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STEREOSPECIFIC EPOXIDATION OF AN OLEAN-18(19)-ENE-TYPE TRITERPENOID

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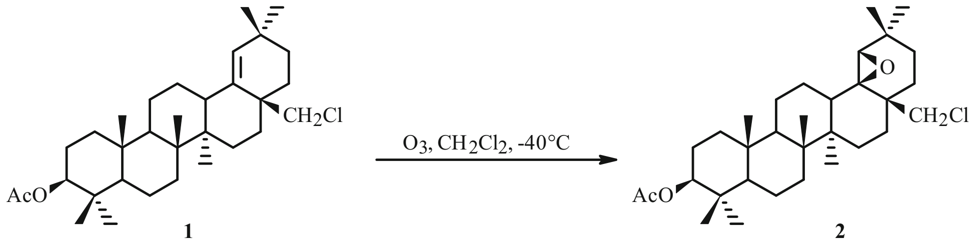
*An effective method for stereospecific epoxidation of olean-18(19)-ene-type triterpenoids with ozone is proposed using 3*S*-acetoxy-17-chloromethylolean-18(19)-ene as an example.*

Keywords: olean-18(19)-ene triterpenoids, morolic acid, ozonolysis, stereospecificity, x-ray structure analysis.

Morolic [olean-18(19)-enoic] acid derivatives are promising compounds for medicinal chemistry. Thus, it was discovered that morolic acid exhibits antiviral activity against herpes virus HSV-1 [1] and HIV-1 [2]. Derivatives of morolic acid, especially the 3′,3′-dimethylsuccinylmorolic acid amide with L-leucine, are new promising anti-HIV agents [3, 4]. 3,21-Dioxoolean-18(19)-enoic acid became the first natural non-protein inhibitor of Tie2-kinase [5]. The unavailability of olean-18(19)-ene-type compounds from natural sources stimulated work on their synthesis from other triterpenoids, e.g., betulin and allobetulin [6–8].

Herein we report the reaction of 3*S*-acetoxy-17-chloromethylolean-18(19)-ene (**1**) with ozone. In several instances the reaction of ozone with a sterically hindered double bond formed epoxides [9]. Carrying out low-temperature ozonolysis of **1** in CH_2Cl_2 produced in quantitative yield 18*R*,19*S*-epoxide **2**. The structure of **2** was confirmed by NMR spectral data. The stereospecificity of the epoxidation was proved by an x-ray structure analysis (XSA) (Fig. 1).



1 **2**

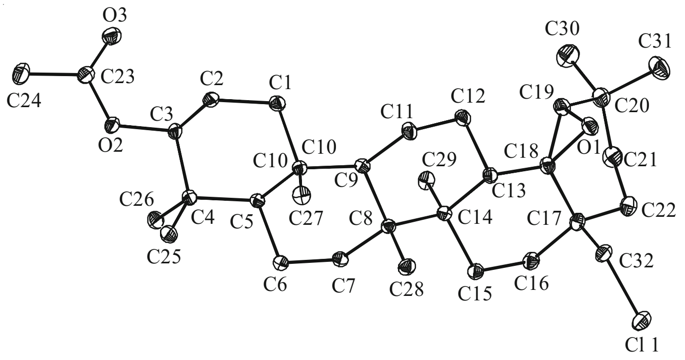


Fig. 1. Molecular structure of 3*S*-acetoxy-17-chloromethyl-18*R*,19*S*-epoxyoleane (**2**) with 50% probability of thermal ellipsoids; H atoms are not shown.

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Thus, ozonolysis of olean-18(19)-ene-type triterpenoids is an effective method for their stereospecific epoxidation that can be applied to other compounds.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker AM-300 (300 and 75.5 MHz, respectively) spectrometer. Melting points were determined on a Boetius microstage. Optical density was measured in a 1-dm tube on Perkin–Elmer 241 MC polarimeter. An Ozon-2K ozonator was used for ozonolysis. TLC was performed on Sorbfil plates (ZAO Sorbpolimer, Russia) using $CHCl_3$:EtOAc (40:1). Compounds were detected by H_2SO_4 (10%) with subsequent heating at 100–120°C for 2-3 min. 3*S*-Acetoxy-17-chloromethylolean-18(19)-ene (**1**) was prepared as before [8].

