One-Step Synthesis of Diaza Macrocycles by Rh(II)-Catalyzed [3+6+3+6] Condensations of Morpholines and α-Diazo-β-ketoesters

Supporting Information

Alexandre Homberg,[†] Daniele Poggiali,[†] Mahesh Vishe,[†] Céline Besnard,[‡] Laure Guénée[‡] and Jérôme Lacour*,[†]

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

[‡]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, $CHCl_3$, $CDCl_3$ and tetrahydrofuran). Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. *t*-BuOK was sublimed prior to use.

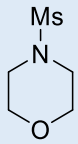
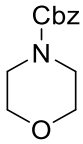
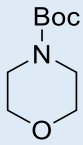
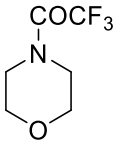
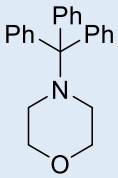
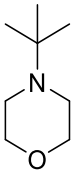
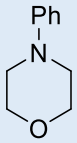
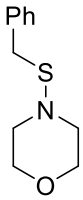
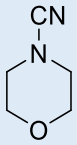
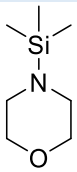
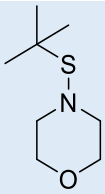
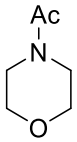
Analytical thin-layer chromatography (TLC) were performed with Silicagel 60 F_{254} aluminum sheets from Merck. Flash column chromatography were performed with Silica SiliaFlash P60, 40-63 µm (230-400 mesh). NMR spectra were recorded on a Bruker AVANCE I 300 MHz spectrometer, equipped with a 5 mm QNP D133 probe, a Bruker AVANCE III HD-*NanoBay* 300 MHz spectrometer, equipped with a 5 mm BB(F)-H-D probe, on a Bruker AVANCE 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, DMSO-d_6 δ = 2.50 ppm, acetone-d_6 δ = 2.05 ppm, CD_2Cl_2 δ = 5.32 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, DMSO-d_6 δ = 39.52 ppm, acetone-d_6 δ = 29.84 ppm, CD_2Cl_2 δ = 54.00 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). GC-MS analyses were performed on a HP-5MS achiral 6890 GC chromatograph coupled with an Agilent 5973 Network mass-selective detector (column 30 m x 250 µm with He as carrier gaz).

2 Synthesis and characterization of organic compounds

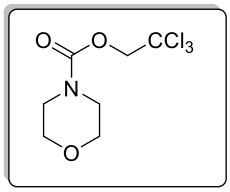
2.1 Synthesis of morpholines

Protected morpholines **2** were purchased from commercial sources or prepared according to reported literature (Table **S1**):

Table S1. References for the synthesis of morpholines.

Entry	Morpholine		Reference
1		**2a**	[1]
2		**2b**	[2]
3		**2c**	[3]
4		**2e**	[4]
5		**2f**	[5]
6		**2g**	[6]
7		**2h**	commercial
8		**2i**	[7]
9		**2j**	commercial
10		**2k**	commercial
11		**2l**	[7]
12		**2m**	commercial

2.2 Synthesis of 2,2,2-trichloroethyl morpholine-4-carboxylate **2d**



In a 100 mL flask, 5.0 g (57.4 mmol) of morpholine and 8.81 mL (63.1 mmol, 1.1 equiv.) of triethylamine are dissolved in 10 mL of CH_2Cl_2. To this stirred solution, 8.63 mL (60.3 mmol, 1.05 equiv.) of 2,2,2-trichloroethyl chloroformate are added dropwise over 1 hour (Caution: very vigorous reaction) and the mixture is stirred for 15 hours at 25 °C. The volatiles are evaporated and the product is purified by column chromatography (SiO_2, Et_2O/pentane gradient 3:7 then 4:6) to yield 14.9 g (56.6 mmol, 262.51 g/mol, 98%) of 2,2,2-trichloroethyl morpholine-4-carboxylate **2d** as a white solid.

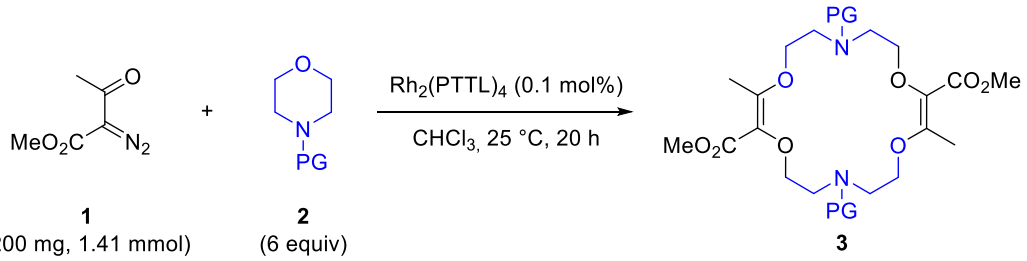
R_f = 0.65 (SiO_2, EtOAc/pentane 1:1)
m.p.: 49.5 °C
^{1}H-NMR (500 MHz, DMSO-*d_6*, 333 K): δ/ppm = 3.46 (s, 4H, -CH_2-), 3.60 – 3.62 (m, 4H, -CH_2-), 4.85 (s, 2H, -CH_2-).
^{13}C-NMR (126 MHz, DMSO-*d_6*, 333 K): δ/ppm = 43.9 (1 -CH_2-), 65.5 (2 -CH_2-), 74.1 (2 -CH_2-), 95.7 (1 CCl_3), 152.6 (1 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2977, 2858, 1703, 1460, 1424, 1362, 1302, 1275, 1239, 1220, 1135, 1099, 1050, 1026, 957, 841, 819, 751, 715, 637, 587, 569, 551, 501.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_7H_{11}Cl_3NO_3$ 261.9799, observed 261.9800.

2.3 Synthesis of diaza-polyether macrocycle

2.3.1 Procedure for the screening of Rh(II) catalysts

In a 10 ml vial, Rh(II) catalyst (Table **S2**) and 349 mg (2.11 mmol, 6 equiv.) of *N*-mesyl morpholine **2a** are dissolved in 0.7 ml of $CDCl_3$. To this solution, 50 mg (0.35 mmol) of α-diazo-β-ketoester **1** is added in one portion. The vial is sealed and the solution stirred at 25 °C for 20 hours. The conversion of the diazo reagent is monitored by TLC analysis and infrared spectroscopy (2146 cm^{-1}). After completion of the reaction, an aliquot of 0.15 mL is taken and 0.35 mL of a $5 \cdot 10^{-3}$ M of a 1,4-bis(trimethylsilyl)benzene solution are added. The crude mixture is analyzed by ^1H NMR (and GC-MS, see section 6) and results are reported in Table **1**.

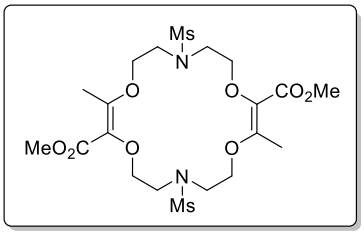
2.3.2 General procedure for the synthesis of diaza-polyether macrocycle



(S1)

In a 10 ml vial, 2 mg (0.00141 mmol, 0.1 mol%) of Rh_2(*S*-PTTL)$_4$ and *N*-protected morpholine **2** (8.46 mmol, 6 equiv.) are dissolved in 2.8 ml of $CHCl_3$. To this solution, 200 mg (1.41 mmol) of α-diazo-β-ketoester **1** is added in one portion. The vial is sealed and the solution stirred at 25 °C for 20 hours. The conversion of the diazo reagent is monitored by TLC analysis and infrared spectroscopy (2146 cm^{-1}). After completion of the reaction, the volatiles are evaporated and the corresponding macrocycle **3** is isolated by column chromatography or selective precipitation.

2.3.3 Synthesis of N-mesyl diaza-polyether macrocycle **3a**

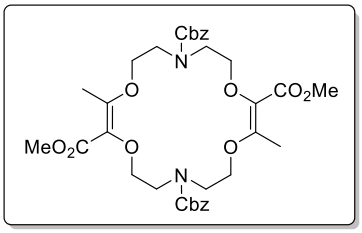


According to the general procedure, 1.40 g (8.46 mmol, 6 equiv.) of *N*-mesyl protected morpholine **2a** yield 61% (240 mg, 0.43 mmol, 558.61 g/mol) of *N*-mesyl diaza-polyether macrocycle **3a** as a white solid.

Purification conditions: 10 mL of MeOH/pentane (1:1) are added to the crude solid. The heterogeneous solution is stirred for 2 hours a 25 °C and the solid is filtered and washed with MeOH/pentane (1:1).

R_f = 0.31 (SiO_2, CH_2Cl_2/MeOH 96:4)
m.p.: 156 °C
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.38 (s, 6H, -CH_3), 2.98 (s, 6H, -CH_3), 3.72 (t, *J* = 5.1 Hz, 4H, -CH_2-), 3.74 (s, 6H, -CH_3), 3.78 (t, *J* = 5.6 Hz, 4H, -CH_2-), 3.88 (t, *J* = 5.6 Hz, 4H, -CH_2-), 4.17 (t, *J* = 5.1 Hz, 4H, -CH_2-).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 13.2 (2 -CH_3), 38.5 (2 -CH_3), 47.4 (2 -CH_2-), 48.0 (2 -CH_2-), 50.6 (2 -CH_3), 68.1 (2 -CH_2-), 70.3 (2 -CH_2-), 128.5 (2 =C), 157.5 (2 =C), 164.9 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2945, 2880, 1703, 1621, 1437, 1388, 1309, 1265, 1187, 1140, 1087, 1042, 1014, 1014, 998, 970, 941, 912, 861, 828, 774, 700.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{20}H_{35}N_2O_{12}S_2$ 559.1626, observed 559.1615.

2.3.4 Synthesis of N-benzyl carbamate diaza-polyether macrocycle **3b**

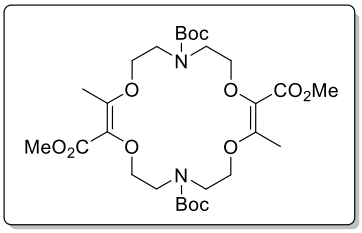


According to the general procedure, 1.87 g (8.46 mmol, 6 equiv.) of *N*-benzyl carbamate protected morpholine **2b** yield 72% (340 mg, 0.51 mmol, 670.71 g/mol) of *N*-benzyl carbamate diaza-polyether macrocycle **3b** as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: EtOAc/pentane (4:6)

R_f = 0.26 (SiO_2, EtOAc/pentane 1:1)
m.p.: 120 °C
^{1}H-NMR (400 MHz, DMSO-d_6, 368 K): δ/ppm = 2.24 (s, 6H, -CH_3), 3.63 – 3.70 (m, 14H, -CH_2-, -CH_3), 3.74 - 3.78 (m, 4H, -CH_2-), 4.10 (t, *J* = 5.2 Hz, 4H, -CH_2-), 5.11 (s, 4H, -CH_2-), 7.29 – 7.39 (m, 10H, aromatics).
^{13}C-NMR (101 MHz, DMSO-d_6, 368 K): δ/ppm = 13.2 (2 -CH_3), 47.2 (2 -CH_2-), 47.5 (2 -CH_2-), 50.3 (2 -CH_3), 66.0 (2 -CH_2-), 66.9 (2 -CH_2-), 70.1 (2 -CH_2-), 126.9 (4 CH aromatics), 127.2 (2 CH aromatics), 127.8 (4 CH aromatics), 128.9 (2 =C), 136.4 (2 C aromatics), 154.8 (2 C=O), 156.7 (2 =C), 164.9 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2947, 1698, 1612, 1476, 1451, 1407, 1389, 1365, 1301, 1276, 1231, 1184, 1142, 1097, 1017, 996, 972, 871, 770, 727, 692, 618.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{43}N_2O_{12}$ 671.2811, observed 671.2799.

2.3.5 Synthesis of N-t-Bu carbamate diaza-polyether macrocycle **3c**

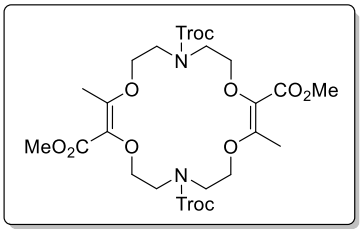


According to the general procedure, 1.58 g (8.46 mmol, 6 equiv.) of *N-t*-butyl carbamate protected morpholine **2c** yield 70% (297 mg, 0.49 mmol, 602.68 g/mol) of *N-t*-butyl carbamate diaza-polyether macrocycle **3c** as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: EtOAc/pentane gradient (4:6 then 5:5)

R_f = 0.28 (SiO_2, EtOAc/pentane 1:1)
m.p.: 131 °C
^{1}H-NMR (500 MHz, DMSO-d_6, 343 K): δ/ppm = 1.41 (s, 18H, -CH_3), 2.30 (s, 6H, -CH_3), 3.55 (t, *J* = 5.1 Hz, 4H, -CH_2-), 3.60 (t, *J* = 6.5 Hz, 4H, -CH_2-), 3.66 (s, 6H, -CH_3), 3.71 (dd, *J* = 7.2, 5.9 Hz, 4H, -CH_2-), 4.08 (t, *J* = 5.0 Hz, 4H, -CH_2-).
^{13}C-NMR (126 MHz, DMSO-d_6, 343 K): δ/ppm = 13.3 (2 -CH_3), 27.7 (6 -CH_3), 47.0 (2 -CH_2-), 47.0 (2 -CH_2-), 50.6 (2 -CH_3), 67.4 (2 -CH_2-), 70.2 (2 -CH_2-), 78.7 (2 C), 128.6 (2 =C), 154.2 (2 C=O), 157.4 (2 =C), 165.2 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2955, 1686, 1620, 1461, 1427, 1407, 1386, 1364, 1301, 1263, 1144, 1090, 1011, 967, 944, 858, 801, 763, 641, 605, 524.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{28}H_{47}N_2O_{12}$ 603.3124, observed 603.3125.

2.3.6 Synthesis of N-2,2,2-trichloroethoxy carbamate diaza-polyether macrocycle **3d**

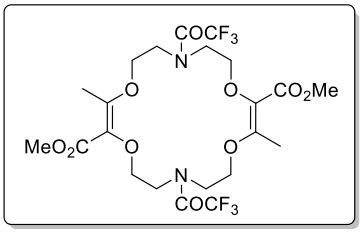


According to the general procedure, 2.22 g (8.46 mmol, 6 equiv.) of *N*-2,2,2-trichloroethoxy carbamate protected morpholine **2d** yield 74% (393 mg, 0.53 mmol, 753.22 g/mol) of *N*-2,2,2-trichloroethoxy carbamate diaza-polyether macrocycle **3d** as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: EtOAc/pentane (3:7)

R_f = 0.58 (SiO_2, EtOAc/pentane 1:1)
m.p.: 137 °C
^{1}H-NMR (400 MHz, DMSO-d_6, 368 K): δ/ppm = 2.29 (s, 6H, -CH_3), 3.66 (s, 6H, -CH_3), 3.72 - 3.84 (m, 12H, -CH_2-), 4.17 (t, *J* = 4.6 Hz, 4H, -CH_2-), 4.84 (s, 4H, -CH_2-).
^{13}C-NMR (101 MHz, DMSO-d_6, 368 K): δ/ppm = 13.2 (2 -CH_3), 47.5 (2 -CH_2-), 47.9 (2 -CH_2-), 50.4 (2 -CH_3), 66.8 (2 -CH_2-), 70.0 (2 -CH_2-), 74.1 (2 -CH_2-), 95.6 (2 CCl_3), 128.9 (2 =C), 153.2 (2 C=O), 156.8 (2 =C), 164.8 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2949, 1705, 1624, 1468, 1414, 1392, 1376, 1275, 1225, 1187, 1134, 1084, 1057, 1040, 1017, 995, 968, 921, 866, 838, 814, 780, 761, 711, 608.
HR MS (ESI) $[M+Na]^+$ *m/z* calculated for $C_{24}H_{32}Cl_6N_2O_{12}Na$ 772.9977, observed 772.9979.

2.3.7 Synthesis of N-trifluoroacetamide diaza-polyether macrocycle **3e**



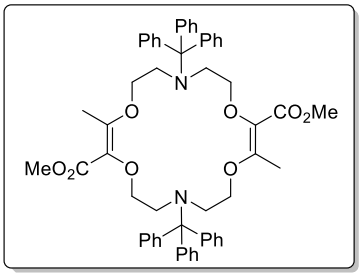
According to the general procedure, 1.55 g (8.46 mmol, 6 equiv.) of *N*-trifluoroacetamide protected morpholine **2e** yield 55% (231 mg, 0.39 mmol, 594.46 g/mol) of *N*-trifluoroacetamide diaza-polyether macrocycle **3e** as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: EtOAc/pentane (4:6)

R_f = 0.47 (SiO_2, EtOAc/pentane 1:1)
m.p.: 147 °C
^{1}H-NMR (300 MHz, DMSO-d_6, 393 K): δ/ppm = 2.31 (s, 6H, -CH_3), 3.70 (s, 6H, -CH_3), 3.85 – 3.99 (m, 12H, -CH_2-), 4.23 (t, *J* = 5.0 Hz, 4H, -CH_2-).
^{13}C-NMR (75 MHz, DMSO-d_6, 393 K): δ/ppm = 13.0 (2 -CH_3), 47.5 (4 -CH_2-), 50.2 (2 -CH_3), 65.8 (br(s), 2 -CH_2-), 69.6 (br(s), 2 -CH_2-), 115.8 (q, *J* = 288.8 Hz, 2 CF_3), 128.9 (2 =C), 155.7 (q, *J* = 35.4 Hz, 2 C=O), 156.4 (2 =C), 164.4 (2 C=O).
^{19}F-NMR (282 MHz, DMSO-d_6, 393 K): δ/ppm = -68.02 (2 -CF_3, broad). [8]
IR (neat): $\tilde{\nu}$/cm^{-1} 2954, 2343, 1689, 1623, 1434, 1379, 1299, 1271, 1207, 1177, 1141, 1091, 1048, 892, 861, 775, 759, 736, 704, 654.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{22}H_{29}N_2O_{10}F_{16}$ 595.1721, observed 595.1731.

Note on gram scale: **3e** is purified by first evaporation of the volatiles (mainly solvent) under reduced pressure. Then the excess of morpholine is distilled under high vacuum. The resulting crude solid is triturated with 20 mL of MeOH/pentane (1:1) and filtered. The white solid is finally washed carefully and slowly with an additional 20 mL of MeOH/pentane (1:1).

2.3.8 Synthesis of N-trityl diaza-polyether macrocycle *3f*

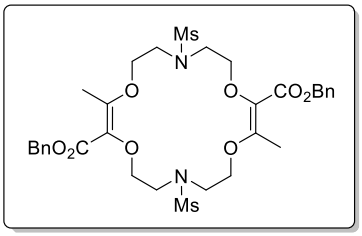


According to the general procedure, 2.79 g (8.46 mmol, 6 equiv.) of *N*-trityl protected morpholine **2f** yield 46% (286 mg, 0.32 mmol, 886.42 g/mol) of *N*-trityl diaza-polyether macrocycle **3f** as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: Et_2O/pentane gradient (1:9, 2:8, 3:7, 4:6, 5:5)

R_f = 0.43 (SiO_2, Et_2O/pentane 1:1)
m.p.: 123 °C
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.28 (s, 6H, -CH_3), 2.68 - 2.70 (m, 4H, -CH_2-), 2.77 - 2.80 (m, 4H, -CH_2-), 3.64 (s, 6H, -CH_3), 3.69 - 3.72 (m, 4H, -CH_2-), 4.10 - 4.13 (m, 4H, -CH_2-), 7.12 - 7.15 (m, 6H, aromatics), 7.19 - 7.22 (m, 12H, aromatics), 7.48 - 7.50 (m, 12H, aromatics).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 16.1 (2 -CH_3), 51.5 (2 -CH_3), 52.2 (2 -CH_2-), 52.5 (2 -CH_2-), 68.4 (2 -CH_2-), 72.6 (2 -CH_2-), 78.6 (2 C), 126.3 (6 aromatics), 127.8 (12 aromatics), 129.0 (2 =C), 129.4 (12 aromatics), 143.7 (6 aromatics), 158.7 (2 =C), 166.7 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2943, 1702, 1619, 1486, 1445, 1377, 1298, 1271, 1187, 1156, 1086, 1010, 934, 900, 760, 742, 708, 632.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{56}H_{59}N_2O_8$ 887.4266, observed 887.4251.

2.3.9 Synthesis of N-mesyl diaza-polyether macrocycle benzyl ester



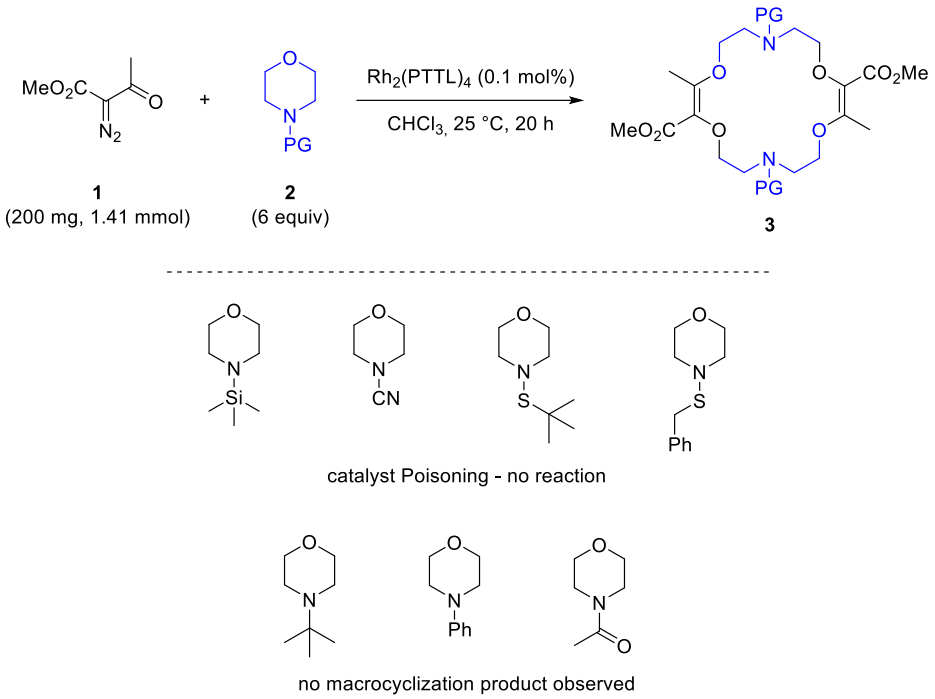
According to the general procedure, 1.40 g (8.46 mmol, 6 equiv.) of *N*-mesyl protected morpholine **2a** and 308 mg (1.41 mmol) of α-diazo-β-keto-benzyl-ester yield 12% (60 mg, 0.08 mmol, 710.81 g/mol) of *N*-mesyl diaza-polyether macrocycle benzyl ester as a white solid.

