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Reaction of androst-5-en-17-one with hypobromous acid and its use for synthesis of 19-oxygenated 5-ene and 4-en-6-one steroids

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*Reaction of androst-5-en-17-one (**1**) with hypobromous acid using a short reaction time (30 min) along with a careful isolation procedure gave, for the first time, the addition product, 5α-bromo-6β-hydroxyandrostan-17-one (**3**), in 43% yield. This bromohydrin was much more reactive than 5α-bromo-3β-acetoxy-6β-hydroxyandrostan-17-one (**4**) towards $KHCO_3$ and $HClO_4$. The high reactivity of compound **3** was found to be a principal reason for the difficulty in isolating this compound by the addition reaction so far. 19-Hydroxyandrost-5-en-17-one (**16**) and androst-5-ene-17,19-dione (**18**), as well as 19-hydroxyandrost-4-ene-6,17-dione (**28**) and androst-4-ene-6,17,19-trione (**29**), were synthesized through hypoiodite reaction of the bromohydrin **3** as a key reaction.* (*Steroids* **63**:62–69, 1998) © *1998 by Elsevier Science Inc.*

Keywords: hypobromous acid; addition reaction; 5-ene; neighboring group participation; 19-oxygenated; aromatase inhibitor

Introduction

In connection with work in our laboratory on the biochemical evaluation of 3-deoxy steroids, such as androst-5-en-17-one (**1**)[1] and androst-4-en-6-one (**20**),[2] as catalytic probes of aromatase, which is a unique cytochrome P-450 enzyme complex responsible for the conversion of androgens to the phenolic estrogens, we were interested in the 19-oxygenated derivatives of the 3-deoxy steroids. An obvious synthetic route to these compounds seemed to involve the addition of hypobromous acid (HOBr) to the olefin **1** to yield 5α-bromo-6β-ol **3**; its conversion to 6β,19-epoxide **15** by hypoiodite reaction followed by zinc reduction[3] was expected to give rise to the desired unsaturated 19-hydroxy steroid **16**, which was also expected to become a starting material for the synthesis of 19-oxygenated 4-en-6-one steroids **28** and **29**. However, Kocovsky's group[4,5] previously reported that judicious anchoring of a functional group near a double bond at C-5 can dramatically affect the course of the HOBr addition. For instance, the addition reaction of a 5-ene steroid having no oxygen function at C-3 has been reported to produce a complex mixture of products and failure with respect to isolation of the desired 5α-bromo-6β-ol derivative.[4]

The HOBr addition reaction was examined precisely using the 3-deoxy steroid **1** as the substrate under various conditions to successfully obtain the bromohydrin **3**. We report the participation of a neighboring 3β-acetoxy function in the stability of a 5α-bromo-6β-hydroxy steroid under acidic and basic conditions and the synthesis of the 19-oxygenated steroids **16**, **28**, and **29** through the bromohydrin **3**.

Experimental

General methods

Melting points were measured on a Yanagimoto melting point apparatus (Kyoto, Japan) and are uncorrected. Unless otherwise noted, infrared (IR) spectra were recorded in KBr pellets on a Perkin-Elmer FT-IR 1725X spectrometer (Norwalk, Connecticut, USA) and UV spectra in a 95% ethanol solution on a Hitachi 150-20 spectrophotometer (Tokyo, Japan). ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution with a JEOL GX 270 (270 MHz for ^1H and 67.9 MHz for ^{13}C) spectrometer (Tokyo, Japan) using tetramethylsilane (δ 0.00) as an internal standard, and mass spectra (MS; electron impact) were obtained with a JEOL JMS-DX 303 spectrometer. Thin-layer chromatography (TLC) was performed using precoated plates (silica gel 60F-254, layer thickness 0.25 or 0.5 mm for analytical or preparative use, respectively; E. Merck, Darmstadt, Germany). Column chromatography was conducted on silica gel 60, 70-230, or 230–400 mesh (flash chromatography; E. Merck).

Reaction of androst-5-en-17-one 1 with *N*-bromoacetamide (NBA) in the presence of $HClO_4$ in dioxane. *Method A.* NBA (830 mg; 6.0 mmol) was added to a solution of compound **1** (1.03 g, 2.8 mmol) in dioxane (18 mL) containing 0.28 M $HClO_4$ (0.7 mL; 0.2 mmol), and the mixture was stirred at room temperature

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for 30 min in the dark. After this time, the mixture was poured into ice-water, the precipitates were collected by filtration, washed well with water, dried under vacuum, and triturated with EtOAc, giving a solid material, which was recrystallized from acetone to yield 5α-bromo-6β-hydroxyandrost-17-one **3** (602 mg, 43%). M.p. 121–124°C; IR 3532 (OH) and 1732 (C=O) cm^{-1}; ^1H NMR δ 0.88 (3H, s, 18-Me), 1.30 (3H, s, 19-Me), and 4.25 (1H, t, *J* 2.8 Hz, 6α-H); ^{13}C NMR δ 13.9, 17.9, 20.2, 20.3, 21.6, 22.5, 30.3, 31.4, 33.3, 34.0, 35.5, 35.8, 41.0, 47.8, 48.2, 50.9, 75.8, 90.9 and 221.0; MS (*m/z*) (relat. int.) 288 (M^+-81; 35%), 270 (100), 255 (25) and 233 (15). Analysis calculated for $C_{19}H_{29}O_2 \cdot \frac{1}{2}H_2O$: C, 60.32; H, 7.99. Found: C, 60.34; H, 8.06.

