

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

Anielka Rosado-Abón, Margarita Romero-Ávila, Martín A. and Iglesias-Arteaga*

Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria

E-mail: martin.iglesias@servidor.unam.mx

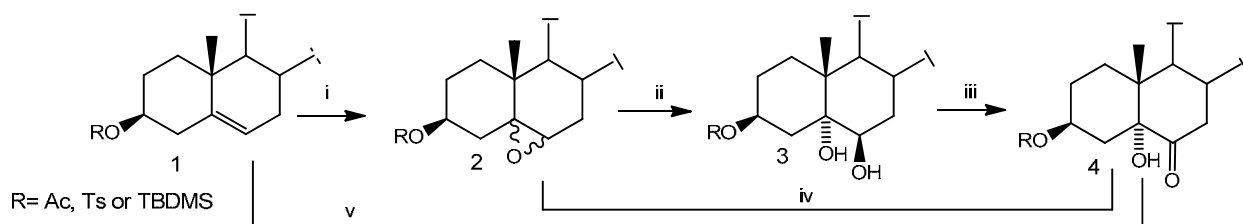
Abstract

A fast one-pot procedure for the synthesis of 5 α -hydroxy-6-oxo steroids is described. Epoxidation of 3 β -hydroxy- Δ^5 steroids followed by oxidative cleavage of the resulting epoxide with aqueous CrO₃ lead to the desired compounds without affection of labile side chains.

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

Introduction

Steroids bearing a 3 β ,5 α -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 5 α -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 3 β -hydroxy- Δ^5 -steroids and involve the oxidation of 5,6-diols (iii),^{1,3} or the oxidative cleavage of 5 ξ ,6-epoxides by treatment with Jones reagent² or CrO₃ (iv)⁵ (Scheme 1).



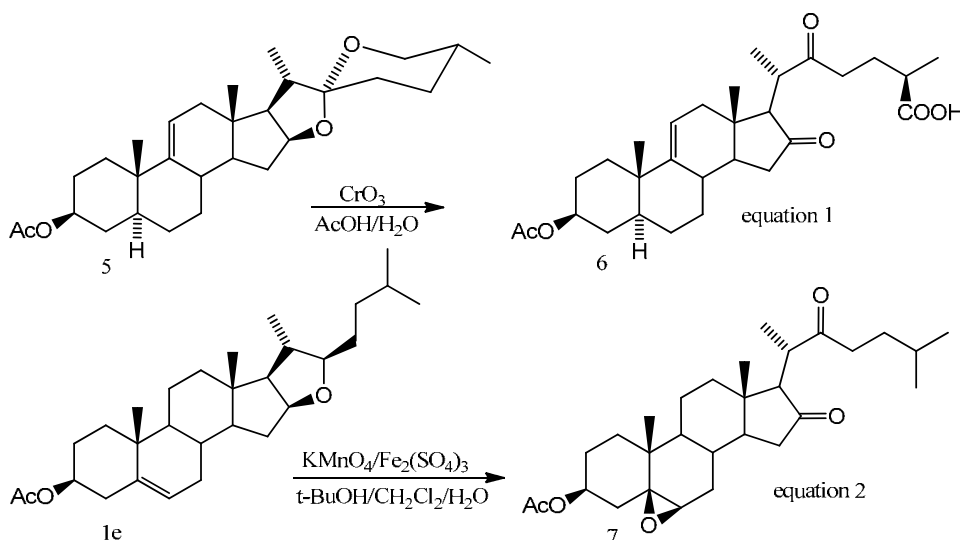
i) MCPBA/CH₂Cl₂ or KMnO₄/Fe₂(SO₄)₃, t-BuOH/CH₂Cl₂/H₂O; ii) H₂O/HClO₄/acetone; iii) Jones reagent or PCC; iv) Jones reagent or CrO₃; v) KMnO₄ / Fe(ClO₄)₃ · nH₂O

Scheme 1

Recently, Salvador and coworkers reported that treatment of different 3 β -acetoxy- Δ^5 -steroids (androstane, pregnanes and cholestane series) with KMnO₄/Fe(ClO₄)₃ in heterogeneous media

for 8 to 24 hours (v), produced the corresponding 3 β -acetoxy-5 α -hydroxy-6-oxo steroids in 70 to 81% yields⁷ in an elegant approach in which the risks associated to the explosive nature of Fe(ClO₄)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 CrO₃ in acetic acid yielded the corresponding sapogenoic acid as a result of the oxidative opening of the spirostanoic side chain (equation 1).⁸ On the other hand, we described that treatment of furostanols with the KMnO₄/Fe₂(SO₄)₃ cleaved the E-ring to afford 16,22-diones, (equation 2).⁹

