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# An Enzyme-Based Synthesis of (*S*)-(-)-3-Methyl-2-[(phenylsulfonyl)-methyl]butyl Phenyl Sulfide and the Stereochemical Course of its Alkylation

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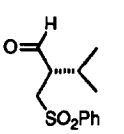
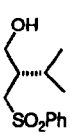
**Abstract:** The two title reactions have been explored. In the first instance, best results were achieved if the chloroacetate ester of 3-methyl-2[(phenylsulfonyl)methyl]-1-butanol was subjected to enzymatic hydrolysis with lipase P30 (Amano). Subsequent conversion to the sulfide of high optical purity (~ 95% e.e.) was accomplished by means of tri-*n*-butylphosphine and diphenyl disulfide. The alkylation of this difunctional intermediate with several electrophiles has proven to be rather impressively diastereoselective. The relative (and absolute) course of these transformations has been established by means of X-ray crystallographic and NMR methods and is rationalized at the mechanistic level.

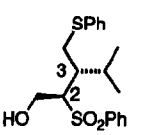
Stereogenic centers that carry an isopropyl group are an important structural component of many cembranolides and diterpenes. An emerging synthetic approach to these targets involves the enantioselective elaboration of small polyfunctional building blocks such as represented by **1** and **2**.[2] In the course of our




**1**




**2**



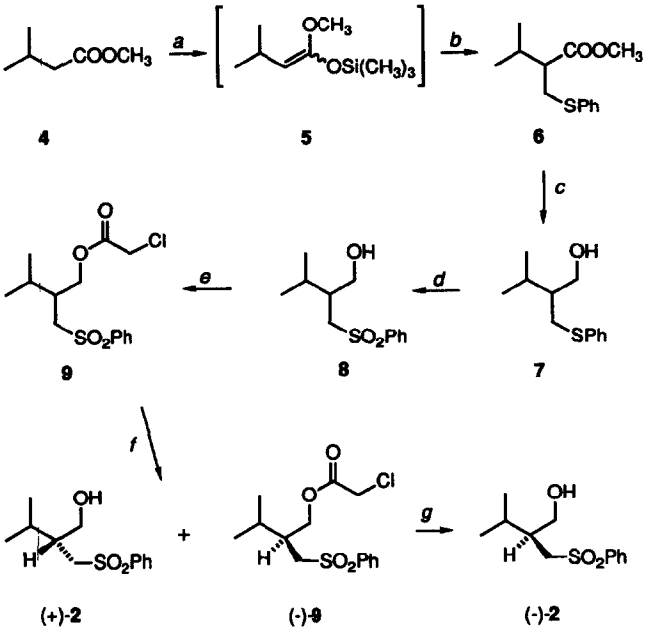

**3**

development of an asymmetric approach to vinigrol,[3] retrosynthetic considerations led us to consider (2*R*,3*S*)-**3**, a molecule endowed with vicinal chiral carbon atoms and three well differentiated functional groups, as a key early intermediate. The progression of reactions leading to **3** was designed to proceed via **2**. However, the earlier route to **2**[2,4] appeared to be inordinately tedious and insufficiently stereoselective (85% e.e.) for our purposes. Herein, we detail a short pathway to this hydroxy sulfone, which by virtue of an enzymatic hydrolysis provides both the (-)-(2*S*) and (+)-(2*R*) enantiomers in very good optical purity (~ 95% e.e.) and in multigram amounts. Also described is the conversion of the levorotatory antipode of **2** into **3** with high level stereoinduction, as well as the relative (and absolute) stereochemical course of related α-sulfonyl carbanion alkylations.

## Results

**Arrival at (*R*)- and (*S*)-3-Methyl-2[(phenylsulfonyl)methyl]-1-butanol.** Commercially available methyl isovalerate (**4**) served as the starting material (Scheme I). Following conversion to the silyl ketene acetal, *viz.* **5**, direct coupling with chloromethyl phenyl sulfide occurred uneventfully in the presence of anhydrous zinc bromide[5] to give **6** in 66% yield. Other Lewis acids such as $TiCl_4$, $SnCl_4$, and $Et_2AlCl$ were also examined, but found to be very much less satisfactory. Hydride reduction of ester **6** gave **7** whose oxidation with hydrogen peroxide and benzeneselenenic acid[6] provided **8** in very efficient fashion.

