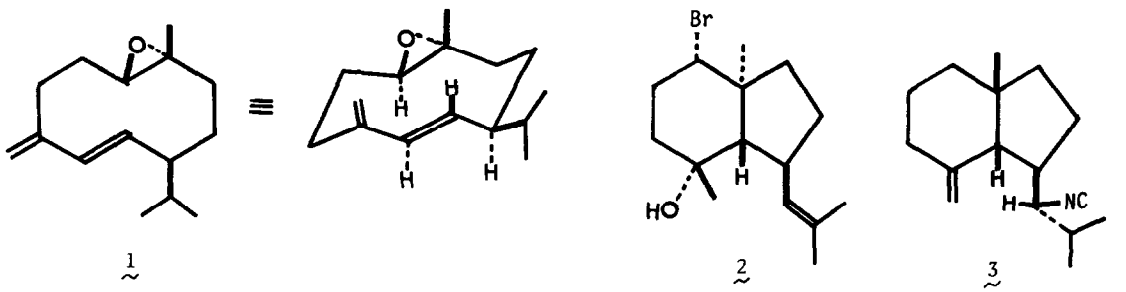
Tetrahedron Letters No. 42, pp 4043 - 4046.
0040-4039/78/1015-4043$02.00/0

BIOMIMETIC REACTIONS OF EPOXYGERMACRENE-D

Masatake Niwa, Masanobu Iguchi, and Shosuke Yamamura*
Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya, Japan

Our continuous studies have been made on biomimetic reactions of germacrenes.[1] We further examined the biomimetic reactions of epoxygermacrene-D (1) in connection with our synthetic studies on periplanone-B,[2] a sexual stimulant for the American cockroach. Although epoxygermacrene-D has been already produced on oxidation of germacrene-D[3] with m-chloroperbenzoic acid,[4] its stereostructure remains undecided. In the present paper, we wish to describe the acid-catalyzed reactions of epoxygermacrene-D (1) leading to the formation of the new interesting compounds having the same carbon skeleton as those of oppositol (2)[5] and axisonitrile-1 (3).[6] In addition, the selinane-type compounds were also produced, one of which further converted into (+)-junenol (4).[7,8] In the course of these experiments, the stereostructure of epoxygermacrene-D was unambiguously established as 1, as expected.



1 2 3

4

5 R = Ac
6 R = H

11

When treated with 80% aq.AcOH at 0° for 1 h,[1] epoxygermacrene-D (1)[8] was easily converted into two selinane-type compounds (5 and 6) and four oppositol-type compounds (7, 8, 9, and 10) (5, 11.6%; 6, 9.3%; 7, 8.5%; 8, 9.6%; 9, 5.9%; 10, 5.1%).[9] The structures of these reaction products were determined on the basis of their spectral data coupled with some chemical

evidences, as follows.

5: mp 106-108° (from hexane); $C_{17}H_{28}O_3$ [m/e 280(M^+) and 220]; ν_{max}(KBr) 3350br., 1730, 1655, and 1255 cm^{-1}; $\delta(CDCl_3)$ 0.74(3H, s), 0.87(3H, d, J= 7Hz), 0.92(3H, d, J= 7Hz), 1.99(3H, s), 3.44(1H, dd, J= 11,5Hz), 4.55(1H, br.s), 4.79(1H, br.s), and 5.07(1H, t, J= 10Hz).

6 as a colorless oil: $C_{15}H_{26}O_2$ [m/e 238(M^+) and 220]; ν_{max}(film) 3380br., and 1650 cm^{-1}; $\delta(CDCl_3)$ 0.70(3H, s), 0.88(3H, d, J= 7Hz), 0.95(3H, d, J= 7Hz), 1.92(2H, OH), 3.39(1H, dd, J= 11,5Hz), 3.68(1H, t, J= 9.5Hz), 4.69(1H, br.s), and 4.96(1H, br.s).

