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New One-step Process for the Synthesis of Functionalized 1,6-Dioxaspiro[4,5]decanes

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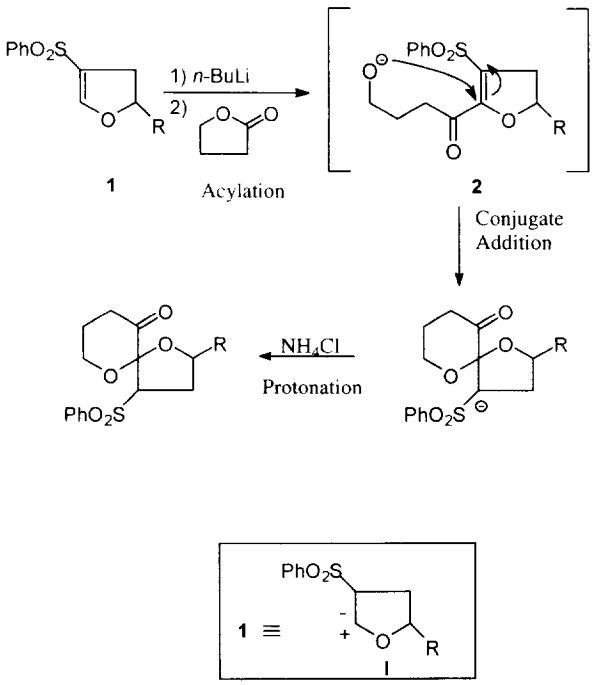
Abstract: β-Phenylsulfonyl dihydrofurans **1** were readily prepared by reduction of α-phenylsulfonyl-γ-lactones with DIBAL-H, followed by dehydration with $MsCl-Et_3N$. Dihydrofurans **1** were deprotonated with n-BuLi and the resulting α-lithiated carbanion reacted with a wide variety of electrophiles. Particularly interesting is its reaction with γ-lactones because affords 1,6-dioxaspiro[4,5]decanes in good yields in one-step procedure. This new method of synthesis of spiroketals, in non-acid conditions, is thermodynamically controlled and occurs with high stereoselectivity at C-4, C-5 and C-7, but not at C-2.

INTRODUCTION

The spiroketal unit is found in a wide variety of natural products such as avermectins, milbemycins, steroidal saponins, insect pheromones, talaromycins, polyether ionophores and toxic metabolites deriving from algae. Due to the biologically important nature of these molecules, a considerable attention has been focused on the development of methods for the synthesis of their building blocks spiroketals[1], such as 1,7-dioxaspiro[5,5]undecanes, 1,6-dioxaspiro[4,5]decanes and the less extended 1,6-dioxaspiro[4,4]nonanes. Up to date, most of the methods for the assembly of the spiroketal moiety were based on the synthesis of a dihydroxyketone or analogues with subsequent thermodynamically controlled acid-catalyzed spiroketalization. However, one-step syntheses of spiroketals from two readily available starting materials remain unusual[2].

In connection with our current interest in the development of new and efficient synthetic methods based on conjugate additions to functionalized vinylsulfones,[3] we have reported in a preliminary communication that the reaction of γ-lactones with the α-lithiated anion generated from β-phenylsulfonyldihydrofurans **1** afforded in one-step process 4-phenylsulfonyl-1,6-dioxaspiro[4,5]decan-10-ones[4] (scheme 1). In this approach to spiroketals the sulfonyl group provides with two distinguish features. First, it increases the acidity of the H-α of dihydrofuran and stabilizes the resulting α-lithiated carbanion. Second, after acylation with the γ-lactone, the vinylsulfone moiety of the intermediate β-sulfonylenone **2** acts as a Michael acceptor, allowing an intramolecular conjugate addition of the oxyanion to the α-position[5]. Thus, substrate **1** can behave as a dual synthon I (scheme 1). In this paper we wish to describe in detail these findings along with additional examples and some stereochemical and mechanistic considerations.



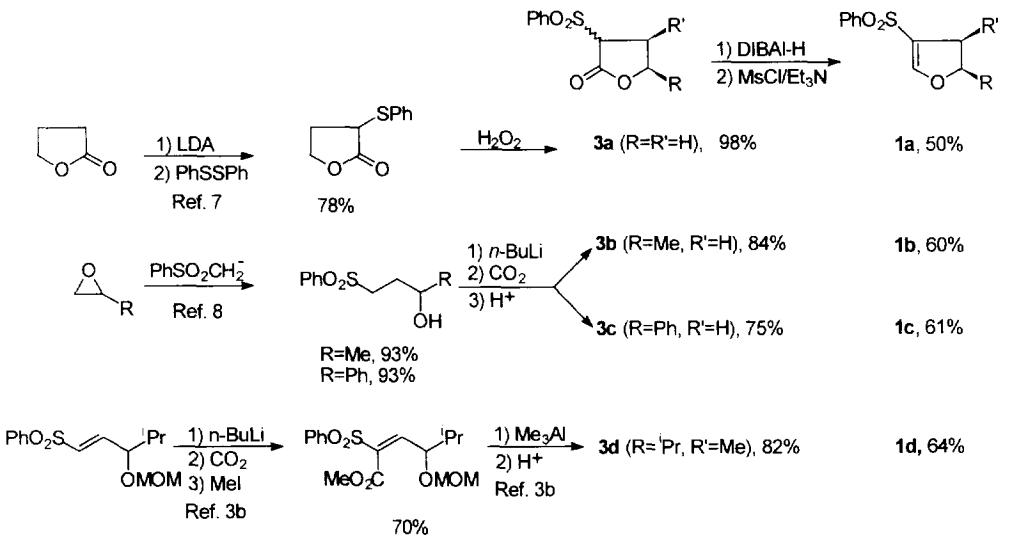
Scheme 1

RESULTS AND DISCUSSION

Synthesis of β-phenylsulfonyldihydrofurans 1

The four substrates **1a-d** described here were prepared in two steps from their readily available α-phenylsulfonyl-γ-butyrolactones **3a-d** (scheme 2). The general procedure implies a reduction of **3** with 1.3 equiv of DIBAL-H in THF at -30°C which afforded in high yield the corresponding hemiketal, as a mixture of two diastereomers. Subsequent treatment of the crude mixture with MsCl (4 equiv) and Et_3N (4 equiv) in CH_2Cl_2 gave the desired dihydrofurans **1** in 50-64% overall yield after flash chromatography[6].

The synthesis of the starting γ-lactones **3a-b** were achieved by using three different and complementary approaches (scheme 2). Straightforward sulfenylation of the enolate of the γ-butyrolactone with PhS-SPh in THF-HMPA[7], followed by oxidation with H_2O_2 in acetic acid at 120°C furnished the α-sulfonyl-γ-lactone **3a** in 76% overall yield. The second method involved a regiocontrolled ring opening of either propene oxide or styrene oxide with the carbanion of phenyl methyl sulfone[8] (in THF at rt), followed by carboxylation of the resulting γ-hydroxysulfone (2.2 equiv of n-BuLi in THF at -78°C; then CO_2) and further lactonization in acidic conditions (0.1 equiv of p-TsOH in CH_2CL_2 at rt). Purification by flash chromatography gave **3b** and **3c** in 78% and 70% overall yields, respectively. Finally, as a third approach, the *cis*-β,γ-disubstituted-α-sulfonyl-γ-lactone **3d** was prepared from a γ-hydroxy-α,β-unsaturated phenyl sulfone, in 59% yield, according to the procedure previously reported by us.[3b]



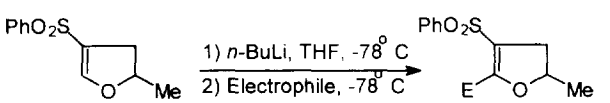
Scheme 2

Deprotonation of 1 and reaction with electrophiles

In substrates **1a-d** the presence of the oxygen at α-position and the phenylsulfonyl group at β-position should cooperate in increasing strongly the acidity of the vinylic hydrogen. Therefore, one would expect an easy deprotonation at α-position after treatment with alkyllithiums, leading to a vinyl carbanion which would act as nucleophile[9].

Indeed, it was the case, substrate **1b** was quantitatively deprotonated at α-position after treatment with n-BuLi (1.1 equiv), in THF at -78°C for 15 min. This was actually checked by the quantitative conversion of the resulting vinyl carbanion into its methyl derivative **4** after addition of MeI (1.5 equiv, 15 min at -78°C). Moreover, the α-lithiated intermediate was shown to react at -78°C with other electrophiles to furnish the corresponding α-substituted products in good yields, as it is given in table 1.[10] It is important to note that the reaction with esters, such as HCO_2Et or $PhCO_2Me$ (entries 4 and 5), furnished the α-acyl derivatives **7a** and **7b** in good yields (84% and 80% respectively) and without being affected by some side reactions such as the alcohol formation .

Table 1: Deprotonation of **1b** and reaction with electrophiles



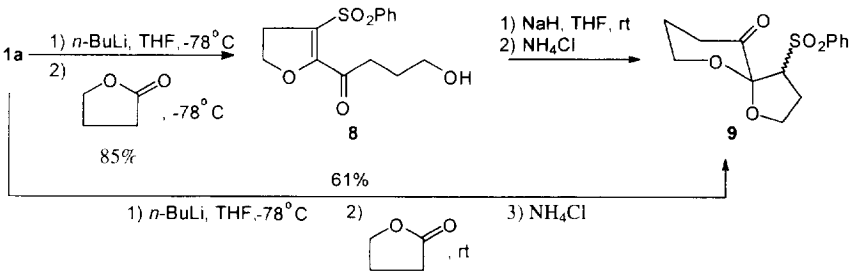
1b

Entry	Electrophile	Product	E	Yield[a](%)
1	MeI	**4**	Me	100
2	TMSCl	**5**	TMS	68
3	CH_3COCH_3	**6**	$C(OH)(CH_3)_2$	74
4	HCO_2Et	**7a**	CHO	84
5	$PhCO_2Me$	**7b**	COPh	80

[a] After flash chromatography

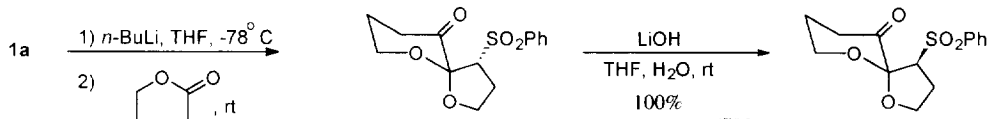
Reaction of 1a with γ-butyrolactone

Similarly, when γ-butyrolactone was used as electrophile in the reaction with the α-carbanion derived from **1a** (at -78°C for 1h), the expected α-acyl derivative **8** was obtained in 85% yield after chromatography. Interestingly, when **8** was treated with NaH (1.0 equiv) in THF at rt the intramolecular conjugate addition of the alkoxide to the vinyl sulfone moiety occurred, leading to the spiroketal **9** as the main product[11] (scheme 3). *The most remarkable finding is that the overall process: deprotonation of* ***1a*** *with n-BuLi, acylation with the γ-lactone and cyclization to the spiroketal could be shortened to one-step procedure simply by allowing the reaction mixture stand at rt for several hours (16h) after addition of the γ-lactone* (scheme 3). Using the latter strategy, spiroketal **9** was indeed obtained in 61% yield from γ-butyrolactone and **1a**.



