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DEFENSE MECHANISMS OF ARTHROPODS. XXV. STEREOSPECIFIC SYNTHESIS OF AN ALLENIC SESQUITERPENOID FROM THE GRASSHOPPER ROMALEA MICROPTERA

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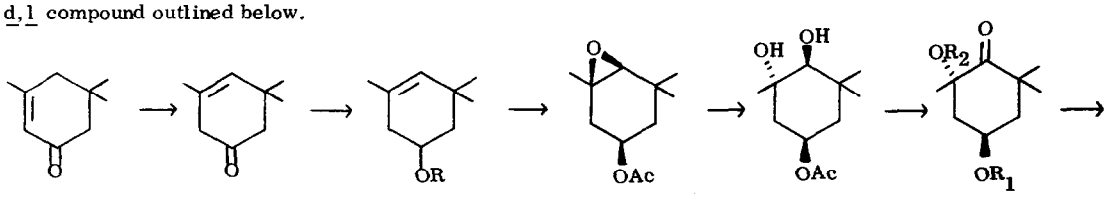
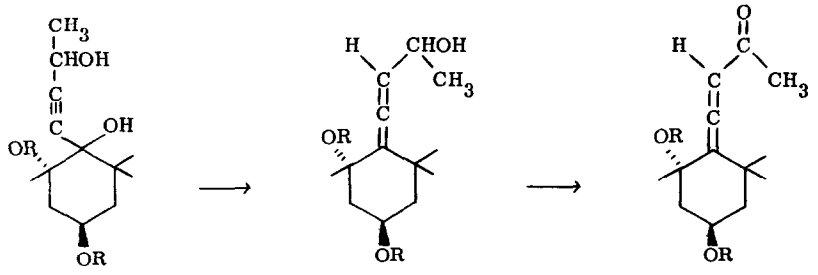
The proposed structure of the novel allenic sesquiterpene 1,[1] isolated from a secretion of the large, flightless grasshopper, Romalea microptera, has now been confirmed by the stereospecific synthesis of the d,l compound outlined below.



2 → 3 → 4 R = H / 5 R = Ac → 6 → 7 → 8 R_1 = Ac, R_2 = H / 9 R_1 = R_2 = H / 10 R_1 = R_2 = TMS / 11 R_1 = R_2 = CH_3

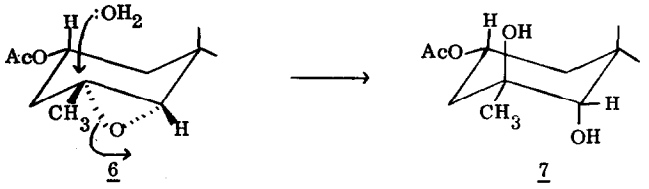


12 R = TMS / 13 R = CH_3 / 14 R = H → 15 R = H / 16 R = TMS / 17 R = CH_3 → 18 R = CH_3 / 19 R = TMS / 1 R = H

β-Phorone(3), prepared by deconjugation of isophorone(2),[2] was reduced with lithium aluminum hydride to give a quantitative yield of the alcohol 4, b.p. ~92°/9.5 mm; IR 2.98 μ; NMR ($CDCl_3$) δ 1.00 (s, 6H), 1.67 (s, 3H), 2.9 (s, 1H, disappears in D_2O), 3.65-4.25 (mult., 1H), 5.08 (broad, s, 1H). Acetic anhydride in pyridine converted 4 to acetate 5, b.p. ~53°/1.3 mm; IR 5.76, 8.0 μ; NMR ($CDCl_3$) δ 1.02 (s, 6H), 1.65 (broad, s, 3H), 2.02 (s, 3H), 4.8-5.2 (mult., 1H), 5.16 (broad, 1H); MS m/e 122 (M-HOAc).

Epoxidation of 5 with m-chloroperbenzoic acid gave 99% of 6, b.p. ~70°/1.5 mm; IR 5.76, 8.05 μ; NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.13 (s, 3H), 1.33 (s, 3H), 2.00 (s, 3H), 2.50 (s, 1H), 4.6-5.2 (mult., 1H); MS m/e 138 (M-HOAc). Epoxide opening with aqueous $HClO_4$ in acetone gave 96% of crude diol acetate 7 (m.p. 126.5° after crystallization from heptane/$CHCl_3$), b.p. ~126°/0.5 mm; IR ($CHCl_3$) 2.86, 2.88, 2.9 (broad), 5.80, 8.0 μ; NMR ($CDCl_3$) δ 1.05 (s, 3H), 1.22 (s, 3H), 1.37 (s, 3H), 2.03 (s, 3H), 2.2 (broad, s, 2H disappear in D_2O), 3.11 (s, 1H), 4.8-5.4 (mult., 1H); MS m/e 156 (M-HOAc).

