Steroids 76 (2011) 317–323

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Studies on the $BF_3{\cdot}Et_2O$ catalyzed Baeyer–Villiger reaction of spiroketalic steroidal ketones

Mariana Macias-Alonso[a], Jacek W. Morzycki[b], Martin A. Iglesias-Arteaga[a,*]

[a] Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, D.F., Mexico
[b] University of Białystok, Institute of Chemistry, al. J. Piłsudskiego 11/4, 15-443 Białystok, Poland

ARTICLE INFO

Article history:
Received 28 October 2010
Received in revised form
27 November 2010
Accepted 8 December 2010
Available online 16 December 2010

Dedicated to the memory of Rosa de la Luz Arteaga Borgos.

Keywords:
23-Oxosapogenins
16β,23:23,26-Diepoxy-cholestan-22-ones
Baeyer–Villiger reaction
$BF_3{\cdot}Et_2O$ catalysis
Dinorcholanic lactones

ABSTRACT

During reactions of 23-oxosapogenins and the corresponding isomeric 22-oxo-23-spiroketals with MCPBA in the presence of $BF_3{\cdot}Et_2O$, equilibration occurs between the ketones. The Baeyer–Villiger type oxidation is followed by fragmentation to the dinorcholanic lactones and 3-methylbutyrolactone. The mechanistic aspects of these reactions in the 25*R* and 25*S* series are discussed.

1. Introduction

The study on the reactivity of the spiroketal moiety present in steroid sapogenis has attracted attention of chemists for more than 70 years. The special reactivity of this fragment has provided a wide spectrum of interesting reactions that have proved useful from both, synthetic and mechanistic points of view [1–17].

In particular, steroid sapogenins bearing a substituent at position C-23 show different reactivity profiles compared with the unsubstituted ones. The presence of a substituent enhances the spectrum of reactions in which the spiroketal moiety, depending on the nature of the substituent, can participate including solvolytic, radical, and nucleophilic reactions and sigmatropic rearrangements, etc. [18–29].

We have recently described the Baeyer–Villiger (BV) reaction of 23-oxosapogenins with MCPBA in CH_2Cl_2, which produces a mixture of a bisnorcholanic lactone **2** and a cyclic carbonate **3** in a ratio that depends on the temperature at which the reaction was carried out (see Scheme 1 and Table 1) [30,31].

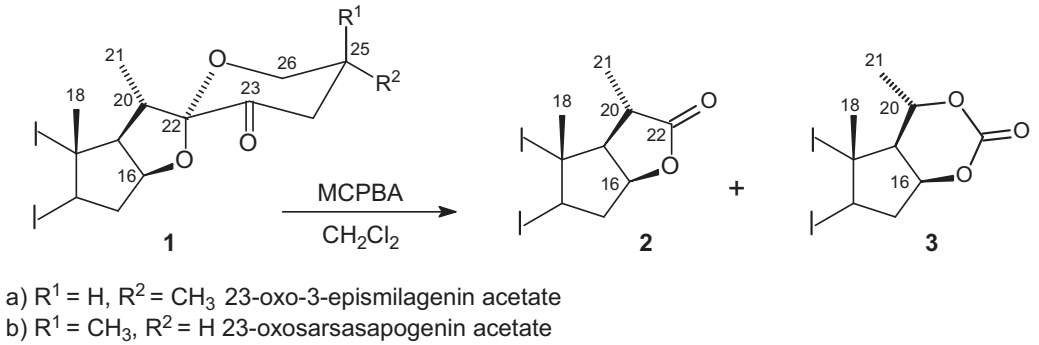
The outcome of the reaction can be explained by an initial nucleophilic attack of the peroxy acid to C-23 to produce the Criegee intermediate **I**. Its rearrangement leads to the unstable orthoester **II** that may undergo fragmentation to the dinorcholanic lactone **2a** and 3-methylbutyrolactone (its formation was confirmed by GC–MS) or alternatively may be again attacked by the peroxy acid to afford **III**, which rearranges to the cyclic carbonate **3a** (see Scheme 2).

The fact that the carbonate **3b** predominates over the dinorcholanic lactone, when the reaction was carried out at higher temperature (see entry 3, Table 1), was attributed to the preference of the reaction of MCPBA with the orthoester **II** over its collapse to the lactone **2b**. Similar results were obtained for both 23-oxosarsasapogenins.

Marker reported that treatment of 23-oxosarsasapogenins with the von Baeyer reagent (potassium persulfate, potassium sulfate and concentrated sulfuric acid) in acetic acid for 16 days led to a mixture of a bisnorcholanic lactone and the pregnan-3β,16,20-triol that is the product of hydrolysis of the cyclic carbonate [32]. Although the postulated mechanism for the BV brought about by the von Baeyer reagent is in some ways different, the fact that even in the presence of a strong Brønsted acid the observed reaction is slow, accounts for the low reactivity of the C-23 carbonyl towards peroxy acids. There were also reports on direct degradation of tigogenin to pregnan-3β,16,20-triol with peroxy acids in strongly acidic medium [33,34].

* Corresponding author. Tel.: +52 55 56223803; fax: +52 55 56223803.
E-mail address: martin.iglesias@servidor.unam.mx (M.A. Iglesias-Arteaga).

0039-128X/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2010.12.004



Scheme 1.

Table 1
Non catalyzed BV reaction of 23-oxosapogenins (see Scheme 1).

Entry	Starting material	Temperature	Reaction time	Yield **2** (%)	Yield **3** (%)	Reference
1	**1a**	Room	29 days	63	26	[31]
2	**1b**	Room	66 days	54	24	[31]
3	**1b**	Reflux	24 h	13	32	[30]

