Pergamon

Tetrahedron Vol. 50, No. 25, pp. 7557-7566, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00379-3

Flexible and Stereoselective Construction of Polypropionate Chains from Enantiomerically Pure γ-Hydroxy-α,β-unsaturated Sulfones

Esteban Domínguez and Juan C. Carretero*

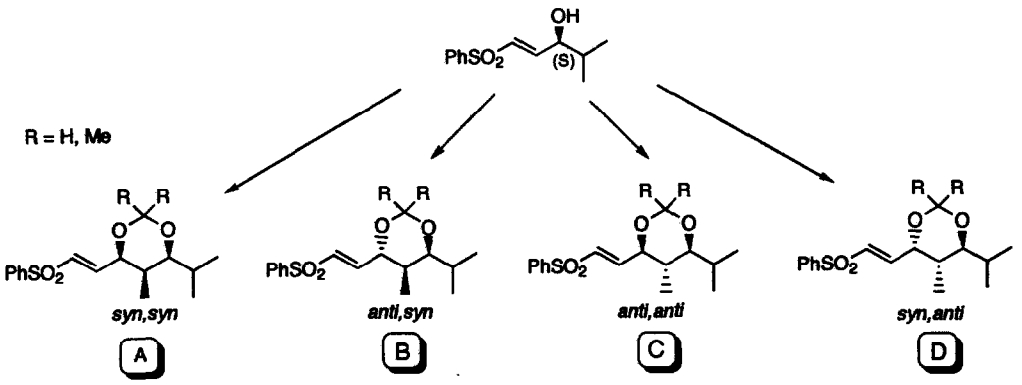
Departamento de Química, Facultad de Ciencias, Universidad Autónoma de Madrid,
Cantoblanco, 28049 Madrid, Spain

Abstract: Following an homologation sequence the readily available enantiomerically pure γ-hydroxy vinyl sulfone **2** has been transformed, with complete control of the stereochemistry, into γ-hydroxy vinyl sulfones of polypropionate structure. The four stereotriads have been prepared by stereoselective additions of organometallics to the vinyl sulfone moiety and by stereoselective reduction of β-hydroxyketones. In a similar way, these triads are the substrates for the stereoselective introduction of the fourth consecutive asymmetric center.

Introduction

Natural products containing polypropionate fragments are ubiquitous. These structures, derived from the condensation of propionic acid units, consist on carbon chains with consecutive asymmetric centers showing an alternation of methyl groups and oxygen functionalities. Some emblematic examples of such natural products are, for instance, erythromycins, ryfamycins or monensin. As a consequence of the great biological relevance of polypropionate chains, in the last years many efforts have been devoted to the development of highly stereoselective and enantioselective methods of acyclic stereocontrol.[1] Among these synthetic strategies, the aldol reaction with chiral enolates has been the most widely used due to its generality and flexibility in the stereoselective generation of different stereochemistries.[1,2] Other outstanding stereoselective method for the synthesis of polypropionate chains is the addition of crotyl-metal compounds to quiral aldehydes.[1,3]

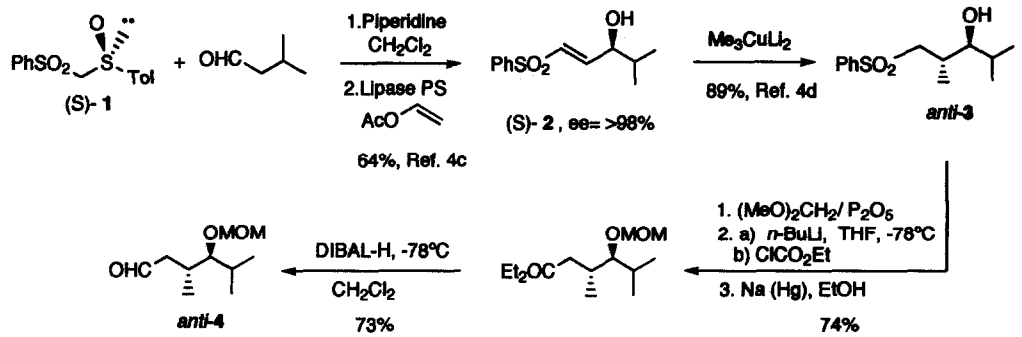
As a part of our studies on the development of highly stereoselective methods of acyclic stereocontrol from the readily available enantiomerically pure γ-hydroxy-α,β-unsaturated phenyl sulfones,[4] recently we have reported an iterative procedure for the stereoselective preparation of triads A and B (scheme 1) based on the *syn*-stereoselective addition of methyl lithium to α-trimethylsilyl derivatives of this kind of vinyl sulfones.[5] Herein, we describe the efficient preparation of the other two stereotriads (C and D) by applying the *anti*-stereoselective addition of organocopper reagents.[4d] Thus, we show the great flexibility of this methodology of acyclic stereocontrol based on optically pure γ-hydroxy vinyl sulfones. Additionally, the stereoselective preparation of several tetrads from triads is also reported.



