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A PRACTICAL ROUTE TO (E)-γ-HYDROXY-α,β-UNSATURATED PHENYL SULFONES

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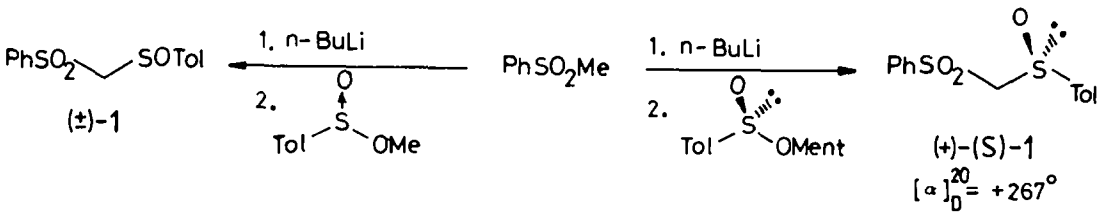
SUMMARY: *Reaction of enolizable aldehydes with p-tolylsulfinylmethyl phenyl sulfone (1), in the presence of piperidine in acetonitrile, gave selectively E-γ-hydroxy-α,β-unsaturated phenyl sulfones (2) in good yields. Reaction from enantiomerically pure sulfoxide 1 gave unsaturated sulfones 2 in moderate optical yields (ee= 10-50%).*

γ-Hydroxy-α,β-unsaturated sulfones and derivatives have a functionality suitable for a wide range of chemical manipulations. For instance, these compounds have recently been used in highly stereocontrolled processes such as conjugate additions[1] and cycloaddition reactions[2]. However little attention has been paid to the development of a general method for the preparation of this kind of functionality[3]. Recently in a preliminary paper[4], we have described a novel and practical approach to the synthesis of E-γ-hydroxy-α,β-unsaturated sulfones from enolizable aldehydes and p-tolylsulfinylmethyl phenyl sulfone[5] (1). We herein present this work in detail, along with additional examples, showing the scope and limitations of this methodology.

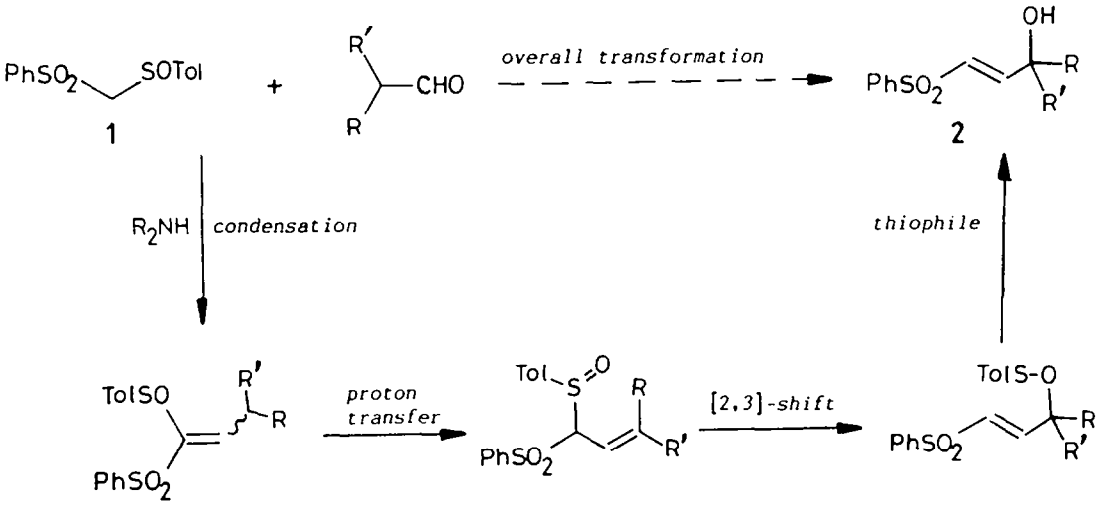
Racemic sulfoxide 1 as well as its (S) enantiomer were easily prepared, *via* sulfinilation of phenyl methyl sulfone, according to the procedure reported by Annunziata[5] (scheme 1). Deprotonation of phenyl methyl sulfone with n-butyl lithium (THF, 0°C), followed by reaction of the resulting carbanion with 0.5 equiv. of (±)-methyl p-toluenesulfinate or (-)-menthyl (S)-p-toluenesulfinate[6] (THF, 20°C, 5h) and further purification by flash chromatography afforded pure (±)-1 (80%) or (+)-(S)-1 (75%, ee> 98%) respectively.

