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Synthesis and Absolute Configuration of (20*R*)-20-Acetyl-23,24-bisnorcholanic Lactones Prepared from (*E*)-(20*S*,25*R*)- and (*E*)-(20*S*,25*S*)-20,23-Diacetylfurost-22-enes

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Abstract. The synthesis of (20*R*)-20-acetyl-23,24-bisnorcholanic lactones from (*E*)-(20*S*,25*R*)- and (*E*)-(20*S*,25*R*)-20,23-diacetylfurost-22-enes (derived from diosgenin, hecogenin and sarsasapogenin) is reported. The configuration of the stereogenic center at C-20 was determined by NMR and single crystal X-ray diffraction studies. The lactones can be used in the synthesis of a variety of steroidal derivatives.

Keywords: Absolute configuration; 23,24-bisnorcholanic lactones; 20,23-diacetylfurost-22-enes; molecular structure.

Resumen. Se reporta la síntesis de lactonas (20*R*)-20-acetil-23,24-bisnorcolánicas a partir de (*E*)-(20*S*,25*R*)- y (*E*)-(20*S*,25*R*)-(*E*)-20,23-diacetilfurost-22-enos (obtenidos a partir de diosgenina, hecogenina y sarsasapogenina). La configuración del centro estereogénico C-20 fue determinada por estudios de RMN y difracción de rayos X de monocristal. Las lactonas pueden ser usadas en la síntesis de una variedad de derivados esteroidales.

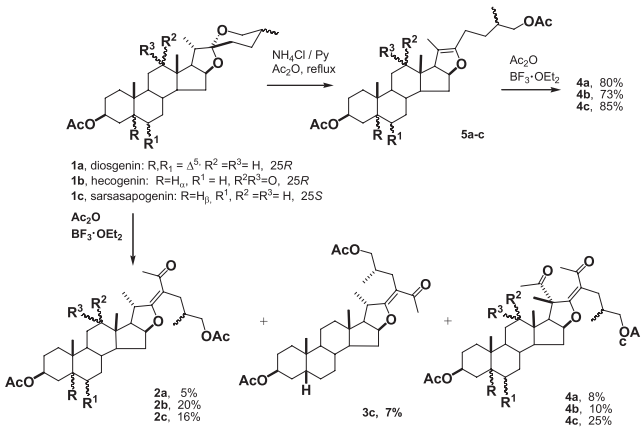
Palabras clave: Configuración absoluta; lactonas 23,24-bisnorcolánicas; 20,23-diacetilfurost-22-enos; estructura molecular.

Introduction

The lactone moiety in 23,24-bisnorcholanic lactone is extremely resistant to acidic and basic hydrolysis, however, a possible useful synthetic transformation can be regarded from the attack of Grignard reagents, i.e. phenylmagnesium bromide [1a] or by a hydride attack [1b]. Some lactones are naturally occurring in plants, as free aglycones or as glycosides [2], showing relevant biological activities. For example, (20*S*)-20-hydroxy-23,24-bisnorcholanic lactone (isolated from *Solanum vespertilio*) [2] displays cytostatic activity [3]. The lactone has been synthesized starting from diosgenin [4]. Some 20-chloro- and 20-iodo derivatives have been obtained by oxidation of 23-hydroxysapogenins [5]. The bisnorcholanic lactones have been prepared by a number of synthetic methodologies [6]; in this manuscript we report the oxidation of 20,23-diacetylfurost-22-enes affording (20*R*)-acetyl-23,24-bisnorcholanic lactones, following a methodology reported by us [7]. The furostenes were obtained from diosgenin, hecogenin and sarsasapogenin [7,8].

