Enolates of 2-Isothiocyanatocarboxylic Esters – Synthesis of Thiazolo[5,4-d] thiazole Derivatives and 2-Thioxo-1,3-thiazolidine-4-carboxylates

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Experimental section

NMR spectra were determined on a Bruker Avance II 300 MHz spectrometer (using TMS as an internal standard). IR spectra were measured using a FT-IR spectrometer Nicolet IR200 with a single-reflection ATR head. Microanalyses were carried out using CHNS Vario Micro Cube analyzer and their results were in good agreement with the calculated values. Column chromatography was performed using commercial Merck silica gel 60 (230-400 mesh ASTM) and TLC analysis was carried out using Merck TLC silica gel 60 plates. Gas chromatography was performed using PerkinElmer Clarus 500 apparatus equipped with Elite-5MS capillary column. GC/MS analyses were carried out using Thermo Scientific ISQ Single Quadrupole GC-MS equipped with Elite-5MS capillary column whereas EI-MS spectra were recorded on a Finnigan MAT 95S apparatus. Optical rotations were performed using Jasco P-2000 polarimeter. Melting points were measured on an Electrothermal 9100 apparatus. X-ray diffraction data were collected at 110 K using Super Nova diffractometer (Oxford Diffraction) with MoKα radiation (λ = 0.71073Å).

L-menthyl 2-isothiocyanopropanoate 1a

Erlenmeyer flask (250 mL) was placed on a magnetic stirrer and charged with chloroform (45 mL), water (25 mL) and DL-alanine L-menthyl ester hydrochloride1 (1.86 g; 7.05 mmol). To a stirred solution thiophosgene (0.54 mL; 0.814 g; 7.08 mmol) and sodium hydrogen carbonate (1.78 g; 21.19 mmol) were added in one portion and the reaction mixture was stirred vigorously until the orange solution turns pale (40-70 min.). After the thiophosgene was consumed, the lower organic layer was separated and dried over MgSO4. Next the solvent was removed and crude oily product was purified using column chromatography (silica gel, cyclohexane – ethyl acetate 5:1) to give pure L-menthyl (±)-2-isothiocyanopropanoate 1a (1,727 g; 91%).

C14H23NO2S; MW = 269.40; yellow, viscous oil; elemental analysis: calcd. %C (62.41), %H (8.61), %N (5.20); found %C (62.35), %H (8.60), %N (5.28).

1H-NMR (CDCl3, 300 MHz): δ[ppm] 4.75 and 4.74 (m, 1H, ABX spin system, OCH), 4.28 and 4.27 (2q, 1H, JHH = 7.09 Hz, α-CH), 2.02 (m, 1H, 6-CHaH2), 1.86 (m, 1H, CH3-CH-CH3), 1.72 (m, 1H, 3-CHbH2), 1.68 (m, 1H, 4-CHaH2), 1.58 (d, 3H, JHH = 7.09 Hz, β-CH3), 1.46 (m, 2H, 5-CH-CH3 and 2-CH), 1.05 (m, 2H, 3-CHbH2, 6-CHaH2), 0.92 (d, 3H, JHH = 6.52, CH3-CH-CH3), 0.91 (d, 3H, JHH = 7.00 Hz, CH3-CH-CH3), 0.87 (m, 1H, 4-CHbH2), 0.77 and 0.76 (2d, 3H, JHH = 6.96 Hz, CH3-CH3).

13C-NMR (CDCl3, 75 MHz); δ[ppm] 168.77 and 168.70 (COO), 137.56 and 137.42 (NCS), 77.20 and 76.87 (C-O), 55.11 and 54.99 (α-CH), 46.88 (C-2), 40.58 (C-6), 34.06 (C-4), 31.39 (C-5), 26.28 and 26.18 (CH3-CH-CH3), 23.37 and 23.28 (C-3), 21.93 (CH3-CH3), 20.76 and 20.70 (CH3-CH-CH3), 19.53 (β-CH3), 16.27 and 16.03 (CH3-CH3).

IR (ATR): 2955, 2928, 2870, 2059, 1741, 1454, 1374, 1289, 1205, 1151 cm⁻¹.
D-menthyl 2-isothiocyanatopropanoate 1b

![Chemical structure of D-menthyl 2-isothiocyanatopropanoate 1b](image)

The ester has been prepared from DL-alanine D-menthyl ester hydrochloride\(^1\) (2.635 g; 10 mmol) in accordance with above mentioned method giving 1b (2.295 g after column chromatography, 85%) as yellow oil.

\(\text{C}_{14}\text{H}_{23}\text{NO}_2\text{S}; \text{MW} = 269.40\); elemental analysis: calcd. %C (62.41), %H (8.61), %N (5.20); found %C (62.49), %H (8.51), %N (5.33).

GC-MS (EI; 70 eV): \(m/z\) (%) 269 (3), 183 (19), 139 (88), 86 (53), 83 (100), 69 (68).

Ethyl isothiocyanatoacetate 1f

![Chemical structure of Ethyl isothiocyanatoacetate 1f](image)

L-menthyl isothiocyanatoacetate 1g

![Chemical structure of L-menthyl isothiocyanatoacetate 1g](image)

The ester has been prepared from glycine L-menthyl ester hydrochloride\(^1\) and thiophosgene in accordance with above mentioned method giving 1g as yellowish oil in 76% yield. Product 1g has been purified using column chromatography (SiO\(_2\); cyclohexane – ethyl acetate 5:1; \(R_f = 0.51\)).

\(\text{C}_{13}\text{H}_{21}\text{NO}_2\text{S}; \text{MW} = 255.39\); elemental analysis: calcd. %C (61.14), %H (8.29), %N (5.48); found %C (61.21), %H (8.22), %N (5.55).

\(^1\)H-NMR (CDCl\(_3\), 300 MHz): \(\sigma\) [ppm] 4.78 (td, 1H, J 4.41 and 10.1 Hz, OCH\(_3\)), 4.18 (s, 2H, \(\text{CH}_2\text{NCS}\)), 2.03 (m, 1H, 6-\(\text{CH}_2\text{H}_e\)), 1.83 (m, 1H, \(\text{CH}_3\)-CH-\(\text{CH}_3\)), 1.69 (m, 2H, 3-\(\text{CH}_3\text{H}_e\) and 4-\(\text{CH}_2\text{H}_e\)), 1.50 (m, 2H, 5-\(\text{CH}-\text{CH}_3\) and 2-CH), 1.05 (m, 2H, 3-\(\text{CH}_3\text{H}_e\), 6-\(\text{CH}_2\text{H}_e\)), 0.91 (d, 3H, J = 6.30 Hz, \(\text{CH}_3\)-CH-\(\text{CH}_3\)), 0.90 (d, 3H, J = 6.92 Hz, \(\text{CH}_3\)-CH-\(\text{CH}_3\)), 0.86 (m, 1H, 4-\(\text{CH}_2\text{H}_e\)), 0.77 (d, 3H, J = 6.90 Hz, \(\text{CH}-\text{CH}_3\)).

\(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): \(\sigma\) [ppm] 165.7 (CO), 138.6 (NCS), 77.2 (OCH), 46.9 (C-2), 46.5 (\(\text{CH}_3\text{NCS}\)), 40.7 (C-6), 34.0 (C-4), 31.4 (C-5), 26.9 (\(\text{CH}_3\)-CH-\(\text{CH}_3\)), 23.4 (C-3), 21.9 (CH-\(\text{CH}_3\)), 20.7 (CH-\(\text{CH}_3\)-CH-\(\text{CH}_3\)), 16.3 (CH-\(\text{CH}_3\)).

IR (ATR): 2957, 2928, 2871, 2073, 1748, 1455, 1370, 1271, 1210, 981, 958 cm\(^{-1}\).

\([\alpha]_D^{24} = -75.9\) (c 0.011; CHCl\(_3\)).

Endo-(1S)-bornyl isothiocyanatoacetate 1j
The ester has been prepared from glycine \textit{endo}-(1S)-bornyl ester hydrochloride$^3$ and thiophosgene in accordance with above mentioned method giving \textbf{1j} as colorless oil in 41\% yield. Product \textbf{1j} has been purified using column chromatography (SiO$_2$; cyclohexane – ethyl acetate 5:1; $R_f = 0.41$).

C$_{13}$H$_{19}$NO$_2$S; MW = 253.37; elemental analysis: calcd. %C (61.63), %H (7.56), %N (5.53); found %C (61.73), %H (7.36), %N (5.59).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\sigma$[ppm] 5.00 (m, 1H, ABX spin system, OCH), 4.22 (s, 2H, $\alpha$CH$_2$), 2.40 (m, 1H, 3-CH$_{exo}$), 1.93 (m, 1H, 6-CH$_{endo}$), 1.76 (m, 1H, 5-CH$_{exo}$), 1.72 (m, 1H, 4-CH), 1.32 (m, 2H, 5-CH$_{endo}$ and 6-CH$_{exo}$), 1.01 (m, 1H, 3-CH$_{endo}$), 0.91 (s, 3H, CH$_3$), 0.89 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz); $\sigma$ = 166.4 (COO), 137.5 (NCS), 82.9 (C-O), 48.9 (1-C), 48.0 (CH$_3$-C-CH$_3$), 46.6 (R-CH$_2$), 44.8 (4-C), 36.6 (3-C), 28.0 (5-C), 27.1 (6-C), 19.7 (CH$_3$-C-CH$_3$), 18.8 (CH$_3$-C-CH$_3$), 13.5 (C-CH$_3$).

IR (ATR): 2956, 2882, 2083, 1752, 1454, 1350, 1270, 1211 cm$^{-1}$.

$[\alpha]_{D}^{24} = -29.4$ (c 0.007; CHCl$_3$).

\textbf{Ethyl (R/S)-2-isothiocyanatopropanoate 1k}$^2$

Representative synthesis of \textbf{(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino] propanoate 3d}

Erlenmeyer 100 mL flask was charged with DCM (50 mL), N-Boc-L-AlaOH (2 g; 10.57 mmol) and DCC (2.177 g; 10.57 mmol). Reactants were stirred at room temperature for 30 minutes and (2S)-(–)-2-methyl-1-butanol (1.20 mL; 0.983 g; 11.14 mmol) and DMAP (0.123 g; 1.01 mmol) were added. The reaction mixture was stirred overnight and next evaporated under reduced pressure. The remainder was dissolved in ethyl acetate (80 mL); DCU was filtered off and the organic solution was washed with 5\% HCl aq (36 mL) and brine (30 mL). Organic layer was dried using anhydrous MgSO$_4$. Evaporation of the solvent gave a crude product which was purified by column chromatography (SiO$_2$; eluent CHCl$_3$ – MeOH 30:1) to give pure \textbf{3d} (1.96 g; 72\% yield) as a colorless oil.

C$_{13}$H$_{25}$NO$_4$; MW = 259.35; elemental analysis: calcd %C (60.21), %H (9.72), %N (5.40); found %C (60.15), %H (9.75), %N (5.51).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\sigma$[ppm] 5.05 (br s, 1H, NH), 4.30 (m, 1H, CHNH), 3.98 (dd, 1H, $J = 6.05$ and 10.8 Hz, OCH$_a$H$_b$), 3.94 (dd, 1H, $J = 6.61$ and 10.8 Hz, OCH$_a$H$_b$), 1.70 (m, 1H, CH$_2$); $^{13}$C NMR (CDCl$_3$, 75 MHz); $\sigma$ = 166.4 (COO), 137.5 (NCS), 82.9 (C-O), 48.9 (1-C), 48.0 (CH$_3$-C-CH$_3$), 46.6 (R-CH$_2$), 44.8 (4-C), 36.6 (3-C), 28.0 (5-C), 27.1 (6-C), 19.7 (CH$_3$-C-CH$_3$), 18.8 (CH$_3$-C-CH$_3$), 13.5 (C-CH$_3$).

