STUDIES IN RING D FRAGMENTATION OF ESTRONE

BY

PETER CHRISTOPHER RAY

STUDIES IN RING D FRAGMENTATION OF ESTRONE

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CHEMISTRY

by

PETER CHRISTOPHER RAY

Supervisor: Professor J.R. Bull

Department of Chemistry
University of Cape Town

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SUMMARY

Studies have been conducted in synthesising 14-allyl 19-norsteroids. The eventual aim is to convert the 14-allyl derivatives into bridge-functionalised 19-norsteroids. Two approaches were investigated, with the immediate aim of generating fragmentation intermediates suitable for 14-allylation. The approaches were based on cleavage of the 16,17-bond *via* oxidative cleavage or fragmentation methodology.

The oxidative cleavage routes involved the preparation of 3-methoxy-17-methylestra-1,3,5(10),16-tetraen-15-one, which was shown not to undergo regioselective 14-methylation. In an alternative approach 3-methoxy-17α-methylestra-1,3,5(10),14-tetraene-16β,17β-diol was synthesised. However, the lability of the primary cleaved product prompted synthesis of 3-methoxy-16,17-seco-17a-homoestra-1,3,5(10)-triene-16,17a-dione. Chemodifferentiation of the carbonyl groups of the seco derivative provided access to 16-acetoxy-3-methoxy-16,17-seco-17a-homoestra-1,3,5(10)-trien-17a-one, in an overall yield of 60 % from estrone 3-methyl ether.

The fragmentation approaches involved conjugate stannylation and silylation of 3-methoxyestra-1,3,5,(10),15-tetraen-17-one to give the 15β-trimethylstannyl and 15β-trimethylsilyl 17-ketones respectively. The stannyl ketone was converted to the 3-methoxy-17α-methyl-15β-trimethylstannylestra-1,3,5,(10)-trien-17β-ol. Generation of the derived alkoxy radical resulted in formation of 3-methoxy-16,17-seco-17a-homoestra-1,3,5(10),15-tetraen-17a-one, in low yield. The silyl ketone was converted to the 17-acetoxyimino-3-methoxy-15β-trimethylsilylestra-1,3,5(10)-trien. Fragmentation with the borontrifluoride diethyl ether complex resulted in formation of the undesired 3-methoxy-13,17-secoestra-1,3,5(10),14-tetraen-17-nitrile. Since the 15β-trimethylsilyl group did not direct the fragmentation, the 17-acetoxyimino-3-methoxy-16β-trimethylsilylmethylestra-1,3,5(10)-triene was synthesised in the hope that it would be more amenable to silicon directed fragmentation. However, fragmentation with the boron trifluoride diethyl ether complex resulted in formation of the undesired 17-acetoxy-3-methoxy-16β-trimethylsilylmethyl-17a-aza-17a-homoestra-1,3,5(10),17-tetraene.

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1. INTRODUCTION

Current knowledge of the synthesis and action of the female sex hormones has permitted rational therapeutic intervention in certain diseases. Most impressive is the chemical use of agents that can mimic or antagonize the effects of these hormones, and that are used as contraceptives or for the treatment of certain neoplasms. The most potent naturally occurring estrogens in humans are 17β-estradiol, followed by estrone and estriol (Figure 1.1).[1]

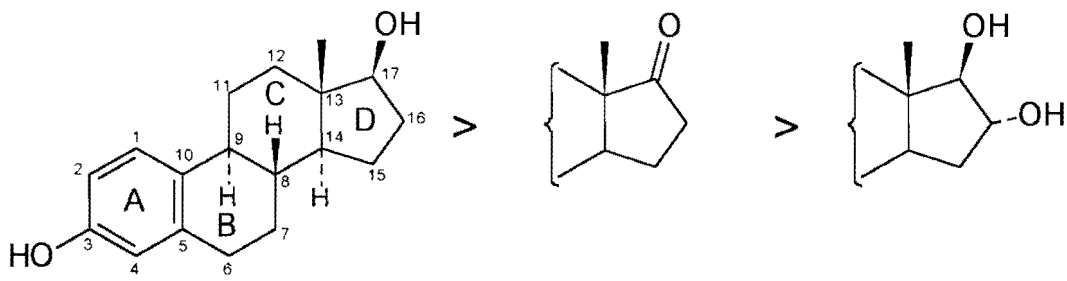


Figure 1.1: Binding affinity order of naturally occurring estrogens.

The phenolic A ring is the principle structural feature accountable for the selective, high-affinity binding to estrogen receptors.[2,3] Most alkyl substituents on the phenolic A ring impair binding, however, substitution on certain positions of ring B, C or D may be tolerated.[1,6] The quest for highly potent estradiol analogues which exhibit a minimum of side effects, has prompted a great deal of work to make synthetic estradiols which have a greater activity and resilience to metabolic degradation. One of the first examples of a synthetic estradiol with enhanced oral activity was the 17α-ethynyl estradiol (Figure 1.2).[4]

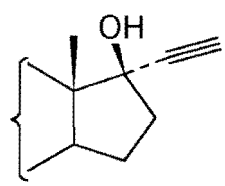


Figure 1.2: 17α-Ethynyl estradiol

The enhanced oral activity is largely as a result of protection from inactivation by the liver. Nonsteroidal compounds with estrogenic activity occur naturally in a variety of plants (eg flavone, isoflavone, and coumestan derivatives). Most of these compounds contain a phenolic A ring that mimics the A ring of estrogenic steroids. Synthesis of the nonsteroidal estrogen diethylstilbestrol (Figure 1.3) was viewed as a milestone, since it could be administered orally, and had a potency comparable to estradiol. Thus, in a time when natural product synthesis was not feasible, diethylstilbestrol provided a cheap, plentiful, orally active estrogen for endocrine therapy.[1]

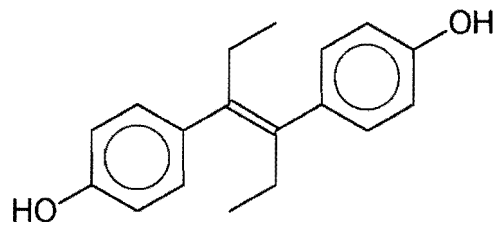


Figure 1.3: Diethylstilbestrol

Rational drug design in the 1990's is based on the three dimensional structure of the active protein sites. The design of molecules with an appropriate fit to the three dimensional structure is thus the target. In the steroid field, however, this is not feasible since pure, stable, crystalline steroids receptor proteins have not been obtained for X-ray analysis.[5] The findings that minor chemical alterations of the natural hormone alter the stability of the receptor-hormone complex,[2,6] have stimulated a broad investigation into structure-activity relationships in steroidal hormones. The chemical alterations suggest that the modulating groups influence the ability of the functional groups (3 and 17β-hydroxy groups) to interact with the receptor, by creating a favourable or unfavourable environment.[7]

In the steroid research group at University of Cape Town, the binding affinity of 14,17-bridged estradiol analogues[8,9,10,11] (Figure 1.4) has prompted further investigation into the structure activity relationships of further bridged analogues.

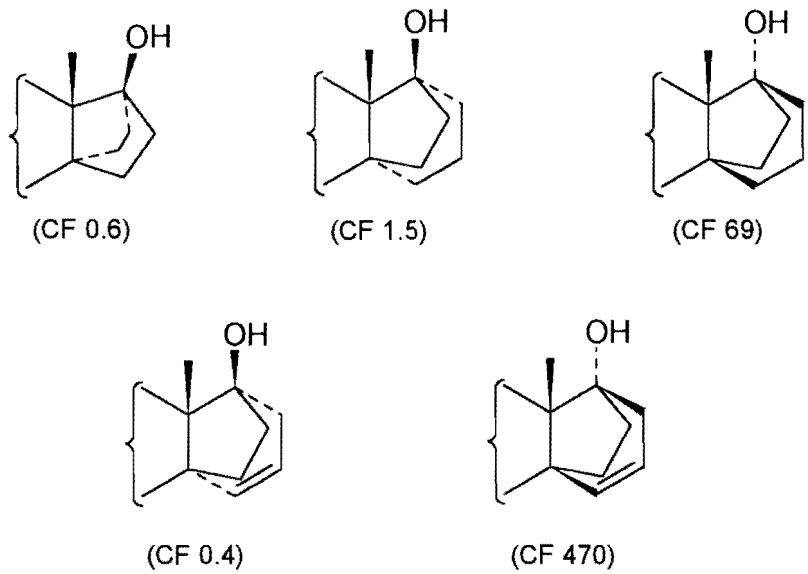
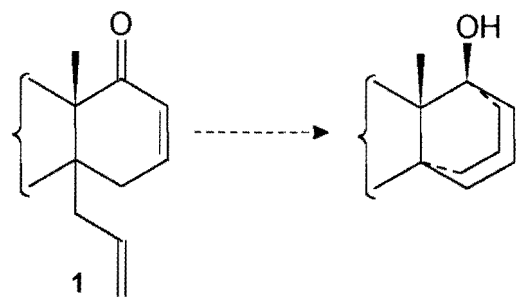


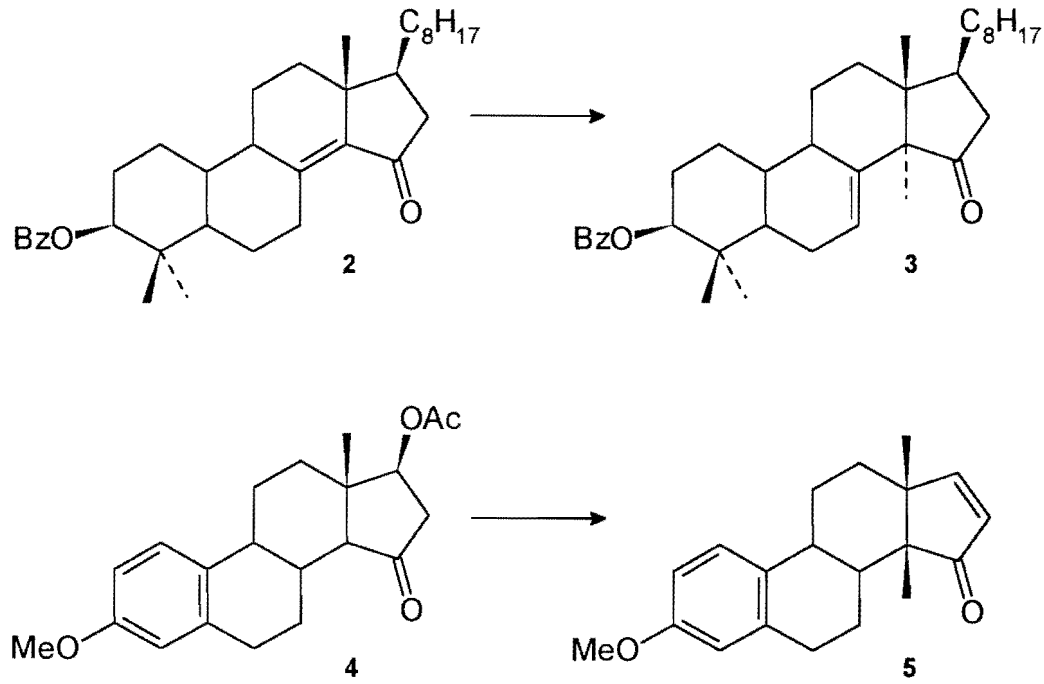
Figure 1.4: 14,17-Bridged estradiol analogues (CF<1 indicates a binding affinity greater than estradiol.[21])

The aforementioned analogues have been analysed by molecular modelling, and this has given clear evidence of the structure-activity trends.[12] In this study the efficient synthesis of ring D homologated 14-allyl 19-norsteroids **1** is attempted, with the aim of generating the derived bridged estradiol analogues (as illustrated below) for completion of the binding affinity studies of this series of compounds.



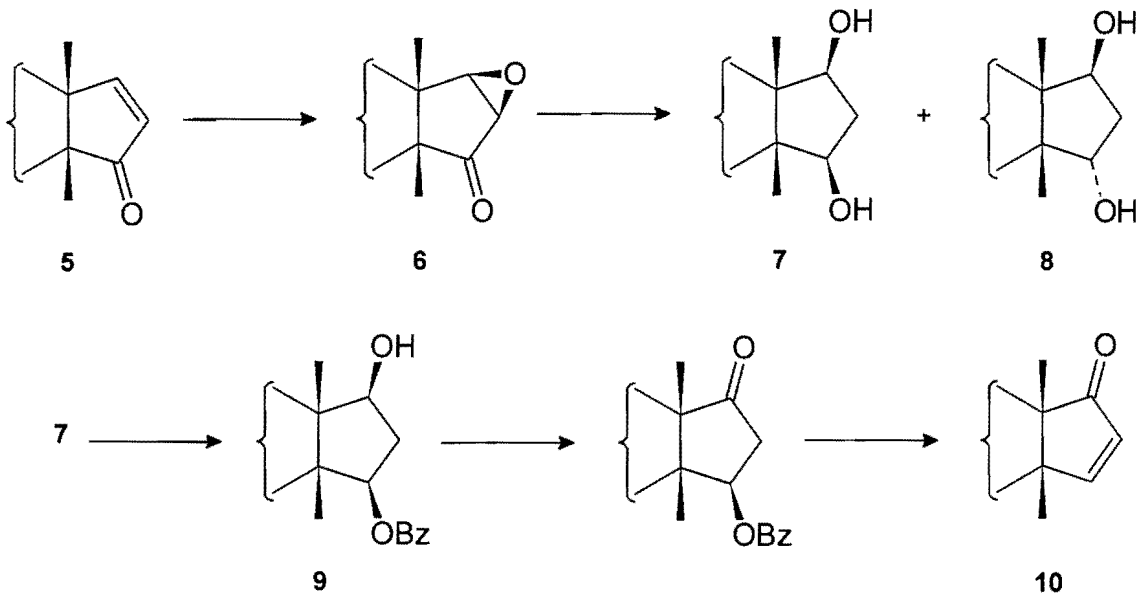
Numerous pathways to 14α-alkyl steroids have been described, based upon degradation of natural products.[13] An example is the biosynthetic relation between cholesterol and lanosterol, which was established by base-mediated alkylation of cholest-8(14)-en-15-one **2** to afford the 14α-methyl cholest-7-en-15-one **3** (Scheme 1.1).[14] This method of

14-methylation was adopted for the 17β-acetoxy 15-ketone **4**, to give the derived 14β-methyl compound **5**.[15,16] In a program directed toward the synthesis of 14-alkyl 19-norsteroids, it was found that the stereoselectivity of ring junction alkylation of steroidal 15-ketones was strongly influenced by the surrounding structural features.[17]



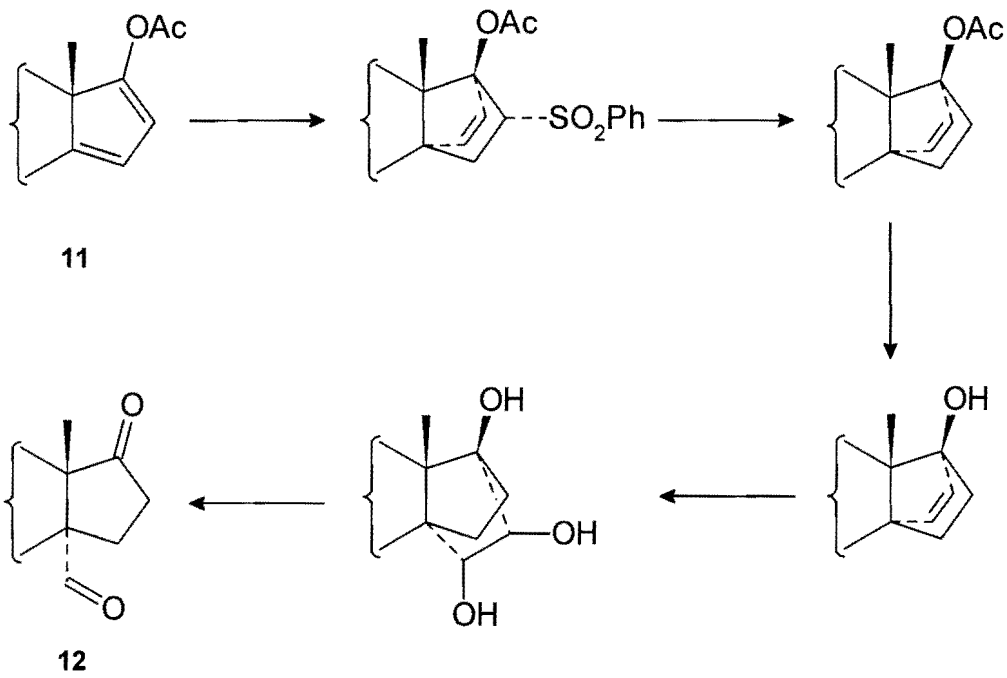
Scheme 1.1

Subsequent restoration of the appropriate ring D functionality of steroidal 15-ketones is however cumbersome, and entails transposition methodology. This is exemplified by the re-introduction of oxygen functionality at C-17 of the Δ^{16} 15-ketone **5** by the sequence illustrated in Scheme 1.2.[18] Stereoselective epoxidation gave exclusively the 16β,17β-epoxide **6**, lithium aluminium hydride treatment of which gave an epimeric mixture of the 15β,17β- **7** and 15α,17β- **8** diols (8.5:1). Benzoylation of the 15β,17β-diol **7** gave a complex mixture, containing mainly the 15β-benzoyloxy 17β-alcohol **9**. Oxidation of the 17β-hydroxy group, followed by β-elimination gave the 3-methoxy-14β-methylestra-1,3,5(10),15-tetraen-17-one **10**.



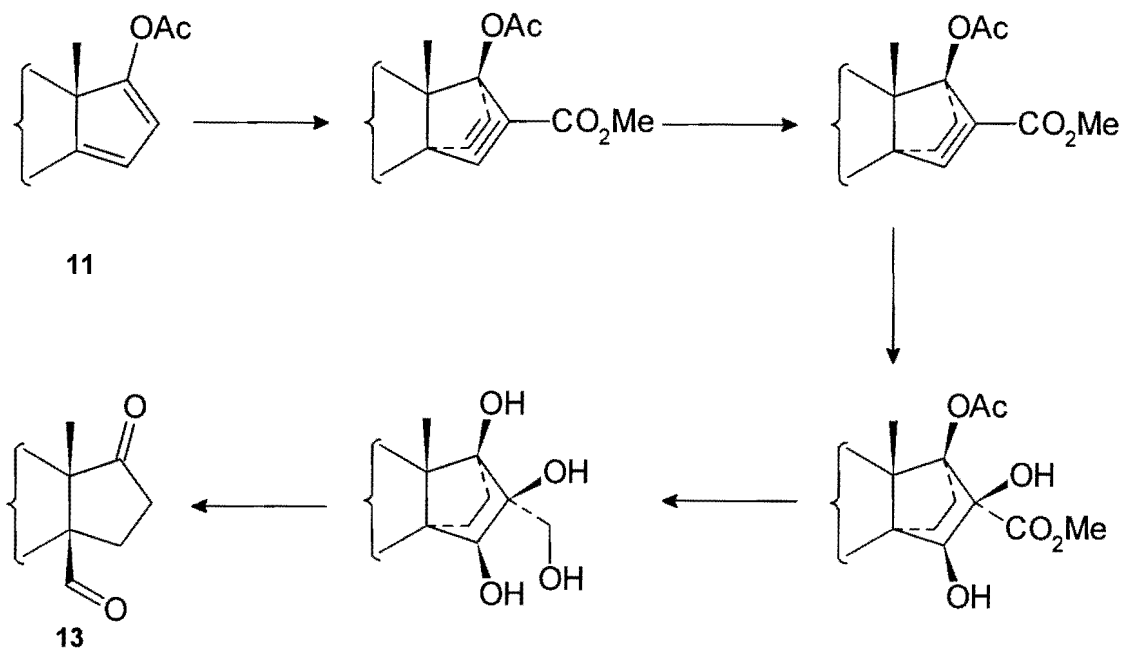
Scheme 1.2

In an effort to develop a more versatile synthetic approach to 14-alkyl-19-norsteroids, Bull *et al* made use of Diels-Alder methodology to ensure the desired stereoselectivity at C-14. Thus, 14α-formyl estrone **12** was prepared by cycloaddition of phenyl vinyl sulfone to 3-methoxyestra-1,3,5(10),14,16-pentaen-17yl acetate **11**, followed by desulphonylation, deacetylation, *cis*-hydroxylation and oxidative cleavage (Scheme 1.3).[8]



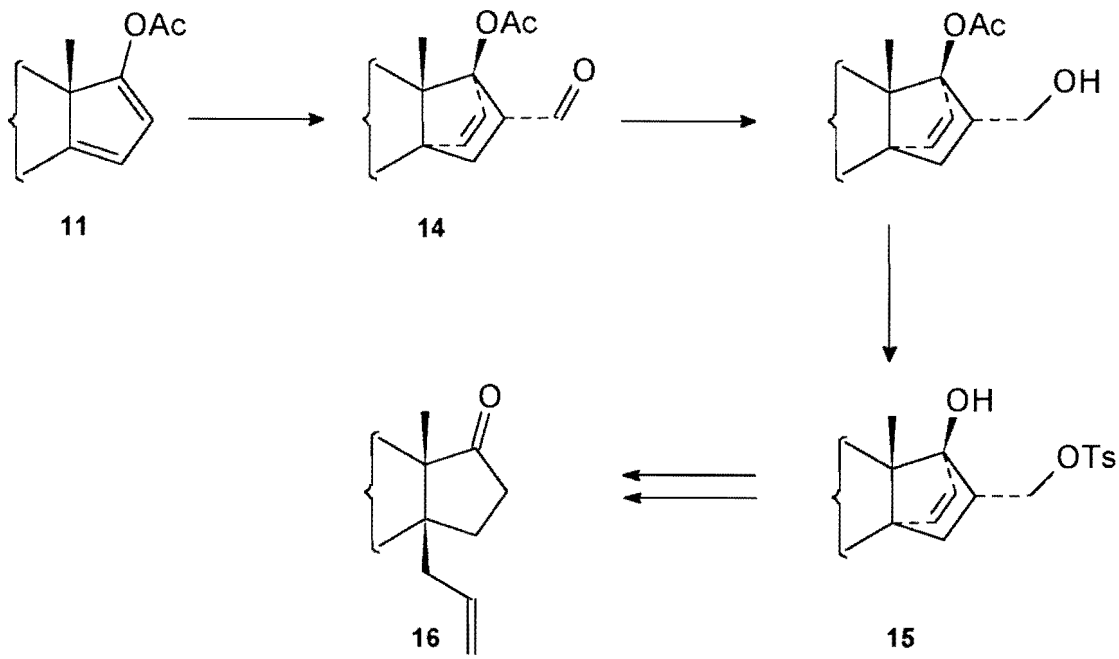
Scheme 1.3

Stereoselective synthesis of the 14β-formyl estrone **13** was accomplished by cycloaddition of methyl propiolate to dienyl acetate **11**, followed by chemoselective hydrogenation, *cis*-hydroxylation, reduction, and oxidative cleavage (Scheme 1.4).[19]



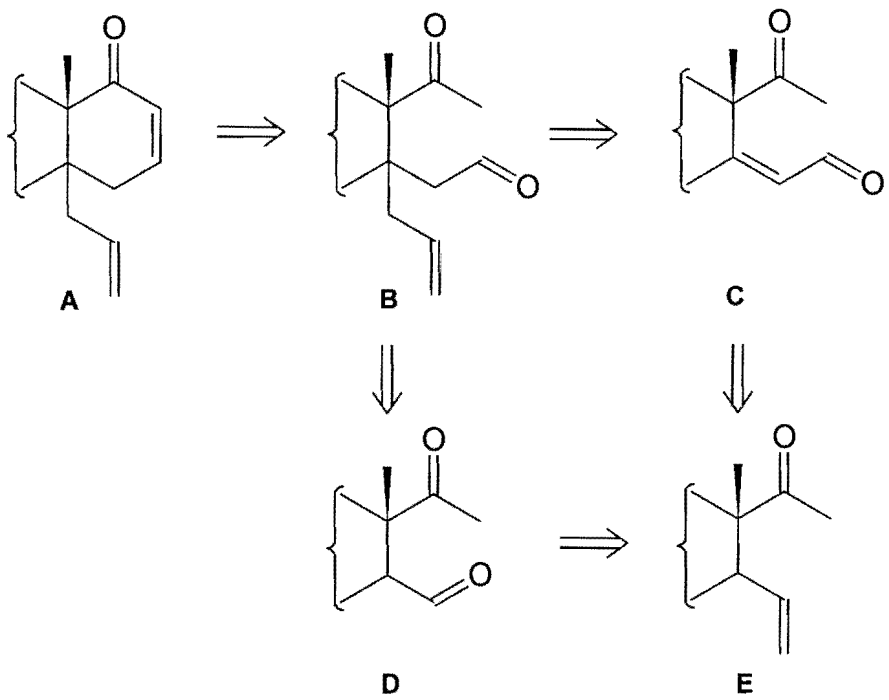
Scheme 1.4

The need for an efficient route to 14-allyl 19-norsteroids then prompted Bull *et al* to conduct a cycloaddition of acrolein with dienyl acetate **11** to afford a cycloadduct **14**, which could be converted to a hydroxy tosylate **15**. Wharton fragmentation of the 1,3-transposed hydroxy tosylate **15** thus gave stereoselectively access to 14β-allyl estrone **16** *via* a Δ^{15}-intermediate. (Scheme 1.5).[20]



Scheme 1.5

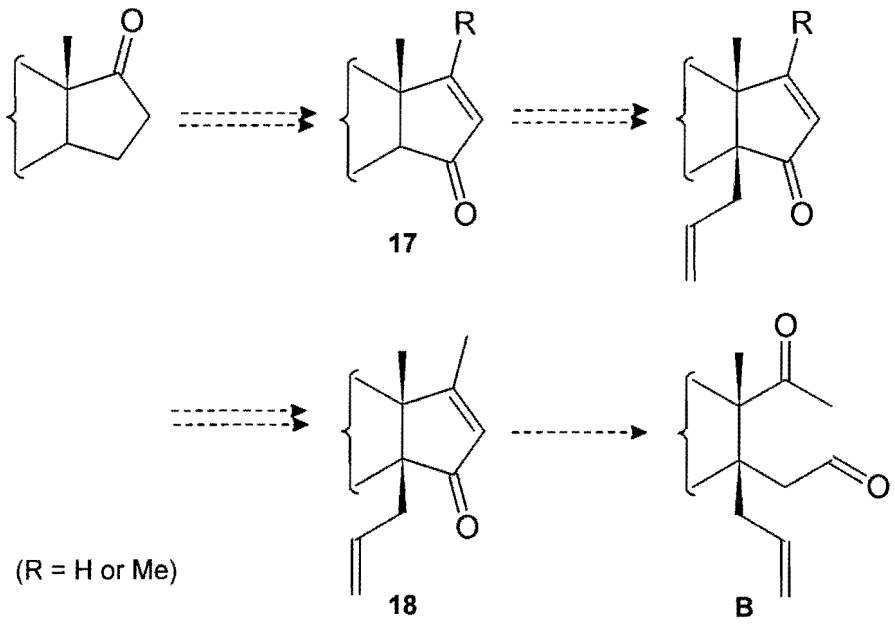
Retrosynthetic analysis of 14-allyl 17a-homoestrone A: Retrosynthetic analysis based on cleavage of the Δ^{16} bond in the target molecule **A** leads to a three group functional array **B**. This array is highly desirable, as chemodifferentiation of the 14-substituents could serve interchangeably as the elements for reconstitution of ring D, resulting in a versatile synthetic pathway to both 14α- and 14β-allyl 17a-homoestrone **A**. Synthon **B** would thus require the addition of an allyl group at C-14 of a suitably fragmented ring D precursor. This could be envisaged by conjugate addition to an intermediate of type **C**, or enolate mediated addition to an intermediate of type **D**. Intermediates **C** and **D** could in turn be obtained by cleavage of the 16,17-bond of a suitable estrone derivative (Scheme 1.6).



Scheme 1.6

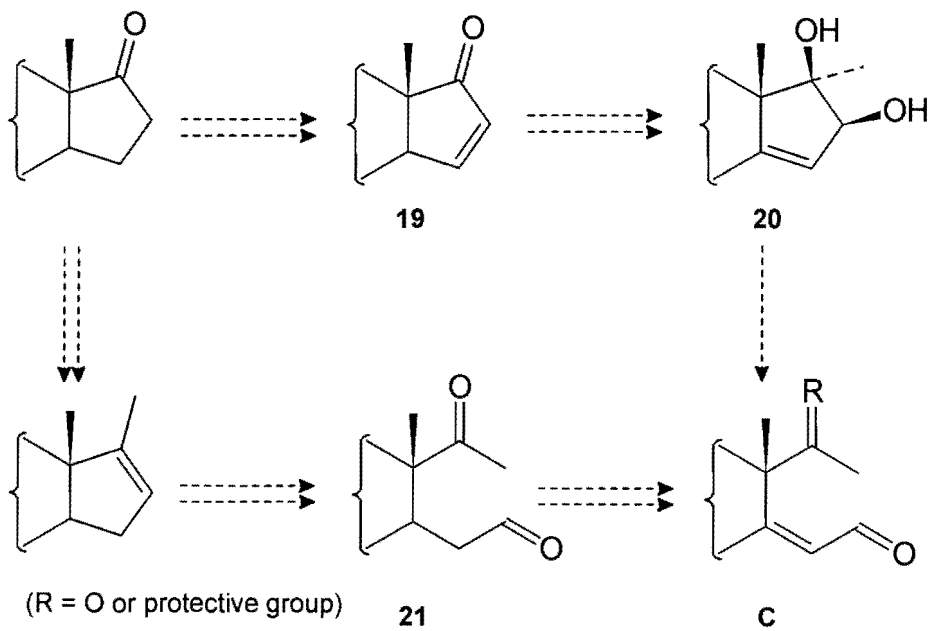
Estrone 3-methyl ether is an appropriate starting material in this study since it is readily available, and the essential features pertaining to the 19-norsteroid skeleton are in place.

