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A ROUTE TO STEREOCHEMICALLY COMPLEX TETRAHYDROFURANS USING α-SULFINYL CARBANIONS

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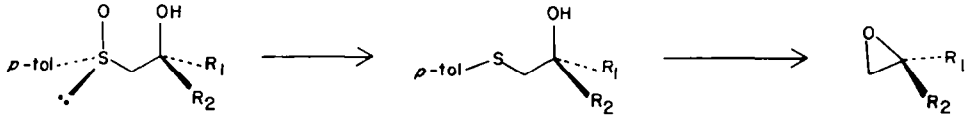
Abstract—Condensations involving α-lithiosulfinyl carbanions provide an efficient strategy for preparation of highly substituted tetrahydrofurans.

The presentation of our studies of α-sulfinyl carbanions would be incomplete without some mention of the general reactivity and synthetic utility of the β-hydroxysulfoxide products.[1] We have previously described a strategy for construction of 1,3-asymmetry by desulfurization, and in this report we will direct attention toward the preparation of stereochemically complex ethers. Several laboratories have reported procedures for the generation of oxiranes **3** via alkylation of the β-hydroxysulfide **2** with trimethyloxonium tetrafluoroborate followed by treatment with base.[2] Yields for the overall process range from 40–70%, and the availability of both diastereomeric chiral sulfoxides (*R*- or *S*-carbinols) **1** provides a valuable source of optically active epoxides.



1 **2** **3**

Our investigations have uncovered a remarkably facile transformation of acyclic β-hydroxysulfoxide precursors to tetrasubstituted tetrahydrofurans with complete stereospecificity.[3] Thus, when the major sulfoxide adduct **4** was treated with excess acetyl bromide (3 equiv) in CH_2Cl_2 at 0° with warming to room temperature, a dehydration occurred, producing the single tetrahydrofuran isomer **5** in 77% yield. Cyclizations were performed more efficiently and in higher yields from the corresponding phenylsulfides available via sulfoxide reduction with borane in tetrahydrofuran. As compiled in Table 1, treatment of phenylsulfide **6** with dimethylsulfate (CH_2Cl_2, 0°, 10 min) cleanly afforded tetrahydrofuran **5** in 85% yield. Likewise, the isomeric sulfides **7**, **8**, **9** (R = H), and **10** (R = H) were individually submitted to the reaction conditions, providing tetrahydrofurans **11**–**14**, respectively, demonstrating the stereospecificity of the process.‡

Although spectroscopic data supported the products, coupling constants of vicinal protons in these heterocycles often fail to offer a completely reliable basis for stereochemical assignment. One could anticipate preferred loss of the benzylic alcohol owing to a more favorable stabilization of charge. However, our experiments also demonstrated the stereospecific cyclization of benzylic ethers **9** and **10** (R = $CH_2C_6H_5$), under the usual conditions of *S*-methylation, affording tetrahydrofurans **13** (70%) and **14** (72%), as previously obtained from their corresponding alcohols. In addition, the phenyl ring (originally derived from benzaldehyde) could be replaced by an alkyl substituent, as shown in **15**, **17**, **19** and **21**, without affecting the ease or course of the reaction.§ Subsequently, the stereochemical features of our products were unambiguously confirmed by X-ray crystallography of the sulfone of cyclic ether **14**, thus demonstrating complete retention of configuration at each of the four asymmetric carbon centers.‖ A mechanistic rationale is suggested in Scheme 1 by an initial alkylation and solvolysis of methanol assisted by backside participation of the neighboring sulfur yielding a sulfonium salt **23**. Interaction of the remaining hydroxy (alkoxy) substituent through a five-membered transition state provides a developing oxonium ion **24**, which suffers deprotonation or dealkylation, affording the observed tetrahydrofurans.

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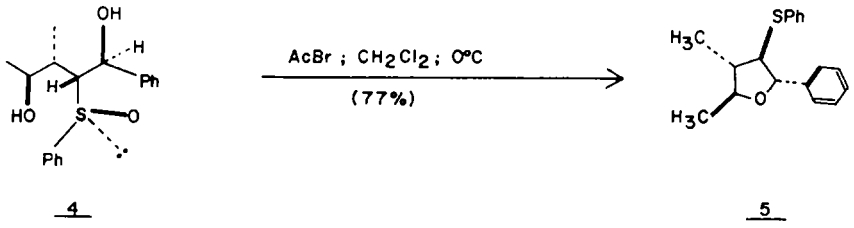
‡ The t-butylsulfide **6** (Table 1) was generated as the major product of condensation using the corresponding (*R*)-t-butylsulfoxide with benzaldehyde. In spite of extensive efforts, we have been unable to detect evidence of *S*-methylation for this family of compounds.

§ Starting acyclic sulfoxides may be directly used for cyclization, although these reactions proceed via initial reduction to the corresponding phenylsulfides with subsequent ring closure. Structure assignments of **19** are based on its single crystal X-ray diffraction (−162°). All atoms were located, $R(F) = 0.66$ and $R_w(F) = 0.061$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 81030.

‖ Structure **14** was determined as its sulfone by single crystal analysis (−161°). All atoms were located and refined by full-matrix techniques to final residuals of $R(F) = 0.043$ and $R_w(F) = 0.042$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 81053.

