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Novel synthesis of chiral, enantiomerically pure thiodiglycols and diglycols

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Abstract

Natural α-hydroxy acids have been converted in a sequence of *O*-protection, reduction, *O*-activation, thioether and ether formation and deprotection to chiral, non-racemic β,β′-dihydroxy thioethers **1a**, **1b** and ether **1c**. Overall yields are excellent (75%). In an attempt to synthesize the respective dihydroxy ether **1d** derived from mandelic acid 1,3-dioxolane derivatives **7** were obtained. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Whereas chiral bidentate ligands have become ubiquitous in catalytic asymmetric synthesis over the past decades,[1,2] other multidentate[3–6] ligands have rarely found applications in this field. In particular, we are interested in the development of chiral metal catalysts with C_2-symmetric tridentate ligands of the general type **1** with different donor sets, *e.g.* X=N, P, S, O; Y=S, O (Scheme 1).[7] In this context we planned to synthesize the chiral thiodiglycols **1a** and **1b** as well as chiral diglycols **1c**[8,9] and **1d**. These enantiopure compounds **1a–d**, which have already been synthesized in different ways as racemic materials,[10–13] shall serve for the complexation of alkali and alkali earth metals in the catalysis of base mediated processes (aldol and Michael reactions).[14,15] Moreover, **1a–d** are useful intermediates for the preparation of other tripodal ligands of the general type **1**, since the transformations OH→SR′ and OH→PR′$_2$ (R′=aryl, alkyl) have readily been performed.[3]

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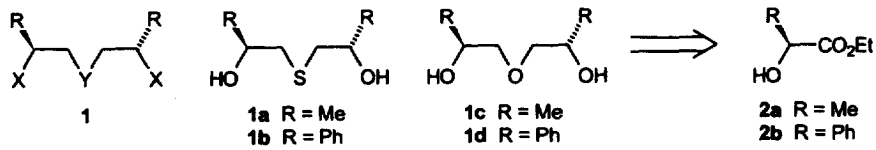
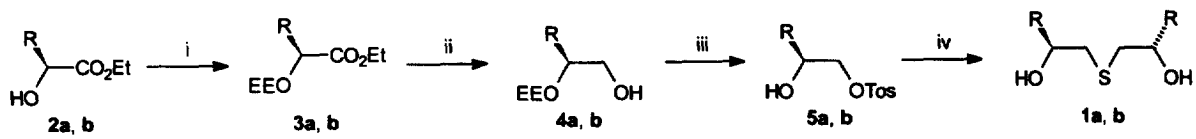


Scheme 1. C_2-Symmetric tripodal ligands **1**, chiral thiodiglycoles **1a** and **1b**, chiral diglycoles **1c** and **1d**, retrosynthesis from ethyl lactate (**2a**) and ethyl mandelate (**2b**)

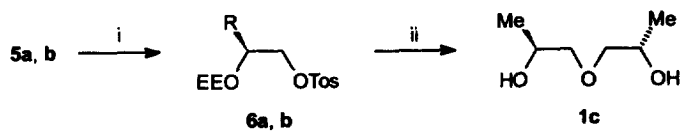
2. Results and discussion

Reasonable starting materials for the preparation of **1a–d** are (*S*)-ethyl lactate (**2a**, R=Me) and (*S*)-ethyl mandelate (**2b**, R=Ph), because the stereoinformation is derived from the *chiral pool* and the oxygen functionalities are preexisting. The synthesis of **1a,b** reported in this work is summarized in Scheme 2. After introduction of the protecting group (EE=ethoxyethyl) by stirring the esters **2** in ethyl vinyl ether as solvent and a catalytic amount of TosOH,[16] reduction of the intermediate ethyl carboxylates **3** with $LiAlH_4$[17,18] furnished the primary alcohols **4**. Subsequently, the hydroxy functions were activated by tosylate formation with TosCl–pyridine.[19] Acidic workup in this step cleanly removed the ethoxyethyl protective group,[20] and the resulting tosylates **5**[21–23] were converted to the corresponding thioethers **1a** and **1b** by S_N reaction with Na_2S in acetone. Interestingly, although an excess of Na_2S was applied to achieve good conversion of the tosylates **5**, no thiol formation was detectable. Obviously, intermediate thiolates are significantly more nucleophilic than sulfide under our reaction conditions. Thanks to excellent yields in all four synthetic steps the overall yields from esters **2** were 77% for **1a** and 76% for **1b**.



