S-(+)-5-(Phenylthio)-2-pentanol and S-(+)-4-(Phenylthio)-2-butanol: Readily Prepared, Useful Additions to the Chirality Pool. Highly Enantioselective Syntheses of Naturally Occurring Spiroketal Pheromones

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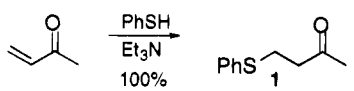
The new chirons (*S*)-4-(phenylthio)-2-butanol (**4**) and (*S*)-5-(phenylthio)-2-pentanol (**3**) have been prepared efficiently in high enantiomeric excess by enzymatic reduction of the corresponding readily available ketones. Using the latter as a chiral building block, the highly optically enriched insect pheromonal components (5*S*,7*S*)-7-methyl-1,6-dioxaspiro[4.5]decane (**7**), (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.5]undecane (**8**), and (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.6]dodecane (**9**) have been synthesized in one pot by sequential deprotonation, reductive lithiation, transmetalation with cerium(III) chloride, treatment with lactones, and acidification.

Herein, we outline two-pot syntheses of *S*-(+)-5-(phenylthio)-2-pentanol (**3**) and *S*-(+)-4-(phenylthio)-2-butanol (**4**), and we demonstrate one of a variety of conceivable uses, the one-pot conversions of **3** to three spiroketal insect pheromones. Because of the enormous versatility of organosulfur compounds in chemistry,[1] these simple, readily generated, highly enantiomerically enriched alcohols bearing divalent sulfur should be valuable additions to the chirality pool;[2] not only is divalent sulfur extremely useful in its own right, but it is easily oxidized to sulfoxides and sulfones.

The phenylthio ketones which are immediate precursors of the chiral phenylthio alcohols were prepared efficiently by conjugate additions to methyl vinyl ketone (MVK). In the case of 4-(phenylthio)-2-butanone (**1**), the conjugate addition of thiophenol occurred in quantitative yield (eq 1).[3] In the case of 5-(phenylthio)-2-pentanone

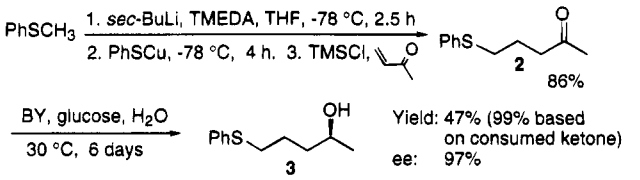


(1)

(**2**), the easily prepared mixed cuprate, derived from thioanisole by lithiation using *sec*-butyllithium in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) followed by the addition of cuprous thiophenoxide, undergoes efficient conjugate addition in the presence of trimethylsilyl chloride (TMSCl)[4] (Scheme 1).

A thorough literature survey indicated that most readily available chirally modified hydride reagents fail to give good enantioselectivity in the reduction of dialkyl ketones that do not possess considerable steric or electronic bias.[5] Masamune's borolane is a better choice, but the lengthy synthesis of the chiral ligand makes the method less practical.[6] The literature on enzymatic catalysis was more encouraging.[7] The exploitation of baker's yeast (BY)-mediated reduction is one of the best documented procedures because it is cheap, versatile, easy to perform, and frequently gives high enantiomeric excesses (ee).[8] Many ketones with varying substituents have been reduced by BY and the secondary alcohols obtained were predominately *S*-configured according to Prelog's Rule.[9] This prompted our use of BY to reduce ketones **1** and **2**. To our delight, **3** was obtained with ≥97% ee in a simple operation in which BY, ketone **2**, and glucose were suspended in water and allowed to ferment for 6 days (Scheme 1). The optical purity of **3** was determined by ^1H and ^{19}F NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester).[10] Evidence for the *S*-configuration is given below. While the yield was only 47%, almost all of the unreacted starting material **2** was recovered easily so that the yield based on consumed **2** is 99%.

Scheme 1



Ketone **1** was reduced under the same conditions to provide (*S*)-4-(phenylthio)-2-butanol (**4**) in 95% ee but in considerably lower yield (22%; 26% based on consumed ketone **1**) (Table 1, entry 2). We surmised that the major cause of this poor result is that the acidity of the reaction mixture, due to the evolution of carbon dioxide, induced β-elimination of thiophenoxide from **1**. Indeed, pH

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(2) Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optical Active Compounds*; Marcel Dekker: New York, 1993; p 143.

