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BIOMIMETIC REACTION OF GERMACRENE-D EPOXIDES IN CONNECTION WITH PERIPLANONE A≠

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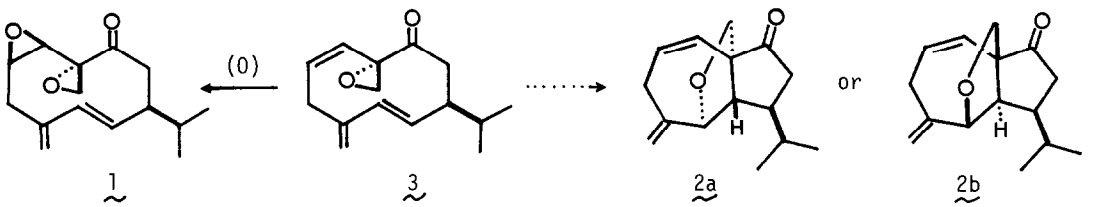
Summary: In order to elucidate the structure of periplanone A, which has been proposed by Persoons et al., one of the two possible 7-methylene-4-isopropyl-12-oxatricyclo[4.4.2.$0^{1,5}$]-9-dodecen-2-ones (2a) has been synthesized from germacrene-D (4), giving some information on periplanone A.

Sex pheromones of the American cockroach Periplaneta americana have been well-known for a long time.[1] Particularly, two biologically active pheromones, periplanone A and periplanone B, have been isolated by Persoons et al.[2] In 1976, the structure of the latter was proposed by the same authors,[3] and then its stereostructure including the absolute configuration was unambiguously determined by its synthesis.[4] In 1982, Persoons et al. also reported that the structure of periplanone A is represented by 2a or 2b.[5] Quite recently, however, Hauptmann et al. have isolated an important epoxygermacrone (3),[6] which is biogenetically regarded as a common precursor of both periplanone A and periplanone B, as shown in Scheme 1, and named it periplanone A, although this pheromone (3) is completely different from Persoons' periplanone A in all respects of its spectral data. Thus, Hauptmann's publication[6] prompted us to report our recent results in a series of our study on biomimetic syntheses of bioactive sesquiterpenes.[7] From a biogenetic point of view, we herein describe the synthesis of the most plausible compound (2a).

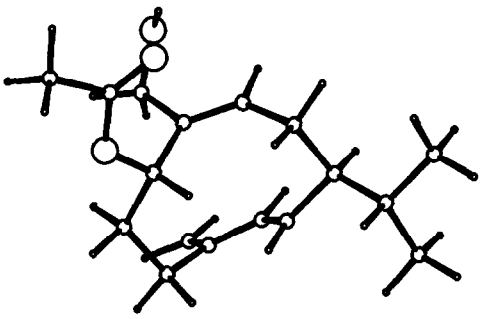


1 3 2a 2b

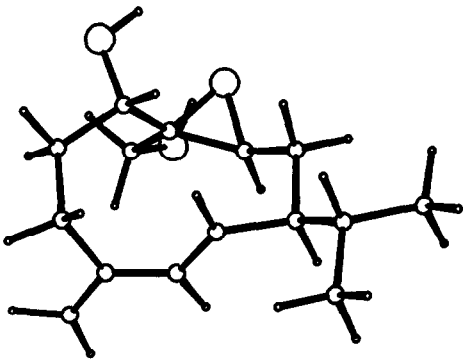
Scheme 1.

On oxidation with SeO_2 (0.2 equiv.) - TBHP (2.0 equiv.) in CH_2Cl_2 (room temp., 5 h) followed by $NaBH_4$ reduction in dioxane - MeOH (10 : 1) (room temp., 5 h), germacrene-D (4)[7] was converted into a desired diol (5), which could be easily separated from the reaction mixture, although its yield was 11%. The stereostructure of 5 was confirmed by its spectral data,[8] particularly ^1H NMR spectrum with aid of NOE experiments (see 5), coupled with molecular mechanics calculations[9] indicating that 5 as an acetate adopts only one CC conformation [A]. Further oxidation of 5 was carried out using $VO(acac)_2$ (2.0% mol) - TBHP (2.2

≠ Dedicated to Professor George H. Büchi on the occasion of his 65th birth day.



