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Synthesis of C_2-symmetric tris-thioethers via optically active mustards

Jens Christoffers[a,*] and Ulrich Rößler[b]

[a]*Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany*
[b]*Institut für Organische Chemie der Technischen Universität Berlin, Sekretariat C 3, Straße des 17. Juni 135, D-10623 Berlin, Germany*

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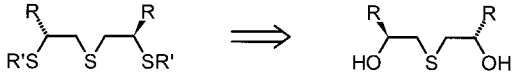
Abstract—Chiral dihydroxy thioethers derived from L-mandelic and L-lactic acid are activated with $SOCl_2$, $SOBr_2$ and by bis-trifluoroacetate formation to give optically active mustard gas analogues. These compounds serve as substrates for stereospecific nucleophilic substitution reactions with NaSEt and NaSPh to furnish C_2-symmetric tris-thioethers with overall inversion of configuration. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the course of our combinatorial catalysis project on asymmetric Michael reactions[1–3] we prepared a number of new chiral bi- and tridentate ligands being phosphines,[4] amines,[5–6] imines,[7] and oxazolines[8] having a thioether moiety as an additional donor function. In continuation of this work, we herein wish to report on novel C_2-symmetric tris-thioethers **1a**–**d** (Scheme 1) being accessible from chiral dihydroxy thioethers **2a**,**b** by a sequence of alcohol activation and stereospecific nucleophilic substitution. The starting materials **2a**,**b** are readily available on a multigram scale from optically active ethyl lactate and mandelate in 75–76% yield over five steps.[9–10]



1a R = Me, R' = Et
1b R = Me, R' = Ph
1c R = Ph, R' = Et
1d R = Ph, R' = Ph

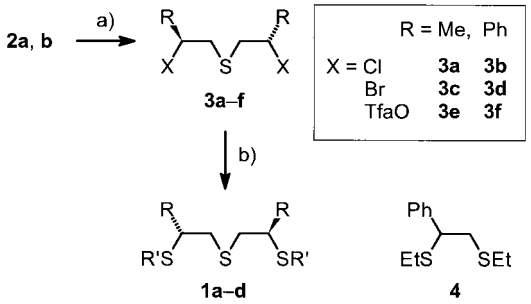
2a R = Me
2b R = Ph

Scheme 1. Retrosynthesis of tris-thioethers **1a**–**d** from dihydroxy thioethers **2a**,**b**.

2. Results and discussion

In initial attempts to activate alcohols **2a**,**b** as sulfonates we tried to synthesize the corresponding tosylates, mesylates, or triflates according to standard protocols. However, in every case we were neither able to detect the product in the reaction mixture nor to isolate any unique compound. Obviously, there is a significant neighboring group effect of the adjacent thioether function preventing the formation of unique materials. Having in mind that mustard gas—bis(2-chlororethyl)sulfide—is a very reactive but stable compound we considered alcohol activation by formation of the corresponding halides with $SOCl_2$ and $SOBr_2$ (Scheme 2). Compounds **3a**[11,12] and **3c**[13] have been reported before as racemic materials. Conversion of **2a**,**b** with the two thionyl halides proceeded with almost quantitative conversion in all four cases (Table 1). For **2a** elevated temperatures were required in both cases. As detectable by NMR spectroscopy all four products were obtained as single diastereoisomers and moreover as optically active materials. Partial racemization would have caused at least some formation of the meso-diastereoisomer.

Only compound **3b** showed long-term stability at ambient temperature and was obtained as an analytically pure material without particular purification (on SiO_2 decomposition is observed). Congeners **3a** and **3c**,**d** always contained



Scheme 2. Activation of dihydroxy thioethers **2a**,**b** and synthesis of tris-thioethers **1a**–**d**. Reagents, conditions, and yields: (a) see Table 1, (b) see Table 2. For definition of **2a**,**b** and **1a**–**d** see Scheme 1. Tfa=trifluoroacetyl.

