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Applications of Highly Enantioenriched Alcohols Bearing a Phenylthio Group in the Preparation of Ring Compounds. The Two-Pot Synthesis of an Enantiopure Spiroacetal Pheromone Bearing Three Chiral Centers

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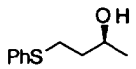
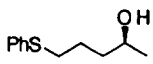
Abstract: The new chiron (*S*)-6-phenylthio-2-hexanol (**3**) was prepared in high enantiomeric excess by baker's yeast reduction of the corresponding ketone. Enantioenriched alcohols **1, 2** and **3**, prepared previously by a similar procedure, or their racemic counterparts, were transformed into ring closed compounds 5-methyl-2-(phenylthio)tetrahydrofuran (**9**), 6-methyl-2-(phenylthio)tetrahydropyran (**10**), 2-methyl-1-phenylsulfonyl cyclopropane (**14**), cyclobutane (**15**), cyclopentane (**16**), and a bee pheromone, (2S,6R,8S)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**20**). © 1997 Elsevier Science Ltd.

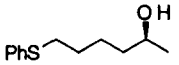
Because there is a variety of methods of producing simple enantioenriched alcohols and because of the great versatility of organosulfur compounds in synthesis and their ease of preparation, simple, readily generated, highly enantiomerically enriched compounds bearing divalent sulfur should be very valuable additions to the chirality pool.[1] A previous publication from this laboratory described the efficient preparation of two highly enantioenriched chirons, (*S*)-4-phenylthio-2-butanol (**1**) and (*S*)-5-phenylthio-2-pentanol (**2**), by baker's yeast (BY) reduction of the corresponding ketones, themselves prepared by conjugate addition of thiophenol or the cuprate derived from (phenylthio)methyllithium to methyl vinyl ketone.[2] The conversion of (S)-**2** to three spiroacetal pheromones, at least one of which was in its natural enantiomeric state, was also outlined. In the present paper, we describe the preparation by a related method of a homologue, (S)-**3**, of (S)-**1** and -**2** and methods that can be used for the conversion of (S)-**1**-**3** to highly enatioenriched cyclic synthons as well as a virtually enantiomerically pure spiroacetal bee pheromone possessing three chiral centers.



(S)-1

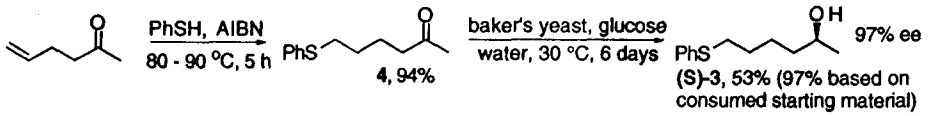


(S)-2



(S)-3

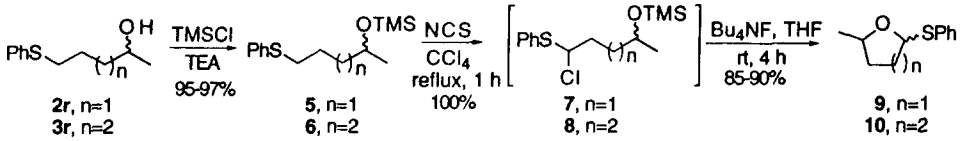
Scheme 1 outlines the efficient two-pot synthesis of the highly optically enriched alcohol (*S*)-6-phenylthio-2-hexanol (**3**). By the free-radical addition[3] of thiophenol to the commercially available 5-hexene-2-one, 6-phenylthio-2-hexanone (**4**) was obtained in exceptionally high yield and it was submitted to baker's yeast reduction to give the alcohol **3** in nearly quantitative yield based on consumed ketone and in very high ee. The optical purity of the **3** was determined by ^{1}H and ^{19}F NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester).[4] While the absolute configuration of **3** has not been determined, it is safe to assume that, like its lower homologues and many other secondary alcohols that have been produced by BY reduction of ketones,[5] it is of the *S* configuration.



Scheme 1

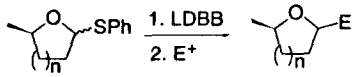
To demonstrate the utility of these new chirons, alcohols **1, 2 and 3** or their racemic counterparts **1r, 2r** and **3r**[6] were submitted to two series of ring closure reactions. Finally, the two-pot high yield synthesis from **2** of a virtually enantiopure spiroacetal pheromone bearing three chiral centers is described.

Firstly, the racemic counterparts, **2r** and **3r**, of the alcohols **2** and **3** were transformed into 5-methyl-2-(phenylthio)tetrahydrofuran (**9**) and 6-methyl-2-(phenylthio)tetrahydropyran (**10**), respectively, by a highly efficient reaction sequence. This consisted of protecting the hydroxyl group by silylation with trimethylsilyl chloride (TMSCl), chlorinating the α-carbon atom of the thioether with N-chlorosuccinimide (NCS),[3b,7] and, without isolation of the chlorination product, one-step deprotection and intramolecular substitution (Scheme 2). Direct chlorination of the phenylthio alcohol **2r** followed by base mediated intramolecular substitution of chlorine with oxygen was tried but it failed to give the desired product **9**. It is reasonable to assume that chlorination was unsuccessful because of the hydroxyl oxygen attacking the sulfur atom of the S-chlorosulfonium ion intermediate.[8] However, protecting the hydroxyl groups of **2r** and **3r** as trimethylsilyl ethers **5** and **6**, followed by chlorination and desilylation produced the target molecules **9** and **10** in satisfactory yields. Thus, a remarkable improvement was made in the chlorination step after the protection of the hydroxyl groups. NMR analysis of the crude products of the chlorination steps indicated that the chlorinated silyl ethers **7** and **8** were produced quantitatively in very pure form. Cleavage of the silyl groups with tetrabutylammonium fluoride directly gave the ring-closed products **9** and **10** as roughly 1 : 1 mixtures of trans and cis isomers.