Scheme 3

An unexpected result was the observation that the stereoselectivity of the process was strongly dependent on the work-up of the reaction. While spiroketal **9A** was the sole isomer detected by ^{1}H-NMR of the crude mixture when the reaction was stopped by addition of sat. NH_4Cl, the diastereomer **9B** was the major isomer when the reaction was stopped by addition of water. It appeared also that the ratio **9A/9B** was dependent on the lapse of time between the addition of water and the extraction of the spiroketals. This would suggest that under basic conditions, which was actually generated after addition of water, a smooth epimerization of the stereogenic center attached to the sulfonyl group (C-4) had occurred. Such a process would convert the spiroketal **9A** into its thermodynamically more stable stereoisomer **9B**. This assumption was checked by treating **9A** with 1.0 equiv of LiOH in a 1:1 mixture of THF:H_2O. After 1h at rt the reaction has led to the isomer **9B** in quantitative yield (scheme 4).



Scheme 4

The stereochemical assignment of these spiroketals has been firmly established by NMR studies (see further discussions) and confirmed by X-ray analysis of **9B**[12] (figure 1). As it could be expected, the X-ray diffraction of **9B** shows that the six membered ring exhibits a chair conformation and that both C-O bonds are oriented in axial position in order to maximize the anomeric effect[13].

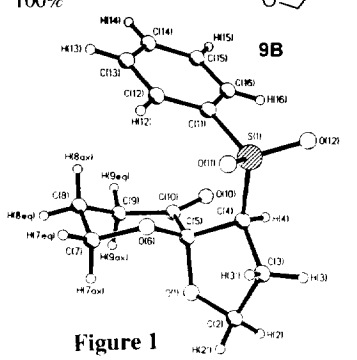


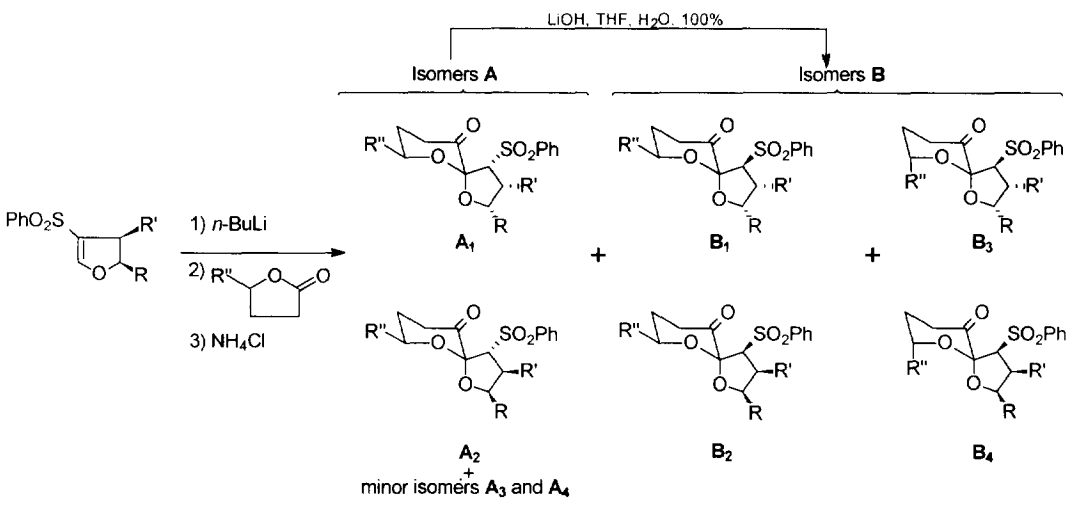
Figure 1

One-step synthesis of [4,5]-spiroketals from 1 and γ-lactones

To establish the scope of this one-step synthesis of spiroketals and determine the stereoselectivity of the process when using substituted substrates, we have investigated the spiroketalization reaction of **1a-d** with γ-butyrolactone and γ-valerolactone[14] (table 2). In all cases the stereoisomer ratio was determined, in one hand, after quenching the reaction by addition of sat NH_4Cl and, on the other hand, after basic treatment with LiOH in THF-H_2O. In the last case only the isomers **B** (sulfonyl and carbonyl groups on opposite sides of the molecule) were detected and isolated.

As can be seen from table 2, the spiroketals **9-15** were obtained in acceptable to good yields (50-74% yield after flash chromatography). Usually, the spiroketals **9-15** were isolated as a mixture of diastereomers that could not be separated by flash chromatography. However, in some cases, the major isomer was obtained in its pure form after several recrystallisations of the mixture of isomers.

Table 2: One step synthesis of [4,5]spiroketals from **1** and γ-lactones



Entry	Substrate **1**	R	R'	R''	Spiroketal	Isomer ratio[a] **A_1:A_2:B_1:B_2** after protonation	Yield(%)[b]	Isomer ratio[c] **B_1:B_2:B_3:B_4** after basic treatment
1	**1a**	H	H	H	**9**	>96: -- :<4: --[d]	61	>96: -- : -- : -
2	**1a**	H	H	Me	**10**	75: -- :25: --[d]	50	91: -- : 9 : -
3	**1b**	Me	H	H	**11**	64:23: 7 : 6	74	71:29: -- : --
4	**1b**	Me	H	Me	**12**	63:27: 5 : 5[d,e]	64	71:29: -- : --
5	**1c**	Ph	H	H	**13**	43:31:14:12	58	57:43: -- : --
6	**1c**	Ph	H	Me	**14**	40:25:16:19[f]	64	44:38:10: 8
7	**1d**	^{i}Pr	Me	H	**15**	17: -- :77: 6	50	94: 6 : -- : --

[a] Determined by ^{1}H-RMN (usually by integration of H-4) on the crude mixture after protonation. [b] in pure spiroketals after flash chromatography of the crude mixtures obtained after protonation. [c] Determined by ^{1}H-RMN on the mixtures obtained after basic treatment of the purified spiroketals. [d] Around 10% of other minor isomers (especially A_3+A_4) was also detected. [e] Determined on the mixture of spiroketals after chromatography. [f] The amount of the minor isomers A_3 and A_4 has not been determined.

Stereochemical assignments of the diastereomers were established by NMR analyses and confirmed by X-ray analysis in the case of the 2,7-dimethyl spiroketal **12B$_1$**[12]. The X-ray structure of **12B$_1$** (figure 2) appears to be quite similar to that of **9B**

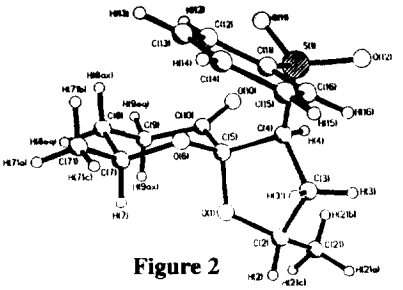
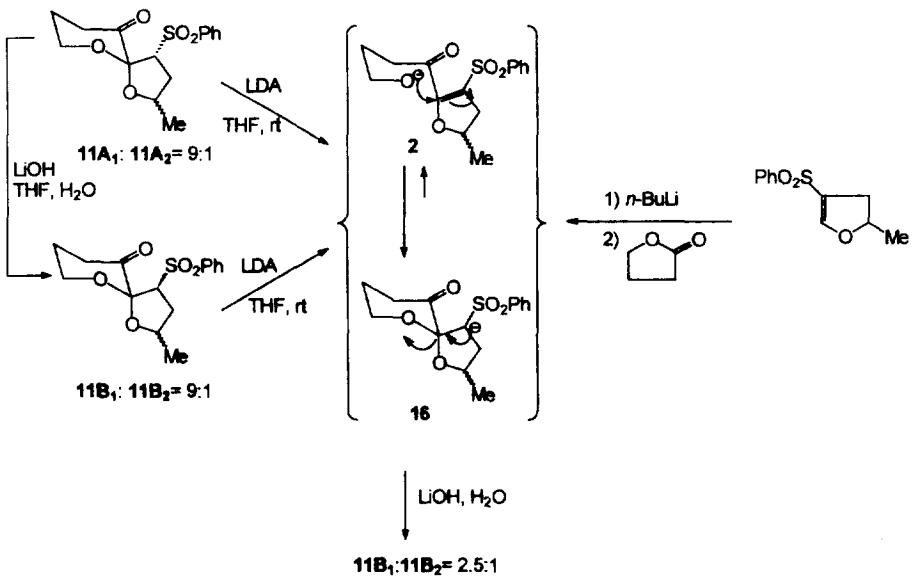


Figure 2

Stereoselectivity

To explain the origin of the stereoselectivity observed in these reactions one needs to ascertain whether the cyclization step is kinetically or thermodynamically controlled. The latter would imply a reversible intramolecular conjugate addition of the oxyanion to the vinyl sulfone moiety of the intermediate **2** in the reaction conditions. In this case, the product distribution should be determined by the relative thermodynamic stability of the different isomers.

In order to clear up this question we treated, independently, a 9:1 mixture of isomers **11A$_1$:11A$_2$** (obtained by recrystallisation of the spirocyclization reaction mixture shown in entry 3 of table 2) and a 9:1 mixture of isomers **11B$_1$:11B$_2$** (obtained by treatment with LiOH of the 9:1 mixture of isomers **11A$_1$:11A$_2$**) with 1.0 equiv of LDA in THF at rt for 16h. In both cases, after addition of sat. NH_4Cl[15] and basic equilibration with LiOH (1 equiv) in THF-H_2O, a 2.5:1 mixture of isomers **11B$_1$:11B$_2$** was obtained quantitatively (scheme 5). Moreover, this ratio of isomers **11B$_1$:11B$_2$** was identical to that obtained from the reaction of **1b** with γ-butyrolactone (entry 3 of table 2). It appears that, whatever is the initial ratio of spiroketal isomers at C-2 or C-4, after deprotonation with LDA a constant ratio of isomers is obtained. To account for this result one may assume that once the α-sulfonylcarbanion **16** is formed, it gets involved in an equilibration process with its β-elimination product: the alkoxide-vinylsulfone intermediate **2**. Consequently, the isomer spiroketal distribution should be the result of the thermodynamic control in the cyclization step.



