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Cycloaddition Mediated Synthesis and Rearrangement of 16-Functionalised 14α,17α-Etheno-19-norsteroids

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Abstract: Estra-1,3,5(10),14,16-pentaen-17-yl acetates (1) undergo cycloaddition with 2-acetoxyacrylonitrile to give the corresponding 16α,17β-diacetoxy 14α,17α-etheno 16β-carbonitriles (3), accompanied by minor regio- and stereoisomers depending upon reaction conditions. An X-ray crystal structure analysis of the major isomer derived from the reaction with **1b**(3-OAc) confirmed the structure as 3,16α,17β-triacetoxy-14,17α-ethenoestra-1,3,5(10)-triene-16β-carbonitrile (**3b**). Hydrolysis of the 16α-acetoxy 16β-cyano moiety of **3** furnishes 17β-hydroxy 16-ketones which undergo stereoselective reduction to give mainly the corresponding 16β,17β-diols. Acid-mediated rearrangement of these diols or base treatment of the derived 17β-hydroxy 16β-mesylates results in ready 17→(17 → 16)*abeo* rearrangement, thus providing synthetic access to 14α,16α-ethano derivatives of estrone.

Cycloaddition of phenyl vinyl sulfone to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1a**) provides efficient synthetic access to 14α,17α-etheno-19-norsteroids,[1] a family of compounds which has attracted growing interest following the finding[2] that the 14α,17α-ethano analogue of estradiol displays superior oral estrogenicity. This has stimulated extended studies to delineate the influence of ring D bridged structures upon hormonal activity[3—6] and to exploit cycloaddition methodology in the elaboration of functionally modified steroids.[7—9] In complementary investigations, the utility of steroidal and related ring D diene models as homochiral templates in sequential cycloaddition–chiral induction–retro-Diels-Alder protocols has been demonstrated.[10]

An extension of cycloaddition strategy to the synthesis of 14α,17α-ethano-19-norsteroids bearing additional functionality on ring D would entail the choice of dienophiles in which the appended group(s) ensure appropriate regioselectivity as well as ready modification into the desired ring D substituents. This approach was considered for the synthesis of 16-oxygenated 14α,17α-ethano-19-norsteroids, in which one of the objectives was to extend comparative structure–activity studies to bridged hormone analogues resembling the important short-lived estrogen, estra-1,3,5(10)-triene-3,16α,17β-triol.[11,12]

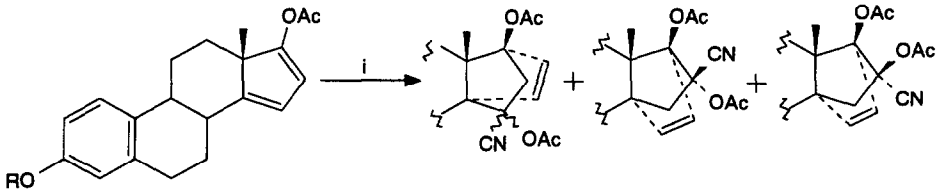
With this objective in mind, consideration was given to cycloaddition of ketene equivalents to the dienyl acetates (**1**), in order to introduce latent oxygen functionality at C(16) in the bridged intermediate, for further modification into the target system. The initial choice of 2-acetoxyacrylonitrile was indicated by the facility with which the geminal acetoxy-cyano group in the derived cycloadducts can be converted into the corresponding oxo group.[13] In this work, we describe cycloadditions of this dienophile to the dienyl acetates

(**1**) and, further transformations of the major cycloadduct.

Initial studies carried out upon 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1a**) revealed that cycloaddition of 2-acetoxyacrylonitrile in a sealed tube proceeded slowly over a wide temperature range, and that reactions conducted at elevated temperatures (> 160 °C) were accompanied by considerable darkening of the medium and decomposition of reactants. The reaction appeared to be unresponsive to Lewis acid catalysis at lower temperatures, conditions which rather accelerated decomposition of the dienyl acetate moiety in **1a**. However, the addition of small amounts of polymerisation inhibitors were well tolerated in protracted reactions conducted at temperatures up to 150 °C. For example, a cycloaddition in benzene at 150 °C, in the presence of hydroquinone, was incomplete after 210 h, but the medium suffered minimal discoloration. Furthermore, the addition of further aliquots of the dienophile at intervals was beneficial. Under these conditions, it was possible to recover starting material (**1a**) (16%) and an 81% yield of a single cycloadduct (**3a**).

By contrast, the reaction of **1a** in mesitylene and 2,6-di-*t*-butyl-*p*-cresol, conducted over 36 h in the temperature range 160—180 °C gave a complex mixture which was separated, in moderate overall yield, into the cycloadducts (**2a**) (13%), (**3a**) (32%), and (**4**) (4%). Similar experiments conducted at temperatures in excess of 180 °C resulted in altered ratios of products, apparently favouring the regioisomer (**2a**).

In another variation, the reaction of estra-1,3,5(10),14,16-pentaene-3,17-diyl diacetate (**1b**) with 2-acetoxyacrylonitrile in dichloromethane at 100 °C proceeded slowly but relatively cleanly to give, after 140 h, a satisfactory yield (71%) of the cycloadduct (**3b**) accompanied by the regioisomer (**2b**) (3.1%).



1a R=Me **1b** R=Ac **2a** (3-OMe) **2b** (3-OAc) **3a** (3-OMe) **3b** (3-OAc) **4** (3-OMe)

Reagent: (i) CH_2=C(OAc)CN, 100—180 °C

The foregoing experiments typify the problems encountered in attempting to optimise and reproduce this cycloaddition; furthermore, the variability in the reaction outcome invited speculation upon the structures of the products and factors controlling regio- and stereoselectivity. Precedent suggested that overall β-face cycloaddition should predominate and that the preferred regioselectivity would result in 16,16-disubstituted product(s). The gross structural features compatible with [4 + 2] cycloaddition products were evident from spectroscopic and analytical data for **2**—**4**. In each case, NMR evidence for the presence of a geminally disubstituted bicyclo[2.2.1]heptenoid system was clear, but the sites of substitution and the configurations of the geminal substituents were not apparent. However, a comparison of ^{1}H and ^{13}C NMR data for the 3-methoxy and 3-acetoxy series of compounds verified the ring D structural correspondence of **2a** with **2b** and **3a** with **3b**.

The structural uncertainties were partly dispelled by conducting an X-ray crystal structure determination upon the major cycloadduct (**3b**). Details of the structure determination are reported in the Experimental section, and the structure is depicted in Figure 1. By extension, this also confirmed the structure of the corresponding 3-methoxy compound (**3a**). The structure determination confirmed the expectation of overall β-face cycloaddition and *'ortho'* regioselectivity. However, it is notable that the configuration at C(16) suggests that the respective steric demands of the acetoxy and cyano groups in the dienophile dictate the reaction outcome, and presumably override secondary orbital interactions which might be expected to favour *endo*-orientation of the cyano group in the transition state, and hence, a 16β-acetoxy 16α-cyano structure in the major product.

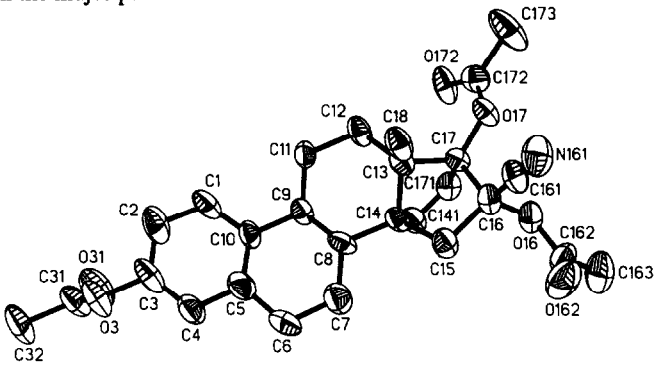


Figure 1 X-Ray crystal structure of cycloadduct(**3b**) showing crystallographic numbering

The structure of the stereoisomer (**4**) has since also been confirmed by X-ray crystallography, and the chemistry of the regioisomeric series will be described elsewhere.[14] The ensuing discussion deals with further transformations of the major cycloadduct (**3a**). Parallel experiments on the 3-acetoxy derivative (**3b**) displayed close correspondence with these findings,[14] and are omitted for clarity.

