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First synthesis of the chiral mixed O/S ligands, 1,2-sulfinyl thiols: application as chiral proton sources in enantioselective protonations of enolates

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Abstract

A suitable method for the preparation of the chiral mixed O/S ligands 1,2-sulfinyl thiols is described. These compounds have then been used as a chiral proton source in the enantioselective protonation of 2-methyl tetralone enolate and the results are compared with those obtained from the analogous alcohols. A theoretical model is proposed to explain the different behaviors exhibited in the protonation reaction for each of these proton sources. Configurational assignments for the new chiral thiols have been carried out by means of X-ray analysis.

1. Introduction

In the course of our research on the enantioselective protonation of enolates[1] we have undertaken the preparation of 1,2-sulfinyl thiols (*S*,*Rs*)-**1**. This topic constitutes a new aspect of the field of enantioselective protonation of enolates since, while chiral alcohols have been widely used as proton sources,[2] there are no precedents for the utilization of chiral thiols. In addition to their application as chiral proton sources, these compounds and their related derivatives, such as the corresponding thioethers, have structural features which make them attractive for use as chiral catalysts; they are chiral ligands with a heteroatom pair containing a strong sulfur donor and a weak oxygen donor. This type of chiral mixed O/S ligands have gained increasing attention because, as is the case with C_2 symmetry ligands, they exhibit powerful stereochemical restrictions that are the consequence of electronic effects.[3] An additional class of thiol derivatives with interesting potential applications are thioesters, which can be used as mild acylating reagents of amines and alcohols.[4,5] The asymmetric version of these reactions should result from the use of the *S*-acyl derivatives of 1,2-sulfinyl thiols and can most likely be applied to alcohol and amine resolution or desymmetrization.

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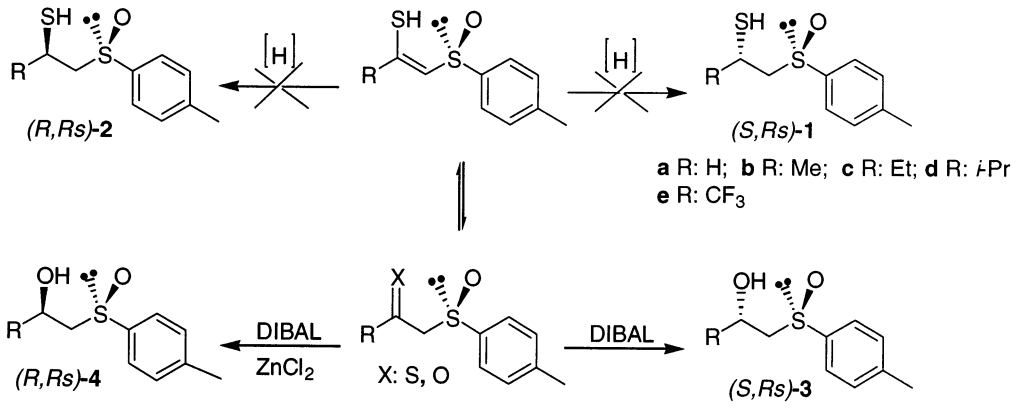
Due to the interesting nature of chiral 1,2-sulfinyl thiols and the lack of references in the literature as to their preparation, we considered it of interest to develop a suitable method to synthesize these compounds. In addition, we have also undertaken the testing of these compounds as chiral proton sources in the enantioselective protonation of 2-methyl tetralone enolate in order to compare the results with those obtained from the analogous 1,2-sulfinyl alcohols that we have previously described.[1]

2. Results and discussion

2.1. Synthesis of 1,2-sulfinyl thiols

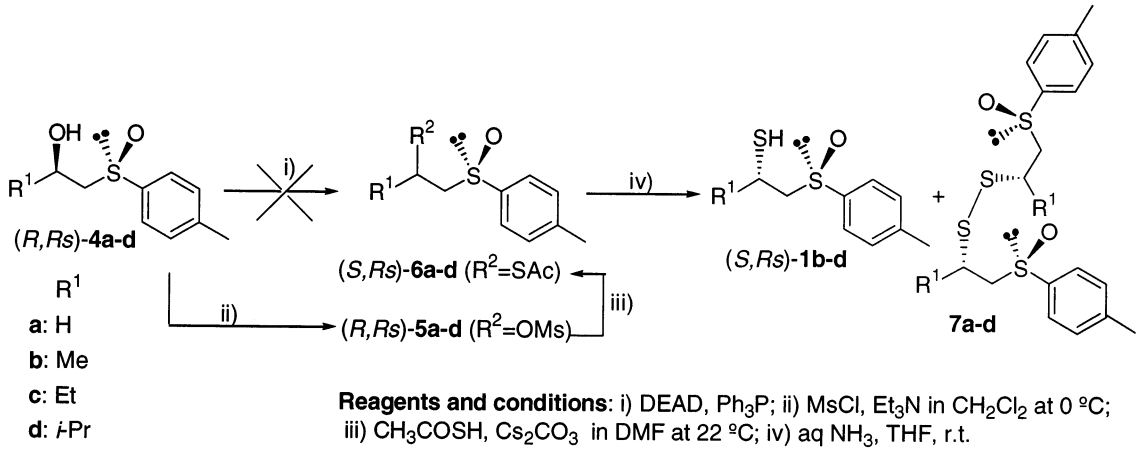
Since the 1,2-sulfinyl thiols have two stereogenic atoms, two diastereomers (*S*,*Rs*)-**1** and (*R*,*Rs*)-**2** can, in principle, be considered as proton sources. However, since among the analogous compounds 1,2-sulfinyl alcohols (*S*,*Rs*)-**3** and (*R*,*Rs*)-**4**, sulfinyl alcohols **3** with the (*S*,*Rs*) configuration have been shown to be more effective as protonating reagents than the corresponding diastereomers (*R*,*Rs*)-**4**,[6] our objective was the preparation of compounds **1** having the configuration (*S*,*Rs*) (Scheme 1).



Scheme 1. Preparation of 1,2-sulfinyl alcohols

The preparation of compounds (*S*,*Rs*)-**1** following a procedure similar to that described by Solladié for 1,2-sulfinyl alcohols (*S*,*Rs*)-**3**[7] was not feasible due to the high tendency of thioketones to undergo enolization and oligomerization.[8] Thus, since alcohols are among the most usual precursors of thiols,[9] we devised the preparation of 1,2-sulfinyl thiols **1** from the corresponding sulfinyl alcohols. In order to prepare compounds **1** with the (*S*,*Rs*) configuration and taking into consideration that the methods of conversion of alcohols into other derivatives such as amines[10] (or, in our case, thiols) involve configuration inversion at the stereogenic carbon, sulfinyl alcohols (*R*,*Rs*)-**4** were chosen as precursors. The interconversion was originally assayed in the case of **4b** by means of a modified Mitsunobu procedure,[11] but the purification of the products was difficult due to contamination from by-products derived from azodicarboxylate. We thus performed an alternative pathway based on a previously described procedure for the synthesis of analogous compounds.[12] The method involves the conversion of alcohol (*R*,*Rs*)-**4** into mesylate (*R*,*Rs*)-**5**, the displacement of mesylate anion with cesium thioacetate to

afford thioester (*S*,*Rs*)-**6** and the subsequent hydrolysis of (*S*,*Rs*)-**6** to afford the corresponding thiol (*S*,*Rs*)-**1** (Scheme 2).