Keywords: alcohols; diols; substitution; sulfur compounds; thioethers.
* Corresponding author. Fax: +49-711-685-4269;
e-mail: jchr@po.uni-stuttgart.de

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Table 1. Activation of dihydroxy thioethers **2a**,**b**

Starting material	Reagent	Solvent	Conditions	Product	Yield (%)
2a	$SOCl_2$	None	1.5 h, 50°C	**3a**	94[a]
2b	$SOCl_2$	None	2 h, 23°C	**3b**	94[b]
2a	$SOBr_2$	CH_2Cl_2	2 h, reflux	**3c**	100[a]
2b	$SOBr_2$	CH_2Cl_2	4 h, 23°C	**3d**	100[a]
2a	Tfa_2O[c]	CH_2Cl_2	3 h, 23°C	**3e**	97[b]
2b	Tfa_2O	CH_2Cl_2	2 h, 23°C	**3f**	97[b]

[a] Crude materials, decomposition even at −20°C within days.
[b] Analytically pure without purification, no decomposition at −20°C over weeks.
[c] Tfa=Trifluoroacetyl.

Table 2. Synthesis of tris-thioethers **1a**–**d**, solvent: DMF

Starting material	Nucleophile	Temperature (°C)	Product	Yield (%)
3a	NaSEt	23	**1a**	61[a]
3e	NaSEt	60	**1a**	8[b]
3a	NaSPh	23	**1b**	60[a]
3e	NaSPh	70	**1b**	24[b]
3b	NaSEt	23	**1c**	50[b]
3b	NaSEt	70	**4**	78[b]
3f	NaSEt	60	**1c**	21[b]
3b	NaSPh	23	**1d**	33[b]
3b	NaSPh	70	**1d**	39[b]
3f	NaSPh	70	**1d**	17[b]

[a] Contains impurities even after repeated chromatography.
[b] Analytically pure after chromatography.

impurities resulting from continuous decomposition. Attempts to purify them by chromatography or distillation lead to complete decomposition. As expected for a mustard gas analogue, **3a** showed a strong biological activity in a primary anticancer assay. Since the instability of **3a** and **3c**,**d** turned out to be problematic in terms of clean conversion of these compounds we additionally decided to activate alcohols **2a**,**b** as the bis-trifluoroacetate **3e**,**f**, which were readily available in quantitative yields and as analytically pure products without chromatography (Table 1).

Compounds **3a**–**f** were converted with sodium thioethanolate and thiophenolate in order to prepare tris-thioethers **1a**–**d** (Scheme 2, Table 2). The bis-bromides **3c**,**d** turned out to be too unstable to give products in satisfying purity. Bis-chloride **3a** gave acceptable yields of **1a**,**b** at ambient temperature, however, since decomposition of **3a** occurred along with the substitution reaction, impurities resulted which could not be removed from the products **1a**,**b**, not even by repeated chromatography. Conversion of the bis-trifluoroacetate **3e** at elevated temperature furnished **1a**,**b** in analytically pure form after chromatography, but in low yields. Reaction of the more stable bis-chloride **3b** yielded analytically pure products **1c**,**d** after chromatography, however, the yields were moderate at ambient temperature. Attempts to raise the yields by elevation of the reaction temperature did not significantly improve the formation of **1d**. In the case of conversion of **3b** with NaSEt at 70°C no product **1c** was isolable after workup. Instead the bis-thioether **4**[14] was formed in good yield as a racemic material. A number of pathways can be considered for the formation of **4** under the reaction conditions all involving thiiranium species as intermediates. Application of the bis-trifluoroacetate **3f** for the synthesis of **1c**,**d** at elevated temperature resulted—similar to **3e**—in lower yields.

All products **1a**–**d** were formed stereospecifically with inversion of configuration independently from the nature of the starting material (bis-chloride or bis-trifluoroacetate). Meso-diastereoisomers were not detectable by NMR spectroscopy in any case. Moreover, all products were of course optically active. The values of optical rotations were independent from the starting material (bis-chloride or bis-trifluoroacetate) or the reaction temperature applied. We have included compounds **1a**–**d** in our library of chiral ligands and investigations on the asymmetric catalysis of Michael reactions, as mentioned in the introduction, are presently in process.

