Tetrahedron Vol 49, No 43, pp 9787-9800, 1993
Printed in Great Britain

0040-4020/93 $6 00+ 00

Stereoselective Synthesis of Substituted γ-Butyrolactones from γ-Hydroxy-α,β-unsaturated Phenyl Sulfones

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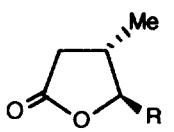
(*Received in UK* 12 *July* 1993)

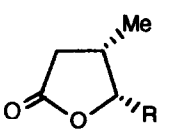
Abstract. *A stereoselective route for the preparation of cis and trans disubstituted (and trisubstituted) γ-lactones starting from the readily available α-(phenylsulfonyl)-α,β-unsaturated esters* ***3*** *or α-(phenylsulfonyl)butenolides* ***4*** *is described This method is based on the conjugate addition of organoaluminum reagents (Me_3Al, Et_3Al and Et_2AlCN) to substrates* ***3*** *and* ***4****. Whereas the conjugate addition to Michael acceptors* ***3*** *occurs with complete syn-selectivity, the conjugate addition to butenolides* ***4*** *is usually anti-selective. This methodology has been applied to the stereoselective and enantioselective synthesis of (-)-cis cognac lactone*

Introduction

Many natural products such as pheromones, flavor components or tetronic acids contain γ-lactone subunits [1] Additionally these units are versatile intermediates in organic synthesis and are widely used as starting materials in the synthesis of natural products [2] We have previously reported that (E)-γ-hydroxy-α,β-unsaturated phenyl sulfones (**1**) are prepared in one step by condensation of (phenylsulfonyl)(*p*-tolylsulfinyl)methane with enolizable aldehydes [3] As a part of our programme of developing new stereoselective methods in organic synthesis from these readily available Michael acceptors, in a recent preliminary paper we described the use of substrates **1** in the stereoselective synthesis of *cis* and *trans* substituted γ-lactones [4] We herein present this work in detail along with additional examples and its application to the enantioselective synthesis of (-)-*cis* cognac lactone (figure 1) Quercus lactones (+)-*trans* and (-)-*cis* whisky and cognac lactones, have been identified as key flavors of aged alcoholic beverages[5] such as whisky, brandy, wine and cognac However, although a considerable number of stereoselective and enantioselective syntheses of the *trans*-isomers have been reported[6], there are very few precedents concerning the enantioselective preparation of the *cis*-isomers [7]



trans
(+)-(4S,5R)



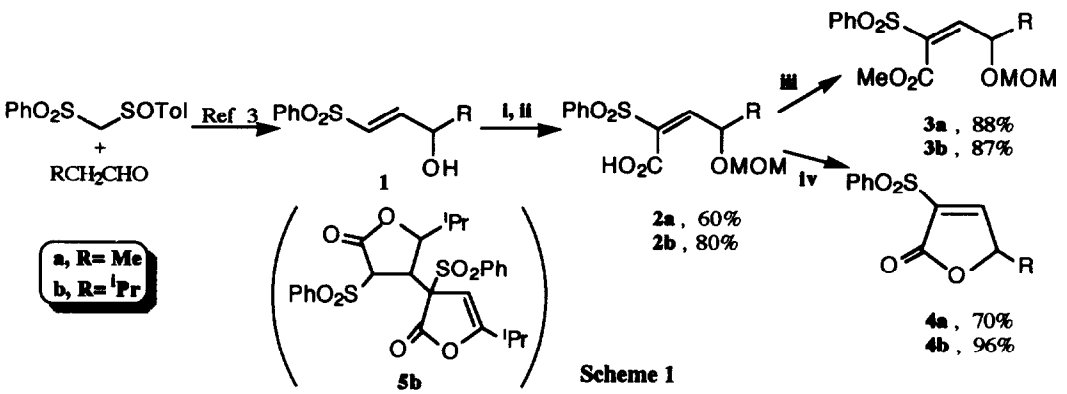
cis
(-)-(4S,5S)

Quercus Lactones
Whisky lactones R= n-butyl
Cognac lactones R= n-pentyl

Figure 1

Discussion and results

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[8] (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[9] (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 (CF_3SO_3H, EtOH, 70-96% yield) Unlike esters **3** which were readily purified by flash chromatography, when butenolides **4** were submitted to silica gel chromatography a great amount of the dimeric compound **5** was formed[10] (e g 40% of **5b** was obtained from **4b**) Therefore, butenolides **4** were purified by crystallization or used without further purification



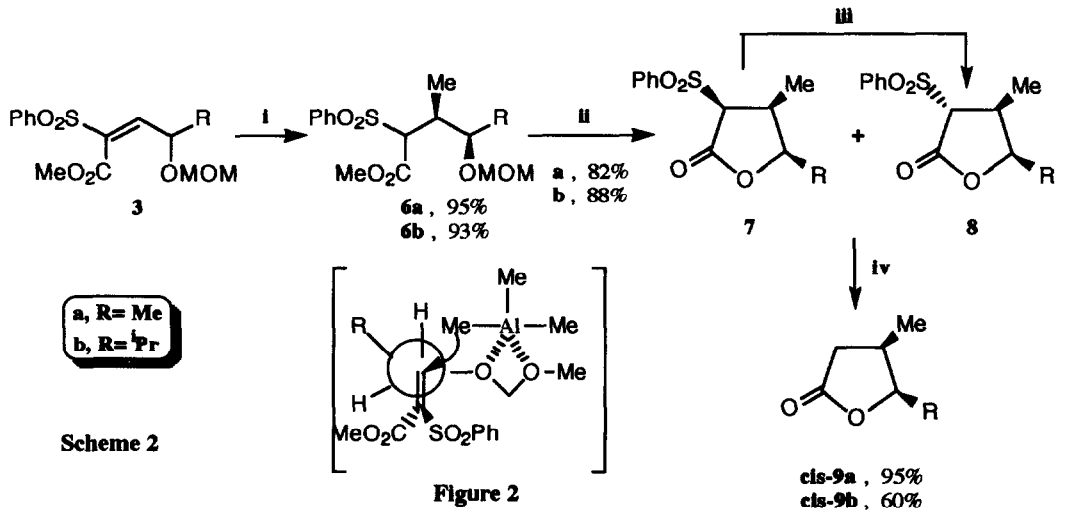
Scheme 1

i) $CH_2(OCH_3)_2$, P_2O_5, $CHCl_3$, r t, **ii)** n-BuLi or LDA, THF, -78°C, then CO_2, **iii)** MeI, $NaHCO_3$, DMF, r t , **iv)** CF_3SO_3H, EtOH, r t

With Michael acceptors **3** and **4** in hand, we focused our attention to the addition of organometallics We observed a 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 in THF at 0°C provided regioselectively the 1,4-adducts, this Michael addition occurred with very low facial stereoselectivity Remarkably, reaction of substrates **3** with Me_3Al took place exclusively through 1,4-addition and with complete facial stereoselectivity (scheme 2) The reactions were performed at low temperature (-20°C) by adding the substrate **3** to a solution of a large excess of Me_3Al (4 equiv) in CH_2Cl_2[11], to give stereoselectively and in excellent yield (93-95%) a mixture of both *syn*-adducts **6** epimers at C-2 (1 1 6 mixture), which in turn were lactonized by acid treatment (H_2SO_4, ether-H_2O, 80-88% yield after chromatography) Whereas from adducts **6a** only the *trans,cis* lactone **8a** was obtained after acid treatment (82% yield), showing that a thermodynamic equilibration at α-position took place under these acid conditions, in the case of adducts **6b** a mixture of lactones **7b+8b** was isolated (88% yield) This mixture can be thermodynamically equilibrated to the most stable *trans,cis*-lactone **8b** under basic conditions (Na_2CO_3, THF-H_2O, rt) The stereochemistry of α-sulfonyl-γ-lactones **7** and **8** has been established by analysis of their ^{1}H-NMR data as it will be later discussed In agreement with this assignment, the reductive elimination of the sulfonyl group[12] (Na-Hg, Na_2HPO_4, MeOH) on lactones **8** (or in mixtures

