Asymmetric Synthesis of Highly Functionalized Tetrahydrothiophenes by Organocatalytic Domino Reactions

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General. The ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to CDCl_3 ($\delta = 7.26$) for ^1H NMR and relative to the central resonances of CDCl_3 ($\delta = 77.0$) for ^{13}C NMR. Chromatography was carried out by flash chromatography using Merck silica gel 60 (230-400 mesh) using mixtures of Et_2O and *n*-pentane as eluents. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Micromass LCT spectrometer. Enantiomeric excesses were determined by HPLC using a system of Waters with a 600E multisolvent delivery system with an in-line degasser and a 2996 PDA detector. NMR data of known compounds are in agreement with literature values.

Materials. All solvent were of p.a. quality and were dried by standard procedures prior to use if necessary. Unless otherwise specified, materials were obtained from commercial sources and used without purification. The α,β -unsaturated aldehyde **4h** were prepared following the procedure described in the literature.¹ Thiol **5** was prepared in a two-step synthesis as described in the literature.² Catalysts (*R*)-**6** and (*S*)-**6** were prepared as described in the literature.³ Racemates were prepared with a mixture of 5 mol% (*R*)-**6** and 5 mol% (*S*)-**6**.

General procedure for the asymmetric synthesis of tetrahydrothiophene carbaldehydes 1: The catalyst 15.0 mg (0.025 mmol, 0.1 equiv.) **6** was added to a stirred solution of the α,β -unsaturated aldehyde (0.75 mmol, 3.0 equiv.) **4** in 2.5 mL solvent followed by the addition of 61.0 mg (0.50 mmol, 2.0 equiv.) benzoic acid and 38.1 mg (0.25 mmol, 1.0 equiv.) thiol **5**. The reaction mixture was stirred for 48 h at room temperature and then filtered through 1-2 cm bed of silica washing through with Et_2O . The solvents were evaporated under vacuum. The crude product was subjected to FC on silica gel ($\text{Et}_2\text{O}/n$ -pentane) to yield the desired tetrahydrothiophene carbaldehyde **1**.

(2*R*,3*R*,4*S*)-4-Hydroxy-2-isopropyl-4-phenyltetrahydrothiophene-3-carbaldehyde (1a)

1a

Yellow oil. Yield: 56% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.60 (d, ³*J* = 1.6 Hz, 1H), 7.67 (dd, ³*J* = 7.2 Hz, ⁴*J* = 1.4 Hz, 2H), 7.50 (t, ³*J* = 7.2 Hz, 2H), 7.41 (tt, ³*J* = 7.2 Hz, ⁴*J* = 1.4 Hz, 1H), 4.01 (dd, ³*J* = 5.6 Hz, ³*J* = 8.5 Hz, 1H), 3.63 (bs, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.25 (dd, ³*J* = 1.7 Hz, ³*J* = 8.5 Hz, 1H), 2.93 (d, ²*J* = 12.0 Hz, 1H), 2.02 (m, 1H), 1.14 (d, ³*J* = 6.6 Hz, 3H), 1.06 (d, ³*J* = 6.6 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.3, 140.1, 128.7, 127.9, 124.9, 86.1, 66.7, 52.4, 47.1, 32.9, 21.5, 18.6. HRMS: C₁₄H₁₈O₂S [M+Na]⁺ calcd: 273.0925, found: 273.0934. [α]_D²³ = −61.1 (c = 0.35, CHCl₃, 94% ee (2*R*,3*R*,4*S*)). The ee was determined after reduction to the corresponding alcohol **7a**.

(2*S*,3*S*,4*R*)-4-Hydroxy-2-isopropyl-4-phenyltetrahydrothiophene-3-carbaldehyde (*ent*-1a)

ent-1a

Yellow oil. Yield: 51% using catalyst (*R*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.60 (d, ³*J* = 1.6 Hz, 1H), 7.67 (dd, ³*J* = 7.2 Hz, ⁴*J* = 1.4 Hz, 2H), 7.50 (t, ³*J* = 7.2 Hz, 2H), 7.41 (tt, ³*J* = 7.2 Hz, ⁴*J* = 1.4 Hz, 1H), 4.01 (dd, ³*J* = 5.6 Hz, ³*J* = 8.5 Hz, 1H), 3.63 (bs, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.25 (dd, ³*J* = 1.7 Hz, ³*J* = 8.5 Hz, 1H), 2.93 (d, ²*J* = 12.0 Hz, 1H), 2.02 (m, 1H), 1.14 (d, ³*J* = 6.6 Hz, 3H), 1.06 (d, ³*J* = 6.6 Hz, 3H). The ee was determined after reduction to the corresponding alcohol **7a**.

