A New Method for the Iterative Construction of Enantiomerically Pure Polypropionate Chains

Juan C. Carretero* and Esteban Domínguez

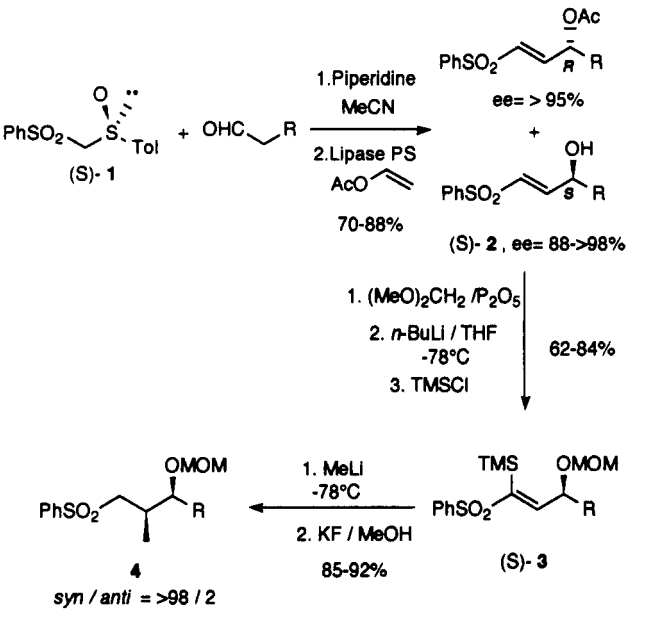
Departamento de Química, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Received November 24, 1992

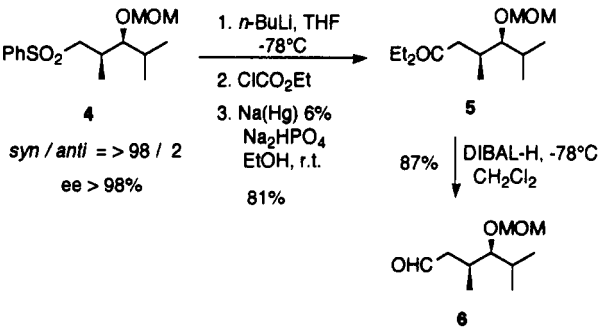
The polypropionate-derived chains found in many naturally occurring substances, which include antibiotics, ionophores, and immunosuppressive and antitumor agents, consist of sequences of consecutive asymmetric centers with methyl and hydroxyl groups arranged in an alternating way. In the last decade the quest for synthetically viable routes to these important natural products has promoted the development of outstanding methodologies for acyclic stereocontrol,[1] among which the stereoselective aldol reaction with chiral enolates has played a fundamental role.[2] In recent years much effort has been focused on the development of methods that allow the stereoselective construction of polypropionate chains by an iterative approach.[3] Herein we describe a new iterative method based on the stereoselective conjugate addition of methyllithium to enantiomerically pure γ-alkoxy-α,β-unsaturated phenyl sulfones.

Recently we reported a practical procedure for the synthesis of (*E*)-γ-hydroxy-α,β-unsaturated phenyl sulfones (**2**) by condensation of (phenylsulfonyl)(*p*-tolylsulfinyl)methane (**1**) with enolizable aldehydes.[4] Although vinyl sulfones **2** were obtained from enantiomerically pure reagent (*S*)-**1** in moderate optical yields (10–50% ee),[4b] these compounds were efficiently resolved by enantioselective acetylation using the pair lipase PS (fom *Pseudomonas cepacia*)/vinyl acetate in diisopropyl ether[5] (Scheme I). Moreover, the highly stereoselective conjugate addition

Scheme I



Scheme II



of organolithiums[6] to the Michael acceptors **3**, readily prepared in two steps from **2**, gave exclusively the syn adducts **4**. It should be noted that this sequence of reactions can be performed without isolation of the trimethylsilyl derivative **3** (see the Experimental Section). With this methodology in hand, we assumed that the transformation of optically pure sulfones **4** into the corresponding homologated aldehydes and their further incorporation in the sequence of reactions shown in Scheme I would allow us the stereoselective preparation of acyclic chains with four consecutive chiral centers.

Scheme II and Table I show the preparation of the optically pure aldehyde **6** from sulfone **4** (R = ^{i}Pr)[7] and the results concerning its condensation with both enantiomers of sulfoxide **1**.[8] Aldehyde **6** was prepared in 70% overall yield from **4** following the straightforward three-

(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) Heatchcock, 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 some recent references, see: (a) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2141. (b) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797–800. (c) Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, *32*, 1749–1752. (d) Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613–7630. (e) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313. (f) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977. (g) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121–7124. (h) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, N. *J. Am. Chem. Soc.* **1989**, *111*, 3441–3442.

(3) (a) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483–6485. (b) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495–4499. (c) Ziegler, F. E.; Kneisley, A.; Thottathil, J. K.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5434–5442 and 5442–5452. (d) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565. (e) Ziegler, F. E.; Kneisley, A. *Heterocycles* **1987**, *25*, 105–108. (f) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090–6093.

(4) (a) Domínguez, E.; Carretero, J. C. *Tetrahedron Lett.* **1990**, *31*, 2487–2490. (b) Domínguez, E.; Carretero, J. C. *Tetrahedron* **1990**, *46*, 7197–7206. (c) See also: Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1991**, *56*, 3189–3192.

(5) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867–3873.

