

Isolation and Synthesis of 3- and 4-Hydroxy-1,7-dioxaspiro[5.5]undecanes from the Olive Fly (*Dacus oleae*)

Raymond Baker,* Richard H. Herbert, and Andrew H. Parton

Department of Chemistry, The University, Southampton SO9 5NH, U.K.

Two novel hydroxyspiroacetals, 3- and 4-hydroxy-1,7-dioxaspiro[5.5]undecane have been isolated from the rectal gland of the female olive fly (*Dacus oleae*) and a stereoselective synthesis of the latter developed.

Alkyl spiroacetals have been isolated from several insect species.¹⁻⁴ Hydroxy-substituted spiroacetals have recently become more important as structural elements of certain antibiotics and anthelmintics such as monensin⁵ and the avermectins.⁶ We now report the isolation and synthesis of two interesting and novel hydroxyspiroacetals from female *Dacus oleae*. In addition a synthesis of 4-hydroxy-1,7-dioxaspiro[5.5]undecane (**2**) is reported which utilises the stereoselective cyclisation and hydration of an unsaturated precursor. The formation of predominantly one product is controlled by the anomeric effect which appears to be crucial in determining the

most favourable conformation of 1,7-dioxaspiro[5.5]undecanes.⁷

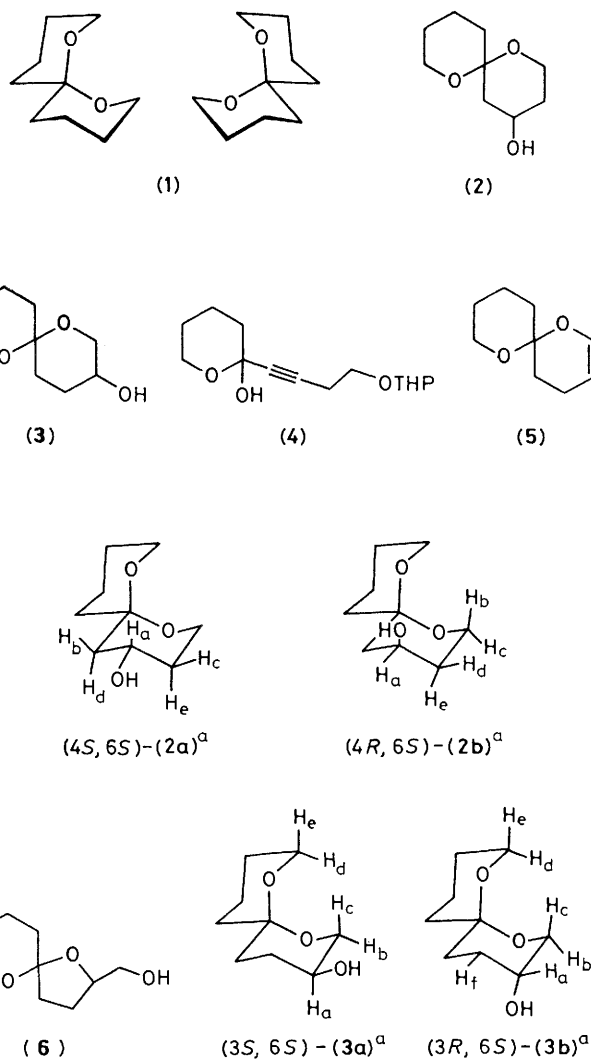
Analysis of the rectal glands of sexually mature *Dacus oleae* by solid sample gas chromatography (s.s.g.c.) previously indicated that the major pheromone component was 1,7-dioxaspiro[5.5]undecane (**1**).⁸ Further studies using s.s.g.c. and g.l.c.-mass spectrometry have confirmed the presence of two minor components at levels of ca. 10 ng per insect. High resolution mass spectroscopy showed the two components (**2**) and (**3**) to have the molecular formula C₉H₁₆O₃; (**2**) *m/z* 172(4%; M⁺), 155(15%), 127(35), 117(100), 114(57), 101(69),

98(77), 83(14), 55(42); (3) m/z 172(5%; M^+), 142(18%), 127(3), 117(16), 114(15), 101(29), 98(100), 83(12), 55(14). The pairs of ions at m/z 98($C_6H_{10}O$), 101($C_5H_9O_2$) and m/z 114($C_6H_{10}O_2$), 117($C_5H_9O_3$) suggested that these were oxygenated 1,7-dioxaspiro[5.5]undecanes. From a consideration of the detailed fragmentation patterns of (2) and (3), and those of alkyl-1,6-dioxaspiro[4.4]nonanes⁹ and alkyl-1,6-dioxaspiro[4.5]decanes,¹⁰ the structures were assigned as 4-hydroxy-1,7-dioxaspiro[5.5]undecane (2) and 3-hydroxy-1,7-dioxaspiro[5.5]undecane (3), respectively. These structures have now been confirmed by synthesis.

