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Steroids

The effect of 4β and 19 ester functionalities on some electrophilic addition reactions of Δ^5-steroids

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Abstract

The reactions of 3β-acyloxyandrost-5-enes with bromine/silver acetate (Petrow reaction) and mercury(II) trifluoroacetate (modified Treibs oxidation) have been used previously to effect allylic oxidation on these substrates en route to biologically active compounds. In both these reactions, which involve electrophilic addition to the Δ^5-bond, the 3-acyloxy substituent plays a significant role. In this report, the effect of introducing other substituents proximate to the Δ^5-bond has been studied by using derivatives of 3β-acetoxyandrost-5-en-17-one (**1**), namely, 3β,4β-diacetoxyandrost-5-en-17-one (**13**), 3β,19-diacetoxyandrost-5-en-17-one (**14**), 3β-acetoxyandrost-5-ene-7,17-dione (**15**), and 3β-acetoxy-4,4-dimethylandrost-5-en-17-one (**17**). Our results indicate that in both sets of reactions the effect of the introduced functional groups was pronounced. In the Petrow reaction, electrophilic addition rather than allylic oxidation on the diacetates was observed. With the Treibs reaction, allylic oxidation on the diacetates occurred. The 7-keto and 4,4-dimethyl steroids proved to be poor substrates in both reactions.

Keywords: Δ^5-Steroid; Treibs; Petrow; Bromine; Silver acetate; Mercury(II) trifluoroacetate

1. Introduction

Our studies in the electrophilic substitution of 3-substituted-Δ^5-steroids by bromine/silver acetate (Petrow reaction) [1,2] and mercury(II) trifluoroacetate (modified Treibs oxidation) [3–5] have led us to examine the effect of structural modification of the substrate on these reactions.

The treatment of 3β-acetoxy-Δ^5-steroids, e.g. **1**, with bromine at −78°C followed by silver acetate in pyridine [6,7] produces mainly 4β-acetoxy-3β-hydroxy-Δ^5-derivatives, e.g. **5**, in good yield. Several biologically active steroids possess a C-4 oxygen function, some of which selectively inhibit estrogen synthases in tumor cells [8–10]. The mechanism of the Petrow reaction on **1** is believed to involve the formation of the 5α,6β-dibromide **2,** which loses hydrogen bromide to give the Δ^4 compound **3**. The latter undergoes an anchimeric assisted S_N2' reaction to give **5** via the dioxolenium ion **4** (Scheme 1) [2].

The addition of dehydroepiandrosterone acetate (**1**) to a solution of mercury(II) trifluoroacetate in dichloromethane [11,12] leads to the formation of 3β-acetoxy-6β-hydroxyandrost-4-en-17-one (**9**) (43% yield) and 3β-acetoxy-6-chloromercuriandrost-5-en-17-one (**12**) (6%) [4]. The cholesterol analog of the latter has been implicated indirectly for use in the treatment of Addison's disease [13], a potentially fatal affliction of the adrenal glands. A small quantity of the Δ^4-6-ketone **10** (1.5%) was also formed presumably via oxidation of 6β-alcohol **9**, with the rest of the steroid apparently going to a polymer that remains on the silica gel column. The first intermediate in the reaction is thought to be the 5α,6α-mercurinium ion (**6**). Loss of the 4β-proton [3] and opening of the mercurinium ion would lead to the allylic organomercurial compound **7,** which after nucleophilic attack by trifluoroacetate on the β face would form the allylic ester **8**. Hydrolysis of the trifluoroacetate on workup would give the 6β-alcohol **9** (Scheme 2). Alternately, mercurinium ion **6** could suffer loss of the 6β-proton, giving the 6-trifluoroacetoxymercuri-Δ^5-steroid **11,** which would undergo ligand exchange with the solvent to form the chloromercury steroid **12** (Scheme 3) [4].

We decided to examine the effects of insertion of an acetoxyl moiety at C-4β or C-19 on the product(s) of the two above-mentioned reactions. In view of this, we also

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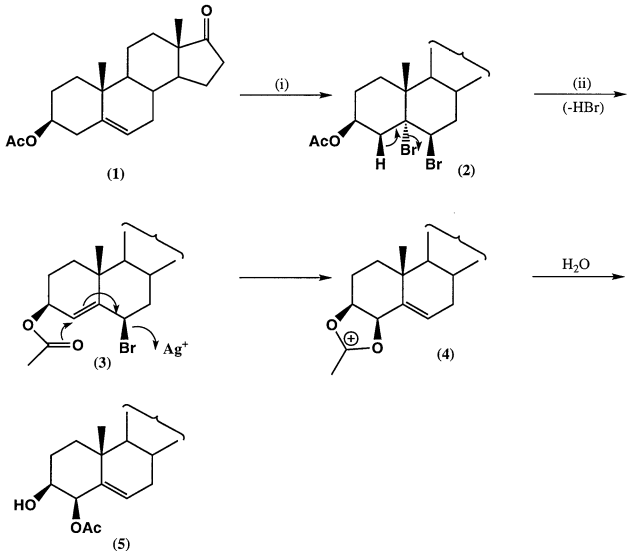
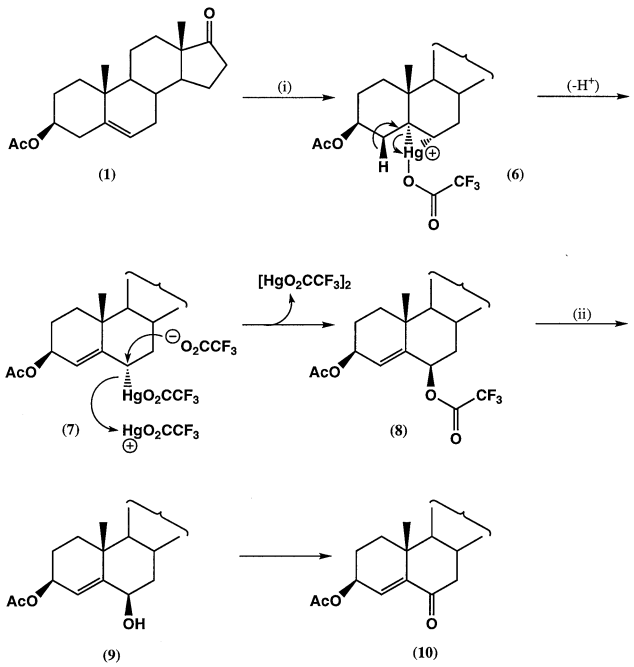


Scheme 1. Reagents: (i) $Br_2/CHCl_3$. (ii) AgOAc/py −78°C.

