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Oxidation of betulin and its acetates with dimethyldioxirane

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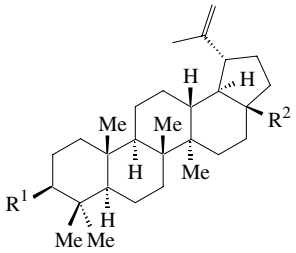
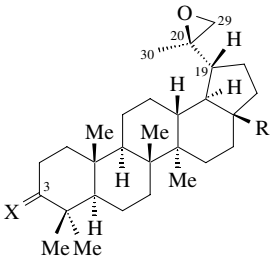
The stereospecificity of epoxidation and the chemoselectivity of oxidation of hydroxy groups in the reactions of 20,29-lupene triterpenoids with dimethyldioxirane is discovered.

Oxidation with dimethyldioxirane (DMD) is widely used in the chemistry of low-molecular-weight natural compounds. Application of DMD is described for the preparation of earlier not available 2,3-epoxycarbohydrates[1–5] and oxidative transformations of diterpenes[6] and diterpene alkaloids.[7]

This report is the first example of an oxidation of triterpenoids with DMD. We studied the interaction of DMD with four triterpenoids of the 20,29-lupene-type: betulin **1**, 3β,28-di-*O*-acetate **2**, 3β-*O*-monoacetate **3** and 28-*O*-monoacetate **4**.† As expected, di-*O*-acetate **2**, which has the double bond as a single object of attack, gave 20,29-epoxide **5** in 90% yield. The reaction is stereospecific because the only product is a single diastereomer, 20*R*-configuration of which is obvious from the X-ray diffraction analysis (Figure 1).‡‡ The formation of an epoxide as an individual compound is also confirmed by the ^{13}C and ^{1}H NMR data, which include the characteristic signals of atoms 20-C, 29-C and 30-H, 29-H.

Oxidation of 28-*O*-monoacetate **4** proceeds exact consequently. The use of one DMD equivalent led to epoxide **6** (95% yield), whereas oxidation with two equivalents gave 3-oxo-epoxide **7** in 86% yield. According to ^{13}C and ^{1}H NMR data,





1 R^1 = OH, R^2 = CH_2OH
2 R^1 = OAc, R^2 = CH_2OAc
3 R^1 = OAc, R^2 = CH_2OH
4 R^1 = OH, R^2 = CH_2OAc

5 X =  , R = CH_2OAc
6 X =  , R = CH_2OAc
7 X = O, R = CH_2OAc
8 X =  , R = CHO
9 X =  , R = COOH
10 X =  , R = CH_2OH
11 X = O, R = CH_2OH
12 X = O, R = CHO
13 X = O, R = COOH

† *General procedure of the oxidation of triterpenoids* **1**–**4**: 1 equiv. of a DMD solution in acetone (≈0.08 mol dm^{-3}) was added in small portions with stirring to a solution of triterpenoid **1**–**4** (100 mg) in methylene chloride and acetone (10 ml, 1:1) at room temperature. The mixture was stirred until the complete consumption of DMD (monitored by iodometry). After completion of the reaction, the solvent was removed *in vacuo*, and the residue was crystallised from ethanol.

3β,28-Di-O-*acetyllup-20*R,*29-epoxide* **5**: yield 90%, mp 192 °C (MeOH) (lit.,[12] 193 °C), $[\alpha]_D^{20}$ +19.4° (*c* 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82, 0.83, 0.89, 0.98, 1.06 (5s, 15H, 5Me), 0.90–1.90 (m, 24H, CH, CH_2), 1.22 (s, 3H, 30-H), 2.00 and 2.05 (2s, 6H, OAc), 2.30 (dt, 1H, 19-H, *J* 10.0 and 4 Hz), 2.61 and 2.66 (2d, 2H, 29-H, *J* 4.8 Hz), 2.66 and 2.70 (2d, 2H, 28-H, *J* 9.8 Hz), 4.52 (dd, 1H, 3-H, *J* 10.6 and 5.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 171.4, 170.9, 80.7 (3-C), 62.4 (28-C), 59.9 (20-C), 57.0 (29-C), 55.2, 49.6, 46.6, 46.0, 42.6, 40.8, 38.3, 37.7, 36.9, 36.5, 34.3, 34.0, 29.6, 29.7, 27.6, 26.7, 25.7, 23.5, 21.3, 21.0, 20.9, 20.8, 18.0 (30-C), 17.9, 16.4, 16.1, 15.8, 14.6. Found (%): C, 75.51; H, 9.21. Calc. for $C_{34}H_{54}O_5$ (%): C, 75.23; H, 10.03.