7+8) afforded exclusively disubstituted *cis*-lactones **9** (cis-**9a**: 90%, $J_{\beta\gamma}$=6 5Hz[13], cis-**9b**: 72%, $J_{\beta\gamma}$=4 8Hz)

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 2) in the most stable conformation[14] 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-alkoxy-α,β-unsaturated sulfones [8,15]



Scheme 2

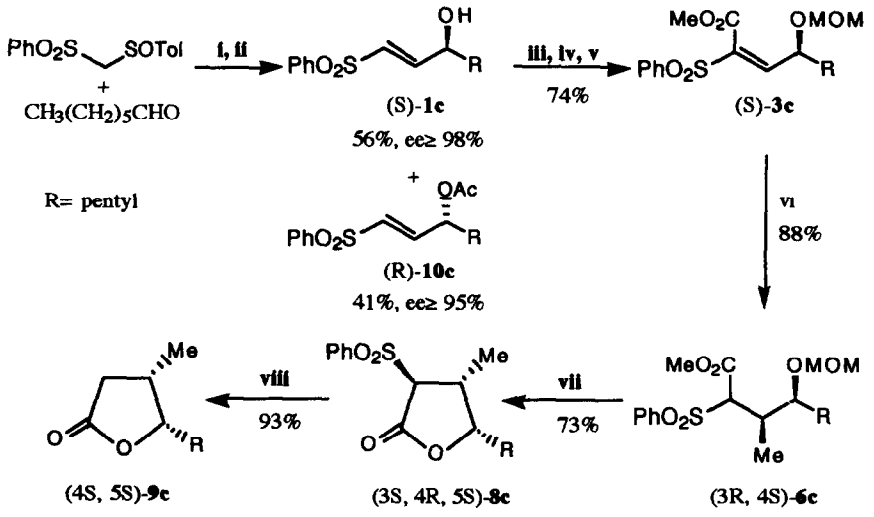
Figure 2

i) Me_3Al (4 eq), CH_2Cl_2, -20°C, **ii**) H_2SO_4, Et_2O/H_2O, 60°C, **iii**) Na_2CO_3, H_2O/THF, r t ,

iv) Na(Hg), Na_2HPO_4, MeOH, r t

Scheme 3 shows the application of this methodology to the enantioselective synthesis of (-)-*cis* cognac lactone The condensation of enantiomerically pure (S)-(phenylsulfonyl)(*p*-tolylsulfinyl)methane[3b] with heptanal, catalyzed by piperidine (CH_3CN, 0°C), afforded the (E)-γ-hydroxyvinyl sulfone **1c** in 93% yield as a 1 8 1 mixture of S/R enantiomers (ee= 28%, determined from their Mosher's esters) [3b] As we have previously reported for other related γ-hydroxy-α,β-unsaturated sulfones[16], the enzymatic acetylation of alcohols **1c** by using lipase PS and vinyl acetate (in $^iPr_2O$ and in the presence of molecular sieves) was completely enantioselective, affording, after chromatographic purification, acetate (R)-**10c** (41%) and unreacted alcohol (S)-**1c** (56%) with optical purities higher than 95% and 98% respectively [17] (S)-**1c** was converted into the Michael acceptor (S)-**3c** in 74% overall yield following the three step sequence shown in scheme 1 The treatment of (S)-**3c** with excess of Me_3Al (4 equiv , inverse addition) in CH_2Cl_2 at -20°C led to the formation of a 2 9 1 mixture of only two adducts, epimers at α-position (*syn*-**6c**), showing that the conjugate addition occurred again with complete facial selectivity As in the case of adducts **6b**, the mixture of adducts **6c** was lactonized under acid conditions (2 7M H_2SO_4, Et_2O-H_2O, 60°C) to afford, exclusively, the *trans,cis* -α–sulfonyl lactone **8c** (73% yield after chromatography) In agreement with the 4R,5S configuration of **8c**, the reductive elimination of the sulfonyl group (Na-Hg, Na_2HPO_4, MeOH) afforded (-)-*cis* cognac

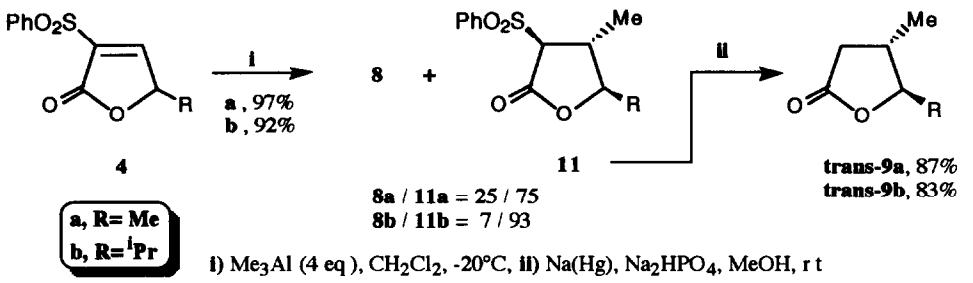
lactone (93% yield), whose spectroscopical data were identical to the previously reported for this compound[7], and hence, showing that the conjugate addition of Me_3Al to **3c** took place with complete *syn*-selectivity Both the rotary power[7] $[\alpha]_D^{25}$= -73° (c 1, $CHCl_3$) and the study with Yb(hfc)$_3$ of this compound confirmed its very high enantiomeric purity (ee> 90%)



i) pipendine (2 eq), CH_3CN, 0°C, 5 h., **ii)** Lipase PS, vinyl acetate, molecular sieves, iPr_2O, rt, 16 h , **iii)** $CH_2(OCH_3)_2$, P_2O_5, $CHCl_3$, r t., 1 5 h., **iv)** n-BuLi, THF, -78°C, 30 min, then CO_2, **v)** MeI, $NaHCO_3$, DMF, r t., 2 h, **vi)** Me_3Al (4 eq), CH_2Cl_2, -20°C, 2 h, **vii)** H_2SO_4, Et_2O/H_2O, 60°C, 24 h, **viii)** Na(Hg), Na_2HPO_4, MeOH, r t , 1 h

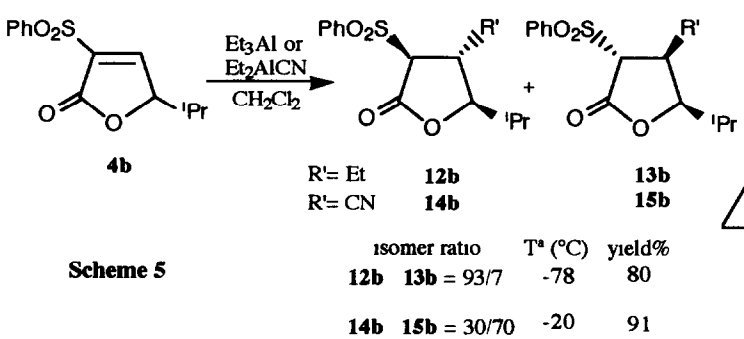
Scheme 3

On the other hand, the addition of Me3Al to butenolides **4**, under the same experimental conditions previously described for the acyclic Michael acceptors **3**, afforded a mixture of *trans,trans*-lactones **11** and *trans,cis*-lactones **8** in excellent yield (92-97%, scheme 4) As it was expected on steric grounds the *trans,trans*-lactones **11** were obtained as the major isomers (*anti*-selectivity) and this *anti*-stereoselectivity was higher in the case of **4b** (R=^{i}Pr, **11b/8b**= 93/7) than that observed from **4a** (R= Me, **11a/8a**= 75/25) The major isomers **11** were easily purified by crystallization In accordance with this stereochemical assignment, the further elimination of the sulfonyl group (Na-Hg)[12] on lactones **11** gave the disubstituted *trans*-lactones **9** (83-87% yield, *trans*-**9a** $J_{\beta\gamma}$= 7 6 Hz[13], *trans*-**9b** $J_{\beta\gamma}$= 6 0 Hz)