Purification conditions: column chromatography (SiO_2)
Column eluent: EtOAc/pentane (4:6)

R_f = 0.45 (SiO_2, EtOAc/pentane 8:2)
m.p.: 134 °C
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.38 (s, 6H, -CH_3), 2.66 (s, 6H, -CH_3), 3.64 (t, *J* = 4.9 Hz, 4H, -CH_2-), 3.74 (t, *J* = 5.5 Hz, 4H, -CH_2-), 3.85 (t, *J* = 5.5 Hz, 4H, -CH_2-), 4.13 (t, *J* = 4.9 Hz, 4H, -CH_2-), 5.17 (s, 4H, -CH_2-), 7.31 – 7.39 (m, 10H, aromatics).
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ/ppm = 14.3 (2 -CH_3), 39.3 (2 -CH_3), 48.5 (2 -CH_2-), 49.1 (2 -CH_2-), 66.5 (2 -CH_2-), 69.6 (2 -CH_2-), 71.6 (2 -CH_2-), 128.6 (2 CH aromatics), 128.7 (4 CH aromatics), 128.8 (4 CH aromatics), 129.5 (2 =C), 136.1 (2 C aromatics), 159.1 (2 =C), 165.4 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2936, 1692, 1602, 1500, 1479, 1452, 1406, 1379, 1322, 1293, 1276, 1256, 1242, 1132, 1095, 1061, 1026, 1000, 969, 861, 843, 790, 771, 734, 696, 620, 584, 562.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{32}H_{43}N_2O_{12}S_2$ 711.2252, observed 711.2247.

2.4 Scope of morpholine that do not lead to macrocyclization

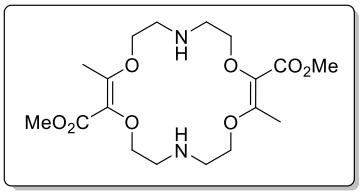
In a 10 ml vial, 2 mg (0.00141 mmol, 0.1 mol%) of Rh_2(*S*-PTTL)$_4$ and *N*-protected morpholine **2** (8.46 mmol, 6 equiv.) are dissolved in 2.8 ml of $CHCl_3$. To this solution, 200 mg (1.41 mmol) of α-diazo-β-ketoester **1** is added in one portion. The vial is sealed and the solution stirred at 25 °C for 20 hours. The results are analysed by TLC analysis, ^{1}H NMR, LR-ESI-MS or GC-MS. Results are gathered in Scheme **S1**.



Scheme S1. Scope of morpholines **2** that do not lead to macrocyclization

2.5 *N*-Deprotection and double bond hydrogenation

*2.5.1 Synthesis of N-H diaza-polyether macrocycle **4***

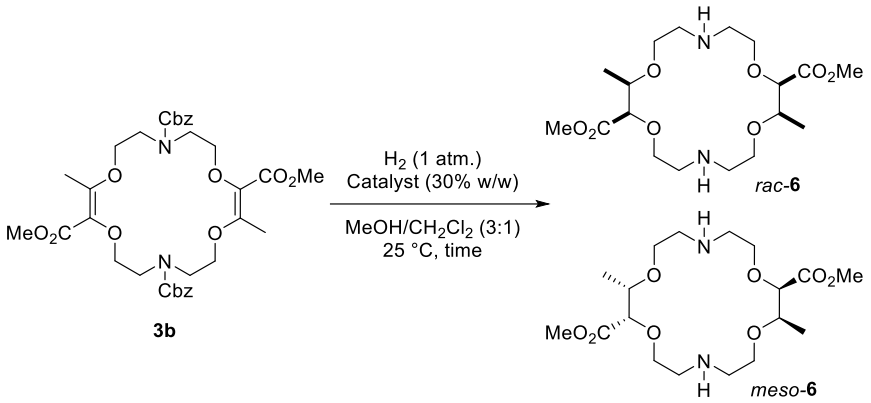


From 3e by reduction. In a 10 mL vial, 150 mg (0.25 mmol) of **3e** is dissolved in 1 mL of dry CH_2Cl_2 then 1 mL of dry MeOH is added. To this stirred solution, 48 mg (1.26 mmol, 5.0 equiv.) of $NaBH_4$ is added in small portion over 20 minutes. The solution is stirred for an additional 2 hours. The conversion is monitored by TLC analysis and LR-ESI-MS. The solvent is evaporated and the crude mixture is dissolved in CH_2Cl_2, filtered on a pad of silica (2 x 3 cm) with CH_2Cl_2/MeOH (9:1, 2% NEt_3) to yield 92% (93 mg, 0.23 mmol, 402.44 g/mol) of N-H diaza-polyether macrocycle **4** as a white solid.

From 3b by hydrogenolysis. In a 10 mL vial, 150 mg (0.22 mmol) of **3b** is dissolved in 2 mL of CH_2Cl_2/MeOH (1:1). To this stirred solution, 15 mg (10% w/w) of Pd/C (10% Pd, unreduced) is added. The vial is then flushed with H_2 and stirred under H_2 atmosphere (balloon, 1 atm.) for 2 hours. The conversion is monitored by TLC analysis and LR-ESI-MS. The suspension is filtered (syringe filter) and the solvent evaporated under vacuum and yield 94% (84 mg, 0.21 mmol, 402.44 g/mol) of N-H diaza-polyether macrocycle **4** as a white solid.

R_f = 0.33 (SiO_2, CH_2Cl_2/MeOH 9:1, 2% NEt_3)
m.p.: 143 °C
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K): δ/ppm = 2.37 (s, 6H, -CH_3), 2.50 (s, 2H, broad, NH), 2.81 – 2.88 (m, 4H, -CH_2-), 2.93 – 3.00 (m, 4H, -CH_2-), 3.73 (s, 6H, -CH_3), 3.78 – 3.83 (m, 4H, -CH_2-), 4.06 – 4.13 (m, 4H, -CH_2-).
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K): δ/ppm = 14.2 (2 -CH_3), 48.9 (2 -CH_2-), 49.4 (2 -CH_2-), 51.5 (2 -CH_3), 67.2 (2 -CH_2-), 72.6 (2 -CH_2-), 130.1 (2 =C), 158.2 (2 =C), 166.4 (2 C=O),
IR (neat): $\tilde{\nu}$/cm^{-1} 2939, 2833, 1701, 1618, 1436, 1391, 1297, 1258, 1196, 1153, 1129, 1092, 1049, 990, 958, 910, 855, 795, 766, 731, 647.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{18}H_{31}N_2O_8$ 403.2075, observed 403.2070.

2.5.2 Conditions screening for hydrogenation and hydrogenolysis of **3b**



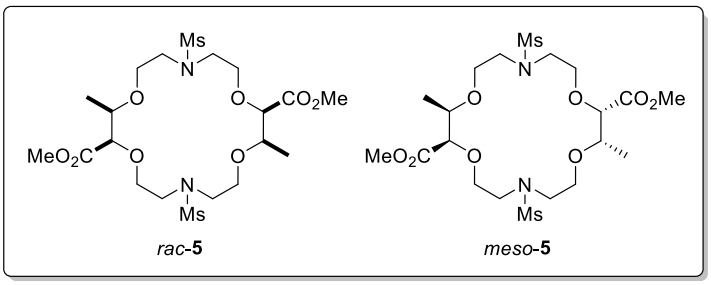
(S3)

Table S2. Conditions screening for the hydrogenation and hydrogenolysis of **3b**

entry	Catalyst	Time (h)	Conversion	*dr*[a]
1	Pd/C (20% Pd, 50% H_2O)	5	>99	6.5:1.0
2	Pd/Alumina (5% Pd)	22	>99	5.0:1.0
3	Rh/WoodC (5% Rh, 50% H_2O)	22	41	2.5:1.0
4	Rh/Alumina (5% Rh)	22	>99	4.5:1.0
5	Pd/C (10% Pd)	3	>99	3.0:1.0
6	$Pd(OH)_2$/C (20% Pd, 60% H_2O)	5	>99	7.5:1.0
7[b]	$Pd(OH)_2$/C (20% Pd, 60% H_2O)	4	>99	12:1.0

[a] configuration not determined; [b] solvent: MeOH (100%), catalyst loading : 50% w/w.

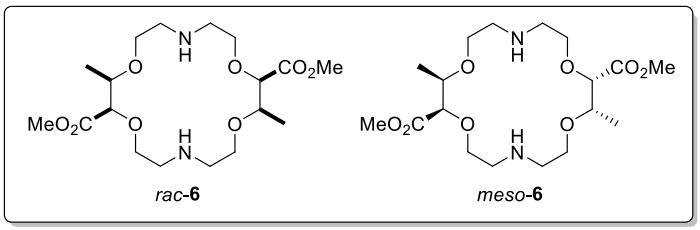
2.5.3 Synthesis of N-mesyl diaza-polyether 4[H]-macrocycle **5**



In a 10 mL vial, 150 mg (0.27 mmol) of **3a** is suspended in 2 mL of MeOH. To this stirred solution, 75 mg (50% w/w) of $Pd(OH)_2/C$ (20% Pd, 60% water) is added. The vial is then flushed with H_2 and stirred under H_2 atmosphere (balloon, 1 atm.) for 5 hours. The conversion is monitored by TLC analysis and LR-ESI-MS. The suspension is filtered (syringe filter) and the solvent evaporated under vacuum and yield 84% (127 mg, 0.23 mmol, 562.65 g/mol) of N-mesyl diaza-polyether 4[H]-macrocycle **5** as an inseparable diastereomeric mixture (16:1)[9] as a colorless oil.

R_f = 0.50 (SiO_2, CH_2Cl_2/MeOH 96:4)
^{1}H-NMR (400 MHz, $CDCl_3$, 298 K, major diastereoisomer): δ/ppm = 1.16 (d, *J* = 6.6 Hz, 6H, -CH_3), 2.89 (s, 6H, -CH_3), 3.45 – 3.65 (m, 10H, -CH_2-), 3.66 – 3.92 (m, 14H, -CH_2-), 4.04 (d, *J* = 1.9 Hz, 2H, -CH-).
^{13}C-NMR (101 MHz, $CDCl_3$, 298 K, major diastereoisomer): δ/ppm = 15.4 (2 -CH_3), 38.4 (2 -CH_3), 48.1 (2 -CH_2-), 48.5 (2 -CH_2-), 51.9 (2 -CH_3), 68.2 (2 -CH_2-), 70.4 (2 -CH_2-), 76.9 (2 -CH-), 82.3 (2 -CH-), 170.2 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2936, 1744, 1438, 1323, 1268, 1209, 1136, 1002, 965, 915, 850, 772, 700, 731, 700, 605, 559.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{20}H_{39}N_2O_{12}S_2$ 563.1939, observed 563.1945.

2.5.4 Synthesis of N-H diaza-polyether 4[H]-macrocycle **6**

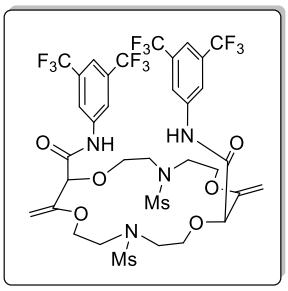


In a 10 mL vial, 150 mg (0.22 mmol) of **3b** is suspended in 2 mL of MeOH. To this stirred solution, 75 mg (50% w/w) of $Pd(OH)_2/C$ (20% Pd, 60% water) is added. The vial is then flushed with H_2 and stirred under H_2 atmosphere (balloon, 1 atm.) for 5 hours. The conversion is monitored by TLC analysis and LR-ESI-MS. The suspension is filtered (syringe filter) and the solvent evaporated under vacuum and yield 96% (86 mg, 0.21 mmol, 406.48 g/mol) of N-H diaza-polyether 4[H]-macrocycle **6** as an inseparable diastereomeric mixture (12:1)[10] as a colorless oil.

R_f = 0.05 (SiO_2, CH_2Cl_2/MeOH 9:1)
^{1}H-NMR (400 MHz, CD_2Cl_2, 298 K, major diastereoisomer): δ/ppm = 1.11 (d, *J* = 6.5 Hz, 6H, -CH_3), 2.7 – 2.86 (m, 8H, -CH_2-), 3.45 - 3.49 (m, 2H, -CH_2-), 3.54 - 3.57 (m, 3H, -CH_2-), 3.66 – 3.78 (m, 11H, -CH_2-, -CH_3, NH), 3.84 - 3.88 (m, 2H, -CH_2-), 4.20 (d, *J* = 2.3 Hz, 2H, -CH-).
^{13}C-NMR (101 MHz, CD_2Cl_2, 298 K, major diastereoisomer): δ/ppm = 15.0 (2 -CH_3), 49.2 (2 -CH_2-), 49.6 (2 -CH_2-), 52.1 (2 -CH_3), 68.8 (2 -CH_2-), 70.7 (2 -CH_2-), 76.9 (2 -CH-), 80.0 (2 -CH-), 171.7 (2 C=O).
IR (neat): $\tilde{\nu}$/cm^{-1} 2937, 2886, 1748, 1634, 1455, 1437, 1379, 1341, 1266, 1208, 1104, 1080, 1006, 957, 927, 833, 764, 731, 701.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{18}H_{35}N_2O_8$ 407.2388, observed 407.2390.

2.6 Amidation - olefin transposition procedures

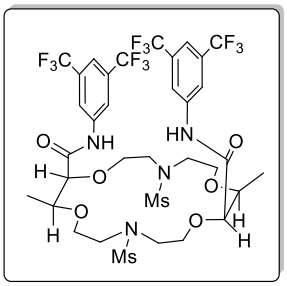
2.6.1 Synthesis of 3,5-bistrifluoromethyl-anilide-N-mesyl-diaza-18C6 ***7a***



In a 10 mL flask under nitrogen atmosphere, 1 mL of dry THF is added to 56 mg (0.1 mmol) of **3a** and 47 µL (69 mg, 0.3 mmol, 3 equiv) of 3,5-bistrifluoromethyl-aniline. The mixture is cooled down to -100 °C (in an EtOH/liquid nitrogen bath). Then 45 mg (0.4 mmol, 4 equiv) of *t*-BuOK is added in one portion. After stirring 1-2 minutes at -100 °C, the cooling bath is removed and the reaction is allowed to reach 25 °C on its own and stirred for an additional 3 hours. The conversion is followed by TLC analysis and LR-ESI-MS. The reaction is quench with a few drops of MeOH and directly purified by column chromatography (SiO_2, EtOAc/pentane 3:7, 1:1, 7:3, then CH_2Cl_2/MeOH 1:0, 95:5, 90:10) without further treatment. The resulting oil is purified by selective precipitation (a minimum of CH_2Cl_2 for solubility, followed by a large excess of pentane) over 15 hours affording 77% (73 mg, 0.077 mmol, 952.78 g/mol) of **7a** as an off-white solid.

R_f = 0.57 (SiO_2, CH_2Cl_2/MeOH 90:10)
m.p.: 150 °C
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 2.92 (s, 6H, -CH_3), 3.34 - 3.38 (m, 2H, -CH_2-), 3.51 - 3.57 (m, 6H, -CH_2-), 3.66 - 3.70 (m, 2H, -CH_2-), 4.01 -4.06 (m, 6H, -CH_2-), 4.37 (d, 2H, *J* = 3.2 Hz, =CH_2), 4.40 (s, 2H, -CH-), 4.42 (d, 2H, *J* = 3.2 Hz, =CH_2), 7.59 (s, 2H, aromatics), 8.25 (s, 4H, aromatics), 9.59 (s, 2H, NH).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 36.4 (2 -CH_3), 51.0 (2 -CH_2-), 51.1 (2 -CH_2-), 67.7 (2 -CH_2-), 68.6 (2 -CH_2-), 81.7 (2 -CH-), 88.1 (2 =CH_2), 117.6 (2 CH aromatics), 119.8 (4 CH aromatics), 123.1 (q, *J* = 273 Hz, 4 -CF_3), 132.2 (q, *J* = 33 Hz, 4 C aromatics), 139.3 (2 C aromatics), 157.2 (2 =C), 167.7 (2 C=O).
^{19}F-NMR (282 MHz, $CDCl_3$): δ/ppm = -63.0 (4 -CF_3).
IR (neat): $\tilde{\nu}$/cm^{-1} 3301, 2941, 1693, 1633, 1550, 1475, 1442, 1382, 1328, 1282, 1231, 1168, 1126, 1032, 1006, 969, 935, 887, 846, 777, 582.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{37}F_{12}N_4O_{10}S_2$ 953.1754, observed 953.1739.

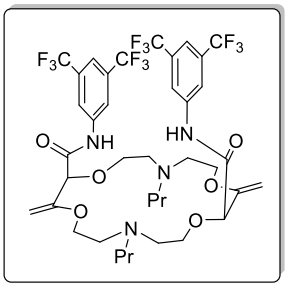
2.6.2 Synthesis of 4[H]-3,5-bistrifluoromethyl-anilide-N-mesyl-diaza-18C6 ***8***



In a 10 mL flask, 48 mg (0.05 mmol) of **7a** is suspended in 1 mL of dry THF. Then 4.8 mg (10% w/w) of Pd/C (10% Pd, unreduced) is added. The flask is then flushed with H_2 and stirred under H_2 atmosphere (balloon, 1 atm.) for 3 hours. The conversion is monitored by TLC analysis and LR-ESI-MS. The suspension is filtered (syringe filter) and the solvent evaporated under vacuum. The resulting oil is purified by selective precipitation (a minimum of CH_2Cl_2 for solubility, followed by a large excess of pentane) over 15 hours, affording 79% (38 mg, 0.04 mmol, 956.81 g/mol) of **8** as an inseparable diastereomeric mixture (9:1) as an off-white solid.[10]

R_f = 0.63 (SiO_2, CH_2Cl_2/MeOH 90:10)
m.p.: 195 °C
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K, major diastereoisomer): δ/ppm = 1.21 (d, 6H, *J* = 6.4 Hz, -CH_3), 2.94 (s, 6H, -CH_3), 3.34 - 3.48 (m, 4H, -CH_2-), 3.56 - 3.66 (m, 4H, -CH_2-), 3.69 - 3.73 (m, 2H, -CH_2-), 3.76 - 3.80 (m, 2H, -CH_2-), 3.86 -3.90 (m, 2H, -CH_2-), 4.16 (qd, 2H, *J* = 6.4 Hz, 1.7 Hz, -CH-), 4.25 (d, 2H, *J* = 1.7 Hz, -CH-), 4.29 - 4.33 (m, 2H, -CH_2-), 7.60 (s, 2H, aromatics), 8.27 (s, 4H, aromatics), 9.57 (s, 2H, NH).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K, major diastereoisomer): δ/ppm = 13.5 (2 -CH_3), 37.3 (2 -CH_3), 50.8 (2 -CH_2-), 51.6 (2 -CH_2-), 70.1 (2 -CH_2-), 71.0 (2 -CH_2-), 78.5 (2 -CH-), 83.7 (2 -CH-), 117.7 (2 CH aromatics), 119.9 (4 CH aromatics), 123.3 (q, *J* = 278 Hz, 4 -CF_3), 132.3 (q, *J* = 33 Hz, 4 C aromatics), 139.2 (2 C aromatics), 168.5 (2 C=O).
^{19}F-NMR (282 MHz, $CDCl_3$, major diastereoisomer): δ/ppm = 63.0 (4 -CF_3).
IR (neat): $\tilde{\nu}$/cm^{-1} 3293, 2917, 1686, 1622, 1545, 1474, 1442, 1381, 1325, 1275, 1131, 1100, 1022, 1004, 969, 932, 889, 847, 771, 728, 703, 682, 612, 576.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{34}H_{41}F_{12}N_4O_{10}S_2$ 957.2067, observed 957.2061.

2.6.3 Synthesis of 3,5-bistrifluoromethyl-anilide-N-propyl-diaza-18C6 **9**

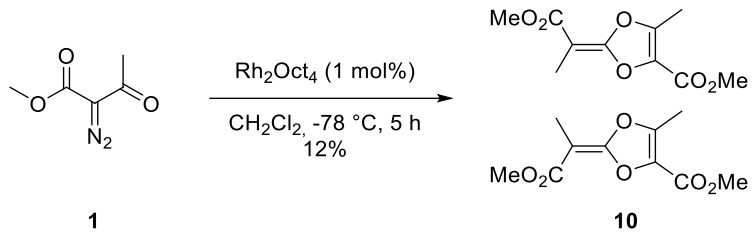


In a 10 mL flask under nitrogen atmosphere, 1 mL of dry THF is added to 59 mg (0.1 mmol) of **3e** and 94 µL (137 mg, 0.6 mmol, 6 equiv) of 3,5-bistrifluoromethyl-aniline. The mixture is cooled down to -100 °C (in an EtOH/liquid nitrogen bath). Then 67 mg (0.6 mmol, 6 equiv) of *t*-BuOK is added in one portion. After stirring 1-2 minutes at -100 °C, the cooling bath is removed and the reaction is allowed to reach 25 °C on its own and stirred for an additional 3 hours. The conversion is followed by TLC analysis and LR-ESI-MS. The reaction is quench with a few drops of MeOH. Then 58 µL (46 mg, 0.8 mmol, 8 equiv) of propionaldehyde is added and the solution is stirred for 10 min at 25 °C. The formed imine is reduced by adding 212 mg (1.0 mmol, 10 equiv) of $NaBH(OAc)_3$ (in three portions, 15 min between additions) and stirred for an additional 1 hour at 25 °C. The conversion is followed by TLC analysis and LR-ESI-MS. The reaction is quench with a few drops of MeOH and directly purified by column chromatography (SiO_2, EtOAc then CH_2Cl_2/MeOH 99:1, 95:5, 90:10) without further treatment. The resulting oil is purified by selective precipitation (a minimum of CH_2Cl_2 for solubility, followed by a large excess of pentane and evaporation of the solvent under vacuum) affording 73% (64 mg, 0.073 mmol, 880.77 g/mol) of **9** as an off-white solid.

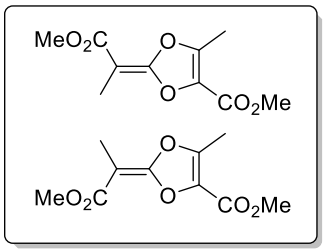
R_f = 0.53 (SiO_2, CH_2Cl_2/MeOH 90:10)
m.p.: 151 °C
^{1}H-NMR (500 MHz, $CDCl_3$, 298 K): δ/ppm = 0.61 (t, 6H, *J* = 7.3 Hz, $-CH_3$), 1.21 - 1.30 (m, 2H, $-CH_2-$), 2.28 -2.36 (m, 4H, $-CH_2-$), 2.65 - 2.76 (m, 6H, $-CH_2-$), 2.82 - 2.87 (m, 2H, $-CH_2-$), 3.48 - 3.52 (m, 2H, $-CH_2-$), 3.79 -3.91 (m, 6H, $-CH_2-$), 4.35 (d, 2H, *J* = 2.8 Hz, $=CH_2$), 4.44 (s, 2H, -CH-), 4.53 (d, 2H, *J* = 2.8 Hz, $=CH_2$), 7.52 (s, 2H, aromatics), 8.14 (s, 4H, aromatics), 10.23 (s, 2H, NH).
^{13}C-NMR (126 MHz, $CDCl_3$, 298 K): δ/ppm = 11.4 (2 $-CH_3$), 17.2 (2 $-CH_2-$), 51.8 (2 $-CH_2-$), 53.8 (2 $-CH_3$), 55.5 (2 $-CH_2-$), 65.5 (2 $-CH_2-$), 67.6 (2 $-CH_2-$), 83.0 (2 -CH-), 88.1 (2 -CH-), 117.1 (2 CH aromatics), 119.2 (4 CH aromatics), 123.1 (q, *J* = 273 Hz, 4 $-CF_3$), 132.1 (q, *J* = 34 Hz, 4 C aromatics), 139.7 (2 C aromatics), 156.7 (2 C=), 168.7 (2 C=O).
^{19}F-NMR (282 MHz, $CDCl_3$): δ/ppm = 63.2 (4 $-CF_3$).
IR (neat): $\tilde{\nu}$/cm^{-1} 3217, 2930, 1688, 1625, 1548, 1471, 1442, 1381, 1276, 1173, 1112, 1065, 1003, 933, 888, 850, 818, 705, 681.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{38}H_{45}F_{12}N_4O_6$ 881.3142, observed 881.3109.