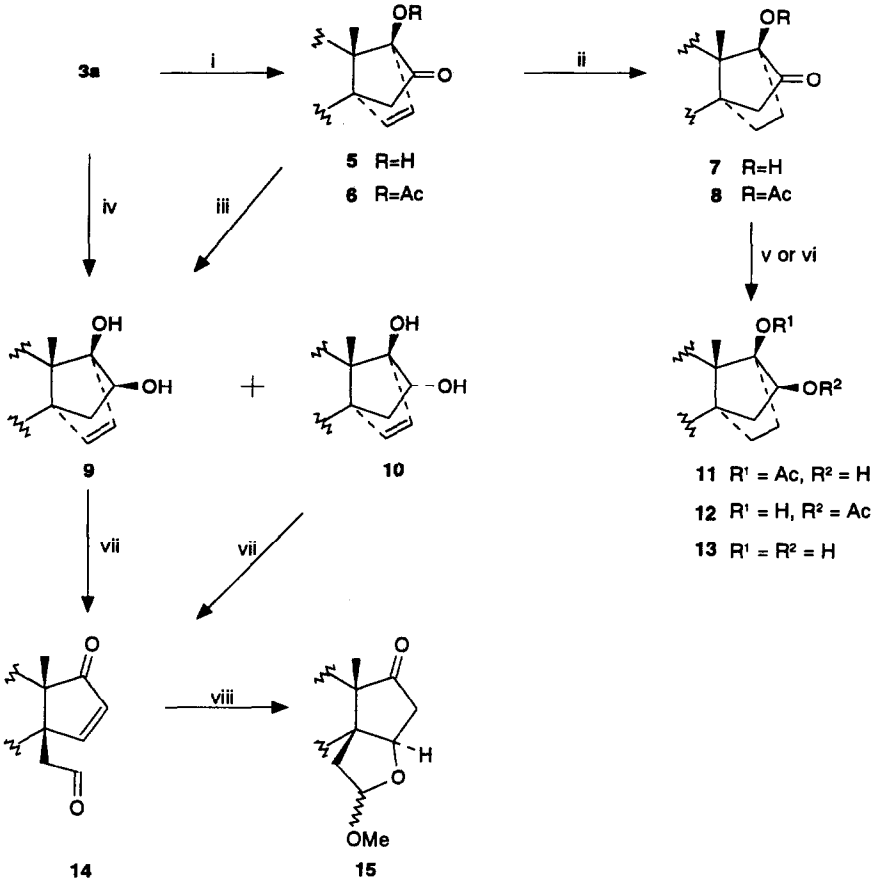
Alkaline hydrolysis of **3a** furnished the expected 17β-hydroxy 16-ketone (**5**) (82%); when the reaction was conducted in dimethyl sulfoxide–tetrahydrofuran at 0 °C, it was evident (TLC) that hydrolysis of the 16,16-functionality preceded that of the 17β-acetoxy group, but it proved impractical to isolate the intermediate 17β-acetoxy 16-ketone (**6**), which was instead prepared by subsequent acetylation of **5**.

Catalytic hydrogenation of **5** or **6** proceeded readily at atmospheric pressure [unlike the precursor (**3b**) which proved highly resistant to this transformation], to give the corresponding 14α,17α-ethano compounds (**7**) or (**8**) respectively, thus providing the desired suite of substrates for a study of stereoselectivity of reduction at C(16) and, hence, possible access to 14,17-bridged analogues of estriol.

Initial experiments, in which the 17β-hydroxy 16-ketone (**5**) was treated with lithium aluminium hydride in tetrahydrofuran at 0 °C, resulted in a separable mixture (*ca* 85:15) of the 16β,17β- and 16α,17β-diols (**9**) and (**10**). A similar product distribution was obtained through direct treatment of the cycloadduct (**3a**) with sodium borohydride in ethanol.[15] Although the NMR signals of the 16-proton in the isomeric diols (**9**) and (**10**) displayed remarkably similar couplings, the diagnostic chemical shift differences of the 16-H and 13β-Me signals were consistent with the assignment as 16β,17β-diol (**9**) for the major isomer. This is further supported by the reasonable expectation that *endo*-delivery of hydride would be favoured, owing to the steric constraints imposed upon reagent approach *syn* to the 13β-methyl group. The foregoing trend in

stereoselectivity was amplified by the use of hindered hydride reagents; typically, when diisobutylaluminium hydride was used as reductant, only the 16β,17β-diol (**9**) was detected.

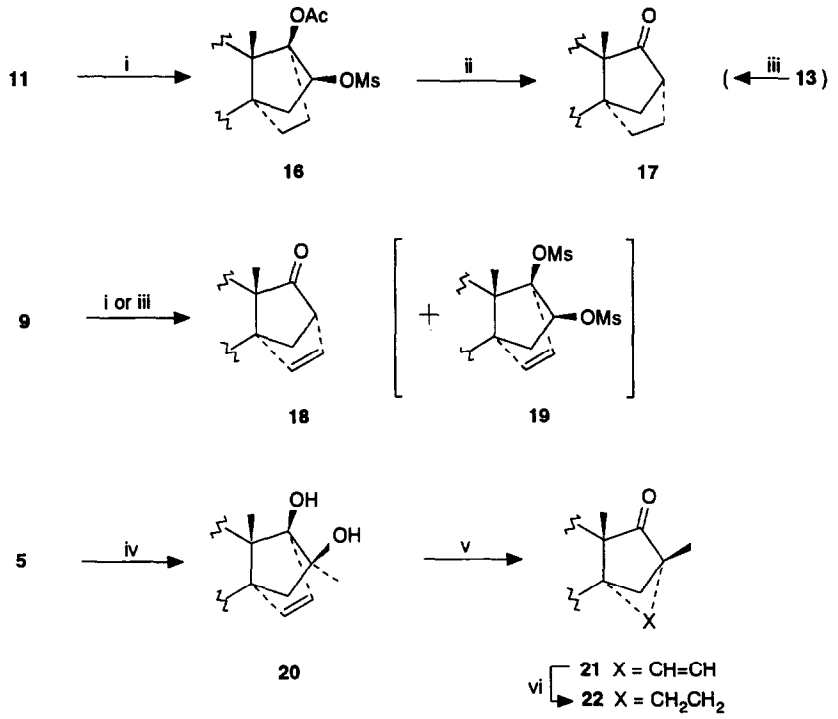
In a parallel attempt to prepare bridgehead protected 16-alcohols for possible chemoselective manipulation, the 17β-acetoxy 16-ketone (**8**) was treated with sodium borohydride in ethanol at 0 °C. Reduction proceeded slowly (incomplete after 30 h) and gave a separable mixture of the 16β-hydroxy 17β-acetate (**11**) (47%) and the 17β-hydroxy 16β-acetate (**12**) (16%), accompanied by a small amount of 16β,17β-diol (**13**) (2%). In this instance, no 16α-alcohols were detected, and it is evident from the product distribution that 16-*exo* 17-bridgehead orientation of the initial reduction product (**11**) facilitates transacetylation. The structures of **11**—**13** were confirmed by appropriate interconversions. More efficient reduction of **8** was achieved by sodium borohydride–cerium(III) chloride in tetrahydrofuran at 0 °C, which afforded only the 16β-hydroxy 17β-acetate (**11**) in 90% yield.



Reagents: (i) KOH, H_2O, DMSO, THF, 0 °C (ii) Pd-C, H_2 (iii) LAH, THF, 0 °C (iv) $NaBH_4$, EtOH, 22 °C (v) $NaBH_4$, EtOH, 0 °C (vi) $NaBH_4$, $CeCl_3.7H_2O$, THF (vii) $NaIO_4$, EtOH, H_2O, (viii) KOH, MeOH, THF, 22 °C

Oxidative cleavage of the 14α,17α-etheno 16,17-diols (**9**) and (**10**) corroborated the foregoing evidence for the configurational assignments at C(16). Thus, reaction of the 16β,17β-diol (**9**) with sodium periodate in aqueous ethanol at 20 °C proceeded rapidly to completion (1 h) to give the 14β-formylmethyl enone (**14**), whereas the analogous reaction of the 16α,17β-diol (**10**) resulted in less than 50% conversion to **14** after 24 h at 20 °C. The structure of the 14β-formylmethyl compound (**14**) was confirmed by characteristic spectroscopic data, but it proved to be especially labile in solution; one of the contributory factors is suggested by the ease with which sequential hemiacetalisation and intramolecular conjugate addition occurred in the presence of methanolic alkali to give a product formulated as the acetal (**15**). The structure of **15** followed from a well-dispersed 200 MHz NMR spectrum, in which the signals of all of the ring D and lactol protons were clearly discernible, and could be unambiguously assigned with the exception of the configuration at C(5').

