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$BF_3{\cdot}Et_2O$-induced Beckmann rearrangement of 23-hydroxyiminosapogenins. A shortcut to bisnorcholanic lactones

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Abstract—Treatment of 23-hydroxyiminosapogenins with $BF_3{\cdot}Et_2O$ in acetic acid produced good yields of the corresponding bisnorcholanic lactones as the sole products.
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23,24-Bisnorcholanic acid 22→16 lactones or bisnorcholanic lactones (BNLs) have been isolated from natural sources.[1] In particular, vespertilin (**1**) has shown antipyretic and anticarcinogenic activities.[2] This class of compounds may be considered as useful starting materials in steroid partial synthesis (i.e., vespertilin (**1**) has been transformed into BNLs with weak plant growth promoting activity).[3] In addition, the presence of the lactone moiety adds potential utility to BNLs (see Fig. 1).

BNLs may be also obtained as by-products on different reactions of steroid sapogenins.[4] Several multi-step approaches to BNLs have been reported[5] but despite all the cumulated work, the low availability of BNLs in both the synthetic and the natural domains limits their applicability.

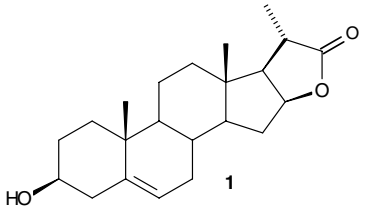

Figure 1.

We have recently found that treatment of 23-hydroxyiminodiosgenin acetate (**2**) with $POCl_3$ in pyridine produces a mixture of the nitriles **3** and **3b** together with a small amount of vespertilin acetate (**4**) due to an abnormal Beckmann rearrangement (Scheme 1).[6]

According to our proposal of mechanism,[6] nitrile **3a** arises from a nucleophilic attack (Nu = chloride anion) to C-16 from the α side, meanwhile **3b** is produced due to hydrolysis of oxonium **I**. Occurrence of vespertilin acetate (**4**) may be justified by both hydrolysis of the oxonium **I** and nucleophilic attack (Nu = chloride anion) to C-1′ (Scheme 1).

Examination of molecular models of **I** (Fig. 2) indicates that while the nucleophilic attack of chloride to the α side of C-16 should not be appreciably hindered due to its small anionic radius, similar approach of a bulky nucleophile (i.e., acetic acid) should be less probable, leaving the nucleophilic attack to C-1′, that leads to the BNLs, as the unique possibility of reaction (see Scheme 2).

With this analysis, we envisaged the $BF_3{\cdot}Et_2O$-induced Beckmann rearrangement of 23-hydroxyiminosapogenins in acetic acid as an alternative for the synthesis of BNLs.

Treatment of the oximes **2**[6] or **5** in glacial acetic acid with $BF_3{\cdot}Et_2O$ at room temperature for 48 h produced the corresponding BNLs as the sole product. No product of nucleophilic attack of acetic acid to C-16 was observed (Nu = acetic acid or acetate anion).

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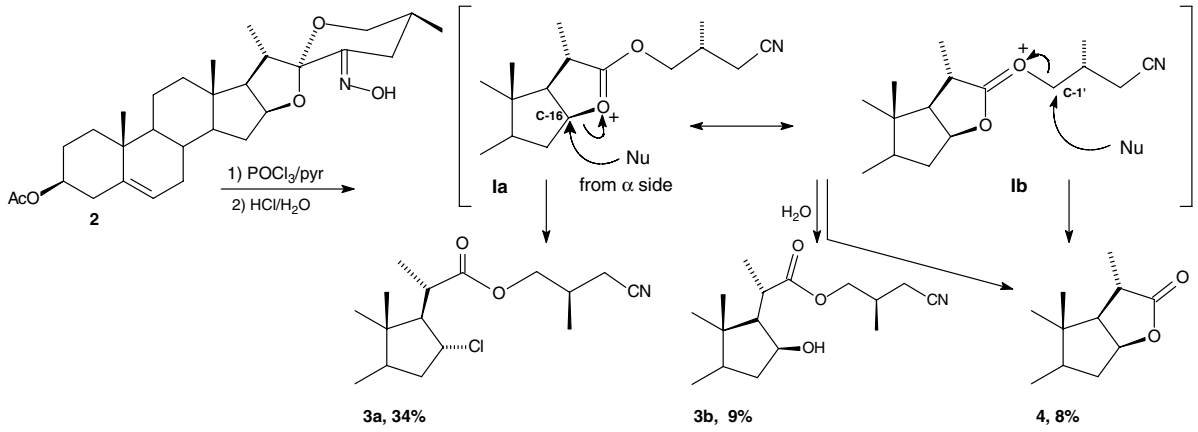


Scheme 1. $POCl_3$-induced Beckmann rearrangement of 23-hydroxyiminodiosgenin acetate (**2**).

