Electronic Supplementary Material (ESI) for Chemical Communications.

Using steric bulk for selective recognition; blocking the binding site to differentiate guests

Ryan N. Robson, and Frederick M. Pfeffer

Research Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, 3216, Australia.

Email: fred.pfeffer@deakin.edu.au

Contents

Salt formation 3

Synthesis 5

Titrations data 29

All reagents were obtained from commercial sources and used as provided unless otherwise stated. Dimethyl acetylene dicarboxylate 90% supplied by AK scientific inc. was distilled prior to use by means of a Kugelrohr short-path vacuum distillation apparatus at 85 °C / 7 mbar. The Mitsudo catalyst $RuH_2(CO)(PPh_3)_3$ was prepared as described in literature[1] and used without additional purification. A solution of *t*-BuOOH in $PhCH_3$ was prepared as outlined by Sharpless.[2]

All microwave reactions were performed using CEM discover S-class microwave reactor in capped 10 or 35 mL vessels.

TLC was performed on Merck TLC silica gel 60 F_{254} plates and unless otherwise specified visualised using UV light (λ = 254 nm) and/or potassium permanganate oxidising dip (1:1:100 $KMnO_4$, K_2CO_3, H_2O) except for epoxide **5** which was observed with a ninhydrin dip (Ninhydrin 1.5g, isopropanol 100 mL, acetic acid 3 mL). Column chromatography was performed using silica gel 60 (230-400 mesh).

All melting points were obtained using a Stuart SMP30 melting point apparatus.

High-resolution mass spectral data was collected on a Thermo NanoLC/OrbiTRAP ELITE mass spectrometer. Samples were dissolved in a solution of MeCN containing 0.1% formic acid at a concentration of less than 0.1 mg/mL.

Solution state NMR were obtained using a JEOL-Ex 270 MHz, Eclipse JNM-ECP 400 MHz or a Bruker AVANCE III 500 MHZ FT-NMR spectrometer and samples were dissolved in $CDCl_3$, DMSO-d_6 or D_2O as specified. Samples are reported as: chemical shift (ppm), integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad), *J* (coupling constant in Hz), assignment. All spectra were referenced against the residual solvent. Spectra without an internal solvent peak were referenced using an external reference as follows; CH_3OH in D_2O for ^{13}C spectra run in D_2O, trifluorotoluene in the corresponding solvent for ^{19}F spectra.

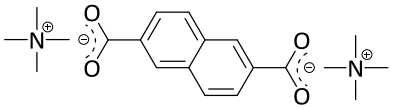
The ^1H NMR spectroscopy titration experiments were carried out using a JEOL EX 270 MHz FT-NMR spectrometer. Stock solutions of the host (2.5 mM in DMSO-d_6) and guest (32.5 mM in host solution) were prepared. A spectrum was collected after each addition of the respective guest, and the thiourea and aromatic proton chemical shifts were recorded. The data was then plotted as a titration isotherm and the data fitted using *Bindfit* online fitting program[3] to determine binding constants.[4]

Compounds were named according to the IUPAC guidelines following the von Baeyer system for polycyclic compounds.[5] The relative stereodescriptors α/β are used to describe the configuration of the substituents on the ring system.

Salt formation

The desired salts were prepared by stirring the corresponding dicarboxylic acid (1 eq) and tetramethylammonium hydroxide (25% in CH_3OH, 2.0 eq) in CH_3OH (0.5M) at 21 °C for 48 h. The solvent was then removed *in vacuo* to afford the desired compounds. All salts were stored in a vacuum desiccator and additional drying prior to titration was achieved using high vacuum for 12 hours.

Bis(tetramethylammonium)-2,6-naphthalate (G1)

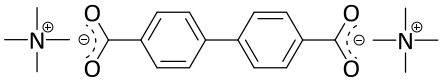


Prepared using 2,6-naphthalene dicarboxylic acid (198.0 mg, 0.92 mmol), CH_3OH (1.84 mL) and tetramethylammonium hydroxide (780 µL, 1.85 mmol, 25% in CH_3OH). The title compound (331.3 mg, 99%) was isolated as a white solid.

^{1}H NMR (270 MHz, D_2O) δ 8.40 (2H, s, H1,5), 8.03 (2H, d, *J* = 8.5 Hz, H3,7), 7.95 (2H, d, *J* = 8.6 Hz, H4,8), 3.06 (24H, s, 8 × Me).

^{13}C NMR (68 MHz, D_2O) δ 176.4, 143.6, 136.9, 130.8, 128.1, 56.4 (t, *J* = 4.1 Hz).

Bis(tetramethylammonium)-4,4'-diphenylate (G2)

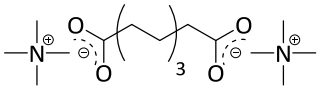


Prepared using biphenyl-4,4'-dicarboxylic acid (198.9 mg, 0.82 mmol), CH_3OH (1.65 mL) and tetramethylammonium hydroxide (695 µL, 1.65 mmol, 25% in CH_3OH). The title compound (311.5 mg, 98%) was isolated as a white solid.

^{1}H NMR (270 MHz, D_2O) δ 7.95 (4H, d, *J* = 8.2 Hz), 7.77 (4H, d, *J* = 8.2, Hz), 3.10 (24H, s, 8 × Me).

^{13}C NMR (68 MHz, D_2O) δ 175.9, 143.1, 136.4, 130.3, 127.6, 55.8 (t, *J* = 4.1 Hz)

Bis(tetramethylammonium) azelate (G3)

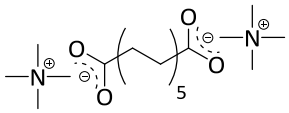


Prepared using azelaic acid (245.5 mg, 1.30 mmol), CH_3OH (2.60 mL) and tetramethylammonium hydroxide (1.10 mL, 2.61 mmol, 25% in CH_3OH). The title compound (412.5 mg, 94%) was isolated as a white solid.

^{1}H NMR (400 MHz, D_2O) δ 3.16 (24H, s), 2.14 (4H, t, *J* = 7.5 Hz, 2 × CH_2C=O), 1.56 – 1.50 (4H, m, 2 × $C\underline{H}_2CH_2C$=O), 1.29 (6H, brs, 3 × CH_2).

^{13}C NMR (101 MHz, D_2O) δ 185.0, 55.9 (t, *J* = 4.0 Hz), 38.3, 29.3, 29.0, 26.6.

Bis(tetramethylammonium) Dodecanedioate (G4)



Prepared using dodecanedioic acid (272.8 mg, 1.18 mmol), CH_3OH (2.4 mL) and tetramethylammonium hydroxide (1.0 mL, 2.37 mmol, 25% in CH_3OH). The title compound (436.5 mg, 98%) was isolated as a white solid.

^{1}H NMR (400 MHz, D_2O) δ 3.16 (24H, s), 2.14 (4H, t, *J* = 7.5 Hz, 2 × CH_2C=O), 1.53 – 1.51 (4H, m, 2 × $C\underline{H}_2CH_2C$=O), 1.297 (12H, brs, 6 × CH_2).

^{13}C NMR (101 MHz, D_2O) δ 185.0, 55.9 (t, *J* = 4.2 Hz), 38.4, 29.5, 29.4, 29.3, 26.6.

Synthesis

Dimethyl (1α,2α,3α,4α,7α,8β,9β,10α)-pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodeca-5,11-diene-8,9-dicarboxylate (3)[6-8]

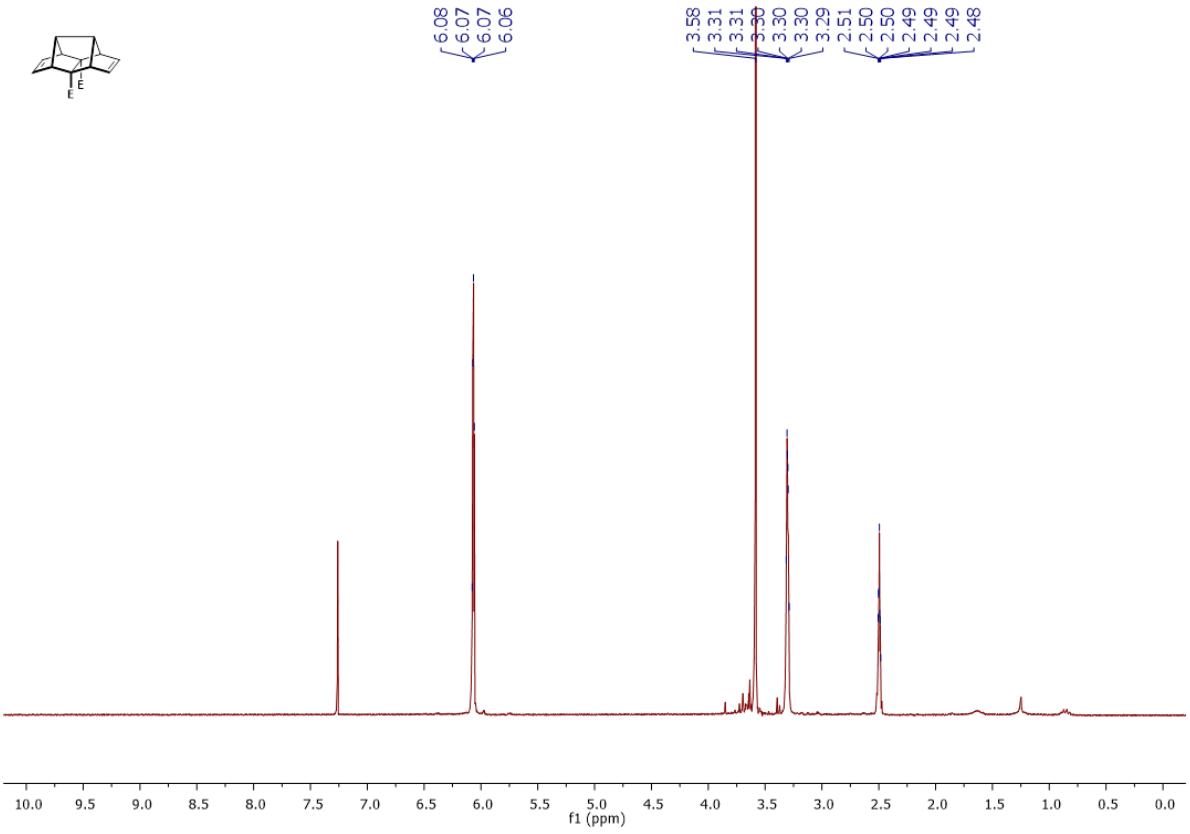
Under a flow of N_2 a predried 3-neck roundbottom flask was charged with NaH (11.8 g, 0.29 mol, 60% in mineral oil) and anhydrous THF (200 mL). The resulting slurry was stirred vigorously and cooled to 0 °C followed by cannula transfer of CPD (24.8 mL, 0.29 mol) at -80 °C over 90 min. The solution was allowed to warm to ambient temperature and stirred for 1 h before being cooled to -80 °C whereupon dropwise addition of a solution of I_2 (37.6 g, 0.15 mol) in THF (35 mL) was performed over 70 min. The cold solution was stirred for a further 15 min followed by dropwise addition of neat DMAD (20.2 mL, 0.16 mol) over 10 min. The reaction mix was stirred for 1 h at -80 °C before being allowed to slowly warm to ambient temperature and stirred for a further 4 h. The black slurry was filtered through celite and the filter cake flushed with THF (4 × 50 mL). The combined solvent was reduced to approximately 1/3 its volume *in vacuo* at a temperature ≤ 30 °C. The solution was diluted with Et_2O (200 mL) and stirred for 15 min followed again by filtration through celite. The filter cake was flushed with Et_2O (4 × 50 mL) the solvent removed *in vacuo* at a temperature ≤ 30 °C and the crude material stored in the fridge under a N_2 atmosphere overnight.

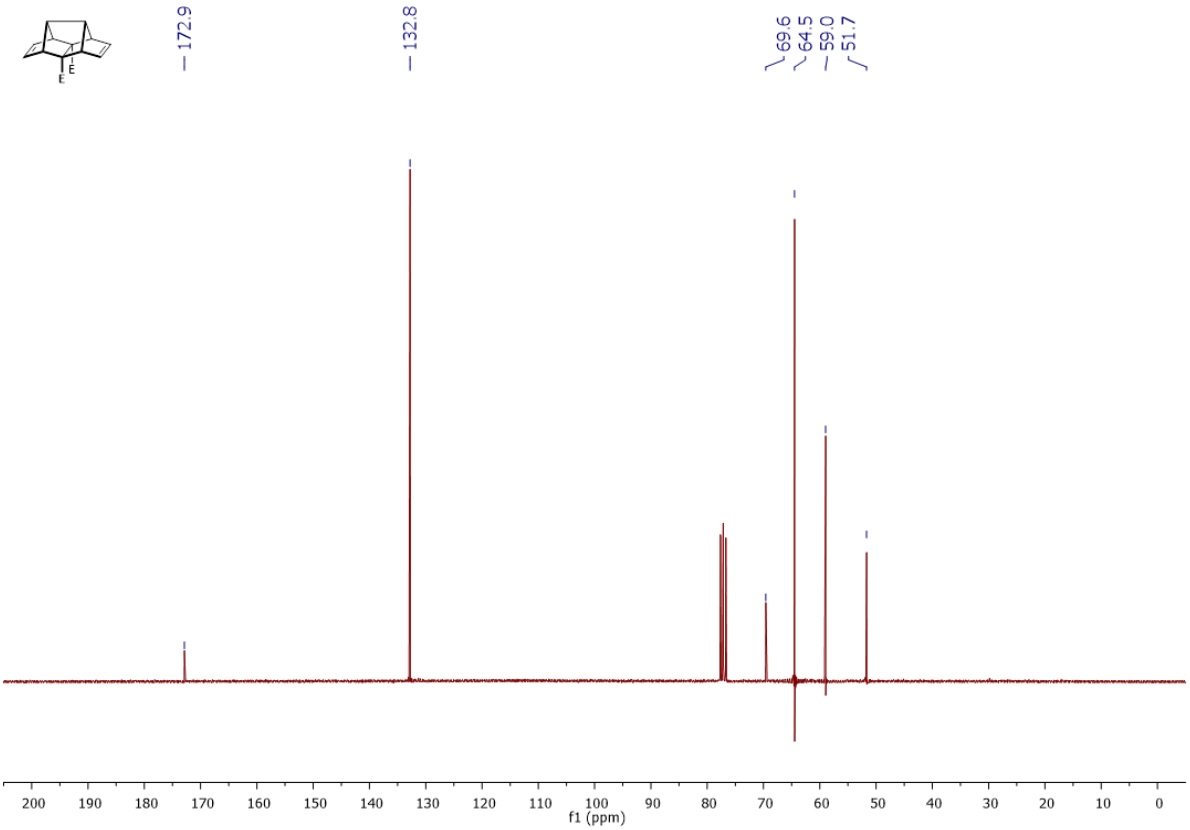
The crude material was dissolved in CH_3OH (200 mL), cooled to -15 °C followed by dropwise addition of a cold solution of KOH (14.2 g, 0.25 mol) in H_2O (40 mL) with the reaction mixture kept below -5 °C. Upon completion of the addition the solution was stirred for 2 h at 0 °C then 3 h at ambient temperature. The reaction mixture was filtered through celite and the filter cake flushed with CH_3OH (4 × 50 mL). The filtrate was reduced to approximately 1/3 its volume *in vacuo* at a temperature ≤35 °C. The solution was diluted with H_2O (250 mL) and extracted with Pet. Sp. (6 × 50 mL), the combined organics were washed with sat. aq. $Na_2S_2O_3$ (2 × 80 mL), sat. aq. NaCl (80 mL), dried ($MgSO_4$), filtered then concentrated *in vacuo* at a temperature ≤30 °C. The orange oil was purified using column chromatography (20% EtOAc/Pet. Sp., R_f = 0.43) to afford the title compound (2.6 g, 7%) as a tan solid.

