NOVEL REARRANGEMENTS OF THE 2-CHLOROACRYLONITRILE CYCLOADDUCTS OF STEROIDAL 14,16-DIEN-17-YL ACETATES

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Received October 31, 2001
Accepted November 27, 2001

Dedicated to the memory of Professor Václav Černý.

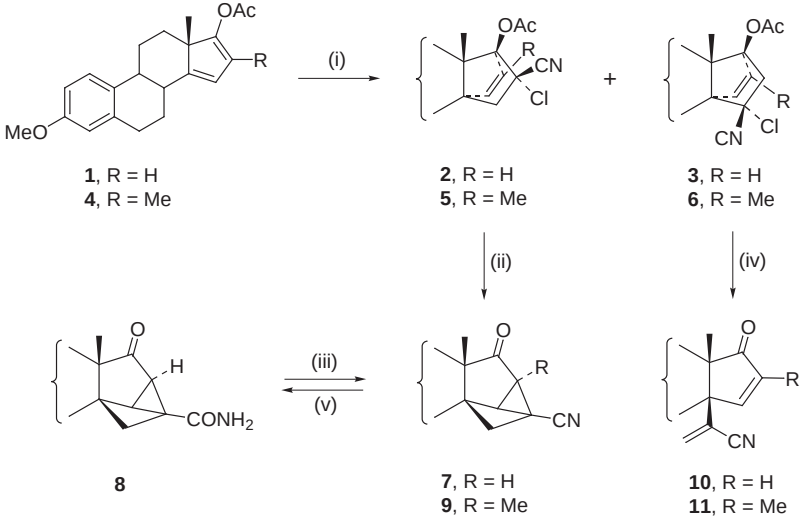
Cycloaddition of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) with 2-chloroacrylonitrile furnishes 17β-acetoxy-16α-chloro-3-methoxy-14,17α-ethenoestra-1,3,5(10)-triene-16β-carbonitrile (**2**) as the major product, which undergoes alkali-mediated rearrangement to (16[1]*R*)-3-methoxy-17-oxo-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16[1]-carbonitrile (**7**). A similar reaction course is followed by the related 16-methyl derivative **4**, and it is shown that minor 15-chloro-15-cyano cycloadducts **3** and **6** undergo Grob fragmentation. Functional group manipulations and regioselective bond-scission processes are described, for conversion of rearrangement product **7** into 16β,15β,14-(ethane[1,1,2]triyl) and cyclobuta[14β,15β] analogues of estradiol.

Keywords: [4 + 2]Cycloadditions; 2-Chloroacrylonitrile; Rearrangements; 19-Norsteroids; Estradiols; Steroids.

Structure–activity investigations into the molecular basis for estrogenicity and estrogen antagonism have generated a plethora of steroidal and non-steroidal probes for these properties[1–4], and recently gained additional impetus from the new insights afforded by the first crystal structure study of the ligand-binding domain (LBD) of the human estradiol receptor complex with estradiol and with the non-steroidal estrogen antagonist, raloxifene[5]. As part of an ongoing investigation into skeletally modified analogues of steroidal hormones, we have recently reported on some aspects of the design and synthesis of structural variants of estradiol, based upon ring D bridging elements and alkyl residues[6–10]. This investigation has its origins in an early finding of potent oral estrogenicity associated with incorporation of 14,17-alkano bridges into the estradiol template[11], and has generated numerous estradiol analogues that display highly competitive *in vitro* affinity toward the estrogen receptor[12,13].

During an investigation into the scope for carrying out cycloaddition of formal ketene equivalents to ring D dienyl acetates, it was discovered that 2-chloroacrylonitrile readily undergoes efficient cycloaddition with 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**), but attempted alkali-mediated conversion of the major 16-chloro-16-cyano cycloadduct **2** into the targeted 16-ketone resulted instead in an unprecedented rearrangement. In this account, we report more fully on the preliminary findings[14] of this cycloaddition–rearrangement sequence in steroidal 14,16-dien-17-yl acetates, and discuss aspects of the further chemistry of derived products.

The reaction of dienyl acetate **1** (Scheme 1) with 2-chloroacrylonitrile was the subject of extensive experimentation, owing to the tendency of the dienophile to decompose and polymerise at the elevated temperature needed to promote reaction. Furthermore, attempts to catalyse the reaction were accompanied by extensive destruction of the labile diene **1**. The most consistent results were achieved by conducting the reaction in concentrated benzene solution at 90 °C (sealed tube) for periods up to 120 h, with intermittent additions of fresh reagent. In most cases, reaction mixtures darkened progressively during the course of reaction, but at a rate that minimised complications during work-up and isolation. The major cycloadduct (isolated yield 79%) was formulated as the 16α-chloro-16β-cyano compound **2**, on the basis of well-established precedent for regioselectivity



SCHEME 1

(i) CH_2=C(Cl)CN, C_6H_6, 90 °C; (ii) KOH, THF–DMSO, 0 °C; (iii) KOH, THF–DMSO, 25 °C; (iv) KOH, EtOH, Δ; (v) P_2O_5, $C_6H_5CH_3$, Δ

and β-face stereoselectivity[6,11]. An X-ray crystal structure determination has since confirmed the structure of **2** (ref.[15]), and verified the assignment of 16-configuration. Chromatography of mixed fractions led to isolation of a minor by-product formulated as the 15α-chloro-15β-cyano compound **3**, the structure of which was verified by ensuing chemistry.

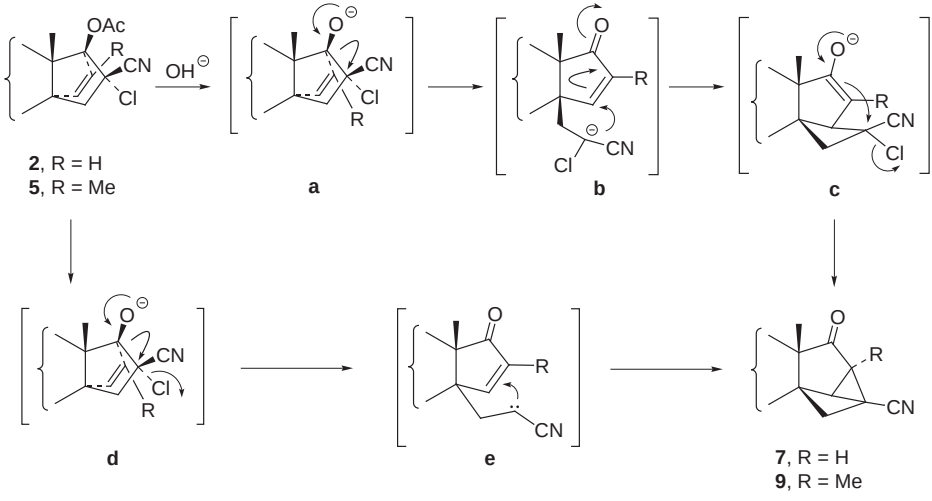
Previous studies have shown that the cycloaddition reactivity and head-to-head, β-face selectivity of steroidal 14,16-dien-17-yl acetates are significantly perturbed by the presence of a 16-methyl group[16], and this was borne out by extending this investigation to treatment of the 16-methyl-14,16-dien-17-yl acetate **4** with 2-chloroacrylonitrile. After 120 h at 90 °C, the reaction was incomplete but the mixture was severely discoloured, necessitating repeated chromatography of overlapping fractions to give starting material **4** (30%), accompanied by the cycloadducts **5** (28%) and impure **6** (≈12%). The spectroscopic properties, although inconclusive for isomer differentiation, were consistent with the assigned structures, which were confirmed by subsequent transformations.

A reported method[17] for revealing the masked 16-oxo group in **2** by treatment with sodium sulfide in refluxing methanol failed, giving only intractable mixtures, but treatment with aqueous alkali in a mixed-solvent medium at 0 °C gave a single product in high yield (90%), which displayed analytical and spectroscopic characteristics compatible with structure **7**. Thus, a 500 MHz ^{1}H NMR spectrum of **7** displayed multiplets for a closed four-proton spin system, which was uniquely assigned to a ring D tricyclo[3.2.0.0^{2,7}]heptanoid substructure, since it was possible to assign all the remaining ^{1}H signals by comparison with those of estrone 3-methyl ether. Furthermore, the ring D interproton couplings displayed good overall correspondence with those reported for a structurally similar tricyclic ring systems[18], including a distinctively large four-bond coupling of 2.4 Hz between 15α-H and 16^2-H$_{endo}$. The apparent lack of precedent for the rearrangement of **2** prompted an X-ray crystal structure determination of the product **7** (ref.[14]), which confirmed the structural assignment. More prolonged alkaline treatment of **2** at 25 °C resulted in formation of the 16^1-carboxamide **8**, which displayed closely analogous spectroscopic properties to those of **7**. It is evident that the rearranged carbonitrile **7** is the obligatory intermediate which undergoes partial hydrolysis to the corresponding carboxamide **8**, since conventional dehydration of **8** resulted in ready regeneration of **7**.

The 17^1-methyl cycloadduct **5** underwent similarly facile rearrangement in the presence of aqueous alkali at 0 °C to give the corresponding 16α-methyl

product **9**, verified by the simplified three-proton array of ^{1}H NMR signals associated with the ring D substructure.

