Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Stereoselective deconjugation of macrocyclic α,β-unsaturated esters by sequential amidation and olefin transposition: application to enantioselective phase-transfer catalysis

Supporting Information

Alexandre Homberg,[a] Radim Hrdina,[a] Mahesh Vishe,[a] Laure Guénée,[b] Jérôme Lacour*,[a]

[a] Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva 4, Switzerland.

[b] Laboratory of Crystallography, University of Geneva, Quai Ernest Ansermet 24, 1211 Geneva 4, Switzerland.

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1 General Information and Materials

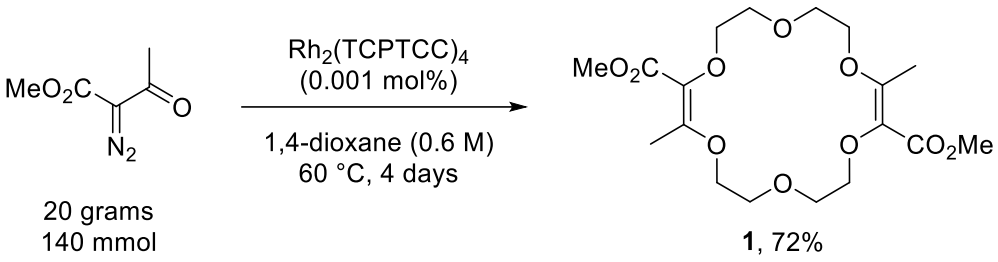
All reactions involving air sensitive compounds were carried out under N_2 or argon by means of an inert gas/vacuum double manifold line and standard Schlenk techniques using dry solvents (CH_2Cl_2, tetrahydrofuran and 1,4-dioxane). Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. *t*-BuOK was sublimed prior to use.

Analytical thin-layer chromatography (TLC) were performed with Silicagel 60 F_{254} aluminum sheets from Merck. Flash column chromatography were performed with Silica SiliaFlash P60, 40-63 µm (230-400 mesh). NMR spectra were recorded on a Bruker AVANCE I 300 MHz spectrometer, equipped with a 5 mm QNP D133 probe, a Bruker AVANCE III HD-*NanoBay* 300 MHz spectrometer, equipped with a 5 mm BB(F)-H-D probe, on a Bruker ADVANCE III HD-NanoBay 400 MHz spectrometer, equipped with a 5 mm CryoProbe Prodigy, or on a Bruker II 500 MHz spectrometer, equipped with a 5 mm Cryogenic DCH ($^1H/^{13}C$) probe. ^1H NMR chemical shifts are given in ppm relative to Me_4Si using solvent resonances as internal standards ($CDCl_3$ δ = 7.26 ppm). Data were reported as follows: chemical shift (δ) in ppm, multiplicity (s = singulet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet and m = multiplet), coupling constant (Hz) and integration. ^{13}C-NMR chemicals shifts are given in ppm relative to Me_4Si with solvent resonances used as internal standards ($CDCl_3$ δ = 77.16 ppm). ^{19}F-NMR chemicals shifts are given in ppm. IR spectra were recorded with a Perkin-Elmer 100 FT-IR spectrometer using a diamond ATR Golden Gate sampling and are reported in wave numbers (cm^{-1}). Melting points (m.p.) were measured in open capillary tubes with a Büchi B-550 melting point apparatus and were uncorrected. Electrospray mass spectra were obtained on an API 150EX (AB/MDS Sciex) for the low resolution mass spectra (LR-ESI-MS) and on a QSTAR Pulsar (AB/MDS Sciex) spectrometer by the Department of Mass Spectroscopy at the University of Geneva for the high resolution mass spectra (HR-MS). HPLC traces were performed on Agilent analytical LC 1200 (binary high pressure solvent mixer, automatic sampler, two-column heating-chilling Oven, diode-array detector); LC machine is coupled to PC (Analysis program: ChemStation).

2 Synthesis and characterization of organic compounds

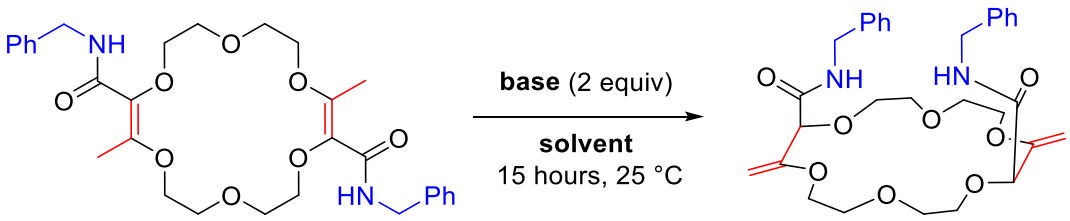
2.1 Synthesis of unsaturated ester macrocycle **1**

Unsaturated ester macrocycle **1** was synthetized according to previously reported procedure from the literature[1] :



(S1)

2.2 Conditions screening for olefin transpositions



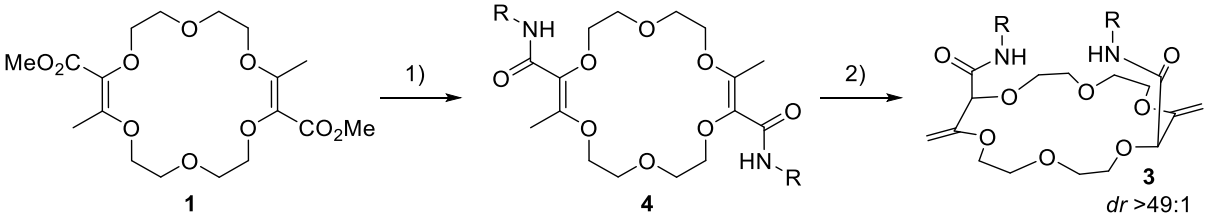
(S2)

Table S1. Optimization of the olefin transposition conditions.

Entry	Base	equiv	Solvent	Yield (%)
1	*t*-BuOK	2.2	THF	63
2	***t*-BuOK**	**2.2**	**1,4-dioxane**	**65**
3	*t*-BuOK	2.2	Et_2O	low conversion
4	*t*-BuOK	2.2	*t*-BuOMe	no conversion
5	*t*-BuOK	0.2	1,4-dioxane	low conversion
6	NaOMe	2.2	1,4-dioxane	no conversion
7	DBU	2.2	1,4-dioxane	no conversion
8	TBD	2.2	1,4-dioxane	no conversion

3 Synthesis of polyether macrocycle **3**

3.1 General procedure[1]



1) First step (aminolysis): In a 4 mL vial, 2 mL of dry THF (*c* = 0.1 M) are added to 101 mg (0.25 mmol, 1 equiv) of **1** and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene, 2 or 4 equiv). The amine (1.00 mmol, 4 equiv) is the added in one portion to the suspension and the mixture is stirred at 60 °C for 15 hours (or 10 days). The conversion is followed by TLC analysis (SiO_2, CH_2Cl_2/MeOH (10%)) and LR-ESI-MS (soft positive mode, CH_2Cl_2). The reaction is cooling down to 25 °C and the compound is purified according to the following procedures.

Purification method A: the product is purified by filtration and the solid is washed with 3 mL of Et_2O.

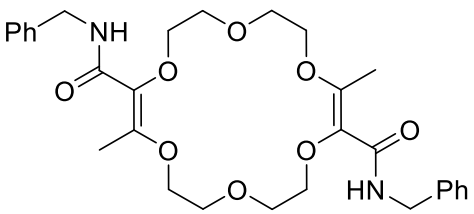
Purification method B: a drop of MeOH is added and the crude mixture is directly purified by column chromatography (SiO_2, EtOAc then CH_2Cl_2/MeOH gradient (5%, 10%)). The resulting oil is purified by selective precipitation (a minimum of EtOAc for solubility, followed by a large excess of pentane, 15 hours). The non-isomerized bis-amide compound **4** is used without further purification in the second step.

2) Second step (transposition): Considering the non-isomerized bis-amide compound **4** as pure, *t*-BuOK (2.2 equiv) is added in one portion to a suspension (or solution) of non-isomerized bis-amide compound **4** in dry 1,4-dioxane (*c* = 0.1 M). The mixture is stirred at 25 °C for 15 hours. The conversion is followed by TLC analysis (SiO_2, CH_2Cl_2/MeOH, (10%), CMAS stain). The reaction mixture is quench with a drop of MeOH and directly purified by column chromatography (neutral Al_2O_3, EtOAc then CH_2Cl_2/MeOH gradient (1%, 3%, 5%)). Finally, the resulting oil is purified by selective precipitation (a minimum of EtOAc for solubility, followed by a large excess of pentane, 15 hours) affording the desired derivative **3** as a white solid.

[1] The use of freshly neutralized $CDCl_3$ (filtration over basic alumina) was necessary for this series of compounds to avoid degradation of the crown ethers in the NMR tube during the analysis.

3.2 Synthesis of **4a** and **3a**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 109 µL (107 mg, 1.00 mmol, 4 equiv) of benzylamine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield:



First step: 104 mg (0.19 mmol, 554.64 g/mol, 75%) of **4a** as a white solid (purification method A).

R_f = 0.6 (SiO_2, CH_2Cl_2/MeOH (10%))

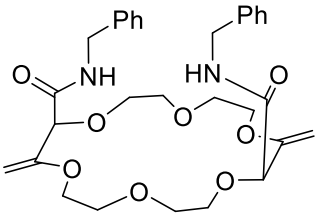
m.p.: 173 °C – 174 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 2.47 (s, 6H, -CH_3), 3.74 - 3.77 (m, 8H, -CH_2-), 3.95 - 3.97 (m, 4H, -CH_2-), 4.05 - 4.07 (m, 4H, -CH_2-), 4.48 (s, 4H, -CH_2-), 6.99 - 7.01 (m, 2H, NH), 7.25 - 7.29 (m, 6H, aromatics), 7.31 - 7.34 (m, 4H, aromatics).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 13.9 (2 -CH_3), 43.0 (2 -CH_2-), 67.3 (2 -CH_2-), 70.0 (2 -CH_2-), 70.5 (2 -CH_2-), 71.6 (2 -CH_2-), 127.4 (2 CH aromatic), 127.6 (4 CH aromatic), 128.8 (4 CH aromatic), 131.9 (2 =C), 138.9 (2 C aromatic), 153.7 (2 =C), 166.3 (2 C=O).

IR (neat): ṽ/cm^{-1}3347, 2934, 1646, 1607, 1503, 1453, 1421, 1371, 1303, 1259, 1205, 1161, 1129, 1098, 1058, 1031, 975, 929, 883, 847, 812, 768, 742, 698, 663, 608, 569.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{30}H_{39}N_2O_8$ 555.2701, observed 555.2710 (1.7 ppm).



Second step (overall two step from **1** yield)**:** 75 mg (0.14 mmol, 554.64 g/mol, 59%) of **3a** as a white solid.

R_f = 0.5 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 122 °C – 123 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 3.49 - 3.53 (m, 2H, -CH_2-), 3.56 - 3.60 (m, 4H, -CH_2-), 3.62 - 3.75 (m, 8H, -CH_2-), 3.78 - 3.82 (m, 2H, -CH_2-), 4.10 (dd, 2H, *J* = 15.0, 5.3 Hz, benzylic), 4.19 (d, 2H, 2.7 Hz, =CH_2), 4.30 (s, 2H, -CH-), 4.35 (d, 2H, 2.7 Hz, =CH_2), 4.53 (dd, 2H, *J* = 15, 6.9 Hz, benzylic), 7.20 - 7.23 (m, 6H, aromatics), 7.26-7.29 (m, 4H, aromatics), 7.50 (m, 2H, NH).

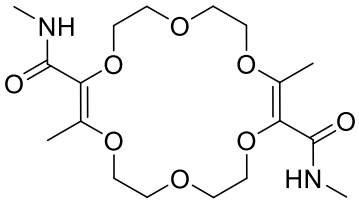
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 42.8 8 (2 -CH_2-), 67.5 (2 -CH_2-), 68.2 (2 -CH_2-), 68.9 (2 -CH_2-), 70.7 (2 -CH_2-), 82.1 (2 -CH-), 87.8 (2 =CH_2), 127.2 (2 CH aromatic), 127.7 (4 CH aromatic), 128.8 (4 CH aromatic), 138.8 (2 C aromatic), 157.1 (2 =CH), 169.1 (2 C=O).

IR (neat): ṽ/cm^{-1} 3333, 3262, 3031, 2921, 2882, 1658, 1525, 1454, 1430, 1348, 1294, 1259, 1240, 1116, 1089, 1071, 1024, 993, 961, 937, 887, 827, 778, 734, 696, 621.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{30}H_{39}N_2O_8$ 555.2701, observed 555.2686 (-2.6 ppm).

3.3 Synthesis of 4b and 3b

According to general procedure, with 101 mg (0.25 mmol) of **1**, 500 µL (2 M solution in THF, 0.99 mmol, 4 equiv) of methylamine, 69 mg (0.50 mmol, 2 equiv) of TBD and 1.5 mL of THF (total of 2 mL) for 15 hours to yield:



First step: 53 mg (0.13 mmol, 402.44 g/mol, 53%) of **4b** as a white solid (purification method A).

R_f = 0.3 (SiO_2, CH_2Cl_2/MeOH (10%))

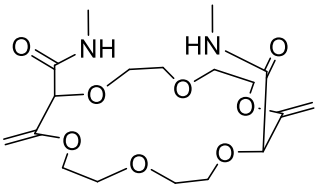
m.p.: 166 °C - 167 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 2.46 (s, 6H, $-CH_3$), 2.84 (d, 6H, *J* = 4.9 Hz, $-CH_3$), 3.79 - 3.81 (m, 8H, $-CH_2-$), 3.95 - 3.97 (m, 4H, $-CH_2-$), 4.08 - 4.10 (m, 4H, $-CH_2-$), 6.65 - 6.65 (m, 2H, NH).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 13.8 (2 $-CH_3$), 26.0 (2 $-CH_3$), 67.3 (2 $-CH_2-$), 70.1 (2 $-CH_2-$), 70.6 (2 $-CH_2-$), 71.6 (2 $-CH_2-$), 132.2 (2 =C), 153.1 (2 =C), 166.1 (2 C=O).

IR (neat): ṽ/cm^{-1} 3371, 2944, 2923, 2882, 1654, 1612, 1513, 1450, 1374, 1308, 1256, 1232, 1168, 1131, 1101, 1057, 1033, 978, 931, 891, 855, 810, 793, 775, 696, 665, 615, 575.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{18}H_{31}N_2O_8$ 403.2075, observed 403.2072 (-0.8 ppm).



Second step (overall two step from **1** yield)**:** 46 mg (0.12 mmol, 402.44 g/mol, 46%) of **3b** as a white solid.

R_f = 0.3 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 141 °C - 142 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 2.81 (d, 6H, *J* = 4.9 Hz, $-CH_3$), 3.53 - 3.57 (m, 2H, $-CH_2-$), 3.68 - 3.72 (m, 6H, $-CH_2-$), 3.76 - 3.80 (m, 4H, $-CH_2-$), 3.84 - 3.93 (m, 4H, $-CH_2-$), 4.22 (d, 2H, *J* = 2.8 Hz, $=CH_2$), 4.29 (s, 2H, CH), 4.37 (d, 2H, *J* = 2.7 Hz, $=CH_2$), 7.34 - 7.36 (m, 2H, NH).

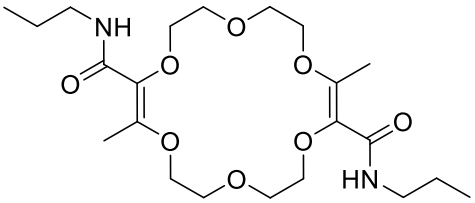
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 26.0 (2 $-CH_3$), 67.6 (2 $-CH_2-$), 68.6 (2 $-CH_2-$), 69.0 (2 $-CH_2-$), 70.5 (2 $-CH_2-$), 82.3 (2 -CH-), 87.6 (2 $=CH_2$), 157.3 (2 =C), 169.7 (2 C=O).

IR (neat): ṽ/cm^{-1} 3518, 3276, 3097, 2911, 2881, 1661, 1639, 1545, 1454, 1405, 1362, 1280, 1241, 1130, 1097, 1071, 1005, 944, 842, 783, 753, 677, 622, 572.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{18}H_{31}N_2O_8$ 403.2075, observed 403.2073 (-0.5 ppm).

3.4 Synthesis of **4c** and **3c**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 81 µL (59 mg, 1.00 mmol, 4 equiv) of *n*-propylamine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield:



First step: 68 mg (0.15 mmol, 458.55 g/mol, 59%) of **4c** as a white solid (purification method B).

R_f = 0.4 (SiO_2, CH_2Cl_2/MeOH (10%))

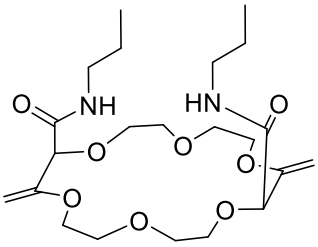
m.p.: 130 °C – 131 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 0.93 (t, 6H, *J* = 7.4 Hz, -CH_3), 1.54 (dq, 4H, *J* = 14.6, 7.4 Hz, -CH_2-), 2.46 (s, 6H, -CH_3), 3.22 - 3.26 (m, 4H, -CH_2-), 3.80 - 3.82 (m, 8H, -CH_2-), 3.96 (t, 4H, *J* = 5.3 Hz, -CH_2-), 4.08 - 4.10 (m, 4H, -CH_2-), 6.96 - 6.72 (m, 2H, NH).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 11.6 (2 -CH_3), 13.9 (2 -CH_3), 23.2 (2 -CH_2-), 40.7 (-CH_2-), 40.8 (-CH_2-), 67.3 (2 -CH_2-), 70.1 (2 -CH_2-), 70.6 (2 -CH_2-), 71.6 (2 -CH_2-), 132.3 (2 =C), 153.2 (2 =C), 165.4 (2 C=O).

IR (neat): ṽ/cm^{-1} 3345, 2927, 2870, 1650, 1612, 1506, 1460, 1372, 1305, 1259. 1235, 1166, 1127, 1063, 1036, 978, 935, 915, 884, 812, 790, 773, 708, 674, 621, 573, 547.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{39}N_2O_8$ 459.2701, observed 459.2698 (-0.7 ppm).



Second step (overall two step from **1** yield)**:** 48 mg (0.11 mmol, 458.55 g/mol, 42%) of **3c** as a white solid.

R_f = 0.4 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 134 °C - 136 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 0.93 (t, 6H, *J* = 7.4 Hz, -CH_3), 1.55 (hd, 4H, *J* = 7.3, 1.5 Hz, -CH_2-), 3.20 (dq, 2H, *J* = 13.1, 6.9 Hz, -CH_2-), 3.29 (dq, 2H, *J* = 13.4, 7.0 Hz, -CH_2-), 3.51 - 3.61 (m, 2H, -CH_2-), 3.64 - 3.83 (m, 12H, -CH_2-), 3.87 - 3.91 (m, 2H, -CH_2-), 4.21 (d, 2H, *J* = 2.7 Hz, =CH_2), 4.27 (s, 2H, -CH-), 4.36 (d, 2H, *J* = 2.7 Hz, =CH_2), 7.37 (t, 2H, *J* = 5.7 Hz, NH).

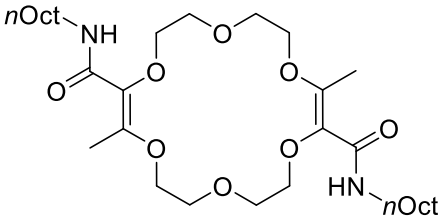
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 11.6 (2 -CH_3), 22.9 (2 -CH_2-), 41.0 (2 -CH_2-), 67.4 (2 -CH_2-), 68.4 (2 -CH_2-), 69.1 (2 -CH_2-), 70.7 (2 -CH_2-), 82.4 (2 =CH_2), 87.5 (2 -CH-), 157.3 (2 =C), 169.0 (2 C=O).

IR (neat): ṽ/cm^{-1} 3304, 2961, 2933, 2874, 1678, 1656, 1636, 1527, 1460, 1347, 1292, 1263, 1218, 1135, 1115, 1093, 1058, 1019, 988, 856, 826, 810, 783, 732, 672, 621, 566.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{39}N_2O_8$ 459.2701, observed 459.2699 (-0.5 ppm).

3.5 Synthesis of 4d and 3d

According to general procedure, with 101 mg (0.25 mmol) of **1**, 164 µL (128 mg, 1.00 mmol, 4 equiv) of *n*-octylamine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield:



First step: 97 mg (0.16 mmol, 598.82 g/mol, 65%) of **4d** as a white solid (purification method B).

R_f = 0.6 (SiO_2, CH_2Cl_2/MeOH (10%))

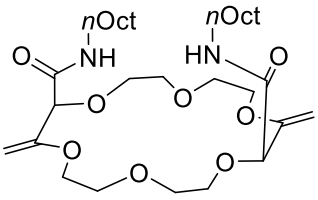
m.p.: 129 °C – 131 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 0.87 (t, 6H, *J* = 6.9 Hz, $-CH_3$), 1.24 - 1.32 (m, 20H, $-CH_2-$), 1.49 - 1.52 (m, 4H, $-CH_2-$), 2.45 (s, 6H, $-CH_3$), 3.24 - 3.28 (m, 4H, $-CH_2-$), 3.79 - 3.82 (m, 8H, $-CH_2-$), 3.95 (t, 4H, *J* = 5.3 Hz, $-CH_2-$), 4.08 - 4.10 (m, 4H, $-CH_2-$), 6.67 - 6.69 (m, 2H, NH).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 13.9 (2 $-CH_3$), 14.3 (2 $-CH_3$), 22.8 (2 $-CH_2-$), 27.2 (2 $-CH_2-$), 29.4 (2 $-CH_2-$), 29.4 (2 $-CH_2-$), 29.9 (2 $-CH_2-$), 31.9 (2 $-CH_2-$), 39.2 (2 $-CH_2-$), 67.3 (2 $-CH_2-$), 70.1 (2 $-CH_2-$), 70.6 (2 $-CH_2-$), 71.6 (2 $-CH_2-$), 132.3 (2 =C), 153.1 (2 =C), 165.3 (2 C=O).

IR (neat): $\tilde{\nu}$/cm^{-1} 3342, 2921, 2851, 1650, 1613, 1508, 1464, 1425, 1372, 1305, 1260, 1237, 1166, 1128, 1096, 1066, 1037, 978, 947, 934, 897, 877, 811, 773, 716, 675, 622, 576, 547, 521.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{59}N_2O_8$ 599.4266, observed 599.4291 (4.3 ppm).



Second step (overall two step from **1** yield)**:** 82 mg (0.14 mmol, 598.82 g/mol, 55%) of **3d** as a white solid.

R_f = 0.5 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 115 °C - 116 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 0.88 (t, 6H, *J* = 6.8 Hz, $-CH_3$), 1.21 - 1.36 (m, 20H, $-CH_2-$), 1.51 (q, 4H, *J* = 7.1 Hz, $-CH_2-$), 3.19 - 3.33 (m, 4H, $-CH_2-$), 3.55 - 3.59 (m, 2H, $-CH_2-$), 3.84 - 3.65 (m, 12H, $-CH_2-$), 3.87 - 3.91 (m, 2H, $-CH_2-$), 4.20 (d, 2H, *J* = 2.7 Hz, $=CH_2$), 4.28 (s, 2H, -CH-), 4.35 (d, 2H, *J* = 2.7 Hz, $=CH_2$), H_2O and NH signals not detected.

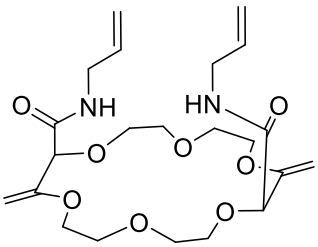
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 14.3(2 $-CH_3$), 22.8 (2 $-CH_2-$), 27.1 (2 $-CH_2-$), 29.4 (2 $-CH_2-$), 29.5 (2 $-CH_2-$), 29.7 (2 $-CH_2-$), 32.0 (2 $-CH_2-$), 39.3 (2 $-CH_2-$), 67.5 (2 $-CH_2-$), 68.4 (2 $-CH_2-$), 69.1 (2 $-CH_2-$), 70.7 (2 $-CH_2-$), 82.2 (2 $=CH_2$), 87.3 (2 -CH-), 157.5 (2 =C), 168.9 (2 C=O).

IR (neat): $\tilde{\nu}$/cm^{-1} 3315, 2921, 2853, 1679, 1657, 1635, 1528, 1464, 1432, 1374, 1348, 1298, 1258, 1222, 1153, 1135, 1117, 1089, 1057, 1021, 988, 938, 922, 858, 826, 804, 722, 669, 621, 572.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{58}N_2O_8$ 599.4266, observed 599.4272 (1.0 ppm).

3.6 Synthesis of **3e**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 74 µL (57 mg, 1.00 mmol, 4 equiv) of allyl-amine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield 50 mg (0.11 mmol, 454.52 g/mol, 44%, overall two step from **1** yield) of **3e** as a white solid. (purification method B).



R_f = 0.5 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 126 °C - 128 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 3.54 - 3.58 (m, 2H, -CH_2-), 3.64 - 3.91 (m, 16H, -CH_2-), 3.94 - 4.00 (m, 2H, -CH_2-), 4.22 (d, 2H, *J* = 2.7 Hz, =CH_2), 4.30 (s, 2H, -CH-), 4.36 (d, 2H, *J* = 2.7 Hz, =CH_2), 5.10 (dq, 2H, *J* = 10.3, 1.4 Hz, =CH_2), 5.24 (dq, 2H, *J* = 17.2, 1.6 Hz, =CH_2), 5.85 (ddt, 2H, *J* = 17.1, 10.5, 5.3, =CH-), 7.41 - 7.43 (m, 2H, NH).

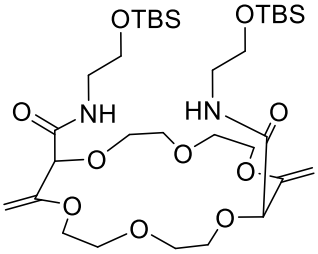
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 41.6 (2 -CH_2-), 67.4 (2 -CH_2-), 68.3 (2 -CH_2-), 69.0 (2 -CH_2-), 70.7 (2 -CH_2-), 82.3 (2 -CH-), 87.8 (2 =CH_2), 115.9 (2 =CH_2), 134.5 (2 =CH-), 157.1 (2 =C), 169.0 (2 C=O).

IR (neat): ṽ/cm^{-1} 3300, 1917, 2878, 1680, 1657, 1639, 1520, 1463, 1418, 1345, 1292, 1266, 1221, 1135, 1114, 1097, 1056, 1021, 988. 959, 922, 854, 825, 800, 781, 742, 674, 653, 617, 558.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{35}N_2O_8$ 455.2388, observed 455.2390 (0.4 ppm).

3.7 Synthesis of 3f

According to general procedure, with 101 mg (0.25 mmol) of **1**, 175 mg (1.00 mmol, 4 equiv) of *tert*-butyl dimethylsilane ethanolamine[2] and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield 60 mg (0.09 mmol, 691.02 g/mol, 35%, overall two step from **1** yield) of **3f** as a white solid (purification method B).



R_f = 0.54 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 100 °C - 101 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 0.06 (s, 12H, $-CH_3$), 0.89 (s, 18H, $-CH_3$), 3.28 - 3.34 (m, 2H, $-CH_2-$), 3.47 - 3.53 (m, 2H, $-CH_2-$), 3.57 - 3.61 (m, 2H, $-CH_2-$), 3.68 - 3.79 (m, 14H, $-CH_2-$), 3.83 - 3.90 (m, 4H, $-CH_2-$), 4.22 (d, 2H, *J* = 2.7 Hz, $=CH_2$), 4.28 (s, 2H, -CH-), 4.32 (d, 2H, *J* = 2.7 Hz, $=CH_2$), 7.33 (t, 2H, *J* = 5.7 Hz, NH).

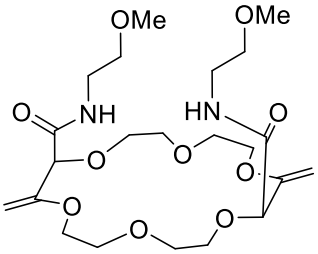
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = -5.2 (2 $-CH_3$), -5.2 (2 $-CH_3$), 18.4 (2 C), 26.0 (6 $-CH_3$), 41.5 (2 $-CH_2-$), 61.9 (2 $-CH_2-$), 67.7 (2 $-CH_2-$), 68.6 (2 $-CH_2-$), 69.1 (2 $-CH_2-$), 70.6 (2 $-CH_2-$), 82.1 (2 -CH-), 87.4 (2 $=CH_2$), 157.6 (2 =C), 169.1 (2 C=O).

IR (neat): $\tilde{\nu}$/cm^{-1} 3306, 2936, 2860, 1678, 2657, 1638, 1526, 1467, 1298, 1253, 1223, 1133, 1097, 1057, 1021, 940, 834, 775, 665, 622.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{63}N_2O_{10}Si_2$ 691.4016, observed 691.4016 (0.0 ppm).

3.8 Synthesis of **3g**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 87 µL (75 mg, 1.00 mmol, 4 equiv) of 2-methoxyethlylamine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield 66 mg (0.14 mmol, 490.25 g/mol, 54%, overall two step from **1** yield) of **3g** as a white solid (purification method B).



R_f = 0.4 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 109 °C - 110 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 3.34 (s, 6H, $-CH_3$), 3.43 - 3.53 (m, 8H, $-CH_2-$), 3.54 - 3.58 (m, 2H, $-CH_2-$), 3.67 – 3.80 (m, 10H, $-CH_2-$), 3.83 - 3.91 (m, 2H, $-CH_2-$), 4.23 (d, 2H, *J* = 2.6 Hz, $=CH_2$), 4.27 (s, 2H, -CH-), 4.34 (d, 2H, *J* = 2.6 Hz, $=CH_2$), 7.44 (s, 2H, NH).

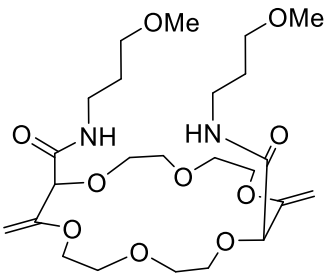
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 39.0 (2 $-CH_2-$), 58.8 (2 $-CH_3$), 67.9 (2 $-CH_2-$), 68.3 (2 $-CH_2-$), 69.1 (2 $-CH_2-$), 70.7 (2 $-CH_2-$), 71.2 (2 $-CH_2-$), 82.2 (2 $=CH_2$), 87.8 (2 -CH-), 157.2 (2 =C), 169.3 (2 C=O).

IR (neat): $\tilde{\nu}/cm^{-1}$ 3308, 2936, 2882, 2820, 1658, 1635, 1528, 1457, 1347, 1320, 1296, 1264, 1221, 1132, 1117, 1089, 1057, 1021, 988, 961, 945, 924, 882, 858, 826, 805, 738, 673, 622, 568.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{39}N_2O_{10}$ 491.2599, observed 491.2612 (2.6 ppm).

3.9 Synthesis of 3h

According to general procedure, with 101 mg (0.25 mmol) of **1**, 102 µL (89 mg, 1.00 mmol, 4 equiv) of 3-methoxypropylamine and 69 mg (0.50 mmol, 2 equiv) of TBD for 15 hours to yield 70 mg (0.14 mmol, 518.60 g/mol, 54%, overall two step from **1** yield) of **3h** as a white solid (purification method B).



R_f = 0.4 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 99 °C - 100 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.81 (p, 4H, *J* = 6.5 Hz, -CH_2-), 3.32 (s, 6H, -CH_3), 3.33 - 3.41 (m, 4H, -CH_2-), 3.44 (t, 4H, *J* = 6.3 Hz, -CH_2-), 3.53 - 3.57 (m, 2H, -CH_2-), 3.66 - 3.84 (m, 12H, -CH_2-), 3.87 - 3.91 (m, 2H, -CH_2-), 4.21 (d, 2H, *J* = 2.6 Hz, =CH_2), 4.25 (s, 2H, -CH-), 4.34 (d, 2H, *J* = 2.6 Hz, =CH_2), 7.55 - 7.57 (m, 2H, NH).

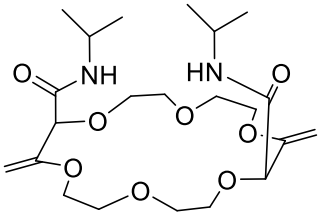
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 29.5 (2 -CH_2-), 36.9 (2 -CH_2-), 58.8 (2 -CH_3), 67.5 (2 -CH_2-), 68.4 (2 -CH_2-), 69.1 (2 -CH_2-), 70.7 (2 -CH_2-), 70.9 (2 -CH_2-), 82.4 (2 -CH-), 87.7 (2 =CH_2), 157.3 (2 =C), 169.1 (2 C=O).

IR (neat): ṽ/cm^{-1} 3296, 2932, 2874, 1678, 1656, 1639, 1518, 1454, 1397, 1370, 1349, 1298, 1258, 1222, 1194, 1114, 1085, 1057, 1021, 991, 942, 856, 824, 790, 739, 683, 621, 574.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{24}H_{43}N_2O_{10}$ 519.2912, observed 519.2927 (2.8 ppm).

3.10 Synthesis of 3i

According to general procedure, with 101 mg (0.25 mmol) of **1**, 86 µL (59 mg, 1.00 mmol, 4 equiv) of isopropylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 34 mg (0.07 mmol, 458.55 g/mol, 29%) of **3i** as a white solid (purification method B).



R_f = 0.3 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 101 °C - 107 °C

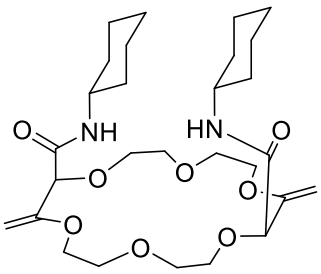
^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.17 (d, 6H, *J* = 4.0 Hz, -CH_3), 1.18 (d, 6H, *J* = 4.0 Hz, -CH_3), 3.54 - 3.58 (m, 2H, -CH_2-), 3.64 - 3.81 (m, 12H, -CH_2-), 3.88 - 3.92 (m, 2H, -CH_2-), 4.10 - 4.17 (m, 2H, -CH-), 4.20 (d, 2H, *J* = 2.7 Hz, =CH_2), 4.21 (s, 2H, -CH-), 4.35 (d, 2H, *J* = 2.7 Hz, =CH_2), 7.20 - 7.22 (m, 2H, NH).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 22.7 (2 -CH_3), 22.8 (2 -CH_3), 41.1 (2 -CH-), 67.3 (2 -CH_2-), 68.3 (2 -CH_2-), 69.2 (2 -CH_2-), 70.7 (2 -CH_2-), 82.3 (2 -CH-), 87.6 (2 =CH_2), 157.4 (2 =C), 168.1 (2 C=O.