2.7 Synthesis of the carbene by-product 10

The by-product obtained during the reaction was synthesized separately according to the following procedure:



(S2)

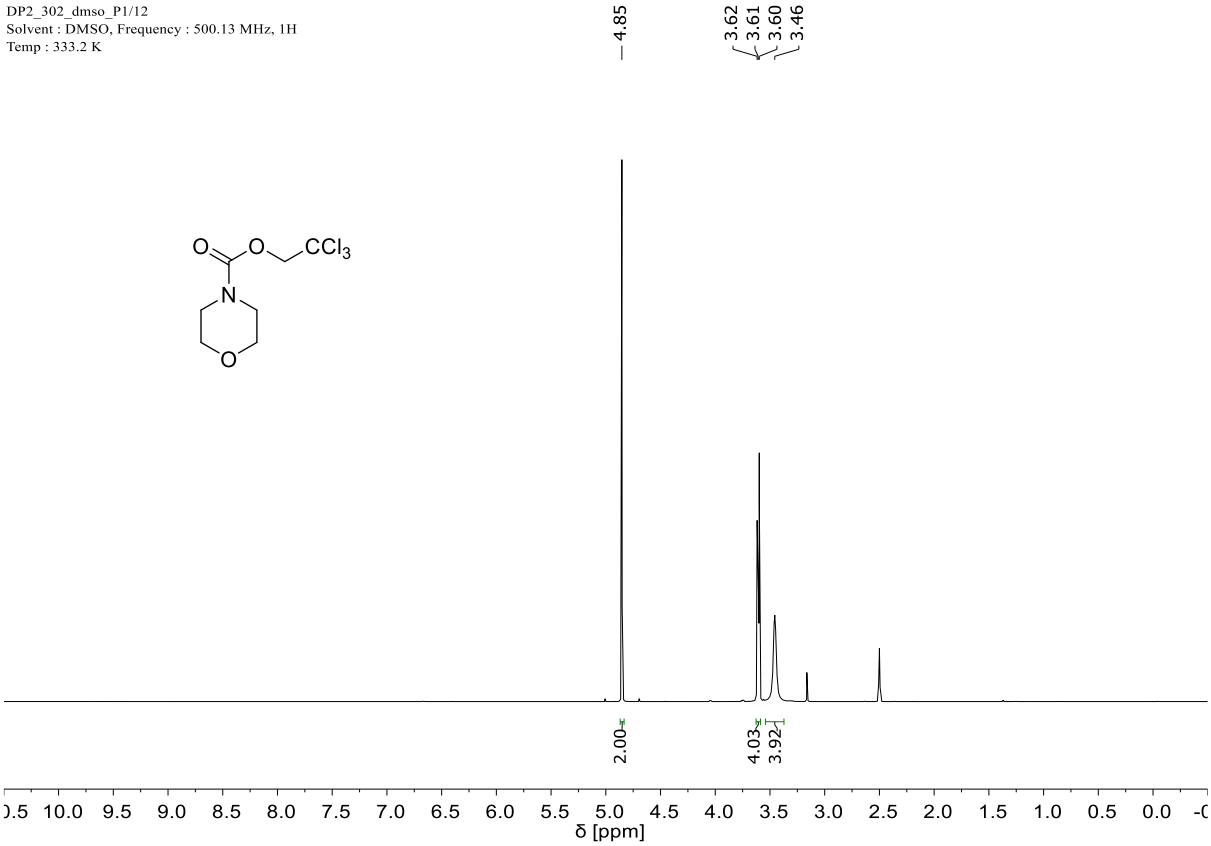


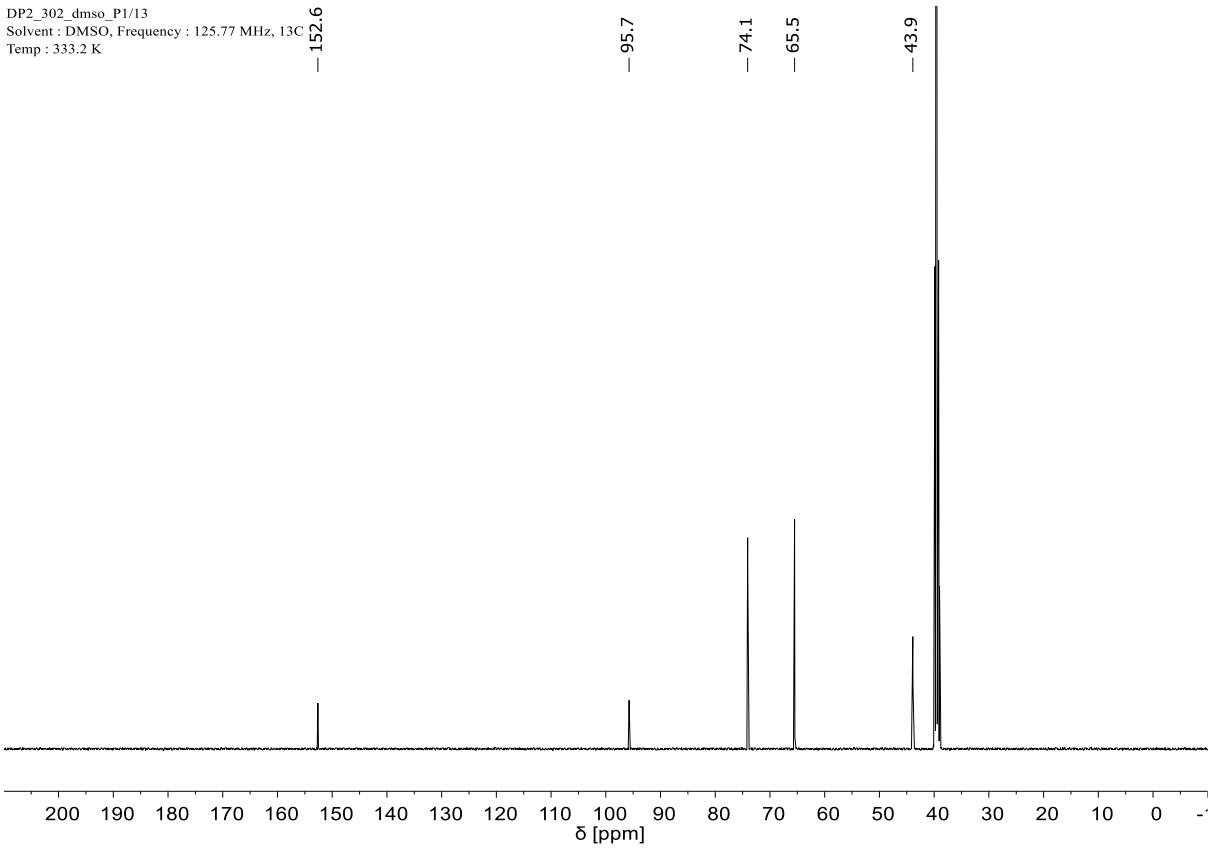
In a 10 mL sealed vial, 16.44 mg (0.0211 mmol, 1 mol%) of $Rh_2(Oct)_4$ is dissolved in 3.5 mL of CH_2Cl_2 and cool down to −78 °C. 300 mg (2.11 mmol) of α-diazo-β-ketoester **1** was added in one portion, and the mixture is stirred at −78 °C for 5 hours and the reaction is slowly warm to 25 °C. The brown crude mixture is concentrated, and purified by column chromatography (SiO_2, EtOAc/pentane gradient 1:9, 2:8 and 3:7) to yield 54 mg (0.24 mmol, 228.20 g/mol, 12%) of an inseparable mixture of geometrical isomers (1.0:0.3 ratio)[11] of **10** as a colorless oil. **10** is very sensitive and decompose rapidly even at low temperature (-20 °C).

R_f = 0.32 (SiO_2, EtOAc/pentane 3:7)
^{1}H-NMR (500 MHz, acetone-*d_6*, 298 K): δ/ppm = 1.78 (major) and 1.79 (minor) (s, 3H, -CH_3), 2.43 (minor) and 2.44 (major) (s, 3H, -CH_3), 3.65 (major/minor) (s, 3H, -CH_3), 3.87 (major) and 3.88 (minor) (s, 3H, -CH_3).
^{13}C-NMR (126 MHz, acetone-*d_6*, 298 K): δ/ppm = 10.6 (major) and 10.84 (minor) and 10.90 (minor) and 10.94 (major) (2 CH_3), 51.1 (major/minor) and 52.6 (major) and 52.6 (minor) (2 CH_3), 76.2 (major) and 76.4 (minor) (1 C), 130.0 (minor) and 131.0 (major) (1 C), 149.5 (major) and 150.7 (minor) (1 C), 158.66 (major) and 158.71 (minor) (1 C=O), 164.4 (minor) and 164.5 (major) (1 C=O), 167.2 (major/minor) (1 C).
IR (neat): $\tilde{\nu}$/cm^{-1} 2958, 1704, 1649, 1680, 1434, 1391, 1339, 1260, 1196, 1151, 1109, 1066, 994, 963, 912, 847, 811, 757, 672, 601.
HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{10}H_{13}O_6$ 229.0707, observed 229.0700.

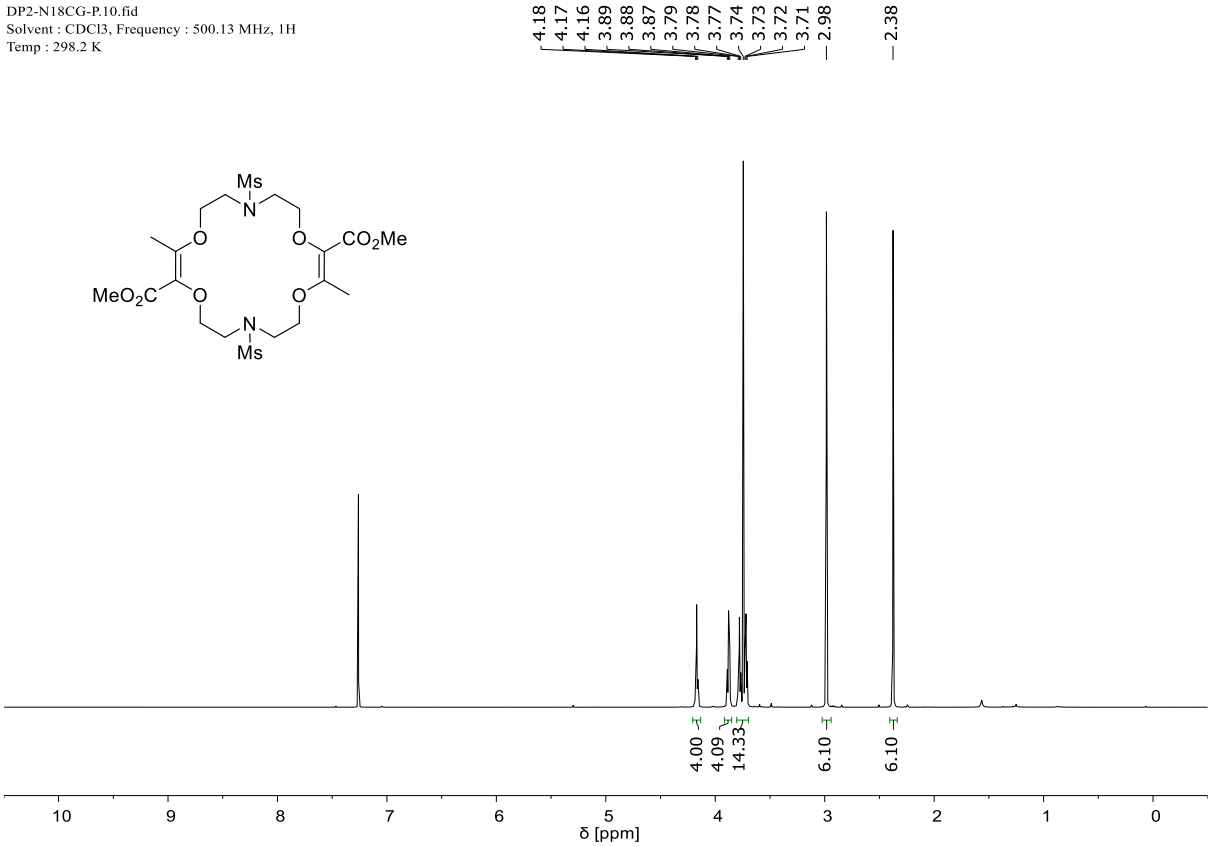
2.8 ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

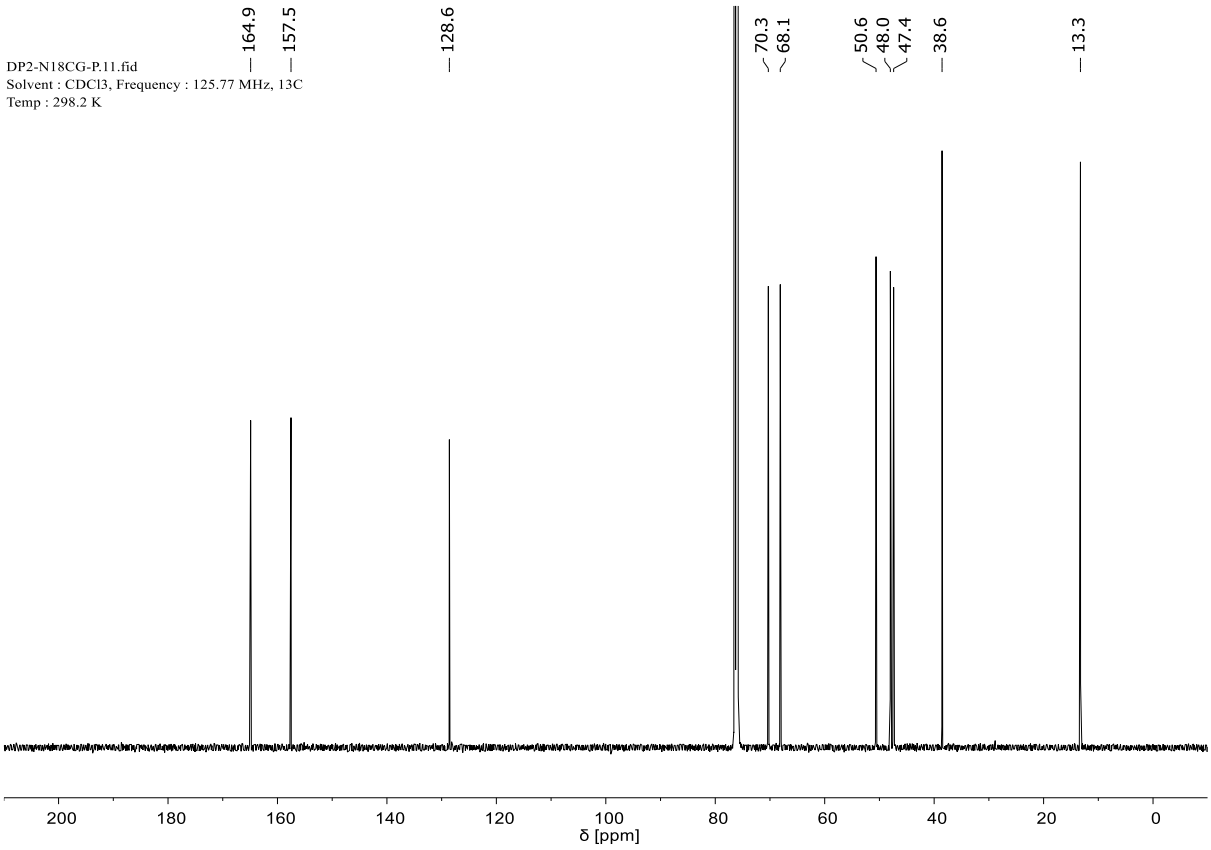
*2.8.1 2,2,2-trichloroethyl morpholine-4-carboxylate **2d** (at 333 K)*



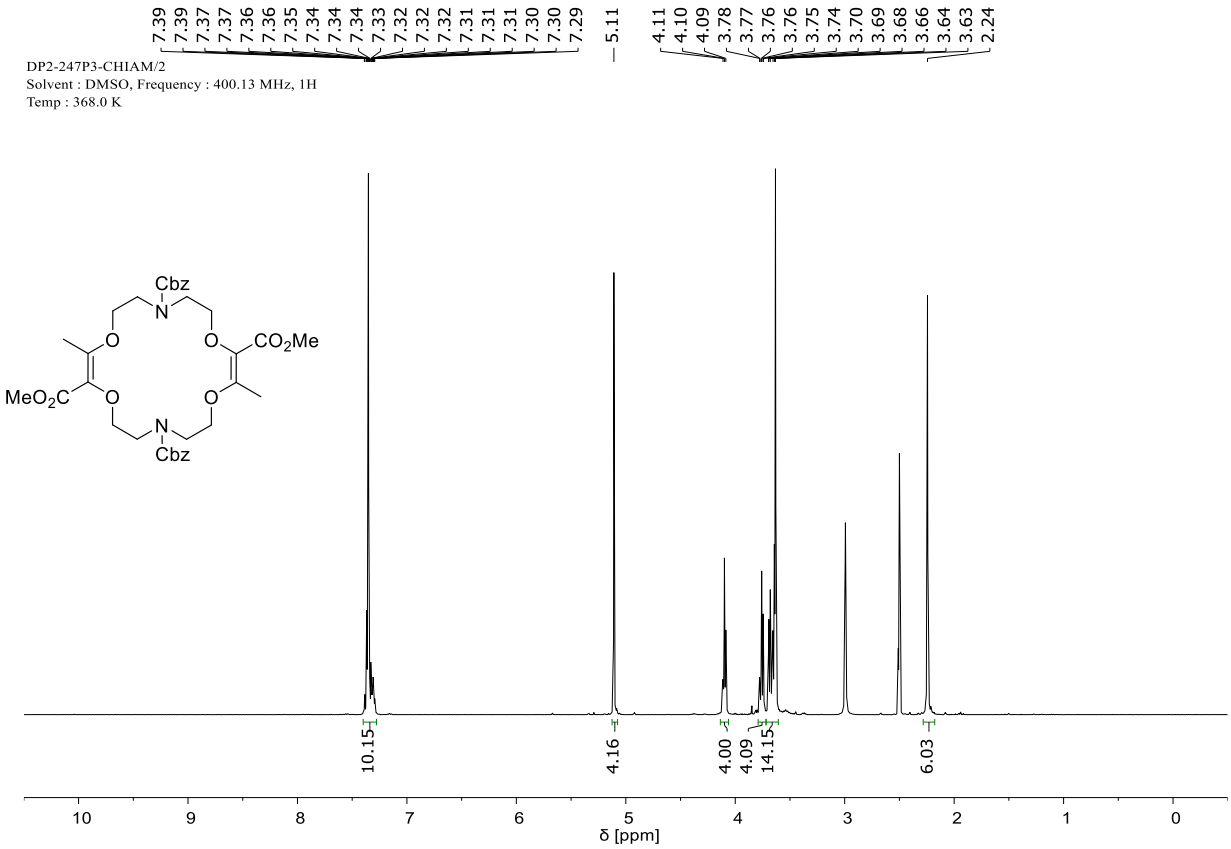


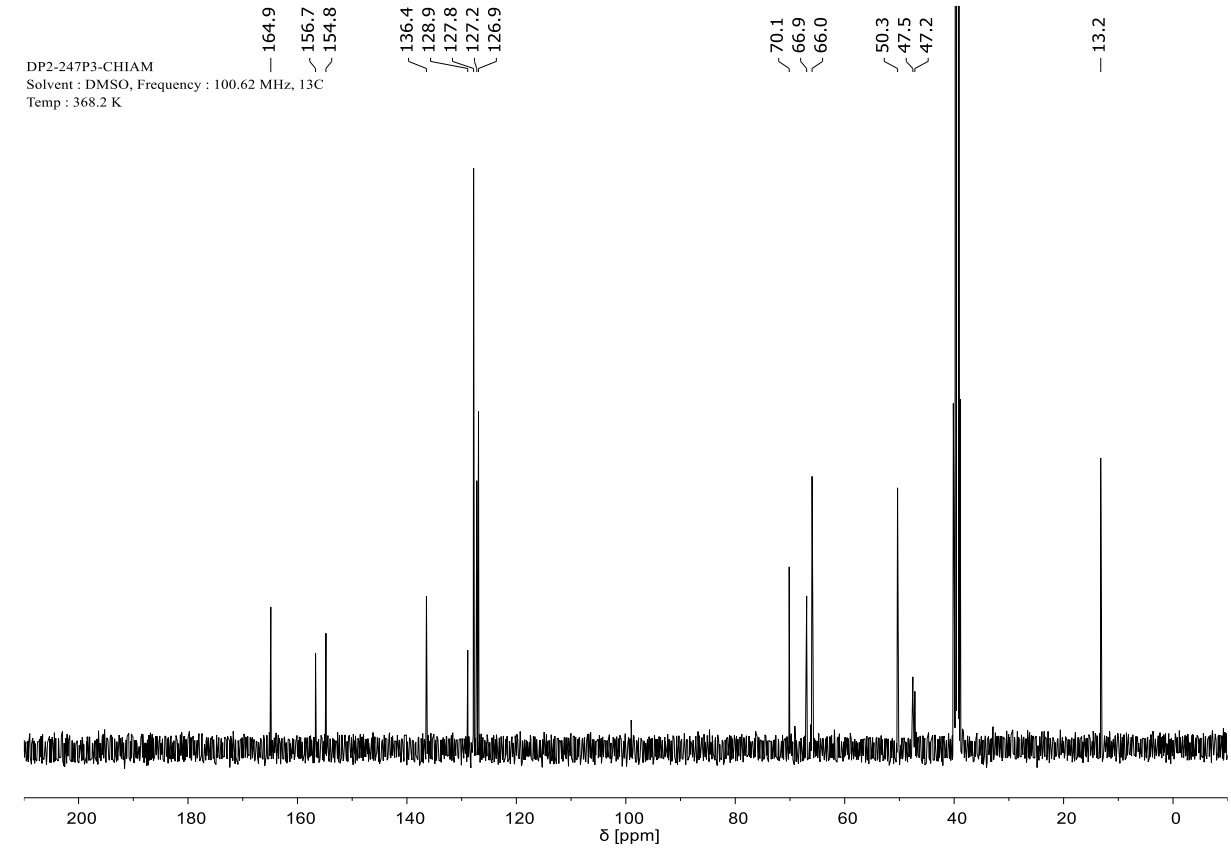
2.8.2 N-mesyl diaza-polyether macrocycle **3a** (at 298 K)