Method B. A mixture of compound **1** (520 mg; 1.9 mmol), NBA (414 mg; 3.0 mmol), 0.28 M $HClO_4$ (0.35 mL; 0.1 mmol), and dioxane (9 mL) was stirred at room temperature for 60 min in the dark. Subsequently, the mixture was diluted with EtOAc (200 mL), washed sequentially with chilled 5% $Na_2S_2O_3$, 5% $NaHCO_3$, and ice-water, dried (Na_2SO_4), and evaporated under reduced pressure below 40°C to give an oily residue. Flash chromatography (hexane-EtOAc; 3:1) of the residue afforded the following eight products in addition to the bromohydrin **3** (208 mg; 30%). 5α,6α-Epoxyandrostan-17-one **5** (28 mg; 5%); m.p. 130–134°C (from acetone) (lit.[6] 140–143°C); ^1H NMR δ 0.82 (3H; s; 18-Me), 1.07 (3H; s; 19-Me), and 2.93 (1H, d, *J* 4.3 Hz, 6β-H). 5β,6β-Epoxyandrostan-17-one **6** (82 mg; 15%); m.p. 108–110°C (from EtOH; lit.[6] 113–115°C); ^1H NMR δ 0.85 (3H; s; 18-Me), 1.01 (3H; s; 19-Me), and 3.08 (1H, d, *J* 2.6 Hz, 6α-H). 6α-Bromo-5β-hydroxyandrost-17-one **8** (54 mg, 8%); m.p. 190–193°C (from acetone) IR 3539 (OH) and 1732 (C=O) cm^{-1}; ^1H NMR δ 0.86 (3H, s, 18-Me), 0.98 (3H, s, 19-Me), 4.69 (1H, dd, *J* 4.8 and 12.7 Hz, 6β-H); MS (*m/z*) (relat. int.) 288 (M^+-81, 100%), 270 (45), 255 (20), 244 (65). Analysis calculated for $C_{19}H_{29}O_2Br$: C, 61.79; H, 7.91. Found: C, 61.84; H, 7.95. 5α-Hydroxyandrosta-6,17-dione **9** (36 mg, 6%); m.p. 215–217°C (from AcOEt); IR 3425 (OH) and 1700 and 1739 (C=O) cm^{-1}; ^1H NMR δ 0.81 (3H, s, 18-Me), 0.86 (3H, s, 19-Me), 2.87 (1H, t, *J* 12.3 Hz, 7β-H); ^{13}C NMR δ 13.7, 13.8, 19.8, 20.2, 20.3, 21.5, 26.8, 30.5, 31.2, 35.6, 36.8, 40.9, 42.9, 45.1, 48.2, 51.4, 79.0, 212.3 and 220.2; MS (*m/z*) (relat. int.) 304 (M^+; 100%), 286 (25), 271 (12) and 243 (10). Analysis calculated for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.18; H 9.32. 5α,6β-Dihydroxyandrost-17-one **10** (10 mg, 2%); m.p. 232–235°C (from acetone); IR 3508 and 3387 (OH) and 1723 (C=O) cm^{-1}; ^1H NMR δ 0.88 (3H, s, 18-Me), 1.18 (3H, s, 19-Me), 3.56 (1H, s, 6α-H); ^{13}C NMR δ 13.9, 16.5, 20.0, 20.4, 20.6, 21.7, 30.0, 31.2, 31.6, 33.4, 33.6, 35.8, 39.0, 46.1, 47.9, 51.1, 74.0, 75.9 and 221.3. Analysis calculated for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.63; H, 9.75. 5α-Bromo-6β-acetoxyandrost-17-one **12** (40 mg; 5%); m.p. 145–148°C (from MeOH); IR 1738 (C=O) cm^{-1}; ^1H NMR δ 0.89 (3H, s, 18-Me), 1.26 (3H, s, 19-Me), 2.10 (3H, s, 6β-OCOMe), and 5.40 (1H, dd, *J* 2.1 and 3.6 Hz, 6α-H). Analysis calculated for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.60. Found: C, 61.55; H, 7.62. 5α,6β-Dibromoandrost-17-one **13** (86 mg; 10%); m.p. 119–121°C (from acetone) (lit.[7] 118–120°C); ^1H NMR δ 0.92 (3H, s, 18-Me), 1.44 (3H, s, 19-Me), and 4.91 (1H, dd, *J* 1.7 and 4.2 Hz, 6α-H). 5β,6α-Dibromoandrost-17-one **14** (10 mg; 1%); m.p. 173–176°C (from acetone) (lit.[7] m.p. 171–173°C); ^1H NMR δ 0.86 (3H, s, 18-Me), 1.21 (3H, s, 19-Me) and 5.01 (1 H, dd, *J* 5.0 and 12.4 Hz, 6β-H).

Treatment of the bromohydrin 8 with NaOH. A mixture of compound **8** (19 mg; 0.051 mmol), 1 M NaOH (1 mL; 1 mmol), and MeOH (4 mL) was allowed to stand overnight at 60°C under a N_2 atmosphere. The mixture was diluted with EtOAc (100 mL), washed sequentially with 5% HCl, 5% $NaHCO_3$, and water, and dried (Na_2SO_4). Evaporation of the solvent gave the crude β-epoxide **6**, which was recrystallized from EtOH to yield compound **6** (10 mg; 69%), m.p. 107–109°C. This compound was identical to the authentic sample obtained above.

Acetylation of the bromohydrin 3. Compound **3** (20 mg, 0.054 mmol) was dissolved in pyridine (0.2 mL) and acetic anhydride (0.1 mL), and the mixture was allowed to stand at room temperature overnight. After the usual treatment, the crude product obtained was recrystallized from MeOH to produce the 6β-acetate **12** (18 mg; 80%), m.p. 147–149°C. This compound was identical to compound **12** produced by the reaction of compound **1** with the NBA-$HClO_4$ system.

^1H NMR analysis of the reaction of compound 1 and its 3β-acetoxy analog 2 with the NBA-$HClO_4$ system. A solution of the 5-ene steroids **1** and **2** (0.092 mmol) and NBA (20 mg; 145 μmol) in dioxane (1.2 mL) containing 0.28 M $HClO_4$ (0.05 mL) was separately stirred at 10°C. After 5, 10, 15, 25, and 35 min, 0.2 mL portions of the reaction mixture was transferred to EtOAc (30 mL), washed sequentially with 5% $Na_2S_2O_3$, 5% $NaHCO_3$, and water, and then dried (Na_2SO_4). After evaporation of the solvent below 40°C, the residue was subjected to ^1H NMR analysis. The relative peak heights of the 19-methyl angular methyl protons of the remaining substrate were determined (δ 1.02 for **1** or δ 1.05 for **2**) and compared to those of the main products: the bromohydrin (δ 0.88 for **3** or δ 0.89 for **4**), the β-epoxide (δ 1.01 for **6** or δ 1.04 for **7**), and the diol (δ 1.18 for **10** or δ 1.21 for **11**).

^1H NMR analysis of reaction of the bromohydrins 3 and 4 with $HClO_4$ and $KHCO_3$. *(A) $HClO_4$.* $HClO_4$ (0.3 mL, 0.28 M, 0.084 mmol) was separately added to solutions of compounds **3** and **4** (0.080 mmol) in dioxane (1.5 mL), and each mixture was stirred at room temperature. After 1.5, 3, 5, and 8 h, 0.2 mL portions of the reaction mixture were diluted with EtOAc (30 mL), washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was subjected to ^1H NMR analysis. The relative peak height of the 6α-proton of the substrates (δ 4.25 for **3** and 4.24 for **4**) were compared to those of the 6α-protons of the products: the epoxide (δ 3.08 for **6** and δ 3.15 for **7**) and the diol (δ 3.56 for **10** and δ 3.70 for **11**).

