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SYNTHESIS OF 30-AMINO DERIVATIVES OF 3,28-DI-O-ACETYLBETULIN

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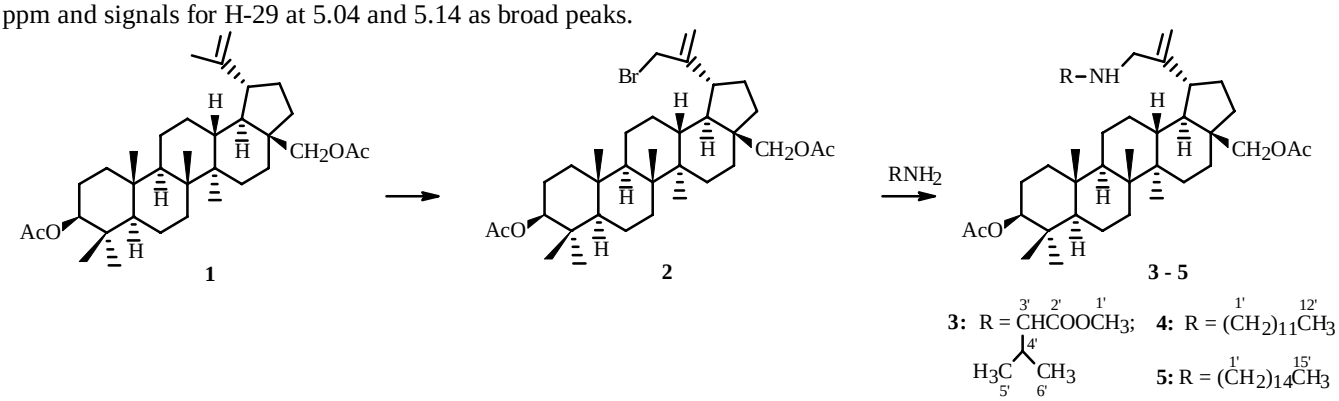
30-Amino derivatives of the lupane group were prepared by reaction of 3,28-di-O-acetyl-30-bromolup-20(29)-ene with L-valine methyl ester and aliphatic amines.

Key words: betulin, amines, allylic bromination.

Lupane triterpenoids are usually modified at the C-3 and C-28 positions in order to prepare biologically active compounds [1-3]. Conversions involving the isopropenyl group are relatively unstudied [4, 5]. It has been noted that 30-amino derivatives of lupeol exhibit distinct antimalarial activity toward *Plasmodium falciparum* [6].

We synthesized derivatives of betulin at the C-30 position with various amino-containing compounds using 30-bromobetulin acetate (**2**) as the starting material. Compound **2** was prepared by allylic bromination of 3,28-di-O-acetylbetulin (**1**) with N-bromosuccinimide in CCl_4 in 72% yield. The PMR spectrum of **2** contains a characteristic singlet for H-30 at δ 4.00 ppm and signals for H-29 at 5.04 and 5.14 as broad peaks.



Reaction of **2** with L-valine methyl ester in dry MeOH in the presence of K_2CO_3 producd the 30-N-(O′-methyl-L-valino) derivative **3** in 52% yield after chromatographic purification. The ^{13}C NMR spectrum of **3** exhibits a signal for C-30 at δ 51.3 ppm and signals for the amino-acid residue (δ 175.8, 66.8, 53.4, 31.3, 19.2, 18.8 ppm). The PMR spectrum contains characteristic signals for H-30 (δ 3.49 ppm), methoxyl (δ 3.73 ppm), and isopropyl (δ 0.84, 2.95, 3.20 ppm).

Since the reaction of **2** with aliphatic amines (dodecyl- and pentadodecyl-) proceeded under analogous conditions with exceedingly low yields, the triterpene amines were synthesized in DMSO. The yields of 30-amino derivatives **4** and **5** were after chromatographic purification 68 and 67%, respectively. The ^{13}C NMR spectra of **4** and **5** exhibit signals for C-30 at δ 44.9 ppm. Signals for the CH_2 groups of the aliphatic amine are clearly visible in the range δ 20.8-49.8 ppm. The PMR spectra contain signals for H-12′ or H-15′ (1.03 and 1.09 ppm) and amine protons H-6′-H-11′ or H-9′-H-14′ (1.05-1.19 and 1.10-1.21 ppm). Furthermore, signals for H-2′-H-5′ in the range δ 1.22-1.87 ppm for **4** and H-2′-H-8′ in the range δ 1.23-1.90 for **5** are observed in addition to the signals of the aglycon.