7 as a colorless oil: $C_{17}H_{28}O_3$ [m/e 280(M^+) and 220]; ν_{max}(film) 3400br., 1740, 1655, and 1250 cm^{-1}; $\delta(CDCl_3)$ 0.63(3H, s), 0.87(3H, d, J= 6.5Hz), 0.93(3H, d, J= 6.5Hz), 1.91(3H, s), 3.52(1H, dd, J= 11,5Hz), 4.65(1H, br.s), 4.70(1H, dd, J= 9,2.5Hz), and 4.73(1H, br.s).

8 as a colorless oil: $C_{15}H_{26}O_2$ [m/e 238(M^+) and 220]; ν_{max}(film) 3400br., and 1650 cm^{-1}; $\delta(CDCl_3)$ 0.66(3H, s), 0.91(3H, d, J= 7Hz), 0.98(3H, d, J= 7Hz), 3.20(1H, dd, J= 9,2Hz), 3.54 (1H, dd, J= 11,5Hz), 4.76(1H, br.s), and 4.90(1H, br.s).

9 as a colorless oil: $C_{17}H_{28}O_3$ [m/e 280(M^+) and 220]; ν_{max}(film) 3400br., 1740, 1655, and 1265 cm^{-1}; $\delta(CDCl_3)$ 0.66(3H, s), 1.51(6H, br.s), 1.99(3H, s), 3.55(1H, dd, J= 12, 5Hz), 4.60(1H, br.s), and 4.87(1H, br.s).

10 as a colorless oil: $C_{15}H_{26}O_2$ [m/e 238(M^+) and 220]; ν_{max}(film) 3350 and 1655 cm^{-1}; $\delta(CDCl_3)$ 0.65(3H, s), 1.25(6H, s), 3.51(1H, dd, J= 10,5Hz), 4.57(1H, br.s), and 4.82(1H, br.s).

The acetoxy compound (5) has each one of hydroxyl and acetoxyl groups, both of which should be in an equatorial configuration, as judged from the coupling constants of the NMR signals at δ3.44 and 5.07. On the other hand, the second selinane-type compound (6) has two equatorial OH groups (δ3.39 and 3.68), one of which must be the acetoxyl group in 5.[10] Thus, when treated with $LiAlH_4$ in ether (room temp., overnight), the compound (5) was readily converted into 6 in a high yield. Finally, the stereostructures of these compounds (5 and 6) were established in connection with that of (+)-junenol (4), as follows.

On oxidation with pyridinium chlorochromate in CH_2Cl_2 (room temp., 2 h), the acetate (5) was easily converted into the corresponding keto acetate [11, mp 132-133° (from hexane); $C_{17}H_{26}O_3$ [m/e 218(M^+- 60)]; ν_{max}(KBr) 1735 and 1710 cm^{-1}(no OH band)], which was further treated with 80% aq. NH_2NH_2 and KOH in triethylene glycol under N_2 (120°, 1.5 h, and then 180°, 2 h) to give (+)-junenol (4)[7] in an 84% yield.

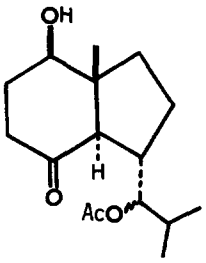
The structures of the remaining four reaction products (7, 8, 9, and 10) were also determined on the basis of their spectral data coupled with some chemical evidences.

As seen in the case of the selinane-type compounds (5 and 6), the acetates (7) and (9) were also converted into the corresponding hydroxy compounds (8) and (10), respectively, on reduction with $LiAlH_4$ in ether (room temp., overnight). From the NMR spectrum of 7, clearly, it has one equatorial OH group (δ3.52), which must come from the epoxy group in 1. In addition, this compound has each one of tertiary Me and i-Pr groups and one exocyclic double bond. Furthermore, the secondary acetoxyl group is newly formed in 7 (δ1.91 and 4.70).