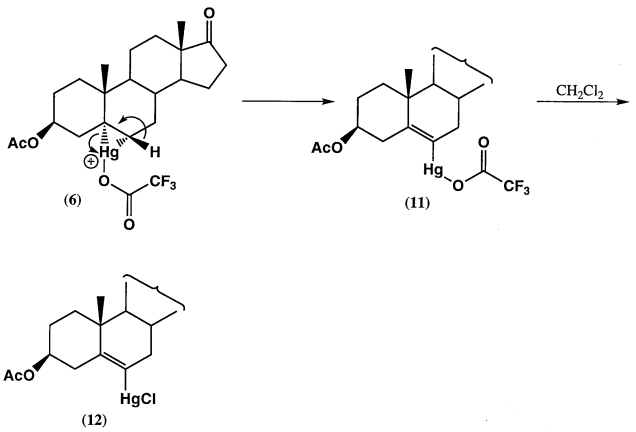
sought to observe the route of the reactions on a 7-keto- (**15**) and a 4,4-dimethyl-steroid (**17**).

2. Experimental

Melting points were determined on a Thomas–Hoover melting point apparatus by using open-ended capillary tubes or on a Köfler hot stage instrument. Ultraviolet spectra were recorded on a Pye Unicam PU8800 spectrophotometer. Rotations were measured, unless otherwise stated, for solutions



Scheme 2. Reagents: (i) $Hg(O_2CCF_3)_2/CH_2Cl_2$. (ii) aq $NaHCO_3$.



Scheme 3.

in chloroform with a Perkin–Elmer 241 mc polarimeter (Norwalk, CT, USA). Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR and 735b spectrometers with KBr disks being the primary medium employed. Mass spectral data (high-resolution electron impact ionization [EI] and chemical ionization [CI]) were determined at an ionizing voltage of 70 eV on Kratos A.E.I. MS-50 and MS-12 spectrometers (Kratos Analytical Instruments, Chestnut Ridge, NY, USA), respectively. ^{1}H NMR spectra were recorded on Bruker AM 300 and AC 200 instruments (Bruker, Billerica, MA, USA) operating at 300 MHz and 200 MHz, respectively, in the indicated solvent and were referenced to internal tetramethylsilane. ^{13}C NMR spectra were determined on the same instruments but at 75 MHz and 50 MHz, respectively. The ^{13}C data were compared where possible to those published by Blunt and Stothers [14]. Petrol refers to the petroleum fraction of boiling range 60–70°C.

3β,4β-Diacetoxyandrost-5-en-17-one (**13**) [15], 3β,19-diacetoxyandrost-5-en-17-one (**14**) [16] and 3β-acetoxyandrost-5-ene-7,17-dione (**15**) [17] were prepared by literature methods. 3β-Acetoxy-4,4-dimethylandrost-5-en-17-one (**17**) is a new compound.

2.1. 3β-Acetoxy-4,4-dimethylandrost-5-en-17-one (17) (Scheme 4)

A solution of 17,17-ethylenedioxy-3β-hydroxy-4,4-dimethylandrost-5-ene (**16**) [18] (540 mg, 1.5 mmol) in ethanol (30 ml) containing dilute aqueous sulfuric acid (4 ml, 8.5% v/v) was refluxed for 1 h. The solvent was removed under reduced pressure and the precipitated steroid was redissolved in ethyl acetate. This solution was washed with water and saturated sodium hydrogen carbonate solution and was dried. Removal of the solvent on a rotary evaporator afforded a white crystalline solid (410 mg), which was dissolved in pyridine (5 ml) and treated with acetic anhydride (2.5 ml, 26.5 mmol). The mixture was stirred overnight at room temperature. Ethyl acetate was added and the diluted solution was washed with cold dilute hydrochloric

acid, water, and saturated sodium hydrogen carbonate solution. The organic layer was dried and the solvent was removed in vacuo to give a white crystalline residue, which was chromatographed. Elution with 15% ethyl acetate in petrol gave 3β-acetoxy-4,4-dimethylandrost-5-en-17-one (**17**) (402 mg, 1.22 mmol, 81%), which crystallized from acetone as needles, m.p. 180–182°C, $[\alpha]_D$ −12° (c = 0.09);

IR ν_{max} 1740, 1725, 1252 cm^{-1};

MS (EI) $^m/_z$ (%) 358.2508 (M^+, 50), 298.2292 (47), 283.2061 (100), 280.1671 (38). ($C_{23}H_{34}O_3$ requires 358.2508);

^1H NMR ($CDCl_3$) δ 0.90 (3H, s, H-18), 1.05 (3H, s, H-19), 1.15 (3H, s, CH_3-4β), 1.17 (3H, s, CH_3-4α), 2.08 (3H, s, CH_3CO_2), 4.50 (1H, dd, J = 7, 10 Hz, H-3α), 5.58 (1H, dd, J = 3, 4 Hz, H-6);

^{13}C NMR ($CDCl_3$) δ 13.5 (C-18), 19.8 (C-11), 21.2 (C-19), 21.3 (CH_3CO_2), 21.7 (C-15), 23.7 (C-2), 24.9 (CH_3-4β), 27.1 (CH_3-4α), 30.4 (C-8), 31.3 (C-7), 31.3 (C-12), 35.8 (C-16), 36.1 (C-1), 36.7 (C-10), 40.3 (C-4), 47.4 (C-13), 50.8 (C-9), 52.1 (C-14), 79.1 (C-3), 119.9 (C-6), 149.3 (C-5), 170.7 (CH_3CO_2), 220.9 (C-17).

