A rapid and simple one-pot procedure for the synthesis of 3β-acetoxy-5α-hydroxy-6-oxo steroids

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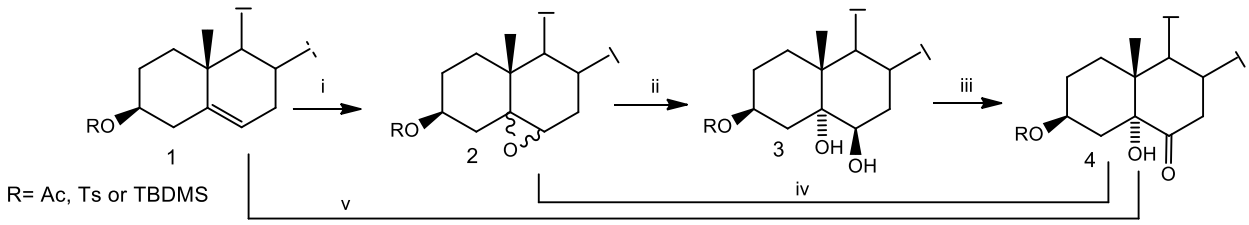
Abstract

A fast one-pot procedure for the synthesis of 5α-hydroxy-6-oxo steroids is described. Epoxidation of 3β-hydoxy-Δ^5 steroids followed by oxidative cleavage of the resulting epoxide with aqueous CrO_3 lead to the desired compounds without affection of labile side chains.

Keywords: Epoxides, oxidative cleavage, 5α-hydroxy-6-oxo steroids, one-pot

Introduction

Steroids bearing a 3β,5α-dihydroxy-6-oxo moiety have served as starting materials for the synthesis of different bioactive compounds including plant growth regulators,[1,2] ecdysteroids antagonists,[3] 5α-reductase inhibitors[4,5] or antagonists of the androgen receptor,[6] among others. In general, the limited number of protocols for the preparation of such compounds start from derivatives of 3β-hydroxy-Δ^5-steroids and involve the oxidation of 5,6-diols (iii),[1,3] or the oxidative cleavage of 5ξ,6-epoxides by treatment with Jones reagent[2] or CrO_3 (iv)[5] (Scheme 1).



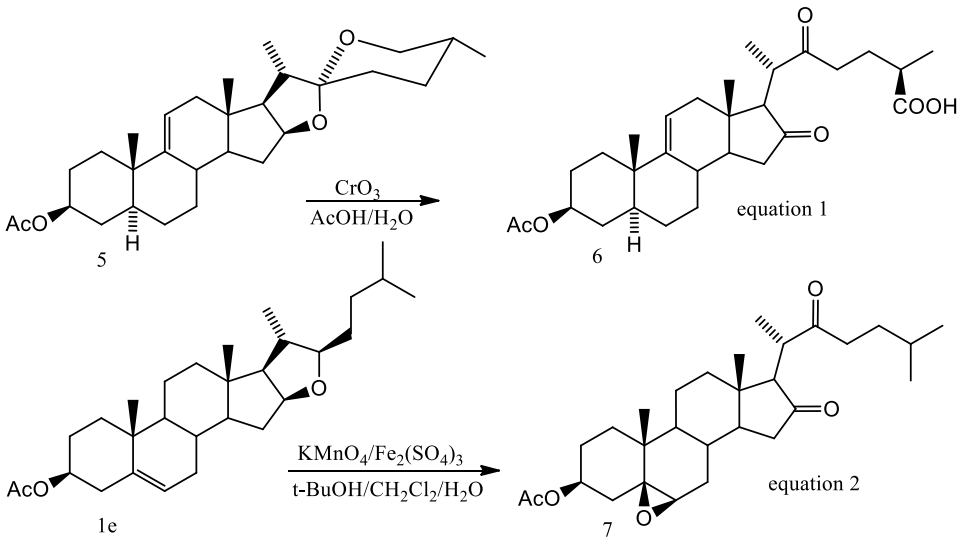
i) MCPBA/CH_2Cl_2 or $KMnO_4$/$Fe_2(SO_4)_3$, t-BuOH/CH_2Cl_2/H_2O; ii) H_2O/$HClO_4$/acetone; iii) Jones reagent or PCC; iv) Jones reagent or CrO_3 v) $KMnO_4$ / $Fe(ClO_4)_3.nH_2O$

Scheme 1

Recently, Salvador and coworkers reported that treatment of different 3β-acetoxy-Δ^5-steroids (androstane, pregnanes and cholestane series) with $KMnO_4/Fe(ClO_4)_3$ in heterogeneous media

for 8 to 24 hours (v), produced the corresponding 3β-acetoxy-5α-hydroxy-6-oxo steroids in 70 to 81% yields[7] in an elegant approach in which the risks associated to the explosive nature of $Fe(ClO_4)_3$ may constitute a general limitation in the preparation of large amounts of the desired ketols (Scheme 1).

