First Asymmetric Synthesis of Enantiopure α-Sulfenyl Dithioacetals and α-Sulfenyl Aldehydes

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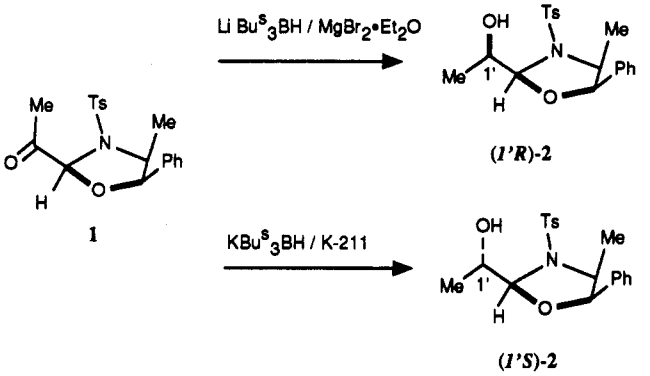
During our investigations on oxazolidines as chiral templates in asymmetric synthesis we recently synthesized methyl ketone **1** in order to test it for hydride additions. In this study we showed that addition of tri-*sec*-butyl borohydrides to **1** under "chelating" or "naked" conditions proceeded with virtually complete *si* or *re* face selectivity, respectively (Scheme I).[1]

Since our original aim was to develop a new route to enantiopure α-alkoxy aldehydes,[2] the release of the norephedrine moiety from the oxazolidine ring was planned as a subsequent step. Accordingly,[2,3] carbinols (1′*R*)-**2** and (1′*S*)-**2** were submitted to a Lewis acid-promoted thiolysis. In striking contrast with our previous results,[2,3] separate treatment of these carbinols with *p*-thiocresol (5 mol equiv) and $BF_3{\cdot}Et_2O$ (2.0 mol equiv) in CH_2Cl_2 at 25 °C afforded the α-sulfenyl dithioacetals (α-SDTA's) **5**. Thus, the oxazolidine-to-dithioacetal conversion took place with concomitant replacement of the hydroxy group in C-1′ by a third thiol moiety (Scheme II).[4] This finding, although precluding our original goal, prompted us to study the above-mentioned reaction in greater detail and to investigate the possible chemical discrimination of the sulfur atom in **5**. In particular, an entry to α-sulfenyl aldehydes[5] in enantiopure form[6] appeared interesting.

A survey of the liteature ruled out an intermolecular mechanism for the thioether formation, such an event being limited to allylic[7] and benzylic[7] alcohols or methyl[8] ethers. On the other hand, the known[9] proclivity of the 1-oxy-2-alkylthio moiety to give intramolecular displacement under acid conditions suggests the intervention of

Scheme I



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thiiranium (episulfonium) ions such as **4**, in turn generated from intermediates **3** (Scheme II). Final addition of a third thiol molecule to these transient ions (vide infra) would thus produce the observed α-SDTA's.

Ancillary experiments further corroborate the proposed mechanism. Thus, submission of the racemic dithioacetal *rac*-**6**[10] to the same conditions as above gave, as expected, *rac*-**5** as the only new product, but at a much higher rate than starting from (1′*R*)-**2** or (1′*S*)-**2**. (Scheme III). This result supports the path shown in Scheme II and rationalizes the impossibility of isolating the postulated intermediates **3** and **4** (k_1 and $k_4 \ll k_2 \ll k_3$). Separate treatment of *rac*-**5** and *rac*-**6** with excess thiophenol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave in both cases the same product, assigned as structure *rac*-**7**.[11] This result reveals the following features: (1) thiiranium ion formation via displacement at C-2 (see Scheme III for numbering) is allowed from *rac*-**6** (path a) whereas is forbidden from *rac*-**5**[12] (path b). (2) *Trans*-thioacetalization, which implies displacement at C-1, is the only process allowed from *rac*-**5**. This may involve equilibration through either the parent thiiranium ion (path c) or the isomeric thionium

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(2) See for example: Bernardi, A.; Piarulli, U.; Poli, G.; Scolastico, C.; Villa, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 751 and ref 9b cited therein.

