Supplementary Material

Triazole groups as biomimetic amide groups in peptides can trigger racemization

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1 General information

1.1 Analytical methods

Melting points were measured with a BUCHI MELTING-POINt B-540 apparatus with open end glass capillary tubes. All IR spectra were measured on a FT-IR 430 spectrometer by JASCO via ATR unit. The NMR spectra were recorded with a BRUKER NEO 400 spectrometer [^{1}H: 400 MHz, ^{13}C: 101 MHz]. All measurements were performed at room temperature and using DMSO-d_6 as solvents. The chemical shifts are referenced relative to the residual proton signals of the solvents in the ^{1}H-NMR (DMSO-d_6: δ = 2.50 ppm) or relative to the solvent signal in the ^{13}C-NMR (DMSO-d_6: δ = 39.51 ppm). Assignments were made based on 2D-spectra (HSQC and HMBC). The apparent coupling constants are given in Hertz. The description of the fine structure means: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. High resolution ESI mass spectra were recorded on a THERMO SCIENTIFIC ORBITRAP LTQ-XL mass spectrometer or on a BRUKER DALTONICS MICROTOF ESI mass spectrometer. Normal phase analytical high performance liquid chromatography (HPLC) was performed was performed with the following setup: ERMA DEGASSER ERC-3512, MERCK HITACHI INTELLIGENT PUMP L-6200A, CHIRALCEL AD-H column, IF-3 column, OD-H column (0.46 x 25 cm), KNAUER SMARTLINE UV-Detector 2600 (detection wavelength 220 nm).

1.2 Materials and methods

Materials

For thin layer chromatography (TLC) analysis throughout this work, PolygramR SIL G/UV254 TLC plates (silica gel 0.2 mm, 40 x 80 mm) were used. Visualization of the spots was carried under a 254 nm UV light source and, if necessary, stained by permanganate or ninhydrin or and heated with heat gun. The products were purified by flash column chromatography on silica gel 60M (40-63 µm) which was purchased from MACHERY-NAGEL. Tetrahydrofuran was freshly distilled from sodium-benzophenone. Dimethylformamide was distilled under vacuum and stored under argon over drying agent. Ethyl acetate was distilled under vacuum and stored under argon with potassium carbonate as a drying agent. Aqueous work-ups and column chromatographies were carried out using technical grade solvents.

Chemicals

Fmoc-(*L*)-Arg(Pbf)-OH, Fmoc-(*D*)-Arg(Pbf)-OH, propargylamine, sodium azide and 4-(dimethylamino)-pyridine (DMAP) were purchased from FLUOROCHEM and used without further purification. Boc-(*L*)-Arg(Pbf)-OH, Boc-(*D*)-Arg(Pbf)-OH were purchased from CARBOLUTION and used without further purification. Lithiumhydroxide and diethylamine were purchased from ACROS and used without further purification. 1-Octyne and 4-methylmorpholine (NMM) were purchased from ALFA AESAR and used without further purification. O-(1*H*-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophos-phate (HCTU) was purchased from IRIS BIOTECH and used without further purification. *N,N*-Dicyclohexylcarbodiimide (DCC) was purchased from MERCK and used without further purification. Sulfury chloride was purchased from SIGMA ALDRICH and used without further purification. Imidazole was purchased from BASF and used without further purification. Potassium carbonate was purchased from ROTH and used without further purification. Copper sulphate pentahydrate was purchased from APPLICHEM and used without further purification. Monosodium ascorbate was purchased from TCI and used without further purification. Compound Fmoc-(*L*)-Arg(Pbf)-OMe ((*L*)-**1**)[1] and Boc-(*L*)-Arg(Pbf)-OMe

((*L*)-**8**)[2] were prepared according to a modified literature procedure. *N*-succinimide-GCP[3] and the diazo transfer reagent imidazol-1-sulfonyl azide hydrogensulfate (**10**)[4] were synthesized according to literature procedures.

2 Syntheses procedures

2.1 Overview

Synthesis of GCP-arginine derivative (*L*)-**5**:

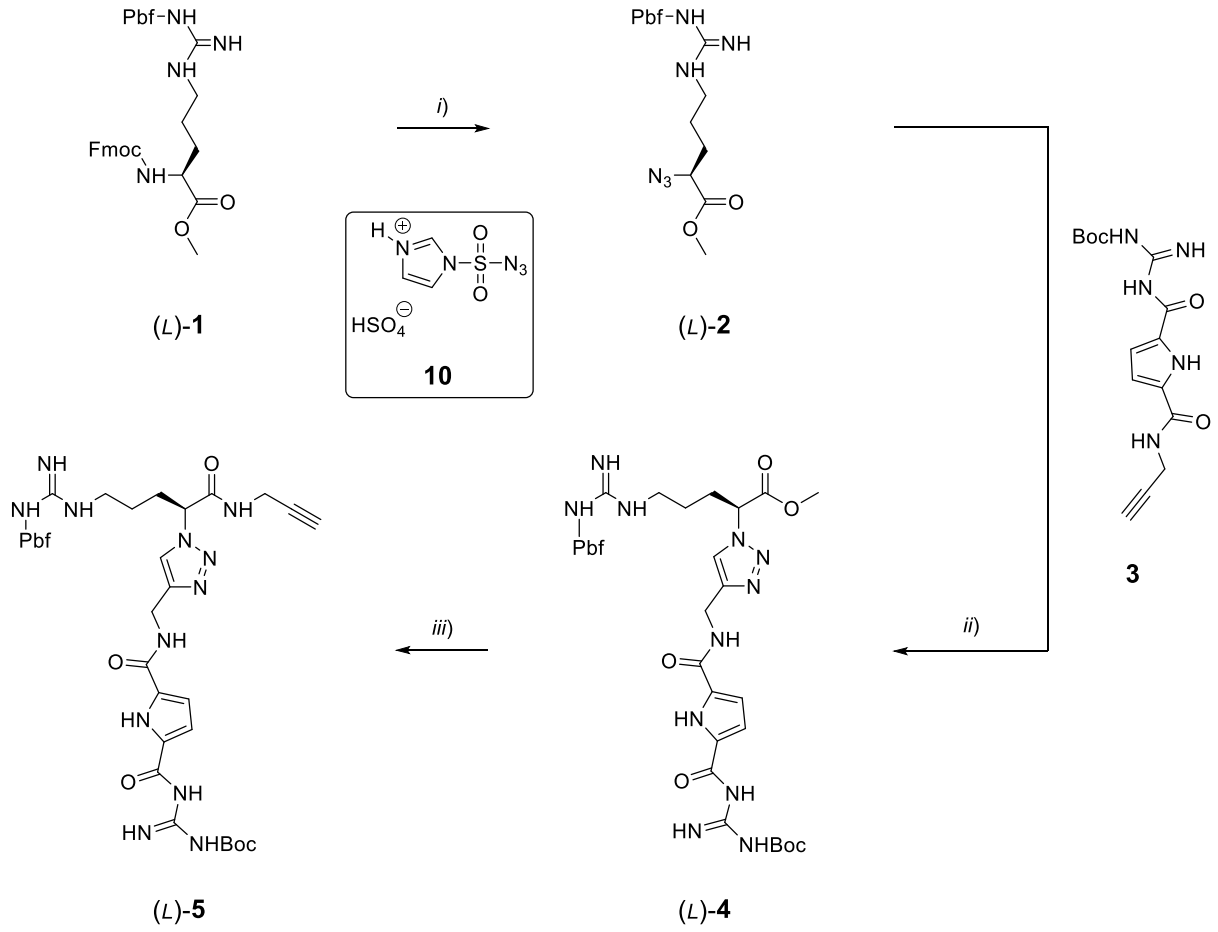
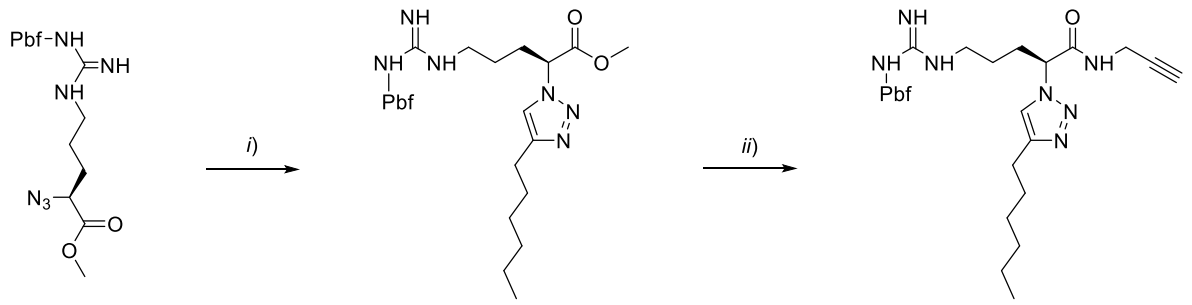


Figure S1: Synthesis of GCP-arginine derivative (*L*)-**5**. Reagents and conditions: *i*) Et_2NH, DMF, RT, 2 h, then K_2CO_3, $CuSO_4 \cdot 5\ H_2O$, **10**, MeOH, RT, 12 h, 69%; *iii*) $CuSO_4 \cdot 5\ H_2O$, NaAsc, THF/H_2O, RT, 12 h, 90%; i*v*) LiOH, THF/H_2O, 3 h, RT, then propargylamine, NMM, HCTU, DMF, RT, 12 h, 68%.

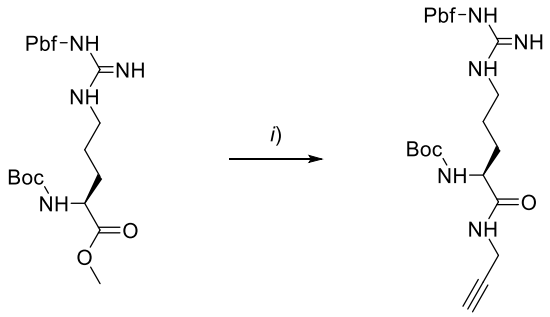
Synthesis of hexyl-arginine derivative (*L*)-**7**:



(*L*)-**2** (*L*)-**6** (*L*)-**7**

Figure S2: Synthesis of hexyl-arginine derivative (*L*)-**7**. Reagents and conditions: *i*) 1-octyne, $CuSO_4 \cdot 5\ H_2O$, NaAsc, THF/H_2O, RT, 12 h, 66%; *ii*) LiOH, THF/H_2O, 3 h, RT, then propargylamine, NMM, HCTU, DMF, RT, 12 h, 70%.

Synthesis of control compound (*L*)-**9**:



(*L*)-**8** (*L*)-**9**

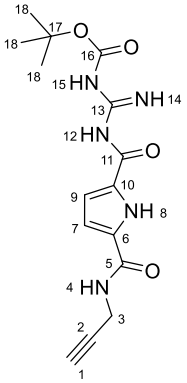
Figure S3: Synthesis of arginine derivative (*L*)-**9**. Reagents and conditions: *i*) LiOH, THF/H_2O, 3 h, RT, then propargylamine, NMM, HCTU, DMF, RT, 12 h, 73%.

2.2 Syntheses and analyses

The syntheses of all products ((*L*)-**5**, (*L*)-**7** and (*L*)-**9**) is described starting from the enantiomerically pure precursors, i.e. (*L*)-**1** and (*L*)-**8**. We also performed the same synthesis starting from (*rac*)-**1** and (*rac*)-**8** to obtain the racemic products ((*rac*)-**5**, (*rac*)-**7** and (*rac*)-**9**) as HPLC references substances. Racemic mixtures were prepared by using equimolar amounts of (*L*)- and (*D*)-starting materials.

2.2.1 Reagents and precursors

Synthesis of the GCP-alkyne 3:



N-Succinimide-GCP[3] (1.00 g, 2.54 µmol, 1 eq), propargylamine (250 mg, 5.08 mmol, 2 eq) and 4-(dimethylamino)-pyridine (31.1 mg, 254 µmol, 0.1 eq) were dissolved in dry dimethylformamide (40 mL) under argon atmosphere. The solution was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo* and redissolved in ethyl acetate (20 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (6 cm x 25 cm, dichloromethane:ethyl acetate = 1:2) to afford a **3** as a white crystalline solid (622 mg, 1.87 mmol, 73.4%).

Chemical formular: $C_{15}H_{19}N_5O_4$ **Molecular weight:** 333.14 g/mol

^{1}H-NMR (400 MHz, DMSO-d$_6$) [ppm] δ = 11.10 (br s, 1 H, H_8), 10.84 (br s, 1 H, H_{14}), 9.33 (br s, 1 H, H_{12}), 8.78 (t, ^3J = 5.4 Hz, 1 H, H_4), 8.56 (br s, 1 H, H_{15}), 6.81 (m, 2 H, $H_{7,9}$), 4.04 (dd, ^3J = 5.6 Hz, ^4J = 2.5 Hz, 2 H, H_3), 3.17 (t, ^4J = 2.4 Hz, 1 H, H_1), 1.46 (s, 9 H, H_{18}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] δ **=** 159.3 (3 C, $C_{5,11,16}$), 158.4 (1 C, C_{13}), 112.1 (4 C, $C_{6,7,9,10}$), 81.0 (2 C, $C_{2,17}$), 73.2 (1 C, C_1), 28.0 (1 C, C_3), 27.8 (3 C, C_{18}).

HR-ESI-neg (MeOH): m/z = 332.1353 (calcd 332.1366 for $[M-H]^-$).

Melting point: 182 °C

Anal. Calc for $C_{15}H_{19}N_5O_4$ (333.14): C 54.05, H 5.75, N 21.01; found: C 54.6, H 5.67, N 20.5.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3415 (m), 3372 (s), 3334 (m), 3278 (m), 3120 (w), 2979 (w), 2931 (w), 1734 (w), 1666 (s), 1622 (s), 1540 (m), 1446 (w), 1396 (w), 1363 (w), 1282 (s), 1248 (s), 1155 (m), 1130 (m), 1084 (w), 1043 (w), 1005 (w), 972 (m), 847 (m), 808 (s), 754 (s), 690 (w), 654 (m), 615 (w).

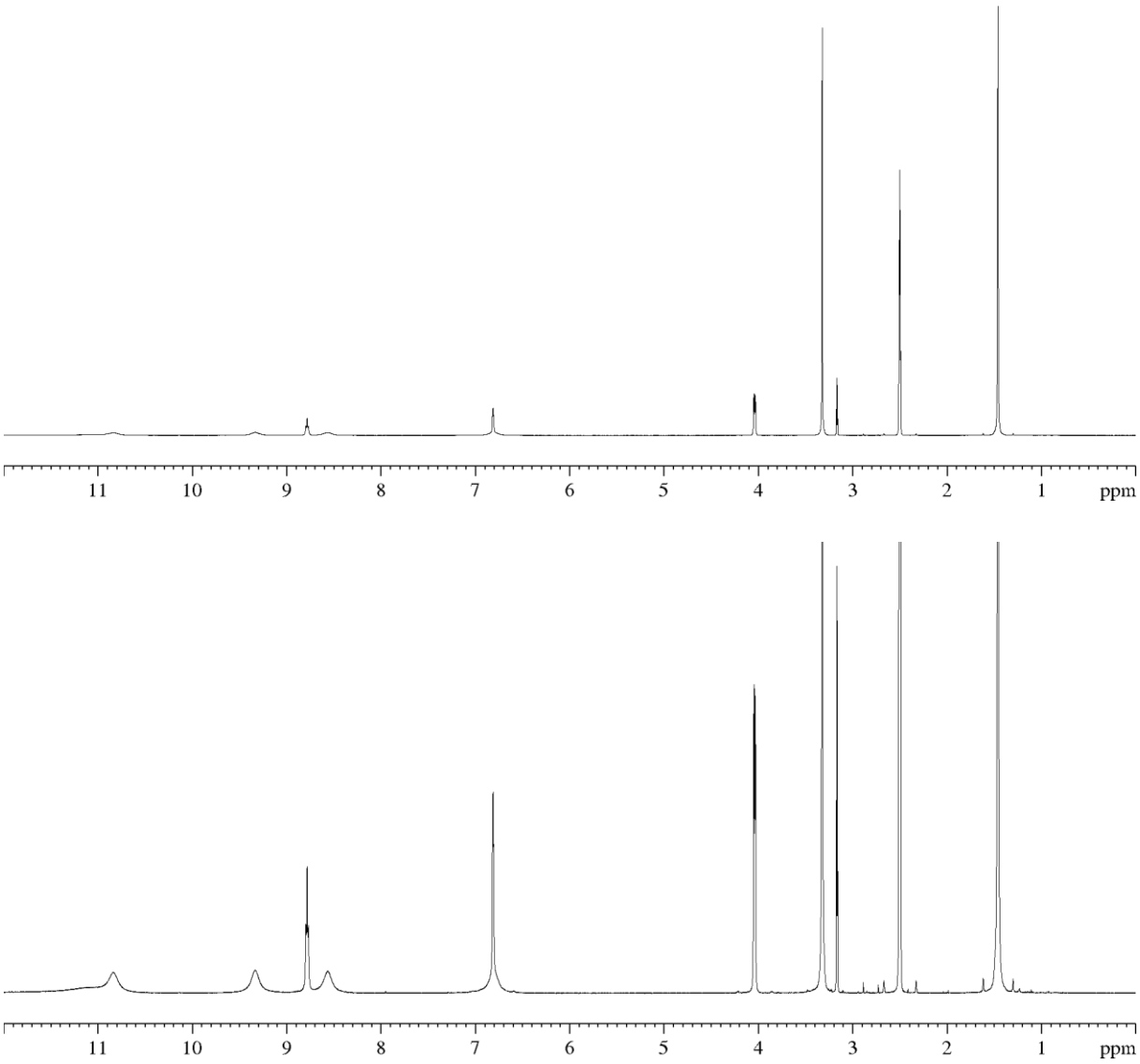


Figure S4: ^{1}H-NMR spectrum of **3** (298 K, 400 MHz, DMSO-d_6).

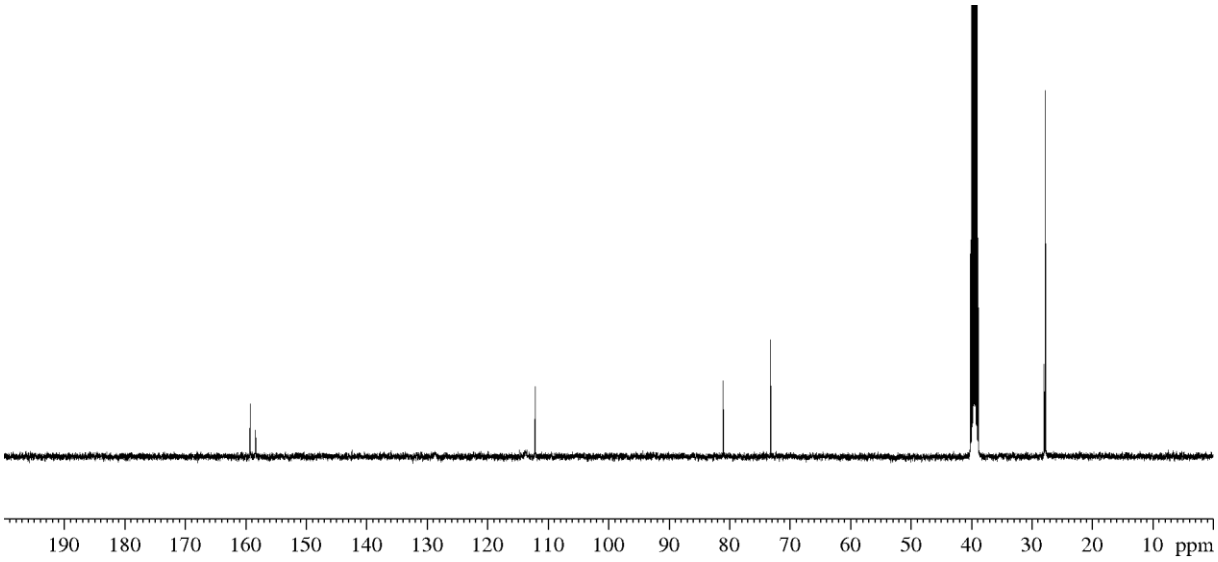
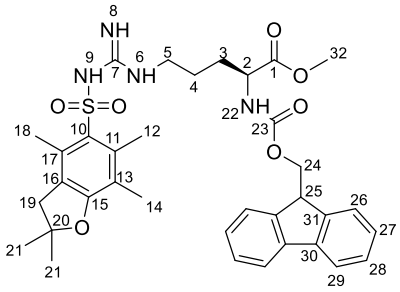


Figure S5: ^{13}C-NMR spectrum of **3** (298 K, 101 MHz, DMSO-d_6).