Rearrangements initiated by bridgehead oxygen functionality are quite familiar, and include numerous examples involving participation by *gem*-chlorocyano functionality α-located to the bridgehead[19], but none which follow the extraordinary course observed in these examples. A first interpretation of the reaction course (Scheme 2) suggests that bridgehead saponification triggers alkoxide-mediated α-bond cleavage (**a**), followed by intramolecular Michael addition (**b**) to the resultant ring D enone function and intramolecular capture of the derived enolate anion with expulsion of the chloro group (**c**). The apparent ease with which this sequential reaction occurs may be attributable to the formation of a bis-functionalised cyclopropyl moiety, but is nevertheless remarkable in generating a highly strained bridge structure without observable evidence of discrete intermediates or competing processes. Indeed it is tempting to argue that the strained bridge structure in the starting materials may accommodate a charge-delocalised species engaging all six reaction centres in a concerted process, following 17-alkoxide formation, or that an initial, rate-limiting α-bond cleavage is accompanied by expulsion of the chloro group (**d**) to generate a highly reactive carbenoid intermediate which promptly adds across the proximate Δ^{15}-bond (**e**). In the absence of further evidence in support of



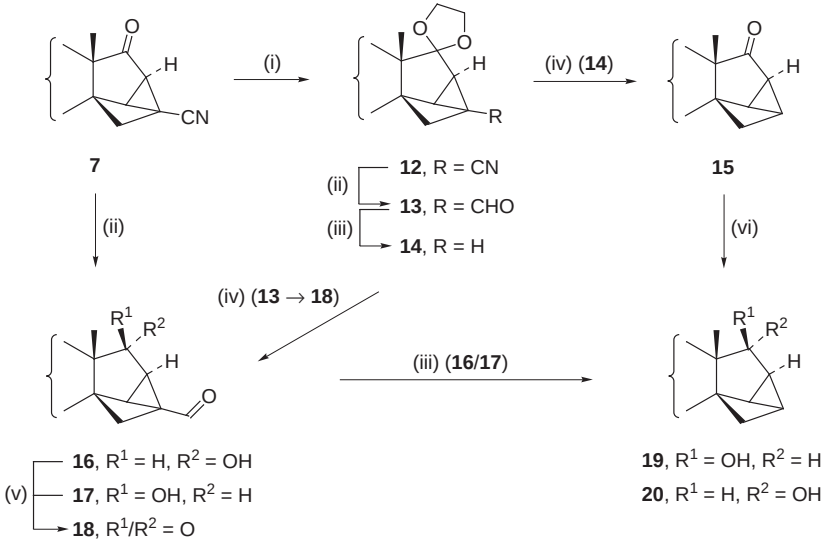
SCHEME 2

Alkali mediated rearrangement of 16α-chloro 16β-cyano cycloadducts: alternative domino-reaction pathways *via* **2**/**5** → **a** → **b** → **c** → **7**/**9** or **2**/**5** → **d** → **e** → **7**/**9**

these arguments the mechanistic detail is conjectural, and offers scope for more detailed study.

It was of interest to examine the alkali-mediated reactions of the regio-isomers **3** and **6**, in the expectation that the 1,3-disposition of functionality might allow for hydrolytic cleavage to the corresponding 15-ketones. In the event, both compounds underwent slow transformation in refluxing ethanolic potassium hydroxide, to give the respective products of Grob fragmentation **10** and **11**, the structures of which were supported by distinctive spectroscopic properties. Again, there is no direct analogy for this mode of fragmentation involving bridgehead-functionalised systems, but the result is mechanistically reasonable, and is also unsurprising given that the alternative, hydrolytic process may be impeded by steric congestion.

The 16[1]-cyano 17-ketone **7** (Scheme 3) provided unexpected access to a skeletally-novel 16β,15β,14-(ethane[1,1,2]triyl) ring system and the attendant opportunity to explore synthesis of new analogues of estradiol. In the first instance, the scope for direct reductive decyanation to the parent estrone analogue was examined, but without success. However, treatment of the derived 17-ketal **12** with diisobutylaluminium hydride (DIBAL-H) in toluene at –78 °C gave the 16[1]-carbaldehyde **13** (83%), which underwent smooth decarbonylation (92%) in the presence of Wilkinson's catalyst in



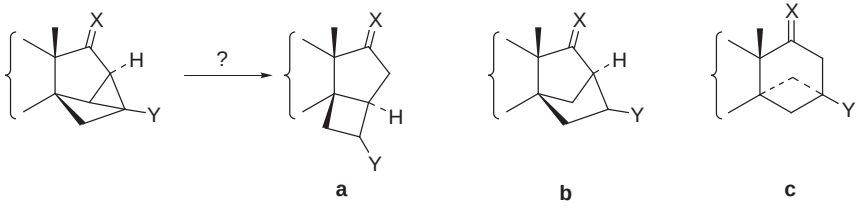
SCHEME 3

(i) $(CH_2OH)_2$, TsOH, $C_6H_5CH_3$, Δ; (ii) DIBAL-H, $C_6H_5CH_3$, –78 °C; (iii) $RhCl(PPh_3)_3$, $C_6H_5CH_3$, Δ; (iv) HCl, MeOH, 0 °C; (v) PDC, CH_2Cl_2, 0 °C; (vi) LAH, THF, Δ

refluxing toluene, and 17-deprotection of the product **14** furnished the parent 16β,15β,14-(ethane[1,1,2]triyl) 17-ketone **15**. Again, it proved possible to analyse the closed five-proton spin system of ring D fully, with the aid of high-field ^{1}H NMR spectroscopy and appropriate correlation techniques, and the couplings confirm the structure and provide insight into the constraints inherent in this rigid ring system.

In an alternative approach, targeted at more direct synthesis of estradiol analogues, the cyano ketone **7** was subjected to DIBAL-H reduction, to give a separable mixture of 17α- and 17β-hydroxy 16^1-carbaldehydes **16** (43%) and **17** (38%). Although these intermediates were separated and characterised for the purpose of isomer differentiation, the subsequent chemistry was expeditiously performed on the total DIBAL-H reaction product. Thus, pyridinium dichromate oxidation of the mixture furnished the 16^1-formyl 17-ketone **18**, whereas decarbonylation gave a separable mixture (≈45 : 55) of the respective estradiol 3-methyl ethers **19** and **20**. The latter compounds were also available more circuitously by hydride reduction of the corresponding 17-ketone **15**. The respective 17-epimers were readily differentiated by ^{1}H NMR confirmation of the near-eclipsing vicinal relationship between 17α-H and 16α-H (J = 4.8 Hz) in the 17β-alcohol **19**, in contrast to orthogonality between 17β-H and 16α-H ($J \approx 0$ Hz) in the 17α-alcohol **20**.

Among the further, inviting objectives in this phase of the investigation was exploration of the scope for chemoselective bond cleavage in the bridged tricyclic system, leading to new skeletal variants of the estratriene core structure (Scheme 4). In the first instance, dissolving metal reductions of the cyano ketone **7** were examined, in expectation that the doubly potentiated 16,16^1-bond would be susceptible to reductive cleavage. Initial experiments using zinc in acetic acid were based on analogy with reduction of small-ring linked 1,4-dicarbonyl compounds[20], but failed to react cleanly, as did lithium–liquid ammonia or samarium(II) iodide in the presence of compatible co-solvents. These outcomes suggested the need for a milder

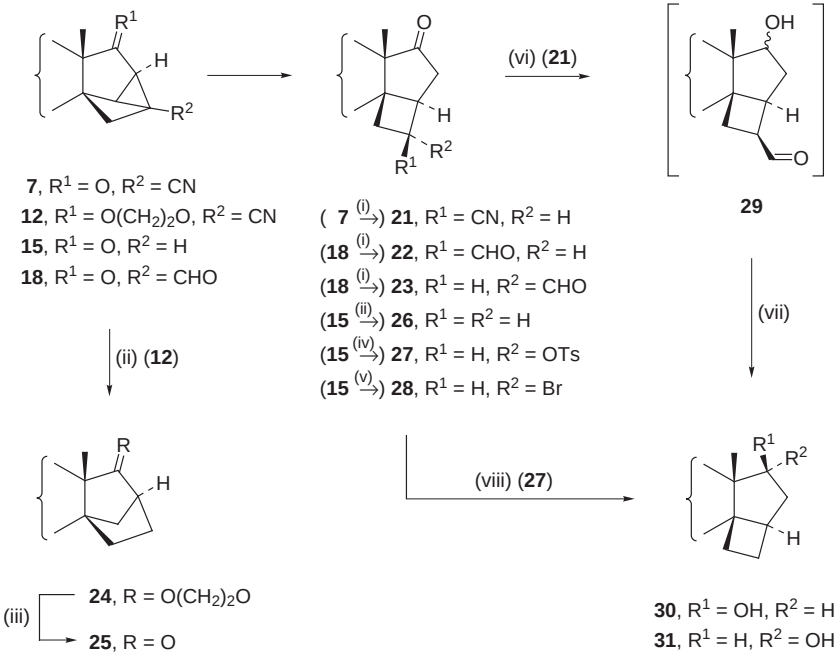


SCHEME 4

Pathways to skeletal simplification of the 16β,15β,14-(ethane[1,1,2]triyl) ring system, based upon bond cleavage at: **a** C(16)–C(16^1); **b** C(15)–C(16^1); **c** C(15)–C(16)

and possibly more selective reducing agent, for which calcium–liquid ammonia seemed a likely candidate[21]. Indeed, brief treatment of **7** with this reagent in THF at –78 °C furnished a single dihydro compound (71%), formulated as the 14β,15β-cyclobuta 17-ketone **21** (Scheme 5). ^{1}H NMR spectroscopy revealed signals for 16-H_2, diagnostic for a 16,16^1-seco structure, and an appropriate pattern of signals for the 3′-H and 4′-H_2, but failed to furnish unambiguous evidence for the 3′-configuration. However, subsequent experiments (see later) confirmed the provisional assignment of 3′β-configuration to the CN group in **21**, based upon an assumption of more ready 3′-*exo*-directed protonation of the reaction intermediate.

Analogous reduction of the 16^1-formyl 17-ketone **18** was less successful, and the major product **22** (≈42%) was accompanied by a small amount (≈7%) of isomeric material which was assumed to be the 3′α-epimer **23**. However, this reaction has not yet been optimised, and the poor yield is partly attributable to lability of the products. Nevertheless, it is evident that



SCHEME 5

(i) Ca–NH_3, THF, –78 °C; (ii) Li–NH_3, THF, –78 °C; (iii) HCl, MeOH, 0 °C; (iv) TsOH, $C_6H_5CH_3$, Δ; (v) HBr, $C_6H_5CH_3$, Δ; (vi) DIBAL-H, $C_6H_5CH_3$, –78 °C; (vii) $RhCl(PPh_3)_3$, $C_6H_5CH_3$, Δ; (viii) LAH, THF, Δ

the bis-functionalised tricyclic compounds **7** and **18** are susceptible to regiodefined reductive cleavage of the 16,16^1-bond as expected, and attention was turned to examining the course of reduction in mono-functionalised systems.