Scheme 1



The synthesis of γ-hydroxy-α,β-unsaturated sulfones from reagent 1 and enolizable aldehydes is based on a sequence of reactions, -Knoevenagel condensation, prototropic shift and allylic sulfoxide-sulfenate rearrangement-, such as it is shown in scheme 2. This one-step procedure takes place without isolation of any intermediate[7].

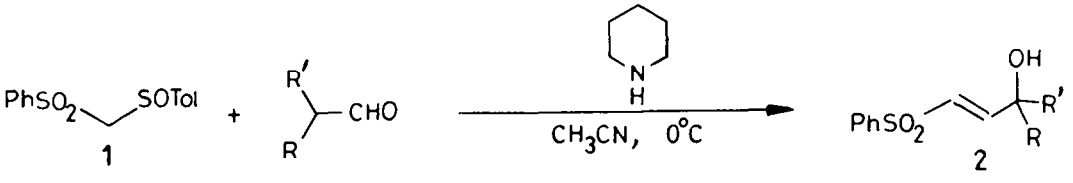
Scheme 2



In order to optimize this method, we carried out a systematic study of the reaction conditions. These experiments were performed in the presence of different secondary amines (piperidine, pirrolidine, diethylamine or piperazine) and using several solvents (CH_3CN, CH_2Cl_2, C_6H_6 or THF) and temperatures. We have also studied the effect of the amount of aldehyde and base with respect to the amount of reagent 1. With all this data in our hands we concluded that the best results were obtained by using 2.0 equiv. of aldehyde, piperidine (2.0 equiv.) as the base and performing the reaction in acetonitrile at 0°C.

In a typical procedure, 1 was treated with aldehyde (2.0 equiv.) and piperidine (2.0 equiv.) in acetonitrile at 0°C for several hours (1-8 h). Work-up with diluted hydrochloric acid and dichloromethane and further purification by flash chromatography afforded γ-hydroxy-α,β-unsaturated phenyl sulfones (2) in good yields. These results are collected en table 1. The α,β-unsaturated sulfones 2 were obtained exclusively in the (E)-form ($J_{CH=CH}$ = 14.7-15.0 Hz), as expected on the basis of a variety of previous observations for related allylic sulfoxide-mediated syntheses of allylic alcohols[7,8].

Table 1: Synthesis of E-γ-hydroxy-α,β-unsaturated phenyl sulfones (2)



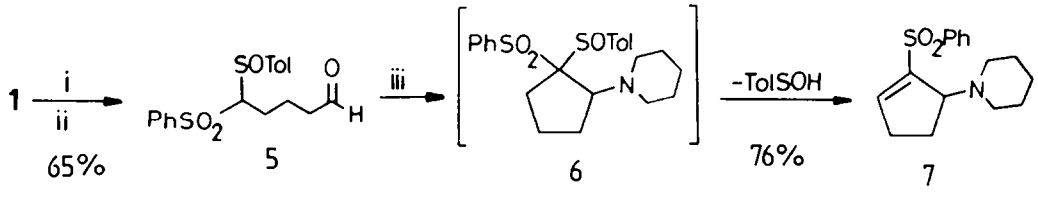
Entry	R	R'	t(h)	Product	Yield(%)[a]
a	CH_3	H	5	2a	84
b	$CH_3(CH_2)_4CH_2$	H	5	2b	89
c	$(CH_3)_2CH$	H	5	2c	86
d	$(CH_3)_2C=CHCH_2CH_2CH(CH_3)$	H	5	2d	77
e	$PhCH_2OCH_2CH_2$	H	1	2e	87
f	$PhSCH_2$	H	3	2f	45[b]
g	$MeO_2C(CH_2)_3CH_2$	H	4	2g	85
h	CH_3	CH_3	8	2h	75[c]
i	$-(CH_2)_5-$		8	2i	81[c]

