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SYNTHESIS AND STRUCTURE OF AN ACETYLENE DERIVATIVE OF LUPEOL

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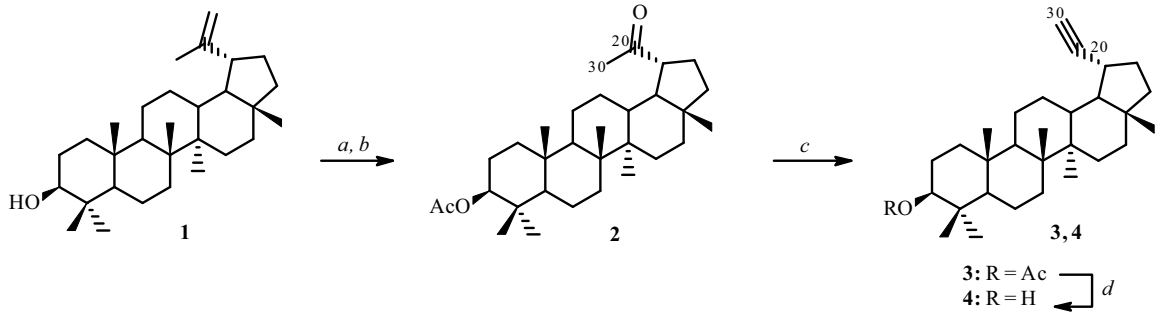
The synthesis and x-ray crystal structure of 3-acetoxy-29-norlup-20(30)-yne were carried out.

Keywords: triterpenoids, lupeol, acetylenes, synthesis, x-ray structure analysis.

Acetylene compounds are known to be a rather representative group of natural metabolites with pronounced anticancer activity [1]. However, triterpenoid derivatives with triple bonds, except for a few reports [2–4], are relatively unknown. Therefore, their synthesis is a critical problem. Furthermore, the alkyne group is one of the most convenient moieties in the design of new compounds because of its high reactivity and ease of functionalization [5].

We synthesized lupeol (**1**) derivative using the previously reported method for preparing triterpenoids with an alkyne moiety [4]. Refluxing 3-acetoxy-29-nor-20-oxolupeol (**2**) and $POCl_3$ in Py produced 3-acetoxy-29-norlup-20(30)-yne (**3**) in 77% yield after purification by column chromatography (Scheme 1).



a. Ac_2O/pyridine, 115°C; *b.* O_3, CH_2Cl_2, –60°C; *c.* $POCl_3$/pyridine, 115°C; *d.* 5% KOH/MeOH

Scheme 1

The resonance of the acetylenic proton appeared in the PMR spectrum of **3** as a characteristic doublet at δ 2.03 ppm with SSCC 2.2 Hz. The resonance of the C20(30) triple bond was observed in the ^{13}C NMR spectrum at δ 67.8 and 90.8 ppm. The molecular and crystal structures of **3** were established unambiguously by an x-ray structure analysis. The symmetric unit of the unit cell contained two molecules of **3** (A and A′) with the same absolute configuration and nearly identical structures (Fig. 1, which shows molecule A) that were similar to those of related compounds characterized by us earlier [4, 6, 7]. All six-membered rings had the chair conformation and were situated *trans* relative to each other. The five-membered ring had a slightly distorted envelope conformation with C17 deviating by 0.690(8) Å [by 0.685(8) Å for C17′ in A′] from the plane of the other ring atoms. The crystal structure of **3** was stabilized by ordinary van-der-Waals interactions. Deprotection of the acetate under alkaline conditions produced lupeol acetylene derivative **4** from **3**.

