Synthesis of Racemic and Enantiopure 2-Alkylsulfinyl Dithioacetates and Thioacetamides

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Abstract: New 2-alkylsulfinyl dithioacetates and thioacetamides have been prepared. The asymmetric synthesis of (*R*)-2-(cyclohexylsulfinyl)-*N*,*N*-dimethylthioacetamide from previously unreported (*S*)-diacetone-D-glucose cyclohexanesulfinate was achieved in excellent yield (91%) and enantiomeric excess (98%). Methyl (*R*)-2-(cyclohexylsulfinyl)dithioacetate (98% ee) was obtained from chiral cyclohexyl methyl sulfoxide (99% ee).

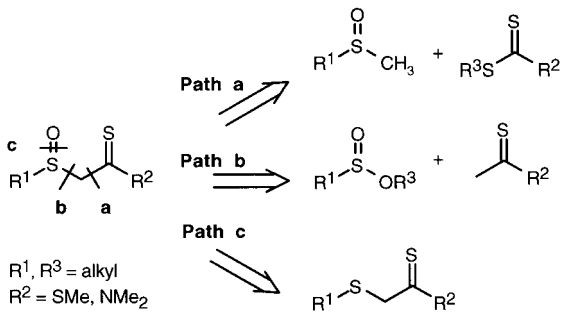
Key words: sulfoxide, thioamide, dithioester, asymmetric synthesis, chiral sulfinate

Chiral sulfoxides play a key role as versatile tools in asymmetric synthesis.[1] For example, highly stereoselective aldol-type condensations[2,3] as well as carbonyl reduction reactions,[4,5] Diels–Alder reactions,[6,7] Pummerer reactions[8,9] and very recently Heck reactions[10] have been reported. The two main strategies to prepare optically pure sulfoxides are: (1) the Andersen synthesis[11,12] which involves the nucleophilic substitution of chiral sulfinate esters by Grignard reagents and proceeds with inversion of configuration at sulfur; and (2) the enantioselective oxidation of prochiral sulfides with chiral reagents (the modified Sharpless reagent developed by Kagan[13,14] and Modena[15,16] or the Davis chiral oxaziridine[17]and related procedures[18]) or with chiral catalysts[19,20] which proceeds efficiently with aromatic prochiral sulfides. The Andersen synthesis requires a chiral sulfinate, the most popular reagent is menthyl (*S*)-*p*-toluenesulfinate which is readily prepared on a large scale[2] and is also commercially available. It is, therefore, not surprising that most of the reported examples of asymmetric syntheses involve aromatic sulfoxides. However the search for efficient and general protocols giving access to chiral dialkyl sulfoxides is very active.[21,48]

In connection with our work on the stereocontrolled thio-Claisen rearrangement mediated by a sulfinyl group,[22] we were interested in the preparation of thiocarbonyl compounds bearing a chiral alkylsulfinyl moiety. A few examples of these compounds have been described in the literature.[23–27]

The great synthetic interest in thiocarbonyl molecules stems from several unique features[28] when compared to their oxygen analogues: (1) under kinetic conditions, deprotonation leads preferentially to the enethiolates of *cis* geometry which are configurationally stable and possess good thermal stability; (2) enethiolates are soft, ambident nucleophiles, they may react through the carbon atom (with ketones or aldehydes) or through the sulfur atom (with alkyl halides) depending on the electrophile; and (3) the attack of a nucleophile on the thiocarbonyl function may be carbophilic or thiophilic, opening up a range of possible transformations.

We report herein the preparation of new α-alkylsulfinyl dithioesters and thioamides in racemic and enantiopure forms. Three retrosynthetic schemes were envisaged for such a synthesis (Scheme 1). Pathway **a** consists of the reaction of a sulfinyl anion with a thiocarbonyl compound. The few examples of 2-sulfinyl dithioesters described in the literature were prepared according to this route.[24,26,27] Pathway **b** corresponds to the reaction of a sulfinate with an enethiolate. Such a reaction is not known with dithioester enolates, but has been successfully applied to the preparation of (*R*)-*N*,*N*-dimethyl-2-(*p*-tolylsulfinyl)thioacetamide by Cinquini and co-workers.[25] Pathway **c** involves the oxidation of a sulfide bearing a thiocarbonyl function. Some problems of chemoselectivity may be encountered as thiocarbonyls are very sensitive towards oxidizing agents.[29,30] However Aloup et al. reported the selective oxidation of a sulfide bearing dithioester and pyridyl moieties by using MCPBA as oxidant.[24] Another drawback of this approach is the difficulty of achieving enantioselective oxidation of dialkyl sulfides. In the present study, we did not consider pathway **c** further.