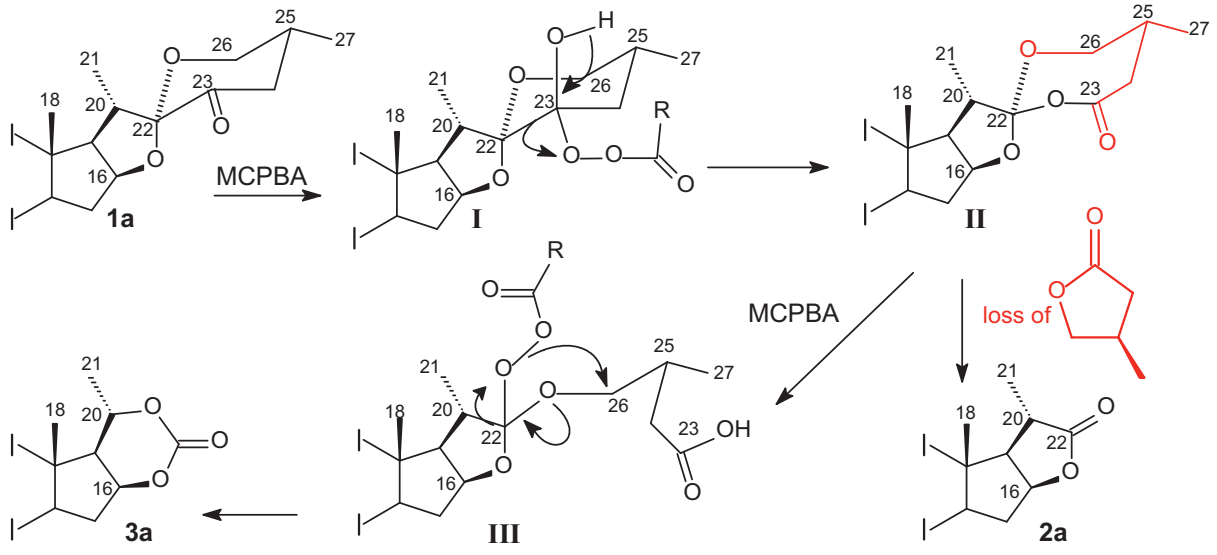
This prompted us to explore the effect of $BF_3{\cdot}Et_2O$ catalysis on the BV reaction of 23-oxosapogenins. Herein we report on the $BF_3{\cdot}Et_2O$ catalyzed BV reaction of 23-oxosapogenins and the related rearranged products bearing the 16β,23:23,26-diepoxy-22-oxo-cholestane side chain.

2. Experimental

Reactions were monitored by TLC on ALUGRAM® SIL G/UV254 plates from MACHEREY-NAGEL. Chromatographic plates were sprayed with a 1% solution of vanillin in 50% $HClO_4$ and heated until color developed. Melting points were measured on a Melt-Temp II instrument and are uncorrected. NMR spectra were recorded in $CDCl_3$ solution with a Varian INOVA 300 and 400 spectrometers using the solvent signal 7.26 ppm for ^1H and 77.00 ppm for ^{13}C as references. The ^1H and ^{13}C NMR spectra were processed using MestreNova (http://mestrelab.com).

(25*R*)-3α-acetoxy-5β-spirostan-23-one (*23-oxo-3-epismilagenin acetate*) (**1a**) *obtained as described in Ref.* [31]. *Mp.:* 155–157 °C. *^1H NMR:* (400 MHz, $CDCl_3$): 4.71 (m, 1H, H-3), 4.59 (ddd, *J* = 7.6, 7.6, 6.2 Hz, 1H, H-16), 3.77 (dd, *J* = 11.3, 11.3 Hz, 1H, H-26 *Pro-R*), 3.57 (ddd, *J* = 11.2, 4.6, 1.4 Hz, 1H, H-26 *Pro-S*), 2.86 (dq, *J* = 6.9, 6.9 Hz, 1H, H-20), 2.43 (m, 1H, H-24), 2.27 (m, 1H, H-25), 2.01 (s, 3H, CH_3 acetyl), 0.93 (s, 3H, H-19), 0.92 (d, *J* = 5.8 Hz, 3H, H-27), 0.92 (d, *J* = 7.6 Hz, 3H, H-21), 0.74 (s, 3H, H-18). *^{13}C NMR:* (100 MHz, $CDCl_3$): C-1 35.0, C-2 26.5, C-3 74.2, C-4 32.2, C-5 41.8, 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 40.0, 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 14.4, C-22 109.8, C-23 201.8, C-24 45.2, C-25 35.8, C-26 65.6, C-27 17.1, CH_3 acetyl 21.4, C=O acetyl 170.5.

$BF_3{\cdot}Et_2O$-catalyzed BV reaction of *23-oxo-3-epismilagenin acetate* (**1a**). MCPBA (74.2 mg, 0.33 mmol) and $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) were added to a solution of 23-oxo-3-epismilagenin acetate (**1a**) (56.2 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred for 10 min before addition of water (20 mL) and dilution with CH_2Cl_2 (25 mL). The organic layer was separated and washed with saturated $NaHSO_3$ (aq.) solution (2 × 20 mL), 10% Na_2CO_3 (aq.) (2 × 20 mL) and water (2 × 20 mL), dried (anh. Na_2SO_4) and evaporated to afford the pure 3α-acetoxy-16β-hydroxy-5β-bisnorcholanoic acid 22 → 16 lactone **2a** (45.7 mg, 0.118 mmol,



Scheme 2.

98.3%), identical as described in Ref. [31]. *^{1}H NMR (300 MHz, $CDCl_3$):* 4.94 (ddd, *J* = 7.8, 7.8, 4.6 Hz, 1H, H-16), 4.72 (dddd, *J* = 11.4, 11.4, 4.9, 4.9 Hz, 1H, H-3), 2.57 (dd, *J* = 0.7, 7.5 Hz, 1H, H-20), 2.02 (s, 3H, CH_3 acetyl), 1.31 (d, *J* = 7.6 Hz, 3H, H-21), 0.94 (s, 3H, H-19), 0.73 (s, 3H, H-18). *^{13}C NMR:* (75.5 MHz, $CDCl_3$): C-1 35.0, C-2 26.6, C-3 74.1, C-4 32.2, C-5 41.7, C-6 26.8, C-7 26.5, C-8 35.2, C-9 40.6, C-10 34.7, C-11 20.1, C-12 38.5, C-13 41.8, C-14 54.7, C-15 33.0, C-16 82.8, C-17 59.2, C-18 13.8, C-19 23.3, C-20 36.1, C-21 18.0, C-22 181.3, CH_3 acetyl 21.4, C=O acetyl 170.5.