IR (neat): ṽ/cm^{-1} 3399, 3361, 2973, 2928, 2886, 1665, 1528, 1463, 1297, 1261, 1248, 1213, 1135, 1076, 1031, 994, 955, 887, 833, 811, 790, 679, 627, 584.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{39}N_2O_8$ 459.2701, observed 459.2708 (1.5 ppm).

3.11 Synthesis of **3j**



According to general procedure, with with 101 mg (0.25 mmol) of **1**, 115 µL (99 mg, 1.00 mmol, 4 equiv) of cyclohexylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 24 mg (0.05 mmol, 538.68 g/mol, 18 %) of **3j** as a white solid (purification method B).

R_f = 0.3 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 131 °C - 133 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.10 - 1.27 (m, 6H, -CH_2-), 1.31 - 1.41 (m, 4H, -CH_2-), 1.61 - 1.65 (m, 2H, -CH_2-), 1.69 - 1.74 (m, 4H, -CH_2-), 1.88 - 1.92 (m, 4H, -CH_2-), 3.55 - 3.59 (m, 2H, -CH_2-), 3.64 - 3.91 (m, 16H, -CH_2-, -CH-), 4.19 (d, 2H, *J* = 2.7 Hz, =CH_2), 4.23 (s, 2H, -CH-), 4.34 (d, 2H, *J* = 2.7 Hz, =CH_2), 7.23 - 7.25 (m, 2H, NH).

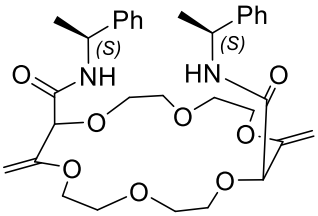
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 25.2 (4 -CH_2-), 25.7 (2 -CH_2-), 33.2 (4 -CH_2-), 48.1 (2 -CH-), 67.4 (2 -CH_2-), 68.3 (2 -CH_2-), 69.3 (2 -CH_2-), 70.8 (2 -CH_2-), 82.4 (2 -CH-), 87.3 (2 =CH_2), 157.5 (2 =C), 168.1 (2 C=O).

IR (neat): ṽ/cm^{-1} 3391, 3350, 3275, 2981, 2926, 2861, 1676, 1645, 1524, 1451, 1296, 1250, 1129, 1101, 1089, 1073, 1058, 1033, 990, 949, 860, 831, 808, 781, 748, 681, 623, 577.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{28}H_{47}N_2O_8$ 539.3327, observed 539.3326 (-0.2 ppm).

3.12 Synthesis of 3k

According to general procedure, with 101 mg (0.25 mmol) of **1**, 129 µL (121 mg, 1.00 mmol, 4 equiv) of (*S*)-α-methyl-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 36 mg (0.06 mmol, 582.69 g/mol, 25%) of **3k** as a white solid and as an inseparable mixture of diastereoisomers (*dr* 1.3:1) (purification method B).



R_f = 0.46 and 0.43 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 116 °C - 117 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = [1.41 (*minor*) and 1.43 (*major*) (d, 6H, *J* = 7.1 Hz, $-CH_3$)], 3.49 - 3.91 (m, 16H, $-CH_2-$), [4.15 (*minor*) and 4.20 (*major*) (d, 2H, 2.6 Hz, $=CH_2$)], [4.24 (*minor*) and 4.25 (*major*) (s, 2H, -CH-)], [4.31 (*minor*) and 4.36 (*major*) (d, 2H, 2.6 Hz, $=CH_2$)], 5.18 (p, 2H, *J* = 7.1 Hz, -CH-), 7.18 - 7.37 (m, 10H, aromatics), [7.78 (*major*)and 7.92 (*minor*) (d, 2H, *J* = 8.4 Hz, NH)].

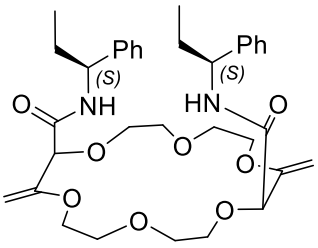
^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = [22.0 (*major*) and 22.1 (*minor*) (2 $-CH_3$)], [48.2 (*minor*) and 48.4 (*major*) (2 -CH-)], [66.9 (*major*) and 67.0 (*minor*) (2 $-CH_2-$)], [68.2 (*minor*) and 68.4 (*major*) (2 $-CH_2-$)], [70.6 (*major*) and 70.6 (*minor*) (2 $=CH_2$)], [82.4 (*major*) and 83.0 (*minor*) (2 -CH-)], [87.4 (*major*) and 87.9 (*minor*) (2 $=CH_2$)], [126.5 (*minor*) and 126.6 (*major*) (4 CH aromatic)], [127.0 (*minor*) and 127.2 (*major*) (2 CH aromatic)], [128.4 (*minor*) and 128.5 (*major*) (4 CH aromatic)], [143.6 (*major*) and 144.0 (*minor*) (2 C aromatic)], [156.8 (*minor*) and 157.3 (*major*) (2 =C)], [168.1 (*minor*) and 168.3 (*major*) (2 C=O)].

IR (neat): $\tilde{\nu}$/cm^{-1} 3279, 3060, 3027, 2969, 2930, 2878, 1678, 1654, 1524, 1469, 1453, 1347, 1294, 1253, 1232, 1215, 1132, 1118, 1097, 1062, 1031, 988, 940, 824, 798, 760, 740, 696, 622, 560.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{43}N_2O_8$ 583.3014, observed 583.3026 (2.0 ppm).

3.13 Synthesis of **3l**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 144 µL (135 mg, 1.00 mmol, 4 equiv) of (*S*)-α-ethyl-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 23 mg (0.04 mmol, 610.75 g/mol, 15%) of **3l** as a white solid and as inseparable diastereoisomers (*dr* 1:1.1) (purification method B).



R_f = 0.49 and 0.46 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 123 °C - 124 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1:1.1)): δ/ppm = [0.90 (*major*) and 0.92 (*minor*) (t, 6H, *J* = 7.4 Hz, $-CH_3$)], 1.75 - 1.83 (m, 4H, $-CH_2$), 3.48 - 3.93 (m, 16H, $-CH_2$-), [4.12 (*major*) and 4.21 (*minor*) (d, 2H, 2.6 Hz, $=CH_2$)], [4.26 (*minor*) and 4.26 (*major*) (s, 2H, -CH-)], [4.29 (*major*) and 4.37 (*minor*) (d, 2H, 2.6 Hz, $=CH_2$)], 4.89 - 4.97 (m, 2H, -CH-), 7.18 - 7.37 (m, 10H, aromatics), [7.73 (*minor*) and 7.95 (*major*) (m, 2H, NH)].

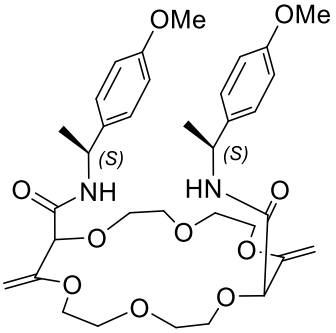
^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1:1.1)): δ/ppm = [11.1 (*minor*) and 11.2 (*major*) (2 $-CH_3$)], [29.4 (*minor*) and 29.7 (*major*) (2 $-CH_2$-)], 54.6 (2 -CH-), [66.7 (*major*) and 66.9 (*minor*) (2 CH_2-)], [68.4 (*major*) and 68.5 (*minor*) (2 CH_2-)], 69.1 (2 CH_2-), [70.5 (*major*) and 70.6 (*minor*) (2 $=CH_2$)], [82.6 (*minor*) and 83.1 (*major*) (2 -CH-)], [87.3 (*minor*) and 87.7 (*major*) (2 $=CH_2$)], 126.9 (4 CH aromatic), [127.0 (*minor*) and 127.1 (*major*) (2 CH aromatic)], [128.4 (*minor*) and 128.5 (*major*) (4 CH aromatic)], [142.8 (*minor*) and 143.1 (*major*) (2 C aromatic)], [156.9 (*major*) and 157.3 (*minor*) (2 =C)], 168.5 (2 C=O).

IR (neat): ṽ/cm^{-1}3258, 2940, 2874, 1672, 1649, 1521, 1464, 1346, 1286, 1241, 1136, 1113, 1069, 1019, 987, 939, 822, 760, 700, 635, 567.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{47}N_2O_8$ 611.3327, observed 611.3333 (0.9 ppm).

3.14 Synthesis of 3m

According to general procedure **III**, with 101 mg (0.25 mmol) of **1**, 151.21 µL (151.21 mg, 1.00 mmol, 4 equiv) of (*S*)-α-methyl-*p*-methoxy-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 56 mg (0.09 mmol, 642.75 g/mol, 35%) of **3m** as a white solid and as inseparable diastereoisomers (*dr* 1.2:1) (purification method B).



R_f = 0.42 and 0.39 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 77 °C - 78 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = 1.42 (d, 6H, *J* = 6.9 Hz, -CH_3), 3.49 - 3.82 (m, 20 H, -CH_2- and -OCH_3), 3.87-3.91 (m, 2H, -CH_2-), [4.14 (*minor*) and 4.20 (*major*) (d, 2H, *J* = 2.7 Hz, =CH_2)], [4.22 (*minor*) and 4.23 (*major*) (s, 2H, -CH-)], [4.30 (*minor*) and 4.36 (*major*) (d, 2H, *J* = 2.7 Hz, =CH_2)], 5.10 - 5.16 (m, 2H, -CH-), 6.78 - 6.82 (m, 4H, aromatics), 7.23 - 7.30 (m, 4H, aromatics), [7.74 (*major*) and 7.87 (*minor*) (d, 2H, *J* = 8.6 Hz, NH)].

^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = [22.1 (*major*) and 22.1 (*minor*) (2 -CH_3)], [47.7 (*minor*) and 47.9 (*major*) (2 -CH-)], [55.4 (*major*) and 55.4 (*minor*) (2 -OCH_3)], 67.0 (2 -CH_2-), [68.2 (*minor*) and 68.4 (*major*) (2 -CH_2-)], [69.2 (*minor*) and 69.2 (*major*) (2 -CH_2-)], [70.6 (*major*) and 70.6 (*minor*) (2 -CH_2-)], [82.5 (*major*) and 83.0 (*minor*) (2 -CH-)], [87.5 (*major*) and 87.9 (*minor*) (2 =CH_2)], [113.9 (*minor*) and 113.9 (*major*) (4 CH aromatics)], [127.6 (*minor*) and 127.7 (*major*) (4 CH aromatics)], [135.8 (*major*) and 136.3 (*minor*) (2 C aromatics)], [156.9 (*minor*) and 157.3 (*major*) (2 =C)], [158.6 (*minor*) and 158.7 (*major*) (2 C-OMe aromatics)], [168.0 (*minor*) and 168.2 (*major*) (2 C=O)].

IR (neat): ṽ/cm^{-1} 3280, 2927, 1660, 1613, 1512, 1455, 1375, 1287, 1242, 1179, 1126, 1082, 1031, 994, 935, 829.

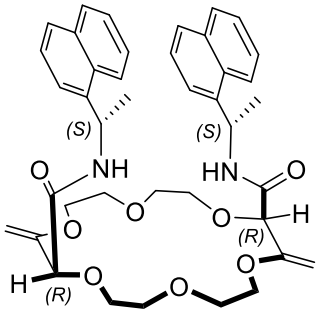
HR MS (ESI) $[M+Na]^+$ *m/z* calculated for $C_{34}H_{47}N_2O_{10}Na$ 665.3045, observed 665.3019 (-3.9 ppm).

3.15 Synthesis of 3n

According to general procedure, with 101 mg (0.25 mmol) of **1**, 160 µL (171 mg, 1.00 mmol, 4 equiv) of (*S*)-α-methyl-1-naphthylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 34 mg (0.05 mmol, 682.81 g/mol, 20%) of **3n** as a white solid and as diastereoisomers (*dr* 1.4:1) (purification method B).

Separation of the two diastereoisomers: On a 50 mg scale, the two diastereoisomers are separated by column chromatography (SiO_2, CH_2Cl_2/MeOH gradient (1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10% and 20%)) followed by a column of each fractions (neutral Al_2O_3, EtOAc then CH_2Cl_2/MeOH gradient (1%, 3%)) and by a precipitation (a minimum of EtOAc for solubility, followed by a large excess of pentane, 15 hours).

1st eluted diastereoisomer (minor diastereoisomer) (*S*,*R*,*R*,*S*)-**3n**



R_f (first eluted) = 0.49 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 117 °C - 118 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.62 (d, 6H, *J* = 6.9 Hz, -CH_3), 2.76 - 2.81 (m, 2H, -CH_2-), 3.18 -3.22 (m, 2H, -CH_2-), 3.26 - 3.30 (m, 2H, -CH_2-), 3.32 - 3.39 (m, 6H, -CH_2-), 3.54 - -3.63 (m, 4H, -CH_2-), 4.05 (d, 2H, *J* = 2.7 Hz, =CH_2), 4.17 (s, 2H, -CH-), 4.25 (d, 2H, *J* = 2.7 Hz, =CH_2), 5.96 - 6.02 (m, 2H, -CH-), 7.34 - 7.37 (m, 2H, aromatics), 7.43 - 7.49 (m, 4H, aromatics), 7.55 - -5.57 (m, 2H, aromatics), 7.71 - 7.73 (m, 2H, aromatics), 7.81 - -7.83 (m, 2H, aromatics), 7.90 (d, 2H, *J* = 8.9 Hz, NH), 8.13 - 8.15 (m, 2H, aromatics).

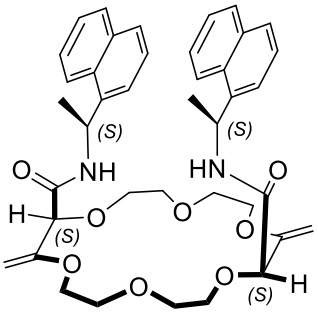
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 21.2 (2 -CH_3), 44.0 (2 -CH-), 66.9 (2 -CH_2-), 68.0 (2 -CH_2-), 68.6 (2 -CH_2-), 70.2 (2 -CH_2-), 82.9 (2 -CH-), 87.6 (2 =CH_2), 122.8 (2 CH aromatics), 124.1 (2 CH aromatics), 125.4 (2 CH aromatics), 125.7 (2 CH aromatics), 126.3 (2 CH aromatics), 128.0 (2 CH aromatics), 128.7 (2 CH aromatics), 131.4 (2 C aromatics), 134.0 (2 C aromatics), 139.1 (2 C aromatics), 156.6 (2 =C), 167.8 (2 C=O).

IR (neat): ṽ/cm^{-1} 3267, 2908, 1665, 1522, 1455, 1289, 1244, 1126, 1093, 1077, 994, 800, 779

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{40}H_{47}N_2O_8$ 683.3327, observed 683.3314 (-1.9 ppm);

$[\alpha]^{20}_D$ = -0.07 (*c* 0.07, CH_2Cl_2).

2nd eluted diastereoisomer (major diastereoisomer) (*S*,*S*,*S*,*S*)-**3n**



R_f (second eluted) = 0.43 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 154 °C - 155 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.57 (d, 6H, *J* = 6.8 Hz, $-CH_3$), 3.10 - 3.14 (m, 2H, $-CH_2-$), 3.20 - 3.24 (m, 2H, $-CH_2-$), 3.29 - 3.41 (m, 6H, $-CH_2-$), 3.45 - 3.52 (m, 4H, $-CH_2-$), 3.63 - 3.67 (m, 2H, $-CH_2-$), 4.16 (d, 2H *J* = 2.6 Hz, $=CH_2$), 4.26 (s, 2H, -CH-), 4.42 (d, 2H, *J* = 2.6 Hz, $=CH_2$), 5.95 - 6.01 (m, 2H, -CH-), 7.25 -7.28 (m, 2H, aromatics), 7.41 - 7.48 (m, 8H, aromatics, NH), 7.68 - 7.69 (m, 2H, aromatics), 7.78 - 7.80 (m, 2H, aromatics), 8.07 - 8.09 (m, 2H, aromatics).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 20.9 (2 $-CH_3$), 44.1 (2 -CH-), 66.9 (2 $-CH_2-$), 68.1 (2 $-CH_2-$), 68.3 (2 $-CH_2-$), 70.2 (2 $-CH_2-$), 81.7 (2 -CH-), 86.49 (2 $=CH_2$), 123.1 (2 CH aromatics), 124.0 (2 CH aromatics), 125.3 (2 CH aromatics), 125.8 (2 CH aromatics), 126.4 (2 CH aromatics), 128.1 (2 CH aromatics), 128.7 (2 CH aromatics), 131.5 (2 C aromatics), 133.9 (2 C aromatics), 138.6 (2 C aromatics), 158.0 (2 =C), 168.2 (2 C=O).

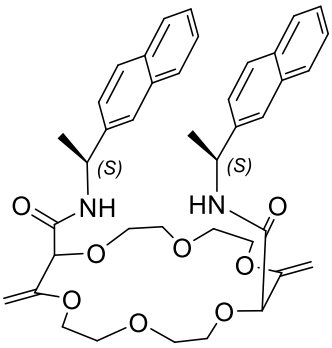
IR (neat): $\tilde{\nu}$/cm^{-1} 3328, 3039, 2936, 2883, 2845, 1665, 1645, 1537, 1522, 1455, 1288, 1250, 1209, 1150, 1124, 1082, 1000, 795, 773, 674, 662, 606.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{40}H_{47}N_2O_8$ 683.3327, observed 683.3312 (-2.2 ppm);

$[\alpha]^{20}_D$ = -0.19 (*c* 0.07, CH_2Cl_2).

3.16 Synthesis of 3o

According to general procedure, with 101 mg (0.25 mmol) of **1**, 171 mg (1.00 mmol, 4 equiv) of (*S*)-α-methyl-2-naphthylamine and 138 mg (1.00 mmol, 4 equiv) of TBD to yield 25 mg (0.04 mmol, 682.81 g/mol, 15%) of **3o** as a white solid and as inseparable diastereoisomers (*dr* 1.4:1) (purification method B).



R_f = 0.48 and 0.38 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 60 °C - 63 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.4:1)): δ/ppm = 1.47 - 1.50 (m, 6H, -CH_3), 3.36 - 3.45 (m, 1H, -CH_2-), 3.50 - 3.80 (m, 14H, -CH_2-), 3.87 - 3.91 (m, 1H, -CH_2-), [4.11 (*minor*) and 4.20 (*major*) (d, 2H, *J* = 2.7 Hz, =CH_2)], [4.25 (*minor*) and 4.28 (*major*) (s, 2H, -CH-)], [4.30 (*minor*) and 4.38 (*major*) (d, 2H, *J* = 2.7 Hz, =CH_2)], 5.30 - 5.36 (m, 2H, -CH-), 7.40 - 7.47 (m, 6H, aromatics), 4.68 - 7.81 (m, 8H, aromatics), [7.92 - 7.94 (*major*) and 8.17 - 8.19 (*minor*) (m, 2H, NH)].

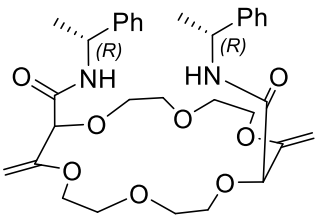
^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.4:1)): δ/ppm = [21.7 (*major*) and 22.1 (*minor*) (2 -CH_3)], [48.2 (*major*) and 48.5 (*minor*) (2 -CH-)], [66.8 (*minor*) and 66.8 (*major*) (2 -CH_2-)], [68.2 (*minor*) and 68.4 (*major*) (2 -CH_2-)], [69.1 (*minor*) and 69.2 (*major*) (2 -CH_2-)], 70.5 (2 -CH_2-), [82.5 (*major*) and 83.1 (*minor*) (2 -CH-)], [87.4 (*major*) and 87.8 (*minor*) (2 =CH_2)], 124.8 (2 CH aromatics), [125.3 (*major*) and 125.4 (*minor*) (2 CH aromatics)], [125.7 (*minor*) and 125.8 (*major*) (2 CH aromatics)], [126.1 (*minor*) and 126.1 (*major*) (2 CH aromatics)], [127.6 (*minor*) and 127.7 (*major*) (2 CH aromatics)], [128.0 (*major*) and 128.1 (*minor*) (2 CH aromatics)], [128.1 (*minor*) and 128.2 (*major*) (2 CH aromatics)], 132.7 (2 C aromatics), [133.4 (*major*) and 133.5 (*minor*) (2 C aromatics)], [141.0 (*major*) and 141.5 (*minor*) (2 C aromatics)], [156.8 (*minor*) and 157.4 (*major*) (2 =C)], [168.2 (*minor*) and 168.4 (*major*) (2 C=O)].

IR (neat): ṽ/cm^{-1} 3503, 3276, 3056, 2973, 2925, 2878, 1664, 1529, 1453, 1378, 1289, 1244, 1181, 1130, 1096, 1077, 993, 949, 895, 858, 821, 750.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{40}H_{47}N_2O_8$ 683.3327, observed 683.3327 (0.1 ppm).

3.17 Synthesis of 3p

According to general procedure, with 101 mg (0.25 mmol) of **1**, 129 µL (121 mg, 1.00 mmol, 4 equiv) of (*R*)-α-methyl-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 36 mg (0.06 mmol, 582.69 g/mol, 25%) of **3p** as a white solid and as inseparable diastereoisomers (*dr* 1.3:1) (purification method B).



R_f = 0.46 and 0.43 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 118 °C - 119 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = [1.41 (*minor*) and 1.43 (*major*) (d, 6H, *J* = 7.1 Hz, $-CH_3$)], 3.50 - 3.91 (m, 16H, $-CH_2-$), [4.15 (*minor*) and 4.20 (*major*) (d, 2H, 2.7 Hz, $=CH_2$)], [4.24 (*minor*) and 4.26 (*major*) (s, 2H, -CH-)], [4.31 (*minor*) and 4.37 (*major*) (d, 2H, 2.7 Hz, $=CH_2$)], 5.18 (p, 2H, *J* = 7.1 Hz, -CH-), 7.18 - 7.37 (m, 10H, aromatics), [7.71 (*major*) and 7.84 (*minor*) (d, 2H, *J* = 8.5 Hz, NH)].

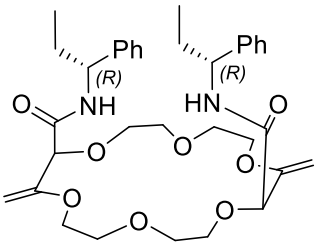
^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)): δ/ppm = [22.0 (*major*) and 22.1 (*minor*) (2 $-CH_3$)], [48.2 (*minor*) and 48.4 (*major*) (2 -CH-)], [67.0 (*major*) and 67.0 (*minor*) (2 CH_2-)], [68.2 (*minor*) and 68.4 (*major*) (2 CH_2-)], [69.1 (*major*) and 70.6 (*minor*) (2 $=CH_2$-)], [82.3 (*major*) and 82.9 (*minor*) (2 -CH-)], [87.4 (*major*) and 87.9 (*minor*) (2 $=CH_2$)], [126.4 (*minor*) and 126.6 (*major*) (4 CH aromatic)], [127.0 (*minor*) and 127.2 (*major*) (2 CH aromatic)], [128.5 (*minor*) and 128.6 (*major*) (4 CH aromatic)], [143.5 (*major*) and 144.0 (*minor*) (2 C aromatic)], [156.9 (*minor*) and 157.4 (*major*) (2 =C)], [168.1 (*minor*) and 168.3 (*major*) (2 C=O)].

IR (neat): ṽ/cm^{-1} 3277, 3060, 3031, 2965, 2929, 2874, 1676, 1653, 1523, 1496, 1451, 1350, 1294, 1254, 1232, 1214, 1132, 1118, 1099, 1062, 1031, 987, 942, 827, 798, 760, 742, 696, 624, 561.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{43}N_2O_8$ 583.3014, observed 583.3026 (1.6 ppm).

3.18 Synthesis of **3q**

According to general procedure, with 101 mg (0.25 mmol) of **1**, 144 µL (135 mg, 1.00 mmol, 4 equiv) of (*R*)-α-ethyl-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 23 mg (0.04 mmol, 610.75 g/mol, 15%) of **3q** as a white solid and as inseparable diastereoisomers (*dr* 1:1.1) (purification method B).



R_f = 0.49 and 0.46 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 124 °C - 125 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1:1.1)): δ/ppm = [0.91 (*major*) and 0.93 (*minor*) (t, 6H, *J* = 7.4 Hz, -CH_3)], 1.75 - 1.86 (m, 4H, -CH_2), 3.45 - 3.96 (m, 16H, -CH_2-), [4.12 (*major*) and 4.21 (*minor*) (d, 2H, 2.6 Hz, =CH_2)], 4.23 (s, 2H, -CH-), [4.29 (*major*) and 4.37 (*minor*) (d, 2H, 2.6 Hz, =CH_2)], 4.89 - 4.97 (m, 2H, -CH-), 7.17 - 7.40 (m, 10H, aromatics), [7.98 (*minor*) and 8.22 (*major*) (m, 2H, NH)].

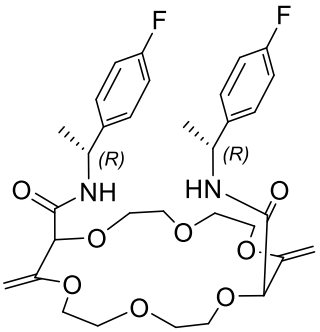
^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1:1.1)): δ/ppm = [11.2 (*minor*) and 11.2 (*major*) (2 -CH_3)], [29.5 (*minor*) and 29.8 (*major*) (2 -CH_2-)], [54.7 (*major*) and 54.7 (*minor*) (2 -CH-)], [66.4 (*major*) and 66.7 (*minor*) (2 -CH_2-)], [68.3 (*major*) and 68.4 (*minor*) (2 -CH_2-)], [69.2 (*major*) and 69.3 (*minor*) (2 -CH_2-)], [70.5 (*major*) and 70.5 (*minor*) (2 -CH_2-)], [83.0 (*minor*) and 83.5 (*major*) (2 -CH-)], [87.6 (*minor*) and 87.8 (*major*) (2 =CH_2)], 126.9 (1 CH aromatic), [126.9 (*minor*) and 127.1 (*major*) (5 CH aromatic)], [128.3 (*major*) and 128.5 (*minor*) (4 CH aromatic)], [142.9 (*minor*) and 143.3 (*major*) (2 C aromatic)], [156.7 (*major*), and 157.1 (*minor*) (2 =C)], [168.5 (*major*) and 168.5 (*minor*) (2 C=O)].

IR (neat): ṽ/cm^{-1} 3553, 3285, 2965, 2924, 2878, 1668, 1639, 1535, 1496, 1457, 1376, 1294, 1244, 1207, 1095, 1079, 1054, 989, 928, 899, 834, 766, 705.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{47}N_2O_8$ 611.3327, observed 611.3307 (-3.2 ppm).

3.19 Synthesis of 3r

According to general procedure, with 101 mg (0.25 mmol) of **1**, 133 µL (139 mg, 1.00 mmol, 4 equiv) of (*R*)-α-methyl-*p*-fluoro-benzylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 40 mg (0.07 mmol, 618.67 g/mol, 26%) of **3r** as a white solid and as inseparable diastereoisomers (*dr* 1.2:1). (purification method B).



R_f = 0.49 and 0.46 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 128 °C - 129 °C

^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.2:1)): δ/ppm = 1.40 (d, 6H, *J* = 7.0 Hz, -CH_3), 3.51 - 3.92 (m, 16H, -CH_2-), [4.16 (*minor*) and 4.21 (*major*) (d, 2H, 2.7 Hz, =CH_2)], [4.23 (*minor*) and 4.25 (*major*) (s, 2H, -CH-)], [4.32 (*minor*) and 4.37 (*major*) (d, 2H, 2.7 Hz, =CH_2)], 5.15 (h, 2H, *J* = 7.0 Hz, -CH-), 6.90 - 6.97 (m, 4H, aromatics), 7.27 - 7.28 (m, 2H, aromatics), 7.33 - 7.35 (m, 2H, aromatics), [7.92 (*major*) and 8.01 (minor) (d, 2H, *J* = 8.5 Hz, NH)].

^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.2:1)): δ/ppm = [22.1 (*major*) and 22.2 (*minor*) (2 -CH_3)], [47.7 (*minor*) and 47.7 (*major*) (2 -CH-)], [66.7 (minor) and 66.7 (*major*) (2 -CH_2-)], [68.1 (*minor*) and 68.3 (*major*) (2 -CH_2-)], [69.2 (*minor*) and 69.2 (*major*) (2 -CH_2-)], [70.6 (*major*) and 70.6 (*minor*) (2 -CH_2-)], [82.6 (*major*) and 83.0 (*minor*) (2 -CH-)], [87.6 (*major*) and 88.1 (*minor*) (2 =CH_2)], [115.1 (*minor*) and 115.2 (*major*) (d, *J* = 21.2 Hz, 4 CH aromatic)], 128.1 (d, *J* = 8.0 Hz, 4 CH aromatic), [139.5 (*major*) and 139.9 (*minor*) (d, *J* = 3.2 Hz, 2 C aromatic)], [156.7 (2 =C, *minor*), 157.1 (2 =C, *major*)], [161.9 (*minor*) and 161.9 (*major*) (d, *J* = 244.0 Hz, 2 C-F aromatic)], [168.1 (*minor*) and 168.3 (*major*) (2 C=O)].

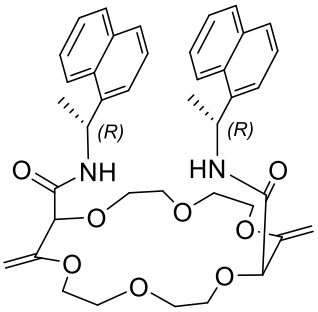
^{19}F-NMR (282 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.3:1)) δ/ppm = [-115.6 (minor) and -115.3 (*major*)].

IR (neat): ṽ/cm^{-1} 3279, 2973, 2933, 2878, 1678, 1653, 1608, 1510, 1457, 1349, 1294, 1256, 1224, 1155, 1132, 1118, 1097, 1062, 1033, 1017, 987, 941, 856, 828, 794, 748, 721, 674, 623, 578.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{41}F_2N_2O_8$ 619.2826, observed 619.2805 (-3.3 ppm).

3.20 Synthesis of 3s

According to general procedure, with 101 mg (0.25 mmol) of **1**, 160 µL (171 mg, 1.00 mmol, 4 equiv) of (*R*)-α-methyl-1-naphthylamine and 138 mg (1.00 mmol, 4 equiv) of TBD for 10 days to yield 34 mg (0.05 mmol, 682.81 g/mol, 20%) of **3s** as a white solid and as inseparable diastereoisomers (*dr* 1.4:1) (purification method B).



R_f = 0.49 and 0.43 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 84 °C - 89 °C

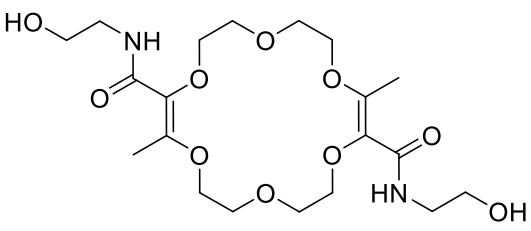
^{1}H-NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.4:1)): δ/ppm = 1.57 - 1.60 (t, 6H, -CH_3), [2.86 - 2.93 (minor) and 3.11 - 3.16 (*major*) (m, 2H, -CH_2-)], 3.22 -3.69 (m, 15H, -CH_2-), [4.04 (*major*) and 4.17 (minor) (d, 2H, *J* = 2.7 Hz, =CH_2)], [4.18 (*major*) and 4.26 (minor) (s, 2H, -CH-)], [4.25 (*major*) and 4.42 (minor) (d, 2H, *J* = 2.7 Hz, =CH_2)], 5.95 - 6.01 (m, 2H, -CH-), [7.22 - 7.27 (*major*) and 7.30 - 7.34 (minor) (m, 2H, aromatics)], 7.41 - 7.49 (m, 8H, aromatics, NH), 7.67 - 7.71 (m, 2H, aromatics), 7.78 - 7.82 (m, 2H, aromatics), [8.08 (*major*) and 8.13 (minor) (d, 2H, *J* = 8.3 Hz, aromatics)].

^{13}C-NMR (126 MHz, $CDCl_3$, inseparable mixture of diastereoisomers (*dr* 1.4:1)): δ/ppm = [20.9 (*major*) and 21.1 (minor) (2 -CH_3)], [44.0 (minor) and 44.1 (*major*) (2 -CH-)], [66.8 (*major*) and 67.1 (minor) (2 -CH_2-)], [68.1 (minor) and 68.2 (*major*) (2 -CH_2-)], [68.3 (*major*) and 68.6 (minor) (2 -CH_2-)], 70.2 (2 -CH_2-), [81.8 (*major*) and 82.6 (minor) (2 -CH-)], [86.6 (*major*) and 87.5 (minor) (2 -CH-)], [122.7 (minor) and 123.1 (*major*) (2 CH aromatics)], [123.9 (*major*) and 124.1 (minor) (2 CH aromatics)], [125.3 (*major*) and 125.4 (minor) (2 CH aromatics)], 125.7 (2 CH aromatics), [126.3 (minor) and 126.4 (*major*) (2 CH aromatics)], 128.1 (2 CH aromatics), [128.7 (*major*) and 128.7 (minor) (2 CH aromatics)], [131.4 (minor) and 131.5 (*major*) (2 C aromatics)], [133.9 (*major*) and 140.0 (minor) (2 C aromatics)], [138.6 (*major*) and 139.0 (minor) (2 C aromatics)], [156.8 (minor) and 157.9 (*major*) (2 =C)], [167.8 (minor) and 168.1 (*major*) (2 C=O)].

IR (neat): ṽ/cm^{-1} 3288, 2907, 1665, 1521, 1452, 1289, 1124, 1093, 1081, 994, 800, 779.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{40}H_{47}N_2O_8$ 683.3327, observed 683.3320 (-1.0 ppm).

3.21 Synthesis of macrocycles with unprotected alcohol functional groups (no isomerization)



According to general procedure, with 101 mg (0.25 mmol) of **1**, 60 µL (60 mg, 1.00 mmol, 4 equiv) of ethanolamine and 69 mg (0.50 mmol, 2 equiv) of TBD to yield 88 mg (0.20 mmol, 452.50 g/mol, 78%) of ethyl alcohol macrocycle as a white solid (purification method A).