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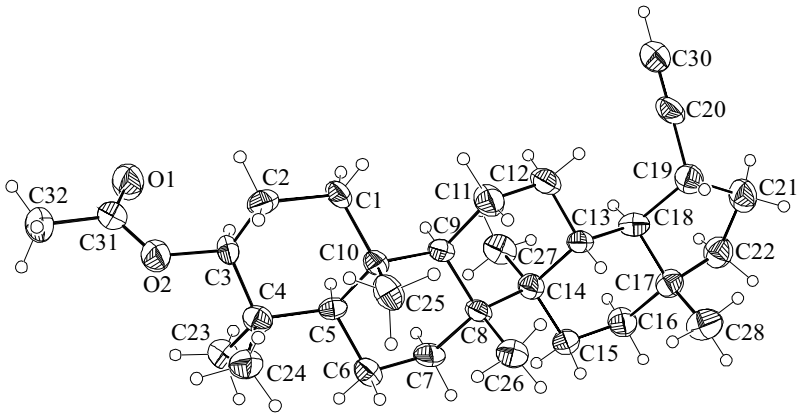

Fig. 1. Structure of 3-acetoxy-29-norlup-20(30)-yne (**3**) with 50% probability atomic thermal ellipsoids.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (operating frequency 300 and 75.5 MHz, respectively) with TMS internal standard. Chemical shifts are given on the δ scale. Melting points were determined on a Boetius microstage. Specific rotation angles were measured on a Perkin–Elmer 241 MC polarimeter. TLC analysis was performed on Sorbil plates using $CHCl_3$:EtOAc (40:1). Compounds were detected by H_2SO_4 solution (10%) with subsequent heating at 100–120°C for 2–3 min. Lupeol (**1**) was isolated from birch bark as before [8].

3-Acetoxy-29-norlup-20(30)-yne (3). A solution of **1** (2.1 g, 5 mmol) in Py (100 mL) and acetic anhydride (5 mL) was refluxed for 3 h and poured into cold water (200 mL). The solid was filtered off, washed, dried, and dissolved in CH_2Cl_2 (150 mL). The solution was cooled to –60°C, purged with ozone until the starting material disappeared (TLC monitoring), and held for 1 d at room temperature. The solvent was evaporated in vacuo (water-jet). The resulting **2** was crystallized from $CHCl_3$:MeOH. Then, **2** (1.55 g, 3.3 mmol) in anhydrous Py (40 mL) was cooled, treated dropwise with $POCl_3$ (7 mL), refluxed for 8 h, and poured onto ice (100 g). The product was extracted with $CHCl_3$ (3 × 100 mL), washed with H_2O (3 × 100 mL), dried over $CaCl_2$, and evaporated in vacuo (water-jet). The solid was purified over a column of Al_2O_3 with elution successively by petroleum ether and benzene. Yield 1.05 g (77%), mp 206–207°C, $[\alpha]_D^{20}$ –33° (*c* 0.05, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.70, 0.81, 0.82, 0.85, 0.93, 1.03 (18H, 6s, $6CH_3$), 1.30–1.90 (24H, m, CH_2 and CH), 2.00 (1H, d, J = 2.2, H-30), 2.03 (3H, s, OAc), 2.25–2.30 (1H, m, H-19), 4.43–4.50 (1H, m, H-3).

^{13}C NMR spectrum (δ, ppm): 14.7, 16.4, 16.8, 17.0, 17.5, 17.6, 18.2, 20.8, 21.3, 23.7, 26.6, 27.2, 27.9, 29.7, 31.1, 34.1, 35.0, 37.1, 37.5, 37.8, 38.3, 39.3, 40.7, 42.7, 42.8, 50.1, 53.6, 67.8, 80.9, 90.8, 171.1. $C_{31}H_{48}O_2$.