(2*R*,3*R*,4*S*)-2-Methyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1b)

1b

Yellow solid. Yield: 59% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.55 (d, ³*J* = 1.7 Hz, 1H), 7.52–7.32 (m, 5H), 4.06 (dq, ³*J* = 6.6 Hz, ³*J* = 9.6 Hz, 1H), 3.57 (d, ²*J* = 12.0 Hz, 1H), 3.05 (dd, ³*J* = 1.7 Hz, ³*J* = 9.6 Hz, 1H), 2.97 (d, ²*J* = 12.0 Hz, 1H), 1.52 (d, ³*J* = 6.6 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.7, 140.4, 128.8, 128.1, 124.9, 85.9, 70.7, 47.1, 40.5, 21.8. HRMS: C₁₂H₁₄O₂S [M+Na]⁺ calcd: 245.0612, found: 245.0605. [α]_D²³ = −12.3 (c = 0.07, CHCl₃, 90% ee (2*R*,3*R*,4*S*)). The ee was determined after reduction to the corresponding alcohol **7b**.

(2*R*,3*R*,4*S*)-2-Ethyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1c)

Yellow solid. Yield: 73% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.53 (d, ³*J* = 1.6 Hz, 1H), 7.57 (dd, ³*J* = 7.3 Hz, ⁴*J* = 1.3 Hz, 2H), 7.41 (t, ³*J* = 7.3 Hz, 2H), 7.32 (tt, ³*J* = 7.3 Hz, ⁴*J* = 1.3 Hz, 1H), 3.88 (dt, ³*J* = 4.3 Hz, ³*J* = 9.1 Hz, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.07 (dd, ³*J* = 1.6 Hz, ³*J* = 9.1 Hz, 1H), 2.91 (d, ²*J* = 12.0 Hz, 1H), 1.91 (m, 1H), 1.65 (m, 1H), 1.05 (t, ³*J* = 7.3 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.5, 140.8, 128.8, 128.0, 125.0, 85.8, 69.0, 47.8, 46.8, 29.9, 14.0. [α]_D²³ = -68.7 (c = 0.34, CHCl₃, 95% ee (2*R*,3*R*,4*S*)). The ee was determined after reduction to the corresponding alcohol **7c**.

(2*R*,3*R*,4*S*)-4-Hydroxy-4-phenyl-2-propyltetrahydrothiophene-3-carbaldehyde (1d)

Yellow solid. Yield: 74% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.54 (d, ³*J* = 1.7 Hz, 1H), 7.58 (dd, ³*J* = 7.3 Hz, ⁴*J* = 1.4 Hz, 2H), 7.42 (t, ³*J* = 7.3 Hz, 2H), 7.33 (tt, ³*J* = 7.3 Hz, ⁴*J* = 1.4 Hz, 1H), 3.95 (dt, ³*J* = 4.2 Hz, ³*J* = 9.2 Hz, 1H), 3.47 (d, ²*J* = 12.0 Hz, 1H), 3.38 (bs, 1H), 3.09 (dd, ³*J* = 1.7 Hz, ³*J* = 9.2 Hz, 1H), 2.92 (d, ²*J* = 12.0 Hz, 1H), 1.83 (m, 1H), 1.65 (m, 1H), 1.44 (m, 2H), 0.91 (t, ³*J* = 7.3 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.7, 140.3, 128.8, 128.0, 125.0, 85.6, 69.3, 46.8, 46.0, 39.1, 22.2, 13.8. [α]_D²³ = -28.5 (c = 0.17, CHCl₃, 94% ee (2*R*,3*R*,4*S*)). The ee was determined after reduction to the corresponding alcohol **7d**.

(2*R*,3*R*,4*S*)-2-Butyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1e)

White solid. Yield: 62% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.53 (d, ³*J* = 1.6 Hz, 1H), 7.57 (d, ³*J* = 7.2 Hz, 2H), 7.41 (t, ³*J* = 7.2 Hz, 2H), 7.33 (tt, ³*J* = 7.2 Hz, ⁴*J* = 1.2 Hz, 1H), 3.90 (dt, ³*J* = 4.4 Hz, ³*J* = 9.6 Hz, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.35 (bs, 1H), 3.07 (dd, ³*J* = 1.6 Hz, ³*J* = 9.2 Hz, 1H), 2.92 (d, ²*J* = 12.0 Hz, 1H), 1.85 (m, 1H), 1.64 (m, 1H), 1.42-1.28 (m, 4H), 0.92 (t, ³*J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.7, 140.3, 128.8, 128.0, 125.0, 85.7, 69.3, 46.8, 46.2, 36.7, 31.0, 22.5, 13.9. [α]_D²³ = -24.0 (c = 0.15, CHCl₃, 90% ee (2*R*,3*R*,4*S*)). The ee was determined after reduction to the corresponding alcohol **7e**.

(2*R*,3*R*,4*S*)-2-Heptyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1f)

White solid. Yield: 44% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.53 (d, ³*J* = 1.6 Hz, 1H), 7.57 (d, ³*J* = 7.2 Hz, 2H), 7.41 (t, ³*J* = 7.6 Hz, 2H), 7.33 (tt, ³*J* = 7.6 Hz, ⁴*J* = 1.2 Hz, 1H), 3.90 (dt, ³*J* = 4.0 Hz, ³*J* = 9.6 Hz, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.36 (bs, 1H), 3.07 (dd, ³*J* = 1.6 Hz, ³*J* = 9.2 Hz, 1H), 2.92 (d, ²*J* = 12.0 Hz, 1H), 1.84 (m, 1H), 1.62 (m, 2H), 1.45-1.22 (m, 9H), 0.92 (t, ³*J* = 7.2 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.7, 140.3, 128.8, 128.0, 125.0, 85.6, 69.3, 46.8, 46.3, 37.0, 31.7, 29.3, 29.1, 29.0, 22.6, 14.1. [α]_D²³ = -19.4 (c = 0.18, CHCl₃, 90% ee (*2R,3R,4S*)). The ee was determined after reduction to the corresponding alcohol **7f**.

