

The Baeyer-Villiger reaction of 23-oxosapogenins

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Dedicated to Professor Eusebio Juaristi on occasion of his 55th birthday
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Abstract

The Baeyer-Villiger reactions of 25*R*- and 25*S*-23-oxosapogenins with MCPBA produced a mixture of bisnorcholanic 22→16 lactones and pregnan-16,20-diol carbonates. The postulated mechanism explains the reaction times in terms of the transition states for the peroxyacid attack. The explanation of the regioselectivity of the studied reaction relays on the conformational preference of the Criegee's intermediate. Reaction barriers calculated using the semiempirical PM3 method justify the observed reaction times.

Keywords: Baeyer-Villiger reaction, oxosapogenin, semiempirical PM3 calculations

Introduction

For a long time steroid sapogenins have been used as starting materials for the synthesis of different steroidal drugs,¹ and more recently on the synthesis of ecdysone,² spirostanic and furostanic analogues of brassinosteroids with modified side chains.³ All synthetic procedures relay on the degradation or modification of the spirostanic side chain. The reactivity of the spirostanic side chain was extensively studied during the mid part of the last century.⁴ More recently, new transformations have been reported,^{5,6} some of these reactions have been reported to produce the cleavage of the spiroketal side chain to the C-22→16 lactone moiety characteristic of bisnorcholanic lactones.⁶

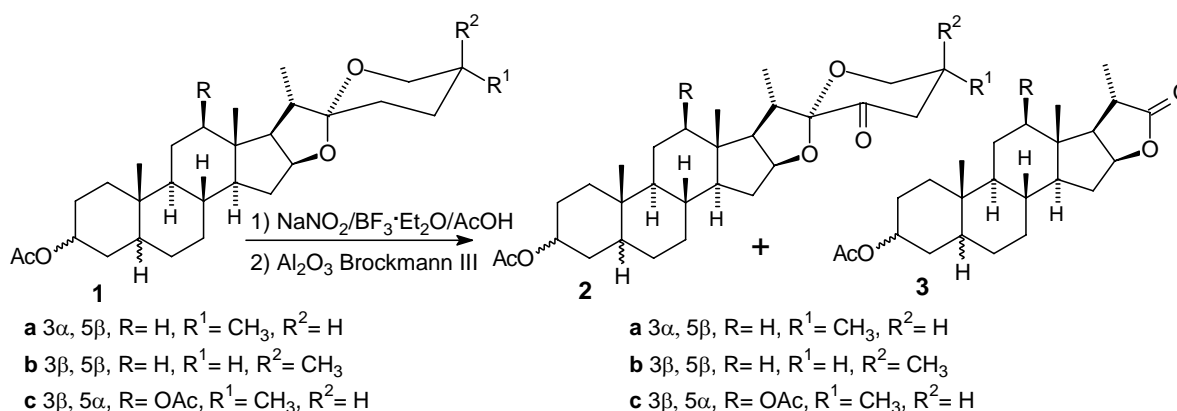
Bisnorcholanic lactones have called the attention of scientists due to their biological properties.⁷ Early reports show that such compounds can be produced in low yield by treatment of the corresponding steroid sapogenin with CrO₃, HNO₃ or as a byproduct of reaction with NaNO₂ and BF₃·Et₂O in acetic acid.⁸ The conversion of solasodine and tomatidine into the corresponding

lactones have been also reported.⁹ New synthetic alternatives to the mentioned lactones are always desirable. Herein, we report on the Baeyer-Villiger reaction (BV) of 23-oxosapogenin acetates as an alternative to the synthesis of bisnorcholanic lactones and as a source of steroid diversity.

Results and Discussion

Sapogenin acetates **1a** (*3-epismilagenin acetate*) and **1b** (*sarsasapogenin acetate*) were prepared from the parent sapogenin using the standard Ac₂O/pyridine procedure. Rockogenin acetate **1c** can be easily prepared by NaBH₄/methanol reduction of hecogenin followed by acetylation and fractional crystallization as we have previously described.¹⁰

Treatment of sapogenin acetates **1a-c** with NaNO₂ and BF₃·Et₂O followed by chromatography in neutral Al₂O₃ (Brockmann activity III) led to the desired 23-oxosapogenin acetates **2a-c** and a minor amount of the corresponding bisnorcholanic lactones **3a-c**, (Scheme 1).



Scheme 1

The ¹H NMR spectra of the 23-oxosapogenins (Table 1) show the downfield shift of the signals of the diastereotopic H-26 ax. and H-26 eq. in both 25*R* and 25*S* series, which together with the deshielding of H-16 and H-20 have been outlined as the main effects of the presence of a carbonyl function at C-23.¹¹ Downfield shift of H-26 have been attributed to magnetic anisotropy of the carbonyl function meanwhile deshielding of H-20 have been rationalized as a result of the combination of a δ -syn interaction between H-20 and the carbonylic oxygen and magnetic anisotropy of the C=O bond. For comparison see ¹H NMR spectra of rockogenin acetate (**1c**) and 23-oxorockogenin acetate (**2c**), (Figures 1 and 2).

The ^1H NMR spectra of bisnorcholanolic lactones **3a-c** (Figure 3) are characterized by the absence of the signals corresponding to the protons 23 to 27 and the downfield shift of the signals corresponding to H-16 (now part of the lactone moiety) and H-21 (due to magnetic anisotropy of the carboxy group). Shielding of H-20 may be attributed to a combination of magnetic anisotropy of the carboxyl and the absence of the deshielding interactions present in the 23-oxosapogenins between H-20 and the carbonylic oxygen. (Compare with the corresponding 23-oxosapogenin, see Table 1).

The ^{13}C NMR spectra of bisnorcholanolic lactones **3a-c** are characterized by the absence of the signals corresponding to C-23 to C-27, the downfield shifts of C-22 (now carboxy), C-21 and C-20 and the upfield shift of C-18 and C-17. (Compare with the corresponding 23-oxosapogenin, see Table 2).

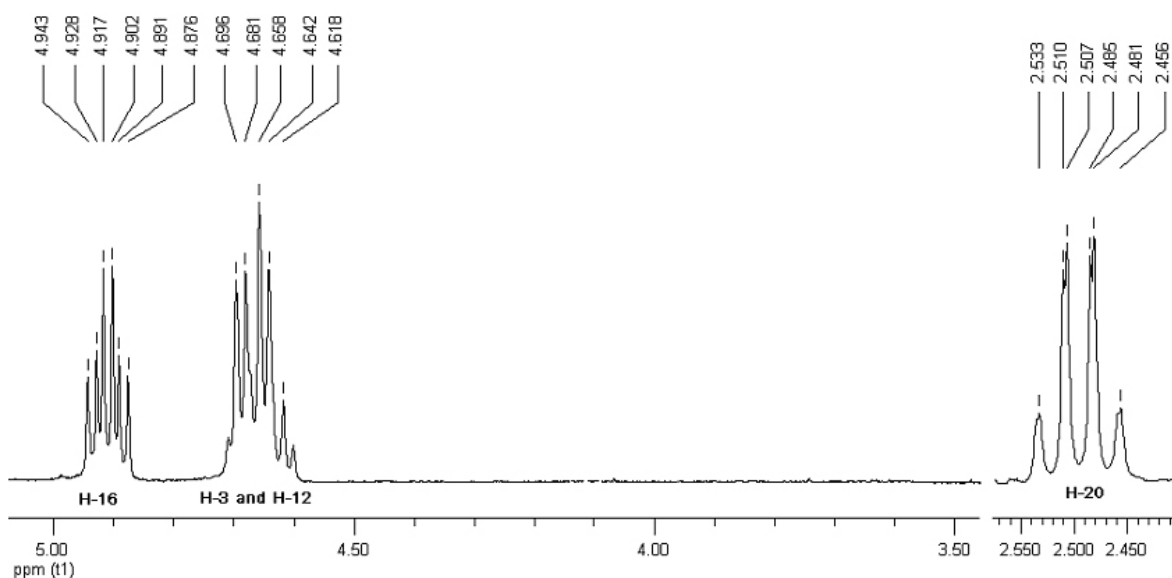
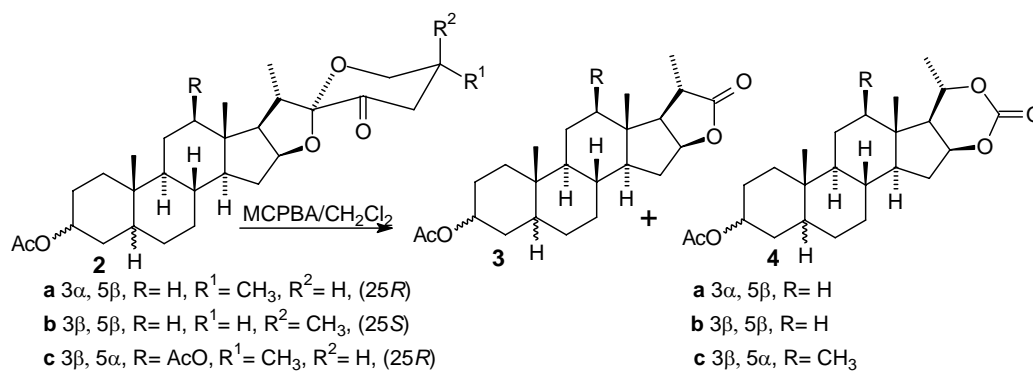