^{1}H NMR (270 MHz, $CDCl_3$) δ 6.07 (4H app. t, *J* = 1.9 Hz, H5,6,11,13), 3.59 (6H, s, 2 × Me), 3.31 (4H, dt, *J* = 2.8, 2.0 Hz, H1,4,7,10), 2.5 (2H, tt, *J* = 2.0, 0.9 Hz, H2,3).

^{13}C NMR (68 MHz $CDCl_3$) δ 172.9, 132.8, 69.6, 64.5, 59.0, 51.7.

mp 53.7–57.8 °C (lit. 61-62 °C[6,7])


E
E
6.08
6.07
6.07
6.06
3.58
3.31
3.31
3.30
3.30
3.30
3.29
2.51
2.50
2.50
2.49
2.49
2.49
2.48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


E
E
172.9
132.8
69.6
64.5
59.0
51.7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

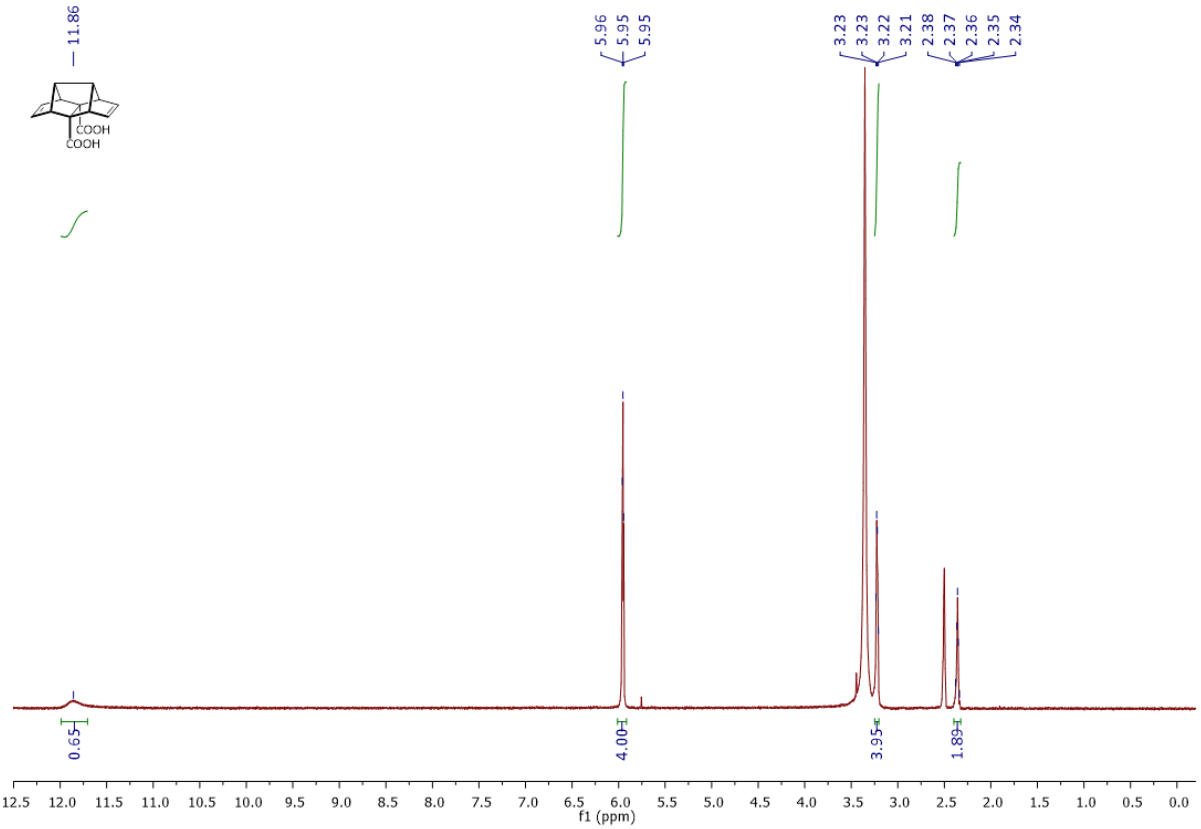
(1α,2α,3α,4α,7α,8β,9β,10α)-pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodeca-5,11-diene-8,9-dicarboxylic acid[7,9]

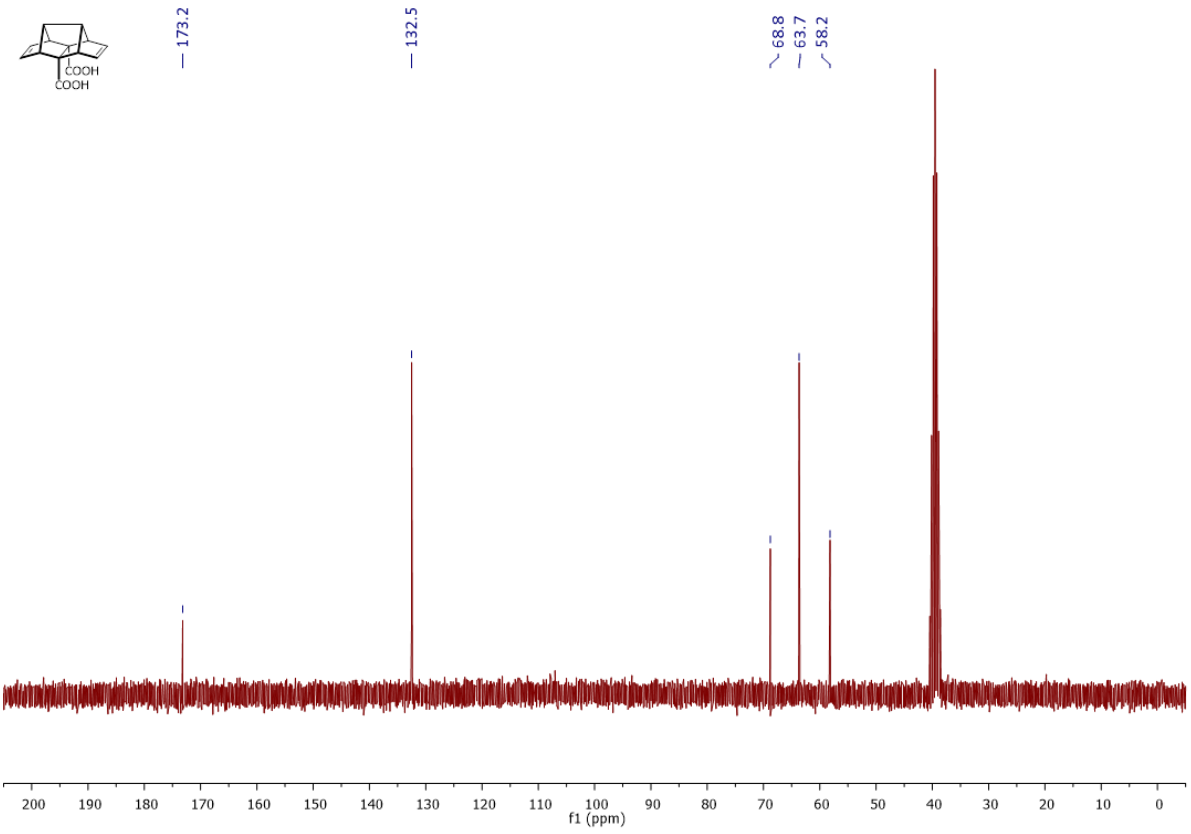
A solution of diester **3** (314.4 mg, 42.1 mmol) and KOH ([4M] aq., 4.1 mL, 16.4 mmol) in CH_3OH (4.1 mL) was heated at 60 °C for 4 h. The reaction mixture was transferred to a separatory funnel and washed with EtOAc (15 mL). The aqueous layer was acidified to pH 1 using HCl 4M followed by extraction with EtOAc (5 × 15 mL) The combined organics were washed with sat. aq. NaCl (30 mL), dried ($MgSO_4$), filtered then concentrated in vacuo. The crude brown solid was triturated with minimal Et_2O (2 mL) and the resultant white solid collected by vacuum filtration as the title compound (251.5 mg, 89%).

^{1}H NMR (270 MHz, $CDCl_3$) δ 2H 11.86 COOH, 5.95 (4H, app. t, *J* = 1.9 Hz, H5,6,11,13), 3.22(4H, app. q *J* = 2.0 Hz, H1,4,7,10), 2.34-2.38 (m, 2H, H2,3).

^{13}C NMR (68 MHz $CDCl_3$) δ 173.2, 132.5, 68.8, 63.7, 58.2.

mp 238.4 °C (dec) (lit. 235 – 240 °C dec.[7])



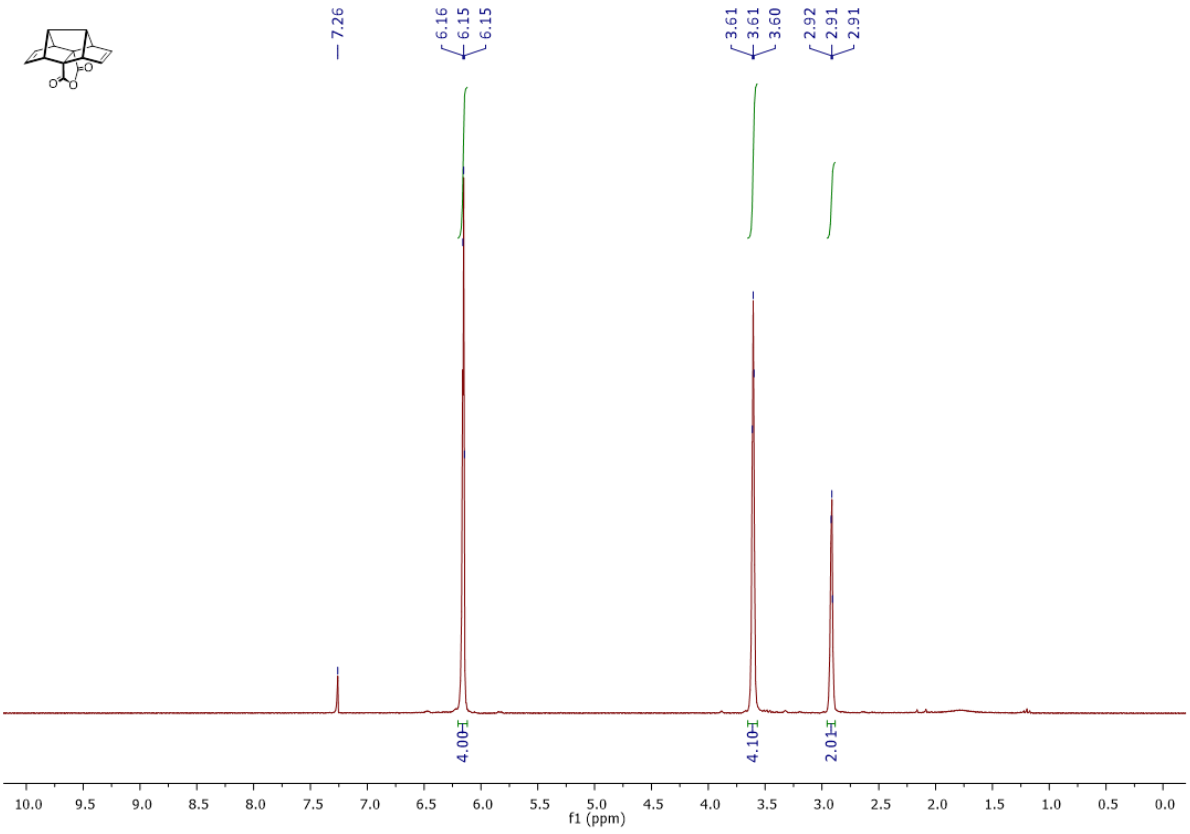


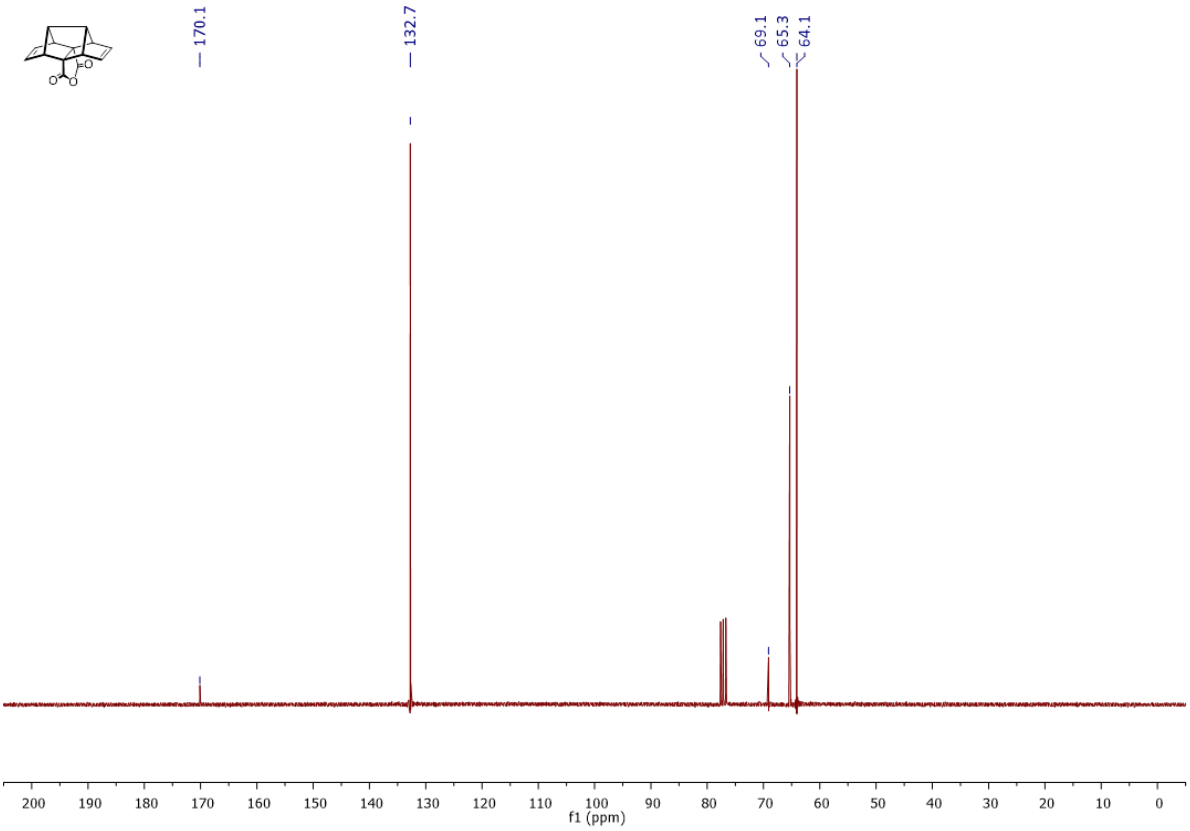
(6α,9α,10α,11α,12α,15α)-3-Oxahexacylco[7.6.0.0^{1,5}.0^{5,12}.0^{6,10}.0^{11,15}]pentadeca-7,13-diene-2,4-dione[9]

The above diacid (247.7 mg, 1.01 mmol) was dissolved in CH_2Cl_2 (2.8 mL) then Ac_2O (1.4 mL, 14.81 mmol) added. The solution was stirred for 4 h at 40 °C before the volatiles were removed *in vacuo* to afford the title compound (227.5 mg, 99%) as a tan solid.

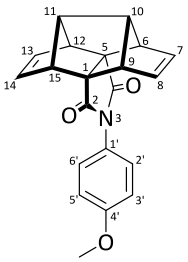
^{1}H NMR (270 MHz, $CDCl_3$) δ 6.16 (4H, app. t, *J* = 2.0 Hz, H7,8,13,14), 3.61 (4H, app. q, *J* = 2.2 Hz, H6,9,12,15), 2.92 (2H, app. t, *J* = 1.8 Hz, H10,11).

^{13}C NMR (68 MHz $CDCl_3$) δ 170.1, 132.7, 69.1, 65.3, 64.1.