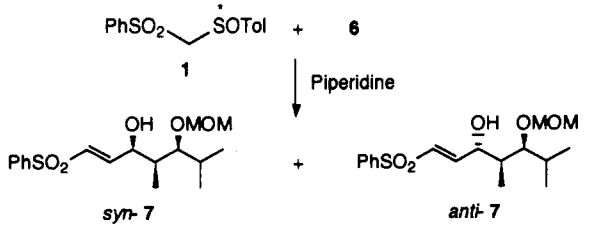
(6) (a) Alcaraz, C.; Carretero, J. C.; Domínguez, E. *Tetrahedron Lett.* **1991**, *32*, 1385–1388. For other conjugate additions to γ-alkoxy-α,β-unsaturated sulfones, see: (b) Isobe, M. *Perspectives in the Organic Chemistry of Sulfur*; Zwanemburg, B., Klander, A. J. H., Ed.; Elsevier: New York; 1987, Vol. 28, pp 209–229. (c) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863–2872.

(7) Enantiomerically pure sulfone **4** (R = ^{i}Pr) has been prepared from isovaleraldehyde in 35% overall yield as it is shown in Scheme I. The condensation of isovaleraldehyde with reagent (*S*)-**1** in CH_2Cl_2 at −25 °C afforded alcohols **2** (91% yield, ee = 50%, (*S*)-**2**/(*R*)-**2** = 75/25), which were resolved by enantioselective acetylation with lipase PS and vinyl acetate (see ref 5) to give optically pure (*S*)-**2** in 60% yield from isovaleraldehyde.

(8) Reagent (R)-**1** was prepared by the same method reported for (*S*)-**1** (see ref 4b) using (+)-menthyl (*R*)-*p*-toluenesulfinate instead of its enantiomer (Solladie, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173).

0022-3263/93/1958-1596$04.00/0

Table I. Condensation of Optically Pure 6 with Both Enantiomers 1



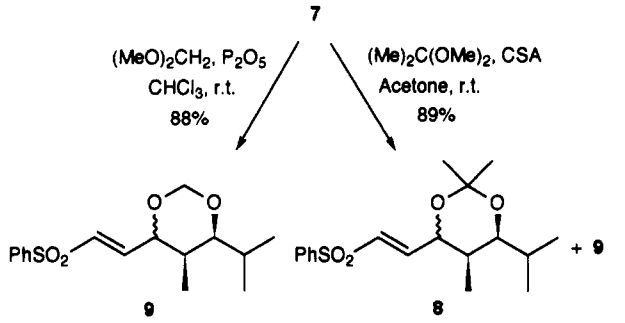
1 (config)	solvent, temp (°C)	syn/anti[a]	yield (%)[b]	
a (*S*)	CH_3CN, 0	48/52	80	mismatched pair
b (*S*)	CH_2Cl_2, 0	45/55	79	mismatched pair
c (*R*)	CH_3CN, 0	20/80	89	matched pair
d (*R*)	CH_2Cl_2, 0	14/86	94	matched pair
e (*R*)	CH_2Cl_2, −20	11/89	82	matched pair

[a] Determined by ^1H NMR on the crude mixtures. [b] In pure compound 7 after silica gel chromatography.

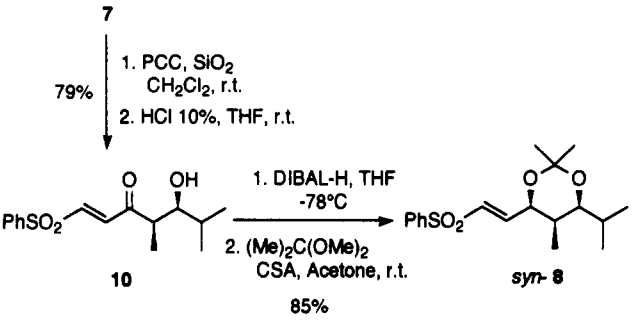
step sequence: carboxyethylation of the α-sulfonyl carbanion (1.1 equiv of *n*-BuLi, THF, −78 °C, then $ClCO_2Et$) and reductive elimination of the sulfonyl group (Na–Hg, Na_2HPO_4, EtOH, rt) to give the ester **5**, which was reduced with DIBAL-H (1.0 equiv, CH_2Cl_2, −78 °C) to afford aldehyde **6**. As was the case in the reaction of simple prochiral aldehydes, the condensation of reagent **1** with aldehyde **6** in the presence of 2.0 equiv of piperidine proceeded with high yield to give the pair of (*E*)-γ-hydroxy-α,β-unsaturated sulfones **7**. Whereas the condensation with reagent (*S*)-**1** was hardly stereoselective (mismatched pair, entries a and b), the reaction with (*R*)-**1** occurred with a significant anti stereoselectivity (matched pair, entries c–e). The best stereochemical result was obtained when the reaction was carried out in CH_2Cl_2 at −20 °C (entry e, *syn*-**7**/*anti*-**7** = 11/89). The stereochemical configurations of compounds **7** have been unequivocally established by conversion into their 1,3-acetonides **8** and studying, according to the Rychnovsky's[9a] and Evans' rules,[9b] the characteristic ^{13}C-NMR chemical shifts of the three acetonide carbons.[9] The treatment of the mixture of stereoisomers **7** with 2,2-dimethoxypropane and catalytic CSA in acetone at rt afforded a 1:2 mixture of ketals **8**:**9**, which were separated by chromatography.[10] Moreover, formaldehyde ketals **9** were prepared in high yield by treatment of **7** with $(MeO)_2CH_2$ and P_2O_5 in $CHCl_3$ at rt (Scheme III).