(B) $KHCO_3$. $KHCO_3$ (9.8 mg, 0.097 mmol) was separately added to solutions of compounds **3** and **4** (0.081 mmol), and the reaction mixtures were stirred at room temperature. After 5, 15, 25, 35, and 40 min, 0.8 mL portions of the mixture were diluted with EtOAc (30 mL), washed with water, and dried (Na_2SO_4). The relative amounts of the substrates remaining were determined based on ^1H NMR analysis as described in the $HClO_4$ treatment.

5α-Bromo-6β,19-epoxyandrostan-17-one 15. A mixture of lead (IV) acetic acid (528 mg, 1.19 mmol), calcium carbonate (247 mg; 2.47 mmol), and cyclohexane (60 mL) was heated under reflux for 10 min with irradiation by a 500 W-tungsten lamp; compound **3** (127 mg; 0.34 mmol) and iodine (149 mg; 0.59 mmol) were then added simultaneously. The reaction was carried out under reflux for 1 h. The mixture was then filtered through a bed of celite, which was washed with EtOAc. The filtrate was sequentially washed with 10% $Na_2S_2O_3$, 5% $NaHCO_3$, and water, and then dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by silica gel column chromatography (hexane-EtOAc, 10:1), and subsequent recrystallization from acetone yielded the title compound **15** (80 mg, 63%). M.p. 179–181°C; IR 1730 (C=O) cm^{-1}; ^1H NMR δ 0.91 (3H, s, 18-Me), 3.71 and 3.96 (1H each, d, *J* 8.3 Hz, 19-CH_2) and 4.09 (1H, d, *J* 4.3 Hz, 6α-H); ^{13}C NMR δ 14.2, 21.1, 21.3, 21.4, 21.6, 23.7, 31.4, 32.3, 33.1, 35.7, 36.7, 46.4, 48.2, 49.3, 49.6, 67.7, 76.8, 82.0, and 220.3. Analysis calculated for $C_{19}H_{27}O_2Br$: C, 62.13; H, 7.37. Found: C, 62.35; H, 7.47.

19-Hydroxyandrost-5-en-17-one 16. Compound **15** (70 mg; 0.19 mmol) in 5 mL of EtOH was treated with zinc dust (220 mg, freshly activated by washing with 5% HCl several times, followed by water, and then dried under reduced pressure) under reflux with stirring for 4 h. The suspension was filtered, and the residue was washed with EtOH. Removal of the solvent from the combined filtrates afforded a solid, which was dissolved in EtOAc (100 mL), washed with water, dried (Na_2SO_4), and evaporated to give a solid. Recrystallization of the crude product from acetone-hexane gave the title compound **16** (40 mg, 71%). M.p. 121–124°C (lit.[1] m.p. 120–124°C); ^{1}H NMR δ 0.94 (3H, s, 18-Me), 3.59 and 3.89 (1H each, d, *J* 11.2 Hz, 19-CH_2) and 5.72 (1H, m, 6-H).

19-Acetoxyandrost-5-en-17-one 17. Compound **16** (200 mg, 0.69 mmol) was dissolved in pyridine (2 mL) and acetic anhydride (1 mL), and the solution was allowed to stand at room temperature overnight. After addition of MeOH (1 mL), the reaction mixture was diluted with EtOAc (100 mL), washed sequentially with 5% HCl, 8% $NaHCO_3$, and water, and then dried (Na_2SO_4). Evaporation of the solvent afforded an oil, which was purified by silica gel column chromatography (hexane-EtOAc; 6:1) to yield the title compound **17** as an oil; IR (neat) 1741 (C=O) cm^{-1}; ^{1}H NMR δ 0.90 (3H, s, 18-Me), 2.05 (3H, s, 19-OCOMe), 3.96 and 4.56 (1H each, d, *J* 11.9 Hz, 19-CH_2), and 5.56 (1H, m, 6-H); MS (*m/z*) (relat. int.) 330 (M^+, 1%), 270 (95), 257 (100) and 239 (35). Exact mass found: 330.2231; calculated for $C_{21}H_{30}O_3$: 330.2195.

Androst-5-ene-17,19-dione 18. Pyridinium dichromate oxidation of compound **16** (20 mg, 0.07 mmol), according to the method[1] previously reported, produced the title compound **18** (10 mg, 50%), m.p. 101–103°C (from acetone) (lit.[1] m.p. 100–103°C).

5α-Bromoandrosta-6,17-dione 19. Jones reagent was added dropwise with stirring at 0°C to a solution of compound **3** (33 mg, 0.089 mmol) in acetone (20 mL) until there was a permanent orange color, and the mixture was further stirred at 0°C for 3 min; excess reagent was then destroyed by adding MeOH (0.2 mL). After evaporation of the solvent, the residue was dissolved in EtOAc (100 mL), washed with 5% $NaHCO_3$ and water, and then dried (Na_2SO_4). Evaporation of the solvent gave a solid product, which was recrystallized from acetone to yield the title compound **19** (22 mg, 67%). M.p. 146–149°C; IR 1710 and 1736 (C=O) cm^{-1}; ^{1}H NMR δ 0.86 (3H, s, 18-Me), 0.97 (3H, s, 19-Me), 3.27 and 3.32 (2H, d, *J* 12.0 Hz, 7-H); ^{13}C NMR δ 13.8, 14.4, 20.0, 20.6, 21.3, 21.4, 29.6, 30.7, 31.0, 35.6, 35.7, 39.9, 43.1, 47.9, 48.0, 51.3, 83.1, 204.5, and 219.7. Analysis calculated for $C_{19}H_{27}O_2Br$: C, 62.12; H, 7.41. Found: C, 61.88; H, 7.31.

Androst-4-ene-6,17-dione 20. Compound **19** (18 mg; 0.049 mmol) was dissolved in *N,N*-dimethylacetamide (0.7 mL), and calcium carbonate (16 mg; 0.16 mmol) was added to this solution. The mixture was heated under reflux for 1 h and then diluted with EtOAc (50 mL), washed sequentially with 5% HCl, 5% $NaHCO_3$, and water, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by preparative TLC (hexane-EtOAc, 2:1), followed by recrystallization from acetone to give the title compound **20** (8 mg, 56%). M.p. 188–190°C (lit.[2] m.p. 189–191°C); IR 1682 and 1730 (C=O) cm^{-1}; ^{1}H NMR δ 0.92 (3H, s, 18-Me), 1.00 (3H, s, 19-Me), and 6.45 (1H, m, 4-H).