Scheme 4

We have also studied the conjugate addition of other organoaluminum reagents, such as Et_3Al and Et_2AlCN, to butenolide **4b**. The results are summarized in scheme 5 Whereas the results obtained in the addition of Et_3Al (**12b:13b**=97 3) were very similar to the obtained in the addition of Me_3Al, the addition of Et_2AlCN was less stereoselective (**14b:15b**= 30/70) and, unexpectedly, the major adduct was the *trans,cis*-lactone **15b** (*syn*-selectivity) instead of the *trans,trans*-lactone **14b** (*anti*-selectivity) It should be noted that the conjugate addition of a wide variety of nucleophiles to α-unsubstituted butenolides usually takes place with very high *anti* selectivity[18] The lower *anti*-selectivity observed in the conjugate addition of organoaluminum reagents to α-sulfonyl-butenolides **4** (always the *syn* adduct has been detected) could be due to the opposite facial selectivities induced by the steric effects of R and Ph groups in the presumably most stable conformation around C-S bond (figure 3) The quite different stereochemical results obtained from Me_3Al and Et_3Al (*anti*-selectivity) or from Et_2AlCN (*syn*-selectivity) suggest that the balance between both steric effects would be very dependent on the nature of the organoaluminum reagent



Scheme 5

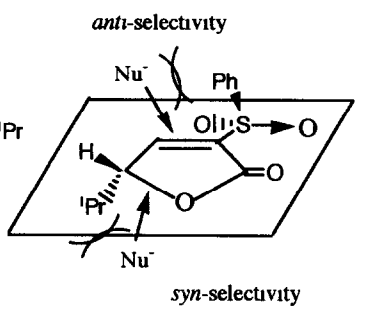
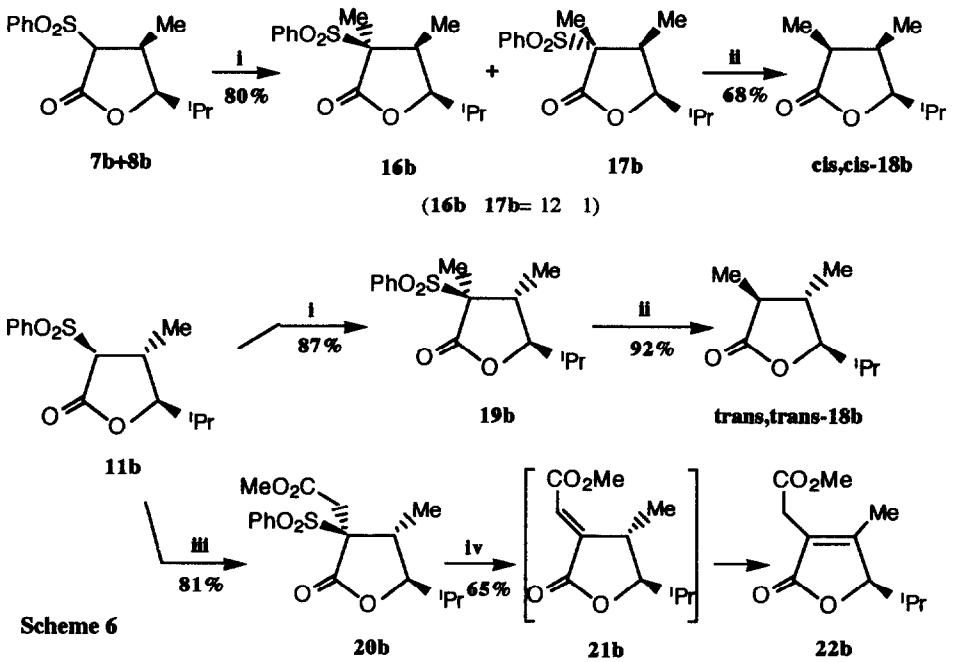


Figure 3

Finally, α-phenylsulfonyl-γ-lactones constitute also useful intermediates for the introduction of carbon substituents at α-position and hence, for the stereoselective synthesis of trisubstituted γ-lactones after sulfonyl elimination (scheme 6) The methylation of **7b+8b** with NaH/MeI in DMF at 40°C afforded a 12 1 mixture of α-sulfonyl–γ-butyrolactones **16b:17b** in 80% yield. The reductive elimination (Na-Hg) of this mixture gave exclusively the *cis,cis*-lactone[19] **18b** in 68% yield Similarly, the methylation of **11b** was completely stereoselective yielding **19b** (87% yield), which gave exclusively the *trans,trans* lactone[19] **18b** by sulfonyl elimination (92% yield) Additionally, alkylation of enolate of lactone **11b** with methyl bromoacetate yielded exclusively **20b** which, after treatment with DBU in CH_2Cl_2 at rt, afforded the butenolide **22b** in 52% overall

yield The intermediate **21b,** bearing the double bond in exocyclic position, was detected by ^{1}H-NMR when the reaction was carried out by using a defect of base



Scheme 6

i) MeI, NaH, DMF, 40°C, **ii)** Na(Hg), Na_2HPO_4, MeOH, r t , **iii)** $BrCH_2CO_2Me$, NaH, DMF, 40°C

iv) DBU (1 5 eq), CH_2Cl_2, r t

Stereochemical assignment by ^{1}H-NMR

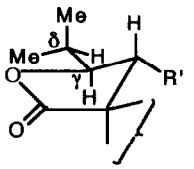
Table 1 ^{1}H-NMR data in $CDCl_3$ of γ-butyrolactones (δ in ppm and J in Hz)

Compound	δH_α	δH_β	δH_γ	$\Delta\delta H_\gamma$	$J_{\alpha\beta}$	$J_{\beta\gamma}$	$J_{\gamma\delta}$	$\Delta J_{\gamma\delta}$
7b	4 25	3 22	3 76		6 5 c	4 0 c	**10.6**)	
11b	3 80	2 94	**3.80**)		8 9 t	7 0 t	**6.6**)	4 0
8b	3 65	3'42	**4.49**)	0 69	1 5 t	5 3 c	10 3	
c-9b	-	2 55	3 95		-	4 8 c	**10.2**)	
t-9b	-	2 36	3 86		-	6 0 t	**6.0**)	4 2
8a	3 71	3 35	**4.98**)		4 3 t	7 1 c	6 6	
11a	3 85	2 77	**4.10**)	0 88	10 1 t	8 3 t	6 2	
12b	3 85	2 91	**3.85**)		6 0 t	5 9 t	**7.6**)	
13b	-*	-*	**4.06**)	0 21	-*	2 8 c	**10.3**)	2 7
15b	4 31	4 31	**4.49**)		1 6 t	6 4 c	**10.0**)	
14b	4 50	3 78	**4.30**)	0 19	9 6 t	8 3 t	**7.0**)	3 0
17b	-	-	**4.72**)		-	5 5 c	10 7	
16b	-	2 76	**3.96**)	0 76	-	4 7 c	**10.5**)	
19b	-	3 16	3 80		-	8 9 t	**4.3**)	6 2
t,t-18b	2 21	1 88	3 78		11 0 t	9 3 t	**4.7**)	
c,c-18b	2 78	2 48	3 80		7 1 c	4 2 c	**10.6**)	5 9

c = *cis*, t = *trans* * The signals could not be detected in the mixture **12b** + **13b**

For the stereochemical assignment of these compounds the values of $J_{\beta\gamma}$, $J_{\gamma\delta}$ and δ_γ are especially significant Thus, as it is usual in alkyl substituted γ-lactones[19], for each pair of diastereomers it is observed that $J_{\beta\gamma}$ *cis* < $J_{\beta\gamma}$ *trans* (compare the pairs **8a/11a, 8b/11b, c-9b/t-9b, 12b/13b, 14b/15b, 16b/19b** and **c,c-18b/t,t-18b**) It is also interesting to note that in the case of butyrolactones with R=^{i}Pr, whereas in all *cis*$_{\alpha,\beta}$-compounds the value of $J_{\gamma\delta}$ is high ($J_{\gamma\delta}$= 10 2-10 7 Hz in compounds **7b, 8b, c-9b, 13b, 15b, 16b, 17b** and **c,c-18b**) in the *trans* $_{\beta,\gamma}$ isomers $J_{\gamma\delta}$ is much smaller ($J_{\gamma\delta}$= 4 3-7 6 Hz in compounds **11b, t-9b, 12b, 14b, t,t-18b** and **19b**) This effect can be easily explained taking into account the conformational equilibria around Cγ-Cδ bond The most stable conformation for each stereochemistry (conformation avoiding Me/R' 1,3-*syn* diaxial interactions) is depicted in figures 4 and 5

