Supplementary Information for
Facile synthesis of a C4-symmetrical inherently chiral calix[4]arene

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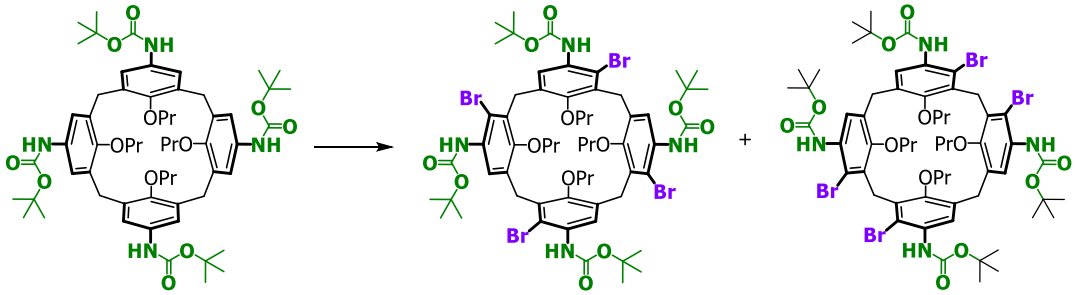
Contents

S1) Details regarding the optimisation of the tetrabromination reaction.

Table S1. Optimisation study towards C_4 isomer **3b**.



2b **3b** **4b**

Entry[a]	Br source (equiv)	Catalyst (equiv)	Temp (°C)	Solvent	Time (h)[b]	Yield (%)[c] 3b	Yield (%)[c] 4b	Ratio[d] (3b:4b)
1	NBS (5)	PTSA (2)	–35	CH_2Cl_2	5	46	17	2.8:1
2	NBS (5)	-	–78	CH_2Cl_2	9	15	19	0.8:1
3	NBS (5)	PTSA (12)	–78	CH_2Cl_2	3	28	22	1.1:1
4	NBS (5)	PTSA (20 mol %)	–78	CH_2Cl_2	6	56	17	3.4:1
5	NBS (5)	H_2SO_4 (20 mol %)	–78	CH_2Cl_2	4	36	28	1.3:1
6	NBS (5)	PTSA (20 mol %)	–60	CH_2Cl_2	5	59	15	3.8:1
7	NBS (5)	PTSA (20 mol %)	–42	CH_2Cl_2	4	69	14	4.9:1
8	NBS (5)	PTSA (20 mol %)	–35	CH_2Cl_2	3	62	15	4.0:1
9	NBS (5)	PTSA (20 mol %)	0	CH_2Cl_2	1	44	17	2.6:1
10	Br_2 (5)	-	–42	CH_2Cl_2	4	26	19	1.3:1
11	Br_2 (5)	PTSA (20 mol %)	–42	CH_2Cl_2	3	44	15	2.8:1
12	Br_2 (5)	H_2SO_4 (20 mol %)	–42	CH_2Cl_2	2	20	17	1.2:1
13	NBS (5)	PTSA (20 mol %)	–42	CH_3CN	5	40	10	3.9:1
14	NBS (5)	PTSA (20 mol %)	–42	THF	4	n.d.[e]	n.d.[e]	n.d.[e]
15	NBS (5)	PTSA (20 mol %)	–42	Butanone	4	68	14	4.8:1
16	NBS (5)	Camphorsulfonic acid (2)	–42	CH_2Cl_2	4	72	n.d.[e]	n.d.[e]

[a]Conditions: Reactions performed on 60 mg scale, catalysts added at rt followed by stirring for 15 min at designated temperature followed by addition of brominating reagent. [b]Time taken for starting material to be completely consumed (monitored hourly by TLC), which was followed by stirring for a further 8h while warming to rt. [c]Isolated yields. [d]Ratio of isolated mass. [e]not determined (see text).

The bromination reaction on tetra-Boc calixarene **2b** using the original conditions used with the methyl carbamate (see paper), gave an improved yield of the major (C_4) isomer (Table S1, entry 1). Encouraged by this, an optimisation study was carried out. The first step was to look at the acid additive (Table S1, entries 2-5). Whilst the reaction did proceed without any PTSA (entry 2), it was rather sluggish and seemed to slightly favour the C_{2v} isomer **4b**. Excess PTSA (entry 3) led to rapid bromination, but gave a poor ratio of **3b**:**4b**, which was deemed undesirable. Reducing the equivalents to the acid to catalytic amounts (20% - entry 4) appeared to be an optimum, with a good ratio (3.4:1) and yield (56%) of **3b** being observed after 6 hours at –78 °C. The use of PTSA also checked against sulfuric acid (entry 5), but this gave lower yields and observable cleavage of the Boc-groups. A temperature study was also evaluated (entries 5-9), with an optimum temperature being found at –42 °C; temperatures above or below this gave lower ratios of **3b**:**4b**. Swopping out NBS for molecular bromine (Br_2) was also undesirable (entries 10-12), giving poorer yields and ratios which attributed (in part) to HBr being formed and cleaving the Boc-groups. Finally, the choice of solvent was looked at (entries 13-15), guided by literature examples. Acetonitrile (entry 13) resulted in a slower reaction with a slightly weaker ratio for the desired product. THF (entry 14) performed even worse with starting material still visible on TLC after 4 hours @ –42 °C. Inspection of the TLC also revealed both final product spots forming with no hint of a better ratio for the desired product. Butanone (entry 15) was the only other solvent tested that showed a similar profile to our optimised results, and could thus be considered an alternative, more environmentally friendly option. Camphorsulfonic acid was also attempted (entry 16) to see if the chiral acid might influence the enantioselectivity of the reaction. Whilst the yield was good, unfortunately the isolated product showed no optical activity and so was deemed racemic.

S2) Details of procedures attempted for the removal of the Boc-groups.

Three methods for removing the Boc-groups were investigated.

1. The first was that of a standard deprotection with trifluoroacetic acid. During this procedure calixarene **3b** was stirred at 40 °C with trifluoroacetic acid for 27 hours. Subsequently the reaction was neutralized, and the product extracted. The products of the reaction were isolated *via* silica gel flash chromatography. On inspection of the NMR spectrum, it was evident that the signal produced by the $(CH_3)_3$ group of the Boc group was still partially present at 1.40 ppm – 1.46 ppm. Thus, only a partial deprotection was achieved.
2. An unconventional method was then explored. During purification of **3b** it was noted that the Boc-groups were partially cleaved when 'dry-loading'[1] the silica-gel column. A method was identified in the literature where Boc groups can be removed when heated under reflux in toluene.[2] Thus calixarene **3b** was heated under reflux in toluene with silica gel for 20 hours. This reaction was more successful than the trifluoroacetic acid reaction resulting in an isolated yield of 43% for calixarene **5**. This was confirmed by inspection of the ^{1}H NMR spectrum where the signal produced by the Boc groups was completely absent at 1.40 ppm.
3. A third method was investigated where a medium strength acid (10% aqueous hydrochloric acid solution) was used in THF (approximately 1:1 ratio). It was found that doing this for 3 hours @ 50 °C or under reflux, gave optimum yields (80-88% over 5 experiments). Using a sealed vessel gave slightly lower yields (~70%), whilst leaving the reaction for longer than 3 hours, resulted in slightly lower yields, suggesting decomposition of the product.

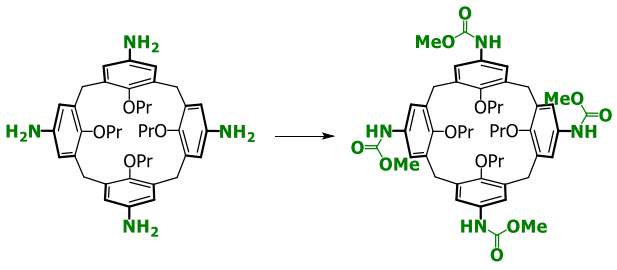
S3) General Experimental details

All chemicals were purchased from Merck or Sigma-Aldrich; tetraamino calix[4]arene **1** was synthesized using established literature procedures.[3] Dry tetrahydrofuran was distilled under nitrogen from sodium wire/sand and using benzophenone as an indicator. Dichloromethane was dried from calcium hydride under nitrogen. Other reagents that required purification were done so according to standard procedures.[4] All reactions were performed under positive pressure of 2.8 kPa of 5.0 grade argon (Air Products). Low temperature reactions were performed in a Dewar containing ice (0 °C), solid CO_2 and acetonitrile (–42 °C) or solid CO_2 and acetone (–78 °C). Other temperatures were controlled manually through monitoring the temperature of the cooling liquid and adjusting with dry ice. Column chromatography was performed using 230 – 400 nm silica and thin layer chromatography (TLC) was performed using Macherey-Nagel DC-Fertigfolien ALUGRAM Xtra SIL G/UV_{254} TLC plates. Visualization of compounds on TLC plates was performed by using a UV lamp or using a cerium ammonium molybdate (CAM) solution followed by heating. Preparative TLC plates were Macherey-Nagel Pre-coated TLC plates SIL G-100 UV_{254} 1.00 mm silica gel 60 with fluorescent indicator (glass backed). Both ^{1}H and ^{13}C NMR spectra were obtained using either a Varian 300 MHz VNMRS or Varian 400 MHz Unity INOVA NMR spectroscopy instruments. Chemical shifts were recorded using the residual solvent peaks (chloroform-*d* or DMSO-d_6) and reported in ppm. Unless otherwise stated, NMR spectra was obtained at room temperature. All mass spectrometry spectra were obtained by Central Analytical Facility (CAF) at Stellenbosch University using a Waters API Q-TOF Ultima mass spectrometer. IR spectra were obtained using a Thermo Nicolet Nexus FTIR instrument using the ATR attachment. Melting points were obtained using a Gallenkamp Melting Point Apparatus.

[1] The crude sample was dissolved in a minimum amount of methylene chloride and added to a small amount of silica gel. The solvent was then removed on a rotary evaporator with heating and the solid then added directly to the top of the column.
[2] M.-J. Zhang, X.-H. Yuan, L. Ma, J.-Y. Zhao and L.-X. Gao, *Chemical Journal of Chinese Universities*, 2007, **28**, 2330–2332.
[3] A. M. A. Van Wageningen, E. Snip, W. Verboom, D. N. Reinhoudt and H. Boerrigter, *Liebigs Ann.*, 1997, **11**, 2235–2245.
[4] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon Press: Oxford, 1988.

S4) Experimental details and spectra for all new compounds.

S4.1) 5,11,17,23-tetrakis(methoxycarbonylamino)-25,26,27,28-tetrapropoxycalix[4]arene (2a)



1 **2a**

In an oven dried 2-neck round-bottomed flask, tetra-aminocalixarene **1** (600 mg, 0.919 mmol) was dissolved in DCM (30 mL). The reaction mixture was cooled to −10 °C (acetone/ice bath) and pyridine (592 µL, 7.35 mmol, 8 eq) was added, followed by the dropwise addition of methyl chloroformate (568 µL, 7.35 mmol, 8 eq). The reaction was then allowed to warm to room temperature and stirred for another hour, after which the mixture was diluted with DCM (20 mL) and H_2O (30 mL) and the layers separated. The organic layer was then successively washed with aliquots of H_2O (30 mL × 3), brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified *via* silica gel flash column chromatography (EtOAc:PET 1:1) to afford calixarene **2a** as a pale orange solid (797 mg, 98%).

***R_f* =** 0.14 (EtOAc:PET 1:1);

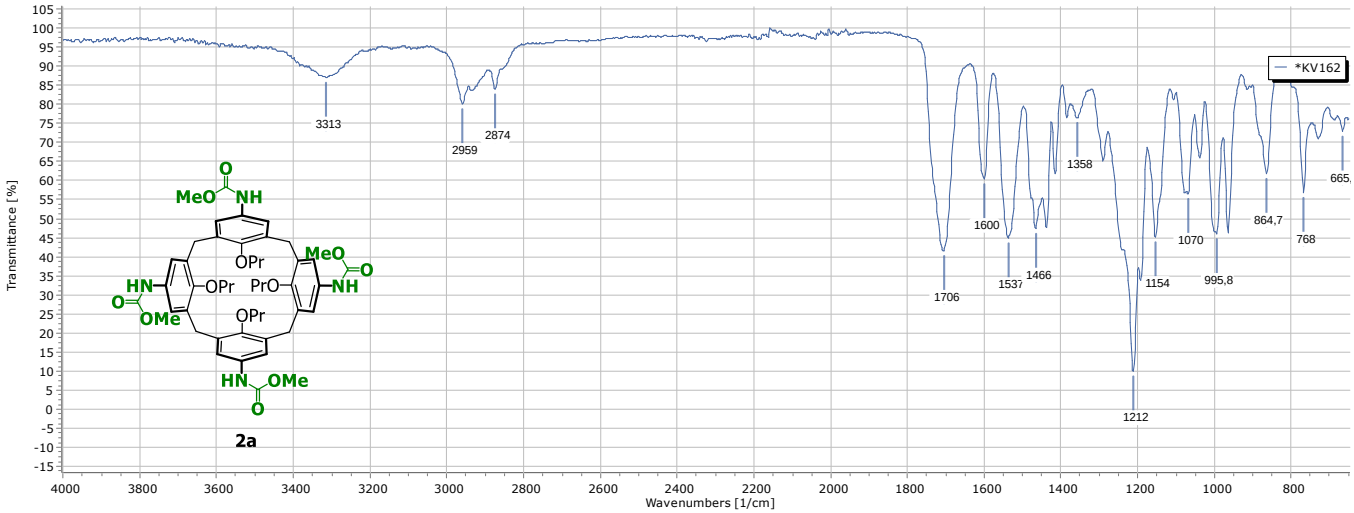
Mp = 228-232 °C;

IR (ATR, cm^{-1}) 3313 (N-H) 2959 and 2874 (C-H) 1705 (C=O) 1600 (arene) 1537 and 1466 (C=C) 1212 (C-O-C) 995 and 964 (C-N) 768 (C-H);

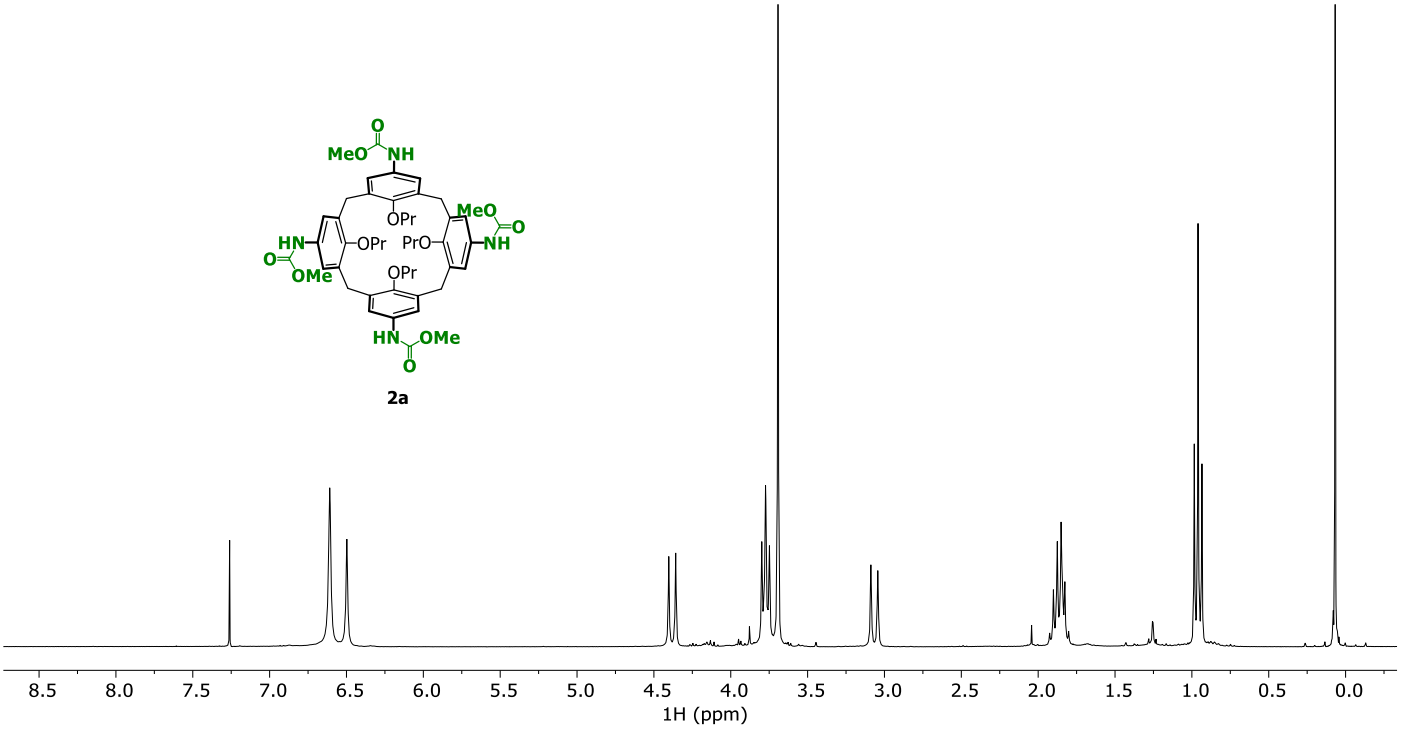
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 6.61 (br. s, 2H, Ar*H*), 6.56 (br. s, 1H, N*H*) 4.38 (d, $^2J_{HH}$ = 13.4 Hz, 1H, ArC$H_{2(ax.)}$Ar), 3.77 (t, $^3J_{HH}$ = 7.4 Hz, 2H, OCH_2CH$_2$), 3.68 (s, 3H, OCH_3), 3.06 (d, $^2J_{HH}$ = 13.5 Hz, 1H, ArC$H_{2(eq.)}$Ar), 1.93 – 1.80 (m, 2H, OCH$_2$CH_2CH$_3$), 0.96 (t, $^3J_{HH}$ = 7.4 Hz, 3H, OCH$_2$CH$_2$CH_3);

^{13}C{1H} (100 MHz, Chloroform-*d*) δ ppm 154.6 (Ar*C*), 153.0 (NH*C*OO), 135.3 (Ar*C*), 131.6 (Ar*C*), 119.7 (Ar*C*), 76.7 (O*C*H$_2$CH$_2$), 52.2 (O*C*H$_3$), 31.1 (Ar*C*H$_2$Ar), 23.1 (OCH$_2$*C*H$_2$CH$_3$), 10.3 (OCH$_2$CH$_2$*C*H$_3$);

HRMS–Positive: m/z [M+NH$_4$]$^+$ calcd. for $C_{48}H_{64}N_5O_{12}$: 902.4551; found 902.4543.

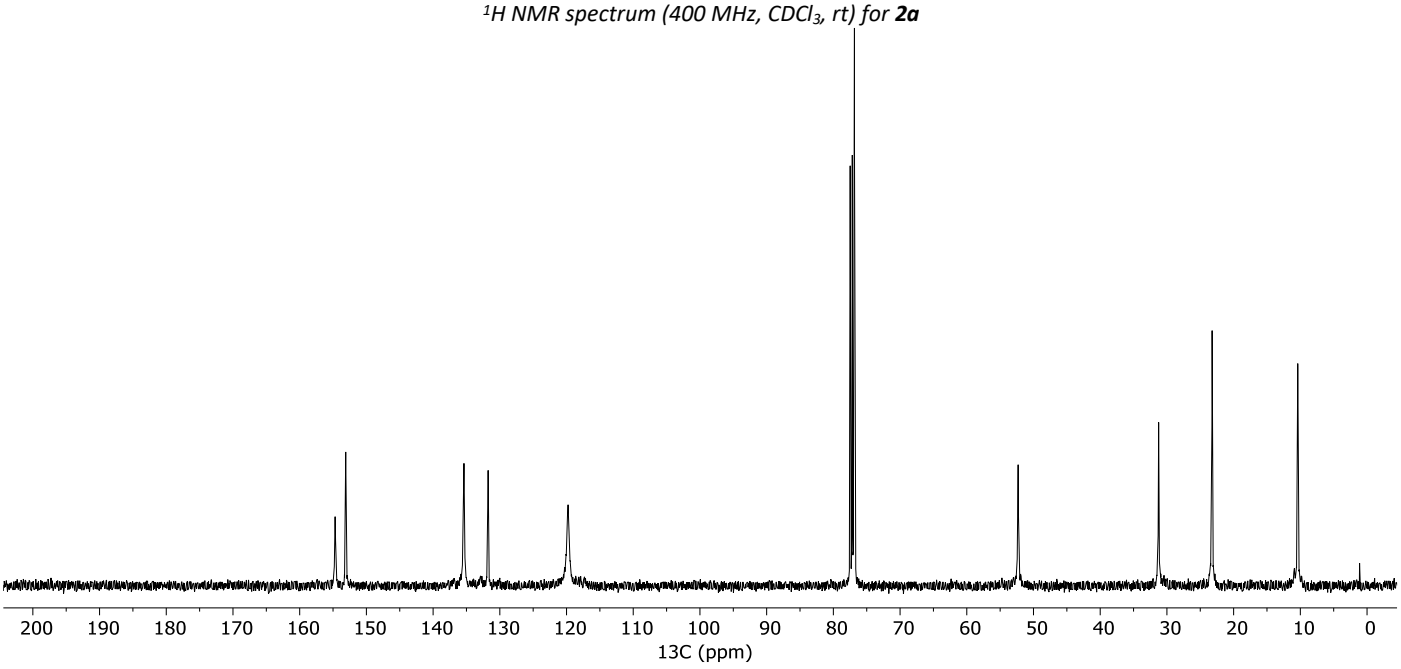


*Infrared spectrum for **2a***

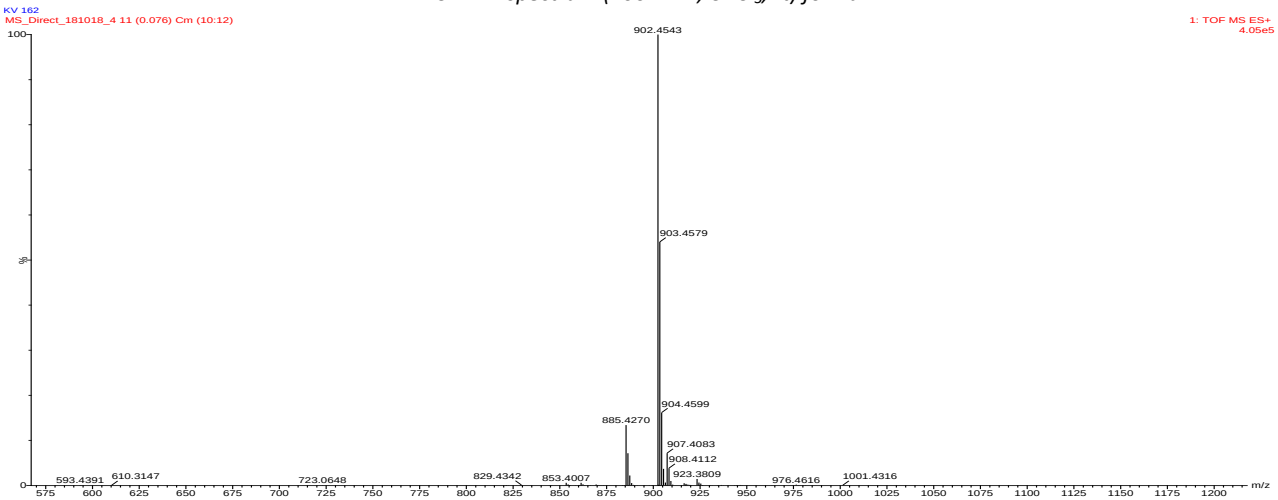


2a

*^{1}H NMR spectrum (400 MHz, $CDCl_3$, rt) for **2a***

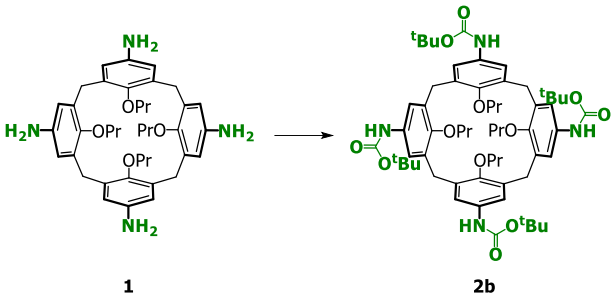


*^{13}C NMR spectrum (100 MHz, $CDCl_3$, rt) for **2a***



*ES+ HRMS for **2a***

S4.2) 5,11,17,23- tetrakis(*tert*-butoxycarbonylamino)-25,26,27,28-tetrapropoxycalix[4]arene (2b)



1 **2b**

In an oven dried 2-neck round-bottomed flask, tetra-aminocalixarene **1** (800 mg, 1.23 mmol) was dissolved in THF (30 mL). To this was added Et_3N (1.37 mL, 9.80 mmol, 8 eq), followed by the dropwise addition of a solution of Boc_2O (2.14 g, 9.80 mmol, 8 eq) in THF (15 mL) which resulted in vigorous bubbling. The reaction mixture was then heated to reflux and stirred further for two hours. After allowing to cool to rt, the reaction mixture was diluted with EtOAc (60 mL) and H_2O (30 mL) and the layers separated. The organic layer was then successively washed with sat. $NaHCO_3$ (30 mL), brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified *via* silica gel flash column chromatography (EtOAc:PET 1:9) to afford calixarene **2b** as a white solid (1.28 g, 99%).

