An unexpected and useful E-ring oxidative cleavage in furostanes

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Abstract
Treatment of acetylated furostanols derived from steroid sapogenins with a wet mixture of KMnO₄ and Fe₂(SO₄)₃.nH₂O in CH₂Cl₂/tert-butyl alcohol produces the unexpected E-ring oxidative cleavage to afford the corresponding cholestan-22,16-diones. Based in this new reaction, facile syntheses of an OSW-1 precursor and kryptogenin acetate have been designed.

Keywords: Oxidative cleavage, furostanes, kryptogenin, OWS-1, 16,22-dioxosteroids

Introduction
The stereoselective β-epoxidation of Δ⁵-steroids using biphasic systems that involve potassium permanganate and metal salts has received considerable attention.¹ In particular, we have reported the transformation of 3β-hydroxy-Δ⁵-steroids into the corresponding 3β-hydroxy-6-oxosteroids [i.e cholesterol acetate into 3β-hydroxy-cholestan-6-one and diosgenin acetate into laxogenin], using a protocol that involves β-epoxidation, HBr induced oxirane ring opening, oxidation the resulting bromohydrin to a bromoketone and reduction to the parent ketone by treatment with Zn dust in refluxing acetic acid, (see Scheme 1).²
Attempts to apply the above described procedure to furostanic compounds led to an unexpected oxidative cleavage reaction in which the furostanic compounds were converted into the corresponding cholestan-16,22-diones. Herein we report on the oxidative cleavage of the E-ring of furostanes and some of its synthetic applications.

Results and Discussion

Attempt at β-epoxidation of the acetylated furostanol 1a using wet KMnO₄/Fe₂(SO₄)₃ in CH₂Cl₂/tert-butyl alcohol afforded the unchanged starting material and two compounds that after separation were characterized as the desired epoxidated furostanol 2a (16.6%) and the unexpected epoxidated diketone 3a (43.3%), (see Scheme 2 and Table 1, entry 1). In an experiment conducted without the ferric salt the unchanged starting material was recovered after 24 hours.

Scheme 2
Some reports have shown that the E-ring of furostanes undergoes cleavage in the presence of Lewis acids. For instance, Ac₂O/BF₃.Et₂O treatment of furostanes has been reported to produce E-ring cleavage followed by 17→16 hydride shift and Wagner-Meerwein rearrangement to afford Δ¹³-17β-methyl-18-norsteroids (Scheme 3).³ Activation of acetic anhydride by BF₃.Et₂O resulted in acetylation of O-16 that triggers the observed rearrangement. The absence of a nucleophile capable to produce the nucleophilic displacement of the acetylated oxygen, justifies the observed course.

Scheme 3

In this new reaction of furostanic compounds with wet KMnO₄/Fe₂(SO₄)₃, the fact that in absence of the ferric salt no reaction was observed suggests a mechanism in which, after coordination to the ferric cation, the tetrahydrofuranic oxygen attached to both C-16 and C-22 can be displaced by water present in the reaction media leading to a diol which is rapidly oxidized to the observed 16,22-diketone, (Scheme 4).

Scheme 4
The distribution of products indicates that the epoxidation of the double bond is faster than the E-ring cleavage and prompted us to study the reaction conditions for the total conversion of $1a$ into $3a$. We were pleased to find that the simple increase on the amounts of the reagents and reaction time resulted in the conversion of the starting material $1a$ into $3a$ (see Table 1, entry 2).

### Table 1. Results of epoxidation-oxidative E-ring opening of compound 1a

<table>
<thead>
<tr>
<th>KMnO$_4$ (g)</th>
<th>Fe$_2$(SO$_4$)$_3$.nH$_2$O (g)</th>
<th>H$_2$O (ml)</th>
<th>Time (min.)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0.4</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2.5</td>
<td>0.5</td>
<td>120</td>
</tr>
</tbody>
</table>

