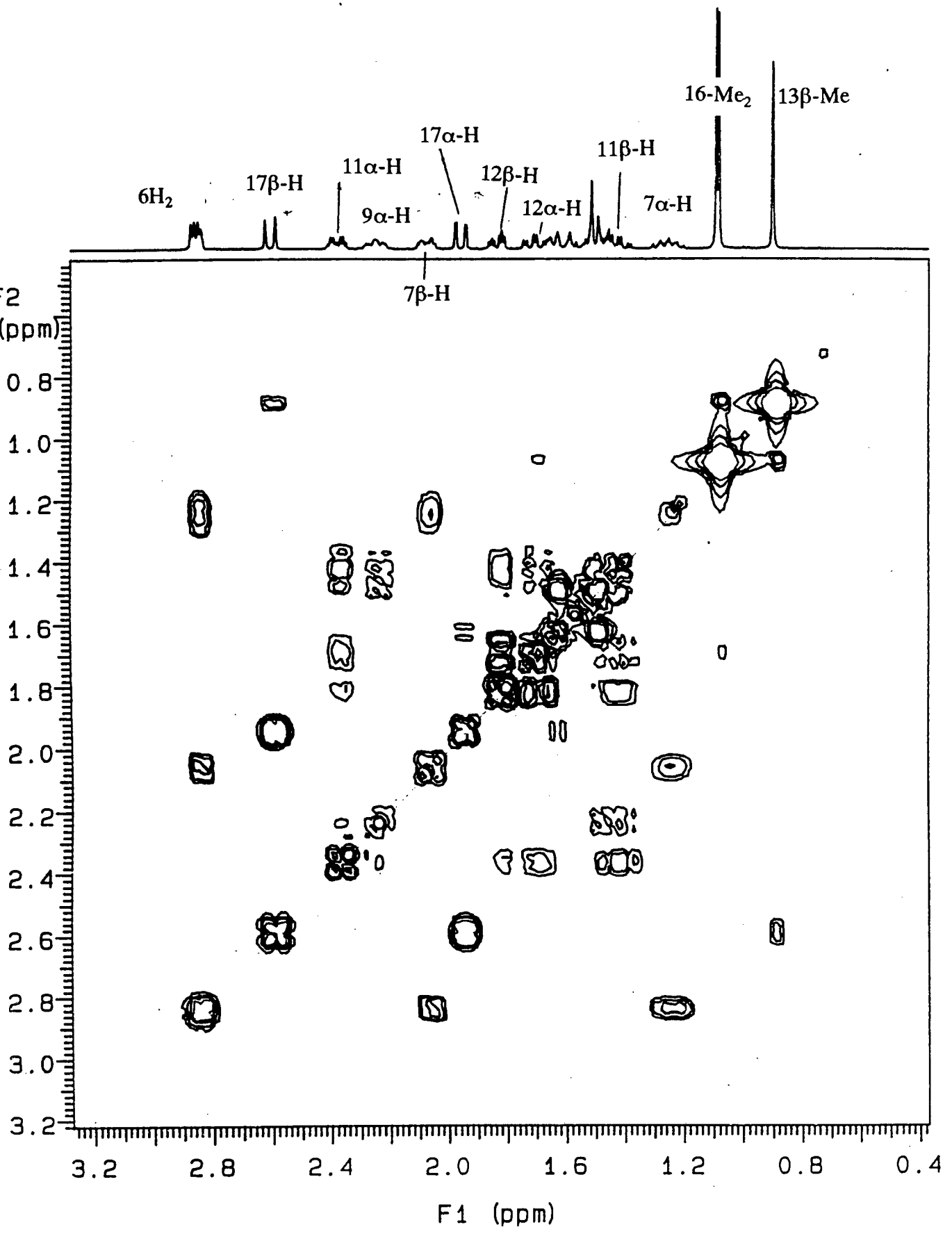


Figure 3.67: COSY plot of 16,16-dimethyl 17a-ketone **207**

stereoelectronically preferred axial approach by the hydride. A mixture of alcohols, favouring the product of equatorial hydride approach (i.e. the 'axial' alcohol), was therefore obtained. The use of sterically more demanding hydrides merely led to diminished amounts of the 'equatorial' alcohol (i.e. axial hydride approach). However, when a dissolving metal was used as reducing reagent, the thermodynamically preferred equatorial alcohol was obtained as the major product.

Routine demethylation of the 3-methyl ethers **208** and **209** gave the 16,16-dimethylhomoestradiols **210** and **211** (Scheme 3.66). Biological data of these analogues were not yet available.

An analysis of the Cotton effect (CE) of the series of 16-methyl 17a-homo-17a-ketones **199**, **206** and **207** was carried out. The octant projection of a steroidal 17a-homo 17a-ketone is shown in Figure 3.68.

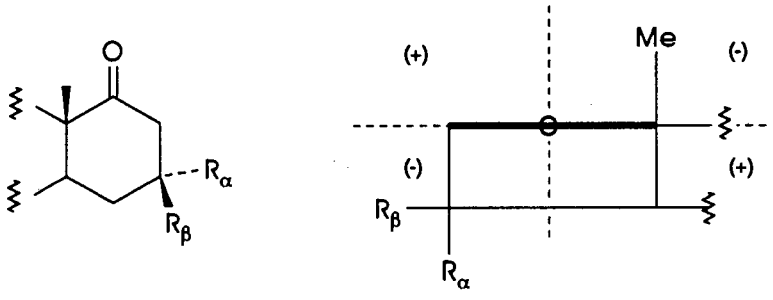


Figure 3.68: Octant projection of a 17a-homo-17a-ketone

A comparison of the CE for the 16α-methyl 17a-ketone **199** [$\Delta\varepsilon_{max}$ -0.22 (292 nm)] with the literature value for the unsubstituted ketone **212** [$\Delta\varepsilon_{max}$ -0.31 (290 nm)][135] indicated the weak octant-dissignate (i.e. positive) effect ($\Delta\Delta\varepsilon$ +0.09) of the axial 16α-methyl group. In a circular dichroism study on decalone systems by Kirk,[91] an empirical relation between the length and substitution mode of the zig-zag of carbon-carbon bonds and their contribution to the CE was formulated. The ketone 16α-methyl 17a-ketone **62** is representative of a case in which the β-removed methyl group occupies an axial position on a 'short' zig-zag (Figure 3.69), thereby exhibiting dissignate behaviour. The magnitude of the octant-dissignate contribution of this methyl group is in accordance to the reported value. For the diastereomeric 16β-methyl ketone **206** [$\Delta\varepsilon_{max}$ -1.02 (291 nm)] the octant-consignate, negative increment ($\Delta\Delta\varepsilon$ -0.71) of an equatorial β-removed methyl group is indicated. This effect originates from an extension of the zig-zag of C-C bonds, as indicated in Figure 3.69. The 16,16-dimethyl compound **207** shows $\Delta\varepsilon_{max}$ -0.90 (290 nm), which is virtually a direct summation of the increments determined for the 16α- and 16β-methyl groups. Table 3.5 lists the circular dichroism data for the series of 17a-homo 17a-ketones.

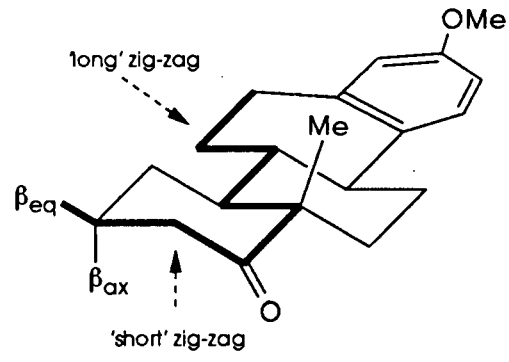


Figure 3.69: Coplanar C–C bonds for a 17a-homo 17a-ketone

Table 3.5: CD data for 16-substituted 17a-homo 17a-ketones

Compound	$\Delta\varepsilon_{max}$ (λ_{max}/nm)	$\Delta\Delta\varepsilon$
212 16,16-H_2	-0.31 (290)[46]	
199 16α-Me	-0.22 (292)	+0.09
206 16β-Me	-1.02 (291)	-0.71
207 16,16-Me_2	-0.90 (290)	-0.59

Chapter 4

BINDING AFFINITY RESULTS

This study has led to the successful synthesis of novel ring D alkylated estradiol and estriol analogues. The 14α,15α-methylene and 14-methylestriol analogues **123–124**, **130–131**, as well as the 15,15-dialkylestradiols **162**, **177–180**, and **189** (Scheme 4.1) were subjected to receptor binding assays.[136] Receptor binding assay plays a significant role in studies on structure–activity relations of hormones.[2] The primary consideration of such work is the development of active compounds superior to the natural hormone. These may be reflected as greater differentiation of activities, as well as oral activation.

The affinities of the estradiol and estriol analogues were measured by the method of competitive binding. This procedure requires a radioactively labelled reference hormone. The proportion of reference material bound by the receptor protein diminishes on addition of the test substance, as the test material competes for receptor site occupancy. The affinity of the hormone analogue towards the receptor is measured in terms of the 'competition factor' (CF), which is defined as the ratio of the concentration of test sample (c_{test}) to that of the reference substance (c_{ref}) required for 50% competition.[2]

$$CF = \frac{c_{test} \text{ at 50\% competition}}{c_{ref} \text{ at 50\% competition}}$$

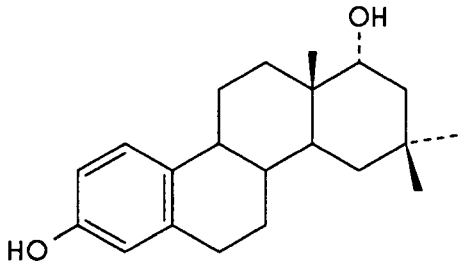
The reference substance has a CF value of unity. Hormone analogues with competition factors in the region of unity are regarded as highly competitive, whereas analogues with competition factors much higher than unity would not normally be considered as potential biological active analogues.

Scheme 4.1 summarises the binding affinity results for the hormone analogues prepared in this study.

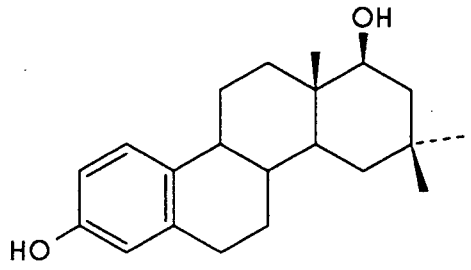
methyl- to an isopropyl group. On the other hand, the presence of a 15β-ethyl group had a strongly deactivating influence, as evidenced by the high CF values for **179** and **180**. The conclusion drawn was that steric bulk in the region of C(15) does not interfere with substrate–receptor binding, provided that it is limited to geminal dimethyl substitution. Further, chain extension of 15-alkyl groups are tolerated better on the α-face. The enhanced estrogenicity of the 15,15-dimethyl analogue **162** was rationalised in terms of steric inhibition of subsequent metabolic change and deactivation.

Biological data for the homoestradiol analogues **210** and **211** (Scheme 4.2) were not yet available, and will be reported elsewhere.

Scheme 4.2



210



211

Chapter 5

EXPERIMENTAL

General

Melting points were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrometer as chloroform solutions. All ^{1}H spectra were recorded in deuteriochloroform, unless otherwise specified, with tetramethylsilane as internal standard on a Varian VXR-200 instrument at 200 MHz or a Varian Unity spectrometer at 400 MHz, while all ^{13}C spectra were recorded on the same instruments at 50 or 100 MHz, respectively. Mass spectra were determined on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV and a source temperature of either 100 or 200 °C. Optical rotations were measured for chloroform solutions at 20 °C on a Perkin-Elmer 141 polarimeter and are in units of 10^{-1} deg cm^2 g^{-1}. Circular dichroism spectra were recorded on a Jasco J-20 instrument as methanol solutions. Microanalyses for C, H and N were performed on a Carlo Erba EA 1108 instrument.

All reactions were monitored by thin layer chromatography on aluminium-backed silica gel 60 F_{254} plates in various solvent systems, applying the ascending technique. Upon development, the plates were viewed under an ultra-violet lamp (wavelength 254 nm), then sprayed with ceric ammonium sulfate in 8 mol dm^{-3} sulfuric acid and baked at 200 °C for 5 min. Silica gel for column chromatography refers to Merck Kieselgel 60: 70-230 mesh for gravity columns, and 230-400 mesh for flash chromatography.

Commonly uesd solvents were purified as described below.

Tetrahydrofuran and diethyl ether: Dried over sodium wire and distilled under an argon atmosphere immediately prior to use from sodium wire and benzophenone as indicator.

Benzene and Toluene: Dried, distilled from and stored over sodium wire.

Acetic anhydride: Fractionally distilled and stored over molecular sieve (type 4A).

Triethylamine and pyridine: Distilled from potassium hydroxide and stored over potassium hydroxide pellets.

Unless oterwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen.

Concentration of the organic phase refers to removal of the solvent under reduced pressure on a Büchi Rotary Evaporator.

16α-*Hydroxy*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **82**

Copper(II) bromide (35.0 g, 156 mmol) was added to a refluxing solution of estrone 3-methyl ether **80** (18.0 g, 63.3 mmol) in methanol–benzene (1:1, 120 cm^3). The mixture was heated to reflux for 1 h. The warm solution was filtered (Celite pad) and the methanol was removed from the filtrate under reduced pressure. The residue of was suspended in water (50 cm^3) and extracted into chloroform. Combined organic phase was washed (water and brine), dried (magnesium sulfate) and evaporated to dryness under reduced pressure to give the 16α-bromo 17-ketone **81** (23.0 g, 100%), m.p. (176–177 °C) (from chloroform-methanol) (lit.,[36] m.p. 176–177 °C).

To a suspension of this bromo ketone **81** (23.0 g, 63.3 mmol) in aqueous 75% *N,N*-dimethylformamide (DMF) (300 cm^3) was added a solution of 2 mol dm^{-3} potassium hydroxide in aqueous DMF (37 cm^3). The mixture was heated to 80 °C. After 3 h, the warm solution was poured into a mixture of glacial acetic acid–water (1:4; 100 cm^3) and the organic material was extracted into ethyl acetate. Combined organic extracts were washed (saturated aqueous sodium hydrogen carbonate and brine), dried (magnesium sulfate) and evaporated to yield the 16α-hydroxy 17-ketone **82** (15.6 g, 82%), m.p. 155–158 °C (from chloroform-methanol) (lit.,[39] m.p. 156–157 °C); $[\alpha]_D$ +150 (*c* 1.0); ν_{max}/cm^{-1} 3560 (OH), 1746 (CO); δ_H (200 MHz) 0.98 (3H, s, 13β-Me), 2.85–2.87 (2H, m, 6α- and 6β-H), 3.76 (3H, s, 3-OMe), 4.40 (1H, dd, *J* 7.4 and 2.4, 16β-H), 6.63 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8,6 and 2.8, 2-H) and 7.18 (1H, d, *J* 8.6, 1-H) (Found: C, 75.6; H, 7.9%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.1%; *M*, 300).

17β-*Hydroxy*-3-*methoxyestra*-1,3,5(10)-*trien*-16-*one* **83**

The 16α-hydroxy 17-ketone **82** (15.6 g, 52.0 mmol) was dissolved in methanol – benzene (1:1, 250 cm^3). Aqueous 2 mol dm^{-3} potassium hydroxide (52 cm^3) was added to this solution and the mixture was heated to reflux for 2 h. The methanol was removed under reduced pressure and the residue was suspended in water (100 cm^3) and extracted into ethyl acetate. Combined organic extracts were sequentially washed with water and brine, dried ($MgSO_4$), and evaporated to give the 17β-hydroxy 16-ketone **83** (16.4 g, 94%), m.p. 166–169 °C (from methanol) (lit.,[36] m.p. 164–170 °C); $[\alpha]_D$ -76 (*c* 1.1); ν_{max}/cm^{-1} 3682 (OH), 1743 (CO); δ_H (400 MHz) 0.75 (3H, s, 13β-Me), 1.43-1.52 (1H, m, 7α-H), 1.72 (1H, td, *J* 2 x 12.7 and 8.0, 14α-H), 1.84 (1H, ddt, *J* 12.4, 5.5 and 2 x 2.9, 7β-H), 1.94 (1H, dd, *J* 18.8 and 12.7, 15β-H), 2.12 (1H, dt, *J* 12.4 and 2 x 3.1, 12β-H), 2.43 (1H, dd, *J* 18.8 and 8.0, 15α-H), 2.70 (1H, s, 17β-OH, exch. by D_2O), 2.86–2.88 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 3.84 (1H, s, 17α-H), 6.63 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.8, 1-H); δ_C (50 MHz) 11.4 (q, C-18), 26.0 (t, C-7), 27.8 (t, C-11),

29.6 (t, C-6), 35.2 (t, C-12), 36.5 (t, C-15), 37.6 (d, C-8), 42.9 (s, C-13), 43.9 (d, C-9), 44.1 (d, C-14), 55.2 (q, 3-OMe), 86.4 (d, C-17), 111.7 (d, C-2), 113.9 (d, C-4), 126.1 (d, C-1), 131.9 (s, C-10), 137.5 (s, C-5), 157.7 (s, C-3) and 216.9 (s, C-16) (Found: C, 75.6; H, 7.9 %; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05 %; *M*, 300).

17β-tert-*Butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10)-*trien*-16-*one* **84**

Imidazole (9.3 g, 136 mmol) and *tert*-butyldimethylchlorosilane (9.9 g, 65.7 mmol) were added to a solution of the 17β-hydroxy 16-ketone **83** (16.4 g, 54.6 mmol) in dry DMF (35 cm^3). The solution was stirred at 60 °C for 1 h. Water (20 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (aq $NaHCO_3$, brine), dried ($MgSO_4$) and evaporated to give 17β-tert-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10)-*trien*-16-*one* **84** (21.4 g, 95%), m.p. 122–124 °C (from chloroform-methanol); $[\alpha]_D$ -43 (*c* 0.9); $\Delta\varepsilon_{max}$ -5.50 (303 nm); ν_{max}/cm^{-1} 1751 (CO); δ_H (200 MHz, C_6D_6) 0.20 and 0.38 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.66 (3H, s, 13β-Me), 1.09 (9H, s, *Bu*^{t}SiMe$_2$), 2.68–2.70 (2H, m, 6α- and 6β-H), 3.44 (3H, s, 3-OMe), 3.51 (1H, s, 17α-H), 6.74 (1H, d, *J* 2.8, 4-H), 6.80 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.27 (1H, d, *J* 8.8, 1-H); δ_H (200 MHz, $CDCl_3$) 0.07 and 0.15 (each 3H, s, Bu^{t}SiMe$_2$), 0.78 (3H, s, 13β-Me), 0.92 (9H, s, *Bu*^{t}SiMe$_2$), 2.87–2.89 (2H, m, 6α- and 6β-H), 3.78 (4H, s, 3-OMe and 17α-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) -5.0 and -4.2 (*Me*$_2$SiCMe$_3$), 11.9 (C-18), 18.4 (Me$_2$Si*C*Me$_3$), 25.8 (3C, Me$_2$SiC*Me*$_3$), 26.1 (C-7), 27.7 (C-11), 29.7 (C-6), 35.9 (C-12), 36.9 (C-15), 37.8 (C-8), 42.9 (C-13), 44.0 (C-9), 44.1 (C-14), 55.2 (3-OMe), 87.2 (C-17), 111.7 (C-2), 113.9 (C-4), 126.1 (C-1), 132.1 (C-10), 137.7 (C-5), 157.7 (C-3) and 215.5 (C-16) (Found: C, 72.0; H, 9.1 %; M^+ -57, 357. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2 %; *M*, 414).

17β-tert-*Butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16-*one* **86**

A solution of *n*-butyllithium (1.6 mol dm^{-3} in hexanes; 52 cm^3, 83.2 mmol) was added to a solution of diisopropylamine (24 cm^3, 169 mmol) in dry tetrahydrofuran (15 cm^3) at 0 °C. This temperature was maintained, with stirring, for 5 min. The resulting clear solution of lithium diisopropylamide was cooled to -78 °C, and the 16-ketone **84** (17.3 g, 41.8 mmol) in dry tetrahydrofuran (120 cm^3) was added slowly. Low temperature stirring was maintained for 45 min. Chlorotrimethylsilane (25 cm^3, 197 mmol) was added, and the mixture was allowed to warm to 0 °C. After 30 min, saturated aqueous ammonium chloride was added, the mixture was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (19.3 g) was dissolved in dry acetonitrile (250 cm^3).

Palladium(II) acetate (9.4 g, 41.9 mmol) was added, and the reaction was heated to 80 °C for 1 h. The cooled solution was filtered and concentrated to give a dark solid mass (19.7 g). Chromatography on silica gel (10 g), eluting with ethyl acetate-toluene (1:49) gave 17β-*tert*-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16-*one* **86** (13.9 g, 81% from **84**), m.p. 128–131°C (from chloroform-methanol); $[\alpha]_D$ +209 (*c* 1.1); ν_{max}/cm^{-1} 1709 (CO); δ_H (200 MHz) 0.12 and 0.20 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.94 (9H, s, *Bu*^{t}SiMe$_2$), 1.15 (3H, s, 13β-Me), 2.94–2.96 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 3.91 (1H, s, 17α-H), 5.84 (1H, d, *J* 1.4, 15-H), 6.66 (1H, d, *J* 2.7, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -5.2 and -4.2 (*Me*$_2$SiCMe$_3$), 18.5 (Me$_2$Si*C*Me$_3$), 21.0 (C-18), 25.1 (C-7), 25.8 (3C, Me$_2$SiC*Me*$_3$), 27.1 (C-11), 29.5 (C-6), 39.0 (C-12), 40.4 (C-8), 43.7 (C-9), 47.1 (C-13), 55.2 (3-OMe), 84.7 (C-17), 112.1 (C-2), 113.8 (C-4), 121.6 (C-15), 126.8 (C-1), 130.9 (C-10), 137.3 (C-5), 157.9 (C-3), 185.3 (C-14) and 206.4 (C-16) (Found: C, 72.5; H, 8.6 %; M$^+$ - 57, 355. $C_{25}H_{36}O_3Si$ requires C, 72.8; H, 8.8 %; *M*, 412).

