An unexpected and useful E-ring oxidative cleavage in furostanes

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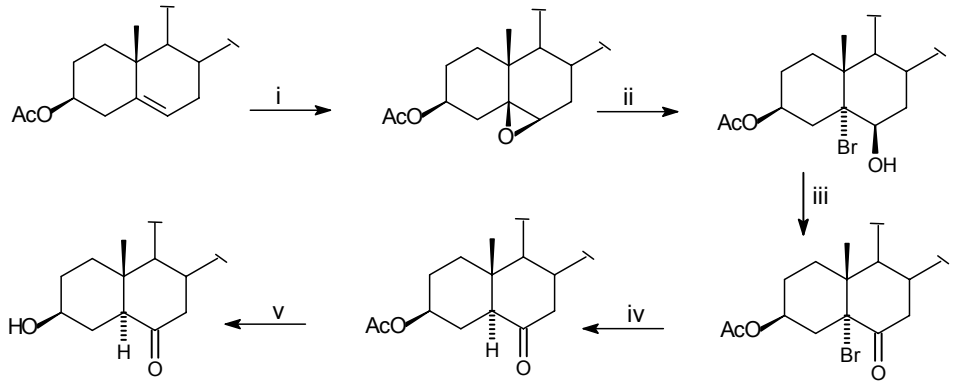
Abstract
Treatment of a acetylated furostanols derived from steroid sapogenins with a wet mixture of $KMnO_4$ and $Fe_2(SO_4)_3.nH_2O$ in CH_2Cl_2/*tert*-butyl alcohol produces the unexpected E-ring oxidative cleavage to afford the corresponding cholestan-22,16-diones. Based in this new reaction, facile 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 Δ^5-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-Δ^5-steroids into the corresponding 3β-hydroxy-6-oxo-steroids [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]



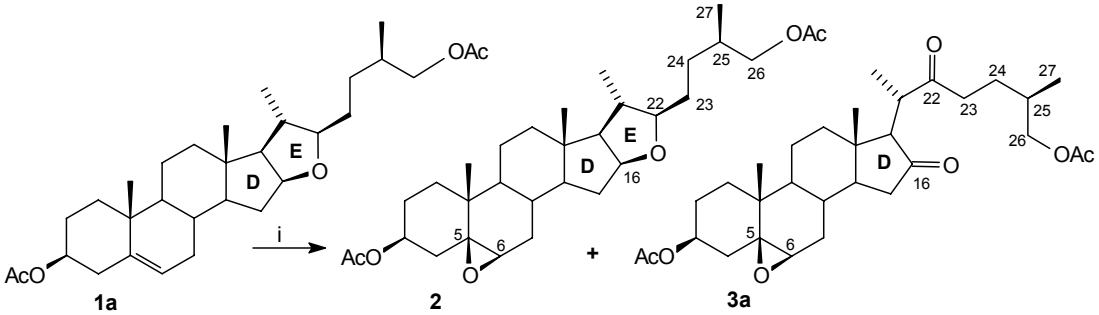
i) Wet $KMnO_4$, $Fe_2(SO_4)_3$, *tert*-BuOH, ii) CH_2Cl_2/ HBr/CH_2Cl_2/ iii) Jones oxidation, iv) Zn/AcOH reflux, v) KOH/ metanol