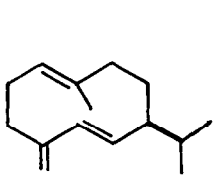
[A] (S.E., 26.1501 Kcal/mol)



[B] (S.E., 31.1455 Kcal/mol)

Fig. 1. The most favorable conformations of the acetate of 5 and the epoxide (6).

equiv.) in CH_2Cl_2 (-18 °C, 4.2 h, under argon) to afford the corresponding epoxide (6),[8] in 68% yield, whose molecular mechanics calculations[10] also indicated that 6 adopts only one CC conformation [B] (see Fig. 1). The acetate (7) was also produced from 5 in 4 steps [1) $^tBuMe_2SiCl$ (1.5 equiv.) - Imidazol (3.0 equiv.) in DMF (room temp., 2.3 h; under argon) (71%); 2) Ac_2O - pyridine (room temp., overnight) (97%); 3) $^nBu_4N^+F^-$ (1.4 equiv.) in THF (0 °C - room temp., 4 h; under argon) (99%); 4) $VO(acac)_2$ (2.0% mol) - TBHP (2.0 equiv.) in CH_2Cl_2 (-15 °C, 7.8 h; under argon) (98%)]. The compound (7) so far obtained was subjected to biomimetic cyclization using HCOOH (room temp., 6 min) to afford a desired tricyclic compound (8),[8] in 25% yield,[11] the stereostructure of which was unambiguously determined by it ^1H NMR spectrum



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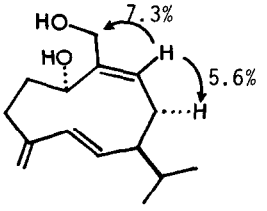

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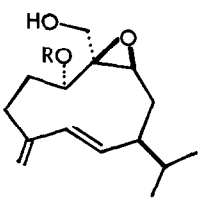
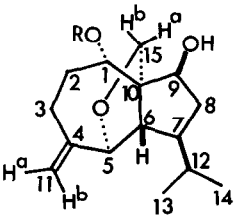
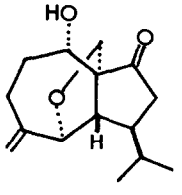


6 R = H
7 R = Ac



8 R = Ac
10 R = H



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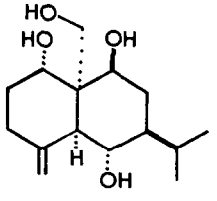

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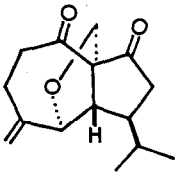

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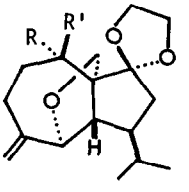
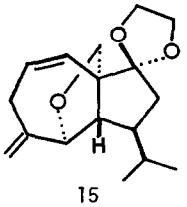


13 R = OH, R'= H
14 R = H, R'= OH



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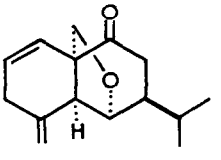

16

with aid of NOE experiments [C_1-H → C_3-β-H (6.4%); C_1-H → C_6-H (9.7%); C_5-H → C_6-H (2.2%); C_5-H → C_7-H (8.5%); C_9-H → C_8-α-H (4.8%); C_{11}-H^a → C_{11}-H^b (18%); C_{11}-H^b → C_5-H (13.2%); C_{15}-H^a → C_9-H (9.2%); C_{15}-H^a → C_{15}-H^b (30%)]. This tricyclic compound (8) was further converted into a ketone (9)[8] in 2 steps [1) PCC (2.0 equiv.) - Celite in CH_2Cl_2 (room temp., overnight); 2) K_2CO_3 in MeOH (room temp., overnight); 73% overall yield], which was also obtained from 6, as follows. On acid-catalyzed cyclization with HCOOH (0 °C, 5 min) followed by treatment with $KHCO_3$ in MeOH (room temp., 2.8 h), 6 was converted into a desired tricyclic compound (10),[8] in 36% yield, in addition to a tetraol (11).[12] The former (10) was further oxidized with PCC (2.1 equiv.) - Celite in CH_2Cl_2 (room temp., 2 h, under argon) to afford 9 and a diketone (12)[8] in 59 and 28% yields, respectively. Finally, the ketone (9) was successfully converted into 2a.