(3) Cherkauskas, J. P.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 6.

(4) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

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(7) For a recent review on enzymatic reductions, see: Jones, J. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 183.

(8) For recent reviews on BY-mediated reactions, see: Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49. Servi, S. *Synthesis* **1990**, 1.

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(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

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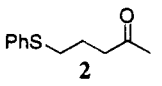
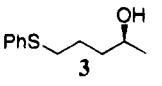
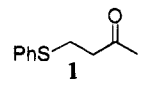
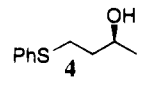
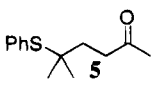
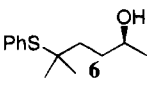
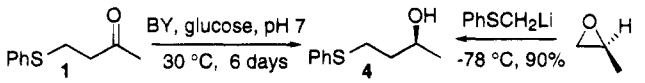
Table 1. Baker's Yeast-Mediated Asymmetric Reduction

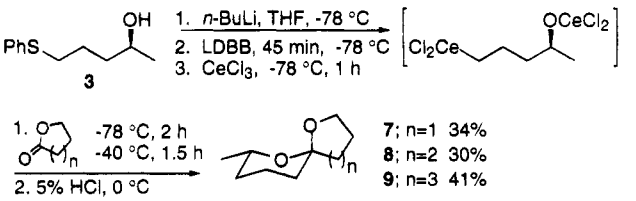
Entry	Ketone	Alcohol	pH	ee (%)	Yield (%)[a]	Conversion (%)[b]
1	 2	 3	uncontrolled	97	99	47
2	 1	 4	uncontrolled	95	26	22
3	1	4	6.0	95	52	32
4	1	4	7.0	96	70	41
5	1	4	8.0	96	40	32
6	 5	 6	uncontrolled	74	36	17

[a] Yields based on consumed starting materials. [b] Moles of product alcohol/moles of ketone used.

Scheme 2



Scheme 3



controlled experiments showed that a satisfying yield could be achieved under neutral conditions (Table 1, entry 4), while slightly acidic or basic conditions gave inferior yields (Table 1, entry 3 and 5). The *S*-configuration of **4** was originally surmised by analogy as well as the near identity of the ^{19}F spectra of the Mosher's esters of **3** and **4**; proof of this configuration was obtained by treatment of (*S*)-(−)-propylene oxide with the lithio derivative of thioanisole (Scheme 2).[11]

5-Methyl-5-(phenylthio)-2-hexanone (**5**), also prepared[12] by conjugate addition of a sulfur-stabilized cuprate to MVK, is reduced to **6** in low yield and inferior optical purity (Table 1, entry 6). It is reasonable to speculate that the bulky end group in **5** impedes its binding with the yeast alcohol dehydrogenase (YADH), the enzyme that catalyzes the desired asymmetric reduction. Other enzymes may thus intervene to transform the starting material to the *R*-isomer of **6** and other intractable products which might account for the low yield and low ee.[13]

Scheme 3 demonstrates one-pot conversions of **3** to the insect pheromones (5*S*,7*S*)-7-methyl-1,6-dioxaspiro[4.5]-decane (**7**), (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.5]undecane (**8**), and (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.6]dodecane (**9**) using a recently revealed strategy.[14-16] The preference for the methyl substituent to reside in the equatorial position coupled with oxygen anomeric effects controls the absolute configuration at the spirocenter.[17] The absolute configuration of **7** from natural sources is known[18] but those of **8** and **9** are not.[19]

The expected *S* absolute configuration of **3** was confirmed by comparing the signs of the optical rotations of the spiroketals **7** and **9** derived from it to those reported for synthetic samples of known absolute configuration.[20,21] The absolute configuration of our synthetic 7-methyl-1,6-dioxaspiro[4.5]decane (**7**) is the same as that from natural sources. The measured value for the enantiomeric excess of **3** (≥97% ee) is consistent with the optical purity of the derived **9** which was measured to be 97.8% ee by comparing its optical rotation with the literature value of an enantiopure synthetic sample.[21a] The synthetic samples of **7**−**9** exhibited all of the ^1H, ^{13}C NMR, IR, and mass spectral characteristics of the natural products.[20-22]

In conclusion, a two-pot synthetic process has been

(11) The preparation of **4** from (*S*)-(−)-propylene oxide is inferior to our method because of its high expense and volatility, the difficulty in drying it, and its potential carcinogenicity.

