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Unexpected fragmentation of 16β-acetoxy-22-oxocholestanes on the action of methylenetriphenylphosphorane

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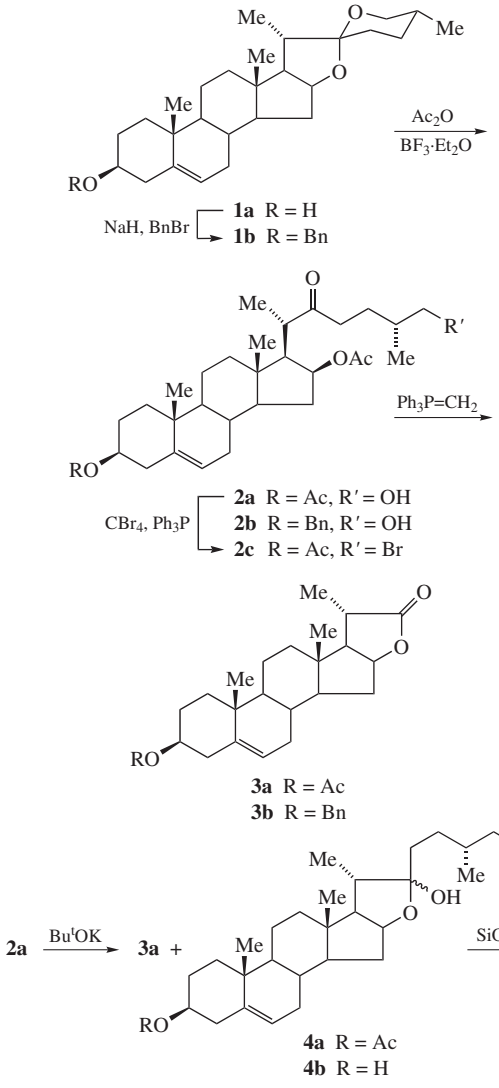
Treatment of 16β-acetoxy-22-oxocholestanes with methylenetriphenylphosphorane results in the cleavage of C^{22}–C^{23} bond and formation of bisnorcholanic (22→16)-lactones. The analogous fragmentation also partially proceeds on Bu^{t}OK action.

Methylenetriphenylphosphorane (CH_2=PPh_3) has wide synthetic application for methylenation of ketones, aldehydes, esters, *etc*.[1,2] Olefination reactions usually proceed successfully under mild conditions and in good yields, nevertheless, some difficulties may be encountered in the case of enolisable and sterically hindered ketones.[3,4] Moreover, numerous 'deviations' from the normal reaction course with the formation of abnormal products are known for CH_2=PPh_3.[5,6]

During the development of synthesis of anticancer steroid saponin OSW-1[7] structural analogues from diosgenin **1a**, we have discovered the unexpected side-chain fragmentation of cholestanic 22-ketones **2a–c** (Scheme 1).† The latter were derived from diosgenin **1a** (for the synthesis[8] see Online Supplementary Materials).

When attempting olefination of ketones **2a–c** with CH_2=PPh_3 under standard conditions the formation of bisnorcholanic lactones **3a**,**b** as the single products was observed as a result of cleavage of the (C^{23}–C^{27}) side chain fragment and loss of the 16-acetyl group. Formation of lactone **3a** (vespertilin acetate) with other side-chain fragmentation of diosgenin derivatives has already been reported.[9,10]

Taking into account the necessity to generate the enolate in the start of the fragmentation, we treated **2a** with Bu^{t}OK. As a result, the same fragmentation was also observed with formation of lactone **3a** (10%). Competitive process was deacetylation of hindered 16-OAc group primarily by 16→22 migration and then