7.26
6.16
6.15
6.15
3.61
3.61
3.60
2.92
2.91
2.91
4.00
4.10
2.01
f1 (ppm)


170.1
132.7
69.1
65.3
64.1
f1 (ppm)

(6α,9α,10α,11α,12α,15α)-3-(4'-Methoxyphenyl)-3-azahexacylco[7.6.0.0^{1,5}.0^{5,12}.0^{6,10}.0^{11,15}] pentadeca-7,13-diene-2,4-dione (4)



A microwave vessel was charged with anhydride **9** (141.4 mg, 0.63 mmol), *p*-anisidine (103.8 mg, 0.84 mmol) and PhMe (3.2 mL). The vessel was capped and heated by microwave irradiation for 30 min at 150 °C. The reaction mixture was transferred to a separatory funnel and diluted with $CHCl_3$ (15 mL). The organics were washed with HCl 1M (15 mL), sat. aq. NaCl (15 mL), dried ($MgSO_4$), filtered then the solvent removed *in vacuo*. The crude material was triturated in $CHCl_3$ (4 mL) and the solid impurities isolated by vacuum filtration (identified as the amic acid). The filtrate solvent was removed i*n vacuo* and the resulting solid purified by column chromatography (20% EtOAc/Pet. sp., R_f = 0.30) to afford the title compound (44.0 mg, 21%) as a white powder.

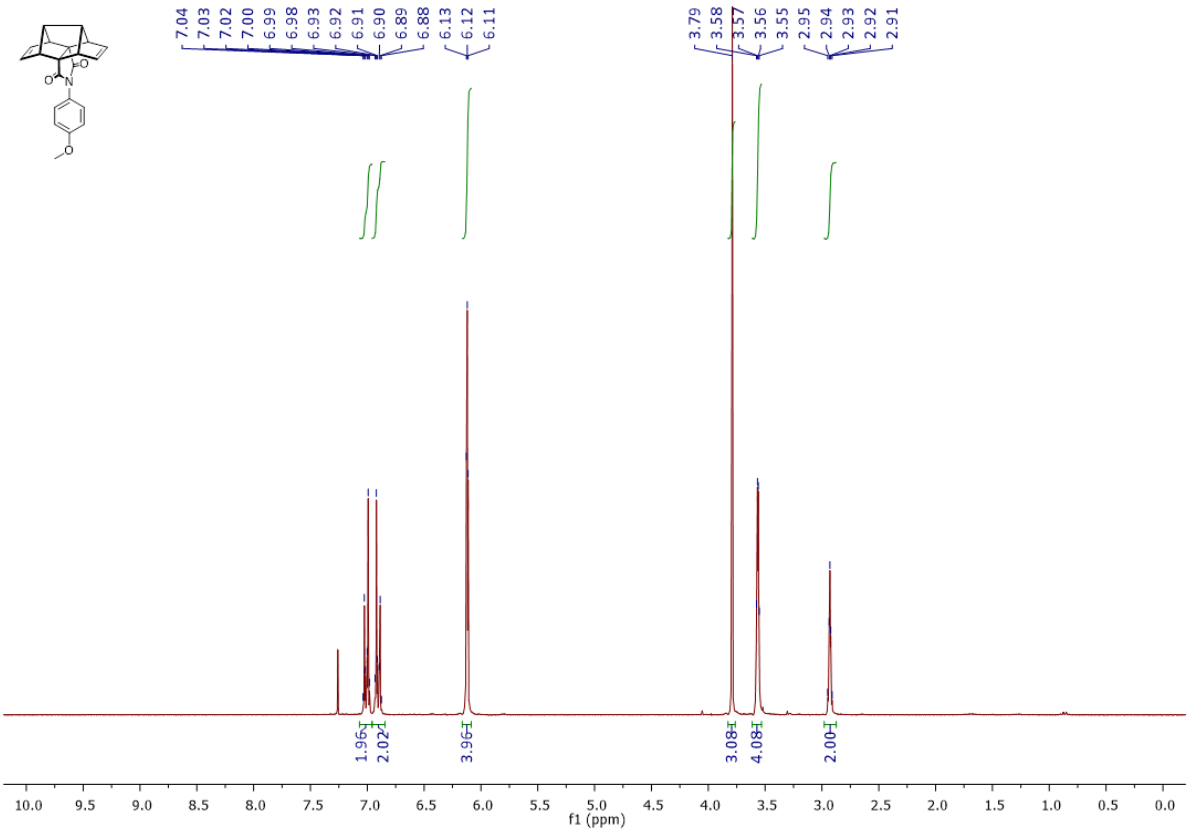
^{1}H NMR (270 MHz, $CDCl_3$) δ 7.02 (4H, AA'BB', *J* = 9.1, 5.3, 5.3, 0.0† Hz, H2',H6'), 6.75 (4H, AA'BB', *J* = 9.1, 5.3, 5.3, 0.0 Hz, H3',H5'), 6.12 (4H, app. t, *J* = 2.0 Hz, H7,8,13,14), 3.79 (3H, s, Me), 3.56 (4H, app. q, *J* = 2.1 Hz, H6,9,12,15), 2.93 (2H, app. quin., *J* = 3.4, 1.8, H10,11).

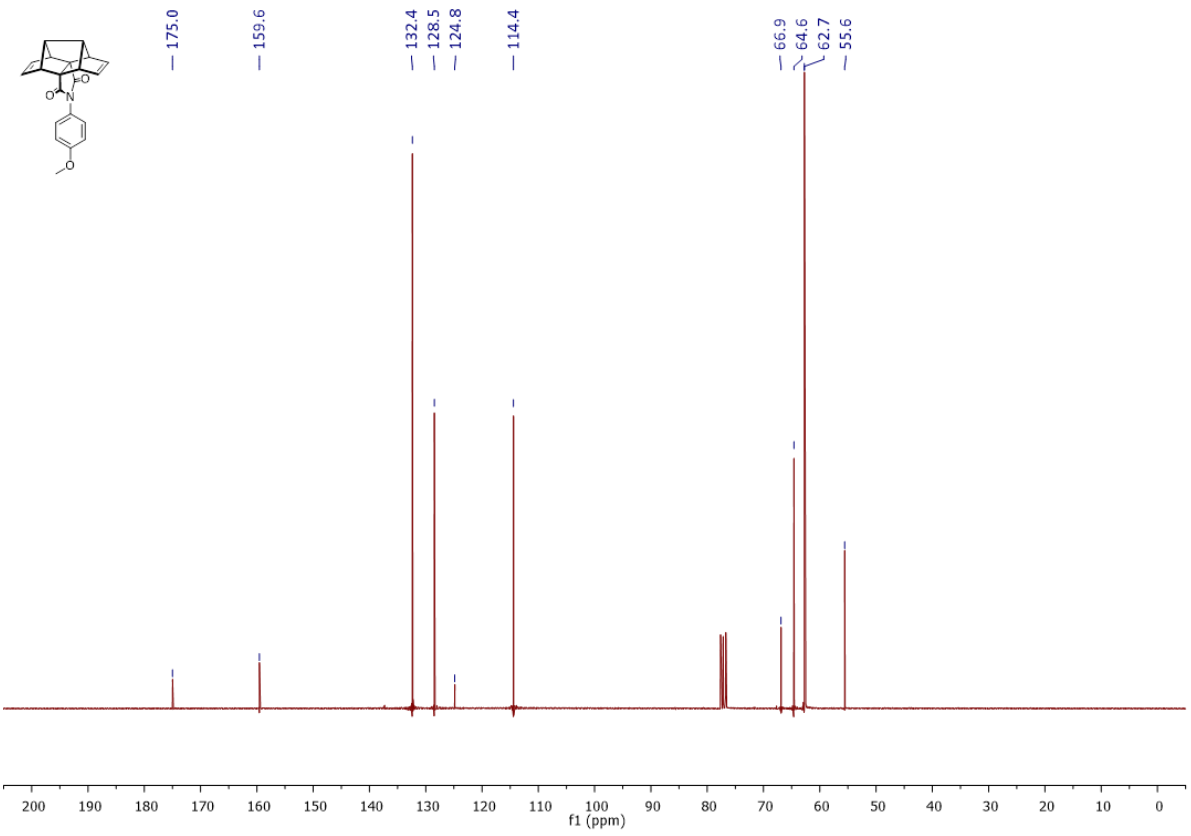
†AA'BB' J_{AB} = 9.1 Hz, $J_{AA'}$ = $J_{BB'}$ = 5.3 Hz, $J_{AB'}$ = 0.0 Hz.

^{13}C NMR (68 MHz, $CDCl_3$) δ 175.0, 159.6, 132.4, 128.5, 124.9, 114.4, 66.9, 64.6, 62.7, 55.6.

HRMS (ESI-OrbiTRAP) *m/z*; $[M + H]^+$ Calc. for $C_{21}H_{18}NO_3$ 332.1242, found 332.1281.

mp 197.0 – 198.5 °C



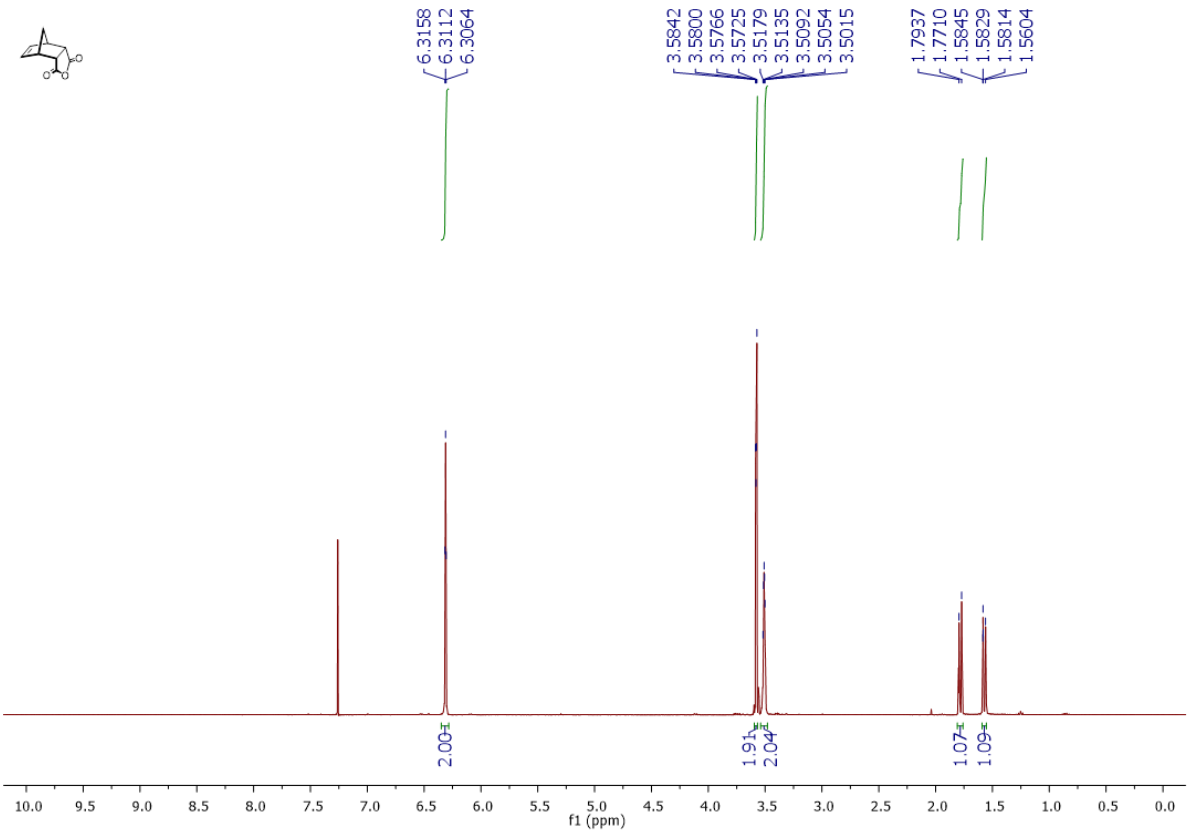


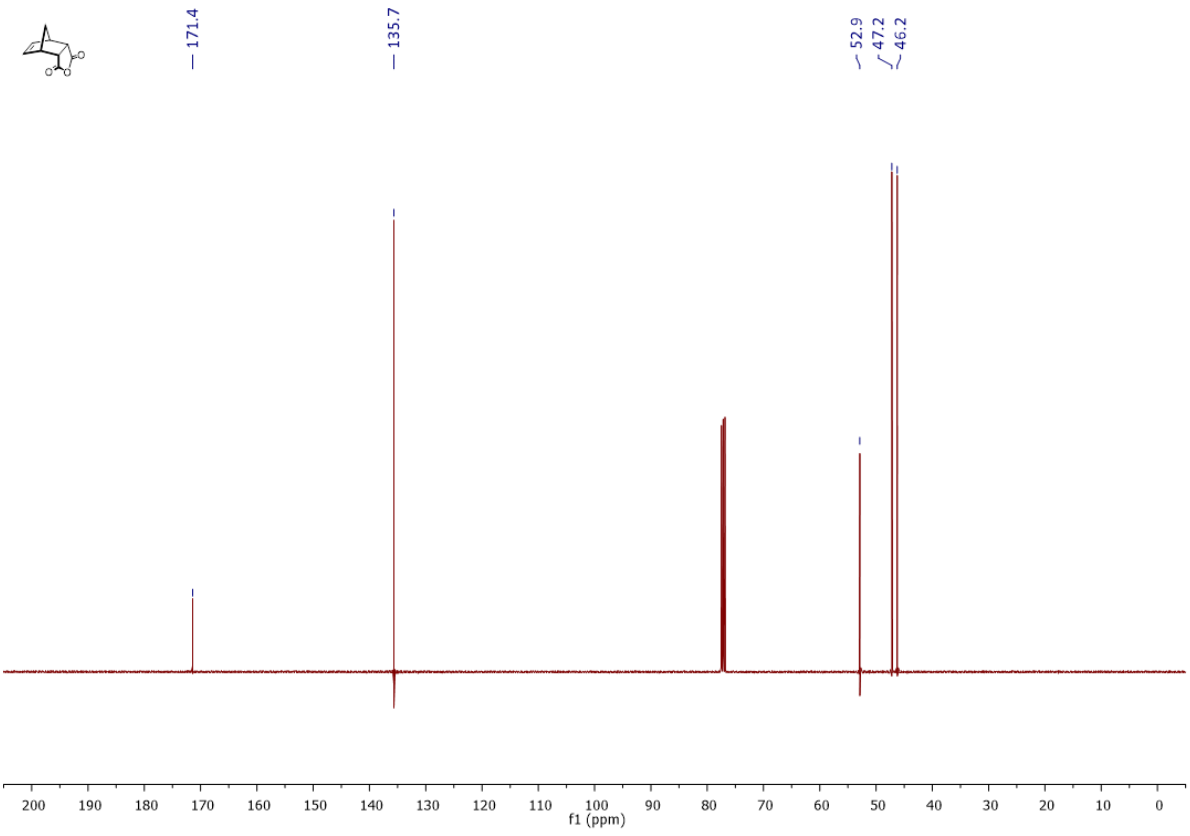
(1α,2α,6α, 7α)-4-oxotricylco[5.2.1.0^{2,6}]dec-8-ene-3,5-dione[10]

A stirring solution of maleic anhydride (11.6 g) in 50/50 EtOAc/Pet. Sp. (150 mL) was cooled to 0 °C followed by addition of CPD (10.9 mL). The solution was stirred for 30 min at 0 °C and a further 30 min at ambient temperature during which time a white precipitate formed. The reaction mixture was heated until complete dissolution of the precipitate occurred and then allowed to cool slowly to afford the title compound (6.3 g) as clear needle like crystals. Subsequent crystallisations of the filtrate afforded a further 8.7 g to give an overall yield of 15 g 77%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (2H, t, *J* = 1.8 Hz, H8,9), 3.58 (2H, dd, *J* = 3, 1.6 Hz, H2,6), 3.52 – 3.50 (2H, m, H1,7), 1.79 (1H, dt *J* = 9.0, 1.7, $H10_a$), 1.57 (1H, dt, *J* = 9.0, 1.4 Hz, $H10_s$).

^{13}C NMR (101 MHz $CDCl_3$) δ 171.4, 135.7, 52.9, 47.2, 46.3.


