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A Novel Stereoselective Synthesis of Substituted γ-Butyrolactones

Juan C. Carretero* and Javier Rojo

Departamento de Química. Universidad Autónoma de Madrid.
Cantoblanco. 28049-Madrid. Spain

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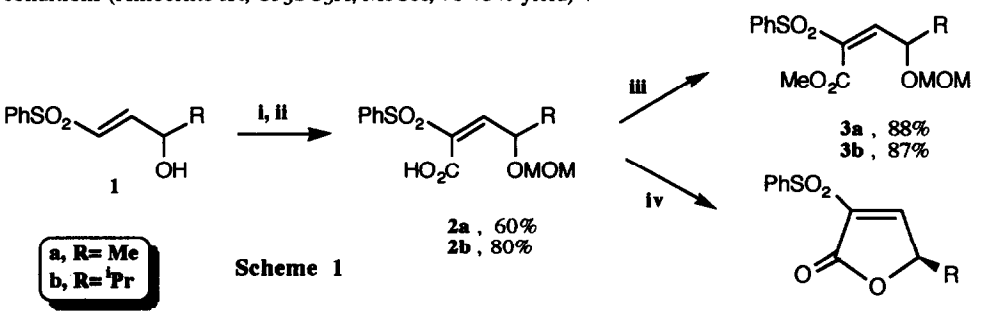
Abstract: *A new stereoselective synthetic route for the preparation of cis and trans disubstituted (and trisubstituted) γ-lactones starting from the readily available α-phenylsulfonyl-α,β-unsaturated esters 3 or α-phenylsulfonylbutenolides 4 is described. This method is based on the conjugate addition of Me_3Al to compounds 3 and 4, which occurs with high, though opposite, facial selectivity.*

Substituted butenolides and γ-lactones are versatile synthetic intermediates currently used in organic synthesis[1]. Additionally, these units are frequently found in a large variety of natural products[2]. Recently we reported a practical method for the synthesis of racemic (E)-γ-hydroxy-α,β-unsaturated phenyl sulfones[3] (**1**) and their efficient resolution by enzymatic methods[4]. Herein, we describe that vinyl sulfones **1** can be used as useful starting products for the stereoselective syntheses of *cis* and *trans* di- and trisubstituted γ-butyrolactones.

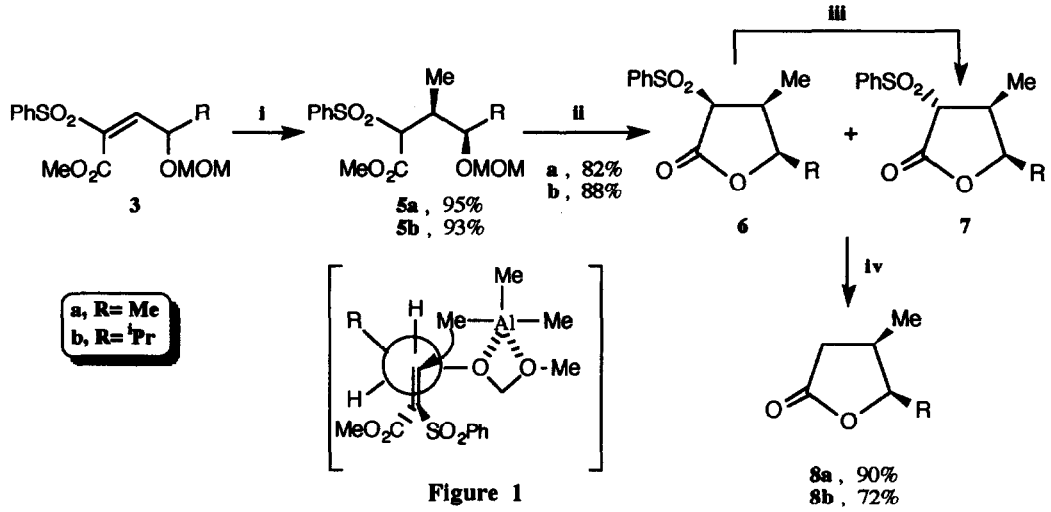
As a first step, the hydroxyl group of vinyl sulfones **1** was protected as MOM derivative. The C-α deprotonation of these α,β-unsaturated sulfones with n-BuLi or LDA[5] (1,1 equiv., THF, -78°C, 30 min.), followed by reaction with dry CO_2 afforded the expected (E)-α,β–unsaturated carboxylic acids **2** in 60-80% overall yield[6] (scheme 1). The carboxylic acids **2** were readily converted into methyl esters **3**, by methylation with MeI/$NaHCO_3$ in DMF (88% yield after chromatography), or into butenolides **4**, by lactonization under acid conditions (Amberlite IR, CF_3SO_3H, MeOH, 70-73% yield)[7].



