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A NEW ROUTE TO SPIRO-KETALS USING THE HORNER-WITTIG REACTION OF 2-DIPHENYLPHOSPHINOXY CYCLIC ETHERS

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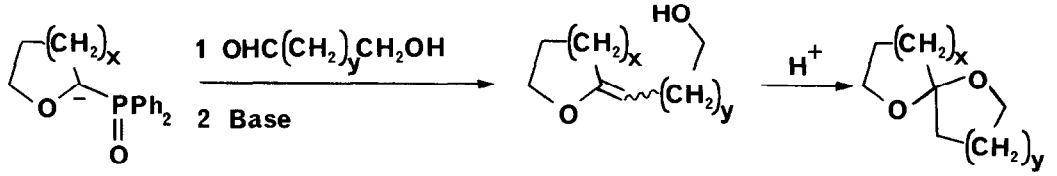
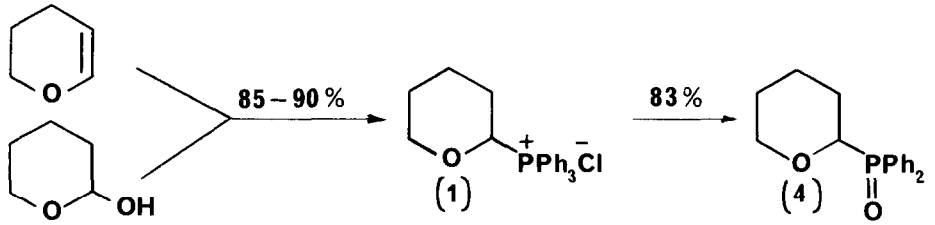
Summary: Two insect pheromones along with other spiro-ketals have been synthesised by a new route which involves Horner-Wittig coupling of 2-diphenylphosphinoxy cyclic ethers with aldehydes and lactols followed by acid catalysed cyclisation.

Owing to the increased interest in the formation of spiro-ketals,[1] we report here a new method which is potentially very general and applicable to a wide range of compounds. The method relies upon the Horner-Wittig coupling of cyclic ethers with either aldehydes or lactols, followed by acid catalysed spiro-ketal formation (Scheme).

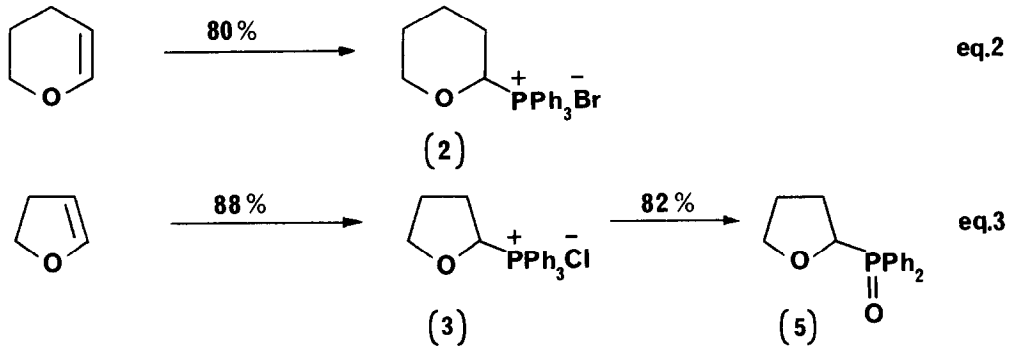


Scheme

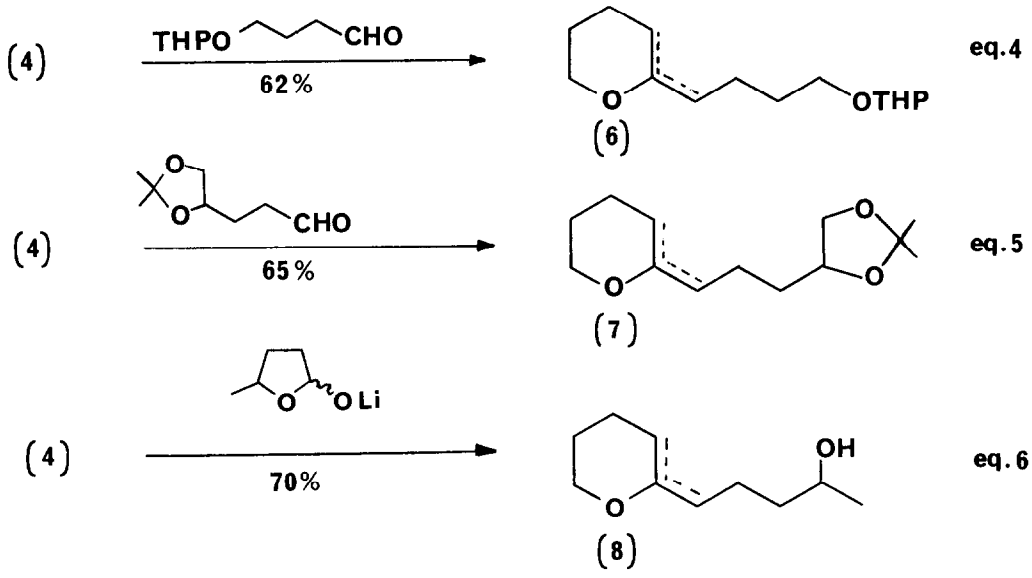
The cyclic ether phosphonium salt[2] (**1**) was readily prepared by treatment of a benzene solution of either 5-hydroxypentanal lactol or 3,4-dihydro-2H-pyran and triphenylphosphine with gaseous hydrogen chloride over a period of 5-10 h at ambient temperature (eq. 1). The phosphonium salt (**1**) was difficult to purify to acceptable microanalytical levels, however similar preparation of the bromide (**2**) using HBr (eq. 2) gave analytically pure material[3]. Preparation of (**3**) was achieved from dihydrofuran by an analogous method (eq. 3). The salts (**1**) and (**3**) were subsequently converted to the corresponding diphenylphosphine oxides (**4**) and (**5**) by brief (30 min) treatment with 3N sodium hydroxide under reflux[4].