**Scheme I**




[a] LDA, $(CH_3)_3SiCl$, THF, -78 °C → 0 °C. [b] $PhSCH_2Cl$, $ZnBr_2$,$CH_2Cl_2$, rt. [c] $LiAlH_4$, THF, 0 °C. [d] PhSe(O)OH, $H_2O_2$, $CH_2Cl_2$. [e] $ClCH_2COCl$, $(C_2H_5)_3N$, $CH_2Cl_2$. [f] Lipase P30, $H_2O$, phosphate buffer, THF; 0.1N NaOH, rt. [g] NaOH, $C_2H_5OH$, $H_2O$.

At this point, two operational alternatives for enzymatic resolution presented themselves. The first option was to conduct the hydrolysis on a suitable derivative of sulfide **7**. However, when early results showed the lipase-promoted deesterification[7] of its chloroacetate[8] to proceed at a level no higher than 37% e.e., attention was turned to **8**. The presence of two additional oxygen atoms at sulfur serves to generate a much greater imbalance in the comparative steric bulk of the substituents linked to the stereogenic center. As a consequence of this structural modification, the hydrolysis of **9** with lipase P30 (Amano) was found to be usefully enantioselective in both directions. Thus, by conducting the enzymatic hydrolysis to 35% conversion, (+)-(2*R*)-**2** was routinely obtained at a quality level of 90-95% e.e. as determined by Mosher ester analysis.[9] Application of this approach to the acquisition of (-)-(2*S*)-**2** required only that the hydrolysis be allowed to

proceed to 65% completion. Saponification of the remaining unreacted (-)-**9** provided hydroxy sulfone that was almost completely (>95:5) the levorotatory enantiomer ($^1$H NMR analysis).

The absolute configurational assignments given in Scheme I follow from an independent unequivocal synthesis of (-)-(2*S*)-**2** starting from **10** by the route originally developed by Thomas and Astles.[2,4]

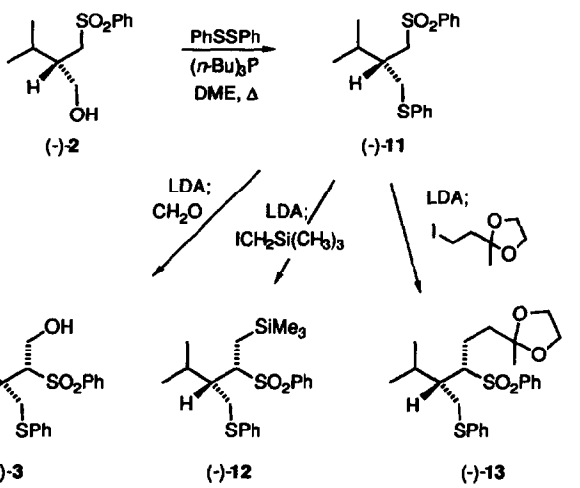

**10** (-)-**2**

$[\alpha]_D^{20}$ = -14.9° $[\alpha]_D^{20}$ = -13.4°
(*c* 1.0, $CHCl_3$) (*c* 1.0, $CHCl_3$)
84% e.e. 85% e.e.

**Production of (*S*)-3-Methyl-2-[(phenylsulfonyl)methyl]butyl Phenyl Sulfide and the Stereochemical Course of its Alkylation.** Next to be addressed was introduction of the phenylthio group and implementation of selected alkylation reactions involving **11**. Pilot experiments conducted on racemic material showed that **11** was produced most efficiently (91%) by exposure of **2** to the action of diphenyl disulfide and tri-*n*-butylphosphine in hot 1,2-dimethoxyethane[10] (Scheme II).

The anion of **11**, easily generated by deprotonation with LDA in THF at -78 °C, captured formaldehyde in a highly diastereoselective manner (14:1). The major isomer was easily obtained in a homogeneous state following MPLC purification. Since the stereochemistry at C-2 in **3** could not be rigorously deduced by high-field NMR spectroscopy, recourse was made to an X-ray crystallographic determination (Table I). The ORTEP diagram presented in Figure 1 reveals the preferred stereoselectivity of electrophilic capture by the α-sulfonyl carbanion.

