

A New Route to the Synthesis of Cortodoxon from Progesterone

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Among corticoids, hydrocortisone **1** which is the major hormone secreted by the human adrenal cortex is widely used for the therapeutic purpose.¹ Although various synthetic methods have been reported,² the introduction of hydroxyl group in β -phase at 11-position is the major obstacle to reduce multi-synthetic steps of hydrocortisone. Because of this obstacle, main commercial routes to hydrocortisone are based on naturally occurring steroids which have an oxygen at 11-position such as 20-cyano-4,17-pregnene-21-ol-3,11-dione³ (Merck process) or diosgenin⁴ (Upjohn process).

Recently, selective β -hydroxylation of steroids by microbial biotransformation has been focused as a new route to syntheses of various corticoids.⁵ Based on this report, we have considered the β -hydroxylation of cortodoxon^{6a} (**2**, or named as Reichstein's Substance S) as a new route to the synthesis of hydrocortisone since β -hydroxylation of cortodoxon by the reported biotransformation can produce hydrocortisone without much difficulty to control the stereochemistry at 11-position. Although cortodoxon was prepared from various materials,⁶ interestingly, there has been no attempt to synthesize cortodoxon from inexpensive progesterone. As of alternative synthetic method of cortodoxon, we started from progesterone and could synthesize cortodoxon in 31% total yield. In this report, we describe an efficient synthetic procedure of cortodoxon from progesterone.

Progesterone **3** was reacted with ethyl oxalate in the presence of sodium methoxide to generate the sodium enolate of 21-ethoxy oxalylprogesterone,⁷ which was then treated with 2 equivalents of bromine followed by Favorskii rearrangement⁸ with the addition of sodium methoxide to give **4** in 91% yield. The protection of the keto group at 3-position in **4** with ethylene glycol and *p*-toluenesulfonic acid gave **5**, where the methyl ester group at 20-position was reduced with LiAlH_4 to give the allylic alcohol **6**. After **7** was obtained by acid catalyzed hydrolysis of the ketal group, the hydroxy group was acetylated with acetic anhydride to give **8** in 80% yield. Finally, oxidation of the double bond at 17-

position with OsO_4/NMO ⁹ followed by deacetylation with basic hydrolysis gave cortodoxon **2**.^{6a}

In summary, cortodoxon was synthesized from progesterone in 31% total yield as a key intermediate for the synthesis of hydrocortisone.

Experimental Section

Instruments. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz. Chemical shifts were given in relative tetramethylsilane. Infrared spectra were recorded on a Nicolet FT-IR 550 spectrometer. Flash column chromatography was done by using Merck silica gel 60 (15-40 μm).

3-Keto-4,17(20)-pregnadiene-21-oic acid methyl ester (4). The solution of sodium methoxide (30% solution in MeOH, 6.70 mL, 35.0 mmol) in absolute ethanol (1.40 mL) and dry benzene (6.40 mL) were distilled until the total volume was reduced to 16 mL. To a cooled remaining solution, ethyl oxalate (4.70 mL, 35.0 mmol) and progesterone (10.0 g, 32.0 mmol) in dry benzene (76 mL) were added. After the reaction mixture was stirred for 90 min, it was diluted with ether (150 mL), then stirred for another 60 min. The yellow precipitate, which is the sodium enolate of 21-ethoxy oxalyl progesterone, was filtered and dried. The product was used in subsequent reaction without further purification. To a mixture of sodium enolate of 21-ethoxy oxalyl progesterone (13.0 g, 30.0 mol) and potassium acetate (6.00 g, 61.0 mmol) in methanol (450 mL) were added bromine (9.27 g, 180 mmol) and sodium methoxide (30% solution in methanol, 34.3 mL, 180 mmol) dropwise. The mixture was stirred for 16 h at room temperature. After the reaction mixture was quenched with water (200 mL), it was extracted with benzene (3 \times 100 mL) followed by methylene chloride (3 \times 100 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **4** (9.76 g, 91%). R_f = 0.3 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 2947, 1736, 1683 (C=O), 1433 cm^{-1} ; ¹H NMR (CDCl_3) δ 0.69 (s, 3H, - CH_3), 0.75-2.20 (m, 13H), 1.19 (s, 3H, - CH_3), 2.20-2.78 (m, 6H), 3.65 (s, 3H, - OCH_3), 5.65 (s, 1H), 5.71 (s, 1H); ¹³C NMR (CDCl_3) δ 15.4, 17.2, 17.3, 20.9, 23.5, 23.6, 31.8, 32.6, 33.6, 33.8, 34.9, 35.5, 35.6, 50.8, 53.5, 55.7, 111.2, 123.8, 166.1, 171.0, 174.1, 199.2.