3-*Methoxy*-17β-*hydroxyestra*-1,3,5(10),14-*tetraen*-16-*one* **87**

Tetrabutylammonium fluoride (1.1 mol dm^{-3} in tetrahydrofuran; 2.5 cm^3, 2.75 mmol) was added to a solution of the 17β-silyl ether **86** (207 mg, 0.50 mmol) in dry tetrahydrofuran (5 cm^3) at 0 °C. Stirring was maintained at 20 °C for 1 h. The mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and evaporated. The residue (200 mg) was chromatographed on silica gel (20 g) with methanol-chloroform (1:49) to obtain 3-*methoxy*-17β-*hydroxyestra*-1,3,5(10),14-*tetraen*-16-*one* **87** (124 mg, 83%), m.p. 182–184 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ +217 (*c* 1.1); ν_{max}/cm^{-1} 3675 (OH), 1700 (CO); δ_H (400 MHz) 1.18 (3H, s, 13β-Me), 2.18 (1H, ddt, *J* 12.5, 5.1 and 2.5, 7β-H), 2.26-2.29 (1H, m, 12β-H), 2.86 (1H, s, 17β-OH, exch. by D_2O), 2.94–2.96 (2H, s, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 3.95 (1H, s, 17α-H), 5.93 (1H, d, *J* 1.4, 15-H), 6.66 (1H, d, *J* 2.7, 4-H), 6.76 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 20.5 (q, C-18), 25.2 (t, C-7), 27.1 (t, C-11), 29.5 (t, C-6), 38.3 (t, C-12), 40.5 (d, C-8), 43.7 (d, C-9), 47.1 (s, C-13), 55.2 (q, 3-OMe), 83.9 (d, C-17), 111.2 (d, C-2), 113.9 (d, C-4), 120.7 (d, C-15), 126.9 (d, C-1), 130.6 (s, C-10), 137.2 (s, C-5), 157.9 (s, C-3), 186.6 (s, C-14) and 206.5 (s, C-16) (Found: C, 76.1; H, 7.4%; M$^+$, 298. $C_{19}H_{22}O_3$ requires C, 76.5, H, 7.4%; *M*, 298).

Hydride Reduction of the Δ^{14}-16-*ketone* **86**

(*a*) A solution of the Δ^{14}-16-ketone **86** (1.03 g, 2.50 mmol) in dry tetrahydrofuran (15 cm^3) at 0 °C was treated with lithium aluminium hydride (474 mg, 12.49 mmol). Stirring was maintained at 0 °C for 1 h. Saturated aqueous sodium hydrogen carbonate was added and the precipitate was filtered. The filtrate was extracted into ethyl acetate, washed (water

and brine), dried ($MgSO_4$) and concentrated. Chromotography of the residue (954 mg) on silica gel (50 g) with ethyl acetate-toluene (1:49) as eluent gave 17β-*tert-butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16α-*ol* **92** (631 mg, 61%), m.p. 115–119 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ +75 (*c* 1.0); ν_{max}/cm^{-1} 3433 (OH); δ_H (400 MHz) 0.10 and 0.14 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.93 (9H, s, *Bu*^{t}SiMe$_2$), 1.02 (3H, s, 13β-Me), 1.63 (1H, d, *J* 5.9, 17α-OH, exch. by D_2O), 1.92 (1H, dt, *J* 12.2 and 2 x 2.5, 12β-H), 2.04 (1H, dq, *J* 11.4 and 3 x 2.5 Hz, 7α-H), 2.08-2.13 (1H, m, 8β-H), 2.88–2.90 (2H, m, 6α- and 6β-H), 3.71 (1H, d, *J* 5.9, 17α-H), 3.77 (3H, s, 3-OMe), 4.59 (1H, dddd, *J* 2 x 5.9, 3.2 and 1.9 → ddd, *J* 5.9, 3.2 and 1.9 on D_2O exch., 16β-H), 5.24 (1H, t, *J* 2 x 1.9, 15-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.9 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.9, 1-H); δ_C (50 MHz) -4.6 and -4.2 (each q, *Me*$_2$SiCMe$_3$), 18.1 (s, Me$_2$Si*C*Me$_3$), 18.7 (q, C-18), 25.0 (t, C-7), 25.9 (3C, q, Me$_2$SiC*Me*$_3$), 27.2 (t, C-11), 29.8 (t, C-6), 38.8 (d, C-8), 39.7 (t, C-12), 43.2 (d, C-9), 47.7 (s, C-13), 55.2 (q, 3-OMe), 82.4 (d, C-16), 91.8 (d, C-17), 111.8 (d, C-2), 113.8 (d, C-4), 119.2 (d, C-15), 126.7 (d, C-1), 131.9 (s, C-10), 137.9 (s, C-5), 153.7 (s, C-14) and 157.6 (s, C-3) (Found: C, 72.4; H, 9.3%; M$^+$ - 57, 357. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2%; *M* 414). Further elution of the column with ethyl acetate gave 3-methoxyestra-1,3,5(10),14-tetraene-16β,17β-diol **90** (252 mg, 30%), m.p. 112–114 °C (from chloroform-methanol) (lit.,[44] m.p. 114–116 °C); $[\alpha]_D$ +152 (*c* 0.8); ν_{max}/cm^{-1} 3605 and 3514 (OH); δ_H (400 MHz) 1.12 (3H, s, 13β-Me), 1.38 (1H, td, *J* 2 x 12.5 and 3.8, 12α-H), 1.66 (1H, d, *J* 5.8, 16β-OH, exch. by D_2O), 2.14 (1H, dt, *J* 12.5 and 2 x 3.8, 12β-H), 2.18-2.23 (1H, m, 8β-H), 2.35 (1H, dq, *J* 13.2 and 4 x 3.8, 7α-H), 2.75 (1H, d, *J* 9.6, 17β-OH, exch. by D_2O), 2.92–2.94 (2H, m, 6α- and 6β-H), 3.77 (1H, dd, *J* 9.6 and 5.8 → d, *J* 5.8 on D_2O exch., 17α-H), 3.78 (3H, s, 3-OMe), 4.46 (1H, dt, *J* 2 x 5.8 and 2.9 → dd, *J* 5.8 and 2.9 on D_2O exch., 16α-H), 5.57 (1H, dd, *J* 2.9 and 1.3, 15-H), 6.65 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 21.2 (q, C-18), 25.3 (t, C-7), 27.2 (t, C-11), 29.8 (t, C-6), 39.2 (d, C-8), 39.8 (t, C-12), 43.7 (d, C-9), 47.3 (s, C-13), 55.2 (q, 3-OMe), 74.2 (d, C-17), 81.5 (d, C-16), 111.9 (d, C-2), 113.8 (d, C-4), 118.0 (d, C-15), 126.9 (d, C-1), 131.6 (s, C-10), 137.7 (s, C-5), 157.7 (s, C-3) and 160.2 (s, C-14) (Found: C, 76.3; H, 8.0%; M$^+$, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.1%; *M*, 300).

(*b*) Diisobutylaluminium hydride (1.5 mol dm^{-3} in toluene; 9.7 cm^3, 14.5 mmol) was added to a solution of the Δ^{14}-16-ketone **86** (1.50 g, 3.64 mmol) in dry tetrahydrofuran at 0 °C. After 30 min at this temperature, saturated aqueous ammonium chloride was added. The aqueous phase was acidified (1 mol dm^{-3} HCl), extracted into ethyl acetate, washed (aq $NaHCO_3$, water and brine), dried ($MgSO_4$) and evaporated. The residue (1.41 g) was chromatographed on silica gel (140 g), eluting with ethyl acetate-hexane (1:9) to give 17β-tert-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16β-*ol* **93** (342 mg, 28%), m.p. 91–93 °C (from chloroform-methanol); $[\alpha]_D$ +118 (*c* 1.2); ν_{max}/cm^{-1} 3511 (OH); δ_H (200 MHz) 0.14 and 0.15 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.97 (9H, s, *Bu*^{t}SiMe$_2$), 1.09 (3H, s,

13β-Me), 2.03 (1H, dt, *J* 12.3 and 2 x 3.3, 12β-H), 2.80 (1H, s, 16β-OH, exch. by D_2O), 2.90–2.92 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 3.83 (1H, d, *J* 6.0 17α-H), 4.29 (1H, dd, *J* 6.0 and 2.8, 16β-H), 5.59 (1H, dd, *J* 2.8 and 1.3, 15-H), 6.66 (1H, d *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) -4.8 and -4.5 (Me_2SiCMe_3), 18.2 (Me_2SiCMe_3), 20.9 (C-18), 25.2 (C-7), 25.9 (3C, Me_2SiCMe_3), 27.2 (C-11), 29.9 (C-6), 39.2 (C-8), 40.1 (C-12), 43.6 (C-9), 47.7 (C-13), 55.2 (3-OMe), 73.9 (C-16), 82.4 (C-17), 111.9 (C-2), 113.8 (C-4), 118.4 (C-15), 126.8 (C-1), 131.7 (C-10), 137.9 (C-5), 157.7 (C-3) and 158.3 (C-14) (Found: C, 72.1; H, 9.2%; M^+ - 57, 357. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2%; *M*, 414), followed by the Δ^{14}-16α-alcohol **92** (909 mg, 60%).

(*c*) A solution of the Δ^{14}-16-ketone **86** (502 mg, 1.22 mmol) in dry tetrahydrofuran (10 cm^3) was cooled to -40 °C. Lithium tri-*sec*-butylborohydride (L-Selectride®) (1.0 mol dm^{-3} in tetrahydrofuran; 1.5 cm^3, 1.5 mmol) was added. After 5 min the temperature was slowly raised to -20 °C. The latter was maintained for 15 min, after which the mixture was poured into 0.5 mol dm^{-3} HCl (15 cm^3), pre-cooled to 0 °C. The mixture was extracted into ethyl acetate, washed (aqueous sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated. The residue (500 mg) was chromatographed on silica gel (50 g), eluting with ethyl acetate-toluene (1:19) to give 16β-tert-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-17β-*ol* **94** (24 mg, 5%), m.p. 105–108 °C (from chloroform-methanol); $[\alpha]_D$ +172 (*c* 1.4); ν_{max}/cm^{-1} 3519 (OH); δ_H (400 MHz) 0.04 and 0.07 (each 3H, s, Bu^{t}SiMe_2), 0.91 (9H, s, *Bu*^{t}SiMe$_2$), 1.07 (3H, s, 13β-Me), 1.36 (1H, td, *J* 2 x 13.2 and 3.7, 12α-H), 2.34 (1H, dq, *J* 13.5 and 3 x 3.7, 11α-H), 2.84–2.86 (2H, m, 6α- and 6β-H), 3.64 (1H, dd, *J* 6.0 and 2.7 → d, *J* 6.0 on D_2O exch., 17α-H), 3.71 (3H, s, 3-OMe), 4.39 (1H, dd, *J* 6.0 and 2.6, 16β-H), 5.35 (1H, dd, *J* 2.6 and 1.3, 15-H), 6.59 (1H, d, *J* 2.6. 4-H), 6.67 (1H, dd, *J* 8.5 and 2.6, 2-H) and 7.17 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) -4.7 and -4.4 (Me_2SiCMe_3), 18.1 (Me_2SiCMe_3), 20.3 (C-18), 25.3 (C-7), 25.9 (3C, Me_2SiCMe_3), 27.3 (C-11), 29.8 (C-6), 37.1 (C-8), 39.7 (C-12), 43.7 (C-9), 47.3 (C-13), 55.2 (3-OMe), 74.7 (C-16), 81.4 (C-17), 111.8 (C-2), 113.8 (C-4), 118.2 (C-15), 127.0 (C-1), 131.8 (C-10), 137.7 (C-5), 157.6 (C-3) and 158.6 (C-14) (Found: C, 72.1; H, 9.2%; M^+ - 57, 357. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2%; *M*, 414). Further elution of the column with the same solvent gave the Δ^{14}-16β-alcohol **93** (454 mg, 90%).

3-*Methyoxyestra*-1,3,5(10),14-*tetraene*-16β-17β-*diol* **90**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 mol dm^{-3}; 1.1 cm^3, 1.21 mmol) was dried over pulverised 4A molecular sieves for 30 min. Hexamethylphosphoric triamide (0.2 cm^3, 1.08 mmol), followed by a solution of the 17β-silyl ether **93** (207 mg, 0.50 mmol) in dry tetrahydrofuran (2 cm^3). The mixture was stirred

at 20 °C for 1 h, and then filtered. The filtrate was diluted with ethyl acetate, washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$), and evaporated. The residue (140 mg) was chromatographed on silica gel (7 g) with methanol-chloroform (1:49) as eluent to give the Δ^{14}-16β,17β-diol **90** (133 mg, 89%).

3-*Methoxyestra*-1,3,5(10),14-*tetraene*-16α,17β-*diol* **91**

The 17β-silyl ether **92** (50 mg, 0.12 mmol) in dry tetrahydrofuran (5 cm^3) and hexamethylphosphoric triamide (0.05 cm^3) was treated at 20 °C for 45 min with anhydrous tetrabutylammonium fluoride (0.5 cm^3, 0.55 mmol) (prepared as described above). Solid material was removed by filtration and the 16α,17β-diol **91** (29 mg, 80%) was precipitated with cold methanol, m.p. 133–135 °C (from methanol) (lit.,[45] m.p. 133–135 °C); $[\alpha]_D$ +120 (*c* 1.0) (Found: C, 76.1; H, 8.0%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.1%; *M*, 300).

16β,17β-*Isopropylenyldioxy*-3-*methoxyestra*-1,3,5(10),14-*tetraene* **95**

A drop of perchloric acid was added to a solution of the 16β,17β-diol **90** (85 mg, 0.28 mmol) in acetone (4 cm^3). After 5 min at room temperature, water was added, the precipitate was filtered and recrystallised from acetone to give 16β,17β-*isopropylenedioxy*-3-*methoxyestra*-1,3,5(10),14-*tetraene* **95** (86 mg, 91%), m.p. 126–130 °C (from acetone-methanol); $[\alpha]_D$ +219 (*c* 1.0); δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 1.37 and 1.46 [each 3H, s, -OC(CH_3)$_2$O-], 2.87–2.89 (2H, m, 6α- and 6β-H), 3.68 (3H, s, 3-OMe), 4.34 (1H, d, *J* 6.6, 17α-H), 5.08 (1H, dd, *J* 6.6 and 2.1, 16α-H), 5.38 (1H, dd, *J* 3.2 and 2.1, 15-H), 6.64 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.19 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 18.9 (C-18), 25.0 (C-7), 25.9 and 26.7 [-OC(CH_3)$_2$O-], 27.2 (C-11), 29.8 (C-6), 38.7 (C-8), 40.4 (C-12), 45.5 (C-9), 48.4 (C-13), 55.2 (3-OMe), 85.3 (C-16), 87.3 (C-17), 111.0 [-*O*C(CH_3)$_2$O-], 111.8 (C-2), 113.8 (C-4), 115.5 (C-15), 126.6 (C-1), 131.8 (C-10), 137.7 (C-5), 157.7 (C-3) and 159.7 (C-14) (Found: C, 77.3; H, 8.2%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6, H, 8.3%; *M*, 340).

Attempted acetonide formation on the 16α,17β-*diol* **91**

A solution of the 16α,17β-diol **91** (29 mg, 0.1 mmol) in acetone (3 cm^3), containing a drop of perchloric acid was stirred 20 °C for 3 days. Starting material was recovered.

Attempted Conjugate Allylation on the Δ^{14}-16-*ketone* **86**

Tetrabutylammonium fluoride (38 mg, 0.15 mmol) (freshly dried under high vacuum for 30 min at 20 °C) was dissolved in dry DMF (1 cm^3) and stirred with activated molecular sieves for 30 min. A solution of the enone **86** (120 mg, 0.29 mmol) in DMF (2 cm^3), followed by freshly distilled allyltrimethylsilane (0.15 cm^3, 1.04 mmol) and hexamethylphosphoric triamide (0.5 cm^3) were added sequentially. The temperature was slowly raised to 80 °C, but no products of allylation were isolated.

Attempted Conjugate Methylation of the Δ^{14}-16-*ketone* **86**

(*a*) Ethereal 1.4 mol dm^{-3} methyllithium (1.4 cm^3, 1.96 mmol) was added to a stirred suspension of copper(I) iodide (95 mg, 0.50 mmol) in dry diethyl ether (2 cm^3) at 0 °C. The resultant clear solution of lithium dimethylcuprate was cooled to -78 °C and chlorotrimethylsilane (0.06 cm^3, 0.47 mmol) was added. After 5 min at this temperature, a solution of Δ^{14}-16-ketone **86** (100 mg, 0.24 mmol) in dry tetrahydrofuran (3 cm^3) was added. The mixture was stirred at -78 °C for 20 min, after which the temperature was slowly increased to 0 °C. After 30 min at 0 °C, saturated aqueous ammonium chloride was added. The mixture was filtered and the filtrate was extracted into ethyl acetate, washed (saturated aqueous sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated. The residue (105 mg) was chromatographed on silica gel (10 g), eluting in ethyl acetate-toluene (1:49) to obtain 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-16α-*methylestra*-1,3,5(10),14-*tetraen*-16β-*ol* **103** (83 mg, 81%), m.p. 107–109 °C (from chloroform-hexane); $[\alpha]_D$ +106 (*c* 1.0); ν_{max}/cm^{-1} 3501 (OH); δ_H (200 MHz) 0.15 and 0.16 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.99 (9H, s, *Bu*^{t}SiMe$_2$), 1.10 (3H, s, 13β-Me), 1.31 (3H, s, 16α-Me), 2.88–2.90 (2H, m, 6α- and 6β-H), 3.00 (1H, s, 16β-OH, exch. by D_2O), 3.57 (1H, s, 17α-H), 3.77 (3H, s, 3-OMe), 5.40 (1H, d, *J* 1.4, 15-H), 6.64 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) -4.5 and -3.9 (*Me*$_2$SiCMe$_3$), 18.1 (Me$_2$Si*C*Me$_3$), 19.8 (C-18), 25.1 (C-7), 25.9 (3C, Me$_2$SiC*Me*$_3$), 27.2 (C-11), 27.3 (16α-Me), 29.8 (C-6), 38.8 (C-8), 40.3 (C-12), 43.4 (C-9), 48.6 (C-13), 55.2 (3-OMe), 78.2 (C-16), 87.3 (C-17), 111.8 (C-2), 113.7 (C-4), 123.1 (C-15), 126.7 (C-1), 131.8 (C-10), 137.9 (C-5), 155.0 (C-14) and 157.6 (C-3) (Found: C, 72.4; H, 9.2%; M^+ - 57, 371. $C_{26}H_{40}O_3Si$ requires C, 72.8; H, 9.4%; *M*, 428).

(*b*) Methyl iodide (0.16 cm^3, 2.58 mmol) in dry diethyl ether (1.0 cm^3) was added to magnesium turnings (60 mg, 2.50 mmol) at 20 °C. After complete reaction of the magnesium, copper(I) iodide (47 mg, 0.25 mmol), followed by a solution of the Δ^{14}-16-ketone **86** (100 mg, 0.24 mmol) in dry tetrahydrofuran (1 cm^3) were added. The mixture was stirred at 20 °C for 10 min. Saturated aqueous ammonium chloride was added and the products were extracted into diethyl ether, washed (aqueous sodium thiosulfate, water and

brine), dried ($MgSO_4$), and evaporated. The residue (104 mg) was chromatographed on silica gel (10 g), eluting with ethyl acetate-hexane (1:9) to obtain the 16α-methyl Δ14-16β-alcohol **103** (59 mg, 58%), followed by 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-16β-*methylestra*-1,3,5(10),14-*tetraen*-16α-*ol* **105** (34 mg, 34%), m.p. 120–122 °C (from chloroform-methanol); $[\alpha]_D$ +92 (*c* 1.0); ν_{max}/cm^{-1} 3588 (OH); δ_H (200 MHz) 0.01 and 0.04 (each 3H, s, $Bu^tSi\mathit{Me}_2$), 0.86 (9H, s, Bu^tSiMe_2), 0.91 (3H, s, 13β-Me), 1.15 (3H, s, 16β-Me), 2.81–2.83 (2H, m, 6α- and 6β-H), 3.67 (3H, s, 3-OMe), 3.74 (1H, s, 17α-H), 5.15 (1H, d, *J* 1.9, 15-H), 6.54 (1H, d, *J* 2.8, 4-H), 6.63 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.12 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -4.6 and -4.2 (each q, Me_2CSiMe_3), 18.1 (s, $Me_2\mathit{C}SiMe_3$), 18.4 (s, C-18), 23.8 (q, 16β-Me), 25.2 (t, C-7), 26.0 (3C, $Me_2CSi\mathit{Me}_3$), 27.2 (t, C-11), 29.8 (t, C-6), 38.6 (d, C-8), 40.8 (t, C-12), 43.4 (d, C-9), 48.0 (s, C-13), 55.2 (q, 3-OMe), 83.8 (s, C-16), 91.8 (d, C-17), 111.8 (d, C-2), 113.8 (d, C-4), 124.1 (d, C-15), 126.7 (d, C-1), 131.9 (s, C-10), 137.8 (s, C-5), 151.8 (s, C-14) and 157.6 (s, C-3) (Found: C, 72.5; H, 9.3%; M^+ - 57, 371. $C_{26}H_{40}O_3Si$ requires C, 72.8; H, 9.4%; *M*, 428).

1,2 Methylation of the Δ14-16-*ketone* **86**

(*a*) Ethereal 1.5 mol dm^{-3} methyllithium (0.4 cm^3, 0.6 mmol) was added to a solution of the Δ14-16-ketone **86** (50 mg, 0.12 mmol) in dry tetrahydrofuran (1 cm^3) at 0 °C. After 15 min at 0 °C, saturated aqueous ammonium chloride was added. The product was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (53 mg) was chromatographed on silica gel (5 g), eluting with ethyl acetate-toluene (1:49) to give the 16α-methyl Δ14-16β-alcohol **103** (42 mg, 82%).

(*b*) Methylmagnesium iodide (1.25 mmol) in dry diethyl ether (0.5 cm^3) was prepared as detailed above. To this reagent was added a solution of the Δ14-16-ketone **86** (50 mg, 0.12 mmol) in dry tetrahydrofuran (1 cm^3) at 20 °C. The mixture was stirred at 20 °C for 5 min. Saturated aqueous ammonium chloride was added and the products were extracted into diethyl ether, washed (aqueous sodium thiosulfate, water and brine), dried ($MgSO_4$), and evaporated. The residue (51 mg) was chromatographed on silica gel (5 g), eluting with ethyl acetate-hexane (1:9) to obtain the 16α-methyl Δ14-16β-alcohol **103** (32 mg, 62%), followed by the 16β-methyl Δ14-16α-alcohol **105** (16 mg, 31%).