Scheme 5

Thus, to have more valuable data to explain the stereoselectivity of these spirocyclization reactions and account for the product distribution shown in table 2, we focused our attention in the theoretical analysis of the relative thermodynamic stability of the spiroketal stereoisomers. For this goal, it was found particularly convenient to perform a semi-empirical calculation using AM1 Hamiltonian[16].

All possible stereoisomers of spiroketals **9**, **10** and **11** were studied by AM1. The conformational profile calculated by AM1 for each structure (**9A**, **9B**, **10A$_1$**, **10B$_1$**, **10A$_3$**, **10B$_3$**, **11A$_1$**, **11B$_1$**, **11A$_2$** and **11B$_2$**,) exhibits two important minima very close in energy that differ mainly in the conformation of the phenyl sulfonyl moiety[17]. In figure 3 are collected the calculated geometries and heats of formation of the most stable conformer found in each case. With regard to the geometry, there is a close correlation between the structure found in the solid state and the AM1 results.

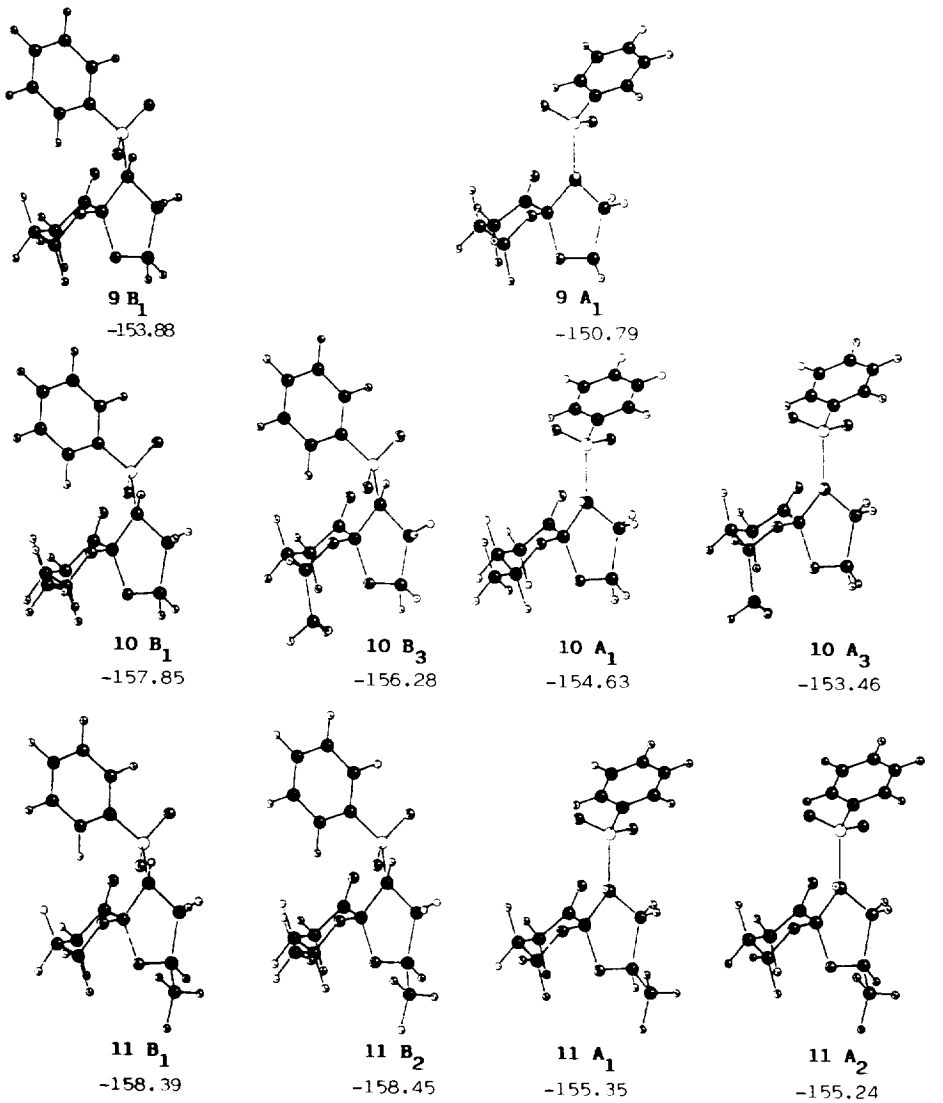


Figure 3: Geometries and heat of formation (Kcal/mol) calculated by AM1

a) Stereoselectivity at C-4

The theoretical calculations predict a strong preference for the isomers **B**, in which the carbonyl and sulfonyl groups are in opposite sides of the molecule, over the stereoisomers named **A**, in which both groups are positioned in the same side. In all the cases shown in figure 3 the isomer **B** is preferred by about 3 Kcal/mol over its epimer **A** (**9A/9B**= -3.09 Kcal/mol, **$10A_1/10B_1$**= -3.22 Kcal/mol, **$10A_3/10B_3$**= -2.89 Kcal/mol, **$11A_1/11B_1$**= -3.04 Kcal/mol, **$11A_2/11B_2$**= -3.21 Kcal/mol). The considerable energy differences found by AM1 between the isomers **A** and **B**would explain that under thermodynamic conditions isomers **A** completely isomerize to isomers **B**. Our experimental observations are in perfect agreement with these predications. Thus, the isomers **A** were quantitatively transformed to their epimers **B** after basic treatment with LiOH in H_2O-THF.

b) Stereoselectivity at C-7

The reactions with γ-valerolactone was used (entries 2, 4 and 6) gave spiroketals bearing a methyl substituent at C-7 (compounds **10**, **12** and **14**). As expected on the basis of a thermodynamically controlled spirocyclization process, the reactions occurred with high stereoselectivity at C-7 giving predominantly the stereoisomers with the methyl group in equatorial position. After basic treatment of the spiroketal mixture, the minor products detected by ^{1}H-NMR were those with the methyl group in axial position. Thus, beside of the major isomers **B_1** and **B_2**, it was formed 9% of **$10B_3$** (entry 2), around 10% of **$12B_3$+$12B_4$** (entry 4) and 18% of **$14B_3$+$14B_4$** (entry 6). Again, the theoretical calculations performed on isomers **10** agree with the experimental stereoselectivity shown in entry 2. The calculated thermodynamic difference, as expressed by the heat of formation, for the pair **$10A_1/10A_3$** is 1.04 Kcal/mol and for the pair **$10B_1/10B_3$** is 1.57 Kcal/mol. This last value would lead at rt to a 93:7 ratio of isomers **$10B_1$:$10B_3$**, very close to the 91:9 ratio experimentally observed.

c) Stereoselectivity at C-2

Unlike the case of epimers at C-7, the theoretical calculations performed on the spiroketals **11** did not predict a significant thermodynamic difference between the pair of epimers at C-2 (**$11A_1/11A_2$**= 0.11 Kcal/mol, **$11B_1/11B_2$**= -0.06 Kcal/mol). This would suggest a lower stereoselectivity at this position compared to the high stereocontrol exhibited at C-4 and C-7. Indeed, we observed a very low stereoselectivity at C-2 in the reactions from **1c** (R= Ph, entries 5 and 6: **$13B_1/13B_2$**= 1.3/1 and **$14B_1/14B_2$**= 1.2/1) and a modest stereoselectivity in the reactions from **1b** (R=Me, entries 3 and 4: **$11B_1/11B_2$**= 2.4/1 and **$12B_1/12B_2$**= 2.4/1). Only in the case of spiroketals **15**, which have a much more sterically demanding substituent at C-2 (R= ^{i}Pr), it was observed a high stereoselectivity at this position (entry 7, **$15B_1/15B_2$**= 16/1).

Configurational assignment

The configurational assignment of the stereoisomers of spiroketals **9-15** has been firmly established by NMR studies. Usually, the signals of the ^{1}H-NMR spectra could be assigned by analysis of the coupling patterns, relative chemical shifts, decoupling experiments and HMQC and NOESY experiments. In some cases the spectra were taken in a variety of deuterated solvents ($CDCl_3$, C_6D_6, CD_3CN and/or $(CD_3)_2CO$) in order to avoid problems due to the overlapping signals. The signals of the most characteristic hydrogens (5.2-3.2 ppm) were found to be quite distinct when benzene-d_6 was used as solvent.

In figure **4** are summarized the criteria that were particularly diagnostic for the configurational assignment.

