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INTRAMOLECULAR CONDENSATION OF STEROIDAL 17α-FORMYL 17β-ACETATES: SYNTHESIS OF 14-FUNCTIONALISED 17-SPIROLACTONES [1]

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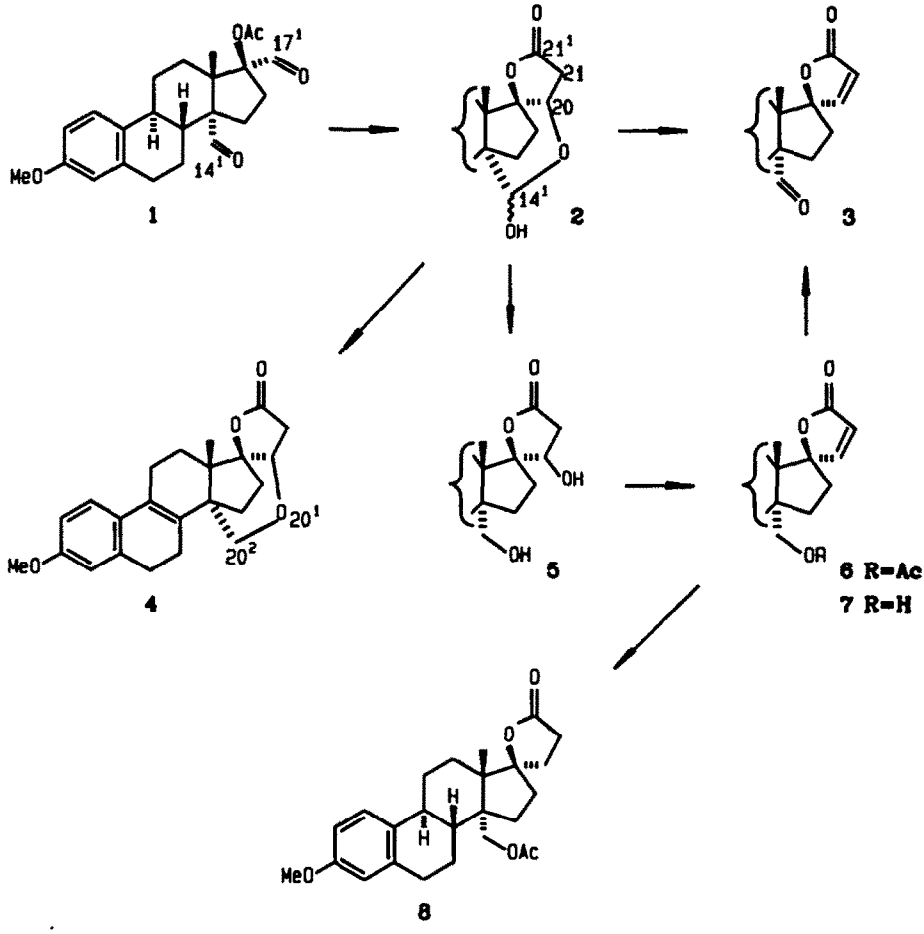
17β-Acetoxy-3-methoxyestra-1,3,5(10)-triene-14,17α-dicarbaldehyde (**1**) undergoes base-mediated intramolecular condensation to give a mixture of the (14^1R)- and (14^1S)-14^1,20-hemiacetals of (20*R*)-14-formyl-20-hydroxy-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**2**). The synthesis of derived 19-nor 17-spirolactones is described, and it is shown that 14-functionality participates in unusual intramolecular rearrangements.

The foregoing publication[2] describes a new approach to the synthesis of 3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone, mediated by intramolecular condensation of a 17β-acetoxy 17α-carbaldehyde precursor. The approach is characterised by exceptionally mild conditions for 17-spirolactone ring formation, which suggests that it should be compatible with substrates bearing sensitive functional groups elsewhere in the molecule.

In an unrelated study,[3] we have developed a cycloaddition method for the synthesis of 14α,17α-etheno 19-norsteroids and hence the derived 14α-formyl 19-norsteroids. One of the intermediates in this reaction sequence, 17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-14,17α-dicarbaldehyde (**1**), has a stereochemically appropriate array of functionality to serve as a precursor of novel 14α-functionalised 19-nor analogues of spironolactone. In view of the continuing interest in synthesis and structure-activity studies of aldosterone antagonists,[4] we undertook to examine the intramolecular condensation of compound (**1**) and to explore the scope and limitations of further modification of the expected condensation product into the target compound (**11**).[5]

Treatment of the acetoxy dialdehyde (**1**) with lithium 2,2,6,6-tetramethylpiperidide in dry tetrahydrofuran at −100°C resulted in complete reaction within 15 min to give, after chromatography, a major crystalline fraction (62%) which displayed typical γ-lactone infrared absorption (ν_{max} 1780 cm^{-1}), but the absence of absorption for the 14α-formyl group. Although this material appeared to be chromatographically homogeneous, a 500 MHz n.m.r. spectrum displayed doubled signals (*ca* 1:1) for protons around ring D. One such pair at δ 4.61 ('0.5H', dd, *J* 11.6 and 7.7 Hz) and 4.9 ('0.5H', dd, *J* 11.5 and 7.9 Hz) was assigned to 20-H, and another at δ 5.0 ('0.5H', d, *J* 3.0 Hz) and 5.6 ('0.5H', d, *J* 5.0 Hz) to 14^1-H, in a product formulated as a 14^1-*R*,*S*-mixture of hemiacetals (**2**). Although diagnostic evidence for 20-configuration was not present, the similarity of the signals at δ 4.61 and 4.9 suggested that

stereoselective closure to a 20*R*-intermediate had occurred, and that the mixture (**2**) comprised 14^1-diastereomers. This was supported by analogy,[2] and was verified in subsequent transformations (see later). Formation of the hemiacetal mixture (**2**) from the initial condensation product is a reasonable consequence of the close mutual proximity of the 20-OH and 14α-CHO groups.



