Convenient Methods for Synthesis of C_2-Symmetric Diphenyltetrahydrothiophenes

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Abstract: Racemic and optically pure (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene, (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene, and (–)-(3*S*,6*S*)-3,6-diphenyl-1,2-dithiane were synthesized by use, in the crucial steps, of the easy-to-handle borane systems tetrabutylammonium borohydride–iodine and tetrabutylammonium borohydride–iodomethane.

Key words: diphenyltetrahydrothiophenes, 3,6-diphenyl-1,2-dithiane, asymmetric reduction, tetrabutylammonium borohydride, sulfur heterocycles

Chiral ligands containing sulfide moieties are useful for many asymmetric transformations, such as asymmetric epoxidations,[1] catalytic asymmetric cyclopropanation of electron-deficient alkenes,[2] electrophilic sulfenylation of unsaturated carbon–carbon bonds,[3] and aziridination of N-electron-withdrawn imines.[4] They are useful for the synthesis of chiral alcohols and amines from organoboranes,[5] the synthesis of certain carbocycles[6] and functionalized N-heterocycles,[7] as well as the synthesis of biologically active molecules such as iso-agatharesinol,[8] swainsonine,[9] a side chain of Taxol,[10] and the anti-inflammatory agents[11] neobenodine, cetirizine, and CDP-840. Previously, a simple protocol for accessing chiral C_2-symmetric 3,4-diphenylpyrrolidines via reduction of 2,3-diphenylsuccinic acid derivatives by use of the sodium borohydride–iodine reagent system was reported from this laboratory.[12] More recently, it was reported that the reagent systems tetrabutylammonium borohydride–iodine[13a] and tetrabutylammonium borohydride–iodomethane[13b] give better yields in borane reductions. Herein, we report simple, convenient methods for the preparation of both racemic and optically pure (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene [(±)-**1** and (–)-**1**], (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene [(+)-**2**],[14] and (–)-(3*S*,6*S*)-3,6-diphenyl-1,2-dithiane [(–)-**3**] (Figure 1) by use of these modified borane reagent systems in crucial steps in the synthesis.

(±)-3,4-Diphenyltetrahydrothiophene [(±)-**1**] is readily accessed by the synthetic protocol outlined in Scheme **1**. Dimethyl (±)-2,3-diphenylsuccinate (**5**) is prepared in 80% yield from methyl phenylacetate in the presence of titanium(IV) chloride–triethylamine in dichloromethane at –45 °C.[15] Subsequent reduction of diester **5** by the easy-to-handle tetrabutylammonium borohydride–iodine or tetrabutylammonium borohydride–iodomethane system in anhydrous tetrahydrofuran provides (±)-2,3-diphenylbutane-1,4-diol (**6**) in 75% or 74% yield, respectively. Further conversion into the corresponding ditosylate **7** by use of *p*-toluenesulfonyl chloride and pyridine followed by cyclization with sodium sulfide nonahydrate gives (±)-**1** in 91% yield.[16]

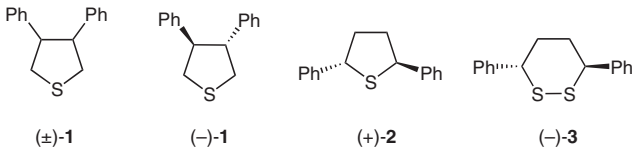
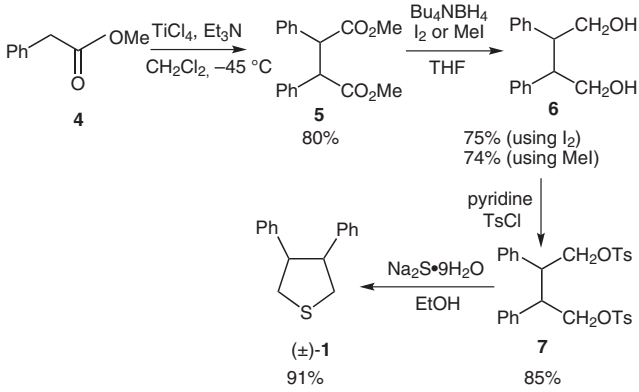