(2*R,3R,4S,3Z*)-2-Hex-3-enyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1g)

Yellow oil. Yield: 61% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.53 (d, ³*J* = 1.7 Hz, 1H), 7.58 (dd, ³*J* = 7.3 Hz, ⁴*J* = 1.4 Hz, 2H), 7.42 (t, ³*J* = 7.3 Hz, 2H), 7.33 (tt, ³*J* = 7.2 Hz, ⁴*J* = 1.4 Hz, 1H), 5.43 (m, 1H), 5.34 (m, 1H), 3.95 (dt, ³*J* = 3.7 Hz, ³*J* = 9.5 Hz, 1H), 3.48 (d, ²*J* = 12.0 Hz, 1H), 3.09 (dd, ³*J* = 1.7 Hz, ³*J* = 9.5 Hz, 1H), 2.93 (d, ²*J* = 12.0 Hz, 1H), 2.20 (m, 2H), 2.09 (dq, ³*J* = 7.5 Hz, ⁴*J* = 0.9 Hz, 2H), 1.92 (m, 1H), 1.70 (m, 1H), 0.99 (t, ³*J* = 7.5 Hz, 3H). ¹³C NMR (CDCl₃) δ 200.5, 140.2, 133.0, 128.8, 128.0, 127.2, 125.0, 85.6, 69.3, 46.7, 45.7, 36.9, 26.5, 20.6, 14.3. HRMS: C₁₇H₂₂O₂S [M+Na]⁺ calcd: 313.1238, found: 313.1218. [α]_D²³ = -40.5 (c = 0.22, CHCl₃, 93% ee (*2R,3R,4S,3Z*)). The ee was determined after reduction to the corresponding alcohol **7g**.

(2*R*,3*R*,4*S*)-(2-*tert*-Butyldimethylsilyl)-2-ethyl-4-hydroxy-4-phenyltetrahydrothiophene-3-carbaldehyde (1h)

Colorless oil. Yield: 44% using catalyst (*S*)-**6** and toluene as solvent. ¹H NMR (CDCl₃) δ 9.53 (d, ³*J* = 1.6 Hz, 1H), 7.57 (d, ³*J* = 7.2 Hz, 2H), 7.42 (t, ³*J* = 7.2 Hz, 2H), 7.42 (tt, ³*J* = 7.2 Hz, ⁴*J* = 1.2 Hz, 1H), 4.06 (dt, ³*J* = 4.4 Hz, ³*J* = 8.8 Hz, 1H), 3.80 (m, 1H), 3.70 (m, 1H), 3.46 (d, ²*J* = 12.0 Hz, 1H), 3.25 (dd, ³*J* = 1.6, ³*J* = 9.2 Hz, 1H), 2.92 (d, ²*J* = 12.0 Hz, 1H), 2.08 (m, 1H), 1.87 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H). ¹³C NMR (CDCl₃) δ 200.6, 140.3, 128.8, 128.0, 125.0, 90.7, 68.9, 61.7, 47.0, 43.0, 39.3, 25.9, 18.5, -5.4. [α]_D²³ = -44.3 (c = 0.24, CHCl₃, 96% ee (2*R*,3*R*,4*S*). The ee was determined after reduction to the corresponding alcohol **7h**.

General procedure for the reduction of tetrahydrothiophene carbaldehydes 1:

Representative procedure: 25.0 mg (0.10 mmol, 1.0 equiv.) **1a** were solved in 3 mL THF and the solution was cooled down to 0 °C. 0.75 mL concentrated AcOH were injected followed by the addition of 9.9 mg (0.15 mmol, 1.5 equiv., 95% purity) NaCNBH₃. The solution was warmed up to room temperature over 4 h. 5 mL brine and 5 mL saturated NaHCO₃ solution were added. The resulting mixture was extracted 3 times with 10 mL Et₂O and the combined organic phases were dried over MgSO₄. It was filtered through 1-2 cm bed of silica washing through with Et₂O and the solvents were evaporated under vacuum yielding quantitative pure alcohol **7a**.