Compound (*L*)-1:



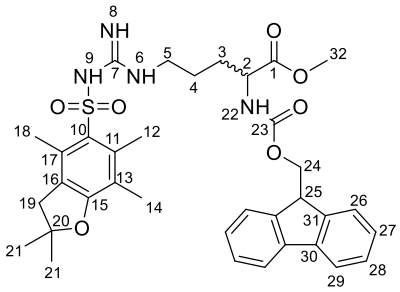
Fmoc-(*L*)-Arg(Pbf)-OH (5.00 g, 7.71 mmol, 1 eq) and methanol (4.95 g, 154 mmol, 20 eq) were dissolved in dry dichloromethane (20 mL). 4-(Dimethylamino)-pyridine (94.2 mg, 771 µmol, 0.1 eq) was added and the reaction solution was cooled to 0 °C. *N,N*-Dicyclohexylcarbodiimide (2.23 g, 10.8 mmol, 1.4 eq) was added and the reaction mixture was warmed to room temperature overnight. The urea byproduct was removed by filtration washed with cold toluene (100 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (4.5 cm x 24 cm, dichloromethane:ethyl acetate = 1:1) to afford a (*L*)-**1** as a white solid (4.89 g, 7.38 mmol, 95.7%).

Chemical formular: $C_{35}H_{42}N_4O_7S$ **Molecular weight:** 662.80 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 7.89 (d, ^3J = 7.4 Hz, 2 H, H_{29}), 7.78 (d, ^3J = 7.8 Hz, 1 H, H_{22}), 7.71 (d, ^3J = 7.4 Hz, 2 H, H_{26}), 7.42 (t, ^3J = 7.4 Hz, 2 H, H_{28}), 7.33 (t, ^3J = 7.4 Hz, 2 H, H_{27}), 6.71-6.44 (m, 3 H, $H_{6, 8, 9}$), 4.32-4.30 (m, 2 H, H_{24}), 4.24-4.20 (m, 1 H, H_{25}), 4.00 (m, 1 H, H_2), 3.62 (s, 3 H, H_{32}), 3.05 (q, ^3J = 6.5 Hz, 2 H, H_5), 2.95 (s, 2 H, H_{19}), 2.49 (s, 3 H, H_{18}), 2.44 (s, 3 H, H_{12}), 2.02 (s, 3 H, H_{14}), 1.69-1.57 (m, 2 H, H_3), 1.45-1.36 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}).

For more data, see reference [1].

Compound (*rac*)-1:



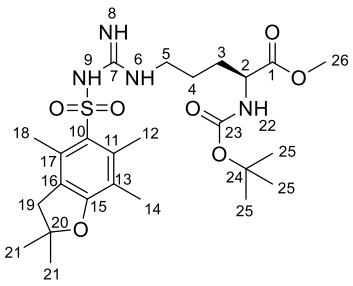
Fmoc-(*rac*)-Arg(Pbf)-OH (500 mg, 0.770 mmol, 1.0 eq) and methanol (494 mg, 15.4 mmol, 20 eq) were dissolved in dry dichloromethane (20 mL). 4-(Dimethyl-amino)-pyridine (9.41 mg, 77.1 µmol, 0.1 eq) was added and the reaction solution was cooled to 0 °C. *N,N*-Dicyclohexylcarbodiimide (223 mg, 1.08 mmol, 1.4 eq) was added and the reaction mixture was warmed to room temperature overnight. The urea byproduct was removed by filtration washed with cold toluene (100 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2.5 cm x 24 cm, dichloromethane:ethyl acetate = 1:1) to afford a (*rac*)**-1** as a white solid (492 mg, 326 µmol, 84.6%).

Chemical formular: $C_{35}H_{42}N_4O_7S$ **Molecular weight:** 662.80 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 7.90 (d, ^3J = 7.4 Hz, 2 H, H_{29}), 7.78 (d, ^3J = 7.8 Hz, 1 H, H_{22}), 7.71 (d, ^3J = 7.4 Hz, 2 H, H_{26}), 7.41 (t, ^3J = 7.4 Hz, 2 H, H_{28}), 7.33 (t, ^3J = 7.4 Hz, 2 H, H_{27}), 6.69-6.41 (m, 3 H, $H_{6, 8, 9}$), 4.31-4.29 (m, 2 H, H_{24}), 4.22-4.20 (m, 1 H, H_{25}), 4.00 (m, 1 H, H_2), 3.61 (s, 3 H, H_{32}), 3.04 (q, ^3J = 6.5 Hz, 2 H, H_5), 2.94 (s, 2 H, H_{19}), 2.48 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.00 (s, 3 H, H_{14}), 1.69-1.60 (m, 2 H, H_3), 1.45-1.36 (m, 2 H, H_4), 1.39 (s, 6 H, H_{21}).

For more data, see reference [1].

Compound (*L*)-8:



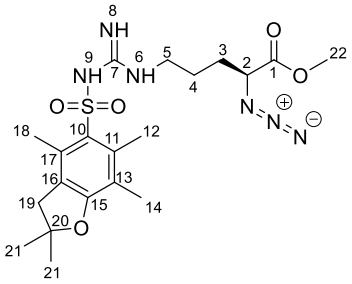
Boc-(*L*)-Arg(Pbf)-OH (200 mg, 380 µmol, 1 eq) and methanol (243 mg, 7.60 mmol, 20 eq) were dissolved in dry dichloromethane (10 mL). 4-(Dimethylamino)-pyridine (4.64 mg, 37.0 µmol, 0.1 eq) was added and the reaction solution was cooled to 0 °C. *N,N*-Dicyclohexylcarbodiimide (110 mg, 532 µmol, 1.4 eq) was added and the reaction mixture was warmed to room temperature overnight. The urea byproduct was removed by filtration washed with cold toluene (100 mL). The organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (3.5 cm x 30 cm, dichloromethane:ethyl acetate = 1:1) to afford a (*L*)-**8** as a white solid (127 mg, 235 µmol, 61.9%).

Chemical formular: $C_{27}H_{41}N_5O_6S$ **Molecular weight:** 563.71 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] □□ = 7.24 (d, 1 H, ^3J = 7.8 Hz, H_{22}), 6.66-6.37 (m, 3 H, $H_{6, 8, 9}$), 3.90 (m, 1 H, H_2), 3.60 (s, 3 H, H_{26}), 2.99 (q, ^3J = 6.6 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.47 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.01 (s, 3 H, H_{14}), 1.60-1.32 (m, 4 H, $H_{3, 4}$), 1.41 (s, 6 H, H_{21}), 1.37 (s, 9 H, H_{25}).
For more data, see reference [2].

2.2.2 Synthesis of compound (*L*)-**5,** (*L*)-**7** and (*L*)-**9**

Compound (*L*)-2:



Fmoc-(*L*)-Arg(Pbf)-OMe ((*L*)-**1**) (3.00 g, 4.53 mmol, 1 eq) was dissolved in dimethylformamide (20 mL) and diethylamine (9 mL) was added. The solution was stirred for 2 hours at room temperature. The crude mixture was concentrated *in vacuo*. The residue was dissolved in methanol (20 mL). Potassium carbonate (1.81 g, 13.6 mmol, 3 eq), **10** (1.84 g, 6.79 mmol, 1.5 eq) and copper sulfate pentahydrate (113 mg, 453 µmol, 0.1 eq) were added and the reaction mixture was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (50 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (5.5 cm x 18 cm, dichloromethane:ethyl acetate = 1:2) to afford a (*L*)-**2** as a clear, yellow oil (1.46 g, 3.13 mmol, 69.1%).

Chemical formular: $C_{20}H_{30}N_6O_5S$ **Molecular weight:** 466.56 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 6.71-6.45 (m, 3 H, $H_{6, 8, 9}$), 4.27 (dd, ^3J = 5.1 Hz, ^3J = 8.3 Hz, 1 H, H_2), 3.70 (s, 3 H, H_{22}), 3.05 (q, ^3J = 6.5 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.48 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.01 (s, 3 H, H_{14}), 1.69-1.57 (m, 2 H, H_3), 1.45-1.36 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}).

^{13}C-NMR (151 MHz, DMSO-d$_6$) [ppm] = 170.6 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 60.9 (1 C, C_2), 52.5 (1 C, C_{22}), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 28.0 (2 C, C_{21}), 28.3 (1 C, C_3), 25.3 (1 C, C_4), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 467.2017 (calcd 467.2071 for $[M+H]^+$), m/z = 489.1887 (calcd 489.1891 for $[M+Na]^+$).

Melting point: 88 °C

Anal. Calc for $C_{20}H_{30}N_6O_5S$ (466.56): C 51.49, H 6.48, N 18.01; found: C 53.1, H 6.93, N 16.40.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3444 (w), 3330 (w), 2929 (w), 2848 (w), 2106 (m), 1741 (m), 1624 (m), 1547 (s), 1436 (m), 1369 (w), 1242 (m), 1088 (s), 1034 (w), 993 (m), 903 (w), 852 (w), 808 (m), 783 (m), 733 (w), 660 (s), 642 (s), 621 (m).

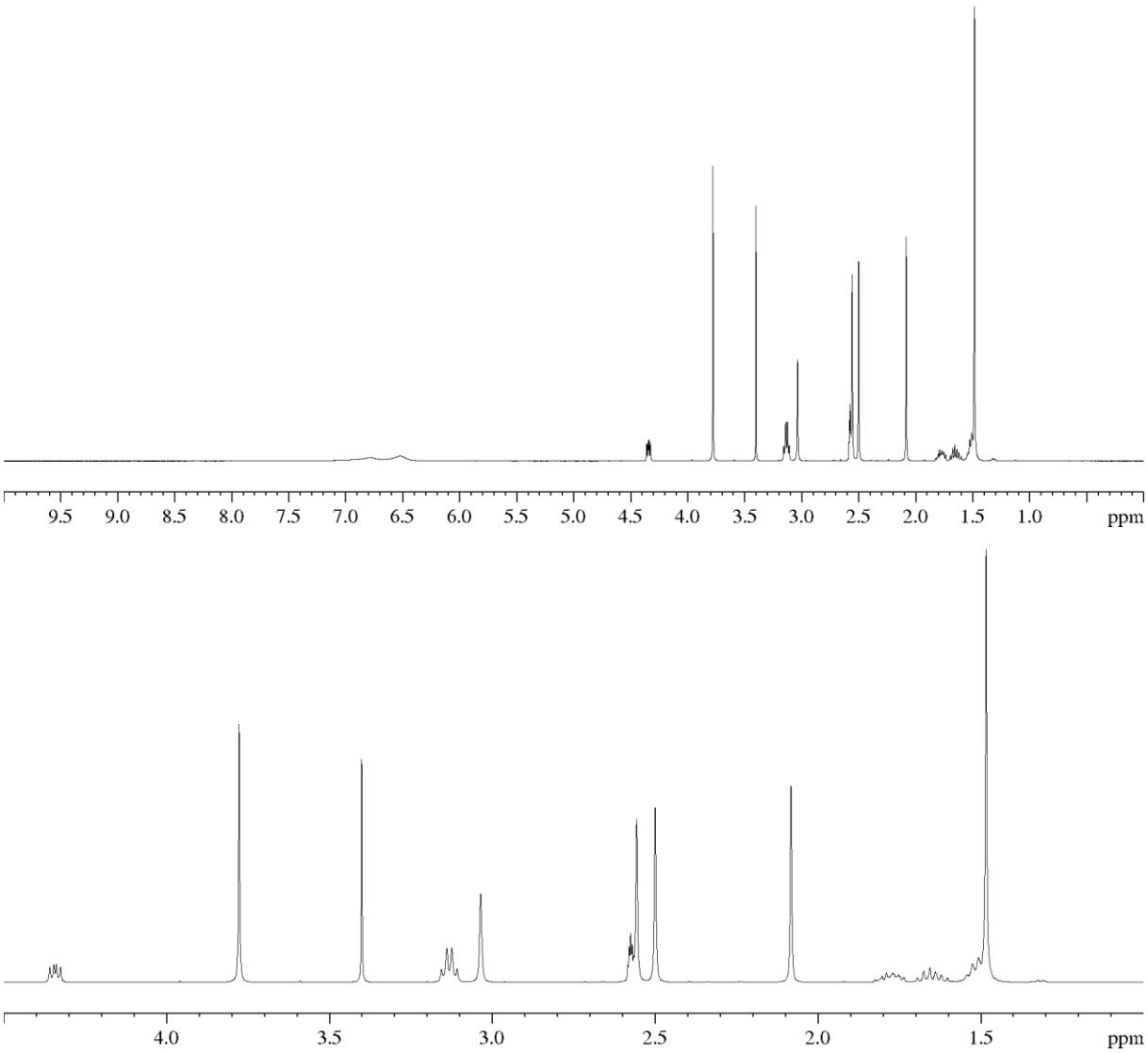


Figure S6: ^{1}H-NMR spectrum of (*L*)-**2** (298 K, 400 MHz, DMSO-d_6).

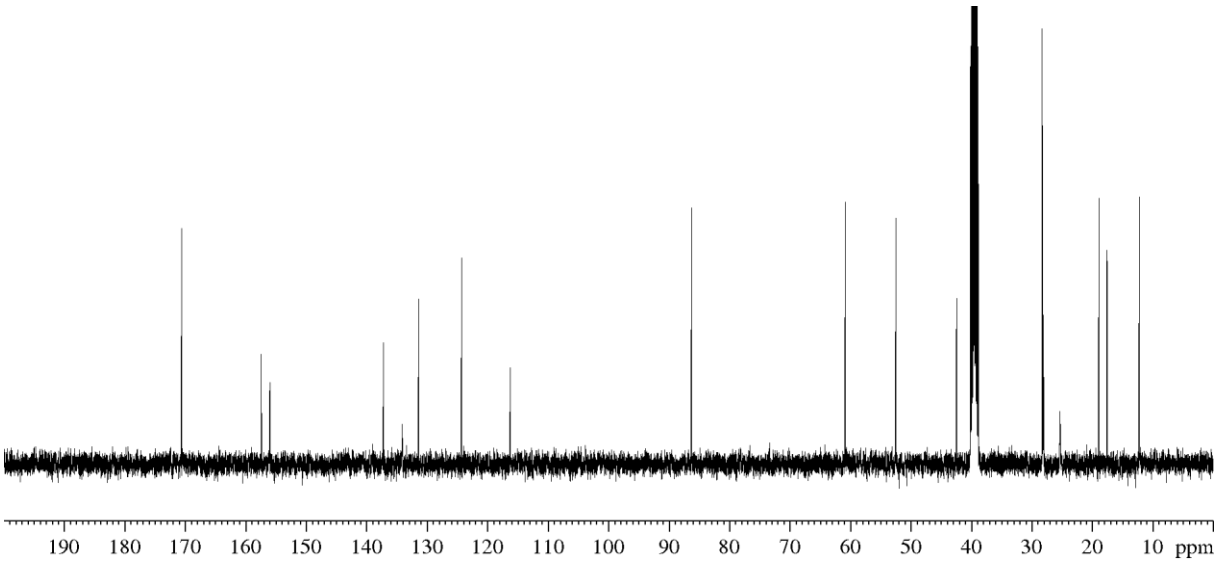
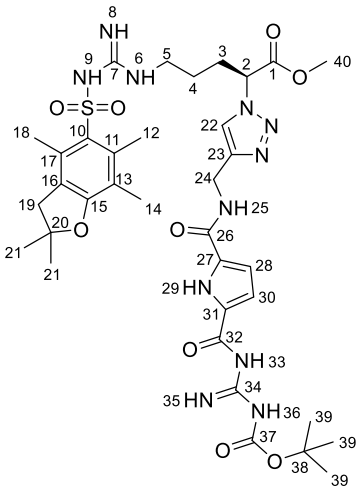


Figure S7: ^{13}C-NMR spectrum of (*L*)-**2** (298 K, 101 MHz, DMSO-d_6).

Compound (*L*)-4:



Azido acid (*L*)**-2** (400 mg, 1.20 mmol, 1 eq) and GCP alkyne **3** (672 mg, 1.44 mmol, 1.1 eq) were dissolved in tetrahydrofuran (20 mL). A solution of copper sulfate pentahydrate (30.0 mg, 120 µmol, 0.1 eq) and sodium ascorbate (47.5 mg, 240 µmol, 0.2 eq) in degassed water (1 mL) was freshly prepared. An aliquot of the fresh catalyst solution (100 µL, 12.0 µmol, 0.01 eq) was added to the reaction solution and the reaction mixture was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (50 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (4 cm x 18 cm, dichloro-methane:methanol:ammonia$_{(25\% \text{ in } H2O)}$ = 9:0.9:0.1) to afford a (*L*)**-4** as a white solid (860 mg, 1.08 mmol, 89.6%).

Chemical formular: $C_{35}H_{49}N_{11}O_9S$ **Molecular weight:** 799.91 g/mol

^{1}H-NMR (400 MHz, DMSO-d$_6$) [ppm] = 11.10 (br s, 1 H, H_{29}), 10.86 (br s, 1 H, H_{35}), 9.33 (br s, 1 H, H_{33}), 8.90 (t, ^3J = 5.6 Hz, 1 H, H_{25}), 8.56 (br s, 1 H, H_{36}), 8.06 (s, 1 H, H_{22}), 6.81 (m, 2 H, $H_{28, 30}$), 6.76-6.50 (m, 3 H, $H_{6, 8, 9}$), 5.51 (dd, ^3J = 9.5 Hz, ^3J = 5.9 Hz, 1 H, H_2), 4.51 (d, ^3J = 5.5 Hz, 2 H, H_{24}), 3.66 (s, 3 H, H_{40}), 3.03 (q, ^3J = 6.5 Hz, 2 H, H_5), 2.95 (s, 2 H, H_{19}), 2.46 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.14 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.46 (s, 9 H, H_{39}), 1.40 (s, 6 H, H_{21}), 1.33-1.15 (m, 2 H, H_4).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 169.1 (2 C, $C_{1, 37}$), 159.5 (2 C, $C_{26, 32}$), 157.5 (1 C, C_{15}), 156.0 (2 C, $C_{7, 34}$), 144.8 (1 C, C_{23}), 137.3 (1 C, C_{10}), 134.1 (2 C, $C_{27, 31}$), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 123.1 (1 C, C_{22}), 116.3 (1 C, C_{13}), 112.1 (2 C, $C_{28, 30}$), 86.3 (1 C, C_{20}), 61.3 (1 C, C_2), 52.7 (1 C, C_{40}), 42.5 (2 C, $C_{19, 38}$), 39.3 (1 C, C_5), 34.2 (1 C, C_{24}), 28.3 (4 C, $C_{3, 39}$), 28.2 (2 C, C_{21}), 25.5 (1 C, C_4), 18.9 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 800.3502 (calcd 800.3508 for $[M+H]^+$).

Melting point: 191 °C

Anal. Calc for $C_{35}H_{49}N_{11}O_9S$ (799.91): C 52.55, H 6.17, N 19.26; found: C 52.2, H 6.29, N 18.6.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3338 (w), 2974 (w), 2931 (w), 1734 (m), 1624 (m), 1558 (s), 1541 (s), 1458 (m), 1369 (m), 1286 (m), 1236 (s), 1144 (s), 1088 (m), 1043 (w), 837 (m), 781 (m), 663 (m), 615 (w).

