An improved synthesis of 18-norandrost-4-ene-3,17-dione

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*We describe the synthesis of 13β- and 13α-H-18-nor-androst-4-ene-3,17-dione (**1a** and **1b**) from 18-hydroxyprogesterone (18 → 20) hemiketal, via the 18-acetoxy-17β-hydroxyandrost-4-en-3-one formed by a modified Baeyer-Villiger reaction. Saponification of 18-acetoxyandrost-4-ene-3,17-dione with sonication, then retroaldolization in the presence of a formaldehyde trap, methone, afforded the mixture of **1a** and **1b** with 80% yield in a "one-pot" procedure and at room temperature. This yield was greatly improved, compared with the already published procedure.* (*Steroids* **58:**141–144, 1993)

Keywords: steroids; 18-norsteroids; retroaldolization; methone

Introduction

Because recent evidence suggested that androstenedione can also be hydroxylated at C-18 by the cytochrome P450 ($P450_{11\beta}$) involved in the corticosterone transformation (Piffeteau A, personal communication), we turned our attention to androstenedione analogs[1] in order to develop new inhibitors of $P450_{11\beta}$ that would be easier to synthesize than in the progesterone series.[2,3] In the course of these studies, we had to prepare 13β- and 13α-H-18-norandrost-4-ene-3,17-dione (**1a** and **1b**). 3β-Hydroxy-13α-18-norandrost-5-en-17-one synthesis was reported,[4] through a series of low-yield steps via a Baeyer-Villiger type oxidation of 3β-acetoxy-18-hydroxypregn-5-en-20-one, followed by retroaldolization of 3β,18-dihydroxyandrost-5-en-17-one, either by pyrolysis (24%) or by treatment with base (17%). We describe here an efficient high-yield synthesis of **1a** and **1b** from 18-hydroxyprogesterone (**2a**) (Scheme 1).

Experimental

Melting points (mp) were determined on a Kofler apparatus and were uncorrected. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$, either on a JEOL 400 or on a Brucker AC 200 spectrometer. Chemical shifts are expressed in ppm relative to TMS (tetramethylsilone) and coupling constants in hertz. The chemical shifts and assignments for the ^{13}C spectra of steroids **1–7** are given in Table 1. Infrared (IR) spectra were recorded in $CHCl_3$ on a Perkin Elmer 1420 spectrometer. Optical rotations were measured in $CHCl_3$ with a Perkin Elmer 241 polarimeter. Mass spectrometry was performed by the Centre de Spectrochimie de l'Université Paris VI and by the Service de spectrométrie de masse de l'ENSCP. CI (chemical ionization) (NH_3) mass spectra were obtained with a RIBER MAG R 10.10 and high-resolution mass spectra on a KRATOS MS 50 spectrometer. Microanalyses were performed by the Centre de Microanalyse de l'Université Paris VI. Starting material [18-hydroxyprogesterone (**2a**)] was a gift of the Roussel-Uclaf Company.

18-Hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal (or 18-Hydroxyprogesterone) (2a)

Melting point 180 C (lit.[5] 173–182 C; lit.[6] 180–182 C). IR: ν cm^{-1} 3,595 (OH), 3,430 broad (OH), 1,655 (conjugated C=O). Mass spectrum (CI/NH_4^+): m/z 348 $(M + NH_4)^+$, 331 $(MH^+$, 313 $(MH^+ - H_2O)$. ^{1}H NMR (200 MHz): δ ppm 1.13 (s, 3H, H-19); 1.5 (s, 3H, H-21); 3.73 (s, 2H, H-18); 5.73 (s, 1H, H-4). $[\alpha]_D^{22} = +122°$ (c = 0.5).

