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An unexpected $BF_3{\cdot}Et_2O$-catalyzed rearrangement of 23*E*-benzylidenespirostanes to spiro[furan-indenes]

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ABSTRACT

Treatment of 23*E*-benzylidenespirostanes with $BF_3{\cdot}Et_2O$ in 2/1 acetic acid/CH_2Cl_2 led to novel steroids bearing a spiro[furan-indene] moiety in the side chain. When steroid sapogenins were treated with benzaldehyde and $BF_3{\cdot}Et_2O$ in the same mixture of solvents, similar compounds were obtained. The structures of the novel spirocyclic steroids were confirmed by NMR and X-ray diffraction.

Introduction

Steroid sapogenins have served as starting materials in the synthesis of a wide variety of bioactive steroids that include adrenocortical hormones,[1] plant grow promoting substances,[2] cephalostatins and ritterazines,[3] and antioxidants,[4] among many others.[5] Since the preparation of bioactive steroids starting from this family of compounds implies the modification or cleavage of the spiroketal side chain, considerable attention has been devoted to the development of new methods for the transformation on this fragment.[6] In particular we have recently described that treatment of acetylated steroid sapogenins with benzaldehyde and a large excess of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 produced good yields of 23*E*-benzylidenspirostanes. (Scheme 1).[6g]

A study to produce a more environment friendly procedure led us to change the conditions of the aldol condensation in a way that the amount of $BF_3{\cdot}Et_2O$ can be reduced. During the course of this study, we found that the simple change of solvent from CH_2Cl_2 to 2/1 acetic acid/CH_2Cl_2 allowed the reduction in the amount of $BF_3{\cdot}Et_2O$ necessary to produce the above mentioned aldol condensation and also promoted an unexpected rearrangement that produces hereto unknown spirocyclic steroids bearing a spiro[furan-indene] moiety in the side chain.

Results and discussion

When a solution of 1 mmol of tigogenin acetate (**1a**) in 2/1 acetic acid/CH_2Cl_2 mixture (9 mL) was treated with benzaldehyde (2 mmol) and $BF_3{\cdot}Et_2O$ (0.6 mL) the expected 23*E*-benzylidenspirostane **2a** was produced in 41.5% yield after 4.5 h. Surprisingly during the same treatment of **1b**, the expected 23*E*-benzylidenspirostane **2b** was slowly produced together with a more polar compound that arose after 24 h (TLC). Consumption of the staring material **1b** was achieved only after 50 h and no trace of the expected 23*E*-benzylidenspirostane **2b** was observed in TLC after that time. Chromatographic separation of the reaction mixture afforded the unexpected compound **3b** in 50.9% (Scheme 2 Eq. 1, Table 1 entry 2). The same reaction with tigogenin acetate (**1a**) afforded the corresponding compound **3a** in only 19.7% after 63 h (Scheme 2 Eq. 1, Table 1 entry 1). Additionally, when solutions of our previously reported 23*E*-benzylidenespirostanes **2a** and **2b**[6g] (1 mmol) in 2/1 acetic acid/CH_2Cl_2 mixture (9 mL) were treated with $BF_3{\cdot}Et_2O$ (0.6 mL), compounds **3a** and **3b** were produced in almost similar yields as described above (Scheme 2 Eq. 2; Table 1, entries 3 and 4).

The hereto unknown compounds **3a** and **3b** bear an indene moiety fused to the furostane side chain through positions C-22 (spiro) and C-23 (olefinic). Assignments of the NMR signals and elucidation of the structures of the new spirocyclic compounds were carried out employing a combination of 1D and 2D NMR techniques that included ^1H, ^{13}C, HSQC, HMBC, NOESY, and COSY. The observed H-6′ ↔ H-16 and H-6′ ↔ H-17 NOE effects indicate that the bond