Figure 1



Scheme 1 Synthesis of (±)-3,4-diphenyltetrahydrothiophene [(±)-**1**]

(–)-(3*R*,4*R*)-3,4-Diphenyltetrahydrothiophene [(–)-**1**] is readily prepared by a similar synthetic protocol starting from (*R*)-(+)-1,1′-binaphthalene-2,2′-diyl bis(phenylacetate) (**9**), which, in turn, is easily accessed by the reaction of phenylacetic acid with 1,1′-binaphthalene-2,2′-diol (**8**) (Scheme **2**). Diester **9** is converted into the intramolecularly coupled diester (–)-(*R*,*R*,*R*)-**10** in 80% yield in the presence of titanium(IV) chloride–triethylamine.[17] Subsequent reduction of **10** with tetrabutylammonium borohydride–iodine or tetrabutylammonium borohydride–iodomethane gives (–)-(2*R*,3*R*)-2,3-diphenylbutane-1,4-diol [(–)-**6**] in 71% or 75% yield, respectively. We observed that these reducing systems give better yields than the sodium borohydride–iodine system for the reduction of **10**. Direct reduction of **10** to (–)-**6** is necessary, since the hydrolysis of (–)-(*R*,*R*,*R*)-**10** when potassium hydrox-

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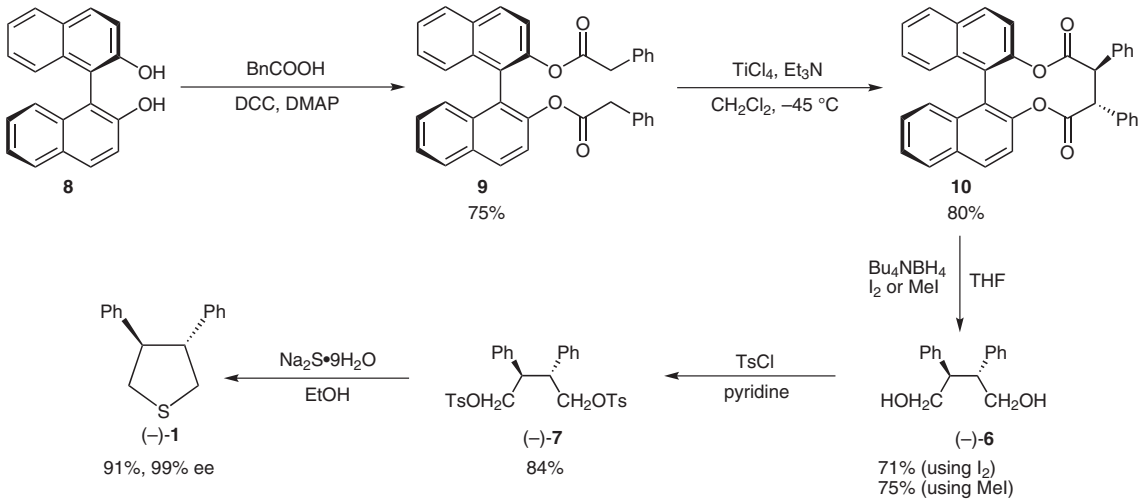


Scheme 2 Synthesis of (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene [(–)-**1**]

ide in methanol is used leads to racemization of the resulting 2,3-diphenylsuccinic acid. Diol (–)-**6** is tosylated with *p*-toluenesulfonyl chloride–pyridine to give (–)-**7** in 84% yield; ditosylate (–)-**7** is cyclized in the presence of sodium sulfide nonahydrate in refluxing ethanol to give (–)-(3*R*,4*R*)-3,4-diphenyltetrahydrothiophene [(–)-**1**] (91%). The structure of (–)-**1** was further confirmed by X-ray crystal structure analysis. The ORTEP diagram is given in Figure 2.