6α-Bromo-5β-hydroxy-19-acetoxyandrost-17-one 21. Compound **17** (100 mg, 0.30 mmol) was dissolved in dioxane (1.7 mL), and NBA (70 mg; 0.51 mmol) and 0.28 M $HClO_4$ (0.05 mL) were added to this solution. The mixture was stirred at room temperature for 40 min in the dark and then poured into water. The product was extracted with EtOAc (100 mL). The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oily product, which was purified by column chromatography (hexane-EtOAc, 5:1) followed by recrystallization from EtOAc to yield the title compound **21** (98 mg, 76%). M.p. 113–115°C; IR 1737 (C=O) cm^{-1}; ^{1}H NMR δ 0.84 (3H, s, 18-Me), 2.09 (3H, s, 19-OCOMe), 4.28 and 4.36 (1H each, d, *J* 11.9 Hz, 19-CH_2), 4.82 (1H, dd, *J* 4.8 and 13.0 Hz, 6β-H). Analysis calculated for $C_{21}H_{31}O_4Br$: C, 59.01; H, 7.31. Found: C, 58.74; H, 7.15.

19-Hydroxy-5β, 6β-epoxyandrost-17-one 22. A mixture of compound **21** (100 mg, 0.23 mmol), K_2CO_3 (66 mg, 0.48 mmol), MeOH (5 mL), and water (2 mL) was allowed to stand at room temperature for 2.5 h, and then diluted with EtOAc (200 mL), washed with water, and dried (Na_2SO_4). Evaporation of the solvent afforded an oil, which was purified by column chromatography (hexane-EtOAc, 4:1) followed by recrystallization from acetone-hexane to give the title compound **22** (41 mg, 58%). M.p. 90–93°C; IR 1736 (C=O) cm^{-1}; ^{1}H NMR δ 0.92 (3H, s, 18-Me), 3.07 (1H, d, *J* 2.3 Hz, 6α-H), 3.14 and 4.26 (1H each, d, *J* 12.0 Hz, 19-CH_2), and 3.55 (1H, t, *J* 11.4 Hz, 8β-H); MS (*m/z*) (relat. int.) 304 (M^+, 10%), 286 (60), 274 (75), 256 (100). Analysis calculated for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.10; H, 9.06.

Epoxydation of the 19-acetoxy-5-ene steroid 17 with *m*-chloroperbenzoic acid (MCPBA). MCPBA (306 mg, 1.77

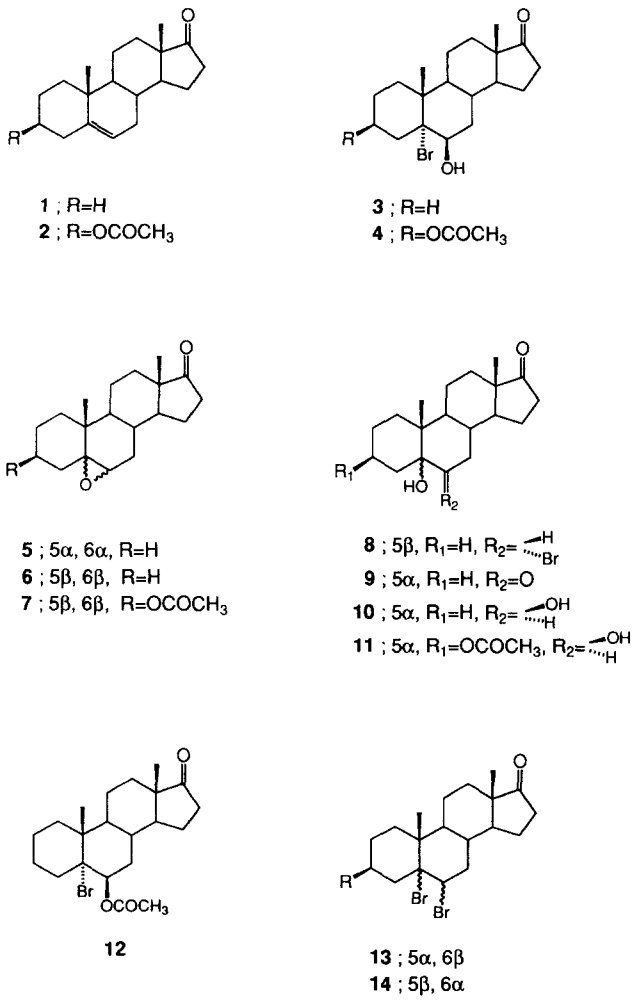

Figure 1 Structures of starting materials and products of the HOBr addition reaction.

mmol) was added to a solution of compound **17** (343 mg, 1.04 mmol) in CH_2Cl_2 (9.3 mL). The reaction mixture was allowed to stand at 4°C overnight, and was subsequently diluted with EtOAc (200 mL), washed sequentially with 5% $Na_2S_2O_3$, 5% $NaHCO_3$, and water, and dried (Na_2SO_4). After evaporation of the solvent, the resulting oily residue was subjected to column chromatography (hexane-EtOAc, 6:1), yielding about a 3:2 mixture of 19-acetoxy-5α,6α-epoxyandrost-17-one and its 5β, 6β-epoxy isomer, **23**, based on ^{1}H NMR spectroscopy: the 5α, 6α-epoxide, ^{1}H NMR δ 0.81 (3H, s, 18-Me), 2.98 (1H, d, *J* 2.0 Hz, 6β-H), and 4.02 and 4.46 (2H, d, *J* 12.2 Hz, 19-CH_2); and the 5β, 6β-epoxide, ^{1}H NMR δ 0.88 (3H, s, 18-Me), 3.02 (1H, d, *J* 4.0 Hz, 6α-H), 4.31 and 4.61 (2H, d, *J* 12.2 Hz, 19-CH_2).

