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EPOXIDATION OF ALNUS-5-EN-3β-YL ACETATE AND CONVERSION OF DENDROPANOXIDE INTO DATURADIOL

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Contrary to the reported literature, the main epoxide derived from alnus-5-en-3β-yl acetate (1) was shown to be a β-epoxide. Daturadiol (=olean-12-ene-3β,6β-diol) was prepared from dendropanoxide *via* 1 and its α-epoxide.

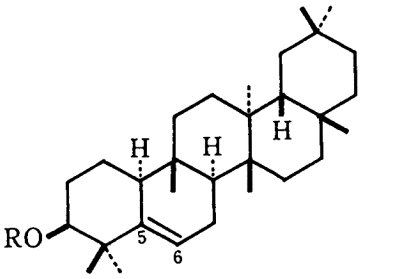
We have been investigating $BF_3 \cdot OEt_2$-catalyzed backbone rearrangement of triterpene epoxides which possess the epoxy ring on the terminal ring, such as 3,4-epoxyfriedelane,[1] 3,4-epoxyshionanes,[2] 3,4-epoxy-D:A-friedo-18β,19αH-lupanes,[3] and 13,18-epoxybaccharane derivative.[4] Being interested in the reaction behavior of a carbonium cation or its equivalent induced by a cleavage of an epoxide ring on B-ring, we examined $BF_3 \cdot OEt_2$-catalyzed backbone rearrangement of 5,6-epoxy-alnusan-3β-yl acetate.

Sengupta *et al.*[5] reported the epoxidation of glut-5-en-3β-yl acetate (=alnus-5-en-3β-yl acetate) (1) with *m*-chloroperbenzoic acid (*m*CPBA) to give an epoxide as the sole product and the molecular rearrangement of the epoxide, to which α-orientation of the epoxy ring was assigned from steric consideration and NMR spectra. In this paper, we wish to describe the conclusion that the assignment of the epoxide was erroneous, and also the conversion of dendropanoxide (2)[6] into daturadiol (3).[7]

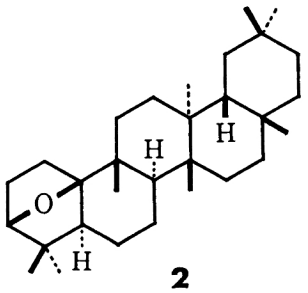
Alnus-5-en-3β-ol (4),[6] prepared from dendropanoxide (2)[8] was acetylated to give alnus-5-en-3β-yl acetate (1), which was epoxidized with *m*CPBA in $CHCl_3$ at 0 °C. The reaction product showed two spots on TLC. Column chromatographic separation afforded a major epoxide (5; in 77% yield) with a small R_f value, mp 220.5-221 °C (lit.[5] mp 216-218 °C), ^{1}H NMR δ 3.05 (t, J=3 Hz) and 4.74 (t-like, $W_{\frac{1}{2}}$=6 Hz) and a minor epoxide (6; in 16% yield) with a large R_f value, mp 234-245 °C (decomp.), ^{1}H NMR δ 3.20 (t-like, $W_{\frac{1}{2}}$=3 Hz) and 4.86 (dd, J=9 and 6 Hz). The major epoxide (5) was identical with "Sengupta's epoxide."

Treatment of the minor epoxide (6; 33 mg) with $BF_3 \cdot OEt_2$ in C_6H_6 at room temperature afforded two products. The less polar product (8 mg) was shown to be alnusa-1(10),5-dien-3β-yl acetate (7)[5] containing a small amount of other diene-mixture. The polar product (25 mg) was found to be a mixture of two unsaturated hydroxy acetates (8 and 9) by ^{1}H NMR spectrum (δ 2.06 (3H, s, -OAc), 4.03 (1H, m, $C_{(6)}$-H), 4.44 (1H, dd, J=9 and 6 Hz, $C_{(3\alpha)}$-H), 4.84 (0.5H, s, an olefinic-H), and