On the other hand, compound *anti*-**7** (or mixtures syn + anti) has been efficiently converted to compounds of syn stereoselectivity following the oxidation–reduction

Scheme III



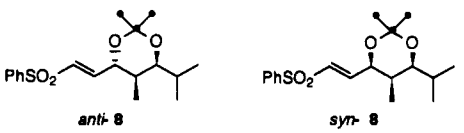
Scheme IV



sequence shown in Scheme IV. The oxidation of **7** with PCC–silica gel under sonication[11] and further acid hydrolysis of the ketal moiety (HCl 10%, THF, rt) gave β-hydroxy ketone **10** in 79% overall yield. Reduction of **10** with DIBAL in THF[12] at −78 °C was highly syn stereoselective[13] (syn/anti = 94/6), as was proved by conversion of the resulting 1,3-diol into the *syn*-acetonide **8** after treatment with 2,2-dimethoxypropane and CSA in acetone at rt (85% yield from **10**).

Finally, once the introduction of the third chiral center was solved, it was necessary to protect the α-position of vinyl sulfones **8** or **9** in order to introduce the fourth consecutive chiral center by conjugate addition of MeLi. However, all attempts of α-silylation of acetonides **8** or ketals **9** were unsuccessful.[14] Fortunately, α-deprotonation of *anti*-**7** with *n*-BuLi (2.2 equiv) in THF at −78 °C, followed by trapping with TMSCl, gave the desired compound **11** in 70% yield, which was converted to ketal **12** in 95% yield by reaction with $(MeO)_2CH_2/P_2O_5$ in $CHCl_3$. As was expected, the conjugate addition of MeLi to **12** in Et_2O at −78 °C, followed by desilylation (KF, MeOH), afforded exclusively a single adduct **13** in 87% yield. We propose for this stereoisomer **13** the 2,3-syn stereochemistry shown in Scheme V in agreement with the very high syn stereoselectivity always observed[6] in the conjugate addition of alkyllithiums to γ-alkoxy-α-(trimethylsilyl)-α,β-unsaturated phenyl sulfones in Et_2O. Interestingly, if the addition of MeLi to **12** is performed in THF,[15] an inversion

(9) (a) Rychnovsky, S. D.; Skalitzky, K. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) 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 both acetonides **8** agree perfectly with these rules.



(10) Unlike the mixture of anti/syn sulfones **7**, the mixture of anti/syn ketals **9** (or **8**) were readily separated by silica gel chromatography.

(11) (a) Leon, F. M.; Carretero, J. C. *Tetrahedron Lett.* **1991**, *32*, 5405–5408. (b) Adams, L. L.; Luzzio, F. A. *J. Org. Chem.* **1989**, *54*, 5387–5390.

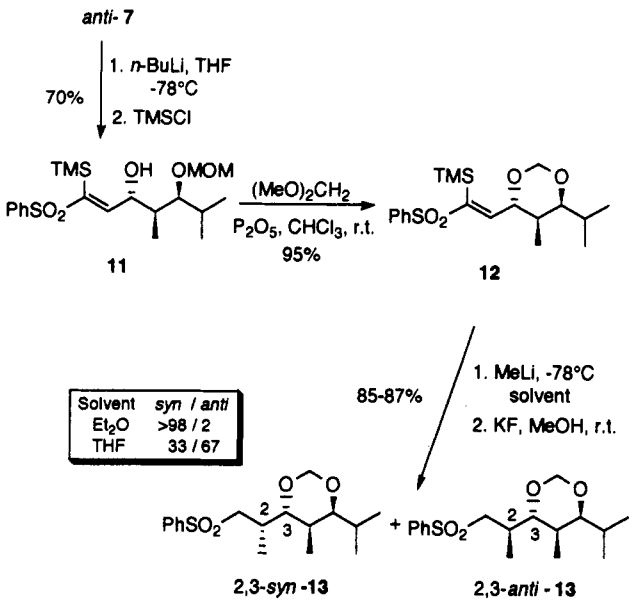
(12) The reduction of **10** with DIBAL-H in Et_2O is significantly less stereoselective (syn/anti = 25/75).

(13) Reduction of β-hydroxy ketones with DIBAL-H usually affords syn diols. For instance, see: (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868. (b) Kiyooka, H.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3012.

(14) All trials of α-deprotonation of compounds **8** and **9** with n-BuLi in different solvents and further treatment with TMSCl gave complex mixtures of products, which coould not be characterized.

(15) In the case of addition of organolithiums to vinyl sulfones **4** (see ref 6) we had observed a slightly lower syn stereoselectivity when the reaction was performed in THF instead of Et_2O.

Scheme V



of the stereoselectivity is observed, affording a 2:1 mixture of anti/syn adducts **13**, which were separated by chromatography.

In summary, the above results show that the readily available enantiomerically pure γ-hydroxy-α,β-unsaturated phenyl sulfones can be used as useful starting materials for the iterative construction of polypropionate segments with four consecutive chiral centers. All reactions involved in the sequence take place with high yields. Studies toward the elaboration of all stereotriads **8** and stereotetrads **13** by judicious choice of protecting groups and by anti addition to other γ-hydroxy vinyl sulfones derivatives is underway.

Experimental Section

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) relative to Me_4Si. $[\alpha]_D$ were measured at 25 °C. All solvents were dried before use. THF was distilled from sodium benzophenone under argon. Flash column chromatographies were performed with silica gel Merck-60 (230–400 mesh).