We anticipated that the epoxidation of 5 would occur from the less hindered side, and that trans diaxial epoxide opening would result in the preferential formation of 7 with the stereochemistry shown.[3] Sarett



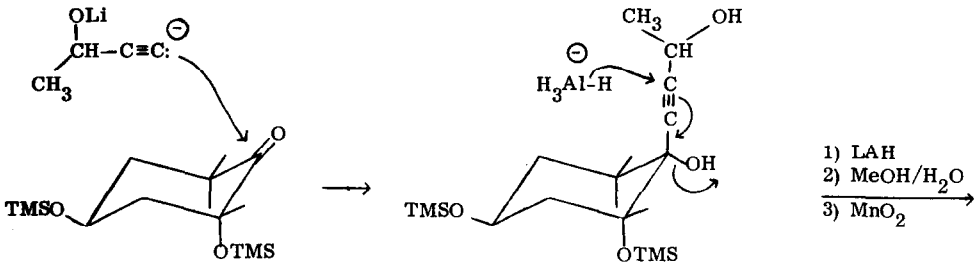
oxidation of 7 gave ketone 8 in 50% yield, b.p.~95°/0.1 mm; IR 2.9, 5.80 (broad), and 8.0μ; NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.29 (s, 3H), 1.38 (s, 3H), 2.08 (s, 3H), 3.9 (1H, disappears in D_2O), 5.13-5.63 (mult., 1H); MS m/e 214.1214 ($C_{11}H_{18}O_4$ requires 214.1204). A 92% yield of 9, whose IR and NMR spectra proved identical to those of an authentic sample of optically active 9 of established structure and stereochemistry,[4] was obtained by treatment of 8 with sodium carbonate in aqueous methanol under nitrogen for 24 hours at room temperature. Racemic 9 showed m.p. 103.5° (recrystallized from hexane/CH_2Cl_2); IR (CH_2Cl_2) 2.8, 5.85 μ; NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.30 (s, 3H), 1.45 (s, 3H), 4.2-4.6 (mult., 1H); MS m/e 172.1104 ($C_9H_{16}O_3$ requires 172.1099).

The acetylenic tetrol 14 was produced by treatment of 9 with a solution made by the reaction of two molar equivalents of methyl lithium with 3-butyn-2-ol. The tetrol showed m.p. 196.5-197° (recrystallized from CH_3CN); IR (KBr) 2.98 μ (strong); NMR (D_2O, external TMS) δ 1.25 (s, 3H), 1.45 (s, 3H), 1.57 (s, 3H), 1.64 (d, J ~ 6.5 cps, 3H); NMR (pyridine, external TMS) δ1.48 (s, 3H), 1.60 (s, J ~ 6.5 cps, 3H), 1.79 (s, 3H), 1.89 (s, 3H); MS m/e 206.1296 (M-2H_2O, $C_{13}H_{18}O_2$ requires 206.1306). Attempts at converting 14 to the allenic triol 15 with lithium aluminum hydride, based on the report of a very similar allene synthesis,[5] were unsuccessful. Protection of the hydroxyl groups of 9 with diazomethane and BF_3 etherate gave the dimethyl ether 11 in quantitative yield; b.p. ~100°/0.1 mm; IR 5.84, 9.10, 9.27 μ; NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 3.07 (s, 3H), 3.37 (s, 3H); MS m/e 200 (M). Addition of the lithium derivative of 3-butyn-2-ol to 11 yielded a mixture of epimeric diols 13; IR 2.95, 9.24 μ; NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.25 (s, 3H), 1.35 (s, 3H), 1.45 (d, J ~ 6.5 cps, 3H), 3.27 (s, 3H), 3.35 (s, 3H), 3.3 (mult., 1H), 4.58 (q., J ~ 6.5 cps, 1H). Lithium aluminum hydride reduction of 13 yielded allene 17;