***R*$_f$ =** 0.42 (EtOAc:PET 1:4);

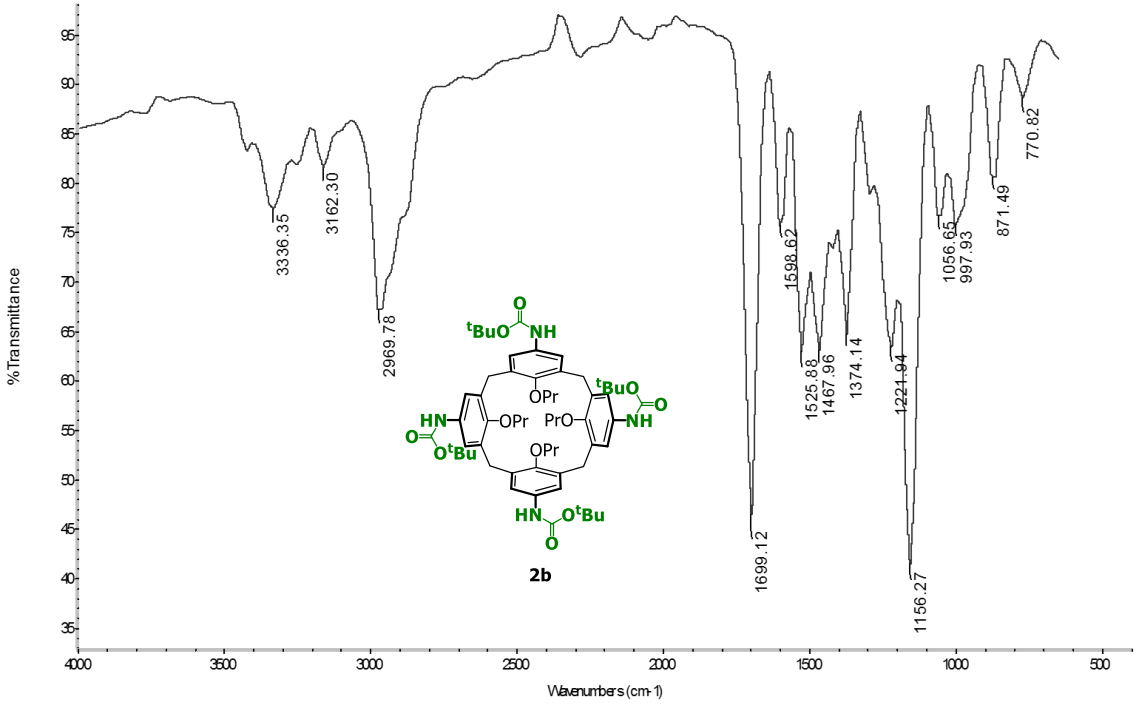
Mp = 199.5-201.1 °C;

IR (ATR, cm^{-1}) 3336 (N-H), 3162 and 2970 (C-H), 1699 (C=O), 1599 (arene), 1526 and 1468 (C=C), 1222 (C-O-C), 1057 and 998 (C-N), 771 (C-H);

^{1}H NMR (300 MHz, Chloroform-*d*)[5] δ ppm 6.60 (s, 2H, Ar*H*), 6.14 (s, 1H, N*H*), 4.37 (d, *J* = 13.3 Hz, 1H, ArC*H*$_{2(ax.)}$Ar), 3.76 (t, *J* = 7.5 Hz, 2H, OC*H*$_2$CH$_2$), 3.08 (d, *J* = 13.4 Hz, 1H, ArC*H*$_{2(eq.)}$Ar), 1.86 (h, *J* = 7.3 Hz, 2H, OCH$_2$C*H*$_2$CH$_3$), 0.95 (t, *J* = 7.4 Hz, 3H, OCH$_2$CH$_2$C*H*$_3$);

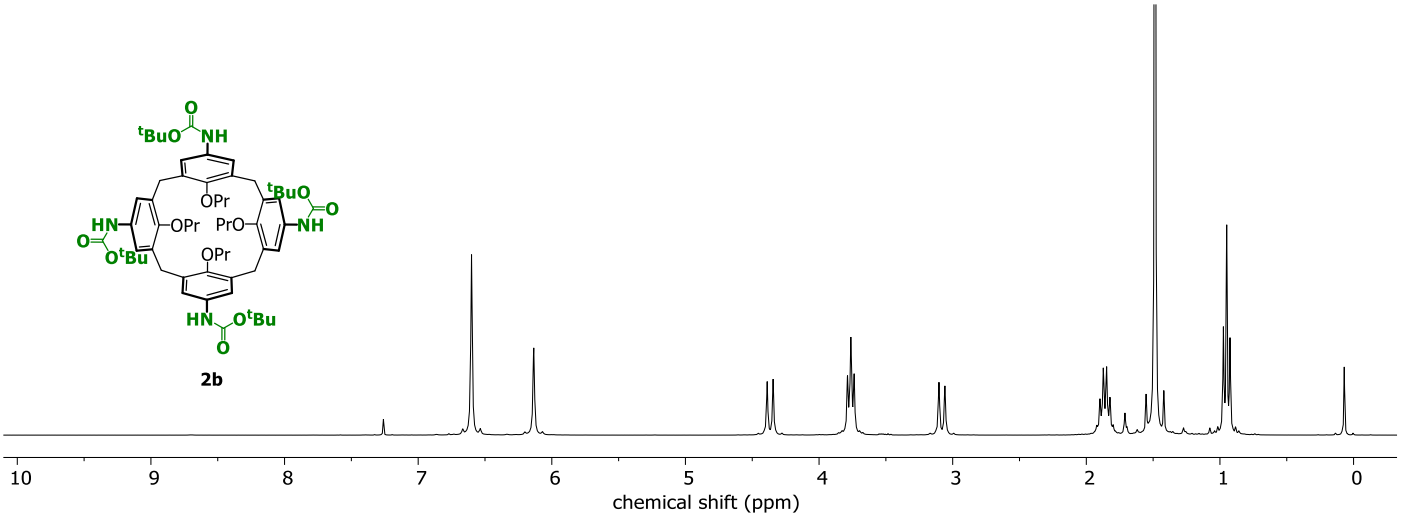
^{13}C{1H} (75 MHz, Chloroform-*d*)[5] δ ppm δ 153.5 (Ar*C*), 153.0 (NH*C*OO), 135.4 (Ar*C*), 132.1(Ar*C*), 120.0 (Ar*C*), 80.1 (O*C*(CH$_3$)$_3$), 76.9 (O*C*H$_2$CH$_2$), 31.2 (Ar*C*H$_2$Ar), 28.6 (OC(*C*H$_3$)$_3$), 23.2 (OCH$_2$*C*H$_2$CH$_3$), 10.4 (OCH$_2$CH$_2$*C*H$_3$);

HRMS–Positive: m/z $[M+NH_4]^+$ calcd. for $C_{60}H_{88}N_5O_{12}$: 1070.6429; found 1070.6421.

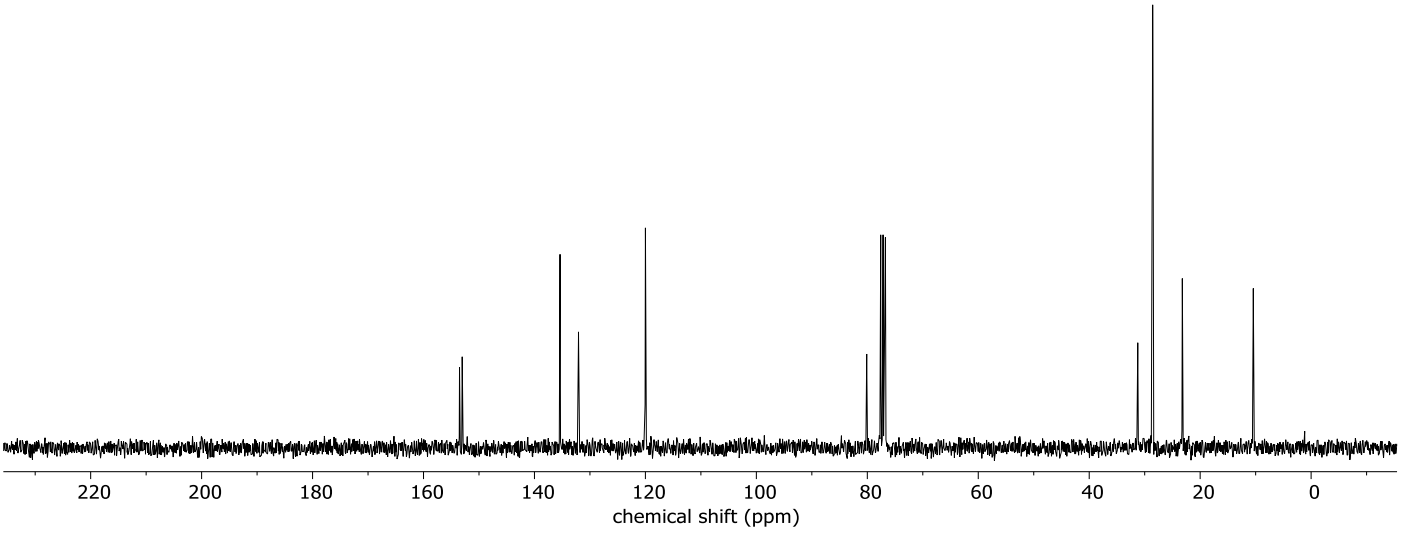


*Infrared spectrum of **2b***

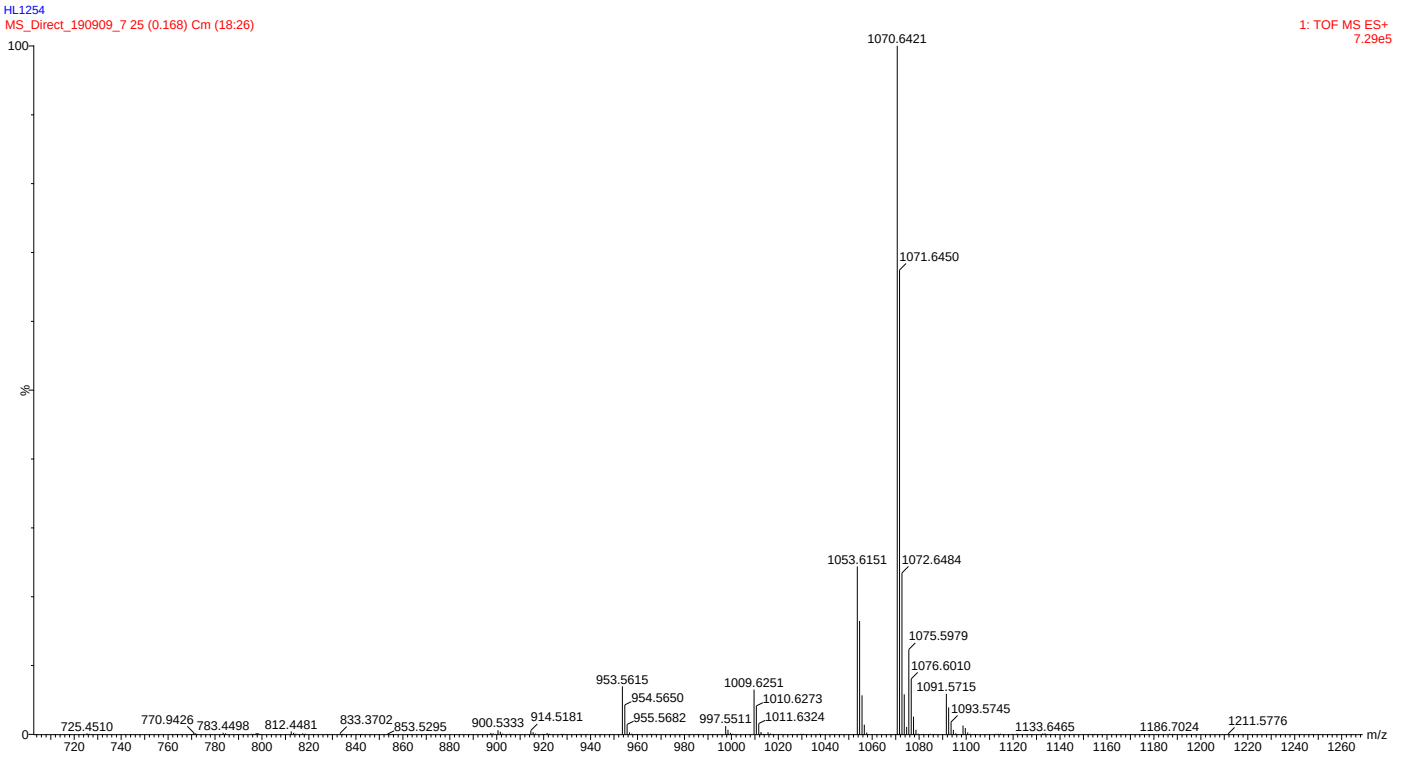
[5] Assignments tentative based on analogous and predicted spectra



*^{1}H NMR spectrum (300 MHz, $CDCl_3$, rt) for **2b***

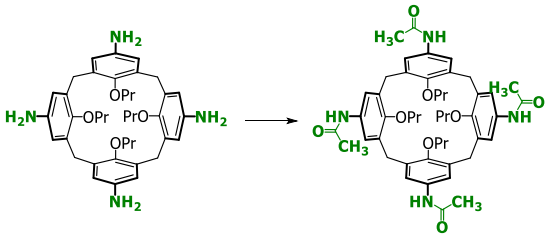


*^{13}C NMR spectrum (75 MHz, $CDCl_3$, rt) for **2b***



*ES+ HRMS for **2b***

S4.3) 5,11,17,23- tetrakis(*acetamide*)-25,26,27,28-tetrapropoxycalix[4]arene (2c)



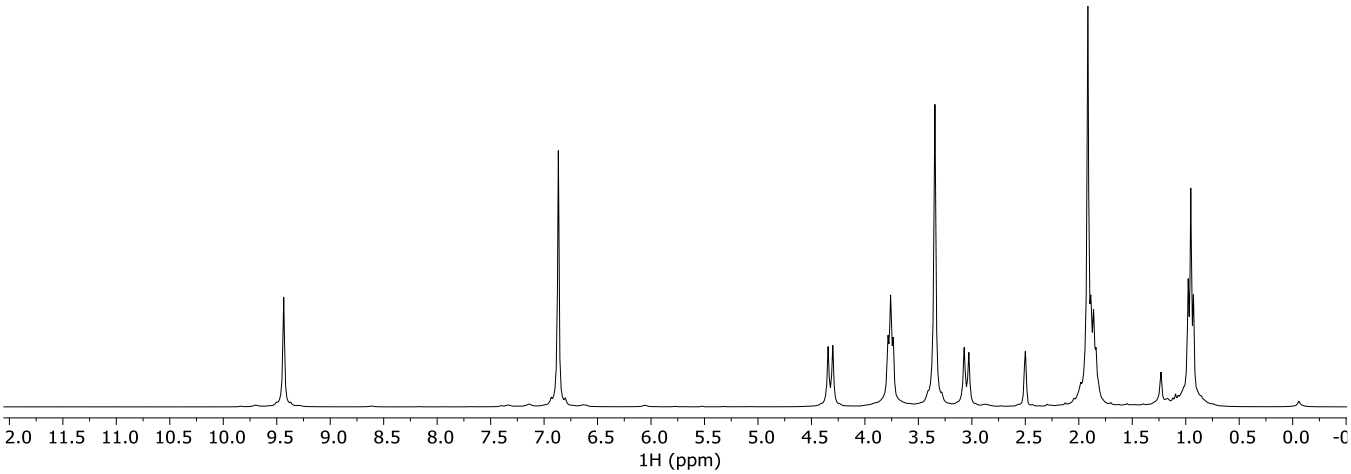
1 **2c**

In an oven dried 2-neck round-bottomed flask, tetra-aminocalixarene **1** (250 mg, 0.366 mmol) was dissolved in THF (15 mL). To this was added Et_3N (1.37 mL, 9.80 mmol, 8 eq), followed by the dropwise addition of Ac_2O (2.14 g, 9.80 mmol, 8 eq) which resulted in the formation of a white precipitate. The reaction mixture was then heated under reflux for two hours. After allowing to cool to rt, the reaction mixture was diluted with DCM (40 mL) and H_2O (30 mL) and the layers separated. The organic layer was then successively washed with sat. $NaHCO_3$ (30 mL), brine (30 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified *via* silica gel flash column chromatography (MeOH:DCM 5:95) to afford calixarene **2d** as a white solid (261 mg, 87%).[6]

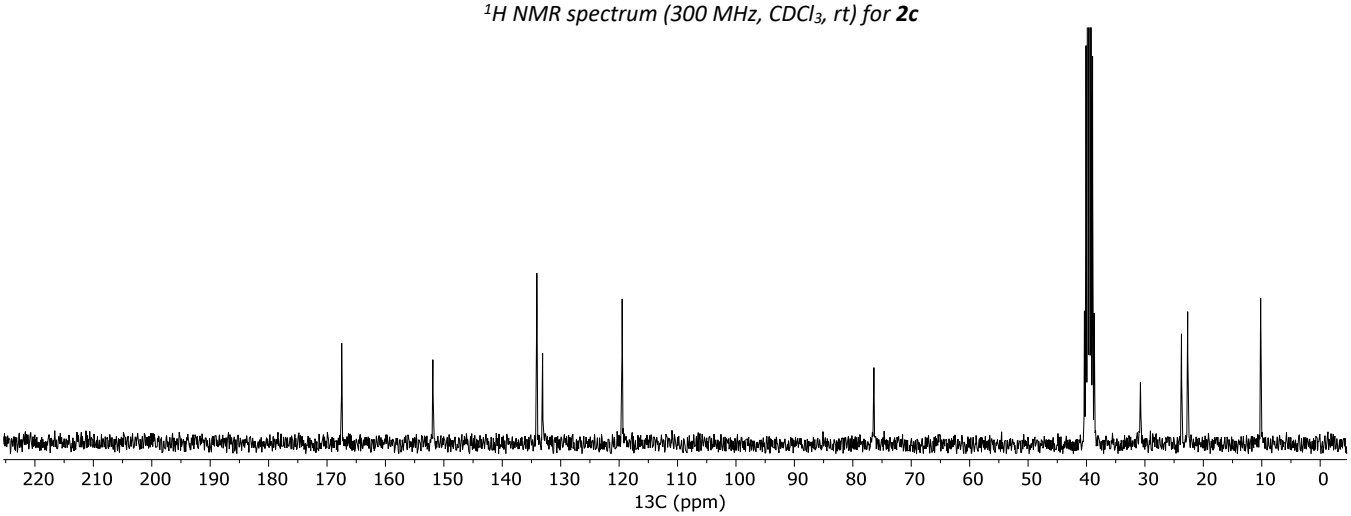
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.4 (s, 1H, NH), 6.9 (s, 2H, Ar-H), 4.3 (d, *J* = 13.0 Hz, 1H, ArC$H_{2(ax.)}$Ar), 3.8 (t, *J* = 7.4 Hz, 2H, OCH_2CH$_2$), 3.0 (d, *J* = 13.0 Hz, 1H, ArC$H_{2(eq.)}$Ar), 1.9 (m, 5H, C(O)CH_3 + OCH$_2$CH_2CH$_3$), 1.0 (t, *J* = 7.4 Hz, 3H, OCH$_2$CH$_2$CH_3).

^{13}C NMR (75 MHz, DMSO-d_6) δ 167.5, 151.9, 134.1, 133.1, 119.5, 76.4, 30.8, 23.7, 22.7, 10.2.

HRMS–Positive: m/z $[M+H]^+$ calcd. for $C_{48}H_{60}N_4O_{12}$: 821.449; found 821.449.



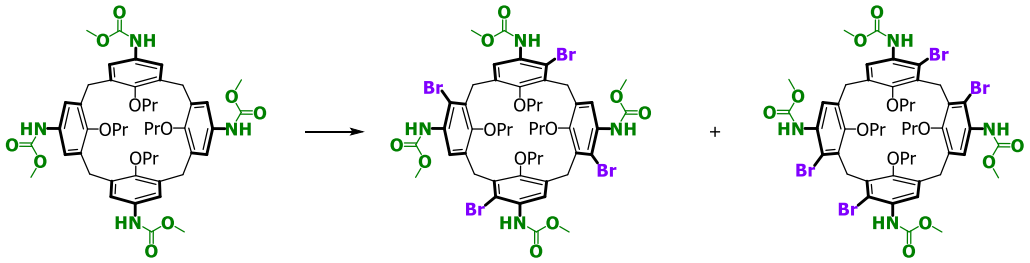
*^{1}H NMR spectrum (300 MHz, $CDCl_3$, rt) for **2c***



*^{13}C NMR spectrum (75 MHz, $CDCl_3$, rt) for **2c***

[6] ^{1}H, ^{13}C NMR and HRMS were consistent with the previously reported values: S. Tommasone, C. Talotta, C. Gaeta, L. Margarucci, M. C. Monti, A. Casapullo, B. MacChi, S. P. Prete, A. Ladeiradearaujo and P. Neri, *Angew. Chemie - Int. Ed.*, 2015, **54**, 15405–15409.

S4.4) 4,10,16,22-tetrabromo-5,11,17,23-tetrakis(methoxycarbonylamino)-25,26,27,28-tetrapropoxycalix[4]arene (3a)



2a **3a** (*41%*) **4a** (*15%*)

In an oven dried 2-neck round-bottomed flask charged with a magnetic stir bar and flushed with argon, calixarene **2a** (150 mg, 0.169 mmol) was dissolved in DCM (10 mL). PTSA (2 equiv) was added and the contents were cooled to –35 °C. After 15 minutes, NBS (151 mg, 0.647 mmol, 5 eq) was added, after which the reaction was left to stir at –35 °C for another five hours. Once complete, the reaction was diluted with H_2O (10 mL) and extracted with DCM (5 mL × 3). The organic layers were then combined and was first washed with sat. $NaHCO_3$ (15 mL) and then brine (15 mL), before being dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified *via* 2 separate silica gel flash column chromatography (EtOAc:PET 2:8) to produce C_4-calixarene **3a** as a pale yellow glass (69 mg, 41%).