There are some reports that indicate that steroids bearing labile side chain may be affected by the acid conditions that predominate in the hydrolytic and oxidative cleavage of epoxides or in Jones oxidation of diols. Barton reported that treatment of steroid sapogenins with CrO_3 in acetic acid yielded the corresponding sapogenoic acid as a result of the oxidative opening of the spirostanic side chain (equation 1).[8] On the other hand, we described that treatment of furostanols with the $KMnO_4/Fe_2(SO_4)_3$ cleaved the E-ring to afford 16,22-diones, (equation 2).[9]

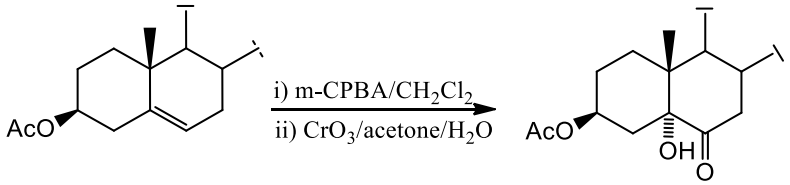


As a part of our project on the synthesis of bioactive compounds, we have directed our attention to a series of 3β-acetoxy-5α-hydroxy-6-oxo steroids bearing different oxygenated side chains as starting materials in the preparation of potentially bioactive compounds. Consequently, we decided to set up optimized experimental conditions that avoid the above-mentioned limitations that hinder the preparation of 3β-acetoxy-5α-hydroxy-6-oxo steroids bearing acid labile side chains. Herein we report on a simple one-pot procedure that allows the rapid preparation of such compounds in 1 to 10 mmol amounts without isolation of the intermediate epoxides **2** or diols **3**.[10] In addition, a carefully assignment of NMR signals of the obtained compounds is provided.

Results and Discussion

As expected, treatment of the 3β-acetoxy-Δ^5-steroids **1a-f** with *m*-CPBA in CH_2Cl_2 produced mixtures of the corresponding 5α-and 5β-epoxides. While oxidative cleavage of the epoxides

derived from compounds **1a-d**, could be carried out by treatment with Jones reagent, similar treatment of those derived from **1e-f** produced mixtures of the desired ketol and variable amounts of products due to reaction of the side chain. The avoidance of strongly acidic conditions by substitution of Jones oxidant by a solution of CrO_3 in water prevents the reaction of the acid sensitive furostanic E-ring and spirostanic side chain, affording the desired ketols in high yield and purity. In those conditions, addition of acetone to the CH_2Cl_2 solution resulting from the epoxidation reaction, followed by cooling and treatment with CrO_3 produces the conversion of the epoxides into the corresponding ketol in 77-95 % yields, in a fast and convenient one-pot procedure that does not affect the studied labile side chains (see Scheme 2 and Table 1).