(3*S*,4*S*,5*R*)-4-Hydroxymethyl-5-isopropyl-3-phenyltetrahydrothiophene-3-ol (7a)

Yellow oil. Yield: >99%. ¹H NMR (CDCl₃) δ 7.51 (t, ³*J* = 6.8 Hz, 2H), 7.39 (t, ³*J* = 7.6 Hz, 3H), 7.30 (tt, ³*J* = 7.6 Hz, ³*J* = 1.2 Hz, 1H), 3.87 (dd, ³*J* = 3.6 Hz, ³*J* = 9.6 Hz, 1H), 3.73 (bs, 1H), 3.64 (m, 2H), 3.25 (d, ²*J* = 11.6 Hz, 1H), 2.79 (d, ²*J* = 11.6 Hz, 1H), 2.56 (dd, ³*J* = 4.0 Hz, ³*J* = 7.2 Hz, 1H), 2.18 (dt, 2.97, ³*J* = 3.2 Hz, ³*J* = 10.0 Hz, 1H), 2.10 (m, 1H), 1.06 (d, ³*J* = 6.8 Hz, 6H). ¹³C NMR (CDCl₃) δ 141.8, 128.5, 127.5, 125.0, 87.2, 59.8, 55.1, 53.2, 46.0, 30.1, 22.9, 16.3. HRMS: C₁₄H₂₀O₂S [M+Na]⁺ calcd: 275.1082, found: 275.1086. [α]_D²³ = +9.7 (c = 0.10, CHCl₃, 80% ee (3*S*,4*S*,5*R*), optical rotation of the reaction yielding 94% ee not measured). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min (τ₁ = 30.5 min. (minor enantiomer); τ₂ = 33.3 min. (major enantiomer)).

(3*R*,4*R*,5*S*)-4-Hydroxymethyl-5-isopropyl-3-phenyltetrahydrothiophene-3-ol (*ent*-7a)

ent-7a

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.51 (t, $^3J = 6.8$ Hz, 2H), 7.39 (t, $^3J = 7.6$ Hz, 3H), 7.30 (tt, $^3J = 7.6$ Hz, $^3J = 1.2$ Hz, 1H), 3.87 (dd, $^3J = 3.6$ Hz, $^3J = 9.6$ Hz, 1H), 3.73 (bs, 1H), 3.64 (m, 2H), 3.25 (d, $^2J = 11.6$ Hz, 1H), 2.79 (d, $^2J = 11.6$ Hz, 1H), 2.56 (dd, $^3J = 4.0$ Hz, $^3J = 7.2$ Hz, 1H), 2.18 (dt, 2.97, $^3J = 3.2$ Hz, $^3J = 10.0$ Hz, 1H), 2.10 (m, 1H), 1.06 (d, $^3J = 6.8$ Hz, 6H). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min ($\tau_1 = 30.5$ min. (major enantiomer); $\tau_2 = 33.3$ min. (minor enantiomer)).

(3*S*,4*S*,5*R*)-4-Hydroxymethyl-5-methyl-3-phenyl-tetrahydrothiophene-3-ol (7b)

7b

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.79 (d, $^3J = 7.3$ Hz, 2H), 7.68 (t, $^3J = 7.3$ Hz, 2H), 7.58 (t, $^3J = 7.2$ Hz, 1H), 4.30 (bs, 1H), 4.22 (dq, $^3J = 6.5$ Hz, $^3J = 10.6$ Hz, 1H), 3.99 (dd, $^2J = 11.6$ Hz, $^3J = 3.2$ Hz, 1H), 3.87 (dd, $^2J = 11.6$ Hz, $^3J = 2.4$ Hz, 1H), 3.70 (d, $^2J = 11.8$ Hz, 1H), 3.18 (d, $^2J = 11.8$ Hz, 1H), 2.26 (dt, $^3J = 2.6$ Hz, $^3J = 10.6$ Hz, 1H), 1.77 (d, $^3J = 6.5$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.6, 128.5, 127.4, 125.0, 87.0, 60.3, 58.8, 46.0, 40.4, 20.2. HRMS: $\text{C}_{12}\text{H}_{16}\text{O}_2\text{S}$ [$\text{M}+\text{Na}$] $^+$ calcd: 247.0769, found: 247.0772. $[\alpha]_{\text{D}}^{23} = +1.0$ ($c = 0.10$, CHCl_3 , 81% ee (3*S*,4*S*,5*R*), optical rotation of the reaction yielding 90% ee not measured). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min ($\tau_1 = 38.6$ min. (minor enantiomer); $\tau_2 = 46.0$ min. (major enantiomer)).

(3*S*,4*S*,5*R*)-5-Ethyl-4-hydroxymethyl-3-phenyltetrahydrothiophene-3-ol (7c)

7c

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.51 (d, $^3J = 7.3$ Hz, 2H), 7.39 (t, $^3J = 7.3$ Hz, 2H), 7.30 (t, $^3J = 7.2$ Hz, 1H), 3.90 (bs, 1H), 3.79 (dt, $^3J = 3.3$ Hz, $^3J = 10.5$ Hz, 1H), 3.71 (dd, $^2J = 11.6$ Hz, $^3J = 3.3$ Hz, 1H), 3.59 (dd, $^2J = 11.6$ Hz, $^3J = 2.4$ Hz, 1H), 3.36 (d, $^2J = 11.6$ Hz, 1H), 2.88 (d, $^2J = 11.6$ Hz, 1H), 2.07 (dt, $^3J = 3.0$ Hz, $^3J = 10.5$ Hz, 1H), 2.02 (m, 1H), 1.59 (m, 1H), 1.11 (t, $^3J = 7.3$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.2, 128.5, 127.4, 125.0, 87.0, 59.3, 58.3, 48.4, 45.6, 28.6, 13.2. HRMS: $\text{C}_{13}\text{H}_{18}\text{O}_2\text{S}$ [$\text{M}+\text{Na}$] $^+$ calcd: 261.0925, found: 261.0931. $[\alpha]_{\text{D}}^{23} = +18.2$ ($c = 0.34$, CHCl_3 , 95% ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OJ, *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min ($\tau_1 = 17.4$ min. (minor enantiomer); $\tau_2 = 23.0$ min. (major enantiomer)).