(23*R*,25*R*)-3α-acetoxy-16β,23:23,26-diepoxy-5β-cholestan-22-one (**4a**) *obtained as described in Ref.* [28]. *Mp.:* 184–186 °C (*from ethyl acetate-hexane*). *^{1}H NMR:* (300 MHz, $CDCl_3$): 4.71 (m, 1H, H-3); 4.36 (ddd, 1H, *J* = 6.3, 8.1, 8.1 Hz, 1H, H-16); 4.13 (dd, 1H, *J* = 7.6, 7.6 Hz, H-26 *Pro-S*); 3.54 (dd, 1H, *J* = 8.2, 9.0 Hz, H-26 *Pro-R*); 2.79 (m, 1H, H-20); 2.41 (m, 1H, H-25); 2.01 (s, 3H, CH_3 acetyl); 1.08 (d, 3H, *J* = 6.4 Hz, H-21); 1.05 (d, 3H, *J* = 6.7 Hz, H-27); 0.95 (s, 6H, H-18 and H-19). *^{13}CNMR:* (75.5 MHz, $CDCl_3$): C-1 35.0; C-2 26.5; C-3 74.2; C-4 32.9; C-5 41.8; C-6 26.6; C-7 26.9; C-8 35.5; C-9 40.5; C-10 34.6; C-11 20.7; C-12 40.1; C-13 43.0; C-14 53.2; C-15 32.2; C-16 72.9; C-17 57.7; C-18 14.7; C-19 23.3; C-20 39.9; C-21 12.9; C-22 213.1; C-23 107.9; C-24 43.9; C-25 33.4; C-26 75.3; C-27 16.5; CH_3 acetyl 21.4; C=O acetyl 170.6.

When the rearranged ketone (**4a**) (50 mg, 0.11 mmol) was submitted to the $BF_3{\cdot}Et_2O$-catalyzed BV reaction for 10 min, the pure lactone **2a** (38.9 mg, 0.10 mmol, 90.9%) was produced.

(25*S*)-3β-acetoxy-5β-spirostan-23-one *23-oxosarsasapogenin acetate* (**1b**) *obtained as described in Ref.* [31]. *Mp.:* 168–170 °C. *^{1}H NMR:* (300 MHz, $CDCl_3$): 5.06 (m, 1H. H-3), 4.61 (m, 1H, H-16), 4.26 (dd, *J* = 11.2, 2.9 Hz, 1H, H-26 *Pro-R*), 3.42 (ddd, *J* = 11.1, 2.1, 2.1 Hz, 1H, H-26 *Pro-S*), 2.89 (m, 1H, H-20), 2.38 (m, 1H, H-25), 2.04 (s, 3H, CH_3 acetyl), 1.07 (d, *J* = 7.1 Hz, 3H, H-21), 0.98 (s, 3H, H-19), 0.95 (d, *J* = 7.0 Hz, 3H, H-27), 0.77 (s, 3H, H-18). *^{13}C NMR (75.5 MHz, $CDCl_3$):* 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 20.8, C-12 40.0, C-13 41.2, C-14 56.5, C-15 31.7, C-16 83.6, C-17 61.8, C-18 16.2, C-19 23.9, C-20 35.1, C-21 14.2, C-22 110.7, C-23 202.4, C-24 43.9, C-25 33.7, C-26 64.6, C-27 17.7, CH_3 acetyl 21.5, C=O acetyl 170.7.

When *23-oxosarsasapogenin acetate* (**1b**) (50 mg, 0.11 mmol) was submitted to the $BF_3{\cdot}Et_2O$-catalyzed BV reaction procedure for 10 min the pure lactone **2b** (31.7 mg, 0.08 mmol, 72.7%) was produced. 3β-Acetoxy-16β-hydroxy-5β-bisnorcholanoic acid 22 → 16 lactone (**2b**) *identical as described in Ref.* [31]. *^{1}H NMR:* (300 MHz, $CDCl_3$): 5.05 (m, 1H, H-3), 4.93 (ddd, *J* = 7.7, 7.7, 4.6 Hz, 1H, H-16), 2.56 (m, 1H, H-20), 2.03 (s, 3H, CH_3 acetyl), 1.30 (d, *J* = 7.6 Hz, 3H, H-21), 0.97 (s, 3H, H-19), 0.73 (s, 3H, H-18). *^{13}C NMR (75 MHz, $CDCl_3$):* C-1 30.5, C-2 24.9, C-3 70.5, 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 35.0, C-11 20.3, C-12 38.5, C-13 41.8, C-14 54.7, C-15 33.0, C-16 82.8, C-17 59.1, C-18 13.8, C-19 23.7, C-20 36.0, C-21 18.0, C-22 181.2, CH_3 acetyl 21.4, C=O acetyl 170.6.

(23*R*,25*S*)-3β-acetoxy-16β,23:23,26-diepoxy-5β-cholestan-22-one (**4b**) *obtained following the procedure described in Ref.* [24]. *Mp.:* 169–171 °C. *^{1}H NMR (400 MHz, $CDCl_3$):* 5.04 (m, 1H, H-3), 4.34 (ddd, *J* = 8.1, 8.1, 6.4 Hz, 1H, H-16), 4.11 (dd, *J* = 7.7, 7.7 Hz, 1H, H-26 *Pro-R*), 3.60 (dd, *J* = 7.9, 7.9 Hz, 1H, H-26 *Pro-S*), 2.74 (dq, *J* = 9.8, 6.4 Hz, 1H, H-20), 2.55 (m, 1H, H-25), 2.02 (s, 3H, CH_3 acetyl), 1.07 (d, *J* = 6.4 Hz, 3H, H-21), 1.03 (d, *J* = 6.7 Hz, 3H, H-27), 0.97 (s, 3H, H-19), 0.93 (s, 3H, H-18). *^{13}C NMR (100 MHz, $CDCl_3$):* C-1 30.5, C-2 24.9, C-3 70.5, C-4 30.6, C-5 37.2, C-6 26.3, C-7 26.3, C-8 35.2, C-9 40.5, C-10 34.9, C-11 20.9, C-12 40.1, C-13 42.9, C-14 53.1, C-15 32.8, C-16 72.1, C-17 57.4, C-18 14.7, C-19 23.8, C-20 39.8, C-21 13.0, C-22 213.2, C-23 107.6, C-24 44.3, C-25 32.7, C-26 76.1, C-27 17.0, CH_3 acetyl 21.5, C=O acetyl 170.7.

When the rearranged ketone (**4b**) (50 mg, 0.11 mmol) was submitted to the $BF_3{\cdot}Et_2O$-catalyzed BV reaction procedure for 10 min the pure lactone **2b** (27.2 mg, 0.07 mmol, 63.6%) was produced.

2.1. Isomerization experiments

$BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) was added to a solution of 23-oxo-3-epismilagenin acetate (**1a**) (50 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 10 min before addition of water (20 mL) and dilution with CH_2Cl_2 (20 mL). The organic layer was washed with water (3 × 25 mL), dried (anh. Na_2SO_4) and evaporated to afford a 1/3.4 mixture of **1a** and **4a** (*ratio determined by relative integration of H-26 Pro-R of **1a** y H-26 Pro-S of **4a***, see Fig. 1 and Supplementary information).