Scheme 2. Synthesis of 1,2-sulfinyl thiols **1** from 1,2-sulfinyl alcohols **4**

1,2-Sulfinyl alcohols (*R*,*Rs*)-**4a–d** were converted into mesylates (*R*,*Rs*)-**5a–d** with high yields (80–85%). Mesylates (*R*,*Rs*)-**5a–c** reacted with cesium acetate in DMF affording the thioacetates (*S*,*Rs*)-**6a–c** with acceptably good yields (65–85%); however, with the branched mesylate (*R*,*Rs*)-**5d**, only a 25% yield of the substitution product (*S*,*Rs*)–**6d** was obtained as elimination was an important side reaction in this case. The substitution reaction took place as expected with complete inversion of the configuration, which was unequivocally assigned by X-ray diffraction (see below). Hydrolysis of thioacetates (*S*,*Rs*)-**6** was accomplished in ammonia and lead to thiols (*S*,*Rs*)-**1** and sulfides **7** as by-products. In the case of thioacetate (*S*,*Rs*)-**6a**, the disulfide **7a** was the only product. We observed that thiols (*S*,*Rs*)-**1b–d** yielded the corresponding disulfides **7** even under an inert atmosphere. In view of the lack of stability of thiols (*S*,*Rs*)-**1**, no further assays were carried out. The conversion of thioacetates into thiols in aprotic media was not undertaken since disulfides can be produced during the work-up.

Although the conversions of thiols into disulfides are, in the context of our work, undesirable reactions, it is worth noting that chiral disulfides can also be useful catalysts in asymmetric reactions.[13]

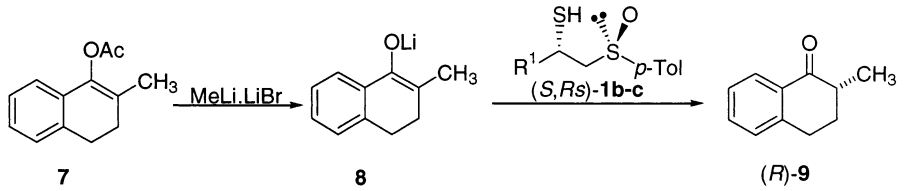
2.2. Enantioselective protonation with 1,2-sulfinyl thiols as chiral proton sources

There are no precedents in the literature about the application of thiols as chiral proton sources in the enantioselective protonation of enolates.[2] This fact can be related in part to the lack of commercially available chiral thiols, but also to their greater acidity if compared with alcohols, which may result in a difficult kinetic control in the proton transfer step. However, thiols have an acidity similar to that of succinimides,[14] the chiral derivatives of which have been shown by Yamamoto et al. to be efficient protonating reagents.[15] We were thus interested in testing the 1,2-sulfinyl thiols (*S*,*Rs*)-**1b–c** as chiral proton transfer reagents.

Enantioselective protonation runs were performed under the same conditions used previously for protonations with 1,2-sulfinyl alcohols (*S*,*Rs*)-**3**.[1] 2-Methyl tetralone enolate **8** was generated upon treatment of the corresponding enol acetate precursor **7**[16] with 2.2 equiv. of methyl lithium

complexed with lithium bromide and submitted to protonation with sulfinyl thiols (*S*,*Rs*)-**1** in dichloromethane. Runs were carried out at two different temperatures (−78 and −100°C). Interestingly, compounds (*S*,*Rs*)-**1** lead to a higher ee at the lower temperature (entries 1–4, Table 1). Upon comparison with the series of related alcohols (*S*,*Rs*)-**3**, we observed the same behavior for the alcohol (*S*,*Rs*)-**3e**,[17] the most acidic member of the series (entries 11 and 12, Table 1). With the less acidic alcohols (*S*,*Rs*)-**3a**–**d**, the stereoselection obtained was similar regardless of whether the reactions were performed at −78 (entries 5–7, Table 1) or −100°C (8–10, Table 1).

Table 1
Enantioselective protonations with 1,2-sulfinyl thiols **1** and 1,2-sulfinyl alcohols **3**



7 **8** (*R*)-**9**

Entry	Proton source	Temperature (°C)	(*R*)-**9** ee
1	(*S*,*Rs*)-**1b**	−78	45
2	(*S*,*Rs*)-**1c**	−78	44
3	(*S*,*Rs*)-**1b**	−100	61
4	(*S*,*Rs*)-**1c**	−100	55
5	(*S*,*Rs*)-**3b**	−78	80[a]
6	(*S*,*Rs*)-**3c**	−78	84
7	(*S*,*Rs*)-**3b**	−100	85
8	(*S*,*Rs*)-**3c**	−100	83
9	(*S*,*Rs*)-**3e**	−78	67
10	(*S*,*Rs*)-**3e**	−100	92[b]

[a] Ref. 17.
[b] Ref. 1.

These results show the dependence of the enantioselectivity on the acidity of the proton source and the reaction temperature. This trend fits well with the fact that the enantioselective protonation is a kinetically controlled reaction. It would be interesting to see whether the stereoselection could be improved by using temperatures below −100°C, but the freezing of the solvent prevents any further investigation. 1,2-Sulfinyl thiols (*S*,*Rs*)-**1** prove to be less effective as chiral proton sources compared with alcohols (*S*,*Rs*)-**3**. While alcohols (*S*,*Rs*)-**3** lead to the corresponding ketone (*R*)-**9** with high enantiomeric excess (entries 5–7, Table 1), the stereoselection achieved with 1,2-sulfinyl thiols (*S*,*Rs*)-**1** was only moderate (entries 1–4, Table 1). This fact may be related to both structural factors and reaction conditions. First, structural features of compounds (*S*,*Rs*)-**1** might negatively influence the stereoselection since C–S and S–H bonds are longer than C–O and O–H bonds, respectively, and as a consequence, the proton will be delivered from a position farther from the stereogenic center in the case of compounds **1** than in that of compounds **3**. The impossibility of any practical work below −100°C does not allow for the determination of the optimal reaction temperature for effective kinetic control in the proton transfer with compounds **1**.

