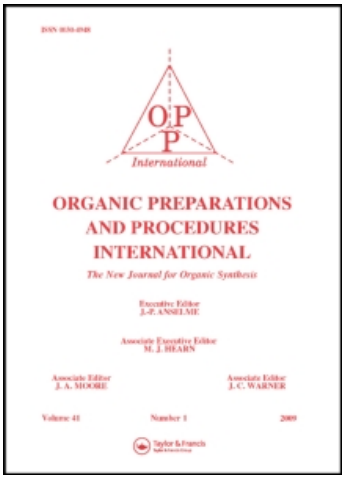

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IMPROVED PREPARATION OF 14β-HYDROXYPROGESTERONE

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IMPROVED PREPARATION OF 14β-HYDROXYPROGESTERONE

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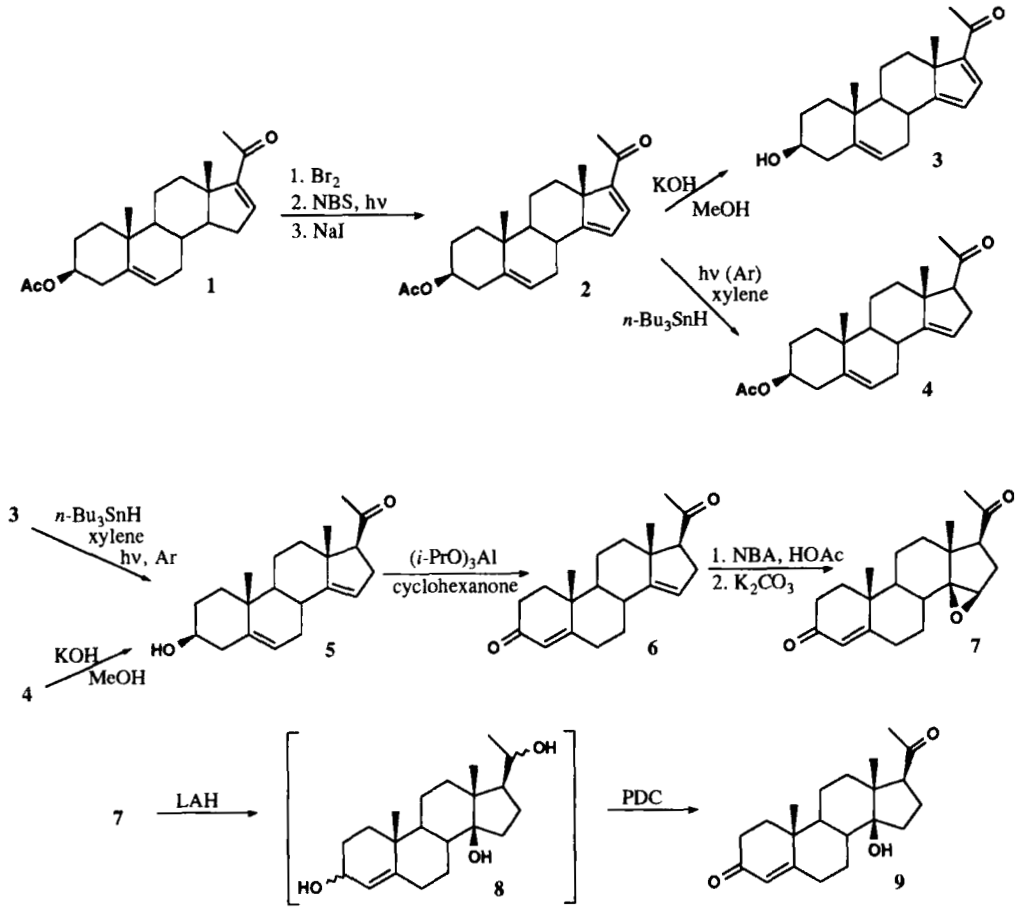
As part of our studies on pregnanes with digitalis-like activity,[1,2] we required C-4 unsaturated pregnane derivatives. We previously reported the synthesis of the novel cardioactive steroid, 14β-hydroxyprogesterone (**9**),[3] from 14α-hydroxyprogesterone obtained by microbial oxidation of progesterone.[4] Now we describe an efficient chemical synthesis of **9** from 3β-acetoxypregna-5,16-dien-20-one (**1**) in a 30% overall yield.



Conversion of the diene acetate **1** to the triene acetate **2** was carried out, after bromination of the C-5 double bond, by allylic bromination at C-15 with N-bromosuccinimide and introduction of the double bonds, using a modification of the procedure reported by Solo *et al.*[5] Hydrolysis of the triene acetate **2** gave the triene alcohol **3**. Selective reduction of the C-16 double bond in **2** has been reported using sodium in propanol[6] and lithium in ammonia[7] as reducing agents; however, these methods gave low yields. Trialkyltin hydrides,[8-11] silicon hydrides[11-13] and dialkyldisiloxanes[13] have also been employed.

