Stereoselectivity in the epoxidation and *cis*-hydroxylation of 16-methylene-estra-1,3,5(10)-trienes

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Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one in the presence of alkaline hydrogen peroxide gives rise to (16R)- and (16S)-spiro[3-methoxy-17-oxoestra-1,3,5(10)-triene-16,2'-oxirane] in similar proportions. Epoxidation of the corresponding 16-methylene 17β-alcohol and 16-methylene-17β-acetate with m-chloroperbenzoic acid does not display any significant directing effects associated with allylic functionality, whereas Sharpless epoxidation of the 16-methylene 17β-alcohol is highly stereoselective, leading exclusively to the (16R) isomer. cis-Hydroxylation of the 16-methylene 17-ketone with osmium tetroxide/4-methylmorpholine-4-oxide proceeds stereoselectively to give mainly 16α-hydroxy-16β-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one. The isomeric addition products derived from these reactions are correlated by appropriate interconversions, and the assignments are corroborated by comparative reactivity of derived products. (*Steroids* **59:** 628–633, 1994)

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Introduction

A new class of oral estrogens, characterized by 14,17-bridged structures has recently been developed through the application of cycloaddition methodology to estra-1,3,5(10),14,16-pentaen-17-yl acetates.[1,2] In addition, oxidative cleavage of the residual olefinic bond in the cycloadducts provided ready access to 14-functionalized-alkyl estra-1,3,5(10)-trienes.[1] An extension of this cycloaddition-oxidative cleavage reaction sequence, carried out upon 16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetates, led to 14-functionalized-alkyl 19-norpregna-1,3,5(10)-trienes.[3]

We were interested in examining comparative cycloadditions upon 16-functionalized-methyl dienyl acetates, since the derived cycloadducts were expected to undergo oxidative cleavage to 19-norpregna-1,3,5(10)-triene systems additionally functionalized at C-21. Accordingly, we sought synthetic routes to 16-functionalized-methyl estra-1,3,5(10),15-tetraen-17-ones as precursors of the cycloaddition substrates. One such approach would be to perform appropriate addition-elimination reaction sequences upon the exocyclic olefinic bond of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one **1**.

Steroidal 16-methylene 17-ketones have received particular attention as intermediates for stereoselective synthesis of the 16β-methyl products,[4–6] but examples of addition of functional groups across the olefinic bond are rare. Early reports in the patent literature[7,8] refer to epoxidation of **1**, but with little information about isomer distribution and the basis for configurational assignments. Furthermore, a recent investigation of peracid-mediated epoxidation of steroidal 16-arylidene and 16-alkylidene 17-ketones[9] was not expected to provide insights into this problem, owing to the expected differences in reactivity and steric access of electrophilic reagents. We therefore undertook an investigation into epoxidation and *cis*-hydroxylation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one **1**, with the further intention of comparing the influence of 17β-hydroxy and 17β-acetoxy functionality upon the stereoselectivity of the former reaction.

Experimental

Melting points were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. Unless otherwise stated, physical and spectroscopic data were recorded as follows: specific rotations, Perkin-Elmer 141 polarimeter, chloroform solutions at 20°C; infrared spectra (IR), Perkin-Elmer 983, chloroform solutions; proton nuclear magnetic resonance

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spectra (^{1}H NMR), Varian VXR spectrometer at 200 MHz, deuteriochloroform solutions, electron impact mass spectra (EI-MS), VG Micromass 16F at 70 eV. 'Work-up' refers to a standard procedure in which the quenched reaction mixture is extracted (solvent in parentheses), and the extract is washed (water or brine), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography was performed as follows: thin-layer chromatography (TLC), 0.25 mm silica gel plates with F 254 indicator (Merck); column chromatography, Merck Kieselgel 60 (70–230 mesh for gravity columns, and 230–400 mesh for flash chromatography).

3-methoxy-16-methylene-estra-1,3,5(10)-trien-17β-ol **2**

The methylene ketone **1** (900 mg, 3 mmol) in dry tetrahydrofuran (25 mL) at 0°C was treated with lithium aluminum hydride (180 mg, 4.5 mmol). After 1 h at 0°C, saturated aqueous ammonium chloride was added and the mixture was extracted with chloroform (×3). The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17β-ol **2** (0.87 g, 96%), m.p. 132–135°C (chloroform/hexane); $[\alpha]_D = 11$ (c 1.0) (lit.,[10] m.p. 132–135°C; $[\alpha]_D = 12$); IR ν_{max} 3600 cm^{-1}; ^{1}H NMR δ 0.71 (3H, s, 13β-Me), 2.86 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 3.98 (1H, br s after D_2O exchange, $W_{1/2}$ 5 Hz, 17α-H), 5.07 and 5.18 (each 1H, q, $J = 3 \times 2.2$ Hz, 16 = CH_2), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H). Analysis calculated for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.2; H, 8.5.