2.3. Theoretical model

In order to clarify the influence of the structural factors in the stereoselection achieved with thiols (*S*,*Rs*)-**1**, we have performed quantum mechanical calculations at the PM3 semiempirical level (see Section 4 for details). Calculations have been carried out with the aid of our theoretical model for alcohols (*S*,*Rs*)-**3**.[1] This model is based on the existence of a lithium enolate and lithium bromide mixed dimer defined as a four-membered ring, in which the bromide anion and the oxygen atom are connected by two lithium cations. These bridging cations are in a nearly tetrahedral environment provided by coordination with the oxygen and sulfur atoms of thiol (*S*,*Rs*)-**1b** and two molecules of dimethyl ether. The corresponding transition structures **TS1-R** and **TS1-S** that account for the two possible enolate protonation pathways can be described as six-membered rings in which the proton transfer takes place via a favorable intramolecular pathway (Fig. 1). The PM3 calculations indicate that **TS1-R** is 1.47 kcal/mol more favorable than **TS1-S**. Consequently, the theoretical calculations based on our model are in good agreement with the experimental results and predict the enantioselective formation of ketone (*R*)-**9**. The calculated length of the breaking S–Ht bond and the forming C–Ht bond in **TS1-R** are 1.758 and 1.301 Å, respectively, whereas in **TS1-S** they are 1.745 and 1.314 Å, respectively (Fig. 1). The distance between the donor and acceptor proton centers in **TS1-R** and **TS1-S** are 3.036 and 3.028 Å, respectively.

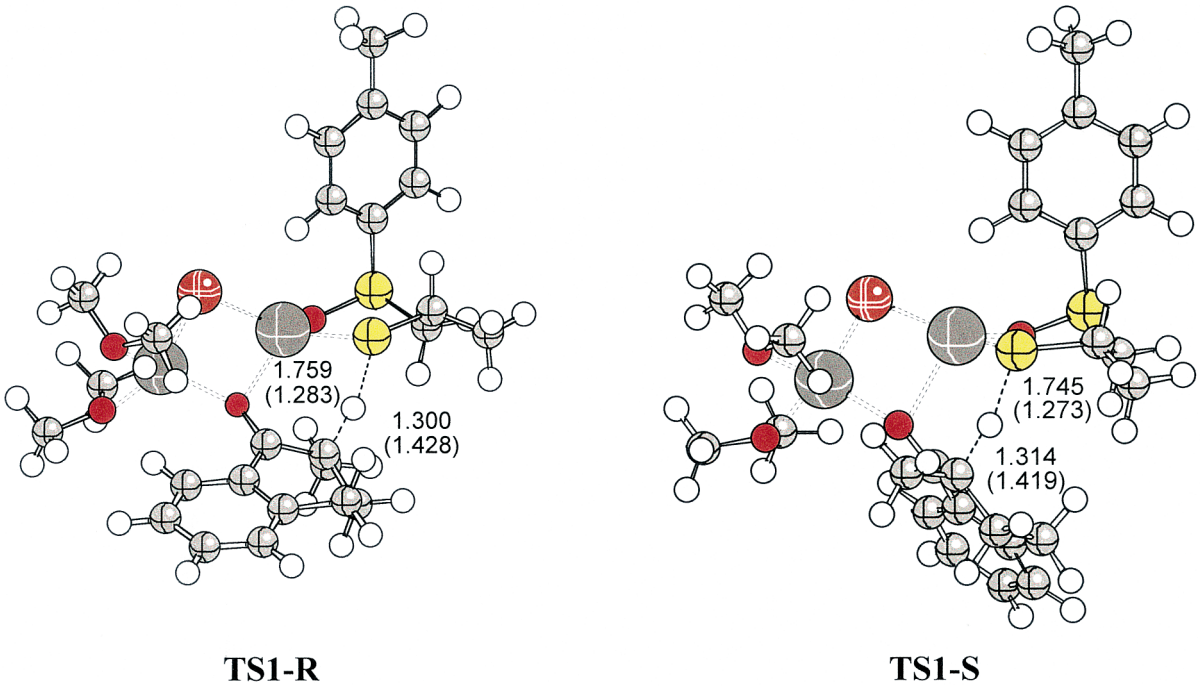


Figure 1. PM3 selected geometrical parameters (in angstroms) for the transition structures **TS1-R** and **TS1-S**. Data in parenthesis correspond to **TS2-R** and **TS2-S**, respectively

The energy difference for thiol (*S*,*Rs*)-**1b** between **TS1-R** and **TS1-S** (1.47 kcal/mol) is lower than that previously determined for alcohol (*S*,*Rs*)-**3e** between the transition structures **TS2-R** and **TS2-S** (3.9 kcal/mol). These transition structures arise from the linkage of lithium enolate

8, lithium bromide, the corresponding chiral thiol or alcohol and two molecules of dimethyl ether (Fig. 1). The **TS** energy differences calculated on the basis of our model are also in good agreement with the lower stereoselection found experimentally with the chiral thiol (*S*,*Rs*)-**1b** relative to the alcohol (*S*,*Rs*)-**3e**. Inspection of **TS1-S** and **TS2-S** allows us to deduce that the distance between the S-donor and the C-acceptor in **TS1-S** (3.028 Å) is longer than that existing between the O-donor and the C-acceptor in **TS2-S** (2.646 Å) (Fig. 1). Consequently, **TS1-S** is less crowded than **TS2-S** because the unfavorable steric interactions between thiol (*S*,*Rs*)-**1b** and enolate **8** are weaker than those in the case of alcohol (*S*,*Rs*)-**3e**. Thus, **TS1-S** becomes closer in energy to **TS1-R** and the kinetically controlled stereoselection of the proton transfer process decreases. According to our model, the structural differences observed in the calculated transition structures account for the different behavior of 1,2-sulfinyl thiols (*S*,*Rs*)-**1** and 1,2-sulfinyl alcohols (*S*,*Rs*)-**3** as chiral proton transfer reagents.

