Supporting information

Enantiomerically Pure trans–3,4-Disubstituted Tetrahydrothiophenes from Diastereoselective Thiocarbonyl Ylide Addition to Chiral α,β–Unsaturated Amides

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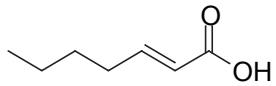
Experimental

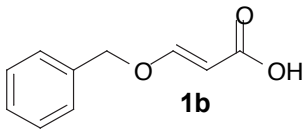
All chemicals were used as received unless otherwise stated. THF (K, benzophenone) and diethyl ether ($LiAlH_4$) were distilled from the indicated drying agents. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DMX 250 (250 MHz ^{1}H and 62.9 MHz ^{13}C) instrument. TLC was performed on silica gel plates (60 F_{254}, Merck) and preparative liquid chromatography on straight phase silica gel (Merck 60, 230-400 mesh, 0.040-0.063 mm) with an increasing concentration of distilled ethyl acetate or dichloromethane in distilled c-hexane as eluent. GC analyses were carried out using a capillary column EC-5, 30 m, 0.32 mm i.d., d_f= 0.25μm, or a CP-Sil 19 CB, 30 m, 0.25 mm i.d., d_f= 0.25μm, carrier gas N_2. The elemental analyses (C, H, N) were performed by Mikro Kemi AB, SE-752 28 Uppsala, Sweden. Melting and boiling points are uncorrected and the latter are, unless otherwise stated, given as air bath temperatures (bath temp./mbar) in a bulb to bulb (Büchi GKR-51) apparatus. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter in a 1 dm cell. Mass spectra were recorded on a Saturn 2000 instrument, operating in the EI or CI (CH_3CN as chemical ionization gas) mode, coupled to a Varian 3800 GC instrument. FT-IR spectra were recorded on a Perkin Elmer 16 PC instrument.



1a

2-(E)-Heptenoic acid (**1a**)

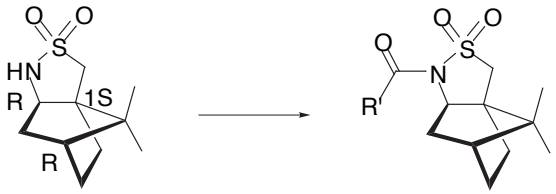
Following the general procedure reported by Gerwick *et al*[1] the title compound was obtained from malonic acid (17.4g, 170 mmol), pyridine (39 ml) and pentanal (12.2 g, 141 mmol) to give 12.8 g (71%) of **1a** as a colorless oil after distillation using a short distillation column, bp. 116°C/7mm Hg). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, 3H, J = 7.2 Hz), 1.27-1.53 (m, 4H), 2.24 (dq, 2H, J = 1.5, 7.3 Hz), 5.83 (dt, 1H, J = 1.5, 15.6 Hz), 7.10 (dt, 1H, J = 6.8, 15.6 Hz), 11.40 (br, s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.8, 22.2, 29.9, 32.0, 120.6, 152.5, 172.4, IR (film): 3300-2400 (br, OH), 1697, 1651, 1421, 1286, 985 cm^{-1}.



1b

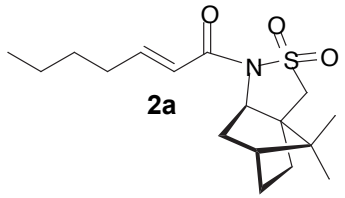
(E)-3-Benzyloxyacrylic acid (**1b**)

The preparation of the title compound follows the procedure reported by Hirsenkorn *et al*[2] but with minor modifications. To a solution of methyl propiolate (10 g, 0.12 mol) and benzyl alcohol (12.9 g, 0.12 mol) in 35 ml of dry ether was added N-methylmorpholine (13.1 ml, 0.12 mol) in 35 ml of dry ether during 1h at 0°C. The reaction was stirred for 30 h at room temperature followed by the addition of hydrochloric acid (2M, 250 ml). The aqueous phase was extracted with ether (250 ml) followed by extraction of the organic phase with Na_2CO_3 (aq. Sat. 100 ml). Concentration gives a crude ester, which was immediately hydrolysed by adding KOH (2M, 70 ml) and benzyl alcohol (3 ml) and warming to 70°C for 1h. 20 ml of hydrochloric acid (aq. conc.) was added followed by extraction with ether (3 × 250 ml). Drying (Na_2SO_4), concentration and recrystallization from ether furnished **1b** (10.0 g, 56 mmol) as a colorless solid. Mp. 116-118°C, lit.[2] mp 116°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.92 (s, 2H), 5.30 (d, 1H, *J* = 12.5 Hz), 7.31-7.42 (m, 5H), 7.75 (d, 1H, *J* = 12.5 Hz), 11.31 (s, br, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 73.1, 96.7, 127.7, 128.6, 128.7, 134.9, 164.0, 173.7.