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EXPERIMENTAL

^{13}C NMR and PMR spectra were recorded on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) in $CDCl_3$ with $SiMe_4$ internal standard. Melting points were determined on a Boetius microstage. TLC was performed on Silufol plates (Chemapol, Czech Rep.) using $CHCl_3$:CH_3OH (20:1). Compounds were detected using phosphotungstic acid (10%) in ethanol with subsequent heating at 100-120°C for 2-3 min. Optical density was measured on a Perkin—Elmer 241 MC polarimeter with a 1-dm tube. 3,28-Di-O-acetylbetulin was prepared from betulin by the literature method [7]. Elemental analyses of **2-5** agreed with those calculated.

3,28-Di-O-acetyl-30-bromolup-20(29)-ene (2). A solution of **1** (1 mmol, 0.53 g) in dry CCl_4 (10 mL) was treated with freshly recrystallized NBS (1.7 mmol, 0.3 g) and refluxed for 3 h. The solid was filtered off. The mother liquor was evaporated in vacuum. The solid was recrystallized from EtOH. Yield 0.44 g (72%), R_f 0.86, mp 189-190°C (lit. [5] 185°C), $C_{34}H_{53}BrO_4$.

PMR spectrum (δ, ppm, J/Hz): 0.84, 0.85, 0.96, 1.04 (4s, 15H, $5CH_3$), 1.13-1.98 (m, 24H, CH_2, CH), 2.03 and 2.08 (2s, 6H, $2OCOC\underline{H}_3$), 2.42 (dt, 1H, J = 5, J = 10, H-19), 3.83 and 4.27 (both d, 2H, J = 11, H-28), 4.00 (s, 2H, H-30), 4.46 (dd, 1H, J = 6, J = 10, H-3), 5.04 and 5.14 (both br.s, 2H, H-29).

^{13}C NMR spectrum (δ, ppm): 14.7, 16.1, 16.2, 16.5, 18.2, 20.9, and 21.2 ($OCO\underline{C}H_3$), 23.7, 27.0, 27.1, 27.9, 29.9, 32.5, 34.2, 34.3, 37.1, 37.2, 37.5, 37.8, 38.4, 40.9, 42.7, 43.4, 46.3, 46.4, 48.9, 50.3, 55.4, 62.6 (C-28), 80.9 (C-3), 113.3 (C-29), 150.8 (C-20), 170.9 and 171.5 ($O\underline{C}OCH_3$).

3,28-Di-O-acetyl-30-N-(O′-methyl-L-valino)-lup-20(29)-ene (3). A solution of **2** (2 mmol, 1.2 g) in dry MeOH (40 mL) was treated with K_2CO_3 (4.5 mmol, 0.8 g) and L-valine methyl ester hydrochloride (4.5 mmol, 0.6 g), refluxed for 10 h, and poured into water (100 mL). The resulting solid was filtered off, washed with water, and dried. The solid was purified over a column of Al_2O_3 with elution by $CHCl_3$. Yield 0.69 g (52%), mp 81-83°C, $C_{40}H_{65}NO_6$.

PMR spectrum (δ, ppm, J/Hz): 0.84 (s, 6H, $2CH_3$, H-5′, H-6′), 0.94, 0.96, 0.98, 1.03 (4s, 15H, $5CH_3$), 1.04 (br.s, 1H, N$\underline{H}$), 1.05-1.95 (m, 23H, CH_2, CH), 2.04 and 2.07 (both s, 6H, 2OAc), 2.30-2.40 (m, 1H, H-19), 2.95 and 3.20 (both d, 2H, J = 15, H-4′), 3.05 (d, H, J = 6, H-3′), 3.49 (s, 2H, CH_2-30), 3.73 (s, 3H, C-1′), 3.83 and 4.23 (both d, 2H, J = 11, H-28), 4.45-4.53 (m, 1H, H-3), 4.84 and 4.93 (both s, 2H, H-29).

^{13}C NMR spectrum (δ, ppm): 14.8, 16.0, 16.1, 16.4, 18.1, 18.8 (C-5′), 19.2 (C-6′), 20.8, 21.0, 21.3, 23.6, 26.5, 27.0, 27.9, 29.7, 31.3 (C-4′), 31.7, 34.1, 34.3, 37.0, 37.5, 37.7, 38.4, 40.9, 42.6, 44.8, 46.3, 49.2, 50.2, 51.3, 53.4 (C-1′), 55.3, 62.6 (C-28), 66.8 (C-3′), 80.9 (C-3), 108.1 (C-29), 152.6 (C-20), 171.0 and 171.6 ($O\underline{C}OCH_3$), 175.8 (C-2′).