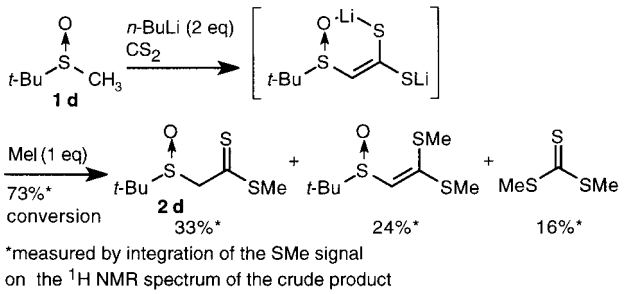


Scheme 1

We first examined the route outlined by pathway **a**. Typically, dithioesters can be prepared by the addition of a Grignard reagent to carbon disulfide in THF and the subsequent alkylation of the resulting dithioacid magnesium salt.[31,32] The analogous reaction with alkyllithiums usual-

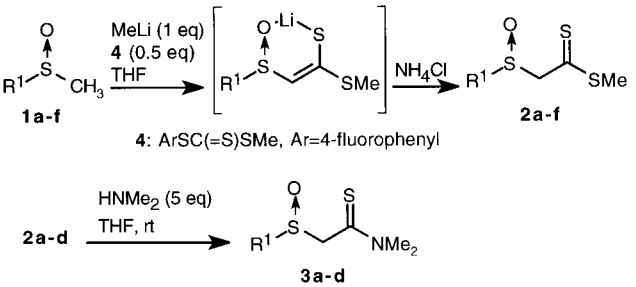
ly (though not always) is low yielding.[33] It is thought that this is due to the disproportionation reaction of the dithioacid lithium salt into the corresponding enedithiolate and dithioacid.[34]

Recently, Barton and co-workers reported an efficient preparation of 2-sulfonyl dithioesters based on the carefully controlled addition of only 1 equivalent of methyl iodide to a dilithium salt intermediate.[35] We attempted to apply this method to the synthesis of dithioester **2d** starting from *tert*-butyl methyl sulfoxide **(1d)** (Scheme 2); in this case, the reaction was unselective. We identified as major byproducts the corresponding ketene dithioacetal and dimethyl trithiocarbonate which is the alkylation product of CS_3^{2-} resulting from the addition of butyllithium to carbon disulfide.



Scheme 2

To circumvent these problems we chose to use dimethyl trithiocarbonate instead of carbon disulfide by analogy with the work of Yokoyama et al.[26,27] They isolated the moderately stable dithioester **2a** as a red oil in 71% yield by reaction of the dimsyl anion with dimethyl trithiocarbonate. The same method, applied to the preparation of dithioester **2d** from the sulfinyl anion of *tert*-butyl methyl sulfoxide, was low yielding. We, thus investigated other trithiocarbonates as well as dithiocarbamates. No reaction was observed with methylimidazoledithiocarboxylate. The best results were obtained with aromatic trithiocarbonates and in particular one bearing a good leaving group, namely, 4-fluorophenyl methyl trithiocarbonate **(4)** (Scheme 3).



Scheme 3

Table 1 Synthesis of Racemic Dithioesters **2** and Thioamides **3**

Entry	R^1	**2**	mp (°C)	Yield (%)	**3**	mp (°C)	Yield (%)
1	Me	**2a**	–	37	**3a**	82	57
2	*i*Pr	**2b**	–	67	**3b**	62	91
3	C_6H_{11}	**2c**	43	74	**3c**	69	95
4	*t*-Bu	**2d**	38	52	**3d**	113	95
5	1-adamantyl	**2e**	123	72	–		–
6	Ph	**2f**	–	30	–		–

Deprotonation of sulfoxides **1a–f** by 1 equivalent of methyllithium in THF at –40 °C and subsequent addition of 0.5 equivalents of compound **4** led to the dithioesters **2a–f** which were deprotonated in situ by the remaining 0.5 equivalents of sulfinyl anions. This deprotonation is unavoidable due to the relatively high acidity of the protons of the methylene group. Protonation by ammonium chloride of the intermediate enethiolates gave dithioesters **2a–f** with yields ranging from 30 to 74% (Table 1). The lowest yields (entries 1 and 6) reflect the very low stability of dithioesters **2a** and **2f** which decompose at room temperature. However, dithioesters **2b–e** can be stored for several months at –30°C as crystalline solids.

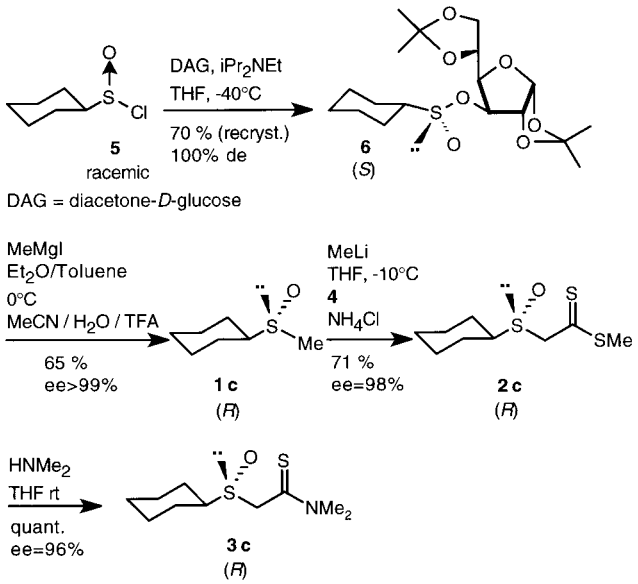
Many methods for the synthesis of thioamides exist and have been reviewed;[36,37] the reaction of an amide with phosphorus pentasulfide or Lawesson's reagent is the most commonly employed process.[38–40] As we had several dithioesters to hand, aminolysis appeared to be the most direct route to the required thioamides. The thioacylation of amines is much faster with dithiocarboxylates than with *O*-alkyl thiocarboxylates and esters.[41] Dithioesters are known to be very useful thioacylating reagents in endothiopeptide synthesis.[42–44]