**Scheme II**




(-)-**2** (-)-**11**

(-)-**3** (-)-**12** (-)-**13**

**Table I.** Crystallographic Details for (±)-3.

| | |
|---|---|
| Formula | $C_{19}H_{24}O_3S_2$ |
| Formula wt. | 364.52 |
| Space group | $P2_1/n$ |
| a, Å | 8.183(2) |
| b, Å | 25.396(2) |
| c, Å | 9.954(2) |
| β, deg | 111.43(1) |
| Volume, Å$^3$ | 1925.5(6) |
| Z | 4 |
| Density (calc), g/cm$^3$ | 1.26 |
| Bounding planes | {010), (01$\bar{1}$), (011), (001), ($\bar{1}$11), (11$\bar{1}$) |
| Crystal size, mm | 0.27 x 0.31 x 0.46 |
| Radiation | MoKα with graphite monochromator |
| Linear abs. coeff., cm$^{-1}$ | 2.77 |
| Transmission factors | 0.92 to 0.95 |
| Temperature | ambient |
| 2θ limits | $4° \leq 2\theta \leq 55°$ |
| Scan speed | 4°/min in ω with maximum of 4 scans per reflection |
| Background time/scan time | 0.5 |
| Scan range | (1.05 + 0.35 tanθ)° in ω |
| Data collected | +h, +k, ±l |
| Scan type | ω |
| Unique data | 4543 |
| Unique data, with $F_o^2 > 3\sigma(F_o^2)$ | 2130 |
| Final number of variables | 221 |
| R(F)[a] | 0.044 |
| $R_\omega(F)$[b] | 0.048 |
| Error in observation of unit weight | 1.49 |

[a] $R(F) = \Sigma||F_o|-|F_c||/\Sigma|F_o|$

[b] $R_\omega(F) = [\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega|F_o|^2]^{1/2}$ with $\omega = 1/\sigma^2(F_o)$

It follows, therefore, that when optically enriched (2*S*)-**11** was subjected to the same reaction, (2*R*,3*S*)-**3** was obtained in 63% yield. The efficiencies with which **12** (>14:1) and **13** (>12:1) were produced by alkylation with iodomethyltrimethylsilane and 2-methyl-2-(2-iodoethyl)-1,3-dioxolane were somewhat more impressive (74% and 79%, respectively). The configuration of the newly generated stereogenic center in **12** could be ascertained by nOe measurements performed at 300 MHz. The assignment to **13** was adopted by analogy to the other two examples. Other electrophilic reagents not discussed here exhibited the same trend. Only methyl chloroformate was found to be less selective (3.3:1). However, the dropoff in this particular case may be the result of epimerization during workup because of the very acidic nature of the C-2 proton in this β-sulfonyl ester.

**Mechanistic Rationalization of the Alkylative Stereoinduction.** The findings made herein with respect to the alkylative stereoinduction not only hold importance with respect to our long-range synthetic goals, but are of fundamental significance as well. Of the two diastereotopic α-sulfonyl protons available for initial abstraction, the process leading to **B** gives rise to a sterically less congested pyramidalized carbanion[11,12] than the alternative route that produces **A**. Both reactive intermediates are presumably monomeric in

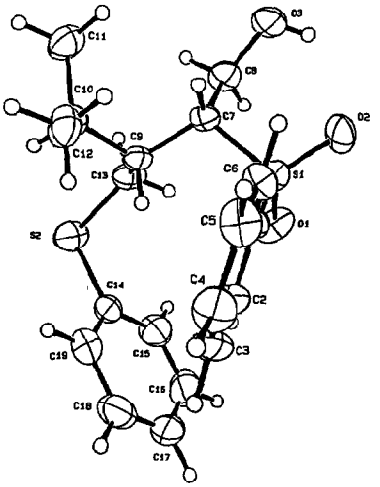
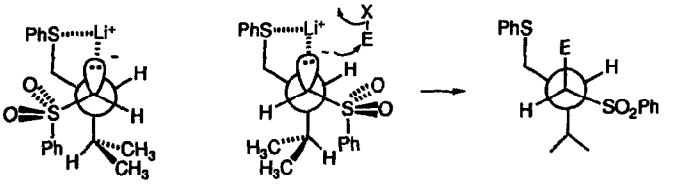



Figure 1. ORTEP diagram of **3**. The non-hydrogen atoms are represented by 30% probability thermal elipsoids. The hydrogen atoms are drawn with an artificial radius. The atom numbering scheme used is arbitrary.