Acetylation of **2** (acetic anhydride/pyridine, 20°C) gave the corresponding acetate **3**, m.p. 123–126°C (aqueous methanol); $[\alpha]_D = 26$ (c 1.0) (lit.,[10] m.p. 124–127°C; $[\alpha]_D = 27$); IR ν_{max} 1730 cm^{-1}; ^{1}H NMR δ 0.78 (3H, s, 13β-Me), 2.15 (3H, s, 17β-OAc), 2.83 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.94 and 5.05 (each 1H, q, $J = 3 \times 2.3$ Hz, 16 = CH_2), 5.26 (1H, q, $J = 3 \times 2.3$ Hz, 17α-H), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H). Analysis calculated for $C_{22}H_{28}O_3$: C, 77.6; H, 8.3. Found: C, 77.3; H, 8.3.

Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one **1**

(a) Aqueous 4 M sodium hydroxide (0.2 mL) was added slowly to a stirred solution of the methylene ketone **1** (155 mg, 0.52 mmol) in tetrahydrofuran (5 mL) and *t*-butyl alcohol (5 mL) at 0°C, then 30% hydrogen peroxide (3 mL) was added dropwise over 10 min. After 1 h at 0°C, further 30% hydrogen peroxide (2 mL) was added, and the solution was stirred at 20°C for 2 h. Saturated aqueous sodium sulfite was added at 0°C, followed by saturated aqueous ammonium chloride. The mixture was extracted with chloroform (×4), and the combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography of the residue on silica gel (8 g; ethyl acetate/toluene 1:49) gave a mixture (~44:56) of **4** and **5** (140 mg, 86%). Column chromatography of a portion of this mixture on silica gel (ethyl acetate/toluene, 1:49) gave (16*R*)-spiro[3-methoxy-17-oxoestra-1,3,5(10)-triene-16,2′-oxirane] **4**, m.p. 141–144°C (dichloromethane/methanol) (lit.,[8] m.p. 142–143°C); $[\alpha]_D$ + 140 (c 1.1); IR ν_{max} 1747 cm^{-1}; ^{1}H NMR δ 1.07 (3H, s, 13β-Me), 2.17 (1H, dd, $J = 12.7$ and 5.9 Hz, 15α-H), 2.90 (2H, m, 6-H_2), 2.95 (1H, d, $J = 6.8$ Hz, 3′-H), 3.20 (1H, dd, $J = 6.8$ and 0.7 Hz, 3′-H), 3.79 (3H, s, 3-OMe), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H); EI-MS m/z 312 (M^+). Analysis calculated for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 76.9; H, 7.8; followed by (16*S*)-spiro[3-methoxy-17-oxoestra-1,3,5(10)-triene-16,2′-oxirane] **5**, m.p. 164–166°C (methanol) (lit.,[7] m.p. 169–173°C); $[\alpha]_D$ + 150 (c 1.0); IR ν_{max} 1751 cm^{-1}; ^{1}H NMR δ 1.06 (3H, s, 13β-Me), 2.90 (2H, m, 6-H_2), 2.97 and 3.13 (each 1H, d, $J = 6.3$ Hz, 3′-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H); EI-MS m/z 312 (M^+). Analysis calculated for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 76.6; H, 7.8.

(b) Similar treatment of the methylene ketone **1** (100 mg, 0.34 mmol) in dioxane (20 mL) at 20°C was heterogeneous and required 45 h to proceed to completion (TLC). Work-up and chromatography of the product (82 mg) as above gave **4** (29 mg, 27%) and **5** (37 mg, 35%).

(c) Similar treatment of the methylene ketone **1** (1 g, 3.4 mmol) in tetrahydrofuran (25 mL) and methanol (20 mL) at 0°C was complete after 1.5 h (TLC). Work-up as above, and chromatography of the product (778 mg) on silica gel (80 g, ethyl acetate/hexane 3:17) gave 3-methoxy-16β-methoxymethylestra-1,3,5(10)-trien-17-one **6** (290 mg, 26%), m.p. 124–128°C (chloroform/methanol); $[\alpha]_D$ + 102 (c 0.9); IR ν_{max} 1732 cm^{-1}; ^{1}H NMR δ 0.94 (3H, s, 13β-Me) 2.74 (1H, tdd, $J = 9.4$, 2 × 5.4, and 1.7 Hz, 16α-H), 2.90 (2H, m, 6-H_2) 3.33 (3H, s, 16^1-OMe), 3.54–3.60 (2H, m, 16^1-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H); EI-MS m/z 328 (M^+). Analysis calculated for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.9; H, 8.7. Further elution (ethyl acetate/hexane 1:4) gave mixed fractions (340 mg) of **4** and **6** followed by pure **5** (84 mg).

Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17β-ol **2**

(a) The methylene alcohol **2** (59 mg, 0.2 mmol) in dry tetrahydrofuran (5 mL) at 0°C was treated with 75% *m*-chloroperbenzoic acid (147 mg, 0.64 mmol), then the reaction mixture was stirred at 20°C for 16 h. Saturated aqueous sodium sulfite and saturated aqueous sodium hydrogen carbonate were added and the mixture was extracted with chloroform (×3). The extract was dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the product (67 mg) on silica gel (3.5 g, ethyl acetate/toluene, 1:49) gave (16*R*)-spiro[17β-hydroxy-3-methoxyestra-1,3,5(10)-triene-16,2′-oxirane] **7** (33 mg, 53%), m.p. 136–140°C (chloroform/hexane); $[\alpha]_D$ + 59 (c 1.0); IR ν_{max} 3523 cm^{-1}; ^{1}H NMR δ 0.84 (3H, s, 13β-Me), 2.15 (1H, dd, $J = 14$ and 7.2 Hz, 15α-H), 2.78 and 2.92 (each 1H, d, $J = 4.8$ Hz, 3′-H_2), 2.87 (2H, m, 6-H_2), 3.59 (1H, s after D_2O exchange, 17α-H), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H); EI-MS m/z 314 (M^+). Analysis calculated for $C_{20}H_{26}O_3$: C, 76.4; H, 8.3. Found: C, 76.4; H, 8.3. Further elution (ethyl acetate/toluene 1:9) gave (16*S*)-spiro[17β-hydroxy-3-methoxyestra-1,3,5(10)-triene-16,2′-oxirane] **8** (25 mg, 41%), m.p. 145–152°C decomp. (dichloromethane/hexane); $[\alpha]_D$ + 32 (c 1.1); IR ν_{max} 3608 cm^{-1}; ^{1}H NMR δ 0.90 (3H, s, 13β-Me), 2.67 and 3.14 (each 1H, d, $J = 5.2$ Hz, 3′-H_2), 2.87 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 3.82 (1H, s after D_2O exchange, 17α-H), 6.64 (1H, d, $J = 2.7$ Hz, 4-H), 6.73 (1H, dd, $J = 8.5$ and 2.7 Hz, 2-H), and 7.20 (1H, d, $J = 8.5$ Hz, 1-H); EI-MS m/z 314 (M^+). Analysis calculated for $C_{20}H_{26}O_3$: C, 76.4; H, 8.3. Found: C, 76.6; H, 8.6.

(b) An experiment, in which the methylene alcohol **2** (205 mg, 0.7 mmol) was treated with *m*-chloroperbenzoic acid in dry dichloromethane (12 mL) at 20°C for 2 h, followed by work-up, and slow column chromatography on silica gel (15 g) gave **7** (88 mg, 40%) and **8** (31 mg, 14%), followed by impure material (60 mg) which, after repeated recrystallization from dichloromethane/hexane, furnished 16β-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one **9**, m.p. 138–142°C; $[\alpha]_D$ + 141 (c 1.0); IR ν_{max} 3616 and 1724 cm^{-1}; ^1H NMR δ (C_6D_6) 0.68 (3H, s, 13β-Me), 2.72 (2H, m, 6-H_2), 3.42 (3H, s, 3-OMe), 3.48 (1H, dd, J = 10.7 and 5.8 Hz, 16^1-H), 3.73 (1H, dd, J = 10.7 and 5.0 Hz, 16^1-H), 6.70 (1H, d, J = 2.7 Hz, 4-H), 6.78 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.09 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 314 (M^+). Analysis calculated for $C_{20}H_{26}O_3$; C, 76.4; H, 8.3. Found: C, 75.9; H, 8.2.

Treatment of the (16*S*) epoxy alcohol **8** (31 mg, 0.1 mmol) in dry tetrahydrofuran (3 mL) at 20°C under nitrogen, with toluene-*p*-sulfonic acid (15 mg) for 1 h, followed by work-up and chromatography gave the 16β-hydroxymethyl 17-ketone **9** (20 mg, 64%), m.p. and mixed m.p. 138–142°C.

(c) Aqueous 80% *t*-butylhydroperoxide (0.1 ml, ~0.09 mmol) was added to a stirred mixture of the methylene alcohol **2** (49 mg, 0.16 mmol) and vanadyl acetylacetonate (5.5 mg, 0.02 mmol) in dry benzene (2 mL) at 25°C. After 15 min at 25°C, saturated aqueous sodium sulfite was added, and the reaction mixture was worked up and the product chromatographed as above, to give the (16*R*) isomer **7** (44 mg, 85%).

Epoxidation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17β-yl acetate **3**

The methylene acetate **3** (100 mg, 0.29 mmol) in dry tetrahydrofuran (8 mL) at 20°C was treated with 75% *m*-chloroperbenzoic acid (335 mg, 1.9 mmol), added in small portions at intervals during a total reaction period of 72 h. Work-up as described for **2** (experiment a) and chromatography on silica gel (10 g, ethyl acetate/toluene 1:49) gave (16*S*)-spiro [17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-16,2′-oxirane] **10** (15 mg, 14%), m.p. 160–168°C decomp. (chloroform/hexane); $[\alpha]_D$ − 32 (c 1.0); IR ν_{max} 1737 cm^{-1}; ^1H NMR δ 0.91 (3H, s, 13β-Me), 2.07 (3H, s, 17β-OAc), 2.70 and 3.00 (each 1H, d, J = 5.2 Hz, 3′-H_2), 2.87 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 5.07 (1H, s, 17α-H), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 356 (M^+). Analysis calculated for $C_{22}H_{28}O_4$: C, 74.1; H, 7.9. Found: C, 73.7; H, 7.9; followed by (16*R*)-spiro[17β-acetoxy-3-methoxyestra-1,3,5(10)-triene-16,2′-oxirane] **11** (63 mg, 60%), m.p. 135–140°C (chloroform/hexane); $[\alpha]_D$ + 42 (c 1.0); IR ν_{max} 1728 cm^{-1}; ^1H NMR δ 1.01 (3H, s, 13β-Me), 1.73 (1H, t, J = 2 × 13.3 Hz, 15β-H), 2.10 obsc(1H, dd, J = 13.3 and 7.1 Hz, 15α-H), 2.10 (3H, s, 17β-OAc), 2.74 and 2.78 (each 1H, d, J = 5.3 Hz, 3′-H_2) 2.88 (2H, m, 6-H_2), 4.95(1H, s, 17α-H), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 356 (M^+). Analysis calculated for $C_{22}H_{28}O_4$: C, 74.1; H, 7.9. Found: C, 74.0; H, 7.8.