6.3158
6.3112
6.3064
3.5842
3.5800
3.5766
3.5725
3.5179
3.5135
3.5092
3.5054
3.5015
1.7937
1.7710
1.5845
1.5829
1.5814
1.5604
2.00
1.91
2.04
1.07
1.09
f1 (ppm)

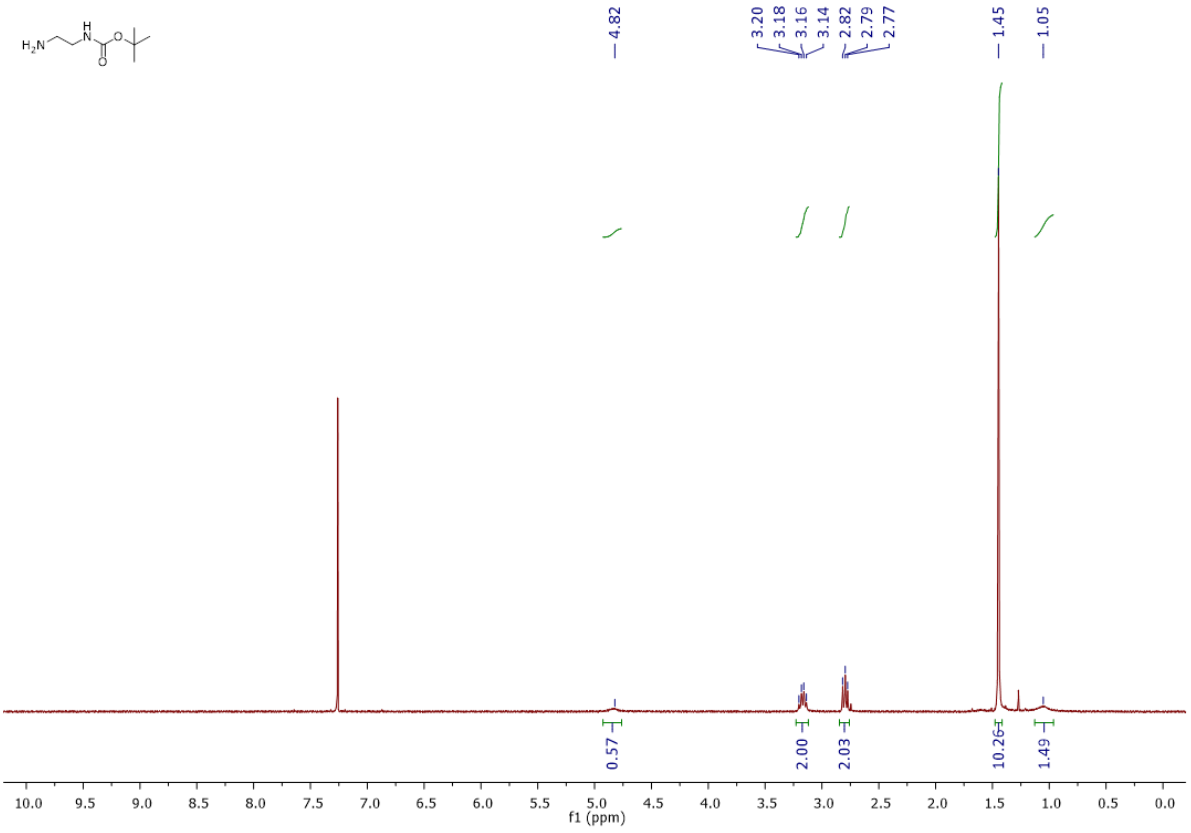

171.4
135.7
52.9
47.2
46.2
f1 (ppm)

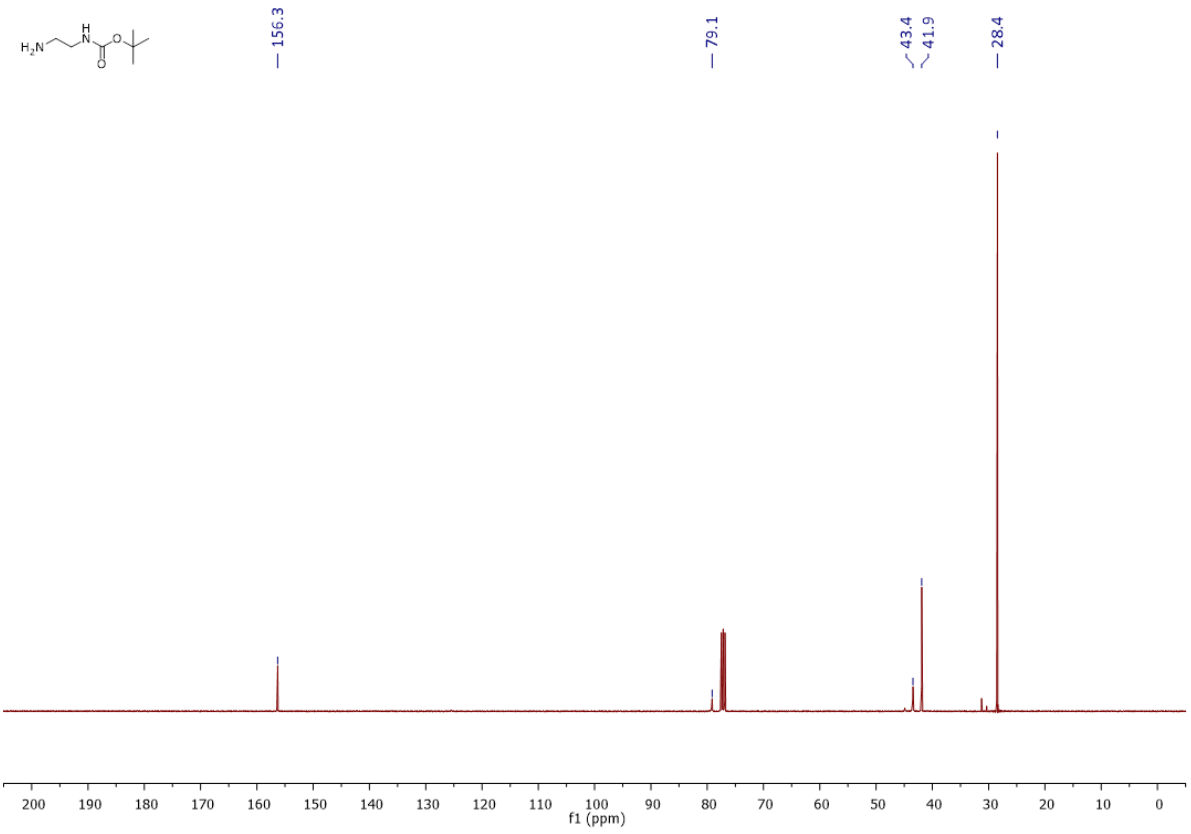
***tert*-Butyl *N*-(2-aminoethyl)carbamate**[11]

A solution of di-*tert*-butyl dicarbonate (10.4 g, 47.7 mmol) in THF (30 mL) was added dropwise over 1 h to a vigorously stirring solution of ethylenediamine (10 mL, 149.8 mmol) in THF (90 mL). The solution was stirred for 16 h at 21 °C before the solid impurities were removed using vacuum filtration. The filtrate was transferred to a round bottom flask and the volatiles were removed *in vacuo* to afford the title compound (6.7 g, 88%) as a yellow oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 4.82 (1H, brs, NH), 3.17 (2H, app. q, *J* = 5.9 Hz, $C\underline{H_2}NH$), 2.80 (2H, t, *J* = 5.9 Hz, $C\underline{H_2}NH_2$), 1.45 (9H, s, *t*-Bu), 1.05 (2H, brs, NH_2).

^{13}C NMR (101 MHz $CDCl_3$) δ 156.3, 79.1, 43.4, 41.9, 28.4.



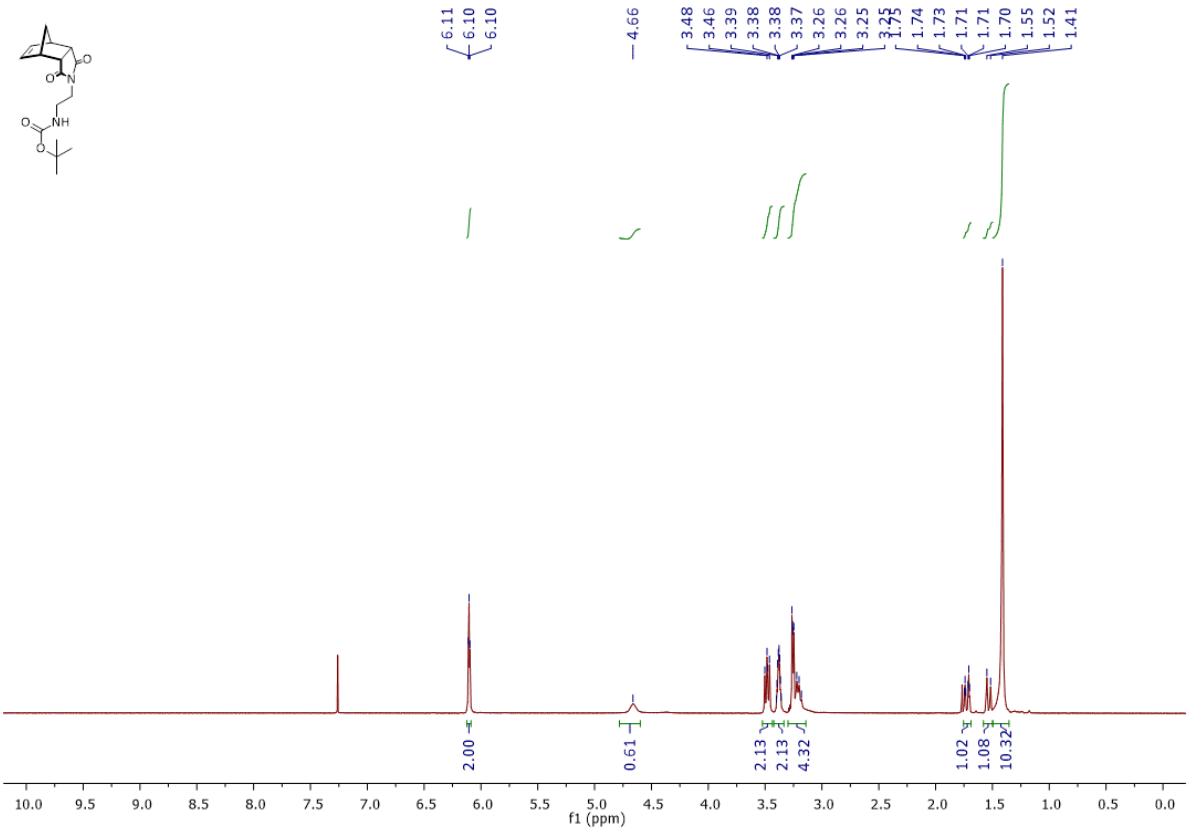


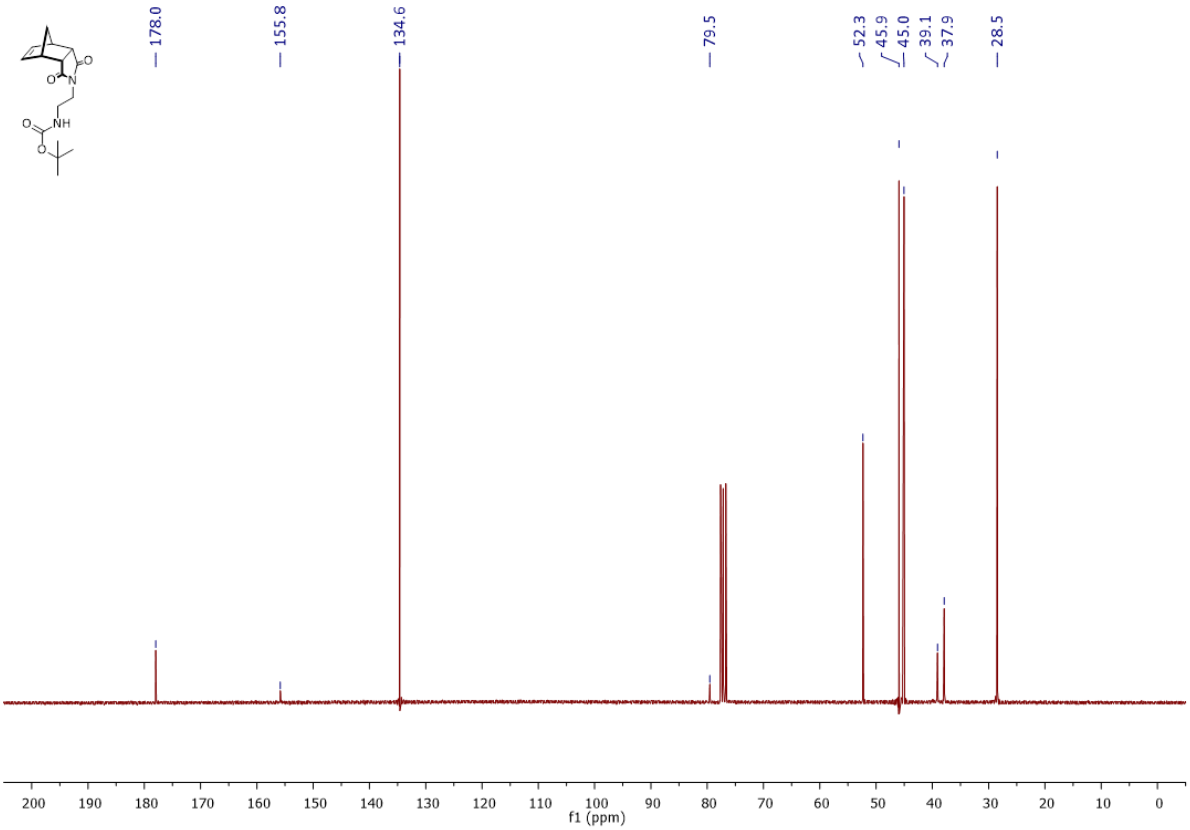
(1α,2α,6α,7α)-4-(2'-*tert*Butoxycarbonylaminoethyl)-3,5-dioxo-4-azatricyclo [5.2.1.0^{2,6}]dec-8-ene[12]

A solution of norbornene anhydride (999.6 g, 6.1 mmol) and *tert*-Butyl *N*-(2-aminoethyl)carbamate (989.9 mg, 6.2 mmol) in $PhCH_3$ (13 mL) was heated by microwave irradiation for 30 min at 100 °C. The solution was transferred to a separatory funnel and diluted with $CHCl_3$ (20 mL), and the organic phase was washed with 1M aq. HCl (25 mL), sat. aq. $NaHCO_3$ (25 mL), sat. aq. NaCl (25 mL) then dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound (1.85 g, 99%) as a white powder.

^{1}H NMR (270 MHz, $CDCl_3$) δ 6.10 (2H, app. t, *J* = 1.8 Hz, H8,9), 4.66 (1H, brs, NH), 3.48 (2H, app. t, *J* = 5.7 Hz, H1'), 3.40-3.36 (2H, m, H1,7), 3.26 (2H, dd, *J* = 2.9, 1.6 Hz, H2,6), 3.21 (2H, app. q, *J* = 5.5 Hz, H2'), 1.72 (1H, dt, *J* = 8.8, 1.6 Hz, 10_a), 1.53 (1H, d, *J* = 8.8 Hz, $H10_s$), 1.41 (9H, s, *t*-Bu).

^{13}C NMR (68 MHz $CDCl_3$) δ 178.0, 155.8, 134.6, 79.5, 52.3, 46.0, 45.0, 39.1, 37.9, 28.5.


