Supporting Information

Diastereoselective Synthesis of [1]Rotaxane via Active Metal Template Strategy.

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I. Chemistry Section

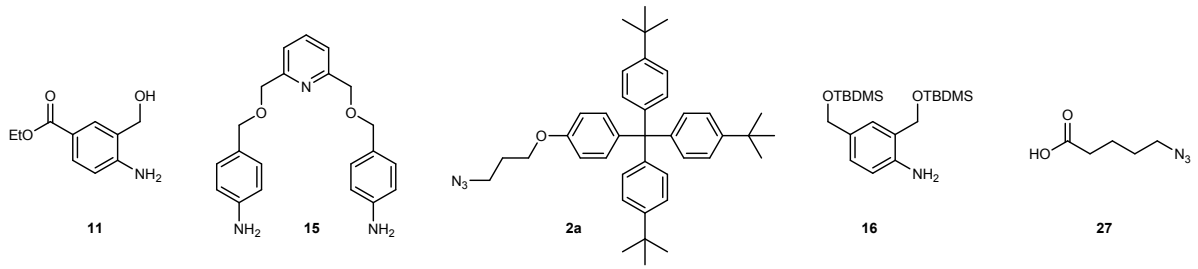
I.1. General experimental methods

Synthesis: All reactions were performed under an argon atmosphere. Unless otherwise stated, solvents used were of HPLC quality. For oxygen sensitive reactions like copper catalysed reaction, solvents were deoxygenated by purging with argon. Chemicals were of analytical grade from commercial sources and were used without further purification. Reaction were monitored using precoated silica gel TLC plates MACHEREY-NAGEL ALUGRAM® SIL G/UV_{254}. (0.2 mm silica gel 60). Spots were visualized under 254 nm UV light and/or by dipping the TLC plate into a solution of phosphomolybdic acid (3 g) in ethanol (100 mL) followed by heating with a heat gun. Automatic flash chromatography was performed on Combi Flash 210i (Teledyne-Isco) with pre-packed column purchased from Interchim, Silicycle or Buchi. Particles size (from 50 µm to 15 µm) and column size (4 g to 280 g) were adapted according the difficulty of the purification and the quantity of crude product.

Analysis: ^{1}H, ^{13}C and ^{19}F NMR spectra were respectively recorded at 400 MHz, 100MHz and 376 MHz, on a Bruker 400 Avance III instrument, equipped with an ultrashielded plus magnet and a BBFO 5 mm broadband probe or at 500 MHz, 126 MHz, and 470 MHz on a Bruker 500 Avance NEO instrument, equipped with an ultrashielded magnet and a Prodigy cryoprobe. ^{1}H and ^{13}C NMR spectra of compound **(S)-3** were respectively recorded at 500 and 126 MHz on a BRUKER TXI-1H-13C-15N cryoprobe based on Rennes analytical platform PRISM. Chemical shifts (δ) are reported in parts per million (ppm) from low to high field and referenced to residual solvent peaks or using C_6F_6 as external reference for ^{19}F. Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity are used as follows: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, m = multiplet, dd = doublet of doublets. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform and by the mass spectrometry service or Poitiers (Platina) on a LC-QTof MaXis Impact, Bruker. Circular dichroism (CD) spectra were recorded on a Jasco (model J-815) spectropolarimeter equipped with a Peltier thermostated cell holder and Xe laser. Data were recorded in distillated methylene chloride at 20 °C using a 1 mm*1 cm cell. The obtained signals were processed by substracting solvent and cell contribution.

HPLC method: Reaction follow-up and compound purity were performed on DIONEX Ultimate 3000 with UV light set to 254 nm with MACHEREY-NAGEL Nucleoshell®(150/4.6, RP18, 5 µm) column in a thermostatically controlled oven at 30 °C. Spectra analysis was carried out with the software Chromeleon. Eluents were A (H_2O + 0.2 % TFA), B (MeCN) and solvent flow: 1.25 mL.min^{-1}. Method: linear gradient beginning with A/B 80:20 reaching A/B 0:100 within 8 minutes, then isocratic A/B 0:100 for 5 minutes and linear gradient toward A/B 80:20 within 2 minutes.

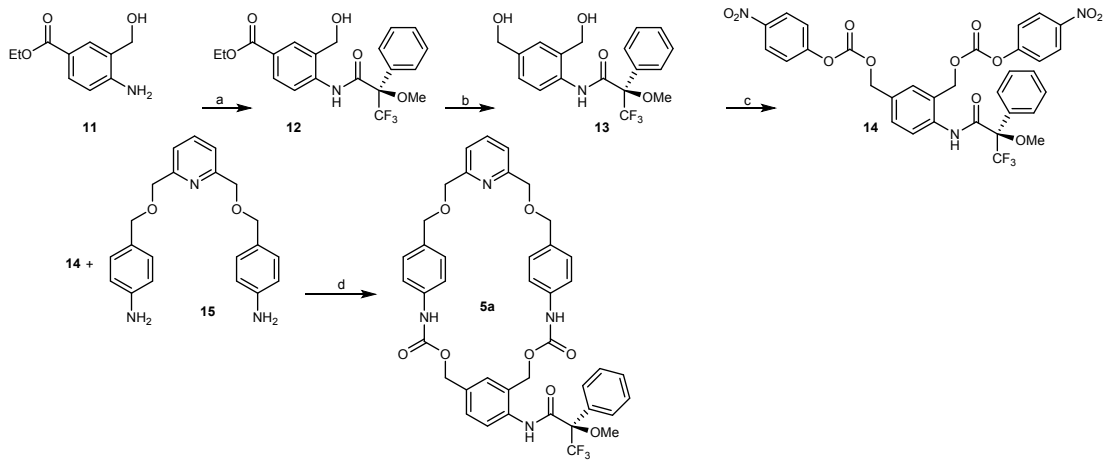
The following compounds were synthesized according to literature procedures:



Scheme S1. *References of literature procedures:* compound **11**,[1] compound **15**,[2] compound **2a**,[3] compound **16**,[4] compound **27**.[5]

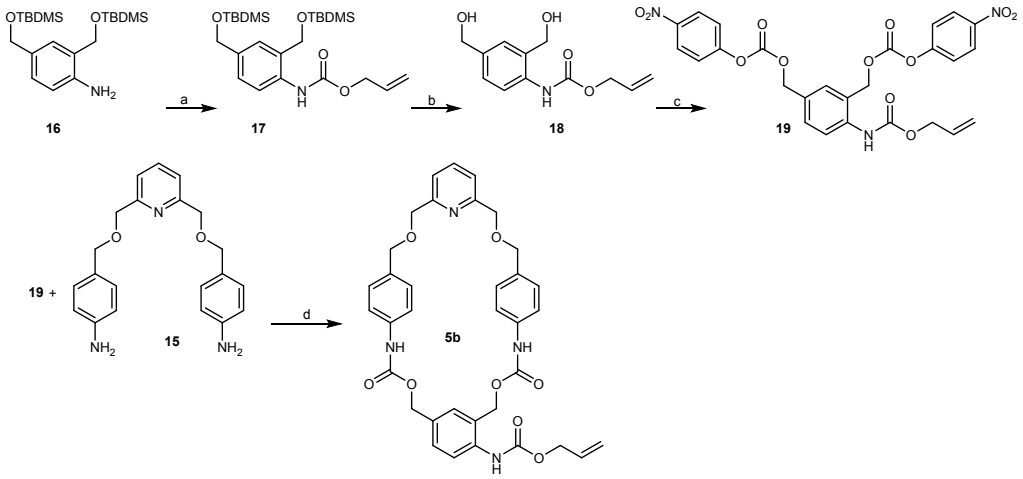
I.2. Synthetic schemes towards compounds 5a, 5b, (*S*)-1/(*R*)-1, 4, (*S*)-3/(*R*)-3, 2b, 29, (*S*)-7, (*S*)-32, (*S*)-9.

Compound **5a** was prepared according to the following strategy:



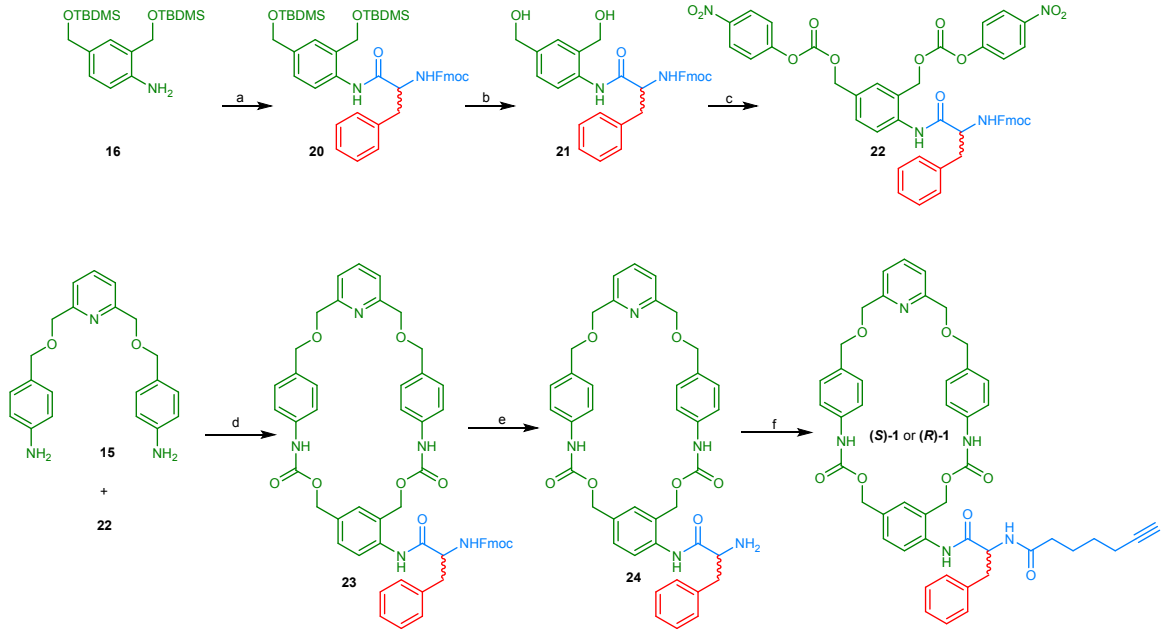
Scheme S2. *Reagents and conditions:* (a) DMF, MeCN, $CO(Cl)_2$, (*R*)-Mosher's acid, Et_3N, 0 °C to RT, 22 h, 36%; (b) DIBAL-H, THF, -78 °C, 1 h, 93%; (c) 4-nitrophenyl chloroformate, pyridine, DCM, 0 °C to RT, 5 h, 83%; (d) i) HOBt, DMF [0.08M], 33 °C, 8 h; ii) DMF [0.001M], 33 °C, 48 h, 36%.

Compound **5b** was prepared according to the following strategy:



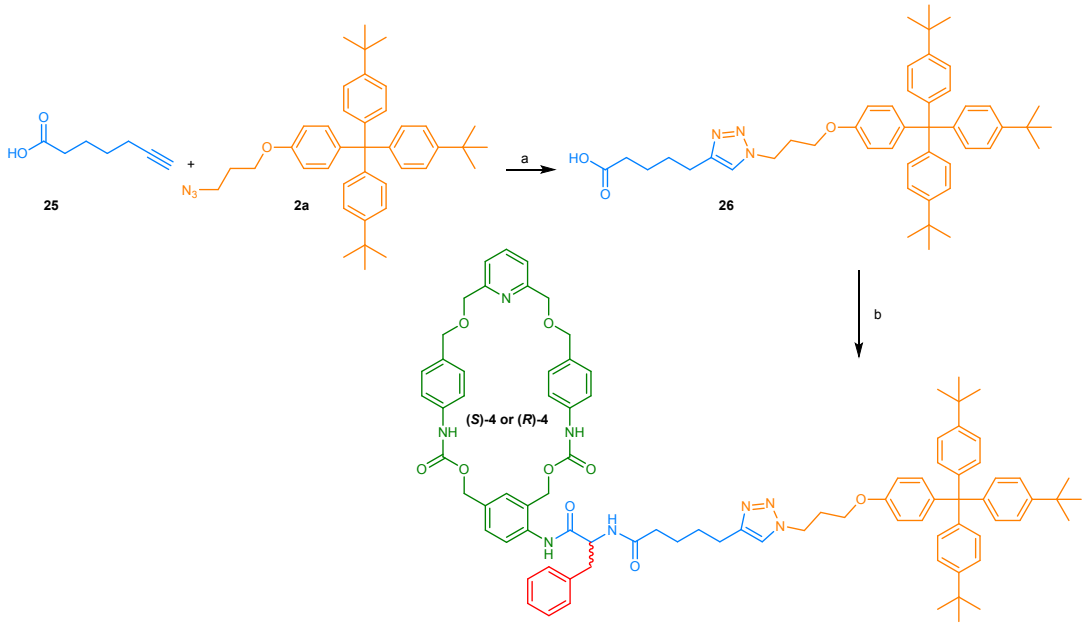
Scheme S3. *Reagents and conditions:* (a) allyl chloroformate, pyridine, DCM, 0 °C to RT, 3 h, 94%; (b) APTS.H_2O, THF, H_2O, 0 °C to RT, 24 h, not purified; (c) 4-nitrophenyl chloroformate, pyridine, DCM, 0 °C to RT, 3 h, 68% (two steps); (d) HOBt, DMF [0.08M], RT, 8 h; ii) DMF [0.001M], RT, 96 h, 42%.

Compound **(*S*)-1 and (*R*)-1** were prepared according to the following strategy:



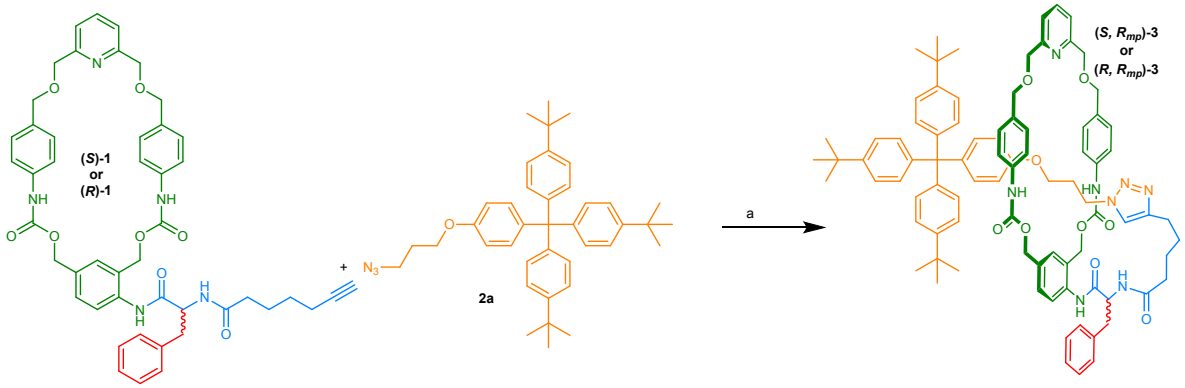
Scheme S4. *Reagents and conditions:* (a) (*R*)- or (*S*)-Fmoc-Phe-OH, ethyl chloroformate, Et_3N, DMF/DCM, RT, 18 h, quantitative.; (b) APTS.H_2O, THF, H_2O, 0 °C to RT, 5 h, not purified; (c) 4-nitrophenyl chloroformate, pyridine, THF, 0 °C to RT, 5 h, 80% (over two steps); (d) HOBt.H_2O, DMF [0.08M], 33 °C, 8 h; ii) DMF [0.001M], 33 °C, 4 days, not purified; (e) piperidine, DMF, RT, 1 h, 36% (over two steps); (f) 6-heptynoic acid **25**, DMAP, EDC.HCl, DMF, RT, 24 h, 86%.

Compounds **(*S*)-4** and **(*R*)-4** were prepared according to the following strategy:



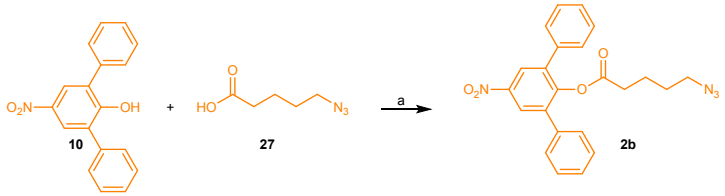
Scheme S5. *Reagents and conditions:* (a) $[Cu(MeCN)_4]PF_6$, DCM, RT, 18 h, 49%; (b) **(*R*)- or (*S*)-24**, DMAP, EDC.HCl, DMF, RT, 24 h, 84%.

Compounds **(*S*)-3 and (*R*)-3** were prepared according to the following strategy:



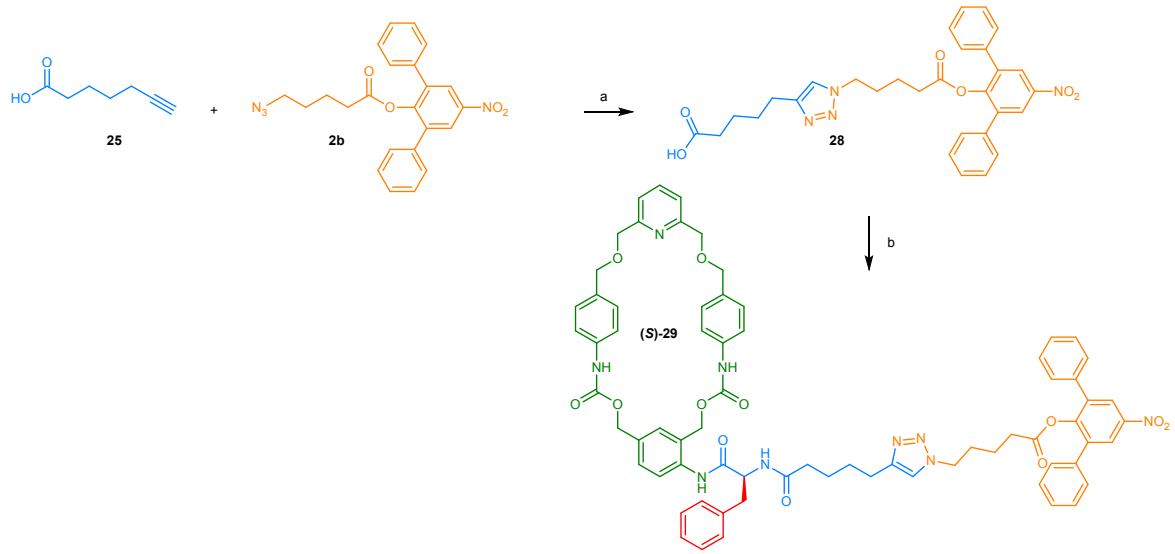
Scheme S6. *Reagents and conditions:* (a) $[Cu(MeCN)_4]PF_6$, **5a** or **5b**, DCM, 60 °C, 24 h, 45%. *Mechanical planar chirality drawn as (R_{mp}) for visual purposes, not experimentally determined.*

Compound **2b** was prepared according to the following strategy:



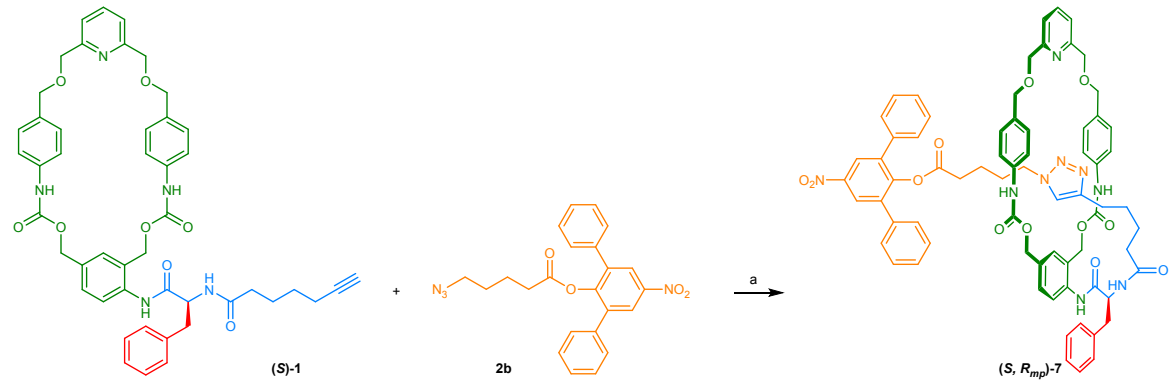
Scheme S7. *Reagents and conditions:* (a) DMAP, EDC.HCl, DCM, RT, 3 h, 95%.

Compound **(*S*)-29** was prepared according to the following strategy:



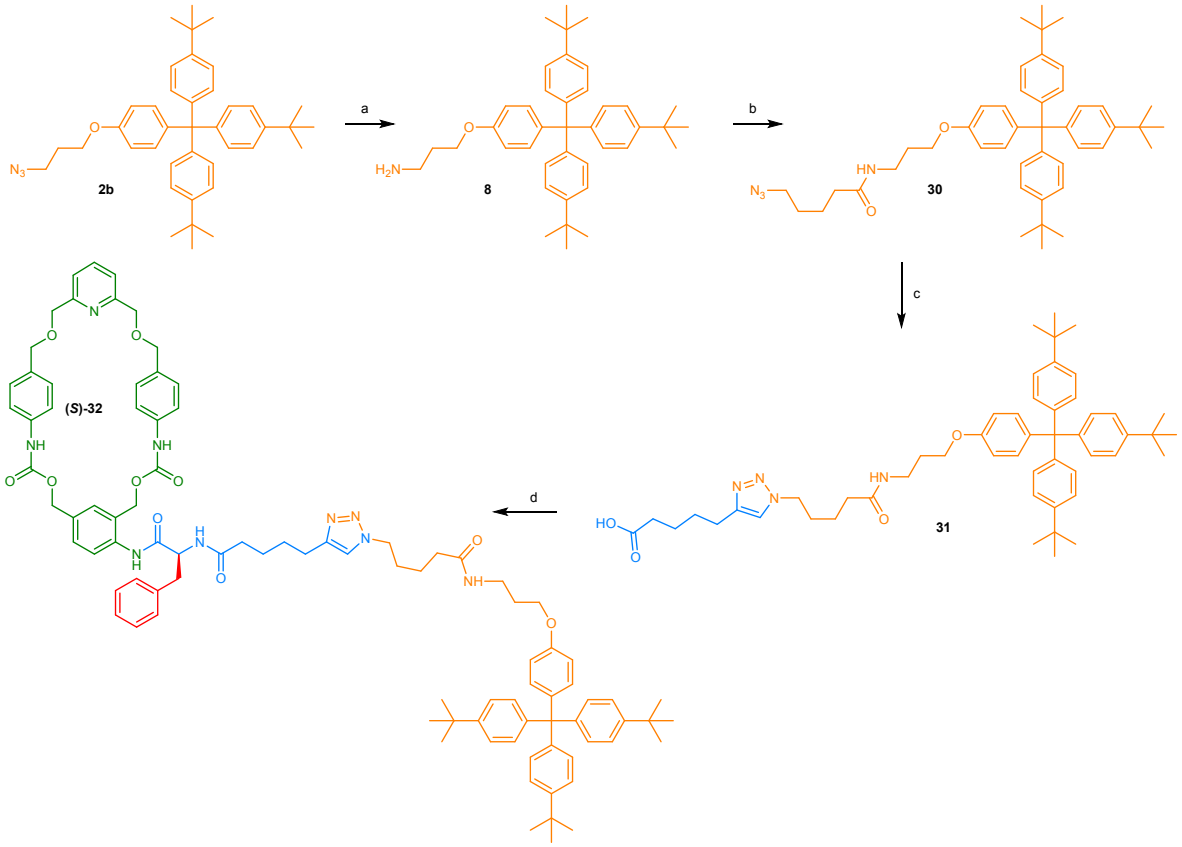
Scheme S8. *Reagents and conditions:* (a) $[Cu(MeCN)_4]PF_6$, DCM, RT, 20 h, 60%; (b) **(*S*)-24**, DMAP, EDC.HCl, DMF, 35 °C, 24 h, 45%.

Compound **(*S*)-7** was prepared according to the following strategy:



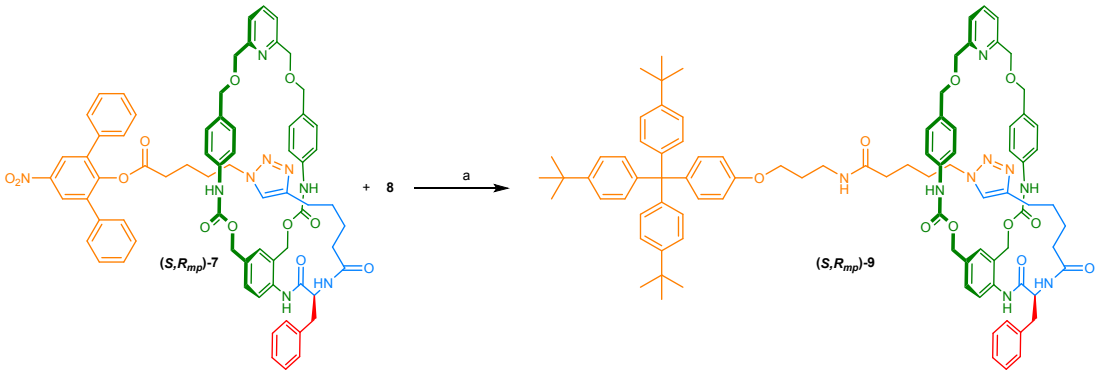
Scheme S9. *Reagents and conditions:* $[Cu(MeCN)_4]PF_6$, **5a**, DCM, 60 °C, 24 h, 26%. *Mechanical planar chirality drawn as (R_{mp}) for visual purposes, not experimentally determined.*

Compound **(*S*)-32** was prepared according to the following strategy:



Scheme S10. *Reagents and conditions:* (a) triphenylphosphine, THF/NH_4OH, 65 °C, 5 h, 97%; (b) **27**, DMAP, EDC.HCl, DMF, RT, 12 h, 66%; (c) **25**, $[Cu(MeCN)_4]PF_6$, DCM, RT, 18 h, 74%; (d) **(*S*)-24**, DMAP, EDC.HCl, DMF, RT, 48 h, 85%.

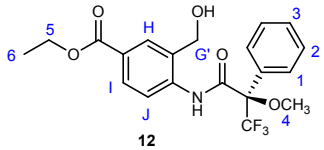
Compound **(*S*)-9** was prepared according to the following strategy:



Scheme S11. *Reagents and conditions:* (a) DIPEA, DCM, 40 °C, 48 h, 54%. *Mechanical planar chiralities drawn as (R_{mp}) for visual purposes, not experimentally determined.*

I.3. Synthetic procedures and characterization details with ^{1}H NMR and ^{13}C NMR plots

Preparation of compound 12



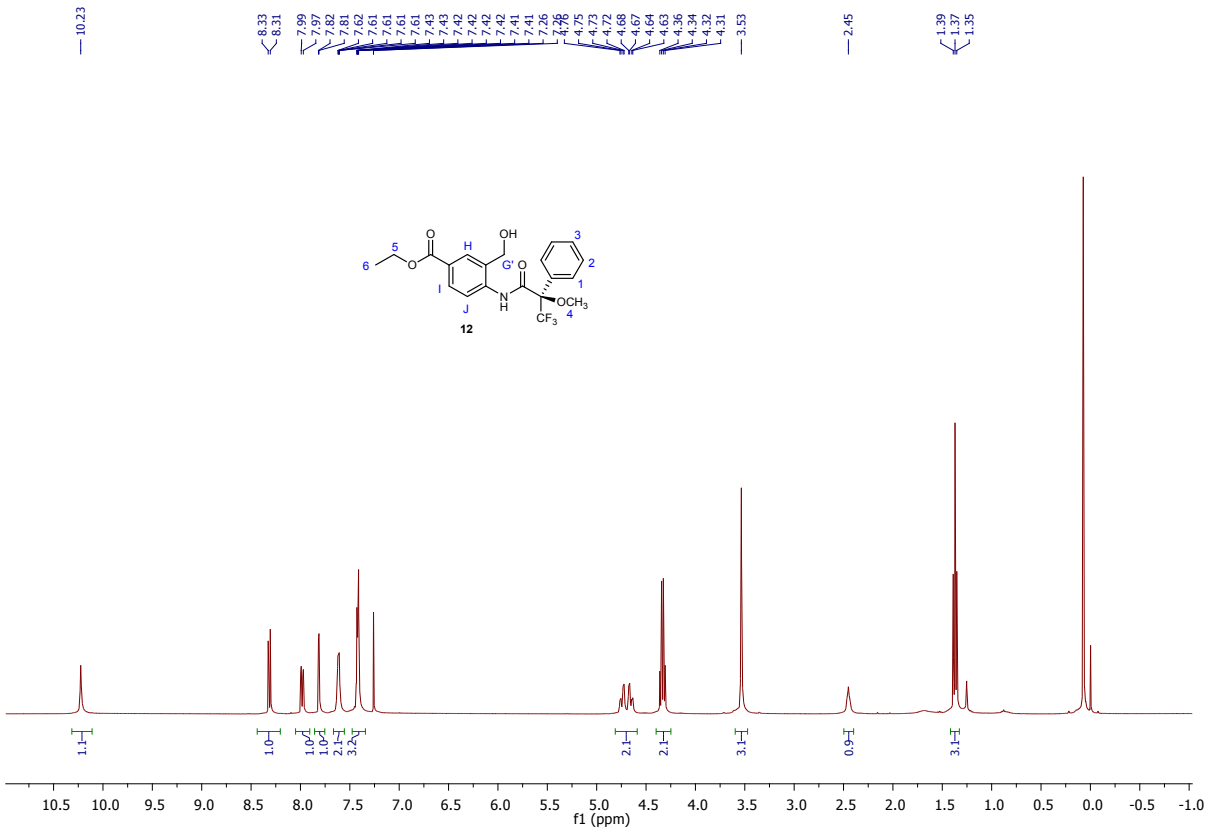
12

Oxalyl chloride (1.7 mL, 19.4 mmol, 1 equiv.) was added to a cooled solution at 0 °C of dry DMF (2.14 mL, 27.6 mmol, 1.4 equiv.) in MeCN (60 mL). A solution of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid ((*R*)-Mosher's acid) (5.0 g, 21.4 mmol, 1.1 equiv.) in MeCN (15 mL) was then added. After 30 minutes stirring, a solution of aniline **11** (3.79g, 19.4 mmol, 1 equiv.) in MeCN (25 mL) was added followed by addition of a solution of dry Et_3N (3.0 mL, 19.4 mmol, 1 equiv.) in MeCN (100 mL). The reaction mixture was allowed to room temperature and stirring was pursued for 22 hours. Solvents were removed *in vacuo* and the crude was diluted with DCM (100 mL). The organic layer was washed with saturated $NaHCO_{3(aq)}$ (3 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 90:10 to 70:30, R_f = 0.4 (70:30)) gave **12** as a colorless wax (2.87 g, 6.98 mmol, 36%).

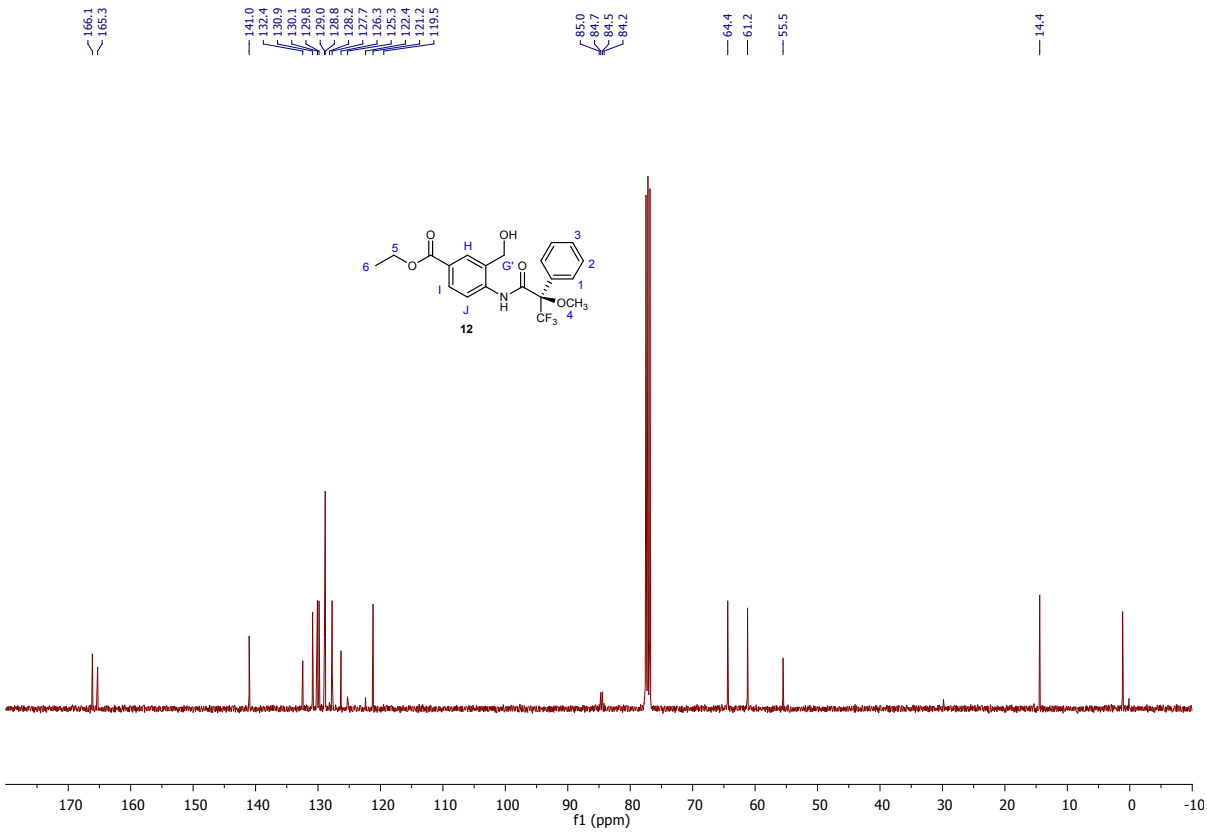
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (bs, 1H, $H_{NH\text{-}amide}$), 8.32 (d, *J* = 8.6, 1H, H_J), 7.98 (dd, *J* = 8.6, 2.0, 1H, H_I), 7.81 (d, *J* = 2.0, 1H, H_H), 7.62 (m, 2H, H_2), 7.43 – 7.40 (m, 3H, H_1, H_3), 4.74 (dd, *J* = 12.6, 4.2, 1H, $H_{G'}$), 4.66 (dd, *J* = 12.6, 3.9, 1H, $H_{G'}$), 4.33 (q, *J* = 7.1, 2H, H_5), 3.53 (s, 3H, H_4), 2.45 (bs, 1H, H_{OH}), 1.37 (t, *J* = 7.1, 3H, H_6).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 ($C_{CO\text{-}ester}$), 165.3 ($C_{CO\text{-}amide}$), 141.0-132.4 ($C_{quat.\ arom.}$), 130.9 (C_I), 130.1 (C_H), 129.8 (C_3), 129.0 ($C_{quat.\ arom.}$), 128.8 (C_1), [128.2-125.3-122.4-119.5] (q, *J* = 290, C_{CF3}), 127.7 (C_2), 126.3 ($C_{quat.\ arom.}$), 121.2 (C_J), [8.0-84.7-84.5-84.2] (q, *J* = 27, $C_{quat.}$), 64.4 ($C_{G'}$), 61.2 (C_5), 55.5 (C_4), 14.4 (C_6).

HRMS (ESI$^+$) *m/z* = 434.1187 $[M+Na]^+$ (calc. for $C_{20}H_{20}F_3NO_5Na$: 434.1191 $[M+Na]^+$).

