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One-step Synthesis of Functionalized Dioxaspiro[4,5]decanes from β-Phenylsulfonyl Dihydrofurans and γ-Lactones

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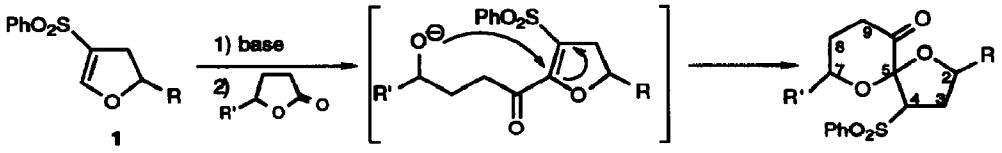
Abstract: A one-step synthesis of differently substituted 1,6-dioxaspiro[4,5]decanes from readily available starting materials is described. The process is based on the condensation of the α-anion derived from β-phenylsulfonyl dihydrofurans with γ-lactones. The spirocyclization occurs with high stereoselectivity at C-4, C-5 and C-9, but not at C-2.

The spiroketal unit shows a widespread occurrence as a sub-structure in many naturally occurring substances with important biological activity, such as avermectins, milbemycins, steroidal saponins, insect pheromones, talaromycins, polyether ionophores and toxic metabolites from algae. As a consequence of this increasing biological importance, much effort has been focused on the development of general methods for the synthesis of spiroketals.[1] At present, most of the synthetic methods are based on thermodynamically controlled acid-catalyzed spiroketalizations.

Herein we describe a general one-step process for the synthesis of 1,6-dioxaspiro[4,5]decanes from γ-lactones and the readily available β-phenylsulfonyldihydrofurans **1**.[2] The method is based on the acylation of the anion derived from **1** with γ-lactones[3] to afford the intermediate alkoxides **2**, which undergo *in situ* intramolecular conjugate addition to the vinyl sulfone moiety[4] to give the highly functionalized 1,6-dioxaspiro[4,5]decanes **3-7**[5] (scheme 1).



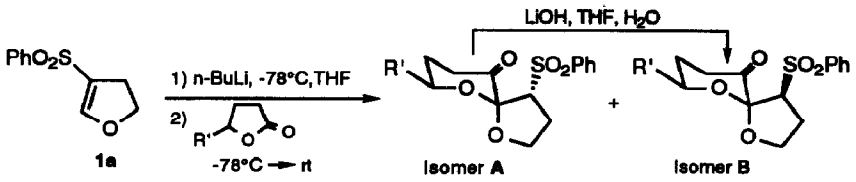
1 **2** **3-7**

Scheme 1

In table 1 are summarized the results obtained in the reaction of the unsubstituted dihydrofuran **1a** (R=H) with γ-butyrolactone (R'=H) and γ-valerolactone (R'=Me). The experimental procedure is very simple: deprotonation of **1a** with *n*-BuLi (1.1 equiv) in THF at -78°C (30 min) and further addition of the γ-lactone (1.5 equiv.), allowing the reaction mixture evolve into rt (16 h at rt).[6] The spiroketals **3** and **4** were isolated in 61% and 50% yield, respectively, after silica gel chromatography.[7] The stereochemistry of all spiroketals has been unequivocally established by analysis of their ^{1}H-NMR parameters and by NOESY experiments.[8] Concerning the stereoselectivity of these spirocyclizations, the reaction with γ-butyrolactone occurred with very high stereoselectivity yielding a single isomer **3A**. On the other hand, the reaction with γ-valerolactone, that could yield four different isomers, afforded almost exclusively a 3:1 mixture of isomers **4A+4B** (epimers at

C-4), which were separated by flash chromatography. However, this reaction is highly stereoselective in the formation of the six-membered ring, as it is deduced from the fact that both products (**4A** and **4B**) posses the same relative configuration at C-5 and C-9 (anomeric effect and methyl group in equatorial position).[9]

Table 1: Condensation of unsubstituted dihydrofuran **1a** with γ-lactones.



