SYNTHESIS OF 4,5-SECO-DERIVATIVES OF ALLOBETULIN

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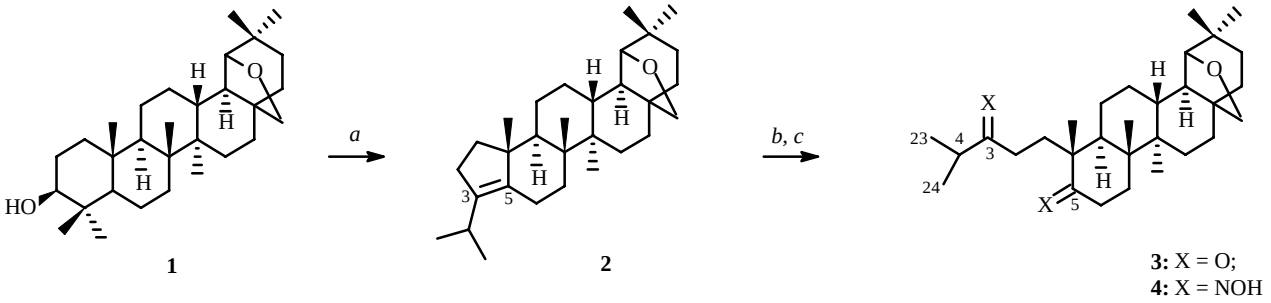
4,5-Seco-19β,28-epoxy-18α-olean-3,5-dione was prepared by ozonation of 19β,28-epoxy-18α-olean-3(5)-ene. The structures of the synthesized compounds were confirmed using spectral data.

Key words: oleanane triterpenoids, seco-derivatives, ozonolysis.

Allobetulin is a pentacyclic oleanane triterpenoid found among triterpene compounds of birch bark. It is easily formed from betulin via acid-catalyzed isomerization. It has been found that allobetulin possesses moderate inhibitory activity for type B flu virus [1] and that 28-oxoallobetulone is an effective inhibitor of type A flu virus multiplication [2]. The *nor*-derivative of allobetulin is an antifeedant for *Heliothis zea* larvae [3]. Derivatives of allobetulin are used as biomarkers [4]. 3,4-Seco-derivatives of allobetulin possess antibacterial activity [5]. Furthermore, highly active inhibitors of nitric oxide production in murine macrophages were found among oleanane triterpenoids with a modified ring A [6-8]. 19β,28-Epoxy-18α-oleanane 1,2-seco-lactone was synthesized by oxidation of 3-keto-allobetulin with CrO_3 in AcOH [9]. 3,4-Seco-derivatives of allobetulin can be prepared by decomposing lactones, Baeyer—Villager oxidation products of triterpene 3-ketones [10, 11]. Nevertheless, the synthesis of 4,5-seco-oleanane triterpenoids has not been reported.

In order to synthesize 4,5-seco-derivatives of allobetulin, we developed a scheme based on ozonolytic cleavage of the *endo*-cyclic $\Delta^{3,5}$-bond of 19β,28-epoxy-18α-olean-3(5)-ene (**2**), which, in turn, was prepared from allobetulin (**1**) by Wagner—Meerwein rearrangement in the presence of PCl_5 in a benzene:toluene mixture at room temperature in 80% yield. The structures of the prepared compounds were established using NMR spectroscopy. Thus, the ^{13}C NMR spectrum of **2** contains signals for C-3 and C-5 (δ 139.8 and 136.1 ppm); the PMR spectrum, a signal for H-4 at δ 2.65 ppm as a septet (J = 6.8 Hz).



a. PCl_5, benzene:toluene, 20°C; *b*. O_3, –60 °C, Zn/AcOH; *c*. $NH_2OH \cdot HCl$, pyridine

Ozonation of **2** in CH_2Cl_2 at -60°C gave 4,5-seco-19β,28-epoxy-18α-olean-3,5-dione (**3**). The yield after chromatographic purification was 56%. The ^{13}C NMR spectrum contains signals for the C-3 and C-5 ketones (δ 214.4 and 217.0 ppm); the PMR spectrum, a signal for H-4 as a septet at δ 2.55 ppm. Signals for the C-23 and C-24 methyls resonate at δ ~1.00 ppm as characteristic doublets. The structure of the 4,5-seco-fragment was confirmed by data for 4,5-seco-19β,28-epoxy-18α-olean-3,5-dioxime (**4**), prepared by reaction of triterpene 3,5-diketone **3** with hydroxylamine. Thus, the ^{13}C NMR

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spectrum of **4** has signals for C-3 and C-5 shifted to strong field compared with those of diketone **3** (δ 167.5 and 167.9 ppm). The signal for H-4 in the PMR spectrum remained as a septet. Signals for H-2 and H-6 were observed at 2.10-2.45 ppm.

Thus, we prepared for the first time 4,5-seco-derivatives of allobetulin that are interesting as potential biologically active compounds.

EXPERIMENTAL

IR spectra were recorded on Specord M80 spectrometers for samples as mulls in mineral oil. PMR and ^{13}C NMR spectra were recorded on an AM-300 spectrometer (Bruker, 300 and 75.5 MHz, respectively) in $CDCl_3$ with TMS internal standard. Melting points were determined on a Boetius microstage. Optical density was measured on a 241 MC polarimeter (Perkin—Elmer) in a 1-dm tube. TLC was performed on Silufol plates (Chemapol, Czech. Rep.) using $CHCl_3$:CH_3OH (25:1). Compounds were developed with phosphotungstic acid in ethanol (20%) with subsequent heating at 100-120°C for 2-3 min. Allobetulin (**1**) was prepared as before [12].