X-ray Structure Analysis of 3. Colorless crystals (thin plates) of $C_{31}H_{48}O_2$ (MW 452.69) were monoclinic $a = 13.173(3)$, $b = 14.054(3)$, $c = 14.407(3)$ Å, $\beta = 97.729(4)°$, $V = 2643.0(10)$ Å^3, space group $P2_1$, $Z = 4$, $d_{calc} = 1.138$ g/cm^3. A dataset of 27,659 reflections was obtained on a Bruker SMART APEX2 CCD diffractometer at 100 K (λ Mo K_α-radiation, $\theta_{max} = 28°$) from a single crystal of size 0.18 × 0.12 × 0.02 mm. The initial set of measured intensities was processed using the SAINT and SADABS programs included in the APEX2 program package [9]. The structure was solved by direct methods and refined over F^2_{hkl} by anisotropic full-matrix least-squares methods for nonhydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions and refined using a rider model [$U_{iso}(H) = nU_{eq}(C,O)$, where $n = 1.5$ for methyl C atoms and 1.2 for other C atoms]. The refinement used 6630 independent reflections. The refinement over all independent reflections converged to $wR_2 = 0.0955$ [$R_1 = 0.0612$ over 2360 reflections with $I > 2\sigma(I)$]. All calculations were carried out on an IBM PC using the SHELXTL program set [10]. Atomic coordinates and thermal factors were deposited in the Cambridge Crystallographic Data Centre (CCDC), No. 794332; http://www.ccdc.cam.ac.uk/products/csd/request.

3-Hydroxy-29-norlup-20(30)-yne (4). A solution of **3** (0.45 g, 1 mmol) in MeOH (50 mL) was treated with KOH (0.17 g, 3 mmol), stirred for 3 h (TLC monitoring), and poured into H_2O (100 mL). The precipitate was filtered off, washed with H_2O, dried, and crystallized from $CHCl_3$:MeOH. Yield 0.40 g (89%), mp 183–185°C, $[\alpha]_D^{20}$ –14° (*c* 2.60, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.72. 0.78, 0.85, 0.95, 0.97, 1.03 (18H, 6s, $6CH_3$), 1.20–1.90 (24H, m, CH_2 and CH), 2.02 (1H, d, J = 2.3, H-30), 2.30 (1H, br.s, H-19), 3.25–3.30 (1H, m, H-3).

^{13}C NMR spectrum (δ, ppm): 14.3, 15.3, 15.9, 16.0, 17.5, 18.3, 20.8, 26.6, 27.1, 27.4, 27.9, 29.7, 31.1, 34.2, 35.0, 37.1, 37.5, 38.7, 38.8, 39.3, 40.7, 42.7, 42.7, 50.2, 53.6, 55.2, 68.2, 78.9, 90.8. $C_{29}H_{46}O$.

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REFERENCES

1. V. M. Dembitsky and D. O. Levitsky, *Nat. Prod. Commun.*, **1**, 405 (2006).
2. G. A. Tolstikov, M. I. Goryaev, and L. F. Tolstikova, *Dokl. Akad. Nauk*, **5**, 1110 (1967).
3. S. F. Vasilevsky, A. I. Govdi, E. E. Shults, M. M. Shakirov, I. V. Sorokina, T. G. Tolstikova, D. S. Baev, G. A. Tolstikov, and I. V. Alabugin, *Bioorg. Med. Chem.*, **17**, 5164 (2009).
4. O. V. Kazakova, N. I. Medvedeva, G. A. Tolstikov, O. S. Kukovinets, E. Yu. Yamansarov, L. V. Spirikhin, and A. T. Gubaidullin, *Mendeleev Commun.*, **20**, 234 (2010).
5. B. A. Trofimov and N. K. Gusarova, *Russ. Chem. Rev.*, **76**, 507 (2007).
6. O. B. Kazakova, N. I. Medvedeva, E. V. Salimova, and K. Yu. Suponitskii, *Zh. Strukt. Khim.*, **51**, 810 (2010).
7. O. B. Flekhter, G. V. Giniyatullina, F. Z. Galin, N. Zh. Baschenko, N. S. Makara, F. S. Zarudii, E. I. Boreko, O. V. Savinova, N. I. Pavlova, Z. A. Starikova, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 582 (2005).
8. G. A. Tolstikov, M. I. Goryaev, Khya Ok Kim, and R. A. Khegai, *Zh. Prikl. Khim.*, **40**, No. 4, 920 (1967).
9. APEX2 and SAINT, Bruker AXS Inc., Madison, Wisconsin, USA, 2005.
10. G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, **64**, 112 (2008).