A direct approach to synthon **B** can be envisaged by the oxidative cleavage of a 14β-allyl Δ^{16} 17-methyl precursor **18**, which in turn could presumably be obtained from 14β-allylation of a suitable 15-ketone **17** (Scheme 1.7).



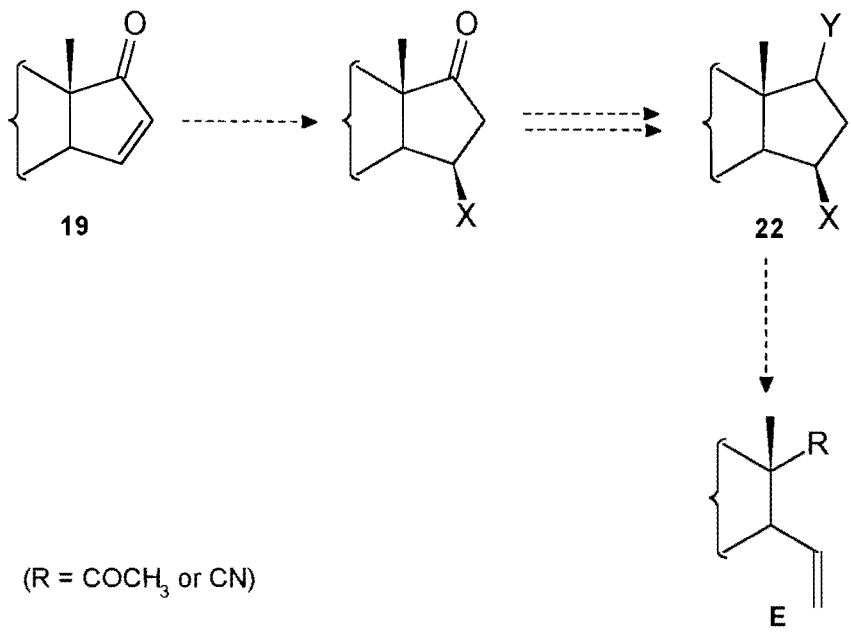
Scheme 1.7

Synthon **C** can be envisaged from the oxidative cleavage of a Δ^{14} 16,17-diol **20**, which in turn could be obtained from the Δ^{15} 17-ketone **19**. Alternatively, an approach based on chemoselective differentiation and trapping of a seco formyl ketone **21** precursor, would render a synthon of type **C** with a latent 13-acetyl group (Scheme 1.8).



Scheme 1.8

Grob and related fragmentations offer a alternative route to ring D fragmentation intermediates of type **E**, which may serve as precursors for stereoselective introduction of 14-functionalised alkyl groups onto the steroid nucleus. Synthon **E** can thus be envisaged from the fragmentation of a suitably 1,3-functionalised intermediate **22** (in which X and Y are the nucleofugal and electrofugal components), which could be obtained by conjugate addition to the Δ^{15} 17-ketone **19**, followed by 17-fuctionalization (Scheme 1.9)



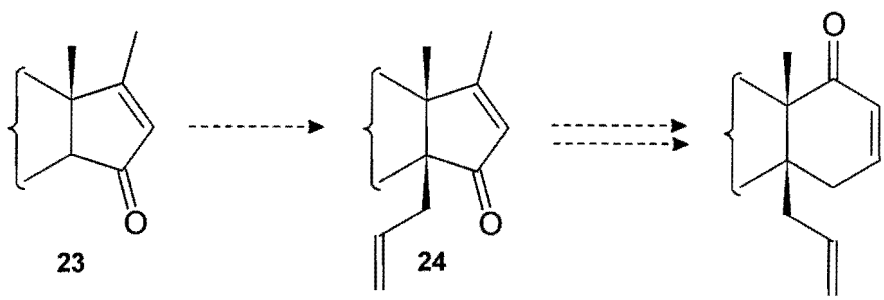
Scheme 1.9

2. DISCUSSION

2.1. OXIDATIVE CLEAVAGE ROUTES TO 16,17-SECO COMPOUNDS

Amongst the methods which have been used for the stereoselective introduction of 14-alkyl groups onto the steroid skeleton, base mediated alkylation of 15-ketones is the most direct and well defined. It has been demonstrated that simple 15-ketones undergo highly stereoselective 14β-alkylation.[13,14,15,16,17,18] The reaction course is however influenced by steric and stereoelectronic factors, with the presence of 17β-alkyl residues or central ring unsaturation resulting in reversal of stereoselectivity, to give mainly or exclusively 14α-alkylation products.[18] Furthermore, the synthetic utility of this approach to 14-alkyl steroids relies on subsequent transposition methodology if 17-oxygen functionality is required in the products, a process which may be rendered non-trivial by the presence of the newly introduced 14-alkyl group.[18]

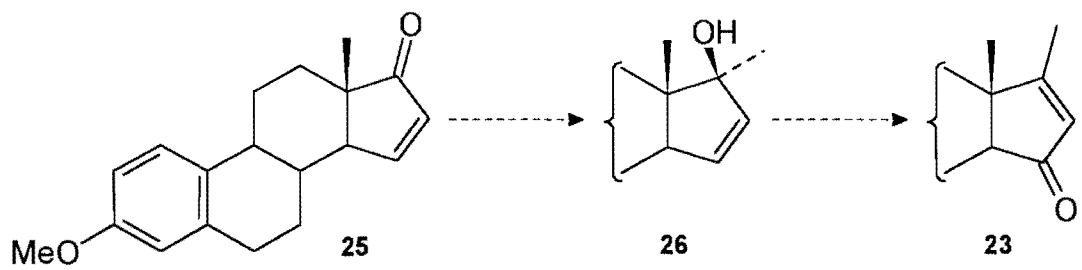
Nevertheless, it was decided to reinvestigate 14-allylation, using a 17-methyl Δ^{16} 15-ketone **23** as the substrate, since it was reasoned that the expected 14β-allylation, followed by 15-deoxygenation would furnish a 14β-allyl 17-methyl Δ^{16} precursor **24** that could be oxidatively cleaved to provide access to a key intermediate for the purpose of preparing a 14β-allyl 17a-homo derivative of estrone (Scheme 2.1).



Scheme 2.1

The starting material for this study, 3-methoxyestra-1,3,5(10),15-tetraen-17-one **25**, was prepared by standard methodology,[22] involving sequential ketalization, 16α-bromination, dehydrobromination, and deketalization of estrone 3-methyl ether. The overall yield for this sequence was *ca* 70 %.

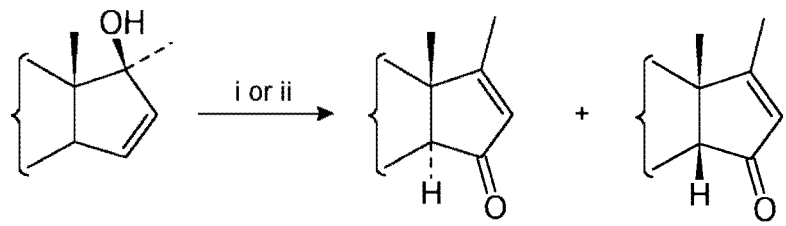
Synthesis of the 17-methyl Δ^{16} 15-ketone **23** was envisaged through oxidative transposition of a Δ^{15} 17-alcohol **26** which, in turn, would be readily obtained by 1,2-methylation of the Δ^{15} 17-ketone **25** (Scheme 2.2).



Scheme 2.2

Methylation of the Δ^{15} 17-ketone **19** has been reported.[23] Thus, treatment of the Δ^{15} 17-ketone **19** with methyllithium in tetrahydrofuran, at -78 °C, afforded the Δ^{15} 17β–alcohol **26**, in a quantitative yield.

The oxidative transposition of tertiary allylic alcohols to α,β-unsaturated compounds is known to occur with pyridinium chlorochromate (PCC).[24,25] Treatment of the allylic alcohol **26** with freshly prepared PCC on alumina, in dichloromethane at room temperature for 5 h, resulted in formation of the 17-methyl Δ^{16} 15-ketone **23** (79 %). More prolonged treatment (for 18 h) afforded a separable mixture of the 14α- (18 %) **23** and 14β-epimers **27** (42 %) (Scheme 2.3), through progressive equilibration to the latter, thermodynamically favoured isomer.



26 **23** **27**

i	79 %	0 %
ii	18 %	42 %

Reagents: i) PCC on alumina, 5h.
ii) PCC on alumina, 18h.

Scheme 2.3

The IR spectra of the C-14 epimers gave absorption bands at ν_{max} 1702 and 1690 cm^{-1} for the carbonyl groups of the respective 14α- and 14β-epimers. The ^{1}H-NMR spectra of the 14-epimers showed the 17-methyl signals as doublets (*J* 1.3 and 1.1 Hz), which arise from allylic coupling to the olefinic 16-proton. The configuration at C-14 was assigned on the basis of the coupling between 14-H and 8β-H, and was confirmed by nuclear Overhauser effect (nOe) difference experiments. The signal for the 14α-proton in **23** appeared as a doublet at δ 2.14 (*J* 11 Hz), showing the expected large anti periplanar coupling to 8β-H (Figure 2.1). Further confirmation of the 14-configuration was obtained by irradiation of the 13β-methyl signal (δ 1.06), resulting in enhancement of the olefinic 16-proton signal (amongst others). No enhancement of the 14α-proton signal was observed.

The 14β-signal in **27** appeared as a doublet at δ 2.29, with coupling to 8β-H (5.3 Hz) indicative of the expected synclinal relationship (Figure 2.1). In this case, irradiation of the 13β-methyl group (δ 1.23), resulted in enhancement of the 14β-H signal (amongst others), with no enhancement of the olefinic 16-proton signal being observed.

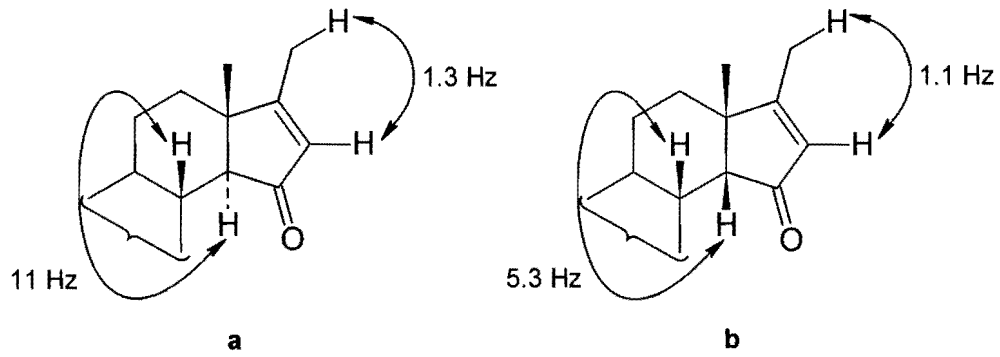
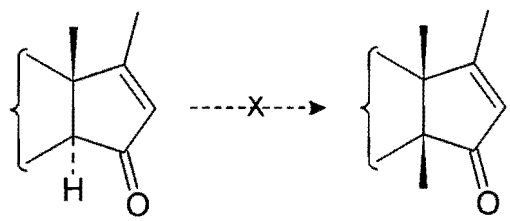


Figure 2.1 **a:** Coupling constants of the 17-methyl Δ^{16} 14α-*H* 15-ketone **23**.
b: Coupling constants of the 17-methyl Δ^{16} 14β-*H* 15-ketone **27**.

Attempts at 14-methylation of the 17-methyl Δ^{16} 15-ketone **23** with excess iodomethane as the electrophile, and sodium amide and lithium diisopropylamide (LDA) as the bases (used in separate attempts), resulted in complex mixtures of inseparable products. The reactions conducted with LDA tended not to go to completion, while those conducted in the presence of sodium amide resulted in complete consumption of starting material **23**. In an attempt to overcome the formation of complex mixtures, sodium amide was used with one equivalent of iodomethane. Once again, a complex mixture of inseparable products was obtained together with starting material **23** (Scheme 2.4).



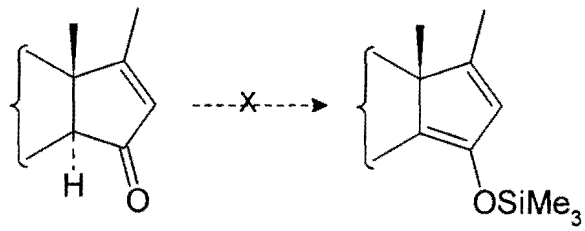
23

Scheme 2.4

The synthetic difficulties associated with performing α-alkylation of ketones in a highly controlled manner is well known.[26] It can only be achieved when the enolate anion is regioselectively generated and allowed to react with an alkylating agent,

before the enolate ion undergoes equilibration *via* proton transfer. Thus, polyalkylation and nonregioselective alkyation often accompany a desired reaction. It is assumed that the presence of the 17-methyl group allows competing deprotonation of the acidic 17'-protons with attendant possibility of methylation at C-16 and/or C-17'.

The utilisation of silyl enol ethers,[26,27] as precursors of enolate anions is an excellent alternative approach for ensuring regioselective monoalkylation. In an attempt to determine the regiochemistry of enolate formation, an experiment involving the trapping of the enolate intermediate as the silyl enol ether was attempted. However, all attempts at forming the enolate with LDA, and trapping with trimethylsilyl chloride, failed to give a stable product (Scheme 2.5).



23

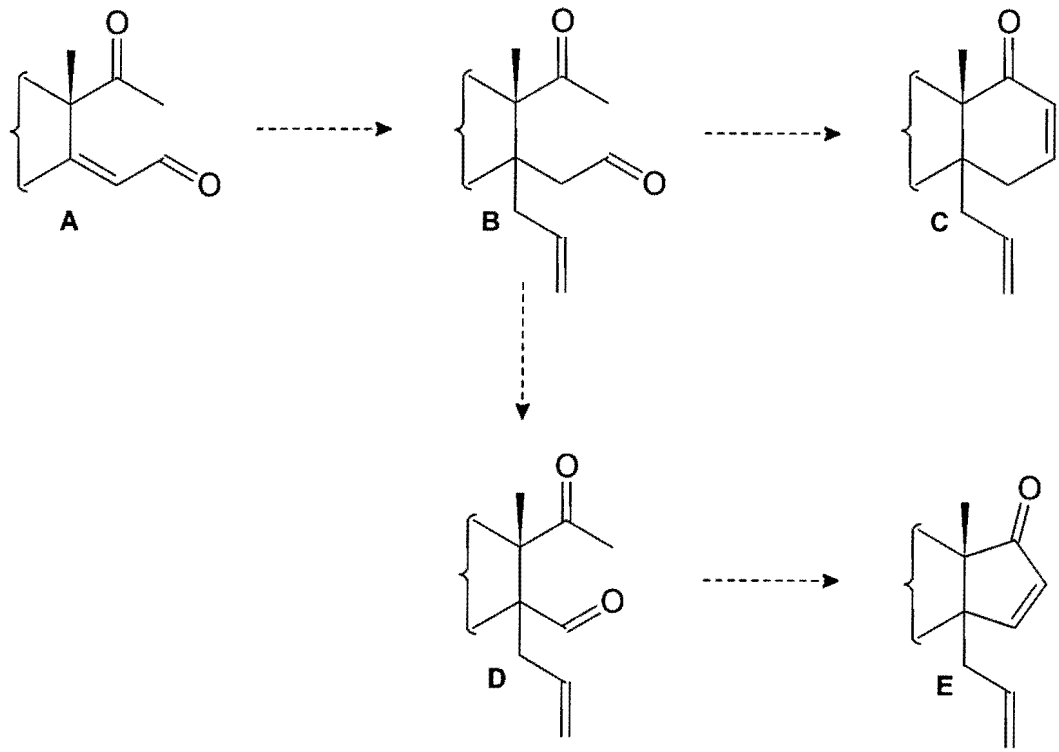
Scheme 2.5

Due to the problems encountered with this preliminary study, an approach towards a more versatile synthetic strategy was embarked upon.

Alternative methods for the stereoselective synthesis of 14-functionalised steroids include sequential cycloaddition-fragmentation of 14,16-dienyl acetates, and have been successfully applied in the synthesis of both 14α- and 14β-substituted steroids.[8,19,20] However, these methods lack general applicability. Accordingly, consideration has been given in this study to alternative and more versatile strategies for the stereoselective introduction of 14-functionalised alkyl groups onto the steroid nucleus. One such approach can be envisaged through fragmentation of ring D into

an intermediate amenable to stereoselective alkylation at C-14, followed by reassembly of ring D.

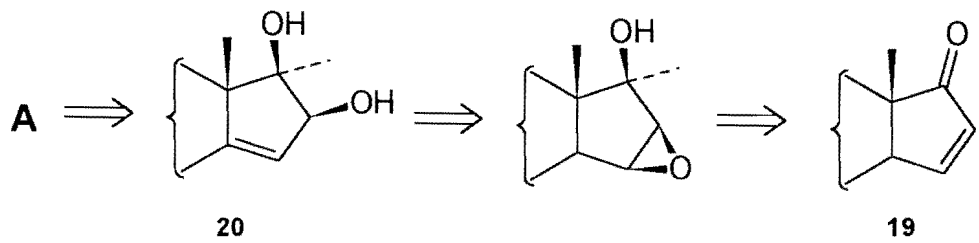
The potential of such an approach is illustrated for the hypothetical seco-compound **A** (Scheme 2.6), in which the stereoselective introduction of a 14-allyl group to give **B**, followed by direct reassembly of ring D would lead to the 17a-homo product **C**; or by indirect reassembly, preceded by chain truncation, to **E** (Scheme 2.6). The virtue of this approach is that the chemodifferentiated 14-substituents in **B** could serve interchangeably as the elements for reconstitution of ring D, resulting in a versatile synthetic pathway to both 14α- and 14β-allyl steroids and 17a-homosteroids.



Scheme 2.6

It was recognised that a prerequisite for the success in this approach would be a lack of interference from the potential ring D fragment attached to C-13, as well as adequate stereoselectivity during 14-alkylation.

In the first phase of the investigation the seco-compound **A** was targeted, although it was recognised that both the preparation and subsequent reaction could be attended by interfering intramolecular aldol reaction. An approach to **A** is outlined retrosynthetically in Scheme 2.7, *via* oxidative cleavage of the 16β,17β-diol **20**, synthesis of which from the Δ^{15} 17-ketone **19** could be envisaged through successive epoxidation, 17-methylation and epoxide isomerisation.



20 **19**

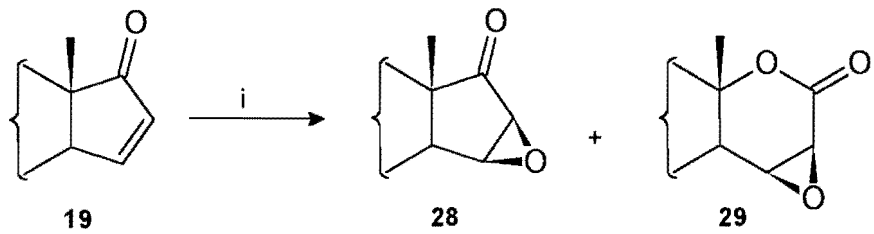
Scheme 2.7

2.1.2 Synthesis and reactions of 3-methoxy-17α-methylestra-1,3,5(10),14-tetraene-16β,17β-diol

It is well known that conjugate addition of a variety of nucleophiles to steroidal Δ^{15} 17-ketones favours 15β-substitution.[28] This is stereoelectronically appropriate, and is also reflected in base mediated epoxidation, in which the initial 1,4-addition of the hydroperoxy anion to C-15 proceeds with 15β-stereoselectivity leading to the 15β,16β-epoxy 17-ketone **28**.[29]

The synthesis of the 15β,16β-epoxy 17-ketone **28** has been reported in the patent literature.[29] However, few details are available. Thus, the base mediated epoxidation was studied systematically, in order to explore the scope for obtaining a reliable and selective conversion to the desired product. The best result was achieved by adding hydrogen peroxide to a solution of Δ^{15} 17-ketone **19** in a mixture of *t*-butyl alcohol and

tetrahydrofuran, then sodium hydroxide at -5 °C. This gave the desired epoxy ketone **28** in good yield (73 %), but accompanied by a product (8 %) formulated as the derived epoxy lactone **29** (Scheme 2.8).



Reagents: i) H_2O_2, NaOH

Scheme 2.8

Conclusive structural proof of the epoxy ketone **28** was obtained by comparison of analytical data to that reported. For the epoxy lactone **29**, the IR spectrum showed an absorption band at ν_{max} 1732 cm^{-1} for the carbonyl group. The mass spectrum showed a molecular ion confirming epoxy lactone **29** formation. The 200 MHz ^{1}H-NMR spectrum showed doublets for the 16α- and 15α-protons at δ 3.62 and 3.81 respectively (Figure 2.2). The coupling constants of **28** and **29** is shown in Figure 2.2.

Further evidence for the Baeyer Villiger oxidation is the 13β-Me resonance at δ 1.61, which is deshielded relative to that of the epoxy ketone **28** (δ 1.19), as a result of the oxygen insertion.

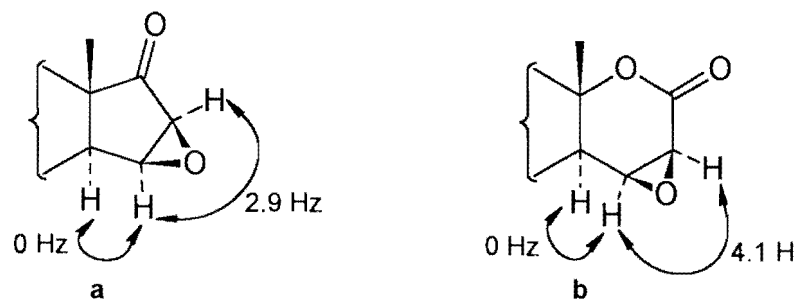
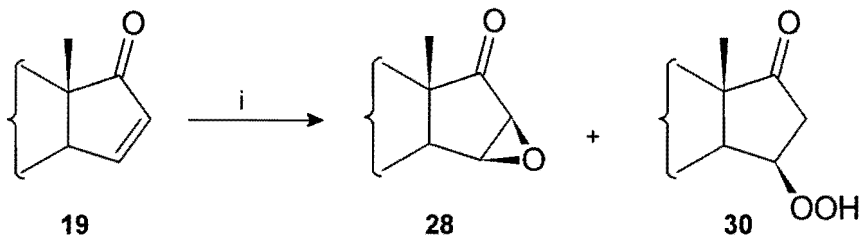


Figure 2.2 **a:** Coupling constants for the epoxy ketone **28**.

b: Coupling constants for the epoxy lactone **29**.

In a separate experiment the sodium hydroxide was first added to a solution of the Δ^{15} 17-ketone **19** in a mixture of *t*-butyl alcohol and tetrahydrofuran, followed by addition of hydrogen peroxide at -10 to -5 °C. This afforded the desired epoxy ketone **28** in poor yield (38 %), accompanied by a product formulated as the intermediate 15β-hydroperoxy 17-ketone **30** (43 %) (Scheme 2.9).



Reagents: i) H_2O_2, NaOH

Scheme 2.9

The IR spectrum of the hydroperoxy ketone **30** showed absorption bands at ν_{max} 3531 and 1732 cm^{-1}, for the hydroperoxy and carbonyl groups respectively. The mass spectrum gave the molecular ion expected for the hydroperoxy ketone **30**. The 200 MHz ^{1}H-NMR spectrum showed the 14α-proton at δ 1.71, as a doublet of doublets. The 16α-proton resonated at δ 2.48, as a doublet of doublets, and the 16β-proton at δ 3.00, as a doublet. The 15α-proton resonated at δ 4.90, as a triplet. These coupling connectivities are depicted in Figure 2.3, and are in accordance with 15β–substitution.[30]

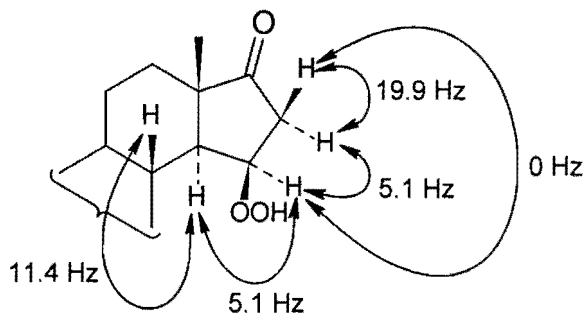
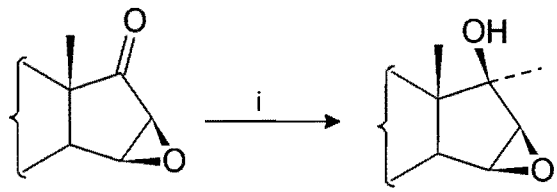


Figure 2.3: Coupling constants for the 15β-hydroperoxy 17-ketone **30**.

Isolation of the hydroperoxy intermediate **30** is unusual, but in line with the mechanism, which proceeds by initial nucleophilic addition of the hydroperoxy anion to the α,β-unsaturated system. In this case, protonation of the intermediate enolate evidently intervenes to give the hydroperoxy intermediate **30**, instead of undergoing epoxide formation.

Reports of epoxy lactone formation being avoided during the epoxidation of the 3β–(*t*-butyldimethylsilyloxy)androsta-5,15-diene-11,17-dione by the use of sodium hypochlorite, to give a high yield of the desired epoxide (80 %),[31] prompted an investigation of its use for epoxidation of the Δ^{15} 17-ketone **19**. Thus, the dropwise addition of an aqueous solution of sodium hypochlorite to a solution of the Δ^{15} 17-ketone **19** in a mixture of pyridine and ethanol, at -10 °C, resulted in a good yield of the desired epoxy ketone **28** (*ca* 78 %). Although this yield is not significantly better than the optimised hydroperoxy anion mediated epoxidation (73 %), the reaction is uncomplicated and highly reproducible, unlike the latter reaction.

Methylation of the epoxy ketone **28** with ethereal methyllithium in tetrahydrofuran at -78 °C, gave the 17α-methyl epoxy alcohol **31** in excellent yield (93 %) (Scheme 2.10).



28 **31**

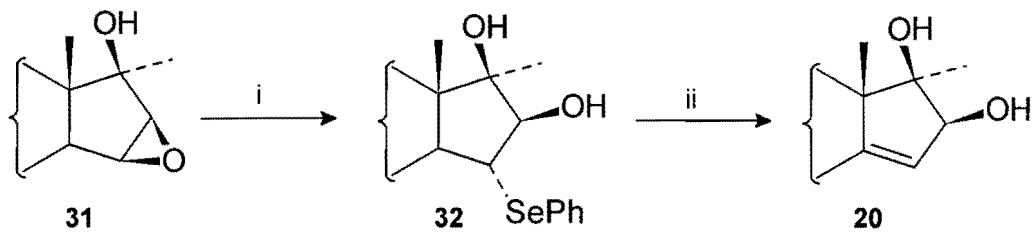
Reagents: i) MeLi

Scheme 2.10

The physical data of the epoxy alcohol **31** are in accordance with the expected structure. The configuration at C-17 was confidently assigned on the basis of the

almost invariable preference for α-face attack by nucleophiles upon steroidal 17-ketones.[32]

Transformation of the epoxy alcohol **31** into the 16β,17β-diol **20** could be accomplished indirectly or directly *via* opening of the epoxide. In the first instance, it was reasoned that the epoxide should undergo regioselective addition at C-15 with the phenylselanyl anion, leading to an intermediate for *syn*-elimination of the derived 15α-phenylselenoxide (Scheme 2.11).[33,34] Indeed, when the epoxide was treated with sodium phenylselenide (generated *in situ* by treatment of diphenyl diselenide with sodium borohydride) in ethanol at 80 °C, the desired 15α-phenylselanyl compound **32** was formed efficiently in good yield (80 %).



Reagents: i) Ph_2Se_2, $NaBH_4$ ii) H_2O_2, Δ

Scheme 2.11

Since the 15β-proton in **32** was expected to couple with 14α-H and 16-H, the doublet of doublets at δ 3.36 was assigned to 15β-H. The large coupling of 11.5 Hz is in accordance with the *trans* alignment to 14α-H, and the small coupling of 3.3 Hz is associated to 16α-H, which resonates as a doublet at δ 3.88 (Figure 2.4). The regioselective addition at C-15 was thus verified from the ^{1}H-NMR spectrum, and confirmed by the success of the subsequent transformation (see below).

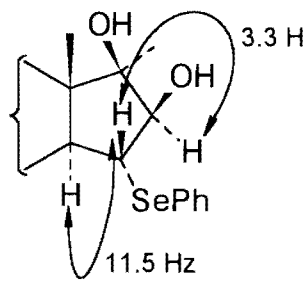
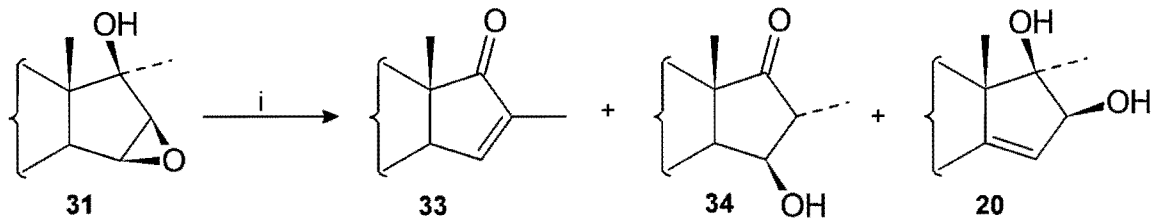


Figure 2.4: Coupling constants of the 15β-phenylselanyl compound **32**.

Oxidation of the 15β-phenylselanyl compound **32** with hydrogen peroxide in ethanol occurred within 2h with concomitant thermolysis on refluxing for a further 2.5 h, to afford the desired Δ^{14} 16β,17β-diol **20** in excellent yield (94 %) (Scheme 2.12).

The IR spectrum of the 16β,17β-diol **20** gave absorption bands at ν_{max} 3682 and 3592 cm^{-1} for the hydroxyl groups, and the mass spectrum gave the expected molecular ion. The 200 MHz ^{1}H-NMR spectrum showed the 16α-proton at δ 4.15, as a doublet, with a coupling constant of 2.4 Hz. The olefinic 15-proton was observed as a broad singlet at δ 5.46.