Addition of allylmagnesium chloride to the 17β-*silyloxy*-Δ14-16-*ketone* **86**

A solution of allyl chloride (1.0 cm^3, 12.27 mmol) in dry diethyl ether (5 cm^3) was added to magnesium turnings (294 mg, 12.25 mmol) at 20 °C. After complete reaction of the magnesium, a solution of the Δ14-16-ketone **86** (1.0 g, 2.43 mmol) in dry tetrahydrofuran (20 cm^3) was added. The mixture was stirred at 20 °C for 10 min. Saturated aqueous

ammonium chloride was added at 0 °C. The products were extracted into ethyl acetate, washed (aq sodium thiosulfate, water and brine), dried ($MgSO_4$) and evaporated. The residue (1.04 g) was carefully chromatographed on silica gel (110 g), eluting with ethyl acetate-hexane (1:9) to obtain 16α-*allyl*-17β-tert-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16β-*ol* **106** (597 mg, 54%) as an oil, ν_{max}/cm^{-1} 3498 (OH); δ_H (200 MHz) 0.15 and 0.16 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.97 (9H, s, *Bu*^{t}SiMe$_2$), 1.09 (3H, s, 13β-Me), 2.29–2.36 (1H, m, 16^1-H), 2.50 (1H, ddt, *J* 14.0, 5.4 and 2 x 1.6, 16^1-H), 2.86–2.88 (2H, m, 6α- and 6β-H), 3.63 (1H, s, 17α-H), 3.77 (3H, s, 3-OMe), 5.03–5.12 (2H, m, 16^3-H$_2$), 5.43 (1H, d, *J* 1.4, 15-H), 5.70–5.91 (1H, m, 16^2-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -4.3 and -4.0 (*Me*$_2$SiCMe$_3$), 18.3 (Me$_2$Si*C*Me$_3$), 21.6 (C-18), 25.9 (C-11), 27.6 (3C, Me$_2$SiC*Me*$_3$), 27.9 (C-7), 29.8 (C-6), 39.2 (C-8), 39.3 (C-12), 43.7 (C-9), 44.0 (C-16^1), 48.1 (C-13), 55.2 (3-OMe), 80.6 (C-16), 83.2 (C-17), 111.9 (C-2), 113.9 (C-4), 118.9 (C-16^3), 120.8 (C-15), 126.8 (C-1), 131.8 (C-10), 133.7 (C-16^2), 137.7 (C-5), 157.7 (C-14) and 157.9 (C-3) (Found: C, 73.6; H, 9.4%; M$^+$ - 57, 397. $C_{28}H_{42}O_3Si$ requires C, 74.0; H, 9.3%; *M*, 454), followed by 16β-*allyl*-17β-tert-*butyldimethylsilyloxy*-3-*methoxyestra*-1,3,5(10),14-*tetraen*-16α-*ol* **107** (398 mg, 36%) as an oil, ν_{max}/cm^{-1} 3499 (OH); δ_H (200 HMz) 0.09 and 0.15 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.95 (9H, s, *Bu*^{t}SiMe$_2$), 1.03 (3H, s, 13β-Me), 2.86–2.89 (2H, m, 6-H$_2$), 3.76 (3H, s, 3-OMe), 3.93 (1H, s, 17α-H), 5.09–5.24 obsc. (3H, m, 15-H and 16^3-H$_2$), 5.86–6.07 (1H, m, 16^2-H), 6.63 (1H, d, *J* 2.6, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6, 2-H) and 7.21 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) -4.6 and -4.1 (*Me*$_2$SiCMe$_3$), 18.3 (Me$_2$Si*C*Me$_3$), 18.6 (C-18), 25.2 (C-11), 26.0 (3C, Me$_2$SiC*Me*$_3$), 27.2 (C-7), 29.8 (C-6), 38.7 (C-8), 40.9 (C-12), 42.2 (C-9), 43.4 (C-16^1), 47.8 (C-13), 55.2 (3-OMe), 84.4 (C-16), 91.3 (C-17), 111.8 (C-2), 113.8 (C-4), 118.7 (C-16^3), 122.3 (C-15), 126.7 (C-1), 131.9 (C-10), 134.4 (C-16^2), 137.8 (C-5), 152.5 (C-14) and 157.6 (C-3) (Found: C, 74.2; H, 9.2%; M$^+$ - 57, 397. $C_{28}H_{42}O_3Si$ requires C, 74.0; H, 9.3%; *M*, 454).

16α-*Allyl*-3-*methoxyestra*-1,3,5(10),14-*tetraen*e-16β,17β-*diol* **108**

(*a*) A solution of the 17β-hydroxy-Δ^{14}-16-ketone **87** (50 mg, 0.17 mmol) in dry tetrahydrofuran (1.5 cm^3) was added to allylmagnesium chloride [prepared as above from magnesium turnings (21 mg, 0.88 mmol) and allyl chloride (0.07 cm^3, 0.86 mmol)]. After 5 min at 20 °C, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride was added. The product was extracted into diethyl ether, washed (water and brine), dried ($MgSO_4$) and evporated. The residue (53 mg) was chromatographed on silica gel (5 g), eluting with ethyl acetate-toluene (3:7) to obtain 16α-*allyl*-3-*methoxyestra*-1,3,5(10),14-*tetraen*e-16β,17β-*diol* **108** (51 mg, 88%), m.p. 129–133 °C (from ethyl acetate); $[\alpha]_D$ +142 (*c* 1.0); ν_{max}/cm^{-1} 3073 (OH); δ_H (400 MHz) 1.10 (3H, s, 13β-Me), 1.87 (1H, s, 16β-OH,

exch. by D_2O), 2.33 (1H, ddd, *J* 13.3, 6.7 and 3.3, 11α-H), 2.39 (1H, ddt, *J* 13.7, 7.7 and 2 x 1.0, 16^1-H), 2.50 (1H, ddt, *J* 13.7, 4.1 and 2 x 1.3, 16^1-H), 2.60 (1H, d, *J* 9.8, 17β-OH, exch. by D_2O), 2.88–2.90 (2H, m, 6α- and 6β-H), 3.57 (1H, d, *J* 9.8 → s on D_2O exch., 17α-H), 3.77 (3H, s, 3-OMe), 5.16–5.20 (2H, m, 16^3-H_2), 5.41 (1H, d, *J* 1.7, 15-H), 5.88–5.98 (1H, m, 16^2-H), 6.64 (1H, d, *J* 2.7, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 20.0 (q, C-18), 25.3 (t, C-11), 27.2 (t, C-7), 29.8 (t, C-6), 38.9 (d, C-8), 39.9 (t, C-12), 43.7 (d, C-9), 44.1 (t, $C\text{-}16^1$), 48.1 (s, C-13), 55.2 (q, 3-OMe), 80.6 (s, C-16), 84.6 (d, C-17), 111.8 (d, C-2), 113.8 (d, C-4), 118.9 (t, $C\text{-}16^3$), 120.8 (d, C-15), 126.8 (d, C-1), 131.7 (s, C-10), 133.7 (d, $C\text{-}16^2$), 137.7 (s, C-5), 157.6 (s, C-14) and 157.9 (s, C-3) (Found: C, 77.4; H, 8.2%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

(*b*) A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 mol dm^{-3}; 0.5 cm^3, 0.55 mmol) was stirred with 4A-molecular sieves (*ca* 100 mg) at 20 °C for 30 min. Hexamethylphosphoric triamide (0.1 cm^3, 0.57 mmol), followed by a solution of the silyl ether **106** (50 mg, 0.11 mmol) in dry tetrahydrofuran (1 cm^3) were added sequentially. The reaction was stirred at 20 °C for 30 min. Solid material was filtered and the filtrate was diluted with ethyl acetate (*ca* 30 cm^3), washed (saturated aqueous sodium hydrogen carbonate and brine), dried ($MgSO_4$), and concentrated. Chromatography of the residue (39 mg) on silica gel (4 g) with methanol-chloroform (1:49) gave the 16β,17β-diol **108** (29 mg, 80%).

Attempted acetonide formation on the allyl diols

(*a*) A solution of the 16β,17β-diol **108** (50 mg, 0.15 mmol) in dry acetone (5 cm^3) was treated with anhydrous copper(II) sulfate (120 mg, 0.75 mmol) at 20 °C for 20 min. The mixture was filtered and evaporated to give 3-*methoxy*-16-*propenylene-estra*-1,3,5(10),14-*tetraene* **110** (40 mg, 82%), m.p. 125–129 °C (from acetone-methanol); $[\alpha]_D$ +184 (*c* 0.7); ν_{max}/cm^{-1} 3504 (OH); δ_H (200 MHz) 1.00 (3H, s, 13β-Me), 2.93–2.95 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 4.45 (1H, d, *J* 1.3, 17α-H), 4.87 (1H, dd, *J* 10.1 and 1.8, 3′-H_{cis}), 5.13 (1H, dd, *J* 16.8 and 1.8, 3′-H_{trans}), 5.81 (1H, dd, *J* 11.6 and 1.3, 1′-H), 6.16 (1H, d, *J* 1.7, 15-H), 6.59 (1H, ddd, *J* 16.8, 11.6 and 10.1, 2′-H), 6.66 (1H, d, *J* 2.9, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.9, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H) (Found: C, 81.0; H, 8.8; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7; *M*, 324).

(*b*) Tetrabutylammonium fluoride (1.1 mol dm^{-3} in tetrahydrofuran; 0.5 cm^3, 0.55 mmol) was dried as detailed previously. Hexamethylphosphoric triamide (0.1 cm^3), followed by a solution of the 17β-silyl ether **107** (50 mg, 0.11 mmol) in dry tetrahydrofuran (1 cm^3) were added. Stirring was maintained at 20 °C for 45 min. Solid material was filtered, and the filtrate was diluted with ethyl acetate (*ca* 30 cm^3), washed (saturated aqueous

sodium hydrogen carbonate, water and brine), dried ($MgSO_4$), and evaporated. The total crude (39 mg) was dissolved in dry acetone (4 cm^3) and treated with anhydrous copper(II) sulfate (120 mg, 0.75 mmol) at 20 °C for 20 min. The mixture was filtered and evaporated to give the product of dehydration **110** (31 mg, 80%).

Attempted oxy-Cope rearrangements of the Δ^{14}-16-*allyl* 16-*alcohols*

(*a*) Hexamethyldisilazane (0.5 cm^3, 2.37 mmol) was added to a suspension of potassium hydride (35%) (271 mg, 2.36 mmol) in dry tetrahydrofuran (2 cm^3) at 0 °C. The solution was stirred for 10 min at this temperature. 1,4,7,10,13,16-Hexaoxacyclooctadecane (18-crown-6) (623 mg, 2.36 mmol) was added to the resulting solution of potassium hexamethyldisilazide, and the temperature was lowered to -78 °C. The above addition was followed by a solution of the Δ^{14}-16α-allyl alcohol **106** (100 mg, 0.22 mmol) in dry tetrahydrofuran (2 cm^3). The mixture was slowly warmed to 20 °C over 3 h. No change was effected.

(*b*) The above reaction was repeated in the absence of the crown ether. Starting material was recovered.

(*c*) The above procedure was repeated, using only potassium hydride and crown ether. No reaction was noted.

(*d*) A solution of the Δ^{14}-16α-allyl alcohol **106** (50 mg, 0.11 mmol) in dry DMF (5 cm^3) was heated to refluxing temperature. After 3 h, complete degradation of the starting material was noted.

(*e*) All of the above variations were repeated on the Δ^{14}-16β-allyl carbinol **107**, without effecting any product of rearrangement.

(*f*) Of the above variations, (*a*) and (*c*) were repeated on the 17β-hydroxy-Δ^{14}-16α-allyl alcohol **108**, without success.

Attempted Pd-catalysed oxy-Cope rearrangement of the Δ^{14}-16-*allyl* 16-*alcohols*

(*a*) The 16α-allyl-Δ^{14}-alcohol **106** (70 mg, 0.15 mmol) was dissolved in dry tetrahydrofuran (1 cm^3). *bis*-Acetonitriledichloropalladium (15 mg, 0.06 mmol) was added and the mixture was stirred at 20 °C for 15 min. Aqueous potassium cyanide was added. The product was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (68 mg) was chromatographed on silica gel (7 g), eluting with ethyl acetate-hexane (1:49) to give 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-16-*propenylene-estra*-1,3,5(10),14-*tetraene* **113** (60 mg, 89%), m.p. 139–142 °C (from chloroform-methanol); $[\alpha]_D$ +208 (*c* 1.0); δ_H (400 MHz) 0.12 and 0.17 (each 3H, s, Bu^tSiMe_2), 0.98 (9H, s, Bu^tSiMe_2), 1.00 (3H, s, 13β-Me), 2.06 (1H, dt, *J* 12.2 and 2 x 3.4, 12β-H), 2.91–2.93 (2H,

m, 6α- and 6β-H), 3.76 (3H, s, 3-OMe), 4.41 (1H, d, *J* 1.7, 17α-H), 4.98 (1H, dd, *J* 10.1 and 1.9, 3′-H_{cis}), 5.11 (1H, dd, *J* 16.9 and 1.9, 3′-H_{trans}), 5.82 (1H, dd, *J* 11.4 and 1.7, 1′-H), 6.15 (1H, d, *J* 1.8, 15-H), 6.64 (1H, ddd, *J* 16.9, 11.4 and 10.1, 2′-H), 6.65 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -4.3 and -4.0 (each q, Me_2SiCMe_3), 18.3 (s, Me_2SiCMe_3), 18.9 (s, C-18), 25.2 (t, C-11), 26.0 (3C, q, Me_2SiCMe_3), 27.6 (t, C-7), 29.8 (d, C-6), 39.4 (t, C-12), 39.5 (d, C-8), 43.8 (d, C-9), 48.8 (s, C-13), 55.2 (q, 3-OMe), 85.5 (d, C-17), 111.9 (d, C-2), 113.9 (d, C-4), 114.1 (t, C-16³), 116.8 (d, C-15), 118.2 (d, C-16¹), 126.9 (d, C-1), 131.8 (s, C-10), 133.7 (d, C-16²), 137.8 (s, C-5), 149.2 (s, C-16), 157.7 (s, C-14) and 159.6 (C-3) (Found: C, 77.2; H, 9.2%; M^+ - 57, 379. $C_{28}H_{40}O_2Si$ requires C, 77.0; H, 9.2%; *M*, 436).

(*b*) The above experiment was repeated on the 16β-allyl Δ¹⁴-16-alcohol **107**, to produce the same result.

17β-tert-*Butyldimethylsilyloxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16α-*ol* **118**

(*a*) Zinc dust (1.11 g, 17.0 mmol) was added to a hot, stirring solution of silver acetate (57 mg, 0.34 mmol) in glacial acetic acid (2 cm³). After 5 min, the solvent was decanted, the black bimetallic couple was sequentially washed with glacial acetic acid (2 cm³) and dry diethyl ether (3 x 2 cm³), and suspended in dry ether (2 cm³). A small piece of silver wool, followed by diiodomethane (1.0 cm³, 12.4 mmol) was added. The mixture was allowed to reflux for 15 min. A solution of the Δ¹⁴-16α-alcohol **92** (351 mg, 0.85 mmol) and diiodomethane (0.5 cm³, 6.2 mmol) in dry ether (2 cm³) was added and the mixture was heated to reflux for 30 min. The reaction was cooled to 20 °C and saturated aqueous ammonium chloride was added. Organic material was extracted into diethyl ether, washed (aqueous sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and concentrated. The residue (371 mg) was chromatographed on silica gel (37 g), eluting with ethyl acetate-toluene (1:19) to yield 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16α-*ol* **118** (282 mg, 77%), m.p. 128–130 °C (from chloroform-methanol); $[\alpha]_D$ +55 (*c* 1.2); ν_{max}/cm⁻¹ 3483 (OH); δ_H (400 MHz) 0.05 and 0.09 (each 3H, s, Bu^{t}SiMe_2), 0.36 (1H, dd, *J* 7.8 and 5.5, 3′-H_{exo}), 0.64 (1H, dd, *J* 5.5 and 2.9, 3′-H_{endo}), 0.91 (9H, s, *Bu*^{t}SiMe₂), 1.00 (3H, s, 13β-Me), 1.17 (1H, qd, *J* 3 x 12.5 and 5.7, 7α-H), 1.30 (1H, ddt, *J* 12.5, 5.2 and 2 x 2.6, 7β-H), 1.68 (1H, ddd, *J* 7.8, 4.2 and 2.9, 15β-H), 2.10 (1H, td, *J* 2 x 11.4 and 2.3, 8β-H), 2.45 (1H, td, *J* 2 x 11.4 and 4.4, 9α-H), 2.78–2.80 (2H, m, 6α- and 6β-H), 3.21 (1H, d, *J* 6.6, 17α-H), 3.78 (3H, s, 3-OMe), 4.12 (1H, m → dd, *J* 6.6 and 4.2 on D_2O exch., 16β-H), 6.60 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.2 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.2, 1-H); δ_C (50 MHz) -4.6 and -4.1 (each q, Me_2SiCMe_3), 5.3 (t, C-15¹), 16.2 (q, C-18), 18.1 (s, Me_2SiCMe_3), 22.6 (d, C-15), 23.8 (t, C-7), 25.9 (3C, q, Me_2SiCMe_3),

27.1 (t, C-11), 30.1 (t, C-6), 33.6 (t, C-12), 36.4 (s, C-14), 36.8 (d, C-8), 42.5 (s, C-13), 42.9 (d, C-9), 55.2 (q, 3-OMe), 79.3 (d, C-16), 82.8 (d, C-17), 111.8 (d, C-2), 113.7 (d, C-4), 126.8 (d, C-1), 132.8 (s, C-10), 137.9 (s, C-5) and 157.4 (s, C-3) (Found: C, 72.9%; H, 9.6%; M^+, 428. $C_{26}H_{40}O_3Si$ requires C, 72.8; H, 9.4%; *M*, 428).

(*b*) A solution of diethyl zinc (1.6 cm^3, 15.60 mmol) in dry diethyl ether (10 cm^3) and diiodomethane (1.0 cm^3, 12.41 mmol) were added sequentially to a solution of the Δ^{14}-16α-alcohol **92** (1.10 g, 2.66 mmol) in dry benzene (20 cm^3) at 20 °C. After 10 min at this temperature, water was added. The white precipitate was filtered and the filtrate was extracted into ethyl acetate, washed (aq sodium thiosulfate, water and brine), dried ($MgSO_4$) and evaporated. The residue (1.10 g) was chromatographed on silica gel (50 g), eluting with ethyl acetate-toluene (1:19) to give the 14α,15α-methylene 16α-alcohol **118** (1.07 g, 94%).

17β-tert-*Butyldimethylsilyloxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16-*one* **119**

(*a*) A solution of oxalyl chloride (2.0 mol dm^{-3} in dichloromethane; 0.8 cm^3, 1.6 mmol) was added to a solution of dimethyl sulfoxide (0.25 cm^3, 3.52 mmol) in dichloromethane (1.0 cm^3) at -78 °C. The mixture was stirred at this temperature for 5 min. A solution of the 16-alcohol **118** (614 mg, 1.43 mmol) in dichloromethane (0.5 cm^3) was added slowly and low temperature stirring was maintained for 20 min. Triethylamine (1.0 cm^3, 7.21 mmol) was added and stirring was continued at 0 °C for a further 5 min. Water was added and the mixture was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$) and evaporated to give 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16-*one* **119** (555 mg, 91%), m.p. 164–167 °C (from chloroform-methanol); $[\alpha]_D$ +124 (*c* 1.0); ν_{max}/cm^{-1} 1735 (CO); δ_H (400 MHz) 0.02 and 0.12 (each 3H, s, Bu^tSiMe_2), 0.91 (9H, s, Bu^tSiMe_2), 1.04 (3H, s, 13β-Me), 1.16 (1H, dd, *J* 8.3 and 5.2, 3′-H_{exo}), 1.24 (1H, dd, *J* 5.2 and 2.1, 3′-H_{endo}), 1.22-1.29 (2H, m, 7α- and 7β-H), 1.68 (1H, qd, *J* 3 x 11.2 and 4.1, 11β-H), 1.78 (1H, td, *J* 2 x 11.2 and 4.1, 12α-H), 1.87 (1H, dt, *J* 11.2 and 2 x 4.1, 12β-H), 2.00 (1H, dd, *J* 8.3 and 2.1, 15β-H), 2.27 (1H, td, *J* 2 x 11.2 and 3.4, 8β-H), 2.44 (1H, dq, *J* 11.2 and 3 x 4.1, 11α-H), 2.61 (1H, td, *J* 2 x 11.2 and 4.1, 9α-H), 2.83–2.85 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 3.98 (1H, s, 17α-H), 6.63 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.24 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -5.4 and -4.4 (each q, Me_2SiCMe_3), 14.4 (t, C-15[1]), 16.7 (q, C-18), 18.5 (s, Me_2SiCMe_3), 23.4 (t, C-7), 25.8 (3C, q, Me_2SiCMe_3), 27.1 (t, C-11), 28.3 (d, C-15), 29.8 (t, C-6), 33.1 (t, C-12), 36.5 (d, C-8), 42.4 (s, C-14), 42.5 (s, C-13), 43.6 (d, C-9), 55.2 (q, 3-OMe), 78.7 (d, C-17), 112.0 (d, C-2), 113.8 (d, C-4), 126.6 (d, C-1), 132.1 (s, C-10), 137.5 (s, C-5), 157.7 (s, C-3) and 210.8 (s, C-16) (Found: C, 73.0; H, 8.9%; M^+, 426. $C_{26}H_{38}O_3Si$ requires C, 73.2; H, 9.0%; *M*, 426).

(*b*) A solution of the 16-alcohol **118** (428 mg, 1.00 mmol) in dry dichloromethane (20 cm^3) was treated with the Dess-Martin periodinane[84] (1.32 g, 3.51 mmol) for 3 h at 20 °C. The reaction was subsequently poured into a mixture of aqueous sodium thiosulfate and aqueous sodium hydrogen carbonate. The product was extracted into diethyl ether, washed (water and brine), dried ($MgSO_4$) and evaporated to give the 16-ketone **119** (405 mg, 95%).

Attempted cyclopropanation on the Δ^{14}-16β-*alcohol* **93**

(*a*) A solution of the Δ^{14}-16β-alcohol **93** (50 mg, 0.12 mmol) in dry benzene (3 cm^3) was treated with a solution of diethylzinc (0.1 cm^3, 0.98 mmol) in dry diethyl ether (1 cm^3) and diiodomethane (0.1 cm^3, 1.24 mmol) at 20 °C. No product formation was noted.

(*b*) The above reaction was repeated in toluene, heating up to refluxing temperature. Starting material was left unchanged.

(*c*) A solution of the Δ^{14}-16β,17β-diol **90** (50 mg, 0.17 mmol) in dry toluene (3 cm^3) was treated with diethylzinc (0.1 cm^3, 0.98 mmol) and diidomethane (0.1 cm^3, 1.24 mmol) as detailed in (*a*) above. The mixture was heated to refluxing temperature, without converting the starting material.