General method for amidation of camphorsultam:[3]

To one of the acrylic acids **1a** or **1b** (1 mol eq.) was added thionyl chloride (4 mol eq.) and CH_2Cl_2 (1.2 ml/mmol of substituted acrylic acid). The mixture was refluxed for 1 h followed by concentration of the resulting acid chloride in *vacuo*. To a solution of (1*S*)-(-)-2,10-camphorsultam (0.77 mol eq.) in THF (7.5 ml/mmol of acid) was added MeMgBr (3M, Et_2O, 0.79 mol eq.) at 0°C under an atmosphere of argon. The reaction was stirred at 0°C for 30 minutes followed by slow addition of one of the acid chlorides in THF (1.2 ml/mmol of acid). The reaction was stirred at 0°C for 1h followed by the addition of NH_4Cl (aq. sat., 9 ml/mmol of acid). The aqueous phase was extracted twice with EtOAc (12 ml/mmol of acid). The combined organic phases were extracted with Na_2CO_3 (aq., sat., 12 ml/mmol of acid) followed by drying with Na_2SO_4. Concentration followed by column chromatography (EtOAc/c-hexane 0->100%) and recrystallization furnished one of the compounds **2a** or **2b**.

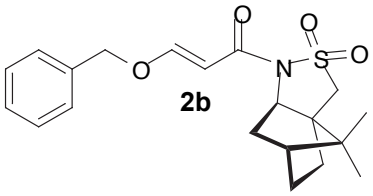


2a

(E)-Heptenoyl]-(1S)-camphorsultam (**2a**)

Compound **2a** (1.5 g, 4.6 mmol, 74 % based on starting sultam) was obtained as a colorless solid, after recrystallization from n-hexane, from 2-(*E*)-heptenoic acid **1a** (1.0 g, 8.0 mmol) and (-)-(1*S*)-2,10-camphorsultam (1.3 g, 6.2 mmol) according to the general method for amidation. Mp. 69-71°C. $[\alpha]_D^{25}$ = -87.7 (c = 0.41, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* =

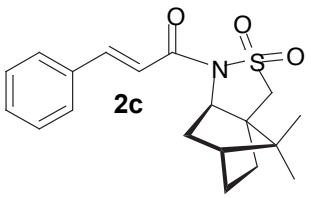
7.1 Hz), 0.98 (s, 3H), 1.18 (s, 3H), 1.27-1.53 (m, 6H), 1.83-1.98 (m, 3H), 2.08-2.16 (m, 2H), 2.20-2.32 (m, 2H), 3.43 (d, 1H, *J* = 13.8 Hz), 3.52 (d, 1H, *J* = 13.8 Hz), 3.93 (dd, 1H, *J* = 5.4, 7.3 Hz), 6.55 (dt, 1H, *J* = 1.5, 15.1 Hz), 7.10 (dt, 1H, *J* = 7.0, 15.1 Hz), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.8, 19.9, 20.8, 22.3, 26.5, 30.1, 32.2, 32.8, 38.5, 44.7, 47.8, 48.4, 53.2, 65.1, 120.7, 151.1, 164.2. IR (KBr): 1672, 1634, 1133, 533 cm^{-1}. MS (EI): m/z (%) 326 [51, $(M+1)^+$], 204 (38), 111 (100). Anal. Calcd. for $C_{17}H_{27}NO_3S$: C, 62.7; H, 8.4; N, 4.3. Found: C, 62.9; H, 8.4; N, 4.3.