When the triene alcohol **3**, under irradiation in an argon atmosphere, was treated with tri-*n*-butyltin hydride in xylene, it was converted to the diene alcohol **5** in high yield; similar treatment of 3β-acetoxypregna-5,14,16-trien-20-one (**2**) gave the diene **4**. The reaction time of 2 hrs was sufficiently short to allow reduction of the triene to go to completion despite the instability of the hydride to heat.[12] Finally, treatment of the diene alcohol **5** under Oppenauer oxidation conditions gave pregna-4,14-diene-3,20-dione (**6**).

Introduction of the 14β-hydroxy group was carried out by treatment with N-bromoacetamide in acetic acid, milder conditions than previously described,[3] followed by alkali to give the 14β,15β – epoxide 7.[3] Reduction of **7** was carried out with lithium aluminum hydride[14] to give a diastereomeric mixture of 3ξ,14β,20ξ-trihydroxypregn-4-ene (**8**). The triol mixture was treated with an excess of pyridinium dichromate in dimethylformamide to ensure complete oxidation of the less reactive quasi-axial 3α-alcohol[15] to 14β-hydroxypregn-4-ene-3,20-dione (**9**).

All structural assignments are consistent with their ^{1}H and ^{13}C NMR and mass spectra.

EXPERIMENTAL SECTION

Melting points were determined on a Koffler melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 instrument operating at 300 MHz for hydrogen and 75 MHz for carbon (TMS internal standard). Mass spectra were determined on a VG-7070E-HF instrument at 70eV. A commercial 275 Watt sun-lamp was used for irradiation of reactions in a pyrex flask. Reactions were monitored by TLC on silica gel (Merck type 60H) plates and developed in 25-75% ethyl acetate-hexane and visualized with a UV lamp where appropriate and by dipping in 8% aqueous sulfuric acid followed by heating. Flash chromatography was carried out on silica gel (Terochem, silica gel 20 - 45 microns for column chromatography) unless otherwise stated. Products were isolated by dilution of the reaction mixture with water followed by dichloromethane extraction. The organic layer was washed with water, saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude reaction product which was purified by flash chromatography, if required, and recrystallized.

3β-Acetoxypregna-5,16-dien-20-one (**1**) was obtained from the Tienjin No. 1 Pharmaceutical Co., Tienjin, P. R. China.

3β-Acetoxypregna-5,14,16-trien-20-one (2).- To a stirred solution of **1** (5.0 g) in anhydrous diethyl ether (170 mL) was added anhydrous KOAc (10 g) in glacial HOAc (100 mL). The solution was cooled in an ice-bath while bromine (2.25 g) in HOAc (50 mL) was added dropwise over a period of 3 hrs. The solution was stirred at 0-15° for an additional 4 hrs and at room temperature for 15 hrs.

After work-up, the residue was dissolved in carbon tetrachloride (75 mL), N-bromosuccinimide (4.84 g) added and the mixture refluxed with stirring under UV irradiation in an argon atmosphere for 20 min and reflux continued for a further 1 hr. The reaction mixture was cooled, filtered and evaporated. The residue was dissolved in acetone (75 mL) and NaI (10 g) added in one portion and the mixture refluxed under argon for 5 hrs. The mixture was diluted with water and extracted with dichloromethane which was washed with aqueous $Na_2S_2O_3$ to give, after flash chromatography over Merck acid-washed alumina and elution with petroleum ether-ethyl acetate, **2** (3.44 g, 69%), mp. 157-159° (acetone), lit.[4] mp. 159-160° . ^{1}H NMR: δ 0.82 (dt, J = 5.5, 12.6, 12.6 Hz, 1H, 9-H), 1.15 (s, 3H, 10-Me), 1.20 (s, 3H, 13-Me), 2.04 (s, 3H, 3-OAc), 2.33 (s, 3H, 20-Me), 4.61 (m, 1H, 3-H), 5.48 (m, 1H, 6-H), 6.02 (t, J = 2 Hz, 1H, 15-H), 7.23 (d, J = 2 Hz, 1H, 16-H). MS(EI): m/z (%) 294 $[M\text{-}HOAc]^+$ (4.1), 171 (6.3), 84 (100).

3-Hydroxypregna-5,14,16-triene-20-one (3).- To a stirred solution of methanol (800 mL) and 0.5 M KOH (700 mL) was added **2** (13.6 g). After 20 hrs at room temperature the mixture was diluted with water and extracted with dichloromethane-methanol to give **3** (11.4 g, 95%), mp. 199-202° (dichloromethane-methanol), lit.[16] mp. 185-187°. ^{1}H NMR: δ 0.82 (dt, J = 5.5, 12.6, 12.6 Hz, 9-H), 1.15 (s, 3H, 10-Me), 1.20 (s, 3H, 13-Me), 2.33 (s, 3H, 20-Me), 3.53 (m, 1H, 3-H), 5.45 (m, 1H, 6-H), 6.02 (t, J = 2 Hz, 1H, 15-H), 7.23 (d, J = 2 Hz, 1H, 16-H). ^{13}C NMR: δ 37.54 (1), 31.59 (2), 71.65 (3), 42.17 (4), 140.47 (5), 120.74 (6), 28.90 (7), 32.38 (8), 54.14 (9), 37.44 (10), 20.74 (11), 35.72 (12), 53.54 (13), 173.22 (14), 119.03 (15), 141.74 (16), 154.76 (17), 18.38 (18), 19.51 (19), 192.57 (20), 26.68 (21). MS(EI): m/z (%) 312 $[M]^+$ (28.5), 294 $[M\text{-}H_2O]^+$ (16.1), 269 (7.8), 122 (100).