17β-*Hydroxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16-*one* **120**

Tetrabutylammonium fluoride (1.1 mol dm^{-3} in tetrahydrofuran; 1.5 cm^3, 1.65 mmol) was added to a solution of the 17β-silyl ether **119** (360 mg, 0.84 mmol) in dry tetrahydrofuran (15 cm^3). Stirring was maintained at 25 °C for 2 h. The mixture was diluted with ethyl acetate and sequentially washed with saturated sodium hydrogen carbonate and brine. The organic phase was dried ($MgSO_4$) and evaporated. The residue (300 mg) was chromatographed on silica gel (3 g), eluting with ethyl acetate-toluene (1:4) to give 17β-*hydroxy*-3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*trien*-16-*one* **120** (227 mg, 87%), m.p. 148–151 °C (from chloroform-methanol); $[\alpha]_D$ +143 (*c* 1.0); ν_{max}/cm^{-1} 3505 (OH), 1728 (CO); δ_H (200 MHz) 0.99 (3H, s, 13β-H), 1.29 (1H, dd, *J* 8.3 and 5.4, 3′-H_{exo}), 1.37 (1H, dd, *J* 5.4 and 2.3, 3′-H_{endo}), 2.11 (1H, dd, *J* 8.3 and 2.3, 15β-H), 2.83–2.85 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7, 4-H), 6.75 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.24 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 14.7 (C-15[1]), 15.9 (C-18), 23.4 (C-7), 27.0 (C-11), 27.8 (C-15), 29.8 (C-6), 33.1 (C-12), 36.5 (C-8), 42.4 (C-13), 43.7 (C-9), 44.3 (C-14), 55.2 (3-OMe), 77.2 (C-17), 112.0 (C-2), 113.8 (C-4), 126.6 (C-1), 131.8 (C-10), 137.4 (C-5), 157.7 (C-3) and 212.3 (C-16) (Found: C, 76.3; H, 7.7%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312).

3-*Methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*triene*-16β,17β-*diol* **121**

Lithium aluminium hydride (60 mg, 1.58 mmol) was added to a solution of the 17β-hydroxy-16-ketone **120** (100 mg, 0.32 mmol) in dry tetrahydrofuran (3 cm^3) at 0 °C. Stirring was maintained at 0 °C for 15 min, then at 20 °C for an additional 1 h. The mixture was cooled to 0 °C, saturated aqueous sodium hydrogen carbonate was added, and the precipitate was filtered. The filtrate was suspended in water and the product was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$), and evaporated to give 3-*methoxy*-14,15α-*methylene-estra*-1,3,5(10)-*triene*-16β,17β-*diol* **121** (94 mg, 94%) m.p. 135–138 °C (from diisopropyl ether); $[\alpha]_D$ +123 (*c* 1.0); ν_{max}/cm^{-1}; δ_H (400 MHz) 0.14 (1H, dd, *J* 5.6 and 2.7, 3^1-H_{endo}), 0.45 (1H, dd, *J* 8.5 and 5.6, 3^1-H_{exo}), 1.12 (3H, s, 13β-Me), 1.19 (1H, qd, *J* 3 x 12.2 and 5.8, 7α-H), 1.38 (1H, ddt, *J* 12.2, 5.2 and 2 x 2.4, 7β-H), 1.52 (1H, td, *J* 2 x 12.2 and 3.7, 12α-H), 1.64 (1H, qd, *J* 3 x 12.2 and 3.2, 11β-H), 1.73 (1H, dd, *J* 8.5 and 2.7, 15β-H), 1.85 (1H, dt, *J* 12.2 and 2 x 3.2, 12β-H), 2.19 (1H, td, *J* 2 x 12.2 and 2.4, 8β-H), 2.32–2.38 (1H, m, 11α-H), 2.42 (1H, td, *J* 2 x 12.2 and 4.5, 9α-H), 2.79–2.81 (2H, m, 6α- and 6β-H), 3.46 (1H, t, *J* 2 x 5.2, → d, *J* 5.2 on D_2O exch., 16α-H), 3.77 (3H, s, 3-OMe), 4.09 (1H, d, *J* 5.2, 17α-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 6.6 (t, C-15^1), 17.0 (q, C-18), 23.6 (t, C-11), 23.9 (d, C-15), 27.1 (t, C-7), 30.1 (t, C-6), 34.2 (t, C-12), 37.2 (d, C-8), 39.6 (s, C-14), 42.2 (s, C-13), 43.0 (d, C-9), 55.2 (q, 3-OMe), 74.6 (d, C-16), 77.8 (d, C-17), 111.7 (d, C-2), 113.7 (d, C-4), 126.9 (d, C-1), 132.7 (s, C-10), 137.8 (s, C-5) and 157.4 (s, C-3) (Found: C, 76.0, H, 8.3%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

14,15α-*Methylene-estra*-1,3,5(10)-*triene*-3,16α,17β-*triol* **123**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 mol dm^{-3}; 1.0 cm^3, 1.1 mmol) was stirred with 4A-molecular sieves (*ca* 150 mg) at 20 °C for 30 min. Hexamethylphosphoric triamide (0.2 cm^3, 1.14 mmol), followed by a solution of the 17β-silyl ether **118** (100 mg, 0.24 mmol) in dry tetrahydrofuran (2 cm^3) were sequentaily added to this mixture. The reaction was stirred at 20 °C for 30 min. The suspension was filtered and the product (64 mg) was precipitated from the filtrate with cold methanol. The total crude was dissolved in dry toluene (10 cm^3). A solution of diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 1.0 cm^3, 1.5 mmol) was added and the reaction was heated to refluxing temperature for 24 h. The reaction mixture was cooled to 0 °C, saturated aqueous ammonium chloride was added and the aqueous phase was further acidified with 1 mol dm^{-3} hydrochloric acid. The product was extracted into ethyl acetate, washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated to give 14,15α-*methylene-estra*-1,3,5(10)-*triene*-3,16α,17β-*triol* **123** (60 mg, 62% from **118**), m.p.

248–250 °C (from ethanol) $[\alpha]_D$ +71 (*c* 0.8 in tetrahydrofuran) (Found: C, 76.6; H, 8.0%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0, H, 8.1%; *M*, 300).

14,15α-*Methylene-estra*-1,3,5(10)-*triene*-3,16β,17β-*triol* **124**

Diisobutylaluminium hydride (1.5 mol dm^{-3}; 1.0 cm^3, 1.5 mmol) was added to a solution of the methyl ether **121** (50 mg, 0.14 mmol) in dry toluene (5 cm^3). The reaction was stirred at refluxing temperature for 24 h. The mixture was cooled to 0 °C, saturated aqueous ammonium chloride was added and the aqueous phase was acidified with 1 mol dm^{-3} HCl. The product was extracted into ethyl acetate, washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and evaporated to give 14,15α-*methylene-estra*-1,3,5(10)-*triene*-3,16β,17β-*triol* **124** (39 mg, 93%), m.p. 231–234 (from ethyl acetate); $[\alpha]_D$ +132 (*c* 0.5 in tetrahydrofuran) (Found: C, 75.6; H, 8.1%; M^+, 300. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.1%; *M*, 300).

17β-tert-*Butyldimethylsilyloxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16-*one* **125**

Freshly cut lithium (90 mg, 12.9 mg atom) was dissolved in freshly distilled liquid ammonia (50 cm^3). A solution of the 14α,15α-methylene 16-ketone **119** (550 mg, 1.29 mmol) in dry tetrahydrofuran (5 cm^3) was added. The mixture was kept at -78 °C for 5 min. Solid ammonium chloride was added to discharge the blue colour. The ammonia was allowed to evaporate, and the residue was suspended in water. The mixture was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$) and concentrated. The residue (539 mg) was chromatographed on silica gel (50 g), eluting with toluene to obtain 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16-*one* **125** (480 mg, 87%), m.p. 179–182 °C (from ethyl acetate-methanol); $[\alpha]_D$ -29 (*c* 1.0); $\Delta\varepsilon_{max}$ -6.30 (309 nm); ν_{max}/cm^{-1} 1746 (CO); δ_H (400 MHz) 0.07 and 0.15 (each 3H, s, Bu^{t}SiMe_2), 0.91 (9H, s, *Bu*^{t}SiMe$_2$), 1.09 (3H, s, 14-Me), 1.19 (3H, s, 13β-Me), 1.92 (1H, td, *J* 2 x 11.3 and 2.5, 8β-H), 2.01 and 2.12 (each 1H, d, *J* 18.0, 15α- and 15β-H), 2.79 (1H, td, *J* 2 x 11.3 and 5.1, 9α-H), 2.85–2.87 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 4.16 (1H, s, 17α-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) -5.2 and -4.2 (Me_2SiCMe$_3$), 14.7 (14-Me), 17.7 (C-18), 18.4 (Me$_2$Si*C*Me$_3$), 24.6 (C-7), 25.8 (3C, Me$_2$SiCMe_3), 26.2 (C-11), 29.3 (C-12), 30.7 (C-6), 36.9 (C-9), 39.4 (C-13), 41.7 (C-8), 45.2 (C-14), 46.3 (C-15), 55.2 (3-OMe), 81.9 (C-17), 111.8 (C-2), 113.7 (C-4), 126.7 (C-1), 133.3 (C-10), 137.6 (C-5), 157.5 (C-3) and 216.9 (C-16) (Found M^+ - 57, 371. $C_{26}H_{40}O_3Si$ requires C, 72.8; H, 9.4%; *M*, 428).

17β-*Hydroxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16-*one* **126**

A solution of the 17β-silyl ether **125** (309 mg, 0.72 mmol) in dry tetrahydrofuran (15 ml) was treated with 1.3 cm^3 of a 1.1 mol dm^{-3} solution of tetrabutylammonium fluoride in tetrahydrofuran. Stirring was maintained at 25 °C for 2 h. The mixture was diluted with ethyl acetate and washed with aqueous sodium hydrogen carbonate and brine. The organic phase was dried ($MgSO_4$) and evaporated. The residue (299 mg) was chromatographed on silica gel (25 g), eluting with ethyl acetate-dichloromethane (1:99) to give 17β-*hydroxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16-*one* **126** (130 mg, 60%), m.p. 122–125 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ -29 (*c* 1.0); ν_{max}/cm^{-1} 2997 (OH), 1744 (CO); δ_H (400 MHz) 0.89 (3H, s, 14α-Me), 1.15 (3H, s, 13β-Me), 1.76 (1H, ddd, *J* 13.3, 5.2 and 2.1, 12β-H), 1.93 (1H, td, *J* 2 x 13.3 and 2.5, 8β-H), 2.07 (1H, td, *J* 2 x 13.3 and 4.5, 12α-H), 2.15 (2H, s, 15α- and 15β-H), 2.82 (1H, td, *J* 2 x 13.3 and 5.8, 9α-H), 2.86–2.88 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 4.26 (1H, s, 17α-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.4, 1-H); δ_C (50 MHz) 14.1 (q, C-18), 17.8 (q, 14α-Me), 24.8 (t, C-7), 26.1 (t, C-11), 29.0 (t, C-12), 30.6 (t, C-6), 36.9 (d, C-9), 40.0 (s, C-13), 41.5 (d, C-8), 44.9 (s, C-14), 45.7 (t, C-15), 55.2 (q, 3-OMe), 81.4 (d, C-17), 111.8 (d, C-2), 113.7 (d, C-4), 126.7 (d, C-1), 133.1 (s, C-10), 137.5 (s, C-5), 157.5 (s, C-3) and 218.4 (s, C-16) (Found: C, 76.2; H, 8.2%; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%; *M*, 314).

17β-tert-*Butyldimethylsilyloxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16α-*ol* **127**

Freshly cut lithium (20 mg, 2.86 mg atom) was dissolved in distilled liquid ammonia (15 cm^3). The 16-ketone **125** (120 mg, 0.30 mmol) was added as a solution in dry tetrahydrofuran (10 cm^3). The reaction was stirred without any external cooling for 5 min. Saturated ammonium chloride was added and the ammonia was evaporated. The residue was suspended in water and the product was extracted into ethyl acetate, washed (water and brine), dried ($MgSO_4$), and concentrated. The residue (112 mg) was chromatographed on silica gel (10 g), eluting with ethyl acetate-toluene (1:99) to obtain 17β-tert-*butyldimethylsilyloxy*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-16α-*ol* **127** (98 mg, 76%), m.p. 131–135 °C (from chloroform-methanol); $[\alpha]_D$ +40 (*c* 1.0); ν_{max}/cm^{-1} 3609 (OH); δ_H (400 MHz) 0.08 and 0.11 (each 3H, s, Bu^{t}Si*Me*$_2$), 0.97 (3H, s, 14-Me), 0.91 (9H, s, *Bu*^{t}SiMe$_2$), 1.09 (3H, s, 13β-Me), 1.36 (1H, dd, *J* 13.2 and 1.5, 15α-H), 1.74 (1H, td, *J* 2 x 11.6 and 8.3, 8β-H), 2.07 (1H, dd, *J* 13.2 and 9.3, 15β-H), 2.67 (1H, ddd, *J* 2 x 11.6 and 5.5, 9α-H), 2.84–2.86 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 4.00 (1H, d, *J* 4.7, 17α-H), 4.15 (1H, m → ddd, *J* 9.3, 4.7 and 1.5 on D_2O exch., 16β-H), 6.61 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.3 and 2.8, 2-H) and 7.18 (1H, d, *J* 8.3, 1-H); δ_C (50 MHz) -4.7 and

-4.2 (each q, Me_2SiCMe_3), 15.1 (q, 14-Me), 16.4 (q, C-18), 18.1 (s, Me_2SiCMe_3), 24.2 (t, C-7), 25.9 (3C, q, Me_2SiCMe_3), 26.1 (t, C-11), 29.7 (t, C-12), 30.8 (t, C-6), 36.7 (d, C-8), 42.6 (d, C-9), 43.5 (t, C-15), 44.4 (s, C-13), 47.5 (s, C-14), 55.2 (q, 3-OMe), 80.1 (d, C-16), 86.7 (d, C-17), 111.6 (d, C-2), 113.7 (d, C-4), 126.7 (d, C-1), 134.0 (s, C-10), 137.9 (s, C-5) and 157.3 (s, C-3) (Found: C, 72.8; H, 9.9%; M^+ - 57, 373. $C_{26}H_{42}O_3Si$ requires C, 72.5; H, 9.8%; *M*, 430).

3-*Methoxy*-14-*methylestra*-1,3,5(10)-*triene*-16β,17β-*diol* **128**

A solution of the 17β-hydroxy-16-ketone **126** (121 mg, 0.39 mmol) in dry tetrahydrofuran (10 cm^3) was treated with lithium aluminium hydride (76 mg, 2.00 mmol) at 0 °C for 15 min. Saturated aqueous sodium hydrogen carbonate was added and the precipitate was filtered. The filtrate was extracted with ethyl acetate, washed (water and brine), dried ($MgSO_4$) and concentrated. The residue (110 mg) was chromatographed on silica gel (10 g), eluting with methanol-chloroform (1:24) to give 3-*methoxy*-14-*methylestra*-1,3,5(10)-*triene*-16β,17β-*diol* **128** (102 mg, 83%), m.p. 163–166 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ +88 (*c* 0.8); ν_{max}/cm^{-1} 3621 (OH); δ_H (400 MHz) 0.89 (3H, s, 14-Me), 0.95 (3H, s, 13β-Me), 1.59 (1H, dd, *J* 12.7 and 5.6, 15β-H), 2.15 (1H, dd, *J* 12.7 and 7.5, 15α-H), 2.30-2.40 (1H, m, 11β-H), 2.55 br (2H, s, 16β- and 17β-OH, exch. by D_2O), 2.70 (1H, td, *J* 2 x 11.8 and 5.4, 9α-H), 2.86–2.88 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 4.00 (1H, d, *J* 7.5, 17α-H), 4.39 (1H, td, *J* 2 x 7.5 and 5.6, 16α-H), 6.63 (1H, d, *J* 2.6, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.6, 2-H) and 7.23 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 14.1 (q, 14-Me), 17.2 (q, C-18), 24.3 (t, C-7), 26.2 (t, C-11), 30.2 (t, C-12), 30.7 (t, C-6), 36.7 (d, C-8), 42.3 (d, C-9), 42.6 (s, C-13), 43.6 (t, C-15), 45.8 (s, C-14), 55.2 (q, 3-OMe), 70.1 (d, C-16), 76.9 (d, C-17), 111.6 (d, C-2), 113.7 (d, C-4), 126.8 (d, C-1), 133.7 (s, C-10), 137.7 (s, C-5) and 157.3 (s, C-3) (Found: C, 75.5; H, 8.8%; M^+, 316. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%; *M*, 316).

14-*Methylestra*-1,3,5(10)-*triene*-3,16α,17β-*triol* **130**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 mol dm^{-3}; 1.3 cm^3, 1.43 mmol) was dried over molecular sieves (*ca* 200 mg) as detailed above. Hexamethylphosphoric triamide (0.15 cm^3, 0.86 mmol) was added, followed by a solution of the 17β-silyl ether **127** (120 mg, 0.28 mmol) in dry tetrahydrofuran (2.5 cm^3). The mixture was stirred at 20 °C for 45 min, and then filtered. The product (72 mg) was precipitated from the filtrate with cold methanol. The total crude was dissolved in dry toluene (10 cm^3). Diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 0.7 cm^3, 1.05 mmol) was added and the solution was heated to refluxing temperature for 24 h. The

solution was cooled to 0 °C, saturated aqueous ammonium chloride was added and the aqueous phase was further acidified with 1 mol dm^{-3} hydrochloric acid. The product was extracted into ethyl acetate, washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and concentrated to give 14-*methylestra*-1,3,5(10)-*triene*-3,16α,17β-*triol* **130** (53 mg, 62% from **127**), m.p. 260–262 °C (from ethanol) $[\alpha]_D$ +62 (*c* 1.0 in tetrahydrofuran) (Found C, 75.8, H, 8.6%; M^+, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%; *M*, 302).

14-*Methylestra*-1,3,5(10)-*triene*-3,16β,17β-*triol* **131**

A solution of the methyl ether **128** (40 mg, 0.16 mmol) in dry toluene (4 cm^3) was treated with diisobutylaluminium hydride (1.5 mol dm^{-3} in toluene; 1.0 cm^3, 1.5 mmol) at refluxing temperature for 36 h. The reaction was cooled to 0 °C, saturated aqueous ammonium chloride was added and the mixture was further acidified with 1 mol dm^{-3} HCl. Extraction of the product into ethyl acetate, followed by washing (aq sodium hydrogen carbonate and brine), drying ($MgSO_4$) amd evaporation gave 14-*methylestra*-1,3,5(10)-*triene*-3,16β,17β-*triol* **131** (44 mg, 91%), m.p. 238–241 °C (from ethyl acetate); $[\alpha]_D$ +95 (*c* 0.5) (Found: C, 75.6; H, 8.8%; M^+, 302. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7; *M*, 302).

17β-tert-*Butyldimethylsilyloxy*-14β-*estra*-1,3,5(10)-*trien*-16-*one* **132**

Freshly cut lithium (35 mg, 5 mg atom) was dissolved in freshly distilled liquid ammonia (10 cm^3). A solution of the enone **86** (206 mg, 0.50 mmol) in dry tetrahydrofuran (20 cm^3) was added, and stirring was maintained for 15 min. Solid ammonium chloride was added and the ammonia was evaporated. The residue was suspended in water and the product was extracted with ethyl acetate, washed (water and brine), dried ($MgSO_4$), and evaporated. Chromatography of the residue (180 mg) on silica gel (18 g) with ethyl acetate-toluene (1:49) as eluent gave 17β-tert-*butyldimethylsilyloxy*-14β-*estra*-1,3,5(10)-*trien*-16-*one* **132** (169 mg, 82%), m.p. 126–128 °C (from chloroform-methanol); $[\alpha]_D$ +155 (*c* 0.5); $\Delta\varepsilon_{max}$ +3.31 (318 nm); ν_{max}/cm^{-1} 1746 (CO); δ_H (400 MHz, C_6D_6) 0.17 and 0.24 (each 3H, s, Bu^{t}Si*Me*$_2$), 1.00 (9H, s, *Bu*^{t}SiMe$_2$), 1.05 (3H, s, 13β-Me), 1.51 (1H, tdd, *J* 2 x 11.5, 4.3 and 2.6, 8β-H), 1.89 (1H, dd, *J* 19.4 and 9.3, 15β-H), 2.03 (1H, td, *J* 2 x 11.5 and 4.0, 9α-H), 2.15 (1H, dd, *J* 19.4 and 9.3, 15α-H), 2.31 (1H, td, *J* 2 x 9.3 and 4.3, 14β-H), 2.51–2.72 (2H, m, 6α- and 6β-H), 3.26 (1H, s, 17α-H), 3.42 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.8, 4-H), 6.87 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.09 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) -5.1 and -4.7 (each q, *Me*$_2$CSiMe$_3$), 17.9 (q, C-18), 18.3 (s, Me$_2$*C*SiMe$_3$), 25.7 (3C, q, Me$_2$CSi*Me*$_3$), 26.7 (t, C-7), 28.5 (t, C-11), 30.4 (t, C-15), 30.6 (t, C-6), 34.6 (t, C-12), 25.5 (d, C-14), 36.5 (d, C-8), 42.4 (s, C-13), 43.5 (d, C-9), 55.2 (q, 3-OMe), 82.7 (d, C-17), 111.9 (d, C-2), 113.8 (d,

C-4), 126.9 (d, C-1), 131.9 (s, C-10), 137.9 (s, C-5), 157.6 (s, C-3) and 216.2 (s, C-16) (Found: C, 72.2; H, 9.4; M^+ - 57, 357. $C_{25}H_{38}O_3Si$ requires C, 72.4; H, 9.2%; *M*, 414).