2.4. *X-ray crystal structures of compounds (*S,Rs*)-**1b**, (*S,Rs*)-**1d** and (*S,Rs*)-**6c***

Both configurational assignment and conformational analysis for the thiols (*S*,*Rs*)-**1b** and (*S*,*Rs*)-**1d** (Fig. 2) and the thioacetate (*S*,*Rs*)-**6c** (Fig. 3) were carried out after X-ray crystal structure determination. The absolute configuration was determined as (*S*,*Rs*) for compounds (*S*,*Rs*)-**1b**, (*S*,*Rs*)-**1d** and (*S*,*Rs*)-**6c** [absolute structure parameters 0.04(7), 0.0(3) and 0.03(8),

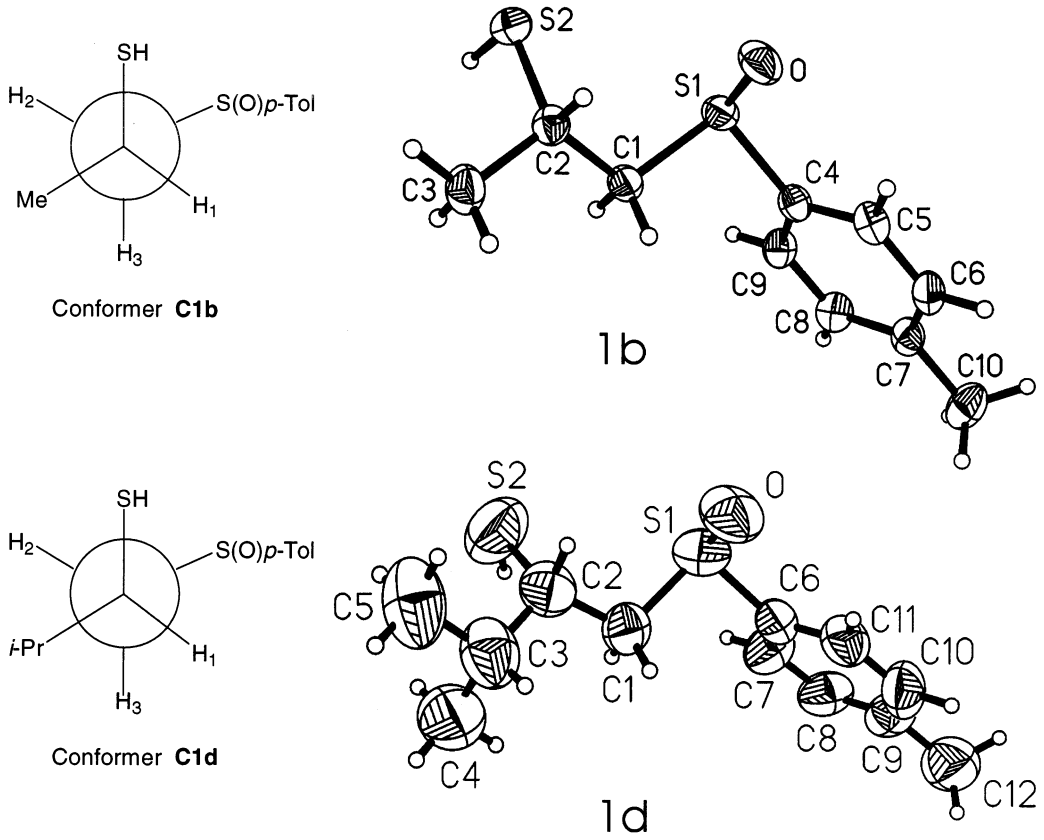


Figure 2. Ellipsoid plot (50% probability level) of compounds **1b** and **1d** with the labeling scheme

respectively].[18] The conformational analysis of compound (*S*,*Rs*)-**1b** based on the corresponding vicinal coupling constant values of the methyne proton H_1 with the methylene protons H_2 and H_3 ($^3J_{1,2}=9.9$ and $^3J_{1,3}=4.4$ Hz) led us to propose structure **C1b** as the prevalent conformer in solution (Fig. 2). The analogous conformer **C1d** (Fig. 2) can account for the coupling constants ($^3J_{1,2}=11.5$ and $^3J_{1,3}=3.2$ Hz) found for thiol (*S*,*Rs*)-**1d** in solution. The deduced major conformations in solution **C1b** and **C1d** corresponding to thiols (*S*,*Rs*)-**1b** and (*S*,*Rs*)-**1d**, respectively, correspond to the conformations adopted in the solid state having torsion angles O-S1···C2–S2 100.8(1)° and 123.7(4)° (Fig. 2). In addition, the structures of the major conformers **C1b** and **C1d** are in good agreement with the most stable conformations determined by molecular mechanics force field analysis for related 1,2 sulfinyl alcohols.[19] Conformational analysis of compound (*S*,*Rs*)-**6c**, also based on the coupling constant values of methyne H_1 and methylene H_2 and H_3, reveals the prevalence in solution of a different conformer **C6c** since in this case the coupling constant values are similar ($^3J=8.1$ and 6.4 Hz). The same conformation was found for compound (*S*,*Rs*)-**6c** in solution and in the solid state corresponding to the *gauche* conformation for the ethyl and sulfinyl groups with respect to the C1–C2 bond [torsion angles S1–C1–C2–C3 51.7(2)°, S1–C1–C2–S2 74.5(2)°], as determined by X-ray analysis (Fig. 3).

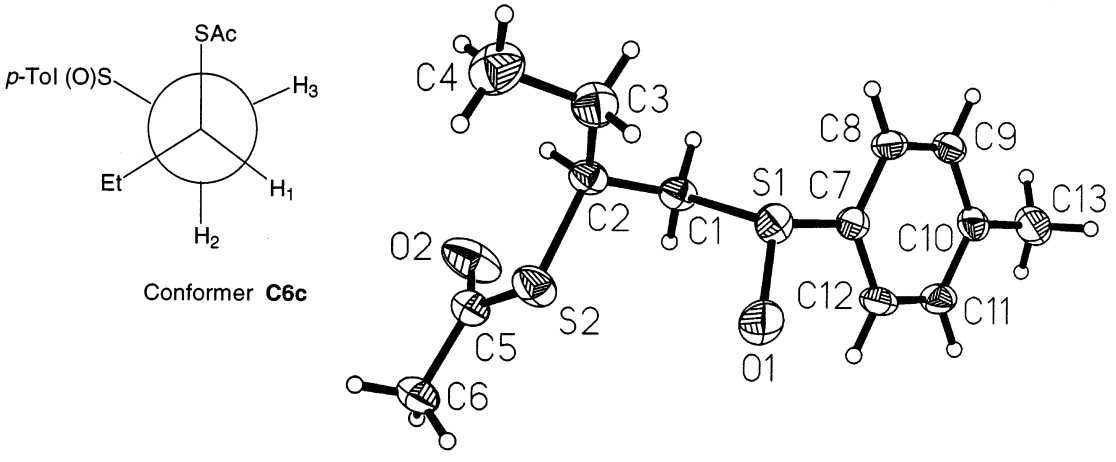


Figure 3. Ellipsoid plot (50% probability level) of compound **6c** with the labeling scheme

For both thiols (*S*,*Rs*)-**1b** and (*S*,*Rs*)-**1c** an intermolecular S–H···O hydrogen bond producing infinite chains is present in the crystals [(*S*,*Rs*)-**1b**: H(2)···O# (#: *x*+1/2, −*y*−1/2, −*z*−1) 2.14, S(2)···O# 3.426(1), S(2)–H(2)···O# 157.3; (*S*,*Rs*)-**1d**: H(2)···O# (#: *x*−1, *y*, *z*) 2.63, S(2)···O# 3.751(6), S(2)–H(2)···O# 139.0] (see Fig. 4).

