

SHORT
COMMUNICATIONS

Synthesis of 7,8-Dihydro Analogs by Reaction of 20-Hydroxyecdysone Derivatives with Lithium Aluminum Hydride

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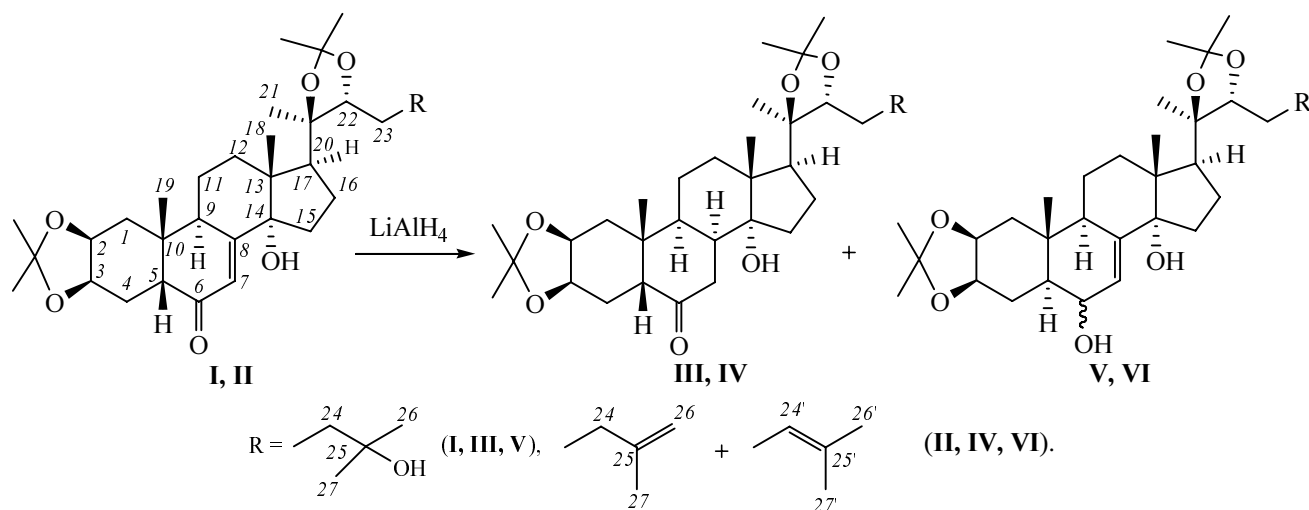
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We reported formerly on a hydride reduction of the 6-keto group in 20-hydroxyecdysone derivatives leading to the formation of the corresponding 6 α - and 6 β -epimeric alcohols of the 5 α -series [1]. We established in this study that the reaction of 20-hydroxyecdysone diacetonide (**I**) and its 24,25/25,26-anhydro derivatives **II** (a mixture of Δ^{24}/Δ^{25} -alkenes, ~3:2) with LiAlH₄ gave rise to the corresponding 7,8-dihydro analogs **III** and **IV** (alongside with 6-hydroxy derivatives **V** and **VI** respectively).

In the ¹³C NMR spectra of saturated ketones **III** and **IV** the changes observed compared with the spectra of initial conjugated enones **I** and **II** are due to the reduction of the Δ^7 -bond. The difference consists in the disappearance of the signals from the *sp*²-hybridized carbons in the region ~120 and 165 ppm and the appearance of the peaks from atoms C⁷ and C⁸ further upfield (δ ~41 and ~44 ppm respectively). The lack of the Δ^7 -bond caused a considerable downfield shift ($\Delta\delta$ ~9 ppm) of



the signal of the C⁶ atom in the spectra of ketones **III** and **IV**.

Although the poor solubility of the 20-hydroxyecdysone decreased its conversion (less than 20%), its reaction with LiAlH₄ in ethers (THF, Et₂O) led to the formation

of the corresponding dihydro analog whose ¹H and ¹³C NMR were identical to those of 7,8 α -dihydro-20-hydroxyecdysone [2]. Thus the reduction of the Δ^7 -bond with LiAlH₄ does not cause epimerization at the C⁵, and the hydrogen at the newly arising chiral center C⁸ has

the α -orientation. Consequently, the dihydro derivatives **III** and **IV** obtained are 7,8 α -dihydro-20-hydroxyecdysone and 7,8 α -dihydro-24,25/25,26-anhydro-20-hydroxyecdysone diacetonides respectively.