16,16-*Ethylenedithio*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **134**

A solution of the 17-hydroxy-16-ketone **126** (100 mg, 0.32 mmol) in glacial acetic acid (10 cm^3) was treated with ethylene dithiol (0.15 cm^3, 5.47 mmol) and toluene-*p*-sulfonic acid monohydrate (30 mg, 0.48 mmol) for 24 h at 20 °C. Water was added and the product was extracted into ethyl acetate, washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$), and evaporated. Chromatography of the residue (112 mg) on silica gel (11 g), eluting with ethyl acetate-toluene (1:24) gave 16,16-*ethylenedithio*-3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **134** (81 mg, 65%), m.p. 157–160 (from chloroform-methanol); $[\alpha]_D$ +68 (*c* 1.2); ν_{max}/cm^{-1} 3440 (OH); δ_H (200 MHz) 0.81 (3H, s, 14-Me), 1.14 (3H, s, 13β-Me), 1.71 (1H, td, *J* 2 x 11.3 and 2.9, 12α-H), 2.72 (1H, td, *J* 2 x 11.8 and 6.0, 9α-H), 2.77 (1H, s, 17β-OH, exch. by D_2O), 2.79–2.81 (2H, m, 6α- and 6β-H), 3.13–3.24 and 3.29–3.35 [each 2H, m, 16-S(CH_2)$_2$S-], 3.76 (3H, s, 3-OMe), 4.07 (1H, d, *J* 10.7 → s on D_2O exch., 17α-H), 6.59 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.17 (1H, d, *J* 8.7, 1-H) (Found: C, 67.3; H, 7.8; S, 16.4%; M^+, 390. $C_{22}H_{30}O_2S_2$ requires C, 67.7; H, 7.7; S, 16.4%; *M*, 390).

3-*Methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **135**

Sodium borohydride (101 mg, 2.67 mmol) was added portionwise to a solution of the dithioketal **134** (50 mg, 0.13 mmol) and nickel chloride hexahydrate (213 mg, 0.90 mmol) in ethanol–tetrahydrofuran (4:1; 5 cm^3) at 0 °C. Stirring was maintained at 20 °C for 18 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was dissolved in ethyl acetate and sequentially washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue (36 mg) on silica gel, with ethyl acetate-toluene (3:22) as eluent gave 3-*methoxy*-14-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **135** (33 mg, 85%), m.p. 162–163 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ +103 (*c* 0.4); ν_{max}/cm^{-1} 3612 (OH); δ_H (400 MHz) 0.88 (3H, s, 14-Me), 0.89 (3H, s, 13β-Me), 1.37 (1H, td, *J* 2 x 11.3 and 2.1, 8β-H), 2.65 (1H, td, *J* 2 x 11.3 and 5.5, 9α-H), 2.83–2.86 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 4.13 (1H, dd, *J* 9.2 and 6.6, 17α-H), 6.61 (1H, d, *J* 2.9, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.9, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H) (Found: C, 79.7; H, 9.4%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; *M*, 300).

3-Methoxy-14-methylestra-1,3,5(10)-trien-17-one **133**

A solution of the 17β-alcohol **135** (10 mg, 0.03 mmol) in dry dichloromethane (1 cm^3) was treated with the Dess-Martin periodinane (62 mg, 0.16 mmol) at 20 °C for 30 min. The mixture was poured into aqueous sodium thiosulfate and aqueous sodium hydrogen carbonate. The product was extracted with diethyl ether, washed (water and brine), dried ($MgSO_4$) and evaporated to give 3-methoxy-14-methylestra-1,3,5(10)-trien-17-one **135** (8 mg, 81%), m.p. 139–141 °C; $[\alpha]_D$ +112 (*c* 0.5) (lit.,[22] m.p. 139–141 °C; $[\alpha]_D$ +113); δ_H (200 MHz) 0.87 (3H, s, 13β-Me), 1.00 (3H, s, 14-Me), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H).

Attempted ring-opening reactions on the 14α,15α-*methylene ketone* **119**

(*a*) A solution of lithium dimethylcuprate (0.24 mmol) [prepared conventionally at 0 °C from copper(I) iodide (45 mg, 0.24 mmol) and ethereal 1.6 mol dm^{-3} methyllithium (0.3 cm^3, 0.48 mmol)] in dry diethyl ether (0.5 cm^3) was cooled to -78 °C. Boron trifluoride-diethyl ether complex (0.01 cm^3, 0.08 mmol) was added, and the reagent was stirred at low temperature for 5 min. A solution of the 14α,15α-methylene ketone **119** (50 mg, 0.12 mmol) in dry tetrahydrofuran (3 cm^3) was added. The reaction was stirred at -78 °C for 30 min, then at 0 °C for 1h, without effecting any transformation. Starting material was recovered.

(*b*) A solution of lithium dimethylcyanocuprate (0.23 mmol) prepared at 0 °C from copper(I) cyanide (21 mg, 0.23 mmol) and ethereal 1.6 mol dm^{-3} methyllithium (0.3 cm^3, 0.48 mmol)] in dry diethyl ether (3 cm^3) was cooled to -78 °C. Boron trifluoride-diethyl ether complex (0.01 cm^3, 0.08 mmol) was added, and the reagent was stirred at -78 °C for 5 min. The 14α,15α-methylene ketone **119** (50 mg, 0.12 mmol) was added as a solution in dry tetrahydrofuran (3 cm^3). The reaction was stirred at -78 ° → 0 °C for 3h. Starting material was recovered.

(*c*) Chlorotrimethylsilane (0.05 cm^3, 0.39 mmol) was added to sodium iodide (58 mg, 0.38 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min. To the resulting solution of iodotrimethylsilane was added the 14α,15α-methylene 16-ketone **119** (83 mg, 0.19 mmol) in dry dichloromethane (2 cm^3). Stirring was maintained at 0 °C for 30 min. Saturated sodium thiosulfate was added and the residue upon work-up (ethyl acetate) (50 mg) was chromatographed on silica gel (5 g), eluting with ethyl acetate-toluene (1:49) to obtain 17β-hydroxy-3-methoxy-14,15α-methylene-estra-1,3,5(10)-trien-16-one **120** (44 mg, 74%).

3-*Methoxy*-17aβ-*hydroxy*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17-*one* **139**

A solution of *p*-toluenesulfonic acid monohydrate (75 mg, 0.39 mmol) in benzene (3 cm^3) was dried by refluxing over 4A-molecular sieves for 20 min in a Soxhlet condenser. To this solution was added the 14,15α-methylene 16-ketone **119** (84 mg, 0.20 mmol) in dry benzene (2 cm^3). The mixture was heated to refluxing temperature for 15 min. Water was added and the product was extracted into ethyl acetate. Combined extracts were washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (8 g), eluting with ethyl acetate-toluene (1:49) to give 3-*methoxy*-17aβ-*hydroxy*-17a-*homoestra*-1,3,5(10),15-*tetraen*-17-*one* **139** (48 mg, 77%), m.p. 187–191 °C (from chloroform-methanol); $[\alpha]_D$ -116 (*c* 0.6); ν_{max}/cm^{-1} 3598 (OH), 1676 (CO); δ_H (C_6H_6) (400 MHz) 0.68 (3H, s, 13β-Me), 1.62 (1H, ddd, *J* 11.4, 3.2 and 1.8, 14α-H), 2.62–2.64 (2H, m, 6α- and 6β-H), 3.42 (3H, s, 3-OMe), 3.68 (1H, d, *J* 2.3 → s on D_2O exch., 17aα-H), 3.88(exch. by D_2O) (1H, d, *J* 2.3, 17aβ-OH), 5.94 (1H, dd, *J* 10.2 and 3.2, 16-H), 6.34 (1H, dd, *J* 10.2 and 1.8, 15-H), 6.70 (1H, d, *J* 2.8, 4-H), 6.77 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.05 (1H, d, *J* 8.6, 1-H) (Found: C, 76.4; H, 7.8%; M^+, 312. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.7%; *M*, 312.), followed by desilylated material **120** (15 mg, 24%).

3-*Methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **149**

Ethereal 1.6 mol dm^{-3} methyllithium, (0.75 cm^3, 1.20 mmol) was added to a stirred slurry of copper(I) iodide (120 mg, 0.63 mmol) in dry diethyl ether (1 cm^3) at 0 °C. The resultant clear solution of lithium dimethylcuprate was cooled to -78 °C. Triethylamine (0.1 cm^3, 0.8 mmol) and chlorotrimethylsilane (0.1 cm^3, 0.72 mmol) were added, followed by the Δ^{15}-17-ketone **148** (84 mg, 0.30 mmol) in dry tetrahydrofuran (4 cm^3). After 5 min at -78 °C, saturated aqueous ammonium chloride and 1 mol dm^{-3} hydrochloric acid were added. The reaction mixture was stirred at 20 °C for 15 min. Aqueous sodium hydrogen carbonate was added and the product was extracted into ethyl acetate (x3), washed (water and brine) dried ($MgSO_4$), and evaporated. The residue (72 mg) was chromatographed on silica gel (6 g), eluting with ethyl acetate-toluene (1:4), to give 3-methoxy-15β-methylestra-1,3,5(10)-trien-17-one **149** (82 mg, 92%), m.p. 127–129 °C (from acetone-methanol) (lit.,[28] m.p. 122–124 °C); $[\alpha]_D$ +74 (*c* 1.0); $\Delta\varepsilon_{max}$ +2.83 (295 nm); ν_{max}/cm^{-1} 1725 (CO); δ_H (400 MHz) 1.07 (3H, s, 13β-Me), 1.16 (3H, d, *J* 7.4, 15β-Me), 1.68 (1H, dd, *J* 11.3 and 6.8, 14α-H), 1.75 (1H, qd, *J* 3 x 11.3 and 2.9, 8β-H), 1.89 (1H, dt, *J* 11.6 and 2 x 2.3, 12β-H), 2.09 (1H, ddt, *J* 12.7, 5.7 and 2 x 2.9, 7β-H), 2.30 and 2.51 (each 1H, obsc m, 16α- and 16β-H), 2.55 (1H, m, 15α-H), 2.90–2.95 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 6.69 (1H, d, *J* 2.7, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 17.0 (q, 15β-Me), 17.9 (q, C-18), 25.6 (t, C-11), 26.8 (t, C-7), 27.7 (d, C-15),

29.5 (t, C-6), 34.1 (t, C-12), 36.0 (d, C-8), 44.5 (d, C-9), 44.8 (t, C-16), 47.5 (s, C-13), 52.3, (d, C-14), 55.2 (q, 3-OMe), 111.4 (d, C-2), 113.9 (d, C-4), 126.0 (d, C-1), 132.5 (s, C-10), 137.8 (s, C-5), 157.7 (s, C-3) and 221.3 (s, C-17) (Found: C, 80.7; H, 8.6%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

15β-*Ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **163**

Copper(I) iodide (119 mg, 0.62 mmol) was added to ethylmagnesium iodide (6.25 mmol) [prepared from reaction of iodoethane (0.5 cm^3) with magnesium (150 mg)] in dry diethyl ether (1.5 cm^3) at 0 °C. A solution of the Δ^{15}-17-ketone **148** (340 mg, 1.20 mmol) in dry tetrahydrofuran (10 cm^3) was added slowly at 20 °C with stirring. After 10 min at 20 °C, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride was added. The product was extracted into ethyl acetate (x3), washed (aq sodium thiosulfate, water and brine), dried ($MgSO_4$) and evaporated. Crystallisation of the residue (341 mg) from chloroform-methanol gave 15β-*ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **163** (326 mg, 87%), m.p. 125–129 °C; $[\alpha]_D$ +85 (*c* 0.95); $\Delta\varepsilon_{max}$ +3.22 (294 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H (400 MHz) 0.95 (3H, t, *J* 2 x 7.5, 15β-CH_2*Me*), 1.02 (3H, s, 13β-Me), 1.34 and 1.65 (each 1H, m, 15β-C*H*$_2$Me), 1.73 (1H, m, 14α-H), 1.90 (1H, dt, *J* 11.7 and 2 x 2.4, 12β-H), 2.06 (1H, ddt, *J* 12.6, 5.5 and 2 x 2.9, 7β-H), 2.16-2.25 (1H, m, 15α-H), 2.29 (1H, td, *J* 2 x 10.6 and 3.7, 9α-H), 2.37 (1H, dd, *J* 19.4 and 2.5, 16β-H), 2.43 (1H, dd, *J* 19.4 and 7.8, 16α-H), 2.90–2.94 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.9, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.9, 2-H) and 7.20 (1H, d, *J* 8.4, 1-H); δ_C (50 MHz) 13.9 (q, 15β-CH_2*Me*), 17.8 (q, C-18), 23.8 (t, 15β-*C*H_2Me), 25.6 (t, C-11), 26.8 (t, C-7), 29.5 (t, C-6), 34.0 (t, C-12), 36.0 (d, C-8), 36.5 (d, C-15), 42.2 (t, C-16), 44.6 (d, C-9), 47.1 (s, C-13), 52.9 (d, C-14), 55.2 (q, 3-OMe), 111.4 (d, C-2), 113.9 (d, C-4), 126.0 (d, C-1), 132.4 (s, C-10), 137.8 (s, C-5), 157.7 (s, C-3) and 221.4 (s, C-17) (Found: C, 80.6; H, 8.9%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

15β-*Isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **164**

Copper(I) iodide–dimethyl sulfide (215 mg, 0.85 mmol) and hexamethylphosphoric triamide (HMPA) (2.0 cm^3, 11.5 mmol) were added to a solution of isopropylmagnesium bromide (8.50 mmol) [prepared at 0 °C from 2-bromopropane (0.8 cm^3) and magnesium (204 mg)] in dry diethyl ether (10 cm^3) at 0 °C. After 5 min at 0 °C, a solution of the Δ^{15}-17-ketone **148** (500 mg, 1.77 mmol) and chlorotrimethylsilane (1.6 cm^3, 12.6 mmol) in dry tetrahydrofuran (10 cm^3) was added slowly with stirring. After 20 min at 0 °C, saturated aqueous ammonium chloride and aqueous ammonia were added. The mixture was extracted into ethyl acetate (x3), washed (aq sodium thiosulfate, water and brine), dried ($MgSO_4$) and

evaporated. Chromatography of the residue (581 mg) on silica gel (50 g) with ethyl acetate-toluene (1:49) as eluent gave 15β-*isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **164** (508 mg, 88%), m.p. 104–108 °C (from diisopropyl ether); $[\alpha]_D$ +106 (*c* 1.0); $\Delta\varepsilon_{max}$ +4.69 (296 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 0.96 and 1.10 (each 3H, d, *J* 6.4, 15β-CH*Me*$_2$), 1.08 (3H, s, 13β-Me), 1,43 (1H, qd, *J* 3 x 13.1 and 3.8, 7α-H), 1.77 (1H, dd, *J* 11.8 and 6.0, 14α-H), 1.92 (1H, dt, *J* 10.6 and 2 x 3.1, 12β-H), 2.22 (1H, td, *J* 2 x 10.6 and 4.4, 9α-H), 2.30 (1H, ddt, *J* 13.1, 5.7 and 2 x 2.9, 7β-H), *ca* 2.38 obsc. (1H, dd, *J* 19.2 and 3.1, 16β-H), 2.44 (1H, dd, *J* 19.2 and 7.0, 16α-H), 2.88–2.91 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.4 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.4, 1-H); δ_C (50 MHz) 17.4 (C-18), 21.8 and 24.3 (15β-CH*Me*$_2$), 25.4 (C-11), 28.2 (C-7), 29.5 (C-6), 32.3 (C-8), 34.8 (C-12), 38.0 (15β-*C*HMe$_2$), 42.4 (C-16), 45.0 (C-9), 45.5 (C-15), 46.5 (C-13), 55.2 (3-OMe), 55.5 (C-14), 111.4 (C-2), 113.9 (C-4), 126.0 (C-1), 132.4 (C-10), 137.9 (C-5), 157.7 (C-3) and 222.8 (C-17) (Found: C, 80.5; H, 9.3%; M$^+$, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

3-*Methoxy*-15-*methylestra*-1,3,5(10),15-*tetraen*-17-*one* **158**

Lithium dimethylcuprate (5.41 mmol) in dry diethyl ether (5 cm^3) was prepared as described previously. The reagent was cooled to -78 °C, triethylamine (0.75 cm^3, 5.40 mmol) and chlorotrimethylsilane (0.7 cm^3, 5.50 mmol) were added, followed by the Δ^{15}-17-ketone **148** (1.0 g, 3.55 mmol) in dry tetrahydrofuran (10 cm^3). After 15 min at -78 °C, saturated aqueous ammonium chloride and aqueous ammonia were added. The mixture was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated to give the crude silyl enol ether **154** (1.51 g) as a colourless oil. The total crude was dissolved in dry acetonitrile (30 cm^3) and treated with palladium(II) acetate (770 mg, 3.43 mmol) at refluxing temperature for 15 min, then cooled to 20 °C, filtered and evaporated. Chromatography of the residue (950 mg) on silica gel (45 g) with ethyl acetate-toluene (1:19) as eluent gave 3-*methoxy*-15-*methylestra*-1,3,5(10),15-*tetraen*-17-*one* **158** (861 mg, 82% from **148**), m.p. 156–158 °C (from ethyl acetate-methanol); $[\alpha]_D$ -17 (*c* 1.0); ν_{max}/cm^{-1} 1688 (CO); δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 2.25 (3H, s, 15-Me), 2.93–2.96 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 5.77 (1H, br s, 16-H), 6.66 (1H, d, *J* 2.5, 4-H), 6.75 (1H, dd, *J* 8.6 and 2.5, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 20.9 (q, 15-Me), 21.5 (q, C-18), 25.6 (t, C-11), 27.7 (t, C-7), 29.2 (t, C-6), 29.4 (t, C-12), 36.8 (d, C-8), 45.2 (d, C-9), 52.6 (s, C-13), 55.2 (q, 3-OMe), 57.3 (d, C-14), 111.5 (d, C-2), 113.6 (d, C-4), 126.1 (d, C-1), 128.7 (d, C-16), 132.0 (s, C-10), 137.3 (s, C-5), 157.7 (s, C-3), 175.2 (s, C-15) and 212.1 (s, C-17) (Found: C, 81.3; H, 8.15%; M$^+$, 296. $C_{20}H_{24}O_2$ requires C, 81.0, H, 8.2%; *M*, 296).

15-*Ethyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **167**

Butyllithium (1.5 mol dm^{-3} in hexane; 5.1 cm^3, 7.65 mmol) was added to a solution of diisopropylamine (2.2 cm^3, 15.52 mmol) in dry tetrahydrofuran (3 cm^3) at 0 °C. The mixture was stirred at 0 °C for 5 min, then cooled to -78 °C. A solution of the 15β-ethyl 17-ketone **163** (496 mg, 1.58 mmol) in dry tetrahydrofuran (12 cm^3) was added slowly. The reaction was stirred at -78 °C for 30 min, then chlorotrimethylsilane (2.5 cm^3, 19.7 mmol) was added and the mixture was allowed to warm to 20 °C. After 15 min at 0 °C, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride was added. The product was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated. The crude silyl enol ether **165** (577 mg) was dissolved in acetonitrile (20 cm^3). Palladium(II) acetate (340 mg, 1.51 mmol) was added and the mixture was heated to refluxing temperature for 20 min, cooled to 20 °C, filtered, and concentrated under reduced pressure to give a dark crystalline product (523 mg). Chromatography on silica gel (25 g), eluting with ethyl acetate-toluene (1:19) gave 15-*ethyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **167** (419 mg, 85% from **163**), m.p. 103–106 °C (from chloroform-methanol); $[\alpha]_D$ -14 (*c* 0.9); ν_{max}/cm^{-1} 1689 (CO); δ_H (400 MHz) 1.11 (3H, s, 13β-Me), 1.20 (3H, t, *J* 2 x 7.6, 15-CH_2*Me*), 2.35–2.46 (2H, m, 15-C*H*$_2$Me), 2.90–2.95 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 5.79 (1H, br s, 16-H), 6.64 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.3 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.3, 1-H); δ_C (50 MHz) 11.6 (q, 15-CH_2*Me*), 21.5 (q, C-18), 25.6 (t, C-11), 27.3 (t, C-7), 28.0 (t, C-12), 29.2 (t, 15-*C*H_2Me), 29.4 (t, C-6), 37.0 (d, C-8), 45.3 (d, C-9), 52.6 (s, C-13), 55.2 (q, 3-OMe), 57.0 (d, C-14), 111.6 (d, C-2), 113.6 (d, C-4), 125.7 (d, C-16), 126.2 (d, C-1), 132.1 (s, C-10), 137.3 (s, C-5), 157.5 (s, C-3), 181.1 (s, C-15) and 212.2 (s, C-17) (Found: C, 81.1; H, 8.5%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%; *M*, 310).

15-*Isopropyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **168**

The 15β-isopropyl 17-ketone **164** (521 mg, 1.60 mmol) was converted into the crude silyl enol ether **166** and treated with palladium(II) acetate as described above to yield 15-*isopropyl*-3-*methoxyestra*-1,3,5(10),15-*tetraen*-17-*one* **168** (441 mg, 85% from **164**), m.p. 113–116 °C (from chloroform-methanol); $[\alpha]_D$ -18 (*c* 1.0); ν_{max}/cm^{-1} 1690 (CO); δ_H (200 MHz) 1.10 (3H, s, 13β-Me), 1.16 and 1.22 (each 3H, d, *J* 2 x 6.6, 15-CH*Me*$_2$), 2.57 (1H, dd, *J* 11.2 and 2.7, 14α-H), 2.90–2.94 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 5.80 (1H, dd, *J* 2.7 and 1.2, 16-H), 6.65 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.24 (1H d, *J* 8.6, 1-H); δ_C (50 MHz) 21.1 (q, C-18), 21.6 and 21.7 (each q, 15-CH*Me*$_2$), 25.6 (t, C-11), 28.1 (t, C-7), 29.1 (t, C-6), 29.7 (t, C-12), 30.3 (d, 15-*C*HMe$_2$), 30.8 (d, C-8), 45.4 (d, C-9), 52.6 (q, C-13), 55.2 (q, 3-OMe), 56.3 (d, C-14), 111.6 (d, C-2), 113.6 (d, C-4),

123.9 (d, C-16), 126.3 (d, C-1), 132.2 (s, C-10), 137.2 (s, C-5), 157.7 (s, C-3), 185.7 (s, C-15) and 212.4 (s, C-17) (Found: C, 81.6; H, 8.9%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324).