[a] *Yield of pure products after silica gel chromatography* [b] *Carried out with 1.3 equiv. of aldehyde.* [c] *Carried out at room temperature.*

As it is shown in table 1 the method is quite general. Unbranched (entries a and b), β-branched (entries c and d) as well as α-branched enolizable aldehydes (entries h and i) can be used. In the case of the α-branched aldehydes the best yields were obtained performing the reaction at room temperature. What is even more interesting, this methodology can also be applied to functionalized aldehydes (entries e, f and g), affording highly functionalized unsaturated sulfones 2 (2e, 2f and 2g), which are very difficult to prepare by other previous routes[3].

A first limitation of this procedure comes from the fact that it cannot be applied to C-substituted reagents of type 1 , due to the necessary presence of two acidic hydrogens between both sulfur functions. This limitation has been shown in an intramolecular process (scheme 3). Deprotonation of 1 with NaH in DMF and treatment with the bromoketal 3 gave the corresponding alkylated product 4 as a 5:1 mixture of diastereomers (65% yield). Subsequent hydrolysis with diluted hydrochloric acid afforded aldehyde 5 quantitatively. When 5 was submitted to the standard conditions (2.0 equiv. of piperidine in CH_3CN), the cyclopentannulated product 7 was obtained as the major product in 76% yield[9]. The absence of one hydrogen in α position with respect to the sulfonyl group determines that intermediate 6 cannot accomplish the Knoevenagel condensation (first step of scheme 2), giving 7 *via* sulfenic acid elimination. β-Aminocyclopentenyl sulfones related to 7 have been widely used by Fuchs in a variety of stereoselective conjugate-addition reactions[10].

Scheme 3

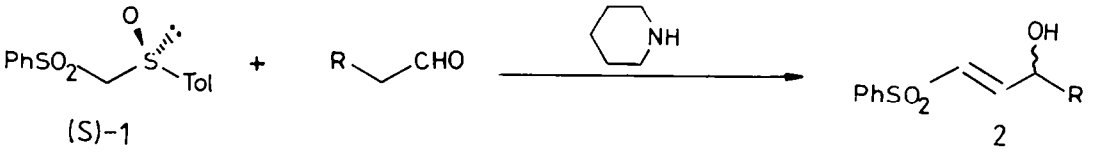


i: NaH (1.4 equiv.), $Br(CH_2)_3$-$CH(OMe)_2$ (3), DMF, 25°, 12h; ii: HCl 3N-THF (1:3), 25°C, 1h; iii: piperidine (2.0 equiv.), CH_3CN, 25°C, 2h.

A second limitation comes from the fact that ketones fail to react with compound 1. For instance, cyclohexanone was quantitatively recovered after treatment with reagent 1 and piperidine in refluxing acetonitrile or benzene for 18 h. A similar behaviour has been reported with other substituted sulfoxides related to 1[7].

Finally, we have focused our efforts in the study of the chirality transfer from the sulfur atom in the homochiral sulfoxide (S)-1[5] to the C-4 atom in the α,β-unsaturated sulfones 2. It has been reported that, in some homochiral sulfoxide-sulfenate [2,3] rearrangements, the solvent plays an important role in the asymmetric induction[11], hence we performed the reaction of (S)-1 with aldehydes in standard conditions and in the presence of a wide variety of solvents. The results are collected in table 2.

Table 2: Reaction of (S)-1 with propionaldehyde and isovaleraldehyde.



		Reaction conditions			Product 2		
Entry	R	Solvent	T(°C)	time(h)	Yield(%)[a]	Ratio S/R (ee%)[b]	[α][c]
a	Me	DMSO	25	15	72	55/45 (10)	+2.5°
b	Me	CH_3CN	0	5	84	57/43 (14)	+4.1°
c	Me	THF	25	5	79	57/43 (14)	+4.3°
d	Me	C_6H_6	25	2	88	58/42 (16)	+6.1°
e	Me	CCl_4	25	2	70	62/38 (24)	+9.3°
f	Me	CH_2Cl_2	25	5	76	62/38 (24)	+9.4°
g	Me	CH_2Cl_2	-35	20	70	67/33 (34)	+13.2°
h	^{i}Pr	CH_3CN	0	4	72	66/34 (32)	+15.7°
i	^{i}Pr	CH_2Cl_2	0	4	83	72/28 (44)	+24.1°
j	^{i}Pr	CH_2Cl_2	-35	20	76	75/25 (50)	+27.3°

a) Yield of pure products after silica gel chromatography. b) Determined from ^{1}H-NMR of (MTPA) Mosher's ester derivatives[12,13] or/and by using Yb(hfbc)$_3$ (0.2-0.4 equiv.). c) $[\alpha]_D^{20}$,c=1.0, $CHCl_3$.