(2*R*,3*S*)-3-(Methoxymethoxy)-2,4-dimethyl-1-(phenylsulfonyl)pentane (4). To a solution of the alcohol (*S*)-**2** (R = ^{i}Pr, 4.78 g, 19.9 mmol) in $CHCl_3$ (100 mL) were added 15 mL of dimethoxymethane and 25 g of P_2O_5. The solution was stirred for 2 h a 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 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 4:1) to afford 5.5 g (97% yield) of the MOM derivative of (*S*)-**2**. Mp: 50–2 °C. $[\alpha]^{25}_D$: −32.2 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2960, 1315, 1300, 1145, 1080, 835, and 680 cm^{-1}. ^{1}H NMR: δ 7.89 (m, 2 H, $PhSO_2$), 7.58 (m, 3 H, $PhSO_2$), 6.90 (dd, 1 H, *J* = 15.0 and 5.5 Hz, C*H*=CHS), 6.52 (dd, 1 H, *J* = 15.0 and 1.4 Hz, CH=C*H*S), 4.55 (s, 2 H, OCH_2O), 4.02 (m, 1 H, CHO), 3.30 (s, 3 H, CH_3O), 1.90 (m, 1 H, $CHMe_2$), 0.93 (d, 3 H, *J* = 6.9 Hz, CH_3), and 0.89 (d, 3 H, *J* = 6.9 Hz, CH_3). ^{13}C NMR: δ 144.8, 140.3, 133.3, 131.7, 129.2, 127.4, 95.2, 79.4, 55.6, 32.5, and 13.9. Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; S, 11.27. Found: C, 58.92; H, 6.84; S, 11.13.

A solution 2.5 M of *n*-BuLi in hexane (7.74 mL, 19.36 mmol) was slowly added to a solution of the MOM derivative (5.5 g, 19.36 mmol) in dry THF (100 mL) at −78 °C under argon. The solution was kept at −78 °C for 20 min and then at 0 °C for 30 min. The solution was cooled again at −78 °C, and 4.9 mL (38.72 mmol) of trimethylsilyl chloride was added. After 1 h at −78 °C a solution of 1.5 M MeLi in ether (16.8 mL, 25.16 mmol) was slowly added. The solution was kept at −78 °C for 30 min. Then, a saturated solution of aqueous NH_4Cl (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (100 mL), and 10.5 g of KF was added. The reaction was stirred at rt for 1 h. Water was added (50 mL), and the resulting solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 6:1) to give 4.58 g (79% yield) of **4**. Mp = 65–7 °C. $[\alpha]^{25}_D$: +47.1 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2950, 1440, 1300, 1145, 1080, 1030, 910, and 680 cm^{-1}. ^{1}H NMR: δ 7.92 (m, 2 H, $PhSO_2$), 7.59 (m, 3 H, $PhSO_2$), 4.61 and 4.54 (AB system, 2 H, *J* = 6.7 Hz, OCH_2O), 3.54 (dd, 1 H, *J* = 14.2 and 5.4 Hz, $CHSO_2$), 3.32 (s, 3 H, OCH_3), 3.16 (dd, 1 H, *J* = 8.0 and 2.6 Hz, CHOMOM), 2.94 (dd, 1 H, *J* = 14.2 and 6.3 Hz, $CHSO_2$), 2.42 (m, 1 H, CHMe), 1.77 (m, 1 H, $CHMe_2$), 1.04 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.89 (d, 3 H, *J* = 6.9 Hz, CH_3) and 0.86 (d, 3 H, *J* = 6.9 Hz, CH_3). Anal. Calcd. for $C_{15}H_{24}O_4S$: C, 59.97; H, 8.05; S, 10.67. Found: C, 59.82; H, 8.01; S, 10.52.

Ethyl (3*S*,4*S*)-4-(Methoxymethoxy)-3,5-dimethylhexanoate (5). A solution 2.5 M of *n*-BuLi in hexane (6.61 mL, 16.5 mmol) was slowly added to a solution of **4** (4.51 g, 15.0 mmol) in THF (100 mL) at −78 °C under an argon atmosphere. The solution was kept at −78 °C for 30 min. Then, 1.87 mL (19.5 mmol) of ethyl chloroformate was added, and the solution was stirred at −78 °C for 1 h. 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 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford 5.45 g (96% yield) of 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 9 g of Na_2HPO_4 and 22 g of powdered 6% sodium amalgam (recently prepared). The solution was vigorously stirred at rt for 2 h. The reaction was poured into water and extracted with ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 9:1) to afford 2.8 g (81% yield) of **5**. $[\alpha]^{25}_D$: +25.3 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2950, 1720, and 1030 cm^{-1}. ^{1}H NMR: δ 4.67 and 4.62 (AB system, 2 H, *J* = 6.7 Hz, OCH_2O), 4.14 (q, 2 H, *J* = 7.0 Hz, CH_2O_2C), 3.41 (s, 3 H, OCH_3), 3.09 (dd, 1 H, *J* = 7.5 and 2.7 Hz, CHOMOM), 2.60–2.10 (m, 3 H, $CHCH_2CO_2$), 1.82 (m, 1 H, $CHMe_2$), 1.26 (t, 3 H, *J* = 7.0 Hz, CH_3CH_2C), 0.96 (d, 3 H, *J* = 6.7 Hz, CH_3), 0.94 (d, 3 H, *J* = 6.7 Hz, CH_3) and 0.93 (d, 3 H, *J* = 6.7 Hz, CH_3).