3-*Methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17-*one* **160**

To a solution of lithium dimethylcuprate (0.79 mmol) in dry diethyl ether (2 cm^3) [prepared at 0 °C from copper(I) iodide (150 mg, 0.79 mmol) and ethereal 1.6 mol dm^{-3} methyllithium (1.0 cm^3, 1.60 mmol)] at -78 °C was added boron trifluoride-diethyl ether complex (0.1 cm^3, 0.80 mmol), followed by the 15-methyl Δ^{15}-17-ketone **158** (163 mg, 0.55 mmol) in dry tetrahydrofuran (2 cm^3). After 30 min at 0 °C, saturated aqueous ammonium chloride was added. The mixture was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated. Chromatography of the residue (132 mg) on silica gel (5 g), eluting with ethyl acetate-toluene (1:19), gave 3-*methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17-*one* **160** (120 mg, 70%), m.p. 145–148 °C (from ethyl acetate-toluene); $[\alpha]_D$ +75 (*c* 1.0); $\Delta\varepsilon_{max}$ +2.08 (295 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H (400 MHz) 1.10 (3H, s, 13β-Me), 1.28 and 1.29 (each 3H, s, 15α- and 15β-Me), 1.47 (1H, d, *J* 10.9, 14α-H), 2.09 (1H, d, *J* 19.4, 16α-H), 2.23 (1H, ddt, *J* 12.7 and 2 x 2.6, 7β-H), 2.61 (1H, d, *J* 19.4, 16β-H), 2.91–2.97 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 17.8 (q, C-18), 24.5 (q, 15-Me), 26.0 (t, C-11), 28.2 (t, C-7), 29.8 (t, C-6), 34.2 (t, C-12), 34.6 (q, 15-Me), 35.5 (s, C-15), 37.5 (d, C-8), 44.9 (d, C-9), 50.2 (s, C-13), 53.6 (t, C-16), 55.2 (q, 3-OMe), 58.4 (d, C-14), 111.6 (d, C-2), 113.6 (d, C-4), 126.4 (d, C-1), 132.2 (s, C-10), 137.4 (s, C-5), 157.6 (s, C-3) and 221.4 (s, C-17) (Found: C, 80.5; H, 8.8%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

15α-*Ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **169**

Lithium dimethylcuprate (0.96 mmol) in dry diethyl ether (2 cm^3) was prepared as described above and cooled to -78 °C. Boron trifluoride-diethyl ether complex (0.12 mmol, 0.96 mmol) was added, followed by a solution of the 15-ethyl Δ^{15}-17-ketone **167** (150 mg, 0.48 mmol) in dry tetrahydrofuran (5 cm^3). After 20 min at 0 °C, saturated aqueous ammonium chloride was added. The product was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate, water and brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crystalline residue (187 mg). Chromatography on silica gel (9 g), with ethyl acetate-toluene (1:19) as eluent gave 15α-*ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **169** (127 mg, 81%), m.p. 110–113 °C (from chloroform-methanol); $[\alpha]_D$ +90 (*c* 1.0); $\Delta\varepsilon_{max}$ +2.18 (294 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 0.89 (3H, t,

J 2 x 7.4, 15α-CH_2*Me*), 1.12 (3H, s, 13β-Me), 1.25 (3H, s, 15β-Me), 1.36 and 1.76 (each 1H, dq, *J* 14.8 and 3 x 7.4, 15α-C*H*$_2$Me), 1.48 (1H, d, *J* 11.0, 14α-H), 2.18 (1H, d, *J* 19.4, 16α-H), 2.26 (1H, ddt, *J* 12.8, 5.4 and 2 x 2.6, 7β-H), 2.44 (1H, d, *J* 19.4, 16β-H) 2.84–2.89 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.9, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.9, 2-H) and 7.20 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 9.4 (15α-CH_2*Me*), 18.2 (C-18), 21.8 (15α-*C*H$_2$Me), 26.1 (C-11), 28.3 (C-7), 29.9 (C-6), 30.3 (15β-Me), 34.2 (C-12), 37.8 (C-8), 38.9 (C-15), 44.9 (C-9), 49.8 (C-16), 50.0 (C-13), 55.2 (3-OMe), 56.6 (C-14), 111.6 (C-2), 113.6 (C-4), 126.5 (C-1), 132.2 (C-10), 137.4 (C-5), 157.6 (C-3) and 220.4 (C-17) (Found: C, 81.2; H, 9.5%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

15α-*Isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **170**

The 15-isopropyl Δ^{15}-17-ketone **168** (200 mg, 0.62 mmol) in dry tetrahydrofuran (6 cm^3) was treated with lithium dimethylcuprate (1.24 mmol) and boron trifluoride-diethyl ether complex (0.16 mmol, 1.27 mmol) as described above to give 15α-*isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17-*one* **170** (184 mg, 86%), m.p. 113–115 °C (from diisopropyl ether); $[\alpha]_D$ +87 (*c* 0.9); $\Delta\varepsilon_{max}$ +1.85 (293 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz, C_6D_6) 0.68 (6H, d, *J* 6.0, 15α-CH*Me*$_2$), 0.87 (3H, s, 15β-Me), 0.98 (3H, s, 13β-Me), 1.45 (1H, td, *J* 2 x 13.2 and 3.6, 12α-H), 1.62 obsc. (1H, sept, *J* 6 x 6.0, 15α-C*H*Me$_2$), 1.95 (1H, d, *J* 19.1, 16α-H), 2.08 (1H, m, 7β-H), 2.15 (1H, d, *J* 19.1, 16β-H), 2.65–2.65 (2H, m, 6α- and 6β-H), 3.44 (3H, s, 3-OMe), 6.70 (1H, d, *J* 2.6, 4-H), 6.79 (1H, dd, *J* 8.8 and 2.6, 2-H) and 7.09 (1H, d, *J* 8.8, 1-H); δ_H (400 MHz, $CDCl_3$) 0.87 and 0.89 (each 3H, d, *J* 6.7, 15α-CH*Me*$_2$), 1.13 (3H, s, 13β-Me), 1.32 (3H, s, 15β-Me), 1.49 (1H, d, *J* 10.1, 14α-H), 1.84 (1H, qd, *J* 3 x 10.1 and 2.6, 8β-H), 1.94 (1H, sept, *J* 6 x 6.7, 15α-C*H*Me$_2$), 2.20 (1H, d, *J* 19.4, 16α-H), 2.26 (1H, d, *J* 19.4, 16β-H), 2.37 (1H, m, 7β-H), 2.85–2.88 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.68 (1H, d, *J* 2.8, 4-H), 6.75 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.8, 1-H); δ_C (50 MHz) 17.8 (q, C-18), 18.4 and 18.8 (each q, 15α-CH*Me*$_2$), 23.0 (q, 15β-Me), 26.1 (t, C-11), 27.8 (t, C-7), 30.0 (t, C-6), 34.5 (t, C-12), 36.9 (d, 15α-*C*HMe$_2$), 37.7 (d, C-8), 41.5 (s, C-15), 44.6 (t, C-16), 45.0 (d, C-9), 49.9 (s, C-13), 51.6 (d, C-14), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.6 (d, C-4), 126.5 (d, C-1), 132.2 (s, C-10), 137.4 (s, C-5), 157.6 (s, C-3) and 220.3 (s, C-17) (Found: C, 81.2; H, 9.6%; M^+, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; *M*, 340).

15β-*Ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17-*one* **171**

The 15-methyl Δ^{15}-17-ketone **158** (200 mg, 0.68 mmol) in dry tetrahydrofuran (10 cm^3) was treated with ethylmagnesium iodide [prepared from ethyl iodide (0.27 cm^3, 3.38 mmol) and magnesium (81 mg, 3.38 mmol)] in the presence of copper(I) iodide

(64 mg, 0.34 mmol). After 15 min at 20 °C the mixture was cooled to 0 °C and saturated aqueous ammonium chloride was added. The product was extracted into diethyl ether (x3), washed (aq sodium thiosulfate, water and brine), dried ($MgSO_4$) and evaporated to give 15β-*ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17-*one* **171** (186 mg, 84%), m.p. 104–107 °C (from diisopropyl ether); $[\alpha]_D$ +90 (*c* 1.0); $\Delta\varepsilon_{max}$ +2.30 (294 nm); ν_{max}/cm^{-1} 1724; δ_H (400 MHz) 0.94 (3H, t, *J* 2 x 7.6, 15β-CH_2*Me*), 1.09 (3H, s, 13β-Me), 1.22 (3H, s, 15α-Me), 1.49 (1H, d, *J* 10.1, 14α-H), 1.63 and 1.76 (each 1H, dq, *J* 15.2 and 3 x 7.6, 15β-C*H*$_2$Me), 1.87 (1H, d, *J* 19.3, 16α-H), 2.27 (1H, ddt, *J* 12.8 and 2 x 2.6, 7β-H), 2.80 (1H, d, *J* 19.3, 16β-H), 2.90–2.94 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 9.0 (q, 15β-CH_2*Me*), 18.3 (q, C-18), 25.9 (t, 15α-*C*H$_2$Me), 27.4 (t, C-11), 28.6 (t, C-7), 29.8 (t, C-6), 30.3 (q, 15α-Me), 34.4 (t, C-12), 37.3 (d, C-8), 39.4 (s, C-15), 45.1 (d, C-9), 48.9 (t, C-16), 49.8 (s, C-13), 55.2 (q, 3-OMe), 59.8 (d, C-14), 111.6 (d, C-2), 113.6 (d, C-4), 126.4 (d, C-1), 132.3 (s, C-10), 137.4 (s, C-5), 157.6 (s, C-3) and 220.3 (s, C-17) (Found: C, 80.9; H, 9.6%; M$^+$, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

15,15-*Diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **172**

Treatment of the 15-ethyl Δ^{15}-17-ketone **167** (124 mg, 0.4 mmol) with ethylmagnesium iodide in the presence of copper(I) iodide (as in the foregoing experiment) gave 15,15-*diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **172** (122 mg, 90%), m.p. 111–113 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ +94 (*c* 1.1); $\Delta\varepsilon_{max}$ +2.99 (293 nm); ν_{max}/cm^{-1} 1725 (CO); δ_H (400 MHz) 0.87 and 0.93 (each 3H, t, *J* 2 x 7.4, 15α- and 15β-CH_2*Me*), 1.10 (3H, s, 13β-Me), 1.42, 1.55, 1.65 and 1.65 (each 1H, m, 15α- and 15β-C*H*$_2$Me), 1.49 (1H, d, *J* 10.1, 14α-H), 1.95 (1H, d, *J* 19.6, 16α-H), 2.25 (1H, ddt, *J* 12.9, 5.3 and 2 x 2.5, 7β-H), 2.64 (1H, d, *J* 19.6, 16β-H), 2.85–2.88 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 9.1 (q, 2C, 15α- and 15β-CH_2*Me*), 18.3 (q, C-18), 25.9 (t, C-11), 27.8 (t, C-7), 28.1 (t, 15β-*C*H$_2$Me), 29.9 (t, C-6), 32.7 (t, 15α-*C*H$_2$Me), 34.3 (t, C-12), 37.5 (d, C-8), 42.1 (s, C-15), 44.7 (t, C-16), 45.0 (d, C-9), 49.5 (s, C-13), 52.6 (d, C-14), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.6 (d, C-4), 126.4 (d, C-1), 132.3 (s, C-10), 137.4 (s, C-5), 157.6 (s, C-3) and 220.5 (s, C-17) (Found C, 81.2; H, 9.5%; M$^+$, 340. $C_{23}H_{32}O_2$ requires C, 81.1; H, 9.5%; M, 340).

3-*Methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17β-*ol* **161**

The 15,15-dimethyl 17-ketone **160** (50 mg, 0.16 mmol) in dry tetrahydrofuran (2 cm^3) was treated with lithium aluminium hydride (30 mg, 0.79 mmol) at 0 °C for 15 min.

Saturated aqueous sodium hydrogen carbonate was added and the mixture was filtered. The filtrate was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated to give 3-*methoxy*-15,15-*dimethylestra*-1,3,5(10)-*trien*-17β-*ol* **161** (43 mg, 85%), m.p. 87–91 °C (from chloroform-hexane); $[\alpha]_D$ +75 (*c* 1.1); ν_{max}/cm^{-1} 3606 (OH); δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 1.06 (1H, d, *J* 11.2, 14α-H), 1.11 and 1.14 (each 3H, s, 15α- and 15β-Me), 1.61 (1H, dd, *J* 13.0 and 10.2, 16α-H), 1.90 (1H, dd, *J* 13.0 and 7.9, 16β-H), 2.84–2.87 (2H, m, 6α- and 6β-H), 3.71 (1H, dd, *J* 10.2 and 7.9, 17α-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 13.5 (q, C-18), 25.6 (q, 15β-Me), 26.1 (t, C-11), 28.5 (t, C-7), 29.9 (t, C-6), 35.0 (q, 15α-Me), 36.2 (s, C-15), 37.1 (d, C-8), 38.8 (t, C-12), 44.9 (d, C-9), 45.6 (s, C-13), 50.1 (t, C-16), 55.2 (q, 3-OMe), 58.1 (d, C-14), 79.8 (d, C-17), 111.4 (d, C-2), 113.6 (d, C-4), 126.3 (d, C-1), 132.9 (s, C-10), 137.7 (s, C-5) and 157.5 (s, C-3) (Found: C, 80.0; H, 9.5%; M$^+$, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

15α-*Ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **173**

The 15α-ethyl 15β-methyl 17-ketone **169** (80 mg, 0.25 mmol) was treated with lithium aluminium hydride (48 mg, 1.26 mmol) as described above to yield 15α-*ethyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **173** (75 mg, 89%), m.p. 133–136 °C (from chloroform-methanol); $[\alpha]_D$ +67 (*c* 0.9); ν_{max}/cm^{-1} 3604 (OH); δ_H (400 MHz) 0.88 (3H, t, *J* 2 x 7.2, 15α-CH_2*Me*), 0.93 (3H, s, 13β-Me), 1.06 (3H, s, 15β-Me), 1.10 (1H, d, *J* 11.1, 14α-H), 1.32 obsc. (2H, m, 15α-C*H*$_2$Me), 1.39 (1H, dd, *J* 13.2 and 10.0, 16α-H), 1.73 (1H, qd, *J* 3 x 11.1 and 2.3, 8β-H), 1.87 (1H, dt, *J* 12.3 and 2 x 2.8, 12β-H), 2.14 (1H, ddt, *J* 12.8, 5.2 and 2 x 2.3, 7β-H), 2.04 (1H, dd, *J* 13.2 and 7.9, 16β-H), 2.82–2.85 (2H, m, 6α- and 6β-H), 3.60 (1H, dd, *J* 10.0 and 7.9, 17α-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.9, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.9, 2-H) and 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 9.4 (q, 15α-CH_2*Me*), 13.9 (q, C-18), 23.7 (q, 15β-Me), 26.1 (t, C-11), 28.6 (t, C-7), 29.9 (t, C-6), 37.1 (d, C-8), 37.7 (t, 15α-*C*H$_2$Me), 38.9 (t, C-12), 39.7 (s, C-15), 45.0 (d, C-9), 45.3 (s, C-13), 45.6 (t, C-16), 55.2 (q, 3-OMe), 55.6 (d, C-14), 80.2 (d, C-17), 111.4 (d, C-2), 113.6 (d, C-4), 126.3 (s, C-1), 133.0 (s, C-10), 137.7 (s, C-5) and 157.5 (s, C-3) (Found: C, 80.0; H, 9.7%; M$^+$, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328).

15α-*Isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **174**

Treatment, as detailed above, of the 15α-isopropyl 15β-methyl 17-ketone **170** (63 mg, 0.19 mmol) in dry tetrahydrofuran (4 cm^3) with lithium aluminium hydride (35 mg, 0.92 mmol) gave 15α-*isopropyl*-3-*methoxy*-15β-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **174** (60 mg, 95%) as an oil, $[\alpha]_D$ +54 (*c* 1.3); ν_{max}/cm^{-1} 3604 (OH); δ_H (200 MHz) 0.88 and 0.92

(each 3H, d, *J* 6.8, 15α-CH*Me*$_2$), 0.96 (3H, s, 13β-Me), 1.13 (3H, s, 15β-Me), 1.45 (1H, d, *J* 11.4, 14α-H), 1.73 (1H, dd, *J* 13.4 and 10.2, 16α-H), 1.88 (1H, dt, *J* 11.2 and 2 x 2.4, 12β-H), 2.13 (1H, dd, *J* 13.4 and 7.9 Hz, 16β-H), 2.31 (1H, td, *J* 2 x 10.1 and 3.5, 9α-H), 2.82–2.84 (2H, m, 6α- and 6β-H), 3.54 (1H, dd, *J* 10.2 and 7.9, 17α-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, dd, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 14.1 (q, C-18), 18.2 and 18.6 (each q, 15α-CH*Me*$_2$), 23.7 (q, 15β-Me), 26.2 (t, C-11), 28.5 (t, C-7), 29.9 (t, C-6), 36.6 (d, 15α-*C*HMe$_2$), 37.3 (t, C-8), 39.3 (d, C-12), 40.7 (t, C-16), 42.7 (s, C-15), 44.7 (s, C-13), 51.8 (d, C-14), 55.2 (q, 3-OMe), 80.8 (d, C-17), 111.4 (d, C-2), 113.6 (d, C-4), 126.3 (d, C-1), 133.0 (s, C-10), 137.6 (s, C-5) and 157.7 (s, C-3) (Found: C, 80.4; H, 9.9%; M$^+$, 342. $C_{23}H_{34}O_2$ requires C, 80.65; H, 10.0%; *M*, 342).

15β-*Ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **175**

Similar treatment as above of the 15β-ethyl 15α-ethyl 17-ketone **171** (100 mg, 0.31 mmol) in dry tetrahydrofuran (3 cm^3) with lithium aluminium hydride (58 mg, 1.53 mmol) gave 15β-*ethyl*-3-*methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17β-*ol* **175** (92 mg, 90%) as an oil, $[\alpha]_D$ +70 (*c* 1.0); ν_{max}/cm^{-1} 3604 (OH); δ_H (400 MHz) 0.88 (3H, t, *J* 2 x 7.2, 15β-CH$_2$*Me*), 0.90 (3H, s, 13β-Me), 1.10 (3H, s, 15α-Me), 1.13 (1H, d, *J* 11.5, 14α-H), 1.28 (1H, td, *J* 2 x 12.8 and 3.2, 12α-H), 1.51 obsc. (2H, m, 15α-C*H*$_2$Me), 1.73 obsc. (2H, m, 16α- and 16β-H), 1.87 (1H, dt, *J* 12.8 and 2 x 3.2, 12β-H), 2.83–2.85 (2H, m, 6α- and 6β-H), 3.74 (1H, dd, *J* 9.9 and 8.2, 17α-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.4, 1-H); δ_C (50 MHz) 8.6 (15β-CH$_2$*Me*), 13.9 (C-18), 25.9 (C-11), 28.6 (C-7), 29.0 (15α-Me), 29.9 (C-6), 30.3 (15β-*C*H$_2$Me), 36.8 (C-8), 39.0 (C-12), 40.0 (C-15), 45.2 (C-9), 45.3 (C-13), 45.7 (C-16), 55.2 (3-OMe), 59.6 (C-14), 80.0 (C-17), 111.4 (C-2), 113.6 (C-4), 126.2 (C-1), 133.0 (C-10), 137.7 (C-5) and 157.5 (C-3) (Found: C, 80.1; H, 9.7%; M$^+$, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328).

15,15-*Diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* **176**

Reduction of the 15,15-diethyl 17-ketone **172** (205 mg, 0.60 mmol) in dry tetrahydrofuran (10 cm^3) with lithium aluminium hydride (46 mg, 1.21 mmol),as detailed above, gave 15,15-*diethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17β-*ol* **176** (93 mg, 94%) as an oil, $[\alpha]_D$ +37 (*c* 0.95); ν_{max}/cm^{-1} 3603 (OH); δ_H (200 MHz) 0.86 and 0.93 (each 3H, t, *J* 2 x 7.5, 15α- and 15β-CH$_2$*Me*), 0.91 (3H, s, 13β-Me), 1.19-1.38 (4H, m, 15α- and 15β-C*H*$_2$Me), 1.88 (1H, dt, *J* 11.5 and 2 x 2.7, 12β-H), 2.19 (1H, m, 7β-H), 2.83–2.86 (2H, m, 6α- and 6β-H), 3.62 (1H, dd, *J* 9.0 and 7.9, 17α-H), 3.78 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7,

4-H), 6.71 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.22 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 8.3 and 9.2 (q, 15α- and 15β-CH_2*Me*), 14.2 (q, C-18), 26.0 (t, C-11), 28.6 (t, C-7), 28.7 (t, 15β-*C*H_2Me), 29.8 (t, C-6), 31.9 (t, 15α-*C*H_2Me), 36.9 (d, C-8), 39.2 (t, C-12), 41.6 (t, C-16), 43.1 (s, C-15), 44.7 (d, C-9), 45.1 (s, C-13), 51.2 (d, C-14), 55.2 (q, 3-OMe), 80.7 (d, C-17), 111.4 (d, C-2), 113.6 (d, C-4), 126.2 (d, C-1), 133.1 (s, C-10), 137.7 (s, C-5) and 157.5 (s, C-3) (Found: C, 80.4; H, 9.9%; M^+, 342. $C_{23}H_{34}O_2$ requires 80.7; H, 10.0%; *M*, 342).

15,15-*Dialkylestra*-1,3,5(10)-*triene*-3,17β-*diols* **162, 177 – 180**

General Procedure. – A toluene solution of 1.5 mol dm^{-3} diisobutylaluminium hydride (5 equivalents) was added to the 15,15-dialkyl 17β-alcohol in dry toluene. The solution was heated to refluxing temperature for 24 h, cooled to 0 °C, and saturated aqueous ammonium chloride was added. The aqueous phase was acidified with dilute hydrochloric acid. The product was extracted into ethyl acetate, (x3) washed (water and brine), dried ($MgSO_4$) and evaporated to give the 3,17β-diol.

15,15-*Dimethylestra*-1,3,5(10)-*triene*-3,17β-*diol* **162** (90%), m.p. 167–170 °C (from ethyl acetate); $[\alpha]_D$ +49 (*c* 1.1 in ethanol) (Found: C, 79.6; H, 9.3%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; *M*, 300).

15α-*Ethyl*-15β-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **177** (92%), amorph., $[\alpha]_D$ +59 (*c* 1.0 in ethanol) (Found: C, 79.8; H, 9.5%; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2, H, 9.6%; *M*, 314).

15α-*Isopropyl*-15β-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **178** (90%), m.p. 201–205 °C (from ethyl acetate); $[\alpha]_D$ +71 (*c* 1.0 in tetrahydrofuran) (Found: C, 80.7; H, 9.8%; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328).

15β-*Ethyl*-15α-*methylestra*-1,3,5(10)-*triene*-3,17β-*diol* **179** (94%), m.p. 132–136 °C (from ethyl acetate); $[\alpha]_D$ +54 (*c* 1.0 in ethanol) (Found: C, 80.4; H, 9.5%; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

15,15-*Diethylestra*-1,3,5(10)-*triene*-3,17β-*diol* **180** as a foam (90%), $[\alpha]_D$ +72 (*c* 1.0 in ethanol) (Found: C, 80.0; H, 9.7%; M^+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328).