Thioamides **3a–d** were readily obtained by aminolysis of dithioesters **2a–d** using 2 M dimethylamine in THF (Scheme 3). The reaction proceeded smoothly at room temperature (Table 1). All thioamides **3** are stable, crystalline solids.

It should be mentioned that our attempts to prepare the 2-sulfinyl thioamides *via* the addition of a sulfinyl anion to various dithiocarbamates failed. Indeed, dithiocarbamates are much less electrophilic than trithiocarbonates because of the greater electronegativity of the nitrogen atom compared to the sulfur atom.

By analogy with our previous studies in the racemic series, we first examined the synthesis of enantiopure dithioester **2c** via path **a**. The preparation of the chiral sulfoxide **1c** by enzymatic oxidation of the corresponding sulfide has recently been published,[45] but it has not been optimized for preparative scale synthesis. As mentioned above, the enantioselective chemical oxidation of prochiral sulfides is not as efficient with dialkyl substrates

as with aromatic sulfides. The enantioselective synthesis of dialkyl sulfoxides from chiral sulfinates or *N*-sulfinyloxazolidinones via Andersen-type syntheses has been reported.[46,47] Recently Alcudia et al. have published the preparation of enantiopure sulfoxides from diacetone-D-glucose (DAG) sulfinates.[48,49] The method is very attractive: (1) the synthesis of DAG sulfinates is highly diastereoselective; (2) it leads to either diastereomer by merely changing the nature of the base (*N*,*N*-diisopropylethylamine and pyridine give sulfinates of (*S*)- and (*R*)-configuration respectively); (3) dialkyl sulfoxides (3 examples) are obtained with high enantioselectivity; and (4) the chiral auxiliary is inexpensive (glucose). Thus we applied the Alcudia method to prepare the previously unreported DAG cyclohexanesulfinate **6** (Scheme 4). The reaction of racemic cyclohexanesulfinyl chloride **(5)**[50] with DAG and *N*,*N*-diisopropylethylamine quantitatively led to sulfinate **6** with (*S*) configuration at sulfur, the diastereomeric excess was 86%, based on ^{1}H NMR analysis of the crude product. Recrystallization from ethyl acetate/petroleum ether (1:4) afforded enantiopure (*S*)-sulfinate **6** in 70% yield. The absolute configuration of **6** was confirmed by X-ray crystallography,[51] and this is the first direct assignment of the stereochemistry of a chiral DAG sulfinate. Previous assignments of analogous DAG sulfinates were made indirectly by their transformation into known sulfoxides. Reaction of (*S*)-sulfinate **6** with methylmagnesium iodide led to cyclohexyl methyl (*R*)-sulfoxide **(1c)** with 65% yield after purification by medium pressure chromatography. The enantiomeric excess was greater than 99% (chiral HPLC, Daicel OB column). It was then converted into dithioester **2c** in 71% yield according to the procedure followed in the racemic series. Retention of enantiopurity (98% ee) was observed by ^{1}H NMR in the presence of a chiral shift reagent: addition of (*S*)-methoxyphenylacetic acid (3 equiv) into the NMR tube induced a split (0.03 ppm) of the SMe signal.[52]



Scheme 4

Table 2 Synthesis of Enantiopure Thioamide **3c** from Chiral Sulfinate **6**

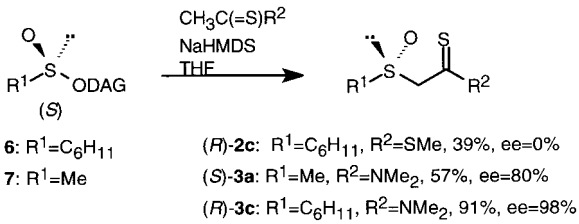
Entry	Equiv **6**	Base	Temp (°C)	Time	Yield (%)	ee (%)
1	0.5	BuLi	–78	1 h	–	–
2	0.5	BuLi	–40	2 h	28	78
3	0.5	BuLi	0	3 h	59	46
4	0.5	LDA	0	3.5 h	82	40
5	0.5	NaHMDS	–40	2 h	70	92
6	0.25	NaHMDS	–78	30 min	91	98
7	0.25	KHMDS	–78	30 min	70	14

Enantiopure thioamide **3c** was obtained quantitatively by aminolysis of **2c** without any significant loss of enantiopurity. The enantiomeric excess (96% ee) was measured by ^{1}H NMR in the presence of (*S*)-methoxyphenylacetic acid.