Hydrolysis of the 5,6-epoxides 23 with $HClO_4$. A mixture of the epoxides **23** (230 mg, 0.66 mmol), 0.28 M $HClO_4$ (2.5 mL, 0.70 mmol), and dioxane (12.4 mL) was stirred at room temperature for 15 h. After this time, the mixture was diluted with EtOAc (200 mL), washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by column chromatography (hexane-EtOAc, 3:1) to yield the following two compounds. 5α, 6β-Dihydroxy-19-acetoxyandrost-17-one **24** (76 mg, 31%), semi-solid; IR 3492 (OH) and 1731 (C=O) cm^{-1}; ^{1}H NMR δ 0.88 (3H, s, 18-Me), 2.06 (3H, s, 19-OCOMe), 3.55 (1H, d, *J* 2.8 Hz, 6α-H), 4.49 and 4.67 (1H each, d, *J* 12.9 Hz, 19-CH_2); MS (*m/z*) (relat. int.) 364 (M^+, 5%), 346 (25), 304 (50), 286 (45), 273 (65) and 255 (100). Exact mass found: 364.2230; calculated for $C_{21}H_{32}O_5$: 364.2250. 5β, 6α-Dihydroxy-19-acetoxyandrost-17-one **25** (110 mg, 45%), semi-solid; IR 3465 and 3488 (OH) and 1736 (C=O) cm^{-1}; ^{1}H NMR δ 0.86 (3H, s, 18-Me), 2.09 (3H, s, 19-OCOMe), 3.97 (1H, dd, *J* 4.8 and 12.2 Hz, 6β-H) and 4.31 (2H, s, 19-CH_2); MS (*m/z*) (relat. int.) 364 (M^+, 5%), 346 (10), 304 (10), 286 (30) and 273 (100). Exact mass found: 364.2236; calculated for $C_{21}H_{32}O_5$: 364.2250.

5α-Hydroxy-19-acetoxyandrosta-6,17-dione 26. *N*-Bromosuccinimide (NBS) (140 mg, 0.79 mmol) and acetic acid (0.087 mL) were added to a solution of compound **24** (150 mg, 0.41 mmol) in acetone (6.9 mL) and water (0.9 mL), and the reaction mixture was stirred at room temperature for 1.8 h. After dilution with EtOAc (200 mL), the mixture was washed sequentially with 5% $Na_2S_2O_3$, 5% $NaHCO_3$, and water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by column chromatography (hexane-EtOAc, 2:1) to yield the title compound **26** (130 mg, 87%) as an oil; IR (neat) 1738 (C=O) cm^{-1}; ^{1}H NMR δ 0.87 (3H, s, 18-Me), 1.99 (3H, s, 19-OCOMe), 4.09 and 4.37 (1H, d, *J* 12.3 Hz, 19-CH_2); MS (*m/z*) (relat. int.) 362 (M^+, 100%), 344 (10), 302 (20), 284 (25) and 273 (65). Exact mass found: 362.2124; calculated for $C_{21}H_{30}O_5$: 362.2093.

19-Acetoxyandrost-4-ene-6,17-dione 27. Compound **26** (180 mg, 0.50 mmol) was dissolved in dry pyridine, and $SOCl_2$ (0.31 mL, 4.2 μmol) was added to this solution at 0°C. The mixture was stirred at 0°C for 50 min and then poured into water and extracted with EtOAc (100 mL × 2). The combined organic layer was washed sequentially with 10% HCl, 5% $NaHCO_3$, and water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by column chromatography to give the title compound **27** as an oil; UV 233 nm (ε = 4800); ^{1}H NMR δ 0.92 (3H, s, 18-Me), 1.99 (3H, s, 19-OCOMe), 4.11 and 4.18 (1H each, d, *J* 11.6 Hz, 19-CH_2), and 6.62 (1H, dd, *J* 3.1 and 4.7 Hz, 4-H); MS (*m/z*) (relat. int.) 344 (M^+, 40%), 284 (50) and 271 (100). Exact mass found: 344.1978; calculated for $C_{21}H_{28}O_4$: 344.1988.

19-Hydroxyandrost-4-ene-6,17-dione 28. K_2CO_3 (60 mg, 0.43 mmol) was added to a solution of compound **27** (120 mg, 0.35 mmol) in MeOH (8 mL) and water (4 mL), and the mixture was stirred at room temperature for 7 h. After this time, the reaction mixture was neutralized by adding acetic acid, concentrated to about 4 mL, diluted with EtOAc (100 mL), washed with water, and dried (Na_2SO_4). Evaporation of the solvent afforded an oily residue, which was purified by column chromatography (hexane-EtOAc, 2:1) followed by recrystallization to give the title compound **28** (72 mg, 68%). M.p. 188–190°C; IR 3532 (OH) and 1687 and 1737 (C=O) cm^{-1}; UV 238 nm (ε = 6700); ^{1}H NMR δ 0.96 (3H, s, 18-Me), 3.60 and 3.82 (1H each, d, *J* 11.3 Hz, 19-CH_2), and

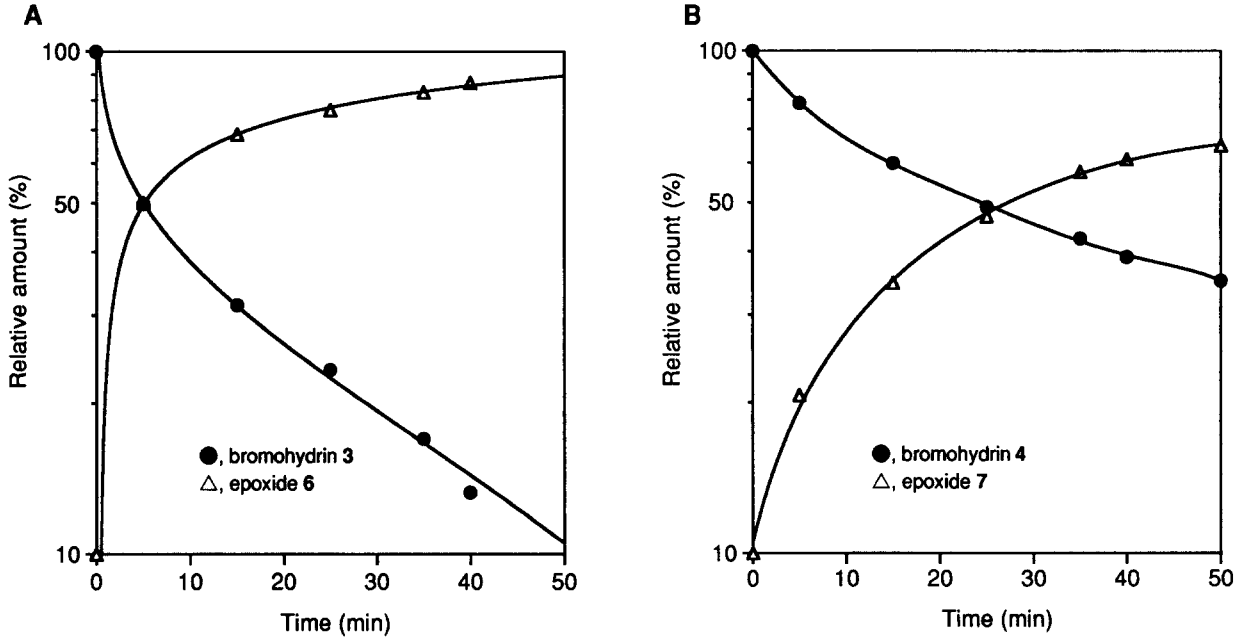

Figure 2 Time course for the reaction of bromohydrin **3** or **4** with $KHCO_3$ in methanol.