18-Hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal-20-hydroperoxide (3)

Hemiketal (**2a**) (6 mmol, 2 g) was dissolved in 50 ml of dry dioxane, and *p*-toluenesulfonic acid monohydrate (0.16 mmol, 30 mg) was added. The suspension was cooled to 8–10 C and 10 ml of 30% hydrogen peroxide was added dropwise over 20 minutes. The reaction mixture was stirred for an additional hour at 10 C. The obtained suspension was concentrated without heating, then diluted with methylene chloride, washed with a saturated ammonium chloride solution then water, dried over sodium sulfate and concentrated to dryness in vacuo to afford 2.1 g of crude extract, which consisted mainly of 18-hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal-20-hydroperoxide (**3**).

An analytical sample of **3** was obtained by chromatography

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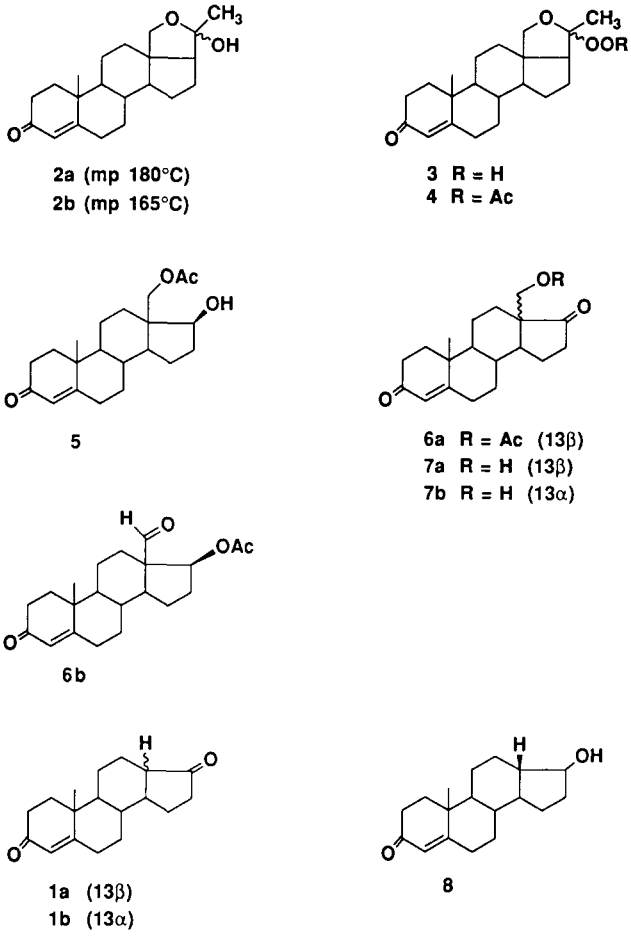

Scheme 1

on silica gel with cyclohexane/ethyl acetate (1 : 1), R_f = 0.37 on TLC chromatography, mp 195–196 C decomposition (lit.[7] 185–190 C decomposition). IR: ν cm^{-1} 3,370 (O—O—H), 1,660 (conjugated C=O). Mass spectrum (CI/NH_4^+): m/z 364 $(M + NH_4)^+$, 347 $(MH)^-$. ^1H NMR (200 MHz): δ ppm 1.1 (s,3H, H-19); 1.53 (s,3H, H-21); 3.7, 3.8 (AB, J = 9.3 Hz, 2H, H-18); 5.73 (s, 1H, H-4). $[\alpha]_D^{22}$ = +160° (c = 0.5).

*18-Hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal (**2b**)*

When the hydroperoxidation reaction was stopped before completion, 18-hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal (**2b**) could be isolated by chromatography of the crude reaction product on silica gel with cyclohexane/ethyl acetate (1 : 1), R_f = 0.48 on TLC chromatography, mp 165 C (lit.[6] mp 164–165 C, lit.[8] mp 159–160 C). IR: ν cm^{-1} 3,500 (OH), 1,655 (conjugated C=O). Mass spectrum (CI/NH_4^+): m/z 348 $(M + NH_4)^+$, 331 $(MH)^+$, 313 $(MH^+ - H_2O)$. ^1H NMR (200 MHz): δ ppm 1.11 (s, 3H, H-19); 1.53 (s, 3H, H-21); 3.71, 3.9 (AB, J = 8 Hz, 2H, H-18); 5.73 (s, 1H, H-4). $[\alpha]_D^{22}$ = +182° (c = 0.625).