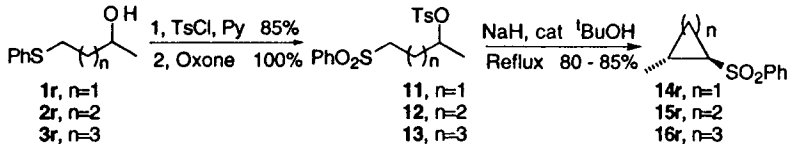
Scheme 2

Obviously, the non-racemic alcohols (S)-5-phenylthio-2-pentanol (**2**) and (S)-6-phenylthio-2-hexanol (**3**) can be converted to (5S)-5-methyl-2-(phenylthio)tetrahydrofuran (**9a**) and (6S)-6-methyl-2-(phenylthio)tetrahydropyran (**10a**) in the same manner. Considering their chirality and the huge versatility of sulfur, chiral synthons **9a** and **10a** should find extensive use in the syntheses of molecules of high enantiomeric purity. For an example, they can be reductively lithiated[9] by lithium 4,4'-di-*tert*-butylbiphenylide[10] or other aromatic radical-anions and treated with electrophiles to give various nonracemic molecules (eq 1). This procedure is particularly useful in the tetrahydropyran series since the stereochemistry of substituted 2-lithiotetrahydropyrans generated in this way usually can be controlled.[9b,11]



(1)

Secondly, the racemic counterparts of alcohols **1**, **2** and **3** (**1r**, **2r** and **3r**) were efficiently transformed into a cyclopropane, a cyclobutane and a cyclopentane, respectively by sulfone-mediated bond formation. Compared with divalent sulfur, a sulfone group is better at stabilizing an adjacent carbanion.[12] If the hydroxyl group in any of the alcohols discussed could be converted to a better leaving group, a sulfone-stabilized carbanion would undergo an intramolecular attack to give a cyclic product.[13] Based on these considerations, alcohols **1r**, **2r** and **3r** were converted to the corresponding tosylates which were oxidized to the sulfones **11**, **12** and **13**. While various oxidizing reagents can be employed to convert a sulfide to a sulfone,[14] in our case, Oxone ($KHSO_5$, $KHSO_4$, K_2SO_4 mixture)[15] proved to be ideal, conveniently providing sulfones in quantitative yields. Subsequent deprotonation of the sulfonyl tosylates **11**, **12** and **13** by sodium hydride, in the presence of a catalytic amount of *t*-butyl alcohol as a proton carrier, allowed facile ring closure to afford 2-methyl-1-phenylsulfonylcyclopropane (**14**), -cyclobutane (**15**) and -cyclopentane (**16**), in high yields (Scheme 3). Each product was a single diastereomer believed to be trans because of likely epimerization during the basic ring closure conditions. This assignment was confirmed in the cases of **15** and **16** by the NOE signal between the methyl protons and the adjacent tertiary proton and the absence of such interaction between the two tertiary protons . Although both interactions were absent in the NOESY spectrum of **14**, it is not unreasonable to assign it the trans configuratiion as well.

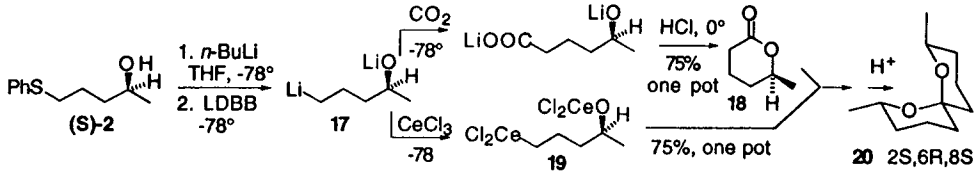


Scheme 3

Assuming that the sulfonyl carbanion executed an S_N2 displacement leading to expulsion of the tosylate ion in the ring forming step, (2R)-2-methyl-1-phenylsulfonylcyclopropane (**14a**), -cyclobutane (**15a**) and -cyclopentane (**16a**) can be prepared from the chiral alcohols **1**, **2** and **3**, respectively. Chiral synthons **15a** and **16a** can almost certainly be prepared in a slightly different manner as well since it was previously reported[16] that (S)-1-tolylsulfonyl-3-butanol and (S)-1-tolylsulfonyl-4-pentanol are produced in high ee by bakers yeast reduction of the corresponding ketones; while, strangely, (S)-1-tolylsulfonyl-5-hexanol can not be prepared by the use of baker's yeast,[16,17] it can be produced by reduction using a different organism.[17] Furthermore, the recent report[18] that (R)-1-tolylsulfonyl-3-butanol can be prepared by two enzymatic steps and one chemical step from 1-phenylthio-1-butanone makes it almost certain that the S-isomer of **14a** will also be available. Considering the vast flexibility of the sulfonyl group[19] combined with the chirality in the same molecule, these chiral cyclic synthons should be useful additions to the chirality pool.