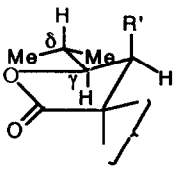
Concerning the chemical shifts of α-sulfonyl-γ-butyrolactones[20] it is observed a strong deshielding effect induced by the phenylsulfonyl group in H_γ in the diastereoisomers bearing both groups ($PhSO_2$ and H_γ) in *syn*-relationship, compared to the diastereoisomer with both groups in *anti*-relationship ($\Delta\delta_\gamma$=0 2-0 9 ppm in the pairs of isomers **8b/11b, 8a/11a, 12b/13b, 14b/15b** and **16b/17b**) This effect is probably due to the important participation of the conformation bearing $PhSO_2$ and H_γ in a 1,3-*syn* diaxial arrangement (figure 6)



trans β,γ-isomers

$J_{\gamma\delta}$= 4 3-7 6 Hz

Figure 4



cis β,γ-isomers

$J_{\gamma\delta}$= 10 2-10 7 Hz

Figure 5

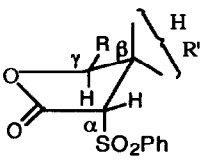


Figure 6

EXPERIMENTAL

Melting points were determined with a Gallenkamp apparatus in open capillaries and are uncorrected ^{1}H-NMR and ^{13}C-NMR spectra were recorded in the FT mode on a Bruker WP-200-SY instrument coupled to an ASPECT 2000 computer, transforming 16K data point Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constans (Hz) were obtained by first order analysis of spin patterns Mass spectra (MS) were recorder at electron impact (EI, 70 eV) or by FAB Mass data are reported in mass units (m/z) and the values in brackets regard the relative intensity from base peak (as 100%) Infrared (IR) spectra were recorded on a Philips PU-9716 spectrometer Elemental analysis were performed by the University Autonoma of Madrid Microanalitycal Laboratory with a Perkin-Elmer 2400 CHN Elemental analyzer Optical rotations were measured with a Perkin-Elmer 141 polarimeter

All solvents were destilled before use Tetrahydrofuran was dried from sodium-benzophenone under argon Dichloromethane was destilled from calcium hydride and chloroform was destilled from P_2O_5 All comercial reagents were purchased from Aldrich and used without further purification Flash chromatography was performed by using silica gel SDS 60 (230-400 mesh)

Alcohols **1** were prepared following the general procedure described in ref 3 The optically pure alcohol (S)-**1c** was obtained by enantioselective enzymatic acetylation of (±)-**1c** following the general procedure described in ref 16

General procedure for the preparation of carboxylic acids 2

To a solution of alcohol **1** (2 mmol) in dry chloroform (6 ml) was added dimethoxymetane (40 mmol) and phosphorus pentoxide (20 mmol) at rt The mixture was stirred for 1 5 h at rt. Then, a saturated aqueous solution of sodium carbonate was added and the mixture was extracted with dichloromethane (3x50 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The crude product was purified by flash chromatography (hexane-ethyl acetate 3 1) affording the MOM derivative in 92-97% yield

A solution 2 4 M of n-BuLi (or LDA) in hexane (1 1 equiv) was slowly added to a solution of the MOM derivative in dry THF (5 ml) at -78°C under argon The solution was kept at -78°C for 30 min and then dry CO_2 was bubbled during 5 min After 1h at -78°C 5% HCl (5 ml) was added and the mixture was extracted with dichloromethane (3x50 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The crude product was dissolved in dichloromethane (20 ml) and it was washed with a saturated aqueous solution of Na_2CO_3(20 ml) The aqueous phase was acidified to pH=2 by addition of 10% HCl and it was extracted with dichloromethane (2x30 ml) The combined organic layers were dried (Na_2SO_4) and evaporated to give carboxylic acids **2** which were used without further purification (the yields are indicated below for each case)

(E)-4-(Methoxymethoxy)-2-(phenylsulfonyl)-2-pentenoic Acid (2a)

Yield 60% (360 mg of **2a** were obtained from 424 mg of **1a**) IR ($CHCl_3$) 2980, 1720, 1450, 1320, 1150, 1030 and 920 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 8 90 (s_b, 1H, CO_2H), 7 95-7 87 (m, 2H, $PhSO_2$), 7 70-7 48 (m, 4H, $PhSO_2$ and CH=C), 4 94 (m, 1H, CHO), 4 67 and 4 62 (AB system, 2H, J= 7 2 Hz, OCH_2O), 3 38 (s, 3H, CH_3O) and 1 46 (d, 3H, J= 6 6 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ: 162 4, 158 5, 139 4, 133 7, 129 0, 128 4, 96 0, 71 5, 65 9, 55 7 and 19 9 MS (FAB) 301 (M^++1, 11)

(E)-4-(Methoxymethoxy)-5-methyl-2-(phenylsulfonyl)-2-hexenoic Acid (2b)

Yield 80% (525 mg of **2b** were obtained from 480 mg of **1b**) m p 99-100°C IR ($CHCl_3$) 3000, 1720, 1450, 1320, 1155, 1030 and 910 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 93-7 88 (m, 2H, $PhSO_2$), 7 67-7 49 (m, 3H, $PhSO_2$), 7 46 (d, 1H, J= 9 0 Hz, CH=C), 4 63, (s, 2H, OCH_2O), 4 55 (dd, 1H, J= 6 0 and 9 0 Hz, CHO), 3 36 (s, 3H, CH_3O), 1 93 (m, 1H, C<u>H</u>$(CH_3)_2$), 0 98 (d, 3H, J= 6 8 Hz, CH_3) and 0 91 (d, 3H, J= 6 8 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 163 1, 155 0, 139 4, 136 0, 133 7, 128 9, 128 4, 95 8, 78 9, 55 6, 33 0, 18 3 and 17 7 MS(FAB) 267 (M^+-MOM, 100)

(2E,4S)-4-(Methoxymethoxy)-2-(phenylsulfonyl)-2-nonenoic Acid [(S)-2c]

Yield 93% (662 mg of **2c** were obtained from 536 mg of **1c**) $[\alpha]^{25}_D$ -12° (c 1,$CHCl_3$) IR ($CHCl_3$) 3020, 2960, 1770, 1610, 1450, 1330, 1170, 1150 and 920 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 73 (s_b, 1H, COOH), 7 96-7 87 (m, 2H, $PhSO_2$), 7 69-7 46 (m, 4H, $PhSO_2$ and C=CH), 4 82 (dt, 1H, J= 8 0 and 4 0 Hz, CHO), 4 64 (s, 2H, OCH_2O), 3 38 (s, 3H, CH_3O), 1 84-1 17 (m, 8H, $(CH_2)_4$) and 0 94-0 81 (m, 3H, CH_3) ^{13}C-NMR ($CDCl_3$) δ 162 8, 157 4, 139 2, 134 2, 133 4, 128 7, 128 2, 95 7, 74 8, 55 3, 33 8, 31 1, 24 4, 22 1 and 13 7 MS (FAB) 295 (M^+-MOM, 38)

General procedure for the preparation of α,β–unsaturated esters 3

To a solution of the carboxylic acid **2** (4 mmol) in dry DMF (25 ml) was added powdered $NaHCO_3$ (16 mmol) and methyl iodide (80 mmol) The solution was stirred at rt for 4 h under argon Then, water (20 ml) was added and the mixture was extracted with ether (3x50 ml) The combined organic layers were dried ($MgSO_4$) and evaporated The crude ester **3** was purified by flash chromatography (the eluents and the yields are indicated below for each case)

(E)-Methyl 4-(Methoxymethoxy)-2-(phenylsulfonyl)-2-pentenoate (3a)