*2.2. Petrow reaction on 3β,4β-diacetoxyandrost-5-en-17-one (**13**)*

3β,4β-Diacetoxyandrost-5-en-17-one (**13**) (0.92 g, 2.37 mmol) was dissolved in dichloromethane (10 ml) and the solution was cooled to −78°C in the dark. Bromine (0.22 ml, 4.27 mmol) was added with stirring to the cold solution followed by a suspension of silver acetate (0.99 g, 5.93 mmol) in pyridine (1.5 ml). The reaction mixture was stirred in the dark for 10 h and allowed to attain room temperature. The yellow-green suspension was filtered through celite and the filtrate was washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate solution and was dried. The organic solution was evaporated to dryness and the off-white residue was chromatographed (25% ethyl acetate in petrol). 3β,4β-Diacetoxy-6α-bromo-5β-hydroxyandrostan-17-one (**19**) (213 mg, 0.439 mmol, 19%) was obtained and crystallized from ethyl acetate as very small needles, m.p. 203–205°C (dec.), $[\alpha]_D$ 62° (c = 0.12);

IR ν_{max} 3525, 1730, 1250 cm^{-1};

MS (CI NH_3) $^m/_z$ (%) 504 (89), 502 (M^+, 100), 422 (26), 345 (11), 329 (18), 285 (22), 269 (8). ($C_{23}H_{33}{}^{79}BrO_6NH_4$ requires 502);

MS (EI) $^m/_z$ (%) 424.1230 (1), 405.2267 (4), 328.2030 (5), 285.1862 (38), 283.2062 (100). ($C_{23}H_{33}{}^{79}BrO_6$–CH_3CO_2H requires 424.1249);

^1H NMR ($CDCl_3$) δ 0.86 (3H, s, H-18), 1.10 (3H, s, H-19), 2.13 (3H, s, CH_3CO_2-3β)*, 2.14 (3H, s, CH_3CO_2-4β)*, 4.50 (1H, d, J = 9 Hz, H-6β), 5.26 (1H, d, J = 3 Hz, H-3α), 5.66 (1H, d, J = 3 Hz, H-4α). (* interchangeable assignments);

^{13}C NMR ($CDCl_3$) δ 13.7 (C-18), 16.8 (C-19), 20.8 (C-11), 21.3 (CH_3CO_2-3β)*, 21.6 (CH_3CO_2-4β)*, 21.9 (C-15), 23.7 (C-7)†, 26.3 (C-2)†, 31.2 (C-12), 35.7 (C-16), 37.0 (C-8), 38.3 (C-1), 43.7 (C-9), 45.7 (C-10), 47.8 (C-13), 50.6 (C-14), 56.2 (C-6), 67.4 (C-4), 70.7 (C-3), 76.1 (C-5), 169.9 (CH_3CO_2-4β)††, 170.2 (CH_3CO_2-3β)††, 219.5 (C-17). (*,†,†† interchangeable assignments).

Further elution gave 3β,4β-diacetoxy-5α-bromo-6β-hydroxyandrostan-17-one (**18**) (259 mg, 0.534 mmol, 23%) which crystallized from ethyl acetate as needles, m.p. 166–167°C (dec.), $[\alpha]_D$ −5° (c = 0.10);

IR ν_{max} 3400, 1730, 1240 cm^{-1};

Combustion analysis: Found: C, 56.83%; H, 6.82%. ($C_{23}H_{33}BrO_6$ requires C, 56.91%; H, 6.85%);

MS (CI NH_3) $^m/_z$ (%) 504 (13), 502 (M^+, 14), 422 (14), 406 (37), 286 (23), 268 (100). ($C_{23}H_{33}{}^{79}BrO_6NH_4$ requires 502);

^1H NMR ($CDCl_3$) δ 0.93 (3H, s, H-18), 1.64 (3H, s, H-19), 2.09 (3H, s, CH_3CO_2-3β)*, 2.10 (3H, s, CH_3CO_2-4β)*, 4.45 (1H, t, J = 2 Hz, H-6α), 5.68 (1H, t, J = 3 Hz, H-4α), 5.78 (1H, m, $^w/_2$ = 18 Hz, H-3α). (* interchangeable assignments);

^{13}C NMR ($CDCl_3$) δ 13.9 (C-18), 18.4 (C-19), 19.9 (C-11), 21.1 (CH_3CO_2-4β)*, 21.6 (C-15), 21.7 (CH_3CO_2-3β)*, 22.2 (C-2), 30.8 (C-8), 31.2 (C-12), 32.2 (C-1), 34.7 (C-7), 35.7 (C-16), 40.3 (C-10), 47.7 (C-13), 49.4 (C-9), 50.7 (C-14), 71.9 (C-6), 73.9 (C-4), 75.6 (C-3), 83.5 (C-5), 169.5 (CH_3CO_2-4β)†, 170.5 (CH_3CO_2-3β)†, 220.3 (C-17). (*,† interchangeable assignments).

*2.3. Petrow reaction on 3β,19-diacetoxyandrost-5-en-17-one (**14**)*

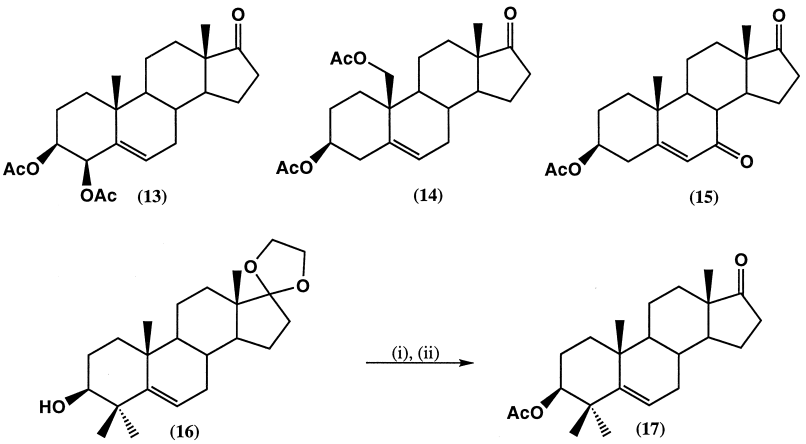
A solution of 3β,19-diacetoxyandrost-5-en-17-one (**14**) (1.75 g, 4.50 mmol) in dichloromethane was prepared and cooled to −78°C in the dark. Bromine (0.30 ml, 5.95 mmol) was added with stirring to the cold solution followed by a suspension of silver acetate (2.26 g, 13.5 mmol) in pyridine (3.5 ml). The reaction mixture was stirred overnight in the dark and allowed to attain room temperature. The silver salts were removed by filtration through celite and the filtrate was washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate solution, and was dried. The resultant dark-brown foam was chromatographed (25% ethyl acetate in petrol) to give starting material (167 mg, 0.430 mmol, 9.6%). Further elution afforded 3β,19-diacetoxy-6α-bromo-5β-hydroxyandrostan-17-one (**23**) (437 mg, 0.900 mmol, 20%), which resisted crystallization,

IR ν_{max} 3513, 1730, 1250 cm^{-1};

MS (CI NH_3) $^m/_z$ (%) 504 (100), 502 (M^+, 99), 422 (40), 362 (12), 327 (45), 267 (27). ($C_{23}H_{33}{}^{79}BrO_6NH_4$ requires 502);

MS (EI) $^m/_z$ (%) 486.1438 (3), 484.1453 (M^+, 3), 345.2063 (67), 326.1879 (55), 285.1846 (100). ($C_{23}H_{33}{}^{79}BrO_6$ requires 484.1461);

^1H NMR ($CDCl_3$) δ 0.85 (3H, s, CH_3-18), 2.10 (3H, s, CH_3CO_2-19)*, 2.11 (3H, s, CH_3CO_2-3β)*, 3.19 (1H, bs, OH), 4.38 (1H, d, J = 3.5 Hz, H-6β), 4.61 (1H, d, J = 3.8



Scheme 4. Reagents: (i) aq H_2SO_4. (ii) Ac_2O/py.