Three conclusions can be withdrawn from the data of table 2:

a) Sulfoxide (S)-1 gives products 2 of moderate optical activity (range 10-50% ee). However it is interesting to point out that the (S)-enantiomer predominates in all cases. The configurational assignment of the enantiomeric alcohols has been assigned from the ^{1}H-NMR data of their Mosher's ester derivatives[12,13].

b) The solvent (compare entries a to f) and the temperature (compare entries f,g and i,j) show a moderate effect on the asymmetric induction. The highest enantioselectivities are obtained by using CH_2Cl_2 or CCl_4 as solvents.

c) A significant increase of enantioselectivity is observed when isovaleraldehyde is used instead of propanal (compare entries b,h and g,j). This fact suggests that the asymmetric induction increases with the size of the aldehyde.

In conclusion, the present one-step method of synthesis of acyclic γ-hydroxy-α,β-unsaturated phenyl sulfones has the following advantages: both reagents, -sulfoxide 1 and enolizable aldehydes are readily available-, the method is experimentally simple and the reaction can be performed with a wide range of aldehydes that allows for many structural variations. Unfortunately, the enantioselectivity of this process from homochiral sulfoxide 1 is low or moderate (ee= 10-50%).

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 points. Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constants (Hz) were obtained by first order analysis of spin patterns. Mass spectra (MS) were recorded on a Hewlett-Packard 5985 spectrometer at electron impact (70eV). 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 dried before use. Tetrahydrofuran and benzene were distilled from sodium-benzophenone under argon. Dichloromethane, dimethylsulfoxide and carbon tetraclhoride were distilled from calcium hydride. Acetonitrile and chloroform were distilled from P_2O_5. Propionaldehyde was distilled prior to use. Octyl aldehyde, isobutyraldehyde, isovaleraldehyde and cyclohexanecarboxaldehyde were purchased from Aldrich and used without further purification. The functionalized aldehydes (entries d to f in table 1) and the bromoketal 3 were prepared by straightforward methods. Flash chromatography was performed by use of silica gel (MN-Kieselgel 60, 230-400 mesh).

p-Tolylsulfinylmethyl phenyl sulfone (1)

A solution of phenyl methyl sulfone (10 g, 64.1 mmol) in anhydrous THF (50 ml) was treated at -78°C under argon atmosphere with 2.45 M n-BuLi in hexane (28.75 ml, 70.5 mmol). The solution was kept at -78°C for 20 min and allowed to stay at 0°C for 30 min, then the solution was cooled again at -78°C and a solution of the sulfinate ester (32.05 mmol) in anhydrous THF (10 ml) was added slowly . The mixture was allowed to warm to room temperature and was stirred at 20°C for 5 h. A saturated solution of aqueous ammonium chloride (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2x50 ml). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (hexane-ethyl acetate 2:1) to give (±)-1 (7.74 g, yield: 80%) from methyl p.toluenesulfinate or (+)-(S)-1 (7.26 g, yield: 75%) from (-)-menthyl (S)-p-toluenesulfinate[6]. Data for (±)-1: m.p. 83-84°C (Lit[5]. 68-69°C). Data for (+)-(S)-1: m.p. 112-114°C, $[\alpha]_D^{20}$ +267° (c=1, $CHCl_3$), ee >97% (Lit[8]. m.p. 71-72°, $[\alpha]_D^{20}$ +251° (c=1, $CHCl_3$), ee >97%). IR (KBr) 3000, 2920, 2890, 1600, 1590, 1450, 1320, 1150, 1050 and 820 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.03 (m, 2H, $PHSO_2$), 7.80-7.30 (m, 7H, arom), 4.40 and 4.29 (AB system, 2H, J=13.6 Hz, CH_2) and 2.42 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 142.2, 138.6, 138.4, 134.1, 129.8, 129.0, 127.9, 123.7, 78.7 and 20.9. MS :294 (2, M^+), 139 (100), 91 (14), 77 (20), 69 (29). Anal. Calcd for $C_{14}H_{14}O_3S_2$: C, 57.15%; H, 4.80%. Found: C, 57.16%; H, 4.75%.