3. Conclusions

A convenient synthesis of the chiral mixed O/S ligands 1,2-sulfinyl thiols (*S*,*Rs*)-**1** is described for the first time. These compounds are readily accessible in three steps from the corresponding sulfinyl alcohols (*R*,*Rs*)-**4**. The absolute configuration of these new chiral thiols (*S*,*Rs*)-**1** has been established by X-ray analysis. Compounds (*S*,*Rs*)-**1** are moderately good proton sources when the enantioselective protonation of enolates is carried out at very low temperatures, a fact which reflects their high acidity, but they are less effective than the related 1,2-sulfinyl alcohols

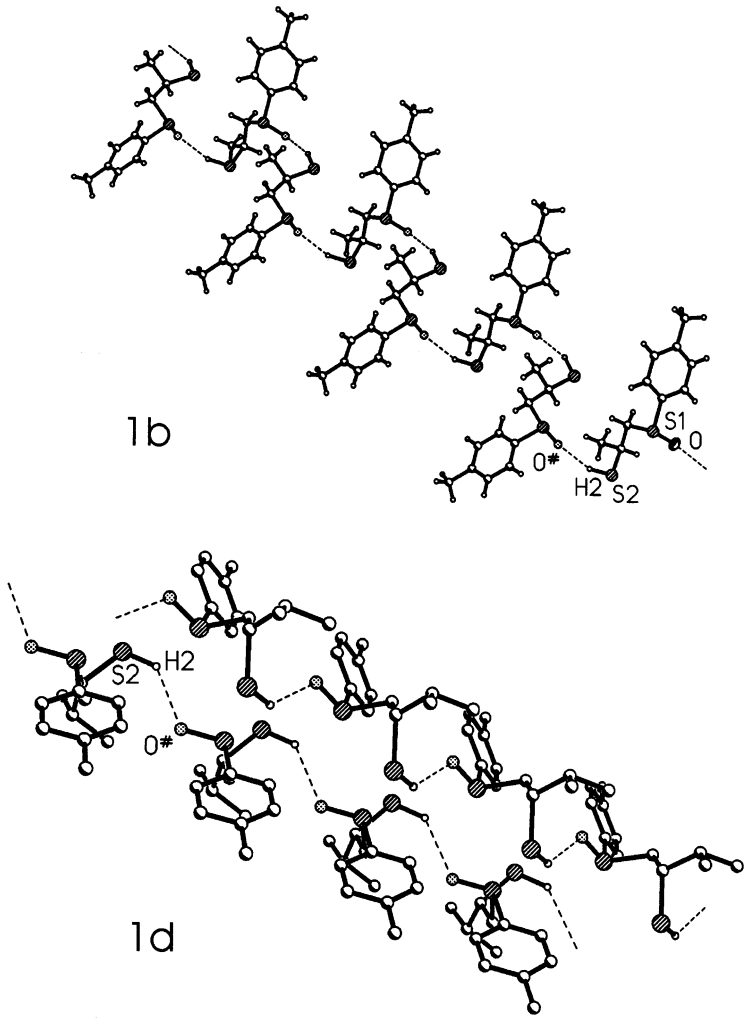


Figure 4. Infinite chains formed in compounds **1b** and **1c** through SH···O hydrogen bonds

(*S*,*Rs*)-**3** with the same configuration at the stereogenic centers. The differences found between the protonating reagents (*S*,*Rs*)-**1** and (*S*,*Rs*)-**3** can be explained with the aid of the proposed theoretical model on the basis of their different structural parameters.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 with tetramethylsilane as an internal reference in $CDCl_3$. Melting points were determined with a Cambridge Instruments apparatus and are uncorrected. Optical rotation measurements were determined on a Perkin–Elmer 241 polarimeter at room temperature.

4.2. Materials

Methyllithium 1.5 M solution in diethyl ether, $d=0.852$; 1.0 M in LiBr was purchased from Aldrich. All solvents were dried before use. Diethyl ether was distilled under argon from sodium benzophenone and dichloromethane from calcium hydride.

4.3. Computational details

The computational study was carried out using the PM3 semiempirical method[20] implemented in the MOPAC program.[21] The molecular geometries of the transition structures (TS) were optimized with the optimization routine TS.[22] Stationary points on the potential energy surface (PES) were located by minimizing the gradients of energy to 0.1 kcal/mol/Å-radian. Examination of the TSs was achieved by the evaluation of the Hessian matrix; the nature of these stationary points was established by analytical calculations and diagonalization of the matrix of energy second derivatives in order to determine the unique imaginary frequency.

4.3.1. (S,Rs)-1-(4-Methylphenylsulfinyl)-2-propanethiol (S,Rs)-**1b**

White solid; isolated yield: 78%; mp (hexane/ethyl acetate): 62–64°C; $[\alpha]_D^{20}=+257$ ($c=1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.53 (d, $J=8.2$ Hz, 2H), 7.33 (d, $J=8.2$ Hz, 2H), 3.51–3.43 (m, 1H), 3.05 (dd, $J=13.1$ and 4.4 Hz, 1H), 2.77 (dd, $J=13.1$ and 9.9 Hz, 1H), 2.41 (s, 3H), 2.05 (d, $J=6.7$ Hz, 1H) and 1.45 (d, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) (DEPT): δ 141.7 (C), 140.6 (C), 130.0 (CH), 123.9 (CH), 69.3 (CH_2), 30.1, 25.1 and 21.4 (CH_3); EIMS: m/z (rel. int.%) 214 (M^+, 88), 198 ([M–O]$^+$, 5), 165 ([M–SH–O]$^+$, 21), 151 (96), 137 (50), 123 (72), 93 (100) and 77 ([M–137], 80); CIMS: m/z (rel. int.%) 215 (MH^+, 29), 198 (M–O, 25), 181 (MH^+-H_2S, 34), 165 (M–SH–O, 72), 153 ($M-C_2H_5S$, 54), 139 ($M-C_3H_7S$, 56), 125 (100) and 91 ($C_7H_7^+$, 68); HRMS (FAB): m/z 215.0558; calcd for $C_{10}H_{15}OS_2$: 215.0564.

4.3.2. (S,Rs)-1-(4-Methylphenylsulfinyl)-2-butanethiol (S,Rs)-**1c**

White solid; isolated yield: 51%; mp (hexane): 51–52.5°C; $[\alpha]_D^{20}=+280$ ($c=1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, $J=8.1$ Hz, 2H), 7.33 (d, $J=8.1$ Hz, 2H), 3.36–3.22 (m, 1H), 3.07 (dd, $J=13.1$ and 3.8 Hz, 1H), 2.73 (dd, $J=13.1$ and 10.7 Hz, 1H), 2.41 (s, 3H), 1.87 (d, $J=7.3$ Hz, 1H), 1.82–1.54 (m, 2H) and 1.03 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.6, 140.7, 130.0, 123.9, 67.8, 36.7, 31.5, 21.4 and 11.2; HRMS (EI): m/z 228.0642; calcd for $C_{11}H_{16}OS_2$: 228.0643.