R_f **=** 0.28 (EtOAc:PET 2:3);

Mp = 118-124 °C;

IR (ATR, cm^{-1}): 3409 (N-H) 2959 and 2874 (C-H) 1732 (C=O) 1578 (arene) 1511 (C=C) 1216 and 1186 (C-O-C) 998 and 964 (C-N) 767 (C-H);

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 100 °C)[7] δ ppm 7.94 (s, 1H, N*H*), 7.00 (s, 1H, Ar$H_{[5]}$), 4.48 (d, $^2J_{HH}$ = 14.1 Hz, 1H, ArC$H_{2(ax.)}$Ar), 4.01 (ddd, $^2J_{HH}$ = 10.4, 8.6, 6.4 Hz, 1H, OCH_2CH$_2$), 3.82 (ddd, $^2J_{HH}$ = 10.4, 8.5, 6.2 Hz, 1H, OCH_2CH$_2$), 3.63 (s, 3H, OCH_3), 3.62 (d, $^2J_{HH}$ = 14.1 Hz, 1H, ArC$H_{2(eq.)}$Ar), 1.90 – 1.76 (m, 2H, OCH$_2$CH_2CH$_3$), 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3);

^{13}C NMR (400 MHz, DMSO-*d*$_6$, 100 °C)[7] δ ppm 154.3 (Ar$C_{[3]}$), 153.9 (N$C_{[16]}$), 133.4 (Ar$C_{[6]}$), 131.2 + 130.0 (Ar$C_{[2]}$ + Ar$C_{[4]}$), 127.0 (Ar$C_{[5]}$), 118.8 (Ar$C_{[1]}$), 76.2 ($C_{[11]}$), 51.1 ($C_{[19]}$), 30.6 ($C_{[8]}$), 21.7 ($C_{[12]}$), 9.3 ($C_{[13]}$);

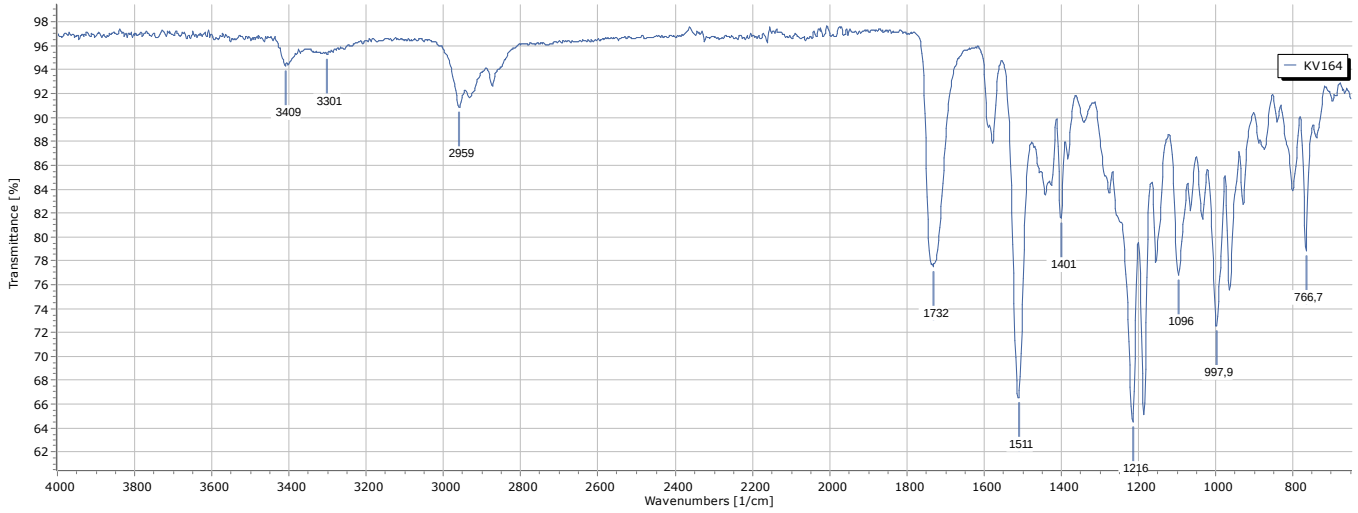
^{1}H, ^{1}H GCOSY (400/400 MHz, DMSO-*d*$_6$, 100 °C)[7] δ ^{1}H/δ ^{1}H ppm 7.00 / 4.48, 3.82 (Ar$H_{[5]}$ / ArC$H_{(ax.)}$Ar, ArC$H_{(eq.)}$Ar), 4.48 / 3.62 (ArC$H_{(ax.)}$Ar / ArC$H_{(eq.)}$Ar), 4.00 / 1.83 (OCH_2CH$_2$ / CH$_2$CH_2CH$_3$), 3.82 / 1.83 (OCH_2CH$_2$ / CH$_2$CH_2CH$_3$), 3.62 / 4.48 (ArC$H_{(eq.)}$Ar / ArC$H_{(ax.)}$Ar), 1.83 / 4.00, 3.82, 0.97 (CH$_2$CH_2CH$_3$ / OCH_2CH$_2$, OCH_2CH$_2$, CH$_2$CH$_2$CH_3), 0.97 / 1.83 (CH$_2$CH$_2$CH_3 / CH$_2$CH_2CH$_3$);

^{1}H,^{13}C GHSQC (400/400 MHz, DMSO-*d*$_6$, 100 °C)[7] δ ^{1}H/δ ^{13}C ppm 7.00 / 127.0 (Ar$H_{[5]}$ / Ar$C_{[5]}$), 4.48 / 30.6 (ArC$H_{(ax.)}$Ar / $C_{[8]}$), 4.01 / 76.2 (OCH_2CH$_2$ / $C_{[11]}$), 3.82 / 76.2 (OCH_2CH$_2$ / $C_{[11]}$), 3.63 / 51.1 (OCH_3 / $C_{[19]}$) 3.62 / 30.6 (ArC$H_{1(eq.)}$Ar / $C_{[8]}$), 1.83 / 21.7 (CH$_2$CH_2CH$_3$ / $C_{[12]}$), 0.97 / 9.3 (CH$_2$CH$_2$CH_3 / $C_{[13]}$);

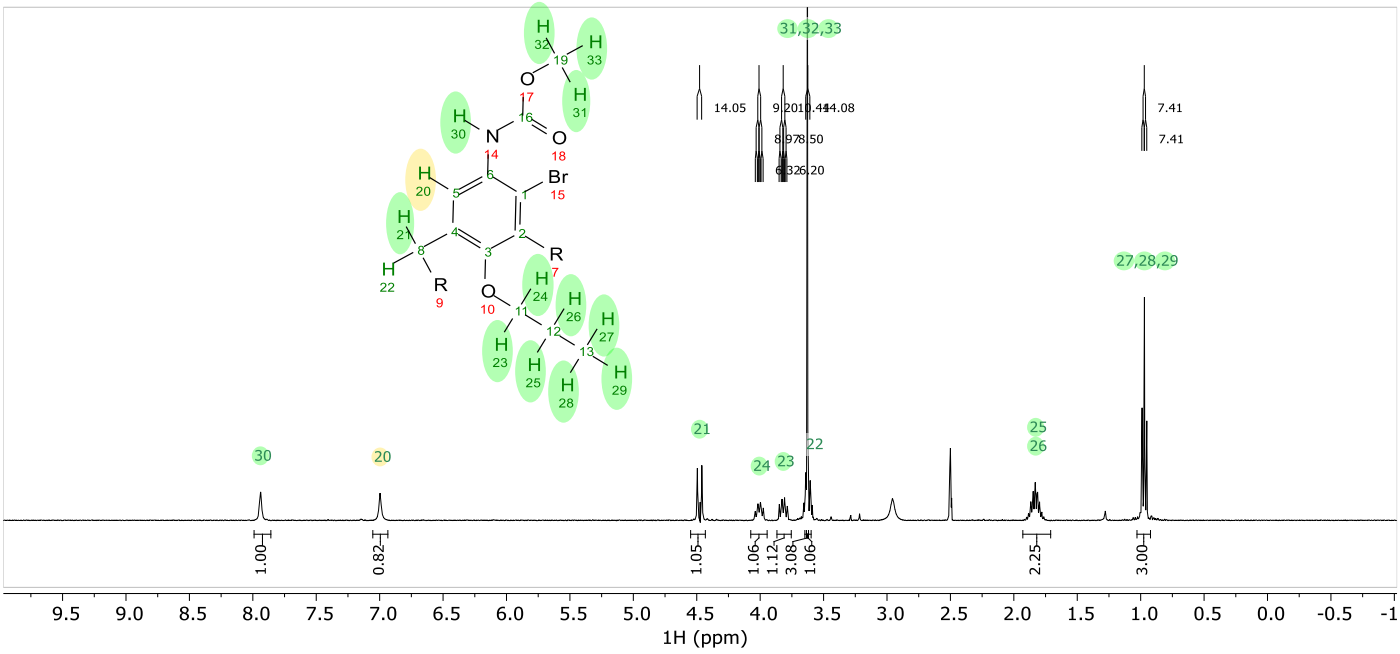
^{1}H,^{13}C GHMBC (400/400 MHz, DMSO-*d*$_6$, 100 °C)[7] δ ^{1}H/δ ^{13}C ppm 4.48 / 154.3, 131.2, 130.0, 127.0, 118.8 (ArC$H_{(ax)}$Ar / Ar$C_{[3]}$, Ar$C_{[4]}$, Ar$C_{[2]}$, Ar$C_{[5]}$, Ar$C_{[1]}$),3.63 / 153.9 (OCH_3 / N$C_{[16]}$), 3.62 / 131.2, 130.0, 127.0, 118.8 (ArC$H_{(eq.)}$Ar / Ar$C_{[4]}$, Ar$C_{[2]}$, Ar$C_{[5]}$, Ar$C_{[1]}$), 0.97 / 76.2, 21.7 (CH$_2$CH$_2$CH_3 / $C_{[11]}$, $C_{[12]}$);

HRMS–Positive: m/z $[M+H]^+$ calcd. for $C_{48}H_{57}Br_4N_4O_{12}$: 1197.0707; found 1197.0710.

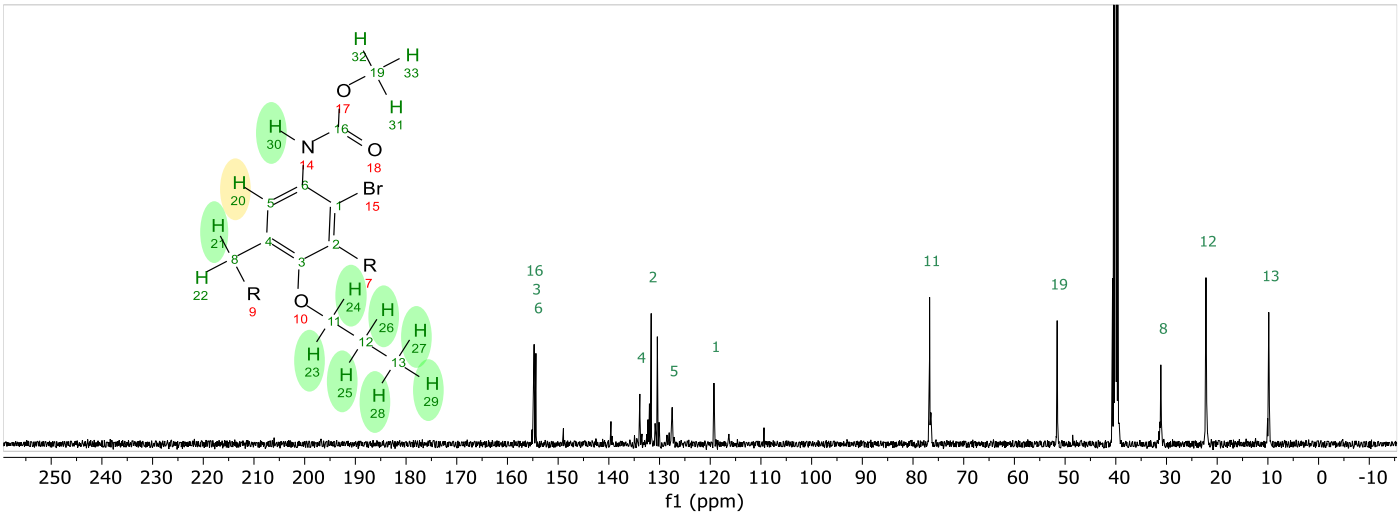
[7] Assignments made using full 2D NMR data; numbering system used is different to IUPAC numbering due to symmetry, see structures on spectra for numbers and correlations



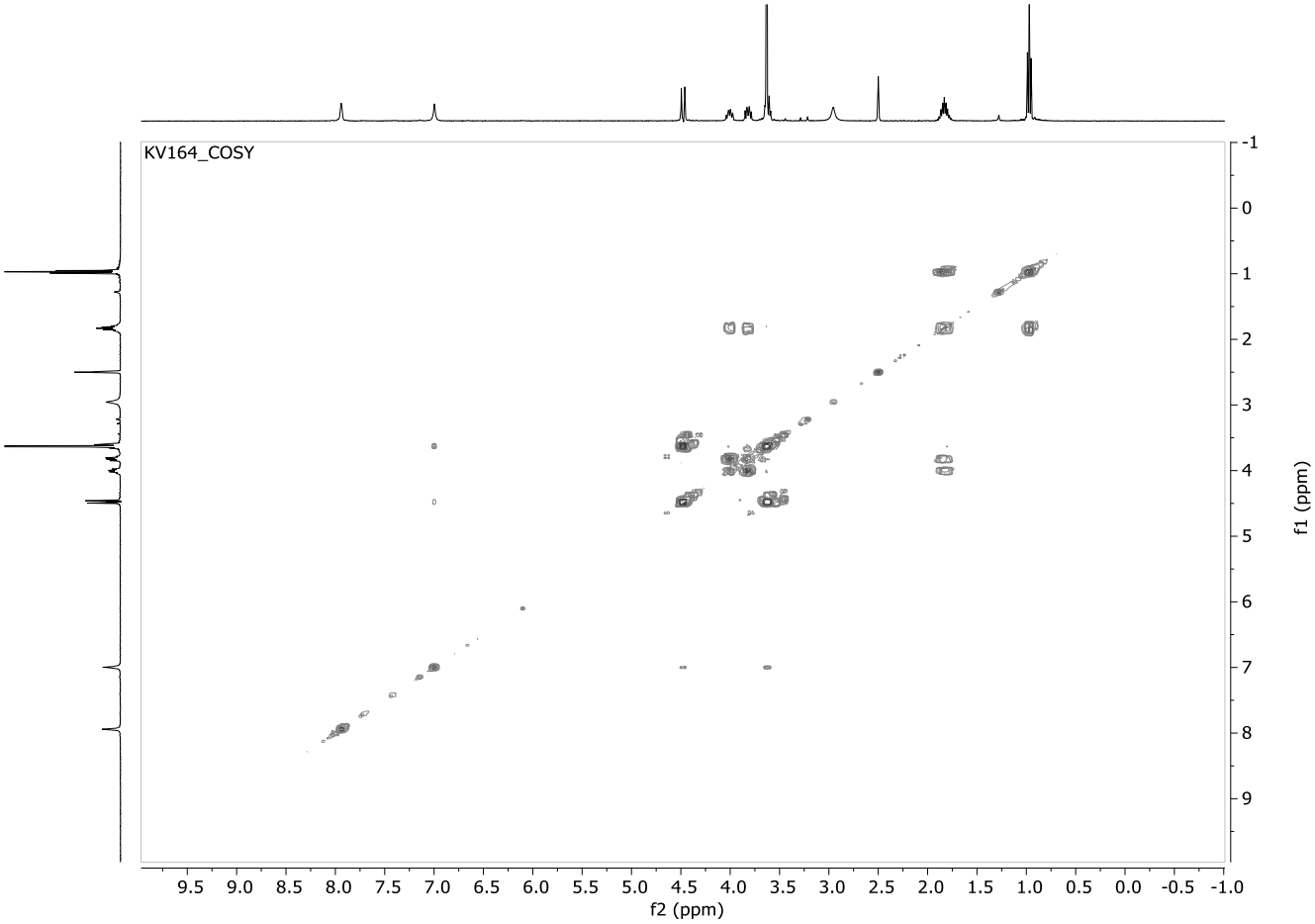
*Infrared spectrum for **2a***



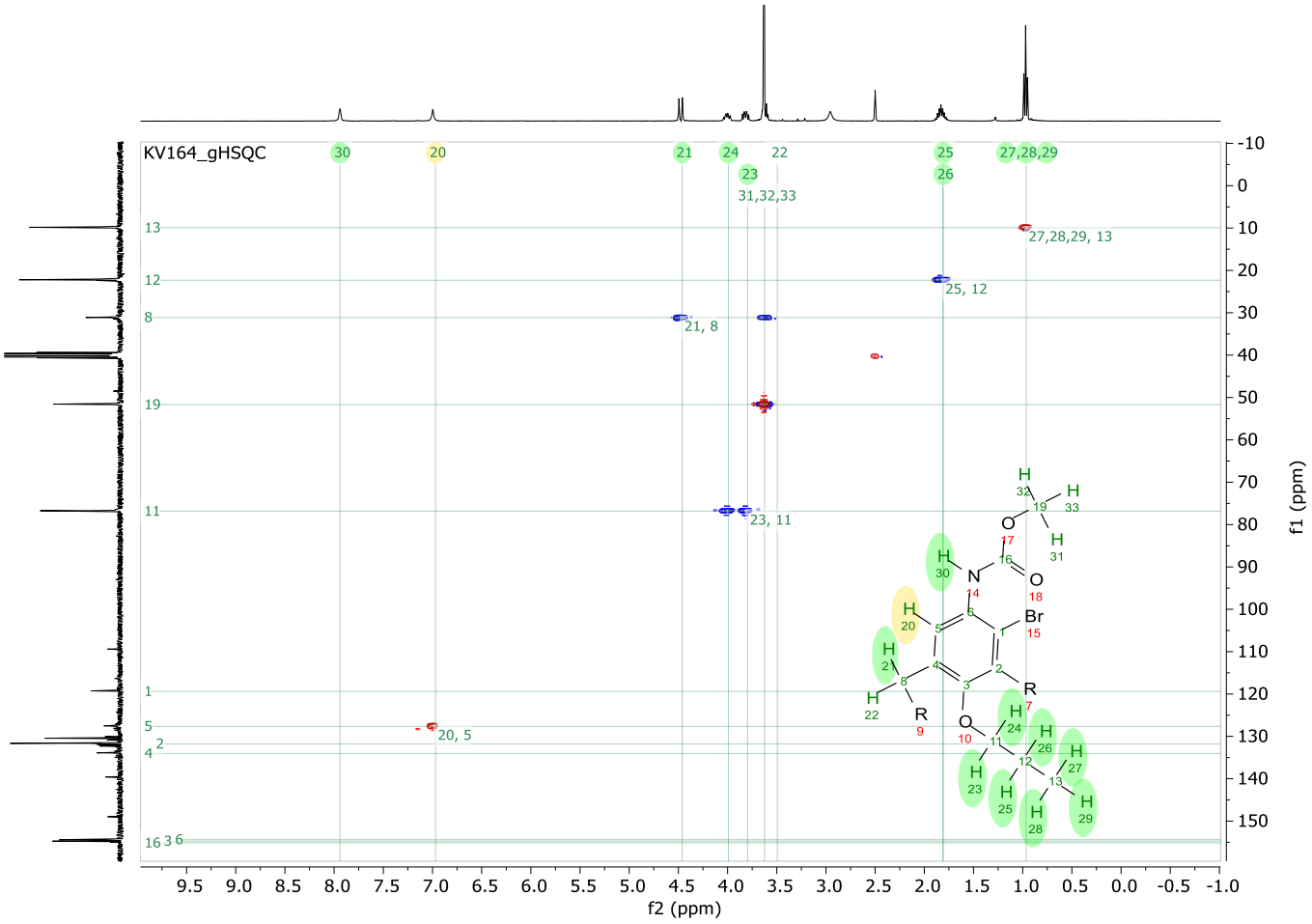
*^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100 °C) for **3a***



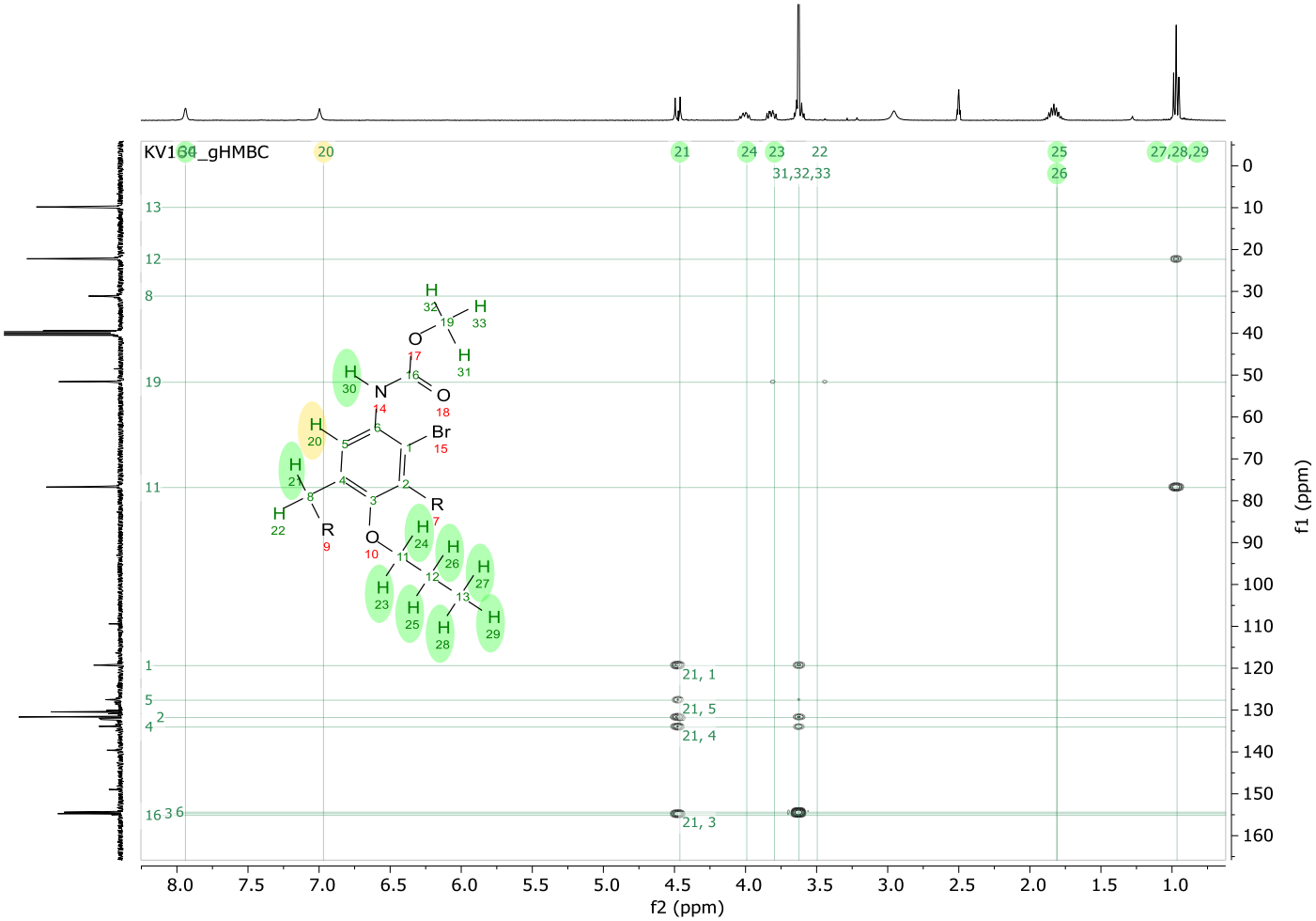
*^{13}C NMR spectrum (100 MHz, DMSO-d_6, 100 °C) for **3a***



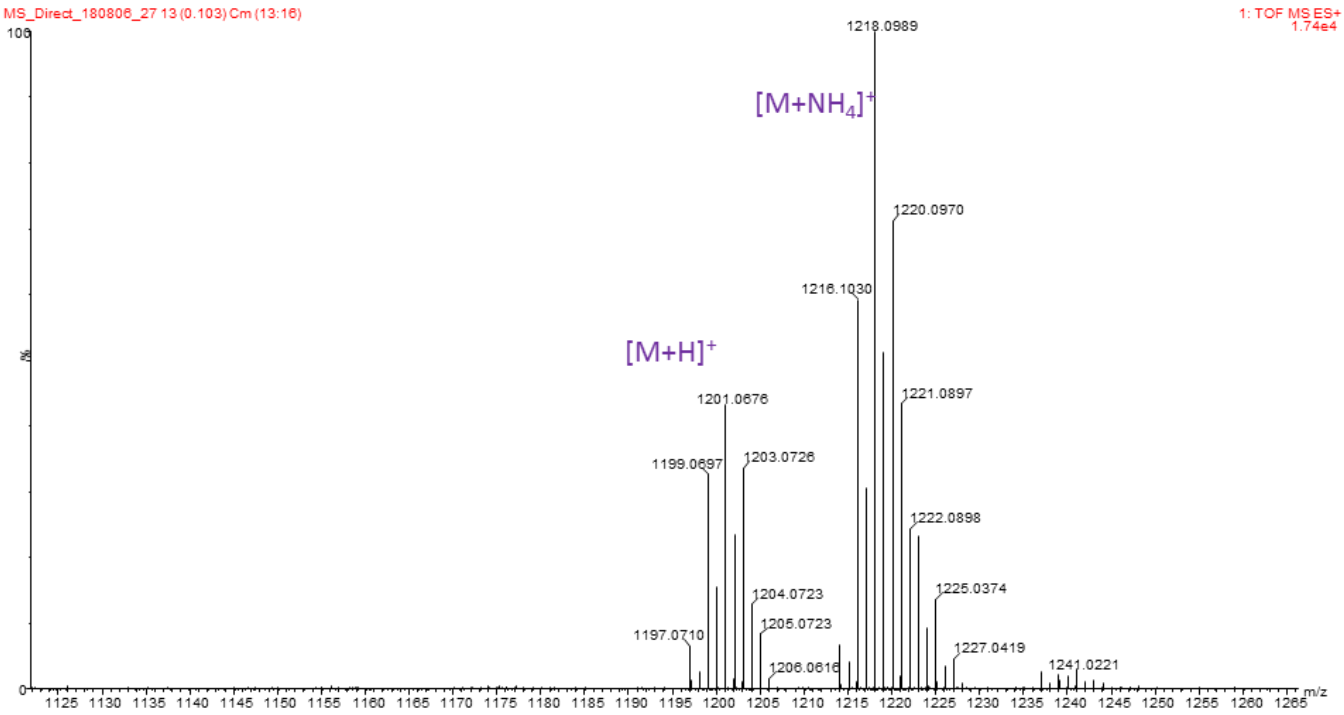
*gCOSY spectrum (400/400 MHz, DMSO-d_6, 100 °C) for compound **3a**.*



*gHSQC spectrum (DMSO-d_6, 100 °C) for compound **3a**.*



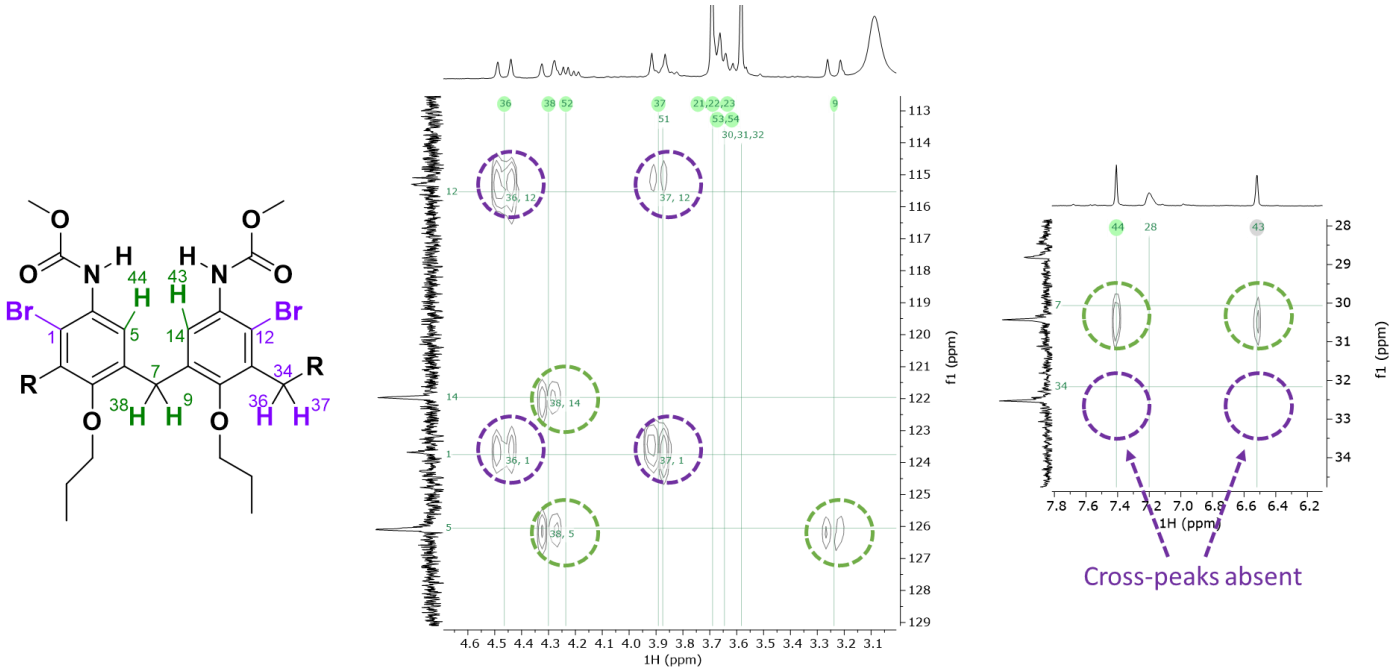
*gHMBC spectrum (DMSO-d_6, 100 °C) for compound **3a**.*



*ES+ HRMS for **3a***

S4.5) 4,8,16,20-tetrabromo-5,11,17,23-tetrakis(methoxycarbonylamino)-25,26,27,28-tetrapropoxycalix[4]arene (4a)

C_{2v}-calixarene **4a** was obtained in 15% yield. Owing to the boat conformation, the symmetry is C_2 and not C_{2v}. 2D NMR could establish most of the connections, but in many cases the absolute assignments distinguishing the two 'different' aromatic subsections could not be determined unambiguously and so were tentatively assigned to complete the correlations. The most significant correlations that prove that the isomer is indeed the C_2 **4a** and not the C_s-isomer can be found in the gHMBCAD spectrum; below is the zoomed in areas of the most important parts that prove this.