General procedure for the preparation of (E)-γ-hydroxy-α,β-unsaturated phenyl sulfones (2)

To a solution of 0.68 mmol (200 mg, 1.0 eq) of 1 in 3 ml of dry acetonitrile, cooled at 0°C, were added sequentially 1.36 mmol (134 µl, 2.0 eq) of piperidine and 1.36 mmol (2.0 eq) of the corresponding aldehyde (table 1). Stirring was continued for 1-8 h at 0°C. Then 5% hydrochloric acid (10 ml) was added. The reaction mixture was extracted with dichloromethane (2x15 ml), the combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography to give pure unsaturated sulfones 2.

(E)-4-Phenylsulfonyl-3-buten-2-ol (2a)

Reaction time: 5 h. Eluent: dichloromethane-acetone 15:1. Yield: 120 mg of **2a** (84%). m.p. 64-66°C. IR (KBr): 3500, 3070, 2090, 1630, 1450, 1280 and 1140 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.89 (m, 2H, $PhSO_2$), 7.59 (m, 3H, $PhSO_2$), 7.00 (dd, 1H, J=14.9 and 3.6 Hz, CH=CHS), 6.59 (dd, 1H, J= 14.9 and 1.9 Hz, CH=CHS), 4.55 (ddq, 1H, J=6.7, 3.6 and 1.9 Hz, CHOH), 1.83 (br s, 1H, OH) and 1.36 (d, 3H, J=6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 149.3, 139.9, 133.4, 129.2, 128.7, 127.4, 66.1 and 22.2. MS: 183 (3, M^+-CHO), 169 (100), 125 (30), 91 (24), 77 (32). Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.65%; H, 5.70%. Found: C, 56.85%; H, 5.67%.

(E)-1-Phenylsulfonyl-1-nonen-3-ol (2b)

Reaction time: 5 h. Eluent: hexane-ethyl acetate 2:1. Yield: 170 mg of **2b** (89%). m.p. 59-60°C. IR (KBr): 3500, 3060, 2930, 1300, 1145, 1090, 760 and 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.89 (m, 2H, $PhSO_2$), 7.60 (m, 3H, $PhSO_2$), 7.00 (dd, 1H, J=15.0 and 3.7 Hz, CH=CHS), 6.60 (dd, 1H, J= 15.0 and 1.7 Hz, CH=CHS), 4.37 (ddt, 1H, J=7.1, 3.7 and 1.8 Hz, CHOH), 1.81 (br s, 1H, OH), 1.72-1.20 (m, 10H, $(CH_2)_5$) and 0.88 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 148.5, 140.2, 133.4, 129.3, 129.2, 127.5, 70.2, 36.2, 31.6, 28.9, 25.0, 22.4 and 14.0. MS: 253 (11, M^+-CHO), 169 (100), 141 (18), 125 (54), 77 (22). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.88%; H, 7.86%. Found: C, 63.84%; H, 7.86%.

(E)-1-Phenylsulfonyl-4-methyl-1-penten-3-ol (2c)

Reaction time: 5 h. Eluent: hexane-ethyl acetate 5:2. Yield: 140 mg of **2c** (86%). m.p. 61-63°C. IR (KBr): 3500, 3060, 2965, 1630, 1450, 1285, 1145, 1090, 1035, 845, 750, 690 and 670 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.88 (m, 2H, $PHSO_2$), 7.60 (m, 3H, $PHSO_2$), 7.01 (dd, 1H, J=15.0 and 3.7 Hz, CH=CHS), 6.61 (dd, 1H, J=15.0 and 1.7 Hz, CH=CHS),4.19 (ddd, 1H, J=6.7, 3.8 and 1.8 Hz, CHOH), 1.85 (m, 2H, OH and $CH(CH_3)_2$), 0.94 (d, 3H, J=6.7 Hz, CH_3) and 0.91 (d, 3H, J=6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 147.1, 140.3, 133.4, 130.5, 129.3, 127.6, 74.9, 33.7, 18.2 and 17.2. MS: 211 (5, M^+-CHO), 198 (100), 169 (32), 143 (27), 125 (47), 77 (34). Anal. Cald for $C_{12}H_{16}O_3S$: C, 60.05%; H, 6.72%. Found: C, 59.99%; H, 6.68%.