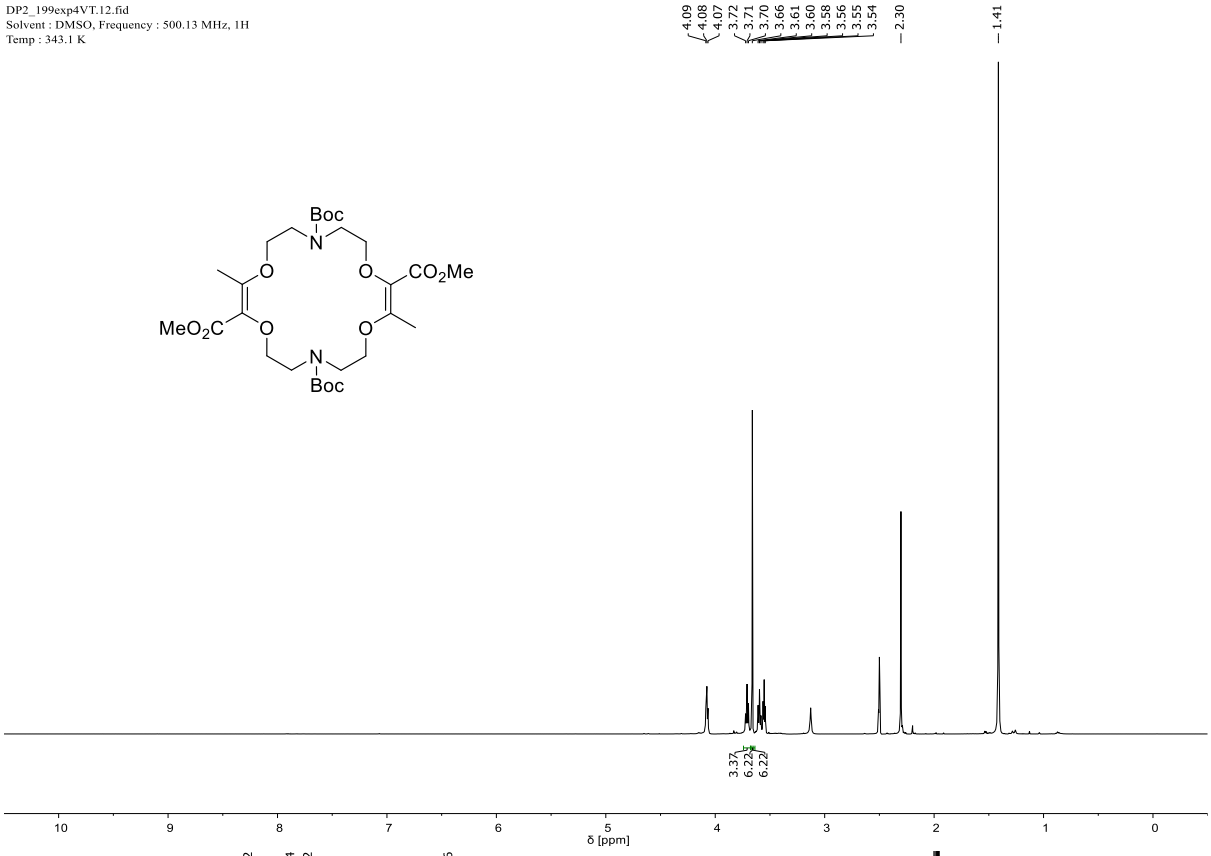


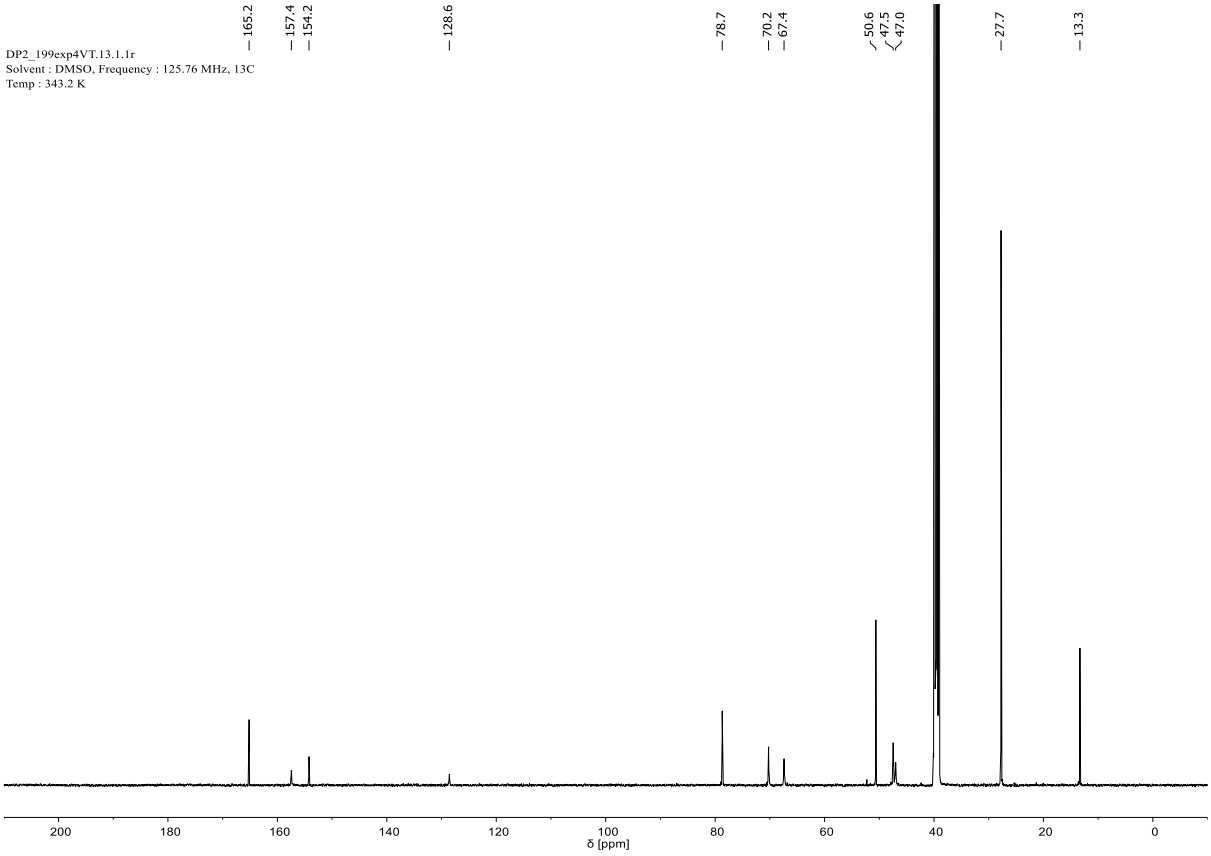
2.8.3 N-benzyl carbamate diaza-polyether macrocycle **3b** (at 368 K)



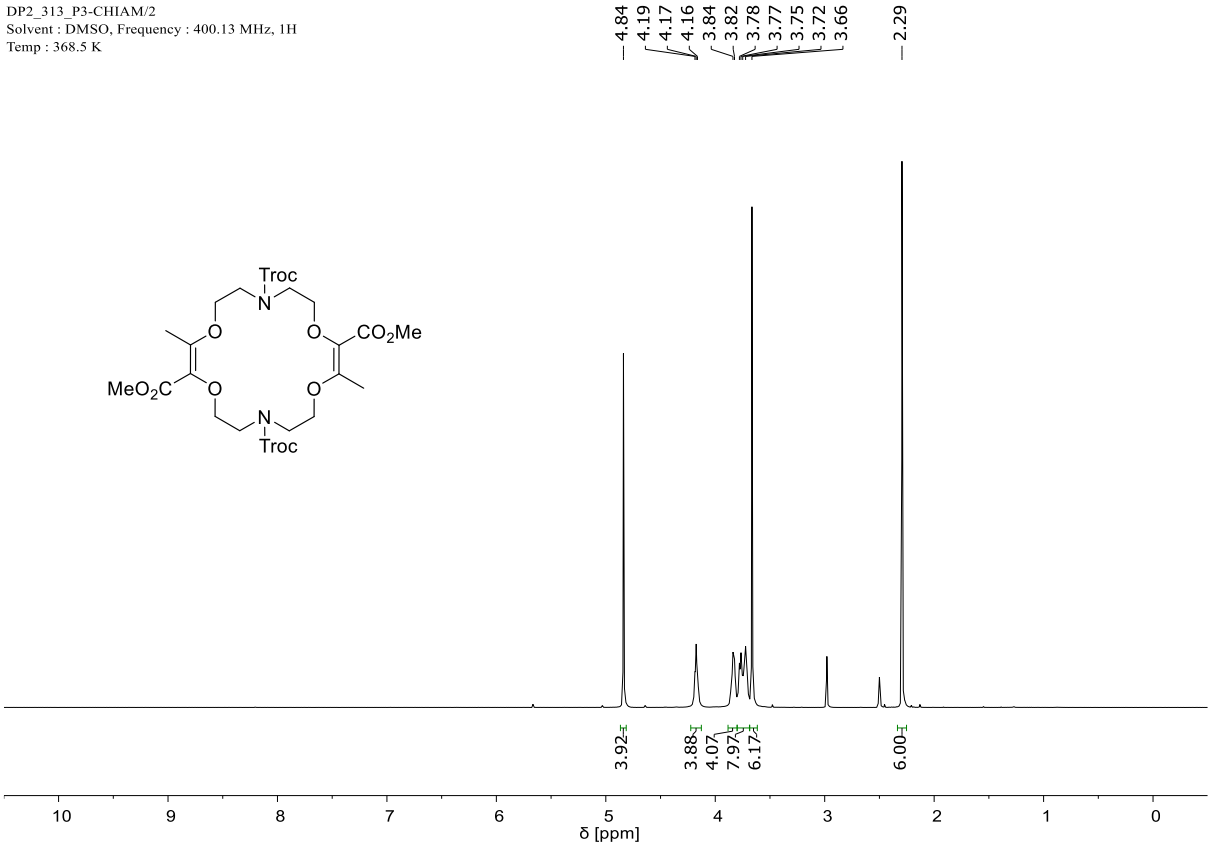


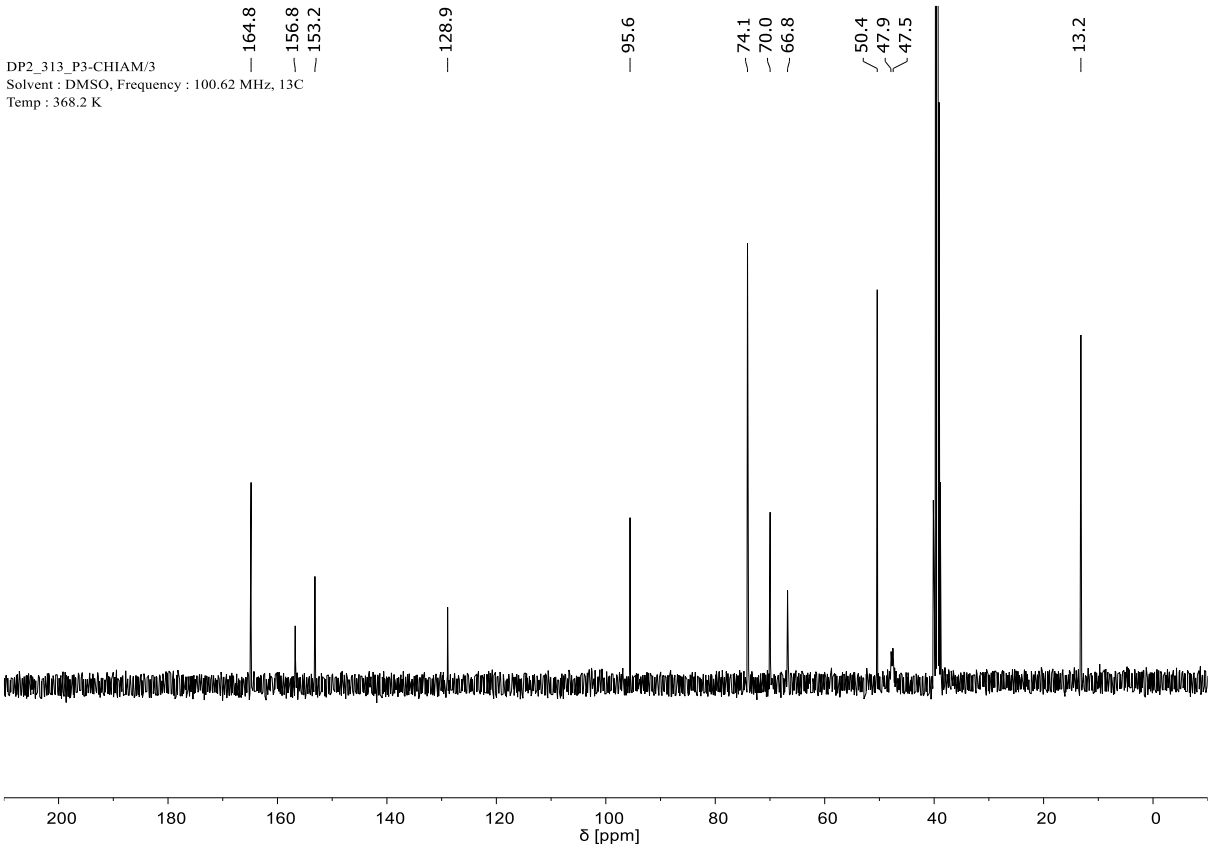
2.8.4 N-t-Bu carbamate diaza-polyether macrocycle **3c** (at 343 K)



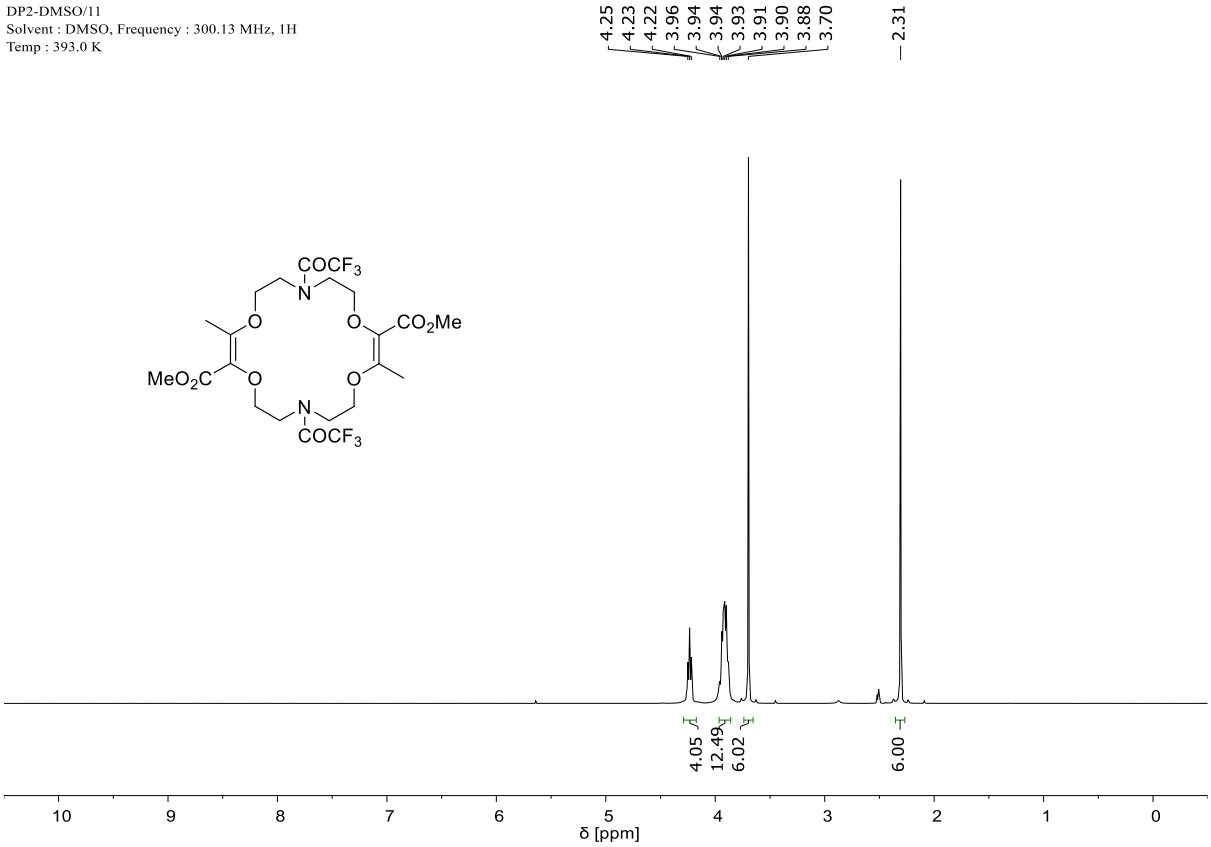


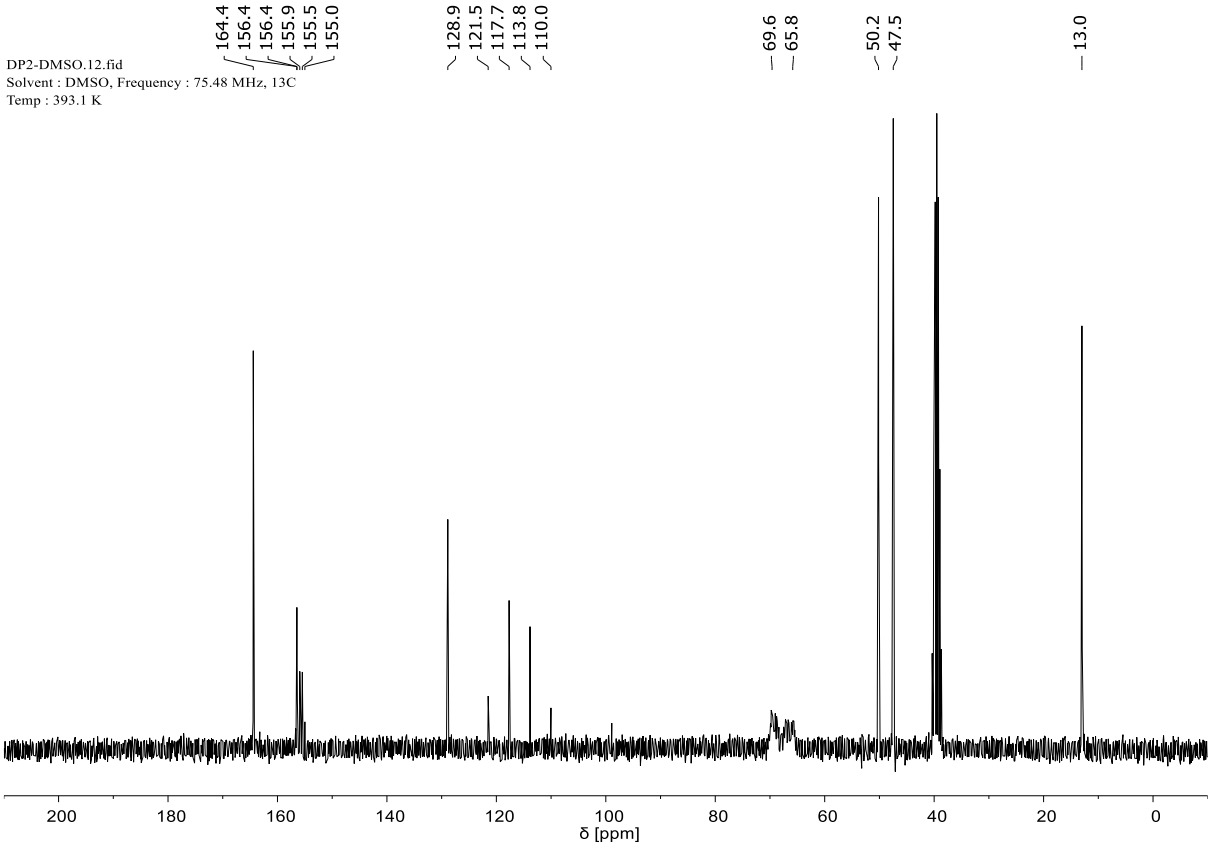
2.8.5 N-2,2,2-trichloroethoxy carbamate diaza-polyether macrocycle **3d** (at 369 K)





2.8.6 N-trifluoroacetamide diaza-polyether macrocycle **3e**[8] (at 393 K)





ah-1179-F-393.11.fid
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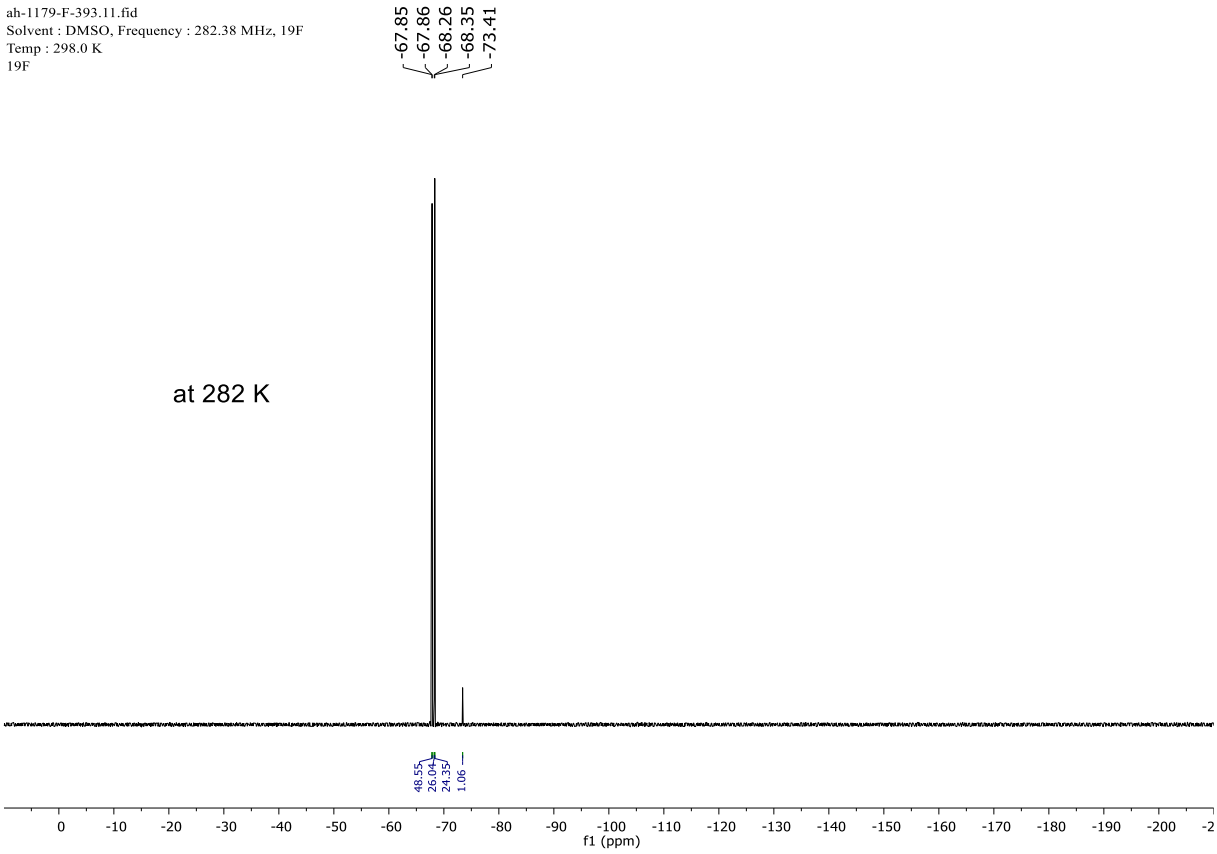
Temp : 298.0 K
19F