(20R,22R)-2 β ,3 β :20,22-Bis[(dimethylmethylene)-dioxy]-14 α ,25-dihydroxy-5 β ,8 α -cholestan-6-one (7,8 α -dihydro-20-hydroxyecdysone 2,3:20,22-diacetonide) (III). To a stirred suspension of 0.27 g (7.1 mmol) of LiAlH₄ in 25 ml of Et₂O was added under an argon atmosphere at ~25°C a solution of 0.82 g (1.46 mmol) of diacetonide **I** [3] in 25 ml of anhydrous Et₂O. The mixture was stirred for 20 min at room temperature and 30 min at 36°C. Then the reaction mixture was cooled to 0°C, 3 ml of H₂O and ~2 ml of 5% HCl was added (till weakly acidic reaction). The organic layer was separated, the water layer was extracted with Et₂O (3 \times 20 ml). The combined ether solutions were evaporated in a vacuum, and the residue was subjected to column chromatography (5 g of SiO₂, eluent CHCl₃). A fraction of formerly described [1] alcohols **V** was isolated, 0.59 g (72%), *R_f* 0.30, CHCl₃–MeOH, 10:1, and 0.2 g (24%) of compound **III** (*R_f* 0.69, CHCl₃–MeOH, 10:1), mp 275–277°C, $[\alpha]_D^{19} +14.2^\circ$ (*c* 11.97, CHCl₃). IR spectrum, ν , cm⁻¹: 1700 (C=O). ¹H NMR spectrum, δ , ppm: 1.10 s (3H, H₃C²¹), 1.19 s (9H, H₃C¹⁸, H₃C²⁶, H₃C²⁷), 1.35 s (3H, H₃C¹⁹), 1.26 s, 1.27 s, 1.38 s and 1.47 s (12H, Me₂C), 1.54–2.09 m (17H, CH, CH₂), 2.16 m (1H, HC^{7 α}), 2.29 m (1H, HC¹⁷), 2.33 d.t (1H, HC⁸, *J*_{8–9} 13.5, *J*_{8–7 α} 4.0 Hz), 2.55 br.s (1H, HC⁵, *w*_{1/2} 8.9 Hz), 2.68 t (1H, HC^{7 β} , *J* 13.4 Hz), 3.62 m (1H, HC²², *w*_{1/2} 13.0 Hz), 4.17 m (1H, HC³, *w*_{1/2} 12 Hz), 4.45 m (1H, HC², *w*_{1/2} 13.5 Hz). ¹³C NMR spectrum, δ , ppm: 18.1 t (C¹¹), 18.4 q (C¹⁸), 21.0 t (C¹⁶), 21.3 q (C²¹), 23.5 t (C²³), 25.3 t (C⁴), 26.7 q (C¹⁹), 25.8 q and 28.9 q (2,3-Me₂CO₂), 26.7 q and 29.6 q (20,22-Me₂CO₂), 28.4 q (C²⁶), 29.0 q (C²⁷), 31.3 t (C¹⁵), 33.1 t (C¹²), 34.2 t (C¹), 39.5 s (C¹⁰), 41.3 t (C²⁴), 41.3 t (C⁷), 41.5 d (C⁹), 43.7 d (C⁸), 46.8 s (C¹³), 49.7 d (C¹⁷), 50.5 d (C⁵), 70.2 s (C²⁵), 70.8 d (C³), 73.5 d (C²), 81.8 d (C²²), 84.4 s (C²⁰), 84.9 s (C¹⁴), 106.8 s (20,22-Me₂CO₂), 107.6 s (2,3-Me₂CO₂), 212.1 s (C⁶).