Second step: no isomerization (with 2.2 or 4.4 equiv of *t*-BuOK)

R_f = 0.0 (SiO_2, CH_2Cl_2/MeOH (10%))

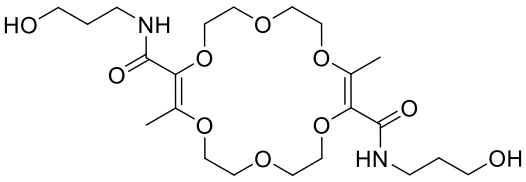
m.p.: 137 °C – 139 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 2.44 (s, 6H, -CH_3), 3.43 - 3.45 (m, 4H, -CH_2-), 3.70 - 3.72 (m, 4H, -CH_2-), 3.79 - 3.83 (m, 8H, -CH_2-), 3.96 - 3.98 (m, 4H, -CH_2-), 4.10 – 4.11 (m, 4H, -CH_2-) (N-H not seen).

^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 13.9 (2 -CH_3), 42.3 (2 -CH_2-), 63.0 (2 -CH_2-), 67.4 (2 -CH_2-), 70.1 (2 -CH_2-), 70.6 (2 -CH_2-), 71.6 (2 -CH_2-), 131.9 (2 =C), 153.9 (2 =C), 166.8 (2 C=O).

IR (neat): ṽ/cm^{-1} 3349, 2950, 2881, 1662, 1605, 1506, 1456, 1431, 1378, 1361, 1306, 1264, 1234, 1165, 1128, 1057, 1030, 980, 934, 891, 810, 769, 689, 628, 558.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{20}H_{35}N_2O_{10}$ 463.2286, observed 463.2295 (1.8 ppm).



According to general procedure **III** (first step only), with 101 mg (0.25 mmol) of **1**, 76 µL (74 mg, 1.00 mmol, 4 equiv) of propanolamine and 69 mg (0.50 mmol, 2 equiv) of TBD to yield 80 mg (0.16 mmol, 490.55 g/mol, 65%) of propyl alcohol macrocycle as a white solid (purification method A).

Second step: no isomerization (with 2.2 or 4.4 equiv of *t*-BuOK)

R_f = 0.0 (SiO_2, CH_2Cl_2/MeOH (10%))

m.p.: 123 °C – 124 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ/ppm = 1.67 (p, 4H, J = 5.8 Hz, -CH_2-), 2.45 (s, 6H, -CH_3), 3.43 - 3.46 (m, 4H, -CH_2-), 3.57 - 3.60 (m, 4H, -CH_2-), 3.79 - 3.82 (m, 8H, -CH_2-), 3.95 (t, 4H, *J* = 5.3 Hz, -CH_2-), 4.09 - 4.11 (m, 4H, -CH_2-) (N-H not seen).

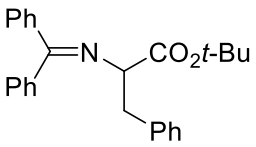
^{13}C-NMR (126 MHz, $CDCl_3$): δ/ppm = 13.9 (2 -CH_3), 32.8 (2 -CH_2-), 35.3 (2 -CH_2-), 58.9 (2 -CH_2-), 67.3 (2 -CH_2-), 70.1 (2 -CH_2-), 70.6 (2 -CH_2-), 71.6 (2 -CH_2-), 131.6 (2 =C), 154.0 (2 =C), 166.6 (2 C=O).

IR (neat): ṽ/cm^{-1} 3481, 3427, 2948, 2882, 1656, 1611, 1509, 1457, 1376, 1305, 1265, 1234, 1163, 1129, 1069, 1049, 1029, 978, 938, 906, 810, 790, 685, 623.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{39}N_2O_8$ 491.2599, observed 491.2603 (0.8 ppm).

4 Phase-transfer catalysis

4.1 Synthesis of 6



Representative procedure: In a 1 mL vial, 3.4 mg (0.005 mmol, 10 mol%) of (*S*,*S*,*S*,*S*)-**3n** and 14.8 mg (0.05 mmol, 1 equiv.) of N-(diphenylmethylene)glycine *t*-butylester **5** are dissolved in 0.25 mL of CH_2Cl_2. 7.2 µL (10.3 mg, 0.06 mmol, 1.2 equiv.) of benzylbromide and 75 µL of a freshly prepared solution of NaOH (aq. 50% w/v) are added consecutively. The solution is stirred for 15 hours at 10 °C at 1500 rpm. The consumption of **5** is monitored by TLC analysis. After completion of the reaction, the crude mixture is directly purified by column chromatography (SiO_2, pentane/Et_2O 9 :1) to yield 17 mg (0.043 mmol, 385.51 g/mol, 86%) of N-(diphenylmethylene)phenylalanine *t*-butylester (+)-**6** (enriched in **(*R*)-6**) as a colorless oil.

Spectral and physical data are in agreement with previously reported literature.[3]

^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 1.44 (s, 9H, CH_3-), 3.14 - 3.25 (m, 2H, -CH_2-), 4.10 (dd, *J* = 9.3, 4.2 Hz, 1H, -CH_2-), 6.59 - 6.61 (m, 2H, aromatics), 7.04 - 7.06 (m, 2H, aromatics), 7.15 - 7.20 (m, 3H, aromatics), 7.26 - 7.38 (m, 6H, aromatics), 7.26 - 7.58 (m, 2H, aromatic).

^{13}C NMR (126 MHz, $CDCl_3$): δ/ppm = 28.2 (3 -CH_3), 39.7 (1 -CH_2-), 68.1 (1 -CH-), 81.3 (1 -CH-), 126.3 (1 CH aromatic), 127.8 (2 CH aromatic), 128.1 (2 CH aromatic), 128.19 (2 CH aromatic), 128.22 (2 CH aromatic), 128.3 (1 CH aromatic), 128.9 (2 CH aromatic), 130.0 (2 CH aromatic), 130.2 (1 CH aromatic), 136.5 (1 C aromatic), 138.5 (1 C aromatic), 139.7 (1 C aromatic), 170.5 (1 C=O), 171.0 (1 C=N).

CSP HPLC (Chiralcel® OD-H column, hexanes/*i*-PrOH (99:1), 0.5 mL/min, 23 °C, 2 µL/inj., λ = 254 nm): retention time, t_{R1} =(+/*R*) 12.2 min and t_{R2} = (–/*S*) 16.9 min.

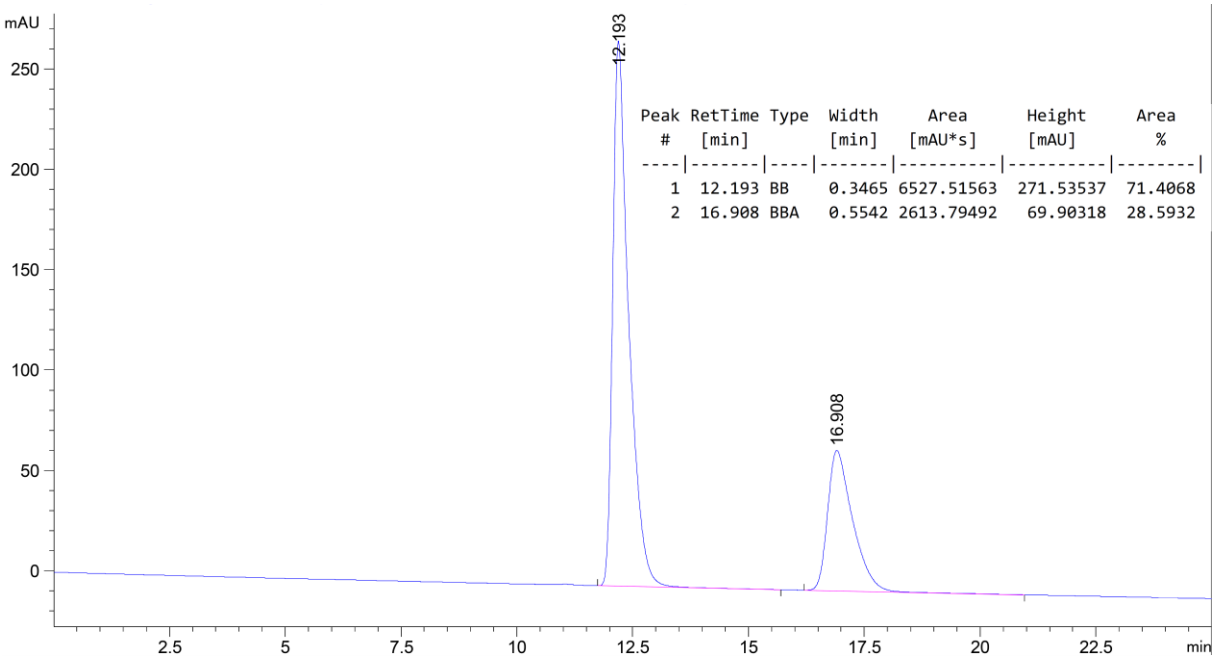
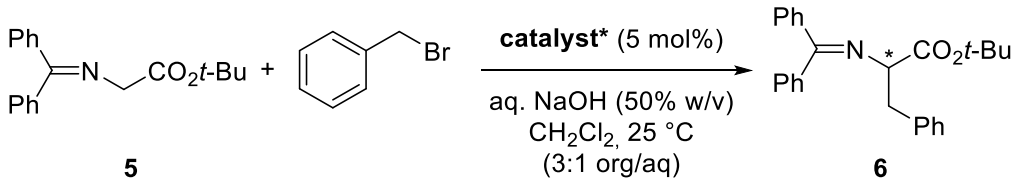


Figure S1 CSP HPLC of **6**: Chiralcel® OD-H column, hexanes/*i*-PrOH (99:1), 0.5 mL/min, 23 °C, 2 µL/inj., λ = 254 nm.

4.2 Screening PTC

First the influence of the configuration of the catalysts, the substrate concentration and solvent were tested.

Table S2. Alkylation of protected glycine using asymmetric PTC and chiral crown ethers.



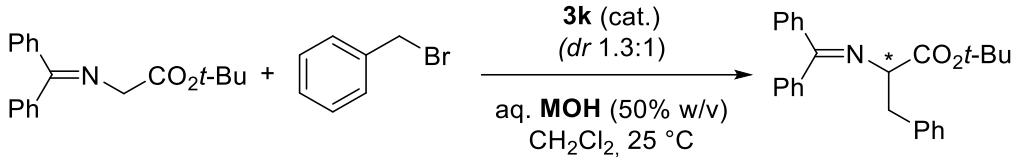
5 **6**

Entry	Catalyst*[a]	Time	Yield (%)	*ee* (%)	Preferred configuration
1	**3k**	15 hours	86	17	*R*
2	**3p**	15 hours	86	-17	*S*
3[b]	**3k**	15 hours	86	11	*R*
4[b]	**3p**	15 hours	86	-11	*S*
5[c]	**3k**	4 days	86	-12	*S*

[a] *dr* 1.3:1; [b] ratio 5:1 (instead of 3:1) between organic and aqueous phases; [c] toluene instead of CH_2Cl_2.

Then the effect of the base counterion and the catalyst amount was tested.

Table S3. Screening of the conditions for asymmetric PTC.



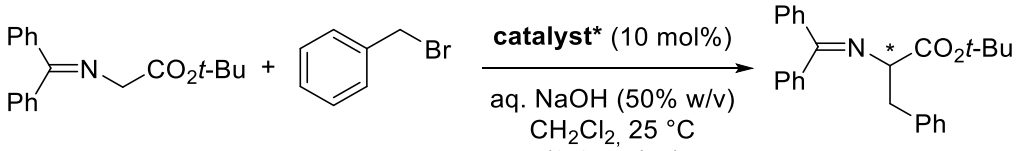
5 **6**

Entry	Cat. loading	MOH	Time	Conversion (%)	*ee* (%)
1	5 mol%	NaOH	15 hours	>99	17
2	5 mol%	KOH	4 days	75%	4
3	10 mol%	KOH	4 days	>99%	5
4	5 mol%	CsOH	4 days	10%	3
5[a]	5 mol%	NaOH	4 days	<1	n.d.[b]
6	**10 mol%**	**NaOH**	**15 hours**	**>99**	**21**

[a] 1 M NaOH instead of 50% (w/v); [b] n.d. = not determined.

The different macrocycles were tested as catalyst.

Table S4. Screening of the catalysts for asymmetric PTC.

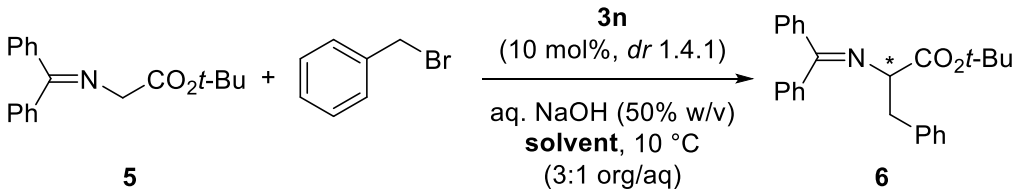


5 **6**

Entry	Catalyst*	*dr* (cat.)	*ee* (%)
1	**3k**	1.3:1	21
2	**3l**	1.1:1	27
3	**3m**	1.2:1	26
4	**3n**	1.4:1	32
5	**3o**	1.4:1	22
6	**3r**	1.2:1	-18

Finally, different solvents were also tested.

Table S5. Screening of the solvent for asymmetric PTC.



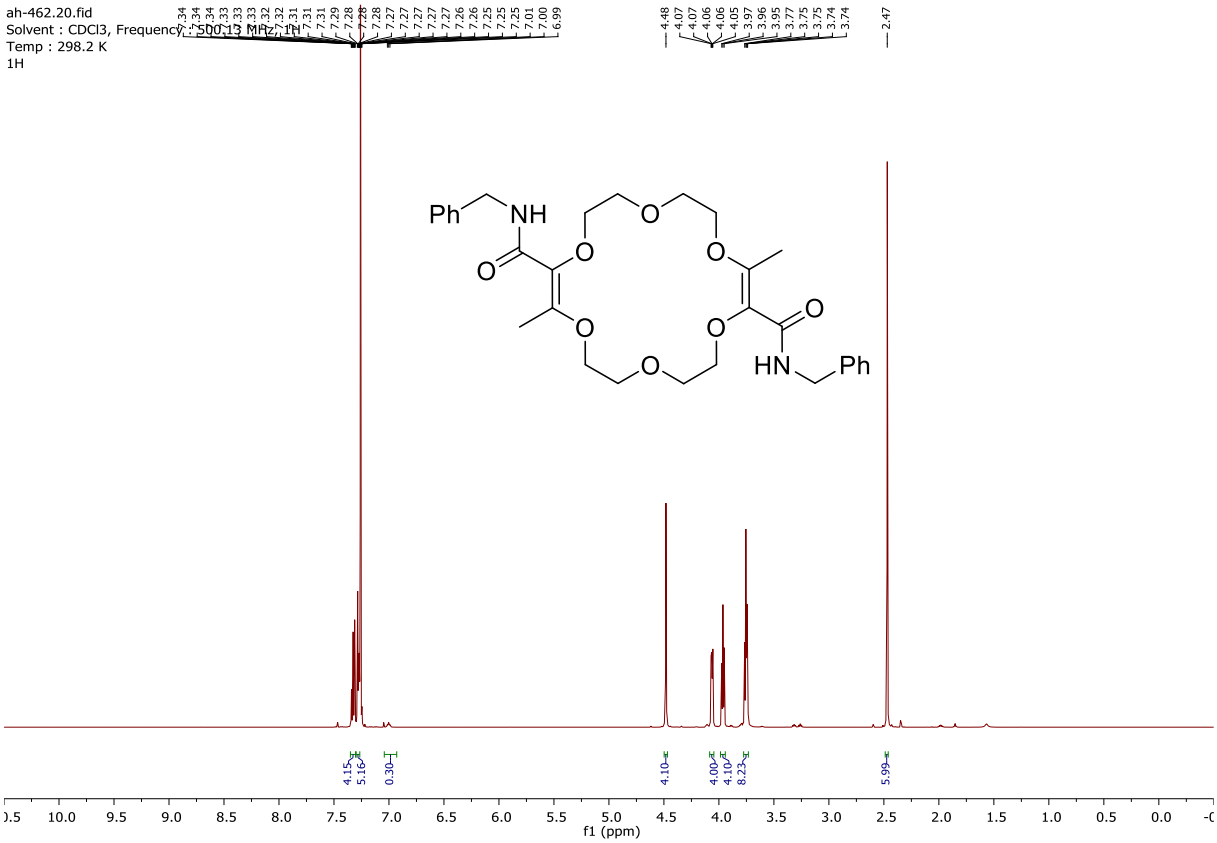
5 **6**

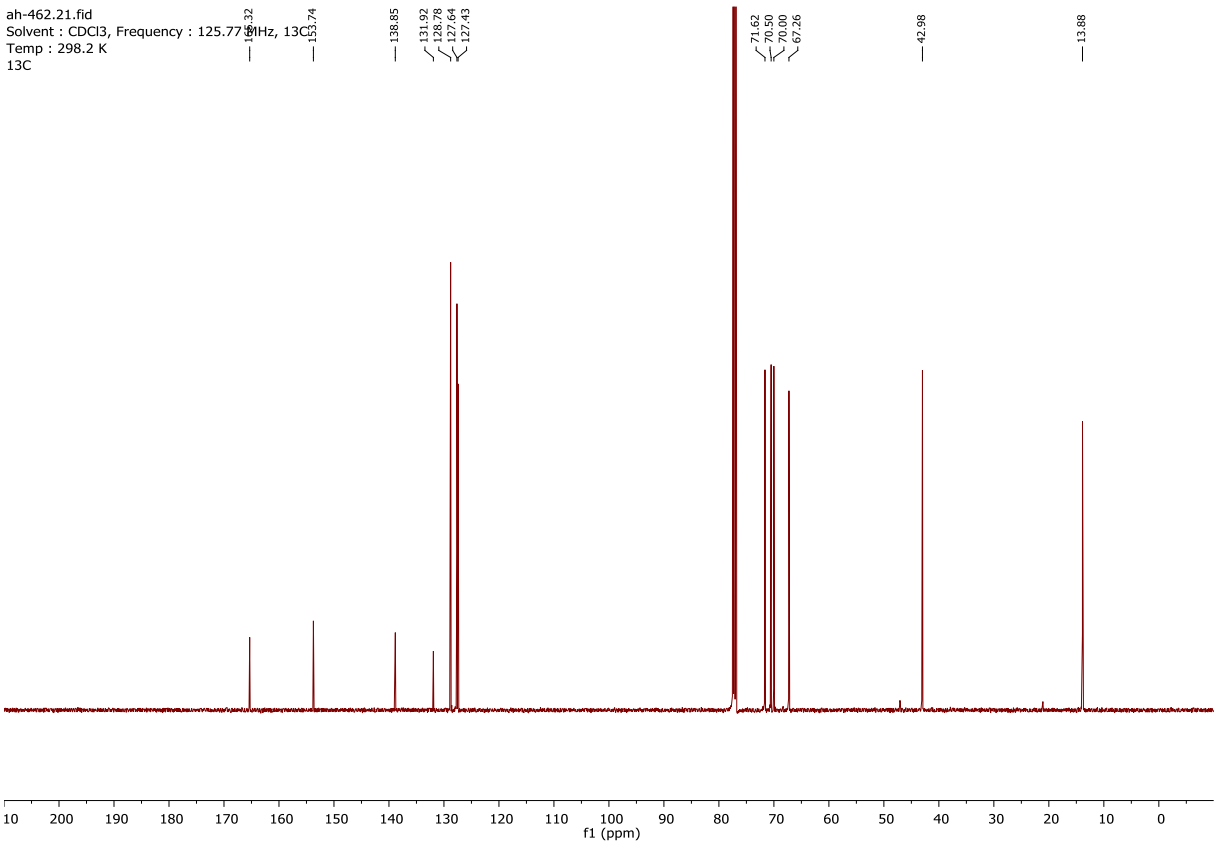
Entry	Solvent	Time	Conversion (%)	*ee* (%)
1	Chlorobenzene	36 hours	>99	31
2	Ethylacetate	1 month	86	n.d.[a]
3	CH_3CN	36 hours	>99	racemic
4	Hexanes	1 month	80	n.d.
5	1,1-Dichloroethane	2 days	>99	40
6	1.2-Dichloroethane	2 days	>99	33
7	Perchlorobuta-1,3-diene	15 hours	degradation	n.d.
8	1,1,2,2-Tetrachloroethane	15 hours	<1	n.d.
9	1,1,2,2-Tetrachloroethene	7 days	80	n.d.
10	1,1,1-Trichloroethane	2 days	>99	40
11	1,1,1-Trichlorotoluene	2 days	>99	31
12	Diiodomethane	7 days	>99	31
13	Perfluorohexane	7 days	<1	n.d.

[a] n.d. = not determined.

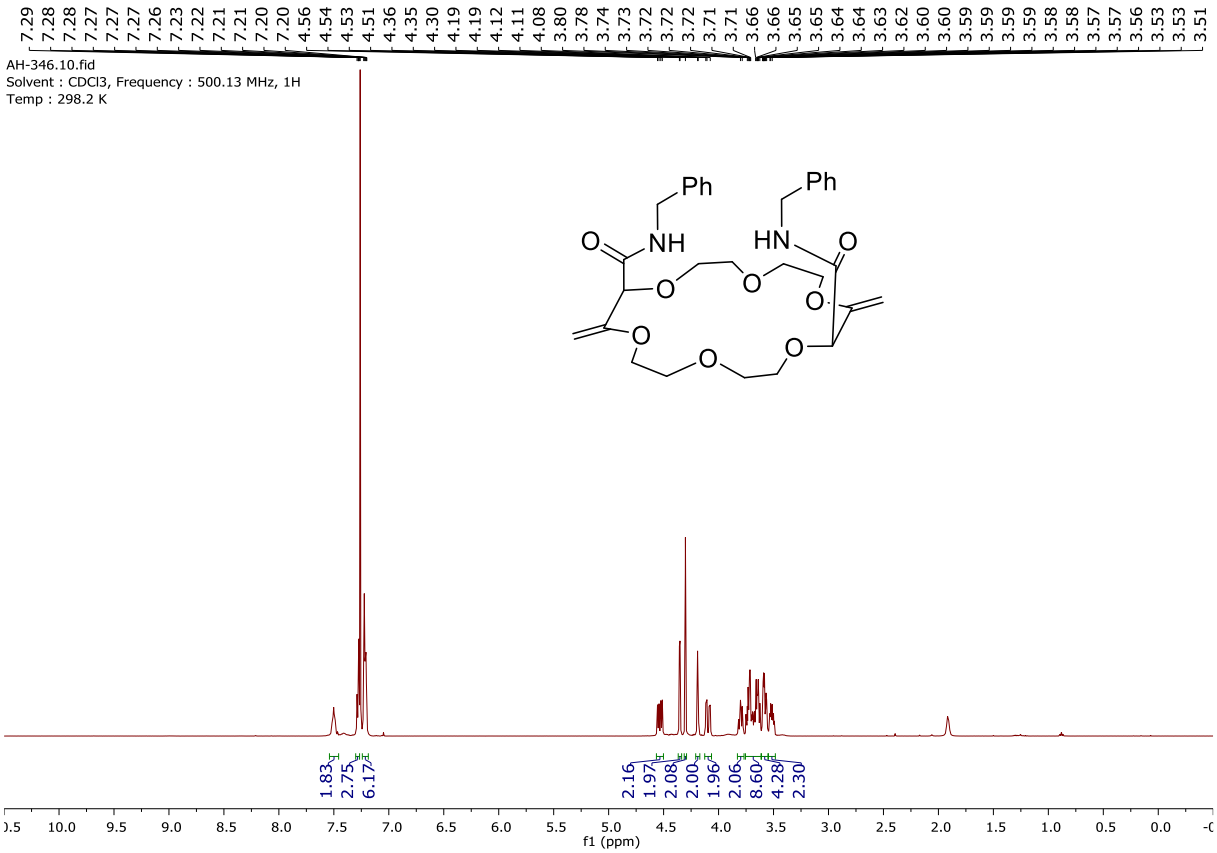
5 ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