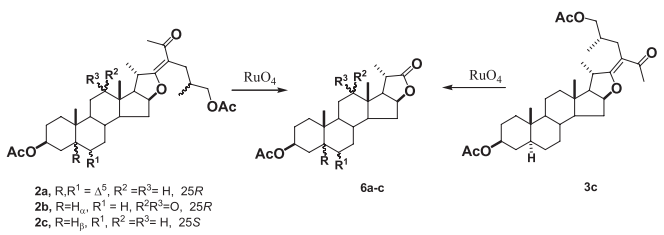
Results and Discussion

We have previously reported [7,8] the Ac_2O/Lewis acid catalyzed transformation of sarsasapogenin, hecogenin and diosgenin into their (*E*)-20,23-diacetyl-, (*E*)-23-acetyl- and (*Z*)-23-acetylfurost-22-ene derivatives (**2a-c**, **3c, 4a-c**). The preparation of **4a-c** could be improved from the pseudosapogenins **5a-c** as starting materials (Scheme 1).



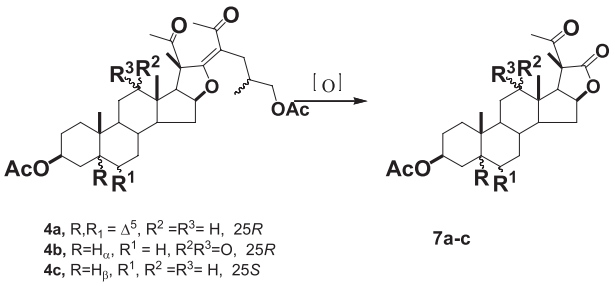
Scheme 1. Transformation of sapogenins into 23-acetyl- and 20,23-diacetylfurost-22-enes.

The double bonds present in α,β-unsaturated ketones **2a-c** and **3c** could be selectively oxidized by RuO_4 (generated *in situ*, from $RuCl_3$/$NaIO_4$)[7] providing the 23,24-bisnorcholanic lactones **6a-c** in excellent yields (Scheme 2).



Scheme 2. Preparation of 23,24-bisnorcholanic lactones.

The RuO_4 methodology was successfully applied for the preparation of 20-acetyl-23,24-bisnorcholanic lactones **7a-c** in excellent yields, using 20,23-diacetylfurost-22-enes **4a-c** as starting materials (Scheme 3). When CrO_3 was used as an oxidizing reagent, low yields were obtained (See Table 1).



4a, R,R_1 = Δ^5, R^2 =R^3= H, 25*R*
4b, R=H_α, R^1 = H, R^2R^3=O, 25*R*
4c, R=H_β, R^1, R^2 =R^3= H, 25*S*

Scheme 3 Oxidation of 20,23-diacetylfurost-22-enes **4a-c** .

Table 1. Comparative oxidation yields of the lactones **7a-c**.

Starting material	Product	Yield CrO_3 (%)	Yield RuO_4 (%)
4a	**7a**	81	94
4b	**7b**	71	94
4c	**7c**	71	94

The IR spectra of **7a-c** showed the characteristic carbonyl band at 1764-1770 cm^{-1} for the five membered ring lactones and esters, 1721-1731 cm^{-1} for ketones. The mass spectra showed their molecular ions; and in particular, two fragments (M^+- 42) and 43 are due to the presence of the 20-acetyl group. In the ^{1}H NMR spectra of **7a-c** important signals are those of Me-18, Me-19, Me-20^2 and Me-21 (See Table 2). The assignment of signals for Me-18 and 19 was made considering the HMBC spectra. The signals for Me-21 in lactones **7a-c** are shifted to higher frequency with respect to the corresponding 20-unsusbstituted lactones, **6a-c** due to the deprotection effect of the 20-acetyl group ($\Delta\delta$ = 0.23 ppm).