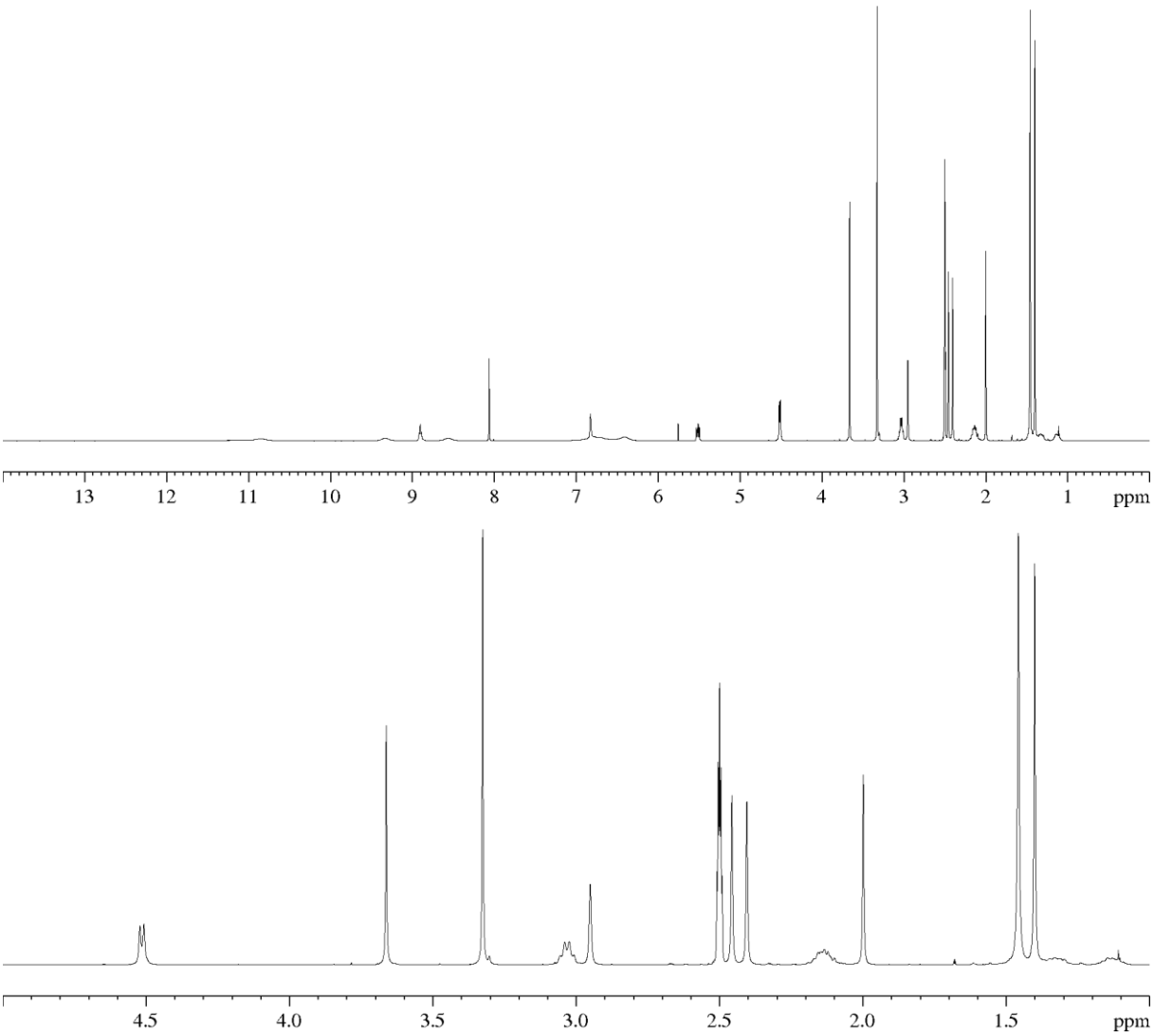


Figure S8: ^{1}H-NMR spectrum of (*L*)-**4** (298 K, 400 MHz, DMSO-d_6).

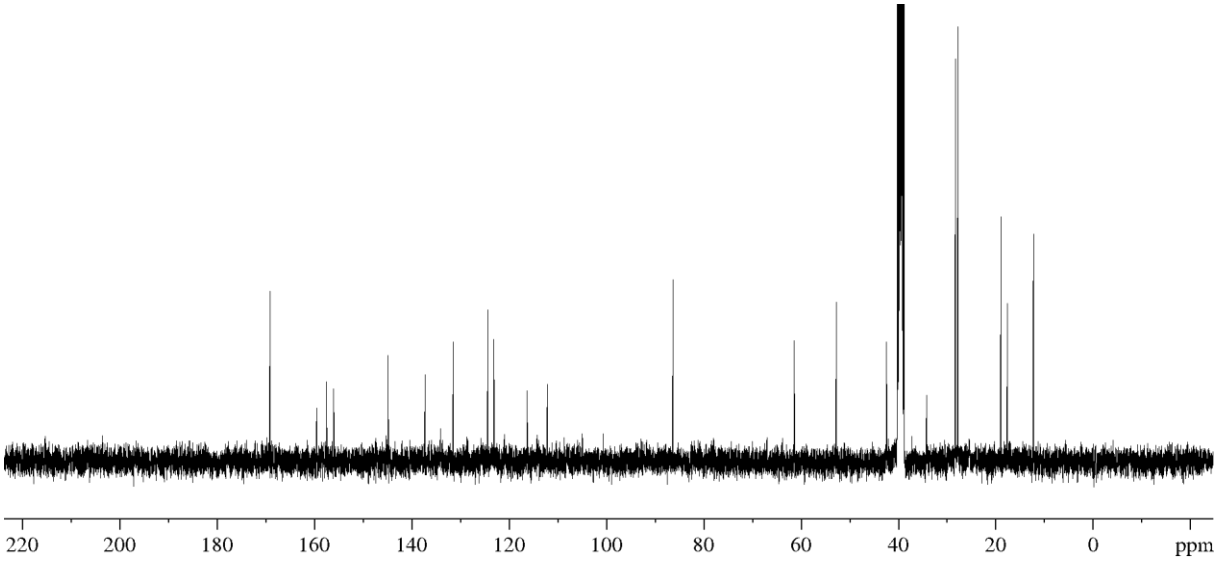
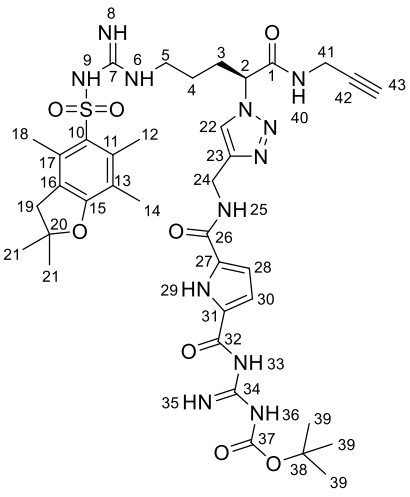


Figure S9: ^{13}C-NMR spectrum of (*L*)-**4** (298 K, 101 MHz, DMSO-d_6).

Compound (*L*)-5:



Methyl ester (*L*)-**4** (500 mg, 625 µmol, 1 eq) was dissolved in tetrahydrofuran (20 mL). An aqueous solution of lithium hydroxide (45.1 mg, 1.88 mmol, 3 eq) in water (5 mL) was added. The solution was stirred for 3 hours at room temperature. Ethyl acetate (50 mL) was added to the solution and the aqueous phase was extracted repeatedly with ethyl acetate (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Evaporation of organic solvents gave the Me-deprotected compound as a white solid (491 mg), which could directly be used for the next step. The crude carboxylic acid (400 mg, 508 µmol, 1 eq), propargylamine (63.1 mg, 1.15 mmol, 2 eq) and 4-methyl-morpholine (290 mg, 2.86 mmol, 5 eq) were dissolved in dry dimethylformamide (20 mL) under argon atmosphere. After stirring for 10 minutes at room temperature, HCTU (709 mg, 1.72 mmol, 2 eq) was added the mixture was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (50 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (4.5 cm x 20 cm, dichloromethane:methanol:ammonia$_{(25\% \text{ in } H2O)}$ = 9:0.9:0.1) to afford a (*L*)-**5** as a white solid (309 mg, 375 µmol, 67.5%).

Chemical formular: $C_{37}H_{50}N_{12}O_8S$ **Molecular weight:** 822.94 g/mol

^{1}H-NMR (400 MHz, DMSO-d$_6$) [ppm] = 11.15 (br s, 1 H, H_{29}), 10.85 (br s, 1 H, H_{35}), 9.33 (br s, 1 H, H_{33}), 8.94 (t, ^2J = 5.2 Hz, 1 H, H_{40}), 8.86 (t, ^2J = 5.6 Hz, 1 H, H_{25}), 8.56 (br s, 1 H, H_{36}), 8.03 (s, 1 H, H_{22}), 6.82 (m, 2 H, $H_{28, 30}$), 6.73-6.50 (m, 3 H, $H_{6, 8, 9}$), 5.25 (t, ^3J = 7.4 Hz, 1 H, H_2), 4.50 (t, ^3J = 4.6 Hz, 2 H, H_{24}), 3.89 (dd, ^3J = 5.4 Hz, ^4J = 2.3 Hz, 2 H, H_{41}), 3.15 (t, ^4J = 2.6 Hz, 1 H, H_{43}), 3.03 (q, ^2J = 5.4 Hz, 2 H, H_5), 2.95 (s, 2 H, H_{19}), 2.46 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.04-1.97 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.46 (s, 9 H, H_{39}), 1.40 (s, 6 H, H_{21}), 1.30-1.23 (s, 2 H, H_4).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 167.5 (2 C, $C_{1, 37}$), 159.5 (2 C, $C_{26, 32}$), 157.5 (1 C, C_{15}), 156.0 (2 C, $C_{7, 34}$), 144.8 (1 C, C_{23}), 137.3 (1 C, C_{10}), 134.1 (2 C, $C_{27, 31}$), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 121.9 (1 C, C_{22}), 116.3 (1 C, C_{13}), 112.1 (2 C, $C_{28, 30}$), 86.3 (1 C, C_{20}), 80.3 (1 C, C_{42}), 73.7 (1 C, C_{43}), 62.1 (1 C, C_2), 42.5 (2 C, $C_{19, 38}$), 39.3 (1 C, C_5), 34.2 (1 C, C_{24}), 29.5 (1 C, C_{41}), 28.3 (3 C, C_{39}), 28.2 (1 C, C_3), 27.8 (1 C, C_{21}), 25.5 (1 C, C_4), 18.9 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 823.3670 (calcd 823.3668 for $[M+H]^+$), 845.3486 (calcd 845.3487 for $[M+Na]^+$).

Melting point: 189 °C

Anal. Calc for $C_{37}H_{50}N_{12}O_8S$ (822.94): C 54.00, H 6.12, N 20.42; found: C 52.7, H 6.27, N 20.1.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3307 (w), 2973 (w), 2938 (w), 1733 (w), 1624 (m), 1541 (s), 1458 (m), 1369 (w), 1299 (m), 1232 (s), 1144 (s), 1088 (s), 1047 (m), 837 (m), 781 (m), 660 (m), 609 (w).

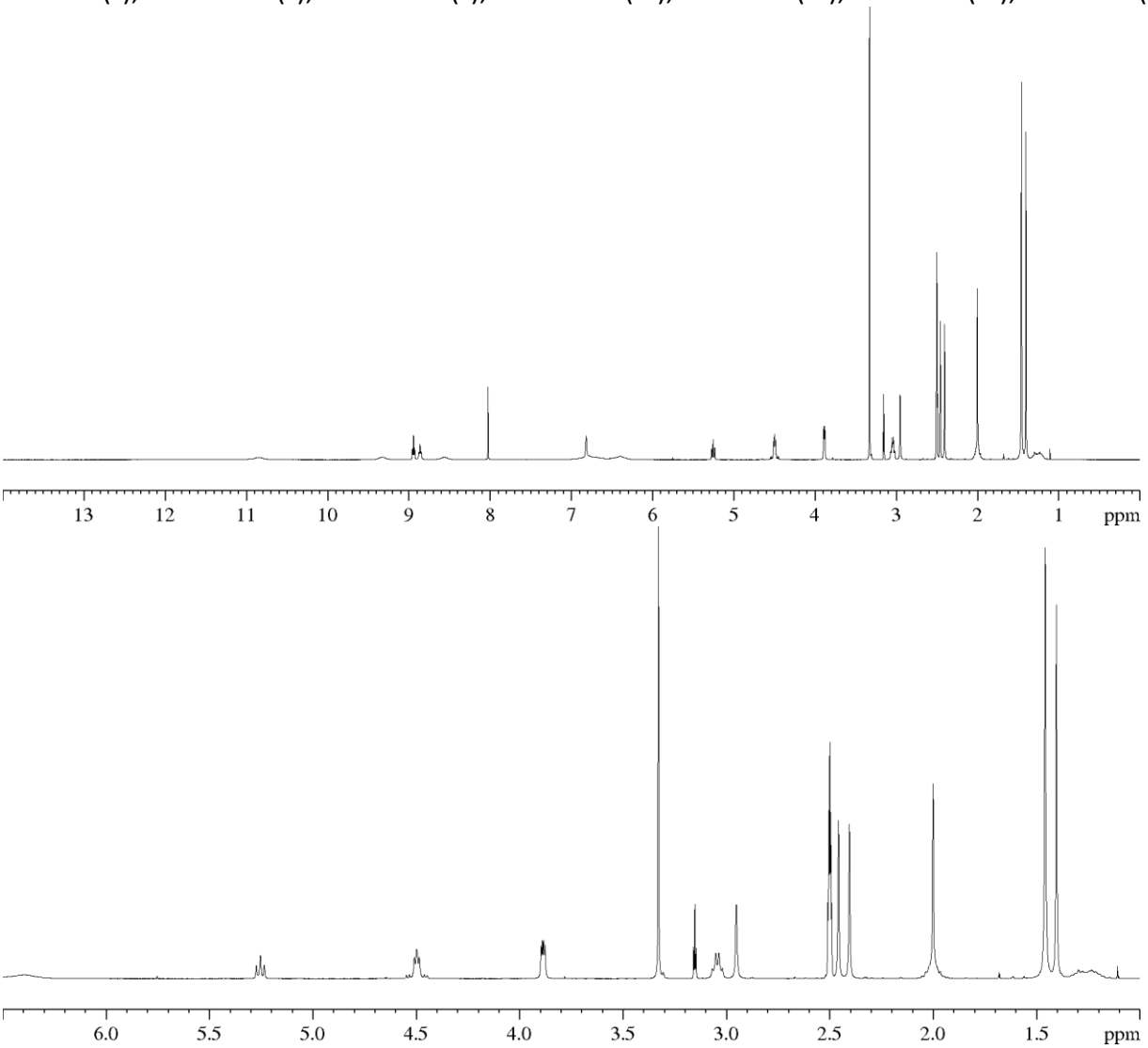


Figure S10: ^{1}H-NMR spectrum of (*L*)-**5** (298 K, 400 MHz, DMSO-d$_6$).

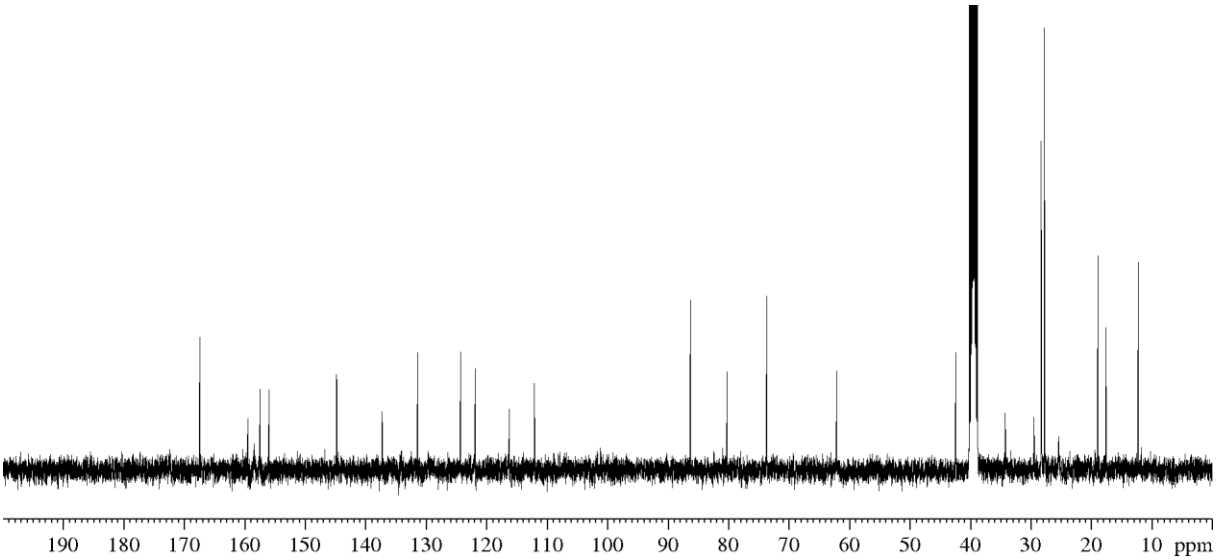
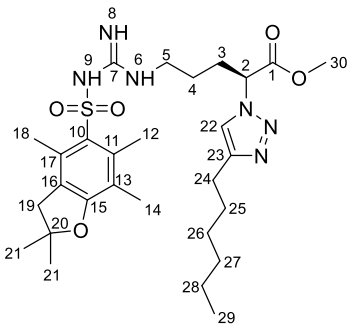


Figure S11: ^{13}C-NMR spectrum of (*L*)-**5** (298 K, 101 MHz, DMSO-*d*$_6$).

Compound (*L*)-6:



Azido acid (*L*)-**2** (300 mg, 429 µmol, 1 eq) and 1-octyne (70.9 mg, 643 µmol, 1.5 eq) were dissolved in tetrahydrofuran (20 mL). A solution of copper sulfate pentahydrate (10.7 mg, 42.9 µmol, 0.1 eq) and sodium ascorbate (17.0 mg, 85.8 µmol, 0.2 eq) in degassed water (1 mL) was freshly prepared. An aliquot of the fresh catalyst solution (100 µL, 4.29 µmol, 0.01 eq) was added and the reaction was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (20 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (3.5 cm x 18 cm, dichloromethane:ethyl acetate = 1:1) to afford a (*L*)-**6** as a white solid (162 mg, 281 µmol, 65.5%).

Chemical formular: $C_{28}H_{44}N_6O_5S$ **Molecular weight:** 576.76 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 7.91 (s, 1 H, H_{22}), 6.69-6.40 (m, 3 H, $H_{6, 8, 9}$), 5.44 (dd, ^3J = 9.8 Hz, ^3J = 5.5 Hz, 1 H, H_2), 3.66 (s, 3 H, H_{30}), 3.06 (q, ^3J = 7.7 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.60 (t, ^3J = 7.4 Hz, 2 H, H_{24}), 2.45 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.15-2.07 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.61-1.54 (m, 2 H, H_4), 1.40 (s, 6 H, H_{21}), 1.27-1.11 (m, 8 H, H_{25-28}), 0.85 (t, ^3J = 6.9 Hz, 3 H, H_{29}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 169.2 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 147.0 (1 C, C_{23}), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 121.7 (1 C, C_{22}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 61.3 (1 C, C_2), 52.7 (1 C, C_{30}), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 31.0 (1 C, C_{CH2}), 28.8 (1 C, C_{CH2}), 28.3 (2 C, C_{21}), 28.2 (1 C, C_3), 25.4 (2 C, C_{CH2}), 25.0 (1 C, C_4), 22.0 (1 C, C_{CH2}), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 13.9 (1 C, C_{CH3}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 577.3171 (calcd 577.3167 for $[M+H]^+$), m/z = 599.2986 (calcd 599.2989 for $[M+Na]^+$).

Melting point: 99 °C

Anal. Calc for $C_{28}H_{44}N_6O_9S$ (576.76): C 58.31, H 7.69, N 14.57; found: C 57.3, H 7.01, N 14.2.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3444 (w), 3334 (w), 3145 (w), 2931 (w), 2862 (w), 1751 (m), 1618 (m), 1541 (s), 1458 (m), 1367 (w), 1255 (m), 1151 (w), 1090 (s), 993 (w), 901 (w), 808 (w), 783 (m), 733 (w), 660 (s), 619 (w).

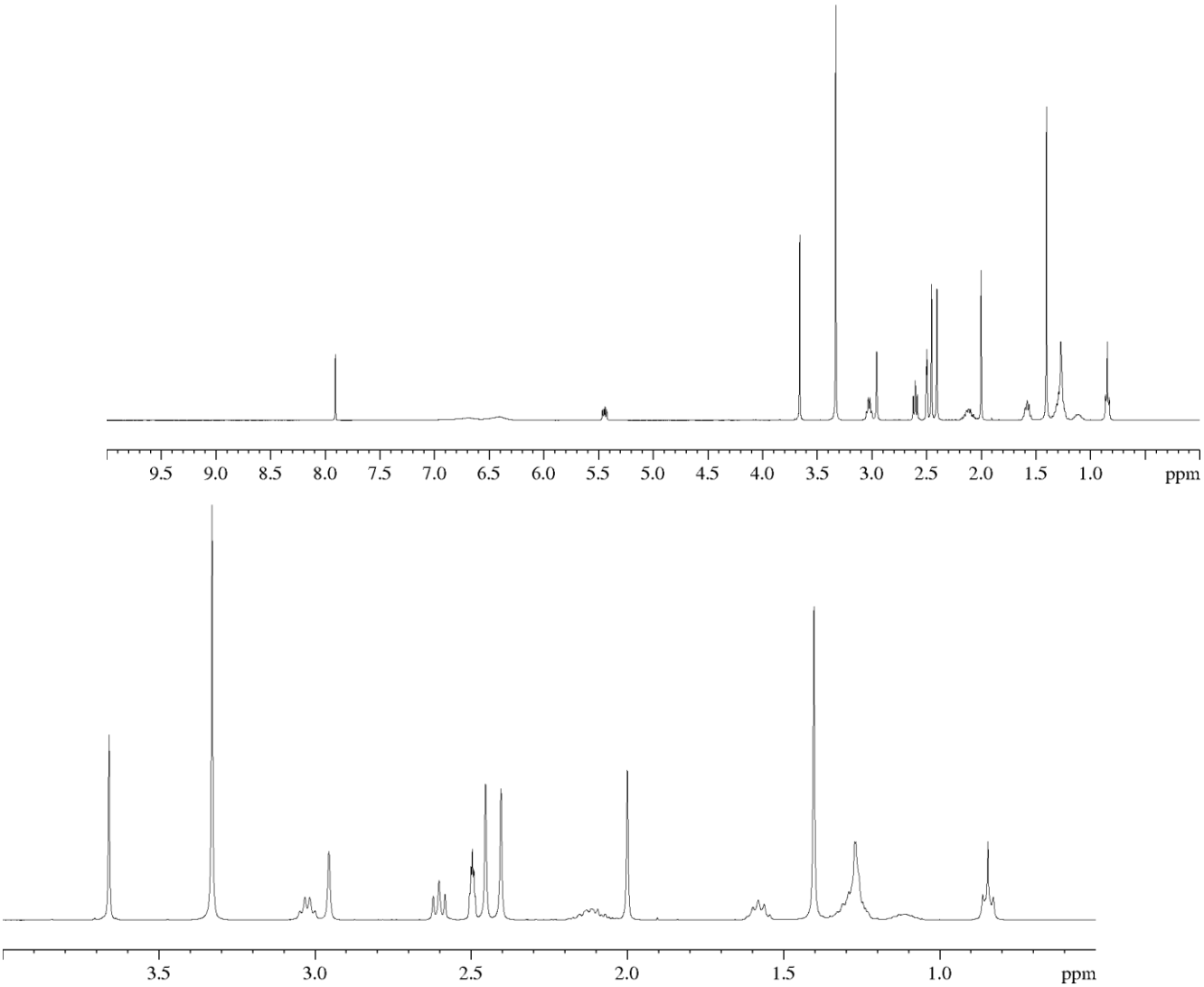


Figure S12: ^{1}H-NMR spectrum of (*L*)-**6** (298 K, 400 MHz, DMSO-d_6).