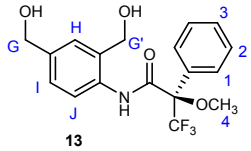


^{1}H NMR spectrum of **12**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **12**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound 13



13

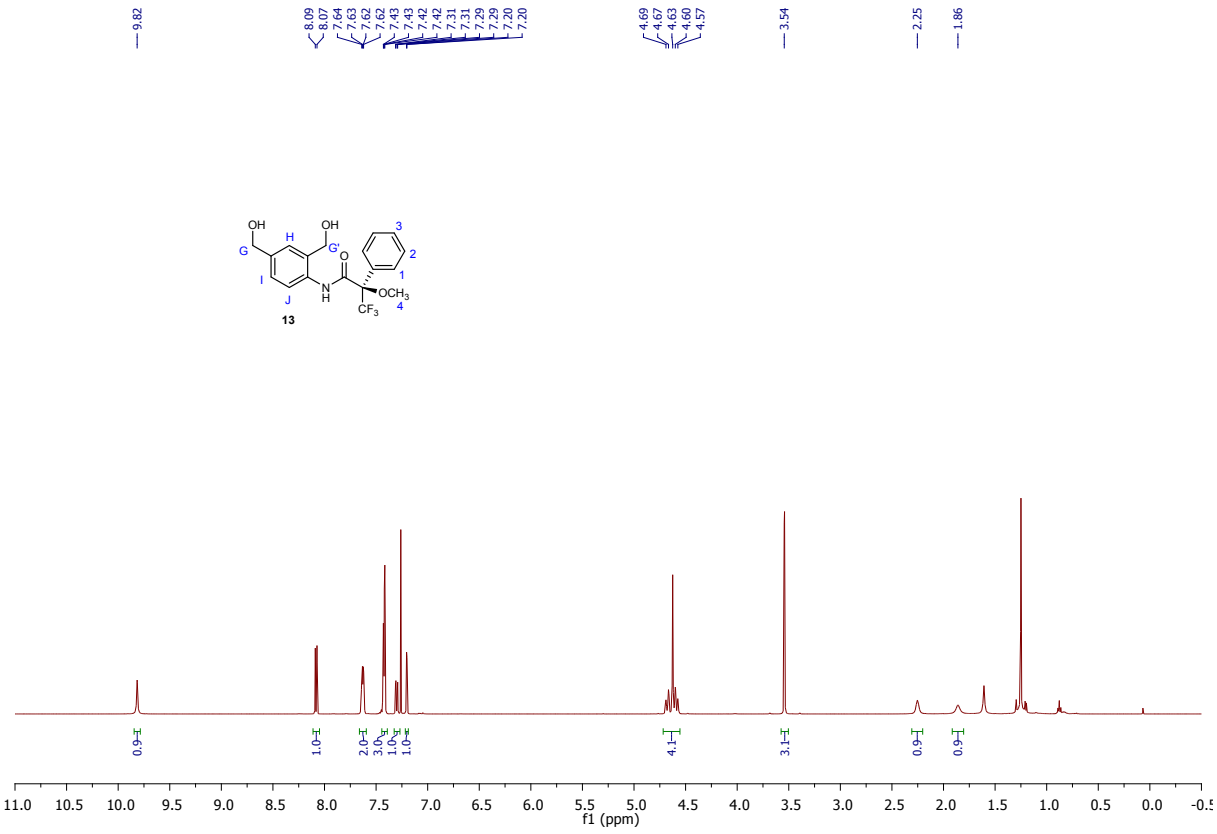
A solution of **12** (314 mg, 0.76 mmol, 1 equiv.) in anhydrous THF (8.4 mL) was cooled to -78 °C and a 1 M solution of DIBAL-H in DCM (3.05 mL, 3.05 mmol, 4 equiv.) was added dropwise. The reaction mixture was stirred for 7 hours at –78 °C and then poured in 20 mL of a saturated aqueous solution of Rochelle salt. The mixture was stirred for 1 hour and subsequently extracted with diethyl ether (3 x 10 mL) and AcOEt (3 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 60:40 to 40:60, R_f = 0.4 (40:60)) gave **13** as a colorless wax (260 mg, 0.704 mmol, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H, $H_{NH\text{-}amide}$), 8.08 (d, *J* = 8.3, 1H, H_J), 7.63 (dd, *J* = 2.6, 6.5, 2H, H_1), 7.43-7.42 (m, 3H, H_2, H_3), 7.30 (dd, *J* = 8.3, 1.9, 1H, H_I), 7.20 (d, *J* = 1.8, 1H, H_H), 4.68 (d, *J* = 12.3, 1H, $H_{G'}$), 4.63 (s, 2H, H_G), 4.59 (d, *J* = 12,4, 1H, $H_{G'}$), 3.54 (s, 3H, H_4), 2.25 (bs, 1H, H_{OH}), 1.86 (bs, 1H, H_{OH}).

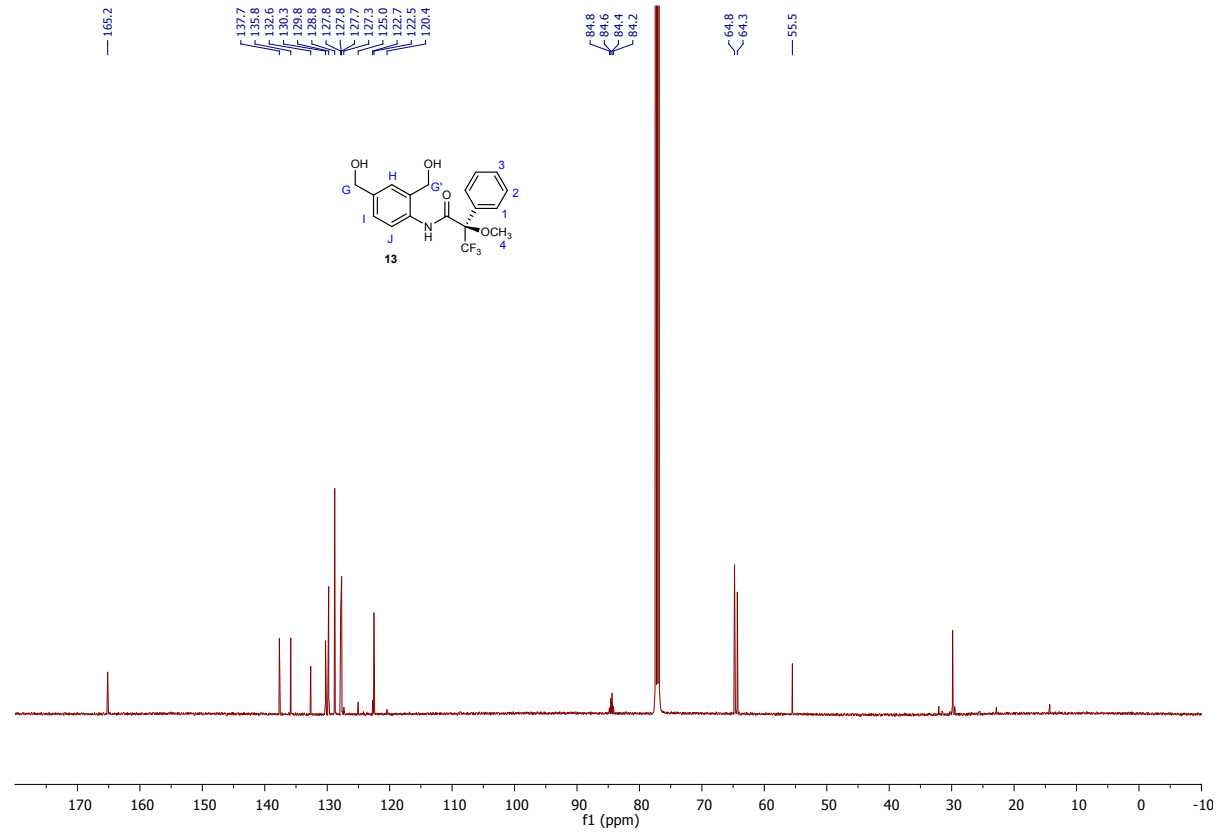
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2 ($C_{CO\text{-}amide}$), 137.7-135.8-132.6-130.3 ($C_{quat.\ arom.}$), 129.8 (C_2), 128.8 (C_3), 127.8 (C_1, C_I), 127.7 (C_H), [127.3-125.0-122.7-120.4] (q, *J* = 290, C_{CF3}), 122.5 (C_J), [84.8-84.6-84.4-84.2] (q, *J* = 26, $C_{quat.}$), 64.8 ($C_{G'}$), 64.3 (C_G), 55.5 (C_4).

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.75 (s, CF_3)

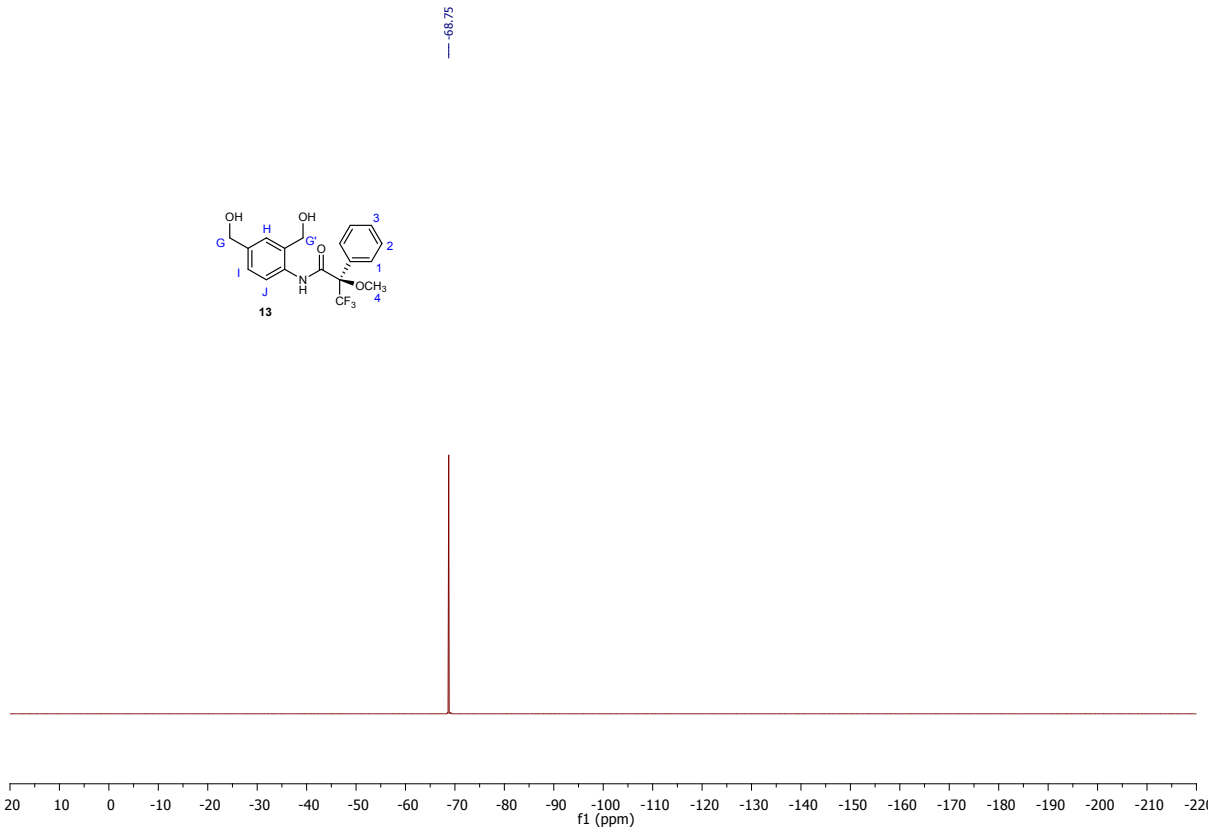
HRMS (ESI$^+$) *m/z* = 392.1086 $[M+Na]^+$ (calc. for $C_{18}H_{18}F_3NO_4Na$: 392.1085 $[M+Na]^+$).



^{1}H NMR spectrum of **13**, 500 MHz, 298 K, $CDCl_3$

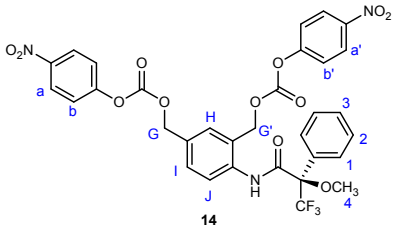


^{13}C NMR spectrum of **13**, 126 MHz, 298 K, $CDCl_3$



^{19}F NMR spectrum of **13**, 470 MHz, 298 K, $CDCl_3$

Preparation of compound 14



14

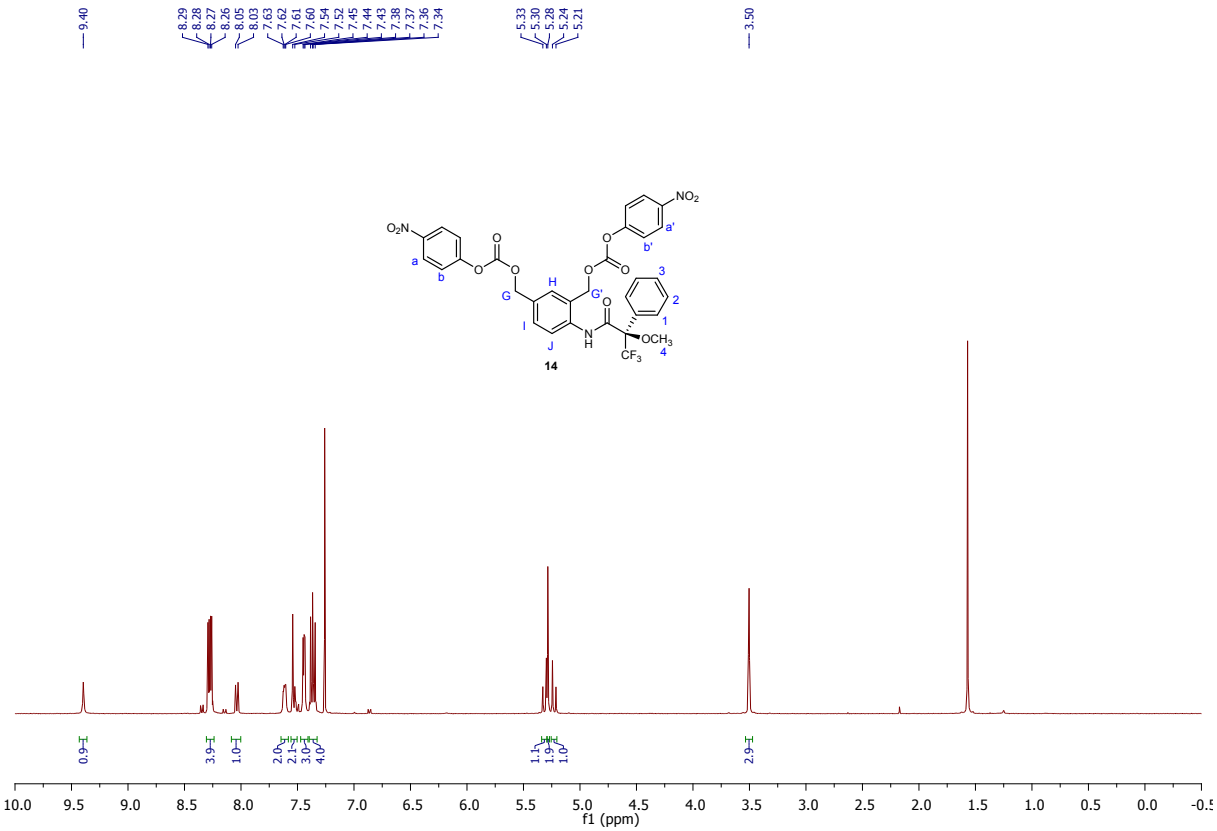
To a stirred solution of dialcohol **13** (627 mg, 1.7 mmol, 1 equiv.) and 4-nitrophenyl chloroformate (1.37 g, 6.8 mmol, 4 equiv.) in anhydrous DCM (32 mL) cooled at 0 °C, was added pyridine (96 µL, 1.18 mmol, 4 equiv.) dropwise. The reaction mixture was stirred for 20 minutes at 0°C and warmed up to room temperature for 5 hours. The reaction was hydrolyzed with saturated $NaHCO_{3(aq)}$ and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 90:10 to 70:30, R_f = 0.4 (60:40)) gave **14** as a colorless wax (984 mg, 1.41 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H, $H_{NH\text{-}amide}$), 8.29 – 8.26 (m, 4H, H_a, $H_{a'}$), 8.01 (d, *J* = 8.2, 1H, H_J), 7.63 – 7.60 (m, 2H, H_1), 7.54 – 7.51 (m, 2H, H_I, H_H), 7.44 (m, 3H, H_2, H_3), 7.39 – 7.34 (m, 4H, H_b, $H_{b'}$), 5.32 (d, *J* = 12.6, 1H, $H_{G'}$), 5.29 (s, 2H, H_G), 5.24 (d, *J* = 12.6, 1H, $H_{G'}$), 3.50 (s, 3H, H_4).

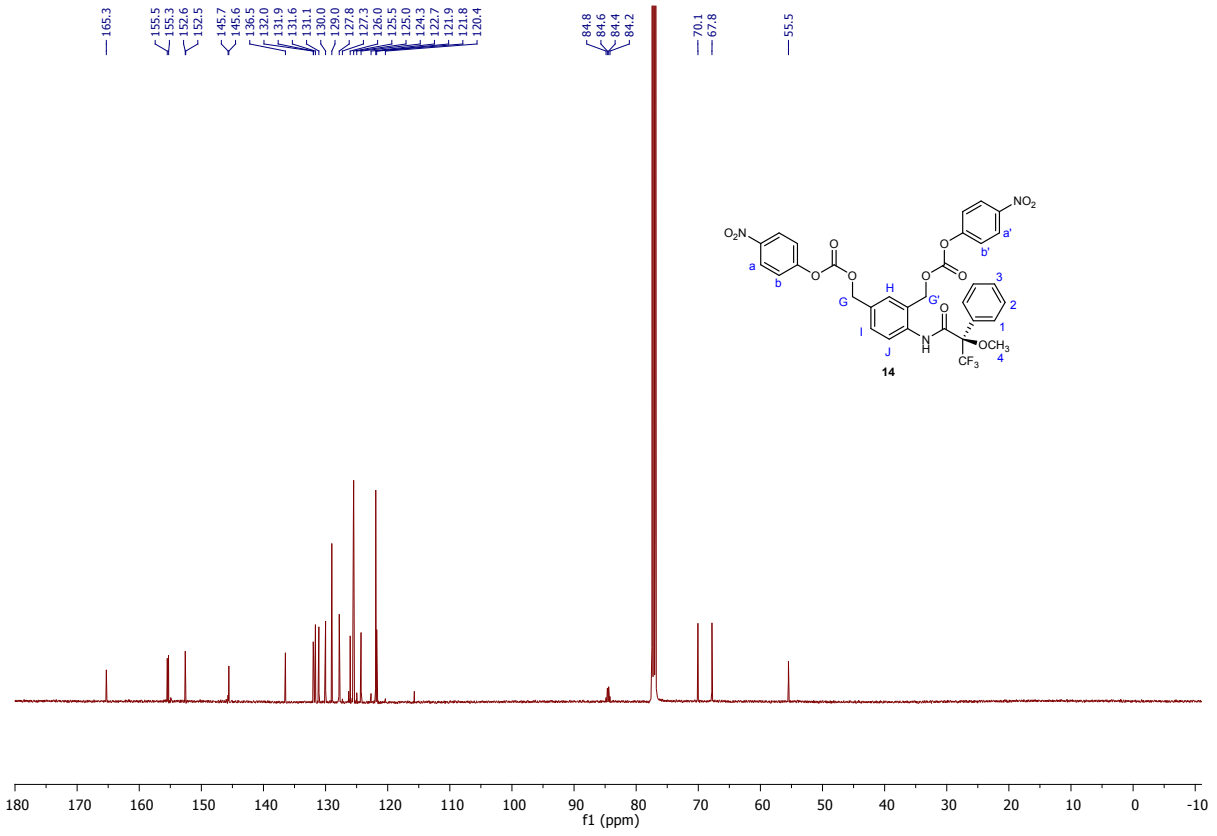
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 ($C_{CO\text{-}amide}$), 155.5-155.3 ($C_{CO\text{-}carbonate}$), 152.6-152.5-145.7-145.8-136.5-132.0-131.9 ($C_{quat.\ arom.}$), 131.6 (C_H), 131.1 (C_I), 130.0 (C_2), 129.0 (C_3), 127.8 (C_1), [127.3-125.0-122.7-120.4] (q, *J* = 290, C_{CF3}), 126.0 ($C_{quat.\ arom.}$), 125.5 (C_a, $C_{a'}$), 124.3 (C_J), 121.9-121.8 (C_b, $C_{b'}$), 84.5 (q, *J* = 26.6, $C_{quat.}$)70.1 (C_G), 67.8 ($C_{G'}$), 55,5 (C_4).

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.72 (s, CF_3)

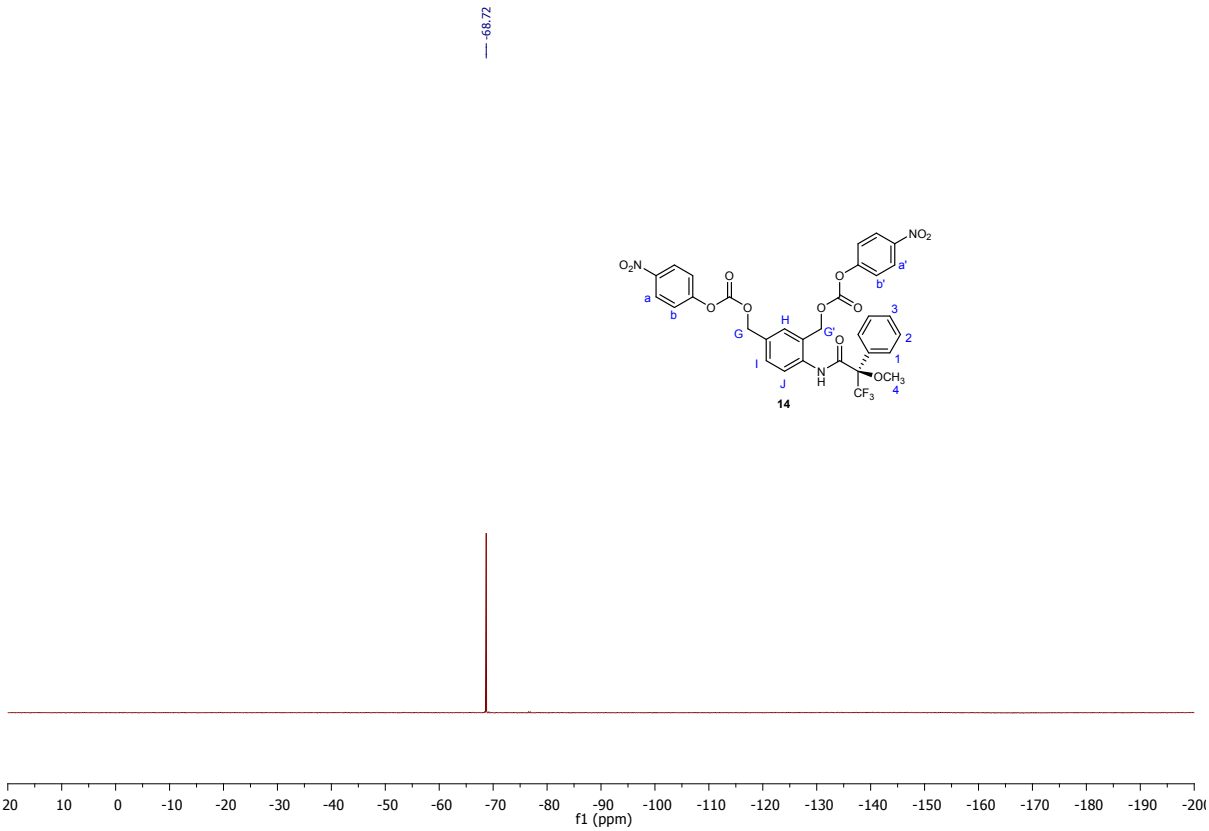
HRMS (ESI$^+$) *m/z* = 722.1203 $[M+Na]^+$ (calc. for $C_{32}H_{24}F_3N_3O_{12}Na$: 722.1204 $[M+Na]^+$).



^{1}H NMR spectrum of **14**, 400 MHz, 298 K, $CDCl_3$

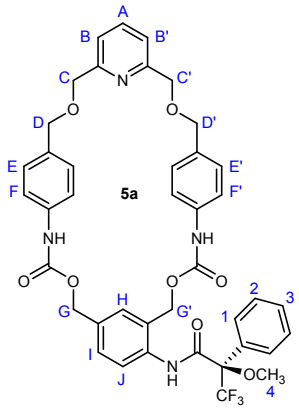


^{13}C NMR spectrum of **14**, 126 MHz, 298 K, $CDCl_3$



^{19}F NMR spectrum of **14**, 376 MHz, 298 K, $CDCl_3$

Preparation of compound 5a



To a solution of carbonate **14** (300 mg, 0.43 mmol, 1 equiv.) and di-aniline **15** (345 mg, 0.98 mmol, 2.3 equiv.) in DMF (5.4 mL), was added HOBt (58 mg, 0.43 mmol, 1 equiv.) and the solution was stirred for 8 hours at 33 °C. The solution was diluted with DMF (430 mL) and stirred for 48 hours at 33 °C. The solvent was removed *in vacuo* and the crude material was diluted with DCM (100 mL) and washed with saturated $NaHCO_{3(aq)}$ (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.5 (95:5)) gave **5a** as a white solid (119 mg, 0.155 mmol, 36%).

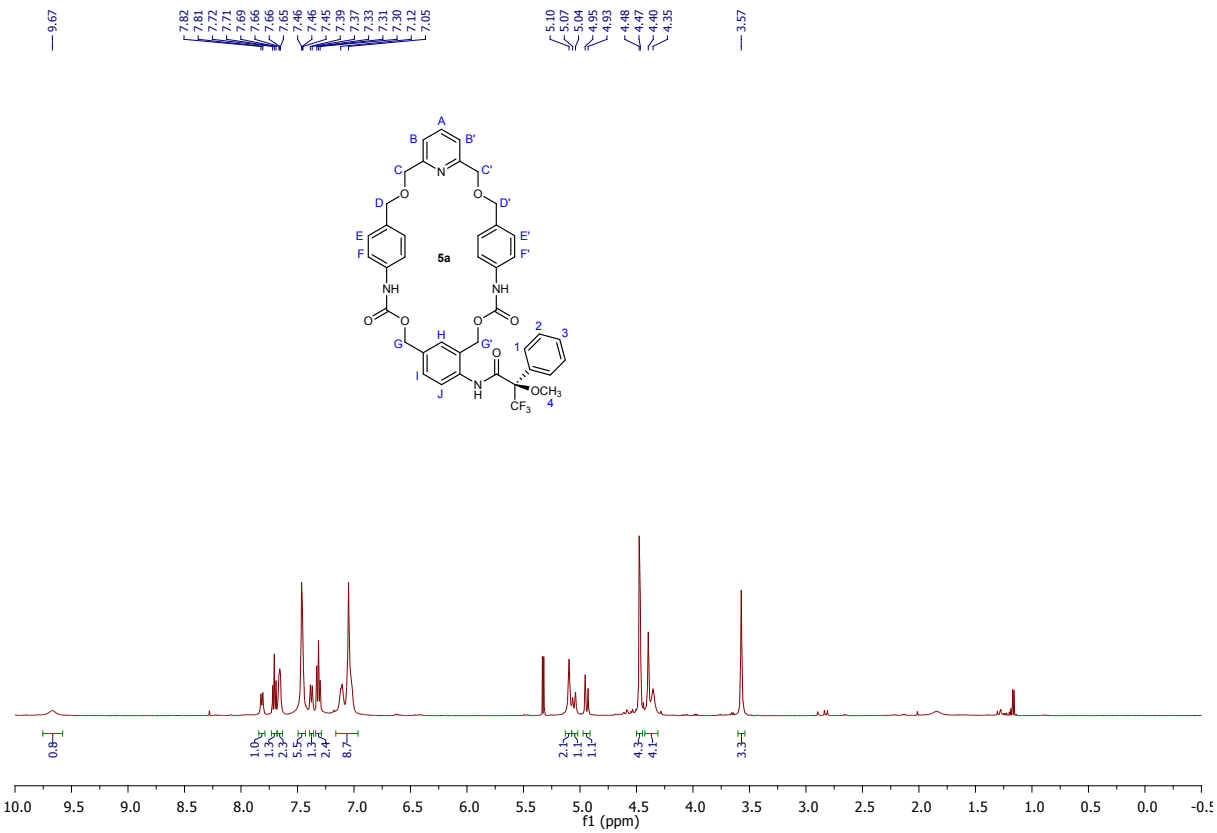
^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.67 (bs, 1H, $H_{NH\text{-}amide}$), 7.82 (d, *J* = 8.2, 1H, H_J), 7.71 (t, *J* = 7.7, 1H, H_A), 7.66 (m, 2H, H_1), 7.46 (m, 5H, H_H, H_3, H_2), 7.38 (d, *J* = 8.3, 1H, H_I), 7.31 (2d, *J* = 7.4, 2H, H_B, $H_{B'}$),7.19 – 7.105 (m, 9H, H_E, $H_{E'}$, H_F, $H_{F'}$,$H_{NH\text{-}carbamate}$), 5.10 (s, 2H, H_G), 5.05 (d, *J* = 12.9, 1H, $H_{G'}$), 4.94 (d, *J* = 12.8, 1H, $H_{G'}$), 4.47 (2s, 4H, H_C, $H_{C'}$), 4.40-4.35 (2s, 4H, H_D, $H_{D'}$), 3.57 (s, 3H, H_4).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 165.6 ($C_{CO\text{-}amide}$), 158.1-157.9 ($C_{quat.\ arom.}$), 153.8-153.6 ($C_{CO\text{-}carbamate}$), 138.2 ($C_{quat.\ arom.}$), 137.7 (C_A), 135.7-135.0-133.1-132.8 ($C_{quat.\ arom.}$), 131.7 (C_H), 130.2 (C_I), 129.8 (C_3), 129.7-129.7 (C_E, $C_{E'}$), 129.4 (C_2), 129.2 ($C_{quat.\ arom.}$), 128.2 (C_1), [127.9-125.6-123.3-121.7] (q, *J* = 126, C_{CF3}), 124.5 (C_J), 121.2 (C_B), 118.7 (C_F, $C_{F'}$), 85.0 (q, *J* = 26, $C_{quat.}$), 72.3-72.1 (C_D, $C_{D'}$), 71.8-71.3 (C_C, $C_{C'}$), 66.3 (C_G), 63.2 ($C_{G'}$), 55.9 (C_4).

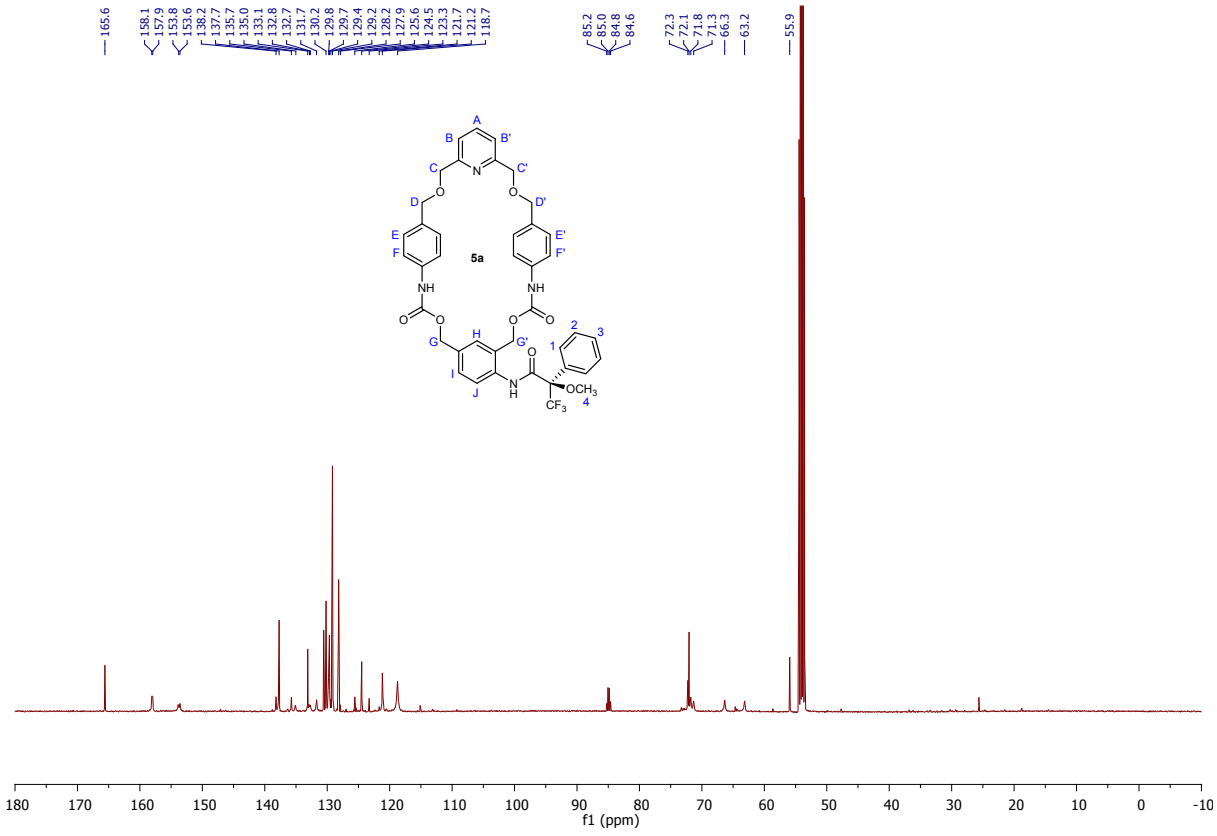
^{19}F NMR (376 MHz, CD_2Cl_2) δ -69.25 (s, CF_3).

HRMS (ESI$^+$) *m/z* = 793.2457 $[M+Na]^+$ (calc. for $C_{41}H_{37}F_3N_4O_8Na$: 793.2456 $[M+Na]^+$)

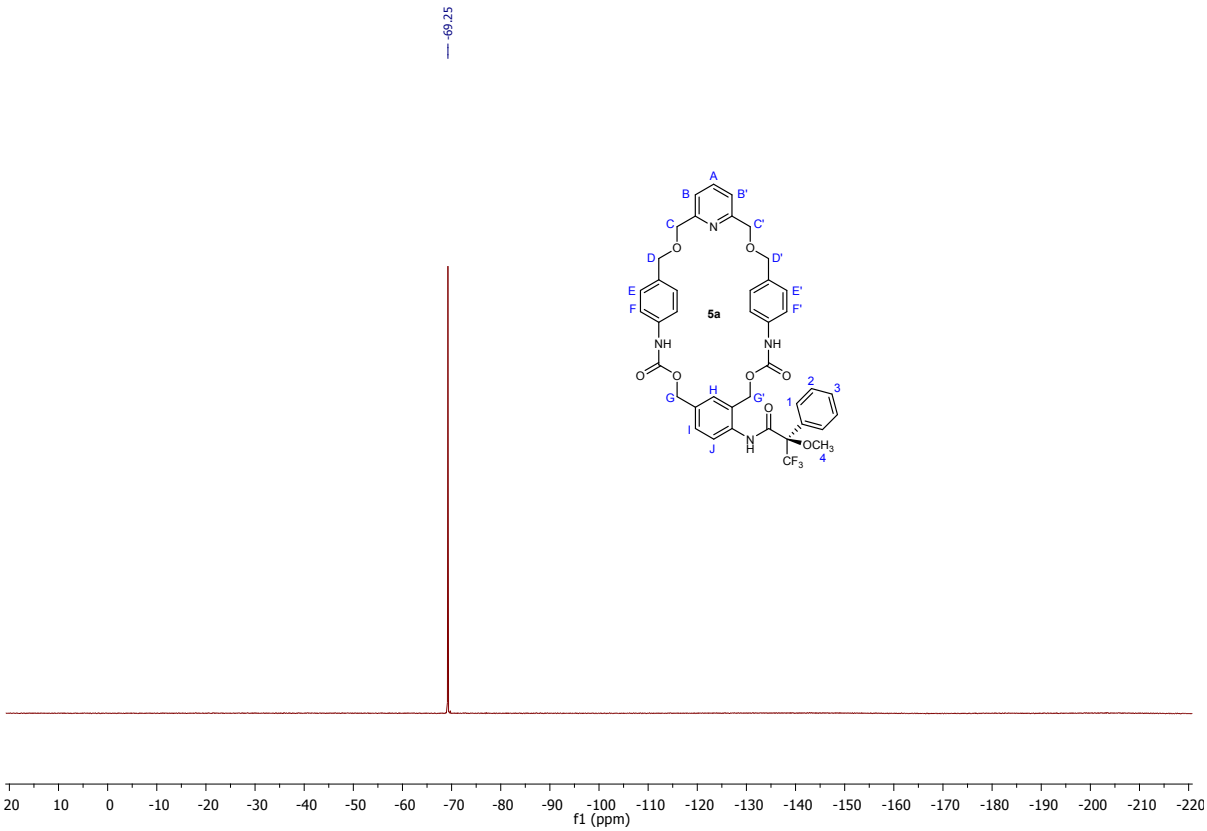
HPLC rt: 5.45 minutes



^{1}H NMR spectrum of **5a**, 500 MHz, 298 K, CD_2Cl_2

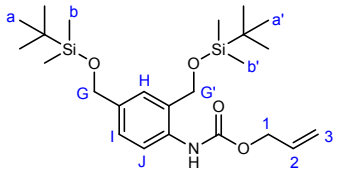


^{13}C NMR spectrum of **5a**, 126 MHz, 298 K, CD_2Cl_2



^{19}F NMR spectrum of **5a**, 376 MHz, 298 K, $CDCl_3$

Preparation of compound 17



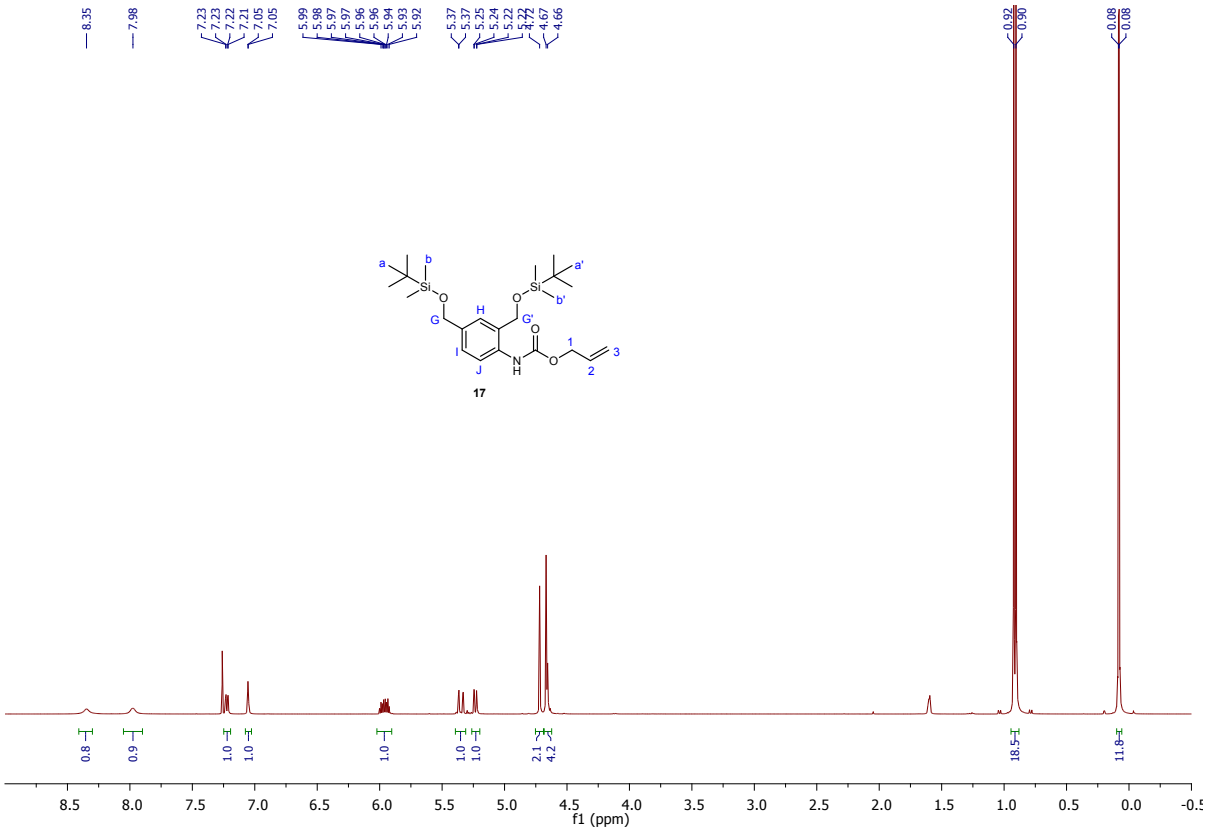
17

To a stirred solution of aniline **16** (1.95 g, 5.12 mmol, 1 equiv.) in anhydrous DCM (49 mL) cooled at 0 °C, was added pyridine (0.83 mL, 10.24 mmol, 2 equiv.) and allyl chloroformate (0.57 mL, 5.38 mmol, 1.05 equiv.). The reaction mixture was stirred for 20 minutes at 0 °C and warmed up to room temperature for 3 hours. The reaction was hydrolyzed with saturated $NH_4Cl_{(aq)}$ (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 100:0 to 95:5, R_f = 0.6 (90:10)) gave **17** as a light brown oil (2.25 g, 4.83 mmol, 94%).

