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THE SYNTHESIS OF A TRICYCLIC HYDROAZULENONE FROM EXO-EPOXYGERMACRENE-D IN CONNECTION WITH PERIPLANONE A

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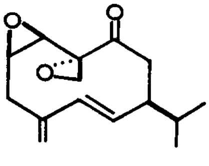
Summary: In connection with periplanone A, acid-catalyzed reaction of germacrene-D epoxide has been carried out using $AlCl_3$ in ether to afford a hydroazulene which has been further transformed into one of the hydroazulenones proposed to be periplanone A.

Two sex pheromones of the American cockroach *Periplaneta americana*, periplanone A and periplanone B, which enter into the corresponding different receptors,[1,2] have been isolated by Persoons et al.[1] The former has been also detected by Nishino et al.[2] Of these two compounds, the stereostructure of periplanone B has been unambiguously determined as 1.[3] Furthermore, the structure (2) of periplanone A has been proposed by Persoons et al., on the basis of its spectral data together with some chemical evidence.[4] In 1986, however, Hauptomann et al. have reported on the isolation and structure of an epoxygermacrone (3), a common precursor of both periplanone A and periplanone B, and named it as periplanone A,[5] although its spectral data are completely different from those of Persoons' periplanone A. On the other hand, we reported the revised structure (4) of Persoons' periplanone A on the basis of an exhaustive comparison of spectral data among the synthetic hydroazulenone (5),[6] periplanone A and its rearrangement product.[4,6] Quite recently, however, Macdonald et al. proposed that germacratrienone oxide (6), a stereoisomer of 3, is periplanone A.[7] In addition, they assigned the structure of Persoons' periplanone A to be 7,[7] which contains a rare trans-fused oxabicyclo[3.3.0]-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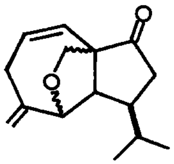
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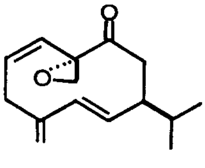
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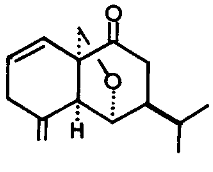
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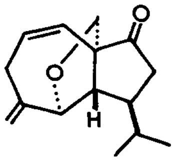
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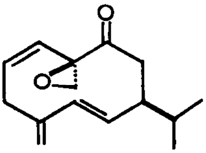
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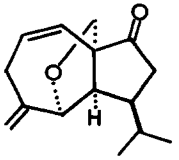
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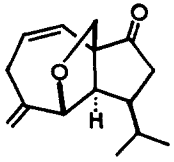
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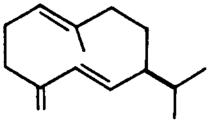
octane system. Their publication prompted us to report on the stereospecific synthesis of another hydroazulenone (8), a stereoisomer of 5 and 7.

Germacrene-D (9)[8] was treated with mCPBA in Et_2O at -15 °C overnight and then LDA in Et_2O at room temperature overnight to give the corresponding allyl alcohol (10),[9] in 95% overall yield, which was oxidized with SeO_2 (0.2 equiv.) - TBHP (2.0 equiv.) in CH_2Cl_2 at room temperature for 24 h to afford two α,β-unsaturated ketones (11 and 12),[9,10] in 26 and 32% yields, respectively. The desired ketone (11) was readily converted into an epoxide (13)[9] in 5 steps: 1) ethyl vinyl ether - PPTS in CH_2Cl_2 (89%); 2) DIBAL-H in THF (88%); 3) Ac_2O - pyridine and then 4) PPTS in EtOH (95% in 2 steps); 5) $VO(acac)_2$ (2.0% mol) - TBHP (2.0 equiv.) in CH_2Cl_2 at -15 °C overnight (90%). This epoxide was further oxidized with CrO_3 - pyridine/Celite in CH_2Cl_2 and then hydrolyzed with K_2CO_3 in MeOH to give rise to a ketone (14),[9]