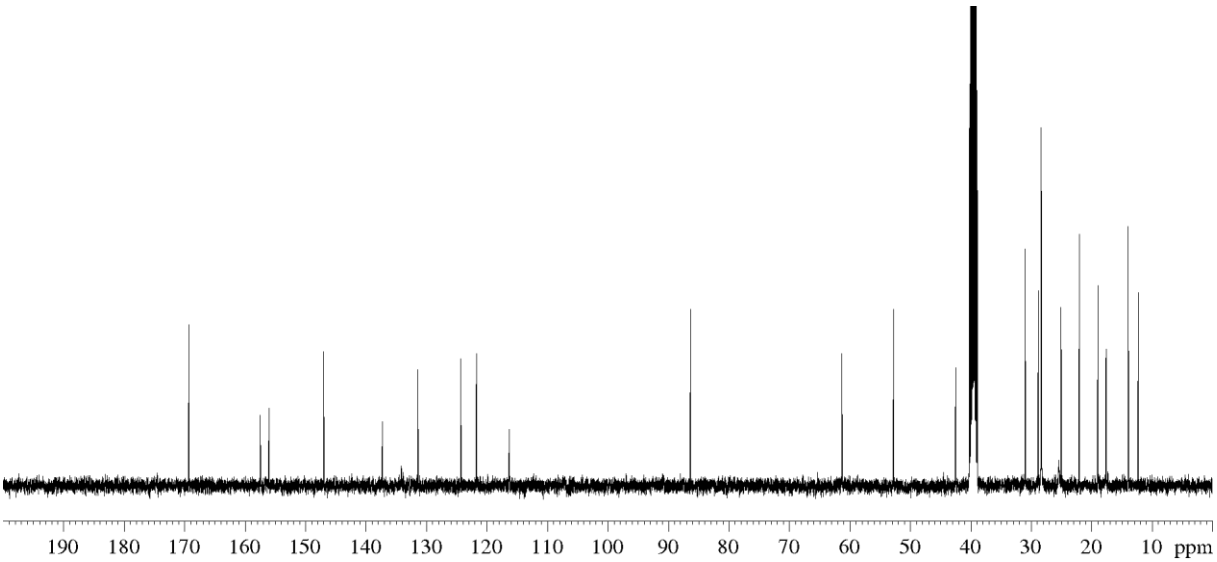
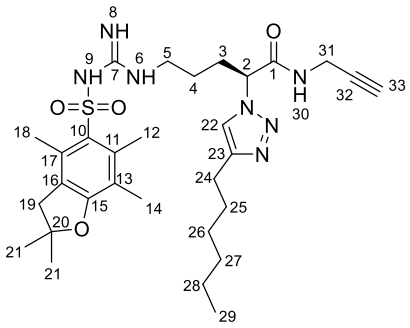


Figure S13: ^{13}C-NMR spectrum of (*L*)-**6** (298 K, 101 MHz, DMSO-d_6).

Compound (*L*)-7:



Methyl ester (*L*)-**6** (75.0 mg, 130 µmol, 1 eq) was dissolved in tetrahydrofuran (20 mL). An aqueous solution of lithium hydroxide (9.34 mg, 390 µmol, 3 eq) in water (5 mL) was added. The solution was stirred for 3 hours at room temperature. Ethyl acetate (50 mL) was added to the solution and the aqueous phase was extracted repeatedly with ethyl acetate (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Evaporation of organic solvents gave the Me-deprotected compound as a white solid (74 mg), which could directly be used for the next step. The crude carboxylic acid (60.0 mg, 107 µmol, 1 eq), propargylamine (11.7 mg, 213 µmol, 2 eq) and 4-methylmorpholine (53.9 mg, 533 µmol, 5 eq) were dissolved in dry dimethylformamide (20 mL) under argon atmosphere. After stirring 10 minutes at room temperature, HCTU (88.0 mg, 213 µmol, 2 eq) was added and the solution and was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (50 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (5.5 cm x 20 cm, dichloromethane:ethyl acetate = 1:2) to afford a (*L*)-**7** as a white solid (45.0 mg, 75.0 µmol, 69.7%).

Chemical formular: $C_{30}H_{45}N_7O_4S$ **Molecular weight:** 599.80 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 8.88 (t, ^3J = 5.6 Hz, 1 H, H_{30}), 7.87 (s, 1 H, H_{22}), 6.70-6.40 (m, 3 H, $H_{6, 8, 9}$), 5.20 (t, ^2J = 5.8 Hz, 1 H, H_2), 3.88 (dd, ^3J = 5.5 Hz, ^4J = 2.6 Hz, 2 H, H_{31}), 3.15 (t, ^4J = 2.6 Hz, 1 H, H_{33}), 3.04 (q, ^3J = 7.7 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.59 (t, ^3J = 7.8 Hz, 2 H, H_{24}), 2.46 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.00 (s, 3 H, H_{14}), 1.98 (m, 2 H, H_3), 1.59-1.56 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}), 1.27-1.18 (m, 8 H, H_{25-28}), 0.85 (t, ^2J = 7.4 Hz, 3 H, H_{29}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 167.7 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 146.9 (1 C, C_{23}), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 120.7 (1 C, C_{22}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 80.3 (1 C, C_{32}), 73.6 (1 C, C_{33}), 62.0 (1 C, C_2), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 31.0 (1 C, C_{CH2}), 29.4 (1 C, C_{CH2}), 28.9 (2 C, C_{CH2}), 28.31 (1 C, C_3), 28.29 (2 C, C_{21}), 28.2 (1 C, C_{31}), 25.1 (1 C, C_4), 22.0 (1 C, C_{CH2}), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 13.9 (1 C, C_{CH3}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 600.3325 (calcd 600.3327 for $[M+H]^+$), m/z = 622.3141 (calcd 622.3146 for $[M+Na]^+$).

Melting point: 102 °C

Anal. Calc for $C_{30}H_{45}N_7O_4S$ (599.80): C 60.08, H 7.56, N 16.35; found: C 59.8, H 7.33, N 15.3.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3440 (w), 3307 (w), 2927 (w), 2861 (w), 1684 (w), 1617 (w), 1540 (s), 1458 (m), 1367 (w), 1242 (m), 1089 (s), 1047 (m), 808 (m), 782 (m), 660 (s).

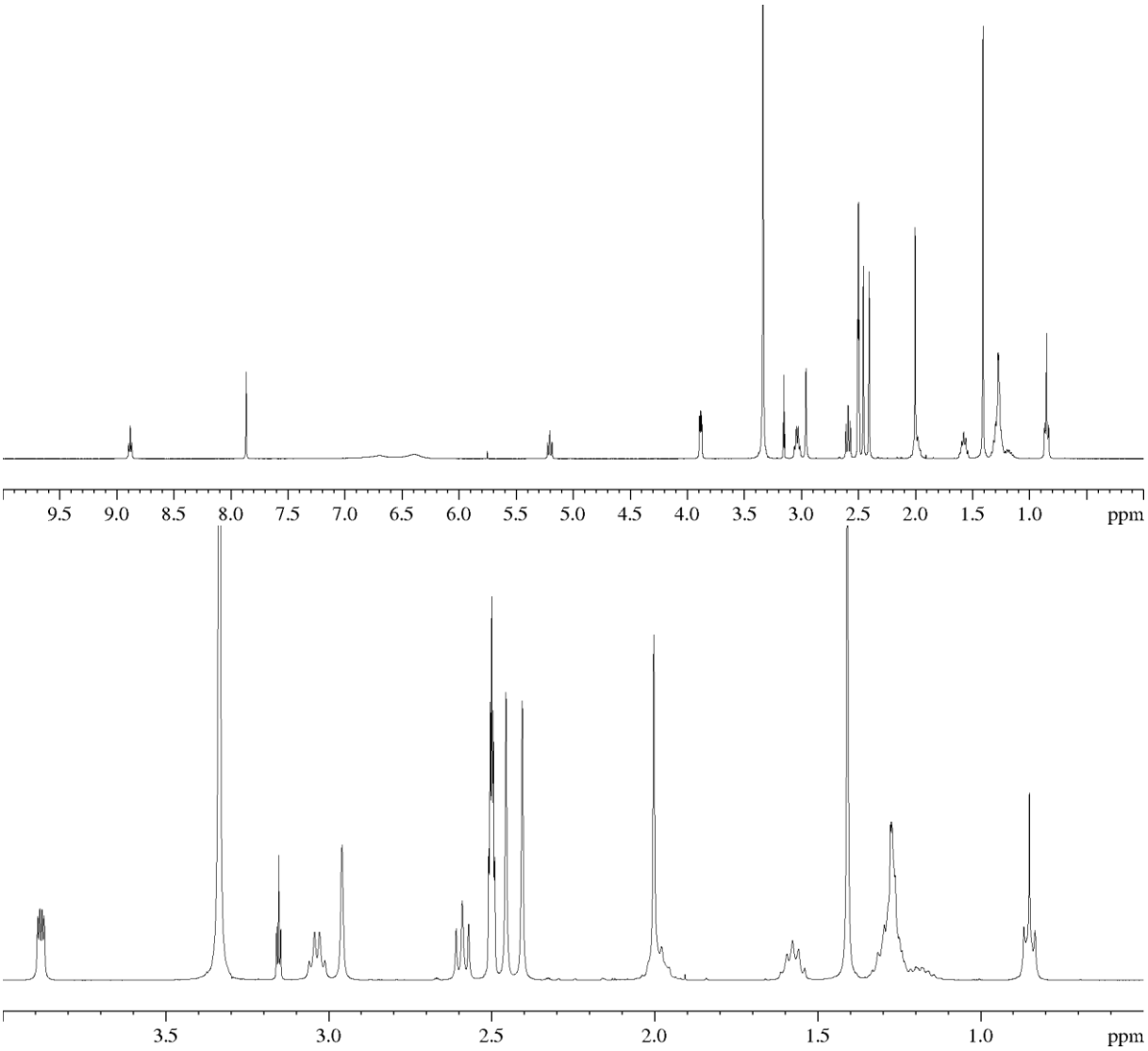


Figure S14: ^{1}H-NMR spectrum of (*L*)-**7** (298 K, 400 MHz, DMSO-d_6).

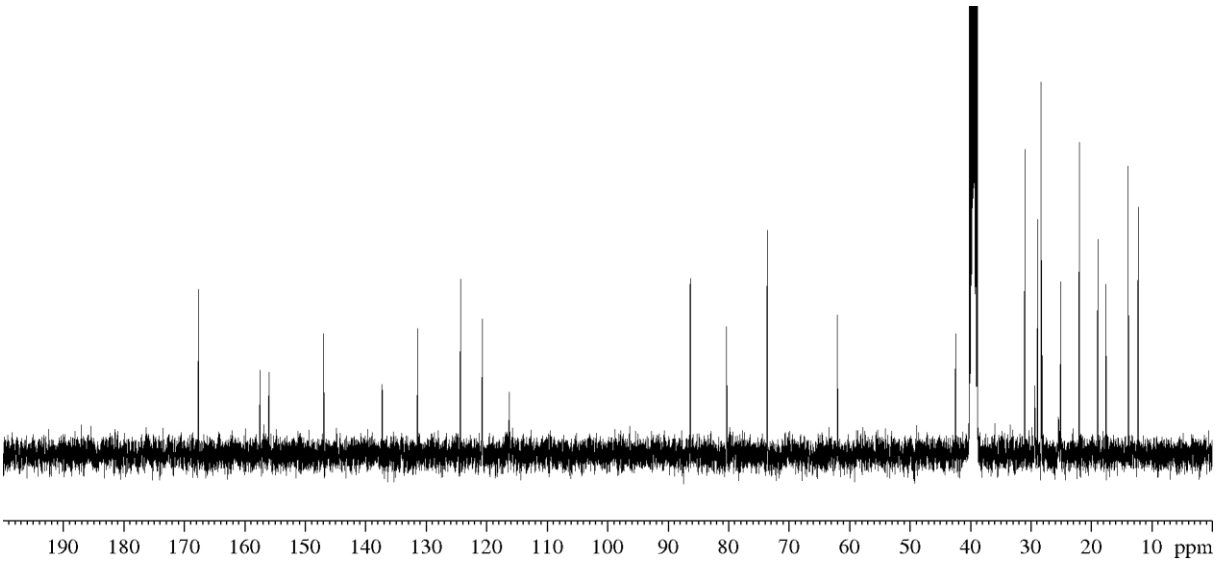
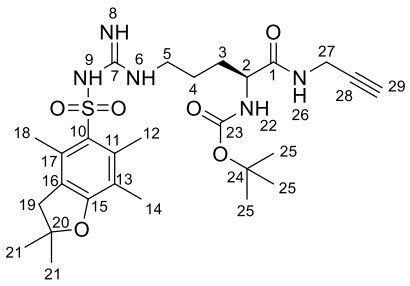


Figure S15: ^{13}C-NMR spectrum of (*L*)-**7** (298 K, 101 MHz, DMSO-d_6).

Compound (*L*)-9:



Boc-(*L*)-Arg(Pbf)-OMe ((*L*)-**8**) (100 mg, 185 µmol, 1 eq), was dissolved in tetrahydrofuran (10 mL). An aqueous solution of lithium hydroxide (13.3 mg, 555 µmol, 3 eq) in water (2.5 mL) was added. The solution was stirred for 3 hours at room temperature. Ethyl acetate (20 mL) was added to the solution and the aqueous phase was extracted repeatedly with ethyl acetate (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Evaporation of organic solvents gave the Me-deprotected compound as a white solid (98 mg), which could directly be used for the next step. The crude carboxylic acid (98.0 mg, 186 µmol, 1 eq), propargylamine (20.5 mg, 372 µmol, 2 eq) and 4-methylmorpholine (94.1 mg, 930 µmol, 5 eq) were dissolved in dry dimethylformamide (15 mL) under argon atmosphere. After stirring 10 minutes at room temperature, HCTU (115 mg, 297 µmol, 1.5 eq) was added and the solution and was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (20 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2.5 cm x 10 cm, dichloromethane:ethyl acetate = 1:4) to afford a (*L*)-**9** as a white solid (76.0 mg, 135 µmol, 72.5%).

Chemical formular: $C_{27}H_{41}N_5O_6S$ **Molecular weight:** 563.71 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 8.25 (t, 1 H, ^3J = 5.4 Hz, H_{26}), 6.83 (d, 1 H, ^3J = 8.2 Hz, H_{22}), 6.66-6.37 (m, 3 H, $H_{6, 8, 9}$), 3.89-3.85 (m, 1 H, H_2), 3.84-3.83 (m, 2 H, H_{27}), 3.08 (t, 1 H, ^3J = 2.4 Hz, H_{29}), 3.01 (q, ^3J = 6.6 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.47 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.00 (s, 3 H, H_{14}), 1.57-1.34 (m, 4 H, $H_{3, 4}$), 1.41 (s, 6 H, H_{21}), 1.37 (s, 9 H, H_{25}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 171.8 (1 C, C_{23}), 157.4 (1 C, C_{15}), 156.0 (1 C, C_7), 155.3 (1 C, C_1), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 81.0 (1 C, C_{28}), 78.0 (2 C, $C_{24, 27}$), 73.0 (1 C, C_{29}), 53.8 (1 C, C_2), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 28.3 (3 C, C_{25}), 28.2 (1 C, C_3), 27.9 (2 C, C_{21}), 25.6 (1 C, C_4), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 564.2849 (calcd 564.2850 for $[M+H]^+$), m/z = 586.2666 (calcd 586.2670 for $[M+Na]^+$).

Melting point: 112 °C

Anal. Calc for $C_{27}H_{41}N_5O_6S$ (563.71): C 57.53, H 7.33, N 12.42; found: C 56.5, H 7.37, N 12.2.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ =3437 (w), 3313 (w), 2933 (w), 1684 (m), 1618 (m), 1541 (s), 1457 (w), 1396 (w), 1244 (s), 1160 (s), 1090 (s), 991 (w), 904 (w), 852 (m), 782 (m), 734 (w), 658 (s), 625 (w).

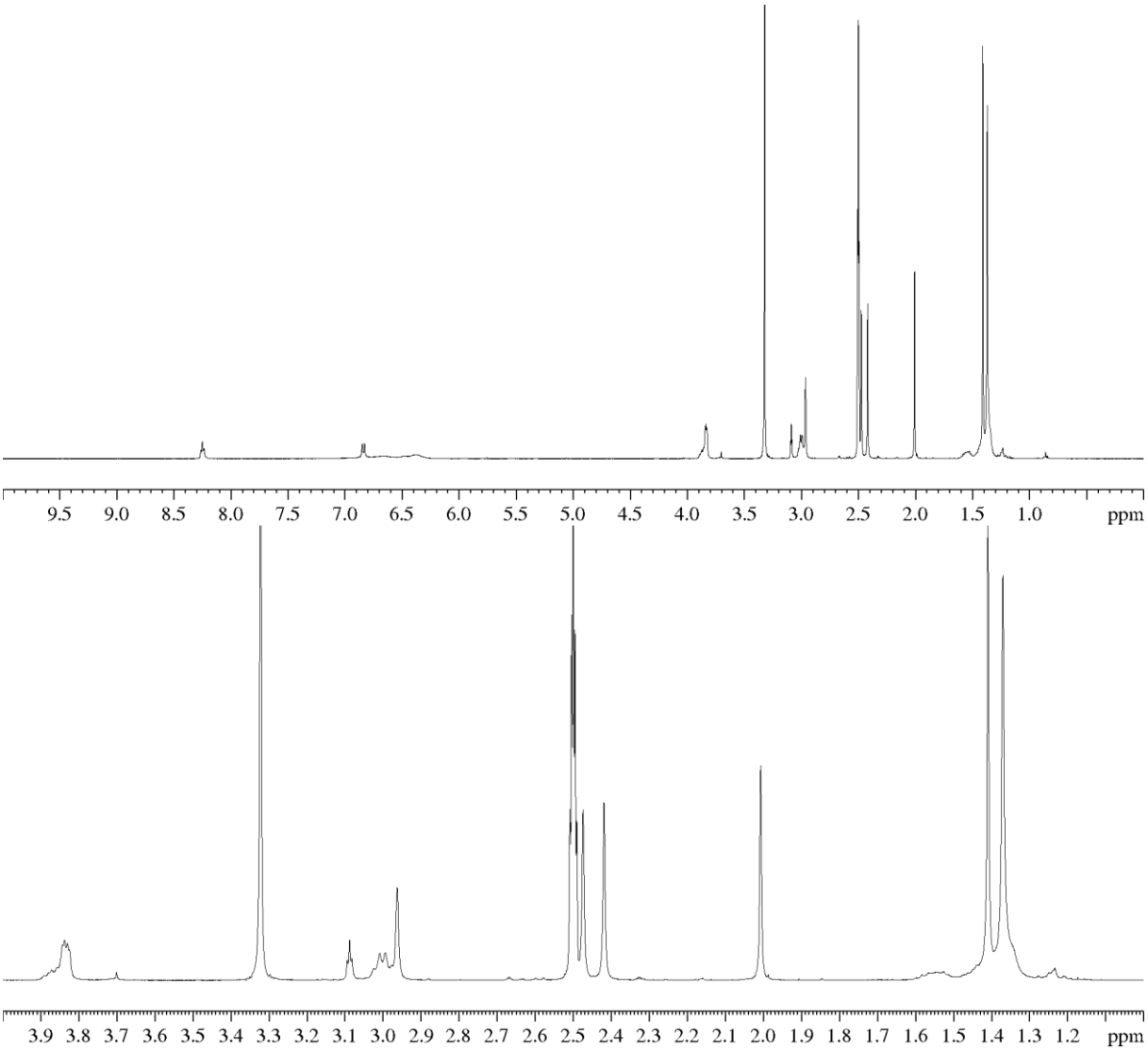


Figure S16: ^{1}H-NMR spectrum of (*L*)-**9** (298 K, 400 MHz, DMSO-d_6).