Scheme 1

i) $CH_2(OCH_3)_2$, P_2O_5, $CHCl_3$, r.t., 1.5 h; **ii)** n-BuLi or LDA, THF, -78°C, 30 min.; then CO_2; **iii)** MeI, $NaHCO_3$, DMF, r.t., 4 h.; **iv)** Amberlite IR, CF_3SO_3H, MeOH, r.t., 48 h.

With Michael acceptors **3** and **4** in hand, we focused our attention in the addition of organometallics. We observed competence between 1,4 and 1,2-addition in the reaction of RMgBr and RLi with substrates **3**. On the other hand, although the reaction of **3** with Bu_2CuLi provided regioselectively the 1,4-adducts, this Michael addition occured with very low facial stereoselectivity. Remarkably, reaction of substrates **3** with Me_3Al took place through complete regioselective 1,4-addition and with very high facial stereoselectivity (scheme 2). The reactions were performed at low temperature (-20°C) adding the substrate **3** to a solution of a large excess of Me_3Al (4 equiv.) in CH_2Cl_2, to give stereoselectively in excellent yield (93-95%) a mixture of both *syn*-adducts **5** (1:1.6 mixture of epimers at C-2), which in turn were converted into the corresponding mixtures of *cis*-lactones **6+7** by acid treatment[8] (H_2SO_4, ether-H_2O, 80-88% yield after chromatography). These mixtures of lactones **6+7** can be thermodynamically equilibrated to the most stable *trans,cis*-lactones **7** under basic conditions (Na_2CO_3, THF-H_2O). The stereochemistry of lactones **6** and **7** has been established by study of their ^{1}H-NMR data[9,10]. In agreement with this assignment, the reductive elimination of the sulfonyl group[11] (Na-Hg, Na_2HPO_4, MeOH) on the mixtures of lactones **6+7** afforded exclusively the disubstituted *cis*-lactones **8** (72-95%, **8a:** $J_{3,4}$= 6.5 Hz[12]; **8b:** $J_{3,4}$= 4.8 Hz). The very high *syn*-diastereoselection, observed in the conjugate addition of Me_3Al to Michael acceptors **3**, is consistent with a model based on a prior chelation between the oxygen atoms of the MOM group and the electrophilic aluminum atom (figure 1) in the most stable conformation[13] of substrates **3**, which would force the addition of Me by the same side of the MOM group. A similar stereochemical behaviour has been previously reported in the addition of organolithiums to α–trimethylsilyl-γ-MOM-α,β-unsaturated sulfones[5,14].