3β-Acetoxypregna-5,14-dien-20-one (4).- To **2** (100 mg) in xylene (20 mL) was added tri-n-butyltin hydride (0.4 mL) and the solution stirred under irradiation in an argon atmosphere for 1 hr and heated to reflux for a further hr. Methanol (10 mL) was added and reflux continued for 1 hr to terminate the reaction. The reaction product was flash chromatographed over silica and eluted with hexane to remove hexa-n-butylditin followed by 10% methanol-dichloromethane which yielded **4** (50 mg, 50%), mp. 158-161° (dichloromethane-methanol), lit.[9] mp. 158-161°. ^{1}H NMR: δ 0.88 (s, 3H, 13-Me), 1.04 (s, 3H, 10-Me), 2.03 (s, 3H, 20-Me), 2.16 (s, 3H, 3-OAc), 2.92 (dd, J = 7.9, 9.9 Hz, 1H, 17-H), 4.60 (m, 1H, 3-H), 5.18 (d, J = 2 Hz, 1H, 15-H), 5.43 (t, J = 2 Hz, 1H, 6-H).

3β-Hydroxypregna-5,14-dien-20-one (5).- From **3**: Compound **3** (1.6 g) was treated in xylene (60 mL) with tri-n-butyltin hydride (8.6 g) as described above for **4** to give on flash chromatography, after washing with hexane, on elution with 10% methanol-dichloromethane **5** (1.35 g, 84%), mp. 212-215° (dichloromethane-methanol), lit.[17] mp. 215-218°. ^{1}H NMR: δ 0.87 (s, 3H, 13-Me), 1.03 (s, 3H, 10-Me), 2.17 (s, 3H, 20-Me), 2.92 (dd, J = 7.9, 9,9, 1H, 17-H), 3.54, (m, 1H, 3-H), 5.19 (m, 1H, 15-H), 5.41 (m, 1H, 6-H). ^{13}C NMR: δ 37.08 (1), 31.55 (2), 71.66 (3), 42.17 (4), 139.87 (5), 121.26 (6), 29.73[a] (7), 30.91 (8), 50.07 (9), 36.90 (10), 21.66 (11), 41.31 (12), 48.20 (13), 151.04 (14), 118.15 (15), 31.24[a] (16), 65.23 (17), 18.25 (18), 19.14 (19), 209.28 (20), 31.41 (21); [a]interchangeable. MS(EI): m/z(%) 314 $[M]^+$ (96), 296 $[M\text{-}H_2O]^+$ (37).

From Compound 4.- Compound **4** (50 mg) in 0.025 M methanolic KOH (12 mL) was allowed to

stand at room temperature for 18 hrs to give, after flash chromatography in 10% dichloromethane-hexane, fractions of **5** (38 mg, 86%) as determined by ^{1}H NMR.

Pregna-4,14-diene-3,20-dione (6).- To dry toluene (145 mL) containing the diene alcohol **5** (1 g) and freshly distilled cyclohexanone (50 mL) was added a solution of aluminum isopropoxide (3 g) in dry toluene (50 mL) over 1.5 hrs during distillation. Sodium potassium tartrate solution was added and the mixture steam distilled. The aqueous layer was extracted with chloroform to give, after flash chromatography over silica, on elution in 25% ethyl acetate-hexane, **6** (800 mg, 80%), mp. 142-145° (ether-methanol), lit.[3] 143-145°.

14β,15β-Epoxypregn-4-ene-3,20-dione (7).- To a stirred solution of **6** (150 mg), HOAc (10 mL), acetone (30 mL) and water (20 mL) was added N-bromoacetamide (80 mg) and the mixture stirred under argon at room temperature for 40 min. The solution was then adjusted to pH 9 with saturated aqueous K_2CO_3 to give **7** (127 mg, 80%), mp. 186-188° (methanol-water), lit.[3] mp. 187-188°.

14β-Hydroxypregn-4-ene-3,20-dione (9).- To a stirred solution of **7** (166 mg) in dry tetrahydrofuran (30 mL) was added LAH (300 mg) to give the diol **8** as reported in ref. 14. The reaction product in DMF was treated with PDC (800 mg) and stirred at room temperature for 18 hrs to give **9** (145 mg, 87%), mp. 181-184° (dichloromethane-acetone), lit.[3] mp. 180-181°. ^{1}H and ^{13}C NMR agree with the data in ref. 3.

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