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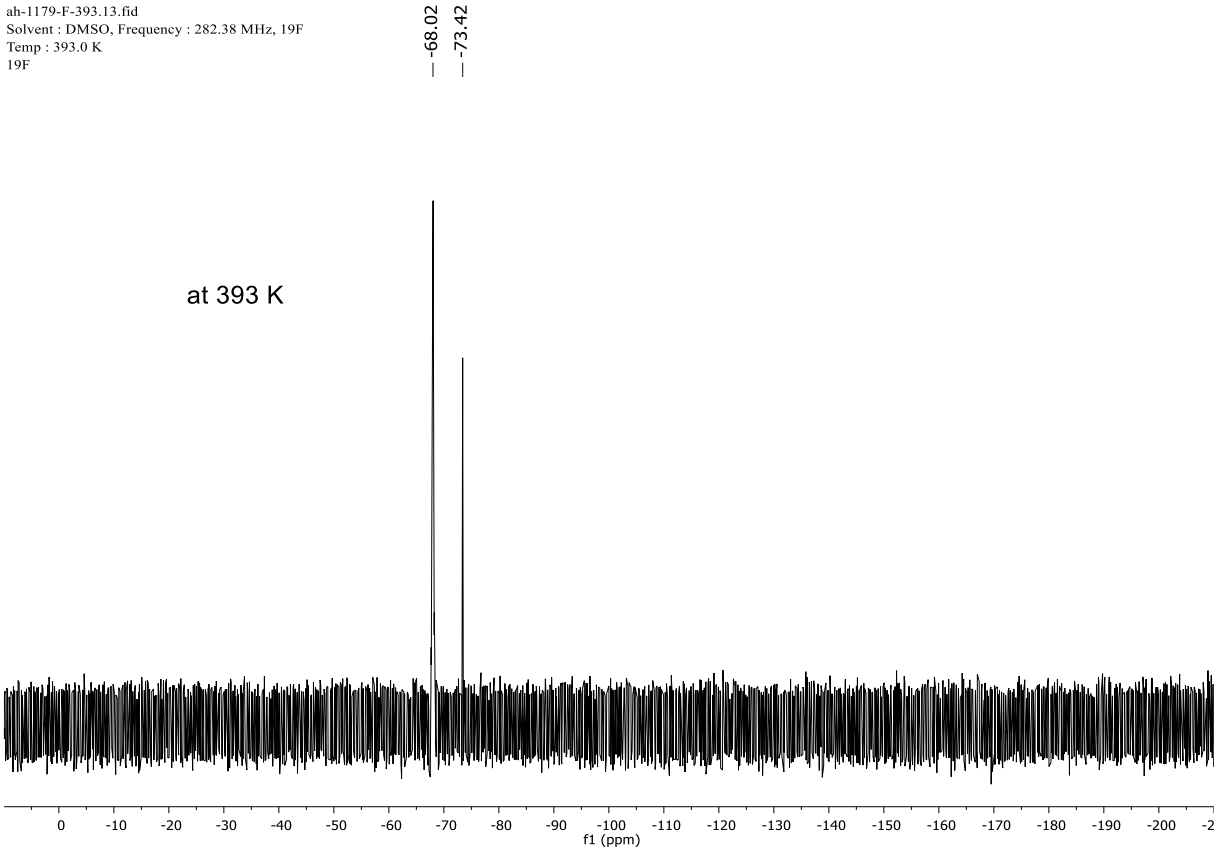
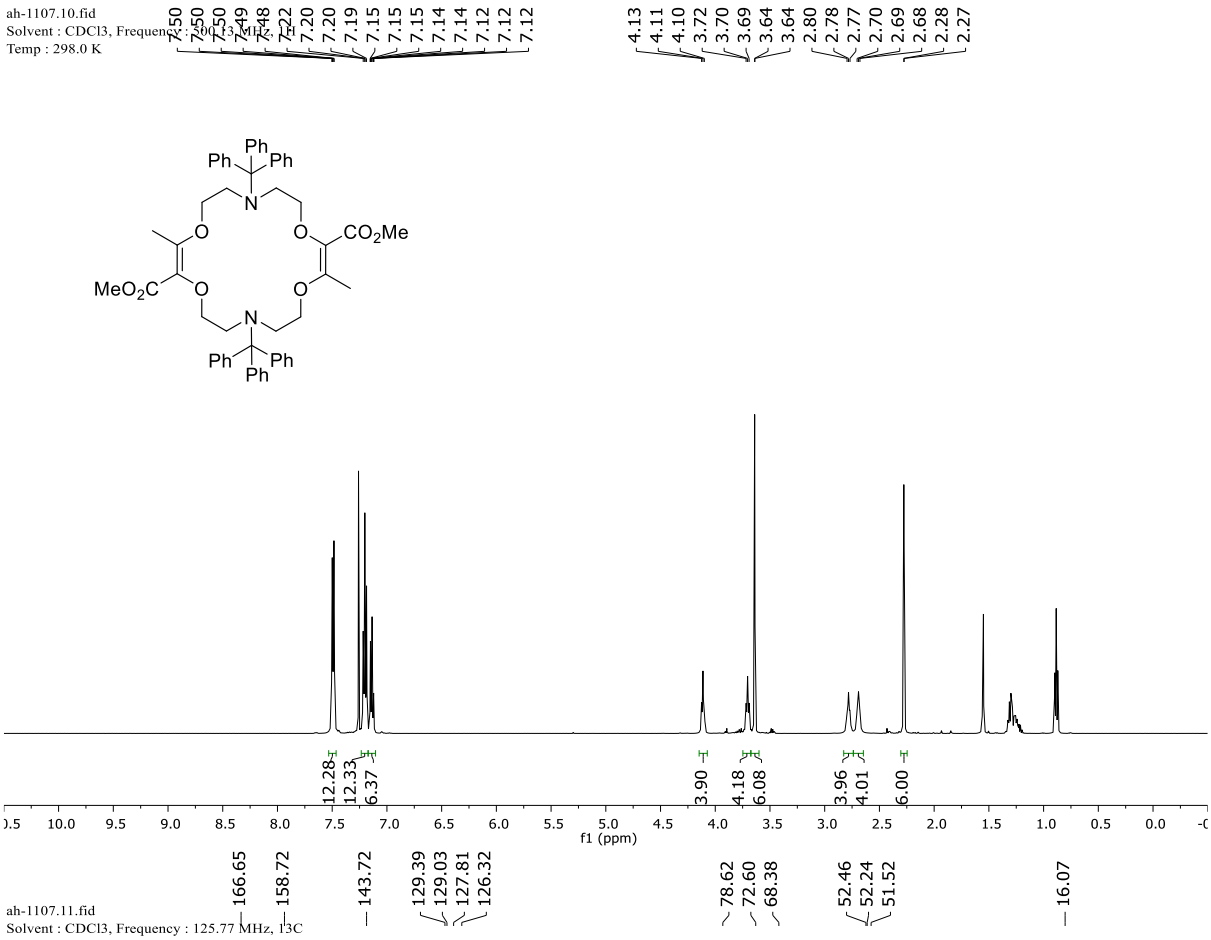
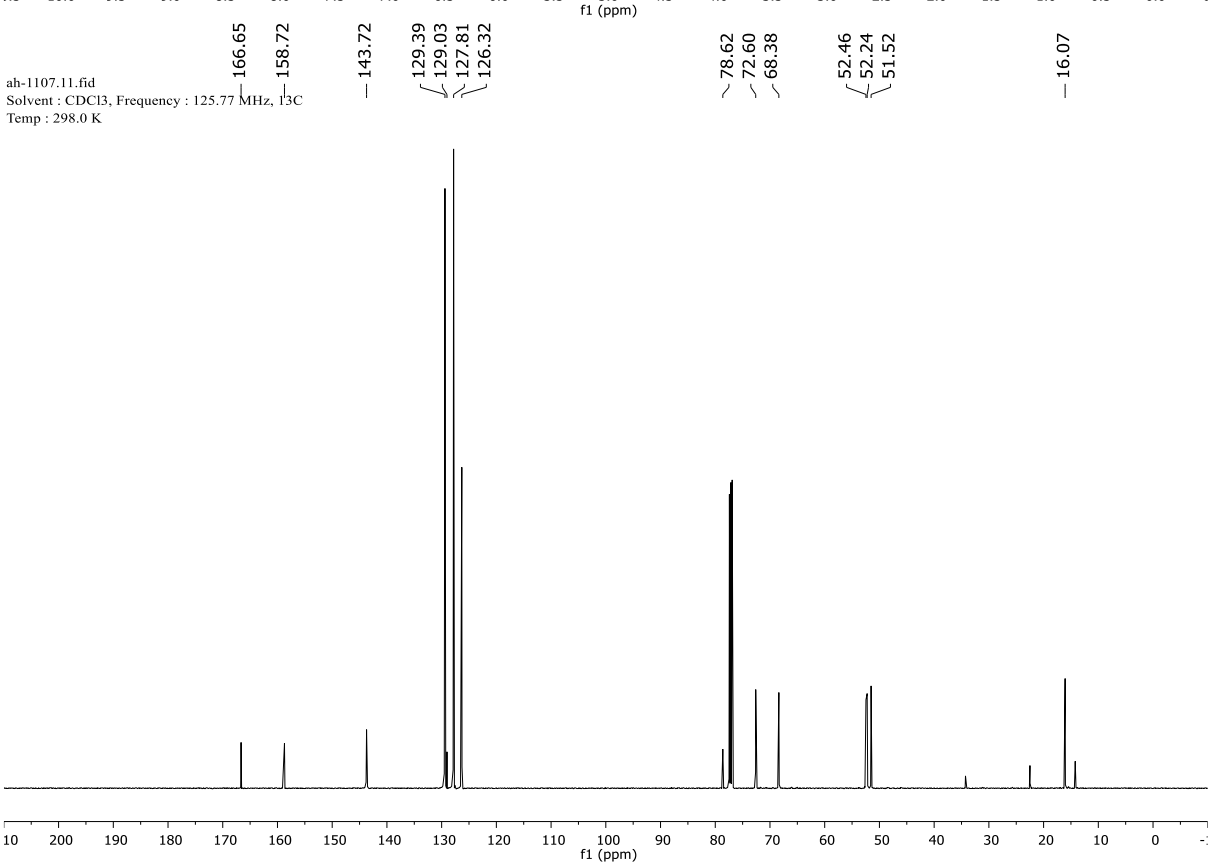
Temp : 393.0 K
19F

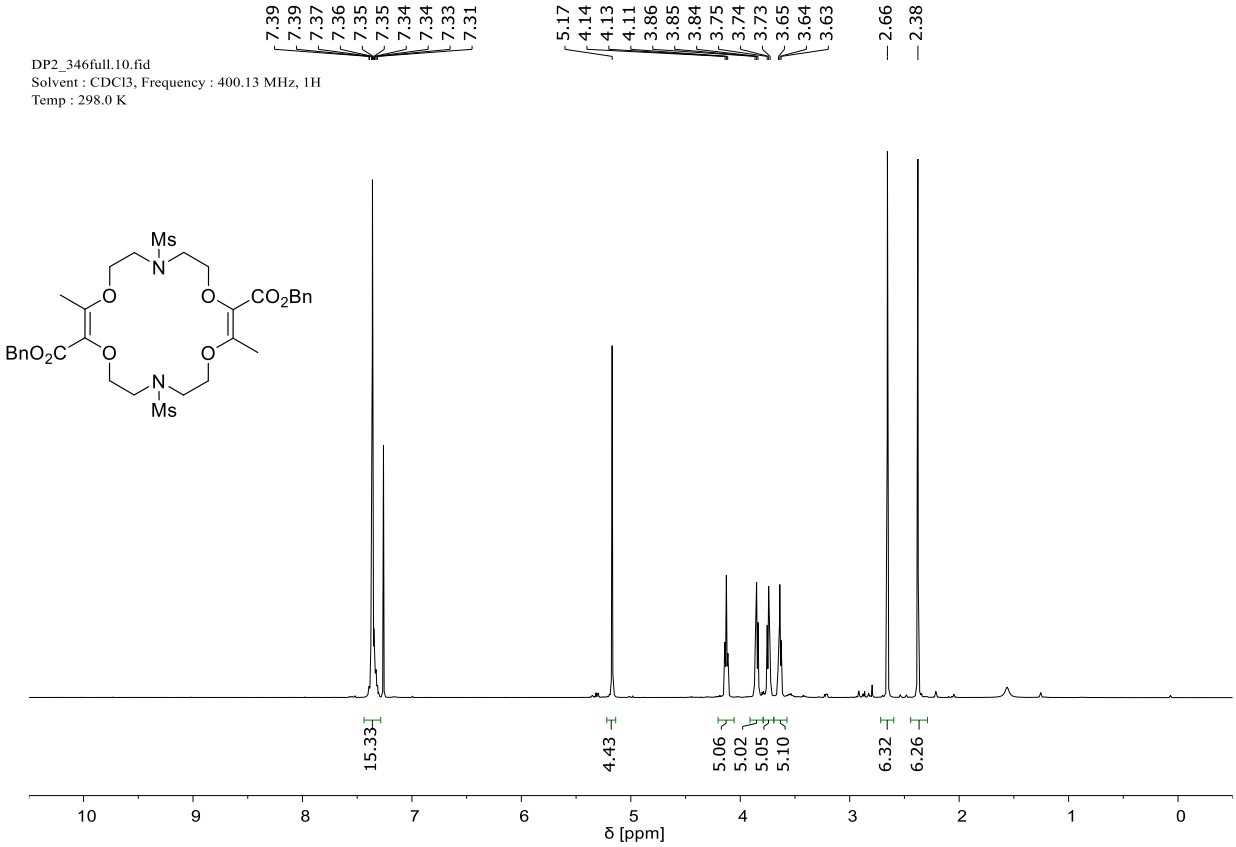


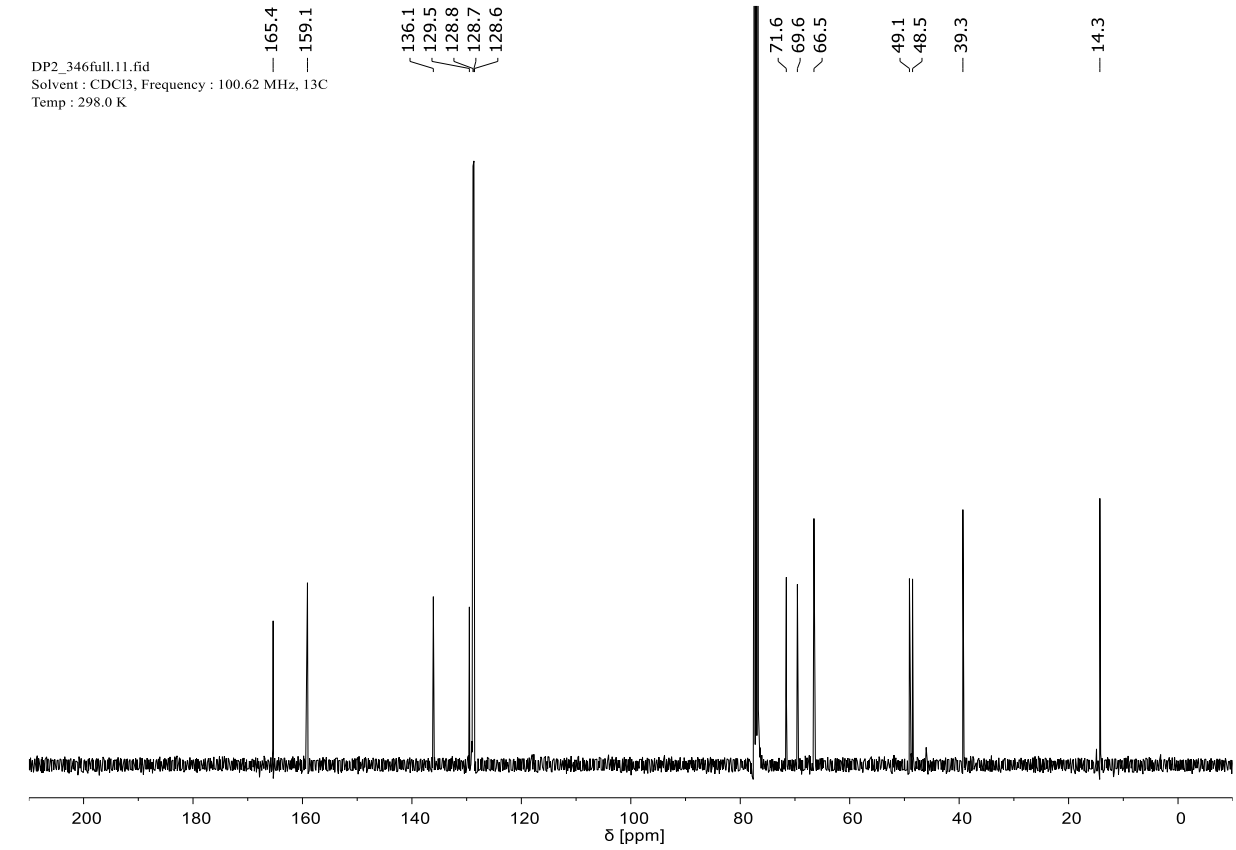
2.8.7 N-trityl diaza-polyether macrocycle **3f** (at 298 K)



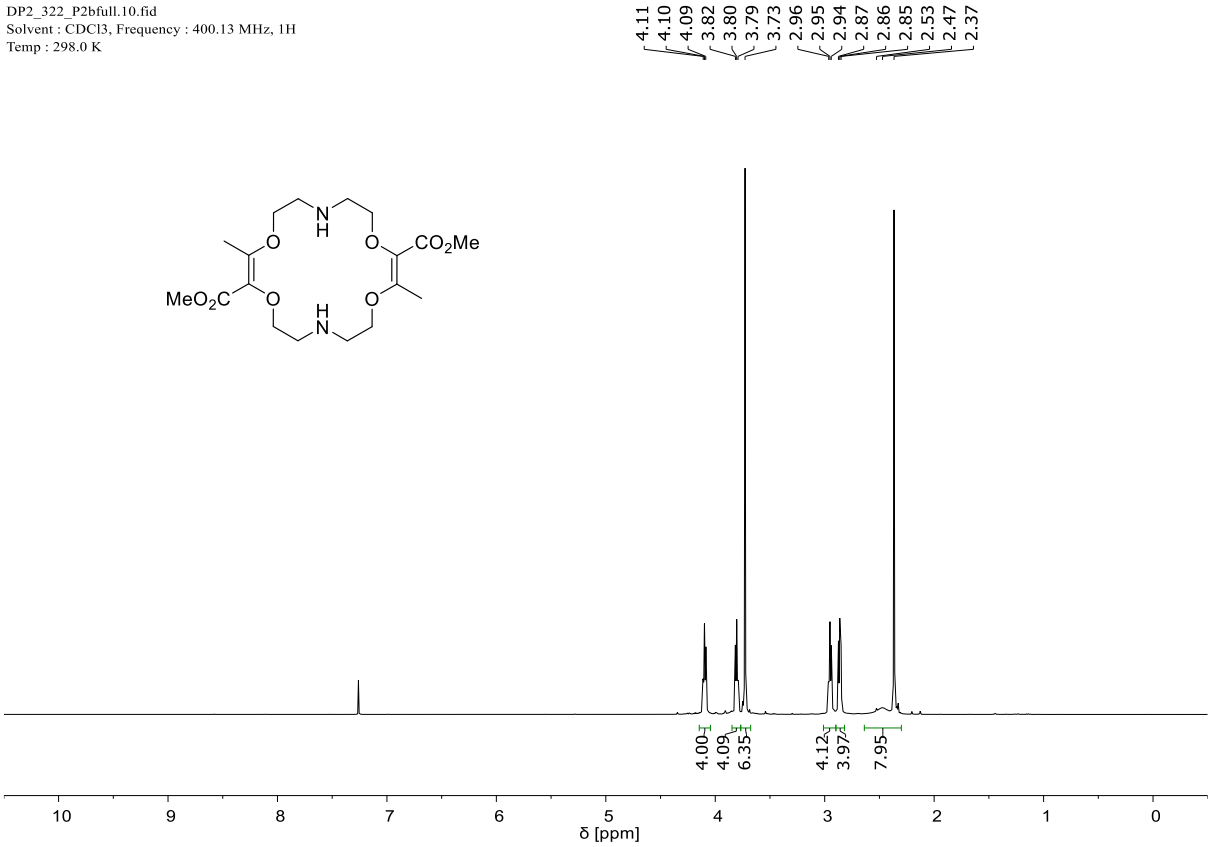


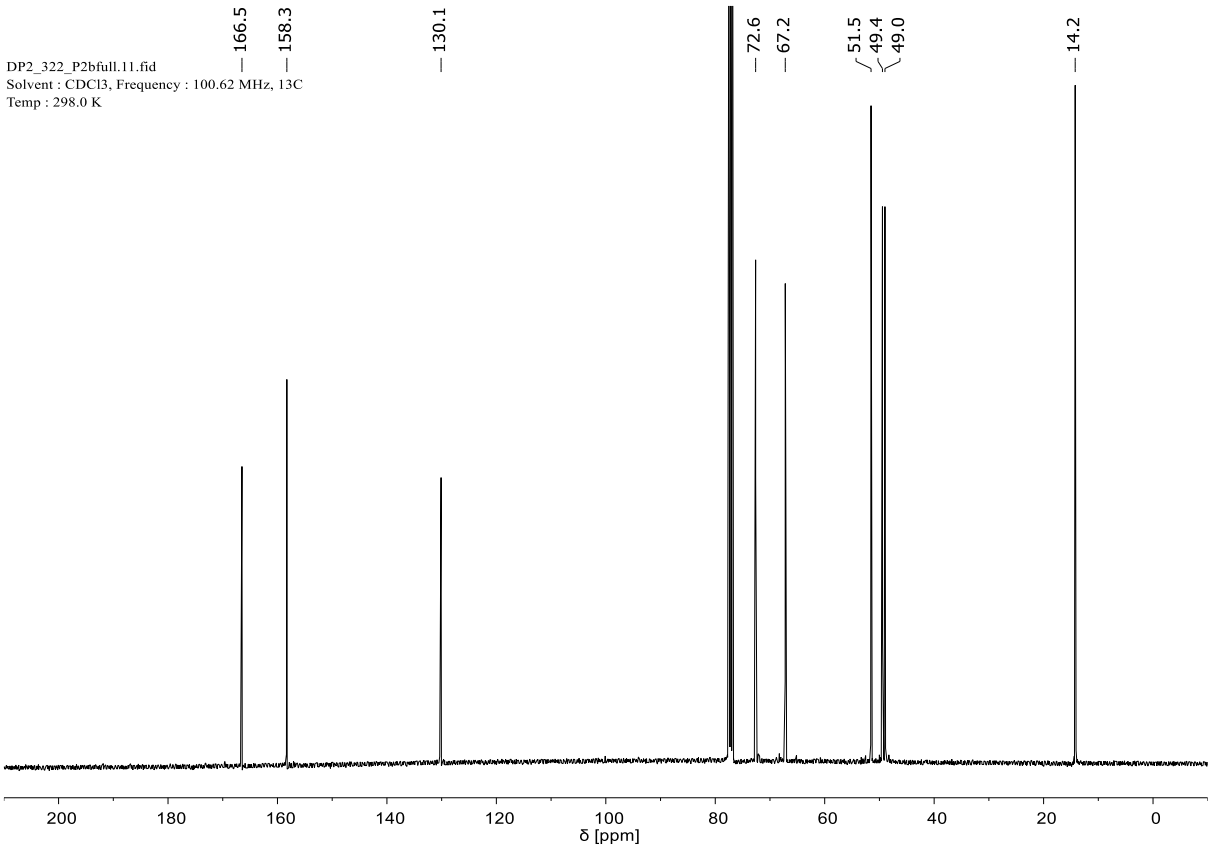
2.8.8 N-mesyl diaza-polyether macrocycle benzyl ester (at 298 K)