It has been reported that treatment of $1b$ with K$_2$Cr$_2$O$_7$ in acetic acid led to the 16,22-diketone $4b$ in poor yields.$^{4a}$ In an alternative approach, oxidation with Oxone$^\text{®}$ of the acetylated $i$-sterol $5$, derived from diosgenin, produced the hemiketal $6$ and the desired 16,22-diketone $7$. Four times recirculation of the mixture through the same oxidation procedure afforded $7$ in 80% that was isomerised to $4b$ in a long sequence to the synthesis of the potent antitumor agent OSW-1.$^{4b}$

![Scheme 5](image)

**Scheme 5**

After those facts we decided to explore the application of this new reaction to the synthesis of kriptogenin acetate ($4a$),$^5$ and $4b$ that has been employed as synthetic precursor of OSW-1.$^{4b}$ Application of the new reaction conditions to $1a$ or to our previously reported $1b$,$^6d$ led to the
corresponding epoxidated diketones 3a and 3b which were converted into the desired 5,6 unsaturated derivatives 4a (kryptogenin acetate) and 4b by consecutive treatments with HBr in CH₂Cl₂ and Zn dust in refluxing acetic acid.

Scheme 6

Conclusions

We have found that KMnO₄/Fe₂(SO₄)₃.nH₂O produces the oxidative cleavage of the E-ring of furostanes to afford a 16,22-diketone. This new reaction constitutes a convenient alternative for the preparation of 16,22-dioxo steroids that may find diverse and interesting synthetic applications. (i.e synthesis of OSW-1, kriptogenin derivatives or novel heterocyclic steroids). Additional experiments to extend this reaction to other steroidal and non-steroidal tetrahydrofuranic compounds are in development.

Experimental Section

General Procedures. Reactions were monitored by TLC on ALUGRAM® SIL G/UV₂₅₄ 5 cm x 2.5 cm plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% HClO₄ and heated until colour developed. NMR spectra were recorded in on Varian Unity INOVA (300 or 400 MHz) spectrometers using TMS for ¹H or the solvent signal (CDCl₃) for ¹³C as reference. Mass spectra were recorded on a Jeol SX-102-A spectrometer. Melting points were measured on Melt-Temp II equipment and are uncorrected.

Procedure for epoxidation-E-ring cleavage
KMnO₄ and Fe₂(SO₄)₃.nH₂O were finely ground in a mortar, H₂O was added and the mixture was placed in a round bottom flask containing CH₂Cl₂ (10 ml) (see Table 1 for amounts of KMnO₄, Fe₂(SO₄)₃.nH₂O and H₂O). A solution of the corresponding furostanic compound 6 3a or 3b (2 mmol) in CH₂Cl₂ (5 ml) was added followed by addition of tert-butyl alcohol (1 ml) and
the mixture was stirred at room temperature for the indicated time. Ethyl ether (25 ml) and celite (2 g) were added and the mixture was stirred for 15 min before filtering through a small pad of silicagel and elution with ethyl ether (25 ml) and ethyl acetate (2 x 30 ml). The filtrate was washed with H2O (5 x 30 ml), saturated aqueous NaCl solution (2 x 30 ml), dried (anh. Na2SO4) and evaporated to afford the desired compound.

(25R)-5β,6β-Epoxyfurostan-3β,26-diol diacetate (2). M.p. 117-118 °C (from ethyl acetate). 1H NMR (400 MHz, CDCl3) δ ppm 4.82-4.67 (m, 1H), 4.26 (dt, J = 7.72, 7.72, 5.35 Hz, 1H), 3.89 (ddd, J = 17.59, 10.73, 6.35 Hz, 1H), 3.27 (dt, J = 8.20, 8.16, 4.05 Hz, 1H), 3.06 (d, J = 2.10 Hz, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.00 (s, 3H), 0.96 (d, J = 6.72 Hz, 3H), 0.91 (d, J = 6.73 Hz, 3H), 0.74 (s, 3H). 13C NMR (100 MHz) δ ppm 32.50 C-1, 27.14 C-2, 71.21 C-3, 37.92 C-4, 62.40 C-5, 63.34 C-6, 36.63 C-7, 29.37 C-8, 51.00 C-9, 35.12 C-10, 21.48 C-11, 39.42 C-12, 40.60 C-13, 56.30 C-14, 32.05 C-15, 83.00 C-16, 65.08 C-17, 16.26 C-18, 17.03 C-19, 37.87 C-20, 18.84 C-21, 90.12 C-22, 30.41 C-23, 30.74 C-24, 32.73 C-25, 69.33 C-26, 16.72 C-27, 21.26 and 20.93 C