1a-f 4a-f

Scheme 2

Experimental Section

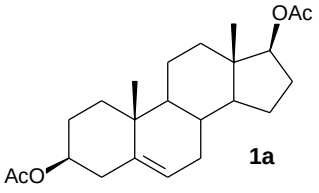
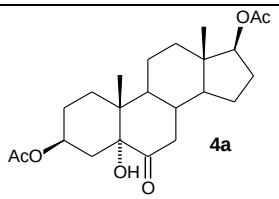
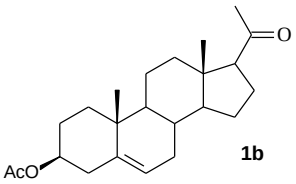
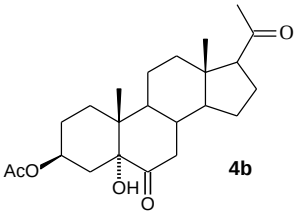
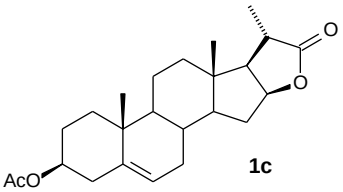
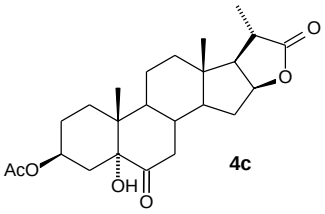
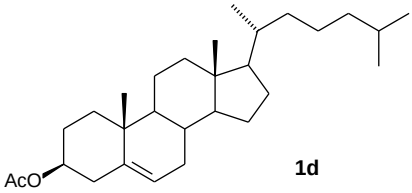
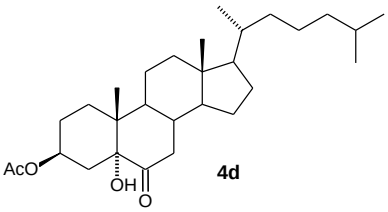
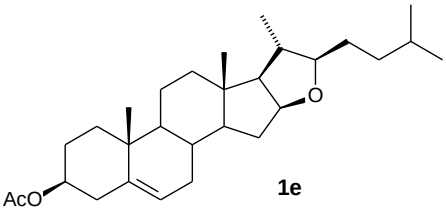
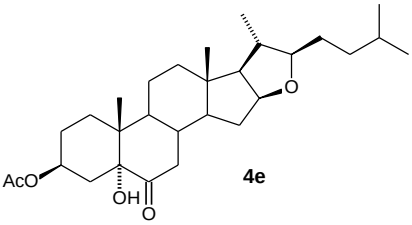
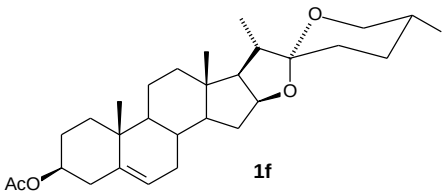
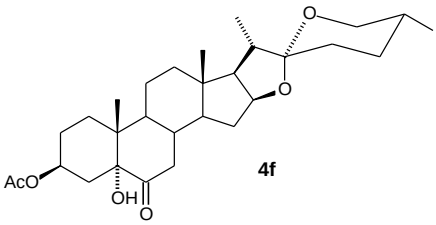
General. Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. NMR spectra were recorded in $CDCl_3$ solutions in Varian INOVA 400 and 300 MHz spectrometers using the solvent signal 7.26 ppm for ^1H and 77.00 ppm for ^{13}C as reference. NMR signals were assigned with the aid of DEPT and combination of ^1H–^1H COSY and Heteronuclear Single Quantum Correlation (HSQC). All 2D NMR spectra were recorded by using the standard pulse sequences and parameters recommended by the manufacturer. Melting points were measured on a Melt-Temp II apparatus and are uncorrected.

General procedure for ketol formation

m-CPBA (0.968 g, 5.61 mmol) was added to a solution of the 3β-acetoxy-Δ^5-steroid (4 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred until the starting material disappeared (1 to 1.5 h, TLC). Acetone (50 mL) was added and the mixture was cooled to 0°C in an ice bath before addition of a solution of CrO_3 (1.43 g, 14.3 mmol) in water (4.3 mL) The ice bath was removed, the mixture was stirred at room temperature for 20 min. and cooled to 0°C in the ice bath prior to dropwise addition of a solution of CrO_3 (0.71 g, 7.1 mmol) in water (2.2 mL). The ice bath was removed and the mixture stirred for 50 min, before addition of water (50 mL) and extraction with ethyl acetate (2x50 mL). The organic layer was washed with water (9x50 mL), 10% $NaHCO_3$

solution (5x50 mL), water (2x50 mL) and saturated NaCl solution (1x50 mL), dried and evaporated to afford the desired ketol (see Table 1 for yields).