Eluent: hexane-ethyl acetate 5 1 Yield 88% (1 1 g of **3a** were obtained from 1 2 g of **2a**) m p 56-57 5°C IR ($CHCl_3$) 2945, 1725, 1450, 1440, 1320, 1160 and 1030 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 95-7 86 (m, 2H, PhSO2), 7 69-7 47 (m, 4H, $PhSO_2$ and CH=C), 4 92 (m, 1H, CHO), 4 60 (s, 2H, CH_2O), 3 71 (s, 3H, CO_2CH_3), 3 37 (s, 3H, OCH_3), 1 40 (d, 3H, J= 6 6 Hz, C<u>H</u>$_3$-CH) ^{13}C-NMR ($CDCl_3$) δ 161 2, 157 2, 139 6, 134 0, 133 4, 128 7, 128 3, 95 8, 71 0, 55 5, 52 4 and 19 7 Anal Calcd for $C_{14}H_{18}O_6S$ C, 53 49, H, 5 77 Found C, 53 42, H, 5 77

(E)-Methyl 4-(Methoxymethoxy)-5-methyl-2-(phenylsulfonyl)-2-hexenoate (3b)

Eluent: hexane-ethyl acetate 7 1 Yield 93% (1 27 g of **3b** were obtained from 1 3 g of **2b**) m p 68-69°C IR ($CHCl_3$) 3020, 2970, 2900, 1725, 1620, 1440, 1430, 1320, 1220, 1150, 1040 and 920 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 93-7 88 (m, 2H, $PhSO_2$), 7 70-7 53 (m, 3H, $PhSO_2$), 7 47 (d, 1H, J= 8 6 Hz, CH=C), 4 58 (s, 2H, OCH_2O), 4 55 (dd, 1H, J= 8 6 and 5 6 Hz, C=C-CH), 3 71 (s, 3H, CH_3O_2C), 3 34 (s, 3H, C<u>H</u>$_3$OCH$_2$), 1 95 (m, 1H, C<u>H</u>$(CH_3)_2$), 1 00 (d, 3H, J= 6 8 Hz, CH_3) and 0 95 (d, 3H, J= 6 8

Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 161 5, 154 6, 139 8, 136 2, 133 4, 128 8, 128 3, 96 1, 78 5, 55 6, 52 3, 33 1, 18 5 and 17 7 MS (EI) 299 (2, M^+-^{i}Pr), 283 (13), 269 (22), 201 (20), 141 (13), 125 (34), 77 (40) and 45 (100) Anal Calcd for $C_{16}H_{22}O_6S$ C, 56 12, H, 6 47 Found C, 56 30, H, 6 31

(2E,4S)-Methyl 4-(Methoxymethoxy)-2-(phenylsulfonyl)-2-nonenoate [(S)-3c]

Eluent hexane-ethyl acetate 4 1 Yield 89% (1 32 g of **3c** were obtained from 1 42 g of **2c**) $[\alpha]^{25}_D$= -41° (c 1, $CHCl_3$) IR ($CHCl_3$) 2910, 2860, 1730, 1620, 1450, 1330, 1220, 1160, 1040 and 910 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 93-7 88 (m, 2H, $PhSO_2$), 7 67-7 49 (m, 3H, $PhSO_2$), 4 77 (dt, 1H, J= 7 9 and 4 1 Hz, CHO), 4 61 and 4 59 (AB system, 2H, J= 7 0 Hz, OCH_2O), 3 70 (s, 3H, CO_2CH_3), 3 36 (s, 3H, OCH_3), 1 76-1 27 (m, 8H, $(CH_2)_4$) and 0 92-0 85 (m, 3H, CH_3) ^{13}C-NMR ($CDCl_3$) δ 161 3, 156 7, 139 8, 134 6, 133 4, 128 8, 128 3, 96 2, 74 7, 55 7, 52 4, 34 1, 31 3, 24 7, 22 3 and 13 8

General procedure for the preparation of α–sulfonylbutenolides 4

To a solution of acid **2** (2 mmol) in absolute ethanol (6 ml) was added trifluoromethanesulfonic acid (9 mmol) The solution was stirred at room temperature during the time indicated below for each case Then, water (5 ml) was added and the mixture was extracted with dichloromethane (3x25 ml) The combined organic layers were dried (Na_2SO_4) and evaporated to give crude butyrolactones **4** which were used without further purification

5-Methyl-3-(phenylsulfonyl)-2(5H)-furanone (4a)

Reaction time 1 h Yield 70% (333 mg of **4a** were obtained from 600 mg of **2a**) IR ($CHCl_3$) 3000, 1770, 1445, 1320, 1150, 1090 and 1000 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 23 (d, 1H, J= 1 5 Hz, C=CH), 8 15-8 07 (m, 2H, $PhSO_2$), 7 77-7 32 (m, 3H, $PhSO_2$), 5 20 (dq, 1H, J= 1 5 and 7 0 Hz, CHO) and 1 52 (d, 3H, J= 7 0 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 164 5, 162 5, 137 6, 135 9, 134 6, 129 3, 128 8, 77 5 and 17 8 MS (EI) 238 (M^+, 3), 174 (11), 131 (35), 97 (100)

5-Isopropyl-3-(phenylsulfonyl)-2(5H)-furanone (4b)

Reaction time 6 5 h Yield 96% (511 mg of **4b** were obtained from 656 mg of **2b**) m p 105-106 5°C IR ($CHCl_3$) 2980, 1780, 1455, 1340 and 1170 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 24 (s, 1H, C=CH), 8 12-8 09 (m, 2H, $PhSO_2$), 7 73-7 54 (m, 3H, $PhSO_2$), 4 87 (d, 1H, J= 5 9 Hz, CHO), 2 10 (m, 1H, $CH(CH_3)_2$) and 1 01 (d, 6H, J=6 5 Hz, $CH(CH_3)_2$) ^{13}C-NMR (CDCl3) δ 164 5, 160 5, 137 8, 137 0, 134 6, 129 3, 128 8, 85 6, 31 8, 17 8 and 17 5 Anal Calcd for $C_{13}H_{14}O_4S$ C, 58 63, H, 5 30 Found C, 58 47, H, 5 43

General procedure for the conjugate addition of Me_3Al to Michael acceptors 3

A solution of the Michael acceptor **3** (1 mmol) in dry dichloromethane (7 ml) was slowly added to a solution of Me_3Al (4 mmol, 1 M solution in hexane) in dry dichloromethane (3 ml) cooled at -20°C under argon The mixture was stirred for 1 h at -20°C Then, water (5 ml) and 5% HCl (5 ml) were added The organic phase was separated and the aqueous layer was extracted with dichloromethane (2x50 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The residue was dissolved in ether (15 ml) and 2 7 M H_2SO_4 (12 ml) was added The mixture was stirred at 60°C for 24 h The organic layer was separated and the aqueous phase was extracted with more ether (2x50 ml) The combined organic layers were dried ($MgSO_4$) and evaporated The product was purified by flash chromatography

(3R*,4S*,5R*)-4,5-Dihydro-4,5-dimethyl-3-(phenylsulfonyl)-2(3H)-furanone (8a)

Eluent hexane-ethyl acetate 3 1 Yield 82% (208 mg of **8a** were obtained from 314 mg of **3a**) m p 58-60°C IR ($CHCl_3$) 2980, 1765, 1445, 1220, 1150, 1080, 1010, 960 and 940 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 99-7 91 (m, 2H, $PhSO_2$), 7 79-7 53 (m, 3H, $PhSO_2$), 4 98 (q, 1H, J= 6 6 Hz, CHO), 3 71 (d, 1H, J= 4 3 Hz, CH), 3 35 (dq, 1H, J= 4 3 and 7 1 Hz, CH), 1 33 (d, 3H, J= 6 8 Hz, CH_3) and 1 21 (d, 3H, J= 6 8 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 3, 136 8, 134 5, 129 0, 78 7, 71 1, 35 3, 15 5 and 14 1 Anal Calcd for $C_{12}H_{14}O_4S$ C, 56 68, H, 5 55 Found C, 56 66, H, 5 63

(3R*,4S*,5R*)-4,5-Dihydro-5-isopropyl-4-methyl-3-(phenylsulfonyl)-2(3H)-furanone (8b)

