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SYNTHESIS OF KETALS OF METHYL 3-OXO-LUP-20(29)-EN-28-OATE

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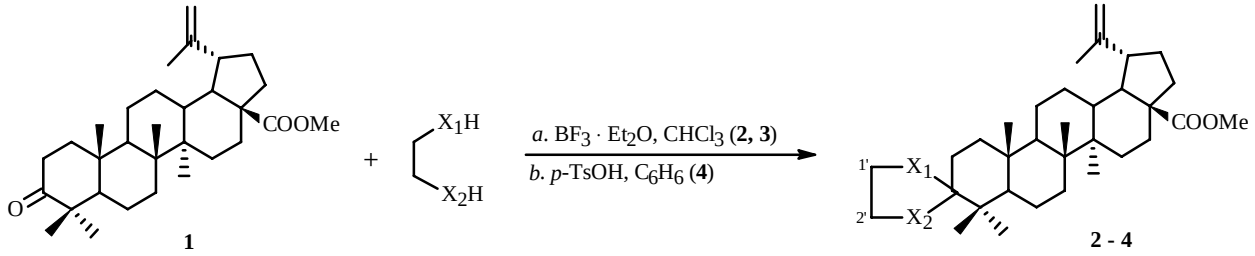
Ketals were synthesized by reacting methylbetulonate and ethylenediol.

Key words: methylbetulonate, ketals.

The high and varied biological activities (anti-inflammatory, antitumor, antimalarial, antiviral, etc.) of lupane triterpenoids (betulin, lupeol, betulinic acid) stimulate interest in the synthetic transformations of functional groups in order to prepare new modified analogs with properties valuable in medicine [1-3]. It has been shown that lupane triterpenoids modified on ring A exhibit antibacterial [4], anti-inflammatory, anti-ulcer [5], and hepatoprotective activities [6].

In continuation of research on the chemical modification of lupane triterpenoids [5, 6], we studied the ketal formation of methylbetulonate (**1**). It is known that ketal formation is interesting as one of the methods for protecting ketones of complex polyfunctional molecules before carrying out synthetic transformations at other functional groups.



Condensation of **1** with ethanedithiol occurred at 0°C in $CHCl_3$ in the presence of boron trifluoride etherate in 15 min with a good yield (78%) of 3-ethylenethioketal (**2**). Ethylenemonothioketal (**3**) was prepared via an analogous reaction of **1** with β-mercaptoethanol in 74% yield. Compound **1** reacts with ethyleneglycol upon boiling in benzene in the presence of *p*-toluenesulfonic acid with azeotropic removal of benzene to form 3-ethyleneketal (dioxalane) (**4**) in 82% yield.

The structures of the prepared compounds were confirmed by elemental analyses and IR and NMR spectra. Thus, the signal of C-3 with a chemical shift of 218 ppm for starting **1** undergoes in the ^{13}C NMR spectra a strong-field shift to 62.9 ppm in **2**; 104.1 in **3**, and 113.1 in **4**. The other CH_2 groups in the ethyleneketals appear at 36.2 (**2**), 32.8 and 70.6 (**3**), and 64.5 and 64.7 (**4**). Protons 2H-1′ and 2H-2′ of **3** resonate in the PMR at 2.92 and 4.29 ppm as broad signals; in **4**, at 3.84-3.93 ppm as a multiplet.

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EXPERIMENTAL

IR spectra were recorded on Specord M80 and UR-20 spectrometers as mineral-oil mulls. PMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75.5 MHz, respectively) in $CDCl_3$ with TMS internal standard. Melting points were measured on a Boetius microstage.

TLC was performed on Silufol plates (Chemapol, Czech Rep.) using $CHCl_3$—CH_3OH (25:1). Compounds were developed using phosphotungstic acid in ethanol (10%) with subsequent heating at 100-120°C for 2-3 min.

Methylbetulonate **1** was prepared as before [6]. Elemental analyses agreed with those calculated.

General Synthetic Method for Compounds 2 and 3. A solution of **1** (0.94 g, 2 mmole) in dry $CHCl_3$ was treated with ethanedithiol or β-mercaptoethanol (1.5 mL), cooled to 0°C, and treated slowly dropwise with freshly distilled boron trifluoride etherate (1.5 mL). The solution was stirred for 15 min at 0°C, brought to room temperature, poured into NaOH solution (10%), and extracted with $CHCl_3$ (2×15 mL). The $CHCl_3$ extract was washed several times with water and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was chromatographed over Al_2O_3 (eluent $CHCl_3$).

3-Ethylenethioketal of Methyl-lup-20(29)-en-28-oate (2). Yield 0.84 g (78%), R_f 0.74, mp 119-121°C, $C_{33}H_{52}O_2S_2$. IR spectrum (ν, cm^{-1}): 1744, 1712, 1696, 1652, 1632, 1470, 1448, 1390, 1356, 1330, 1260, 1230, 1136, 1045, 1008, 968, 912, 888, 824, 760. PMR spectrum (δ, ppm, J/Hz): 0.85, 0.87, 0.95, 0.96, 0.99 (5s, 15H, $5CH_3$), 1.10-2.00 (m, H, CH_2, CH), 1.72 (s, 3H, CH_3), 2.25-2.35 (m, 1H, H13), 3.00-3.05 (m, 1H, H19), 3.20 (t, 4H, H1′, H2′, J = 4.2), 3.64 (s, 3H, OCH_3), 4.57 and 4.68 (both broad, 1H each, H29).

