Communications to the Editor

Chem. Pharm. Bull.
32(6)2464—2467(1984)

A PARTIAL SYNTHESIS OF ISOMULTIFLORENOL FROM DENDROPANOXIDE

Masaki Takai,[a] Motoo Tori,[a] Takahiko Tsuyuki,[a] Takeyoshi Takahashi,*,[a]
Akiko Itai,[b] and Yoichi Iitaka[b]
Department of Chemistry, Faculty of Science, The University of Tokyo,[a]
Faculty of Pharmaceuticial Sciences, The University of Tokyo,[b]
Hongo, Bunkyo-ku, Tokyo 113, Japan

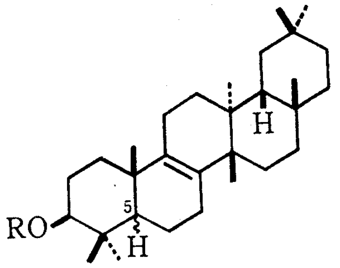
Epoxidation of alnus-5(10)-en-3β-yl acetate (3) with *m*-chloroperbenzoic acid gave a 5α,10α-epoxide (4), which was subjected to the $BF_3 \cdot OEt_2$-catalyzed backbone rearrangement to afford multiflora-5,8-dien-3β-yl acetate (6) as a main product. Hydrogenation of the diene (6) followed by hydrolysis gave isomultiflorenol (1a).

KEYWORDS —— dendropanoxide; 5α,10α-epoxyalnusan-3β-yl acetate; multiflora-5,8-dien-3β-yl acetate; isomultiflorenyl acetate; 5β-isomultiflorenol; epoxidation; backbone rearrangement; X-ray analysis

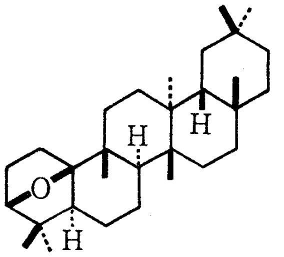
Isomultiflorenol (1a) is a triterpene alcohol isolated from *Cucumis*[1)] and *Bryonia*[2)] (Cucurbitaceae), *Zanthoxylum* (Rutaceae)[3)], and *Pelargonium* (Geraniaceae)[4)] species. The structure, 5α-multiflor-8-en-3β-ol (=D:C-friedoolean-8-en-3β-ol) was determined by isomerization from multiflorenol and rearrangement of 1a into β-amyrin, together with spectral data.[5)] This paper describes a partial synthesis of isomultiflorenol (1a) from dendropanoxide (2) through a thermodynamically favorable pathway.[6)]

Alnus-5(10)-en-3β-yl acetate (3)[7)] was prepared from dendropanoxide (2)[8)] and epoxidized with *m*-chloroperbenzoic acid (MCPBA) in chloroform at 0°C. The reaction product, showing a single spot on TLC, was purified by silica-gel column chromatography to give 5α,10α-epoxyalnusan-3β-yl acetate (4)[9)] in 97% yield. The unambiguous structure of 4 was provided by X-ray single crystal analysis.[10)] Contrary to the epoxidation of alnus-5-en-3β-yl acetate (5),[11)] it was shown that the epoxidation of the 5(10)-ene (3) occurred from the α-side exclusively.

The α-epoxide (4; 52mg) was treated with $BF_3 \cdot OEt_2$ (1.2 eq) in benzene (10 ml) at room temperature for 25 min under nitrogen atmosphere. After the usual work-up, the reaction mixture was shown to consist of a main product (6; *ca.* 80% yield) and more than seven minor components by HPLC examination (column: μPORASIL, solvent: 1% ether-hexane, detector: RI). The reaction mixture was subjected to separation by column chromatography on silica gel (elution: 50% benzene-hexane) to give the crude product (6), which was further separated by chromatography on alumina impregnated with silver nitrate (elution: 5% ethyl acetate-hexane). The product (6; 40 mg)[12)] gave a single peak at t_R 18.9 min on HPLC; mp 190-193°C (from benzene-methanol); no characteristic UV absoption maximum. The ^{1}H NMR spectrum[12)] showed the presence of a doubly allylic methylene (δ 2.60, 2H, m) and an olefinic proton (δ 5.71, 1H, dd), which are assignable from mechanistic considerations to $C_{(7)}$-H_2 and $C_{(6)}$-H, respectively, the methylene group being located in the allylic position both to the trisubstituted $C_{(5)}$- $C_{(6)}$ double bond and to a tetrasubstituted $C_{(8)}$-$C_{(9)}$ double bond. This is also supported by the mass spectral measurement; the appearance of peaks at *m/z* 239 (**A**), *m/z* 227 (**B**), and *m/z* 171 (**C**) indicates the presence of $C_{(8)}$-$C_{(9)}$ double bond together with $C_{(5)}$- $C_{(6)}$ double bond. Thus multiflora-5,8-dien-3β-yl acetate (**6**) is proposed for the main rearranged product.