IR (ATR): 2956, 2882, 2083, 1752, 1454, 1350, 1270, 1211 cm$^{-1}$.

$[\alpha]_{D}^{24} = -29.4$ (c 0.007; CHCl$_3$).
1H, CHCH₃), 1.43 (s, 9H, CH₃), 1.41 (m, 1H, CH₄H₆), 1.37 (d, 3H, J = 7.20 Hz, CHCH₃), 1.18 (m, 1H, CH₄H₆), 0.91 (d, 3H, J = 6.75 Hz, CHCH₃), 0.89 (t, 3H, J = 7.42 Hz, CH₂CH₃). ¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] 173.4 (COO), 155.1 (NH-CO), 79.7 (C-O), 69.8 (CH₂O), 49.3 (NH-CH), 34.1 (CH₃), 28.3 (C-CH₃), 18.8 (CH₂CH₃), 16.3 (CH₃CH₂). IR (ATR): 3361, 2967, 2935, 2880, 1712, 1505, 1455, 1366, 1248, 1160, 1064 cm⁻¹. [α]D²⁴ = -4.1 (c 0.011; CHCl₃).

(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino]-4-methylpentanoate 3e

Pure 3e has been obtained after column chromatography as colorless oil in 75% yield. C₁₆H₃₃NO₄; MW = 301.44; elemental analysis: calcd %C (63.76), %H (10.37), %N (4.65); found %C (63.65), %H (10.52), %N (4.69).

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] 4.92 (br d, 1H, NH), 4.28 (m, 1H, CHNH), 3.99 (dd, 1H, J = 5.88 and 10.8 Hz, OCH₃H₆), 3.94 (dd, 1H, J = 6.76 and 10.8 Hz, OCH₃H₆), 1.71 (m, 3H, CHCH₃ and CH₂-iPr), 1.48 (m, 1H, CH₄H₆), 1.42 (s, 9H, CH₃), 1.14 (m, 1H, CH₄H₆), 1.99 (sept, 1H, CHMe₂), 0.92 (2d, 6H, J = 5.16 Hz, CH₂CH₃), 0.91 (t, 3H, J = 5.30 Hz, CH₂CH₃), 0.87 (d, 3H, J = 7.42 Hz, CHCH₃). ¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] 173.5 (COO), 155.3 (NH-CO), 79.7 (C-O), 66.7 (CH₂O), 52.1 (CH), 41.9 (NH-CH), 34.1 (CH₃), 28.3 (C-CH₃), 25.9 (CHCH₃), 24.8 (CH₂), 22.7 (CHCH₃), 21.9 (CH₂CH₃), 16.3 (CH₃CH₂), 11.1 (CH₂CH₃). IR (ATR): 3352, 2961, 2933, 2875, 1712, 1505, 1462, 1366, 1249, 1160, 1047, 1048 cm⁻¹. [α]D²⁴ = -3.2 (c 0.004; CHCl₃).

(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino]-3-phenylpropanoate 3f

Pure 3f has been obtained after column chromatography as colorless oil in 71% yield. C₁₉H₂₉NO₄; MW = 335.45; elemental analysis: calcd %C (68.03), %H (8.71), %N (4.18); found %C (67.95), %H (8.58), %N (4.22).

¹H-NMR (CDCl₃, 300 MHz): δ [ppm] 7.25 (m, 3H, ArH), 7.13 (m, 2H, ArH), 4.98 (br d, 1H, NH), 4.58 (m, 1H, CHNH), 3.99 (dd, 1H, J = 5.96 and 10.8 Hz, OCH₃H₆), 3.86 (dd, 1H, J = 6.74 and 10.8 Hz, OCH₃H₆), 3.08 (m, 2H, CH₂Ph), 1.68 (m, 1H, CHCH₃), 1.41 (s, 9H, CH₃), 1.38 (m, 1H, CH₄H₆), 1.14 (m, 1H, CH₄H₆), 0.88 (m, 6H, CHCH₃ and CH₂CH₃). ¹³C-NMR (CDCl₃, 75 MHz): δ [ppm] 171.9 (COO), 155.0 (NH-CO), 136.1 (Ph), 129.2 (Ph), 128.5 (Ph), 126.9 (Ph), 79.8 (C-O), 69.9 (CH₂O), 54.4 (NH-CH), 38.4 (PhCH₂), 33.9 (CHCH₃), 28.2 (C-CH₃), 25.9 (CH₂CH₃), 16.3 (CH₃CH₂), 11.1 (CH₂CH₃). IR (ATR): 3352, 2961, 2933, 2875, 1712, 1462, 1366, 1249, 1160, 1047, 1048 cm⁻¹. [α]D²⁴ = +32.3 (c 0.004; CHCl₃).
Representative synthesis of (2S)-2-methylbutyl (2S)-2-isothiocyanatopropanoate 5d

Three-necked 100 mL flask equipped in argon inlet and protected against moisture was placed on a magnetic stirrer and (2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino]propanoate 3d (1.764 g; 6.80 mmol) was dissolved in DCM (55 mL). Next TFA (12.4 mL; 19.03 g; 167 mmol) was added and reaction mixture was stirred under argon at room temperature for 2.5 hours. After the deprotection was completed, DCM and TFA were evaporated at 45 °C under reduced pressure and remainder was transferred into Erlenmeyer 250 mL flask and dissolved in CHCl₃ (40 mL). Next thiophosgene (0.52 mL; 0.786 g; 6.80 mmol) was dropped to the flask, sodium hydrogen carbonate (1.714 g; 20.4 mmol) and water (60 mL) were added and reactants were intensively stirred for 1 hour. Lower organic layer was separated, dried with anhydrous MgSO₄ and solvent was evaporated giving a crude oily product. Purification was carried out by distillation under reduced pressure (124-126 °C at 9 mmHg) to furnish pure 5d as the yellowish oil (750 mg; yield 55%).

C₉H₁₅NO₂S; MW = 201.29; elemental analysis: calcd %C (53.70), %H (7.51), %N (6.96); found %C (53.78), %H (7.65), %N (7.05).

1H-NMR (CDCl₃, 300 MHz): σ[ppm] 4.33 (q, 1H, J = 7.10 Hz, CHNCS), 4.08 (dd, 1H, J = 5.94 and 10.5 Hz, OCHaHb), 4.01 (dd, 1H, J = 6.62 and 10.5 Hz, OCHaHb), 1.77 (m, 1H, CHCH₃), 1.59 (d, 3H, J = 7.10 Hz, CHC₃H₃), 1.44 (m, 1H, CHaHb), 1.22 (m, 1H, CH₃Hb), 0.95 (d, 3H, J = 6.76 Hz, CHC₃H), 0.91 (t, 3H, J = 7.42 Hz, CH₂C₃H₃).

13C-NMR (CDCl₃, 75 MHz); σ[ppm] 169.0 (COO), 137.3 (NCS), 70.9 (C-O), 54.9 (CHNCS), 34.0 (CHCH₃), 25.9 (CH₂CH₃), 16.3 (CHCH₃), 11.1 (CH₃CH₂). IR (ATR): 2964, 2933, 2875, 2058, 1744, 1464, 1387, 1316, 1269, 1192, 1149, 1054 cm⁻¹.

GC-MS (EI, 70 eV): m/z (%) 201 (8), 132 (9), 86 (100), 71 (57).

[α]D²⁺ = +17.8 (c 0.003; CHCl₃).

(2S)-2-methylbutyl (2S)-2-isothiocyanato-4-methylpentanoate 5e

Pure 5e has been obtained after column chromatography (SiO₂; CHCl₃ – MeOH 50:1) as yellow oil;
C₁₂H₂₁NO₂S; MW = 243.38; elemental analysis: calcd %C (59.22), %H (8.70), %N (5.76); found %C (59.15), %H (8.64), %N (5.86).

1H-NMR (CDCl₃, 300 MHz): σ[ppm] 4.27 (m, 1H, ABX spin system, CHNCS), 4.08 (dd, 1H, J = 5.91 and 10.8 Hz, OCHAHb), 4.01 (dd, 1H, J = 6.65 and 10.8 Hz, OCHAHb), 1.80 (m, 4H, CHCH₂, CH₂-iPr, CHMe₂), 1.49 (m, 1H, CH₁H₃), 1.22 (m, 1H, CH₃Hb), 0.94 (m, 12H, CH₃).

13C-NMR (CDCl₃, 75 MHz); σ[ppm] 169.0 (COO), 136.8 (NCS), 70.9 (C-O), 58.1 (CH₂-iPr), 42.1 (CH₂-iPr), 34.0 (CHCH₃), 25.9 (CH₂CH₃), 25.1 (CHMe₂), 22.7 (CH₃), 21.2 (CH₃), 16.3 (CHCH₃), 11.2 (CH₂CH₃). IR (ATR): 2961, 2933, 2875, 2058, 1744, 1464, 1387, 1316, 1269, 1192, 1149 cm⁻¹.

[α]D²⁴ = -45.6 (c 0.002; CHCl₃).
(2S)-2-methylbutyl (2S)-2-isothiocyanato-3-phenylpropanoate 5f

Pure 5f has been obtained after column chromatography (SiO2; CHCl3 – MeOH 50:1) as orange oil; C15H19NO2S; MW = 277.39; elemental analysis: calcd %C (64.95), %H (6.90), %N (5.05); found %C (65.04), %H (6.78), %N (5.12).

\[ \text{H-NMR (CDCl3, 300 MHz): } \delta \text{[ppm]} 7.32 \text{ (m, } 3\text{H, ArH)}, 7.24 \text{ (m, } 2\text{H, ArH)}, 4.46 \text{ (m, } 1\text{H, ABX spin system, CHNCS)}, 4.07 \text{ (dd, } 1\text{H, } J = \text{5.93 and 10.5 Hz, OCH}_2\text{H}_3\text{), 3.97 (dd, } 1\text{H, } J = \text{6.61 and 10.5 Hz, OCH}_3\text{H}_2\text{), 3.26 (dd, } 1\text{H, } J = \text{4.95 and 13.8 Hz, PhCH}_2\text{H}_3\text{), 3.13 (dd, } 1\text{H, } J = \text{8.12 and 13.8 Hz, PhCH}_3\text{H}_2\text{), 1.78 (m, } 1\text{H, CHCH}_3\text{), 1.38 (m, } 1\text{H, CH}_2\text{H}_3\text{), 1.18 (m, } 1\text{H, CH}_3\text{H}_2\text{), 0.90 (d, } 3\text{H, } J = \text{6.76 Hz, CHCH}_3\text{), 0.90 (t, } 3\text{H, } J = \text{7.40 Hz, CH}_2\text{CH}_3\text{).} \]

\[ \text{13C-NMR (CDCl3, 75 MHz); } \delta \text{[ppm]} 168.0 \text{ (COO), 137.9 (NCS), 135.1 (Ar), 129.3 (Ar), 128.7 (Ar), 127.6 (Ar), 71.0 (C-O), 60.9 (CHNCS), 39.7 (PhCH}_2\text{), 34.0 (CHCH}_3\text{), 25.8 (CH}_2\text{CH}_3\text{), 16.3 (CHCH}_3\text{), 11.1 (CH}_2\text{CH}_3\text{).} \]

IR (ATR): 2963, 2932, 2877, 2060, 1741, 1457, 1381, 1334, 1268, 1199, 1014 cm\(^{-1}\).

\[ \alpha_D^{23} = -54.8 \text{ (c 0.013; CHCl}_3\text{).} \]

Cyclohexyl (2S)-2-isothiocyanatopropanoate 5g

Pure 5g has been obtained after column chromatography (SiO2; CHCl3 – MeOH 30:1) as yellow oil; C10H15NO2S; MW = 213.31; elemental analysis: calcd %C (56.31), %H (7.09), %N (6.57); found: %C (56.21), %H (7.20), %N (6.44).

\[ \text{H-NMR (300 MHz, CDCl3): } \delta = 1.41 \text{ (m, } 6\text{ H, cyclohexyl)}, 1.57 \text{ (d, } J = \text{7.09 Hz, } 3\text{ H, CH}_3\text{), 1.73 (m, } 2\text{ H, cyclohexyl)}, 1.83 \text{ (m, } 2\text{ H, cyclohexyl)}, 4.28 \text{ (q, } J = \text{7.09 Hz, } 1\text{ H, OCH}), 4.86 \text{ (m, } 1\text{ H, ABX spin system, CHNCS).} \]

\[ \text{13C-NMR (75 MHz, CDCl3): } \delta = 19.4, 23.4, 25.2, 31.3, 55.0, 75.1, 137.4, 168.4. \]

IR (ATR): 2963, 2932, 2877, 2060, 1741, 1457, 1381, 1334, 1268, 1199, 1014 cm\(^{-1}\).

