SYNTHESIS OF 21-HYDROXY-6β,19-EPOXYPREGN-4-ENE-3,20-DIONE+

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Received February 2, 2000
Accepted March 4, 2000

21-Hydroxy-6β,19-epoxypregn-4-ene-3,20-dione was prepared from 20-oxopregn-5-en-3β-yl acetate in seven steps.

Key words: Steroids; NMR spectroscopy, ^{1}H; Radical functionalization; Bromohydrins.

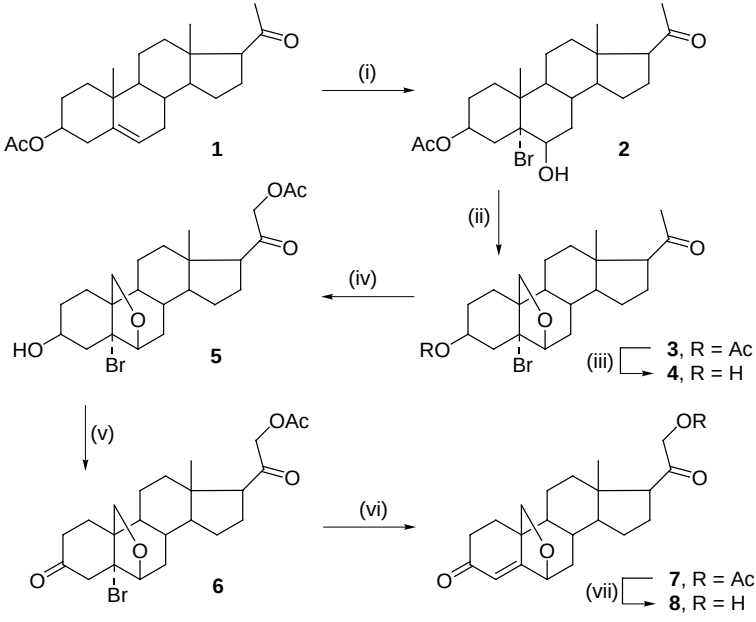
For diagnostic purposes, we needed to synthesize 21-hydroxy-6β,19-epoxypregn-4-ene-3,20-dione (**8**). Though some steps of the synthesis have been described in literature[2–4], a complete synthesis from 20-oxopregn-5-en-3β-yl acetate (**1**) has never been described.

The seven-step synthesis (Scheme 1) started with 20-oxopregn-5-en- 3β-yl acetate (**1**) which on addition of hypobromous acid afforded 5-bromo-6β-hydroxy-20-oxo-5α-pregnan-3β-yl acetate (**2**). This bromohydrin **2** on treatment with lead tetraacetate afforded 5-bromo-20-oxo-6β,19-epoxy-5α-pregnan-3β-yl acetate (**3**). This step was one of the most critical steps of the whole synthesis because of the yield. If irradiation reaction of bromohydrin **2** was carried out only with lead tetraacetate, the yield of **3** was very low, almost negligible. It was not possible to increase the yield either by changing the molar ratio of the reaction components or the reaction temperature. If iodine was added to the reaction mixture, the yield was higher, more than 50%.

The next step, alkaline hydrolysis of 3β-acetate function in compound **3**, was carried out with potassium carbonate in methanol. The product obtained, 5-bromo-3β-hydroxy-6β,19-epoxy-5α-pregnan-20-one (**4**), was acetoxylated at carbon atom 21 on treatment with lead tetraacetate in the presence of boron trifluoride etherate to yield 5-bromo-3β-hydroxy-

+ Part CDVII in the series On Steroids. Part CDVI see ref.[1]

20-oxo-6β,19-epoxy-5α-pregnan-21-yl acetate (**5**). Oxidation of the 3β-hydroxyl group with Jones reagent afforded 5-bromo-3,20-dioxo-6β,19-epoxy-5α-pregnan-21-yl acetate (**6**). Dehydrobromination of this compound with sodium acetate gave 3,20-dioxo-6β,19-epoxypregn-4-en-21-yl acetate (**7**). The final step, the hydrolysis of 21-acetate with potassium hydrogen carbonate in methanol, was another critical step. When this hydrolysis is carried out under the presence of air oxygen, the yield is very low due to a side reaction which affords a carboxylic acid as described in literature[5]. Therefore this last step of the sequence had to be carried out carefully in the absence of air oxygen. Only then, 21-hydroxy-6β,19-epoxypregn-4-ene-3,20-dione (**8**), was obtained in a good yield (80%). The overall yield of ketone **8** was 16% from compound **1**.