1 a: R=H, 5α-H
b: R=H, 5β-H
8 a: R=Ac, 5α-H
b: R=Ac, 5β-H



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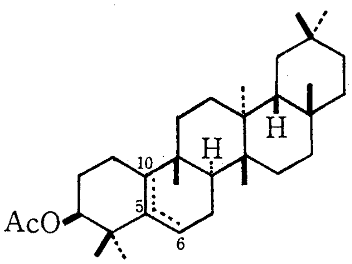
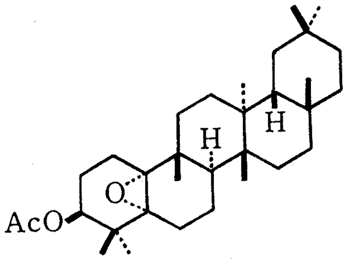


3 : 5(10)-ene
5 : 5-ene



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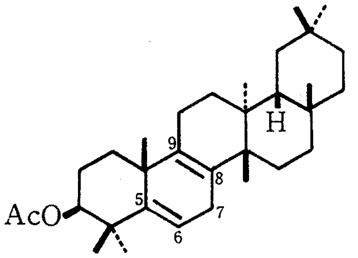
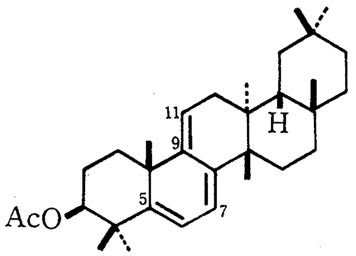
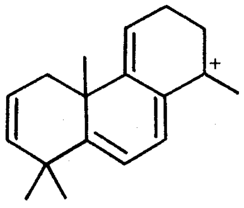


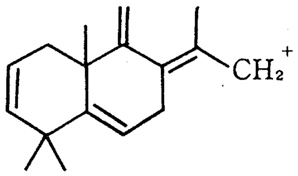
6



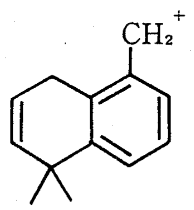
7



A



B



C

The diene (**6**; 30 mg) was treated with selenium dioxide (14 mg) in boiling aqueous benzene for 38 h to give a dehydrogenation product (**7**; 21.6 mg),[13)] the ^{1}H NMR and UV spectra (λ_{max} 307 and 317 nm) indicating the presence of a $\Delta^{5,7,9(11)}$-triene moiety. Thus the structure of **7** was inferred to be multiflora-5,7,9(11)-trien-3β-yl acetate.

The diene (6) in a mixture of ethyl acetate and acetic acid was hydrogenated over 5% palladium on carbon. The hydrogenation required a very long reaction time and the starting material remained, even after hydrogenation, for more than a week. Using an amount of the catalyst equivalent to that of **6**, the hydrogenation of **6** was completed within 2.5 d to afford the product in 91% yield, which was found to consist of **8a** and **8b** in a ratio of 2:5 by GC (column: Dexsil 300 GC, 2%, 1.5 m; t_R 21.4 and 16.3 min for **8a** and **8b**) and HPLC (t_R 17.0 and 18.8 min for **8a** and **8b**). Inspection using a Dreiding model revealed that the hydrogenation from the α-side was hindered because the diene molecule bends towards the α-side so much that the adsorption onto the surface of catalyst was impeded. Hydrogenation from the β-side is also hindered by the presence of 4β- and 10β-methyl groups, but the steric hindrance on the β-side is less effective than that on α-side. Therefore the major hydrogenation product is deduced to be a 5β-isomer (8b) and the minor one is a 5α-isomer, isomultiflorenyl acetate (8a). Separation of the mixture by HPLC afforded **8a** and **8b**, both of which exhibited nearly the same mass spectra characteristic of multiflor-8-ene skeleton.14) The minor product (8a)15), mp 223-225°C (from dichloromethane-methanol) was identical with isomultiflorenyl acetate in respect to ^{1}H NMR, IR, and mass spectra.2) On alkaline hydrolysis of **8a** afforded isomultiflorenol (1a).4,16,17) The 5β-isomer (8b)18), mp 151-152°C (from dichloromethane-methanol) gave 5β-isomultiflorenol (1b)19) by hydrolysis.