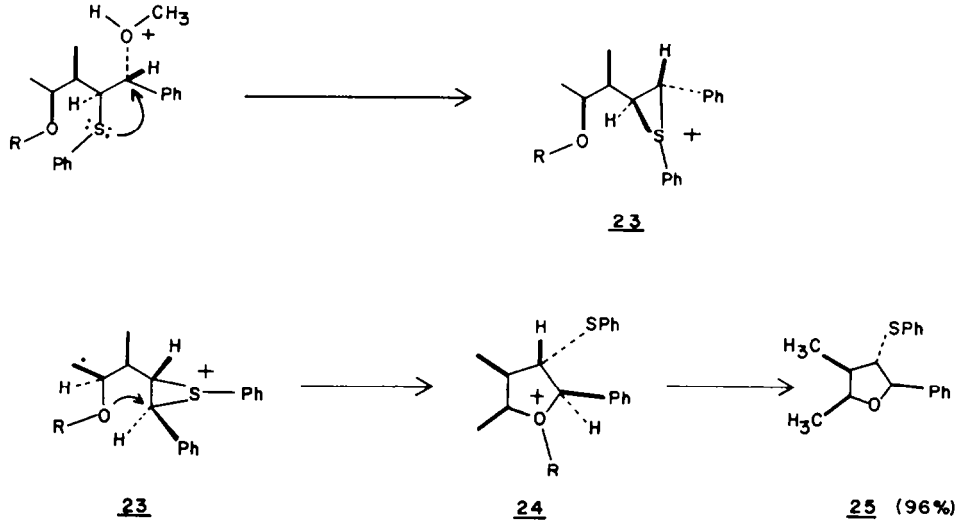


4 5

Evidence of the role of sulfur was provided by reaction of the β-hydroxysulfide **26** with dimethylsulfate (CH_2Cl_2 at 0°) yielding an efficient conversion (82%) to the complex acyclic ether **27**.† Once again, our stereoassignments for **27** were unambiguous as a result of an X-ray diffraction study, displaying a unique and highly symmetrical arrangement of the six phenyl substituents.‡ This further confirmed the stereointegrity necessarily maintained by formation of an episulfonium intermediate.

The overall reaction sequence has also been applied to simple ketones. For example, condensation of the α-sulfinyl carbanion of **28** with the methyl ketone **29** gave two major β-hydroxysulfoxide adducts **30** and **31** in 2:1 ratio (43% yield).§ Upon separation and reduction (BH_3·THF), the corresponding individual phenylsulfides were cyclized by treatment with methyl triflate in methylene chloride giving tetrahydrofurans **32** and **33**, respectively.

In conclusion, the stereochemical consequences for the addition of α-lithiosulfinyl carbanions to aldehydes have been unambiguously determined. We have identified steric factors and chelation as key elements responsible for stereocontrol. Our mechanistic discussion is intended to offer a working hypothesis which should serve to stimulate additional research in this fascinating area. Finally, the utility of this methodology has been demonstrated as an elegant and efficient route for synthesis of stereochemically complex cyclic and acyclic ethers.



Scheme 1.

† Starting β-hydroxysulfide **26** was prepared via reduction (BH_3 in THF) of one of two major adducts from the (*R*)-sulfoxide condensations with benzaldehyde.

‡ Structure **27** was determined by single crystal analysis (−161°). All atoms were located and refined by full-matrix techniques to final residuals of $R(F) = 0.067$ and $R_w(F) = 0.059$. Complete crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 81055.

§ Ketones lead to reduced yields. The major side reaction was identified as deprotonation of the methyl ketone.

‖ For the general experimental description, see the preceding paper. Combustion data and mass spectral fragmentations were virtually identical for each compound within a family of diastereoisomers. To avoid repetition, these data have been supplied for only one isomer in each series of related diastereomers.

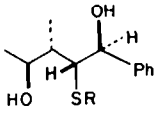
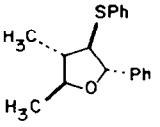
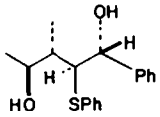
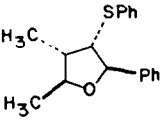
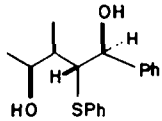
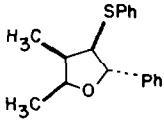
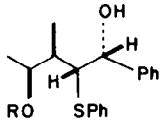
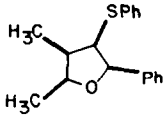
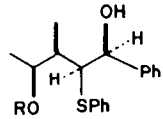
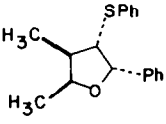
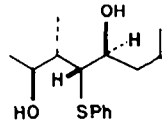
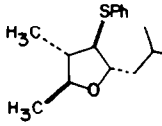
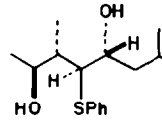
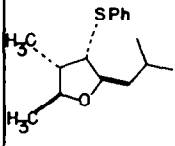
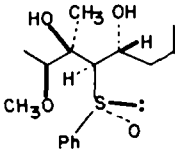
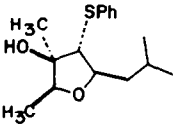
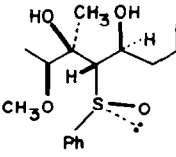
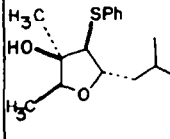
EXPERIMENTAL‖

Borane reductions of β-hydroxysulfoxides to β-hydroxysulfides

A soln of borane–THF complex (Aldrich) was added via syringe to a soln of β-hydroxysulfoxide (0.3–0.6 mmol) in anhyd THF (3–5 ml) at 22° under Ar. Excess borane (3 mmol equiv) was generally used with an additional 1 equiv if another OH group was present in the substrate. The colorless mixture was stirred at room temp for 18–24 h, and quenched by careful addition of NH_4Cl aq (~5 ml). After dilution with water and extraction with EtOAc, the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* leaving the crude sulfides which were purified by preparative TLC or flash chromatography. Yields were in the 85–95% range.

(±) - (1*R**,2*S**,3*R**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol*. R_f 0.63 (EtOAc–hexane 3:2);