The foregoing experiments led to the conclusion that cycloaddition of ketene equivalents to the dienyl acetates (**1**) is unlikely to afford a practical route to the desired bridged analogues of estriol, owing to the preference for reductive generation of 16β-alcohols from the derived 16-ketones. Attempts to circumvent this unsurprising outcome through other methods of reduction of the 16-ketones or Mitsunobu inversion of the 16β-alcohols were also unsuccessful.



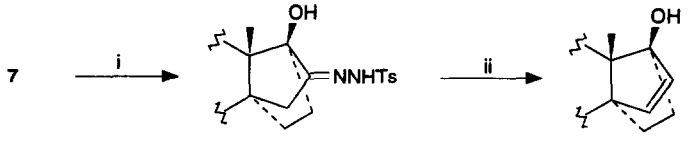
Reagents: (i) MsCl, C_5H_5N, 0 °C (ii) KOH, Al_2O_3 (iii) pTsOH, Al_2O_3, C_6H_6
(iv) MeMgI, THF, 21 °C (v) $BF_3.Et_2O$, C_6H_6, 21 °C (vi) Pd-C, H_2

Accordingly, attention was turned to alternative uses for the 16-functionalised cycloadducts as intermediates in the preparation of new bridged hormone analogues. Initially, it was reasoned that appropriate potentiation at C(16) could provide scope for introducing β-bridged unsaturation or inducing molecular rearrangement. In an attempt to achieve controlled elimination of the 16β-hydroxy group, the 16β-hydroxy 17β-acetate (**11**) was converted into the corresponding 16β-mesylate (**16**) which failed to react in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene or neutral alumina. However, exposure of **16** to basic alumina resulted in rapid conversion into a product formulated as the 14α,16α-ethano 17-ketone (**17**). The structure followed from spectroscopic data, and the reasonable expectation that hydrolysis of the bridgehead acetoxy group would be followed by a facile pinacol-type $17^1(17 \rightarrow 16)$*abeo* rearrangement. Indeed, it proved possible to convert the 16β,17β-diol (**13**) directly and efficiently into the rearrangement product (**17**) by treatment with toluene-*p*-sulfonic acid in refluxing benzene.

Parallel experiments on the 14α,17α-etheno 16β,17β-diol (**9**) proceeded similarly. Treatment of **9** with an excess of methanesulfonyl chloride in pyridine at 0—20 °C did not give isolable 17β-hydroxy 16β-mesylate; instead, the 14α,16α-etheno 17-ketone (**18**) (70%) was recovered, together with the 16,17-dimesylate (**19**) (24%). Again, direct acid treatment of the diol (**9**) resulted in efficient pinacol rearrangement to give **18** (86%). The NMR spectrum of **18** displayed diagnostic signals for all of the bridged ring protons, and catalytic hydrogenation to **17** established the correspondence between the saturated and unsaturated bridged systems.

The generality of the rearrangement was demonstrated in a reaction sequence leading to the 16β-methyl 14α,16α-ethano 17-ketone (**22**), previously prepared by an unrelated route.[9] Thus, methylation of the 17β-hydroxy 16-ketone (**5**) afforded the 16α-methyl 16β,17β-diol (**20**). In this instance treatment with boron trifluoride–diethyl ether proved to be particularly effective, and resulted in formation of the 16β-methyl 14α,16α-etheno 17-ketone (**21**) (95%), catalytic hydrogenation of which furnished **22** which was identified by direct comparison with authentic material.[9]

A further application of the cycloadducts described here was to provide an improved route to Δ^{15}-14α,17α-ethano compounds, which had previously been obtained in poor yield *via* oxidative decarboxylation of the corresponding 16α-carboxylic acid.[16] The 17β-hydroxy 16-ketone was converted into the corresponding tosylhydrazone (**23**), treatment of which with n-butyl-lithium in tetrahydrofuran at 65 °C resulted in smooth conversion into the desired olefin (**24**) (78%).



23 **24**

Reagents: (i) $pTsNHNH_2$, TFA, THF, 20 °C (ii) nBuLi, THF, Δ

In conclusion, it has been shown that, despite the limitations of 2-acetoxyacrylonitrile as a ketene equivalent in cycloaddition to **1**, and the failure to establish an efficient route to the 14α,17α-ethano analogue of estriol,[17] the cycloadducts provide scope for efficient rearrangement-mediated routes to 14α,16α-ethano-19-norsteroids, a new class of ring D bridged hormone analogues.

EXPERIMENTAL

M.p.s were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. Unless otherwise stated spectra were recorded as follows: IR, Perkin-Elmer 983, chloroform solutions; ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz), Varian VXR, deuteriochloroform solutions; mass (electron impact), VG Micromass 16F. Optical rotations were measured at 20 °C with a Perkin Elmer 141 polarimeter. Silica gel for column chromatography refers to Merck Kieselgel 60: 70—230 mesh (gravity) and 230—400 mesh (flash).

Cycloadditions of the Dienyl Acetates (1) with 2-Acetoxyacrylonitrile – (a) A solution of the dienyl acetate (**1a**) (R=Me) (2 g, 6.2 mmol), 2-acetoxyacrylonitrile (0.7 ml, 6.6 mmol), and hydroquinone (50 mg) in dry benzene (6 ml) was purged with nitrogen and heated in a sealed tube at 150 °C (oil bath). The progress of the reaction was monitored (TLC) and aliquots of 2-acetoxyacrylonitrile (0.1 ml) were added at intervals of 30—40 h. After 210 h at 150 °C the cooled reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue was adsorbed on silica gel (150 g). Elution with toluene gave starting material (**1a**) (320 mg, 16%) followed by 16α,17β-*diacetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β-*carbonitrile* (**3a**) (2.18 g, 81%), m.p. 140—145 °C (from dichloromethane–methanol); $[\alpha]_D$ +161° (*c* 1.0); ν_{max} 2240 (CN) and 1748 (AcO) cm^{-1}; δ_H (200 MHz) 1.23 (3H, s, 13β-Me), 1.85 and 2.69 (each 1H, d, *J* 14.2 Hz, 15-H$_2$), 2.07 and 2.21 (each 3H, s, 16α- and 17β-OAc), 2.51 (1H, m, 9α-H), 2.84 (2H, m, 6-H$_2$), 3.76 (3H, s, 3-OMe), 6.23 and 6.38 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 169.2 and 169.0 (each s, 16α- and 17β-O*C*OCH$_3$), 157.6 (s, C-3), 137.4 (s, C-5), 134.7 and 131.2 (each d, C-17^1 and C-17^2), 131.4 (s, C-10), 126.9 (d, C-1), 117.0 (s,16β-CN), 113.7 (d, C-4), 111.9 (d, C-2), 97.4 (s, C-17), 79.4 (s, C-16), 61.1 (s, C-13), 55.7(s, C-14), 55.2 (q, 3-OMe), 44.1 (t, C-15), 39.6 (d, C-9), 38.4 (d, C-8) 29.8 (2 x t, C-6 and C-12), 26.4 (t, C-11), 23.7 (t, C-7), 21.3 and 20.9 (each q, 16α- and 17β-OCO*C*H$_3$), and 15.6 (q, C-18) (Found: C, 71.8; H, 6.6; N, 3.2%; M$^+$, 435. $C_{26}H_{29}NO_5$ requires C, 71.7; H, 6.7; N, 3.2%; M, 435).