Figure 3. Fragment of ^1H NMR spectrum of bisnorcholanolic lactone **3c**.

Treatment of the 23-oxosapogenins with MCPBA afforded a mixture of the bisnorcholanolic lactone and the cyclic carbonate after long reaction times (4 weeks for the 25*R*-ketosapogenins **2a** and **2c** and 9 weeks for 25*S*-ketosapogenin **2b**), (see Scheme 2). The carbonates may be unequivocally recognized in the ^1H NMR spectra by the new downfield signal corresponding to H-20 (now carbonylic) which shows correlation with the deshielded H-21 protons, (Figure 4). Additionally, downfield shift of H-18 and upfield shift of H-16 characterize these structures. (Compare with bisnorcholanolic lactones, see Table 1).



Scheme 2

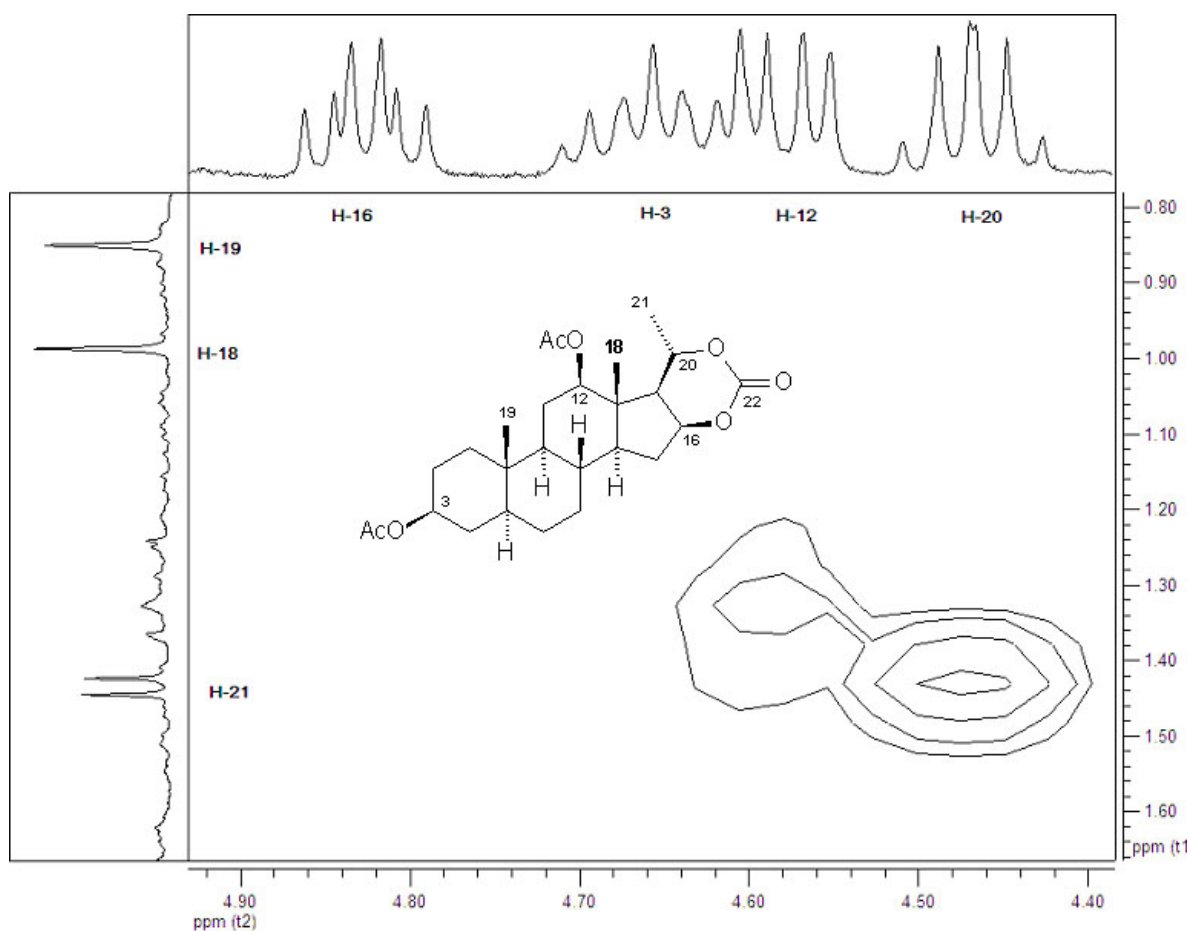


Figure 4. Fragment of H-H COSY of carbonate 4c.

The ¹³C NMR spectra of carbonates **4a-c** are characterized by: **a**) the new functional signal corresponding to the carbonate; **b**) the downfield shifts of C-20, C-18 and C-21; and **c**) upfield shifts of C-16 and C-17, (Compare with bisnorcholanic lactones, see Table 2 and Figure 5).

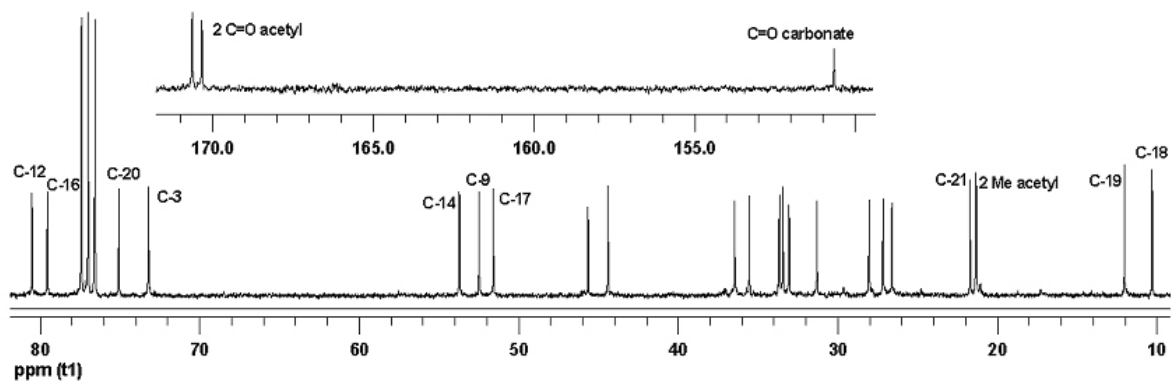


Figure 5. ^{13}C NMR spectrum of carbonate 4c.