Finally, as a demonstration of the utility of this type of chiron, the highly enantioenriched alcohol (**S**)-**2**, itself prepared in a 2-pot procedure involving the reduction of a ketone by the use of baker's yeast,[2] was transformed into the chiral lactone **18** in one pot.[20,21] Another one-pot reaction between **18** and the cerium analog, **19**, of its key precursor, dilithio intermediate **17**, provided the insect pheromone, (2S,6R,8S)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**20**) possessing three chiral centers in virtually enantiomerically pure form (Scheme 4) using our recently revealed strategy for spiroacetal synthesis.[2,22,23] The ^1H NMR, ^{13}C NMR and mass spectra of (2S,6R,8S)-**20** are identical with those of the same compound prepared by Mori.[24a,b] It is obvious that no racemization step was involved in either the synthesis of the lactone **18** or of the spiroketal **20**. Therefore, the lactone **18** should have an *S*-configured chiral center with the same high

optical purity as **2** (>97% ee) and, because of the preference in **20** (1) of the methyl substituents to reside in the equatorial positions and (2) of the oxygen atoms to be axially oriented due to the anomeric effect, the absolute configuration at the spirocenter in **20** must be *R*.[25] Thus, **20** should be the enantiomer (2S,6R,8S)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane shown as confirmed by the sign of its optical rotation (see below).



Scheme 4

Because the spiroketal formation is a simple coupling reaction between **2** and **18**, both of which have ee's >97%, with no possible racemization step in the course of the synthesis, and because the other diastereomer formed was separated easily, the optical purity of (2S,6R,8S)-**20** can be calculated to be 99.95% (eq 2).[24a,26] Its enantiomer arises by coupling of the enantiomeric impurity present to the extent of less than 1.5% in both **2** and **18** and it thus constitutes a negligible impurity in the sample of **20**. The enantiomeric purity is confirmed by comparing the rotation of the chromatographed and distilled sample[27] ($[\alpha]_D^{26}$ = -58.8°, *n*-pentane, c = 0.85) with that of optically pure samples ($[\alpha]_D^{24}$ -58.8° c = 1.27, *n*-pentane[24a] and $[\alpha]_D^{23}$ -58.7° c = 1.6, *n*-pentane[24c]).

$$\text{Theoretical ee\% of } \mathbf{20} = \frac{98.5^2 - 1.5^2}{98.5^2 + 1.5^2} \times 100\% = 99.95\% \qquad (2)$$

Compared with previous asymmetric syntheses[24] of the same target, the present synthesis appears to be more efficient, requiring only four steps and producing ~50% overall yield of the compound (2S,6R,8S)-**20** with extremely high enantioselectivity from commercially available, achiral starting materials. The asymmetric syntheses of this pheromone and the previous one[2] from the chiron (S)-**2** demonstrate that it will be of use in the syntheses of some methylated spiroketals and it implies that chirons **1** and **3** will probably be as well. The R-enantiomers of **1**, **2**, and **3** should be available by Mitsunobu inversion.[28] **(R)-1** is also available by using a different kind of yeast in the reduction of the corresponding ketone, in addition to two other steps.[18] Finally, it has recently been revealed that both enantiomers of **1** are available in high yield and ee by asymmetric hydrogenation of 4-phenylthio-2-butanone and that similar reduction of 5-phenylthio-3-butanone also yields either enantiomer of 5-phenylthio-3-butanol; similar syntheses of **2** provide either enantiomer in 68 - 70% ee.[29]

EXPERIMENTAL

All reactions were carried out under an atmosphere of prepurified argon. All solvents were dried by using standard procedures and were freshly distilled. A dry ice / acetone slush bath was used to generate -78 °C and an ice bath was used to obtain 0 °C. When a temperature of -78 °C was needed for an extended period of time, the FTS Systems, Inc Model TC-10 Flexi cool probe was used.

General Methods. ^1H and ^{13}C NMR spectra were recorded on either a Bruker WH-300 or a Bruker AF-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. ^{19}F NMR spectra were recorded on a Bruker AM-500 spectrometer operating at 470.5 MHz. Infrared spectra were recorded on an IR/32 FT-IR

spectrometer. Low and high resolution mass spectra were recorded on a VG-70SE mass spectrometer in EI mode at 70 eV or in CI mode in an isobutane atmosphere. Optical rotations were obtained as solutions in a 1-dm cell on a Perkin-Elmer 241 polarimeter. Silica gel 60 (40-60 μm, E. Merck) was used for flash column chromatography. The preparation of lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[30] and anhydrous cerium (III) chloride suspension in THF[22b] have been described previously.

(*S*)-6-Phenylthio-2-hexanol (3). 150 mL of water in a 1000 mL Erlenmeyer flask was autoclaved at 120 °C, under 15 atm of pressure for 1 h. Baker's yeast (80.0 g), D-(+)-glucose (3.0 g), and 6-phenylthio-2-hexanone (**4**) (1.43 g, 6.88 mmol) were mixed in the flask carefully and shaken mildly at 30 °C in an incubator for 6 days. The resulting slurry was diluted with ethyl acetate (500 mL) and centrifuged at 3800 rpm for 25 min. The supernatant was collected. The residue was mixed with ethyl acetate (500 mL) and centrifuged again. The combined supernatant was washed successively with water (2 × 50 mL) and brine (2 × 50 mL) and dried. The solvent was removed by rotary evaporation. Purification by flash chromatography afforded 0.644 g (45%) of unreacted **7** (10% ethyl acetate / hexanes, R_f 0.20) and 0.766 g (53%) of the title compound **3** (20% ethyl acetate / hexanes, R_f 0.18) as a colorless oil. $[\alpha]_D^{23}$ = +6.6° (c = 1.25, chloroform, α = +8.2°); IR (neat) 3360, 2967, 2954, 2934, 1481, 1438, 1093, 1025, 738, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 - 7.34 (m, 5 H, Ph), 3.74 - 3.82 (m, 1 H, C*H*OH), 2.94 (t, J = 7.2 Hz, 2 H, SCH_2), 1.39- 1.71 (m, 7 H), 1.19 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.7, 128.9 (two carbons), 125.7, 67.8, 38.7, 33.5, 29.1, 24.9, 23.5; MS (EI) *m/z* (relative intensity) 210 (M^+, 56), 192 (22), 165 (10), 123 (60), 110 (100), 82 (46), 55 (53; HRMS (EI) calcd for $C_{12}H_{18}OS$ 210.1078, found 210.1076.