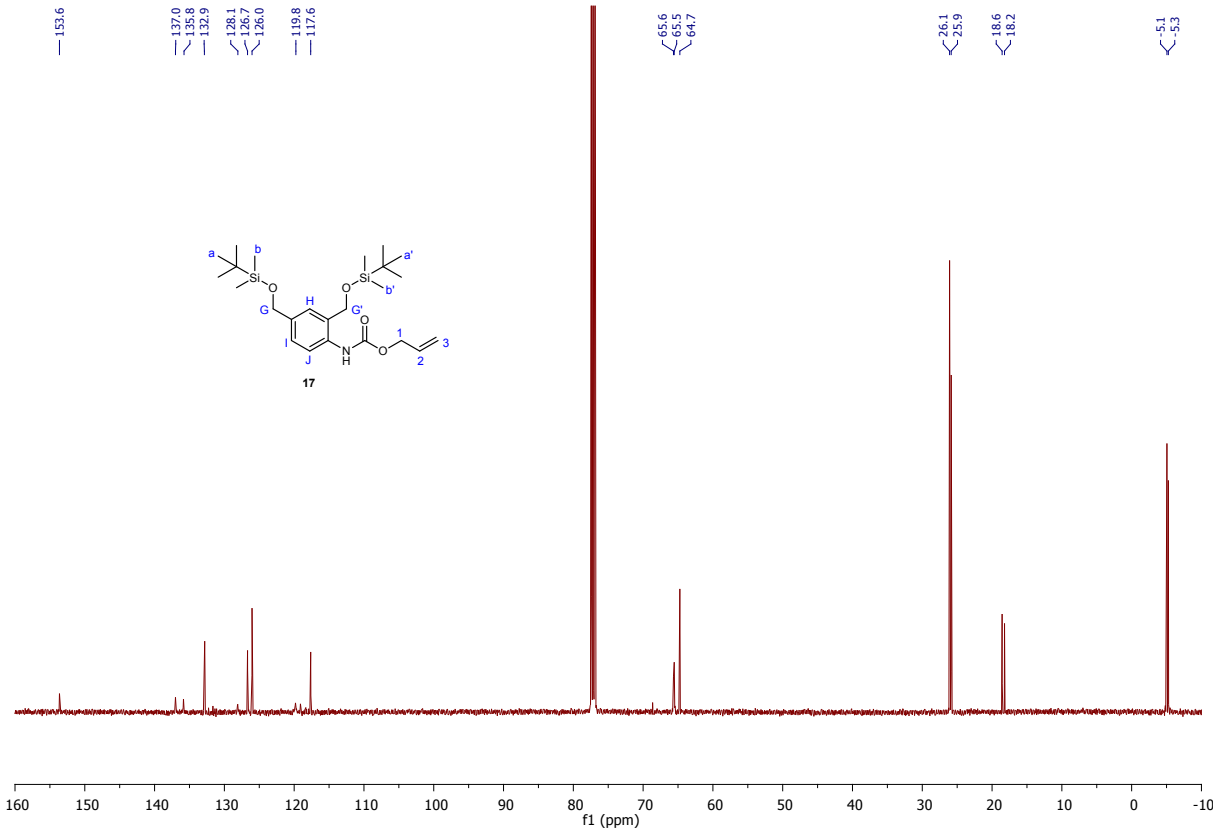
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.35 (bs, 1H, H_{NH}), 7.99 (bs, 1H, H_J), 7.22 (dd, *J* = 8.4, 1.7, 1H, H_I), 7.05 (d, *J* = 1.2, 1H, H_H), 5.97 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H, H_2), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1H, $H_{3\text{-trans}}$), 5.23 (dq, *J* = 10.5, 1.4 Hz, 1H, $H_{3\text{-cis}}$), 4.72 (s, 2H, $H_{G'}$), 4.67 – 4.66 (m, 4H, H_G, H_1), 0.92-0.90 (2s, 18H, H_a, $H_{a'}$), 0.09-0.08 (2s, 12H, H_b, $H_{b'}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (CO), 137.0-135.9 ($C_{quat.\ arom.}$), 132.9 (C_2), 128.1 ($C_{quat.\ arom.}$), 126.7 (C_I), 126.0 (C_H), 119.8 (C_J), 117.6 (C_3), 65.6 (C_1), 65.5 ($C_{G'}$), 64.7 (C_G), 26.1-25.9 (C_a, $C_{a'}$), 18.6-18.2 ($C_{quat.\ t\text{-bu}}$), -5.1 (C_b), -5.3 ($C_{b'}$).

HRMS (ESI$^+$) *m/z* = 488.2625 $[M+Na]^+$ (calc. for $C_{24}H_{43}NO_4Si_2Na$: 488.2623 $[M+Na]^+$)

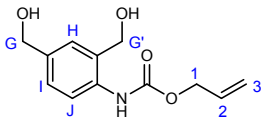


^{1}H NMR spectrum of **17**, 500 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **17**, 126 MHz, 298 K, $CDCl_3$

Preparation of compound 18

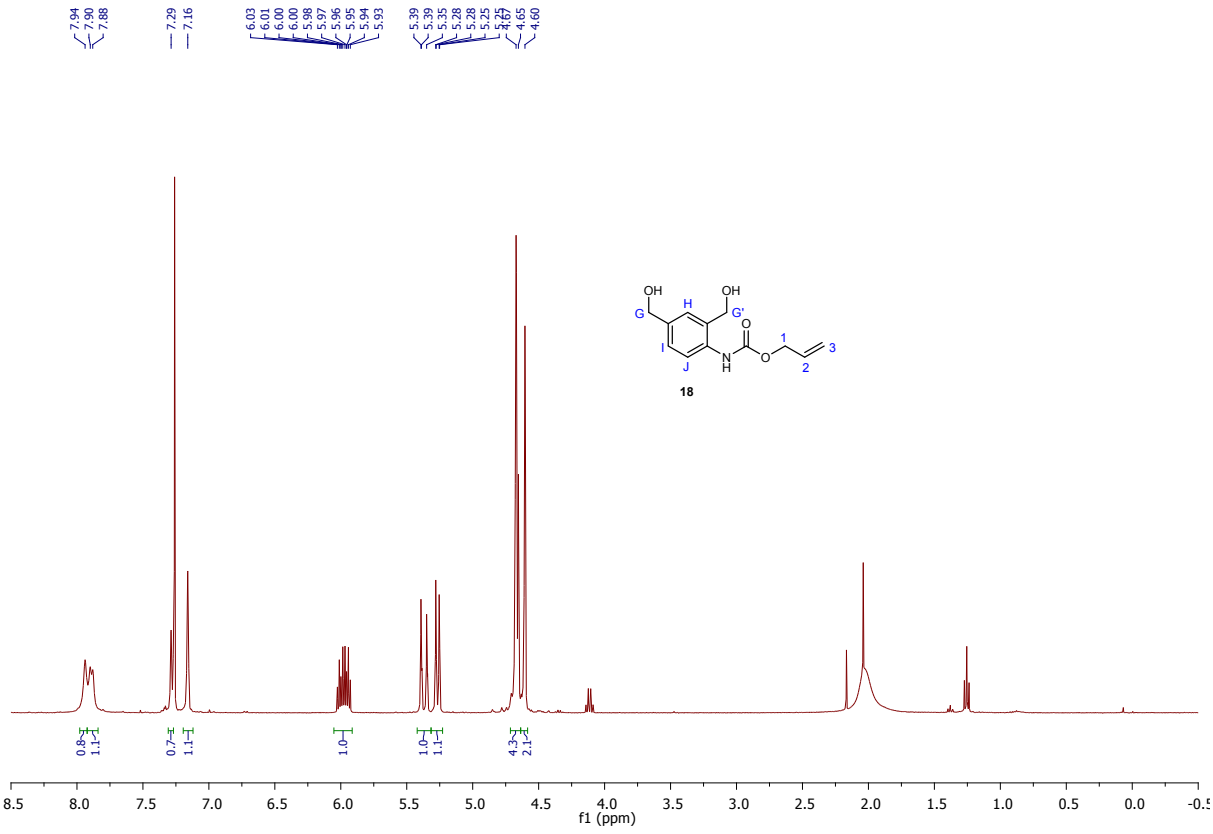


18

To a stirred solution of compound **17** (1.33 g, 2.85 mmol, 1 equiv.) in THF (26 mL) cooled at 0 °C, was added dropwise a solution of APTS.H_2O (326 mg, 1.71 mmol, 0.6 equiv.) in water (3 mL). The reaction mixture was stirred at room temperature for 24 hours. The reaction was hydrolyzed with water and the solution was extracted with Et_2O (2x). The aqueous layer was saturated with NaCl and extracted with Et_2O (2x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **18** without further purification as a white solid (1.1 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (bs, 1H, H_{NH}), 7.89 (d, *J* = 7.4, 1H, H_J), 7.29 (s, 1H, H_I), 7.16 (s, 1H, H_H), 5.97 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H, H_2), 5.35 (dd, *J* = 17.2, 1.4, 1H, $H_{3\text{-trans}}$), 5.23 (dd, *J* = 10.5, 1.4, 1H, $H_{3\text{-cis}}$), 4.6 (2s, 4H, $H_{G'}$, H_1), 4.60 (s, 2H, H_G).

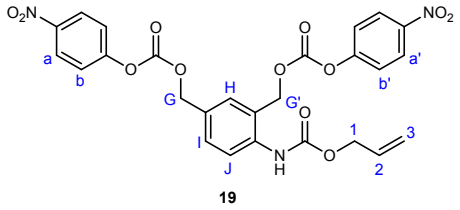
HRMS (ESI$^+$) *m/z* = 260.0893[M+Na]$^+$ (calc. for $C_{12}H_{15}NO_4Na$: 260.0893[M+Na]$^+$)



18

^{1}H NMR spectrum of **18**, 400 MHz, 298 K, $CDCl_3$

Preparation of compound 19



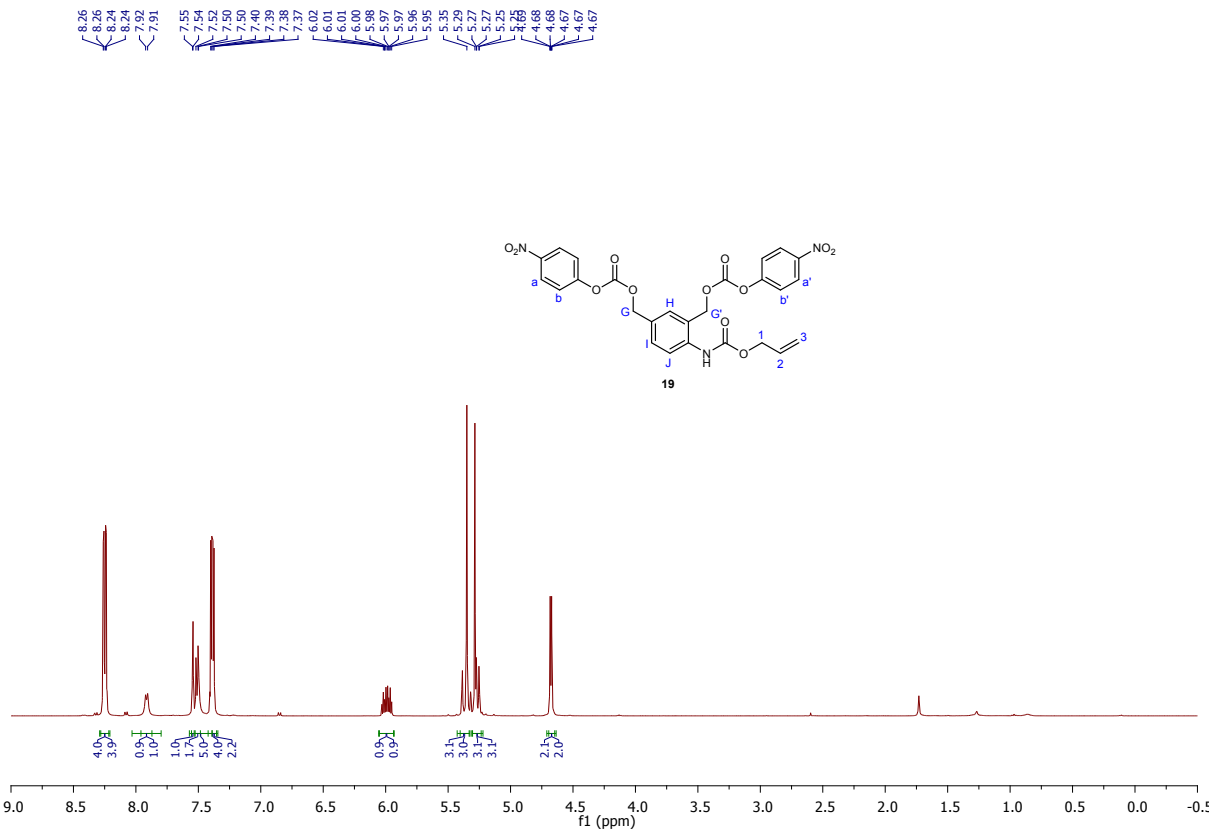
19

To a stirred solution of crude dialcohol **18** (1.1 g, 4.6 mmol, 1 equiv.) and 4-nitrophenyl chloroformate (3.7 g, 18.4 mmol, 4 equiv.) in anhydrous DCM (80 mL) cooled at 0 °C, was added pyridine (1.5 mL, 18.4 mmol, 4 equiv.) dropwise. The reaction mixture was stirred for 20 minutes at 0 °C and warmed up to room temperature for 3 hours. The reaction was hydrolyzed with saturated $NaHCO_{3(aq)}$ and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 80:20 to 40:60, R_f = 0.3 (70:30)) gave **19** as a white solid (1.1 g, 1.94 mmol, 68% over two steps).

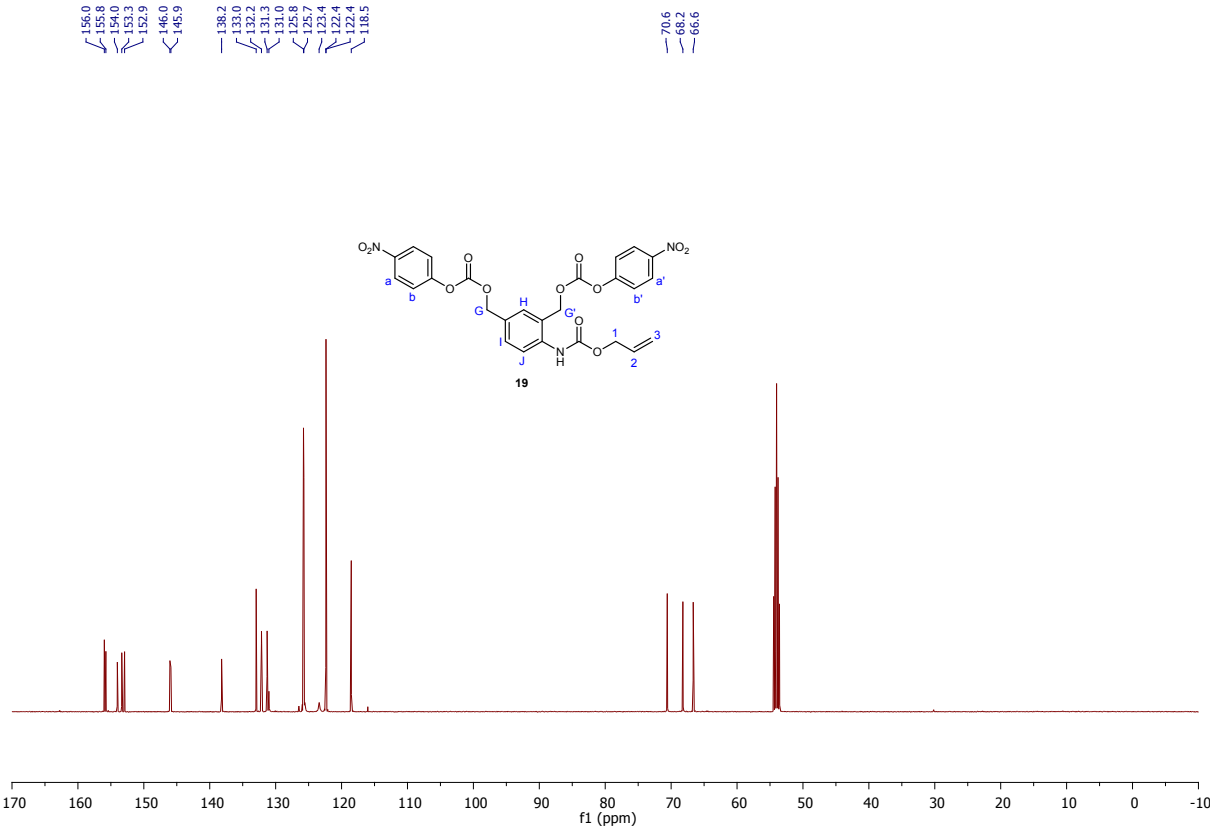
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.25 (2d, *J* = 9.3, 4H, H_a, $H_{a'}$), 7.91 (d, *J* = 7.9, 1H, H_J), 7.54 (d, *J* = 1.9, 1H, H_H), 7.51 (m, 2H, H_{NH}, H_I), 7.39 (2d, *J* = 9.2, 4H, H_b, $H_{b'}$), 5.99 (ddt, *J* = 16.2, 10.5, 5.7, 1H, H_2), 5.44 – 5.16 (m, 6H, H_3, H_G, $H_{G'}$), 4.66 (dt, *J* = 5.7, 1.3, 2H, H_1).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 156.0-155.8-154.0-153.3-152.9-146.0-145.9-138.2 ($C_{CO\text{-}carbonate}$, $C_{CO\text{-}carbamate}$, $C_{quat.\ arom.}$), 133.0 (C_2), 132.2 (C_H), 131.3 (C_I), 131.0 ($C_{quat.\ arom.}$), 125.8-125.7 (C_a, $C_{a'}$), 123.4 (C_J), 122.3 (C_b, $C_{b'}$), 118.5 (C_3), 70.6 (C_G), 68.2 ($C_{G'}$), 66.6 (C_1).

HRMS (ESI$^+$) *m/z* = 590.1011 $[M+Na]^+$ (calc. for $C_{26}H_{21}N_3O_{12}Na$: 590.1017 $[M+Na]^+$).

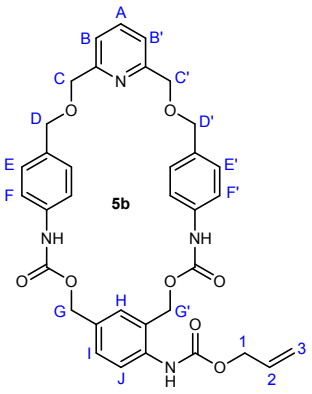


^{1}H NMR spectrum of **19**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **19**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound 5b



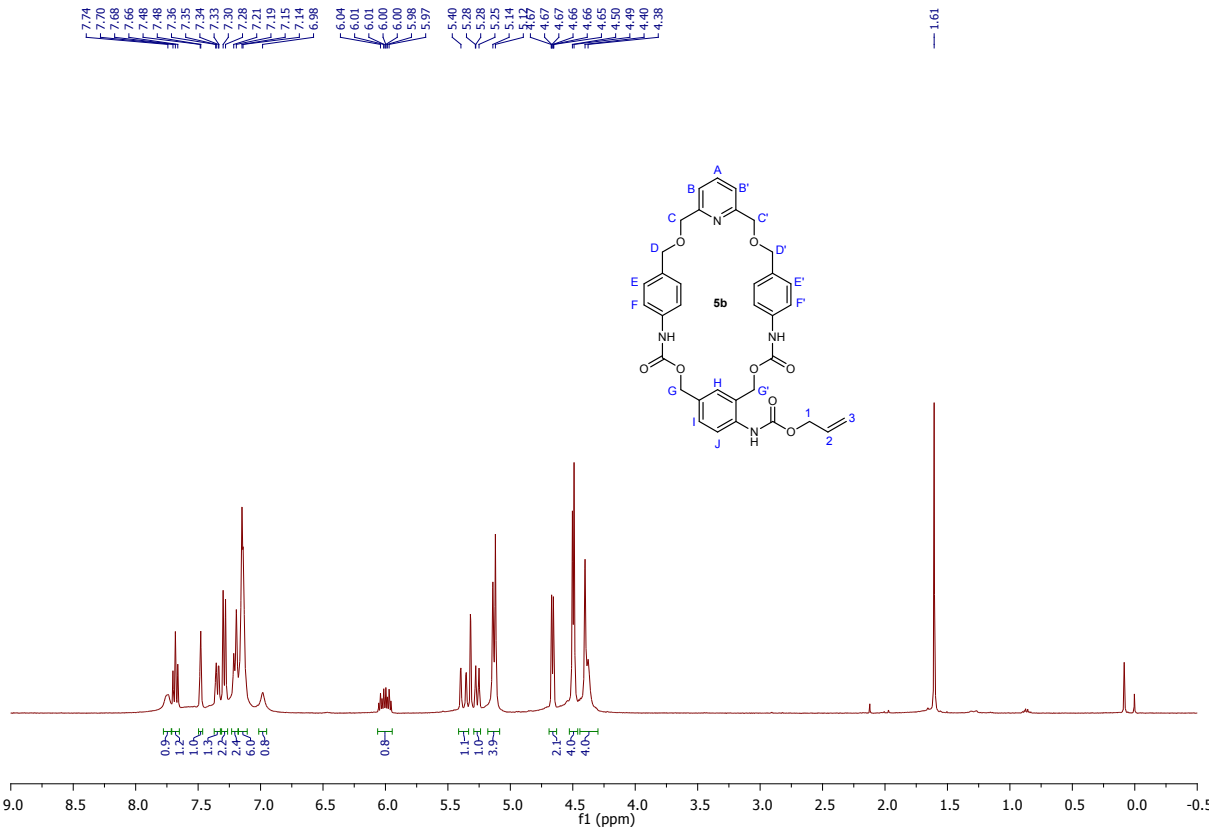
To a solution of carbonate **19** (283 mg, 0.5 mmol, 1 equiv.) and di-aniline **15** (402 mg, 1.15 mmol, 2.3 equiv.) in DMF (6.85 mL), was added HOBt.H_2O (68 mg, 0.5 mmol, 1 equiv.) and the solution was stirred for 8 hours at room temperature. The solution was diluted with DMF (500 mL) and stirred for 96 hours at room temperature. The solvent was removed *in vacuo*, the crude material was diluted with DCM (100 mL) and washed with saturated $NaHCO_{3(aq)}$ (3 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 97:3, R_f = 0.4 (95:5)) gave **5b** as a white solid (133 mg, 0.21 mmol, 42%).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.74 (bs, 1H, H_J), 7.68 (t, *J* = 7.7, 1H, H_A), 7.48 (d, *J* = 1.9, 1H, H_H), 7.35 (dd, *J* = 8.4, 1.9, 1H, H_I) 7.29 (d, J= 7.7, 2H, H_B, $H_{B'}$), 7.21 – 7.14 (m, 8H, H_E, $H_{E'}$, H_F, $H_{F'}$), 6.98 (bs, 1H, $H_{NH\text{-}carbamate}$), 6.01 (ddt, *J* = 17.1, 10.0, 5.7, 1H, H_2), 5.38 (dd, J_{trans} = 17.2, 1.5, H_3), 5.27 (dd, J_{cis} = 10.4, 1.3, 1H, H_3), 5.12 – 5.14 (2s, 4H, H_G, $H_{G'}$), 4.66 (dt, *J* = 5.7, 1.3, 2H, H_1), 4.50-4.49 (2s, 4H, H_C, $H_{C'}$), 4.39 (m, 4H, H_D, $H_{D'}$).

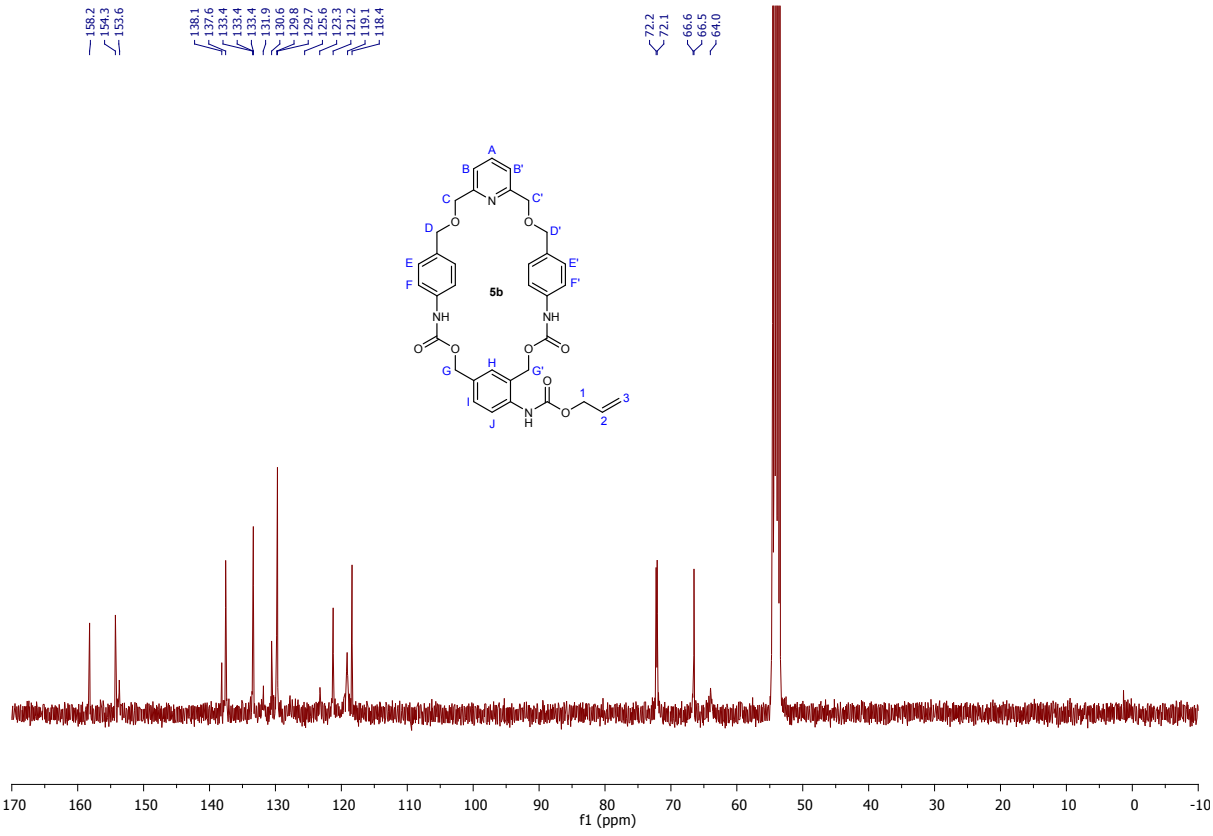
^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.2-154.3-153.6 138.1 (C_{CO}, $C_{quat.\ arom.}$), 137.6 (C_A), 133.5-133.4 ($C_{quat.\ arom.}$), 133.3 (C_2), 131.9 (C_H), 130.6 (C_I), 129.8-129.7 (C_E, $C_{E'}$), 123.3 (C_J), 121.2 (C_B, $C_{B'}$), 119.1 (C_F, $C_{F'}$), 118.4 (C_3), 72.2-72.1 (C_C, $C_{C'}$, C_D, $C_{D'}$), 66.6-66.5 (C_G, C_1), 64.0 ($C_{G'}$).

HRMS (ESI$^+$) *m/z* = 639.2461 $[M+H]^+$ (calc. for $C_{35}H_{35}N_4O_8$: 639.2449 $[M+H]^+$)

HPLC rt: 4.45 minutes

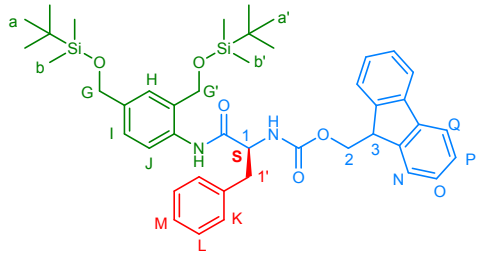


^{1}H NMR spectrum of **5b**, 400 MHz, 298 K, CD_2Cl_2

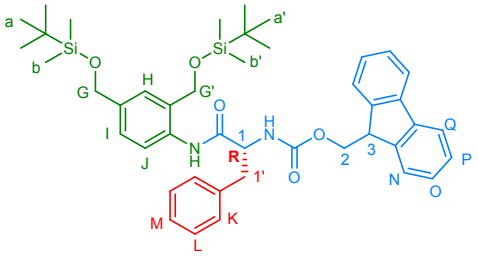


^{13}C NMR spectrum of **5b**, 100 MHz, 298 K, CD_2Cl_2

Preparation of compound (S)-20 (same procedure for (R)-20)



(*S*)-20



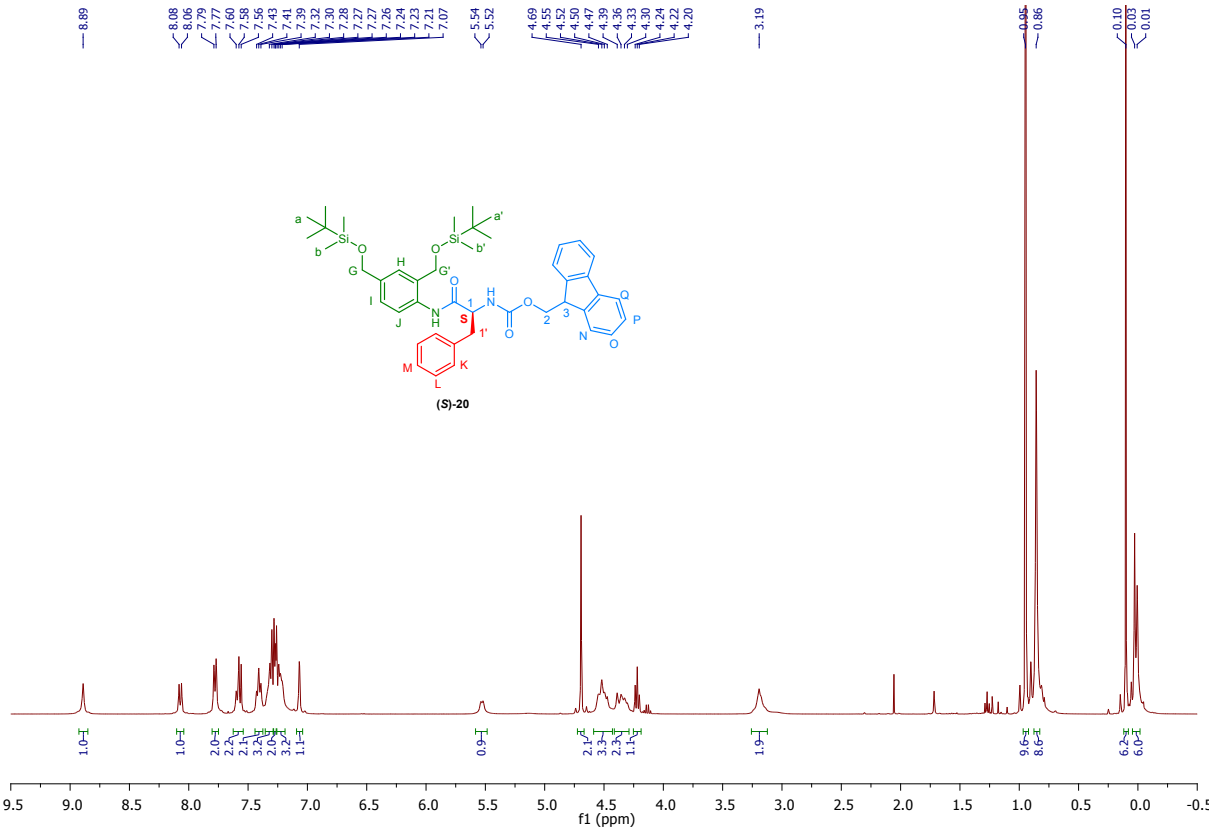
(*R*)-20

To a solution of *N*-(9-Fluorenylmethoxycarbonyl)-L-phenylalanine for **(*S*)-20** (or *N*-(9-Fluorenylmethoxycarbonyl)-D-phenylalanine for **(*R*)-20**) (3.42 g, 8.65 mmol, 1.1 equiv.) in dry mixture of 9:1 DMF/DCM (35 mL) were succesively added Et_3N (1.20 mL, 8.65 mmol, 1.1 equiv.), ethyl chloroformate (853 µL, 8.65 mmol, 1.1 equiv.) and a solution of aniline **16** (2.98 g, 7.81 mmol, 1 equiv.) in dry mixture of 9:1 DMF/DCM (35 mL). The solution was stirred for 18 hours at room temperature and solvents were removed under reduced pressure. The crude was diluted with AcOEt (400 mL) and washed with saturated $NH_4Cl_{(aq)}$ (2 x 200 mL) and saturated $NaCl_{(aq)}$ (300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (petrol/AcOEt, gradient elution 100:0 to 85:15, R_f = 0.3 (85:15)) gave **(*S*)-20** as a white solid wax (5.86 g, 7.80 mmol, quantitative).