Table 1. ^1H NMR selected signals of sapogenin acetates (1), 23-oxosapogenins (2), bisnor-cholanic lactones (3) and carbonates (4)

	1a	2a	3a	4a	1b	2b	3b	4b	1c	2c	3c	4c
H-16	4.38	4.59	4.95	4.73	4.39	4.60	4.92	4.77	4.37	4.67	4.91	4.83
H-18	0.74	0.74	0.74	0.86	0.75	0.76	0.72	0.88	0.82	0.84	0.82	0.98
H-20	1.86 ^a	2.86	2.58	4.43	1.81 ^a	2.88	2.56	4.45	1.86 ^a	2.85	2.50	4.47
H-21	0.95	0.93	1.32	1.45	1.06	1.06	1.30	1.46	0.90	0.94	1.24	1.42
H-26 ax.	3.36	3.77	-	-	3.94	4.26	-	-	3.32	3.76	-	-
H-26 eq.	3.47	3.57	-	-	3.29	3.40	-	-	3.43	3.58	-	-

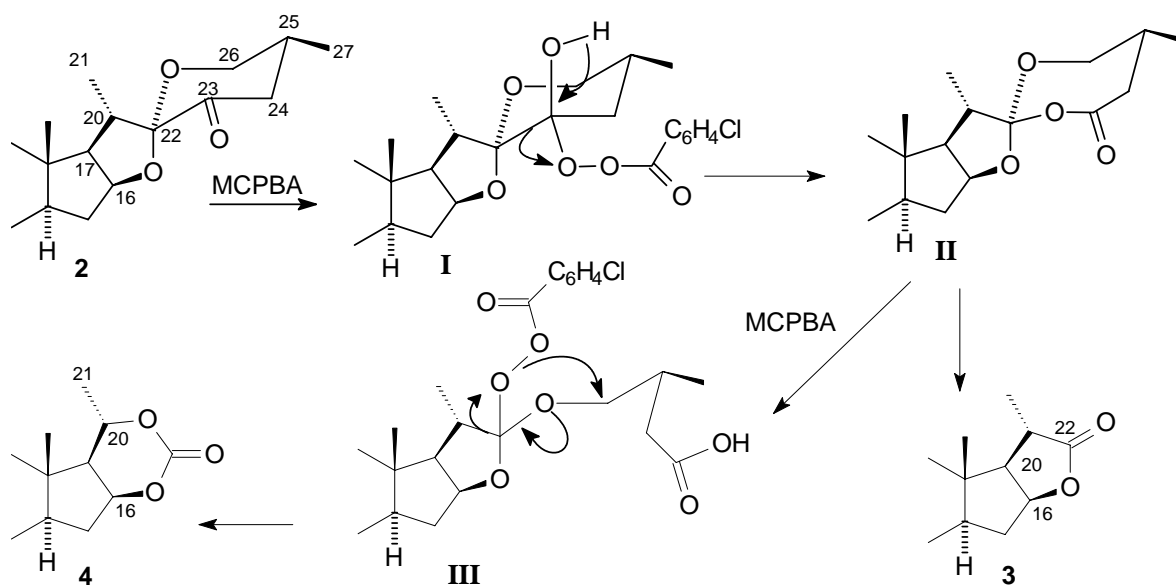
^a See reference 11.

Table 2. ^{13}C NMR selected signals of sapogenin acetates (1), 23-oxosapogenins (2), bisnor-cholanic lactones (3) and carbonates (4)

	1a	2a	3a	4a	1b	2b	3b	4b	1c	2c	3c	4c
C-16	80.8	83.4	82.7	80.3	81.0	83.5	82.8	80.3	80.4	82.9	82.1	79.6
C-17	62.2	61.8	59.1	55.4	62.1	61.8	59.1	55.3	61.2	60.7	57.6	51.5
C-18	16.4	16.1	13.8	14.9	16.0	16.2	13.8	14.9	11.5	11.4	9.4	10.3
C-20	41.7	34.7	36.0	74.6	42.1	35.1	36.2	74.6	42.1	35.7	37.1	75.5
C-21	14.5	14.3	17.9	21.4	14.3	14.2	17.9	21.5	13.6	13.5	17.3	21.7
C-22	109.2	109.8	181.2	152.0*	109.7	110.7	181.4	152.0*	109.2	109.8	181.0	150.7*
C-23	31.3	201.8	-	-	25.9	202.3	-	-	31.3	201.7	-	-
C-24	28.7	45.2	-	-	25.7	43.9	-	-	28.7	45.2	-	-
C-25	30.3	35.8	-	-	27.1	33.7	-	-	30.2	35.2	-	-
C-26	66.8	65.6	-	-	65.1	64.5	-	-	66.8	65.6	-	-
C-27	17.1	17.0	-	-	16.0	17.7	-	-	17.1	17.0	-	-

* Now carbonate.

The occurrence of the observed products may be explained by a reaction path in which, after addition of the peroxyacid to C-23, migration of C-22 leads to the ortoester **II** that may rearrange to the lactones **3a-c** or be attacked by another molecule of peroxyacid at C-22 to produce **III** which on migration of C-20 leads to the cyclic carbonates **4a-c**, (see Scheme 4). The 20*S* configuration of the carbonates **4a-c** stems from the known fact that in BV reactions, migration occurs with retention of the configuration of the migrating group.¹²



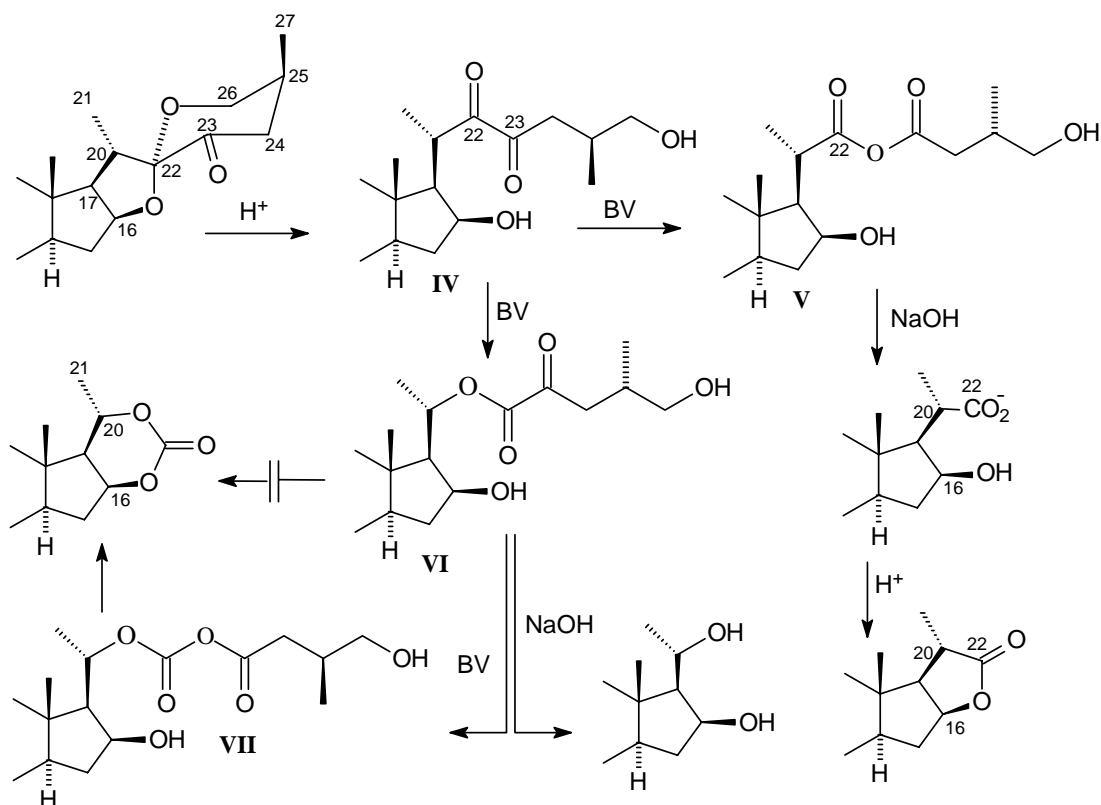
Scheme 3. Possible mechanism.