(E)-1-Phenylsulfonyl-4,8-dimethyl-1,7-nonadien-3-ol (2d)

Reaction time: 15 h. Eluent: hexane-ethyl acetate 3:1. Yield: 160 mg of **2d** (77%, mixture 1:1 of diastereomers). IR (nujol): 3500, 3060, 2960, 1710, 1620, 1440, 1370, 1300, 1145, 1080, 840, 750 and 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.89 (m, 2H, $PhSO_2$), 7.57 (m, 3H, $PhSO_2$), 6.99 (m, 1H, CH=CHS), 6.61 (m, 1H, CH=CHS), 5.04 (m, 1H, CH=C), 4.32 (m, 1H,, CHOH), 2.43 (br s, 1H, OH), 1.95 (m, 1H, $CHCH_3$), 1.85-1.10 (m, 4H, CH_2CH_2), 1.67 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 0.89 (d, J=6.8 Hz, CH_3-CH, isomer a) and 0.83 (d, J=6.8 Hz, CH_3-CH, isomer b). MS: 308 (1, M^+), 198 (100), 169 (21), 143 (25), 125 (47), 111 (31).

(E)-5-Benzyloxy-1-phenylsulfonyl-1-penten-3-ol (2e)

Reaction time: 1 h. Eluent: hexane-ethyl acetate 2:1. Yield: 192 mg of 2e (87%). m.p. 72-74°C. IR (nujol): 3460, 3050, 1295, 1150, 740 and 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.90 (m, 2H, $PhSO_2$), 7.60 (m, 3H, $PhSO_2$), 7.33 (m, 5H, Ph), 6.98 (dd, 1H, J=14.7 and 3.2 Hz, CH=CHS), 6.66 (dd, 1H, J=14.7 and 1.8 Hz, CH=CHS), 4.59 (m, 1H, CHOH), 4.48 (s, 2H, OCH_2Ph), 3.70 (m, 2H, CH_2O) and 2.1-1.7 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 147.6, 140.3, 137.3, 133.3, 129.9, 129.2, 128.5, 127.9, 127.7, 127.6, 73.4, 69.9, 68.2 and 35.0. Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.11%; H, 6.07%. Found: C, 65.15%; H, 6.19%.

(E)-4-Phenylsulfonyl-1-phenylthio-3-buten-2-ol (2f)

Reaction time: 3 h. Eluent: hexane-ethyl acetate 3:1. Yield: 96 mg of 2f (45%). m.p. 90-91°C. IR (KBr): 3460, 3060, 1580, 1445, 1295, 1280, 1140, 1090, 1080, 990 and 740 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.88 (m, 2H, $PhSO_2$), 7.75-7.20 (m, 8H, arom), 6.95 (dd, 1H, J=15.0 and 3.7 Hz, CH=CHS), 6.68 (dd, 1H, J=15.0 and 1.7 Hz, CH=CHS), 4.37 (m, 1H, CHOH), 3.23 and 2.90 (m, 2H, CH_2) and 2.84 (d, 1H, J=3.6 Hz, OH). MS: 320 (1, M^+), 179 (100), 135 (15), 125 (13), 123 (98), 77 (19). Anal. Calcd for $C_{16}H_{16}O_3S_2$: C, 60.05%; H, 5.04%. Found: C, 60.16%; H, 5.04%.