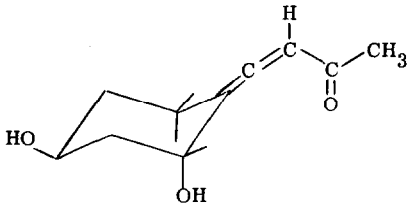
IR 2.95 (broad), 5.10, 9.26 μ; NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.25 (s, 6H), 1.30 (d, J ~ 5.5 cps, 3H), 3.07 (s, 3H), 3.37 (s, 3H), 4.1-4.6 (mult., 1H), 5.40 (d, J ~ 5.5 cps, 1H). This allene was oxidized with MnO_2 in ether to produce 18; IR 2.86, 5.15 (strong), 5.95, 9.12, 9.20 μ; NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.30 (s, 6H), 2.17 (s, 3H), 3.10 (s, 3H), 3.40 (s, 3H), 5.87 (s, 1H); UV (EtOH) λ_{max} 233 mμ; MS m/e 252.1729 ($C_{15}H_{24}O_3$ requires 252.1725). While these spectral data indicated that this product was the dimethyl ether corresponding to the natural allene, demethylation could not be achieved.[6] It appeared, however, that a synthesis of 1 itself might be accomplished if a more readily removable protecting group were used.

The silylated ketone 10, IR 5.80, 7.95 μ; NMR ($CDCl_3$) δ 0.05 (s, 9H), 0.10 (s, 9H), 1.05 (s, 3H), 1.32 (s, 6H), 4.2-4.7 (mult., 1H), was prepared in the standard fashion. Addition of the lithium salt of 3-butyn-2-ol to 10 yielded 12, b.p. ~100°/1 mm; IR 2.95, 7.95 μ; NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.20 (s, 9H), 1.12 (s, 6H), 1.45 (d, J ~ 6.5 cps, 3H), 1.50 (s, 3H), 2.35 (s, 2H, disappear in D_2O), 4.56 (q, J ~ 6.5 cps, 1H); MS m/e 386 (M), 368 (M-H_2O), 371 (M-CH_3), 296 (M-$(CH_3)_3SiOH$). Lithium aluminum hydride reduction of 12 produced a mixture of stereoisomers corresponding to 16, IR 2.95, 5.10, 7.99 μ; NMR ($CDCl_3$) δ 5.38 (d, J ~ 6 cps, 1H), with many overlapping peaks in the methyl region, and hydrolysis of the silyl ethers in aqueous methanol gave an oil whose major component was 15, IR 2.95, 5.10 μ; NMR ($CDCl_3$) δ 1.10 (s, 3H), ~1.28 (d, J ~ 6 cps, 3H), 1.33 (s, 6H), 3.95-4.52 (mult., 1H), 5.41 (d, J ~ 5.5 cps, 1H). Manganese dioxide oxidation and chromatography on silica gel using 3% MeOH/CH_2Cl_2 gave an oil which crystallized from hexane/acetone. The IR, MS, NMR, UV, TLC, and GC of the natural product were identical to those of the crystalline solid (1), m.p. 95.5°; IR (CH_2Cl_2) 2.79 (sharp), 2.89 (broad), 5.15 (strong), 5.96 μ; NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 2.13 (s, 2H, disappears in D_2O), 2.17 (s, 3H), 4.34 (broad, 1H), 5.86 (s, 1H); MS m/e 224.1420 ($C_{13}H_{20}O_3$ requires 224.1412); UV (EtOH) λ_{max} 232 mμ (ε = 12,500). Analogous data for the disilyl ethers 19 derived from the synthetic and natural products correlate excellently.

This synthesis suggests the stereochemistry of the final allene. Assuming that the acetylenic diol 12 is formed with the stereochemistry shown, S_N2' attack by a hydride donor, proceeding with the trans stereochemistry recently suggested for such reactions, would place the allenic proton trans to the adjacent hydroxyl group.[7] An independent synthesis of 1 has just been described,[8,9] and although a direct comparison of the product with the natural material was not carried out, the route also seems to imply this stereochemistry. X-Ray work is now in progress to confirm the three-dimensional structure.



10 12



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Footnotes and References

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3. It should be noted that the epoxide formed by addition of oxygen to the other side of 5 would also give product 7, if trans diaxial opening occurs.
4. T. Wada, Pharm. Bull. Japan, 13, 43 (1965).
5. T. Miki and Y. Hara, Pharm. Bull. Japan, 4, 87 (1956).
6. S. D. Géro, Tetrahedron Letters, 591 (1966).
7. W. T. Borden and E. J. Corey, Tetrahedron Letters, 313 (1969). It is possible that the secondary hydroxyl group of 12 may be coordinated with the hydride donor, however, this would not change the stereochemistry of the final product.
8. S. W. Russell and B. C. L. Weedon, Chem. Commun., 85 (1969).
9. The melting point of natural 1 reported by S. W. Russell and B. C. L. Weedon is higher than that of our d,l product; it is possible that the allene exists in several polymorphic forms.