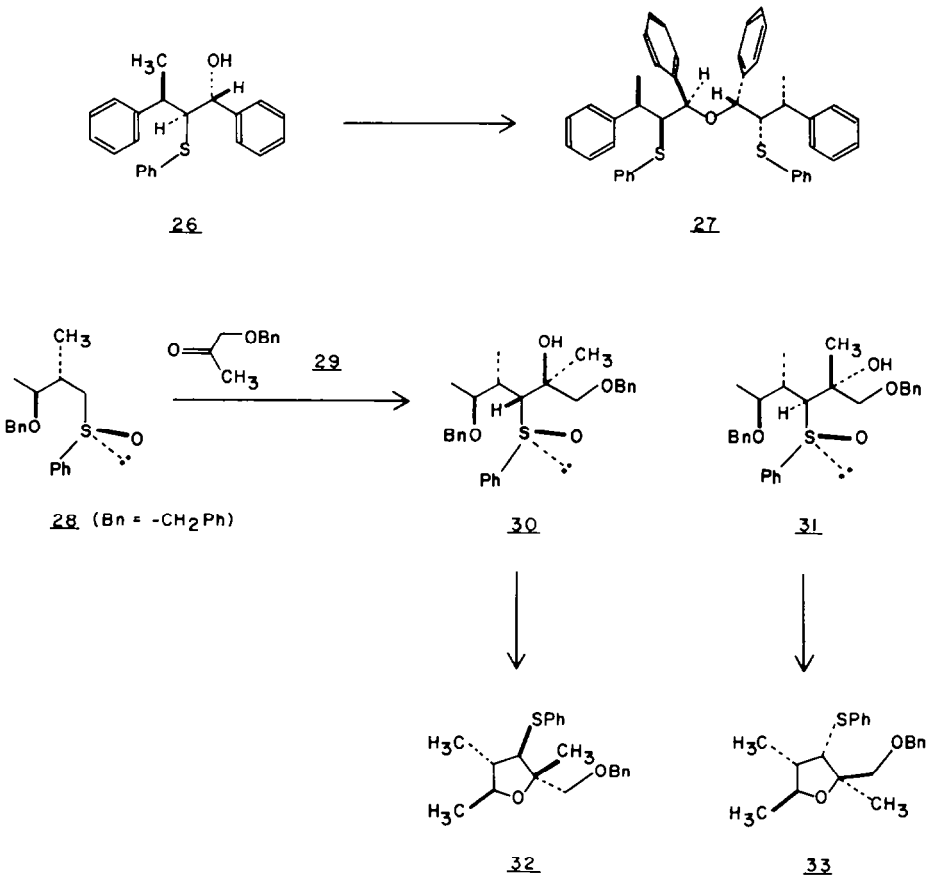
Table 1

SUBSTRATE	METHOD	PRODUCT	YIELD
 6	a, c	 5	85% (R=Ph) 96% (R=t-Bu)
 7	a	 11	90%
 8	a	 12	85%
 9	a	 13	70% (R = CH_2Ph)
 10	a	 14	81% (R = H)
 15	a	 16	100%
 17	a	 18	98%
 19	b	 20	84%
 21	b	 22	78%

(a) $(CH_3O)_2SO_2$; CH_2Cl_2; 0°C

(b) ClCOCOCl; NaI; CH_3CN; 22°C

(c) $(CH_3)_3O^+ BF_4^-$; CH_2Cl_2; 0°C



m.p. 97–98°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.27 (m, 5H), 7.20 (s, 5H), 4.80, (d, 1H, J = 6.5 Hz), 4.07 (m, 1H), 3.45 (dd, 1H, J = 6.5, 2 Hz), 2.91 (br s, OH), 2.68 (br s, OH), 2.08 (m, 1H), 1.16 (d, 3H, J = 6 Hz), 1.11 (d, 3H, J = 7 Hz); IR ($CHCl_3$) 3590, 3490, 3040, 2970, 1085, 1050, 700, 690 cm^{-1}.

(±) - (1*S**,2*R**,3*R**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol* (**8**). R_f 0.63 (EtOAc–hexane 3:2); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.23 (m, 10H), 4.80 (br, OH), 4.70 (d, 1H, J = 9.5 Hz), 4.07 (m, 1H), 3.41 (dd, 1H, J = 9.5, 2.5 Hz), 2.05 (m, 1H), 1.07 (d, 6H, J = 7 Hz); IR (film) 3260, 3060, 3020, 2960, 1580, 1475, 1450, 1035, 1020, 700, 690 cm^{-1}. (Found: C, 71.15; H, 7.48; S, 10.51. Calc for $C_{18}H_{22}O_2S$: C, 71.48; H, 7.33; S, 10.60%.)

(±) - (1*R**,2*R**,3*R**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol* (**9**). R_f 0.70 (EtOAc–hexane 3:2); m.p. 91–93°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.32 (m, 5H), 7.16 (s, 5H), 5.05 (d, 1H, J = 5 Hz), 4.39 (m, 1H), 3.63 (t, 1H, J = 5, 5 Hz), 1.82 (m, 1H), 1.16 (d, 3H, J = 7 Hz), 1.11 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3595, 3485, 3060, 2975, 2925, 1580, 1480, 1450, 1435, 1080, 1040, 700, 690 cm^{-1}.

(±) - (1*S**,2*S**,3*R**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol* (**10**). R_f 0.70 (EtOAc–hexane 3:2); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.25 (m, 10H), 5.02 (d, 1H, J = 3.5 Hz), 4.34 (m, 1H), 4.00 (br s, OH), 3.39 (dd, J = 3.5, 1 Hz), 2.68 (br s, OH), 1.73 (m, 1H), 1.11 (d, 3H, J = 7 Hz), 1.07 (d, 3H, J = 7 Hz); IR ($CHCl_3$) 3595, 3400, 3060, 2985, 1580, 1480, 1450, 1440, 1380, 1050, 700, 690 cm^{-1}; MS (70 eV), *m/e* 213 (1), 198 (4), 197 (8), 196 (54), 178 (12), 163 (5), 151 (100), 149 (20), 123 (35), 110 (34).

(±) - (1*S**,2*R**,3*S**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol* (**6**). R_f 0.55 (EtOAc–hexane 1:1); m.p. 128–129°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.18 (m, 10H), 4.76 (d, 1H, J = 6.5 Hz), 4.00 (dd, 1H, J = 6.5, 1.5 Hz), 3.91 (m, 1H), 2.86 (br s, OH), 1.98 (m, 1H), 1.17 (d, 3H, J = 7 Hz), 1.00 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3590, 3420, 3060, 2960, 2930, 1055, 1030 cm^{-1}. (Found: C, 71.23; H, 7.38. Calc for $C_{18}H_{22}O_2S$: C, 71.48; H, 7.33%.)