H3COO, 171.23 and 170.48 CH3COO. MS (FAB): 516 M+, 515 M+-1, 455, 437, 411, 211, 154, 109, 95, 83, 81, 69, 57, 55. HRMS (FAB) estimated for C31H47O6 (M+-H) 515.3367, found 515.3364.

(25R)-3β,26-Diacetoxy-5β,6β-epoxycholestan-16,22-dione (3a). Syrup. 1H NMR (400 MHz, CDCl3) δ ppm 4.74 (tdd, J = 11.55, 9.87, 4.74, 4.74 Hz, 1H), 4.00-3.81 (m, 2H), 3.09 (d, J = 2.31 Hz, 1H), 2.75 (ddt, J = 17.83, 9.47, 5.59 Hz, 1H), 2.56 (q, J = 5.88, 5.86, 5.86 Hz, 2H), 2.03 (s, 3H), 2.01 (s, 3H), 1.00 (d, J = 7.55 Hz, 6H), 0.93 (d, J = 6.70 Hz, 3H), 0.73 (s, 3H). 13C NMR (100 MHz) δ ppm 32.39 C-1, 27.03 C-2, 71.05 C-3, 37.78 C-4, 62.45 C-5, 62.99 C-6, 36.41 C-7, 28.88 C-8, 50.61 C-9, 35.14 C-10, 21.26 C-11, 39.64 C-12, 41.53 C-13, 50.52 C-14, 38.55 C-15, 213.20 C-16, 66.11 C-17, 15.26 C-18, 16.95 C-19, 217.44 C-22, 37.05 C-23, 26.63 C-24, 32.00 C-25, 68.96 C-26, 16.72 C-27, 21.20 and 20.88 CH3COO, 171.20 and 170.41 CH3COO. MS (FAB): 531 MH+, 515, 513, 472, 471, 411, 295, 229, 223, 211, 115, 97, 107, 95, 81, 69, 12.81 C-21, 217.44 C-22, 37.05 C-23, 26.63 C-24, 32.00 C-25, 68.96 C-26, 16.72 C-27, 21.20 and 20.88 CH3COO, 171.20 and 170.41 CH3COO. MS (FAB): 531 MH+, 515, 513, 472, 471, 411, 295, 229, 223, 211, 115, 97, 107, 95, 81, 69, 57, 55. HRMS (FAB) estimated for C31H47O7 (MH+) 531.3316, found 515.3364.

3β-Acetoxy-5β,6β-epoxycholestan-16,22-dione (3b). Obtained from 1 mmol (442 mg) of 1b as described for 3a (KMnO4 5g, Fe2(SO4)3.nH2O 2.5, H2O 0.5 ml, reaction time 120 min) yield 283.7 mg (0.60 mmol, 60 %) M.p. 134-135 °C (from MeOH). 1H NMR (400 MHz, CDCl3) δ ppm: 4.74 (m, 1H, H-3), 3.12 (a, H-6), 2.60 (d, J= H-17), 2.03 (s, CH3-21), 0.99 (s, CH3-19), 0.85 (d, CH3-26 y CH3-27), 0.74 (s, CH3-18). 13C-NMR (100 MHz): 32.39 C-1, 27.04 C-2, 71.07 C-3, 37.79 C-4, 62.48 C-5, 63.04 C-6, 36.42 C-7, 28.88 C-8, 50.59 C-9, 35.14 C-10, 21.27 C-11, 40.40 C-12, 41.54 C-13, 50.53 C-14, 38.55 C-15, 213.89 C-16, 66.11 C-17, 15.31 C-18, 16.97 C-19, 43.20 C-20, 12.81 C-21, 217.44 C-22, 37.05 C-23, 26.63 C-24, 32.00 C-25, 68.96 C-26, 16.72 C-27, 21.20 and 20.88 CH3COO, 171.20 and 170.41 CH3COO. MS (FAB): 531 MH+, 515, 513, 472, 471, 411, 295, 229, 223, 211, 115, 97, 107, 95, 81, 69, 57, 55. HRMS (FAB) estimated for C31H47O7 (MH+) 531.3316, found 515.3272