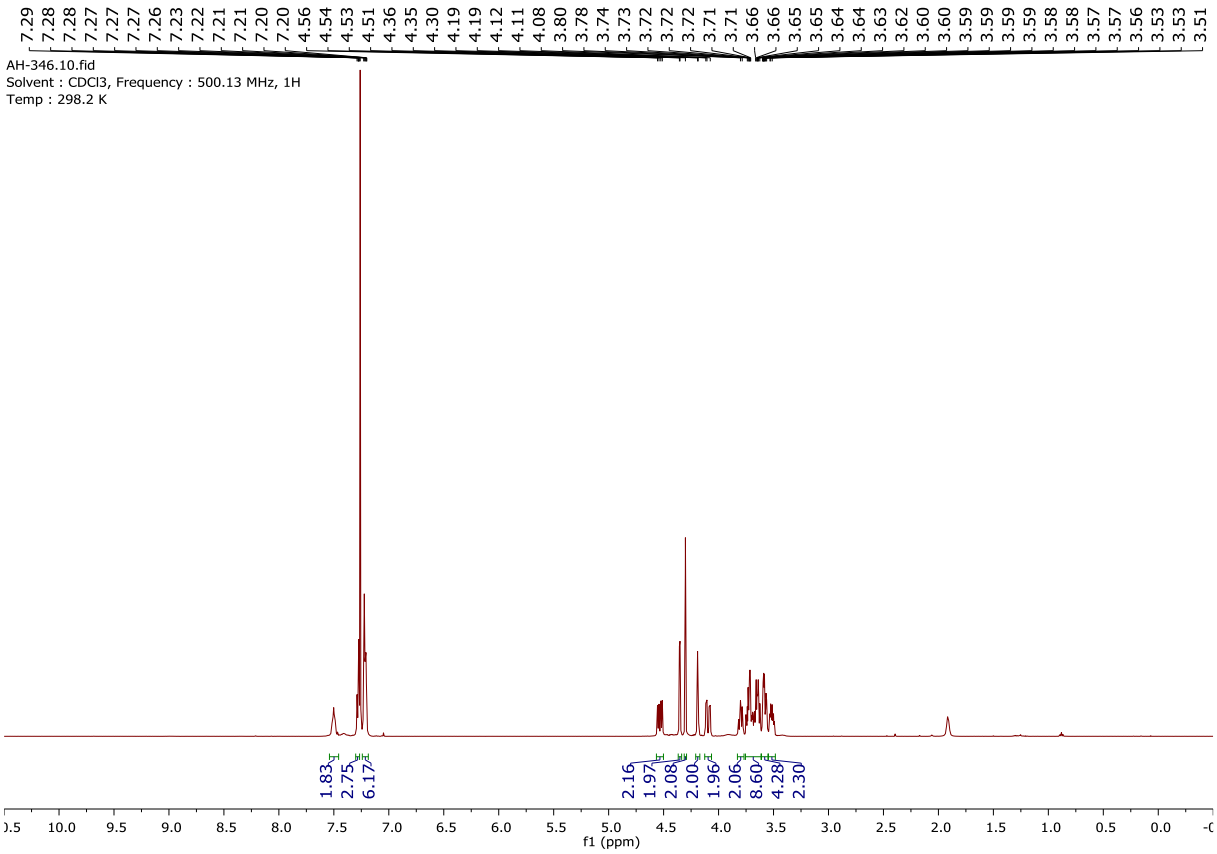
5.1 Compounds of **4a**



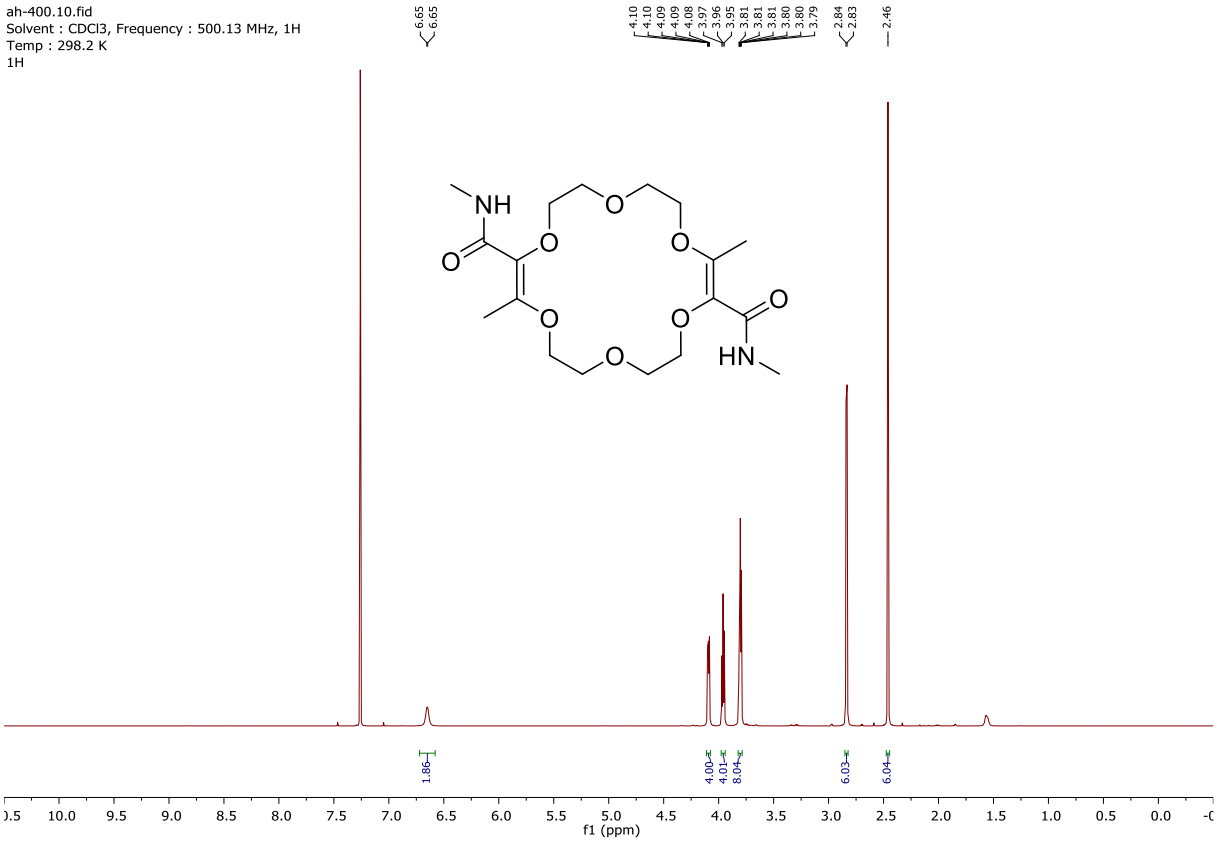


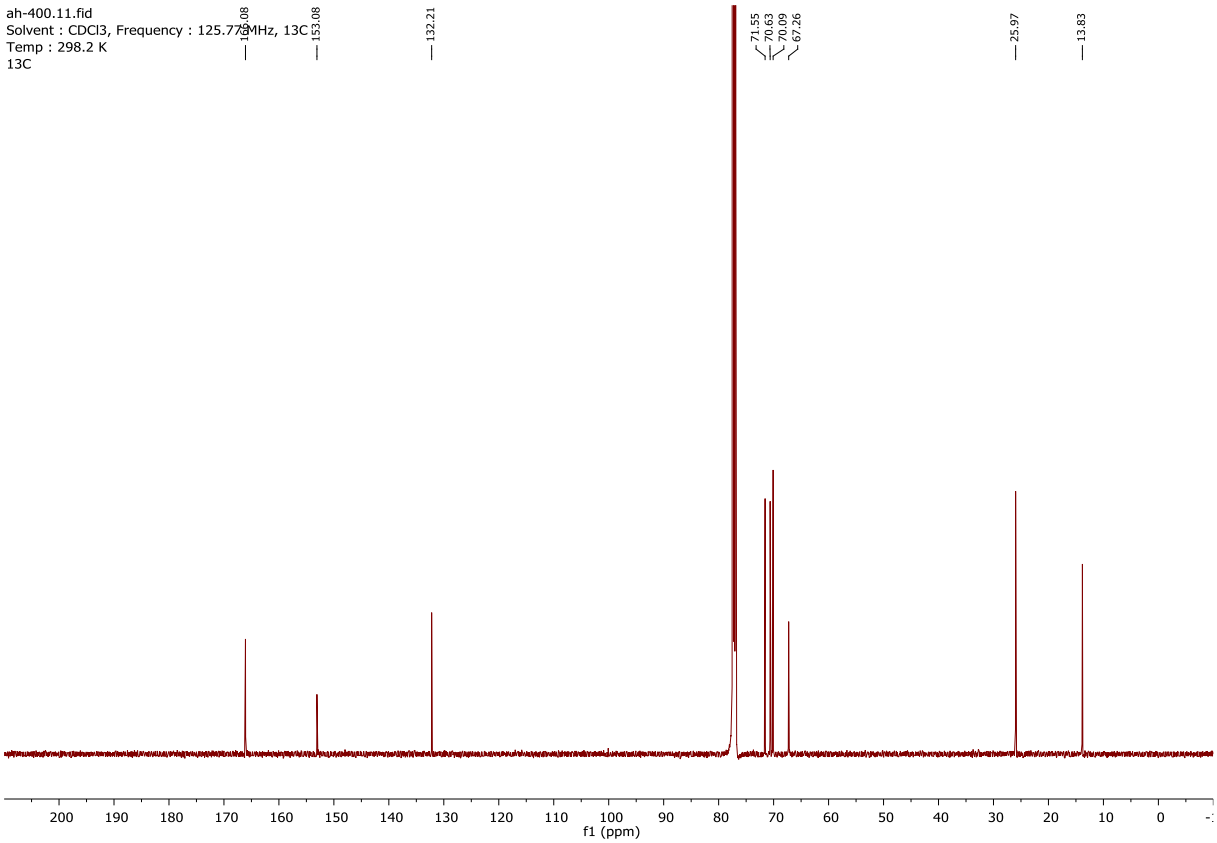
5.2 Compounds of **3a**



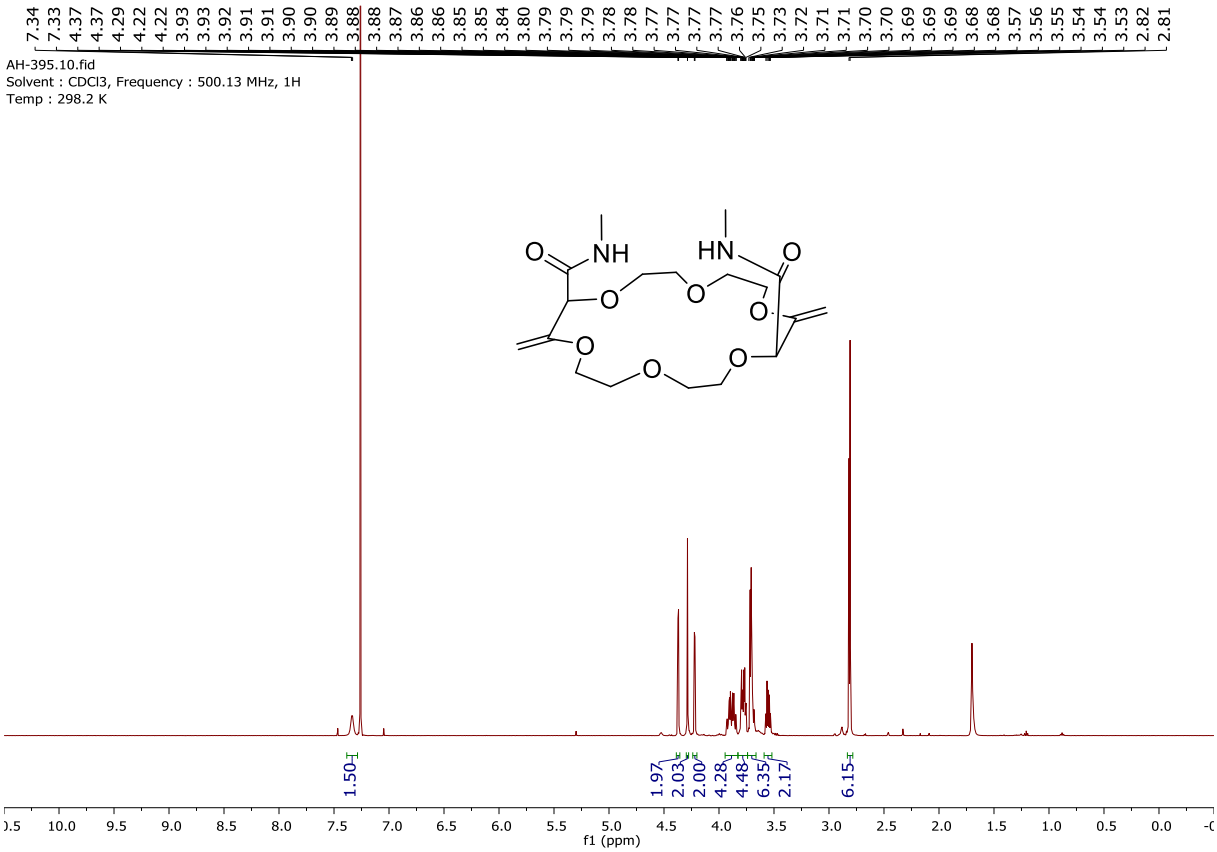


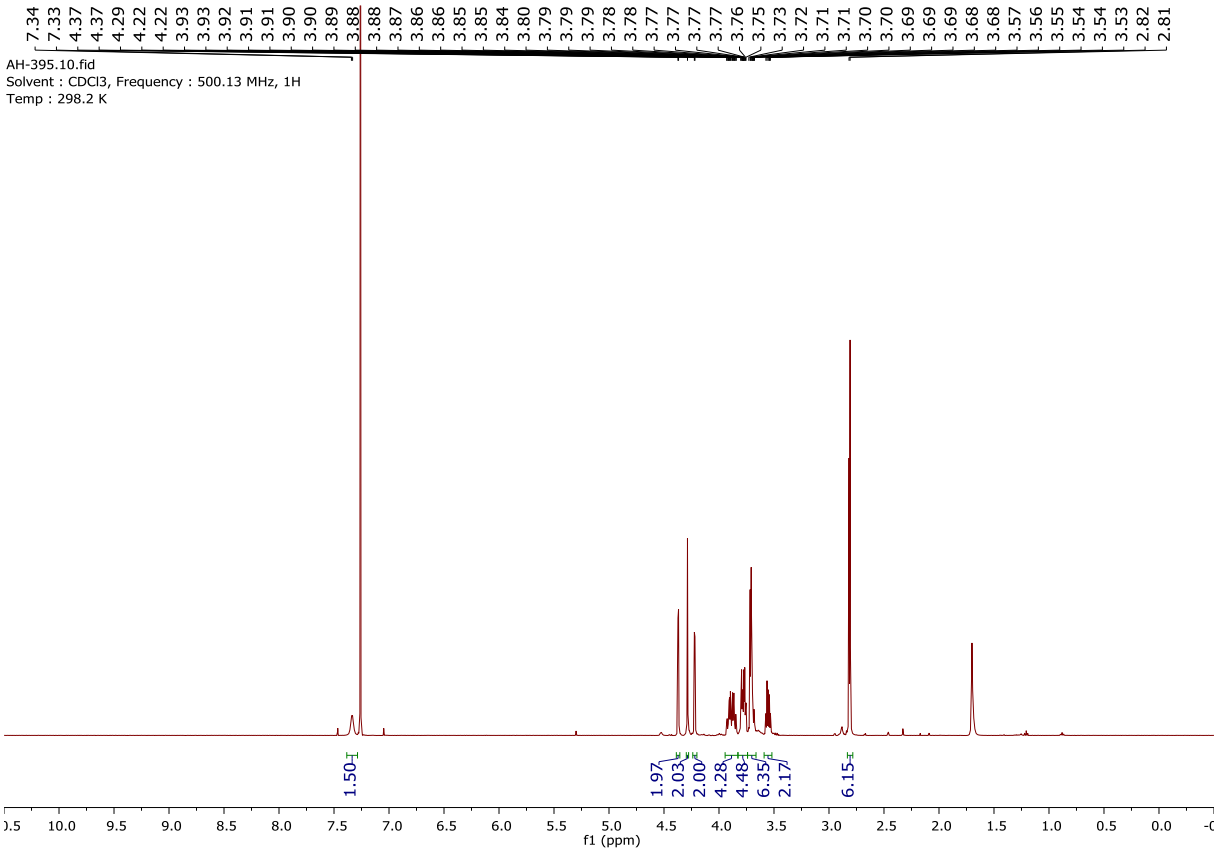
5.3 Compounds of **4b**



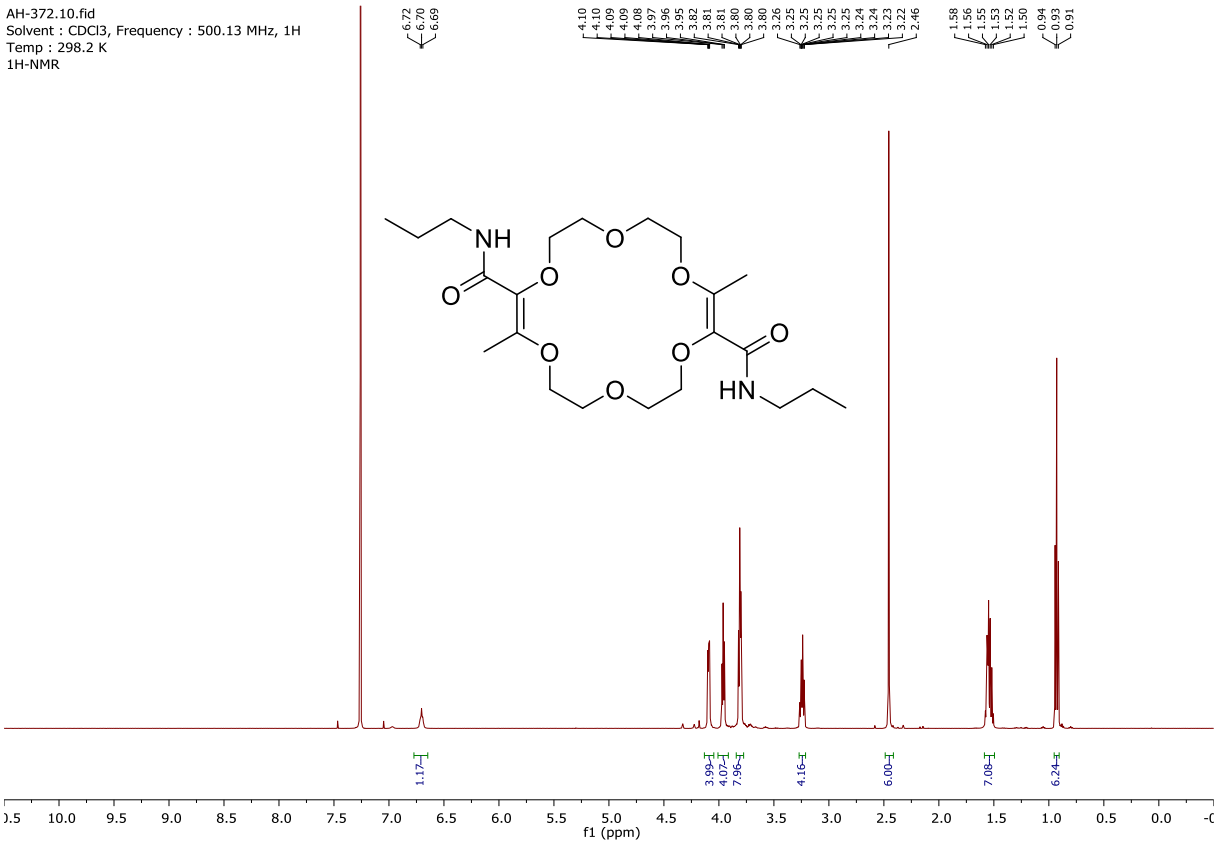


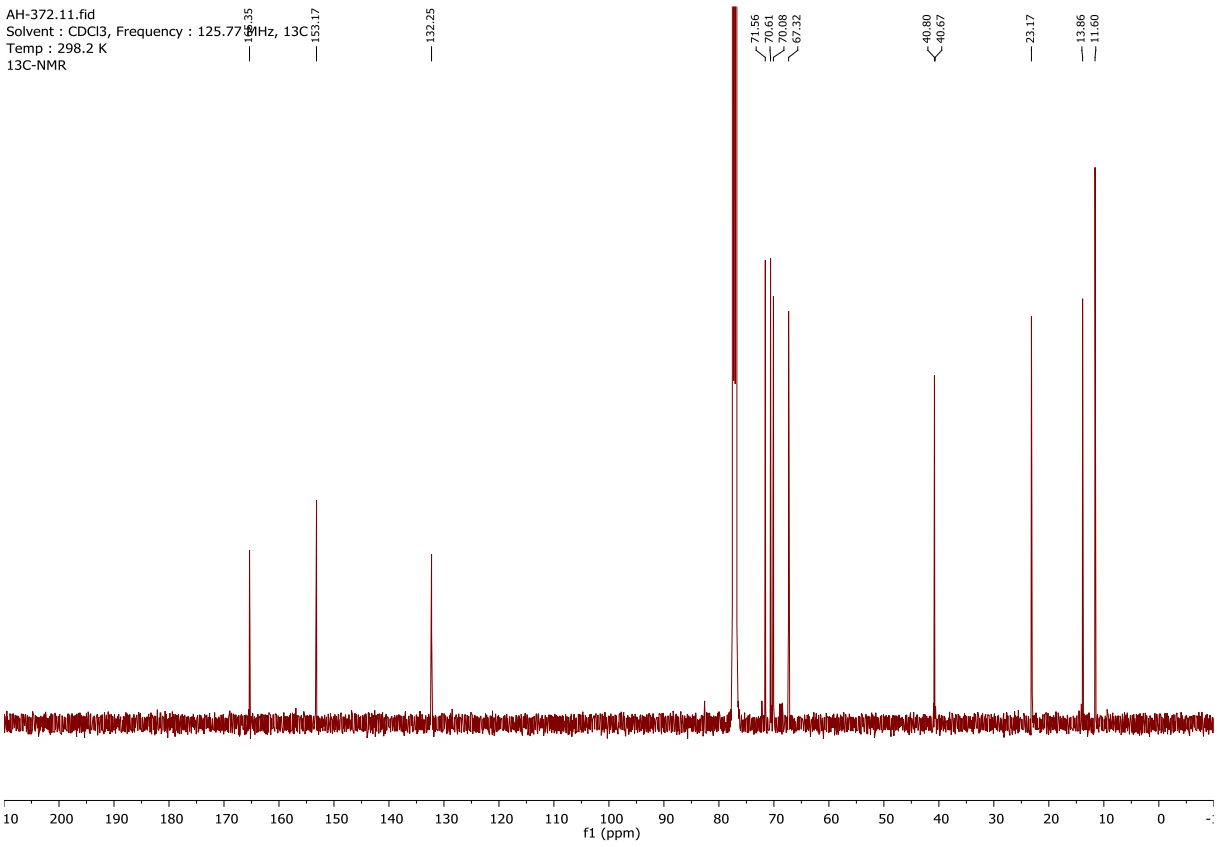
5.4 Compounds of **3b**



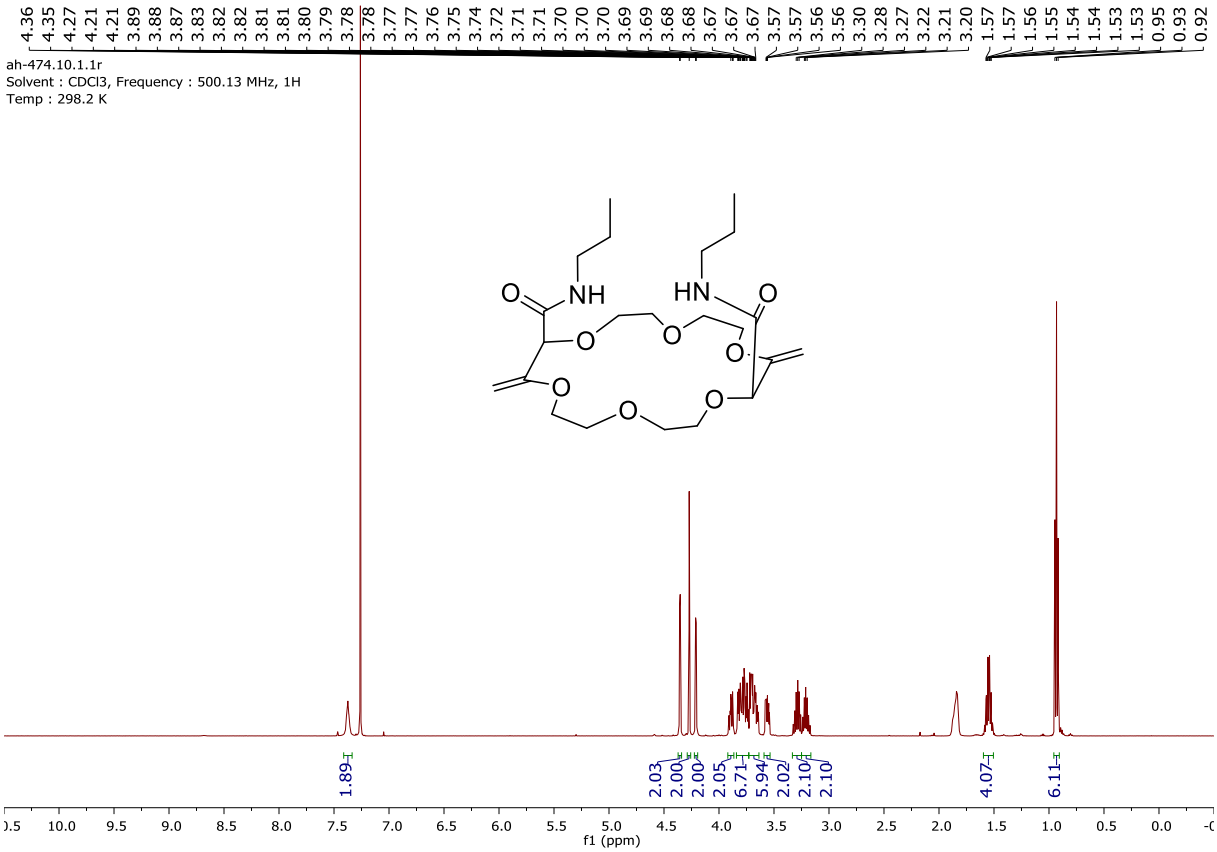


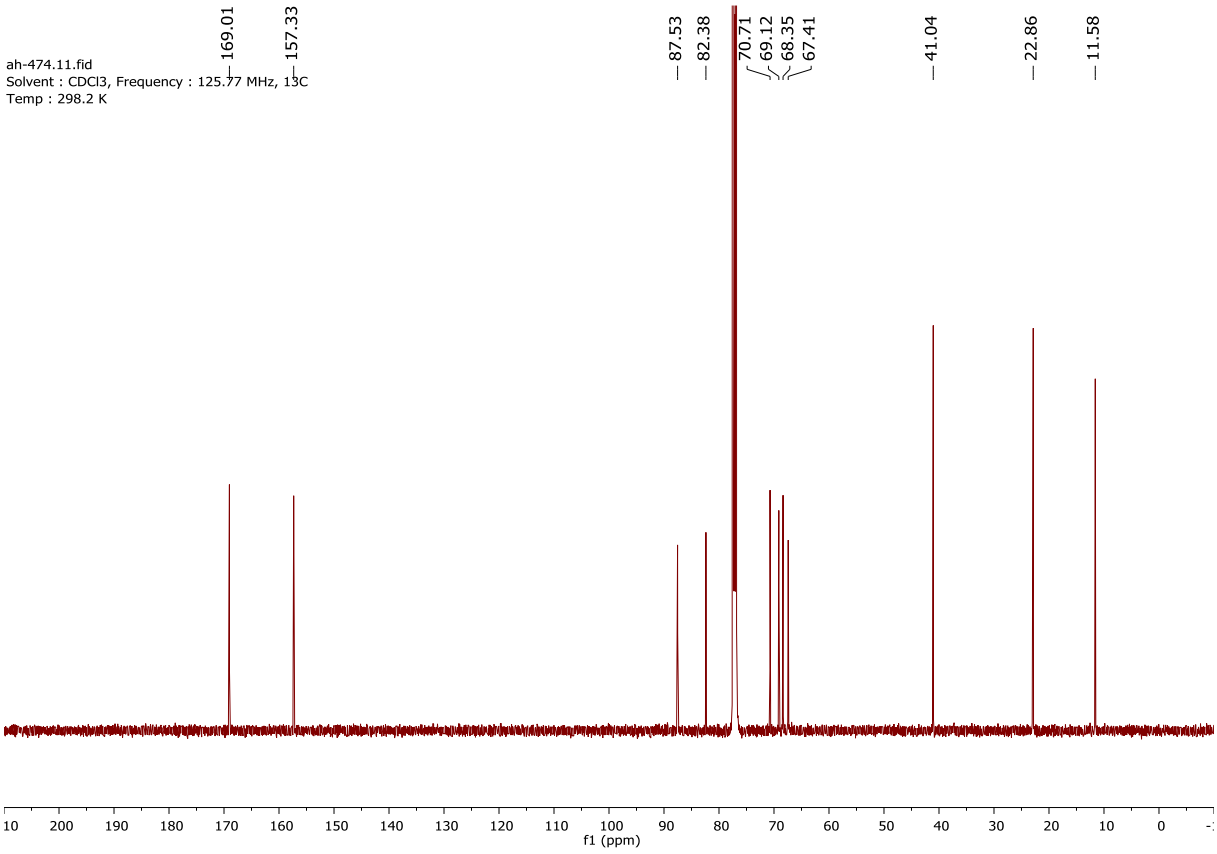
5.5 Compounds of **4c**



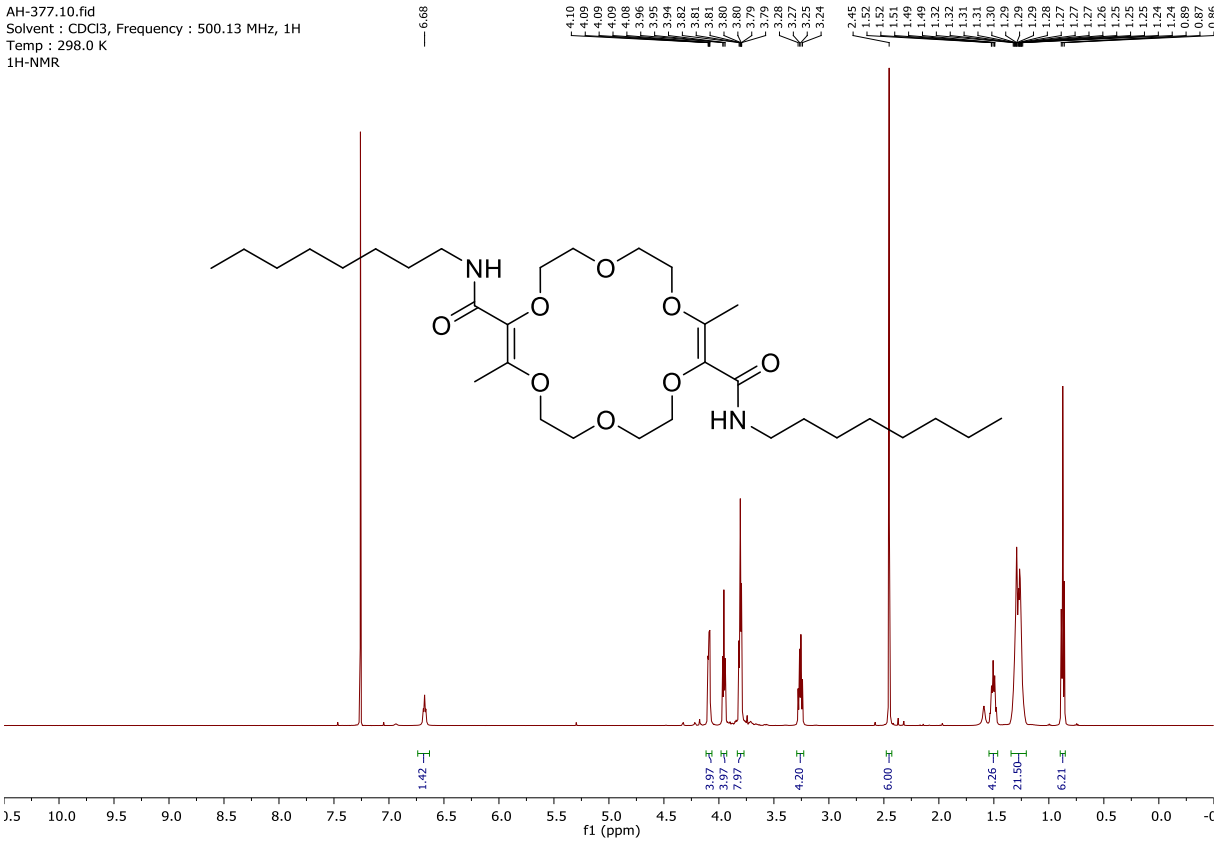


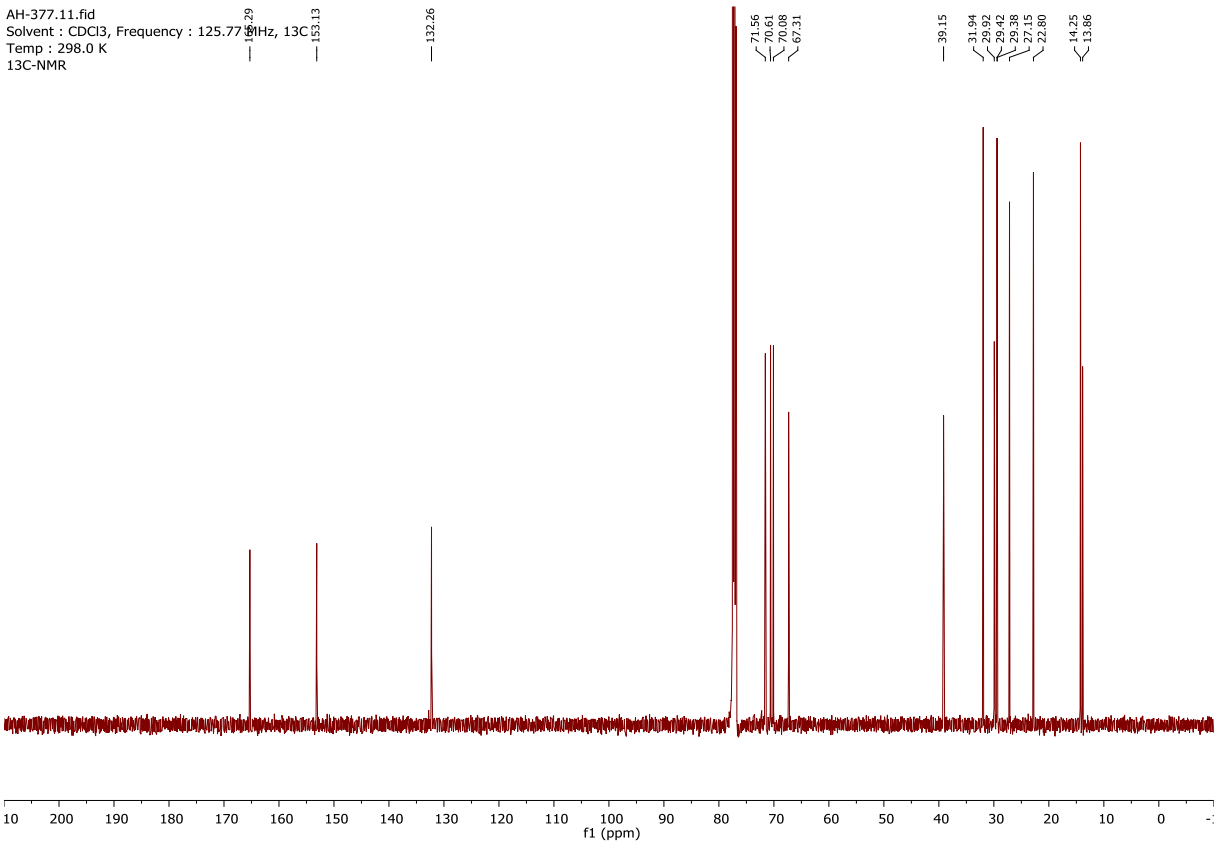
5.6 Compounds of **3c**