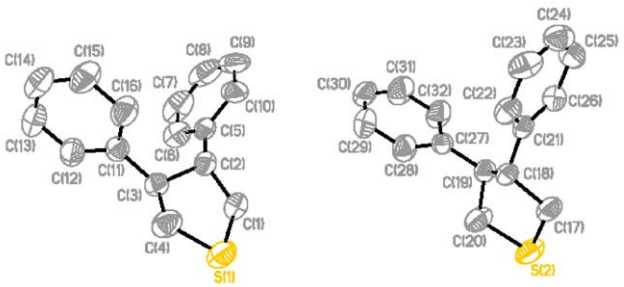


Figure 2 ORTEP representation of the crystal structure of (–)-**1**; thermal ellipsoids are drawn at 35% probability and all the hydrogens are omitted for the sake of clarity

The chiral (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene [(+)-**2**] is synthesized by the protocol outlined in Scheme 3. (*E*)-1,4-Diphenylbut-2-ene-1,4-dione (**11**) is prepared in 74% yield by Friedel–Crafts acylation of benzene with fumaryl chloride.[18] Subsequent reduction of **11** with tin(II) chloride/hydrogen chloride in ethanol gives 1,4-diphenylbutane-1,4-dione (**12**) in 76% yield.[19] Diketone **12** is reduced with tetrabutylammonium borohydride–iodine in the presence of a chiral oxazaborolidine system in anhydrous tetrahydrofuran to give (+)-(1*R*,4*R*)-1,4-diphenylbutane-1,4-diol (**13**) in 90% yield and 90% ee. We observed that in this case better yields are obtained when a smaller amount of tetrabutylammonium borohydride (0.8 equiv) is used compared to sodium borohydride (2.2 equiv).[13b,c] The nonracemic diol **13** (90% ee) was enriched by use of L-proline and boric acid to give (+)-(1*R*,4*R*)-diol **13** in 98% ee.[20] The (+)-(1*R*,4*R*) diol **13** (98% ee) was mesylated with methanesulfonyl chloride–triethylamine in anhydrous dichloromethane to give (1*R*,4*R*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane (**14**) in 82% yield.[21] Finally, (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene [(+)-**2**] was obtained in 80% yield by the reaction of **14** with sodium sulfide nonahydrate in dimethyl sulfoxide.[14] Its structure was further confirmed by X-ray crystal structure analysis. The ORTEP diagram of (+)-**2** is given in Figure 3.

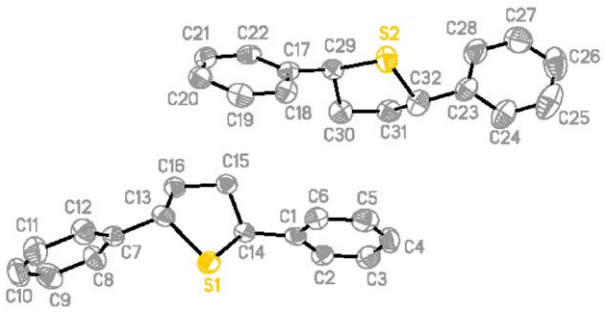
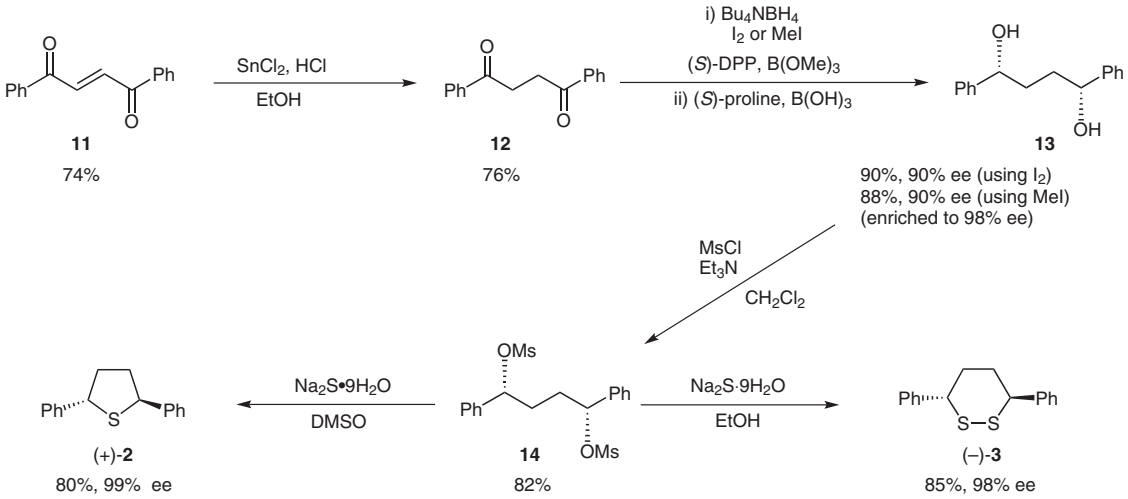