The 17-protected 16^1-carbonitrile **12** proved resistant to attempted hydrogenolysis of the cyclopropyl ring, and starting material was recovered unchanged under various catalysed reaction conditions, probably owing to steric hindrance. Dissolving metal methodology gave rise to complex and usually intractable mixtures of polar products, but an experiment in which **12** was subjected to very brief treatment with lithium–liquid ammonia/THF at –78 °C furnished a modest yield (25%) of the 14β,16β-ethano 17-ketal **24**, as proven by conversion into the known[22] 17-ketone **25**. Although this evidence of selective (perhaps preferred?) cleavage of the 15,16^1-bond is stereoelectronically understandable in terms of orbital alignment and probably also, strain relief, it is less evident how reductive decyanation can take place in the absence of a proton donor, and further work is necessary to optimise and interpret this process. By contrast, the 16β,15β,14-(ethane-[1,1,2]triyl) 17-ketone **15** underwent rapid and efficient reduction in lithium–liquid ammonia/THF at –78 °C to give the 16,16^1-seco 17-ketone **26** (84%), as evidenced by the appearance of the diagnostic ^{1}H NMR signals for 16-H_2, and in accordance with stereoelectronic expectations based upon colinearity of that bond with the 17-CO group. A complementary experiment entailed attempted hydrogenolysis of **15**. Although the 15,16-bond of the cyclopropyl moiety in **15** is sterically embedded, it was not obvious which of the remaining bonds is sterically more amenable to hydrogenolytic cleavage, and this was demonstrated when catalytic hydrogenation, which proceeded slowly and unselectively, gave a separable mixture of **25** (39%) and **26** (25%).

During experiments to explore the scope for acid-mediated rearrangement of the 16β,15β,14-(ethane[1,1,2]triyl) ring system, it was noted that the 17-ketone **15** underwent a slow non-catalytic transformation in the presence of 4-methylbenzenesulfonic acid in refluxing benzene, to give a product (69%) displaying analytical and spectroscopic properties consistent with addition of the elements of the reagent, and assigned as the 3′α-tosyloxy 17-ketone **27**. The ^{1}H NMR spectrum displayed 16-H_2 signals comparable to those of the foregoing cyclobuta[14β,15β] compounds, and a 3′-H signal differing diagnostically from those of the 3′-cyano and 3′-formyl compounds **21** and **22**. Since the obligatory reaction trajectory for Michael addition at C-16^1 in **15** is *anti* to the 16,16^1-bond, these differences constitute compelling evidence for the assigned configurations in this series of

compounds. A further example of conjugate reactivity of the 17-ketone **15** was furnished by treatment with hydrogen bromide in benzene at 70 °C, to give the corresponding 3′α-bromo 17-ketone **28** (66%). These reactions offer additional methods of entry to the cyclobuta[14β,15β] system, but the reductive cleavage product **21** was clearly the most accessible candidate for further elaboration to hormone analogues. This was demonstrated through DIBAL-H reduction of **21**, followed by treatment of the crude product with Wilkinson's catalyst in refluxing toluene, to give a separable mixture of the 17β- and 17α-alcohols **30** (8%) and **31** (52%). The compounds were differentiated on the basis of distinctive ^{1}H NMR signals for their respective 17-protons, comparable to those of related cycloalka[14β,15β] analogues of estradiol[8]. The isomer distribution was also in accordance with trends observed in hydride reduction in structurally related 17-ketones[6,8]. An alternative pathway, based on hydride reduction of the 3′α-tosyloxy 17-ketone **27** also furnished the 17-alcohols **30** and **31**.

The formation and chemistry of the rearrangement products **7** and **9** has opened opportunities for the study of unusual new steroidal substructures, as well as entries into new classes of skeletally modified hormone analogues. The synthesis and hormonal properties of some of the estradiol analogues based upon the 16β,15β,14-(ethane[1,1,2]triyl) and cyclobuta[14β,15β] ring systems form part of a systematic structure–activity study in this series, aspects of which have been reported elsewhere[6–12], or are the subject of ongoing investigations[13].

EXPERIMENTAL

Melting points were determined using a Reichert–Jung Thermovar hot-stage microscope and are uncorrected. Infrared spectra (wavenumbers in cm^{-1}) were recorded as chloroform solutions on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR were recorded on a Varian VXR-200 instrument at 200 MHz or a Varian Unity spectrometer at 400 MHz. All spectra were recorded in deuteriochloroform, unless otherwise stated, using $CHCl_3$, δ 7.26 as internal standard. All chemical shifts are reported in ppm, coupling constants (*J*) and half-width of multiplets ($w_{1/2}$) in Hz. Elemental analyses were performed using a Fison's Instruments Elemental Analyser EA1108. Mass spectra were recorded on a VG micromass 16F spectrometer and accurate mass determinations were performed on a Kratos Limited MS9/50 spectrometer. All mass spectra data were performed using electron impact techniques unless otherwise stated. Reagents and solvents were purified according to standard procedures.

Cycloaddition of 14,16-Dien-17-yl Acetates **1** and **4** with 2-Chloroacrylonitrile

A) A solution of 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate (**1**) (10 g, 30.9 mmol) and 2-chloroacrylonitrile (7.5 ml, 93.9 mmol) in anhydrous benzene (40 ml) was maintained at 90 °C in a sealed tube. Further aliquots of 2-chloroacrylonitrile (each 0.5 ml, 6.3 mmol)

were added after 68 and 92 h. After 114 h, the reaction mixture was filtered through Celite and evaporated under reduced pressure. Crystallisation of the solid residue (12 g) from chloroform–methanol, gave *17*β-*acetoxy-16*α-*chloro-3-methoxy-14,17*α-*ethenoestra-1,3,5(10)-triene-16*β-*carbonitrile* (**2**) (8.17 g, 64%), m.p. 182–185 °C, $[\alpha]_D$ +130 (*c* 0.6). For $C_{24}H_{26}ClNO_3$ (411) calculated: 70.0% C, 6.4% H, 3.4% N; found: 70.1% C, 6.6% H, 3.4% N. IR: 2 242 (CN), 1 749 (CO), 716 (CCl). ^{1}H NMR: 1.21 s, 3 H (13β-Me); 2.02 d, 1 H, *J* = 13.7 (15α-H); 2.24 s, 3 H (17β-OAc); 2.55 m, 1 H (9α-H); 2.75 d, 1 H, *J* = 13.7 (15β-H); 2.88 m, 2 H (6α- and 6β-H); 3.77 s, 3 H (3-OMe); 6.27 and 6.44 each d, 1 H, *J* = 6.2 (17^1- and 17^2-H); 6.63 d, 1 H, *J* = 2.7 (4-H); 6.73 dd, 1 H, *J* = 8.6 and 2.7 (2-H); 7.19 d, 1 H, *J* = 8.6 (1-H). ^{13}C NMR: 169.2 (17-OCOCH_3), 157.6 (C-3), 137.3 (C-5), 133.6 and 132.8 (C-17^1 and C-17^2), 131.3 (C-10), 127.0 (C-1), 118.4 (16-CN), 113.7 (C-4), 112.0 (C-2), 98.2 (C-17), 62.3, 62.0 and 56.7 (C-13, C-14 and C-16), 55.2 (3-OMe), 46.5 (C-15), 39.4 (C-9), 38.6 (C-8), 31.0, 26.7 and 23.8 (C-7, C-11 and C-12), 29.8 (C-6), 21.3 (17-OCOCH_3), 15.7 (C-18). MS (EI, *m/z*): 411 [M^+].

Chromatography of the mother-liquor residue (3.8 g) on silica gel (200 g), with toluene as eluent, gave the dienyl acetate **1** (250 mg, 2.5%), a mixed fraction of the cycloadducts **2** and **3** (2.45 g, 19%), and decomposition products (880 mg). Recrystallisation of the mixed fraction gave further cycloadduct **2** (1.9 g, 15%), and chromatography of the derived mother-liquor residue (0.5 g) on silica gel (100 g), with toluene as eluent, gave *17*β-*acetoxy-15*α-*chloro-3-methoxy-14,17*α-*ethenoestra-1,3,5(10)-triene-15*β-*carbonitrile* (**3**) (270 mg, 2%), m.p. 162–164 °C (chloroform–methanol), $[\alpha]_D$ +73 (*c* 1.0). For $C_{24}H_{26}ClNO_3$ (411) calculated: 70.0% C, 6.4% H, 3.4% N; found: 69.6% C, 6.2% H, 3.3% N. IR: 2 220 (CN), 1 742 (CO). ^{1}H NMR: 1.26 s, 3 H (13β-Me); 1.72 m, 1 H (7α-H); 2.12 s, 3 H (17β-OAc); 2.60 m, 1 H (9α-H); 2.81 d, 1 H, *J* = 13.7 (16α-H); 2.92 m, 2 H (6α- and 6β-H); 3.04 d, 1 H, *J* = 13.7 (16β-H); 3.78 s, 3 H (3-OMe); 6.19 and 6.55 each d, 1 H, *J* = 6.1 (17^1- and 17^2-H); 6.65 d, 1 H, *J* = 2.8 (4-H); 6.73 dd, 1 H, *J* = 8.5 and 2.8 (2-H); 7.20 d, 1 H, *J* = 8.5 (1-H). ^{13}C NMR: 170.5 (17-OCOCH_3), 157.8 (C-3), 137.6 (C-5), 136.1 and 132.5 (C-17^1 and C-17^2), 131.0 (C-10), 127.5 (C-1), 118.3 (15-CN), 113.8 (C-4), 112.0 (C-2), 91.3 (C-17), 63.5, 62.0 and 60.2 (C-13, C-14 and C-15), 55.3 (3-OMe), 49.2 (C-16), 40.0 (C-9), 38.0 (C-8), 31.1, 27.1 and 24.0 (C-7, C-11 and C-12), 30.0 (C-6), 21.2 (17-OCOCH_3), 16.3 (C-18). MS (EI, *m/z*): 411 [M^+].