Scheme 1

Results and discussion

Enantiomerically pure vinyl sulfone (S)-**2** was readily prepared in multigram quantities, in 64% overall yield, by condensation of reagent (S)-**1** with isovaleraldehyde, followed by enzymatic enantioselective acetylation.[4c] According with our recent study concerning the conjugate addition of higher order cuprates to γ-hydroxy vinyl sulfones, the addition of Me_3CuLi_2 to substrate **2** was highly *anti*-stereoselective affording in 89% yield a 15:1 mixture of *anti*-**3**:*syn*-**3** (de= 88%)[4d]. In order to introduce the second hydroxyl group by applying again the condensation of reagent **1** with aldehydes, it was necessary the conversion of sulfone *anti*-**3** into the homologated aldehyde *anti*-**4** (scheme 2). This process was carried out in 54% overall yield following the straightforward four-step sequence: protection of the hydroxyl group as MOM derivative, carboxyethylation (n-BuLi, THF, -78°C then $ClCO_2Et$), reductive elimination of sulfonyl group (Na-Hg, Na_2HPO_4, EtOH) and reduction of the ester with DIBAL (1.0 equiv., CH_2Cl_2, -78°C).

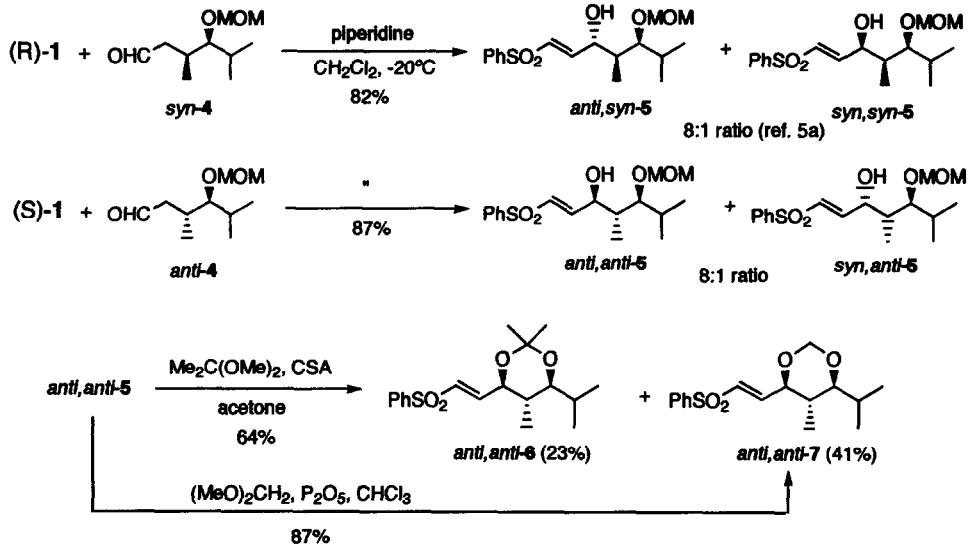


Scheme 2

With aldehyde *anti*-**4** in hand we performed its condensation with both enantiomers of reagent **1** in the standard conditions (piperidine, CH_2Cl_2). Taking into account that in the condensation of the isomer *syn*-**4** (3S, 4S) with reagent **1** the best stereoselectivity was obtained by using (R)-**1** (matched pair, d.e.= 76%)[5a], in the case of *anti*-**4** -which has opposite configuration at the chiral center nearest the carbonyl group (3R, 4S)- it was expected that the matched pair would correspond to the use of (S)-**1**. In fact, whereas the condensation of *anti*-**4** with (R)-**1** gave a nearly equimolecular mixture of both possible isomers **5** (*anti,anti*-**5** and *syn,anti*-**5**), the

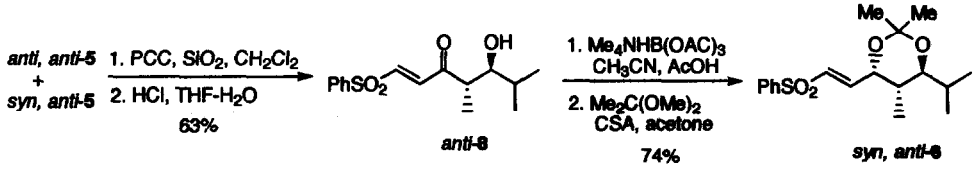
reaction with (S)-1 afforded a 8:1 mixture of *anti,anti*-5 and *syn,anti*-5 respectively (d.e.= 78%, scheme 3).[6] After chromatographic purification on silica gel, 50% of pure *anti,anti*-5 was obtained together with 37% of mixture of both isomers 5.

The *anti*-stereochemistry at position C_3-C_4 in the major isomer 5 was unequivocally established by conversion into its 1,3-acetonide 6. The treatment of 5 with 2,2-dimethoxypropane and catalytic CSA in acetone afforded a 1:2 mixture of ketals 6 and 7 respectively, which were separated by chromatography (23% and 41% yield respectively). The ^{13}C-NMR chemical shifts of the acetonide carbons of 6 were in perfect agreement with the values predicted by the Rychnovsky's and Evans' rules for acetonides of *syn*-1,3-diols[7]. Moreover, the ketal *anti,anti*-7 was prepared in high yield by reaction of *anti,anti*-5 with $(MeO)_2CH_2$ in the presence of P_2O_5 (87% yield).