Further elution with ethyl acetate/toluene (3:7) gave mixed fractions (25 mg); those fractions which comprised largely one component (TLC) were combined to give colorless non-crystalline material formulated as impure 16β-acetoxymethyl-3-methoxyestra-1,3,5(10)-triene-16α,17β-diol **12**, IR ν_{max} 3500 br and 1734 cm^{-1}; ^1H NMR δ 0.88 (3H, s, 13β-Me), 2.12 (3H, s, 16^1-OAc), 2.86 (2H, m, 6-H_2), 3.31 (1H, s after D_2O exchange, 17α-H), 3.77 (3H, s, 3-OMe), 4.06 and 4.12 (each 1H, d, J = 11.5 Hz, 16^1-H_2), 6.63 (1H, d, J = 2.7 Hz, 4-H), 6.71 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 374 (M^+).

Correlation experiments

(a) The (16*R*) epoxy ketone **4** (50 mg, 0.16 mmol) in dry ethanol (5 mL) at 20°C under nitrogen, was treated with sodium borohydride (7.6 mg, 0.2 mmol). After 1 h, ice-water was added and the mixture was worked up (chloroform) to give the (16*R*) epoxy alcohol **7** (48 mg, 96%), m.p. and mixed m.p. 136–140°C (chloroform/hexane). Treatment of **7** with acetic anhydride/pyridine at 20°C for 24 h, and the usual work-up, gave the corresponding acetate **11**, m.p. and mixed m.p. 136–140°C.

(b) Sodium borohydride reduction of the (16*S*) epoxy ketone **5** (229 mg, 0.73 mmol) as described above gave the (16*S*) epoxy alcohol **8** (202 mg, 88%), m.p. and mixed m.p. 145–152°C decomp. (dichloromethane/hexane), acetylation of which afforded the corresponding acetate **10**, m.p. and mixed m.p. 159–165°C decomp. (chloroform/hexane).

Reduction-oxidative cleavage of the epoxides **4** *and* **5**

(a) Lithium aluminum hydride (15 mg, 0.4 mmol) was added to a stirred solution of the (16*R*) epoxy ketone **4** (50 mg, 0.16 mmol) in dry tetrahydrofuran (3 mL) at 0°C under nitrogen. After 1 h, saturated aqueous ammonium chloride was added, and the mixture was worked up (chloroform). Chromatography of the residue on silica gel (4 g, ethyl acetate/toluene 1:5) gave 3-methoxy-16α-methylestra-1,3,5(10)-triene-16β,17β-diol **13** (48 mg, 96%), m.p. 168–172°C (dichloromethane/hexane) (lit.[7] m.p. 171–174°C); $[\alpha]_D$ + 61 (c 0.9); IR ν_{max} 3613 and 3420 br cm^{-1}; ^1H NMR δ 0.85 (3H, s, 13β-Me), 1.35 (3H, s, 16α-Me), 2.83 (2H, m, 6-H_2), 3.16 (1H, s after D_2O exchange, 17 α-H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 316 (M^+). Analysis calculated for $C_{20}H_{28}O_3$: C, 75.9; H, 8.9. Found: C, 76.1; H, 9.0.

Aqueous 6% sodium periodate (0.6 mL, 0.17 mmol) was added to a stirred solution of the diol **13** (48 mg, 0.15 mmol) in methanol (5 mL) at 20°C. After 30 min water was added, and the product was worked up (chloroform). Flash chromatography of the residue on silica gel (3 g; ethyl acetate/toluene 1:19) gave 3-methoxy-16-methyl-16-oxo-16,17-secoestra-1,3,5(10)-trien-17-al **14** (40 mg, 80%) as an oil, $[\alpha]_D$ + 55 (c 1.04) (lit.[11] + 65); IR ν_{max} 1717 cm^{-1}; δ_H 1.02 (3H, s, 13β-Me), 1.86 (1H, dt, J = 13.2 and 2 × 3.5 Hz), 2.16 (3H, s, COMe), 2.82 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), 7.20 (1H, d, J = 8.5 Hz, 1-H), and 9.35 (1H, s, CHO); EI-MS m/z 314 (M^+).