No evidence was found for co-occurrence of the open form of the hemiacetal mixture (**2**), nor was it possible to induce efficient opening or trapping of the intermediate under mild reaction conditions. Thus, the β-elimination sequence, which was successfully applied in the model study *via* mesylation and slow chromatography on silica gel,[2] gave a poor yield (*ca* 33%) of the corresponding 14α-formyl α,β-unsaturated γ-lactone (**3**). The structure of the product was evident from n.m.r. signals at δ 5.93 and 7.18 (each 1H, d, *J* 5.9Hz) for the vinyl protons, and at δ 10.41 (1H, d, *J* 1.2 Hz) for the formyl proton.

An attempt to conduct a referred β-elimination, by treating the hemiacetal mixture (**2**) with toluene-*p*-sulphonic acid in refluxing benzene, had an unexpected outcome. The complex reaction mixture showed evidence of much decomposition, and the only pure product isolated by chromatography was the 20,14-epoxymethano compound (**4**) (36%). Structural elucidation of this product with the aid of spectroscopic data proved elusive. Although microanalysis and mass spectrometry confirmed the loss of the elements of water, infrared and n.m.r. data proved that the β-substituted γ-lactone was retained in the product. This, together with n.m.r. evidence for a CH_2 group adjacent to oxygen, and u.v. absorption for a styryl chromophore suggested that an unfamiliar mode of dehydration had occurred.

Accordingly, the structure of compound (**4**) was determined by *X*-ray crystallography, and is illustrated in Figure 1. The ring conformations are defined by the following puckering parameters:[6] Q 0.46Å, θ 66.8°, and ϕ 277.2° for ring B; Q 0.497Å, θ 51.8°, and ϕ 230.7° for ring C; and Q 0.541Å and ϕ 356.3° for ring D. These data reflect the flattening effect of the Δ^8-bond upon the conformations of rings B and C, and the constraints imposed upon ring D and the spirolactone ring by the 14α,20-bridge.

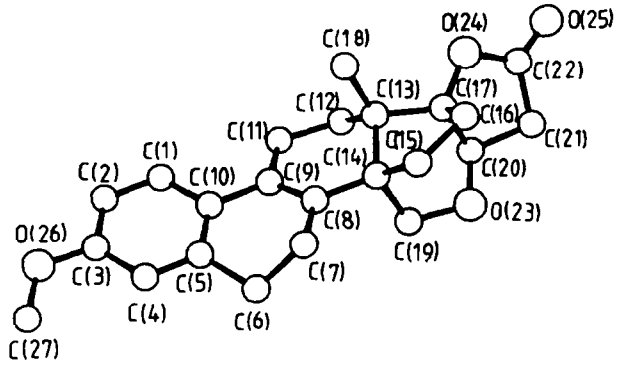
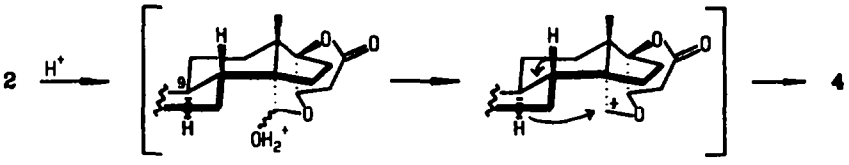


Figure 1: Molecular Structure of Compound (**4**) with Crystallographic Numbering

The structure determination had the additional effect of confirming 20*R*-configuration in the rearrangement product (**4**) and hence, also in the hemiacetal mixture (**2**). Furthermore, it was now possible to correlate the n.m.r. data for (**4**) with distinctive structural features. The signals for spirolactone ring protons, 20-H and 21-H_2, showed the expected close correspondence with those of (**2**), and the coupling constraints for ring D protons fitted the ^{13}E conformation in which 15- and 16-H_2 are approximately isoclinal. This relationship differs from those observed for ring D in 17-spirolactones lacking the 14α,20-bridge. In addition, the 15β-H signal was further split by a four-bond coupling with 20^2-H_{exo} (^4J 2Hz), denoting the imposition of a planar W-conformation on the interacting protons.[3]

Formation of the product (**4**) can be rationalised in terms of protonation of the hemiacetal hydroxy group in (**2**), and generation of a 14[1]-carbocation, leading to intramolecular 1,4-hydride transfer from C(9) to C(14[1]) (Scheme 1). We have been unable to find a direct analogy for this reaction; indeed, 1,4-hydride shifts represent a difficult and relatively rare class of intramolecular rearrangements.[7] In this instance, the rearrangement is facilitated by the close mutual proximity of 9α-H and C(14[1]) in a conformationally rigid structure, and by the resultant stabilisation of the product (**4**) through conjugation with the aromatic ring.