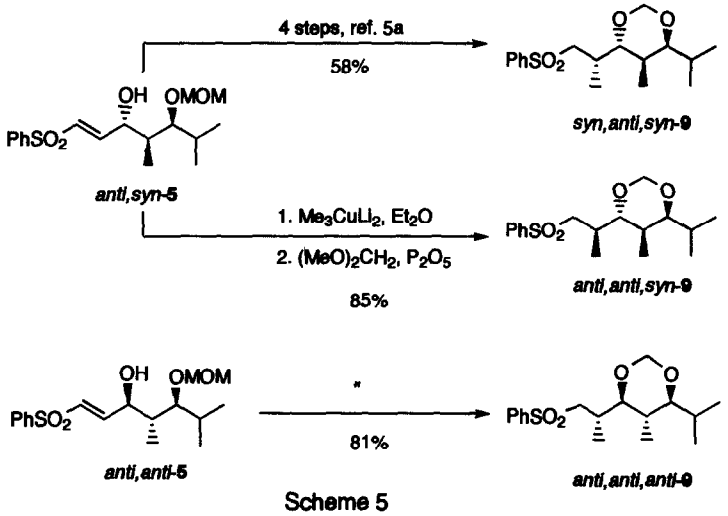
Scheme 3

On the other hand, as the condensation of *anti*-4 with (R)-1 did not give stereoselectively the triad of *syn,anti* stereochemistry, we undertook its stereoselective preparation following an oxidation-reduction strategy. The oxidation of a mixture of isomers 5 with PCC-silica gel under sonication, followed by further acid hydrolysis of the ketal moiety (HCl 10%, THF, rt), gave the β-hydroxy ketone 8 in 63% overall yield (scheme 4). As is was expected, the reduction of 8 with $Me_4NHB(OAc)_3$ was highly stereoselective affording exclusively the *anti* 1,3-diol[8], whose stereochemistry was again unequivocally established by ^{13}C-NMR analysis of its 1,3-acetonide *syn,anti*-6[7] (74% overall yield from 8).



Scheme 4

In a similar way, vinyl sulfones **5** can be used as substrates for the stereoselective conjugate addition of organometallics, affording the corresponding tetrads. So, previously we described the highly *syn*-conjugate addition of MeLi to a α-trimethylsilylderivative of *anti,syn*-**5** to give the *syn,anti,syn* tetrad **9**[5a] (scheme 5). In order to show the complementarity and flexibility of the *syn* or *anti* stereoselective addition of organolithium or organocopper reagents, respectively, we studied the addition of Me_3CuLi_2 to the triads *anti,syn*-**5** and *anti,anti*-**5**. As it was expected, in comparation to the addition of MeLi to *anti,syn*-**5** derivatives, opposite configuration at C_2 was obtained in the addition of the copper reagent[4d] (*anti* stereochemistry at C_2-C_3). The reaction of Me_3CuLi_2 with vinyl sulfone *anti,syn*-**5** was performed under the standard conditions (Et_2O, rt), affording a single alcohol in 89% yield. After transketalization (P_2O_5, $(MeO)_2CH_2$, rt), the tetrad **9** of *anti* configuration at C_2-C_3 (*anti,anti,syn*) was formed in 95% yield after chromatography. In a similar manner, the addition of Me_3CuLi_2 to the triad *anti,anti*-**5** was again completely stereoselective giving a single isomer of presumed *anti*-stereochemistry at C_2-C_3 position (87% yield).[9] This compound was converted in 93% yield into the ketal *anti,anti,anti*-**9** under the usual transketalization conditions.



Scheme 5

In summary, a flexible, stereoselective and iterative sequence for the construction of polypropionate fragments from the readily available optically pure γ-hydroxy vinyl sulfones has been described.

EXPERIMENTAL

Melting points were determined with a Gallenkamp apparatus in open capillaries and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra in $CDCl_3$ 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. 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 distilled before use. THF and diethyl ether (ether) were dried from sodium-benzophenone under argon. Dichloromethane was distilled 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).

(2*S*, 3*S*)-2,4-Dimethyl-1-(phenylsulfonyl)-pentan-3-ol (*anti*-3)

A solution 1.5M of MeLi in ether (233 mL, 350 mmol, 12 equiv.) was slowly added to a suspension of CuI (22.3 g, 117 mmol, 4 equiv.) in ether (100 mL) at 0°C under an argon atmosphere. The suspension was kept at 0°C for 30 min. Then, a solution of (S)-2 (7.0 g, 29.2 mmol, 1.0 equiv.) in ether (20 mL) was added and the mixture was allowed to warm to rt and stirring was continued during 2h. The reaction was quenched by adding a 1:1 mixture (50 mL) of saturated NH_4Cl aqueous solution and aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with ether (2 x 50 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 (hexane-ethyl acetate, 3:1) to afford 6.72 g (89% yield) of a 15:1 mixture of *anti*-3: *syn*-3 (de=88%).

$[\alpha]_D$= +16.4 (c=1, $CHCl_3$). IR ($CHCl_3$): 3500, 2980, 1440, 1300, 1140 and 1085 cm^{-1}. ^{1}H-NMR: 7.93 (m, 2H, $PhSO_2$), 7.60 (m, 3H, $PhSO_2$), 3.46 (dd, 1H, J= 14.2 and 2.7 Hz, CH_2S), 3.10 (dd, 1H, J= 11.5 and 5.8 Hz, CH-O), 2.94 (dd, 1H, J= 14.2 and 8.6 Hz, CH_2S), 2.27 (m, 1H, C<u>H</u>-CH_2), 1.78 (br s, 1H, OH), 1.71 (m, 1H, CH-Me_2), 1.15 (d, 3H, J= 6.8 Hz, CH_3), and 0.87 (d, 6H, J= 6.8 Hz, CH_3 x 2). ^{13}C-NMR: 139.6, 133.3, 129.0, 127.4, 79.5, 58.1, 31.3, 29.7, 19.2, 17.5 and 16.2.