(i) N-bromoacetamide, $HClO_4$, dioxan; (ii) $Pb(OAc)_4$, I_2, irradiation, benzene; (iii) K_2CO_3, methanol, water; (iv) $Pb(OAc)_4$, $BF_2{\cdot}Et_2O$, methanol, benzene; (v) Jones' reagent, acetone; (vi) NaOAc, methanol, reflux; (vii) $KHCO_3$, benzene, methanol, N_2, 40 °C

SCHEME 1

EXPERIMENTAL

Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Optical rotations were measured at 25 °C on a Perkin–Elmer 141 MC polarimeter in chloroform and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were measured in tetrachloromethane on a Bruker IFS 88 (wavenumbers are given in cm^{-1}) and ^{1}H NMR spectra in deuteriochloroform solutions on a Varian XL-200 (FT-mode, 200.04 MHz, internal standard tetramethylsilane) instruments. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and half-width of multiplets ($W_{1/2}$) in Hz. All values were obtained by first-order analysis. Mass spectra were obtained with a ZAB-EQ spectrometer at 70 eV. Column chromatography was performed on silica gel (60–120 μm), preparative thin-layer chromatography (PLC) on silica gel Woelm DC (200 × 200 × 0.7 mm), detection by spraying the plates with a 0.2% morin solution in methanol by UV detection or by spraying with sulfuric acid and heating of the side strips of the plates. The identity of samples was checked by TLC, melting points, IR and ^{1}H NMR spectra.

A "usual work-up" means washing an organic solution with water, 5% aqueous potassium hydrogen carbonate, water, drying over anhydrous sodium sulfate, filtering and evaporation of the solvent *in vacuo* (at about 3 kPa) to dryness.

Light petroleum was a fraction boiling at 40–62 °C.

5-Bromo-6β-hydroxy-20-oxo-5α-pregnan-3β-yl Acetate (**2**)

To a solution of compound **1** (1.5 g, 4.4 mmol) in dioxane (12 ml) and 0.28 M aqueous perchloric acid (0.69 ml) in dark, *N*-bromoacetamide (1.29 g, 9.3 mol) was added at room temperature and the mixture was stirred for 25 min. The mixture was cooled with ice, water was added and then aqueous sodium sulfite. After usual work-up crystallization from methanol afforded compound **2** (1.4 g, 70%), m.p. 171–174 °C, $[\alpha]_D^{20}$ +8 (*c* 2.1); ref.[2] gives m.p. 171–174 °C, $[\alpha]_D^{20}$ +7. IR: 3 615 (OH); 1 724 (C=O, acetate); 1 707 (C=O, ketone); 1 252 (C–O, acetate); 592, 504 (C–Br). ^{1}H NMR: 0.62 s, 3 H (3 × H-18); 1.32 s, 3 H (3 × H-19); 2.02 s, 3 H (CH_3COO); 2.10 s, 3 H (3 × H-21); 2.50 t, 1 H, *J* = 8 (H-17α); 4.19 d, 1 H, *J* = 5 (H-6α); 5.45 m, 1 H, $W_{1/2}$ = 20 (H-3α).