(±) - (1*R**,2*S**,3*S**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol* (**7**). R_f 0.55 (EtOAc–hexane 1:1); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.27 (m, 10H), 4.82 (d, 1H, J = 6 Hz), 3.82 (m, 1H), 3.48 (dd, 1H, J = 6 Hz), 1.95 (m, 1H), 1.12 (d, 3H, J = 6 Hz), 0.99 (d, 3H, J = 7 Hz); IR ($CHCl_3$) 3590, 3465, 2980, 1585, 1055, 1030 cm^{-1}; MS (40 eV), *m/e* calc for $C_{18}H_{22}O_2S$ 302.1340; found 302.1335, and 284.1240 ($M^+ - H_2O$, 21%)

(±) - (1*R**,2*R**,3*S**,4*S**) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*phenylthio*) - 1,4 - *pentanediol*. R_f 0.63 (EtOAc–hexane 1:1); m.p. 101–102°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.32 (m, 8H), 4.73 (d, 1H, J = 8.5 Hz), 4.00 (dd, 1H, J = 8.5, 2 Hz), 3.82 (m, 1H), 3.36 (br s, OH), 1.42 (m, 1H), 1.07 (d, 3H, J = 6 Hz), 0.93 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3595, 3470, 2980, 1585, 1060, 1030 cm^{-1}.

(+) - (1*R*,2*S*,3*R*) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*p* - *tolylthio*) - 1 - *pentanol*. $[\alpha]_D^{23}$ +12.08° (*c* 1.82, $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.17 (m, 2H), 7.05 (m, 2H), 4.80 (d, 1H, J = 6 Hz), 3.30 (dd, 1H, J = 6, 2.6 Hz), 2.92 (br s, OH), 2.30 (s, 3H), 1.80 (m, 1H), 1.50 (m, 2H), 1.03 (d, 3H, J = 7 Hz), 0.81 (t, 3H, J = 6 Hz); IR (film) 3440, 3050, 3020, 2945, 2860, 1590, 1480, 1450, 1370, 1025, 1010, 800, 750, 700 cm^{-1}; MS (70 eV), *m/e* 300 (M^+), 196 (1), 195 (5), 194 (24), 193 (38), 151 (16), 137 (92), 124 (19), 101 (20), 91 (33), 79 (35), 77 (33), 69 (100). All diastereoisomers of this series give virtually identical mass spectra.

(−) - (1*S*,2*S*,3*R*) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*p* - *tolylthio*) - 1 - *pentanol*. $[\alpha]_D^{23}$ −172° (*c* 0.66, $CHCl_3$); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.44 (m, 7H), 7.10 (m, 2H), 4.66 (d, 1H, J = 9.4 Hz), 3.33 (dd, 1H, J = 9.4, 1.5 Hz), 2.32 (s, 3H), 1.38 (m, 3H), 0.95 (d, 3H, J = 6.2 Hz), 0.62 (t, 3H, J = 7 Hz); IR (film) 3460, 3040, 3020, 2950, 1480, 1445, 1030, 1010, 800, 700 cm^{-1}.

(−) - (1*S*,2*R*,3*R*) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*p* - *tolylthio*) - 1 - *pentanol*. $[\alpha]_D^{23} - 14.9°$ (*c* 1.34, $CHCl_3$); m.p. 73–74°; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.25 (m, 5H), 7.17 (m, 2H), 7.05 (m, 2H), 4.82 (d, 1H, J = 6.2 Hz), 3.21 (dd, 1H, J = 6.2, 3.2 Hz), 2.75 (br s, OH), 2.30 (s, 3H), 1.84 (m, 2H), 1.23 (m, 1H), 1.08 (d, 3H, J = 7 Hz), 0.85 (t, 3H, J = 7 Hz); IR (film) 3445, 3060, 3025, 2950, 1480, 1445, 1020, 1005, 800, 700 cm^{-1}. (Found: C, 75.72; H, 8.16. Calc for $C_{19}H_{24}OS$: C, 75.97; H, 8.05%.)

(1*R*,2*R*,3*R*) - 3 - *Methyl* - 1 - *phenyl* - 2 - (*p* - *tolylthio*) - 1 - *pentanol*. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.27 (m, 7H), 7.06 (m, 2H), 4.76 (d, 1H, J = 8.5 Hz), 3.25 (br s, OH), 3.18 (dd, 1H, J = 8.5, 3.2 Hz), 2.31 (s, 3H), 1.57 (m, 2H), 1.25 (m, 1H), 0.99 (d, 3H, J = 6.5 Hz), 0.82 (t, 3H, J = 7 Hz); IR ($CHCl_3$) 3450, 3050, 3025, 2955, 1475, 1440, 1015, 1005, 800, 695 cm^{-1}.

General procedure for preparation of tetrahydrofurans

A soln of β-hydroxysulfide (0.1–0.2 mmol) in 5 ml of dry CH_2Cl_2 was cooled to 0° under Ar. Addition of Me_2SO_4, or trimethyloxonium tetrafluoroborate, or methyl fluorosulfonate or methyl triflate (1.1 equiv) at 0° with stirring for 10–30 min, followed by concentration *in vacuo*, led to yellow or reddish oil, which was purified by preparative TLC using EtOAc–hexane (1 : 19 by volume) elution.

The parent β-hydroxysulfoxides were cyclized directly using freshly distilled acetyl bromide (3 equiv) under the conditions described above (CH_2Cl_2, 0°), with the addition of 2-methyl-1-butene in excess to scavenge bromine generated in the reaction. Alternatively sulfoxides **19** and **21** were treated with freshly distilled oxalyl chloride (2.1 equiv) and NaI (2.1 equiv) in dry acetonitrile at 22° under N_2 with purification as reported above.†

(±) - (2*S**,3*S**,4*R**,5*S**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**5**) (R = Ph). ^{1}H-NMR (220 MHz) δ 7.23 (m, 10H), 4.82 (d, 1H, J = 9 Hz), 3.92 (m, 1H), 3.03 (dd, 1H, J = 11, 9 Hz), 1.84 (m, 1H), 1.30 (d, 3H, J = 7 Hz), 1.11 (d, 3H, J = 7 Hz); IR (film) 3060, 3040, 2980, 1480, 1440, 1090, 1020, 695 cm^{-1}; MS (40 eV), *m/e* 284.8 (M^+, 18), 283.8 (86), 177.8 (100), 173.9 (51), 158.9 (20), 109.9 (63), 68 (52). All other diastereomers of **5** gave nearly identical mass spectral data.