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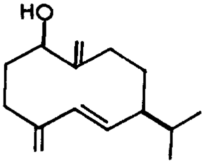

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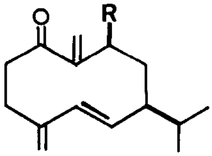
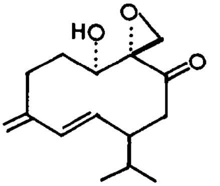
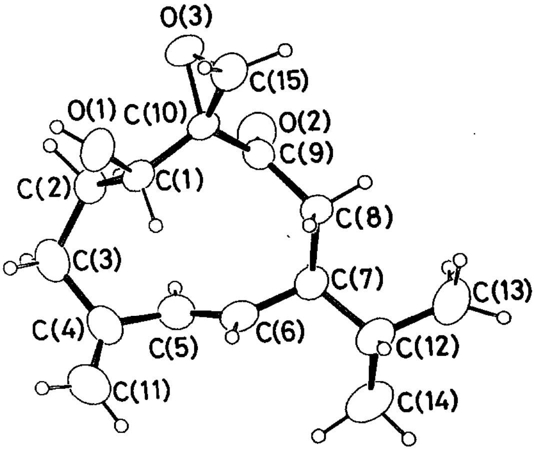


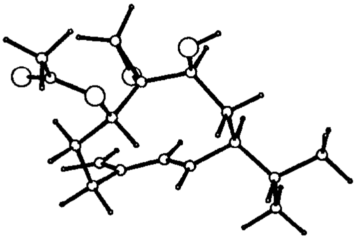
11 R = OH
12 R = H



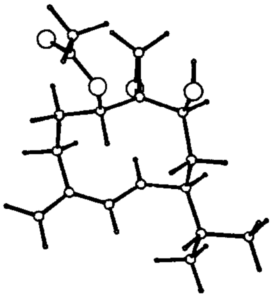
14



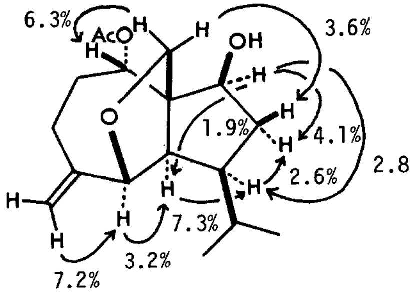
[A]



13a



13b



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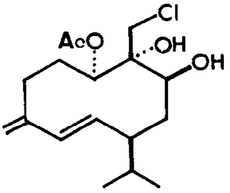
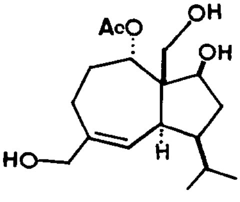


17



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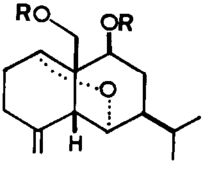

16 R = H
19 R = OAc

in 66% overall yield. The stereostructure of 14 was unambiguously determined by means of an X-ray crystallographic analysis,[11] as shown in an ORTEP drawing [A]. This ketone (14) so far obtained was subjected to acid-catalyzed reaction under various conditions giving a complex mixture. Instead of 14, therefore, the corresponding alcohol (13) was used for cyclization reaction.