Representative oxidative coupling of 3a: preparation of di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6a

L-menthyl (±)-2-isothiocyanopropanoate 1a (1.954 g; 7.23 mmol) was dissolved under argon in anhydrous dichloromethane (30 mL) and the solution was cooled to -96 °C. Next titanium(IV) chloride TiCl4 (0.88 mL; 1.522 g; 8.02 mmol) in 5 ml DCM was added dropwise and the solution was stirred for 30 min at -96 °C. After the yellow titanium(IV) complex was formed, solution of N,N-diisopropylethylamine DIEA (1.40 ml; 1.04 g; 8.09 mmol) in 4 ml DCM was dropped to the reaction mixture resulting a deep blue titanium(IV) enolate. The reactants were stirred for 60 minutes at -96 °C, next an ice-bath was removed and the solution was allowed to richness room temperature. After 24 hours the brown reaction mixture was quenched with a saturated solution of NH4Cl and the organic phase was dried using
magnesium sulfate. Next the solvent was evaporated and a crude product was purified by column chromatography on silica gel using chloroform-methanol 30:1 as eluent. Di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6a was isolated as the first fraction (Rt = 0.80 on TLC plates; CHCl₃-MeOH 30:1). Crystallization from methanol gave 1.05 g of pure 6a as colorless crystals (56%).

**di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6a**

![6a]

Yield 56%.

C₂₈H₄₆N₂O₄S₂; MW = 538.84; colorless crystals, MP = 122-123 °C; elemental analysis: calcd %C (62.42), %H (8.60), %N (5.20); found %C (62.33), %H (8.52), %N (5.00).

¹H-NMR (CDCl₃, 300 MHz): δ[ppm] 4.69 (m, 2H, ABX spin system, CH-O), 2.05 and 2.01 (s, 6H, β-CH₃), 2.02 (m, 2H, 6-CH₃H₂), 1.86 (m, 2H, CH₃-CH-CH₃), 1.70 (m, 2H, 3-CH₃H₂), 1.66 (m, 2H, 4-CH₃H₂), 1.46 (m, 4H, 5-CH-CH₃ and 2-CH), 1.05 (m, 4H, 3-CH₃H₂, 6-CH₃H₂), 0.89 (m, 12H, CH₃-CH-CH₃ and CH-CH₃), 0.87 (m, 2H, 4-CH₃H₂), 0.75 and 0.73 (2d, 6H, JHH = 6.93 Hz, CH₃-CH-CH₃).

¹³C-NMR (CDCl₃, 75 MHz); δ[ppm] 178.1 and 177.9 (C=S), 168.3 and 168.1 (COO), 99.1 and 98.9 (α-C), 77.3 and 77.1 (C-O), 46.9 (C-2), 40.2 and 40.1 (C-6), 34.1 (C-4), 31.3 (C-5), 27.1 and 26.6 (β-CH₃), 26.3 and 26.2 (CH₃-CH-CH₃), 23.5 and 23.3 (C-3), 21.9 (CH-CH₃), 20.7 and 20.6 (CH₃-CH-CH₃), 16.3 and 16.2 (CH₃-CH-CH₃).

IR (ATR): 3480, 2956, 2932, 2869, 1729, 1620, 1462, 1384, 1372, 1259, 1125 cm⁻¹.

EI-MS: m/z (%) 537 (22), 399 (23), 261 (17), 216 (16), 171 (100), 139 (17), 83 (97).

[α]D²³ = -72.2 (c 0.010; acetone).

**di-D-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6b**

![6b]

Yield 59%.

C₂₈H₄₆N₂O₄S₂; MW = 538.84; MP = 122-123 °C; elemental analysis: calcd %C (62.42), %H (8.60), %N (5.20); found %C (62.36), %H (8.48), %N (5.12).

[α]D²³ = 71.9 (c 0.010; acetone).

**di-endo-(1S)-bornyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]-thiazole-2,5-dicarboxylate (6c)**
Representative oxidative coupling of 5d: synthesis of di-(2S)-2-methylbutyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6d and di-(2S)-2-methylbutyl 2,3-diisothiocyanato 2,3-dimethylsuccinate 7d

A solution of (2S)-2-methylbutyl (2S)-2-isothiocyanatopropanoate 5e (0.652 g; 3.24 mmol) in DCM (40 mL) was cooled to -96 °C under argon and titanium(IV) chloride (0.39 mL; 0.675 g; 3.56 mmol) was added in one batch. The reaction mixture was stirred for 20 minutes at -96 °C and DIEA (0.62 mL; 0.463 g; 3.58 mmol) in DCM (4 mL) was dropped. The solution turned deep blue owing to the formation of titanium(IV) enolate. The reactants were stirred at -96 °C, next an ice-bath was removed and solution was allowed to rich room temperature. After 4 hours – when GC analysis showed that the substrate has been fully consumed - the reaction mixture was poured into saturated solution of NH₄Cl (80 mL), lower organic phase was separated and dried using MgSO₄. Evaporation of the solvent gave a mixture of crude dimers 6d and 7d. Purification of the products using column chromatography (SiO₂; CHCl₃ – MeOH 50:1) furnished diisothiocyanato 2,3-dimethylsuccinate 7d (Rf = 0.80; CHCl₃ – MeOH 50:1) and thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6d (Rf = 0.70; CHCl₃ – MeOH 50:1) as colorless oils.

di-(2S)-2-methylbutyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6d

6d: yield 36%
C₁₈H₂₈N₂O₄S₂; MW = 400.57; elemental analysis: calcd %C (53.97), %H (7.05), %N (6.99); found %C (53.88), %H (7.15), %N (7.08).

1H-NMR (CDCl₃, 300 MHz): δ [ppm] 4.04 (m, 4H, OCH₂), 2.04 (s, 6H, β-CH₃), 1.75 (m, 2H, CH₂CH₃), 1.38 ((m, 2H, CH₃H₆), 1.17 (m, 2H, CH₃H₆), 0.91 (d, 6H, J = 5.91 Hz, CH₃CH), 0.90 (t, 6H, J = 7.70 Hz, CH₂CH₃).
\[^{13}\text{C}-\text{NMR (CDCl}_3, 75 \text{ MHz); \sigma[ppm]} 178.2 (\text{CS-NH}), 168.6 (\text{COO}), 98.9 (\alpha\text{C}), 71.0 (\text{OCH}_2), 34.0 (\text{CH}_3\text{CH}_2), 26.7 (\text{CH}_3\text{CH}_3), 25.9 (\text{CH}_2\text{CH}_3), 16.3 (\text{CHCH}_3), 11.2 (\text{CH}_2\text{CH}_3).\]

\[\text{IR (ATR): 3480, 2960, 2933, 2867, 1730, 1620, 1460, 1383, 1375, 1257, 1120 \text{ cm}^{-1}.}\]

**di-(2S)-2-methylbutyl 2,3-diisothiocyanato 2,3-dimethylsuccinate 7d**

![Chemical structure](image)

\[\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 400.57; \text{yield 43%}; \text{elemental analysis: calced %C (53.97), %H (7.05), %N (6.99); found %C (53.85), %H (7.14), %N (6.92).}\]

\[^{1}\text{H-NMR (CDCl}_3, 300 \text{ MHz); \sigma[ppm]} 4.08 (m, 4\text{H, OCH}_2), 1.79 (m, 2\text{H, CH}_3\text{C}_2\text{H}_5), 1.74 (s, 6\text{H, }\beta\text{CH}_3), 1.47 (m, 2\text{H, CH}_3\text{CH}_3), 1.25 (m, 2\text{H, CH}_3\text{CH}_3), 0.98 (d, 6\text{H, J = 6.77 Hz, CH}_3\text{CH}_3), 0.93 (t, 6\text{H, J = 7.45 Hz, CH}_2\text{CH}_3).\]

**GC-MS (EI; 70 eV): m/z (%) 401 (2), 201 (31), 200 (24), 130 (33), 71 (100).**

**di-(2S)-2-methylbutyl 2,3-diisobutyl-2,3-diisothiocyanatosuccinate 7e**

![Chemical structure](image)

\[\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 484.74; \text{yield 41%}; \text{elemental analysis: calced %C (59.47), %H (8.32), %N (5.78); found %C (59.57), %H (8.14), %N (5.92).}\]

\[^{1}\text{H-NMR (CDCl}_3, 300 \text{ MHz); \sigma[ppm]} 4.06 (m, 2\text{H, OCH}_2), 1.79 (m, 8\text{H, CHCH}_3, \text{CH}_2\text{-iPr, CHMe}_2), 1.51 (m, 2\text{H, CH}_3\text{CH}_3), 1.25 (m, 1\text{H, CH}_3\text{CH}_3), 0.97 (m, 2\text{H, CH}_3).\]

**GC-MS (EI; 70 \text{ eV): m/z (%) 401 (2), 201 (31), 200 (24), 130 (33), 71 (100).**

**di-(2S)-2-methylbutyl 2,3-dibenzyl-2,3-diisothiocyanatosuccinate 7f**

![Chemical structure](image)

\[\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 552.77; \text{yield 48%}; \text{elemental analysis: calced %C (65.19), %H (6.56), %N (5.07); found %C (65.07), %H (6.45), %N (5.22).}\]
1H-NMR (CDCl₃, 300 MHz): \( \sigma \) [ppm] 7.31 (m, 6H, ArH), 7.22 (m, 4H, ArH), 4.00 (m, 4H, OCH₂), 3.58 (d, 2H, J = 13.2 Hz, PhCH₂H₆b), 3.51 (d, 2H, J = 13.2 Hz, PhCH₂H₆b), 1.69 (m, 2H, CHCH₃), 1.36 (m, 2H, CH₃H₆b), 1.12 (m, 2H, CH₃H₆b), 0.84 (m, 12H, CH₃CH and CH₂CH₃).

13C-NMR (CDCl₃, 75 MHz); \( \sigma \) [ppm] 167.3 (COO), 141.3 (NCS), 133.4 (Ar), 130.6 (Ar), 128.5 (Ar), 127.9 (Ar), 72.1 (C-O), 70.0 (αC), 40.1 (PhCH₂), 33.8 (CHCH₃), 25.8 (CH₂CH₃), 16.3 (CHCH₃), 11.1 (CH₂CH₃).