3. Experimental

3.1. General procedure

Column chromatography was accomplished with Merck silica gel (Type 60, 0.063–0.200 mm) using *tert*-butyl methyl ether (MTB) and hexanes (PE) as solvents. Preparative TLC was performed on ICN silica gel plates (type 60A, F254, 20 cm×20 cm). Absolute CH_2Cl_2 was freshly distilled from CaH_2, DMF (HPLC grade quality) was used as purchased. ^1H NMR: Bruker AM 400 (400 MHz). ^{13}C NMR: Bruker AC 200 (50 MHz), assignments were made using DEPT experiments. MS: Varian MAT 711 and MAT 955Q (high resolution). IR: Nicolet Magna IR 750. Elemental analyses: Analytik Jena Vario EL. Optical rotations: Perkin–Elmer polarimeter 341.

Dihydroxy thioethers were prepared as reported previously,[10] all other starting materials were commercially available.

3.1.1. (*S*,*S*)-(+)-Bis(2-chloropropyl)sulfide (3a). Under an atmosphere of nitrogen $SOCl_2$ (2.00 ml, 27.5 mmol) was added to diol **2a** (375 mg, 2.50 mmol). After being stirred for 90 min at 50°C water was added (15 ml), and the mixture extracted with CH_2Cl_2 (3×25 ml). Drying of the combined organic layers ($MgSO_4$) and filtration was followed by evaporation of all volatile materials to yield the dichloride **3a** (440 mg, 2.35 mmol, 94%) as a brown liquid, which decomposes upon chromatography as well as on storage at ambient temperature. $[\alpha]_D^{20}=+9.61$ (*c* 3.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.60$ (d, $J=6.6$ Hz, 3H), 2.83 (dd, $J=13.7$, 7.9 Hz, 1H), 3.01 (dd, $J=13.7$, 5.8 Hz, 1H), 4.06–4.16 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=23.89$ (CH_3), 42.58 (CH_2), 56.68 (CH) ppm. IR (ATR): $\nu=2976$ (m), 2928 (m), 1713 (vs), 1450 (m), 1419 (m), 1377 (m), 1362 (s), 1221 (s), 1107 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 186 (31) [M^+], 137 (35), 123 (100), 110 (21), 87 (43), 77 (43), 61 (17). $C_6H_{12}Cl_2S$ (187.13): Mol. mass calcd 186.0037; found 186.0039 (HRMS).

3.1.2. (*S*,*S*)-(+)-Bis(2-phenyl-2-chloroethyl)sulfide (3b). According to the previous procedure for **3a** $SOCl_2$ (2.00 ml, 27.5 mmol) and diol **3b** (640 mg, 2.33 mmol) were converted for 2 h at 23°C to yield the dichloride **2b** (685 mg, 2.20 mmol, 94%) as an analytically pure brown

oil, which is stable below 0°C over weeks, but decomposes upon chromatography on SiO_2. $[\alpha]_D^{20}=+125$ (*c* 2.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.98$ (dd, $J=13.9$, 8.5 Hz, 1H), 3.06 (dd, $J=13.9$, 6.4 Hz, 1H), 4.79 (dd, $J=8.5$, 6.4 Hz, 1H) 7.28–7.48 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=41.70$ (CH_2), 62.04 (CH), 127.27 (CH), 128.63 (CH), 128.78 (CH), 139.57 (C) ppm. IR (ATR): $\nu=1493$ (m), 1454 (s), 768 (m), 723 (m), 696 (vs) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 310 (10) [M^+], 149 (100), 135 (20), 125 (26), 115 (16), 104 (60), 103 (47), 91 (25), 77 (22), 51 (12). $C_{16}H_{16}Cl_2S$ (311.27): Anal. calcd C 61.74, H 5.18; found C 61.84, H 5.31. Mol. mass calcd 310.0350; found 310.0349 (HRMS).