When the rearranged ketone **4a** was submitted to the same procedure, a 1/2.45 mixture of **1a** and **4a** was obtained (*ratio determined as described for **1a***, see Supplementary information).

When 23-oxosarsasapogenin acetate (**1b**) was submitted to the same procedure a 1/10.37 mixture of **1b** and **4b** was obtained (*ratio determined by relative integration of the H-26 Pro-S of **1b** and **4b***, see Fig. 1 and Supplementary information).

When the rearranged ketone **4b** was submitted to the same procedure a 1/9.79 mixture of **1b** and **4b** was obtained (*ratio determined by relative integration of the* H-26 *Pro-S of **1b** and **4b***, see Supplementary information).

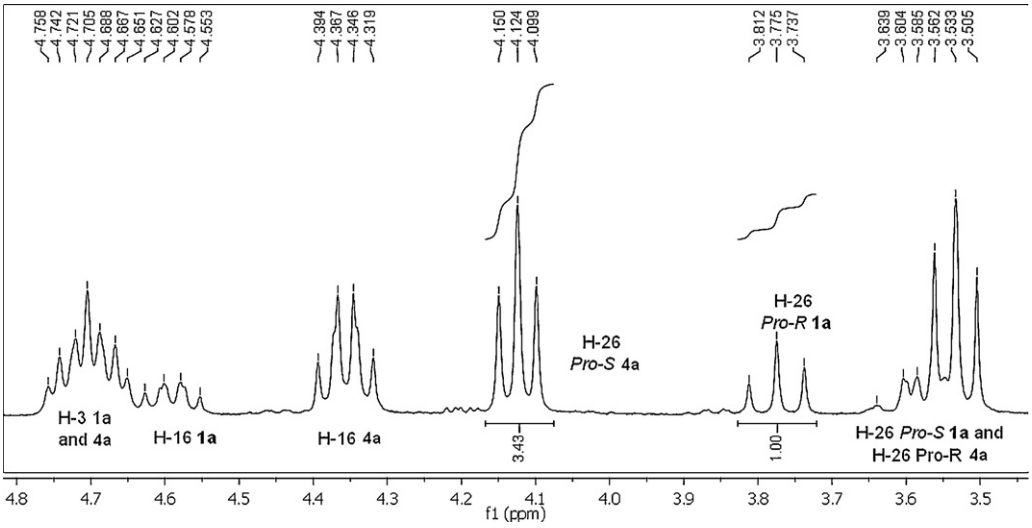
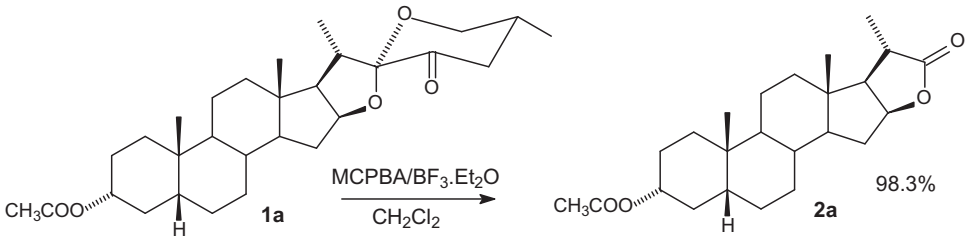
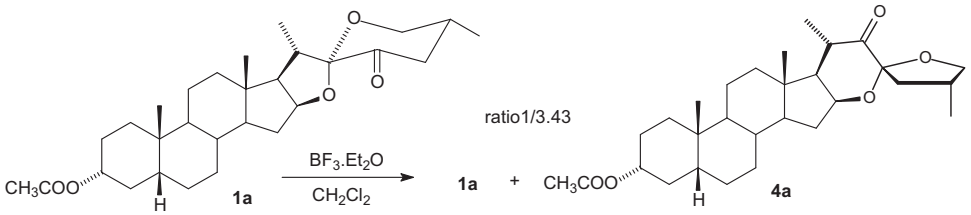


Fig. 1. Relative integration of the H-26 *Pro-S* (**4a**) and H-26 *Pro-R* (**1a**) signals.



Scheme 3.



Scheme 4.

3. Results and discussion

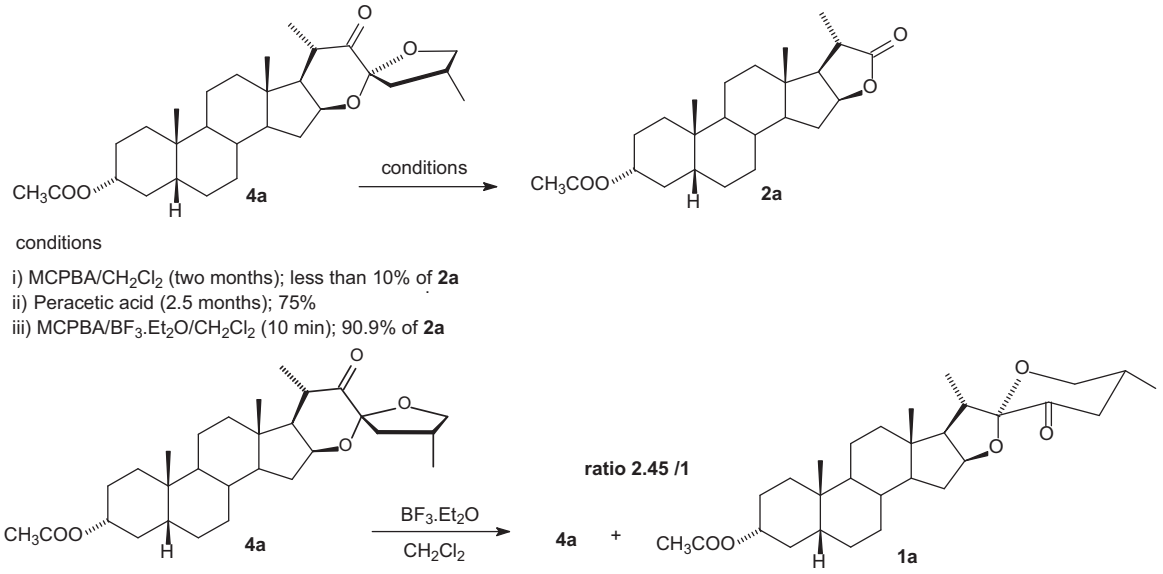
Treatment of 23-oxosmilagenin acetate **1a** with MCPBA and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 resulted in a very fast BV reaction to produce the dinorcholanic lactone **2a** in 98.3% after only 10 min (see Scheme 3).

