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Synthesis of the 11β-hydroxymethyl-androst-4-en-3,17-dione

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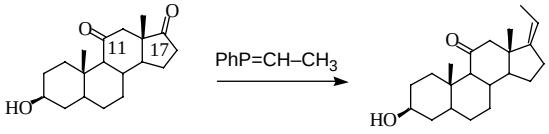
Abstract—The 11β-hydroxymethyl-androst-4-en-3,17-dione **5** was prepared within five synthetic steps starting from the commercially available adrenosterone with an overall yield of 24%. The 11-ketosteroid **1** was subjected to a Peterson methylenation. The subsequent hydroboration/oxidation sequence in position 11 was regio- and stereoselectively conducted using the borane–methyl sulfide complex at 0 °C. The target molecule was then obtained by deprotection using in situ generated TMSI.

1. Introduction

Several differently substituted androstenediones have been described in the literature as aromatase inhibitors or testosterone precursors.[1–5] However, only one example of C-11β modified androstenedione bearing a lateral carbon chain has been reported to date: the 11β-(4-methoxy-phenyl)-androstenedione, which was prepared within 11 synthetic steps in low yield.[5] The access to C-11 substituted steroids in androstane and androstene series is rather limited by the low reactivity at that position. As an example, a 100% regioselective Wittig olefination was done at C-17 on 3β-hydroxy-androstan-11,17-dione (Scheme 1).[6]



Scheme 1.

However, our group has recently shown that some organometallic reagents could be efficiently added to 11-keto androstenes.[7–9] After those encouraging results, we have thus turned our attention to the methylenation reaction of that position, the 11-methylene androstene **3** obtained could then be transformed into the corresponding 11β-hydroxymethyl derivative **4**, which in turn could lead to the androstenedione **5** expected.

2. Results and discussion

Scheme 2 describes the synthetic route chosen to the 11β-hydroxymethyl-androstenedione **5**. The ketosteroid **1** was prepared by protection of the C-3 and C-17 ketones of the commercially available adrenosterone using standard procedure.[10]

Various methylenation conditions were tested. Although the Tebbe reagent,[11] the CH_2Br_2–Zn–$TiCl_4$ system,[12] and the Olah conditions[13] are usually efficient on hindered ketones, when working on the steroid **1**, no methylenation product could be observed. The Peterson procedure,[14] already used in the nor-pregnene series,[15] was more suitable to our case (Scheme 3).

Table 1 presents the results obtained for the addition of Me_3SiCH_2M (M = MgCl, Li) to the 11-keto androstene **1**.

No addition was observed when the (trimethylsilyl)methyl magnesium chloride (1 M solution in diethylether) was used in THF at room temperature or at 50 °C (Table 1, entries 1 and 2). In toluene, increasing the temperature from room temperature to reflux allowed to get 23% addition (Table 1, entries 1 and 3). The use of (trimethylsilyl)methyl lithium (1 M solution in pentane) in THF or toluene gave about 50% addition at room temperature, and the addition was almost quantitative in refluxing toluene within 1 h (Table 1, entries 4 and 5).

The elimination reaction of the β-hydroxysilyl derivative **2** did not proceed under the addition conditions. The 11-methylene steroid **3** was thus prepared using potassium hydride in refluxing THF (78% yield).

Keywords: 11-Ketosteroids; Methylenation; Stereoselection.
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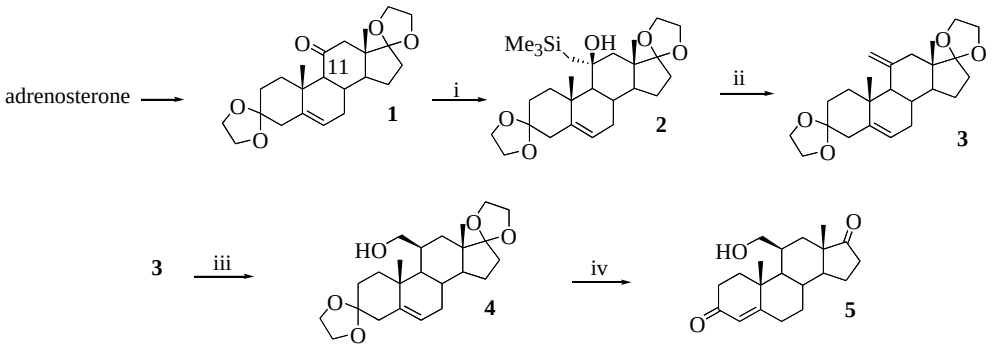
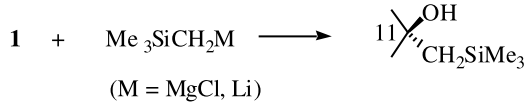


Scheme 2. Reagents and conditions: (i) Me_3SiCH_2Li/toluene, reflux; (ii) KH/THF, reflux; (iii) a. $BH_3 \cdot SMe_2$/THF, 0 °C; b. H_2O_2/NaOH; (iv) TMSCl, NaI/CH_3CN.