Scheme 2. Synthesis of chiral thiodiglycoles **1a** (R=Me) and **1b** (R=Ph); reagents, conditions, and yields: (i) H_2C=CHOEt, cat. TosOH·H_2O, **3a**: 98%, **3b**: 100%; (ii) $LiAlH_4$, Et_2O, **4a**: 95%, **4b**: 98%; (iii) 1. TosCl, pyridine, 2. HCl–H_2O, **5a**: 91%, **5b**: 94%; (iv) Na_2S, acetone, 70°C, **1a**: 88%, **1b**: 82%; EE=EtO(Me)CH, Tos=*p*Me$C_6H_4SO_2$

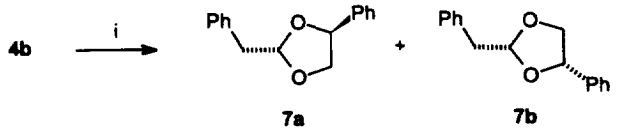
Scheme 3 outlines our synthetic strategy leading to the chiral β,β′-dihydroxy ethers **1c** and **1d**. Tosylates **5** were first re-protected with ethyl vinyl ether–cat. TosOH,[24] and the resulting compounds **6** were converted with the deprotonated primary alcohols **4** in DMF. Acidic workup directly cleaved the protective groups and furnished the diol **1c** in good yield.



Scheme 3. Synthesis of chiral diglycol **1c**; reagents, conditions, and yields: (i) H_2C=CHOEt, cat. TosOH·H_2O, **6a** (R=Me): 97%, **6b** (R=Ph): 97%; (ii) 1. **4a**, NaH, DMF, 2. H^+ (ion exchanger resin), CH_2Cl_2, **1c**: 41%; EE=EtO(Me)CH, Tos=*p*Me$C_6H_4SO_2$

However, compound **1d** was not accessible by this method. Presumably due to steric reasons we were not able to achieve any conversion of **4b** with **6b**. Consequently, we decided to enhance reactivity of the electrophile **6** by choosing a different leaving group. Following a literature strategy[25] we converted a stoichiometric mixture of **4b** and pyridine with 0.5 equivalents of triflic anhydride. Below 0°C the

starting material **4b** converted cleanly to a mixture of two diastereomeric products, which were separable by chromatography. Their constitution was elucidated by standard spectroscopic means to be the 1,3-dioxolane derivatives **7a** and **7b**. These racemic materials are known in the literature as dimers of styrene oxide[26,27] (Scheme 4). Target compound **1d** was not detectable in the reaction mixture. The relative configuration of **7a** and **7b** was established by NOE experiments: whereas 2-CH showed a NOE to one of the 5-CH protons in isomer **7a** only, in compound **7b** a NOE was detected between 2-CH and 4-CH as well as to one 5-CH proton. Consequently, phenyl and benzyl substituents are situated trans to one another in **7a**, and compound **7b** is the *cis* isomer. A mechanistic rationale for the formation of **7a** and **7b** suggests a cyclic arenium ion (phenonium ion)[28–30] as an intermediate resulting from an intramolecular substitution of the triflate leaving group. This three membered ring intermediate can be opened by a deprotonated equivalent of **4b** under either retention or inversion of the configuration, thus leading to two diastereomeric products. The absolute configuration of the 4,5-C_2 fragments is assumed to be retained in the reaction sequence. Loss of the ethoxyethyl protective function is thought to be caused by pyridinium triflate present in the reaction mixture.



7a **7b**

Scheme 4. Formation of dioxolane derivatives **7a** and **7b** from **4b**; reagents, conditions, and yields: (i) 0.5 equiv. $(CF_3SO_2)_2O$, 1.0 equiv. pyridine, THF, −30°C, 45 min, **7a**: 19%, **7b**: 17%

The final products **1a–c** and **7a** and **7b**, as well as all intermediates, were fully characterized, and **1a–c** showed only one set of signals in their NMR spectra, which was important with respect to enantiomeric excess: partially racemic starting materials would have caused formation of a certain amount of (*S*,*R*)-diastereoisomers, which were not detectable in samples of **1a–c**.

In summary, the conversion of α-hydroxy esters derived from (*S*)-lactic **2a** and (*S*)-mandelic acid **2b** to chiral, C_2-symmetric thiodiglycoles **1a** and **1b** and diglycol **1c** in excellent overall yields was reported. In attempts to synthesize a dihydroxy ether derived from mandelic acid 1,3-dioxolane derivatives **7a** and **7b** were obtained.

3. Experimental[†]

3.1. General

Column chromatography was accomplished with Merck silica gel (Type 60, 0.063–0.200 mm). ^1H NMR spectra were recorded on a Bruker AM 400 (400 MHz), and reported in parts per million (ppm) using the residual proton solvent peak of $CDCl_3$ at 7.26 ppm as an internal standard, with coupling constants (*J*) in hertz (Hz). NOE experiments were performed on a Bruker AC 200 (200 MHz). ^{13}C NMR spectra were recorded on a Bruker AC 200 (50 MHz), and reported in parts per million (ppm) using the solvent triplet of $CDCl_3$ at 77.0 ppm as an internal standard. Assignments were made using DEPT experiments. MS spectra were obtained with Varian MAT 711 and MAT 95SQ (high resolution) spectrometers. IR spectra were recorded on a Nicolet Magna IR 750 spectrophotometer. Elemental

[†] Abbreviations: ATR: attenuated total reflection; MTB: *tert*-butyl methyl ether; Tos: *p*-tolylsulfonyl.

analyses were obtained with an Analytik Jena Vario EL. Optical rotations were measured with a Perkin–Elmer polarimeter 341. Melting points were measured with a Leica Galen III and are uncorrected.