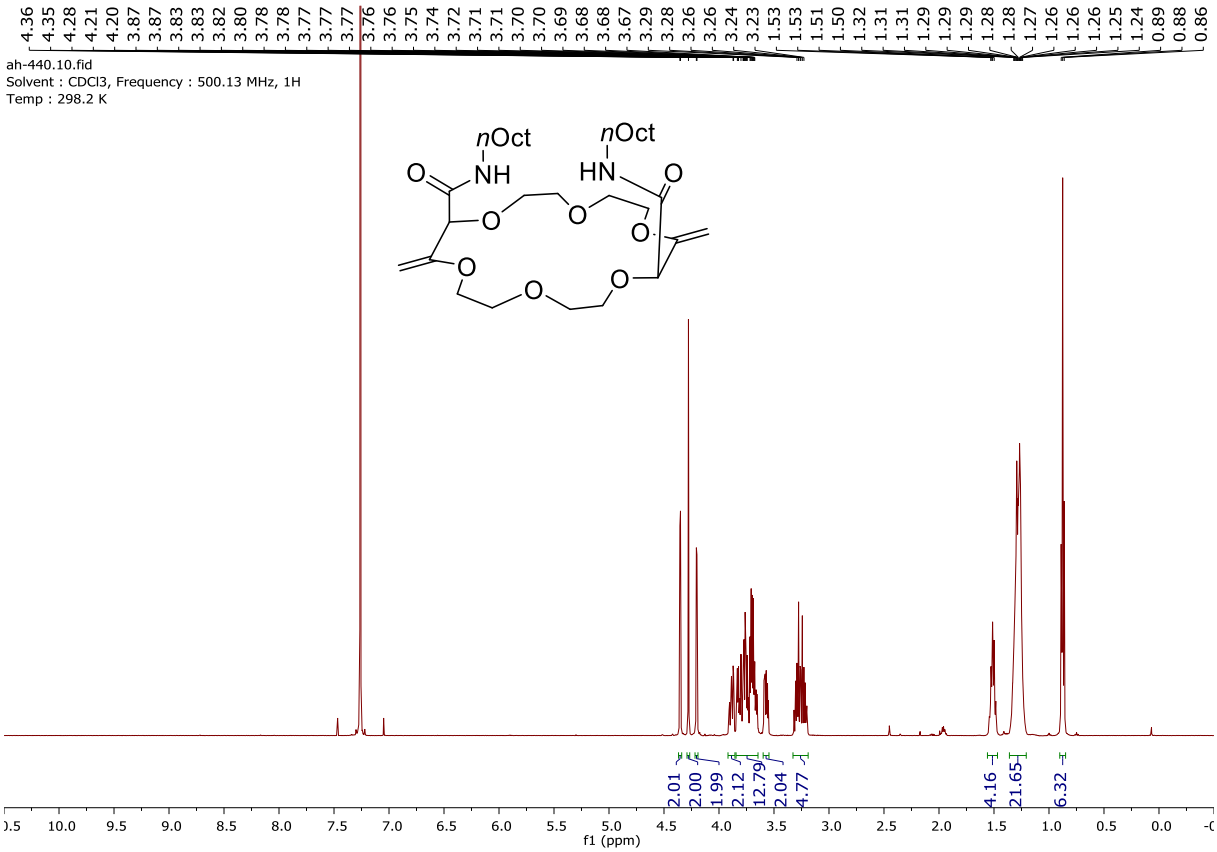


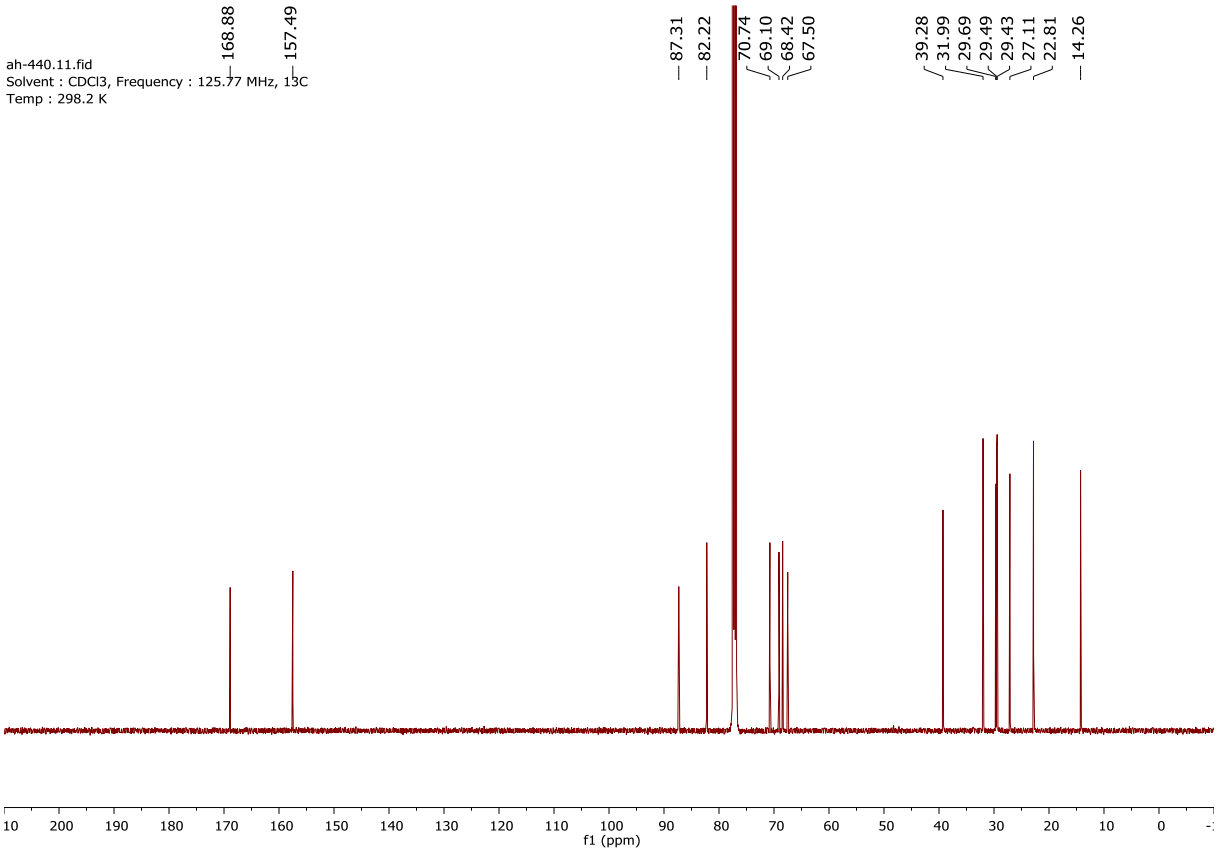
5.7 Compounds of **4d**



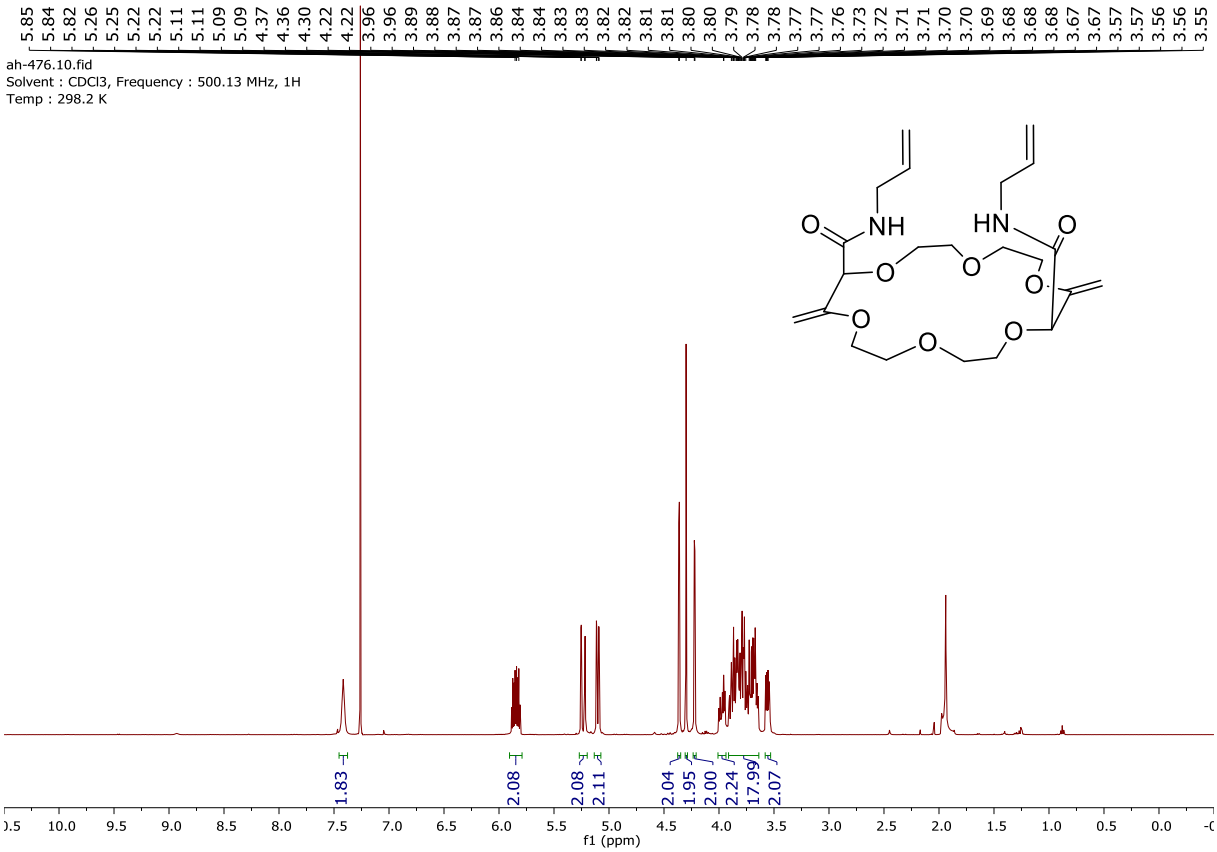


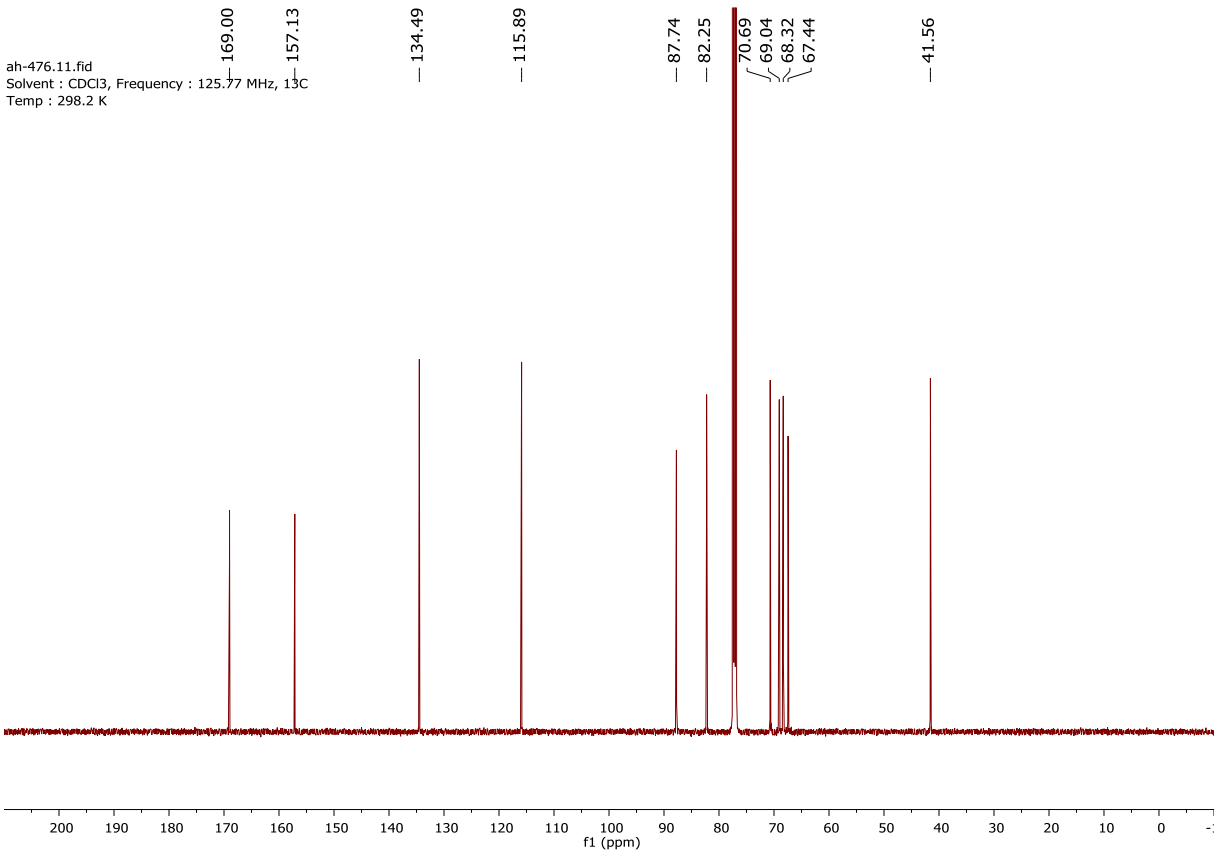
5.8 Compounds of **3d**



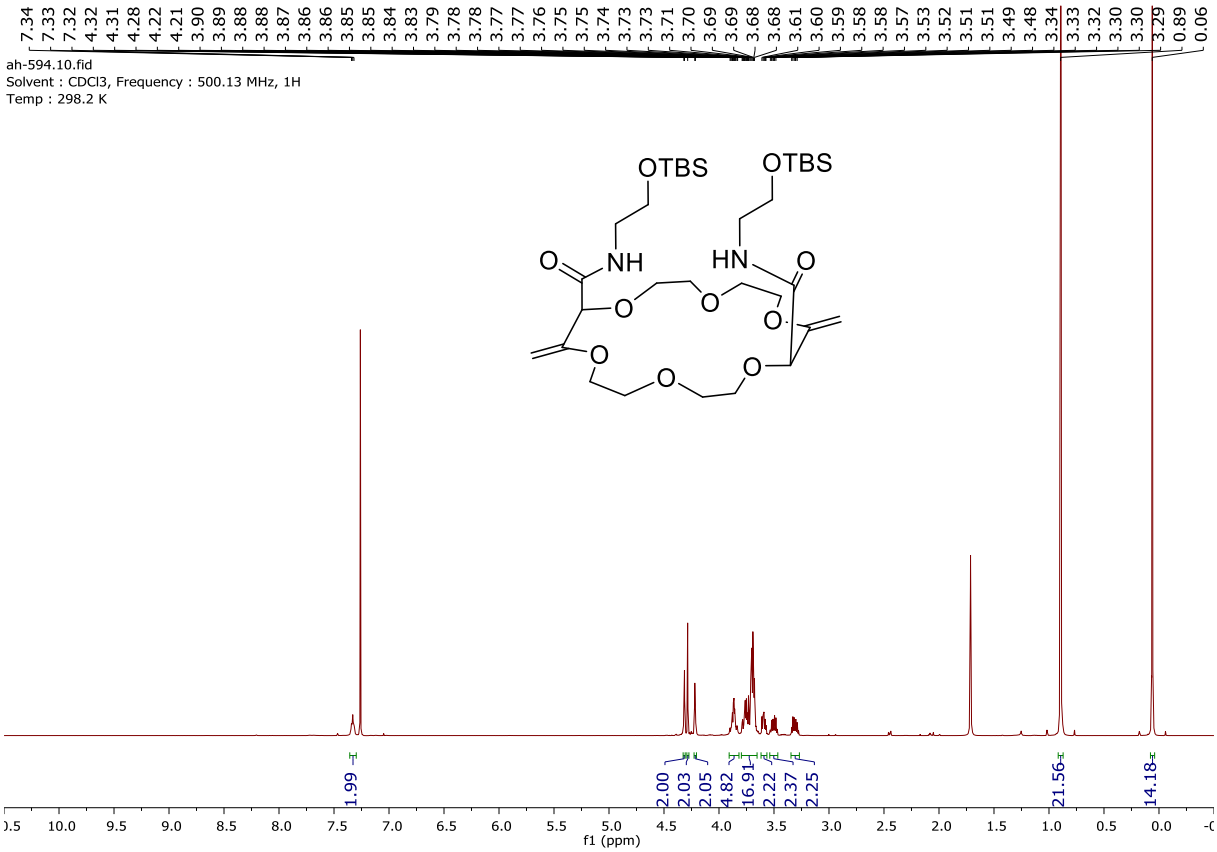


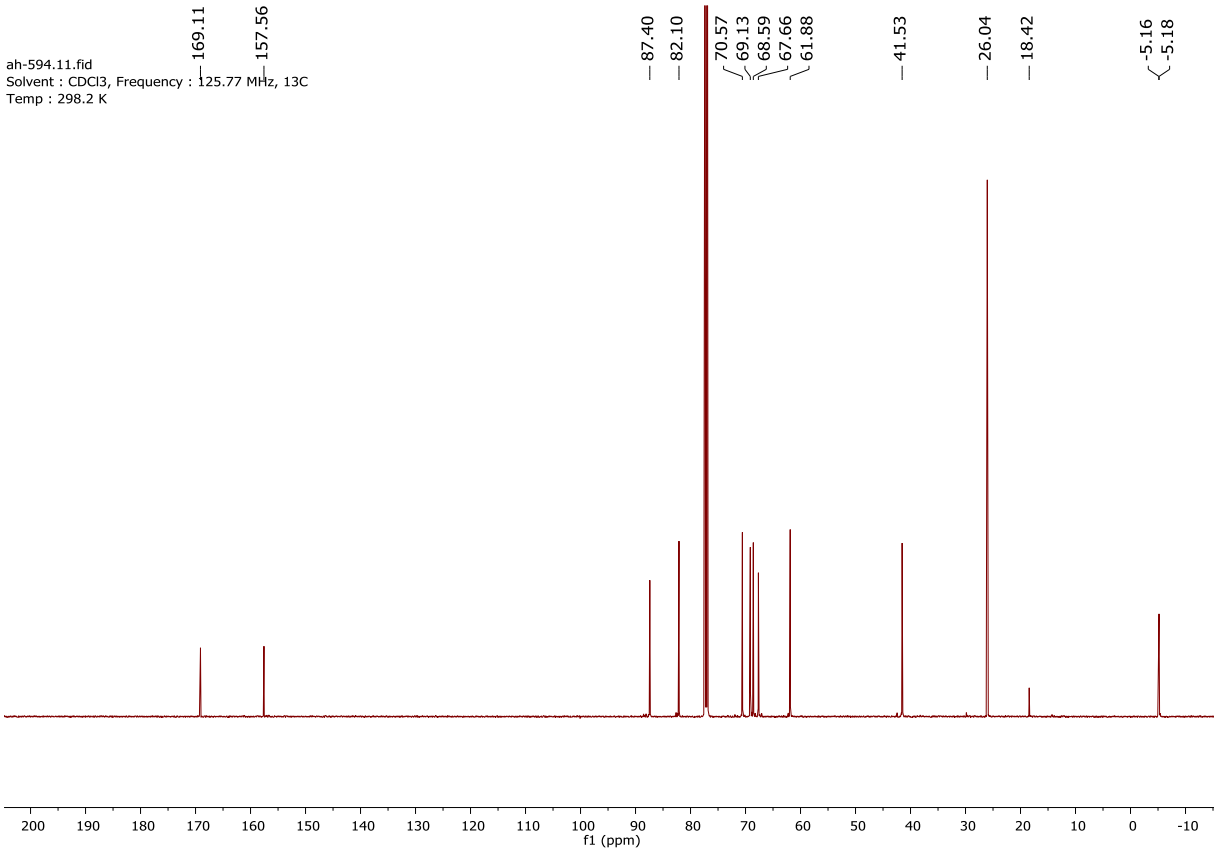
5.9 Compound of **3e**



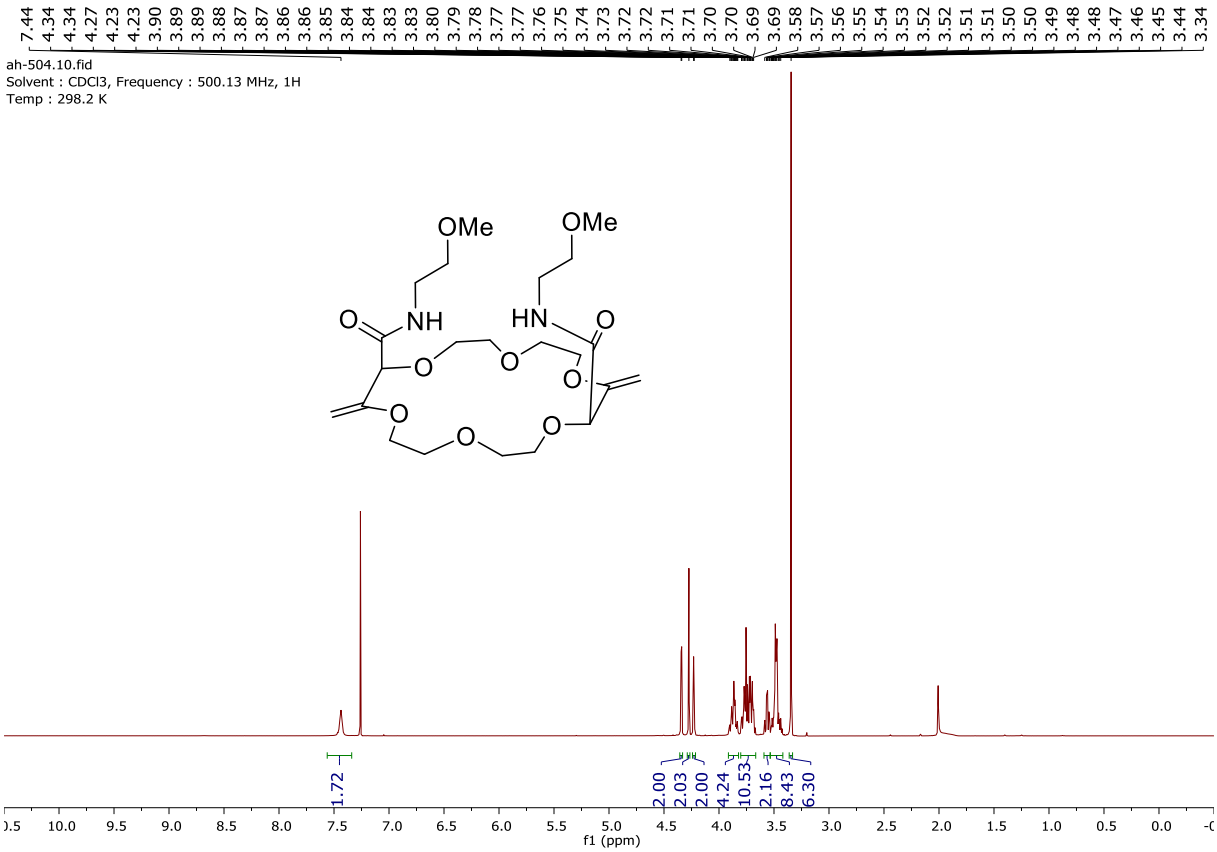


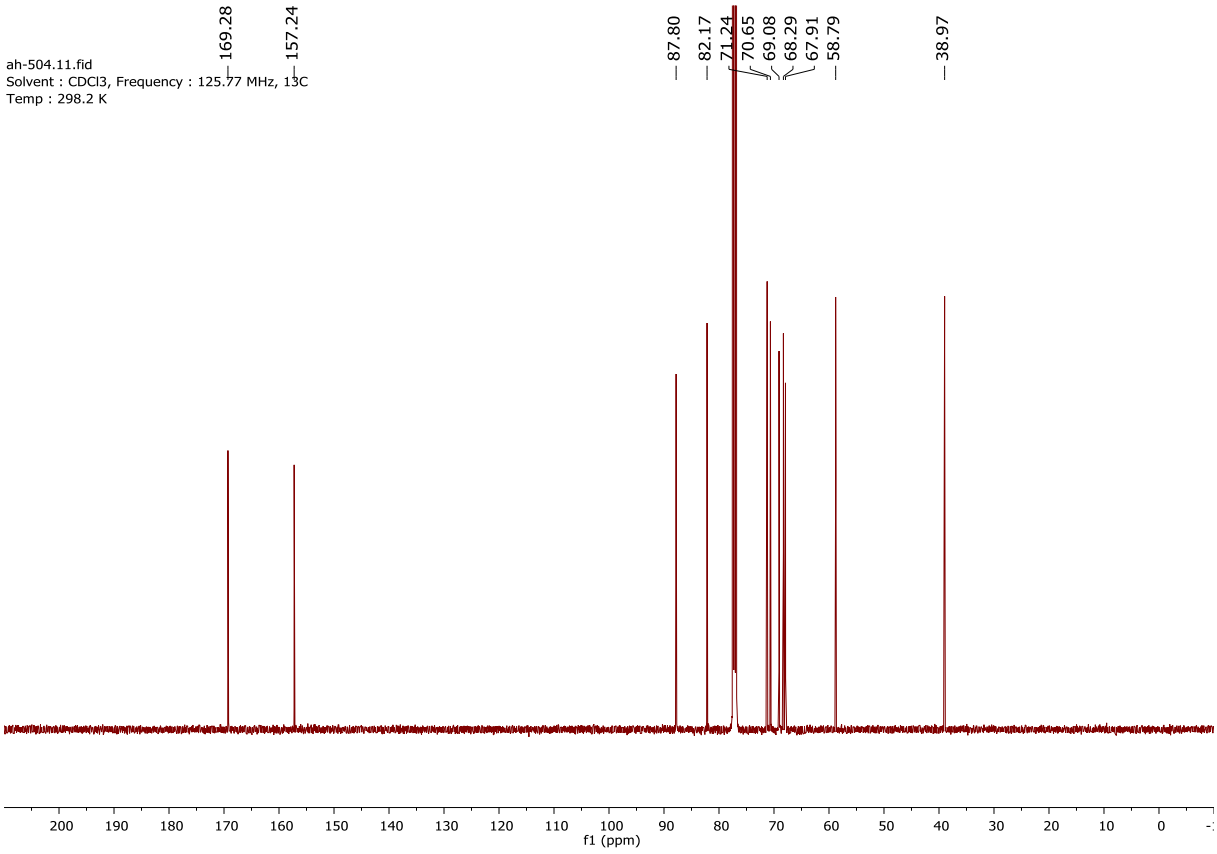
5.10 Compound of **3f**



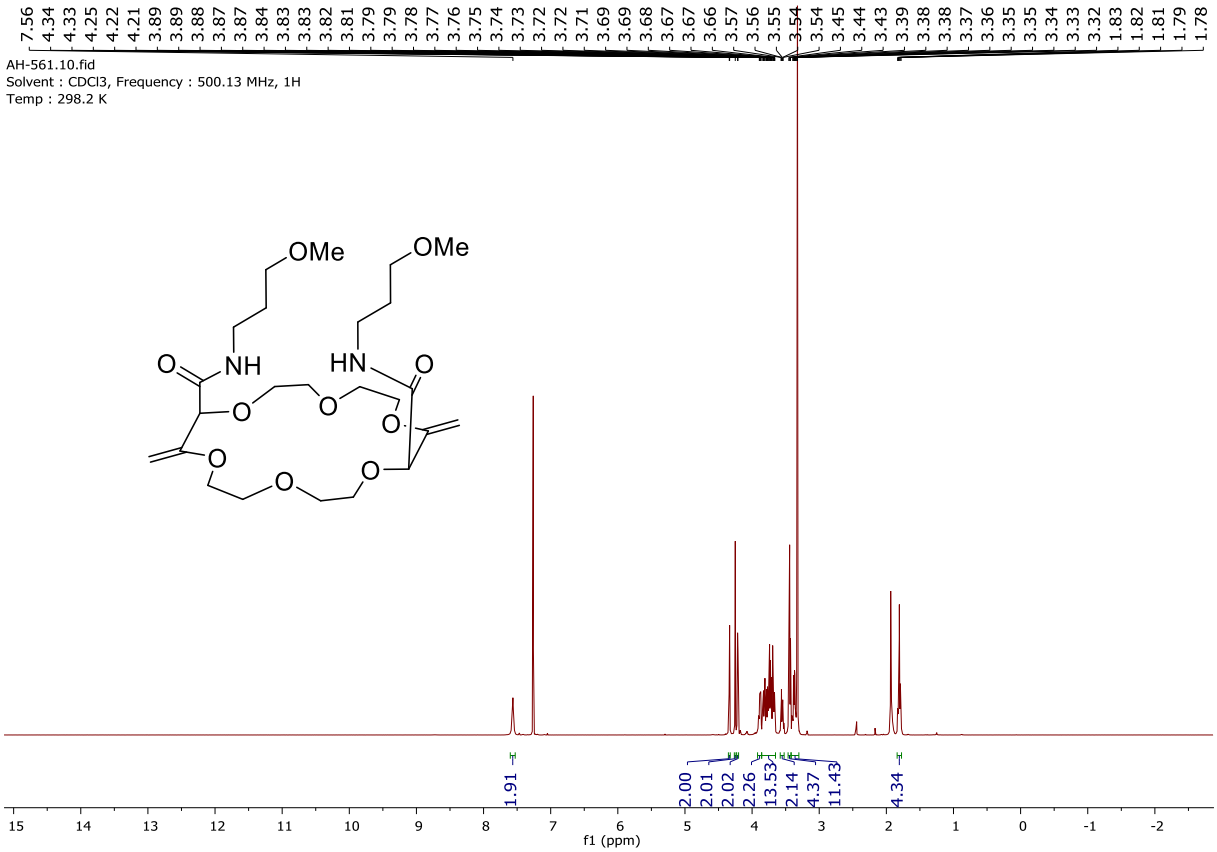


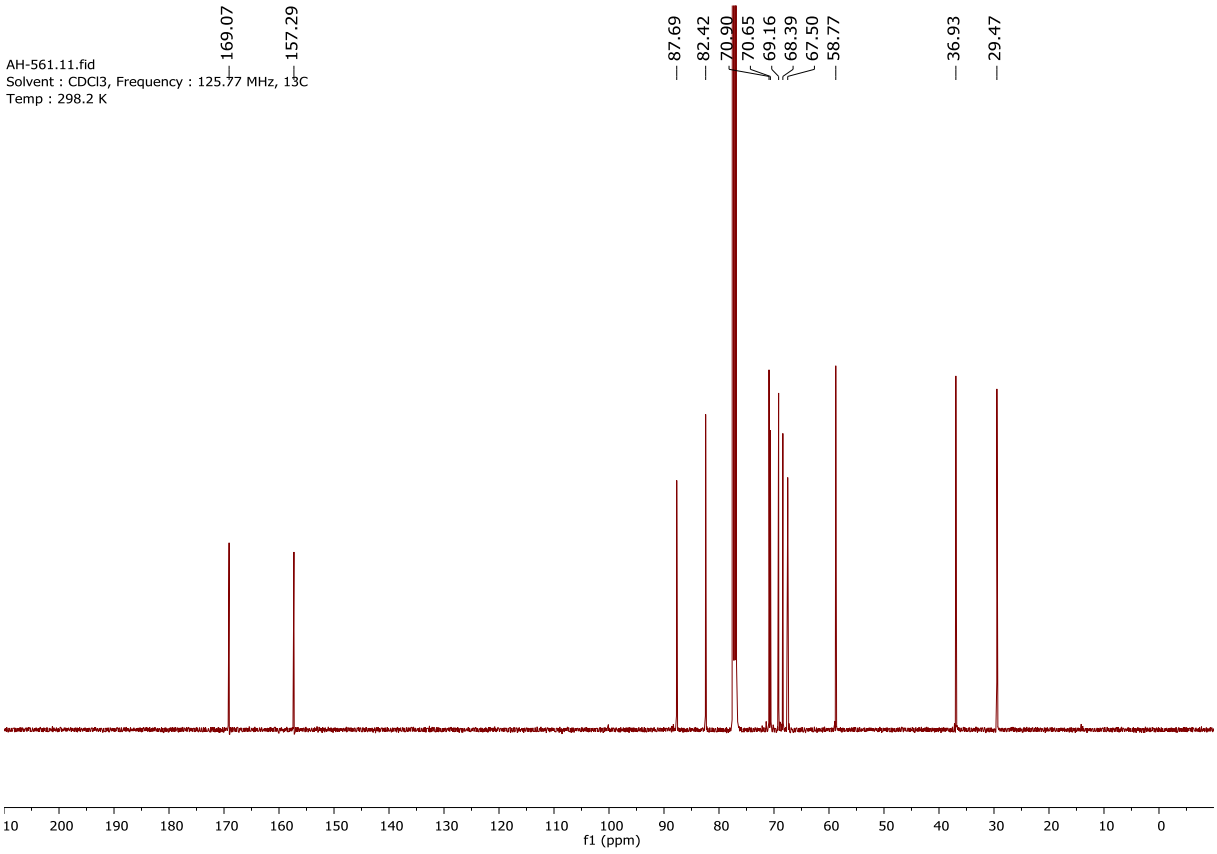
5.11 Compound of **3g**



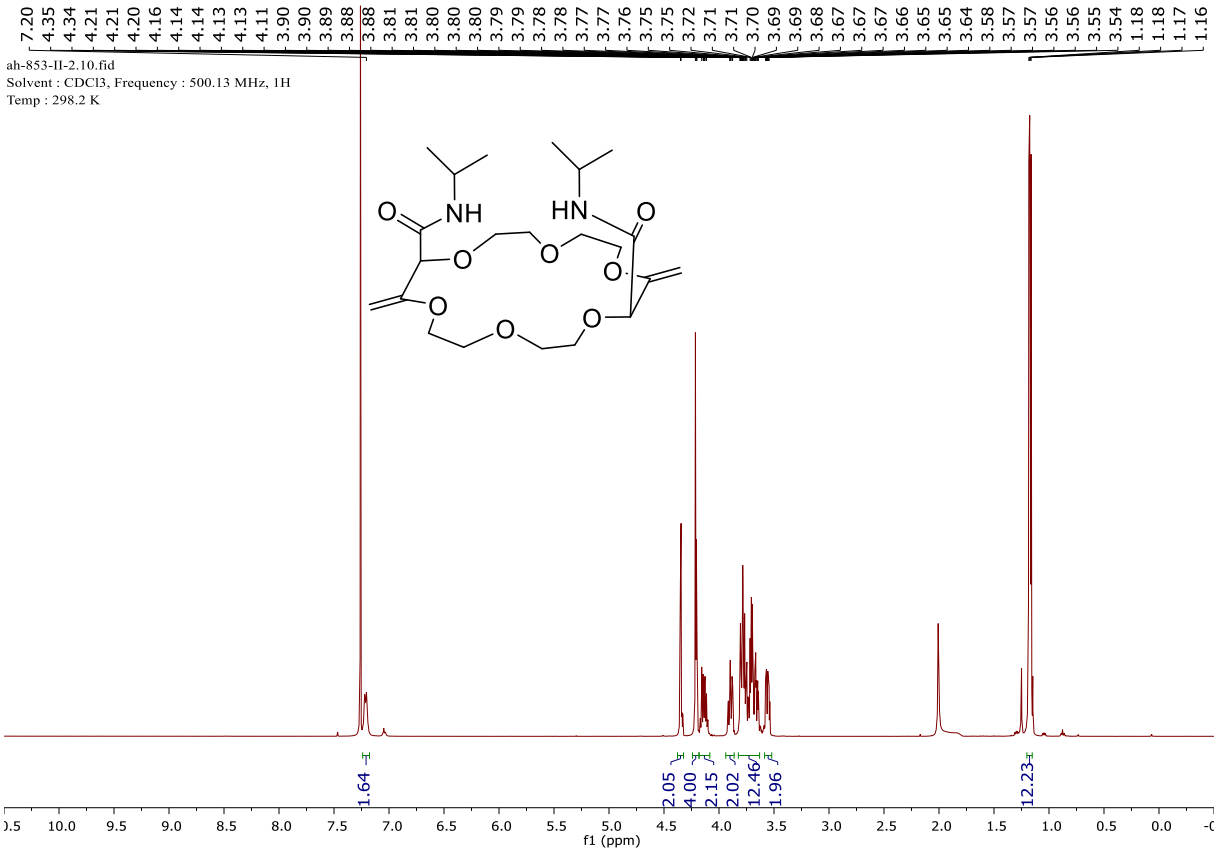


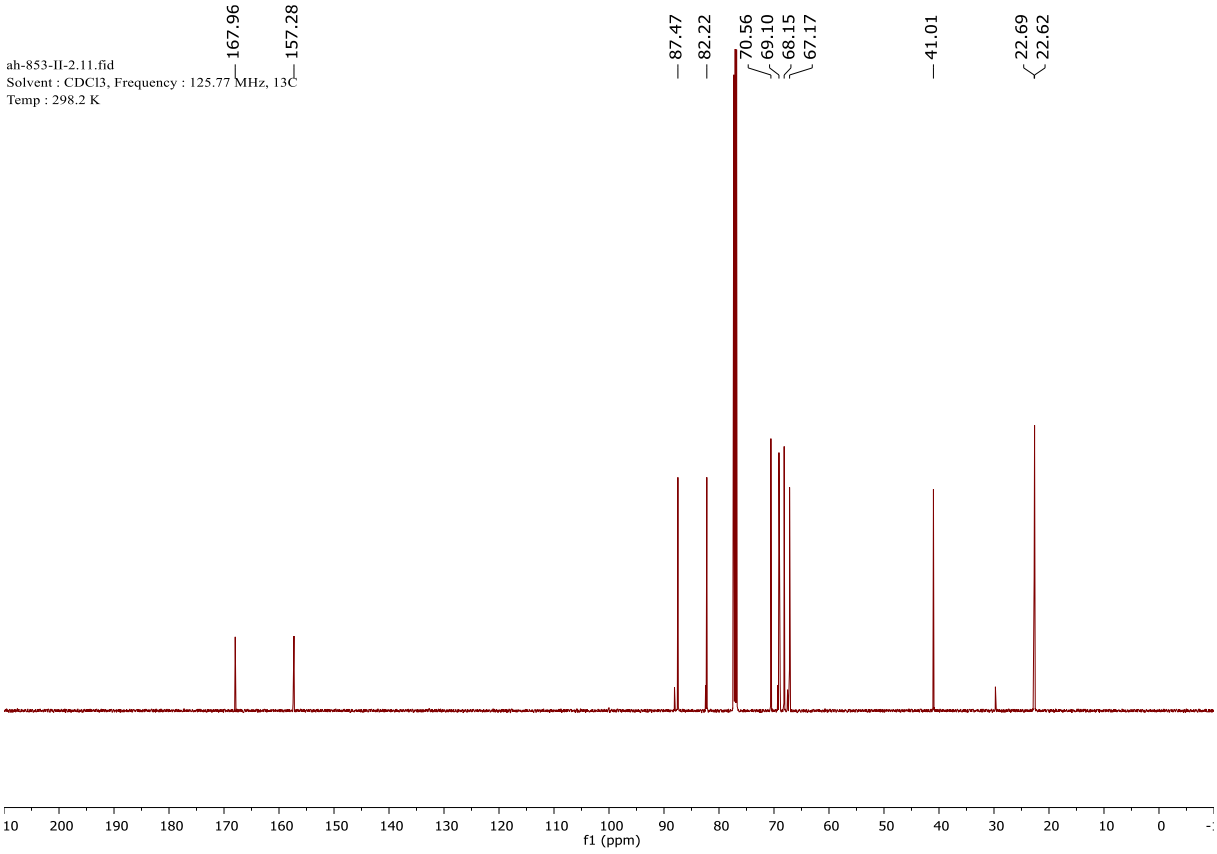
5.12 Compound of **3h**