Despite the success of this stepwise method, the direct approach was also investigated, *via* base-mediated isomerisation.[33] Addition of a tetrahydrofuran solution of the epoxide **31** to lithium diethylamide (generated *in situ* by treatment of diethylamine with a solution of methyllithium in diethyl ether), resulted in formation of a mixture of products which after separation afforded the desired 16β,17β-diol **20** (69 %), accompanied by products formulated as the 16-methyl Δ^{15} 17-ketone **33** (13 %) and the 16α-methyl 15β-hydroxy 17-ketone **34** (8 %) (Scheme 2.12).

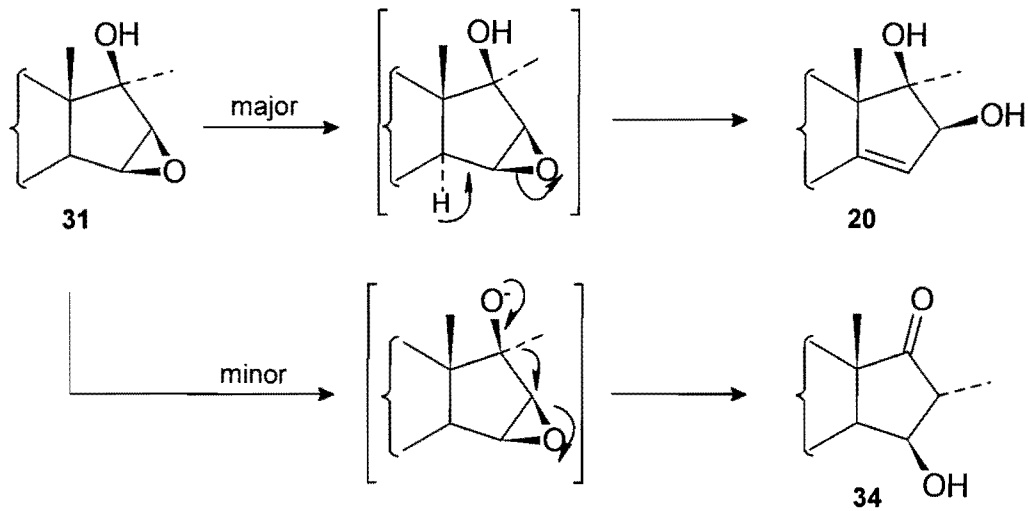


Reagents: i) MeLi, Et_2NH

Scheme 2.12

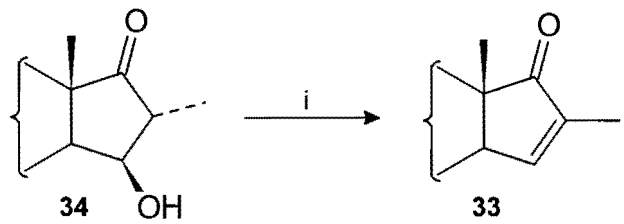
The physical data of the 16-methyl Δ^{15} 17-ketone **33** were in accordance with those reported in the literature.[35] The IR spectrum of the 16α-methyl 15β-hydroxy 17-ketone **34** gave an absorption band at ν_{max} 1700 cm^{-1} for the carbonyl group, and the mass spectrum gave the expected molecular ion. The 200 MHz ^{1}H-NMR spectrum showed a signal for the 16α-methyl group at δ 1.26 as a doublet, with a coupling constant of 7.6 Hz to 16β-H. The 15α-proton was observed as a broad singlet at δ 4.57.

The 16-methyl Δ^{15} 17-ketone **33** is assumed to arise from dehydration of the 16α-methyl 15β-hydroxy 17-ketone **34**, which in turn results from rearrangement of the epoxy alcohol **31**. This postulated 1,2-methyl shift is presumably mediated by the lithium diethylamide (Scheme 2.13).



Scheme 2.13

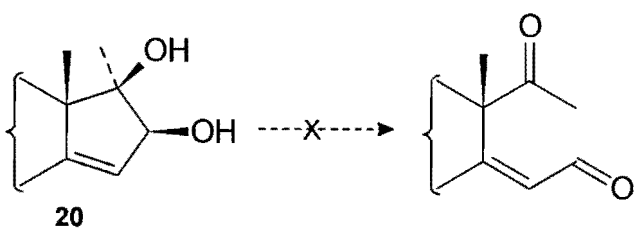
In order to confirm that formation of the 16-methyl Δ^{15} 17-ketone **33** was *via* β-elimination of the 15β-hydroxy 17-ketone **34**, the alcohol **34** was treated with toluene-*p*-sulfonic acid in dichloromethane, to afforded the desired product **33**, in a quantitative yield (Scheme 2.14).



Reagents: i) TsOH

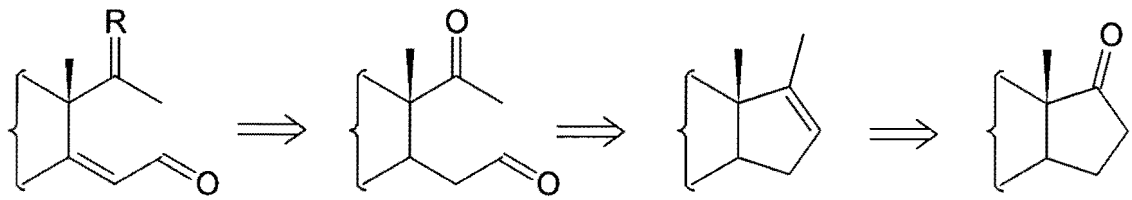
Scheme 2.14

It is known that 1,2-diols can be oxidatively cleaved under mild conditions to the corresponding aldehydes or ketones.[36] Treatment of the diol **20** with sodium metaperiodate, resulted in a slow reaction with initial formation of a single product, however, the prolonged time resulted in the development of further products which were observed by thin layer chromatography (TLC). Since lead tetraacetate is known to significantly enhance the rate of cleavage of diols, compared to sodium metaperiodate,[37] it was used in an attempt to allow rapid formation of a single product. Although the reaction gave predominantly one product (TLC), attempts at isolating the product were unsuccessful, resulting in the development of further products (TLC). A reported procedure,[38] using sodium metaperiodate/wet silica gel in the presence of dichloromethane (supported reagent approach), was also attempted. However, the reaction rate was very slow (TLC), resulting in a complex mixture of products (Scheme 2.15).



Scheme 2.15

The problems associated with the foregoing procedure are evidently the result of lability of the primary cleavage product. Accordingly, it was reasoned that oxidative cleavage of the 16,17-bond in a system lacking the Δ^{14} bond might give a more stable intermediate, in which the terminal functional groups could be differentiated for subsequent introduction of the Δ^{14} bond, without interference from intramolecular reactions. Retrosynthetic analysis of the protected seco compound identified the seco formyl ketone **21** as an appropriate precursor for chemoselective differentiation and subsequent trapping. This seco precursor could in turn could be synthesised from readily available estrone 3-methyl ether **25** (Scheme 2.16).



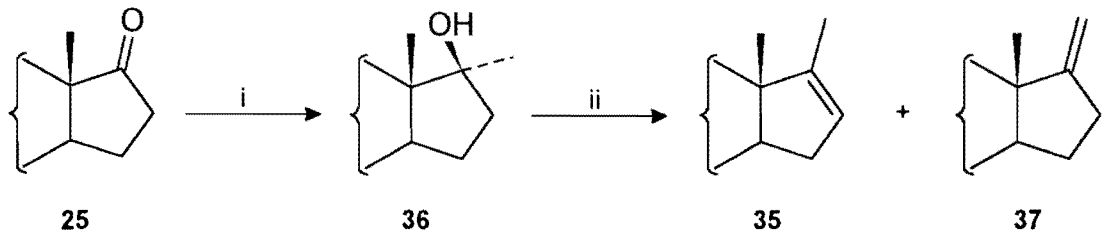
21 **25**

Scheme 2.16

The initial aim of this investigation was therefore to prepare the seco formyl ketone **21** as starting material for chemoselective differentiation and trapping.

2.1.3 Synthesis and reactions of 3-methoxy-16,17-seco-17a-homoestra-1,3,5(10)-triene-16,17a-dione

The previously reported synthesis of the Δ^{16} 17-methyl compound **35**, involves Grignard methylation of estrone 3-methyl ether **25** to give the 17α-methyl 17β-alcohol **36**, which on dehydration afforded a mixture of the exo- **37** and endocyclic **35** methylene compounds (Scheme 2.17).[11]



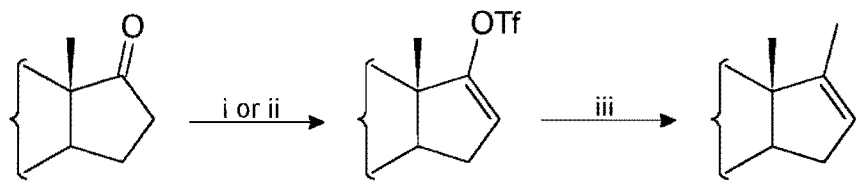
25 **36** **35** **37**

Reagents: i) MeMgI ii) $Me(PhO)_3P^+I^-$

Scheme 2.17

Due to the lack of regioselectivity in the dehydration step, an alternative synthesis of the 17-methyl Δ^{16} precursor **35** was investigated, *via* coupling of the enol triflate **38** with lithium dimethylcuprate. The enol triflate **38** was prepared by treating estrone 3-methyl ether **25** with triflic anhydride and pyridine, resulting in a heterogenous reaction (Scheme 2.18). Although the reaction gave the enol triflate **38** in good yield (90 %), treatment with 2,6-di-*tert*-butyl-4-methylpyridine and triflic anhydride,[40] gave a homogenous and more efficient reaction, in excellent yield (99 %).

Addition of a tetrahydrofuran solution of the enol triflate **38** to lithium dimethylcuprate (generated *in situ* by treatment of a solution of copper(I) iodide in tetrahydrofuran with methyllithium in diethylether), resulted in formation of the methyl olefin **35**, in excellent yield (99 %) (Scheme 2.18).



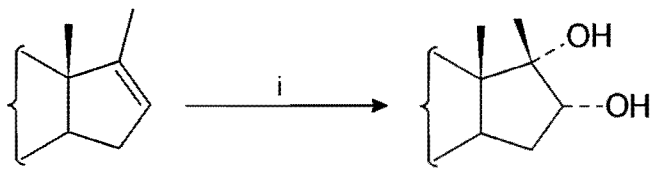
25 **38** **35**

Reagents: i) Tf_2O, py ii) Tf_2O, DTBMP iii) $LiMe_2Cu$

Scheme 2.18

Due to difficulties encountered with attempted ozonolysis of the methyl olefin **35**, the indirect approach of *cis*-hydroxylation and subsequent oxidative cleavage of the

resultant *cis*-diol was undertaken. Treatment of the methyl olefin **35** with osmium(IV) tetroxide, resulted in formation of the 17β-methyl 16α,17α-diol **39**, in excellent yield (90 %) (Scheme 2.19)



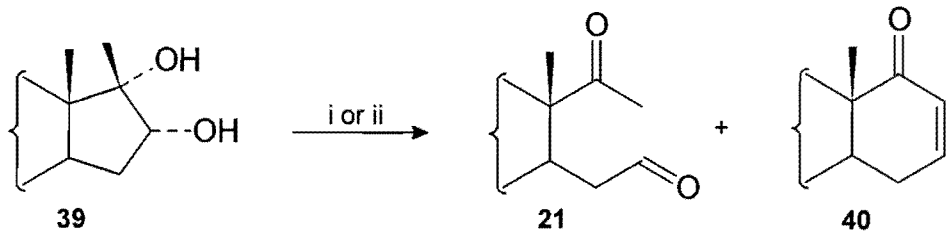
35 **39**

Reagents: i) OsO_4

Scheme 2.19

Spectroscopic data were consistent with the proposed structure and the configuration at C-16 and C-17 was assigned on the basis of literature precedent.[41]

Treatment of the 16α,17α-diol **39** with lead tetraacetate resulted in a rapid reaction (4 min), which after work up under non-acidic conditions, and flash chromatography gave the expected seco compound **21**, in excellent yield (93 %). The seco compound **21** proved stable to handling, and rapid acid (1M HCl) treatment allowed removal of the lead residues. Thus, large scale preparations could be conducted without any loss in yield. Treatment of the diol **39** with sodium metaperiodate, however, resulted in a slower reaction during which some 17a-homo enone **40** formed (Scheme 2.20).



39 **21** **40**

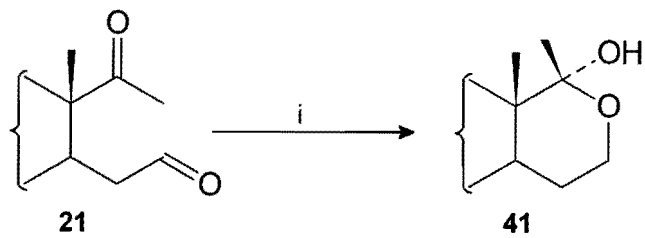
Reagents: i) $Pb(OAc)_4$, acid workup 94 % 0 %

ii) $NaIO_4$ (37 % recovery of **39**) 50 % 5 %

Scheme 2.20

The spectroscopic data for the seco compound **21** were consistent with the proposed structure. The ^{1}H-NMR spectrum showed the 17-methyl group resonating at δ 2.18 as a singlet and the aldehydic 16-H signal appearing at δ 9.79 (br d, *J* 1.9 Hz), all in agreement with reported precedent.[11] Structural proof of the 17a-homo enone **40** was obtained by a mixed melting point comparison to analytical material obtained from a related study.[11] Treatment of a solution of the 16,17-seco compound **21** in dichloromethane with toluene-*p*-sulfonic acid for 20 h, resulted in formation of the homo enone **40** (85 %), as a result of acid catalysed aldol ring closure and subsequent dehydration, giving absolute proof of the seco structure **21**.

For the purpose of introducing a Δ^{14}-bond in **21**, it was considered necessary to first protect the 17a-oxo group and, with this objective in mind, the chemoselectivity of CO group differentiation in **21** was investigated. Chemoselective lithium tri-*s*-butylborohydride (L-Selectride) reduction of an aldehyde in the presence of a ketone is known.[8] Thus, the 16,17-seco compound **21** was treated with L-Selectride in tetrahydrofuran, at -78 °C, resulting in the chemoselective reduction of the aldehyde to afford the cyclic hemiacetal **41** as a crystalline product (66 %) (Scheme 2.21).



21 **41**

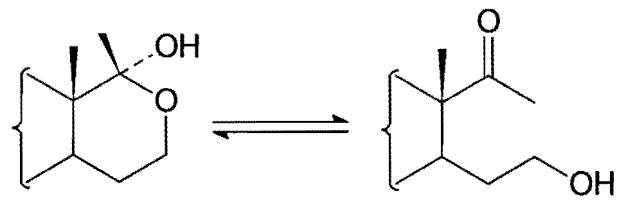
Reagents: i) L-Selectride

Scheme 2.21

The 400 MHz ^{1}H-NMR spectrum of **41** recorded in deuteriobenzene showed a singlet at δ 1.13 for the 17aβ-methyl group. The 16β-proton was assigned to the signal at δ 3.60 (ddd) since a large geminal coupling (11.5 Hz) and two smaller vicinal

couplings (5.1 and 1.4) are observed. The signal at δ 3.88 (ddd) was therefore assigned to the 16α-proton, since it consisted of large anti periplanar and geminal couplings (12.5 and 11.5 Hz respectively), along with a small synclinal vicinal coupling (3.7 Hz) (Table 2.1).

Assignment of the configuration at C-17a was made by an nOe difference experiment, in which irradiation of the 13β-methyl group (δ 0.91) resulted in significant enhancement of the signal for the 17aβ-methyl (δ 1.13). The IR spectrum ($CHCl_3$) displayed absorption bands at ν_{max} 3598 and 1727 cm^{-1} (the band at 1727 cm^{-1} was of low intensity), assigned to the hydroxyl group of the cyclic hemiacetal **41**, and the carbonyl group of the seco hydroxy ketone **42** respectively. It is therefore assumed that some free hydroxy ketone **42** is in equilibrium with the cyclic hemiacetal **41** in chloroform, but this is not observed in the NMR solvent (C_6D_6) (Scheme 2.22).

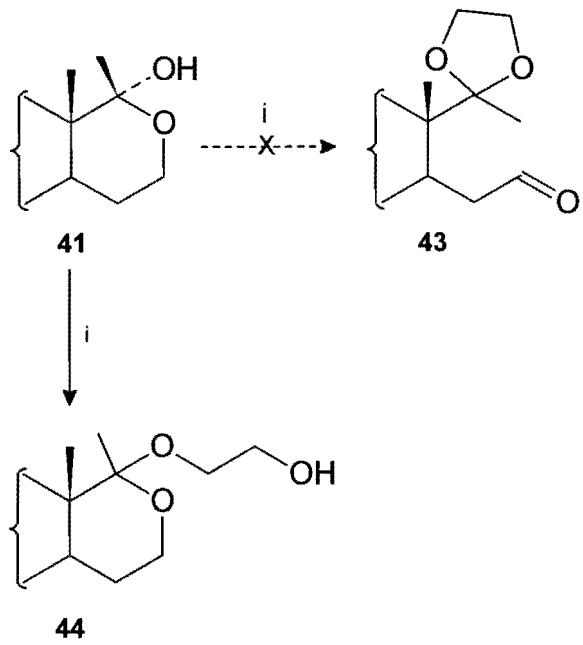


41 **42**

Scheme 2.22

Encouraged by this IR evidence, it was hoped that the open form **42** might be trapped as a ketal. Thus, the cyclic hemiacetal **41** was treated under the conventional conditions (ethylene glycol, catalytic *p*-TsOH, benzene, Δ) for ketal formation, to give an isolated crystalline product (66 %). The IR spectrum of the product showed an absorption band at ν_{max} 3602 cm^{-1}, which was assigned to the expected hydroxyl absorption. Mass spectral data was consistent with the formation of a ketal (M^+, 360), and the ^1H and ^{13}C-NMR data also appeared to be consistent with formation of the expected seco ketal **43**. However, evidence from subsequent oxidation and

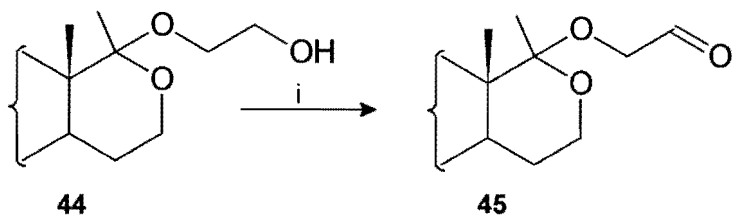
careful analysis of the COSY and HETCOR spectra, supported the formation of a 2'-hydroxy ketal **44** (Scheme 2.23).



Reagents: i) $(CH_2OH)_2$, *p*-TsOH

Scheme 2.23

Thus, for the 2'-hydroxy ketal **44** the NMR signals for the 16-H_2 protons were correlated to those of the 15-H_2 protons, which in turn showed further connectivity to 14α-H. The triplet which was assigned to 2'-H_2 protons showed correlation to the 1'-H_2. The relevant NMR data are tabulated in Table 2.1. Further support of 2'-hydroxy ketal **44** formation was obtained from oxidation of the primary alcohol to the 2'-aldehyde **45**. Swern oxidation[36,37,42] of the 2'-hydroxy ketal **44** gave the 2'-aldehyde **45** in high yield (86 %) (Scheme 2.24).

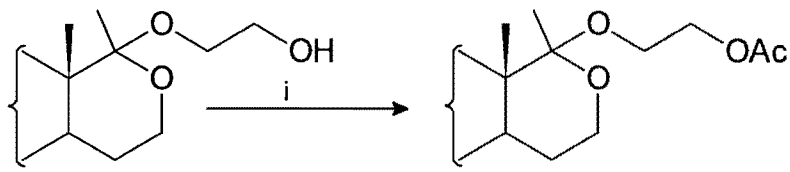


Reagents: i) $(COCl)_2$, DMSO, NEt_3

Scheme 2.24

The 400 MHz ^{1}H-NMR spectrum of **45** showed the 1'-H_2 signals at δ 4.06 and 4.13, as a doublet of doublets, arising from a large geminal coupling (17.9 Hz) and a small vicinal coupling to the aldehydic 2'-H (1.2 Hz), which resonated at δ 9.82, as a triplet (2x1.2 Hz). The 16-H_2 protons were observed as multiplets at δ 3.57 and 3.75.

Acetylation of the 2'-hydroxy ketal **44** under conventional conditions (acetic anhydride and pyridine) afforded the 2'-acetate **46** as a non-crystalline product (98 %) (Scheme 2.25).



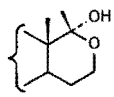
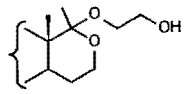
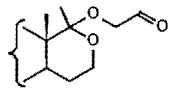
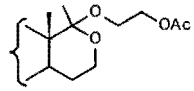
44 **46**

Reagents: i) Ac_2O, py

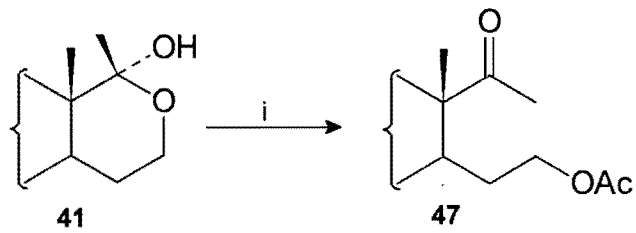
Scheme 2.25

The 2'-proton signals of **46** were shifted downfield (m, δ 4.28), relative to the 2'-hydroxy ketal **44**, as a result of the deshielding anisotropic influence of the acetoxy group. This 2'-H_2 signal was then correlated to the 1'-H_2 protons (m, δ 3.65), which showed no further coupling. The 16-H_2 protons were observed as a multiplet at δ 3.69. The relevant data for **41**, **44**, **45**, and **46** are tabulated in Table 2.1.

Table 2.1: NMR Data for **41**, **44**, **45**, and **46**.

Proton	 **41**	 **44**	 **45**	 **46**
16-H_2	(C_6D_6) δ 3.60, ddd, *J* 11.1, 5.1, and 1.4 Hz, 16β-H. δ 3.88, ddd, *J* 12.5, 11.5, and 3.7 Hz, 16α-H.	(C_6D_6) δ 3.65, 2H, m. ($CDCl_3$) δ 3.70 2H, m.	($CDCl_3$) δ 3.57 and δ 3.75, each 1H, m.	($CDCl_3$) δ 3.69, 2H, m.
1'-H_2	-	(C_6D_6) δ 3.37 and 3.46, each 1H, m. ($CDCl_3$) δ 3.80 2H, m.	($CDCl_3$) δ 4.06 and 4.13 each 1H, dd, *J* 17.9 and 1.2 Hz.	($CDCl_3$) δ 3.65, 2H, m.
2'-H_2	-	(C_6D_6) δ 3.60, 2H, t, *J* 2x4.8 Hz. ($CDCl_3$) δ 3.59 2H, t, *J* 2x4.5 Hz.	($CDCl_3$) 2'-H, δ 9.82, *J* 2x1.2 Hz.	($CDCl_3$) δ 4.28, 2H, m.

Since trapping of the carbonyl group of the hydroxy ketone **42** was unsuccessful, attempted trapping of the hydroxy group was investigated. Treatment of the cyclic hemiacetal **41** with acetic anhydride and pyridine failed to give any reaction, however, addition of a catalytic amount of 4,4-dimethylamino pyridine (DMAP) afforded the acetoxy ketone **47**, in a quantitative yield (Scheme 2.26).



41 **47**

Reagents: i) Ac_2O, py, DMAP

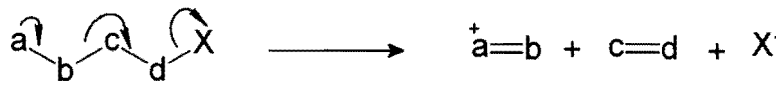
Scheme 2.26

The IR spectrum of the acetoxy ketone **47** gave absorption bands at ν_{max} 1694 and 1730 cm^{-1} for the carbonyl groups, and the mass spectrum gave the expected molecular ion. The 400 MHz ^{1}H-NMR spectrum showed methyl singlets at δ 2.04 and 2.21, which were assigned to the 13-acetyl and 16-acetate (cf the signal for the 13-acetyl of **21** at δ 2.18). The diastereotopic 16-protons were observed at δ 3.99 and 4.18, as a doublet of doublet of doublets (*J* 10.4, 9.2 and 7.1 Hz) and a triplet of doublets (*J* 2x10.4 and 5.3 Hz) respectively. The ^{13}C-NMR spectrum showed the C-16 carbonyl at δ 178.4 and the C-17a carbonyl at δ 178.6 (the C-16 and C-17a carbons were observed at δ 61.0 and 99.4 respectively, for the cyclic hemiacetal **41**).

The formation of the 16-protected derivative **47**, thus opens the way for modification at C-17a and hence, conversion of the 14-attached functionality into an enal moiety for investigation of conjugate alkylation.

2.2. FRAGMENTATION APPROACH TO 16,17-SECO COMPOUNDS

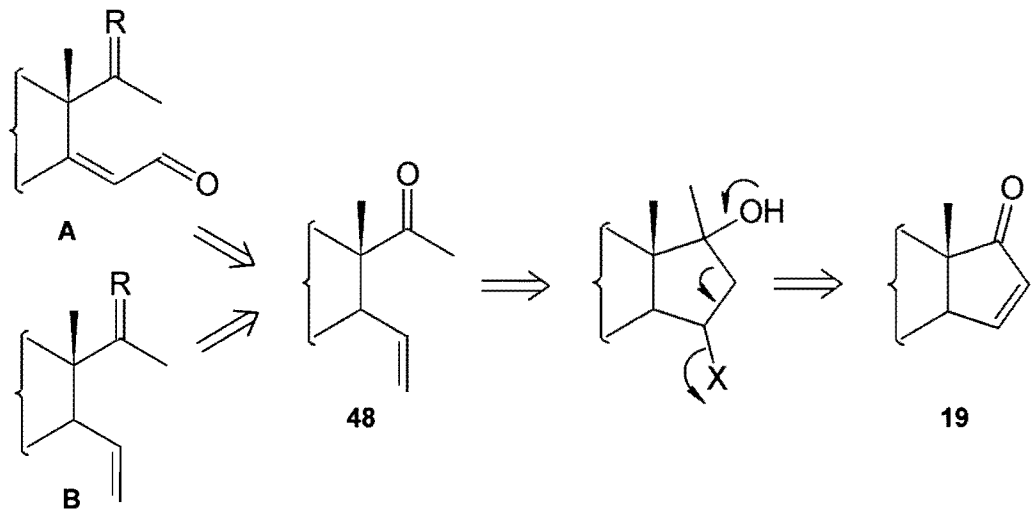
Grob and related fragmentations,[43] offer a alternative route to ring D fragmentation intermediates which may serve as precursors for stereoselective introduction of 14-functionalised alkyl groups into the steroid nucleus. The typical Grob fragmentation is a process in which the reacting part of the molecule breaks into three fragments. In the figure below, the a-b group is referred to as the electrofugal group, as it generally forms a stabilised cation, but can also be neutral depending on its initial charge. The c-d group is referred to as the middle group, and the X group as the nucleofugal group, since on fragmentation the d-X bond breaks and results in an X group with a bonding electron pair.



The scope, mechanism and stereochemistry of the reaction type described above was investigated extensively by Grob in the mid 1950s.[43,44] It was, however, the later work by Wharton[45] which demonstrated the great utility of 1,3-diol monosulfonates in fragmentations, resulting in the construction of functionalised medium-sized cycloalkenes. Wharton's work substantiated a mechanism which was largely dependent on the relative stereochemistry of the electrofugal, middle, and nucleofugal groups.[44,45] Thus, provided the compound can adopt a conformation where the nucleofuge (X) and the electrofuge (a-b) are antiperiplanar in relation to the c-d bond, a one-step synchronous fragmentation mechanism is possible.[45] When a substrate does not achieve or closely approximate the required stereochemical arrangement, direct displacement of the leaving group or elimination reactions can interfere.[45]

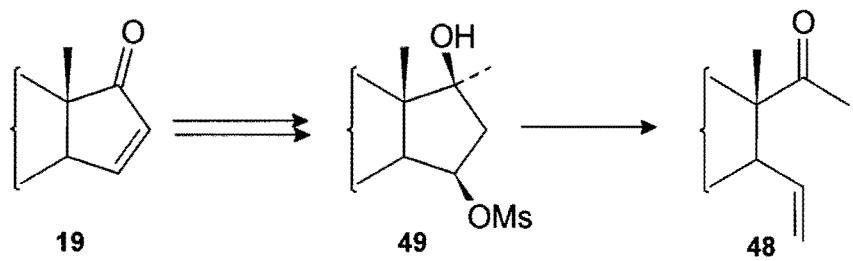
Fragmentation methodology was thus identified as a strategy for the introduction of key functionality into ring D. Accordingly, consideration in this study has been given to fragmentation of ring D into an intermediate amenable to stereoselective alkylation at C-14, followed by reassembly of ring D into the 14-functionalised compounds discussed previously. A retrosynthetic approach from hypothetical seco-compounds **A** and **B** is

outlined in Scheme 2.27, *via* functional group manipulation of the 16,17-seco Δ^{15} fragmentation intermediate **48**, synthesis of which from the Δ^{15} 17-ketone **19** could be envisaged through successive 15-functionalisation, 17-methylation, and Grob fragmentation.



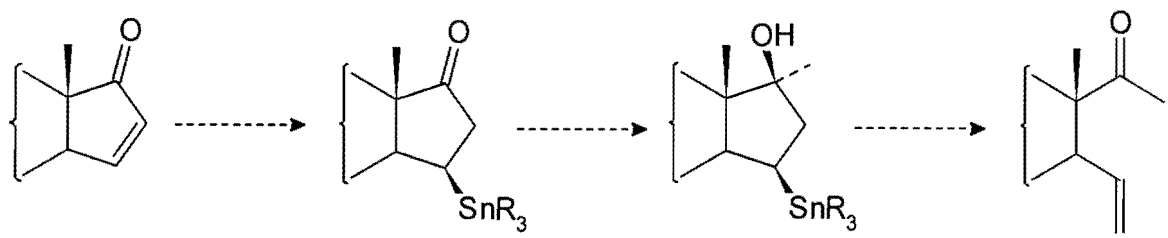
Scheme 2.27

Recent work conducted by de Koning,[46] has demonstrated the feasibility of fragmentation of the 3-methoxy-17α-methylestra-1,3,5(10)-triene-15β,17β-diol 15-methanesulfonate **49** (Scheme 2.28). The hydroxy mesylate is synthesised *via* conjugate benzyloxylation of the Δ^{15} 17-ketone **19**, followed by 17-methylation, debenzylation, and conversion of the 15-alcohol to the 15-mesylate. The overall yield for this sequence is however low.