21-Carbomethoxy-5,17(20)-pregnadiene-3-ethylene glycol ketal (5). To a solution of **4** (0.700 g, 20.0 mmol) in benzene (75 mL) were added ethylene glycol (3.75 mL, 6.70

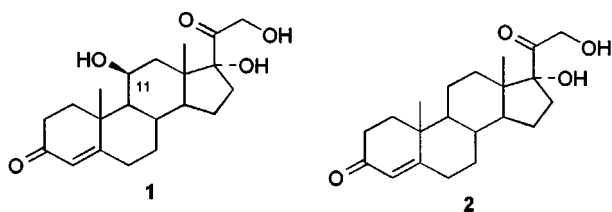


Figure 1

mmol) and *p*-toluenesulfonic acid (0.090 g, 4.80 mmol). After the reaction mixture was refluxed for 5.5 h, it was cooled to room temperature, and then washed with saturated sodium bicarbonate solution (50 mL). The organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **5** (0.730 g, 95%). R_f = 0.5 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 2947, 1736, 1670 (C=O), 1433 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.66 (s, 3H, $-\text{CH}_3$), 0.75-2.74 (m, 19H), 1.24 (s, 3H, $-\text{CH}_3$), 2.2-2.7 (m, 2H, $-\text{CH}_2-$), 3.65 (s, 3H, $-\text{OCH}_3$), 3.93 (s, 4H), 5.36 (s, 1H), 5.66 (s, 1H); ^{13}C NMR (CDCl_3) δ 15.3, 18.8, 21.0, 23.6, 23.8, 31.0, 31.6, 33.7, 36.29, 36.6, 38.1, 41.7, 49.6, 51.1, 11.1, 16.1, 64.1, 109.3, 111.0, 121.8, 140.3, 166.3, 171.8, 174.5.

21-Hydroxy-5,17(20)-pregnadiene-3-ethylene glycol ketal (6). To a solution of **5** (0.580 g, 1.50 mmol) in benzene (27 mL) was added LiAlH_4 (0.0580 g, 1.50 mmol) in anhydrous ether (19 mL). After the reaction mixture was refluxed for 1 h, it was quenched with water (20 mL) and then extracted with methylene chloride (2 \times 40 mL). The organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **6** (0.450 g, 84%). R_f = 0.1 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 3374 ($-\text{OH}$), 2940, 1663, 1453 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.65 (s, 3H, $-\text{CH}_3$), 0.75-2.60 (m, 19H), 1.0 (s, 3H, $-\text{CH}_3$), 3.5 (m, 1H), 3.5 (m, 1H), 3.90 (s, 4H), 5.25 (m, 2H); ^{13}C NMR (CDCl_3) δ 12.4, 18.8, 18.9, 20.7, 24.6, 25.5, 31.0, 31.6, 36.3, 36.7, 38.6, 41.7, 41.8, 49.9, 52.9, 56.2, 64.2, 64.4, 109.4, 114.8, 119.0, 122.0, 140.1, 154.3.

21-Hydroxy-4,17(20)-pregnadiene-3-one (7). To a solution of **6** (1.17 g, 3.20 mmol) in acetone (85 mL) were added water (107 mL) and $\text{c-H}_2\text{SO}_4$ (0.7 mL). After the reaction mixture was stirred for 24 h at room temperature, it was basified with saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride (3 \times 30 mL) and the organic layer was washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **7** (0.850 g, 84%). R_f = 0.16 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 3414 ($-\text{OH}$), 2945, 2874, 1750 (C=O), 1682 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.67 (s, 3H, $-\text{CH}_3$), 0.75-2.49 (m, 19H), 1.17 (s, 3H, $-\text{CH}_3$), 3.49 (dd, J =10.4, 7.4 Hz, 1H), 3.62 (dd, J =10.4, 6.8 Hz, 1H), 5.19 (m, 1H), 5.68 (s, 2H). ^{13}C NMR (CDCl_3) δ 12.3, 17.2, 20.6, 24.3, 25.3, 31.9, 32.7, 33.7, 35.2, 35.5, 38.3, 38.5, 52.6, 53.9, 55.2, 64.0, 115.9, 123.6, 154.3, 171.4, 199.5.