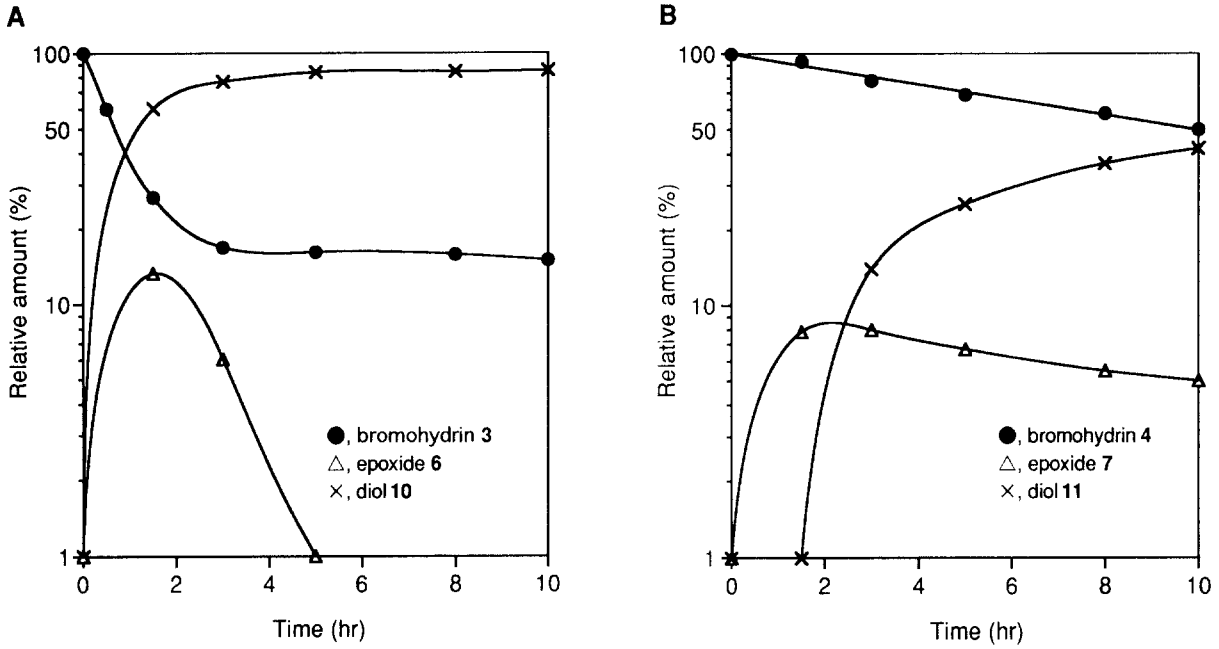

Figure 3 Time course for the reaction of bromohydrin **3** or **4** with $HClO_4$ in aqueous dioxane.

6.61 (1H, t, *J* 3.7 Hz, 4-H). Analysis calculated for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.41; H, 8.85.

Androst-4-ene-6,17,19-trione 29. Pyridinium dichromate (125 mg, 0.33 mmol) was added to a solution of compound **28** (72 mg, 0.24 mmol) in CH_2Cl_2 (4.7 mL), and the mixture was stirred at room temperature for 3 h. After this time, the solid material was removed by filtration, and the filtrate was diluted with EtOAc (100 mL), washed with a 5% $NaHCO_3$ and water, and dried (Na_2SO_4). After evaporation of the solvent, the residue obtained was purified by column chromatography (hexane-EtOAc, 1:1) followed by recrystallization from acetone to yield the title compound **29** (40 mg, 56%). M.p. 171–174°C; IR 1686, 1713 and 1733 (C=O) cm^{-1}; UV 242 nm (ε = 5500); ^1H NMR δ 0.85 (3H, s, 18-Me), 6.86 (1H, t, *J* 3.5 Hz, 4-H), and 9.78 (1H, s, 19-H). Analysis calculated for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.93; H, 8.30.

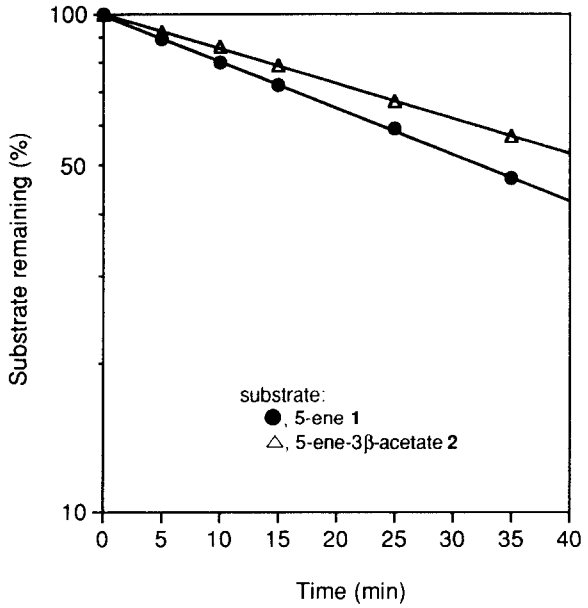

Figure 4 Disappearance of 5-ene steroid **1** or **2** in the reaction with NBA in the presence of $HClO_4$ in aqueous dioxane.