3.1.3. (*S,S*)-(+)-Bis(2-bromopropyl)sulfide (3c). Under an atmosphere of nitrogen $SOBr_2$ (1.65 g, 7.92 mmol) was added to a solution of diol **2a** (297 mg, 1.98 mmol) in CH_2Cl_2 (10 ml). After being heated to reflux for 2 h water was added (30 ml) and the mixture extracted with CH_2Cl_2 (3×30 ml). Drying of the combined organic layers ($MgSO_4$) and filtration was followed by evaporation of all volatile materials to yield the dibromide **3c** (547 mg, 1.98 mmol, 100%) as a brown liquid, which decomposes upon chromatography as well as on storage below 0°C. $[\alpha]_D^{20}=+23$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.78$ (d, $J=6.6$ Hz, 3H), 2.91 (dd, $J=13.7$, 8.9 Hz, 1H), 3.15 (dd, $J=13.7$, 5.3 Hz, 1H), 4.06–4.32 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=24.66$ (CH_3), 42.93 (CH_2), 47.68 (CH) ppm. IR (ATR): $\nu=2970$ (s), 2923 (s), 1727 (m), 1447 (s), 1416 (m), 1375 (vs), 1243 (m), 1220 (m), 1163 (vs), 1099 (m), 1045 (m), 996 (s) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 274 (19) [M^+], 195 (100) [M^+–Br], 153 (38), 125 (20), 121 (64), 75 (30). $C_6H_{12}Br_2S$ (276.03): Mol. mass calcd 273.9027; found 273.9022 (HRMS).

3.1.4. (*S,S*)-(+)-Bis(2-phenyl-2-bromoethyl)sulfide (3d). Under an atmosphere of nitrogen $SOBr_2$ (208 mg, 1.00 mmol) was added to a solution of diol **2b** (94.1 mg, 0.343 mmol) in CH_2Cl_2 (2 ml). After being stirred for 4 h at 23°C water was added (10 ml), and the mixture extracted with CH_2Cl_2 (2×20 ml). Drying of the combined organic layers ($MgSO_4$) and filtration was followed by evaporation of all volatile materials to yield the dibromide **3d** (137 mg, 0.343 mmol, 100%) as a green liquid, which decomposes upon chromatography as well as on storage below 0°C. $[\alpha]_D^{20}=+12$ (*c* 0.95, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.03$ (dd, $J=10.6$, 10.3 Hz, 1H), 4.09 (dd, $J=10.3$, 5.5 Hz, 1H), 5.15 (dd, $J=10.6$, 5.5 Hz, 1H), 7.28–7.50 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=34.99$ (CH_2), 50.83 (CH), 127.59 (CH), 128.79 (CH), 128.89 (CH), 139.52 (C) ppm. IR (ATR): $\nu=1496$ (m), 1454 (s), 1155 (m), 1137 (m), 767 (s), 694 (vs) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 398 (1) [M^+], 319 (12), 183 (46), 104 (100), 103 (31), 91 (15), 78 (17), 77 (17), 51 (14). $C_{16}H_{16}Br_2S$ (400.17): Mol. mass calcd 397.9340; found 397.9337 (HRMS).

3.1.5. (*S,S*)-(−)-Bis(2-trifluoroacetoxypropyl)sulfide (3e). Under an atmosphere of nitrogen Tfa_2O (1.21 g, 5.76 mmol) was added at 0°C to a solution of diol **2a** (217 mg, 1.44 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 3 h while warming up to ambient temperature, then water (5 ml) and saturated Na_2CO_3 solution (30 ml) were added. After extraction with CH_2Cl_2 (3×30 ml), drying ($MgSO_4$), and filtration, all volatile materials were removed yielding the bisacetate **3e** (479 mg, 1.40 mmol, 97%) as a yellowish, analytically pure oil. $[\alpha]_D^{20}=-13.1$ (*c* 11.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.45$ (d, $J=6.2$ Hz, 3H), 2.81 (d, $J=6.2$ Hz, 2H), 5.21 (sextet, $J=6.2$ Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=18.48$ (CH_3), 37.18 (CH_2), 74.71 (CH), 114.30 (q, $J=286$ Hz, CF_3), 156.74 (q, $J=42$ Hz, CO) ppm. IR (ATR): $\nu=1781$ (vs), 1380 (m), 1331 (m), 1218 (s), 1154 (vs), 1122 (vs), 1031 (m), 862 (m), 776 (m), 728 (m) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 342 (4) [M^+], 228 (38), 155 (16), 114 (100) [$CF_3CO_2H^+$], 99 (15), 87 (58), 73 (15), 69 (83), 59 (13). $C_{10}H_{12}F_6O_4S$ (342.25): Anal. calcd C 35.09, H 3.53; found C 35.14, H 3.82. Mol. mass calcd 342.0360; found 342.0361 (HRMS).