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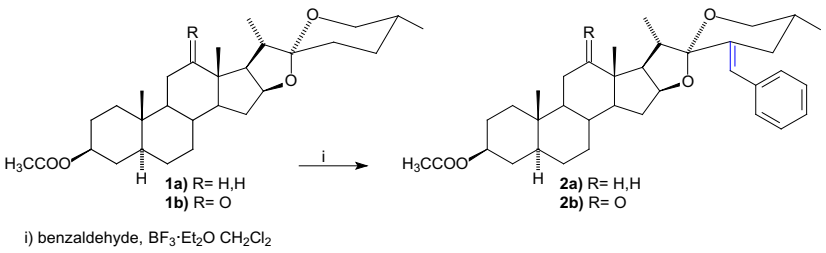
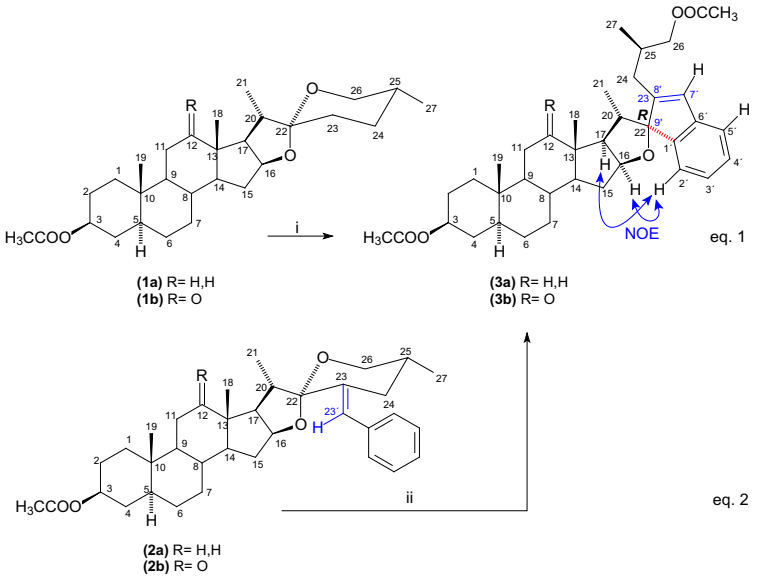


Scheme 1. Synthesis of 23*E*-benzylidenespirostanes.



Scheme 2. Synthesis of the spiro[furan-indenes] **3a** and **3b**.

Table 1
Synthesis of the spiro[furan-indenes] **3a** and **3b**

Entry	Starting material	Product	Time (h)	Yield (%)
1	**1a**	**3a**	63	19.7
2	**1b**	**3b**	50	50.9
3	**2a**	**3a**	48	13.2
4	**2b**	**3b**	48	40.4

between C-22 and the phenyl ring is oriented to the α-side of the steroid nucleus, which results in the 22*R* configuration (see Scheme 2). X-ray diffraction of compound **3b** corroborated the proposed structures (Fig. 1).[7]

(22*R*,25*R*)Indene[9′,8′:22,23]-5α-furostan-3β,26-diol diacetate (**3a**) Mp. 194.5–196.7 °C (*from CH_2Cl_2/MeOH*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 1H, H-2′), 7.16 (td, *J* = 7.4, 1.1 Hz, 1H, H-3′), 7.12–7.09 (m, 1H, H-5′), 7.05 (td, *J* = 7.4, 1.3 Hz, 1H, H-4′), 6.36 (d, *J* = 1.5 Hz, 1H, H-7′), 4.99 (dt, *J* = 9.2, 7.0 Hz, 1H, H-16α), 4.70 (tt, *J* = 11.3, 4.9 Hz, 1H, H-3α), 4.09–3.92 (m, 2H, H-26), 2.58–2.52 (m, 1H, H-20β), 2.49 (ddd, *J* = 15.3, 5.2, 1.8 Hz, 1H, H-24a), 2.31 (ddt, *J* = 13.2, 6.5, 1.7 Hz, 1H, H-l25), 2.20 (dd, *J* = 9.3, 7.8 Hz, 1H, H-17α), 2.07 (s, 3H, CH_3 acetyl), 2.05 (d, *J* = 1.6 Hz, 1H, H-24b), 2.02 (s, 3H, CH_3 acetyl), 0.99 (s, 3H, H-18), 0.98 (d, *J* = 6.5 Hz, 3H, H-27), 0.87 (s, 3H, H-19), 0.72 (td, *J* = 11.8, 10.4, 3.1, 1H, H-9α), 0.55 (d, *J* = 6.9 Hz, 3H, H-21). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.7 C-1, 27.5 C-2, 73.7 C-3, 34.0 C-4, 44.7 C-5, 28.5 C-6, 32.2 C-7, 35.0 C-8, 54.2 C-9, 35.6 C-10, 21.1 C-11, 40.3 C- 12, 41.6 C-13, 56.7 C-14, 32.5 C-15, 84.3 C-16, 63.2 C-17, 16.9 C-18, 12.3 C-19, 36.2 C-20, 15.3 C-21, 101.2 C-22, 148.5 C-23, 31.0 C-24, 31.4 C-25, 69.6 C-26, 17.1 C-27, 128.5 C-7′, 142.8 C-1′, 124.0 C-2′, 127.9 C-3′, 124.6 C-4′, 120.6 C-5′, 145.5 C-6′, 21.5, 21.0 2 × CH_3 acetyl, 170.7, 171.2 2 × C=O acetyl.