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(4) Such an unexpected behavior appears to be due to a particularly slow *trans*-thioacetalization of **2** (*vide infra*). 1,3-Propanedithiol, used in place of *p*-thiocresol in preliminary experiments, brought about the same type of reactivity. This suggests that the nature of the thiol used is unimportant for the success of the process.

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(11) ^{1}H-NMR and mass spectra are consistent with a double arylthio replacement. The material from *rac*-**6** contained small amounts of other byproducts. One of these impurities is believed to be the triphenylsulfenyl derivative $MeCH(SPh)CH(SPh)_2$, probably due to a small extent of thioacetalization prior to thiiranium ion formation. In any case the ratio *rac*-**7**/byproducts, being constant at different reaction times, does not conflict with the mechanism proposed in Scheme III.

(12) Only the triphenylsulfenyl derivative $MeCH(SPh)CH(SPh)_2$ would have otherwise been obtained.

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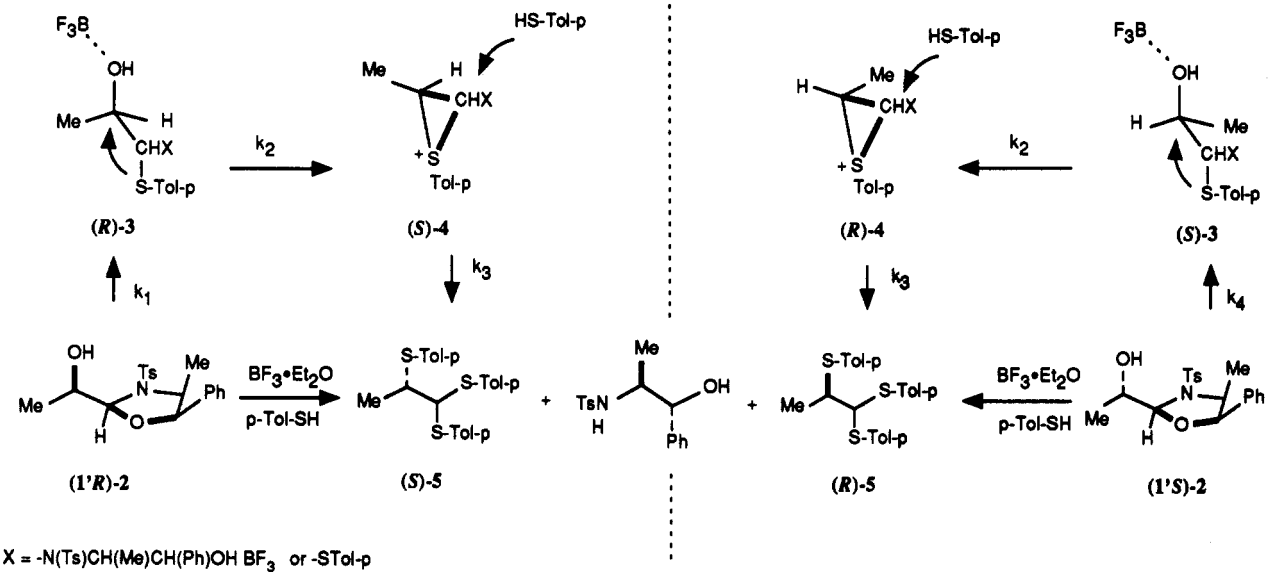
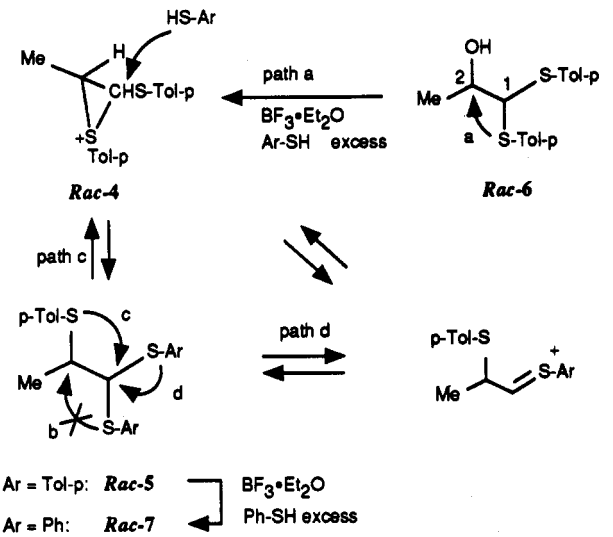
Scheme II