5-Bromo-20-oxo-6β,19-epoxy-5α-pregnan-3β-yl Acetate (**3**)

The bromohydrin **2** (1.5 g, 3.3 mmol) was dissolved in benzene (100 ml) and 35 ml of the solvent was distilled off. The solution was treated with lead tetraacetate (2.5 g, 5.64 mmol), iodine (0.07 g, 0.55 mmol) was added and the mixture was refluxed under stirring and irradiation (500 W, Nitraphot). After 1 h another iodine crystal (0.03 g, 0.24 mmol) was added and stirring and irradiation were continued for 3 h. The reaction mixture was then diluted with wet ether (50 ml), stirred for 5 min and filtered. After the usual work-up, the oily residue was chromatographed on a column of silica gel (150 g), eluted with benzene–ether (30 : 1). Working up the corresponding fractions afforded 0.85 g (57%) of compound **3**, m.p. 152–154 °C (after two recrystallizations from ethanol), $[\alpha]_D^{20}$ +54 (*c* 1.2); ref.[3] gives m.p. 152–154 °C, $[\alpha]_D^{20}$ +58. IR: 1 737 (C=O, acetate); 1 707 (C=O, ketone); 1 241, 1 038 (C–O, acetate); 1 164, 1 098, 919 (C–O–C); 592, 504 (C–Br). ^{1}H NMR: 0.65 s, 3 H (3 × H-18); 2.03 s, 3 H (CH_3COO); 2.13 s, 3 H (3 × H-21); 2.54 t, 1 H, *J* = 8 (H-17α); 3.72 d and 3.94 d, 2 H, AB system, *J* = 9 (2 × H-19); 4.07 d, 1 H, *J* = 5 (H-6α); 5.20 m, 1 H, $W_{1/2}$ = 21 (H-3α). FAB MS, *m/e*: 455, 453 (M^+); 437, 435 $(M - H_2O)^+$; 395, 393 $(M - HOAc)^+$; 375, 377 $(M - H_2O - HOAc)^+$.

5-Bromo-3β-hydroxy-6β,19-epoxy-5α-pregnan-20-one (**4**)

Compound **3** (1.0 g, 2.2 mmol) was dissolved in methanol (100 ml) and potassium carbonate (1.0 g, 7.2 mmol) in water (20 ml) was added under stirring. The course of the reaction was followed by TLC. After 30 min, the mixture was evaporated to half of its volume, the product was extracted with ether, washed with water, dried and evaporated under reduced pressure. Crystallization from methanol gave 850 mg (93%) of compound **4**, m.p. 183–185 °C, $[\alpha]_D^{20}$ +60 (*c* 1.1); ref.[2] gives m.p. 179–180 °C, $[\alpha]_D^{20}$ +61. IR: 3 625 (OH); 1 709 (C=O); 1 164, 1 097, 1 054, 909 (C–O–C). ^{1}H NMR: 0.66 s, 3 H (3 × H-18); 2.09 s, 3 H (3 × H-21); 2.54 t, 1 H, *J* = 8 (H-17α); 3.92 d and 4.08 d, 2 H, AB system, *J* = 10.5 (2 × H-19); 4.08 d, 1 H, *J* = 7.5 (H-6α); 4.05–4.23 m, 1 H, $W_{1/2}$ = 22 (H-3α). EI MS, *m*/*e*: 413, 411 $(M + H)^+$; 393, 395 $(M^+ - H_2O)$. HR MS: for $C_{21}H_{31}BrO_3$ calculated: 411.153481; found: 411.154100.

5-Bromo-3β-hydroxy-20-oxo-6β,19-epoxy-5α-pregnan-21-yl Acetate (**5**)

Compound **4** (700 mg, 1.7 mmol) in 5% methanolic benzene (21 ml) was stirred with boron trifluoride etherate (3.5 ml, 28.5 mmol) for 20 min at room temperature. Lead tetraacetate (1.49 g, 3.36 mmol) was added and the stirring was continued for 5 h. The mixture was diluted with benzene and worked up as usual. Evaporation gave 750 mg (94%) of oily product **5**. Crystallization from acetone–light petroleum afforded crystaline product as needles, m.p. 153–155 °C; ref.[4] gives m.p. 153–155 °C. IR (KBr): 1 750 (C=O, acetate); 1 724, 1 703 (C=O, ketone); 1 232, 1 020 (C–O, acetate); 1 056 (C–O, hydroxyl); 594 (C–Br). ^{1}H NMR: 0.65 s, 3 H (3 × H-18); 2.09 s, 3 H (CH_3COO); 2.52 t, 1 H, *J* = 8 (H-17α); 3.65 d and 3.92 d, 2 H, *J* = 9 (2 × H-19); 4.08 d, 1 H, *J* = 6.5 (H-6α); 4.05–4.23 m, 1 H, $W_{1/2}$ = 22 (H-3α); 4.71 d and 4.45 d, *J* = 15 (2 × H-21). FAB MS, *m*/*e*: 471, 469 $(M + H)^+$.