We also examined path **b** (Scheme 1) as a more straightforward route to the required thioamides from compound **6**. The reaction between chiral sulfinates and magnesium ester enolates is reported to be enantioselective.[2,53] However epimerization is observed when lithium ketone enolates are used.[54] This problem can be circumvented by their transformation into α-lithio *N*,*N*-dimethylhydrazones.[54,55] In the thiocarbonyl series, only one example is described in the literature (by the group of Cinquini): (*R*)-*N*,*N*-dimethyl-(*p*-tolylsulfinyl)thioacetamide which can be obtained from menthyl (*S*)-*p*-toluenesulfinate in 60% yield and 98% ee.[25] Recently Alcudia reported that the reaction of potassium methyl 2-pyridyl ketone enolate with DAG methanesulfinate proceeded in 70% yield and 33% ee.[56] We studied the reactivity of sulfinate **6** with *N*,*N*-dimethylthioacetamide enolate. With lithium bases (BuLi, LDA), the reaction was very slow at low temperature and poorly stereoselective (Table 2, entries 2–4). Careful analysis of the crude product (Table 2, entry 4) by TLC and ^{1}H NMR revealed the formation of some (*R*)-sulfinate **6** (that is with the configuration opposite to that of the starting material). We believe that there is competitive attack of the DAG alcoholate, which is produced in situ, on chiral sulfinate **6** and this results in the loss of diastereopurity of the sulfinate; some precedence for this can be found in the literature.[57]

We decided to change the counterion from lithium to sodium; the increased ionic nature should boost the reactivity of the enethiolate and, indeed, it proved to be much more reactive. The reaction was carried out with 0.25 equivalents of **6** and was complete after 30 minutes at –78 °C resulting in thioamide **3c** in 91% isolated yield with 98% ee (Scheme 5). Under the same experimental conditions, thioamide **3a** was obtained from DAG methanesulfinate **7**[48] in 57% yield and 80% ee. Moreover, analysis by ^{1}H NMR of the mixture of **3a** or **3c** with (*S*)-α-

methoxyphenylacetic acid in $CDCl_3$ after several days at room temperature revealed no change in enantiomeric excess. Thus these compounds appear to be configurationally stable.



Scheme 5

By contrast the same reaction does not work well with dithioester enolates. We attempted the reaction of sodium methyl dithioacetate enolate with sulfinate **6** (Scheme 5). We were able to isolate a 39% yield of dithioester **2c** when the reaction was carried out at –40 °C. All of the sulfinate was consumed. Side reactions probably account for the low yield. For example, sulfinylation of the sulfur atom due to the ambident nucleophilic character of enethiolates (as mentioned before)[28,58] would lead to an unstable, unsaturated thiosulfinate. At –78 °C the reaction rate of side reactions is presumably reduced, thus resulting in the recovery of unreacted sulfinate. However, the conversion into dithioester **2c** was then also slower and the isolated yield was only 30%. Additionally, the isolated compound **2c** was racemic. As in the case of the lithium thioamide enolate the racemization of the sulfinate can be invoked to explain this result. Analysis of the crude product by ^{1}H NMR revealed that the diastereomeric excess of the remaining sulfinate had changed from 100% to 90%. However another process that is worthy of consideration especially in view of the ambident nucleophilic character of enethiolates is the *S*-sulfinylation of the enethiolate and subsequent sulfinyl exchange with another enethiolate unit via a S_N2 process.[54]

The results above demonstrate the different reactivity of dithioester and thioamide enolates towards DAG sulfinates. The former seems to react through the sulfur atom while the latter reacts through the carbon atom.[59] Access to enantiopure α-sulfinyl dithioesters from reaction of the sulfinyl anion of the corresponding chiral methyl sulfoxide could be achieved while the analogous thioamide could not be obtained by this scheme. Pathways **a** and **b** (Scheme 1) are then complementary in allowing access to enantiopure α-sulfinyl dithioesters and thioamides.

In summary a large range of new thiocarbonyl compounds bearing a racemic alkylsulfinyl group were synthesized. We were able to prepare enantiopure alkylsulfinyl compounds in both the thioamide and dithioester series following different strategies. We developed an asymmetric synthesis of 2-(cyclohexylsulfinyl)-*N*,*N*-dimethylthioacetamide with excellent yield and enantiomeric excess. Use of the enantiopure titled molecules as substrates for a new asymmetric version of the thio-Claisen rearrangement is underway.

Compounds **1b–c**,**e**,[60,61] **4**,[62] and **7**[48] were prepared according to the literature. All solvents were purified and dried by standard methods.

