Hydroxy-functionalized Conjugated Nitroolefins as Immediate Precursors of Spiroketals. A New Synthesis of 1,7-Dioxaspiro[5.5]undecane and (*E*)-2-Methyl-1,7-dioxaspiro[5.6]dodecane

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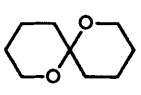
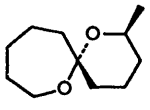
The syntheses of 1,7-dioxaspiro[5.5]undecane **6a**, the major component of sex pheromones of the fruit fly (*Dacus oleae*), and (*E*)-2-methyl-1,7-dioxaspiro[5.6]dodecane **6b**, a component of the pheromone of *Andrena haemorrhoa*, have been achieved in two steps in 64 and 66% yields respectively.

Spiroketals are important subunits of a plethora of biologically active natural products.[1–15]

In the course of our current research program directed towards the total synthesis of insect pheromones incorporating the spiroketal sub-structure, we have reported that functionalized nitroalkanes, which can act as acyl anion synthons, are important precursors in the synthesis of spiro[4.4],[16] spiro[4.5][17] and spiro[4.6]ketal[18] systems. Now we have found that hydroxy-functionalized conjugated nitroolefins can act as immediate precursors for the preparation of spiro[5.5] and spiro[5.6]ketal systems, by a key step realized by their reduction with sodium borohydride. We selected 1,7-dioxaspiro[5.5.]undecane **6a**, the major component of the olive



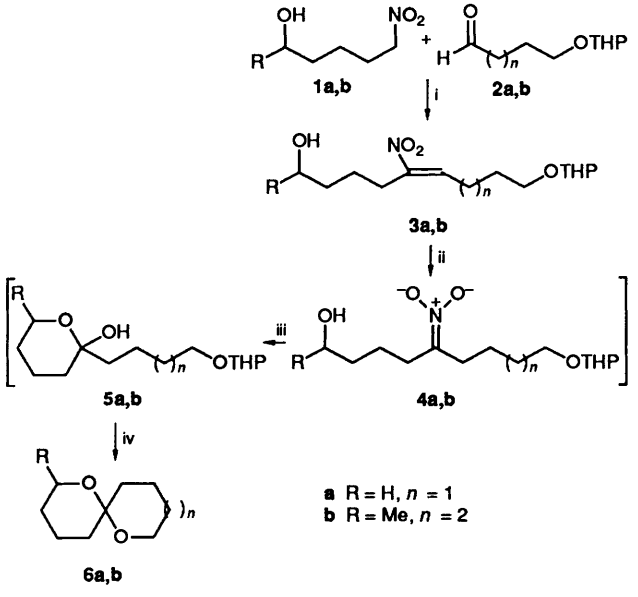
6a



6b

fruit fly (*Dacus oleae*) sex pheromone[14b,d] and (*E*)-2-methyl-1,7-dioxaspiro[5.6]dodecane **6b**, a component of the pheromone of *Andrena haemorrhoa*,[15a,f] as target molecules for a total synthesis to demonstrate this finding.

The starting point of our synthesis (See Scheme 1) was the solvent free nitroaldol reaction, between protected hydroxy aldehydes **2** and 5-nitroalcohols **1** on alumina at room temperature. *In situ* dehydration,[19] with addition of dichloromethane and warming at 40 °C provided, in a one-pot reaction, the nitroalkenes **3**, which were converted directly into the spiroketals **6** by reduction with sodium borohydride in methanol. The tandem reduction–spiroketalization of the nitroalkene **3** probably proceeded *via* the nitronate **4**, that by acidification was converted into a carbonyl derivative which spontaneously cyclized to the hemiketals **5**. Removal of the tetrahydropyranyl group, by heating the acidic mixture at 50 °C, afforded, in a one-pot reaction from **3**, the desired spiroketals **6** in 64–66% yields.



Scheme 1 *Reagents and conditions:* i, Al_2O_3, CH_2Cl_2, 40 °C; ii, $NaBH_4$, MeOH; iii, H^+; iv, 50 °C.

The high stereoselectivity in spiroketalization of **3b** to **6b** was not unexpected in view of previously observations.[20,21]

In summary, the present methodology to obtain spiro[5.5] and spiro[5.6]ketals represents a progressive evolution of a practical utilization of functionalized nitro derivatives as strategic tools for spiroketal synthesis.