The results of the $BF_3{\cdot}Et_2O$ catalyzed BV reaction of the 23-oxo derivative **2a** can be explained by basically the same mechanism as depicted in Scheme 2, in which coordination of $BF_3{\cdot}Et_2O$ to the C-23 carbonyl catalyzes the attack of the peracid to this position leading to the fast production of the Criegee intermediate **I**. Once the rearrangement to the orthoester **II** has occurred, $BF_3{\cdot}Et_2O$ catalyzes its fast collapse to the lactone **2a**, avoiding the second nucleophilic attack of the peroxy acid and preventing the concurrent formation of the cyclic carbonate **3a**.

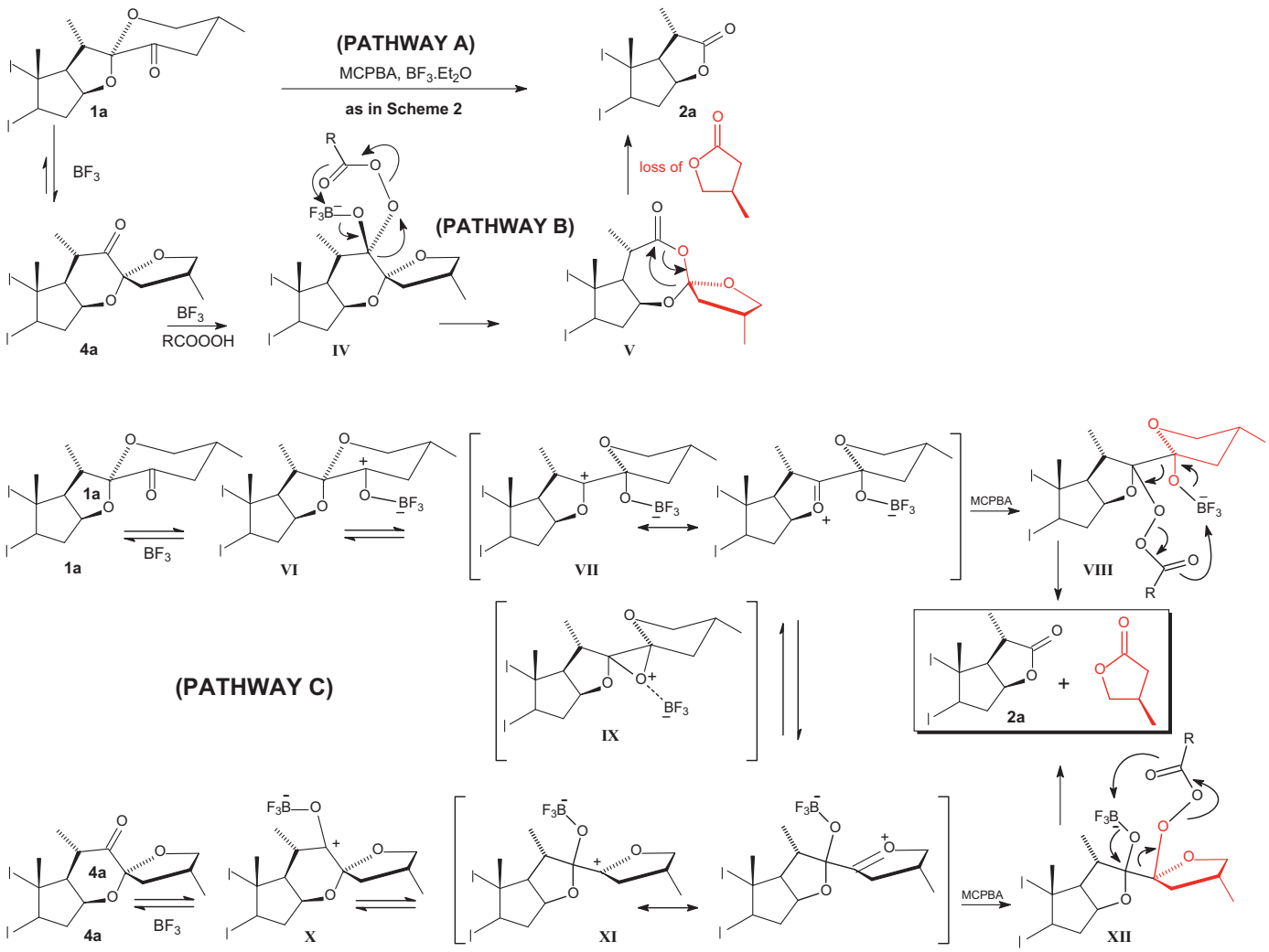
Examination of the TLC plates after 5 min indicated the presence of the starting material **1a**, the more polar lactone **2a** and an additional product of intermediate polarity which disappeared when the starting material was consumed. A blank experiment, in which the starting material **1a** was treated only with $BF_3{\cdot}Et_2O$ for 10 min produced a 1/3.43 mixture of the staring material **1a** and the above mentioned product, which was separated and identified as the known (23*R*,25*R*)-3α-acetoxy-16β,23:23,26-diepoxy-5β-cholestan-22-one **4a** [28] (see Scheme 4 and Fig. 1). When the **1a**/**4a**/$BF_3{\cdot}Et_2O$ mixture was allowed to stand overnight a mixture of at least three inseparable compounds was produced.

This highly stereoselective (only the *R* configuration is formed at the new spiro carbon atom) rearrangement, for the first time reported by Suárez (employing $TiCl_4$) [18], has been also described to proceed under $BF_3{\cdot}Et_2O$ catalysis in different solvents (formic acid, THF) [13,24].

This led us to investigate the BV reaction of **4a** under the same reaction conditions as those explored for **1a**. Meanwhile **4a** proved to be inert to MCPBA after more than 1.5 month, when it was treated with peroxyacetic acid the lactone **2a** was produced in 75% yield after 2.5 months, indicating the considerably low reactivity of **4a** to the peroxy acid attack. In contrast, treatment of **4a** with MCPBA and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 produced the lactone **2a** in 90.9% after only 10 min. A blank experiment showed that the treatment of **4a** in CH_2Cl_2 solution with $BF_3{\cdot}Et_2O$ for 10 min afforded a 2.45/1 mixture of **4a** and **1a** (see Scheme 5 and supplementary information).