Hz, H-19), 4.68 (1H, d, J = 3.8 Hz, H-19), 5.27 (1H, bs, $^{w}/_{2}$ = 7 Hz, H-3α). (* interchangeable assignments);

^{13}C ($CDCl_3$) δ 13.7 (C-18), 21.1 (C-11), 21.4 (CH_3CO_2-3β), 21.4 (CH_3CO_2-19), 21.6 (C-15), 23.8 (C-7), 31.4 (C-2), 31.8 (C-12), 35.6 (C-4, C-16), 36.6 (C-8), 38.8 (C-1), 42.9 (C-9), 45.9 (C-10), 47.7 (C-13), 51.5 (C-14), 60.8 (C-6), 65.2 (C-19), 69.3 (C-3), 74.8 (C-5), 169.3 (CH_3CO_2-19)*, 170.3 (CH_3CO_2-3β)*, 219.5 (C-17). (* interchangeable assignments).

Elution with 30% ethyl acetate in petrol afforded 3β,19-diacetoxy-5β,6β-epoxyandrostan-17-one (**26**) (502 mg, 1.241 mmol, 28%), which crystallized from ethyl acetate as flat prisms, m.p. 119–120°C, $[\alpha]_D$ 14° (c = 0.10), lit [19]. m.p. 133–134°C, $[\alpha]_D$ 26°;

IR ν_{max} 1735, 1240, 910, 840 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.88 (3H, s, H-18), 2.03 (3H, s, CH_3CO_2-19), 2.11 (3H, s, CH_3CO_2-3β), 3.05 (1H, d, J = 2 Hz, H-6α), 4.06 (1H, d, J = 12 Hz, H-19), 4.55 (1H, d, J = 12 Hz, H-19), 4.84 (1H, m, $^{w}/_{2}$ = 23 Hz, H-3α);

^{13}C NMR ($CDCl_3$) δ 13.4 (C-18), 21.2 (CH_3CO_2-3β), 21.2 (CH_3CO_2-19), 21.3 (C-11), 21.7 (C-15), 27.3 (C-2), 30.1 (C-8), 31.2 (C-7), 31.6 (C-12), 32.3 (C-4), 35.6 (C-16), 38.1 (C-1), 38.3 (C-10), 47.4 (C-13), 50.0 (C-9), 51.3 (C-14), 60.57 (C-6), 60.64 (C-5), 65.3 (C-19), 70.5 (C-3), 170.5 (CH_3CO_2-3β)*, 170.7 (CH_3CO_2-19)*, 220.3 (C-17). (* interchangeable assignments).

*2.4. Treibs oxidation of 3β,4β-diacetoxyandrost-5-en-17-one (**13**)*

Mercury(II) oxide (2.79 g, 12.9 mmol) and trifluoroacetic anhydride (2.50 ml, 11.7 mmol) were stirred together in dichloromethane (200 ml). 3β,4β-Diacetoxyandrost-5-en-17-one (**13**) (2.00 g, 5.15 mmol) was added and the solution was stirred for 4 days. Thin layer chromatographic analysis of the orange colored reaction mixture suggested that the starting material had not reacted, but small amounts of mercury(I) deposits were seen in the reaction vessel. The mixture was refluxed for 24 h, during which time it became dark green and the amount of mercury(I) salts increased. The mixture was filtered through celite and the filtrate was washed with saturated sodium hydrogen carbonate solution and was dried. Evaporation of the solvent in vacuo gave a brown foam (1.13 g), which was chromatographed. Elution with 30% ethyl acetate in petrol produced 3β-acetoxy-6β-hydroxyandrost-4-en-17-one (**9**) (170 mg, 0.491 mmol, 9.5%) which was identified by comparison with an authentic sample. Further elution gave 6β-acetoxy-3β-hydroxyandrost-4-en-17-one (**30**) [20] (102 mg, 0.294 mmol, 5.7%) as a gum, which resisted crystallization,

IR ν_{max} 3425, 1730, 1250 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.93 (3H, s, H-18), 1.18 (3H, s, H-19), 2.06 (3H, s, CH_3CO_2), 4.15 (1H, dt, J = 3, 8 Hz, H-3α), 5.30 (1H, t, J = 4 Hz, H-6α), 5.73 (1H, s, H-4);

^{13}C NMR ($CDCl_3$) δ 13.6 (C-18), 19.9 (C-11), 20.5 (C-19), 21.5 (CH_3CO_2), 21.5 (C-15), 28.6 (C-2), 30.4 (C-8), 31.1 (C-12), 35.6 (C-16), 35.8 (C-7), 36.6 (C-10), 36.7 (C-1), 47.5 (C-13), 50.8 (C-14), 53.8 (C-9), 67.4 (C-3), 75.1 (C-6), 132.4 (C-4), 141.2 (C-5), 170.1 (CH_3CO_2), 220.7 (C-17).