Anal. Calcd. for $C_{13}H_{20}O_3S$: C, 60.90; H, 7.86. Found: C, 60.78; H, 7.71.

(3*R*, 4*S*)-4-(methoxymethoxy)-3,5-dimethylhexanal (*anti*-4)

To a solution of the alcohol *anti*-3 (6.0 g, 23.4 mmol) in $CHCl_3$ (50 mL) were added 10 mL of dimethoxymethane and 20 g of P_2O_5. The solution was stirred for 2h to rt. The reaction was cooled at 0°C, and a saturated solution of aqueous Na_2CO_3 (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 5:1) to afford 6.54 g (93% yield) of the MOM derivative.

$[\alpha]_D$= +24.1(c=1, $CHCl_3$). IR ($CHCl_3$): 2940, 1430, 1290, 1135, 1065, 1020, 900 and 670 cm^{-1}. ^{1}H-NMR: 7.94 (m, 2H, $PhSO_2$), 7.60 (m, 3H, $PhSO_2$), 4.57 (s, 2H, OCH_2O), 3.40 (dd, 1H, J= 14.4 and 1.8 Hz, CH_2SO_2), 3.32 (s, 3H, CH_3O), 2.98 (dd, 1H, J= 6.2 and 4.2 Hz, CH-OMOM), 2.88 (dd, 1H, J= 14.4 and 9.8 Hz, CH_2SO_2), 2.34 (m, 1H, C<u>H</u>Me), 1.70 (m, 1H, CH-Me_2), 1.18 (d, 3H, J= 6.9 Hz, CH_3), 0.86 (d, 3H, J= 6.6 Hz, CH_3) and 0.80 (d, 3H, J= 6.8 Hz, CH_3). ^{13}C-NMR: 140.0, 133.3, 129.0, 127.6, 98.4, 88.7, 58.5, 55.8, 30.5, 30.4, 19.2, 18.2 and 17.6.

Anal. Calcd. for $C_{15}H_{24}O_4S$: C, 59.97; H, 8.05. Found: C, 60.18; H, 7.99.

A solution 2.5M of n-BuLi in hexane (8.79 mL, 21.9 mmol) was slowly added to a solution of the MOM derivative of *anti*-3 (6.0 g, 20 mmol) in THF (100 mL) at -78°C under an argon atmosphere. The solution was kept at -78°C for 30 min. Then, 2.5 mL (26 mmol) of ethyl chloroformate was added and the solution was stirred at -78°C for 1h. The reaction mixture was quenched by addition of a saturated solution of aqueous NH_4Cl (100 mL). 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 to afford a 1:1 mixture of α-phenyl sulfonyl esters (epimers at C-α). To a solution of this mixture of α-sulfonyl esters in EtOH (100 mL) were added 12 g of Na_2HPO_4 and 29 g of powdered 6% sodium amalgam (recently prepared). The reaction was vigorously stirred at rt for 2h. The reaction was poured into water and extracted with ether (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 9:1) to afford 3.71 g of the ester (80% yield).

$[\alpha]_D$= +19.5 (c=1, $CHCl_3$). IR ($CHCl_3$): 2900, 1700, 1440, 1010 and 890 cm^{-1}. ^{1}H-NMR: 4.60 (s, 2H, OCH_2O), 4.10 (q, 2H, J= 7.2 Hz, $C\underline{H}_3CH_2O$), 3.36 (s, 3H, CH_3O), 2.99 (t, 1H, J= 5.3 Hz, CHOMOM), 2.53 (dd, 1H, J= 14.3 and 3.3 Hz, CH_2CO_2), 2.20 (m, 1H, CHMe), 2.07 (dd, 1H, J= 14.3 and 9.5 Hz, CH_2CO_2), 1.79 (m, 1H, $CHMe_2$), 1.22 (t, 3H, J= 7.2 Hz, CH_3CH_2O), 0.95 (d, 3H, J= 5.9 Hz, CH_3), 0.92 (d, 3H, J= 6.5 Hz, CH_3) and 0.90 (d, 3H, J= 6.7 Hz, CH_3)

To a solution of the previously prepared ester (3 g, 12.9 mmol) in CH_2Cl_2 (50 mL) was slowly added a 1M solution of DIBAL-H in CH_2Cl_2 (12.9 mL, 12.9 mmol) at -78°C. After 30 min. at this temperature, a saturated solution of aqueous $NaHCO_3$ (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 9:1) to afford 1.77 g (73% yield) of ***anti*-4** (54% overall yield from the 15:1 mixture of ***anti*-3**: ***syn*-3**).

$[\alpha]_D$= +24.0 (c=1, $CHCl_3$). IR ($CHCl_3$): 2945, 1705, 1450, 1365, 1075 and 1015 cm^{-1}. ^{1}H-NMR: 9.74 (t, 1H J= 3.9 Hz, CHO), 4.61 (s, 2H, OCH_2O), 3.38 (s, 3H, CH_3O), 3.03 (dd, 1H, J= 5.9 and 4.8 Hz, CHOMOM), 2.59 (m, 1H, $C\underline{H}_2CHO$), 2.33(m, 1H, $C\underline{H}_2CHO$), 2.23 (m, 1H, CHMe), 1.84 (m, 1H, $CHMe_2$), 0.99 (d, 3H, J= 6.6 Hz, CH_3), 0.95 (d, 3H, J= 6.7 Hz, CH_3) and 0.93 (d, 3H, J= 6.7 Hz, CH_3).