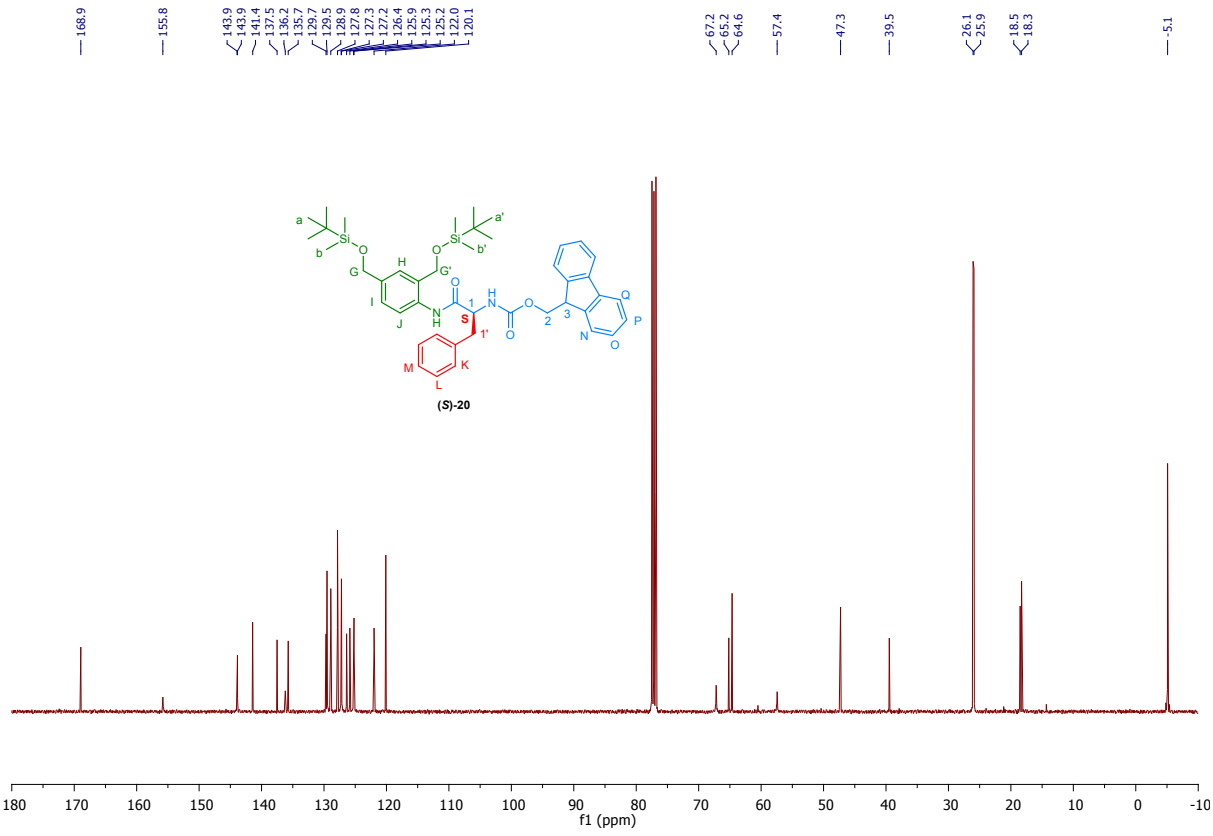
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (bs, 1H, $H_{NH\text{-}amide}$), 8.07 (d, *J* = 8.3, 1H, H_J), 7.78 (d, *J* = 7.5, 2H, H_Q), 7.58 (2d, *J* = 8.4, 2H, H_N), 7.41 (t, *J* = 7.3, 2H, H_P), 7.32 – 7.21 (m, 8H, H_I, H_K, H_L, H_M, H_O), 7.07 (s, 1H, H_H), 5.53 (d, 1H, *J* = 7.2, $H_{NH\text{-}carbamate}$), 4.69 (s, 2H, H_G), 4.50 (m, 3H, $H_{G'(1H)}$, H_1, $H_{2(1H)}$), 4.39 – 4.30 (m, 2H, $H_{G'(1H)}$, $H_{2(1H)}$), 4.21 (t, *J* = 7.0, 1H, H_3), 3.19 (m, 2H, $H_{1'}$), 0.95 (s, 9H, H_a), 0.86 (s, 9H, $H_{a'}$), 0.1 (s, 6H, H_b), 0,03-0.01 (2s, 6H, $H_{b'}$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 168.9 ($C_{CO\text{-}amide}$), 155.8 ($C_{CO\text{-}carbamate}$), 143.9-141.4-137.5-136.2-135.7-129.7 ($C_{arom.quat.}$), 129.5-128.9-127.8-127.3-127.2-126.4 (C_I, C_K, C_L, C_M, C_O, C_P), 125.9 (C_H), 125.3-125.2 (C_N), 122.0 (C_J), 120.1 (C_Q), 67.2 (C_2), 65.2 ($C_{G'}$), 64.6 (C_G), 57.4 (C_1), 47.3 (C_3), 39.5 ($C_{1'}$), 26.1-25.9 (C_a, $C_{a'}$), 18.5-18.3 ($C_{quat.\ t\text{-}Bu.}$), -5.1 (C_b, $C_{b'}$).

HRMS (ESI$^+$) *m/z* = 773.3786 $[M+Na]^+$ (calc. for $C_{44}H_{58}N_2O_5Si_2Na$ 773.3776 $[M+Na]^+$).

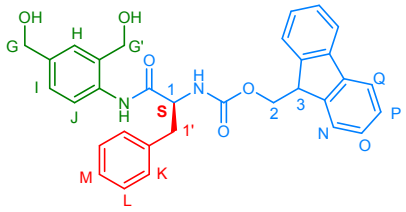


^{1}H NMR spectrum of **(*S*)-20**, 400 MHz, 298 K, $CDCl_3$

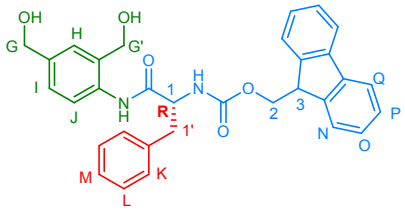


^{13}C NMR spectrum of **(*S*)-20**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound (S)-21 (same procedure for (R)-21)



(*S*)-21



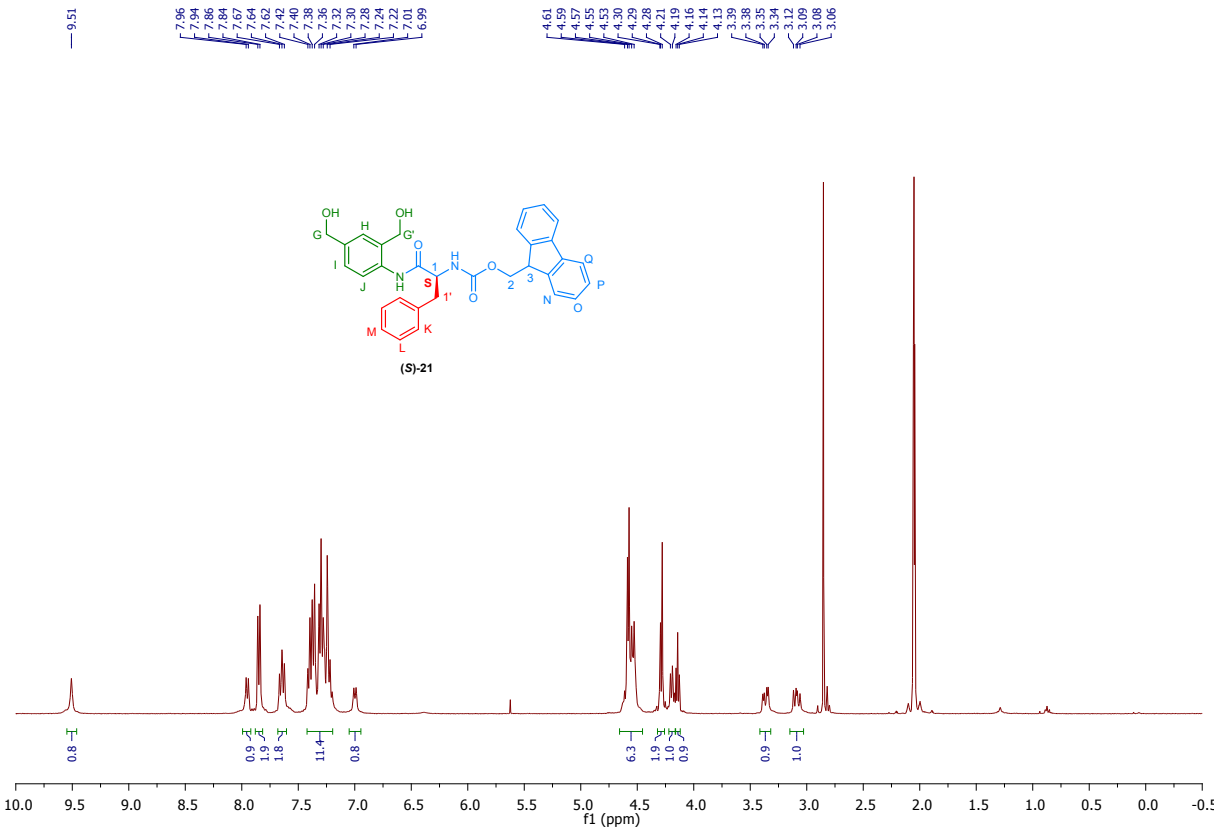
(*R*)-21

To a stirred solution of compound **(*S*)-20** (4.07 g, 5.41 mmol, 1 equiv.) in THF (54 mL) cooled at 0 °C, was added a solution of APTS.H_2O (309 mg, 1.6 mmol, 0.3 equiv.) in water (6 mL) dropwise. The reaction mixture was stirred at room temperature for 5 hours. The solvents were removed *in vacuo* and the crude residue was triturated with Et_2O. The solid was filtrated and dried *in vacuo* to give **(S)-21** without further purification as a white solid (2.87 g, 5.49 mmol, quantitative). R_f = 0.3 (DCM/MeOH : 95:5).

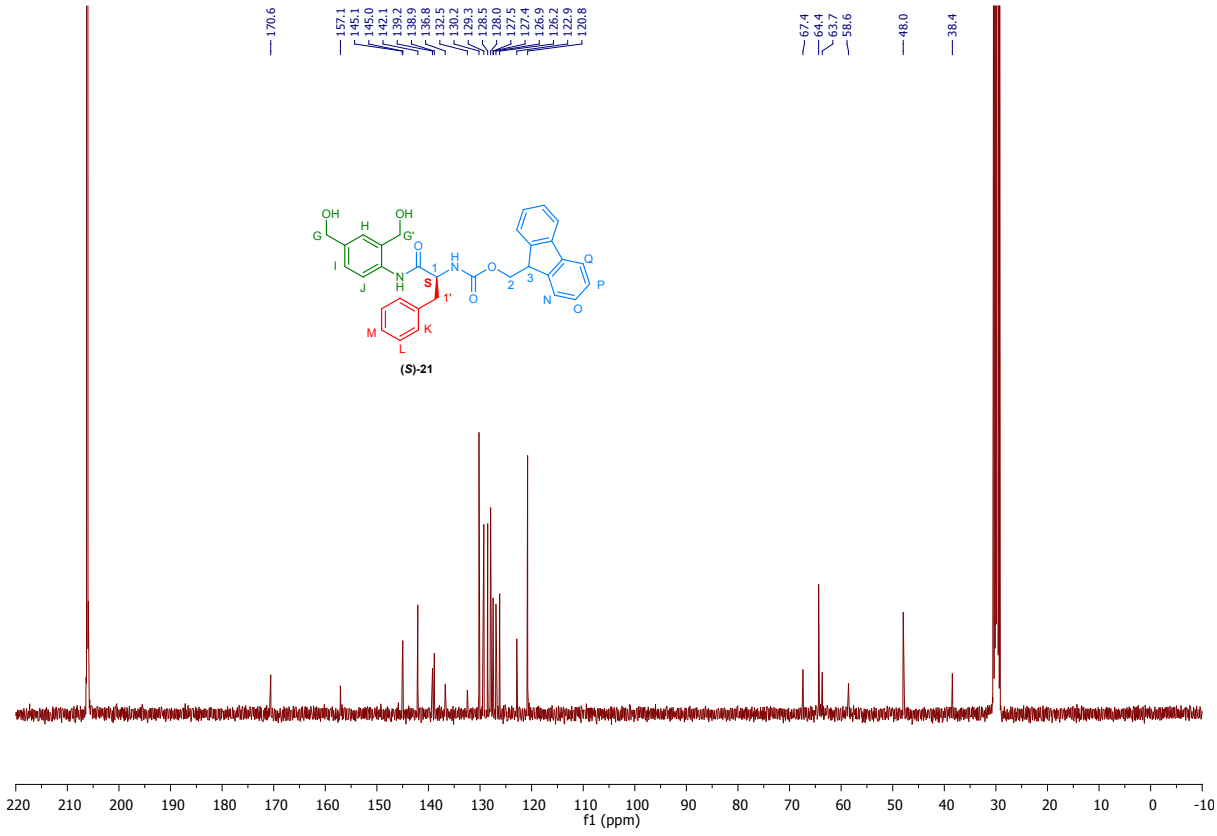
^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.51 (bs, 1H, $H_{NH\text{-}amide}$), 7.95 (d, *J* = 7.9, 1H, H_J), 7.85 (d, *J* = 7.5, 2H, H_Q), 7.64 (t, *J* = 8.7, 2H, H_L), 7.41 – 7.20 (m, 11H, H_H, H_I, H_K, H_M, H_N, H_O, H_P), 7.00 (d, *J* = 8.0, 1H, $H_{NH\text{-}carbamate}$), 4.61 – 4.53 (m, 6H, H_G, $H_{G'}$, H_1, H_{OH}), 4.28 (m, 2H, H_2), 4.9 (m, 1H, H_3), 4.14 (t, *J* = 5.8, 1H, H_{OH}), 3.36 (dd, *J* = 13.8, 5.2, 1H, $H_{1'}$), 3.09 (dd, *J* = 13.8, 9.3, 1H, $H_{1'}$).

^{13}C NMR (100 MHz, $(CD_3)_2CO$), δ: 170.6 ($C_{CO\text{-}amide}$), 157.1 ($C_{CO\text{-}carbamate}$), 145.1-145.0-142.1-139.2-138.9-136.8-132.5 ($C_{quat.\ arom.}$), 130.2-129.3-128.5-128.0-127.5-127.4-126.9 (C_H, C_I, C_K, C_M, C_N, C_O, C_P), 126.2 (C_L), 122.9 (C_J), 120.8 (C_Q), 67.4 (C_2), 64.4-63.7 (C_G, $C_{G'}$), 58.6 (C_1), 48.0 (C_3), 38.4 ($C_{1'}$).

HRMS (ESI$^+$) *m/z* = 545.2064 $[M+Na]^+$ (calc. for $C_{32}H_{30}N_2O_5Na$ 545.2047 $[M+Na]^+$).

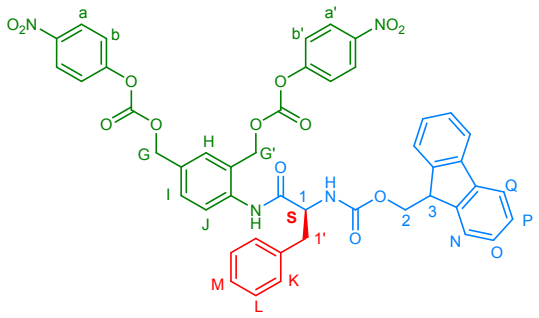


^{1}H NMR spectrum of **(*S*)-21**, 400 MHz, 298 K, $(CD_3)_2CO$

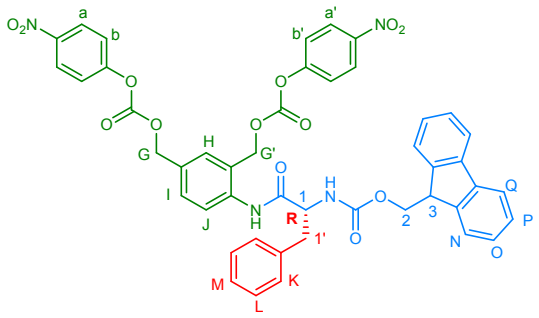


^{13}C NMR spectrum of **(*S*)-21**, 100 MHz, 298 K, $(CD_3)_2CO$

Preparation of compound (S)-22 (same procedure for (R)-22)



(*S*)-22



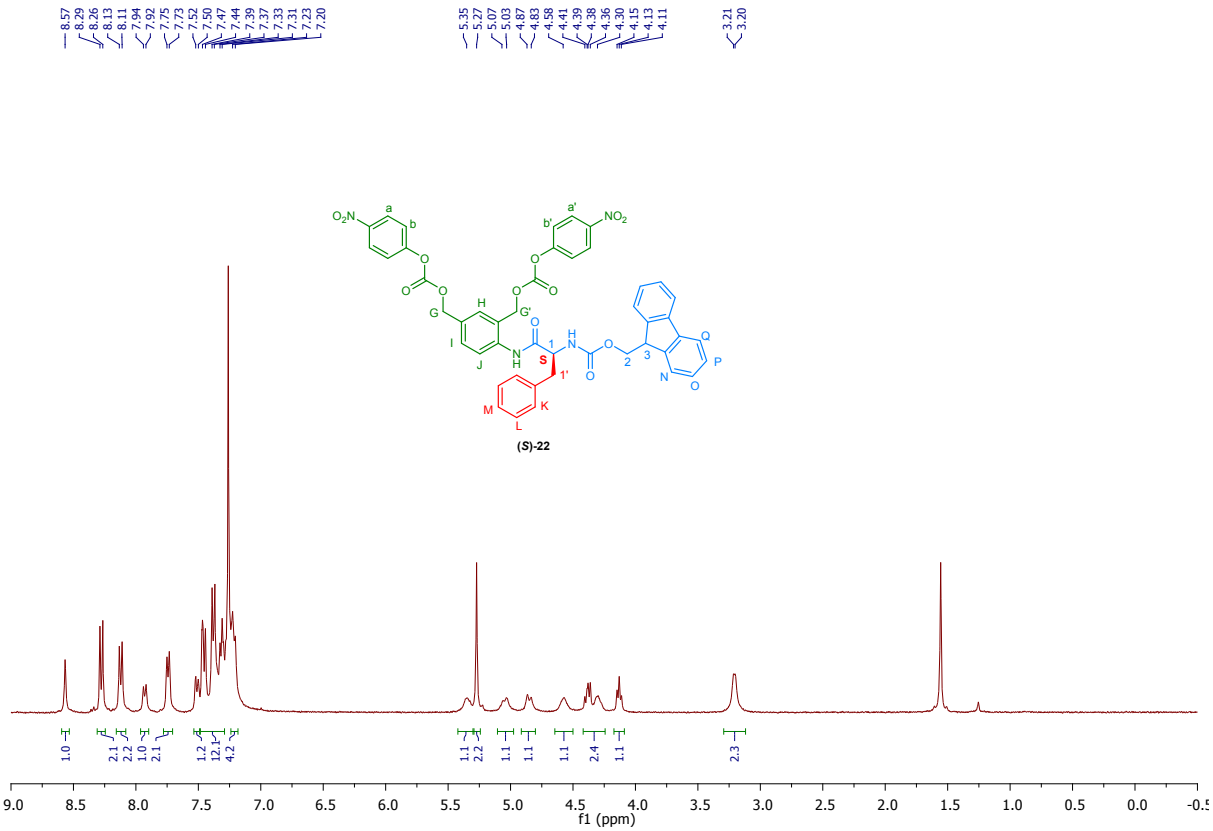
(*R*)-22

To a stirred solution of 4-nitrophenyl chloroformate (4.12 g, 21.9 mmol, 4 equiv.) in anhydrous THF (130 mL) cooled at 0 °C, was added pyridine (1.75 mL, 21.9 mmol, 4 equiv.) dropwise. After five minutes the crude dialcohol **(*S*)-21** (2.87 g, 5.49 mmol, 1 equiv.) was added portionwise and the reaction mixture was stirred at room temperature for 5 hours. The solvent was removed *in vacuo* and the crude residue was diluted with DCM and washed with saturated $NaHCO_{3(aq)}$ (3x). Organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was dissolved with a minimum of DCM and precipitated with a large volume of petrol. After filtration, compound **(*S*)-22** as obtained as a white solid (3.7 g, 4.4 mmol, 80% over two steps. R_f = 0.3 (DCM/AcOEt : 95:5).

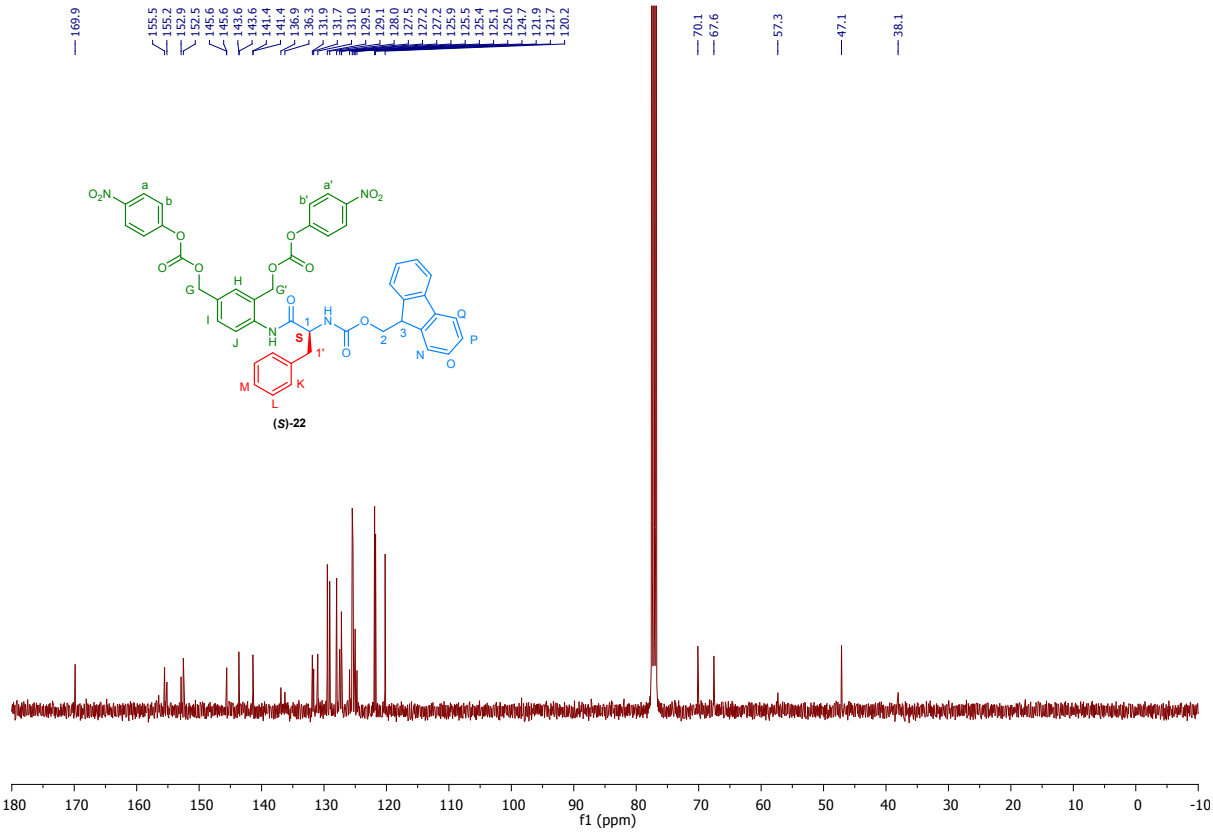
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, $H_{NH\text{-}amide}$), 8.27 (d, *J* = 8.6, 2H, H_a), 8,12 (d, *J* = 8.3, 2H, $H_{a'}$), 7.92 (d, *J* = 7.3, 1H, H_J), 7.74 (d, *J* = 6.5, 2H, H_Q), 7.51 (d, *J* = 7.2, 1H; H_I), 7.47 – 7.20 (m, 16H, H_b, $H_{b'}$, H_H, H_K, H_L, H_M, H_N, H_O, H_P), 5.35 (bs, 1H, $H_{NH\text{-}carbamate}$), 5.27 (s, 2H, H_G), 5.08 (d, *J* = 15, 1H, $H_{G'}$), 4.85 (d, *J* = 13.7, 1H, $H_{G'}$), 4.58 (bs, 1H, H_1), 4.41 – 4.30 (m, 2H, H_2), 4.13 (t, *J* = 6.8, 1H, H_3), 3.21 (m, 2H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$), δ 169.9 ($C_{CO\text{-}amide}$), 155.5-155.2-152.9-152.5-145.6-143.6-141.4-136.9-136.3 ($C_{quat.\ arom.}$, $C_{CO\text{-}carbonate}$, $C_{CO\text{-}carbamate}$), 131.9 ($C_{arom.}$), 131.7 ($C_{quat.\ arom.}$), 131.0 (C_I), 129.5-129.1-128.0-127.5-127.2 ($C_{arom.}$), 125.9 ($C_{quat.\ arom.}$), 125.5-125.4 (C_a, $C_{a'}$), 125.0 ($C_{arom.}$), 124.7 (C_J), 121.9-121.7 (C_b, $C_{b'}$), 120.2 (C_Q), 70.1 (C_G), 67.6 ($C_{G'}$, C_2), 57.3 (C_1), 47.1 (C_3), 38.1 ($C_{1'}$).

HRMS (ESI$^+$) *m/z* = 875.2186 $[M+Na]^+$ (calc. for $C_{46}H_{36}N_4O_{13}Na$ 875.2171 $[M+Na]^+$).

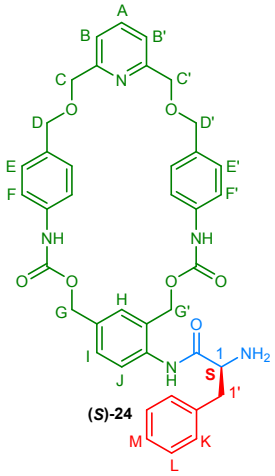


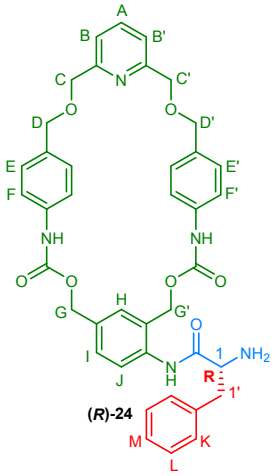
^{1}H NMR spectrum of **(*S*)-22**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **(*S*)-22**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound (S)-24 (same procedure for (R)-24)



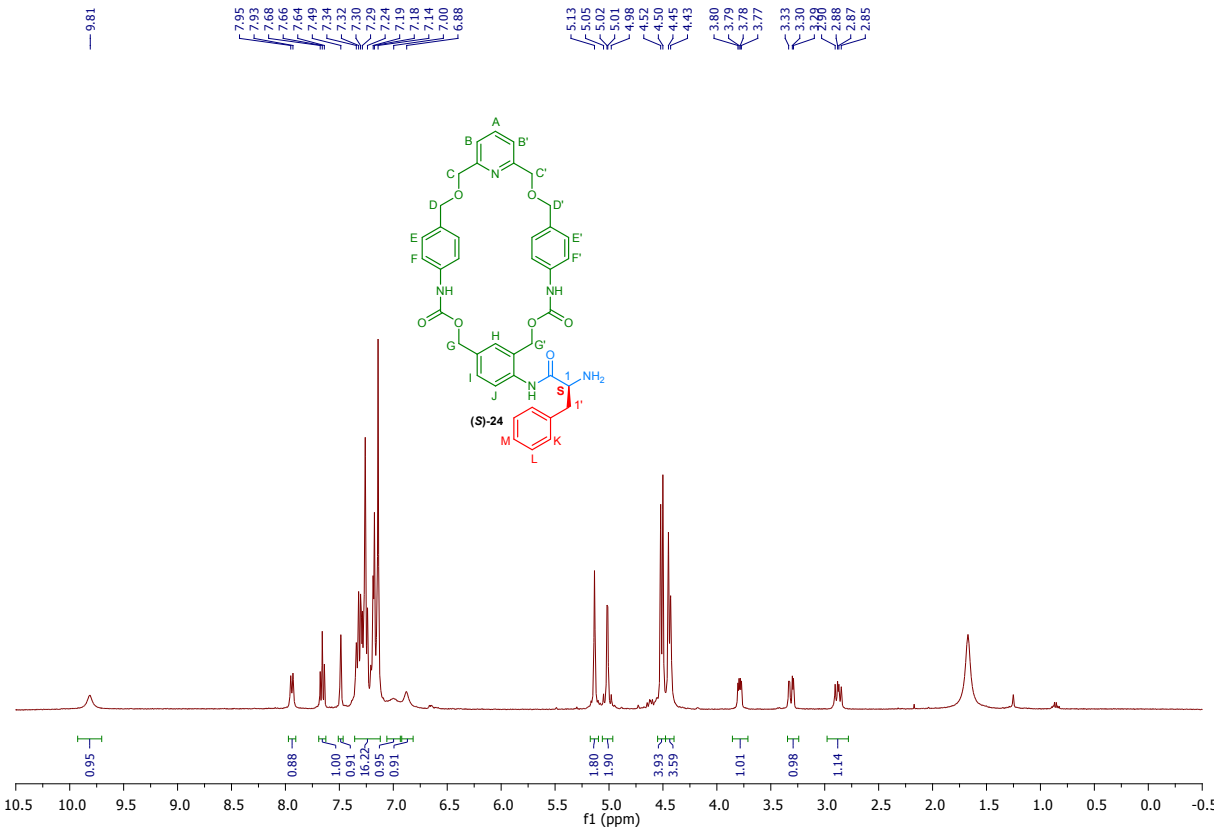


To a solution of bis-carbonate **(*S*)-22** (426 mg, 0.5 mmol, 1 equiv.) and di-aniline **15** (402 mg, 1.15 mmol, 2.3 equiv.) in DMF (6.25 mL), was added HOBt.H_2O (68 mg, 0.5 mmol, 1 equiv.) and the solution was stirred for 8 hours at 33°C. The solution was diluted with DMF (500 mL) and stirred for four days at 33°C. The solvent was removed *in vacuo* and the crude material was diluted with DCM (100 mL) and washed with saturated $NaHCO_{3(aq)}$ (3 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. This crude macrocycle **(*S*)-23** was engaged in the next step without further purification. To a solution of the crude fmoc derivative macrocycle **(*S*)-23** in DMF (5 mL) was added piperidine (0.5 mL) and the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.3 (95:5)) gave **(*S*)-24** as a solid wax (125 mg, 0.18 mmol, 36% over two steps).

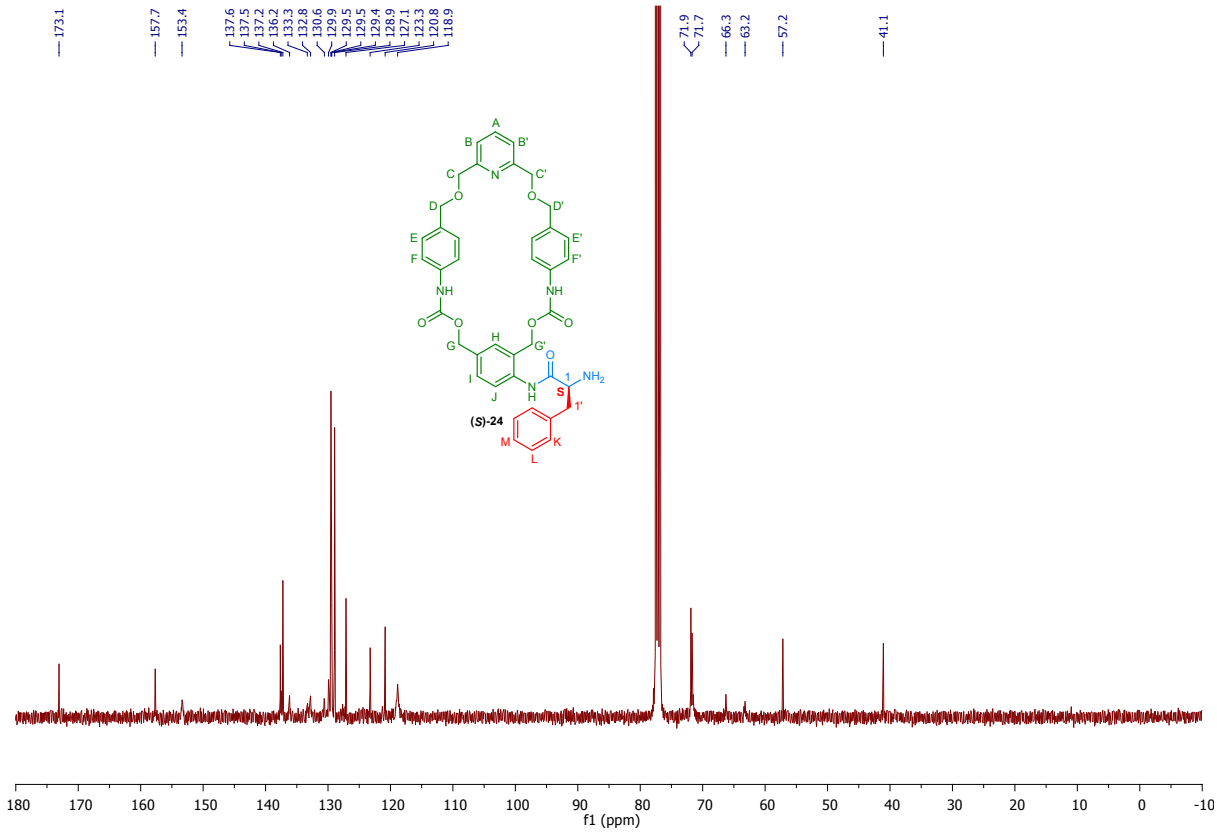
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H, $H_{NH\text{-}amide}$), 7.94 (d, *J* = 8.3, 1 H, H_J), 7.86 (t, *J* = 7.7, 1H, H_A), 7.49 (s, 1H, H_H), 7.34 – 7.14 (m, 16 H, H_B, $H_{B'}$, H_E, $H_{E'}$, H_F, $H_{F'}$, H_I, H_K, H_L, H_M), 7.00 (bs, 1H, $H_{NH\text{-}carbamate}$), 6.88 (bs, 1H, $H_{NH\text{-}carbamate}$), 5.13 (s, 2H, H_G), 5.02 (m, 2H, $H_{G'}$), 4.52-4.50 (2s, 4H, H_C, $H_{C'}$), 4.45-4.43 (2s, 4H, H_D, $H_{D'}$), 3.79 (dd, *J* = 8.7, 4.2, 1H, H_1), 3.31 (dd, *J* = 13.7, 4.3, 1H, $H_{1'}$), 2.87 (dd, *J* = 13.7, 8.9, 1H, $H_{1'}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 ($C_{CO\text{-}amide}$), 157.7-153.4 ($C_{CO\text{-}carbamate}$), 137.7, 137.5 ($C_{quat.\ arom.}$), 137.2 (C_A), 136.2-133.3-132.8 ($C_{quat.\ arom.}$), 130.6 (C_H), 129.9 (C_I), 129.5-129.4-128.9-127.1 ($C_{arom.}$), 123.3 (C_J), 120.8-118.9 ($C_{arom.}$), 71.9-71.7 (C_C, $C_{C'}$, C_D, $C_{D'}$), 66.3 (C_G), 63.2 ($C_{G'}$), 57.2 (C_1), 41.1 ($C_{1'}$).