The conversion of dendropanoxide (2) into isomultiflorenol (1a) was thus achieved *via* 5α,10α-epoxyalnusan-3β-yl acetate (4), which formally constitutes the total synthesis of **1a**.20)

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8) Dendropanoxide (2) was obtained from leaves of *Gilibertia trifidas* MAKINO, which were collected at the Botanical Gardens, Faculty of Science, the University of Tokyo.
9) mp 272-273°C (from chloroform-methanol); ^{1}H NMR (CDCl$_3$) δ 0.97 (3H, s), 0.99, 1.02, and 1.03 (each 6H,s), 1.15 (3H, s), 2.00 (3H, s), 4.77 (1H, dd, *J*=10 and 4 Hz); MS *m/z* 484 (M$^+$), 466, 406 (base peak), 391, 205, and 202; Found: *m/z* 484.3867. Calcd for $C_{32}H_{52}O_3$: M 484.3914.
10) Crystals of **4** belong to a monoclinic space group C_2 with the cell parameters

of a=13.446(4), b=6.739(2), c=32.257(7) Å, and β=103.71(3)° ; Z=4. Intensity data were measured on a Philips PW1100 automatic four-circle diffractometer using monochromated Cu Kα radiation. A total of 2951 independent reflections with $F_o \geq 2.5\sigma(F_o)$ were obtained by 2θ - θ scanning mode. The structure was solved by the direct method using the MULTAN80 program and was refined by the block-diagonal least-squares method. The final R-value was 0.056.

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12) IR (KBr) 1735, 1250, 1035, 1020, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (6H, s) 1.01 (3H, s), 1.10 (6H, s), 1,12, 1.14, and 1.18 (each 3H, s), 2.04 (3H, s), 2.60 (2H, m), 4.50 (1H, dd, J=8 and 6 Hz), and 5.71 (1H, dd, J=5 and 3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.2, 21.2, 21.3, 24.1, 25.1, 25.2, 25.2, 25.8, 27.1, 27.6, 28.3, 30.9, 31.1, 31.7, 33.1, 33.8, 34.2, 34.5, 34.5, 36.8, 36.8, 37.3, 38.4, 40.4, 40.7, 44.2, 79.1, 120.2, 131.1, 134.0, 146.4, and 170.7; MS m/z (%) 466 (M^+; 5), 406 (15), 391 (100), 239 (13), 227 (28), 187 (18), 185 (20), and 171 (43); Found: m/z 466.3791. Calad for $C_{32}H_{50}O_2$: M 466.3809.

13) mp 211-214°C (from chloroform-methanol); IR (KBr) 1740, 1250, 1035, 1005, 980, and 850 cm^{-1}; UV (ethanol) λ_{max} (ε) 307 (11600) and 317 nm (12200); ^1H NMR ($CDCl_3$) δ 0.84, 0.96, 0.99, 1.02, 1.06, and 1.09 (each 3H, s), 1.21 (6H, s), 2.07 (3H, s), 4.57 (1H, dd, J=6 and 5 Hz), 5.38 (1H, m), 5.57 (1H, d, J=6 Hz), and 5.89 (1H, d, J=6 Hz); MS m/z (%) 464 (M^+;7), 404 (100), 389 (21), 251 (26), 237 (26), and 225 (80); Found: m/z 464.3649. Calcd for $C_{32}H_{48}O_2$: M 464.3654.

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15) ^1H NMR ($CDCl_3$) δ 0.88 (6H, s), 0.98 (12H, s), 1.07 (6H, s), 2.03 (3H, s), and 4.48 (1H, dd, J=11 and 5 Hz); IR (KBr) 1735, 1445, 1380, 1255, 1025, 1005, and 990 cm^{-1} ; MS m/z (%) 468 (M^+; 58), 453 (15), 408 (21), 393 (23), 301 (28), 289 (17), 241 (26), 229 (27), 218 (64), 205 (100), and 189 (23).

16) mp 182-183°C (from chloroform-methanol); IR (Nujol) 3370 and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3H, s), 0.97 (9H, s), 0.99, 1.00, 1.06, and 1.07 (each 3H, s), and 3.23 (1H, dd, J=11 and 5 Hz); MS m/z (%) 426 (M^+; 100), 411 (29), 408 (31), 393 (43), 259 (83), 247 (55), 241 (56), 229 (65), 218 (77), 205 (98), 204 (50), 191 (40), and 189 (44).

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18) IR (film) 1730, 1245, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (3H, s) and 4.54 (1H, t, J=3 Hz); MS m/z (%) 468 (M^+; 74), 453 (58), 408 (21), 393 (62), 301 (57), 289 (29), 241 (100), 229 (93), 205 (94), 203 (49), and 189 (58).

19) MS m/z (%) 426 (M^+; 69), 411 (100), 408 (36), 393 (55), 259 (64), 247 (32), 241 (66), 229 (64), 218 (10), 205 (50), 203 (37), and 189 (60).

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(Received April 19, 1984)