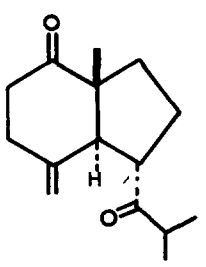
Ozonization of 7 in MeOH followed by decomposition of the ozonide with Me_2S afforded a keto compound in a 65% yield [12: $C_{16}H_{26}O_4$; ν_{max}(film) 3450br., and 1720 cm^{-1}; $\delta(CDCl_3)$ 0.72(3H, s), 0.91(6H, d, J= 7Hz), 1.96(3H, s), 3.94(1H, dd, J= 12,5Hz), and 4.60(1H, dd, J= 8,5Hz); CD spectrum in MeOH: $[\Theta]_{287} = -12.3 \times 10^2$]. The diol (8) was also oxidized with pyridinium

chlorochromate in CH_2Cl_2 (0°, overnight) to give the corresponding diketone in a 78% yield [13: $C_{15}H_{22}O_2$ [m/e 234(M^+) and 163]; ν_{max}(film) 1710 and 1655 cm^{-1} (no OH band); $\delta(CDCl_3)$ 0.98(3H, s), 1.11(6H, d, J= 6Hz), 4.57(1H, br.s), and 4.93(1H, br.s)]. Of the spectral data, particularly, the mass spectrum of the diketone has the remarkable fragment ion peak at m/e 163, indicating the presence of a C_3H_7CO grouping. Furthermore, this diketone (13) was quite stable under basic conditions: e.g. 13 was completely recovered when treated with NaOMe - MeOH (under reflux, 13 h). From these data, the structures of the two reaction products can be represented by 7 and 8, respectively.

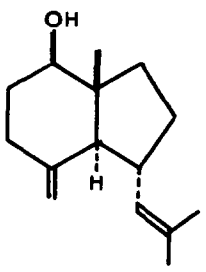
The structures of the remaining two oppositol-type compound (9 and 10) were confirmed by comparing their NMR spectra with those of 7 and 8. As described earlier, the only different point is that 7 has one isopropyl group (δ0.87 and 0.93) and one acetoxymethine group (δ4.70), while 9 has two tertiary Me groups (δ1.51). In the cases of the dihydroxy compounds (8 and 10), the similar differences are also found (δ 0.91, 0.98, and 3.20 in 8; δ1.25 in 10).



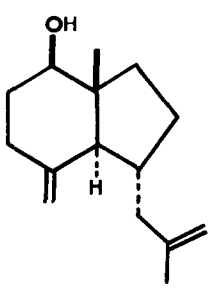
12



13



14



15

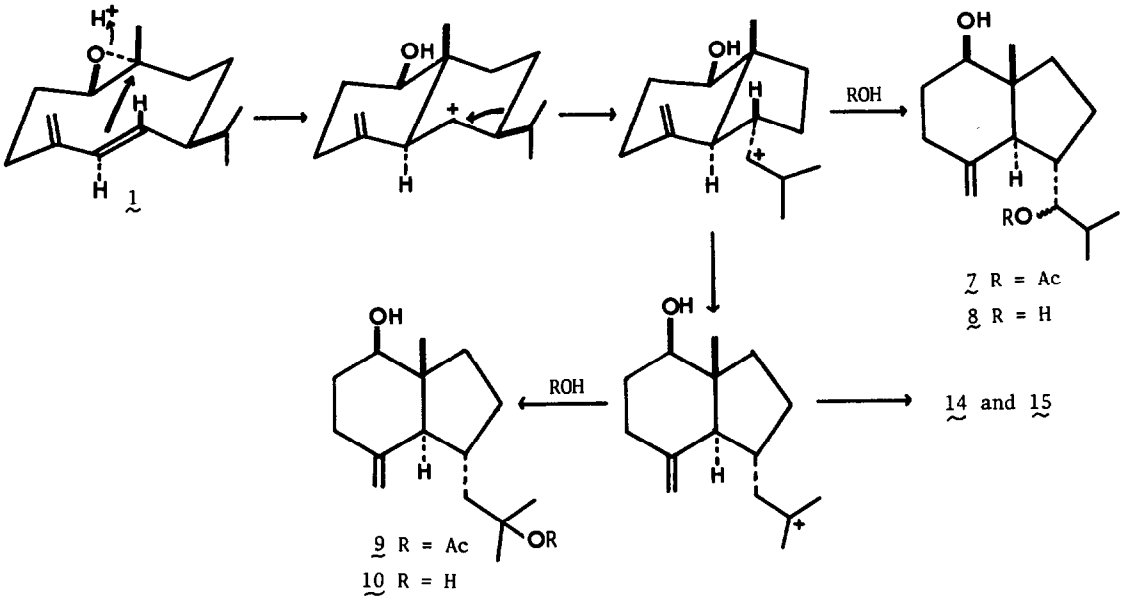
We further examined the acid-catalyzed reaction of epoxygermacrene-D (1) using $AlCl_3$ in ether, as follows.