Figure 3 ORTEP representation of the crystal of structure (+)-**2**; thermal ellipsoids are drawn at 35% probability and all the hydrogens are omitted for the sake of clarity

Surprisingly, (–)-(3*S*,6*S*)-3,6-diphenyl-1,2-dithiane [(–)-**3**] was formed in 85% yield when the reaction of **14** with sodium sulfide nonahydrate was carried out in ethanol as solvent (Scheme 3). Such sulfur–sulfur-bond-containing compounds were previously reported to be obtained from the reaction of bromoisobutyrophenone and sodium sulfide in ethanol.[22] Disulfides are useful synthons, as the sulfur–sulfur bond can be cleaved by numerous nucleophiles and electrophiles, and is also prone to oxidation.[23] The structure of compound **3** was further confirmed by X-ray crystal structure analysis. The ORTEP diagram is given in Figure 4.[24]



Scheme 3 Synthesis of (+)-(2*S*,5*S*)-2,5-diphenyltetrahydrothiophene [(+)-**2**] and (–)-(3*S*,6*S*)-3,6-diphenyl-1,2-dithiane [(–)-**3**]

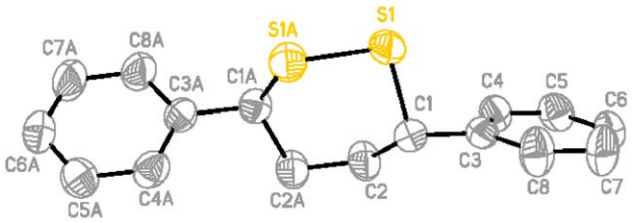


Figure 4 ORTEP representation of the crystal structure of (–)-**3**; thermal ellipsoids are drawn at 35% probability and all the hydrogens are omitted for the sake of clarity

Since the chiral tetrahydrothiophene derivatives **1** and **2** and 1,2-dithiane **3** are readily prepared from simple and readily accessible reagents, the methods described here have considerable potential for further synthetic exploitation.

$TiCl_4$ (Spectrochem, India) and (*R*)-(+)-1,1′-bi(2-naphthol) (Gerchem, Hyderabad) were used as obtained. CH_2Cl_2 was distilled over CaH_2 and dried over 4-Å molecular sieves. THF was used freshly distilled over benzophenone/sodium. Melting points were determined on a Superfit capillary point apparatus and are uncorrected. IR (KBr) spectra were recorded on a Jasco FT-IR model 5300 spectrometer with polystyrene as reference. The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra of samples in $CDCl_3$, with TMS as internal standard, were recorded on a Bruker Avance 400 spectrometer. Optical rotations were measured on an Autopol II automatic polarimeter at 25 °C. TLC analyses were carried out on plates coated with silica gel (hexane–EtOAc mixtures); spots were developed in an I_2 chamber. For column chromatographic separations under gravity, column-grade silica gel (100–200 and 230–400 mesh) was employed.

Use of Tetrabutylammonium Borohydride–Iodine for the Reduction of Diester 5; Typical Procedure

Diester **5** (1.49 g, 5 mmol) and Bu_4NBH_4 (6.168 g, 24 mmol) were mixed in anhyd THF (60 mL) under N_2 in a two-necked septum-capped round-bottom flask. I_2 (3.048 g, 12 mmol) dissolved in anhyd THF (30 mL) was added under N_2 at 0 °C over 1 h; the mixture was stirred at 25 °C for 4 h and refluxed for 12 h. The mixture was cooled to 25 °C and the excess hydride was carefully quenched with 3 N aq HCl (10 mL). After gas evolution had ceased, the reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with aq $NaHCO_3$ (15 mL), H_2O (10 mL), and brine (10 mL) and dried (Na_2SO_4). The solvent was removed and the product was purified by column chromatography (silica gel, 100–200 mesh, hexane–EtOAc, 80:20) and recrystallized from hexane.