Eluent hexane-ethyl acetate 6 1 Yield 88% (242 mg of a 1 25 1 mixture of **7b+8b** were obtained from 342 mg of **3b**) This mixture was equilibrated to the most stable lactone **8b** by treatment in basic conditions (5% Na_2CO_3 in a 3 1 solution of water THF at rt for 24 h) IR ($CHCl_3$) 2980, 2965, 1765, 1450, 1325, 1155 and 990 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 98-7 89 (m, 2H, $PhSO_2$), 7 79-7 53 (m, 3H, $PhSO_2$), 4 49 (dd, 1H, J= 5 3 and 10 3 Hz, CHO), 3 65 (d, 1H, J= 1 5 Hz, C<u>H</u>SO_2Ph), 3 42 (ddq, 1H, J= 1 5, 5 3 and 7 2 Hz, CH), 1 88 (dh, 1H, J= 10 3 and 6 4 Hz, C<u>H</u>$(CH_3)_2$), 1 17 (d, 3H, J= 7 2 Hz, CH_3), 1 10 (d, 3H, J= 6 4 Hz, CH_3) and 0 97 (d, 3H, J= 6 4 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 2, 136 9, 134 4, 129 0, 128 8, 88 1, 73 0, 34 4, 27 8, 19 5, 17 5 and 13 7 Anal Calcd for $C_{14}H_{18}O_4S$ C, 59 55, H, 6 42 Found C, 59 30, H, 6 50

(3S,4R,5S)-4,5-Dihydro-4-methyl-5-pentyl-3-(phenylsulfonyl)-2(3H)-furanone [(-)-8c]
Eluent hexane-ethyl acetate 6 1 Yield 73% (226 mg of (-)-**8c** were obtained from 370 mg of (-)-**3c**) $[\alpha]^{25}_D$= -43° (c 1, $CHCl_3$) IR ($CHCl_3$) 2980, 1790, 1610, 1470, 1350, 1180, 1110 and 970 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 01-7 90 (m, 2H, $PhSO_2$), 7 78-7 55 (m, 3H, $PhSO_2$), 4 81 (ddd, 1H, J= 4 7, 6 2 and 9 8 Hz, CHO), 3 69 (d, 1H, J= 3 3 Hz, C<u>H</u>SO_2Ph), 3 36 (ddq, 1H, J= 3 3, 9 8 and 7 7 Hz, CH), 1 72-1 23 (m, 8H, $(CH_2)_4$), 1 20 (d, 3H, J= 7 7 Hz, CH_3) and 0 96-0 82 (m, 3H, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 6, 137 0, 134 7, 129 2, 83 1, 72 3, 35 1, 31 5, 30 0, 25 4, 22 4, 14 4 and 13 9 Anal Calcd for $C_{16}H_{22}O_4S$ C, 61 94, H, 7 09 Found C, 61 94, H, 6 96

General procedure for the conjugate addition of organoaluminum reagents to butenolides 4
A solution of the butenolide **4** (1 mmol) in anhydrous dichloromethane (7 ml) was slowly added to a solution of R_3Al (4 mmol) in anhydrous dichloromethane (3 ml) cooled at -20°C under argon The mixture was stirred for 30-60 min Then, water (5 ml) and 5% HCl (5 ml) were added The organic phase was separated and the aqueous layer was extracted with dichloromethane (2x50 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The crude lactones were purified and separated by flash chromatography (eluents and yields are indicated below for each case)

(3S*,4R*,5R*)-4,5-Dihydro-4,5-dimethyl-3-(phenylsulfonyl)-2(3H)-furanone (11a)
Reaction time 1 h A 3 1 mixture of **11a+8a** was obtained Eluent hexane ethyl acetate (5 1) Yield 97% (246 mg of **11a** + **8a** were obtained from 238 mg of **4a**) IR ($CHCl_3$) 2985, 2920, 1765, 1440, 1320, 1155, 1080 and 960 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 05-7 92 (m, 2H, $PhSO_2$), 7 77-7 55 (m, 3H, $PhSO_2$), 4 10 (dq, 1H, J= 8 3 and 6 2 Hz, CHO), 3 85 (d, 1H, J= 10 1 Hz, C<u>H</u>SO_2Ph), 2 77 (ddq, 1H, J= 10 1, 8 3 and 6 6 Hz, CH), 1 45 (d, 3H, J= 6 2 Hz, CH_3) and 1 37 (d, 3H, J= 6 6 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 1, 137.1, 134.5, 129 6, 129 2, 81 1, 70 4, 39 7, 18 9 and 16 9.MS (EI). 254 (M^+, 1), 190 (54), 175 (34), 141 (26), 77 (78) and 69 (100)

(3S*,4R*,5R*)-4,5-Dihydro-5-isopropyl-4-methyl-3-(phenylsulfonyl)-2(3H)-furanone (11b)
Reaction time 30 min A 12 5 1 mixture of **11b+8b** was obtained Eluent hexane-ethyl acetate 6 1 Yield 92% (259 mg of **11b** + **8b** were obtained from 266 mg of **4b** and 4ml of 1M Me_3Al in hexane) m p 87 5-89°C IR ($CHCl_3$) 2990, 2950, 1760, 1450, 1320, 1150 and 1020 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 02-7 90 (m, 2H, $PhSO_2$), 7 72-7 53 (m, 3H, $PhSO_2$), 3 80 (d, 1H, J= 8 9 Hz, C<u>H</u>SO_2Ph), 3 80 (dd, 1H, J= 6 6 and 7 Hz, CHO), 2 94 (m, 1H, CH), 1 91 (m, 1H, C<u>H</u>$(CH_3)_2$), 1 38 (d, 3H, J= 7Hz, CH_3), 0 98 (d, 3H, J= 7 0 Hz, CH_3) and 0 93 (d, 3H, J= 6 7 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 1, 136 7, 134 3, 129 4, 128 9, 89 2, 70 4, 34 6, 31 1, 18 8, 18 3 and 16 8 Anal Calcd for $C_{14}H_{18}O_4S$ C, 59 55, H, 6 42 Found C, 60 04, H, 6 74

(3S*,4R*,5R*)-4,5-Dihydro-4-ethyl-5-isopropyl-3-(phenylsulfonyl)-2(3H)-furanone (12b)
Reaction time 30 min Temperature -78°C A 33 1 mixture of **12b+13b** was obtained Eluent hexane-ethyl acetate 5 1 Yield 80% (237 mg of **12b** were obtained from 266 mg of **4b** and 4 ml of Et_3Al 1M in hexane) m p 92-93°C IR ($CHCl_3$) 2980, 1765, 1450, 1330, 1180, 1150, 1090 and 1010 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 7 98-7 94 (m, 2H, $PhSO_2$), 7 76-7 55 (m, 3H, $PhSO_2$), 3 85 (dd, 1H, J= 7 6 and 5 1 Hz, CHO), 3 85 (d, 1H, J= 6 0 Hz, C<u>H</u>SO_2Ph), 2 91 (m, 1H, CH), 1 94 (m, 1H, J= 6 9 Hz, C<u>H</u>$(CH_3)_2$), 1 69 (m, 2H, CH2), 1 00 (t, 3H, J= 7 3 Hz, CH_3), 0 99 (d, 3H, J= 6 9 Hz, CH_3) and 0 97

(d, 3H, J= 6 9 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 167 5, 137 0, 134 4, 129 4, 129 1, 89 0, 69 2, 40 0, 32 2, 27 4, 18 5, 17 6 and 10 6 Anal Calcd for $C_{15}H_{20}O_4S$ C, 60 81, H, 6 76 Found C, 60 42, H, 6 81

4,5-Dihydro-4-cyano-5-isopropyl-3-(phenylsulfonyl)-2(3H)-furanone (15b+14b)

Reaction time 1 h A 2 3 1 mixture of **15b+14b** was obtained Eluent hexane-ethyl acetate 7 1 Yield 91% (34 mg of **15b** and 15 mg of **14b** were obtained from 49 mg of **4b**) IR ($CHCl_3$, mixture of **15b+14b**) 2960, 2240, 1780, 1585, 1450, 1330, 1150, 1080 and 1000 cm^{-1} Anal Calcd for $C_{14}H_{20}O_4NS$ C, 57 14, H, 5 44, N, 4 76 Found C, 56 79, H, 5 10, N, 4 58