Scheme 2.28

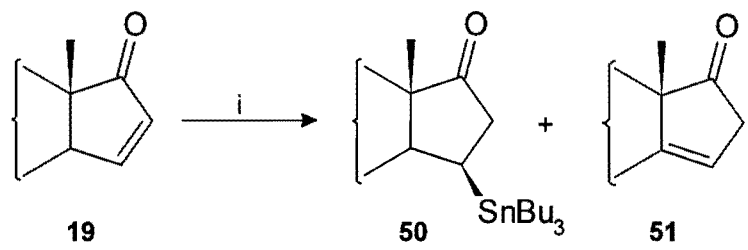
Most reported Grob fragmentations employ electron accepting groups as the leaving groups (anion induced fragmentation), but there are few reported examples which employ electron donating groups as the leaving groups (cation or radical induced fragmentation). An example of this kind is the oxidative cleavage of γ-stannyl alcohols, resulting from the generation of an oxygen centred radical. The direction of the β-fragmentation in unsymmetrical molecules is influenced by several factors. These include ring strain, stereoelectronic effects and the relative stability of the radical adduct. The observed fragmentation results from a combination of these factors, and hence the outcome is difficult to predict from analysis of the individual effects. With this in mind an investigation into the fragmentation of a 1,3-transposed stannyl alcohol was initiated, hopefully providing a more efficient fragmentation approach than that employing the 15β-mesylate.[52,53,54,55] The initial aim of this project was therefore to prepare a 15β-trialkylstannyl 17β-alcohol. The approach was to perform a conjugate stannylation on the Δ^{15} 17-ketone, whereupon methylation at C-17 would lead to a substrate for testing the feasibility of inducing alkoxy radical mediated fragmentation of ring D (Scheme 2.29).



Scheme 2.29

2.2.1. Synthesis and reactions of 3-methoxy-17α-methyl-15β-trimethylstannylestra-1,3,5(10)-trien-17β-ol

It is generally accepted that trialkylstannyllithium reagents, react with most α,β-unsaturated compounds *via* a 1,4-mode of addition. That this occurs similarly with hindered enones, at rapid rates, is probably due to the length (~2.2 Å) of the tin-carbon bond that is formed.[47] Initial attempts at introducing a stannyl group to the Δ^{15} 17-ketone involved conjugate tributylstannylation. Tributylstannyllithium was prepared by treating tributyltin hydride with n-butyllithium.[48] The reagent was then cooled to -78 °C, upon which the Δ^{15} 17-ketone **19** was added, to afford the desired 15β-tributylstannyl 17-ketone **50** (47 %), accompanied by the Δ^{14} 17-ketone **51** (45 %) (Scheme 2.30).



19 **50** **51**

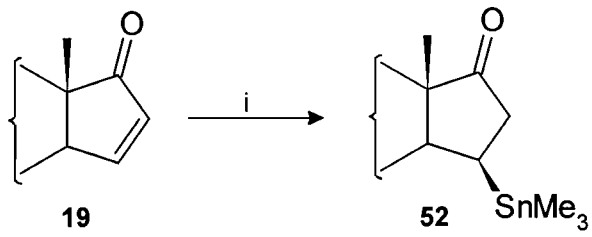
Reagents: i) Bu_3SnH, $LiN[CH(CH_3)]_2$

Scheme 2.30

The IR spectrum of the 15β-tributylstannyl 17-ketone **50** displayed an absorption band at ν_{max} 1729 cm^{-1} assigned to the carbonyl group, and the mass spectrum gave the expected molecular ion. The presence of the 15β-tributylstannyl group induced overlapping of signals in the ^{1}H-NMR spectrum, precluding full assignment. The Δ^{14} 17-ketone **51** was identified by comparison of its physical characteristics to those reported.[49]

Conjugate stannylation with the less hindered trimethylstannyl lithium was attempted. Trimethylstannyl lithium was prepared by treating trimethyltin chloride with freshly cut

lithium.[50] The reagent was then added to a solution of Δ^{15} 17-ketone **19** in tetrahydrofuran, at -78 °C, to afford the 15β-trimethylstannyl 17-ketone **52** in good yield (74 %) (Scheme 2.31). The 15β-trimethylstannyl 17-ketone **52** gave all the expected analytical and spectroscopic data.

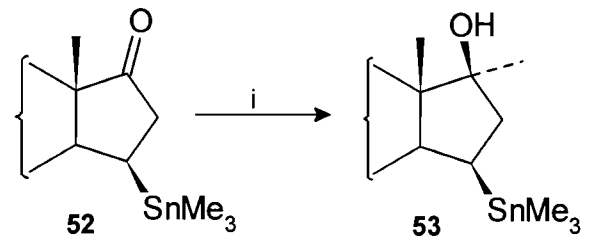


19 **52**

Reagents: i) Me_3SnCl, Li(s)

Scheme 2.31

Treatment of the stannyl ketone **52** with methyllithium in tetrahydrofuran, at -78 °C, resulted in partial reaction to give the corresponding 17α-methyl 17β-alcohol **53** (52 %) (Scheme 2.32). The product displayed all the expected analytical and spectroscopic properties.



52 **53**

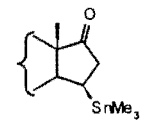
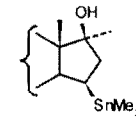
Reagents: i) MeLi, THF

Scheme 2.32

The failure of the reaction to go to completion is possibly the result of some competing enolization of the 17-oxo group. The problem of lack of reactivity of addition reactions to enolisable ketones is not uncommon, and the development of cerium reagents to promote these processes is well documented.[51]

Various attempts were thus made to optimise the yield of the transformation. In the second attempt anhydrous cerium trichloride was prepared, and solvated with tetrahydrofuran. The 15β-trimethylstannyl 17-ketone **52** was then added at 0 °C and left for an induction period, after which methyllithium was added dropwise, at -78 °C. The third method involved the slow addition of **52**, to a pre-generated solution of the dichloromethyl cerate, at -78 °C. The fourth attempt involved treatment of **52** with methylmagnesium iodide at elevated temperature. The results above are summarised in table (Table 2.2).

Table 2.2: Results of methylations of **52**.

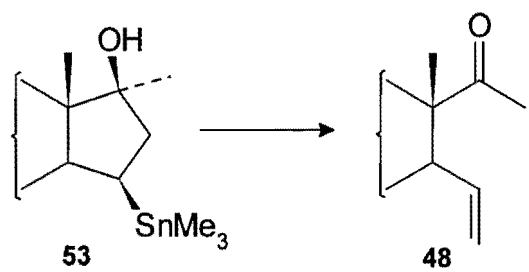
Entry	**Method**	 **52**	 **53**
1	MeLi / THF / -78 °C	41 %	52 %
2	$CeCl_3$ / THF / # / -78 °C / MeLi	36 %	58 %
3	$MeCeCl_2$ / # / THF / -78 °C	19 %	57 %
4	MeMgI / # / THF / Δ	47 %	22 %

Since the solvated anhydrous cerium trichloride method gave the best yield of **53** (58 %), and almost complete recovery of starting material **52** (36 %), it was used to prepare the γ-hydroxy stannane **52** for subsequent fragmentation studies.

In order that fragmentation may occur, the generation of an alkoxy radical is of key importance. Several methods for the generation of alkoxy radicals have been developed.[52] In this study the methods investigated have been those previously applied to fragmentations of γ-hydroxy stannanes. The first of these methods is the use of lead

tetraacetate to form the lead alkoxide, which is cleaved on heating or irradiation, to generate an alkoxy radical.[53] The second involves irradiation of the alcohol, in cyclohexane in the presence of (diacetoxyiodo)benzene (DAIB) and iodine, at 40 °C. Under these conditions, however, a possible interfering side reaction is the possible substitution of the trialkyltin group by iodine. This is a radical process that is inhibited by oxygen, and hence the method can be modified by bubbling a stream of oxygen through the reaction mixture.[54] The third involves the use of iodosylbenzene, boron trifluoride diethyl ether complex ($BF_3.OEt_2$), and dicyclohexylcarbodiimide.[55]

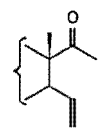
The γ-hydroxy stannane fragmentation was attempted under all the conditions mentioned above, and in all cases the reactions resulted in a complex mixture of products. However, for the lead tetraacetate and (diacetoxyiodo)benzene systems, the desired fragmentation product **48** was obtained in low yield, as the only isolable product (Scheme 2.33 and Table 2.3).



53 **48**

Scheme 2.33

Table 2.3: Results of attempted γ-hydroxy stannane **53** fragmentation.

Entry	Method	 **48**
1	$Pb(OAc)_4$ / C_6H_6 / Δ	5 %
2	DAIB / I_2 / C_6H_{12} / *hv* / O_2	23 %
3	$PhIO^-$ / $BF_3(OEt)_2$ / DCC / CH_2Cl_2	-

The IR spectrum of the fragmentation product **48** displayed a strong carbonyl group absorption band at ν_{max} 1693 cm^{-1}, and the mass spectrum showed the expected molecular ion. The deuteriochloroform ^{1}H-NMR spectrum showed a diagnostic signal for the acetal methyl group at δ 2.15, and the signal at δ 4.99 (dd, *J* 17.1 and 2.1 Hz) was assigned to the 16-H_E proton, based on the 16.7 Hz coupling to 15-H, as expected for *trans*-related olefinic protons,[56] and the geminal coupling of 2.1 Hz to the 16-H_Z proton. The signal at δ 5.08 (dd, *J* 10.2 and 2.1 Hz) was assigned to the 16-H_Z proton, based on the 10.2 Hz coupling to 15-H, as expected for *cis*-related olefinic protons,[56] and the geminal coupling of 2.1 Hz to the 16H_E proton. The signal at δ 5.52 (dt, *J* 17.1 and 10.2 Hz) was assigned to 15-H proton in accordance with the couplings mentioned above, along with an equivalent coupling of 10.2 Hz to 14α-H (Figure 2.4.). A 400 MHz deuteriobenzene ^{1}H-NMR spectrum was also recorded, and a downfield shift of the 14α-H was observed to δ 2.24 (t, *J* 10.4 Hz), confirming the equivalent coupling of 14α-H and 16-H_Z to 15-H. A crosspeak in the the 400 MHz deuteriobenzene COSY spectrum verified the coupling of 15-H to 14α-H.

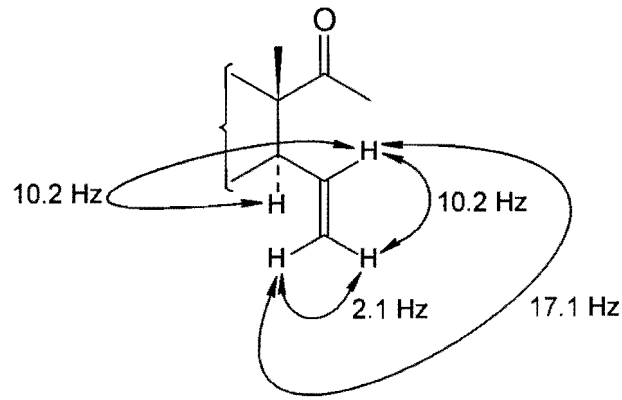


Figure 2.5: Coupling constants ($CDCl_3$) of the fragmentation product **48**.

The poor yield of the fragmentation product **48** suggests that the fragmentation does not proceed *via* a synchronous pathway, involving both the alkoxy radical and the 15-stannyl group, but rather *via* a stepwise procedure in which the described reaction course is a minor pathway (Figure 2.6).

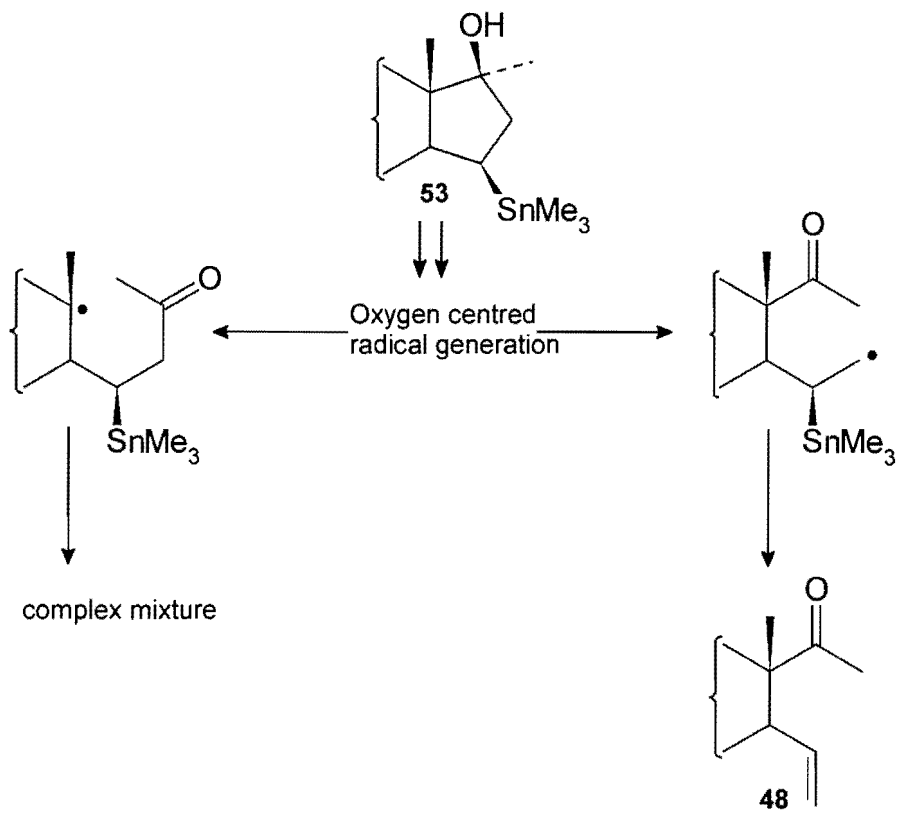
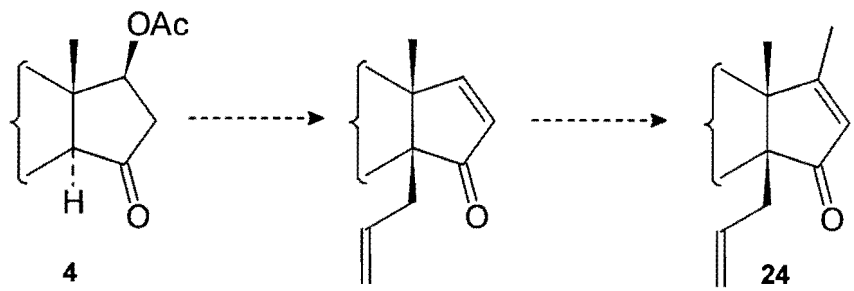


Figure 2.6: Diagram of proposed routes.

In an attempt to overcome the difficulties, an alternative fragmentation approach based on silicon-directed Beckmann fragmentation of a β-silyl oxime acetate,[58] was investigated.

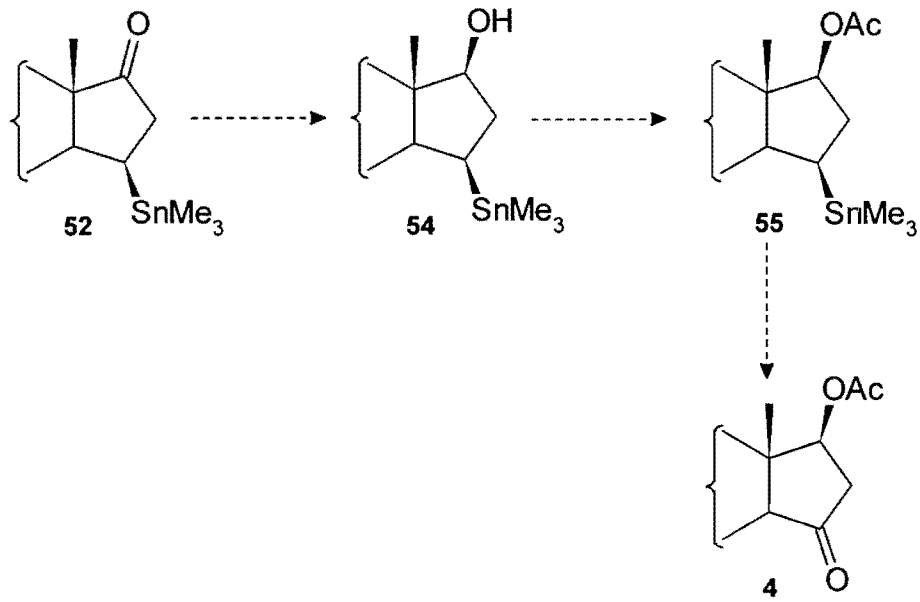
2.2.2 Attempted novel synthesis of 3-methoxy-17β-acetoxyestra-1,3,5(10)-trien-15-ketone.

The stereoselective introduction of 14-alkyl groups onto the steroid skeleton, by base mediated alkylation of 15-ketones, was previously discussed. It is exemplified by efficient 14β-methylation of the 17-acetoxy 15-ketone **4**.[15] The 17β-acetoxy 15-ketone **4** is thus a suitable candidate for 14β-allylation. Subsequent to 14β-allylation, it is possible that conjugate methylation followed by regeneration of the enone functionality would provide access to the 14β-allyl 17-methyl Δ^{16} precursor **24** discussed previously (Scheme 2.34).



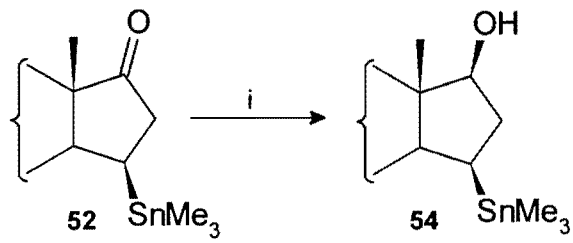
Scheme 2.34

The ready availability of 15β-trimethylstannyl 17-ketone **52** in this work, suggested a novel alternative synthesis of the 17-acetoxy 15-ketone **4**. Reports of the oxidation of secondary alkylstannanes to carbonyl compounds,[47] with Collins reagent, prompted a synthesis of the 17β-acetoxy 15β-trimethylstannyl precursor **55**, for attempted oxidation to the 17β-acetoxy 15-ketone **4** (Scheme 2.35).



Scheme 2.35

Thus, the 15β-trimethylstannyl 17-ketone **52** was treated with sodium borohydride in methanol and tetrahydrofuran, to afford the 15β-trimethylstannyl 17β-alcohol **54**, in excellent yield (98 %) (Scheme 2.36).



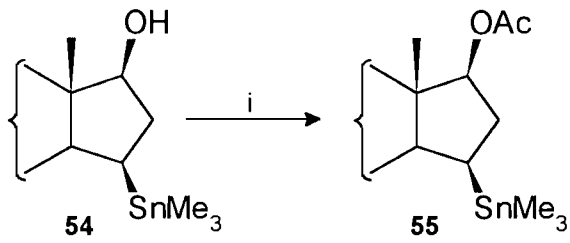
Reagents: i) $NaBH_4$

Scheme 2.36

The IR spectrum of the 15β-trimethylstannyl 17β-alcohol **54** showed an absorption band at ν_{max} 3612 cm^{-1} for the 17β-hydroxy group, and the mass spectrum gave the expected molecular ion. The 400 MHz ^{1}H-NMR spectrum showed the 15β-trimethyl stannyl group as a singlet at δ 0.1. The 17α-proton was observed at δ 3.77, as a doublet of doublets, with

coupling constants of 10.5 and 6.6 Hz. The coupling constant of 10.5 Hz being assigned to the 16α-proton, and that of 6.6 Hz being assigned to the 16β-proton.

Treatment of the γ-hydroxy stannane **54** with acetic anhydride and pyridine, gave the 17β-acetoxy precursor **55**, in good yield (93 %) (Scheme 2.37)



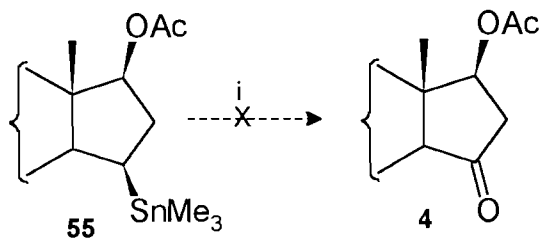
54 **55**

Reagents: i) Ac_2O, Py

Scheme 2.37

The 400 MHz ^{1}H-NMR spectrum of **55** showed the 15β-trimethylstannyl group as a singlet at δ 0.12, and the diagnostic acetate methyl singlet at δ 2.07. Due to the anisotropic deshielding effect of the 17β-acetoxy group, the 16β-proton was observed at δ 2.53 (ddd, *J* 13.7, 10.4, and 8.7 Hz). The 13.7 Hz coupling was ascribed to the geminal 16α-H, the 10.4 Hz coupling to the vicinal 15α-H, and the 8.7 Hz coupling to the vicinal 17α-H. The 17α-proton was observed at δ 4.75 (t, *J* 8.7 Hz), and assigned on the basis of equivalent coupling to the vicinal 16-protons.

All attempts to oxidise the 17β-acetoxy 15β-trimethylstannyl precursor **55**, according to a literature procedure, using the Collins reagent, failed to give any reaction (Scheme 2.38)



55 **4**

Reagents: i) $CrO_3 .2C_5H_5N$

Scheme 2.38

Since there were no other literature procedures for alkyl stannane oxidation,[47,59,60] a Jones oxidation (CrO_3-H_2SO_4) was also attempted, however no reaction was observed. It was speculated that steric hindrance might prevent the approach of the chromium reagent for oxidative cleavage of the C-Sn bond.

2.2.3 Attempted silicon-directed Beckmann-type fragmentation

The Beckmann rearrangement is well known, and has been the subject of frequent review.[61] The rearrangement involves nitrogen insertion into carbonyl carbon-α-carbon bonds of aldehydes and ketones *via* rearrangement of the derived oximes. Before discussing the silicon-directed Beckmann fragmentation, an analysis of the stereoselectivity of the Beckmann rearrangement is given. The generally accepted mechanism for Beckmann rearrangement (Figure 2.7) is the rendering of the hydroxy group of the oxime more nucleofugal by protonation or esterification. The subsequent migration of the group *anti* to the leaving group on nitrogen predominates. However, the tendency for oxime isomerization to occur under certain reaction conditions, and the differing migratory aptitudes of oxime substituents are such that this 'rule' should be used with caution.

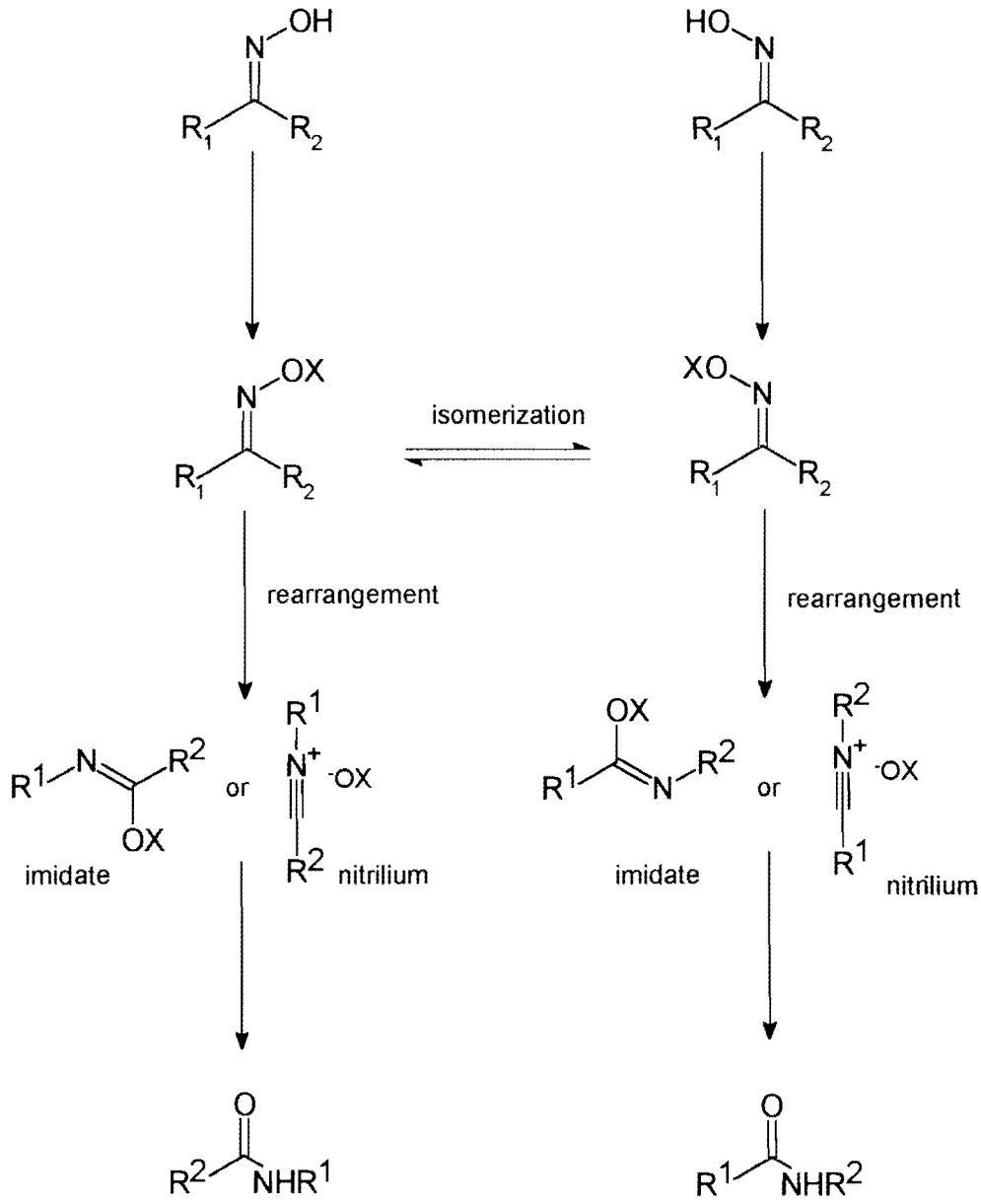
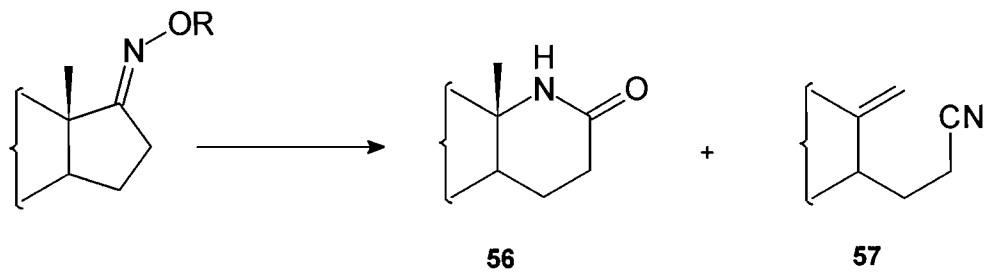


Figure 2.7: Reaction pathway in the Beckmann rearrangement.[61]

The fragmentation of the α-carbon-carbon bond, may compete and override the rearrangement process above, when there is assistance from a neighbouring centre.[61] For the silicon-directed Beckmann fragmentation this assistance is provided in the form of the β-effect of a trimethylsilyl centre. Beckmann reactions carried out on 17-keto steroids,

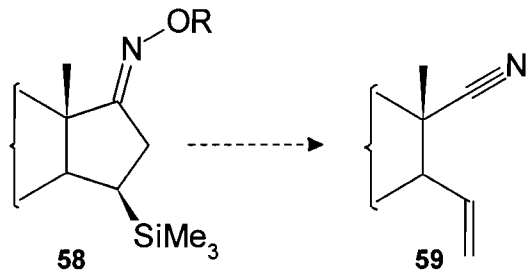
give rise to the lactam **56**, and an 'abnormal' Beckmann carbonitrile **57** (see Scheme 2.39).[62]



56 **57**

Scheme 2.39

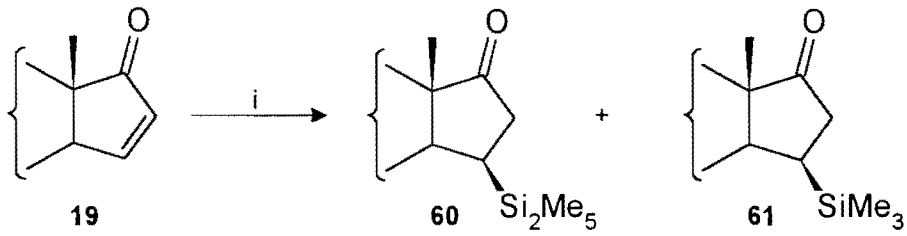
With this in mind it was reasoned that a 15β-trimethylsilyl oxime **58** could possibly undergo silicon assisted fragmentation to a desired fragmentation product **59** (Scheme 2.40).



58 **59**

Scheme 2.40

For conjugate addition, trimethylsilyl lithium was prepared by adding methyllithium dropwise to a solution of hexamethyldisilane and HMPA at 0 °C. After stirring for 30 min tetrahydrofuran was added, and the solution was cooled to -78 °C.[63] The Δ^{15} 17-ketone **19** was then added at -78 °C. After 45 min, at -78 °C, the reaction was complete, and the product mixture was chromatographed to give an unexpected 15β-pentamethyldisilyl 17-ketone **60** (40 %), followed by 15β-trimethylsilyl 17-ketone **61** (30 %) (Scheme 2.41).