Scheme 3.

The hydroboration reaction of the steroid **3** was initially performed using 9-BBN or catechol borane to induce high selectivity, but no reaction was observed with these reagents. The more reactive borane BH_3 (used as a complex with dimethylsulfide (BMS) or with THF), was thus employed at different temperatures, reaction times and concentrations (Table 2). After oxidation, both the hydroxy compound **4** and the dihydroxy compound **9**, were obtained (Scheme 4), and their configuration was determined by NMR.

The NOESY spectrum of **4** presented cross-peaks between protons of the hydroxymethyl moiety and those of the angular methyls CH_3-18 and 19, thus indicating the C-11β configuration. Concerning **9**, using the shape of its ^{1}H NMR signal, the configuration C-6α was attributed.[16]

The selectivity was low at room temperature (Table 2, entries 1 and 2), but was improved when working at lower temperature (Table 2, entries 3–6). The best result was obtained after 24 h at 0 °C using 2.5 equiv of BMS (Table 2, entry 5), allowing us to prepare the alcohol **4** with 45% isolated yield.

The double bond in position 11 was more reactive than the one in position 5,6 (Table 2, entries 3, 4 and 6). Thus, once formed, the alkyl borane **7**, could react with remaining BH_3 to give the diborane compound **8**. Both additions proceeded through the least hindered α face of the steroid, at C-11 or C-5,6. An opposite result was observed for the hydroboration by BH_3 of the 3,3;17,17-bisethylenedioxy-androst-5-ene, which occurred predominently through the β face (β/α 4/1).[17] The first hydroboration reaction, producing **7**, thus prevents the second hydroboration (from **7** to **8**) occuring from the β face.

Using in situ generated TMSI, from TMSCl and NaI, the protecting groups in position 3 and 17 of the 11β-hydroxymethyl-androst-4ene-3,17-dione **5** were quantitatively removed in acetonitrile at room temperature. Under such conditions, alcohols may be converted into halogenated species.[18] That reaction was likely to be slowed down

Table 1. Addition of Me_3SiCH_2M (3 equiv) to steroid **1**

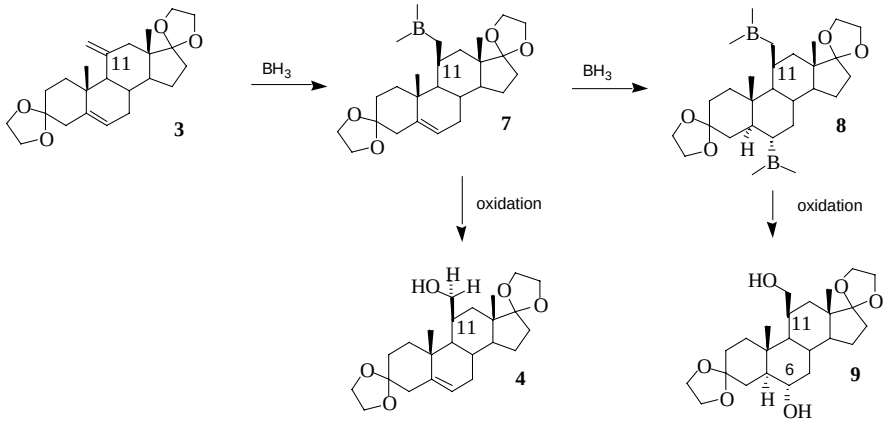
Entry	M	Solvent	*T* (°C)	*t* (h)	Conversion (%) **2**[a]
1	MgCl	THF or toluene	rt	2	0
2	MgCl	THF	50	1.5	0
3	MgCl	Toluene	Reflux	2	23
4	Li	THF or toluene	rt	3	45–50
5	Li	Toluene	Reflux	1	90–95 (76% yield)

[a] Determined by ^{1}H NMR.

Table 2. Hydroboration/oxidation of steroid **3** (in THF, with nBH_3)

Entry	Borane[a]	*n* (equiv)	*T* (°C)	*t* (h)[b]	% **3**[c]	% **4**[c]	% **9**[c]
1	BMS	1	rt	1	37	50	13
2	$BH_3 \cdot THF$	1.1	rt	4	33	41	26
3	BMS	1	0	1	90	10	0
4	BMS	1	0	24	70	30	0
5	BMS	2.5	0	24	15	70	15
6	BMS	3	−10	24	40	60	0

[a] Commercially avalaible borane–dimethyl sulfide complex (BMS) or borane·THF 1 M in THF.
[b] Time for hydroboration step.
[c] Determined by ^{1}H NMR.