In the light of molecular mechanics calculations,[12] this compound adopts two main conformations [13a (S.E.: 34.4436 Kcal/mol); 13b (S.E.: 35.5685 Kcal/mol); 13a : 13b : other conformers = 86 : 13 : 1 at 25 °C]. When treated with $AlCl_3$ (1.2 equiv.) in ether (-70 °C, 40 min and then room temp., 15 min), 13 was readily converted into three reaction products (15, 16 and 17)[9] in 26, 19 and 37% yields, respectively. On treatment of 13 with 6M HCl in THF - H_2O (2 : 5) at room temperature for 24 h, a new hydroazulene (18)[9,13] was obtained in 15% yield, in addition to both 15 and 17 [15 (10%) and 17 (20%)]. Interestingly, all of the cyclization products are formed from 13b. The stereostructure of the desired hydroazulene (15) was based on the NOE experiments, as shown in 15. On acetylation of 16 with Ac_2O - pyridine giving the corresponding diacetate (19),[9] the two doublets at δ 3.71 and 3.97 and one triplet at δ 4.10 were shifted to δ 3.91, 4.27 and 5.02, respectively. The compound (17) was reconverted into the original epoxide (13) in 82% yield when treated with NaH (2.1 equiv.) in THF. Finally, the hydroazulene (15) was successfully converted into the desired hydroazulenone (8) in 3 steps: 1) PCC/Celite in CH_2Cl_2 (88%); 2) K_2CO_3 in MeOH (100%); 3) $SOCl_2$ (5.0 equiv.) - pyridine (15 equiv.) - DMAP (0.9 equiv.) in CH_2Cl_2 (0 °C - room temp., 7.3 h) (15%).[14] The synthetic compound (8) so far obtained has the following spectral data: $C_{15}H_{20}O_2$ [m/z 232.1438(M^+)]; IR (film) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95(3H, d, J= 6.3Hz), 1.07(3H, d, J= 6.4Hz), 1.70(1H, m), 2.06(1H, m), 2.25(1H, dd, J= 8.5, 17.0Hz), 2.58 (1H, dd, J= 11.7, 17.0Hz), 2.70(1H, d, J= 10.8Hz), 2.93(1H, dd, J= 6.9, 18.1Hz), 3.23(1H, m), 3.98(1H, d, J= 9.3Hz), 4.13(1H, d, J= 9.3Hz), 4.83(1H, br.s), 4.90(1H, br.s), 5.19(1H, s), 5.76(1H, ddd, J= 3.3, 6.9, 11.1Hz) and 6.38(1H, dd, J= 3.2, 11.1Hz).

The spectral data (^1H NMR and IR) of both 5 and 8 are quite different from those of Persoons' periplanone A.[4] Particularly, our synthetic hydroazulenones have the CO absorption band at *ca.* 1740 cm^{-1}, while the CO absorption band in periplanone A is observed at 1710 cm^{-1} indicating the presence of a six-membered ring ketone,[4] as seen in 4. Clearly, the unstable structure (7) proposed by Macdonald et al.[7] for Persoons' periplanone A is incorrect. In connection with periplanone A, further study on acid-catalyzed cyclization reaction of germacrene-D epoxides is in progress.