First of all, direct dehydration of 9 was attempted using a number of different methods without success. Therefore, 9 was treated with ethyleneglycol - TsOH in benzene (refluxing temp., 4.3 h; under argon) to afford a ketal (13),[8] in quantitative yield, which was converted into a desired epimer (14)[8] in 2 steps [1) PCC (2.5 equiv.) - Celite in CH_2Cl_2 (room temp., 8 h, under argon) (100%); 2) $NaBH_4$ (2.7 equiv.) in dioxane - MeOH (10 : 1) (room temp., 1.3 h) (81%)[13]]. Then, 14 was subjected to dehydration in 2 steps [1) MsCl (4.0 equiv.) - Et_3N (6 equiv.) in CH_2Cl_2 (-50 °C - room temp., 6.5 h, under argon) (90%); 2) DBU (7.7 equiv.) in DMF (95 °C, 40 min, under argon) (42%)], giving rise to the corresponding olefin (15),[8] which was finally treated with 1M HCl in acetone (room temp., 1 day) to afford 2a in 92% yield. The synthetic compound (2a), in racemic form, showing no biological activity, has the following spectral data: $C_{15}H_{20}O_2$ [m/z 232.1461(M^+)]; IR (film) 1735 and 1640 cm^{-1}; ^1H NMR (400 MHz, CS_2) δ 0.97(3H, d, J= 6.4Hz), 1.07(3H, d, J= 6.8Hz), 1.60(1H, m), 1.83(1H, ddt, J= 6.6, 8.3, 9.8Hz), 1.91(1H, dd, J= 9.8, 18.6Hz), 2.13(1H, d, J= 9.8Hz), 2.64(1H, dd, J= 8.3, 18.6Hz), 2.76(1H, dd, J= 7.8, 17.6Hz), 3.21(1H, ddd, J= 2.5, 3.4, 17.6Hz), 3.83(2H, s), 4.69 (1H, br.s), 4.75(1H, br.s), 4.81(1H, s), 5.65(1H, ddd, J= 2.5, 7.8, 11.2Hz), and 6.09(1H, dd, J= 3.4, 11.2Hz).

Clearly, the spectral data of 2a are quite different from those of periplanone A.[4] As judged from the spectral data of 2a together with molecular model of 2b, furthermore, the structure of periplanone A is not 2b. From a biogenetic point of view, the structure of Persoons' periplanone A seems to be represented by 16.[14]