*18-Hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal-20-hydroperoxide acetate (**4**)*

The crude product **3** (2.1 g) was dissolved immediately in 5 ml of dry pyridine, cooled to 8–10 C, and 6 ml of acetic anhydride was added dropwise. The solution was stirred at 8–10 C for 1 hour, then left at room temperature for 16 hours to give 2.52 g of 18-hydroxypregn-4-ene-3,20-dione (18 → 20) hemiketal-20-hydroperoxide acetate (**4**).

An analytical sample of **4** was obtained by chromatography on silica gel with cyclohexane/ethyl acetate (1.5 : 1), mp 119–120 C decomposition (lit.[7] 110–114 C decomposition). IR: ν cm^{-1} 1,770 (OC=O), 1,660 (conjugated C=O). ^1H NMR (200 MHz): δ ppm 1.10 (s, 3H, H-19); 1.54 (s, 3H, H-21); 2.07 (s, 3H, —$COCH_3$), 3.76, 3.86 (AB, J = 9.2 Hz, 2H, H-18; 5.72 (s, 1H, H—4). $[\alpha]_D^{22}$ = +121° (c = 0.5).

*18-Acetoxy-17β-hydroxyandrost-4-en-3-one (**5**)*

Without purification, the hydroperoxide acetate **4** (2.52 g) was refluxed for 1 hour 30 minutes with 65 ml of dioxane and 8 ml of an aqueous solution of trimethylamine 25%. The reaction mixture was then neutralized with a 1N HCl solution, diluted with 70 ml of a saturated ammonium chloride solution, and extracted with ethyl acetate. The organic phase was washed with water, dried, and evaporated, giving 2.04 g of crude mixture. Crystallization (1.12 g) occurred in ethanol. Purification of the mother liquors by Flash chromatography through silica gel and elution with cyclohexane/ethyl acetate (2 : 8) gave 0.62 g of pure18-acetoxy-17β-hydroxyandrost-4-en-3-one (**5**) (82% from **2a**), mp 170–171 C (lit.[1] mp 170–172 C). IR: ν cm^{-1} 3,592 (OH), 1,730 (OC=O), 1,660 (conjugated C=O). ^1H NMR (200 MHz): δ ppm 1.18 (s, 3H, H-19); 2.1 (s, 3H, —$COCH_3$), 3.77 (t, 1H, H-17); 4.25, 4.42 (AB, J = 12.3 Hz, 2H, H-18); 5.8 (s, 1H, H-4). $[\alpha]_D^{22}$ = +110° (C = 0.5).

*18-Acetoxyandrost-4-ene-3,17-dione (**6a**) and 17β-acetoxy-3-oxoandrost-4-en-18-al (**6b**)*

18-Acetoxy-17β-hydroxyandrost-4-en-3-one(**5**) (1.6 mmol, 560 mg) was dissolved in dry distilled methylene chloride (56 ml). Pyridinium dichromate (14.9 mmol, 5.6 g) was added, and the solution was stirred under argon and in darkness at room temperature. After 17 hours, 180 ml of diethyl ether was added and the salts were removed by filtration through Celite. The organic phase was washed with water, dried over Na_2SO_4, and evaporated, giving 568 mg of crude extract, which consisted mainly of 18-acetoxyandrost-4-ene-3,17-dione (**6a**) (85%, deduced from ^1H NMR spectrum), contaminated with 17β-acetoxy-3-oxoandrost-4-en-18-al (**6b**) (10%). The crude mixture was used for next step.