(b) The (16*S*) epoxy ketone **5** (51 mg, 0.16 mmol) was treated with lithium aluminum hydride and the product was isolated as described in the foregoing experiment. Chromatography on silica gel (3.5 g; ethyl acetate/toluene 1:5) gave the epoxy alcohol **8** (7 mg, 13%) followed by 3-methoxy-16β-methylestra-1,3,5(10)-triene-16α,17β-diol **15** (42 mg, 82%), m.p. 84–86°C, resolidifying above 90°C, m.p. 120–122°C (from benzene) (lit.[7] m.p. for hydrate 85–90, 123–127, 151–153°C); $[\alpha]_D$ + 68 (c 0.9); IR ν_{max} 3595 and 3400 br cm^{-1}; ^1H NMR δ 0.77 (3H, s, 13β-Me), 1.33 (3H, s, 16β-Me), 2.85 (2H, s, 6-H_2), 3.63 (1H, s, 17α-H), 3.77 (3H, s, 3-OMe), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 316 (M^+). Analysis calculated for $C_{20}H_{28}O_3 \cdot H_2O$: C, 71.8; H, 9.0. Found: C, 71.9; H, 9.0.

Lead tetraacetate (68 mg, 0.15 mmol) was added to a stirred solution of the 16α,17β-diol **15** (40 mg, 0.13 mmol) in dry

benzene (2 mL) at 20°C. After 1 h, water was added and the mixture was extracted with chloroform (× 3). The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash chromatography on silica gel (3 g; ethyl acetate/toluene 1:19) gave the seco compound **14** (30 mg, 74%).

cis-Hydroxylation of 3-methoxy-16-methylene-estra-1,3,5(10)-trien-17-one **1**

(a) Osmium tetroxide (250 mg, 0.98 mmol) was added to a solution of the methylene ketone **1** (3 g, 10.1 mmol) and 4-methylmorpholine-4-oxide monohydrate (2.67 g, 19.7 mmol) in tetrahydrofuran (73 mL) and water (7.3 mL) under nitrogen, and the mixture was stirred at 20°C for 22 h. Water (4 mL) was added followed by sodium disulfite (2 g) and the mixture was stirred for 45 min, then extracted with ethyl acetate (× 3). The combined aqueous phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a crystalline residue (3.3 g) which was treated with acetic anhydride/pyridine at 20°C for 40 min. The usual work-up (chloroform) gave crystalline material which was chromatographed on silica gel (250 g; ethyl acetate/toluene 1:19) to give 16α-acetoxy-16β-acetoxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one **16** (178 mg, 4%), m.p. 107–109°C (chloroform/methanol); $[\alpha]_D$ + 132 (c 0.9); IR ν_{max} 1735 br cm^{-1}; ^1H NMR δ 0.99 (3H, s, 13β-Me), 2.15 and 2.17 (each 1H, s, 16α- and 16^1-OAc), 2.87 (2H, m, 6-H_2), 3.80 (3H, s, 3-OMe), 4.38 and 4.45 (each 1H, d, J = 11.7 Hz, 16^1-H_2), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 414 (M^+). Analysis calculated for $C_{24}H_{30}O_6$: C, 69.5; H, 7.3. Found: C, 69.3; H, 7.2. Further elution (ethyl acetate/toluene 1:9) gave 16β-acetoxymethyl-16α-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one (**17**) (2.79 g, 74%), m.p. 140–143°C (chloroform/hexane); $[\alpha]_D$ + 174 (c 1.1); IR ν_{max} 3552 and 1743 cm^{-1}; ^1H NMR δ 0.99 (3H, s, 13β-Me), 2.07 (3H, s, 16^1-OAc), 2.88 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.10 and 4.30 (each 1H, d, J = 11.5 Hz, 16^1-H_2), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 372 (M^+). Analysis calculated for $C_{22}H_{28}O_5$: C, 70.9; H, 7.6. Found: C, 70.5; H, 7.6; followed by 16α-acetoxymethyl-16β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17-one **18** (450 mg, 12%), m.p. 139–141°C (dichloromethane/hexane); $[\alpha]_D$ + 80 (c 1.1); IR ν_{max} 3554 and 1743 cm^{-1}; ^1H NMR δ 1.06 (3H, s, 13β-Me), 1.78 (1H, t, J = 2 × 12.8 Hz, 15β-H), 2.11 (3H, s, 16^1-OAc), 2.26 (1H, dd, J = 12.8 and 5.1 Hz, 15α-H), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 4.00 and 4.36 (each 1H, d, J = 11.8 Hz, 16^1-H_2), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 4-H); EI-MS m/z 372 (M^+). Analysis calculated for $C_{22}H_{28}O_5$: C, 70.9; H, 7.6. Found: C, 70.6; H, 7.4.