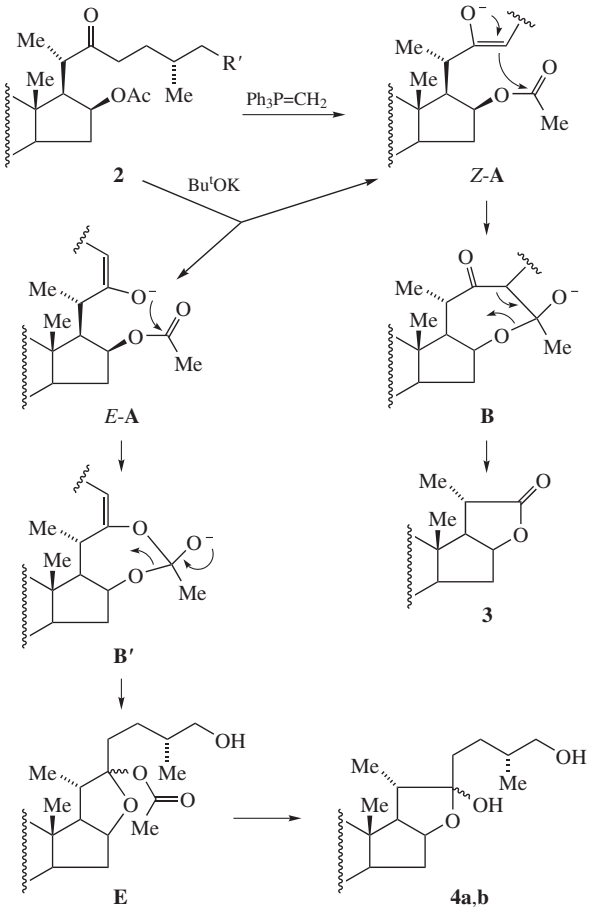
Scheme 1

† *3β-Benzyloxy-16β-hydroxydinorchol-5-enoic acid (22→16)-lactone* **3b**. The 1.0 M solution of BuLi in hexane (0.32 ml, 0.32 mmol) was added dropwise at –50 to –40 °C under argon to a suspension of methyltriphenylphosphonium iodide (130 mg, 0.32 mmol) in anhydrous THF (10 ml) and the mixture was stirred for 1 h at the same temperature. Then a solution of ketone **2b** (60 mg, 0.106 mmol) in THF (5 ml) was added. The mixture was allowed to warm to room temperature and stirred for 2 h, then quenched with saturated NH_4Cl solution. THF was removed from the mixture *in vacuo* before the aqueous layer was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel chromatography using EtOAc–light petroleum (1:9) as the eluent to obtain lactone **3b** (25 mg, 56%), mp 232–233 °C, $[\alpha]_D^{20}$ –18 (*c* 1.00, $CHCl_3$), R_f (EtOAc–light petroleum, 3:7) 0.38. IR (Nujol, ν_{max}/cm^{-1}): 2930, 1763, 1462, 1456, 1377, 1366, 1307, 1239, 1188, 1180, 1113, 1102, 1075, 1035, 737. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.78 (s, 3H, Me), 1.04 (s, 3H, Me), 1.33 (d, 3H, Me, *J* 7.5 Hz), 1.57 (s, 3H, Me), 2.28 (m, 2H, C^{15}H), 2.41–2.47 (m, 1H, CH), 2.59 (q, 1H, C^{20}H, *J* 7.7 Hz), 3.28 (m, 1H, C^3H), 4.57 (s, 2H, OCH_2), 4.96 (dt, 1H, C^{16}H, *J* 4.7 and 7.7 Hz), 5.35 (d, 1H, C^6H, *J* 5.2 Hz), 7.34 (m, 5H, Ph). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ: 13.73 (Me), 18.02 (Me), 19.39 (Me), 20.34 (C^{11}), 28.36 (C^2), 31.24 (C^8), 31.92 (C^7), 33.10 (C^{15}), 36.01 (C^{20}), 36.98 (C^{10}), 37.19 (C^{12}), 38.22 (C^4), 39.06 (C^1), 41.46 (C^{13}), 50.16 (C^9), 54.83 (C^{14}), 58.94 (C^{17}), 69.92 (OCH_2), 78.34 (C^3), 82.70 (C^{16}), 120.87 (C^6), 127.42, 127.55, 128.35 and 138.97 (Ph), 141.09 (C^5), 181.32 (C=O). MS (EI), *m*/*z* (%): 434 (0.03, M^+), 377 (1), 330 (3), 328 (100 [MH – $OCH_2Ph]^+$), 311 (30), 287 (22), 269 (8), 255 (6), 145 (13), 121 (14), 91 (36), 79 (8).

removal to form lactol **4a** (10%) and its 3-deacetylated analogue **4b** (50%). The latter was unstable on silica gel, converting into diosgenin **1a**.

Most likely, the unexpected reaction of ketones **2** is due to two features of their structure – the well known sterically hindered nature of 22-carbonyl group and its proximity to 16β-acetoxyl group. As a result, the bulky phosphorane reagent is hardly able to form a Wittig intermediate and provides instead an easier reaction – enolization of 22-keto group, because CH_2=PPh_3 also possesses the base properties (Scheme 2). Generated enolate *Z*-**A** attacks closely located carbonyl group of C^{16}-acetoxyl and the resulting intermediate **B** fragmentizes to lactones **3** by retro-Claisen mechanism. The distinction of Bu^{t}OK (from CH_2=PPh_3 as the base) is that it is much more basic. Weak base (CH_2=PPh_3) enolizes under thermodynamic conditions, producing a more stable enolate *Z*-**A**, whereas strong base (Bu^{t}OK) enolizes under kinetic conditions, leading to less stable enolate *E*-**A**. Nucleophilic attack of 16-OAc group in enolate *E*-**A** is sterically hindered for the anionic C^{23} center and is more preferable for anionic O^{22} center. Therefore, for Bu^{t}OK catalyzed reaction the main route is through intermediates **B′** and **E** followed by the migration and removal of acetyl group to form products **4**.