Analytical samples of **6a** and **6b** were obtained by chromatography on silica gel with cyclohexane/ethyl acetate (3 : 7):

1. **6a** was the more polar product. R_f = 0.32 on TLC chromatography with cyclohexane/ethyl acetate (1 : 1), mp 127–128 C (lit.[1] 127–128 C, lit.[9] 128–129C). IR: ν cm^{-1} 1,738 (OC=O and C=O), 1,663 (conjugated C=O). ^1H NMR (400 MHz): δ ppm 1.14 (s, 3H, H-19); 1.99 (s, 3H, $COCH_3$); 4.16, 4.28 (AB, J = 13 Hz, 2H, H-18); 5.69 (s, 1H,H-4). Analysis of $C_{21}H_{28}O_4$: C, 73.05%; H, 8.35% (calculated: C, 73.25%; H, 8.13%). $[\alpha]_D^{22}$ = +160° (c = 0.5).

2. **6b** was the less polar product. R_f = 0.49 on TLC chromatography with cyclohexane/ethyl acetate (1 : 1), mp 194–195 C. IR: ν cm^{-1} 1,720 (OC=O and C=O), 1,662 (conjugated C=O). Mass spectrum electron impact (EI): m/z 344 (M^+). High-resolution mass spectrum for $C_{21}H_{28}O_4$: 344.1992 (calculated 344.19876). ^1H NMR (400 MHz): δ ppm 1.03 (s, 3H, H-19); 1.95 (s, 3H, $COCH_3$); 4.84 (t, 1H, H-17); 5.69 (s, 1H, H-4), 9.72 (s, 1H, H-18). $[\alpha]_D^{22}$ = +121° (c = 0.5).

*13β- and 13α-H-18-norandrost-4-ene-3,17-dione (**1a** and **1b**) (one-pot procedure)*

A solution of potassium carbonate (1.53 g) and methone (0.9 g) in 7.2 ml of water was added to 45 ml of a methanolic solution

Table 1 Chemical shifts and assignments for the ^{13}C spectra of steroids **1–7** in $CDCl_3$ (ppm)

	2a	2b	3	4	5	6a	6b	7a	7b	1a	1b
C-3	199.44	199.77	199.49	199.46	199.38	198.96	199.53	199.38	199.48	199.11	199.20
C-4	123.85	124.27	124.00	123.98	123.93	124.09	124.35	124.21	124.08	123.91	123.74
C-5	170.91	171.13	170.73	170.71	171.13	170.87	170.85	170.08	170.19	170.21	170.30
C-10	38.43	38.83	38.47	38.48	38.50	38.41	38.78	38.64	38.64	38.47	38.47
C-13	54.08	53.68	53.74	53.57	45.07	50.50	58.46	52.61	55.85	54.56	49.66
C-17	56.15	55.38	54.94	54.96	81.77	216.37	81.28	219.73	221.02	217.38	219.23
C-18	72.74	73.49	73.69	74.16	61.97	59.63	205.09	58.28	66.88	—	—
C-19	17.36	17.80	17.40	17.38	17.27	17.18	17.69	17.28	17.56	17.42	17.55
C-20	107.39	114.91	116.06	117.4	—	—	—	—	—	—	—
C-21	24.60	19.10	17.89	17.73[a]	—	—	—	—	—	—	—
$\underline{O}COCH_3$	—	—	—	168.02	170.60	169.57	170.43	—	—	—	—
$O\underline{C}OCH_3$	—	—	—	18.72[a]	21.11	19.89	21.17	—	—	—	—

[a] May be interchanged.

of the crude product **6** (447 mg). The solution was sonicated, and after 10 minutes saponification was complete. The solution, consisting mainly of 13β-18-hydroxyandrost-4-en-3,17-dione (**7a**), was then stirred at room temperature for 17 hours. The solvent was evaporated. The retroaldolization products were extracted with ethyl acetate (100 ml), washed with water, and dried. The organic phase was evaporated and the products were filtered through 25 g of silica gel and eluted with cyclohexane/ethyl acetate (1 : 1) to give 250 mg of the two epimers **1a** and **1b** (80%), IR: ν cm^{-1} 1,730 (C=O), 1,662 (conjugated C=O). Mass spectrum EI: m/z 272 (M^+). High-resolution mass spectrum for $C_{18}H_{24}O_2$: 272.1777 (calculated 272.17763).