(3R*,4S*,5R*) (15b) m p 148-149°C ^{1}H-NMR ($CDCl_3$) δ 8 02-7 93 (m, 2H, $PhSO_2$), 7 86-7 61 (m, 3H, $PhSO_2$), 4 49 (dd, 1H, J= 6 4 and 10 Hz, CHO), 4 31 (dd, 1H, J= 6 4 and 1 6 Hz, CHCN), 4 31 (d, 1H, J= 1 6 Hz, C<u>H</u>SO_2Ph), 2 20 (dh, 1H, J= 6 5 and 10 0 Hz, $CH(CH_3)_2$), 1 23 (d, 3H, J= 6 5 Hz, CH_3) and 1 13 (d, 3H, J= 6 5 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 164 5, 135 7, 129 7, 129 5, 114 7, 84 4, 68 5, 33 1, 31 4, 19 4 and 17 4

(3S*,4R*,5R*) (14b): ^{1}H-NMR ($CDCl_3$) δ 8 10-8 02 (m, 2H, $PhSO_2$), 7 85-7 60 (m, 3H, $PhSO_2$), 4 50 (d, 1H, J= 9 6 Hz, C<u>H</u>SO_2Ph), 4 3 (dd, 1H, J= 8 3 and 7 0 Hz, CHO), 3 78 (dd, 1H, J= 9 6 and 8 3 Hz, CHCN), 2 12 (dh, 1H, J= 7 0 and 6 7 Hz, C<u>H</u>$(CH_3)_2$), 1 12 (d, 3H, J= 6 7 Hz, CH_3) and 1 09 (d, 3H, J= 6 7 Hz, CH_3)

General procedure for alkylation of γ-butyrolactones

To a solution of the γ–butyrolactone (1 mmol) in DMF (5 ml) was added sodium hydride (2 mmol) at rt under argon The reaction was stirred at rt for 10 min and then the corresponding alkylating reagent (4 mmol) was added The mixture was stirred at 40°C for 24 h Water (5 ml) was added and the mixture was extracted with ether (2x20 ml) The combined organic layers were dried ($MgSO_4$) and evaporated The residue was purified by flash chromatography (the eluents and yields are indicated below for each case)

(3S*,4S*,5R*)-4,5-Dihydro-3,4-dimethyl-5-isopropyl-3-(phenylsulfonyl)-2(3H)-furanone (16b)

Eluent hexane-ethyl acetate 8 1 Yield 80% (237 mg of a 12 1 mixture of **16b** and **17b** were obtained from 282 mg of **7b+8b** and 568 mg of MeI) m p 172-173°C IR ($CHCl_3$) 2940, 1770, 1440, 1310, 1160, 1150, 1070 and 980 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 17-8 09 (m, 2H, $PhSO_2$), 7 71-7 53 (m, 3H, $PhSO_2$), 3 96 (dd, 1H, J= 4 7 and 10 5 Hz, CHO), 2 76 (dq, 1H, J= 4 7 and 7 1 Hz, CH), 2 07 (dh, 1H, J= 10 5 and 6 5 Hz, C<u>H</u>$(CH_3)_2$), 1 55 (d, 3H, J= 7 1 Hz, CH_3), 1 50 (s, 3H, CH_3), 1 11 (d, 3H, J= 6 5 Hz, CH_3) and 0 93 (d, 3H, J= 6 5 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 171 6, 137 3, 134 3, 131 4, 128 7, 86 0, 72 6, 43 8, 29 8, 20 5, 20 2, 17 8 and 10 5 Anal Calcd for $C_{15}H_{20}O_4S$ C, 60 79, H, 6 80 Found C, 60 43, H, 6 70

(3S*,4R*,5R*)-4,5-Dihydro-3,4-dimethyl-5-isopropyl-3-(phenylsulfonyl)-2(3H)-furanone (19b)

Eluent hexane-ethyl acetate 8 1 Yield 87% (257 mg of **19b** were obtained from 212 mg of **11b** and 568 mg of MeI) m p 64-66°C IR ($CHCl_3$) 2980, 2960, 1755, 1450, 1310, 1145, 1085, 1010 and 980 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 01-7 93 (m, 2H, $PhSO_2$), 7 75-7 51 (m, 3H, $PhSO_2$), 3 80 (dd, 1H, J= 4 3 and 8 9 Hz, CH), 3 16 (dq, 1H, J= 8 9 and 6 9 Hz, CH), 1 95 (dh, 1H, J= 4 3 and 6 8 Hz, C<u>H</u>$(CH_3)_2$), 1 49 (s, 3H, CH_3), 1 22 (d, 3H, J= 6 9 Hz, CH_3), 1 05 (d, 3H, J= 6 8 Hz, CH_3) and 0 90 (d, 3H, J= 6 8 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 171 8, 134 4, 131 1, 128 6, 87 9, 70 4, 36 5, 30 2, 19 3, 16 0, 14 2 and 13 0 Anal Calcd for $C_{15}H_{20}O_4S$ C, 60 79, H, 6 80 Found C, 60 91, H, 6 99

(3R*,4R*,5R*)-4,5-Dihydro-3,4-dimethyl-5-isopropyl-3-(methoxycarbonylmethyl)-2(3H)-furanone (20b)

Eluent hexane-ethyl acetate 8 1 Yield 81% (287 mg of **20b** were obtained from 282 mg of **11b** and 612 mg of methyl bromoacetate), m p 103 5-105°C IR ($CHCl_3$) 3030, 2990, 1770, 1755, 1455, 1320, 1155, 1090, 1010 and 915 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 8 05-7 89 (m, 2H, $PhSO_2$), 7 80-7 55 (m, 3H, $PhSO_2$), 4 04 (dd, 1H, J= 6 6 and 8 4 Hz, CHO), 3 69 (s, 3H, CO_2CH_3), 3 25 (dq, 1H, J= 8 1 and 7 1 Hz, CH), 3 13 and 3 05 (AB system, 1H, J= 17 4 Hz, OCH_2O), 1 86 (m, 1H, C<u>H</u>$(CH_3)_2$), 1 17 (d, 3H, J= 7 2 Hz, CH_3), 1 05 (d, 3H, J= 6 9 Hz, CH_3) and 0 98 (d, 3H, J= 6 6 Hz, CH_3) ^{13}C-NMR ($CDCl_3$)

δ 170 6, 169 7, 134 7, 133 6, 131 1, 128 8, 89 1, 72 2, 52 5, 35 8, 34 0, 31 3, 18 8, 17 1 and 13 6 Anal Calcd for $C_{17}H_{22}O_6S$ C, 57 61, H, 6 26 Found C, 57 43, H, 6 34

General procedure for the desulfonylation of α-sulfonylbutyrolactones

To a mixture of 1 mmol of the corresponding α-sulfonylbutyrolactone and 4 mmol of anhydrous disodium hydrogen phosphate in 10 ml of dry methanol was added at rt 1 5 g of pulverized 6% sodium amalgam (freshly prepared) The suspension was stirred at rt during the time indicated below for each The mixture was poured into water and it was extracted with dichloromethane (2x15 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The lactone was purified by flash chromatography

(4R*,5R*)-4,5-Dihydro-4,5-dimethyl-2(3H)-furanone (cis-9a)

Reaction time 2 5 h Eluent hexane-ethyl acetate 10 1 Yield. 95% (108 mg of **cis-9a** were obtained from 254 mg of **8a**) The spectral data were identical to those previously reported in the literature (see ref 19) ^{1}H-NMR ($CDCl_3$) δ 4 67 (dq, 1H, J= 6 and 6 8 Hz, CHO), 2 5-2 8 (m, 2H, C<u>H</u>CH_3, C<u>H_2</u>), 2 1-2 4 (m, 1H, CH_2), 1 30 (d, 3H, J= 6 6 Hz, CH_3) and 1 03 (d, 3H, J= 6 8 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 176 9, 76 9, 36 9, 33 4, 15 3 and 13 9

(4S*,5R*)-4,5-Dihydro-4,5-dimethyl-2(3H)-furanone (trans-9a)