(b) A mixture of the dienyl acetate (**1a**) (R=Me) (11.5 g, 35.4 mmol), 2,6-di-*t*-butyl-*p*-cresol (1.15 g), mesitylene (1.15 ml), and 2-acetoxyacrylonitrile (4.1 g, 38.6 mmol) was purged with argon and heated at 160 °C (oil bath) for 16 h and then at 180 °C (oil bath) for 21 h. The reaction mixture was cooled, methanol (55 ml) was added, and the mixture was heated to reflux, then cooled and filtered, and the filtrate was evaporated under reduced pressure. The residue was adsorbed on silica gel (1 kg). Elution with ethyl acetate–hexane (3:7) gave 15ξ,17β-*diacetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15ξ-*carbonitrile* (**2a**) (2.0 g, 13%), m.p. 80 °C (from diethyl ether–hexane); $[\alpha]_D$ +12° (*c* 0.5); δ_H (300 MHz) 1.30 (3H, s, 13β-Me), 1.18 (2H, m, 11β- and 12β-H), 1.72 (1H, ddd, *J* 18, 12, and 5 Hz, 7α-H), 2.07 and 2.11 (each 3H, s, 15ξ- and 17β-OAc), 2.05—2.35 (4H, m, 7β-, 8β-, 11α-, and 12β-H), 2.58 and 2.96 (each 1H, d, *J* 14 Hz, 16-H$_2$), 2.58 (1H, m, 9α-H), 2.85 and 3.02 (each 1H, m, 6-H$_2$), 3.79 (3H, s, 3-OMe), 6.10 and 6.56 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.66 (1H, d, *J* 3 Hz, 4-H), 6.73 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.21 (1H, d, *J* 8 Hz, 1-H); δ_C (75 MHz) 170.6 and 168.7 (each s, 15ξ- and 17β-O*C*OCH$_3$), 157.7 (s, C-3), 137.7 (s, C-5), 137.0 and 131.1 (each d, C-17^1 and C-17^2), 131.1 (s, C-10), 127.1 (d, C-1), 117.2 (s, 15ξ-CN), 113.6(d, C-4), 112.0 (d, C-2), 91.3 (s, C-17), 78.0 (s, C-15), 62.1 (s, C-14), 60.8 (s, C-13), 55.2 (q, 3-OMe),

46.6 (t, C-16), 39.9 (d, C-9), 37.2 (d, C-8), 30.2 (t, C-12), 29.9 (t, C-6), 26.9 (t, C-11), 24.5 (t, C-7), 21.2 and 21.1 (each q, 15ξ- and 17β-OCO*C*H_3), and 16.6 (q, C-18) (Found: C, 71.6; H, 7.3; N, 3.0. $C_{26}H_{29}NO_5$ requires C, 71.7; H, 6.7; N, 3.2%), followed by a mixture (6.5 g) which was rechromatographed on silica gel (300 g). Elution with diethyl ether–pentane (1:4) gave the 16α,17β-diacetoxy 16β-carbonitrile (**3a**) (5.0 g, 32%), followed by 16β,17β-*diacetoxy*-3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α-*carbonitrile* (**4**) (0.6 g, 4%), m.p. 128—130 °C (from diethyl ether–hexane); $[\alpha]_D$ +172° (*c* 0.5); δ_H (300 MHz) 1.06 (3H, s, 13β-Me), 1.35 (2H, m, 11β- and 12β-H), 1.48 (1H, m, 8β-H), 1.66 (1H, m, 7α-H), 1.81 (1H, m, 7β-H), 2.17 and 2.21 (each 3H, s, 16β- and 17β-OAc), 2.20 and 2.59 (each 1H, d, *J* 14 Hz, 15-H_2), 2.20—2.35 (2H, m, 11α- and 12α-H), 2.51 (1H, m, 9α-H), 2.87 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.34 and 6.53 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 3 Hz, 4-H), 6.72 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.20 (1H, d, *J* 8 Hz, 1-H); δ_C (75 MHz) 169.5 and 168.8 (each s, 16β- and 17β-O*C*OCH$_3$), 157.6 (s, C-3), 137.5 (s, C-5), 137.5 and 132.3 (each d, C-17^1 and C-17^2), 131.4 (s, C-10), 127.0 (d, C-1), 118.3 (s, 16α-CN), 113.7 (d, C-4), 112.0 (d, C-2), 95.2 (s, C-17), 77.5 (s, C-16), 61.2 (s, C-13), 55.2 (q, 3-OMe), 54.8 (s, C-14), 43.8 (t, C-15), 39.5 (d, C-9), 38.3 (d, C-8), 30.4 (t, C-12), 29.9 (t, C-6), 26.5 (t, C-11), 23.8 (t, C-7), 21.2 and 21.0 (each q, 16β- and 17β-OCO*C*H_3), and 15.1 (q, C-18) (Found: C, 70.9; H, 6.8; N, 3.0. $C_{26}H_{29}NO_5$ requires C, 71.7; H, 6.7; N, 3.2%).

(c) A solution of the dienyl acetate (**1b**) (R=Ac) (16 g, 45.4 mmol) and 2-acetoxyacrylonitrile (30 ml, 281 mmol) in dichloromethane (40 ml) was heated in a sealed tube at 100 °C for 140 h. The reaction mixture was cooled, diluted with dichloromethane (100 ml) and filtered. The filtrate was evaporated under] reduced pressure and the residue was adsorbed on silica gel (800 g). Elution with dichloromethane–ethyl acetate–hexane (2:3:5) gave 3,16α,17β-*triacetoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β-*carbonitrile* (**3b**) (14.9 g, 71%), m.p. 171 °C (from dichloromethane–diisopropyl ether); $[\alpha]_D$ +150° (*c* 1.0); ν_{max} 2240 (CN) and 1750 (AcO) cm^{-1}; δ_H (400 MHz) 1.25 (3H, s, 13β-Me), 1.26 (1H, m, 12β-H), 1.40 (1H, qd, *J* 3 x 13, and 4 Hz, 11β-H), 1.50 (1H, td, *J* 2 x 11, and 3 Hz, 8β-H), 1.63 (1H, m, 7α-H), 1.76 (1H, m, 7β-H), 1.87 and 2.71 (each 1H, d, *J* 14 Hz, 15-H_2), 2.08, 2.23, and 2.29 (each 3H, s, 3-, 16α-, and 17β-OAc), 2.26 (1H, m, 11α-H), 2.38 (1H, td, *J* 2 x 13, and 4 Hz, 12α-H), 2.56 (1H, m, 9α-H), 2.88 (2H, m, 6-H_2), 6.24 and 6.39 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.81 (1H, d, *J* 3 Hz, 4-H), 6.86 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.29 (1H, d, *J* 8 Hz, 1-H); δ_C (75 MHz) 169.7, 169.2, and 169.0 (each s, 3-, 16α-, and 17β-O*C*OCH$_3$), 148.6 (s, C-3), 137.7 (s, C-5), 136.9 (s, C-10), 134.5 and 131.4 (each d, C-17^1 and C-17^2), 127.0 (d, C-1), 121.5 (d, C-4), 119.0 (d, C-2), 116.9 (s, 16β-CN), 97.4 (s, C-17), 79.4 (s, C-16), 61.1 (s, C-13), 55.7 (s, C-14), 44.1 (t, C-15), 39.8 (d, C-9), 38.0 (d, C-8), 29.8 (t, C-12), 29.5 (t, C-6), 26.3 (t, C-11), 23.5 (t, C-7), 21.3, 21.0, and 20.9 (each q, 3-, 16α-, and 17β-OCO*C*H_3), and 15.6 (q, C-18) (Found: C, 68.8; H; 6.2; N, 2.7%; M^+, 463. $C_{27}H_{29}NO_6$ requires C, 69.95; H, 6.3; N, 3.0%; *M*, 463).