2b

(E)-3-Benzyloxypropenoyl-(1S)–camphorsultam (**2b**)

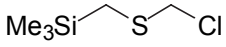
Compound **2b** (1.9 g, 5.1 mmol, 82 % based on starting sultam) was obtained as a colorless solid, after recrystallization from EtOAc/n-hexane (30%), from (*E*)-3-benzyloxyacrylic acid **1b** (1.4 g, 8.0 mmol) and (-)-(1*S*)-2,10-camphorsultam (1.3 g, 6.2 mmol) according to the general method for amidation. Mp. 143-145°C. $[\alpha]_D^{25}$ = -76.5 (c = 0.52, $CHCl_3$), ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.18 (s, 3H), 1.30-1.49 (m, 2H), 1.82-2.22 (m, 5H), 3.43 (d, 1H, *J* = 13.8 Hz), 3.50 (d, 1H, *J* = 13.8 Hz), 3.92 (dd, 1H, *J* = 5.1, 7.5 Hz), 4.94 (s, 2H), 6.09 (d, 1H, *J* = 12.1 Hz), 7.33-7.42 (m, 5H), 7.78 (d, 1H, *J* = 12.1 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.9, 20.7, 26.5, 32.7, 38.5, 44.6, 47.8, 48.2, 53.0, 65.0, 73.2, 97.6, 127.9, 128.6, 128.7, 134.8, 163.0, 164.7; IR (KBr): 2965, 1673, 1601, 1458, 1323, 552 cm^{-1}. MS (EI): m/z (%) 376 [27, $(M+1)^+$], 161 (15), 135 (16), 91 (100). Anal. Calcd. for $C_{20}H_{25}NO_4S$: C, 64.0; H, 6.7; N, 3.7. Found: C, 63.7; H, 7.0; N, 3.7.



2c

(E)-3-Phenylpropenoyl-(1S)-camphorsultam (**2c**)

The title compound was obtained from the batch prepared by Karlsson *et al*.[4]



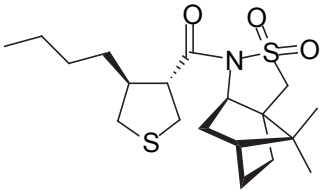
3

Chloromethyl trimethylsilylmethyl sulfide (**3**)

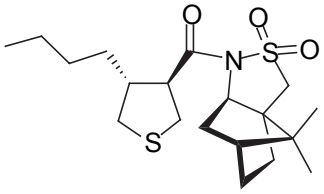
Following the general procedure reported by Evans *et al*[5], anhydrous hydrogen chloride was carefully bubbled through a magnetically stirred, cooled (-10°C) solution of trimethylsilylmethylsulfide[6] (3.0 g, 25 mmol) and 1,3,5-trioxane (0.78 g, 8.6 mmol) until full conversion was achieved (80 min). The reaction was then stirred over night at 0°C. The water formed was decanted and the residue was dried ($CaCl_2$) at 0°C for 2 h. Distillation gives **3** (3.5 g, 21 mmol, 84 %) as a colorless oil. Bp. 70°C/9 mbar, lit.[7] bp. 75°C/20 mm Hg. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.12 (s, 9H), 2.04 (s, 2H), 4.73 (s, 2H), MS (CI): m/z (%) 169 [22, $(M+1)^+$], 153 (40), 133 (100).

General method for the 1,3-dipolar cycloaddition:[7]

Chloromethyl trimethylsilylmethyl sulfide **3** (1.3 mol eq.) was added to one of the dipolarophiles **2a**, **2b** or **2c** (1 mol eq.) in CH_3CN (8 ml/mmol dipolarophile) followed by the addition of CsF (3 mol eq.) at the temperature specified in Table 1 in the paper, under an atmosphere of argon. The reaction was stirred until full conversion was achieved as judged by GC, followed by quenching with H_2O (20-40 ml/mmol dipolarophile). The aqueous phase was extracted three times with EtOAc (20-40 ml/mmol dipolarophile. The organic phase was dried ($MgSO_4$) and concentrated to give two diastereomers, **4** and **5**, separable from each other by means of column chromatography.