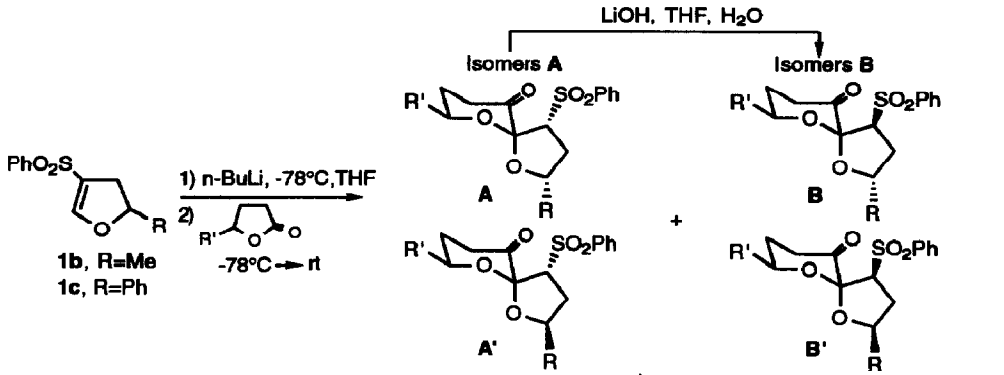
Entry	R'	Spiroketal	Isomer ratio A:B[a] after spirocyclization	Yield (%)[b]	Isomer ratio A:B[a] after basic treatment
1	H	**3**	>96:<4	61	<4:>96
2	Me	**4**	75:25[c]	50	<4:>96

a) Determined by ^{1}H-NMR. b) Isolated product after silica gel chromatography.
c) Around 10% of the other two possible isomers was detected by ^{1}H-NMR

It was interesting to find out that the products of both spirocyclizations, **3A** and the mixture **4A+4B**, underwent quantitative and complete epimerization at the carbon bearing the phenylsulfonyl group (C-4) to give their corresponding **B** isomers (**3B** and **4B**, respectively), when they were treated with LiOH (1.0 equiv.) in THF:H_2O for 1 h. Hence, these basic equilibrations under thermodynamic conditions show that, as it was expected on steric grounds, the most stable epimer at C-4 is that bearing the carbonyl and phenylsulfonyl groups on opposite sides of the molecule (in the **A** isomers both groups are in a 1,3-*syn* parallel arrangement).

In order to extend this procedure to the preparation of 1,6-dioxaspiro[4,5]decanes substituted at the five-membered ring we studied the condensation of the α-anion of dihydrofurans **1b**[2] and **1c**[2] (R= Me and Ph, respectively) with γ-lactones under the same experimental conditions.[7] The results are shown in table 2.

Table 2: Condensation of substituted dihydrofurans **1b** y **1c** with γ-lactones.

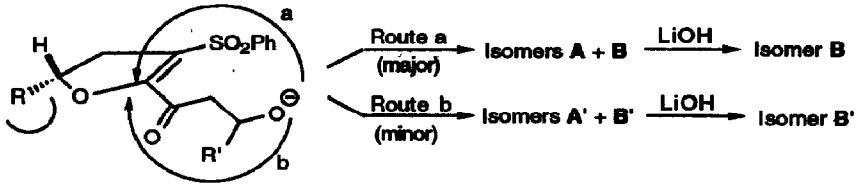


Entry	1	R	R'	Spiroketal	Isomer ratio A:A':B:B'[a] after spirocyclization	Yield (%)[b]	Isomer ratio A:A':B:B'[a] after basic treatment
1	**1b**	Me	H	**5**	64:23:7:6	74	<4:<4:71:29
2	**1c**	Ph	H	**6**	43:31:14:12	58	<4:<4:57:43
3	**1b**	Me	Me	**7**	63:27:5:5[c]	64[d]	<4:<4:71:29

a) and b) as in table 1. c) Around 10% of other minor isomers was also detected by NMR. d) Yield of the purified mixture **7B+7B'** after basic treatment. Pure **7B** was obtained after further crystallization of the mixture.