(3*S*,4*S*,5*R*)-4-Hydroxymethyl-3-phenyl-5-propyltetrahydrothiophene-3-ol (7d)

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.78 (d, $^3J = 8.0$ Hz, 2H), 7.67 (t, $^3J = 8.0$ Hz, 2H), 7.58 (t, $^3J = 8.0$ Hz, 1H), 4.50 (bs, 1H), 4.13 (dt, $^3J = 2.9$ Hz, $^3J = 10.4$ Hz, 1H), 4.00 (dd, $^2J = 11.7$ Hz, $^3J = 3.3$ Hz, 1H), 3.85 (dd, $^2J = 11.7$ Hz, $^3J = 2.3$ Hz, 1H), 3.64 (d, $^2J = 11.9$ Hz, 1H), 3.17 (d, $^2J = 11.7$ Hz, 1H), 2.32 (dt, $^3J = 2.8$ Hz, $^3J = 10.4$ Hz, 1H), 2.22 (m, 1H), 1.84 (m, 3H), 1.26 (t, $^3J = 7.2$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.2, 128.5, 127.4, 125.0, 87.0, 59.1, 58.6, 46.5, 45.5, 37.9, 22.4, 14.1. HRMS: $\text{C}_{14}\text{H}_{20}\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd: 275.1082, found: 275.1079. $[\alpha]_{\text{D}}^{23} = +33.3$ ($c = 0.11$, CHCl_3 , 94% ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OJ, *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min ($\tau_1 = 22.9$ min. (minor enantiomer); $\tau_2 = 32.5$ min. (major enantiomer)).

(3*S*,4*S*,5*R*)-5-Butyl-4-hydroxymethyl-3-phenyltetrahydrothiophene-3-ol (7e)

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.80 (d, $^3J = 7.8$ Hz, 2H), 7.68 (t, $^3J = 7.8$ Hz, 2H), 7.59 (t, $^3J = 7.8$ Hz, 1H), 4.11 (m, 2H), 4.00 (dd, $^2J = 11.8$ Hz, $^3J = 3.1$ Hz, 1H), 3.87 (dd, $^2J = 11.8$ Hz, $^3J = 2.1$ Hz, 1H), 3.65 (d, $^2J = 11.8$ Hz, 1H), 3.16 (d, $^2J = 11.8$ Hz, 1H), 2.34 (dt, $^3J = 2.3$ Hz, $^3J = 10.2$ Hz, 1H), 2.25 (m, 1H), 1.76 (m, 5H), 1.23 (t, $^3J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.2, 128.5, 127.4, 125.0, 86.9, 59.3, 58.7, 46.7, 45.7, 35.6, 31.3, 22.7, 14.0. $[\alpha]_{\text{D}}^{23} = +31.5$ ($c = 0.20$, CHCl_3 , 90% ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min ($\tau_1 = 29.5$ min. (minor enantiomer); $\tau_2 = 32.7$ min. (major enantiomer)).

(3*S*,4*S*,5*R*)-5-Heptyl-4-hydroxymethyl-3-phenyltetrahydrothiophene-3-ol (7f)

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.79 (d, $^3J = 7.9$ Hz, 2H), 7.68 (t, $^3J = 7.9$ Hz, 2H), 7.59 (t, $^3J = 7.9$ Hz, 1H), 4.11 (m, 2H), 3.99 (dd, $^2J = 11.5$ Hz, $^3J = 2.7$ Hz, 1H), 3.87 (dd, $^2J = 11.5$ Hz, $^3J = 1.9$ Hz, 1H), 3.65 (d, $^2J = 11.9$ Hz, 1H), 3.16 (d, $^2J = 11.7$ Hz, 1H), 2.33 (dt, $^3J = 2.4$ Hz, $^3J = 10.2$ Hz, 1H), 2.23 (m, 1H), 1.83 (m, 3H), 1.58 (m, 8H), 1.18 (t, $^3J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.2, 128.5, 127.4, 125.0, 86.9, 59.3, 58.7, 46.7, 45.7, 35.9, 31.8, 30.3, 29.6, 29.2, 22.6, 14.1. $[\alpha]_{\text{D}}^{23} = +31.3$ ($c = 0.20$, CHCl_3 , 90%

ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min (τ_1 = 26.5 min. (minor enantiomer); τ_2 = 30.0 min. (major enantiomer)).