(25R)-3β,26-Diacetoxy-cholest-5-en-16,22-dione, krytogenin acetate (4b). A solution of 3a (400 mg, 0.73 mmol) in CH2Cl2 (20 ml) was shaken for 20 min with 48% HBr (10 ml). The organic layer was washed with water (5x10 ml), dried (anh. Na2SO4) and evaporated. The
residue was refluxed for 30 min. with Zn dust (950 mg) in AcOH (15 ml). Ethyl acetate was added, the resulting mixture was filtered and washed with 10% aqueous NaCl (5 x 10 ml), water (3x10 ml), 5% aqueous Na₂CO₃ (10 ml portions until evolution of CO₂ ceased), 10% aqueous NaCl (2x10 ml), dried (anh. Na₂SO₄) and evaporated to afford 5, (224.4 mg, 57.8 %) after chromatographic purification in silica gel. M.p. 143-144 ⁰C (from ethyl acetate); lit.⁷ 152-153 ⁰C. ¹H NMR (400 MHz, CDCl₃), δ ppm 5.36 (d, J = 4.83 Hz, 1H, H-6), 4.67-4.52 (m, 1H, H-3), 3.93 (dd, J = 6.07, 3.08 Hz, 2H, H-26), 2.77 (m, 1H, H-20), 2.04 (s, 3H, CH₃ acetyl), 2.02 (s, 3H, CH₃ acetyl), 1.04 (m, 6H, H-19 and H-21), 0.95 (d, J = 6.72 Hz, 3H, H-21), 0.79 (s, 3H, H-18). ¹³C NMR (100 MHz) δ ppm 36.61 C-1, 27.59 C-2, 73.64 C-3, 37.97 C-4, 139.83 C-5, 121.73 C-6, 31.66 C-7, 30.87 C-8, 49.53 C-9, 36.61 C-10, 20.44 C-11, 39.61 C-12, 41.61 C-13, 51.10 C-14, 38.51 C-15, 213.20 C-16, 66.09 C-17, 15.33 C-18, 19.25 C-19, 43.31 C-20, 12.92 C-21, 217.86 C-22, 37.13 C-23, 26.65 C-24, 32.02 C-25, 68.97 C-26, 16.76 C-27, 21.33 and 20.90 CH₃COO, 171.19 and 170.40 CH₃COO.

3β-Acetoxy-cholest-5-en-16,22-dione (4b). Obtained in 56.5 % (117 mg, 0.26 mmol) from 3b (215.9 mg, 0.46 mmol) as described for kryptogenin acetate (4a). M.p. 152-154 ⁰C (from MeOH) lit.⁴a 151-152 ⁰C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 5.36 (d, J= 4.8 Hz, H-6), 4.65-4.54 (m, H-3), 2.61 (d, J= 3.6 Hz, H-17), 2.02 (s, CH₃COO-3), 1.03 (s, CH₃-19), 0.89 (d, J= 6 Hz, CH₂-26 y CH₃-27), 0.79 (s, CH₃-18) ¹³C NMR (100 MHz): 31.67 C-1, 27.60 C-2, 73.66 C-3, 37.98 C-4, 139.81 C-5, 121.76 C-6, 36.62 C-7, 30.88 C-8, 51.09 C-9, 36.62 C-10, 20.45 C-11, 38.51 C-12, 41.62 C-13, 49.54 C-14, 40.38 C-15, 217.85 C-16, 66.01 C-17, 12.94 C-18, 19.26 C-19, 43.29 C-20, 15.37 C-21, 213.86 C-22, 37.16 C-23, 32.17 C-24, 27.60 C-25, 21.36 C-26, 22.41 CH₃COO, 170.42 CH₃COO.

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References