(12) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1994**, *50*, 12793.

(13) Zhou, B.-N.; Gopalan, A. S.; VanMiddlesworth, F.; Shieh, W.-R.; Sih, C. J. *J. Am. Chem. Soc.* **1983**, *105*, 5925. Shieh, W.-R.; Gopalan, A. S.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2993.

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(15) For a review on the chemistry and synthesis of spiroketal-containing natural products, see: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(16) For recent reviews on spiroketal synthesis, see: Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley Interscience: New York, 1992; Vol. 8, p 553. Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley Interscience: New York, 1992; Vol. 9, p 444.

(17) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

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(19) Francke, W. Personal communication. Mori, K. Personal communication.

(20) For previous syntheses of **7**, see: Hintzer, K.; Weber, R.; Schurig, V. *Tetrahedron Lett.* **1981**, *22*, 55. Jacobson, R.; Taylor, R. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140, and ref 18b.

(21) Leading references to asymmetric syntheses of **9**: (a) Mori, K.; Katsurada, M. *Liebigs Ann. Chem.* **1984**, 157. (b) Nakamura, K.; Kitayama, T.; Inoue, Y.; Ohno, A. *Tetrahedron* **1990**, *46*, 7471. (c) Solladié, G.; Almario, A.; Colobert, F. *Synlett* **1992**, 167.

(22) To the best of our knowledge, no asymmetric synthesis of **8** has ever been reported. For syntheses in racemic form, see: Ley, S. V.; Lygo, B.; Sternfeld, F.; Wonnacott, A. *Tetrahedron* **1986**, *42*, 4333, and ref 17.

demonstrated whereby highly optically enriched spiroketals can be prepared in a rather unified approach which features an enzymatic reduction of a phenylthio-substituted ketone to an enantiomerically enriched alcohol **3** and its one-pot conversions to the spiroketals **7**–**9** as key steps. Despite the relatively low yields in the spirocyclization steps, an unexplained phenomenon as well in all previous asymmetric syntheses of the same targets, these syntheses appears to be the most efficient ever reported. They require only three steps and produce ~30% overall yields of compounds **7**–**9** with high enantioselectivity from commercially available, nonchiral starting materials. Other synthetic applications of chirons **3** and **4** will be reported in due course.

Experimental Section

General Methods. Low and high resolution mass spectra were recorded in EI mode at 70 eV. Optical rotations were obtained as solutions in a 1-dm cell. Silica gel 60 (40–60 μm, E. Merck) was used for flash chromatography.[23] Baker's yeast (type II) and D-(+)-glucose were purchased from Sigma. All other commercially available chemicals were purchased from Aldrich. The preparation of lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[24] and cerium(III) chloride suspension in THF have been described previously.[14c] In the reductive lithiations, nominal concentrations of 0.4 M of LDBB were used. The actual concentrations were always somewhat less due to reaction of lithium metal or the radical anion with moisture. Between 2.1 and 2.5 molar equiv of reducing agent were used depending on the relative humidity of the atmosphere during the reaction. The exact concentrations of *n*-BuLi and *sec*-BuLi were determined by titration with diphenylacetic acid.[25]

4-(Phenylthio)-2-butanone (1). A solution of thiophenol (5.3 mL, 50 mmol) and triethylamine (0.6 mL, 4 mmol) in dry THF (10 mL) was cooled to 0 °C prior to the slow addition of methyl vinyl ketone (3.4 mL, 40 mmol). After being warmed to rt, the reaction mixture was stirred for 18 h under argon, diluted with ether (40 mL), and washed with 5% NaOH (3 × 20 mL), 1 N HCl (10 mL), 5% $NaHCO_3$ (10 mL), and brine (2 × 10 mL). After the organic layer was dried and the solvent was removed by rotary evaporation, the crude oily product was purified by flash chromatography (10% ethyl acetate/hexanes, R_f 0.22) to yield 7.19 g (100%) of the title product **1**: IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.40 (m, 5 H), 3.10 (t, J = 7.2 Hz, 2 H), 2.72 (t, J = 7.2 Hz, 2 H), 2.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.4, 135.6, 129.2, 128.9, 126.1, 42.8, 29.9, 27.2; MS (EI) m/z (relative intensity) 180 (M^+, 100), 137 (42), 110 (95); HRMS (EI) calcd for $C_{10}H_{12}OS$ 180.0609, found 180.0607.