(3*S*,4*S*,5*R*,3*Z*)-5-Hex-3-enyl-4-hydroxymethyl-3-phenyltetrahydrothiophene-3-ol (7g)

7g

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.79 (d, 3J = 8.0 Hz, 2H), 7.68 (t, 3J = 8.0 Hz, 2H), 7.59 (t, 3J = 8.0 Hz, 1H), 5.68 (m, 2H), 4.12 (dt, 3J = 3.0 Hz, 3J = 10.5 Hz, 1H), 3.99 (dd, 2J = 11.7 Hz, 3J = 3.4 Hz, 1H), 3.87 (dd, 2J = 11.7 Hz, 3J = 2.4 Hz, 1H), 3.66 (d, 2J = 11.8 Hz, 1H), 3.17 (d, 2J = 11.8 Hz, 1H), 2.51 (m, 2H), 2.34 (m, 4H), 1.93 (m, 1H), 1.28 (t, 3J = 7.5 Hz, 3H). ^{13}C NMR (CDCl_3) δ 142.1, 132.7, 128.5, 127.8, 127.4, 125.0, 86.9, 59.2, 58.7, 46.3, 45.8, 36.0, 26.7, 20.6, 14.4. HRMS: $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd: 315.1395, found: 315.1404. $[\alpha]_{\text{D}}^{23}$ = +26.8 (c = 0.28, CHCl_3 , 93% ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min (τ_1 = 40.3 min. (minor enantiomer); τ_2 = 45.1 min. (major enantiomer)).

(3*S*,4*S*,5*R*)-5-(2-*tert*-Butyldimethylsilyloxyethyl)-4-hydroxymethyl-3-phenyltetrahydrothiophene-3-ol (7h)

7h

Yellow oil. Yield: >99%. ^1H NMR (CDCl_3) δ 7.51 (d, 3J = 7.2 Hz, 2H), 7.38 (t, 3J = 7.2 Hz, 2H), 7.29 (tt, 3J = 7.2 Hz, 3J = 1.2 Hz, 1H), 3.90 (m, 3H), 3.74 (m, 2H), 3.57 (dd, 2J = 11.6 Hz, 3J = 2.4 Hz, 1H), 3.35 (d, 2J = 11.6 Hz, 1H), 2.17 (m, 2H), 1.84 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (CDCl_3) δ 142.3, 128.5, 127.4, 125.1, 86.6, 62.4, 59.3, 58.6, 46.0, 43.1, 38.4, 25.9, 18.4, -5.31, -5.33. $[\alpha]_{\text{D}}^{23}$ = +6.5 (c = 0.27, CHCl_3 , 96% ee (3*S*,4*S*,5*R*)). HPLC: Daicel Chiralpak OD (2x), *n*-hexane/2-propanol (95/5), flow rate = 1.0 mL/min (τ_1 = 20.8 min. (minor enantiomer); τ_2 = 24.2 min. (major enantiomer)).

General procedure for the asymmetric synthesis of tetrahydrothiophen-2-ylphenyl methanones 2: 15.0 mg (0.025 mmol, 0.1 equiv.) catalyst **6** was added to a stirred solution of the α,β -unsaturated aldehyde (0.75 mmol, 3.0 equiv.) **4** in 2.5 mL solvent followed by the addition of 42.0 mg (0.50 mmol, 2.0 equiv.) NaHCO_3 and 38.1 mg (0.25 mmol, 1.0 equiv.) thiol **5**. The reaction mixture was stirred for 48 h at room temperature and then filtered through 1-2 cm bed of silica washing through with Et_2O . The solvents were evaporated under vacuum. The crude product

was subjected to FC on silica gel (Et₂O/*n*-pentane) to yield the desired tetrahydrothiophen-2-ylphenyl methanone **2**.

(2*S*,3*R*,5*R*)-(3-Hydroxy-5-isopropyltetrahydrothiophen-2-yl)phenyl methanone (2a)

2a

White solid. Yield: 61% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.97 (d, ³*J* = 7.5 Hz, 2H), 7.61 (tt, ³*J* = 7.6 Hz, ³*J* = 1.2 Hz, 1H), 7.49 (t, ³*J* = 7.5 Hz, 2H), 4.87 (quin, ³*J* = 3.2 Hz, 1H), 4.73 (m, 1H), 4.72 (d, ³*J* = 3.2 Hz, 1H), 3.71 (ddd, ²*J* = 6.0 Hz, ³*J* = 8.8 Hz, ³*J* = 10.0 Hz, 1H), 2.41 (ddd, ³*J* = 2.8 Hz, ²*J* = 6.0 Hz, ³*J* = 13.0 Hz, 1H), 1.79 (m, 2H), 1.02 (d, ³*J* = 6.4 Hz, 3H), 1.00 (d, ³*J* = 6.4 Hz, 3H). ¹³C NMR (CDCl₃) δ 199.6, 136.1, 134.1, 128.8, 128.7, 75.6, 56.7, 52.8, 42.3, 34.7, 22.0, 21.0. HRMS: C₁₄H₁₈O₂S [M+Na]⁺ calcd: 273.0925, found: 273.0927. [α]_D²³ = +115.5 (c = 0.75, CHCl₃, 80% ee (2*R*,3*R*,4*S*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ₁ = 12.2 min. (minor enantiomer); τ₂ = 28.4 min. (major enantiomer)).