Table 2. Selected ^{1}H NMR chemical shifts in lactones **6a-c** and **7a-c**. (δ, $CDCl_3$)

	Lactones					
H	**6a**	**6b**	**6c**	**7a**	**7b**	**7c**
H-16	4.96	4.90	4.94	4.59	4.68	4.67
Me-18	0.77	1.07	0.74	0.90	1.17	0.87
Me-19	1.04	0.93	0.99	1.03	0.92	0.98
H-20	2.59	2.59	2.57	—	—	—
Me-21	1.32	1.39	1.31	1.55	1.54	1.55
Me-20^2	—	—	—	2.27	2.32	2.27

The signals for C-20 in the ^{13}C NMR spectra of **7a-c** are strongly influenced by the 20-acetyl group, and are shifted to higher frequency by around 25 ppm, in comparison with their 20-unsubstituted analogs **6a-c**. Signals for C-17, C-21 and C-22 for **7a-c** were shifted to lower frequencies; this β-effect is enhanced for C-22 than for C-21 or C-17 (Table 3).

The COSY, HSQC and HMBC experiments were very useful for the assignment of the Me-18, Me-19 and Me-21 signals.

Table 3. Selected ^{13}C NMR chemical shifts for lactones **6a-c** and **7a-c** (δ, $CDCl_3$).

	Lactones					
C	6a	6b	6c	7a	7b	7c
C-11	20.2	37.1	20.3	20.4	37.2	20.2
C-12	38.0	212.3	38.4	38.1	211.9	39.1
C-13	41.3	55.5	41.8	41.4	55.23	41.8
C-14	54.6	53.7	54.6	55.4	55.17	55.3
C-15	33.0	32.2	33.0	33.1	31.5	32.0
C-16	82.6	80.7	82.8	82.3	80.4	82.4
C-17	58.7	50.6	59.1	56.7	50.4	56.9
C-18	13.6	13.6	13.8	14.4	14.2	14.4
C-19	19.2	11.7	23.7	19.4	11.8	23.7
C-20	35.9	36.5	36.0	61.3	60.9	61.3
C-21	17.9	17.1	17.9	15.4	15.9	15.3
C-22	181.3	180.7	181.3	176.3	176.1	176.5
C-20^1	—	—	—	202.7	202.7	202.9
C-20^2	—	—	—	25.0	24.8	24.9

The new lactones **7a-c** could be crystallized as colorless crystals. Single-crystal structures determinations for **7a-c** (Table 4) support the correct assignment of the molecular structures based on spectroscopic data. Compounds **7a** (Figure 1) and **7b** crystallize with two independent molecules in the asymmetric unit, with almost identical conformations, a common feature for steroidal compounds, while **7c** is a *Z*'=1 crystal. The steroidal nuclei have the expected junction configurations, identical to those of their respective starting materials **1a-c**. The absolute configuration of the stereogenic center C20 is *R* for the three molecules, confirming that oxidation reaction is carried out, as previously observed for the synthesis of **6a-c**.

By comparison with **6a-c**, molecules **7a-c** are expected to experience hindrance at C20, which is substituted by a sterically demanding acetyl group. However, at least in the solid state, no exceptionally short intramolecular contacts are observed. This feature should be related to the *R* configuration at C20, which places the acetyl group oriented toward the α-face of the steroidal nucleus, while methyl groups C18 and C21 are on the same β side freely rotating about their C–C bonds. The shortest C18···C21 approach in **7a-c** is 3.278 Å for **7a**, and assuming an accurate determination of H positions, the short-

Table 4. Selected Crystallographic data for compounds **7a**-**c**.

Compound	**7a**	**7b**	**7c**
Empirical Formula	$C_{26}H_{36}O_5$	$C_{26}H_{36}O_6$	$C_{26}H_{38}O_5$
Space group	$P2_1$	$P2_1$	$P2_12_12_1$
a, Å	7.5827(13)	7.7363(12)	7.4138(11)
b, Å	23.795(3)	16.964(2)	9.9821(13)
c, Å	12.7877(16)	18.1899(18)	33.194(4)
β, deg	97.033(15)	96.188(14)	-
V, Å^3	2289.9(6)	2373.3(5)	2456.5(6)
Z, *Z*'	4, 2	4, 2	4, 1
ρ_{calc} gcm^{-3}	1.243	1.244	1.164
2θ range, deg	4 - 50	4 - 50	4 - 55
Data / param. ratio	4133 / 570	4344 / 588	3228 / 285
R_1[a] % [$I > 2\sigma(I)$]	$R_1 = 4.10$	$R_1 = 4.07$	$R_1 = 5.00$
wR_2[b] % [$I > 2\sigma(I)$]	$wR_2 = 9.91$	$wR_2 = 9.52$	$wR_2 = 12.09$