Elution with 40% ethyl acetate in petrol afforded 6β-acetoxy-3α-hydroxyandrost-4-en-17-one (**32**) (107 mg, 0.309 mmol, 6.0%), which crystallized from acetone-petrol as needles, m.p. 168–169°C, $[\alpha]_D$ 179° (c = 0.11);

IR ν_{max} 3450, 1720, 1250 cm^{-1};

MS (CI NH_3) $^{m}/_{z}$ (%) 364 (M^+, 12), 329 (100), 286 (81), 269 (71) ($C_{21}H_{30}O_4NH_4$ requires 364);

MS (EI) $^{m}/_{z}$ (%) 328.2035 (10), 286.1930 (100), 271.1697 (15). ($C_{21}H_{30}O_4$–H_2O requires 328.2039);

^{1}H NMR ($CDCl_3$) δ 0.92 (3H, s, H-18), 1.08 (3H, s, H-19), 2.04 (3H, s, CH_3CO_2), 2.64 (1H, b s, OH), 4.13 (1H, m, $^{w}/_{2}$ = 14 Hz, H-3β), 5.36 (1H, d, J = 4 Hz, H-6α), 5.88 (1H, d, J = 5 Hz, H-4);

^{13}C NMR ($CDCl_3$) δ 13.6 (C-18), 19.5 (C-19), 20.4 (C-11), 21.5 (CH_3CO_2), 21.5 (C-15), 27.3 (C-2), 30.1 (C-8), 31.2 (C-12), 32.3 (C-1), 35.5 (C-7)*, 35.6 (C-16)*, 36.7 (C-10), 47.5 (C-13), 50.8 (C-14), 53.1 (C-9), 63.0 (C-3),

75.4 (C-6), 129.4 (C-4), 143.5 (C-5), 169.9 (CH_3CO_2), 220.7 (C-17). (* interchangeable assignments).

*2.5. Treibs oxidation of 3β,19-diacetoxyandrost-5-en-17-one (**14**)*

Mercury(II) oxide (2.44 g, 11.2 mmol) and trifluoroacetic anhydride (2.0 ml, 14.0 mmol) were stirred together in dichloromethane (175 ml). 3β,19-Diacetoxyandrost-5-en-17-one (**14**) (1.75 g, 4.50 mmol) was added and the solution was stirred for 49 h. The reaction mixture was filtered through celite to remove the deposits of mercury(I) trifluoroacetate. The clear yellow filtrate was washed with saturated sodium hydrogen carbonate solution and was dried. Removal of the solvent on a rotary evaporator gave a dark brown foamy gum (2.02 g), which was chromatographed. Elution with 20% ethyl acetate in petrol gave unreacted starting material (**14**) (249 mg, 0.641 mmol, 14%). Further elution with 30% ethyl acetate in petrol gave 3β-acetoxy-19-hydroxyandrost-5-en-17-one (**35**) (27 mg, 0.078 mmol, 1.7%) which crystallized from ethyl acetate-petrol as plates, m.p. 153–155°C, $[\alpha]_D$ 8° (c = 0.10), lit [21]. m.p. 157–158°C, $[\alpha]_D$ 7°;

IR ν_{max} 3475, 1730, 1250 cm^{-1};

^1H NMR ($CDCl_3$) δ 0.93 (3H, s, H-18), 2.03 (3H, s, CH_3CO_2), 3.64 (1H, d, J = 12 Hz, H-19), 3.90 (1H, d, J = 12 Hz, H-19), 4.64 (1H, m, $^w/_2$ = 27 Hz, H-3α), 5.80 (1H, d, J = 5 Hz, H-6);

^{13}C NMR ($CDCl_3$) δ 13.9 (C-18), 20.9 (C-11), 21.3 (CH_3CO_2), 21.7 (C-15), 28.0 (C-2), 30.1 (C-12), 31.7 (C-7), 32.9 (C-8), 33.2 (C-1), 35.8 (C-16), 38.1 (C-4), 41.7 (C-10), 47.9 (C-13), 50.4 (C-9), 52.5 (C-14), 62.8 (C-19), 73.2 (C-3), 127.5 (C-6), 134.9 (C-5), 170.5 (CH_3CO_2), 220.9 (C-17).

Elution with 35% ethyl acetate in petrol gave 3β,19-diacetoxy-6-chloromercuriandrost-5-en-17-one (**34**) (71 mg, 0.114 mmol, 2.5%), which resisted crystallization,

IR ν_{max} 1735, 1720, 1250 cm^{-1};

MS (CI NH_3) $^m/_z$ (%) 646 (1), 645 (2), 644 (6), 643 (5), 642 (M^+, 14), 641 (8), 640 (10), 639 (7), 638 (4), 406 (100), 327 (2), 268 (10). ($C_{23}H_{31}{}^{35}Cl^{202}HgO_5NH_4$ requires 642);

MS (EI) $^m/_z$ (%) 505.1149 (3), 504.1137 (9), 503.1132 (5), 267.1748 (100). ($C_{23}H_{31}{}^{35}Cl^{202}HgO_5$–2 × CH_3CO_2H requires 504.1136);

^1H NMR ($CDCl_3$) δ 0.90 (3H, s, H-18), 2.03 (3H, s, CH_3CO_2-19)*, 2.06 (3H, s, CH_3CO_2-3β)*, 3.97 (1H, d, J = 12 Hz, H-19), 4.62 (1H, d, J = 12 Hz, H-19), 4.65 (1H, m, $^w/_2$ = 27 Hz, H-3α). (* interchangeable assignments);

^{13}C NMR ($CDCl_3$) δ 13.6 (C-18), 20.9 (C-11), 21.1 (CH_3CO_2-3β)*, 21.2 (CH_3CO_2-19)*, 21.7 (C-15), 27.7 (C-2), 31.4 (C-12), 33.8 (C-1), 34.3 (C-8), 35.7 (C-16), 39.8 (C-7), 43.7 (C-10), 44.4 (C-4), 47.6 (C-13), 49.7 (C-9), 52.0 (C-14), 64.5 (C-19), 72.5 (C-3), 141.4 (C-5), 150.2 (C-6), 170.3 (CH_3CO_2-3β), 170.3 (CH_3CO_2-19), 220.0 (C-17). (* interchangeable assignments).

Further elution (40% ethyl acetate in petrol) produced 3β,19-diacetoxy-6β-hydroxyandrost-4-en-17-one (**33**) [19] (212 mg, 0.524 mmol, 12%), which crystallized from ethyl acetate as amorphous crystals, m.p. 165–166°C, $[\alpha]_D$ 46° (c = 0.120);

IR ν_{max} 3475, 1730, 1250 cm^{-1};

Combustion analysis: Found: C, 68.66%; H, 8.22%. ($C_{23}H_{32}O_6$ requires C, 68.28%; H, 7.98%);

MS (CI NH_3) $^m/_z$ (%) 422 (M^+, 60), 387 (100), 346 (41), 327 (14), 285 (11). ($C_{23}H_{32}O_6NH_4$ requires 422);

^1H NMR ($CDCl_3$) δ 0.90 (3H, s, H-18), 2.10 (6H, s, CH_3CO_2-3β,19), 4.32 (1H, s, H-6α), 4.40 (1H, d, J = 12 Hz, H-19), 4.60 (1H, d, J = 12 Hz, H-19), 5.25 (1H, m, $^w/_2$ = 27 Hz, H-3α), 5.73 (1H, s, H-4);

^{13}C NMR ($CDCl_3$) δ 13.9 (C-18), 20.7 (C-11), 21.3 (CH_3CO_2-3β), 21.3 (CH_3CO_2-19), 21.6 (C-15), 24.9 (C-2), 30.3 (C-8), 31.7 (C-12), 32.6 (C-1), 35.7 (C-16), 37.8 (C-7), 40.0 (C-10), 47.7 (C-13), 51.3 (C-14), 54.3 (C-9), 68.1 (C-19), 69.6 (C-3), 73.2 (C-6), 127.5 (C-4), 144.1 (C-5), 170.8 (CH_3CO_2-3β)*, 170.9 (CH_3CO_2-19)*, 220.3 (C-17). (* interchangeable assignments).