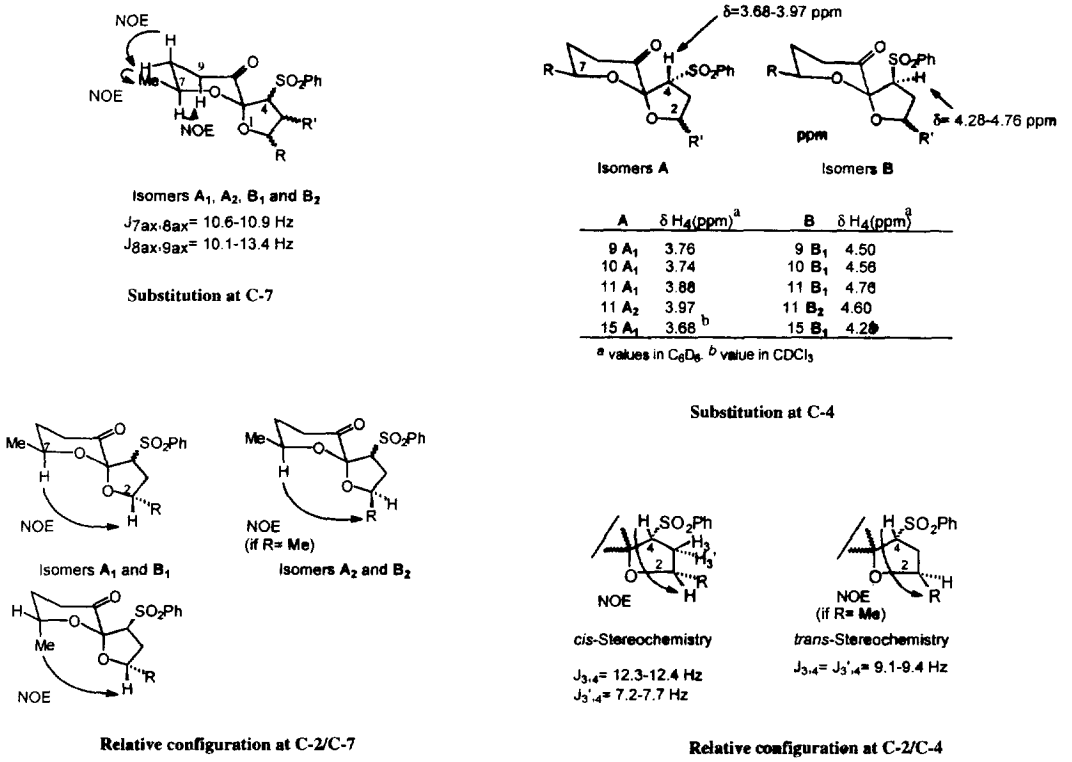


Figure 4

The chemical shift of H_4 was found to be an excellent probe for determining the relative configuration at C-4 (epimers **A/B**). The signal attributed to H_4 appears, in all the examples reported, much more deshielded in the epimers **B** compared to the epimers **A** (δH_4 **B** - δH_4 **A** > 0.6 ppm). In figure 4 are indicated the usual intervals and the exact values in $CDCl_3$ for several pairs of **A/B** isomers. This important difference in the chemical shifts can be easily explained by the strong deshielding effect exercised by the carbonyl group on H_4 in the epimers **B**, in which the C_4-H_4 bond and the C=O bond are placed in an almost 1,3-syn-parallel arrangement.

The assignment of a chair conformation for the six-membered ring, as well as an equatorial disposition of the substituent at C-7 (R=Me), in the major isomers $\mathbf{A_1}$, $\mathbf{A_2}$, $\mathbf{B_1}$ and $\mathbf{B_2}$ was made on the basis of the high coupling constants $^3J(H_7H_{8ax})$= 10.6-10.9 Hz and $^3J(H_{8ax}H_{9ax})$= 10.1-13.4 Hz (figure 4). This assigment was also confirmed by the NOE's observed between the pairs of protons H_{7ax}/H_{9ax}, H_{7ax}/H_{8eq}, Me/H_{8ax} and Me/H_{8eq} and by the absence of NOE's between H_{7ax}/H_{8ax} and H_{8ax}/H_{9ax}.

Concerning the relative configuration of the five membered ring at C-2/C-4, the most significant data is provided by the presence or absence of a strong NOE between H_2 and H_4 (figure 4). The former indicates a *cis*-relationship between both hydrogens, whereas the latter means a *trans*-relationship. It has also been found that, while in the spiroketals with *cis*-stereochemistry at C-2/C-4 H_4 appears as a dd with two different coupling constants ($^3J(H_3H_4)$ = 12.3-12.5 Hz and $^3J(H_3'H_4)$=7.2-7.7 Hz), in the spiroketals with *trans*-stereochemistry both coupling constants are very similar and, hence, H_4 usually appears as a pseudo triplet ($^3J(H_3H_4) \cong {}^3J(H_3'H_4)$ = 9.1 -9.4 Hz).

Finally, the relative configuration at C-2/C-7 was deduced from the NOE's between their substituents as it is shown in figure 4. The most diagnostic data were the presence of a moderate NOE between H_2 and H_{7ax},

which implies that Me and R groups are placed on opposite sides (isomers $\mathbf{A_1}$ and $\mathbf{B_1}$), and the presence in isomers $\mathbf{A_2}$ and $\mathbf{B_2}$ of a small NOE between H_{7ax} and R groups. In a similar way, the minor steroisomer $\mathbf{B_3}$ shows NOE between H_2 and the axially oriented methyl group at C-7.

In summary β-phenylsulfonyl dihydrofurans **1**, readily prepared from α-phenylsulfonyl-γ-lactones, are quantitatively deprotonated with n-BuLi in THF and the resulting α-lithiated carbanions react with γ-lactones to afford in an one-step procedure highly functionalized 1,6-dioxaspiro[4,5]decanes in good yields (50-74%). The stereochemical outcome of these reactions could be resumed in the following: a) the spirocyclization process favors the formation of stereoisomers **A**, which undergo a complete isomerization at C-4 under basic conditions to give the stereoisomers **B**; b) a high stereocontrol is exhibited during the formation of the six-membered ring (substituent at C-7 in equatorial position); c) the stereoselectivity at C-2 is highly dependent on the size of the substituents in the substrates **1**.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H-NMR (200 or 300 MHz) spectra and ^{13}C-NMR (50 or 75 MHz) spectra were recorded in $CDCl_3$, C_6D_6 or acetone-d_6.

Mass spectra (MS) were recorded with electron impact (EI, 70 eV) or FAB. Mass data are reported in mass units (m/z), and values in brackets report the relative intensity from the base peak (as 100%). Analytical thin-layer chromatography was performed on DC-Alufolien 0.2 mm silica gel 60-F plates. Visualization was accomplished with UV light, iodine and ethanolic phosphomolybdic acid solution followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) and, in some cases, on allumina (90 active, neutral, activity I). All solvents were dried before use. THF was destilled from sodium-benzophenone under argon. Lactone **3d** was prepared according to the procedure described in reference 3b.

Computational details: the calculations were performed with AM1 Hamiltonian, on a VAX 7610-vms, using the general-purpose semi-empirical molecular orbital package (MOPAC 6.0)[16a]. The parameters for C, H and O are taken from reference 16b while the parameters for S are taken from the ref 16c. Data files were created in internal coordinates in order to obtain the starting geometries for the reported structures. All the structures were fully optimized without any restriction. A multiconformer run (reaction path) was performed on each stereoisomer with simultaneous rotation of the most significant dihedral angles. The geometry optimization was stopped when Herbert test was achieved in the Broyden-Fletcher-Goldfarb-Shano method (BFGS). The option Precise was employed to refine the geometries and energies of the selected conformers. The gradient norms for the reported structures dropped below 0.01 kcal/mol when combining the Eigenvector Following routine and the Precise option. The heats of formation were compared for different calculated structures, in order to determine the most stable structure.

4,5-Dihydro-3-(phenylsulfonyl)-2(3H)-furanone (3a). A solution of 13.04 mL (93 mmol, 2 equiv) of diisopropylamine in dry THF (100 mL) was cooled at -78°C and 37.5 mL (93 mmol, 2 equiv) of *n*-BuLi 2.5M in hexane were added under argon. After 15 min, 3.6 mL (46 mmol, 1 equiv) of γ-butyrolactone were added and 30 min later a solution of 16.2 mL of HMPA (93 mol, 2 equiv) and 10.2 g (46 mmol, 1 equiv) of diphenyldisulfide in 40 mL of dry THF was slowly added. The reaction mixture was stirred at 0°C for 2 h, and then a satured solution of aqueous NH_4Cl (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (ethyl acetate-hexane, 1:4) to give 7.0 g (78%) of the pure sulfenyllactone as a yellow oil. IR ($CHCl_3$): 3000, 1770, 1370, 1190, 1040, 1000 and 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (m, 1H), 2.66 (m, 1H), 3.90 (dd, 1H, J= 6.3 and 8.7 Hz), 4.23 (t, 1H, J= 6.3 Hz), 7.29-7.39 (m, 3H) and 7.50-7.59 (m, 2H).

To a solution of 7.0 g (36 mmol) of this compound in 17.6 mL of glacial acetic acid, cooled at 0°C, 15 mL of H_2O_2 (33% in water) were added dropwise and the solution was heating to reflux for 1 h. The mixture was cooled and concentrated to dryness under reduced pressure to give 8.0 g (98%) of **3a** as a white solid. Mp: 114-117°C (Lit[18] Mp: 116-118°C). IR ($CDCl_3$): 3.000, 1960, 1340, 1210, 1040, 930, 770 and 660 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 2.75 (m, 1H), 3.05 (m, 1H), 4.05 (dd, 1H, J= 4.4 and 9.8 Hz), 4.50 (m, 1H), 7.57-7.77 (m, 3H) ad 7.94-7.99 (m, 2H).

General procedure for the reaction of methyl phenyl sulfone with epoxides. To a solution of 10 g of methyl phenyl sulfone (64.1 mmol, 1.0 equiv) in 50 mL of dry THF were added 28.2 mL of a 2.5 M solution of *n*-BuLi (70.5 mmol, 1.1 equiv) at -78°C under argon. The solution was kept at -78°C for 30 min and then the epoxide (styrene oxide or propylene oxide) (70.5 mmol, 1.1 equiv) was added. The reaction mixture was slowly warmed to room temperature and it was stirred for 2 h. A saturated solution of aqueous NH_4Cl (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (eluents and yield are indicated below for each case).

4-(Phenylsulfonyl)-butan-2-ol. Epoxide: propylene oxide. Eluent: ethyl acetate-hexane (1:2). Yield: 93%. IR ($CHCl_3$): 3480, 2960, 1445, 1300, 1145, 1085 and 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (d, 3H, J= 6.2 Hz), 1.66-1.99 (m, 2H), 2.35 (s_b, 1H), 3.1-3.4 (m, 2H), 3.90 (m, 1H), 7.51-7.72 (m, 3H) and 7.86-7.96 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 22.6, 30.8, 52.3, 64.9, 127.2, 128.8, 133.2 and 138.0. Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.58. Found: C, 55.74; H, 6.50.

1-Phenyl-3-(phenylsulfonyl)-propan-1-ol. Epoxide: styrene oxide. Eluent: ethyl acetate-hexane (1:2). Yield: 93%. Mp= 115-6°C. IR ($CHCl_3$): 3500, 3020, 1450, 1310, 1155, 1090, 1060 and 915 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (m, 2H), 2.36 (s_b, 1H), 3.21 (m, 2H), 4.80 (m, 1H), 7.18-7.40 (m, 5H), 7.48-7.72 (m, 3H) and 7.80-7.92 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 31.6, 52.7, 71.9, 125.5, 127.8, 128.5, 129.2, 133.7, 138.7 and 143.0. Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.83. Found: C, 65.00; H, 5.62.