Alkaline hydrolysis (methanolic 3% potassium hydroxide, 20°C, 10 min) of **17** gave the 16α,16^1-diol **19**, m.p. 154–157°C (methanol); $[\alpha]_D$ + 168 (c 1.1); IR ν_{max} 3545 and 1733 cm^{-1}; ^1H NMR δ 0.99 (3H, s, 13β-Me), 2.90 (2H, m, 6-H_2), 3.70 (2H, s after D_2O exchange, 16^1-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 Hz and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 330 (M^+). Analysis calculated for $C_{20}H_{26}O_4$: C, 72.7; H, 7.9. Found: C, 72.4; H, 8.1.

Similarly, alkaline hydrolysis of **18** gave the 16β,16^1-diol **20**, m.p. 143–146°C (dichloromethane/hexane); $[\alpha]_D$ + 109 (c 1.1); IR ν_{max} 3544 and 1728 cm^{-1}; ^1H NMR δ 1.11 (3H, s, 13β-Me), 1.82 (1H, t, J = 2 × 13.0 Hz, 15β-H), 2.13 (1H, dd, J = 13.0 and 5.8 Hz, 15α-H), 3.55 and 3.72 (each 1H, d after D_2O exchange, J = 11.8 Hz, 16^1-H_2), 3.78 (3H, s, 3-OMe), 6.64 (1H, d, J = 2.7 Hz, 4-H) 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), and 7.20 (1H, d, J = 8.5 Hz, 1-H); EI-MS m/z 330 (M^+). Analysis calculated for $C_{20}H_{26}O_4$: C, 72.7; H, 7.9. Found: C, 72.8; H, 7.8.

Correlation experiments

(a) The (16*R*) epoxy ketone **4** (50 mg, 0.16 mmol) in butan-2-one (2 mL) at 20°C was treated with 70% perchloric acid (0.1 mL). After 3 h, the reaction was incomplete (TLC), but was quenched by the addition of saturated aqueous sodium hydrogen carbonate (in order to prevent decomposition arising from more protracted reaction). Work-up (chloroform) and chromatography on silica gel (5 g; ethyl acetate/toluene 3:7) gave impure starting material **4** (32 mg) followed by the 16β,16^1-diol **20** (14 mg, 26%), m.p. and mixed m.p. 141–145°C.

(b) Similar treatment of the (16*S*) epoxy ketone **5** (87 mg, 0.27 mmol) for 3 h, followed by work-up and chromatography of the product as in (a), gave starting material **5** (52 mg) contaminated with material of similar R_F, followed by the 16α,16^1-diol **19** (34 mg, 37%), m.p. and mixed m.p. 150–155°C.

(c) A mixture of the (16*S*) epoxy ketone **5** (171 mg, 0.22 mmol) and *p*-toluenesulfonic acid (76 mg 0.4 mmol) in dry benzene (5 mL) was refluxed for 1 h. The cooled reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate, and worked up (chloroform) to give 16α-hydroxy-3-methoxy-16β-(*p*-toluenesulfonyloxymethyl)estra-1,3,5(10)-trien-17-one **21** (104 mg) as a slightly discolored labile oil, IR ν_{max} 3545, 1742, 1364, and 1174 cm^{-1}; ^1H NMR δ 0.89 (3H, s, 13β-Me), 2.42 (3H, s, 4′-Me), 2.89 (2H, m, 6-H_2), 3.74 (3H, s, 3-OMe), 4.02 (2H, s, 16^1-H_2), 6.64 (1H, d, J = 2.7 Hz, 4-H), 6.73 (1H, dd, J = 8.5 and 2.7 Hz, 2-H), 7.20 (1H, d, J = 8.5 Hz, 1-H), 7.32 (2H, d, J = 8.3 Hz, 3′- and 5′-H), and 7.75 (2H, d, J = 8.3 Hz, 2′- and 6′-H); EI-MS m/z 312 (M^+-TsOH). Attempted purification of the product **21** through chromatography or crystallization resulted in rapid and quantitative reversion to starting material **5**.

(d) Treatment of the 16α,16^1-diol **19** (167 mg, 0.5 mmol) with *p*-toluenesulfonyl chloride (103 mg, 0.54 mmol) in dry pyridine (5 mL) at 0°C furnished the crude 16^1-tosylate **21**, identical with the product described in (c).

Results and discussion

The starting materials for this investigation were prepared conventionally. Thus, α-methylenation of estrone 3-methyl ether with dimethylmethyleneiminium chloride in refluxing acetonitrile followed by β-elimination of the Mannich intermediate,[6] proceeded efficiently (98%), and the product **1** underwent clean hydride reduction to the 16-methylene 17β-alcohol **2** (96%). Both **2** and the derived 17β-acetate **3** displayed NMR properties consistent with the expected stereochemical outcome of reduction.