In general, we have discovered a new fragmentation of 16β-acetoxy-22-oxocholestanes with formation of bisnorcholanic (22→16)-lactones, which proceeds under the action of methylenetriphenylphosphorane reacting as a base.



Scheme 2

3β-Acetoxy-16β-hydroxydinorchol-5-enoic acid (22→16)-lactone **3a**. *Method A.* Similarly, reaction of ketone **2a** (108 mg, 0.209 mmol) with CH_2=PPh_3 (0.836 mmol) produced lactone **3a**, yield 43 mg (60%), mp 216–217 °C, $[\alpha]_D^{20}$ –106 (*c* 1.0, $CHCl_3$) [lit.,[11] mp 212–215 °C, $[\alpha]_D^{20}$ –90 ($CHCl_3$); lit.,[10] mp 225–228 °C], R_f (EtOAc–light petroleum, 3:7) 0.30. IR (Nujol, ν_{max}/cm^{-1}): 2925, 2854, 1748, 1723, 1463, 1377, 1308, 1246, 1193, 1030, 963. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 3H, Me), 1.04 (s, 3H, Me), 1.32 (d, 3H, C^{21}H, *J* 7.7 Hz), 2.04 (s, 3H, MeCO), 2.26 (m, 1H, C^{15}H), 2.34 (m, 2H, CH), 2.59 (dq, 1H, C^{20}H, *J* 7.7 and 0.9 Hz), 4.56–4.64 (m, 1H, C^3H), 4.96 (td, 1H, C^{16}H, *J* 4.6 and 7.7 Hz), 5.38 (d, 1H, C^6H, *J* 5.0 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 13.73 (Me), 18.02 (Me), 19.33 (Me), 20.30 (C^{11}), 21.43 (*Me*CO), 27.69 (C^2), 31.21 (C^8), 31.88 (C^7), 33.11 (C^{15}), 36.05 (C^{20}), 36.68 (C^{10}), 36.96 (C^1), 38.03 (C^4), 38.15 (C^{12}), 41.47 (C^{13}), 50.01 (C^9), 54.75 (C^{14}), 58.94 (C^{17}), 73.74 (C^3), 82.72 (C^{16}), 121.94 (C^6), 139.83 (C^5), 170.59 (Me*C*O), 181.32 (C=O). MS (EI), *m*/*z* (%): 326 (100, [M–AcOH]$^+$), 311 (24), 255 (4), 237 (3), 145 (12), 121 (13), 107 (14), 91 (7), 43 (6). *Method B.* Analogously, ketone **2c** (140 mg, 0.24 mmol) and CH_2=PPh_3 (0.72 mmol) provided lactone **3a** in 40% yield at 71% conversion.

Reaction of ketone **2a** *with Bu^{t}OK*. Potassium *tert*-butoxide (43 mg, 0.38 mmol) was added to a stirred solution of the ketone **2a** (100 mg, 0.19 mmol) in anhydrous THF (6 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then quenched with saturated NH_4Cl solution. Further treatment as above afforded the mixture which according to TLC contained one major product as the most polar spot and several minor ones. This major product was identified as most probably an unstable triol **4b** because it completely converted into diosgenin **1a** (yield 50%) in the course of column chromatography on silica gel. Lactone **3a** (10%), lactol **4a** (10%) and traces of vespertilin (4%) were also isolated by chromatography.

*(25*R*)-3β-Acetoxyfurost-5-ene-22,26-diol* **4a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.85 (s, 3H, Me), 0.88 (d, 3H, Me, *J* 7.0 Hz), 1.02 (d, 3H, Me, *J* 7.0 Hz), 1.07 (s, 3H, Me), 1.98 (s, 3H, MeCO), 3.35–3.42 (m, 1H, C^{26}H), 3.50 (br. s, 1H, OH), 4.48 (m, 1H, C^3H), 4.55 (m, 1H, C^{16}H), 5.38 (d, 1H, C^6H, *J* 4.9 Hz). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ: 16.19 (Me), 16.73 (Me), 17.24 (Me), 19.64 (Me), 21.20 (Me), 21.54 (C^{11}), 28.22 (C^{24}), 28.49 (C^2), 32.26 (C^8), 32.70 (C^7), 32.76 (C^{15}), 37.08 (C^{25}), 37.28 (C^1), 37.49 (C^{10}), 37.80 (C^4), 38.88 (C^{12}), 40.47 (C^{23}), 40.48 (C^{13}), 41.32 (C^{20}), 51.02 (C^9), 57.16 (C^{14}), 64.10 (C^{17}), 67.87 (C^{26}), 74.23 (C^3), 81.27 (C^{16}), 110.83 (C^{22}), 122.96 (C^6), 140.78 (C^5), 170.37 (Me*C*O).

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Online Supplementary Materials

Supplementary data associated with this article (syntheses and characteristics for the starting compounds **1b** and **2a–c**) can be found in the online version at doi:10.1016/j.mencom.2014.09.008.

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