(±)-2,3-Diphenylbutane-1,4-diol [(±)-6]

Yield: 0.9 g (75%); mp 100–101 °C.

IR (KBr): 3290, 3060, 1601 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.2 (br s, 2 H), 3.1–3.4 (m, 2 H), 3.8–4.1(m, 4 H), 6.8–6.95 (m, 4 H), 7.0–7.2 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.03, 65.5, 126.5, 128.1, 128.6, 140.6.

(–)-2,3-Diphenylbutane-1,4-diol [(–)-6]

Yield: 0.85 g (71%); 98% ee; $[\alpha]_D^{25}$ –48.0 (*c* 0.404, $CHCl_3$) {(Lit.[16] $[\alpha]_D^{25}$ –48.2 (*c* 0.249, $CHCl_3$)}.

Use of Tetrabutylammonium Borohydride–Iodomethane for the Reduction of Diester 10; Typical Procedure

Diester **10** (2.6 g, 5 mmol) and Bu_4NBH_4 (6.168 g, 24 mmol) were mixed in anhyd THF (60 mL) under N_2 in a two-necked septum-capped round-bottom flask. MeI (3.4 g, 1.5 mL, 24 mmol) dissolved in anhyd THF (30 mL) was added under N_2 at 0 °C over 1 h; the mixture was stirred at 25 °C for 4 h and refluxed for 12 h. It was then cooled to 25 °C and the excess hydride was carefully quenched with 3 N HCl (10 mL). After the gas evolution had ceased, the reaction mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with aq $NaHCO_3$ (15 mL), H_2O (10 mL), and brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, 100–200 mesh, hexane–EtOAc, 80:20) and recrystallized from hexane.

(–)-2,3-Diphenylbutane-1,4-diol [(–)-6]

Yield: 0.9 g (75%); 98% ee; mp 100–101 °C; $[\alpha]_D^{25}$ –48.0 (*c* 0.560, $CHCl_3$) {Lit.[16] $[\alpha]_D^{25}$ –48.2 (*c* 0.249, $CHCl_3$)}.

IR (KBr): 3290, 3060, 1601 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.2 (br s, 2 H), 3.1–3.4 (m, 2 H), 3.8–4.1 (m, 4 H), 6.8–6.95 (m, 4 H), 7.0–7.2 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.03, 65.5, 126.5, 128.1, 128.6, 140.6.

(±)-2,3-Diphenylbutane-1,4-diol [(±)-6]
Yield: 0.89 g (74%); mp 100–101 °C.

(±)-3,4-Diphenyltetrahydrothiophene [(±)-1]
$Na_2S·9H_2O$ (freshly recrystallized from EtOH; 4.8 g, 20 mmol) was added to (±)-ditosylate **7** (2.63 g, 5 mmol) in EtOH (40 mL), and the mixture was refluxed for 24 h. H_2O (10 mL) was then added and the mixture was extracted with Et_2O (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified by column chromatography (silica gel, 230–400 mesh, hexane).

Yield: 1.094 g, (91%); mp 109–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12–3.17 (m, 2 H), 3.28–3.32 (m, 2 H), 3.48–3.5 (m, 2 H), 7.1–7.26 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6, 55.8, 126.8, 127.4, 128.5, 140.5.

LCMS: *m*/*z* = 241 [M + 1].

(–)-3,4-Diphenyltetrahydrothiophene [(–)-1]
Compound (–)-**1** was prepared from ditosylate (–)-**7**, by following the procedure described above for (±)-**1**.

Yield: 1.094 g (91%); 99% ee; mp 109–110 °C; $[\alpha]_D^{25}$ –205 (*c* 1.08, $CHCl_3$).