General procedure for the preparation of the 4,5-dihydro-3-(phenylsulfonyl)-2(3H)-furanones 3b and 3c. To a solution of 18.0 mmol (1.0 equiv) of the corresponding γ-hydroxysulfone in dry THF (25 mL) was slowly added a 2.5 M solution of *n*-BuLi (39.6 mmol, 2.2 equiv) at -78°C under argon. The solution was kept at -78°C for 30 min and then dry CO_2 was bubbled during 10 min. After 1 h at -78°C, 10% HCl (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was dissolved in CH_2Cl_2 (25 mL) and 0.34 g of *p*-TsOH (1.8 mmol, 0.1 equiv) and molecular sieves 4Å (3.0 g) were added. The mixture was stirred for 1 h at rt and then water (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude lactones **3b** and **3c** were purified by flash chromatography (the eluents, yields and ratio of stereoisomers are indicated below for each case).

4,5-Dihydro-5-methyl-3-(phenylsulfonyl)-2(3H)-furanone (3b). Eluent: ethyl acetate-hexane (1:2). Yield: 84%. 1.6:1 mixture of isomers *cis*/*trans*. Mp= 110-1°C. IR ($CHCl_3$): 2990, 1770, 1450, 1325, 1180, 1150, 1080 and 950 cm^{-1}. Isomer *cis*: ^{1}H-NMR ($CDCl_3$) δ: 1.43 (d, 3H, J= 6.5 Hz), 2.27 (dt, 1H, J= 8.5 and 14.6 Hz), 3.12 (ddd, 1H, J= 2.8, 6.5 and 14.6 Hz), 4.10 (dd, 1H, J= 3.1 and 9.8 Hz), 4.86 (dq, 1H, J= 6.2 and 8.8 Hz), 7.53-7.79 (m, 3H) and 7.89-8.03 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 31.9, 64.8, 77.0, 129.5, 135.1, 137.3 and 168.1. Isomer *trans*: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (d, 3H, J= 6.0 Hz), 2.49 (ddd, 1H, J= 8.0, 9.7 and 14.0 Hz), 2.82 (ddd, 1H, J= 7.0, 10.1 and 14.0 Hz), 4.27 (t, 1H, J= 9.7 Hz), 4.61 (h, 1H, J= 6.5 Hz), 7.53-7.79 (m, 3H) and 7.89-8.03 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.2, 31.0, 65.7, 75.1, 129.6, 129.8, 134.9, 137.0 and 167.9. Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03. Found: C, 55.06; H, 5.05.

4,5-Dihydro-5-phenyl-3-(phenylsulfonyl)-2(3H)-furanone (3c). Eluent: ethyl acetate-hexane (1:3). Yield: 75%. 1.5:1 mixture of isomers *cis*/*trans*. Mp= 144-5°C. IR ($CHCl_3$): 3050, 1775, 1450, 1330, 1170, 1150, 1085, 1050 and 955 cm^{-1}. Isomer *cis*: ^{1}H-NMR ($CDCl_3$) δ: 2.62 (dt, 1H, J= 9.5 and 14.7), 3.39 (ddd, 1H, J= 2.9, 6.9 and 14.7 Hz), 4.22 (dd, 1H, J= 2.9 and 9.9 Hz), 5.77 (dd, 1H, J= 6.8 and 9.1 Hz), 7.13-7.45 (m, 5H), 7.50-7.80 (m, 3H) and 7.90-8.06 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 32.6, 65.2, 80.6, 125.0, 129.3, 129.6, 134.8, 136.5, 137.8 and 167.6. Isomer *trans*: ^{1}H-NMR ($CDCl_3$) δ: 2.77 (dt, 1H, J= 9.9 and 13.7 Hz), 3.05 (ddd, 1H, J= 6.7, 9.5 and

13.7 Hz), 4.47 (dd, 1H, J= 9.9 and 11.0 Hz), 5.37 (dd, 1H, J= 6.7 and 9.5 Hz), 7.13-7.45 (m, 5H), 7.50-7.80 (m, 3H) and 7.90-8.06 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 32.1, 64.2, 78.6, 125.8, 128.9, 129.0, 134.6, 136.6, 137.4 and 167.2. Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.41; H, 4.51.

General procedure for the preparation of 3-(phenylsulfonyl)-4,5-dihydrofurans (1). To a solution of 4.0 mmol of the corresponding 4,5-dihydro-3-(phenylsulfonyl)-2(3H)-furanone in dry THF (10 mL) cooled at -30°C were added 5.2 mmol of a 1 M solution of DIBAL-H (1.3 equiv) in hexane under argon. The solution was stirred at -30°C for 15 min. Then, water (10 mL) and 5% HCl (10 mL) were slowly added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and 2.2 mL of Et_3N (16.0 mmol, 4.0 equiv) and 1.2 mL of MsCl (16.0 mmol, 4.0 equiv) were sequentially added at 0°C. The mixture was stirred a rt (at 50°C in the case of R= ^{i}Pr) for 1 h. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography to afford pure dihydrofurans **1** (eluents and yields are indicated below).

3-(Phenylsulfonyl)-4,5-dihydrofuran (1a). Starting lactone: **3a**. Eluent: ethyl acetate-hexane (1:4). Yield: 50%. Mp: 79-81°C. IR ($CHCl_3$): 1600, 1300, 1165 and 1155 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (dt, 2H, J= 1.8 and 9.7 Hz), 4.62 (t, 2H, J= 9.7 Hz), 7.25 (t, 1H, J= 1.8 Hz), 7.52-7.72 (m, 3H) and 7.86-7.98 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 73.9, 117.2, 127.2, 129.1, 133.1, 140.6 and 156.8. MS (EI): 210 (100.0, M^+), 192 (5.8), 133 (10.7), 125 (45.2), 85 (35.9) and 77 (88.0). Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found: C, 56.66; H, 4.65.

5-Methyl-3-(phenylsulfonyl)-4,5-dihydrofuran (1b). Starting lactone: **3b**. Eluent: ethyl acetate-hexane (1:6). Yield: 60%. IR ($CHCl_3$): 2985, 1600, 1440, 1380, 1300, 1135, 1100, 1075, 1020 and 910 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (d, 3H, J= 6.4 Hz), 2.39 (ddd, 1H, J= 1.6, 7.8 and 14.0 Hz), 2.89 (ddd, 1H, J= 1.6, 10.1 and 14.0 Hz), 4.98 (dq, 1H, J= 6.3 and 10.1 Hz), 7.18 (t, 1H, J= 1.6 Hz), 7.49-7.69 (m, 3H) and 7.84-7.94 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 34.5, 83.2, 115.8, 126.8, 128.9, 132.8, 140.4 and 155.6. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.39. Found C, 58.96; H, 5.58.

5-Phenyl-3-(phenylsulfonyl)-4,5-dihydrofuran (1c). Starting lactone: **3c**. Eluent: ethyl acetate-hexane (1:6). Yield: 61%. Mp= 93-4°C. IR ($CHCl_3$): 3060, 1600, 1440, 1300, 1140, 1100, 1070 and 910 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.82 (ddd, 1H, J= 1.7, 8.8 and 14.1 Hz), 3.20 (ddd, 1H, J= 1.7, 10.8 and 14.1 Hz), 5.80 (dd, 1H, J= 8.8 and 10.8 Hz), 7.20-7.47 (m, 6H), 7.49-7.67 (m, 3H) and 7.88-7.98 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 35.7, 87.4, 116.6, 125.6, 127.1, 128.7, 129.1, 133.1, 139.5, 140.4 and 155.6. MS (EI): 286 (3.0, M^+), 163 (39.8), 145 (31.3), 117 (75.8), 107 (96.4) and 77 (100.0). Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 66.97; H, 4.92.

2-Isopropyl-3-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran (1d). Starting lactone: **3d**. Eluent: ethyl acetate-hexane (1:6). Yield: 64%. Mp: 156-7° C. IR ($CHCl_3$): 3.000, 1600, 1460, 1310, 1150, 1115, 1090, 980 and 890 cm^{-1} ($CDCl_3$) δ: 0.88 (d, 3H, J= 6.5 Hz), 1.02 (d, 3H, J= 6.9 Hz), 1.03 (d, 3H, J= 6.5 Hz), 2.04 (dh, 1H, J= 6.5 and 10.4 Hz), 2.88 (m, 1H), 4.09 (dd, 1H, J= 7.8 and 10.4 Hz), 7.27 (s, 1H), 7.46-7.66 (m, 3H) and 7.87-7.95 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 13.0, 19.0, 19.3, 27.2, 37.6, 95.9, 123.7, 126.9, 128.9, 132.7, 141.9 and 156.3. MS(EI): 266 (64.6, M^+), 251 (20.3), 223 (14.8), 211 (51.4), 141 (22.1), 125 (57.6), 109 (88.3), 95 (15.9) and 77 (100.0). HRMS: exact mass calcd for $C_{14}H_{18}O_3S$ (M^+) 266.0980, found 266.0977.

General procedure for the functionalization at C-2 in dihydrofuran 1b. To a solution of 0.1 g of **1b** (0.46 mmol, 1.0 equiv) in 2 mL of dry THF was added a 2.5 M solution of *n*-BuLi in hexane (0.51 mmol, 1.1 equiv) at -78°C under argon. The mixture was stirred at -78°C for 15 min and then, the corresponding electrophile (0.67 mmol, 1.5 equiv) was added. The reaction mixture was stirred at -78°C for 15 min. A saturated NH_4Cl aqueous solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography to give the pure compounds **4-7b** (eluents and yields are indicated below).

2,5-Dimethyl-3-(phenylsulfonyl)-4,5-dihydrofuran (4). Electrophile: MeI. Eluent: ethyl acetate-hexane (1:7). Yield: 100%. IR ($CHCl_3$): 3000, 1625, 1445, 1280, 1200, 1165, 1130 and 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (d, 3H, J= 6.2 Hz), 2.23 (t, 3H, J= 1.6 Hz), 2.46 (ddq, 1H, J= 1.6, 7.6 and 13.5 Hz), 2.95 (ddq, 1H, J= 1.6, 11.7 and 13.5 Hz), 4.73 (ddq, 1H, J= 6.2, 7.6 and 11.7 Hz), 7.46-7.64 (m, 3H) and 7.81-7.91 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 13.4, 21.5, 37.1, 78.8, 108.0, 126.7, 129.1, 132.7, 142.1 and 165.8. MS (EI): 238 (100.0, M^+), 143 (21.5), 131 (28.8), 125 (23.4), 97 (29.7) and 77 (91.7). HRMS: exact mass calcd for $C_{12}H_{14}O_3S$ (M^+) 238.0663, found 238.0663.