Methyl (E)-8-phenylsulfonyl-6-hydroxy-7-octenoate (2g)

Reaction time: 4 h. Eluent: hexane-ethyl acetate 4:1.Yield: 180 mg of 2g (85%). m.p. 72-73°C. IR (KBr): 3450, 3030, 2970, 1725, 1450, 1305, 1200, 1150, 1080, 995, 840, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.90 (m, 2H, $PhSO_2$), 7.60 (m, 3H, $PhSO_2$), 6.98 (dd, 1H, J=14.9 and 3.6 Hz, CH=CHS), 6.61 (dd, 1H, J=14.9 and 1.7 Hz, CH=CHS), 4.41 (m, 1H, CHOH), 3.67 (s, 3H, CO_2CH_3), 2.32 (t, 2H, J=7.1 Hz, CH_2CO_2), 2.20 (br s, 1H, OH) and 1.80-1.30 (m, 6H, $(CH_2)_3$). ^{13}C NMR ($CDCl_3$) δ: 174.0, 148.4, 140.0, 133.3, 129.2, 129.1, 127.3, 69.5, 51.4, 35.5, 33.5, 24.4, and 24.2. Anal. Calc for $C_{15}H_{20}O_5S$: C, 57.74%; H, 6.46%. Found: C, 57.41%; H, 6.58%.

(E)-4-Phenylsulfonyl-2-methyl-3-buten-2-ol (2h)

Reaction time: 8 h. Eluent: hexane-ethyl acetate 3:1. Yield: 115 mg of 2h (75%). IR (KBr): 3480, 3060, 2990, 1620, 1490, 780, 710 and 680 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.90 (m, 2H, $PhSO_2$), 7.55 (m, 3H, $PhSO_2$), 7.02 (d, 1H, J=14.9 Hz, CH=CHS), 6.57 (d, 1H, J=14.9 Hz, CH=CHS), 1.7 (br s, 1H, OH) and 1.38 (br s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 152.4, 140.2, 133.4, 129.3, 127.8, 127.5, 70.8 and 29.0. MS: 211 (11, M^+-CH_3), 183 (100), 143 (23), 125 (71), 77 (34). Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.45%; H, 6.24%. Found: C, 58.03%; H, 6.14%.

(E)-1-(2-Phenylsulfonylvinyl)cyclohexanol (2i)

Reaction time: 8 h. Eluent: hexane-ethyl acetate 3:1. Yield: 147 mg of 2i (81%). m.p. 127-129°C. IR (KBr): 3500, 3045, 2930, 1620, 1445, 1390, 1315, 1285, 1210, 1090, 850, 770 and 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.87 (m, 2H, $PhSO_2$), 7.57 (m, 3H, $PhSO_2$), 7.05 (d, 1H, J=14.7 Hz, CH=CHS), 6.60 (d, 1H, J=14.9 Hz, CH=CHS), 1.75-1.58 (m, 10H, $(CH_2)_5$) and 1.57 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 152.5, 140.3, 133.3, 129.2, 128.2, 127.5, 71.9, 36.6, 34.9 and 21.2. MS: 195 (12), 143 (22), 125 (100), 97 (26), 81 (40), 77 (26). Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.21%; H, 6.82%. Found: C, 62.93%; H, 6.81%.

5-Phenylsulfonyl-5-p-tolylsulfinylpentanaldehyde dimethyl acetal (4)

To a suspension of sodium hydride (57 mg, 2.38 mmol) in dried dimethylformamide (50 ml) was added, under argon and at room temperature, a solution of 1 (500 mg, 1.7 mmol) in dimethylformamide (10 ml). The reaction mixture was stirred for 30 min. Then a solution of bromoketal 3 (500 mg, 2.55 mmol) in dimethylformamide (10 ml) was added. After 12 h at room temperature a saturated solution of aqueous ammonium chloride (50 ml) was added. The mixture was extracted with ether (3x50 ml) and the combined organic layers were washed with water (3x50 ml), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate 2:1) to give **4** (450 mg, yield 65%). m.p. 77-79°C. IR (KBr): 2900, 1580, 1445, 1320, 1310, 1150, 1040, 810 and 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.02 (m, 2H, $PhSO_2$), 7.85-7.25 (m, 7H, arom), 4.15 (m, 1H, $CHSO_2$), 3.81 (t, 1H, J=5.9 Hz, $CH(OCH_3)_2$), 3.20 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3Ar), 2.15-1.60 (m, 2H, CH_2) and 1.40-1.10 (m, 4H, $(CH_2)_2$). ^{13}C NMR ($CDCl_3$) δ: 142.0, 139.4, 136.5, 134.7, 130.2, 129.5, 129.4, 123.6, 103.6, 86.9, 52.7, 52.6, 31.7, 22.9, 21.3 and 20.7. MS: 255 (20), 239 (13), 202 (15), 146 (15), 139 (100), 125 (22), 97 (65), 77 (31). Anal. Calcd for $C_{20}H_{28}O_5S_2$: C, 58.58%; H, 6.39%. Found: C, 58.40%; H, 6.24%.