Scheme 1: Rearrangement of (**2**) through intramolecular 1,4-hydride shift

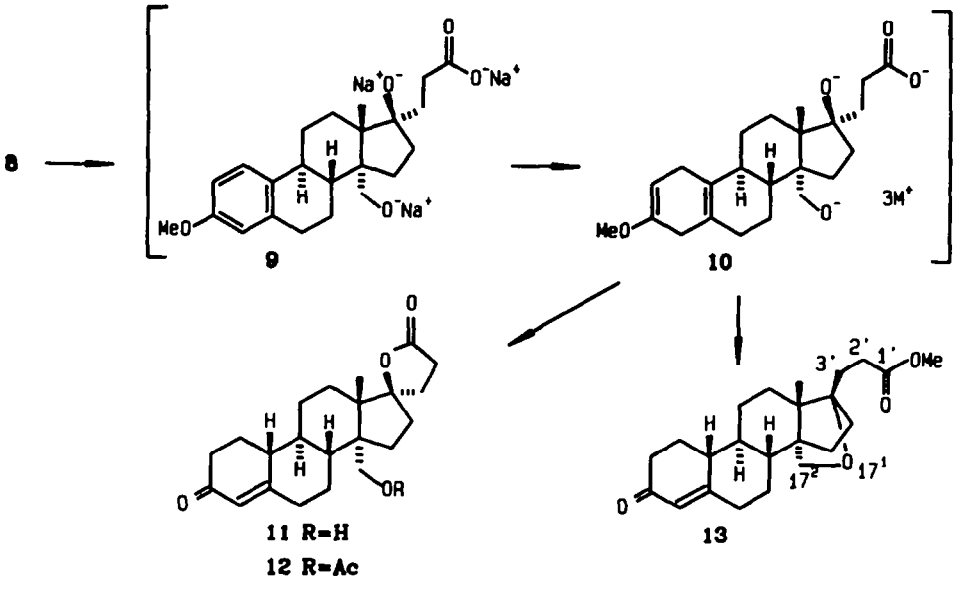
Cleavage of the hemiacetal mixture (**2**) was achieved reductively by treatment with sodium borohydride in ethanol at 0°C to give a 76% yield of the (20*R*)-14[1],20-diol (**5**), the stereochemical integrity of which was confirmed by the deshielding effect of the 20-hydroxy group upon 16α-H.[2] The n.m.r. spectrum of (**5**) displayed an ABX pattern for the spirolactone protons ($J_{20,21R^*}$ 6.5, $J_{20,21S^*}$ 0, $J_{21R^*,21S^*}$ 18.2 Hz) which reflected a conformational change in the ring, possibly as a consequence of intramolecular hydrogen bonding.

β-Elimination of compound (**5**) *via* the 20-mesylate was not considered, for fear that the accompanying 14[1]-mesylate might initiate a concomitant rearrangement. However, the desired result was simply achieved through sequential acetylation–basic alumina treatment, which gave a nearly quantitative yield of the 14α-acetoxymethyl Δ^{20}-lactone (**6**). Deacetylation of compound (**6**), and oxidation of the derived product (**7**) with pyridinium chlorochromate, afforded a much improved albeit indirect route to the 14α-formyl Δ^{20}-17-spirolactone (**3**).

The 14α-acetoxymethyl compound (**6**) underwent efficient hydrogenation in the presence of palladium on calcium carbonate to give 14-acetoxymethyl-3-methoxy-19-nor-17α-pregna-1,3,5(10)-triene-21,17-carbolactone (**8**). The reaction sequence from (**1**) to (**8**) proceeded in 44% overall yield.

The further transformation of the product (**8**) into the Birch reduction product was preceded by treatment with methanolic sodium hydroxide, which resulted in hydrolysis of the 14[1]-acetoxy group and cleavage of the spirolactone ring, to give the trisodium salt (**9**). The presumed intermediate (**10**) of Birch reduction was not isolated, but was subjected to sequential treatment with oxalic acid (to hydrolyse the enol ether and reconstitute the spirolactone ring) and sodium methoxide (to effect conjugation in

ring A). These steps furnished 14-hydroxymethyl-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (**11**) in an overall yield of 60% from (**8**). The product (**11**) exhibited the expected spectroscopic and chiroptical characteristics for ring A functionality and the 17-spirolactone ring, together with the distinctive AB spin system for 14^1-H_2 at δ 3.66 and 3.69 (each 1 H, d, *J* 12.7 Hz).

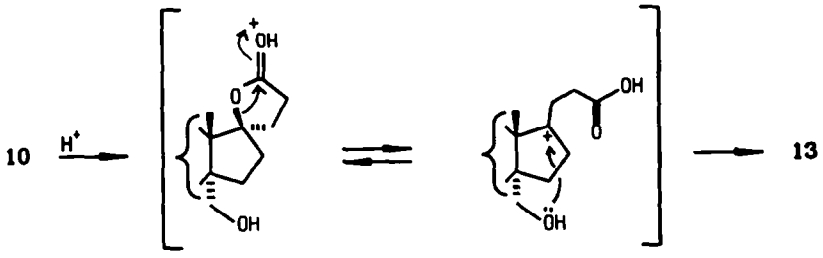


A modification of the foregoing procedure, in which the intermediate (**10**) was treated with acetic acid, then acetylated [acetic anhydride–triethylamine–4-(dimethylamino)pyridine] and treated with hydrochloric acid in aqueous tetrahydrofuran, gave an improved overall conversion of (**8**) into the corresponding 14-acetoxymethyl 21,17-carbolactone (**12**) (80%).

An attempt to expedite the overall conversion of compound (**8**) into the final product (**11**) by treating the Birch reduction intermediate (**10**) with methanolic hydrochloric acid, instead of using the foregoing stepwise processes, resulted in a poor recovery of the spirolactone (**11**) (25%) accompanied by methyl 3-(17α,14-epoxymethano-3-oxoestr-4-en-17β-yl)propanoate (**13**) (28%). Evidence for the latter structure included infrared absorption for an ester (1725 cm^{-1}) rather than a γ-lactone carbonyl group, and 500 MHz n.m.r. signals at δ 1.8 – 2.48 for a clearly resolved open-chain AA′BB′ spin system, a methyl ester singlet at δ 3.65, and one-proton multiplets at δ 3.31 and 3.88 for 17^2-H_2, in which the magnitude of geminal (*J* 7.3Hz) and long range couplings ($^4J_{17^2exo,15\beta}$ 4.1 Hz) are characteristic of the 17α,14α-epoxymethano bridge.[3]

Under the strongly acidic conditions used here, it may be assumed that 17-functionality in the intermediate (**10**) was rapidly converted into the protonated spirolactone ring, and it is suggested that the 17α,14α-epoxymethano compound (**13**) is formed through intramolecular capture of an incipient 17-carbocation by the proximate 14[1]-hydroxy group (Scheme 2). The process is reminiscent of other acid catalysed rearrangements of 17-spirolactones,[8] in which ring D rearrangements associated with 17-carbocationic character were observed.

The method described herein provides access to a new class of 19-nor 17-spirolactones, and further demonstrates the synthetic utility of ester enolate mediated intramolecular condensation of geminal acetoxy aldehydes.



Scheme 2: Rearrangement of (**10**) through intramolecular 14[1]–OH closure

EXPERIMENTAL

For general directions, see reference 2.