Scheme III



ion[13] (path d). (3) As anticipated in Scheme II, thiol addition to the thiiranium ion takes place on the most electron-poor carbon atom[9c,9e,14] (Scheme III).

Hence it follows that the α-SDTA's **5** are generated from **2** with net inversion of stereochemistry. Moreover, they are not expected to racemize[15] in the presence of BF_3·Et_2O/*p*-TolSH. Further evidence is provided by the fact that (*S*)-**5** and (*R*)-**5**, obtained by exposure of the parent carbinols to the above conditions for increasing periods of time, did not show any appreciable lowering of optical rotation [(*S*)-**5**: $[\alpha]^{23}_D$ +141.0° (*c* = 1.21, $CHCl_3$); (*R*)-**5**: $[\alpha]^{23}_D$ −139.8° (*c* = 1.04, $CHCl_3$)].

Having established the absolute stereochemistry of the α-SDTA's, we next undertook the cleavage of the dithioacetal function. Such a delicate transformation calls for discrimination between a dithioacetal and a thioethereal sulfur atom, a problem for which we could not find useful hints in the literature. Among the possible options available, an oxidative hydrolysis was considered as the most viable method since its preference for C–S bond cleavage over sulfur oxidation could be anticipated.[16] Indeed, treatment of *rac*-**5** with $(CF_3CO_2)_2PhI$ in MeCN/H_2O[17] afforded the desired aldehyde in 75% yield. The same hydrolysis was thus applied to the pure antipodes (*S*)-**5** and (*R*)-**5**. $LiAlH_4$ reduction of the resulting crude aldehydes or, alternatively, in situ $NaBH_4$ quenching of the above hydrolyses, gave the corresponding alcohols (*S*)-**9** and (*R*)-**9** which were eventually esterified with (*R*)-α-methoxyphenylacetic acid.[18] As indicated by the ^{1}H-NMR spectra of the mandelates **10** and **11** (Figure 1) the stereochemical integrity of (*S*)-**8** and (*R*)-**8** (Scheme IV) was preserved. However, it must be pointed out that chromatographic purification of the latter compounds brings about complete racemization, as may be detected by conversions **8** → **10** and **8** → **11** using the silica gel-purified aldehydes.

Since the absolute configuration of (+)-**5**, (−)-**5**, and their derivatives was inferred only from the mechanism of the thiolysis, a chemical correlation was also undertaken as a definitive proof.[19] Treatment of ethyl lactate with di-*p*-tolyl disulfide (5 mol equiv) and tri-*n*-butylphosphine (5 mol equiv), according to the protocol developed by Hata,[20] gave the α-sulfenyl ester **12** which was subsequently reduced to the corresponding primary alcohol with $LiAlH_4$. The levorotatory power of this alcohol confirmed the stereochemical assignments given above (Scheme IV).

(13) For the Lewis acid-promoted formation of thionium ions from dithioacetals see: (a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966. (b) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544. (c) Reetz, M. T.; Ginnauis, A. *Synth. Commun.* **1981**, *11*, 315. (d) Trost, B. M.; Sato, T.; *J. Am. Chem. Soc.* **1985**, *107*, 719.

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(15) The configurational stability of some chiral thiiranium ions has recently been demonstrated: (a) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Tetrahedron Lett.* **1991**, *32*, 4317. (b) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Chem. Lett.* **1992**, 239.