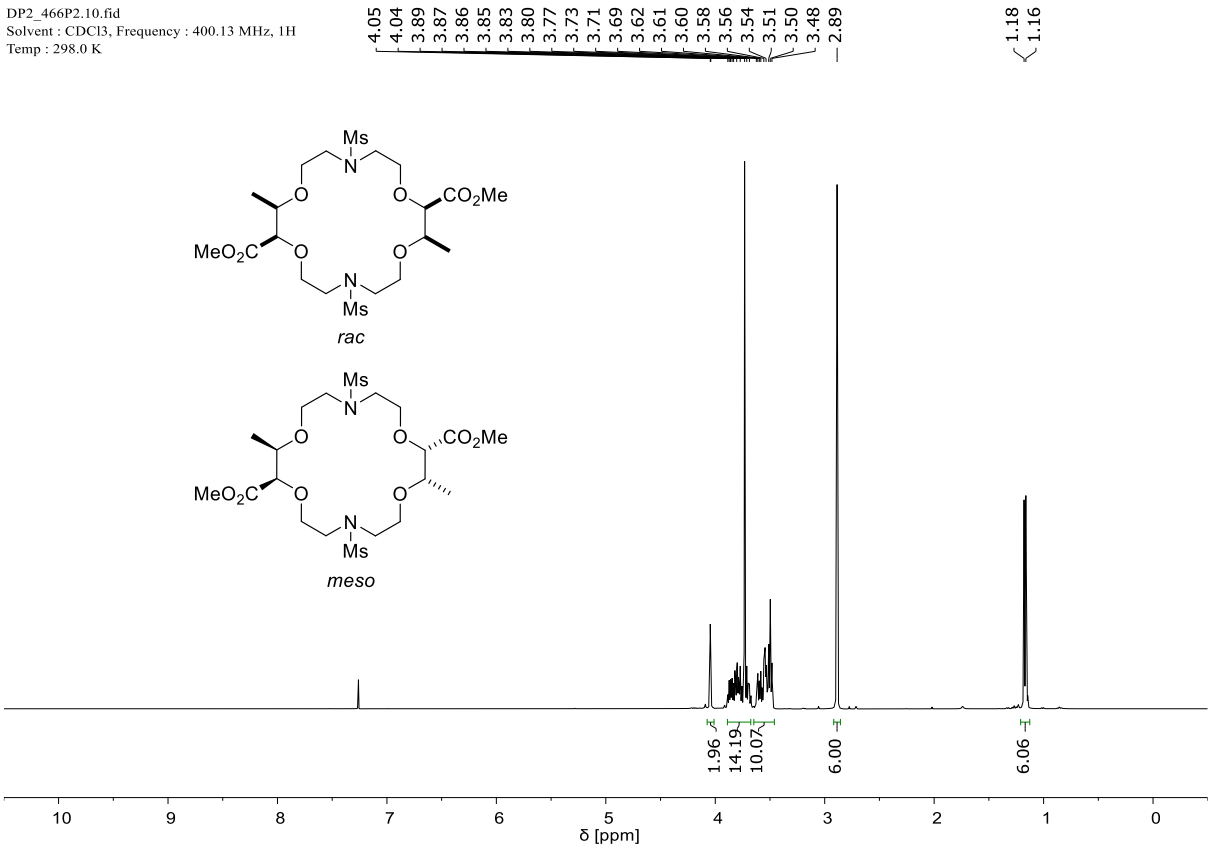


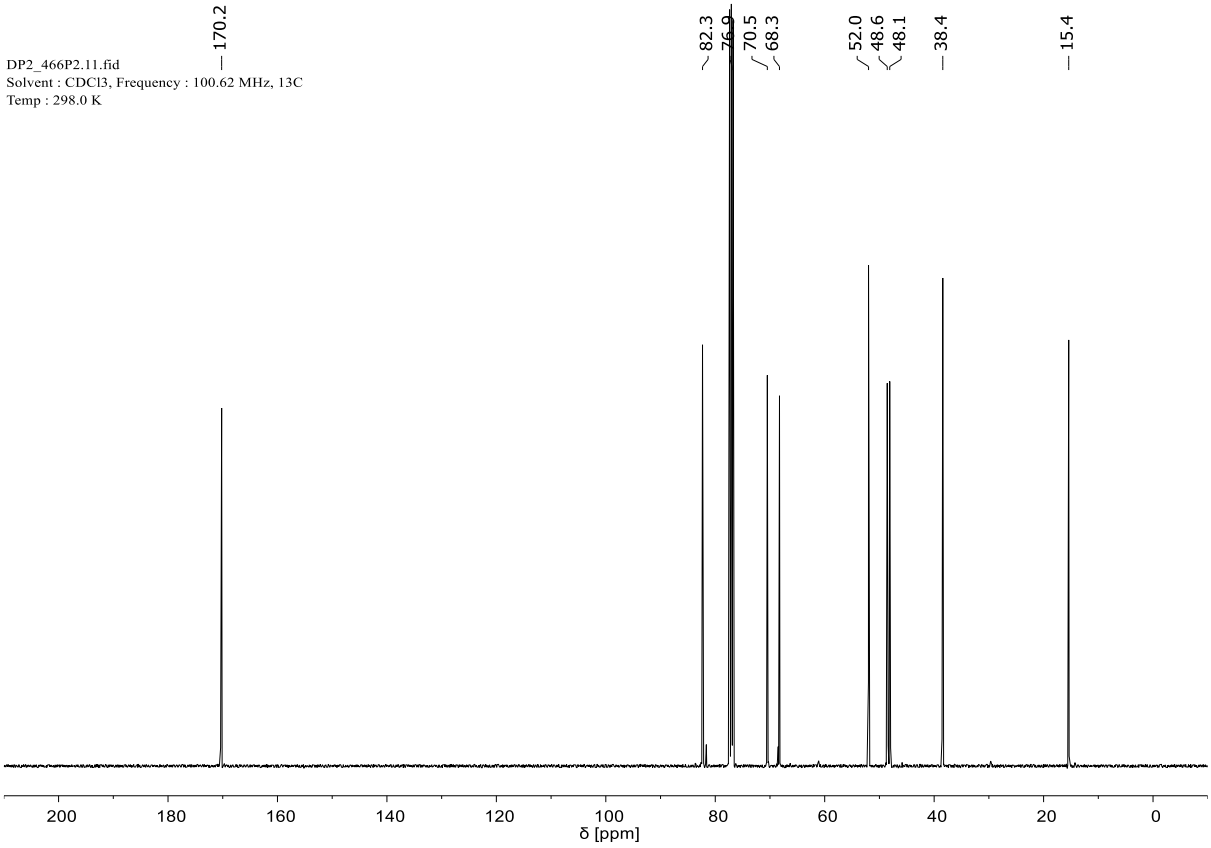
2.8.9 N-H diaza-polyether macrocycle **4** (at 298 K)



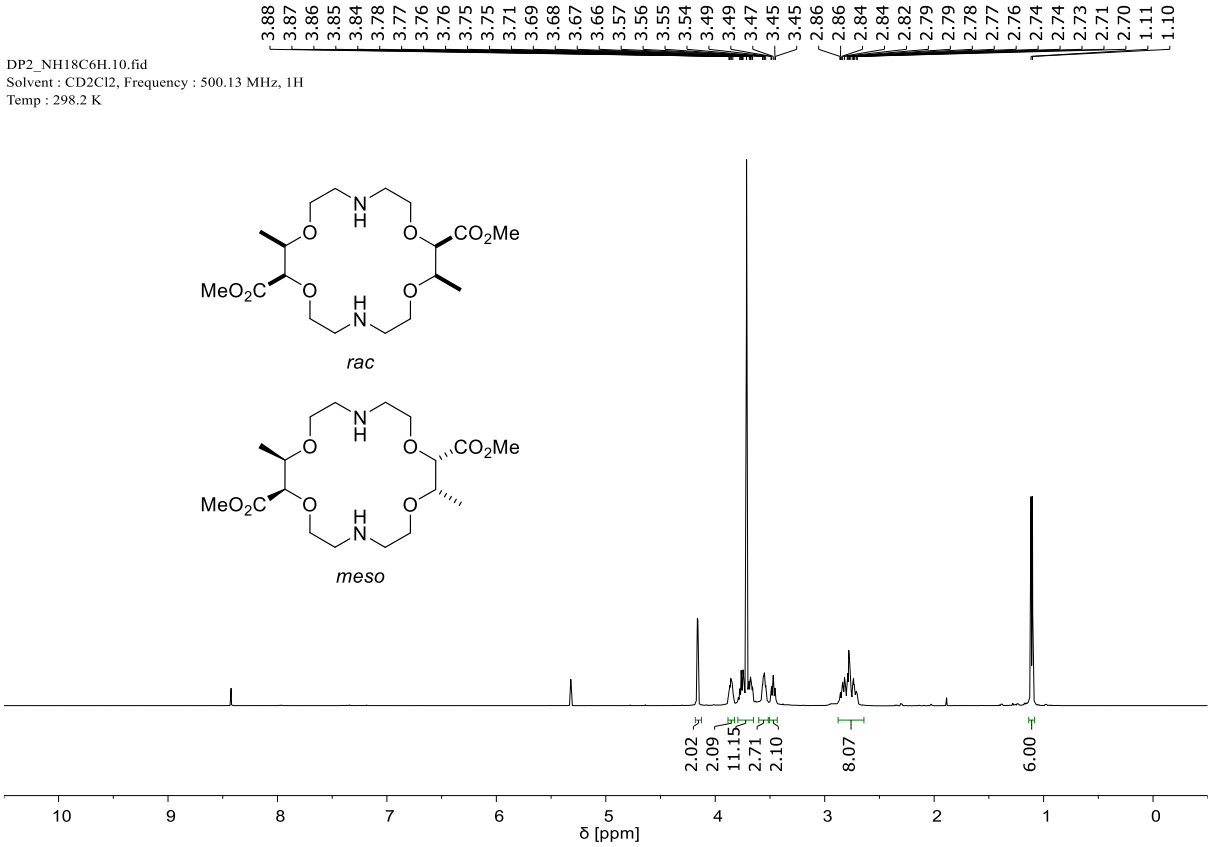


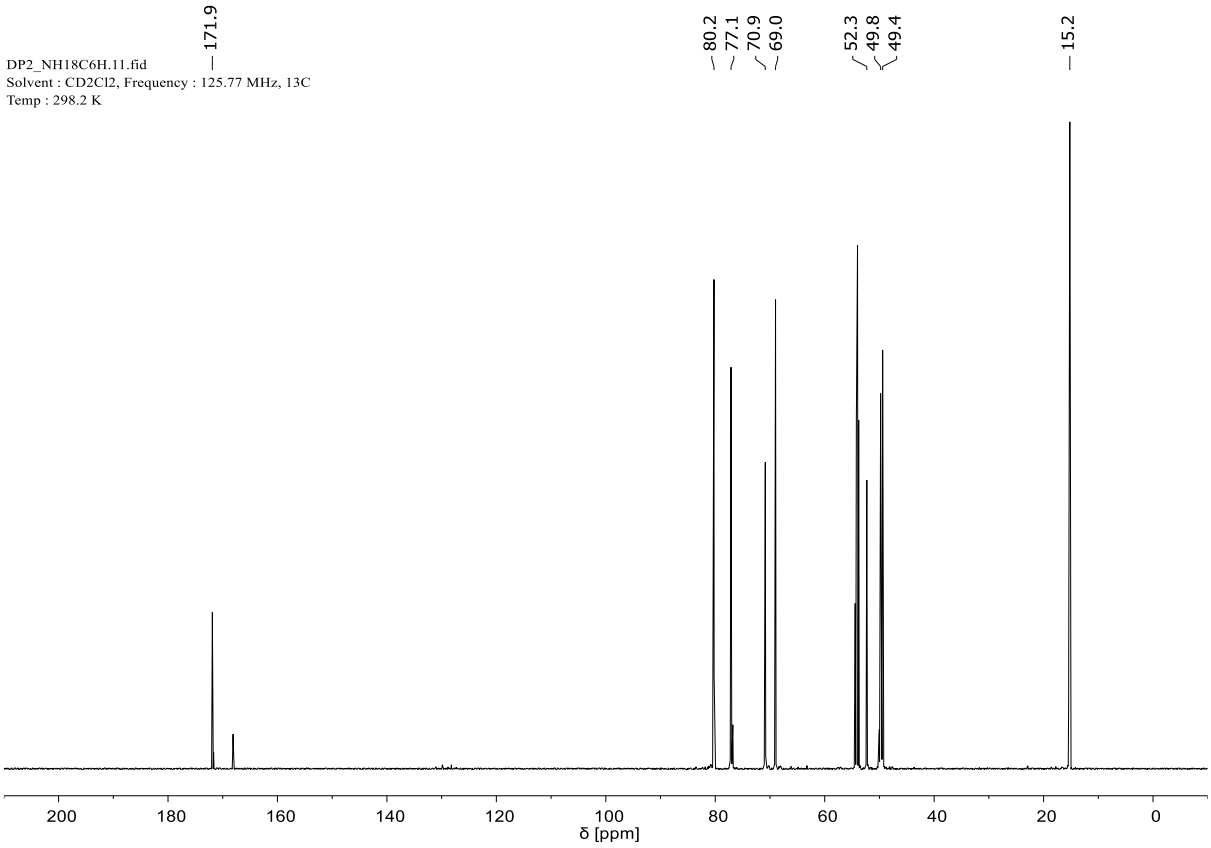
2.8.10 N-mesyl diaza-polyether 4[H]-macrocycle **5** (at 298 K)



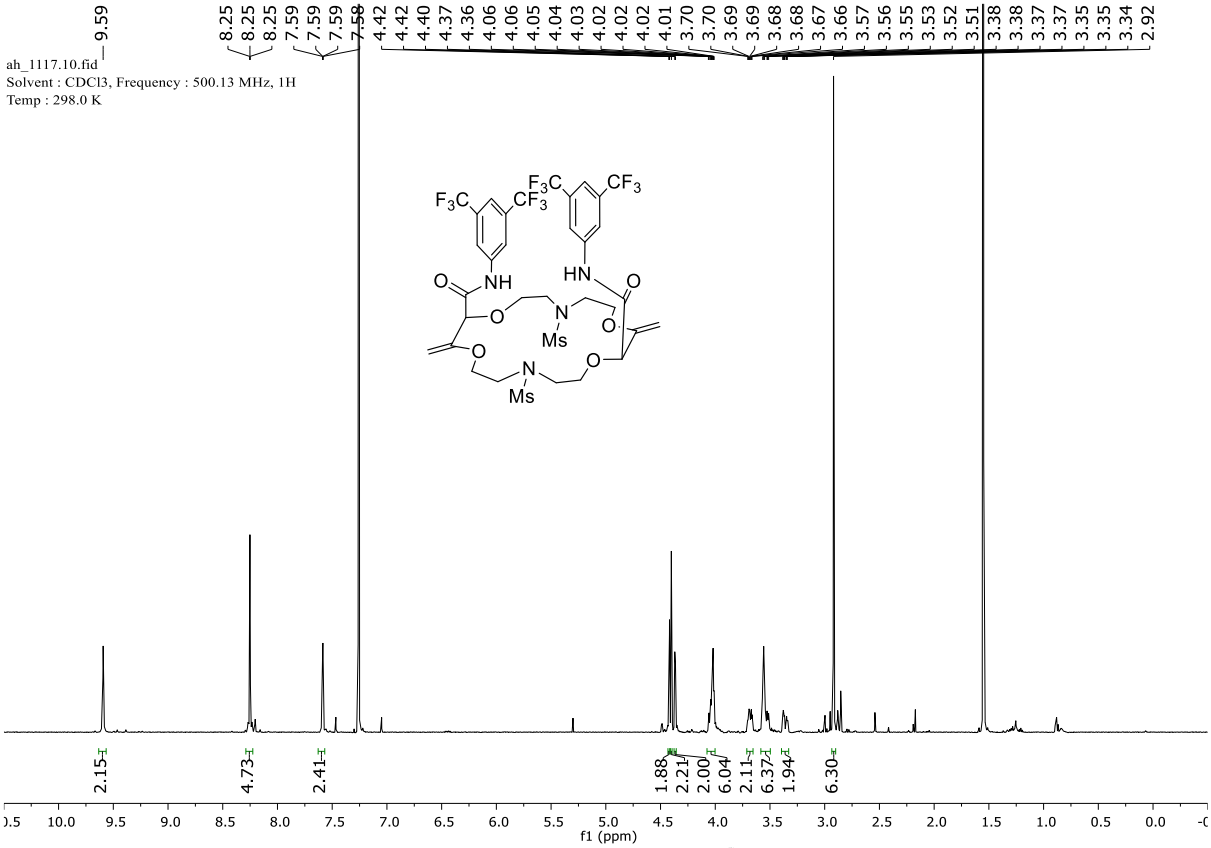


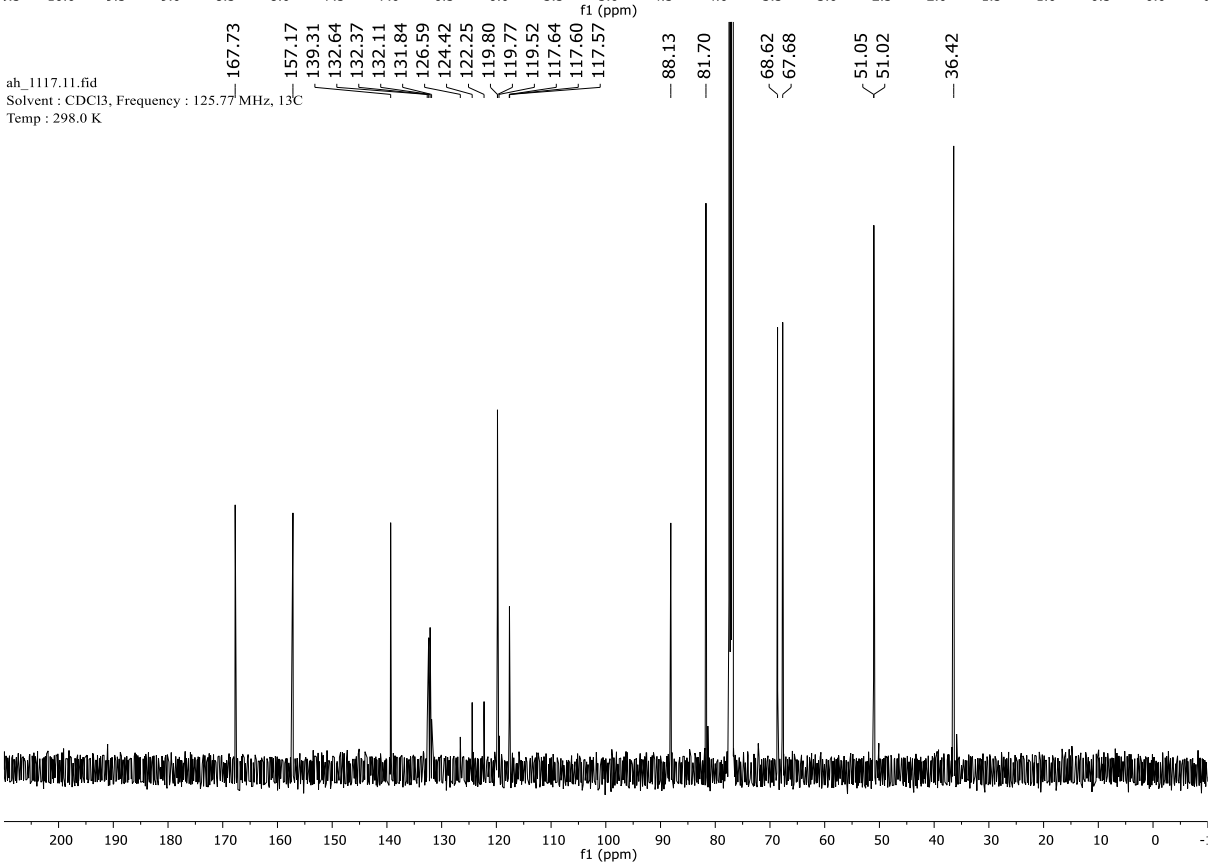
2.8.11 N-H diaza-polyether 4[H]-macrocycle **6** (at 298 K)

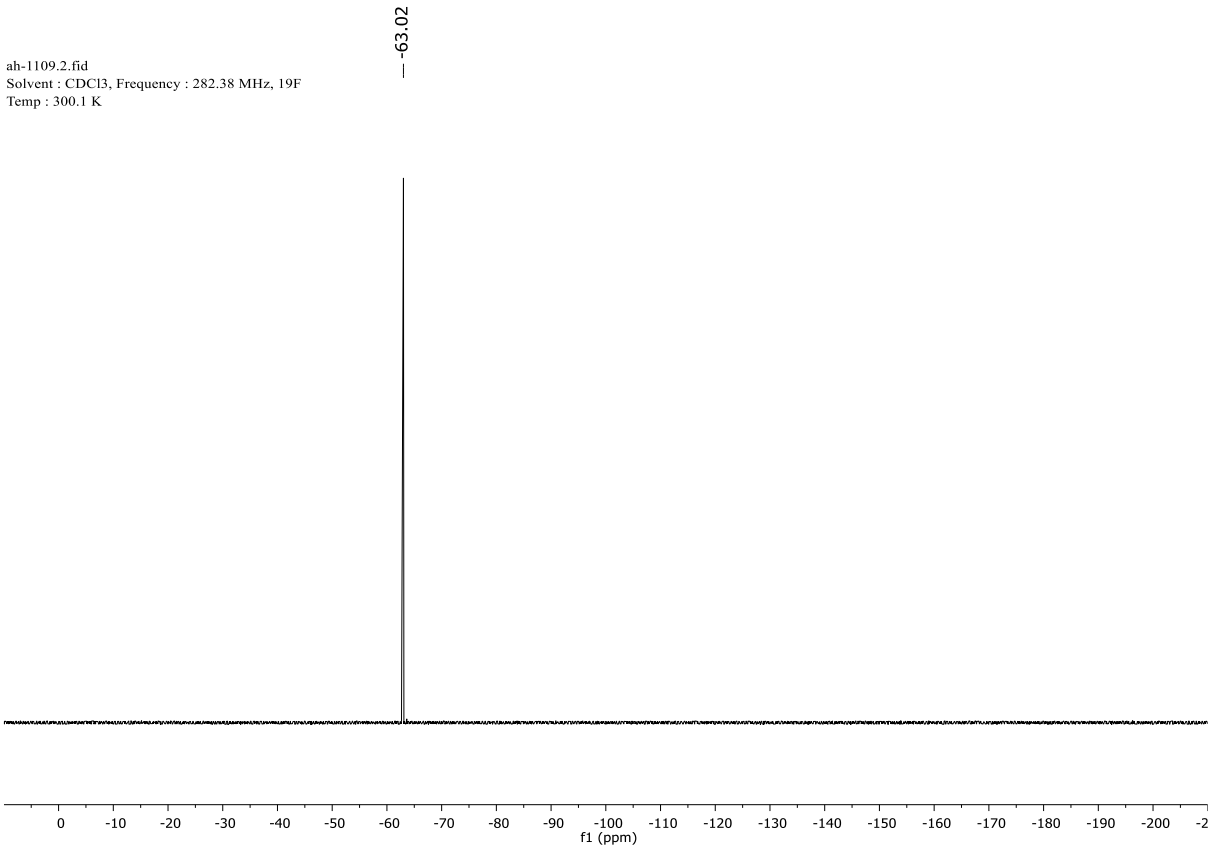




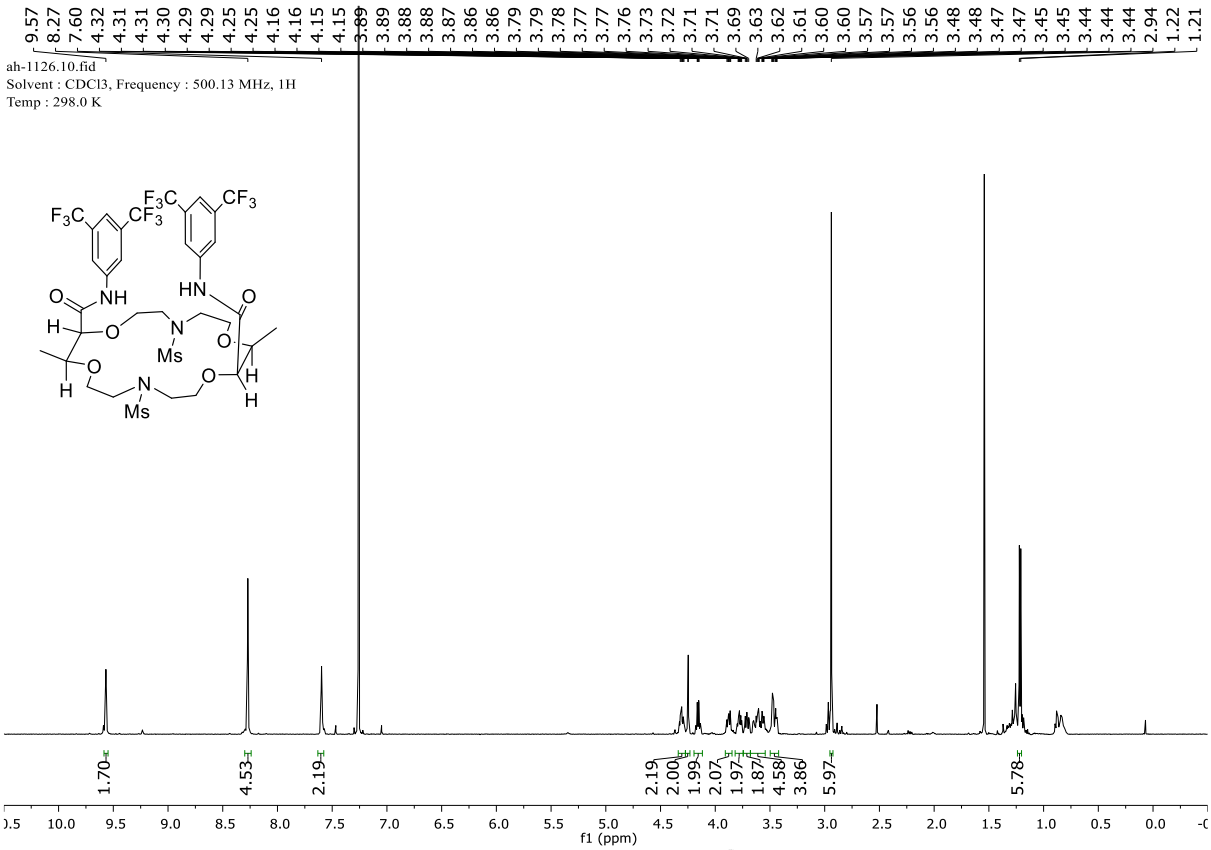
2.8.12 3,5-bistrifluoromethyl-anilide-N-mesyl-diaza-18C6 **7a** (at 298 K)

