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SYNTHESIS OF METHYL-1,6-DIOXASPIRO[4.5]DECANES USING ORGANOSELENIUM MEDIATED CYCLIZATION REACTIONS

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SUMMARY:- Three naturally occurring methyl-1,6-dioxaspiro[4.5]decanes have been prepared in good yield using organoselenium mediated reactions during the crucial cyclization process.

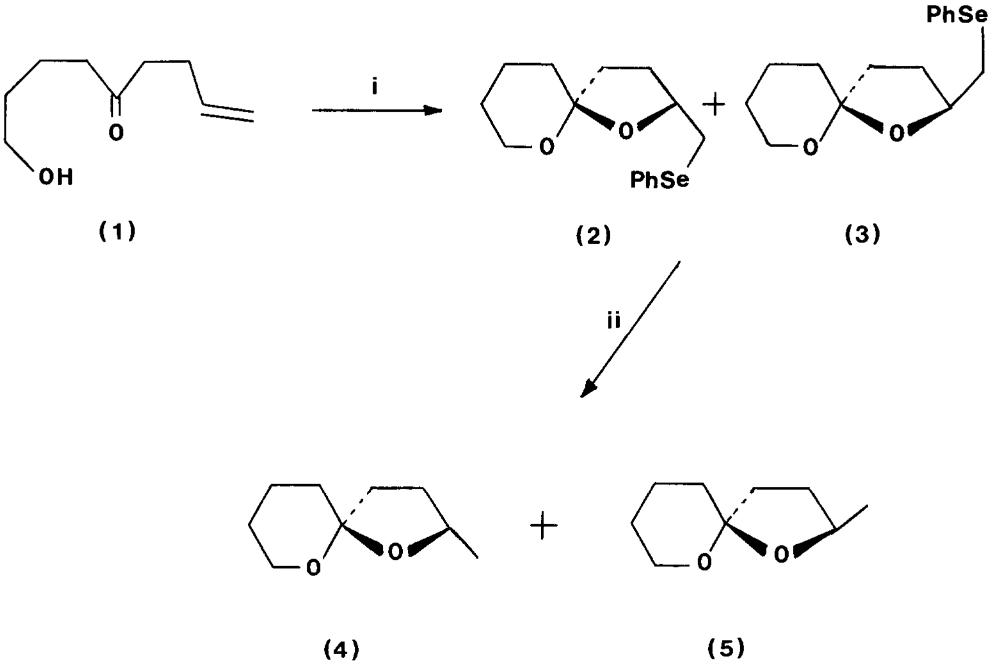
The spiro-ketal moiety occurs in many biologically active natural products including insect pheromones[1], polyether antibiotics[2] and the extremely potent antiparasitic agents, the avermectins[3]. Consequently new methods for their preparation are becoming increasingly important.

The use of organoselenium mediated cyclization reactions to synthesise oxygen containing heterocyclic species is known[4] however, application to natural product synthesis has so far been limited to only a few examples.[4e,h,5] In this Letter we show how natural 1,6-dioxaspiro-[4.5]decanes can be prepared using organo-selenium based methodology. In principle this route could be applied to many other related spiro-ketal systems.

In the first of these syntheses the alkenylhydroxy ketone[6] (1) was treated with N-phenylselenophthalimide[7], NPSP, and zinc bromide (0.1 eq) in dichloromethane at room temperature for 1.5h to give a *Z:E* mixture (1:2) of the phenylseleno-spiroketals (2) and (3) in 78.3% yield. These were not isolated separately but were reduced with Raney-nickel in ethanol at 50°C to afford the methyl-1,6-dioxaspiro[4.5]decanes (4) and (5) in the same ratio in 90% yield(Scheme 1) These compounds were identical to the pheromone components isolated recently from the common wasp *P. vulgaris*[8]. No attempt was made to separate these materials,although this is possible, as it is known that these *Z:E*-diastereomers undergo equilibration at 5°C within a few days.[8c]

During the cyclization reaction of (1) it was not possible to detect by ^{1}H n.m.r. spectroscopy any intermediate formation of the related dioxaspiro[5.5]analogues that one may expect to be the kinetic cyclization product.