6.11
6.10
6.10
4.66
3.48
3.46
3.39
3.38
3.38
3.37
3.26
3.26
3.25
1.74
1.73
1.71
1.71
1.70
1.55
1.52
1.41
2.00
0.61
2.13
2.13
4.32
1.02
1.08
10.32
f1 (ppm)

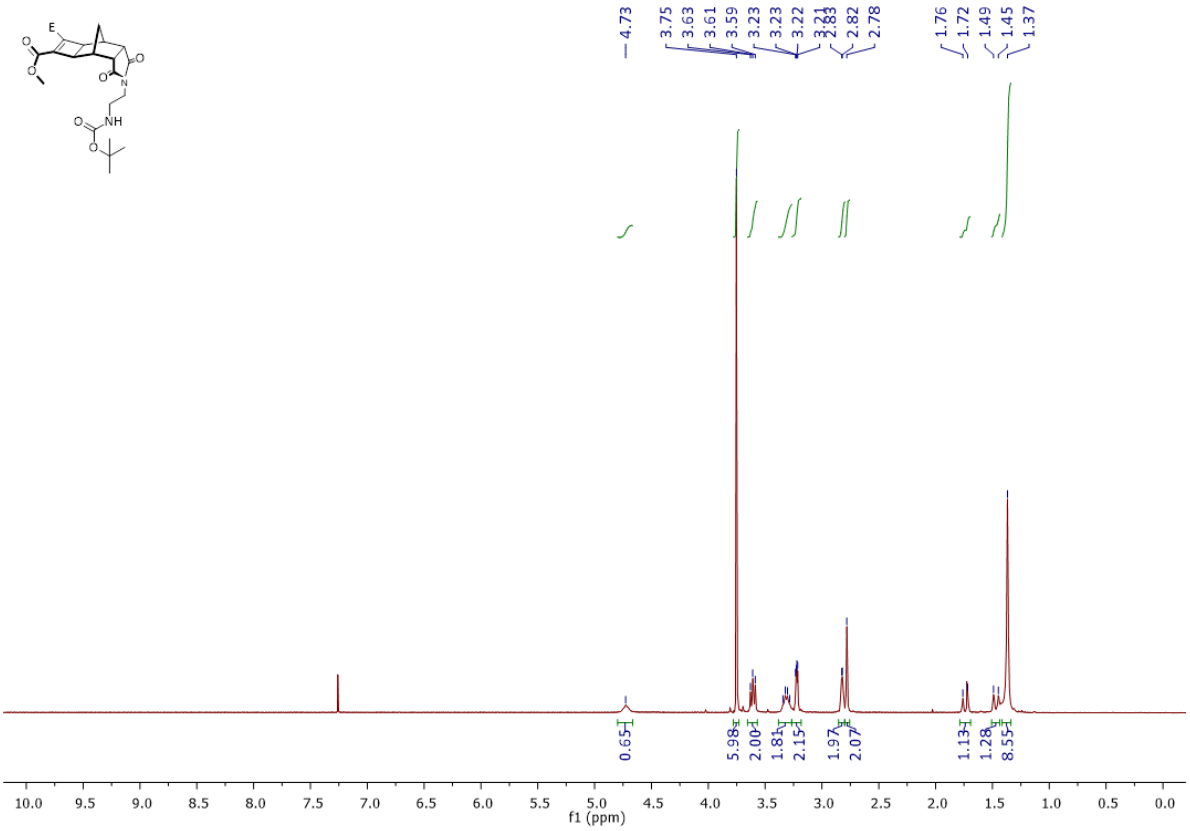

178.0
155.8
134.6
79.5
52.3
45.9
45.0
39.1
37.9
28.5
f1 (ppm)

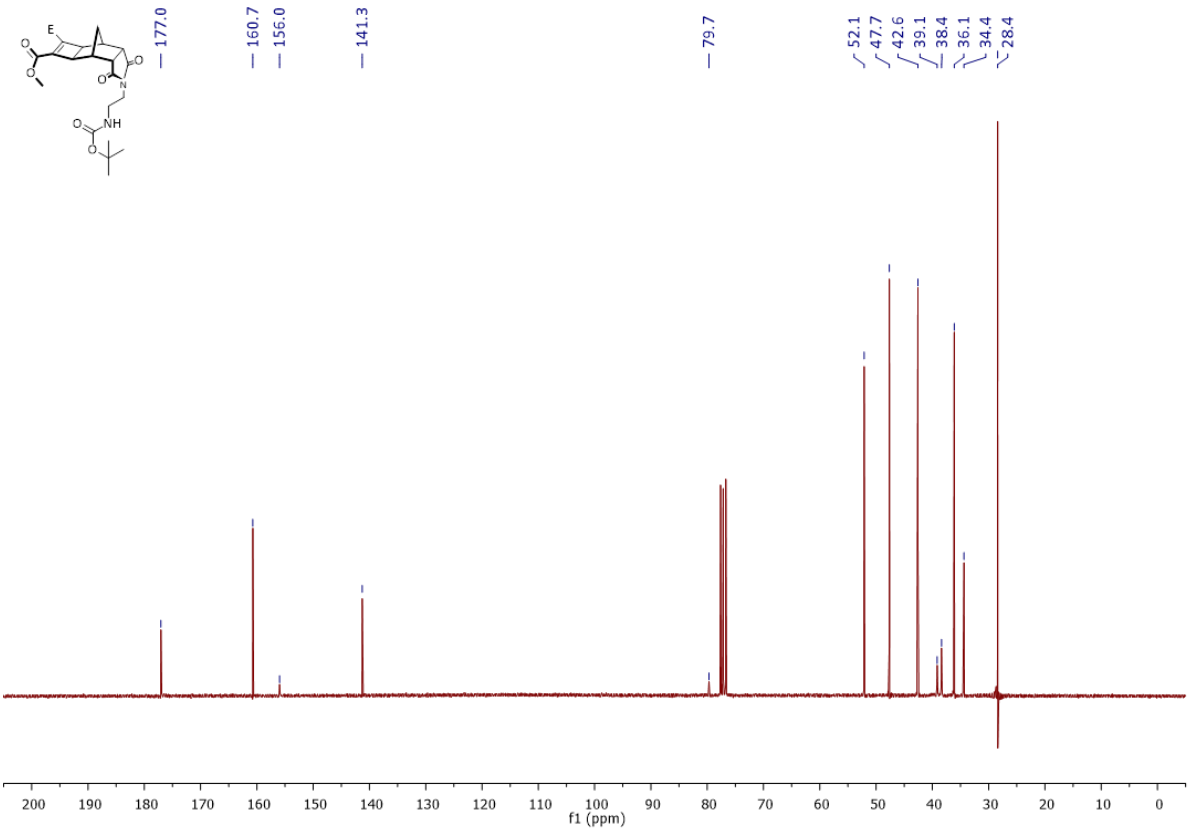
Dimethyl (1α,2α,6α,7α,8β,11β)-4-(2'-*tert*-butoxycarbonylaminoethyl)-3,5-dioxo-4-azatetracyclo [5.4.1.0^{2,6}.0^{8,11}]dodec-9-ene-9,10-dicarboxylate[12]

A microwave vessel was charged with the above norbornene imide (1.03 g, 3.15 mmol), $RuH_2(CO)(PPh_3)_3$ (282.9 mg, 0.31 mmol) and DMF (5 mL) and the resulting slurry stirred for 5 min followed by addition of DMAD (940 µL, 7.65 mmol). The vessel was sealed and heated using microwave irradiation for 15 min at 100 °C (CAUTION: Exothermic reaction; monitor until stable). The solvent was removed *in vacuo* and the crude black oil was purified using column chromatography (50% EtOAc/Pet. Sp., R_f = 0.30). The resulting yellow powder was recrystalised from EtOAc and Pet. Sp. to afford the title compound (954.2 mg, 68%) as a white powder.

^{1}H NMR (270 MHz, $CDCl_3$) δ 4.73 (1H, brs NH), 3.75 (6H, s, 2 × Me), 3.61 (2H, t, *J* = 5.7z Hz, H1'), 3.31 (2H, app. q, *J* = 5.3 Hz, H2'), 3.22 (2H, dd, *J* = 3.3, 1.9 Hz, H2,6), 2.82 (2H, d, *J* = 1.4 Hz, H1,7), 2.78 (2H, s, H8,11), 1.74 (1H, d, *J* = 11.5 Hz, H12$_a$), 1.47 (1H, d, *J* = 11., H12$_2$), 1.37 (9H, s, *t*-Bu).

^{13}C NMR (68 MHz $CDCl_3$) δ 177.1, 160.7, 156.0, 141.3, 79.7, 52.1, 47.7, 42.6, 39.1, 38.4, 36.1, 34.4, 28.4.



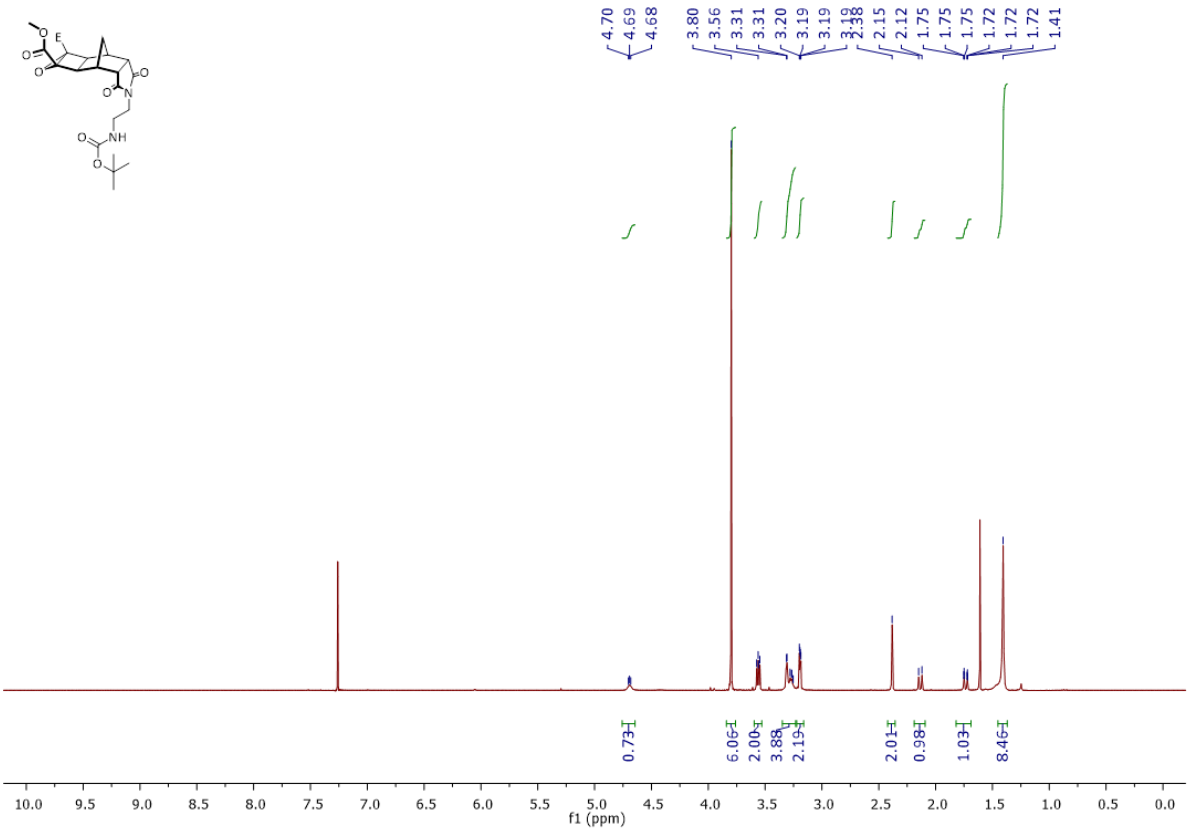


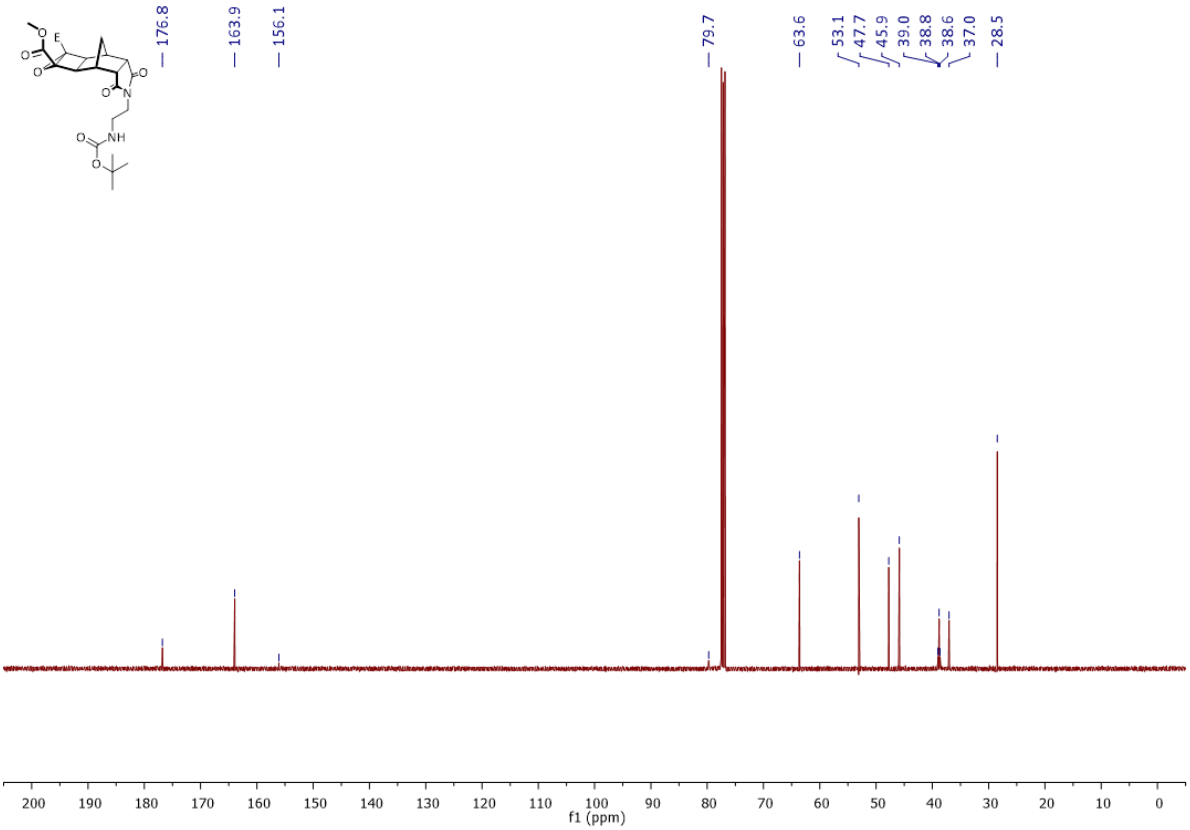
Dimethyl (1α,3β,5α,6β,7α,8α,12α)-10-(2'-*tert*-butoxycarbonylaminoethyl)-9,11-dioxo-4-oxa-10-azapentacycl[5.5.1.$0^{2,6}$.$0^{3,5}$.$0^{8,12}$]tridecane-3,5-dicarboxylate (5)[12]

A predried 3 neck round bottom flask was flushed with N_2 and charged with anhydrous THF (300 mL) and alkene **13** (980.3 mg, 2.18 mmol) before stirring until a homogenous solution was formed. The solution was cooled to 0 °C whereupon *t*-BuOOH (0.98 mL, 3.72 mmol, 3.8M in $PhCH_3$) was added and stirred for 15 min followed by addition of *t*-BuOK (38.4 mg, 0.34 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for a further 16 h before being quenched with $Na_2S_2O_4$ (30 mL, 10 % aq.). The solvent was then evaporated to approximately 1/3 its original volume under reduced pressure. The mixture was transferred to a separatory funnel and extracted with $CHCl_3$ (4 × 25 mL), the organics combined and washed with sat. aq. NaCl (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified using column chromatography (50% EtOAc/Pet. Sp., R_f = 0.26, observed with a ninhydrin dip) to afford the title compound (646.9 mg, 64%) as a white solid.