The MTPA ester[4] of **3** was prepared as follows. A mixture of (*R*)-(-)-MTPA chloride (43.2 mg, 0.170 mmol), **3** (24.0 mg, 0.110 mmol), pyridine (0.4 mL) and CCl_4 (0.4 mL) was stirred at room temperature for 18 h. To this mixture was added *N,N*-dimethylethylenediamine (23 mg, 0.27 mmol) and the mixture was stirred for an additional 5 min and diluted with ether (20 mL). The organic solution was washed with 1 N HCl (2 mL), saturated sodium bicarbonate solution (2 mL), and brine (2 mL). The resulting solution was dried and the solvent was removed by rotary evaporation. Purification by flash chromatography (5% ethyl acetate / hexanes, R_f 0.20) afforded 35.3 mg (98%) of MTPA ester as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.18 - 7.54 (m, 10 H, Ph), 5.08 - 5.19 (m, 1 H, C*H*OH), 3.56 (s, 3 H, CH_3O), 2.90 (t, *J* = 6.8 Hz, 2 H, SCH_2), 1.40 - 1.68 (m, 6 H), 1.26 (d, *J* = 6.3 Hz, 3 H, CH_3CH). The MTPA ester derived from (±)-5-phenylthio-2-pentanol (**3**) displays two sets of signals due to the OCH_3 (s, δ 3.54; δ 3.57, 1:1 peak area), SCH_2 (t, δ 2.81, *J* = 7.0 Hz; δ 2.90, *J* = 6.8 Hz, 1:1 peak area) and CH_3 (d, δ 1.25, *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 spectroscopy shows two peaks for MTPA ester derived from the racemic alcohol **3a** (δ -71.91, δ -71.86, 1:1 peak area). The ^{19}F NMR spectrum of the MTPA ester of **(S)-3** shows a major peak at δ -71.86 and a very minor peak at δ -71.90. The peak ratio of OCH_3 from proton NMR was ≥ 55 and thus the optical purity of **3** should be no less than 96% ee.

Racemic 6-Phenylthio-2-hexanol (3r). A solution of 6-phenylthio-2-hexanone (**4**) (2.08 g , 10.0 mmol) in 15 mL of ethanol was stirred at 20 °C during dropwise addition of an aqueous solution of sodium borohydride (0.454 g, 12.0 mmol in 5 mL of water). The mixture was stirred for 1 h at room temperature, poured into water (10 mL) and extracted with ether (3 × 50 mL). The combined ether extract was washed with 1 N HCl (20 mL) and brine (3 × 20 mL), dried, filtered and evaporated under reduced pressure. Purification by

flash chromatography afforded 2.10 g (100%) of the title compound **3r** (20% ethyl acetate / hexanes, R_f 0.20) as a colorless oil. IR, ^{1}H NMR, ^{13}C NMR and mass spectra were identical with those of **3**.

6-Phenylthio-2-hexanone (4). To a solution of 5-hexene-2-one (6.48 g, 66 mmol) in thiophenol (30 mL, 254 mmol) was added AIBN (1.08 g 6.6 mmol). The reaction mixture was stirred at 80 °C overnight. After being cooled to room temperature, the mixture was diluted with ether (150 mL) and washed successively with 5% NaOH (5 × 15 mL) and brine (3 × 15 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by chromatography afforded 12.9 g (94%) of the titled compound **4** (10% ethyl acetate / hexanes, R_f 0.20) as a colorless oil. IR (neat) 2936, 2362, 1712, 1481, 1439, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10 - 7.30 (m, 5 H, Ph), 2.87 (t, J = 6.6 Hz, 2 H, SCH_2), 2.38 (t, J = 6.4 Hz, 2 H, CH_2CO), 2.07 (s, 3 H, CH_3), 1.58 - 1.69 (m, 6 H , $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 208.1, 136.4, 128.7 (two carbons), 125.6 , 42.8, 33.0, 29.8, 28.3, 22.6 MS (EI) *m/z* (relative intensity) 208 (M^+, 87), 165 (7), 123 (47), 99 (100), 77 (28), 65 (34), 55 (19), ; HRMS (EI) calcd for $C_{12}H_{16}OS$ 208.0922, found 208.0929.