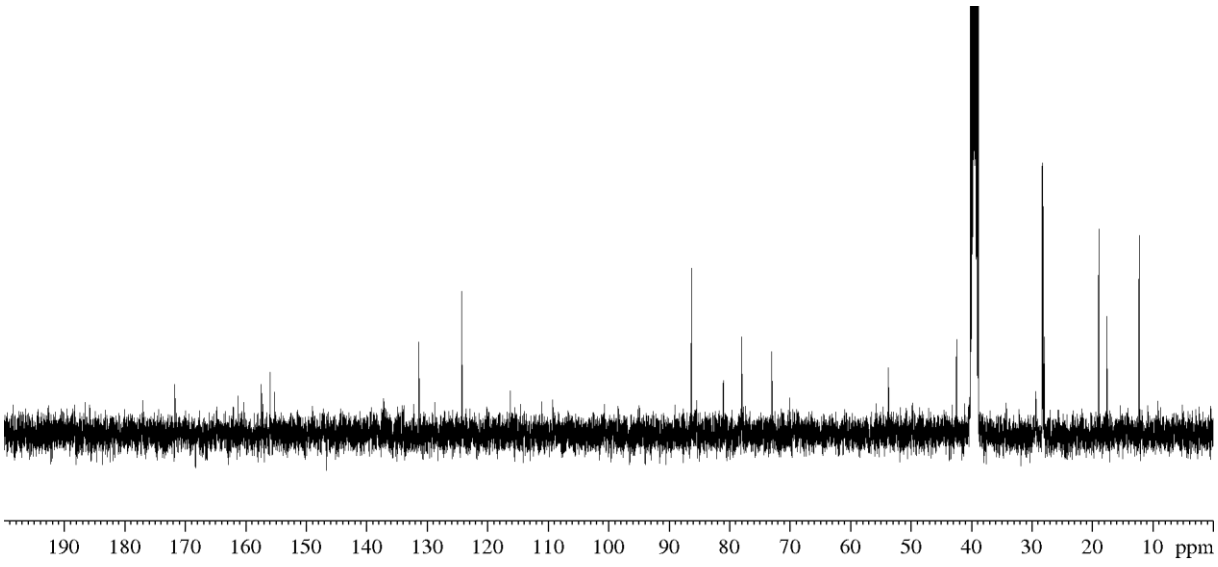
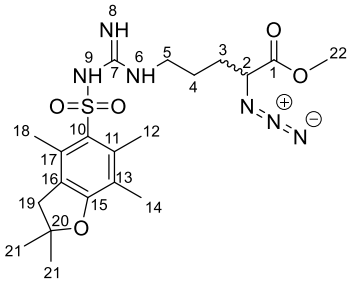


Figure S17: ^{13}C-NMR spectrum of (*L*)-**9** (298 K, 101 MHz, DMSO-d_6).

2.2.3 Synthesis of the racemic product (*rac*)-**5,** (*rac*)-**7** and (*rac*)-**9**

Compound (*rac*)-2:



Amino acid (*rac*)-**1** (300 mg, 453 µmol, 1 eq) was dissolved in dimethylformamide (5 mL) and diethylamine (2.5 mL) was added. The solution was stirred for 2 hours at room temperature. The crude mixture was concentrated *in vacuo*. The residue was dissolved in methanol (10 mL). Potassium carbonate (188 mg, 1.36 mmol, 3 eq), **10** (184 mg, 679 µmol, 1.5 eq) and copper sulfate pentahydrate (11.3 mg, 45.2 µmol, 0.1 eq) were added and the reaction mixture was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (50 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (5.5 cm x 18 cm, dichloromethane:ethyl acetate = 1:2) to afford a (*rac*)-**2** as a clear, yellow oil (135 mg, 289 µmol, 63.9%).

Chemical formular: $C_{20}H_{30}N_6O_5S$ **Molecular weight:** 466.56 g/mol

^{1}H-NMR (600 MHz, DMSO-d_6) [ppm] = 6.71-6.45 (m, 3 H, $H_{6, 8, 9}$), 4.27 (dd, ^3J = 5.1 Hz, ^3J = 8.3 Hz, 1 H, H_2), 3.70 (s, 3 H, H_{22}), 3.05 (q, ^3J = 6.5 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.48 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.01 (s, 3 H, H_{14}), 1.69-1.57 (m, 2 H, H_3), 1.45-1.36 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}).

^{13}C-NMR (151 MHz, DMSO-d_6) [ppm] = 170.6 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 60.9 (1 C, C_2), 52.5 (1 C, C_{22}), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 28.0 (2 C, C_{21}), 28.0 (1 C, C_3), 25.3 (1 C, C_4), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 467.2074 (calcd 467.2071 for $[M+H]^+$), 489.1891 (calcd 489.1891 for $[M+Na]^+$).

Melting point: 89 °C

Anal. Calc for $C_{20}H_{30}N_6O_5S$ (466.56): C 51.49, H 6.48, N 18.01; found: C 52.5, H 6.65, N 16.8.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3450 (w), 3330 (w), 2929 (w), 2104 (s), 1741 (m), 1618 (m), 1546 (s), 1452 (w), 1369 (w), 1254 (w), 1203 (w), 1088 (s), 1034 (w), 993 (w), 903 (w), 852 (w), 806 (m), 783 (m), 733 (w), 660 (s), 642 (s), 619 (m), 604 (w).

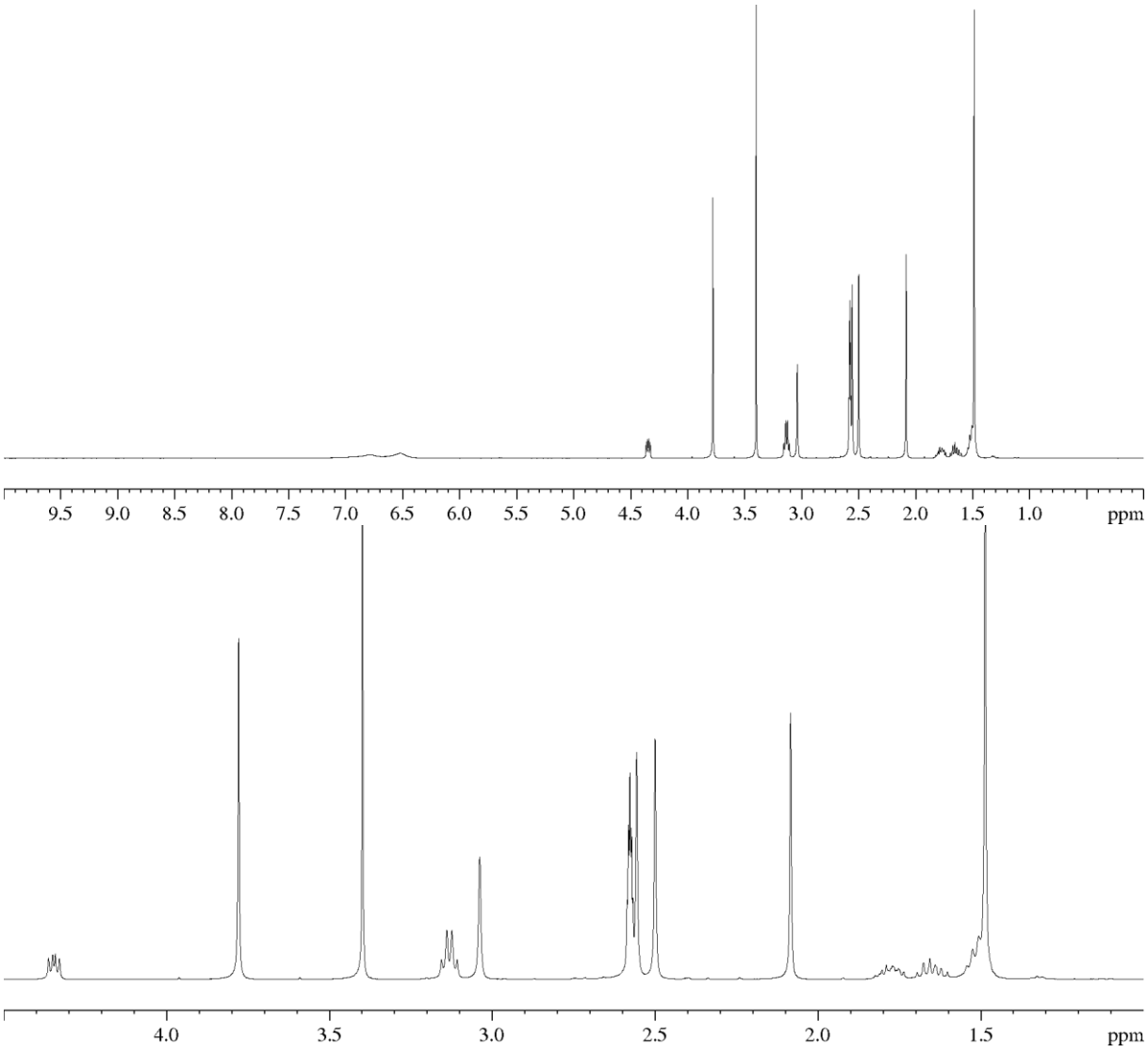


Figure S18: ^{1}H-NMR spectrum of (*rac*)-**2** (298 K, 400 MHz, DMSO-d_6).

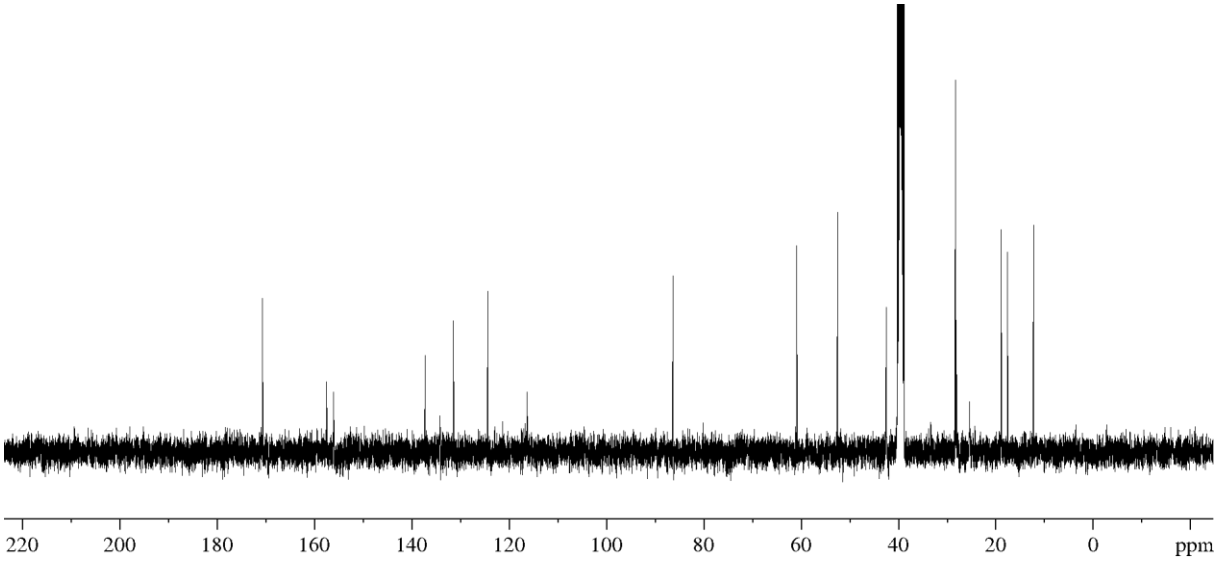
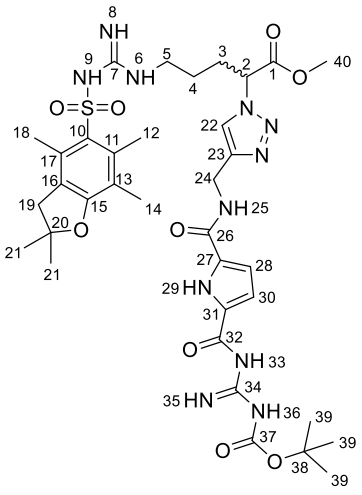


Figure S19: ^{13}C-NMR spectrum of (*rac*)-**2** (298 K, 101 MHz, DMSO-d_6).

Compound (*rac*)-4:



Azido acid (*rac*)-**2** (70.0 mg, 150 µmol, 1 eq) and GCP alkyne **3** (60.0 mg, 180 µmol, 1.2 eq) were dissolved in tetrahydrofuran (15 mL). A solution of copper sulfate pentahydrate (3.75 mg, 15.0 µmol, 0.1 eq) and sodium ascorbate (5.96 mg, 30.0 µmol, 0.2 eq) in degassed water (1 mL) was freshly prepared. An aliquot of the fresh catalyst solution (100 µL, 1.50 µmol, 0.01 eq) was added to the reaction solution and the reaction mixture was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (20 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (3.5 cm x 18 cm, dichloro-methane:methanol:ammonia$_{(25\% \text{ in } H2O)}$ = 9:0.9:0.1) to afford a (*rac*)-**4** as a white solid (102 mg, 128 µmol, 85.0%).

Chemical formular: $C_{35}H_{49}N_{11}O_9S$ **Molecular weight:** 799.91 g/mol

^{1}H-NMR (400 MHz, DMSO-d$_6$) [ppm] = 11.32 (bs, 1 H, H_{29}), 10.90 (bs, 1 H, H_{35}), 9.33 (bs, 1 H, H_{33}), 8.90 (t, ^2J = 5.6 Hz, 1 H, H_{25}), 8.56 (bs, 1 H, H_{36}), 8.06 (s, 1 H, H_{22}), 6.82 (m, 2 H, $H_{28, 30}$), 6.70-6.41 (m, 3 H, $H_{6, 8, 9}$), 5.51 (dd, ^3J = 9.5 Hz, ^3J = 5.9 Hz, 1 H, H_2), 4.51 (d, ^3J = 5.5 Hz, 2 H, H_{24}), 3.66 (s, 3 H, H_{40}), 3.03 (q, ^2J = 6.5 Hz, 2 H, H_5), 2.95 (s, 2 H, H_{19}), 2.46 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.13 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.46 (s, 9 H, H_{39}), 1.40 (s, 6 H, H_4), 1.33-1.15 (m, 2 H, H_4).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 169.1 (2 C, $C_{1, 37}$), 159.5 (2 C, $C_{26, 32}$), 157.5 (1 C, C_{15}), 156.0 (2 C, $C_{7, 34}$), 144.8 (1 C, C_{23}), 137.3 (1 C, C_{10}), 134.1 (2 C, $C_{27, 31}$), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 123.1 (1 C, C_{22}), 116.3 (1 C, C_{13}), 112.1 (2 C, $C_{28, 30}$), 86.3 (2 C, $C_{20, 38}$), 61.3 (1 C, C_2), 52.8 (1 C, C_{40}), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 34.2 (1 C, C_{24}), 28.3 (4 C, $C_{3, 39}$), 28.2 (2 C, C_{21}), 25.5 (1 C, C_4), 18.9 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 800.3510 (calcd 800.3508 for $[M+H]^+$), 822.3326 (calcd 822.3328 for $[M+Na]^+$).

Melting point: 195 °C

Anal. Calc for $C_{35}H_{49}N_{11}O_9S$ (799.91): C 52.55, H 6.17, N 19.26; found: C 51.6, H 6.06, N 18.5.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3340 (w), 2924 (w), 1726 (m), 1712 (w), 1691 (w), 1657 (w), 1630 (s), 1562 (m), 1547 (s), 1502 (w), 1462 (m), 1369 (w), 1286 (m), 1236 (s), 1144 (s), 1043 (w), 840 (w), 781 (w), 733 (w), 663 (m), 604 (w).

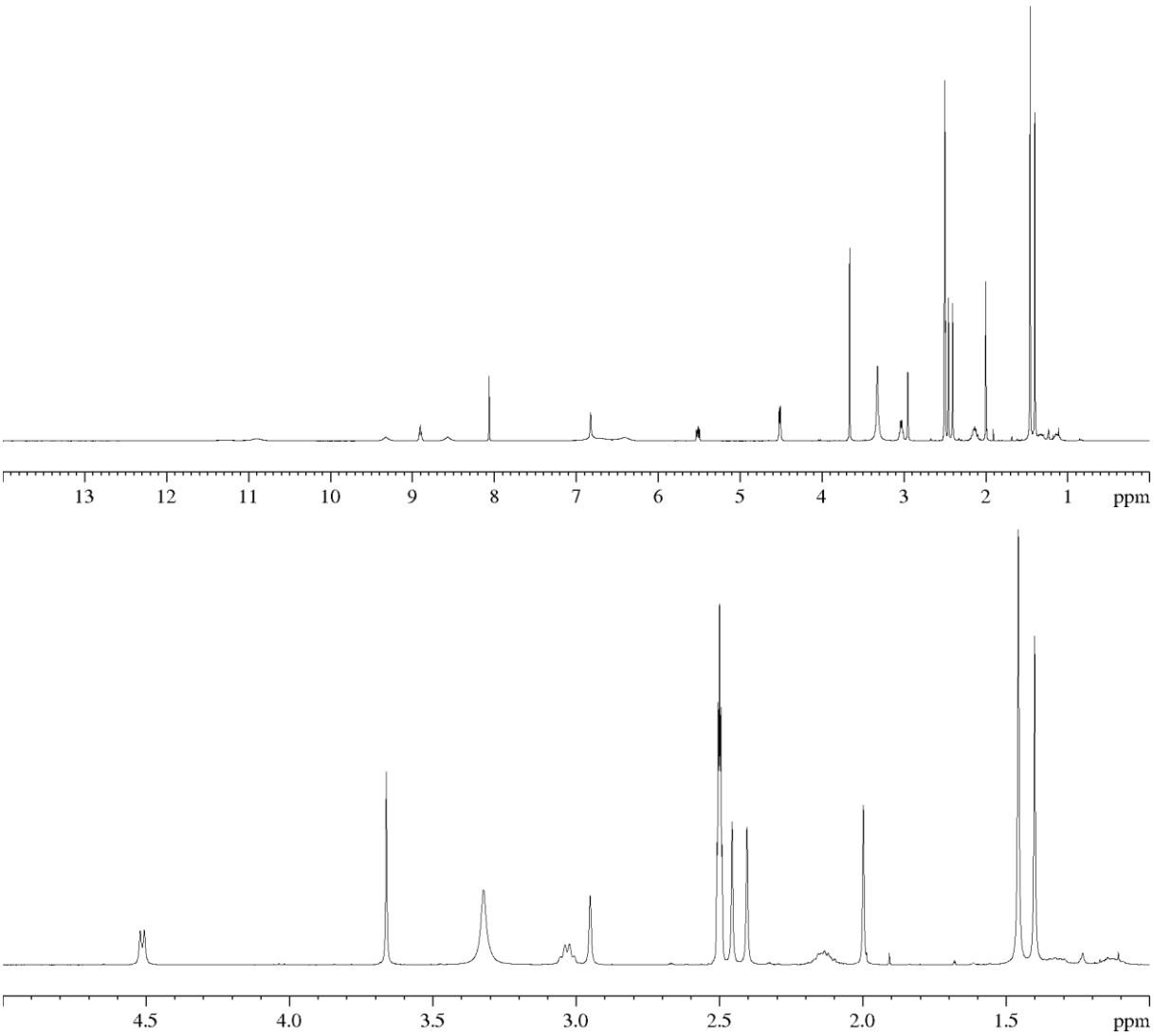


Figure S20: ^{1}H-NMR spectrum of (*rac*)-**4** (298 K, 400 MHz, DMSO-d_6).