The mother-liquor residue from the above crystallisation of **3b** was adsorbed on silica gel (350 g). The product eluted with diethyl ether–pentane (3:7) was crystallised from dichloromethane–diisopropyl ether to give 3,15ξ,17β-*triacetoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-15ξ-*carbonitrile* (**2b**) (503 mg, 3.1%), m.p. 175 °C; $[\alpha]_D$ +10° (*c* 1.0); ν_{max} 2240 (CN) and 1750 (AcO) cm^{-1}; δ_H (300 MHz) 1.30 (3H, s, 13β-Me), 1.49 (2H, m, 11β- and 12β-H), 1.73 (1H, ddd, *J* 18, 12, and 5 Hz, 7α-H), 2.07, 2.11, and 2.28 (each 3H, s, 3-, 15ξ-, and 17β-OAc), 2.05—2.35 (4H, m, 7β-, 8β-, 11α-, and 12α-H), 2.58 and 2.96 (each 1H, d, *J* 14 Hz, 16-H_2), 2.60 (1H, m, 9α-H), 2.87 and 3.01 (each 1H, m, 6-H_2), 6.08 and 6.56 (each 1H, d, *J* 6 Hz, 17^1- and

17²-H), 6.83 (1H, d, *J* 3 Hz, 4-H), 6.87 (1H, dd, *J* 8 and 3 Hz, 2-H), and 7.30 (1H, d, *J* 8 Hz, 1-H) (Found: C, 69.4; H, 6.2; N, 2.9. $C_{27}H_{29}NO_6$ requires C, 69.95; H, 6.3; N, 3.0%).

17β-Hydroxy-3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-16-one (**5**) – Aqueous 2M-potassium hydroxide was added to a solution of the cycloadduct (**3a**) (2.92 g, 6.7 mmol) in dimethyl sulfoxide (50 ml) and tetrahydrofuran (50 ml) at 0 °C under nitrogen. After 30 min at 0 °C the solution was kept at 20 °C for 25 h, then aqueous ammonium chloride was added. The mixture was extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue which was adsorbed on silica gel (150 g). Elution with ethyl acetate–toluene (1:9) gave the 17β-*hydroxy* 16-*ketone* (**5**) (1.79 g, 82%), m.p. 154—158 °C (from chloroform–methanol); $[\alpha]_D$ +432° (*c* 1.0); ν_{max} 3525 (OH) and 1745 (CO) cm^{-1}; δ (400 MHz) 0.94 (3H, d, *J* 0.6 Hz, 13β-Me), 2.0 (1H, dd, *J* 16.9 and 0.9 Hz, 15β-H), 2.2 (1H, d, *J* 16.9 Hz, 15α-H), 2.59 (1H, m, 9α-H), 2.89 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.82 (1H, dt, *J* 6.0 and 2 x 0.9 Hz, 17²-H), 6.43 (1H, d, *J* 6.0 Hz, 17¹-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz), and 7.24 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.3; H, 7.7%; M^+, 324. $C_{21}H_{24}O_3$ requires C, 77.8; H, 7.5%; M, 324).

The derived 17β-*acetate* (**6**) (Ac_2O–pyridine–cat. 4-dimethylaminopyridine, 17 °C for 20 h) had m.p. 222—225 °C (from chloroform–methanol); $[\alpha]_D$ +360° (*c* 1.0); ν_{max} 1747br (17-OAc and 16-CO) cm^{-1}; δ (200 MHz) 1.04 (3H, d, *J* 0.6 Hz, 13β-Me), 1.97 (1H, dd, *J* 16.7 and 0.8 Hz, 15β-H), 2.18(3H, s, 17β-OAc), 2.2(1H, d, *J* 16.7 Hz, 15α-H), 2.59 (1H, m, 9α-H), 2.89 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.39 and 6.47 (each 1H, d, *J* 6.1 Hz, 17¹- and 17²-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.3 and 2.7 Hz, 2-H), and 7.23 (1H, d, *J* 8.3 Hz, 1-H) (Found: C, 75.1; H, 7.5%; M^+, 366. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.2%, M, 366).

17β-Hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-16-one (**7**) – The etheno compound (**5**) (946 mg, 2.9 mmol) in ethyl acetate (15 ml) at 23 °C was hydrogenated at atmospheric pressure in the presence of palladium on carbon (10%; 280 mg). After 3 h, hydrogen uptake ceased and the filtered solution was evaporated under reduced pressure, and the residue was crystallised from chloroform–methanol to give the *ethano compound* (**7**) (624 mg), m.p. 169—171 °C ; $[\alpha]_D$ -62° (*c* 1.0); ν_{max} 3526 (OH) and 1746 (CO) cm^{-1}; δ (200 MHz) 0.82 (3H, s, 13β-Me), 2.89 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.74 (1H, dd, *J* 8.8 and 2.4 Hz, 2-H), and 7.23 (1H, d, *J* 8.8 Hz, 1-H) (Found: C, 77.1; H, 7.7%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; M, 326). Chromatography of the mother-liquor residue on silica gel with ethyl acetate–toluene (1:4) as eluent gave further product (**7**) (240 mg) (overall yield 91%).

The derived 17β-*acetate* (**8**) (Ac_2O–pyridine–cat. 4-dimethylaminopyridine, 20 °C for 11 h) had m.p. 215—216 °C (from chloroform–methanol); $[\alpha]_D$ -30° (*c* 0.9); ν_{max} 1762 (17-OAc) and 1741 (16-CO) cm^{-1}; δ (200MHz) 0.93 (3H, s, 13β-Me), 2.13 (3H, s, 17β-OAc), 2.76 (1H, m, 9α-H), 2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.21 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 74.6; H, 7.6%; M^+, 368. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.7%; M, 368).

Hydride Reduction to 16-Hydroxy Compounds – (a) Lithium aluminium hydride (150 mg, 4 mmol) was added to the 16-ketone (**5**) (400 mg, 1.23 mmol) in dry tetrahydrofuran at 0°C under nitrogen. The mixture was stirred at 0 °C for 2 h, then aqueous ammonium chloride was added followed by water, and the mixture was extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and

evaporated under reduced pressure. The residue (430 mg) was chromatographed on silica gel (40 g) with ethyl acetate–toluene (3:7 → 1:1) as eluent to give 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β,17β-*diol* (**9**) (300 mg, 75%), m.p. 158—162 °C (from chloroform–methanol); $[\alpha]_D$ +146° (*c* 1.0); ν_{max} 3605 and 3430 (OH) cm^{-1}; δ 1.1 (3H, d, *J* 0.8 Hz, 13β-Me), 1.5 (1H, dd, *J* 12.5 and 2.9 Hz, 15β-H), 1.87 (1H, dd, *J* 12.5 and 7.6 Hz, 15α-H), 2.31 (1H, d, *J* 2.9 Hz, exch. by D_2O, 16β-OH), 2.42 (1H, m, 9α-H), 2.83 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 3.83 (1H, dt, *J* 7.6 and 2 x 2.9 Hz → dd, *J* 7.6 and 2.9 Hz on D_2O exch., 16α-H), 5.86 and 5.98 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 77.1; H, 8.1%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; M, 326), followed by 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16α,17β-*diol* (**10**) (58 mg, 14%), m.p. 187—192 °C (from toluene–methanol); $[\alpha]_D$ +169° (*c* 1.0); ν_{max} 3593 and 3420 (OH) cm^{-1}; δ (200 MHz) 0.9 (3H, s, 13β-Me), 1.12 (1H, dd, *J* 12.6 and 2.4 Hz, 15α-H), 2.17 (1H, dd, *J* 12.6 and 7.7 Hz, 15β-H), 2.36 (1H, br s, exch. by D_2O, 16α-OH), 2.83 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.38 (1H, br → br dd, *J* 7.7 and 2.4 Hz on D_2O exch., 16β-H), 5.92 and 6.31 (each 1H, d, *J* 6 Hz, 17^1- and 17^2-H), 6.6 (1H, d, *J* 2.6 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.18 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 77.0; H, 8.3%, M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%, M, 326).

(b) The cycloadduct (**3a**) (1.56 g, 3.6 mmol) was suspended in dry ethanol (25 ml) and treated with sodium borohydride (647 mg, 17.1 mmol). The mixture was stirred at 22 °C for 23 h, then water was added and the mixture was extracted with ethyl acetate. The extract was washed with aqueous ammonium chloride, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1.33 g) on silica gel gave the 16β,17β-diol (**9**) (907 mg, 78%) and the 16α,17β-diol (**10**) (48 mg, 4%).