(1*E*, 3*S*, 4*R*, 5*S*) and (1*E*, 3*R*, 4*R*, 5*S*)-5-(Methoxymethoxy)-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3-ol (*anti,anti*-5 and *syn,anti*-5)

To a solution of (*S*)-1 (1.0 g, 3.4 mmol) in CH_2Cl_2 (50 mL), cooled at -20°C, were added sequentially 6.8 mmol of piperidine and 640 mg (3.4 mmol) of aldehyde ***anti*-4**. Stirring was continued for 12h at -20°C. Then, 5% HCl (25 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was analyzed by ^{1}H-NMR (mixture 8:1 epimers at C-3) and purified by flash chromatography (hexane-ethyl acetate, 4:1) to afford 554 mg (50% yield) of ***anti,anti*-5** and 409 mg (37% yield) of mixture ***anti,anti*-5** + ***syn,anti*-5**.

***anti,anti*-5**: $[\alpha]_D$= +49.6 (c=1, $CHCl_3$). IR ($CHCl_3$): 3450, 2960, 1305, 1220, 1145, 1085, 1025 and 840 cm^{-1}. ^{1}H-NMR: 7.90 (m, 2H, $PhSO_2$), 7.57 (m, 3H, $PhSO_2$), 7.13 (dd, 1H, J= 15.0 and 3.7 Hz, $C\underline{H}$=CHS), 6.61 (dd, 1H, J= 15.0 and 2.1 Hz, CH=C$\underline{H}$S), 4.59 (s, 2H, OCH_2O), 4.48 (m, 1H, CH-OH), 3.44 (d, 1H, J= 5.7 Hz, OH), 3.34 (s, 3H, OCH_3), 3.24 (dd, 1H, J= 7.5 and 4.0 Hz, CHOMOM), 2.0-1.7 (m, 2H, CHMe and $CHMe_2$), 0.95 (d, 6H, J= 7.0 Hz, CH_3 x 2) and 0.88 (d, 3H, J= 6.7 Hz, CH_3). ^{13}C-NMR: 148.1, 140.5, 133.1, 129.5, 129.0, 127,4, 98.5, 87.5, 72.0, 55.9, 41.5, 30.6, 20.0, 16.4 and 14.2.

***syn,anti*-5**: ^{1}H-NMR: 7.90 (m, 2H, $PhSO_2$), 7.57 (m, 3H, $PhSO_2$), 6.93 (ddd, 1H, J= 15.0, 2.7 and 1.0 Hz, $C\underline{H}$=CHS), 6.68 (dd, 1H, J= 15.0 and 2.7 Hz, CH=C$\underline{H}$S), 4.81 (m, 1H, CH-OH), 4.68 and 4.62 (AB system, 2H, J= 6.3 Hz, OCH_2O), 3.85 (dd, 1H, J= 4.1 and 1.0 Hz, OH), 3.38 (s, 3H, OCH_3), 3.23 (dd, 1H, J= 8.4 and 3.5 Hz, CHOMOM), 2.0-1.8 (m, 2H, CHMe and $CHMe_2$), 0.96 (d, 3H, J= 6.9 Hz, CH_3), 0.88 (d, 3H, J= 6.9 Hz, CH_3) and 0.76 (d, 3H, J= 6.7 Hz, CH_3).

(1*E*, 3*S*, 4*S*, 5*S*)-3,5-*O*-Isopropyliden-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3,5-diol (*anti,anti*-6)

To a solution of *anti,anti*-**5** (100 mg) in acetone (2 mL) were added 2,2-dimethoxypropane (2 mL) and CSA (2 mg) at rt. The reaction was stirred while refluxing overnight. A saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford 65 mg of a 1:2 mixture of ketals **6**:**7**; 23 mg of *anti,anti*-**6** (23% yield) and 39 mg of *anti,anti*-**7** (41% yield) were obtained after chromatography (hexane-ethyl acetate, 9:1)

$[\alpha]_D$= +11.8 (c=1, $CHCl_3$). IR ($CHCl_3$): 2960, 1380, 1315, 1305, 1200, 1145, 1085 and 1025 cm^{-1}. ^{1}H-NMR: 7.90 (m, 2H, $PhSO_2$), 7.59 (m, 3H, $PhSO_2$), 7.08 (dd, 1H, J= 14.8 and 4.0 Hz, C<u>H</u>=CHS), 6.62 (dd, 1H, J= 14.8 and 1.8 Hz, CH=C<u>H</u>S), 4.12 (ddd, 1H, J= 10.3, 3.9 and 1.7 Hz, C<u>H</u>-CH=C), 3.38 (dd, 1H, J= 10.3 and 2.2 Hz, CH-^{i}Pr), 2.0-1.5 (m, 2H, CHMe and $CHMe_2$), 1.38 (s, 3H, CH_3-C), 1.35 (s, 3H, CH_3-C), 0.94 (d, 3H, J= 6.9 Hz, CH_3), 0.85 (d, 3H, J= 6.6 Hz, CH_3) and 0.81 (d, 3H, J= 6.8 Hz, CH_3). ^{13}C-NMR: 143.9, 140.4, 133.3, 130.8, 129.3, 127.8, 98.3, 77.5, 73.1, 35.9, 29.7, 27.9, 19.9, 19.4, 14.0 and 11.7.

