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BIOMIMETIC CONVERSION OF EPOXYGERMACRENE-D TO A NOVEL SESQUITERPENE OF THE PLANT TORILIS JAPONICA DC.

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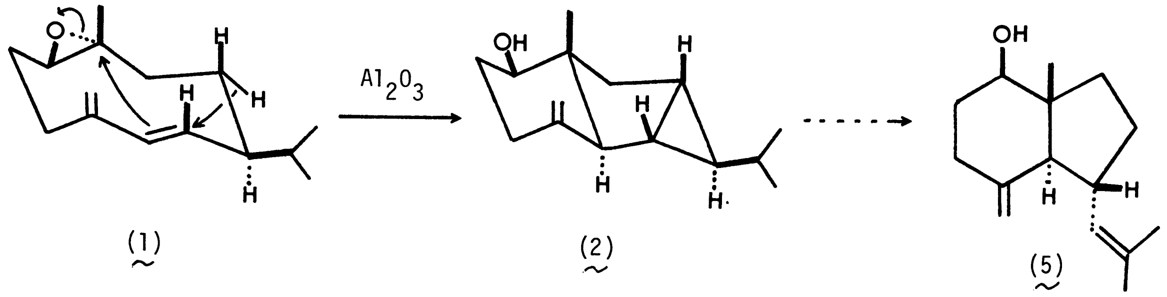
Epoxygermacrene-D was treated with basic alumina to afford a new type of sesquiterpene, whose stereostructure was determined on the basis of its spectral data coupled with an X-ray crystallographic analysis of the corresponding ketone produced on CrO_3 oxidation.

In the light of sesquiterpene biosyntheses, we reported the biomimetic reactions of germacrones and epoxygermacrones affording a number of sesquiterpenes with new carbon skeleton,[1] although some of them have not yet been found in nature. In the present paper, we wish to describe biomimetic reaction of epoxygermacrene-D (1) with basic alumina, affording a biogenetically interesting sesquiterpene (2), which has been recently isolated from the plant Torilis japonica DC. (Japanese name, "Yabujirami"),[2] in addition to the known periplanone-A-type compound.[3]

A solution of epoxygermacrene-D (1) in hexane was adsorbed on basic alumina [Nakarai Chemicals, 300 mesh] at room temperature for 2.5 h, and then eluted with successively with hexane, hexane - Et_2O (1 : 1) and AcOEt.[3] The AcOEt fraction was directly acetylated with Ac_2O - pyridine (room temp., overnight),[4] and then purified by a combination of column chromatography [1) Mallinckrodt 100 mesh, $CHCl_3$; 2) 10% $AgNO_3$ - SiO_2, hexane - benzene (5 : 1)] and preparative TLC [10% $AgNO_3$ - SiO_2, hexane - benzene (3 : 1)] to afford a tricyclic sesquiterpene with one AcO group (3)[5] in ca. 11% overall yield, which was readily converted into the original hydroxy compound (2),[6] in almost quantitative yield, on hydrolysis with 1% methanolic KOH (room temp., overnight).

2 as a colorless oil: $C_{15}H_{24}O$ [m/e 220(M^+)]; ν_{max} (film) 3350br., 3080, 1665 and 885 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.52(1H, br.s), 0.80(3H, s), 0.94(6H, s),[7] 3.48(1H, dd, J= 5, 11Hz) and 4.78(2H, br.s); ^{13}C NMR ($CDCl_3$): δ13.8(q), 21.7(q), 21.7 (q), 24.4(d), 24.6(d), 31.1(t), 32.3(d), 34.0(t), 42.7(t), 48.5(d), 57.7 (d), 59.0(s), 77.2(d), 105.4(t) and 145.7(s).

Scheme 1. Formation process of the tricyclic sesquiterpene (2)

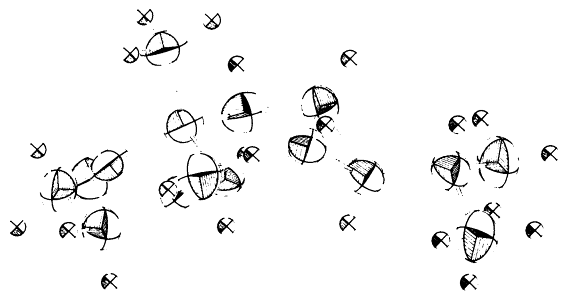


The ^1H and ^{13}C NMR spectra of 2 indicate the presence of three Me groups (δ0.80 and 0.94), one secondary OH group (δ3.48 and 77.2) and one exocyclic double bond (δ4.78, 105.4 and 145.7). This compound (2) was subjected to oxidation using CrO_3 - pyridine (room temp., 5 h) to afford the corresponding ketone (4)[8] [mp 94 - 95 °C (from hexane - Et_2O); $C_{15}H_{22}O$ (m/e 218(M^+))], in ca. 50% yield, whose stereostructure was directly determined by means of an X-ray crystallographic analysis, as follows.

CRYSTAL DATA: $C_{15}H_{22}O$, MW 218.3, monoclinic, $P2_1/c$, a = 11.457(2), b = 10.402(2), c = 11.022(2) Å, β = 91.06(2)°, Z = 4, U = 1313.4(4) Å^3, D_x= 1.10 g.cm^{-3}, D_o= 1.10 g·cm^{-3}.