Experimental

General.—5-Nitropentan-1-ol **1a** was easily obtained, in 85% yield,* from 2-nitrocyclopentanone,[18] while 6-nitrohexan-2-ol **1b** was obtained, in 80% yield, by reduction of 6-nitrohexan-2-one.[17] The aldehydes **2a** and **2b** were obtained from butane-1,4-diol and pentane-1,5-diol, respectively, following the reported procedure.[22,23]

6-Nitrohexan-2-ol **1b**; ν_{max}/cm^{-1} 3200(OH) and 1530(NO_2); δ_H 1.2–1.8 (6 H, m), 1.1 (3 H, d, *J* 6.14), 3.8–3.9 (1 H, m) and 4.4 (2 H, t, *J* 6.7) (Found: C, 49.1; H, 9.08; N, 9.38. Calc. for $C_6H_{13}NO_3$: C, 48.97; H, 8.9; N, 9.52%).

Synthesis of Nitroalkenes **3**.—A cooled (0 °C) solution of aldehyde **2** (20 mmol) and nitro alcohol **1** (20 mmol) was mechanically stirred for 15 min after which alumina (3 g) was added, and stirring maintained for 30 min at 0 °C. The mixture was then allowed to stand at room temp. for 8 h, before the addition of CH_2Cl_2 (40 cm^3). After stirring at 45 °C for 9 h, the mixture was filtered, and the alumina was washed with CH_2Cl_2 (3 × 20 cm^3). The organic layer of the filtrate was separated off, evaporated and purified by chromatography (cyclohexane–ethyl acetate–ethanol, 3.5:0.5).

(E)-5-*Nitro*-9-*tetrahydropyranyloxynon*-5-*en*-1-*ol* **3a** (3.04 g, 53%); an oil; ν_{max}/cm^{-1} 3380 (OH) and 1500 (NO_2); δ_H 1.4–2.0 (12 H, m), 2.28–2.40 (2 H, m), 2.6–2.7 (2 H, m), 3.18–3.9 (6 H,

* The yield of 5-nitropentan-1-ol **1a** has been improved compared with the original work (Ref. 18), simply by the addition of brine to the reaction mixture, before the extraction with diethyl ether.

m), 4.55 (1 H, m) and 7.15 (1 H, t, *J* 7.8) (Found: C, 58.7; H, 8.9; N, 4.75. Calc. for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87%).

(E)-6-*Nitro*-11-*tetrahydropyranyloxyundec*-6-*en*-2-*ol* **3b** (3.4 g, 54%); oil; ν_{max}/cm^{-1} 3360 (OH) and 1500 (NO_2); δ_H 1.2 (3 H, d, *J* 6.2), 1.4–1.75 (14 H, m), 2.2–2.38 (2 H, m, *J* 7), 2.62 (2 H, t, *J* 7.36), 3.35–3.90 (5 H, m), 4.58 (1 H, m) and 7.10 (1 H, t, *J* 7.8) (Found: C, 61.1; H, 9.4; N, 4.35. Calc. for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44%).

Synthesis of Spiroketals **6**.—A solution of nitroalkene **3** (5.1 mmol) in ethanol (30 cm^3) was cooled at 0 °C, then sodium borohydride (0.45 g, 11.7 mmol) was added. The mixture was stirred for 2 h, then poured into cold 2 mol dm^{-3} HCl (30 cm^3). The solution was extracted with pentane, and the organic layers were combined and dried (Na_2SO_4) to give the spiroketal **6**.

1,7-*Dioxaspiro*[5.5]*undecane* **6a** (0.51 g, 64%); b.p. 160 °C (110 mmHg) (Kugelrohr) [lit.,[24] 68–70 °C (25 mmHg) (Kugelrohr)]; δ_H 1–1.7 (12 H, m) and 3.5–3.75 (4 H, m); δ_C 18.519, 25.301, 35.731, 60.355 and 94.996; *m/z* 156 (M^+, 13%), 128(8), 111(13), 102(6), 101(100), 100(59), 99(7), 98(82), 97(4), 83(30), 70(6), 56(16), 55(38), 43(19), 42(10) and 41(19) (Found: C, 69.2; H, 10.6. Calc. for $C_9H_{16}O_2$: C, 69.19; H, 10.32%).

(E)-2-*Methyl*-1,7-*Dioxaspiro*[5.6]*dodecane* **6b** (0.62 g, 66%); an oil; δ_H 1.13 (3 H, d, *J* 6.25), 1.15–1.9 (14 H, m), 3.5–3.6 (1 H, m) and 3.7–3.9 (2 H, m); δ_C 19.24, 22.015, 22.509, 29.856, 30.576, 32.899, 34.978, 41.84, 61.196, 65.914 and 100.45; *m/z* 184 (M^+, 9%), 125(31), 115(100), 112(92), 97(57), 83(11), 69(43) and 55(48) (Found: C, 72.05; H, 11.05. Calc. for $C_{11}H_{20}O_2$: C, 71.7; H, 10.94%).

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