(±) - (2*S**,3*S**,4*R**,5*S**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (t - *butylthio*)*furan* (**5**) (R = t-Bu). ^{1}H-NMR (220 MHz) δ 7.36 (m, 5H), 4.66 (d, 1H, J = 9 Hz), 4.02 (m, 1H), 2.66 (m, 1H), 1.34 (d, 3H, J = 6 Hz), 1.16 (d, 3H, J = 7 Hz), 0.95 (s, 9H); IR (film) 3030, 2955, 1455, 1365, 1160, 1070, 755, 700 cm^{-1}; MS (70 eV), *m/e* 264 (M^+, 1.2), 174 (6), 158 (18), 102 (100), 91 (16), 101 (15), 77 (14), 57 (68).

(±) - (2*S**,3*S**,4*S**,5*R**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**11**). ^{1}H-NMR (220 MHz) δ 7.25 (m, 10H), 4.85 (d, 1H, J = 5 Hz), 3.91 (m, 1H), 3.70 (dd, 1H, J = 8, 5 Hz), 2.19 (m, 1H), 1.41 (d, 3H, J = 6 Hz), 1.11 (d, 3H, J = 7 Hz); IR (film) 3060, 2985, 1090, 1015, 750, 695 cm^{-1}; MS, *m/e* calc for $C_{18}H_{20}OS$ 284.1235, found 284.1239 (33.2%), 178.082 (100), 174 (48), 163 (24), 110 (51%).

(±) - (2*S**,3*R**,4*R**,5*S**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**12**). ^{1}H-NMR (220 MHz) δ 7.27 (m, 10H), 4.84 (d, 1H, J = 9 Hz), 4.52 (m, 1H), 3.77 (dd, 1H, J = 9, 7 Hz), 2.52 (m, 1H), 1.32 (d, 3H, J = 6 Hz), 1.14 (d, 3H, J = 7 Hz); IR (film) 3060, 3040, 2980, 1440, 1095, 1020, 745, 695 cm^{-1}.

(±) - (2*S**,3*R**,4*R**,5*R**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**13**). ^{1}H-NMR (220 MHz) δ 7.18 (m, 10H), 5.18 (d, 1H, J = 9 Hz), 4.23 (m, 1H), 4.07 (dd, 1H, J = 9, 6 Hz), 2.68 (m, 1H), 1.34 (d, 3H, J = 6 Hz), 1.10 (d, 3H, J = 7 Hz); IR (film) 3060, 3045, 2980, 1585, 1445, 1090, 1020, 740, 695 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*S**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**14**). ^{1}H-NMR (220 MHz) δ 7.23 (m, 10H), 5.48 (d, 1H, J = 6 Hz), 4.70 (m, 1H), 3.82 (dd, 1H, J = 6, 5 Hz), 2.39 (m, 1H), 1.25 (d, 3H, J = 6 Hz), 1.09 (d, 3H, J = 7 Hz); IR (film) 3060, 3035, 2985, 1580, 1480, 1440, 1090, 1020, 735, 695 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*R**) - *Tetrahydro* - 2,3 - *dimethyl* - 5 - *phenyl* - 4 - (*phenylthio*)*furan* (**25**). ^{1}H-NMR (220 MHz) δ 7.25 (m, 10H), 4.66 (d, 1H, J = 7 Hz), 4.32 (m, 1H), 3.09 (overlapping dd, 1H, J = 7 Hz), 2.30 (m, 1H), 1.27 (d, 3H, J = 7 Hz), 1.05 (d, 3H, J = 7 Hz); IR (film) 3060, 3040, 2980, 2940, 2880, 1585, 1480, 1440, 1095, 1020, 740, 690 cm^{-1}. (Found: C, 75.50; H, 6.95; S, 11.33. Calc for $C_{18}H_{20}OS$: C, 76.01; H, 7.08; S, 11.27%.)

Synthesis of tetrahydrofurans **16** *and* **18**

Condensation of the (*R**)-phenylsulfoxide (**14a**, see the accompanying paper), with 3-methylbutanal under the general conditions as described for benzaldehyde gave three adducts in 3.6 : 1.4 : 1.0 ratio totaling 88% yield. The two major β-hydroxysulfoxide adducts were more efficiently separated after reduction with acetyl bromide (2.1 equiv, 2-methyl-1-butene, 15 equiv, CH_2Cl_2, 0°, 10 min) to their corresponding sulfides. Reactions using the (*S**)-phenylsulfoxide **14b** with 3-methylbutanal afforded all four diastereoisomeric products. However, the major adduct shared the same asymmetry along the carbon framework as obtained in the principal product from **14a**. All of the phenylsulfides were efficiently cyclized to their respective tetrahydrofuran derivatives with dimethylsulfate in 95–100% yields. Characterizations for these substances are provided as follows below.‡

(±) - (2*S**,3*S**,4*R**,5*S**) - 3,7 - *Dimethyl* - 4 - [(*R**) - *phenylsulfinyl*] - 2,5 - *octanediol* (*major adduct*). R_f 0.32 (EtOAc–hexane 6 : 4); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.50 (m, 3H), 4.43 (m, 1H, OH), 3.98 (m, 1H), 2.93 (s, 1H), 2.18 (m, 1H), 1.82 (m, 1H), 1.55 (d, 3H, J = 6 Hz), 1.48 (m, 2H), 1.27 (d, 3H, J = 7 Hz), 0.68 (d, 3H, J = 6 Hz), 0.55 (d, 3H, J = 6 Hz); IR (neat) 3400, 3060, 2960, 1445, 1030, 750 cm^{-1}.

(±) - (2*S**,3*S**,4*S**,5*R**) - 3,7 - *Dimethyl* - 4 - [(*R**) - *phenylsulfinyl*] - 2,5 - *octanediol* (*minor adduct*). R_f 0.16 (EtOAc–hexane 6 : 4); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.50 (m, 3H), 5.00 (br s, OH), 3.89 (m, 2H), 2.70 (d, 1H, J = 6 Hz), 2.18 (m, 1H), 1.80 (m, 1H), 1.54 (m, 2H), 1.18 (d, 3H, J = 6 Hz), 0.86 (d, 6H, J = 7 Hz), 0.79 (d, 3H, J = 6 Hz); IR (neat) 3400, 3060, 1440, 1080–1000, 740 cm^{-1}.