Table 1. Formation of ketols

	Starting material	Product	Yield
1	 **1a**	 **4a**	91%
2	 **1b**	 **4b**	90%
3	 **1c**	 **4c**	77%
4	 **1d**	 **4d**	96%
5	 **1e**	 **4e**	92%
6	 **1f**	 **4f**	87.2%

3β,17β-Diacetoxy-5-hydroxy-5α-androstan-6-one (4a). M.p. 236-238 °C (dec.), *from ethyl acetate*. Lit. 236-237.5 °C.[11] ^{1}H NMR (δ ppm): 5.03 (m, 1H, H-3); 4.62 (dd, *J* = 9.1, 7.8 Hz, 1H, H-17); 2.76 (dd, *J* = 13.9, 11.4 Hz, 1H, H-7 ax.); 2.03 (s, 3H, CH_3COO-17); 2.00 (s, 3H,

CH_3COO-3); 0.82 (s, 3H, H-19); 0.77 (s, 3H, H-18). ^{13}C NMR (δ ppm): 29.50 C-1; 26.20 C-2; 70.73 C-3; 32.21 C-4; 80.06 C-5; 212.16 C-6; 41.12 C-7; 37.02 C-8; 44.17 C-9; 42.47 C-10; 20.82 C-11; 36.50 C-12; 43.12 C-13; 50.64 C-14; 23.22 C-15; 27.37 C-16; 82.37 C-17; 12.01 C-18; 13.84 C-19; 21.09 and 21.32 $\underline{C}H_3COO$-3 and $\underline{C}H_3COO$-17; 171.12, 171.15 $CH_3\underline{C}OO$-3 and $\underline{C}H_3COO$-17.

3β-Acetoxy-5-hydroxy-5α-pregnan-6,20-dione (4b). M.p. 220-222 °C (dec.), *from diethyl ether*, Lit. 223-224.5 °C.[12] ^1H NMR (δ ppm): 5.02 (m, 1H, H-3); 2.78 (dd, *J* = 12.6, 12.6 Hz, H-7 ax.); 2.54 (dd, *J* = 8.9, 8.9 Hz, H-17); 2.10 (s, 3H, CH_3COO-3); 0.58 (s, 3H, H-18); 0.79 (s, 3H, H-21); 1.99 (s, 3H, H-21). NMR ^{13}C (δ ppm): 29.52 C-1; 26.21 C-2; 70.63 C-3; 32.27 C-4; 80.09 C-5; 211.94 C-6; 41.46 C-7; 37.09 C-8; 44.49 C-9; 42.39 C-10; 21.28 C-11; 38.57 C-12; 44.11 C-13; 56.34 C-14; 24.06 C-15; 22.72 C-16; 63.40 C-17; 13.34 C-18; 13.85 C-19; 209.22 C-20; 31.41 C-21; 21.33 $\underline{C}H_3COO$-3; 171.06 $CH_3\underline{C}OO$-3.

3β-Acetoxy-5,16β-dihydroxy-6-oxo-5α-dinorcholanic acid 22→16 lactone (4c). Identical to our previous report.[13] M.p. 282.2–280.6 °C *from acetone*. ^1H NMR (δ ppm): 0.71 (s, 3H, H-18); 0.80 (s, 3H, H-19); 1.30 (d, *J* = 7.6 Hz, 3H, H-21); 1.98 (s, 3H, CH_3COO-3); 2.08 (dd, *J* = 4.5 Hz, 12.3 Hz, 1H, H-7 equatorial); 2.21 (m, 1H, H-15); 2.56 (m, 1H, H-20); 2.78 (dd, *J* = 12.3, 12.3 Hz, 1H, H-7 axial); 4.93 (m, 1H, H-16); 5.01 (m, H-3). ^{13}C NMR (δ, ppm): 26.2 C-1; 29.5 C-2; 70.6 C-3; 32.2 C-4; 79.9 C-5; 211.4 C-6; 41.5 C-7; 36.4 C-8; 44.2 C-9; 42.4 C-10; 20.6 C-11; 37.9 C-12; 42.2 C-13; 54.3 C-14; 32.7 C-15; 82.3 C-16; 58.8 C-17; 13.7 C-18; 13.9 C-19; 36.0 C-20; 17.9 C-21; 181.0 C-22; 171.1 $CH_3\underline{C}OO$-3; 21.3 $\underline{C}H_3COO$-3.