Marker and Shabica¹³ found that treatment of 23-oxosarsapogenin acetate with von Baeyer persulfuric reagent (potassium persulfate, potassium sulfate and concentrated sulfuric acid) in acetic acid for 16 days led to a mixture of a bisnorcholanic lactone and a pregnan-3,16,20 triol, (Scheme 5). The proposed mechanism postulates that in such acidic conditions, the spiroketal side chain is opened to the α -diketone **IV** which produces BV reactions to a mixture of the anhydride **V** and the ketoester **VI**. Saponification followed by acidification leads to a mixture of the pregnan-3,16,20 triol and the bisnorcholanic lactone.

A similar mechanism may be postulated for the studied BV reaction with MCPBA, the occurrence of observed carbonates can be explained only if an additional BV step from **VI** to **VII** is accepted. In our case, the following facts allow us to discard Marker's open chain mechanism:

- The strong acidic media derived from the von Baeyer reagent used by Marker may produce both, the opening of the spiroketal side chain and acid catalysis resulting in shorter reaction times. By contrast, the reaction conditions used in our case (MCPBA in CH_2Cl_2), are not acid enough to produce opening of the spiroketal side chain or acid catalysis.
- If the observed BV reaction with MCPBA acid follows the open chain mechanism, steric hindrance to the attack of the peroxyacid would be minimized and no differences between the re-

activity of 25*R* and 25*S* compounds should be encountered. The significant difference between the reaction times on the 25*R* and 25*S* series, accounts for a closed chain mechanism in which the axial position of the 27-methyl group hinders the nucleophilic attack of the peroxyacid to the carbonylic C-23.



Scheme 4. Marker's open chain mechanism.

Theoretical calculations¹⁴

Semiempirical PM3 calculations of the fragments corresponding to 23-oxosapogenins of both 25*R* and 25*S* series indicate that neither charges nor LUMO energies can explain the different reactivity observed for the two C-25 epimers. Both reactivity indexes are almost the same for both epimers, therefore the cause of these differences should be other than electronic effects (see Table 3).

Table 3. PM3 obtained LUMO energies and charges at C-23 of ketones **2a**, **2b**

	Charge at C-23	Energy of LUMO (eV)
2a (25<i>R</i>)	0.2673	0.59062
2b (25<i>S</i>)	0.2689	0.59074

Figure 6 shows the PM3 optimized geometries of the fragments corresponding to the side chains of both 25*R*- and 25*S*-23-oxosapogenins. These optimized geometries are consistent with the previously described NMR data for steroid 25*R*- and 25*S*-sapogenins and the coupling pattern of both axial and equatorial H-26 with H-25.¹¹

From these results it can be assumed that in the 25*S* epimer, the β -side of ring F is sterically hindered by two methyl groups, as a consequence, axial approach to C=O is expected to be highly disfavored. In contrast, equatorial approach to C=O (from the α -side) seems to be less hindered in both 25*R* and 25*S* series as well as axial approach to C=O in the 25*R* epimer (see Figure 6).

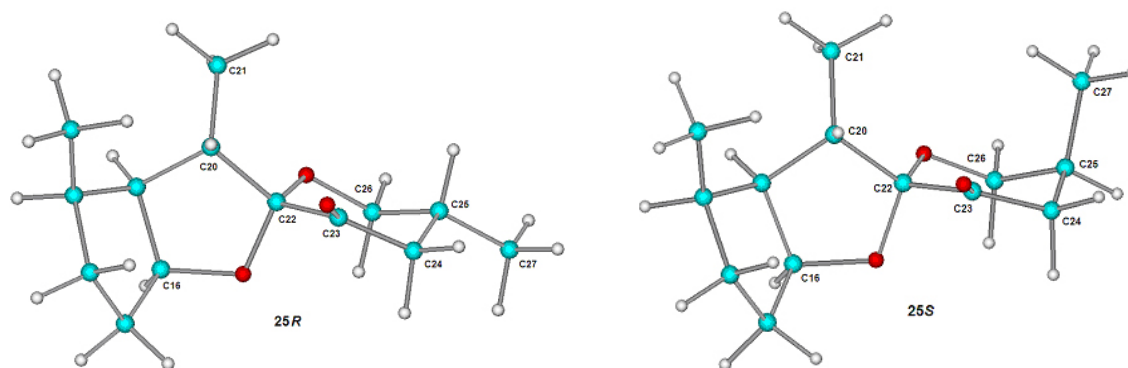


Figure 6. Fragments of the side chains of 25*R*- and 25*S*-23-oxosapogenins.

PM3 calculations of the barriers of all possible reaction paths derived from the approach of the peroxyacid to C=O from the axial or equatorial directions in both 25*R* and 25*S* series, were performed. The results of the reaction barriers calculations as well as the molecular graphics of transition states are shown in Figure 7. The 25*R* epimer appears to be slightly more reactive to equatorial attack but also axial attack is possible. By contrast, according to the results, the axial approach to the 25*S* epimer is undoubtedly disfavored because of the steric hindrance previously mentioned, leaving only one possibility, the equatorial attack, for the production of the Criegee's intermediate. In addition the barrier for equatorial attack in the 25*R* is 0.6 kcal/mole lower than this of 25*S* indicating its higher reactivity. These results plenty justify the experimental evidence that the reaction time in the 25*S* epimer is twice longer than this of the 25*R* epimer.