3. Results and discussion

3.1. Preparation of the substrates

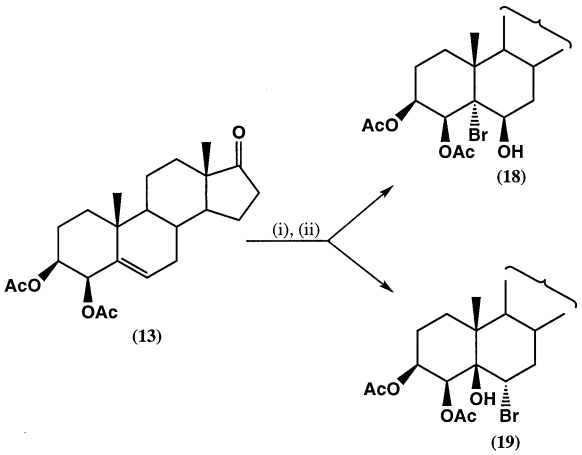
The preparations of the substrates were done according to literature procedures [1–2,18,22–30].

3.2. Petrow reaction on substrates

Treatment of the 3β,4β-diacetate **13** with bromine produced two new compounds, 3β,4β-diacetoxy-5α-bromo-6β-hydroxyandrostan-17-one (**18**) (23%) and 3β,4β-diacetoxy-6α-bromo-5β-hydroxyandrostan-17-one (**19**) (19%), which remained unchanged on addition of the silver salt. The 4β-acetoxyl moiety of the bromonium ion intermediate successfully competed with the bromide nucleophile to afford attack at C-5β and C-6β. The resulting five- and six-membered dioxolenium ions were solvolyzed to give the respective products (Scheme 5).

The 3β,19-diacetate **14** provides an interesting substrate in that the proposed intermediary 6β-bromo-Δ^4-steroid would have two potential functionalities to assist in anchimeric expulsion of the bromide ion. However, attack at both the 5β- and 6β-positions only by the 19-acetyl group to quench the bromonium ion occurred [31] (Scheme 6). The 5β,19-acetoxonium ion (**21**) was hydrolyzed to give the previously unreported 3β,19-diacetoxy-6α-bromo-5β-hydroxyandrostan-17-one (**23**) (20%). The 5β,6β-epoxide **26** (28%), the other product, was possibly formed from the 6β,19-acetoxonium ion (**24**). Some starting material (10%) was also recovered.

The 7-ketone (**15**) was inert to the reaction conditions and was recovered unchanged. The 4,4-dimethylsteroid (**17**) reacted readily under Petrow conditions giving a very com-

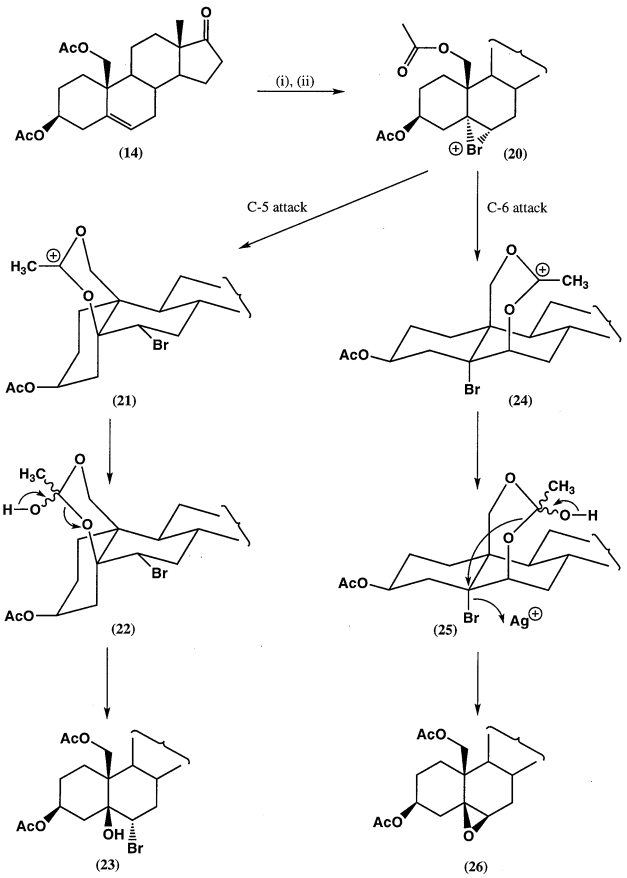


Scheme 5. Reagents: (i) $Br_2/CHCl_3$. (ii) AgOAc/py −78°.