THF solution,[13,14] with their sulfonyl oxygens so arranged that both O atoms are gauche to the neighboring electron pair.[13-15] Furthermore, added stabilization is likely available by intramolecular coordination to divalent sulfur (as shown).[16] Electrophilic capture of **B** with retention of configuration leads directly to **3**, **12**, or **13**.




**A** **B** **3, 12, 13**

## Experimental Section

Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter; concentrations are given in grams/100 mL. Infrared spectra were recorded with a Perkin-Elmer 1320 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were determined on Bruker WP 300 and AC 300 FT spectrometers. Exact mass measurements were made with a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were undertaken at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods and all reactions were performed under an inert atmosphere. Flash chromatography was performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents.

**Methyl 3-Methyl-2-[(phenylthio)methyl]butyrate (6).** To a solution of **5**[17] (72.8 g, 0.39 mol) and freshly distilled chloromethyl phenyl sulfide[18] (73.0 g, 0.46 mol) in $CH_2Cl_2$ (800 mL) was added powdered anhydrous zinc bromide (1.7 g, 7.7 mmol). The reaction mixture was stirred for 2 d at rt, treated with saturated $NaHCO_3$ solution (100 mL) and distilled water (400 mL), and extracted several times with $CH_2Cl_2$. The combined organic layers were washed with brine (400 mL), dried, and concentrated. Distillation of the residue afforded 60.2 g (66%) of **6** as a faintly yellow oil, bp 118-120 °C at 0.1 Torr; IR (neat, $cm^{-1}$) 1725; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5 H), 3.66 (s, 3 H), 3.12-3.08 (m, 2 H), 2.46 (m, 1 H), 1.97 (septuplet, $J$ = 6.8 Hz, 1H), 0.95 (d, $J$ = 6.7 Hz, 3 H), 0.91 (d, $J$ = 6.7 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 174.2, 135.8, 130.2 (2 C), 128.9 (2 C), 126.4, 52.4, 51.4, 34.0, 30.6, 20.2, 19.9; MS *m/z* ($M^+$) calcd 238.1027, obsd 238.1040.

*Anal.* Calcd for $C_{13}H_{18}O_2S$; C, 65.51; H, 7.61. Found: C, 65.59; H, 7.60.

**3-Methyl-2-[(phenylthio)methyl]-1-butanol (7).** A cold (0 °C), mechanically stirred slurry of lithium aluminum hydride (5.6 g, 0.15 mol) in dry THF (1600 mL) was treated dropwise with a solution of **6** (50.0 g, 0.21 mol) in the same solvent (500 mL). After 5 h, the reaction mixture was quenched by careful sequential addition of water (5.6 g), 15% sodium hydroxide solution (5.6 g), and water (16.8 g), then filtered. The white solids were washed several times with ether and the combined organic solutions were concentrated to afford 43.4 g (97%) of **7** as a colorless oil. An analytical sample was prepared by MPLC on silica gel (elution with 20% ether in petroleum ether); IR ($CHCl_3$, $cm^{-1}$) 3610, 3540-3300, 1100; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.24-7.04 (m, 5 H), 3.65-3.59 (m, 2 H), 2.96 (dd, $J$ = 12.8, 4.8 Hz, 1 H), 2.83 (dd, $J$ = 12.8, 8.1 Hz, 1 H), 1.89 (br s, 1 H), 1.80-1.76 (m, 1 H), 1.52-1.48 (m, 1 H), 0.82 (d, $J$ = 6.7 Hz, 3 H), 0.81 (d, $J$ = 6.7 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 136.8, 128.9, 128.8 (2 C), 125.8 (2 C), 62.7, 46.1, 33.4, 28.1, 19.6 (2 C); MS *m/z* ($M^+$) calcd 210.1078, obsd 210.1074.

*Anal.* Calcd for $C_{12}H_{18}OS$: C, 68.52; H, 8.63. Found: C, 68.23; H, 8.68.