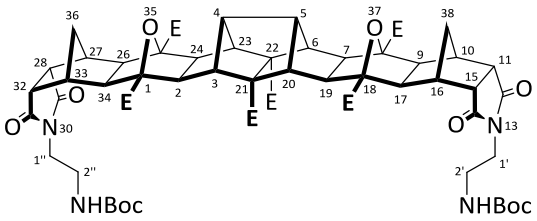
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, t, *J* = 4.0 Hz, NH), 3.80 (6H, s, 2 × Me), 3.56 (4H t, *J* = 5.0 Hz, H1'), 3.31 (2H, q unresolved *J* = 1.4, Hz, H2,6), 3.27 (2H, app. q, *J* = 5.1 Hz, H2'), 3.19 (2H, dd, *J* = 3.4, 2.0 Hz, H8,12), 2.38 (2H, s, H2,6), 2.13 (1H, d, *J* = 11.6 Hz, $H13_s$), 1.74 (1H dt, *J* = 11.5. 1.4 Hz, $H13_a$) 1.41 (9H, s, *t*-Bu).

^{13}C NMR (101 MHz $CDCl_3$) δ 176.8, 163.9, 156.1, 79.7, 63.6, 53.1, 47.7, 45.9, 39.0, 38.8, 38.6, 37.0, 28.5.


4.70
4.69
4.68
3.80
3.56
3.31
3.31
3.20
3.19
3.19
2.15
2.12
1.75
1.75
1.75
1.72
1.72
1.41
0.73
6.06
2.00
3.88
2.19
2.01
0.98
1.03
8.46
f1 (ppm)


176.8
163.9
156.1
79.7
63.6
53.1
47.7
45.9
39.0
38.8
38.6
37.0
28.5
f1 (ppm)

Hexamethyl (1α,2β,3α,4α,5α,6α,7β,8α,9β,10α,11α,15α,16α,17β,18α,19β,20α,21β,22β,23α,24β, 25α,26β,27α,28α,32α,33α,34β)-12,14,29,31-tetraoxo-13,30-bis(2',2''-*tert*-butoxycarbonylamino ethyl)-35,37-dioxa-13,30-diazapentadecacyclo[23.9.1.1^{8,18}.1^{10,16}.1^{27,33}.0^{2,24}.0^{3,21}.0^{4,23}.0^{5,20}.0^{6,22}.0^{7,19} 0.^{9,17}.0^{11,15}.0^{26,34}.0^{28,32}] octatriaconta-1,8,18,21,22,25-hexacarboxylate (6)



A microwave vessel was charged with alkene **3** (28.2 mg, 0.10 mmol), epoxide **5** (99.3 mg. 0.21 mmol) and DMF (430 µL). The vessel was then heated using microwave irradiation for 10 min at 150 °C. The solvent was removed *in vacuo* and the crude material purified by trituration in CH_3OH (5 mL) to afford the title compound (81.1 mg, 65%) as a white solid.

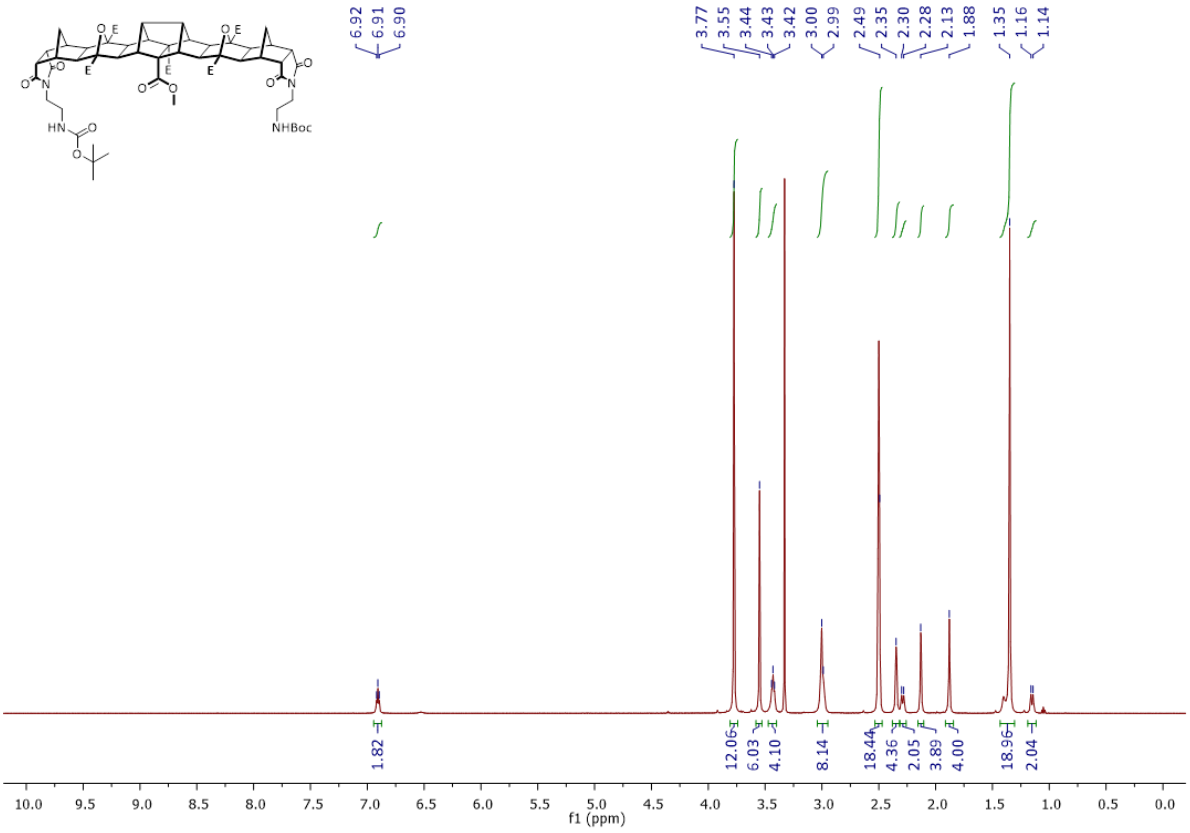
^{1}H NMR (500 MHz, DMSO-d_6) δ 6.91 (2H, t, *J* = 5.9 Hz, 2 × NH), 3.78 (12H, s, 4 × Me), 3.55 (6H, s, 2 × Me), 3.43 (4H, t, *J* = 6.2 Hz, 2 × H1'), 3.00 – 2.99 (8H, m, H11,15,28,32, 2 × H2'), 2.35 (4H, s, H10,16,27,34), 2.29 (2H, d, *J* = 9 Hz, H36$_s$,38$_s$), 2.13 (4H, s, H3,6,20,23), 1.88 (4H, s, H9,17,26,34), 1.35 (18H, s, 2 × *t*-Bu), 1.15 (2H, d, *j* = 9.3 Hz, H36$_a$H38$_a$).

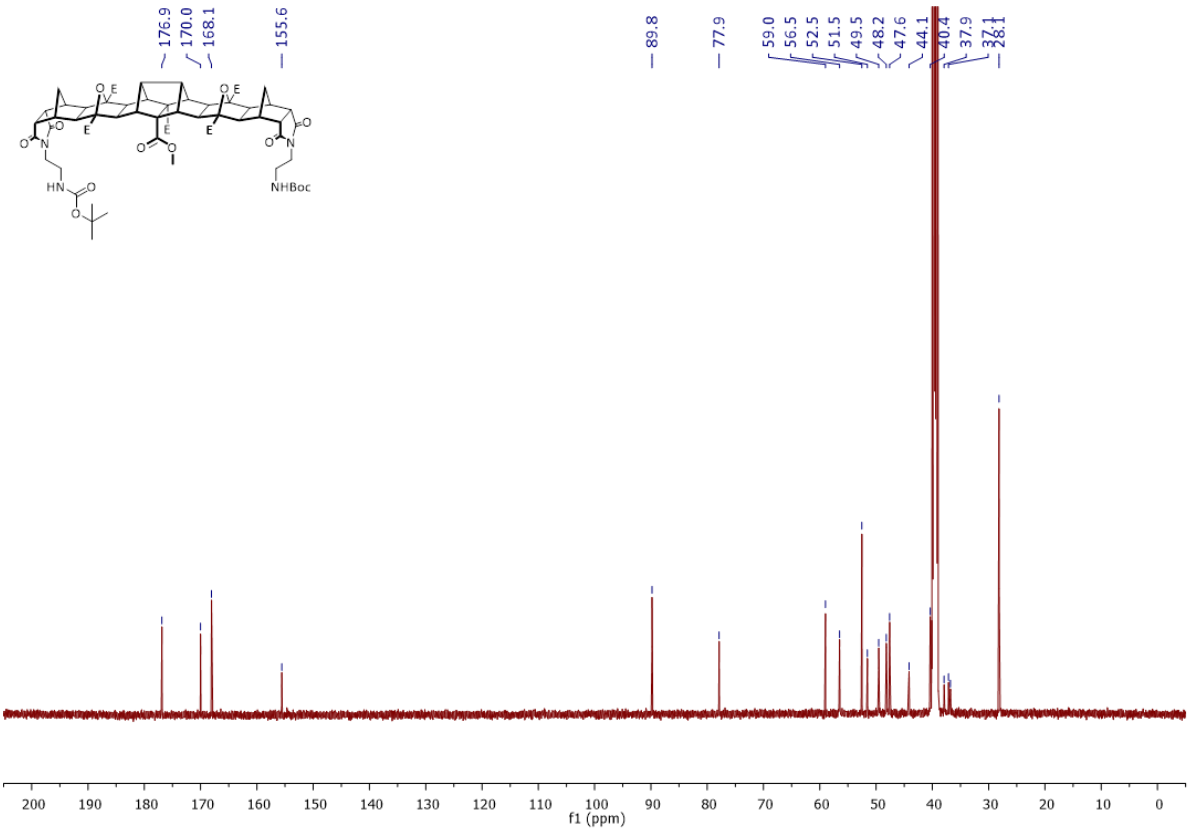
Two ^{1}H signals (H2,5,6,7,19,24) under DMSO confirmed by direct correlation with two ^{13}C signals through HSQC experiments.

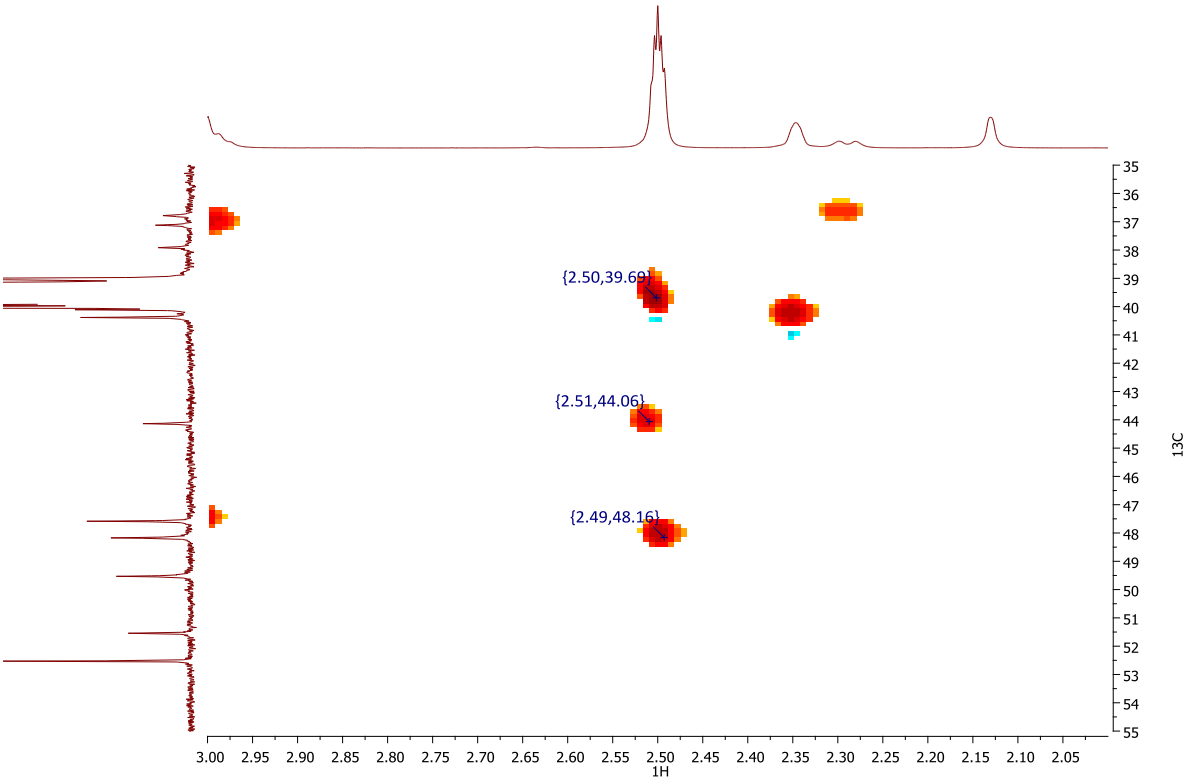
^{13}C NMR (126 MHz DMSO-d_6) δ 176.9, 170.0, 168.1, 155.6, 89.8, 77.9, 59.0, 56.5, 52.5, 51.5, 49.5, 48.2, 47.6, 44.1, 40.4, 37.9, 37.1, 36.8, 28.1.

HRMS (ESI-OrbiTRAP) *m/z*; $[M + H]^+$ Calc. for $C_{60}H_{73}N_4O_{22}$ 1201.4672, found 1201.4711.

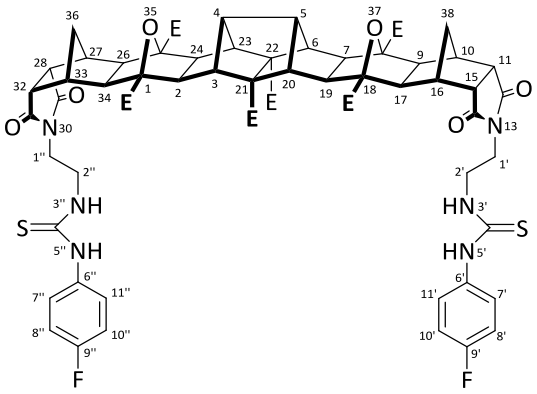
mp > 261.9 °C dec.




176.9
170.0
168.1
155.6
89.8
77.9
59.0
56.5
52.5
51.5
49.5
48.2
47.6
44.1
40.4
37.9
37.1
28.1
NHBoc
f1 (ppm)


{2.50,39.69}
{2.51,44.06}
{2.49,48.16}
1H
13C

Hexamethyl (1α,2β,3α,4α,5α,6α,7β,8α,9β,10α,11α,15α,16α,17β,18α,19β,20α,21β,22β,23α,24β, 25α,26β,27α,28α,32α,33α,34β)-12,14,29,31-tetraoxo-13,30-bis(9',9''-fluorophenylthiouredioethyl) -35,37-dioxa-13,30-diazapentadecacyclo[23.9.1.1^{8,18}.1^{10,16}.1^{27,33}.0^{2,24}.0^{3,21}.0^{4,23}.0^{5,20}.0^{6,22}.0^{7,19}0.^{9,17}. 0^{11,15}.0^{26,34}.0^{28,32}] octatriaconta-1,8,18,21,22,25-hexacarboxylate (1)



The boc-protected amine **6** (58.6 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (500 µL) followed by addition of TFA (90 µL, 1.53 mmol) and the reaction stirred for 4 h at 21 °C. The volatiles were removed *in vacuo* followed by coevaporation with $CHCl_3$ (3 x 2 mL). The white salt was combined with 4-fluorophenyl isothiocyanate (15.9 mg, 0.10 mmol) and the solid materials dissolved in $CHCl_3$ (980 µL) followed by addition of DIPEA (55 µL, 0.32 mmol). The resulting solution was stirred for 24 h at 21 °C before the resulting white precipitate was collected by vacuum filtration and washed with CH_3OH (2 × 2 mL). The crude material was sonicated in CH_3OH (2 mL) before being cooled to 0 °C and the solid material collected to afford the title compound (49.3 mg, 77%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (2H, brs, H5',5''), 7.67 (2H, brs, H3'3,''), 7.27-7.24 (4H, m, H8',8'',10',10''), 7.19 – 7.16 (4H, m, H7',7'',11',11''), 3.77 (12H, s, 4 × Me), 3.60 (8H, brs, H1',1'',2',2"), 3.57 (6H, s, 2 × Me), 2.99 (4H, s, H11,15,31,35), 2.35 (4H, s, H10,16,27,34), 2.31 (2H, d, *J* = 8.8 Hz, H36$_s$,38$_s$), 2.13 (4H, s, H3,6,20,23), 1.91 (4H, s, H9,17,26,34), 1.16 (2H, d, *J* = 8.9 Hz, H36$_a$H38$_a$).