2-Sulfinyl Dithioacetates 2a–f; General Procedure

To a solution of methyl sulfoxide **1a–f** (14.4 mmol) in THF (60 mL) was added dropwise at –40 °C 1.6 M MeLi in Et_2O (9.0 mL, 14.4 mmol, 1 equiv). The mixture was stirred for 40 min at –20 °C then cooled to –40 °C and a solution of methyl 4-fluorophenyl trithiocarbonate **(4)** (1.57 g, 7.2 mmol, 0.5 equiv) in THF (6 mL) was added. The mixture was stirred 1.5 h at –20 °C then allowed to warm up to 0 °C. The mixture was worked up by addition of sat. aq NH_4Cl (20 mL) followed by extraction with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) then concentrated to dryness. Purification of the residue by column chromatography (silica gel, petroleum ether/EtOAc 1:1) afforded the dithioesters **2a–f**.

Methyl (*R*,*S*)-2-(Methylsulfinyl)ethanedithioate (2a)[26]

Orange oil; yield: 37%.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.70 (s, 6 H, CH_3SO + SCH_3), 4.35 and 4.47 (AB, J_{AB} = 12.4 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 21.1 (SCH_3), 38.7 (CH_3SO), 73.5 (CH_2), 221.3 (C=S).

Methyl (*R*,*S*)-2-(Isopropylsulfinyl)ethanedithioate (2b)

Orange oil; yield: 67%.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.34 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.36 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.70 (s, 3 H, SCH_3), 2.97 (sept, *J* = 6.9 Hz, 1 H, CH), 4.31 (s, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 13.6 (CH_3), 16.9 (CH_3), 21.0 (SCH_3), 50.0 (CH), 68.9 (CH_2CS), 222.7 (C=S).

IR (NaCl): ν = 2964, 2922, 2348, 1458, 1418, 1386, 1366, 1222, 1184, 1134, 1058, 1026, 970, 836 cm^{-1}.

MS (EI): *m/z* (%) = 196 (M^+, 5), 106 (6), 105 (5), 91 (12), 75 (41), 73 (41), 61 (100), 59 (39), 58 (71), 48 (9), 47 (23), 45 (43), 43 (78), 41 (80).

Anal. calcd for $C_6H_{12}OS_3$: C, 36.70; H, 6.16; O, 8.15; S, 48.99. Found: C, 36.47; H, 6.24; O, 8.42; S, 48.79.

Methyl (*R*,*S*)-2-(Cyclohexylsulfinyl)ethanedithioate (2c)

Orange crystals; yield: 74%; mp 43 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.18–2.15 (m, 10 H, CH_2), 2.70 (s, 3 H, SCH_3), 2.75 (tt, *J* = 3.6, 11.5 Hz, 1 H, CH), 4.32 and 4.37 (AB, J_{AB} = 12.5 Hz, 2 H, CH_2CS).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 21.1 (SCH_3), 24.0, 25.2, 25.5, 25.6, 26.9 (5 CH_2), 58.5 (CH), 68.8 (CH_2CS), 222.8 (C=S).

IR (NaCl): ν = 3424, 2930, 2852, 1648, 1448, 1414, 1264, 1202, 1124, 1054, 970, 730 cm^{-1}.

MS (EI): *m/z* (%) = 236 (M^+, 0.8), 106 (18), 91 (14), 84 (12), 83 (15), 81 (7), 73 (32), 61 (59), 59 (31), 58 (67), 55 (96), 48 (11), 47 (28), 45 (42), 43 (33), 41 (100).

Anal. calcd for $C_9H_{16}OS_3$: C, 45.76; H, 6.83; S, 40.64. Found: C, 45.80; H, 6.86; S, 40.39.

Methyl (*R*,*S*)-2-(*tert*-Butylsulfinyl)ethanedithioate (2d)

Orange crystals; yield: 52%; mp 38 °C.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.33 (s, 9 H, CH_3), 2.71 (s, 3 H, SCH_3), 4.09 and 4.18 (AB, J_{AB} = 12.1 Hz, 2 H, CH_2CS).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 21.1 (SCH_3), 23.1 (CH_3), 55.2 [$C(CH_3)_3$], 68.2 (CH_2CS), 224.5 (C=S).

IR (NaCl): ν = 2972, 2960, 2920, 2864, 1472, 1462, 1440, 1416, 1404, 1394, 1368, 1228, 1178, 1130, 1052, 974, 838, 668, 652 cm^{-1}.

MS (EI): *m/z* (%) = 210 (M^+, 6), 154 (16), 153 (24), 152 (100), 73 (9), 61 (18), 57 (97), 41 (21).

HRMS: found 210.0195, $C_7H_{14}OS_3$ (M^+) requires 210.0207.

Methyl (*R,S*)-2-(1-Adamantylsulfinyl)ethanedithioate (2e)
Orange crystals; yield: 72%; mp 123 °C.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.71–1.98 (m, 12 H), 2.22 (m, 3 H), 2.71 (s, 3 H), 4.16 and 4.20 (AB, J_{AB} = 12.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 21.1 (SCH_3), 28.8 (CH), 35.4 (CH_2), 36.3 (CH_2), 57.6 (CSO), 66.5 (CH_2CS), 225.0 (C=S).