A total of 1102 non-zero independent reflections with $2\theta<50°$ was measured on a Rigaku-automated four-circle diffractometer using $2\theta-\omega$ scan technique and graphite monochromated Mo Kα radiation. The structure was solved by direct method usnig MULTAN program.[9] Block-diagonal least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens reduced R to 0.045.[10] The figure is a computer generated ORTEP drawing of the molecule (50% ellipsoids). Accordingly,

Fig. A computer generated ORTEP drawing of the molecule 4

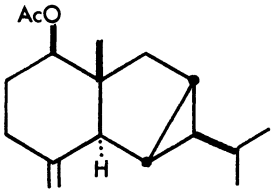


the stereostructure of the tricyclic sesquiterpene must be represented by 2, in which the carbinyl proton at C_1-position is in an axial configuration, as judged from its ^1H NMR signal at δ3.48(1H, dd, J = 5, 11Hz).

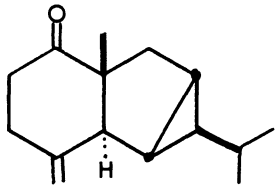
As shown in Scheme 1, 2 may be directly produced from epoxygermacrene-D (1) and, biogenetically, we can not rule out a possibility, in which 2 is a plausible intermediate of the oppositol-type compound such as 5 produced on acid-catalyzed cyclization of 1,[11] although its acetate (3) is quite stable to such acids as 80% aq.AcOH, AcOH - H_2SO_4, BF_3 etherate and $AlCl_3$ in Et_2O. We further examined some chemical properties of the acetate (3), as follows.

When ozonized in MeOH at -78 °C and then decomposed with Me_2S, 3 was readily converted into the corresponding acetoxy ketone (6)[12] in 90% yield, which was further treated with 1% methanolic KOH (room temp., 5 h) and then with Ac_2O - pyridine (room temp., overnight) to afford a stable epimer (7)[13] of 6 *via* 8[14] in 54% overall yield. This epimer seems to be converted into axisonitrile-1.[15]

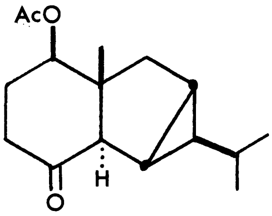
Further studies on chemical conversion of 2 into oppositol- and axisonitrile-type sesquiterpenes are in progress.



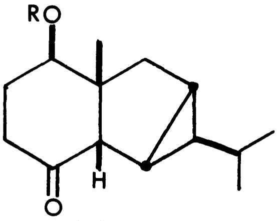
(3)



(4)



(6)



(7) R = Ac
(8) R = H

References

1. M. Niwa, M. Iguchi, and S. Yamamura, Bull. Chem. Soc. Jpn., **49**, 3137 (1976); *ibid.*, **49**, 3148 (1976) and many references cited therein.
2. Private communication from Prof. S. Mihashi (Tokyo Colledge of Pharmacy): the structure of the newly isolated sesquiterpene from the plant *Torillis japonica* DC. was elucidated by direct comparison of its spectral data with those of our synthetic compound (2).
3. M. Niwa, M. Iguchi, and S. Yamamura, Tetrahedron Lett., **1979**, 4291.
4. At this stage, we could not separate the tricyclic compound (2) in completely pure state.
5. 3 as a colorless oil: $C_{17}H_{26}O_2$ [m/e 262(M^+)]; ν_{max} (film) 3080, 3040, 1740, 1660 and 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ0.55(1H, m), 0.86(3H, s), 0.93(3H, s), 1.98(3H, s), 4.71(1H, dd, J= 5, 11Hz) and 4.80(2H, br.s).
6. On acetylation with Ac_2O - pyridine, this compound was readily converted into 3.
7. In the ^1H NMR signals assignable to the isopropyl group, the δ-value of the methine proton seems to be quite similar to those of the remaining two methyls, although the methine signal is overlapped with other signals and not observed accurately.

8. Spectral data of 4: ν_{max} (film) 3090, 1715, 1665 and 890 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.58(1H, m), 0.98(3H, s), 0.97(3H, s), 1.12(3H, s) and 5.08(2H, m). On crystallization, this ketone was obtained in racemic form ($[\alpha]_D^{23}$ ±0°), because the optical purity of the starting sample of germacrene-D is 18.0% (M. Niwa, M. Iguchi, and S. Yamamura, Chem. Pharm. Bull., 28, 997 (1980)).
9. G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., A27, 368 (1971).
10. The atomic coordinates, the bond lengths and angles between inter- and intra-molecule, and some details will be published elsewhere.
11. M. Niwa, M. Iguchi, and S. Yamamura, Tetrahedron Lett., 1978, 4043.
12. 6 as a colorless oil: $C_{16}H_{24}O_3$ [m/e 264(M^+)]; ν_{max} (film) 1730br. cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.48 (1H, m), 0.92(6H, s), 0.97(3H, s), 2.01(3H, s) and 5.02(1H, dd, J= 5, 11Hz).
13. 7 as a colorless oil: $C_{16}H_{24}O_3$ [m/e 264(M^+)]; ν_{max} (film) 1740 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.54(1H, m), 0.94(6H, s), 1.19(3H, s), 2.10(3H, s) and 4.98(1H, dd, J= 4, 8Hz).
14. 8 as a colorless oil: $C_{14}H_{22}O_2$ [m/e 222(M^+)]; ν_{max} (film) 3440 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.50(1H, m), 0.93(6H, br.s), 1.17(3H, s) and 3.78(1H, dd, J= 5, 8Hz).
15. H. Adinolfi, L. De Napoli, B. Di Blasio, A. Iengo, C. Pedone, and C. Santacroce, Tetrahedron Lett., 1977, 2815 and references cited therein.

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