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Scheme IV

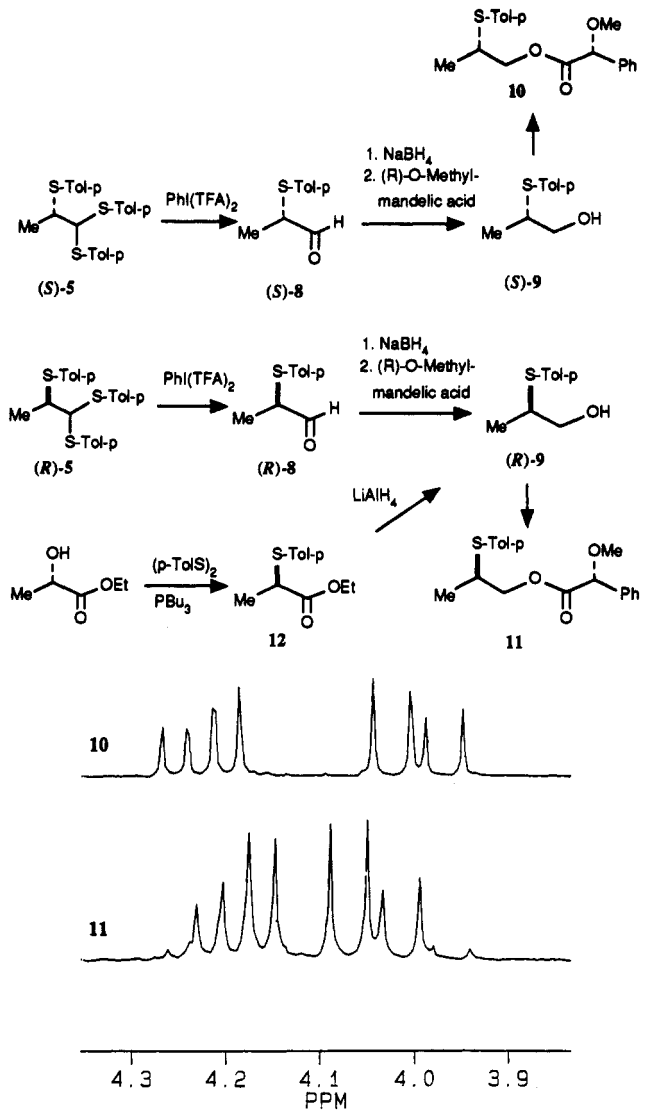

Figure 1. ^{1}H-NMR spectra (δ 3.9–4.3, $-CH_2O-$) of the diastereomeric mandelate esters **10** and **11**.

In summary, these results show that the $BF_3{\cdot}Et_2O$ thiolysis of carbinols (1′*R*)-**2** and (1′*S*)-**2**, selectively obtained from the parent methyl ketone **1**, led to the α-SDTA's (*S*)-**5** and (*R*)-**5** respectively. With the help of additional experiments and a chemical correlation, the stereochemistry of this transformation has been elucidated and its mechanism postulated. Oxidative hydrolysis of these dithioacetals gave the corresponding α-sulfenyl aldehydes (*S*)-**8** and (*R*)-**8** which were shown to be enantiomerically pure. To the best of our knowledge this method represents the first successful asymmetric synthesis of an enolizable enantiopure α-sulfenyl aldehyde and provides information on the potential configurational lability of these derivatives. In light of the increasing interest that α-sulfenyl aldehydes are receiving in stereoselective synthesis[21,22] the present study may be a stimulus to the synthesis and use of new enantiopure members of this family. Further selective manipulation of (*S*)-**5** and (*R*)-**5** is under current study.

Experimental Section

General. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with tetramethylsilane as internal standard and using $CDCl_3$ as the solvent unless otherwise stated. Optical rotations were measured in a 1-dm cell of 1-mL capacity. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC and 270–400 mesh silica gel (Merck) for flash chromatography.