Scheme 5.



Scheme 6.

In the case of **4a**, the observed slow BV reaction with MCPBA or peracetic acid, can be explained by taking into account that the approach of the peroxy acid to C-22 is strongly hindered by the F-ring attached to C-23 and by the 18- and 21-methyl groups placed in the β and α sides of the steroid framework, respectively.

For the $BF_3{\cdot}Et_2O$ catalyzed reaction of **4a**, a pathway through the Criegee intermediate **IV** and the orthoester **V** (see Scheme 6, pathway B) may also explain the results, but considering the strong steric hindrance around C-22, and provided that $BF_3{\cdot}Et_2O$ catalyzes the interconversion of **1a** and **4a**, it is more reasonable to assume that the reaction of **4a** follows pathway A consisting of a conversion to the 23-oxo derivative **1a**, which being more accessible to the peroxy acid attack, readily undergoes the $BF_3{\cdot}Et_2O$ catalyzed BV reaction shifting the **4a** ⇆ **1a** equilibrium towards **1a**, until **4a** is completely consumed (see Scheme 6).

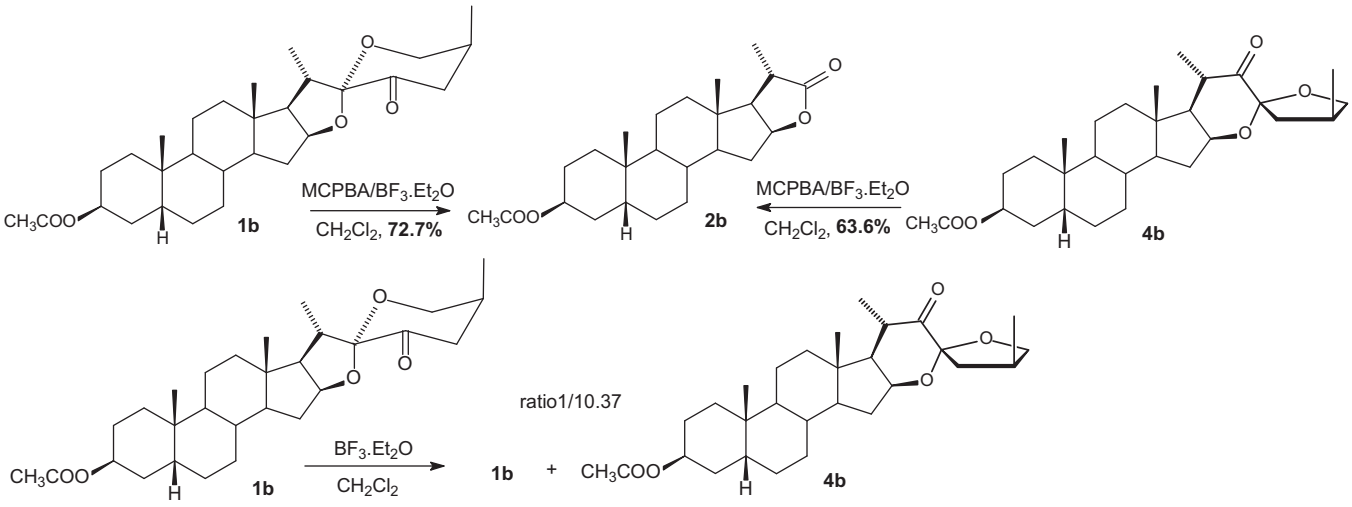
Alternatively intermediates **VII** and **XI** involved in the **1a** ⇆ **4a** equilibrium may undergo nucleophilic attack of the peroxy acid respectively leading to **VIII** and **XII** that rearrange to the lactone **2a** with loss of 3-methylbutyrolactone (see Scheme 6, pathway C).

3.1. Experiments in the 25S series

The BV reactions of 23-oxosarsasapogenin acetate **1b** and the rearranged ketone **4b** catalyzed by $BF_3{\cdot}Et_2O$ afforded the same dinocholanic lactone **2b** in 72.7 and 63.6% yield, respectively (see Scheme 7). As described for **1a**, a blank experiment, in which **1b** was treated only with $BF_3{\cdot}Et_2O$ for 10 min, produced a 1/10.37 mixture of **1b** and **4b** (see Fig. 2 and Supplementary information). Similar treatment of **4b** afforded a 1/9.79 mixture of **1b** and **4b** (see Supplementary information).

In the 25*S* series yields of the dinocholanic lactone **2b** proved considerably lower when compared with yields of analogous lactone **2a** from ketones (**1a** or **4a**) of the 25*R* series. It seems that in this case the BV reaction is accompanied by a side, rather messy, reaction. We have recently shown [29] that the treatment of 23-oxosapogenins with trimethylsilyl triflate results in the formation of the rearranged dienes (such as **5**, see Fig. 3) in addition to the isospirostanic ketones (analogous to **4**). Such dienes may be also formed in minor amounts in the reactions catalyzed by $BF_3{\cdot}Et_2O$. The dienes are formed by elimination reactions of some intermediates (e.g. **VII** or **XI**, see Scheme 6).

The elimination reactions are irreversible and affect the equilibrium between **1** and **4**. In addition, dienes may react with peroxy acids leading to a variety of products. In the 25*S* series the rearrangement of the unreactive ketone (**4b**) to the reactive one (**1b**) is apparently slower than in the 25*R* series due to a steric hindrance from the methyl group at C-25, which becomes axial as a result of the transformation. That is why the competitive elimination reactions, that reduce the yield of the BV reaction in the 25*S* series, have time to occur.



Scheme 7.

