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Regioselective cleavage of 22-oxo-23-spiroketals. Novel cholestanic frameworks with pyranone and cyclopentenone E rings on the side chain

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ABSTRACT

The regioselective opening of the F ring of 22-oxo-23-spiroketals using a saturated solution of HCl in acetic anhydride yielded novel cholestanic frameworks with pyranone or cyclopentenone E rings. The structures of the new derivatives of sarsasapogenin, diosgenin and hecogenin thus obtained were established using one and two dimensional ^{1}H, ^{13}C experiments (DEPT, COSY, HETCOR, HMBC, ROESY, and NOESY). The X-ray analysis for compound **11b** confirmed the 23*R* configuration for the new stereogenic center.

1. Introduction

Saponins are widely distributed in plants with reputed medicinal properties [1]. For this reason, there is a great interest in the preparation of synthetic derivatives, as well as the study of their structural characterization and biological properties. Additionally, since most of the commercial steroidal drugs [2,3] are prepared from spirostanic sapogenins, the chemistry of 22-spiroketal steroidal sapogenins has been studied in detail [4–8]. Due to the presence of a spiroketal moiety on C-22, sapogenins are highly sensitive to acidic conditions, thus acid catalyzed cleavage constitutes a common procedure for the preparation of different analogs of this family of compounds [9,10].

To the best of our knowledge, there are no reports in the literature of naturally occurring steroidal 23-spiroketal saponins, which is in contrast with the triterpenic analogs. For instance, actein [11], with a 23-spiroketal, exhibits potent immunosuppressive activity. This saponin is present in *Cimicifuga racemosa*, commonly known as black cohosh which is used by Native Americans for the treatment of diarrhea and rheumatism. Nowadays black cohosh has become a popular dietary supplement in the United States [12], as a potential alternative to estrogen therapy for the treatment of menopausal symptoms (Fig. 1). Additionally, it has been reported that shengmanol, a triterpenic sapogenin isolated from *Cimicifuga acerina*, incorporating a tetrahydropyran E ring, shows activity against breast cancer cells (Fig. 1) [13,14]. Other natural products possessing a unique pentacyclic steroid skeleton with a C16–C23 bond and *cis* C/D ring junction like xestobergsterols are potent inhibitors of histamine release from rat mast cells induced by anti-IgE. This class of compounds was isolated in 1992 from the Okinawan marine sponge, *Xestospongia bergquistia* [15] and 3 years later, from the marine sponge *Ircinia* [16], and the synthesis of some members of this family of compounds has been reported [17,18].

With respect to the chemistry of steroidal 23-spirostanes a *de novo* rearrangement of (25*R*)-23-oxotigogenin to 22-oxo-23-spiroketal with $TiCl_4$ in CH_2Cl_2 [19] was reported by Suárez. In the last years, several variations of this rearrangement have been reported, many of them using BF_3 as the catalyst, in different solvents (THF, formic acid and CH_2Cl_2) [20–24]; TMSOTf in nonpolar solvents (CH_2Cl_2 and benzene) [25] and even using different reagents such as DIB or BSA in the presence of a Lewis acid, [21,26]. In all cases the reactions are promoted by Lewis acids and the resulting 22-oxo-23-spiroketal products contain the *R* configuration at C-23.

Considering the broad spectrum of bioactivities of saponins, our group has been interested in recent years in the study of the acid catalyzed cleavage of the spiroketal ring of steroidal sapogenins.