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8. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 5: $C_{15}H_{24}O_2$ [m/z 236.1764(M^+)]; IR (film) 3350br., 1630, and 1600 cm^{-1}; δ (C_6D_6) 3.89(1H, br.d, J= 11Hz), 4.24(1H, m), 4.33(1H, br.d, J= 11Hz), 4.80(1H, br.s), 4.83(1H, br.s), 4.98(1H, dd, J= 9.0, 15.8Hz), 5.16(1H, dd, J= 7.2, 9.1Hz), and 5.44(1H, br.d, J= 15.8Hz). 6: $C_{15}H_{24}O_3$ [m/z 252.1707(M^+)]; IR (film) 3420, 1640, and 1600 cm^{-1}; δ (C_6D_6) 3.07(1H, dd, J= 4, 11Hz), 3.45(1H, dd, J= 3, 10Hz), 3.55 (1H, d, J= 12Hz), and 4.08(1H, d, J= 12Hz). 7: $C_{17}H_{26}O_4$ [m/z 294.1814(M^+)]; IR (film) 3480, 1730, and 1605 cm^{-1}; δ (C_6D_6) 1.79(3H, s) and 5.02(1H, dd, J= 4, 10Hz). 8: $C_{17}H_{26}O_4$ [m/z 294.1839(M^+)]; IR (film) 3470, 1720, and 1635 cm^{-1}; δ ($CDCl_3$) 0.91(3H, d, J= 6Hz), 0.94(3H, d, J= 6Hz), 1.60(1H, dd, J= 5, 16Hz), 1.65(1H, m), 1.81(1H, m), 1.87 - 2.12(2H, complex), 2.09(3H, s), 2.26(1H, d, J= 9Hz), 2.23 - 2.45(3H, complex), 3.05(1H, br., OH), 3.43(1H, br.d, J= 10Hz), 3.90(1H, br.d, J= 6Hz), 4.07(1H, d, J= 10Hz), 4.43 (1H, s), 4.84(1H, br.s), 4.89(1H, br.s), and 5.21(1H, dd, J= 5, 11Hz). 9: mp 94 - 95 °C; $C_{15}H_{22}O_3$ [m/z 250.1537(M^+)]; IR (film) 3500, 1720, and 1635 cm^{-1}; δ($CDCl_3$) 3.69(1H, br.d, J= 9.3Hz), 3.93(1H, dd, J= 4.4, 10.3Hz), 4.30(1H, d, J= 9.3Hz), 4.40(1H, s, OH), 4.67(1H, s), 4.89(1H, br.s), and 4.94(1H, br.s). 10: $C_{15}H_{24}O_3$ [m/z 252.1716(M^+)]; IR (film) 3400 and 1635 cm^{-1}; δ ($CDCl_3$) 2.08(1H, br., OH) and 4.05(1H, m). 12: mp 106 - 108 °C; $C_{15}H_{20}O_3$ [m/z 248.1398(M^+)]; IR (film) 1750 and 1690 cm^{-1}; δ($CDCl_3$) 4.05(1H, d, J= 10Hz), 4.31(1H, d, J= 10Hz), 4.91(1H, br.s), 4.95(1H, s), and 5.00(1H, br.s). 13: $C_{17}H_{26}O_4$ [m/z 294.1811(M^+)]; IR (film) 3520sh., 3450, and 1630 cm^{-1}; δ ($CDCl_3$) 4.16 (1H, br.dd, J= 4.6, 10.6Hz). 14: $C_{17}H_{26}O_4$ [m/z 294.1814(M^+)]; IR (film) 3500 and 1635 cm^{-1}; δ ($CDCl_3$) 4.06(1H, dd, J= 3.4, 6.4Hz). 15: $C_{17}H_{24}O_3$ [m/z 276.1748(M^+)]; IR (film) 1635 cm^{-1}; δ ($CDCl_3$) 5.67(1H, ddd, J= 3.4, 6.8, 11.7Hz) and 5.99(1H, dd, J= 2.9, 11.7Hz).
9. Program MM2: N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977): QCPE #395.
10. Program MM1 was used in this case.
11. Other reaction products will be presented elsewhere.
12. This compound was characterized as the corresponding acetate, which was obtained on acetylation with Ac_2O - pyridine: $C_{23}H_{34}O_8$ [m/z 438.2232(M^+)]; IR (film) 1730 and 1640 cm^{-1}; δ ($CDCl_3$) 0.80(3H, d, J= 7Hz), 0.83(3H, d, J= 7Hz), 1.93(3H, s), 1.96(3H, s), 2.01(3H, s), 2.07(3H, s), 4.05(1H, d, J= 11Hz), 4.27(1H, d, J= 11Hz), 4.62(1H, br.s), 4.77(2H, complex), 5.04(1H, t, J= 8Hz), and 5.40(1H, dd, J= 5, 11Hz).
13. The ketal (13) was recovered in 18% yield.
14. Will be discussed in the following paper.

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