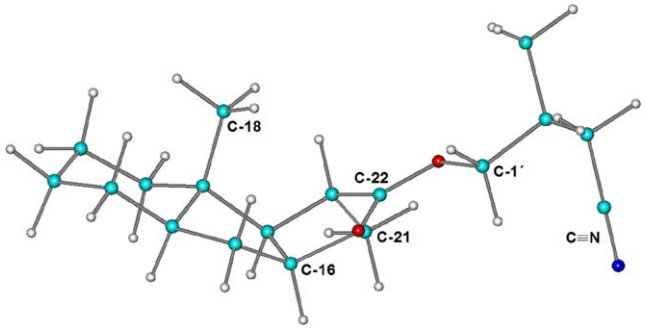


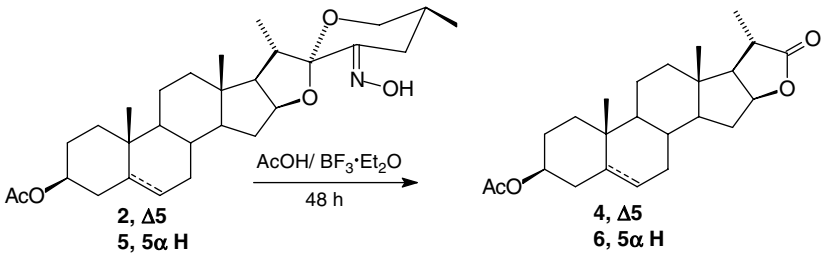
Figure 2. PM3 optimized geometry of oxonium **I**.[7]

23-Hydroxyiminotigogenin acetate (**5**). Mp 258–259 °C desc. (from ethyl acetate/hexane). ^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm 4.68 (m, 1H, H-3), 4.46 (dd, $J = 7.4$, 15.3 Hz, 1H, H-16), 3.61 (dd, 1H, $J = 11.1$, 11.1 Hz, H-26$_{ax.}$), 3.53 (dd, $J = 3.3$, 10.6 Hz, 1H, H-26$_{eq.}$), 3.32 (dd, $J = 2.1$, 13.8 Hz, H-24$_{eq.}$), 2.81 (dddd, $J = 6.8$, 6.8, 6.8, 6.8 Hz, 1H, H-20) 2.02 (s, 3H, CH_3 acetyl), 0.98 (d, $J = 6.9$ Hz, 3H, H-21), 0.90 (d, $J = 6.5$ Hz, 3H, H-27), 0.83 (s, 3H, H-19), 0.79 (s, 3H, H-18). ^{13}C NMR (100 MHz) δ ppm 36.67 C-1, 27.41 C-2, 73.67 C-3, 33.95 C-4, 44.59 C-5, 28.42 C-6, 32.12 C-7, 35.00 C-8, 54.17 C-9, 35.94 C-10, 20.36 C-11, 39.96 C-12, 40.91 C-13, 56.21 C-14, 31.81 C-15, 81.53 C-16, 61.21 C-17, 16.46 C-18, 12.22 C-19, 35.96 C-20, 14.38 C-21, 108.57 C-22, 154.68 C-23, 28.23 C-24, 31.54 C-25, 65.70 C-26, 16.97 C-27, 170.77 C=O acetyl, 21.43 CH_3 acetyl.

Typical procedure for the BF$_3$·Et$_2$O-induced Beckmann rearrangement of 23-hydroxyiminosapogenins: $BF_3{\cdot}Et_2O$ (0.5 ml) was added to a solution of the oxime (1 mmol) in glacial acetic acid (10 ml). The mixture was stirred for 48 h and diluted with saturated NaCl solution, the corresponding solid lactone was filtered and washed with water.