[a] $R_1 = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$. [b] $wR_2 = [\Sigma w(\left| F_o \right| - \left| F_c \right|)^2 / \Sigma w \left| F_o \right|^2]^{1/2}$.

est H···H contact for these functional groups is 2.037 Å in **7b** (van der Waals radii for H: 1.20 Å).

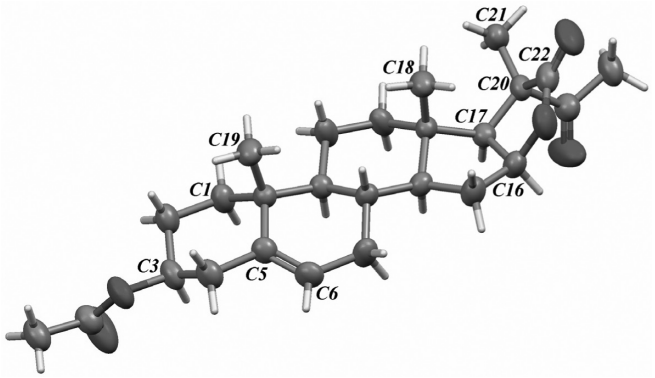


Figure 1 Molecular structure of one of the two independent molecules in the crystal structure of **7a**. Displacement ellipsoids for non-H atoms are shown at the 50% probability level.

Experimental

General. 1D and 2D ^{1}H and ^{13}C NMR spectra (DEPT, COSY, HMQC, HMBC) were recorded on a VARIAN Mercury spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) 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 $CDCl_3$. Coupling constants (*J*) are quoted in Hz. IR spectra were acquired on a Nicolet Magna FT-IR 750 spectrophotometer using KBr pellets (ν, cm^{-1}). Mass spectra were obtained on a HP 5989 spectrometer adapted to a HP 6890A using electron impact ionization. Optical rotations were determined on a Perkin Elmer 241 polarimeter at room temperature using chloroform solutions. Melting points were obtained from a Mel-Temp apparatus and were not corrected.

(20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (6a). White powder, mp 213-215°C. $[\alpha]_D$ -46º (*c* 1.0); IR ν_{max}: 1747, 1720, 1677 cm^{-1}; ^{1}H NMR δ: 5.37 (1H, d, $J_{6\text{-}7}$ = 4.5 Hz, H-6), 4.96 (1H, m, H-16), 4.60 (1H, m, H-3), 2.59 (1H, dq, $J_{20\text{-}21} = J_{20\text{-}17}$ = 6.6 Hz, H-20), 2.28 (1H, m, H-15α), 2.04 (3H, s, $C\underline{H}_3CO_2$-3), 1.32 (3H, d, $J_{21,20}$ = 7.0 Hz, CH_3-21), 1.04 (3H, s, CH_3-19), 0.77 (3H, s, CH_3-18); ^{13}C RMN δ: 36.2 (C-1), 27.2 (C-2), 73.7 (C-3), 38.1 (C-4), 139.7 (C-5), 121.8 (C-6), 31.7 (C-7), 31.1 (C-8), 49.8 (C-9), 35.9 (C-10), 20.2 (C-11), 38.0 (C-12), 41.3 (C-13), 54.6 (C-14), 33.0 (C-15), 82.6 (C-16), 58.7 (C-17), 13.6 (C-18), 19.2 (C-19), 35.9 (C-20), 17.9 (C-21), 181.3 (C-22), 170.5 ($CH_3\text{-}\underline{C}O_2$-3), 21.3 ($\underline{C}H_3\text{-}CO_2$-3).