4a



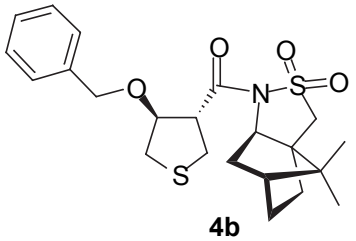
5a

(3R,4S)- and (3 S,4R)-4-butyl-tetrahydrothiophene-3-carboxylic (1S)-camphorsultam amide (**4a** and **5a**)

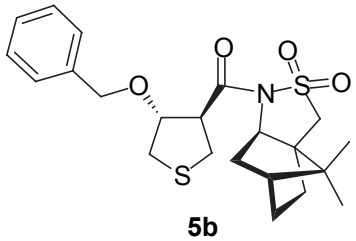
The title compounds were obtained in the yields stated in Table 1 following the general method for the 1,3-dipolar cycloaddition from **2a** and **3**. The diastereomers were separated by column chromatography (SiO_2, eluent: EtOAc 0 –>100%, in c-hexane) to give the two individual diastereomers **4a** and **5a** as colorless solids.

(3*R*,4*S*)-**4a** (major diastereomer): Mp. 110-112°C. $[\alpha]_D^{25}$ = -170.0 (c = 0.99, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 6.4 Hz), 0.97 (s, 3H), 1.13 (s, 3H), 1.22-1.60 (m, 8H), 1.84-1.97 (m, 3H), 2.04-2.09 (m, 2H), 2.56-2.71 (m, 2H), 2.77-2.92 (m, 1H), 3.04-3.16 (m, 1H), 3.22-3.38 (m, 2H), 3.45 (d, 1H, *J* = 13.8 Hz), 3.53 (d, 1H, *J* = 13.8 Hz), 3.91 (t, 1H, *J* = 6.3 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 19.8, 20.8, 22.7, 26.4, 30.3, 32.4, 32.7, 35.1, 35.9, 38.3, 44.5, 46.4, 47.8, 48.4, 53.1, 54.1, 65.2, 172.0. IR (KBr): 2960, 1687, 1458, 1069, 766, 534 cm^{-1}. MS (EI): m/z (%) 386 (89, M^+), 338 (37), 270 (30), 142 (100). Anal. Calcd. for $C_{19}H_{31}NO_3S_2$: C, 59.2; H, 8.1; N, 3.6. Found: C, 59.6; H, 8.2; N, 3.6.

(3*S*,4*R*)-**5a** (minor diastereomer): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.8 Hz), 0.99 (s, 3H), 1.18 (s, 3H), 1.20-1.50 (m, 8H), 1.83-1.98 (m, 3H), 2.02-2.17 (m, 2H), 2.47-2.67 (m, 2H), 2.96-3.36 (m, 4H), 3.45 (d, 1H, *J* = 13.8 Hz), 3.55 (d, 1H, *J* = 13.8 Hz), 3.91 (dd, 1H, *J* = 5.4, 7.2 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2, 20.3, 21.3, 23.2, 26.8, 30.4, 32.4, 33.4, 34.5, 36.2, 39.0, 45.2, 48.1, 48.7, 50.6, 53.7, 54.2, 65.9, 173.5.



4b



5b

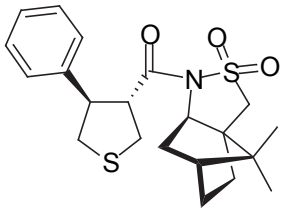
(3R,4S)- and (3S,4R)-4-benzyloxy-tetrahydrothiophene-3-carboxylic (1S)-camphorsultam amide (**4b** and **5b**)

The title compounds were obtained in the yields stated in Table 1 following the general method for the 1,3-dipolar cycloaddition from **2b** and **3**. The diastereomers were separated by column chromatography (SiO_2, eluent: CH_2Cl_2, 0 –>100%, in c-hexane) to give the individual di-

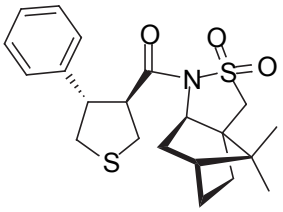
astereomers **4b** and **5b** (3*S*,4*R*)-**5b** as a colorless solid and (3*R*,4*S*)-**4b** as a highly viscous colorless oil.

