STEREOSELECTIVE SYNTHESIS OF THE TWO *trans*-(16-HYDROXYMETHYL)-3-METHOXY-13α-ESTRA-1,3,5(10)-TRIEN-17-OL ISOMERS

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Reduction of 16-(hydroxymethylidene)-3-methoxy-13α-estra-1,3,5(10)-trien-17-one yielded a mixture of two diastereomeric diols in the 6:1 ratio. The configurations of the newly formed stereogenic centres were determined by X-ray crystallography and NMR spectroscopy (NOE experiments) on the compounds in their cyclic acetaldehyde acetal forms.

Keywords: Steroids; 13α-Estrones; X-Ray diffraction; NMR spectroscopy; Stereoselective reduction; Diols; Cyclic acetals; Claisen condensation.

Hydrophilic functional groups attached to ring D in the steroid skeleton have strong effects on biological properties of these compounds. The traditional chemical modification of steroids is rather complex, requiring multistep reactions combined with regioselective protections and deprotections, and can usually be carried out only with abundant and readily available steroids. On the other hand, the preparation of steroid analogues with abnormal configurations at the stereogenic centres, on which the influence of such stereochemical changes on physiological properties can be evaluated, has received relatively little consideration[1,2].

Earlier we reported preparations and configuration determinations of the four possible isomers of 16-(hydroxymethyl)-estra-1,3,5(10)-triene-3,17-diol[3], and their 3-methyl[4,5] and 3-benzyl ethers[3]. The 17-hydroxy-16-hydroxymethyl-substituted estrane derivatives provided different possibilities for the construction of heterocycles fused to ring D of the steroid[6–8].

In connection with our earlier investigations, we are interested in compounds with an inverted configuration at C-13, *i.e.* derivatives of 3-methoxy-13α-estra-1,3,5(10)-trien-17-ones containing a *cis* junction of rings C and D. These compounds, similarly to natural steroids, should have

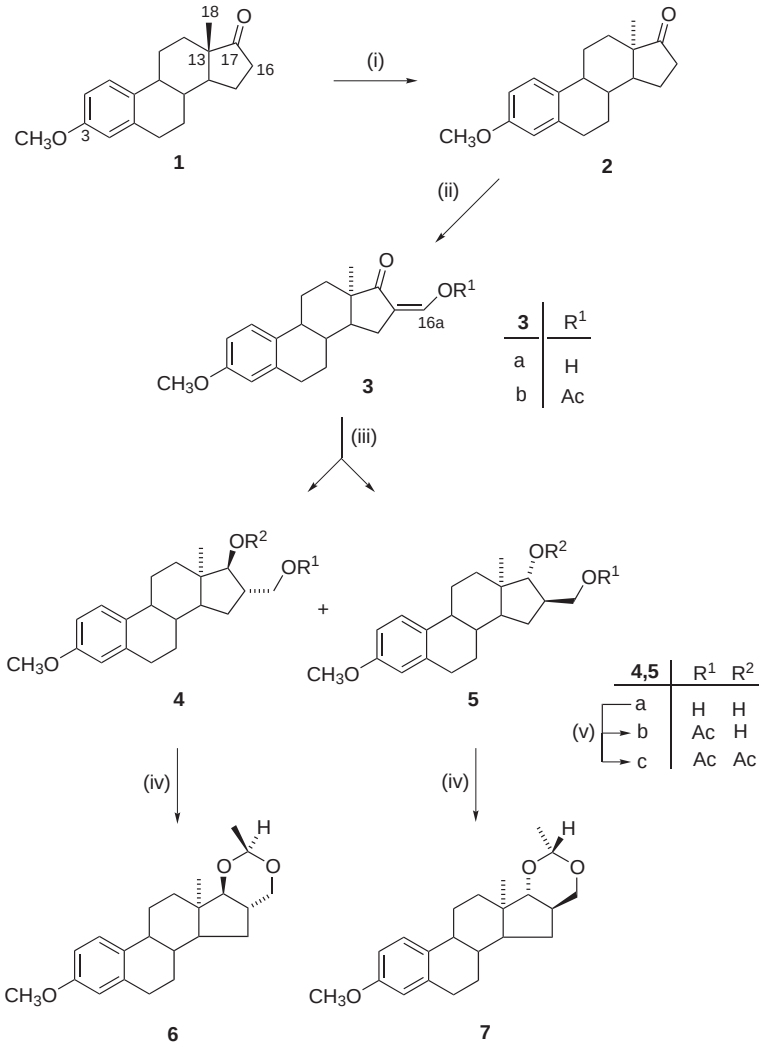
a relatively rigid molecular framework. In contrast to the natural 13β-estra-1,3,5(10)-trien-17-one, these derivatives possess a quasi-equatorial 13α-methyl group, their ring D is directed to the β side and, like natural estrone, exhibit a strongly restricted pseudorotation.