**3-Methyl-2-[(phenylsulfonyl)methyl]-1-butanol (8).** To a cold (0 °C), vigorously stirred solution of **7** (43 g, 0.204 mol) and benzeneselenenic acid (0.39 g, 2 mmol) in $CH_2Cl_2$ (200 mL) was added 30% hydrogen peroxide (70 g, 0.61 mol) dropwise. After the mixture had been stirred vigorously at rt for 60 h, the aqueous phase was separated and extracted several times with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHSO_3$ solution (2 x 100 mL) and brine (100 mL), dried, and concentrated to give **8** (48.5 g, 97%) as a colorless viscous oil; IR ($CHCl_3$, $cm^{-1}$) 3600-3300, 1310, 1150; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J$ = 7 Hz, 2 H), 7.63-7.52 (m, 3 H), 3.78 (dd, $J$ = 11.2, 5.0 Hz, 1 H), 3.64 (dd, $J$ = 11.2, 5.8 Hz, 1 H), 3.23 (dd, $J$ = 11.2, 8.1 Hz, 1 H), 3.04 (dd, $J$ = 14.3, 3.4 Hz, 1 H), 2.47 (s, 1 H), 2.02-1.98 (m, 1 H), 1.90 (septuplet, $J$ = 6.7 Hz, 1 H), 0.81 (d, $J$ = 6.7 Hz, 3 H), 0.79 (d, $J$ = 6.7 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 139.4, 133.7, 129.2 (2 C), 127.8 (2 C), 62.4, 55.5, 41.6, 28.9, 19.4, 18.9; MS *m/z* ($M^+$-$CH_2O$) calcd 212.0871, obsd 212.0903.

*Anal.* Calcd for $C_{12}H_{18}O_3S$: C, 59.48; H, 7.49. Found: C, 59.37; H, 7.51.

**3-Methyl-2-[(phenylsulfonyl)methyl]butyl Chloroacetate (9).** A solution of **8** (48 g, 0.20 mol), freshly distilled triethylamine (56 mL, 0.4 mol), and 4-(dimethylamino)pyridine (several crystals) in $CH_2Cl_2$ (400 mL) was treated slowly at 0 °C with chloroacetyl chloride (23.9 mL, 0.3 mol). After 6 h, the dark reaction mixture was diluted with ether (400 mL), filtered, and washed with 10% HCl (2 x 300 mL), saturated

$NaHCO_3$ solution (300 mL), and brine (300 mL). The resulting organic layer was dried and concentrated to leave a residue, purification of which by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) afforded 52 g (82%) of **9** as a very viscous, colorless oil; IR ($CHCl_3$, $cm^{-1}$) 1740, 1310, 1150; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.1 Hz, 2 H), 7.70-7.56 (m, 3 H), 4.32 (dd, *J* = 11.3, 5.6 Hz, 1 H), 4.24 (dd, *J* = 11.3, 5.7 Hz, 1 H), 4.02 (s, 2 H), 3.19-3.06 (m, 2 H), 2.29-2.20 (m, 1 H), 1.90 (septuplet, *J* = 6.8 Hz, 1 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 167.0, 139.4, 133.8, 129.3 (2 C), 127.9 (2 C), 65.4, 54.8, 40.7, 38.4, 28.6, 19.0, 18.9; MS *m/z* ($M^+$+1) calcd 319.0771, obsd 319.0809.

*Anal.* Calcd for $C_{14}H_{19}ClO_4S$: C, 52.74; H, 6.01. Found: C, 53.08; H, 6.04.

**Enzymatic Hydrolysis of 9 (65% Conversion Level).** A solution of **9** (690 mg, 2.16 mmol) in 150 mL of a 9:1 mixture of distilled water and pH 7 phosphate buffer and 1 mL of THF was stirred vigorously with 40 mg of lipase P30 (Amano). The pH of the reaction mixture was maintained at 7.0-7.1 by the addition of 0.1 N sodium hydroxide from a syringe pump interfaced with a pH controller. The progression of the reaction was stopped after 65% conversion (14.1 mL of 0.1 N NaOH added), which was achieved after a reaction time of 4 h. The reaction mixture was poured into a separatory funnel containing 200 mL of $CH_2Cl_2$. The combined organic layers were filtered through a pad of Celite, dried, and concentrated. Silica gel chromatography of the residue (elution with 20% ethyl acetate in petroleum ether) afforded 191 mg (80%) of (-)-**9** and 299 mg (88%) of (+)-**2**.

For (-)-**9**: colorless oil: $[\alpha]_D^{20}$ -14.2 (*c* 1.01, $CHCl_3$).