IR (ATR): 2961, 2932, 2877, 2059, 1739, 1460, 1381, 1334, 1274, 1142 cm⁻¹.

di-cyclohexyl-(2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6g

![6g](image)

C₂₀H₂₈N₂O₄S₂; MW = 424.60; yield 53%; \( R_f \) = 0.75 (CHCl₃-MeOH, 30:1); colorless crystals; MP = 113-114 °C; elemental analysis: calcd %C (56.58), %H (6.65), %N (6.60); found %C (56.64), %H (6.55), %N (6.47).

1H-NMR (CDCl₃, 300 MHz): \( \sigma \) [ppm] 4.87 (m, 1H, ABX spin system, OCH), 2.03 (s, 3H, CH₃), 1.78 (m, 2H, cyclohexyl), 1.67 (m, 2H, cyclohexyl), 1.51 (m, 3H, cyclohexyl), 1.38 (m, 3H, cyclohexyl).

13C-NMR (CDCl₃, 75 MHz); \( \sigma \) [ppm] 178.1 (COO), 167.9 (C=N), 99.0 (C-2 and C-5), 74.9 (C-O), 30.8 (cyclohexyl), 26.8 (CH₃), 25.2 (cyclohexyl), 23.1 (cyclohexyl).

IR (ATR): 2935, 2033, 1736, 1449, 1372, 1333, 1252, 1113 cm⁻¹.

di-cyclohexyl 2,3-diisothiocyanato 2,3-dimethylsuccinate 7g

![7g](image)

C₂₀H₂₈N₂O₄S₂; MW = 424.60; yield 35%; colorless oil; \( R_f \) = 0.85 (CHCl₃-MeOH, 30:1); elemental analysis: calcd %C (56.58), %H (6.65), %N (6.60); found %C (56.50), %H (6.51), %N (6.68).

1H-NMR (CDCl₃, 300 MHz): \( \sigma \) [ppm] 4.89 (m, 1H, ABX spin system, OCH), 1.86 (m, 2H, cyclohexyl), 1.76 (m, 2H, cyclohexyl), 1.72 (s, 3H, CH₃), 1.56 (m, 3H, cyclohexyl), 1.37 (m, 3H, cyclohexyl).

13C-NMR (CDCl₃, 75 MHz); \( \sigma \) [ppm] 167.2 (COO), 140.4 (NCS), 76.4 (C-O), 70.4 (C-2 and C-3), 31.2 (cyclohexyl), 25.2 (cyclohexyl), 23.4 (cyclohexyl). 22.4 (CH₃).

IR (ATR): 2935, 2033, 1736, 1449, 1381, 1252, 1169, 1113 cm⁻¹.

A three-step syntheses of 2-isothiocyanatocarboxylic esters of chiral diols 12-15
Representative synthesis of (R)-1,1′-bi-2-naphtol ester of isothiocyanatoacetic acid 12

Protected N-Boc glycine (1.000 g; 5.71 mmol) and dicyclohexylcarbodiimide DCC were dissolved in dichloromethane (40 mL) at 5 °C and stirred for 30 min. R-(+)-1,1′-bi-naphtyl-2,2′-diol (0.682 g; 2.64 mmol) and DMAP (0.067 g; 0.55 mmol) were added to the solution and the reaction mixture was stirred at room temperature for 24 hours. After the esterification was completed, the solvent was evaporated and the remainder was solved in ethyl acetate (75 mL). After filtration through a sintered glass filter (porosity G3) the solution was washed with 5% HCl (30 mL), water (30 mL) and brine (30 mL) and dried over sodium sulfate Na₂SO₄. Evaporation of the solvent furnished (R)-1,1′-bi-2-naphtol ester of N-tertbutoxycarbonylglycine which was pure enough to be applied to the next step without purification (Rₜ = 0.79; CHCl₃-MeOH 30:1).

Round bottomed 250 mL flask was charged under argon with (R)-1,1′-bi-2-naphtol ester of N-tertbutoxycarbonylglycine (1.205 g; 2.01 mmol) and 4M solution of HCl in dioxane (46 mL). The reactants were stirred at room temperature for 2 hours and then dioxane was evaporated under reduced pressure (NOTE! Evaporation should be carried out at the temperature below 65 °C). The crude, amorphous product was dried under vacuum at 70 °C, suspended in diethyl ether (8 mL), cooled to -30 °C and filtered off. The described procedure gives pure and hygroscopic (R)-1,1′-bi-2-naphtyl glycinate dihydrochloride (0.93 g; 1.96 mmol; yield 97.5 %).

A stirred suspension of (R)-1,1′-bi-2-naphtyl glycinate dihydrochloride (0.878 g; 1.85 mmol) in chloroform (50 mL) was cooled to -50 °C and thiophosgene (0.31 mL; 0.467 g; 4.1 mmol) was added to the reaction mixture. Next a solution of DIEA (1.93 mL; 1.442 g; 11.15 mmol) in CHCl₃ (5 mL) was carefully dropped and an ice-bath was removed. Reactants were stirred at room temperature for 60 minutes and the solution turned black. After the reaction was completed the solvent was evaporated under reduced pressure at 40 °C and the crude product was isolated and purified by column chromatography (SiO₂; CHCl₃-MeOH 30:1; Rₜ = 0.85). Chromatography gave pure (R)-1,1′-bi-2-naphtol ester of isothiocyanatoacetic acid 12 (0.61 g; yield 68%) as red solid.
C_{34}H_{36}N_{2}O_{8}; \text{ MW = 600.69}; \text{ yield 2.95 g (93\%)}; \text{ colorless solid}; \text{ MP = 93-94 °C}; \text{ elemental analysis: calcd %C (67.99), %H (6.04), %N (4.66); found %C (68.08), %H (6.21), %N (4.55).}

{^1}\text{H-NMR (CDCl}_3, 300 MHz): \sigma [\text{ppm}] 8.00 (d, 2H, J_{HH} = 8.94 Hz, C4-H), 7.94 (d, 2H, J_{HH} = 8.17 Hz, C5-H), 7.48 (m, 2H, C6-H), 7.44 (d, 2H, J_{HH} = 8.90 Hz, C3-H), 7.28 (m, 2H, C7-H), 7.11 (d, 2H, J_{HH} = 8.48 Hz, C8-H), 4.93 (br. s, 2H, NH), 3.84 (dd, 2H, J_{gem} = 18.3 Hz, J_{HH} = 6.55 Hz, CH$_a$H$_b$), 3.58 (dd, 2H, J_{gem} = 18.3 Hz, CH$_a$H$_b$), 1.40 (s, 18H, CH$_3$).

{^{13}}\text{C-NMR (CDCl}_3, 75 MHz); \sigma [\text{ppm}] 170.4 (COO), 156.4 (CONH), 146.9 (Ar), 133.9 (Ar), 132.3 (Ar), 130.5 (Ar), 128.8 (Ar), 127.6 (Ar), 126.7 (Ar), 126.6 (Ar), 123.6 (Ar), 122.3 (Ar), 80.6 (CMe$_3$), 43.0 (CH$_2$), 28.9 (CH$_3$).

IR (ATR): 3355, 2977, 2932, 1769, 1703, 1509, 1366, 1144, 1052 cm$^{-1}$.

[\alpha]_D^{24} = -47.6 (c 0.011; acetone).

(R)- 1,1′-bi-2-naphtyl glycinate dihydrochloride

C$_{24}$H$_{22}$N$_2$O$_4$Cl$_2$; \text{ MW = 473.37}; \text{ yield 0.93 g (98\%)}; \text{ colorless solid}; \text{ MP = 150-151 °C}; \text{ elemental analysis: calcd %C (60.90), %H (4.68), %N (5.92); found %C (60.72), %H (4.78), %N (5.81).}

{^1}\text{H-NMR (DMSO-d$_6$/CDCl}_3, 300 MHz): \sigma [\text{ppm}] 8.66 (br. s, 6H, NH$_3$), 8.23 (d, 2H, J_{HH} = 8.99 Hz, C4-H), 8.11 (d, 2H, J_{HH} = 8.14 Hz, C5-H), 7.60 (d, 2H, J_{HH} = 8.96 Hz, C3-H), 7.55 (m, 2H, C6-H), 7.35 (m, 2H, C7-H), 6.92 (d, 2H, J_{HH} = 8.46 Hz, C8-H), 3.56 (s, 4H, CH$_2$).

{^{13}}\text{C-NMR (DMSO-d$_6$/CDCl}_3, 75 MHZ); \sigma [\text{ppm}] 166.7 (COO), 146.6 (Ar), 132.4 (Ar), 131.3 (Ar), 130.1 (Ar), 128.4 (Ar), 127.2 (Ar), 126.1 (Ar), 125.3 (Ar), 121.7 (Ar), 121.5 (Ar), 66.2 (CH$_2$).

IR (ATR): 2929, 2855, 1764, 1590, 1427, 1395, 1195 cm$^{-1}$.

[\alpha]_D^{24} = -4.4 (c 0.009; acetone).

(R)- 1,1′-bi-2-naphtol ester of isothiocyanatoacetic acid 12

C$_{26}$H$_{16}$N$_2$O$_4$S$_2$; \text{ MW = 484.57}; \text{ yield 0.61 g (68\%)}; \text{ red solid}; \text{ MP = 125-126 °C}; \text{ elemental analysis: calcd %C (64.45), %H (3.33), %N (5.78); found %C (64.51), %H (3.28), %N (5.81).}

{^1}\text{H-NMR (CDCl}_3, 300 MHz): \sigma [\text{ppm}] 8.05 (d, 2H, J_{HH} = 8.90 Hz, C4-H), 7.97 (d, 2H, J_{HH} = 8.24 Hz, C5-H), 7.52 (m, 2H, C6-H), 7.46 (d, 2H, J_{HH} = 8.94 Hz, C3-H), 7.33 (m, 2H, C7-H), 7.15 (d, 2H, J_{HH} = 8.49 Hz, C8-H), 4.06 (d, 2H, J_{gem} = 19.3 Hz, CH$_a$H$_b$), 3.98 (d, 2H, J_{gem} = 19.3 Hz, CH$_a$H$_b$).
$^{13}$C-NMR (CDCl$_3$, 75 MHz); $\delta$[ppm] 165.2 (COO), 146.9 (Ar), 138.9 (NCS), 133.1 (Ar), 131.8 (Ar), 130.3 (Ar), 128.2 (Ar), 127.3 (Ar), 126.4 (Ar), 126.0 (Ar), 122.7 (Ar), 121.0 (Ar), 46.0 (CH$_3$).

IR (ATR): 3068, 2042, 1761, 1507, 1356, 1173, 1145 cm$^{-1}$.

$[\alpha]_D^{24} = 1.7$ (c 0.010; acetone).

(R)- 1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanatopropanoic acid 13

The isothiocyanatocarboxylic ester has been obtained in a similar way to 12 from R- (+)-1,1′-bi-naphtyl-2,2′-diol and protected N-Boc alanine in a three step synthesis.

(R)- 1,1′-bi-2-naphtol ester of N-tertbutoxycarbonyl-L-alanine

C$_{36}$H$_{40}$N$_2$O$_8$; MW = 628.74; yield 90%; colorless solid; MP = 91-92 °C; elemental analysis: calcld %C (68.77), %H (6.41), %N (4.46); found %C (68.85), %H (6.31), %N (4.42).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$[ppm] 8.00 (d, 2H, J$_{HH} = 8.85$ Hz, C4-H), 7.92 (d, 2H, J$_{HH} = 8.20$ Hz, C5-H), 7.46 (m, 2H, C6-H), 7.44 (d, 2H, J$_{HH} = 8.86$ Hz, C3-H), 7.30 (m, 2H, C7-H), 7.23 (d, 2H, J$_{HH} = 8.43$ Hz, C8-H), 4.65 (d, 2H, J$_{HH} = 7.87$ Hz, NH), 4.20 (m, 2H, CH), 1.37 (s, 18H, CH$_3$), 0.48 (d, 6H, J$_{HH} = 6.48$ Hz, CH$_3$).