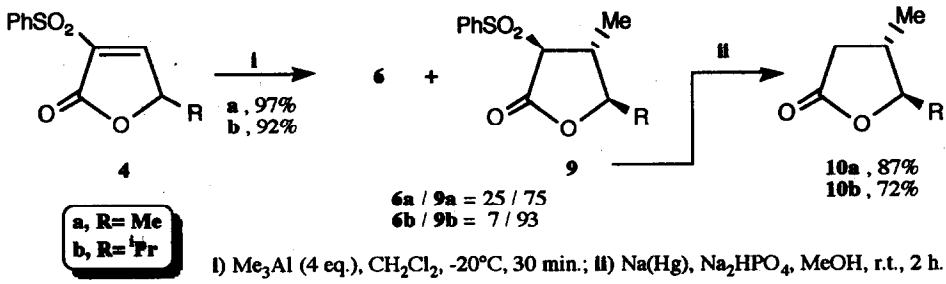


i) Me_3Al (4 eq.), CH_2Cl_2, -20°C, 30 min.; **ii)** H_2SO_4, Et_2O/H_2O, 60°C, 24 h.; **iii)** Na_2CO_3, H_2O/THF, r.t., 24 h. **iv)** Na(Hg), Na_2HPO_4, MeOH, r.t., 1.5 h.

Scheme 2

On the other hand, the addition of Me_3Al to the butenolides **4**, under the same experimental conditions (scheme 3), afforded a mixture of *trans,trans*-lactones **9** and *cis,cis*-lactones **6** in excellent yield (92-97 %). As it was expected on steric grounds the *trans,trans*-lactone **9** (*anti*-diastereoselection) was obtained as the major isomer, the stereoselectivity being dependent on the size of R group (R=Me **9a/6a**= 75/25; R=^{i}Pr **9b/6b**=

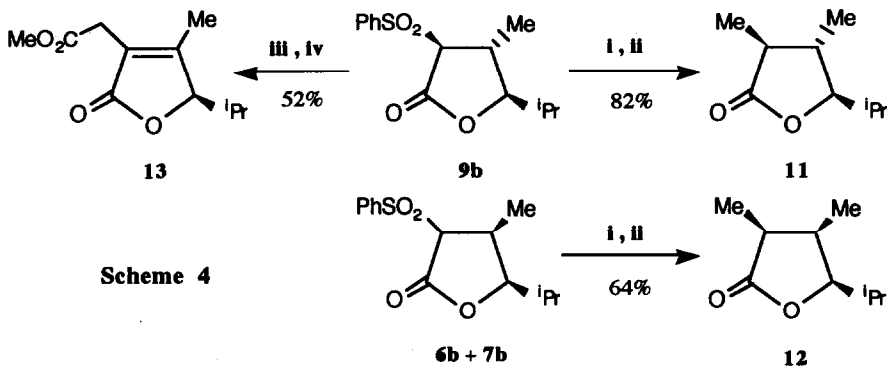
93/7). The major isomers **9** have been easily purified by crystallization. The further elimination of the sulfonyl group on lactones **9** gave the disubstituted *trans*-lactones **10** (72-87% yield, **10a** $J_{3,4}$= 7.6 Hz[12]; **10b** $J_{3,4}$= 6.0 Hz).



i) Me_3Al (4 eq.), CH_2Cl_2, -20°C, 30 min.; ii) Na(Hg), Na_2HPO_4, MeOH, r.t., 2 h.

Scheme 3

The α-phenylsulfonyl γ-lactones[15] (compounds **9** and mixtures **6+7**) constitute useful intermediates for the introduction of carbon substituents at α-position and hence, for the stereoselective synthesis of trisubstituted γ-lactones (scheme 4). The methylation of **9b** and **6b+7b** with NaH/MeI (80-93% yield)[16] followed by reductive elimination of the phenylsulfonyl group (Na-Hg) led to the stereoselective preparation of the *trans,trans*-γ-lactone **11** and the *cis,cis*-γ-lactone **12** respectively, in good overall yields (79-88%). Additionally, alkylation of enolate of lactone **9b** with methyl bromoacetate[16] and further basic elimination of the sulfonyl group (DBU, CH_2Cl_2) afforded the 2,3,4-trisubstituted butenolide **13** in 52% overall yield after chromatography.