(c) The 17-ketone (**8**) (100 mg, 0.27 mmol) in ethyl acetate (10 ml) and ethanol (10 ml) was stirred at 0 °C with sodium borohydride (24 mg, 0.63 mmol). After 30 h the reaction was still incomplete (TLC). Water was added and the mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (102 mg) with ethyl acetate–toluene (3:17) as eluent gave, in order of elution, starting material (**8**) (35 mg); 17β-*acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-16β-*ol* (**11**) (47 mg, 47%), m.p. 149—154 °C (from chloroform–methanol); $[\alpha]_D$ +58° (*c* 0.9); ν_{max} 3601 (OH) and 1722 (OAc) cm^{-1}; δ (200 MHz) 1.09 (3H, s, 13β-Me), 1.82 (1H, s, exch. by D_2O, 16β-OH), 2.1 (1H, dd, *J* 12.4 and 8.3 Hz, 15α-H), 2.11 (3H, s, 17β-OAc), 2.63 (1H, m, 9α-H), 2.87 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.54 (1H, dd, *J* 8.3 and 4.4 Hz, 16α-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), and 7.22 (1H, d, *J* 8.4 Hz, 1-H) (Found: C, 74.4; H, 8.0%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.5; H, 8.2%; M, 370); 16β-*acetoxy*-3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*trien*-17β-ol (**12**) (16 mg, 16%), m.p. 165—170 °C (from chloroform–methanol); $[\alpha]_D$ +76° (*c* 0.9); ν_{max} 3584 (OH) and 1738 (OAc) cm^{-1}; δ (200 MHz) 0.98 (3H, s, 13β-Me), 2.08 (3H, s, 16β-OAc), 2.19 (1H, dd, *J* 12.9 and 8.1 Hz, 15α-H), 2.63 (1H, m, 9α-H), 2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.75 (1H, dd, *J* 8.1 and 4.0 Hz, 16α-H), 6.63 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.4 Hz, 2-H), and 7.22 (1H, d, *J* 8.5 Hz, 1-H) (Found: C. 74.4; H, 8.2%; M^+, 370); and 3-*methoxy*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-16β,17β-*diol* (**13**) (2 mg; 2%), m.p. 169—171 °C (from dichloromethane–pentane); $[\alpha]_D$ +44° (*c* 0.9); ν_{max} 3606 (OH) cm^{-1}; δ (200 MHz) 1.0 (3H, s, 13β-Me), 2.06 (1H, dd, *J* 12.8 and 7.9 Hz, 15α-H), 2.61 (1H, m, 9α-H), 2.85 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.8 obsc (1H, dd, 7.9 and

4.0 Hz, 16α-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.22 (1H, d, *J* 8.6 Hz, 1-H) (Found: M^+, 328. $C_{21}H_{28}O_3$ requires M, 328).

(d) The foregoing experiment on **8** (100 mg, 0.27 mmol) was repeated in the presence of cerium(III) chloride heptahydrate (103 mg, 0.28 mmol), with further addition of sodium borohydride (5 mg, 0.13 mmol) after 45 min. After a total reaction time of 65 min, the reaction was worked up and the product was chromatographed to give the 16β-hydroxy 17β-acetate (**11**) (90 mg, 90%).

14-Formylmethyl-3-methoxy-14β-estra-1,3,5(10),15-tetraen-17-one (**14**) – (a) A solution of the 16β,17β-diol (**9**) (100 mg, 0.31 mmol) in ethanol (12 ml) was treated at 20 °C with aqueous 6% sodium periodate (5 ml, 1.4 mmol) for 1 h. Ethylene glycol and water were added, and the product was isolated by extraction with chloroform. Flash chromatography on silica gel (10 g) with ethyl acetate–toluene (1:9) as eluent gave material (95 mg), which was crystallised from ethyl acetate–hexane to give the *product* (**14**), m.p. 80—87 °C, ν_{max} 1706br (CO) cm^{-1}; δ (200 MHz) 1.04 (3H, s, 13β-Me), 2.74 (1H, dd, *J* 17 and 1.5 Hz, 14^1-H), 2.75 (2H, m, 6-H_2), 2.93 (1H, dd, *J* 17 and 2.7 Hz, 14^1-H), 3.74 (3H, s, 3-OMe), 6.29 (1H, d, *J* 5.9 Hz, 16-H), 6.54 (1H, d, *J* 2.5 Hz, 4-H), 6.69 (1H, dd, *J* 8.6 and 2.5 Hz, 2-H), 7.03 (1H, d, *J* 8.6 Hz, 1-H), 7.4 (1H, d, *J* 5.9 Hz, 15-H), and 9.9 (1H, br s, 14^1-CHO) (Found: M^+, 324. $C_{21}H_{24}O_3$ requires M, 324). The lability of the product precluded more complete purification and characterisation.

(b) A similar reaction of the 16α,17β-diol (**10**) (28 mg; 0.09 mmol) was incomplete (TLC) after 24 h. Work-up and flash chromatography gave the product (**14**) (12 mg, 41%) followed by starting material (**10**) (12 mg).

3,5′ξ-Dimethoxy-15α*H*-dihydrofuro[3′,2′; 14,15]-14β-estra-1,3,5(10)-trien-17-one (**15**) – The formyl compound (**14**) (50 mg; 0.15 mmol) in tetrahydrofuran (2 ml) at 22 °C was treated with methanolic 2M-potassium hydroxide (0.03 ml) for 30 min. Aqueous ammonium chloride was added and the product was isolated by extraction with chloroform, and filtered through silica gel (5 g) with ethyl acetate–hexane (1:4) as eluent, to give the *product* (**15**) (51 mg, 93%), m.p. 125—130 °C (from chloroform–methanol); $[\alpha]_D$ +52° (*c* 0.6), ν_{max} 1731 (CO) cm^{-1}; δ (200 MHz) 1.12 (3H, s, 13β-Me) 1.77(1H, dd, *J* 14.5 and 4.3 Hz, 4′ξ-H), 2.19(1H, dd, *J* 14.5 and 6.2 Hz, 4′ξ-H), 2.53 (1H, dd, *J* 20.1 and 4.5 Hz, 16β-H), 2.89 (2H, m, 6-H_2), 3.02 (1H, dd, *J* 20.1 and 9.2 Hz, 16α-H), 3.35 (3H, s, 5′ξ-OMe), 3.78 (3H, s, 3-OMe), 4.8 (1H, dd, *J* 9.2 and 4.5 Hz, 15α-H), 5.13 (1H, dd, *J* 6.2 and 4.3 Hz, 5′ξ-H), 6.64 (1H, d, *J* 2.6, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), and 7.22 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 73.9; H, 8.0%; M^+, 356. $C_{22}H_{28}O_4$ requires C, 74.1; H, 7.9%; M, 356).

16β-Methanesulfonyloxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl Acetate (**16**) – A solution of the 16β-hydroxy 17β-acetate (**11**) (90 mg, 0.24 mmol) and methanesulfonyl chloride (0.09 ml, 1.1 mmol) in pyridine (6 ml) was kept at 0 °C under nitrogen for 48 h. Aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue (137 mg) on silica gel (9 g) with ethyl acetate–toluene (3:17) gave the 16β-*mesylate* (**16**) (105 mg, 96%), m.p. 152—154 °C (from ethyl acetate); $[\alpha]_D$ +97° (*c* 1.0); ν_{max} 1727 (AcO), 1356 and 1177 (MsO) cm^{-1}; δ 1.07 (3H, s, 13β-

Me), 2.09 (3H, s, 17β-OAc), 2.34 (1H, dd, *J* 14.1 and 7.6 Hz, 15α-H), 2.84 (2H, m, 6-H_2), 2.94 (3H, s, 16β-OMs), 3.76 (3H, s, 3-OMe), 5.17 (1H, dd, *J* 7.6 and 3.8 Hz, 16α-H), 6.12 (1H, d, *J* 2.4 Hz, 4-H), 6.71 (1H, dd, *J* 8.3 and 2.4 Hz, 2-H), and 7.2 (1H, d, *J* 8.3 Hz, 1H) (Found: C, 64.1; H, 7.4%; M^+, 448. $C_{24}H_{32}O_6S$ requires C, 64.3; H, 7.2%; M, 448).