B) Similar reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate (**4**) (1.25 g, 3.55 mmol) with 2-chloroacrylonitrile in benzene at 90 °C (sealed tube) for 120 h gave an oily product which was chromatographed on silica gel (150 g), with ethyl aceatate–hexane (1 : 9) as eluent, to give starting material (378 mg, 30%) followed by *17*β-*acetoxy-16*α-*chloro-3-methoxy-17*^{1}-*methyl-14,17*α-*ethenoestra-1,3,5(10)-triene-16*β-*carbonitrile* (**5**) (432 mg, 28%), m.p. 189–192 °C (dichloromethane–methanol), $[\alpha]_D$ +131 (*c* 1.7). For $C_{25}H_{28}ClNO_3$ (425) calculated: 70.5% C, 6.6% H, 3.3% N; found: 70.6% C, 6.7% H, 3.3% N. IR: 2 236 (CN), 1 726 (CO), 688 (CCl). ^{1}H NMR: 1.21 d, 3 H, *J* = 0.8 (13β-Me); 1.88 d, 3 H, *J* = 1.7 (17^1-Me); 2.08 d, 1 H, *J* = 13.7 (15α-H); 2.25 s, 3 H (17β-OAc); 2.5 m, 1 H (9α-H); 2.7 d, 1 H, *J* = 13.7 (15β-H); 2.83 m, 2 H (6α- and 6β-H); 3.76 s, 3 H (3-OMe); 5.95 br m, 1 H, *W* ≈ 5 (17^2-H); 6.64 d, 1 H, *J* = 2.8 (4-H); 6.72 dd, 1 H, *J* = 8.6 and 2.8 (2-H); 7.2 d, 1 H, *J* = 8.6 (1-H). MS (EI, *m/z*): 425. Further elution gave impure material which was chromatographed repeatedly to give an oily fraction (186 mg, 12%), largely comprising *17*β-*acetoxy-15*α-*chloro-3-methoxy-17*^{1}-*methyl-14,17*α-*ethenoestra-1,3,5(10)-triene-15*β-*carbonitrile* (**6**). IR: 2 236 (CN), 1 726 (CO), 688 (CCl). ^{1}H NMR: 1.13 d, 3 H, *J* = 0.8 (13β-Me); 1.82 d, 3 H, *J* = 1.8 (17^1-Me); 2.12 s, 3 H (17β-OAc); 2.6 m, 1 H (9α-H); 2.85 d, 1 H, *J* = 14.1 (16α-H); 2.95 m, 2 H (6-H_2); 3.15 d, 1 H, *J* = 14.1 (16β-H); 3.76 s, 3 H (3-OMe); 5.78 m, 1 H (17^2-H); 6.64 d, 1 H, *J* = 2.7 (4-H); 6.7 dd, 1 H, *J* = 8.6 and 2.7 (2-H); 7.18 d, 1 H, *J* = 8.6 (1-H). MS (EI, *m/z*): 425 [M^+].

Alkaline Treatment of 16-Chloro-16-cyano 17-Acetates **2** and **5**

A) A solution of the cycloadduct **2** (1.7 g, 4.1 mmol) in tetrahydrofuran (25 ml) and dimethyl sulfoxide (25 ml) at 0 °C under nitrogen was treated with aqueous 2 M potassium hydroxide (5.2 ml, 10.4 mmol). After 5 h at 0 °C, saturated aqueous ammonium chloride was added and the mixture was concentrated under reduced pressure. Water was added and the residue was extracted with chloroform. The extract was washed with brine and water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (1.8 g) on silica gel (130 g), with ethyl acetate–toluene (1 : 9) as eluent, gave *(16^{1}R)-3-methoxy-17-oxo–16*β,*15*β,*14-(ethane[1,1,2]triyl)-14*β*-estra-1,3,5(10)-triene-16^1-carbonitrile* (**7**) (1.24 g, 90%), m.p. 158–161 °C (chloroform–methanol), $[\alpha]_D$ +164 (*c* 1.0). For $C_{22}H_{23}NO_2$ (333) calculated: 79.3% C, 7.0% H, 4.2% N; found: 79.2% C, 7.0% H, 4.1% N. IR: 2 232 (CN), 1 733 (CO). ^{1}H NMR: 0.89 s, 3 H (13β-Me); 1.36 qd, 1 H, *J* = 2 × 13.1, 12.0 and 3.4 (11β-H); 1.43 dt, 1 H, *J* = 13.1 and 2 × 3.4 (12β-H); 1.49 td, 1 H, *J* = 2 × 12.0 and 2.6 (8β-H); 1.55 dd, 1 H, *J* = 10.6 and 2.4 (16^2*S*-H); 1.59 td, 1 H, *J* = 2 × 13.1 and 3.4 (12α-H); 1.73 qd, 1 H, *J* = 3 × 12.0 and 6.2 (7α-H); 2.22 ddt, 1 H, *J* = 12.0, 5.7 and 2 × 2.6 (7β-H); 2.30 ddt, 1 H, *J* = 13.1 and 3 × 3.4 (11α-H); 2.44 td, 1 H, *J* = 2 × 12.0 and 3.4 (9α-H); 2.60 d, 1 H, *J* = 4.5 (16α-H); 2.71 d, 1 H, *J* = 10.6 (16^2*R*-H); 2.87–2.98 m, 2 H (6α- and 6β-H); 3.35 dd, 1 H, *J* = 4.5 and 2.4 (15α-H); 3.77 s, 3 H (3-OMe); 6.65 d, 1 H, *J* = 2.6 (4-H); 6.72 dd, 1 H, *J* = 8.6 and 2.6 (2-H); 7.17 d, 1 H, *J* = 8.6 (1-H). ^{13}C NMR: 212.5 (C-17), 157.9 (C-3), 137.3 (C-5), 130.6 (C-10), 126.4 (C-1), 117.6 (16^1-CN), 113.6 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.2 and 52.9 (C-13 and C-14), 39.0 (C-9), 37.5 (C-16), 37.2 (C-8), 36.5 (C-15), 30.0 (C-12), 29.7 (C-6), 27.7 (C-16^2), 25.0 (C-11), 24.5 (C-7), 12.4 (C-16^1), 11.8 (C-18). MS (EI, *m/z*): 333.

B) A solution of the cycloadduct **2** (1 g, 2.4 mmol) in tetrahydrofuran (13 ml) and dimethyl sulfoxide (30 ml) was treated with aqueous 1.5 M potassium hydroxide (10 ml, 15.0 mmol) at 25 °C under nitrogen. After 23 h at 25 °C, saturated aqueous ammonium chloride was added, and the mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a solid residue (0.8 g), which was crystallised from ethanol to give *(16^{1}R)-3-methoxy-17-oxo-16*β,*15*β,*14-(ethane-[1,1,2]triyl)-14*β*-estra-1,3,5(10)-triene-16^1-carboxamide* (**8**) (684 mg, 80%), m.p. 252–255 °C, $[\alpha]_D$ +96 (*c* 0.8). For $C_{22}H_{25}NO_3$ (351) calculated: 75.2% C, 7.2% H, 4.0% N; found: 75.3% C, 6.9% H, 3.8% N. IR: 3 407 (NH), 1 725 (17-CO), 1 675 ($CONH_2$). ^{1}H NMR: 0.96 s, 3 H (13β-Me); 1.37 obsc. qd, 1 H, *J* = 2 × 13.2, 12.4 and 3.2 (11β-H); 1.44 obsc. dt, 1 H, *J* = 13.4 and 2 × 3.2 (12β-H); 1.45–1.51 obsc. m, 1 H (8β-H); 1.47 obsc. dd, 1 H, *J* = 10.0 and 2.3 (16^2*S*-H); 1.63–1.76 m, 2 H (7α- and 12α-H); 2.16 ddt, 1 H, *J* = 12.8, 5.5 and 2 × 2.6 (7β-H); 2.30 ddt, 1 H, *J* = 13.2 and 3 × 3.2 (11α-H); 2.46 td, 1 H, *J* = 2 × 12.4 and 3.2 (9α-H); 2.57 d, 1 H, *J* = 10.0 (16^2*R*-H); 2.73 d, 1 H, *J* = 4.3 (16α-H); 2.85–2.93 m, 2 H (6α- and 6β-H); 3.23 dd, 1 H, *J* = 4.3 and 2.3 (15α-H); 3.76 s, 3 H (3-OMe); 5.88 br d, exch. by D_2O, 2 H (16^1-$CONH_2$); 6.63 d, 1 H, *J* = 2.6 (4-H); 6.72 dd, 1 H, *J* = 8.6 and 2.6 (2-H); 7.18 d, 1 H, *J* = 8.6 (1-H). MS (EI, *m/z*): 351 [M^+].

C) Alkaline treatment of the cycloadduct **5** (270 mg, 0.63 mmol) as described in experiment *A*, and crystallisation of the product from dichloromethane–methanol gave (16^1*-R)-3-methoxy-16*α*-methyl-17-oxo-16*β,*15*β,*14-(ethane[1,1,2]triyl)-14*β*-estra-1,3,5(10)-triene-16^1-carbonitrile* (**9**) (150 mg, 68%), m.p. 175–177 °C, $[\alpha]_D$ +193 (*c* 1.1). For $C_{23}H_{25}NO_2$ (347) calculated: 79.5% C, 7.2% H, 4.0% N; found: 79.2% C, 7.3% H, 4.1% N. IR: 2 230 (CN), 1 731 (CO). ^{1}H NMR: 0.92 s, 3 H (13β-Me); 1.36 qd, 1 H, *J* = 2 × 13.2, 11.6 and 3.3 (11β-H); 1.48 td, 1 H, *J* = 2 × 11.6 and 2.6 (8β-H); 1.49 s, 1 H (16α-Me); 1.55 dd, 1 H, *J* = 10.6 and 2.2 (16^2*S*-H); 1.59 obsc. m,

1 H (12α-H); 1.71 qd, 1 H, *J* = 3 × 11.6 and 6.4 (7α-H); 2.22 ddt, 1 H, *J* = 11.6, 5.7 and 2 × 2.6 (7β-H); 2.30 ddt, 1 H, *J* = 13.2 and 3 × 3.4 (11α-H); 2.43 td, 1 H, *J* = 2 × 11.2 and 2.9 (9α-H); 2.71 d, 1 H, *J* = 10.6 (16^2*R*-H); 2.86 br m, 2 H (6α- and 6β-H); 3.18 d, 1 H, *J* = 2.2 (15α-H); 3.78 s, 3 H (3-OMe); 6.64 d, 1 H, *J* = 2.6 (4-H); 6.74 dd, 1 H, *J* = 8.6 and 2.6 (2-H); 7.20 d, 1 H, *J* = 8.6 (1-H). ^{13}C NMR: 214.8 (C-17), 157.8 (C-3), 137.3 (C-5), 130.7 (C-10), 126.5 (C-1), 117.1 (16^1-CN), 113.6 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.2 (C-13), 51.2 (C-14), 42.8 (C-15), 41.6 (C-16), 38.9 (C-9), 37.1 (C-8), 30.2 (C-12), 29.8 (C-6), 28.0 ($C\text{-}16^2$), 25.1 (C-11), 24.5 (C-7), 18.1 ($C\text{-}16^1$), 12.1 (C-18), 10.9 (16α-Me). MS (EI, *m/z*): 347 [M^+].