HRMS (ESI$^+$) *m/z* = 702.2941 $[M+H]^+$ (calc. for $C_{40}H_{40}N_5O_7$: 702.2922 $[M+H]^+$)

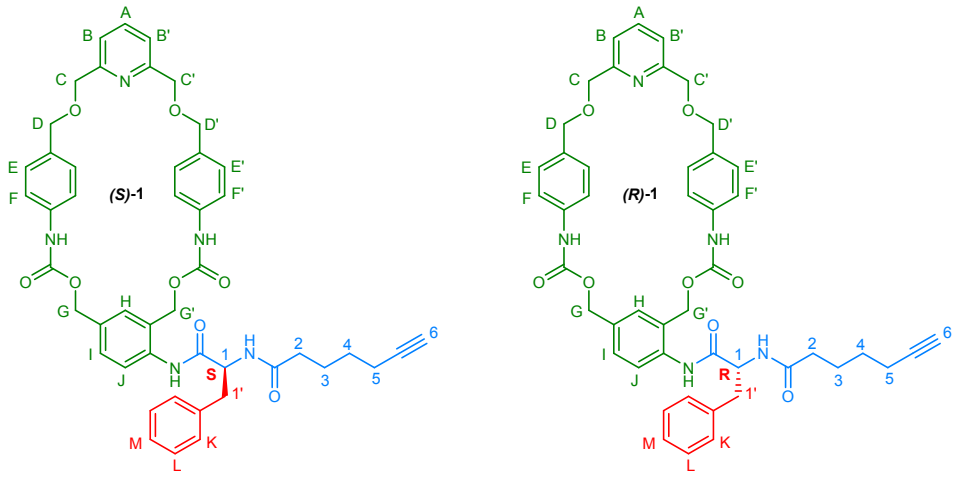


^{1}H NMR spectrum of **(*S*)-24**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **(*S*)-24**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound (S)-1 (same procedure for (R)-1)



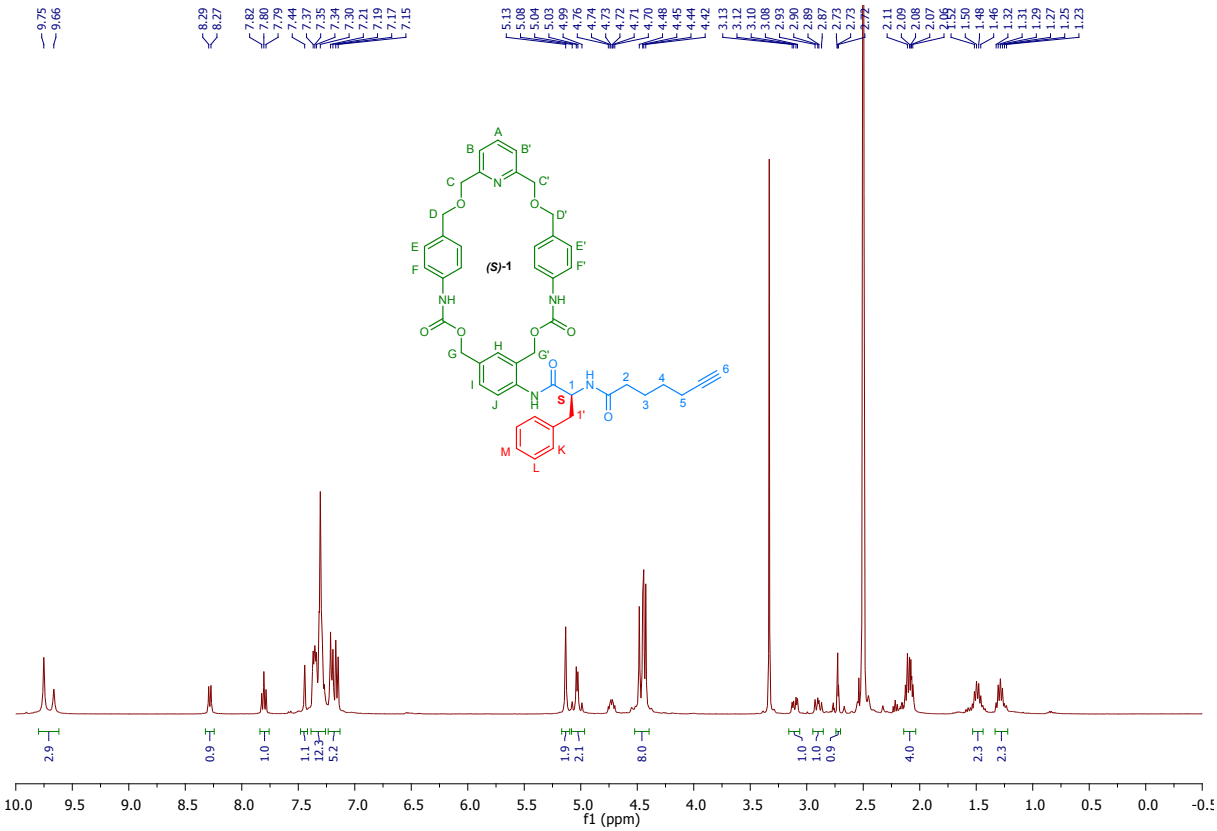
To a solution of macrocycle **(*S*)-24** (105 mg, 0.15 mmol, 1 equiv.) and 6-heptynoic acid **25** (38 mg, 0.30 mmol, 2 equiv.) in DMF (3 mL) was added DMAP (37 mg, 0.30 mmol, 2 equiv.) and EDC.HCl (58 mg, 0.30 mmol, 2 equiv.). The solution was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.5 (95:5)) gave ***(S)*-1** as a beige solid (105 mg, 0.13 mmol, 86%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75-9.66 (2bs, 3H, $H_{NH\text{-}amide}$, $H_{NH\text{-}carbamate}$), 8.28 (d, J = 8.0, 1H, $H_{NH\text{-}amide}$), 7.80 (t, J = 7.7, 1H, H_A), 7.44 (s, 1H, H_H), 7.37 – 7.15 (m, 17H, H_B, $H_{B'}$, H_E, $H_{E'}$, H_F, $H_{F'}$, H_I, H_J, H_K, H_L, H_M), 5.13 (s, 2H, H_G), 5.04 (AB syst., J = 14.4, 2H, $H_{G'}$), 4.72 (m, 1H, H_1), 4.48-4.45-4.44-4.42 (4s, 8H, H_C, $H_{c'}$, H_D, $H_{D'}$), 3.11 (dd, J = 13.6, 5.4, 1H, $H_{1'}$), 2.90 (dd, J = 13.4, 9.5, 1H, $H_{1'}$), 2.73 (t, J = 2.6, 1H, H_6), 2.08 (m, 4H, H_2, H_5), 1.49 (m, 2H, H_3), 1.28 (m, 2H, H_4).

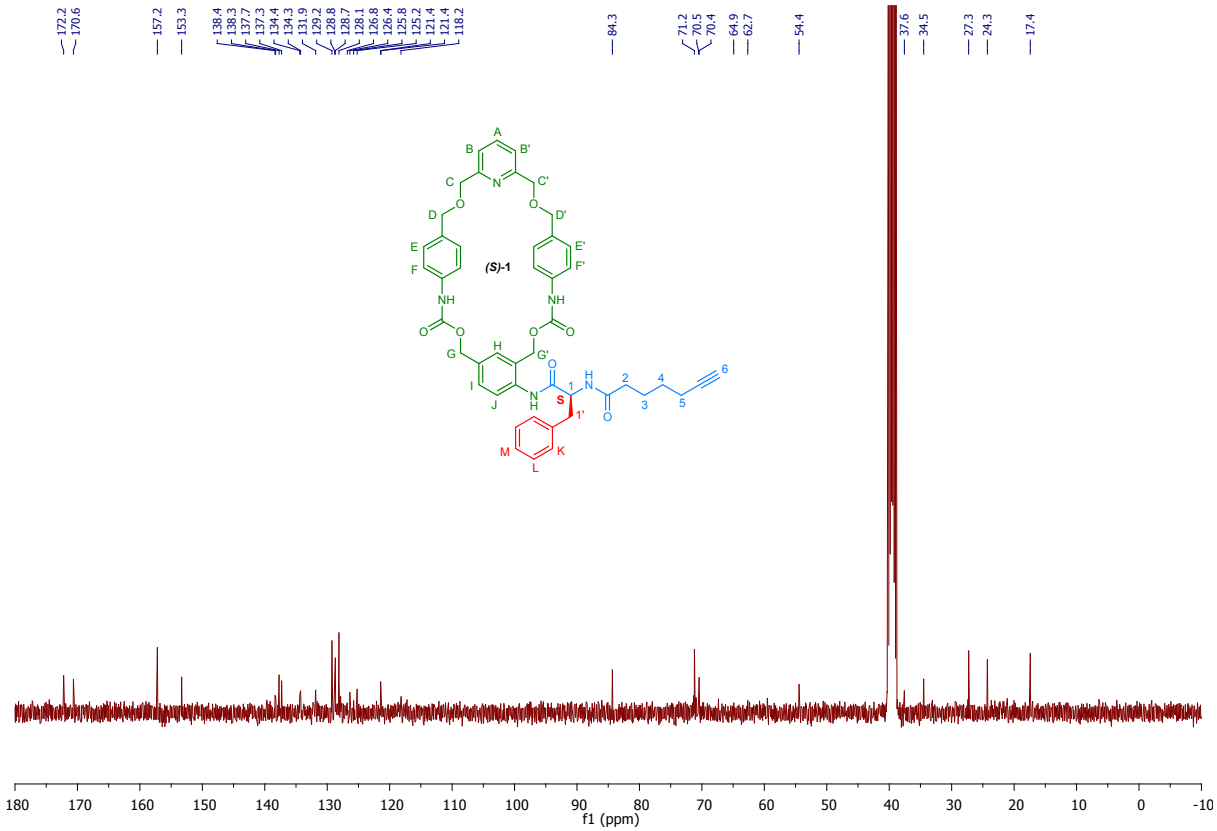
^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2-170.6 ($C_{CO\text{-}amide}$), 157.2-153.3-138.4-138.3-137.7 ($C_{CO\text{-}carbamate}$, $C_{quat.\ arom.}$), 137.3 (C_A), 134.4-134.3-131.9 ($C_{quat.\ arom.}$), 130.8 (C_H), 129.3-128.9-128.8-128.2 ($C_{arom.}$), 126.8 (C_H), 126.4-125.3-121.5-121.4-118.5-118.2 ($C_{arom.}$), 84.3 ($C_{quat.\ alkyne}$), 71.4 (C_6), 71.3 – 70.5 (C_C, $C_{c'}$, C_D, $C_{D'}$), 69.4 (C6), 64.9 (C_G), 61.4 ($C_{G'}$), 54.5 (C_1), 37.6 ($C_{1'}$), 34.5 (C_2), 27.3 (C_4), 24.3 (C_3), 17.4 (C5).

HRMS (ESI$^+$) m/z = 810.3488 $[M+H]^+$ (calc. for $C_{48}H_{46}N_5O_8$: 810.3497 $[M+H]^+$)

HPLC rt: 4.95 minutes

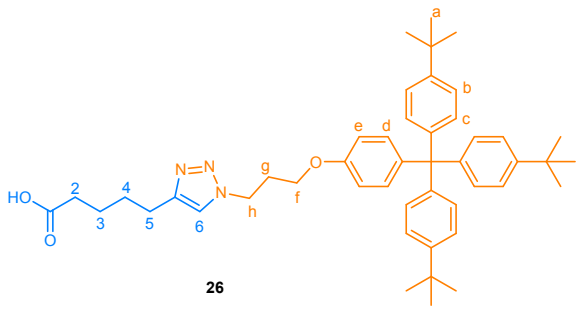


^{1}H NMR spectrum of **(*S*)-1**, 400 MHz, 298 K, DMSO-d_6



^{13}C NMR spectrum of **(*S*)-1**, 100 MHz, 298 K, DMSO-d_6

Preparation of compound 26



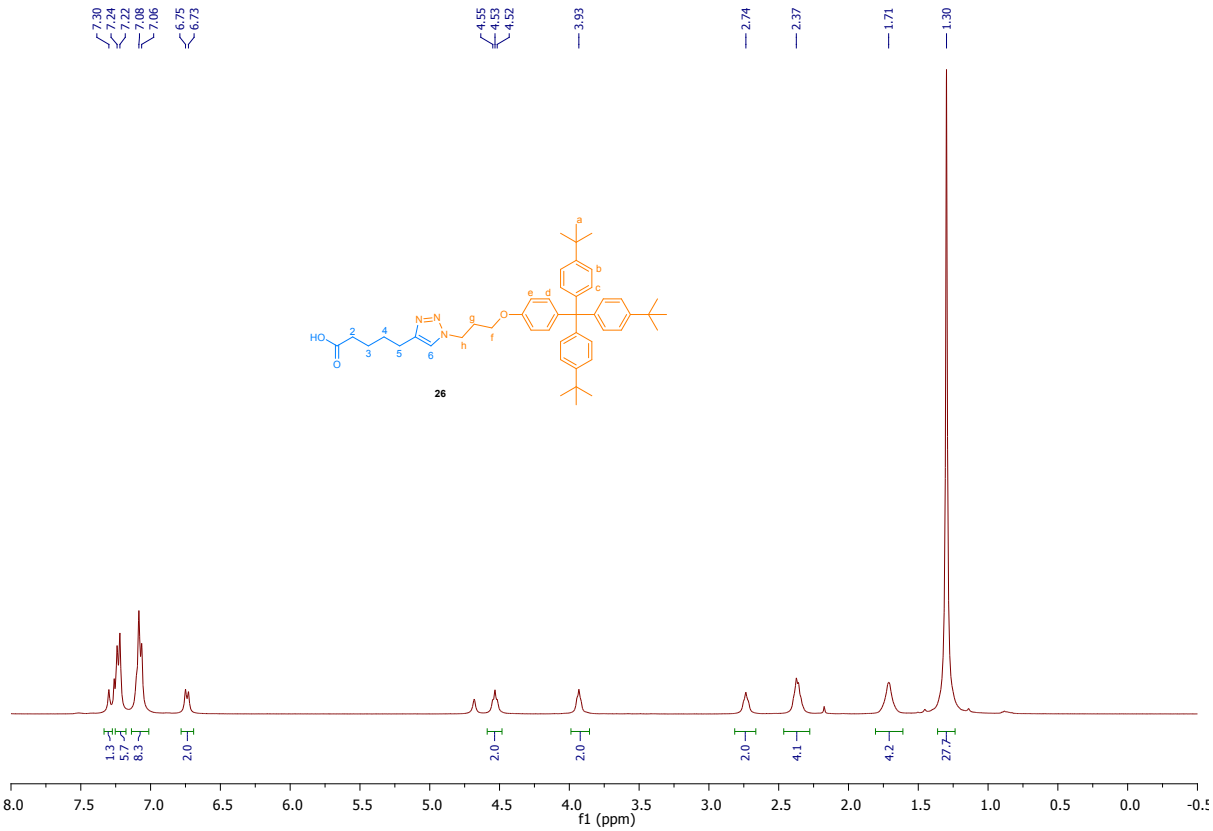
26

To a solution of azide **2a** (209.4 mg, 0.35 mmol, 1 equiv.) and 6-heptynoic acid **25** (44.8 mg, 0.35 mmol, 1 equiv.) in degassed DCM (7 mL) was added $[Cu(MeCN)_4]PF_6$ (136.0 mg, 0.35 mmol, 1 equiv.). The solution was stirred at room temperature for 18 hours. The reaction was hydrolyzed with saturated $EDTA.2Na_{(aq)}$ (10 mL) for one hour and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.3 (95:5)) gave **26** as a white solid (125.3 mg, 0.17 mmol, 49%).

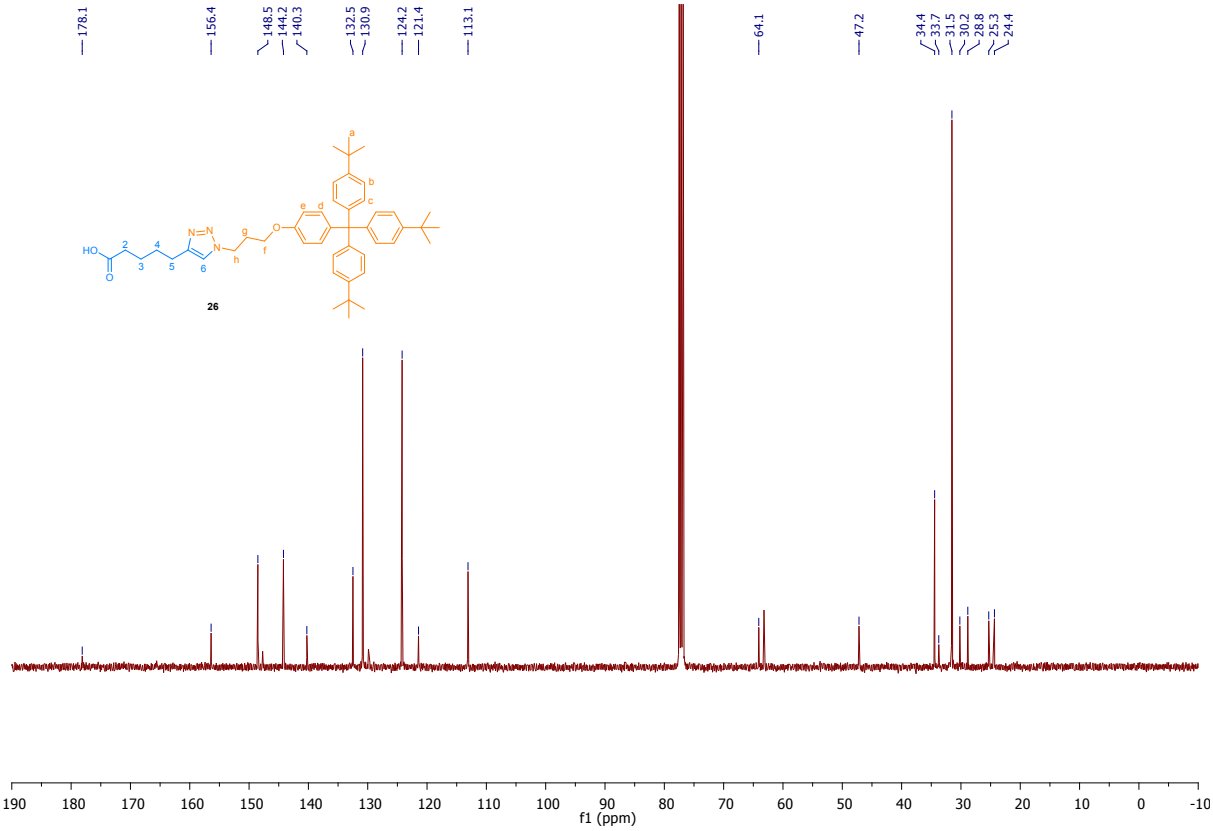
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H, H_6), 7.23 (d, *J* = 8.1, 6H, H_a), 7.07 (m, 8H, H_b, H_d), 6.74 (d, *J* = 8.4, 2H, H_e), 4.53 (t, *J* = 6.3, 2H, H_h), 3.93 (m, 2H, H_f), 2.74 (m, 2H, H_5), 2.37 (m, 4H, H_2, H_g), 1.71 (m, 4H, H_3, H_4), 1.30 (s, 27H, H_a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C_{CO}), 156.5-148.5-144.2-140.3 ($C_{quat.\ arom.}$), 132.5-130.9 (C_b, C_d), 124.2 (C_a), 121.4 (C_6), 113.1 (C_c), 64.1 (C_f), 47.2 (C_h), 34.4 ($C_{quat.\ t\text{-but}}$), 33.7 (C_2 or C_g), 31.5 (C_a), 30.2 (C_2 or C_g), 28.8 (C_3 or C_4), 25.3 (C_f), 24.4 (C_3 or C_4).

HRMS (ESI$^+$) *m/z* = 714.4636 $[M+H]^+$ (calc. for $C_{47}H_{60}N_3O_3$: 714.4629 $[M+H]^+$)

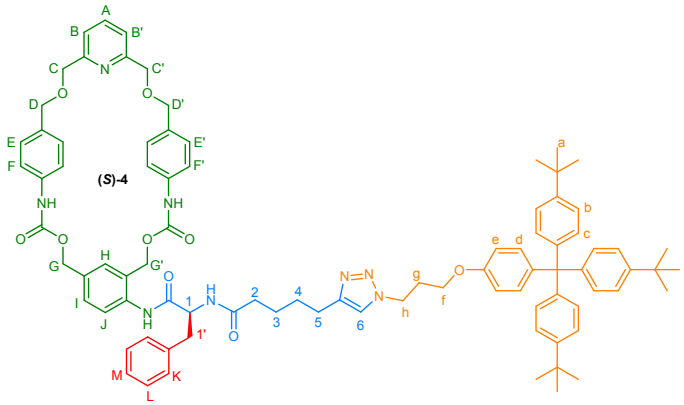


^{1}H NMR spectrum of **26**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **26**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound (S)-4



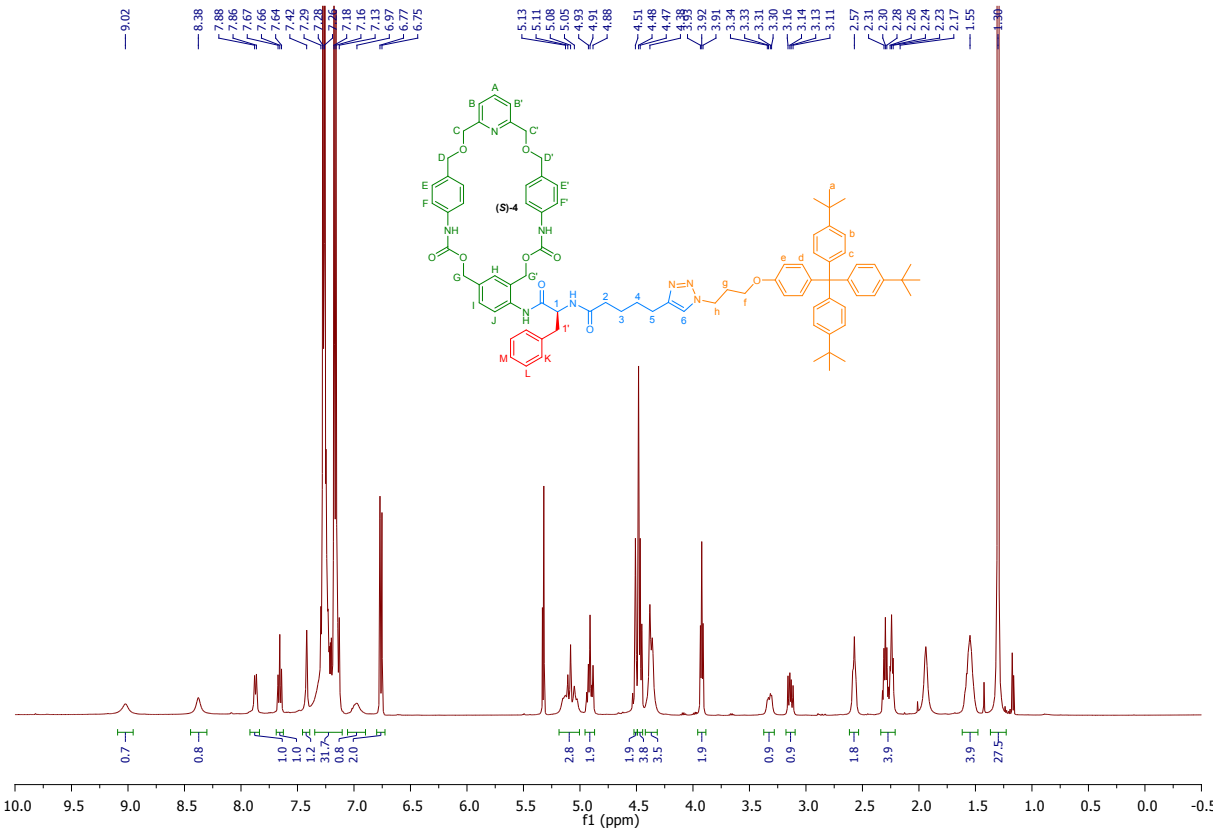
To a solution of macrocycle **(*S*)-24** (30.2 mg, 0.04 mmol, 1 equiv.) and acid **26** (33.7 mg, 0.047 mmol, 1.2 equiv.) in DMF (0.5 mL) was added DMAP (6.6 mg, 0.054 mmol, 1.4 equiv.) and EDC.HCl (9.7 mg, 0.049 mmol, 1.2 equiv.). The solution was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 98:2 to 95:5, R_f = 0.5 (95:5)) gave **(*S*)-4** as a white solid (46.3 mg, 0.033 mmol, 84%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.02 (bs, 1H, $H_{NH\text{-amide arom.}}$), 8.38 (bs, 1H, $H_{NH\text{-carbamate}}$), 7.87 (d, 1H, *J* = 8.1, H_J), 7.66 (t, 1H, *J* = 7.7, H_A), 7.42 (s, 1H, H_H), 7.29 (m, 1H, H_I), 7.29 – 7.13 (m, 32H, H_I, H_B, $H_{B'}$, H_E, $H_{E'}$, H_F, $H_{F'}$, H_K, H_L, H_M, H_6, H_b, H_c, H_d, $H_{NH\text{-carbamate}}$), 6.76 (bs, 1H, $H_{NH\text{-amide}}$), 6.76 (d, 2H, *J* = 8.9, H_e), 5.10 (m, 3H, H_G, $H_{G'(1H)}$), 4.93 – 4.88 (m, 2H, $H_{G'(1H),}$ H_1), 4.51 (s, 2H, H_C or $H_{C'}$), 4.49 (s, 2H, H_C or $H_{C'}$), 4.47 (t, 2H, *J* = 7.0, H_h), 4.35 (2s, 4H, H_D, $H_{D'}$), 3.92 (t, 2H, *J* = 5.8, H_f), 3.32 (m, 1H, $H_{1'}$), 3.14 (dd, 1H, *J* = 8.3, 14.2, $H_{1'}$), 2.57 (m, 2H, H_5), 2.30 (qi, 2H, *J* = 6.4, H_g), 2.25 (t, 2H, *J* = 6.6, H_2), 1.55 (m, 4H, H_3, H_4), 1.30 (s, 27H, H_a).

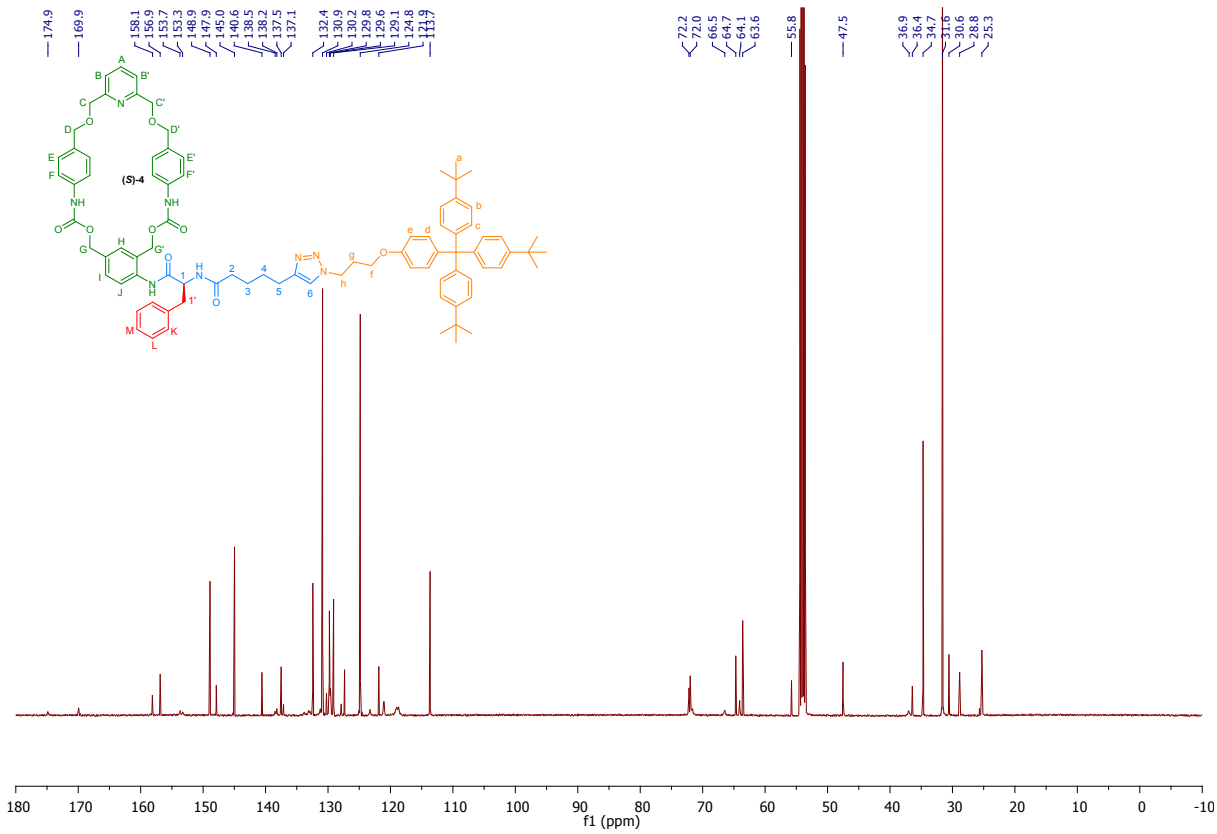
^{13}C NMR (126 MHz, CD_2Cl_2) δ 174.9-169.9 ($C_{CO\text{-amides}}$), 158.1-156.9-153.5-153.1-148.9-147.8-145.0-140.6-138.5-138.1 ($C_{quat.\ arom.,\ CO\text{-carbamate}}$), 137.5 ($C_A$), 137.4 – 132.4 ($C_{arom.}$), 131.4 ($C_H$), 130.8 – 124.8 ($C_{arom.}$), 123.0 ($C_J$), 121.8 – 118.6 ($C_{arom.}$), 113.7 ($C_e$), 72.2 ($C_C$, $C_{C'}$), 72.0 (C_D, $C_{D'}$), 66.5 (C_G), 64.7 (C_f), 64.1 ($C_{G'}$), 63.6 ($C_{quat.}$), 55.8 (C_1), 47.5 (C_h), 36.9 ($C_{1'}$), 36.4 (C_2), 34.7 ($C_{quat.\ t\text{-But}}$), 31.6 (C_a), 30.6 (C_g), 28.8 (C_4), 25.3 (C_5, C_3).

HRMS (ESI$^+$) *m/z* = 714.4636 $[M+H]^+$ (calc. for $C_{47}H_{60}N_3O_3$: 714.4629 $[M+H]^+$)

HPLC rt: 9.19 minutes

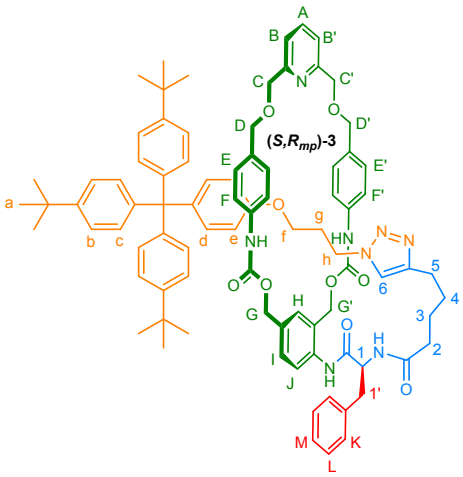


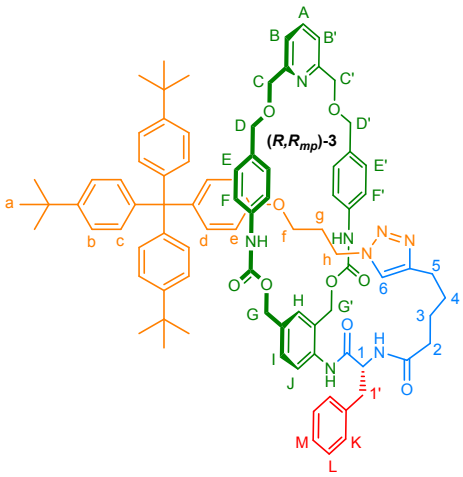
^{1}H NMR spectrum of **(*S*)-4**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **(*S*)-4**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound (S)-3 (same procedure for (R)-3)





Mechanical planar chirality drawn as (R_{mp}) for visual purposes, not experimentally determined.

Macrocycle **(*S*)-1** (30.0 mg, 0.037 mmol, 1 equiv.) and $[Cu(MeCN)_4]PF_6$ (13.8 mg, 0.037 mmol, 1 equiv.) were placed in a 100 mL two-neck round-bottom flask equiped with a condenser. The system is purged with argon. Degassed DCM (18 mL) was added and the solution was stirred at 60°C for 30 minutes. Stopper **2a** (109 mg, 0.185 mmol, 5 equiv.) and additive **5a** or **5b** (0.0185 mmol, 0.5 equiv.) were placed in a 50 mL two-neck round-bottom flask and purged with argon. Degassed DCM (19 mL) was added to obtain a clear solution. This solution was carefully added under argon to the solution of **(*S*)-1** and Cu(I) catalyst. The crude yellow solution was stirred at 60 °C for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved with a solution of DCM/MeOH 1:1 (4 mL). The resulting yellow dark solution was stirred with KCN (12 mg, 0.185 mmol, 5 equiv.) for one hour until it turned out white and solvent were removed by air bubbling. The crude material was dissolved in DCM and washed with water (5x). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.4 (95:5)) gave **(*S*)-3** as a solid colorless wax (23 mg, 0.016 mmol, 45%).

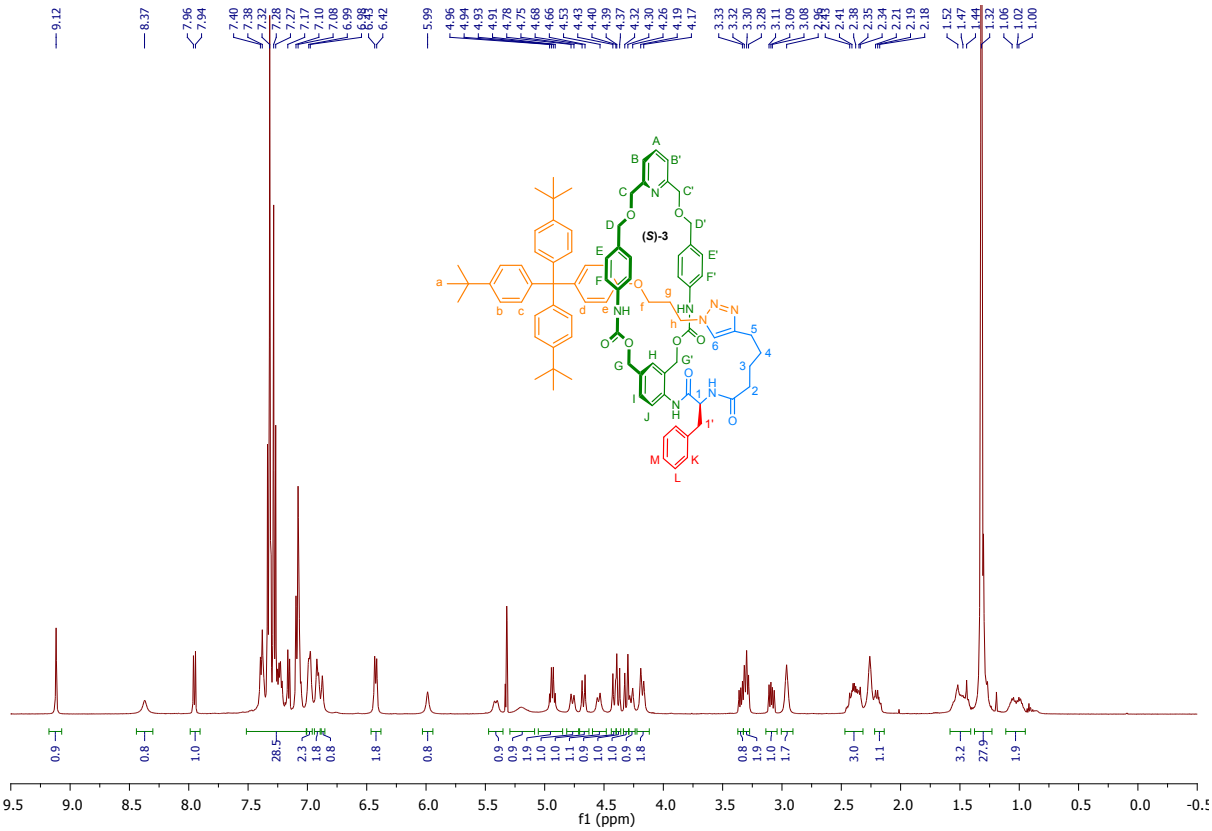
^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.1 (s, 1H, $H_{NH\text{-amide arom.}}$), 8.37 (bs, 1H, $H_{NH\text{-carbamate}}$), 7.95 (d, 1H, *J* = 8.1, H_J), 7.40 – 6.91 (m, 33H, H_A, H_B, $H_{B'}$, H_E, $H_{E'}$, H_F, $H_{F'}$, H_K, H_L, H_M, H_H, H_I, H_b, H_c, H_d, $H_{NH\text{-carbamate}}$), 6.87 (bs, 1H, $H_{NH\text{-carbamate}}$), 6.76 (d, 2H, *J* = 8.9, H_e), 5.99 (s, 1H, H_6), 5.41 (d, J = 11.5, 1H, $H_{G'}$), 5.20 (bs, 1H, H_G), 4.94 (dd, 2H, *J* = 8.1, 7.9, H1, H_G), 4.77 (d, *J* = 12.6, 1H, $H_{G'}$), 4.67 (d, *J* = 12.5, 1H, H_C or $H_{C'}$), 4.55 (d, *J* = 11.6, 1H, H_C or $H_{C'}$), 4.41 (d, *J* = 12.7, 1H, H_C or $H_{C'}$), 4.38 (d,

J = 12.1, 1H, H_C or $H_{C'}$), 4.31 (d, *J* = 13.1, 1H, H_D or $H_{D'}$), 4.27 (d, *J* = 12.6, 1H, H_D or $H_{D'}$), 4.18 (d, *J* = 12.6, 2H, H_D or $H_{D'}$), 3.34 (dd, *J* = 14.2, 7.4, 1H, $H_{1'}$), 3.30 (t, *J* = 8.2, 2H, H_h), 3.09 (dd, 1H, *J* = 14.1, 7.9, $H_{1'}$), 2.96 (bs, 2H, H_f), 2.38 (m, 3H, $H_{2(1H)}$, H_5), 2.19 (m, 1H, H_2), 1.49 (m, 3H, H_3, $H_{4(1H)}$), 1.32 (s, 28H, $H_{4(1H)}$, H_a), 1.02 (m, 2H, H_g).