3-Methoxy-14,16α-ethanoestra-1,3,5(10)-trien-17-one (17) – (a) The 16β-mesylate (**16**) (69 mg, 0.15 mmol) in toluene (3 ml) at 22 °C was stirred in the presence of basic alumina (1 g) for 3 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Chromatography of the residue (48 mg) on silica gel (8 g) with ethyl acetate–toluene (1:19) as eluent gave the 14α,16α-*ethano* 17-*ketone* (**17**) (38 mg, 80%), m.p. 179—181 °C (from chloroform–methanol); $[\alpha]_D$ +112° (*c* 1.1); ν_{max} 1729 (CO) cm^{-1}; δ (200 MHz) 1.02 (3H, s, 13β-Me), 2.59 obsc (1H, m, 9α-H), 2.66 obsc (1H, br d, *J* 4.2 Hz, 16β-H), 2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, *J* 2.4 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.4 Hz, 2-H), 7.2 (1H, d, *J* 8.6 Hz, 1-H) (Found: C, 81.3; H, 8.0%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H 8.4%; M, 310), followed by starting material **16** (10 mg).

(b) A mixture of the 16β,17β-diol (**13**) (15 mg, 0.05 mmol) and toluene-*p*-sulfonic acid (3% adsorbed on silica gel; 0.8 g) in dry benzene (2 ml) was refluxed for 3 h, filtered, and evaporated under reduced pressure to give the 14α,16α-ethano 17-ketone (**17**) (13 mg, 92%), m.p. and mixed m.p. 179—181 °C (from chloroform–methanol).

(c) Hydrogenation of the 14α,16α-etheno 17-ketone (**18**) (70 mg, 0.23 mmol) in ethyl acetate (8 ml) at 24 °C and atmospheric pressure, in the presence of palladium on carbon (10%; 20 mg), for 1 h, followed by filtration and concentration of the filtrate, gave the 14α,16α-ethano 17-ketone (**17**) (70 mg, 99%), m.p. and mixed m.p. 179—181 °C (from chloroform–methanol).

Rearrangement of the 14α,17α-Etheno 16β,17β-Diol (9) – (a) Methanesulfonyl chloride (0.07 ml, 0.9 mmol) was added to a solution of the diol (**9**) (100 mg, 0.31 mmol) in dry pyridine (1 ml) at 0 °C under nitrogen, and the mixture was stirred at 20 °C for 2 h. Water was added and the product was extracted into chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure, and the residue was adsorbed on silica gel (10 g). Elution with ethyl acetate–toluene (1:19) gave 3-*methoxy*-14,16α-*ethenoestra*-1,3,5,(10)-*trien*-17-*one* (**18**) (66 mg, 70%), m.p. 199—203 °C (from chloroform–methanol); $[\alpha]_D$ -392° (*c* 1.0); ν_{max} 1726 (CO) cm^{-1}; δ (400 MHz) 1.1 (3H, s, 13β-Me), 1.38 (1H, td, *J* 2 x 13.3, and 3.9 Hz, 12α-H), 1.84 (1H, td, *J* 2 x 11.5, and 2.3 Hz, 8β-H), 2.03 br and 2.14 (each 1H, d, *J* 9.1 Hz, 15-H_2), 2.33 (1H, dq, *J* 13.6 and 3 x 4.2 Hz, 11α-H), 2.74 (1H, td, *J* 2 x 11.8, and 4.2 Hz, 9α-H), 2.93 (2H, m, 6-H_2), 3.17 (1H, m, $W_{1/2}$ 6.3 Hz, 16β-H), 3.78 (3H, s, 3-OMe), 6.13 (1H, m, $W_{1/2}$ 10.9 Hz, 16^1-H), 6.59 (1H, d, *J* 5.8 Hz, 16^2-H), 6.66 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.21 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 81.7; H, 7.7%; M^+, 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8%; M, 308), followed by 3-*methoxy*-14,17α-*ethenoestra*-1,3,5(10)-*triene*-16β,17β-*diyl bis-methanesulfonate* (**19**) (35 mg, 24%), m.p. 128—131 °C (from chloroform–methanol); $[\alpha]_D$ +129° (*c* 0.7); ν_{max} 1350 and 1330 (MsO) cm^{-1}; δ (200 MHz) 1.21 (3H, s, 13β-Me), 1.98 (1H, dd, *J* 12.9 and 2.9 Hz, 15β-H), 2.18 (1H, dd, *J* 12.9 and 7.5 Hz, 15α-H), 2.86 (2H, m, 6-H_2), 3.1 and 3.16 (each 3H, s, 16β- and 17β-OMs), 3.77 (3H, s, 3-OMe), 4.87 (1H, dd, *J* 7.5 and 2.9 Hz, 16α-H), 6.28 and 6.41 (each 1H, d, *J* 6.4 Hz, 17^1- and 17^2-H), 6.63 (1H, d, *J* 2.6 Hz,

4-H), 6.72 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 57.4; H, 6.0%; M^+, 482. $C_{23}H_{30}O_7S_2$ requires C, 57.2; H, 6.3%; M, 482).

(b) A mixture of the 16β,17β-diol (**9**) (250 mg, 0.77 mmol) and toluene-*p*-sulfonic acid (3%, adsorbed on silica gel; 1 g) in benzene (25 ml) was refluxed for 2 h. The filtered solution was evaporated under reduced pressure, and the residue (250 mg) was chromatographed on silica gel (13 g) with ethyl acetate–toluene (1:19) as eluent to give the 14α,16α-etheno 17-ketone (**18**) (204 mg, 86%), identical with the product obtained in the foregoing experiment.

3-Methoxy-16α-methyl-14,17α-ethenoestra-1,3,5(10)-triene-16β,17β-diol (20) – The 16-ketone (**5**) (60 mg, 0.19 mmol) in dry tetrahydrofuran (10 ml) at 21 °C was treated with ethereal 0.4M methylmagnesium iodide (4 ml). After 2.5 h, water was added and the product was isolated by extraction with chloroform and adsorbed on silica gel (16 g). Elution with ethyl acetate–toluene (1:9) gave the *product* (**20**) (56 mg, 89%), m.p. 170—185 °C decomp(from chloroform–methanol); $[\alpha]_D$ +170° (*c* 1.0); ν_{max} 3607 and 3555 (OH) cm^{-1}; δ (200 MHz) 1.11 (3H, d, *J* 0.8 Hz, 13β-Me), 1.23 (3H, s, 16α-Me), 1.52 and 1.89 (each 1H, d, *J* 12.2 Hz,15-H_2), 2.46 (1H, m, 9α-H), 2.83 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 5.91 and 5.96 (each 1H, d, *J* 6.2 Hz, 17^1- and 17^2-H), 6.6 (1H, d, *J* 2.8 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), and 7.2 (1H, d, *J* 8.5 Hz, 1-H) (Found: C, 77.2; H, 8.1%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; M, 340).

3-Methoxy-16β-methyl-14,16α-ethenoestra-1,3,5(10)-trien-17-one (21) – A solution of the 16α-methyl-16β,17β-diol(**20**) (40 mg, 0.12 mmol) in dry benzene (1 ml) at 21 °C was treated with boron trifluoride–diethyl ether (60 μl). After 50 min at 21 °C, aqueous sodium hydrogen carbonate was added and the mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. Filtration of the residue (37 mg) through silica gel (4 g) with ethyl acetate–toluene (1:49) gave the 14α,16α-*etheno* 17-*ketone* (**21**) (36 mg, 95%), m.p. 148—149 °C (from chloroform–methanol); $[\alpha]_D$ -340° (*c* 1.0); ν_{max} 1723 (CO) cm^{-1}; δ (200 MHz) 1.1 (3H, s, 13β-Me), 1.33 (3H, s, 16β-Me), 1.92 and 2.15 (each 1H, d, *J* 9.0 Hz, 15-H_2), 2.35 (1H, ddt, *J* 13.4, 2 x 4.6, and 3.9 Hz, 11α-H), 2.75 (1H, dt, *J* 11.0 and 2 x 4.4 Hz, 9α-H), 2.95 (2H, m, 6-H_2), 3.8 (3H, s, 3-OMe), 5.8 and 6.58 (each 1H, d, *J* 5.5 Hz, 16^1- and 16^2-H), 6.68 (1H, d, *J* 2.7 Hz, 4-H), 6.75 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), and 7.24 (1H, d, *J* 8.7 Hz, 1-H) (Found: C, 81.9; H, 8.2%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 82.0; H, 8.1%; M, 322).