3β-Hydroxy-28-O-*acetyllup-20*R,*29-epoxide* **6**: yield 95%, mp 202–204 °C (MeOH), $[\alpha]_D^{20}$ +26.0° (*c* 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.78, 0.84, 0.98, 0.99, 1.01 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH, CH_2), 1.26 (s, 3H, 30-H), 2.08 (s, 3H, OAc), 2.55 (dt, 1H, 19-H, *J* 10.0 and 5.0 Hz), 2.63 and 2.67 (2d, 2H, 29-H, *J* 4.8 Hz), 3.20–3.25 (m, 1H, 3-H), 3.84 and 4.23 (2d, 2H, 28-H, *J* 11.0 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 171.1, 78.9 (3-C), 62.9 (28-C), 60.0 (20-C), 57.1 (29-C), 55.1, 49.4, 49.1, 46.4, 45.8, 42.4, 40.6, 38.5, 36.9, 36.5, 36.2, 33.9, 33.5, 30.6, 29.4, 27.8, 27.0, 26.3, 26.0, 20.9, 20.6, 18.3 (30-C), 17.8, 15.7, 15.5, 15.2, 14.4. Found (%): C, 76.39; H, 10.50. Calc. for $C_{32}H_{52}O_4$ (%): C, 76.75; H, 10.47.

these compounds have the same configuration at 20-C as epoxide **5**.

Oxidation of 3β-*O*-monoacetate **3** with two equivalents of DMD led to a mixture of epoxy aldehyde **8**, which was not isolated in a pure form,§ and epoxy acid **9**. The last one was obtained in 81% yield using three equivalents of the reagent. The NMR data indicate the stereospecificity of the oxidation.

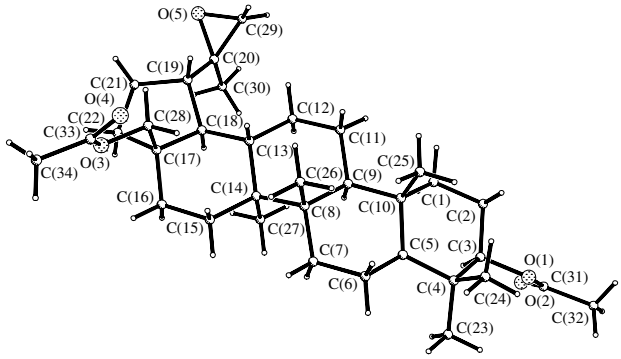


Figure 1 Molecular structure of compound **5**.

The revealed consecution of oxidation holds also for the case of betulin **1**. Thus, the use of 1–1.2 equivalents of DMD gave epoxide **10** in 92% yield. Two equivalents of the reagent lead to 3-oxo-epoxide **11**. As in the case of the oxidation of monoacetate **3**, the use of three equivalents of DMD gave a mixture of 3-oxo-aldehyde **12** (which was not isolated in a pure form)§ and 3-oxo-acid **13**. With four equivalents of DMD acid **13** was obtained in 86% yield. From the NMR data, it follows that the epoxidation of the double bond is stereospecific as in the earlier cases.

Thus, it could be demonstrated that DMD is a reagent for stereospecific epoxidation of olefinic double bonds and chemoselective oxidation of hydroxy groups for triterpenoids of the 20,29-lupene type. An important fact is the preparation of earlier not available compounds **6**, **7**, **9**–**11**, **13**. Taking into account the high biological activity of lupane triterpenes,[8–11] the oxidation of betulin and its acetates with DMD is highly promising.

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*3-Oxo-28-*O*-acetyllup-20*R*,29-epoxide* **7**: yield 86%, mp 185 °C (EtOH), $[\alpha]_D^{20}$ +11.3° (*c* 1.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75, 0.81, 0.96, 1.00, 1.02 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH, CH_2), 1.24 (s, 3H, 30-H), 2.00 (s, 3H, OAc), 2.40 (dt, 1H, 19-H, *J* 10.0 and 4.5 Hz), 2.60 and 2.65 (2d, 2H, 29-H, *J* 4.8 Hz), 3.80 and 4.21 (2d, 2H, 28-H, *J* 11.0 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 217.3 (3-C), 171.1, 62.9 (28-C), 60.5 (20-C), 57.2 (29-C), 55.1, 49.8, 49.3, 46.4, 45.8, 42.4, 41.6, 38.5, 36.9, 36.5, 36.4, 34.0, 33.5, 30.6, 28.4, 27.8, 27.5, 26.3, 26.3, 20.9, 20.4, 18.3 (30-C), 17.8, 15.8, 15.7, 15.2, 14.1. Found (%): C, 77.10; H, 10.05. Calc. for $C_{32}H_{50}O_4$ (%): C, 77.06; H, 10.11.

*3β-*O*-Acetyllup-20*R*,29-epoxy-28-oic acid* **9**: yield 81%, mp 217–219 °C (MeOH), $[\alpha]_D^{20}$ –4.2° (*c* 6.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84, 0.86, 0.97, 1.00, 1.02 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH, CH_2), 1.21 (s, 3H, 30-H), 2.04 (s, 3H, OAc), 2.35–2.42 (m, 1H, 19-H), 2.58 and 2.64 (2d, 2H, 29-H, *J* 4.8 Hz), 4.42–4.47 (m, 1H, 3-H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 180.4 (28-C), 170.6, 80.9 (3-C), 59.9 (20-C), 57.0 (29-C), 55.2, 49.9, 47.5, 43.2, 43.1, 42.7, 40.9, 36.2, 37.7, 36.9, 36.5, 34.1, 33.3, 29.5, 29.2, 28.7, 27.8, 26.5, 23.5, 21.1, 20.7, 18.1 (30-C), 17.1, 16.4, 15.9, 15.8, 14.4. Found (%): C, 74.72; H, 9.70. Calc. for $C_{32}H_{50}O_5$ (%): C, 74.67; H, 9.79.