5-Methyl-2-trimethylsilyl-3-(phenylsulfonyl)-4,5-dihydrofuran (5). Electrophile: TMSCl. Eluent: ethyl acetate-hexane (1:5). Yield: 68%. IR ($CHCl_3$): 2980, 1570, 1460, 1395, 1320, 1180, 1135, 1090, 980, 905 and 860 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.35 (s, 9H), 1.29 (d, 3H, J= 6.1 Hz), 2.36 (dd, 1H, J= 8.0 and 14.1 Hz), 2.84 (dd, 1H, J= 10.3 and 14.1 Hz), 4.79 (ddq, 1H, J= 6.4, 8.0 and 10.3 Hz), 7.45-7.63 (m, 3H) and 7.80-7.90 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: -1.3, 21.6, 37.4, 81.6, 122.7, 127.0, 129.0, 132.6, 141.4 and 175.3. MS (EI): 296 (11.8, M^+), 281 (100.0), 135 (70.2), 125 (9.7), 77 (17.4) and 73 (26.8).

2-(1-Hydroxy-1-methylethyl)-5-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran (6). Electrophile: acetone. Eluent: ethyl acetate-hexane (1:6). Yield: 79%. IR ($CHCl_3$): 3460, 3000, 1610, 1460, 1400, 1305, 1175, 1135, 1090 and 985 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (d, 3H, J= 6.1 Hz), 1.48 (s, 3H), 1.50 (s, 3H), 2.53 (dd, 1H, J= 7.4 and 13.7 Hz), 3.01 (dd, 1H, J= 10.2 and 13.7 Hz), 4.76 (ddq, 1H, J= 6.4, 7.3 and 10.2 Hz), 7.49-7.65 (m, 3H) and 7.94-7.99 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.2, 28.4, 28.6, 38.3, 70.6, 78.9, 106.2, 127.1, 129.1, 133.0, 141.1 and 173.4. MS (EI): 282 (18.5, M^+), 267 (100.0), 239 (73.2), 189 (34.0), 141 (44.4), 125 (62.2), 97 (57.5), 77 (67.8) and 59 (33.4).

2-Formyl-5-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran (7a). Electrophile: HCO_2Et. Eluent: ethyl acetate-hexane (1:4). Yield: 84%. IR ($CHCl_3$): 3000, 1690, 1625, 1600, 1445, 1320, 1160, 1125, 1080 and 920 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (d, 3H, J= 6.3 Hz), 2.63 (dd, 1H, J= 8.6 and 16.5 Hz), 3.11 (dd, 1H, J= 10.2 and 16.5 Hz), 4.84 (ddq, 1H, J= 6.3, 8.6 and 10.2 Hz), 7.51-7.73 (m, 3H), 7.88-7.97 (m, 2H) and 10.40 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 38.0, 79.7, 125.2, 127.5, 129.2, 129.6, 134.0, 139.5 and 182.3. MS (EI): 252 (19.9, M^+), 224 (10.2), 176 (11.9), 141 (20.0), 125 (26.6), 105 (30.2) and 77 (100.0).

2-Benzoyl-5-methyl-3-(phenylsulfonyl)-4,5-dihydrofuran (7b). Electrophile: $PhCO_2Et$. Eluent: ethyl acetate-hexane (1:5). Yield: 80%. Mp= 104-5°C. IR ($CHCl_3$): 2960, 1680, 1600, 1450, 1320, 1170, 1085 and 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (d, 3H, J= 6.4 Hz), 2.68 (dd, 1H, J= 8.0 and 14.2 Hz), 3.16 (dd, 1H, J= 10.1 and 14.2 Hz), 5.11 (ddq, 1H, J= 6.4, 8.0 and 10.1 Hz), 7.44-7.72 (m, 6H) and 7.89-8.03 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 36.4, 83.1, 114.3, 127.4, 128.7, 129.0, 129.6, 133.2, 134.6, 140.2, 159.7 and 187.2. MS (EI): 328 (30.2, M^+), 313 (7.3), 187 (18.1), 131 (10.3), 105 (100.0), 77 (73.2) and 51 (18.0). Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91; S, 9.76. Found: C, 65.27; H, 5.02; S, 9.80.

General procedure for the synthesis of spiroketals. To a solution of 0.44 mmol (1.0 equiv) of the corresponding dihydrofuran **1** in 2 mL of dry THF was slowly added a 2.5 M solution of *n*-BuLi in hexane (0.49 mmol, 1.1 equiv) at -78°C under argon. The mixture was stirred at -78°C for 15 min. Then, the γ-lactone (0.67 mmol, 1.5 equiv) was added. The reaction was slowly warmed to rt and the stirring was continued for 16 h. A saturated NH_4Cl aqueous solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was analyzed by ^{1}H-NMR and purified by flash chromatography to give pure spiroketals **9-15** as mixture of diastereoisomers (the eluents, yields and isomer ratios are indicated below for each compound). These spiroketals **9-15** can be quantitatively equilibrated at C-4 by its treatment with 1.0 equiv of LiOH in a 1:1 solution of THF:H_2O at rt for 1 h.

4-(Phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (9). Dihydrofuran: **1a**. γ-Lactone: γ-butyrolactone. Eluent: ethyl acetate-hexane (1:4). Yield: 61%. Isomer ratio **9A** (4R*,5R*)/**9B** (4S*,5R*)= >96:<4 (after addition of NH_4Cl) and <4:>96 (after basic treatment). IR ($CHCl_3$): 2980, 1680, 1310, 1150, 1100 and 1010

cm^{-1}. Isomer **9A**: Mp= 112-3°C. ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.25 (m, 1H), 1.55 (m, 1H), 1.75 (ddddd, 1H, J= 5.3, 6.4, 8.6, 9.8 and 11.6 Hz), 2.27 (ddd, 1H, J= 6.5, 8.6 and 16.3 Hz), 2.48 (ddt, 1H, J= 8.8, 10.4 and 12.4 Hz), 2.63 (ddt, 1H, J= 1.0, 6.2 and 16.3 Hz), 3.45 (m, 2H), 3.54 (dt, 1H, J= 2.9 and 8.3 Hz), 3.63 (ddd, 1H, J= 3.7, 9.7 and 11.5 Hz), 3.76 (dd, 1H, J= 8.2 and 10.4 Hz), 6.85-6.95 (m, 3H) and 7.41-7.87 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 24.4, 28.3, 36.5, 62.6, 66.9, 73.1, 106.6, 128.6, 129.1, 133.8, 139.7 and 201.6. Isomer **9B**: Mp= 140-2°C. ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.13 (dddt, 1H, J= 2.6, 4.3, 5.4 and 13.0 Hz), 1.60 (m, 2H), 2.16 (m, 2H), 2.55 (dddd, 1H, J= 8.3, 9.1, 10.9 and 12.1 Hz), 3.25 (dt, 1H, J= 7.5 and 8.1 Hz), 3.41 (ddd, 1H, J= 2.5, 4.1 and 11.3 Hz), 3.70 (m, 2H), 4.50 (dd, 1H, J= 8.9 and 10.9 Hz), 6.87-6.95 (m, 3H) and 7.89-7.93 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 25.3, 25.8, 35.9, 60.7, 65.1, 67.7, 104.9, 128.7, 128.9, 133.7, 139.5 and 199.3. MS (EI): 268 (16.9, M^+-CO), 227 (100.0), 182 (10.8), 162 (8.3), 141 (34.4), 125 (24.0) and 77 (72.2). Anal. Calcd for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44. Found: C, 56.40; H, 5.45.

7-Methyl-4-(phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (10). Dihydrofuran: **1a**. γ-Lactone: γ-valerolactone. Eluent: ethyl acetate-hexane (1:4). Yield: 50%. Isomers ratio **10A$_1$** (4R*,5S*,7S*)/**10B$_1$** (4S*,5S*,7S*)= 75:25 (after addition of NH_4Cl). Isomer ratio **10B$_1$** (4S*,5S*,7S*)/**10B$_3$** (4S*,5S*,7R*)= 91:9 (after basic treatment). IR ($CHCl_3$): 2990, 1730, 1445, 1310, 1150, 1085 and 1030 cm^{-1}. Isomer **10A$_1$**: Mp= 167-8°C. ^{1}H-NMR (C_6D_6, 300 MHz) δ: 0.99 (d, 3H, J= 6.2 Hz), 1.23 (dddd, 1H, J= 2.9, 3.9, 7.3 and 14.0 Hz), 1.25 (m, 2H), 2.25 (ddd, 1H, J= 7.3, 10.1 and 17.1 Hz), 2.61 (ddd, 1H, J= 3.9, 6.8 and 17.1 Hz), 2.61 (m, 1H), 3.48 (ddd, 1H, 6.1, 8.2 and 9.6 Hz), 3.66 (dt, 1H, 2.3 and 8.3 Hz), 3.74 (dd, 1H, J= 8.1 and 11.5 Hz), 3.90 (ddq, 1H, J= 2.9, 6.2 and 10.6 Hz), 6.85-6.93 (m, 3H) and 7.80-7.84 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 21.1, 28.2, 30.8, 35.3, 66.8, 68.6, 73.6, 105.9, 128.4, 128.9, 133.7, 140.1 and 202.4. Isomer **10B$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.01 (d, 3H, J= 6.3 Hz), 1.14 (dddd, 1H, J= 2.3, 3.0, 6.1 and 13.4 Hz), 1.40 (ddt, 1H, J= 5.3, 10.9 and 13.4 Hz), 1.62 (dddd, 1H, J= 3.8, 8.3, 8.8 and 11.8 Hz), 2.13 (ddd, 1H, J= 3.0, 5.2 and 15.7 Hz), 2.23 (ddd, 1H, J= 6.1, 12.6 and 15.9 Hz), 2.56 (ddt, 1H, J= 8.9, 10.8 and 11.8 Hz), 3.27 (q, 1H, J= 8.2 Hz), 3.73 (dt, 1H, J= 3.8 and 8.6 Hz), 4.00 (ddq, 1H, J= 2.3, 6.3 and 10.9 Hz), 4.56 (dd, 1H, J= 8.8 and 10.8 Hz), 6.86-6.96 (m, 3H) and 7.85-7.95 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 20.6, 25.5, 33.1, 35.4, 65.2, 67.2, 67.6, 104.4, 128.5, 129.3, 133.5, 139.4 and 199.7. Isomer **10B$_3$**: ^{1}H-NMR (C_6D_6, 300 MHz) (significative signals) δ: 4.45 (dd, 1H, 9.7 and 11.2 Hz). MS (EI): 282 (11.1, M^+-CO), 227 (100.0), 162 (7.8), 141 (23.9), 125 (20.8) and 77 (36.2). Anal. Calcd for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.84. Found: C, 57.67; H, 5.73.