(1*E*, 3*S*, 4*S*, 5*S*)-3,5-*O*-Methyliden-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3,5-diol (*anti,anti*-7)

To a solution of *anti,anti*-**5** (50 mg) in $CHCl_3$ (3 mL) were added 0.5 mL of dimethoxymethane and 500 mg of P_2O_5 at rt. The solution was vigorously stirred for 2h at rt. The reaction was cooled at 0°C and a saturated solution of aqueous Na_2CO_3 (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 5:1) to afford 40 mg (87% yield) of *anti,anti*-**7**.

$[\alpha]_D$= +11.4 (c=1, $CHCl_3$). IR ($CHCl_3$): 3010, 1200, 1145, 1025 and 660 cm^{-1}. ^{1}H-NMR: 7.89 (m, 2H, $PhSO_2$), 7.55 (m, 3H, $PhSO_2$), 7.09 (dd, 1H, J= 14.8 and 3.9 Hz, C<u>H</u>=CHS), 6.65 (dd, 1H, J= 14.8 and 1.7 Hz, CH=C<u>H</u>S), 5.10 and 4.70 (AB system, 2H, J= 6.3 Hz, OCH_2O), 3.88 (ddd, 1H, J= 10.1, 3.9 and 1.7 Hz, C<u>H</u>-CH=C), 3.11 (dd, 1H, J= 9.8 and 2.1 Hz, CH-^{i}Pr), 1.93 (m, 1H, CHMe), 1.67 (m, 1H, $CHMe_2$), 0.99 (d, 3H, J= 6.9 Hz, CH_3), 0.86 (d, 3H, J= 6.6 Hz, CH_3) and 0.85 (d, 3H, J= 6.9 Hz, CH_3). ^{13}C-NMR: 142.3, 140.1, 133.4, 131.4, 129.4, 127.6, 93.1, 85.9, 79.4, 36.7, 27.9, 19.9, 14.4 and 11.7.

(1*E*, 4*S*, 5*S*)-5-Hidroxy-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3-one (*anti*-8)

Commercial grade PCC (600 mg) was ground with silica gel (1 wt equiv.) in a mortar. The resulting free-running light orange solid was suspended in CH_2Cl_2 (5 mL) and was inserted in a ultrasonic processor beneath the surface (1 cm) of the suspension at 18°C (water bath). A solution of alcohols **5** (300 mg) in CH_2Cl_2 (5 mL) was added in one portion. The reaction was stopped after 5h, and the brown residue was treated with ether (20 mL) and vacuum filtered through a Buchner funnel packed with Celite. The residue was washed again with ether (50 mL), and the combined filtrates were concentrated to afford 232 mg (78% yield) of the crude β-methoxymethoxy ketone.

^{1}H-NMR: 7.93 (m, 2H, $PhSO_2$), 7.61 (m, 3H, $PhSO_2$), 7.26 and 7.14 (AB system, 2H, J= 15.0 Hz, CH=CH), 4.52 and 4.48 (AB system, 2H, J= 6.6 Hz, OCH2O), 3.54 (dd, 1H, J= 7.6 and 3.7 Hz,

CHOMOM), 3.20 (s, 3H, OCH_3), 3.05 (quintuplet, 1H, J= 7.2 Hz, CHMe), 1.85 (m, 1H, $CHMe_2$), 1.08 (d, 3H, J= 7.0 Hz, CH_3), 0.95 (d, 3H, J= 7.0 Hz, CH_3) and 0.92 (d, 3H, J= 6.9 Hz, CH_3).

This compound (232 mg) was dissolved in THF (20 mL) and 10% HCl (20 mL) was added. The mixture was stirring at rt for 5h. A saturated solution of aqueous $NaHCO_3$ (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 5:1) to afford 162 mg (81% yield) of *anti*-**8**.

$[\alpha]_D$= + 4.6 (c=1, $CHCl_3$). IR ($CHCl_3$): 2950, 1690, 1145, 1325, 1150, 1085 and 960 cm^{-1}. ^{1}H-NMR: 7.93 (m, 2H, $PhSO_2$), 7.62 (m, 3H, $PhSO_2$), 7.25 and 7.16 (AB system, 2H, J= 15.0 Hz, CH=CH), 3.5 (dd, 1H, J= 6.8 and 3.9 Hz, CHOH), 2.94 (quintuplet, 1H, J= 7.2 Hz, CHMe), 1.95 (br s, 1H, OH), 1.74 (m, 1H, $CHMe_2$), 1.12 (d, 3H, J= 7.1 Hz, CH_3), 0.96 (d, 3H, J= 6.9 Hz, CH_3) and 0.90 (d, 3H, J= 6.7 Hz, CH_3).