IR (KBr): ν = 2904, 2850, 1058, 1030, 970 cm^{-1}.

MS (EI): *m/z* (%) = 289 (MH^+, 3), 288 (M^+, 4), 135 (99), 93 (100), 79 (99), 48 (23).

Anal. calcd for $C_{13}H_{20}OS_3$: C, 54.12; H, 6.99; S, 33.34. Found: C, 53.92; H, 6.91; S, 33.43.

Methyl (*R,S*)-2-(Phenylsulfinyl)ethanedithioate (2f)
Orange oil; yield: 30%.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.60 (s, 3 H, SCH_3), 4.30 and 4.54 (AB, J_{AB} = 12.1 Hz, 2 H, CH_2CS), 7.50–7.55 (m, 3 H, aromatic H), 7.64–7.69 (m, 2 H, *ortho* aromatic H).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 20.9 (SCH_3), 77.4 (CH_2), 124.5, 129.4, 131.9 (aromatic C), 142.8 (quaternary aromatic C), 221.1 (C=S).

2-Sulfinyl Thioacetamides 3a–d; General Procedure for the Aminolysis of Dithioacetates 2a–d

To a solution of dithioester **2a–d** (3 mmol) in THF (5 mL) was added dropwise at r.t. 2 M $HNMe_2$ in THF (7.5 mL, 15 mmol, 5 equiv). The mixture was stirred for 15–20 min then concentrated to dryness. Purification of the residue by column chromatography (silica gel, EtOAc) afforded the thioamides **3a–d**. An analytically pure sample was obtained by recrystallization from EtOAc/pentane.

(*R,S*)-*N,N*-Dimethyl-2-(methylsulfinyl)ethanethioamide (3a)
Pale yellow crystals; yield: 57%; mp 82 °C.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.86 (s, 3 H, CH_3SO), 3.46 (s, 3 H, NCH_3), 3.51 (s, 3 H, NCH_3), 4.27 and 4.33 (AB, J_{AB} = 13.3 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 39.5 (CH_3SO), 43.2 (NCH_3), 44.8 (NCH_3), 65.9 (CH_2), 190.3 (C=S).

IR (NaCl): ν = 3418, 2932, 1520, 1418, 1394, 1278, 1088, 1032 cm^{-1}.

MS (EI): *m/z* (%) = 165 (M^+, 63), 150 (26), 149 (14), 70 (10), 59 (46), 58 (38), 44 (100), 42 (46).

Anal. calcd for $C_5H_{11}NOS_2$: C, 36.34; H, 6.71; N, 8.48; O, 9.68; S, 38.79. Found: C, 36.45; H, 6.46; N, 8.35; O, 9.88; S, 38.69.

(*R,S*)-2-(Isopropylsulfinyl)-*N,N*-dimethylethanethioamide (3b)
Pale yellow crystals; yield: 91%; mp 62 °C.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.36 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.37 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.27 (sept, *J* = 6.9 Hz, 1 H, CH), 3.48 (s, 3 H, NCH_3), 3.52 (s, 3 H, NCH_3), 4.21 and 4.24 (AB, J_{AB} = 12.9 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 13.8 (CH_3), 16.7 (CH_3), 43.4 (NCH_3), 45.0 (NCH_3), 50.2 (CH), 61.4 (CH_2), 191.3 (C=S).

IR (NaCl): ν = 3444, 2966, 1530, 1392, 1280, 1084, 1048, 1022 cm^{-1}.

MS (EI): *m/z* (%) = 193 (M^+, 18), 189 (10), 149 (19), 70 (84), 58 (32), 44 (100).

HRMS: found 193.0663, $C_7H_{15}ONS_2$ (M^+) requires 193.0595.

(*R,S*)-2-(Cyclohexylsulfinyl)-*N,N*-dimethylethanethioamide (3c)
White crystals; yield: 95%; mp 69 °C.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.18–2.17 (m, 10 H, CH_2), 3.05 (tt, *J* = 3.6, 11.5 Hz, 1 H, CH), 3.48 (s, 3 H, NCH_3), 3.52 (s, 3 H, NCH_3), 4.22 and 4.31 (AB, J_{AB} = 12.9 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 24.0, 25.2, 25.52, 25.54, 26.9 (5 CH_2), 43.4 (NCH_3), 45.0 (NCH_3), 58.6 (CH), 61.2 (CH_2), 191.5 (C=S).

IR (KBr): ν = 2930, 2876, 2852, 1520, 1442, 1392, 1278, 1148, 1116, 1024, 894, 866, 670 cm^{-1}.

MS (EI): *m/z* (%) = 233 (M^+, 9), 228 (18), 216 (27), 211 (31), 151 (11), 150 (34), 149 (70), 102 (28), 70 (100), 58 (36), 56 (16), 55 (61), 45 (13), 44 (90), 43 (39), 42 (34).