5-(Phenylthio)-2-pentanone (2). A solution of thioanisole (1.1 mL, 10 mmol) and TMEDA (3.8 mL, 25 mmol) in THF (40 mL) was stirred at −78 °C as *sec*-BuLi (7.2 mL, 1.45 M in cyclohexanes, 10 mmol) was slowly added. After 2.5 h, cuprous thiophenoxide (2.29 g, 13.0 mmol) was added to the yellow organolithium solution, and the resulting mixture was stirred for 4 h at −78 °C. TMSCl (1.68 mL, 13.0 mmol) was added followed by dropwise addition of methyl vinyl ketone (1.00 mL, 12.0 mmol). After being stirred at −78 °C for 12 h, the mixture was warmed to rt, quenched with 5% NaOH solution (40 mL) and 40% aqueous tetrabutylammonium hydroxide (5 drops), filtered through Celite, and extracted with ether (3 × 50 mL). The organic layer was washed successively with 5% HCl (2 × 10 mL) and brine (3 × 15 mL), dried, and concentrated by rotary evaporation. Purification by flash chromatography (10% ethyl acetate/hexanes, R_f 0.2) afforded 1.69 g (86%) of **2** as a pale yellow oil: IR (neat) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H), 2.94 (t, J = 7.0 Hz, 2 H), 2.60 (t, J = 7.0 Hz, 2 H), 2.13 (s, 3 H), 1.91 (quintet, J = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 208.1, 136.1, 129.2, 129.0, 126.0, 41.9, 32.9, 30.1, 22.9; MS (EI) m/z (relative intensity) 194 (M^+, 30), 123 (14), 110 (15), 43 (100); HRMS (EI) calcd for $C_{11}H_{14}OS$ 194.0765, found 194.0750.

(*S*)-5-(Phenylthio)-2-pentanol (3). Baker's yeast (60.0 g), D-(+)-glucose (1.50 g), sterile water (120 mL, filtered through Nalgene filterware), and ketone **2** (1.25 g, 6.45 mmol) in an autoclaved (120 °C, 15 atm, 30 min) 1000 mL Erlenmeyer flask were mixed carefully and shaken mildly at 30 °C in an incubator for 6 d. The resulting slurry was diluted with ethyl acetate (100 mL) and centrifuged at 10 000 rpm for 10 min. The supernatant was collected. The residue was washed with ethyl acetate (50 mL) and centrifuged again. The combined supernatant was washed successively with water (2 × 20 mL) and brine (20 mL) and dried. The solvent was removed by rotary evaporation. Purification by flash chromatography afforded 0.65 g (52%) of unreacted **2** (10% ethyl acetate/hexanes, R_f 0.20) and 0.60 g (47%) of the title compound **3** (25% ethyl acetate/hexanes, R_f 0.10) as a colorless oil: $[\alpha]^{23}_D$ = +3.2° (c = 1.58, $CHCl_3$, α = +5.0°); IR (neat) 3364 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14–7.34 (m, 5 H), 3.78–3.84 (m, 1 H), 2.95 (t, J = 7.1 Hz, 2 H), 1.66–1.84 (m, 2 H), 1.55–1.64 (m, 2 H), 1.34 (s, 1 H), 1.19 (d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.7, 129.1, 129.0, 125.9, 67.7, 38.2, 33.7, 25.5, 23.7; MS (EI) m/z (relative intensity) 196 (M^+, 50), 123 (64), 110 (100); HRMS (EI) calcd for $C_{11}H_{16}OS$ 196.0922, found 196.0912.