(22*R*,25*R*)Indene[9′,8′:22,23]-3β,26-diacetoxy-5α-furostan-12-one (**3b**) Mp. 249.0–249.3 °C (*from acetone/hexane*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.4 Hz, 1H, H-2′), 7.18 (td, *J* = 7.4, 1.0 Hz, 1H, H-3′), 7.13–7.09 (m, 1H, H-5′), 7.07 (td, *J* = 7.4, 1.3 Hz, 1H, H-4′), 6.38 (d, *J* = 1.5 Hz, 1H, H-7′), 4.92 (td, *J* = 8.4, 7.3, 4.2 Hz, 1H, H-16α), 4.77–4.56 (m, 1H, H-3α), 4.15–3.87 (m, 2H, H-26), 3.04 (dd, *J* = 9.4, 8.1 Hz, 1H, H-17α), 2.44 (1H, m, H-24a), 2.39 (m, 1H, H-20β), 2.30 (m, 1H, H-25), 2.07 (s, 3H, CH_3 acetyl), 2.03 (s, 3H, CH_3 acetyl), 2.01 (m, 1H, H-24b), 1.26 (s, 3H, H-18), 0.98 (d, *J* = 6.7 Hz, 3H, H-27), 0.95 (s, 3H, H-19), 1.19 (m, 1H, H-9α), 0.64 (d, *J* = 6.8 Hz, 3H, H-21). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 36.2 C-1, 27.2 C-2, 73.1 C-3, 33.8 C-4, 44.5 C-5, 28.1 C-6, 32.5 C-7, 34.2 C-8, 55.5 C-9, 36.1 C-10, 37.7 C-11, 213.0 C- 12, 55.8 C-13, 56.0 C-14, 32.0 C-15, 82.5 C-16, 53.9 C-17, 16.5 C-18, 11.9 C-19, 36.7 C-20, 14.0 C-21, 101.2 C-22, 147.9 C-23, 30.9 C-24, 31.3 C-25, 69.5 C-26, 17.0 C-27, 128.8 C-7′, 142.6 C-1′, 124.0 C-2′, 128.1 C-3′, 124.7 C-4′, 120.6 C-5′, 145.1 C-6′, 21.4, 21.0 2 × CH_3 acetyl, 170.6, 171.1 2 × C=O acetyl.

In a rational reaction pathway, activation of acetic acid by BF_3·Et_2O leads to acetylation of the hydroxyl group attached to C-26, that results on the F-ring opening and concomitant generation of the carbocation **I**. Resonance weakens the C-23–C-23′ double