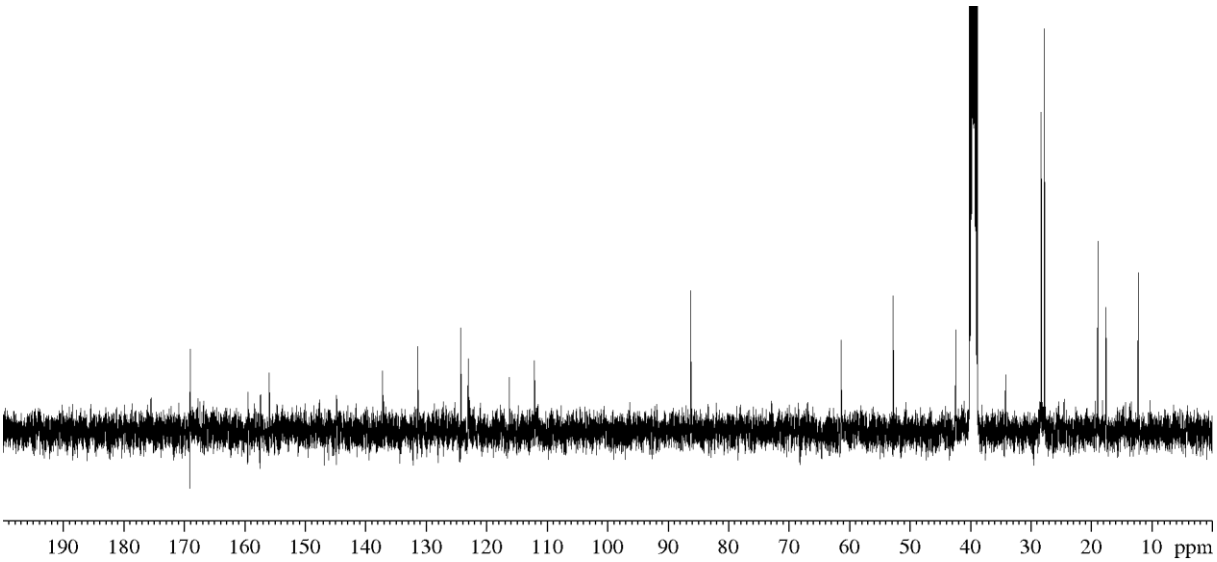
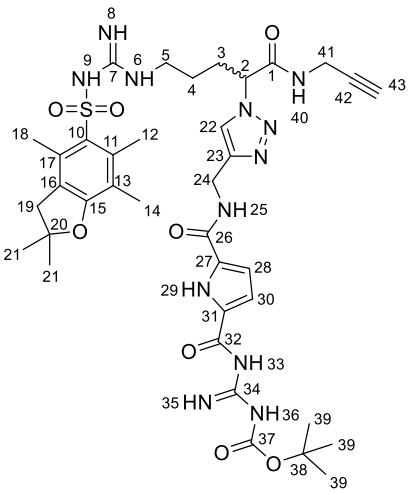


Figure S21: ^{13}C-NMR spectrum of (*rac*)-**4** (298 K, 101 MHz, DMSO-d_6).

Compound (*rac*)-5:



Methyl ester (*rac*)-**4** (60.0 mg, 75.0 µmol, 1 eq) was dissolved in tetrahydrofuran (10 mL). An aqueous solution of lithium hydroxide (5.39 mg, 225 mmol, 3 eq) in water (2.5 mL) was added. The solution was stirred for 3 hours at room temperature. Ethyl acetate (20 mL) was added to the solution and the aqueous phase was extracted repeatedly with ethyl acetate (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo.* Evaporation of organic solvents gave the Me-deprotected compound as a white solid (57 mg), which could directly be used for the next step. The crude carboxylic acid (45 mg, 57.3 µmol, 1 eq), propargylamine (6.31 mg, 115 µmol, 2 eq) and 4-methyl-morpholine (29.0 mg, 286 µmol, 5 eq) were dissolved in dry dimethyl-formamide (10 mL) under argon atmosphere. After stirring for 10 minutes at room temperature, HCTU (70.9 mg, 172 µmol, 2 eq) was added the mixture was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (50 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2.5 cm x 20 cm, dichloromethane:methanol:ammonia$_{(25\% \text{ in } H2O)}$ = 9:0.9:0.1) to afford a (*rac*)-**5** as a white solid (31 mg, 37.7 µmol, 65.2%).

Chemical formular: $C_{37}H_{50}N_{12}O_8S$ **Molecular weight:** 822.94 g/mol

^{1}H-NMR (400 MHz, DMSO-d$_6$) [ppm] = 11.21 (bs, 1 H, H_{29}), 10.85 (bs, 1 H, H_{35}), 9.32 (bs, 1 H, H_{33}), 8.94 (t, ^2J = 5.2 Hz, 1 H, H_{40}), 8.86 (t, ^2J = 5.6 Hz, 1 H, H_{25}), 8.56 (bs, 1 H, H_{36}), 8.03 (s, 1 H, H_{22}), 6.82 (m, 2 H, $H_{28, 30}$), 6.73-6.40 (m, 3 H, $H_{6, 8, 9}$), 5.25 (t, ^2J = 7.4 Hz, 1 H, H_2), 4.50 (t, ^3J = 4.6 Hz, 2 H, H_{24}), 3.89 (dd, ^3J = 5.4 Hz, ^4J = 2.3 Hz, 2 H, H_{41}), 3.15 (t, ^4J = 2.6 Hz, 1 H, H_{43}), 3.03 (q, ^2J = 5.4 Hz, 2 H, H_5), 2.95 (s, 2 H, H_{19}), 2.46 (s, 3 H, H_{18}), 2.40 (s, 3 H, H_{12}), 2.04-1.97 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.46 (s, 9 H, H_{39}), 1.40 (s, 6 H, H_{21}), 1.30-1.23 (s, 2 H, H_4).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 167.5 (2 C, $C_{1, 37}$), 159.5 (2 C, $C_{26, 32}$), 157.5 (1 C, C_{15}), 156.0 (2 C, $C_{7, 34}$), 144.8 (1 C, C_{23}), 137.3 (1 C, C_{10}), 134.1 (2 C, $C_{27, 31}$), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 121.9 (1 C, C_{22}), 116.3 (1 C, C_{13}), 112.1 (2 C, $C_{28, 30}$), 86.3 (1 C, C_{20}), 80.3 (1 C, C_{42}), 73.7 (1 C, C_{43}), 62.3 (1 C, C_2), 42.5 (2 C, $C_{19, 38}$), 39.3 (1 C, C_5), 34.2 (1 C, C_{24}), 29.5 (1 C, C_{41}), 28.3 (3 C, C_{39}), 28.2 (1 C, C_3), 27.8 (1 C, C_{21}), 25.5 (1 C, C_4), 18.9 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 823.3667 (calcd 823.3668 for $[M+H]^+$), 845.3487 (calcd 845.3487 for $[M+Na]^+$).

Melting point: 194 °C

Anal. Calc for $C_{37}H_{50}N_{12}O_8S$ (822.94): C 54.00, H 6.12, N 20.42; found: C 52.8, H 6.08, N 20.0.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3340 (w), 2924 (w), 1726 (m), 1712 (w), 1691 (w), 1657 (w), 1630 (s), 1562 (s), 1547 (s), 1461 (m), 1369 (w), 1286 (s), 1144 (s), 841 (w), 732 (w), 663 (m), 604 (w).

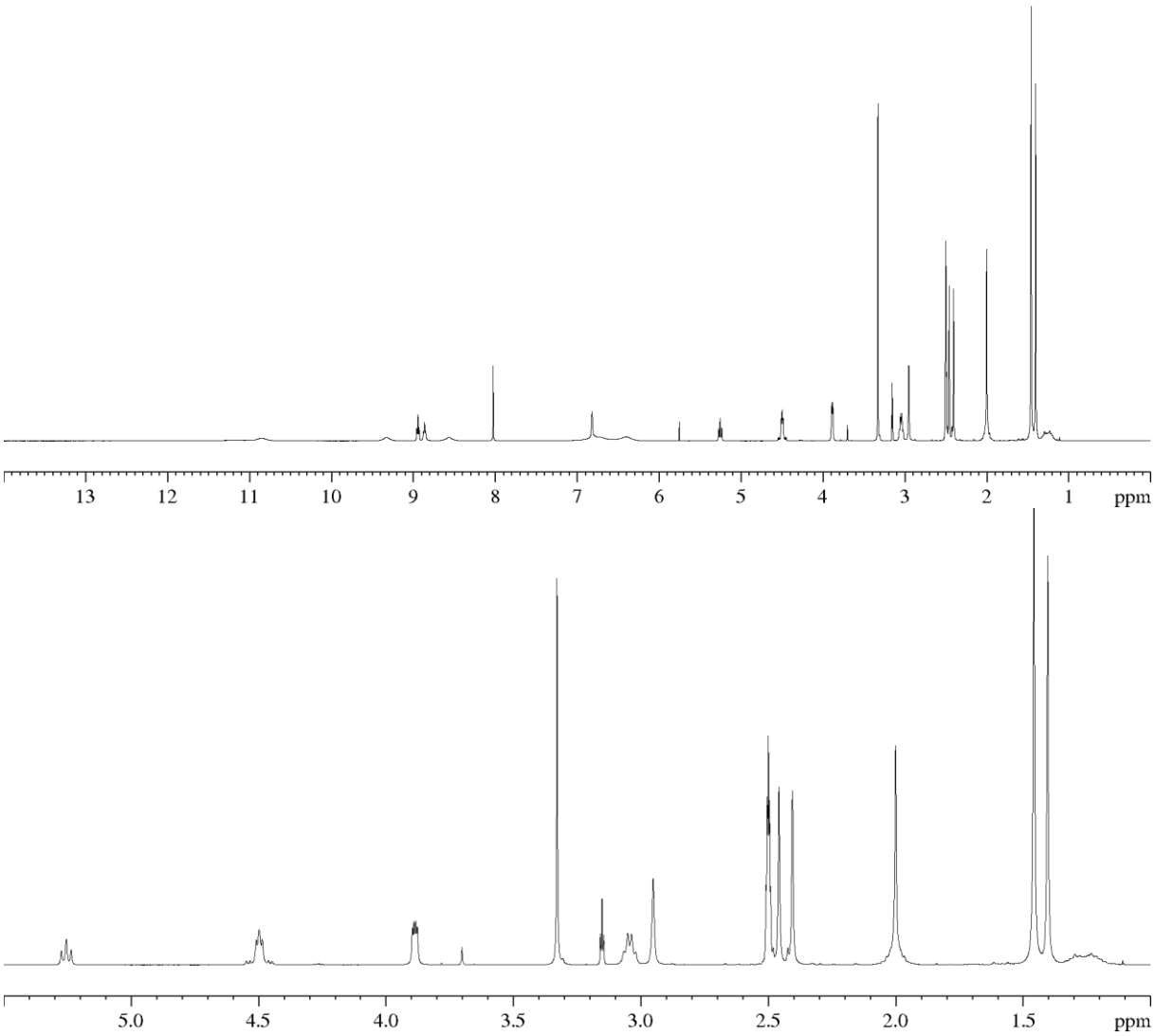


Figure S22: ^{1}H-NMR spectrum of (*rac*)-**5** (298 K, 400 MHz, DMSO-d_6).

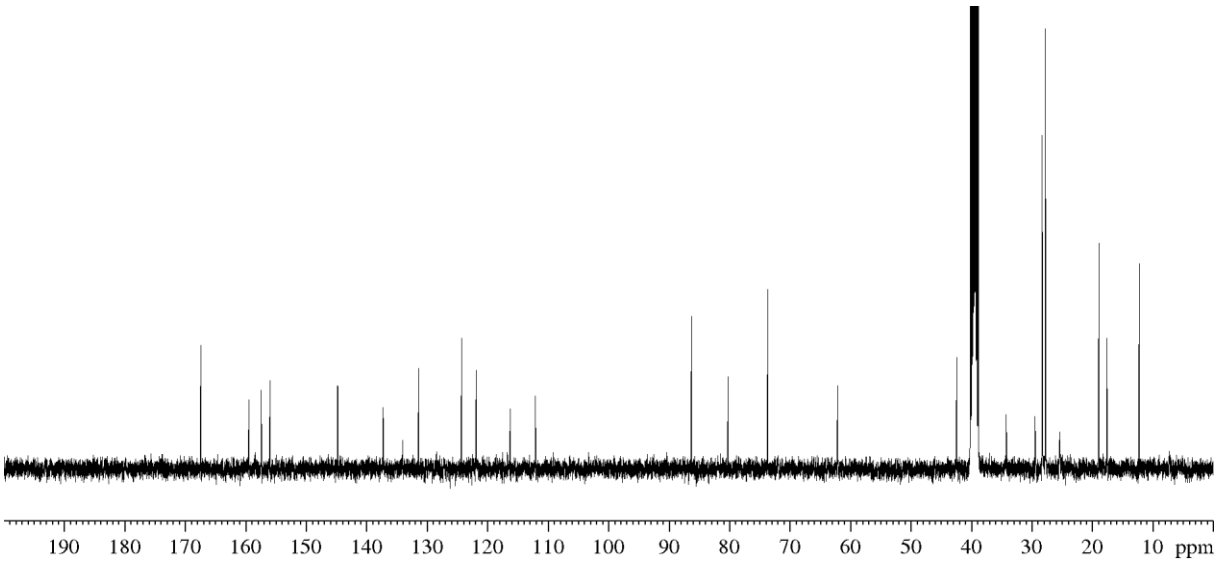
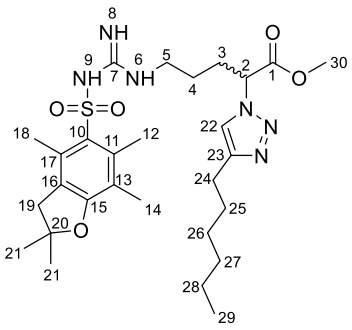


Figure S23: ^{13}C-NMR spectrum of (*rac*)-**5** (298 K, 101 MHz, DMSO-d_6).

Compound (*rac*)-6:



Azido acid (*rac*)-**2** (100 mg, 214 µmol, 1 eq) and 1-octyne (35.4 mg, 322 µmol, 1.5 eq) were dissolved in tetrahydrofuran (20 mL). A solution of copper sulfate pentahydrate (5.34 mg, 21.4 µmol, 0.1 eq) and sodium ascorbate (8.48 mg, 42.8 µmol, 0.2 eq) in degassed water (1 mL) was freshly prepared. An aliquot of the fresh catalyst solution (100 µL, 2.14 µmol, 0.01 eq) was added and the reaction was stirred at room temperature overnight. The crude mixture was concentrated *in vacuo* and then dissolved in ethyl acetate (20 mL). The organic phase was washed with saturated sodium chloride solution (3 x 50 mL) and water (3 x 50 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2.5 cm x 18 cm, dichloromethane:ethyl acetate = 1:1) to afford a (*rac*)-**6** as a white solid (96 mg, 166 µmol, 77.6%).

Chemical formular: $C_{28}H_{44}N_6O_5S$ **Molecular weight:** 576.76 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 7.91 (s, 1 H, H_{22}), 6.69-6.41 (m, 3 H, $H_{6, 8, 9}$), 5.44 (dd, ^3J = 9.8 Hz, ^3J = 5.5 Hz, 1 H, H_2), 3.66 (s, 3 H, H_{30}), 3.04 (q, ^3J = 7.7 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.61 (t, ^3J = 7.4 Hz, 2 H, H_{24}), 2.46 (s, 3 H, H_{18}), 2.41 (s, 3 H, H_{12}), 2.16-2.08 (m, 2 H, H_3), 2.00 (s, 3 H, H_{14}), 1.62-1.55 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}), 1.27-1.12 (m, 8 H, H_{25-28}), 0.85 (t, ^3J = 6.9 Hz, 3 H, H_{29}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 169.2 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 147.0 (1 C, C_{23}), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 121.7 (1 C, C_{22}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 61.3 (1 C, C_2), 52.7 (1 C, C_{30}), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 31.0 (1 C, C_{CH2}), 28.8 (1 C, C_{CH2}), 28.3 (2 C, C_{21}), 28.2 (1 C, C_3), 25.4 (2 C, C_{CH2}), 25.0 (1 C, C_4), 22.0 (1 C, C_{CH2}), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 13.9 (1 C, C_{CH3}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 577.3176 (calcd 577.3167 for $[M+H]^+$), m/z = 599.2989 (calcd 599.2989 for $[M+Na]^+$).

Melting point: 102 °C

Anal. Calc for $C_{28}H_{44}N_6O_9S$ (576.76): C 58.31, H 7.69, N 14.57; found: C 58.3, H 6.56, N 14.6.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ = 3437 (w), 3336(w), 3136 (w), 2929 (m), 2852 (w), 1747 (m), 1618 (w), 1540 (s), 1452 (m), 1255 (m), 1090 (s), 993 (w), 804 (w), 783 (m), 732 (w), 659 (s), 642 (m), 615 (w).

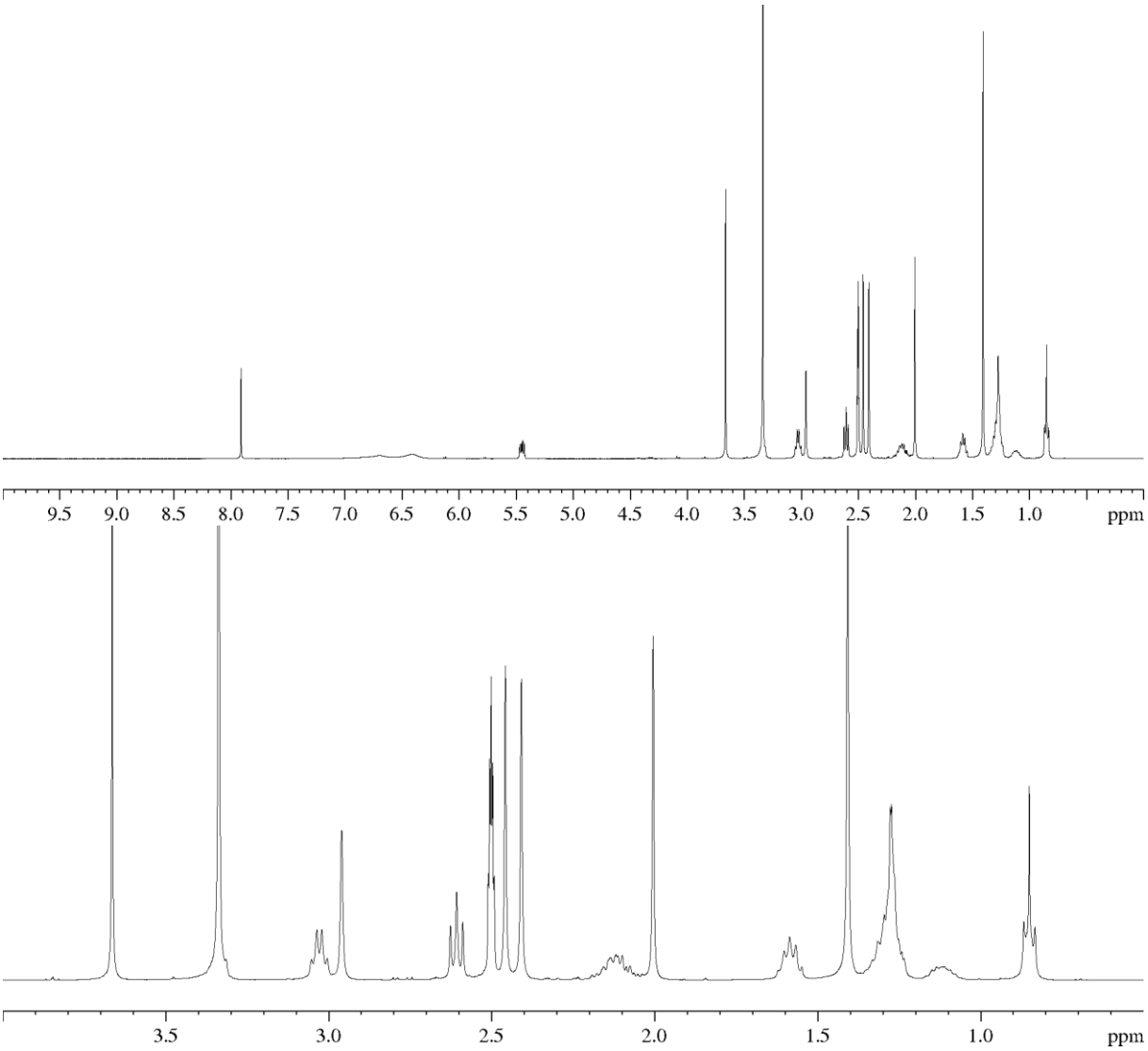


Figure S24: ^{1}H-NMR spectrum of (*rac*)-**6** (298 K, 400 MHz, DMSO-d_6).