1,1-Dimethyl-1-(1-methyl-4-phenylthiobutoxy)-1-silaethane (5). To a solution of 5-phenylthio-2-pentanol (**2r**) (0.392 g, 2.00 mmol) in 5 mL THF was added trimethylsilyl chloride (TMSCl) (0.51 mL, 4.0 mmol) and triethylamine (1 mL). The mixture was stirred at room temperature for 3 h. Ice water (5 mL) was added and the solution was extracted with ether (3 × 20 mL). The combined organic layers were washed with cold brine (3 × 5 mL)and dried over magnesium sulfate. Removal of the solvent and triethylamine on a rotary evaporator at 50 °C gave 0.509 g (95%) of the desired compound **5** as a colorless oil. IR (neat) 2953, 1678, 1647, 1554, 1491, 1458, 1246, 843, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.14 – 7.36, (m, 5 H), 3.76 - 3.82 (m, 1 H, OCH), 2.90 - 2.95 (t, J = 7.2 Hz, 2 H, SCH_2), 1.54 - 1.77 (m, 4 H, CH_2CH_2), 1.14 (d, J = 6.0 Hz, 3 H, $OCHCH_3$), 0.11 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 136.8, 129.1, 128.8, 125.7, 68.1, 38.5, 33.8, 25.6, 23.9, 0.25; MS (EI) *m/z* (relative intensity) 268 (M^+, 39), 253 (22), 159 (27), 136 (100), 117 (44); 110 (19), 73 (86); HRMS (EI) calcd for $C_{14}H_{24}OSiS$ 268.1323 found 268.1317.

1,1-Dimethyl-1-(1-methyl-5-phenylthiopentyloxy)-1-silaethane (6). **6** (0.536 g, 95%) was prepared from the reaction of 6-phenylthio-2-hexanol (**3r**) (0.420 g, 2.00 mmol) and TMSCl (0.51 mL, 4.0 mmol) following the procedure described above for the synthesis of **5**. IR (neat) 2953, 1653, 1554, 1491, 1458, 1419, 1246, 843, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.14 – 7.36, (m, 5 H), 3.75 - 3.81 (m, 1 H, OCH), 2.91 - 2.96 (t, 2 H, SCH_2), 1.37 - 1.70 (m, 6 H, $CH_2CH_2CH_2$), 1.15 (d, J = 6.0 Hz, 3 H, $OCHCH_3$), 0.14 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 136.9, 128.8 (two carbons), 125.6, 68.3, 39.0, 33.5, 29.2, 25.2, 23.9, 0.25; MS (EI) *m/z* (relative intensity) 282 (M^+, 43), 267 (26), 192 (24), 123 (20), 117 (81); 110 (88), 73 (100); HRMS (EI) calcd for $C_{15}H_{26}OSiS$ 282.1464 found 282.1473.

5-Methyl-2-(phenylthio)tetrahydrofuran (9). To a solution of trimethyl-(1-methyl-4-phenylthiobutoxy)-silane (**5**) (0.268 g, 1.00 mmol) in 5 mL of CCl_4 was added N-chlorosuccinimide (NCS) (0.150 g, 1.12 mmol). The suspension was heated at reflux for 1 h. After being cooled to ambient temperature, the mixture was filtered and the filtrate evaporated to give 0.345 g (100%) of the crude α-chlorinated phenyl thioether **7**. To a solution of the crude product **7** in 3 mL of THF was added tetrabutylammonium fluoride (1.5 mL 1.0 M solution in THF, 1.50 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with water (5 mL) and extracted with ether (3 × 20 mL). The combined organic extract was washed with brine (3 × 5 mL) and dried over magnesium sulfate. Removal of the solvent on a rotary evaporator followed by flash chromatography on silica gel (1% ethyl acetate / hexanes, R_f 0.2) gave 0.163 g (84%) of a mixture of the two diastereomers of **9** as a pale yellow oil. IR (neat) 3066, 2975, 2932, 2874,

1586, 1437, 1071, 992, 929 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 – 7.55, (m, 5 H), 5.71, (dd, J_1 = 7.2 Hz, J_2 = 4.6 Hz, 0.52 H), 5.50 (dd, J_1 = 6.9 Hz, J_2 = 3.9 Hz, 0.48 H), 4.30 - 4.37 (m, 0.48 H), 4.18 - 4.24 (m, 0.52 H), 2.28 - 2.60 (m, 1 H), 1.92 - 2.21 (m, 2 H), 1.45 - 1.75 (m, 1 H), 1.36 (d, J = 6.3 Hz, 1.4 H), 1.31 (d, J = 6.1 Hz, 1.6 H); ^{13}C NMR ($CDCl_3$) δ 136.1, 135.2, 131.4, 130.6, 128.7 (two carbons), 126.8, 126.5, 86.9, 86.7, 77.7, 74.4, 33.5, 33.0, 32.4 (two carbons), 22.0, 20.0; MS (EI) *m/z* (relative intensity) 194 (M^+, 10), 109 (45), 85 (100), 77 (7), 65 (20); HRMS (EI) calcd for $C_{11}H_{14}OS$ 194.0767 found 194.0765.