Zoomed in section of gHMBCAD showing the separate connections between the methylene bridge protons connected to the bromine aromatic carbon (purple) and the methylene bridge protons connected to the carbon with the aromatic hydrogen atom (green). Note numbering was generated automatically by MNOVA for assignments.

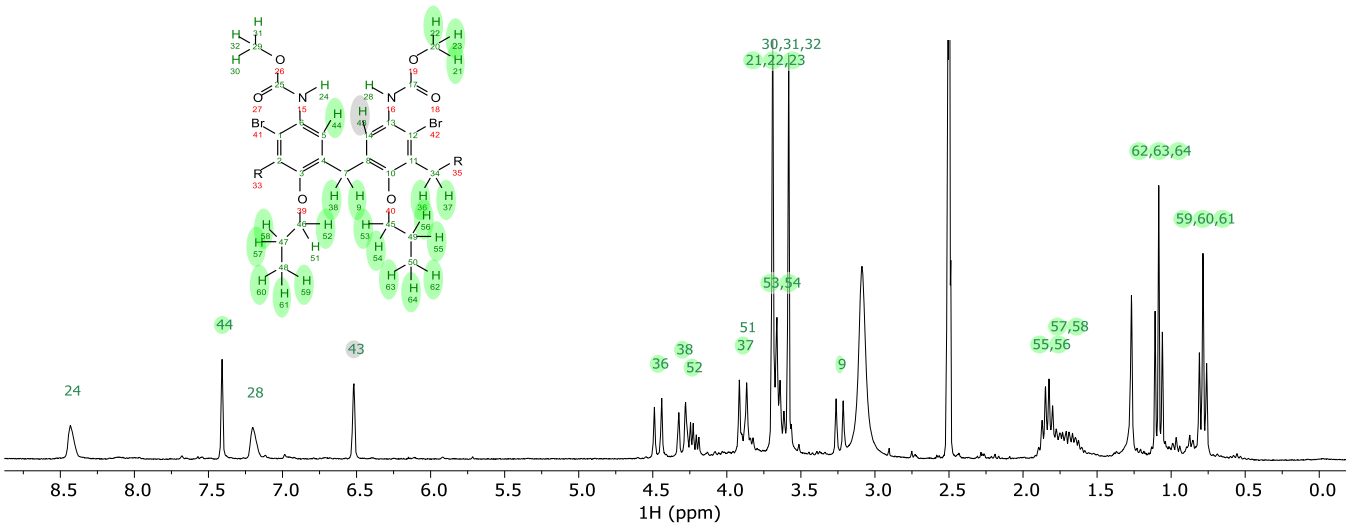
^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 8.43 (s, 1H, NH), 7.41 (s, 1H, $H_{[44]}$), 7.20 (s, 1H, NH), 6.52 (s, 1H, $H_{[43]}$), 4.46 (d, J = 14.7 Hz, 1H, $H_{[36]}$), 4.30 (d, J = 14.0 Hz, 1H, $H_{[38]}$), 4.24 (td, J = 11.7, 5.4 Hz, 1H, $H_{[52]}$), 3.89 (d, J = 14.7 Hz, 1H, $H_{[37]}$), 3.93 – 3.81 (m, 1H, $H_{[51]}$), 3.69 (s, 3H, OCH_3), 3.71 – 3.61 (m, 2H, $H_{[53,54]}$), 3.58 (s, 3H, OCH_3), 3.24 (d, J = 14.0 Hz, 1H, $H_{[9]}$), 1.82 (p, J = 7.1 Hz, 2H, $H_{[55,56]}$), 1.83 – 1.58 (m, 2H, $H_{[57,56]}$), 1.08 (t, J = 7.3 Hz, 3H, -CH_3), 0.79 (t, J = 7.3 Hz, 3H, -CH_3).

^{13}C NMR (75 MHz, DMSO-d_6, 100 °C) δ 155.4 ($C_{[3]}$), 154.3 ($C_{[17]}$), 153.5 ($C_{[10]}$), 153.2 ($C_{[25]}$), 134.9 ($C_{[4]}$), 133.3 ($C_{[2]}$), 132.4 ($C_{[8]}$), 132.1 ($C_{[11]}$), 130.3 ($C_{[13]}$), 129.9 ($C_{[6]}$), 125.7 ($C_{[5]}$), 123.3 ($C_{[1]}$), 121.6 ($C_{[14]}$), 114.9 ($C_{[12]}$), 76.6 ($C_{[45]}$), 76.1 ($C_{[46]}$), 51.3 ($C_{[20,29]}$), 32.2 ($C_{[34]}$), 30.1 ($C_{[7]}$), 22.4 ($C_{[49]}$), 21.0 ($C_{[47]}$), 10.0 ($C_{[50]}$), 8.8 ($C_{[48]}$).

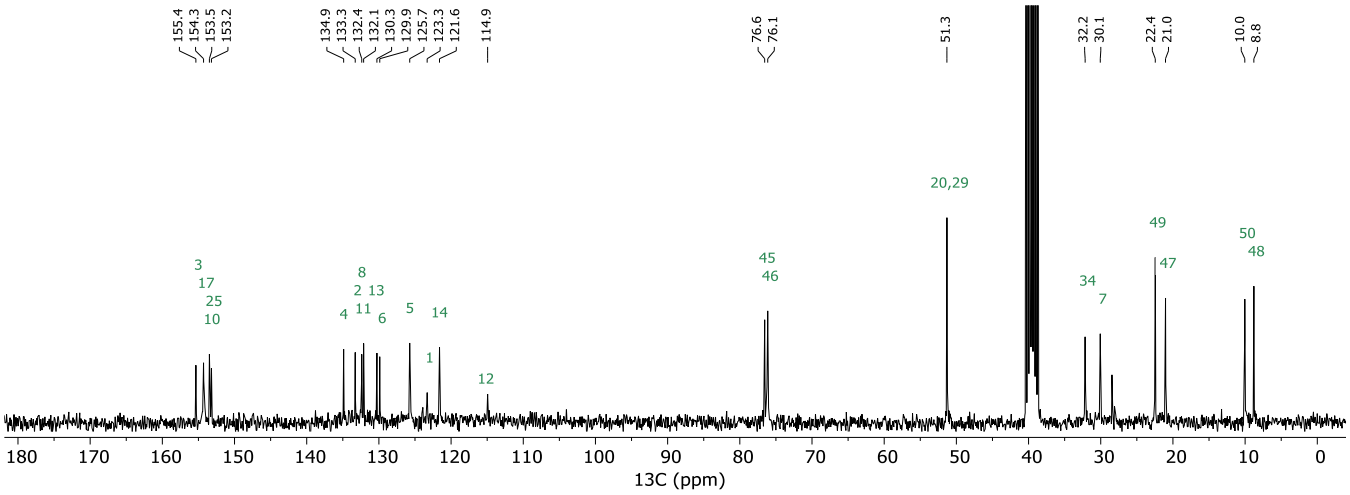
^{1}H, ^{1}H COSY (300/300 MHz, DMSO-d_6, 100 °C) δ ^{1}H/δ ^{1}H ppm 6.52 / 3.24 (Ar$H_{[43]}$ / $H_{[9]}$), 4.46 / 3.89 ($H_{[36]}$ / $H_{[37]}$), 4.30 / 3.24 ($H_{[38]}$ / $H_{[9]}$), 3.66 / 1.82 ($H_{[53,54]}$ / $H_{[55,56]}$), 1.82 / 1.08 ($H_{[55,56]}$ / $H_{[62,63,64]}$);

^{1}H,^{13}C gHSQCAD (300/75 MHz, DMSO-d_6, 100 °C) δ ^{1}H/δ ^{13}C ppm 7.41 / 125.7 ($H_{[44]}$ / $C_{[5]}$), 6.52 / 121.6 ($H_{[43]}$ / $C_{[14]}$), 4.46 / 32.2 ($H_{[36]}$ / $C_{[34]}$), 4.30 / 30.1 ($H_{[38]}$ / $C_{[7]}$), 4.24 / 76.1 ($H_{[52]}$ / $C_{[46]}$), 3.89 / 32.2 ($H_{[37]}$ / $C_{[34]}$), 3.85 / 76.1 ($H_{[51]}$ / $C_{[46]}$), 3.69 / 51.3 (OCH_3 / $C_{[20,29]}$), 3.66 / 76.6 ($H_{[53,54]}$ / $C_{[45]}$), 3.58 / 51.3 (OCH_3 / $C_{[20,29]}$), 3.24 / 30.1 ($H_{[9]}$ / $C_{[7]}$), 1.82 /22.4 ($H_{[55,56]}$ / $C_{[49]}$), 1.83 – 1.58 / 21.0 ($H_{[57,56]}$ / $C_{[47]}$), 1.08 / 10.0 (-CH_3 / $C_{[50]}$), 0.79 / 8.8 (-CH_3 / $C_{[48]}$).

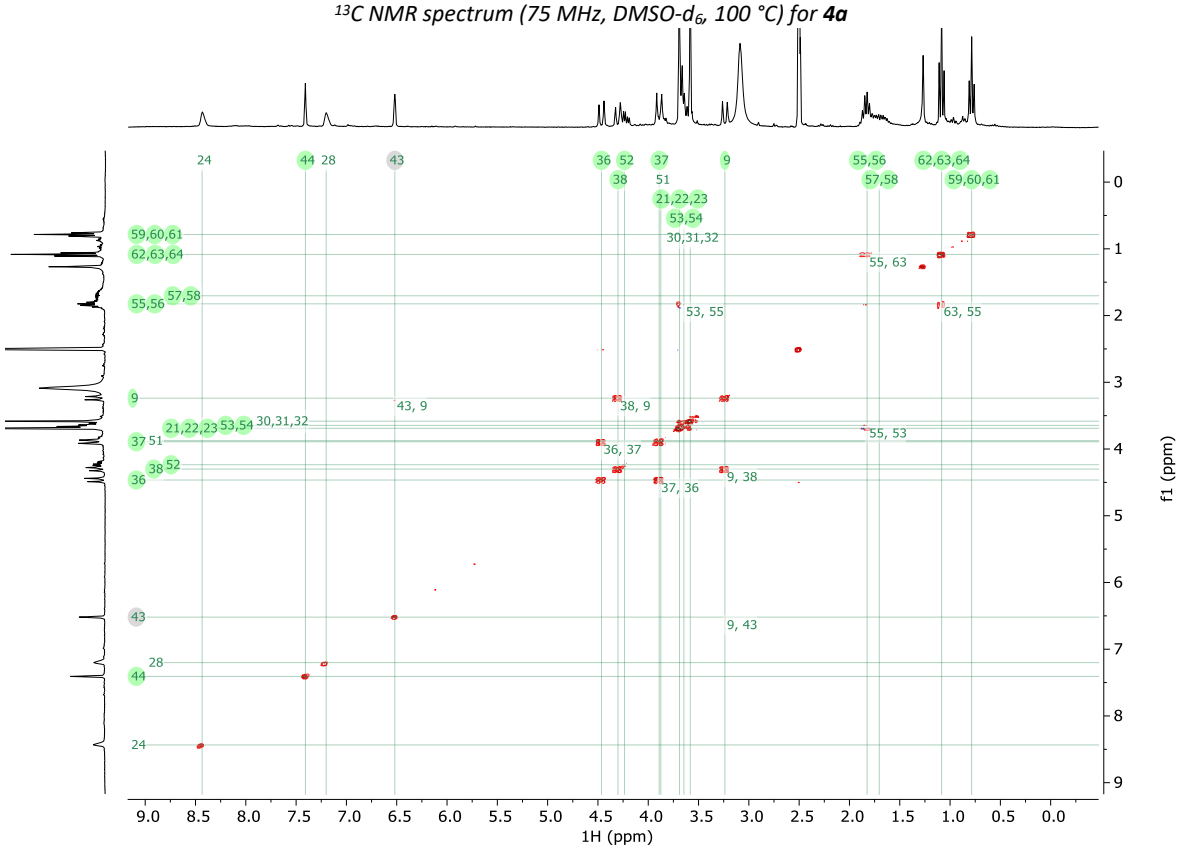
^{1}H,^{13}C gHMBCAD (300/75 MHz, DMSO-d_6, 100 °C) δ ^{1}H/δ ^{13}C ppm 7.41 / 155.4, 129.9, 123.3, 30.1 ($H_{[44]}$ / $C_{[3,6,1,7]}$), 6.52 / 153.5, 130.3, 114.9, 30.1 ($H_{[43]}$ / $C_{[10,13,12,7]}$), 4.46 / 155.4, 153.5, 133.3, 132.1, 123.3, 114.9 ($H_{[36]}$ / $C_{[3,10,2,11,1,12]}$), 4.30 / 153.5, 134.9, 132.4, 125.7, 121.6 ($H_{[38]}$ / $C_{[10,4,8,5,14]}$), 4.24 / 155.4 ($H_{[52]}$ / $C_{[3]}$), 3.89 / 155.4, 153.5, 133.3, 132.1, 123.3, 114.9 ($H_{[37]}$ / $C_{[3,10,2,11,1,12]}$), 3.69 / 154.3 (OCH_3 / $C_{[17]}$), 3.66 / 22.4, 10.0 ($H_{[53,54]}$ / $C_{[49,50]}$), 3.58 / 153.2 (OCH_3 / $C_{[25]}$), 3.24 / 155.4, 153.5, 134.9, 132.4, 125.7 ($H_{[9]}$ / $C_{[3,10,4,8,5]}$), 1.82 /76.6, 10.0 ($H_{[55,56]}$ / $C_{[45,50]}$), 1.08 / 76.6, 22.4 (-CH_3 / $C_{[45,49]}$), 0.79 / 76.1, 21.0 (-CH_3 / $C_{[46,47]}$).



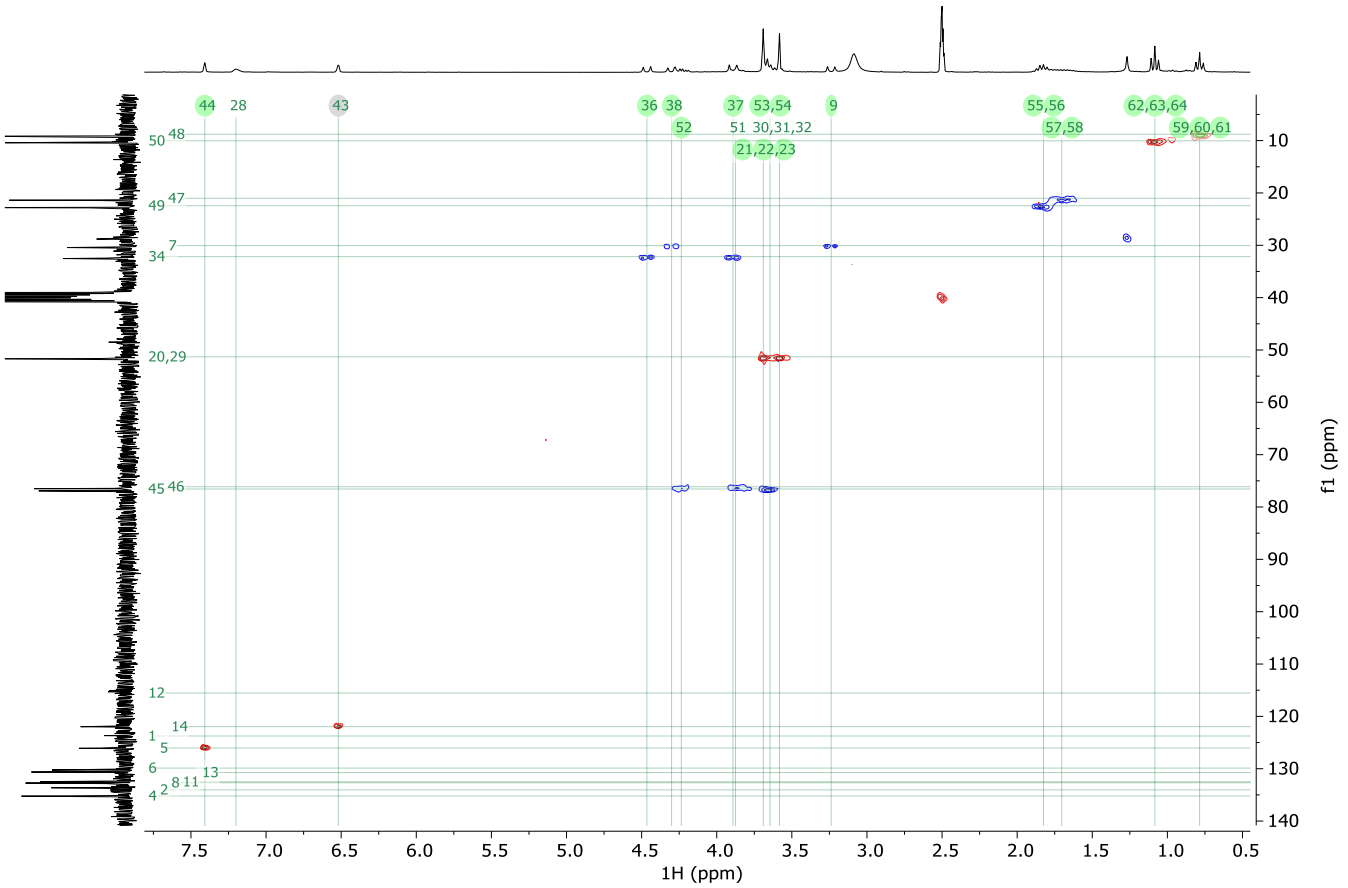
*^{1}H NMR spectrum (300 MHz, DMSO-d_6, 100 °C) for **4a***



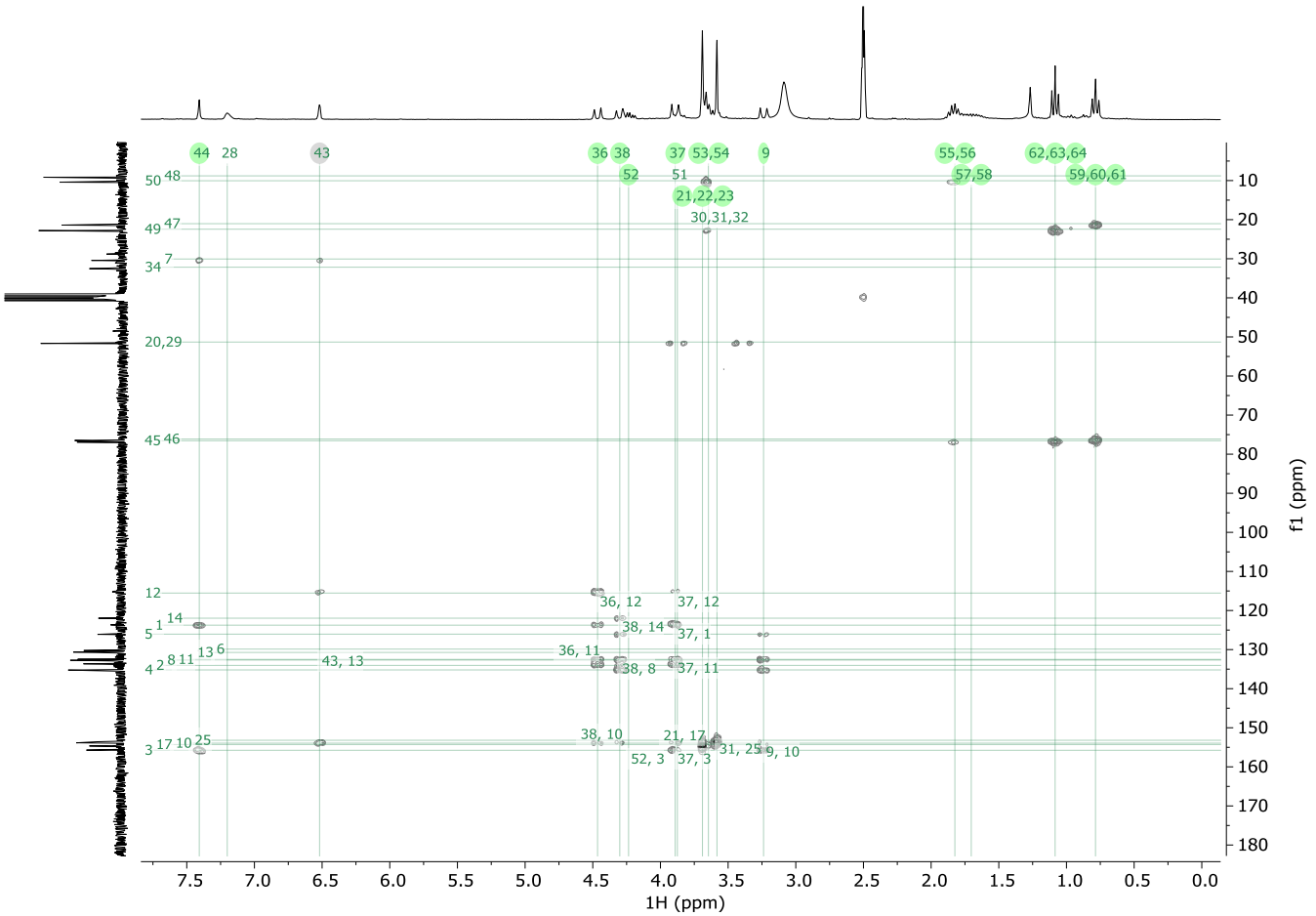
*^{13}C NMR spectrum (75 MHz, DMSO-d_6, 100 °C) for **4a***



*COSY spectrum (300/300 MHz, DMSO-d_6, 100 °C) for compound **4a**.*

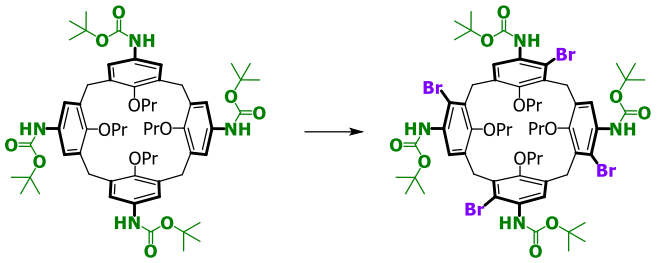


*gHSQCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for compound **4a**.*



*gHMBCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for compound **4a**.*

S4.6) 4,10,16,22-tetrabromo-5,11,17,23- tetrakis(*tert*-butoxycarbonylamino)-25,26,27,28-tetrapropoxycalix-[4]arene (3b)