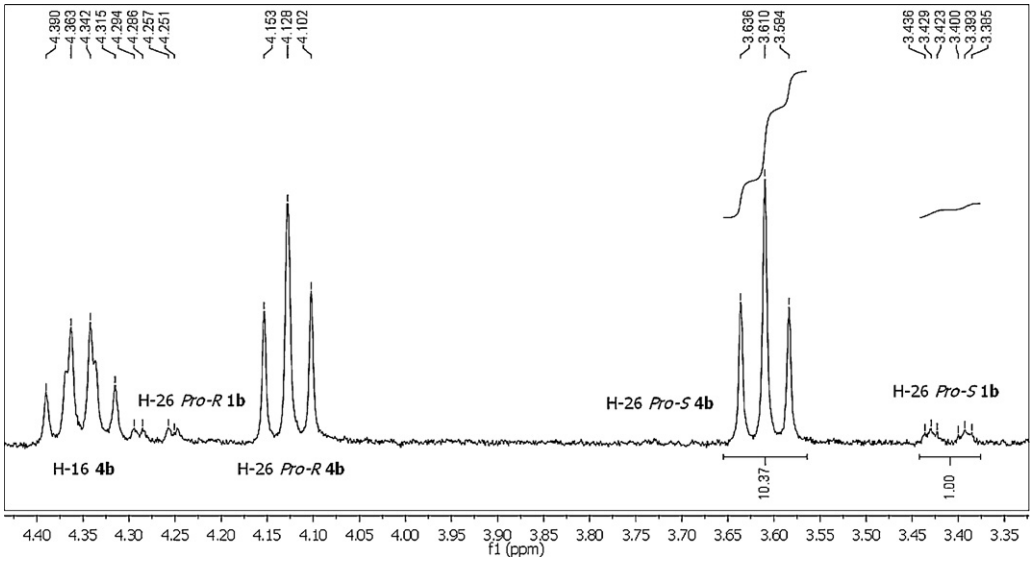
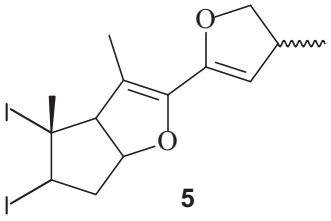


Fig. 2. Relative integration of the H-26 *Pro-S* (**4b**) and H-26 *Pro-S* (**1b**) signals.

3.2. Molecular modeling

The experimental results presented above showed that the 23-oxosapogenins readily undergo rearrangement catalyzed by $BF_3{\cdot}Et_2O$ to the isomeric 22-oxo-23-spiroketals. Assuming that the equilibrium between both ketones is reached within 10 min at room temperature (25 °C), we can calculate the ΔG value ($\Delta G = -RT \ln K$) from the isomeric ratio ($K = n(\mathbf{1})/n(\mathbf{4})$). In both 25*R* and 25*S* series, the 22-oxo-23-spiroketals are isomers of lower energy but the ΔG(**1a**–**4a**) and ΔG(**1b**–**4b**) values are substantially different (0.53–0.73 kcal/mol vs. 1.35–1.38 kcal/mol, respectively).



5

Fig. 3. Rearranged diene.

To justify these results we performed molecular modeling using molecular mechanics (HyperChem TM release 3 from Hypercube, Inc.; employing the MM+ force field and the Polak-Ribiere conjugate gradient algorithm) and results are presented in Table 2.

The Molecular modeling confirmed that the isomeric 22-oxo-23-spiroketals are thermodynamically more stable than the 23-oxosapogenins and that it is clear that release of energy is a driving force for rearrangement. The calculated difference in the 25*R* series: ΔG(**1a**–**4a**) = 0.33 kcal/mol proved to be smaller than in the 25*S* series: ΔG(**1b**–**4b**) = 1.35 kcal/mol and for this reason the equilibrium in the latter case is more shifted towards the rearranged ketone. The energy release during rearrangement in the 25*S* series results mainly from change of an axial methyl group at

Table 2
Calculated steric energies for studied compounds **1a**, **1b**, **4a**, and **4b**.

Compound	Steric energy (kcal/mol)
1a	59.86
4a	59.53
1b	60.92
4b	59.57

C-25 in 23-oxosarsasapogenin acetate (**1b**) into *pseudo*-equatorial one in the corresponding 22-oxo-23-spiroketal (**4b**). It should be remarked that the agreement between experimental results and MM+ calculated values is quite satisfactory.

4. Conclusions

The $BF_3{\cdot}Et_2O$-catalyzed reactions of 23-oxosapogenins and isomeric 22-oxo-23-spiroketals of both, the 25*R* and 25*S* series, with MCPBA rapidly afford analogous lactone products. The BV rearrangement is accompanied by fragmentation into the dinorcholanic lactone and 3-methylburyrolactone. It was proved that fast interconversion of the isomeric ketones occur under the reaction conditions. In the 25*S* series the equilibrium between them is significantly shifted towards the less reactive 22-oxo-23-spiroketal that justifies the lower yield of the lactone in this case.

Acknowledgements

The authors thank the Dirección General de Asuntos del Personal Académico (DGAPA-UNAM) for financial support via project IN204008-3 and CONACyT for scholarship granted to MM-A. Financial support from the University of Białystok within the project BST 124 is gratefully acknowledged. Thanks are due to Rosa I. del Villar Morales, Georgina Duarte Lisci (USAI-UNAM) for recording NMR and mass spectra.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2010.12.004.