$^{13}$C-NMR (CDCl$_3$, 75 MHz); $\delta$[ppm] 171.6 (COO), 154.8 (CONH), 146.3 (Ar), 133.1 (Ar), 131.7 (Ar), 129.8 (Ar), 127.9 (Ar), 126.9 (Ar), 126.0 (Ar), 125.9 (Ar), 123.3 (Ar), 121.6 (Ar), 79.8 (CMe$_3$), 48.9 (CH), 28.2 (CH$_3$), 17.0 (CH$_3$).

IR (ATR): 3349, 2979, 2933, 1765, 1702, 1506, 1365, 1143, 1062 cm$^{-1}$.

$[\alpha]_D^{24} = -28.9$ (c 0.004; acetone).

(R)- 1,1′-bi-2-naphtyl L-alanylate dihydrochloride

C$_{26}$H$_{26}$N$_2$O$_4$Cl$_2$; MW = 501.42; yield 90%; colorless solid; MP = 186-187 °C; elemental analysis: calcld %C (62.28), %H (5.23), %N (5.59); found %C (61.99), %H (5.33), %N (5.54).

$^1$H-NMR (DMSO-d$_6$/CDCl$_3$, 300 MHz): $\delta$[ppm] 8.56 (br. s, 6H, NH$_3$), 8.09 (d, 2H, J$_{HH} = 8.83$ Hz, C4-H), 8.00 (d, 2H, J$_{HH} = 8.10$ Hz, C5-H), 7.52 (d, 2H, J$_{HH} = 8.92$ Hz, C3-H), 7.49 (m, 2H, C6-H), 7.29 (m, 2H, C7-H), 7.08 (d, 2H, J$_{HH} = 8.21$ Hz, C8-H), 3.73 (m, 2H, CH), 0.60 (d, 6H, J$_{HH} = 7.20$ Hz, CH$_3$).

$^{13}$C-NMR (DMSO-d$_6$/CDCl$_3$, 75 MHz); $\delta$[ppm] 168.3 (COO), 145.2 (Ar), 132.2 (Ar), 131.2 (Ar), 129.7 (Ar), 127.8 (Ar), 126.7 (Ar), 125.7 (Ar), 125.1 (Ar), 122.1 (Ar), 120.9 (Ar), 66.2 (CH), 14.2 (CH$_3$).

IR (ATR): 3366, 2920, 2855, 1764, 1591, 1506, 1246, 1185, 1109 cm$^{-1}$. 

(R)- 1,1′-bi-2-naphtyl L-alanylate dihydrochloride

C$_{26}$H$_{26}$N$_2$O$_4$Cl$_2$; MW = 501.42; yield 90%; colorless solid; MP = 186-187 °C; elemental analysis: calcld %C (62.28), %H (5.23), %N (5.59); found %C (61.99), %H (5.33), %N (5.54).

$^1$H-NMR (DMSO-d$_6$/CDCl$_3$, 300 MHz): $\delta$[ppm] 8.56 (br. s, 6H, NH$_3$), 8.09 (d, 2H, J$_{HH} = 8.83$ Hz, C4-H), 8.00 (d, 2H, J$_{HH} = 8.10$ Hz, C5-H), 7.52 (d, 2H, J$_{HH} = 8.92$ Hz, C3-H), 7.49 (m, 2H, C6-H), 7.29 (m, 2H, C7-H), 7.08 (d, 2H, J$_{HH} = 8.21$ Hz, C8-H), 3.73 (m, 2H, CH), 0.60 (d, 6H, J$_{HH} = 7.20$ Hz, CH$_3$).

$^{13}$C-NMR (DMSO-d$_6$/CDCl$_3$, 75 MHz); $\delta$[ppm] 168.3 (COO), 145.2 (Ar), 132.2 (Ar), 131.2 (Ar), 129.7 (Ar), 127.8 (Ar), 126.7 (Ar), 125.7 (Ar), 125.1 (Ar), 122.1 (Ar), 120.9 (Ar), 66.2 (CH), 14.2 (CH$_3$).

IR (ATR): 3366, 2920, 2855, 1764, 1591, 1506, 1246, 1185, 1109 cm$^{-1}$. 

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\([\alpha]_D^{24} = -3.6 \text{ (c 0.006; acetone).}\)

(R)- 1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanatopropanoic acid 13

\[\text{C}_{28}\text{H}_{20}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 512.62; \text{yield 73%; yellow oil; elemental analysis: calcd \%C (65.61), }\]
\[\%\text{H (3.93), }\%\text{N (5.46); found \%C (65.68), }\%\text{H (3.91), }\%\text{N (5.50).}\]

\(^1\text{H-NMR (CDCl}_3, 300 \text{ MHz): } \sigma[\text{ppm}] 8.04 \text{ (d, 2H, } J_{HH} = 8.82 \text{ Hz, C4-H}), 7.96 \text{ (d, 2H, } J_{HH} = 8.24 \text{ Hz, C5-H}), 7.52 \text{ (m, 2H, C6-H}), 7.46 \text{ (d, 2H, } J_{HH} = 8.92 \text{ Hz, C3-H}), 7.33 \text{ (m, 2H, C7-H), 7.25 (d, 2H, } J_{HH} = 8.16 \text{ Hz, C8-H}), 4.13 \text{ (q, 2H, } J_{HH} = 7.09 \text{ Hz, CH}), 0.82 \text{ (d, 6H, } J_{HH} = 7.09 \text{ Hz, CH}).\]

\(^{13}\text{C-NMR (CDCl}_3, 75 \text{ MHz); } \sigma[\text{ppm}] 167.3 \text{ (COO), } 147.0 \text{ (Ar), } 137.9 \text{ (NCS), } 133.0 \text{ (Ar), 131.8 (Ar), 130.1 (Ar), 128.1 (Ar), 127.5 (Ar), 126.4 (Ar), 125.9 (Ar), 123.0 (Ar), 121.0 (Ar), 54.5 (CH), 18.5 (CH3).}\]

IR (ATR): 3059, 2991, 2936, 2054, 1766, 1508, 1171, 1050 cm\(^{-1}\).

\([\alpha]_D^{24} = -78.7 \text{ (c 0.006; acetone).}\)

(S)- 1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanato-4-methylpentanoic acid 14

The isothiocyanatoacarboxylic ester has been obtained in a similar way to 12 from S-(−)-1,1′-bi-naphtyl-2,2′-diol and protected N-Boc leucine in a three step synthesis.

(S)- 1,1′-bi-2-naphtol ester of N-tertbutoxycarbonyl-L-leucine

\[\text{C}_{42}\text{H}_{52}\text{N}_2\text{O}_8; \text{MW = 712.91; yield 87%; colorless solid; MP = 132-133 °C; elemental analysis: calcd \%C (70.76), }\]
\[\%\text{H (7.35), }\%\text{N (3.93); found \%C (70.91), }\%\text{H (7.31), }\%\text{N (3.85).}\]

\(^1\text{H-NMR (CDCl}_3, 300 \text{ MHz): } \sigma[\text{ppm}] 7.99 \text{ (d, 2H, } J_{HH} = 8.90 \text{ Hz, C4-H}), 7.92 \text{ (d, 2H, } J_{HH} = 8.19 \text{ Hz, C5-H}), 7.48 \text{ (m, 2H, C6-H}), 7.41 \text{ (d, 2H, } J_{HH} = 8.95 \text{ Hz, C3-H}), 7.32 \text{ (m, 2H, C7-H), 7.23 (d, 2H, } J_{HH} = 8.16 \text{ Hz, C8-H}), 4.92 \text{ (d, 2H, } J_{HH} = 8.76 \text{ Hz, NH}), 4.16 \text{ (br. s, 2H, CH)}, 1.44 \text{ (s, 18H, CH3)}, 1.11 \text{ (m, 2H, CH}_{2}\text{H}_{3}), 0.94 \text{ (m, 2H, CH)}, 0.72 \text{ (m, 2H, CH}_{2}\text{H}_{3}), 0.52 \text{ (d, 6H, } J_{HH} = 6.55 \text{ Hz, CH3), 0.45 (d, 6H, } J_{HH} = 6.26 \text{ Hz, CH3).}\]

\(^{13}\text{C-NMR (CDCl}_3, 75 \text{ MHz); } \sigma[\text{ppm}] 171.7 \text{ (COO), 155.5 (CONH), 146.5 (Ar), 133.3 (Ar), 131.7 (Ar), 129.7 (Ar), 128.0 (Ar), 127.0 (Ar), 126.1 (Ar), 126.0 (Ar), 123.2 (Ar), 121.9 (Ar), 79.8 (CMethylene), 52.0 (CH), 40.4 (CH2), 24.2 (CH), 22.5 (CH3), 21.0 (CH3).}\]

IR (ATR): 3394, 2959, 2032, 1764, 1715, 1501, 1365, 1252, 1210, 1152 cm\(^{-1}\).

\([\alpha]_D^{24} = -109.4 \text{ (c 0.007; acetone).}\)

(S)- 1,1′-bi-2-naphtyl L-leucinate dihydrochloride
C₃₂H₃₈N₂O₄Cl₂; MW = 585.58; yield 88%; colorless solid; MP = 203-204 °C; elemental analysis: calcd %C (65.64), %H (6.54), %N (4.78); found %C (65.73), %H (6.45), %N (4.66).

₁H-NMR (DMSO-d₆/CDCl₃, 300 MHz): δ(ppm) 8.73 (br. s, 6H, NH₃), 8.23 (d, 2H, JHH = 8.88 Hz, C4-H), 8.12 (d, 2H, JHH = 8.09 Hz, C5-H), 7.66 (d, 2H, JHH = 8.96 Hz, C3-H), 7.58 (m, 2H, C6-H), 7.43 (m, 2H, C7-H), 7.14 (d, 2H, JHH = 8.15 Hz, C8-H), 3.66 (m, 2H, CH), 1.13 (m, 2H, CH₃), 0.89 (m, 2H, CH), 0.52 (m, 2H, CH₂H₃₆), 0.28 (d, 6H, JHH = 6.44 Hz, CH₃), 0.16 (d, 6H, JHH = 6.44 Hz, CH₃).

₁³C-NMR (DMSO-d₆/CDCl₃, 30 MHz): δ(ppm) 168.2 (COO), 145.8 (Ar), 132.4 (Ar), 131.5 (Ar), 130.1 (Ar), 128.2 (Ar), 127.2 (Ar), 126.2 (Ar), 125.0 (Ar), 122.1 (Ar), 121.5 (Ar), 66.2 (CH), 50.4 (CH₂), 22.9 (CH), 22.0 (CH₃), 20.4 (CH₃).

IR (ATR): 2957, 2928, 2867, 1762, 1591, 1507, 1470, 1364, 1185, 1129 cm⁻¹.

[α]D²⁴ = -94.3 (c 0.012; acetone).