3-*Methoxy*-15α-*methylestra*-1,3,5(10)-*trien*-17-*one* **181**

Freshly cut lithium (11 mg) was dissolved in liquid ammonia (distilled from sodium, 20 cm^3) and the 15-methyl Δ^{15}-17-ketone **158** (50 mg, 0.17 mmol) in dry tetrahydrofuran (7 cm^3) was added slowly with stirring. After 15 min, solid ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was suspended in water. The product was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and

evaporated. The crude material (40 mg) was chromatographed on silica gel (4 g), eluting with ethyl acetate-toluene (1:9), gave 3-methoxy-15α-methylestra-1,3,5(10)-trien-17-one **181** (35 mg, 70%), m.p. 137–140 °C (from chloroform-methanol); $[\alpha]_D$ +192 (*c* 1.0) (lit.,[27] m.p. 135-138 °C; $[\alpha]_D$ +198); $\Delta\varepsilon_{max}$ +2.70 (295 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 0.95 (3H, s, 13β-Me), 1.22 (1H, t, *J* 2 x 10.8, 14α-H), 1.23 (3H, d, *J* 6.4, 15α-Me), 1.73 (3H, dd, *J* 19.3 and 8.4, 16α-H), 1.76 (1H, qd, *J* 3 x 10.8 and 2.4, 8β-H), 1.89 (1H, dt, *J* 9.6 and 2 x 2.7, 12β-H), 2.22 (1H, dq, *J* 12.9 and 3 x 2.9, 11α-H), 2.38 (1H, ddt, *J* 11.6, 4.9 and 2 x 2.4, 7β-H), 2.77 (3H, dd, *J* 19.3 and 8.7, 16β-H), 2.85–2.89 (2H, m, 6α- and 6β-H), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.19 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 15.8 (q, C-18), 22.0 (q, 15α-Me), 26.5 (t, C-7), 27.7 (t, C-11), 29.8 (t, C-6), 30.8 (d, C-15), 31.7 (t, C-12), 39.6 (d, C-8), 44.2 (d, C-9), 47.5 (t, C-16), 50.8 (s, C-13), 55.2 (q, 3-OMe), 57.2 (d, C-14), 111.7 (d, C-2), 113.5 (d, C-4), 126.7 (d, C-1), 131.9 (s, C-10), 137.4 (s, C-5), 157.5 (s, C-3) and 220.1 (s, C-17) (Found: C, 80.3; H, 8.7%; M$^+$, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

15α-*Ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **182**

A solution of the 15-ethyl Δ^{15}-17-ketone **167** (50 mg, 0.16 mmol) in dry tetrahydrofuran (8 cm^3) was treated with lithium (11 mg) in liquid ammonia (20 cm^3) as described above to yield 15α-*ethyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **182** (40 mg, 80%), m.p. 91–95 °C (from chloroform-methanol); $[\alpha]_D$ +170 (*c* 1.1); $\Delta\varepsilon_{max}$ +2.94 (292 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H (400 MHz) 0.94 (3H, t, *J* 2 x 7.4, 15α-CH_2*Me*), 0.97 (3H, s, 13β-Me), 1.22 and 2.02 (each 1H, m, 15α-C*H*$_2$Me), 1.29 (1H, t, *J* 2 x 10.7, 14α-H), 1.78 (1H, qd, *J* 3 x 10.7 and 2.9, 8β-H), 1.79 (1H, dd, *J* 19.4 and 7.9, 16α-H), 1.90 (1H, dt, *J* 10.9 and 2 x 2.0, 12β-H), 2.23 (1H, ddt, *J* 12.7, 5.7 and 2 x 2.9, 7β-H), 2.30 (1H, td, *J* 2 x 10.7 and 4.8, 9α-H), 2.78 (1H, dd, *J* 19.4 and 8.8, 16β-H), 2.84–2.88 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, 8.7 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 12.4 (q, 15α-CH_2*Me*), 15.7 (q, C-18), 26.5 (t, C-11), 27.8 (t, C-7), 29.9 (t, C-6), 30.0 (t, 15α-*C*H$_2$Me), 31.6 (t, C-12), 37.8 (d, C-8), 39.7 (d, C-15), 42.7 (t, C-16), 44.2 (d, C-9), 50.5 (s, C-13), 54.5 (d, C-14), 55.2 (q, 3-OMe), 111.8 (d, C-2), 113.5 (d, C-4), 126.8 (d, C-1), 131.9 (s, C-10), 137.4 (s, C-5), 157.5 (s, C-3) and 220.2 (s, C-17) (Found: C, 80.4; H, 8.9%; M$^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%, *M*, 312).

15α-*Isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **183**

Similar treatment of the 15-isopropyl Δ^{15}-ketone **168** (50 mg, 0.15 mmol) gave 15α-*isopropyl*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **183** (35 mg, 72%), m.p. 128–131 °C (from chloroform-methanol); $[\alpha]_D$ +173 (*c* 0.45); $\Delta\varepsilon_{max}$ +1.70 (293 nm); ν_{max}/cm^{-1} 1727 (CO); δ_H

(400 MHz) 0.83 and 0.92 (each 3H, d, J 6.7, 15α-CH*Me*$_2$), 0.97 (3H, s, 13β-Me), 1.45 (1H, t, *J* 2 x 10.8, 14α-H), 1.76 (1H, qd, *J* 3 x 10.8 and 2.6, 8β-H), 1.90 (1H, dt, *J* 10.5 and 2 x 2.4, 12β-H), 1.95 (1H, dd, *J* 18.5 and 7.7, 16α-H), 2.42 (1H, dd, *J* 18.5 and 8.5, 16β-H), 2.84–2.89 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 14.9 and 27.7 (each q, 15α-CH*Me*$_2$), 15.6 (q, C-18), 26.4 (t, C-11), 27.4 (t, C-7), 28.5 (d, 15α-*C*HMe$_2$), 30.1 (t, C-6), 31.8 (t, C-12), 35.7 (t, C-16), 39.9 (d, C-8), 41.7 (d, C-15), 44.4 (d, C-9), 50.1 (s, C-13), 50.6 (d, C-14), 55.2 (q, 3-OMe), 111.7 (d, C-2), 113.5 (d, C-4), 126.8 (d, C-1), 132.0 (s, C-10), 137.4 (s, C-5), 157.5 (s, C-3) and 220.1 (s, C-17) (Found: C, 80.4; H, 9.2%; M$^+$, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

3-*Methoxy*-14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* **184**

A solution of the 15-methyl Δ^{15}-ketone **158** (178 mg, 0.6 mmol) in dry benzene (12 cm^3) was treated with toluene-*p*-sulfonic acid monohydrate (126 mg, 0.6 mmol) at refluxing temperature for 30 min. Water was added and the product was extracted into ethyl acetate (x3). Combined organic phase was washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and concentrated under reduced pressure. The residue (180 mg) was chromatographed on silica gel (9 g), eluting with ethyl acetate-toluene (1:19) to give 3-methoxy-14β-estra-1,3,5(10),15-teraen-17-one **184**[124] (170 mg, 96%) as a clear oil, $[\alpha]_D$ +24 (*c* 1.0); ν_{max}/cm^{-1} 1690 (CO); δ_H (200 MHz) 1.12 (3H, s, 13β-Me), 2.17 (3H, s, 15-Me), 2.72 (1H, d, *J* 5.1, 14β-H), 6.58 (1H, d, *J* 2.6, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6, 2-H) and 7.05 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 20.9 (C-18), 28.4 (C-11), 28.8 (C-7), 30.5 (C-9), 31.6 (C-6), 33.8 (C-12), 38.9 (C-8), 50.3 (C-13), 55.2 (3-OMe), 57.9 (C-14), 111.4 (C-2), 113.2 (C-4), 126.6 (C-1), 131.1 (C-16), 133.4 (C-10), 137.3 (C-5), 157.3 (C-3), 177.1 (C-15) and 213.7 (C-17) (Found: C, 80.9; H, 8.0%; M$^+$, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296).

3-*Methoxy*-15,15-*dimethyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **186**

Lithium dimethylcuprate – chlorotrimethylsilane was prepared from copper(I) iodide (1.27 g, 6.67 mmol), etheral 1.5 mol dm^{-3} methyllithium (8.9 cm^3, 13.35 mmol) and chlorotrimethylsilane (0.8 cm^3, 7.10 mmol) in dry diethyl ether (7 cm^3) at -78 °C in the usual fashion. Triethylamine (0.9 cm^3, 6.49 mmol) and a solution of 3-methoxy-15-methyl-14β-estra-1,3,5(10),15-tetraen-17-one **184** (396 mg, 1.33 mmol) in dry tetrahydrofuran (15 cm^3) was added slowly. Stirring at -78 °C was maintained for 15 min. Saturated aqueous ammonium chloride, followed by 1 mol dm^{-3} hydrochloric acid (5 cm^3) were added. Stirring

was continued at 0 °C, to ensure complete hydrolysis of the silyl enol ether. The product was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and concentrated to give a crystalline residue (401 mg). Chromatographed on silica gel, eluting with ethyl acetate-toluene (1:49), to yield 3-*methoxy*-15,15-*dimethyl*-14β-*estra*-1,3,5(10)-*trien*-17-*one* **186** (352 mg, 80%), m.p. 151–153 °C (from chloroform-methanol); $[\alpha]_D$ +184 (*c* 1.0); $\Delta\varepsilon_{max}$ +2.80 (287 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 1.14 (3H, s, 13β-Me), 1.27 and 1.33 (each 3H, s, 15α and 15β-Me), 1.60 (1H, dt, *J* 14.0 and 2 x 2.9, 12β-H), 1.77 (1H, td, *J* 2 x 14.0 and 4.1, 12α-H), 1.98 (1H, d, *J* 4.7, 14β-H), 2.29 (2H, s, 16α and 16β-H), 2.36 (1H, dq, *J* 3 x 4.1 and 14.0, 11α-H), 2.84–2.88 (3H, m, 6α-, 6β- and 9α-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.20 (1H, d, *J* 8.7, 1-H); δ_C (100 MHz) 23.0 (q, C-18), 27.7 (q, 15-Me), 28.4 (t, C-7), 28.5 (t, C-11), 31.4 (t, C-12), 31.6 (t, C-6), 33.5 (q, 15-Me), 36.5 (d, C-9), 38.5 (s, C-15), 40.1 (d, C-8), 48.8 (s, C-13), 55.2 (q, 3-OMe), 55.8 (t, C-16), 56.9 (d, C-14), 112.0 (d, C-2), 113.7 (d, C-4), 127.5 (d, C-1), 132.1 (s, C-10), 137.8 (s, C-5), 157.4 (s, C-3) and 223.3 (s, C-17) (Found: C, 80.7; H, 9.1%; M$^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7, H, 9.0%; *M*, 312).

3-*Methoxy*-15,15-*dimethyl*-14β-*estra*-1,3,5(10)-*trien*-17α-*yl acetate* **188**

A solution of the dimethyl ketone **186** (92 mg, 0.29 mmol) in dry tetrahydrofuran (7 cm^3) was cooled to 0 °C. Lithium aluminium hydride (40 mg, 1.05 mmol) was added, and low temperature stirring was maintained for 15 min. Saturated aqueous sodium hydrogen carbonate was added. The solution was filtered, and the filtrate was worked up in the standard way (ethyl acetate) to give the crude 17-alcohol **187** as a clear oil (82 mg). This residue was dissolved in dry pyridine (2 cm^3) and acetic anhydride (0.2 cm^3). After 30 min at 20 °C, water and solid sodium hydrogen carbonate were added, and the product was extracted into ethyl acetate. The combined organic phase was washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallisation of the residue (88 mg, 96%) gave 3-*methoxy*-15,15-*dimethyl*-14β-*estra*-1,3,5(10)-*trien*-17α-*yl acetate* **188**, m.p. 130–132 °C (from chloroform-methanol), $[\alpha]_D$ +112 (*c* 1.0); ν_{max}/cm^{-1} 1722 (CO), δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 1.71 and 1.31 (each 3H, s, 15α and 15β-Me), 1.67 (1H, dd, *J* 13.1 and 9.9, 16α-H), 2.02 (1H, dd, *J* 13.1 and 8.2, 16β-H), 2.06 (3H, s, 17α-OAc), 2.82 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.83 (1H, dd, *J* 9.9 and 8.2, 17β-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.7, 2-H) and 7.23 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 21.2 (q, C-18), 23.8 (q, 15-Me), 27.5 (t, C-11), 27.6 (t, C-7), 29.4 (t, C-6), 30.2 (q, 17α-OCO*C*H$_3$), 31.5 (t, C-12), 36.0 (q, 15-Me), 36.6 (d, C-9), 38.7 (s, C-15), 39.1 (d, C-8), 45.2 (s, C-13), 45.7 (t, C-16), 55.2 (q, 3-OMe), 56.7 (d, C-14), 80.9 (d, C-17), 111.9 (d, C-2), 113.7 (d, C-4), 127.2 (d, C-1), 133.2 (s, C-10), 138.1 (s, C-5),

157.4 (s, C-3) and 171.2 (s, 17α-$OCOCH_3$) (Found: C, 77.4; H, 9.1%; M^+, 356. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.0%; *M*, 356).

15,15-*Dimethyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* **189**

1.5 mol dm^{-3} Diisobutylaluminium hydride (1.0 cm^3, 1.5 mmol) was added to a solution of the methyl ether **187** (97 mg, 0.31 mmol) in dry toluene (10 cm^3). The mixture was heated to refluxing temperature for 30 h. The flask was cooled to 0 °C, and saturated aqueous ammonium chloride was added. Standard work-up (ethyl acetate) gave 15,15-*dimethyl*-14β-*estra*-1,3,5(10)-*triene*-3,17α-*diol* **189** (92 mg, 98%), m.p. 101–104°C (from ethanol); $[\alpha]_D$ +195 (*c* 1.0 in tetrahydrofuran) (Found: C, 80.3; H, 9.4%; M^+, 300. $C_{20}H_{28}O_2$ requires C, 80.0; H, 9.4%; *M*, 300).

3-*Methoxy*-15β-*methyl*-14β-*estra*-1,3,5,(10)-*trien*-17-*one* **190**

Freshly cut lithium (37 mg, 5.29 mmol) was dissolved in freshly distilled liquid ammonia (10 cm^3). A solution of 3-methoxy-15-methyl-14β-estra-1,3,5(10),15-tetraen-17-one **184** (160 mg, 0.54 mmol) in dry tetrahydrofuran (15 cm^3) was added. The mixture was stirred for 10 min. Solid ammonium chloride was added, then the ammonia was allowed to evaporate and the residue suspended in water. The residue after work-up into ethyl acetate (145 mg) was chromatographed on silica gel (14 g), eluting with ethyl acetate-toluene (1:19), to obtain 3-*methoxy*-15β-*methyl*-14β-*estra*-1,3,5,(10)-*trien*-17-*one* **190** (126 mg, 78%), m.p. 107–110 °C (from chloroform-methanol); $[\alpha]_D$ +188 (*c* 1.0); $\Delta\varepsilon_{max}$ +1.90 (284 nm); ν_{max}/cm^{-1} 1725 (CO); δ_H (400 MHz) 1.11 (3H, s, 13β-Me), 1.19 (3H, d, *J* 6.3, 15β-Me), 1.65 (1H, dd, *J* 11.1 and 2.4, 14β-H), 1.85 (1H, dd, *J* 19.2 and 9.5, 16α-H), 2.39–2.51 (1H, m, 15α-H), 2.77 (1H, dd, *J* 19.2 and 8.4, 16β-H), 2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.6, 4-H), 6.73 (1H, dd, *J* 8.4 and 2.6, 2-H) and 7.20 (1H, d, *J* 8.4, 1-H); δ_C (100 MHz) 18.8 (q, C-18), 22.1 (q, 15β-Me), 27.9 (t, C-7), 28.0 (d, C-15), 29.6 (t, C-11), 29.9 (t, C-12), 31.5 (t, C-6), 37.1 (d, C-9), 38.9 (d, C-8), 45.8 (t, C-16), 50.6 (s, C-13), 55.2 (q, 3-OMe), 56.0 (d, C-14), 111.2 (d, C-2), 113.7 (d, C-4), 127.4 (d, C-1), 131.9 (s, C-10), 138.0 (s, C-5), 157.5 (s, C-3) and 221.3 (s, C-17) (Found: C, 80.2; H, 8.8%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298).

3-*Methoxy*-15,15-*dimethyl*-3'H,16ξH-*cyclopropa*[16,17]*estra*-1,3,5(10)-*trien*-17ξ-ol 17-*trimethylsilyloxy ether* **194**

(*a*) The 15-methyl Δ^{15}-17-ketone **158** (380 mg, 1.28 mmol) in dry tetrahydrofuran (10 cm^3) was treated with lithium dimethylcuprate – chlorotrimethylsilane [prepared

conventionally from copper(I) iodide (1.22 g, 6.41 mmol), ethereal 1.5 mol dm^{-3} methyllithium (8.5 cm^3, 12.8 mmol) and chlorotrimethylsilane (0.8 cm^3, 6.5 mmol)] at -78 °C for 15 min. Saturated aqueous ammonium chloride and aqueous ammonia were added and the mixture was extracted into ethyl acetate (x3). The organic phase was washed (saturated sodium hydrogen carbonate and brine), dried ($MgSO_4$) and concentrated under reduced pressure to give the 15,15-dimethyl Δ^{16}-trimethylsilyl ether **193** (476 mg, 97%). This was dissolved in dry benzene (15 cm^3), and treated with diethylzinc (0.3 cm^3, 2.93 mmol) in dry benzene (3 cm^3) and diiodomethane (0.5 cm^3, 6.21 mmol) at 20 °C for 72 h. Water was added and the reaction was extracted into ethyl acetate. Combined extracts were washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (520 mg) was flash chromatographed on silica gel (32 g, eluting in toluene) to give 3-*methoxy*-15,15-*dimethyl*-3′H,16ξH-*cyclopropa*[16,17]*estra*-1,3,5(10)-*trien*-17ξ-ol 17-*trimethylsilyloxy ether* **194** (163 mg, 32%) as an oil; $[\alpha]_D$ +52 (*c* 1.0); δ_H (200 MHz) 0.15 (9H, s, 17-OSiMe_3), 0.70 (1H, dd, *J* 9.3 and 6.3, 3′-H_{exo}), 0.85 (1H, dd, *J* 6.3 and 3.9, 3′-H_{endo}), 1.01 (3H, s, 13β-Me), 1.17 and 1.19 (each 3H, s, 15α- and 15β-Me), 1.24 (1H, dd, *J* 9.3 and 3.9, 16ξ-H), 2.84–2.91 (2H, m, 6α- and 6β-H), 3.79 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.20 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 1.5 (q, 3C, 17β-OSiMe_3), 14.8 (t, C-3′), 16.4 (q, C-18), 19.7 (q, 15-Me), 25.2 (q, 15-Me), 25.4 (t, C-11), 27.0 (t, C-7), 29.6 (t, C-6), 30.1 (d, C-16), 34.1 (s, C-15), 35.1 (d, C-8), 36.2 (t, C-12), 43.8 (s, C-13), 33.7 (d, C-9), 50.0 (d, C-14), 55.2 (q, 3-OMe), 70.0 (s, C-17), 111.2 (d, C-2), 113.8 (d, C-4), 125.6 (d, C-1), 133.3 (s, C-10), 137.9 (s, C-5) and 157.6 (s, C-3) (Found: C, 75.0; H, 9.7%; M^+, 398. $C_{25}H_{38}O_2Si$ requires C, 75.3; H, 9.6; *M*, 398). Further elution of the column with ethyl acetate-toluene (1:9) gave the 15,15-dimethyl 17-ketone (200 mg).

(*b*) The silyl enol ether **193** (200 mg, 0.52 mmol) in benzene (10 cm^3) was treated with diiodomethane and diethylzinc at refluxing temperature as described in (*a*) to give the cyclopropyl compound **194** (60 mg, 29%).

(*c*) A solution of the silyl enol ether **193** (203 mg, 0.53 mmol) in dry benzene (25 cm^3) was treated with diiodomethane and diethylzinc at 20 °C as detailed in (*a*) to give the cyclopropyl compound **194** (73 mg, 35%).

(*d*) The silyl enol ether **193** (240 mg, 0.63 mmol) was dissolved in dry pentane (10 cm^3) and treated with diiodomethane and diethylzinc at 20 °C as in (*a*) to give the cyclopropyl compound **194** (77 mg, 31%).

Attempted Ring Expansion on **194**

A solution of the trimethylsilyloxy cyclopropyl compound **194** (180 mg, 0.45 mmol) and pyridine (0.04 cm^3, 0.49 mmol) in dry dimethylformamide (5 cm^3) was added dropwise over 2 h to a solution of anhydrous iron(III) chloride (110 mg, 0.68 mmol) in

dimethylformamide (2 cm^3) at 0 °C. The mixture was warmed to 20 °C and stirred for 30 min, then poured into 1 mol dm^{-3} hydrochloric acid at 0 °C. Extractive work-up into ethyl acetate gave a residue (150 mg), which was dissolved in methanol (20 cm^3) and treated with sodium acetate trihydrate (91 mg, 0.67 mmol) at refluxing temperature for 18 h. The mixture was concentrated and suspended in water. Standard work-up into ethyl acetate gave 3-*methoxy*-15,15-*dimethyl*-3'H,16ξH-*cyclopropa*-[16,17]*estra*-1,3,5(10)-*trien*-17ξ-ol **195** (109 mg, 70%) as an oil; $[\alpha]_D$ +71 (*c* 0.7); δ_H (200 MHz) 0.73 (1H, dd, *J* 9.1 and 6.0, 3'-H_{exo}), 0.85 (1H, dd, *J* 6.0 and 3.7, 3'-H_{endo}), 1.01 (3H, s, 13β-Me), 1.16 and 1.21 (each 3H, s, 15α- and 15β-Me), 1.26 (1H, dd, *J* 9.1 and 3.7, 16ξ-H), 2.83–2.90 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7, 4-H), 6.70 (1H, dd, *J* 8.7 and 2.7, 2-H) and 7.20 (1H, d, *J* 8.7, 1-H) (Found: C, 80.5; H, 9.4%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326).