Scheme 4.

by the steric hindrance of the position 11β and was not observed in our case.

3. Conclusion

The new 11β-hydroxymethyl-androst-4-en-3,17-dione **5** was prepared within 5 synthetic steps starting from the commercially available adrenosterone with an overall yield of 24%. This synthesis involves the preparation of several intermediates, such as the 11-methylene androstene **3** or the 11β-hydroxymethyl steroid **4**. Those steroids may be used for the preparation of new androstenediones or substituted testosterones bearing subtituents in C-11. This work is currently under investigation in our laboratory.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AC 300 spectrometer. Chemical shifts are reported in ppm and referenced to the residual proton resonances of the solvent used. Infrared (IR) spectra were recorded by using a BOMEN MB spectrometer. Mass spectra were obtained on NERMAG R 1010C apparatus. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm and room temperature. Melting points were measured on a Kofler apparatus. Silica gel Merck Gerudan SI (40–60 μm) was used for column chromatography. Elemental analysis were measured at the microanalysis laboratory of the Pierre et Marie Curie University (Paris, France). All solvents and reagents were purified when necessary using standard procedures.

4.1.1. 3,3,17,17-(Ethylenedioxy)-androst-5-ene-11-one (1). This ketosteroid was prepared, as described by Bernstein,[10] using toluene instead of benzene as solvent, from the adrenosterone (Aldrich). Yields of 80–90% are obtained after crystallization in ether.

4.1.2. 3,3,17,17-(Ethylenedioxy)-11β-hydroxy-11α-(methyltrimethylsilyl)-androst-5-ene (2). 12.8 g (33 mmol) of the ketosteroid **1** and dry toluene (120 mL) were introduced into a three-necked flask under argon. (Trimethylsilylmethyl)lithium (100 mL, 1 M in pentane, 100 mmol) was then slowly added and the mixture was stirred at reflux for 2 h, after which water was added. The organic layer was separated, washed with water, dried on magnesium sulfate and evaporated. The crude product was purified by chromatographic column on silica gel (dichloromethane then diethylether) to give 12 g (76% yield) of steroid **2**, white powder: mp 124 °C; $[\alpha]_D$ −47.8 (*c* 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (m, 9H, $Si(CH_3)_3$) 1.03 and 1.37 (s, 3H, CH_3-18 and CH_3-19) 3.85–3.95 (m, 8H, CH_2-ketal) 5.28 (m, 1H, H-6) ppm; ^{13}C (75 MHz, $CDCl_3$) δ 0.0, 14.0, 20.3, 22.5, 30.1, 31.9, 32.2, 33.0, 37.2, 38.9, 40.1, 40.6, 43.7, 48.5, 48.9, 56.6, 63.1, 63.3, 63.4, 64.2, 77.4, 107.8, 118.6, 120.4, 141.2 ppm; MS (EI 70 eV) *m/z* 476 ($M^{+\cdot}$), 458 ($[M-H_2O]^{+\cdot}$), 346, 140, 115, 99, 73, 55, 42; IR (KBr) ν_{OH}=3509 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_5Si$ (476.3): C 68.02, H 9.30. Found C 67.72, H 9.63.

4.1.3. 3,3,17,17-(Ethylenedioxy)-11-methylidene-androst-5-ene (3). Nine grams (18.9 mmol) of the steroid **2**, dry THF (100 mL) and 2.6 g (19.4 mmol) of KH (30 wt% dispersion in mineral oil) were introduced into a flask under argon. The mixture was stirred under reflux for 2 h. Ethyl acetate and water were then added. The organic layer was separated, washed with water, dried on magnesium sulfate and evaporated. The crude product was crystallized in pentane to give 5.7 g (78% yield) of steroid **3** mp 234 °C. The spectra of this steroid are in good accordance with our previous description.[19]

4.1.4. 3,3,17,17-(Ethylenedioxy)-11β-hydroxymethyl-androst-5-ene (4). 1.1 g (2.8 mmol) of the steroid **3** was dissolved in dry THF (15 mL) under argon and this solution was cooled at 0 °C. 0.7 mL (7 mmol) of borane–methyl sulfide complex was then added and the mixture was stirred at 0 °C for 24 h. The reaction mixture was oxidized by the addition of 1 mL of methanol, 1 mL of 3 M NaOH and 0.9 mL of 30% aqueous H_2O_2. After stirring for 3 h at room temperature, water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried on magnesium sulfate and evaporated. The crude product was purified on silica gel chromatographic column (diethylether) to give unreacted steroid **3** followed by 0.51 g (45% yield) of steroid **4**, white powder: mp 76 °C; $[\alpha]_D$ −40 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 and 1.13 (s, 3H, CH_3-18 and CH_3-19), 2.32 (m, 1H, H-11), 3.68