Reagents and starting materials were purchased from common commercial suppliers and used as received. (*S*)-(+)-Ethyl mandelate was synthesized according to the literature procedure from commercially available (*S*)-(+)-mandelic acid.[31] Et_2O was freshly distilled from sodium.

3.2. (S)-(−)-Ethyl 2-(1-ethoxyethoxy)propanoate 3a

TosOH·H_2O (95 mg, 0.50 mmol) was added to a solution of (*S*)-(−)-ethyl lactate **2a** (11.8 g, 100 mmol) in ethyl vinyl ether (30 ml) at −20°C, and stirred for 45 min. The mixture was diluted with MTB (50 ml), washed with a saturated solution of $NaHCO_3$ (3×50 ml), and dried over $MgSO_4$. Evaporation of all volatile materials gave **3a** (18.6 g, 97.8 mmol, 98%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ −80 (c 4.1, $CHCl_3$), lit.[24] $[\alpha]_D^{20}$ −78.9 (c 4.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, t, J=6.9 Hz), 1.18 (3H, t, J=6.8 Hz), 1.21–1.32 (9H, m), 1.34–1.66 (9H, m), 3.43–3.71 (4H, m), 4.14–4.22 (5H, m), 4.33 (1H, q, J=6.9 Hz), 4.77 (1H, q, J=5.3 Hz), 4.78 (1H, q, J=5.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.94 ($2CH_3$), 14.83 (CH_3), 15.03 (CH_3), 18.65 ($2CH_3$), 19.45 (CH_3), 19.75 (CH_3), 59.98 (CH_2), 60.48 ($2CH_2$), 60.83 (CH_2), 69.43 (CH), 69.63 (CH), 99.01 (CH), 99.17 (CH), 173.07 (C), 173.35 (C). IR (ATR): 3513 (w), 2981 (s), 2936 (m), 2903 (m), 2876 (m), 1759 (vs), 1736 (s), 1604 (w), 1447 (m), 1373 (m), 1341 (w), 1299 (m), 1271 (m), 1194 (s), 1174 (s), 1145 (s), 1096 (vs), 1081 (vs), 1055 (s), 1027 (m), 966 (m), 925 (w), 889 (w), 853 (w), 757 (w), 702 (w). MS (EI, 70 eV) *m/z* (%)=175 (5), 145 (25), 117 (9), 102 (10), 73 (100). HRMS: mol. mass calcd 189.1127 (for $C_9H_{17}O_4$), found 189.1132 ($M-H^+$).

3.3. (S)-(+)-Ethyl 2-(1-ethoxyethoxy)-2-phenylethanoate 3b

TosOH·H_2O (190 mg, 1.00 mmol) was added to a solution of (*S*)-(+)-ethyl mandelate **2b** (18.0 g, 100 mmol) in ethyl vinyl ether (60 ml) at 0°C, and stirred for 1 h. The mixture was diluted with MTB (50 ml), washed with a saturated solution of $NaHCO_3$ (3×50 ml), and dried over $MgSO_4$. Evaporation of all volatile materials gave **3b** (25.2 g, 100 mmol, 100%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ +62 (c 3.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (6H, t, J=7.1 Hz), 1.18 (3H, t, J=7.2 Hz), 1.19 (3H, t, J=7.2 Hz), 1.35 (6H, d, J=5.4 Hz), 3.40–3.66 (4H, m), 4.00–4.21 (4H, m), 4.78 (1H, q, J=5.4 Hz), 4.93 (1H, q, J=5.4 Hz), 5.16 (1H, s), 5.23 (1H, s), 7.18–7.37 (6H, m), 7.42–7.48 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.67 ($2CH_3$), 14.77 ($2CH_3$), 19.37 (CH_3), 19.63 (CH_3), 60.10 (CH_2), 60.33 (CH_2), 60.63 ($2CH_2$), 74.85 (CH), 75.01 (CH), 98.41 (CH), 98.79 (CH), 126.70 (2CH), 126.81 (2CH), 127.94 (CH), 128.08 (3CH), 128.14 (2CH), 136.61 (C), 136.94 (C), 170.76 (2C). IR (ATR): 3090 (w), 3065 (w), 3032 (w), 2980 (s), 2935 (m), 2902 (m), 1751 (vs), 1733 (s), 1603 (w), 1587 (w), 1496 (w), 1478 (w), 1454 (m), 1386 (m), 1370 (m), 1338 (m), 1298 (m), 1267 (m), 1205 (s), 1176 (s), 1155 (s), 1137 (s), 1081 (vs), 1056 (vs), 1029 (s), 951 (m), 933 (m), 900 (w), 867 (m), 860 (m), 815 (w), 730 (m), 698 (s). MS (EI, 70 eV) *m/z* (%)=207 (6), 179 (53), 163 (82), 145 (5), 135 (20), 118 (8), 107 (29), 90 (19), 79 (25), 73 (100). HRMS: mol. mass calcd 252.1362 (for $C_{14}H_{20}O_4$), found 252.1367 (M^+). Anal. calcd for $C_{14}H_{20}O_4$ (252.31): C 66.65, H 7.99, found C 66.47, H 7.93.