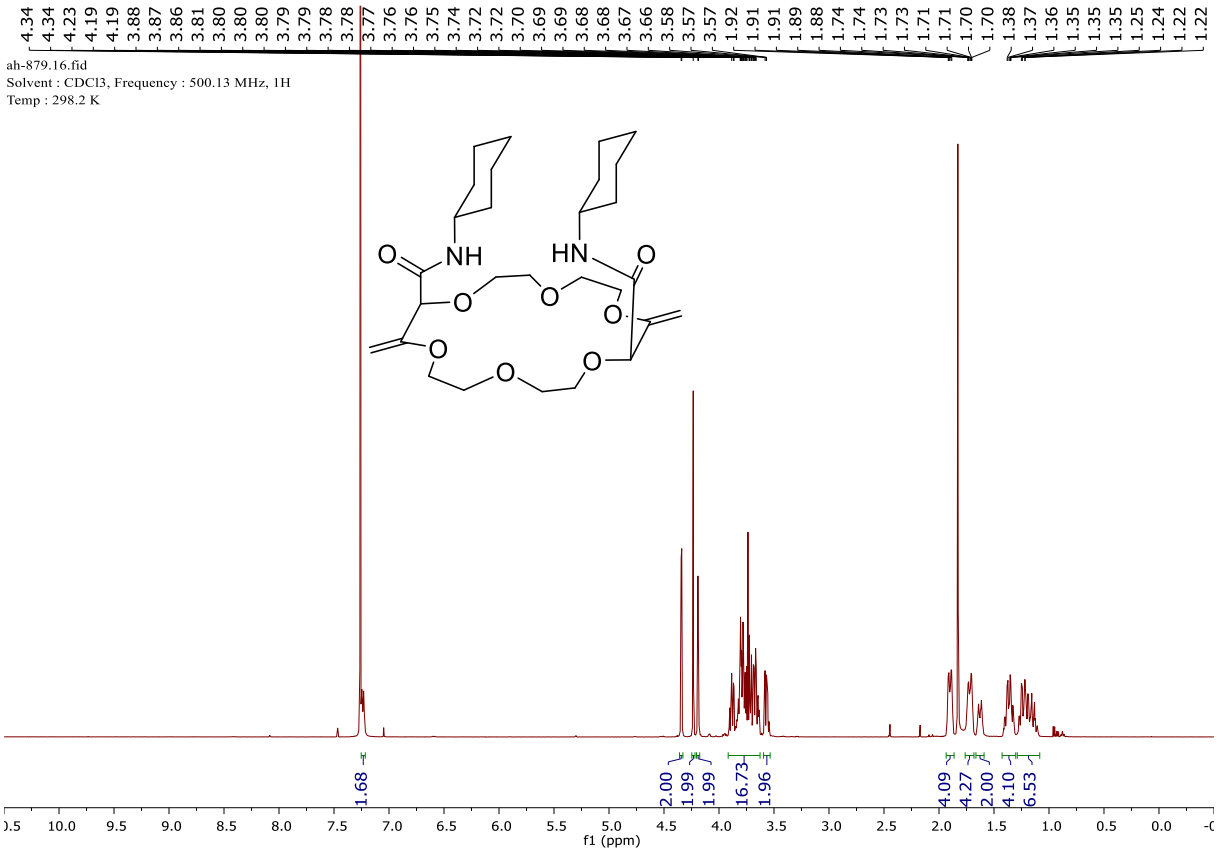


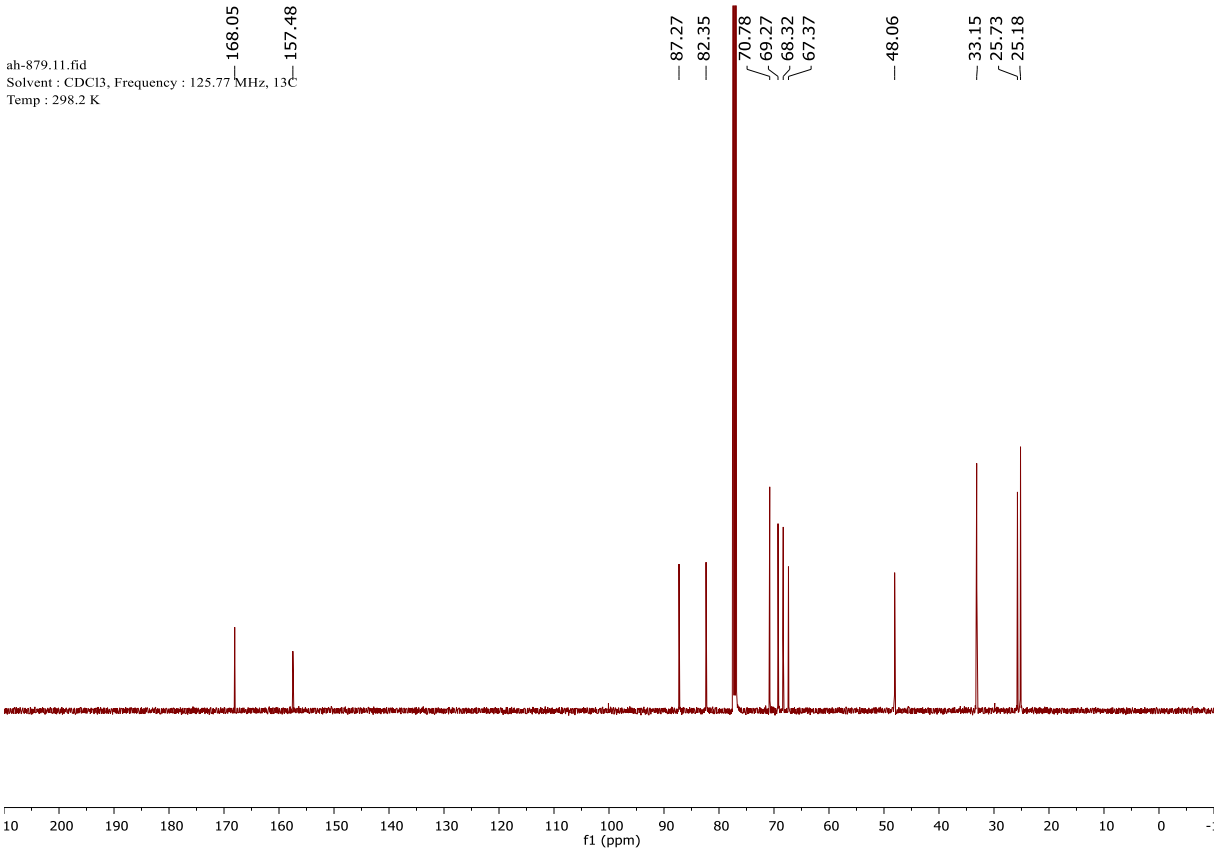
5.13 Compound of **3i**



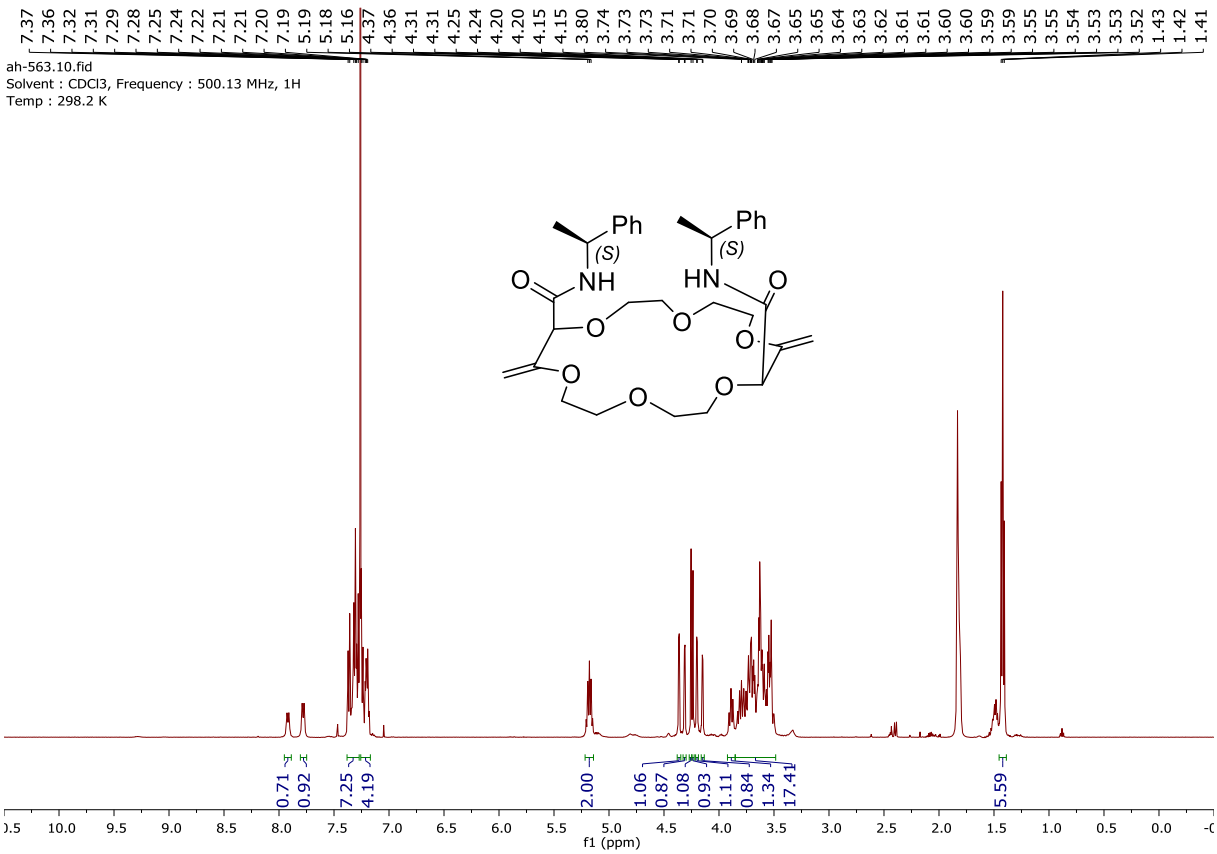


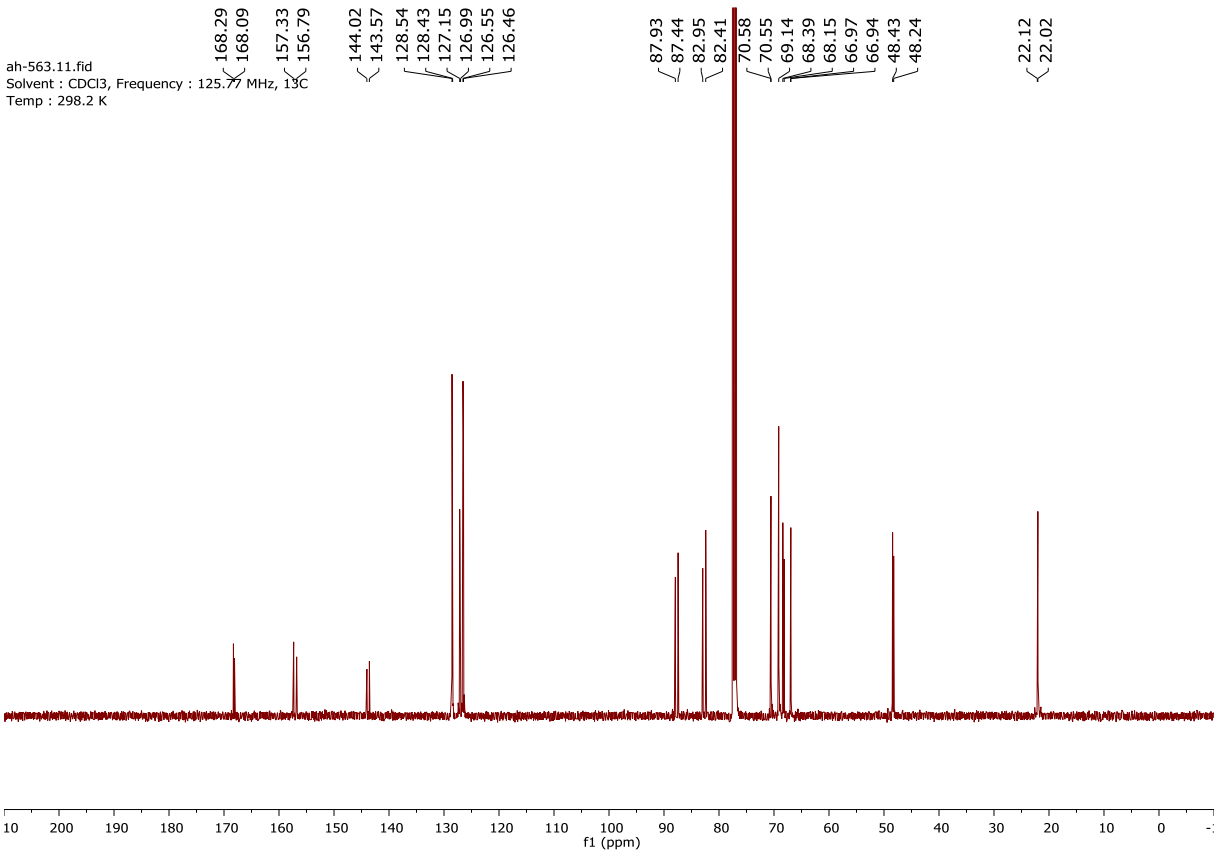
5.14 Compound of **3j**



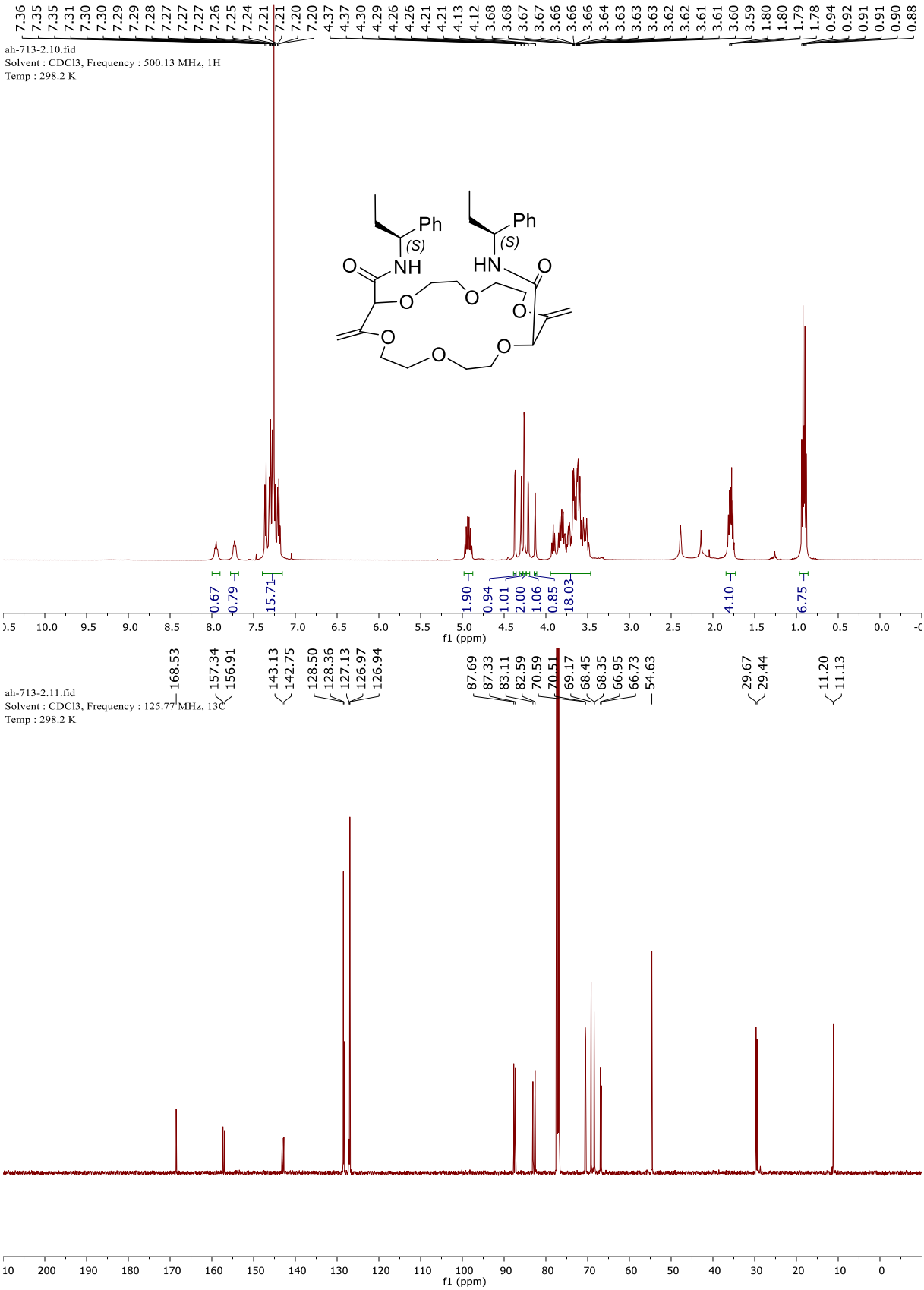


5.15 Compound of **3k**

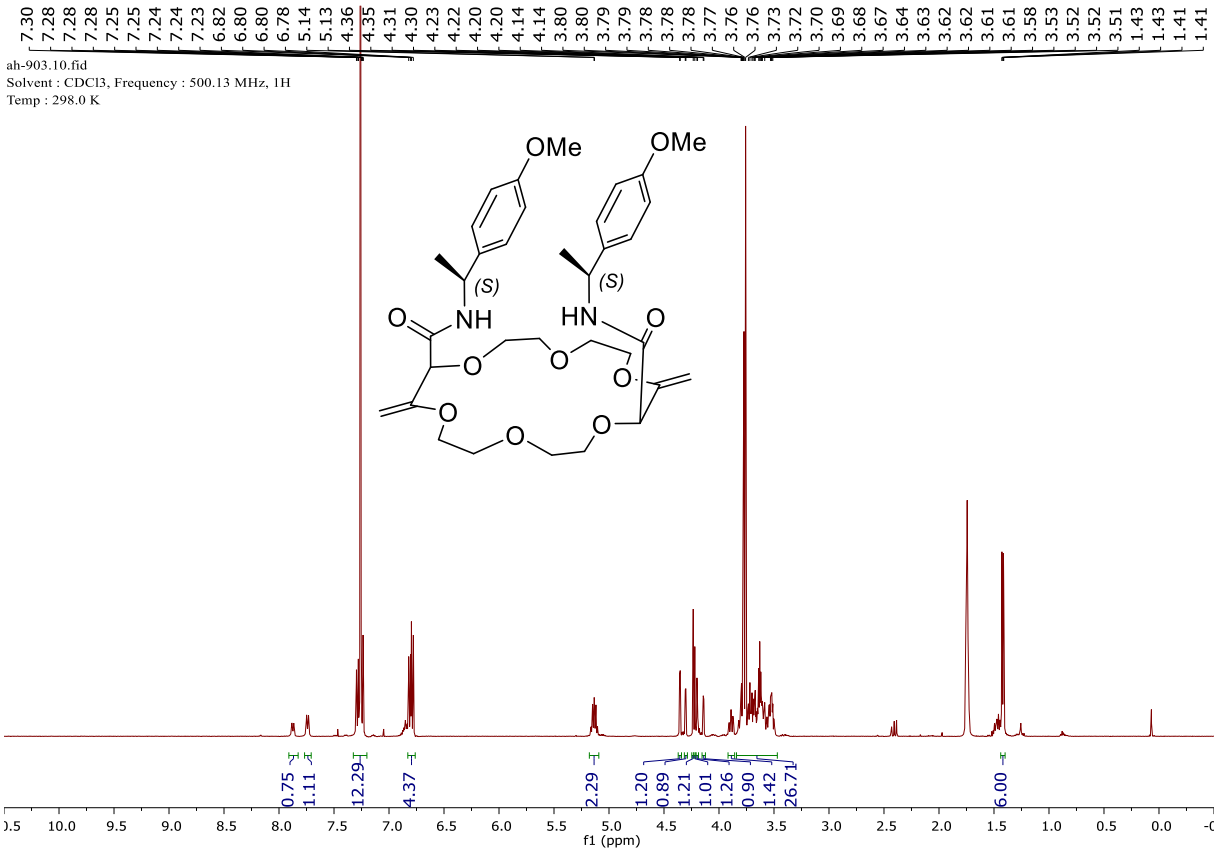


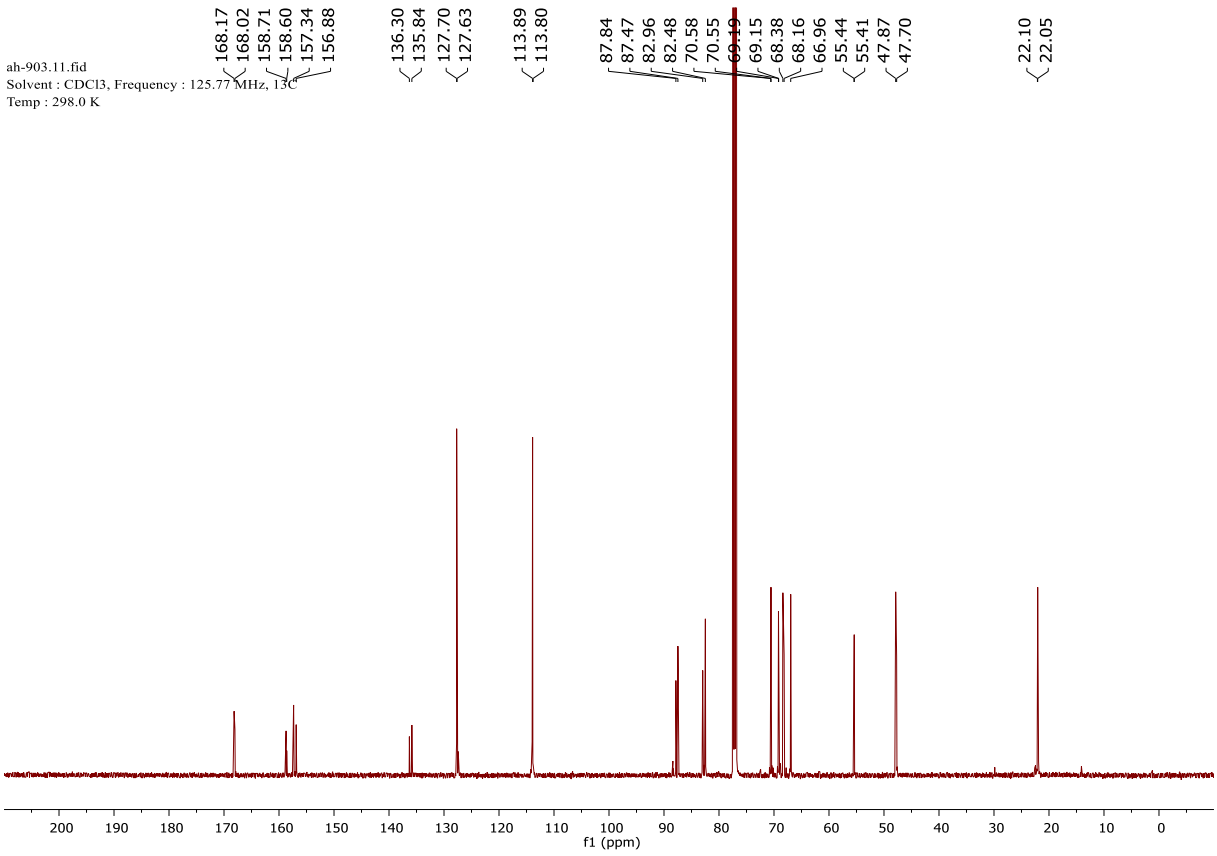


5.16 Compound of **3l**

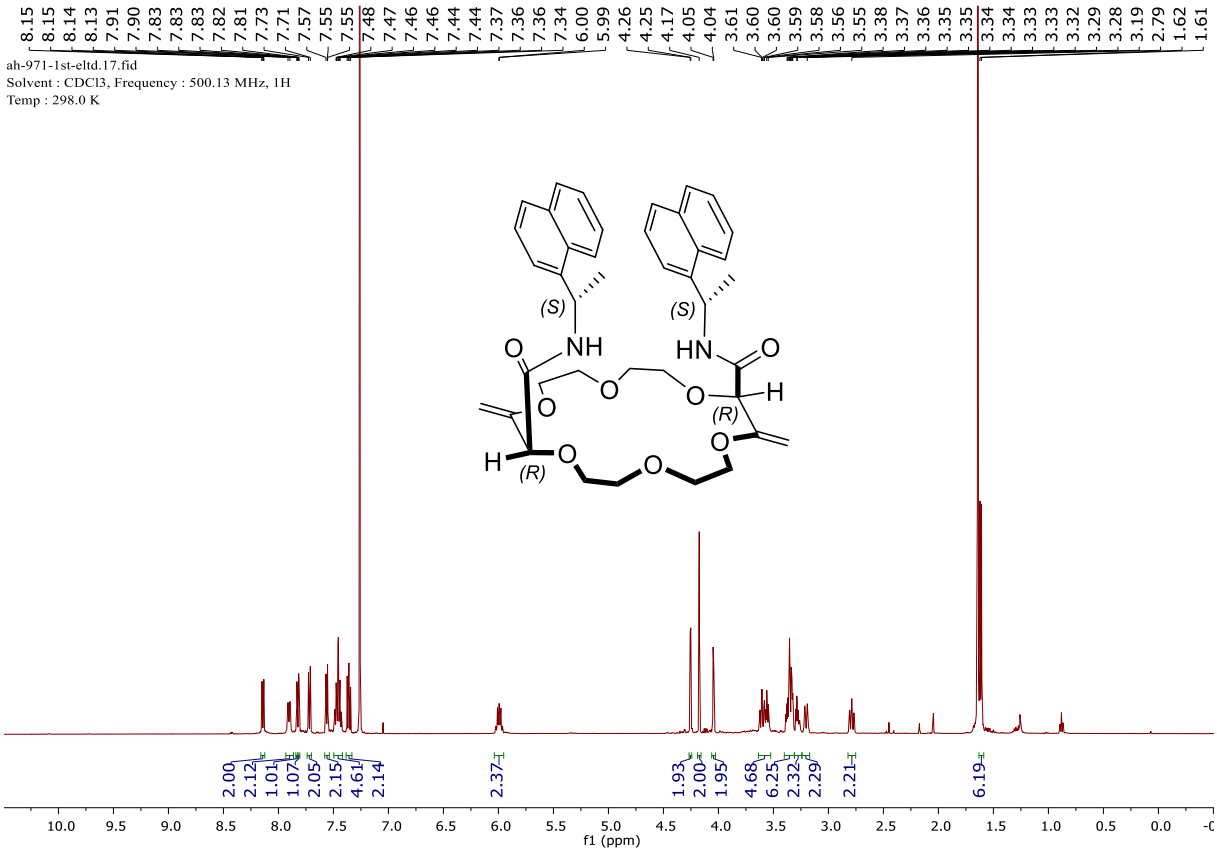


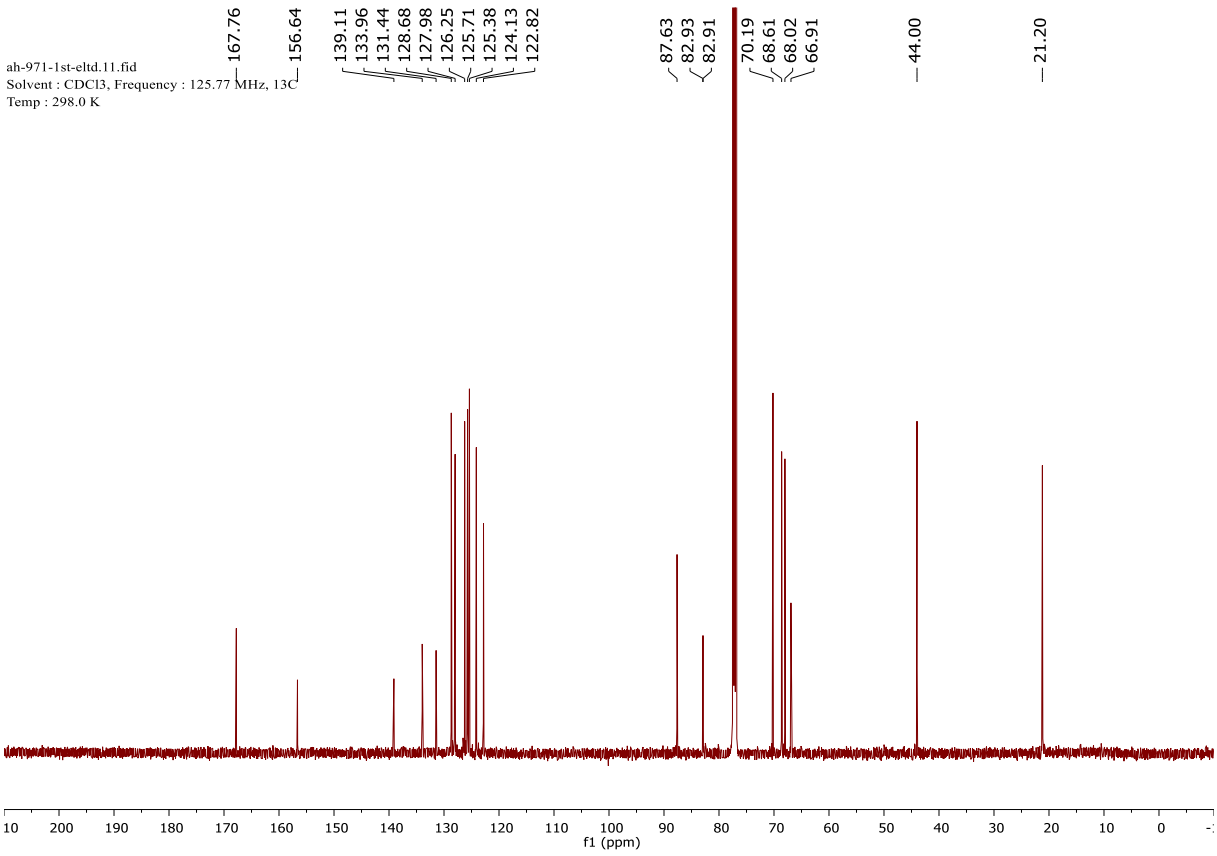
5.17 Compound of **3m**



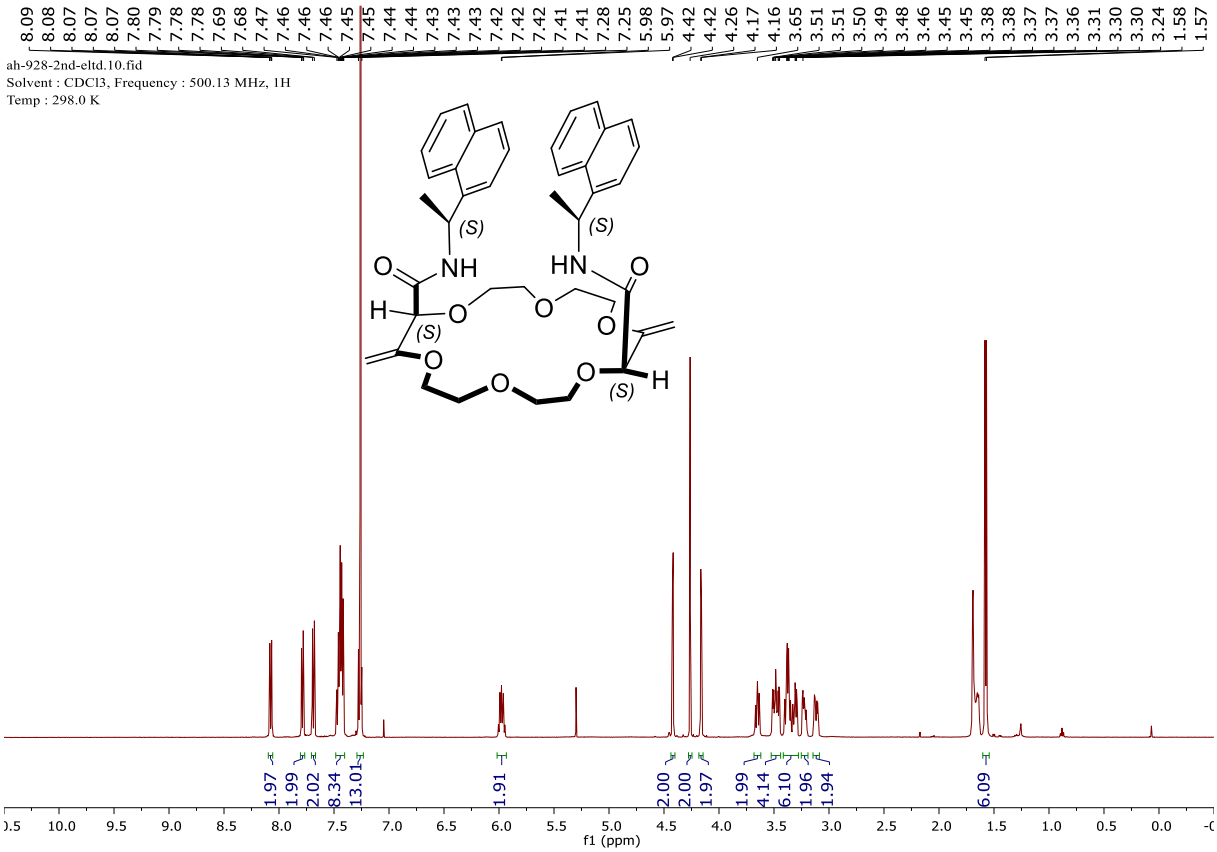


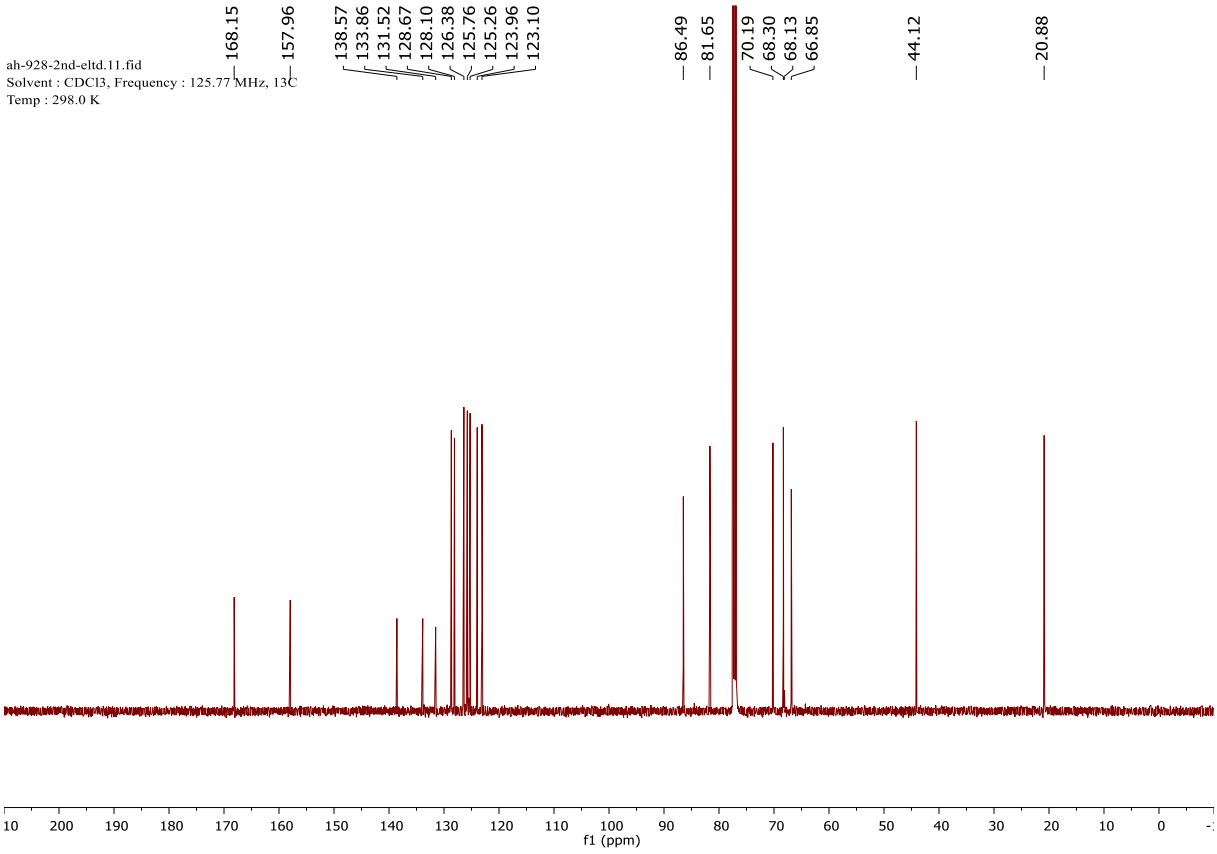
5.18 Compound of (*S*,*R*,*R*,*S*)-**3n**