Solvents. CH_2Cl_2 was distilled from CaH_2 under N_2 just before use. All reactions employing this solvent were run in oven-dried glassware and under a nitrogen (from liquid N_2) atmosphere.

Starting Materials. Unless otherwise noted, commercial reagents were purchased and used without further purification. $BF_3{\cdot}Et_2O$ was distilled from flame-dried glassware prior to use.

(2*S*)- and (2*R*)-1,1,2-Tris(*p*-tolylsulfenyl)propane [(*S*)-5 and (*R*)-5]. To a stirred solution of (1′*R*)-**2** or (1′*S*)-**2** (67 mg, 0.18 mmol) and *p*-thiocresol (115.2 mg, 0.93 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (44.3 μL, 0.36 mmol). After 25 h of stirring at rt, the reaction was treated with pH 7 phosphate buffer (2 mL). The organic solution was extracted with Et_2O, and the collected extracts were dried (Na_2SO_4) and evaporated to dryness. Flash chromatography of the crude (hexane/AcOEt 98:2) gave the pure α-sulfenyl dithioacetals **5** (60.7 mg, 82% from (1′*R*)-**2**, 56.3 mg, 76% from (1′*S*)-**2**). (*S*)-**5**: $[\alpha]^{23}_D$ +141.0° (*c* = 1.21, $CHCl_3$). (*R*)-**5**: $[\alpha]^{23}_D$ −139.8° (*c* = 1.04, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.51 (d, *J* = 7 Hz, 3 H), 2.35 (s, 9 H), 3.52 (dq, *J* = 3 and 7 Hz, 1 H), 4.4 (d, *J* = 3 Hz, 1 H), 6.8–7.5 (m, 12 H); ^{13}C-NMR δ 133.0, 132.8, 132.4, 129.7, 129.6, 64.9, 47.8, 21.1, 21.0, 15.6; IR ($CHCl_3$) 3020, 2925, 2880, 1600, 1490 cm^{-1}; MS (EI, 70 eV) *m*/*z* 410, 163 (100). Anal. Calcd for $C_{24}H_{26}S_3$: C, 70.20: H, 6.38. Found: ((*S*)-**5**) C, 70.11; H, 6.32; ((*R*)-**5**) C, 70.08; H, 6.30.

(2*RS*)-1,1,2-Tris(*p*-tolylsulfenyl)propane (*rac*-5). To a stirred solution of *rac*-**6**, prepared as described in ref 10 (293.3 mg, 0.964 mmol), and *p*-thiocresol (239.6 mg, 1.929 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}Et_2O$ (237.4 μL, 1.929 mmol). After 5 h of stirring at rt, the reaction mixture was treated with pH 7 phosphate buffer (8 mL). The organic solution was extracted with Et_2O, and the extracts were dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (hexane/AcOEt 98:2) of the crude gave the pure racemic α-sulfenyl dithioacetal **5** (361.5 mg, 91%). For the physical data see the preparation of the enantiopure antipodes.

(2*RS*)-1,1-Bis(phenylsulfenyl)-2-(*p*-tolylsulfenyl)propane (*rac*-7) (from either *rac*-**6** or *rac*-**5**). The same procedure as that above described for the preparation of *rac*-**5** starting from *rac*-**6** was followed, but using thiophenol instead of *p*-thiocresol (81% from *rac*-**6**; 88% from *rac*-**5**): ^{1}H-NMR ($CDCl_3$) δ 1.55 (d, *J* = 7 Hz, 3 H), 2.35 (s, 3 H), 3.55 (dq, *J* = 3 and 7 Hz, 1 H), 4.52 (d, *J* = 3 Hz, 1 H), 6.8–7.76 (m, 14 H); MS (FAB) 382 M$^+$.