(±) - (2*S**,3*S**,4*R**,5*S**) - 3,7 - *Dimethyl* - 4 - (*phenylthio*) - 2,5 - *octanediol* (**15**) (*major*). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.27 (m, 3H), 3.93 (m, 1H), 3.80 (m, 1H), 3.66 (dd, 1H, J = 6, 1 Hz), 2.61 (br s, OH), 2.09 (m, 1H), 1.80 (m, 1H), 1.45 (m, 2H), 1.25 (d, 3H, J = 6 Hz), 1.00 (d, 3H, J = 7 Hz), 0.84 (d, 6H, J = 7 Hz); IR ($CHCl_3$) 3350, 2960, 1480, 1440, 1375, 1065–1040, 690 cm^{-1}.

(±) - (2*S**,3*S**,4*S**,5*R**) - 3,7 - *Dimethyl* - 4 - (*phenylthio*) - 2,5 - *octanediol* (**17**) (*minor*). R_f 0.62 (EtOAc–hexane 1:1); m.p. 64–65°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.30 (m, 3H), 3.86 (m, 3H), 3.16 (dd, 1H, J = 7, 3.5 Hz), 2.11 (m, 1H), 1.80 (m, 1H), 1.57 (m, 1H), 1.39 (m, 1H), 1.13 (d, 3H, J = 6 Hz), 1.09 (d, 3H, J = 6 Hz), 0.86 (overlapping doublets, 6H, J = 7 Hz); IR ($CHCl_3$) 3600, 3360, 2960, 1480, 1460, 1440, 1380, 1370, 1120, 1070–1050, 690 cm^{-1}; MS (70 eV), *m/e* 196 (17), 151 (22), 110 (45), 109 (25), 86 (52), 71 (38), 69 (50), 43 (100).

(±) - (2*S**,3*R**,4*S**,5*S**) - *Tetrahydro* - 2 - *isobutyl* - 4,5 - *dimethyl* - 3 - (*phenylthio*)*furan* (**16**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.30 (m, 3H), 3.89 (m, 1H), 3.59 (m, 1H), 2.68 (dd, 1H, J = 10, 9 Hz), 1.75 (m, 1H), 1.64 (m, 1H),

† Oxalyl chloride–sodium iodide has previously been used for reduction of sulfoxides to sulfides.[4]

‡ Desulfurization of sulfides **15** and **17** cleanly provided their respective diols. The 3,7-dimethyl-2,5-octanediol bearing 1,3-*anti* stereochemistry exhibited a methine multiplet at δ 3.77, whereas the 1,3-*syn*-isomer gave the methine (C_3—H) at δ 3.86. These chemical shift differences are consistent with our own benzylic alcohols in this report, as well as with assignments by W. C. Still for analogous alcohols prepared by hydroboration.[5]

1.34 (m, 2H), 1.16 (d, 3H, J = 6 Hz), 1.07 (d, 3H, J = 6 Hz), 0.86 (t, 6H, J = 6 Hz); IR (film) 3060, 2960, 2920, 2860, 1480, 1460, 1440, 1380, 1370, 1090, 740, 690 cm^{-1}; MS (70 eV), *m/e* 264 (M$^+$, 23), 178 (45), 163 (29), 154 (50), 112 (42), 110 (86), 69 (100), 55 (36).

(±) - (2*R**,3*S**,4*S**,5*S**) - *Tetrahydro* - 2 - *isobutyl* - 4,5 - *dimethyl* - 3 - (*phenylthio*)*furan* (**18**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.80 (m, 1H), 3.61 (m, 1H), 3.45 (dd, 1H, J = 9, 7 Hz), 2.07 (m, 1H), 1.75 (m, 1H), 1.41 (m, 2H), 1.27 (d, 3H, J = 6 Hz), 1.07 (d, 3H, J = 7 Hz), 0.86 (d, 3H, J = 7 Hz); IR ($CHCl_3$) 3055, 2960, 1480, 1460, 1440, 1080, 695 cm^{-1}. (Found: C, 72.00; H, 8.72; S, 12.41. Calc for $C_{16}H_{24}OS$: C, 72.65; H, 9.14; S, 12.12%.)

Synthesis of substituted tetrahydrofurans **20** *and* **22**

The dianion of (±) - (2*S**,3*R**) - 2 - methoxy - 3 - methyl - 4 - [(*R**) - phenylsulfinyl] - 3 - butanol was formed by dropwise addition of a soln (THF) of sulfoxide into freshly prepared lithium diisopropylamide (2.5 equiv) in anhyd THF at −78° under Ar, producing a red–orange soln. After stirring for 15 min, the 3-methylbutanal (2.5 equiv) was introduced all at once with subsequent warming to room temp, followed by the usual quenching procedure (NH_4Cl aq) and extraction. Purification by preparative TLC (EtOAc–hexane) led to the identification of four products in approximately 2 : 2 : 1 : 1 ratio with yields of 45–55%. The least polar adduct (**A**; major product) was readily recognized as **21**, and a slightly more polar isomer (**B**; major product) was assigned to the *syn* (*threo*) series bearing a 1,3-*anti*-diol arrangement. Such assignments were feasible by comparison of the ^{1}H-NMR spectra of previous condensations using **14a** and 3-methylbutanal (described above) in concert with ^{1}H-NMR data of the corresponding phenylsulfides. Moreover, the less polar minor adduct (**C**) was recognized as the other possible *anti* (*erythro*) compound, which subsequently afforded the same phenylsulfide as available from **19**. The (*S**)-sulfoxide **19** was obtained as the major *anti* (*erythro*) isomer isolated from analogous condensations using the corresponding (*S**)-sulfoxide, and produced suitable crystals for X-ray diffraction studies.

Tetrahydrofurans **20** and **22** were directly formed by treatment of the pure sulfoxide diastereomers with oxalyl chloride (2.5 equiv) and sodium iodide (2.5 equiv) in distilled acetonitrile at room temp. Data for characterization of this family of isomers has been listed below.