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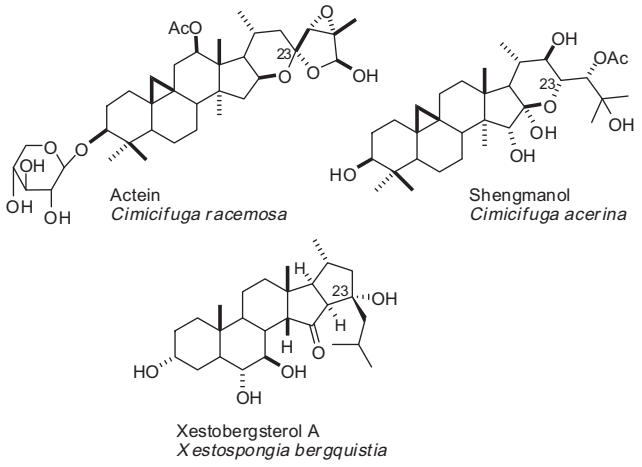

Fig. 1. Examples of naturally occurring steroids.

In the present work, we would like to report the synthesis of novel cholestanic frameworks with a pyranone ring or a cyclopentenone ring on the side chain. These products were obtained by acidic cleavage of 22-oxo-23-spiroketals **2**, **7** and **10** (25*R* and 25*S* series), using a saturated solution of HCl in acetic anhydride. The structures of the cholestanic derivatives were established using one and two dimensional ^{1}H, ^{13}C experiments (DEPT, COSY, HETCOR, HMBC, ROESY, and NOESY). In one case, the relative configurations of the newly formed stereogenic centers were confirmed by an X-ray analysis. A mechanism that accounts for the stereochemistry of the obtained products is proposed.

2. Experimental

2.1. General remarks

IR spectra were acquired on a FT-IR Perkin Elmer Spectrum GX spectrophotometer using KBr pellets ($\overline{\nu}$, cm^{-1}). NMR spectra (^{1}H, ^{13}C, DEPT, HETCOR, COSY, HMBC, ROESY, NOESY) were determined on Bruker DMX 500 and JEOL eclipse +400 spectrometers, and chemical shifts are stated in ppm (δ), and are referred to the residual ^{1}H signal (δ = 7.27) or to the central ^{13}C triplet signal (δ = 77.0) for $CDCl_3$. Mass spectra were obtained at 70 eV with a Hewlett Packard 5989A spectrometer. HRMS of **3** was obtained on a Jeol JMS-SX102A using polyethylene glycol (600) as internal reference and those of **4**, **5**, **8**, **11a** and **11b** were obtained on an Agilent Technologies, model 1100 coupled to a MSD TOF spectrophotometer with APCI as ionization source. The products were separated by chromatography over silica gel (70–230 mesh).

2.2. General procedure for the acid cleavage of 16β,23:23,26-diepoxy-22-oxo moiety (25R and 25S series) with a saturated solution of HCl in acetic anhydride

(23*R*,25*S*)-3β-acetoxy-16β,23:23,26-diepoxy-5β-cholestan-22-one (**2**), (23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxycholest-5-en-22-one (**7**) and (23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxy-5α-cholestan-12,22-dione (**10**) were obtained using the methodology previously described [19]. The formation of the products was confirmed by comparison with the NMR data reported in the literature [20,25].

To a solution of compound **2** (393 mg, 0.83 mmol) in 15 mL of acetic anhydride, was bubbled hydrogen chloride gas (generated *in situ* by dropwise addition of H_2SO_4 to NaCl) during 5 h, maintaining the temperature at 120 °C. When the reaction was completed, the mixture was poured carefully over ice; the organic layer was extracted with dichloromethane and neutralized with a saturated solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum.

Silica gel column chromatography using hexane-ethyl acetate (95:5) as eluent afforded compounds: (23*Z*,25*S*)-3β,26-diacetoxy-16β,23-epoxy-5β-cholest-23-en-22-one (**3**) (106 mg; 25%), (23*R*,25*S*)-3β,26-diacetoxy-16β,23-epoxy-5β-cholest-17-en-22-one (**4**) (91 mg; 21%), and (195 mg; 42%) of (23*R*,25*S*)-3β,23α,26-triacetoxy-16β,23-cyclo-5β-cholest-17-en-22-one (**5**) eluted with hexane-ethyl acetate (90:10).