In the present paper, we describe an extension of the C-16 hydroxymethylation to 3-methoxy-13α-estra-1,3,5(10)-trien-17-one (**2**). We found that the stereochemical course of this process strongly depends on the C/D ring junction of the steroid.

RESULTS AND DISCUSSION

3-Methoxyestra-1,3,5(10)-trien-17-one (**1**) was epimerized (Scheme 1) by the method of Yaremenko and Khvat[9], which was extended to the 3-methoxy-13α-estra-1,3,5(10)-trien-17-one (**2**) by Schönecker *et al.*[1] We obtained the compound **2** in 92% yield when the product was separated from the starting material by means of the Girard-P reagent[10].

Treatment of **2** with sodium methoxide and freshly distilled ethyl formate in Claisen condensation[4] gave **3a** in 87% yield. Structure of compound **3a** was proved by acetylation and the obtained acetate **3b** was characterized by NMR and MS. The formyl compound **3b** was reduced with potassium borohydride in methanol to give selectively **4a** and **5a** in 97% overall yield. Two new chiral centres are formed in this reaction, but only two of the possible four isomers could be obtained, in the 6:1 ratio. These compounds could not be separated by flash chromatography on silica gel. Selective acetylation of the primary hydroxy groups was therefore carried out[5], **4b** and **5b** were separated on a silica gel column, and hydrolysis of the separated compounds led to two diastereomeric diols in pure form. With the aim of confirming the structures of **4a** and **5a**, we transformed them into their acetaldehyde acetals **6** and **7** by using a slight modification of a known method[11]. The stereospecific reactions resulted in only one acetal of each diol, although one further new chiral centre was formed. The structure of acetal **6** was proved by NMR spectroscopy and X-ray crystallography. DNOE experiments showed that saturation of the 17-H signal caused increased intensities of the singlet of the 18-methyl protons, of the quartet of the acetal-hydrogen and the multiplet of 16aα-H. Saturation of the 16-proton multiplet led to increases in the intensities of the signals of the 16aβ-H and of the acetal-methyl protons. The configuration of the acetal-carbon could also be proved by these methods: *S* in **6** and *R* in **7**. Similar NMR spectroscopic experiments were used to confirm the structure of **7**. The minor compound proved to be the other *trans* isomer-16β,17α. The



(i) 1.5 equiv. 1,2-phenylenediamine, AcOH, reflux, 3 h, 92%; (ii) 2 equiv. $NaOCH_3$, 15 equiv. HCOOEt, benzene, 50 °C, 6 h, 87%; (iii) 5 equiv. KBH_4, MeOH, r.t., 4 h, 97%; (iv) 5 equiv. acetaldehyde diethyl acetal, CH_2Cl_2, cat. amount *p*-toluenesulfonic acid, reflux, 1.5 h, 93%; (v) 1 equiv. Ac_2O, pyridine, 0 °C→r.t., 5 h, **4b**:**4c** = 3:1, **5b**:**5c** = 3:1

SCHEME 1

crystal structure determination revealed that ring C of the main product **6** assumes a twist-boat conformation, and that the configurations of C-16 and C-17 are opposite: 16α and 17β (Fig. 1).

Reduction of the analogous 16-formyl-13β-methyl compound resulted in two epimeric diols (16β,17β and 16α,17β) in equal amounts[4]. In contrast to those results, we obtained in the 13α series two *trans* diols in different amounts. Our earlier investigations showed that in the normal estrone series, only the *cis* isomer readily forms an acetal with acetaldehyde diethyl acetal. Surprisingly, in the 13α-estrone series, both *trans* diols give cyclic acetals quantitatively, and each diol gives stereospecifically only one acetal. This special and high selectivity in the reactions of the 13α-steroids is due to their flexible conformation, which is different from that of the 13β compounds.