5.23 (0.5H, m, an olefinic-H)).[9] Since the attempted separation of the mixture was not successful, the mixture was oxidized with Jones reagent and subsequently hydrolyzed with KOH in CH_3OH to give a mixture (18 mg) of keto alcohols (12 and 13), separation of which by HPLC[11] afforded pure keto alcohols 12 and 13. The keto alcohol (12; 9 mg),[12] mp 217.5-219 °C with t_R=15.7 min, showed a base peak at m/e 177 characteristic of olean-18-ene derivatives[13] and a characteristic signal at δ 4.89 due to an olefinic proton at C-19 of olean-18-ene skeleton and, therefore, keto alcohol (12) is inferred to be 3β-hydroxyolean-18-en-6-one. Acetylation of 12 afforded a pure keto acetate (10).[14]



1 R=Ac
4 R=H
16 R=COPh



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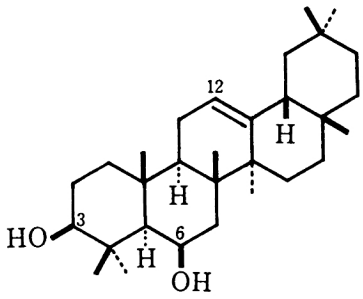

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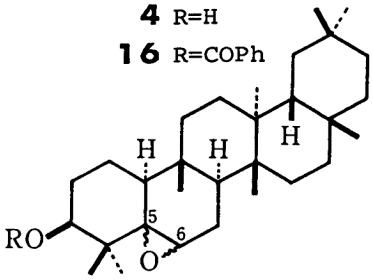
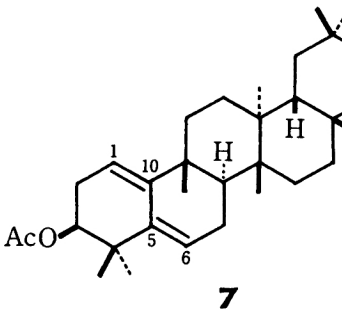


5 5β,6β-epoxide; R=Ac
6 5α,6α-epoxide; R=Ac
15 5β,6β-epoxide; R=H
17 5β,6β-epoxide; R=COPh
18 5α,6α-epoxide; R=COPh



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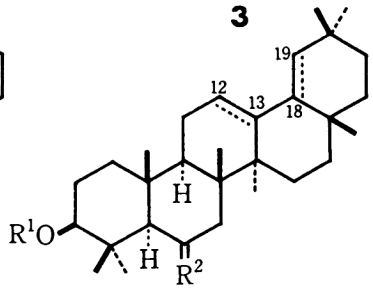
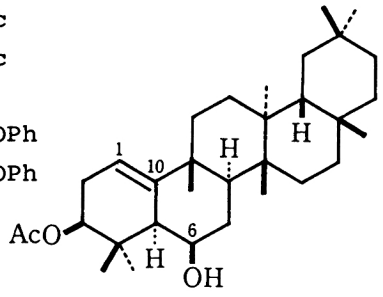


8 R^1=Ac, R^2=α-OH, β-H; Δ^{18}
9 R^1=Ac, R^2=α-OH, β-H; Δ^{12}
10 R^1=Ac, R^2=O; Δ^{18}
11 R^1=Ac, R^2=O; Δ^{12}
12 R^1=H, R^2=O; Δ^{18}
13 R^1=H, R^2=O; Δ^{12}
14 R^1=Ac, R^2=α-H, β-OH; Δ^{12}



