An Improved Synthesis of the Corticoid Side Chain

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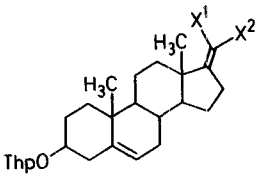
The synthesis of the corticoid side chain has been a subject of interest since androstan derivatives became easily accessible[1]. This problem seemed to be resolved in 1979[2] but not long ago several new methods were published[3].

We have recently reported[4] a new method for the synthesis of the corticoid side chain using a Reformatsky-type reaction[5]. The first step of the sequence was the reaction of an androstan-17-one derivative with ethyl trichloroacetate and zinc in the presence of chlorodiethylalane in order to obtain chloroester A. The key step of the synthesis was the substitution of the vinylic chloride by the methoxide group to give compound B.



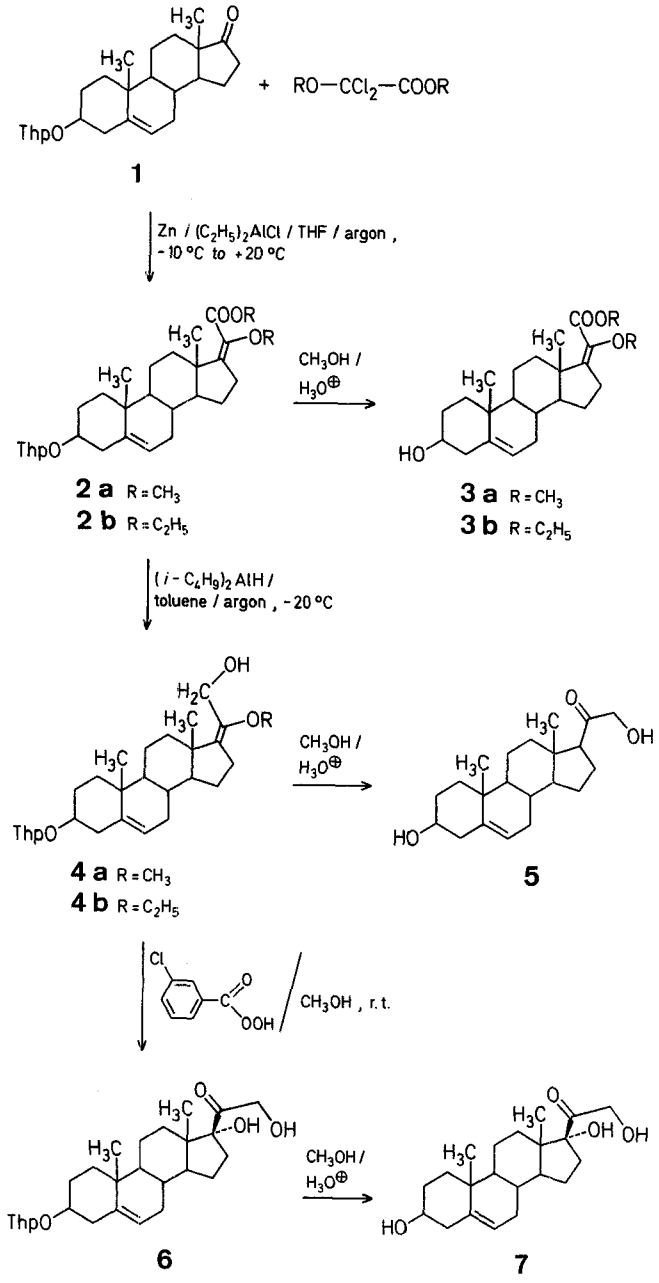
A: $X^1 = COOC_2H_5$; $X^2 = Cl$

B: $X^1 = OCH_3$; $X^2 = COOCH_3$

Compound B appeared to be a very versatile intermediate for further transformations leading to valuable compounds.

We describe here the one-step syntheses of compounds **2a** and **2b** as well as their conversion into the pregnane derivatives **3–7**. The reaction of the *O*-protected androstane-17-one **1** with methyl dichloro-(methoxy)-acetate or ethyl dichloro-(ethoxy)-acetate and zinc in the presence of chlorodiethylalane gave compounds **2a** and **2b** in 80 and 75% yields, respectively. The stereochemistry of A, B, **2a**, and **2b** could be established by their U.V. spectra.

Compound **2a**, obtained directly from Reformatsky-type reaction has an U.V. extinction of $\varepsilon = 7800$, but its isomer B, obtained by methanolysis of chloroester A, has $\varepsilon = 11000$. These data indicate[6] that compounds A, **2a**, and **2b** exist in the (*E*)-geometry, and compound B in the (*Z*)-geometry, which should be more stable. The acidic hydrolysis of α-alkoxyesters **2a** or **2b** at room temperature gave the free alcohols **3a** and **3b**, respectively, with enol ether and ester groups left intact. The reduction of esters **2a** and **2b** with diisobutylaluminum hydride gave the intermediate alcohols **4a** and **4b**, respectively, in quantitative yields. Hydrolysis of **4a** or **4b** afforded the known diol **5** in 98% yield. Oxidation of **4a** or **4b** with 3-chloroperbenzoic acid in methanol, followed by removal of the tetrahydropyranyl group, gave the known triol **7** in 98% yield.