Concluding, we have synthetized two new *trans* 1,3-diols in the 13α-estrone series. These compounds were transformed quantitatively into their acetaldehyde acetals in stereospecific reactions. The structures of the acetals were investigated *via* X-ray crystallography (see Fig. 1), NMR spectroscopy and mass spectrometry. The crystal structure of the major acetal proved the twist-boat conformation for ring C. This flexible molecular structure could never be observed for the 13β-estrone derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. All optical rotations were measured in chloroform (*c* 1.0) on a Polamat-A (Zeiss, Jena) polarimeter at 23 °C, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker DRX 500 instrument at room temperature, using tetramethyl silane as a reference. Chemical shifts are

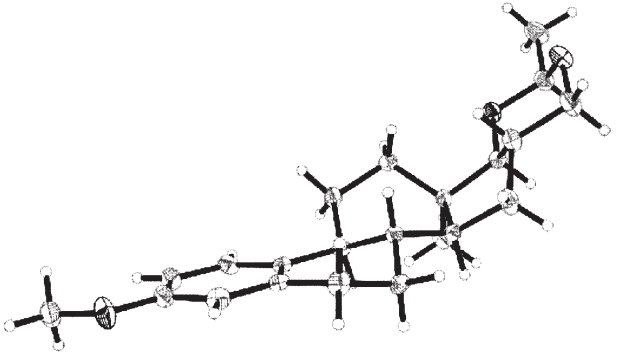


FIG. 1
X-Ray strucure of the major acetal isomer **6**

given in ppm (δ-scale) and coupling constants (*J*) in Hz. For the determination of multiplicities, the J-MOD pulse sequence was used. Mass spectra were measured on a Varian MAT 311A spectrometer (energy of ionizing electrons 70 eV). Elemental analysis data were determined in the analytical laboratory of the University of Szeged. The reactions were monitored by TLC (Merck Silica gel F_{225}). Products were isolated by flash chromatography (Merck Kieselgel 60, 40–63 μm).

CCDC 188827 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

3-Methoxy-13α-estra-1,3,5(10)-trien-17-one (**2**)

A mixture of compound **1** (20 g, 70.3 mmol), acetic acid (200 ml) and 1,2-phenylenediamine (10.8 g, 100 mmol) was stirred at 117 °C for 3 h. After cooling, the mixture was slowly poured onto ice and the resulting precipitate was filtered off, washed with water and dried. The solid was dissolved in chloroform, and the solution was washed with water, dried (anhydrous sodium sulfate) and evaporated. The crude product was dissolved in methanol (200 ml), and Girard-P reagent (15 g, 80 mmol) and acetic acid (15 ml) were added to the solution. The reaction mixture was heated at reflux for 3 h, and then allowed to stand at room temperature overnight. After white crystals formed, the mixture was neutralized with a dilute sodium carbonate solution. The precipitate was filtered off and dissolved in chloroform, and the solution was washed with water, dried (anhydrous sodium sulfate) and evaporated. Yield of pure **2**: 18.5 g (92%), identical with the compound described in ref.[1]

16-(Acetoxymethylidene)-3-methoxy-13α-estra-1,3,5(10)-trien-17-one (**3b**)