Reagents: i) HMPA, Me_6Si_2, MeLi

Scheme 2.41

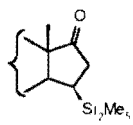
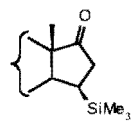
The IR spectrum of the pentamethyldisilyl ketone **60**, gave an absorption band at ν_{max} 1728 cm^{-1} for the carbonyl group, and mass spectrum gave the expected molecular ion. The 400 MHz ^{1}H-NMR spectrum showed the presence of two diastereotopic methyl singlets, and a singlet for the trimethylsilyl group. The spectrum was, however, complicated by the presence of an ABX multiplet for the 16-H_2 protons at δ 2.42-2.48. It is well known that non first order ABX systems are obtained when the chemical shift difference between the A-B part is small, and only the B part couples significantly to the X part.[56]

Due to the complicated splitting, the configuration at C-15 was determined by irradiation of the 13β-Me in an nOe experiment. The β-configuration at C-15 was confirmed in accordance with the literature precedence discussed earlier, and the proposed structure of **60** was further supported by correlation spectra (COSY) and heteronuclear correlation spectra (HETCOR).

The 15β-trimethylsilyl 17-ketone **61**, gave the expected IR and mass spectral data. The 400 MHz ^{1}H-NMR spectrum showed a diagnostic singlet for the trimethylsilyl group, and the signal at δ 1.77 (ddd, *J* 10.1, 8.1, and 3.2 Hz) was assigned to the 15α-H. The small coupling of 3.2 Hz was assigned to the vicinal 16β-H, the coupling of 8.1 Hz to the vicinal 14α-H, and the large coupling of 10.1 Hz to 16α-H. Hence, the signal at δ 2.43 (dd, J 19.7 and 10.1 Hz) was assigned to the 16α-H, with the coupling of 19.7 Hz being assigned to

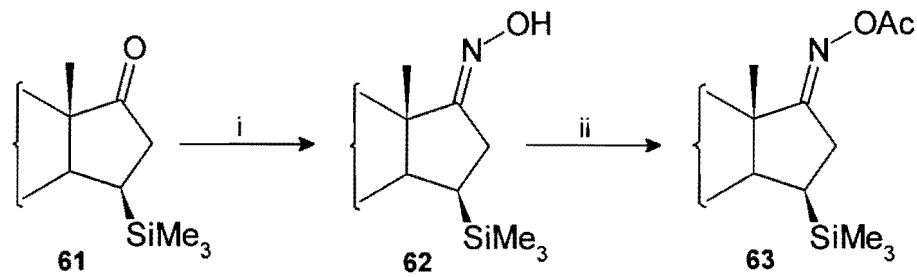
the geminal 16β-H, which resonated at δ 2.52 (dd, J 19.7 and 3.2). The relevant data for **60**, and **61** are tabulated in Table 2.4.

Table 2.4: NMR data for **60** and **61**.

Proton	 **60**	 **61**
14α-H	δ 1.91-2.04, obscured.	δ 1.98, obs. dd, *J* 11.0 and 8.1 Hz.
15α-H	δ 1.91-2.04, obscured.	δ 1.77, ddd, *J* 10.1, 8.1 and 3.2 Hz.
16α-H	δ 2.42-2.48, m.	δ 2.43, dd, *J* 19.7 and 10.1 Hz.
16β-H	δ 2.42-2.48, m.	δ 2.52, dd, *J* 19.7 and 3.2 Hz.

In a survey of the literature, it was discovered that formation of lithium pentamethyldisilane occurs during large scale preparation from hexamethyldisilane.[64,65] Hudrlik *et al* developed a modified procedure to overcome this problem on large scale preparation.[65] This modified procedure entails adding the methyllithium to a solid mixture of hexamethyldisilane and HMPA in a dry ice-acetone bath. Tetrahydrofuran is then added to this mixture in small portions, and the solid mixture is allowed to melt by raising the temperature with an ice bath. The resultant mixture is stirred for 15 min at 0 °C, and thereafter cooled to -78 °C. When the procedure was adopted, the reaction with the Δ^{15} 17-ketone **19**, gave the 15β-trimethylsilyl 17-ketone **61** in a good yield (75 %).

The 15β-trimethylsilyl ketone **61** was treated with hydroxylamine hydrochloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), to afford the 17-oxime **62** (99 %), which was acetylated under standard conditions (acetic anhydride and pyridine), to afford the corresponding oxime acetate **63** (90 %) (Scheme 2.42).

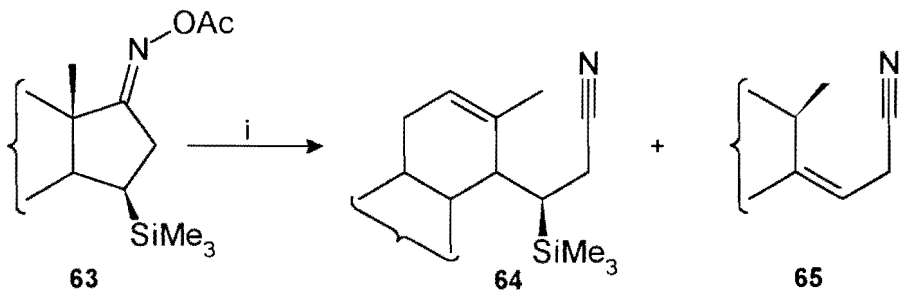


Reagents: i) DABCO, $HONH_2.HCl$ ii) Ac_2O, Py

Scheme 2.42

The oxime acetate **63** gave an adsorption band at ν_{max} 1751 cm^{-1} for the carbonyl group, and the expected molecular ion. The spectroscopic data were consistent with the proposed structure.

Reagents chosen for the attempted silicon directed Beckmann fragmentation were the reported trimethylsilyl trifluoromethanesulfonate (TMSOTf) and the boron trifluoride diethyl ether complex ($BF_3.OEt_2$).[58] Treatment of the 15β-trimethylsilyl oxime acetate **63** with TMSOTf in dichloromethane, at 0 °C, gave a complex reaction mixture, separation of which afforded only two characterizable compounds. The compounds were identified as the Δ^{12}- **64** (8 %) and the Δ^{14}-13,17-seconitriles **65** (12 %), on the basis of analytical and spectroscopic data (Scheme 2.43).



63 **64** **65**

Reagents: i) TMSOTf

Scheme 2.43

The Δ^{12}-13,17-seconitrile **64** gave an absorption band at ν_{max} 2252 cm^{-1} for the cyano group, and the mass spectrum gave the expected molecular ion. The 200 MHz ^{1}H-NMR spectrum showed a singlet for the trimethylsilyl group, a vinylic methyl group at δ 1.74, and a broad doublet for the olefinic proton at C-12.

The Δ^{14}-13,17-seconitrile **65** gave the expected IR and mass spectral data. The 400 MHz ^{1}H-NMR spectrum showed a signal at δ 1.13 (d, *J* 7.2 Hz) for the 13β-methyl group, and a signal at δ 2.94 (m) for the 13α-H. The signal at δ 3.15 (dd, 7.0 and 1.4 Hz) was assigned to the 16-H_2 diastereotopic protons, with the coupling of 7.0 Hz being assigned to 15-H, and the coupling of 1.4 Hz to 8β-H. This 1.4 Hz coupling is known as a 'homo-allylic' or five bond coupling. Although rare, homo-allylic 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*. 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.[66] Analysis of molecular models reveals the possible orthogonality of the 8β-H and 16-H_2 protons (Figure 2.8) The signal at δ 5.12 (td, J 2x7.0 and 1.8 Hz) was assigned to the olefinic 15-proton. Structure assignment for **65** was further supported by COSY and HETCOR spectra.

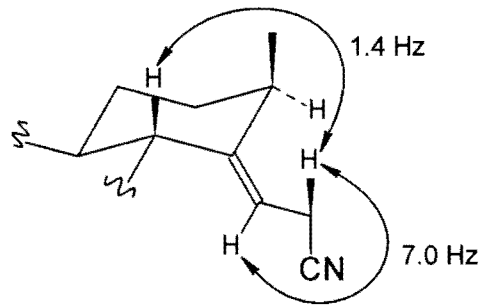
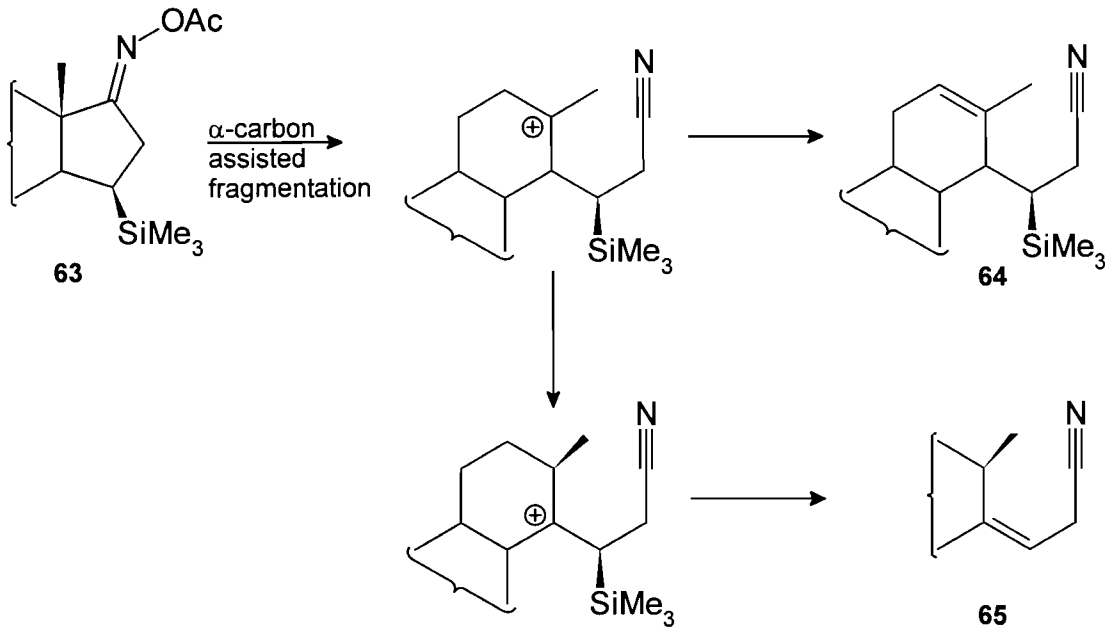


Figure 2.8 Coupling constants of the Δ^{14}-13,17-seconitrile **65**.

Treatment of the oxime acetate **63** with $BF_3.OEt_2$, at 0 °C, gave a cleaner reaction, with the Δ^{14}-13,17-seconitrile **65** as the major product (30 %), together with uncharacterised residues. Since the desired fragmentation product was not obtained above, no attempt was made to improve the yields.

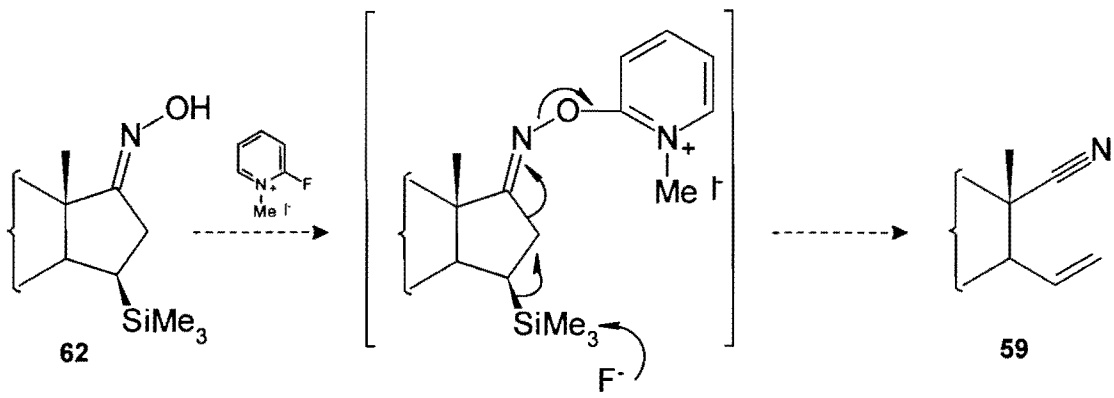
In rationalising the reactions, it was concluded that there is no silicon participation in the initial α-bond cleavage, and that conventional carbon-assisted fragmentation proceeds,[61] leading to a positive charge on the more substituted C-13 centre. The resultant intermediate then gives rise to the Δ^{12}-13,17-seconitrile **64** by proton abstraction or the Δ^{14}-13,17-seconitrile **65** by a 1,2-hydride shift followed by β-desilylation (Scheme 2.44).



Scheme 2.44

In retrospect, failure of the desired fragmentation can be attributed to one or a combination of the following factors. A body of evidence suggests that the geometry of the oxime is important, as the group *anti* to the hydroxy group has the greater migratory aptitude.[61] Secondly, for the β-effect to facilitate fragmentation, development of a β p-orbital is neccesary;[63] along with a *trans* anti-parallel arrangement of the breaking bonds.[45] Thirdly, the nature of the α-carbon must be such that stabilisation of charge is on the α-carbon favouring cleavage to the desired fragmentation product.[61]

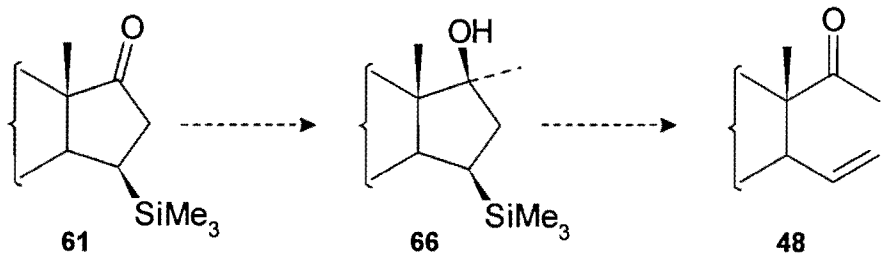
With the above in mind, an attempt was made to induce a fluoride ion anionic-heterolysis, using the N-methyl-2-fluoropyridinium salt, as reported in simpler systems.[67] (Scheme 2.45).



Scheme 2.45

Treatment of the 15β-trimethylsilyl oxime **62**, with the N-methyl-2-fluoropyridinium salt;[68] however, gave rise to a complex mixture of uncharacterised products.

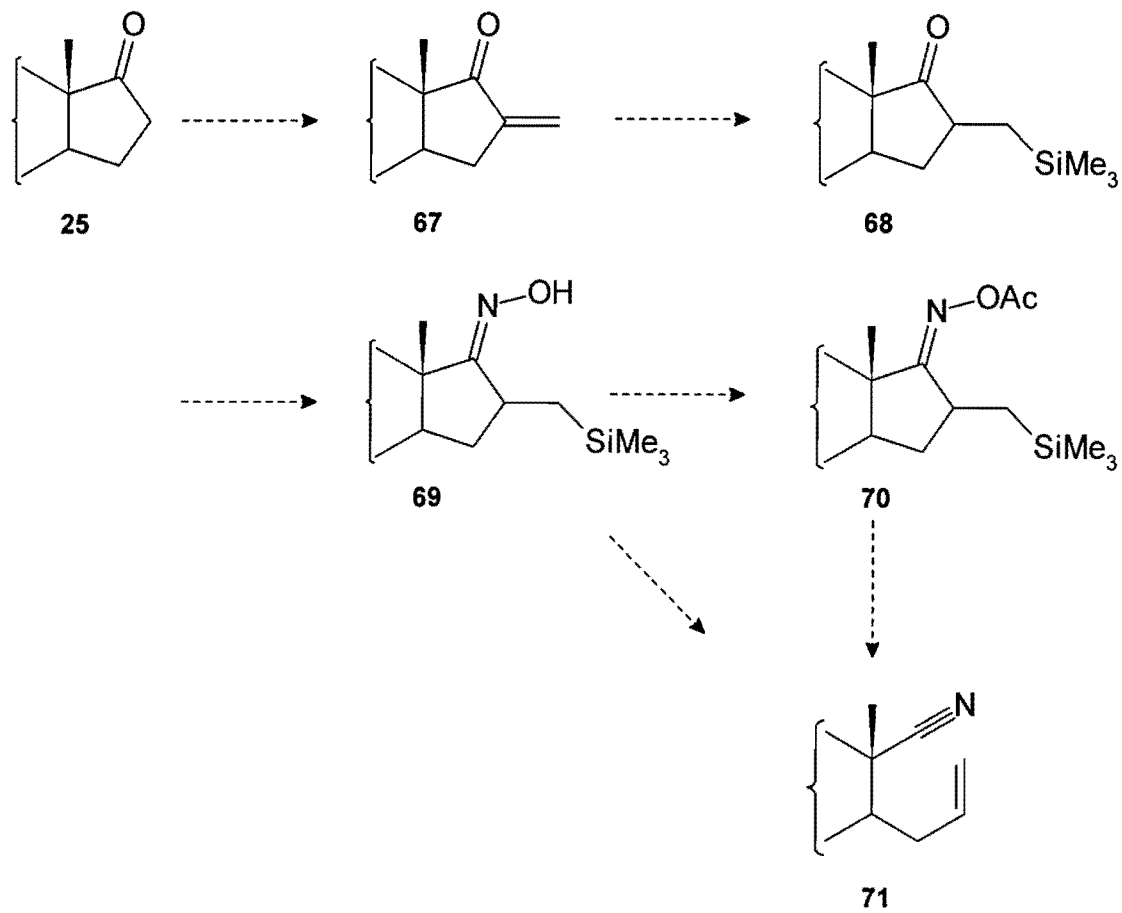
Reports of the oxidative fragmentation of γ-hydroxy silanes with ceric ammonium nitrate (CAN),[69] prompted an investigation into attempted fragmentation of a steroid analogue **66** (Scheme 2.46).



Scheme 2.46

The 15β-trimethylsilyl 17-ketone **61** was treated with methyllithium in tetrahydrofuran, at -78 °C to give resultant alcohol **66** (37 %), with recovery of starting material **61** (37 %). Treatment of the alcohol **66** with CAN, however, resulted in a complex mixture of unidentified products. Thus, it appears that the reaction outcome is analogous to that of the stannyl fragmentation (see discussion above).

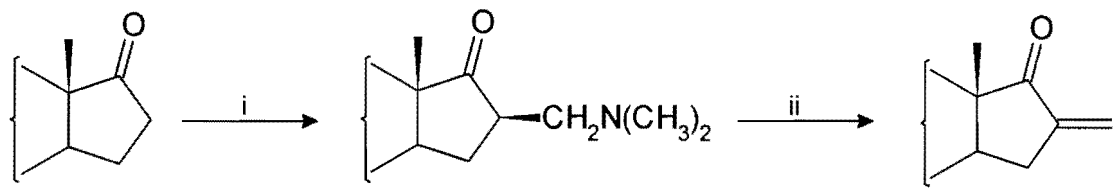
Since there was a lack of control in the fragmentation above, an alternative synthetic route more amenable to silicon directed Beckmann fragmentation was investigated (Scheme 2.47). This involves 16-methylenation, conjugate silylation, oxime acetate formation, followed by attempted fragmentation to the desired fragmentation product **71**. The silyl oxime **69** and oxime acetate **70** should be more amenable to fragmentation since there would be free rotation of the exocyclic silyl group, allowing a *trans* anti parallel arrangement of the breaking bonds. Furthermore, the α-carbon (C-16) is more amenable to the stabilisation and thus development of a positive cationic p-orbital, necessary for the β-effect.



25 **67** **68** **69** **70** **71**

Scheme 2.47

The synthesis of steroidal 16-methylene 17-ketones is well known.[70] Hence, treatment of estrone 3-methyl ether **25** with freshly prepared dimethylmethyleneimmonium chloride gave rise to the crude Mannich base, which was subsequently treated with acetic anhydride to afford the methylene ketone **67**, in high yield (99%) (see Scheme 2.48)

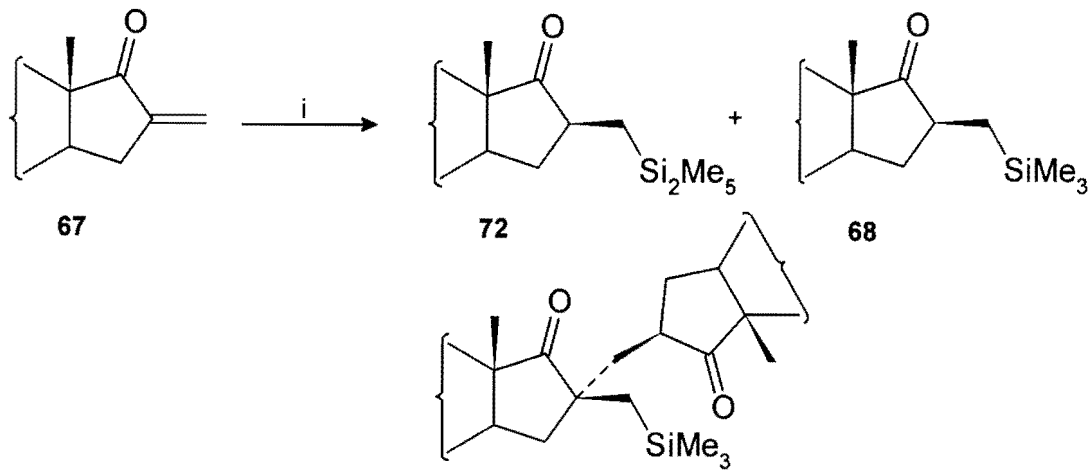


25 **67**

Reagents: (i) CH_3COCl, $[(CH_3)_2N]_2CH_2$ (ii) Ac_2O

Scheme 2.48

Since the conjugate silylation was conducted at the same time as that for Δ^{15} 17-ketone **19**, the analogous problem of lithium pentamethyldisilane formation was encountered. Treatment of the methylene ketone **67** under these conditions led to formation of the pentamethyldisilylmethyl 17-ketone **72** (10 %), the trimethylsilylmethyl 17-ketone **68** (40 %), and a bis-steroid **73** (9 %) (see Scheme 2.49).



67 **72** **68**

73

Reagents: i) HMPA, Me_6Si_2, MeLi

Scheme 2.49

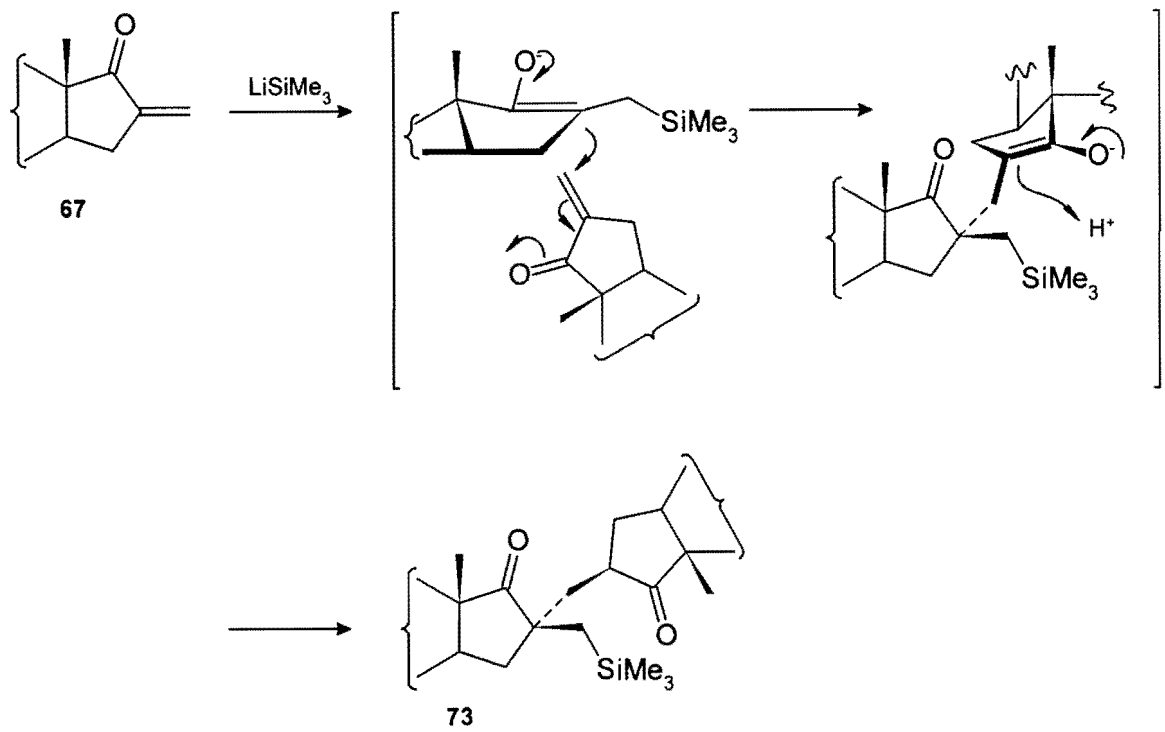
The IR spectrum of the pentamethyldisilylmethyl ketone **72** gave an absorption band at ν_{max} 1734 cm^{-1} for the carbonyl group, and the mass spectrum gave the expected molecular ion. The 400 MHz ^{1}H-NMR spectrum showed the presence of two diastereotopic silylmethyl singlets, and a singlet for the trimethylsilyl group. The diastereotopic 16^1-protons resonated at δ 0.56 (dd, *J* 14.6 and 11.7 Hz) and 1.39 (dd, *J* 14.7 and 3.5 Hz), with the coupling of 14.6 Hz attributable to geminal coupling, and the couplings of 11.7 and 3.5 Hz attributable to the vicinal couplings to 16α-H. The stereochemistry at C-16 was tentatively assigned as 16β-pentamethyldisilylmethyl. This is based on the kinetic protonation of the intermediate enolate from the α-face, due to steric hindrance imposed on the β-face.

The trimethylsilylmethyl ketone **68**, gave the expected IR and mass spectral data. The 400 MHz ^{1}H-NMR spectrum showed the presence of a singlet for the trimethylsilyl group, with the diastereotopic 16^1-protons resonating at δ 0.50 (dd, *J* 14.7 and 11.95 Hz) and 1.30 (dd, *J* 14.7 and 3.4).

The IR spectrum of the bis-steroid **73** gave an intense absorption band at ν_{max} 1736 cm^{-1} for the carbonyl groups, and the mass spectrum gave the expected molecular ion. The diagnostic signals of the 400 MHz ^{1}H-NMR, were the doublets for diastereotopic 16^1-protons. These doublets resonated at δ 0.94 and 1.18, with a geminal coupling of 14.8 Hz. The trimethylsilyl and 13β-methyl groups were observed as there respective singlets, with the appropriate integration. The remaining signals were observed as multiplets, due to their overlapping. The 50 MHz ^{13}C-NMR confirmed the presence of two quaternary carbonyl carbons.

The stereochemistries of the respective centres formed were tentatively assigned on the basis of α-approach of the enone to the intermediate enolate. Thus, formation of the bis-steroid **73** is attributed to conjugate addition to a 16-methylene 17-ketone, by a pregenerated enolate, from conjugate addition of lithium trimethylsilane (Scheme 2.50).

Formation of the bis-steroid **73** is not completely surprising, since dimerizations of steroids have been reported.[30,39]



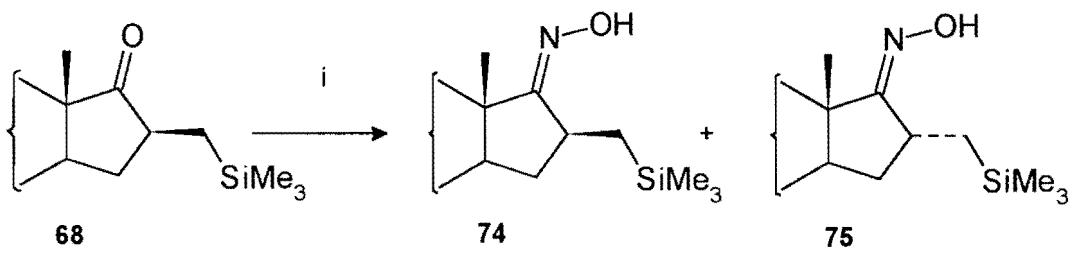
67 73

Scheme 2.50

The modified procedure developed by Hudrlik et al (discussed previously) was used to prepare lithium trimethylsilane.[65] As before, the problem was overcome to give the trimethylsilylmethyl ketone **68** (40 %), however formation of the *bis*-steroid **73** (20 %) still occurred. The bis-steroid **73** formation is presumably concentration dependent, however no attempt was made to exclude it.

The trimethylsilylmethyl ketone **68** was then treated with hydroxylamine hydrochloride and sodium acetate to afford a separable mixture of the 16β-trimethylsilylmethyl 17-oxime **74** (62 %) and the 16α-trimethylsilylmethyl 17-oxime **75** (38 %) (Scheme 2.51). However,

treatment of **68** with hydroxylamine hydrochloride and 1,4-diazabicyclo[2.2.2]octane under reflux conditions, gave rise to the 16α-epimer **75** as the major product (72 %).



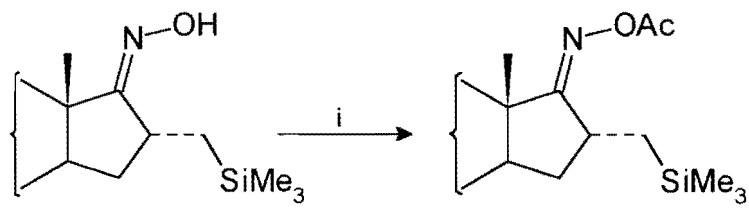
68 **74** **75**

Reagents: i) NaOAc, $HONH_2.HCl$

Scheme 2.51

The 16β-epimer **74** gave the expected molecular ion, and a 400 MHz ^{1}H-NMR spectrum with the characteristic doublet of doublets for the 16^1-protons. The D_2O exchangeable oxime hydroxy proton was also observed. The IR spectrum of the 16α-epimer **75** gave adsorption bands at ν_{max} 3288 and 3587cm^{-1} for the hydroxy group, and the mass spectrum gave the expected molecular ion. The 400 MHz ^{1}H-NMR spectrum similarly gave the characteristic doublet of doublets for the 16^1-protons, along with the D_2O exchangeable oxime hydroxy proton.