(14[1]R/S)-14[1],20-*Hemiacetals of* (20R)-14-*Formyl*-20-*hydroxy*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-21,17-*carbolactone* (**2**).

2,2,6,6-Tetramethylpiperidine (1.32 ml; 10 mmol) was added to n-butyl-lithium (1.65M; 2,36 ml; 5 mmol) in dry tetrahydrofuran (10 ml) at 0°C. After 10 min at 0°C, the solution was cooled to -100°C and the dialdehyde (**1**) (298 mg; 0.78 mmol) in dry tetrahydrofuran (5 ml) was added very slowly with stirring. The reaction was complete after 15 min (t.l.c.) and was quenched by pouring into ice–water. Extraction with benzene afforded crude material (306 mg), which was chromatographed on silica gel (10 g), with ethyl acetate–hexane (1:4) as eluent, to give uncharacterised material followed by a 1:1 mixture of (14[1]R)- and (14[1]S)-14[1],20-*hemiacetals* (**2**) (185 mg; 62%), m.p. 184–189°C (from acetone–hexane); ν_{max} 1780 cm^{-1}; *m/z* 384 (M^+) and 366 ($M^+ - H_2O$); δ (500 MHz) 1.12 and 1.20, (each '1.5H', s, 13β-Me), 2.63 ('0.5H', dd, *J* 15.6 and 7.7 Hz, 21-H), 2.64 ('0.5H', dd, *J* 15.6 and 7.9 Hz, 21-H), 2.78 ('0.5H', dd, *J* 15.6 and 11.6 Hz, 21-H), 2.81 ('0.5H', dd, *J* 15.6 and 11.5 Hz, 21-H), 3.43 ('0.5H', dt, *J* 2 x 11.7, and 5.4 Hz, 9α-H), 3.75 (3H, s, 3-OMe), 4.61 ('0.5H', dd, *J* 11.6 and 7.7 Hz, 20-H), 4.90 ('0.5H', dd, *J* 11.5 and 7.9 Hz,

20-H), 5.00 ('0.5H', d, *J* 3.0 Hz, 14[1]-H), 5.69 ('0.5H', d, *J* 5.0 Hz, 14[1]-H), 6.58 and 6.59 (each '0.5H', d, *J* 2.7 Hz, 4-H), 6.70 and 6.71 (each '0.5H', dd, *J* 8.6 and 2.7 Hz, 2-H), and 7.18 and 7.19 (each '0.5H', d, *J* 8.6 Hz, 1-H).

14-*Formyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10),20-*tetraene*-21,17-*carbolactone* (**3**).

a) Methanesulphonyl chloride (20 μl) was added to the hemiacetal mixture (**2**) (19 mg) at 0°C under nitrogen and the mixture was stirred at 25°C for 24 h, then poured into ice–water. Extraction with ethyl acetate and chromatography of the resulting product (12 mg) on silica gel (5 g), with ethyl acetate–benzene (1:9) as eluent, afforded the 14-*formyl* Δ^{20}-21,17-*carbolactone* (**3**) (6 mg: 33%), m.p. 183–186°C (from ethyl acetate–hexane); $[\alpha]_D$ +59° (*c* 0.9); ν_{max} 1750 and 1715sh cm^{-1}; δ (500 MHz) 1.31 (3H, s, 13β-Me), 1.34 (1H, dddd, *J* 12.8, 12.4, 10.5, and 7.5 Hz, 7α-H), 1.53 (1H, ddd, *J* 13.3, 4.9, and 2.3 Hz, 12β-H), 1.60 (1H, dddd, *J* 12.2, 10.9, 8.5, and 1.2 Hz, 15β-H), 1.80 (1H, dddd, *J*, 13.7, 13.2, 12.6, and 4.9 Hz, 11β-H), 1.82 (1H, ddt, *J* 12.8, 5.8, and 2 x 2.5 Hz, 7β-H), 2.04 (1H, ddd, *J* 15.0, 9.5, and 8.5 Hz, 16α-H), 2.07 (1H, ddd, *J* 13.3, 13.2, and 4.7 Hz, 12α-H), 2.17 (1H, ddd, *J* 12.6, 12.4, and 2.5 Hz, 8β-H), 2.27 (1H, ddd, *J* 15.0, 10.9, and 2.2 Hz, 16β-H), 2.44 (1H, ddd, *J* 12.2, 9.5, and 2.2 Hz, 15α-H), 2.54 (1H, dddd, *J* 13.7, 5.4, 4.7, and 2.3 Hz, 11α-H), 2.80–2.90 (2H, m, 6-H_2), 2.99 (1H, dt, *J* 2 x 12.6, and 5.4 Hz, 9α-H), 3.75 (3H, s, 3-OMe), 5.93 (1H, d, *J* 5.9 Hz, 20-H), 6.59 (1H, d, *J* 2.8 Hz, 4–H), 6.71 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.6 Hz, 1-H), 7.18 (1H, d, *J* 5.9 Hz, 21-H), and 10.41 (1H, d, *J* 1.2 Hz, 14[1]-H) (Found: C, 75.6; H, 7.3%; M^+, 366. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%; *M*, 366).

b) Pyridinium chlorochromate (74 mg; 0.35 mmol) was added to a stirred solution of the 14-hydroxymethyl 21,17-carbolactone (**7**) (35 mg; 0.1 mmol) in dry dichloromethane (3.5 ml). After 0.5 h, propan-2-ol (3 ml) was added, the mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica gel (5 g), with toluene–ethyl acetate (9:1) as eluent afforded the 14-formyl compound (**3**) (30 mg; 86%), m.p. and mixed m.p. 183–186°C (from ethyl acetate–hexane).

(20R)-20,14-*Epoxymethano*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10),8-*tetraene*-21,17-*carbolactone* (**4**).