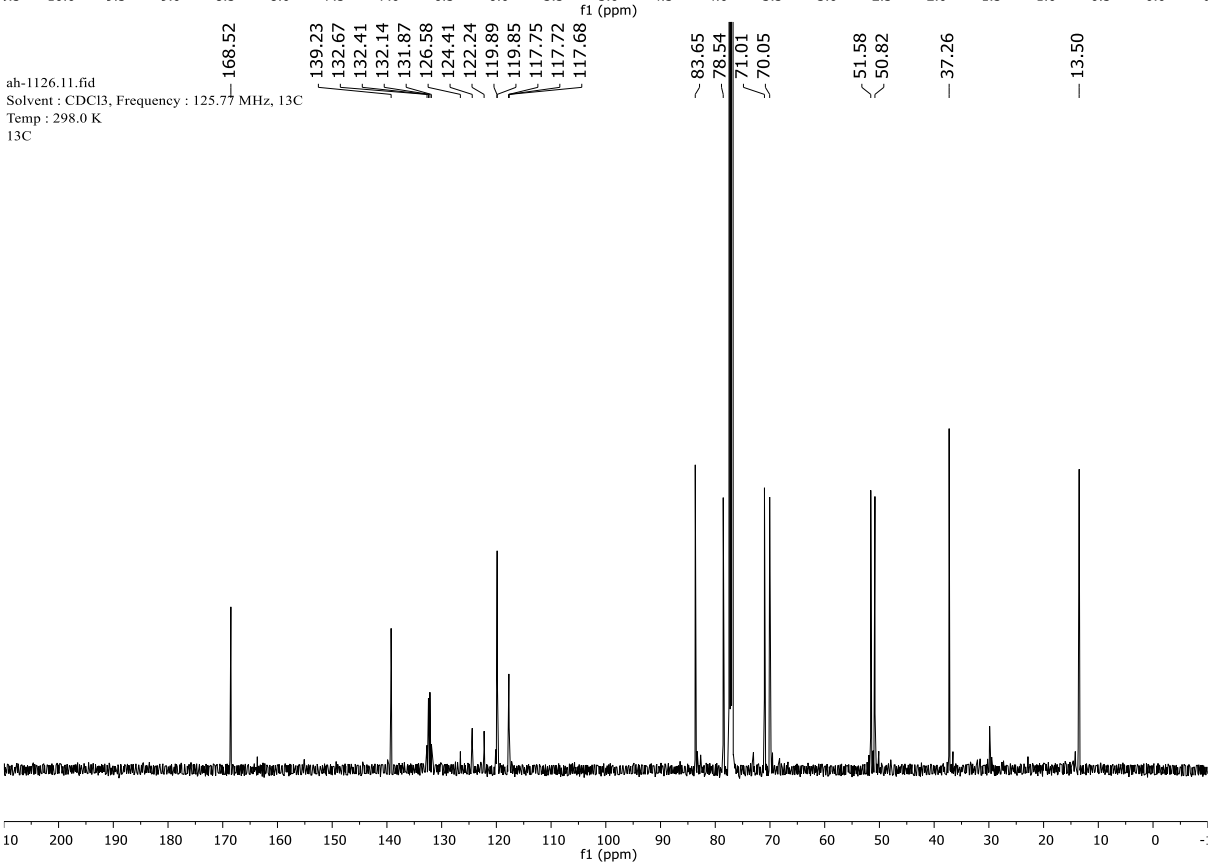


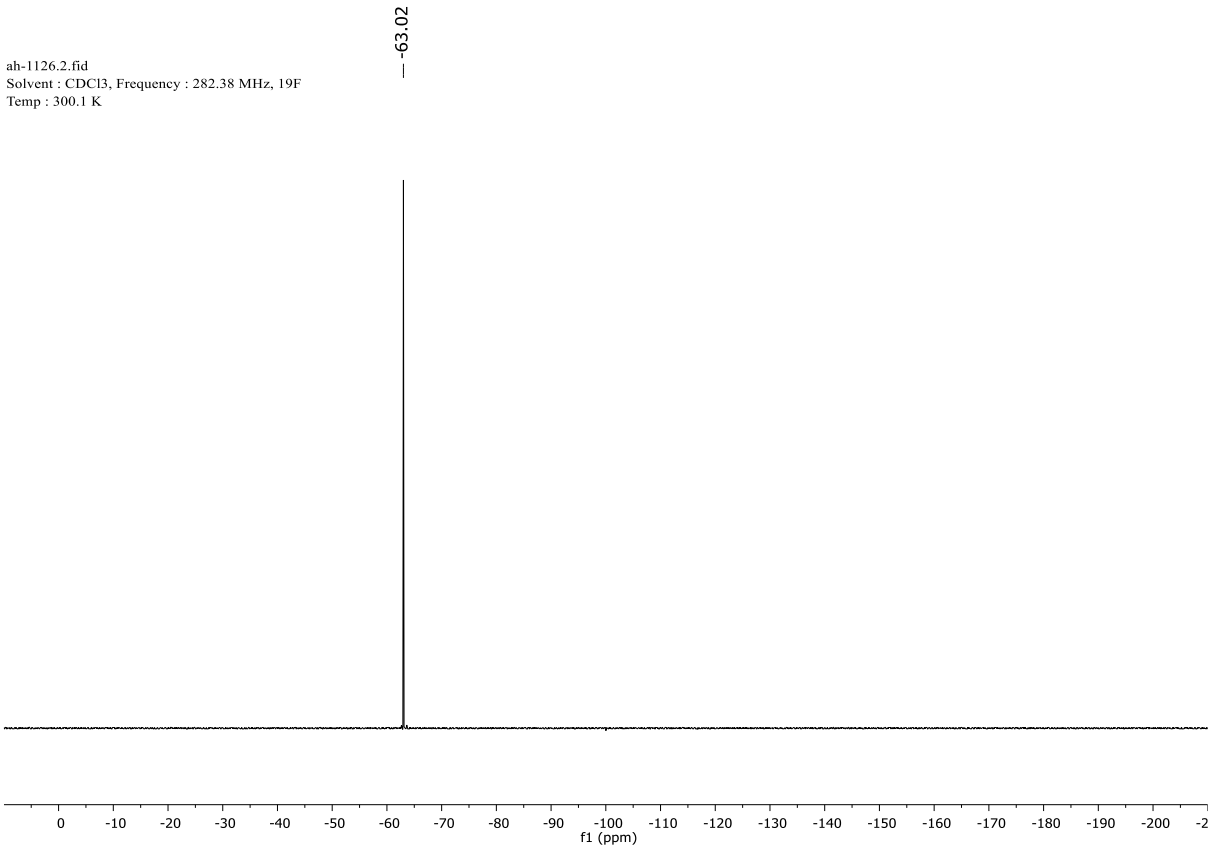



ah-1109.2.fid
Solvent : CDCl3, Frequency : 282.38 MHz, 19F
Temp : 300.1 K
-63.02
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-2
f1 (ppm)

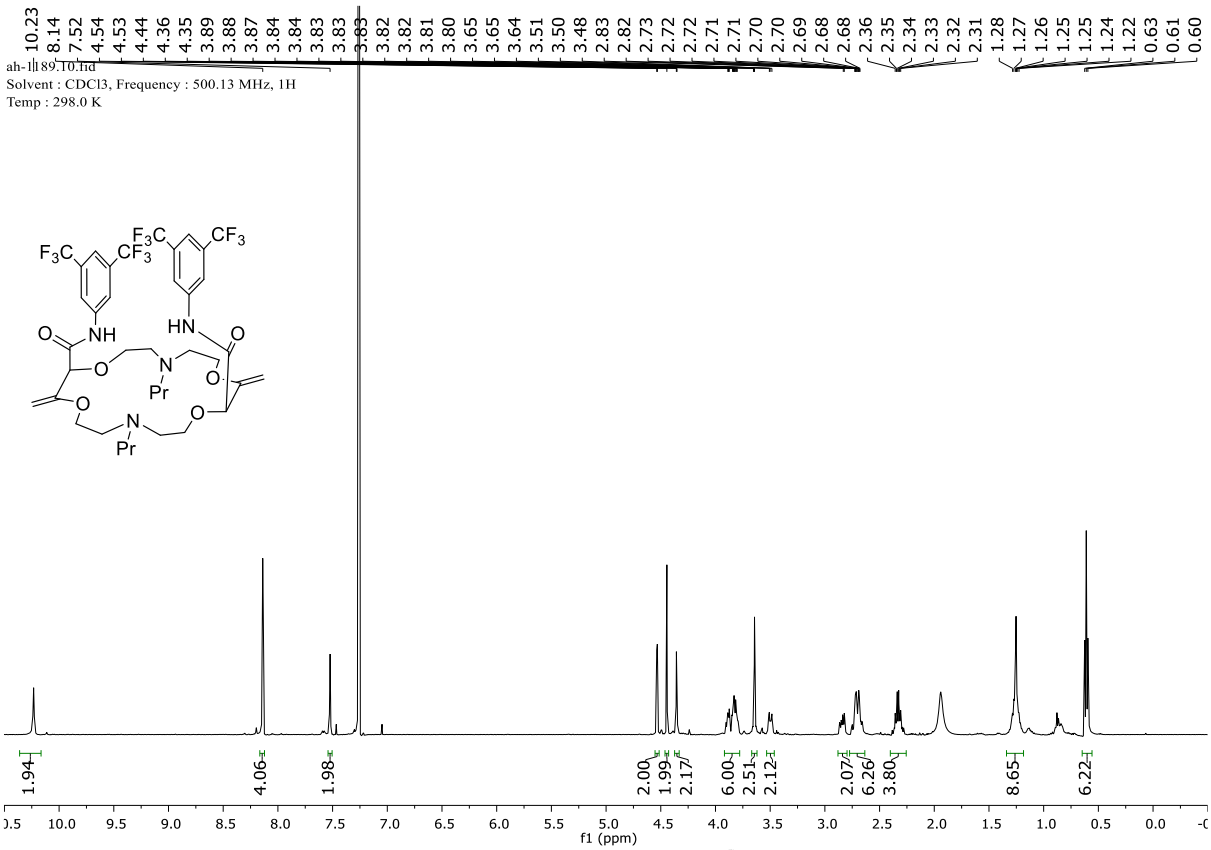
2.8.1 4[H]-3,5-bistrifluoromethyl-anilide-N-mesyl-diaza-18C6 **8** (at 298 K)

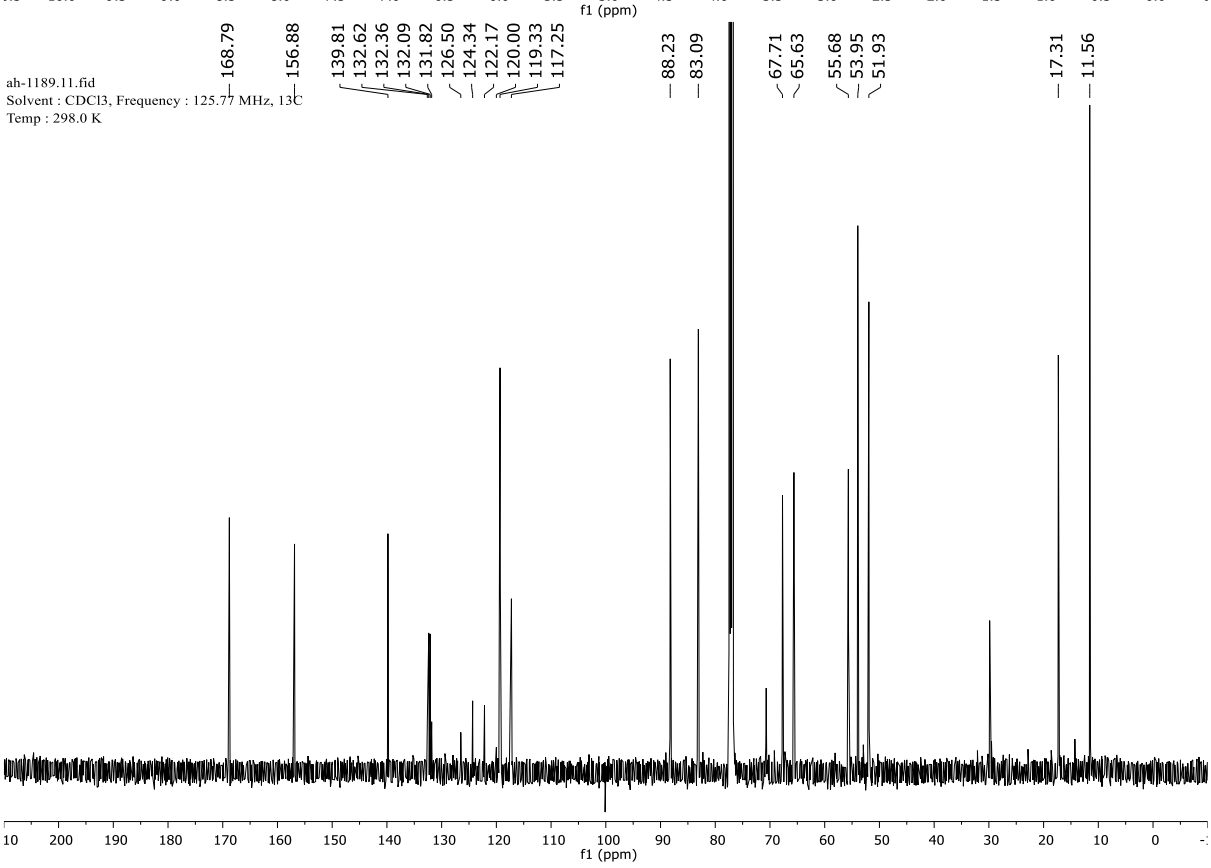


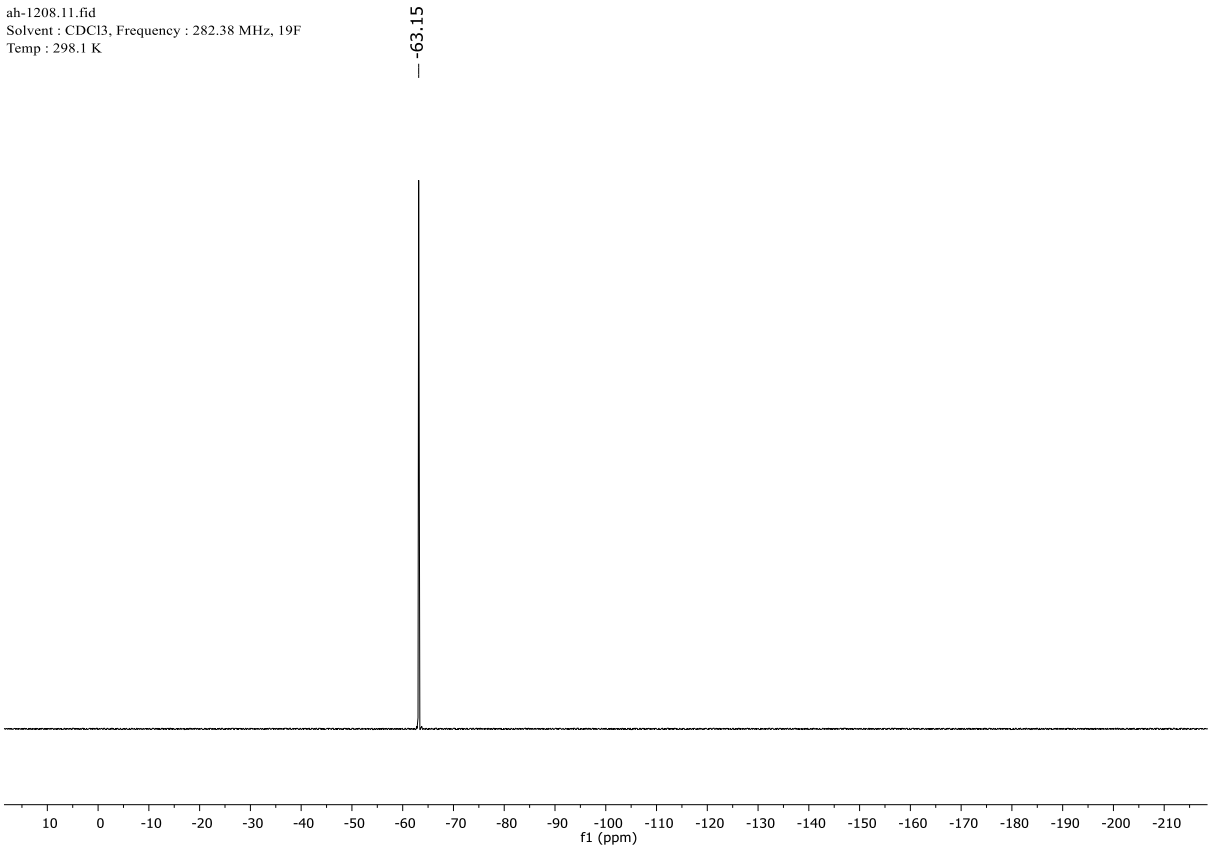



ah-1126.2.fid
Solvent : CDCl3, Frequency : 282.38 MHz, 19F
Temp : 300.1 K
-63.02
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

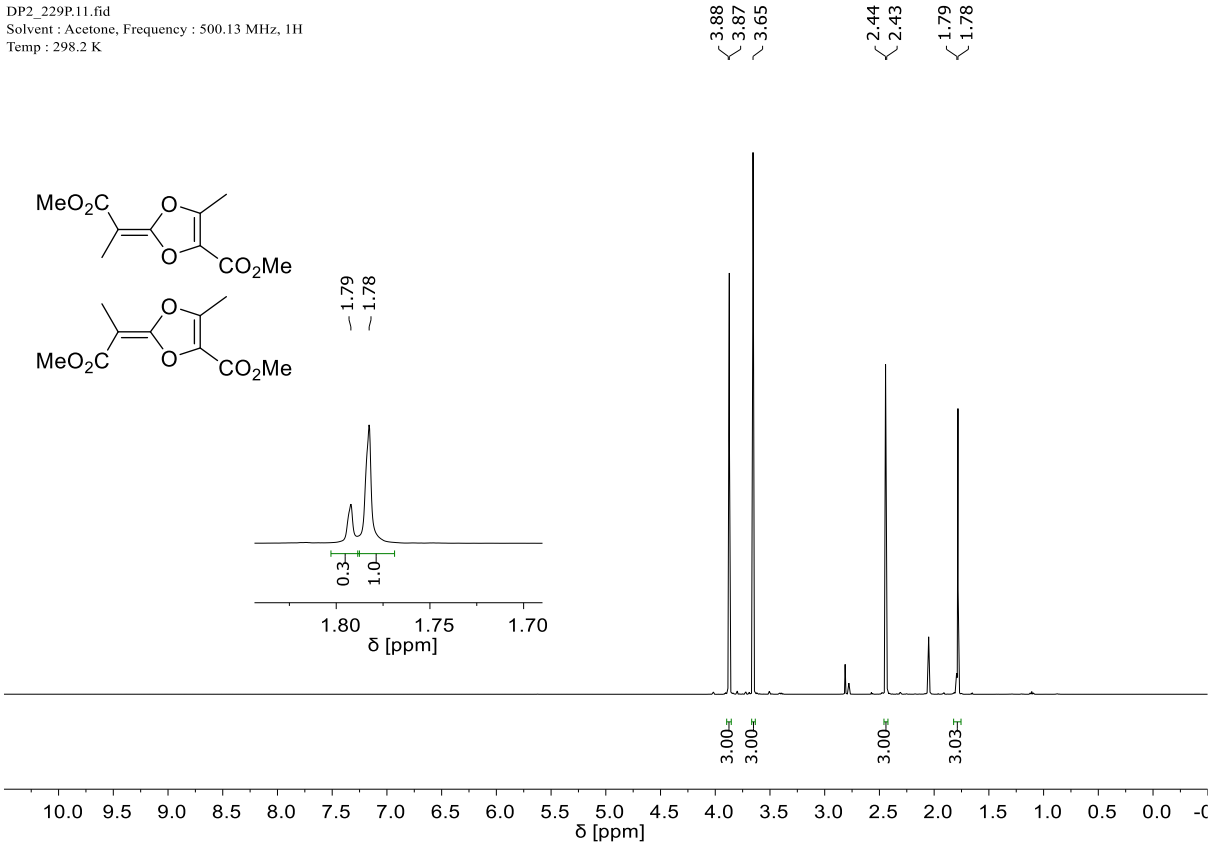
2.8.2 3,5-bistrifluoromethyl-anilide-N-propyl-diaza-18C6 **9** (at 298 K)