Acetylation of the 16α-trimethylsilylmethyl 17-oxime **75** under standard conditions (acetic anhydride and pyridine) afforded the oxime acetate **76**, in good yield (90 %) (Scheme 2.52).



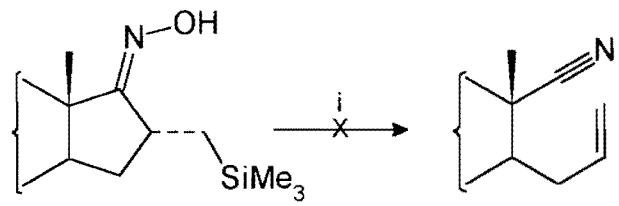
75 **76**

Reagents: i) Ac_2O, Py

Scheme 2.52

The acetate **76** gave all the expected analytical and spectral data.

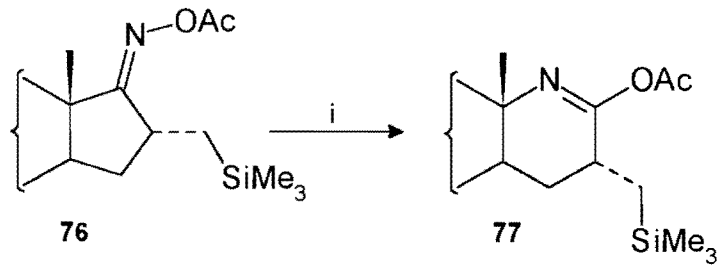
A fluoride ion anionic-heterolysis of the 16α-trimethylsilylmethyl oxime **75** was attempted, using the N-methyl-2-fluoropyridinium salt (discussed previously). However, the reaction once again gave a complex mixture of unidentifiable products (Scheme 2.53).



Reagents: i) N-Methyl-2-fluoropyridinium iodine sa

Scheme 2.53

In light of the result above, $BF_3.OEt_2$ catalysed fragmentation was attempted. However, treatment of the 16α-trimethylsilylmethyl oxime acetate **76** with $BF_3.OEt_2$ at 0 °C resulted only in formation of the O-acetyl amide 77 (52 %) (Scheme 2.54).



Reagents: i) $BF_3.OEt_2$

Scheme 2.54

The 400 MHz 1H-NMR spectrum showed the presence of a trimethylsilyl singlet at δ 0.08, and a acetate methyl singlet at δ 2.30. The 16^1-protons gave the characteristic

doublets of doublets. The 100 MHz ^{13}C-NMR spectrum gave a diagnostic signal at δ 178.6 for the C-17 carbon.

The O-acetyl amide **77** is the outcome of a Beckmann rearrangement (as discussed earlier), with capture of the acetate. In rationalising why the desired fragmentation did not occur with the modified substrate, it was concluded that the geometry of the oxime cannot be ignored. It would also appear that the C-16 centre is still unable to accommodate sufficient positive character, and as a result there is overriding stabilisation by the C-13 centre.

In conclusion, this study has succeeded in developing practical synthetic methods for conjugate stannylation and silylation of steroidal ring D enones, and has demonstrated the impracticality of exploiting derived 15,17-functionality to achieve C(16)-C(17) bond fragmentation.

3. EXPERIMENTAL

Melting points were measured using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using chloroform solutions unless otherwise specified, and are recorde in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in chloroform solutions using a Perkin-Elmer 983 infrared spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectrometer, over the range 4000-800 cm^{-1}. Microanalyses were determined using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV and a variable source temperature (depending on the nature of the compound). Accurate masses were determined on a VG-70E spectrometer at the Cape Technikon. All ^{1}H-NMR spectra were recorded unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian VXR-200 (200 MHz) or a Varian Unity Spectrometer (400 MHz). ^{13}C-NMR spectra were recorde on the same instruments at 50 or 100 MHz (using tetramethylsilane as an internal standard).

Thin layer chromatography was preformed on aluminium backed silica gel 60 F_{254} plates in a variety of solvent systems using the ascending technique. The plates were visualised by spraying with cerium(IV) ammonium sulfate in 8 mol dm^{-3} sulfuric acid and backing at 200 °C. Column chromatography was conducted with Merck Kieselgel 60: 70-230 mesh for gravity and 230-400 mesh for flash chromatographyy.

All solvents used were dried by the appropriate technique[71] and unless otherwise specified, all reactions were carried out under a nitrogen or argon atmosphere with exclusion of water and oxygen.

3-Methoxy-17α-methylestra-1,3,5(10),15-tetraen-17β-ol 26

Ethereal methyllithium (1.6 M, 4.2 cm^3) was added dropwise to a solution of the Δ^{15} 17-ketone **19** (300 mg, 1.12 mmol) in dry tetrahydrofuran (12 cm^3), at -78 °C. The reaction mixture was stirred for 3 h at -78 °C, after which saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give the Δ^{15} 17-alcohol **2** (314 mg, 99 %), m.p. 105-107 °C (from methanol), $[\alpha]_D$ -60° (*c* 1.0); [lit.[23] m.p. 108.6-109.6 °C (from methanol); $[\alpha]_D$ -65°].

3-Methoxy-17-methylestra-1,3,5(10),16-tetraen-15-one 23

a) Pyridinium chlorochromate (5.6 g, 26.16 mmol) was added to a mixture of basic alumina (30 g) in dry acetone, and stirred for 10 min, under nitrogen. The acetone was then evaporated under reduced pressure, and the reagent added to a solution of the Δ^{15} 17-alcohol **26** (1.6 g, 5.6 mmol) in dichloromethane (110 cm^3). The mixture was then stirred for 5 h at room temperature, and then filtered through alumina (100g) under reduced pressure, using chloroform as the eluent. Evaporation of the solvent under reduced pressure gave a brown crystalline residue (1.7 g). The residue was chromatographed on silica gel (200 g) using chloroform-toluene (2:3) as the eluent to afford the 3-*methoxy*-17-*methylestra*-1,3,5(10),16-*tetraen*-15-*one* **23** (1.3 g, 79 %), m.p. 146-147 °C (from chloroform-methanol), $[\alpha]_D$ +336° (*c* 1.0); ν_{max} 1702 (CO) cm^{-1}; δ_H (200 MHz) 1.06 (3H, s, 13β-Me), 2.06 (3H, d, *J* 1.3 Hz, 17-Me), 2.14 (1H, d, *J* 11 Hz, 14α-H), 2.92 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.68 (1H, q, *J* 3x1.3 Hz, 16-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.19 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 14.0 (C-18), 23.6 (17-Me), 25.8 (C-7 and C-11), 29.4 (C-6), 32.0 (C-12), 44.4 (C-8), 35.4 (C-9), 46.7 (C-13), 55.2 (3-OMe), 62.9 (C-14), 111.5 (C-2), 113.8 (C-4), 125.9 (C-16), 127.4 (C-1), 131.8 (C-10), 138.2 (C-5), 157.7 (C-3), 197.7 (C-17), 207.2 (C-15) (Found: C, 81.1; H, 8.4 %; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2 %; M, 296).

b) The procedure above was repeated with the same amounts of reagents and substrate. The reaction mixture was however stirred for 18 h at room temperature, and then filtered through alumina (100 g) under reduced prssure, using chloroform as the eluent. Evaporation under reduced pressure afforded a brown crystalline residue, which was dissolved in chloroform and washed with water. The organic phase was dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (1.22g). The residue was chromatographed on silica gel (150 g) with ethyl acetate-toluene (1:9) as the eluent to afford the 17-methyl Δ^{16} 15-ketone **23** (300 mg, 18 %), followed by the 3-*methoxy*-17-*methyl-14β-estra*-1,3,5(10),16-*tetraen*-15-*one* **27** (700 mg, 42 %), m.p. 144-147 °C (from ethyl acetate-hexane), $[\alpha]_D$ +333° (*c* 1); ν_{max} 1690 (CO) cm^{-1}; δ_H (200 MHz) 1.23 (3H, s, 13β-Me), 2.07 (3H, d, *J* 1.1 Hz, 17-Me), 2.29 (1H, d, *J* 5.3 Hz, 14α-H), 2.83 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.82 (1H, q, *J* 3x1.1 Hz, 16-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), and 7.08 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 14.6 (C-17), 23.5 (17-Me), 26.4 (C-11), 27.8 (C-7), 31.1 (C-12), 34.7 (C-6), 36.3 (C-9), 38.3 (C-8), 46.7 (C-13), 55.1 (3-OMe), 58.7 (C-14), 112.0 (C-2), 113.3 (C-4), 127.8 (C-1), 129.5 (C-16), 133.0 (C-10), 138.1 (C-5), 157.3 (C-3), 183.7 (C-17), 209.0 (C-15) (Found: C, 81.1; H, 8.2 %; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2 %; M, 296).

15β,16β-Epoxy-3-methoxyestra-1,3,5(10)-trien-17-one 28

a) Hydrogen peroxide (30 %, 0.36 cm^3) was added dropwise to a stirred solution of the Δ^{15} 17-ketone **19** (100 mg, 0.35 mmol) in tetrahydrofuran-*t*-butyl alcohol (1:1, 10 cm-3) at -5 °C. This was followed by dropwise addition of aqueous sodium hydroxide (0.9 cm^3, 10 M) over 10 min. The solution was stirred between -5 and 0 °C for 100 min, and then sodium sulfite was added, followed by water. The mixture was extracted with ethyl acetate, and the combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (100 mg). The residue was chromatographed on silica gel (5 g) with ethyl acetate-toluene (5:95) as the eluent to afford the 15β,16β-epoxy 17-ketone **28** (77 mg, 73 %), m.p.188-189 °C (from benzene-methanol) (lit.,[29,30] m.p. 189-190 °C), $[\alpha]_D$ -12° (*c* 0.9); ν_{max} 1742 (CO) cm^{-1}; δ_H (200 MHz) 1.19

(3H, s, 13β-Me), 2.99 (2H, m, 6-H_2), 3.33 (1H, d, *J* 2.9 Hz, 16α-H), 3.79 (3H, s, 3-OMe), 3.93 (1H, d, *J* 2.9 Hz, 15α-H), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H), and 7.17 (1H, d, *J* 8.3 Hz, 1-H); δ_C (50 MHz) 19.4 (C-18), 25.4 (C-11), 26.4 (C-7), 29.2 (C-6), 32.8 (C-12), 35.3 (C-8), 42.3 (C-13), 45.0 (C-9), 52.1 (C-14), 53.4 (C-15), 55.2 (3-OMe), 55.4 (C-16), 111.6 (C-2), 113.9 (C-4), 125.9 (C-1), 131.7 (C-10), 137.4 (C-5), 157.7 (C-3), and 213.0 (C-17) (Found: M^+, 298. $C_{19}H_{22}O_3$ requires M, 298), followed by the 15β,16β-*epoxy*-3-*methoxy*-17a-*oxa*-17a-*homoestra*-1,3,5(10)-*trien*-17-*one* **29** (9 mg, 8 %), m.p. 187-188 °C (from ethyl acetate-hexane), $[\alpha]_D$ +17° (*c* 1.0); ν_{max} 1732 cm^{-1} (CO); δ_H (200 MHz) 1.61 (3H, s, 13β-Me), 2.99 (2H, m, 6-H_2), 3.62 (1H, d, *J* 4.1 Hz, 16α-H), 3.79 (3H, s, 3-OMe), 3.81 (1H, d, *J* 4.1 Hz, 15α-H), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H), and 7.18 (1H, d, *J* 8.4 Hz, 1-H); δ_C (50 MHz) 24.3 (C-18), 26.5 (C-11), 27.5 (C-7), 29.5 (C-6), 38.5 (C-8), 41.0 (C-12), 43.7 (C-9), 46.9 (C-14), 49.1 (C-15), 53.1 (C-16), 55.2 (3-OMe), 82.8 (C-13), 111.9 (C-2), 113.6 (C-4), 126.1 (C-1), 130.7 (C-10), 137.0 (C-5), 157.9 (C-3) and 168.0 (C-17) (Found: C, 72.7; H, 7.0 %; M^+, 314. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05 %; M, 314)

b) Aqueous sodium hydroxide (0.5 cm^3, 10 M) was added to a solution of the Δ^{15} 17-ketone **19** (200 mg; 0.71 mmol) in tetrahydrofuran-*t*-butyl alcohol (1.3:1, 23 cm^3). The solution was cooled to -10 °C and hydrogen peroxide (30 %, 4 cm^3) was added dropwise, over 10 min, with stirring. The stirred solution was maintained between -10 and -5 °C for 85 min, and then water was added, followed by aqueous sodium sulfite, and saturated ammonium chloride. The mixture was extracted with ethyl acetate, and the combined organic extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (250 mg). Flash chromatography of the residue on silica (25 g) with ethyl acetate-toluene (4:96) as the eluent afforded the 15β,16β-epoxy 17-ketone **28** (81 mg, 38 %), followed by the 15β-*hydroperoxy*-3-*methoxyestra*-1,3,5(10)-*trien*-17-*one* **30** (97 mg, 43 %), m.p. 124-126 °C (from ethyl acetate-hexane), $[\alpha]_D$ +71° (*c* 0.8); ν_{max} 3531 (OH) and 1732 (CO) cm^{-1}; δ_H (200 MHz) 1.13 (3H, s, 13β-Me), 1.71 (1H, dd, *J* 11.4 and 5.1 Hz, 14α-H), 2.48 (1H, dd, *J* 19.9 and 5.1 Hz, 16α-H), 2.93 (2H, m, 6-H_2), 3.00 (1H, d, *J* 19.9 Hz, 16β-H), 3.79 (3H, s , 3-OMe), 4.90 (1H, t, *J* 2x5.1 Hz, 15α-H), 6.66

(1H, d, *J* 2.6 Hz, 4-H), 6.73 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H), 7.19 (1H, d, *J* 8.3 Hz, 1-H), and 8.35 (1H, s, 15β-OOH); δ_C (50 MHz) 17.7 (C-18), 25.6 (C-11), 26.3 (C-7), 29.4 (C-6), 32.6 (C-12), 34.9 (C-16), 42.9 (C-9), 44.6 (C-8), 47.1 (C-13), 54.5 (C-14), 55.2 (3-OMe), 80.5 (C-15), 111.5 (C-2), 113.9 (C-4),126.1 (C-1), 131.7 (C-10), 137.7 (C-5), 157.6 (C-3) and 219.1 (C-17) (Found: C, 71.2; H, 7.65 %; M^+, 316. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65 %; M, 316).

c) Sodium hypochlorite (3.5 %, 8 cm^3) was added dropwise over 5 min to a solution of Δ^{15} 17-ketone **19** (500 mg, 1.8 mmol) in pyridine (15 cm^3) and ethanol (10 cm^3), which was vigorously stirred at -10 °C. The mixture was stirred for 25 min at -10 °C, then it was poured into ether. Water was added and the mixture was extracted with ether. The combined organic extract was washed with hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (482 mg). The residue was chromatographed on silica gel (50 g) with ethyl acetate-toluene (5:95) as the eluent to afford the 15β,16β-epoxy 17-ketone **28** (413 mg, 78 %).

15β,16β-Epoxy-3-methoxy-17α-methylestra-1,3,5(10)-trien-17β-ol 31

Ethereal methyllithium (1.5 M, 5.3 cm^3) was added dropwise to a stirred solution of the 15β,16β-epoxy 17-ketone **28** (410 mg, 1.37 mmol) in dry tetrahydrofuran (26 cm^3), at -78 °C. The solution was stirred at -78 °C for 90 min, and then water was added, followed by saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate, and the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the 17α-*methyl* 17β-*alcohol* **31** (425 mg, 93%), m.p. 152-153 °C (from ethyl acetate-hexane), $[\alpha]_D$ +16° (*c* 0.9); ν_{max} 3598 (OH) cm^{-1}; δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 1.21 (3H, s, 17α-Me), 2.04 (1H, s, D_2O exchanged , 17β-OH), 2.96 (2H, m, 6-H_2), 3.23 (1H, d, *J* 3.3 Hz, 16α-H), 3.51 (1H, d, *J* 3.3 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.17 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 76.6; H, 8.5 %; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3 %; M, 314)

3-Methoxy-17α-methyl-15α-phenylselenenylestra-1,3,5(10)-triene-16β,17β-diol 32

Sodium borohydride (57 mg) was added in small portions to a stirred solution of diphenyl diselenide (486 mg) in dry ethanol (6 cm^3), at room temperature, until the solution just turned colourless. The 15β,16β-epoxy 17β-alcohol **31** (49 mg, 0.15 mmol) was added, and the mixture was stirred at 80 °C for 20 h, under nitrogen. The mixture was cooled, water was added, and the mixture extracted with benzene. The combined organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (200 mg). The residue was chromatographed on silica gel (20 g) with ethyl acetate-toluene (1:49) as the eluent to afford the 15α-*phenylselenenyl* 16β,17β-*diol* **32** (58 mg, 80 %) as an oil; δ_H (200 MHz) 0.97 (3H, s, 13β-Me), 1.13 (3H, s, 17α-Me), 2.52 and 2.67 (each 1H, s, exch. by D_2O, 17β-OH and 16β-OH), 2.89 (2H, m, 6-H_2), 3.36 (1H, dd, *J* 11.5 and 3.3 Hz, 15β-H), 3.79 (3H, s, 3-OMe), 3.88 (1H, d, *J* 3.3 Hz, 16α-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.0 and 2.6 Hz, 2-H), 7.22 (1H, d, *J* 8.0 Hz, 1-H), 7.31 and 7.67 (5H, 2xm, SePh); δ_C (50 MHz) 13.9 (C-18), 23.2 (17α-Me), 26.3 (C-7), 28.6 (C-11), 30.1 (C-6), 32.2 (C-12), 39.6 (C-8), 44.3 (C-9), 47.1 (C-13), 48.4 (C-15), 52.2 (C-14), 55.2 (3-OMe), 78.4 (C-17), 87.7 (C-16), 111.7 (C-2), 113.5 (C-4), 126.6 (C-1), 127.7 (C-4'), 129.2 (C-2' and C-6'), 129.6 (C-1'), 132.0 (C-10), 134.7 (C-3' and C-5'), 137.6 (C-5), and 157.5 (C-3) (Found: M^+, 472. $C_{26}H_{32}O_3{}^{80}Se$ requires M, 472).

3-Methoxy-17α-methylestra-1,3,5(10),14-tetraene-16β,17β-diol 20

a) A solution of potassium carbonate (100 mg) in hydrogen peroxide (30 %; 0.8 cm^3) was added dropwise to a stirred solution of the 15β-phenylselenenyl derivative **32** (248 mg; 0.52 mmol) in dry ethanol (22 cm^3), under nitrogen, at room temperature. The mixture was stirred at room temperature, until the 15β-phenylselenenyl derivative # was consumed (TLC) (~110 min). Thereafter the solution was refluxed for 150 min until the intermediate selenoxide was consumed. Water was added to the solution, followed by brine. The mixture was extracted with ethyl acetate, and the combined extracts dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (180 mg). The residue was

chromatographed on silica gel (9 g) with ethyl acetate-hexane-methanol (4:4:1) as the eluent to afford the Δ^{14} 16β,17β-*diol* **20** (154 mg, 94 %), m.p. 119-121 °C (from ethyl acetate-hexane), $[\alpha]_D$ +247° (*c* 0.95); ν_{max} 3682 and 3592 (16β and 17β-OH) cm^{-1}; δ_H (200 MHz) 1.16 (3H, s, 13β-Me), 1.24 (3H, s, 17α-Me), 2.91 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.15 (1H, d, *J* 2.4 Hz, 16α-H), 5.46 (1H, br s, 15-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, J 8.7 and 2.7 Hz, 2-H), and 7.22 (1H, d, J 8.7 Hz, 1-H); δ_C 21.2 (C-18), 22.95 (17α-Me), 25.4 (C-11), 27.2 (C-7), 29.8 (C-6), 33.5 (C-12), 39.1 (C-8), 44.5 (C-9), 50.0 (C-13), 55.2 (3-OMe), 79.35 (C-17), 81.3 (C-16), 111.8 (C-2), 113.8 (C-4), 118.0 (C-15), 126.7 (C-1), 131.8 (C-10), 137.7 (C-5), 157.7 (C-3), and158.7 (C-14) (Found: C, 76.3; H, 8.5 %; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3 %; M, 314).

b) The epoxy alcohol **31** (365 mg, 1.2 mmol) in tetrahydrofuran (5 cm^3) was added to lithium diethylamide [prepared by dropwise addition of diethylamine (2.48 ml) to a stirred solution of ethereal methyllithium (12.41 cm^3, 1.5 M) in ether (7.5 cm^3) at 0 °C, under nitrogen, followed by stirring for 10 min.] at 0 °C. The mixture was stirred at 0 °C for 3.5 h and then at 25 °C for 12 h. The reaction was quenched by the addition of water, and the mixture extracted with ethyl acetate. The combined extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (378 mg). The residue was chromatographed on silica gel (40 g) with ethyl acetate-toluene (3:7) as the eluent to afford the 3-methoxy-16-methylestra-1,3,5(10),15-tetraen-17-one **33** (45 mg, 13 %), m.p. 156-158 °C (from diisopropyl ether)(lit.[35], m.p. 152-153 °C), $[\alpha]_D$ -67° (*c* 1.0); ν_{max} 1700 (CO) cm^{-1}; δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 1.79 (3H, dd, *J* 3.0 and 1.5 Hz, 16-Me), 2.87 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.20 (1H, d, *J* 8.5 Hz, 1-H), and 7.20 (1H, br s, 15-H) (Found: C, 81.25; H, 8.3 %; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2 %; M, 296), followed by the 15β-*hydroxy*-3-*methoxy*-16α-*methylestra*-1,3,5(10)-*trien*-17-*one* **34** (30 mg, 8 %), m.p. 226-228 °C (from ethyl acetate-hexane), $[\alpha]_D$ +124° (*c* 1.0); ν_{max} 1700 (CO) cm^{-1}; δ_H (200 MHz) 1.15 (3H, s, 13β-Me), 1.26 (3H, d, *J* 7.6 Hz, 16-Me), 2.96 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 4.57 (1H, br s,15α-H), 6.67 (1H, d, *J* 2.5 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 10.3 (16α-Me), 18.1 (C-18), 25.8

(C-11), 26.5 (C-7), 29.5 (C-6), 33.4 (C-12), 34.5 (C-8), 44.5 (C-9), 47.4 (C-13), 49.9 (C-16), 53.7 (C-14), 55.2 (3-OMe), 69.9 (C-15), 111.5 (C-2), 113.9 (C-4), 126.1 (C-1), 132.1 (C-10), 137.7 (C-5), 157.7 (C-3), and 222.3 (C-17) (Found: C, 76.7, H, 8.45 %; M^+, 314. $C_{20}H_{26}O_3$ requires C, 76.4, H, 8.3 %; M, 314), followed by the Δ^{14} 16β,17β-diol **20** (236 mg, 69 %).

3-Methoxy-16-methylestra-1,3,5(10),15-tetraen-17-one 33

Toluene-*p*-sulfonic acid (12 mg, 0.06 mmol) was added to a stirred solution of the 15β–hydroxy 16α-methyl 17-ketone **34** (20 mg, 0.06 mmol) in dichloromethane (3 cm^3), under nitrogen. The mixture was stirred for 10 h, after which water was added, and the mixture extracted with chloroform. The combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give the Δ^{14} 16-methyl 17-ketone **33** (18 mg, 100 %), identified with authentic material with physical data as above.

3-Methoxyestra-1,3,5(10),16-tetraen-17-yl trifloromethanesulfonate 38

a.) Trifloromethanesulfonic anhydride (triflic anhydride) (2 cm^3) was added dropwise to a stirred solution estrone 3-methyl ether **25** (1.5 g, 5.3 mmol) in dry dichloromethane (15 cm^3) and pyridine (1 cm^3). A precipitate formed immediately, and the heterogenous mixture was stirred for 24 h at room temperature. Additional dry pyridine (0.45 cm^3) and triflic anhydride (1 cm^3) was added, and stirring was continued for a further 24 h. Saturated aqueous sodium carbonate was added, and the mixture was extracted with chloroform. The combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (2.4 g). Flash chromatography of the residue on silica gel (100 g) with ethyl acetate-toluene (1:19) as the eluent afforded the *enol triflate* **38** (2 g, 90 %), m.p.56-57 °C (from hexane-methanol at -142 °C), $[\alpha]_D$ +61° (*c* 1.0); δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.62 (1H, br s,16-H), 6.65 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 15.3 (C-18), 25.8 (C-11), 26.8 (C-7), 28.4 (C-15), 29.4 (C-6), 32.8 (C-12), 36.7

(C-8), 44.2 (C-9), 45.1 (C-13), 53.6 (C-14), 55.2 (3-OMe), 111.5 (C-2), 113.9 (C-4), 114.5 (C-16), 118.6 (q, *J* 3x320.6 Hz, CF_3), 125.9 (C-1), 132.15 (C-10), 137.7 (C-5), 157.6 (C-3), and 159.3 (C-17) (Found: C, 57.3; H, 5.7; S, 7.3 %; M^+, 417. $C_{20}H_{23}F_3O_4S$ requires C, 57.7; H, 5.6; S 7.7 %; M, 417).

b.) Triflic anhydride (1.91 cm^3, 11.35 mmol) was added dropwise to a stirred solution of estrone 3-methyl ether **25** (3 g, 10.64 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (2.4 g, 11.7 mmol) in dry dichloromethane (30 cm^3). The mixture was stirred for 19.5 h, after which saturated aqueous sodium carbonate was added. The mixture extracted with chloroform, and the combined extract dried ($MgSO_4$), and evaporated under reduced pressure to afford a residue (6.5 g). Flash chromatography of the residue on silica gel (200 g) with ethyl acetate-toluene (1:49) as the eluent afforded the enol triflate **38** (4.38 g, 99 %).

3-Methoxy-17-methylestra-1,3,5(10),16-tetraene 35

Ethereal methyllithium (1.5 M, 16.9 cm^3) was added to a stirred slurrry of copper(I) iodide (3.04 g, 15.95 mmol) in dry tetrahydrofuran (100 cm^3) at 0 °C. The enol triflate **38** (1.33 g, 3.19 mmol) in dry tetrahydrafuran (10 cm^3) was added, at -15 °C, and the mixture was stirred for 15 h, under nitrogen. The mixture was then diluted with hexane and filtered through Florosil, with ethyl acetate. The filtrate was evaporated under reduced pressure to give a crystalline residue (3.24 g). Flash chromatography of the residue on silica gel (120 g) with toluene-hexane (3:2) as the eluent afforded the Δ^{16} 17-*methyl* compound **35** (897 mg, 99 %), m.p. 121-122 °C (from chloroform-methanol), $[\alpha]_D$ +113° (*c* 1.0); δ_H (200 MHz) 0.77 (3H, s, 13β-Me), 1.68 (3H, d, *J* 1.1 Hz, 17-Me), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.32 (1H, br. s, 16-H), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 12.5 (17-Me), 15.2 (C-18), 26.5 (C-11), 27.8 (C-7), 29.8 (C-15), 30.8 (C-6), 34.4 (C-12), 37.5 (C-8), 44.4 (C-9), 46.6 (C-13), 55.2 (3-OMe), 56.3 (C-14), 111.4 (C-2), 113.8 (C-4), 122.5 (C-16), 126.0 (C-1),

133.15 (C-10), 138.1 (C-5), 151.5 (C-17), and 157.4 (C-3) (Found: C, 85.4; H, 9.3 %; M^+, 282. $C_{20}H_{26}O$ requires C, 85.1; H, 9.3 %; M, 282).

3-Methoxy-17β-methylestra-1,3,5(10)-triene-16α,17α-diol 39

Osmium(IV) tetroxide (3.8 g) was added to a solution of methyl olefin **35** (3.1g, 10.97 mmol) in dry pyridine (50 cm^3). The reaction left standing for 27 h at room temperature, and then saturated sodium metabisulfite was added. The mixture was stirred for 2 h, then acidified with hydrochloric acid (1 M), and extracted using chloroform. The combined extract was washed with hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (4 g). Flash chromatography of the residue on silica gel (120 g) with ethyl acetate-toluene (1:1) as the eluent afforded the 17β-methyl 16α,17α-diol **39** (3.12 g, 90 %), m.p.153-154 °C (from methanol), $[\alpha]_D$ +30.6° (*c* 1.0) (lit.[41] m.p. 155 °C; $[\alpha]_D$ +30.5°); ν_{max} 3622 and 3525 (OH) cm^{-1}; δ_H (200 MHz) 0.74 (3H, s, 13β-Me), 1.23 (3H, s, 17β-Me), 1.62 and 2.25 (2x1H, s, D_2O exch., 16α and 17α-OH), 2.84 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.11 (1H, dd after exch. by D_2O, *J* 9.1 and 2.6 Hz, 16β-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.45 and 2.7 Hz, 2-H), and 7.17 (1H, d, *J* 8.45 Hz, 1-H); δ_C (50 MHz) 15.8 (C-18), 20.4 (17β-Me), 25.7 (C-11), 27.9 (C-7), 29.8 (C-6), 30.4 (C-15), 34.9 (C-12), 38.8 (C-8), 43.6 (C-9), 47.0 (C-13), 47.2 (C-14), 55.2 (3-OMe), 77.4 (C-16), 80.6 (C-17), 111.4 (C-2), 113.8 (C-4), 126.1 (C-1), 132.7 (C-10), 138.0 (C-5), and 157.4 (C-3) (Found: M^+, 316. $C_{20}H_{28}O_3$ requires; M, 316)

3-Methoxy-17a-oxo-16,17-seco-17a-homoestra-1,3,5(10)-trien-16-al 21

a) Lead tetraacetate (70 mg) was added to a solution of the 16α,17α-diol **39** (50 mg, 0.158 mmol) in dry dichloromethane (10 cm^3), under nitrogen. The mixture was stirred for 4 min, after which water was added and the mixture was extracted with dichloromethane. The combined extract was dried by rapid suction through magnesium sulfate, and evaporated under reduced pressure to give a residue (50 mg). Flash chromatography of the residue on silica gel (3 g) with ethyl acetate-toluene (1:1) as the eluent afforded the seco

compoud **21** (46 mg, 93 %), as an oil (Lit.[11]); δ_H (200 MHz) 1.14 (3H, s, 13β-Me), 2.18 (3H, s, 17a-Me), 2.82 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.4 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), and 9.79 (1H, d, *J* 1.9 Hz, 16-H) (Found: M^+, 314. $C_{20}H_{26}O_3$ requires; M, 314)

b) The procedure was repeated with lead tetraacetate (729 mg), 16α,17α-diol **39** (400 mg, 1.27 mmol), and dichloromethane (70 cm^3). The mixture was stirred for 7 min, after which water was added, and the resultant mixture acidified with hydrochloric acid (1 M), and rapidly extracted with chloroform. The combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (500 mg). Flash chromatography of the residue on silica gel (40 g) with ethyl acetate-toluene (3:7) as the eluent afforded the seco compoud **21** (372mg, 94%).

c) Sodium periodate (10 %, 4.1 cm^3) was added to a solution of the 16α,17α-diol **39** (600 mg, 1.90 mmol) in ethanol (60 cm^3). The mixture was stirred for 75 min, after which a further aliquot of sodium periodate (10 %, 1 cm^3) was added. The mixture was stirred for a further 75 min, after which water was added. The mixture was extracted with chloroform, and the combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (649 mg). Flash chromatography of the residue on silica gel (90 g) with ethyl acetate-toluene (1:9) as the eluent afforded the homo enone **40** (28 mg, 5 %), mp 148-151 °C (from acetone-methanol) (lit.[11] m.p. 150-153 °C), followed by the seco compoud **21** (300 mg, 50 %), followed by starting material **39** (225 mg, 37 %).