6-Methyl-2-(phenylthio)tetrahydropyran (10). Following the same procedure described above for the synthesis of **9**, trimethyl-(1-methyl-5-phenylthio-pentoxy)-silane (**6**) (0.366 g, 1.30 mmol) was transformed into **10** (0.205g, 76%). IR (neat) 2923, 2847, 1576, 1473, 1433, 1072, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 – 7.48, (m, 5 H), 5.58 - 5.60, (m, 0.4 H), 4.75 - 4.79, (dd, J_1 = 11.0 Hz, J_2 = 1.6 Hz, 0.6 H), 4.27 - 4.31 (m, 0.4 H), 3.49 - 3.56 (m, 0.6 H), 1.31 - 2.00, (m, 6 H), 1.23, (d, J = 6.2 Hz, 0.6 H), 1.13 (d, J = 6.4 Hz, 0.4 H). According to the ^1H NMR spectroscopy, the ratio of trans to cis isomers is 40 : 60. ^{13}C NMR ($CDCl_3$) δ 136.2, 135.3, 130.8, 130.6, 128.8, 128.7, 126.7, 126.5, 85.6, 84.9, 75.1, 65.7, 33.2, 32.3, 31.2, 30.9, 24.3, 22.1, 21.7, 19.7; MS (EI) *m/z* (relative intensity) 208 (M^+, 3), 135 (2.5), 110135 (5), 110 (23), 99 (100); 81 (91), 55 (62); HRMS (EI) calcd for $C_{12}H_{16}OS$ 208.0922 found 208.0918.

Toluene-4-sulfonic Acid 3-Benzenesulfonyl-1-methylpropyl Ester (11). To a solution of 4-phenylthio-2-butanol (**1r**) (0.364 g, 2.00 mmol) in 5 mL of pyridine was added *p*-toluenesulfonyl chloride (0.456 g, 2.40 mmol) at 0 °C. The mixture was stirred at 10 - 15 °C over night. The reaction was quenched with cold water (5 mL) and the mixture was extracted with ether (3 × 20 mL). The combined organic phase was washed with 5% HCl (3 × 5 mL) and brine (3 × 5 mL), dried over magnesium sulfate and concentrated by rotary evaporation. Purification by column flash chromatography on silica gel (8% ethyl acetate / hexanes, R_f 0.2) afforded 0.571 g (85%) of the intermediate tosylate. To a solution of the tosylate (0.504 g, 1.5 mmol) in 6 mL of methanol was added an aqueous solution of Oxone (1.38 g, 2.25 mmol in 6 mL water) dropwise at 0 °C. The mixture was stirred at room temperature for 5 h, diluted with water (5 mL) and extracted with chloroform (3 × 20 mL). The combined organic phase was washed with brine (3 × 5 mL) and dried over magnesium sulfate. After the solvent was removed on a rotary evaporator, 0.552 g (100%) of the titled compound **11** was obtained without further purification. IR (neat) 3048, 2930, 2855, 1590, 1435, 1355, 1300, ^1H NMR ($CDCl_3$) δ 7.27 - 7.84 (m, 9 H), 4.62- 4.68 (m, 1 H OCH), 2.92 - 3.12 (m, 2 H SO_2CH_2), 2.37 (s, 3 H CH_3Ar), 1.92- 2.00 (m, 2 H CH_2CH_2CH) 1.18 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 145.0, 138.6, 133.9, 133.5, 129.9, 129.3, 127.9, 127.6, 77.7, 51.9, 29.2, 21.6 20.7; MS (EI) *m/z* (relative intensity) 368 (M^+, 0.6), 227 (2.5), 197 (100), 155 (62), 143 (84) 125 (36), 91 (55); HRMS (EI) calcd for $C_{17}H_{20}O_5S_2$ 368.0747 found 368.0752.

Toluene-4-sulfonic Acid 4-Benzenesulfonyl-1-methylbutyl Ester (12). Following the procedure described above for the synthesis of **11**, **12** was prepared in 85% overall yield from **2r**. IR (neat) 3062, 2980, 2925, 1597, 1447, 1360, 1339, 1302, 1189, 1176, 1150, 693, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 - 7.78 (m, 9 H), 4.44- 4.48 (m, 1 H OCH), 2.91 - 2.96 (m, 2 H SO_2CH_2), 2.33 (s, 3 H CH_3Ar), 1.50 - 1.65 (m, 4 H CH_2CH_2) 1.10 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.7, 138.6, 133.7, 133.6, 129.7, 129.1, 127.7, 127.4, 78.8, 55.1, 34.5, 21.4, 20.5, 18.2.

Toluene-4-sulfonic Acid 5-Benzenesulfonyl-1-methylpentyl Ester (13). Following the procedure described above for the synthesis of **11**, **13** was prepared in 85% overall yield from **3r**. IR (neat) 2940, 2885, 1603, 1431, 1365, 1301, 1179, 1145, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 - 7.87 (m, 9 H), 4.50- 4.56 (m, 1 H OCH), 2.95 - 3.00 (t, J = 8.1 Hz, 2 H, SCH_2), 2.41 (s, 3 H CH_3Ar), 1.19 - 1.63 (m, 6

H) 1.16 (d, J = 6.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.2, 138.5, 133.7, 133.2, 129.4, 128.8, 127.4, 127.1, 79.3, 55.1, 35.1, 22.9, 21.7, 21.0, 20.1; MS (EI) *m/z* (relative intensity) 396 (M^+, 0.3), 381 (0.3), 255 (2.5), 241 (2), 225 (81), 155 (25), 143 (56), 91 (57), 83 (100), 82 (64), 67 (33), 55 (69).