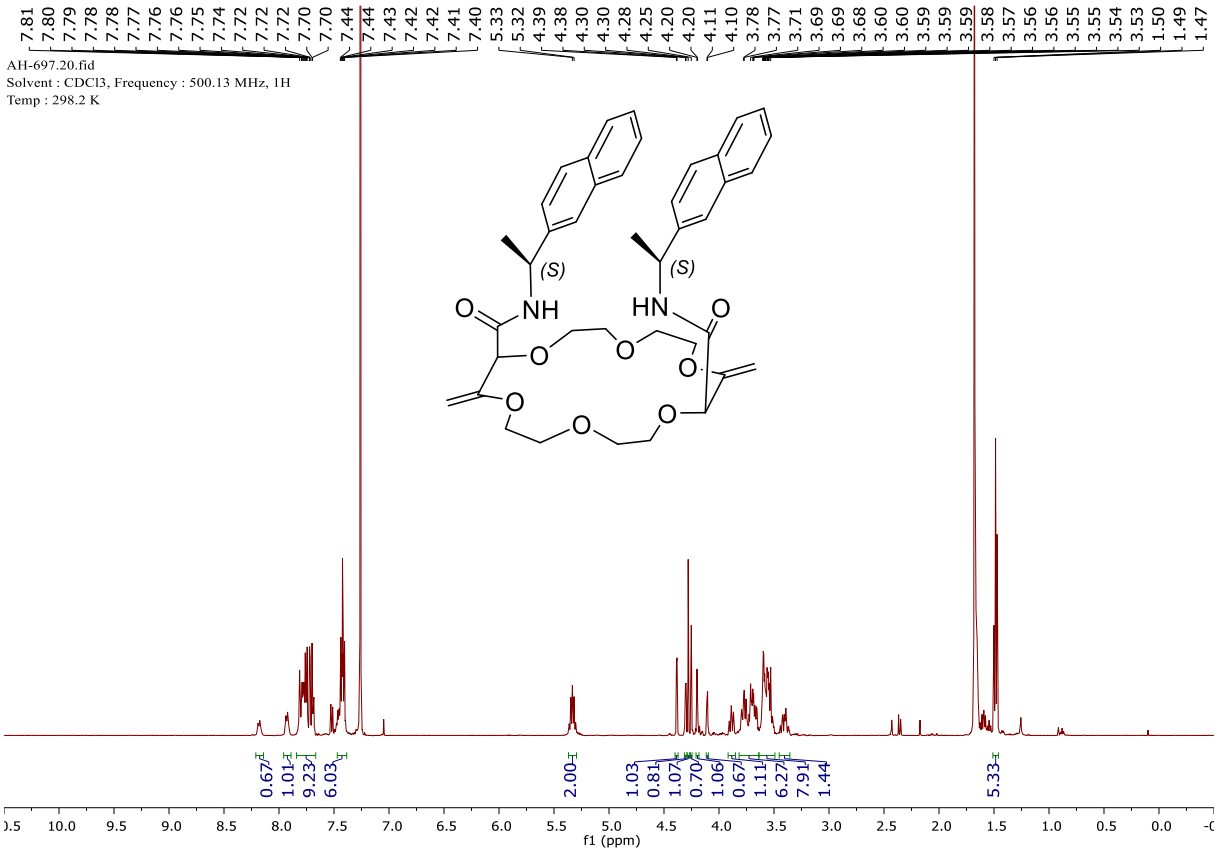


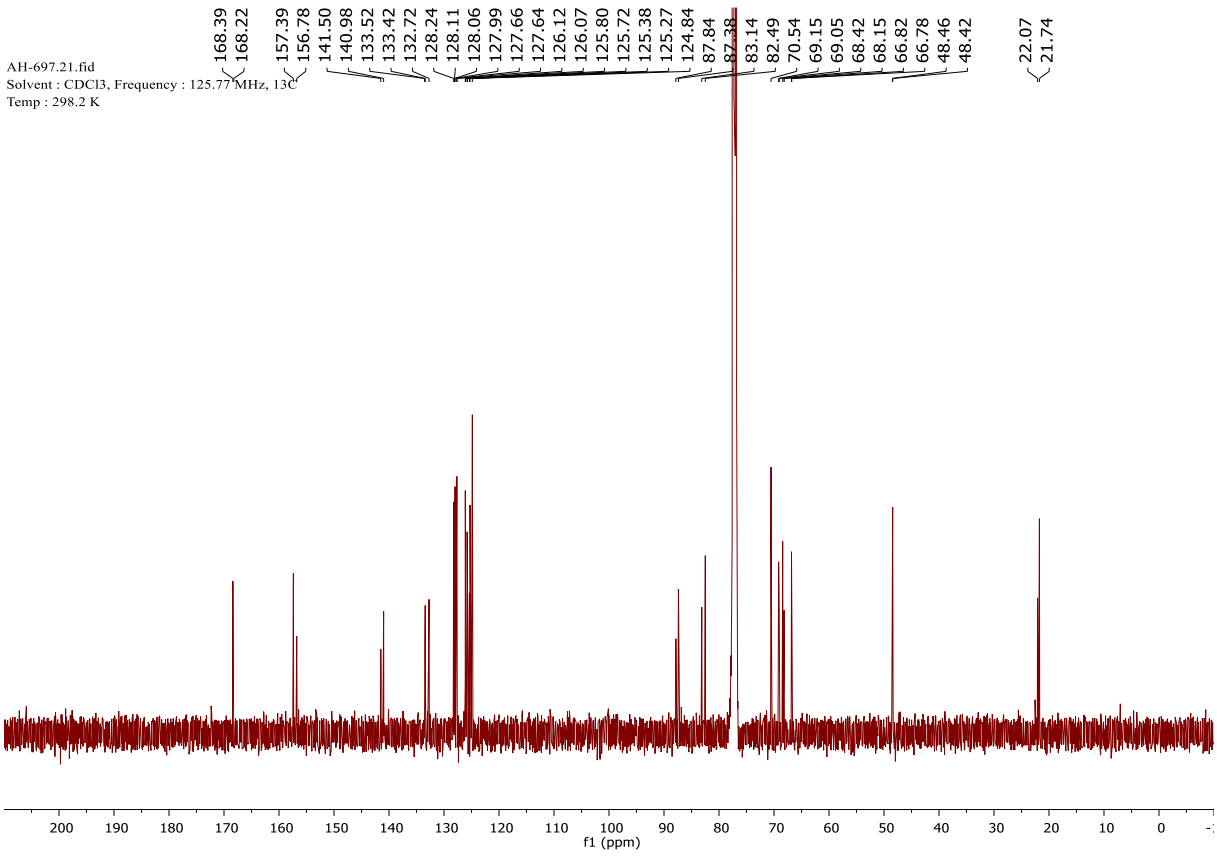
5.19 Compound of (*S*,*S*,*S*,*S*)-**3n**



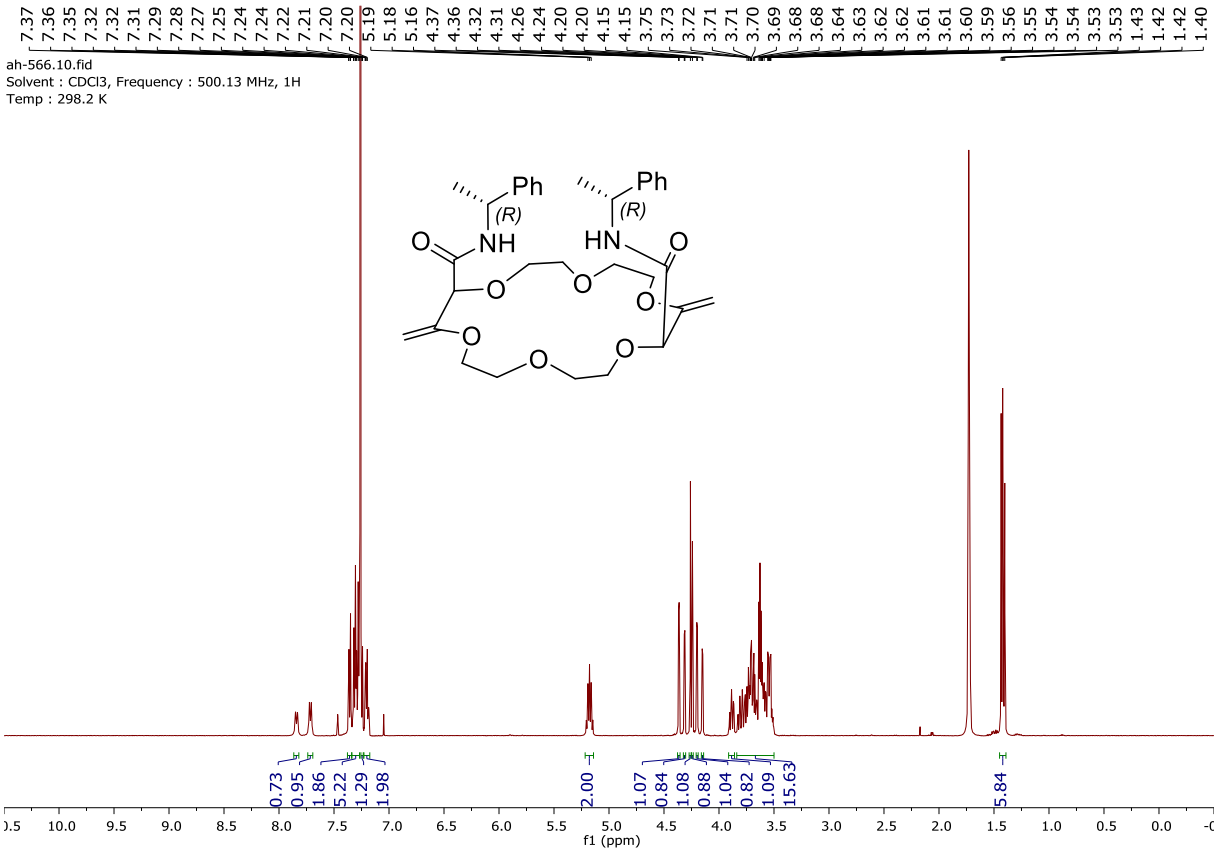


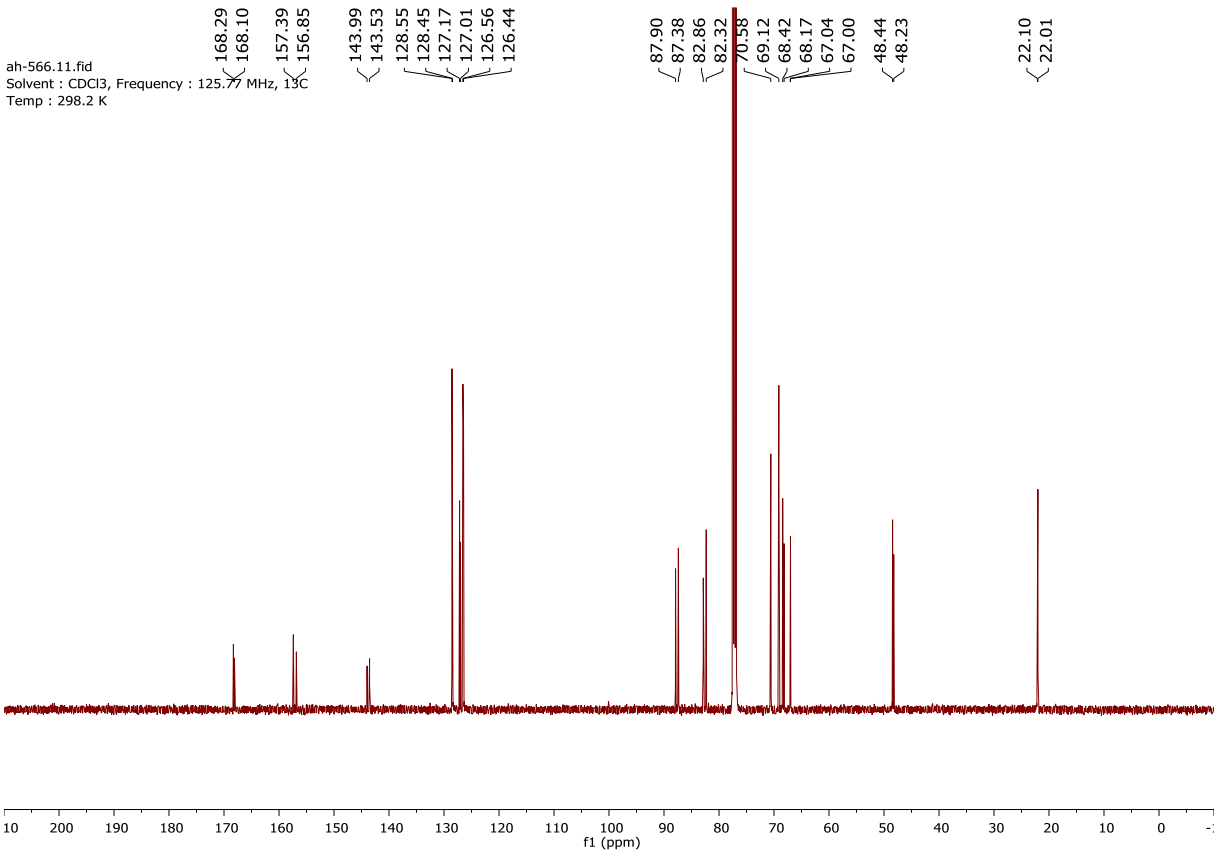
5.20 Compound of **3o**



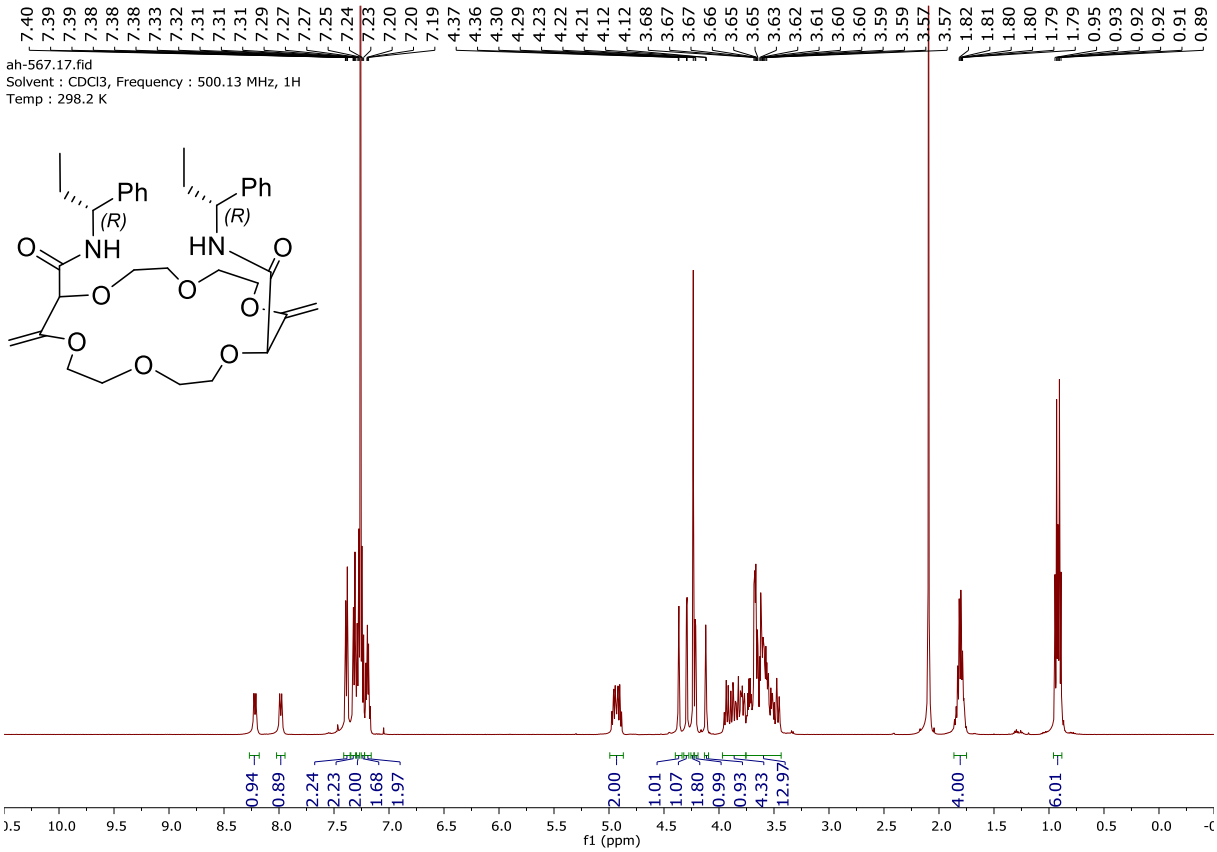


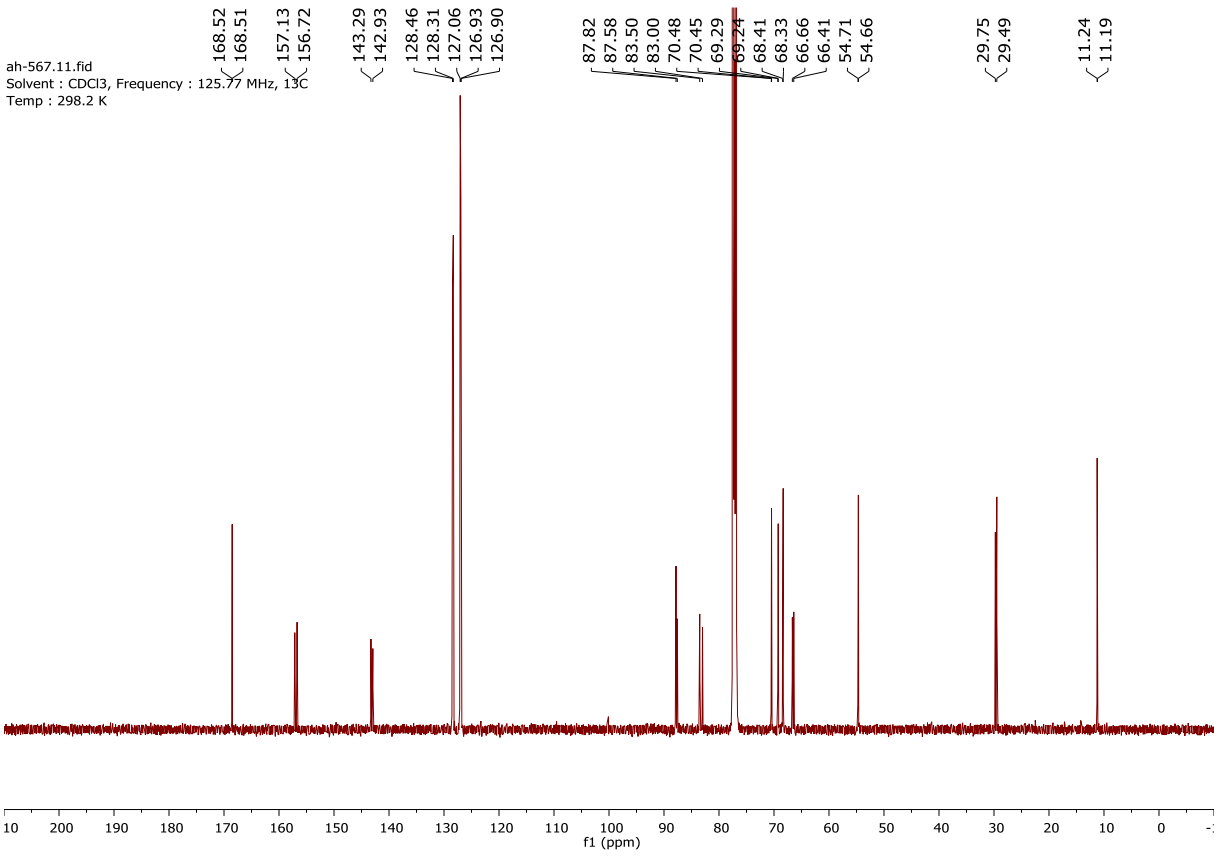
5.21 Compound of **3p**



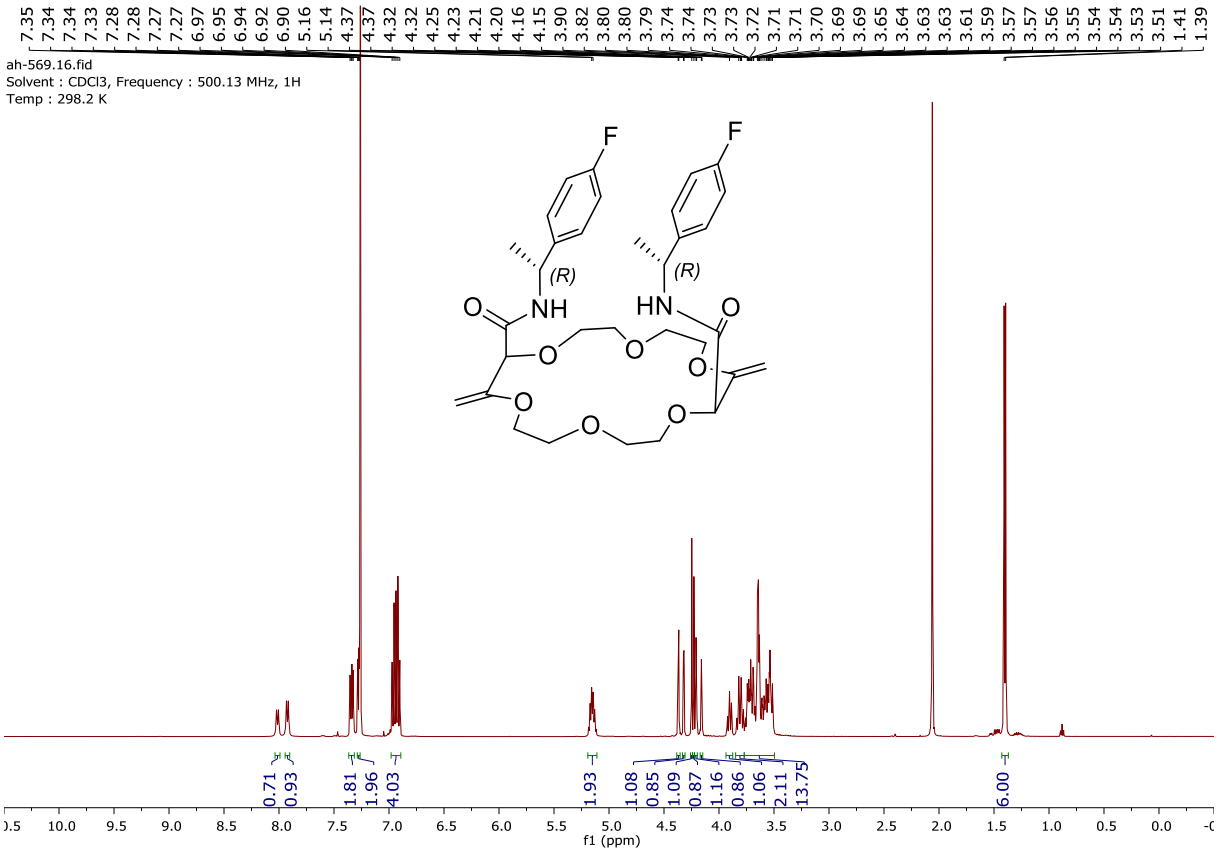


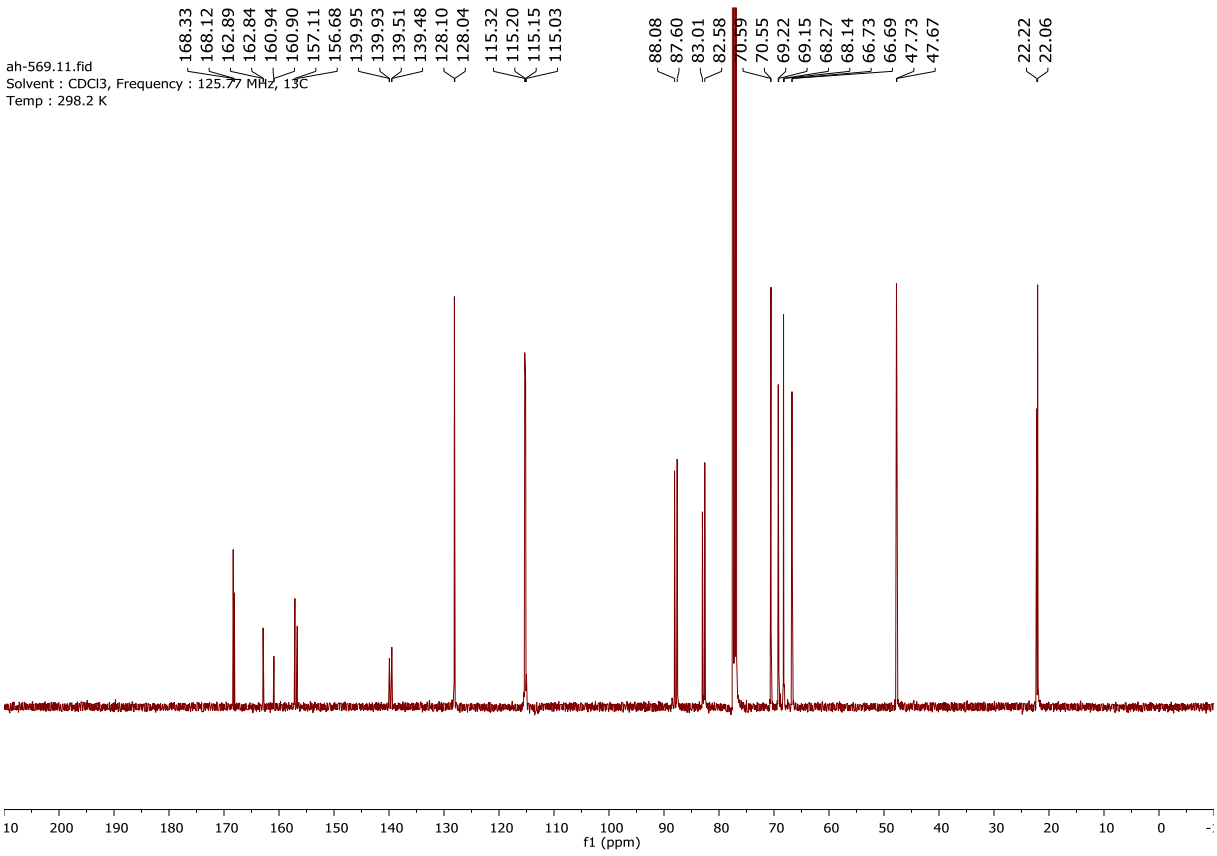
5.22 Compound of **3q**

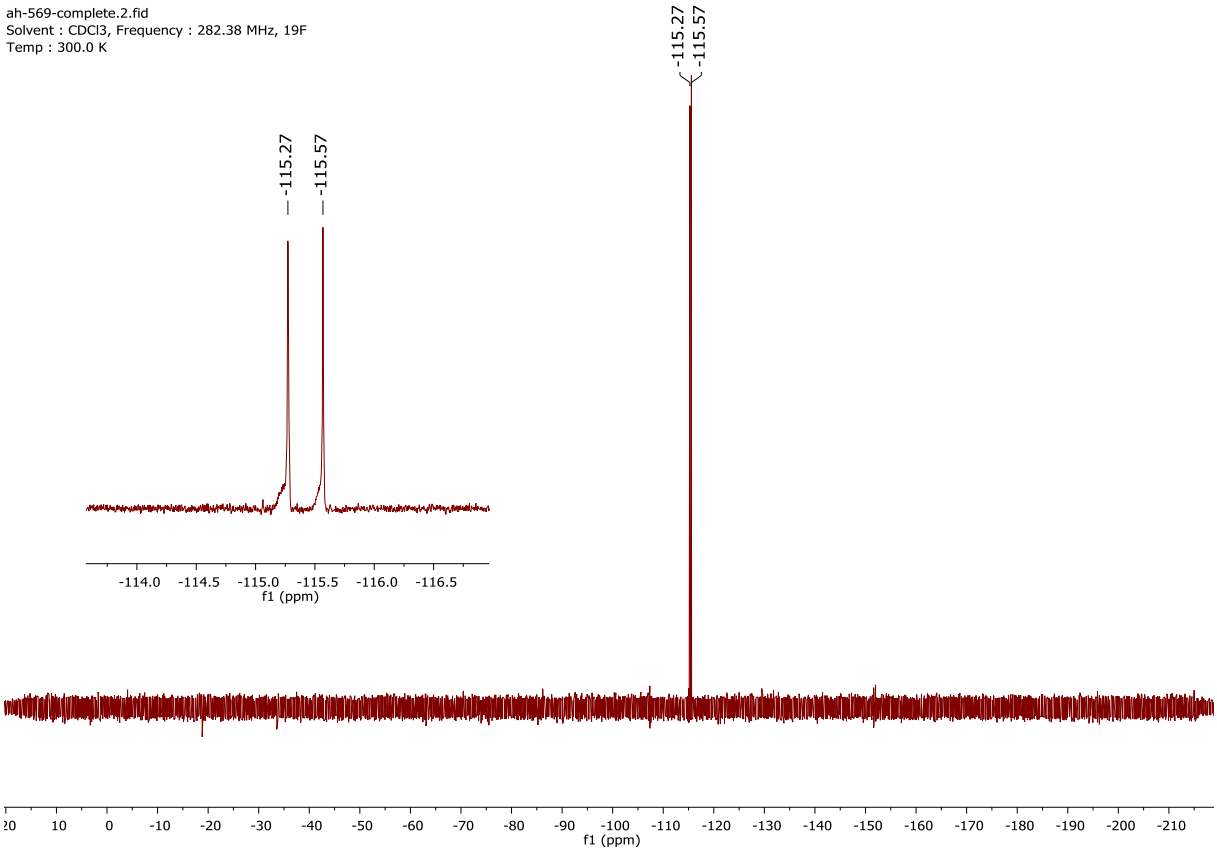




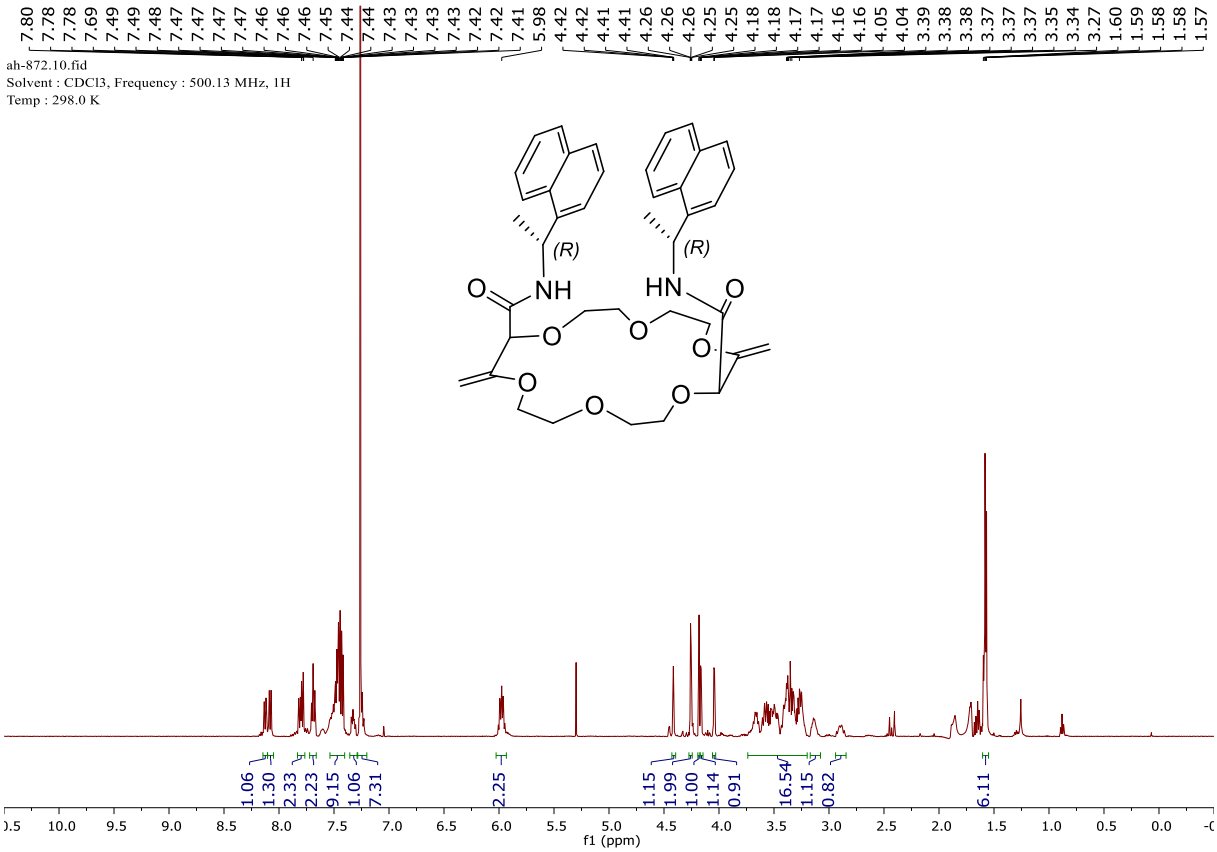
5.23 Compound of **3r**

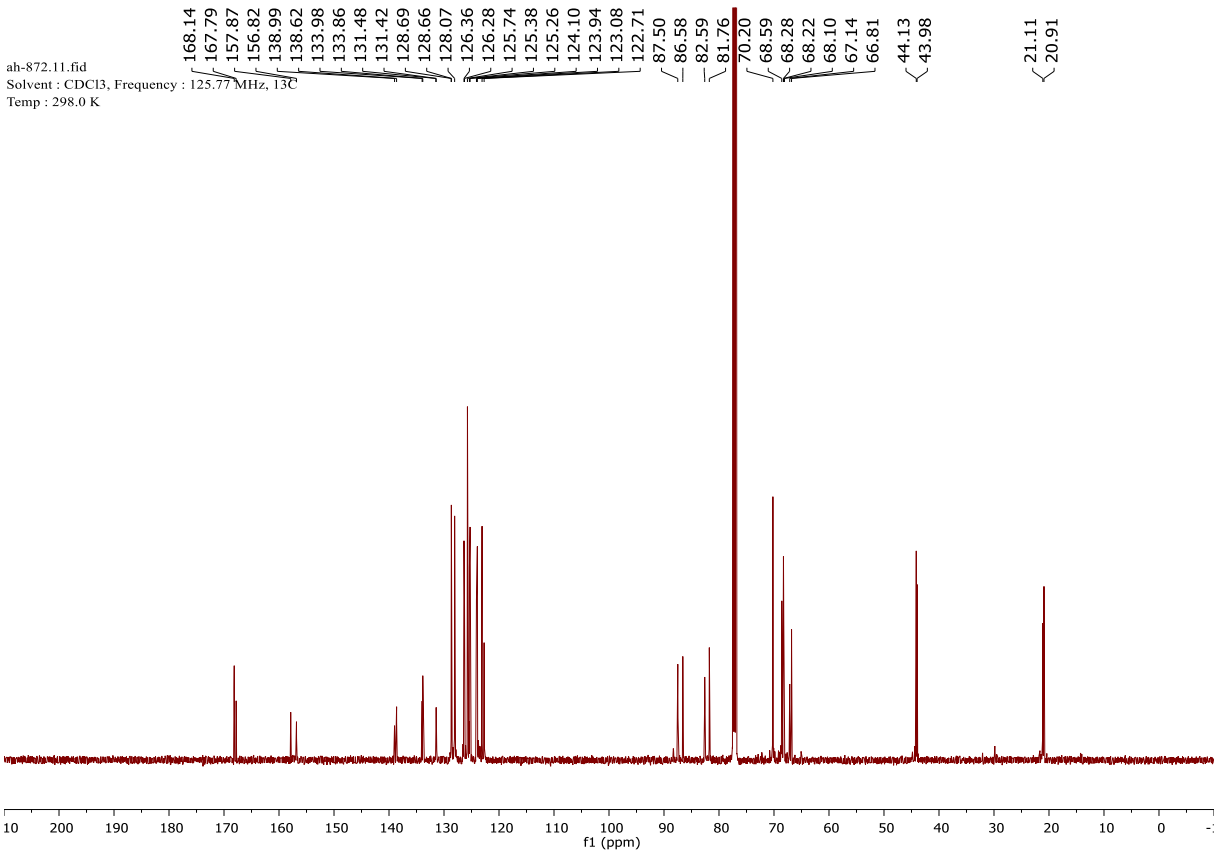




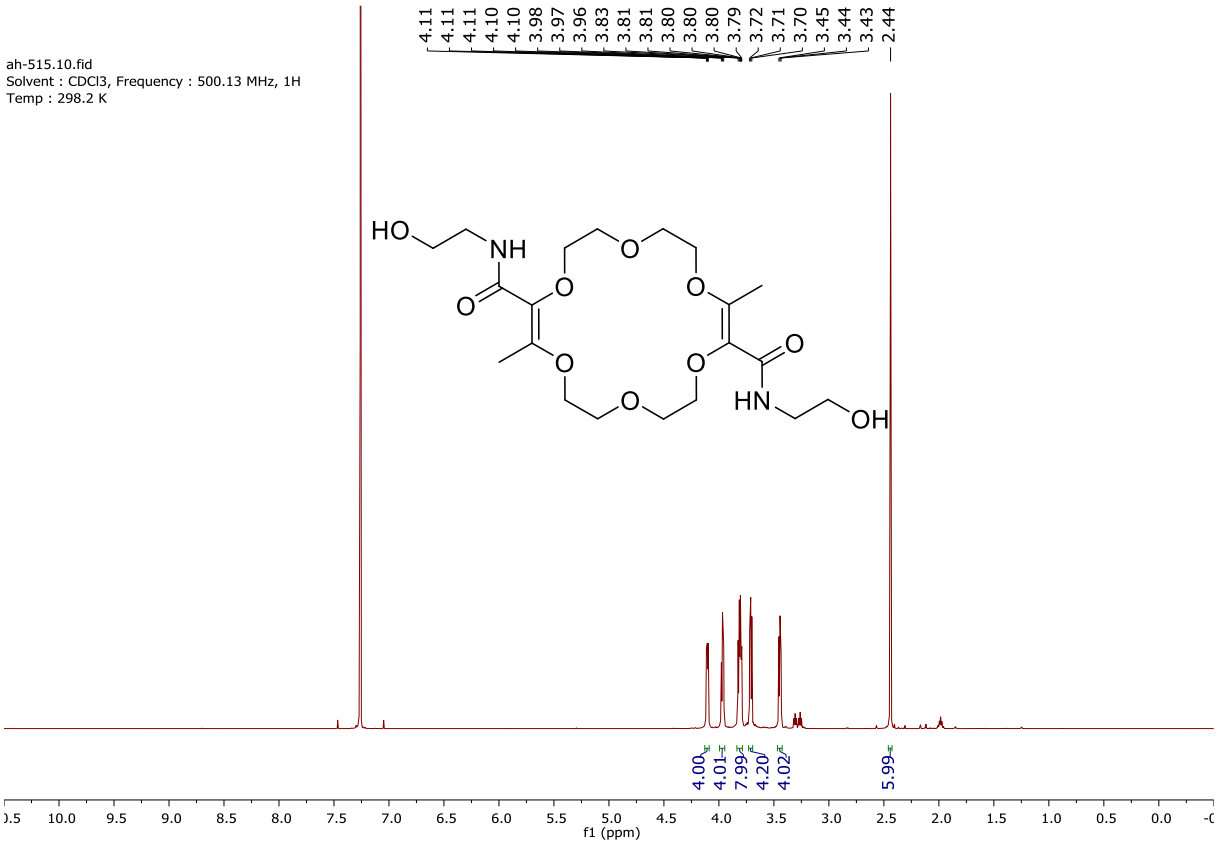

ah-569-complete.2.fid
Solvent : CDCl3, Frequency : 282.38 MHz, 19F
Temp : 300.0 K
-115.27
-115.57
-115.27
-115.57
-114.0
-114.5
-115.0
-115.5
-116.0
-116.5
f1 (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