For (+)-**2**: colorless oil: $[\alpha]_D^{20}$ +9.4 (*c* 1.04, $CHCl_3$).

A solution of (-)-**9** (191 mg, 0.596 mmol) and 0.1 N NaOH solution (0.7 mL, 0.7 mmol) in 50 mL of 20% ethanol was stirred at 35-40 °C for 15 h, cooled to rt, and extracted several times with ether and $CH_2Cl_2$. The combined organic layers were dried and concentrated, and the residue was purified chromatographically (silica gel, elution with ether). There was obtained 136 mg (93%) of (-)-**2** as a viscous, colorless oil, $[\alpha]_D^{20}$ -16.3 (*c* 1.2, $CHCl_3$). Mosher ester analysis of this material indicated it to be 95% e.e.

**(*S*)-(-)-3-Methyl-2-[(phenylsulfonyl)methyl]butyl Phenyl Sulfide [(-)-11].** A solution of (-)-**2**, $[\alpha]_D^{20}$ -16.3 (*c* 1.2, $CHCl_3$) (5.9 g, 24 mmol) and diphenyl disulfide (15.9 g, 73 mmol) in dry dimethoxyethane (150 mL) was treated with tributylphosphine (18 mL, 73 mmol) and gently refluxed for 3 days. The cooled reaction mixture was concentrated in vacuo, diluted with $CH_2Cl_2$ (400 mL), and washed with 10% KOH solution (2 x 200 mL) and brine (200 mL). The aqueous layers were extracted with $CH_2Cl_2$ (2 x 100 mL) and the combined organic solutions were dried and evaporated. Purification of the residue by silica gel chromatography (elution with 15% ethyl acetate in petroleum ether) gave 7.5 g (91%) of (-)-**11** as a viscous colorless oil; IR ($CHCl_3$, $cm^{-1}$) 1320, 1150, 1090; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.0 Hz, 2 H), 7.54-7.09 (series of m, 8 H), 3.14 (dd, *J* = 14.5, 7.0 Hz, 1 H), 3.08 (dd, *J* = 14.5, 6.3 Hz, 1 H), 2.99 (m, 1 H), 2.90 (dd, *J* =13.3, 7.0 Hz, 1 H), 2.20-2.09 (m, 1 H), 1.97-1.89 (m, 1 H), 0.72 (d, *J* = 6.8 Hz, 3 H), 0.68 (d, *J* = 6.8 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 139.0, 135.3, 133.4, 129.8 (2 C), 129.0 (2 C), 128.8 (2 C), 127.8 (2 C), 126.2, 55.9, 38.6, 35.2, 27.8, 18.6, 17.8; MS *m/z* ($M^+$) calcd 334.1061, obsd 334.1058; $[\alpha]_D^{20}$ -10.1 (*c* 1.16, $CHCl_3$).

*Anal.* Calcd for $C_{18}H_{22}O_2S_2$: C, 64.33; H, 6.63. Found: C, 64.73; H, 6.58.

**(2*R*,3*S*)-4-Methyl-2-(phenylsulfonyl)-3-[(phenylthio)methyl]-1-pentanol (3).** Monomeric formaldehyde was prepared according to Schlosser, Jenny, and Guggisberg[19] from dry paraformaldehyde (6 g, 0.2 mol) and *p*-toluenesulfonyl anhydride (1 g, 3 mmol) in 250 mL of dry THF.

To a solution of LDA prepared at 0 °C from diisopropylamine (0.260 mL, 1.86 mmol) and 1.6 M *n*-butyllithium in hexanes (1.1 mL, 1.8 mmol) in dry THF (50 mL) was added at 0 °C a solution of (-)-**11** (477 mg, 1.43 mmol) in dry THF (20 mL). The yellow reaction mixture was stirred at 0-10 °C for 20 min, cooled to -78 °C, and treated with excess monomeric formaldehyde in THF (50 mL) via cannula. The solution was allowed to warm to 0 °C during 1 h, treated with saturated $NH_4Cl$ solution (80 mL), and extracted with ether (2 x 100 mL). The combined organic layers were dried, filtered, and concentrated, and the residue was purified by MPLC on silica gel (elution with 30% ethyl acetate in petroleum ether) to give 265 mg (50%) of pure (-)-**3**, along with 82 mg of a mixture of **3** and its diastereomer.