Melting points were measured on micro-hot stage, and are not corrected. Microanalyses were performed by our Microanalytical Laboratory. Mass spectra were measured with an LKB 9000 S instrument. I.R. spectra were recorded on a Unicam SP-200 spectrometer, U.V. spectra on a Unicam SP-700 spectrometer. ^{1}H-N.M.R. spectra were recorded on a Jeol 100 MHz instrument.

Methyl (*E*)-20-Methoxy-3β-(2-tetrahydropyranyloxy)-5,17(20)-pregnadien-21-oate (2a):

To a stirred suspension of zinc dust (1.3 g, 20 mmol) and diethylaluminum chloride (6.3 mol of an 18% hexane solution) in tetrahydrofuran (20 ml), a solution of methyl dichloro-(methoxy)-acetate[7] (1.73 g, 10 mmol) and compound **1** (1.86 g, 5 mmol) in tetrahydrofuran (20 ml) is added at -10°C over a period of 1 h. The mixture is stirred at 0°C for an additional 2 h and then left for 2 h at room temperature. A mixture of water and pyridine (4/1, 10 ml) is added at 0°C and the product is extracted with ether (5×50 ml). The extract is dried with sodium sulfate, the solvent evaporated, and the residue chromatographed on silica gel using hexane/ethyl acetate (95/5) as eluent; yield of **2a**: 1.83 g (80%); m.p. 130–140°C (methanol).

$C_{28}H_{42}O_5$	calc.	C 73.32	H 9.23
(458.6)	found	73.75	9.38

M.S.: $m/e = 374$ ($M^+ - Thp$).

I.R. (Nujol): $\nu = 1715$ cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 237$ nm ($\varepsilon = 7800$).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.0$ [s, 6H, $2CH_3$ (C-18, C-19)]; 3.5 (s, 3H, OCH_3); 3.8 (s, 3H, OCH_3); 3.3–4.0 (m, 3H, 3-H and Thp); 4.85 (br. s, 1H, Thp); 5.4 ppm (br. s, 1H, 6-H).

Ethyl (*E*)-20-Ethoxy-3β-(2-tetrahydropyranyloxy)-5,17(20)-pregnadien-21-oate (2b):

This ester is prepared from **1** (1.86 g, 5 mmol) and ethyl dichloro-(ethoxy)-acetate[7] (2.01 g, 10 mmol) as described for the preparation of **2a**, the reaction temperature being maintained at 40°C for 6 h; yield of **2b**: 1.82 g (75%); m.p. 96–98.5°C (methanol).

$C_{30}H_{46}O_5$	calc.	C 74.05	H 9.53
(486.7)	found	72.95	9.59

M.S.: $m/e = 486$ (M^+).

I.R. (Nujol): $\nu = 1720$ cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 237$ nm ($\varepsilon = 7600$).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.05$ [s, 6H, $2CH_3$ (C-18, C-19)]; 1.35 (t, 6H, O—CH_2—CH_3, $J = 7.5$ Hz); 3.4-4.0 (m, 5H, 3-H, Thp, O—CH_2—CH_3); 4.32 (q, 2H, O—CH_2—CH_3, $J = 7.5$ Hz); 4.8 (br. s, 1H, Thp); 5.45 ppm (br. s, 1H, 6-H).

Methyl (*E*)-20-Methoxy-3β-hydroxy-5,17(20)-pregnadien-21-oate (3a):

The deprotection of 3β-OH group in compound **2a** is carried out by stirring **2a** (0.458 g, 1 mmol) in methanol/water (95/5; 50 ml) containing perchloric acid (a few drops). After 15 min, the mixture is neutralized with saturated aqueous sodium hydrogen carbonate solution and the alcohol **3a** is isolated by evaporation of methanol, filtration, washing with water, and crystallization from ether; yield: 0.367 g (98%); m.p. 143–145.5°C (ether).

$C_{23}H_{34}O_4$	calc.	C 73.76	H 9.15
(374.5)	found	73.79	9.18

M.S.: $m/e = 374$ (M^+).

I.R. (Nujol): ν 3460, 1725, 1630 cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 237$ nm ($\varepsilon = 10500$).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.05$ [s, 6H, $2CH_3$ (C-18, C-19)]; 3.6 (s, 3H, OCH_3); 3.9 (s, 3H, OCH_3); 5.5 ppm (br. s, 1H, 6-H).

Ethyl (*E*)-20-Ethoxy-3β-hydroxy-5,17(20)-pregnadien-21-oate (3b):

Deprotection of the 3β-OH group in compound **2b** is carried out as described for **2a**; yield of **3b**: 98%; m.p. 140–142.5°C (ether/methanol).

$C_{25}H_{38}O_4$	calc.	C 74.59	H 9.52
(402.55)	found	74.28	9.26

M.S.: $m/e = 402$ (M^+).

I.R. (Nujol): $\nu = 3350$, 1725, 1650 cm^{-1}.