2-Methyl-1-benzenesulfonylcyclopropane (14). To 5 mL of a THF solution of compound **11** (0.184 g, 0.500 mmol) were added sodium hydride (in large excess) and a catalytic amount of *t*-butyl alcohol. The suspension was heated at reflux overnight. After being cooled to the ambient temperature, the reaction mixture was diluted with chloroform (50 mL) and washed with water (5 mL), 5% HCl (5 mL) and brine (3 × 5 mL), dried over magnesium sulfate and concentrated on a rotary evaporator. Purification by column flash chromatography on silica gel (20% ethyl acetate / hexanes, R_f 0.2) afforded 0.085 g (87%) of the titled compound (**14**) as a pale yellow oil. IR (neat) 2965, 1436, 1290, 1146, 1088, 912, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27- 7.91 (m, 5 H), 2.15- 2.21 (m, 1 H), 1.74 - 1.83 (m, 1 H), 1.43 - 1.51 (m, 1 H) 1.12 (d, J = 6.1 Hz, 3 H, CH_3), 0.81 - 0.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 140.8, 133.1, 128.1, 127.2, 39.7, 16.6 , 14.6, 13.8; the NOE behavior is described in the text. MS (EI) *m/z* (relative intensity) 196 (M^+, 10), 156 (12), 142 (10), 126 (17), 83 (100); HRMS (EI) calcd for $C_{10}H_{12}O_2S$ 196.0562 found 196.0558.

1-Benzenesulfonyl-2-methylcyclobutane (15). Following the procedure described above for the synthesis of **14**, **12** (0.191 g, 0.500 mmol) was transformed into **15** (0.082 g 84%). IR (neat) 2957, 2868, 1304, 1282, 1146, 1092, 732; ^1H NMR ($CDCl_3$) δ 7.54 - 7.93 (m, 5 H), 3.37 (q, J = 8.9 Hz, 1 H), 2.83 - 2.93 (m, 1 H), 2.33 - 2.43, (m, 1 H), 2.00 - 2.18, (m, 2 H), 1.45 - 1.58 (m, 1 H), 0.95 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.5, 133.5, 129.1, 128.0, 63.5, 32.4, 25.0, 20.1, 19.6; the NOE behavior is described in the text. MS (EI) *m/z* (relative intensity) 211 (MH^+, 1),[31] 143 (33), 125 (15), 78 (15), 77 (28), 69 (100), 68 (28), 51 922); MS (CI) *m/z* (relative intensity) 211 (MH^+, 100), 143 (24), 125 (25), 77 (20), 69 (93).

1-Benzenesulfonyl-2-methylcyclopentane (16). Following the procedure described above for the synthesis of **14**, **13** (0.198 g, 0.500 mmol) was transformed into **16** (0.094 g, 84%). IR (neat) 2957, 2872, 1147, 1301, 1146, 1071, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50- 7.89 (m, 5 H), 3.03 (m, 1 H), 2.10 - 2.48 (m, 1 H), 2.03 - 2.10 (m, 1 H), 1.80 - 1.95, (m, 2 H), 1.57 - 1.66 (m, 2 H), 1.20 - 1.29 (m, 1 H), 0.95, (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.8, 133.4, 129.1, 128.4, 70.6, 35.7, 35.4, 28.2, 24.8, 20.6; the NOE behavior is described in the text. MS (EI) *m/z* (relative intensity) 225 (MH^+, 15),[31] 197 (13), 186 (28), 83 (26), 78 (36), 77 (100), 67 (21), 55 (65); MS (CI) *m/z* (relative intensity) 225 (MH^+, 100), 143 (18), 125 (19), 83 (78), 77 (17), 67 (12). HRMS (EI) calcd for $C_{12}H_{17}O_2S$ (MH^+) 225.0949 found 225.0940.

(S)-6-Methyloxan-2-one (18). *n*-BuLi (1.32 mL, 1.6 M in hexanes, 2.08 mmol) was added dropwise to a solution of (S)-5-phenylthio-2-pentanol (**2**) (0.396 g, 2.02 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 (4.5 mmol) in THF (12 mL) was cooled to -78 °C, and the lithium alkoxide solution was cannulated to the LDBB. The resulting red brown solution was stirred for 30 min at -78 °C to generate the lithium δ-lithioalkoxide. Dry carbon dioxide was passed vigorously into 30 mL of THF which had been cooled to -78 °C in a 250 mL three-neck flask . The preformed δ-lithioalkoxide solution was then cannulated to the flask very slowly. While carbon dioxide was continuously passed through, the reaction mixture was allowed to warm to 0 °C over a period of 30 min. Dry HCl gas was passed into the mixture for 5 min. before it was diluted with ethyl acetate and dried over magnesium sulfate. Removal of the solvent on a rotary evaporator followed by flash chromatography on silica gel (35% ethyl acetate / hexanes, R_f 0.2) gave 0.173 g (76%) of the

desired compound **18** as a colorless oil. $[\alpha]_D^{23}$ = -11.3° (c = 0.45, chloroform, α = -5.1°); IR (neat) 2955, 1730, 1256, 1366, 1030; ^{1}H NMR ($CDCl_3$) δ 4.41 – 4.47 (m, 1 H), 2.41 - 2.61 (m, 2 H), 1.47 - 1.95 (m, 4 H), 1.37 (d, *J* = 6.2 Hz 3 H); ^{13}C NMR ($CDCl_3$) 172.0, 76.7, 29.6, 29.3, 21.8, 16.6; MS (EI) *m/z* (relative intensity) 114 (M^+, 19), 99 (21), 84 (21), 70 (100), 55 (39); HRMS (EI) calcd for $C_6H_{10}O_2$ 114.0685 found 114.0681.