3.4. (S)-(+)-2-(1-Ethoxyethoxy)-1-propanol 4a

A solution of **3a** (18.6 g, 97.8 mmol) in Et_2O (40 ml) was added dropwise to a suspension of $LiAlH_4$ (2.97 g, 78.2 mmol) in Et_2O (40 ml) at −20°C, the mixture was stirred over night, and hydrolyzed with

water (20 ml). The organic layer was decanted, and the solids were washed twice with MTB (each 50 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), and dried over $MgSO_4$. Evaporation of the solvents gave **4a** (13.8 g, 93.1 mmol, 95%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ +41 (c 6.2, $CHCl_3$), lit.[17] $[\alpha]_D^{29}$ +42.2 (c 5.87, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (3H, d, J=6.3 Hz), 1.17 (3H, d, J=6.4 Hz), 1.21 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.1 Hz), 1.32–1.38 (6H, m), 2.39 (1H, br s), 3.19 (1H, br s), 3.42–3.61 (7H, m), 3.67–3.73 (1H, m), 3.77–3.84 (2H, m), 4.72 (1H, q, J=5.3 Hz), 4.80 (1H, q, J=5.3 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.04 ($2CH_3$), 17.00 (CH_3), 17.39 (CH_3), 20.23 (CH_3), 20.45 (CH_3), 60.42 (CH_2), 60.73 (CH_2), 66.46 (CH_2), 66.83 (CH_2), 72.86 (CH), 75.31 (CH), 99.36 (2CH). IR (ATR): 3453 (br s), 2976 (s), 2933 (m), 2875 (m), 1725 (w), 1706 (w), 1446 (m), 1376 (s), 1336 (m), 1173 (m), 1127 (vs), 1099 (vs), 1052 (vs), 968 (s), 923 (m), 884 (w), 844 (w). MS (EI, 70 eV) *m/z* (%)=133 (3), 117 (7), 103 (17), 73 (100). HRMS: mol. mass calcd 147.1021 (for $C_7H_{15}O_3$), found 147.1019 ($M-H^+$).

3.5. (S)-(+)-2-(1-Ethoxyethoxy)-2-phenyl-1-ethanol *4b*

A solution of **3b** (25.2 g, 100 mmol) in Et_2O (40 ml) was added dropwise to a suspension of $LiAlH_4$ (3.40 g, 89.5 mmol) in Et_2O (40 ml) at −20°C, the mixture was stirred over night, and hydrolyzed with water (30 ml). The organic layer was decanted, and the solids were washed twice with MTB (each 50 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), and dried over $MgSO_4$. Evaporation of the solvents gave **4b** (20.6 g, 97.8 mmol, 98%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ +140 (c 4.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.1 Hz), 1.30–1.36 (6H, m), 2.36 (1H, dd, J=3.9 Hz, J=9.4 Hz), 2.70 (1H, dd, J=3.5 Hz, J=9.4 Hz), 3.20–3.29 (1H, m), 3.52–3.74 (7H, m), 4.58–4.67 (2H, m), 4.74–4.81 (2H, m), 7.25–7.39 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.65 (CH_3), 15.09 (CH_3), 20.12 (CH_3), 20.27 (CH_3), 60.39 (CH_2), 60.57 (CH_2), 66.90 (CH_2), 67.08 (CH_2), 78.51 (CH), 79.67 (CH), 98.32 (CH), 99.52 (CH), 126.62 (2CH), 126.67 (2CH), 127.59 (CH), 127.73 (CH), 128.09 (2CH), 128.20 (2CH), 138.83 (C), 139.68 (C). IR (ATR): 3442 (br vs), 3086 (w), 3063 (w), 3031 (w), 2978 (s), 2932 (m), 2877 (m), 1604 (w), 1586 (w), 1453 (m), 1386 (s), 1340 (m), 1311 (w), 1226 (w), 1128 (vs), 1093 (vs), 1078 (vs), 1047 (vs), 1027 (vs), 954 (s), 918 (m), 957 (m), 849 (m), 759 (s), 701 (vs). MS (EI, 70 eV) *m/z* (%)=179 (45), 134 (9), 121 (99), 107 (20), 103 (44), 91 (37), 79 (22), 77 (37), 73 (100). HRMS: mol. mass calcd 179.1072 (for $C_{11}H_{15}O_2$), found 179.1072 ($M-CH_2OH^+$). Anal. calcd for $C_{12}H_{18}O_3$ (210.27): C 68.55, H 8.63, found C 68.18, H 8.80.