3.1.6. (*S,S*)-(+)-Bis(2-phenyl-2-trifluoroacetoxyethyl)-sulfide (3f). According to the previous procedure for **3e** Tfa_2O (527 mg, 2.51 mmol), diol **2b** (172 mg, 0.627 mmol), and CH_2Cl_2 (4 ml) were converted to yield bisacetate **3f** (284 mg, 0.609 mmol, 97%) as a yellowish, analytically pure oil. $[\alpha]_D^{20}=+92.6$ (*c* 10.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.89$ (dd, $J=14.4$, 5.6 Hz, 1H), 3.03 (dd, $J=14.4$, 8.1 Hz, 1H), 5.92 (dd, $J=8.1$, 5.6 Hz, 1H), 7.24–7.46 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=37.46$ (CH_2), 79.27 (CH), 114.45 (q, $J=284$ Hz, CF_3), 126.49 (CH), 128.88 (CH), 129.37 (CH), 136.34 (C), 156.49 (q, $J=42$ Hz, CO) ppm. IR (ATR): $\nu=1785$ (s), 1224 (s), 1149 (vs), 697 (m) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 466 (10) [M^+], 352 (55), 203 (29), 149 (100), 135 (20), 115 (20), 104 (31), 91 (29), 77 (14), 69 (17). $C_{20}H_{16}F_6O_4S$ (466.40): Anal. calcd C 51.51, H 3.46; found C 51.60, H 3.65. Mol. mass calcd 466.0673; found 466.0678 (HRMS).

3.1.7. (*R,R*)-(+)-Bis[2-(ethylsulfanyl)propyl]sulfide (1a). A solution of bisacetate **3e** (916 mg, 2.68 mmol) in DMF (6 ml) was added to NaSEt (757 mg, 9.00 mmol), and the resulting mixture was stirred overnight at 60°C in a tightly closed reaction vial. After dilution with MTB (75 ml) the solution was washed with water (3×30 ml), dried ($MgSO_4$), filtered and the solvent evaporated. Column chromatography (SiO_2, MTB/PE 1:50, $R_f=0.13$) of the residue followed by removal of small amounts of higher volatile impurities in high vacuum furnished tris-thioether **1a** (52.2 mg, 0.219 mmol, 8%) as an analytically pure, colorless oil.

Analogous conversion of dichloride **3a** (468 mg, 2.50 mmol) with NaSEt in DMF at ambient temperature yielded the title compound **1a** (364 mg, 1.53 mmol, 61%) containing impurities, which could not be removed by chromatography. $[\alpha]_D^{20}=+86$ (*c* 3.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.26$ (t, $J=7.4$ Hz, 3H), 1.36 (d, $J=6.8$ Hz, 3H), 2.52–2.64 (m, 1H), 2.59 (q, $J=7.4$ Hz, 2H), 2.82–2.98 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): $\delta=14.79$ (CH_3), 20.23 (CH_3), 24.65 (CH_2), 39.42 (CH), 40.28 (CH_2) ppm. IR (ATR): $\nu=2962$ (vs), 2925 (vs), 2869 (m), 1451 (s), 1373 (s), 1261 (s), 1225 (w) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 238 (2) [M^+], 176 (7), 135 (12), 103 (100) [$C_5H_{11}S^+$], 102 (47), 93 (8), 89 (54), 75 (25), 61 (38). $C_{10}H_{22}S_3$ (238.46): Anal. calcd C 50.37, H 9.30; found C

50.39, H 9.16. Mol. mass calcd 238.0884; found 238.0883 (HRMS).