Scheme 4

i) MeI, NaH, DMF, r.t., 5 h.; ii) Na(Hg), Na_2HPO_4, MeOH, r.t., 3 h.; iii) $BrCH_2CO_2Me$, NaH, DMF, r.t., 5 h.; iv) DBU (1.5 eq.), CH_2Cl_2, r.t., 17 h.

The application of these methodologies to the enantioselective synthesis of natural products from homochiral compounds **3** and **4**, and the use of other aluminum reagents in the conjugate addition are now in progress in our laboratory.

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References and Notes

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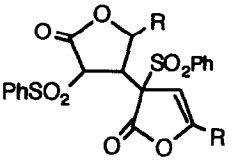
5.- The best results for the preparation of acids **2** were obtained by using LDA in the case of R=Me and n-BuLi for R= i-Pr. For the introduction of other functionalities at α-position in vinyl sulfones **1** see: Alcaraz, C.; Carretero, J.C.; Domínguez, E. *Tetrahedron Lett.* **1991**, *32*, 1385.
6.- For the carboxylation of γ-hydroxy-α,β-unsaturated sulfides see: Takayori, I.; Yamakawa, I.; Okamoto, S.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 371.
7.- Whereas esters **3** have been readily purified by flash chromatography, when butenolides **4** were submitted to silica gel chromatography a great amount of the dimeric compound **14** was formed (e.g. 40% of the stereoisomer **14b** was obtained from **4b**). Therefore, butenolides **4** have been purified by crystallization or used without further purification.
8.- In the lactonization of the mixture of *syn*-adducts **5a** (1.8:1 ratio) we obtained exclusively the *trans,cis*-lactone **7a** (82% after chromatography).



14

9.- For an extensive study about stereochemistry and coupling constants on substituted γ-butyrolactones see: a) Jaime, C.; Ortuño, R.M.; Font. J. *J. Org. Chem.* **1986**, *51*, 3946. See also: b) Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950. c) Bystrom, S.; Högberg, H. E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249. d) Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289. e) Welch, J.T.; Plummer, J.S.; Chou, T. *J. Org. Chem.* **1991**, *56*, 353. f) Hoye, T.R.; Hanson, P.R. *J. Org. Chem.* **1991**, *56*, 5092.
10.- The values of the vicinal coupling constants $J_{2,3}$ and $J_{3,4}$ and the strong deshielding effect induced by the phenylsulfonyl group on the substituent in γ position (H or R groups) in *syn*-relationship are especially significant for the stereochemical assignment of trisubstituted γ-lactones **6**, **7**, **9**, **11** and **12**

	Chemical shifts (ppm)[a]				Coupling constants (Hz)[a]		
Comp.	δH_2	δH_3	δH_4	δH_R	$J_{2,3}$	$J_{3,4}$	$J_{4,R}$
6b	4.25	3.22	3.76	1.92	6.5	4.0	10.6
7a	3.71	3.35	4.98	1.33	4.3	6.6	6.6
7b	3.65	3.42	4.49	1.88	1.5	5.3	10.3
9a	3.84	2.77	4.10	1.45	10.1	8.3	6.2
9b	3.80	2.94	3.80	1.91	8.9	7.0	6.6
11	2.70	2.42	3.75	1.78	7.1	4.1	10.6
12	2.21	1.88	3.78	1.88	11.1	9.3	4.7

[a] Values in $CDCl_3$

11.- Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
12.- *Cis* and *trans*-3,4-dimethyl-γ-butyrolactones (**8a** and **10a**) have been previously reported. Their ^{1}H-NMR data are described in references 8a-d.
13.- For a review about 1,3-strain in stereoselective transformations see: Hoffmann, R.W. *Chem. Rev.* **1989**, *89*, 1841.
14.- Isobe, M. *Perspectives in the Organic Chemistry of Sulfur*, Zwanemburg, B.; Klander, A.J. Eds.; Studies in Organic Chemistry **1987**, *28*, 209.
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16.- These alkylations were completely stereoselective. Only the stereoisomer with sulfone and i-Pr groups in *cis* arrangement was detected.

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