Elemental analyses of all compounds agreed with those calculated.

19β,28-Epoxy-18α-olean-3(5)-ene (2). A solution of **1** (1 mmol, 0.44 g) in anhydrous benzene:toluene (100 mL, 1:1) at 20°C was treated in one portion with PCl_5 (5.5 mmol, 0.50 g), stirred for 30 min (TLC monitoring), diluted with saturated aqueous Na_2CO_3 (30 mL), stirred for another 30 min, and brought to room temperature. The organic layer was separated, washed with water (3 × 20 mL), dried over Na_2SO_4, and evaporated in vacuum. The solid was crystallized from ethanol. Yellow compound, $C_{30}H_{48}O$, yield 0.34 g (80%), R_f 0.85, mp 199-201°C, $[\alpha]_D^{20}$ +82° (*c* 1.0, $CHCl_3$), lit. mp [13] 200-201°C, $[\alpha]_D^{22}$ +81° (*c* 1.23). IR spectrum (ν, cm^{-1}): 1760, 1620, 1530, 1460, 1360, 1310, 1280, 1240, 1160, 1040, 910, 790, 720.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.79, 0.85, 0.86, 0.92, 0.98, 1.00, 1.03 (7s, 21H, $7CH_3$), 1.10-2.30 (m, 23H, CH_2, CH), 2.65 (1H, septet, H-4, J = 6.8), 3.42 and 3.80 (both d, 1H each, H-28, J = 7.8), 3.54 (s, 1H, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.4, 14.2, 19.0, 19.7, 21.3, 21.8, 23.6, 24.5, 26.2, 26.3, 26.5, 26.7, 27.3, 28.7, 32.4, 32.6, 34.5, 36.2, 36.7, 40.6, 40.8, 41.4, 42.1, 46.7, 49.8, 50.0, 71.2 (C28), 87.9 (C19), 136.1 (C4), 139.8 (C3).

4,5-Seco-19β,28-epoxy-18α-olean-3,5-dione (3). Ozone was passed through a solution of **2** (2 mmol, 0.85 g) in CH_2Cl_2 (50 mL) at -60°C until the starting material disappeared (TLC monitoring). The temperature was raised to 0°C. Glacial AcOH (10 mL) and zinc dust (1 g) were added. The mixture was stirred for 1 h and filtered. The organic layer was washed with saturated Na_2CO_3 solution (2 × 20 mL) and water (2 × 20 mL), dried over Na_2SO_4, and evaporated in vacuum. The solid was purified by column chromatography over Al_2O_3 with elution by benzene. Yellow compound, $C_{30}H_{48}O_3$, yield 0.51 g (56%), R_f 0.40, mp 238-239°C, $[\alpha]_D^{20}$ +39° (*c* 1.00, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1720, 1470, 1380, 1160, 1120, 1070, 1040, 1020, 980, 950, 900, 870, 850, 780, 730.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.75, 0.87, 0.88, 0.94, 0.97 (15H, 5s, $5CH_3$), 1.01 and 1.02 (3H each, both d, CH_3-23, J = 1.5, CH_3-24, J = 1.4), 1.10-1.90 (19H, m, CH_2, CH), 2.02-2.08 (2H, m, H-2), 2.31-2.39 (2H, m, H-6), 2.55 (1H, septet, H-4, J = 6.7), 3.40 and 3.78 (1H each, both d, H-28, J = 7.8), 3.54 (1H, s, H-19).

^{13}C NMR spectrum (δ, ppm): 13.3, 15.5, 18.1, 18.3, 20.3, 23.0, 24.4, 25.9, 26.8, 28.6, 30.0, 32.5, 33.4, 34.3, 35.0, 35.6, 36.2, 36.5, 38.9, 40.5, 40.8, 41.3, 4.15, 44.7, 46.4, 49.6, 71.0 (C-28), 87.7 (C-19), 214.4 and 217.0 (C-3, C-5).

4,5-Seco-19β,28-epoxy-18α-olean-3,5-dioxime (4). A solution of **3** (1 mmol, 0.46 g) in anhydrous pyridine (20 mL) was treated with $NH_2OH \cdot HCl$ (1 g), boiled for 2 h, and poured into HCl (50 mL, 5%). The precipitate was filtered off, washed with water, and dried. Yellow compound, $C_{30}H_{50}N_2O_3$, yield 0.37 g (80%), R_f 0.30, mp 143-145°C, $[\alpha]_D^{20}$ +89° (*c* 1.00, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1710, 1670, 1600, 1460, 1390, 1320, 1300, 1280, 1260, 1170, 1150, 1110, 1040, 940, 720.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.79, 0.87, 0.90, 0.94, 0.99 (15H, 5s, $5CH_3$), 1.13 (6H, s, CH_3-23, CH_3-24), 1.00-1.90 (19H, m, CH_2, CH), 2.10-2.18 (2H, m, H-2), 2.35-2.45 (2H, m, H-6), 2.62 (1H, septet, H-4, J = 6.7), 3.41 and 3.80 (1H each, both d, H-28, J = 7.8), 3.54 (1H, s, H-19), 9.20 (2H, m, 2NO<u>H</u>).

^{13}C NMR spectrum (δ, ppm): 13.3, 14.8, 15.1, 15.6, 19.3, 19.9, 20.1, 23.7, 24.5, 26.0, 26.2, 26.3, 26.8, 28.7, 32.6, 33.7, 34.6, 36.2, 36.6, 37.3, 39.4, 40.5, 41.5, 42.5, 42.7, 46.6, 71.2 (C-28), 87.8 (C-19), 164.6 and 165.8 (C-5, C-3).

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