(3*S*,4*S*)-4-(Methoxymethoxy)-3,5-dimethylhexanal (6). To a solution of **5** (1.2 g, 5.17 mmol) in CH_2CL_2 (50 mL) was slowly added a 1 M solution of DIBAL-H in CH_2Cl_2 (5.17 mL, 5.17 mmol) at −78 °C. After 1 h of reaction 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 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 9:1) to afford 846 mg (87% yield) of **6**. $[\alpha]^{25}_D$: +69.1 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 2950, 1705, 1290, 1140, 1095, 1030, and 920 cm^{-1}. ^{1}H NMR: δ 9.78 (t, 1 H, *J* = 2.0 Hz, CHO), 4.66 and 4.61 (AB system, 2 H, *J* = 6.7 Hz, OCH_2O), 3.40 (s, 3 H, OCH_3), 3.07 (dd, 1 H, *J* = 7.5 and 2.7 Hz, CHOMOM), 2.75–2.25 (m, 3 H, $CHCH_2CO_2$), 1.83 (m, 1 H, $CHMe_2$), 0.96 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.95 (d, 3 H, *J* = 6.6 Hz, CH_3) and 0.94 (d, 3 H, *J* = 6.7 Hz, CH_3).

(1*E*,3*S*,4*S*,5*S*)- and (1*E*,3*R*,4*S*,5*S*)-5-(Methoxymethoxy)-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3-ol (*syn*-7 and *anti*-7). To a solution of (*R*)-**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 **6**. Stirring was continued for 12 h 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 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (hexane–ethyl acetate, 4:1) to afford 958 mg (82% yield) of a 8:1 mixture of anti/syn sulfones **7**. $[\alpha]^{25}_D$: +43.8 (*c* = 1, $CHCl_3$, mixture 8:1). Mp: 50–2 °C. ***anti*-7.** IR

($CHCl_3$): 3420, 2960, 1315, 1305, 1145, 1085, 1025, 840, and 680 cm^{-1}. ^1H NMR: δ 7.91 (m, 2 H, $PhSO_2$), 7.56 (m, 3 H, $PhSO_2$), 7.15 (dd, 1 H, J = 14.8 and 3.7 Hz, C*H*=CHS), 6.71 (dd, 1 H, J = 14.8 and 1.9 Hz, CH=C*H*S), 4.68 (s, 2 H, OCH_2O), 4.39 (d, 1 H, J = 5.5 Hz, OH), 4.17 (m, 1 H, CHOH), 3.39 (s, 3 H, CH_3O), 3.38 (m, 1 H, CHOMOM), 1.83 (m, 2 H, $CHMe_2$ and CHMe), 0.97 (d, 3 H, J = 6.6 Hz, CH_3), 0.96 (d, 3 H, J = 6.8 Hz, CH_3) and 0.82 (d, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR: δ 147.2, 140.5, 133.2, 130.3, 129.2, 127.6, 99.2, 85.8, 71.9, 56.0, 40.4, 31.1, 20.0, 19.0, and 9.9. ***syn*-7.** ^1H NMR: δ 7.91 (m, 2 H, $PhSO_2$), 7.56 (m, 3 H, $PhSO_2$), 6.93 (dd, 1 H, J = 14.8 and 3.1 Hz, C*H*=CHS), 6.66 (dd, 1 H, J = 14.8 and 2.0 Hz, CH=C*H*S), 4.74 and 4.65 (AB system, 2 H, J = 5.6 Hz, OCH_2O), 4.58 (m, 1 H, CHOH), 3.41 (s, 3 H, CH_3O), 3.18 (m, 1 H, CHOMOM), 1.83 (m, 2 H, $CHMe_2$ and CHMe), 0.93 (d, 3 H, J = 6.9 Hz, CH_3), 0.89 (d, 3 H, J = 7.1 Hz, CH_3), and 0.85 (d, 3 H, J = 7.1 Hz, CH_3). Anal. Calcd for $C_{17}H_{26}O_5S$: C, 59.62; H, 7.65; S, 9.36. Found: C, 59.29; H, 7.41; S, 9.52.

(1*E*,3*R*,4*R*,5*S*)-3,5-*O*-Isopropylidene-4,6-dimethyl-1-(phenylsulfonyl)-1-heptene-3,5-diol (*anti*-8). To a solution of a 8:1 mixture of *anti*/*syn*-7 (100 mg) in acetone (2 mL) were added 2,2-dimethoxypropane (1 mL) and CSA (2 mg) at rt. The reaction was stirred while refluxing overnight. Then a saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give 88 mg of a 1:2 mixture of ketals 8:9; 35 mg of pure *anti*-8 (26% yield) was obtained after chromatography (hexane–ethyl acetate, 9:1). R_f: 0.1. $[\alpha]^{25}_D$: +8.5 (c = 1, $CHCl_3$). IR ($CHCl_3$): 2950, 2920, 1380, 1315, 1305, 1145, 1085, and 1020 cm^{-1}. ^1H NMR: δ 7.92 (m, 2 H, $PhSO_2$), 7.59 (m, 3 H, $PhSO_2$), 7.04 (dd, 1 H, J = 15.0 and 3.4 Hz, C*H*=CHS), 6.57 (dd, 1 H, J = 15.0 and 2.0 Hz, CH=C*H*S), 3.94 (ddd, 1 H, J = 8.4, 3.3, and 1.8 Hz, CHO), 3.27 (dd, 1 H, J = 10.5 and 4.6 Hz, CH^{i}Pr), 1.88 (m, 1 H, CHMe) 1.67 (m, 1 H, $CHMe_2$), 1.31 (s, 6 H, Me_2C), 0.98 (d, 3 H, J = 6.8 Hz, CH_3), 0.93 (d, 3 H, J = 6.4 Hz, CH_3), and 0.81 (d, 3 H, J = 6.5 Hz, CH_3). ^{13}C NMR: δ 144.6, 140.5, 133.3, 129.3, 128.8, 127.8, 101.4, 74.5, 73.3, 37.9, 27.8, 24.3, 24.0, 19.7, 18.2, and 11.5. Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.87; H, 7.74; S, 9.47. Found: C, 64.04; H, 7.90; S, 9.38.