(20*S*)-3β-acetoxy-12-oxo-5α-pregnane-20,16β-carbolactone (6b) White powder, mp 224–226°C; $[\alpha]_D$ +23º (*c* 1.0); IR n_{max}: 1773, 1731, 1704,1240 cm^{-1}; ^{1}H NMR δ: 4.90 (1H, m, H-16), 4.67 (1H, m, H-3), 2.59 (2H, m, H-17 and H-20), 2.02 (3H, s, $C\underline{H}_3CO_2$-3), 1.39 (3H, d, $J_{21\text{-}20}$= 7.3 Hz, H-21), 1.07 (3H, s, H-18), 0.93 (3H, s, H-19); ^{13}C NMR δ: 36.05 (C-1), 27.0 (C-2), 72.8 (C-3), 33.5 (C-4), 44.2 (C-5), 27.0 (C-6), 31.1 (C-7), 33.9 (C-8), 55.3 (C-9), 35.96 (C-10), 37.1 (C-11), 212.3 (C-12), 55.5 (C-13), 53.7 (C-14), 32.2 (C-15), 80.7 (C-16), 50.6 (C-17), 13.6 (C-18), 11.7 (C-19), 36.5 (C-20), 17.1 (C-21), 180.7 (C-22), 170.5 ($CH_3\text{-}\underline{C}O_2$-3), 21.3 ($\underline{C}H_3\text{-}CO_2$-3). MS, *m/z* (%): 402 ($M^{+\cdot}$) (2). *Anal.* C 71.46%, H 9.61%, O 19.65.76% calcd. for $C_{24}H_{34}O_5$ C 71.61%, H 8.51%, O 19.9%.

(20*S*)-3β-acetoxy-5b-pregnane-20,16β-carbolactone (6c). White powder, mp 183–185°C; $[\alpha]_D$ -31º (*c* 1.0); IR ν_{max}: 1768, 1757, 1734,1254 cm^{-1}; ^{1}H NMR δ: 5.07 (1H, m, H-3), 4.94

(1H, m, H-16), 2.57 (1H, q, $J_{20\text{-}21}$ = 7.3 Hz, H-20), 2.27 (1H, m, H-15α), 2.05 (3H, s, C$\underline{H}_3CO_2$-3), 1.31 (3H, d, $J_{21,20}$ = 7.3 Hz, CH_3-21), 0.99 (3H, s, CH_3-19), 0.74 (3H, s, CH_3-18); ^{13}C RMN δ: 30.7 (C-1), 24.9 (C-2), 70.4 (C-3), 30.5 (C-4), 37.1 (C-5), 26.3 (C-6), 26.2 (C-7), 35.0 (C-8), 40.0 (C-9), 34.9 (C-10), 20.3 (C-11), 38.4 (C-12), 41.8 (C-13), 54.6 (C-14), 33.0 (C-15), 82.8 (C-16), 59.1 (C-17), 13.8 (C-18), 23.7 (C-19), 36.0 (C-20), 17.9 (C-21), 181.3 (C-22), 170.6 (CH_3-$\underline{C}O_2$-3), 21.4 ($\underline{C}H_3$-CO_2-3), MS-FAB, *m/z* (%): 389 ($M^{+\cdot}$+1) (2). *Anal.* C 74.45%, H 9.41%, O 16.76% calcd. for $C_{24}H_{36}O_4$ C 74.19%, H 9.34%, O 16.47%.

Oxidation of the 20,23-diacetylfurost-22-enes 4a-c.

Method A: To a solution of 0.9 mmol of the 20,23-diacetylfurost-22-ene **4a-c** in 10 mL of acetonitrile a solution of $NaIO_4$ (695 mg, 3.25 mmol in 2 mL of H_2O) and a catalytic amount of $RuCl_3$ were added. The mixture was stirred at room temperature under inert atmosphere of argon and was monitored until complete disappearance of the starting material (about 15 min). The crude was filtered trough a short silica gel path with washed of the dichloromethane (3 × 25 mL). The filtrate was washed with brine and water (3 × 25 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to dryness under vacuum. The crude product was submitted to chromatography, over silica gel, using hexane/EtOAc (7:3) yielding **7a-c** (See table 1).