References

[1] Fieser L, Fieser M. Steroids. New York: Reinhold Publishing Corporation; 1959. p. 810–46.
[2] Torgov IV. Chemistry of spirostanols. Moscow: Nauka; 1986 [in Russian].
[3] Iglesias-Arteaga MA, Perez-Gil R, Coll-Manchado F. Aspectos de interés sobre la cadena lateral de las sapogeninas esteroidales. CENIC 1997;28:67–72 [in Spanish].
[4] Djerassi C, Halpern O, Pettit GR, Thomas GH. Reaction of the steroidal sapogenin spiroketal system with ethanedithiol. J Org Chem 1959;24:1–6.
[5] Zedric JA, Cervantes L, Galván MT. Sapogenins. XLI. A new reaction of the spiroketal side chain. J Am Chem Soc 1962;84:102–6.
[6] Faul WH, Failli A, Djerassi C. Side-chain transformations and deuterium labeling in the steroidal sapogenin series. J Org Chem 1970;35:2571–85.
[7] Sandoval-Ramirez J, Castro-Mendez A, Meza-Reyes S, Reyes-Vázquez S, Santillán R, Farfán N. Preparation of 22,26-epoxycholest-22-ene steroids. Novel transformation of the side chain in sapogenins. Tetrahedron Lett 1999;40:5143–6.
[8] Bäsler S, Brunck A, Jautelat R, Winterfeld E. Synthesis of cytostatic tetradecacyclic pyrazines and a novel reduction-oxidation sequence for spiroketal opening in sapogenins. Helv Chim Acta 2000;83:1854–80.
[9] LaCour TG, Tong Z, Fuchs PL. Consequences of acid catalysis in concurrent ring opening and halogenation of spiroketals. Org Lett 1999;1:1815–8.
[10] Sandoval-Ramírez J, Meza-Reyes S, del Río RE, Hernandez-Linares G, Suárez-Rojas A, Rincón S, et al. Regioselective cleavage of rings E and F in sarsasapogenin. Steroids 2003;68:199–204.
[11] Iglesias-Arteaga MA, Arcos-Ramos RO. One-step axial acetoxylation at C-23. A new method for the functionalization of the side chain of steroid sapogenins. Tetrahedron Lett 2006;47:8029–31.
[12] Iglesias-Arteaga MA, Jastrzębska I, Morzycki JW. Reactions of sapogenins with m-chloroperoxybenzoic acid catalyzed by Lewis acids. Polish J Chem 2006;80:667–71.
[13] Iglesias-Arteaga MA, Arcos-Ramos RO, Méndez-Stivalet JM. The unexpected course of the reaction of steroid sapogenins with diacetoxyiodobenzene and $BF_3{\cdot}Et_2O$ in formic acid. Tetrahedron Lett 2007;48:7485–8.
[14] López Y, Ruíz-Pérez KM, Yépez R, Santillán R, Flores-Álamo M, Iglesias-Arteaga MA. Mechanistic insights and new products of the reaction of steroid sapogenins with $NaNO_2$ and $BF_3{\cdot}Et_2O$ in acetic acid. Steroids 2008;73:657–68.
[15] Jiang B, Shi H-p, Tian W-s, Zhou W-s. Tetrahedron 2008;64:469–76.
[16] Ruíz-Pérez KM, Romero-Ávila M, Flores-Pérez B, Flores-Álamo M, Moreno-Esparza R, Iglesias-Arteaga MA. Revisiting 23-iodospirostanes. New facts and full characterization. Steroids 2009;74:996–1002.
[17] Jastrzębska I, Dobrogowska A, Lutostańska E, Morzycki JW. On reactions of spirostane sapogenins with benzeneseleninic anhydride. Tetrahedron 2010;66:5024–9.
[18] Hernández R, Marrero-Tellado JJ, Prout K, Suárez E. Lewis acid-mediated isomerization of (25*R*)-3β-acetoxy-5α-spirostan-23-one, a C-22 spiroacetal: an approach to the synthesis of C-23 spiroacetal steroidal sapogenins. J Chem Soc Chem Commun 1992:275–7.
[19] Morzycki JW, Jastrzębska I. Novel transformation of 23-bromosapogenins. Synthesis of (22*S*, 23*R*)-22-hydroxy-23,26-epoxyfurostanes. Tetrahedron Lett 2001;42:5989–91.
[20] Anulewicz-Ostrowska R, Jastrzębska I, Morzycki JW, Wojcik J. An assisted solvolysis of 23 spirostanyl bromides and tosylates. A new rearrangement of spirostanes to the bisfuran systems. J Org Chem 2002;67:6916–24.
[21] Betancour C, Dorta RL, Freire R, Martin A, Prange T, Suárez E. Stereospecific synthesis of 1,6-dioxadecalins and 2,2(-linked ditetrahydrofurans by rearrangement of steroidal spiroacetals. J Org Chem 1998;63:6355–62.
[22] Jastrzębska I, Morzycki JW, Trochimowicz U. Lead tetraacetate–iodine oxidation of 23-spirostanols. Tetrahedron Lett 2004;45:1929–32.
[23] Iglesias-Arteaga MA, Sandoval-Ramírez J, Mata-Esma MY, Viñas-Bravo O, Bernes S. Abnormal Beckmann rearrangement in 23-hydroxyiminodiosgenin acetate. Tetrahedron Lett 2004;45:4921–6.
[24] Cyrański MK, Frelek J, Jastrzębska I, Morzycki JW. Rearrangement of 23-oxospirostanes to the 22-oxo-23-spiroketal isomers promoted by Lewis acids. X-ray crystal structure of (23*R*, 25*S*)-3-acetoxy-16,23:23,26-diepoxy-5-cholestan-22-one. Steroids 2004;69:395–400.
[25] Iglesias-Arteaga MA, Velázquez-Huerta GA. Favorskii rearrangement of 23-oxo-3-epi-smilagenin acetate induced by iodosobenzene. Tetrahedron Lett 2005;46:6897–9.
[26] Iglesias-Arteaga MA, Alvarado-Nuño AA. $BF_3{\cdot}Et_2O$ induced Beckmann rearrangement of 23 hydroxyiminosapogenins. A shortcut to bisnorcholaniclactones. Tetrahedron Lett 2006;47:5351–3.
[27] Vázquez-Ramírez I, Macías-Alonso M, Arcos-Ramos RO, Ruíz-Pérez KM, Solano-Ramírez DO, Iglesias Arteaga MA. ^1H and ^{13}C NMR characteristics of synthetic derivatives of steroid sapogenins: Part III. 16β,23:23,26-Diepoxy side chains. Steroids 2008;73:642–51.
[28] Macías-Alonso M, Flores-Álamo M, Iglesias-Arteaga MA. Beckmann reactions of steroidal spirocyclic oximes derived from the 16β,23:23,26-diepoxy-22-oxo moiety. Steroids 2009;74:112–20.
[29] Jastrzębska I, Siergiejczyk L, Tomkiel AM, Urbańczyk-Lipkowska Z, Wójcik D, Morzycki JW. On reactions of steroidal 23-oxo and 23,24-epoxysapogenins with Lewis acids. Steroids 2009;74:675–83.
[30] Jastrzębska I, Morzycki JW. Unusual Baeyer–Villiger oxidation of 23-oxosarsasapogenin acetate. Polish J Chem 2005;79:1245–8.
[31] Iglesias-Arteaga MA, Velázquez-Huerta GA, Méndez-Stivalet JM, Galano A, Álvarez-Idaboy JR. The Baeyer–Villiger reaction of 23-oxosapogenins. Arkivoc 2005;VI:109–26.
[32] Marker RE, Shabica A. Sterols. CXXXVII. Sapogenins. LVIII. Oxidation products of sarsasapogenin: keto-sarsasapogenin. J Am Chem Soc 1942;64:813–6.
[33] Hunt KW, Grieco PA. Baeyer–Villiger oxidation promoted by reaction of peracids with cyclic oxocarbenium ions generated in situ from internal hemiketals. Org Lett 2000;2:1717–9.
[34] Marker RE, Turner DL, Wagner RB, Ulshafer PR, Sterols CXVI, Sapogenins XLV. The isosarsasapogenin configuration. J Am Chem Soc 1941;63:772–4.