Alkaline Treatment of 15-Chloro-15-cyano 17-Acetates **3** and **6**

A) A solution of compound **3** (50 mg, 0.12 mmol) in ethanolic 0.1 M potassium hydroxide (25 ml) was refluxed for 7.5 h, then aqueous ammonium chloride was added and the solution was concentrated under reduced pressure and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (55 mg) on silica gel (5 g), with ethyl acetate–toluene (1 : 9) as eluent, gave *2-[3-methoxy-17-oxo-14*β*-estra-1,3,5(10),15-tetraen-14-yl]acrylonitrile* (**10**) (31 mg, 69%), m.p. 125–128 °C (chloroform–methanol), $[\alpha]_D$ +337 (*c* 0.5). For $C_{22}H_{23}NO_2$ (333) calculated: 79.3% C, 7.0% H, 4.2% N; found: 79.1% C, 7.3% H, 4.0% N. IR: 2 222 (CN), 1 710 (CO). ^{1}H NMR: 1.03 s, 3 H (13′β-Me); 2.78–2.89 br m, 2 H (6′α- and 6′β-H); 3.75 s, 3 H (3′-OMe); 5.75 and 6.22 each br s, 2 H ($3\text{-}H_2$); 6.45 d, 1 H, *J* = 5.9 (16′-H); 6.56 d, 1 H, *J* = 2.6 (4′-H); 6.70 dd, 1 H, *J* = 8.6 and 2.6 (2′-H); 7.01 d, 1 H, *J* = 8.6 (1′-H); 7.38 d, 1 H, *J* = 5.9 (15′-H). MS (EI, *m/z*): 333 [M^+].

B) The cycloadduct **6** (190 mg, 0.44 mmol) was subjected to alkaline treatment as described in the foregoing experiment, and the product was chromatographed on silica gel, with ethyl acetate–toluene (1 : 19) as eluent, to give *2-[3-methoxy-16-methyl-17-oxo-14*β*-estra-1,3,5(10),15-tetraen-14-yl]acrylonitrile* (**11**) (106 mg, 69%), m.p. 135–140 °C (dichloromethane–methanol), $[\alpha]_D$ +317 (*c* 0.9). For $C_{23}H_{25}NO_2$ (347) calculated: 79.5% C, 7.2% H, 4.0% N; found: 79.3% C, 7.3% H, 4.0% N. IR: 2 225 (CN), 1 708 (CO). ^{1}H NMR: 1.0 s, 3 H (13′β-Me); 1.89 d, 3 H, *J* = 1.4 (16′-Me); 2.45 br m, 1 H (9′α-H); 2.78–2.89 br m, 2 H (6′α- and 6′β-H); 3.74 s, 3 H (3′-OMe); 5.78 and 6.2 each br s, 2 H ($3\text{-}H_2$); 6.45 d, 1 H, *J* = 5.9 (16′-H); 6.55 d, 1 H, *J* = 2.9 (4′-H); 6.70 dd, 1 H, *J* = 8.5 and 2.9 (2′-H); 6.95 br s, 1 H (15′-H); 7.01 d, 1 H, *J* = 8.5 (1′-H). MS (EI, *m/z*): 347 [M^+].

(16^1*R*)-17,17-(Ethylenedioxy)-3-methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbonitrile (**12**)

A mixture of the 17-ketone **7** (540 mg, 1.6 mmol) and $TsOH{\cdot}H_2O$ (50 mg, 0.29 mmol) in ethylene glycol (2.0 ml) and toluene (54 ml) was refluxed under a Dean–Stark head with slow removal of solvent. After 7.5 h, reflux of the residual mixture (≈30 ml) was continued for a further 17 h with return of the condensate through molecular sieves (4 Å). Aqueous sodium hydrogencarbonate was added to the cooled reaction mixture and the product was extracted with toluene. The extract was washed with water and aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and evaporated under reduced pressure. Crystallisation of the solid residue (632 mg) from chloroform–methanol gave the 17-ketal **12** (565 mg, 92%), m.p. 232–237 °C, $[\alpha]_D$ +133 (*c* 1.1). For $C_{24}H_{27}NO_3$ (377) calculated: 76.4% C, 7.2% H, 3.7% N; found: 76.1% C, 7.3% H, 3.7% N. IR: 2 226 (CN). ^{1}H NMR: 0.72 s, 3 H (13β-Me); 1.84 dd, 1 H, *J* = 9.7 and 2.2 (16^2*S*-H); 2.17 d, 1 H, *J* = 5.2 (16α-H); 2.41 d, 1 H, *J* = 9.7

(16^2*R*-H); 2.89 br m, 2 H (6α- and 6β-H); 2.99 dd, 1 H, *J* = 5.2 and 2.2 (15α-H); 3.75 s, 3 H (3-OMe); 3.84–4.11 m, 4 H (17-OCH$_2$CH$_2$O); 6.62 d, 1 H, *J* = 2.7 (4-H); 6.67 dd, 1 H, *J* = 8.5 and 2.7 (2-H); 7.18 d, 1 H, *J* = 8.5 (1-H). MS (EI, *m/z*): 377 [M$^+$].

(16^1*R*)-17,17-(Ethylenedioxy)-3-methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbaldehyde (**13**)

A solution of the ketal **12** (400 mg, 1.06 mmol) in anhydrous toluene (80 ml) at –78 °C under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 3.6 ml, 3.6 mmol). After 160 min, aqueous ammonium chloride was added at –78 °C. The reaction mixture was acidified with dilute sulfuric acid and extracted with ethyl acetate, and the extract was washed with sodium hydrogencarbonate and water, dried (MgSO$_4$), and evaporated to dryness under reduced pressure. Flash chromatography of the residue (378 mg) on silica gel (40 g), with ethyl acetate–toluene (1 : 9) as eluent, gave the 16^1-carbaldehyde **13** (335 mg, 83%), m.p. 190–194 °C (chloroform–hexane), [α]$_D$ +165 (*c* 0.8). For C$_{24}$H$_{28}$O$_4$ (380) calculated: 75.8% C, 7.4% H; found: 75.7% C, 7.2% H. IR: 1 685 (CO). ^{1}H NMR: 0.77 s, 3 H (13β-Me); 1.62 dd, 1 H, *J* = 10.3 and 1.9 (16^2*S*-H); 2.45 obsc. d, 1 H, *J* ≈ 5 (16α-H); 2.49 obsc. d, 1 H, *J* ≈ 10 (16^2*R*-H); 2.84 m, 2 H (6α- and 6β-H); 3.05 dd, 1 H, *J* = 5.3 and 1.9 (15α-H); 3.74 s, 3 H (3-OMe); 3.83–4.05 m, 4 H (-OCH$_2$CH$_2$O-); 6.61 d, 1 H, *J* = 2.8 (4-H); 6.69 dd, 1 H, *J* = 8.7 and 2.8 (2-H); 7.19 d, 1 H, *J* = 8.7 (1-H); 8.86 s, 1 H (CHO). MS (EI, *m/z*): 380 [M$^+$].

(16^1*S*)-17,17-(Ethylenedioxy)-3-methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene (**14**)

The 16^1-carbaldehyde **13** (340 mg, 0.89 mmol) and RhCl(PPh$_3$)$_3$ (912 mg, 0.99 mmol) in deoxygenated toluene (25 ml) were refluxed under nitrogen. After 20 h ethanol was added to the cooled reaction mixture and most of the RhCl(CO)(PPh$_3$)$_2$ was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. Chromatography of the residue (805 mg) on silica gel (34 g), with ethyl acetate–toluene (1 : 99) as eluent, gave compound **14** (291 mg, 92%), m.p. 159–163 °C (chloroform–methanol), [α]$_D$ +117 (*c* 1.0). For C$_{23}$H$_{28}$O$_3$ (352) calculated: 78.4% C, 8.0% H; found: 78.4% C, 8.2% H. ^{1}H NMR: 0.73 s, 3 H (13β-Me); 2.40 dt, 1 H, *J* = 2 × 11.6 and 3.8 (9α-H); 2.85 m, 2 H (6α- and 6β-H); 3.75 s, 3 H (3-OMe); 3.84–4.09 m, 4 H (-OCH$_2$CH$_2$O-); 6.61 dd, 1 H, *J* = 2.7 (4-H); 6.69 dd, 1 H, *J* = 8.5 and 2.7 (2-H); 7.20 d, 1 H, *J* = 8.5 (1-H). MS (EI, *m/z*): 352 [M$^+$].

(16^1*S*)-3-Methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-trien-17-one (**15**)

A solution of the 17-ketal **14** (150 mg, 0.43 mmol) in tetrahydrofuran (6 ml) and methanol (18 ml) at 0 °C was treated with 6 M hydrochloric acid (1.2 ml, 7.2 mmol). After 6 min at 0 °C, solid sodium hydrogencarbonate was added and the mixture was diluted with water and extracted with chloroform. The extract was washed with aqueous sodium hydrogencarbonate and water, dried (MgSO$_4$), and evaporated under reduced pressure. Crystallisation of the residue (154 mg) from chloroform–methanol gave the 17-ketone **15** (110 mg, 84%), m.p. 179–184 °C, [α]$_D$ +171 (*c* 1.0). For C$_{21}$H$_{24}$O$_2$ (308) calculated: 81.8% C, 7.8% H; found: 81.7% C, 7.7% H. IR: 1 711 (CO). ^{1}H NMR: 0.87 s, 3 H (13β-Me); 1.26 dd, 1 H, *J* = 10.5 and 2.9 (16^2*R*-H); 1.37 qd, 1 H, *J* = 2 × 13.4, 12.0 and 3.2 (11β-H); 1.41–1.49 m, 2 H (12α- and 8β-H); 1.67–1.76 m, 2 H (7α- and 12β-H); 2.04 dd, 1 H, *J* = 6.5 and 4.1 (16α-H); 2.10 ddd, 1 H, *J* = 6.5, 3.9 and 3.7 (16^{1}α-H); 2.22–2.26 m, 1 H (7β-H); 2.29 ddt, 1 H, *J* = 13.2 and 3 ×

3.7 (11α-H); 2.45 dd, 1 H, *J* = 10.5 and 3.9 (16^2*S*-H); 2.48 td, 1 H, *J* = 2 × 11.5 and 3.2 (9α-H); 2.76 ddd, 1 H, *J* = 4.1, 3.7 and 2.9 (15α-H); 2.92 m, 2 H (6α- and 6β-H); 3.78 s, 3 H (3-OMe); 6.66 d, 1 H, *J* = 2.8 (4-H); 6.73 dd, 1 H, *J* = 8.5 and 2.8 (2-H); 7.21 d, 1 H, *J* = 8.5 (1-H). ^{13}C NMR: 218.8 (C-17), 157.6 (C-3), 137.7 (C-5), 131.7 (C-10), 126.5 (C-1), 113.6 (C-4), 111.8 (C-2), 55.2 (3-OMe), 53.9 and 52.9 (C-13 and C-14), 39.2 (C-9), 37.9 (C-8), 32.9 and 20.4 (C-16 and C-16^1), 30.8 (C-15), 30.6 (C-12), 30.0 (C-6), 26.0 (C-16^2), 25.4 and 24.7 (C-7 and C-11), 12.1 (C-18). MS (EI, *m/z*): 308 [M$^+$]. Chromatography of the mother liquor on silica gel (1.6 g), with ethyl acetate–toluene (1 : 19) as eluent, gave further 17-ketone **15** (10 mg, 8%).