(2*RS*)-2-(*p*-Tolylsulfenyl)propanal (*rac*-8). To a solution of *rac*-**5** (17.8 mg, 0.0434 mmol) in MeCN/H_2O 4:1 (0.5 mL) was added $(CF_3CO_2)_2PhI$ (27.95 mg, 0.065 mmol) in one portion, under vigorous stirring. After 1 min the mixture was treated with saturated aqueous $NaHCO_3$ and then extracted with Et_2O. Drying of the organic layers (Na_2SO_4) followed by careful evaporation gave the crude aldehyde which was submitted to flash chromatography (pentane/Et_2O 9:1) (5.9 mg, 75%): ^{1}H-NMR ($CDCl_3$) δ 1.38 (d, *J* = 7 Hz, 3 H), 2.35 (s, 3 H), 3.58 (dq, *J* = 3.1 Hz, *J* = 7 Hz, 1 H), 7–7.4 (AA′BB′, 4 H), 9.45 (d, 3.1 Hz, 1 H); ^{13}C-NMR δ 195.3, 134.1, 129.9, 128.5, 51.6, 21.2, 13.2; IR ($CHCl_3$) 3040, 2980, 2960, 2920, 2870, 2850, 1720, 1450 cm^{-1}.

(*S*)- and (*R*)-2-(*p*-Tolylsulfenyl)propanal [(*S*)-8 and (*R*)-8] and (*S*)- and (*R*)-2-(*p*-Tolylsulfenyl)propanol [(*S*)-9 and (*R*)-9]. To a solution of (*S*)-**5** or (*R*)-**5** (189 mg, 0.461 mmol) in MeCN/H_2O 4:1 (4 mL) was added $(CF_3CO_2)_2IPh$ (297.3 mg, 0.691 mmol), under vigorous stirring, in one portion. After 1 min (TLC

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(22) During the preparation of this article we were informed that an alternative route to enantiopure α-sulfenyl aldehydes is under investigation. Warren, S.; Chibale, K. Personal communication.

indicated formation of the desired aldehydes), $NaBH_4$ (69.7 mg, 1.85 mmol) was added to the mixture and stirring was continued for a further 10 min. Extractive workup with Et_2O followed by drying (Na_2SO_4), evaporation of the organic fractions, and flash chromatography gave the enantiopure alcohols (*S*)-**9** and (*R*)-**9** (75% from (*S*)-**5**; 75% from (*R*)-**5**). For the analytical data of (*S*)-**8** and (*R*)-**8** see the above reported preparation of the racemic compound. (*S*)-**9**: $[\alpha]^{23}_D$ +15.6° (*c* = 0.64, $CHCl_3$). (*R*)-**9**: $[\alpha]^{23}_D$ −11.0° (*c* = 1.53, $CHCl_3$). (*S*)-**9** and (*R*)-**9**: ^{1}H-NMR ($CDCl_3$/D_2O) δ 1.12 (d, *J* = 5.5 Hz, 3 H), 2.21 (s, 3 H), 3.1 (m, 1 H), 3.35 (m, 2 H), 5.21 (s, 1 H), 7–7.4 (AA′BB′, 4 H); ^{13}C-NMR (selected data) δ 133.8, 129.7, 47.0, 22.3, 21.1, 14.0; MS (EI, 70 eV) *m*/*z* 182, 151 (100), 124, 91. Anal. Calcd for $C_{10}H_{14}SO$: C, 65.89; H, 7.74. Found: ((*S*)-**9**) C, 65.68; H, 7.70; ((*R*)-**9**) C, 65.72; H, 7.69.