3.6. (S)-(+)-2-Hydroxy-1-propyl tosylate *5a*

TosCl (13.9 g, 73.1 mmol) was added to a solution of **4a** (7.22 g, 48.7 mmol) in pyridine (70 ml), and stirred over night at room temperature. Water (50 ml) and CH_2Cl_2 (50 ml) were added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed five times with hydrochloric acid (18%, each 100 ml), then with water (200 ml) and brine (200 ml). The solution was dried over $MgSO_4$, evaporated, and the crude product was chromatographed (SiO_2, MTB, R_f=0.45) to give **5a** (10.2 g, 44.4 mmol, 91%) as a colorless solid (mp 34°C, lit.[19] 36°C). $[\alpha]_D^{20}$ +11 (c 5.4, $CHCl_3$), lit.[19] $[\alpha]_D$ +10.3 (c 4.57, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, d, J=7.3 Hz), 2.03 (1H, br s), 2.45 (3H, s), 3.85 (1H, dd, J=7.3 Hz, J=10.0 Hz), 4.00 (1H, dd, J=3.0 Hz, J=10.0 Hz), 4.02–4.09 (1H, m), 7.34–7.38 (2H, m), 7.78–7.82 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.94 (CH_3), 21.62 (CH_3), 65.59 (CH), 74.77 (CH_2), 127.92 (2CH), 129.93 (2CH), 132.63 (C), 145.06 (C). IR (ATR): 3065 (w), 3031 (w), 2979 (w), 2932 (w), 2895

(w), 2875 (w), 1726 (w), 1598 (w), 1494 (w), 1453 (w), 1361 (s), 1307 (w), 1291 (w), 1189 (s), 1176 (vs), 1129 (m), 1096 (s), 1079 (s), 1055 (m), 1026 (m), 976 (s), 958 (s), 922 (m), 874 (m), 814 (m), 775 (m), 760 (m), 701 (s), 666 (s). MS (EI, 70 eV) *m/z* (%)=230 (1), 200 (49), 156 (98), 155 (36), 139 (6), 107 (9), 92 (100), 91 (96), 77 (4), 65 (28). HRMS: mol. mass calcd 230.0613 (for $C_{10}H_{14}O_4S$), found 230.0613 (M^+). Anal. calcd for $C_{10}H_{14}O_4S$ (230.28): C 52.16, H 6.13, found C 52.14, H 6.17.

3.7. (S)-(+)-2-Hydroxy-2-phenyl-1-ethyl tosylate **5b**

TosCl (17.2 g, 90.0 mmol) was added to a solution of **4b** (12.6 g, 60.0 mmol) in pyridine (75 ml), and stirred over night at room temperature. Water (150 ml) and CH_2Cl_2 (50 ml) were added, and the mixture was stirred for 45 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were washed four times with hydrochloric acid (18%, each 200 ml), with water (200 ml), and with brine (200 ml). The solution was dried over $MgSO_4$, evaporated, and the crude product was chromatographed (SiO_2, MTB:hexane 1:1, R_f=0.34) to give **5b** (16.4 g, 56.1 mmol, 94%) as a colorless solid (mp 73°C, lit.[21] 65–66°C). $[\alpha]_D^{20}$ +55 (c 2.4, $CHCl_3$), lit.[21] $[\alpha]_D^{25}$ +51.1 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (3H, s), 2.58 (1H, br s), 4.04 (1H, dd, J=8.6 Hz, J=10.4 Hz), 4.14 (1H, dd, J=3.3 Hz, J=10.4 Hz), 4.97 (1H, dd, J=3.3 Hz, J=8.6 Hz), 7.28–7.37 (7H, m), 7.73–7.79 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.60 (CH_3), 71.85 (CH), 74.27 (CH_2), 126.14 (2CH), 127.90 (2CH), 128.44 (CH), 128.60 (2CH), 129.89 (2CH), 132.58 (C), 138.23 (C), 145.03 (C). IR (ATR): 3523 (br m), 3063 (w), 3031 (w), 2946 (w), 2891 (w), 1597 (w), 1495 (w), 1453 (w), 1401 (w), 1355 (s), 1308 (w), 1293 (w), 1189 (m), 1174 (vs), 1096 (m), 1070 (w), 1019 (w), 968 (s), 917 (w), 867 (m), 814 (m), 774 (m), 759 (w), 700 (m), 667 (s). MS (EI, 70 eV) *m/z* (%)=275 (40), 262 (14), 217 (4), 155 (57), 139 (4), 120 (7), 107 (100), 91 (75), 79 (26), 77 (19), 73 (35), 65 (17). HRMS: mol. mass calcd 275.0742 (for $C_{15}H_{15}O_3S$), found 275.0743 ($M-OH^+$). Anal. calcd for $C_{15}H_{16}O_4S$ (292.36): C 61.63, H 5.52, found C 61.37, H 5.58.