Vespertilin acetate (**4**). Yield 84%. Mp 225–228 °C (from ethyl acetate/hexane), lit.[1a] 218–219.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.35 (d, $J = 5.07$ Hz, 1H, H-6), 4.94 (dt, $J = 7.78$, 7.76, 4.66 Hz, 1H, H-16), 4.58 (ddt, $J = 10.38$, 10.38, 6.29, 4.19 Hz, 1H, H-3), 2.62–2.52 (m, 1H, H-20), 2.02 (s, 3H, CH_3 acetyl), 1.30 (d, $J = 7.63$ Hz, 3H, CH_3-21), 1.02 (s, 3H, CH_3-19), 0.75 (s, 3H, CH_3-18). ^{13}C NMR (100 MHz) δ ppm 36.77 C-1, 27.61 C-2, 73.66 C-3, 37.95 C-4, 139.73 C-5, 121.87 C-6, 31.80 C-7, 31.12 C-8, 49.90 C-9, 36.59 C-10, 20.22 C-11, 38.06 C-12, 41.37 C-13, 54.64 C-14, 33.02 C-15, 82.67 C-16, 58.82 C-17, 13.65 C-18, 19.26 C-19, 35.97 C-20, 17.95 C-21, 181.32 C-22, 170.53 C=O acetyl, 21.38 CH_3 acetyl.

5α-Dihydrovespertilin acetate (**6**). Yield 77.3%. Mp 224–225 °C (from ethyl acetate/hexane), lit.[1a] 222–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.92 (dt, $J = 7.77$, 7.76, 4.63 Hz, 1H, H-16), 4.71–4.61 (m, 1H, H-3), 2.56 (q, $J = 7.67$, 7.58, 7.58 Hz, 1H, H-20), 2.24 (q, $J = 7.77$, 7.76, 7.58 Hz, 1H), 2.00 (s, 3H CH_3 acetyl), 1.29 (d, $J = 7.58$ Hz, 3H, CH_3-21), 0.82 (s, 3H, CH_3-19), 0.72 (s, 3H, CH_3-18). ^{13}C NMR (100 MHz) δ ppm 36.62 C-1, 27.32 C-2, 73.45 C-3, 33.83 C-4, 44.52 C-5, 28.22

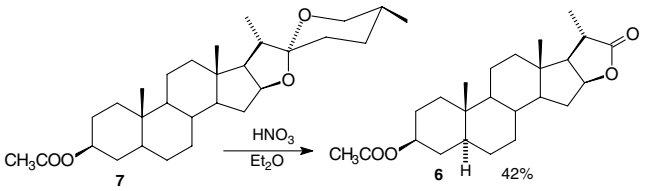


Scheme 2. Synthesis of BNLs by $BF_3{\cdot}Et_2O$-induced Beckmann rearrangement of 23-hydroxyimnosapogenins.

C-6, 31.99 C-7, 34.77 C-8, 54.16 C-9, 35.50 C-10, 20.42 C-11, 38.21 C-12, 41.66 C-13, 54.44 C-14, 32.92 C-15, 82.72 C-16, 58.96 C-17, 13.81 C-18, 12.17 C-19, 36.03 C-20, 17.93 C-21, 181.34 C-22, 170.67 C=O acetyl, 21.41 CH_3 acetyl.

In summary, we have been able to find a different course for our previously reported abnormal Beckmann rearrangement of 23-hydroxyiminosapogenins. In the described conditions the BNLs become the sole reaction product.

Vespertilin acetate (**4**) and 5α-dihydrovespertilin acetate (**6**) were previously prepared by Sato from the corresponding spirosolanes following lengthy protocols.[5a–c] Alternatively, the previously described treatment of tigogenin acetate (**7**) with fuming HNO_3 to produce 5α-dihydrovespertilin acetate (**6**) in low yield (Eq. 1) is not applicable to the synthesis of vespertilin acetate (**4**) from diosgenin acetate (**8**) due to the reactivity of the C5–C6 double bond that leads to the introduction of a nitro group at C-6 (Eq. 2).[4e]



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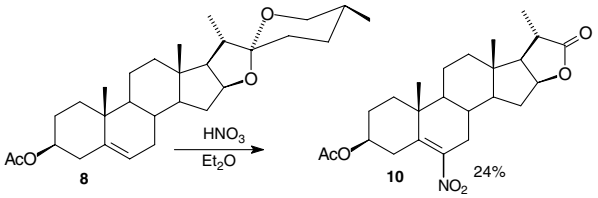
(1)



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(2)

The herein described method constitutes an useful alternative for the synthesis of vespertilin acetate (**2**) and other bisnorcholanic lactones.

Acknowledgments

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