(16^1*S*)-17-Hydroxy-3-methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbaldehydes (**16** and **17**)

A solution of the carbonitrile **7** (0.8 g, 2.4 mmol) in anhydrous toluene (32 ml) at –78 °C under nitrogen was treated with diisobutylaluminium hydride (1.5 M solution in toluene; 5.0 ml, 7.5 mmol). After 60 min at –78 °C the reaction was quenched with water, and the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure. The crystalline residue (1.13 g) was chromatographed on silica gel (80 g), with ethyl acetate–chloroform (1 : 4) as eluent, to give *(16^{1}R)-17α-hydroxy-3-methoxy-16β,15β,14-(ethane-[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbaldehyde* (**16**) (346 mg, 43%), m.p. 134–137 °C (ethyl acetate–hexane), $[\alpha]_D$ +115 (*c* 1.0). For $C_{22}H_{26}O_3$ (338) calculated: 78.1% C, 7.7% H; found: 77.7% C, 7.7% H. IR: 3 608 and 3 436 (OH), 1 684 (CO). ^{1}H NMR: 0.96 s, 3 H (13β-Me); 1.75 d, 1 H, *J* = 6.4, exch. by D_2O (17α-OH); 2.32 obsc. d, 1 H, *J* = 5. 1 (16α-H); 2.48 d, 1 H, *J* = 11.0 (16^2*R*-H); 2.87 m, 2 H (6α- and 6β-H); 3.12 br dd, 1 H, *J* ≈ 5 and 2 (15α-H); 3.78 s, 3 H (3-OMe); 4.28 d, 1 H, *J* = 6.4 → s on D_2O exch. (17β-H); 6.64 d, 1 H, *J* = 2.5 (4-H); 6.73 dd, 1 H, *J* = 8.5 and 2.5 (2-H); 7.22 d, 1 H, *J* = 8.5 (1-H); 8.81 s, 1 H (CHO). MS (EI, *m/z*): 338 [M$^+$], followed by *(16^{1}R)-17β-hydroxy-3-methoxy-16β,15β,14-(ethane-[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbaldehyde* (**17**) (310 mg, 38%), m.p. 178–183 °C (ethyl acetate–hexane), $[\alpha]_D$ +134 (*c* 1.0). For $C_{22}H_{26}O_3$ (338) calculated: 78.1% C, 7.7% H; found: 78.1% C, 7.8% H. IR: 3 608 and 3 440 (OH), 1 688 (CO). ^{1}H NMR: 0.91 s, 3 H (13β-Me); 1.60 dd, 1 H, *J* = 10.5 and 1.9 (16^2*S*-H); 1.73 d, 1 H, *J* = 4.7, exch. by D_2O (17β-OH); 2.58 d, 1 H, *J* = 10.5 (16^2*R*-H); 2.76 t, 1 H, *J* = 2 × 4.7 (16α-H); 2.88 m, 2 H (6α- and 6β-H); 3.09 dd, 1 H, *J* = 4.7 and 1.9 (15α-H); 3.78 s, 3 H (3-OMe); 4.12 t, 1 H, *J* = 2 × 4.7 → d, *J* = 4.7 on D_2O exch. (17α-H); 6.64 d, 1 H, *J* = 2.8 (4-H); 6.72 dd, 1 H, *J* = 8.8 and 2.8 (2-H); 7.20 d, 1 H, *J* = 8.8 (1-H); 8.91 s, 1 H (CHO). MS (EI, *m/z*): 338 [M$^+$].

(16^1*R*)-3-Methoxy-17-oxo-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-triene-16^1-carbaldehyde (**18**)

A) A mixture (pre-chromatography reaction product of foregoing experiment) of the 17ξ-hydroxy-16^1-carbaldehydes **16** and **17** (50 mg, 0.15 mmol) in dichloromethane (3 ml) at 0 °C was treated with pyridinium dichromate (84 mg, 0.22 mmol). After 2 h at 0 °C, the reaction mixture was maintained at 20 °C for 22 h, then water was added and the product was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the product (52 mg) on silica gel (5 g), with ethyl acetate–toluene (1 : 9) as eluent, gave the 17-oxo-16^1-carbaldehyde **18** (30 mg,

60%), m.p. 182–187 °C (ethyl acetate), $[\alpha]_D$ +200 (*c* 0.8). For $C_{22}H_{24}O_3$ (336) calculated: 78.5% C, 7.2% H; found: 78.7% C, 7.1% H. IR: 1 731 (CO), 1 697 (CO). ^{1}H NMR: 0.94 d, 3 H, *J* = 0.6 (13β-Me); 1.37 dd, 1 H, *J* = 11.0 and 2.4 (16^2*S*-H); 2.19 m, 1 H (7ξ-H); 2.33 ddt, 1 H, *J* = 13.4 and 3 × 3.7 (11α-H); 2.48 td, 1 H, *J* = 2 × 11.8 and 3.7 (9α-H); 2.79 d, 1 H, *J* = 11.0 (16^2*R*-H); 2.89 d, 1 H, *J* = 4.5 (16α-H); 2.92 m, 2 H (6α- and 6β-H); 3.39 dd, 1 H, *J* = 4.5 and 2.4 (15α-H); 3.78 s, 3 H (3-OMe); 6.66 d, 1 H, *J* = 2.8 (4-H); 6.74 dd, 1 H, *J* = 8.4 and 2.8 (2-H); 7.21 d, 1 H, *J* = 8.4 (1-H); 8.97 s, 1 H (16^1-CHO). ^{13}C NMR: 214.0 (C-17), 194.0 (16^1-CHO), 157.8 (C-3), 137.5 (C-5), 130.9 (C-10), 126.5 (C-1), 113.6 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.7 and 51.8 (C-13 and C-14), 39.1 (C-9), 38.8 (C-16), 38.5 (C-15), 37.5 (C-8), 37.4 (C-16^1), 30.6, 25.3, 24.5 and 23.6 (C-7, C-11, C-12 and C-16^2), 29.8 (C-6), 12.2 (C-18). MS (EI, *m/z*): 336 [M^+].

B) A solution of the 17,17-(ethylenedioxy)-16^1-carbaldehyde **13** (300 mg, 0.79 mmol) in tetrahydrofuran (8 ml) at 0 °C was treated with 6 M hydrochloric acid (0.3 ml, 1.8 mmol). After 90 min at 0 °C, the reaction was incomplete (TLC), and the temperature was raised to 25 °C for a further 140 min. Aqueous sodium hydrogencarbonate was added and the reaction mixture was extracted with chloroform. The product was isolated and chromatographed as described in *A*, to give the 17-ketone **18** (230 mg, 87%).

3-Methoxy-16β,15β,14-(ethane[1,1,2]triyl)-14β-estra-1,3,5(10)-trien-17ξ-ols (**19** and **20**)

A) The 17-ketone **15** (398 mg, 1.3 mmol) in tetrahydrofuran (24 ml) under nitrogen was treated with excess lithium aluminium hydride at reflux. After 8 h, the reaction mixture was cooled and the excess reagent was destroyed by the addition of aqueous ammonium chloride. The mixture was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (411 mg) on silica gel (40 g), with ethyl acetate–chloroform (1 : 99) as eluent, gave the 17β-alcohol **19** (159 mg, 40%), m.p. 141–145 °C (aqueous methanol), $[\alpha]_D$ +133 (*c* 0.55). For $C_{21}H_{26}O_2$ (336) calculated: 81.3% C, 8.4% H; found: 81.0% C, 8.5% H. IR: 3 606 (OH). ^{1}H NMR: 0.82 s, 3 H (13β-Me); 1.39 obsc. dd, 1 H, *J* = 9.6 and 2.5 (16^2*R*-H); 2.2l obsc. dd, 1 H, *J* = 9.6 and 4.1 (16^2*S*-H); 2.85 m, 2 H (6α- and 6β-H); 3.75 s, 3 H (3-OMe); 3.94 d, 1 H, *J* = 4.8 (17α-H); 6.61 d, 1 H, *J* = 2.7 (4-H); 6.69 dd, 1 H, *J* = 8.5 and 2.7 (2-H); 7.19 d, 1 H, *J* = 8.5 (1-H), followed by the 17α-alcohol **20** (232 mg, 58%), m.p. 129–132 °C (ethyl acetate–hexane), $[\alpha]_D$ +750 (*c* 0.52). For $C_{21}H_{26}O_2$ (336) calculated: 81.3% C, 8.4% H; found: 81.3% C, 8.3% H. IR: 3 606 (OH). ^{1}H NMR: 0.90 s, 3 H (13β-Me); 1.27 dd, 1 H, *J* = 10.2 and 2.5 (16^2*R*-H); 2.13 dd, 1 H, *J* = 10.2 and 4.1 (16^2*S*-H); 2.43 m, 1 H (9α-H); 2.89 m, 2 H (6α- and 6β-H); 3.78 s, 3 H (3-OMe); 4.18 s, 1 H (17β-H); 6.65 d, 1 H, *J* = 2.7 (4-H); 6.73 dd, 1 H, *J* = 8.5 and 2.7 (2-H); 7.24 d, 1 H, *J* = 8.5 (1-H).