3.8. (S,S)-(+)-Bis(2-hydroxy-1-propyl) thioether **1a**

A mixture of **5a** (1.15 g, 5.00 mmol) and $Na_2S \cdot H_2O$ (65%, 480 mg, 4.00 mmol) in acetone (3 ml) was stirred in a tightly closed reaction flask over night at 70°C. The mixture was diluted with CH_2Cl_2 (25 ml), dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed (SiO_2, MTB, R_f=0.16) to give **1a** (330 mg, 2.20 mmol, 88%) as a colorless oil. $[\alpha]_D^{20}$ +110 (c 3.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, d, J=6.2 Hz), 2.49 (2H, dd, J=8.4 Hz, J=13.8 Hz), 2.61 (2H, br s), 2.75 (2H, dd, J=3.4 Hz, J=13.8 Hz), 3.84–3.94 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.98 ($2CH_3$), 41.46 ($2CH_2$), 66.14 (2CH). IR (ATR): 3352 (br vs), 2968 (s), 2913 (m), 1453 (m), 1406 (m), 1371 (s), 1339 (m), 1300 (m), 1328 (w), 1192 (w), 1123 (vs), 1065 (vs), 1030 (vs), 934 (vs), 880 (w), 861 (w), 826 (m). MS (EI, 70 eV) *m/z* (%)=150 (3), 132 (2), 117 (6), 106 (100), 99 (5), 88 (21), 75 (28), 62 (99). HRMS: mol. mass calcd 150.0715 (for $C_6H_{14}O_2S$), found 150.0718 (M^+). Anal. calcd for $C_6H_{14}O_2S$ (150.24): C 47.97, H 9.39, found C 47.88, H 9.57.

3.9. (S,S)-(+)-Bis(2-hydroxy-2-phenyl-1-ethyl) thioether **1b**

A mixture of **5b** (1.46 g, 5.00 mmol) and $Na_2S \cdot H_2O$ (65%, 480 mg, 4.00 mmol) in acetone (3 ml) was stirred in a tightly closed reaction flask over night at 70°C. The mixture was diluted with CH_2Cl_2 (25 ml), dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed (SiO_2, MTB:hexane 1:1, R_f=0.24) to give **1b** (562 mg, 2.05 mmol, 82%) as a colorless oil. $[\alpha]_D^{20}$ +96 (c 1.7,

$CHCl_3$). ^1H NMR (40 MHz, $CDCl_3$): δ 2.77 (2H, dd, J=8.9 Hz, J=14.0 Hz), 2.90 (2H, dd, J=3.7 Hz, J=14.0 Hz), 3.20 (2H, br s), 4.77 (2H, dd, J=3.7 Hz, J=8.9 Hz), 7.24–7.44 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.74 ($2CH_2$), 72.50 (2CH), 125.76 (4CH), 127.88 (2CH), 128.50 (4CH), 142.42 (2C). IR (ATR): 3402 (br vs), 3085 (w), 3061 (w), 3029 (w), 2954 (w), 2914 (w), 2885 (w), 1700 (w), 1602 (w), 1493 (m), 1453 (m), 1408 (m), 1333 (w), 1298 (w), 1230 (w), 1196 (m), 1156 (w), 1081 (w), 1057 (s), 1028 (m), 1003 (m), 916 (w), 865 (w), 848 (w), 768 (m), 737 (m), 698 (vs). MS (EI, 70 eV) *m/z* (%)=274 (1), 257 (100), 239 (49), 213 (25), 205 (33), 174 (22), 137 (84), 135 (34), 121 (23), 107 (60), 104 (81), 91 (31), 79 (31), 77 (28). HRMS: mol. mass calcd 274.1028 (for $C_{16}H_{18}O_2S$), found 274.1033 (M^+).

3.10. (S)-(−)-2-(1-Ethoxyethoxy)-1-propyl tosylate **6a**

TosOH·H_2O (19 mg, 0.10 mmol) was added to a solution of **5a** (1.15 g, 5.00 mmol) in ethyl vinyl ether (10 ml) and MTB (10 ml) at −20°C, and stirred for 1 h. The mixture was diluted with MTB (30 ml), washed three times with a saturated solution of $NaHCO_3$ (each 30 ml), dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed (SiO_2, MTB:hexane 1:2, R_f=0.35) to give **6a** (1.46 g, 4.83 mmol, 97%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ −11 (c 4.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.08–1.19 (12H, m), 1.20–1.24 (6H, m), 2.43 (6H, s), 3.36–3.46 (2H, m), 3.50–3.60 (2H, m), 3.81–4.01 (6H, m), 4.70 (2H, q, J=5.3 Hz), 7.30–7.36 (4H, m), 7.74–7.80 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.10 (CH_3), 15.15 (CH_3), 17.14 (CH_3), 17.95 (CH_3), 20.29 ($2CH_3$), 21.54 ($2CH_3$), 60.00 (CH_2), 60.28 (CH_2), 68.59 (CH), 69.55 (CH), 72.89 ($2CH_2$), 98.45 (CH), 99.88 (CH), 127.84 (2CH), 127.88 (2CH), 129.73 (2CH), 129.79 (2CH), 132.87 (2CH), 144.72 (C), 144.80 (C). IR (ATR): 2980 (m), 2935 (m), 2898 (m), 1598 (m), 1495 (w), 1452 (m), 1360 (vs), 1308 (w), 1292 (w), 1211 (w), 1190 (s), 1177 (vs), 1133 (s), 1121 (s), 1097 (s), 1079 (s), 1055 (m), 1020 (w), 990 (s), 963 (s), 931 (m), 828 (s), 815 (s), 792 (m), 706 (w), 688 (w), 667 (s). MS (EI, 70 eV) *m/z* (%)=302 (1), 287 (2), 257 (5), 217 (6), 213 (21), 200 (15), 173 (4), 156 (33), 155 (58), 139 (3), 107 (5), 92 (50), 91 (81), 73 (100), 65 (21). HRMS: mol. mass calcd 302.1188 (for $C_{14}H_{22}O_5S$), found 302.1191 (M^+).