An analytical sample of epimers **1a** and **1b** was obtained by TLC chromatography with cyclohexane/ethyl acetate (1 : 1):

1. **1a** was the more polar product. R_f = 0.42 on TLC chromatography. ^1H NMR (400 MHz): δ ppm 1.17 (s, 3H, H-19); 5.76 (s, 1H, H-4).

2. **1b** was the less polar product. R_f = 0.48 on TLC chromatography, mp 202–203 C (lit.[10] 198–203 C). ^1H NMR (400 MHz): δ ppm 1.02 (s, 3H, H-19); 5.72 (s, 1H, H-4).

13β- and 13α-18-hydroxyandrost-4-en-3,17-dione (7a and 7b) through to 1a and 1b

Analytical samples of **7a** and **7b** were obtained when the same experiment was conducted without methone under the same conditions, followed by TLC chromatography with cyclohexane/ethyl acetate (1 : 4):

1. **7a** was the more polar product. R_f = 0.30 on TLC chromatography, mp 200–202 C. IR: ν cm^{-1} 3,610 (OH); 3,575–3,430 broad (OH), 1,728 (C=O), 1,662 (conjugated C=O). Mass spectrum EI: m/z 302 (M^+). High-resolution mass spectrum for $C_{19}H_{26}O_3$: 302.1882 (calculated 302.18819). ^1H NMR (400 MHz): δ ppm 1.21 (s, 3H, H-19); 3.71, 3.86 (AB, J = 11.6 Hz, 2H, H-18); 5.75 (s, 1H, H-4). $[\alpha]_D^{22}$ = +155° (c = 0.5).

2. **7b** was the less polar product. R_f = 0.38 on TLC chromatography, amorphous powder. IR: ν cm^{-1} 3,610 (OH), 3425 broad (OH), 1,728 (C=O), 1,662 (conjugated C=O). High-resolution mass spectrum for $C_{19}H_{26}O_3$: 302.1882 (calculated 302.18819). ^1H NMR (200 MHz): δ ppm 1.04 (s, 3H, H-19); 3.4, 3.5 (AB, J = 12 Hz,2H, H-18); 5.73 (s, 1H, H-4). $[\alpha]_D^{22}$ = +19° (c = 0.6).

17β-Hydroxy-13β-H-18-norandrost-4-en-3-one (8)

A solution of the 18-norepimers **1a** and **1b** (0.18 mmol, 50 mg) was dissolved in 12.5 ml of dry distilled methylene chloride/methanol (1 : 1) and cooled between −70 and −60 C. Sodium borohydride (1.3 mmol, 50 mg) was added. After 4 hours, the reaction was stopped with acetone (2.5 ml). The mixture was diluted with methylene chloride, washed with water, dried, and concentrated. Purification by chromatography on silica gel afforded the unreduced 13α-H-18-norandrost-4-ene-3,17-dione **1b** (58%) and 17β-hydroxy-13β-H-18-norandrost-4-en-3-one (**8**) (11 mg, 22% yield after purification). Analysis of **8**: mp 166–167 C. IR: ν cm^{-1} 3,600 (OH), 1,728 (C=O), 1,657 (conjugated C=O). ^1H NMR (400 MHz): δ ppm 1.15 (s, 3H, H-19); 3.77 (m, 1H, H-17); 5.74 (s, 1H, H-4). $[\alpha]_D^{22}$ = +97° (c = 0.5). Mass spectrum EI: m/z 274 (M^+). High-resolution mass spectrum for $C_{18}H_{26}O_2$: 274.1928785 (calculated 274.193278).