(1*E*, 3*R*, 4*S*, 5*S*)-3,5-*O*-Isopropyliden-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3,5-diol (*syn,anti*-6)

To a solution of tetramethylammonium triacetoxyborohydride (89 mg, 0.33 mmol) in a mixture of 2.0 mL of anhydrous acetonitrile and 2.0 mL of anhydrous acetic acid at -40°C was added a solution of 20 mg (0.067 mmol) of the hydroxyketone *anti*-**8** in 1.0 mL of anhydrous acetonitrile. The mixture was slowly warmed to rt and stirring was continued for 24h. The reaction was quenched by addition of 10 mL of 0.5N aqueous sodium potassium tartrate and a vigorous stirring was maintained for 30 min. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with CH_2Cl_2 and the combined organic layers were washed again again with saturated aqueous $NaHCO_3$. This aqueous layer was again extracted with CH_2Cl_2 and the combined organic layers were dried ($NaSO_4$) and evaporated. The residue was dissolved in acetone (5 mL), and 2,2-dimethoxypropane (1 mL) and CSA (2 mg) were sequentially added. The mixture was stirred at rt for 2h. Then, saturated aqueous $NaHCO_3$ (5 mL) and ether (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 9:1) to afford 17 mg (74% yield from *anti*-**8**) of *syn,anti*-**6**.

$[\alpha]_D$= +5.6 (c=1, $CHCl_3$). IR ($CHCl_3$): 2960, 2920, 1375, 1315, 1305, 1225, 1145, 1085 and 1020 cm^{-1}. ^{1}H-NMR: 7.89 (m, 2H, $PhSO_2$), 7.58 (m, 3H, $PhSO_2$), 6.91 (dd, 1H, J= 15.0 and 3.1 Hz, C<u>H</u>=CHS), 6.58 (dd, 1H, J= 15.0 and 2.1 Hz, CH=C<u>H</u>S), 4.56 (m, 1H, C<u>H</u>-CH=C), 3.03 (dd, 1H, J= 7.1 and 5.1 Hz, CH-^{i}Pr), 1.98 (d quintuplet, 1H, J= 6.9 and 4.6 Hz,CHMe), 1.71 (m, 1H, $CHMe_2$), 1.30 (s, 3H, CH_3-C), 1.28 (s, 3H, CH_3-C), 0.94 (d, 3H, J= 6.9 Hz, CH_3), 0.92 (d, 3H, J= 6.8 Hz, CH_3) and 0.76 (d, 3H, J= 6.9 Hz, CH_3). ^{13}C-NMR: 144.7, 133.3, 130.0, 129.2, 127.7, 100.9, 79.0, 68.4, 37.3, 31.7, 25.6, 23.3, 18.7, 17.5 and 13.8.

(2S, 3S, 4S, 5S)-2,4,6-Trimethyl-3,5-O-methylidene-1-(phenylsulfonyl)-3,5-heptanediol (*anti,anti,anti*-9)

A 1.15 M solution of MeLi in ether (2.05 mL, 2.36 mmol, 15.7 equiv.) was slowly added to a suspension of CuI (150 mg, 0.79 mmol, 5.3 equiv.) in ether (3 mL) at 0°C under an argon atmosphere. The suspension was kept at 0°C for 30 min. Then, a solution of *anti,anti*-**5** (50 mg, 0.15 mmol, 1.0 equiv.) in ether

(2 mL) was added, the mixture was allowed to warm at rt and stirring was continued during 2 h. The reaction was quenched by addition of a 1:1 mixture (10 mL) of saturated NH_4Cl aqueous solution and aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane:ethyl acetate, 3:1) to afford 45.5 mg of the *anti* addition adduct (87% yield). This compound was dissolved in $CHCl_3$ (3 mL) and treated with 0.5 mL of dimethoxymethane and 500 mg of P_2O_5 at rt. The suspension was vigorously stirred during 2 h at rt. The reaction was quenched as described in the case of preparation of *anti,anti*-**7**. After chromatographic purification (hexane-ethyl acetate 6:1) 38 mg (93% yield) of *anti,anti,anti*-**9** were obtained.

$[\alpha]_D$= +20.2 (c=1, $CHCl_3$). IR ($CHCl_3$): 3010, 1210, 1145, 930, 750 and 665 cm^{-1}. ^{1}H-NMR: 7.95 (m, 2H, $PhSO_2$), 7.62 (m, 3H, $PhSO_2$), 5.03 and 4.61 (AB system, 2H, J=6.1 Hz, OCH_2O), 3.32 (dd, 1H, J=14.7 and 1.9 Hz, CH_2SO_2), 3.07 (dd, 1H, J=9.9 and 1.3 Hz, CHO), 3.00 (dd, 1H, J=9.7 and 2.2 Hz, CHO), 2.94 (dd, 1H, J=14.7 and 9.1 Hz, CH_2SO_2), 2.42 (m, 1H, C<u>H</u>-CH_2S), 1.85 (m, 1H, $CHMe_2$), 1.48 (m, 1H, CHMe), 1.22 (d, 3H, J=6.9 Hz, CH_3), 0.97 (d, 3H, J=6.9 Hz, CH_3), 0.85 (d, 3H, J=6.9 Hz, CH_3) and 0.59 (d, 3H, J=6.5 Hz, CH_3).^{13}C-NMR: 140.1, 133.6, 129.3, 127.9, 93.7, 85.9, 85.7, 57.7, 33.4, 28.9, 28.1, 20.1, 19.1, 14.6 and 11.3.