(3*R*,4*S*)-**4b** (major diastereomer): Bp. 210°C/0.8 mbar. $[\alpha]_D^{25}$ = -137.3 (c = 0.66, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.13 (s, 3H), 1.30-1.47 (m, 2H), 1.84-1.98 (m, 3H), 2.03-2.09 (m, 2H), 2.88-2.97 (m, 2H), 3.14 (dd, 1H, *J* = 5.6, 11.1 Hz), 3.35 (dd, 1H, *J* = 7.9, 11.1 Hz), 3.46 (d, 1H, *J* = 13.8 Hz), 3.53 (d, 1H, *J* = 13.8 Hz), 3.81-3.92 (m, 2H), 4.53 (d, 1H, *J* = 11.9 Hz), 4.57-4.62 (m, 1H), 4.61 (d, 1H, *J* = 11.9 Hz), 7.25-7.34 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.8, 20.7, 26.4, 32.6, 32.7, 35.6, 38.3, 44.5, 47.8, 48.5, 53.0 (2Cs), 65.0, 71.7, 82.7, 127.6, 127.7, 128.3, 137.9, 170.9. IR (film): 2958, 1694, 1454, 751, 698 cm^{-1}. Anal. Calcd. for $C_{22}H_{29}NO_4S_2$: C, 60.7; H, 6.7; N, 3.2. Found: C, 60.7; H, 6.9; N, 3.2.

(3*S*,4*R*)-**5b** (minor diastereomer): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.09 (s, 3H), 1.26-1.43 (m, 2H), 1.80-2.12 (m, 5H), 2.80-3.22 (m, 4H), 3.43 (d, 1H, *J* = 13.8 Hz), 3.53 (d, 1H, *J* = 13.8 Hz), 3.79-3.92 (m, 2H), 4.42-4.60 (m, 3H), 7.22-7.33 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.8, 20.8, 26.4, 29.6, 32.8, 33.8, 38.4, 44.6, 47.7, 48.3, 52.6, 53.1, 65.2, 72.0, 85.6, 127.6 (2Cs), 128.2, 137.8, 171.6.



4c



5c

(3R,4R)- and (3S,4S)-4-phenyl-tetrahydrothiophene-3-carboxylic (1S)-camphorsultam amide (**4c** and **5c**)

The title compounds were obtained in the yields stated in Table 1 following the general method for the 1,3-dipolar cycloaddition from **2c** and **3**. The diastereomers were separated by column chromatography (SiO_2, eluent: CH_2Cl_2, 0 –>100%, in c-hexane) to give the two individual diastereomers **4c** and **5c** as colorless solids.

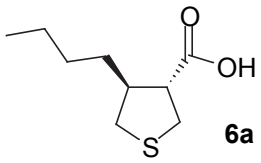
(3*R*,4*R*)-**4c** (major diastereomer): Mp. 58-60°C. $[\alpha]_D^{25}$ = -198.1 (c = 0.62, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.12 (s, 3H), 1.22-1.38 (m, 2H), 1.82-1.90 (m, 3H), 1.99-2.05 (m, 2H), 2.92-3.08 (m, 2H), 3.24 (dd, 1H, *J* = 6.5, 10.6 Hz), 3.39 (d, 1H, *J* = 13.8 Hz), 3.46-3.51 (m, 1H), 3.49 (d, 1H, *J* = 13.8 Hz), 3.73-3.98 (m, 3H), 7.19-7.35 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.8, 20.8, 26.3, 32.6, 34.8, 37.8, 38.2, 44.5, 47.8, 48.4, 51.6, 53.0, 54.2, 65.0, 127.2, 127.7, 128.6, 139.5, 170.5. IR (KBr): 2959, 1687, 1456, 767, 699, 547cm^{-1}. MS (EI): m/z (%) 405 (17, M^+), 358 (83), 270 (37), 216 (100), 162 (78), 135 (75). Anal. Calcd. for $C_{21}H_{27}NO_3S_2$: C, 62.2; H, 6.7; N, 3.4. Found: C, 62.4; H, 6.7; N, 3.4.

(3*S*,4*S*)-**5c** (minor diastereomer): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.45 (s, 3H), 0.85 (s, 3H), 1.18-1.47 (m, 3H), 1.61-1.66 (m, 1H), 1.74-1.91 (m, 3H), 3.02-3.28 (m, 4H), 3.34 (d, 1H, *J* = 13.8 Hz), 3.40 (d, 1H, *J* = 13.8 Hz), 3.60-3.92 (m, 3H), 7.19-7.32 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.7, 20.2, 26.3, 32.8, 34.0, 38.1, 38.7, 44.6, 47.4, 48.1, 53.2, 54.4, 55.8, 65.0, 127.5, 127.9, 128.6, 138.1, 172.0.