Results and discussion

Monitoring the course of the HOBr addition reaction of the olefin **1** with TLC revealed that compound **1** disappeared from the reaction mixture within 30 min and was accompanied by the formation of 5α-bromo-6β-ol **3** as the main product. Elongation of the reaction time increased the formation of artifacts. On the basis of these results, the reaction mixture was poured into a chilled water at the 30 min time point. The precipitates were collected by filtration, dried under vacuum, triturated with ethyl acetate, and recrystallized to give the desired bromohydrin **3** in 43% yield. On the other hand, the products obtained from the reaction mixture after 60 min of reaction time were purified by flash silica gel column chromatography to afford compound **3** in 30% yield in addition to 5α,6α- and 5β,6β-epoxides **5** (5%) and **6** (15%), 6α-bromo-5β-ol **8** (8%), 5α-hydroxy-6-one **9** (6%), 5α,6β-diol **10** (2%), 5α-bromo-6β-acetate **12** (5%), and 5α,6β- and 5β,6α-dibromides **13** (10%) and **14** (1%), which were isolated as by-products or artifacts, as previously seen in the reaction of other 5-ene steroids[8] (Figure 1). The spectral data of these compounds were consistent with the assigned structures. The epoxides **5** and **6**[6] and the dibromides **13** and **14**[7] were identical with the corresponding authentic samples previously synthesized. Treatment of the bromohydrin **8** with NaOH yielded the 5β,6β-epoxides **6** in a good yield. Hydrolysis of steroid **6** with $HClO_4$ gave the *trans*-diaxial diol **10** from which Jones oxidation produced the 5α-ketol **9**. Acetylation of the bromohydrin **3**

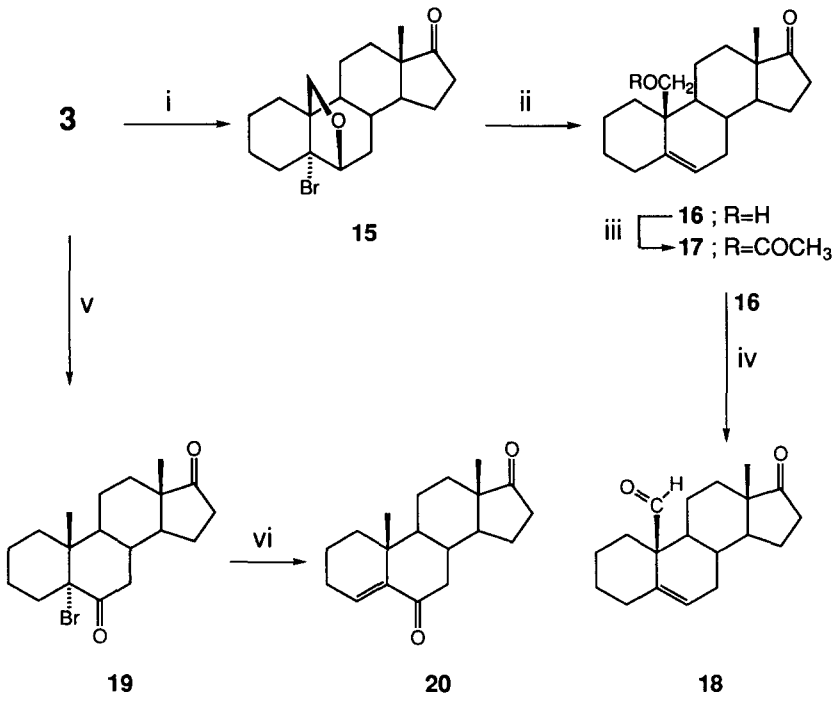

Figure 5 Synthesis of 4-en-6-one steroids **20** and 19-oxygenated 5-ene steroids **16** and **18**. Reagents and conditions: i, $Pb(OCOCH_3)_4$, I_2, $CaCO_3$, cyclohexane, hv, reflux; ii, Zn powder, EtOH, reflux; iii, $(CH_3CO)_2O$, pyridine; iv, pyridinium dichromate, CH_2Cl_2; v, Jones reagent, acetone; vi, $CaCO_3$, DMA.

gave the 6β-acetate **12**. These chemical reactions also supported the assigned structures of the products **3, 6**, and **8**.

The reactivity of the bromohydrin **3** towards $KHCO_3$ or $HClO_4$ was then compared with that of its 3-acetoxy analog **4**. Treatment of compounds **3** and **4** with a 1.5 mol equivalent of $KHCO_3$ in MeOH at room temperature gave the corresponding 5β,6β-epoxides **6** and **7** as the sole products. On the basis of the ^1H NMR analysis (6α-H: δ 4.25 and 4.24 for **3** and **4**, and δ 3.08 and 3.15 for **6** and **7**, respectively) of the reaction, bromohydrins **3** and **4** disappeared from the reaction mixture with $t_{1/2}$ of 5 min and 23 min, respectively (Figure 2). On the other hand, reaction of bromohydrins **3** and **4** with 0.28 M $HClO_4$ in aqueous dioxane at room temperature initially produced the corresponding 5β,6β-epoxides **6** and **7**, which were subsequently hydrolyzed with acid, giving the 5α,6β-diols **10** and **11**, respectively, as the final products (Figure 3). ^1H NMR analysis (6α-H: δ 3.56 and 3.70 for **10** and **11**, respectively) of the reaction revealed that substrates **3** and **4** disappeared from the reaction mixture with $t_{1/2}$ of 40 min and 10 h, respectively.

These results clearly indicate that there is a significant neighboring group participation in the acid- or base-catalyzed conversion of a 5α-bromo-6β-hydroxy steroid to the 5β,6β-epoxy derivative; the 3β-acetoxy function markedly decreases the conversion rate. The relatively lower yield of bromohydrin **3**, which has no oxygen function at C-3, in the HOBr addition reaction of compound **1** appears to be due to its easier conversion to epoxide **6**. Thus, neutralization of the reaction mixture with a weak base such as $NaHCO_3$ during the isolation procedure should be carried out carefully.

To further investigate neighboring group participation, the HOBr addition reaction of 3-deoxy steroid **1** was then compared to that of its 3-acetoxy analog **2**. The remaining amounts of substrates **1** and **2** in the addition reaction, which was carried out at 10°C, were determined by ^1H NMR analysis of signals of the 19-methyl groups of the substrates and the products [δ: 1.02 and 1.05 for **1** and **2**, δ 0.88 and 0.89 for the bromohydrins **3** and **4**, δ 1.01 and 1.04 for the β-epoxides **6** and **7**] in each case. The half-lives for the substrates were found to be 30 min for **1** and 43 min for **2** (Figure 4). This indicates that the 3β-acetoxy function slightly decreases the addition reaction and is analogous to the epoxide formation described above.