(23*Z*,25*S*)-3β,26-diacetoxy-16β,23-epoxy-5β-cholest-23-en-22-one (**3**): White foam; UV, λ_{max} (EtOH): 255 nm; IR$\overline{\nu}_{max}$ cm^{-1} (KBr): 2934 (C–H), 1734 (C=O), 1643 (CO—C=C), 1450, 1375, 1237 (O–CO); MS, *m/z* (%): $C_{31}H_{46}O_6$ 514 ([M^+], 0.5), 454 (100), 315 (61), 255 (27), 173 (39), 147 (12), 107 (69), 94 (53), 43 (34); ^{1}H NMR: (400 MHz, $CDCl_3$), δ: 5.59 (1H, d, $J_{24\text{-}25}$ = 9.2 Hz, H-24), 5.05 (1H, s br, H-3), 4.09 (1H, dt, $J_{16\text{-}17}$ = 8.0, $J_{16\text{-}15a;\ 16\text{-}15b}$ = 6.3 Hz, H-16), 3.96 (1H, dd, J_{gem} = 10.6, $J_{26a\text{-}25}$ = 6.2 Hz, H-26a), 3.90 (1H, dd, J_{gem} = 10.6, $J_{26b\text{-}25}$ = 6.6 Hz, H-26b), 2.94 (1H, m, H-25), 2.70 (1H, m, H-20), 2.03, 2.02 (6H, 2s, 3-OCO$\underline{CH_3}$, 26-OCO$\underline{CH_3}$), 1.12 (3H, d, $J_{21\text{-}20}$ = 6.5 Hz, CH_3-21) 1.02 (3H, d, $J_{27\text{-}25}$ = 6.9 Hz, CH_3-27), 0.99 (3H, s, CH_3-19), 0.96 (3H, s, CH_3-18); ^{13}C NMR: (100 MHz, $CDCl_3$), δ: 200.0 (C-22), 171.0, 170.8 (26-O$\underline{CO}CH_3$, 3-O$\underline{CO}CH_3$), 151.5 (C-23), 116.7 (C-24), 79.5 (C-16), 70.6 (C-3), 68.0 (C-26), 57.0 (C-17), 53.0 (C-14), 43.1 (C-13), 40.1 (C-12), 40.0 (C-9), 39.9 (C-20), 37.3 (C-5), 35.3 (C-8), 35.0 (C-10), 33.0 (C-15), 30.8 (C-1), 30.7 (C-4), 29.4 (C-25), 26.5 (C-6), 26.4 (C-7), 25.0 (C-2), 23.9 (C-19), 21.6, 21.0 (3-OCO$\underline{CH_3}$, 26-OCO$\underline{CH_3}$), 20.9 (C-11), 16.8 (C-27), 15.1 (C-18), 13.5 (C-21); HRMS calculated for $C_{31}H_{46}O_6$ $[M+H]^+$ 515.3367. Found 515.3373.