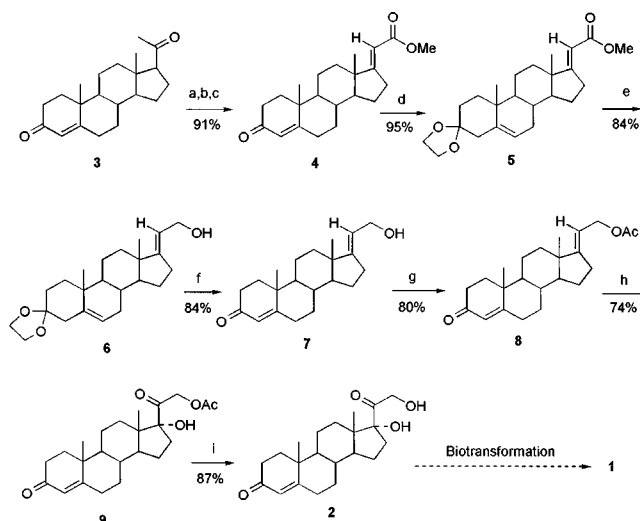
21-Acetoxy-4,17(20)-pregnadiene-3-one (8). To a solution of **7** (0.990 g, 3.00 mmol) in pyridine (9.6 mL) was added acetic anhydride (3.8 mL). After the reaction mixture was stirred for 17 h at room temperature, it was diluted with water (100 mL), and then extracted with methylene chloride (2 \times 50 mL). The organic layer was washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **8** (0.860 g, 80%). R_f = 0.40

(EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 2942, 2875, 1750 (C=O), 1682 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.68 (s, 3H, $-\text{CH}_3$), 0.75-2.50 (m, 19H), 1.18 (s, 3H, $-\text{CH}_3$), 2.03 (s, 3H, $-\text{CH}_3$), 4.03 (d, J =8.0 Hz, 2H), 5.32 (m, 1H), 5.70 (s, 1H); ^{13}C NMR (CDCl_3) δ 12.3, 21.4, 25.0, 29.6, 35.9, 38.7, 48.6, 55.4, 66.0, 123.7, 177.0, 199.3.

17 α -Hydroxy-21-acetoxy-4-pregnene-3,20-dione (9)

To a solution of **8** (0.220 g, 0.617 mmol) in *t*-butyl alcohol (12 mL) were added pyridine (0.3 mL) and OsO_4 (8.00 mg, 0.030 mmol). After the reaction mixture was stirred for 30 min at room temperature, *N*-methylmorpholine *N*-oxide (0.230 g, 1.54 mmol) in *t*-butyl alcohol (5 mL) was added. The mixture was stirred overnight and half of the solvent was evaporated *in vacuo*. The residue was diluted with 5% sodium sulfite solution and then extracted with methylene chloride (2 \times 30 mL). The organic layer was washed with water (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **9** (0.173 g, 74%). R_f = 0.23 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 3459 ($-\text{OH}$), 2952, 1735 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 0.68 (s, 3H, $-\text{CH}_3$), 0.80-2.80 (m, 19H), 1.17 (s, 3H, $-\text{CH}_3$), 2.03 (s, 3H, $-\text{CH}_3$), 4.05 (d, J =7.0 Hz, 1H), 4.80 (dd, J =55.0 Hz, J =18.0 Hz, 1H), 5.10 (dd, J =55.0 Hz, J =18.0 Hz, 1H), 5.70 (s, 1H).

Cortodoxon (2). The mixture of **9** (0.500 g, 1.33 mmol) and K_2CO_3 (0.500 g) in methanol (75 mL) and water (10 mL) was stirred for 24 h at room temperature. After the methanol was evaporated, the mixture was washed with saturated NaCl solution and then extracted with ether (2 \times 50 mL). The etherate was concentrated to give the crude product, which was purified by silica gel column chromatography (EtOAc/ CH_2Cl_2 /hexane = 1/1/2) to give **2** (0.400 g, 87%). R_f = 0.03 (EtOAc/ CH_2Cl_2 /hexane = 1/1/2); IR (neat) 3462 ($-\text{OH}$), 2957, 1715 (C=O) cm^{-1} ; ^1H NMR (CDCl_3) δ 0.63 (s, 3H, $-\text{CH}_3$), 0.80-2.20 (m, 19H), 1.16 (s, 3H, $-\text{CH}_3$),



Scheme 1. (a) NaOMe, ethyl oxalate, EtOH, benzene. (b) Br_2 , AcOK, MeOH. (c) NaOMe, MeOH. (d) ethylene glycol, *p*-TsOH, benzene. (e) LiAlH_4 , ether. (f) dilute H_2SO_4 . (g) Ac_2O , pyridine. (h) OsO_4 , NMO, *t*-BuOH. (i) K_2CO_3 , MeOH/ H_2O .

3.32(s, 2H, -OH), 4.25 (dd, $J=79.0$ Hz, $J=20.0$ Hz, 1H), 4.65 (dd, $J=79.0$ Hz, $J=20.0$ Hz, 1H), 5.70 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.8, 17.2, 20.4, 23.6, 30.1, 31.9, 32.7, 33.7, 34.3, 35.5, 38.5, 48.3, 50.2, 53.2, 67.2, 88.9, 123.6, 171.5, 199.8, 212.4.

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