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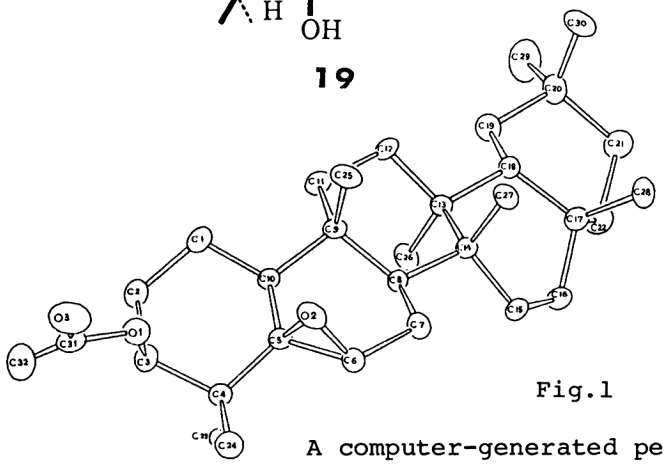

Fig.1

A computer-generated perspective drawing of 5β,6β-epoxyalnusan-3β-yl acetate (5)

The other keto alcohol (11; 9 mg)[15] with t_R=16.3 min, showed a signal at δ 5.21 in ^{1}H NMR, characteristic of an olefinic $C_{(12)}$-proton of olean-12-ene skeleton, and on acetylation, it gave a pure keto acetate (11),[16] mp 246-248 °C. The ^{1}H NMR spectral data of the acetate (11) were identical with those of 6-oxo-olean-12-en-3β-yl acetate derived by Pyrek *et al.*[7] from natural daturadiol (3).

On treatment with $LiAlH_4$, the keto acetate (11) afforded a diol (7 mg) as the sole product, which must have 3β,6β-dihydroxy structure and was shown to be completely identical with daturadiol (3).[7] Thus the conversion of D:B-friedooleane derivatives (2 and 6) into daturadiol (3) was accomplished, which formally constitutes the total synthesis of 3.[17,18] The diol obtained from 11, was acetylated to give a hydroxy acetate (14),[19] whose ^{1}H NMR signals were observed at δ 4.45 ($C_{(3\alpha)}$-H), 4.55 ($C_{(6\alpha)}$-H), and 5.23 ($C_{(12)}$-H). Since $C_{(6\alpha)}$-H of 14 resonates at δ 4.55, C-6 proton of the mixture of unsaturated hydroxy acetates (8 and 9) observed at δ 4.03, should be assigned to β-configuration. This assignment leads to the conclusion that the minor epoxide (6) should be a 5α,6α-epoxide, and therefore, the major epoxide (5) a 5β,6β-epoxide, which is an opposite configuration to that assigned by Sengupta *et al.*[5]

In order to clarify the discrepancy, following experiments were carried out. Alnus-5-en-3β-ol (4) was epoxidized with *m*CPBA in $CHCl_3$ to give a 5β,6β-epoxide (15)[20] as the sole product, which was confirmed by acetylation of 15 into 5. Then, the benzoate (16), on epoxidation under the same conditions, gave both isomers (17 and 18)[20] in 1:1 ratio. The hydrogen-bond[21] assisted an exclusive attack of the reagent from the β-face of 4 in the former case, while in the latter case, the attack from β-face was hindered by the rather bulky benzoate group resulting in a 1:1 ratio of the products. These considerations could explain the formation ratio of the epoxides (5 and 6) in epoxidation of alnus-5-en-3β-yl acetate (1).

Unequivocal proof for the structure of the major epoxide (5) was proven by single-crystal X-ray analysis. Crystals of 5 obtained from CH_3COCH_3 belong to orthorhombic space group $P2_12_12_1$ (z=4) with the cell parameters of a=12.618, b=32.776, and c=6.837 Å and D_c=1.14 g.cm^{-3}. The R-factor was 0.047. Figure 1 is a computer-generated perspective drawing of the molecule of 5.

Treatment of the major epoxide, 5β,6β-epoxyalnusan-3β-yl acetate (5; 147 mg) with $BF_3 \cdot OEt_2$ in C_6H_6 at room temperature afforded mainly alnusa-1(10),5-dien-3β-yl acetate (7; 4 mg) and 6β-hydroxyalnus-1(10)-en-3β-yl acetate (19; 97 mg).