Method B: A solution of 1.0 mmol of 20,23-diacetylfurost-22-ene **4a-c** in 7.5 mL of AcOH at 0ºC was slowly added to a solution of 3.8 mmol CrO_3 in AcOH/H_2O (9/1). This mixture was stirred at room temperature and monitored until complete disappearance of the starting material. The reaction mixture was neutralized with a saturated aqueous solution of $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and washed with H_2O, dried over anhydrous $MgSO_4$ and concentrated to dryness under vacuum. The crude product was submitted to chromatography over silica gel using hexane/EtOAc (8:2) yielding **7a-c** (See table 1).

(20*R*)-20-acetyl-3β-acetoxypregn-5-ene-20,16β-carbolactone (7a). Colorless crystals, mp 236-237°C (acetone), $[\alpha]_D$ -57º (*c* 1.7); IR ν_{max}: 1763, 1721, 1677 cm^{-1}; ^{1}H NMR δ: 5.37 (1H, d, *J*= 4.8 Hz, H-6), 4.68 (1H, m, H-3), 4.59 (1H, m, H-16), 2.64 (1H, d, $J_{17\text{-}16}$= 6 Hz, H-17), 2.33 (1H, m, H-15), 2.27 (3H, s, CH_3-20^2), 2.03 (3H, s, C$\underline{H}_3$COO-3), 1.55 (3H, s, H-21), 1.03 (3H, s, H-19), 0.90 (3H, s, H-18); ^{13}C NMR δ: 36.9 (C-1), 27.7 (C-2), 73.7 (C-3), 38.0 (C-4), 139.5 (C-5), 121.7 (C-6), 31.9 (C-7), 31.2 (C-8), 49.6 (C-9), 36.7 (C-10), 20.4 (C-11), 38.1 (C-12), 41.4 (C-13), 55.4 (C-14), 33.1 (C-15), 82.3 (C-16), 56.7 (C-17), 14.4 (C-18), 19.4 (C-19), 61.3 (C-20), 202.7 (C-20^1), 25.0 (C-20^2), 15.4 (C-21), 176.3 (C-22), 170.3 ($CH_3\underline{C}O_2$-3), 21.5 ($\underline{C}H_3CO_2$-3).

(20*R*)-20-acetyl-3β-acetoxy-12-oxo-5α-pregnane-20,16b-carbolactone (7b). Colorless crystals, mp 268 - 269°C (hexane); $[\alpha]_D$ + 63.90° (*c* 1.4); MS, *m/z* (%): 444 (1), 402 (100); 342 (9); 291 (98); 231 (20); 121 (30); 43 (50); IR ν_{max}: 1771, 1731, 1710 cm^{-1}; ^{1}H NMR δ: 4.68 (2H, m, H-16 y H-3) ; 3.23 (1H, d, $J_{17,16}$ = 6.43 Hz, H-17); 2.46 (1H, dd, $J_{11a,11b}$ =14, $J_{11a,10}$ = 13 Hz, H-11a); 2.34 (1H, m, H-15e); 2.26 (1H, dd, $J_{11b,10}$= 6.8, $J_{11b,11a}$ =14 Hz, H-11b); 2.32 (3H, s, CH_3-20^2); 2.02 (3H, s, C$\underline{H}_3$COO-3); 1.54 (3H, s, H-21); 1.17 (3H, s, H-18); 0.92 (3H, s, H-19); ^{13}C NMR δ: 36.2 (C-1), 27.1 (C-2), 72.9 (C-3), 33.6 (C-4), 44.2 (C-5), 27.9 (C-6), 31.0 (C-7), 33.8 (C-8), 55.5 (C-9), 36.1 (C-10), 37.2 (C-11), 211.9 (C-12), 55.23 (C-13), 55.17 (C-14), 31.5 (C-15), 80.4 (C-16), 50.4 (C-17), 14.2 (C-18), 11.8 (C-19), 60.9 (C-20), 202.7 (C-20^1), 24.8 (C-20^2), 15.9 (C-21), 176.1 (C-22), 170.6 ($CH_3\underline{C}O_2$-3), 21.3 ($\underline{C}H_3CO_2$-3). *Anal.* C 70.21, H 8.22, O 21.54%, calcd. for $C_{26}H_{36}O_6$ C 70.24, H 8.16, O 21.59%.