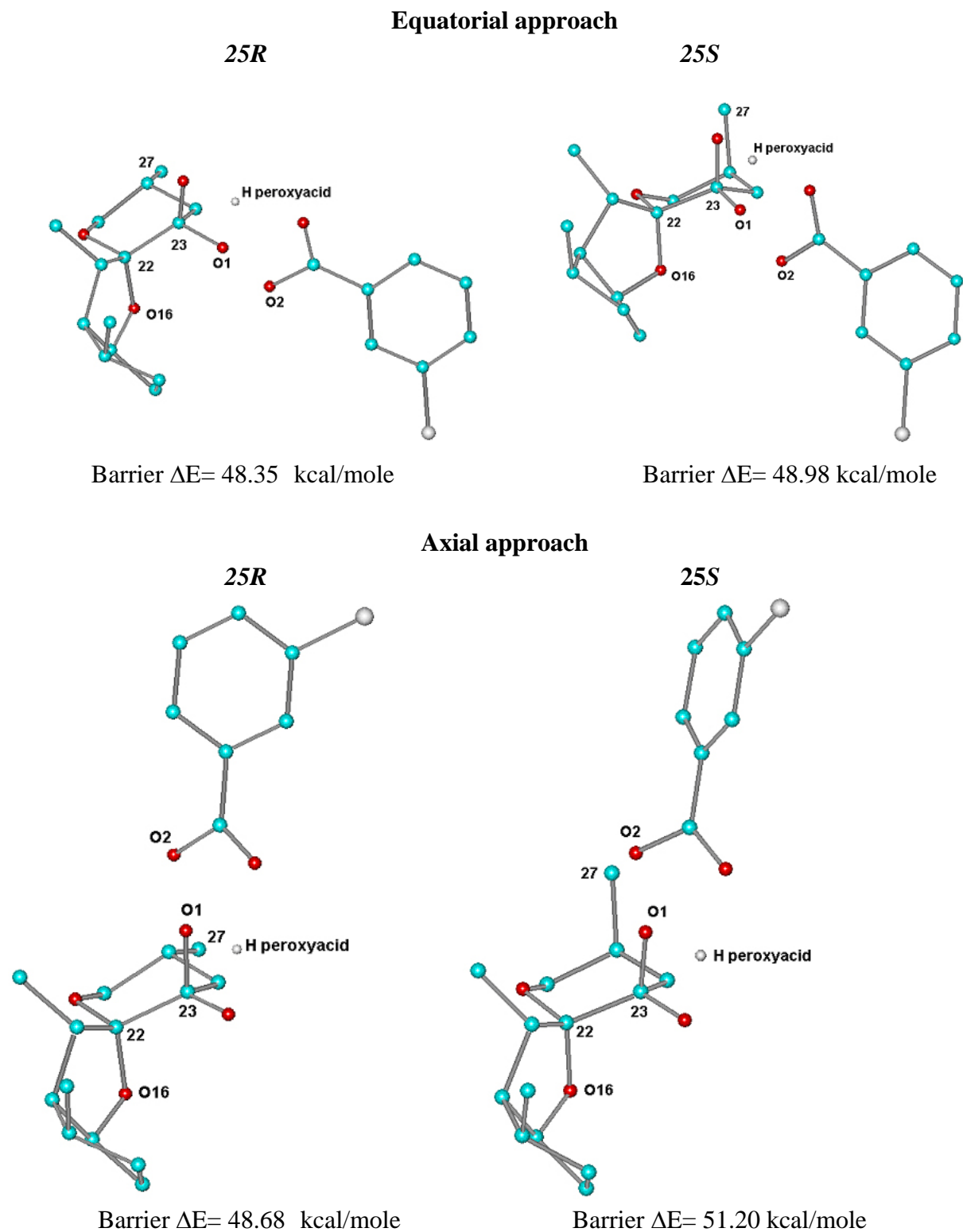
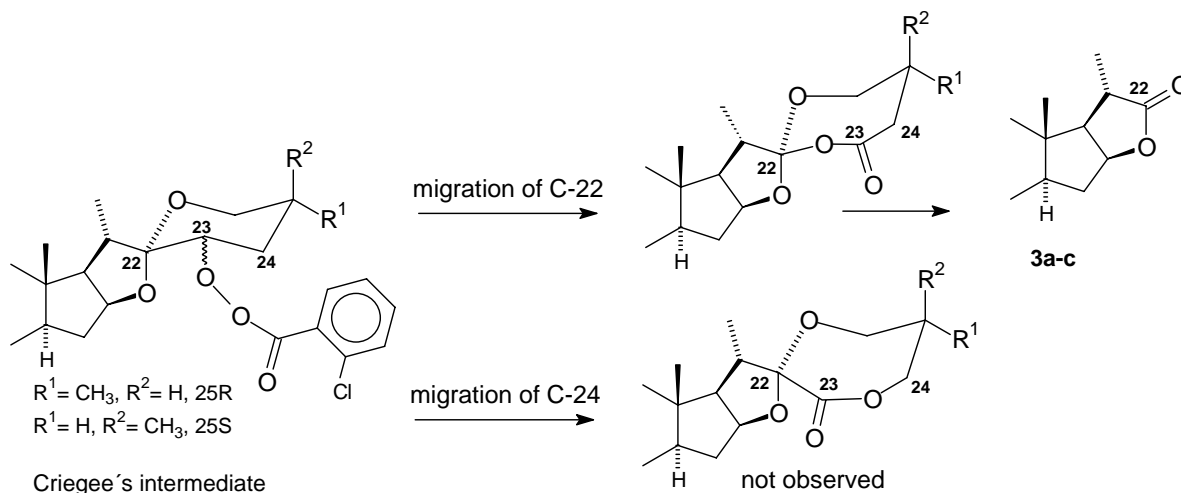


Figure 7. Transition states for the addition of the peroxyacid to the C-23 oxo group. For clarity hydrogens are omitted.

The regioselective production of bisnorcholanolactones **3a-c**, may be explained in terms of the preference for antiperiplanar migration (*App*-migration) in the migration step.¹⁵ This assumption arises from the primary stereoelectronic effect in which orientation of the peroxide bond (O1-O2) should be *App* to that of the migrating group, in such a way that the σ bonding orbital of the migrating group and the σ^* antibonding orbital of the peroxide bond overlap.¹⁶

Radkiewicz-Poutsma and coworkers have shown that *App*-migrations are strongly favored with barriers that can be 58.0 kcal/mol lower in energy than the gauche migration barriers. Additionally they stated that no transition state could be located for gauche migration.¹⁷

In this context, the observed regioselectivity can be a consequence of the conformational preference of the Criegee's peroxyester intermediate. PM3 calculations showed that those conformers of the Criegee's intermediate with *App* arrangement of C22-C23-O1-O2 favorable to the migration of C-22, and hence to produce lactones **3a-c**, are preferred over those with *App* arrangement of C24-C23-O1-O2 favorable to migration of C-24 which would produce the regioisomeric 23-oxo-24-oxa moiety, see Scheme 6 and Figure 8.