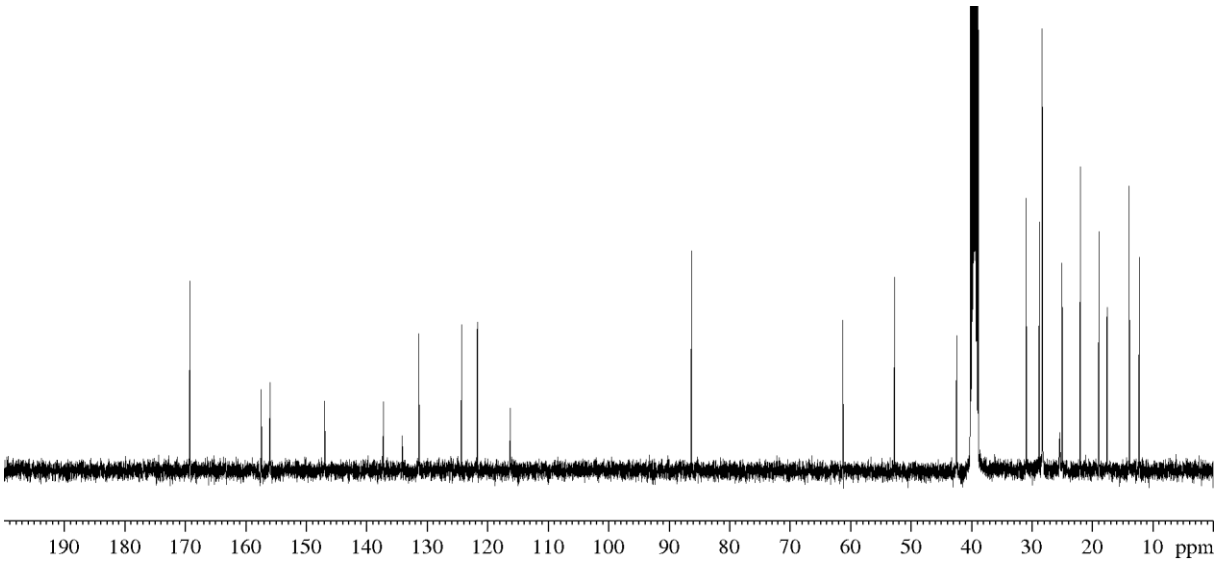
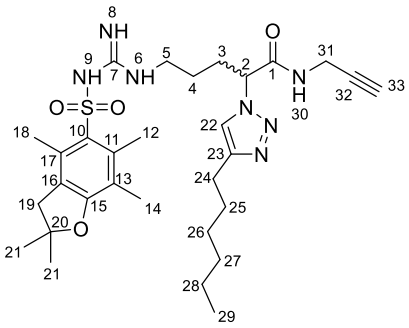


Figure S25: ^{13}C-NMR spectrum of (*rac*)-**6** (298 K, 101 MHz, DMSO-d_6).

Compound (*rac*)-7:



Methyl ester (*rac*)-**6** (75.0 mg, 130 µmol, 1 eq) was dissolved in tetrahydrofuran (10 mL). An aqueous solution of lithium hydroxide (9.34 mg, 390 µmol, 3 eq) in water (2.5 mL) was added. The solution was stirred for 3 hours at room temperature. Ethyl acetate (20 mL) was added to the solution and the aqueous phase was extracted repeatedly with ethyl acetate (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Evaporation of organic solvents gave the Me-deprotected compound as a white solid (55 mg), which could directly be used for the next step. The crude carboxylic acid (40.0 mg, 66.7 µmol, 1 eq), propargylamine (7.35 mg, 133 µmol, 2 eq) and 4-methylmorpholine (33.7 mg, 334 µmol, 5 eq) were dissolved in dry dimethylformamide (10 mL) under argon atmosphere. After stirring 10 minutes at room temperature, HCTU (55.1 mg, 133 µmol, 2 eq) was added and the solution and was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (20 mL) and the organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2.5 cm x 20 cm, dichloromethane:ethyl acetate = 1:2) to afford a (*rac*)-**7** as a white solid (32.0 mg, 53.4 µmol, 52.3%).

Chemical formular: $C_{30}H_{45}N_7O_4S$ **Molecular weight:** 599.80 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 8.88 (t, ^3J = 5.6 Hz, 1 H, H_{30}), 7.87 (s, 1 H, H_{22}), 6.70-6.39 (m, 3 H, $H_{6, 8, 9}$), 5.20 (t, ^3J = 5.8 Hz, 1 H, H_2), 3.88 (dd, ^3J = 5.5 Hz, ^4J = 2.6 Hz, 2 H, H_{31}), 3.16 (t, ^4J = 2.6 Hz, 1 H, H_{33}), 3.03 (q, ^3J = 7.7 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.59 (t, ^3J = 7.8 Hz, 2 H, H_{24}), 2.46 (s, 3 H, H_{18}), 2.41 (s, 3 H, H_{12}), 2.00 (s, 3 H, H_{14}), 1.98 (m, 2 H, H_3), 1.59-1.56 (m, 2 H, H_4), 1.41 (s, 6 H, H_{21}), 1.27-1.18 (m, 8 H, H_{25-28}), 0.85 (t, ^3J = 7.4 Hz, 3 H, H_{29}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 167.7 (1 C, C_1), 157.5 (1 C, C_{15}), 156.0 (1 C, C_7), 146.9 (1 C, C_{23}), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 120.7 (1 C, C_{22}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 80.3 (1 C, C_{32}), 73.6 (1 C, C_{33}), 62.0 (1 C, C_2), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 31.0 (1 C, C_{CH2}), 29.4 (1 C, C_{CH2}), 28.8 (2 C, C_{CH2}), 28.31 (1 C, C_3), 28.29 (2 C, C_{21}), 28.2 (1 C, C_{31}), 25.1 (1 C, C_4), 22.0 (1 C, C_{CH2}), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 13.9 (1 C, C_{CH3}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 600.3324 (calcd 600.3327 for $[M+H]^+$), m/z = 622.3139 (calcd 622.3146 for $[M+Na]^+$).

Melting point: 104 °C

Anal. Calc for $C_{30}H_{45}N_7O_4S$ (599.80): C 60.08, H 7.56, N 16.35; found: C 59.8, H 7.39, N 16.1.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ =3440 (w), 3311 (w), 3149 (w), 2929 (w), 2852 (w), 1677 (w), 1618 (m), 1540 (s), 1452 (m), 1243 (m), 1155 (w), 1089 (s), 1051 (w), 854 (w) 784 (m), 732 (w), 659 (s).

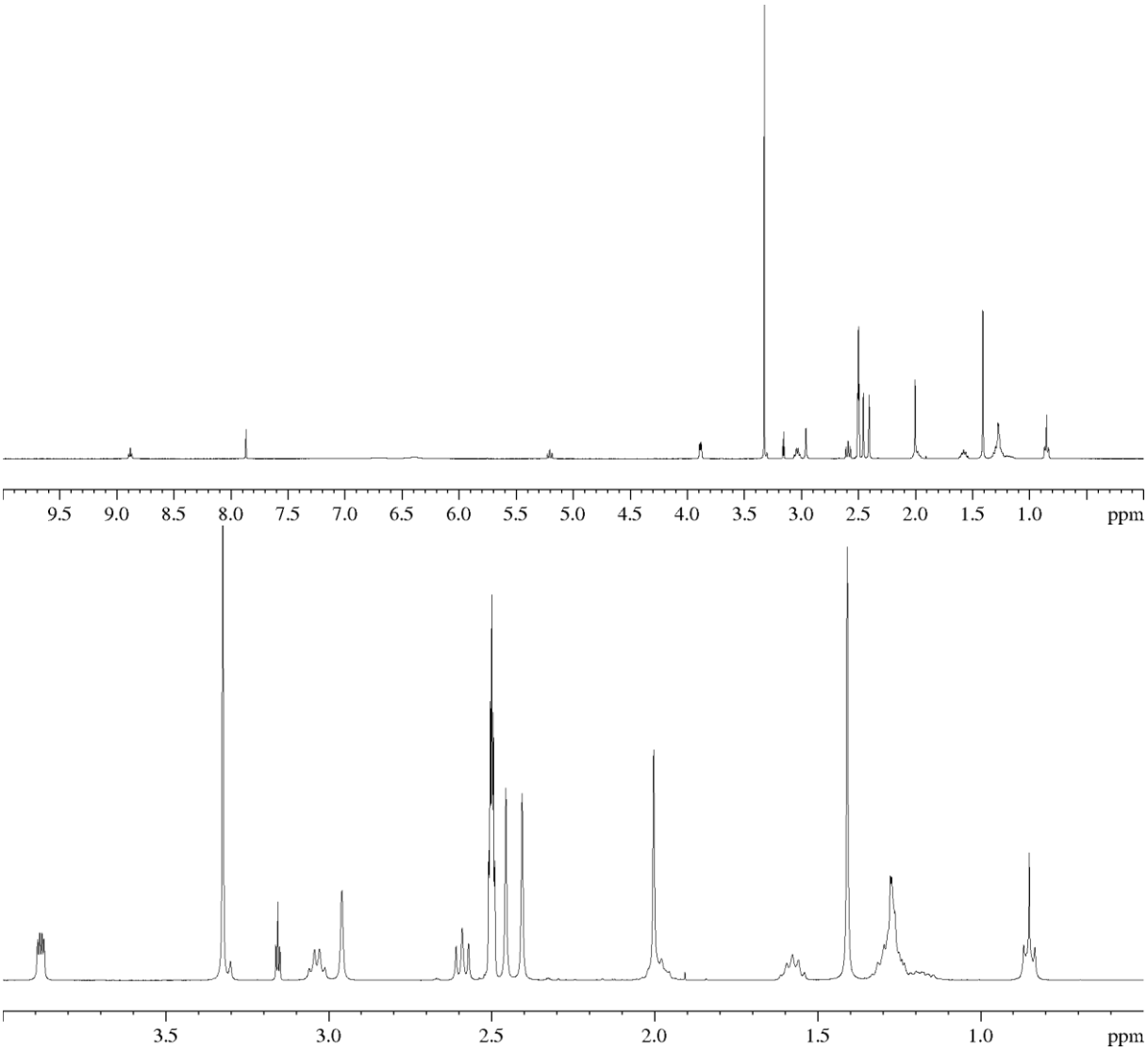


Figure S26: ^{1}H-NMR spectrum of (*rac*)-**7** (298 K, 400 MHz, DMSO-d_6).

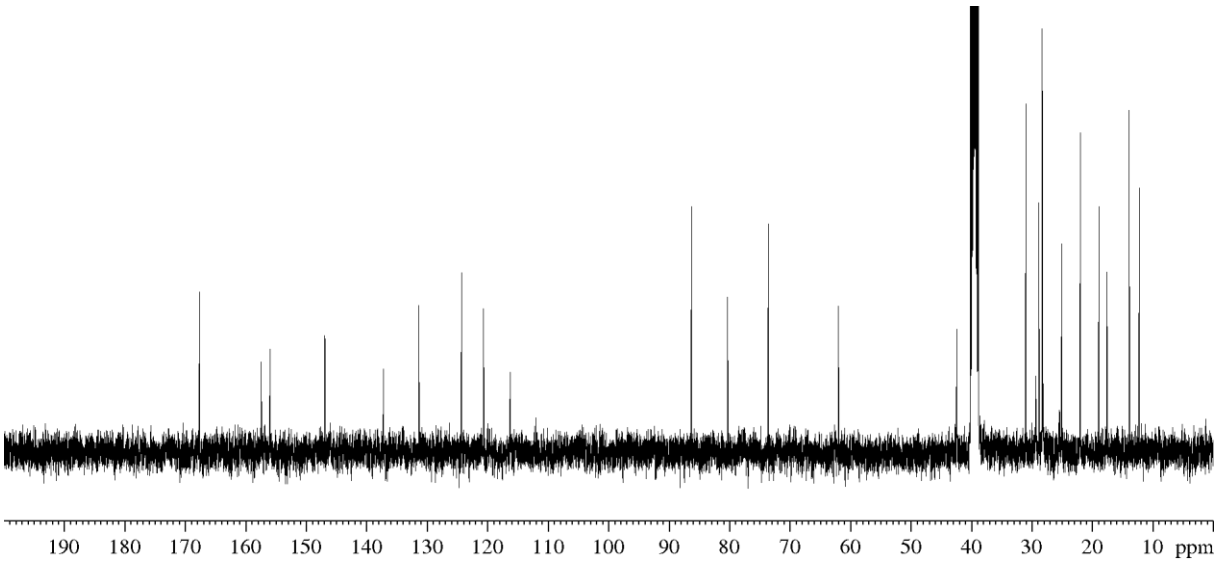
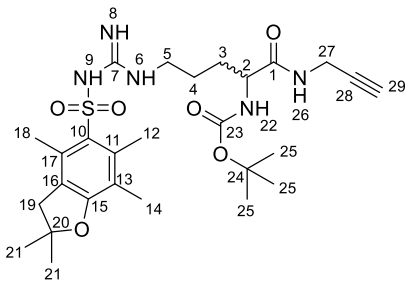


Figure S27: ^{13}C-NMR spectrum of (*rac*)-**7** (298 K, 101 MHz, DMSO-d_6).

Compound (*rac*)-9:



Boc-(*rac*)-Arg(Pbf)-OMe ((*rac*)-**8)** (100 mg, 190 µmol, 1 eq), propargylamine (15.7 mg, 285 µmol, 1.5 eq) and 4-methylmorpholine (71.1 mg, 702 µmol, 3.7 eq) were dissolved in dry dimethylformamide (20 mL) under argon atmosphere. After stirring for 10 minutes at room temperature, HCTU (94.3 mg, 228 µmol, 1.2 eq) was added and the solution and was stirred overnight at room temperature. The crude mixture was concentrated *in vacuo*. The crude mixture was dissolved in ethyl acetate (20 mL). The organic phase was washed with saturated sodium chloride solution (3 x 20 mL) and water (3 x 20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (2 cm x 15 cm, dichloromethane:ethyl acetate = 1:4) to afford a (*rac*)**-9** as a white solid (92.0 mg, 163 µmol, 85.8%).

Chemical formular: $C_{27}H_{41}N_5O_6S$ **Molecular weight:** 563.71 g/mol

^{1}H-NMR (600 MHz, DMSO-d$_6$) [ppm] = 8.25 (t, 1 H, ^3J = 5.4 Hz, H_{26}), 6.83 (d, 1 H, ^3J = 8.2 Hz, H_{22}), 6.66-6.37 (m, 3 H, $H_{6, 8, 9}$), 3.89-3.85 (m, 1 H, H_2), 3.84-8.83 (m, 2 H, H_{27}), 3.09 (t, 1 H, ^4J = 2.4 Hz, H_{29}), 3.01 (q, ^3J = 6.6 Hz, 2 H, H_5), 2.96 (s, 2 H, H_{19}), 2.47 (s, 3 H, H_{18}), 2.42 (s, 3 H, H_{12}), 2.00 (s, 3 H, H_{14}), 1.57-1.34 (m, 4 H, $H_{3, 4}$), 1.41 (s, 6 H, H_{21}), 1.37 (s, 9 H, H_{25}).

^{13}C-NMR (101 MHz, DMSO-d$_6$) [ppm] = 171.8 (1 C, C_{23}), 157.4 (1 C, C_{15}), 156.0 (1 C, C_7), 155.3 (1 C, C_1), 137.3 (1 C, C_{10}), 131.4 (2 C, $C_{11, 17}$), 124.3 (1 C, C_{16}), 116.3 (1 C, C_{13}), 86.3 (1 C, C_{20}), 81.0 (1 C, C_{28}), 78.0 (2 C, $C_{24, 27}$), 73.0 (1 C, C_{29}), 53.8 (1 C, C_2), 42.5 (1 C, C_{19}), 39.3 (1 C, C_5), 28.3 (3 C, C_{25}), 28.2 (1 C, C_3), 27.9 (2 C, C_{21}), 25.6 (1 C, C_4), 19.0 (1 C, C_{12}), 17.6 (1 C, C_{18}), 12.3 (1 C, C_{14}).

HR-ESI-pos (MeOH): m/z = 564.2850 (calcd 564.2850 for $[M+H]^+$), m/z = 586.2668 (calcd 586.2670 for $[M+Na]^+$).

Melting point: 113 °C

Anal. Calc for $C_{27}H_{41}N_5O_6S$ (563.71): C 57.53, H 7.33, N 12.42; found: C 56.6, H 7.16, N 12.1.

IR (ATR) [cm^{-1}] $\tilde{\nu}$ =3440 (w), 3309 (m), 2972 (w), 2931 (w), 1684 (m), 1653 (m), 1635 (m), 1558 (s), 1541 (s), 1508 (m), 1458 (m), 1367 (m), 1244 (m), 1161 (m), 1090 (s), 997 (w), 904 (w), 850 (m), 812 (w), 783 (m), 735 (w), 658 (s), 615 (w).

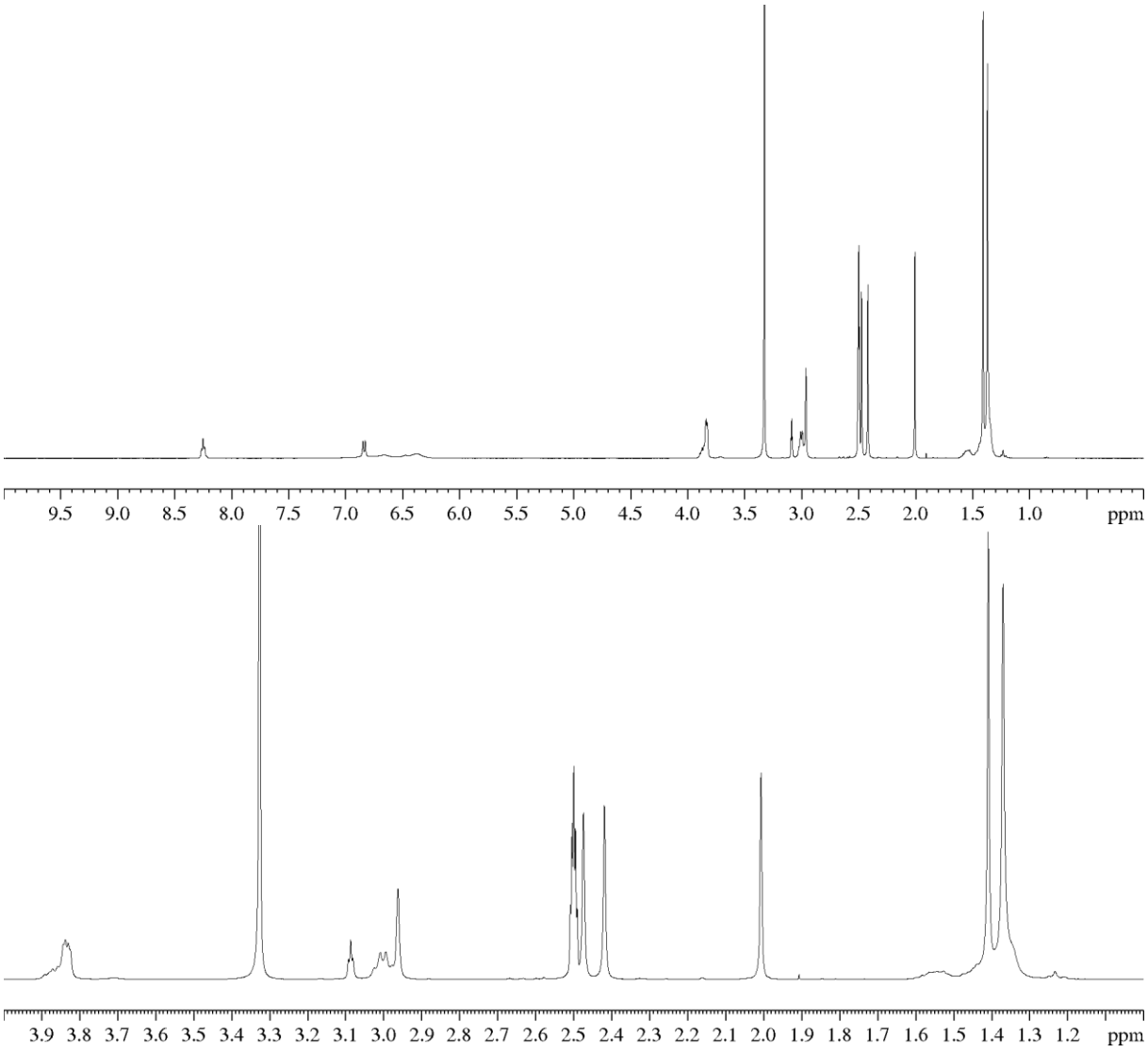


Figure S28: ^{1}H-NMR spectrum of (*rac*)-**9** (298 K, 400 MHz, DMSO-d_6).