4.3.3. (S,Rs)-3-Methyl-1-(4-methylphenylsulfinyl)-2-butanethiol (S,Rs)-**1d**

White solid; isolated yield: 67%; mp: 49–51°C; $[\alpha]_D^{20}=+272.2$ ($c=1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.55 (d, $J=8.2$ Hz, 2H), 7.34 (d, $J=8.2$ Hz, 2H), 3.43–3.32 (m, 1H), 3.00 (dd, $J=13.0$ and 3.2 Hz, 1H), 2.72 (dd, $J=13.0$ and 11.5 Hz, 1H), 2.42 (s, 3H), 2.01–1.88 (m, 1H), 1.69 (d, $J=8.0$ Hz, 1H), 1.02 (d, $J=6.7$ Hz, 3H) and 0.92 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.6, 140.8, 130.0, 123.8, 66.3, 41.3, 33.8, 21.4, 20.0 and 17.3; HRMS (EI): m/z 242.0792; calcd for $C_{12}H_{18}OS_2$: 242.0799.

4.3.4. (R,Rs)-2-(4-Methylphenylsulfinyl)-1-ethanol (R,Rs)-**4a**

Mp: 95–98°C; $[\alpha]_D^{20}=+322$ ($c=1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz), δ 7.54 (d, $J=8.2$ Hz, 2H), 7.36 (d, $J=8.2$ Hz, 2H), 4.25–4.10 (m, 1H), 4.10–3.95, (m, 1H), 3.54 (br. s, 1H), 3.16

(ddd, $J=13.5$, 8.6 and 3.9 Hz, 1H), 2.86 (ddd, $J=13.5$, 5.5 and 3.1 Hz, 1H) and 2.43 (s, 3H).^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.8, 139.6, 130.1, 124.0, 58.0, 57.2 and 21.4.

*4.3.5. (*R,Rs*)-1-(4-Methylphenylsulfinyl)-2-propanol (*R,Rs*)-**4b***

Colorless oil; $[\alpha]_D^{20}=+273$ ($c=1.1$, $CHCl_3$) (de$\geq$90%; by ^{1}H NMR); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, $J=8.2$ Hz, 2H), 7.34 (d, $J=8.2$ Hz, 2H), 4.48–4.38 (m, 1H), 3.93 (br. s, 1H), 2.98 (dd, $J=13.1$ and 8.9 Hz, 1H), 2.74 (dd, $J=13.1$ and 2.8 Hz, 1H), 2.41 (s, 3H) and 1.30 (d, $J=6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.9, 140.4, 130.1, 123.9, 64.9, 63.8, 23.2 and 21.4.

*4.3.6. (*R,Rs*)-1-(4-Methylphenylsulfinyl)-2-butanol (*R,Rs*)-**4c***

White solid; $[\alpha]_D^{20}=+258$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.56 (d, $J=8.1$ Hz, 2H), 7.35 (d, $J=8.1$ Hz, 2H), 4.29–4.21 (m, 1H), 3.85 (br. s, 1H), 2.94 (dd, $J=13.1$ and 9.3 Hz, 1H), 2.78 (dd, $J=13.1$ and 2.3 Hz, 1H), 2.43 (s, 3H), 1.66–1.53 (m, 2H) and 0.96 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.0, 140.5, 130.1, 123.9, 70.1, 62.0, 30.1, 21.4 and 9.4.

*4.3.7. (*R,Rs*)-3-Methyl-1-(4-methylphenylsulfinyl)-2-butanol (*R,Rs*)-**4d***

White solid; mp: 65–66.5°C (hexane); $[\alpha]_D^{20}=+232$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.56 (d, $J=8.1$ Hz, 2H), 7.35 (d, $J=8.1$ Hz, 2H), 4.13–4.05 (m, 1H), 3.86 (d, $J=2.1$ Hz, 1H), 2.91 (dd, $J=13.1$ and 9.7 Hz, 1H), 2.77 (dd, $J=13.1$ and 1.9 Hz, 1H), 2.43 (s, 3H), 1.86–1.74 (m, 1H), 0.93 (d, $J=6.8$ Hz, 3H) and 0.92 (d, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.4, 141.1, 130.5, 124.6, 73.6, 60.5, 34.3, 21.8, 18.3 and 17.7.

*4.3.8. (*R,Rs*)-2-(4-Methylphenylsulfinyl)ethyl methane sulfonate (*R,Rs*)-**5a***

White solid; isolated yield: 84%; mp: 79–80°C; $[\alpha]_D^{20}=+182$ ($c=1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.53 (d, $J=8.1$ Hz, 2H), 7.36 (d, $J=8.1$ Hz, 2H), 4.70–4.60 (m, 1H), 4.54–4.46 (m, 1H), 3.26–3.15 (m, 1H), 3.06 (s, 3H), 3.10–3.01 (m, 1H) and 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.1, 139.4, 130.2, 123.8, 62.2, 56.0, 37.4 and 21.4.

*4.3.9. (*R,Rs*)-1-Methyl-2-(4-methylphenylsulfinyl)ethyl methane sulfonate (*R,Rs*)-**5b***

White solid; isolated yield: 88%; mp: 71–74°C; $[\alpha]_D^{20}=+154$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.57 (d, $J=8.3$ Hz, 2H), 7.36 (d, $J=8.3$ Hz, 2H), 5.07 (sextet, $J=6.1$ Hz, 1H), 3.26 (dd, $J=13.6$ and 5.8 Hz, 1H), 3.03 (s, 3H), 2.99 (dd, $J=13.6$ and 6.2 Hz, 1H), 2.42 (s, 3H) and 1.64 (d, $J=6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) (DEPT): δ 142.1 (C), 139.8 (C), 130.2 (CH), 124.1 (CH), 73.6 (CH), 63.1 (CH_2), 38.7 (CH_3) and 21.4 (2×CH_3).

*4.3.10. (*R,Rs*)-1-(4-Methylphenylsulfinyl)propyl methane sulfonate (*R,Rs*)-**5c***

Colorless oil; isolated yield: 84%; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.57 (d, $J=8.3$ Hz, 2H), 7.35 (d, $J=8.3$ Hz, 2H), 4.95–4.86 (m, 1H), 3.26 (dd, $J=13.7$ and 5.6 Hz, 1H), 3.05 (s, 3H), 3.04 (dd, $J=13.7$ and 5.8 Hz, 1H), 2.42 (s, 3H), 2.04–1.88 (m, 2H) and 1.02 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.1, 139.9, 130.2, 124.1, 78.4, 61.6, 38.6, 27.8, 21.4 and 9.2.