B) A mixture of the 17ξ-hydroxy-16^1-carbaldehydes **16** + **17** (306 mg, 0.9 mmol) in deoxygenated toluene (42 ml) under nitrogen was refluxed with $RhCl(PPh_3)_3$ (700 mg, 0.76 mmol) for 19 h. Ethanol was added to the cooled reaction mixture, which was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue (400 mg) was chromatographed on silica gel (62 g), with ethyl acetate–chloroform (1 : 99) as eluent, to give the 17β-alcohol **19** (97 mg, 36%) and the 17α-alcohol **20** (116 mg, 43%), followed by starting material **7** (20 mg, 7%).

Reductive Cleavage of 16β,15β,14-(Ethane[1,1,2]triyl) Derivatives **7**, **12**, **15** and **18**

A) A solution of the 16[1]-cyano 17-ketone **7** (250 mg, 0.75 mmol) in tetrahydrofuran (15 ml) was added dropwise over 15 min to a stirred mixture of calcium metal (300 mg, 7.5 g atom) in anhydrous liquid ammonia (25 ml) (freshly distilled from sodium) and anhydrous tetrahydrofuran (10 ml) at –78 °C under nitrogen. After a further 3 min, bromobenzene (1 ml, 9.5 mmol) was added to disperse the colour, followed by solid ammonium chloride. Water was then added and the ammonia was allowed to evaporate. The residue was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (348 mg) was chromatographed on silica gel (25 g), with ethyl acetate–toluene (1 : 19) as eluent, to give *3-methoxy-17-oxo-3′,4′-dihydro-15αH-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-triene-3′*β*-carbonitrile* (**21**) (178 mg, 71%), m.p. 158–161 °C (chloroform–methanol), $[\alpha]_D$ +170 (*c* 1.0). For $C_{22}H_{25}NO_2$ (335) calculated: 78.8% C, 7.5% H, 4.2% N; found: 78.7% C, 7.5% H, 4.3% N. IR: 2 237 (CN), 1 735 (CO). ^{1}H NMR: 0.93 s, 3 H (13β-Me); 1.33 qd, 1 H, *J* = 3 × 12.8 and 3.5 (11β-H); 1.45 td, 1 H, *J* = 2 × 12.8 and 3.5 (12α-H); 1.51–1.60 m, 2 H (8β- and 12β-H); 1.71 qd, 1 H, *J* = 3 × 12.1 and 6.8 (7α-H); 1.98 dd, 1 H, *J* = 12.9 and 9.5 (4′α-H); 2.17 m, 1 H, $W_{1/2}$ = 10.1 (7β-H); 2.30 ddt, 1 H, *J* = 12.8, 3 × 3.5 (11α-H); 2.38 ddd, 1 H, *J* = 12.9, 9.5 and 3.9 (4′β-H); 2.46 br t, 1 H, *J* ≈ 2 × 11, $W_{1/2}$ ≈ 3.7 (9α-H); 2.72 dd, 1 H, *J* = 19.3 and 1.5 (16β-H); 2.93–3.02 m, 3 H (6α-, 6β- and 15α-H); 3.13 dd, 1 H, *J* = 19.3 and 10.4 (16α-H); 3.31 ddd, 1 H, *J* = 2 × 9.5 and 7.9 (3′α-H); 3.75 s, 3 H (3-OMe); 6.62 d, 1 H, *J* = 2.8 (4-H); 6.72 dd, 1 H, *J* = 8.6 and 2.8 (2-H); 7.18 d, 1 H, *J* = 8.6 (1-H).

B) A solution of the 16[1]-formyl 17-ketone **18** (100 mg, 0.30 mmol) in tetrahydrofuran (4 ml) was added dropwise over 6 min to a stirred mixture of calcium metal (130 mg, 3.2 g atom) in anhydrous liquid ammonia (55 ml) (freshly distilled from sodium) and tetrahydrofuran (4 ml) at –78 °C under nitrogen. After a further 10 min, bromobenzene (0.5 ml, 4.8 mmol) was added to disperse the colour, and the reaction mixture was worked up as in the foregoing experiment. The crude product (136 mg) was filtered through silica gel (10 g) with ethyl acetate–toluene (1 : 9), and the solid residue (90 mg) was crystallised from ethyl acetate to give *3-methoxy-17-oxo-3′,4′-dihydro-15αH-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-triene-3′*β*-carbaldehyde* (**22**) (19 mg, 19%), m.p. 162–168 °C, $[\alpha]_D$ +185 (*c* 1.0). IR: 1 731 (17-CO), 1 704 (CHO). ^{1}H NMR: 0.97 s, 3 H (13β-Me); 1.33 qd, 1 H, *J* = 3 × 13.3 and 3.0 (11β-H); 1.40 td, 1 H, *J* = 2 × 13.3 and 3.1 (12α-H); 1.51 dt, 1 H, *J* = 13.3 and 2 × 3.0 (12β-H); 1.59 td, 1 H, *J* = 2 × 12.5 and 1.8 (8β-H); 1.70–1.80 m, 1 H (7α-H); 1.97 ddd, 1 H, *J* = 13.0, 8.6 and 3.8 (4′β-H); 2.09 dd, 1 H, *J* = 13.0 and 10.0 (4′α-H); 2.20 dd, 1 H, *J* = 19.4 and 1.7 (16β-H); 2.24–2.31 m, 2 H (7β- and 11α-H); 2.50 br t, 1 H, *J* ≈ 2 × 11.2, $W_{1/2}$ ≈ 7.1 (9α-H); 2.91 dd, 1 H, *J* = 19.4 and 10.3 (16α-H); 2.96 m, 2 H (6α- and 6β-H); 3.15 br t, 1 H, *J* ≈ 2 × 10.3 and $W_{1/2}$ ≈ 7.4 (15α-H); 3.21 ddd, 1 H, *J* = 10.0 and 2 × 8.6 (3′α-H); 3.78 s, 3 H (3-OMe); 6.65 d, 1 H, *J* = 2.8 (4-H); 6.74 dd, 1 H, *J* = 8.6 and 2.8 (2-H); 7.22 d, 1 H, *J* = 8.6 (1-H); 9.67 d, 1 H, *J* = 0.8 (3′α-CHO). MS (EI, *m/z*): 338.187 [M^+]. Flash chromatography of the mother liquor residue (48 mg) on silica gel (10 g), with ethyl acetate–toluene (1 : 9) as eluent, gave *3-methoxy-17-oxo-3′,4′-dihydro-15αH-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-triene-3′*α*-carbaldehyde* (**23**) (7 mg) as an oil. IR: 1 725 (CO). ^{1}H NMR: 1.01 s, 3 H (13β-Me); 2.85 m, 2 H (6α- and 6β-H); 3.24 dd, 1 H, *J* = 17.4 and 9.9 (16α-H); 3.76 s, 3 H (3-OMe); 6.60 d, 1 H, *J* = 2.8 (4-H); 6.72 dd, 1 H, *J* = 8.6 and 2.8 (2-H); 7.19 d, 1 H, *J* = 8.6 (1-H); 9.80 s, 1 H (3′β-CHO). MS (EI, *m/z*): 338 [M^+], followed by mixed fractions (5 mg) and further **22** (23 mg, 23%).

C) A solution of the 17,17-ethylenedioxy-16[1]-carbonitrile **12** (275 mg, 0.73 mmol) in tetrahydrofuran (70 ml) was added to a stirred mixture of lithium metal (63 mg, 9.1 g atom), anhydrous liquid ammonia (30 ml) (freshly distilled from sodium) and anhydrous tetrahydrofuran (22 ml) at –78 °C. After 4 min, solid ammonium chloride was added in small portions, and the reaction mixture was stirred at –78 °C until it became colourless. Water was added, and the mixture was worked up as previously described. The product (277 mg) was chromatographed on silica gel (28 g), with ethyl acetate–hexane (1 : 4) as eluent, to give *17,17-(ethylenedioxy)-3-methoxy-14,16*β*-ethano-14*β*-estra-1,3,5(10)-triene* (**24**) (65 mg, 25%), m.p. 133–137 °C (chloroform–methanol), $[\alpha]_D$ +52 (*c* 1.0). For $C_{23}H_{30}O_3$ (354) calculated: 77.9% C, 8.5% H; found: 77.8% C, 8.5% H. ^{1}H NMR: 0.95 s, 3 H (13β-Me); 2.24 m, 1 H (11α-H); 2.42 m, 1 H (9α-H); 2.82 m, 2 H (6α- and 6β-H); 3.75 s, 3 H (3-OMe); 3.80–3.84 m, 4 H (-OCH_2CH_2O-); 6.60 d, 1 H, *J* = 2.8 (4-H); 6.68 dd, 1 H, *J* = 8.5 and 2.8 (2-H); 7.21 d, 1 H, *J* = 8.5 (1-H). MS (EI, *m/z*): 354 [M^+].

A portion of the ketal **24** (15 mg, 0.04 mmol) in tetrahydrofuran (3 ml) and methanol (4 ml) at 0 °C was treated with 6 M hydrochloric acid (0.2 ml, 1.2 mmol). After 4 h at 0 °C, aqueous sodium hydrogencarbonate was added and the product was isolated by extraction with chloroform and flash-chromatographed on silica gel (3 g), with ethyl acetate–toluene (1 : 49) as eluent, to give the 14β,16β-ethano 17-ketone **25** (13 mg, 99%), m.p. 167–172 °C (chloroform–methanol), $[\alpha]_D$ +174 (*c* 0.5) (ref.[22] gives 168–170 °C, $[\alpha]_D$ +174).