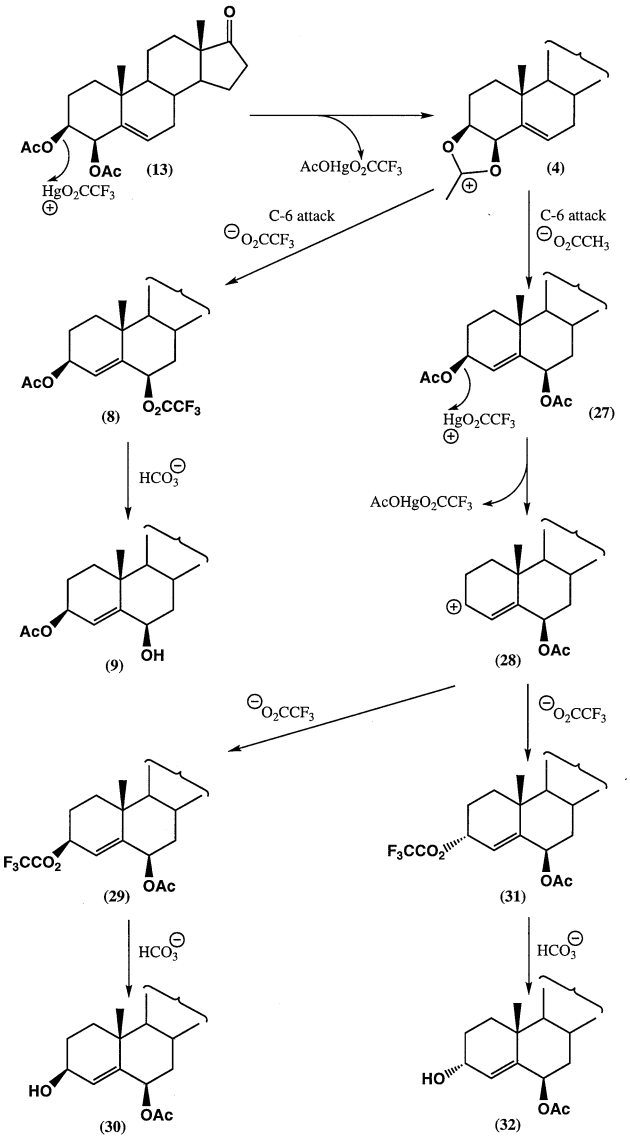
plex mixture of products, none in quantities sufficient for characterization.

3.3. Modified Treibs oxidation on substrates

In view of the proposed mechanism for the Treibs oxidation, the 3β,4β-diacetate (**13**) would provide an interesting substrate, because there can be no 4β-proton loss en-

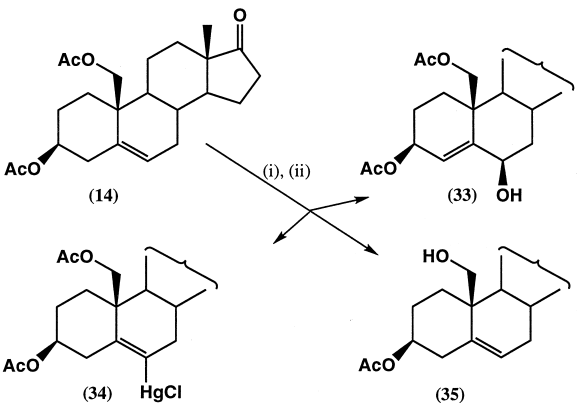


Scheme 6. Reagents: (i) $Br_2/CHCl_3$. (ii) AgOAc/py −78°.



Scheme 7. Reagents: (i) $Hg(O_2CCF_3)_2/CH_2Cl_2$. (ii) aq $NaHCO_3$.

route to the allylic trifluoroacetate. Loss of the 6β-hydrogen would produce the vinylic chloromercury steroid exclusively. Under modified Treibs conditions, this substrate (**13**) was converted to the two Δ^4-3β,6β-diol monoacetates **30** and **9**, as well as the novel 6β-acetoxy-3α-hydroxyandrost-4-en-17-one (**32**) (in 6%, 10%, and 6% yields, respectively). A key intermediate in this reaction is proposed to be the 3β,4β-dioxolenium cation (**4**) formed by mercury mono(trifluoroacetate) ion assisted removal of the 3β-acetoxy group (Scheme 7) [5]. The dioxolenium ion (**4**) could then be quenched at C-6β by trifluoroacetate [20,32] with migration of the double bond and collapse of the acetate bridge to give the 6-trifluoroacetate (**8**). Work-up would afford the 6-alcohol **9**. Alternately, attack on the dioxolenium ion (**4**) by the more nucleophilic acetate ion (originally lost from C-3) would produce the Δ^4-3β,6β-diacetate (**27**). Removal once more of the less hindered 3-acetoxy group by mercury(II)



Scheme 8. Reagents: (i) $Hg(O_2CCF_3)_2$, CH_2Cl_2. (ii) aq $NaHCO_3$.

ion would give the allylic cation (**28**), which would be attacked by trifluoroacetate ion either from the α or β face. Finally, hydrolysis of the resulting epimeric 3-esters would give the 3α- and 3β-alcohols **32** and **30**.

Interest in the 3β,19-diacetoxy-Δ^5-steroid **14** as a substrate stemmed from the possibility of neighboring group participation at C-5 or C-6 by the 19-acetoxy group in the decomposition of the initially formed 5α,6α-mercurinium ion. However, the products of the reaction were those of the normal Treibs reaction, i.e. the 6β-alcohol **33** (12%) and the novel chloromercury steroid **34** (2.5%). Also found was 3β-acetoxy-19-hydroxyandrost-5-en-17-one **35** (1.7%) and unreacted starting material (14%). Surprisingly, the 19-ester functionality does not seem to directly participate in nucleophilic attack on the intermediary mercurinium ion; however, it appears to shield the top face of the molecule thereby reducing the yields of expected products (Scheme 8). It is proposed that the 19-alcohol **35** was formed by slow mercury mono(trifluoroacetate) assisted removal of the acetate [5].

It was thought that the presence of the 7-ketone in compound **15** would increase the acidity of the 6β-hydrogen in the intermediary 5α,6α-mercurinium ion, thus facilitating its loss over that at C-4β and directing the course of the reaction toward the formation of the chloromercury steroid. In a similar vein, because there is no 4β-proton in 3β-acetoxy-4,4-dimethylandrost-5-en-17-one (**17**), it was expected that this would force the formation of the Δ^5-6-chloromercury steroid. However, both substrates remained unaffected by the reagent.

In summary, the substituents proximate to the Δ^5-bond in the substrates had a pronounced influence on electrophilic reactions, and this resulted in the isolation and characterization of several new steroids. The diacetates **13** and **14** reacted with bromine and silver acetate (Petrow reaction) to give addition products exclusively. Mercury(II) trifluoroacetate, on the other hand, effected mainly allylic oxidation. The products reflected the differences in the nature of the C-Br and the C-Hg bonds in the bromonium and mercurinium intermediates, respectively. Bromine, being much more electronegative than mercury, makes the carbon to which it is attached susceptible to nucleophilic attack by the neighboring acetoxy groups. It is apparent that the deactivation and steric hindrance of the Δ^5-bond by the C-7 ketone and dimethyl substituents of **15** and **17,** respectively, are likely to have been responsible for the lack of reactivity shown by these substrates.