3.1.8. (*R*,*R*)-(+)-Bis[2-(phenylsulfanyl)propyl]sulfide (1b). According to the previous procedure for **1a** bisacetate **3e** (758 mg, 2.21 mmol) in DMF (3 ml) was converted with NaSPh (1.17 g, 8.84 mmol) at 70°C. After workup twofold column chromatography on SiO_2 (1. MTB/PE 1:30, R_f=0.37; 2. MTB/PE 1:50, R_f=0.23) yielded a material, which was submitted to preparative TLC on SiO_2 (MTB/PE 1:50) to yield the analytically pure title compound **1b** (180 mg, 0.539 mmol, 24%) as a colorless oil.

Analogous conversion of dichloride **3a** (374 mg, 2.00 mmol) with NaSPh in DMF at ambient temperature yielded the title compound **1b** (398 mg, 1.19 mmol, 60%) containing impurities, which could not be removed by chromatography. $[\alpha]_D^{20}$=+69.5 (*c* 5.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (d, *J*=6.7 Hz, 3H), 2.49 (dd, *J*=13.2, 9.5 Hz, 1H), 2.79 (dd, *J*=13.2, 4.3 Hz, 1H), 3.18–3.30 (m, 1H), 7.16–7.42 (m, 5H) ppm. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ=19.60 (CH_3), 39.53 (CH_2), 42.93 (CH), 127.29 (CH), 128.94 (CH), 132.47 (CH), 134.08 (C) ppm. IR (ATR): ν=2960 (m), 2922 (m), 1583 (m), 1480 (m), 1473 (m), 1540 (m), 1438 (s), 1371 (m), 1025 (m), 738 (vs), 701 (m), 690 (vs) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 334 (36) [M^+], 224 (7), 184 (26), 183 (44), 151 (100) [$C_9H_{11}S^+$], 150 (30), 141 (47), 137 (31), 123 (16), 109 (28). $C_{18}H_{22}S_3$ (334.55): Anal. calcd C 64.62, H 6.63; found C 64.59, H 6.66. Mol. mass calcd 334.0884; found 334.0885 (HRMS).

3.1.9. (*R*,*R*)-(−)-Bis[2-phenyl-2-(ethylsulfanyl)ethyl]sulfide (1c). NaSEt (312 mg, 3.71 mmol) was added to a solution of dichloride **3b** (289 mg, 0.928 mmol) in DMF (7 ml). The mixture was stirred overnight at ambient temperature. After dilution with MTB (50 ml) and extraction with water (3×30 ml) the organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was twice column chromatographed on SiO_2 (MTB/PE 1:50, R_f=0.11) to give tristhioether **1c** (168 mg, 0.463 mmol, 50%) as an analytically pure, colorless oil. $[\alpha]_D^{20}$=−151 (*c* 6.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.14 (t, *J*=7.4 Hz, 3H), 2.30 (q, *J*=7.4 Hz, 1H), 2.31 (q, *J*=7.4 Hz, 1H), 2.84 (dd, *J*=8.9, 13.3 Hz, 1H), 2.89 (dd, *J*=6.3, 13.3 Hz, 1H), 3.86 (dd, *J*=6.3, 8.9 Hz, 1H), 7.20–7.38 (m, 5H) ppm. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ=14.39 (CH_3), 25.45 (CH_2), 39.13 (CH_2), 49.68 (CH), 127.46 (CH), 127.87 (CH), 128.47 (CH), 141.05 (C) ppm. IR (ATR): ν=1490 (m), 1451 (m), 696 (vs) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 362 (1) [M^+], 226 (8), 165 (20), 164 (18), 151 (100) [$C_9H_{11}S^+$], 135 (14), 123 (6), 104 (20), 103 (12), 91 (11), 77 (8). $C_{20}H_{26}S_3$ (362.61): Anal. calcd C 66.25, H 7.23; found C 66.36, H 7.28. Mol. mass calcd 362.1197; found 362.1199 (HRMS).