3-methoxy-17a-homoestra-1,3,5(10),16-tetraen-17a-one 40

Toluene-*p*-sulfonic acid (24 mg) was added to a solution of the seco compoud **21** (39 mg, 0.12 mmol) in dichloromethane (4 cm^3). The mixture was stirred for 20 h, after which water was added. The mixture was extracted with chloroform, and the combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give the homo enone **40** (30 mg, 85 %).

3-Methoxy-17aβ-methyl-17-oxa-17a-homoestra-1,3,5(10)-trien-17aα-ol 41

Lithium tri-*sec*-butylborohydride (1 M solution in tetrahydrofuran, 3 cm^3) was added dropwise to a stirred solution of the seco compoud **21** (300mg, 0.96 mmol) in dry tetrahydrofuran (30 ml) at -78 °C, under nitrogen. The mixture was stirred for 10 min at -78 °C, after which water was added, followed by saturated aqueous ammonium chloride. The mixture was then warmed to room temperature and extracted with ethyl acetate. The combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (450 mg). Flash chromatography of the residue on silica gel (45 g) with ethyl acetate-toluene (1:9) as the eluent afforded the *cyclic hemiacetal* **41** (200 mg, 66%), m.p. 120-122 °C (from ethyl acetate-hexane), $[\alpha]_D$ +24° (*c* 1.0); ν_{max} 3598 (OH) 1727 (17a-CO) cm^{-1}; δ_H (C_6D_6, 400 MHz) 0.91 (3H, s, 13β-Me), 1.13 (3H, s, 17α-Me), 1.42 (1H, td, *J* 12.8 and 3.5, 12β-H), 2.66 (2H, m, 6-H_2), 3.37 (3H, s, 3-OMe), 3.60 (1H, ddd, *J* 11.1, 5.1 and 1.4 Hz, 16β-H), 3.88 (1H, ddd, *J* 12.5, 11.1 and 3.7 Hz, 16α-H), 6.60 (1H, d, *J* 2.75 Hz, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.75 Hz, 2-H), and 7.3 (1H, d, *J* 8.7 Hz, 1-H); δ_C (C_6D_6, 100 MHz) 16.0 (C-18), 24.2 (17β-Me), 24.8 (C-15), 26.5 (C-11), 26.6 (C-7), 30.4 (C-6), 33.8 (C-12), 39.4 (C-8), 40.4 (C-13), 40.5 (C-9), 43.3 (C-14), 54.8 (3-OMe), 61.0 (C-16), 99.4 (C-17a), 112.0 (C-2), 113.9 (C-4), 126.5 (C-1), 133.2 (C-10), 137.9 (C-5), and 158.3 (C-3) (Found: C, 76.1; H, 9.2 %; M^+, 316. $C_{26}H_{28}O_3$ requires C, 75.9; H, 8.9 %; M, 316)

17aξ-2'-hydroxyethoxy-3-methoxy-17aξ-methyl-17-oxa-17a-homoestra-1,3,5(10)-triene 44

A solution of the cyclic hemiacetal **41** (50 mg, 0.16 mmol), benzene (45 cm^3), ethylene glycol (10 cm^3), and toluene-*p*-sulfonic acid (10 mg) was refluxed with azeotropic removal of water, for 6 h. The mixture was cooled to room temperature, poured into saturated aqueous sodium hydrocarbonate, and extracted with ethyl acetate. The combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (130 mg). Flash chromatography of the residue on silica gel (15 g) with ethyl

acetate-toluene (3:7) as the eluent afforded the 2'-*hydroxy ketal* **44** (48 mg, 80%), mp 131-138 °C (from ethyl acetate-hexane), $[\alpha]_D$ -11° (*c* 1.0); ν_{max} 3602 (OH) cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 1.04 (3H, s, 13β-Me), 1.23 (3H, s, 17a-Me), 1.66 (1H, s, D_2O exch., 2'-OH), 2.84 (2H, m, 6-H_2), 3.59 (2H, t, *J* 2x4.5 Hz, 2'-H_2), 3.70 (2H, m, 16-H_2), 3.78 (3H, s, 3-OMe), 3.80 (2H, m, 1'-H_2), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.7 Hz, 1-H); δ_H (C_6D_6, 400 MHz) 0.96 (3H, s, 13β-Me), 1.17 (3H, s, 17a-Me), 2.70 (2H, m, 6-H_2), 3.37 (1H, m, 1'-H), 3.43 (3H, s, 3-OMe), 3.46 (1H, m, 1'-H), 3.60 (2H, t, *J* 2x4.8 Hz, 2'-H_2), 3.65 (2H, m, 16-H_2), 6.69 (1H, d, *J* 2.8 Hz, 4-H), 6.81 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), and 7.19 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 16.4 (C-18), 17.6 (17-Me), 24.2 (C-15), 26.0 (C-11), 26.1 (C-7), 30.1 (C-6), 33.3 (C-12), 39.0 (C-8), 40.1 (C-9), 40.9 (C-13), 42.8 (C-14), 55.2 (3-OMe), 61.3 (C-16), 61.5 (C-2'), 62.4 (C-1'), 102.2 (C-17a), 111.5 (C-2), 113.5 (C-4), 126.1 (C-1), 132.9 (C-10), 137.8 (C-5), and 157.4 (C-3) (Found: C, 73.6; H, 9.1 %; M^+, 360. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95 %; M, 360)

17aξ-2'-Formylmethoxy-3-methoxy-17aξ-methyl-17-oxa-17a-homoestra-1,3,5(10)-triene 45

Oxalyl chloride (2 M in dichloromethane, 4.39 mmol) and dimethyl sulfoxide (0.73 cm^3, 8.77 mmol) were stirred in dichloromethane (12 cm^3) at -78 °C for 5 min. The 2'-hydroxy ketal **44** (150 mg, 0.42 mmol) in dichloromethane (12 cm^3) was added dropwise over 5 min, and the reaction mixture stirred at -78 °C for 35 min. Triethylamine (2.5 cm^3, 17.54 mmol) was added and the mixture was stirred at -78 °C for 5 min, after which the mixture was allowed to warm to room temperature over 45 min. Water was then added, and the mixture extracted with dichloromethane. The combined extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (170 mg). Flash chromatography of the residue on silica gel (20 g) with ethyl acetate-toluene (15:85) as the eluent afforded the 2'-*aldehydic ketal* **45** (130 mg, 86 %) as an oil; δ_H (400 MHz) 1.05 (3H, s, 13β-Me), 1.19 (3H, s, 17a-Me), 2.84 (2H, m, 6-H_2), 3.57 and 3.75 (each 1H, m, 16-H_2), 3.78 (3H, s, 3-OMe), 4.06 and 4.13

(each 1H, dd, *J* 17.8 and 1.2 Hz, 1'-H_2), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.4 Hz, 1-H), 9.82 (1H, t, *J* 1.2 Hz, 2'-H) (Found: M^+, 358.214. $C_{22}H_{30}O_4$ requires M, 358.214)

17aξ-2'-acetoxyethoxy-3-methoxy-17aξ-methyl-17-oxa-17a-homoestra-1,3,5(10)-triene 46

The 2'-hydroxy ketal **44** (50 mg, 0.14 mmol) in pyridine (5 cm^3) and acetic anhydride (0.14 cm^3, 1.40 mmol) was stirred at room temperature for 22h. The reaction was quenched with ice-water, followed by saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate, and the combined extract was washed with dilute hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (60 mg). Flash chromatography of the residue on silica gel (6 g) with ethyl acetate-toluene (1:19) as the eluent afforded the 2'-*acetoxy ketal* **46** (55 mg, 98 %) as an oil; ν_{max} 1737 (CO) cm^{-1}; δ_H (400 MHz) 1.02 (3H, s, 13β-Me), 1.20 (3H, s, 17-Me), 2.08 (3H, s, $COCH_3$), 2.82 (2H, m, 6-H_2), 3.65 (2H, m, 1'-H_2), 3.69 (2H, m, 16-H_2), 3.78 (3H, s, 3-OMe), 4.28 (2H, m, 2'-H_2), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 16.2 (C-18), 17.4 (17-Me), 21.0 (2'-OCO*C*H_3), 24.3 (C-15), 26.0 (C-11), 26.1 (C-7), 30.1 (C-6), 33.1 (C-12), 39.0 (C-8), 39.7 (C-9), 40.7 (C-13), 42.7 (C-14), 55.2 (3-OMe), 58.2 (C-1'), 61.5 (C-16), 63.7 (C-2'), 102.2 (C-17a), 111.5 (C-2), 113.4 (C-4), 126.1 (C-1), 133.0 (C-10), 137.8 (C-5), 157.4 (C-3) and 170.9 (*C*OCH_3) (Found: M^+, 402. $C_{24}H_{34}O_5$ requires M, 402)

16-acetoxy-3-methoxy-16,17-seco-17a-homoestra-1,3,5(10)-trien-17a-one 47

The cyclic hemiacetal **41** (50 mg, 0.158 mmol) in a solution of pyridine (2 cm^3), acetic anhydride (0.1 cm^3), and N,N-dimethylaminopyridine (10 mg) was stirred at room temperature for 2.5 h. The reaction was quenched with ice-water, followed by saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate, and the combined extract was washed with dilute hydrochloric acid (1 M), dried ($MgSO_4$), and

evaporated under reduced pressure to give a residue (70 mg). Flash chromatography of the residue on silica gel (9 g) with ethyl acetate-toluene (1:9) as the eluent afforded the *seco 16-acetate* **47** (56 mg, 99 %), mp 108 °C (from ethyl acetate-hexane), $[\alpha]_D$ 87° (*c* 1.0); ν_{max} 1694 and 1730 (17a-CO and 16-OAc) cm^{-1}; δ_H (400 MHz) 1.15 (3H, s, 13β-Me), 2.04 and 2.21 (each 3H, s, 17a-Me and 16-OAc), 2.88 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.99 (1H, ddd, *J* 10.4, 9.2 and 7.1 Hz, 16-H), 4.18 (1H, td, *J* 2x10.4 and 5.3 Hz, 16-H), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), and 7.19 (1H, d, *J* 8.8 Hz, 1-H); δ_C (100 MHz) 15.1 (C-18), 21.0 (17-Me), 25.6 (17-OAc), 26.0 (C-15), 27.0 (C-11), 30.3 (C-7), 30.6 (C-6), 36.1 (C-12), 41.4 (C-8), 41.8 (C-9), 43.1 (C-14), 53.1 (C-13), 55.2 (3-OMe), 64.8 (C-16), 111.9 (C-2), 113.4 (C-4), 126.5 (C-1), 131.6 (C-10), 137.6 (C-5), 157.6 (C-3), 171.0 (C-17a), and 214 (16-O*C*OCH$_3$) (Found: C, 73.7; H, 8.4 %; M^+, 358. $C_{22}H_{32}O_4$ requires C, 73.7; H, 8.7 %; M, 358)

3-Methoxy-15β-tributylstannylestra-1,3,5(10)-trien-17-one 50

n-Butyllithium (2.5 M in hexane, 0.6 cm^3) was added dropwise to a stirred solution of tetrahydrofuran (3 cm^3) and diisopropylamine (0.23 cm^3), at 0 °C. The mixture was stirred for 5 min, after which tributyltin hydride (0.37 cm^3) was added dropwise. The mixture was stirred at 0 °C for 20 min and then cooled to -78 °C, after which a solution of Δ^{15} 17-ketone **19** (200 mg, 0.71 mmol) in tetrahydrofuran (1 cm^3) was added dropwise. The reaction mixture was stirred for 10 min, and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (700 mg). The residue was chromatographed on silica gel (60 g) with chloroform-toluene (2:49) as the eluent to afford the 15β-*tributylstannyl* 17-*ketone* **50** (190 mg, 47 %) as an oil; ν_{max} 1729 (CO) cm^{-1}; δ_H (200 MHz) 0.965 (3H, s, 13β-Me), 0.97 (9H, m, Sn[$(CH_2)_3$*Me*]$_3$, 2.97 (2H, m, 6H_2), 3.84 (3H, s, 3-OMe), 6.72 (1H, d, *J* 2.7 Hz, 4-H), 6.79 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.11 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 10.6 (3C, Sn*C*$H_2$$CH_2$Me), 13.7 (3C, Sn$(CH_2)_3$*C*$H_3$), 14.5 (C-18), 19.4 (C-15), 25.9 (C-11), 27.2 (C-7), 27.5 and 29.3 (3C, SnCH_2*C*$H_2$$CH_2$Me and Sn$CH_2$$CH_2$*C*$H_2$Me), 29.7 (C-6), 32.7 (C-12), 39.0 (C-8), 40.9

(C-16), 44.4 (C-9), 47.6 (C-13), 54.9 (C-14), 55.2 (3-OMe), 111.6 (C-2), 114.0 (C-4), 126.4 (C-1), 131.9 (C-10), 137.6 (C-5) and 157.7 (C-3) (Found: M^+, 573. $C_{31}H_{50}O_2Sn$ requires M, 573), followed by the Δ^{14} 17-ketone **51** (91 mg, 45 %), mp 90-95 °C (from ethyl acetate-hexane) (lit.,[49] mp 103-104.); ν_{max} 1744 (CO) cm^{-1}; δ_H (200 MHz) 1.16 (3H, s, 13β-Me), 2.93 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.62 (1H, br s, 15-H), 6.68 (1H, d, *J* 2.6 Hz, 4-H), 7.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.22 (1H, d, *J* 8.6 Hz, 1-H)(Found: M^+, 282. $C_{19}H_{22}O_2$ requires M, 282).

Lithium trimethylstannane

The reagent was prepared according to a described method.[50] Thus, freshly cut lithium (1.4 g, 200 mmol) was flattened, and cut into small pieces. The pieces of lithium were suspended in tetrahydrofuran (30 cm^3), under argon, in a three neck round bottom flask adapted with a sintered port for filtration. Chlorotrimethylstannane (20 cm^3, 1 M) was added dropwise, via a dropping funnel, to the vigorously stirred lithium suspension, at 0 to -5 °C. The solution went olive green, and after stirring for 2 h, the unreacted lithium was removed by filtration through the sintered side port into a round bottom flask, under argon, to give a solution of lithium trimethylstannane (~ 0.4 $mol.dm^{-3}$).

3-Methoxy-15β-trimethylstannylestra-1,3,5(10)-trien-17-one 52

Lithium trimethylstannane (freshly prepared) (~2.24 mmol) in tetrahydrofuran (0.4 M, 5.6 cm^3) was added dropwise to a vigorously stirred solution of the Δ^{15} 17-ketone **19** (310 mg, 1.10 mmol) in tetrahydrofuran (15 cm^3) under nitrogen, at -78 °C. The reaction mixture was stirred for 15 min at -78 °C, after which saturated aqueous ammonium chloride was added, and the mixture was stirred for a further 2h at room temperature. The mixture was extracted with ethyl acetate, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (600 mg). The residue was chromatographed on silica gel (55 g) with ethyl acetate-toluene (1:99) as the eluent to afford an unidentified product (15 mg), followed by the 15β-*trimethylstannyl*

17-*ketone* **52** (366 mg, 74%), m.p. 146-148 °C (from ethyl acetate-hexane), $[\alpha]_D$ -5° (*c* 1.0); ν_{max} 1730 (CO) cm^{-1}; δ_H (400 MHz) 0.16 (9H, s, 15β-$SnMe_3$), 0.88 (3H, s, 13β-Me), 2.92 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.40 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) -7.7 (q, 15β-$SnMe_3$), 14.6 (q, C-18), 20.7 (d, C-15), 25.9 (t, C-11), 27.2 (t, C-7), 29.6 (t, C-6), 32.5 (t,C-12), 38.8 (d, C-8), 40.4 (t, C-16), 44.3 (d, C-9), 47.7 (s, C-13), 54.6 (d, C-14), 55.2 (q, 3-OMe), 111.7 (d, C-2), 113.9 (d, C-4), 126.4 (d, C-1), 131.9 (s, C-10), 137.5 (s, C-5), 157.7 (s, C-3), and 221.3 (s, C-17) (Found: C, 59.5; H, 7.4 %; M^+, 447. $C_{22}H_{32}O_2Sn$ requires C, 59.1; H, 7.2 %; M, 447), followed by stating material (19 mg, 6%).

3-Methoxy-17α-methyl -15β-trimethylstannylestra-1,3,5(10)-trien-17β-ol 53

a) Ethereal methyllithium (1.4 M solution, 0.9 cm^3) was added dropwise to a solution of the 15β-trimethylstannyl 17-ketone **52** (110 mg, 0.25 mmol) in tetrahydrofuran (10 cm^3) at -78 °C, under nitrogen. The mixture was stirred at -78 °C for 4 h, after which saturated aqueous ammonium chloride was added and the mixture allowed to warm to room temperature. The mixture was extracted with ethyl acetate, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (130 mg). The residue was chromatographed on silica gel (10 g) with ethyl acetate-toluene (1:9) as the eluent to afford starting material **52** (45mg, 41 %), followed by the 15β-*trimethylstannyl* 17α-*methyl* 17β-*alcohol* **53** (60 mg, 52 %) as an oil, ν_{max} 3608 (OH) cm^{-1}; δ_H (400 MHz) 0.11 (9H, s, 15β-$SnMe_3$), 0.89(3H, s, 13β-Me), 1.30 (3H, s, 17α-Me_3), 2.88 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.75 Hz, 4-H), 2.72 (1H, dd, *J* 8.5 and 2.75 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H) (Found: M^+, 463. $C_{23}H_{36}O_2$ requires M, 463).

b) Cerium(III) chloride (165 mg ,4.47 mmol) was dried at 160 °C and 0.1 torr for 2 h, the suspended in tetrahydrofuran (10 cm^3), and stirred for 1 h at 0 °C. The 15β-trimethylstannyl 17-ketone **52** (200 mg, 0.45 mmol) in tetrahydrofuran (10 cm^3) was then added to the mixture which was stirred for a further 2.5 h, at 0 °C. The temperature

was lowered to -78 °C and ethereal methyllithium (1.5 M solution, 3 cm^3) was added dropwise, with vigorous stirring, over 5 min. The mixture was stirred for 3.5 h at -78 °C, then further ethereal methyllithium (1.5 M solution, 1.5 cm^3) was added, and the mixture stirred at -78 °C for a further 105 min. Standard workup (as above) and chromatography afforded starting material **52** (72 mg, 36 %), followed by the 15β-trimethylstannyl 17α-methyl 17β-alcohol **53** (120 mg, 58%).

c) Cerium(III) chloride (480 mg, 1.3 mmol) was dried at 140 °C and 0.1 torr for 2 h. Thereafter tetrahydrofuran (4 cm^3) was added and the suspension stirred for 1 h at 0 °C, under nitrogen. The temperature was lowered to -78 °C and then ethereal methyllithium (1.5 M solution, 0.8 cm^3) was added dropwise, after which the colour changed from white to yellow. The mixture was stirred for 30 min, at -78 °C, after which a solution of the 15β-trimethylstannyl 17-ketone **52** (447 mg, 1.0 mmol) in tetrahydrofuran (4 cm^3) was added. The mixture was stirred for 8 h, at -78 °C. Standard workup (as above) and chromatography afforded starting material **52** (85 mg, 20 %), followed by the 15β-trimethylstannyl 17α-methyl 17β-alcohol **53** (254 mg, 57 %).

d) The 15β-trimethylstannyl 17-ketone **52** (388 mg, 0.87 mmol) in tetrahydrofuran (10cm^3) was added dropwise to methyl magnesium iodide (~4.42 mmol) in diethylether [magnesium turnings (106 mg, 4.42 mmol), ether (10 cm^3), and methyliodide (0.27 cm^3, 4.3 mmol)], at 0 °C. The mixture was stirred for 1 h at 0 °C, warmed to room temperatured and stirred for a further 90 min. The mixture was then refluxed for 3h. Standard workup (as above) and chromatography afforded starting material **52** (178 mg, 46 %), followed by the 15β-trimethylstannyl 17α-methyl 17β-alcohol **53** (87 mg, 22%).

Fragmentation experiments on the 15β-trimethylstannyl 17α-methyl 17β-alcohol 53

a) A solution of 15β-trimethylstannyl 17β-alcohol **53** (210 mg, 0.45 mmol) in dry benzene (4cm^3) was added to a refluxing suspension of lead tetraacetate (253 mg, 0.6 mmol) in dry benzene (1cm^3). The mixture was refluxed for 3 h, and then poured into

saturated aqueous sodium hydrogen carbonate, and the whole acidified with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, and the combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (210 mg). The residue was chromatographed on silica gel (35 g) with ethyl acetate-toluene (1:49) as the eluent to afford the 3-methoxy-16,17-seco-17a-homoestra-1,3,5(10),15-tetraen-17a-one **48** (9 mg, 5 %) as an oil; ν_{max} 1693 (CO) cm^{-1}; δ_H (400 MHz) 1.19 (3H, s, 13β-Me), 2.15 (3H, s, 17-H_3), 2.82 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.99 (1H, dd, *J* 16.7 and 2.1 Hz, 16-H_{trans}), 5.08 (1H, dd, *J* 10.2 and 2.1 Hz, 16-H_{cis}), 5.52 (1H, dt, *J* 17.1 and 2x10.2 Hz, 15-H), 6.63 (1H, d, *J* 2.75 Hz, 4-H), 6.73 (1H, dd, *J* 2.75 and 8.6 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1H); δ_H (400 MHz, C_6D_6) 0.96 (3H, s, 13β-Me), 1.63 (1H, td, *J* 2x13.2 and 3.6 Hz, 12α-H), 1.81 (3H, s, 17a-H_3), 1.85 (1H, m, 7β-H), 2.00 (1H, dt, *J* 13.4 and 3x3.6 Hz, 11α-H), 2.12 (1H, td, J 2x11.0 and 3.3 Hz, 9β-H), 2.24 (1H, t, *J* 10.42 Hz, 14α-H), 2.62 (2H, m, 6-H_2), 3.37 (3H, s, 3-OMe), 4.90-4.94 (2H, m, 16-H_2), 5.26 (1H, ddd, *J* 16.9, 10.4 and 9.85 Hz, 15-H), 6.63 (1H, d, *J* 2.75 Hz, 4-H), 6.78 (1H, dd, *J* 8.65and 2.75 Hz, 2-H), and 7.07 (1H, d, *J* 8.65 Hz, 1H) (Found: M^+, 298.194. $C_{20}H_{26}O_2$ requires M, 298.193), followed by starting material **53** (60 mg, 29 %). The eluted column and remaining fractions were evaporated under reduced pressure to afford a complex mixture of uncharacterisable products (100 mg).

b) Iodobenzene diacetate (200 mg, 0.62 mmol) and sublimed iodine (84 mg, 0.33 mmol) were added to a solution of 15β-trimethylstannyl 17β-alcohol **53** (190 mg, 0.41 mmol) in dry cyclohexane (43 cm^3). Oxygen was bubbled through the solution, and the mixture was irradiated (100W tungsten filament bulb) for 1h. Thereafter a further portion of dry cyclohexane (20 cm^3) was added and the mixture was irradiated for a further 3h. The mixture was then poured into saturated aqueous sodium thiosulfate and filtered through Celite. The filtrate was extracted with ethyl acetate, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (180 mg). The residue was chromatographed on silica gel (30 g) with ethyl acetate-toluene (1:49) as the eluent to afford the 3-methoxy-16,17-seco-17a-homoestra-1,3,5(10),15-tetraen-17a-one **48** (27 mg, 23%) as an oil. The remaining fractions and

eluted column were evaporated under reduced pressure to give a mixture of uncharacterised products (111 mg).

3-Methoxy-15β-trimethylstannylestra-1,3,5(10)-trien-17β-ol 54

Sodium borohydride (177 mg, 4.68 mmol) was added to a solution of the 15β-trimethylstannyl 17-ketone **52** (450 mg, 1.00 mmol) in methanol (45 cm^3) and tetrahydrofuran (25 cm^3). The mixture was stirred for 20 min at room temperature, and then poured into water. The mixture was acidified with dilute hydrochloric acid (1 M), and extracted with ethyl acetate. The combined extract was washed with dilute hydrochloric acid, dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (500 mg). The residue was chromatographed on silica gel (50 g) with ethyl acetate-toluene (5:95) as the eluent to afford the 15β-*trimethylstannylestra* 17β-*alcohol* **54** (440 mg, 98%), mp 132-135 °C (from ethyl acetate-hexane), $[\alpha]_D$ -72 (*c* 1.0); ν_{max} 3612 (OH) cm^{-1}; δ_H (400 MHz) 0.10 (9H, s, 15β-$SnMe_3$), 0.77 (3H, s, 13β-Me), 2.84 (2H, m, 6-H_2), 3.77 (1H, dd, *J* 10.5 and 6.6 Hz, 17α–H), 3.77 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.0 and 2.7 Hz, 2-H), and 7.20 (1H, d, *J* 8.0 Hz, 1-H); δ_C (100 MHz) -7.7 (q, 15β-$SnMe_3$), 12.2 (q, C-18), 22.6 (d, C-15), 26.0 (t, C-11), 28.3 (t, C-7), 29.7 (t, C-6), 35.6 (t, C-12), 37.2 (t, C-16), 39.1 (d, C-8), 43.2 (s, C-13), 44.4 (d, C-9), 53.8 (d, C-14), 55.2 (q, 3-OMe), 82.5 (d, C-17), 111.5 (d, C-2), 113.8 (d, C-4), 126.3 (d, C-1), 132.5 (s, C-10), 137.7 (s, C-5), and 157.5 (s, C-3) (Found: C, 58.9; H, 7.7 %; M^+, 449. $C_{22}H_{34}O_2Sn$ requires C, 58.8; H, 7.6 %; M, 449)

17β-Acetoxy-3-methoxy-15β-trimethylstannylestra-1,3,5(10)-triene 55

The 15β-trimethylstannyl 17β-alcohol **54** (110 mg, 0.22 mmol) in dry pyridine (5 cm^3) and acetic anhydride (0.3 cm^3) was stirred at room temperature for 45h. The reaction was quenched with ice-water, followed by saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate, and the combined extract was washed with dilute hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a

crystalline residue (118 mg). Flash chromatography of the residue on silica gel (5 g) with ethyl acetate-toluene (2:98) as the eluent afforded the 15β-*trimethylstannyl* 17β-*oxoacetate* **55** (100 mg, 93%), mp 123-125 °C (from ethanol), $[\alpha]_D$ -54 (c 1.0); ν_{max} 1725 (CO) cm^{-1}; δ_H (400 MHz) 0.12 (9H, s, 15β-$SnMe_3$), 0.83 (3H, s, 13β-Me), 2.07 (3H, s, 17β-OAc), 2.53 (1H, ddd, *J* 13.7, 10.4 and 8.7 Hz, 16β-H), 2.88 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.75 (1H, t, *J* 2x8.7 Hz, 17α–H), 6.63 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) -7.6 (15β-$SnMe_3$), 13.2 (C-18), 21.2 ($COCH_3$), 22.6 (C-15), 25.9 (C-11), 28.3 (C-7), 29.6 (C-6), 32.4 (C-12), 37.3 (C-16), 38.9 (C-8), 42.8 (C-13), 44.2 (C-9), 53.4 (C-14), 55.2 (3-OMe), 83.4 (C-17), 111.5 (C-2), 113.8 (C-4), 126.3 (C-1), 132.4 (C-10), 137.6 (C-5), 157.5 (C-3), and 171.2 ($COCH_3$) (Found: C, 58.9; H, 7.5 %; M^+, 491. $C_{24}H_{36}O_3Sn$ requires C, 58.7; H, 7.4 %; M, 491)