Reaction time 1 5 h Eluent hexane-ethyl acetate 10 1 Yield 87% (99 mg of a 3 1 mixture of **trans-9a** and **cis-9a** were obtained from 254 mg of **8a** + **11a** The spectral data were identical to those previously reported in the literature (see ref 19) ^{1}H-NMR ($CDCl_3$) δ 4 15 (dq, 1H, J= 7 8 and 6 3 Hz, CHO), 2 0-3 0 (m, 3H, CH_2CH), 1 4 (d, 3H, J= 6 Hz, CH_3) and 1 1 (d, 3H, J= 6 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 176 1, 83 4, 38 2, 37 2, 19 1 and 16 7

(4R*,5R*)-4,5-Dihydro-5-isopropyl-4-methyl-2(3H)-furanone (cis-9b)

Reaction time 6 5 h Eluent hexane-ethyl acetate 10 1 Yield 60% (85 mg of **cis-9b** were obtained from 282 mg of **7b** + **8b**) IR ($CHCl_3$) 3000, 1760, 1475, 1190, 1170, 1010 and 950 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 95 (dd, 1H, J= 4 6 and 10 2 Hz, CHO), 2 75 (dd, 1H, J= 7 4 and 6 7 Hz, CH_2), 2 55 (ddq, 1H, J= 6 9, 4 6 and 0 7 Hz, C<u>H</u>CH_3), 2 21 (dd, 1H, J= 6 7 and 0 7 Hz, CH_2), 1 91 (dh, 1H, J= 10 2 and 6 6 Hz, C<u>H</u>$(CH_3)_2$), 1 09 (d, 3H, J= 7 Hz, CH_3), 0 99 (d, 3H, J= 7 Hz, CH_3) and 0 91 (d, 3H, J= 6 6 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 176 9, 89 1, 38 9, 32 2, 28 1, 20 1, 17 7 and 13 4

(4S*,5R*)-4,5-Dihydro-5-isopropyl-4-methyl-2(3H)-furanone (trans-9b)

Reaction time 3 h Eluent hexane-ethyl acetate 10 1 Yield 83% (118 mg of **trans-9b** were obtained from 282 mg of **11b**) IR ($CHCl_3$) 2990, 1760, 1465, 1265, 1170, 1005, 980 and 910 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 86 (dd, 1H, J= 6 and 6 Hz, CHO), 2 71 (dd, 1H, J= 8 3 and 17 Hz, CH_2), 2 36 (dh, 1H, J= 6 6 and 8 2 Hz, C<u>H</u>CH_3), 2 18 (dd, 1H, J= 7 9 and 17 0 Hz, CH_2), 1 85 (m, 1H, C<u>H</u>$(CH_3)_2$), 1 16 (d, 3H, J= 6 6 Hz, CH_3), 1 01 (d, 3H, J= 6 7 Hz, CH_3) and 0 98 (d, 3H, J= 6 7 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 176 6, 92 0, 37 2, 32 4, 31 5, 19 2, 18 6 and 17 3 MS (EI) 142 (0 78, M^+), 114 (23), 99 (100), 84 (21), 71 (61) and 56 (16)

(-)-(4S,5S)-Cognac Lactone [(-)-9c]

Reaction time 1 h Yield 93% (188 mg of **9c** were obtained from 310 mg of **8c**) $[\alpha]^{25}_D$= -73° (c 1, $CHCl_3$) ^{1}H-NMR ($CDCl_3$) δ 4 44 (m, 1H, CHO), 2 67 (dd, 1H, J= 16 7 and 7 8 Hz, CH_2), 2 57 (m, 1H, CH), 2 17 (dd, 1H, J= 16 7 and 3 8 Hz, CH_2), 1 20-1 68 (m, 8H, $(CH_2)_4$), 0 97 (d, 3H, J= 7 0 Hz, CH_3) and 0 87 (t, 3H, J= 6 9 Hz, CH_3) ^{13}C-NMR ($CDCl_3$) δ 176 9, 83 7, 37 5, 33 0, 31 6, 29 8, 25 5, 22 5, 14 0 and 13 8 The spectral data were identical to those previously reported in the literature (see ref 7)

(3S*,4R*,5R*)-4,5-Dihydro-3,4-dimethyl-5-isopropyl-2(3H)-furanone (cis,cis-18b)

Reaction time 2 h Eluent hexane-ethyl acetate 10 1 Yield 68% (106 mg of **cis,cis-18b** were obtained from 295 mg of **16b** + **17b**) IR ($CHCl_3$) 2995, 2900, 1760, 1460, 1175, 985 and 955 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 80 (dd, 1H, J= 4 2 and 10 6 Hz, CHO), 2 78 (q, 1H, J= 7 2 Hz, CHCO), 2 48

(dq, 1H, J= 4 2 and, 7 1 Hz, CHCH3), 1 86 (dh, 1H, J= 10 6 and 6 5 Hz, CH(CH3)2), 1 15 (d, 3H, J= 6 5 Hz, CH3), 1 08 (d, 3H, J= 6 5 Hz, CH3), 0 89 (d, 3H, J= 6 7 Hz, CH3) and 0 83 (d, 3H, J= 7 1 Hz, CH3) ^{13}C-NMR (CDCl3) δ 179 2, 87 4, 41 4, 36 7, 27 8, 20 2, 17 4, 9 7 and 7 8 MS(EI) 128 (6, M$^+$-^{i}Pr), 113 (100), 100 (20), 97 (6), 84 (26), 69 (30) and 56 (69)

(3S*,4S*,5R*)-4,5-Dihydro-3,4-dimethyl-5-isopropyl-2(3H)-furanone (trans,trans-18b)

Reaction time 2 5 h Eluent. hexane-ethyl acetate 10 1 Yield 92% (143 mg of **trans,trans-18b** were obtained from 295 mg of **19b**) IR (CHCl3) 2990, 1760, 1420, 1360, 1220, 1010, 980 and 920 cm^{-1} ^{1}H-NMR (CDCl3) δ 3 78 (dd, 1H, J= 4 7 and 9 3 Hz, CHO), 2,21 (dq, 1H, J= 7 0 and 11 0 Hz, CH), 1 88 (m, 2H, CH and CH), 1 23 (d, 3H, J= 7 1 Hz, CH3), 1 14 (d, 3H, J= 6 5 Hz, CH3), 1 04 (d, 3H, J= 6 9 Hz, CH3) and 0 98 (d, 3H, J= 6 8 Hz, CH3) ^{13}C-NMR (CDCl3) δ 178 0, 89 4, 43 5, 41 3, 30 7, 19 2, 17 0, 16 4 and 13 3 MS(GC) 156 (1 5, M$^+$), 128 (7), 113 (100), 85 (15), 69 (40) and 56 (86)

5-Isopropyl-3-(methoxycarbonylmethyl)-4-methyl-2(5H)-furanone (22b)

To a solution of **20b** (177 mg, 0 5 mmol) in dry dichloromethane (5 ml) was slowly added DBU (112 µl, 0 75 mmol) at rt under argon The solution was stirred for 1 h, then 5% HCl (5 ml) was added The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x20 ml) The combined organic layers were dried (Na_2SO_4) and evaporated The residue was purified by chromatography (hexane-ethyl acetate 5 1) to give **22b** (68 mg, 64%) IR (CHCl3) 2990, 1770, 1750, 1445, 1320, 1180, 1065, 1010 and 990 cm^{-1} ^{1}H-NMR (CDCl3) δ 4 75 (s$_b$, 1H, CH-O), 3 70 (s, 3H, CH3O), 3 35 and 3 31 (AB system, 2H, J= 16 9 Hz, CH2), 2 14 (dh, 1H, J= 2 4 and 7 0 Hz, CH(CH3)2), 1 98 (s, 3H, CH3), 1 18 (d, 3H, J= 7 Hz, CH3) and 0 72 (d, 3H, J= 6 9 Hz, CH3) ^{13}C-NMR (CDCl3) δ 173 5, 169 8, 162 3, 121 7, 87 5, 52 2, 29 7, 28 6, 19 7, 13 5 and 12 5 MS (EI) 212 (6, M$^+$), 181 (10), 170 (47), 138 (29), 110 (100) and 82 (9) HRMS Calcd for $C_{11}H_{16}O_4$ 212 1039 Found 212 1039

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

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