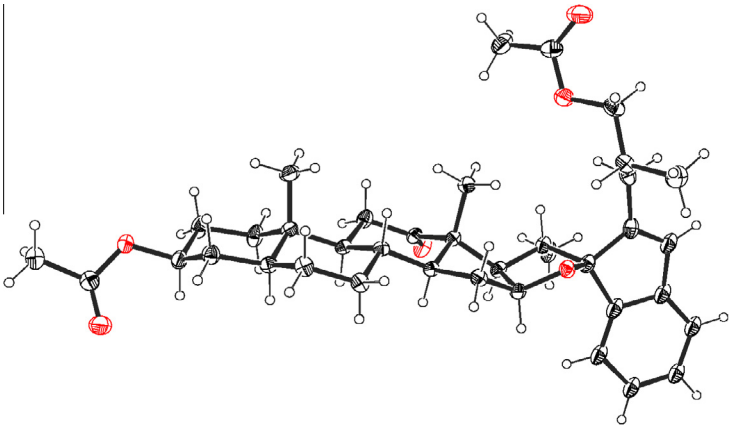
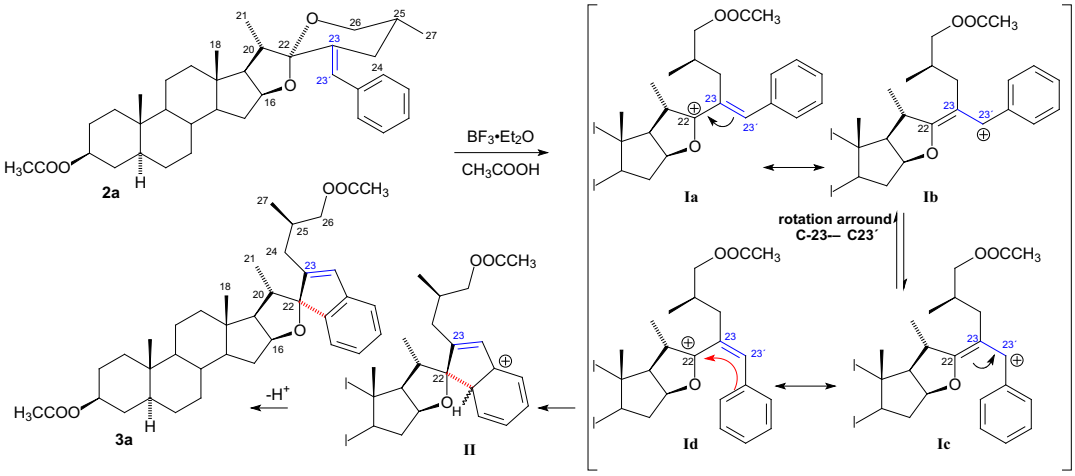


Figure 1. X-ray structure of compound **3b** with the thermal ellipsoids drawn at 30% probability.



Scheme 3. Plausible reaction mechanism.

bond and permits rotation, placing the phenyl ring near to the carbocation at C-22 and allowing the internal S_EAr that locks the indene moiety through the spiro carbon at C-22 (Scheme 3).

Production of the spiro[furan-indene] steroids **3a** and **3b** directly from the corresponding steroid sapogenins **1a** and **1b** can be rationalized in terms of a tandem process that includes our previously reported aldol condensation of steroid sapogenins with benzaldehyde to produce 23*E*-benzylidenespirostanes[6g] followed by the described rearrangement.

Although experimental results clearly indicate that the presence of a carbonyl function at C-12 plays a determinant role in the yield of the reaction, no explanation for this effect appears convincing. Further studies are directed at clarifying the effect of the C-12 carbonyl function on the reaction rate, improving overall reaction yields, and extending the synthetic applications of this new reaction to other spiroketalic compounds.

Conclusions

Treatment of 23*E*-benzylidenespirostanes with $BF_3{\cdot}Et_2O$ in 2/1 acetic acid/CH_2Cl_2 triggers a rearrangement that produces novel steroids bearing a spiro[furan-indene] moiety in the side chain. When steroid sapogenins were treated with benzaldehyde and $BF_3{\cdot}Et_2O$ in the same mixture of solvents, similar compounds were obtained through a tandem process that includes our previously reported aldol condensation of steroid sapogenins with benzaldehyde to produce 23*E*-benzylidenespirostanes[6g] followed by the described rearrangement.

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7. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary material number CCDC 1459086. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail:deposit@ccdc.cam.ac.uk.