2b **3b** (*83%*)

An oven dried 250 mL two-neck round-bottomed flask was flushed with nitrogen gas and thereafter a magnetic stirrer bar was added. Tetra-Boc calix[4]arene **2b** (1.05 g, 0.953 mmol) was added to the flask and dissolved in dichloromethane (55 mL). The mixture was placed in a cooling bath at a temperature of −42 °C (acetonitrile and dry ice mixture in a Dewar). The mixture was left to stir for 15 minutes, subsequently PTSA monohydrate (33 mg, 0.019 mmol) was added to the flask. The mixture was left to stir for 15 minutes after which N-bromosuccinimide (848 mg, 4.77 mmol) was added in a single portion to the mixture and the resulting mixture was left to stir for six hours. The reaction was kept at −42 °C until the starting material was completely consumed, thereafter, the cooling bath was removed and the mixture was left to stir to room temperature (26 °C). Once at room temperature a saturated sodium bicarbonate solution (15 mL) was added and left to stir for 10 minutes. Subsequently the mixture was extracted with dichloromethane (5 × 15 mL). The combined organic layers were washed with distilled water (2 × 15 mL) and a saturated brine solution (2 × 20 mL) and dried over magnesium sulphate. The solvent was removed via reduced pressure to acquire an orange crude product. The product was purified via silica gel flash chromatography in ethyl acetate: petroleum ether (0:1 to 1:4) to obtain the tetrabromo calix[4]arene **3b** as a clear solid (1.088 g, 83%).[8]

R_f : 0.3 (ethyl acetate: *n*-hexane 2:3);

Melting point: 159.0-163.2 °C;

IR (ATR, cm^{-1}): 3414 (N-H) 2968 and 2875 (C-H), 1728 (C=O), 1581 (arene), 1503 (C=C), 1222 and 1150 (C-O-C), 998 and 966 (C-N), 765 (C-H);

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ ppm 7.46 (s, 1H, N*H*), 6.99 (s, 1H, Ar$H_{[13]}$), 4.45 (d, $^2J_{H\text{-}H}$=14.2 Hz, 1H, $H_{[21]}$), 4.01-3.95 (m, 1H, OCH_2CH$_2$), 3.82- 3.76 (m, 1H, OCH_2CH$_2$), 3.60 (d, 1H, $^2J_{H\text{-}H}$=14.2 Hz, $H_{[22]}$), 1.84-1.78 (m, 2H, OCH$_2$CH_2CH$_3$), 1.44 (s, 9H, OC(CH_3)$_3$), 0.96 (t, $^3J_{H\text{-}H}$= 7.4 Hz, 3H, -CH$_2$CH$_2$CH_3);

^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ ppm 154.0 ($C_{[3]}$), 152.4 (C=O), 133.4 ($C_{[6]}$), 131.2 ($C_{[2]}$), 130.3 ($C_{[4]}$), 126.6 ($C_{[5]}$), 118.3 ($C_{[1]}$), 78.6 ($C_{[17]}$), 76.2 ($C_{[23]}$), 30.8 ($C_{[8]}$), 27.7 ($C_{[18,19,20]}$), 21.7 ($C_{[24]}$), 9.4 ($C_{[25]}$)

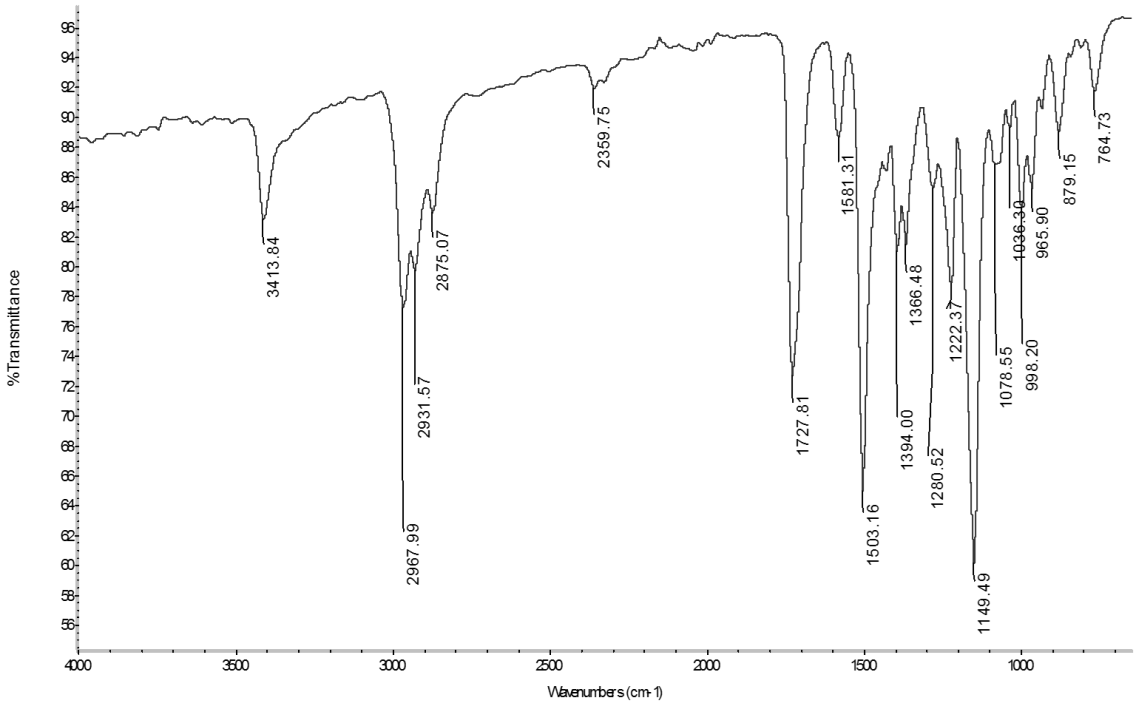
COSY (400/400 MHz, DMSO-d_6, 100 °C) δ^1H/δ^1H ppm 4.45 / 3.60 ($H_{[21]}$ / $H_{[22]}$), 3.98 / 1.82 ($H_{[27]}$ / $H_{[24]}$), 3.79 / 1.80 ($H_{[26]}$ / $H_{[24]}$), 3.62 / 4.46 ($H_{[22]}$ / $H_{[21]}$), 1.82 / 3.98, 3.79, 0.96 ($H_{[24]}$ /$H_{[27,26,25]}$), 0.96 / 1.82 ($H_{[25]}$ / $H_{[24]}$)

gHSQCAD (300/75 MHz, DMSO-d_6, 100 °C) δ^1H/δ^{13}C ppm 6.99 / 126.6 ($H_{[13]}$ / $C_{[5]}$), 4.45 / 30.8 ($H_{[21]}$ / $C_{[8]}$), 3.98 + 3.79 / 76.2 (OCH_2CH$_2$ / $C_{[23]}$), 3.60 / 30.8 ($H_{[22]}$ / $C_{[8]}$), 1.81 / 21.7 ($H_{[24]}$ / $C_{[24]}$), 1.44 / 27.7 ($H_{[18,19,20]}$ / $C_{[18,19,20]}$), 0.96 / 9.20 ($H_{[25]}$ / $C_{[25]}$).

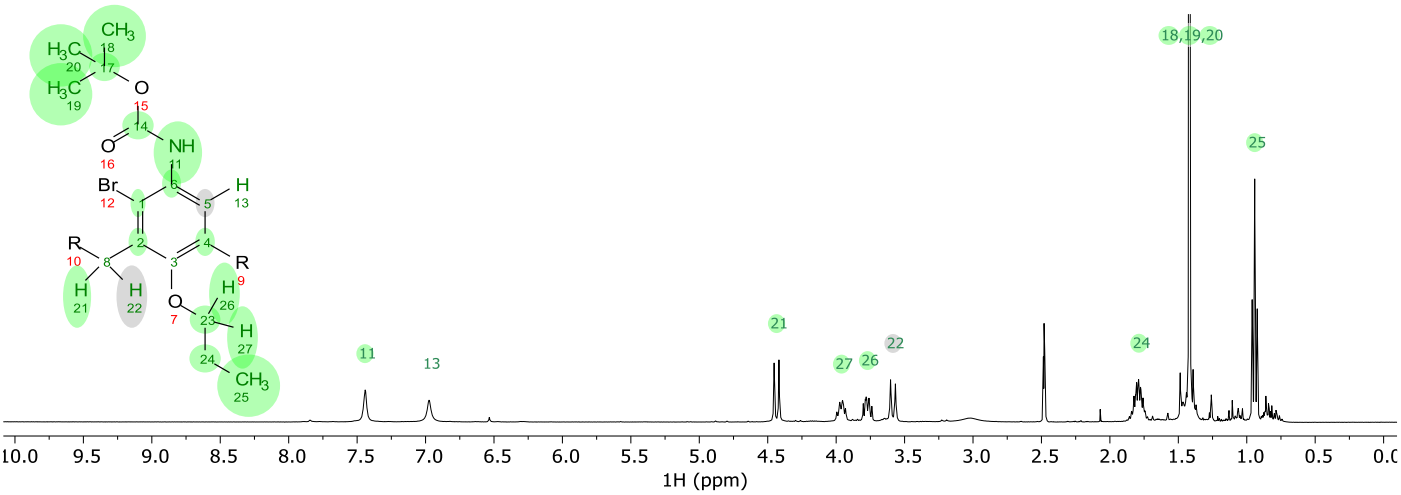
gHMBCAD (300/75 MHz, DMSO-d_6, 100 °C) δ^1H/δ^{13}C ppm 4.45 / 154.0, 131.2, 118.3 ($H_{[21]}$ / $C_{[3,2,1]}$), 3.60 / 154.0, 131.2, 118.3 ($H_{[22]}$ / $C_{[3,2,1]}$), 1.81 / 76.2, 9.4 ($H_{[24]}$ / $C_{[23,25]}$), 0.96 / 76.2, 21.7 ($H_{[25]}$ / $C_{[23,24]}$);

HRMS–Positive: m/z $[M+H]^+$ calcd. for $C_{60}H_{81}Br_4N_4O_{12}$: 1365.2584; found 1365.2555;

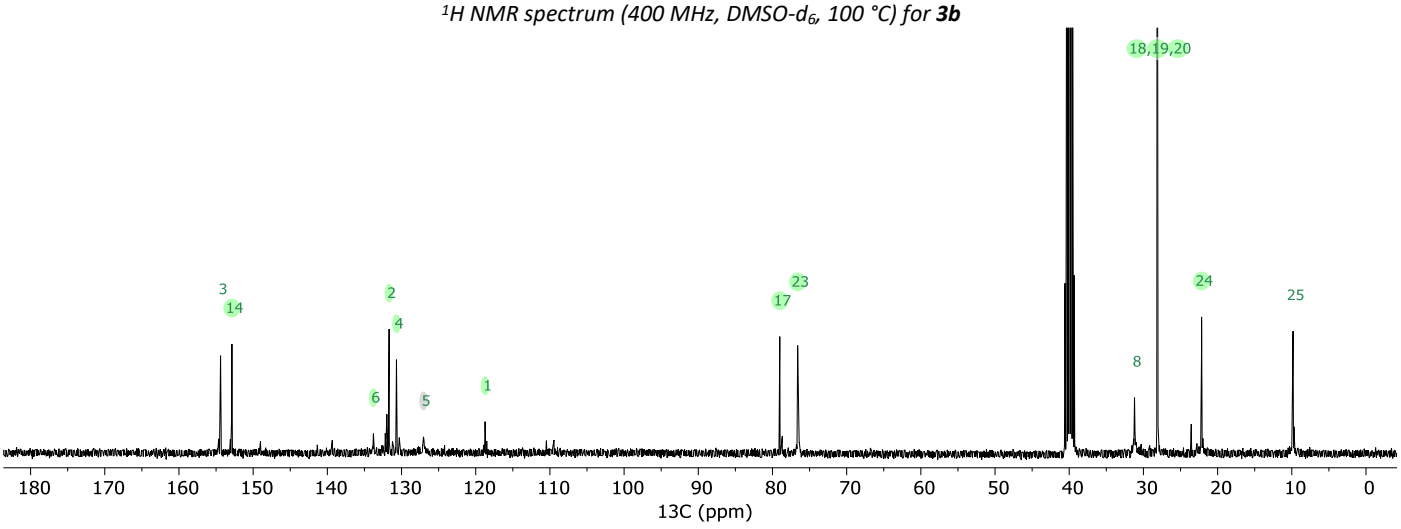
[8] The putative other isomer (**4b**) could not be isolated in a form that was pure enough to characterize.



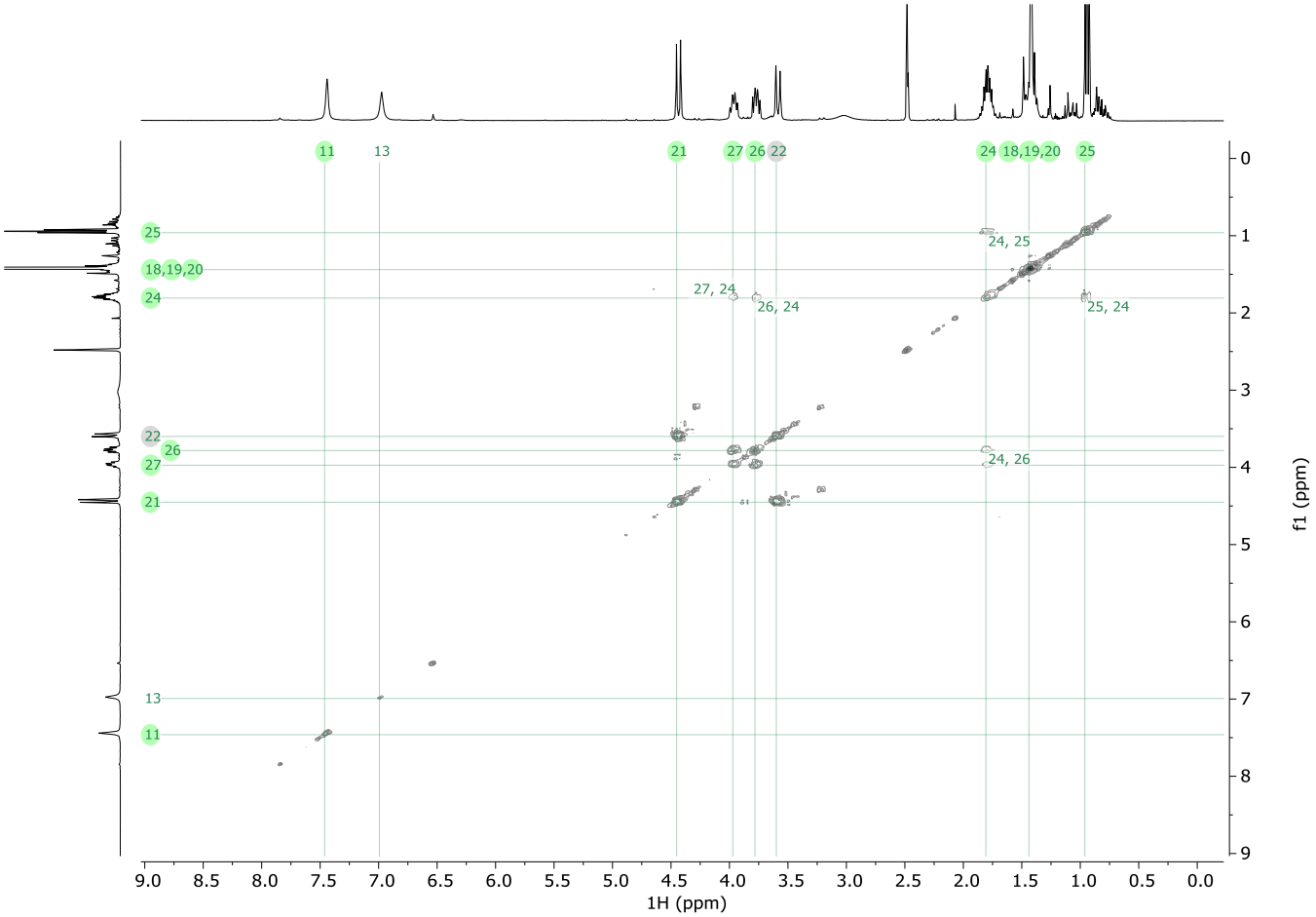
*Infrared spectrum for **3b***



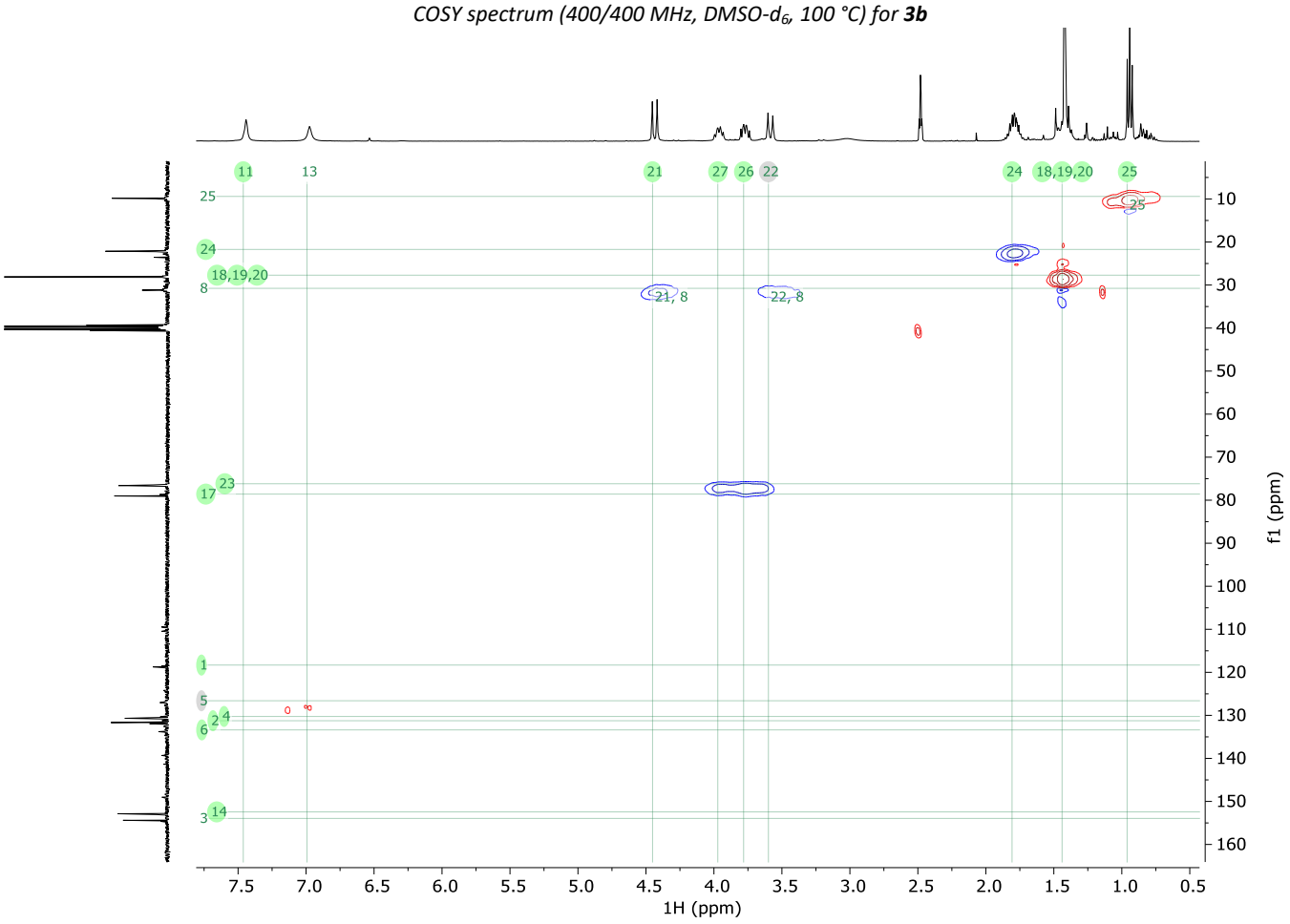
*^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100 °C) for **3b***



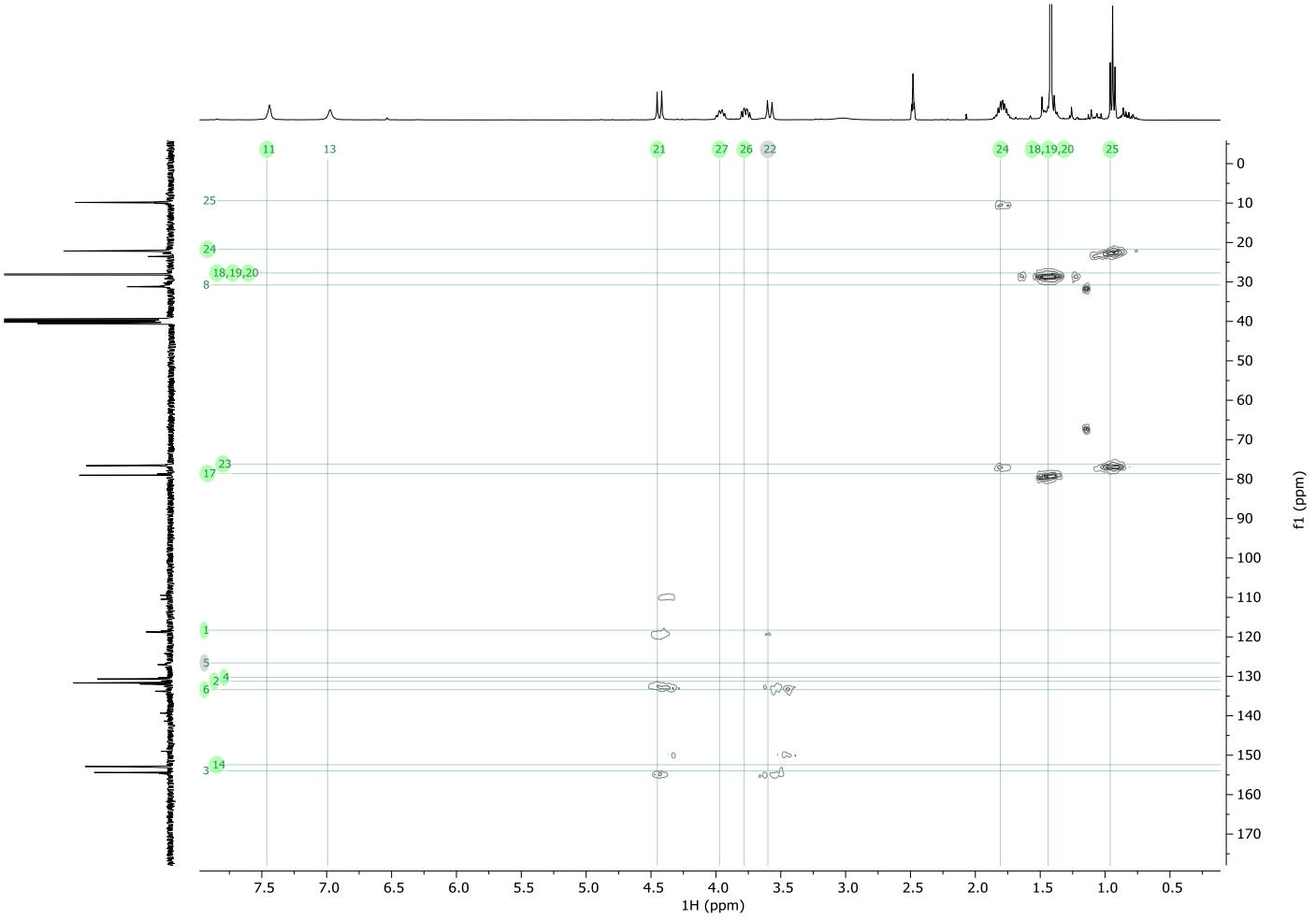
*^{31}C NMR spectrum (100 MHz, DMSO-d_6, 100 °C) for **3b***