(1*E*,3*R*,4*R*,5*S*)- and (1*E*,3*S*,4*R*,5*S*)-3,5-*O*-Methylidene-4,6-dimethyl-1-(phenylsulfonyl)-1-heptene-3,5-diol (*anti*-9 and *syn*-9). To a solution of a 1:1 mixture of 7 (100 mg) in $CHCl_3$ (4 mL) were added 1 mL of dimethoxymethane and 1 g of P_2O_5 at rt. The solution was vigorously stirred for 2 h 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 Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford 80 mg (88% yield) of a 1:1 mixture of anti/syn ketals 9. The mixture was purified by chromatography (hexane–ethyl acetate, 6:1) to afford 33 mg of *anti*-9 (36% yield) and 38 mg of *syn*-9 (42% yield). ***anti*-9.** R_f: 0.19. Mp = 134–6 °C. $[\alpha]^{25}_D$: −94.8 (c = 1, $CHCl_3$). IR ($CHCl_3$): 2960, 1450, 1320, 1310, 1290, 1150, 825, and 680 cm^{-1}. ^1H NMR: δ 7.92 (m, 2 H, $PhSO_2$), 7.60 (m, 3 H, $PhSO_2$), 7.06 (dd, 1 H, J = 15.3 and 3.2 Hz, C*H*=CHS), 6.56 (dd, 1 H, J = 15.2 and 2.3 Hz, CH=C*H*S), 4.89 and 4.85 (AB system, 2 H, J = 6.8 Hz, OCH_2O), 4.46 (m, 1 H, CHO), 3.08 (dd, 1 H, J = 9.8 and 2.2 Hz, CH^{i}Pr), 1.90–1.60 (m, 2 H, CHMe and $CHMe_2$), 1.21 (d, 3 H, J = 6.9 Hz, CH_3), 0.95 (d, 3 H, J = 6.4 Hz, CH_3), and 0.80 (d, 3 H, J = 6.8 Hz, CH_3). ^{13}C NMR: δ 144.5, 139.9, 133.6, 132.7, 129.4, 127.6, 89.4, 81.1, 77.1, 34.2, 29.1, 19.3, 17.1, and 12.2. Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.24; H, 7.38; S, 10.02. ***syn*-9.** R_f: 0.21. Mp = 91–3 °C. $[\alpha]^{25}_D$: +13.5 (c = 1, $CHCl_3$). IR ($CHCl_3$): 3010, 1205, 1145, 1025, 750, and 660 cm^{-1}. ^1H NMR: δ 7.90 (m 2 H, $PhSO_2$), 7.58 (m, 3 H, $PhSO_2$), 6.84 (dd, 1 H, J = 15.0 and 2.8 Hz, C*H*=CHS), 6.60 (dd, 1 H, J = 15.0 and 2.1 Hz, CH=C*H*S), 5.09–4.71 (AB system, 2 H, J = 6.2 Hz, OCH_2O), 4.37 (m, 1 H, CHO), 3.12 (dd, 1 H, J = 9.8 and 2.1 Hz, CH^{i}Pr), 1.90–1.60 (m, 2 H, CHMe and $CHMe_2$), 0.98 (d, 3 H, J = 6.4 Hz, CH_3), 0.83 (d, 3 H, J = 6.8 Hz, CH_3), and 0.81 (d, 3 H, J = 6.8 Hz, CH_3). ^{13}C NMR: δ 143.8, 140.4, 133.4, 130.8, 129.3, 127.6, 93.9, 86.4, 78.4, 33.8, 29.2, 19.6, 17.1, and 6.4. Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 62.19; H, 7.18; S, 10.23.

(1*E*,4*R*,5*S*)-5-Hydroxy-4,6-dimethyl-1-(phenylsulfonyl)-1-hepten-3-one (10). Commercial-grade PCC (400 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). Alcohol 7 (200 mg) in CH_2Cl_2 (5 mL) was added in one portion. The reaction was stopped after 4 h, and the brown residue was treated with Et_2O (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. The residue was purified by chromatography (hexane–ethyl acetate, 4:1) to afford 190 mg of the MOM derivative of 10 (96% yield). $[\alpha]^{25}_D$: −22.1 (c = 1, $CHCl_3$). IR ($CHCl_3$): 3010, 1710, 1210, 930, 750, and 660 cm^{-1}. ^1H NMR: δ 7.93 (m, 2 H, $PhSO_2$), 7.61 (m, 3 H, $PhSO_2$), 7.31 and 7.15 (AB system, 2 H, J = 15.0 Hz, CH=CH), 4.57 and 4.52 (AB system, 2 H, J = 6.8 Hz, OCH_2O), 3.59 (dd, 1 H, J = 7.0 and 3.9 Hz, CHOMOM), 3.20 (s, 3 H, OCH_3), 2.92 (m, 1 H, CHMe), 1.80 (m, 1 H, $CHMe_2$), 1.16 (d, 3 H, J = 6.8 Hz, CH_3), and 0.94 (d, 2 × 3 H, J = 6.8 Hz, 2 CH_3). ^{13}C NMR: δ 199.3, 139.9, 138.8, 135.0, 134.2, 129.5, 128.2, 98.1, 84.0, 55.9, 49.4, 31.6, 19.6, 18.7, and 10.0. Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.97; H, 7.11; S, 9.42. Found: C, 59.65; H, 6.94; S, 9.18. MOM-10 (190 mg) was dissolved in THF (20 mL), and 10% HCl (20 mL) was added. The mixture was stirred at rt for 5 h. Then, 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 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 4:1) to afford 137 mg (82% yield) of 10. $[\alpha]^{25}_D$: +10.0 (c = 1, $CHCl_3$). ^1H NMR: δ 7.93 (m, 2 H, $PhSO_2$), 7.62 (m, 3 H, $PhSO_2$), 7.27 and 7.19 (AB system, 2 H, J = 15.0 Hz, CH=CH), 3.62 (dd, 1 H, J = 8.3 and 3.0 Hz, CHOH), 2.92 (dq, 1 H, J = 7.1 and 3.0 Hz, CHMe), 2.13 (br s, 1 H, OH), 1.68 (m, 1 H, $CHMe_2$), 1.17 (d, 3 H, J = 7.0 Hz, CH_3), 1.01 (d, 3 H, J = 6.5 Hz, CH_3), and 0.89 (d, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR: δ 201.3, 140.8, 138.4, 134.3, 134.2, 129.6, 128.2, 75.8, 48.4, 30.9, 18.9, 18.8, and 8.6. Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.78; H, 6.80; S, 10.82. Found: C, 60.33; H, 6.49; S, 10.47.