(±) - (2*S**,3*R**,4*S**,5*S**) - 2 - *Methoxy* - 3,7 - *dimethyl* - 4 - [(*R**) - *phenylsulfinyl*] - 3,5 - *octanediol* (**21**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.53 (m, 3H), 5.15 (d, 1H, J = 9 Hz), 4.25 (m, 1H), 4.08 (q, 1H, J = 6 Hz), 3.49 (s, 3H), 3.23 (s, 1H), 2.90 (d, 1H, J = 2 Hz), 1.64 (m, 3H), 1.39 (s, 3H), 1.26 (d, 3H, J = 6 Hz), 0.76 (d, 3H, J = 6 Hz), 0.59 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3400, 3010, 2950, 1440, 1425, 1170, 1095, 1005, 990, 960 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*R**) - 2 - *Methoxy* - 3,7 - *dimethyl* - 4 - [(*R**) - *phenylsulfinyl*] - 3,5 - *octanediol* (*major product* **B**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.57 (m, 3H), 5.44 (s, 1H), 4.44 (br s, 1H), 3.79 (q, 1H, J = 6 Hz), 3.77 (m, 1H), 3.47 (s, 3H), 3.20 (d, 1H, J = 4 Hz), 1.61 (m, 3H), 1.53 (s, 3H), 1.19 (d, 3H, J = 6 Hz), 0.73 (d, 3H, J = 6 Hz), 0.60 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3410, 3020, 2960, 1445, 1175, 1095, 1005, 995 cm^{-1}.

(±) - (2*S**,3*R**,4*R**,5*R**) - 2 - *Methoxy* - 3,7 - *dimethyl* - 4 - [(*S**) - *phenylsulfinyl*] - 3,5 - *octanediol* (**19**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.60 (m, 5H), 4.44 (m, 1H), 4.17 (br s, 1H), 3.79 (br s, 1H), 3.73 (q, 1H, J = 7 Hz), 3.39 (s, 3H), 2.82 (d, 1H, J = 3 Hz), 1.77 (m, 1H), 1.58 (s, 3H), 1.57 (m, 2H), 1.27 (d, 3H, J = 7 Hz), 0.63 (d, 3H, J = 7 Hz), 0.62 (d, 3H, J = 7 Hz); IR ($CHCl_3$) 3410, 3025, 2965, 1445, 1425, 1165, 1090, 1010, 995 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*S**) - 2 - *Methoxy* - 3,7 - *dimethyl* - 4 - (*phenylthio*) - 3,5 - *octanediol*. ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.29 (m, 3H), 4.36 (m, 1H), 3.68 (q, 1H, J = 6.0 Hz), 3.42 (s, 1H), 3.31 (s, 3H), 2.76 (s, 1H), 2.67 (d, 1H, J = 7.5 Hz), 1.64 (m, 2H), 1.29 (s, 3H), 1.25 (m, 1H), 1.12 (d, 3H, J = 6.0 Hz), 0.90 (d, 3H, J = 6.0 Hz), 0.83 (d, 3H, J = 6.0 Hz); IR ($CHCl_3$) 3610, 3400, 3045, 2980, 1365, 1090, 1060 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*R**) - 2 - *Methoxy* - 3,7 - *dimethyl* - 4 - (*phenylthio*) - 3,5 - *octanediol*. ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.29 (m, 3H), 4.48 (m, 1H and OH), 3.73 (q, 1H and OH, J = 6.0 Hz), 3.39 (s, 3H), 3.29 (d, 1H, J = 6.5 Hz), 1.89 (m, 1H), 1.73 (m, 1H), 1.53 (m, 1H), 1.19 (s, 3H), 1.07 (d, 3H, J = 6.0 Hz), 0.90 (d, 6H, J = 6.0 Hz); IR ($CHCl_3$) 3600, 3410, 3050, 2975, 2930, 1365, 1090, 1060 cm^{-1}.

(±) - (2*S**,3*R**,4*S**,5*S**) - *Tetrahydro* - 5 - *isobutyl* - 2,3 - *dimethyl* - 4 - (*phenylthio*) - 3 - *furanol* (**22**). R_f 0.60 (EtOAc–hexane 1:1); ^{1}H-NMR ($CDCl_3$) δ 7.76 (m, 2H), 7.32 (m, 3H), 3.98 (m, 1H), 3.84 (q, 1H, J = 6 Hz), 3.14 (d, 1H, J = 9 Hz), 2.34 (s, OH), 1.86 (m, 1H), 1.52 (m, 2H), 1.23 (d, 3H, J = 7 Hz), 1.10 (s, 3H), 1.09 (t, 6H, J = 6 Hz); IR (film) 3360, 3060, 2970, 1450, 1090, 695 cm^{-1}; MS (70 eV), *m/e* 280.1 (M$^+$), 192.1 (52), 149.1 (78), 110 (30), 71 (57.6), 43 (100), 41 (33).

(±) - (2*S**,3*R**,4*S**,5*R**) - *Tetrahydro* - 5 - *isobutyl* - 2,3 - *dimethyl* - 4 - (*phenylthio*) - 3 - *furanol*. R_f 0.27 (EtOAc–hexane 1 : 4); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.30 (dt, 1H, J = 9, 4 Hz), 3.69 (d, 1H, J = 9 Hz), 3.63 (q, 1H, J = 6 Hz), 2.31 (s, OH), 1.87 (m, 1H), 1.60 (m, 2H), 1.23 (d, 3H, J = 6 Hz), 1.20 (s, 3H), 0.92 (t, 6H, J = 6 Hz); IR (film) 3380, 3065, 2980, 1445, 1090, 700 cm^{-1}; MS (70 eV), *m/e* 280 (M$^+$), 192 (52), 149 (78), 43 (100).

(±) - (2*S**,3*R**,4*R**,5*R**) - *Tetrahydro* - 5 - *isobutyl* - 2,3 - *dimethyl* - 4 - (*phenylthio*) - 3 - *furanol* (**20**). R_f 0.66 (EtOAc–hexane 1:1); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.35 (m, 5H), 3.59 (m, 2H), 3.28 (d, 1H, J = 7 Hz), 1.92 (s, OH), 1.84 (m, 1H), 1.54 (m, 2H), 1.28 (s, 3H), 1.22 (d, 3H, J = 6 Hz), 0.89 (t, 6H, J = 6 Hz); IR (film) 3620, 3400, 3060, 2980, 1450, 1090, 695 cm^{-1}; MS (70 eV), *m/e* 280 (M$^+$), 192 (50), 43 (100).