5-Phenylsulfonyl-5-p-tolylsulfinylpentanaldehyde (5)

To a solution of ketal **4** (450 mg, 1.1 mmol) in THF (30 ml) was added 10% hydrochloric acid (10 ml). The mixture was stirred at room temperature for 1 h. Then a saturated solution of aqueous sodium bicarbonate (20 ml) was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane (2x20 ml). The combined organic phases were dried (Na_2SO_4) and evaporated to give 399 mg (yield 100%) of 5 as a colorless oil (due to its instability it is inmediately used in the next step). ^1H NMR ($CDCl_3$) δ: 9.59 (t, 1H, J=1.3 Hz, CHO), 8.05 (m, 2H, $PhSO_2$), 7.85-7.20 (m, 7H, arom), 3.84 (t, 1H, J=5.1 Hz, $CHSO_2$), 2.41 (s, 3H, CH_3Ar), 2.31 (m, 2H, CH_2-CO) and 2.20-1.30 (m, 4H, CH_2-CH_2).

2-Phenylsulfonyl-3-piperidinocyclopenten-1-ene (7)

To a solution of 0.27 mmol (100 mg, 1.0 eq) of 5 in 3 ml of dry acetonitrile were added at room temperature 0.55 mmol (57 µl, 2.0 eq) of piperidine. Stirring was continued for 2h, then the mixture was diluted with water (10 ml) and extracted with dichloromethane (2x10 ml). The organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate 2:1) to give **6** (60.5 mg, yield 76%). m.p. 100-102°C. IR (KBr): 2940, 1615, 1495, 1300, 1150, 1090, 870 and 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.97 (m, 2H, $PhSO_2$), 7.55 (m, 3H, $PhSO_2$), 7.00 (br s, 1H, CH=C), 4.17 (m, 1H, CHN), 2.74-2.28 (m, 2H, CH_2), 2.28-1.65 (m, 6H), 1.39-1.09 (br s, 4H) and 1.09-0.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 146.8, 144.1, 140.8, 132.9, 128.6, 128.5, 69.7, 48.8, 32.2, 25.2, 24.2 and 21.6. MS: 291 (17, M^+), 150 (14), 84 (100). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 66.03%; H, 7.27%; N, 4.81%. Found: C, 65.98%; H, 7.30%; N, 4.59%.

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(9) If the reaction was performed from enantiomerically pure sulfoxide (S)-1, the cyclopentannulated product 7 was obtained with 13% optical purity (determined from ^{1}H NMR by using Yb(hfbc)$_3$).

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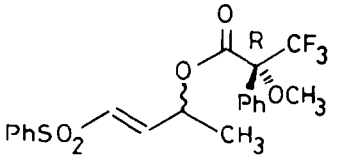
(13) Significative ^{1}H-NMR data of the (R)-MTPA esters derived from **2a**:



Diastereomer R,R; δ: 1.42 (d, J=6.9 Hz, 3H, CH_3), 3.53 (m, 3H, OCH_3), 5.76 (m, 1H, CHO), 6.39 (dd, J=15.5 and 1.9 Hz, 1H, S-CH=C) and 6.94 (dd, J=15.5 and 4.4 Hz, 1H, S-C=CH).

Diastereomer S,R; δ: 1.48 (d, J=6.9 Hz, 3H, CH_3), 3.41 (m, 3H, OCH_3), 5.76 (m, 1H, CHO), 6.14 (dd, J=15.5 and 2.0 Hz, 1H, S-CH=C) and 6.88 (dd, J=15.5 and 4.4 Hz, 1H, S-C=CH).