Compound **2** (25 g, 88 mmol) was dissolved in anhydrous benzene (200 ml), sodium methoxide (9.5 g, 0.18 mol), and freshly distilled ethyl formate (100 ml, 1.3 mol) were added to the solution. The reaction mixture was stirred at 50 °C for 6 h, and allowed to stand at room temperature overnight. The reaction mixture was diluted with water (1 l) and poured onto a mixture of ice (100 g) and concentrated HCl (22 ml). The white precipitate separated was filtered off, washed thoroughly with water, and dried. Yield 24 g (87%) of **3a**. Compound **3a** (5 g, 16 mmol) was dissolved in pyridine (10 ml), and acetic anhydride (10 ml, 0.11 mol) was added. The reaction mixture was allowed to stand at room temperature for 5 h, and then poured onto a mixture of concentrated sulfuric acid (10 ml) and ice (100 g). The precipitate that separated out was filtered off, dissolved in chloroform, and the solution was washed with water, dried (anhydrous sodium sulfate) and evaporated. The crude product was recrystallized from chloroform–light petroleum, yielding 5.3 g (94%) of pure **3b**, m.p. 110–115 °C, $[\alpha]_D$ +55. ^{1}H NMR (500 MHz, $CDCl_3$): 1.06 s, 3 H (18-H_3); 2.25 s, 3 H (CH_3COO); 2.81 m, 2 H (6-H_2); 3.75 s, 3 H (3-OCH_3); 6.58 d, 1 H, *J*(2,4) = 2.6 (4-H); 6.68 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.6 (2-H); 7.17 d, 1 H, *J*(1,2) = 8.6 (1-H); 8.17 s, 1 H (16a-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.67 (CH_3CO); 25.35 (C-18); 26.13 (CH_2); 28.08 (CH_2); 28.29 (CH_2); 30.26 (CH_2); 31.90 (CH_2); 41.30 (CH); 42.70 (CH); 46.89 (CH); 51.08 (C-13); 55.15 (3-CH_3); 111.64 (C-2); 113.55 (C-4); 119.60 (C-16); 126.84 (C-1); 131.86 (C-10); 137.89 (C-5); 141.14 (C-16a); 157.48 (C-3); 167.11 (CH_3CO); 209.24 (C-17). MS, *m/z* (%): 354 (100, M^+), 312 (82), 227 (12), 173 (19), 147 (12), 43 (52). For $C_{22}H_{26}O_4$ (354.4) calculated: 74.55% C, 7.39% H; found: 74.67% C, 7.22% H.

Reduction of 16-(Acetoxymethylidene)-3-methoxy-13α-estra-1,3,5(10)-trien-17-one (**3b**)

Compound **3b** (10 g, 32 mmol) was suspended in methanol (200 ml), and potassium borohydride (8.6 g, 160 mmol) was added in small portions at room temperature. The reaction mixture was allowed to stand for 4 h, then poured onto ice (500 g) and acidified with dilute hydrochloric acid to pH 3. The precipitate separated was filtered off, washed until free from acid and dried; yield 9.8 g (97%). The mixture obtained consisted of the diols **4a** and **5a** in a ratio of 6:1 (based on the ^{1}H NMR data).

Preparation of 16-Hydroxymethyl Compounds **4a** and **5a**

The 6:1 mixture of **4a** and **5a** (2.3 g, 7.3 mmol) was dissolved in pyridine (10 ml), and a solution of acetic anhydride (0.7 ml, 7.3 mmol) in pyridine (15 ml) was added dropwise with cooling in ice. The reaction mixture was allowed to stand at room temperature for 5 h, and then poured onto a mixture of concentrated sulfuric acid (12 ml) and ice (100 g). The precipitate that separated out was filtered off and dissolved in chloroform. The chloroform solution was washed with water, dried (anhydrous sodium sulfate) and evaporated. The oily mixture was subjected to chromatographic separation on a silica gel column with ethyl acetate–chloroform (5:95) as eluent. The separation yielded 1.56 g (60%) of **4b** and **5b** in the 6:1 ratio, and 0.58 g (20%) of **4c** and **5c** in the 6:1 ratio, while 0.46 g (20%) of **4a** and **5a** in the 6:1 ratio remained, which was recycled. The mixture of the monoacetates **4b** and **5b** was subjected to a second chromatographic separation on a silica gel column with ethyl acetate–chloroform (5:95) as eluent. Compounds **4b** and **5b** resulted in pure form. Alkaline hydrolysis of **4b** or **5b** yielded **4a** or **5a** in pure form. The chromatographic method described above was applied in an attempt to separate diacetates **4c** and **5c**, but it resulted only in the main isomer **4c** in pure form, in a yield of 0.29 g (10%).