3.11. (S)-(+)-2-(1-Ethoxyethoxy)-2-phenyl-1-ethyl tosylate **6b**

TosOH·H_2O (19 mg, 0.10 mmol) was added to a solution of **5b** (1.46 g, 5.00 mmol) in ethyl vinyl ether (10 ml) and MTB (20 ml) at −5°C, and stirred for 1 h. The mixture was diluted with MTB (50 ml), washed three times with a saturated solution of $NaHCO_3$ (each 40 ml), dried over $MgSO_4$, and evaporated to dryness. The crude product was chromatographed (SiO_2, MTB:hexane 1:2, R_f=0.39) to give **6b** (1.77 g, 4.85 mmol, 97%) as a colorless oil (mixture of two diastereoisomers; 1:1 by ^1H NMR). $[\alpha]_D^{20}$ +86 (c 2.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.0 Hz), 1.13 (3H, t, J=7.0 Hz), 1.18–1.26 (6H, m), 2.44 (6H, m), 3.18–3.28 (1H, m), 3.46–3.61 (3H, m), 4.00–4.17 (4H, m), 4.60 (1H, q, J=5.4 Hz), 4.75–4.85 (2H, m), 4.88 (1H, dd, J=4.2 Hz, J=8.0 Hz), 7.22–7.36 (14H, m), 7.69–7.79 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.81 (CH_3), 15.17 (CH_3), 20.01 (CH_3), 20.40 (CH_3), 21.56 ($2CH_3$), 59.29 (CH_2), 61.15 (CH_2), 72.63 (CH_2), 72.99 (CH_2), 74.79 (CH), 74.86 (CH), 97.68 (CH), 100.14 (CH), 126.64 (2CH), 127.06 (2CH), 127.83 (4CH), 128.15 (CH), 128.44 (3CH), 128.55 (2CH), 129.69 (2CH), 129.75 (2CH), 132.90 (C), 132.96 (C), 137.45 (C), 138.50 (C), 144.61 (C), 144.69 (C). IR (ATR): 2979 (w), 2936 (w), 2879 (w), 1597 (w), 1495 (w), 1452 (w), 1400 (w), 1353 (s), 1307 (w), 1291 (w), 1189 (m), 1173 (vs), 1096 (m), 1019 (w), 974 (s), 928 (s), 857 (m), 829 (m), 812 (s), 791 (m), 705 (w), 688 (w), 665 (s). MS (EI, 70 eV) *m/z* (%)=319 (1), 275 (6), 228 (4), 217 (8), 155 (16), 104 (6),

91 (27), 77 (4), 73 (100), 65 (6). HRMS: mol. mass calcd 319.1004 (for $C_{17}H_{19}O_4S$), found 319.1006 ($M-OCH_2CH_3^+$). Anal. calcd for $C_{19}H_{24}O_5S$ (364.46): C 62.62, H 6.64, found C 62.29, H 6.61.

3.12. (S,S)-(+)-Bis(2-hydroxy-1-propyl) ether 1c

A solution of **4a** (296 mg, 2.00 mmol) and **6a** (605 mg, 2.00 mmol) in DMF (1 ml) was added dropwise to a suspension of NaH (80% dispersion in mineral oil, 120 mg, 4.00 mmol) in DMF (1 ml) under an atmosphere of Ar. The mixture was stirred over night at room temperature, subsequently hydrolyzed with water (20 ml), and extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residue was taken up in CH_2Cl_2 (5 ml), stirred over an acidic ion exchanger resin (88.0 mg, DOWEX 50 W×8) for three days, filtered, and evaporated to dryness. The residue was chromatographed (SiO_2, MTB, R_f=0.18) to give **1a** (111 mg, 0.827 mmol, 41%) as a colorless oil. $[\alpha]_D^{20}$ +52, $[\alpha]_{365}^{20}$ +148, $[\alpha]_{436}^{20}$ +98, $[\alpha]_{546}^{20}$ +60, $[\alpha]_{578}^{20}$ +53 (c 2.3, $CHCl_3$), lit.[9] $[\alpha]_{Hg}^{26}$ +57.62 (c 2.505, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (6H, d, J=6.3 Hz), 2.45 (2H, br s), 3.32 (2H, dd, J=8.3 Hz, J=9.7 Hz), 3.46 (2H, dd, J=3.0 Hz, J=9.7 Hz), 3.95–4.05 (2H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.50 ($2CH_3$), 65.77 (2CH), 76.42 ($2CH_2$). IR (ATR): 3368 (br vs), 2971 (m), 2931 (m), 2866 (s), 1453 (w), 1422 (w), 1376 (m), 1355 (w), 1144 (s), 1103 (vs), 933 (m), 979 (s), 944 (m), 956 (m), 841 (w). MS (EI, 70 eV) *m/z* (%)=101 (2), 89 (91), 71 (9), 59 (100), 57 (16). HRMS: mol. mass calcd 89.0603 (for $C_4H_9O_2$), found 89.0610 [$M^+-C(OH)HCH_3$]. Anal. calcd for $C_6H_{14}O_3$ (134.17): C 53.71, H 10.52, found C 53.63, H 10.66.