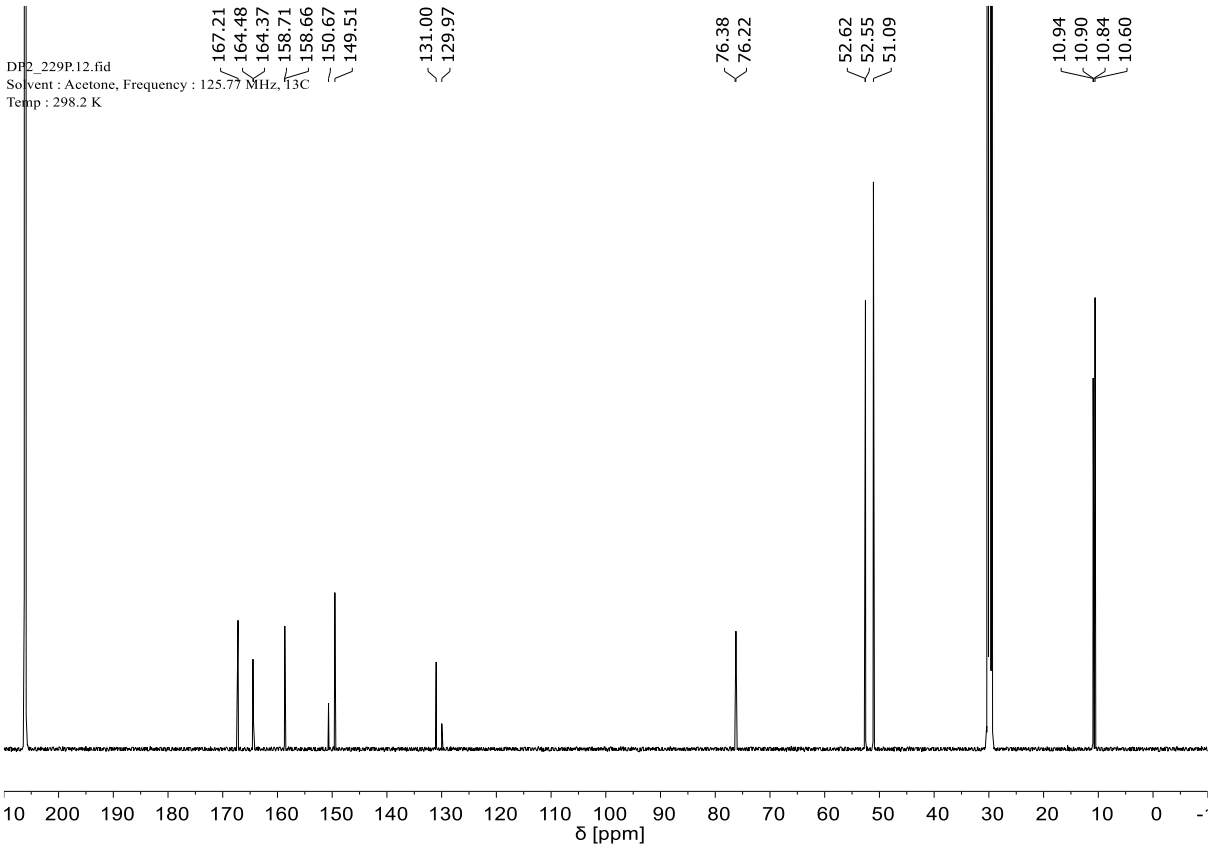





ah-1208.11.fid
Solvent : CDCl3, Frequency : 282.38 MHz, 19F
Temp : 298.1 K
-63.15
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

2.8.3 Carbene by-product **10** (at 298 K)





3 Speciation of Rh(II) Species

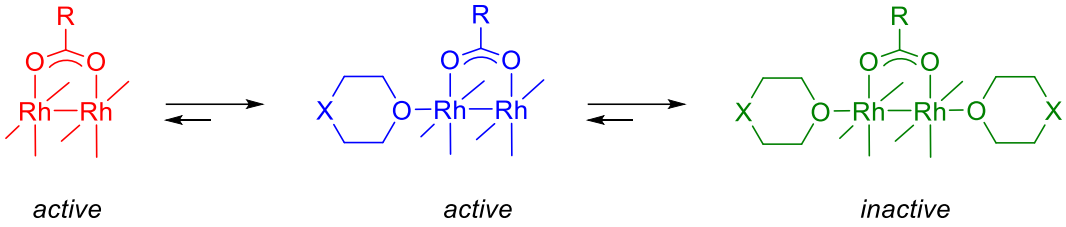


Figure S1. Different Rh(II) species present in the reaction conditions[12]

4 Solid State Structure

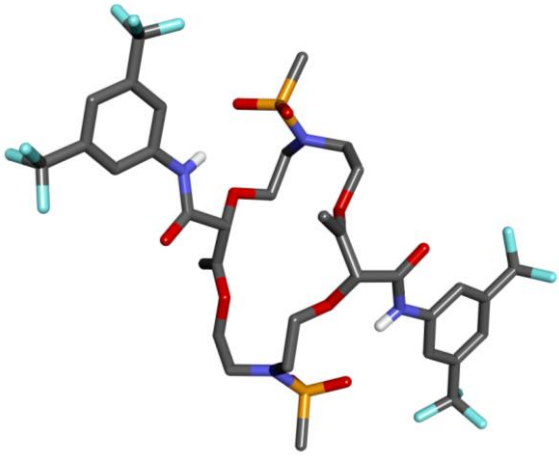


Figure S2. Stick view of the crystal structures of **7a**, hydrogen atoms hidden for clarity.

5 Crystallographic data

5.1 *N*-mesyl diaza-polyether macrocycle **3a**

Identification code	dp2_n18c6_abs	
CDCC number	1881855	
Empirical formula	C20 H34 N2 O12 S2	
Formula weight	558.61	
Temperature	180.00(14) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 14.1263(4) Å	α= 90°.
	b = 9.42572(19) Å	β= 105.768(3)°.
	c = 20.1959(5) Å	γ = 90°.
Volume	2587.92(11) $Å^3$	
Z	4	
Density (calculated)	1.434 Mg/m^3	
Absorption coefficient	2.435 mm^{-1}	
F(000)	1184	
Crystal size	0.2184 x 0.1341 x 0.0765 mm^3	
Theta range for data collection	4.550 to 72.514°.	
Index ranges	-17<=h<=15, -11<=k<=11, -24<=l<=19	
Reflections collected	9225	
Independent reflections	2545 [R(int) = 0.0185]	
Completeness to theta = 67.500°	100.0 %	
Absorption correction	Analytical	
Max. and min. transmission	0.846 and 0.699	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2545 / 0 / 166	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0864	
R indices (all data)	R1 = 0.0322, wR2 = 0.0891	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.359 and -0.316 e.$Å^{-3}$	

5.2 3,5-bistrifluoromethyl-anilide-*N*-mesyl-diaza-18C6 **7a**

CCDC number	1881856	
Empirical formula	C34 H34 F12 N4 O10 S2	
Formula weight	950.77	
Temperature	180.00(80) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2698(5) Å	α= 104.291(6)°
	b = 12.4249(8) Å	β= 99.349(5)°
	c = 18.0119(12) Å	γ = 109.794(5)°
Volume	2017.9(2) $Å^3$	
Z	2	
Density (calculated)	1.565 Mg/m^3	
Absorption coefficient	2.253 mm^{-1}	
F(000)	972	
Crystal size	0.522 x 0.205 x 0.026 mm^3	
Theta range for data collection	3.999 to 73.200°.	
Index ranges	-8<=h<=12, -15<=k<=15, -21<=l<=22	
Reflections collected	13885	
Independent reflections	7746 [R(int) = 0.0499]	
Completeness to theta = 67.684°	99.3 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.988 and 0.510	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7746 / 46 / 599	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1681	
R indices (all data)	R1 = 0.1199, wR2 = 0.2014	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.432 and -0.337 e.$Å^{-3}$	

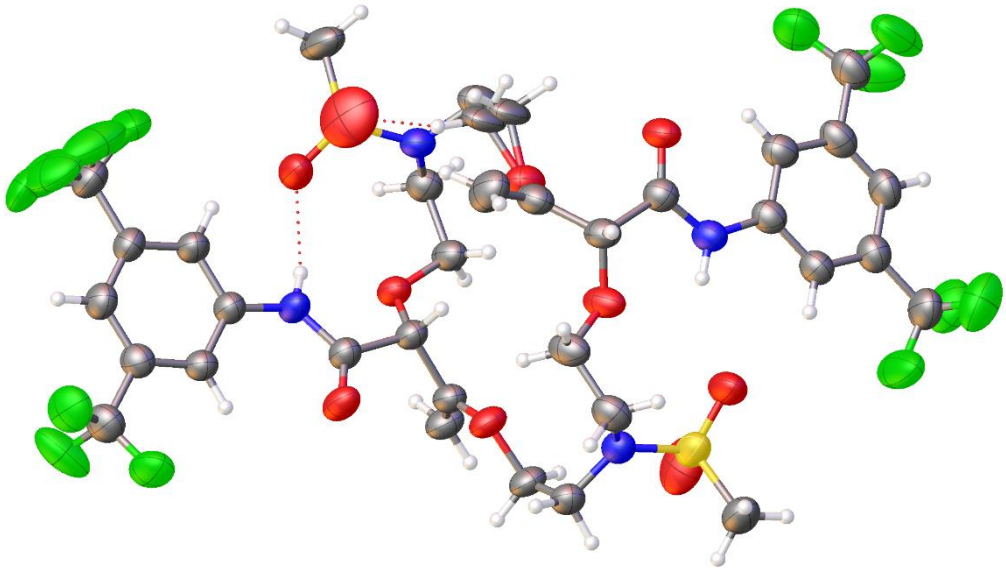


Figure S3: View of the asymmetric unit. Displacement ellipsoids are depicted at 50 percent probability level.

COMMENTS:

A small disorder was refined with 2 positions for C9 (C9A and C9B). This disorder may be induced by short contacts between the hydrogens bound to the C9 atom of one macrocycle and the hydrogens bound to the C9 atom of the symmetry equivalent neighbouring macrocycle.
EADP restraints were applied on C9A and C9B
EADP C9B C9A
One of the CF_3 group is also disordered and was refined using the following restraints:
SADI 0.04 F54A F55A F55A F53A F53A F54A
SADI F53B C52 F52B C52 F54B C52
SADI 0.04 F54B F53B F53B F54B
RIGU C52 F53B F54B F52B
RIGU C52 F53A F55A F54A

5.3 Carbene by-product 10

Empirical formula	C10 H12 O6	
Formula weight	228.20	
Temperature	180(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 9.4737(8) Å	α= 90°.
	b = 14.9377(15) Å	β= 91.353(8)°.
	c = 7.3535(7) Å	γ = 90°.
Volume	1040.34(17) $Å^3$	
Z	4	

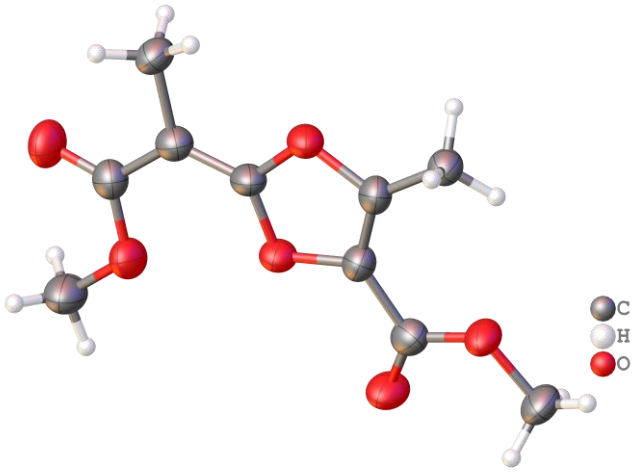


Figure S4: View of the structure of 10.

6 GC-MS traces

6.1 Procedure

An aliquot (0.1 ml) of the crude mixture (section 2.3.1) is taken and passed through 1 cm of neutral alumina eluted with 1:1 EtOAc:DCM solution (5 ml). This solution is then analyzed by GC-MS.

Method: the experiment lasts 46 min. With first heating at 60 °C for 5 min, then a gradient of 10 °C per minute is applied until 320 °C is reached and kept for 15 additional minutes.

6.2 GC-MS traces and mass profile

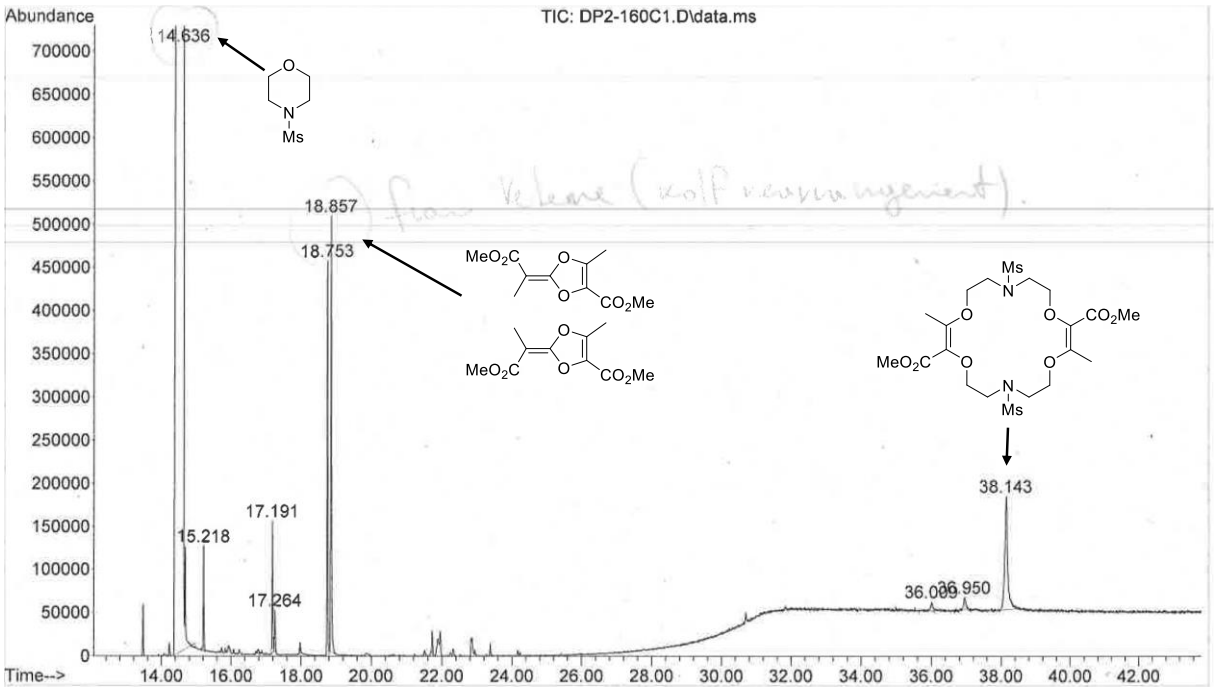


Figure S5: GC-MS trace of the crude reaction mixture.

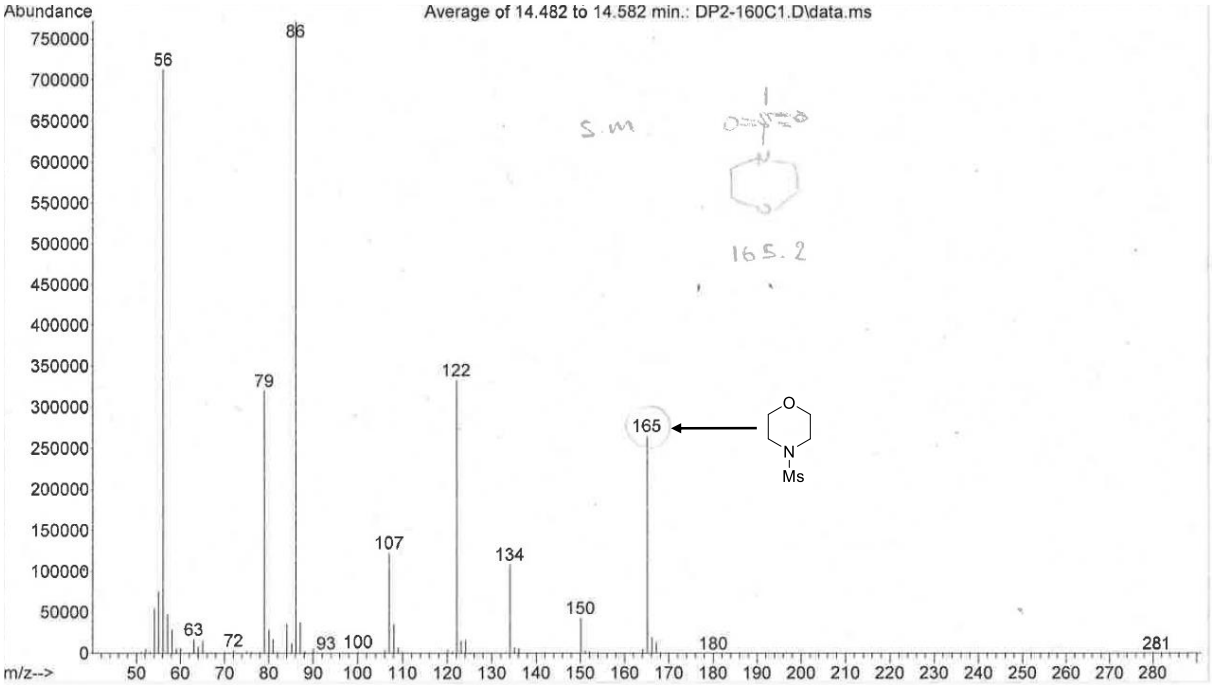


Figure S6: Mass profile the signal at 14 min (morpholine starting material **2a**).

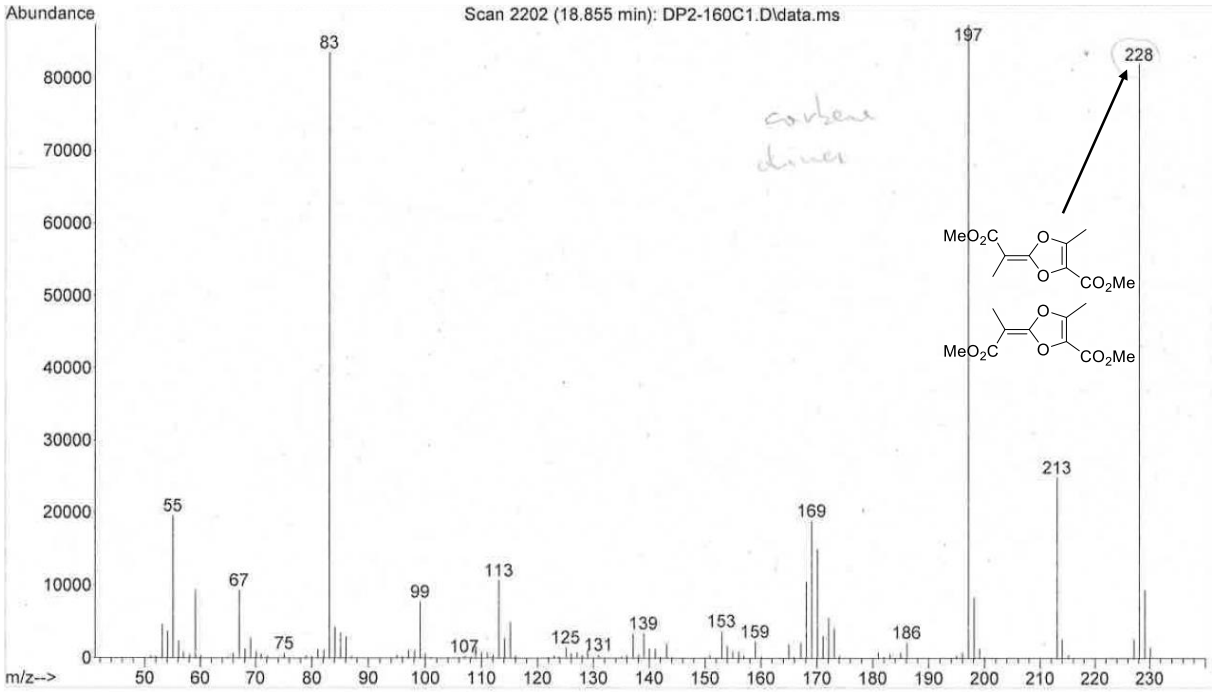


Figure S7: Mass profile the signal at 18 min (carbene by-product **10**).

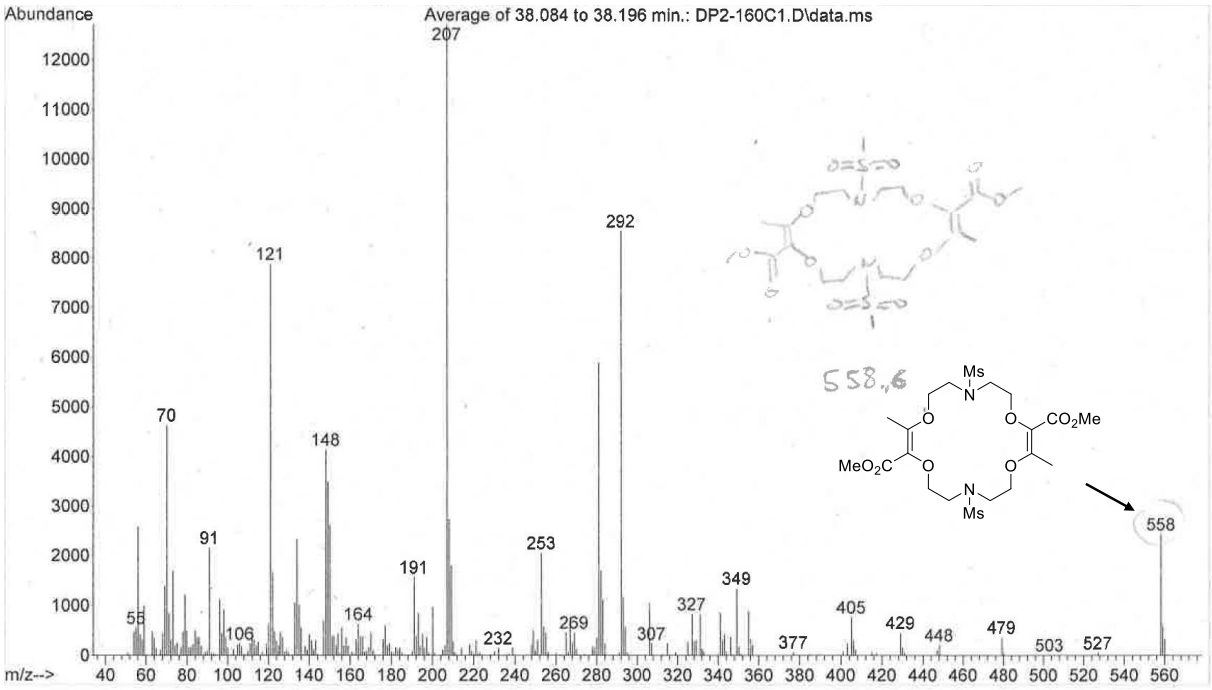


Figure S8: Mass profile the signal at 38 min (diaza macrocycle **3a**).

7 References

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(8) A singlet signal of an unknown impurity at –73.4 ppm in ^{19}F NMR with an integration of 1% is visible both at 282 K and 393 K.
(9) The configuration of the major diastereoisomer could not be attributed unambiguously.
(10) The configuration of the major diastereoisomer could not be attributed unambiguously. The all-*cis* product is assumed to be the major component.
(11) The configuration of the major isomer could not be attributed unambiguously.
(12) Poggiali, D.; Homberg, A.; Lathion, T.; Piguet, C.; Lacour, J., *ACS Catal.* **2016**, *6*, 4877-4881.