2-Methyl-4-(phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (11). Dihydrofuran: **1b**. γ-Lactone: γ-butyrolactone. Eluent: ethyl acetate-hexane (1:4). Yield: 74% Isomers ratio **11A$_1$** (2S*,4R*,5R*)/**11A$_2$** (2R*,4R*,5R*)/**11B$_1$** (2S*,4S*,5R*)/ **11B$_2$** (2R*,4S*,5R*)= 64:23:7:6 (after addition of NH_4Cl) and <4:<4:71:29 (after basic treatment). Mp= 104-5°C (mixture of diastereomers **11A$_1$/11A$_2$**= 3:1). IR ($CHCl_3$): 2990, 1730, 1445, 1300, 1155, 1085 and 910 cm^{-1}. Isomer **11A$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 0.96 (d, 3H, J= 6.1 Hz), 1.23 (m, 1H), 1.64 (ddd, 1H, J= 4.8, 7.2 and 11.8 Hz), 1.81 (m, 1H), 2.25 (m, 2H), 2.68 (ddt, 1H, J= 1.5, 6.6 and 16.6 Hz), 3.52 (dddd, 1H, J= 1.5, 3.8, 5.4 and 11.5 Hz), 3.70 (ddd, 1H, J= 3.7, 10.3 and 11.5 Hz), 3.86 (m, 1H), 3.88 (dd, 1H, J= 7.2 and 12.3 Hz), 6.88-6.93 (m, 3H) and 7.83-7.90 (m, 2H). ^{1}H-NMR (acetone-d_6, 300 MHz) δ: 1.18 (d, 3H, J= 6.1 Hz), 1.95 (m, 1H), 2.10 (m, 1H), 2.11 (ddd, 1H, J= 10.3, 11.6 and 12.1 Hz), 2.34 (ddd, 1H, J= 4.8, 7.3 and 12.1 Hz), 2.53 (ddd, 1H, J= 6.6, 8.5 and 16.5 Hz), 2.74 (ddt, 1H, J= 1.0, 6.5 and 16.5 Hz), 3.93 (m, 2H), 4.05 (dd, 1H, J= 7.3 and 11.6 Hz), 4.33 (ddq, 1H, J= 4.8, 6.0 and 10.3 Hz), 7.63-7.69 (m, 3H) and 7.87-7.94 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 19.9, 23.7, 36.1, 36.4, 62.2, 74.9, 75.5, 106.2, 128.5, 129.1, 133.7, 140.3 and 202.1. Isomer **11A$_2$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 0.86 (d, 3H, J= 6.3 Hz), 1.23 (m, 1H), 1.54 (ddd, 1H, J= 5.8, 9.1 and 12.7 Hz), 1.81 (m, 1H), 2.30 (ddd, 1H, J= 5.4, 8.9 and 13.6 Hz), 2.57 (ddt, 1H, J= 1.2, 6.2 and 13.6 Hz), 2.74 (m, 1H), 3.44 (ddt, 1H, J= 1.2, 4.5 and 12.2 Hz), 3.67 (ddd, 1H, J= 3.6, 9.6 and 12.2 Hz), 3.97 (t, 1H, J= 9.1 Hz), 4.07 (ddq, 1H, J= 5.8, 6.3 and 11.1 Hz), 6.88-6.93 (m, 3H) and 7.83-7.90 (m, 2H). ^{13}C-NMR ($CHCl_3$) δ (significative signals): 22.5, 24.9, 34.1, 36.6, 62.9, 72.4, 75.7 and 201.5. Isomer **11B$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 0.73 (d, 3H, J= 6.4 Hz), 1.13 (m, 1H), 1.45 (ddd, 1H, J= 5.1, 9.6 and 12.5 Hz), 1.60 (m, 1H), 2.16 (m, 2H), 2.77 (ddd, 1H, J= 8.1, 9.6 and 12.5 Hz), 3.41 (m, 1H), 3.75 (dt, 1H, J= 2.6 and 11.6 Hz), 4.26 (ddq, 1H, J= 5.1, 6.4 and 8.1 Hz), 4.76 (t, 1H, J= 9.6 Hz), 6.88-6.98 (m, 3H) and 7.93-7.97 (m, 2H). ^{13}C-NMR ($CHCl_3$) δ: 21.1, 26.1, 32.0, 35.9, 60.5, 64.7, 75.9, 105.4, 128.7, 128.9, 133.6, 139.7 and 199.4.

Isomer **11B$_2$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.01 (d, 3H, J= 6.0 Hz), 1.13 (m, 1H), 1.60 (m, 1H), 1.76 (ddd, 1H, J= 5.8, 7.6 and 11.8 Hz), 2.16 (m, 2H), 2.32 (dt, 1H, J= 9.8 and 11.8 Hz), 3.43 (m, 1H), 3.63 (dq, 1H, J= 6.0 and 9.8 Hz), 3.79 (dt, 1H, J= 2.6, 11.6 Hz), 4.60 (dd, 1H, J= 7.5 and 12.7 Hz), 6.88-6.98 (m, 3H) and 7.93-7.97 (m, 2H). ^{13}C-NMR ($CHCl_3$) δ (significative signals): 22.3, 25.7, 32.8, 35.7, 65.6, 76.9 and 139.5. MS (FAB): 311 (M^++1). MS (EI): 282 (19.1, M^+-CO), 241 (67.4), 223 (28.3), 196 (20.7), 141 (54.4), 125 (71.1), 11 (6.1) and 77 (100.0). Anal. Calcd for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.84. Found: C, 57,68; H, 5.78.

2,7-Dimethyl-4-(phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (12). Dihydrofuran: **1b**. γ-lactone: γ-valerolactone. Purification in Alumina, eluent: ethyl acetate-hexane (1:4). Yield: 64%. Isomer ratio **12A$_1$** (2S*,4R*,5R*,7S*)/**12A$_2$** (2R*,4R*,5R*,7S*)/**12B$_1$** (2S*,4S*,5R*,7S*)/**12B$_2$** (2R*,4S*,5R*,7S*)= 63:27:5:5 (after addition of NH_4Cl) and <4:<4:71:29 (after basic treatment). IR ($CHCl_3$): 2950, 2910, 1720, 1440, 1330, 1310, 1150, 1090, 990 and 910 cm^{-1}. Isomer **12A$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) (significative signal) δ: 2.66 (ddd, 1H, J= 3.9, 6.8 and 17.1 Hz). Isomer **12A$_2$**: ^{1}H-NMR (C_6D_6, 300 MHz) significative signals δ: 2.53 (ddd, 1H, J= 3.8, 6.6 and 16.8 Hz) and 2.85 (ddd, 1H, J= 8.1, 10.0 and 12.5 Hz). Isomer **12B$_1$**: Mp: 94-97°C. ^{1}H-NMR (C_6D_6, 300 MHz) δ: 0.76 (d, 3H, J= 6.3 Hz), 1.01 (d, 3H, J= 6.3 Hz) 1.20 (ddt, 1H, J= 2.7, 6.4 and 13.3 Hz), 1.35 (ddt, 1H, J= 5.0, 10.9 and 12.8 Hz), 1.50 (ddd, 1H, J= 5.3, 9.8 and 12.5 Hz), 2.10 (ddd, 1H, J= 2.9, 5.0 and 15.7), 2.20 (ddd, 1H, J= 6.4, 12.8, 15.8 Hz), 2.80 (ddd, 1H, J= 7.8, 9.1 and 12.5 Hz), 4.03 (ddq, 1H, J= 2.5, 6.4 and 10.2 Hz), 4.30 (ddq, 1H, J= 5.3, 6.2 and 7.8 Hz), 4.80 (t, 1H, J= 9.4 Hz), 6.87-6.96 (m, 3H) and 7.94-7.98 (m, 2H). ^{13}C-NMR (C_6D_6 75 MHz) δ: 20.1, 20.3, 31.9, 32.7, 35.1, 66.5, 75.4, 105.0, 127.7, 128.9, 132.4, 140.7 and 198.7 . Isomer **12B$_2$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.00 (d, 3H, J= 6.3 Hz), 1.02 (d, 3H, J= 6.9 Hz) 1.20-1.45 (m, 2H), 1.88 (ddd, 1H, J= 5.3, 7.7 and 13.4 Hz), 2.05-2.30 (m, 3H), 3.69 (dq, 1H, J= 6.0 and 9.5 Hz), 4.04 (m, 1H), 4.61 (dd, 1H, J= 7.7 and 12.5 Hz), 6.96-7.00 (m, 3H) and 7.92-7.96 (m, 2H). ^{13}C-NMR (C_6D_6 75 MHz) δ: 21.9, 32.4, 64.9, 65.5, 76.4, 104.1, 128.2, 129.1, 132.7, 140.4 and 198.8. MS (EI): 324 (0.1, M^+), 296 (8.9), 241 (100.0), 223 (29.6), 176 (13.1) and 143 (52.9). Anal. calcd for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.21. Found: C, 59.21; H, 6.12.