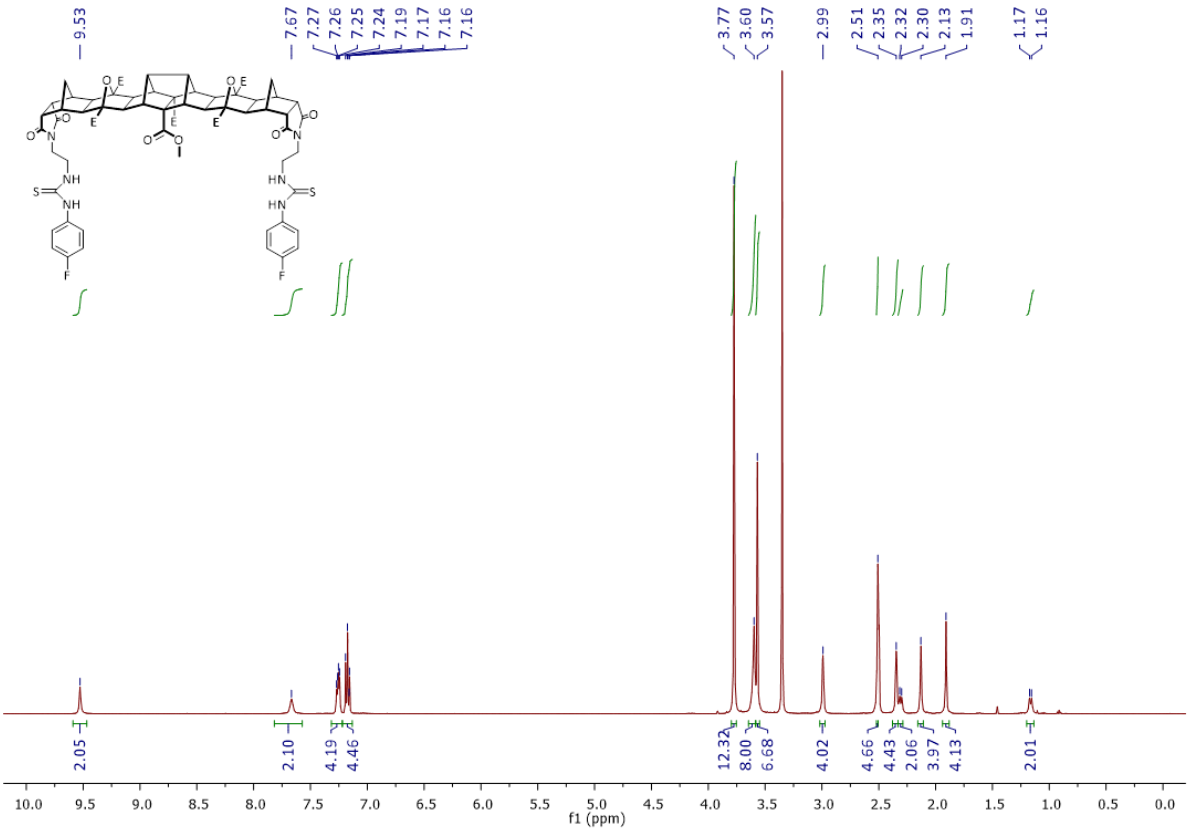
Two ^{1}H signals (H2,5,6,7,19,24) under DMSO confirmed by direct correlation with two ^{13}C signals through HSQC experiments.

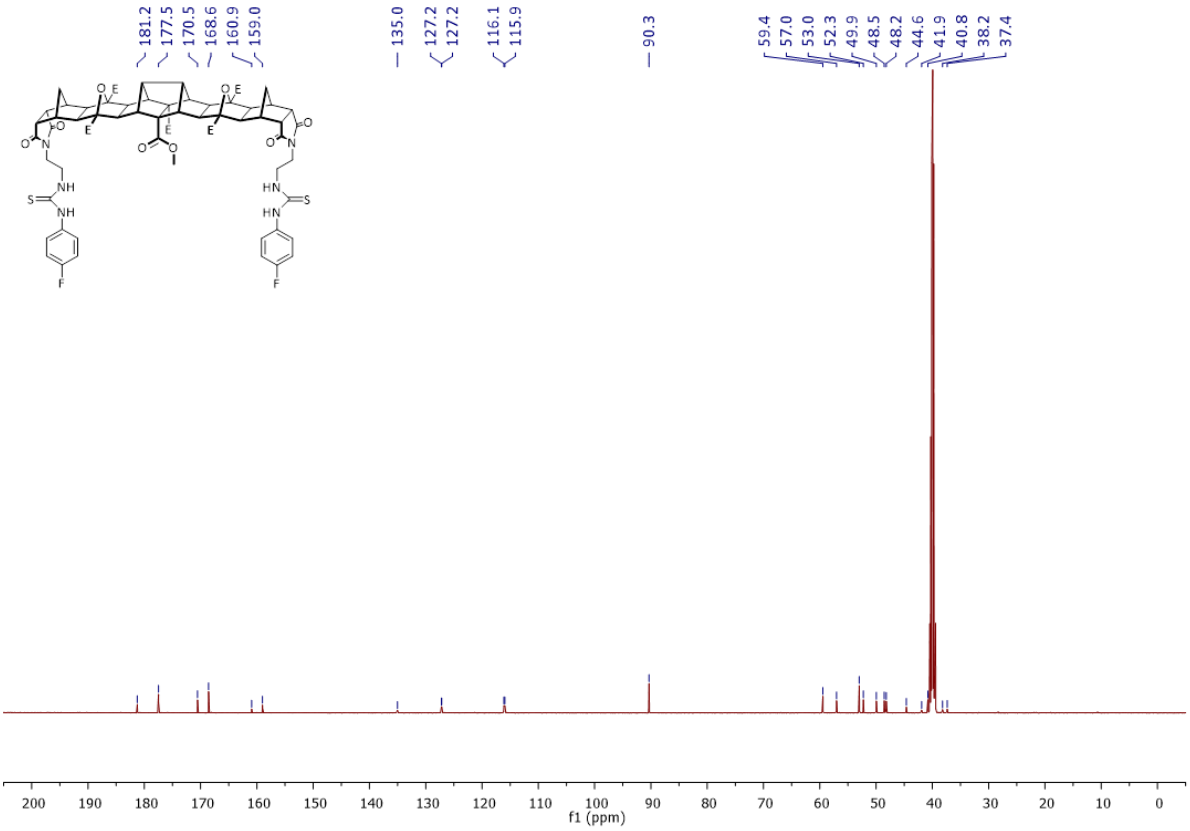
^{13}C NMR (126 MHz DMSO-d_6) δ 181.2, 177.5, 170.5, 168.6, 160.9, 159.0, 135.0, 127.22, 127.16, 116.1, 115.9, 90.33, 59.4, 57.0, 53.0, 52.3, 49.9, 48.5, 48.2, 44.6, 41.9, 40.8, 38.2, 37.4.

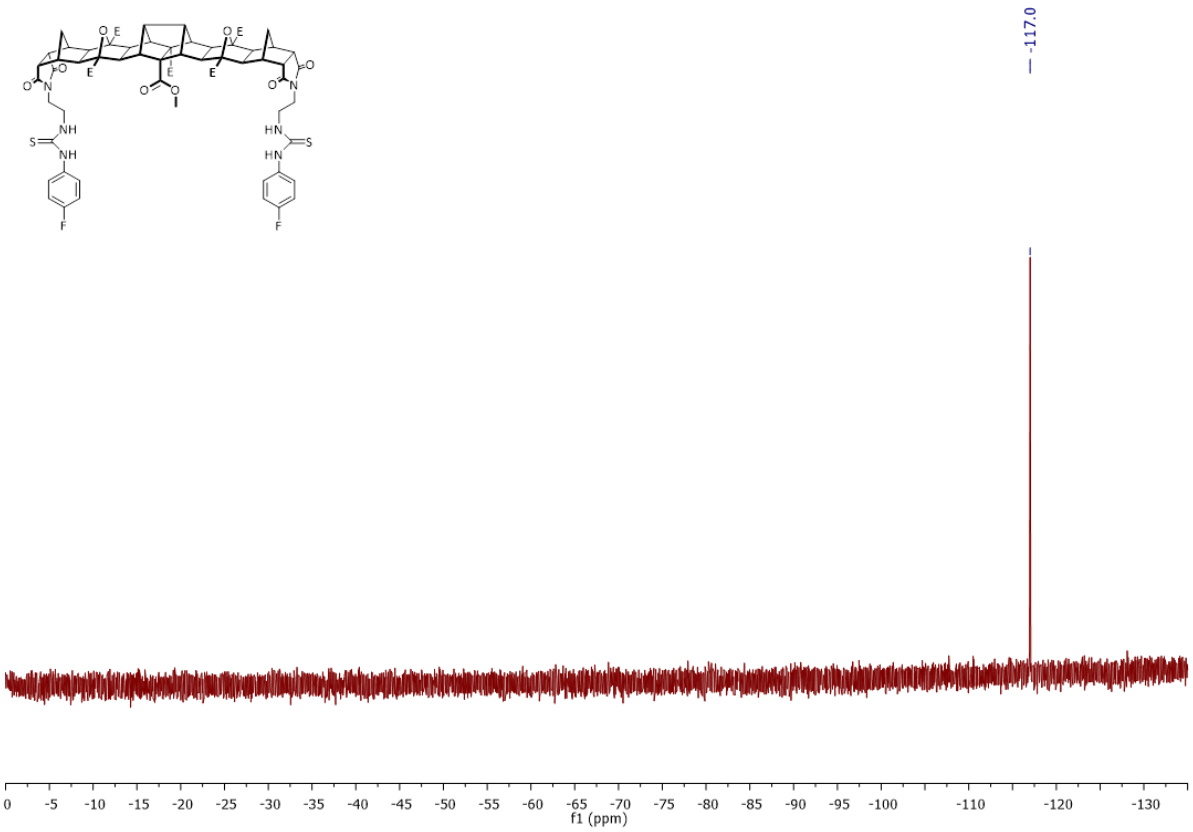
^{19}F NMR (471 MHz DMSO-d_6) δ -171.0.

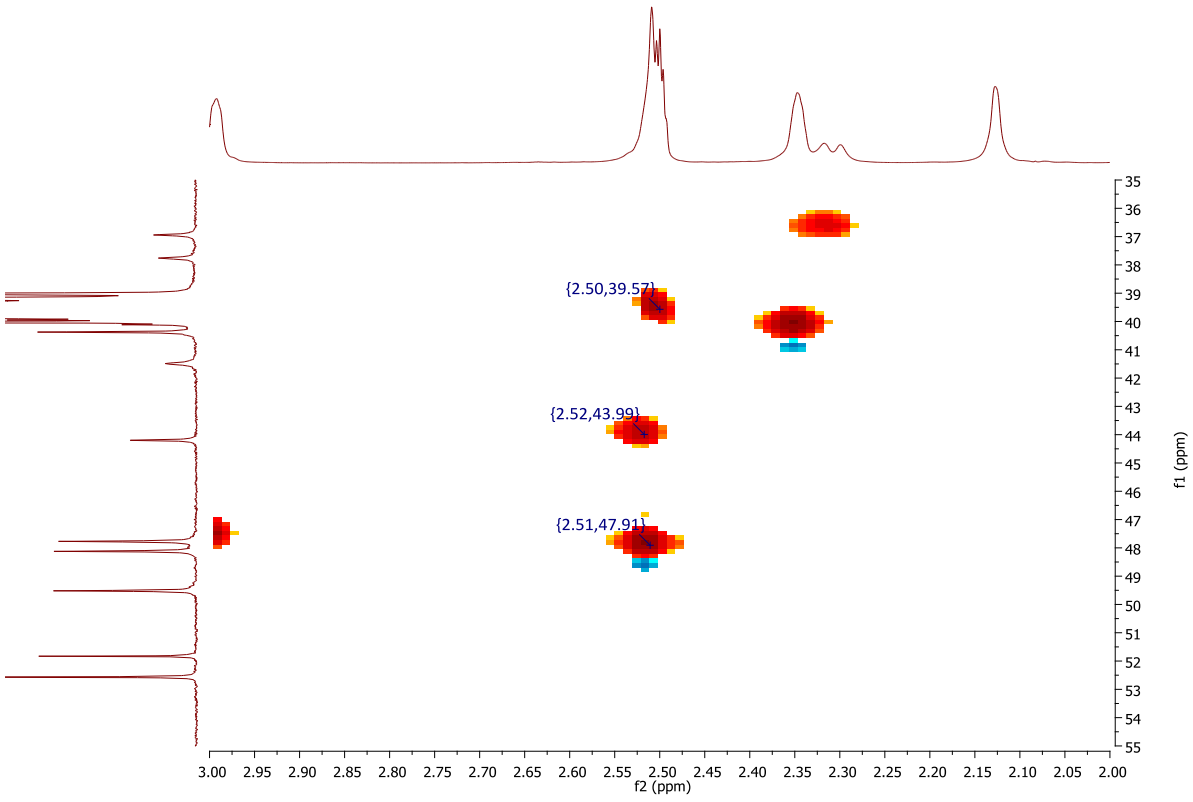
HRMS (ESI-OrbiTRAP) *m/z*; $[M + H]^+$ Calc. for $C_{64}H_{65}F_2N_6O_{18}S_2$ 1307.3720, found 1307.3779.

mp > 249.8 °C dec.

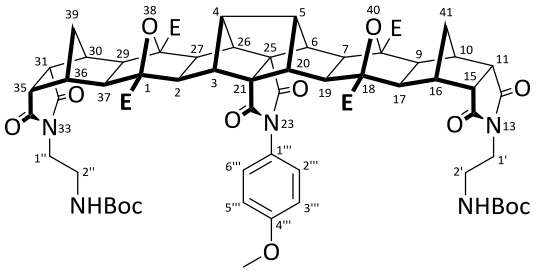

9.53
7.67
7.27
7.26
7.25
7.24
7.19
7.17
7.16
7.16
3.77
3.60
3.57
2.99
2.51
2.35
2.32
2.30
2.13
1.91
1.17
1.16
2.05
2.10
4.19
4.46
12.32
8.00
6.68
4.02
4.66
4.43
2.06
3.97
4.13
2.01
f1 (ppm)


181.2
177.5
170.5
168.6
160.9
159.0
135.0
127.2
127.2
116.1
115.9
90.3
59.4
57.0
53.0
52.3
49.9
48.5
48.2
44.6
41.9
40.8
38.2
37.4
f1 (ppm)


-117.0
0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -110 -120 -130
f1 (ppm)


{2.50,39.57}
{2.52,43.99}
{2.51,47.91}
3.00 2.95 2.90 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.45 2.40 2.35 2.30 2.25 2.20 2.15 2.10 2.05 2.00
f2 (ppm)
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55
f1 (ppm)

Tetramethyl (1α,2β,3α,4α,5α,6α,7β,8α,9β,10α,11α,15α,16α,17β,18α,19β,20α,26α,27β,28α,29β, 30α,31α,35α,36α,37β)-12,14,22,24,32,34-hexaoxo-13,33-bis(2',2''-*tert*-butoxycabronylaminoethyl) -23-(4'''-methoxyphenyl)-38,40-dioxa-13,23,33-triazahexadecacyclo[26.9.$1^{8,18}$.$1^{10,16}$.$1^{30,36}$.$0^{2,27}$.$0^{3,21}$. $0^{4,26}$.$0^{5,20}$.$0^{6,25}$.$0^{7,19}$.$0^{9,17}$.$0^{11,15}$.$0^{21,25}$.$0^{29,37}$.$0^{31,35}$]hentetracontane-1,8,18,28-tetracarboxylate (7)



A microwave vessel was charged with alkene **4** (36.3 mg, 0.11 mmol), epoxide **5** (102.4 mg. 0.22 mmol) and DMF (220 µL). The vessel was capped then heated using microwave irradiation for 10 min at 150 °C. The reaction mixture was transferred to a separatory funnel and diluted with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The organics were combined and washed with sat. NaCl (30 mL), dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by tritration in CH_3OH (3 mL) to afford the title compound (98.0 mg, 71%) as a white solid.