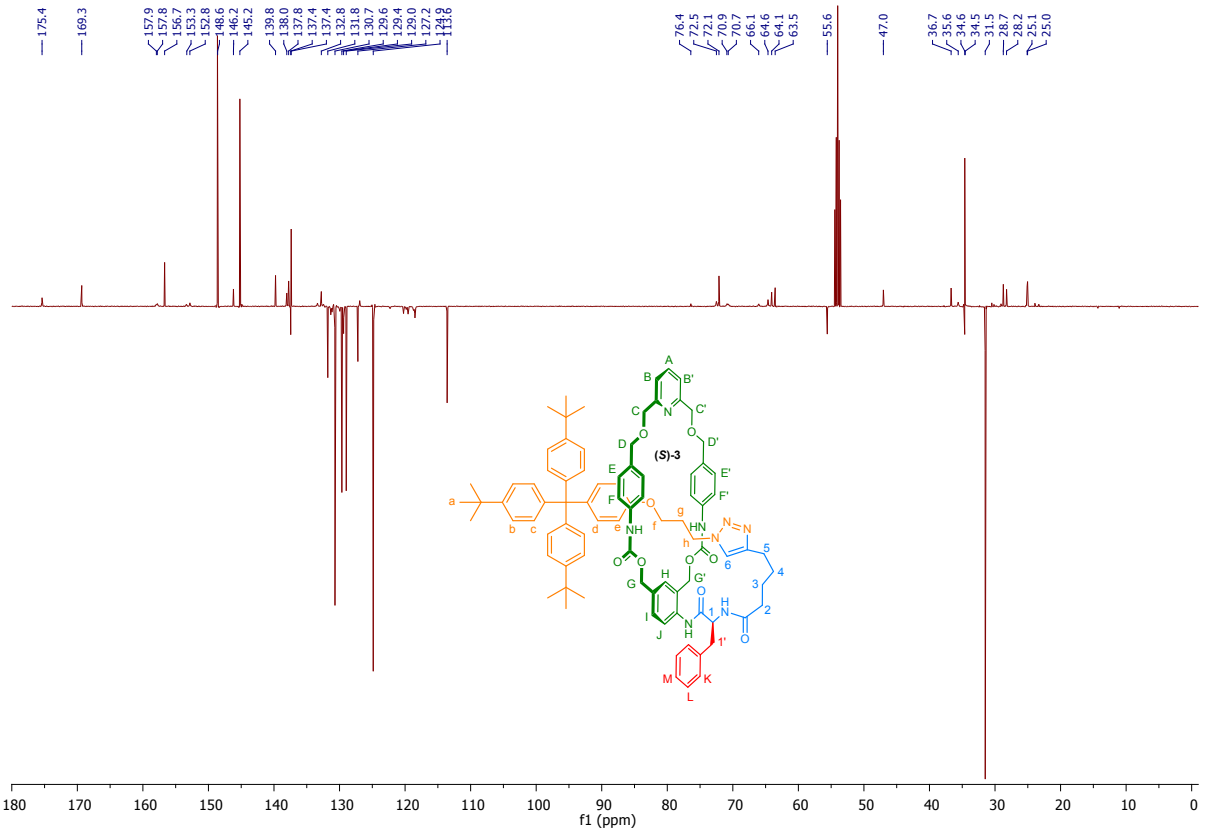
^{13}C NMR (126 MHz, CD_2Cl_2) δ 175.4-169.3 (C_{CO}), 157.9, 157.8, 156.7, 153.3, 152.8, 148.6, 146.2, 145.2, 139.8, 138.0, 137.8, 137.4, 133.4, 132.8, 132.4, 131.8 (C_d), 131.3-131.2 (C_H, $_I$), 130.7, 129.6, 129.4, 129.0, 127.2, 126.9, 124.9, 122.3 (C_J), 120.2 (C_6), 119.8, 119.5, 118.7, 118.5, 113.6 (C_e), 76.4 ($C_{quat.\ triazole}$), 72.5-72.1 (C_C, $C_{C'}$), 70.9-70.7 (C_D, $C_{D'}$), 66.1 (C_G), 64.6 (C_f), 64.1 ($C_{G'}$), 63.5, 55.6 (C_1), 47.0 (C_h), 36.7 (C_2), 35.6 ($C_{1'}$), 34.5 ($C_{quat.\ t\text{-but.}}$), 31.5 (C_a), 28.7 (C_g), 28.1 (C_4), 24.9 (C_3), 24.9 (C_5).

HRMS (ESI$^+$) *m/z* = 1419.7231 $[M+Na]^+$ (calc. for $C_{87}H_{96}N_8O_9Na$: 1419.7192 $[M+H]^+$)

HPLC rt: 9.35 minutes

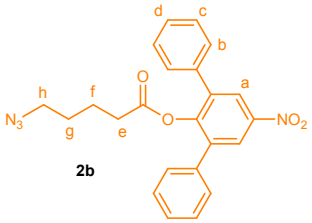


^{1}H NMR spectrum of (***S***)-**3**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **(*S*)-3**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound 2b



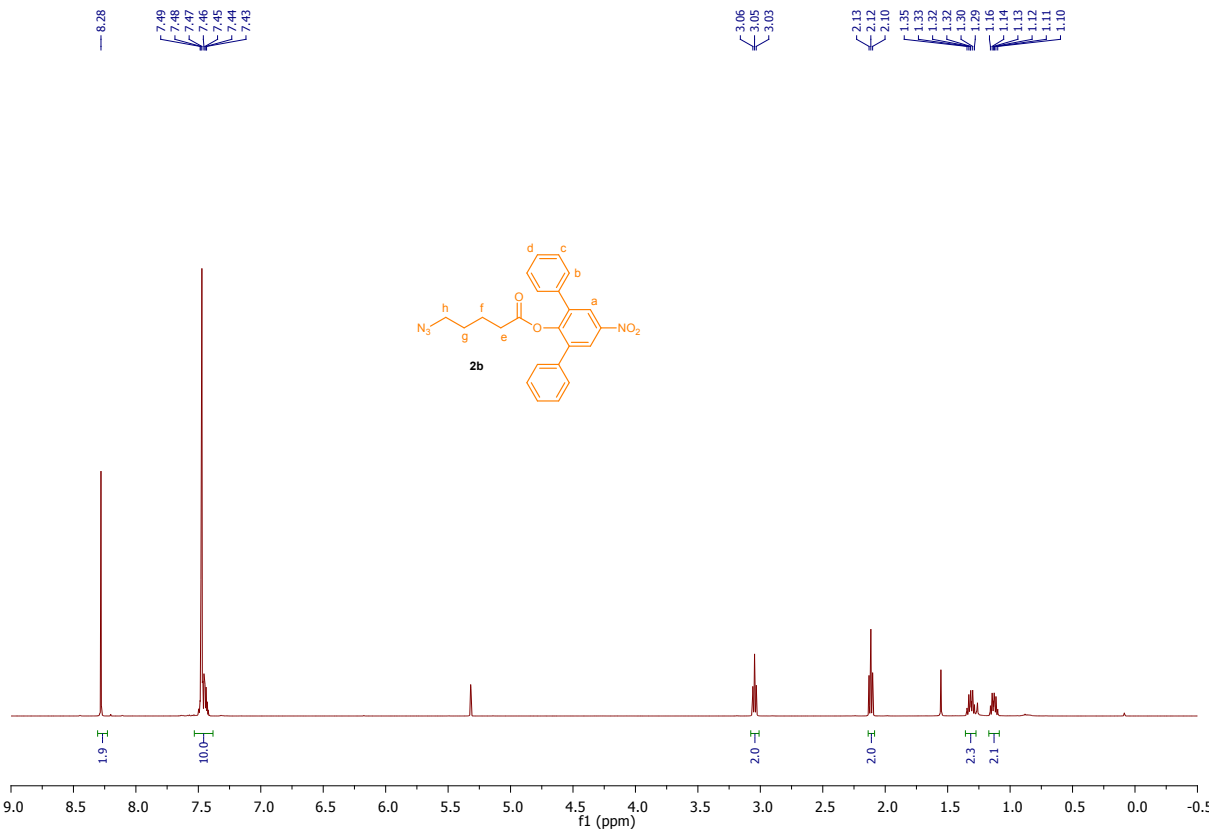
2b

To a solution of 5-azidopentanoic acid **27** (1 g, 7.0 mmol, 1.4 equiv.) in dry DCM (25 mL) were added EDC.HCl (1.34 g, 7.0 mmol, 1.4 equiv.) and DMAP (855 mg, 7.0 mmol, 1.4 equiv.). Solution was stirred 5 min before 2,6-diphenyl-4-nitrophenol **10** (1.46 g, 5.0 mmol, 1 equiv.) was added and stirred for 3 hours at room temperature. DCM was removed *in vacuo* before EtOAc and water were added. Layers were separated and organic layers was washed with saturated $NaHCO_{3(aq)}$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (petrol/AcOEt 95:5, R_f = 0.7 (70:30)) afforded product **2b** as a pale-yellow oil (1.98 g, 4.7 mmol, 95 %).

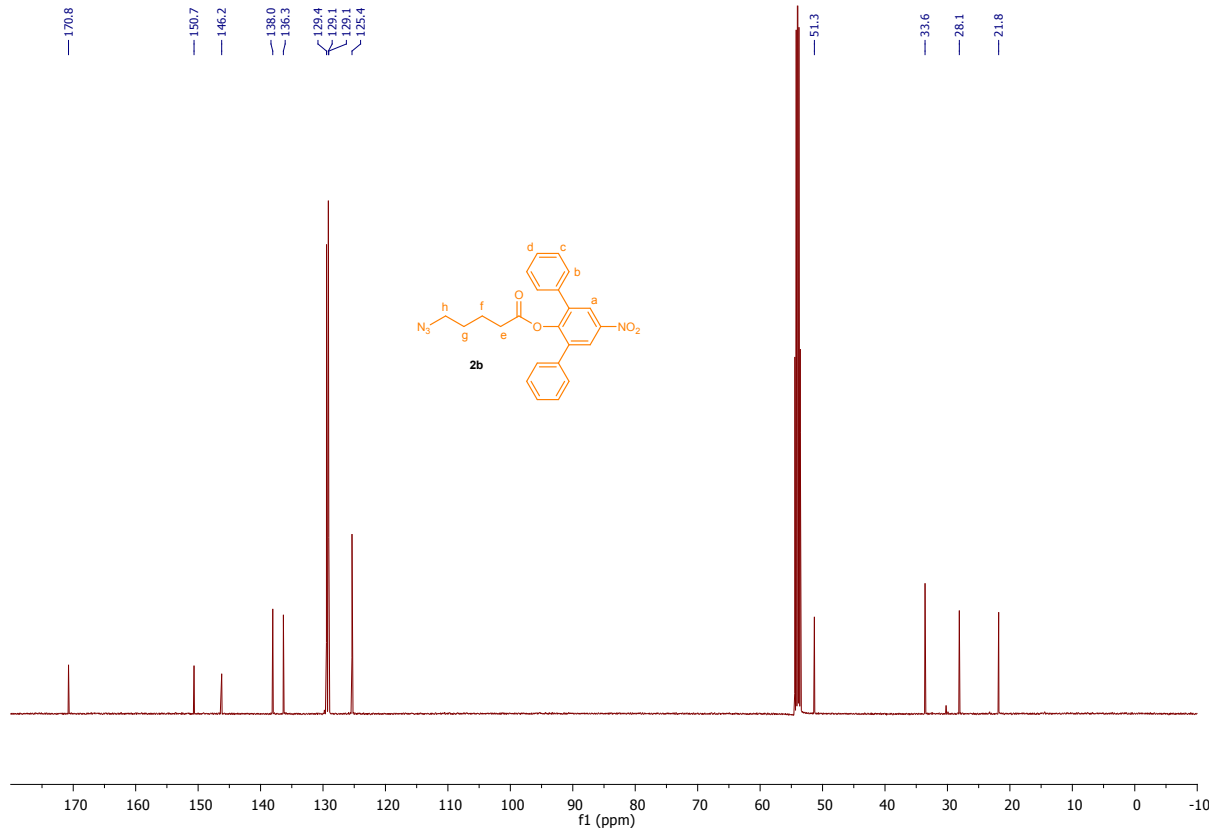
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.28 (s, 2H, H_a), 7.49 – 7.43 (m, 10H, H_b, H_c, H_d), 3.05 (t, J = 6.8, 2H, H_h), 2.12 (t, J = 7.1, 2H, H_e), 1.35 – 1.29 (m, 2H, H_f), 1.16 – 1.10 (m, 2H, H_g).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.8 (C_{CO}), 150.7-146.2-138.0-136.3 ($C_{quat.\ arom.}$), 129.4-129.1-129.1 (C_b, C_c, C_d), 125.4 (C_a), 51.3 (C_h), 33.6 (C_e), 28.1 (C_g), 21.8 (C_f).

HRMS (ESI$^+$) *m/z* = 417.1556 $[M+H]^+$ (calc. for $C_{23}H_{20}N_4O_4$ 417.1557 $[M+H]^+$).

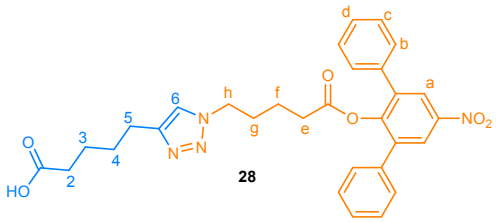


^{1}H NMR spectrum of **2b**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **2b**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound 28



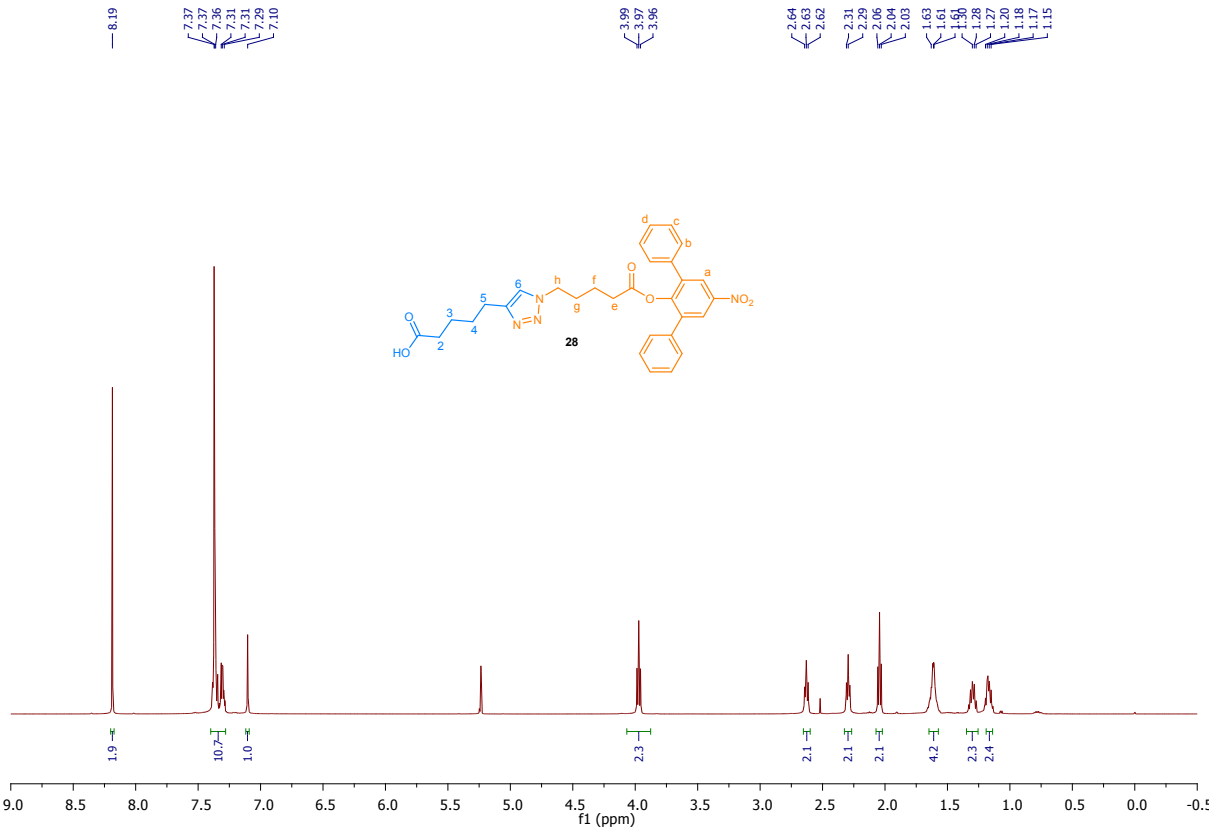
28

To a solution of azide **2b** (57 mg, 0.14 mmol, 1 equiv.) and 6-heptynoic acid **25** (17.3 mg, 0.14 mmol, 1 equiv.) in degassed DCM (6 mL) was added $[Cu(MeCN)_4]PF_6$ (51 mg, 0.14 mmol, 1 equiv.). The solution was stirred at room temperature for 20 hours. The reaction was hydrolyzed with saturated $EDTA.2Na_{(aq)}$ (5 mL) for one hour and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.3 (95:5)) gave **28** as a colorless oil (45 mg, 0.083 mmol, 60%).

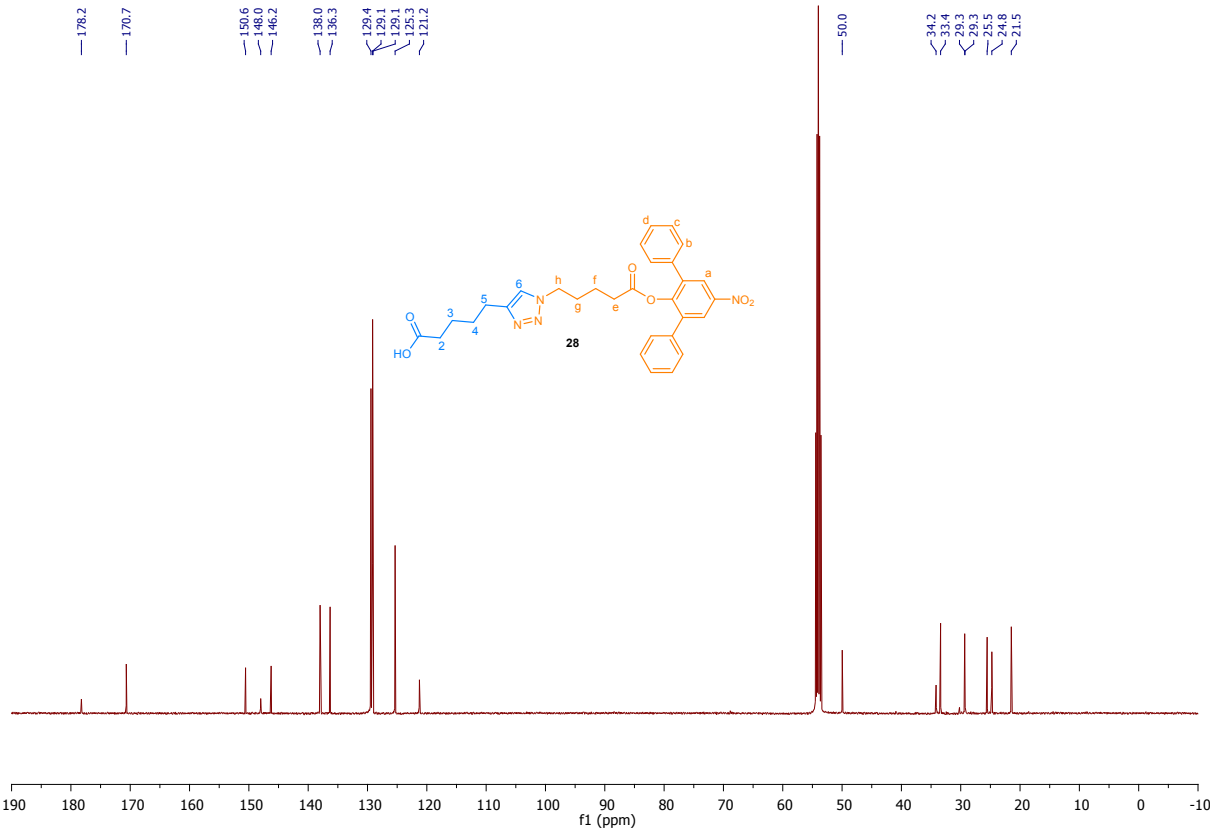
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.19 (s, 2H, H_a), 7.37 – 7.29 (m, 10H, H_b, H_c, H_d), 7.10 (s, 1H, H_6), 3.97 (t, *J* = 7.0, 2H, H_h), 2.63 (t, *J* = 7.1, 2H, H_2), 2.29 (t, *J* = 6.9, 2H, H_5), 2.04 (t, *J* = 7.0, 2H, H_e), 1.61 (m, 4H, H_3, H_4), 1.28 (m, 2H, H_g), 1.17 (m, 2H, H_f).

^{13}C NMR (120 MHz, CD_2Cl_2) δ 178.2-170.7 (C_{Co}), 150.6-148.0-146.2-138.0-136.3 ($C_{quat.\ arom.}$, $C_{quat.\ triazol}$), 129.4-129.1 129.0 (C_b, C_c, C_d), 125.3 (C_a), 121.2 (C_6), 50.0 (C_h), 34.2 (C_5), 34.3 (C_e), 29.3 (C_3 or C_4, C_g), 25.5 (C_2), 24.8 (C_3 or C_4), 21.5 (C_f).

HRMS (ESI$^+$) *m/z* = 543.2237 $[M+H]^+$ (calc. for $C_{30}H_{31}N_4O_6$ 543.2238 $[M+H]^+$).

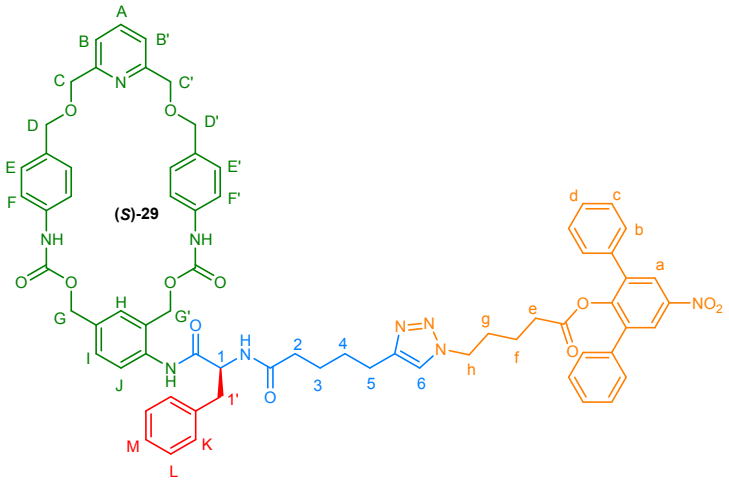


^{1}H NMR spectrum of **28**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **28**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound (S)-29



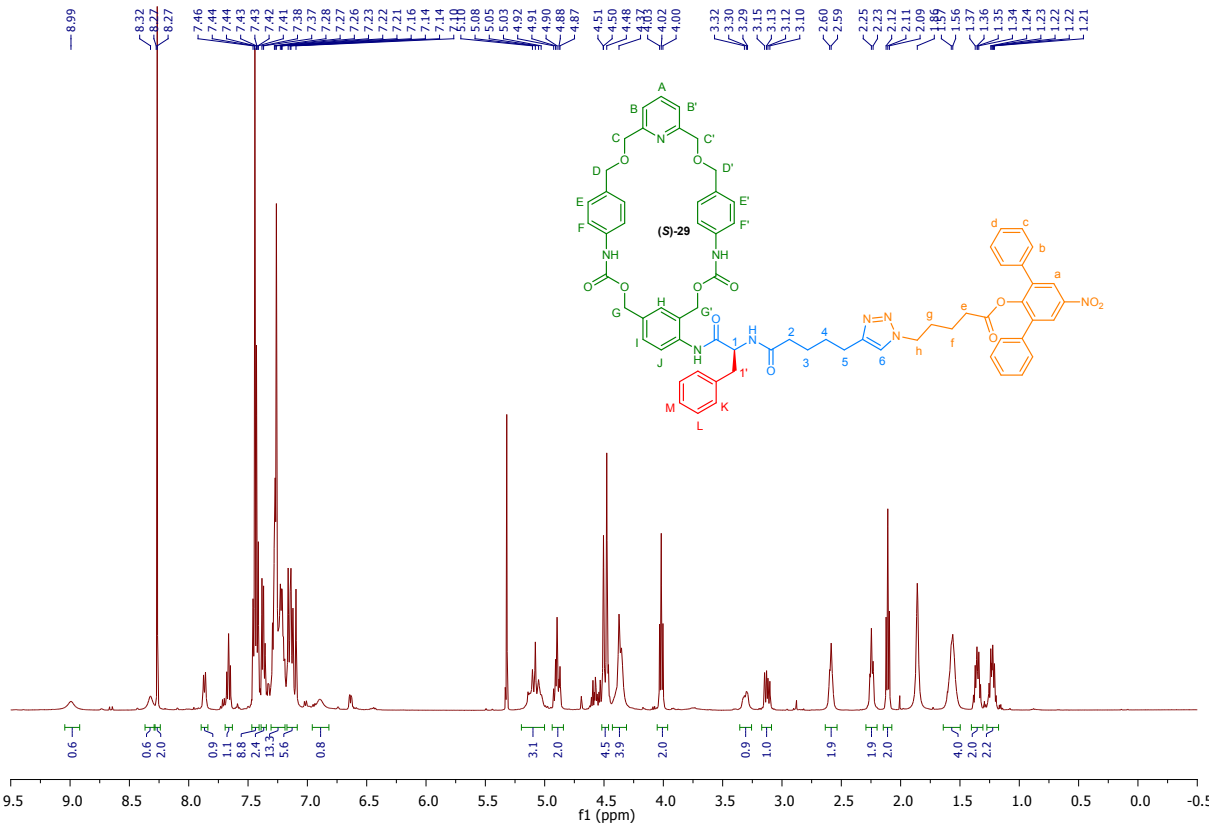
To a solution of macrocycle **(*S*)-24** (58 mg, 0.08 mmol, 1 equiv.) and acid **28** (45 mg, 0.08 mmol, 1 equiv.) in DMF (2 mL) was added EDC.HCl (15.5 mg, 1 equiv.). The solution was stirred at 35 °C for 24 hours and the solvent was removed *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.4 (95:5)) gave **(*S*)-29** as a pale yellow wax (45 mg, 0.036 mmol, 45%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.99 (bs, 1H, H_{NH}), 8.32 (bs, 1H, H_{NH}), 8.27 (s, 2H, H_a), 7.87 (d, *J* = 8.2, 1H, H_J), 7.66 (t, *J* = 7.7, 1H, H_A), 7.47 – 7.41 (m, 9H, H_{NH}, $H_{arom.}$), 7.38 (m, 2H, $H_{arom.}$), 7.28 – 7.21(m, 13H, $H_{arom.}$, H_6), 7.18 – 7.07 (m, 5H, $H_{arom.}$), 6.89 (bs, 1H, H_{NH}) 5.08 (m, 3H, H_G, $H_{G'(1H)}$), 4.90 (m, 2H, H_1, $H_{G'(1H)}$), 4.51-4.48 (2s, 4H, H_C, $H_{C'}$), 4.36 (m, 4H, H_D, $H_{D'}$), 4.02 (t, *J* = 7.0, 2H, H_h), 3.30 (m, 1H, $H_{1'}$), 3.12 (dd, *J* = 14.1, 8.2, 1H, $H_{1'}$), 2.59 (m, 2H, H_5), 2.25 (t, *J* = 6.7, 2H, H_2), 2.11 (t, *J* = 7.0, 2H, H_e), 1.57 (m, 4H, H_4, H_3), 1.37 – 1.34 (m, 2H, H_g), 1.24 – 1.21 (m, 2H, H_f).

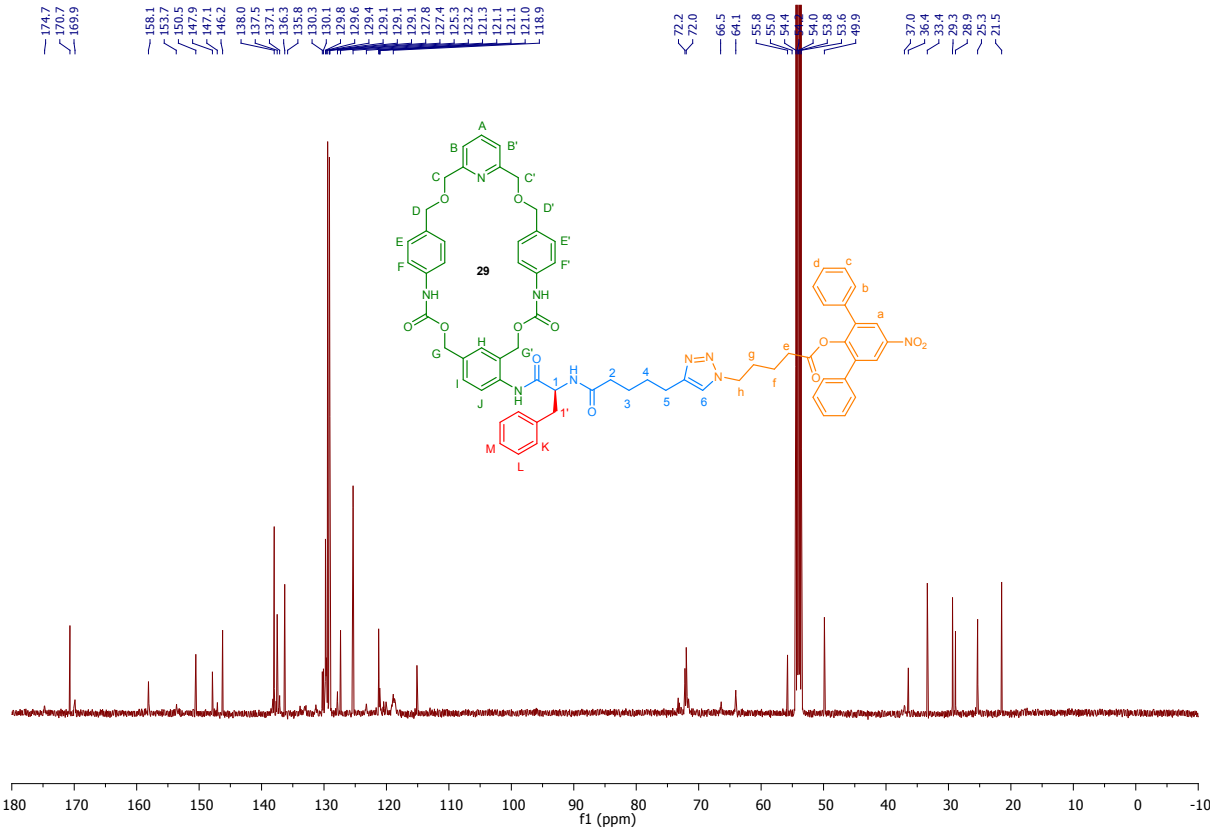
^{13}C NMR (126 MHz, CD_2Cl_2) δ 174.7-170.7-169.9-158.1-153.7-150.5-147.9147.1-146.2-138.0 (C_{CO}, $C_{quat.\ arom.}$), 137.5 (C_A), 137.1-136.3-135.8-130.3-130.1-129.8-129.6-129.4-129.1-127.8-127.4 ($C_{arom.}$), 125.3 (C_a), 123.2 (C_J), 121.3-121.1-121.0-118.9 ($C_{arom.}$), 72.2-72.0 (C_C, $C_{C'}$, C_D, $C_{D'}$), 66.5 (C_G), 64.1 ($C_{G'}$), 55.8 (C_1), 49.9 (C_h), 37.0 ($C_{1'}$), 36.4 (C_2), 33.4 (C_e), 29.3 (C_g), 28.9 (C_3 or C_4), 25.3 (C_5, C_3 or C_4), 21.5 (C_f).

HRMS (ESI$^+$) *m/z* = 1226.4982 $[M+H]^+$ (calc. for $C_{70}H_{68}N_9O_{12}$ 1226.4981 $[M+H]^+$).

HPLC rt: 6.51 minutes

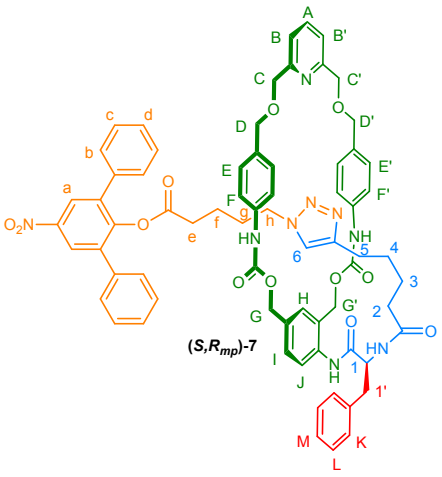


^{1}H NMR spectrum of **(*S*)-29**, 500 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **(*S*)-29**, 126 MHz, 298 K, CD_2Cl_2

Preparation of compound (S)-7



Mechanical planar chirality drawn as (R_{mp}) for visual purposes, not experimentally determined.

Macrocycle **(*S*)-1** (30.0 mg, 0.037 mmol, 1 equiv.) and $[Cu(MeCN)_4]PF_6$ (13.8 mg, 0.037 mmol, 1 equiv.) were placed in a 100 mL two-neck round-bottom flask equipped with a condenser. The system is purged with argon. Degassed DCM (18 mL) was added and the solution was stirred at 60 °C for 30 minutes. Stopper **2b** (77 mg, 0.185 mmol, 5 equiv.) and additive **5a** (14.3 mg, 0.0185 mmol, 0.5 equiv.) were placed in a 50 mL two-neck round-bottom flask and purged with argon. Degassed DCM (19 mL) was added to obtain a clear solution. This solution was carefully added under argon to the solution of **(*S*)-1** and Cu(I) catalyst. The crude yellow solution was stirred at 60 °C for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in DCM (5 mL) and the resulting solution was stirred with saturated $EDTA.2Na_{(aq)}$ (4 x 5 mL) for 24 hours. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.5 (95:5)) gave **(*S*)-7** as a solid colorless wax (12 mg, 0.0097 mmol, 26%).