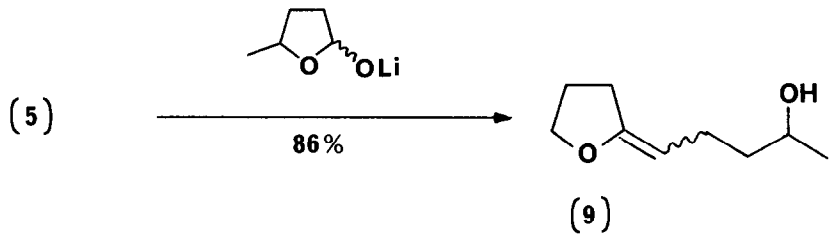


eq. 1

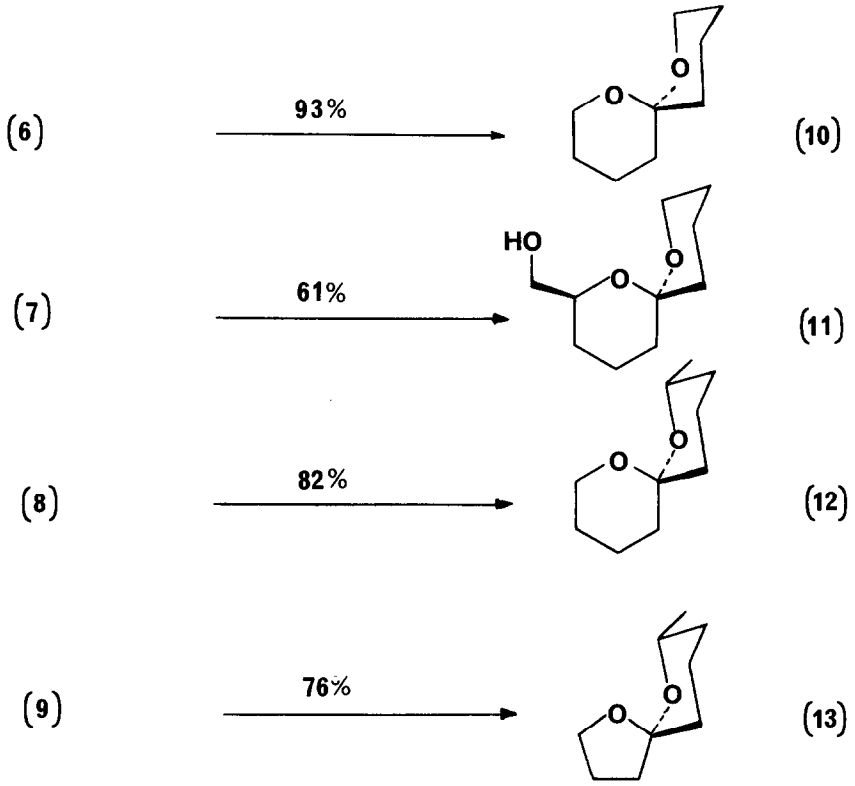


With the 2-diphenylphosphinoxy cyclic ethers to hand, their reactions with various aldehydes and lactols under Horner-Wittig conditions[5] were next examined. In a typical experiment the diphenylphosphine oxides were deprotonated with lithium diisopropylamide (LDA) at -78°C in THF to give a deep red anion which was diluted with diethyl ether. To this mixture was added the appropriate aldehyde (or the lithio salt of the lactol) and, upon loss of the red colour, was quenched by the addition of water.[5] After separation and evaporation of solvent, the residue was dissolved in THF and potassium tert-butoxide (1 eq.) was added to effect the elimination of diphenylphosphinic acid. This elimination was normally complete after 1 h at room temperature. THF was removed and replaced by a small amount of dichloromethane followed by extraction with ether. Removal of the ether afforded the crude enol ethers which could be further purified by Kugelruhr distillation. It was not necessary to separate the various enol ethers formed as they could be used directly in the next reaction. Following the above procedure enol ethers (**6**) to (**9**) were prepared (eq. 4-7).





Cyclisation of the enol ethers (**6**)-(**9**) to the corresponding spiro-ketals (**10**)-(**13**) was straightforward using a trace of camphor sulphonic acid in methanol, over a period of several hours (**6-12**) with concomitant removal of tetrahydropyranyl or acetonide protecting groups in relevant examples.



The spiro-ketal (**10**) was identical to the major sex pheromone isolated from the olive fly Dacus oleae, while (**13**) was identical to a common wasp pheromone from Paravespula vulgaris (L).[8]

The above method is clearly very general and its application to the construction of more biologically important spiro-ketal containing natural products, such as the avermectins and milbemycins,[9] is obvious and will be reported at a later date.

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