A solution of the hemiacetal mixture (**2**) (50 mg) and toluene-*p*-sulphonic acid (5 mg) in benzene (8 ml) was refluxed for 24 h. Aqueous sodium hydrogen carbonate was added, and the product (49 mg) was isolated by extraction with chloroform. Chromatography on silica gel (5 g) with ethyl acetate–toluene (1:9) as eluent, afforded (20R)-20,14-*epoxymethano*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10),8-*tetraene*-21,17-*carbolactone* (**4**) (17 mg; 36%), m.p. 186–189°C (from acetone–methanol); $[\alpha]_D$ +22° (*c* 0.7); λ_{max} 275 nm (log ε 4.39); ν_{max} 1780 cm^{-1}; δ (500 MHz) 1.15 (3H, s, 13β–Me), 1.67 (1H, ddd, *J* 12.3, 6.8, and 1.0 Hz, 11β–H), 1.79 (1H, ddd, *J* 12.5, 9.4, and 4.0 Hz, 15α–H), 1.89 (1H, dddd, *J* 12.5, 12.1, 4.7, and 2.0 Hz, 15β–H), 2.01 (1H, ddd, *J* 12.9, 12.1, and 4.0 Hz, 16β–H), 2.31 (1H, ddd, *J* 12.9, 9.4, and 4.7 Hz, 16α–H), 2.64 (1H, dd, *J* 16.4 and 7.7 Hz, 21–H), 2.77(1H, dd, *J* 16.4 and 11.6 Hz, 21–H), 3.5 (1H, d, *J* 11.6 Hz, 20^2–H_{endo}), 3.79 (3H, s, 3–OMe), 3.83 (1H, dd, *J* 11.6 and 2.0 Hz, 20^2–H_{exo}), 4.58 (1H, dd, *J* 11.6 and 7.7 Hz, 20–H), 6.69 (1H, d, *J* 2.7 Hz, 4–H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2–H), and 7.18 (1H, d, *J* 8.5 Hz, 1–H) (Found: C, 75.7; H, 7.4%; M^+, 366. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%; *M*, 366), followed by uncharacterised material.

(20R)-20-*Hydroxy*-14-*hydroxymethyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-21,17-*carbolactone* (**5**).

Sodium borohydride (14 mg; 0.36 mmol) was added to a solution of the hemiacetal mixture (**2**) (72 mg; 0.18 mmol) in dry ethanol (20 ml) at 0°C. After 6 h, the reaction mixture was poured into water, and extracted with ethyl acetate. Chromatography of the product (97 mg) on silica gel (10 g), with methanol–chloroform (1:9) as eluent, afforded the 14[1],20-*diol* (**5**) (55 mg; 76%), m.p. 187–190°C (from chloroform–methanol); $[\alpha]_D$ +63° (*c* 0.8); ν_{max} 3580–3140 and 1760 cm^{-1}; δ (500MHz) 1.16 (3H, s, 13β–Me), 1.42 (1H, ddd, *J* 12.6, 5.0, and 2.3 Hz, 15α–H), 1.55 (1H, dddd, *J* 12.6, 12.3, 11.7, and 5.9 Hz, 7α–H), 1.75 (1H, ddt, *J* 12.6, 5.1, and 2 x 2.6 Hz, 7β–H), 2.01 (1H, ddd, *J* 15.0, 11.2, and 2.3 Hz, 16β–H), 2.05 (1H, ddd, *J* 12.3, 12.1, and 2.6 Hz, 8β–H), 2.14 (1H, dt, *J* 2 x 12.6, and 4.9 Hz, 12α–H), 2.51 (1H , d, *J* 18.2 Hz, 21–H), 2.58 (1H, dt, *J* 2 x 12.1, and 4.3 Hz, 9α–H), 2.64 (1, ddd, *J* 15.0, 8.0, and 5.0 Hz, 16α–H), 2.81 (1H, dd, *J* 18.2 and 6.5 Hz, 21–H), 2.77–2.90 (2H, m, 6–H_2), 3.75 (3H, s, 3–OMe), 3.82 and 4.09 (each 1H, d, *J* 12.2 Hz, 14[1]–H_2), 4.65 (1H, d, *J* 6.5 Hz, 20–H), 6.59 (1H, d, *J* 2.7 Hz, 4–H), 6.69 (1H, dd, *J* 8.6 and 2.7 Hz 2–H), and 7.13 (1H, d, *J* 8.6 Hz, 1–H) (Found: C, 71.7; H, 7.9%; M^+, 386. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%; *M*, 386).

14-*Acetoxymethyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10),20-*tetraene*-21,17-*carbolactone* (**6**).

The 14[1], 20-diol (**5**) (167 mg; 0.4 mmol) was dissolved in a solution of triethylamine (5 ml), 4-(dimethylamino)pyridine (5 mg), and acetic anhydride (1 ml). After 10 min, methanol was added at 0°C, and the mixture was stirred for 30 min, then concentrated under reduced pressure. Extraction of the residue with chloroform gave material (226 mg), which was adsorbed on basic alumina (5 g). After 2 h, elution with ethyl acetate–toluene (1:9) afforded the 14-*acetoxymethyl* Δ[20]-21,17-*carbolactone* (**6**) (170 mg; 96%), m.p. 215–217°C (from chloroform–methanol); $[\alpha]_D$ +154° (*c* 0.9); ν_{max} 1740 cm^{-1}; δ (500MHz) 1.26 (3H, s, 13β–Me), 1.61 (1H, ddt, *J* 2 x 13.2, 11.6, and 4.7 Hz, 7α–H), 1.77 (1H, ddd, *J* 12.8, 10.1, and 9.3 Hz, 15β–H), 1.81 (1H, dddd, *J* 13.2, 4.7, 2.8, and 2.4 Hz, 7β–H), 1.83 (1H, ddd, *J* 12.8, 8.7, and 2.2 Hz, 15α–H), 2.08 (3H, s, 14[1]–OAc), 2.09 (1H, dt, *J* 2 x 11.8, and 2.4 Hz, 8β–H), 2.24 (1H, ddd, *J* 15.2, 9.3, and 8.7 Hz, 16α–H), 2.31 (1H, ddd, *J* 15.2, 10.1, and 2.2 Hz, 16β–H), 2.75 (1H, ddd, *J* 11.8, 11.2, and 6.4 Hz, 9α–H), 2.81–2.90 (2H, m, 6–H_2), 3.75 (3H, s, 3–OMe), 4.33 and 4.47 (each 1H, d, *J* 12.5 Hz, 14[1]–H_2), 5.98 (1H, d, *J* 5.8 Hz, 20–H), 6.59 (1H, d, *J* 2.8 Hz, 4–H), 6.69 (1H, dd, *J* 8.6 and 2.8 Hz, 2–H), 7.13 (1H, d, *J* 8.6 Hz, 1–H), and 7.59 (1H, d, *J* 5.8 Hz, 21–H) (Found: C, 73.2; H, 7.3%; M^+, 410. $C_{25}H_{30}O_5$ requires C, 73.2; H, 7.3%; *M*, 410).