3.1.10. *rac*-Bis-1,2-(ethylsulfanyl)-1-phenylethane (4). Dichloride **3b** (85.0 mg, 0.273 mmol) was converted with (92.0 mg, 1.09 mmol) in DMF (2 ml) at 70°C according to the procedure given above for **1c** to yield the bis-thioether **4** (48.0 mg, 0.212 mmol, 78%) as a colorless oil after chromatography (SiO_2, MTB/PE 1:50, R_f=0.33). $[\alpha]_D^{20}$=0.00 (*c* 6.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17 (t, *J*=7.4 Hz, 3H), 1.19 (t, *J*=7.4 Hz, 3H), 2.30–2.41 (m, 2H), 2.44 (q, *J*=7.4 Hz, 2H), 2.99 (dd, *J*=8.6, 13.0 Hz, 1H), 3.04 (dd, *J*=6.5, 13.0 Hz, 1H), 3.99 (dd, *J*=6.5, 8.6 Hz, 1H), 7.24–7.38 (m, 5H) ppm. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ=14.34 (CH_3), 14.62 (CH_3), 25.42 (CH_2), 26.71 (CH_2), 37.96 (CH_2), 49.68 (CH), 127.38 (CH), 127.79 (CH), 128.41 (CH), 141.28 (C) ppm. IR (ATR): ν=2966 (s), 2926 (s), 2870 (m), 1491 (m), 1452 (s), 1265 (m), 765 (m), 733 (m), 713 (s), 698 (vs) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 226 (21) [M^+], 165 (26), 151 (100) [$C_9H_{11}S^+$], 135 (50), 123 (24), 121 (13), 103 (47), 91 (27), 77 (27). $C_{12}H_{18}S_2$ (226.39): Anal. calcd C 63.66, H 8.01; found C 63.43, H 7.85. Mol. mass calcd 226.0850; found 226.0843 (HRMS).

3.1.11. (*R*,*R*)-(−)-Bis[2-phenyl-2-(phenylsulfanyl)ethyl]-sulfide (1d). According to the procedure given above for **1c** NaSPh (137 mg, 1.04 mmol) was converted with dichloride **3b** (81.0 mg, 0.260 mmol) in DMF (2 ml) at 70°C to give a crude material, which was purified first by column chromatography (SiO_2, MTB/PE 1:30, R_f=0.27) and subsequently by preparative TLC (SiO_2, MTB/PE 1:30) to furnish the analytically pure compound **1d** (46.0 mg, 0.100 mmol, 39%) as a yellowish oil. $[\alpha]_D^{20}$=−150 (*c* 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.85 (dd, *J*=13.3, 9.3 Hz, 1H), 2.91 (dd, *J*=13.3, 5.8 Hz, 1H), 4.12 (dd, *J*=9.3, 5.8 Hz, 1H), 7.08–7.40 (m, 10H) ppm. ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$): δ=38.50 (CH_2), 53.47 (CH), 127.56 (CH), 127.67 (CH), 127.94 (CH), 128.44 (CH), 128.85 (CH), 132.84 (CH), 134.11 (C), 139.89 (C) ppm. IR (ATR): ν=1581 (m), 1491 (m), 1479 (m), 1452 (m), 1437 (m), 1024 (m), 738 (s), 689 (vs), 658 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 458 (1) [M^+], 349 (18), 245 (43), 213 (16), 199 (29), 141 (94), 135 (100), 109 (39), 104 (30), 91 (17), 77 (10). $C_{28}H_{26}S_3$ (458.71): Anal. calcd C 73.32, H 5.71; found C 73.17, H 5.84. Mol. mass calcd 458.1197; found 458.1199 (HRMS).

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