Using bromohydrin **3** as a starting material, the 5-en-19-ol **16** and its 19-oxo derivative **18** were synthesized through a reaction sequence involving the hypoiodite reaction as a key step[3] (Figure 5). In addition, Jones oxidation of the 6β-ol **3**, followed by dehydrobromination in *N,N*-dimethylacetamide,[9] gave the 4-en-6-one compound **20**, a potent aromatase inhibitor. These reaction sequences are shorter than those previously reported for the synthesis of the 5-ene steroids[1] and the enone,[10] respectively, and their total yields from 3β-hydroxyandrost-5-en-17-one are higher than the corresponding reported ones.[1,10]

Addition of HOBr to a double bond at C-5 of 19-acetate **17** did not give rise to the diaxial 5α-bromo-6β-ol but produced the diequatorial bromohydrin **21** in high yield (Figure 6), as seen previously in the addition reaction of 19-acetoxy-3-deoxycholesterol,[4] which involves a 6 $(0)^{\pi,n}$ participation.[11] The above-mentioned reaction was highly regio- and stereo-selective, and spectral data were consistent with the assigned structure. Treatment of compound **21** with NaOH produced the 5β,6β-epoxy derivative **22**, (^1H NMR δ 3.07 for 6α-H), supporting the assigned structure of bromohydrin **21**.

19-Oxygenated androst-4-en-6-ones **28** and **29** were then synthesized through a different sequence from that used for the synthesis of the 19-oxygenated 5-ene analogs **16** and **18**. The alternate path involved epoxydation of the olefin **17**

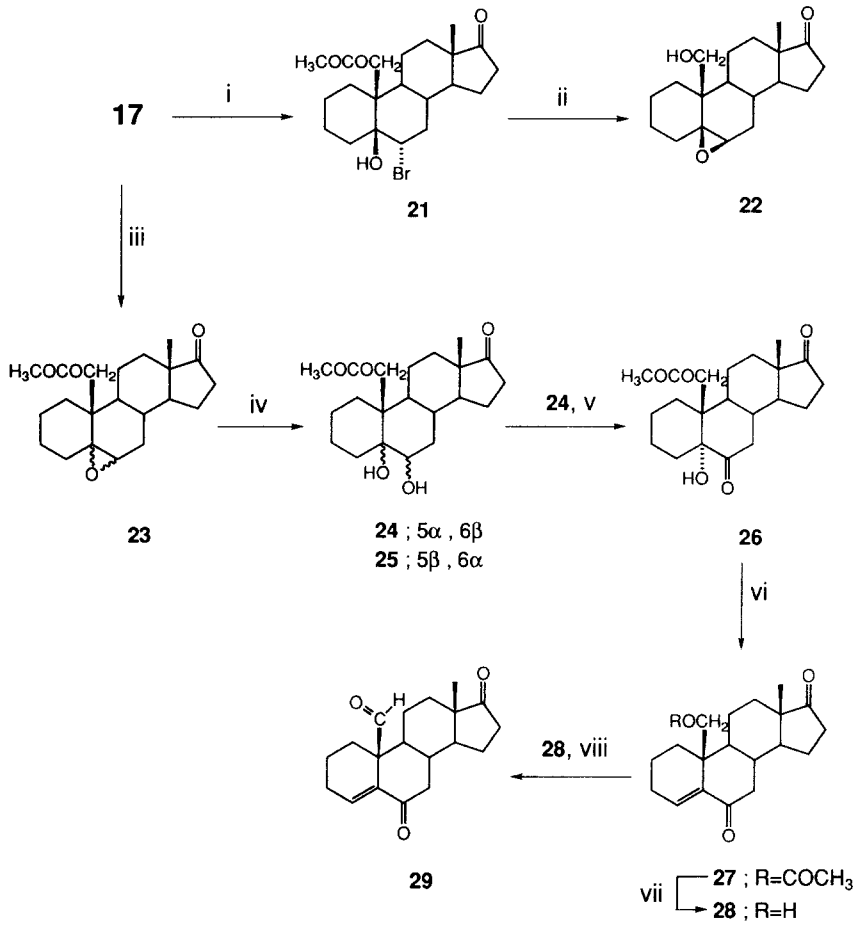

Figure 6 Synthesis of 19-oxygenated 4-en-6-one steroids **28** and **29**. Reagents and conditions: i, NBA, 0.28 M $HClO_4$, dioxane; ii, K_2CO_3, MeOH; iii, MCPBA, CH_2Cl_2; iv, 0.28 M $HClO_4$, dioxane; v, NBS, acetic acid, acetone; vi, $SOCl_2$, pyridine; vii, K_2CO_3, MeOH, viii, pyridinium dichromate, CH_2Cl_2.

as a key reaction. Treatment of steroid **17** with *m*-chloroperbenzoic acid yielded about a 3:2 mixture of α- and β-epoxides, **23** (90%), which, without isolation, was subjected to hydrolysis with aqueous $HClO_4$ to produce about a 2:3 mixture of diols **24** and **25**, which were separated from each other by silica gel column chromatography. It has previously been reported that treatment of 19-acetoxycholestan-5α,6α-epoxide with aqueous $HClO_4$ produces predominantly the *trans*-diequatorial diol, the 5β, 6α-diol compound, along with the *trans*-diaxial 5α,6β-diol analog in a ratio of 96:4, and the participation of the neighboring 19-acetoxy group, the $6(0)^{\pi,n}$ process is known to be involved.[12] When the acetate of the 5β,6β-epoxy-19-ol **22**, which was obtained by treatment of compound **22** with acetic anhydride and pyridine, was treated with aqueous $HClO_4$, the 5α, 6β-diol **24** was obtained as a sole product. Taken together, it is obvious that a similar $6(0)^{\pi,n}$ process is also involved in the hydrolysis of the α-epoxide **23**.

The 5α,6β-diol **24** was oxidized with NBS to yield ketol **26** from which dehydration with $SOCl_2$ and subsequent deprotection of the 19-acetoxy group gave another desired compound, 19-hydroxy-4-en-6-one **28** in 41% yield from the diol. The 19-ol **28** was then converted into the 19-oxo derivative **29** by treatment with pyridinium dichromate. The structures of compounds **28** and **29** were assigned based on the spectral data and elemental analysis.

Aspects of neighboring group participation of the 3β-acetoxy group in the dehydrobromination of the 5α-bromo-6β-ol **3** under acidic and basic conditions as well as in the electrophilic addition of HOBr to a double bond at C-5 of androst-5-en-17-one (**1**) were established in this study. On the basis of these results, the 5α-bromo-6β-ol **3** was obtained for the first time by the HOBr addition reaction. Starting from bromohydrin **3**, the 19-oxygenated compounds **16, 18, 28**, and **29**, which are valuable for understanding the catalytic function of aromatase, were conveniently synthesized.

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