At the outset, it was of interest to ascertain whether the 16-methylene 17-ketone **1** was susceptible to peracid epoxidation, a reaction which has been performed with varying success on steroidal s-*cis* enones.[12,13] In the event, **1** was inert to attempted epoxidation with *m*-chloroperbenzoic acid in various media at temperatures between 0°C and 20°C, nor was evidence of Baeyer-Villiger oxidation encountered under these conditions. However, treatment of **1** with alkaline hydrogen peroxide in aqueous dioxane at 20°C, as originally described,[7] proceeded slowly (48 h) to give a separable mixture (~62%) of the (16*R*) and (16*S*) epoxy

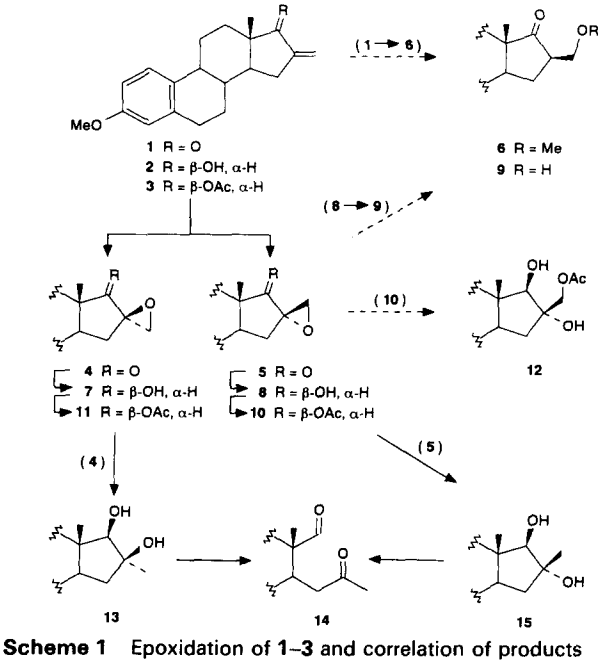
ketones **4** and **5**. The reaction was evidently retarded by heterogeneity of the medium at preparatively useful concentrations, and a much more expedient reaction was achieved in *t*-butyl alcohol/tetrahydrofuran at 20°C (1 h at 0°C, then 2 h at 20°C) to give an 86% yield of products. This medium facilitated homogeneity during the reaction, and the choice of *t*-butyl alcohol as co-solvent was influenced by an experiment in methanol/tetrahydrofuran which also proceeded rapidly, but gave a diminished yield of epoxy ketones, accompanied by a significant amount of the presumed product **6** (~26%) of competing conjugate addition of methoxide to **1**.

The proportions of isomers **4** and **5** were similar (~1:1.27) in all the reactions performed here, and suggest that steric or stereoelectronic influences play a negligible role in the reaction outcome. The gross structural assignments for **4** and **5** followed from diagnostic spectroscopic data, but this evidence alone was inadequate to differentiate the isomers. Epoxidation of the 16-methylene 17β-alcohol **2** with *m*-chloroperbenzoic acid in tetrahydrofuran at 20°C also displayed negligible stereoselectivity. Although the reaction was slow (16 h), a good overall conversion was achieved, and flash chromatography gave the (16*R*) and (16*S*) isomers **7** (53%) and **8** (41%). By contrast, the reaction in dichloromethane was complete within 2 h, but the epoxides **7** (40%) and **8** (14%) were accompanied by more polar material from which a product formulated as the 16β-hydroxymethyl 17-ketone **9** was isolated. It was suspected that the latter product may have arisen through rearrangement of the more labile (16*S*) isomer **8** during the reaction and work-up. Consequently, the isolated yields of **7** and **8** would not reflect the stereoselectivity of the reaction under those conditions. Indeed, treatment of **8** with *p*-toluenesulfonic acid in tetrahydrofuran at 20°C resulted in rapid rearrangement to **9**. Formation of **9** can be rationalized in terms of a Payne-type isomerization[14] of **8**, followed by a hydride shift from the 17α- to the 16α-position in the intermediate 16α-hydroxymethyl 16β,17β-epoxide.

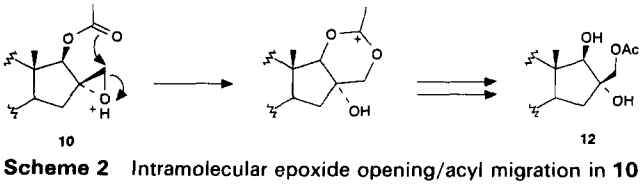
In striking contrast to peracid-mediated epoxidation, treatment of **2** under Sharpless conditions (*t*-butylhydroperoxide/vanadyl acetylacetonate in benzene at 25°C) resulted in rapid and stereoselective formation of the (16*R*) isomer **7** (85%). In view of the report of anomalous stereoselectivity during epoxidations of a steroidal 4-methylene 3β-alcohol,[15] the assignment of configurations to **7** and **8** was clearly crucial to the interpretation of these results. However, comparison of the spectroscopic data for **7** and **8** again failed to provide compelling evidence in support of the assignments, and chemical interconversions (see below) were necessary to confirm the structures.

