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SPIROKETALS: THE SYNTHESIS OF AN OLIVE FLY PHEROMONE COMPONENT, 4-HYDROXY-1,7-DIOXASPIRO[5,5]UNDECANE, VIA A NOVEL CATION-OLEFIN CYCLISATION STEP

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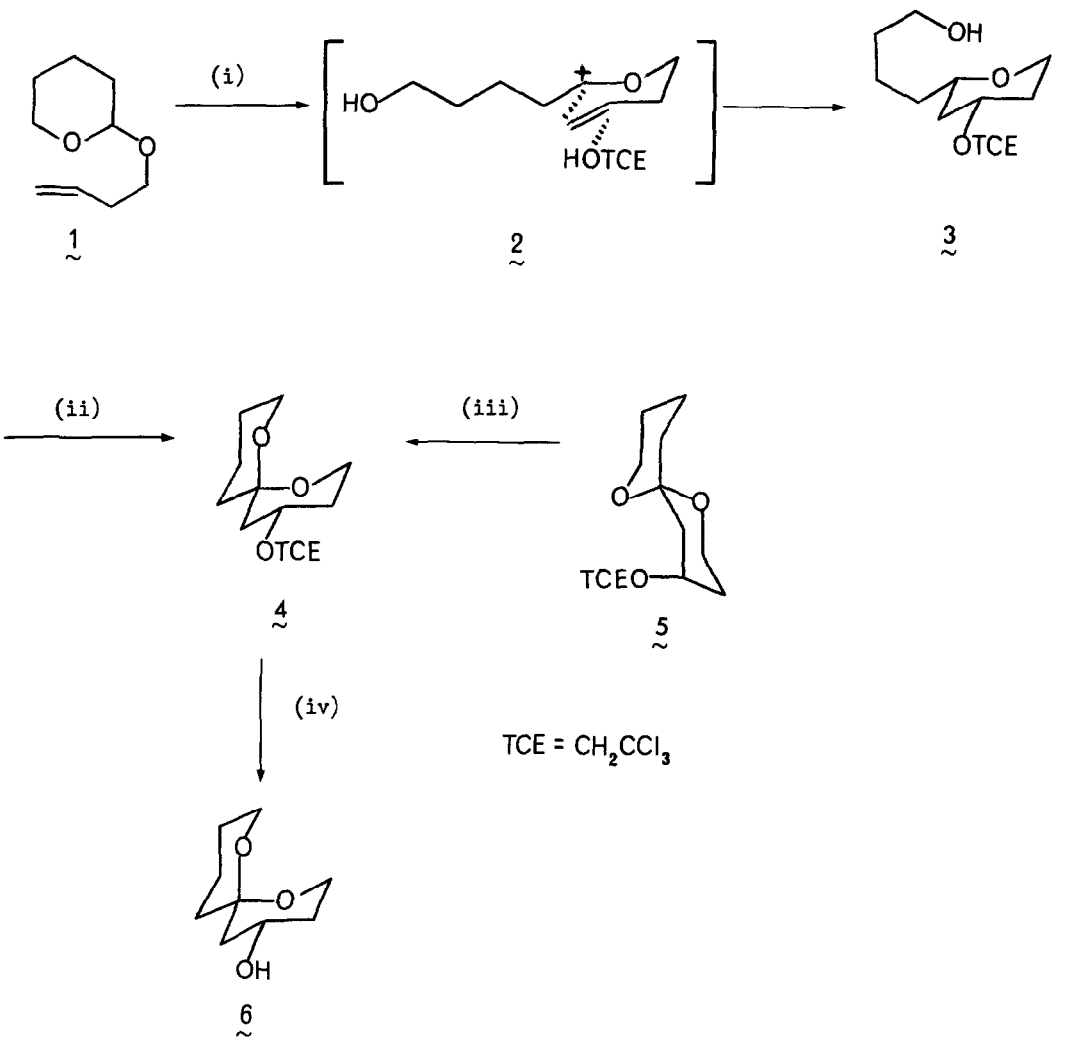
Summary: An acid-catalysed rearrangement of the THP-ether of homoallylic alcohol gives ready access to an O-protected derivative of 4-hydroxytetrahydropyran and thence by two further steps to provide a short and highly stereoselective route to the title spiroketal.

The synthesis of spiroketals, particularly those containing hydroxyl groups has been the subject of much recent work.[1-9] The interest in these spirocycles has been stimulated by their occurrence as structural elements of several important antibiotics[10] as well as their identification as insect pheromones.[11] We have developed a new and highly stereoselective route to 4-hydroxy-1,7-dioxaspiro[5,5]undecanes and report here its application to the synthesis of a pheromone component[1] 6 of the female olive fly Dacus oleae.