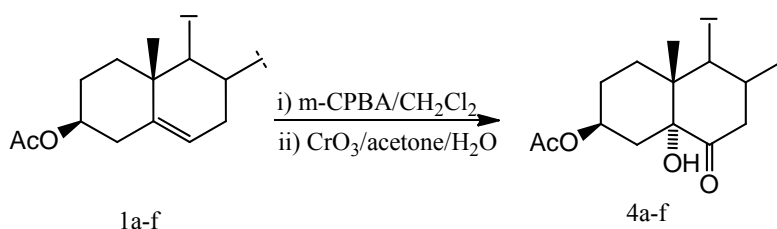


As a part of our project on the synthesis of bioactive compounds, we have directed our attention to a series of 3 β -acetoxy-5 α -hydroxy-6-oxo steroids bearing different oxygenated side chains as starting materials in the preparation of potentially bioactive compounds. Consequently, we decided to set up optimized experimental conditions that avoid the above-mentioned limitations that hinder the preparation of 3 β -acetoxy-5 α -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 3 β -acetoxy- Δ^5 -steroids **1a-f** with *m*-CPBA in CH₂Cl₂ produced mixtures of the corresponding 5 α - and 5 β -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 CrO₃ in water prevents the reaction of the acid sensitive furostane E-ring and spirostane side chain, affording the desired ketols in high yield and purity. In those conditions, addition of acetone to the CH₂Cl₂ solution resulting from the epoxidation reaction, followed by cooling and treatment with CrO₃ 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).



Scheme 2

Experimental Section

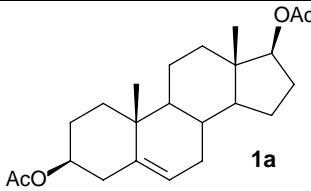
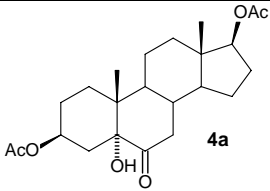
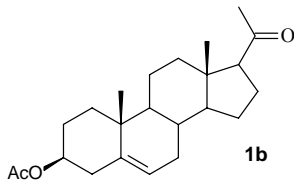
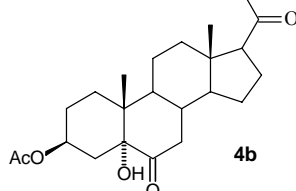
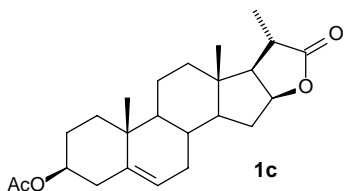
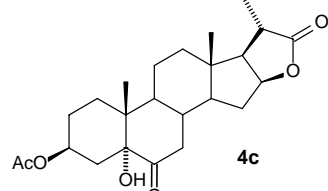
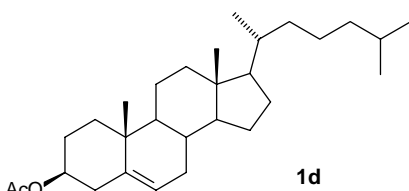
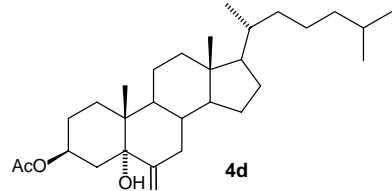
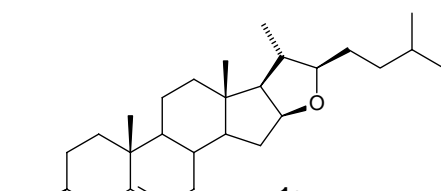
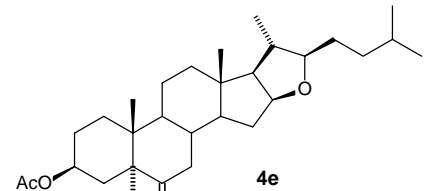
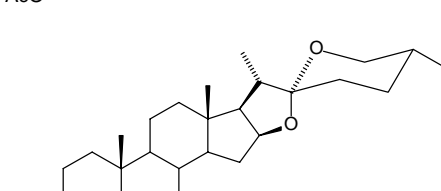
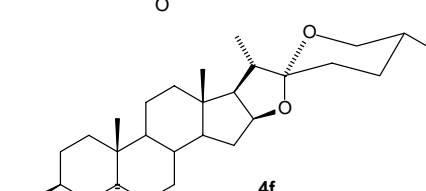
General. Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% HClO₄ and heated until color developed. NMR spectra were recorded in CDCl₃ solutions in Varian INOVA 400 and 300 MHz spectrometers using the solvent signal 7.26 ppm for ¹H and 77.00 ppm for ¹³C 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-Δ⁵-steroid (4 mmol) in CH₂Cl₂ (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 CrO₃ (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 CrO₃ (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% NaHCO₃