The MTPA ester of **3** was prepared as follows. A mixture of (*R*)-(−)-MTPA chloride (38.6 mg, 0.15 mmol), **3** (18.6 mg, 0.095 mmol), pyridine (0.3 mL), and CCl_4 (0.3 mL) was stirred at room temperature for 18 h. To this mixture was added *N,N*-dimethylethylenediamine (19 mg, 0.22 mmol), and the mixture was stirred for additional 5 min and diluted with ether (2 mL). The organic solution was washed with 1 N HCl (2 mL), saturated $NaHCO_3$ solution (2 mL), and brine (2 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation. Purification by flash chromatography (5% ethyl acetate/hexanes, R_f 0.20) afforded 35.3 mg (90%) of MTPA ester as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.10–7.55 (m, 10 H), 5.17–5.20 (m, 1 H), 3.49 (s, 3 H), 2.90 (t, J = 6.8 Hz, 2 H), 1.60–1.88 (m, 4 H), 1.24 (d, J = 6.3 Hz, 3 H). The MTPA ester derived from (±)-5-(phenylthio)-2-pentanol displays two sets of signals due to the OCH_3 (s, δ 3.49, δ 3.53, 1:1 peak area), SCH_2 (t, δ 2.83, J = 7.0 Hz; δ 2.90, J = 6.8 Hz, 1:1 peak area) and CH_3 (d, δ 1.24, J = 6.4 Hz; δ 1.33, J = 6.2 Hz, 1:1 peak area) protons. In the spectrum of the MTPA ester obtained from **3** only single sets of these signals were observed, and thus it is diastereomerically pure within the limit of the ^1H NMR accuracy. ^{19}F NMR shows two peaks for MTPA ester derived from the corresponding racemic alcohol (δ −71.94, δ −71.88, 1:1 peak area). ^{19}F NMR spectrum of the MTPA ester of **3** shows a major peak at δ −71.88 and a very minor peak at δ −71.94. The peak ratio was ≥60 and thus the optical purity of **3** should be no less than 97% ee.

(*S*)-4-(Phenylthio)-2-butanol (4) by Enzymatic Reduction. Baker's yeast (60.0 g), D-(+)-glucose (1.50 g), pH = 7.0 buffer (120 mL, 50 mM of tris(hydroxymethyl)aminomethane adjusted with HCl, filtered through Nalgene filterware) and ketone **1** (1.15 g, 6.36 mmol) were allowed to ferment under the same condition described for the synthesis of **3**. After workup, purification by flash chromatography afforded 0.47 g (41%) of unreacted **1** (20% ethyl acetate/hexanes, R_f 0.39) and 0.48 mg (41%) of the title compound **4** (20% ethyl acetate/hexanes, R_f 0.20) as a colorless oil: $[\alpha]^{23}_D$ = +26.8° (c = 1.34, $CHCl_3$, α = +35.8°); IR (neat) 3374 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–7.40 (m, 5 H), 3.90–4.05 (m, 1 H), 2.90–3.15 (m, 2 H), 1.70–1.90 (m, 3 H), 1.22 (d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.3, 129.0, 129.0, 125.9, 67.0, 38.0, 30.1, 23.6; MS (EI) m/z (relative intensity) 182 (M^+, 80), 123 (38), 110 (100); HRMS (EI) calcd for $C_{10}H_{14}OS$ 182.0765, found 182.0765. The optical purity was determined to be 96% ee by the ^{19}F NMR spectrum of the corresponding MTPA ester.

(*S*)-4-(Phenylthio)-2-butanol (4) from (*S*)-(−)-Propylene Oxide. A solution of thioanisole (1.1 mL, 10 mmol) and TMEDA (3.8 mL, 25 mmol) in THF (20 mL) was stirred at −78 °C as *sec*-BuLi (7.6 mL, 1.45 M in cyclohexanes, 11 mmol) was slowly added. After 2.5 h, (*S*)-(−)-propylene oxide

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(24) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784.
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(1.0 mL, 14 mmol) was added and the mixture was stirred for 12 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), extracted with ether (3 × 25 mL), and dried over $MgSO_4$. Concentration, followed by flash chromatography (20% ethyl acetate/hexanes, R_f 0.20) gave 1.64 g (90%) of the title compound **4**. The specific optical rotation and all other spectra were identical with the same compound prepared by baker's yeast-mediated reduction.

(*S*)-5-Methyl-5-(phenylthio)-2-hexanol (6). Baker's yeast (40.0 g), D-(+)-glucose (1.00 g), sterile water (80 mL, filtered through Nalgene filterware) and ketone **5** (902 mg, 4.06 mmol) were allowed to ferment under the same condition described for the synthesis of **3**. After workup, purification by flash chromatography afforded 471 mg (52%) of unreacted **5** (20% ethyl acetate/hexanes, R_f 0.48) and 157 mg (17%) of the title compound **6** (20% ethyl acetate/hexanes, R_f 0.22) as a colorless oil: $[\alpha]^{23}_D$ = −1.4° (*c* = 0.845, $CHCl_3$, α = −1.2°); IR (neat) 3382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.60 (m, 5 H), 3.60−3.80 (m, 1 H), 1.00−1.70 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 137.5, 132.2, 128.7, 128.5, 68.5, 49.1, 38.3, 34.4, 29.0, 28.8, 23.7; MS (EI) *m*/*z* (relative intensity) 224 (M^+, 65), 110 (82); HRMS (EI) calcd for $C_{13}H_{20}OS$ 224.1234, found 224.1236. The optical purity was determined to be 74% ee by the ^{19}F NMR spectrum of the corresponding MTPA ester.