The yields in spiroketals **5**, **6** and **7** were slightly higher (74%, 58% and 64% respectively) than those of the previous condensations. In the three cases a mixture of isomers **A** + **A'** (epimers at C-2) was obtained predominantly, showing that these spirocyclizations took place with low stereoselective control of the configuration at the five-membered ring. Interestingly, the crude mixtures of spiroketals **A+A'+B+B'** were quantitatively epimerized at C-4 , after treatment with LiOH (1.0 equiv., THF:H_2O, rt, 1h), to give exclusively the corresponding mixture of isomers **B+B'**. Moreover, this ratio of isomers **B:B'** (epimers at C-2) allows to determine the effect of the substituent at C-2 in the stereoselectivity of the cyclization of the intermediate **2** (figure 1). This stereoselectivity was moderate from **1b** (**5B:5B'** and **7B:7B'** = 2.4:1) and very low from **1c** (**6B:6B'**= 1.3:1). The predominance of isomers **B** over **B'** could be easily justified in terms of the presumably more favourable steric effects involved in the addition of the alkoxide to the less hindered face of the double bond (route a).

Figure 1



The results obtained from **1b** and γ-valerolactone (entry 3, R=Me and R'=Me), where out of the eight possible isomers only two were obtained (**7B:7B'**= 2.4:1, 64% yield), clearly show the usefulness of this method of synthesis of 1,7-dioxaspiro[4,5]decanes. Additionally, this example combines all the stereochemical aspects observed in the other spirocyclizations: a) high stereoselective control in the formation of the six-membered ring (anomeric effect and substituent at C-9 in equatorial position), b) low stereoselectivity at the five-membered ring (obtention of epimers at C-2) and c) major formation of spiroketals **A+A'** after cyclization, which undergo a complete isomerization at C-4 under thermodynamic basic conditions to give the spiroketals **B+B'**.

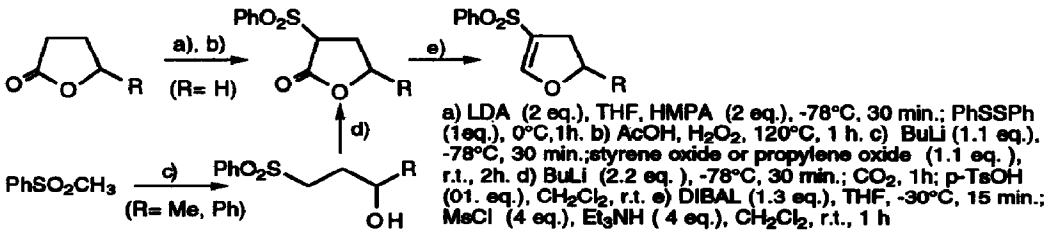
In conclusion, a convergent one-step process for the preparation of highly functionalized 1,6-dioxaspiro[4,5]decanes from readily available starting materials is described. The evaluation of the scope of this method of spirocyclization in the synthesis of differently substituted 1,6-dioxaspiro [4,5]decanes and its extension to the synthesis of 1,7-dioxaspiro[5,5]undecanes and 1,5-dioxaspiro[4,4]nonanes is now under study in our laboratory.

Acknowledgements: We thank DGICYT (Grant PB90-0178) for financial support. One of us (J.R.) also thanks Comunidad de Madrid for a FPI fellowship

References and Notes

1.- For some reviews, see: a) Perron, F.; Albizati, K.F. *Chem. Rev.* **1989**, *89*, 1617. b) Boivin, T.L. *Tetrahedron* **1987**, *43*, 3309. c) Kluge, A.F. *Heterocycles* **1986**, *24*, 1699.

2.- The β-phenylsulfonyl dihydrofurans **1a**, **1b** and **1c** have been prepared in 35-47% overall yields by using the following straightforward methods:



A procedure for the preparation of α-substituted β-phenylsulfonyl dihydrofurans has been recently reported: Jacobs, H.K.; Gopalan, A.S. *J. Org. Chem.* **1994**, *59*, 2014.