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
<p>1</p>  <p>1a</p>	 <p>4a</p>	91%
<p>2</p>  <p>1b</p>	 <p>4b</p>	90%
<p>3</p>  <p>1c</p>	 <p>4c</p>	77%
<p>4</p>  <p>1d</p>	 <p>4d</p>	96%
<p>5</p>  <p>1e</p>	 <p>4e</p>	92%
<p>6</p>  <p>1f</p>	 <p>4f</p>	87.2%

3 β ,17 β -Diacetoxy-5-hydroxy-5 α -androstan-6-one (4a). M.p. 236-238 °C (dec.), from ethyl acetate. Lit. 236-237.5 °C. ¹¹H 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, CH₃COO-17); 2.00 (s, 3H,

CH₃COO-3); 0.82 (s, 3H, H-19); 0.77 (s, 3H, H-18). ¹³C 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 CH₃COO-3 and CH₃COO-17; 171.12, 171.15 CH₃COO-3 and CH₃COO-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, CH₃COO-3); 0.58 (s, 3H, H-18); 0.79 (s, 3H, H-21); 1.99 (s, 3H, H-21). NMR ¹³C (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 CH₃COO-3; 171.06 CH₃COO-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, CH₃COO-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). ¹³C 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 CH₃COO-3; 21.3 CH₃COO-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, CH₃COO-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). ¹³C 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 CH₃COO-3, 22.61 CH₃COO-3.

(22R)-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, CH₃COO-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). ¹³C 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; CH₃COO-3; 21.33 CH₃COO-3.

(25R)-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, CH₃COO-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). ¹³C 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 CH₃COO-3; 21.32 CH₃COO-3.

Acknowledgements

We thank *Dirección General de Asuntos del Personal Académico* (DGAPA-UNAM) for financial support via project IN-204008 and CONACyT (Mexico) for the scholarship granted to A.R-A. We are indebted to Nuria Esturau-Escofet for registering all NMR spectra.

References and Notes

1. Ramírez, J. A.; Teme-Centurión, O. M.; Gros, E. G.; Galagovsky, L. R. *Steroids* **2000**, *65*, 329.
2. Brosa, C.; Soca, L.; Terricabras E.; Ferrer, J. C.; Alsina, A. *Tetrahedron* **1998**, *54*, 12337.
3. Rivera, D. G.; León F.; Coll, F.; Davison G. P. *Steroids* **2006**, *71*, 1.
4. Bratoeff, E.; Cabeza, M.; Pérez-Ornelas, V.; Recillas, S.; Heuze, I. *J. Steroid Biochem.* **2008**, *111*, 275.
5. Perez-Ornelas, V.; Cabeza, M.; Bratoeff, E.; Heuze I.; Sánchez, M.; Ramírez, E.; Naranjo-Rodriguez, E. *Steroids* **2005**, *70*, 217.
6. Cabeza, M.; Bratoeff, E.; Ramírez, E.; Heuze, I.; Recillas, S.; Berrios, H.; Cruz, A.; Cabrera, O.; Pérez, V. *Steroids* **2008**, *73*, 838.
7. Salvador, J. A. R.; Moreira, V. M.; Hanson, J. R. Carvalho, R. A. *Steroids* **2006**, *71*, 266.
8. Barton, D. H. R.; Kulkarni, Y. D.; Sammes, P.G.; *J. Chem. Soc. (C)* **1971**, 1149.
9. Rosado-Abon, A.; Romero-Avila, M.; Iglesias-Arteaga M. A. *Arkivoc* **2008**, (xiv), 274.
10. Copies of the ¹H and ¹³C NMR spectra can be found in the supplementary information file. All spectra were processed using MestReC or MestReNova (<http://mestrelab.com>).
11. Knof, L. *Ann Chem* **1961**, *Bd 647*, 53.
12. Rubin, M. B.; Brown, A. P. *J. Org. Chem.* **1968**, *33*, 2794.
13. Mola-Garate, J. L.; Suárez-García, L.; Pérez-Martinez, C. S.; Iglesias-Arteaga, M. A.; Coll-Herrera, D.; Coll-Manchado, F. *Synth. Commun.* **2003**, *33*, 1203.
14. Fieser, L. F. *J. Am. Chem. Soc.* **1953**, *75*, 4386.
15. Romero-Avila, M.; de Dios-Bravo, G.; Mendez-Stivalet, J. M.; Rodríguez-Sotres, R.; Iglesias-Arteaga, M. A. *Steroids* **2007**, *72*, 955.
16. Wei-Shan, C.; Ta-Chung, H.; Huang-Minlon *Huaxue Xuebao* **1962**, *28*, 394.