Scheme 6

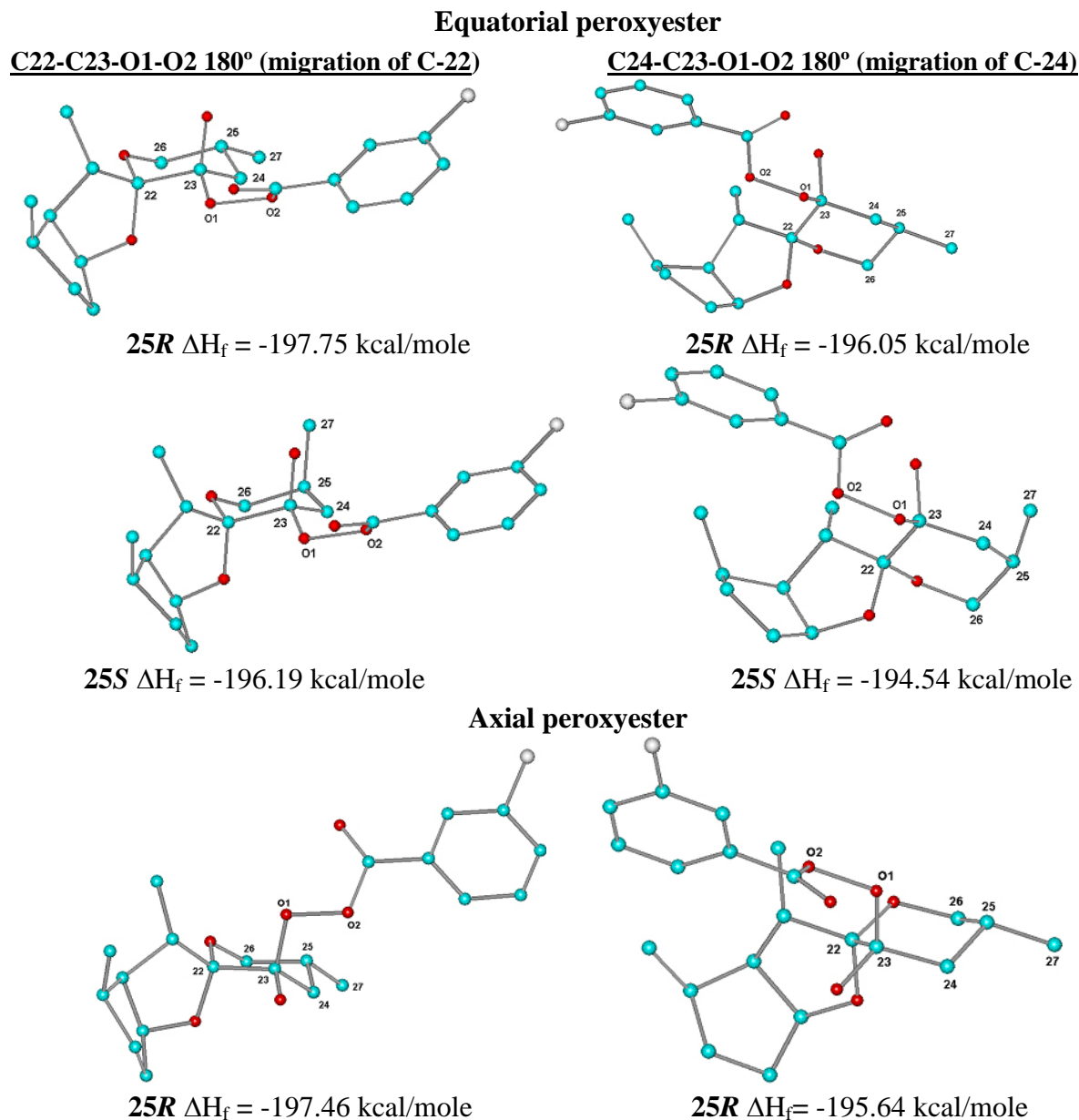


Figure 8. Conformational preferences for all possible Criegee's intermediates. ΔH_f = Calculated heat of formation. For clarity hydrogen atoms are omitted.

Conclusions

The Baeyer-Villiger reactions of (25*R*)- and (25*S*)-23-oxosapogenins produce the cleavage of the spiroketal side chain resulting in a mixture of a bisnorcholanolic lactone and a cyclic carbonate of 16,20 diols. This reaction opens a synthetic alternative to bisnorcholanolic lactones from the readily available steroid sapogenins. Synthetic applications of these reactions and studies on the effects of acid catalysis are on development.

The regioselective production of the bisnorcholanic lactones **3a-c** may be explained in terms of the preference of those conformers which are favorable to migration of C-22. The reaction follows a course in which the steric factors play a determining role. PM3 calculated reaction barriers accurately reproduce the experimentally observed facts, and therefore its results are confident enough to explain the behavior of this system.

Experimental Section

General Procedures. Reactions were monitored by TLC on ALUGRAM[®] SIL G/UV₂₅₄ plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vainillin in 50% HClO₄ and heated until color developed. NMR spectra were recorded in on a Varian Unity INOVA 300 MHz spectrometer using TMS for ¹H or the solvent signal (CDCl₃) for ¹³C as reference. All spectra displayed using the Nuclear Magnetic Resonance data processing software package for desktop computers MestRe-C.¹⁸ Mass spectra were recorded on a Jeol SX-102-A spectrometer. Melting points were measured on a Melt-Temp II equipment and are uncorrected.

(25R)-5 β -Spirostan-3 α -ol acetate, 3-epismilagenin acetate (1a). m.p. 159-160° C, Lit.¹⁹ 162-164 °C. ¹H NMR (300 MHz, CDCl₃): 4.70 (m, 1H, H-3); 4.38 (m, 1H, H-16); 3.47 (dd J 4 Hz 10.6 Hz, 1H, H-26 eq.); 3.36 (t J 10.8 Hz, 1H, H-26 ax.); 2.01 (s, 3H, CH₃ acetyl); 0.95 (d J 7.0 Hz, 3H, Me-21); 0.93 (s, 3H, H-19); 0.77 (d J 6.3Hz, 3H, H-27); 0.74 (s, 3H, H-18) ¹³C NMR (75.5 MHz, CDCl₃): C-1 31.0; C-2 26.5; C-3 74.3; C-4 32.2; C-5 41.6; C-6 26.9; C-7 26.5; C-8 35.4; C-9 40.5; C-10 34.7; C-11 20.6; C-12 40.2; C-13 40.6; C-14 56.3; C-15 31.7; C-16 80.8; C-17 62.2; C-18 16.4; C-19 23.3; C-20 41.7; C-21 14.5; C-22 109.2; C-23 31.3; C-24 28.7; C-25 30.3; C-26 66.8; C-27 17.1; CH₃ acetyl 21.4, C=O acetyl 170.6.

(25S)-5 β -Spirostan-3 β -ol acetate, sarsasapogenin acetate (1b). m.p. 143-144° C, Lit.²⁰ 145 °C. ¹H NMR (300 MHz, CDCl₃): 5.05 (m, 1H, H-3); 4.39 (dd J 7.5 Hz, J 13.9 Hz, 1H, H-16); 3.94 (dd J 2.5 Hz J 10.9 Hz, 1H, H-26 ax.); 3.29 (d J 10.9 Hz, 1H, H-26 eq.); 2.03 (s, 3H, CH₃ acetyl); 1.82 (m 1H, H-20); 1.06 (d J 7.1 Hz, 3H, H-21); 0.98 (d J 5.2 Hz, 3H, H-27); 0.97 (s, 3H, H-19); 0.75 (s, 3H, H-18). ¹³C NMR (75.5 MHz, CDCl₃): C-1 30.6; C-2 25.0; C-3 70.7; C-4 30.7; C-5 37.3; C-6 26.4; C-7 26.4; C-8 35.3; C-9 40.0; C-10 35.0; C-11 20.9; C-12 40.2; C-13 40.6; C-14 56.3; C-15 31.7; C-16 81.0; C-17 62.1; C-18 16.0; C-19 23.8; C-20 42.1; C-21 14.3; C-22 109.7; C-23 25.9; C-24 25.7; C-25 27.1; C-26 65.1; C-27 16.0; CH₃ acetyl 21.5, C=O acetyl 170.7.

(25R)-5 α -Spirostan-3 β ,12 β -diol diacetate, rockogenin acetate (1c). Yield 65.3% Identical as described in ref. 10. ¹H NMR (300 MHz, CDCl₃): 4.65 (m, 1H, H-3); 4.51 (dd, J 4.7 Hz J 11.2 Hz, 1H, H-12); 4.37 (dd J 7.5Hz J 14.6 Hz, 1H, H-16); 3.43 (dd J 2.9 Hz J 10.7 Hz, 1H, H-26 eq.); 3.32 (dd J 10.9 Hz, J 10.9 Hz, 1H, H-26 ax.); 2.01 (s, 3H, CH₃ acetyl); 1.99 (s, 3H, CH₃ acetyl); 0.90 (d J 6.6 Hz, 3H, H-21); 0.85 (s, 3H, H-19); 0.84 (s, 3H, H-18); 0.78 (d J 6.3 Hz, H-27). ¹³C NMR (75.5 MHz, CDCl₃): C-1 36.5; C-2 27.2; C-3 73.3; C-4 33.8; C-5 44.4; C-6 28.3; C-7 31.1; C-8 34.0; C-9 52.6; C-10 35.5; C-11 26.7; C-12 81.6; C-13 44.5; C-14 54.7; C-15

31.6; C-16 80.4; C-17 61.2; C-18 11.5; C-19 12.1; C-20 42.1; C-21 13.6; C-22 109.2; C-23 31.3; C-24 28.7; C-25 30.2; C-26 66.8; C-27 17.1; CH₃ acetyl 21.5, 21.4; C=O acetyl 170.5, 170.4.