2-Phenyl-4-(phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (13). Dihydrofuran: **1c**. γ-Lactone: γ-butyrolactone. Eluent: ethyl acetate-hexane (1:4). Yield: 58%. Isomers ratio: **13A$_1$** (2R*,4R*,5R*)/**13A$_2$** (2S*,4R*,5R*)/**13B$_1$** (2R*,4S*,5R*)/**13B$_2$** (2S*,4S*,5R*)= 43:31:14:12 (after addition of NH_4Cl) and <4:<4:57:43 (after basic treatment). Mp= 136-7°C. IR ($CHCl_3$): 3010, 2985, 1740, 1450, 1320, 1160, 1090 and 980 cm^{-1}. Isomer **13A$_1$** : ^{1}H-RMN ($CDCl_3$) (significative signals) δ: 5.14 (dd, 1H, J= 4.8 and 10.8 Hz). Isomer **13A$_2$**: ^{1}H-RMN ($CDCl_3$) (sinificative signals) δ: 5.26 (dd, 1H, J= 4.8 and 8.4 Hz). Isomer **13B$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.12-1.22 (m, 1H), 1.61-1.83 (m, 1H), 1.93 (ddd, 1H, J= 5.3, 9.9 and 12.6 Hz), 2.17-2.26 (m, 2H), 3.14 (dt, 1H, J= 8.8 and 13.6 Hz), 3.50 (m, 1H), 3.79 (dt, 1H, J= 2.6 and 11.5 Hz), 4.90 (t, 1H, J= 9.6 Hz), 5.25 (dd, 1H, J= 5.3 and 8.6 Hz), 6.88-7.23 (m, 8H) and 7.89-7.94 (m, 2H). ^{13}C-NMR (C_6D_6, 75 MHz) δ: 25.8, 34.4, 36.3, 60.7, 65.3, 81.1, 106.4, 125.9, 128.1, 128.7, 128.8, 129.0, 133.1, 141.0, 141.2 and 199.0. Isomer **13B$_2$**: ^{1}H-NMR (C_6D_6) δ: 1.12-1.22 (m, 1H), 1.61-1.83 (m, 1H), 1.99 (ddd, 1H, J= 5.8, 7.0 and 12.1 Hz), 2.17-2.26 (m, 2H), 2.74 (ddd, 1H, J= 10.7, 12.1 and 13.1 Hz), 3.50 (m, 1H), 3.83 (dt, 1H, J= 2.6 and 11.4 Hz), 4.42 (dd, 1H, J= 5.8 and 10.7 Hz), 4.69 (dd, 1H, J= 7.0 and 13.1 Hz), 6.88-7.23 (m, 8H) and 7.89-7.94 (m, 2H). ^{13}C-NMR (C_6D_6, 75 MHz) δ: 25.6, 35.1, 36.1, 61.0, 66.2, 82.7, 105.3, 127.0, 127.9, 128.5, 128.9, 129.2, 133.2, 141.3, 141.4 and 199.1. MS (EI): 372 (0.1, M^+), 344 (30.3), 302 (11.3), 202 (78.2), 161 (73.1), 145 (72.6), 115 (100.0) and 77 (86.1). HRMS: exact mass calcd for $C_{20}H_{20}O_5S$ (M^+) 372.1035, found 372.1031.

7-Methyl-2-phenyl-4-(phenylsulfonyl)-1,6-dioxaspiro[4,5]decan-10-one (14). Dihydrofuran: **1c**. γ-Lactone: γ-valerolactone. Eluent: ethyl acetate-hexane (1:4). Yield: 64%. Isomers ratio **14A$_1$** (2R*,4R*,5R*,7S*)/ **14A$_2$** (2S*,4R*,5R*,7S*) /**14B$_1$** (2R*,4S*,5R*,7S*) / **14B$_2$** (2S*,4S*,5R*,7S*)= 40:25:16:19 (after addition of NH_4Cl). Isomer ratio **14B$_1$** (2R*,4S*,5R*,7S*)/**14B$_2$** (2S*,4S*,5R*,7S*)/**14B$_3$** (2R*,4S*,5R*,7R*)/**14B$_4$** (2S*,4S*,5R*,7R*)= 44:38:10:8 (after basic treatment). Mp= 131-2°C. IR ($CHCl_3$): 2930, 1725, 1445, 1310, 1150, 1085, 1000, 950 and 900 cm^{-1}. Isomer **14B$_1$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.06 (d, 3H, J= 6.3 Hz), 1.18-1.29 (m, 1H), 1.31-1.64 (m, 1H), 1.99 (ddd, 1H, J= 5.6, 9.9 and 12.7 Hz), 2.13-2.33 (m, 2H), 3.17 (dt, 1H, J= 8.6 and 12.7 Hz), 4.07 (m, 1H), 4.92 (t, 1H, J= 9.3 Hz), 5.31 (dd, 1H, J= 5.6 and 8.4 Hz), 6.83-7.35 (m, 8H) and

7.89-8.10 (m, 2H). ^{13}C-NMR (C_6D_6, 75 MHz) δ: 20.7, 33.1, 34.4, 35.8, 65.4, 67.4, 81.0, 105.9, 125.9, 127.0, 128.8, 129.4, 133.2, 140.8, 141.1 and 199.2. Isomer **14B$_2$**: ^{1}H-NMR (C_6D_6, 300 MHz) δ: 1.07 (d, 3H, J= 6.3 Hz), 1.18-1.29 (m, 1H), 1.31-1.64 (m, 1H), 2.05 (ddd, 1H, J= 5.9, 7.1 and 12.1 Hz), 2.13-2.33 (m, 2H), 2.74 (ddd, 1H, J= 10.6, 12.1 and 13.1 Hz), 4.07 (m, 1H), 4.45 (dd, 1H, J= 5.9 and 10.6 Hz), 4.71 (dd, 1H, J= 7.1 and 13.1 Hz), 6.83-7.35 (m, 8H) and 7.89-8.10 (m, 2H). ^{13}C-NMR (C_6D_6, 75 MHz) δ: 20.6, 32.8, 35.0, 35.7, 66.4, 67.5, 82.2, 104.7, 125.9, 127.0, 128.7, 128.8, 129.5, 133.3, 140.9, 141.2 and 199.2. Isomer **14B$_3$**: ^{1}H-NMR (C_6D_6, 300 MHz) (significative signals) δ: 1.16 (d, 3H, J= 6.4 Hz), 3.87-3.95 (m, 1H), 4.85 (t, 1H, J= 9.9 Hz) and 5.36 (dd, 1H, J= 5.8 and 8.8 Hz). Isomer **14B$_4$**: ^{1}H-NMR (C_6D_6, 300 MHz) (significative signals) δ: 1.15 (d, 3H, J= 6.3 Hz) and 4.41 (dd, 1H, J= 5.3 and 11.4 Hz). MS (EI): 386 (0.1, M^+), 358 (10.3), 303 (46.6), 285 (12.1), 217 (5.9), 161 (100.0), 145 (27.5), 133 (54.2), 115 (63.3) and 77 (44.4). Anal. Calcd for $C_{21}H_{22}O_5S$: C, 65.27; H, 5.74; S, 8.30. Found: C, 65.67; H, 5.92; S, 8.02.

2-Isopropyl-3-methyl-4-(phenylsulfonyl)-1,6-dioxa-spiro[4,5]decan-10-one (15). Dihydrofuran: **1d**. γ-Lactone: γ-butyrolactone. Eluent: ethyl acetate-hexane (1:5). Yield: 50%. Isomer ratio **15A$_1$** (2S*, 3R*, 4R*, 5 R*)/**15B$_1$** (2S*, 3R*, 4S*, 5R*)/**15B$_2$** (2R*, 3S*, 4S*, 5R*)= 17:77:6 (after addition of NH_4Cl) and <4:94:6 (after basic treatment). IR ($CHCl_3$): 2940, 1725, 1440, 1300, 1245, 1080, 1060, 1005, 990 and 955 cm^{-1}. Isomer **15A$_1$**: ^{1}H-NMR ($CDCl_3$) (significative signals) δ: 1.09 (d, 1H, J= 6.5 Hz), 1.17 (d, 1H, J= 7.0 Hz), 3.42 (m, 1H), 3.68 (d, 1H, J= 1.3 Hz) and 4,47 (dd, 1H, J= 5.5 and 9.9 Hz). Isomer **15 B$_1$**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (d, 3H, J= 6.6 Hz), 0.95 (d, 3H, J= 7.1 Hz), 0.99 (d, 3H, J= 6.4 Hz), 1.74 (m, 2H), 1.92 (ddq, 1H, J= 2.8, 5.3 and 13.6 Hz), 2.32 (dddd, 1H, J= 2.1, 3.1, 4.7 and 15.0 Hz), 2.63 (ddd, 1H, J= 6.3, 13.1 and 15.0 Hz), 3.00 (ddc, 1H, J= 3.6, 5.6 and 7.1 Hz), 3.75 (ddt, 1H, J= 2.1, 4.8 and 11.5 Hz), 4.00 (dd, 1H, J= 5.6 and 9.8 Hz), 4.10 (dt, 1H, J= 2.7 and 11.9 Hz), 4.28 (d, 1H, J= 3.7 Hz), 7.47-7.62 (m, 3H) and 7.89-7.92 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 14.9, 18.8, 19.8, 27.2, 27.7, 36.0, 36.3, 60.3, 71.9, 87.4, 104.4, 128.5, 128.8, 133.3, 140.0 and 199.5. Isomer **15 B$_2$**: ^{1}H-NMR ($CDCl_3$, 300 MHz) significative signals δ: 0.70 (d, 3H, J= 6.2 Hz), 0.79 (d, 3H, J= 6.6 Hz), 3.20 (dd, 1H, J= 4.1 and 10.1 Hz) and 4,60 (d, 1H, J= 6.0 Hz). MS (EI): 324 (45.9, M^+-CO), 283 (19.0), 183 (15.1), 141 (46.2), 139 (42.9), 123 (58.2), 83 (100.0) and 77 (70.8). HRMS (FAB): exact mass calcd for $C_{18}H_{25}O_5S$ (M^+) 353.1412, found 353.1422.

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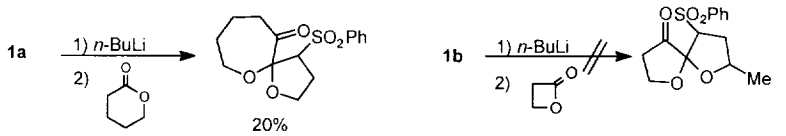
14. We have also briefly explored the condensation of **1** with other types of lactones, such as δ-lactones and β-lactones, but the results were not satisfactory. For instance, the condensation of **1a** with δ-valerolactone afforded the expected spiroketal [4,6] in only 20% yield after chromatography and the reaction of **1b** with β-propiolactone gave a complex mixture of products.



15. In both cases, and as it was expected, after addition of NH_4Cl the isomer **11A$_1$** was the major isomer detected by ^{1}H-NMR.

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17. In the spiroketals **A** the calculated dihedral angle C_3-C_4-S-Ar in each structure were about -90° for the first minima and about 10° for the second, while in the spiroketals **B** this dihedral angle was found to have values around 180° for the first minima and -40° for the second.

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