HPLC (Daicel Chiralcel OB-H, *i*-PrOH–hexane, 5:95, flow rate 1.0 mL/min, 254 nm): t_R (*R*,*R*) = 7.7 min, t_R (*S*,*S*) = 12.3 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12–3.17 (m, 2 H), 3.28–3.32 (m, 2 H), 3.48–3.5 (m, 2 H), 7.1–7.26 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6, 55.8, 126.8, 127.4, 128.5, 140.5.

LCMS: *m*/*z* = 241 [M + 1].

Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71; S, 13.34. Found: C, 79.95; H, 6.71; S, 13.64.

(+)-(1*R*,4*R*)-1,4-Diphenylbutane-1,4-diol (13)
Bu_4NBH_4 (1.891 g, 7.6 mmol) was placed in a 100-mL three-neck round-bottom flask under a N_2 atmosphere in anhyd THF (20 mL). To this I_2 (0.934 g, 3.68 mmol) in anhyd THF (30 mL) was added under N_2 at 0 °C over 1 h by use of a pressure equalizer. The diborane generated in situ was trapped as a BH_3–THF complex. To this reagent, a soln of (*S*)-α,α-diphenyl-2-pyrrolidine methanol [(*S*)-DPP; 0.8 mmol] and trimethyl borate (1 mmol) in THF (8 mL)] was added and the mixture was stirred for 10 min. Then **12** (1 g, 4.6 mmol) dissolved in THF (25 mL) was added slowly to the reaction mixture with a pressure equalizer over 1 h at 10 °C, and the mixture was further stirred at 25 °C for 1 h. The reaction mixture was brought to 25 °C and carefully quenched with 2 N HCl (15 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the product was purified by column chromatography (silica gel, 100–200 mesh, hexane–EtOAc, 75:25).

Yield: 1 g (90%); mp 63–65 °C; 90% ee; $[\alpha]_D^{25}$ +52.6 (*c* 0.25, $CHCl_3$) {Lit.[21] $[\alpha]_D^{25}$ –58.5 (*c* 1.01, $CHCl_3$) for (1*S*,4*S*)-**13**}.

HPLC (Daicel Chiralpak AD-H, *i*-PrOH–hexane, 10:90, flow rate 1.0 mL/min, 254 nm): t_R (*S*,*S*) = 21 min, t_R (*R*,*R*) = 22.5 min.

The non-racemic diol **13** (90% ee) was enriched by a reported procedure[20] using L-proline and boric acid; this gave (+)-(1*R*,4*R*)-diol **13** in 98% ee.

IR (KBr): 3339, 3025, 1207, 990 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.8–2.0 (m, 4 H), 2.6–2.8 (br s, 2 H), 4.7 (m, 2 H), 7.2–7.3 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.1, 74.3, 125.6, 127.0, 128.1, 144.6.

When using Bu_4NBH_4/MeI: Yield: 0.97 g (88%); 90% ee of (1*R*,4*R*); $[\alpha]_D^{25}$ +52.68 (*c* 0.47, $CHCl_3$) {Lit.[21] $[\alpha]_D^{25}$ –58.5 (*c* 1.01, $CHCl_3$, > 98% ee) for (1*S*,4*S*)}.

(+)-(2*S*,5*S*)-2,5-Diphenyltetrahydrothiophene [(+)-2]
Dimesylate **14** (1.990 g, 5 mmol), prepared from (+)-(1*R*,4*R*)-diol **13** (98% ee), was taken up in DMSO (15 mL); $Na_2S·9H_2O$ (freshly recrystallized from EtOH; 4.8 g, 20 mmol) was added and the mixture was stirred at 5 °C for 24 h. H_2O (10 mL) was then added and the contents were extracted with Et_2O (3 × 20 mL). The combined extracts were concentrated and the product was purified by column chromatography (silica gel, 230–400 mesh, hexane).

Yield: 0.96 g (80%); 99% ee; mp 78 °C; $[\alpha]_D^{25}$ +22 (*c* 0.5, $CHCl_3$).