When treated with $AlCl_3$ in ether under N_2 (-60°, 30 min, and then gradually elevated to 0°), epoxygermacrene-D was readily converted into two oppositol-type compounds (14 and 15) in 23 and 26% yields, respectively, whose structures were also based on their spectral data [14: $C_{15}H_{24}O$ (m/e 220(M^+)); ν_{max}(film) 3350br., and 1655 cm^{-1}; $\delta(CDCl_3)$ 0.68(3H, s), 1.66(6H, d, J= 1Hz), 3.55(1H, dd, J= 11,5Hz), 4.47(1H, br.s), 4.79(1H, br.s), and 4.97(1H, d, quintet, J= 9,1Hz).[11] 15: $C_{15}H_{24}O$ (m/e 220(M^+)); ν_{max}(film) 3350br., and 1655 cm^{-1}; $\delta(CDCl_3)$ 0.66(3H, s), 1.76(3H, s), 3.58(1H, dd, J= 11,5Hz), 4.61(1H, br.s), 4.73(2H, br.s), and 4.89(1H, br.s)].

In particular, it is noted that the NMR spectrum of 14 indicates the presence of a Me_2C=CH-CH- grouping (δ1.66 and 4.97). In the case of 15, there is an isopropenyl group (δ1.76 and 4.73). The other signals in both 14 and 15 are quite similar to those of the reaction products (7, 8, 9, and 10).

From a biogenetic point of view, it seems to be very important that these oppositol-type compounds (7, 8, 9, 10, 14, and 15) have been derived from epoxygermacrene-D (1), as shown in Scheme 1.

Scheme 1. Formation process of the oppositol-type compounds[12]



References and Notes

1. M. Niwa, M. Iguchi, and S. Yamamura, Bull. Chem. Soc. Japan, 49, 3137 (1976); ibid., 49, 3148 (1976) and references cited therein.
2. C. J. Persoons, P. E. J. Verwiel, F. J. Ritter, E. Talman, P. J. F. Nooijen, and W. J. Nooijen, Tetrahedron Lett., 1976, 2055.
3. K. Yoshihara, Y. Ohta, T. Sakai, and Y. Hirose Tetrahedron Lett., 1969, 2263.
4. S. Takahashi, C. Kitamura, and I. Horibe, Agric. Biol. Chem., 42, 79 (1978).
5. S. S. Hall, D. J. Faulkner, J. Fayos, and J. Clardy, J. Am. Chem. Soc., 95, 7187 (1973).
6. H. Adinolfi, L. De Napoli, B. Di Blasio, A. Iengo, C. Pedone, and C. Santacroce, Tetrahedron Lett., 1977, 2815 and references cited therein.
7. M. Niwa, M. Iguchi, and S. Yamamura, Bull. Chem. Soc. Japan, 49, 3145 (1976) and references cited therein.
8. Stereochemical problem on germacrene-D and related compounds will be discussed elsewhere.
9. Each value means an isolated yield.
10. This compound seems to be voleneol, although the spectral data of the former has not been compared directly with those of voleneol (J. J. Hoffmann and J. R. Cole, J. Org. Chem., 43, 1254 (1978)).
11. On irradiation at δ1.66, the NMR signal at δ4.97 became doublet. On the other hand, the doublet at δ1.66 became sharp singlet on irradiation at δ4.97.
12. These reactions may take place in a concerted manner.

(Received in Japan 10 July 1978; received in UK for publication 29 August 1978)