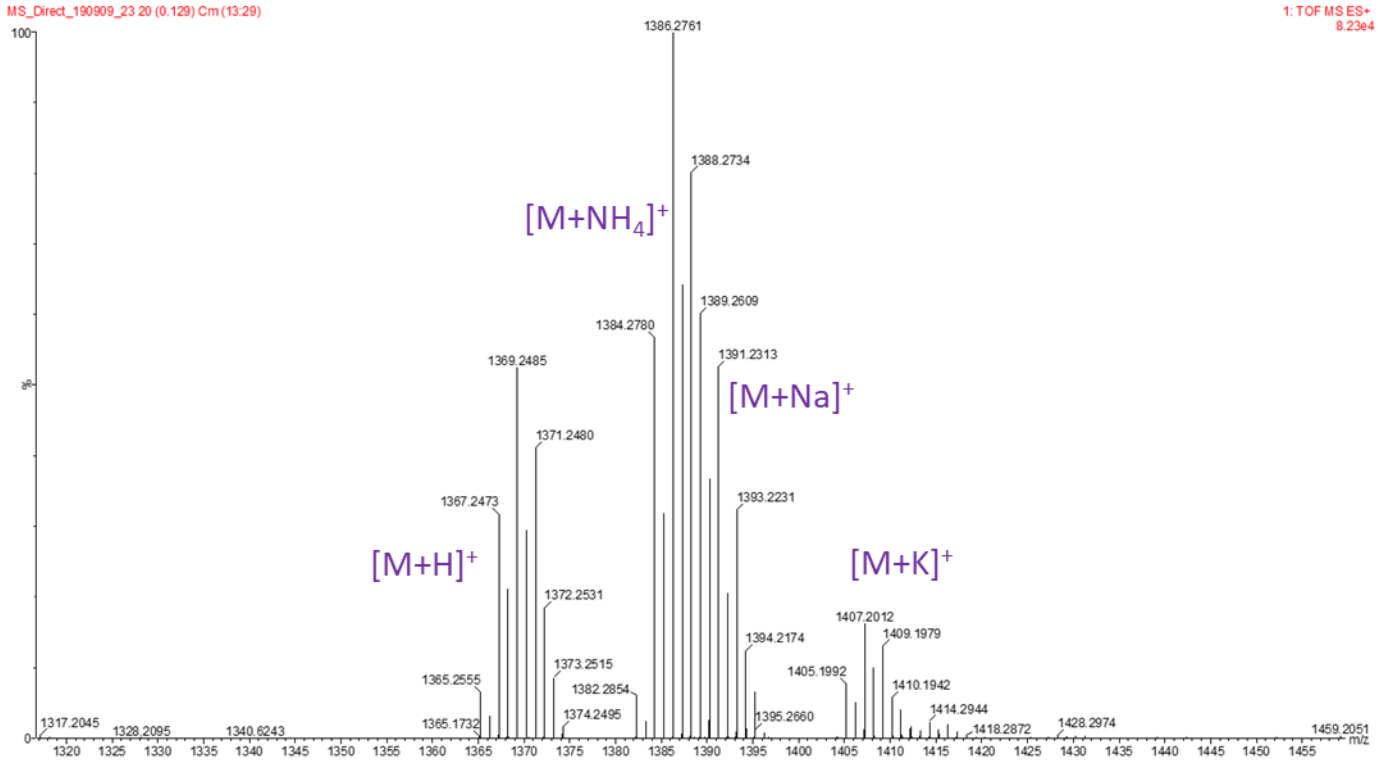
*COSY spectrum (400/400 MHz, DMSO-d_6, 100 °C) for **3b***



*gHSQCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for **3b***

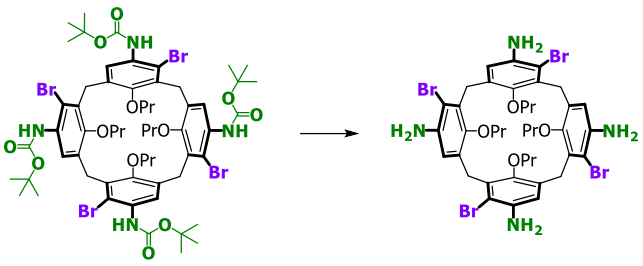


*gHMBCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for **3b***



*ES+ HRMS for **3b***

S4.7) 5,11,17,23- tetra-amino-4,10,16,22-tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene (5)



3b **5** (*73%*)

A magnetic stirrer bar was added to an oven-dried 50 mL round-bottom flask. Calix[4]arene **3b** (250 mg, 0.183 mmol) was added to the flask and dissolved in tetrahydrofuran (8 mL). A 37% hydrochloric acid solution (0.8 mL) was added to the vial and the mixture was left to stir for 3 hours at 50 °C. The reaction was then neutralized with 2 M sodium hydroxide (5 mL). The product was extracted from the reaction mixture with dichloromethane (3 x 30 mL). The combined organic layers were washed with distilled water (30 mL) and a saturated solution of brine (2 x 30 mL). The organic layer was then dried with $MgSO_4$, filtered and the excess solvent removed *via* reduced pressure to give the product in sufficient purity as red-orange crystals (165 mg, 88%).

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 6.30 (s, 1H, $H_{[16]}$), 4.33 (d, $^2J_{H\text{-}H}$ = 13.9 Hz, 1H, $H_{[17]}$), 4.23 (br. s, 2H, NH_2)[9], 3.85 (ddd, *J* = 10.3, 8.5, 6.4 Hz, 1H, $H_{[20]}$), 3.65 (ddd, *J* = 10.4, 8.3, 6.2 Hz, 1H, $H_{[19]}$), 3.40 (d, $^2J_{H\text{-}H}$ = 13.9 Hz, 1H, $H_{[18]}$), 1.82 –1.71 (m, 2H, $H_{[12]}$), 0.93 (t, $^3J_{H\text{-}H}$=7.4 Hz, 3H, $H_{[13]}$)

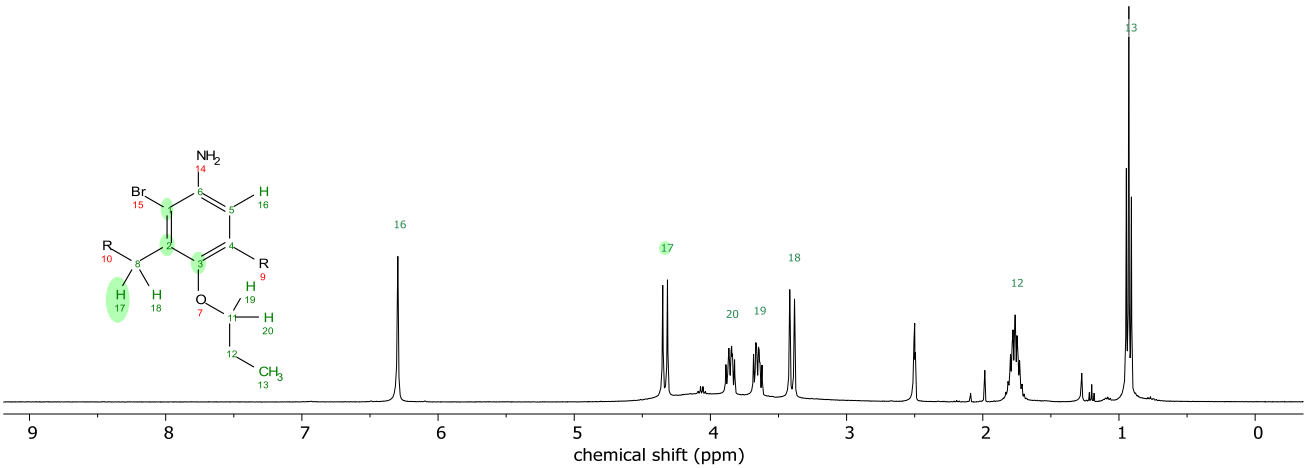
^{13}C NMR (100 MHz, DMSO-d6) δ ppm 148.5 ($C_{[3]}$), 139.2 ($C_{[6]}$), 132.8 ($C_{[4]}$), 131.9 ($C_{[2]}$), 116.3 ($C_{[5]}$), 108.6 ($C_{[1]}$), 75.8 ($C_{[11]}$), 30.6 ($C_{[8]}$), 21.7 ($C_{[12]}$), 9.5 ($C_{[13]}$)

COSY (400/400 MHz, DMSO-d6) δ^1H/δ^1H ppm 4.33 / 3.40 ($H_{[17]}$ / $H_{[18]}$), 3.85/ 3.65, 1.76 ($H_{[20]}$ / $H_{[19,12]}$), 3.65 / 3.85, 1.76 ($H_{[19]}$ / $H_{[20,12]}$), 1.76 / 3.85, 3.65, 0.93 ($H_{[12]}$ / $H_{[20,19,13]}$), 0.93 / 1.76 ($H_{[13]}$ / $H_{[12]}$)

gHSQCAD (300/75 MHz, DMSO-d6) δ^1H/δ^{13}C ppm 6.30 / 116.17 ($H_{[16]}$ / $C_{[5]}$), 4.33 / 30.6 ($H_{[17]}$ / $C_{[8]}$), 3.85 + 3.65 / 75.8 ($H_{[20,19]}$ / $C_{[11]}$), 3.40 / 30.6 ($H_{[18]}$ / $C_{[8]}$), 1.76 / 21.7 ($H_{[12]}$ / $C_{[12]}$), 0.93 / 9.5 ($H_{[13]}$ / $C_{[13]}$)

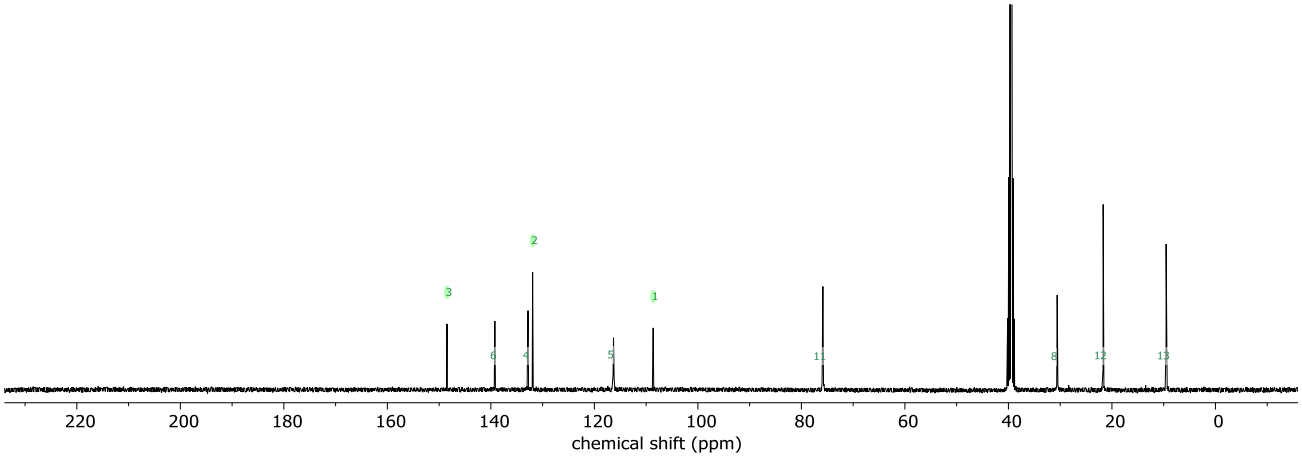
gHMBCAD (300/75 MHz, DMSO-d6) δ^1H/δ^{13}C ppm 6.30 / 148.5, 139.2, 132.8, 108.6, 30.6 ($H_{[16]}$ / $C_{[3,6,4,1,8]}$), 4.33 / 148.5, 132.8, 116.3, 108.6 ($H_{[17]}$ / $C_{[3,4,2,5,1]}$), 3.85 + 3.65 / 148.5, 21.7, 9.5 ($H_{[20,19]}$ / $C_{[3,12,13]}$), 3.40 / 148.5, 132.8, 116.3, 108.6 ($H_{[18]}$ / $C_{[3,4,2,5,1]}$), 1.77 / 75.8, 9.5 ($H_{[12]}$ / $C_{[11,13]}$), 0.93 / 75.8, 21.7 ($H_{[13]}$ / $C_{[11,12]}$);

HRMS–Positive: m/z $[M+H]^+$ calcd. for $C_{40}H_{49}Br_4N_4O_4$: 965.0487; found 965.0481.

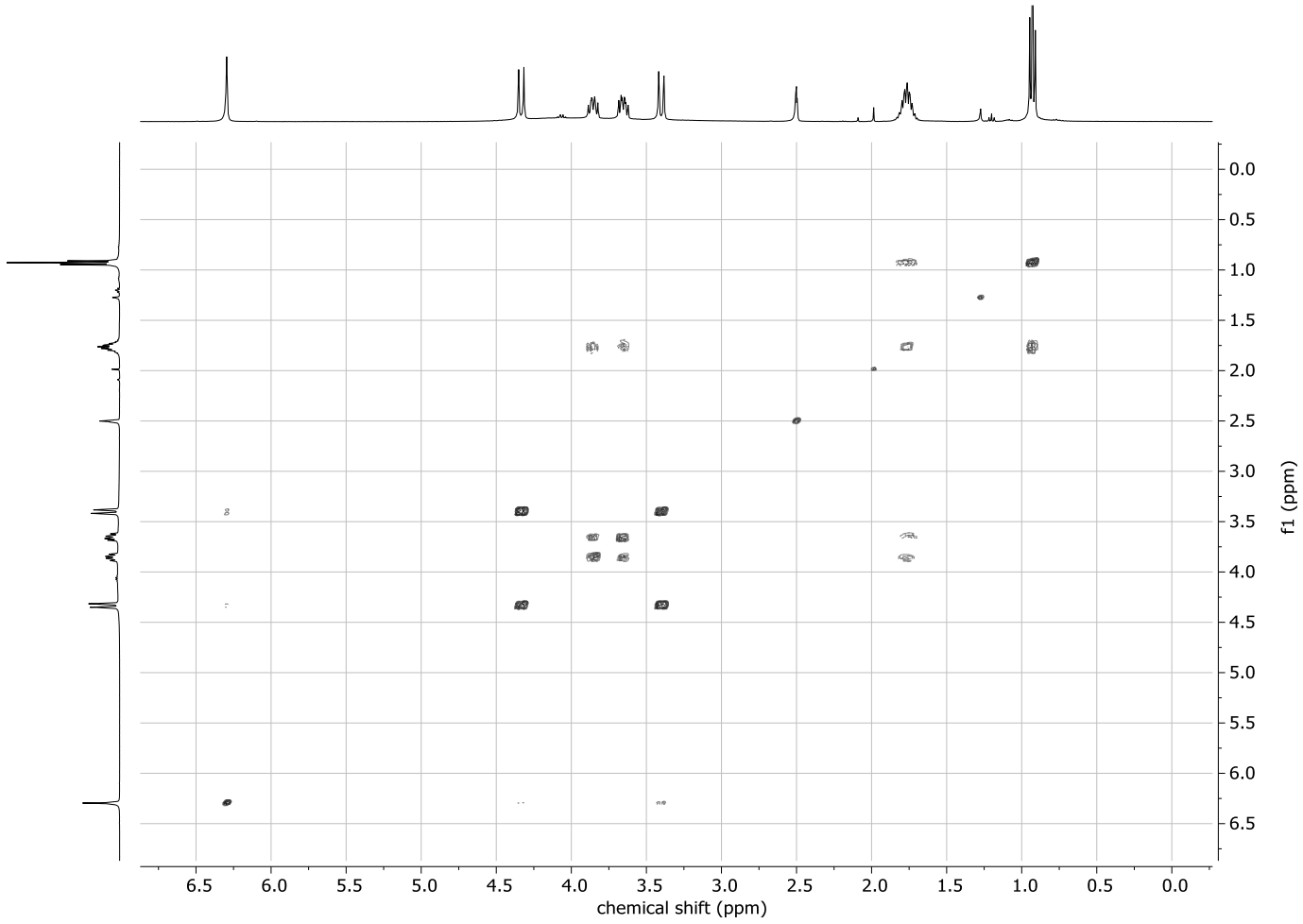


*^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100 °C) for (±)-**5***

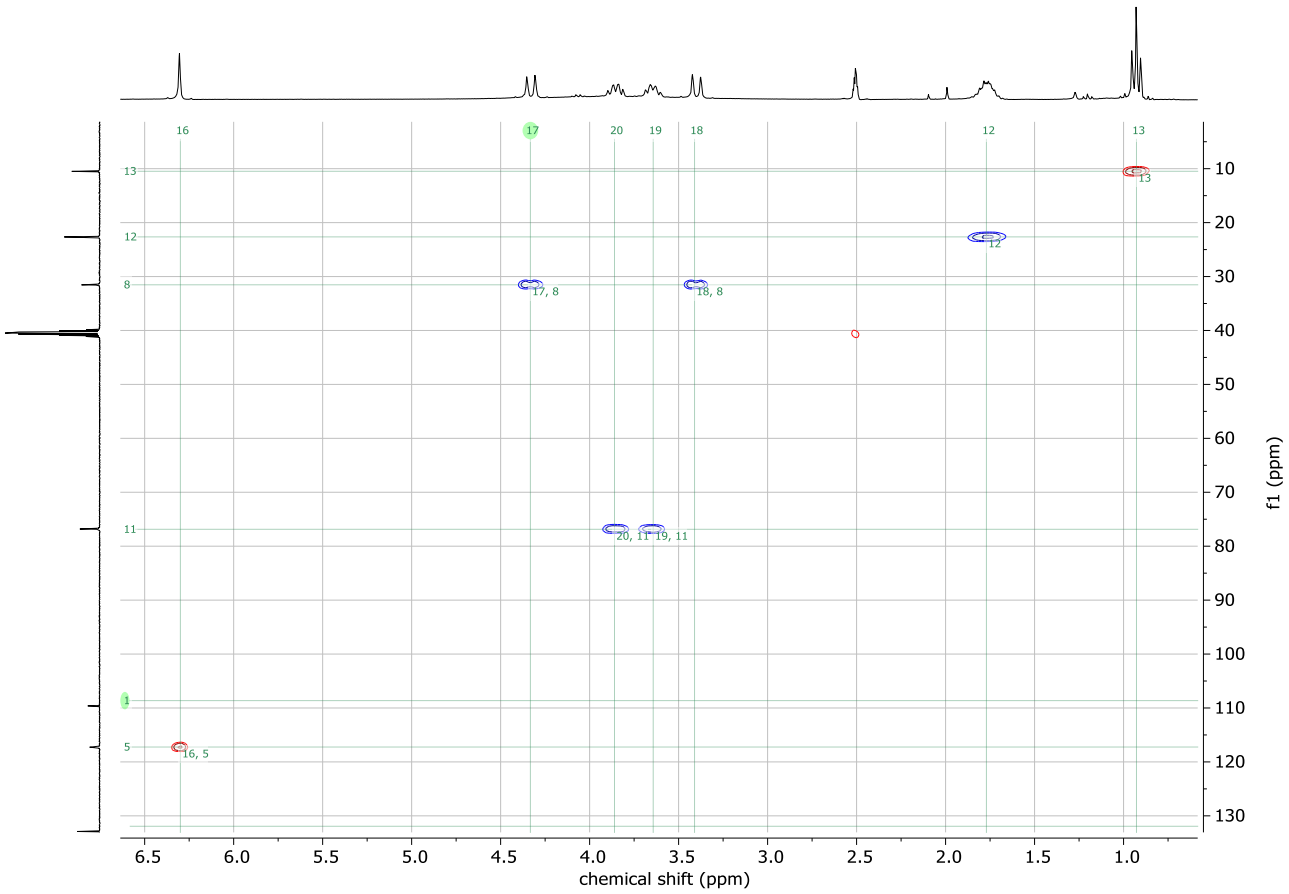
[9] Extremely broad due to H-bonding – appears as bump in baseline (see spectrum).



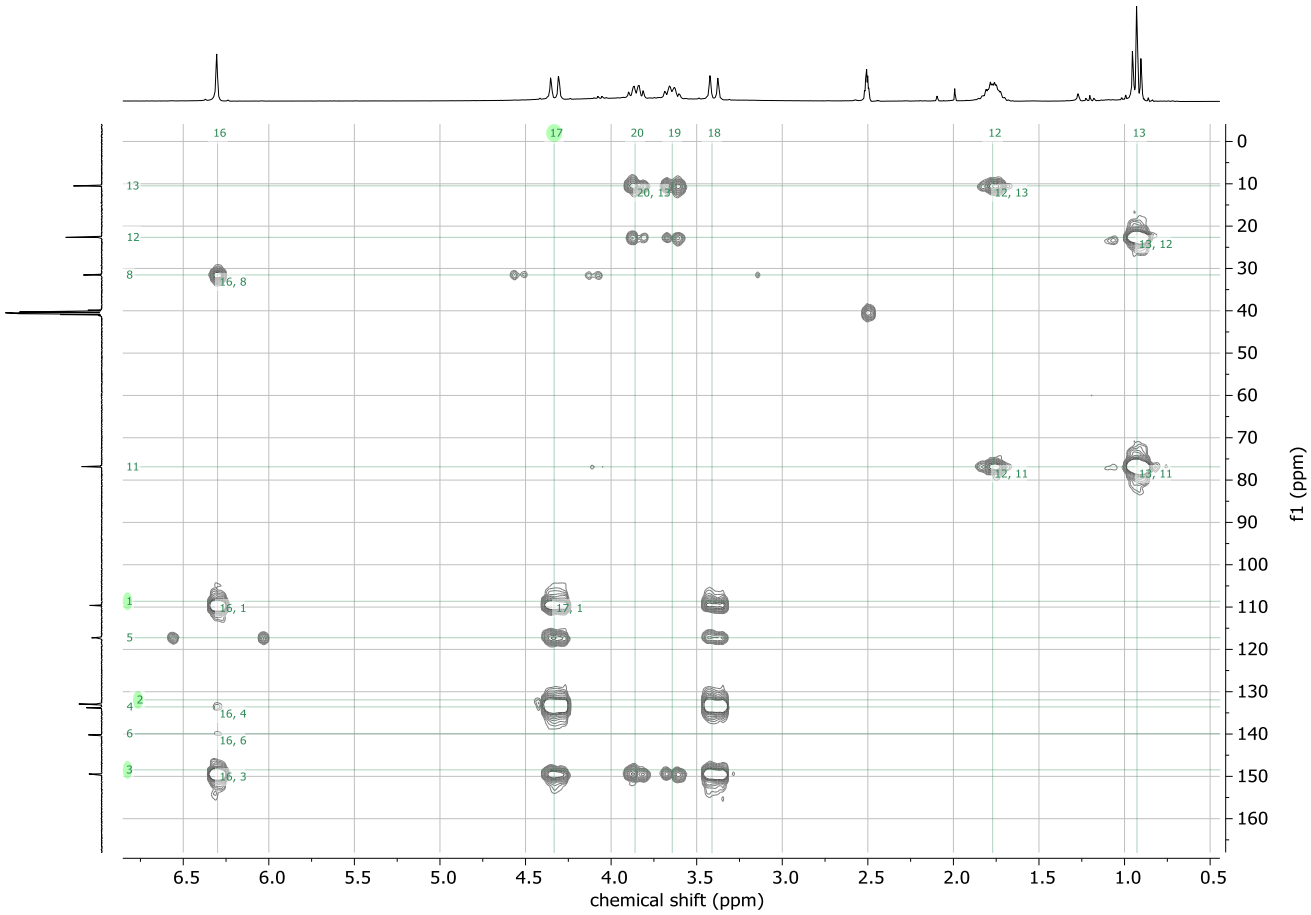
*^{13}C NMR spectrum (100 MHz, DMSO-d_6, 100 °C) for (±)-**5***



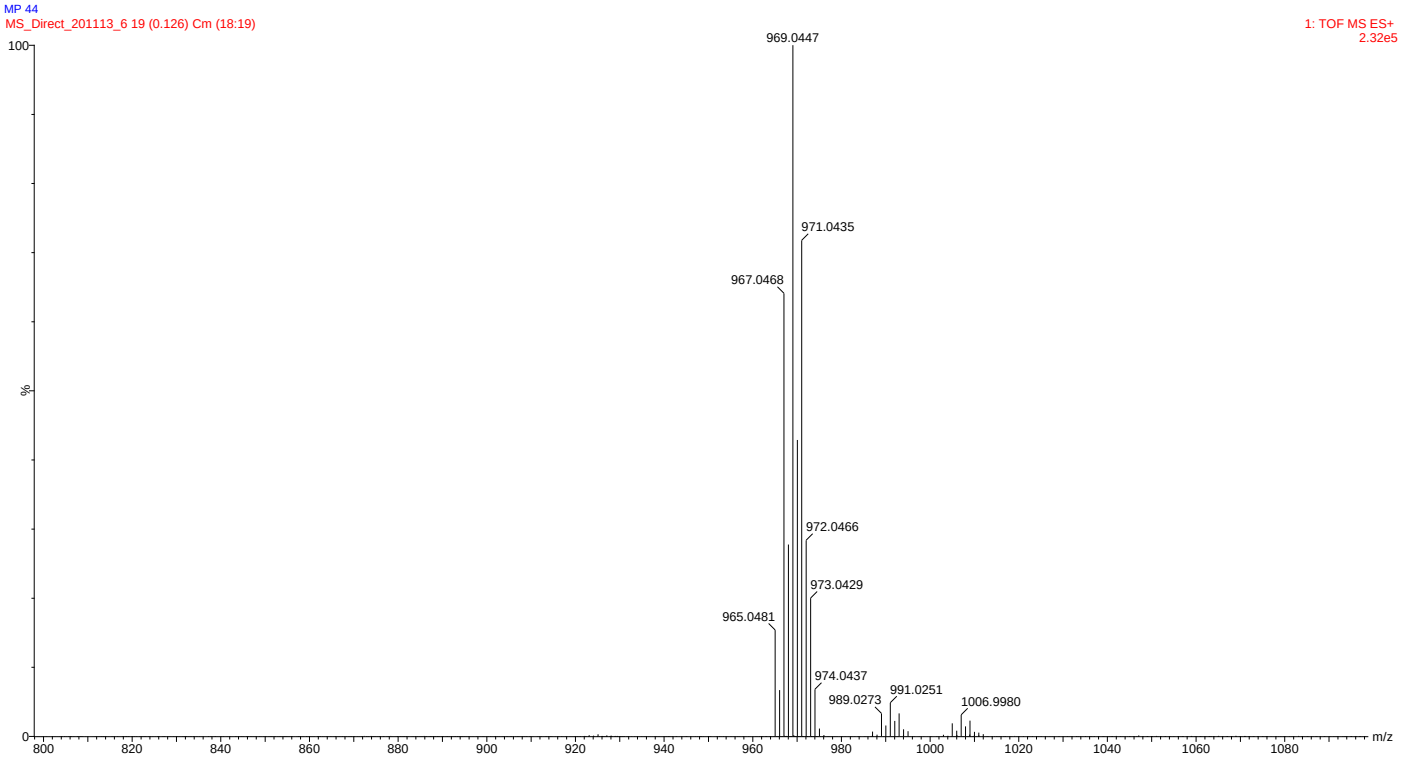
*COSY spectrum (400/400 MHz, DMSO-d_6, 100 °C) for (±)-**5***



*gHSQCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for (±)-**5***

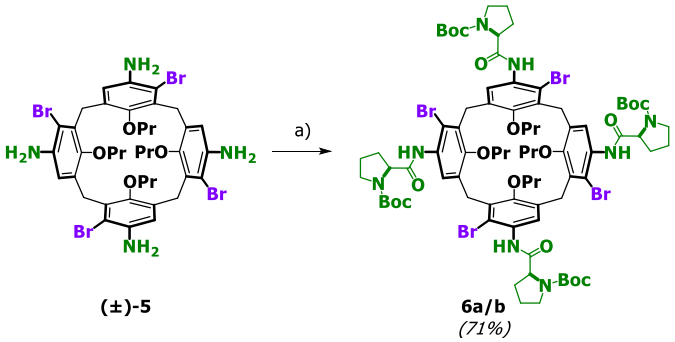


*gHMBCAD spectrum (300/75 MHz, DMSO-d_6, 100 °C) for (±)-**5***



*ES+ HRMS for (±)-**5***

S4.8) 4,10,16,22-tetrabromo-5,11,17,23- tetrakis(*N*-Boc-proline)-25,26,27,28-tetrapropoxycalix[4]arene (6a/b)



To a solution of dichloromethane (3 mL) was added tetraamino-tetrabromo calixarene (±)-**5** (77 mg, 0.080 mmol), Boc-L-Proline (103 mg, 0.48 mmol, 6.0 eq), DCC (99 mg, 0.48 mmol, 6.0 eq), and DMAP (4.9 mg, 0.04 mmol, 0.5 eq). The reaction was stirred at room temperature for 13 hours before filtering off the insoluble urea byproduct. After diluting the mixture with dichloromethane (30 mL), the organic layer was washed with 1M NaOH (10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered, and reduced under vacuum to give a crude solid which was further purified via flash column chromatography (60% EtOAc in hexane). This produced 98 mg (71% yield) of a mixture of diastereomers which were then separated through preparative TLC using a 40% EtOAc in hexane system to produce 25 mg **6a** (18 %) and 27 mg **6b** (19%) of the purified diastereomers.