14-*Hydroxymethyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10),20-*tetraene*-21,17-*carbolactone* (**7**).

Ethanolic sodium ethoxide (0.1 M; 0.5 ml) was added to a solution of the 14-acetoxymethyl compound (**6**) (70 mg) in ethanol (10 ml). The mixture was stirred at 25°C for 4 h, dry ice was added, and the ethanol was removed under reduced pressure. The residue was extracted with chloroform to give material (68 mg) which was adsorbed on silica gel (10 g). Elution with ethyl acetate–toluene (1:4) afforded the 14-*hydroxymethyl* Δ[20]-21,17-*carbolactone* (**7**) (48 mg; 76%), m.p. 179–181°C (from chloroform–methanol); $[\alpha]_D$ +155° (*c* 1.0); ν_{max} 3640, 3260–3610, and 1745 cm^{-1}; δ (500MHz) 1.26 (3H, s, 13β–Me), 1.28 (1H, ddd, *J* 12.8, 5.3, and 2.4 Hz, 15α–H), 1.57 (1H, ddt, *J* 2 x 13.2, 12.1, and 5.1 Hz, 11β–H), 1.65 (1H, dddd, *J* 12.3, 11.9, 11.7, and 5.9 Hz, 7α–H), 1.71 (1H, ddd, *J* 12.8, 10.5, and 8.4 Hz, 15β–H), 1.79 (1H, dddd, *J* 12.3, 5.5, 2.7, and 2.4 Hz, 7β–H), 1.85 (1H, dt, *J* 2 x 13.2, and 5.1 Hz, 12α–H), 2.07 (1H, ddd, *J* 12.1, 11.9, and 2.4 Hz, 8β–H), 2.25 (1H, ddd, *J* 14.8, 8.4, and 5.3 Hz, 16α–H), 2.30 (1H, ddd, *J* 14.8, 10.5, and 2.4 Hz, 16β–H), 2.70 (1H, dt, *J* 2 x 12.1, and 5.7 Hz, 9α–H), 2.83 (1H, ddd, *J* 17.2,

5.9, and 2.7 Hz, 6α–H), 2.88 (1H, ddd, *J* 17.2, 11.7, and 5.5 Hz, 6β–H), 3.75 (3H, s, 3–OMe), 3.91 and 3.98 (each 1H, d, *J* 12.4 Hz, 14^1–H_2), 5.93 (1H, d, *J* 5.8 Hz, 20–H), 6.60 (1H, d, *J* 2.8 Hz, 4–H), 6.69 (1H, dd, *J* 8.6 and 2.8 Hz, 2–H), 7.14 (1H, d, *J* 8.6 Hz, 1–H), and 7.88 (1H, d, *J* 5.8 Hz, 21–H) (Found: C, 74.7; H, 7.8%; M^+, 368. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.6%; *M* 368).

14-*Acetoxymethyl*-3-*methoxy*-19-*nor*-17α-*pregna*-1,3,5(10)-*triene*-21,17-*carbolactone* (**8**).

The Δ^{20}-21,17-carbolactone (**6**) (273 mg; 0.67 mmol) in ethyl acetate (30 ml) was hydrogenated over palladium on calcium carbonate (5%; 50 mg) at room temperature and atmospheric pressure. After 4 h, the catalyst was removed by filtration and the filtrate was concentrated. Chromatography of the residue (281 mg) on silica gel (20 g), with ethyl acetate–toluene (1:4) as eluent, afforded the *dihydro compound* (**8**) (268 mg; 98%), m.p. 170–172°C (from ethyl acetate); $[\alpha]_D$ +55.5° (*c* 1.0); ν_{max} 1760 and 1735 cm^{-1}; δ (500MHz) 1.14 (3H, s, 13β–Me), 1.79 (1H, ddd, *J* 13.0, 9.0, and 1.8 Hz, 15α–H), 1.92 (1H, dt, *J* 2 x 12.8, and 4.8 Hz, 12α–H), 2.04 (1H, dt, *J* 2 x 12.4, and 2.0 Hz, 8β–H), 2.05 (3H, s, 14^1–OAc), 2.10 (1H, dt, *J* 15.0, and 2 x 9.0 Hz, 16α–H), 2.19 (1H, m, 20–H), 2.35 (1H, ddd, *J* 15.0, 10.8, and 1.8 Hz, 16β–H), 2.53 (3H, m, 20–H and 21–H_2), 2.77–2.85 (2H, m, 6–H_2), 3.75 (3H, s, 3–OMe), 4.26 (2H, s, 14^1–H_2), 6.59 (1H, d, *J* 2.4 Hz, 4–H), 6.69 (1H, dd, *J* 8.6 and 2.4 Hz, 2–H), and 7.16 (1H, d, *J* 8.6 Hz, 1–H) (Found: C, 73.0; H, 7.8%; M^+, 412. $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8%; *M*, 412).

Trisodium Salt (**9**) *Derived from the* 14-*Acetoxymethyl* 21,17-*Carbolactone* (**8**).