Results and discussion

18-Hydroxyprogesterone (**2a**) (mp 180 C), isolated as the 18 → 20 hemiketal, was oxidized with hydrogen peroxide in dioxane to give the hydroperoxide **3**, which was immediately acetylated with acetic anhydride in pyridine to give hydroperoxide acetate (**4**). The hydroperoxide acetate, dissolved in aqueous dioxane, was refluxed with trimethylamine to achieve the degradation of carbons 20 and 21, according to a modified Baeyer-Villiger reaction, developed by Pappo,[9] then by Iseli and Fukushima.[11] After workup and silica gel chromatography, crystalline 18-acetoxy-17β-hydroxyandrost-4-en-3-one (**5**) was obtained with 78% yield from **2a**. When the hydroperoxidation reaction was performed at 4 C, the yield of hydroperoxide was substantially reduced and an appreciable quantity of a TLC less polar product was formed. On the basis of NMR and mass spectra, its structure was assigned to be the epimer at C-20 of 18-hydroxyprogresterone hemiketal **2b**[5,6,8] (mp 165 C). Stereochemistry at C-20 of both diastereoisomers could not be determined by NOE (nuclear overhauser effects) experiments.

18-Acetoxy-17β-hydroxyandrost-4-en-3-one (**5**) was oxidized with pyridinium dichromate to give 18-acetoxyandrost-4-ene-3,17-dione (**6a**) and 17β-acetoxy-3-oxoandrost-4-en-18-al (**6b**) produced from the transesterification product of **5**, in the ratio 85 : 10 deduced from the ^1H NMR spectrum. Without purification, the 18-acetoxy-3,17-diketone was then saponified and submitted to retroaldolization by alkaline treatment. The

18-acetoxy group was rapidly hydrolyzed at room temperature in methanol by sonication for 10 minutes with a potassium carbonate aqueous solution to give a mixture of epimers at C-13: 13β- and 13α-(18-hydroxy)diketone (**7a** and **7b**), showing the reversibility of the aldolization, and 13β- and 13α-H-18-nordiketone (**1a** and **1b**). After saponification, if the reaction mixture was stirred for 17 hours at room temperature, the retroaldol cleavage was not complete and afforded the same four products. If the reaction mixture was refluxed for 2 hours, the reaction was complete but gave the two epimeric 18-nordiketones with a low yield (40%) because of thermal decomposition.

We overcame this difficulty by adding methone,[12] a formaldehyde trap, and we propose an efficient one-pot procedure to obtain **1a** and **1b** with a good yield. After saponification with sonication in the presence of methone, no 13α-(18-hydroxy)diketone (**7b**) was detected in the reaction mixture. The reaction was left at room temperature, and after 17 hours retroaldolization was complete. The mixture of the two epimers was purified by silica gel chromatography (80%). The ratio between C/D *cis* and C/D *trans* ring junction was 3 : 1 according to the ^{1}H NMR spectrum. At this stage, the contaminant **6b**, produced during oxidation of **5**, disappeared by reaction with methone.

In the course of further studies, we had to reduce selectively the 17-carbonyl group. This was achieved with $NaBH_4$ in CH_3OH/CH_2Cl_2(1 : 1) between −70 and −60 C.[13] However, the reaction was not complete. After 4 hours, the 13β-H-18-norandrost-4-ene-3,17-dione (**1a**) was completely transformed into the alcohol **8**, whereas the13α-H-18-norandrost-4-ene-3,17-dione (**1b**) was unchanged. Compounds **1b** and **8** were easily separated by chromatography and recovered with a ratio of 3 : 1, which was the ratio of **1a** and **1b**, deduced from the ^{1}H NMR spectrum. The absence of reduction of the 13α-H-18-norandrost-4-ene-3,17-dione **1b** confirmed previous observations, because some 13α-H-18-norsteroids (C/D *cis*) were reported to be resistant to reduction with pyridine-borane in acetic acid.[14,15]

In conclusion,we propose the synthesis of 18-norsteroids **1a** and **1b** with a greatly improved yield, in a procedure that gives ready access to steroids of the 13α series (**1b** and **7b**).

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