Top Spot **6a**

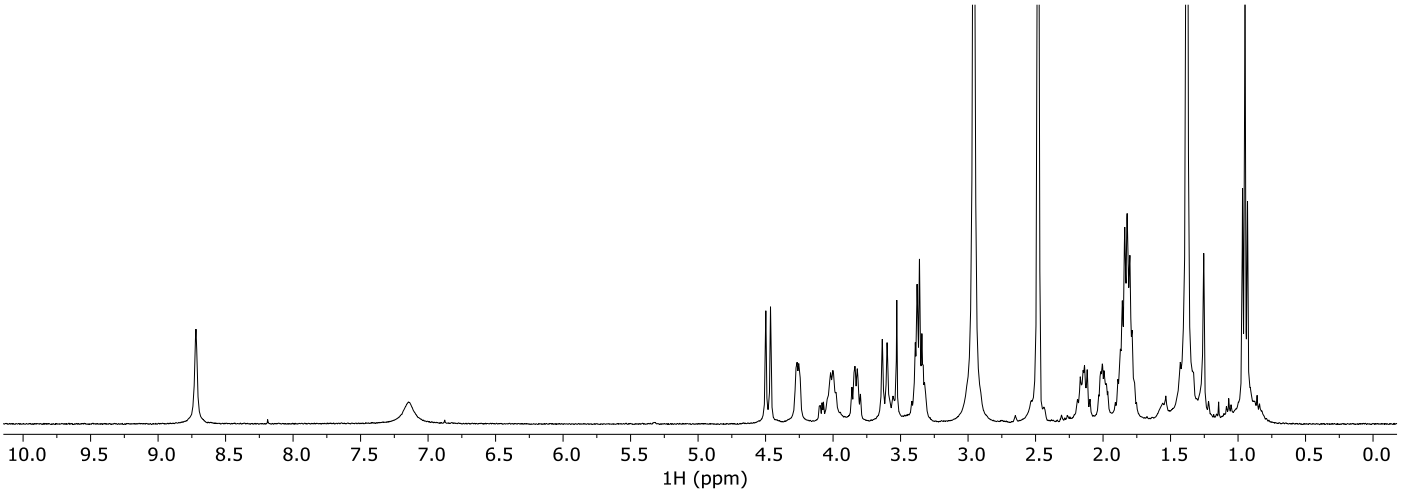
$[\propto]_D^{18}$ = +80° (c = 1 mg/mL in CH_2Cl_2)

R_f = 0.34 (3:2 EtOAc:Pet Ether)

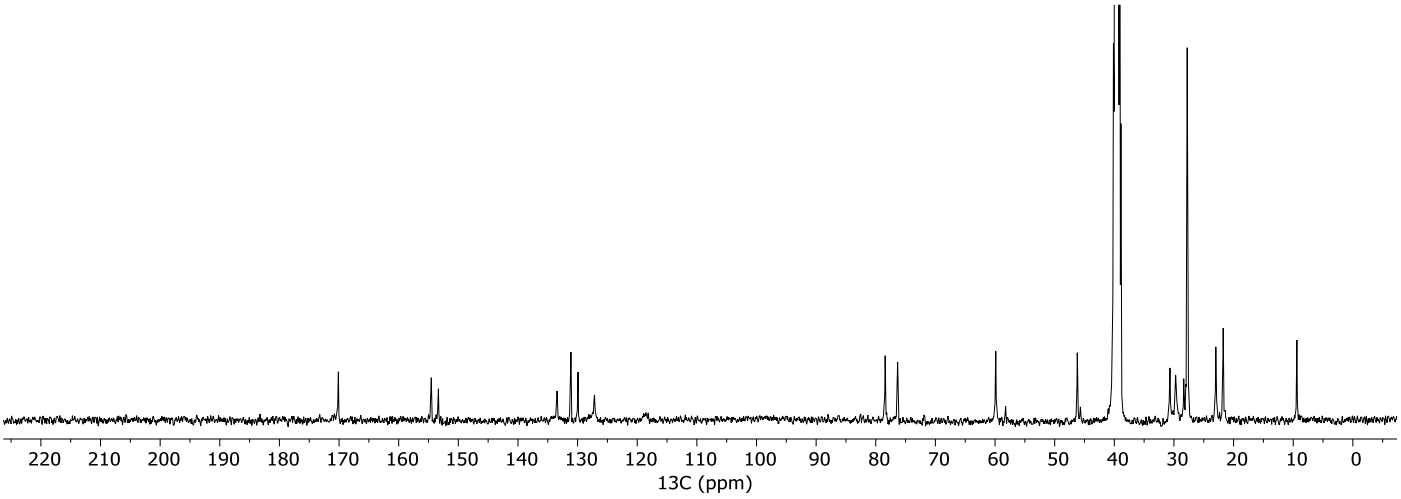
^{1}H NMR (400 MHz, DMSO-d$_6$)[5] δ 8.74 (s, 1H, N*H*), 7.16 (s, 1H, Ar*H*), 4.50 (d, *J* = 13.9 Hz, 1H, ArC$H_{2(ax)}$Ar), 4.28 (dd, *J* = 8.0 & 3.5 Hz, 1H, proline-NC*H*), 4.06 – 3.99 (m, 1H, OCH_2CH$_2$), 3.90 – 3.80 (m, 1H, OCH_2CH$_2$), 3.64 (d, *J* = 13.9 Hz, 4H, ArC$H_{2(eq)}$Ar), 3.44 – 3.32 (m, 2H, proline-NCH_2), 2.20 – 2.12 (m, 1H, proline-CH_2), 2.05 – 1.97 (m, 1H, proline-CH_2), 1.89 – 1.78 (m, 4H, proline-CH_2 and OCH$_2$CH_2CH$_3$), 1.40 (s, 9H, OC(CH_3)$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, OCH$_2$CH$_2$CH_3).

^{13}C NMR (100 MHz, DMSO-d_6)[5] δ 170.1 (NH*C*OCH), 154.5 (Ar*C*), 153.3 (N*C*OO), 133.4 (Ar*C*), 131.1 (Ar*C*), 129.9 (Ar*C*), 127.2 (Ar*C*), 118 (Ar*C*),[10] 78.4 (O*C*(CH_3)$_3$), 76.3 (O*C*$H_2$$CH_2$), 59.9 (proline-N*C*H), 46.2 (proline-N*C*H), 30.7 (Ar*C*Ar), 29.7 (proline-*C*H_2), 27.8 (OC(*C*H_3)$_3$), 23.0 (proline-*C*H_2), 21.7 (OCH_2*C*$H_2$$CH_3$), 9.4 (O$CH_2$$CH_2$*C*$H_3$).

HRMS–Positive: m/z [M+NH_4]$^+$ found 1770.4355, calculated for $C_{80}H_{112}N_9O_{16}Br_4$ 1770.4960

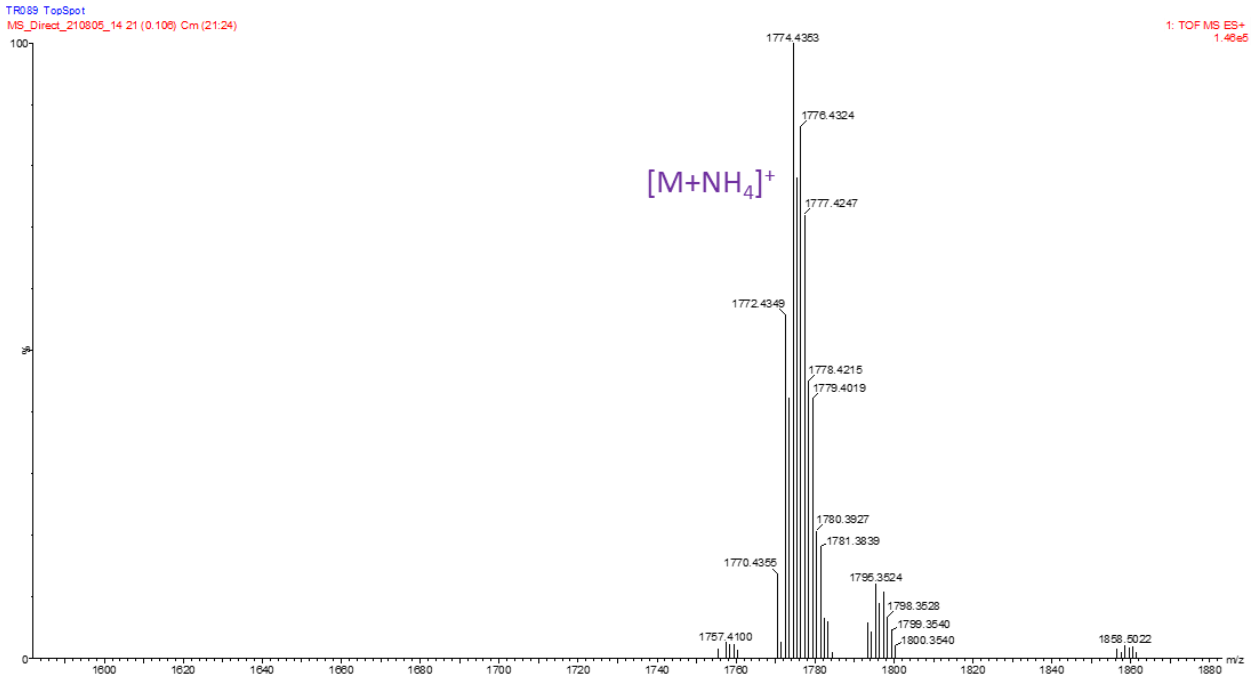


*^{1}H NMR spectrum (400 MHz, DMSO-d_6, 100 °C) for **6a***



*^{13}C NMR spectrum (100 MHz, DMSO-d_6, 100 °C) for **6a***

[10] This signal is weak and broad, but is consistent with he chemical shift of the aromatic carbon attached to the bromine atom in other compounds.



*ES+ HRMS for **6a***

Bottom spot **6b**

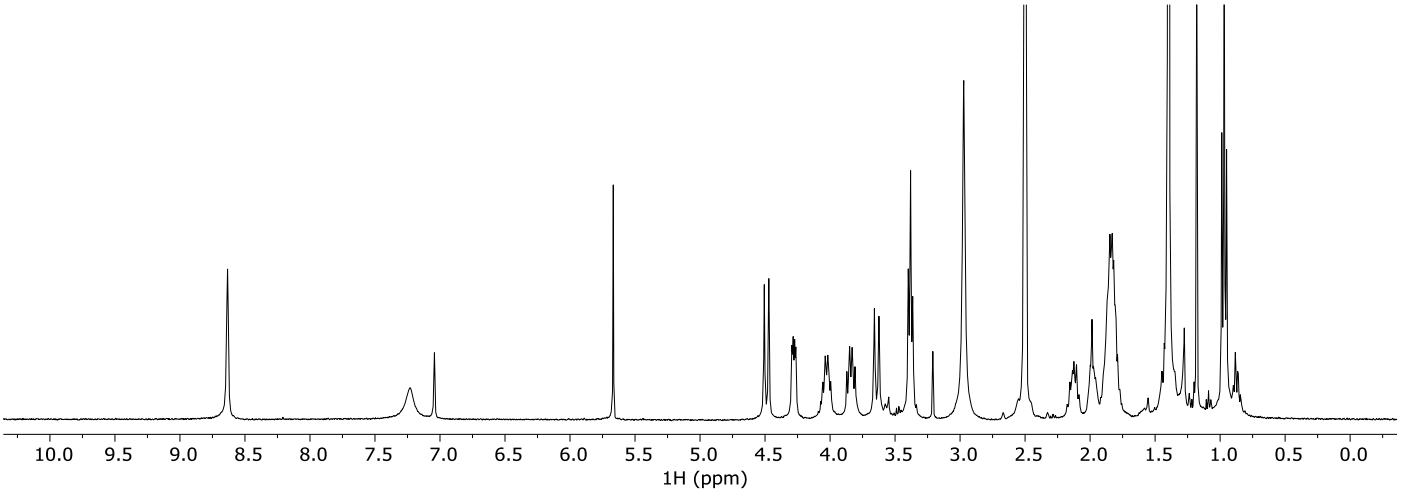
$[\propto]_D^{18}$ = +130° (c = 1 mg/mL in CH_2Cl_2)

R_f = 0.29 (3:2 EtOAc:Pet Ether)

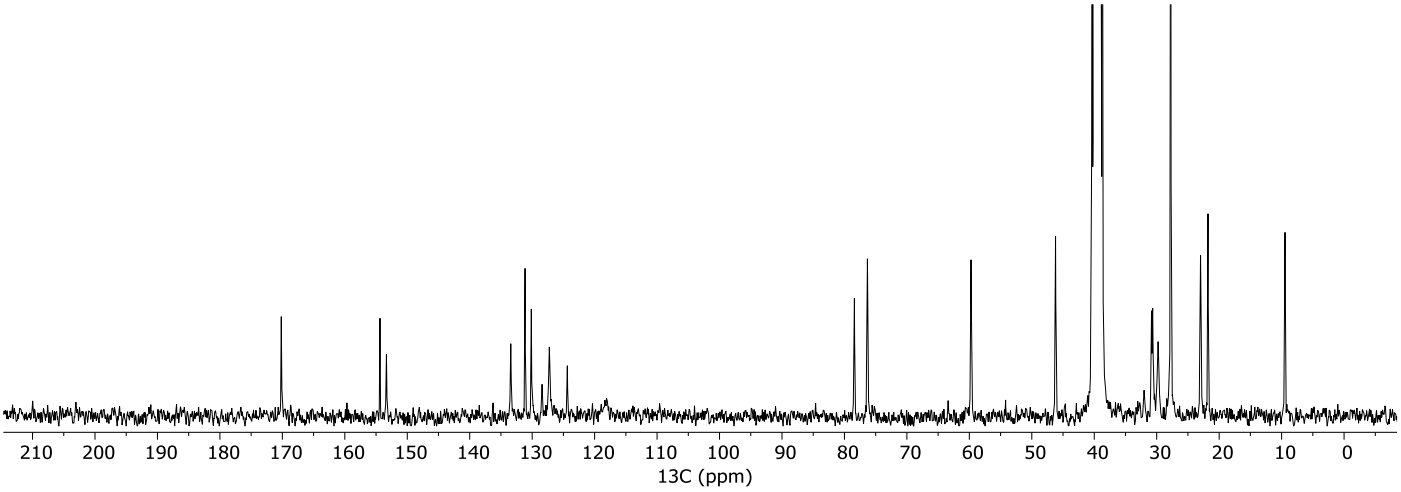
^{1}H NMR (400 MHz, DMSO- d$_6$)[5] δ 8.63 (s, 1H, N*H*), 7.23 (s, 4H, Ar*H*), 4.49 (d, *J* = 13.8 Hz, 1H, ArC$H_{2(ax)}$Ar), 4.28 (dd, *J* = 8.2 & 3.6 Hz, 1H, proline-NC*H*), 4.06 – 3.98 (m, 1H, OCH_2CH$_2$), 3.89 – 3.79 (m, 1H, OCH_2CH$_2$), 3.64 (d, *J* = 13.8 Hz, 1H, ArC$H_{2(eq)}$Ar), 3.44 – 3.32 (m, 8H, proline-NCH_2), 2.18 – 2.10 (m, 1H, proline-CH_2), 2.02 – 1.94 (m, 1H, proline-CH_2), 1.89 – 1.78 (m, 4H, proline-CH_2 and OCH$_2$CH_2CH$_3$), 1.40 (s, 9H, OC(CH_3)$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3).

^{13}C NMR (75 MHz, DMSO-d$_6$) δ 170.2 (NH*C*OCH), 154.4 (ArC), 153.3 (N*C*OO), 133.4 (ArC), 131.1 (ArC), 130.1 (ArC), 127.2 (ArC), 124.4 (ArC), 78.4 (O*C*(CH$_3$)$_3$), 76.3 (O*C*H$_2$CH$_2$), 59.7 (proline-N*C*H), 46.2 (proline-N*C*H), 30.8 (Ar*C*Ar), 29.8 (proline-*C*H$_2$), 27.8 (OC(*C*H$_3$)$_3$), 23.0 (proline-*C*H$_2$), 21.8 (OCH$_2$*C*H$_2$CH$_3$), 9.5 (OCH$_2$CH$_2$*C*H$_3$).

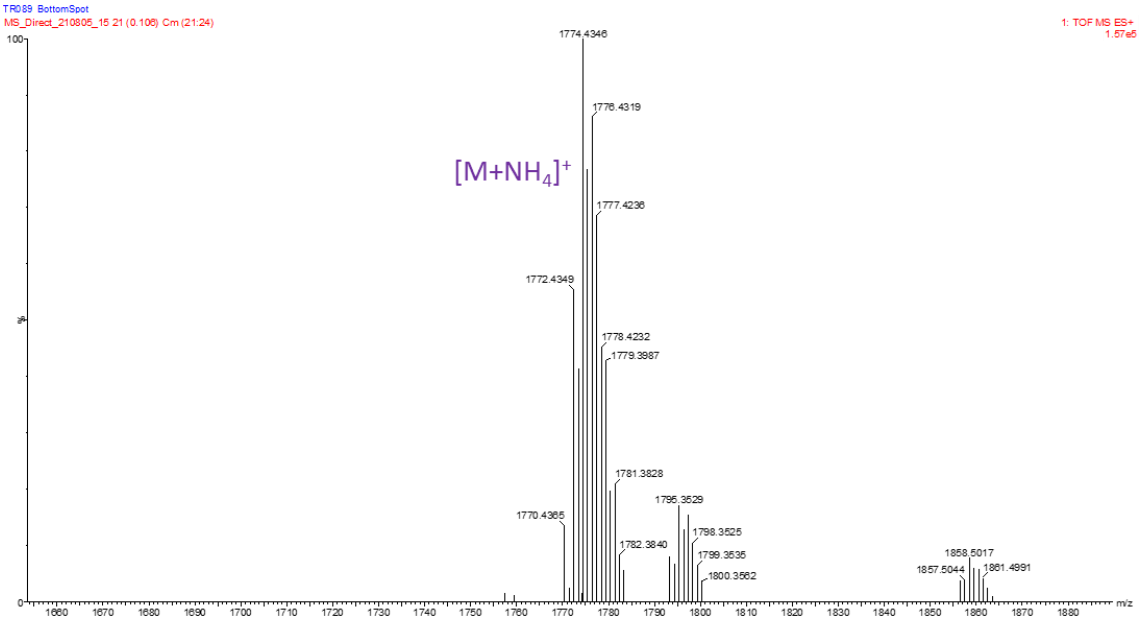
HRMS–Positive: m/z [M+NH$_4$]$^+$ found 1770.4365, calculated for $C_{80}H_{108}N_8O_{16}Br_4$ 1770.4960



*^{1}H NMR spectrum (400 MHz, DMSO-d$_6$, 100 °C) for **6b***



*^{13}C NMR spectrum (100 MHz, DMSO-d_6, 100 °C) for **6b***



*ES+ HRMS for **6b***

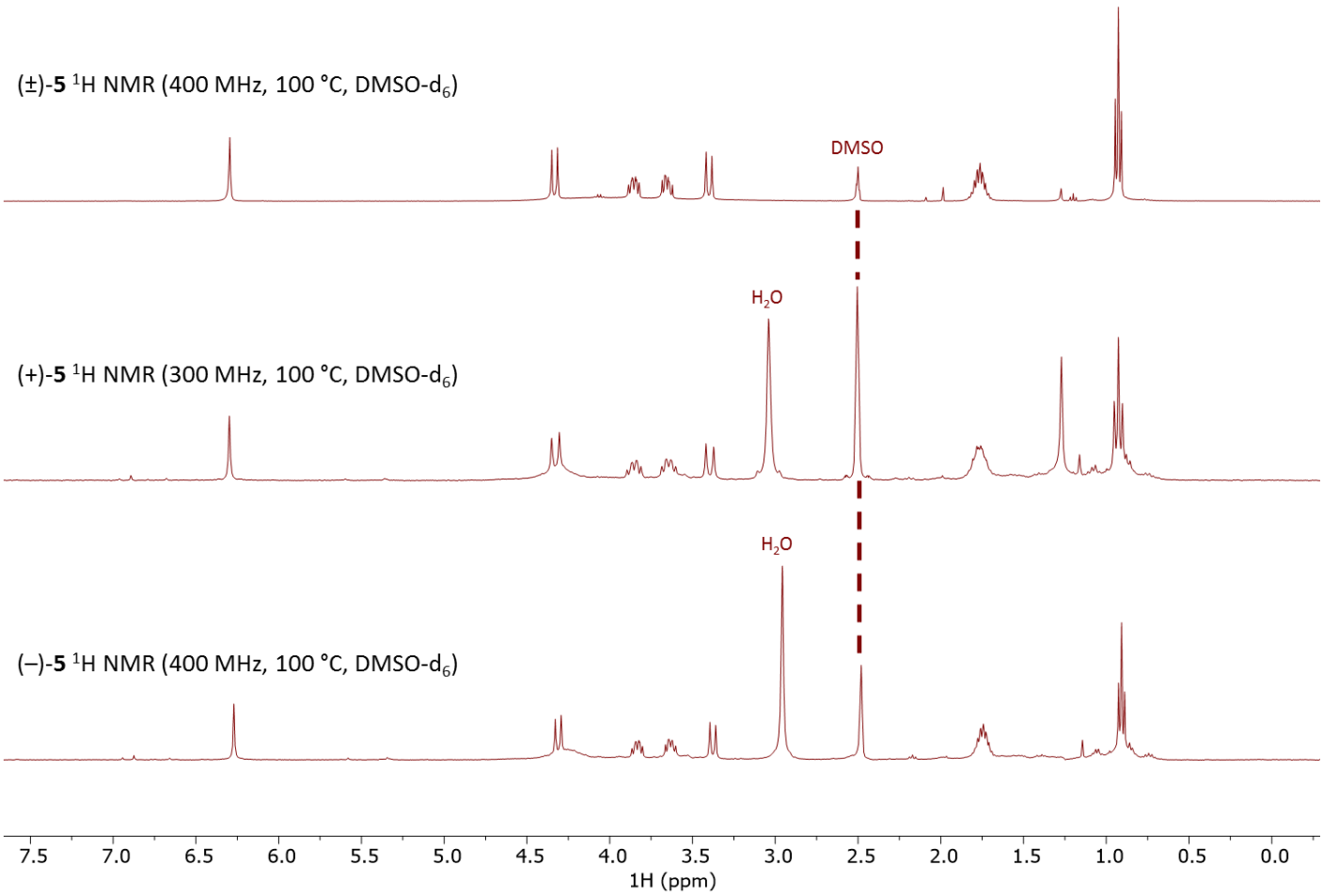
S4.9) General procedure for the removal of the *N*-Boc-proline residues.