The 14-acetoxymethyl 21,17-carbolactone (**8**) (110 mg; 0.27 mmol) was dissolved in methanol (8 ml) and a solution of sodium hydroxide (200 mg) in water (0.5 ml) was added. The reaction mixture was refluxed at 80°C for 3 h, then cooled and concentrated under reduced pressure, to a third of the volume. Water was added and the precipitate was collected and dried at 70°C under high vacuum for 3 h, to afford the trisodium salt (**9**) (109 mg; 94%). The salt was not characterised, but was used directly in the ensuing reactions.

Birch Reduction of the Trisodium Salt (**9**)

a) Liquid ammonia (200 ml; dried over sodium) was added to a solution of the trisodium salt (**9**) (300 mg; 0.69 mmol) in dry tetrahydrofuran (20 ml) and t-butyl alcohol (20 ml). Lithium metal (420 mg; 60 mmol) was then added in portions, and the solution was stirred for 3 h at –35 to –40°C, then cooled to –78°C. Solid ammonium chloride was added to disperse the blue colour of the mixture, and the ammonia was evaporated under a stream of nitrogen. The residue was dissolved in tetrahydrofuran (100 ml), and a solution of oxalic acid (1.2 g) in water (30 ml) was added under nitrogen. The mixture was stirred at 25°C for 3 h, then at 50°C for 1 h to complete the hydrolysis of the intermediate (t.l.c.). Aqueous sodium hydrogen carbonate was added, and extraction of the mixture with chloroform gave the crude product (400 mg) (assumed to comprise largely the $\Delta^{5(10)}$-3-one), which was dissolved in ethanol. Ethanolic sodium ethoxide (0.1M; 0.3 ml) was added and the mixture was stirred for 6 h, then diluted with water, and extracted with chloroform to give material (355 mg) which was adsorbed on silica gel (25 g). Elution with methanol–chloroform (1:49) afforded 14-*hydroxymethyl*-3-*oxo*-19-*nor*-17α-*pregn*-4-*ene*-21,17-*carbolactone* (**11**) (150 mg; 60%), m.p. 204–206°C (from chloroform–ethyl acetate); $[\alpha]_D$ +55.5° (*c* 0.9); λ_{max} 238 nm (log ε 4.21); ν_{max} 1760 and 1660 cm^{-1}; Δε –1.62 (316 nm); δ (500MHz), 1.15 (3H, s, 13β–Me), 1.71 (1H, ddt, *J* 12.6, 5.0, and 2 x 2.6 Hz, 7β–H), 2.00 (1H, dt, *J* 2 x 12.2, and 4.7 Hz, 12α–H), 2.03 (1H, dt, *J* 15.0, and 2 x 8.9 Hz, 16α–H), 2.12 (1H, ddd, *J* 12.8, 9.5, and 8.1 Hz, 20–H), 2.34 (1H, ddd, *J*

15.3, 10.7, and 1.9 Hz, 2β–H), 2.39 (1H, dt, *J* 15.3, and 2 x 3.9 Hz, 2α–H), 2,48 (1H, ddd, *J* 17.9, 8.4, and 2.6 Hz, 6α–H), 2.53 (1H, ddd, *J* 17.9, 9.5, and 5.0 Hz, 6β–H), 2.73 (1H, ddd, *J* 12.8, 9.1, and 5.8 Hz, 20–H), 3.66 and 3.69 (each 1H, d, *J* 12.7 Hz, 14^1–H_2), and 5.80 (1H, br s, 4–H) (Found: C, 73.8; H, 8.3%; M^+, 358. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%; *M*, 358).

(b) The trisodium salt (**9**) (102 mg; 0.24 mmol) in dry tetrahydrofuran (10 ml) was reduced with lithium–liquid ammonia–t-butyl alcohol as described in the foregoing experiment. The residue, after evaporation of ammonia, was treated with aqueous acetic acid at pH4 for 4 h, neutralised with sodium hydrogen carbonate, and the product was isolated by extraction with chloroform. Acetylation of the product (110 mg) with triethylamine (5 ml), acetic anhydride (0.5 ml), and 4-(dimethylamino)pyridine for 1 h, and subsequent treatment (after chloroform extraction) with hydrochloric acid (0.5 ml) in aqueous tetrahydrofuran (6 ml), neutralisation, and extraction with chloroform, gave material (126 mg), which was adsorbed on silica gel (10 g). Elution with ethyl acetate–toluene (3:2) furnished *14-acetoxymethyl-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone* (**12**) (76 mg; 80%), m.p. 192–194°C (from di-isopropyl ether–ethyl acetate); $[\alpha]_D$ +40° (*c* 0.6); λ_{max} 238 nm (log ε 4.24); ν_{max} 1760, 1730, and 1660 cm^{-1}; Δε –1.72 (316 nm); δ (300MHz) 1.17 (3H, s, 13β–Me), 2.04 (3H, s, 14^1–OAc), 4.04 and 4.23 (each 1H, d, *J* 12.5 Hz, 14^1–H_2), and 5.80 (1H, br s, 4–H) (Found: C, 72.0; H, 8.1%; M^+, 400. $C_{24}H_{32}O_5$ requires C, 72.0; H, 8.0%; *M*, 400).