3-*Methoxy*-15,15-*dimethyl*-17a-*homoestra*-1,3,5(10),17-*tetraen*-16-*one* **197**

A solution of 3-methoxy-17a-homoestra-1,3,5(10),17-tetraen-17a-one **145**[105] (500 mg, 1.69 mmol) in dry tetrahydrofuran (20 cm^3) was added to a suspension of potassium *t*-butoxide [freshly prepared from potassium (650 mg) and *t*-butyl alcohol (10 cm^3)] in dry tetrahydrofuran (10 cm^3) at 0 °C. After 5 min, freshly distilled iodomethane (1.1 cm^3, 17.7 mmol) was added and the reaction was stirred at 20 °C for 30 min. Saturated aqueous ammonium chloride was added at 0 °C, and the product was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated to give 3-*methoxy*-15,15-*dimethyl*-17a-*homoestra*-1,3,5(10),17-*tetraen*-16-*one* **197** as an oil (420 mg, 80%); ν_{max}/cm^{-1} 1665 (CO), δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 1.31 and 1.33 (each 3H, s, 15α- and 15β-Me), 2.85–2.88 (2H, m, 6α- and 6β-H), 3.76 (3H, s, 3-OMe), 5.94 (1H, d, *J* 9.8, 17-H), 6.63 (1H, d, *J* 2.7, 4-H), 6.72 obsc. (1H, dd, *J* 8.1 and 2.7, 2-H), 6.75 (1H, d, *J* 9.8, 17a-H) and 7.23 (1H, d, *J* 8.1, 1-H); δ_C (50 MHz) 20.1 (q, C-18), 22.0 (q, 15-Me), 26.9 (t, C-7), 29.5 (t, C-11), 30.5 (t, C-6), 31.7 (q, 15-Me), 36.5 (s, C-15), 39.2 (d, C-8), 40.3 (t, C-12), 44.5 (d, C-9), 46.0 (s, C-13), 53.5 (d, C-14), 55.2 (q, 3-OMe), 111.9 (d, C-2), 113.2 (d, C-4), 125.5 (d, C-17), 126.8 (d, C-1), 132.2 (s, C-10), 137.3 (s, C-5), 157.6 (s, C-3), 160.6 (d, C-17a) and 205.9 (s, C-16) (Found: C, 81.0; H, 8.8; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7; *M*, 324).

17α,17aα-*Epoxy*-3-*methoxy*-15,15-*dimethyl*-17a-*homoestra*-1,3,5(10),17-*tetraen*-16-*one* **198**

A solution of the 15,15-dimethyl Δ^{17}-16-ketone **197** (490 mg, 1.51 mmol) in methanol (50 mmol) was treated with 4 mol dm^{-3} aqueous sodium hydroxide (1.54 cm^3) and

30% aqueous hydrogen peroxide (0.6 cm^3) at 0 °C for 15 min. Saturated aqueous sodium metabisulfate was added and the product was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (493 mg) was chromatographed on silica gel (49 mg) with ethyl acetate-toluene (1:49) as eluent to give 17α,17aα-*epoxy*-3-*methoxy*-15,15-*dimethyl*-17a-*homoestra*-1,3,5(10),17-*tetraen*-16-*one* **198** (459 mg, 90%), m.p. 113–115 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ -48 (*c* 1.0); ν_{max}/cm^{-1} 1697 (CO); δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 1.20 and 1.30 (each 3H, s, 15α- and 15β-Me), 2.06 (1H, d, *J* 11.0, 14α-H), 2.84–2.91 (2H, m, 6α- and 6β-H), 3.26 (1H, d, *J* 4.7, 17β-H), 3.50 (1H, d, *J* 4.7, 17aβ-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.6, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.6, 2-H) and 7.23 (1H, d, *J* 8.8, 1-H); δ_C (50 MHz) 17.2 (q, C-18), 18.9 (q, 15-Me), 25.7 (t, C-7), 29.4 (q, 15-Me), 29.9 (t, C-11), 30.1 (t, C-6), 35.8 (s, C-15), 38.2 (t, C-12), 38.3 (d, C-8), 43.9 (d, C-9), 46.3 (s, C-13), 47.7 (d, C-14), 55.2 (q, 3-OMe), 56.2 (d, C-17a), 65.9 (d, C-17), 111.7 (d, C-2), 113.3 (d, C-4), 126.4 (d, C-1), 132.3 (s, C-10), 137.4 (s, C-5), 157.6 (s, C-3) and 212.3 (s, C-16) (Found: C, 77.7; H, 8.3%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340).

Attempted Wharton rearrangement of the epoxy ketone **198**

(*a*) A solution of the epoxy ketone **198** (50 mg, 0.15 mmol) in ethanol (5 cm^3) was treated with hydrazine hydrate (0.1 cm^3, 2.06 mmol) at refluxing temperature for 24 h.

(*b*) A neat solution of the epoxy ketone **198** (100 mg, 0.29 mmol) in hydrazine hydrate (5 cm^3) was heated to reflux for 24 h. Starting material was recovered.

3-*Methoxy*-16-*methyl*-17a-*homoestra*-1,3,5(10),16-*tetraen*-17a-*one* **201**

(*a*) Lithium dimethylcuprate [prepared from copper(I) iodide (356 mg, 1.87 mmol) and ethereal 1.5 mol dm^{-3} methyllithium (2.5 cm^3, 3.75 mmol)] in dry diethyl ether (2 cm^3) was cooled to -78 °C. Triethylamine (0.2 cm^3, 1.44 mmol), chlorotrimethylsilane (0.2 cm^3, 1.58 mmol) and a solution of the 3-methoxy-17α-homoestra-1,3,5(10),16-tetraen-17α-one **143**[103] (277 mg, 0.93 mmol) in dry tetrahydrofuran (10 cm^3) were added sequentially. Stirring at -78 °C was maintained for 10 min, then saturated aqueous ammonium chloride and aqueous ammonia were added. The mixture was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and evaporated to give 3-*methoxy*-16α-*methyl*-17a-*homoestra*-1,3,5(10),17-*tetraen*-17a-*yl trimethylsilyl ether* **200** (328 mg, 92%), m.p. 112–114 °C (from chloroform-methanol); $[\alpha]_D$ +152 (*c* 1.0); δ_H (200 MHz) 0.20 (9H, s, 17a-OSi*Me*$_3$), 0.97 (3H, s, 13β-Me), 1.00 (3H, d, *J* 7.0, 16α-Me), 2.83–2.89 (2H, m, 6α- and 6β-H), 3.78 (3H, s, 3-OMe), 4.58 (1H, d, *J* 4.6, 17-H), 6.64 (1H,

d, *J* 2.8, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.8, 2-H) and 7.23 (1H, d, *J* 8.8, 1-H) (Found: C, 75.2; H, 9.4%; M^+, 384. $C_{24}H_{36}O_2Si$ requires C, 74.9; H, 9.4%; *M*, 384).

A refluxing solution of the enol silyl ether **200** (250 mg, 0.65 mmol) in dry acetonitrile (10 cm^3) was treated with palladium(II) acetate (310 mg, 1.38 mmol). After 18 h, the mixture was cooled, filtered and concentrated to give a dark oil (282 mg). Chromatography of this residue on silica gel (28 g) with ethyl acetate-toluene (1:19) as eluent gave the 16α-methyl 17a-ketone **199** (142 mg, 70%), m.p. 92–94 °C (from chloroform-diisopropyl ether); $[\alpha]_D$ -8 (*c* 0.8) (lit.,[103] m.p. 96 °C; $[\alpha]_D$ -8), followed by 3-*methoxy*-16-*methyl*-17a-*homoestra*-1,3,5(10),16-*tetraen*-17a-*one* **201** (42 mg, 21%), m.p. 135-138 °C (from chloroform-methanol); $[\alpha]_D$ -14 (*c* 1.0); ν_{max}/cm^{-1} 1658 (CO); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 1.28–1.35 (2H, m, 7α-H and 11β-H), 1.50 (1H, qd, *J* 3 x 11.2 and 2.8, 8β-H), 1.75 (1H, td, *J* 2 x 11.2 and 4.6, 14α-H), 1.95 (3H, d, *J* 2.0, 16-Me), 2.02–2.05 (1H, m, 7β-H), 2.06–2.09 (1H, m, 15α-H), 2.13 (1H, dt, *J* 13.4 and 2 x 3.5, 12β-H), 2.26 (1H, td, *J* 2 x 11.2 and 4.2, 9α-H), 2.41 (1H, td, *J* 2 x 11.2 and 3.0, 15β-H), 2.86–2.89 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 5.80 (1H, quint, *J* 4 x 2.0, 17-H), 6.62 (1H, d, *J* 2.8, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.6, 1-H); δ_C (50 MHz) 15.8 (q, C-18), 24.1 (q, 16-Me), 25.9 (2C, t, C-7 and C-11), 27.2 (t, C-15), 30.0 (t, C-6), 32.2 (t, C-12), 39.2 (d, C-8), 42.7 (d, C-9), 43.4 (s, C-13), 45.3 (d, C-14), 55.2 (q, 3-OMe), 111.7 (d, C-2), 113.6 (d, C-4), 124.6 (d, C-17), 126.4 (d, C-1), 132.2 (s, C-10), 137.5 (s, C-5), 157.6 (s, C-3), 158.9 (s, C-16) and 205.4 (s, C-17a) (Found: C, 81.0; H, 8.4%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310).

(*b*) A solution of the 16α-methyl 17a-ketone **199** (315 mg, 1.01 mmol) in dry toluene (20 cm^3) was treated with benzeneselenenic anhydride (70%; 519 mg, 1.01 mmol) at 80 °C for 4 h. The mixture was cooled to 20 °C, poured into aq sodium hydrogen carbonate, extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (412 mg) was chromatographed on silica gel (40 g) with toluene → ethyl acetate-toluene (1:19) to give the 16-methyl Δ^{16}-17a-ketone **201** (189 mg, 60%).

3-*Methoxy*-16α-*methyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* **199**

The Δ^{16}-17a-ketone **201** (318 mg, 1.07 mmol) in dry tetrahydrofuran (25 cm^3) was added to a solution of lithium dimethylcuprate [prepared at 0°C from copper(I) iodide (510 mg, 2.68 mmol) and ethereal 1.5 mol dm^{-3} methyllithium (3.6 cm^3, 5.4 mmol)] in dry diethyl ether at 0°C. After 15 min, saturated aqueous ammonium chloride was added. The mixture was filtered and the filtrate was extracted into ethyl acetate (x3), washed (water and brine), dried ($MgSO_4$) and evaporated. The residue (320 mg) was chromatographed on silica gel (16 g), eluting in ethyl acetate-toluene (1:19) to give 3-methoxy-16α-methyl-17a-homoestra-1,3,5(10)-trien-17a-one **199** (280 mg, 84%), m.p. 92–94 °C (from chloroform-

diisopropyl ether); $[\alpha]_D$ -8 (*c* 0.8) (lit.,[103] m.p. 96 °C; $[\alpha]_D$ -8); $\Delta\varepsilon_{max}$ -0.22 (292 nm); ν_{max}/cm^{-1} 1723 (CO); δ_H (400 MHz) 0.99 (3H, d, *J* 7.1, 16α-Me), 1.10 (3H, s, 13β-Me), 1.21–1.31 (1H, m, 7α-H), 1.89 (1H, dt, *J* 13.8 and 2 x 3.4, 12β-H), 2.05 (1H, ddd, *J* 14.3, 4.4 and 1.1, 17α-H), 2.24 (1H, td, *J* 2 x 10.9 and 3.9, 9α-H), 2.36 (1H, dq, *J* 13.8 and 3 x 4.1, 11α-H), 2.78 (1H, dd, *J* 14.3 and 6.2, 17β-H), 2.83–2.87 (1H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7, 2-H) and 7.21 (1H, *J* 8.5, 1-H); δ_C (50 MHz) 16.6 (C-18), 20.8 (16-Me), 25.9 (C-11), 26.6 (C-7), 28.9 (C-15), 29.7 (C-16), 30.1 (C-6), 32.5 (C-12), 38.9 (C-8), 43.0 (C-9), 43.8 (C-14), 44.0 (C-17), 47.8 (C-13), 55.2 (3-OMe), 111.6 (C-2), 113.4 (C-4), 126.3 (C-1), 132.5 (C-10), 137.6 (C-5), 157.5 (C-3) and 216.7 (C-17a) (Found: C, 80.5; H, 9.0%; M$^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0; *M*, 312).

3-*Methoxy*-16β-*methyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* **206**

The 16-methyl Δ^{16}-17a-ketone **201** (50 mg, 0.16 mmol) in dry tetrahydrofuran (10 cm^3) was added to a solution of lithium (14 mg) in freshly distilled liquid ammonia (20 cm^3). After 15 min, solid ammonium chloride was added to discharge the blue colour. The ammonia was allowed to evaporate, the residue was suspended in water and the product was extracted into ethyl acetate (x3). The combined organic phase was washed (water and brine), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (41 mg) on silica gel (4g) with ethyl acetate-toluene (1:49) as eluent gave 3-*methoxy*-16β-*methyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* **206** (40 mg, 80%), m.p. 131–134 °C (from chloroform-methanol); $[\alpha]_D$ -10 (*c* 1.0); $\Delta\varepsilon_{max}$ -1.02 (291 nm); ν_{max}/cm^{-1} 1723 (CO); δ_H (400 MHz) 1.06 (3H, d, *J* 8.5, 16β-Me), 1.09 (3H, s, 13β-Me), 1.21–1.31 (1H, m, 7α-H), 1.69 (1H, td, *J* 2 x 13.2 and 3.9, 12α-H), 1.75–1.83 (1H, m, 16α-H), 1.87 (1H, dt, *J* 13.2 and 2 x 3.6, 12β-H), 2.07–2.13 (1H, m, 7β-H), 2.23 (1H, ddd, *J* 13.8, 4.7 and 1.8, 17α-H), 2.37 (1H, t, *J* 2 x 13.8, 17β-H), 2.84–2.87 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.5, 1-H); δ_C (50 MHz) 16.9 (q, C-18), 22.6 (q, 16β-Me), 25.9 (t, C-11), 26.6 (t, C-7), 30.1 (t, C-6), 31.9 (t, C-15), 32.4 (t, C-12), 33.8 (d, C-16), 38.7 (d, C-8), 43.1 (d, C-9), 45.5 (t, C-17), 47.3 (s, C-13), 49.3 (d, C-14), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.4 (d, C-4), 126.4 (d, C-1), 132.5 (s, C-10), 137.6 (s, C-5), 157.5 (s, C-3) and 215.9 (s, C-17a) (Found: C, 80.5; H, 9.1%; M$^+$, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312).

3-*Methoxy*-16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* **207**

A solution of the 16-methyl Δ^{16}-17a-ketone **201** (143 mg, 0.46 mmol) in dry tetrahydrofuran was treated with lithium dimethylcuprate [prepared from copper(I) iodide

(263 mg, 1.38 mmol) and ethereal 1.5 mol dm^{-3} methyllithium (1.8 cm^3, 2.70 mmol)], triethylamine (0.2 cm^3, 1.44 mmol) and chlorotrimethylsilane (0.2 cm^3, 1.58 mmol) at -78 °C for 20 min. Saturated aqueous ammonium chloride and 1 mol dm^{-3} HCl were added. After complete hydrolysis of the silyloxy group (TLC), the mixture was extracted into ethyl acetate (x3), washed (aq sodium hydrogen carbonate and brine), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (150 mg) on silica gel (15 g) with ethyl acetate-toluene (1:49) as eluent gave 3-*methoxy*-16,16-*dimethyl*-17a-*homoestra*-1,3,5(10),16-*trien*-17a-*one* **207** (127 mg, 85%), m.p. 146–149 °C (from chloroform-methanol); $[\alpha]_D$ -12 (*c* 1.0); $\Delta\varepsilon_{max}$ -0.90 (290 nm); ν_{max}/cm^{-1} 1724 (CO); δ_H (400 MHz) 0.90 (3H, s, 16α-Me), 1.08 (3H, s, 16β-Me), 1.09 (3H, s, 13β-Me), 1.21–1.32 (1H, m, 7α-H), 1.39–1.46 (1H, m, 11β-H), 1.70 (1H, td, *J* 2 x 13.9 and 4.1, 12α-H), 1.83 (1H, dt, *J* 13.9 and 2 x 4.1, 12β-H), 1.93 (1H, dd, *J* 13.6 and 1.9, 17α-H), 2.04–2.10 (1H, m, 7β-H), 2.24 (1H, td, *J* 2 x 10.3 and 4.1, 9α-H), 2.37 (1H, dq, *J* 13.5 and 3 x 4.1, 11α-H), 2.60 (1H, d, *J* 13.6, 17β-H), 2.83–2.87 (2H, m, 6α- and 6β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8, 2-H) and 7.21 (1H, d, *J* 8.6, 1-H); δ_C (100 MHz) 16.6 (q, C-18), 25.9 (t, C-11), 26.7 (t, C-7), 26.9 (q, 16-Me), 30.0 (t, C-6), 32.1 (t, C-12), 32.6 (q, 16-Me), 35.1 (s, C-16), 37.0 (t, C-15), 38.5 (d, C-8), 43.1 (d, C-9), 45.6 (d, C-14), 47.4 (s, C-13), 50.2 (t, C-17), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.6 (d, C-4), 126.3 (d, C-1), 132.5 (s, C-10), 137.6 (s, C-5), 157.5 (s, C-3) and 216.1 (s, C-17a) (Found: C, 80.5; H, 9.2; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3; *M*, 326).

Hydride Reduction of 3-*Methoxy*-16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*trien*-17a-*one* **207**

(*a*) The 16,16-dimethyl 17a-ketone **207** (86 mg, 0.26 mmol) in dry tetrahydrofuran (10 cm^3) was treated with lithium aluminium hydride (50 mg, 1.31 mmol) at 0 °C for 5 min. Saturated sodium hydrogen carbonate was added and the precipitate was filtered. Standard work-up of the filtrate into ethyl acetate (x3), followed by chromatography of the residue (84 mg) on silica gel (10 g) with ethyl acetate-toluene (1:19) gave 3-*methoxy*-16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*trien*-17aα-*ol* **208** (58 mg, 68%) as an oil; $[\alpha]_D$ -4 (*c* 1.0); ν_{max}/cm^{-1} 3641 (OH); δ_H (400 MHz) 0.81 and 0.93 (each 3H, s, 16α- and 16β-Me), 1.12 (3H, s, 13β-Me), 1.25 (1H, m, 7-H), 1.35 (1H, dt, *J* 12.8 and 2 x 3.1, 12β-H), 1.52 (1H, dd, *J* 15.0 and 3.1, 17α-H), 1.73 (1H, dd, *J* 15.0 and 3.1, 17β-H), 1.94 (1H, td, *J* 2 x 12.8 and 3.2, 9α-H), 2.82–2.83 (2H, m, 6α- and 6β-H), 3.48 (1H, t, *J* 3.1, 17aβ-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 17.1 (q, C-18), 26.1 (t, C-11), 26.4 (t, C-7), 29.6 (q, 16-Me), 30.2 (t, C-6), 30.5 (s, C-16), 34.2 (2C, q and t, 16-Me and C-12), 37.7 (t, C-15), 37.8 (d, C-8), 39.3 (d, C-14), 41.0 (t, C-17), 43.3 (d, C-9), 47.6 (s, C-13), 55.2 (q, 3-OMe), 76.9 (d, C-17a),

111.5 (d, C-2), 113.4 (d, C-4), 126.2 (d, C-1), 133.3 (s, C-10), 138.1 (s, C-5) and 157.4 (s, C-3) (Found: C, 80.0; H, 9.9%; M+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328). Further elution of the column gave 3-*methoxy*-16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*trien*-17aβ-*ol* **209** as an oil (12 mg, 14%), $[\alpha]_D$ -9 (*c* 1.0); ν_{max}/cm^{-1} 3643 (OH); δ_H (200 MHz) 0.78 (3H, s, 13β-Me), 0.96 and 0.97 (each 3H, s, 16α- and 16β-Me), 1.42 (1H, t, *J* 11.2, 17β-H), 2.26 (1H, dd, *J* 11.2 and 5.2, 17α-H), 2.81–2.83 (2H, m, 6α- and 6β-H), 3.45 (1H, dd, *J* 11.2 and 5.2, 17aα-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.8, 2-H) and 7.22 (1H, d, *J* 8.7, 1-H); δ_C (50 MHz) 17.4 (C-18), 25.4 (C-11), 26.8 (C-7), 29.6 (16-Me), 30.3 (C-6), 30.8 (C-16), 34.7 (C-12), 37.2 (16-Me), 37.4 (C-8), 37.9 (C-15), 40.2 (C-14), 42.3 (C-17), 43.2 (C-9), 49.2 (C-13), 55.2 (3-OMe), 79.5 (C-17a), 111.7 (C-2), 113.4 (C-4), 126.4 (C-1), 133.3 (C-10), 138.2 (C-5) and 157.6 (C-3) (Found: C, 80.1; H, 10.0%; M+, 328. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%; *M*, 328).

(*b*) A solution of the 16,16-dimethyl 17a-ketone **207** (100 mg, 0.31 mmol) in dry tetrahydrofuran (10 cm^3) was treated with lithium (22 mg) in freshly distilled liquid ammonia (20 cm^3). Saturated ammonium chloride was added after 5 min, and the ammonia was allowed to evaporate. The residue was suspended in water and the standard work-up into ethyl acetate followed by chromatography of the crude material (98 mg) on silica gel [10 g, eluting in ethyl acetate-toluene (1:19)] gave the 16,16-dimethyl 17aα-alcohol **208** (11 mg, 11%), followed by the 17aβ-alcohol **209** (79mg, 78%).

16,16-*Dimethyl*-17a-*homoestra*-1,3,5(10)-*triene*-3,17aα-*diol* **210**

A solution of the 3-methyl ether **208** (89 mg, 0.24 mmol) in toluene (10 cm^3) was treated with diisobutylaluminium hydride (1.5 mol dm^{-3} in toluene; 1.5 cm^3) at refluxing temperature for 48 h. The mixture was cooled to 0 °C, saturated aqueous ammonium chloride and 1 mol dm^{-3} hydrochloric acid were added, and the product was extracted into ethyl acetate (x3). Combined organic phase was washed (water and brine), dried ($MgSO_4$) and evaporated to give 16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*triene*-3,17aα-*diol* **210**, amorph. (70 mg, 93%), $[\alpha]_D$ +25 (*c* 1.2 in tetrahydrofuran) (Found C, 80.4; H, 9.7%; M+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

16,16-*Dimethyl*-17a-*homoestra*-1,3,5(10)-*triene*-3,17aβ-*diol* **211**

Similar treatment of the 3-methyl ether **209** (58 mg, 0.18 mmol) gave 16,16-*dimethyl*-17a-*homoestra*-1,3,5(10)-*triene*-3,17aβ-*diol* **211**, amorph. (51 mg, 91%), $[\alpha]_D$ +34 (*c* 1.0 in tetrahydrofuran) (Found C, 80.6; H, 9.5%; M+, 314. $C_{21}H_{30}O_2$ requires C, 80.2; H, 9.6%; *M*, 314).

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