HPLC (Daicel Chiralcel OJ-H, *i*-PrOH–hexane, 20:80, flow rate 1.0 mL/min, 254 nm): t_R (*S*,*S*) = 28.8 min, t_R (*R*,*R*) = 42.5 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11–2.16 (m, 2 H), 2.58–2.62 (m, 2 H), 4.82–4.86 (m, 2 H), 7.22–7.34 (m, 6 H), 7.46–7.47 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0, 54.3, 127.2, 128.4, 142.5.

LCMS: *m*/*z* = 241 [M + 1].

Anal. Calcd for $C_{16}H_{16}S$: C, 79.95; H, 6.71; S, 13.34. Found: C, 79.99; H, 6.74; S, 13.53.

(–)-(3*S*,6*S*)-3,6-Diphenyl-1,2-dithiane [(–)-3]
Dimesylate **14** (1.99 g, 5 mmol), prepared from (+)-(1*R*,4*R*)-diol **13** (98% ee), was taken up in EtOH (20 mL); $Na_2S·9H_2O$ (freshly recrystallized from EtOH; 4.8 g, 20 mmol) was added and the mixture was stirred at 25 °C for 24 h. H_2O (10 mL) was then added and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were concentrated and the product was purified by column chromatography (silica gel, 230–400 mesh, hexane).

Yield: 1.16 g (85%); mp 69–70 °C; 98% ee (based on ee of precursor **13**). (However, X-ray structure data revealed the absence of the other enantiomer. Unfortunately, the corresponding racemic mixture could not be resolved by HPLC using the chiral columns OD, OB, OJ, and AD).

$[\alpha]_D^{25}$ –4.2 (*c* 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.0–2.15 (m, 2 H), 2.53–2.61 (m, 2 H), 4.82–4.86 (m, 2 H), 7.22–7.36 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0, 54.3, 127.5, 127.6, 128.5, 142.5.

LCMS: *m*/*z* = 273 [M + 1].

Anal. Calcd for $C_{16}H_{16}S_2$: C, 70.54; H, 5.92; S, 23.54. Found: C, 70.56; H, 5.94; S, 23.78.

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(24) For compounds **1**, **2**, and **3**, diffraction data were collected on a Bruker SMART APEX CCD area detector system using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Data reduction was carried out with SAINTPLUS, and the structures were solved and refined with SHELXS-97. All non-hydrogen atoms were refined anisotropically.
Crystal data for **1** (CCDC 711632): $C_{16}H_{16}S$, MW = 240.36, monoclinic, space group: *P*21, *a* = 10.363 (2) Å, *b* = 8.6732 (19) Å, *c* = 14.857 (3) Å, β = 91.314 (4)°, *V* = 1335.0(5) Å^3, *Z* = 4, ρ = 1.196 Mg·M^{-3}, μ = 0.218 mm^{-1}, *T* = 298 (2) K. Of the 13820 reflections collected, 5194 were unique (R_{int} = 0.0301). Refinement on all data converged at *R*1 = 0.0487, *wR*2 = 0.1107.
Crystal data for **2** (CCDC 711633): $C_{16}H_{16}S$, MW = 240.35, monoclinic, space group: *P*21, *a* = 13.453 (4) Å, *b* = 5.7139 (18) Å, *c* = 17.416 (5) Å, β = 99.656 (5)°, *V* = 1319.8 (7) Å^3, *Z* = 4, ρ = 1.210 Mg·M^{-3}, μ = 0.220 mm^{-1}, *T* = 298 (2) K. Of the 12428 reflections collected, 4612 were unique (R_{int} = 0.0626). Refinement on all data converged at *R*1 = 0.0750, *wR*2 = 0.1969.
Crystal data for **3** (CCDC 711634): $C_{16}H_{16}S_2$, MW = 272.41, trigonal, space group: $P3_121$, *a* = 9.2159 (14) Å, *b* = 9.2159 (14) Å, *c* = 14.647 (5) Å, α = 90°, β = 90°, γ = 120°, *V* = 1077.3 (4) Å^3, *Z* = 3, ρ = 1.260 Mg·M^{-3}, μ = 0.350 mm^{-1}, *T* = 298 (2) K. Of the 6010 reflections collected, 1401 were unique (R_{int} = 0.0326). Refinement on all data converged at *R*1 = 0.0412, *wR*2 = 0.1092.