(c) The trisodium salt (**9**) (76 mg; 0.18 mmol) in dry tetrahydrofuran (10 ml) was reduced with lithium–liquid ammonia–t-butyl alcohol, as described in the foregoing experiments. The residue, after evaporation of ammonia, was concentrated to half the volume under reduced pressure, then treated with conc. hydrochloric acid (3 ml) in water–methanol (1:5; 36 ml) at 0°C for 18 h. Aqueous sodium hydrogen carbonate was added, and the mixture was concentrated to half the volume under reduced pressure, and extracted with ethyl acetate. Work-up of the extract gave material (81 mg) which was adsorbed on silica gel (5 g). Elution with ethyl acetate–toluene (2:3) afforded *methyl* 3-(17α,14-*epoxymethano-3-oxoestr-4-en-17β-yl)propanoate* (**13**) (18 mg; 28%); m.p. 141–143°C (from ethyl acetate); $[\alpha]_D$ +42° (*c* 0.9); λ_{max} 236 nm (log ε 4.23); ν_{max} 1725 and 1660 cm^{-1}; Δε –1.75 (316 nm); δ (500 MHz) 0.88 (3H, s, 13β–Me), 1.01 (1H, ddt, *J* 2 x 13.0, 12.6, and 4.1 Hz, 9α–H), 1.20 (1H, dq, 3 x 12.6, and 4.1 Hz, 11β–H), 1.68 (1H, ddd, *J* 13.0, 8.4, and 4.9 Hz, 16α–H), 1.73 (1H, ddd, *J* 13.0, 11.2, and 3.7 Hz, 16β–H), 1.80 (1H, ddd, *J* 14.2, 10.6, and 6.0 Hz, 3′–H), 1.89 (1H, ddd, *J* 14.2, 10.4, and 5.6 Hz, 3′–H), 2.06 (1H, m, 11α–H), 2.37 (1H, ddd, *J* 16.0, 10.4, and 6.0 Hz, 2′–H), 2.48 (1H, ddd, *J* 16.0, 10.6, and 5.6 Hz, 2′–H), 3.31 (1H, d, *J* 7.3 Hz, 17^2–H_{endo}), 3.65 (3H, s, CO_2Me), 3.88 (1H, dd, *J* 7.3 and 4.1 Hz, 17^2–H_{exo}), and 5.80 (1H, br s, 4–H) (Found: C, 74.35; H, 8.9%; M^+, 372. $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.6%; *M*, 372), and the 14-hydroxymethyl 21,17-carbolactone (**11**) (16 mg; 25%), m.p. and mixed m.p. 204–206°C.

Crystal Data and Structure Determination of Compound (**4**).

Crystal data for compound (**4**) are: $C_{23}H_{26}O_4$; M_R, 366.2 g mol^{-1}; space group, $P2_12_12_1$; *Z*, 4; *a* 7.468(2), *b* 12.897(2), *c* 19.201 (2)Å; *V*, 1849Å^3; D_c 1.32 g cm^{-3}; μ (Mo–K_α), 0.5 cm^{-1}; *F* (000), 784; scan range, $3 \leq \Theta \leq 27°$; reflections measured, 2325; reflections used [$I > \sigma(I)$], 1997; variables refined, 323; $R = \Sigma(F_o - F_c)/\Sigma F_o = 0.069$; $R_w = \Sigma w(F_o - F_c)^2/\Sigma w F_o^2 = 0.025$.

A colourless crystal of dimensions 0.33 x 0.39 x 0.42 mm was used to diffract graphite monochromated Mo-K_α radiation on an Enraf-Nonius CAD4 diffractometer. Accurate cell dimensions were obtained by fitting the setting angles of 25 control reflections. Data were measured at room temperature in the

interval $3 \leq \theta \leq 27°$. An ω:2θ-scan with a variable scan speed was used (minimum 5.49° min^{-1}; maximum, 50 sec per reflection). The ω-angle changed as $(0.60+0.34 \tan \theta)°$. The horizontal aperture was fixed to 1.3 mm, and the vertical slit to 4 mm. A total of 2325 reflections were measured. No loss of intensity was observed. The data were corrected for Lorentz and polarisation effects only.

The structure was solved by direct methods,[9] and completed by subsequent Fourier methods. Atoms were refined anisotropically, except for the H-atoms which were refined with a common isotropical temperature factor, $U = 0.063Å^2$. The full matrix least squares method[10] converged to $R_w = 0.025$ for 1997 reflections and 323 variables. A final electron density of $0.2eÅ^{-3}$ was observed. Fractional coordinates for non-hydrogen atoms of compound (4) are given in Table 1.[11]

Table 1: Fractional coordinates (x 10^4) and equivalent thermal factors (x $10^3Å^2$)

	x/a	y/b	z/c	U_{eq}
C(1)	-8605(6)	1773(3)	-8933(2)	54(1)
C(2)	-9259(6)	778(3)	-7036(2)	58(1)
C(3)	-8228(5)	-68(3)	-8871(2)	49(1)
C(4)	-8493(5)	76(3)	-8619(2)	47(1)
C(5)	-5859(5)	1071(3)	-6517(2)	44(1)
C(6)	-3965(5)	1223(3)	-6240(2)	57(1)
C(7)	-3937(6)	2142(3)	-5747(2)	58(1)
C(8)	-4790(5)	3083(3)	-6059(2)	44(1)
C(9)	-6163(5)	2986(3)	-6516(2)	42(1)
C(10)	-6874(5)	1956(3)	-6668(2)	44(1)
C(11)	-7056(6)	3918(3)	-6850(2)	54(1)
C(12)	-6216(5)	4973(3)	-6686(2)	50(1)
C(13)	-5487(4)	4992(3)	-5955(2)	42(1)
C(14)	-4077(5)	4130(3)	-5861(2)	40(1)
C(15)	-3486(6)	4297(3)	-5105(2)	60(1)
C(16)	-3532(6)	5486(3)	-5015(2)	54(1)
C(17)	-4288(5)	5875(3)	-5712(2)	45(1)
C(18)	-7113(6)	4872(4)	-5463(2)	62(1)
C(19)	-2410(6)	4317(3)	-6331(3)	59(1)
C(20)	-2788(5)	6088(3)	-6233(2)	51(1)
C(21)	-2127(6)	7152(4)	-5998(2)	62(1)
C(22)	-3843(7)	7630(3)	-5738(2)	63(1)
O(23)	-1513(3)	5288(2)	-6194(1)	63(1)
O(24)	-5105(3)	6889(2)	-5635(1)	57(1)
O(25)	-4166(4)	8531(2)	-5633(2)	81(1)
O(26)	-8989(4)	-1026(2)	-6976(1)	59(1)
C(27)	-7911(7)	-1917(4)	-6830(3)	65(1)

$$U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* (a_i \, a_j)$$

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