(dd, 1H, $J=10.5$, 8.7 Hz), 3.82–3.94 (m, 8H, CH_2-ketal), 3.99 (dd, 1H, $J=10.5$, 6.5 Hz), 5.19 (m, 1H, H-6) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 20.5, 22.8, 29.4, 30.8, 31.5, 32.9, 34.2, 34.7, 36.8, 37.9, 40.8, 45.1, 51.9, 53.3, 64.2, 64.4, 64.6, 64.8, 65.1, 109.0, 119.6, 120.8, 141.1 ppm; MS (EI 70 eV) *m/z* 404 ($M^{+\cdot}$), 99, 86, 55; IR (KBr) $\nu_{OH}=3459\ cm^{-1}$. Anal. Calcd for $C_{24}H_{36}O_5$ (404.2): C 71.26, H 8.97. Found C 71.61, H 9.40.

4.1.5. 3,3,17,17-(Ethylenedioxy)-6α-hydroxy-11β-hydroxymethyl-androstane (9). Steroid **3** (390 mg, 1 mmol) was dissolved in dry THF (5 mL) under argon and 0.5 mL of BMS (5 mmol) was added at room temperature. The mixture was stirred for 2 h and then oxidized by the addition of 0.3 mL of MeOH, 0.3 mL of 3 M NaOH and 0.3 mL of 30% aqueous H_2O_2. After stirring for 3 h at room temperature water was added. After usual work-up, using dichloromethane as solvent, the crude product was crystallized in ether to afford 250 mg (59% yield) of a white solid: mp 250 °C; $[\alpha]_D$ +8.7 (*c* 1.83, $CHCl_3$). An analytical sample was obtained by silica gel chromatography (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 and 0.92 (s, 3H, CH_3-18 and CH_3-19), 2.32 (m, 1H, H-11), 3.37 (dt, $J=$ 4.5, 10.8 Hz, 1H, H-6), 3.56 (dd, 1H, $J=18$, 8.7 Hz), 3.84–4.00 (m, 9H, CH_2 -ketals and 1H) ppm; ^{13}C (75 MHz, $CDCl_3$) δ 14.6, 16.3, 22.7, 25.6, 30.8, 32.1, 34.3, 35.7, 36.5, 37.6, 41.8, 45.4, 51.9, 52.9, 56.1, 56.6, 64.1, 64.2, 64.7, 65.1, 67.9, 68.9, 108.8 et 119.7 ppm; MS (ICP/NH_3) *m/z* 440 $[MNH_4]^+$ 423 $[MH]^+$; IR (KBr) $\nu_{OH}=3449\ cm^{-1}$. Anal. Calcd for $C_{24}H_{38}O_6$ (422.2): C 68.22, H 9.06. Found C 68.14, H 9.05.

4.1.6. 11β-Hydroxymethyl-androst-4-ene-3,17-dione (5). One millilitre of acetonitrile was added under argon to a mixture of 100 mg (0.25 mmol) of the steroid **4** and 35 mg (0.25 mmol) of NaI. 30 μL of TMSCl (0.25 mmol) were then added under stirring at room temperature and the resulting mixture was stirred for 0.33 h. Water was then added, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with aqueous sodium thiosulfate followed by water, dried on magnesium sulfate and evaporated. The crude product was purified on silica gel (diethylether/ethylacetate; 80:20) to give 80 mg (100%) of a white solid: mp 209 °C; $[\alpha]_D$ +131 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 and 1.38 (s, 3H, CH_3-18 and CH_3-19), 3.64 and 3.98 (dd, 1H, $J=10.8$, 6.3 Hz), 5.68 (s, 1H, H-4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 20.2, 21.5, 31.6, 31.7, 32.1, 33.7, 34.2, 35.1, 35.4, 38.7, 39.3, 46.6, 53.6, 55.5, 64.6, 122.0, 171.8, 199.2 and 218.4 ppm; MS (EI 70 eV) *m/z* 316 ($M^{+\cdot}$), 298 ($[M-H_2O]^{+\cdot}$), 285, 256, 241, 180, 133, 124, 105, 91, 79, 67, 55, 41; IR (KBr) 1736 (17-C=O), 1647 (3-C=O), 3391 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_3$ (316.2) C 75.91, H 8.92. Found C 75.51, H 9.21.

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