5-Bromo-3,20-dioxo-6β,19-epoxy-5α-pregnan-21-yl Acetate (**6**)

Acetate **5** (755 mg, 1.6 mmol) in acetone (37.7 ml) at 5 °C was treated with Jones reagent until a permanent orange colour persisted. The excess reagent was destroyed by adding propan-2-ol. After filtration, the solution was diluted with dichloromethane and worked up as usual. Evaporation of the solvent at room temperature gave the unstable keton **6** (600 mg, 80%). Crystallization from methanol gave needles, melting point 99 °C; ref.[4] gives m.p. 103–104 °C. As this compound rapidly decomposed, it was used for the next reaction step without further purification.

3,20-Dioxo-6β,19-epoxypregn-4-en-21-yl Acetate (**7**)

Bromoketone **6** (600 mg, 1.28 mmol) obtained in the previous experiment was mixed with sodium acetate (0.7 g, 8.5 mmol) and methanol (20 ml), and the reaction mixture was heated under reflux until TLC detected no starting material (1 h). Water was added and the product was extracted with chloroform, washed with water and dried. The solvent was evaporated under reduced pressure. Product (360 mg, 73%) on crystallization from acetone–heptane afforded needles of compound **7**, m.p. 190 °C; ref.[2] gives m.p. 193–194 °C. IR: 1 754 (C=O, acetate); 1 730, 1 711 (C=O, 20-ketone); 1 690, 1 679 (C=O, 3-ketone); 1 232, 1 029 (C–O, acetate). ^{1}H NMR: 0.76 s, 3 H (3 × H-18); 2.17 s, 3 H (CH_3COO); 2.51 t, 1 H, *J* = 8 (H-17α); 3.51 d and 4.20 d, 2 H, *J* = 8.2 (2 × H-19); 4.70 d, 1 H, *J* = 7 (H-6α); 4.50 and 4.73, 2 d, AB system, *J* = 16 (2 × H-21); 5.82 s, 1 H (H-4). FAB MS, *m*/*e*: 387 $(M + H)^+$.

21-Hydroxy-6β,19-epoxypregn-4-ene-3,20-dione (**8**)

A solution of compound **7** (39 mg, 0.1 mmol) in benzene (1.4 ml) and methanol (6.9 ml) was heated to 40 °C under nitrogen. A solution of potassium hydrogen carbonate (50 mg, 0.5 mmol) in water (1.2 ml) was added and the reaction mixture was stirred for half an hour. Then the mixture was cooled and product was extracted with chloroform, washed with water, dried, and the solvent was evaporated under reduced pressure. Crystallization of the residue from absolute ethanol afforded compound **8** (28 mg, 80%), m.p. 167 °C. IR ($CHCl_3$): 3 484 (O–H); 1 707 (C=O, 20-ketone); 1 670 (C=O, 3-ketone); 1 074 (C–OH). ^{1}H NMR: 0.75 s, 3 H (3 × H-18); 2.47 t, 1 H, J = 8 (H-17α); 2.97 t, 1 H, J = 8 (H-17α); 3.52 d and 4.19 d, 2 H, J = 8.3 (2 × H-19); 4.71 d, 1 H, J = 7 (H-6α); 4.14 and 4.26, 2 d, AB system, 2 H, J = 16 (H-21); 5.83 s, 1 H (H-4). FAB MS, *m*/*e*: 345 $(M + H)^+$.

The authors are indebted to Dr P. Fiedler for the interpretation of IR spectra measured by Ms K. Matoušková. Proton NMR spectra were measured by Ms J. Snopková, mass spectra by Dr J. Kohoutová. The technical assistance of Ms J. Neumannová is gratefully aknowledged. This work was supported in part by a grant of the Ministry of Health of the Czech Republic (grant No. 4668-3/98).

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