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References

[1] Hanson JR, Reese PB, Wadsworth HJ. Allylic acetoxylation of Δ^5 steroids at C-4. J Chem Soc Perkin Trans I 1984;2941–4.
[2] Hanson JR, Reese PB. Neighbouring group participation in the allylic oxidation of a Δ^5 steroid. J Chem Soc Perkin Trans I 1985;647–9.
[3] Broad RA, Hanson JR, Reese PB. The stereochemistry of the Treibs allylic oxidation of Δ^5 steroids. J Chem Res (S) 1987;172–3.
[4] Ruddock PL, Reese PB. An unexpected product from the reaction of mercury(II) trifluoroacetate with 3-substituted Δ^5 steroids. J Chem Res (S) 1994;442–3.
[5] Ruddock PL, Williams DJ, Reese PB. The scope and limitations of the reaction of Δ^5 steroids with mercury(II) trifluoroacetate. Steroids 1998;63;650–64.
[6] Petrow VA. Steroids and related compounds. Part I. Isomeric cholestenediols. J Chem Soc 1937;1077–81.
[7] Petrow VA, Rosenheim O, Starling WW. Acyl migration in steroids. J Chem Soc 1943;135–9.
[8] Glotter E, Kirsen I, Lavie D, Abraham A. The withanolides—a group of steroids. Bioorg Chem 1978;2:57–97.
[9] Nittala SS, Lavie D. Withanolides of *Acnistus breviflorus*. Phytochemistry 1981;20:2735–9.
[10] Brodie AMH, Garrett WM, Hendrickson JR, Tsai-Morris C-H, Marcotte PA, Robinson CH. Inactivation of aromatase in vitro by 4-hydroxy-4-androstene-3,17-dione and 4- acetoxy-4-androstene-3,17-dione and sustained effects in vivo. Steroids 1981;38:693–702.
[11] Treibs W. Acetylating oxidation of ketones and olefins with mercuric trifluoroacetate. Naturwissenschaften 1948;35:125.
[12] Massiot G, Husson H-P, Potier P. Allylic substitution of steroidal olefins by a modified Treibs reaction. Synthesis 1974;722–3.
[13] Flanagan RJ, Charleson FP, Synnes EI, Weibe LI, Theriault YX, Nakashima TT. Radiolabeling with organomercury compounds. Part 1. The synthesis and structure of 6-halocholest-5-en-3β-ols. Can J Chem 1985;63:2853–60.
[14] Blunt JW, Stothers JB. ^{13}C N.m.r. spectra of steroids—a survey and commentary. Org Magn Reson 1977;9:439–64.
[15] Baldwin D, Hanson JR, Holtom A. Aromatization of some steroidal enediols. J Chem Soc Perkin Trans I 1973;1703–7.
[16] Heusler K, Kalvoda J, Meystre Ch, Ueberwasser H, Wieland P, Anner G, Wettstein A. Ein neues Verfahren zur Herstellung von 19-Norsteroiden. Experientia 1962;18;464–6.

[17] Billeter JR, Meischer K. Uber steroide. Abbauprodukte der sterinoxydation. IV. Isolierung von $\Delta^{3,5}$-androstadien-dion-(7,17). Helv Chim Acta 1948;31:629–32.
[18] Adams WJ, Patel DK, Petrow V, Stuart–Webb IA, Sturgeon B. 4,4-Dimethylsteroids. II. Androstane and pregnane derivatives. J Chem Soc 1956;4490–5.
[19] Mastalerz H, Morand P. 19-Hydroxy-steroids. Part 7. Boron trifluoride-catalysed reactions of 19-hydroxy- and 19-acetoxy-5,6-epoxy-steroids. J Chem Soc Perkin Trans I 1981;154–60.
[20] Hanson JR, Reese PB. A nuclear magnetic resonance study of the conversion of 4β-acetoxy-3β-hydroxy-Δ^5-steroids into 3β,6β-diacetoxy-Δ^4-steroids. J Chem Soc Perkin Trans I 1985;331–4.
[21] Tadanier J. Preparation and solvolysis of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane. J Org Chem 1963;28:1744–51.
[22] Rodewald WJ, Jaszczynski JR, Sicinski RR. 19-Functionalized steroids. Part 1. An improved synthesis of androst-5-ene-3β,17β,19-triol derivatives. Pol J Chem 1978;52:501–9.
[23] Heusler K, Kalvoda J. Selective functionalization of the angular methyl group and further transformation to 19-norsteroids. In: Fried J, Edwards JA, editors. Organic Reactions in Steroid Chemistry (Vol. 2). New York: Van Nostrand Reinhold, 1972. p. 251.
[24] Kirk DN, Yeoh BL. New syntheses of 19,21-dihydroxypregn-4-ene-3,20-dione, 21-hydroxy-19-norpregn-4-ene-3,20-dione and 11β,19,21-trihydroxypregn-4-ene-3,20-dione. J Chem Soc Perkin Trans I 1983;2945–51.
[25] Heusler K, Wettstein A. Uber Steroide. Herstellung von 7,9,11-dienen der Androstan-Reihe. Helv Chim Acta 1952;35:284–94.
[26] Marshall CW, Ray RE, Laos I, Riegel B. 7-Keto Steroids. II. Steroidal 3β-hydroxy-Δ^5-7-ones and -$\Delta^{3,5}$-7-ones. J Am Chem Soc 1957; 79:6308–13.
[27] Julian PL, Meyer EW, Ryden I. Sterols. X. 17α-Hydroxyprogesterone. J Am Chem Soc 1950;72:367–70.
[28] Fieser LF, Fieser M. Reagents for Organic Synthesis. New York: John Wiley & Sons, 1967. p. 35.
[29] Djerassi C. Oppenauer oxidation. Org React 1951;6:207–72.
[30] Ringold HJ, Rosenkranz G. Steroids. LXXXV. Synthesis of 4-methyl and 4,4-dimethyl hormone analogs. J Org Chem 1957;22:602–5.
[31] Kocovsky P, Stary I, Zajicek J, Turecek F, Vasickova. Stereo- and regio-control of electrophilic additions to cyclohexene systems by neighbouring groups: participation of allylic and homoallylic ester groups in hypobromous acid addition to some 5-unsaturated cholestane derivatives. J Chem Soc Perkin Trans I 1988;2297–303.
[32] Hanson JR, Reese PB. Neighbouring group participation in the rearrangement of 4β-acetoxy-Δ^5-steroids to 6β-acetoxy-Δ^4-steroids. Tetrahedron Lett 1983;24:303–6.