*4.3.11. (*R,Rs*)-2-Methyl-1-(4-methylphenylsulfinyl)propyl methane sulfonate (*R,Rs*)-**5d***

White solid; isolated yield: 87%; mp: 82–84°C; $[\alpha]_D^{20}=+111.1$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.59 (d, $J=8.3$ Hz, 2H), 7.35 (d, $J=8.3$ Hz, 2H), 4.80–4.73 (m, 1H), 3.27 (dd, $J=13.9$ and 6.9 Hz, 1H), 3.09 (s, 3H), 3.00 (dd, $J=13.9$ and 4.7 Hz, 1H), 2.42 (s, 3H),

2.28–2.18 (m, 1H), 1.01 (d, $J=6.8$ Hz, 3H) and 0.93 (d, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.2, 140.0, 130.2, 124.2, 81.2, 59.6, 38.8, 32.0, 21.4, 17.8 and 17.0.

*4.3.12. (*S,Rs*)-2-(4-methylphenylsulfinyl)ethyl ethanethioate (*S,Rs*)-**6a***

Pale yellow oil; isolated yield: 83%; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.52 (d, $J=8.2$ Hz, 2H), 7.34 (d, $J=8.2$ Hz, 2H), 3.23–2.97 (m, 4H), 2.42 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 195.1, 141.7, 139.4, 130.0, 124.0, 56.0, 30.5, 21.9 and 21.4.

*4.3.13. (*S,Rs*)-1-Methyl-2-(4-methylphenylsulfinyl)ethyl ethanethioate (*S,Rs*)-**6b***

Colorless oil; isolated yield: 66%; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.53 (d, $J=8.3$ Hz, 2H), 7.33 (d, $J=8.3$ Hz, 2H), 3.90 (sextet, $J=7.1$ Hz, 1H), 3.00 (d, $J=7.2$ Hz, 2H), 2.41 (s, 3H), 2.31 (s, 3H) and 1.49 (d, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 194.7, 141.7, 140.6, 130.0, 124.0, 64.5, 35.3, 30.6, 21.4 and 20.8.

*4.3.14. (*S,Rs*)-1-(4-Methylphenylsulfinylmethyl)propyl ethanethioate (*S,Rs*)-**6c***

Pale yellow solid; isolated yield: 75%; mp: 48–50°C; $[\alpha]_D^{20}=+113.7°$ ($c=1.0$ $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, $J=8.2$ Hz, 2H), 7.33 (d, $J=8.2$ Hz, 2H), 3.83 (m, 1H), 3.08 (dd, $J=13.3$ and 6.4 Hz, 1H), 2.97 (dd, $J=13.3$ and 8.1 Hz, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 1.97–1.71 (m, 2H) and 0.99 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 194.8, 141.7, 140.8, 130.0, 124.0, 63.2, 41.7, 30.8, 27.4, 21.4 and 11.2.

*4.3.15. (*S,Rs*)-2-Methyl-1-(4-methylphenylsulfinylmethyl)propyl ethanethioate (*S,Rs*)-**6d***

Colorless oil; isolated yield: 25%; $[\alpha]_D^{20}=+111.9$ ($c=1.1$, $CHCl_3$); ^{1}H MNR ($CDCl_3$, 250 MHz): δ 7.55 (d, $J=8.1$ Hz, 2H), 7.34 (d, $J=8.1$ Hz, 2H), 3.98 (ddd, $J=9.4$, 5.6 and 3.9 Hz, 1H), 3.07 (dd, $J=13.3$ and 5.6 Hz, 1H), 2.85 (dd, $J=13.3$ and 9.4 Hz, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 2.23–2.11 (m, 1H), 0.96 (d, $J=6.7$ Hz, 3H) and 0.94 (d, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 194.1, 141.7, 140.9, 130.0, 124.0, 62.3, 46.0, 32.0, 30.8, 21.4, 20.0 and 18.4.; HRMS (EI): m/z 285.0974; calcd for $C_{14}H_{21}O_2S_2$: 285.0983.

*4.3.16. (*S,S,Rs,Rs*)-Di[2-(4-methylphenylsulfinyl)ethyl] disulfide (*S,Rs,S,Rs*)-**7a***

Wax; isolated yield: 81%; $[\alpha]_D^{20}=+284$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.49 (d, $J=8.1$ Hz, 2H), 7.33 (d, $J=8.1$ Hz, 2H), 3.24–3.11 (m, 1H), 3.05–2.91 (m, 2H), 2.76–2.64 (m, 1H) and 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.7, 139.4, 130.0, 123.9, 55.4, 29.4 and 21.4; EIMS: m/z (rel. int.%) 259 (**M**–S(O)*p*-tol), 199 (35) and 139 ([S(O)*p*-tol]$^+$, 98]; HRMS (FAB): m/z 399.0578; calcd for $C_{18}H_{23}O_2S_4$: 399.0581.

*4.3.17. (*S,S,Rs,Rs*)-Di[1-methyl-2-(4-methylphenylsulfinyl)ethyl] disulfide (*S,Rs,S,Rs*)-**7b***

Wax; $[\alpha]_D^{20}=+152$ ($c=1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, $J=8.1$ Hz, 2H), 7.33 (d, $J=8.1$ Hz, 2H), 3.35–3.22 (m, 1H), 3.07 (dd, $J=13.2$ and 7.6 Hz, 1H), 2.94 (dd, $J=13.2$ and 6.7 Hz, 1H), 2.41 (s, 3H) and 1.43 (d, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) (DEPT): δ 141.8 (C), 140.6 (C), 130.1 (CH), 123.9 (CH), 64.1 (CH_2), 40.8, 21.4 (CH_3) and 21.0; EIMS: m/z (rel int.%) 427 (**M**H$^+$, 2), 287 (**M**–S(O)*p*-tol, 93), 245 (59), 215 (78), 149 (**M**H$^+$–2× S(O)*p*-tol, 54) and 124 (215-C_7H_7, 100); CIMS: m/z (rel. int.%) 213(1.5), 181 (4), 165 (213-SO, 35), 153 (19), 139 (69) and 125 (100).

*4.3.18. (*S,S,Rs,Rs*)-Di[1-(4-methylphenylsulfinylmethyl)propyl] disulfide (*S,Rs,S,Rs*)-**7c***

Colorless oil; isolated yield, ca. 23%; $[\alpha]_D^{20}=+204$ ($c=1.9$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.54 (d, $J=8.1$ Hz, 2H), 7.33 (d, $J=8.1$ Hz, 2H), 3.19–3.05 (m, 1H), 3.04–2.98 (m, 2H), 2.40 (s, 3H), 1.90–1.65 (m, 2H) and 1.01 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 141.7, 140.7, 130.1, 123.9, 62.7, 47.8, 27.4, 21.4 and 11.1; HRMS (FAB): m/z 455.1213; calcd for $C_{22}H_{31}O_2S_4$: 455.1207.