(2*S*,2′*S*)- and (2*S*,2′*R*)-2-Methoxy-2-phenylacetic Acid 2′-(*p*-Tolylsulfenyl)propyl Ester (10 and 11). To a stirred solution of the alcohols (*S*)-**9** or (*R*)-**9** (80 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) were added DCC (110 mg, 0.533 mmol), (*R*)-α-methoxyphenylacetic acid (136 mg, 0.82 mmol), and DMAP (1.0 mg) in that order. After 10 min the solution was diluted with hexane and washed with 5% aqueous HCl and then with 5% aqueous $NaHCO_3$. After drying (Na_2SO_4) and evaporation of the resulting crude, the mandelates were purified by flash chromatography (PhH/^{i}Pr$_2$O 95:5) (130 mg, 89% from (*S*)-**9**; 132 mg, 90% from (*R*)-**9**). **10**: ^{1}H-NMR ($CDCl_3$) δ 1.12 (d, *J* = 5.5 Hz, 3 H), 2.33 (s, 3 H), 3.3 (m, 1 H), 3.42 (s, 3 H), 4.0 (dd, *J* = 8 Hz, *J* = 10.7 Hz, 1 H), 4.22 (dd, *J* = 5.0 Hz, *J* = 10.7 Hz, 1 H), 4.75 (s, 1 H), 7–7.6 (m, 9 H); IR ν_{max} ($CHCl_3$) 3000, 2920, 1740, 1600 cm^{-1}. **11**: ^{1}H-NMR ($CDCl_3$) δ 1.12 (d, *J* = 5.5 Hz 3 H), 2.33 (s, 3 H), 3.3 (m, 1 H), 3.42 (s, 3 H), 4.03 (dd, *J* = 8 and 11 Hz, 1 H), 4.18 (dd, *J* = 5.5 and 11 Hz, 1 H), 4.75 (s, 1 H), 7–7.6 (m, 9 H); IR ($CHCl_3$) 3000, 1740, 1600 cm^{-1}. Anal. Calcd for $C_{19}H_{22}SO_3$: C, 69.06; H, 6.71. Found: (**10**) C, 68.95; H, 6.75; (**11**) C, 69.20, H, 6.65.

(*R*)-2-(*p*-Tolylsulfenyl)propionic Acid Ethyl Ester (12). To a solution of (*S*)-(−)-2-hydroxypropionic acid ethyl ester (ethyl L-lactate) (100 mg, 0.846 mmol) in DME (10.2 mL) were added di-*p*-tolyl disulfide (1.043 g, 4.23 mmol) and tributylphosphine (0.586 mL, 4.23 mmol), and the resulting mixture was brought to reflux. After 2 h (TLC monitoring) the reaction was cooled to rt and the solvent was evaporated. Flash chromatography of the crude (hexane/AcOEt 98:2) afforded pure **12** (133 mg, 70%): ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, *J* = 7 Hz, 3 H), 1.48 (d, *J* = 7 Hz, 3 H), 2.38 (s, 3 H), 3.75 (q, *J* = 7 Hz, 1 H), 4.15 (q, *J* = 7 Hz, 2 H), 7.10–7.50 (AA′BB′, 4 H). Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 64.20; H, 7.25.

Preparation of (*R*)-9 from 12. To a solution of **12** (47.5 mg, 0.212 mmol) in Et_2O (2.5 mL) at 0 °C was quickly added $LiAlH_4$ (8.6 mg, 0.226 mmol). After 1 h of stirring, the mixture was treated with saturated aqueous NH_4Cl (2 mL). Extractive workup with Et_2O followed by drying (Na_2SO_4), evaporation of the organic fractions, and flash chromatography of the crude (hexane/AcOEt 80:20) gave the pure alcohol (23 mg, 60%). The optical rotation of this alcohol {$[\alpha]^{23}_D$, *c* = 1.5, $CHCl_3$} as well as the ^{1}H-NMR spectrum of its *O*-methoxymandelate derivative were identical to those recorded for the corresponding material derived from (1′*S*)-**2**. This confirmed our previous stereochemical assignments.

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Supplementary Material Available: Experimental procedure for the preparation of (1′*R*)-**2** and (1′*S*)-**2**; ^{1}H-NMR spectra of (1′*R*)-**2**, (1′*S*)-**2**, (*S*)-**5**, (*R*)-**5**, *rac*-**7**, *rac*-**8**, (*S*)-**9**, (*R*)-**9**, **10**, **11**, and **12** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered by ACS; see any current masthead page for ordering information.