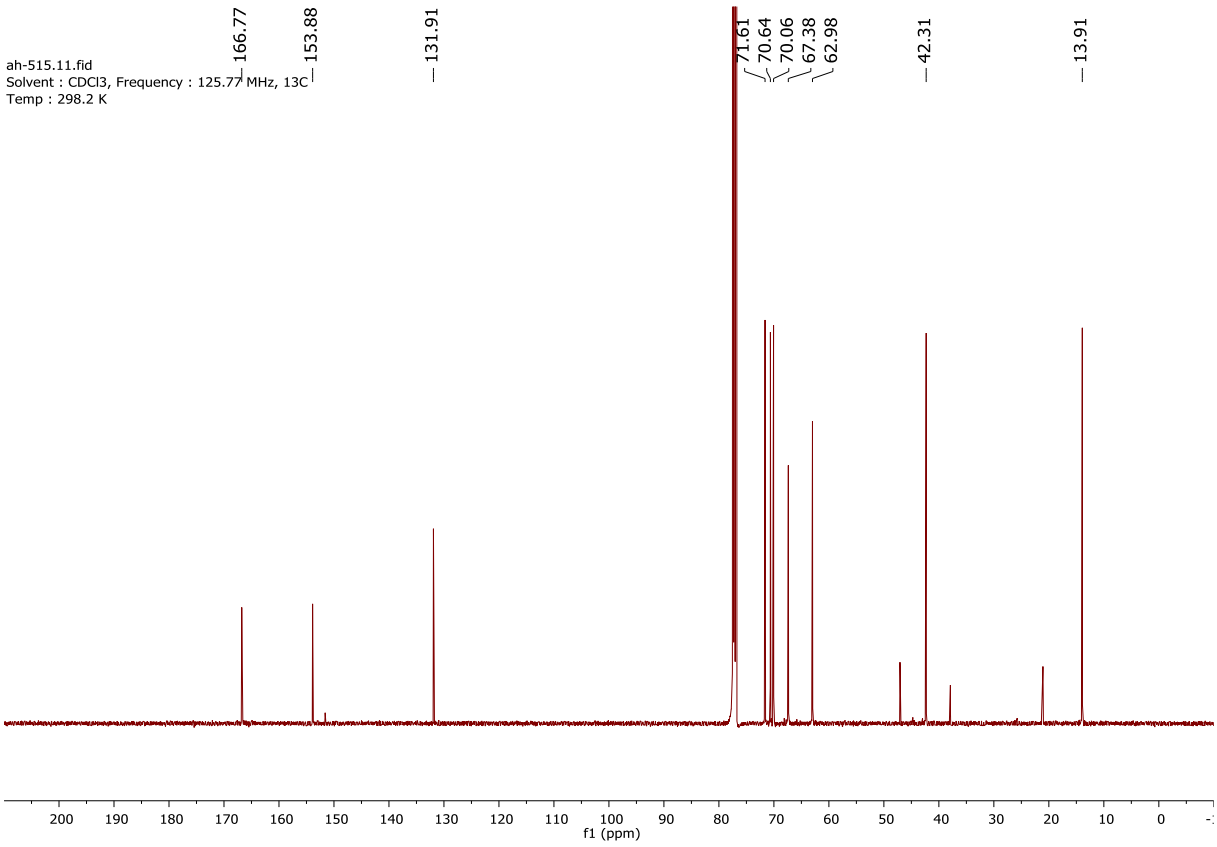
5.24 Compound of **3s**

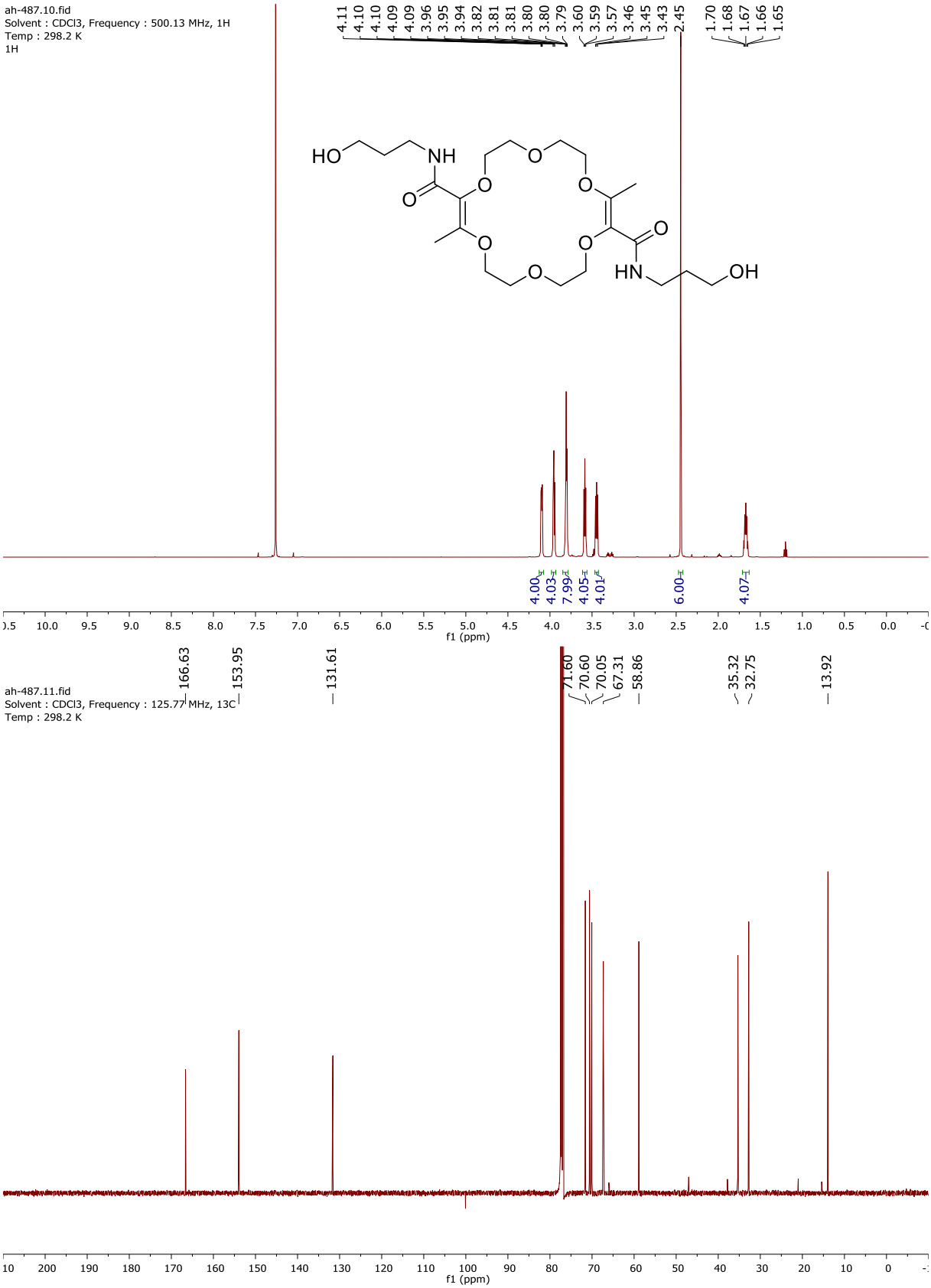




5.25 Macrocycles with unprotected alcohol functional groups






ah-487.10.fid
Solvent : CDCl3, Frequency : 500.13 MHz, 1H
Temp : 298.2 K
1H
4.11
4.10
4.10
4.09
4.09
3.96
3.95
3.94
3.82
3.81
3.81
3.80
3.80
3.79
3.60
3.59
3.57
3.46
3.45
3.43
2.45
1.70
1.68
1.67
1.66
1.65
HO
NH
O
O
O
O
O
O
O
O
O
HN
OH
4.00
4.03
7.99
4.05
4.01
6.00
4.07
f1 (ppm)
ah-487.11.fid
Solvent : CDCl3, Frequency : 125.77 MHz, 13C
Temp : 298.2 K
166.63
153.95
131.61
71.60
70.60
70.05
67.31
58.86
35.32
32.75
13.92
f1 (ppm)

6 Coordination of water in **3a**

A NMR experiment was performed with **3a** with six different concentrations of the crown ether in $CDCl_3$ (8 mM to 116 mM, Figure S2-S3). Only a 0.9 ppm variation is observed. This observations seem to indicate that, in this case, water molecules are not naturally included inside the crown ether, on the contrary to bis-anilide derivatives.[4] This assumption was also corroborated by the fact that the intensity of the proton signal of H_2O remains constant upon incremental addition of macrocycle – this water originating from the solvent used for the NMR solution experiments and not from a possible water adduct.

Procedure: Six NMR tube were prepared with respectively 3 mg, 6 mg, 9 mg, 15 mg, 30 mg and 45 mg of **3a** in 700 µL of $CDCl_3$ of a freshly opened bottle. The spectra were recorded after 15 min in a 500 MHz spectrometer.

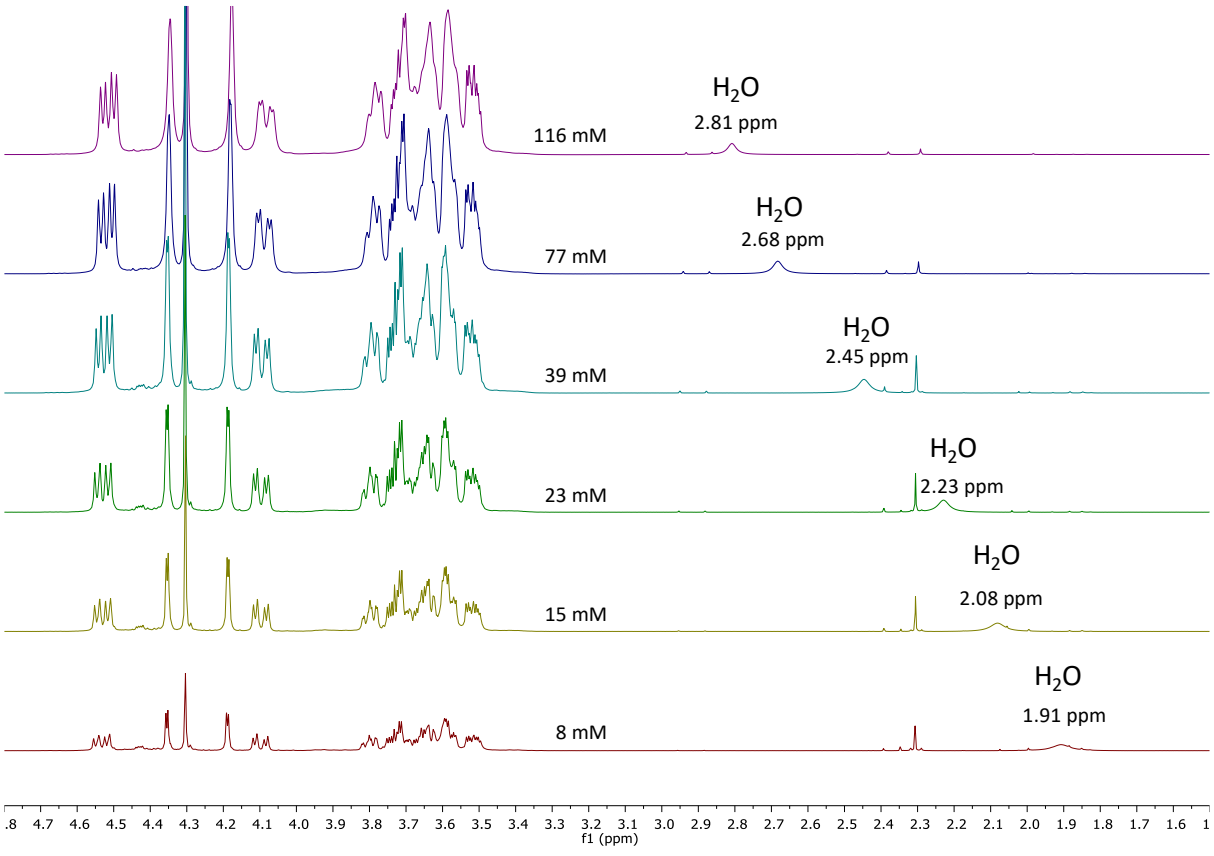


Figure S2. 3a concentration effect by ^1H NMR (400 MHz, δ 4.8-1.5 ppm, $CDCl_3$, 298K).

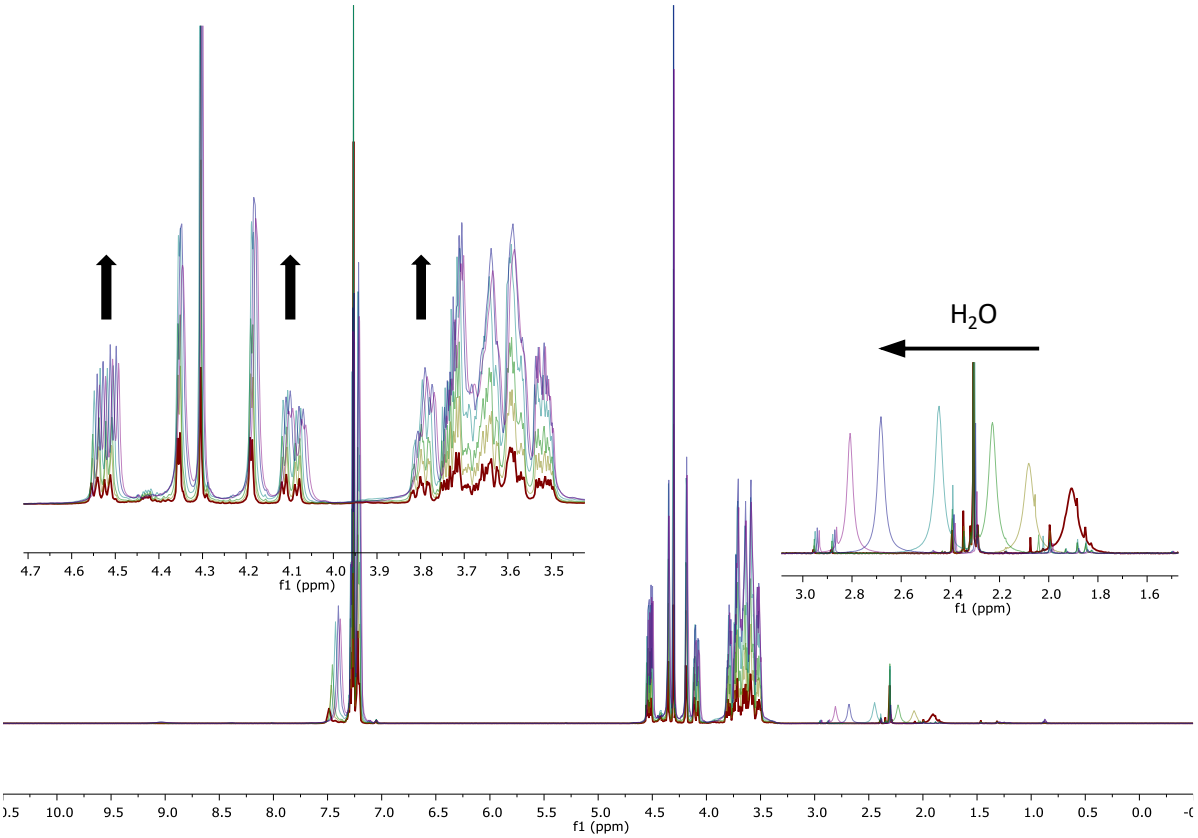
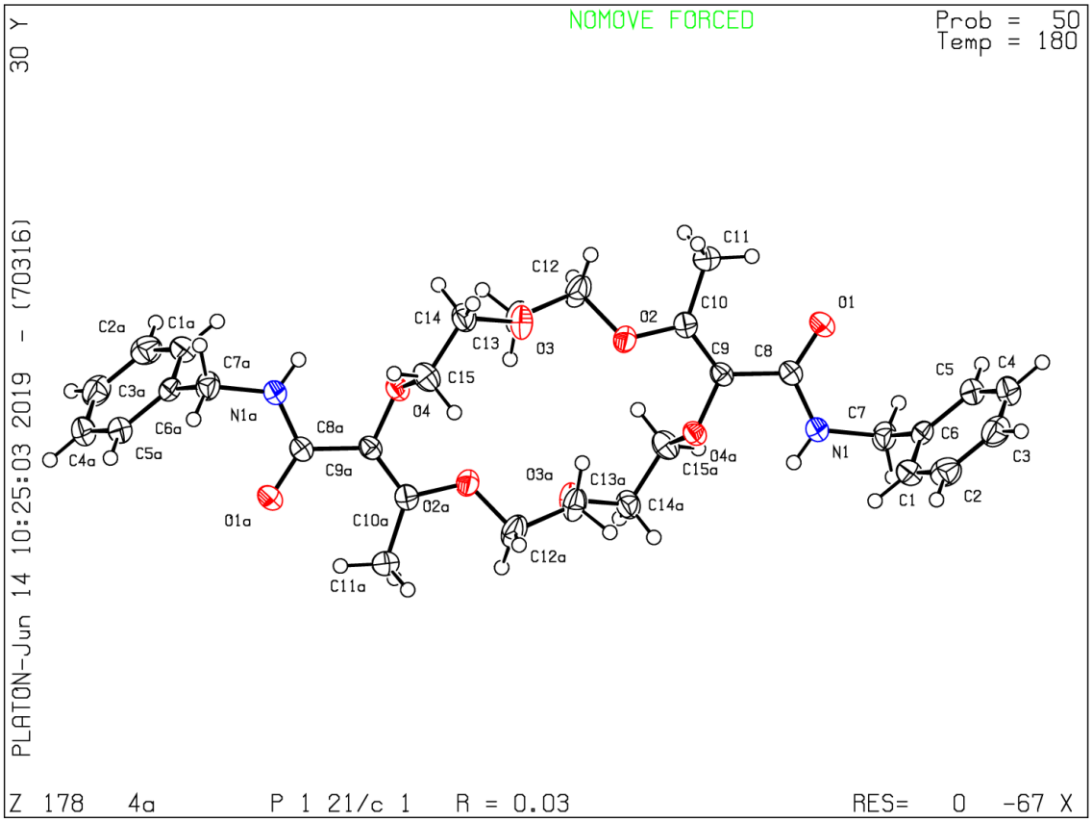


Figure S3. Effect of water signal shift as function of the concentration of **3a**. ^{1}H NMR spectra (500 MHz, -0.5-10.5 ppm), $CDCl_3$, 298 K.

7 Crystallographic data

7.1 Crystallographic data of **4a**

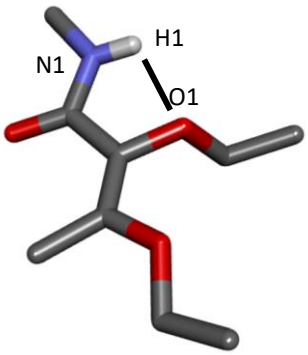


CCDC number	1923025	
Empirical formula	$C_{30}H_{38}N_2O_8$	
Formula weight	554.62	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 17.6634(5) Å	α = 90°.
	b = 8.6515(2) Å	β = 100.296(3)°.
	c = 9.4505(3) Å	γ = 90°.
Volume	1420.93(7) $Å^3$	
Z	2	
Density (calculated)	1.296 Mg/m^3	
Absorption coefficient	0.774 mm^{-1}	

F(000)	592
Crystal size	0.2707 x 0.1869 x 0.0762 mm^3
Theta range for data collection	5.09 to 73.69°.
Index ranges	-21<=h<=21, -10<=k<=10, -11<=l<=11
Reflections collected	10598
Independent reflections	2838 [R(int) = 0.0197]
Completeness to theta = 67.50°	100.0 %
Absorption correction	Analytical
Max. and min. transmission	0.946 and 0.834
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2838 / 0 / 186
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0871
R indices (all data)	R1 = 0.0367, wR2 = 0.0907
Largest diff. peak and hole	0.211 and -0.185 $e.Å^{-3}$

Comments: the molecule is located around a symmetry center (in the middle of the crown ether) thus leading to only one half of the molecule in the asymmetric unit. There is one intermolecular hydrogen bond (see **Table S6**).

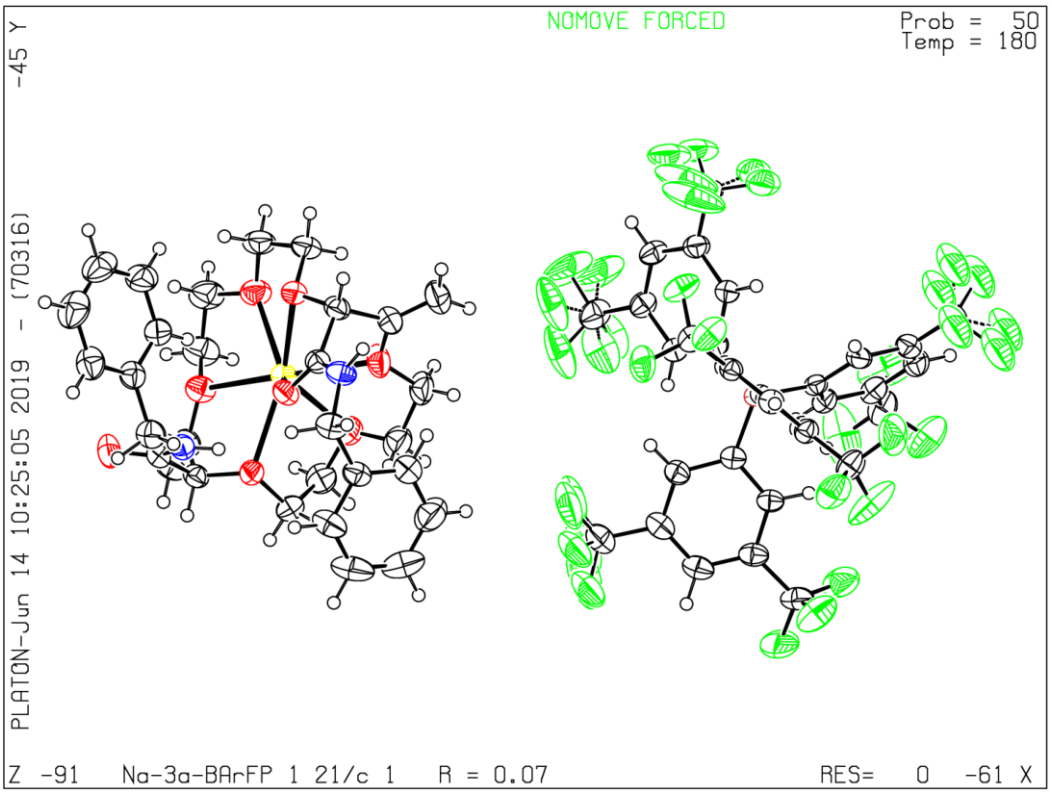
Table S6. Hydrogen bonds for **4a** [Å and °].



D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#2	0.867(15)	2.180(16)	2.9129(12)	142.0(13)

Symmetry transformations used to generate equivalent atoms: #1 -x+1, -y+1, -z #2 x, -y+3/2, z-1/2

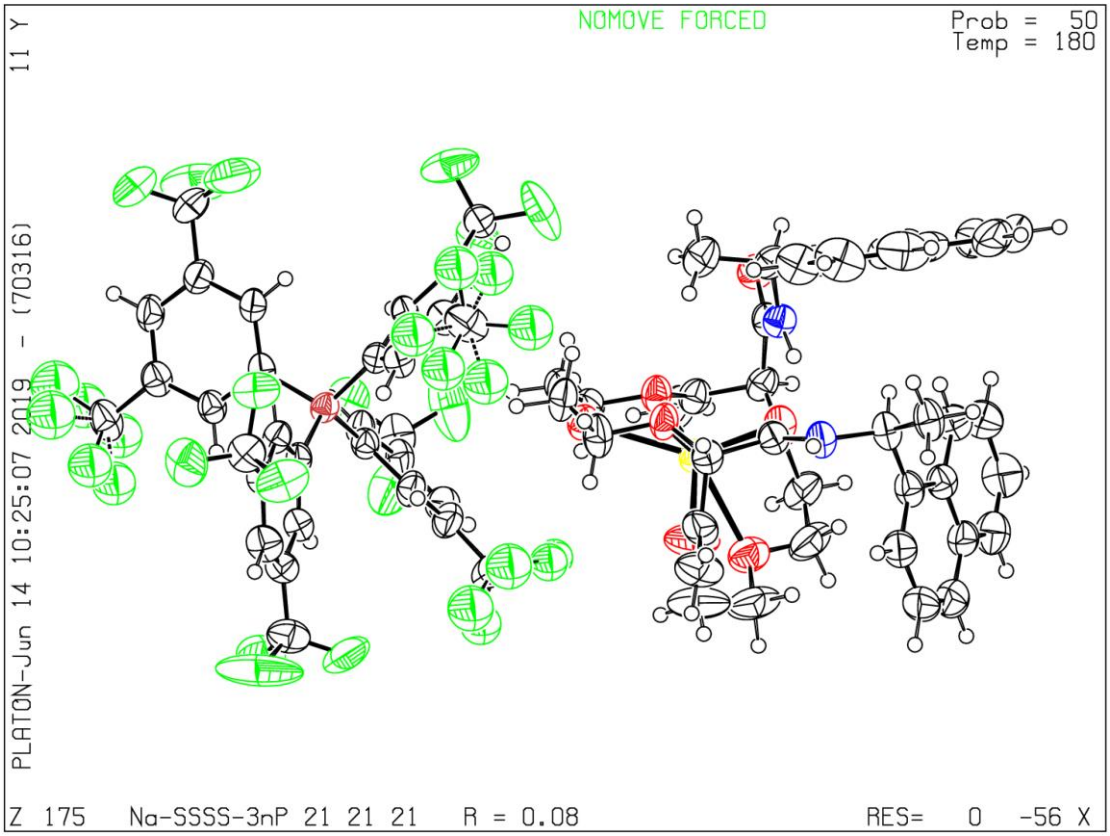
7.2 Crystallographic data of [Na·**3a**][BAr_F]



CCDC number	1923026	
Empirical formula	$C_{62}H_{50}BF_{24}N_2NaO_8$	
Chemical formula moiety	$C_{30}H_{38}N_2NaO_8$, $C_{32}H_{12}BF_{24}$	
Formula weight	1440.84	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 17.7333(3) Å	α = 90°.
	b = 20.1120(3) Å	β = 93.8737(13)°.
	c = 18.2281(3) Å	γ = 90°.
Volume	6486.24(18) $Å^3$	
Z	4	
Density (calculated)	1.475 Mg/m^3	
Absorption coefficient	1.327 mm^{-1}	
F(000)	2928	
Crystal size	0.6999 x 0.4418 x 0.1806 mm^3	

Theta range for data collection	3.33 to 73.65°.
Index ranges	-17<=h<=21, -22<=k<=24, -22<=l<=18
Reflections collected	26287
Independent reflections	12752 [R(int) = 0.0233]
Completeness to theta = 67.50°	99.9 %
Absorption correction	Analytical
Max. and min. transmission	0.801 and 0.545
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12752 / 0 / 911
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0747, wR2 = 0.2070
R indices (all data)	R1 = 0.0820, wR2 = 0.2163
Largest diff. peak and hole	1.390 and -0.973 e.$Å^{-3}$

7.3 Crystallographic data of [Na(*S*,*S*,*S*,*S*)-**3n**][BAr_F]



CCDC number	1923027	
Empirical formula	$C_{72}H_{58}BF_{24}N_2NaO_8$	
Formula weight	1569.00	
Temperature	180.15 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 18.8583(7) Å	α = 90°.
	b = 19.3929(5) Å	β = 90°.
	c = 19.5642(7) Å	β = 90°.
Volume	7155.0(4) $Å^3$	
Z	4	
Density (calculated)	1.457 Mg/m^3	
Absorption coefficient	1.254 mm^{-1}	
F(000)	3200	
Crystal size	0.358 x 0.128 x 0.085 mm^3	
Theta range for data collection	3.209 to 73.620°.	

Index ranges	-23<=h<=22, -23<=k<=13, -24<=l<=16
Reflections collected	18332
Independent reflections	12202 [R(int) = 0.0448]
Completeness to theta = 67.500°	99.9 %
Absorption correction	Analytical
Max. and min. transmission	0.917 and 0.772
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12202 / 0 / 961
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0823, wR2 = 0.2183
R indices (all data)	R1 = 0.0993, wR2 = 0.2426
Absolute structure parameter	-0.19(19)
Extinction coefficient	n/a
Largest diff. peak and hole	0.906 and -0.611 e.$Å^{-3}$

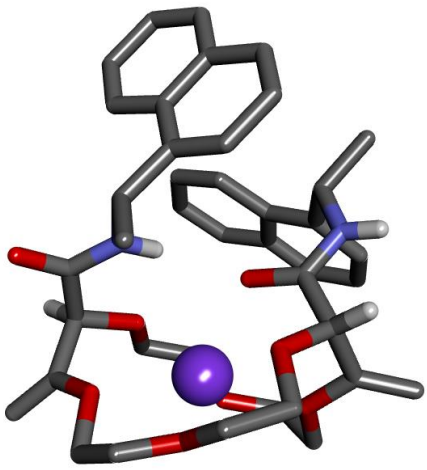


Figure S4. Stick view of the crystal structures of (*S*,*S*,*S*,*S*)-**3n**, major diastereoisomer, second eluted. Hydrogen atoms are hidden for clarity.

8 References

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