3.13. trans-(2S,4S)-(+)-2-Benzyl-4-phenyl-1,3-dioxolan 7a and cis-(2R,4S)-(+)-isomer 7b

Pyridine (79 mg, 1.0 mmol) was added to a solution of **4b** (210 mg, 1.00 mmol) in THF (1 ml) under an atmosphere of Ar at −30°C. The mixture was stirred for 30 min, then $(CF_3SO_2)_2O$ (141 mg, 0.500 mmol) was added dropwise, and the resulting mixture was stirred for another 45 min at −30°C. After hydrolyzation with water (10 ml), the mixture was extracted three times with CH_2Cl_2 (each 10 ml), and the combined organic layers were dried over $MgSO_4$. After removal of the solvents, the residue was chromatographed (SiO_2, MTB:hexane 1:10) to give **7a** (22.5 mg, 0.0936 mmol, 19%, R_f=0.39) as a brownish solid (mp 42°C, lit.[27] 33–34°C) and **7b** (20.0 mg, 0.0832 mmol, 17%, R_f=0.33) as a yellowish oil. **7a**: $[\alpha]_D^{20}$ +45 (c 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (1H, dd, J=5.1 Hz, J=14.0 Hz), 3.10 (1H, dd, J=4.2 Hz, J=14.0 Hz), 3.68 (1H, dd, J=7.7 Hz, J=8.3 Hz), 4.37 (1H, dd, J=6.3 Hz, J=8.3 Hz), 4.99 (1H, dd, J=6.3 Hz, J=7.7 Hz), 5.49 (1H, dd, J=4.2 Hz, J=5.1 Hz), 7.22–7.46 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.24 (CH_2), 72.68 (CH_2), 77.72 (CH), 105.69 (CH), 125.99 (2CH), 126.59 (CH), 127.99 (CH), 128.31 (2CH), 128.58 (2CH), 129.82 (2CH), 136.00 (C), 139.51 (C). IR (ATR): 3086 (w), 3063 (w), 3029 (w), 2950 (w), 2923 (w), 2870 (m), 1604 (w), 1495 (m), 1454 (m), 1399 (w), 1341 (w), 1306 (w), 1208 (w), 1133 (vs), 1079 (m), 1042 (m), 1029 (m), 987 (s), 939 (w), 908 (w), 842 (w), 754 (s), 698 (vs). MS (EI, 70 eV) *m/z* (%)=239 (1), 149 (54), 121 (100), 103 (79), 91 (52), 77 (31), 65 (20). HRMS: mol. mass calcd 239.1072 (for $C_{16}H_{15}O_2$), found 239.1076 ($M-H^+$). **7b**: $[\alpha]_D^{20}$ +48 (c 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (1H, dd, J=4.8 Hz, J=14.0 Hz), 3.17 (1H, dd, J=4.4 Hz, J=14.0 Hz), 3.70 (1H, dd, J=6.7 Hz, J=7.9 Hz), 4.18 (1H, dd, J=7.0 Hz, J=7.9 Hz), 5.01 (1H, dd, J=6.7 Hz, J=7.0 Hz), 5.31 (1H, dd, J=4.4 Hz, J=4.8 Hz), 7.20–7.44 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.80 (CH_2), 71.98 (CH_2), 78.46 (CH), 105.35 (CH), 126.36 (2CH), 126.65 (CH), 128.10 (CH), 128.30 (2CH), 128.49 (2CH), 129.91 (2CH), 135.95 (C), 139.37 (C). IR (ATR): 1/λ=3086 (w), 3063 (w), 3030 (w), 2951 (w), 2924 (w), 2878 (m), 1726 (w), 1605 (w), 1495 (m), 1454 (m), 1404 (w), 1372 (w), 1345 (w), 1307 (w), 1286 (w), 1204 (w), 1134 (vs), 1080 (m), 1042 (m), 1028 (m), 1002 (m), 951 (w), 910

(w), 844 (w), 823 (w), 754 (s), 697 (vs). MS (EI, 70 eV) *m/z* (%)=239 (1), 149 (100), 121 (98), 103 (58), 91 (66), 77 (14), 65 (10). HRMS: mol. mass calcd 239.1072 (for $C_{16}H_{15}O_2$), found 239.1071 ($M-H^+$). Anal. calcd for $C_{16}H_{16}O_2$ (240.30): C 79.97, H 6.71, found C 79.67, H 6.83.

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