(5*S*,7*S*)-7-Methyl-1,6-dioxaspiro[4.5]decane (7). *n*-BuLi (0.60 mL, 1.45 M in hexanes, 0.87 mmol) was added dropwise to a solution of **3** (169 mg, 0.86 mmol) in THF (5 mL) at −78 °C, and the mixture was stirred for 15 min at the same temperature to generate the lithium alkoxide. A preformed solution of LDBB (2.0 mmol) in THF (6 mL) was cooled to −78 °C. The lithium alkoxide solution was cannulated to LDBB. The resulting red brown solution was stirred for 45 min at −78 °C. A preformed $CeCl_3$ (894 mg of $CeCl_3 \cdot 7H_2O$, 2.4 mmol) suspension in THF (10 mL) was cooled to −78 °C and then cannulated to the solution of δ-lithioalkoxide. After the resulting orange red mixture had been stirred for 1 h, γ-butyrolactone (0.10 mL, 1.9 mmol) was added. The mixture was stirred for 2 h at −78 °C and then at −40 °C for 1.5 h. The reaction was quenched with 5% HCl (20 mL) at 0 °C and extracted with ether (4 × 20 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over $MgSO_4$, and concentrated by rotary evaporation. Purification by flash chromatography on silica gel (2% ethyl acetate/hexanes with ca. 0.2% triethylamine, R_f 0.18) afforded 53 mg (34%) of **7** as a colorless oil: $[\alpha]^{23}_D$ = −92.9° (*c* = 0.59, pentane, α = −54.8°); IR (neat) 1385, 1217, 1163, 1082, 1042, 997, 963 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 −3.92 (m, 3 H), 2.10−1.13 (m, 10 H), 1.11 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 106.0, 66.8, 66.5, 38.0, 32.9, 32.7, 23.8, 22.1, 20.5; MS (EI) *m*/*z* (relative intensity) 156 (M^+, 10); HRMS (EI) calcd for $C_9H_{16}O_2$ 156.1150, found 156.1156.

(2*S*,6*R*)-2-Methyl-1,7-dioxaspiro[5.5]undecane (8). **8** (45 mg, 30%) was prepared from the reaction of **3** (173 mg, 0.822 mmol) with δ-valerolactone (0.18 mL, 2.0 mmol) using the procedure described above for the synthesis of **7**. **8**: $[\alpha]^{23}_D$ = −66.1° (*c* = 0.73, pentane, α = −48.2°); IR (neat) 1385, 1231, 1213, 1206, 1182, 1096, 1063, 1048, 997, 964, 897 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55−3.77 (m, 3 H), 1.73−1.95 (m, 2 H), 1.25−1.65 (m, 10 H), 1.15 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 95.6, 65.2, 60.3, 35.8, 35.2, 32.7, 25.4, 21.9, 18.9, 18.6; MS (EI) *m*/*z* (relative intensity) 170 (M^+, 20), 98 (100); HRMS (EI) calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1299.

(2*S*,6*R*)-2-Methyl-1,7-dioxaspiro[5.6]dodecane (9). **9** (110.3 mg, 41%) was prepared from the reaction of **3** (408 mg, 2.08 mmol) with ε-caprolactone (0.17 mL, 1.5 mmol) using the same procedure described above for the synthesis of **7**. **9**: $[\alpha]^{23}_D$ = −102.7° (*c* = 1.045, pentane, α = −107.3°); IR (neat) 1202, 1096, 1055, 1038, 1005, 959 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71−3.85 (m, 2 H), 3.53−3.70 (m, 1 H), 1.27−1.86 (m, 14 H), 1.13 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 100.5, 66.0, 61.3, 41.9, 35.0, 33.0, 30.7, 30.0, 22.6, 22.1, 19.3; MS (EI) *m*/*z* (relative intensity) 184 (M^+, 14); HRMS (EI) calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1456.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **1**−**4**, **6**−**9** (16 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 ACS; see any current masthead page for ordering information.

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