16α-(Acetoxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17β-ol (**4b**). M.p. 104–105 °C, $[\alpha]_D$ +91. ^{1}H NMR (500 MHz, $CDCl_3$): 1.07 s, 3 H (18-H_3); 2.06 s, 3 H (CH_3COO); 2.78 m, 2 H (6-H_2); 3.49 d, 1 H, *J*(16,17) = 7.5 (17-H); 3.76 s, 3 H (3-OCH_3); 4.12 dd, 1 H, *J*(16aa,16ab) = 11.0, *J*(16aa,16) = 6.1 and 4.19 dd, 1 H, *J*(16aa,16ab) = 11.0, *J*(16ab,16) = 6.1 (16a-H_2); 6.58 d, 1 H, *J*(2,4) = 2.6 (4-H); 6.70 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.6 (2-H); 7.15 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.89 (CH_3CO); 27.82 (CH_2); 28.81 (CH_2); 28.99 (C-18); 29.06 (CH_2); 29.29 (CH_2); 30.32 (CH_2); 38.50 (CH); 40.81 (CH); 43.50 (C-13); 44.90 (CH); 50.24 (CH); 55.11 (3-OCH_3); 66.86 (C-16a); 84.44 (C-17); 111.95 (C-2); 113.17 (C-4); 127.48 (C-1); 133.60 (C-10); 137.81 (C-5); 157.16 (C-3); 171.27 (CH_3CO). MS, *m/z* (%): 358 (100, M^+), 227 (4), 212 (5), 186 (9), 147 (6), 43 (4). For $C_{22}H_{30}O_4$ (358.5) calculated: 73.71% C, 8.44% H; found: 73.54% C, 8.25% H.

16β-(Acetoxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17α-ol (**5b**). Oil, $[\alpha]_D$ +19. ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 s, 3 H (18-H_3); 2.03 s, 3 H (CH_3COO); 2.79 m, 2 H (6-H_2); 3.78 s, 3 H (3-OCH_3); 3.94 m, 1 H (17-H), 4.10 dd, 1 H, *J*(16aa,16ab) = 10.9, *J*(16aa,16) = 6.1 and 4.20 dd, 1 H, *J*(16aa,16ab) = 10.9, *J*(16ab,16) = 5.5 (16a-H_2); 6.62 d, 1 H, *J*(2,4) = 2.7 (4-H); 6.73 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.7 (2-H); 7.23 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.81 (CH_3CO); 22.90 (C-18); 26.49 (CH_2); 28.09 (CH_2); 28.26 (CH_2); 30.43 (CH_2); 32.97 (CH_2); 42.11 (CH); 42.30 (CH); 43.19 (CH); 43.85 (C-13); 48.65 (CH); 55.04 (3-OCH_3); 67.47 (C-16a); 75.85 (C-17); 111.69 (C-2); 113.50 (C-4); 126.80 (C-1); 132.14 (C-10); 137.94 (C-5); 157.33 (C-3); 171.11 (CH_3CO). MS, *m/z* (%): 358 (100, M^+), 227 (3), 186 (7), 147 (4), 84 (10), 49 (12). For $C_{22}H_{30}O_4$ (358.5) calculated: 73.71% C, 8.44% H; found: 73.61% C, 8.32% H.

16α-(Acetoxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17β-yl acetate (**4c**). Oil, $[\alpha]_D$ +37.4. ^{1}H NMR (500 MHz, $CDCl_3$): 1.08 s, 3 H (18-H_3); 1.99 s, 3 H (17-CH_3COO); 2.04 s, 3 H (16a-CH_3COO); 2.82 m, 2 H (6-H_2); 3.76 s, 3 H (3-OCH_3); 4.14 dd, 2 H, *J*(16aa,16ab) = 6.3, *J*(16aa,16) = *J*(16ab,16) = 1.5 (16a-H_2); 4.80 d, 1 H, *J*(16,17) = 5.3 (17-H); 6.62 d, 1 H, *J*(2,4) = 2.7 (4-H); 6.72 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.7 (2-H); 7.19 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.73 (CH_3CO); 21.13 (CH_3CO); 28.41 (CH_2); 28.96 (CH_2); 29.55 (CH_2); 29.75 (C-18); 30.36 (CH_2); 32.98 (CH_2); 40.46 (CH); 40.69 (CH); 44.02 (C-13); 44.68 (CH); 51.91 (CH); 55.07 (3-OCH_3); 66.28 (C-16a); 84.58 (C-17); 111.84 (C-2); 113.40 (C-4); 127.13 (C-1); 132.67 (C-10); 138.06 (C-5); 157.39 (C-3); 170.40 (CH_3CO); 170.79 (CH_3CO). For $C_{24}H_{32}O_5$ (400.5) calculated: 71.97% C, 8.05% H; found: 72.10% C, 8.22% H.