3-Methoxy-16β-methyl-14,16α-ethanoestra-1,3,5(10)-trien-17-one (22) – The 14α,16α-etheno compound (**21**) (10 mg, 0.03 mmol) in ethyl acetate (2 ml) at 20 °C was hydrogenated (1 h) in the presence of palladium on carbon (10%, 3 mg). The filtered solution was evaporated, and the residue was filtered through silica gel (1 g) with ethyl acetate–toluene (1:49) to give the 14α,16α-ethano compound (**22**) (9 mg, 90%), m.p. 105—109 °C (from ethyl acetate–hexane) (lit.,[9] m.p. 107—109 °C), identified by spectroscopic and TLC comparison with authentic material.

3-Methoxy-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol (24) – A mixture of the 16-ketone (**7**) (100 mg, 0.31 mmol), toluene-*p*-sulfonohydrazide (80 mg, 0.43 mmol), and trifluoroacetic acid (50 μl) in tetrahydrofuran (2 ml) was stirred at 20 °C for 52 h. Aqueous sodium hydrogen carbonate was added, and the mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The solid residue (170 mg) was crystallised from chloroform–methanol

to give the 16-*tosylhydrazone* (**23**) (115 mg, 76%), m.p. 148—151 °C; $[\alpha]_D$ -33° (*c* 0.6); ν_{max} 3544 (OH), 1675 (C=N), 1374 and 1164 (TsO) cm^{-1}; δ (200 MHz) 0.53 (3H, s, 13β-Me), 1.97 and 2.09 (each 1H, d, *J* 16.0 Hz, 15-H_2), 2.41 (3H, s, 4′-Me), 2.65 (1H, m, 9α-H), 2.84 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.7 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.18 (1H, d, *J* 8.5 Hz, 1-H), and 7.31 and 7.82 (each 2H, d, *J* 8.4 Hz, 2′, 6′- and 3′, 5′-H_2). (Found: C, 67.6; H, 7.0; N, 5.4%; M^+-NNHTs, 310. $C_{28}H_{34}N_2O_4S$ requires C, 70.0; H, 6.9; N, 5.7%; M, 494). Chromatography of the mother-liquor residue furnished starting material (**6**) (7 mg) and further 16-tosylhydrazone (**23**) (25 mg, 16%). n-Butyl-lithium (1.6M) in hexane (0.4 ml, 0.64 mmol) was added to the tosylhydrazone (**23**) (80 mg, 0.16 mmol) in dry tetrahydrofuran (6 ml) at 20 °C under nitrogen. The solution was refluxed for 50 min, then aqueous ammonium chloride was added and the mixture was extracted with dichloromethane. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (58 mg) was chromatographed on silica gel (8 g) with ethyl acetate–toluene (1:4) as eluent to give the *olefin* (**24**) (39 mg, 78%), double m.p. 87—89 and 110—112 °C (from chloroform–methanol); $[\alpha]_D$ -20° (*c* 0.5); ν_{max} 3600 (OH) cm^{-1}; δ (200 MHz) 0.9 (3H, s, 13β-Me), 2.75 (1H, m, 9α-H), 2.92 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.89 and 6.04 (each 1H, d, *J* 6.0 Hz, 15- and 16-H), 6.64 (1H, d, *J* 2.5 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.5 Hz, 2-H), and 7.22 (1H, d, *J* 8.4 Hz, 1-H) (Found: C, 81.0; H, 8.4%; M^+, 310.192. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; M, 310.193).

Crystal Data of 3,16α,17β-Triacetoxy-14,17α-ethenoestra-1,3,5(10)-triene-16β-carbonitrile (3b) – $C_{27}H_{29}NO_6$, M 463.5; monoclinic, space group $P2_1$, a = 10.956(2), b = 10.911(6), c = 12.430(9) Å, β = 106.14(4)°, V = 1427.3(14) $Å^3$, Z = 2, D_c = mg m^{-3}, μ = 0.076 mm^{-1}, F(000) = 492. A colourless crystal of dimensions 0.6× 0.5× 0.08 mm was used for data collection.

Data Collection and Processing – Data collection was performed at 294K on a Siemens P4 diffractometer, using graphite monochromated Mo-*K*α radiation (λ = 0.71073Å); 2θ – θ scan mode with ω scan width = 1.60° + *K*α separation; ω scan speed = 2.00—29.30° min^{-1}; 3420 reflections measured ($3.0 \leq 2\theta \leq 47.5°$; $12 \leq h \leq 6$, $-11 \leq k \leq 0$, $-13 \leq l \leq 13$); 2082 independent reflections (R_{int} = 10.88%) giving 1281 observed reflections with $F > 3.5\sigma(F)$; no absorption correction. Background measurement comprised stationary crystal and stationary counter at the beginning and end of scan, each for 25% of the total scan time. Two standard reflections were measured for every 98 reflections.

Structure Analysis and Refinement – The structure was solved by direct methods using the Siemens SHELXTL PLUS (VMS) program, and refined using a full-matrix least-squares method with unit weights . Analysis and refinement details are: quantity minimised, $\Sigma w(F_o - F_c)^2$; hydrogen atoms, riding model with fixed isotopic U; number of parameters refined, 307; R = 12.18% (all data); final R = 8.01% and final ωR = 9.76% (observed data); goodness-of-fit = 1.79; largest Δ/σ = 0.066; mean Δ/σ = 0.003; data-to-parameter ratio = 4.2:1; largest difference peak, 0.55e $Å^{-3}$; largest difference hole, -0.24e $Å^{-3}$. The refined atomic coordinates are given in Table 1, and tables of bond lengths, bond angles, torsion angles, calculated hydrogen atomic coordinates, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Table 1: Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Coefficients (Å² x 10³)

Atom	*x/a*	*y/b*	*z/c*	*U*equiv.
C(1)	13830(14)	153	3963(14)	62(3)
C(2)	14738(16)	-139(17)	3385(16)	76(3)
C(3)	15730(15)	-865(16)	3893(16)	68(3)
C(4)	15879(14)	-1400(17)	4952(14)	62(3)
C(5)	14946(13)	-1097(17)	5484(13)	59(3)
C(6)	15106(15)	-1748(19)	6573(15)	81(3)
C(7)	14233(14)	-1175(17)	7236(14)	65(3)
C(8)	12934(12)	-985(15)	6497(13)	48(3)
C(9)	12972(12)	28(15)	5622(12)	44(3)
C(10)	13943(13)	-331(15)	5026(12)	46(3)
C(11)	11647(12)	244(16)	4847(11)	49(3)
C(12)	10634(13)	604(14)	5475(13)	51(3)
C(13)	10634(12)	-383(14)	6382(11)	40(3)
C(14)	11954(12)	-601(15)	7151(12)	43(3)
C(15)	11710(13)	-1546(15)	7979(13)	53(3)
C(16)	10402(13)	-1092(15)	8152(12)	49(3)
C(17)	10146(12)	74(14)	7393(11)	37(3)
C(18)	9945(13)	-1469(15)	5767(13)	58(3)
O(3)	16676(9)	-1168(13)	3321(10)	70(3)
C(31)	17425(15)	-235(18)	3180(15)	68(3)
O(31)	17379(12)	767(13)	3513(12)	91(3)
C(32)	18326(15)	-705(20)	2540(16)	93(3)
C(141)	12207(14)	592(15)	7794(12)	51(3)
C(161)	9389(14)	-1990(15)	7897(13)	49(3)
N(161)	8577(14)	-2633(16)	7705(12)	75(3)
O(16)	10539(10)	-601(12)	9281(9)	58(2)
C(162)	10902(14)	-1402(18)	10157(13)	60(3)
O(162)	11057(13)	-2462(14)	10065(10)	93(3)
C(163)	11089(18)	-715(20)	11296(14)	94(3)
C(171)	11124(14)	992(14)	7954(12)	46(3)
O(17)	8819(8)	348(11)	7180(8)	49(2)
C(172)	8415(14)	1478(18)	6815(13)	56(3)
O(172)	9052(10)	2268(12)	6610(10)	67(2)
C(173)	6969(15)	1549(19)	6604(18)	106(3)

*Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor

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