(S)-1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanato-4-methylpentanoic acid 14

Three step synthesis of 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanato-4-methylpentanoate] 15

Protected N-Boc L-alanine (2.270g, 12 mmol) and DCC (2.47 g; 12 mmol) were dissolved in DCM (75 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. and next 1,2,5,6-di-O-cyclohexylidene-D-mannitol⁹ (1.712 g; 5 mmol) and DMAP (0.14 g) were added to the flask. An ice-bath was removed and reactants were stirred for 30 hours at room temperature. Next the solvent was evaporated, ethyl acetate (75 mL) was added to the flask and precipitate DCU was separated by filtration. The filtrate containing diester was washed with 5% HCl (25 mL) and brine (20 mL), dried over Na₂SO₄ and evaporated. The crude product – 1,2,5,6-di-O-
cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxycarbonyl)aminopropanoate] – was purified by column chromatography (SiO2; eluent: CHCl3 – MeOH 10:1; Rf = 0.88) to give pure \(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxycarbonyl)aminopropanoate]} \) (1.965 g, 57%).

Round-bottomed 100 mL flask placed on a magnetic stirrer and equipped in argon inlet was charged with \(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxycarbonyl)aminopropanoate]} \) (0.606 g; 0.885 mmol) and 4N HCl in dioxane (20 mL). The reactants were stirred under argon at room temperature for 2 hours and after the deprotection was completed, dioxane was evaporated under reduced pressure (temperature should not exceed 55 °C) and remainder was dried for 3 hours over CaCl2 at room temperature. Next anhydrous diethyl ether (5 mL) was added and the obtained suspension was cooled to -20 °C, filtered off and the solid product was dried under vacuum. The obtained \(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-aminopropanoate]} \) dihydrochloride (0.303 g, 61%) was pure enough to be transformed into 2-isothiocyanate ester 15.

A suspension of \(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-aminopropanoate]} \) dihydrochloride (0.226 g; 0.405 mmol) in chloroform (50 mL) was placed on a magnetic stirrer and cooled to -78 °C. Next thiophosgene (0.062 mL; 0.093 g; 0.809 mmol) was added in one batch and DIEA (0.42 mL; 0.314 g; 2.43 mmol) in chloroform (3 mL) was dropped to the solution. The reaction mixture was stirred 5 min. at -78 °C and 60 min. at room temperature. Next the solvent was evaporated under reduced pressure (temperature should not exceed 40 °C) and oily product 8 was purified using column chromatography (SiO2; eluent: CHCl3 – MeOH 30:1; Rf = 0.48) to give \(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanatopropanoate]} 15 \) as yellow oil (0.122 g, 54%).

\(1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxycarbonyl)aminopropanoate]} \)

\[
\text{C}_{34}\text{H}_{56}\text{N}_{2}\text{O}_{12}; \text{MW} = 684.84; \text{yield \textit{57\%}; colorless solid; MP = 75-76 °C; elemental analysis: calcd \%C (59.63), \%H (8.24), \%N (4.09); found \%C (59.78), \%H (8.45), \%N (3.92).}
\]

\[
^1\text{H-NMR (CDCl3, 300 MHz): } \delta \text{[ppm]} 5.30 (m, 2H, CH), 4.32 (m, 2H, CH), 4.19 (m, 2H, CH), 1.43 (s, 18H, CH3), 1.38 (t, 6H, JHH = 7.25 Hz, CH3).
\]

\[
^{13}\text{C-NMR (CDCl3, 75 MHz): } \delta \text{[ppm]} 172.2 (COO), 155.2 (CONH), 110.1 (O-C-O), 79.9 (C-O), 73.5 (C-O), 72.5 (C-O), 65.6 (C-O), 49.3 (CH), 36.1 (CH2), 34.6 (CH2), 28.3 (CH3), 25.1 (CH2), 23.9 (CH2), 23.7 (CH2), 18.2(CH3).
\]

IR (ATR): 3332, 2935, 2861, 1750, 1709, 1514, 1451, 1366, 1157, 1098 cm\(^{-1}\).

\[
[a]^23 \text{ +42.9 (c }0.003 \text{ in CHCl3).}
\]

\(+1,2,5,6\text{-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-aminopropanoate]} \) dihydrochloride
C_{24}H_{42}Cl_{2}N_{2}O_{8}; MW = 557.52; yield 61%; colorless solid; MP = 92-93 °C; elemental analysis: calcd %C (51.71), %H (7.59), %N (5.02); found %C (51.48), %H (7.89), %N (4.88).

$^1$H-NMR (DMSO-d$_6$, 300 MHz): $\sigma$[ppm] 8.71 (br. s, 6H, NH$_3$), 5.36 (m, 2H, CH), 4.27 (m, 2H, CH), 4.10 (m, 2H, CH), 3.97 (m, 2H, CH), 3.73 (m, 2H, CH), 1.51 (m, 16H, CH$_2$), 1.74 (m, 4H, CH$_2$), 1.44 (d, $J=6.31$ Hz, 6H).

$^{13}$C-NMR (DMSO-d$_6$, 75 MHz); $\sigma$[ppm] 170.4 (COO), 109.1 (O-C-O), 72.5 (C-O), 69.2 (C-O), 66.3 (C-O), 47.9 (CH), 26.3 (CH$_2$), 24.4 (CH$_2$), 24.2 (CH$_2$), 23.5 (CH$_2$), 23.2 (CH$_2$), 15.6 (CH$_3$).

IR (ATR): 3326, 2930, 1739, 1621, 1510, 1458, 1237, 1202, 1075, 1029 cm$^{-1}$.

$\left[\alpha\right]_D^{23} +41.2$ (c 0.002 in CHCl$_3$).

(+) 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanatopropanoate] 15

C$_{26}$H$_{36}$N$_2$O$_6$S$_2$; MW = 568.73; yield 54%; yellow oil; elemental analysis: calcd %C (54.91), %H (6.38), %N (4.93); found %C (54.97), %H (6.30), %N (4.86).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\sigma$[ppm] 5.37 (d, 2H, $J_{HH} = 7.06$ Hz, CH), 4.38 (q, 2H, $J_{HH} = 7.08$ Hz, CH), 4.16 (m, 2H), 3.98 (dd, 2H, $J_{gem} = 8.40$ Hz, $J_{HH} = 6.07$ Hz, CH$_a$H$_b$), 3.84 (dd, 2H, $J_{gem} = 8.40$ Hz, $J_{HH} = 5.56$ Hz, CH$_a$H$_b$), 3.73 (m, 2H, CH), 1.51 (m, 16H, CH$_2$), 1.74 (m, 4H, CH$_2$), 1.44 (d, $J=6.31$ Hz, 6H). 1.62 (d, 6H, $J_{HH} = 7.08$ Hz, CH$_3$), 1.58 (m, 20H).

$^{13}$C-NMR (CDCl$_3$, 75 MHz); $\sigma$[ppm] 167.8 (COO), 138.1 (NCS), 110.4 (O-C-O), 73.9 (C-O), 73.3 (C-O), 66.0 (C-O), 54.8 (CH), 36.2 (CH), 34.6 (CH$_2$), 26.3 (CH$_2$), 25.0 (CH$_2$), 23.8 (CH$_2$), 23.7 (CH$_2$), 19.5 (CH$_3$).

$\left[\alpha\right]_D^{25} +41.2$ (c 0.012 in CHCl$_3$).

Representative synthesis of dimethyl 2,7-diazydosuberate 17a
Dimethyl 2,7-dibromosuberate4 (3.525 g; 9.79 mmol) was dissolved in DMF (40 mL) and sodium azide (3.208 g; 49.34 mmol) was added to the solution. Suspension was intensively stirred and heated at 75 °C for 4 hours. After cooling the reaction mixture was poured into water with ice (100 mL) and extracted with a diethyl ether (4 * 30 mL). Collected organic layers were washed twice with water (2 * 50 mL) and dried using anhydrous MgSO4. Next the solvent was evaporated and the product 17a was separated as a colorless oil. GC analysis showed that the crude dimethyl 2,7-diazydosuberate 17a was pure enough to be used in the next step of synthesis.

C10H16N6O4; MW = 284.28; elemental analysis: calcd %C (42.25), %H (5.67), %N (29.56); found %C (42.38), %H (5.51), %N (29.87).

1H-NMR (CDCl3, 300 MHz): σ[ppm] 3.84 (m, 2H, ABX spin system, CHN3), 3.79 (s, 6H, OCH3), 1.74 (m, 4H, CH2), 1.44 (m, 4H, CH2).

13C-NMR (CDCl3, 75 MHz); σ[ppm] 170.8 (COO), 61.8 (CHN3), 52.6 (OCH3), 31.0 (CH2), 25.1 (CH2).

IR (ATR): 2954, 2866, 2099, 1739, 1438, 1255, 1200, 1178, 1113, 1004 cm⁻¹.

Representative synthesis of dimethyl 2,7-diazydosebacate 17b

C12H20N6O4; MW = 312.33; elemental analysis: calcd %C (46.15), %H (6.45), %N (26.91); found %C (46.08), %H (6.55), %N (26.81).

1H-NMR (CDCl3, 300 MHz): σ[ppm] 3.81 (m, 2H, ABX spin system, CHN3), 3.79 (s, 6H, OCH3), 1.80 (m, 4H, CH2), 1.36 (m, 8H, CH2).

13C-NMR (CDCl3, 75 MHz); σ[ppm] 171.0 (COOMe), 61.9 (CHN3), 52.5 (OCH3), 31.2 (CH2), 28.7 (CH2), 25.5 (CH2).

IR (ATR): 2933, 2860, 2100, 1740, 1438, 1350, 1256, 1200, 1176, 1012 cm⁻¹.

Dimethyl 2,7-diazidosuberate 17a (1.973 g; 6.94 mmol) was dissolved in dioxane (40 mL) and triphenylphosphine PPh3 (3.641 g; 13.88 mmol) was added to the solution. Reaction mixture was boiled under stirring for 3 hours and cooled. To the yellow-green solution 36% HCl aq (1.20 mL) in MeOH (8 mL) was dropped and the reactants were boiled an additional 1 hour. After cooling a white crystalline precipitate 18a was filtered off and crystallized from MeOH.

C10H22Cl2N2O4; MW = 305.21; colorless crystals; MP = 198-199 °C; elemental analysis: calcd %C (39.36), %H (7.27), %N (9.18); found %C (39.22), %H (7.45), %N (9.26).

1H-NMR (CDCl3, 300 MHz): σ[ppm] 8.70 (br. s, 6H, NH3⁺), 3.87 (m, 2H, ABX spin system, CH), 3.73, (s, 6H, OCH3), 1.86 (m, 4H, CH2), 1.40 (m, 4H, CH2).

13C-NMR (CDCl3, 75 MHz); σ[ppm] 169.3 (COO), 51.7 and 51.5 (CH mezo and dl), 29.2 (CH2), 23.5 and 23.2 (CH2 mezo and dl).

IR (ATR): 3009, 2933, 2864, 1740, 1490, 1443, 1226, 1190, 1173, 1120, 1020 cm⁻¹.
dimethyl 2,9-diaminosebacate dihydrochloride 18b

\[
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{NH}_3 \\
\text{CO}_2\text{Me} \\
\text{NH}_3 \quad 2^+ \\
\text{2Cl}^- \\
\end{array}
\]

C\text{12H}_{26}\text{Cl}_2\text{N}_2\text{O}_4; \text{MW} = 333.26; \text{colorless crystals; MP} = 161-162 \degree \text{C; elemental analysis: calcd %C (43.25), %H (7.86), %N (8.41); found %C (43.12), %H (7.67), %N (8.51).}\n
\begin{align*}
^1\text{H-NMR (CDCl}_3, 300 \text{ MHz): } & \sigma_{[\text{ppm}]} 8.62 (\text{br. s, 6H, NH}_3^+), 3.84 \text{ (m, 2H, ABX spin system, CH), 3.74, (s, 6H, OCH}_3), 1.82 \text{ (m, 4H, CH}_2), 1.40 \text{ (m, 4H, CH}_2), 1.28 \text{ (m, 4H, CH}_2). \\
^{13}\text{C-NMR (CDCl}_3, 75 \text{ MHz); } & \sigma_{[\text{ppm}]} 169.4 \text{ (COO), 52.2 (OCH}_3), 51.8 \text{ (CH), 29.5 (CH}_2), 27.6 \text{ (CH}_2), 23.7 \text{ and 23.6 (CH}_2 \text{ mezo and dl).}
\end{align*}

IR (ATR): 2929, 2851, 1738, 1505, 1438, 1244, 1179, 1119 cm\text{ }^{-1}.