General method for hydrolysis:[8]

One of the compounds **4a** or **4c** (1 mol eq.) was heated (70°C) together with LiOH (10 mol eq.) and THF:H_2O (1:1, 6 ml/mmol substrate) for 6 hours. The mixture was acidified (HCl, aq., 6M) followed by extraction with ether (2 × 25 ml/mmol substrate). The organic phase was extracted with $NaHCO_3$ (aq. Sat. 60 ml/mmol substrate) followed by extraction of the aqueous phase four times with ether (60 ml/mmol substrate). Recovered camphorsultam could be ob-

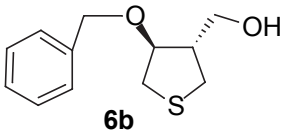
tained in 80-90% yield from the organic phase after drying ($MgSO_4$) and concentration. The aqueous phase was acidified (HCl, aq., 6M) and extracted with ether (3 × 25ml/mmol substrate). Drying (Na_2SO_4) and concentration gives the crude acids **6a** or **6c** in high purity.



6a

(3R,4S)-4-Butyl-tetrahydrothiophene-3-carboxylic acid (**6a**)

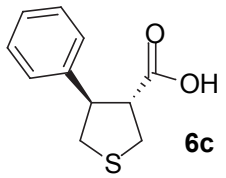
The title compound was obtained following the general method for hydrolysis from **4a** (0.50 g, 1.30 mmol). The crude product was purified by column chromatography (SiO_2, EtOAc/c-hexane 0-100% as eluent) and further distilled to give **6a** (0.16 g, 0.85 mmol, 65 %) as a colorless solid in purity > 99% (GC). Mp. 29-30°C. $[\alpha]_D^{25}$ = -126.1 (c = 0.85, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 6.5 Hz), 1.25-1.42 (m, 5H), 1.52-1.68 (m, 1H), 2.44-2.68 (m, 2H), 2.75 (q, 1H, *J* = 8.4 Hz), 3.00-3.20 (m, 3H), 9.60 (br, s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 22.7, 30.0, 32.6, 33.4, 36.0, 47.3, 53.3, 179.8. IR (KBr): 3300-2300 (br, OH), 1711, 1430, 940, 740, 676 cm^{-1}. MS (EI): m/z (%) 188 (100, M^+), 170 (7), 142 (14), 85 (69). Anal. Calcd. for $C_9H_{16}O_2S$: C, 57.4; H, 8.6. Found: C, 57.4; H, 8.7.



6b

(3S,4S)-3-Hydroxymethyl-4-benzyloxy-tetrahydrothiophene (**6b**)

Following the general procedure reported by Oppolzer *et al*[9] with minor modifications **4b** (0.37 g, 0.85 mmol) was dissolved in THF (4 ml) and diethyl ether (9 ml) and successively added to a suspension of $LiAlH_4$ (0.08 g, 2.1 mmol) in diethylether (2 ml) under an atmosphere of argon at 0°C. The reaction was stirred for one hour at 0°C, followed by the addition of NH_4Cl (25 ml, aq. sat.). To clarify the mixture obatained a few drops of conc. aq. HCl was added. The aqueous phase was extracted with diethylether (100 ml). The combined organic phase was shaken with NaOH (2M, 3 × 40 ml). The aqeuous phase was acidified (HCl, aq., 6M) and the camphorsultam (0.17 g, 95%) was obtained in >99% purity (GC) after extractive work up with diethyl ether. The organic phase from abovewas dried ($MgSO_4$) and concentrated to give 0.14 g (76%) of **6b** as a colorless oil after distillation. Purity >99% (GC). Bp. 180°C/1.2 mbar. $[\alpha]_D^{25}$ = -107.7 (c = 0.34, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.11 (s, 1H), 2.51 (sextet, 1H, *J* = 6.6 Hz), 2.55-3.15 (m, 4H), 3.65 (d, 2H, *J* = 6.0 Hz), 4.02 (q, 1H, *J* = 6.6 Hz), 4.52 (d, 1H, *J* = 11.8 Hz), 4.64 (d, 1H, *J* = 11.8 Hz), 7.28-7.40 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.2, 34.1, 49.2, 63.6, 71.8, 83.7, 127.7, 127.9, 128.5, 137.7. IR (film): 3600-3100 (br, OH), 2932, 1454, 1069, 739, 698 cm^{-1}. MS (EI): m/z (%) 224 (22, M^+), 133 (10), 118 (62), 91 (100). Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.2; H, 7.2. Found: C, 64.3; H, 7.4.