General procedure to obtain 23-oxosapogenins

BF₃.Et₂O (0.8 mL) was slowly added to a well stirred solution of the steroid sapogenin acetate (1 mmol) in glacial acetic acid (20 mL), the mixture was stirred for 5 min followed by addition of NaNO₂ (200 mg, 2.9 mmol) in small portions over a period of one hour. The mixture was stirred for one additional hour, poured into ice/water and extracted with CH₂Cl₂ (2x 30 mL); the organic layer was washed with water (2x20 mL), 5% NaHCO₃ (2x15 mL) and brine (3x20 mL), dried (Na₂SO₄) and evaporated. The syrupy product dissolved in benzene-hexane (3/2, 8 mL) was allowed to stand overnight in a column packed with neutral Al₂O₃ (15 g, Brockmann III). Slow elution with hexane/ethyl acetate (8/1 for **2a** and **2b**, 4/1 for **2c**) afforded the desired 23-oxosapogenin acetate. Further elution with 1/1 hexane/ethyl acetate afforded an small amount of the corresponding bisnorcholanic lactone, (see Table 4 for yields).

Table 4. Synthesis of 23-oxosapogenins

Starting material	Products (yield %)
1a	2a (63), 3a (10)
1b	2b (58), 3b (16)
1c	2c (65), 3c (12)

(25R)-3 α -Acetoxy-5 β -spirostan-23-one, 23-oxo-3-epismilagenin acetate (2a). m.p. 155-157 °C. ¹H NMR (300 MHz, CDCl₃): 4.70 (tt J 4.7Hz, J 11.3Hz, 1H, H-3); 4.59 (m, 1H, H-16); 3.77 (dd, J 11.2 Hz, 11.2 Hz, 1H, H-26 ax.); 3.57 (dd, J 4.2 Hz J 11.2 Hz, 1H, H-26 eq.); 2.86 (q J 7.0Hz, 1H, H-20); 2.27 (m, 1H, H-25); 2.01 (s, 3H, CH₃ acetyl); 0.93 (s, 3H, H-19); 0.92 (d J 6.4 Hz, 3H, H-27); 0.93 (d J 6.6 Hz, 3H, H-21); 0.74 (s, 3H, H-18). ¹³C NMR (75.5 MHz, CDCl₃): C-1 35.0; C-2 26.5; C-3 74.2; C-4 32.2; C-5 41.6; C-6 26.9; C-7 26.6; C-8 35.4; C-9 40.5; C-10 34.7; C-11 20.5; C-12 39.9; C-13 41.1; C-14 56.4; C-15 31.7; C-16 83.4; C-17 61.8; C-18 16.1; C-19 23.3; C-20 34.7; C-21 14.3; C-22 109.8; C-23 201.8; C-24 45.2; C-25 35.8; C-26 65.6; C-27 17.0; CH₃ acetyl 21.4, C=O acetyl 170.5. **MS** (70 eV): 472 M⁺, 444 (M⁺-C=O), 389, 329, 315, 255, 147, 93, 56, 43. **HRMS FAB** observed 473.3263 MH⁺; estimated for C₂₉H₄₅O₅ 473.3267.

(25S)-3 β -Acetoxy-5 β -spirostan-23-one 23-oxosarsasapogenin acetate, (2b). m.p. 168-170° C, Lit.¹³ 172-173° C. ¹H-NMR (300 MHz, CDCl₃): 5.05 (m, 1H, H-3); 4.60 (dt J 6.2 Hz J 7.7 Hz, 1H, H-16); 4.26 (dd J 2.8 Hz J 11.2 Hz, 1H, H-26 ax.); 3.40 (td J 2.0 Hz J 11.1 Hz, 1H, H-26 eq.); 2.88 (m, 1H, H-20); 2.03 (s, 3H, CH₃ acetyl); 1.06 (d J 7.0 Hz 3H, H-21); 0.97 (s, 3H, H-19); 0.94 (d J 7.0 Hz, 1H, H-27) 0.76 (s, 3H, H-18). ¹³C NMR (75.5 MHz, CDCl₃): C-1 30.6; C-2 25.0; C-3 70.6; C-4 30.7; C-5 37.3; C-6 26.4; C-7 26.4; C-8 35.2; C-9 40.0; C-10 35.0; C-11 20.8; C-12 40.0; C-13 41.2; C-14 56.5; C-15 31.7; C-16 83.5; C-17 61.8; C-18 16.2; C-19 23.8; C-20 35.1; C-21 14.2; C-22 110.7; C-23 202.3; C-24 43.9; C-25 33.7; C-26 64.5; C-27 17.7; CH₃

acetyl 21.5, C=O acetyl 170.7. **MS** (70 eV): 472 M⁺, 444 M⁺-C=O, 389, 329, 315, 255, 147, 93, 56, 43.

(25R)-3β,12β-Diacetoxy-5α-spirostan-23-one, 23-oxorockogenin acetate (2c). Identical as described in ref. 10. **¹H-NMR** (300 MHz, CDCl₃): 4.67 (m, 2H, H-3, H-16); 4.54 (dd J 4.6 Hz J 11.0 Hz, 1H, H-12); 3.76 (dd J 11.2 Hz, 1H, H-26 ax.); 3.58 (dd J 4.1 Hz J 11.2 Hz, 1H, H-26 eq.); 2.85 (q J 6.9 Hz, 1H, H-20); 2.04, 2.01 (s, 6H, 2xCH₃ acetyl); 0.94 (d J 6.5 Hz, 1H, H-21); 0.86 (s, 3H, H-19); 0.84 (s, 3H, H-18); 0.86 (d J 7 Hz, 3H, H-27). **¹³C NMR** (75.5 MHz, CDCl₃): C-1 36.5; C-2 27.2; C-3 73.3; C-4 33.8; C-5 44.5; C-6 28.3; C-7 31.1; C-8 34.0; C-9 52.6; C-10 35.6; C-11 26.7; C-12 81.3; C-13 45.0; C-14 54.8; C-15 31.6; C-16 82.9; C-17 60.7; C-18 11.4; C-19 12.1; C-20 35.7; C-21 13.5; C-22 109.8; C-23 201.7; C-24 45.2; C-25 35.3; C-26 65.6; C-27 17.0; CH₃ acetyl 21.5, 21.4; C=O acetyl 170.6, 170.5. **MS** (70 eV): 531 MH⁺, 502 M⁺-C=O, 447, 388, 327, 253, 215, 146, 102, 56, 49.

3α-Acetoxy-16-hydroxy-5β-bisnorcholanolic acid-(22→16) lactone (3a). m.p. 153-155° C, Lit.²¹ 158 °C. **¹H NMR** (300 MHz, CDCl₃): 4.95 (ddd J 4.6 Hz J 7.8 Hz J 7.8 Hz, 1H, H-16); 4.73 (dddd J 4.8 Hz J 4.8 Hz J 11.3 Hz J 11.3 Hz, 1H, H-3); 2.58 (dq J 1.1 Hz, J 7.6 Hz, 1H, H-20); 2.03 (s, 3H, CH₃ acetyl); 1.32 (d J 7.6 Hz, 3H, H-21); 0.95 (s, 3H, H-19); 0.74 (s, 3H, H-18). **¹³C NMR** (75.5 MHz, CDCl₃): C-1 34.9; C-2 26.5; C-3 74.1; C-4 32.1; C-5 41.6; C-6 26.7; C-7 26.5; C-8 35.4; C-9 40.6; C-10 34.6; C-11 20.1; C-12 38.4; C-13 41.8; C-14 54.6; C-15 33.0; C-16 82.7; C-17 59.1; C-18 13.8; C-19 23.2; C-20 36.0; C-21 17.9; C-22 181.2. CH₃ acetyl 21.4, C=O acetyl 170.5. **MS** (70 eV): 389 MH⁺, 328 M⁺-CH₃COOH, 313, 274, 215, 161, 93, 79, 43.