(2*S*,3*R*,5*R*)-(3-Hydroxy-5-methyltetrahydrothiophen-2-yl)phenyl methanone (2b)

2b

Slightly yellow solid. Yield: 59% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.95 (dd, ³*J* = 7.4 Hz, ⁴*J* = 1.4 Hz, 2H), 7.60 (tt, ³*J* = 7.4 Hz, ⁴*J* = 1.4 Hz, 1H), 7.48 (t, ³*J* = 7.4 Hz, 2H), 4.87 (quin, ³*J* = 3.5 Hz, 1H), 4.83 (d, ³*J* = 3.5 Hz, 1H), 4.72 (dd, ⁴*J* = 1.7 Hz, ³*J* = 3.5 Hz, 1H), 3.96 (m, 1H), 2.46 (ddd, ²*J* = 12.8 Hz, ³*J* = 5.9 Hz, ³*J* = 3.5 Hz, 1H), 1.74 (m, 1H), 1.42 (d, ³*J* = 6.6 Hz, 3H). ¹³C NMR (CDCl₃) δ 199.4, 136.0, 134.1, 128.7, 128.6, 75.7, 53.2, 46.2, 42.9, 21.8. HRMS: C₁₂H₁₄O₂S [M+Na]⁺ calcd: 245.0612, found: 245.0605. [α]_D²³ = +77.1 (c = 0.34, CHCl₃, 74% ee (2*S*,3*R*,5*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ₁ = 15.9 min. (minor enantiomer); τ₂ = 19.1 min. (major enantiomer)).

(2*S*,3*R*,5*R*)-(5-Ethyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone (2c)

2c

Slightly yellow solid. Yield: 44% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.95 (d, ³*J* = 7.6 Hz, 2H), 7.60 (t, ³*J* = 7.6 Hz, 1H), 7.48 (t, ³*J* = 7.6 Hz, 2H), 4.86 (quin, ³*J* = 3.4 Hz, 1H), 4.75 (d, ³*J* = 3.4 Hz, 1H), 4.72 (bs, 1H), 3.80 (m, 1H), 2.46 (ddd, ²*J* = 9.4 Hz, ³*J* = 5.8 Hz, ³*J* = 3.4 Hz, 1H), 1.73 (m, 3H), 1.00 (d, ³*J* = 7.3 Hz, 3H). ¹³C NMR (CDCl₃) δ 199.6, 136.1, 134.1, 128.7, 128.7, 75.5, 52.4, 50.6, 43.9, 30.2, 13.3. HRMS: C₁₃H₁₆O₂S [M+Na]⁺ calcd: 259.0769, found: 259.0763. [α]_D²³ = +32.0 (c = 0.03,

CHCl₃, 72% ee (2*S*,3*R*,5*R*). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ_1 = 12.0 min. (minor enantiomer); τ_2 = 16.2 min. (major enantiomer)).

(2*S*,3*R*,5*R*)-(3-Hydroxy-5-propyltetrahydrothiophen-2-yl)phenyl methanone (2d)

White solid. Yield: 43% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.95 (d, ³*J* = 7.2 Hz, 2H), 7.60 (t, ³*J* = 7.2 Hz, 1H), 7.50 (t, ³*J* = 8.0 Hz, 2H), 4.86 (quin, ³*J* = 3.2 Hz, 1H), 4.74 (m, 2H), 3.88 (m, 1H), 2.45 (ddd, ³*J* = 3.2 Hz, ³*J* = 6.0, ²*J* = 9.2 Hz, 1H), 1.75 (m, 2H), 1.64 (m, 1H), 1.37 (m, 2H), 0.93 (t, ³*J* = 7.6 Hz, 3H). ¹³C NMR (CDCl₃) δ 199.6, 136.0, 134.1, 128.8, 128.7, 75.3, 52.5, 48.7, 44.3, 39.3, 22.4, 13.9. HRMS: C₁₄H₁₈O₂S [M+Na]⁺ calcd: 273.0925, found: 273.0932. [α]_D²³ = +116.8 (c = 0.10, CHCl₃, 82% ee (2*S*,3*R*,5*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ_1 = 11.8 min. (minor enantiomer); τ_2 = 18.3 min. (major enantiomer)).

(2*S*,3*R*,5*R*)-(3-Hydroxy-5-propyltetrahydrothiophen-2-yl)phenyl methanone (2e)

White solid. Yield: 66% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.95 (d, ³*J* = 7.2 Hz, 2H), 7.60 (t, ³*J* = 7.6 Hz, 1H), 7.50 (t, ³*J* = 8.0 Hz, 2H), 4.86 (quin, ³*J* = 3.2 Hz, 1H), 4.74 (m, 2H), 3.87 (m, 1H), 2.45 (ddd, ³*J* = 3.6 Hz, ²*J* = 6.0, ³*J* = 9.2 Hz 1H), 1.75 (m, 2H), 1.64 (m, 1H), 1.37 (m, 4H), 0.93 (t, ³*J* = 7.6 Hz, 3H). ¹³C NMR (CDCl₃) δ 199.6, 136.0, 134.1, 128.8, 128.7, 75.3, 52.5, 48.9, 44.3, 36.9, 31.3, 22.5, 13.9. HRMS: C₁₅H₂₀O₂S [M+Na]⁺ calcd: 287.1082, found: 287.1073. [α]_D²³ = +89.6 (c = 0.10, CHCl₃, 64% ee (2*S*,3*R*,5*R*)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min (τ_1 = 17.5 min. (minor enantiomer); τ_2 = 28.4 min. (major enantiomer)).