A mixture of (20R,22R)-2 β ,3 β :20,22-bis[(dimethylmethylene)dioxy]-14 α -hydroxy-5 β ,8 α -cholest-24/25-en-6-ones (a mixture of 24,25/25,26-anhydro-7,8 α -dihydro-20-hydroxyecdysones 2,3:20,22-diacetonides) (IV). To a stirred suspension of 0.46 g (12.1 mmol) of LiAlH₄ in 10 ml of anhydrous THF was added under an argon atmosphere at ~0°C a solution of 1.3 g (2.41 mmol) of alkenes **II** [4, 5] in 5 ml of THF. The reaction mixture was stirred for 3 h at room

temperature, then cooled to 0°C, 5 ml of H₂O and ~13 ml of 5% HCl was added (till weakly acidic reaction). The organic layer was separated, the water layer was extracted with EtOAc (3 \times 50 ml). The combined organic solutions were evaporated in a vacuum, and the residue was subjected to column chromatography (20 g of SiO₂, eluent CHCl₃). A fraction of formerly described [1] alcohols **VI** was isolated, 0.71 g (54%), *R_f* 0.4, CHCl₃–MeOH, 20:1, and 0.33 g (25%) of compound **IV** (*R_f* 0.5, CHCl₃–MeOH, 20:1), mp 190–192°C, $[\alpha]_D^{19} +16.1^\circ$ (*c* 8.83, CHCl₃). IR spectrum, ν , cm⁻¹: 1695 (C=O). ¹H NMR spectrum, δ , ppm: 0.93 s (3H, H₃C¹⁹), 1.11 s (3H, H₃C¹⁸), 1.14 s (3H, H₃C²¹), 1.28 s, 1.38 s, 1.40 s and 1.50 s (12H, 2Me₂C), 1.56–2.20 m (~14.3H, CH, CH₂), 1.62 s (~2.7H, H₃C²⁶), 1.70 s and 1.72 s (~3H, H₃C²⁷ and H₃C²⁷), 2.22 m (1H, HC^{7 α}), 2.30 m (1H, HC¹⁷), 2.37 m (1H, HC⁸), 2.57 br.s (1H, HC⁵, *w*_{1/2} 10.7 Hz), 2.70 t (1H, HC^{7 β} , *J* 13.4 Hz), 3.65–3.71 m (1H, HC²² and HC²²), 4.20 m (1H, HC³, *w*_{1/2} 13.0 Hz), 4.49 m (1H, HC², *w*_{1/2} 22.6 Hz), 4.69 br.s and 4.72 br.s (1.3H, H₂C²⁶, for both *w*_{1/2} 6.8 Hz), 5.17 t (0.7H, H₃C²⁴, *J* 6.2 Hz). ¹³C NMR spectrum, δ , ppm: 17.9 q (C¹⁸), 18.2 t (C¹¹), 18.6 q (C²⁷), 21.1 t (C¹⁶), 21.4 q (C²¹, C²¹), 22.5 q (C²⁷), 25.4 t (C²³), 25.7 q (C¹⁹), 25.9 q (C²⁶), 26.0 q and 28.5 q (2,3-Me₂C), 26.8 q and 29.6 q (20,22-Me₂C), 27.7 t (C⁴), 31.5 t (C¹⁵), 33.3 t (C¹²), 34.4 t (C²⁴), 35.0 t (C¹), 39.6 s (C¹⁰), 41.3 t (C⁷), 41.6 d and 41.7 d (C⁹), 43.8 d and 43.9 d (C⁸), 46.9 s (C¹³), 50.0 d (C¹⁷), 50.1 d (C¹⁷), 50.6 d (C⁵), 70.9 d (C³), 73.5 d (C²), 80.6 d (C²²), 81.0 d (C²²), 84.1 s (C²⁰), 84.98 s and 85.04 s (C¹⁴), 106.7 s and 106.8 s (20,22-Me₂CO₂), 107.6 s (2,3-Me₂CO₂), 110.0 t (C²⁶), 120.4 d (C²⁴), 133.5 q (C²⁵), 145.3 s (C²⁵), 211.9 s (C⁶).

IR spectra were recorded on a spectrophotometer Specord 75IR from mulls in mineral oil. ¹H and ¹³C NMR spectra were registered on a spectrometer Bruker AM-300 (at operating frequencies 300.13 and 75 MHz respectively) from solutions in CDCl₃. Chemical shifts are reported relative to TMS used as an internal reference. Melting points were measured on a small Boëtius heating block. The specific rotation was measured on a Perkin-Elmer 141 polarimeter. TLC monitoring was performed on Silufol plates, development with a vanillin solution in ethanol acidified with sulfuric acid.

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