Scheme 1

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

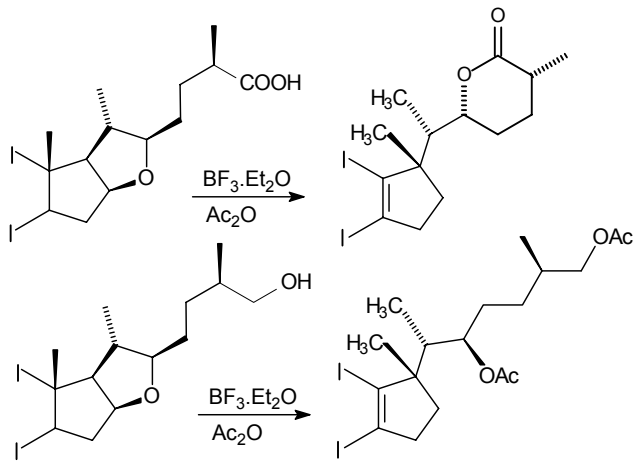
Attempt at β-epoxidation of the acetylated furostanol **1a** using wet $KMnO_4/Fe_2(SO_4)_3$ in CH_2Cl_2 */tert*-butyl alcohol afforded the unchanged starting material and two compounds that after separation were characterized as the desired epoxidated furostanol **2a** (16.6%) and the unexpected epoxidated 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.



i) Wet $KMnO_4/Fe_2(SO_4)_3.nH_2O$ in CH_2Cl_2/*tert*-butanol

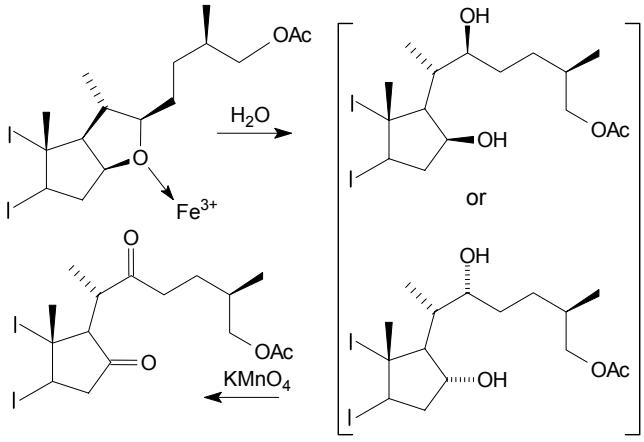
Scheme 2

Some reports have shown that the E-ring of furostanes undergoes cleavage in the presence of Lewis acids. For instance, $Ac_2O/BF_3.Et_2O$ treatment of furostanes has been reported to produce E-ring cleavage followed by 17→16 hydride shift and Wagner-Meerwein rearrangement to afford Δ^{13}-17β-methyl-18-norsteroids (Scheme 3).[3] Activation of acetic anhydride by $BF_3.Et_2O$ 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 $KMnO_4/Fe_2(SO_4)_3$, 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).