(2*S*,3*R*,5*R*,3*Z*)-(5-Hex-3-enyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone (2f)

Slightly yellow solid. Yield: 57% using catalyst (*S*)-**6**. ¹H NMR (CDCl₃) δ 7.96 (dd, ³*J* = 8.2 Hz, ⁴*J* = 1.5 Hz, 2H), 7.61 (tt, ³*J* = 8.2 Hz, ⁴*J* = 1.5 Hz, 1H), 7.49 (t, ³*J* = 8.2 Hz, 2H), 5.34 (m, 2H), 4.86 (quin, ³*J* = 3.5 Hz, 1H), 4.76 (d, ³*J* = 3.5 Hz, 1H), 4.71 (dd, ³*J* = 3.5 Hz, ⁴*J* = 1.7 Hz, 1H), 3.87 (m, 1H), 2.47 (ddd, ³*J* = 3.5 Hz, ²*J* = 6.0 Hz, ³*J* = 12.9 Hz, 1H), 2.11 (q, ³*J* = 8.0 Hz, 2H), 2.03 (quin, ³*J* = 6.5 Hz, 2H), 1.77 (m, 2H), 1.28 (m, 1H), 0.95 (d, ³*J* = 7.5 Hz, 3H).

^{13}C NMR (CDCl_3) δ 199.5, 136.0, 134.1, 132.7, 128.7, 128.7, 127.5, 75.4, 52.4, 48.3, 44.2, 37.3, 26.6, 20.5, 14.3. HRMS: $\text{C}_{17}\text{H}_{22}\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd: 313.1238, found: 313.1243. $[\alpha]_{\text{D}}^{23} = +94.7$ ($c = 0.69$, CHCl_3 , 76% ee ($2S,3R,5R,3Z$)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min ($\tau_1 = 12.6$ min. (minor enantiomer); $\tau_2 = 17.8$ min. (major enantiomer)).

(2*S*,3*R*,5*R*)-(3-Hydroxy-5-(2-*tert*-butyldimethylsilyloxyethyl)-tetrahydrothiophen-2-yl)phenyl methanone (2g)

Colorless oil. Yield: 61% using catalyst (*S*)-**6**. ^1H NMR (CDCl_3) δ 7.91 (dd, $^3J = 8.4$ Hz, $^4J = 1.4$ Hz, 2H), 7.57 (tt, $^3J = 7.2$ Hz, $^4J = 1.6$ Hz, 1H), 7.46 (t, $^3J = 8.0$ Hz, 2H), 4.95 (quin, $^3J = 2.4$ Hz, 1H), 4.73 (d, $^3J = 2.4$ Hz, 1H), 3.82 (m, 1H), 3.63 (m, 2H), 2.39 (ddd, $^3J = 3.6$ Hz, $^2J = 6.0$ Hz, $^3J = 9.6$ Hz, 1H), 2.14 (m, 1H), 1.96 (m, 1H), 1.75 (m, 1H), 0.88 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (CDCl_3) δ 196.3, 135.5, 133.5, 128.7, 128.6, 75.6, 62.0, 61.6, 56.9, 55.5, 44.5, 44.0, 39.8, 25.9, 18.3, -5.4 . $[\alpha]_{\text{D}}^{23} = -9.7$ ($c = 0.22$, CHCl_3 , 70% ee ($2R,3R,4S$)). HPLC: Daicel Chiralpak AD, hexane/2-propanol (90/10), flow rate = 1.0 mL/min ($\tau_1 = 6.8$ min. (major enantiomer); $\tau_2 = 7.3$ min. (minor enantiomer)).

X-ray Data for 1d.

Formula	$\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}$
Weight, g mol^{-1}	250.36
Space group	P 2 ₁ 2 ₁ 2 ₁
Z	4
a, Å	6.2180(2)
b, Å	10.4070(3)

c, Å	20.0759(6)
α , °	90
β , °	90
γ , °	90
V, Å ³	1299.13
T, K	100
ρ , g cm ⁻³	1.28

X-ray Data for 2c.

Formula	C ₁₃ H ₁₆ O ₂ S
Weight, g mol ⁻¹	236.33
Space group	P 2 ₁ 2 ₁ 2 ₁
Z	4
a, Å	5.4322(4)
b, Å	11.6309(10)
c, Å	19.1331(16)
α , °	90
β , °	90
γ , °	90
V, Å ³	1208.86
T, K	150
ρ , g cm ⁻³	1.298

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