Synthetic Method for 4 and 5. A solution of **2** (2 mmol, 1.2 g) in dry DMSO (15 mL) was treated with dodecyl- or pentadodecylamine (4 mmol), stirred with heating at 60°C for 15 h, and extracted with $CHCl_3$ (2 × 50 mL). The combined extracts were washed with HCl solution (5%, 2 × 25 mL) and water (2 × 20 mL) and dried over $CaCl_2$. The solvent was evaporated in vacuum. The solid was chromatographed over a column of Al_2O_3 with elution by $CHCl_3$.

3,28-Di-O-acetyl-30-N-(dodecylamino)-lup-20(29)-ene (4). Yield 0.97 g (68%), mp 138°C, $[\alpha]_D^{20}$ +0.9° (*c* 0.02, $CHCl_3$), $C_{46}H_{79}NO_4$.

PMR spectrum (δ, ppm, J/Hz): 0.85, 0.89, 0.91, 0.97 (4s, 15H, $5CH_3$), 1.03 (s, 3H, H-12′), 1.05-1.19 (m, 12H, H6′-H11′), 1.22-.187 (m, 28H, CH_2, CH, H2′-H5′), 2.05 and 2.07 (both s, 6H, $2OCOC\underline{H}_3$), 2.33 (br.s, 1H, N$\underline{H}$), 2.60-2.63 (m, 3H, H-19, H-1′), 3.12-3.28 (m, 2H, H-30), 3.84 and 4.46 (both d, 2H, H-28, J = 11), 4.45-4.50 (m, 1H, H-3), 4.84 (m, 2H, H-29).

^{13}C NMR spectrum (δ, ppm): 14.1 (C-12′), 14.2, 16.0, 16.1, 16.5, 18.1, 20.8, and 21.0 ($OCO\underline{C}H_3$), 22.7 (C-11′), 23.7, 27.0, 27.4, 27.9, 29.3, 29.6 (C-21, C2′-C10′), 30.2, 32.0, 34.4, 37.0, 37.5, 37.8, 38.3, 40.9, 42.6, 44.9, 46.2, 46.3, 49.3, 49.8 (C-1′), 50.2, 55.3, 62.6 (C-28), 80.9 (C-3), 107.2 (C-29), 152.9 (C-20), 171.0 and 171.6 ($O\underline{C}OCH_3$).

3,28-Di-O-acetyl-30-N-(pentadodecylamino)-lup-20(29)-ene (5). Yield 1.0 g (67%), mp 198-200°C, $[\alpha]_D^{20}$ +2° (*c* 0.004, $CHCl_3$), $C_{49}H_{85}NO_4$.

PMR spectrum (δ, ppm, J/Hz): 0.84, 0.87, 0.89, 1.02 (4s, 15H, $5CH_3$), 1.09 (s, 3H, H-15′), 1.10-1.21 (m, 12H, H9′-H14′), 1.23-1.90 (m, 38H, CH_2, CH, H2′-H8′), 2.04 and 2.06 (both s, 6H, $2OCOC\underline{H}_3$), 2.35 (br.s, 1H, N$\underline{H}$), 2.52-2.64 (m, 3H, H-19, H-1′), 3.18 (m, 2H, H-30), 3.84 and 4.22 (both d, 2H, J = 11, H-28), 4.45-4.50 (m, 1H, H-3), 4.93 (m, 2H, H-29).

^{13}C NMR spectrum (δ, ppm): 14.0 (C-15′), 14.7, 16.0, 16.1, 16.4, 18.1, 20.8 (C-14′), 20.9, 21.2, 22.6, 23.6, 26.5 (C-2′), 27.0, 27.4, 27.9, 29.3 (C-21, C3′-C13′), 29.7, 30.1, 31.9, 34.1, 34.4, 37.0, 37.5, 37.7, 38.4, 40.9, 42.6, 44.9, 46.3, 49.4, 49.7 (C-1′), 50.2, 55.3, 80.9 (C-3), 107.4 (C-29), 152.9 (C-20), 170.9 and 171.5 ($O\underline{C}OCH_3$).

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