Hitherto, most[1-6] approaches to these spiroketals have involved as the key step the addition of carbanions to δ-valerolactones followed by cyclisation of the resultant lactols. Our route (SCHEME) is fundamentally different; the enabling transformation 1-[2]-3 utilises a cation-olefin cyclisation as in 2 to provide a stereoselective route to the protected 4-hydroxytetrahydropyran 3. To our knowledge such a transformation of a THP-ether of an homoallylic alcohol with cleavage of one tetrahydropyran ring and the formation of another has not been reported previously. Thus a mixture of the ether 1 (1 mol), trichloroethanol (3.5 mol) and BF_3OEt_2 (0.5 mol) when kept at room temperature for 18 hr. gave after work up and short-path distillation a 61% yield of the oily product 3[12] as a single[13] isomer. An advantage of using trichloroethanol (rather than, say, formic acid which gives lack of regiospecificity arising from transesterification) as the cation-trapping reagent is that it provides a secure, but easily removeable, O-protecting group leaving the primary -OH group of 3 exposed for further elaboration.

The spirocyclisation of 3 was accomplished via its hypoiodite[14] by heating (ca. 30 min) the compound under reflux in cyclohexane together with iodine (1 equivalent) and mercuric oxide. Under these non-acidic conditions there was obtained mainly the desired spiroketal 4[15] together with variable (up to 30%) amounts of its isomer 5. Brief exposure of the mixture (in cyclohexane) to a catalytic quantity of TFA brought about the complete (C-6) isomerisation of 5 to the less-hindered 4. The formation of 5 probably reflects the cationic (planar) nature of C-6 prior to spirocyclisation. The overall conversion of 3-4 was 50%.



1 2 3 4 5 6

SCHEME

Reagents: (i) HOTCE, BF_3OEt_2; (ii) I_2, HgO; (iii) TFA; (iv) Zn-HCO_2H

Clean removal of the TCE protecting group from 4 proved at first to be unexpectedly difficult due to the intervention of the difficultly reduced dichloroethoxy[16] derivative formed during the zinc-acetic acid reduction. The use of zinc-formic acid overcame this problem. Thus brief (ca. 15 min.) stirring of 4 in 9:1 formic acid and water (NaOAc) together with an excess of activated[17] zinc dust gave (86%) the racemic pheromone component 6 containing less than 2% of its (C-6) isomer[18] (5; TCE=H).

The ^{1}H-NMR and glc retention times for 6 were as reported[1] for the natural product.

We thank Professor R. Baker for an authentic sample of 6 provided for comparative purposes.

References and notes

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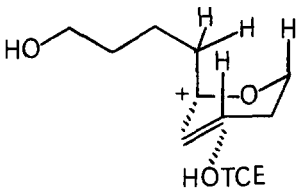
10. For example, milbemycins: H.Mishima, M.Kurabayashi, C.Tamura, S.Sato, H.Kuwano and A.Saito, Tetrahedron Lett., 711 (1975); avermectins: G.Albers-Schonberg, B.H.Arison, J.C.Chabala, A.W.Douglas, P.Eskola, M.H.Fisher, A.Lusi, H.Mrozik, J.L.Smith, and R.L.Tolman, J.Am.Chem.Soc., 103, 4216 (1981); monensin: G.Agtarap, J.W.Chamberlain, M. Pinkerton, and L. Steinrauf, ibid, 89, 5737 (1967); talaromycins: D.G.Lynn, N.J.Phillips, W.C.Hutton, J.Shabanowitz, D.I.Fennell, and R.J.Cole, ibid, 104, 7319 (1982).
11. W.Francke, W.Reith, G.Bergstrom, and J.Tengo, Naturwis., 67, 149 (1980); R.Baker, R.Herbert, P.E.Howse, O.T.Jones, W.Francke, and W.Reith, J.C.S.Chem.Comm., 52 (1980).
12. ^{1}H-NMR, ($CDCl_3$, 90 MHz); 4.12(2H,s),4.0(1H,ddd,J=11.7,5.0,2.5 Hz),3.8(1H,tt,J=10, 5 Hz),3.64(2H,t,J=7 Hz),3.40(1H,td,J=11.7,2.5 Hz),3.24(1H,m),2.1-1.1(11H,m).

13. The alternative mode of cyclisation (below) is presumably disfavoured on steric grounds:



A similar argument has been advanced to account for the stereoselectivity observed in a perhydrohistrionicotoxin synthesis: H.E.Schoemaker and W.N.Speckamp, Tetrahedron, 36, 951 (1980).

14. M.L.Mihailovic, S.Gojkovic, and S. Konstantinovic, ibid, 29, 3675 (1973).

15. ^{1}H-NMR, ($CDCl_3$, 90 MHz): 4.08(2H,s),4.04(1H,tt,J=10,5 Hz),3.8-3.5(4H,m),2.28-1.30 (10H,m).

16. The reduction of trichloroethoxy- to their dichloroethoxy-derivatives has previously been noted but only for electrochemical reduction: M.F.Semmelhack and G.E.Heinsohn, J.Am.Chem.Soc., 94, 5139 (1972).

17. Just prior to use the zinc dust was stirred for 10 min with dilute HCl, washed with water then acetone and dried in vacuo.

18. This is probably formed as the result of the exposure of 5 to the acidic medium (cf. reference 1.) during removal of the protecting group.

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