Although the apparent absence of stereoselectivity during peracid treatment of **2** appears to refute the classical Henbest model for allylic participation in this case, it has been argued that the stereodirecting role of an equatorial or pseudoequatorial hydroxy group allylic to an exocyclic methylene group will not necessarily override steric constraints.[15,16] Epoxidation of the 16-methylene 17β-acetate **3** was expected to shed further light on this problem, since suppression of allylic participation should thus result in an isomer distribution based only on steric considerations. However, the epoxidation of **3** with *m*-chloroperbenzoic acid was not only very slow, but was accompanied by TLC evidence loss of primary products during the reaction, and upon work-up and chromatography. The reaction in tetrahydrofuran at 20°C required 72 h for completion, and chromatography gave the (16*S*) and (16*R*) isomers **10** (14%) and **11** (60%) (which eluted in inverse order to the other isomeric pairs), followed by more polar material, the purer fractions of which displayed spectroscopic properties consistent with the 16β-acetoxymethyl 16α,17β-diol **12**. It was further evident that prolonged contact of the epoxidation mixture with silica gel resulted in progressive accumulation of the more polar material, at the apparent expense of the (16*S*) isomer **10**. The conversion of **10** into **12** may arise through intramolecular acyl participation during epoxide opening, followed by hydration and regioselective opening of the intermediate (Scheme 2), in a process reminiscent of related acyl transfers accompanying rearrangement in α-epoxy acetates.[17,18] The juxtaposition of functionality is uniquely favorable for this process in the (16*S*) isomer **10**.

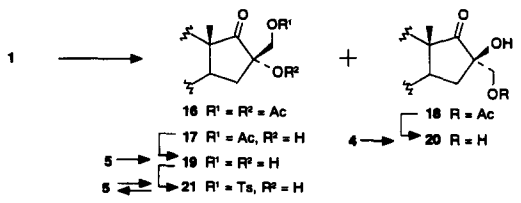
The lack of conclusive spectroscopic evidence for the assigned structures of the epoxides necessitated alternative approaches to structure determination. In the first instance, the relationships between the respective (16*R*) and (16*S*) isomers were confirmed by routine interconversions. Thus, the (16*R*) epoxy ketone **4** was reduced with sodium borohydride to the corresponding 17β-alcohol **7** which was converted into the 17β-acetate **11**,



Scheme 1 Epoxidation of **1–3** and correlation of products



Scheme 2 Intramolecular epoxide opening/acyl migration in **10**



Scheme 3 *cis*-Hydroxylation of **1**, and correlation of products

and the products thus obtained were identified by comparison with those obtained by epoxidation of **2** and **3**, respectively. A similar correlation was conducted on the (16*S*) epoxy ketone **5**, leading successively to **8** and **10**.

It remained to confirm the configurational assignments at C-16 in the respective isomeric pairs. For this purpose, the (16*R*) epoxy ketone **4** was subjected to exhaustive reduction with lithium aluminum hydride to give the 16α-methyl 16β,17β-diol **13**, corresponding in properties with those reported[7] for the product arising from Grignard methylation of 17β-hydroxy-3-methoxy-estra-1,3,5(10)-trien-16-one. Treatment of **13** with sodium periodate in aqueous methanol at 20°C resulted in rapid and efficient oxidative cleavage to the seco compound **14**.[11] By contrast, the 16β-methyl 16α,17β-diol **15**, derived from lithium aluminum hydride reduction of the (16*S*) epoxy ketone **5**, failed to respond to periodate treatment (3 days at 20°C), but underwent oxidative cleavage to **14** only with lead tetraacetate, a reagent for which the *cis*-relationship between vicinal hydroxy groups is not obligatory. These reactions confirm C-16 configuration in **4** and **5** and hence, in the derived isomeric pairs **7/8** and **10/11**.

The comparative investigation of *cis*-hydroxylation stereoselectivity was confined to the 16-methylene 17-ketone **1** (Scheme 3). Treatment of **1** with catalytic osmium tetroxide (10 mol%) in the presence of 4-methylmorpholine-4-oxide in aqueous tetrahydrofuran at 20°C gave an inseparable mixture (~6:1 by NMR estimates and subsequent experiments) of 16-hydroxymethyl 16-hydroxy 17-ketones. Although it was possible to purify the major isomer by direct recrystallization of the total reaction product, prior acetylation gave a readily separable mixture of the 16¹-acetates **17** and **18**, accompanied by some 16α,16¹-diacetate **16**. Alkaline hydrolysis of the respective acetates then furnished the pure 16α,16¹- and 16β,16¹-diols **19** and **20**. Again, the differentiation of isomers with the aid of spectroscopic data was equivocal, although the pattern of ^{1}H NMR chemical shifts of 18-H_3 was consistent with the assignments. However, definitive correlations were achieved by acid-catalysed hydration of the epoxy ketones **4** and **5**, which gave **20** and **19**, respectively, albeit in modest yields. Interestingly, an unrelated attempt to induce acid-catalyzed rearrangement of the epoxy ketone **5** in the presence of *p*-toluenesulfonic acid resulted instead in formation of the labile 16α-hydroxy 16¹-tosylate **21**, which was also prepared by treatment of the 16α,16¹-diol **19** with *p*-toluenesulfonyl chloride in pyridine, thereby adding to the evidence for the configurational assignments of **19** and **20**.

In contrast to the epoxidation findings, it is thus apparent that *cis*-hydroxylation of the 16-methylene group in **1** is governed largely by the steric demands of the reagent, leading to preferred α-face addition.

The further utilisation of those products arising from stereoselective additions described in this work is under investigation.

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