Scheme 1

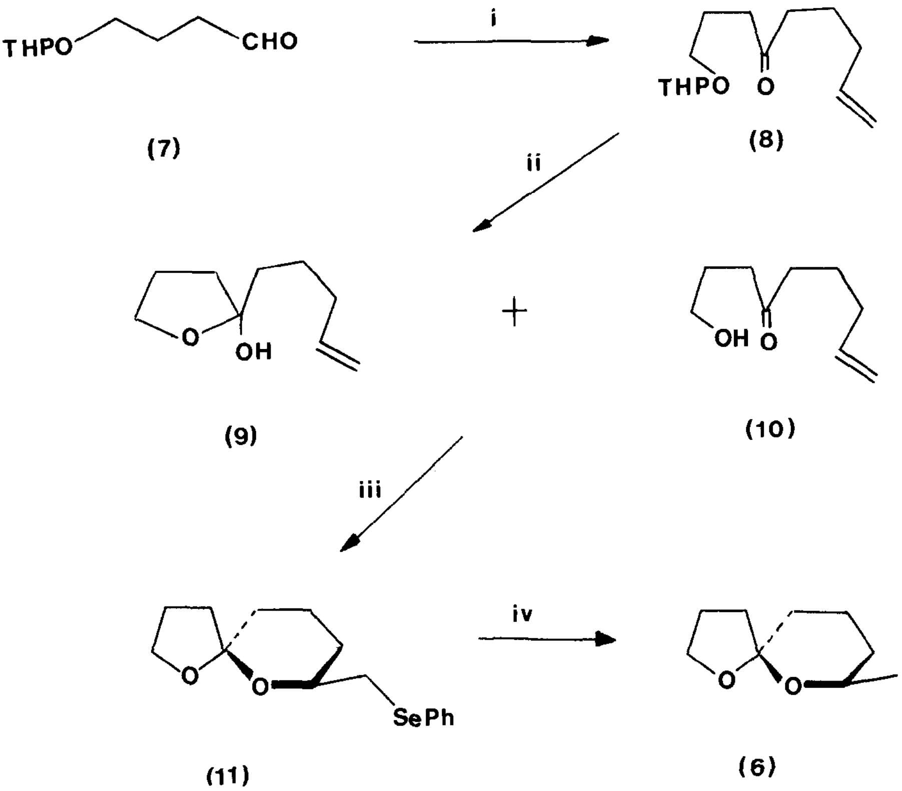


i) NPSP(1.1eq), ZnBr$_2$(0.1eq), CH$_2$Cl$_2$, 1.5h, RT; ii) Raney-nickel, EtOH, 50^o, 1h.

For the synthesis of the remaining methyl-1,6-dioxaspiro[4.5]decane (6) a somewhat longer synthetic sequence was necessary. The tetrahydropyranyl protected hydroxyaldehyde (7) was reacted with pent-4-enyl magnesium bromide to give (8) on oxidation work-up with Collins reagent in greater than 96% yield. Deprotection of (8) with camphor sulphonic acid / methanol at 40-50^{o}C for 30 min gave a mixture of the lactol (9) and the uncyclized ketoalcohol (10) in 70 and 19% yields respectively. Treatment of either (9) or (10) with NPSP / ZnBr$_2$ (1.0:0.1 equiv) in dichloromethane at room temperature gave a single phenylselenospiro-ketal(11) as a colourless oil in 80% yield. Reduction of this ketal with Raney-nickel as before gave exclusively *E*-methyl-1,6-dioxaspiro[4.5]decane (6) (92%) (Scheme 2).

The mechanistic implications of these reactions, together with other examples will be discussed at a later date.

Scheme 2



i) Pent-4-enyl magnesium bromide, -10°C, Ether; CrO$_3$.2py; ii) Camphor sulphonic acid/ methanol, 40-50°C, 30 min; iii) NPSP(1.1eq), ZnBr$_2$(0.1eq); iv) Raney-nickel, EtOH, 50°, 1h.

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^{1}H N.m.r. data (250 M Hz δ $CDCl_3$)

Compound 4: 3.32-4.21 (3H,m), 2.15-1.43 (10H,m), 1.31 (3H,d J=5.5Hz).

Compound 5: 3.32-4.21 (3H,m), 2.15-1.43 (10H,m), 1.24 (3H,d J=5.5Hz)

Compound 6: 3.92-3.60 (3H,m), 2.07-1.21 (10H,m), 1.11 (3H,d J=6.3Hz)

Compound 11: 7.50 (2H,m), 7.22(3H,m), 4.07-3.93(1H,m,H_x), 3.92-3.34 (2H,m,H_c,H_d), 3.04 (1H,dd,H_a $J_{H_aH_b}$=12Hz, $J_{H_aH_x}$=6.9Hz), 2.90 (H,dd,H_b, $J_{H_aH_b}$=12Hz, $J_{H_bH_x}$=4.7Hz), 2.09-1.59(10H,m).

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