4-Hydroxy-1,7-dioxaspiro[5.5]undecane (2) was prepared from (4), obtained by the method of Deslongchamps.⁷ Catalytic hydrogenation of (4) in anhydrous methanol over 5% Pd-BaSO₄ poisoned with quinoline afforded the corresponding monoene as an oil, after filtration and removal of the methanol. The product was dissolved in conc. hydrochloric acid-water-tetrahydrofuran (1:5:20) and stirred for 24 h at room temperature. Neutralisation and ether extraction gave crude (2) (60%). Analysis by g.l.c.† and g.l.c.-mass spectrometry showed that the reaction was very stereoselective, producing the diastereomers (2a) and (2b) in a ratio of 20:1, and these were readily separated by flash chromatography (ether-light petroleum; 1:1); ¹H n.m.r. (C_6D_6): (2a) δ 4.1 (1H, t of t, $J_{a,d} = J_{a,e} = 11$ Hz, $J_{a,b} = J_{a,c} = 5.5$ Hz), 3.5–3.8 (4H, m), 2.0 (1H, d of d of d, $J_{b,d} 13$ Hz, $J_{a,b} 5.5$ Hz, $J_{b,e} 2$ Hz), 1.1–1.9 (10H, m) and (2b) δ 3.8–4.2 (3H, m), 3.2–3.7 (3H, m), 1.1–1.9 (10H, m); addition of a lanthanide shift reagent Eu(fod)₃ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato) to (2b); δ 4.7 (H_a, m), 4.4 (H_b, d of d of d, $J_{b,e} = J_{b,c} = 12$ Hz, $J_{b,d} 3$ Hz). From the ¹H n.m.r. data of (2a) it was observed that the signal for H_a was significantly deshielded by a 1,3-diaxial interaction with a ring oxygen (δ 4.1) and appeared as seven evenly spaced lines, intensity ratio 1:2:3:4:3:2:1. The remaining four protons on carbons adjacent to oxygen had similar chemical shifts to each other, as two were equatorial (deshielded by hyperconjugation) and two were axial and had a 1,3-diaxial interaction with an oxygen. Thus, the ¹H n.m.r. data indicated that (2a) was exclusively in the anomericly stabilised conformation, as shown. From the ¹H n.m.r. spectrum of (2b), after addition of D₂O, it was apparent that H_a and H_b had similar chemical shifts (δ 3.8–4.2, 2H, m), H_b having two 1,3-diaxial interactions with oxygens. Data from lanthanide shift experiments showed that H_a and H_b in (2b) were shifted downfield of H_c–H_e. The signal for H_a in (2b) was an unresolved multiplet, narrow in comparison to that of H_a in (2a). The coupling constants observed for H_b were also consistent with the structure shown. The stereoselectivity of the reaction could be accounted for by epimerisation at the spiro-carbon atom C-6 favouring the sterically less hindered diastereoisomer (2a). The mass spectra and gas chromatographic properties of (2a) were found to be identical to those of the natural product.

The second component (3) was prepared by hydroboration of 1,7-dioxaspiro[5.5]undec-2-ene (5)¹¹ (BH₃-tetrahydrofuran, then alkaline hydrogen peroxide). The two diastereoisomers (3a) and (3b) were purified by preparative h.p.l.c. (Zorbax Sil, ether-heptane, 1:1), and analysed by g.l.c.,† g.l.c.-mass spectrometry, and ¹H n.m.r. (C_6D_6): (3a) δ 3.3–3.8 (5H, m), 1.1–2.2 (11H, m); (3b) δ 3.3–3.7 (5H, m), 1.1–2.2 (11H, m).

These data do not in themselves allow assignment of the specific conformations formed in the reaction. Data from



^a Only one enantiomer shown of each racemic pair. THP = tetrahydropyran-2-yl.

lanthanide shift experiments,‡ however, were fully consistent with formation of the anomericly stabilised conformations (3a) and (3b); ¹H n.m.r. (C_6D_6): (3a) + Eu(fod)₃ δ 5.6 (H_a, br.m), 5.2 (H_b, H_c, m), 3.9 (H_d, H_e, m); (3b) + Eu(fod)₃ δ 5.0 (H_a, m), 4.6 (H_b, d of m, $J_{b,c} 12$ Hz), 4.2 (H_c, d of d, $J_{b,c} 12$ Hz, $J_{a,c} 2$ Hz), 3.9 (H_d, m), 3.7 (H_e, m). The protons on methylenes adjacent to oxygen in (3a) were shifted in pairs (H_b/H_c and H_d/H_e), whereas the corresponding protons H_a–H_e in (3b) were shifted to differing extents (H_d/H_e overlap slightly). This suggested that the hydroxy-group was equatorial in (3a) and axial in (3b). The signal for H_a in (3a) was broad compared to that for H_a in (3b). Coupling constants for (3a) were not readily seen owing to overlap of signals, but the coupling of H_b with H_c in (3b) was observed ($J_{b,c} 12$ Hz). A small observed coupling constant ($J_{a,c} 2$ Hz) is consistent with the fact that H_a and H_c each have a *trans*-coplanar C–O bond. The coupling of H_a to H_b would also be reduced by a C–O bond *trans*-coplanar to the C–H_a bond, but was confused by a further weak coupling to H_f.

Under the conditions of s.s.g.c.-mass spectrometry (140 °C, 5 min) (3a) and (3b) rearranged substantially to 1,6-dioxaspiro-

† G.l.c. analysis; 3 m × FFAP 5% (Diatomite CAAW) analytical column, temperature programme 100–245 °C at 6 °C min⁻¹; retention times (2a) 21.0, (2b) 16.0, (3a) 21.4, and (3b) 19.2 min.

‡ Magnitude of shifts observed not directly comparable between spectra.

[4.5]decan-2-methanol (**6**), identified by comparison of mass spectra and gas chromatographic properties with those of synthetic (**6**).¹¹ This compound was also observed in s.s.g.c.-mass spectrometric studies of female olive flies, but is considered to arise from rearrangement of (**3a**). Under the same conditions (**2a**) and (**2b**) did not undergo any rearrangement.

The biological activity of the components (**2a**) and (**3a**) is currently under investigation and will be reported elsewhere.

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