3β-Acetoxy-16-hydroxy-5β-bisnorcholanolic acid-(22→16) lactone (3b). m.p. 187-188 °C, Lit.²² 184.5-185.5 °C. **¹H-NMR** (300 MHz, CDCl₃): 5.05 (m, 1H, H-3); 4.92 (dt J 4.6Hz J 7.7Hz, 1H, H-16); 2.56 (q J 7.6Hz, 1H, H-20); 2.03 (s, 3H, CH₃ acetyl); 1.30 (d J 7.6 Hz, 3H, H-21); 0.97 (s, 3H, H-19); 0.72 (s, 3H, H-18). **¹³C NMR** (75.5 MHz, CDCl₃): C-1 30.5; C-2 25.0; C-3 70.4; C-4 30.7; C-5 37.1; C-6 26.3; C-7 26.2; C-8 35.0; C-9 40.1; C-10 34.9; C-11 20.3; C-12 38.5; C-13 41.8; C-14 54.6; C-15 33.0; C-16 82.8; C-17 59.1; C-18 13.8; C-19 23.7; C-20 36.2; C-21 17.9; C-22 181.4; CH₃ acetyl 21.4, C=O acetyl 170.6. **MS** (70 eV): 389, MH⁺, 328, M⁺-CH₃COOH, 315, 274, 215, 161, 107, 93, 43.

3β,12β-Diacetoxy-16-hydroxy-5α-bisnorcholanolic acid-(22→16) lactone (3c). Syrup. **¹H-NMR** (300 MHz, CDCl₃): 4.91 (dt J 4.7Hz J 7.8Hz, 1H, H-16); 4.64 (m, 2H, H-3 and H-12); 2.50 (m, 1H, H-20); 2.03 (s, 3H, CH₃ acetyl); 2.00 (s, 3H, CH₃ acetyl); 1.24 (d J 7.7Hz, 3H, H-21); 0.83 (s, 3H, H-19); 0.82 (s, 3H, H-18). **¹³C NMR** (75.5 MHz, CDCl₃): C-1 36.5; C-2 27.2; C-3 73.2; C-4 33.7; C-5 44.4; C-6 28.7; C-7 31.5; C-8 33.8; C-9 52.7; C-10 35.5; C-11 26.5; C-12 80.3; C-13 45.6; C-14 52.6; C-15 32.5; C-16 82.1; C-17 57.6; C-18 9.4; C-19 12.0; C-20 37.1; C-21 17.3; C-22 181.0; CH₃ acetyl 21.4, 21.1; C=O acetyl 170.6, 170.4. **MS** (70 eV): 447 MH⁺, 386 M⁺-CH₃COOH, 326 M⁺-2xCH₃COOH, 272, 253, 213, 161, 108, 43. **HRMS FAB** observed 447.2743 MH⁺; estimated for C₂₆H₃₉O₆ 447.2747

Baeyer-Villiger reaction, general procedure

MCPBA (80% activity) (690 mg, 4 mmol) was added to a solution of the 23-oxosapogenin

(1 mmol) in CH₂Cl₂ (25 mL) and the mixture was stirred, (see Table 3 for reaction times). The mixture without workup²³ was poured into a chromatographic column packed with silica gel (25 g) and eluted with hexane/ethyl acetate mixture (10/0 to 1/1). Evaporation of the adequate fractions afforded (in this order), the bisnorcholanolic lactone (identical as described above) and the more polar carbonate, (see Table 5 for yields).

Table 5. Results of the BV reactions of 23-oxosapogenins

Starting material	Products (yield %)	Reaction time
2a	3a (63), 4a (26)	29 days
2b	3b (69), 4b (19)	66 days
2c	3c (54), 4c (24)	26 days

(20S)-3 α -Acetoxy-16 β ,20-dihydroxy-5 β -pregnan-16,20 carbonate (4a). m.p. 148-150° C (descomp.). ¹H-NMR (300 MHz, CDCl₃): 4.73 (m, 2H, H-3 and H-16); 4.43 (m, 1H, H-20); 2.02 (s, 3H, CH₃ acetyl); 1.45 (d J 6.4Hz, 3H, H-21); 0.94 (s, 3H, H-19); 0.86 (s, 3H, H-18) ¹³C NMR (75.5 MHz, CDCl₃): C-1 34.9; C-2 26.4; C-3 74.1; C-4 32.1; C-5 41.6; C-6 26.7; C-7 26.5; C-8 34.6; C-9 40.5; C-10 34.6; C-11 20.1; C-12 38.7; C-13 41.9; C-14 53.2; C-15 33.2; C-16 80.3; C-17 55.4; C-18 14.9; C-19 23.2; C-20 74.6; C-21 21.4; C=O carbonate 152.0; CH₃ acetyl 21.8, C=O acetyl 170.6. **MS** (70 eV): 405 MH⁺, 344 M⁺-CH₃COOH, 329, 290, 267, 215, 174, 147, 108. **HRMS FAB** observed 405.2635 MH⁺; estimated for C₂₄H₃₇O₅ 405.2641.

(20S)-3 β -Acetoxy-16 β ,20-dihydroxy-5 β -pregnan-16,20 carbonate (4b). m.p. 212-214° C (descomp.). ¹H-NMR (300 MHz, CDCl₃): 5.07 (m, 1H); 4.77 (dt J= 5.7Hz, J=8.2Hz, 1H H-16); 4.45 (m, 1H, H-20); 2.06 (s, 3H, CH₃ acetyl); 1.46 (d J 6.4 Hz, 3H, H-21); 1.00 (s, 3H, H-19); 0.88 (s, 3H, H-18). ¹³C NMR (75.5 MHz, CDCl₃): C-1 30.5; C-2 24.9; C-3 70.5; C-4 30.6; C-5 37.1; C-6 26.2; C-7 26.1; C-8 34.5; C-9 40.0; C-10 34.9; C-11 20.3; C-12 38.7; C-13 41.9; C-14 53.2; C-15 33.2; C-16 80.3; C-17 55.3; C-18 14.9; C-19 23.7; C-20 74.6; C-21 21.5; C=O carbonate 152.0; CH₃ acetyl 21.8, C=O acetyl 170.6. **MS** (70 eV): 405 MH⁺, 344 M⁺-CH₃COOH, 329, 290, 267, 241, 175, 147, 108, 93, 43. **HRMS FAB** observed 405.2644 MH⁺; estimated for C₂₄H₃₇O₅ 405.2641.

(20S)-3 β ,12 β -Diacetoxy-16 β ,20-dihydroxy-5 α -pregnan-16,20 carbonate (4c). m.p. 167-169° C (descomp.). ¹H-NMR (300 MHz, CDCl₃): 4.83 (dt J 5.2 Hz J 8.1 Hz, 1H, H-16); 4.66 (m, 1H, H-3); 4.58 (dd J 4.8 Hz J 11.1 Hz, 1H, H-12); 4.47 (m, 1H, H-20); 2.04 (s, 3H, CH₃ acetyl); 2.00 (s, 3H, CH₃ acetyl); 1.42 (d J 6.5 Hz, 3H, H-21); 0.98 (s, 3H, H-18); 0.84 (s, 3H, H-19). ¹³C NMR (75.5 MHz, CDCl₃): C-1 36.5; C-2 27.2; C-3 73.2; C-4 33.7; C-5 44.4; C-6 28.1; C-7 31.3; C-8 33.4; C-9 52.5; C-10 35.5; C-11 26.6; C-12 80.5; C-13 45.7; C-14 53.7; C-15 33.1; C-16 79.6; C-17 51.5; C-18 10.3; C-19 12.0; C-20 75.1; C-21 21.7; C=O carbonate 150.7; CH₃ acetyl 21.4, 21.3; C=O acetyl 170.7, 170.4. **MS** (70 eV): 463 MH⁺, 402 M⁺-CH₃COOH, 342 M⁺-2xCH₃COOH, 327, 288, 280, 226, 213, 159, 147, 107, 93. **HRMS FAB** observed 463.2692 MH⁺; estimated for C₂₆H₃₉O₇ 463.2696.

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