(1*E*,3*S*,4*R*,5*S*)-3,5-*O*-Isopropylidene-4,6-dimethyl-1-(phenylsulfonyl)-1-heptene-3,5-diol (*syn*-8). To a solution of 10 (100 mg, 0.34 mmol) in THF (10 mL) was slowly added a 1 M solution of DIBAL-H in CH_2Cl_2 (0.34 mL, 0.34 mmol) at −78 °C under argon. The solution was stirred at −78 °C for 1 h. Then, 10% HCl (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($NaSO_4$) and evaporated. The residue was dissolved in acetone (5 mL), and 2,2-dimethoxymethane (2 mL) and CSA (2 mg) were sequentially added. The mixture was stirred at rt for 2 h. Then, saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried ($NaSO_4$) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 9:1) to afford 106 mg (94% yield) of *syn*-8. $[\alpha]^{25}_D$: +6.5 (c = 1, $CHCl_3$). IR ($CHCl_3$): 2960, 1380, 1315, 1260, 1145, 1085, 1010, and 805 cm^{-1}. ^1H NMR: δ 7.92 (m, 2 H, $PhSO_2$), 7.59 (m, 3 H, $PhSO_2$), 6.86 (dd, 1 H, J = 14.9 and 2.7 Hz, C*H*=CHS), 6.57 (dd, 1 H, J = 14.9 and 1.9 Hz, CH=CHS), 4.62 (m, 1 H, CHO), 3.38 (dd, 1 H, J = 9.6 and 2.1 Hz, CH^{i}Pr), 1.80–1.55 (m, 2 H, CHMe and $CHMe_2$), 1.38 (s, 6 H, Me_2C), 0.94 (d, 3 H, J = 6.4 Hz, CH_3), 0.81 (d, 3 H, J = 6.6 Hz, CH_3), 0.73 (d, 3 H, J = 6.9 Hz, CH_3). ^{13}C NMR: δ 145.1, 140.5, 133.3, 130.3, 129.3, 127.7, 99.3, 78.7, 72.0, 33.1, 29.7, 29.3, 19.6, 19.4, 17.3, and 5.7. Anal. Calcd for $C_{18}H_{26}O_4S$: C, 63.87; H, 7.74; S, 9.47. Found: C, 63.95; H, 8.02; S, 9.53.

(1*E*,3*R*,4*S*,5*S*)-5-(Methoxymethoxy)-4,6-dimethyl-1-(trimethylsilyl)-1-(phenylsulfonyl)-1-hepten-3-ol (11). To a solution of 7 (anti/syn, 8:1, 465 mg, 1.36 mmol) in THF (50 mL) was slowly added a 2.5 M solution of *n*-BuLi (1.2 mL, 2.99 mmol) at −78 °C under argon. The solution was stirred at −78 °C for 1 h and then TMSCl (0.69 mL, 5.44 mmol) was added. The reaction was kept at −78 °C for 15 min and then quenched by addition of a saturated solution of aqueous NH_4Cl (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 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 394 mg of (70% yield) of 11. $[\alpha]^{25}_D$: −1.1 (c = 1, $CHCl_3$). IR ($CHCl_3$):

3430, 3010, 1225, 1205, 1140, 1030, 850, 750, and 670 cm^{-1}. ^1H NMR: δ 7.83 (m, 2 H, $PhSO_2$), 7.54 (m, 3 H, $PhSO_2$), 7.33 (d, 1 H, J = 9.7 Hz, CH=C), 4.72 (m, 2 H, OCH_2O), 4.39 (m, 1 H, CHOH), 3.97 (d, 1 H, J = 5.0 Hz, OH), 3.52 (dd, 1 H, J = 9.3 and 2.2 Hz, CHOMOM), 3.41 (s, 3 H, OCH_3), 1.82 (m, 2 H, CHMe and $CHMe_2$), 1.00 (d, 3 H, J = 6.6 Hz, CH_3), 0.86 (d, 3 H, J = 6.7 Hz, CH_3), 0.81 (d, 3 H, J = 7.0 Hz, CH_3), and 0.21 (s, 9 H, Me_3Si). ^{13}C NMR: δ 156.9, 145.6, 141.2, 132.7, 128.8, 127.3, 99.1, 84.6, 69.8, 55.8, 40.9, 30.9, 20.0, 19.0, 9.8, and 0.8. Anal. Calcd for $C_{20}H_{34}O_5SSi$: C, 57.93; H, 8.26; S, 7.73. Found: C, 57.75; H, 8.39; S, 7.38.