*3β,28-Dihydroxylup-20*R*,29-epoxide* **10**: yield 92%, mp 192–194 °C (MeOH), $[\alpha]_D^{20}$ +21.6° (*c* 4.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.73, 0.79, 0.95, 1.01, 1.06 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH_2, CH), 1.25 (s, 3H, 30-H), 2.30 (dt, 1H, 19-H), 2.56 and 2.64 (2d, 2H, 29-H, *J* 4.5 Hz), 3.18 (dd, 1H, 3-H, *J* 9.8 and 5.2 Hz), 3.28 and 3.26 (2d, 2H, 28-H, *J* 9.0 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 78.8 (3-C), 60.3 (20-C), 60.0 (28-C), 57.1 (29-C), 55.2, 50.4, 49.6, 48.0, 46.7, 42.6, 40.8, 39.4, 38.8, 37.0, 36.4, 34.2, 33.7, 29.1, 27.9, 26.7, 26.5, 20.9, 18.2 (30-C), 17.9, 16.2, 17.9, 15.9,. 15.8, 15.4, 14.5. Found (%): C, 78.59; H, 10.50. Calc. for $C_{30}H_{50}O_3$ (%): C, 78.55; H, 10.99.

*3-Oxo-28-hydroxylup-20*R*,29-epoxide* **11**: yield 86%, mp 223–225 °C (EtOH), $[\alpha]_D^{20}$ +25.8° (*c* 6.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.75, 0.79, 0.97, 1.00, 1.10 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH_2, CH), 1.20 (s, 3H, 30-H), 2.38 (dt, 1H, 19-H, *J* 10.0 and 4 Hz), 2.54 and 2.66 (2d, 2H, 29-H, *J* 4.3 Hz), 3.28 and 3.75 (2d, 2H, 28-H, *J* 9.0 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 217.1 (3-C), 60.3 (20-C), 59.8 (28-C), 57.5 (29-C), 54.2, 50.5, 49.8, 48.1, 46.7, 42.6, 40.8, 39.4, 38.6, 37.0, 36.1, 34.9, 33.7, 30.1, 27.9, 26.7, 26.5, 20.7, 18.2 (30-C), 17.9, 16.2, 17.9, 16.0, 15.8, 15.2, 14.8. Found (%): C, 78.82; H, 10.74. Calc. for $C_{30}H_{48}O_3$ (%): C, 78.90; H, 10.59.

*3-Oxolup-20*R*,29-epoxy-28-oic acid* **13**: yield 86%, mp 211–213 °C (MeOH), $[\alpha]_D^{20}$ +17.3° (*c* 4.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.69, 0.78, 0.99, 1.00, 1.02 (5s, 15H, 5Me), 1.00–2.00 (m, 24H, CH_2, CH), 1.25 (s, 3H, 30-H), 2.25 (dt, 1H, 19-H, *J* 10.2 and 4.2 Hz), 2.60 and 2.65 (2d, 2H, 29-H, *J* 4.8 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 217.8 (3-C), 181.6 (28-C), 60.3 (20-C), 57.7 (29-C), 54.9, 50.5, 49.9, 48.0, 46.7, 42.5, 40.8, 39.9, 38.6, 37.0, 36.3, 34.9, 33.7, 30.2, 27.9, 26.5, 26.5, 20.0, 18.2 (30-C), 16.9, 16.2, 16.1, 16.0, 15.9, 15.1, 14.8. Found (%): C, 76.15; H, 9.88. Calc. for $C_{30}H_{46}O_4$ (%): C, 76.55; H, 9.85.

‡ *Crystallographic data*: crystals of **5** ($C_{34}H_{54}O_5$, *M* = 542.77) are orthorhombic, space group $P2_12_12_1$, at 293 K: *a* = 12.568(3), *b* = 15.626(4), *c* = 15.830(4) Å, *V* = 3108.9(13) Å^3, *Z* = 4 (*Z*′ = 1), d_{calc} = 1.160 g cm^{-3}, μ(MoKα) = 0.76 cm^{-1}, *F*(000) = 1192. Intensities of 22872 reflections were measured with a Smart 1000 CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans with 0.3° step in ω and 20 s per frame exposure, 2θ < 56°], and 7471 independent reflections were used in further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The positions of hydrogen atoms were calculated from the geometrical point of view and refined in the riding model. The refinement converged to wR_2 = 0.2262 and GOF = 0.748 for all independent reflections [R_1 = 0.0525 was calculated against *F* for 2126 observed reflections with $I>2\sigma(I)$]. All calculations were performed using the SHELXTL PLUS 5.0 program.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 239561. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

§ Evidence for the formation of the aldehyde group was given by the signals of 28-C atoms at 206 ppm and 28-H at 9.60 ppm, as described elsewhere.[13]

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