3*S*-Acetoxy-17-chloromethyl-18*R*,19*S*-epoxyoleane (2). A solution of **1** (1 mmol) in CH_2Cl_2 (50 mL) was purged with ozone at –40°C with TLC monitoring and held for 3 h at room temperature. The solvent was evaporated using a water aspirator. The solid was crystallized from benzene. Yield 0.47 g (92%), R_f 0.83, mp 95°C, $[\alpha]_D^{20}$ +36° (*c* 0.1, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 0.85, 0.87, 0.89, 0.96, 0.99, 1.05, 1.06 (21H, 7s, $7CH_3$), 1.11-1.81 (22H, m, CH_2, CH), 2.05 (3H, s, OAc), 2.09–2.11 (1H, m, H-13), 2.75 (1H, s, H-19), 3.51 and 4.17 (2H, both d, J = 10.8, H-28), 4.50 (1H, t, J = 7.9, H-3).

^{13}C NMR spectrum (δ, ppm): 16.5, 16.8, 17.8, 18.1, 20.8, 21.3, 21.6, 22.3, 23.7, 24.9, 26.0, 26.4, 27.9, 28.2, 28.6, 29.1, 30.5, 31.2, 33.9, 37.2, 37.8, 37.9, 38.3, 38.6, 40.9, 42.7 (C-28), 50.6, 51.5, 55.6 (C-19), 64.3 (C-18), 80.8 (C-3), 171.0. $C_{32}H_{51}ClO_3$.

XSA of 3*S*-acetoxy-17-chloromethyl-18*R*,19*S*-epoxyoleane (2). Colorless prismatic crystals, $C_{32}H_{51}ClO_3$ (MW = 519.18), monoclinic at 100 K, $a = 7.7487(5)$ Å, $b = 11.2129(7)$, $c = 16.3072(10)$, $\beta = 91.3490(10)°$, $V = 1416.46(15)$ Å^3, space group $P2_1$, $Z = 2$, $d_{calcd} = 1.217$ g/cm^3. An experimental dataset of reflections was obtained on a Bruker APEX II diffractometer (λ Mo K_α-radiation, $2\theta_{max} = 61°$) from a single crystal of size 0.37 × 0.25 × 0.21 mm. The total of 8545 independent reflections that was obtained after averaging equivalent reflections [R(int) = 0.0315] was used to solve and refine the structure. The structure was found by direct methods and refined anisotropically over F^2_{hkl} (H atoms were placed geometrically in their calculated positions and refined isotropically using a rider model). The final agreement factors were $R_1 = 0.0379$ [calculated over F_{hkl} for 7711 reflections with $I > 2\sigma(I)$], $wR_2 = 0.944$ (calculated over F^2_{hkl} for all 8545 reflections), GOOF = 1.010, 333 refined parameters. All calculations were performed using the SHELXTL program set. Atomic coordinates and thermal factors were deposited in the Cambridge Crystallographic Data Centre (CCDC 773824).

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REFERENCES

1. M. Kurokawa, P. Basnet, M. Ohsugi, T. Hozumi, S. Kadota, T. Namba, T. Kawana, and K. Shiraki, *J. Pharmacol. Exp. Ther.*, **289**, 72 (1999).
2. I. C. Sun, Y. Kashiwada, S. L. Morris-Natschke, and K.-H. Lee, *Curr. Top. Med. Chem.*, **3**, 155 (2003).
3. D. Yu. Y. Sakurai, C. H. Chen, F. R. Chang, L. Huang, Y. Kashiwada, and K.-H. Lee, *J. Med. Chem.*, **49**, 5462 (2006).
4. K.-H. Lee, F. R. Chang, Y. Sakurai, and C. H. Chen, WO Pat. 2006001964, 2006.
5. B.-N. Zhou, R. K. Johnson, M. R. Mattern, P. W. Fisher, and D. G. I. Kingston, *Org. Lett.*, **3**, 4047 (2001).
6. O. B. Flekhter, N. I. Medvedeva, G. A. Tolstikov, F. Z. Galin, M. S. Yunusov, Huong Nguen Thi Mai, Le Viet Tian, O. V. Savinova, E. I. Boreko, L. P. Titov, and I. V. Glukhov, *Bioorg. Khim.*, **35**, 253 (2009).
7. P. Zhang, J. Nao, J. Liu, L. Zhang, and H. Sun, *Tetrahedron*, **65**, No. 22, 4304 (2009).
8. O. B. Kazakova, E. F. Khusnutdinova, G. A. Tolstikov, and K. Yu. Suponitskii, *Bioorg. Khim.*, **36**, 552 (2010).
9. N. I. Medvedeva, O. B. Flekhter, A. Gzella, and L. Zaprutko, *Khim. Prir. Soedin.*, 499 (2006).