Preparation of tetrahydrofurans **32** *and* **33**

A soln of the *R**-sulfoxide **28** (330 mg, 1.09 mmol in 4 ml of dry THF) was added dropwise via syringe to a soln of lithium diisopropylamide (generated from 0.19 ml, 1.34 mmol, of amine and 0.51 ml, 1.34 mmol, of titrated n-BuLi in hexanes) at −78° under Ar. The yellow–gold soln was warmed to −20° over 20 min, and **29** (0.17 ml, 1.03 mmol) was added rapidly. The mixture faded instantly to a pale yellow color, and was stirred for an additional minute before quenching by addition of NH_4Cl aq. The aqueous layer was extracted with EtOAc (2 × 40 ml), and the combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to a yellow oil. Flash chromatography with EtOAc–hexanes (1 : 4) afforded 99 mg of pure sulfoxide **30** and 50 mg of sulfoxide **31**, for a combined yield of 43%. Material balance was accounted for with the recovery of **28** and **29**.

(±) - (2*S**,3*R**,4*S**,5*R**) - 1,5 - *Bis*(*benzyloxy*) - 2,4 - *dimethyl* - 3 - [(*R**) - *phenylsulfinyl*] - 2 - *hexanol* (**30**). M.p. 136–137°; ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.27 (m, 8H), 7.20 (m, 5H), 4.45 (d, 1H, J = 12 Hz), 4.45 (s, 2H), 4.06 (s, 1H), 3.91 (d, 1H, J = 12 Hz), 3.50 (s, 2H), 3.42 (m, 1H), 2.97 (br s, OH), 2.07 (m, 1H), 1.50 (s, 3H), 1.37 (d, 3H, J = 6 Hz), 1.07 (d, 3H, J = 6 Hz); IR ($CHCl_3$) 3540, 3360, 1090, 700 cm^{-1}. (Found: C, 72.33; H, 7.47. Calc for $C_{28}H_{34}O_4S$: C, 72.07; H, 7.34%.)

The sulfoxide adduct **31** was contaminated with small amounts of the starting sulfoxide **28** (10–20%), and was more conveniently purified as its corresponding sulfide after the usual borane reduction procedure. Thus, the phenylsulfide from **31** was obtained as a colorless oil: ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.23 (m, 10H), 7.09 (m, 3H), 4.52 (d, 1H, J = 12 Hz), 4.30 (s, 2H), 4.23 (s, 1H), 3.93 (d, 1H, J = 12 Hz), 3.70 (d, 1H, J = 10 Hz), 3.39 (m, 1H), 3.30 (d, 1H, J = 10 Hz), 3.02 (br s, OH), 2.36 (m, 1H), 1.27 (s, 3H), 1.20 (d, 3H, J = 6 Hz), 1.07 (d, 3H, J = 7 Hz); IR (film) 3550, 3450, 1585, 1455, 1385, 1045, 735, 695 cm^{-1}. The phenylsulfide from **30** was characterized as a colorless oil: ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.23 (m, 10H), 7.02

(m, 3H), 4.52 (d, 1H, J = 12 Hz), 4.43 (d, 1H, J = 2 Hz), 4.16 (d, 1H, J = 10 Hz), 4.07 (d, 1H, J = 10 Hz), 3.98 (d, 1H, J = 12 Hz), 3.66 (m, 1H), 3.36 (d, 1H, J = 10 Hz), 3.25 (d, 1H, J = 10 Hz), 2.77 (br s, OH), 2.23 (m, 1H), 1.41 (s, 3H), 1.25 (d, 3H, J = 7 Hz), 1.07 (d, 3H, J = 6 Hz); IR (film) 3480, 3060, 3030, 2985, 1585, 1430, 1452, 1380, 1100, 730, 690 cm^{-1}.

Tetrahydrofurans **32** and **33** were obtained following the general procedure with treatment of the individual sulfides with methyl triflate (1.1 equiv) in CH_2Cl_2 at 0°.

(±) - (2*S**,3*R**,4*S**,5*S**) - 2 - [(*Benzyloxy*)*methyl*] - *tetrahydro* - 2,4,5 - *trimethyl* - 3 - (*phenylthio*)*furan* (**32**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.61 (m, 10H), 4.68 (d, 1H, J = 12 Hz), 4.36 (d, 1H, J = 12 Hz), 3.72 (d, 1H, J = 10 Hz), 3.64 (m, 1H), 3.50 (d, 1H, J = 10 Hz), 3.00 (d, 1H, J = 10 Hz), 2.07 (m, 1H), 1.27 (d, 3H, J = 7 Hz), 1.18 (s, 3H), 1.07 (d, 3H, J = 7 Hz); IR (film) 3060, 3030, 2965, 1585, 1480, 1452, 1440, 1090, 730, 695 cm^{-1}.

(±) - (2*R**,3*S**,4*S**,5*S**) - 2 - [(*Benzyloxy*)*methyl*] - *tetrahydro* - 2,4,5 - *trimethyl* - 3 - (*phenylthio*)*furan* (**33**). ^{1}H-NMR (220 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.27 (m, 8H), 4.52 (d, 1H, J = 12 Hz), 4.41 (d, 1H, J = 12 Hz), 3.64 (m, 1H), 3.59 (d, 1H, J = 11 Hz), 3.39 (d, 1H, J = 11 Hz), 3.24 (d, 1H, J = 11 Hz), 1.73 (m, 1H), 1.25 (d, 3H, J = 6 Hz), 1.23 (s, 3H), 1.07 (d, 3H, J = 7 Hz); IR (film) 3065, 3025, 2965, 1585, 1480, 1455, 1440, 1375, 1095, 730, 690 cm^{-1}; MS (70 eV), *m/e* 222 (3), 221 (9), 179 (6), 111 (12), 97 (11), 91 (64), 69 (14), 65 (18), 43 (100).

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