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9. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 10: $C_{15}H_{24}O$ [m/z 220.1846(M^+)]; IR (film) 3370, 1640, and 1605 cm^{-1}; δ(C_6D_6) 3.73(1H, dd, J= 6, 12Hz), 4.83(1H, s), 4.86(1H, s), 4.89(1H, s), 5.09 (1H, s), 5.40(1H, dd, J= 10, 16Hz), and 5.90(1H, d, J= 16Hz). 11: $C_{15}H_{22}O_2$ [m/z 234.1624 (M^+)]; IR (film) 3450, 1670, and 1610 cm^{-1}; δ(C_6D_6) 4.84(1H, m), 5.04(2H, br.s), 5.30 (1H, dd, J= 9.1, 16.0Hz), 5.58(1H, s), 5.85(1H, br.s), and 5.87(1H, d, J= 16.0Hz). 12: $C_{15}H_{22}O$ [m/z 218.1688(M^+)]; IR (film) 1675 and 1610 cm^{-1}. 13: $C_{17}H_{26}O_4$ [m/z 294.1833(M^+)]; IR (film) 3480 and 1730 cm^{-1}; δ(C_6D_6) 1.62(3H, s), 2.59(2H, s), 3.30(1H, dd, J= 4, 8Hz), 4.83(1H, br.s), 4.89(1H, br.s), 5.62(1H, dd, J= 5, 7Hz), 5.78(1H, br.dd, J= 6, 16Hz), and 6.15(1H, d, J= 16Hz). 14: mp 118 - 119 °C (from hexane - Et_2O); $C_{15}H_{22}O_3$ [m/z 250.1550 (M^+)]; IR (film) 3450 and 1700 cm^{-1}; δ(C_6D_6 + D_2O) 2.17(1H, d, J= 5Hz), 2.82(1H, d, J= 5 Hz), and 4.34(1H, dd, J= 4, 7Hz). 15: $C_{17}H_{26}O_4$ [m/z 294.1827(M^+)]; IR (film) 3450, 1735, 1720sh., and 1635 cm^{-1}; δ(C_6D_6) 0.76(3H, d, J= 5.9Hz), 0.78(3H, d, J= 6.4Hz), 1.32(1H, m), 1.56 - 1.65(3H, complex), 1.67(3H, s), 1.79(1H, m), 1.85(1H, m), 2.08(1H, br.dd, J= 8.7, 15.2Hz), 2.31(1H, m), 2.48(1H, d, J= 10.3Hz), 3.54(1H, d, J= 10.3Hz), 3.83(1H, dd, J= 6.1, 11.0Hz), 4.30(1H, d, J= 10.3Hz), 4.71(1H, br.s), 4.77(1H, s), 4.89(1H, br.s), and 5.10(1H, dd, J= 4.4, 5.4Hz). 16: mp 163 - 164 °C (from hexane - EtOAc); $C_{15}H_{22}O_2$ [m/z 234.1595 (M^+- H_2O)]; IR (film) 3350 cm^{-1}; δ($CDCl_3$) 3.71(1H, d, J= 11.5Hz), 3.97(1H, d, J= 11.5Hz), 4.02(1H, d, J= 4.4Hz), 4.10(1H, t, J= 4.7Hz), 4.20(1H, d, J= 3.4Hz), 4.73(1H, t, J= 2.4 Hz), and 4.75(1H, t, J= 2.4Hz). 17: $C_{17}H_{27}O_4Cl$ [m/z 330.1579(M^+)]; IR (film) 3475, 1730, and 1635 cm^{-1}; δ($CDCl_3$) 47.2(t), 73.8(d), 76.4(d), 77.1(s), 111.3(t), 131.8(d), 139.2(d), and 147.6(s). 18: $C_{17}H_{29}O_5$ [m/z 313.2034(M^+ + 1)]; IR (film) 3350 and 1720 cm^{-1}; δ($CDCl_3$) 1.99(1H, m), 2.20(3H, s), 3.19(1H, dd, J= 5.9, 9.0Hz), 3.59(1H, d, J= 12.5Hz), 3.82(1H, dd, J= 5.8, 10.0Hz), 3.94(1H, d, J= 12.5Hz), 4.05(2H, br.s), 5.66(1H, d, J= 5.9Hz), and 5.75 (1H, dd, J= 2.5, 4.0Hz). 19: $C_{19}H_{28}O_5$ [m/z 336.1929(M^+)]; IR (film) 1745 and 1645 cm^{-1}; δ($CDCl_3$) 2.02(3H, s), 2.06(3H, s), 3.91(1H, d, J= 12.2Hz), 4.27(1H, d, J= 12.2Hz), and 5.02(1H, dd, J= 2.0, 4.4Hz).
10. The β-configuration of the OH group was determined by NOE experiments of 15.
11. CRYSTAL DATA OF 14: monoclinic, $P2_1/c$, a = 9.936(2), b = 5.187(1), c = 28.852(5) Å, β = 110.77(1)°, V = 1390.4(4) $Å^3$, Z = 4, D_x= 1.20, D_m= 1.20(1) $g\cdot cm^{-3}$, $\mu(MoK\alpha)$ = 0.076 mm^{-1}.

    The X-ray intensities up to 2θ= 50° were measured on a Rigaku AFC-5 four-circle diffractometer with graphite-monochromatized $MoK\alpha$ radiation. The structure was solved by direct methods and refined by block-diagonal least squares. Final R value was 0.049 for 1586 reflections. Full details will be published in Acta Cryst. Sec. C separately.
12. Program MM2: N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977); QCPE #395.
13. The stereostructure of 18 was based on its NOE experiments.
14. *The corresponding chloride has been mainly obtained, which will be converted into 8.*

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