(2S,6R,8S)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane (20). *n*-BuLi (0.63 mL, 1.6 M in hexanes, 1.01 mmol) was added dropwise to a solution of **2** (0.194 g, 0.990 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. The lithium alkoxide solution was cannulated to a solution LDBB (2.50 mmol) in THF (8 mL) that had been cooled to -78 °C.. The resulting red brown solution was stirred for 45 min at -78 °C. A preformed suspension of dried $CeCl_3$ (2.60 mmol), prepared[22b] from 0.969 g of $CeCl_3 \cdot 7H_2O$, in THF (10 mL), was cooled to -78 °C, and then cannulated to the solution of the δ-lithioalkoxide. After the resulting orange red mixture had been stirred for 1 h, (S)-5-hydroxyhexanoic acid lactone (**18**) (0.125 g, 1.10 mmol) was added. The mixture was stirred for 2 h at -78 °C and then allowed to warm to 0 °C over a period of 6 h. The reaction was quenched with 5% HCl (20 mL) at 0 °C, and the mixture was extracted with ether (4 × 20 mL). The combined organic layer was washed with brine (3 × 5 mL), dried, and concentrated by rotary evaporation. Purification by flash chromatography on silica gel (2% ethyl acetate / hexanes with ca. 0.2% triethylamine, R_f 0.2) afforded 0.137 g (75%) of **20** as a colorless oil. $[\alpha]_D^{26}$ = - 58.8° (c = 0.85, n-pentane, α = -50.0°); IR (neat) 2955, 2339, 1448, 1255, 1103, 1087, 996, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 - 3.73 (m, 2 H), 1.81 - 1.90 (m, 2 H), 1.17 - 1.59 (m, 10 H), 1.12 (d, *J* = 6.3 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 96.2, 65.1, 35.3, 32.8, 21.9, 19.0; MS (EI) *m/z* (relative intensity) 184 (M^+, 15), 140 (20), 115 (95), 112 (100), 97 (46), 69 (38); HRMS (EI) calcd for $C_{11}H_{20}O_2$ 184.1463 found 184.1458.

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REFERENCES AND NOTES

(1) Sheldon, R. A. *Chirotechnology: Industrial Synthesis of Optical Active Compounds*; Marcel Dekker: New York, 1993, pp 143-171

(2) Liu, H.; Cohen, T. *J. Org. Chem.* **1995**, *60*, 2022-2025.

(3) (a) Stacey, F. W.; Harris, Jr. J. F. *Org. React.* **1963**, *13*, 150-376. (b) Bakuzis, P.; Bakuzis, M. L. F.; Fortes, C. C.; Santos, R. *J. Org. Chem.* **1976**, *41*, 2769-2770.

(4) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

(5) Recent reviews on BY mediated reactions: Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49-97. Servi, S. *Synthesis* **1990**, 1-25.

(6) For the syntheses of **1**, **2**, **1r**, and **2r**, see ref 2.

(7) Ahern, T. P.; Kay, D. G.; Langler, R. F. *Can. J. Chem.* **1978**, *56*, 2422-2429 and citations therein.

(8) Corey, E. J; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

(9) (a) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900-6902. (b) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130-1131.

(10) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924-1930.

(11) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336-4339; Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375-8384.

(12) Bird, R.; Griffiths, G.; Griffiths, G. F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 579-584.

(13) Chang, Y-H.; Pinnick, H. W. *J. Org. Chem.* **1978**, *43*, 373-374.

(14) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603-4614. Matsuda, F.; Tomiyosi, N.; Matsumoto, T. *Chem. Lett.* **1987**, 2097-2100.

(15) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290. (b) Trost, B. M.; Braslau, R. *J. Org. Chem.* **1988**, *53*, 532-537.

(16) Gopalan, A. S.; Jacobs, H. K. *Tetrahedron Lett.* **1990**, *31*, 5575-5578.

(17) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman *J. Am. Chem. Soc.* **1986**, *108*, 284-291.

(18) Ohtsuka, Y.; Katoh, O.; Sugai, T.; Ohta, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 483-491.

(19) Recent review of sulphone chemistry: Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: New York, 1993.

(20) Mudryk, B; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657-5659.

(21) For one of the earliest examples of lactone formation by carbonation of an oxyanion-carbanion, see: Crandall, J. K.; Clark, A. C. *J. Org. Chem.* **1972**, *37*, 4236-4242.

(22) (a) Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389-91. Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866-67. (b) Ahn, Y.; Cohen, T. *J. Org. Chem.* **1994**, *49*, 3142-50.

(23) A review of the chemistry and synthesis of spiroketal-containing natural products: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661. Recent reviews on spiroketal synthesis,: 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, pp 553-691. Mori, K. In *The Total Synthesis of Natural Products;* Apsimon, J., Ed; Wiley Interscience: New York, 1992; Vol. 9, pp 444-478.

(24) (a) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295-304. (b) Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221-3225. (c) Kitching, W.; Perkins, M. V. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2501-06.

(25) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105-1121.

(26) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143-1144.

(27) We thank Professor Mori for informing us that the chromatographed sample must be distilled in order to observe the correct rotation. We indeed found this to be the case.

(28) Mitsunobu, O. *Synthesis* **1981**, 1-28.

(29) Tranchier, J.-P.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Tong, S.; Cohen, T. *Tetrahedron Lett.* **1997**, *38*, 2951-2954.

(30) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784-4786.

(31) Certain types of compounds give M+1 EI peaks: McLafferty, F. W.; TureCek, F. *Interpretation of Mass Spectrometry, 4th ed*; University Science Press: Mill Valley CA, 1993; pp 240, 259, 261, 270, 275.

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