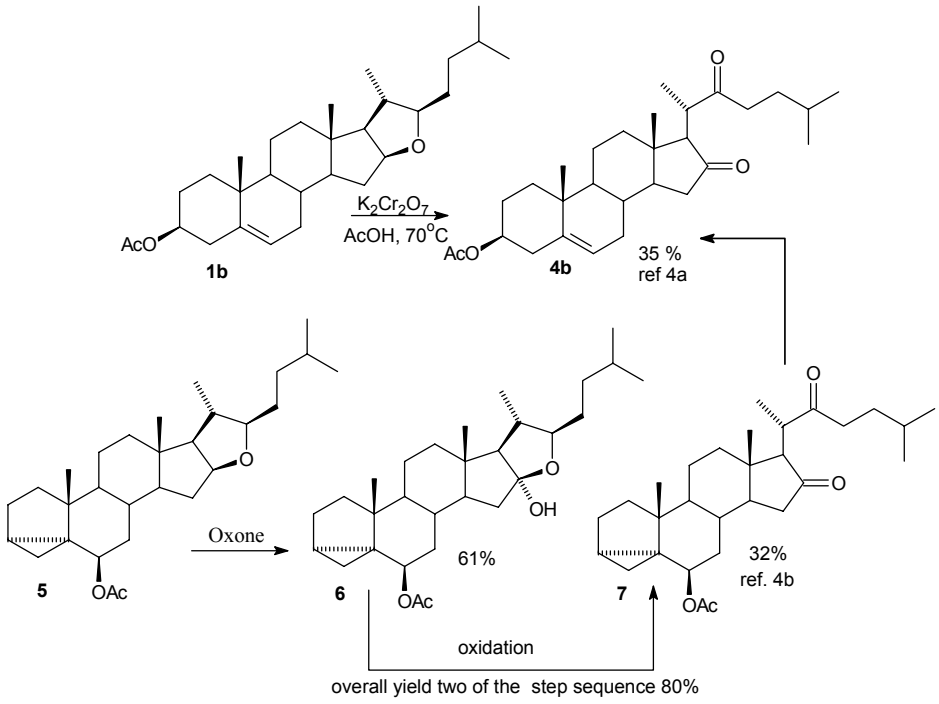
Scheme 4

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 of epoxidation-oxidative E-ring opening of compound **1a**

	$KMnO_4$ (g)	$Fe_2(SO_4)_3.nH_2O$ (g)	H_2O (ml)	Time (min.)	Yield %	
					2	3a
1	4	2	0.4	20	16.6	49.3
2	5	2.5	0.5	120	-	84.4

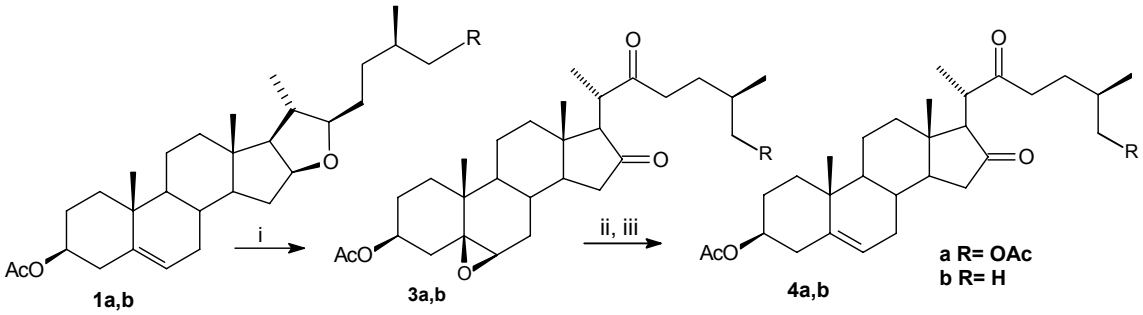
It has been reported that treatment of **1b** with $K_2Cr_2O_7$ in acetic acid led to the 16,22-diketone **4b** in poor yields.[4a] In an alternative approach, oxidation with Oxone® of the acetylated *i*-steroid **5**, derived from diosgenin, produced the hemiketal **6** and the desired 16,22-diketone **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

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 CH_2Cl_2 and Zn dust in refluxing acetic acid.



i) Wet $KMnO_4/Fe_2(SO_4)_3.nH_2O$ in CH_2Cl_2/*tert*-butanol, ii) HBr/CH_2Cl_2 iii) Zn(dust)/acetic acid reflux

Scheme 6

Conclusions

We have found that $KMnO_4/Fe_2(SO_4)_3.nH_2O$ 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/UV_{254} 5 cm x 2.5 cm plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vainillin in 50% $HClO_4$ 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 ($CDCl_3$) for ^{13}C 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

$KMnO_4$ and $Fe_2(SO_4)_3.nH_2O$ were finely grounded in a mortar, H_2O was added and the mixture was placed in a round bottom flask containing CH_2Cl_2 (10 ml) (see Table 1 for amounts of $KMnO_4$, $Fe_2(SO_4)_3.nH_2O$ and H_2O). A solution of the corresponding furostanic compound[6] **3a** or **3b** (2 mmol) in CH_2Cl_2 (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 H_2O (5 x 30 ml), saturated aqueous NaCl solution (2 x 30 ml), dried (anh. Na_2SO_4) and evaporated to afford the desired compound.