6c

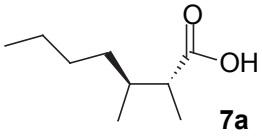
(3R,4R)-4-Phenyl-tetrahydrothiophene-3-carboxylic acid (**6c**)

The title compound was obtained following the general method for hydrolysis from **4c** (0.70 g, 1.73 mmol). The crude product was purified by column chromatography (SiO_2, EtOAc/c-

hexane 0-100% as eluent) to give **6c** (0.24 g, 1.16 mmol, 67 %) as a colorless solid in purity > 99% (GC). Mp. 88-90°C. $[\alpha]_D^{25}$ = -168.4 (c = 0.50, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 2.92-3.32 (m, 5H), 3.59-3.72 (m, 1H), 7.18-7.40 (m, 5H), 10.59 (br, s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 33.8, 37.9, 52.5, 54.3, 127.1, 127.4, 128.8, 139.7, 178.8. IR (KBr): 3300-2300 (br, OH), 1708, 1421, 943, 763, 725, 697 cm^{-1}. MS (EI): m/z (%) 208 (80, M^+), 162 (100), 135 (60), 91 (37). Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.4; H, 5.8. Found: C, 63.7; H, 5.9.

General method for desulfurization:[10]

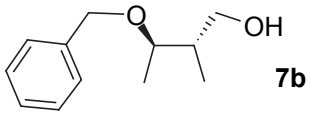
6a, **6b** or **6c** was dissolved in EtOH (99.5%, 15 ml/mmol substrate) together with Raney nickel (50% aqueous suspension, 6 g/mmol substrate, rinsed with acetone and ethanol). The mixture was heated at 70°C for 1 hour, the Raney nickel filtered off and rinsed with CH_2Cl_2. Concentration followed by column chromatography of the residue (SiO_2, EtOAc/c-hexane 0-100%) and distillation furnished **7a**, **7b** or **7c**.



7a

(2R,3S)-2,3-Dimethylheptanoic acid (**7a**)

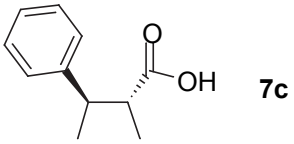
Following the general method for desulfurization the title compound was obtained as a colorless oil after distillation. Purity >99% (GC). Bp. 105°C/7 mbar, lit.[8] 150°C/0.4 Torr. $[\alpha]_D^{25}$ = -38.1 (c = 1.02, CH_2Cl_2), lit.[8] (for enantiomer) $[\alpha]_D^{23}$ = +40.65 (c = 1.64, CH_2Cl_2). Other analytical and spectroscopic data agreed with the literature.[8]



7b

(2S,3R)-3-Benzyloxy-2-methylbutan-1-ol (**7b**)

Following the general method for desulfurization the title compound was obtained as a colorless oil after distillation. Purity = 97% (GC). Bp. 130°C/1.7 mbar, lit.[11] 85°C/0.15 mm Hg. $[\alpha]_D^{25}$ = -55.9 (c = 0.98, CH_2Cl_2), lit.[11] $[\alpha]_D^{20}$ = -41.7 (c = 2.54, CH_2Cl_2). Other analytical and spectroscopic data agreed with the literature.[11]



7c

(2R,3R)-2-Methyl-3-phenylbutanoic acid (**7c**).

Following the general method for desulfurization the title compound was obtained as a colorless oil after distillation. Purity >99% (GC). Bp. 140°C/2.8 mbar, lit.[8] 120-125°C/0.5 Torr. $[\alpha]_D^{25}$ = -63.1 (c = 0.61, $CHCl_3$), lit.[8] (for enantiomer) $[\alpha]_D^{21.5}$ = +53.1 (c = 1.17, $CHCl_3$). Other analytical and spectroscopic data agreed with the literature.[8]

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