3-Methoxy-15β-trimethylsilylestra-1,3,5(10)-trien-17–one 61

a) Ethereal methyllithium (1.4 M,10.5 cm^3) was added dropwise to a mixture of hexamethyldisilane (3.3 cm^3, 16.25 mmol) and hexamethylphosphoramide (HMPA)(6.5 cm^3), at 0 °C, under nitrogen. The resultant reddish solution was stirred for 30 min, after which tetrahydrofuran (35 cm3) was added, and the temperature cooled to -78 °C. The Δ^{15} 17-ketone **19** (1.38 g, 4.9 mmol) was added to the mixture, followed by a further aliquot of tetrahydrofuran (25 cm^3). The mixture was stirred at -78 °C for 45min, after which saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with dilute hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (3.1 g). The residue was chromatographed on silica gel (200 g) with ethyl acetate-toluene (2:98) as the eluent to afford the 15β-*(trimethylsilyl)dimethylsilyl* 17–*ketone* **60** (710 mg, 35 %), mp 100-102 °C (from methanol), $[\alpha]_D$ 66° (c 1.0); ν_{max} 1728 (CO) cm^{-1}; δ_H (400 MHz) 0.08 (9H, s, 15β-$SiMe_2SiMe_3$), 0.18 and 0.22 (2x3H, s, 15β-$SiMe_2SiMe_3$), 0.95 (3H, s, 13β-Me), 1.40-1.54 (3H, m, 12-H, 7-H and 11-H), 1.72 (1H, qd, *J* 3x11.4 and 2.2 Hz, 8β-H), 1.91-2.04 (4H, m, 12-H, 15α-H, 7-H and 14α-H), 2.22 (1H, td, *J* 2x10.9 and 3.5 Hz, 9α-H), 2.32-2.40 (1H, m, 11-H), 2.42-2.48 (2H, m, 16-H_2), 2.90 (2H, m, 6-H_2), 3.77 (3H,

s, 3-OMe), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H), and 7.19 (1H, d, *J* 8.3 Hz, 1-H); δ_C (100 MHz) -2.4 (15β-Si*Me*$_2$SiMe$_3$), -1.9 (15β-SiMe$_2$Si*Me*$_3$), -1.0 (15β-Si*Me*$_2$SiMe$_3$), 15.35 (C-18), 19.05 (C-15), 25.7 (C-11), 27.9 (C-7), 29.5 (C-6), 32.6 (C-12), 37.8 (C-8), 40.7 (C-16), 44.8 (C-9), 47.1 (C-13), 55.2 (3-OMe), 55.6 (C-14), 111.6 (C-2), 113.9 (C-4), 126.3 (C-1), 132.1 (C-10), 137.6 (C-5), 157.7 (C-3), and 221.7 (C-17) (Found: C, 69.2; H, 9.7 %; M^+, 414. $C_{24}H_{38}O_2Si_2$ requires C, 69.5; H, 9.3 %; M, 414), followed by a mixed fraction (300 mg), and the 15β-*trimethylsilyl* 17-*ketone* **61** (444 mg, 25%), mp 140-142 °C (from ethanol), $[\alpha]_D$ 64° (*c* 1.0); ν_{max} 1728 (CO) cm^{-1}; δ_H (400 MHz) 0.18 (3H, s, 15β-SiMe$_3$), 0.91 (3H, s, 13β-Me), 1.40-1.56 (3H, m, 12-H, 7-H and 11-H), 1.72 (1H, obscured qd, *J* 3x11.45 and 2.3 Hz, 8β-H), 1.77 (1H, obscured ddd, *J* 10.1, 8.1 and 3.2 Hz, 15α-H), 1.91-2.04 (2H, m, 12-H and 7-H), 1.98 (1H, obscured dd, *J* 11.0 and 8.1 Hz, 14α-H), 2.22 (1H, td, *J* 2x11.0 and 4.1 Hz, 9α-H), 2.32-2.39 (1H, m, 11-H), 2.43 (1H, dd, *J* 19.7 and 10.1 Hz,16α-H), 2.52 (1H, dd, *J* 19.7 and 3.2 Hz, 16β-H), 2.90 (2H, m, 6-H$_2$), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.75 Hz, 4-H), 6.72 (1H, dd, *J* 8.55 and 2.75 Hz, 2-H), and 7.20 (1H, d, *J* 8.55 Hz, 1-H); δ_C (100 MHz) 1.1 (15β-SiMe$_3$), 15.35 (13β-Me), 21.5 (C-15), 25.7 (C-11), 28.0 (C-7), 29.5 (C-6), 32.7 (C-12), 37.9 (C-8), 39.6 (C-16), 44.8 (C-9), 47.3 (C-13), 54.9 (C-14), 55.2 (3-OMe), 111.6 (C-2), 113.9 (C-4), 126.3 (C-1), 132.1 (C-10), 137.6 (C-5), 157.7 (C-3), and 221.8 (C-17) (Found: C, 74.0; H, 9.1 %; M^+, 356. $C_{22}H_{32}O_2Si$ requires C, 74.1; H, 9.0 %; M, 356).

b) A mixture of hexamethyldisilane (3.43 cm^3, 17.2 mmol) and hexamethylphosphoramide (HMPA)(6.9 cm^3) was cooled to -78 °C, whereapon it solidified. Ethereal methyllithium (1.4 M solution, 9.8 cm^3) was added dropwise onto the frozen solution, followed by tetrahydrafuran (35 cm^3) in small portions. The temperature was heated to 0 °C, whereapon the solid melted, allowing stirring. The mixture was stirred for 15 min, resulting in a reddish solution which was cooled to -78 °C. The Δ^{15} 17-ketone **19** (3 g, 10.6 mmol) was added to the mixture, followed by a further aliquot of tetrahydrafuran (20 cm^3). The mixture was stirred at -78 °C for 45min, and then poured into ice water, after which solid sodium carbonate was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with dilute hydrochloric acid (1

M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (4.6 g). The residue was chromatographed on silica gel (400 g) with ethyl acetate-toluene (2:98) as the eluent to afford the 15β-trimethylsilyl 17–ketone **61** (2.8 g, 75%).

17-Acetoxyimino-3-methoxy-15β-trimethylsilylestra-1,3,5(10)-trien 62

A solution of the 15β-trimethylsilyl 17-ketone **61** (1 g, 2.81 mmol), hydroxylamine hydrochloride (981 mg, 14.1 mmol) and 1,4-diazabicyclo [2.2.2] octane (315 mg, 2.81 mmol) was refluxed in methanol (12 cm^3), for 20 h. The methanol was evaporated under reduced pressure, and the resultant residue dissolved in chloroform. The organic phase was washed with water, hydrochloric acid (1 M), and saturated sodium hydrogencarbonate, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (1.23 g). Flash chromatography of the residue on silica gel (100 g) with ethyl acetate-toluene (1:9) as the eluent afforded the 15β-*trimethylsilyl* 17–*oxime* **62** (1.04 g, 99%) as an oil (Found: M^+, 371.227. $C_{22}H_{33}O_2NSi$ requires M, 371.228)

Acetic anhydride (2.0 cm^3) was added to a solution of the 15β-trimethylsilyl 17-oxime **62** (670 mg, 1.81 mmol) in dry pyridine (20 cm^3), under nitrogen. The mixture was then stirred for 15 h. Thereafter the mixture was poured into water, and solid sodium hydrogen carbonate added till effervescence ceased. The mixture was then stirred for 30 min, and extracted with ethyl acetate. The combined extract was washed with dilute hydrochloric acid, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (892 mg). Flash chromatography of the residue on silica gel (80 g) with ethyl acetate-toluene (5:95) as the eluent afforded the 15β-*trimethylsilylestra* 17–*oxime acetate* **63** (655 mg, 90%) as an oil; ν_{max} 1751 (CO) cm^{-1}; δ_H (400 MHz) 0.14 (3H, s, 15β-$SiMe_3$), 1.05 (3H, s, 13β-Me), 1.95 (1H, dd, *J* 11.5 and 8.6 Hz, 14α-H), 2.17 (3H, s, 17-NOAc), 2.74 (1H, dd, *J* 10.5 and 2.5 Hz,16β-H), 2.86 (1H, dd, *J* 19.7 and 10.5 Hz, 16α-H), 2.90 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 1.04 (15β-$SiMe_3$), 18.6 (C-18), 19.6 (17-$NOCOCH_3$), 22.9 (C-15), 25.8 (C-11), 28.6 (C-7), 29.4 (C-6), 30.2 (C-12), 34.8 (C-16), 37.6 (C-8), 44.5 (C-9), 44.9 (C-13), 55.1 (3-OMe), 57.1 (C-14), 111.5 (C-2), 113.8 (C-4), 126.1 (C-1),

132.0 (C-10), 137.3 (C-5), 157.5 (C-3), 169.0 (C-17), and 178.8 (17-$NOCOCH_3$) (Found: M^+, 413.238. $C_{24}H_{35}NO_3Si$ requires M, 413.238)

Attempted Beckmann fragmentation of 15β-trimethylsilyl 17–oxime acetate 63

a) To a solution of silyl oxime acetate **63** (240 mg, 0.58 mmol) in anhydrous dichloromethane (2 cm^3) was added trimethylsilyl trifluoromethanesulfonate (0.11 cm^3) at 0°C. The mixture was stirred for 35 min, and then saturated sodium carbonate and triethylamine (0.3 cm^3) were added. The mixture was extracted with chloroform, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (220 mg). The residue was chromatographed on silica gel (33 g) with ethyl acetate-toluene (5:95) as the eluent to afford the 3-*methoxy*-15β-*trimethylsilyl*-13,17-*secoestra*-1,3,5(10),12-*tetraen*-17–*nitrile* **64** (16 mg, 8 %) as an oil; ν_{max} 2252 (CN) cm^{-1}; δ_H (200 Mhz) 0.13 (3H, s, 15β-$SiMe_3$), 1.74 (3H, d, *J* 1.0 Hz, 13-Me), 3.78 (3H, s, 3-OMe), 5.73 (1H, br.d, *J* 6.6 Hz, 12-H), 6.63 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.8 and 2.6 Hz, 2-H), and 7.19 (1H, d, *J* 8.6 Hz, 1-H); (Found: M^+, 353. $C_{22}H_{31}NOSi$ requires M, 353), followed by the 3-*methoxy*-13,17-*secoestra*-1,3,5(10),14-*tetraen*-17–*nitrile* **65** (20 mg, 12 %), as an oil; ν_{max} 2252 (CN) cm^{-1}; δ_H (400 MHz) 1.13 (3H, d, *J* 7.2 Hz, 13β-Me), 1.5-1.66 (2H, m, 7α-H and 11-H), 1.70-1.86 (2H, m, 12-H_2), 1.99 (1H, m, 7β-H), 2.18-2.37 (3H, m, 8β-H, 11-H and 9α-H), 2.90 (2H, m, 6-H_2), 2.94 (1H, m, 13α-H), 3.15 (2H, dd, *J* 7.0 and 1.4 Hz, 16-H_2), 3.78 (3H, s, 3-OMe), 5.12 (1H, td, *J* 2x7.0 and 1.8 Hz, 15-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.8 Hz, 1-H); δ_C (100 MHz) 15.5 (C-15), 18.0 (C-18), 25.2 (C-7), 26.8 (C-11), 30.2 (C-6), 30.7 (C-13), 32.7 (C-12), 40.3 (C-8), 45.0 (C-9), 55.2 (3-OMe), 106.3 (C-15), 112.0 (C-2), 113.4 (C-4), 118.8 (C-17), 127.2 (C-1), 131.9 (C-10), 137.5 (C-5), 152.8 (C-14), and 157.5 (C-3) (Found: M^+, 281.177. $C_{19}H_{23}NO$ requires M, 281.178). The combined fractions and eluted column were evaporated under reduced pressure to give a mixture of uncharacterisable residues (100 mg).

b) To a solution of oxime acetate **63** (170 mg, 0.41 mmol) in dry dichloromethane (2 cm^3), was added boron trifluoride etherate (0.1 cm^3) at 0°C. After 40 min, saturated sodium carbonate was added and the mixture extracted with chloroform. The combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (165 mg). The residue was chromatographed on silica gel (17 g) with ethyl acetate-toluene (2:98) as the eluent to afford the 3-methoxy-13,17-secoestra-1,3,5(10),14-tetraen-17–nitrile **65** (35 mg, 30 %). The remaining fractions and flushed column (chloroform) fraction were combined, and evaporated under reduced pressure to give a mixture of polar uncharacterised residues (60 mg).

3-Methoxy-17α-methyl-15β-trimethylsilylestra-1,3,5(10)-trien-17β–ol 66

Ethereal methyl-lithium (1.4 M solution, 2.0 cm^3) was added dropwise to a stirred solution of the 15β-trimethylsilyl 17-ketone **61** (390 mg, 1.09 mmol) in tetrahydrofuran (10 cm^3). The solution was stirred at -78 °C for 3 h, and then saturated ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (430 mg). Flash chromatography of the residue on silica gel (49 g) with ethyl acetate-toluene (4:96) as the eluent afforded starting material **61** (145 mg, 37%), followed by the 15β-*trimethylsilyl* 17α-*methyl* 17β-*alcohol* **66** (151 mg, 37%) as an oil; ν_{max} 3608 (OH) cm^{-1}; δ_H (400 MHz) 0.09 (9H, s, 15β-Si*Me*$_3$), 0.89 (3H, s, 13β-Me), 1.30 (3H, s, 17α-Me), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.55 and 2.7 Hz, 2-H), and 7.22 (1H, d, *J* 8.55 Hz, 1-H); δ_C (100 MHz) 1.4 (q, 15β-$SiMe_3$), 15.7 (q, C-18), 22.0 (d, C-15), 24.6 (q, 17α-Me), 25.6 (t, C-11), 29.5 (t, C-6), 29.6 (t, C-7), 32.0 (t, C-12), 38.9 (d, C-8), 42.5 (t, C-16), 45.0 (d, C-9), 45.5 (s, C-13), 52.7 (d, C-14), 55.2 (s, 3-Ome), 81.2 (s, C-17), 111.3 (d, C-2), 113.8 (d, C-4), 126.1 (d, C-1), 133.0 (s, C-10), 137.8 (s, C-5), and 157.5 (s, C-3) (Found: M^+, 372.247. $C_{23}H_{36}O_2Si$ requires M, 372.248)

3-Methoxy-16-methyleneestra-1,3,5(10)-trien-17-one 67

A solution of acetyl chloride (1.5 cm^3, 21.12 mmol) in dry ether (20 cm^3) was added dropwise to N.N.N'.N'-tetramethyldiaminomethane (2.8 cm^3) at 0 °C, with stirring. After 30 min, the white precipitate which formed was rapidly filtered off and suspended in dry acetonitrile (27 cm^3). Estrone 3-methyl ether **25** (3.1 g, 10.9 mmol) was added and the reaction mixture was stirred at 80 °C for 20 h. The solvent was evaporated under reduced pressure and the residue was made alkaline with aqueous sodium hydroxide (2 M). The mixture was extracted with ether, and the combined extract was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (3.8 g), which was dissolved in acetic anhydride (25 cm^3) and stirred at 140 °C for 2 h. The temperature was lowered to room temperature, and saturated aqueous sodium hydrogen carbonate was carefully added. The mixture was stirred for a further 30 min, and extracted with chloroform. The combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give the 16-methylene 17-ketone **67** (3 g, 93 %), mp 119-124 °C (lit.,[70] 120-122 °C)

Conjugate silylation of the 16-methylene 17-ketone 67

a) Ethereal methyllithium (1.4 M solution, 3.6 cm^3) was added dropwise to a mixture of hexamethyldisilane (1.14 cm^3, 5.06 mmol) and hexamethylphosphoramide (HMPA)(6.5 cm^3), at 0 °C, under nitrogen. The resultant reddish solution was stirred for 30 min, after which tetrahydrofuran (12 cm3) was added, and the temperature cooled to -78 °C. The 16-methylene 17-ketone **67** (0.5 g, 1.69 mmol) was added to the mixture, followed by a further aliquot of tetrahydrofuran (5 cm^3). The mixture was stirred at -78 °C for 40min, after which saturated ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (1.5 g). The residue was chromatographed on silica gel (50 g) with ethyl acetate-toluene (1:99) as the eluent to afford the 3-*methoxy*-16β-*(trimethylsilyl)dimethysilylmethylestra*-1,3,5(10)-*trien*-17–*one* **72** (60 mg, 9 %), mp 133-135 °C (from methanol), $[\alpha]_D$ 126° (*c* 1.0); ν_{max} 1734 (CO) cm^{-1};

δ_H (400 MHz) 0.07 (9H, s, 16^1-$SiMe_2Si\mathit{Me}_3$), 0.08 and 0.09 (3H, s, 16^1-$Si\mathit{Me}_2SiMe_3$), 0.56 (1H, dd, *J* 14.6 and 11.7 Hz, 16^1-H), 0.87 (3H, s, 13β-Me), 1.39 (1H, dd, *J* 14.7 and 3.5 Hz, 16^1-H), 2.90 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.65 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.65 Hz, 2-H), and 7.20 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) -4.0 and -3.2 (q, 16^1-$Si\mathit{Me}_2SiMe_3$), -2.1 (q, 16^1-$SiMe_2Si\mathit{Me}_3$), 14.4 (q, C-18), 18.5 (t, C-16^1), 25.8 (t, C-15), 26.75 (t, C-11), 29.7 (t, C-7), 31.4 (t, C-6), 32.0 (t, C-12), 38.0 (d, C-8), 44.1 (d, C-16), 45.8 (d, C-9), 48.0 (s, C-13), 49.1 (d, C-14), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.9 (d, C-4), 126.3 (d, C-1), 132.1 (s, C-10), 137.7 (s, C-5), 157.6 (s, C-3), and 223.9 (s, C-17) (Found: C, 70.0; H, 9.7 %; M^+, 428. $C_{23}H_{34}O_2Si$ requires C, 70.0; H, 9.4 %; M, 428), followed by a mixed fraction (50 mg), followed by the 3-*methoxy*-16β-*trimethylsilylmethylestra*-1,3,5(10)-*trien*-17–*one* **68** (230 mg, 38%), mp 138-140 °C (from chloroform-methanol), $[\alpha]_D$ 136° (*c* 1.0); ν_{max} 1734 (CO) cm^{-1}; δ_H (400 MHz) 0.05 (9H, s, 16^1-$SiMe_3$), 0.50 (1H, dd, *J* 14.7 and 11.95 Hz, 16^1-H), 0.87 (3H, s, 13β-Me), 1.30 (1H, dd, *J* 14.7 and 3.4 Hz, 16^1-H), 2.90 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) -1.1 (q, 16^1-$SiMe_3$), 14.4 (q, C-18), 20.6 (t, C-16^1), 25.8 (t, C-15), 26.7 (t, C-11), 29.7 (t, C-7), 31.1 (t, C-6), 32.0 (t, C-12), 38.0 (d, C-8), 44.1 (d, C-16), 45.2 (d, C-9), 48.0 (s, C-13), 49.2 (d, C-14), 55.2 (q, 3-OMe), 111.6 (d, C-2), 113.9 (d, C-4), 126.3 (d, C-1), 132.1 (s, C-10), 137.7 (s, C-5), 157.6 (s, C-3), and 224.1 (s, C-17) (Found: C, 74.7; H, 9.5 %; M^+, 370. $C_{23}H_{34}O_2Si$ requires C, 74.5; H, 9.25 %; M, 370), and the 3-*methoxy*-17-*oxoestra*-1,3,5(10)-*trien*-16β-(3-*methoxy*-17-*oxo*-16β-*(trimethylsilyl)dimethylsilylestra*-1,3,5(10)-*trien*-16α-)methane **73** (100mg, 9 %) as an oil, $[\alpha]_D$ 177° (*c* 1.0); ν_{max} 1736 (CO) cm^{-1}; δ_H (400 MHz) 0.14 (9H, s, $16\beta^1$-$SiMe_3$), 0.86 (3H, s, 13β-Me), 0.94 (1H, d, *J* 14.8 Hz, 16^1-H), 1.05 (3H, s, 13β-Me), 1.18 (1H, d, *J* 14.8 Hz, 16^1-H), 2.90 (4H, m, 2x6-H_2), 3.79 (3H, s, 3-OMe), 3.80 (3H, s, 3-OMe), 6.67-6.68 (2H, m, 2x4-H), 6.72-6.77 (2H, m, 2x2-H), and 7.18-7.22 (2H, m, 2x1-H); δ_C (100 MHz) 0.88 ($16\beta^1$-$SiMe_3$), 13.8 and 16.0 (C-18' and C-18"), 25.7 and 25.8 (C-15' and C-15"), 26.7 (C-11' and C-11"), 29.6 (C-7' and C-7"), 30.7 and 31.6 (C-6' and C-6"), 31.8 and 32.5 (C-12' and C-12"), 36.5 (C-16'), 37.8 and 38.1 (C-8' and C-8"), 41.9 (C-1), 44.0 and 44.3 (C-16' and C-16"), 46.7 and 47.9 (C-9' and C-9"), 48.1 and 48.5 (C-13' and C-13"), 49.1 and

50.6 (C-14' and C-14"), 55.1 (2x3-OMe), 111.5 and 111.6 (C-2' and C-2"), 113.8 (C-4' and C-4"), 126.1 and 126.2 (C-1' and C-1"), 131.9 and 132.0 (C-10' and C-10"), 137.65 and 137.7 (C-5' and C-5"), 157.6 (C-3' and C-3"), 222.0 and 224.9 (C-17' and C-17") (Found: M^+, 666.411. $C_{43}H_{58}O_4Si$ requires M, 666.410).

b) A mixture of hexamethyldisilane (1.63 cm^3, 7.87 mmol) and hexamethylphosphoramide (HMPA)(3.2 cm^3) was cooled to -78 °C, whereapon it solidified. Ethereal methyllithium (1.4 M solution, 4.5 cm^3) was added dropwise onto the frozen solution, followed by tetrahydrofuran (16 cm^3) in small portions. The temperature was heated to 0 °C, whereapon the solid melted, allowing stirring. The mixture was stirred for 15 min, resulting in a reddish solution which was cooled to -78 °C. The 16-methylen 17-ketone **67** (1.44 g, 4.86 mmol) was added to the mixture, followed by a further aliquot of tetrahydrofuran (10 cm^3). The mixture was stirred at -78 °C for 45min, and then poured into ice water, after which solid sodium carbonate was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (1.8 g). The residue was chromatographed on silica gel (200 g) with ethyl acetate-toluene (1:49) as the eluent to afford the 16^1-trimethylsilyl 17-ketone **68** (700 mg, 40 %), followed by bis steroid **73** (640 mg, 20 %).

17-Hydroxyimino-3-methoxy-16α-trimethylsilylmethylestra-1,3,5(10)-triene 75

a) Hydroxylamine hydrochloride (113 mg) and sodium acetate (177 mg) were added to a solution of the 16^1β-trimethylsilyl 17-ketone **68** (200 mg, 0.54 mmol) in tetrahydrafuran (4.8 cm^3) and ethanol (18 cm^3). The mixture was stirred at room temperature for 26 h, and then further hydroxylamine hydrochloride (113 mg) and sodium acetate (177 mg) were added. The mixture was stirred for further 26h, after which saturated sodium hydrogen carbonate was added. The mixture was extracted with ethyl acetate, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (245 mg). The residue was chromatographed on

silica gel (35 g) with ethyl acetate-toluene (1:19) as the eluent to afford the 16β-*trimethylsilylmethylestra* 17–*hydroxyimino* compound **74** (131 mg, 62 %) as an oil; δ_H (400 MHz) 0.07 (9H, s, 16^1-$SiMe_3$), 0.71 (1H, dd, *J* 14.8 and 12.0 Hz, 16^1-H), 1.11 (3H, s, 13β-Me), 1.28 (1H, dd, *J* 14.8 and 3.3 Hz, 16^1-H), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.7 and 2.65 Hz, 2-H), 7.22 (1H, d, *J* 8.7 Hz, 1-H), and 8.19 (1H, br.s, D_2O exchanged, 17-NOH); δ_C (100 MHz) -0.8 (16^1-$SiMe_3$), 14.3 (C-18), 23.7 (C-16^1), 26.4 (C-15), 27.3 (C-11), 29.7 (C-7), 33.3 (C-6), 35.4 (C-12), 37.4 (C-16), 39.0 (C-8), 43.7 (C-9), 46.4 (C-13), 52.3 (C-14), 55.2 (3-OMe), 111.5 (C-2), 113.8 (C-4), 126.2 (C-1), 132.5 (C-10), 137.7 (C-5), 157.5 (C-3), and 173.6 (C-17) (Found: M^+, 385. $C_{23}H_{35}O_2NSi$ requires M, 385), followed by the 16α-*trimethylsilylmethylestra* 17–*hydroxyimino* compound **75** (80 mg, 38 %) as an oil; ν_{max} 3288 and 3587 (OH) cm^{-1}; δ_H (400 MHz) 0.06 (9H, s, 16^1-Si*Me*$_3$), 0.53 (1H, dd, *J* 14.65 and 12.2 Hz, 16^1-H), 1.01 (3H, s, 13β-Me), 1.72 (1H, dd, *J* 14.65 and 2.2 Hz, 16^1-H), 2.88 (2H, m, 6-H_2), 2.92 (1H, m, 16β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.3 and 2.7 Hz, 2-H), 7.20 (1H, d, *J* 8.3 Hz, 1-H), and 7.63 (1H, br.s, D_2O exchanged, 17-NOH); δ_C (100 MHz) -0.9 (q, 16^1-$SiMe_3$), 17.2 (q, C-18), 21.7 (t, C-16^1), 26.1 (t, C-15), 27.2 (t, C-11), 29.7 (t, C-7), 33.2 (t, C-6), 34.4 (t, C-12), 35.5 (d, C-16), 38.1 (d, C-8), 44.0 (d, C-9), 44.4 (s, C-13), 51.7 (d, C-14), 55.2 (s, 3-OMe), 111.5 (d, C-2), 113.8 (d, C-4), 126.3 (d, C-1), 132.4 (s, C-10), 137.8 (s, C-5), 157.5 (s, C-3), and 174.6 (s, C-17) (Found: M^+, 385.243. $C_{23}H_{35}O_2NSi$ requires M, 385.2435)

b) A solution of 16^1β-trimethylsilyl 17-ketone **68** (670 mg, 1.81 mmol), hydroxylamine hydrochloride (632 mg, 9.1 mmol) and 1,4-diazabicyclo [2.2.2] octane (204 mg, 1.81 mmol) was refluxed in methanol (10 cm^3), for 20 h. The methanol was evaporated under reduced pressure, and the resultant residue dissolved in chloroform. The organic phase was washed with water, hydrochloric acid (1 M), and saturated sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (770 mg). Flash chromatography of the residue on silica gel (90 g) with ethyl acetate-toluene (1:49) as the eluent afforded the 16β-trimethylsilylmethyl 17-oxime **74** (30

mg, 4%), followed a mixed fraction (46 mg), and the 16α-trimethylsilylmethyl 17-oxime **75** (500 mg, 72%).

17-Acetoxyimino-3-methoxy-16β-trimethylsilylmethylestra-1,3,5(10)-triene 76

Acetic anhydride (0.3 cm^3) was added to a solution of 16α-trimethylsilylmethyl 17-oxime **75** (350 mg, 0.91 mmol) and N,N-dimethylaminopyridine (30 mg) in pyridine (20 cm^3). The mixture was stirred at room temperature for 3 h, then saturated sodium hydrogen carbonate was added, and the resultant mixture was stirred for 1h. The mixture was extracted with ethyl acetate, and the combined extract was washed with hydrochloric acid (1 M), dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (338 mg). The residue was chromatographed on silica gel (80 g) with ethyl acetate-toluene (1:49) as the eluent to afford the 16α-*trimethylsilylmethyl* 17-*acetoxyimino* compound **76** (350 mg, 90%) as an oil; ν_{max} 1758 (CO) cm^{-1}; δ_H (400 MHz) 0.10 (9H, s, 16^1-$SiMe_3$), 0.66 (1H, dd, *J* 14.4 and 12.2 Hz, 16^1-H), 1.09 (3H, s, 13β-Me), 2.15 (3H, s, 17-OAc), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1H) ; δ_C (100 MHz) -1.1 (16^1-$SiMe_3$), 16.7 (C-18), 19.6 (N-$OCOCH_3$), 22.8 (C-16^1), 25.8 (C-15), 27.1 (C-11), 29.5 (C-7), 33.1 (C-6), 34.1 (C-12), 36.9 (C-16), 38.0 (C-8), 43.65 (C-9), 45.4 (C-13), 51.6 (C-14), 55.1 (3-OMe), 111.45 (C-2), 113.7 (C-4), 126.2 (C-1), 131.9 (C-10), 137.5 (C-5), 157.5 (C-3), 168.6 (C-17), and (N-$OCOCH_3$) (Found: M^+, 427.253. $C_{25}H_{37}NO_3Si$ requires M, 427.253)

17a-Acetoxy-3-methoxy-16β-trimethylsilylmethyl-17a-aza-17a-homoestra-1,3,5(10),17-tetraene 77

Boron trifluoride diethyl ether (0.06 cm^3) was added to a solution of the 16α-trimethylsilylmethyl 17-acetoxyimino compound **76** (120 mg, 0.28 mmol) in dichloromethane (2 cm^3) at 0°C. The mixture was stirred for 20 min, then saturated sodium carbonate was added, and the mixture extracted with chloroform. The combined extract

was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (120 mg). The residue was chromatographed on silica gel (12 g) with ethyl acetate-toluene (1:49) as the eluent to afford an uncharacterized product (5 mg), followed by the 17a-*acetoxy*-3-*methoxy*-16β-*trimethylsilylmethyl*-17a-*aza*-17a-*homoestra*-1,3,5(10),17-*tetraen* compound **77** (45 mg, 52 %), mp 98-99 °C (from methanol), $[\alpha]_D$ 56° (c 1.0); ν_{max} 1723 and 1669 (C-17 and 17-O*C*OCH$_3$) cm^{-1}; δ_H (400 Mhz) 0.08 (9H, s, 16β-CH_2SiMe_3), 0.64 (1H, dd, J 14.8 and 9.9 Hz, 16^1-H), 1.43 (3H, s, 13β-Me), 2.30 (3H, s, 17-OAc), 2.90 (2H, m, $6H_2$), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.18 (1H, d, J 8.5 Hz, 1-H); δ_C (100 MHz) -0.6 (q, $SiMe_3$), 20.0 (t, C-16^1), 20.1 (q, C-18), 26.3 (t, C-11), 27.0 (t, C-7), 28.9 (q, 17-OCO*C*H$_3$), 29.2 (t, C-6), 29.8 (t, C-15), 36.3 (t, C-12), 39.2 (d, C-8), 40.8 (d, C-14), 42.6 (d, C-9), 48.2 (d, C-16), 55.2 (q, 3-OMe), 63.2 (s, C-13), 111.7 (d, C-2), 113.5 (d, C-4), 126.2 (d, C-1), 131.7 (s, C-10), 137.4 (s, C-5), 157.8 (s, C-3), 178.4 (s, 17-O*C*O*C*H$_3$), and 178.6 (s, C-17) (Found: M^+, 427.255. $C_{25}H_{37}NO_3Si$ requires M, 427.254).

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