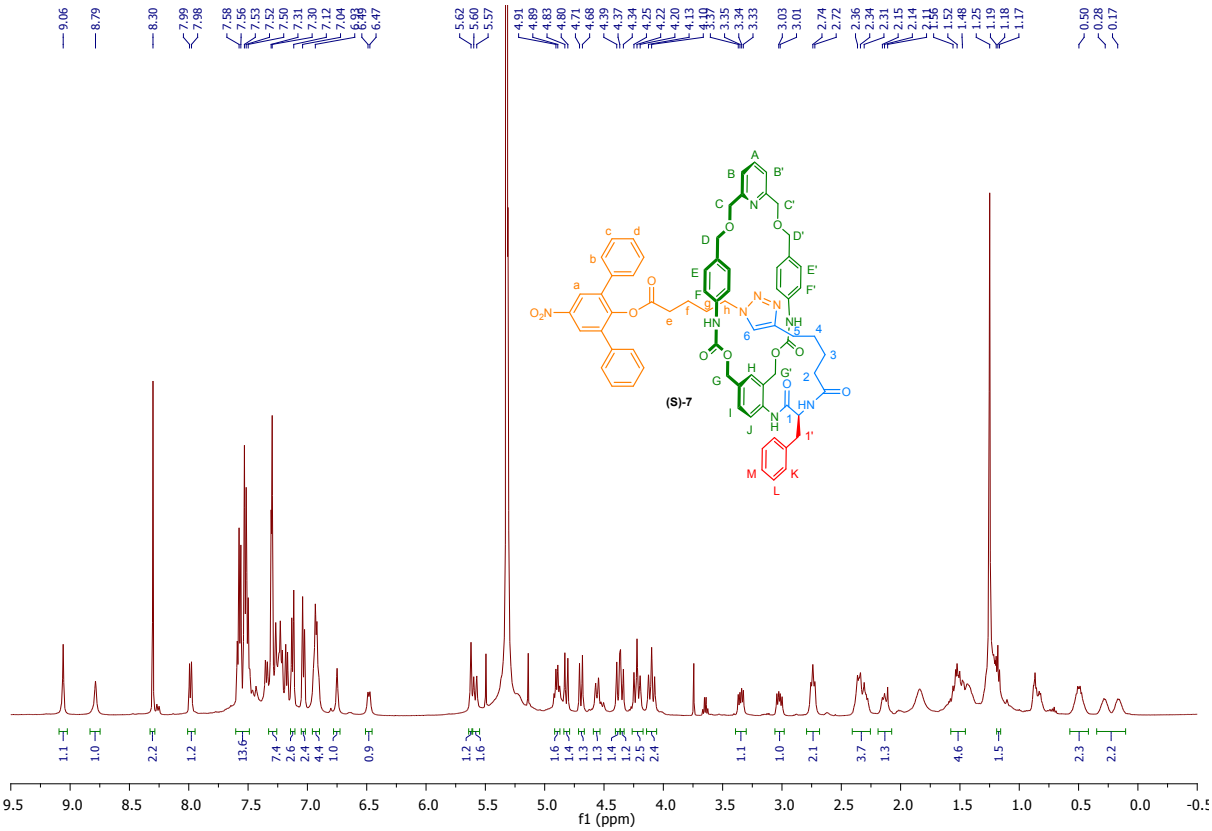
^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.06 (s, 1H, $H_{NH\text{-}amide}$), 8.79 (bs, 1H, $H_{NH\text{-}carbamate}$), 8.3 (s, 2H, H_a), 7.98(d, *J* = 8.4, 1H, H_J), 7,59 – 7.12 (m 20 H, H_b, H_c, H_d, H_A, H_B, $H_{B'}$, H_H, H_I, H_K, H_L, H_M), 7.12 (d, *J* = 8.3, 2H, H_F or $H_{F'}$), 7.03 (d, *J* = 8.3, 2H, H_E or $H_{E'}$), 6,92 (m, 4H, H_E, H_F or $H_{E'}$, $H_{F'}$), 6.75 (s, 1H, $H_{NH\text{-}carbamate}$), 6.47 (d, *J* = 7.9, 1H, $H_{NH\text{-}amide}$), 5.62 (s, 1H, H_6), 5.58 (d, *J* = 12.7, $H_{G'}$), 4.91 (dd, *J* = 7.8, 15.7, 1H, H_1), 4.81 (d, *J* = 12.6, 1H, H_G'), 4,69 (d, *J* = 12.3, 1H, H_G), 4.56 (d, *J* = 11.9, 1H, $H_{C'}$ or $H_{D'}$), 4.38 (d, *J* = 12.7, 1H, H_G), 4.35 (d, *J* = 12.4, 1H, $H_{C'}$ or $H_{D'}$), 4.22 (2d, *J* = 13.1, 2H, H_C or H_D), 4.10 (2d, *J* = 13.0, 2H, H_C or H_D), 3.35 (dd, *J* = 14.2, 7.2, 1H, $H_{1'}$), 3,02 (dd, *J* = 14.2, 8.0, 1H,

$H_{1'}$), 2.74 (t, *J* = 8.3, 2H, H_h), 2.36 – 2.28 (m, 3H, $H_{4,}$ $H_{2(1H)}$), 2.15 – 2.11 (m, 1H, H_2), 1.56 – 1,48 (m, 5H, H_3, $H_{5(1H)}$, H_e), 1.17 (m, 1H, $H_{5(1H)}$), 0.5 (m, 2H, H_f), 0.28-0.17 (m, 2H, H_g).

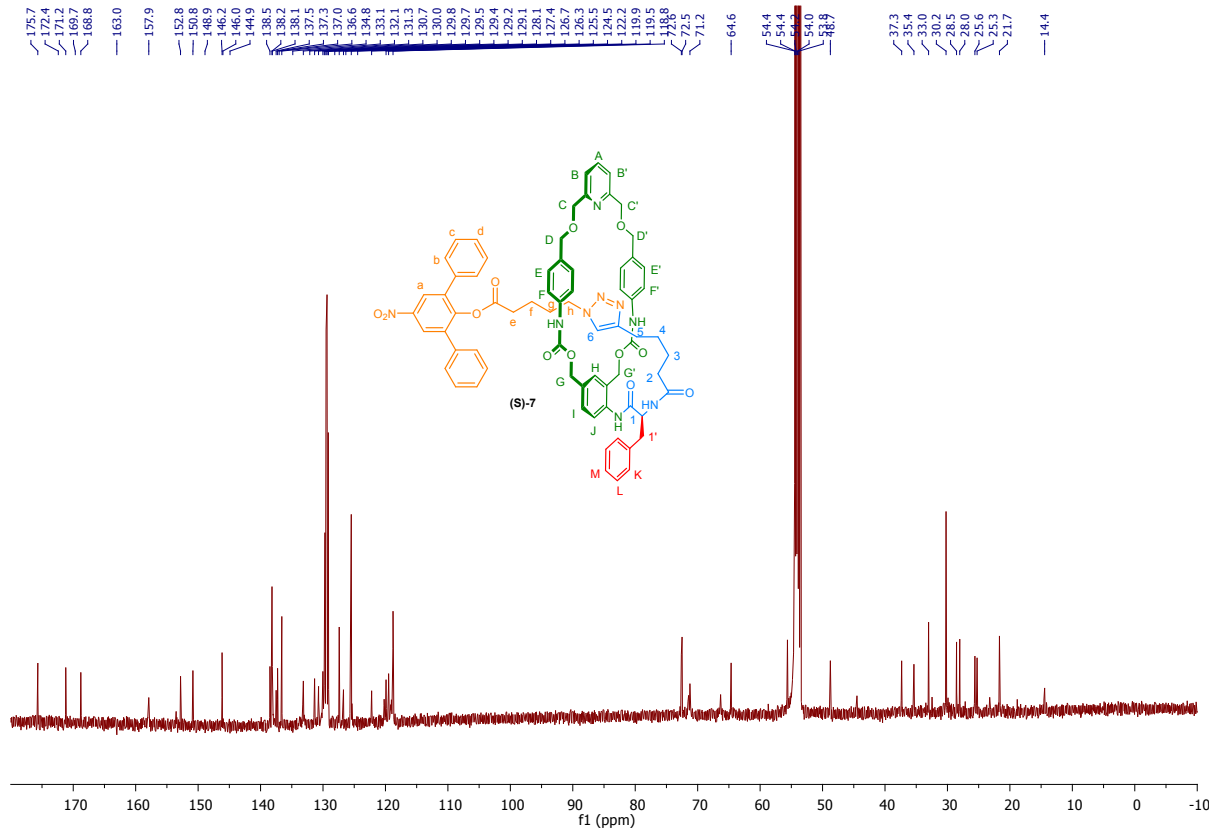
^{13}C NMR (126 MHz, CD_2Cl_2) δ 175.7, 171.23, 169.6, 168.9, 158.1, 152.9, 150.9, 146.2, 146.1, 138.6, 138.2, 138.2, 137.5, 137.4, 136.7, 133.2, 131.4, 130.8, 130.0, 129.8, 129.7, 129.5, 129.5, 129.4, 129.2, 127.4, 126.8, 125.5 (C_a), 122.3 (C_J), 119.9, 119.6 (C_6), 118.8, 72.7-72.6-71.3 (C_G, C_C, $C_{C'}$, C_D, $C_{D'}$)64.7 ($C_{G'}$), 55.7, 54.5 (C_1), 54.3, 54.0, 53.7, 53.5, 48.8, 37.3, 35.4 ($C_{1'}$), 33.1, 28.6, 28.1, 25.7, 25.3, 21.7 (C_f).

HRMS (ESI$^+$) *m/z* = 1226.4985 $[M+H]^+$ (calc. for $C_{70}H_{68}N_9O_{12}$ 1226.4982 $[M+H]^+$).

HPLC rt: 7.97 minutes

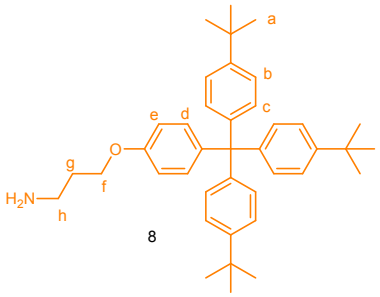


^{1}H NMR spectrum of **(*S*)-7**, 400 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **(S)-7**, 100 MHz, 298 K, CD_2Cl_2

Preparation of compound 8



8

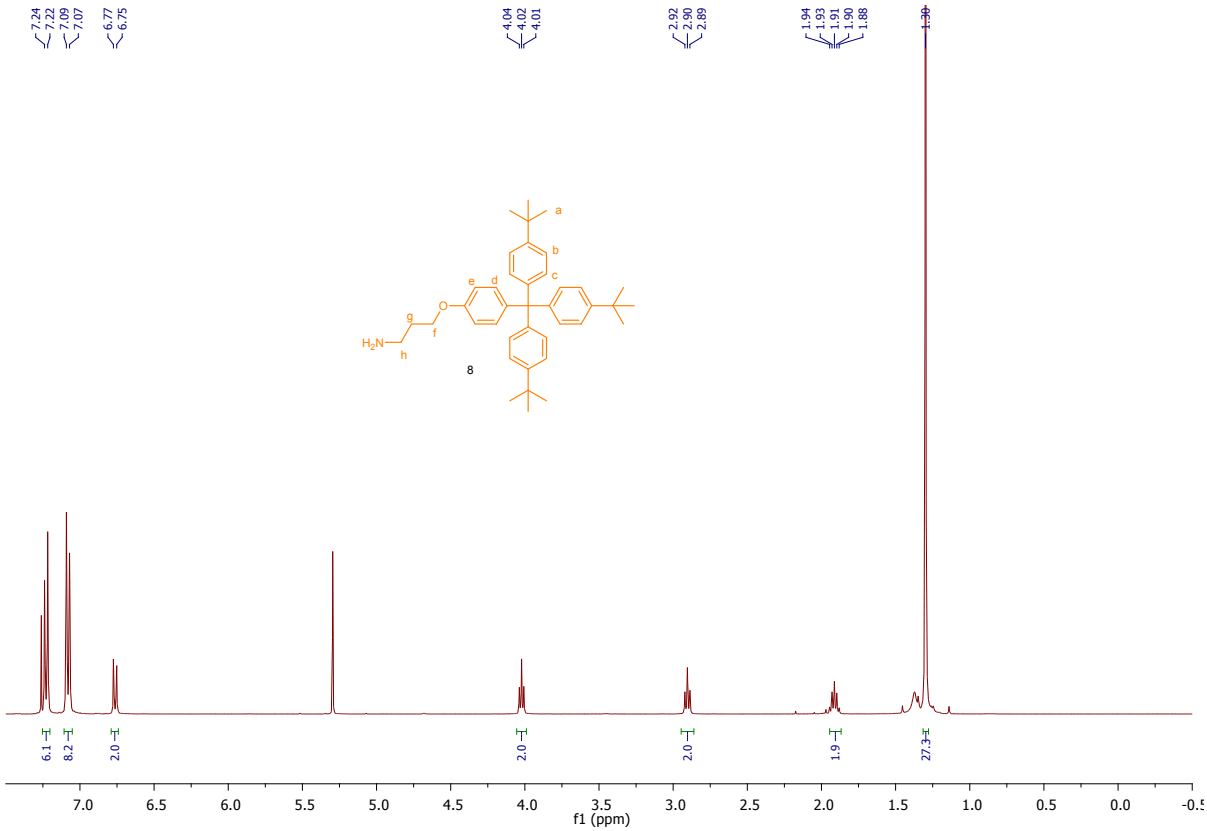
A solution of azide **2a** (377 mg, 0.57 mmol, 1 equiv.) and polymer-bound triphenylphoshine (3 mmol/g loading, 573 mg, 1.72 mmol, 3 equiv.) in a mixture of THF/NH_4OH 9:1 (20 mL) was stirred at 65 °C for 5 hours. The solution was filtrated through a pad of celite and solvents were removed *in vacuo* to give **8** as a yellow powder without further purification (310 mg, 97%, R_f = 0.04 (DCM/MeOH 95:5)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6, 6H, H_b), 7.08 (d, *J* = 8.6, 8H, H_c, H_d), 6.76 (d, *J* = 8.9, 2H, H_e), 4.02 (t, *J* = 6.1, 2H, H_f), 2.90 (t, *J* = 6.8, 2H, H_h), 1.91 (m, 2H, H_g), 1.30 (s, 27H, H_a).

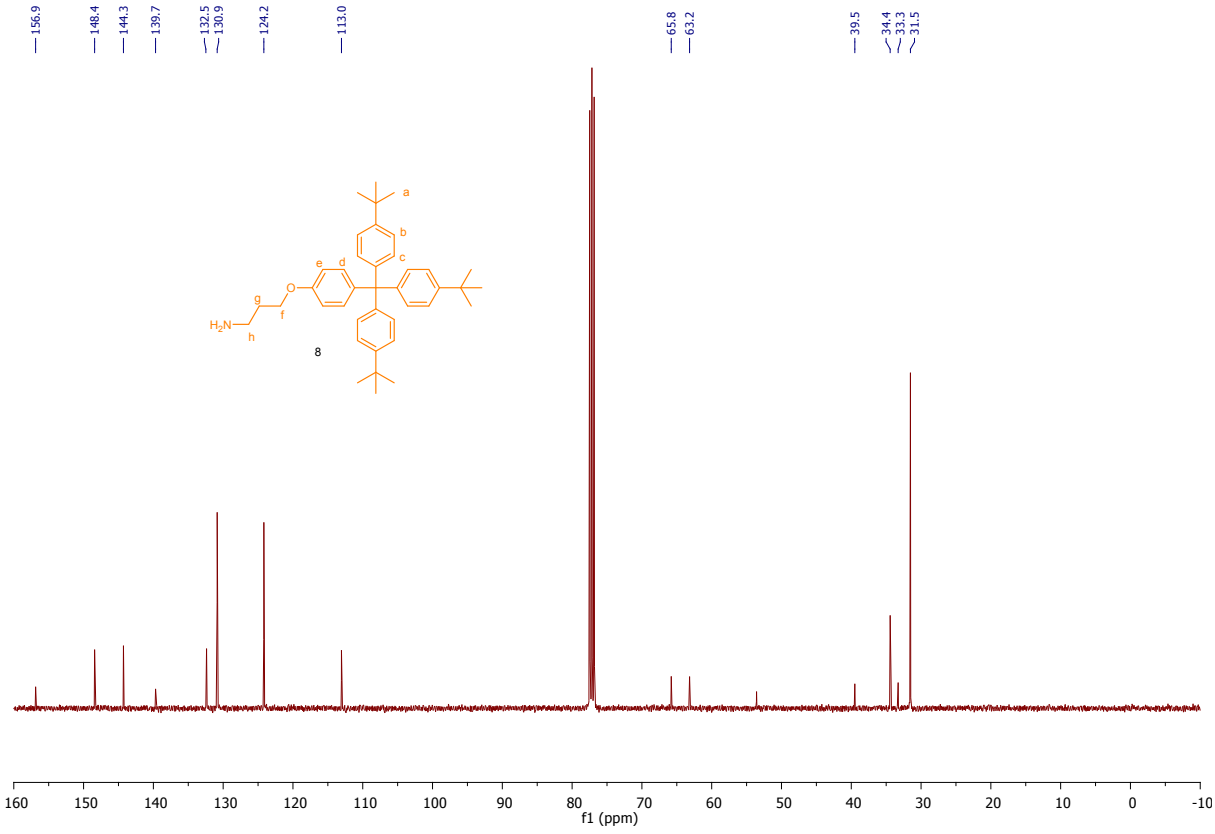
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9-148.4-144.3-139.7 ($C_{quat.\ arom.}$), 132.5 (C_d), 130.9 (C_c), 124.2 (C_b), 113.0 (C_e), 65.8 (C_f), 63.2 ($C_{quat.}$), 39.5 (C_h), 34.4 ($C_{quat.}$), 33.3 (C_g), 31.5 (C_a).

HRMS (ESI$^+$) *m/z* = 562.4049 $[M+H]^+$ (calc. for $C_{40}H_{52}NO$ 562.4043 $[M+H]^+$).

HPLC rt: 8.76 minutes

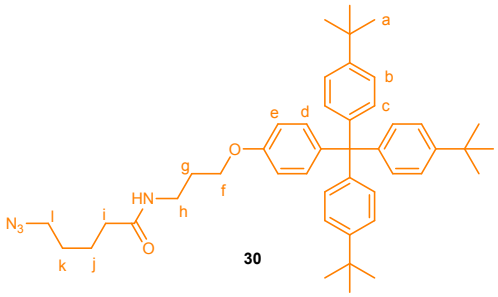


^{1}H NMR spectrum of **8**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **8**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound 30

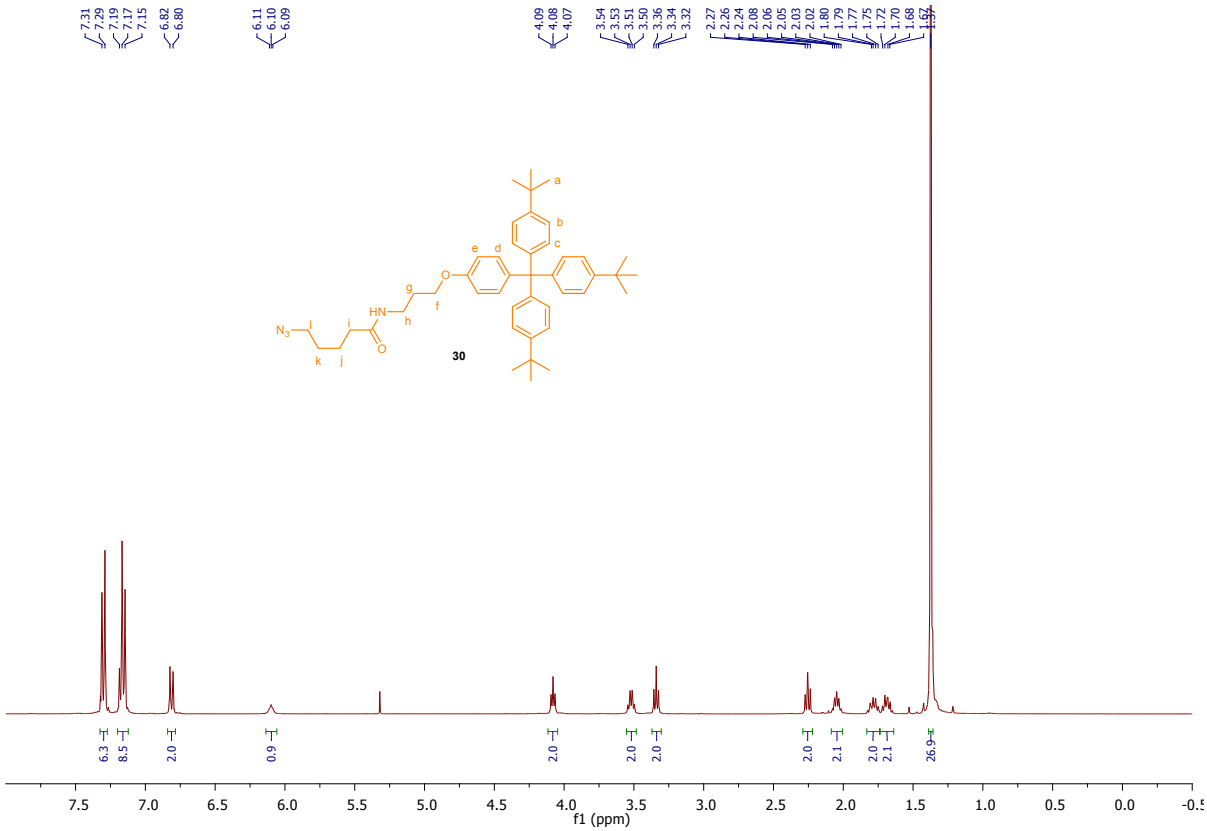


To a solution of 5-azidopentanoic acid **27** (25.5 mg, 0.18 mmol, 1 equiv.) in DMF (3 mL) was added DMAP (22 mg, 0.18 mmol, 1 equiv.) and EDC.HCl (34.5 mg, 0.18 mmol, 1 equiv.). The solution was stirred at room temperature for 15 minutes before amine **8** (100 mg, 0.18 mmol, 1 equiv.) was added and stirred for 12 hours at room temperature. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.6 (95:5)) gave **30** as a white wax (80 mg, 0.12 mmol, 66%).

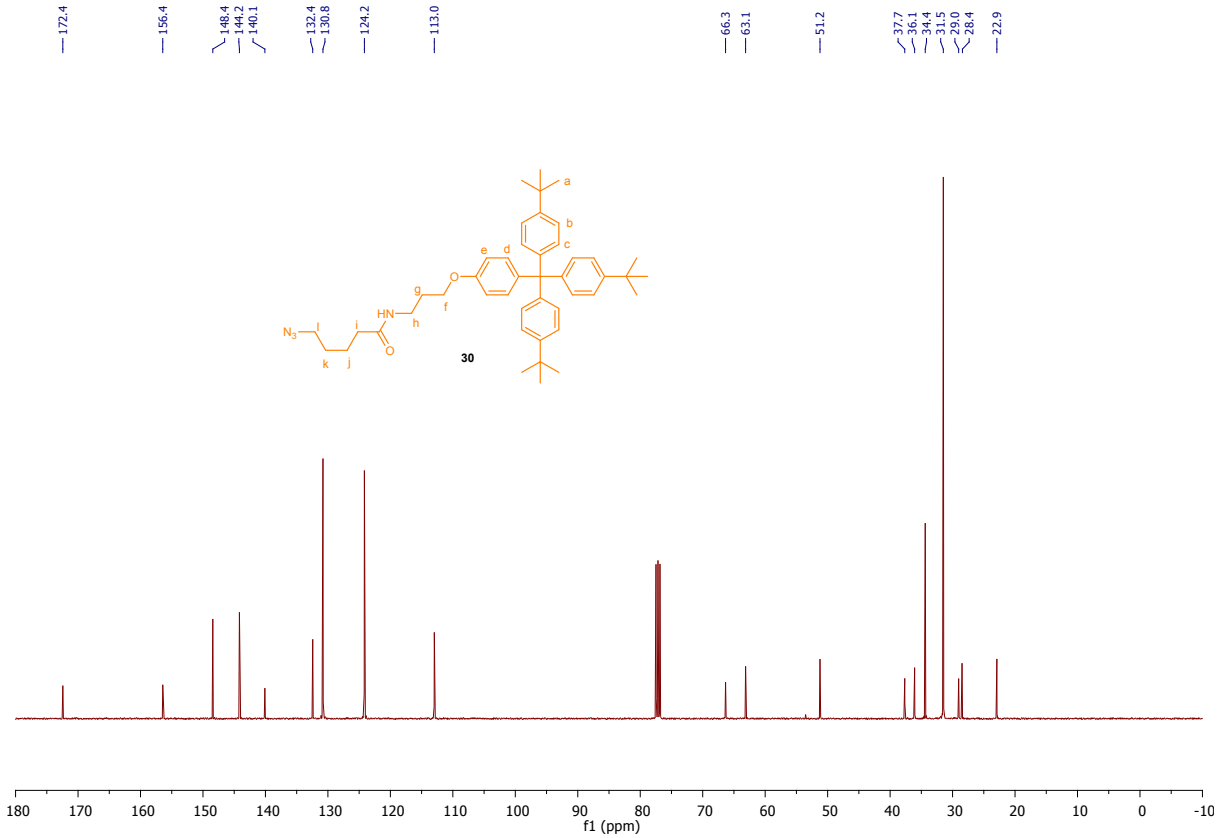
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7, 6H, H_b), 7.16 (m, 8H, H_c, H_d), 6.81 (d, *J* = 8.9, 2H, H_e), 6.10 (t, *J* = 4.8, 1H, H_{NH}), 4.08 (t, *J* = 5.7, 2H, H_f), 3.52 (q, *J* = 6.2, 2H, H_h), 3.34 (t, *J* = 6.7, 2H, H_i), 2.25 (t, *J* = 7.3, 2H, H_l), 2.08 – 2.02 (m, 2H, H_g), 1.85 – 1.74 (m, 2H, H_k), 1.72 – 1.61 (m, 2H, H_j), 1.37 (s, 27H, H_a).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (C_{CO}), 156.4-148.4-144.2-140.1 ($C_{quat.\ arom.}$), 132.4 (C_d), 130.8 (C_c), 124.2 (C_b), 113.0 (C_e), 66.3 (C_f), 63.1 ($C_{quat.}$), 51.2 (C_i), 37.6 (C_h), 36.1 (C_l), 34.4 ($C_{quat.\ t\text{-but}}$), 31.5 (C_a), 29.0 (C_g), 28.4 (C_j), 22.9 (C_k).

HRMS (ESI$^+$) *m/z* = 687.4644 $[M+H]^+$ (calc. for $C_{45}H_{59}N_4O_2$ 687.4632 $[M+H]^+$).

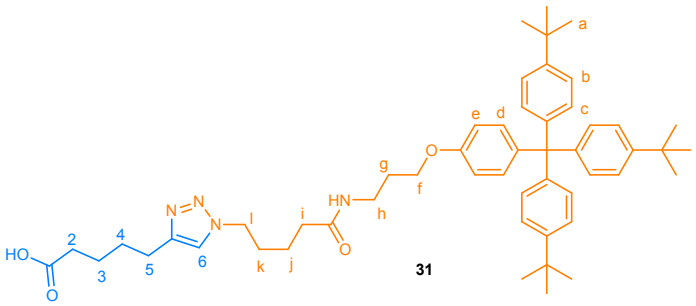


^{1}H NMR spectrum of **30**, 400 MHz, 298 K, $CDCl_3$



^{13}C NMR spectrum of **30**, 100 MHz, 298 K, $CDCl_3$

Preparation of compound 31

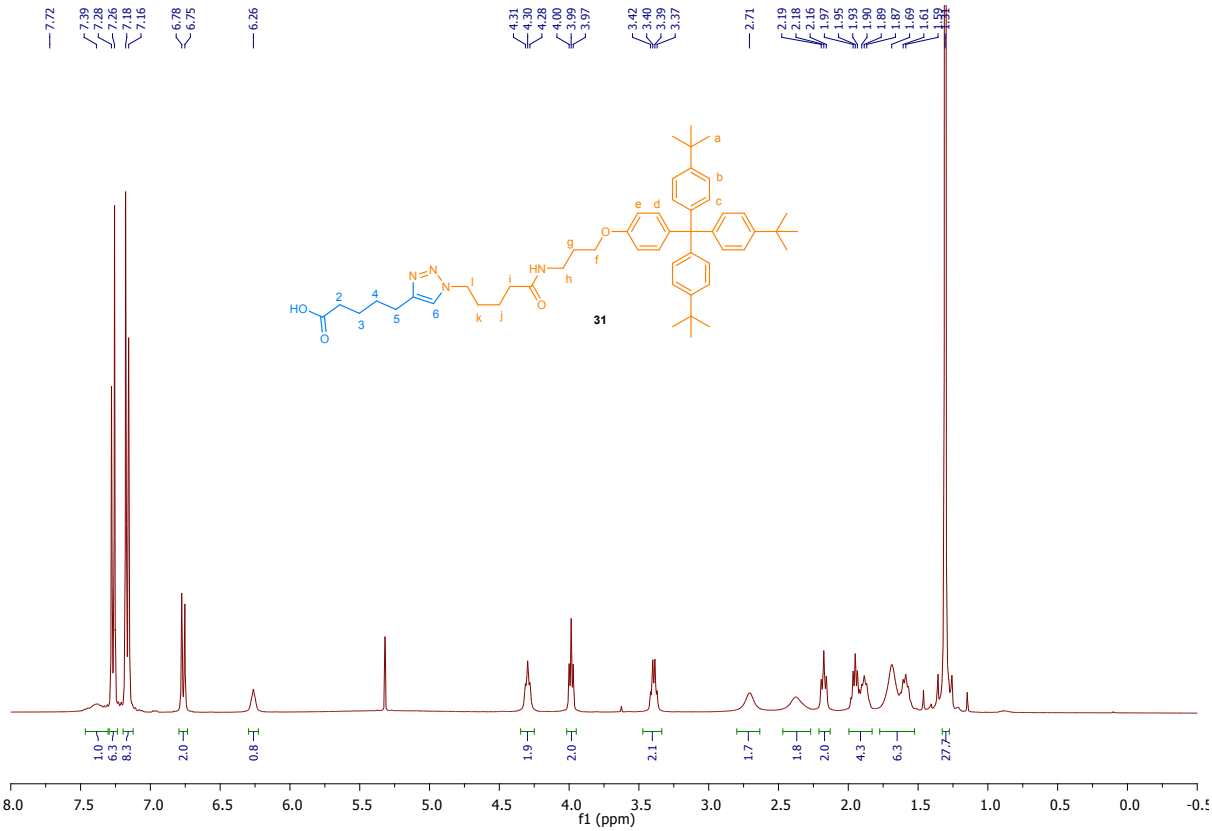


To a solution of azide **30** (80 mg, 0.12 mmol, 1 equiv.) and and 6-heptynoic acid **25** (15 mg, 0.12 mmol, 1 equiv.) in degassed DCM (4 mL) was added $[Cu(MeCN)_4]PF_6$ (45 mg, 0.12 mmol, 1 equiv.). The solution was stirred at room temperature for 18 hours. The reaction was hydrolyzed with saturated $EDTA.2Na_{(aq)}$ (5 mL) for one hour and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.2 (95:5)) gave **31** as a white wax (72 mg, 0.088 mmol, 74%).

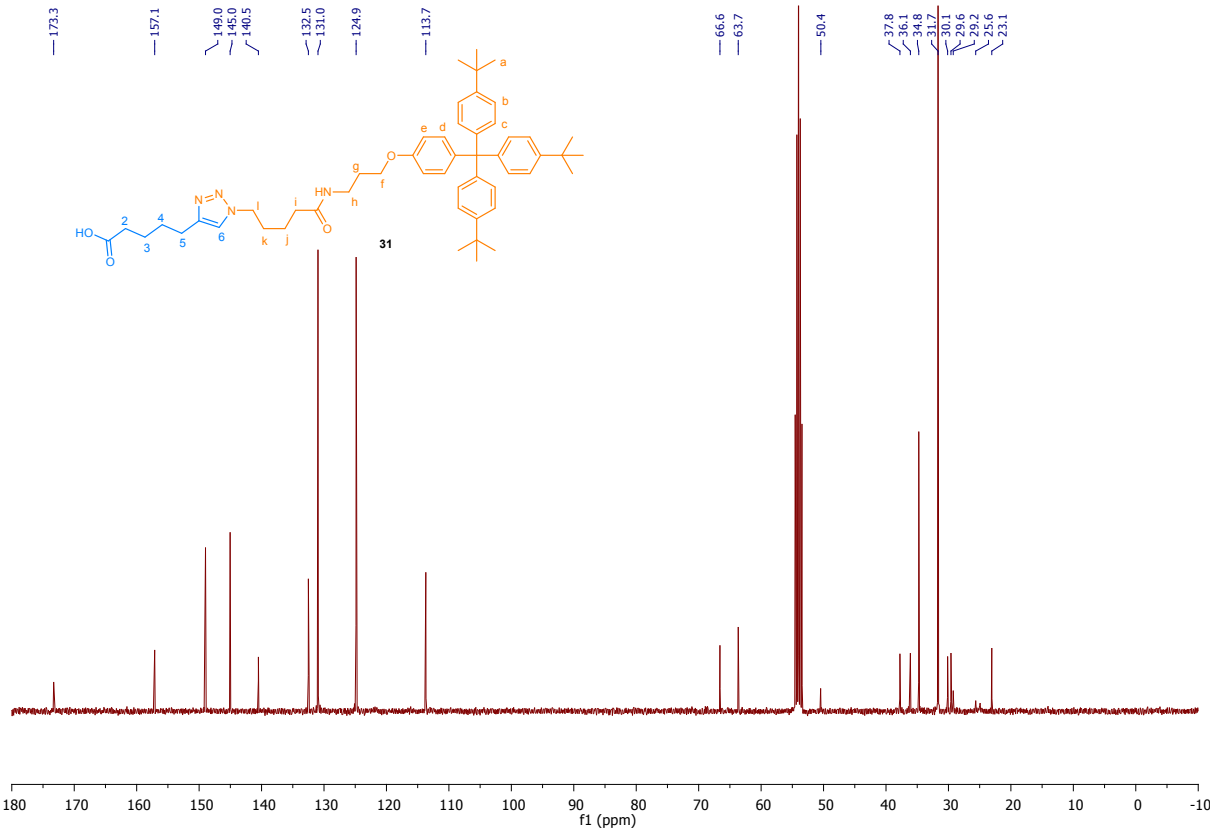
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.72 (bs, 1H, H_6), 7.27 (d, *J* = 8.7, 6H, H_b), 7.17 (d, *J* = 8.7, 8H, H_c, H_d), 6.76 (d, *J* = 8.9, 2H, H_e), 6.26 (bs, 1H, H_{NH}), 4.30 (t, *J* = 6.4, 2H, H_l), 3.99 (t, *J* = 5.8, 2H, H_f), 3.39 (q, *J* = 6.3, 2H, H_h), 2.71 (m, 2H, H_5), 2.38 (m, 2H, H_i), 2.18 (t, *J* = 7.2, 2H, H_2), 1.95 (m, 4H, H_g, H_k), 1.69 – 1.59 (m, 6H, H_3, H_4, H_j), 1.31 (s, 27H, H_a).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 173.3 (C_{CO}), 157.1-149.0-145.0-140.5 ($C_{quat.\ arom.}$), 132.5 (C_d), 131.0 (C_c), 124.9 (C_b, C_6), 113.7 (C_e), 66.6 (C_f), 63.7 ($C_{quat.}$), 50.4 (C_l), 37.8 (C_h), 36.1 (C_2), 34.8 ($C_{quat.\ t\text{-but}}$), 31.7 (C_a), 30.1-29.6 (C_g, C_k), 29.2-25.6-23.1 (C_3, C_4, C_j).

HRMS (ESI$^+$) *m/z* = 813.5314 $[M+H]^+$ (calc. for $C_{52}H_{69}N_4O_4$ 813.5313 $[M+H]^+$).

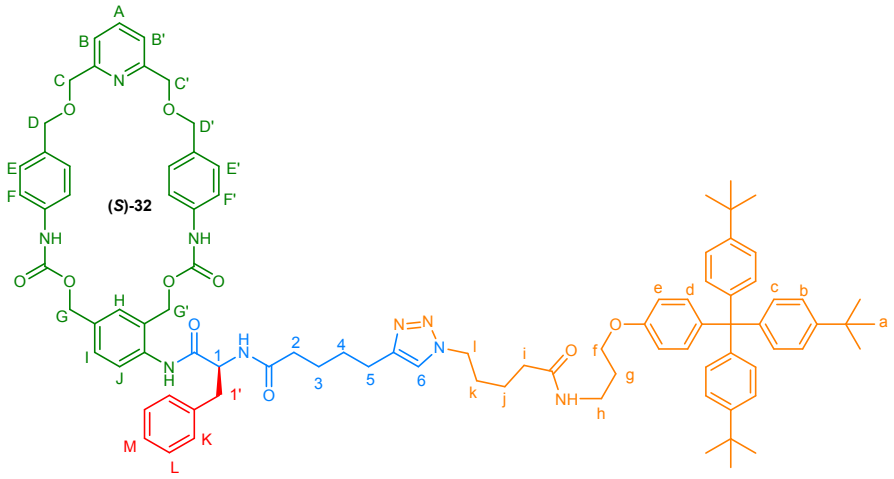


^{1}H NMR spectrum of **31**, 400 MHz, 298 K, CD_2Cl_2



^{13}C NMR spectrum of **31**, 100 MHz, 298 K, CD_2Cl_2

Preparation of compound (S)-32



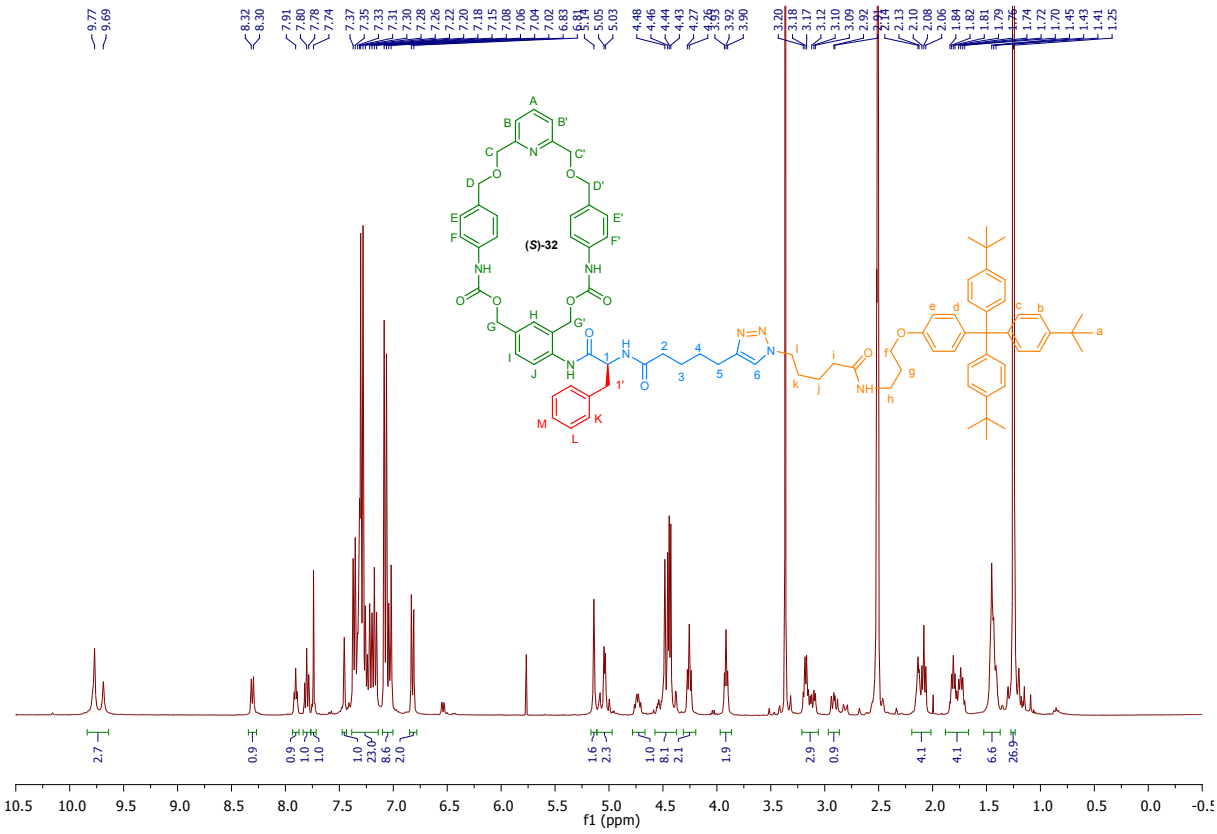
To a solution of acid **31** (18 mg, 0.02 mmol, 1 equiv.) in DMF (1 mL) was added DMAP (3 mg, 0.02 mmol, 1 equiv.) and EDC.HCl (5 mg, 0.02 mmol, 1 equiv.). The solution was stirred at room temperature for 15 minutes before macrocycle **(*S*)-24** (15 mg, 0.02 mmol, 1 equiv.) was added and stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.3 (95:5)) gave **(*S*)-32** as a colorless wax (28 mg, 0.018 mmol, 85%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.77-9.69 (2s, 3H, $H_{NH\text{-}carbamate}$ $H_{NH\text{-}amide}$), 8.31 (d, *J* = 7.9, 1H, $H_{NH\text{-}amide}$), 7.90 (t, *J* = 5.5, 1H, $H_{NH\text{-}amide}$), 7.80 (t, *J* = 7.7, 1H, H_A), 7.74 (s, 1H), 7.46 (s, 1H), 7.37 – 7.02 (m, 31H), 6.82 (d, *J* = 9, 2H, H_e), 5.14 (s, 2H, H_G), 5.04 (m, 2H, $H_{G'}$), 4.74 (m, 1H, H_1), 4.48-4.46-4.44-4.43 (4s, 8H, H_C, $H_{C'}$, H_D, $H_{D'}$), 4.26 (t, *J* = 7.0, 2H, H_l), 3.91 (t, *J* = 6.0, 2H, H_f), 3.18 (m, 2H, H_h), 3.11 (dd, *J* = 13.6, 5.4, 1H, $H_{1'}$), 2.91 (dd, *J* = 13.5, 9.4, 1H, $H_{1'}$), 2.5 (2H masked by DMSO-*d*6), 2.14 – 2.06 (m, 4H), 1.84 –1.70 (m, 4H, H_g, H_k), 1.43 (m, 6H), 1.25 (s, 27H, H_a).