HRMS: found 233.0913, $C_{10}H_{19}NOS_2$ (M^+) requires 233.0908.

Anal. calcd for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00; O, 6.86; S, 27.47. Found: C, 51.62; H, 8.34; N, 6.29; O, 6.88; S, 27.33.

(*R,S*)-2-(*tert*-Butylsulfinyl)-*N,N*-dimethylethanethioamide (3d)
White needles; yield: 95%; mp 113 °C.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.34 (s, 9 H, CH_3), 3.50 (s, 3 H, NCH_3), 3.55 (s, 3 H, NCH_3), 4.01 and 4.19 (AB, J_{AB} = 12.0 Hz, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 23.0 (CH_3), 43.5 (NCH_3), 45.4 (NCH_3), 55.1 [*C*(CH_3)$_3$], 60.5 (CH_2), 193.0 (C=S).

IR (KBr): ν = 2988, 1530, 1464, 1424, 1386, 1364, 1278, 1214, 1174, 1138, 1078, 1042, 926, 838, 698, 530 cm^{-1}.

MS (EI): *m/z* (%) = 207 (M^+, 28), 202 (27), 151 (12), 150 (100), 149 (39), 69 (14), 58 (47), 57 (59), 56 (18), 44 (10), 43 (10), 41 (10).

HRMS: found 207.0753, $C_8H_{17}NOS_2$ (M^+) requires 207.0752.

Anal. calcd for $C_8H_{17}NOS_2$: C, 46.34; H, 8.26; N, 6.76; O, 7.72; S, 30.92. Found: C, 46.04; H, 8.25; N, 6.78; O, 7.53; S, 30.97.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl (*S*)-Cyclohexanesulfinate (6)
Cyclohexanesulfinyl chloride **5** was prepared according to the literature.[50] It was obtained in 91% yield after distillation [bp 65–66 °C/0.075 Torr (lit. [63] bp 62–64 °C/0.07 Torr)].

Cyclohexanesulfinate **6** was prepared according to the method described by Alcudia et al.[48,49] To a cooled (–40 °C) solution of freshly distilled **5** (25 g, 0.15 mol, 1.5 equiv) in anhyd THF (80 mL) was added dropwise and with vigorous stirring a mixture of diacetone-D-glucose (26.03 g, 0.10 mol, 1 equiv) and iPr_2EtN (20.9 mL, 15.5 g, 0.12 mol, 1.2 equiv) in anhyd THF (80 mL). The mixture was stirred at –40 °C for 2 h and then quenched with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were successively washed with 5% aq HCl (100 mL), 2% aq $NaHCO_3$ (100 mL) and brine (100 mL) then dried (Na_2SO_4) and concentrated to dryness to afford the crude sulfinate (39 g) as a white solid. The diastereomeric ratio was determined by ^1H NMR analysis: (*R*)/(*S*) 7:93. This ratio was similar when the reaction was performed at –78 °C. Compound **6** was isolated as white needles (27.3 g, 70% yield) by crystallization from EtOAc/petroleum ether 1:4. mp 114 °C; $[\alpha]_D^{22}$ –60 (*c* = 4, acetone).

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.32, 1.35, 1.44 and 1.52 [4 s, 12 H, $OC(CH_3)_2O$], 1.20–2.05 (m, 10 H, CH_2), 2.62 (m, 1 H, CHSO), 3.96–4.15 (m, 2 H, H-6), 4.26–4.35 (m, 2 H, H-4 and H-5), 4.59 (d, *J* = 3.6 Hz, 1H, H-2), 4.72 (d, *J* = 2.1 Hz, 1H, H-3), 5.90 (d, *J* = 3.6 Hz, 1H, H-1).

^{13}C NMR ($CDCl_3$, 62 MHz): δ = 24.4, 24.6, 25.1 and 25.21 (4 CH_2), 25.25 [1 OC(CH_3)$_2$O], 25.6 (1 CH_2), 26.3, 26.7 and 26.8 [3 OC(CH_3)$_2$O], 64.1 (CHSO), 66.7 (C-6), 72.6 (C-5), 79.9 (C-3), 80.5 (C-4), 83.6 (C-2), 105.0 (C-1), 109.2 and 112.5 [2 OC(CH_3)$_2$O].

MS (CI, isobutane): *m/z* (%) = 391 (MH^+, 100), 333 (23), 261 (32), 131 (13), 89 (12).

HRMS: found 391.1802, $C_{18}H_{31}O_7S$ (MH^+) requires 391.1790;

Anal. calcd for $C_{18}H_{30}O_7S$: C, 55.36; H, 7.74; O, 28.68; S, 8.21. Found: C, 55.24; H, 7.73; O, 28.75; S, 8.25.