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8) Leaves of *Gilibertia trifidas* MAKINO were collected at the Botanical Gardens, Faculty of Science, The University of Tokyo.
9) Mass spectrum of the mixture (8 and 9): m/e 484 (M^+), 466, 451, 424, 406, 391, 218 (base peak), 205, 204, 189, 187, and 177.
10) δ 5.23 (t-like, J=3 Hz, H-12), 4.90 (s, H-19), 4.43 (dd, J=9 and 6 Hz, H-3α), and 2.05 (s, -OAc); m/e 482 (M^+), 467, 422, 407, 218 (base peak), 205, 204, 189, and 177.
11) HPLC: ALC/GPC 202/401 (Waters Assoc.) μ-PORASIL 1/8 (inch) × 1 (foot); solvent 20% Et_2O-hexane; flow rate 2.0 ml/min; RI detector.
12) Mp 217.5-219 °C (from $CHCl_3$-MeOH); δ 4.88 (1H, s, H-19), 3.13 (1H, dd, J=9 and 6 Hz, H-3α); IR (film) 3350 and 1710 cm^{-1}; m/e 440 (M^+), 425, 218, 205, 204, 189, and 177 (base peak); High MS m/e 440.3659. Calcd for $C_{30}H_{48}O_2$; M 440.3654. m/e 177.1623. Calcd for $C_{13}H_{21}$: 177.1643.
13) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, J. Am. Chem. Soc., 85, 3688 (1963).
14) Mp 220.5-222 °C (from Et_2O-MeOH); δ 4.89 (1H, s, H-19), 4.40 (1H, dd, J=8 and 6 Hz, H-3α), and 2.03 (3H, s, -OAc); IR (film) 1730 and 1710 cm^{-1}; m/e 482 (M^+), 467, 218, 205, 204, 189, and 177 (base peak); High MS m/e 428.3741. Calcd for $C_{32}H_{50}O_3$; M 428.3758. m/e 177.1634. Calcd for $C_{13}H_{21}$: 177.1642.
15) Mp 243-245 °C (decomp.) (from Et_2O-hexane); δ 5.21 (1H, t, J=3 Hz, H-12), 3.16 (1H, dd, J=9 and 5 Hz, H-3α); IR (film) 3450 and 1710 cm^{-1}; m/e 440 (M^+), 425, 218 (base peak), 205, and 203; High MS m/e 440.3613. Calcd for $C_{30}H_{48}O_2$ M 440.3653. m/e 218.2027. Calcd for $C_{16}H_{26}$: 218.2033.
16) Mp 246-248 °C (from $CHCl_3$-CH_3COCH_3); δ 5.23 (1H, t, J=3 Hz, H-12), 4.42 (1H, dd, J=9 and 6 Hz, H-3α), 2.05 (3H, s, -OAc); m/e 482 (M^+), 467, 218 (base peak), 205, 203, 189, and 177; High MS m/e 482.3743. Calcd for $C_{32}H_{50}O_3$: M 482.3758. m/e 218.1998. Calcd for $C_{16}H_{26}$: 218.2033.
17) Conversion of friedelin into dendropanoxide (2): M. Tori, T. Torii, K. Tachibana, S. Yamada, T. Tsuyuki, and T. Takahashi, Bull. Chem. Soc. Jpn., 50, 469 (1977).
18) Total synthesis of friedelin: R. E. Ireland and D. M. Walba, Tetrahedron Lett., 1976, 1071.
19) δ 5.23 (t-like, J=3 Hz, H-12), 4.55 (br s, H-6α), 4.45 (m, H-3α), 2.06 (s, -OAc); m/e 484 (M^+), 218 (base peak), 205, 204, 203, and 189.
20) 15: δ 3.51 (br s, H-3α), 3.11 (t-like, J=3 Hz, H-6α); 17 and 18: δ 4.99 (br s, H-3α), 3.27 (br s, H-6α for 18), 3.13 (m, H-6α for 17).
21) The ^1H NMR spectra of 1, 4, and 16 indicate that -OH, -OAc, and -OBz groups are located in 3β-axial conformation, respectively.

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