(25*R*)-5β,6β-Epoxyfurostan-3β,26-diol diacetate (2). M.p. 117-118 ºC (from ethyl acetate). ^{1}H NMR (400 MHz, *CDCl$_3$*) 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). ^{13}C 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 $\underline{C}H_3COO$, 171.23 and 170.48 $CH_3\underline{C}OO$. MS (FAB): 516 M^+, 515 M^+-1, 455, 437, 411, 211, 154, 109, 95, 83, 81, 71, 69, 57, 55. HRMS (FAB): estimated for $C_{31}H_{47}O_6$ **(**M^+-H) 515.3367, found 515.3364.

(25*R*)-3β,26-Diacetoxy-5β,6β-epoxycholestan-16,22-dione (3a). Syrup. ^{1}H NMR (400 MHz, *CDCl$_3$*) 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 (ddd, *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). ^{13}C 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, 43.23 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 $\underline{C}H_3COO$, 171.20 and 170.41 $CH_3\underline{C}OO$. MS (FAB): 531 MH^+, 515, 513, 472, 471, 411, 295, 229, 223, 211, 115, 97, 107, 95, 91, 81, 69, 67, 55. HRMS (FAB) estimated for $C_{31}H_{47}O_7$ **(**MH^+) 531.3316, found 515.3272

3β-Acetoxy-5β,6β-epoxycholestan-16,22-dione (3b). Obtained from 1 mmol (442 mg) of **1b** as described for **3a (**$KMnO_4$ 5g, $Fe_2(SO_4)_3.nH_2O$ 2.5, H_2O 0.5 ml, reaction time 120 min) yield 283.7 mg (0.60 mmol, 60 %) M.p. 134-135 °C (from MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.74 (m,1H, H-3), 3.12 (a, H-6), 2.60 (d, *J*= H-17), 2.03 (s, C$\underline{H}_3$-21), 0.99 (s, C$\underline{H}_3$-19), 0.85 (d, C$\underline{H}_3$-26 y C$\underline{H}_3$-27), 0.74 (s, C$\underline{H}_3$-18). ^{13}C-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, 66.03 C-17, 15.31 C-18, 16.97 C-19, 43.20 C-20, 12.82 C-21, 217.44 C-22, 37.09 C-23, 32.14 C-24, 27.57 C-25, 22.39 C-26, 22.39 C-27, 21.22 $\underline{C}H_3COO$, 170.44 $CH_3\underline{C}OO$. MS (FAB): 473 MH^+, 413, 395, 327, 267, 207, 147, 83, 81, 69. **HRMS (FAB) e**stimated for $C_{29}H_{45}O_5$ (MH^+) 473.3262, found 473.3303.

(25*R*)-3β,26-Diacetoxy-cholest-5-en-16,22-dione, *krytogenin acetate* (4b). A solution of **3a** (400 mg, 0.73 mmol) in CH_2Cl_2 (20 ml) was shaken for 20 min with 48% HBr (10 ml). The organic layer was washed with water (5x10 ml), dried (anh. Na_2SO_4) 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 x10 ml), water (3x10 ml), 5% aqueous Na_2CO_3 (10 ml portions until evolution of CO_2 ceased), 10% aqueous NaCl (2x10 ml), dried (anh. Na_2SO_4) and evaporated to afford **5**, (224.4 mg, 57.8 %) after chromatographic purification in silica gel. M.p. 143-144 ºC (from ethyl acetate*)*; lit.[7] 152-153 ºC. ^{1}H NMR (400 MHz, *CDCl$_3$*), 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, CH_3 acetyl), 2.02 (s, 3H, CH_3 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). ^{13}C 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 $\underline{C}H_3COO$, 171.19 and 170.40 $CH_3\underline{C}OO$.

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 °C *(from MeOH)* lit.[4a] 151-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 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, $C\underline{H}_3COO$-3), 1.03 (s, $C\underline{H}_3$-19), 0.89 (d, *J*= 6 Hz, $C\underline{H}_3$-26 y $C\underline{H}_3$-27), 0.79 (s, $C\underline{H}_3$-18) ^{13}C 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 C-27, 22.41 $\underline{C}H_3COO$, 170.42 $CH_3\underline{C}OO$.

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