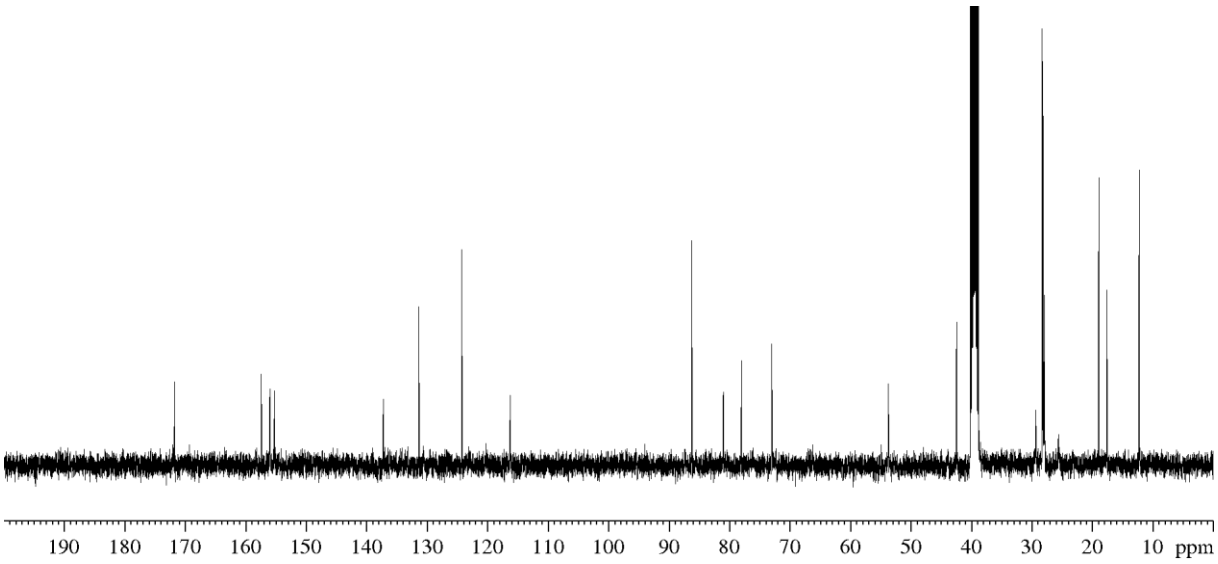
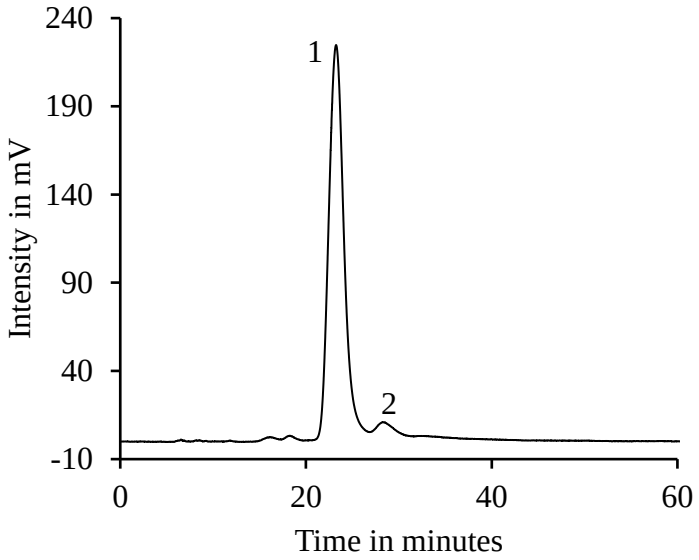
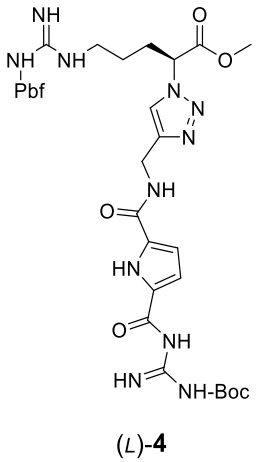


Figure S29: ^{13}C-NMR spectrum of (*rac*)-**9** (298 K, 101 MHz, DMSO-d_6).

3 Chiral HPLC profiles

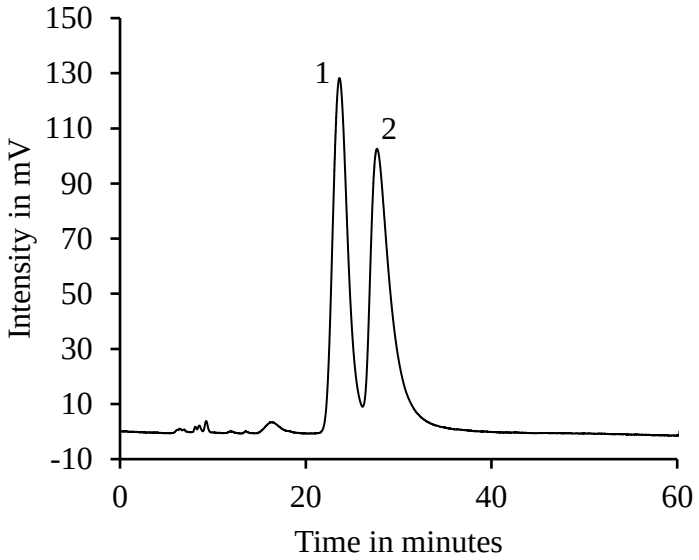


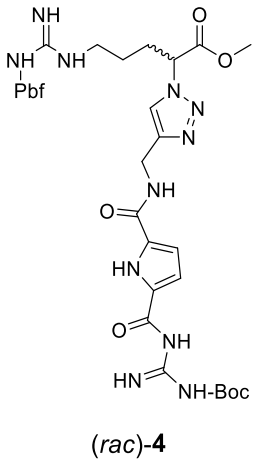


(*L*)-**4**

Peak No.	Ret. Time	Hight	Area	Percent
1	23.24	223.05	$2.523043 \cdot 10^7$	96.21
2	28.32	7.86	994125	3.79

Figure S30: Chiral HPLC of (*L*)-**4** measured with AD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic, 0.5 mL/min).

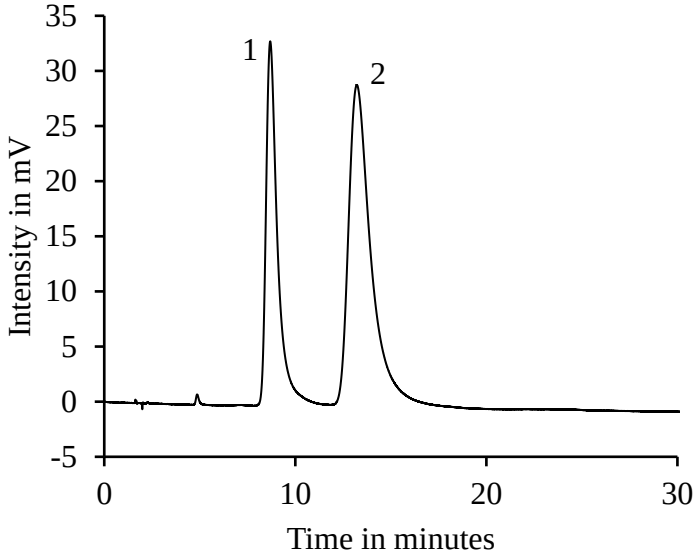


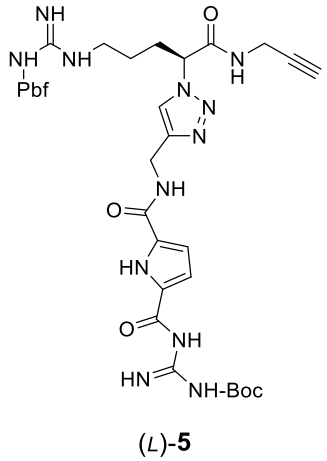


(*rac*)-**4**

Peak No.	Ret. Time	Hight	Area	Percent
1	23.62	128.70	$1.47713 \cdot 10^7$	47.16
2	27.68	102.98	$1.6553 \cdot 10^7$	52.84

Figure S31: Chiral HPLC of (*rac*)-**4** measured with OD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic, 0.5 mL/min).

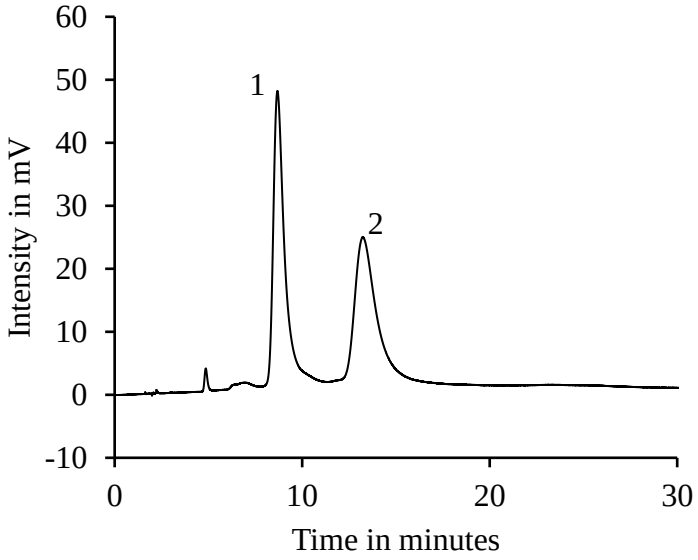


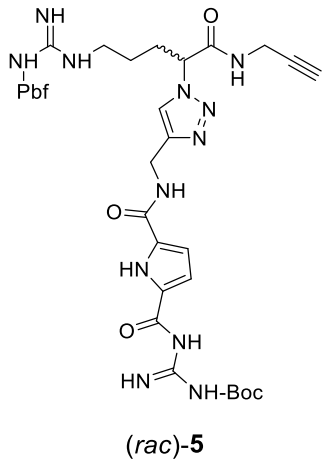


(*L*)-**5**

Peak No.	Ret. Time	Hight	Area	Percent
1	8.69	32.62	-	36.58
2	13.22	28.72	-	63.42

Figure S32: Chiral HPLC of (*L*)-**5** measured with IF-3 column at 305 nm (*n*-heptane:ethanol = 70:30, isocratic, 1.0 mL/min).

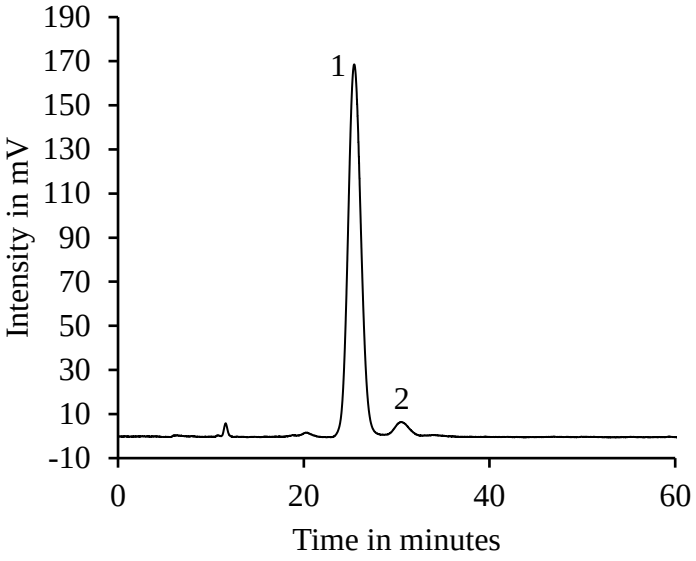


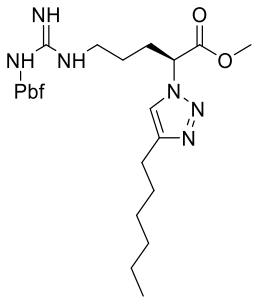


(*rac*)-**5**

Peak No.	Ret. Time	Hight	Area	Percent
1	8.68	47.93	-	49.90
2	13.24	24.58	-	50.10

Figure S33: Chiral HPLC of (*rac*)-**5** measured with IF-3 column at 305 nm (*n*-heptane:ethanol = 70:30, isocratic, 1.0 mL/min).

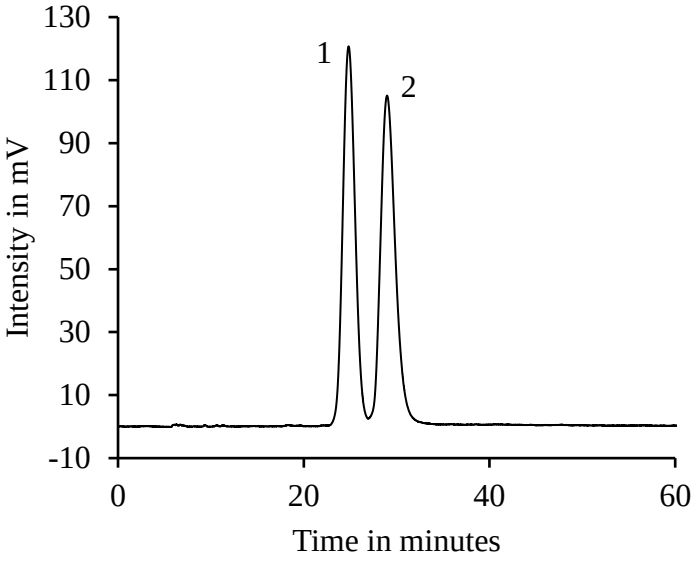


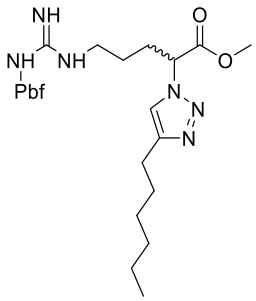


(*L*)-**6**

Peak No.	Ret. Time	Hight	Area	Percent
1	25.43	168.79	$1.63035 \cdot 10^7$	96.06
2	30.43	6.33	668343.8	3.94

Figure S34: Chiral HPLC of (*L*)-**6** measured with AD-H column at 220 nm (*n*-hexane:isopropanol = 85:15, isocratic, 0.5 mL/min).

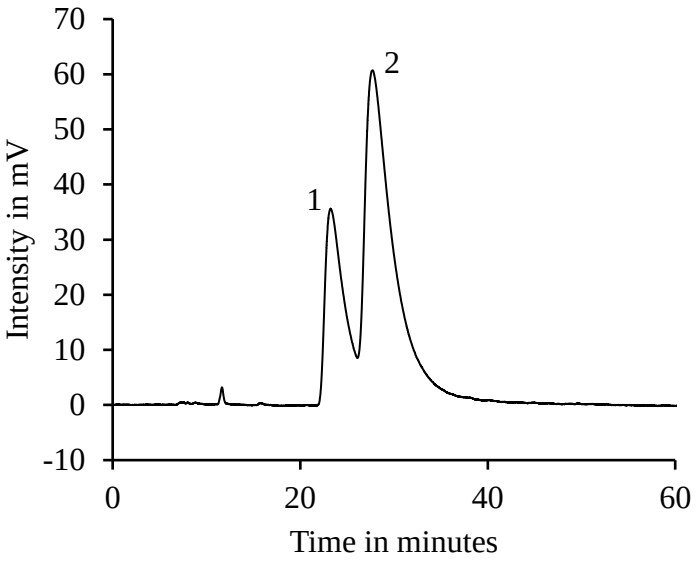


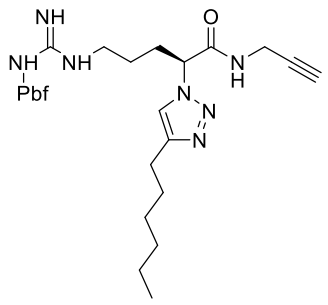


(*rac*)-**6**

Peak No.	Ret. Time	Hight	Area	Percent
1	24.82	120.31	$1.10827 \cdot 10^7$	48.83
2	28.96	104.50	$1.16154 \cdot 10^7$	51.17

Figure S35: Chiral HPLC of (*rac*)-**6** measured with AD-H column at 220 nm (*n*-hexane:isopropanol = 85:15, isocratic, 0.5 mL/min).

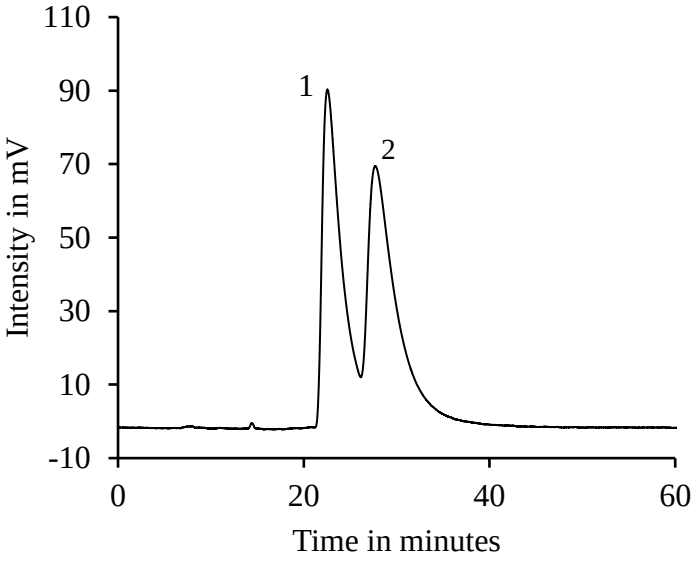


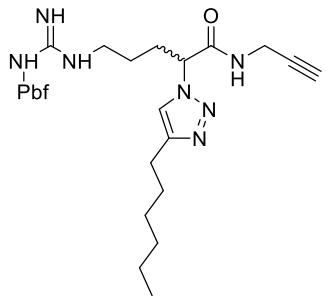


(*L*)-**7**

Peak No.	Ret. Time	Hight	Area	Percent
1	23.26	35.65	5007249	27.29
2	27.70	60.71	$1.334064 \cdot 10^7$	72.71

Figure S36: Chiral HPLC of (*L*)**-7** measured with OD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic, 0.5 mL/min).

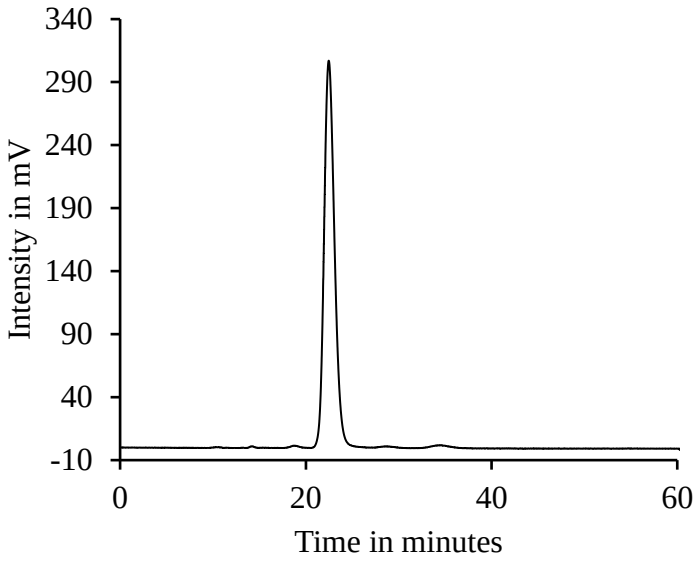


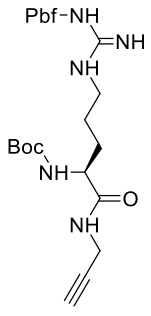


(*rac*)-**7**

Peak No.	Ret. Time	Hight	Area	Percent
1	22.56	91.88	$1.31433 \cdot 10^7$	45.46
2	27.72	71.07	$1.57666 \cdot 10^7$	54.53

Figure S37: Chiral HPLC of (*rac*)**-7** measured with OD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic 0.5 mL/min).

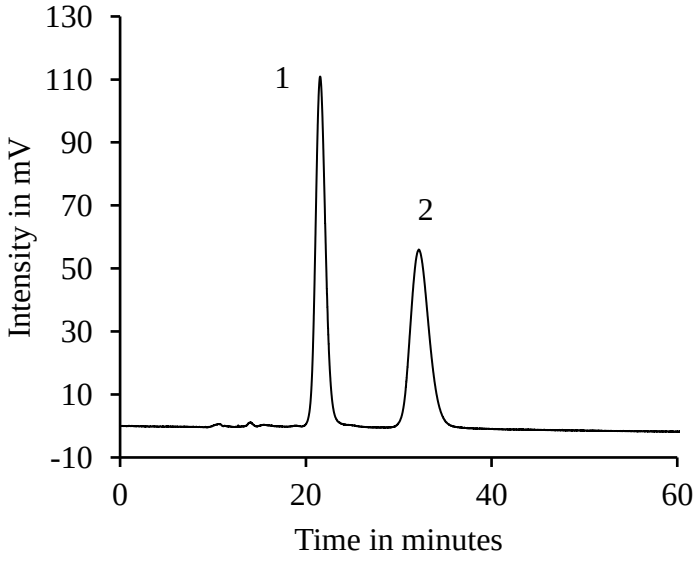


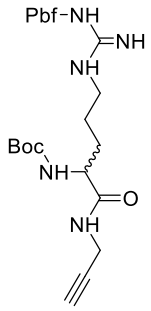


(*L*)-**9**

Peak No.	Ret. Time	Hight	Area	Percent
1	22.47	304.81	$2.322887 \cdot 10^7$	100

Figure S38: Chiral HPLC of (*L*)-**9** measured with AD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic, 0.3 mL/min).





(*rac*)-**9**

Peak No.	Ret. Time	Hight	Area	Percent
1	21.54	110.71	8267932	51.58
2	32.18	56.19	7760326	48.42

Figure S39: Chiral HPLC of (*rac*)-**9** measured with AD-H column at 220 nm (*n*-hexane:isopropanol = 75:25, isocratic 0.3 mL/min).

4 References

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[2] D. J. Ward, H. Van de Langemheen, E. Koehne, A. Kreidenweiss, R. M. J. Liskamp, *Bioorg. Med. Chem*. **2019**, *13*, 2857-2870.

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