(2R, 3R, 4R, 5S)-2,4,6-Trimethyl-3,5-O-methylidene-1-(phenylsulfonyl)-3,5-heptanediol (*anti,anti,syn*-9)

This compound was prepared from *anti,syn*-**5** in two steps (85 % overall yield) following the same experimetal procedure above described for the synthesis of *anti,anti,anti*-**9**. The $[\alpha]_D$, IR, ^{1}H-NMR and ^{13}C-NMR data are described in reference 5a.

Acknowledgments. We would like to acknowledge support of this work from Dirección General de Investigación Científica y Técnica (Grant PB90-0178).

References and Notes

1.- For some reviews, see: a) Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489-503. b) Masamune, S.; Choy, W.; Peterson, J.S.; Sila, L.R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1-30. c) Heathcock, C.H. In *Asymmetric Syntheses*; Morrison, J.D.. Ed.; Academic Press: New York, **1984**; Vol.3. d) Mukaiyama, T. *Org. React.* **1982**, *28*, 203-331. e) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982**, *13*, 1-115.

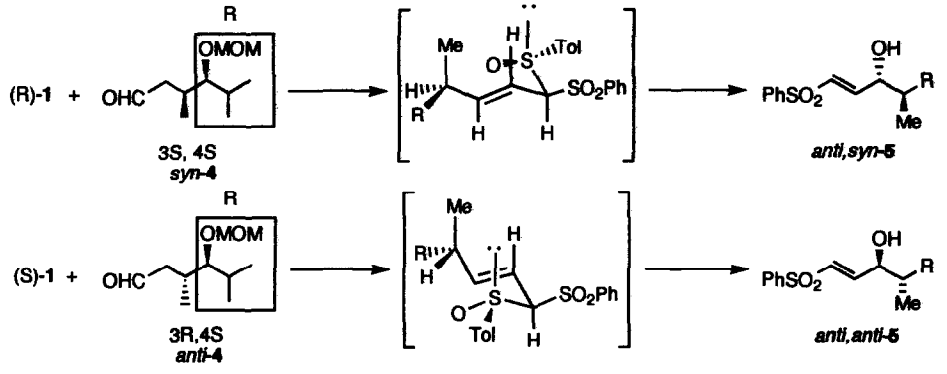
2.- For a review on asymmetric aldol reaction, see: Heathcock, C.H. in Morrison, J. (ed.): Asymmetric Synthesis, Vol. 3, Academic Press, New York 1984.

3.- For some pioneer references, see: a) Hoffmann, R.W. *Angew. Chem.* **1981**, *94*, 569; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555. b) Yamamoto, K.; Maruyama, K. *Heterocycles* **1982**, *18*, 357.

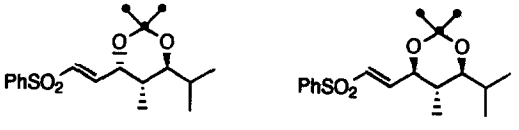
4.- a) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197-7206. b) Alcaraz, C.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1991**, *32*, 1385-1388. c) Carretero, J.C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867-3873. d) Domínguez, E.; Carretero, J. C. *Tetrahedron* Lett. **1993**, *34*, 5803.

5.- a) Carretero, J.C.; Domínguez, E. *J. Org. Chem.* **1993**, *58*, 1596. For other conjugate additions of organolithitium reagents to γ-alkoxy-α,β-unsaturated sulfones, see: b) Isobe, M. *Perspectives in the Organic Chemistry of Sulfur*; Zwanemburg, B.; Klander, A.J.H. Ed. ; Elsevier: New York; **1987**, *28*, 209-229.

6.- The stereoselectivity observed in both cases of double asymmetric condensation (matched pairs: (R)-**1** + *syn*-**4** and (S)-**1** + *anti*-**4**) could be rationalized on the basis of the reactivity and stability of the envelope conformations of the allylic sulfoxides intermediates ($PhSO_2$ and Tol groups at equatorial positions and minor steric strains). See also: Trost, B.M.; Mallart, S. *Tetrahedron Lett.* **1993**, *34*, 8025.



7.- a) Rychnovsky, S.D.; Yang, G.; Powers, J.P. *J. Org. Chem.* **1993**, *58*, 5251. b) Rychnovsky, S.D.; Skalitzky, K. *Tetrahedron Lett.* **1990**, *31*, 945-948. c) Evans, D.A.; Rieger, D.L.; Gage, J.R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100. According to these references *syn* 1,3-diol acetonides display carbon resonances for the acetonide methyl groups at 30 and 19 ppm, while the *anti* isomers have methyl resonances in the range 24-25 ppm. On the other hand, ^{13}C chemical shift of ketal carbon in *syn* diol acetonides resonates below 100 ppm, while *anti* diol acetonides appears above 100 ppm. The ^{13}C NMR resonances observed for *anti,anti*-**6** and *syn,anti*-**6** agree perfectly with these rules.



100.9, 25.6 and 23.3 ppm
syn,anti-**6** = *anti*-1,3-diol

98.3, 29.7 and 19.4 ppm
anti,anti-**6** = *syn*-1,3-diol

8.- Evans, D.A.; Chapman, K.T. *Tetrahedron Lett.* **1986**, *27*, 5939.

9.- For two recent references concerning stereoselective conjugate additions of organocopper reagents to α,β-unsaturated esters, see: a) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652 and references cited therein. b) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083.

(*Received in UK* 3 *February* 1994; *revised* 26 *April* 1994; *accepted* 29 *April* 1994)