(23*R*,25*S*)-3β,26-diacetoxy-16β,23-epoxy-5β-cholest-17-en-22-one (**4**): Amorphous light yellow solid; UV λ_{max} (EtOH): 245 nm; IR$\overline{\nu}_{max}$ cm^{-1} (KBr): 2935 (C–H), 1734 (C=O), 1673 (CO—C=C), 1449, 1375, 1238 (O–$COCH_3$); MS, *m/z* (%): 514 ([M^+], 0.5), 454 (14), 386 (100), 370 (75), 328 (24), 215 (36), 201 (23), 147 (21), 108 (33), 101 (29); ^{1}H NMR: (400 MHz, $CDCl_3$), δ: 5.03 (1H, s br, H-3), 4.30 (1H, m, H-16), 3.90 (1H, m, H-23), 3.96 (2H, m, H-26), 2.00 (6H, s, 3-OCO$\underline{CH_3}$, s, 26-OCO$\underline{CH_3}$), 1.75 (3H, d, $J_{21\text{-}16}$ = 2.0 Hz, CH_3-21), 1.06 (3H, s, CH_3-18) 0.97 (3H, s, CH_3-19), 0.92 (3H, d, $J_{27\text{-}25}$ = 6.5 Hz, CH_3-27); ^{13}C NMR: (100 MHz, $CDCl_3$), δ: 198.4 (C-22), 171.3, 170.8 (26-O$\underline{CO}CH_3$, 3-O$\underline{CO}CH_3$,), 169.8 (C-17), 126.7 (C-20), 80.9 (C-23), 79.1 (C-16), 70.5 (C-3), 68.5 (C-26), 50.8 (C-14), 45.3 (C-13), 40.2 (C-9), 37.3 (C-5), 35.4 (C-12), 35.1 (C-10), 34.8 (C-24), 33.7 (C-8), 30.6 (C-1, C-4), 30.2 (C-15), 29.2 (C-25), 26.3 (C-6, C-7), 25.0 (C-2), 23.8 (C-19), 21.6, 21.0 (3-OCO$\underline{CH_3}$, 26-OCO$\underline{CH_3}$), 20.8 (C-11), 17.9 (C-27), 17.7 (C-18), 10.2 (C-21); HRMS calculated for $C_{31}H_{46}O_6$ $[M+H]^+$ 515.33672. Found 515.33533.

(23*R*,25*S*)-3β,23α,26-triacetoxy-16β,23-cyclo-5β-cholest-17-en-22-one (**5**): Amorphous light yellow solid; UV, λ_{max} (CH_3CN): 241 nm; IR$\overline{\nu}_{max}$ cm^{-1} (KBr): 2934 (C-H), 1735 (C=O), 1661 (CO—C=C), 1449, 1373, 1238 (O–$COCH_3$), 1157, 1024; MS, *m/z* (%): $C_{33}H_{48}O_7$ 557 ([M^++H], 0.1), 514 (1), 496 (10), 471 (1), 437 (32), 436 (100), 393 (2); ^{1}H NMR: (500 MHz, $CDCl_3$), δ: 5.06 (1H, s br, H-3), 4.07 (1H, dd, J_{gem} = 10.7, $J_{26a\text{-}25}$ = 5.0 Hz, H-26a), 3.98 (1H, dd, J_{gem} = 10.7, $J_{26b\text{-}25}$ = 6.4 Hz, H-26b), 3.52 (1H, ddq, $J_{16\text{-}15a}$ = 10.9, $J_{16\text{-}15b}$ = 2.3, $J_{16\text{-}21}$ = 2.3 Hz, H-16), 2.06 (3H, s, 26-OCO$\underline{CH_3}$), 2.05 (3H, s, 23-OCO$\underline{CH_3}$), 2.04 (3H, s, 3-OCO$\underline{CH_3}$), 1.78 (3H, d, $J_{21\text{-}16}$ = 2.3 Hz, CH_3-21) 1.04 (3H, s, CH_3-18), 1.02 (3H, s, CH_3-19), 0.87 (3H, d, $J_{27\text{-}25}$ = 6.8 Hz, CH_3-27); ^{13}C NMR: (125 MHz, $CDCl_3$), δ: 205.8 (C-22), 180.6 (C-17), 171.2 (26-O$\underline{CO}CH_3$), 170.6 (3-O$\underline{CO}CH_3$), 170.0 (23-O$\underline{CO}CH_3$), 125.2 (C-20), 86.8 (C-23), 70.5 (C-3), 68.9 (C-26), 55.1 (C-14), 48.9 (C-16), 44.2 (C-13), 40.1 (C-9), 37.2 (C-5), 36.1 (C-24), 35.6 (C-8), 35.0 (C-10), 34.9 (C-12), 30.7 (C-1) 30.6 (C-4), 27.2 (C-25), 26.2 (C-6), 25.7 (C-7), 24.9 (C-2), 23.7 (C-19), 23.0 (C-15), 21.5 (3-OCO$\underline{CH_3}$, 23-OCO$\underline{CH_3}$), 20.9