*4.3.19. (*S,S,Rs,Rs*)-Di[2-methyl-1-(4-methylphenylsulfinylmethyl)propyl] disulfide (*S,Rs,S,Rs*)-**7d***

Colorless oil; isolated yield ca. 15%; $[\alpha]_D^{20}=+189$ ($c=1.0$, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ 7.56 (d, $J=8.0$ Hz, 2H), 7.33 (d, $J=8.0$ Hz, 2H), 3.22–3.14 (m, 1H), 3.06 (dd, $J=13.3$ and 4.6 Hz, 1H), 2.92 (dd, $J=13.3$ and 10.1 Hz, 1H), 2.40 (s, 3H), 2.27–2.14 (m, 1H), 1.01 (d, $J=6.6$ Hz, 3H) and 1.00 (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 141.6, 141.0, 130.0, 123.9, 61.0, 53.5, 31.6, 21.4, 19.2 and 19.1; HRMS (FAB): m/z 483.1526; calcd for $C_{24}H_{35}O_2S_4$: 483.1520.

*4.3.20. X-Ray structure analysis of (*S,Rs*)-**1b***

Colorless lath of 0.73×0.42×0.14 mm size, orthorhombic, space group $P2_12_12_1$, $a=9.2243(5)$, $b=9.7841(5)$, $c=12.3344(6)$ Å, $V=1113.2(1)$ Å^3, $Z=4$, $\rho_{calcd}=1.279$ g/cm^3, $2\theta_{max}=61°$, diffractometer Smart CCD, Mo Kα ($\lambda=0.71073$ Å), ω-scan, $T=173$ K, 9284 reflections collected of which 3390 ($R_{int}=0.0351$) were independent, absorption correction with SADABS, max. and min. transmission 0.9412 and 0.7402, direct primary solution and refinement on F^2 using the SHELX-97 program,[23] 120 refined parameters, rigid methyl [C(3)] and thiol group hydrogen, others riding, $R_1[I>2\sigma(I)]=0.0329$, wR_2 (all data)$=0.0750$, residual electron density 0.218 (–0.294) Å^{-3}, absolute structure parameter 0.04(7).

*4.3.21. X-Ray structure analysis of (*S,Rs*)-**1d***

Colorless lath of 0.72×0.20×0.04 mm size, orthorhombic, space group $P2_12_12_1$, $a=5.6209(12)$, $b=10.4745(12)$, $c=23.1229(19)$ Å, $V=1361.4(3)$ Å^3, $Z=4$, $\rho_{calcd}=1.183$ g/cm^3, $2\theta_{max}=50°$, diffractometer Nonius CAD4, Mo Kα ($\lambda=0.71073$ Å), ω-scan, $T=293$ K, 4880 reflections collected of which 2391 ($R_{int}=0.0984$) were independent, direct primary solution and refinement on F^2 using the SHELX-97 program, 142 refined parameters, rigid thiol group hydrogen, others riding, a methyl group [C(5)] is disordered over two sites, $R_1[I>2\sigma(I)]=0.0857$, wR_2 (all data)$=0.1519$, residual electron density 0.177 (–0.224) Å^{-3}, absolute structure parameter 0.0(3).

*4.3.22. X-Ray structure analysis of (*S,Rs*)-**6c***

Colorless plate of 0.17×0.11×0.02 mm size, monoclinic, space group $P2_1$, $a=5.5457(6)$, $b=7.5279(9)$, $c=16.6643(19)$ Å, $\beta=94.400(2)°$, V$=693.6(1)$ Å^3, $Z=2$, $\rho_{calcd}=1.295$ g/cm^3, $2\theta_{max}=61°$, diffractometer Smart CCD, Mo Kα ($\lambda=0.71073$ Å), ω-scan, $T=173$ K, 5856 reflections collected of which 3145 ($R_{int}=0.0243$) were independent, absorption correction with SADABS, max. and min. transmission 0.9926 and 0.9395, direct primary solution and refinement on F^2 using the SHELX-97 program, 157 refined parameters, rigid methyl and thiol group hydrogens, others riding, $R_1[I>2\sigma(I)]=0.0372$, wR_2 (all data)$=0.0861$, residual electron density 0.489 (–0.229) Å^{-3}, absolute structure parameter 0.03(8).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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References

1. (a) Asensio, G.; Alemán, P. A.; Gil, J.; Domingo, L. R.; Medio-Simón, M. *J. Org. Chem.* **1998**, *63*, 9342–9347. (b) Asensio, G.; Alemán, P. A.; Cuenca, A.; Gil, J.; Medio-Simón, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4073–4078.
2. Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566–2587.
3. Evans, D. A.; Campos, K. R.; Tedrow, J. S; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994–2995.
4. Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.
5. Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 3019–3020.
6. Kosugi, H.; Hoshino, K.; Uda, H. *Tetrahedron Lett.* **1997**, *38*, 6861–6864.
7. Carreño, M. C.; García Ruano, J. L.; Martín, A.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120–2128.
8. Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* **1993**, *34*, 873–876.
9. Page, P. C. B.; Wilkes, R. D.; Reynolds, D. *Comprehensive Organic Functional Groups Transformations*; Pergamon Press: New York, 1995; Vol. 2, pp. 118–119.
10. Bravo, P.; Cavicchio, G.; Crucianelli, M.; Poggiali, A.; Volonterio, A; Zanda, M. *J. Chem. Res.* (*S*), **1998**, 666–667.
11. Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119.
12. Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664–3671.
13. Braga, A. L.; Appelt, H. R.; Scheneider, P. H.; Silveira, C. C.; Wesshohann, L. A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1733–1738.
14. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
15. Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253–10264.
16. House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361–2371.
17. Asensio, G.; Alemán, P. A.; Domingo, L. R.; Medio-Simón, M. *Tetrahedron Lett.* **1998**, *39*, 3277–3280.
18. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881.
19. Alvarez-Ibarra, C.; Cuervo-Rodríguez, R.; Fernández-Monreal, M. C.; Ruíz, M. P. *J. Org. Chem.* **1994**, *59*, 7284–7291.
20. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220.
21. (a) Weiss, H.; Yakimansky, A. V.; Müller, A. H. E. *J. Am. Chem. Soc.* **1996**, *118*, 8897–8903; (b) Koch, R.; Anders, E. *J. Org. Chem.* **1995**, *60*, 5861–5866; (c) *ibid.* **1994**, *59*, 4529–4534.
22. Baker, J. *J. Comput. Chem.* **1986**, *7*, 385–395.
23. Sheldrick, G. M. SHELX-97; University of Göttingen, 1997.