U.V. (C_2H_5OH): $\lambda_{max} = 237$ nm ($\varepsilon = 7300$).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.05$ [s, 6H, $2CH_3$ (C-18, C-19)]; 1.32 (t, 6H, $2O—CH_2—CH_3$, $J = 7.5$ Hz); 3.5-4.0 (m, 3H, 3-H, O—CH_2—OCH_3); 4.45 (q, 2H, O—CH_2—CH_3, $J = 7.5$ Hz); 5.45 ppm (br. s, 1H, 6-H).

(*E*)-20-Alkoxy-21-hydroxy-3β-(2-tetrahydropyranyloxy)-5,17(20)-pregnadienes (4a, b):
Diisobutylaluminum hydride (0.5 ml) is added to a stirred and cooled solution of compound **2a** or **2b** (1.0 mmol) in dry toluene under argon. After 5 min, water (1 ml) is added and stirring is continued for 2 h. The precipitated aluminum salt is filtered off and the solvent is evaporated to leave the crude, unstable intermediate **4a** or **4b.**

Alcohol **4a**; yield: 95%; m.p. 79–80.5°C.

I.R. (Nujol): $\nu = 3280, 1690\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.97$ [s, 3H, CH_3 (C-18)]; 1.1 [s, 3H, CH_3 (C-19)]; 3.5–3.8 (m, 2H, Thp); 3.7 (s, 3H, OCH_3); 3.8–4.1 (s, 1H, 3-H); 4.35 (q, 2H, 21,21-H_2, $J = 14$ Hz); 4.85 (br. s, 1H, Thp); 5.4 ppm (br. s, 1H, 6-H).

Alcohol **4b**; yield: 95%; amorphous.

I.R. (Nujol): $\nu = 3280, 1690\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.92$ [s, 3H, CH_3 (C-18)]; 1.05 [s, 3H, CH_3 (C-19)]; 1.3 (t, 3H, O—CH_2—CH_3, $J = 7.5$ Hz); 3.3–4.0 (m, 5H, O—CH_2—CH_3, 3-H, Thp); 4.3 (q, 2H, 21,21-H_2, $J = 14$ Hz); 4.8 (br. s, 1H, Thp); 5.45 ppm (br. s, 1H, 6-H).

3β-21-Dihydroxy-5-pregnen-20-one (5):
The acidic hydrolysis of compound **4a** or **4b** is carried out as described for **2a**; yield of **5**: 98%; m.p. 174–177°C (chloroform/ether) (Ref.[8], m.p. 173–176°C, 155–160°C, 156–162°C).

I.R. ($CHCl_3$): $\nu = 3600$ (free OH); 3480 (H-bonded OH); $1710\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.7$ [s, 3H, CH_3 (C-18)]; 1.05 [s, 3H, CH_3 (C-19)]; 3.55 (m, 1H, 3-H); 4.25 (s, 2H, 21,21-H_2); 5.45 ppm (br. s, 1H, 6-H).

17α,21-Dihydroxy-3β-(2-tetrahydropyranyloxy)-5-pregnen-20-one (6):
A solution of compound **4a** or **4b** (1.0 mmol) and 3-chloroperbenzoic acid (182.2 mg, 1.1 mmol) in methanol (20 ml) is allowed to stand at room temperature for 15 min. Then, saturated sodium hydrogen sulfite solution (1 drop) is added and methanol is evaporated under reduced pressure. The residue is dissolved in dichloromethane (500 ml), washed with saturated aqueous sodium hydrogen carbonate solution, and dried with sodium sulfate Filtration and evaporation of solvent gives crude **6**; yield of **6**: 0.424 g (98%); m.p. 165–180°C (crude).

$C_{26}H_{40}O_5$ (432.6)

M.S.: $m/e = 432$ (M^+).

I.R. (Nujol): $\nu = 3300–3400, 1710\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.7$ [s, 3H, CH_3 (C-18)]; 1.02 [s, 3H, CH_3 (C-19)]; 3.6 (m, 2H, Thp); 4.0 (m, 1H, 3-H); 4.56 (q, 2H, 21,21-H_2, $J = 20$ Hz); 4.8 (br. s, 1H, Thp); 5.45 ppm (br. s, 1H, 6-H).

3β,17α,21-Trihydroxy-5-pregnen-20-one (7):
The acidic hydrolysis of compound **6** is carried out as described for **2a**; yield of **7**: 98%; m.p. 219–222°C (methanol/ether) (Ref.[9], m.p. 224–226°C).

$C_{21}H_{32}O_4$ (348.5)

M.S.: $m/e = 348$ (M^+).

I.R. (Nujol): $\nu = 3380, 1705\ cm^{-1}$.

^{1}H-N.M.R. (pyridine-d_5/TMS_{int}): $\delta = 0.75$ [s, 3H, CH_3 (C-18)]; 1.0 [s, 3H, CH_3 (C-19)]; 3.85 (m, 1H, 3-H); 5.0 (q, 2H, 21,21-H_2, $J = 17.5$ Hz); 5.4 ppm (br. s, 1H, 6-H).

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