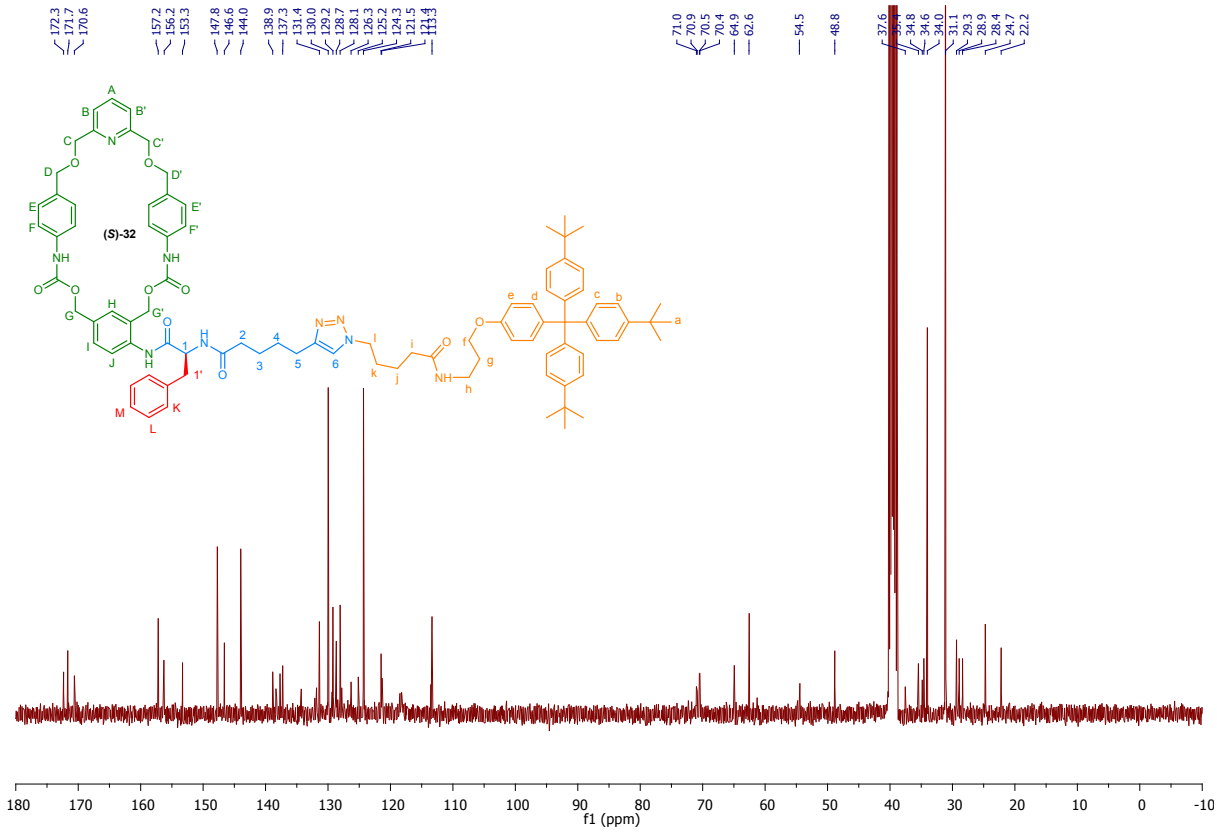
^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3, 171.7, 170.672, 157.2, 156.2, 153.3, 147.7, 146.6, 144.0, 138.9, 138.4, 138.2, 137.6, 137.3, 134.4, 131.4, 130.0, 129.2, 128.8, 128.7, 128.1, 127.8, 126.3, 125.7, 125.1, 124.3, 121.5, 121.4, 113.3, 71.0, 70.9, 70.5, 70.4, 64.9, 62.6, 54.5, 48.8, 37.6, 35.4, 34.8, 34.6, 34.0, 31.1, 29.3, 28.9, 28.4, 24.7, 22.2.

HRMS (ESI$^+$) *m/z* = 1496.8044 $[M+H]^+$ (calc. for $C_{92}H_{106}N_9O_{10}$ 1496.8057 $[M+H]^+$).

HPLC rt: 9.04 minutes

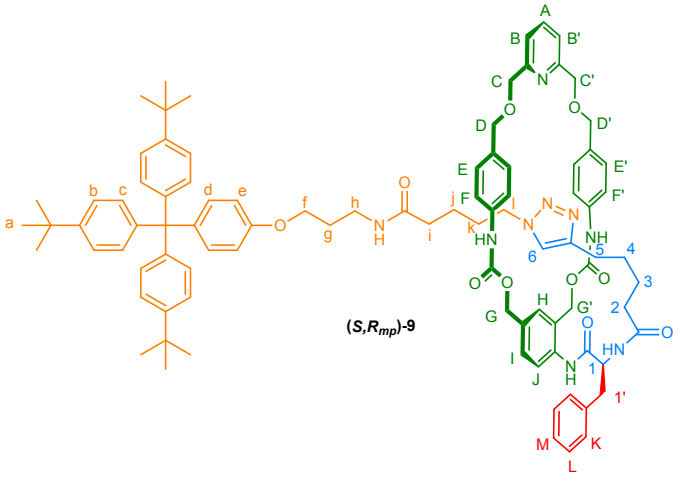


^{1}H NMR spectrum of **(*S*)-32**, 500 MHz, 298 K, DMSO-d_6



^{13}C NMR spectrum of **(*S*)-32**, 126 MHz, 298 K, DMSO-d_6

Preparation of compound (S)-9



Mechanical planar chirality drawn as (R_{mp}) for visual purposes, not experimentally determined.

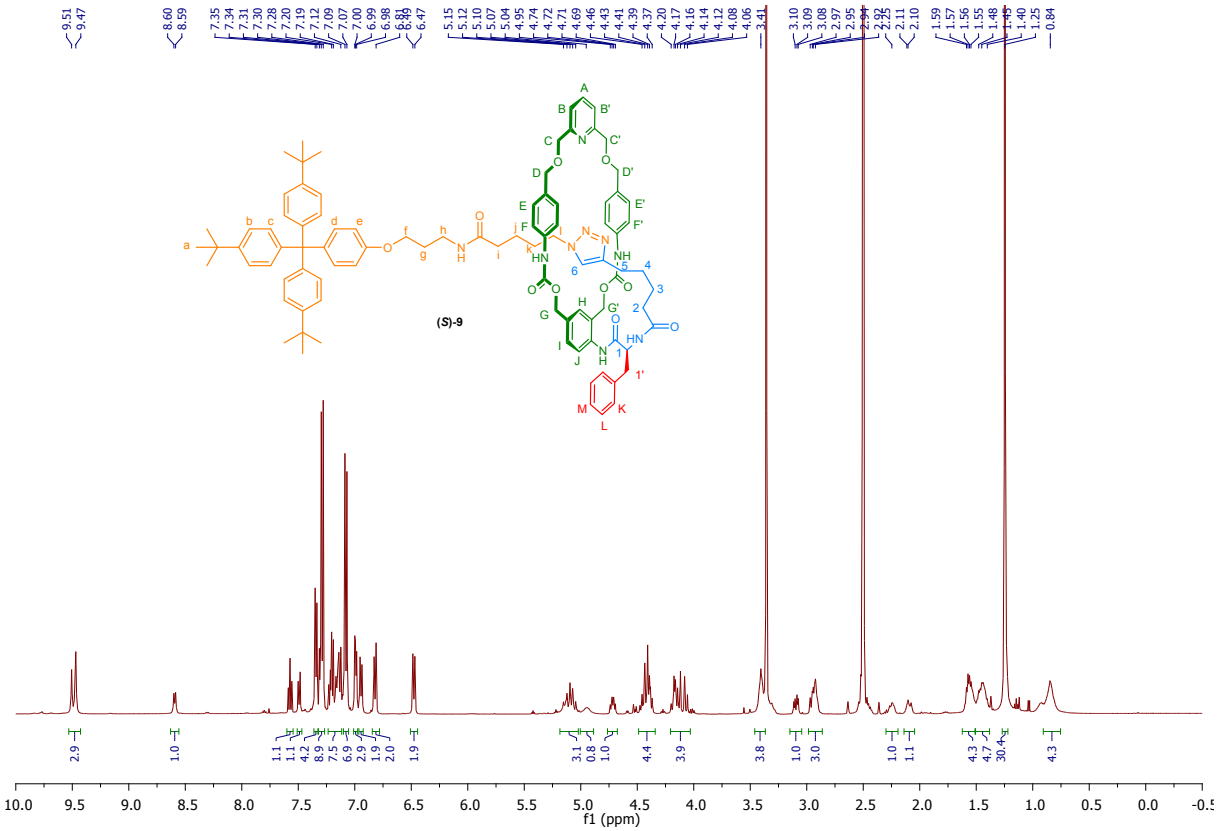
To a solution of [1]rotaxane **(*S*)-7** (20 mg, 0.016 mmol, 1 equiv.) in DCM (2 mL) was added amine **8** (46 mg, 0.081 mmol, 5 equiv.) and DIPEA (0.014 mL, 0.081 mmol, 5 equiv.). The reaction mixture was stirred at 40 °C fot 48 hours. The solvent was removed *in vacuo* and chromatography (DCM/MeOH, gradient elution 100:0 to 95:5, R_f = 0.3 (95:5)) gave **(*S*)-9** as a colorless wax (13 mg, 0.009 mmol, 54%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51-9.47 (2s, 3H, $H_{NH\text{-}carbamate}$ $H_{NH\text{-}amide}$), 8.59 (d, *J* = 7.6, 1H, $H_{NH\text{-}amide}$), 7.57 (t, *J* = 7.8, 1H, H_A), 7.49 (d, *J* = 8.7, 1H, H_J), 7.35 – 6.94 (m, 31H, H_B, $H_{B'}$, H_E, $H_{E'}$, H_F, $H_{F'}$, H_H, H_I, H_K, H_L, H_M, H_b, H_c, $H_{NH\text{-}amide}$, H_6), 6.82 (d, *J* = 8.8, 2H, H_d), 6.48 (d, *J* = 8.9, 2H, H_e,), 5.15 – 5.04 (m, 3H, H_G, $H_{G'(1)}$), 4.95 (bs, 1H, $H_{G'}$), 4.72 (m, 1H, H_1), 4.46 – 4.37 (m, 4H, H_C, $H_{C'}$, or H_D, $H_{D'}$), 4.20 – 4.06 (m, 4H, H_C, $H_{C'}$, or H_D, $H_{D'}$), 3.41 (m, 4H), 3.09 (dd, *J* = 13.8, 5.6, 1H, $H_{1'}$), 2.94 (m, 3H, $H_{1'}$, H_f), 2.25 (m, 1H), 2.11 (m, 1H), 1.59 (m, 4H), 1.45 (m, 4H), 1.25 (29H), 0.84 (m, 4H).

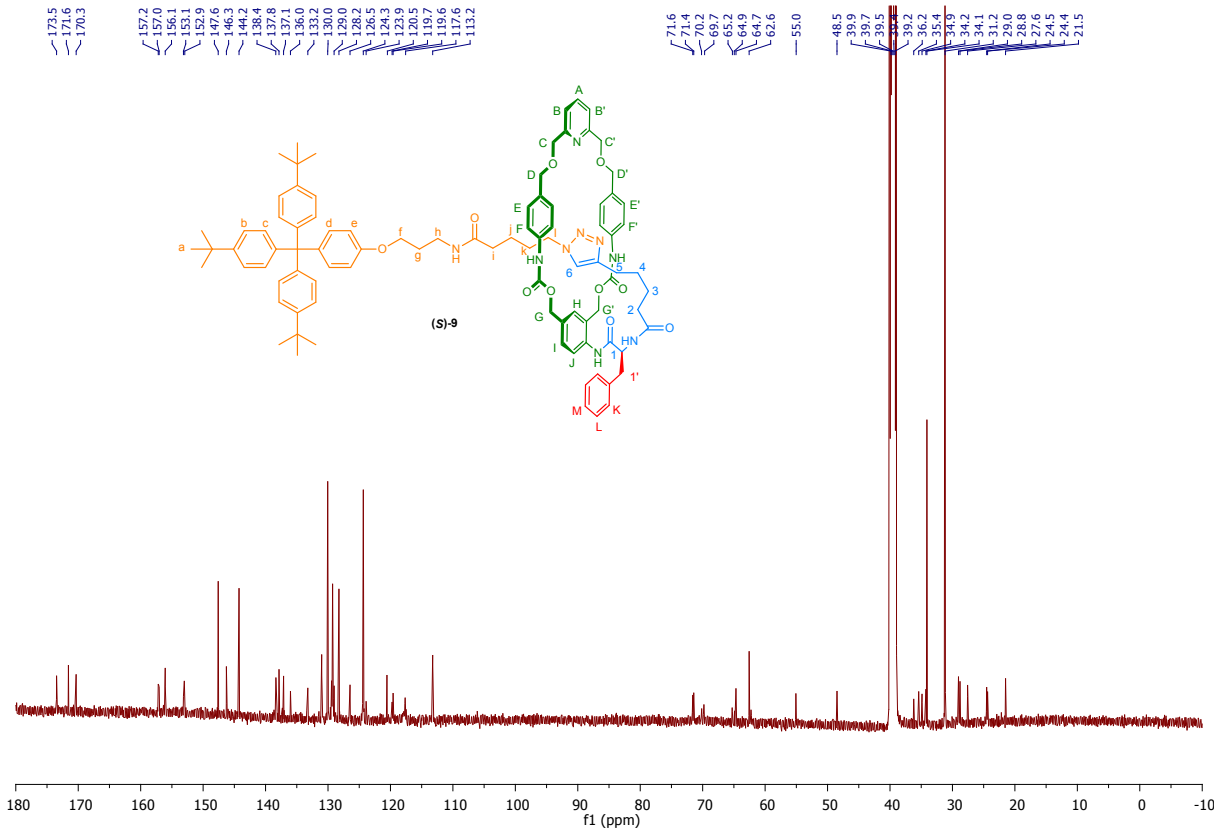
^{13}C NMR (126 MHz, DMSO-d_6) δ 173.5, 171.6, 170.33, 157.2, 157.0, 156.1, 153.2, 152.9, 147.6, 146.3, 144.3, 138.4, 137.9, 137.1, 136.0, 133.2, 130.0, 129.0, 128.2, 126.5, 124.3, 123.9, 120.5, 119.7, 119.6, 117.6, 113.2, 71.6, 71.4, 70.2, 69.7, 65.2, 64.9, 64.7, 62.6, 55.0, 48.5, 39.8, 39.7, 39.5, 39.3, 39.2, 36.2, 35.4, 34.9, 34.2, 34.1, 31.2, 29.0, 28.8, 27.6, 24.5, 24.4, 21.5.

HRMS (ESI$^+$) *m/z* = 1496.8040 $[M+H]^+$ (calc. for $C_{92}H_{106}N_9O_{10}$ 1496.8057 $[M+H]^+$).

HPLC rt: 9.28 minutes



^{1}H NMR spectrum of **(*S*)-9**, 500 MHz, 298 K, DMSO-d_6



^{13}C NMR spectrum of **(*S*)-9**, 126 MHz, 298 K, DMSO-d_6

I.4. Stacked spectra

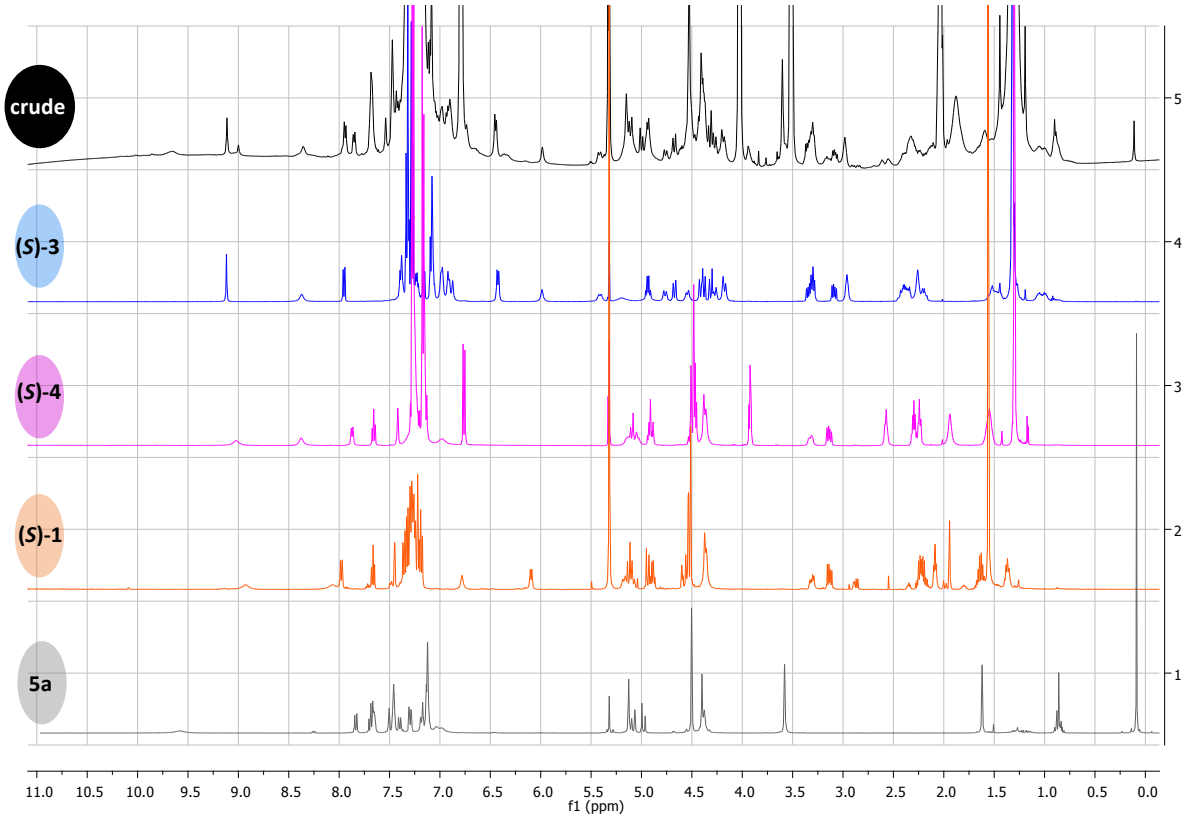


Figure S1. ^{1}H NMR full stacked spectra of crude **(*S*)-3**, isolated **(*S*)-3**, **(*S*)-4**, **(*S*)-1** and **5a**.

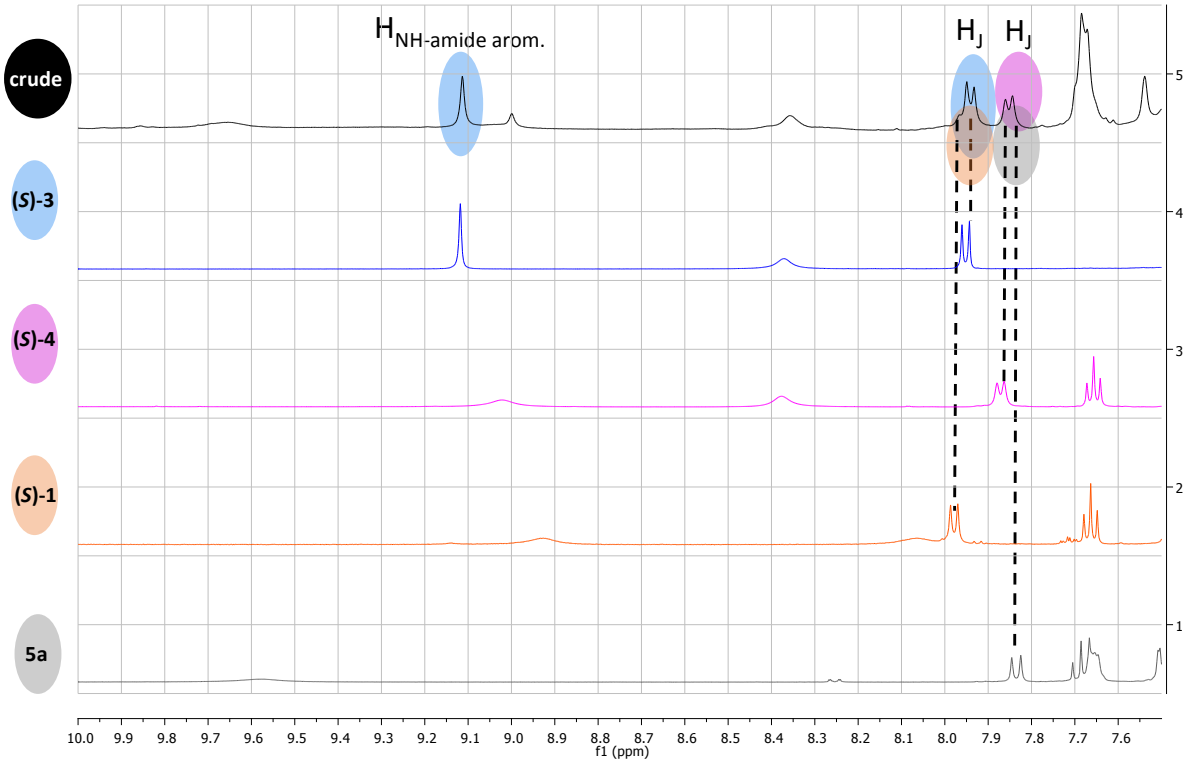


Figure S2. ^{1}H NMR partial stacked spectra of crude **(*S*)-3**, isolated **(*S*)-3**, **(*S*)-4**, **(*S*)-1** and **5a**.

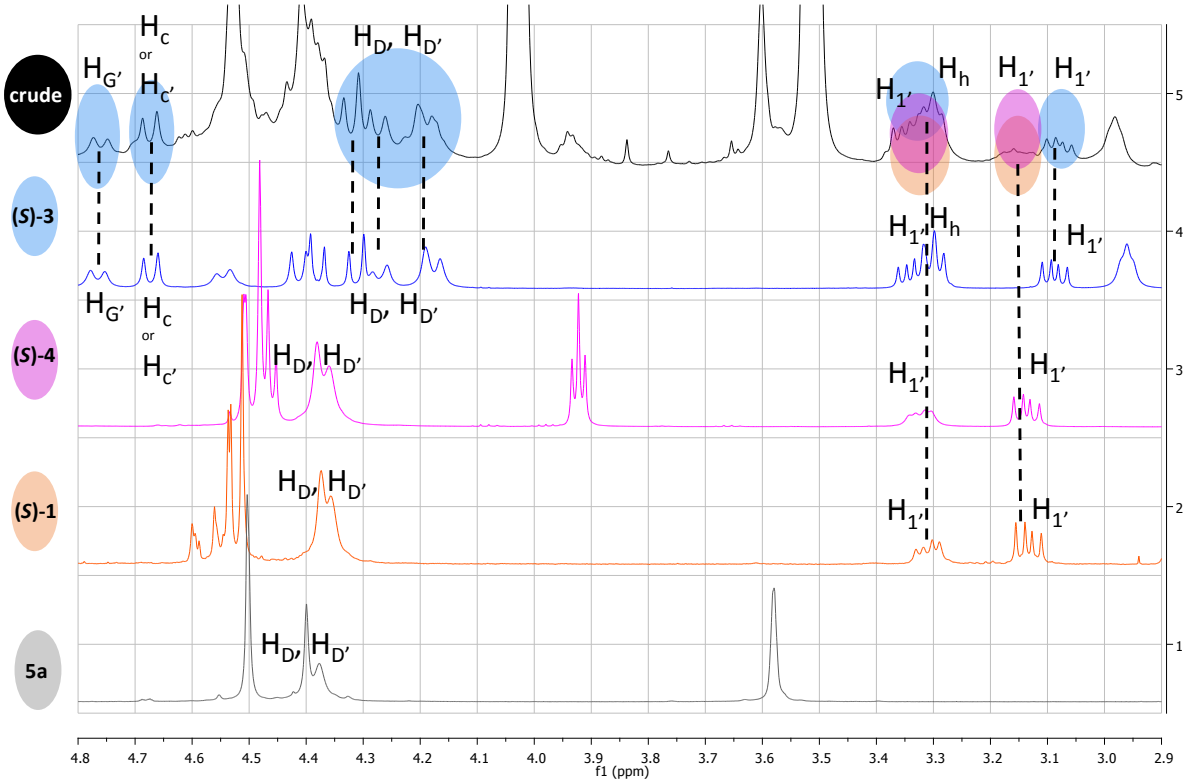


Figure S3. ^{1}H NMR partial stacked spectra of crude **(*S*)-3**, isolated **(*S*)-3**, **(*S*)-4**, **(*S*)-1** and **5a**.

I.5. CD and absorbance spectra of (*S*)-4

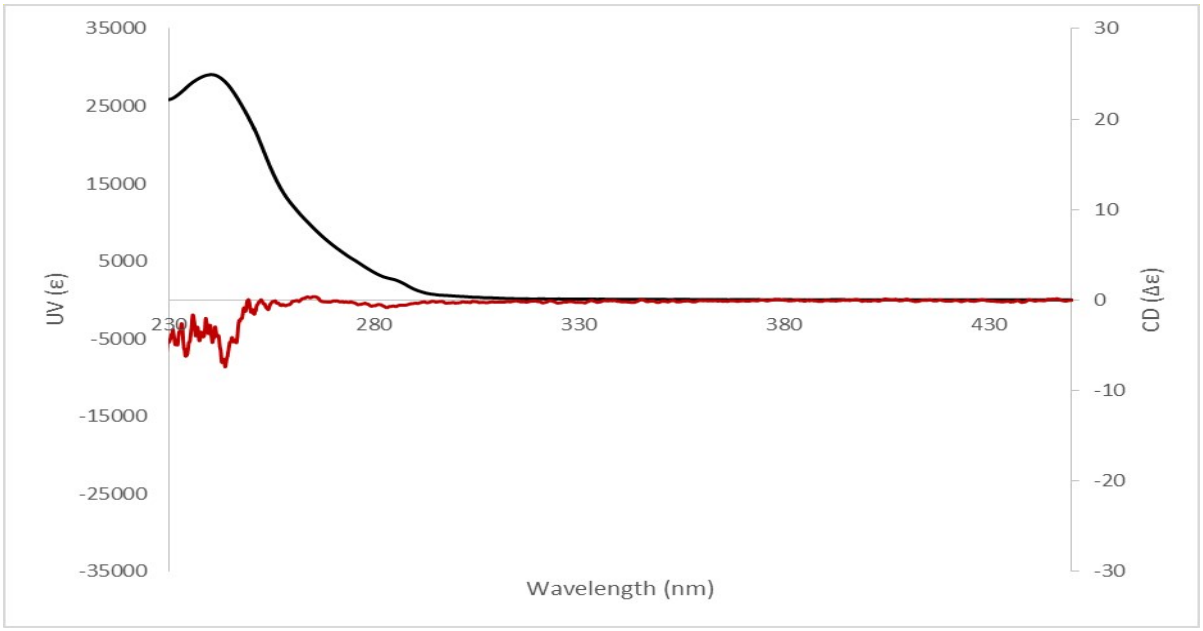


Figure S4. CD spectrum of **(*S*)-4** (red). Absorbance spectrum of **(*S*)-4** (black). Measured in CH_2Cl_2 (c = 10-3 M) at 20 °C.

I.6. Method of mechanical stereodescriptor determination of MPC [1]rotaxane

In order to assign the mechanical stereodescriptor of a [1]rotaxane bearing a dissymmetric macrocycle, we propose the following procedure which is derived from the already known strategy for the MPC [2]rotaxanes[6] For this purpose, the [1]rotaxane has to be visualized as a "virtual" [2]rotaxane using the following rules (**scheme S12**):

Step 1: Break the covalent bond between the macrocycle and the exocyclic chain in order to form the corresponding pseudo[2]rotaxane.

Step 2: Unfold linearly the axle.

Step 3: Extend each new non-covalently linked unit of the pseudo[2]rotaxane by the missing part with which it is linked within the [1]rotaxane. Thus, the interlocked axle is extended by a new macrocycle, playing the role of the second stopper in the newly formed [2]rotaxane (see highlighted grey box n°1, **scheme S12**) while the macrocycle is extended by the axle bearing the terminal stopper (see highlighted grey box n°2, **scheme S12**).

Each newly formed element (highlighted with grey boxes) in the resulting [2]rotaxane is then considered as "virtual" with the following properties:

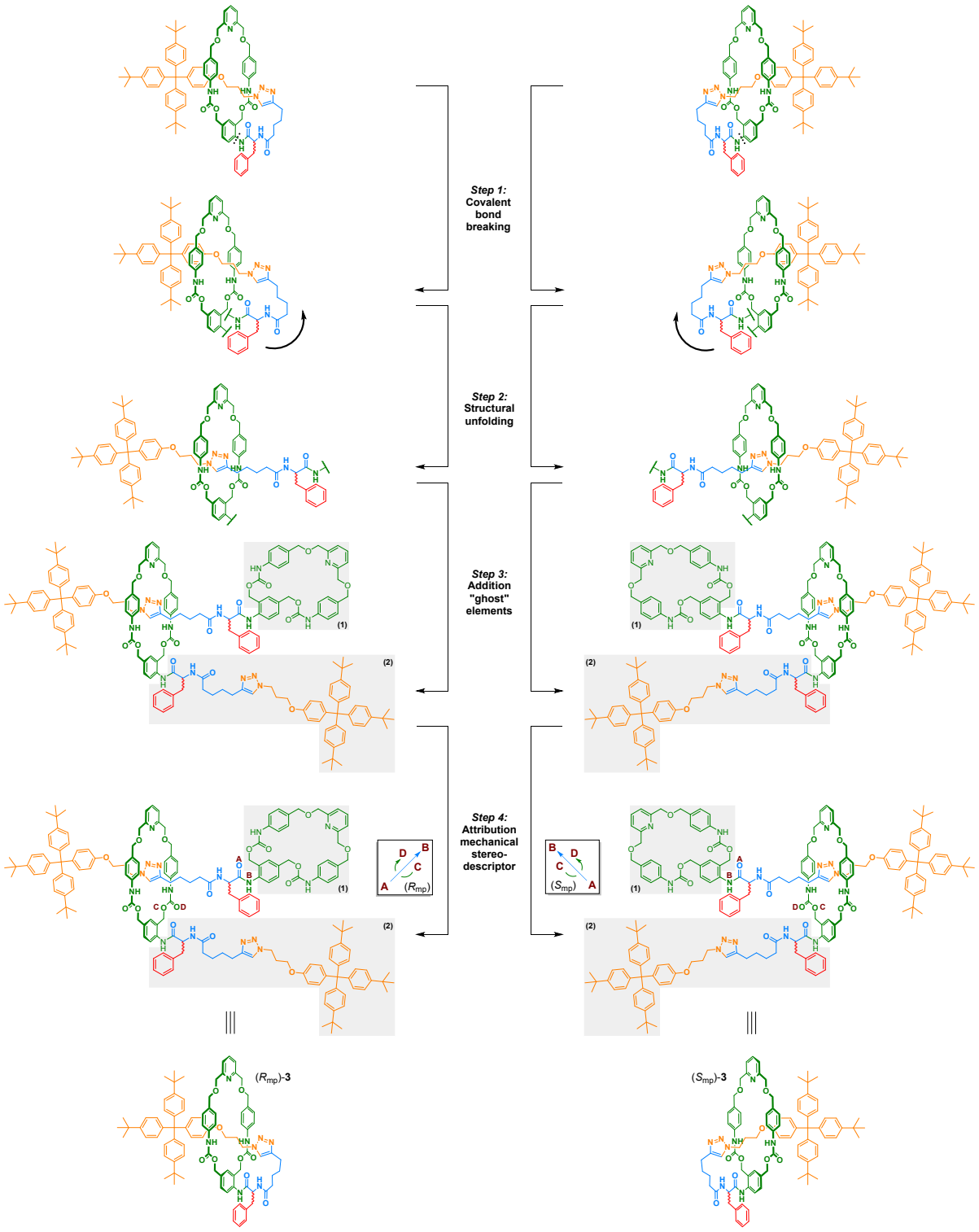
i. None of the newly added atoms can be selected when determining the priority atoms, both into the axle and the macrocycle (e.g. **scheme S12**, for the determination of axle atoms of highest priority, the amide moieties have priority against "virtual" endocyclic carbamates).
ii. However, the addition of these "virtual" fragments can then allow to define the order of priority between two identical functional groups within the pre-existing [1]rotaxane (see the two amide functions of the axle or the two carbamate functions of the macrocycle).

Step 4: Determine the mechanical stereodescriptor of the MPC [2]rotaxane with the new rules previously described in step 3:

i. Determine the atom of highest priority in the axle with the Cahn-Ingold-Prelog (CIP) methodology and attribute the label "A" to it. If the atom of highest priority is out of the axle line, the all functional group connected to the axle, which bears this atom of highest priority, is considered as "A".
ii. From "A", determine the highest priority atom with the CIP methodology and give it the label "B". The directionality of the axle is then directed by the vector A→B.

iii. Execute the same process for the macrocycle with the atom/functional group of highest priority labelled "C" and attribute the label "D" to the atom of highest priority when looking from "C". The orientation of the macrocycle is then directed by the vector C→D.

iv. Look at the [2]rotaxane along the direction of vector A→B and observe the orientation of the vector C→D. If the vector C→D shows a clockwise orientation, the mechanical stereodescriptor is considered (R_{mp}), otherwise, if the vector C→D shows an anticlockwise orientation then the mechanical stereodescriptor is considered as (S_{mp}).



Scheme S12. Representation of the methodology for the mechanical stereodescriptor determination of MPC [1]rotaxane **3**.

II. REFERENCES

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6 a) C. Reuter, A. Mohry, A. Sobanski, F. Vögtle, *Chem. Eur. J.*, 2000, **6**, 1674; b) E. M. G. Jamieson, F. Modicom, S. M. Goldup, *Chem. Soc. Rev.*, 2018, **47**, 5266.