For (-)-**3**: colorless oil; IR ($CHCl_3$, $cm^{-1}$) 3550, 1300, 1250, 1145, 1085, 910; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.61-7.56 (m, 3 H), 7.46-7.27 (m, 7 H), 4.37 (ddd, *J* = 13, 8.5, 3.0 Hz, 1 H), 3.91 (ddd, *J* = 13, 10.5, 2.5 Hz, 1 H), 3.38 (dd, *J* = 13, 3.0 Hz, 1 H), 3.27 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1 H), 3.20 (dd, *J* = 10.5, 3.0 Hz, 1 H), 2.64 (dd, *J* = 13, 11 Hz, 1 H), 2.31 (d of septuplets, *J* = 7.0, 3.5 Hz, 1 H), 1.79 (dddd, *J* = 11, 3.5, 3.0, 1.0 Hz, 1 H), 0.80 (d, *J* = 7.0 Hz, 3 H), 0.38 (d, *J* = 7.0 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) ppm 136.7, 134.5, 134.0, 131.6 (2 C), 129.2 (2 C), 129.0 (2 C), 128.8 (2 C), 127.0, 65.5, 58.4, 40.5, 32.3, 27.1, 20.2, 16.5; MS *m/z* ($M^+$) calcd 364.1167, obsd 364.1168; $[\alpha]_D^{20}$ -140 (*c* 1.28, $CHCl_3$).

The racemic compound is a crystalline solid, mp 74-75.5 °C (from ether-petroleum ether, 1:6).

*Anal.* Calcd for $C_{19}H_{24}O_3S_2$: C, 62.60; H, 6.64. Found: C, 62.25; H, 6.64.

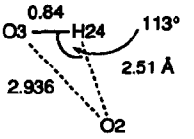
**X-Ray Crystallographic Analysis of (±)-3.** The data collection crystal had been cut from a much larger crystal. It is clear and colorless and in the form of a truncated rectangular pyramid. Examination of the diffraction pattern with a Rigaku AFC5S diffractometer indicated a monoclinic crystal system with systematic absences OkO, k = 2n+1 and hOl, h+l = 2n+1. The space group is uniquely determined as $P2_1/n$. The unit cell constants were obtained from a symmetry-restricted least-squares fit of the diffractometer setting angles for 25 reflections in the 2θ range 21 to 30° with MoKα radiation (λ(Kᾱ) = 0.71073 Å).

Intensities were measured by the ω scan method. Six standard reflections were measured after every 150 reflections and indicated that the crystal was stable throughout data collection. Data reduction was done with the TEXSAN package of crystallographic programs.[20] The data was corrected for absorption by the analytical method.[21]

The structure was solved with the direct methods procedure in SHELXS-86;[22] all the non-hydrogen atoms were located on an electron density map. Full-matrix least-squares refinements were performed in TEXSAN[20] and the function minimized was $\Sigma\omega(|F_o|-|F_c|)^2$ with $\omega = 1/\sigma^2(F_o)$. After anisotropic refinement, most of the hydrogen atoms were located on a difference electron density map. Hydrogen atoms are included in the model as fixed contributions at calculated positions based on C-H = 0.98 Å and $B_H$ = 1.2*Beq (attached carbon atom). Methyl group hydrogen atoms were idealized to $sp^3$ geometry based on positions found in the diffrence map. The hydroxyl hydrogen atom bonded to O(3) was initially fixed at its position from a difference map and then subsequently refined isotropically. The final refinement cycle was based on 2130 intensities with $I > 3\sigma(I)$ and 221 variables and resulted in agreement factors or R = 0.044 and $R_\omega$ = 0.048.