D) A solution of the 17-ketone **15** (50 mg, 0.16 mmol) in tetrahydrofuran (2 ml) was added dropwise over 5 min to a stirred mixture of lithium metal (12 mg, 1.7 g atom) in anhydrous liquid ammonia (10 ml) (freshly distilled from sodium) and tetrahydrofuran (1 ml) at –78 °C under nitrogen. After a further 5 min, solid ammonium chloride was added and the reaction mixture was worked up as described previously. Flash chromatography of the product (47 mg) on silica gel (5 g), with ethyl acetate–toluene (1 : 19) as eluent, gave *3-methoxy-3′,4′-dihydro-15*α*H-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-trien-17-one* (**26**) (42 mg, 84%), m.p. 115–116 °C (ethyl acetate–hexane), $[\alpha]_D$ +213 (*c* 0.4). For $C_{21}H_{26}O_2$ (310) calculated: 81.3% C, 8.4% H; found: 81.3% C, 8.4% H. IR: 1 725 (CO). ^{1}H NMR: 0.93 s, 3 H (13β-Me); 2.13 dd, 1 H, *J* = 19.0 and 1.8 (16β-H); 2.46 td, 1 H, *J* = 2 × 11.3 and 2.4 (9α-H); 2.65 br, 1 H (15α-H); 2.93 m, 2 H (6α- and 6β-H); 3.10 dd, 1 H, *J* = 19.0 and 10.2 (16α-H); 3.78 s, 3 H (3-OMe); 6.65 d, 1 H, *J* = 2.8 (4-H); 6.73 dd, 1 H, *J* = 8.6 and 2.8 (2-H); 7.21 d, 1 H, *J* = 8.6 (1-H). ^{13}C NMR: 221.9 (C-17), 157.5 (C-3), 137.8 (C-5), 131.6 (C-10), 127.3 (C-1), 113.5 (C-4), 112.0 (C-2), 55.2 (3-OMe), 53.5 and 52.4 (C-13 and C-14), 43.1 (C-16), 41.2 (C-9), 38.7 (C-8), 33.0, 26.9, 26.3, 25.7 and 23.9 (C-7, C-11, C-12, C-3′ and C-4′), 30.9 (C-6), 30.3 (C-15), 12.5 (C-18). MS (EI, *m/z*): 310 [M^+].

E) A solution of the 17-ketone **15** (100 mg, 0.32 mmol) in ethyl acetate (5 ml) at 25 °C was hydrogenated in the presence of Pd–C (10%; 100 mg). After 7.5 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. Chromatography of the residue on silica gel, with ethyl acetate–hexane as eluent, gave compound **26** (25 mg, 25%), identical with material obtained in the foregoing experiment, followed by *14,16*β*-ethano-3-methoxy-14*β*-estra-1,3,5(10)-trien-17-one* (**25**) (39 mg, 39%).

Nucleophilic Additions to the 15β,16[1]-Cyclo-14β,16β-ethano 17-Ketone **15**

A) A solution of the 17-ketone **15** (50 mg, 0.16 mmol) and $TsOH \cdot H_2O$ (93 mg, 0.49 mmol) in benzene (5 ml) was refluxed under nitrogen for 6 h, then cooled and neutralised by addition of aqueous sodium hydrogencarbonate. The mixture was extracted with chloro-

form, the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue (84 mg) was chromatographed on silica gel (5 g), with ethyl acetate–hexane (1 : 4) as eluent, to give *3-methoxy-3′α-(tosyloxy)-3′,4′-dihydro-15αH-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-trien-17-one* (**27**) (54 mg, 69%), m.p. 104–109 °C (chloroform–hexane), $[\alpha]_D$ +122 (*c* 0.7). IR: 1 731 (CO), 1 174 (SO). ^{1}H NMR: 0.94 s, 3 H (13β-Me); 1.67 ddd, 1 H, *J* = 3 × 12.0 and 6.6 (7α-H); 2.03 d, 1 H, *J* = 18.1 (16β-H); 2.45 s, 3 H (3′-$OSO_2C_6H_4$**Me**); 2.83–2.92 m, 2 H (6α- and 6β-H); 3.07 dd, 1 H, *J* = 18.1 and 10.9 (16α-H); 3.79 s, 3 H (3-OMe); 4.22 br ddd, 1 H, *J* ≈ 7.5, 2.6 and 1.3 (3′β-H); 6.65 d, 1 H, *J* = 2.6 (4-H); 6.73 dd, 1 H, *J* = 8.6 and 2.6 (2-H); 7.18 d, 1 H, *J* = 8.6 (1-H); 7.35 and 7.76 d, each 2 H, *J* = 8.0, 3′-OSO_2C_6**H**$_4$Me). ^{13}C NMR: 218.7 (C-17), 157.6 (C-3), 145.0 (C-1 of 3′-$OSO_2C_6H_4$Me), 137.9 (C-5), 133.5 (C-4 of 3′-$SO_2C_6H_4$Me), 131.1 (C-10), 129.9 (*m*-C's of 3′-$OSO_2C_6H_4$Me), 127.8 (*o*-C's of 3′-$OSO_2C_6H_4$Me), 127.3 (C-1), 113.4 (C-4), 112.2 (C-2), 79.1 (C-15[1]), 55.2 (3-OMe), 37.8 (C-6), 13.8 (C-18). MS (EI, *m/z*): 480.200 [M^+].

B) A solution of the 17-ketone **15** (140 mg, 0.45 mmol) and hydrogen bromide (48% in acetic acid; 0.14 ml, 1.24 mmol) in anhydrous benzene (2.8 ml) was heated at 70 °C in a sealed tube for 22 h. Aqueous sodium hydrogencarbonate was added to the cooled reaction mixture, and the mixture was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and the residue (180 mg) was chromatographed on silica gel (14 g), with ethyl acetate–toluene (1 : 49) as eluent, to give *3′α-bromo-3-methoxy-3′,4′-dihydro-15αH-cyclobuta[14,15]-14*β*-estra-1,3,5(10)-trien-17-one* (**28**) (116 mg, 66%), m.p. 148–151 °C (chloroform–methanol), $[\alpha]_D$ +164 (*c* 0.7). For $C_{21}H_{25}BrO_2$ (388) calculated: 64.8% C, 6.9% H; found: 64.8% C, 6.9% H. IR: 1 731 (CO), 697 (CBr). ^{1}H NMR: 1.00 s, 3 H (13β-Me); 1.32 dq, 1 H, *J* = 3 × 12.8 and 3.9 (11β-H); 1.51 td, 1 H, *J* = 2 × 12.8 and 3.7 (12α-H); 1.83 ddd, 1 H, *J* = 3 × 12.4 and 5.1 (7α-H); 2.28 ddt, 1 H, *J* = 12.8 and 3 × 3.7 (11α-H); 2.40 br t, 1 H, *J* ≈ 2 × 11.2 and $W_{1/2}$ ≈ 6.8 (9α-H); 3.79 s, 3 H (3-OMe); 3.93 ddd, 1 H, *J* = 9.0, 4.5 and 2.4 (3′β-H); 6.67 d, 1 H, *J* = 2.8 (4-H); 6.74 dd, 1 H, *J* = 8.5 and 2.8 (2-H); 7.20 d, 1 H, *J* = 8.5 (1-H). ^{13}C NMR: 218.8 (C-17), 157.6 (C-3), 137.9 (C-5), 131.2 (C-10), 127.3 (C-1), 113.4 (C-4), 112.1 (C-2), 55.2 (3-OMe), 51.9 and 50.3 (C-13 and C-14), 45.3 (C-3′), 42.3, 41.5 and 39.1 (C-8, C-9 and C-15), 42.1 (C-16), 36.3, 35.2, 27.0 and 25.9 (C-7, C-11, C-12 and C-4′), 30.9 (C-6), 14.2 (C-18), followed by starting material **15** (45 mg, 32%).

3-Methoxy-3′,4′-dihydro-15αH-cyclobuta[14,15]-14β-estra-1,3,5(10)-trien-17-ols (**30** and **31**)

A) A solution of compound **21** (358 mg, 1.1 mmol) in toluene (52 ml) at –78 °C under nitrogen was treated with diisobutylaluminium hydride (20% solution in hexane; 3.2 ml, 3.2 mmol). After 3 h at –78 °C, aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the extract was washed with aqueous ammonium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure to give a mixture of 17ξ-hydroxy-3′-carbaldehydes **29** (350 mg), which was refluxed in deoxygenated toluene (30 ml) under nitrogen in the presence of $RhCl(PPh_3)_3$ (1.31 g, 1.4 mmol). After 7.5 h, ethanol was added to the cooled reaction mixture and most of the catalyst was removed by filtration. The filtrate was evaporated, and the residue (1.3 g) was chromatographed on silica gel (43 g), with ethyl acetate–toluene (1 : 49) as eluent, to give the 17β-alcohol **30** (32 mg, 8%), m.p. 68–69 °C (chloroform–methanol), $[\alpha]_D$ +85 (*c* 1.0). For $C_{21}H_{28}O_2$ (312) calculated: 80.4% C, 9.0% H; found: 80.3% C, 9.0% H. IR: 3 612 (OH). ^{1}H NMR: 0.91 s, 3 H (13β-Me);

2.82 m, 2 H (6α- and 6β-H); 3.71 s, 3 H (3-OMe); 3.81 d, 1 H, *J* = 5.8 (17α-H); 6.57 d, 1 H, *J* = 2.7 (4-H); 6.65 dd, 1 H, *J* = 8.5 and 2.7 (2-H); 7.15 d, 1 H, *J* = 8.5 (1-H). MS (EI, *m/z*): 312 [M^+], followed by the 17α-alcoho1 **31** (203 mg, 51%), m.p. 49–51 °C (dichloromethane–methanol), $[\alpha]_D$ +80 (*c* 0.96). For $C_{21}H_{28}O_2$ (312) calculated: 80.4% C, 9.0% H; found: 80.6% C, 8.9% H. IR: 3 608 (OH). ^{1}H NMR: 0.90 s, 3 H (13β-Me); 2.89 m, 2 H (6α- and 6β-H); 3.77 s, 3 H (3-OMe); 4.38 t, 1 H, *J* = 2 × 8.8 (17β-H); 6.63 d, 1 H, *J* = 2.5 (4-H); 6.72 dd, 1 H, *J* = 8.5 and 2.5 (2-H); 7.24 d, 1 H, *J* = 8.5 (1-H). MS (EI, *m/z*): 312 [M^+].

B) The 3′-tosyloxy 17-ketone **27** (50 mg, 0.1 mmol) and lithium aluminium hydride (50 mg, 1.3 mmol) in benzene (6 ml) was refluxed under nitrogen for 4 h. Aqueous ammonium chloride was added, the organic phase was diluted with ethyl acetate and washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (5 g) to give the 17β-alcohol **30** (4 mg, 12%) followed by the 17α-alcoho1 **31** (18 mg, 55%).

We thank the Foundation for Research Development, AECI Research and Development Department and Schering AG for financial support.

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