Representative synthesis of dimethyl 2,7-diisothiocyanatosuberate 19a

\[
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{NCS} \\
\text{CO}_2\text{Me} \\
\text{NCS} \\
\end{array}
\]

Erlenmeyer 250 mL flask was placed on a magnetic stirrer, charged with a suspension of dimethyl 2,7-diaminosuberate dihydrochloride 18a (1.801 g; 5.90 mmol) in chloroform (60 mL) and next thiophosgene (0.99 mL; 1.493 g; 12.98 mmol) and sodium hydrogen carbonate (3.272 g; 38.95 mmol) were added. To the stirred reaction mixture water (40 mL) was dropped carefully and reactants were stirred 2.5 hours. Next lower organic layer was separated, dried with MgSO\text{4} and evaporated under reduced pressure. Crude dimethyl 2,7-diisothiocyanatosuberate was purified by column chromatography (SiO\text{2}; CHCl\text{3} – MeOH 30:1; \text{R}_f = 0.90) to give yellowish waxy solid.

C\text{12H}_{16}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 316.41; \text{MP} = 47-48 \degree \text{C; elemental analysis: calcd %C (45.55), %H (5.10), %N (8.85); found %C (45.67), %H (5.20), %N (8.66).}\n
\begin{align*}
^1\text{H-NMR (CDCl}_3, 300 \text{ MHz): } & \sigma_{[\text{ppm}]} 4.29 \text{ (m, 2H, ABX spin system, CHNCS), 3.81 \text{ (s, 6H, OCH}_3), 1.92 \text{ (m, 4H, CH}_2), 1.48 \text{ (m, 4H, CH}_2). \\
^{13}\text{C-NMR (CDCl}_3, 75 \text{ MHz); } & \sigma_{[\text{ppm}]} 168.7 \text{ (COO), 137.7 (NCS), 59.2 (CHNCS), 53.2 (OCH}_3), 33.1 \text{ (CH}_2), 24.8 \text{ (CH}_2). \\
\end{align*}

IR (ATR): 2956, 2935, 2862, 2066, 1745, 1436, 1220, 1168, 986 cm\text{ }^{-1}.

dimethyl 2,9-diisothiocyanatosebacate 19b

\[
\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{NCS} \\
\text{CO}_2\text{Me} \\
\text{NCS} \\
\end{array}
\]

C\text{14H}_{20}\text{N}_2\text{O}_4\text{S}_2; \text{MW} = 344.46; \text{yellow oil; elemental analysis: calcd %C (48.82), %H (5.85), %N (8.13); found %C (48.74), %H (5.90), %N (8.24).}\n
\begin{align*}
^1\text{H-NMR (CDCl}_3, 300 \text{ MHz): } & \sigma_{[\text{ppm}]} 4.28 \text{ (m, 2H, ABX spin system, CHNCS), 3.81 \text{ (s, 6H, OCH}_3), 1.88 \text{ (m, 4H, CH}_2), 1.43 \text{ (m, 4H, CH}_2), 1.36 \text{ (m, 4H, CH}_2). \\
^{13}\text{C-NMR (CDCl}_3, 75 \text{ MHz); } & \sigma_{[\text{ppm}]} 168.9 \text{ (COOMe), 137.2 (NCS), 59.4 (CHNCS), 53.1 (OCH}_3), 33.4 \text{ (CH}_2), 28.4 \text{ (CH}_2), 25.3 \text{ (CH}_2). \\
\end{align*}

IR (ATR): 2931, 2859, 2059, 1744, 1437, 1331, 1265, 1206, 1176, 986 cm\text{ }^{-1}. 
Representative oxidative coupling of dimethyl 2,7-diisothiocyanatosuberate 10a: synthesis of cis and trans-dimethyl 1,2-diisothiocyanatocyclohexane-1,2-dicarboxylate 20a

A solution of dimethyl 2,7-diisothiocyanatosuberate 19a (1.451 g; 4.58 mmol) in DCM (40 mL) was cooled to -96 °C under argon and titanium(IV) chloride (1.11 mL; 1.920 g; 10.1 mmol) was added in one batch. The reaction mixture was stirred for 20 minutes at -96 °C and DIEA (1.74 mL; 1.300 g; 10.1 mmol) in DCM (4 mL) was dropped. The solution turned deep blue owing to the formation of titanium(IV) enolate. The reactants were stirred at -96 °C for 30 min. next an ice-bath was removed and solution was allowed to rich room temperature. The reaction was monitored using TLC method. After 5 hours – when the substrate has been fully consumed - the reaction mixture was poured into saturated solution of NH4Cl (80 mL), lower organic phase was separated and dried using MgSO4. Evaporation of the solvent gave a mixture of a crude cyclic 20a. Purification of the products using column chromatography (SiO2; CHCl3 – MeOH 30:1) furnished dimethyl 1,2-diisothiocyanatocyclohexane-1,2-dicarboxylate 20a (Rf = 0.85; CHCl3 – MeOH 30:1) as a near equimolar mixture of cis- and trans-diastereoisomers.

C12H14N2O4S2; MW = 314.38; elemental analysis: calcd %C (45.85), %H (4.49), %N (8.91); found %C (45.94), %H (4.67), %N (8.84).

1H-NMR (CDCl3, 300 MHz): δ [ppm] 3.91, 3.86 and 3.84 (s, 6H, OCH3), 2.29 (m, 2H, CH2), 1.96 (m, 2H, CH2), 1.70 (m, 4H, CH2).

13C-NMR (CDCl3, 75 MHz); δ [ppm] 167.7 (COO), 142.2 and 139.4 (NCS), 75.2, 73.1 and 69.3 (α-C), 54.3, 53.9 and 53.6 (OCH3), 33.5, 32.0 and 31.9 (CH2), 22.5, 20.2 and 20.0 (CH2).

IR (ATR): 2936, 2865, 2032, 1741, 1466, 1368, 1233, 1180, 1095, 1015 cm⁻¹.

cis and trans-dimethyl 1,2-diisothiocyanatocyclooctane-1,2-dicarboxylate 20b

C14H18N2O4S2; MW = 342.45; elemental analysis: calcd %C (49.11), %H (5.30), %N (8.18); found %C (48.95), %H (5.43), %N (8.28).

1H-NMR (CDCl3, 300 MHz): δ [ppm] 3.87, 3.85, 3.82 and 3.81 (s, 6H, OCH3), 2.03 (m, 2H, CH2), 1.88 (m, 2H, CH2), 1.34 (m, 6H, CH2), 1.11 (m, 2H, CH2).

13C-NMR (CDCl3, 75 MHz); δ [ppm] 167.8, 167.7 and 167.2 (COO), 141.1, 140.8 and 140.4 (NCS), 75.9 (α-C), 54.1, 53.9 and 53.1 (OCH3), 34.1 and 33.4 (CH2), 28.8 and 28.1 (CH2), 25.2, 24.6 and 24.4 (CH2).

IR (ATR): 2935, 2863, 2035, 1740, 1465, 1368, 1238, 1183, 1097, 1018 cm⁻¹.

Representative synthesis of ethyl 5-[(2-ethoxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24h
Erlenmeyer 250 mL flask, protected from moisture with a CaCl₂ guard tube, was placed on a stirrer and filled with anhydrous DMF (90 mL) and ethyl isothiocyanatoacetate (3.77 g, 0.026 mol) and cooled to 0 °C in an ice-bath. To a stirred, cold solution of isothiocyanatoacetate a sodium hydride NaH (0.834 g; 0.035 mol) was added carefully in several portions, the ice-bath was removed and the reaction mixture was stirred for 2 hours at room temperature. Next the red-brown solution was poured into cold water and acidified with a 10% HCl aq to pH = 5. Yellow precipitate was filtered off and crystallized from ethanol to give pure 24h. The filtrate was extracted twice with ethyl acetate (2*100 mL), collected organic layers were washed with water (80 mL) and brine (50 mL) and dried with MgSO₄. Evaporation of the solvent gave brown remainder that after crystallization from ethanol gave an additional portion of ethyl-[2-(2-ethoxy-2-oxoethyl)amino]-2-thioxo-2,3-dihydro-1,3-thiazole-4-carboxylate 24h. Crystallizations gave pale yellow product in 65% yield (2.45 g of 24h). C₁₀H₁₄N₂O₄S₂; MW = 290.37; yellow crystals; MP = 188 °C; elemental analysis: calcd %C (41.37), %H (4.83), %N (9.65); found %C (41.45), %H (4.73), %N (9.82).

1H-NMR (CDCl₃): δ [ppm] = 9.77 (br. s.; 1H, NH), 7.11 (br. s.; 1H, NH), 4.32 (q, 2H, JHH = 7.14 Hz, OCH₂), 3.90 (d, 2H, JHH = 5.78 Hz, CH₂), 1.36 (t, 3H, JHH = 7.14 Hz, CH₃), 1.31 (t, 3H, JHH = 7.15 Hz, CH₃).

13C-NMR (CDCl₃): δ [ppm] = 176.8 (C=S), 168.1 (CO₂Et), 158.5 (CO₂Et), 153.9 (C=C), 106.2 (C=C), 62.2 (OCH₂), 48.1 (CH₂), 14.1 (CH₃).

IR (ATR): 3362, 3077, 2974, 2913, 1742, 1652, 1592, 1511, 1428, 1211, 1183, 1020 cm⁻¹.

L-menthyl 5-[(2-L-menthyl oxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24i

C₂₆H₄₂N₂O₄S₂; MW = 510.78; yellow solid; MP = 81-82 °; elemental analysis: calcd %C (61.14), %H (8.29), %N (5.48); found %C (61.07), %H (8.25), %N (5.40).

1H-NMR (CDCl₃): δ [ppm] = 9.51 (br. s.; 1H, NH), 7.99 (br. s.; 1H, NH), 4.83 (m, 2H, OCH), 3.88 (d, 2H, JHH = 6.10 Hz, NH-CH₂), 2.02 (m, 6H), 1.67 (m, 4H), 1.44 (m, 4H), 1.05 (m, 2H), 0.87 (d, 6H, JHH = 7.10 Hz, CH₃), 0.85 (d, 6H, JHH = 7.10 Hz, CH₃), 0.77 (d, 3H, JHH = 6.90 Hz, CH₃), 0.76 (d, 3H, JHH = 6.90 Hz, CH₃).

13C-NMR (CDCl₃): δ [ppm] = 176.4 (C=S), 167.6 (CO₂-Menthyl), 158.1 (CO₂-Menthyl), 145.5 (C=C), 121.9 (C=C), 77.2 and 77.1 (OCH), 48.1 and 46.9 (CH-iPr), 41.1 and 40.8 (CH₂), 34.0 (CH₂), 31.4 (CH-CH₃), 26.3 (CH₃-CH-CH₃), 23.3 (CH₂), 21.9 (CH-CH₃), 20.7 (CH₃-CH-CH₃), 16.2 (CH₂-CH₃).