16β-(Acetoxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17α-yl acetate (**5c**). ^{1}H NMR (500 MHz, $CDCl_3$): 1.01 s, 3 H (18-H_3); 1.99 s, 3 H (17-CH_3COO); 2.06 s, 3 H (16a-CH_3COO); 2.81 m, 2 H (6-H_2); 3.75 s, 3 H (3-OCH_3); 4.05 dd, 2 H, *J*(16aa,16ab) = 6.3, *J*(16aa,16) = *J*(16ab,16) = 1.5 (16a-H_2); 5.29 d, 1 H, *J*(16,17) = 5.3 (17-H); 6.60 d, 1 H, *J*(2,4) = 2.7 (4-H); 6.71 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.7 (2-H); 7.19 d, 1 H, *J*(1,2) = 8.6 (1-H).

16α-(Hydroxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17β-ol (**4a**). M.p. 95–97 °C, $[\alpha]_D$ +103. ^{1}H NMR (500 MHz, $CDCl_3$): 1.10 s, 3 H (18-H_3); 2.78 m, 2 H (6-H_2); 3.57 d, 1 H, *J*(16,17) = 8.3 (17-H); 3.66 dd, 1 H, *J*(16aa,16ab) = 10.1, *J*(16aa,16) = 8.3 and 3.81 dd, 1 H, *J*(16aa,16ab) = 10.1, *J*(16ab,16) = 5.6 (16a-H_2); 3.76 s, 3 H (3-OCH_3); 6.58 d, 1 H, *J*(2,4) = 2.7 (4-H); 6.72 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.7 (2-H); 7.14 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, DMSO-d_6): 28.07 (CH_2); 28.45 (CH_2); 29.34 (C-18); 29.39 (CH_2); 30.03 (CH_2); 30.41 (CH_2); 39.00 (CH); 40.25 (CH); 43.13 (C-13); 48.40 (CH); 50.62 (CH); 54.79 (3-OCH_3); 63.76 (C-16a); 82.32 (C-17); 111.82 (C-2); 112.84 (C-4); 127.23 (C-1); 133.30 (C-10); 137.53 (C-5); 156.72 (C-3). MS, *m/z* (%): 316 (100, M^+), 297 (2), 227 (3), 186(10), 147 (4). For $C_{20}H_{28}O_3$ (316.5): calculated: 75.91% C, 8.92% H; found: 76.06% C, 8.75% H.

16β-(Hydroxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17α-ol (**5a**). M.p. 145–149 °C, $[\alpha]_D$ –18. ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 s, 3 H (18-H_3); 2.79 m, 2 H (6-H_2); 3.60 t and 3.78 t, 2 × 1 H, *J*(16aa,16ab) = *J*(16aa,16) = *J*(16ab,16) = 8.1 (16a-H_2); 3.94 d, 1 H, *J*(16,17) = 7.9 (17-H); 6.60 d, 1 H, *J*(2,4) = 2.4 (4-H); 6.71 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.4 (2-H); 7.20 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, DMSO-d_6): 23.41 (C-18); 26.19 (CH_2); 27.85 (CH_2); 28.13 (CH_2); 29.96 (CH_2); 32.83 (CH_2); 41.81 (CH); 42.21 (CH); 43.40 (C-13); 44.98 (CH); 48.44 (CH); 54.77 (3-OCH_3); 63.67 (C-16a); 73.05 (C-17); 111.55 (C-2); 113.18 (C-4); 126.63 (C-1); 132.11 (C-10); 137.77 (C-5); 156.91 (C-3). MS, *m/z* (%): 316 (100, M^+), 212 (5), 186 (16), 147 (8), 121 (4), 91 (3). For $C_{20}H_{28}O_3$ (316.5) calculated: 75.91% C, 8.92% H; found: 75.83% C, 9.05% H.

16α-(Hydroxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17β-ol Acetaldehyde Acetal (**6**) and 16β-(Hydroxymethyl)-3-methoxy-13α-estra-1,3,5(10)-trien-17α-ol Acetaldehyde Acetal (**7**)

Compound **4a** or **5a** (950 mg, 3 mmol) was dissolved in dichloromethane (40 ml), and acetaldehyde diethyl acetal (2.1 ml, 15 mmol) and 4-toluenesulfonic acid monohydrate (catalytic amount) were added. After reflux for 1.5 h, the reaction mixture was poured into water and neutralized with morpholine. The aqueous solution was extracted with dichloromethane, and the organic phase was washed with water, dried (anhydrous sodium sulfate) and evaporated. The residue was subjected to chromatography on a silica gel column with dichloromethane as eluent (overall yield 956 mg; 93%).