3.- γ- and, especially, δ-lactones have been widely used in the synthesis of spiroketals, see for instance: a) Ahn, Y.; Cohen, T. *J. Org. Chem.* **1994**, *59*, 3142. b) Baker, G.H.; Hussain, N.; Macaulay, G.S.; Morgan, D.O.; Dorgan, R.J.J. *Tetrahedron Lett.* **1994**, *35*, 2381. c) Oikawa, M.; Oikawa, H.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 4797. d) Mudryk, B.; Shook, C.A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389. e) Crimmins, M.T.; Bankaitis-Davis, D.M.; Hollis, W.G. *J. Org. Chem.* **1988**, *53*, 652. f) Chawdarian, C.G.; Chang, L.L.; Onisko, B.C. *Heterocycles* **1988**, *27*, 651. g) Barret, A.G.M.; Carr, R.A.E.; Attwood, S.V.; Richardson, G.; Walshe, N.G.E. *J. Org. Chem.* **1986**, *51*, 4840.

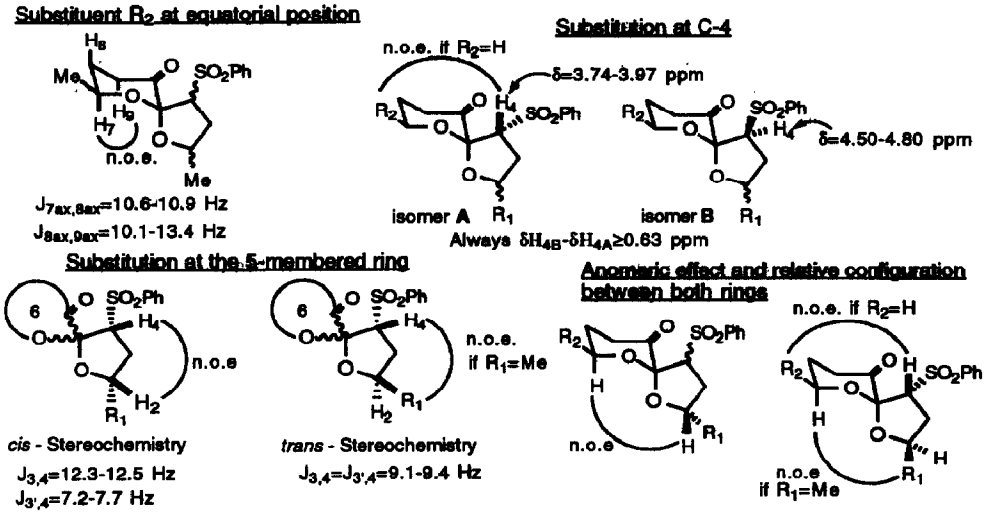
4.- For a synthesis of spiroketals based on the intramolecular addition of an alkoxide to a vinyl sulfoxide, see: Iwata, C.; Moritani, Y.; Sugiyama, K.; Fujita, M.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 2255.

5.- For other method of synthesis of phenylsulfonyl 1,6-dioxaspiro[4,5]decanes, see: Ashwell, M.; Clegg, W.; Jackson, R.F.W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897.

6.- No spiroketals were detected by NMR when the reactions were performed at -78°C.

7.- General procedure for the synthesis of spiroketals **3-7**: To a solution of 0.44 mmol (1.0 equiv.) of **1** in 2 mL of dry THF was slowly added 0.49 mmol (1.1 equiv.) of a 2.5 M solution of n-BuLi in hexane, at -78°C under argon. The mixture was stirred at -78°C for 30 min and then, 0.67 mmol (1.5 equiv) of the γ-lactone were added. The reaction was slowly warmed to rt and stirring was continued for 16h. A saturated NH_4Cl aqueous solution was added (25 mL) and the mixture was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane: ethyl acetate 4:1) to give 50-74% of pure spiroketals **3-7**.

8.- In the following figures are summarized the most significant NMR data and n.o.e. effects (determined by NOESY experiments) that have allowed the configurational assignment of the spiroketals **3-7**



9.- As it is well-known, the typical thermodynamic preference for the six-membered ring in 1,6-dioxaspiro[4,5]decanes and 1,7-dioxaspiro[5,5]undecanes consists on the presence of a chair conformation with anomeric effect and substituents in equatorial positions. For an emblematic study concerning the stability and conformational equilibria in spiroketals, see: Deslongchamps, P.; Rowan, D.D.; Pothier, N.; Sauve, T.; Saunders, J.K. *Can. J. Chem.* **1981**, *59*, 1105.

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