The final difference electron density map contains maximum and minimum peak heights of 0.22 and -0.22 e/Å$^3$. The scattering factors are from the International Tables for X-ray Crystallography.[23]

There is an intramolecular bond between O(2) and O(3) which has the following metrical parameters:




**(2*R*,3*S*)-Trimethyl[4-methyl-2-(phenylsulfonyl)-3-[(phenylthio)methyl]pentyl]silane (12).** To an LDA solution prepared at 0 °C from diisopropylamine (0.27 mL, 1.94 mmol) and 1.6 M *n*-butyllithium in hexanes (1.1 mL, 1.7 mmol) in dry THF (20 mL) was added at 0 °C a solution of (-)-**11** (500 mg, 1.50 mmol) in dry THF (10 mL). The resulting yellow solution was stirred at 0 °C for 15 min, cooled to -78 °C, and treated slowly with freshly purified iodomethyltrimethylsilane (0.8 mL, 5.4 mmol). The reaction mixture was warmed to -10 °C during 1-2 h, maintained at this temperature for 3 h, and quenched with saturated $NH_4Cl$ solution (30 mL). The aqueous layer was extracted with ether (2 x 100 mL) and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (elution with 8% ethyl acetate in petroleum ether) gave 466 mg (74%) of pure (-)-**12** and 70 mg (11%) of a mixture of **12** and its diastereomer.

For **12**: colorless oil; IR ($CHCl_3$, cm$^{-1}$) 1250, 1150, 1085, 850; $^1$H NMR (300 MHz, $C_6D_6$) δ 7.64-7.60 (m, 2 H), 7.47-7.42 (m, 2 H), 7.07-7.00 (m, 2 H), 6.95-6.79 (m, 4 H), 3.78 (dd, *J* = 13.5, 5.2 Hz, 1 H), 3.48 (ddd, *J* = 9.0, 4.5, 1.5 Hz, 1 H), 2.74 (dd, *J* = 13.5, 9.0 Hz, 1 H), 2.28-2.18 (m, 1 H), 1.86-1.80 (m, 1 H), 1.21 (dd, *J* = 16.5, 9.0 Hz, 1 H), 0.78 (dd, *J* = 16.5, 4.5 Hz, 1 H), 0.59 (d, *J* = 6.9 Hz, 3 H), 0.55 (d, *J* = 6.9 Hz, 3 H), 0.08 (s, 9 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 138.0, 135.7, 133.3, 130.4 (2 C), 128.9 (4 C), 128.7 (2 C), 126.4, 59.7, 43.6, 32.7, 27.3, 20.1, 19.3, 11.9, -0.6 (3 C); MS *m/z* ($M^+$) calcd 420.1613, obsd 420.1620; $[\alpha]_D^{20}$ -77 (*c* 1.34, $CHCl_3$).

*Anal.* Calcd for $C_{22}H_{32}O_2S_2Si$: C, 62.81; H, 7.67. Found: C, 62.62; H, 7.62.

**2-Methyl-2-[(3*S*,4*S*)-5-methyl-3-(phenylsulfonyl)-4-[(phenylthio)methyl]hexyl]-1,3-dioxolane (13).** A 1.0 g (3 mmol) sample of (-)-**11** was deprotonated with LDA as described above and treated with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane (2.2 g, 9 mmol). After the reaction mixture had stirred for 6 h at rt, the usual workup provided a gummy residue that was purified by MPLC (silica gel, elution with 20% ethyl acetate in petroleum ether). There was isolated 1.07 g (79%) of (-)-**13** as a very viscous colorless oil; IR ($CHCl_3$, cm$^{-1}$) 1290, 1200, 1140, 1050; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.64-7.22 (series of m, 10 H), 3.94-3.81 (m, 4 H), 3.39 ( dd, *J* = 13, 3.9 Hz, 1 H), 3.05 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1 H), 2.80 (dd, *J* = 13, 10 Hz, 1 H), 2.24-2.19 (m, 1 H), 2.08-1.98 (m, 2 H), 1.95-1.89 (m, 1 H), 1.83-1.62 (m, 2 H), 1.26 (s, 3 H), 0.80 (d, *J* = 6.9 Hz, 3 H), 0.60 (d, *J* = 6.9 Hz, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 138.1, 135.6, 133.4, 130.9, 129.0 (2 C), 128.9 (2 C), 128.8 (2 C), 126.6 (2 C), 109.2, 64.6 (2 C), 63.4, 42.3, 38.2, 33.0, 27.8, 23.6, 20.5, 19.7, 18.0; MS *m/z* ($M^+$) calcd 448.1742, obsd 448.1764; $[\alpha]_D^{20}$ -83 (*c* 1.26, $CHCl_3$).

*Anal.* Calcd for $C_{24}H_{32}O_4S_2$: C, 64.25; H, 7.19. Found: C, 63.93; H, 7.25.

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