(1*E*,3*R*,4*R*,5*S*)-4,6-Dimethyl-3,5-*O*-methylidene-1-(trimethylsilyl)-1-(phenylsulfonyl)-1-heptene-3,5-diol (12). Ketal **12** was prepared as described for ketals **9**. After chromatography (hexane–ethyl acetate, 9:1), 175 mg (95% yield) of **12** were obtained from 200 mg of **11**. $[\alpha]^{25}_D$: −68.9 (c = 1.4, $CHCl_3$). ^1H NMR: δ 7.81 (d, 1 H, J = 7.5 Hz, CH=C), 7.80 (m, 2 H, $PhSO_2$), 7.56 (m, 3 H, $PhSO_2$), 4.96 and 4.88 (AB system, 2 H, J = 6.6 Hz, OCH_2O), 4.57 (dd, 1 H, J = 7.5 and 1.0 Hz, C_3-H), 3.22 (dd, 1 H, J = 9.7 and 2.1 Hz, CH^iPr), 1.71 (m, 2 H, CHMe and $CHMe_2$), 1.21 (d, 3 H, J = 6.9 Hz, CH_3), 0.99 (d, 3 H, J = 6.9 Hz, CH_3), 0.79 (d, 3 H, J = 6.8 Hz, CH_3), and 0.17 (s, 9 H, Me_3Si). ^{13}C NMR: δ 153.7, 148.0, 141.0, 133.0, 129.0, 127.5, 89.2, 80.7, 75.3, 35.0, 29.3, 17.2, 12.1, and 0.15. Anal. Calcd for $C_{19}H_{30}O_4SSi$: C, 59.64; H, 7.90; S, 8.38. Found: C, 59.29; H, 7.64; S, 8.10.

(2*S*,3*R*,4*R*,5*S*)-2,4,6-Trimethyl-3,5-*O*-methylidene-1-(phenylsulfonyl)-3,5-heptanediol (*syn*-13). A 1.5 M solution of MeLi in Et_2O (65 μL, 0.1 mmol) was slowly added to a solution of **12** (25 mg, 0.065 mmol) in Et_2O (2 mL) at −78 °C under argon. The solution was kept at −78 °C for 30 min. Then, a saturated solution of aqueous NH_4Cl (10 mL) was added. Et_2O (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($NaSO_4$) and evaporated. The residue was dissolved in MeOH (15 mL), and 0.5 g of KF was added. The reaction was stirred at rt for 1 h. Water was added, and the resulting solution was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($NaSO_4$) and evaporated. The residue was purified by chromatography (hexane–ethyl acetate, 6:1) to afford 19 mg (87% yield) of *syn*-**13**. $[\alpha]^{25}_D$: −8.7 (c = 0.85, $CHCl_3$). IR ($CHCl_3$): 3010, 1215, 1150, 930, 750 and 665 cm^{-1}. ^1H NMR: δ 7.95 (m, 2 H, $PhSO_2$), 7.62 (m, 3 H, $PhSO_2$), 4.81 and 4.76 (AB system, 2 H, J = 5.8 Hz, OCH_2O), 3.23 (dd, 1 H, J = 9.2 and 2.4 Hz, CHO), 3.14 (dd, 1 H, J = 9.7 and 2.7 Hz, CHO), 2.96 (m, 2 H, CH_2SO_2), 2.75 (m, 1 H, $CHCH_2S$), 1.72 (m, 2 H, CHMe and $CHMe_2$), 1.12 (d, 3 H, J = 6.6 Hz, CH_3), 1.07 (d, 3 H, J = 7.0 Hz, CH_3) 0.94 (d, 3 H, J = 6.5 Hz, CH_3) and 0.75 (d, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR: δ 139.8, 133.8, 129.4, 127.9, 88.9, 81.4, 79.7, 60.1, 30.6, 28.8, 27.8, 19.7, 17.5, 16.4, and 13.0.

(2*R*,3*R*,4*R*,5*S*)-2,4,6-Trimethyl-3,5-*O*-methylidene-1-(phenylsulfonyl)-3,5-heptanediol (*anti*-13). When the preceding reaction was performed in THF as solvent, a 1:2 mixture of syn/anti sulfones **13** was obtained. Both stereoisomers were separated by chromatography. From 25 mg of **12** were obtained 12 mg (56% yield) of *anti*-**13** and 6 mg (29% yield) of *syn*-**13**. *anti*-**13**. $[\alpha]^{25}_D$: −54.6 (c = 0.7, $CHCl_3$). IR ($CHCl_3$): 3020, 1220, 1205, 930, 750, and 665 cm^{-1}. ^1H NMR: δ 7.95 (m, 2 H, $PhSO_2$), 7.61 (m, 3 H, $PhSO_2$), 4.74 and 4.62 (AB system, 2 H, J = 6.4 Hz, OCH_2O), 3.62 (m, 1 H, CH_2SO_2), 3.24 (m, 1 H, CHO), 3.17 (m, 1 H, CHO), 3.10–2.75 (m, 2 H, $CHCH_2SO_2$), 1.90–1.68 (m, 2 H, CHMe and $CHMe_2$), 1.18 (d, 3 H, J = 6.8 Hz, CH_3), 1.17 (d, 3 H, J = 6.4 Hz, CH_3) 1.00 (d, 3 H, J = 6.3 Hz, CH_3), and 0.84 (d, 3 H, J = 6.8 Hz, CH_3). ^{13}C NMR: δ 140.1, 133.7, 129.4, 127.8, 88.2, 82.0, 79.9, 58.7, 29.2, 29.1, 26.4, 19.6, 17.2, 17.1, and 13.1.

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

Supplementary Material Available: ^1H NMR spectra (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.