To a solution of *tert*-butanol (7 mL) and DMSO (0.4 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (194 mg, 0,61 mmol, 41 eq) and the mixture sonicated for 20 minutes to increase the solubility of the base. Tetrabromo-tetraproline calixarene **6a** or **6b** (27 mg, 0,015 eq) was added and the mixture placed under reflux for 48 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the crude solid dissolved in dichloromethane (20 mL). The organic layer was washed with 0.2 M HCl (10 mL), water (10 mL) and brine (10 mL). Drying over $MgSO_4$ was followed by removal of the solvent under reduced pressure at 60 °C to produce the pure enantiomer.

Hydrolysis of **6a** to give **(+)-5**
(using 27 mg **6a**) Yield = 13 mg, 86%

Hydrolysis of **6b** to give **(–)-5**
(using 25 mg **6b**) Yield = 13 mg, 93%

(both ^{1}H NMR spectra matched that already obtained for racemic **5** – see stacked plot below)



*Stacked plot of ^{1}H NMR spectra of the inherently chiral calix[4]arenes **5** obtained in this work*

S5) Details regarding the ECD spectra and assignment of the enantiomers (*M*)-5 and (*P*)-5.

METHODS - DFT calculations

All DFT calculations were performed using the Gaussian16 (C.01 revision) software package.[11] The starting structure of calix[4]arene was prepared from the crystal structure of the Boc-protected calix[4]arene analogue by removing Boc groups using the Avogadro software package.[12] The geometry of the resulting structure was optimised using B3LYP/6-31G* and frequency calculation subsequently performed to ensure a saddle point was not obtained. The electronic circular dichroism (ECD) spectrum was computed under the SMD solvent model[13] for acetonitrile using TD-DFT at the PBE0 level of theory and TZVP basis-set combination (PBE0/TZVP). Visualisation of the ECD spectrum (convoluted using gaussian functions with linewidth of 9 nm) and molecular orbital population was conducted using the GABEDIT[14] and ChemCraft[15] software packages, respectively. Gaussian input scripts used to generate data are available at https://github.com/davidkuter/Papers/tree/master/2020_Arnott.

[11] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

[12] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison, "Avogadro: An advanced semantic chemical editor, visualization, and analysis platform", *J. Cheminformatics*, 2012, **4**, 17. https://doi.org/10.1186/1758-2946-4-17

[13] A. V. Marenich, C. J. Cramer, D. G. Truhlar, "Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions", *J. Phys. Chem.*, 2009, **113**, 6378 - 6396. https://doi.org/10.1021/jp810292n

[14] A. Allouche, "Gabedit—A graphical user interface for computational chemistry softwares", J. Comput. Chem., 2010, 32, 174 - 182. https://doi.org/10.1002/jcc.21600

[15] Chemcraft - graphical software for visualization of quantum chemistry computations. https://www.chemcraftprog.com

METHODS - CD spectroscopy

Samples were made up to 0.04 mg/mL in acetonitrile and run on a Chirascan Plus CD Spectrometer from Applied Photophysics and then the data processed using Pro-Data Viewer (v.4.2.6) from Applied Photophysics. The background (CH_3CN) was also run and removed from the samples.

RESULTS & DISCUSSION

Absolute configuration assignment of closely related resorc[4]arenes has previously been achieved by comparing DFT-computed ECD spectra to experimental spectra.[16,17] It has also been successfully applied to an asymmetrically substituted calix[4]arene derivative.[18] Consequently, the same approach was applied to identify calix[4]arene enantiomers in this study. Using the crystal structure of Boc-protected calix[4]arene as a reference, (*M*)-calix[4]arene **5** was prepared and geometry optimisation performed using the same functional and basis set combination (B3LYP/6-31G*) as employed by Concilio *et al.*[17] (for their resorc[4]arene system) and Talotta *et al*.[18] (for their calix[4]arene system). The resultant geometry was in good structural agreement with the reference crystal structure (see Fig. S1) and adopted the same pinched-crown conformation. Owing to the steric clash of the propanol substituents, boat and crown conformations are not expected to arise in any appreciable amounts under the experimental conditions employed for CD spectroscopic recordings. Indeed, attempts to computationally generate such conformers always lead to the formation of the pinch-crown conformation, thus only this conformer was considered in further calculations.

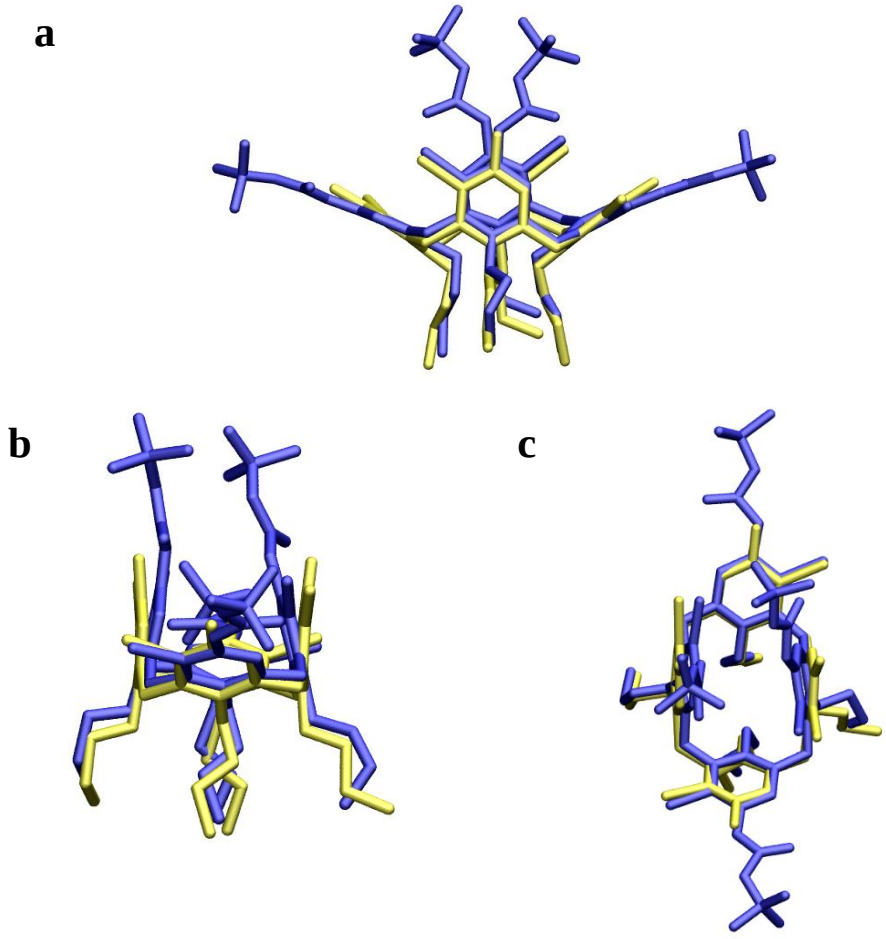


Figure S1. Comparison of the crystal structure of boc-protected calix[4]arene (blue) and DFT optimised (B3LYP/6-31G*) calix[4]arene (yellow) from (**a**) front; (**b**) side; and (**c**) top view points.

[16]C. Schiel, G. A. Hembury, V. V. Borokov, M. Klase, C. Agena, T. Wada, S. Grimme, Y. Inoue and J. Mattay, "New Insights into the Geometry of Resorc[4]arenes: Solvent-Mediated Supramolecular Conformational and Chiroptical Control", *J. Org. Chem.*, 2006, **71**, 976 - 982. https://doi.org/10.1021/jo0518654

[17] G. Concilio, C. Talotta, C. Gaeta, P. Neri, G. Monaco, R. Zanasi, D. Tedesco and C. Bertucci, "Absolute configuration assignment of chiral resorcin[4]arenes from ECD spectra", *J. Org. Chem.*, 2017, **82**, 202 - 210. https://doi.org/10.1021/acs.joc.6b02349

[18] C. Talotta, C. Gaeta, F. Troisi, G. Monaco, R. Zanasi, G. Mazzeo, C. Rosini and P. Neri, "Absolute Configuration Assignment of Inherently Chiral Calix[4]arenes using DFT Calculations of Chiroptical Properties", *Org. Lett.*, 2010, **12**, 2912 – 2915. https://doi.org/10.1021/ol101098x

The ECD spectrum was computed under the implicit acetonitrile solvent continuum and compared to the experimental spectra recorded in acetonitrile at 298 K (Fig. 5, main manuscript). Spectra were calculated using the functional and basis set combinations employed by Concilio *et al.*[17] (B3LYP/6-31++G* and PBE0/6-31++G*) as well as by Schiel *et al.*[16] (PBE0/TZVP, see Fig. S2), the latter was found to best reproduce experimental spectroscopic features (Fig. 5, main manuscript). While the major experimentally observed peak at 227 nm and trough at 246 nm are slightly red-shifted in the computed spectrum (220 nm and 240 nm, respectively), the spectroscopic agreement is sufficient to conclude that the (*M*)-enantiomer is responsible for the purple spectrum (Fig. 5, main manuscript) and, thus, the (*P*)-enantiomer, the green spectrum (Fig 5, main manuscript). Dominant excitations and single electron transitions contributing more than 18% to a single excitation are listed in Table S2. Perhaps unsurprisingly, excitations giving rise to the characteristic spectroscopic features of (*M*)-calix[4]arene primarily involve aromatic π→π* transitions. These largely originate in the 8 highest occupied molecular orbitals (MOs), 244 (HOMO) to 237 (HOMO-7), which mostly consist of aromatic π character, although MOs 241-244 and 237-240 also have notable contributions from amino and bromo substituents, respectively (see Supporting Information Fig. S3). The 8 MOs can be thought of as two separate groups of 4 each admixed with only one of the two degenerate e_{1g} HOMOs of benzene (π_2 and π_3). Because the pinched-crown conformation of calix[4]arene reduces molecular symmetry from C_4 to C_2, the degeneracy of MO pairs 244 and 242 as well as 239 and 237 is lifted, but for the sake of interpretation, can be considered equivalent. Most transitions terminate in π* MOs 245 (LUMO) and 255 (LUMO+10) which correspond to admixtures of the two degenerate e_{2u} LUMOs of benzene (π^*_5 and π^*_4, see Supporting Information Fig. S3), although at least 4 MOs (248, 249, 254 and 254) have significant σ* contributions from the bromine substituents.

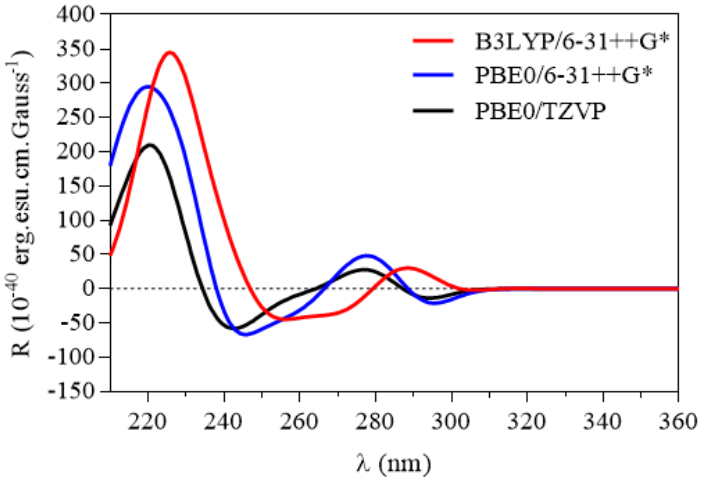


Figure S2. DFT-computed ECD spectra in implicit acetonitrile solvent of calix[4]arene (*M*)-**5**.

Table S2. Dominant excitations in the DFT-computed ECD spectrum of calix[4]arene (*M*)-5 [a]

State	λ (nm)	R[b]	Transition Character [c]
2	291.5	-80.2	243 → 245 (26%) + 241 → 245 (22%)
41	228.2	-66.8	244 → 253 (24%) + 244 → 255 (21%)
42	227.3	62.7	243 → 255 (37%) + 238 → 245 (21%)
47	225.4	-60.0	243 → 255 (38%) + 238 → 245 (18%)
49	223.4	157.7	242 → 255 (25%)
50	223.3	-64.9	239 → 247 (33%) + 238 → 245 (24%) + 241 → 255 (18%)
54	220.2	135.0	237 → 245 (24%) + 243 → 256 (22%)
57	219.0	81.2	237 → 245 (32%) + 241 → 254 (29%)
61	217.2	-73.4	242 → 256 (69%)
67	210.7	-96.3	**239 → 248 (24%)** + 236 → 245 (19%) + **240 → 249 (18%)**
68	210.3	143.4	237 → 247 (25%)

[a] All transitions are π→ π * unless highlighted in bold which are π →σ*; [b] computed rotary strength (x 10^{-40} erg.esu.cm.Gauss^{-1}); [c] see Fig. S3 for orbitals.

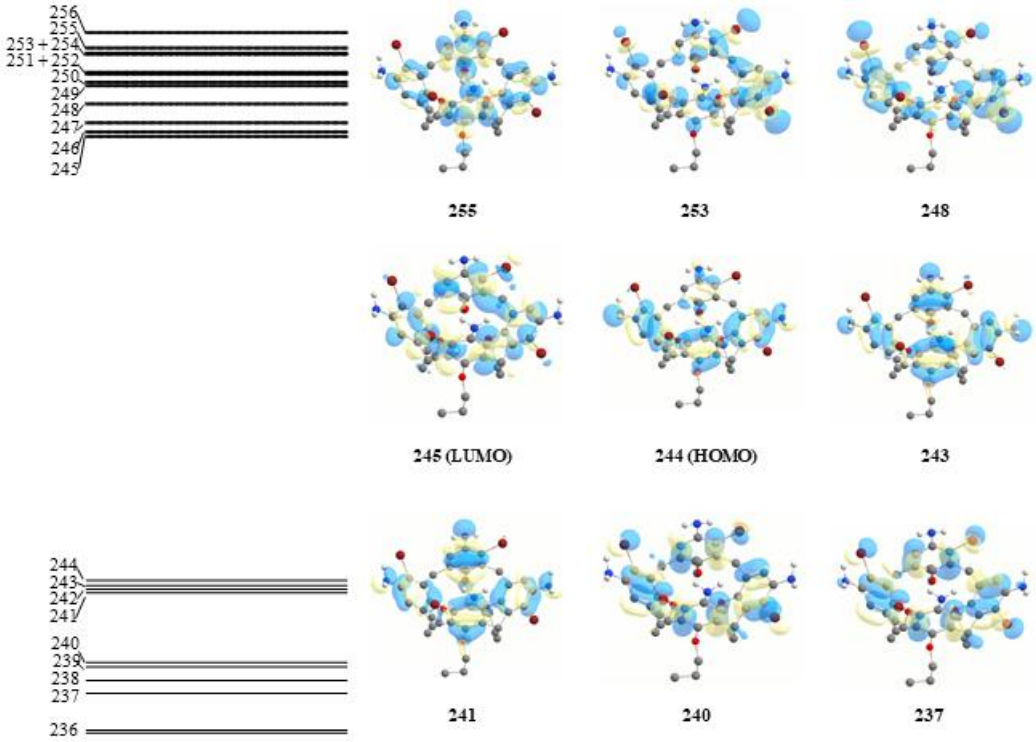


Figure S3. Selected MOs of calix[4]arene **(*M*)-5**.

Table S3. Coordinates of DFT geometry optimised (B3LYP/6-31G*) calix[4]arene (*M*)-5

Br	5.59824	1.3772	-1.31635	C	-0.90023	-2.74166	-2.11551	C	0.61503	2.64227	0.27293
Br	-1.86621	3.32874	-3.04088	C	1.86238	2.06541	-1.70137	C	1.79925	2.16859	-0.31432
Br	1.73547	-3.71158	-2.60317	H	2.78596	1.72949	-2.1654	C	1.83317	-3.21637	0.58389
Br	-5.66249	-1.60177	-0.89375	C	-3.43071	-0.29782	0.42159	H	1.65852	-3.3236	1.65537
O	-0.57465	-2.74334	2.06978	C	-2.63639	0.82665	0.72311	H	2.2699	-4.15563	0.22816
O	1.55622	-0.46553	1.55791	C	4.49679	-0.02525	-0.57139	C	-0.53361	2.90571	-0.49911
O	-1.56773	0.66351	1.57827	C	2.98357	1.72861	0.53925	C	-1.86122	3.22014	0.18473
O	0.57747	2.87312	1.6426	H	3.8347	2.39487	0.37078	H	-1.65026	3.47155	1.22493
N	5.9838	-1.67438	-1.62417	H	2.69831	1.81252	1.58551	H	-2.31255	4.10255	-0.28087
N	0.93749	2.42291	-3.91173	C	2.83178	-2.09103	0.30155	C	-2.99234	-1.66796	0.91364
N	-1.09316	-2.90087	-3.48722	C	-1.84126	-2.22468	0.08093	H	-3.84518	-2.35289	0.88561
C	0.30803	-3.06722	-1.47649	C	2.61214	-0.76526	0.72457	H	-2.65895	-1.59356	1.94648
C	-0.64343	-2.64335	0.68385	C	3.96182	-2.35446	-0.46951	C	-0.4018	2.82133	-1.89152
N	-6.06006	1.36519	-1.66453	H	4.16111	-3.37539	-0.78314	C	0.78829	2.42452	-2.5255
C	0.4821	-2.99247	-0.0879	C	4.83409	-1.34686	-0.90589	C	-4.01133	2.21207	-0.67949
C	3.40117	0.29708	0.23969	C	-2.86562	2.06907	0.10012	H	-4.21805	3.17179	-1.14444

C	-1.94619	-2.28068	-1.30615	H	-1.64872	-4.90212	4.39169	H	1.24668	5.86185	5.05167
H	-2.88106	-1.99207	-1.77867	C	-2.48859	0.28578	3.85753	H	0.72151	6.54372	3.50602
C	-4.89276	1.15105	-0.93223	H	-1.9609	-0.67443	3.90879	C	1.01507	4.19379	1.99883
C	-4.54576	-0.10297	-0.40359	H	-3.49201	0.08271	3.46232	H	0.39838	4.94038	1.47587
C	1.74146	-0.79779	2.94442	C	2.63424	-0.13448	5.21781	H	2.05488	4.3417	1.67087
H	2.25307	-1.76573	3.02964	H	1.64797	-0.25058	5.68436	C	0.89805	4.36508	3.50712
H	0.73002	-0.91799	3.33763	H	3.18087	0.62785	5.78351	H	1.50877	3.59851	4.0004
C	2.51135	0.25553	3.74004	H	3.17109	-1.08353	5.33806	H	-0.14138	4.1788	3.80525
H	1.99261	1.21656	3.64474	C	0.35197	-4.12162	4.64703	H	0.07228	2.33899	-4.43116
H	3.51234	0.38263	3.30853	H	0.87201	-5.0117	4.27142	H	1.65292	1.79071	-4.2482
C	-1.12596	-3.98411	2.54979	H	0.32694	-4.18815	5.7405	H	-6.4424	0.53237	-2.09625
H	-0.56457	-4.82432	2.11327	H	0.94837	-3.24564	4.37756	H	-6.00599	2.14135	-2.31241
H	-2.16734	-4.07308	2.21076	C	-2.60109	0.90089	5.25752	H	-1.81618	-2.3064	-3.87278
C	-1.73789	1.20877	2.89854	H	-1.6115	1.09826	5.68836	H	-0.24417	-2.88338	-4.03896
H	-2.25578	2.17576	2.8397	H	-3.13321	0.23135	5.94187	H	5.91563	-2.54243	-2.14089
H	-0.72308	1.39539	3.25468	H	-3.14748	1.85184	5.23342	H	6.35253	-0.92009	-2.19095
C	-1.06381	-4.02922	4.0711	C	1.33653	5.76029	3.96504				
H	-1.57992	-3.14669	4.4708	H	2.38145	5.95896	3.698				

S6) Details regarding the crystal structure solutions of compound 3b.

Single crystals of **3b** were obtained via a slow diffusion of methanol into a saturated solution of **3b** in heptane. Single-crystal X-ray intensity data were collected on a Bruker 3-circle SMART Apex II X-ray diffractometer equipped with an INCOATEC IμS microfocus sealed tube (MoKα radiation λ = 0.71073 Å) fitted with a multilayer monochromator. Data were captured with a CCD (charge-coupled device) area detector. Data collection was carried out at 100 K using an Oxford Cryosystems cryostat (700 series Cryostream Plus) attached to the diffractometer. Data collection and reduction were carried out using the Bruker software package APEX3,[19] using standard procedures. All structures were solved and refined using SHELX-2016[20] employed within the X-Seed[21] environment. Hydrogen atoms were placed in calculated positions using riding models. Diagrams were generated using POV-Ray.[22]

[19] *APEX3, SAINT, and SADABS*; Bruker AXS Inc.: Madison, WI, 2016.

[20] Sheldrick, G. M. *Acta Cryst.*, 2008, A64, 112−122.; Sheldrick, G.M., *Acta Cryst.*, **2015**, C71, 3-8; Sheldrick, G.M., *Acta Cryst.*, **2015**, A71, 3-8

[21] a) Atwood, J. L.; Barbour, L. J., *Cryst. Growth Des.* 2003, 3, 3−8; b) Barbour, L. J., *J. Supramol. Chem.* 2001, 1, 189−191.

[22] Barbour, L.J., *J. Appl. Cryst*. **2020,** *53,* 1141-1146; b) *POV-Ray for Windows*, version 3.6.1a.icl8.win32; Persistence of Vision Pty. Ltd., 2003.

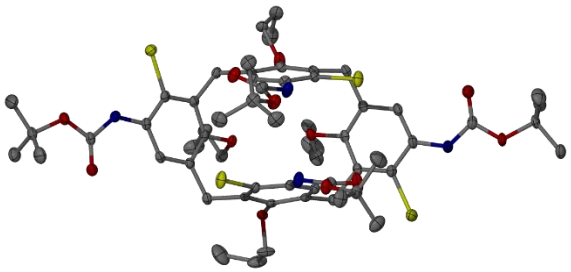


Fig. S1. Top view showing thermal ellipsoids

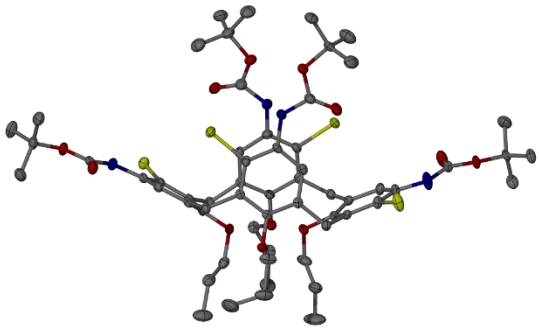


Fig. S2. Side-view showing thermal ellipsoids

Table S2. Crystal data and structure refinement for **3b**.

Identification code	**3b**	
Empirical formula	$C_{61}H_{83}Br_4N_4O_{13}$	
Formula weight	1399.95	
Temperature (K)	100(2)	
Wavelength (Å)	0.71073	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions (Å, °)	a = 13.982(2)	α = 90
	b = 23.272(4)	β = 94.935(3)
	c = 20.029(3)	γ = 90
Volume (Å)	6493.3(17)	
Z	4	
Calculated density (g cm^{-3})	1.432	
Absorption coefficient (mm^{-1})	2.541	
F_{000}	2884	
Crystal size (mm^3)	0.211 × 0.084 × 0.073	
θ range for data collection (°)	1.344 to 27.692	
Miller index ranges	$-18 \le h \le 18$, $-30 \le k \le 30$, $-26 \le l \le 26$	
Reflections collected	145346	
Independent reflections	15072 [R_{int} = 0.1094]	
Completeness to θ_{max} (%)	0.990	
Max. and min. transmission	0.351 and 1.000	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15072 / 0 / 811	
Goodness-of-fit on F^2	1.014	
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0462, $wR2$ = 0.0958	
R indices (all data)	$R1$ = 0.0811, $wR2$ = 0.1102	
Largest diff. peak and hole (e Å^{-3})	1.298 and -0.860	