Cyclohexyl Methyl (*R*)-Sulfoxide (1c)

A solution of MeMgI [prepared from MeI (0.64 mL, 10.27 mmol, 1.5 equiv), magnesium (0.27 g, 11.31 mmol, 1.65 equiv) and Et_2O (11 mL)] was added dropwise to a solution of **6** (2.67 g, 6.85 mmol, 1 equiv) in anhyd toluene (135 mL) at 0 °C. After the addition, the mixture was stirred for 4 h at 0 °C and then quenched by addition of sat. aq sodium bisulfate (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness. The residue was dissolved in MeCN (20 mL) then water (7.5 mL) and TFA (0.36 mL, 0.0047 mmol) were added. The mixture was stirred for 4 h at r.t., then neutralized by addition of powdered $NaHCO_3$ (3 g) and a small amount of water (5 mL) and extracted with CH_2Cl_2 (3 x 30mL). The organic layer was washed with water (20mL) then dried ($MgSO_4$), filtered and concentrated to dryness to afford a brown oil (1.36 g). Purification by medium pressure chromatography (CH_2Cl_2/EtOAc/MeOH 1:1:0.1) gave 0.65 g (65% yield) of **1c** as a yellow oil. Its enantiopurity (ee>99%) was measured by HPLC on a Chiralcel OB Daicel column (hexane/iPrOH 9:1, λ = 214.8 nm); $[\alpha]_D^{21}$ –56 (*c* = 1, $CHCl_3$).

Methyl (*R*)-2-(Cyclohexylsulfinyl)ethanedithioate (2c)

The general procedure described for the preparation of racemic 2-sulfinyl dithioesters **2** was followed with enantiopure sulfoxide **1c** as starting material. However we observed that the reaction of the sulfinyl anion on 4-fluorophenyl methyl trithiocarbonate could be carried out at higher temperature (between –10 °C and –5 °C instead of –20 °C) with a significant gain of time (30 min instead of 1.5 h). **2c** was isolated with a 71% yield after purification by column chromatography (silica gel, petroleum ether/EtOAc 1:1). Its enantiopurity (98% ee) was measured by ^{1}H NMR by addition of 3 equivalents of (*S*)-α-methoxyphenylacetic acid (chiral shift reagent); mp 77 °C; $[\alpha]_D^{23}$ + 313 (*c* = 1, acetone).

Anal. calcd for $C_9H_{16}OS_3$: C, 45.76; H, 6.83; O, 6.78; S, 40.64. Found: C, 45.74; H, 6.98; O, 6.73; S, 40.88.

(*R*)-2-(Cyclohexylsulfinyl)-*N*,*N*-dimethylethanethioamide (3c)

To a cooled (–78 °C) solution of thioacetamide (1.41 g, 13.7 mmol, 1 equiv) in anhyd THF (17 mL) was added dropwise a 2 M NaHMDS in THF (6.9 mL, 13.7 mmol, 1 equiv). The mixture was stirred at –78 °C for 1 h then a solution of **6** (1.34 g, 3.4 mmol, 0.25 equiv) in anhyd THF (17 mL) was added dropwise. The reaction was monitored by TLC. It was complete after 30 min and quenched by addition of a H_2O/THF (1:4) mixture at –78 °C. The mixture was worked up by addition of dil. aq H_2SO_4 solution (10 mL), followed by extraction with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and then concentrated to dryness. Only one enantiomer could be detected by analysis of the ^{1}H NMR spectrum of the mixture of the residue and 3 equivalents of (*S*)-α-methoxyphenylacetic acid (chiral shift reagent). Purification by column chromatography (silica gel, EtOAc) afforded 0.73 g (91% yield) of the (*R*)-enantiomer of **3c** (98% ee) as a white solid; mp 82 °C. Its enantiopurity was measured by ^{1}H NMR by addition of (*S*)-α-methoxyphenylacetic acid (3 equiv).

3c was obtained as white crystals by recrystallization (EtOAc/pentane) (100% ee); mp 86 °C; $[\alpha]_D^{22}$ + 80 (*c* =1.1, acetone).

Anal. calcd for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00; O, 6.86; S, 27.47. Found: C, 51.65; H, 8.08; N, 6.02; O, 6.72; S, 27.38.

It was also obtained by aminolysis of (*R*)-dithioester **2c** according to the general procedure described for racemic thioamides **3a–d** in a quantitative yield and 96% ee.

(*S*)-*N*,*N*-Dimethyl-2-(methylsulfinyl)ethanethioamide (3a)

3a was prepared according to the method described for **3c**, starting from (*S*)-DAG methanesulfinate **7**,[48] in a 57% yield after purification by column chromatography (silica gel, EtOAc/MeOH 98:2). The enantiopurity (80% ee) was measured by ^{1}H NMR by addition of (*S*)-α-methoxyphenylacetic acid (3 equiv). The same enantiomeric ratio was found for the crude and purified products; mp 56–59 °C; $[\alpha]_D^{22}$ +50 (*c* =1.1, acetone).

HRMS: found 165.0272, $C_5H_{11}NOS_2$ (M^+) requires 165.0282.

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