^{13}C NMR spectrum (δ, ppm): 14.6 (C-27), 16.2 (C-24), 16.3 (C-25), 16.7 (C-26), 18.5 (C-6), 19.5 (C-30), 21.0 (C-11), 25.4 (C-12), 26.9 (C-15), 27.8 (C-23), 29.7 (C-16), 30.1 (C-21), 32.3 (C-2), 34.1 (C-7), 34.4 (C-22), 36.2 and 36.2 (C-1′, C-2′), 36.8 (C-13), 37.1 (C-10), 38.3 (C1), 40.7 (C-8), 42.5 (C-14), 43.1 (C-4), 47.6 (C-19), 48.7 (C-18), 50.4 (C-9), 51.3 (OMe), 55.8 (C-5), 56.0 (C-17), 62.9 (C-3), 110.3 (C-29), 150.3 (C-20), 176.8 (C-28).

3-Ethylenemonothioketal of Methyl-lup-20(29)-en-28-oate (3). Yield 0.78 g (74%), R_f 0.72, mp 110-112°C, $C_{33}H_{52}O_3S$. IR spectrum (ν, cm^{-1}): 1700, 1664, 1616, 1480, 1448, 1360, 1320, 1256, 1232, 1192, 1040, 1008, 968, 916, 896, 832, 732. PMR spectrum (δ, ppm): 0.77, 0.85, 0.91, 0.95, 1.00 (5s, 15H, $5CH_3$), 1.00-2.00 (m, H, CH_2, CH), 1.69 (s, 3H, CH_3, 2.10-2.17 (m, 1H, H13), 2.92 (broad, 2H, H2′), 2.98-3.07 (m, 1H, H19), 3.64 (s, 3H, OCH_3), 4.29 (broad, 2H, H1′), 4.56 and 4.66 (both broad, 1H each, H29).

^{13}C NMR spectrum (δ, ppm): 14.9 (C-27), 16.0 (C-24), 16.0 (C-25), 16.6 (C-26), 18.5 (C-6), 19.4 (C-30), 20.9 (C-11), 25.2 (C-12), 26.5 (C-15), 27.9 (C-23), 29.7 (C-16), 30.5 (C-21), 31.9 (C-2), 32.8 (C-2′), 34.1 (C-7), 34.5 (C-22), 37.1 (C-13), 37.6 (C-10), 38.4 (C-1), 40.9 (C-8), 42.8 (C-14), 43.0 (C-4), 47.7 (C-19), 48.8 (C-18), 50.3 (C-9), 51.2 (OMe), 55.2 (C-5), 56.1 (C-17), 70.6 (C-1′), 104.1 (C-3), 109.9 (C-29), 150.1 (C-20), 177.4 (C-28).

3-Ethyleneketal of Methyl-lup-20(29)-en-28-oate (4). Compound **1** (0.94 g, 2 mmole) in absolute benzene (15 mL) was treated with ethyleneglycol (0.12 mL) and a catalytic amount of *p*-TsOH. The mixture was boiled for 2 h with a Dean—Stark trap to remove the benzene azeotrope and poured into cold saturated $NaHCO_3$ solution (50 mL). The organic layer was separated, washed with $NaHCO_3$ (20%) and NaCl solutions (20%), and dried over $MgSO_4$. The solvent was evaporated in vacuo. The solid was purified analogously to compounds **2** and **3**. Yield 0.84 g (82%), R_f 0.76, mp 107-109°C, $C_{33}H_{52}O_4$. IR spectrum (ν, cm^{-1}): 1742, 1714, 1694, 1680, 1652, 1470, 1450, 1388, 1320, 1265, 1234, 1165, 1136, 1040, 1008, 968, 920, 888, 824, 760. PMR spectrum (δ, ppm): 0.78, 0.84, 0.89, 0.95, 0.99 (5s, 15H, $5CH_3$), 1.20-2.00 (m, H, CH_2, CH), 1.61 (s, 3H, CH_3), 2.30-2.44 (m, 1H, H13), 2.87-2.99 (m, 1H, H19), 3.60 (s, 3H, OCH_3), 3.84-3.93 (m, 4H, H1′, H2′), 4.61 and 4.66 (both broad, 1H each, H29).

^{13}C NMR spectrum (δ, ppm): 14.7 (C-27), 15.8 (C-24), 16.0 (C-25), 16.9 (C-26), 19.5 (C-30), 18.3 (C-6), 20.7 (C-11), 25.2 (C-12), 26.7 (C-15), 27.2 (C-23), 29.2 (C-16), 30.4 (C-21), 32.0 (C-2), 33.3 (C-7), 34.0 (C-22), 36.8 (C-13), 37.6 (C-10), 38.5 (C-1), 40.9 (C-8), 42.8 (C-14), 43.4 (C-4), 47.6 (C-19), 48.8 (C-18), 50.1 (C-9), 51.2 (OMe), 55.7 (C-5), 56.3 (C-17), 64.5 (C-1′), 64.7 (C-2′), 113.1 (C-3), 109.5 (C-29), 150.2 (C-20), 177.4 (C-28).

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