(20*R*)-20-acetyl-3β-acetoxy-5b-pregnane-20,16β-carbolactone (7c). Colorless crystals, mp 249 - 251°C (hexane) ; $[\alpha]_D$ = + 26.98° (*c* 1.0); MS-FAB, *m/z* (%): 431 (M^++1) (1), 388 (88), 328 (37), 218 (47), 43 (100); IR ν_{max}: 1763, 1721 cm^{-1}; ^{1}H NMR (400 MHz) δ: 5.07 (1H, s, H-3), 4.67 (1H, ddd, *J* = 3.6, 6.6 y $J_{16\text{-}17}$ = 6.6 Hz, H-16), 2.64 (1H, d, $J_{17\text{-}16}$ = 6.6 Hz, H-17), 0.87 (3H, s, H-18), 0.98 (3H, s, H-19), 1.55 (3H, s, H-21), 2.05 (3H, s, C$\underline{H}_3CO_2$-3), 2.27 (3H, s, CH_3-20^2); ^{13}C NMR δ: 30.7 (C-1), 26.0 (C-2), 70.4 (C-3), 30.5 (C-4), 37.1 (C-5), 26.2 (C-6), 26.1 (C-7), 34.7 (C-8), 39.8 (C-9), 34.9 (C-10), 20.2 (C-11), 39.1 (C-12), 41.8 (C-13), 55.3 (C-14), 32.0 (C-15), 82.4 (C-16), 56.9 (C-17), 14.4 (C-18), 23.7 (C-19), 61.3 (C-20), 202.9 (C-20^1), 24.9 (C-20^2), 15.3 (C-21), 176.5 (C-22), 170.6 ($CH_3\underline{C}O_2$-3), 21.5 ($\underline{C}H_3CO_2$-3). *Anal.* C 72.42, H 8.93, O 18.16%, calcd. for $C_{26}H_{38}O_5$: C 72.53, H 8.90, O 18.58%.

Crystallography. Diffraction data for **7a-c** were collected at room temperature with a Bruker P4 diffractometer equipped with Mo-K_α radiation (λ = 0.71073 Å), using standard procedures [9], and measured Friedel pairs were systematically merged. The structures were solved by direct methods and refined without constraints or restraints for non-H atoms [10]. The absolute configuration was assigned on the basis of known configurations for stereogenic centers in the steroidal nucleus. H atoms were placed in idealized positions [constrained distances: 0.93 Å for C(sp^2)–H, 0.96 Å for methyl CH_3, 0.97 Å for methylene CH_2, and 0.98 Å for methine CH]. Methyl groups were considered as rigid groups but allowed to rotate about their C–C bonds. Complete structural data have been deposited with the CCDC. Deposition numbers: CCDC-657207 for **7a**, CCDC-657208 for **7b**, and CCDC-657209 for **7c**. Structure factors are available on request to authors.

Conclusions

Three (20*R*)-20-acetyl-23,24-bisnorcholanic lactones were synthesized in excellent yields; the stereochemistry at the chiral centre C-20 was determined by NMR and X-ray analyses. The starting materials (20*S*,25*R*)-(*E*)-20,23-diacetylfurost-22-

enes) were rapidly obtained through a selective F ring opening of the corresponding sapogenins. The single-crystal structures determinations for **7a-c** support correct assignment of molecular structures based on spectroscopic data and the configuration of the C-20 was corroborated.

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