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A FACILE SYNTHESIS OF SPIROKETALS

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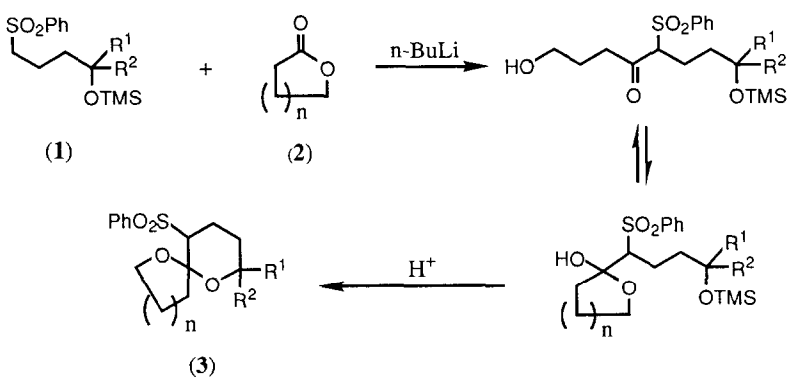
Abstract: A convenient synthetic approach to spiroketals based on the addition of α-sulfonylcarbanions to lactones is described.

There is intense interest in the synthesis of spiroketals since they are commonly found as subunits of biologically potent natural products such as polyether antibiotics[1,2], the avermectins and milbemycins[3] - potent antiparasitic agents, marine[4] and plant toxins[5,6], and a number of insect pheromones[7-9]. One of the most successful of a number of different strategies that have been developed to construct the spiroketal moiety is the reaction of an organometallic reagent with a lactone[2]. We now report a new synthesis of the spiroketal ring system utilising this approach by the previously unreported[10,11] addition of α-sulfonylcarbanions to lactones.

The α-sulfonylcarbanion has gained a prime place in the synthetic methodology for carbon-carbon bond formation due to the ease of preparation of its precursors, its facile generation under mild conditions and the ready removal of the sulfonyl group from the resulting product[4,11,12]. Our interest in spiroketals led us to investigate the addition of α-sulfonylcarbanions to lactones as a simple two-step synthesis of spiroketals as illustrated in the Scheme.

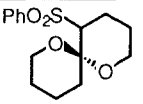
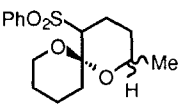
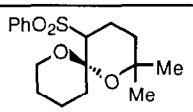
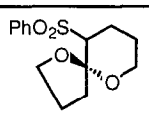
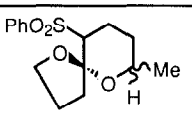
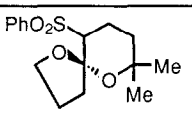


Scheme

The sulfones (**1**) were synthesised in good yields utilising well-established procedures[13]. The lithiated sulfones were coupled to the commercially available lactones (**2**) and the crude product treated

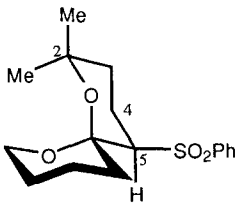
with a catalytic amount of camphorsulfonic acid to effect the cyclisation to spiroketals (**3**). A typical procedure is as follows: n-BuLi (2 equiv.) is added to a stirred solution of the sulfone (**1**) (1 equiv.) in THF at -78°C under nitrogen. After stirring for one hour, a solution of the lactone (**2**) (2 equiv.) in THF is added. The reaction mixture is stirred for a further half an hour then allowed to warm to -30°C. The mixture is quenched with saturated NaH_2PO_4 and extracted with ether. The resulting crude product is dissolved in dichloromethane containing a catalytic amount of camphorsulfonic acid and the solution stirred for 48 hours at ambient temperature to afford the maximum yield of the thermodynamically-favoured product. The results are summarized in the Table. Although the yields are only moderate, the crystalline spiroketals can be readily obtained in gram quantities from easily accessible starting materials.

Table. Synthesis of Spiroketals (**3**) from Sulfones (**1**) and Lactones (**2**) (Scheme)

Entry	Sulfone (**1**)[a]	Lactone (**2**)[b]	Spiroketal (**3**)[c]	Yield (%)[d]	M.p. (°C)
1	R^1=R^2=H	n=2	 (**3a**)	45	111-112
2	R^1=Me R^2=H	n=2	 (**3b**)	52	114-116
3	R^1=R^2=Me	n=2	 (**3c**)	54	143-144
4	R^1=R^2=H	n=1	 (**3d**)	50	93-94
5	R^1=Me R^2=H	n=1	 (**3e**)	55	96-97
6	R^1=R^2=Me	n=1	 (**3f**)	55	88-89

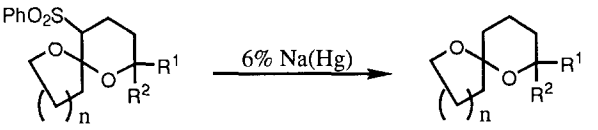
[a]See ref. 13 for the preparation of the sulfones. [b]Commercially available lactones were used as is. [c]The products were obtained as diastereomeric or racemic mixtures and were fully characterized by spectroscopic and analytical data. [d]The yields are of products isolated and purified by flash chromatography.

The condensation of the lithiated sulfones with the lactones (**2**) undoubtedly affords an equilibrium mixture of the open-chain ketols and cyclic hemiketals (see Scheme)[11]. This mixture then undergoes a thermodynamically controlled acid-catalysed cyclisation[16] to give the diastereomeric spiroketals (**3**). The stereochemistry of the resulting spirocentres is governed by the anomeric effect[16], affording the conformation in which the ring oxygens are axial to the adjacent ring[16,17], as illustrated in (**3c**). The phenylsulfonyl group at the neighbouring chiral carbon occupies an equatorial postion as is readily determined from the magnitude of the coupling constants $J_{4ax,5ax}$ and $J_{4eq,5ax}$ (11.6 and 5 Hz, respectively, for (**3c**)).



(**3c**)

The value of this method for spiroketal synthesis is further enhanced by the facile reduction of the phenylsulfonyl group. Thus, treatment of selected spiroketals (**3**)(n=1 or 2, R^1=R^2=Me) with 6% sodium amalgam afforded the fully reduced spiroketals (**4**)(n=1 or 2, R^1=R^2=Me) in good yields (60-70%)[18].



(**3**) (**4**)

Since a number of such compounds have been identified as insect pheromones, *e.g.* 1,7-dioxaspiro[5.5]undecane (**4, n=2, R^1=R^2=H**)[7] and 7-methyl-1,6-dioxaspiro[4.5]decane (**4, n=1, R^1=Me, R^2=H**)[8], this procedure should provide a convenient racemic synthesis of these natural products.

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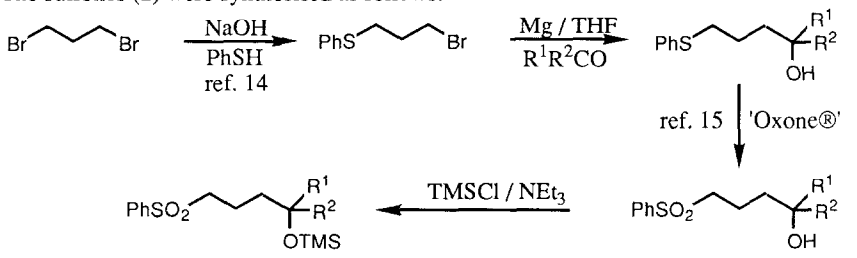

(**1**)

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18. The products were purified by flash chromatography and fully characterised by spectroscopic and analytical data.

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