Yield of **6**: 802 mg (78%), m.p. 126–128 °C, $[\alpha]_D$ +139. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 s, 3 H (18-H_3); 1.35 d, 3 H, *J* = 5.1 (acetal-CH_3); 2.74 m, 2 H (6-H_2); 3.02 d, 1 H, *J*(16,17) = 10.7 (17-H); 3.46 t, 1 H, *J*(16aa,16ab) = *J*(16aa,16) = 10.5 and 4.24 dd, 1 H, *J*(16aa,16ab) = 10.5, *J*(16ab,16) = 4.4 (16a-H_2); 3.76 s, 3 H (3-OCH_3); 4.66 q, 1 H, *J* = 5.1 (acetal-CH); 6.56 d, 1 H, *J*(2,4) = 2.6 (4-H); 6.72 dd, 1 H, *J*(1,2) = 8.5, *J*(2,4) = 2.6 (2-H); 7.11 d, 1 H, *J*(1,2) = 8.5 (1-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.76 (acetal-CH_3); 24.36 (CH_2); 25.76 (CH_2); 27.27 (C-18); 27.46 (CH_2); 29.26 (CH_2); 30.18 (CH_2); 35.69 (CH); 36.07 (CH); 40.46 (CH); 40.83 (C-13); 49.31 (CH); 55.15 (3-OCH_3); 72.71 (C-16a); 91.92 (C-17); 99.57 (OCO); 112.25 (C-2); 112.96 (C-4); 128.00 (C-1); 134.59 (C-10); 137.42 (C-5); 157.09 (C-3). MS, *m/z* (%): 342 (100, M^+), 298 (5), 227 (8), 186 (9), 147 (6), 121 (2). For $C_{22}H_{30}O_3$ (342.5) calculated: 77.16% C, 8.83% H; found: 77.10% C, 8.95% H. Crystal data: $C_{22}H_{30}O_3$, M_w 342.46, orthorhombic, space group $P2_12_12_1$, *a* = 7.0661(14) Å, *b* = 8.1292(16) Å, *c* = 32.543(7) Å, *V* = 1869.3(6) Å^3, *F*(000) = 744, *Z* = 4, *T* = 133 K, μ(MoKα) = 0.079 mm^{-1}, D_{calcd} = 1.217 g cm^{-3}, $2\theta_{max}$ 54° (CCD area detector, MoKα radiation, 96.8% completeness), GOF = 1.302, $wR(F^2)$ = 0.1170 (all 2300 data), *R* = 0.0462 (2266 data with $I > 4\sigma I$).

Yield of **7**: 103 mg (10%), m.p. 125–135 °C, $[\alpha]_D$ +68. ^{1}H NMR (500 MHz, $CDCl_3$): 1.03 s, 3 H (18-H_3); 1.36 d, 3 H, *J* = 5.0 (acetal-CH_3); 2.77 m, 2 H (6-H_2); 3.13 d, 1 H, *J*(16,17) = 10.0 (17-H); 3.48 t, 1 H, *J*(16aa,16ab) = *J*(16aa,16) = 10.3 and 4.26 dd, 1 H, *J*(16aa,16ab) = 10.3, *J*(16ab,16) = 3.8 (16a-H_2); 3.77 s, 3 H (3-OCH_3); 4.67 q, 1 H, *J* = 5.0 (acetal-CH); 6.58 d, 1 H, *J*(2,4) = 2.4 (4-H); 6.72 dd, 1 H, *J*(1,2) = 8.6, *J*(2,4) = 2.6 (2-H); 7.17 d, 1 H, *J*(1,2) = 8.6 (1-H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.84 (acetal-CH_3); 23.93 (C-18); 26.84 (CH_2); 28.32 (2 × CH_2); 30.28 (CH_2); 32.97 (CH_2); 37.23 (CH); 39.50 (CH); 40.35 (C-13); 43.88 (CH); 50.04 (CH); 55.18 (3-OCH_3); 73.15 (C-16a); 88.50 (C-17); 99.67 (OCO); 112.05 (C-2); 113.33 (C-4); 127.77 (C-1); 133.35 (C-10); 137.72 (C-5); 157.29 (C-3). For $C_{22}H_{30}O_3$ (342.5) calculated: 77.16% C, 8.83% H; found: 77.31% C, 8.97% H.

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