IR (ATR): 3365, 3076, 2970, 2915, 1746, 1650, 1590, 1511, 1432, 1210, 1186, 1020 cm⁻¹.

endo-(1S)-bornyl 5-[(2-(1S)-bornyloxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24j
C_{28}H_{38}N_{2}O_{4}S_{2}; MW = 506.74; yellow solid; MP = 67-68 °; elemental analysis: calcd %C (61.03), %H (7.56), %N (5.53); found %C (61.10), %H (7.45), %N (5.56).

$^1$H-NMR (CDCl$_3$): $\delta$ [ppm] = 9.41 (br. s.; 1H, NH), 7.18 (br. s.; 1H, NH), 5.11 (ddd, 1H, $J_{HH} = 9.9, 3.3$ and 2.0 Hz, OCH), 5.00 (ddd, 1H, $J_{HH} = 9.9, 3.3$ and 2.1 Hz, OCH), 3.93 (d, 2H, $J_{HH} = 5.8$ Hz, NH-CH$_2$), 2.39 (m, 2H), 1.79 (m, 6H), 1.31 (m, 4H), 1.10 (dd, 1H, $J_{HH} = 13.8, 3.5$ Hz), 0.99 (dd, 1H, 13.8, 3.4 Hz), 0.93 (s, 3H, CH$_3$), 0.90 (br. s, 6H, 2CH$_3$), 0.88 (br. s, 6H, 2CH$_3$), 0.83 (s, 3H, CH$_3$).

$^{13}$C-NMR (CDCl$_3$): $\delta$ [ppm] = 177.6 (C=S), 169.0 (CO$_2$-bornyl), 159.5 (CO$_2$-bornyl), 137.4 (C=C), 107.0 (C=C), 83.0 (OCH), 82.2 (OCH), 49.7 (C-CH$_3$), 49.4 (C-CH$_3$), 49.0 (CH), 48.7 (CH$_3$-C-CH$_3$), 46.5 (CH), 37.3 (CH$_2$), 37.2 (CH$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 28.2 (CH$_2$), 27.7 (CH$_2$), 20.4 (CH$_3$), 20.3 (CH$_3$), 19.5 (CH$_3$), 14.3 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): 3360, 3072, 2973, 2910, 1744, 1655, 1596, 1515, 1431, 1208, 1180, 1023 cm$^{-1}$.

Representative synthesis of ethyl 5-[(1-ethoxy-1-oxopropan-2-yl)imino]-4-methyl-2-sulfanylidene-1,3-thiazolidine-4-carboxylate 24k

C$_{12}$H$_{18}$N$_{2}$O$_{4}$S$_{2}$; MW = 318.42; elemental analysis: calcd %C (45.26), %H (5.70), %N (8.80); found %C (45.18), %H (5.61), %N (8.74).

$^1$H-NMR (CDCl$_3$): $\delta$ [ppm] = 7.99 (br. s, 1H, NH), 7.96 (br. s, 1H, NH), 5.77 (q, 1H, $J_{HH} = 7.11$ Hz, CH-CH$_3$), 5.73 (q, 1H, $J_{HH} = 7.11$ Hz, CH-CH$_3$), 4.15 (m, 4H, 2 OCH$_2$), 1.79 (s, 3H, CH$_3$), 1.77 (s, 3H, CH$_3$), 1.67 (d, 6H, $J_{HH} = 7.11$ Hz, 2 CH-CH$_3$), 1.21 (t, 3H, $J_{HH} = 7.14$ Hz, CH$_2$-CH$_3$), 1.20 (t, 3H, $J_{HH} = 7.14$ Hz, CH$_2$-CH$_3$).

$^{13}$C-NMR (CDCl$_3$): $\delta$ [ppm] = 182.3 and 181.9 (C=S), 168.3 and 168.2 (CO$_2$Et), 165.7 (CO$_2$Et), 154.8 (C=N), 76.1 and 75.8 (CH$_3$-C-CO$_2$Et), 63.4 and 63.3 (OCH$_2$), 61.7 (CH$_3$-CH-CO$_2$Et), 24.5 and 24.3 (CH$_3$), 14.0 (CH$_3$), 13.8 (CH$_3$), 12.8 and 12.5 (CH$_3$).

IR (ATR): 3297, 2997, 2954, 2898, 1748, 1744, 1515, 1451, 1377, 1222, 1171 cm$^{-1}$.

Representative synthesis of 2-[[4-(ethoxycarbonyl)-2-sulfanylidene-2,3-dihydro-1,3-thiazol-5-yl]amino] acetic acid 25h

Ethyl 5-[(2-ethoxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24h (0.403 g; 1.39 mmol) was dissolved in methanol (5 mL) and a solution of sodium hydroxide (0.090 g; 2.25 mmol) in water (5 mL) was added. The reaction mixture was stirred at room temperature for 3 days, neutralized with equimolar amount of diluted hydrochloric acid (0.135 mL of 36% HCl in 5 mL of water) and allowed to crystallize. Collected fine,
yellowish crystals were collected and recrystallized again from ethanol. The described method gives 2-\{4-(ethoxycarbonyl)-2-sulfanylidene-2,3-dihydro-1,3-thiazol-5-ylamino\} acetic acid 25h in 78% yield (0.28 g).

C₈H₁₀N₂O₄S₂; MW = 262.31; MP = 213 °C (decomposition); elemental analysis: calcd %C (36.63), %H (3.84), %N (10.68); found %C (36.58), %H (3.90), %N (10.61).

¹H-NMR (CDCl₃-DMSO-d₆): δ [ppm] = 12.07 (br. s, 1H, NH), 5.60 (br. t, 1H, NH), 3.95 (q, 2H, JHH = 7.12 Hz, OCH₂), 3.53 (d, 2H, JHH = 5.60 Hz, NH-CH₂), 1.01 (t, 3H, JHH = 7.12 Hz, CH₂-CH₃).

¹³C-NMR (CDCl₃-DMSO-d₆): δ [ppm] = 175.5 (C=S), 169.3 (CO₂Et), 158.0 (CO₂H), 152.6 (=C=), 106.0 (=C=), 59.8 (OCH₂), 47.2 (CH₂-NH), 13.5 (CH₃).

IR (ATR): 3373, 3153, 3000, 1722, 1633, 1572, 1412, 1384, 1348, 1224, 1190 cm⁻¹.
D-menthyl 2-isothiocyanatopropanoate 1b
L-menthyl isothiocyanatoacetate 1i
Endo-(1S)-bornyl isothiocyanatoacetate 1j
(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino] propanoate 3d
(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino]-4-methylpentanoate 3e
(2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino]-3-phenylpropanoate 3f
(2S)-2-methylbutyl (2S)-2-isothiocyanatopropanoate 5d
(2S)-2-methylbutyl (2S)-2-isothiocyanato-4-methylpentanoate 5e
(2S)-2-methylbutyl (2S)-2-isothiocyanato-3-phenylpropanoate 5f
di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6a
di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-
dicarboxylate 6a – DEPT and HMQC spectra
di-endo-(1S)-bornyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]-thiazole-2,5-dicarboxylate 6c
di-(2S)-2-methylbutyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6d
di-cyclohexyl-(2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-
dicarboxylate 6g
di-(2S)-2-methylbutyl 2,3-diisothiocyanato 2,3-dimethylsuccinate 7d
(dl)-di-(2S)-2-methylbutyl 2,3-diisobutyl-2,3-diisothiocyanatosuccinate 7e
di-(2S)-2-methylbutyl 2,3-dibenzyl-2,3-diisothiocyanatosuccinate 7f
di-cyclohexyl 2,3-diisothiocyanato 2,3-dimethylsuccinate 7g
(R)-1,1′-bi-2-naphtol ester of N-tertbutoxycarbonylglycine
(R)- 1,1′-bi-2-naphtyl glycinate dihydrochloride
(R)- 1,1′-bi-2-naphtol ester of isothiocyanatoacetic acid 12
(R)-1,1′-bi-2-naphtol ester of N-tertbutoxycarbonyl-L-alanine
(R)-1,1’-bi-2-naphtyl L-alanylate dihydrochloride
(R)- 1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanatopropanoic acid 13
(S)-1,1'-bi-2-naphthol ester of N-tertbutoxycarbonyl-L-leucine
(S)- 1,1'-bi-2-naphtyl L-leucinate dihydrochloride
(S)- 1,1′-bi-2-naphtol ester of (2S)-2-isothiocyanato-4-methylpentanoic acid 14
1,2,5,6-di-O-cyclohexyldeno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxy carbonyl)aminopropanoate]
(+) 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-aminopropanoate] dihydrochloride.
(+)-1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanatopropanoate]
dimethyl 2,7-diazydosuberate 17a
dimethyl 2,9-diazydosebacate 17b
dimethyl 2,7-diaminosuberate dihydrochloride 18a
dimethyl 2,9-diaminosebacate dihydrochloride 18b
dimethyl 2,7-diisothiocyanatosuberate 19a
dimethyl 2,9-diisothiocyanatosebacate 19b
cis and trans-dimethyl 1,2-diisothiocyanatocyclohexane-1,2-dicarboxylate 20a
cis and trans-dimethyl 1,2-diisothiocyanatocyclooctane-1,2-dicarboxylate 20b
ethyl 5-[(2-ethoxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24h
L-menthyl 5-[(2-L-menthyloxy-2-oxoethyl)amino]-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24i.
endo-(1S)-bornyl 5-\{2-(1S)-bornyloxy-2-oxoethyl|amino\}-2-sulfanylidene-2,3-dihydro-1,3-thiazole-4-carboxylate 24j.
ethyl 5-[(1-ethoxy-1-oxopropan-2-yl)imino]-4-methyl-2-sulfanylidene-1,3-tiazolidine-4-carboxylate 24k.
2-{[4-(ethoxycarbonyl)-2-sulfanylidene-2,3-dihydro-1,3-thiazol-5-yl]amino} acetic acid 25h.
di-L-menthyl (2R,5S)-2,5-dimethyl-2,5-dihydro[1,3]thiazolo[5,4-d][1,3]thiazole-2,5-dicarboxylate 6a – X-ray crystal structure determination

The crystals of compound 6a were transparent, white color and stable in the air. Suitable crystals were obtained after crystallization from methanol via slow evaporation of the solvent at ambient temperature. X-ray diffraction data were collected at 110 K using SuperNova diffractometer (Oxford Diffraction) with MoKα radiation (λ = 0.71073 Å). Data were processed using CRYSLISPro. The phase problem was solved with direct methods with SHELXS-97. All non-hydrogen atoms were refined anisotropically. The positions of all hydrogen atoms were calculated and refined with C-H distance 0.98 Å and Uiso = 1.5Ueq (methylene groups only) or idealised methylene or tertiary C-H distances 0.99 Å and 1.00 Å, respectively, with Uiso = 1.2Ueq of the parent atom. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 862700. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for compound 6a: moiety formula C28H44N2O4S2, crystal size: 0.3x0.2x0.1 mm³, M = 536.77 g/mol, triclinic, space group P1, a = 6.0415(2) Å, b = 8.0460(3) Å, c = 15.5520(7) Å, α = 90.204(3) °, β = 100.791(4) °, γ = 93.488(3) °, V = 741.15(5) Å³, Z = 1, Dc = 1.203 g/cm³, μ(MoKα) = 0.214 mm⁻¹, F(000) = 290; theta range: 3.43–28.50 °, Tmin = 0.950, Tmax = 1.000; 10,054 collected reflections, 6,464 independent (R(int) = 0.02(5)), 6,464 number of reflections included in the refinement. The refinement parameters are R1 = 0.043 for reflections with F² > 2σ(F²), wR2 = 0.085, S = 1.04. Flack parameter x = -0.07(6).
References and Notes.