3β-Acetoxy-5-hydroxy-5α-cholestan-6-one (4d). Mp 230-231 °C, *from ethyl acetate*. Lit. 230-231 °C.[14] ^1H NMR (δ ppm): 5.05-4.94 (m, 1H, H-3); 2.78 (dd, *J* = 12.6, 12.6 Hz, 1H, H-7 ax.); 2.01 (s, 3H, CH_3COO-3); 0.91 (d, *J* = 6.3 Hz, 3H, H-21); 0.87 and 0.85 (d, *J* = 6.6 Hz, 3H each, H-26 and H-27); 0.81 (s, 3H, H-19); 0.64 (s, 3H, H-18). ^{13}C NMR (δ ppm): 32.03 C-1, 28.17 C-2, 71.52 C-3, 28.17 C-4, 79.82 C-5, 213.77 C-6, 41.80 C-7, 37.52 C-8, 44.25 C-9, 42.61 C-10, 21.46 C-11, 39.57 C-12, 43.22 C-13, 56.38 C-14, 26.41 C-15, 29.64 C-16, 56.24 C-17, 12.08 C-18, 13.91 C-19, 35.84 C-20, 18.70 C-21, 36.21 C-22, 24.03 C-23, 29.68 C-24, 28.09 C-25, 22.87 C-26, 23.96 C-27, 171.82 $CH_3\underline{C}OO$-3, 22.61 $\underline{C}H_3COO$-3.

(22*R*)-3β-Acetoxy-5-hydroxy-5α-furostan-6-one (4e). Identical to our previous report.[15] M.p. 184–186 °C, *from ethyl acetate*/*hexane*. ^1H NMR (δ ppm): 5.15–4.88 (m, 1H, H-3); 4.33–4.23 (m, 1H, H-16); 3.33–3.24 (m, 1H, H-22); 2.75 (dd, *J* = 11.6, 11.6 Hz, 1H, H 7ax.); 1.98 (s, 3H, CH_3COO-3); 0.98 (d, *J* = 6.41 Hz, 3H, H-21); 0.86 (d, *J* = 6.37 Hz, 6H, H-26 and H-27); 0.81 (s, 3H, H-18); 0.76 (s, 3H, H-19). ^{13}C NMR (δ ppm): 29.48 C-1; 26.20 C-2; 70.63 C-3; 32.29 C-4; 80.10 C-5; 212.00 C-6; 41.69 C-7; 36.88 C-8; 44.26 C-9; 42.41 C-10; 20.96 C-11; 39.19 C-12; 41.44 C-13; 56.46 C-14; 31.90 C-15; 82.76 C-16; 65.12 C-17; 16.46 C-18; 13.92. C-19; 37.85 C-20; 18.97 C-21; 90.42 C-22; 28.20 C-23; 31.32 C-24; 35.77 C-25; 22.52 C-26; 22.45 C-27; 171.06; $CH_3\underline{C}OO$-3; 21.33 $\underline{C}H_3COO$-3.

(25*R*)-3β-Acetoxy-5-hydroxy-5α-spirostan-6-one (4f). M.p. 270 °C, *from ethyl acetate*. Lit. 268-269°C.[16] ^1H NMR (δ ppm): 5.02 (m, 3H, H-3); 4.41 (m, 1H, H-16); 3.47 (ddd, *J* = 10.8, 4.5, 1.7 Hz, 1H, H-26 eq.); 3.36 (dd, *J* = 10.9, 10.9 Hz, H-26 ax.); 2.77 (dd, *J* = 12, 12.9 Hz, 1H, H-

7); 2.01 (s, 3H, CH_3COO-3); 0.97 (d, *J* = 6.8 Hz, 3H, H-21); 0.83 (s, 3H, H-19); 0.79 (d, *J* = 6.4 Hz, 3H, H-27); 0.76 (s, 3H, H-18). ^{13}C NMR (δ ppm): 29.48 C-1; 26.24 C-2; 70.71 C-3; 32.30 C-4; 80.10 C-5; 212.05 C-6; 41.77 C-7; 36.74 C-8; 44.28 C-9; 42.46 C-10; 21.17 C-11; 39.54 C-12; 41.05 C-13; 56.03 C-14; 31.51 C-15; 80.48 C-16; 62.02 C-17; 16.36 C-18; 13.93 C-19; 41.59 C-20; 14.40 C-21; 109.26 C-22; 31.32 C-23; 28.74 C-24; 30.23 C-25; 66.83 C-26; 17.07 C-27; 171.14 $CH_3\underline{C}OO$-3; 21.32 $\underline{C}H_3COO$-3.

Acknowledgements

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