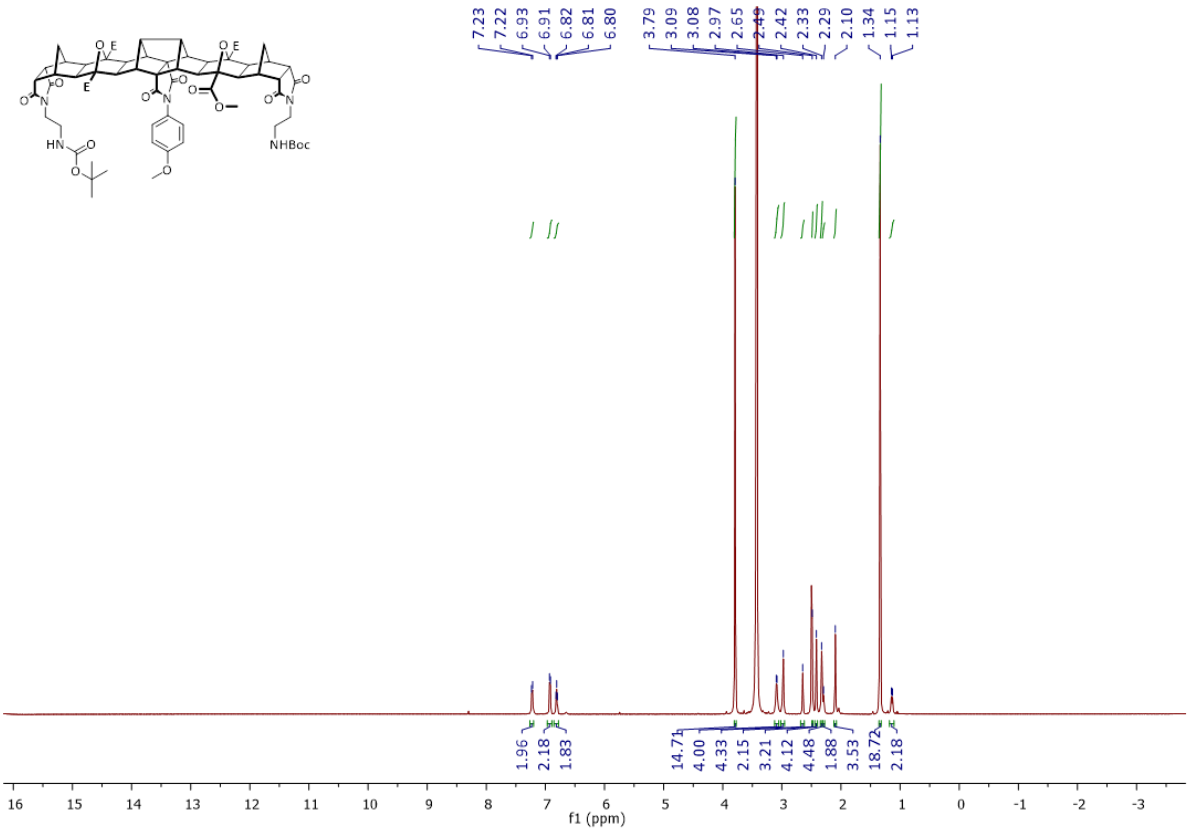
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23 (2H, d, *J* = 8.7 Hz, H2'6'), 6.92 (2H, d, *J* = 8.8 Hz, H3',5'), 6.81 (2H, t, *J* = 5.9 Hz, 2 × NH), 3.79 (15H, s, 5 × Me), 3.09 (4H, app. d, *J* = 5.9 Hz, 2 × H1'), 2.97 (4H, s, H11,15,31,33), 2.65 (2H, s, H4,5), 2.49 (4H, s, H2,7,19,27), 2.42 (4H, s, H3,6,20,26), 2.33 (4H, s, H10,16,30,36), 2.29 (2H, Unresolved d, $H39_s$,41_s), 2.10 (4H, s, H9,17,29,37), 1.34 (18H, s, 2 × *t*-Bu), 1.14 (2H, d, J = 9.0 Hz, $H39_a$,$H41_a$).

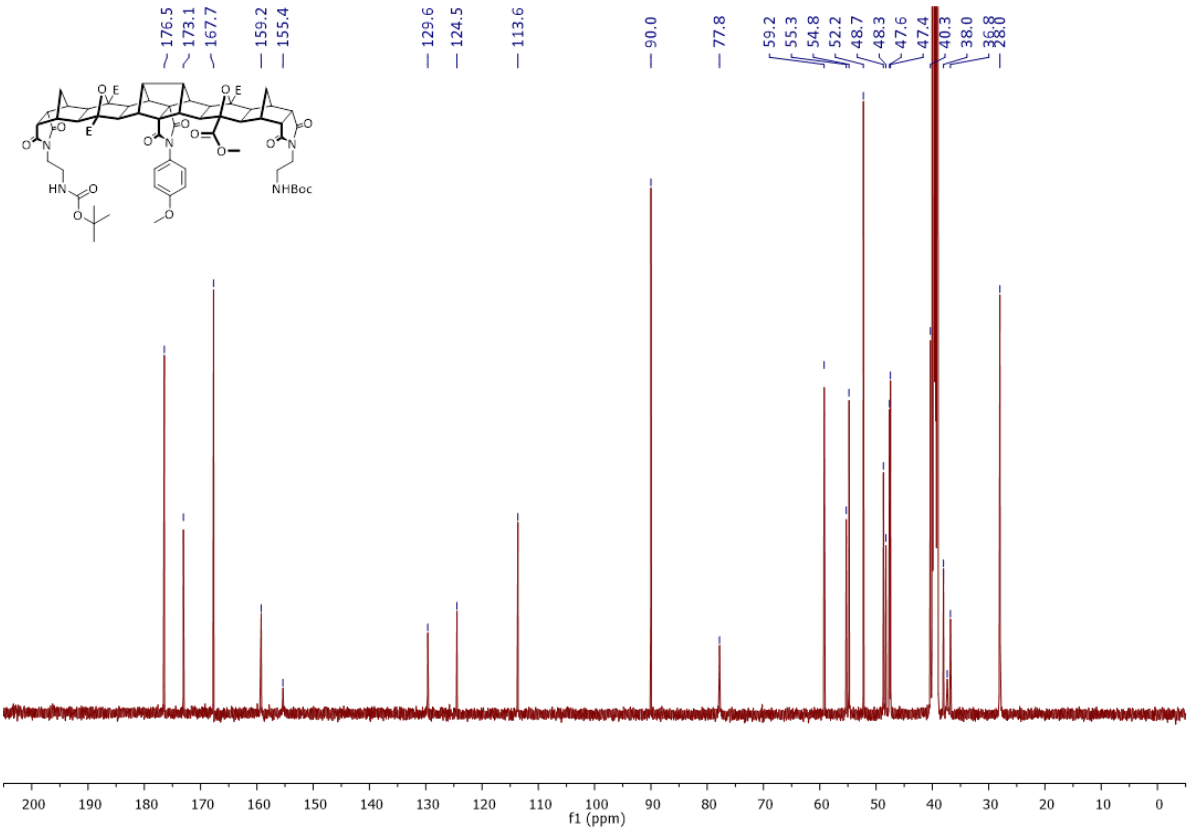
^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 7.20 (2H, d, *J* = 8.6 Hz, H2'6'), 6.93 (2H, d, *J* = 8.9 Hz, H3',5'), 6.62 (2H, 2 × NH), 3.81 (15H, s, 4 × OMe), 3.46 (4H, t, *J* = 6.2 Hz, 2 × H1'), 3.11 (4H, app. d, *J* = 6.0 Hz, 2 × H2'), 2.99 (4H, s, H11,15,31,33), 2.69 (2H, s, H4,5), 2.48 (4H, s, H2,7,19,27), 2.41 (4H, s, H3,6,20,26), 2.35 (4H, s, H10,16,30,36), 2.33 (2H, s, $H39_s$,41_s), 2.10 (4H, s, H9,17,29,37), 1.36 (18H, s, 2 × *t*-Bu), 1.16 (2H, d, J = 9.3 Hz, $H39_a$,$H41_a$).

^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) δ 176.5, 173.1, 167.7, 159.2, 155.4, 129.6, 124.5, 113.6, 90.0, 77.8, 59.2, 55.3, 54.8, 52.2, 48.7, 48.3, 47.6, 47.4, 40.3, 38.0, 36.8, 28.0.

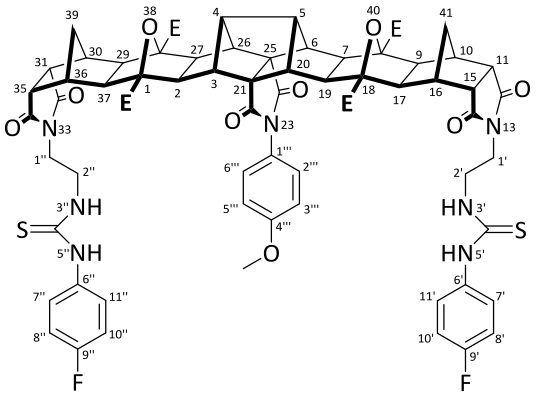
HRMS (ESI-OrbiTRAP) *m/z*; $[M + H]^+$ Calc. for $C_{65}H_{73}N_5O_{21}$ 1260.4832, found 1260.4871.

mp 317.9 °C (dec)


7.23
7.22
6.93
6.91
6.82
6.81
6.80
3.79
3.09
3.08
2.97
2.65
2.42
2.33
2.29
2.10
1.34
1.15
1.13
1.96
2.18
1.83
14.71
4.00
4.33
2.15
3.21
4.12
4.48
1.88
3.53
18.72
2.18
f1 (ppm)


176.5
173.1
167.7
159.2
155.4
129.6
124.5
113.6
90.0
77.8
59.2
55.3
54.8
52.2
48.7
48.3
47.6
47.4
40.3
38.0
f1 (ppm)

Tetramethyl (1α,2β,3α,4α,5α,6α,7β,8α,9β,10α,11α,15α,16α,17β,18α,19β,20α,26α,27β,28α,29β, 30α,31α,35α,36α,37β)-12,14,22,24,32,34-hexaoxo-13,33-bis(9',9''-fluorophenylthiouredioethyl)-23-(4'''-Methoxyphenyl)-38,40-dioxa-13,23,33-triazahexadecacyclo[26.9.1^{8,18}.1^{10,16}.1^{30,36}.0^{2,27}.0^{3,21}. 0^{4,26}.0^{5,20}.0^{6,25}.0^{7,19}.0^{9,17}.0^{11,15}.0^{21,25}.0^{29,37}.0^{31,35}]hentetracontane-1,8,18,28-tetracarboxylate (2)



The boc-protected diamine **7** (53.2 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (420 µL) and TFA (90 µL, 1.18 mmol) added and the reaction stirred for 4 h at 21 °C. The volatiles were removed *in vacuo* followed by coevaporation with $CHCl_3$ (3 x 2 mL). The white salt was combined with 4-fluorophenyl isothiocyanate (20.0 mg, 0.13 mmol) and the solid materials dissolved in $CHCl_3$ (850 µL) followed by addition of DIPEA (45 µL, 0.26 mmol). The resulting solution was stirred for 24 h at 21 °C, and the resulting white precipitate was collected by vacuum filtration and washed with CH_3OH (2 × 2 mL). The crude material was sonicated in CH_3OH (2 mL) before being cooled to 0 °C and the solid material collected to afford the title compound (42.1 mg, 73%) as a white solid.

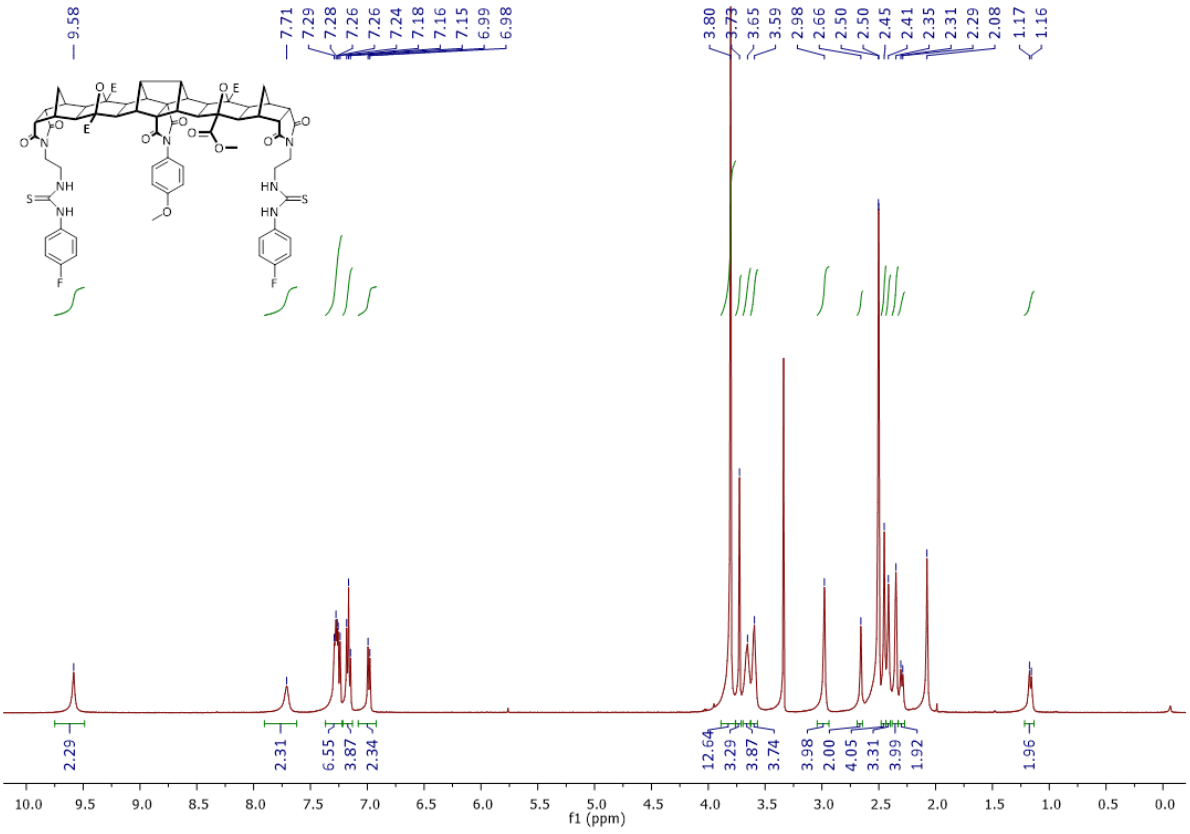
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (2H, s, H5',5''), 7.71 (2H, s, H3',3''), 7.29-7.24 (6H, m, H2''',6''',7',7''11',11'')), 7.16 (4H, t, *J* = 8.6 Hz, H8',8'',10',10''), 6.99 (2H, d, *J* = 8.4 Hz, H3''',5'''), 3.80 (12H, s, 4 × Me), 3.73 (3H, s, Me), 3.65 (4H, brs, H1',1''), 3.59 (4H, brs, H2',2''), 2.98 (4H, s, H11,15,31,35), 2.66 (2H, s, H4,5), 2.45 (4H, s, H2,7,19,27), 2.41 (4H, s, H3,6,20,26), 2.35 (4H, s, H10,16,30,36), 2.30 (2H, d, *J* = 8.7 Hz, H39$_s$,41$_s$), 2.08 (4H, s, H9,17,29,37), 1.17 (2H, d, *J* = 8.3 Hz, H39$_a$,41$_a$).

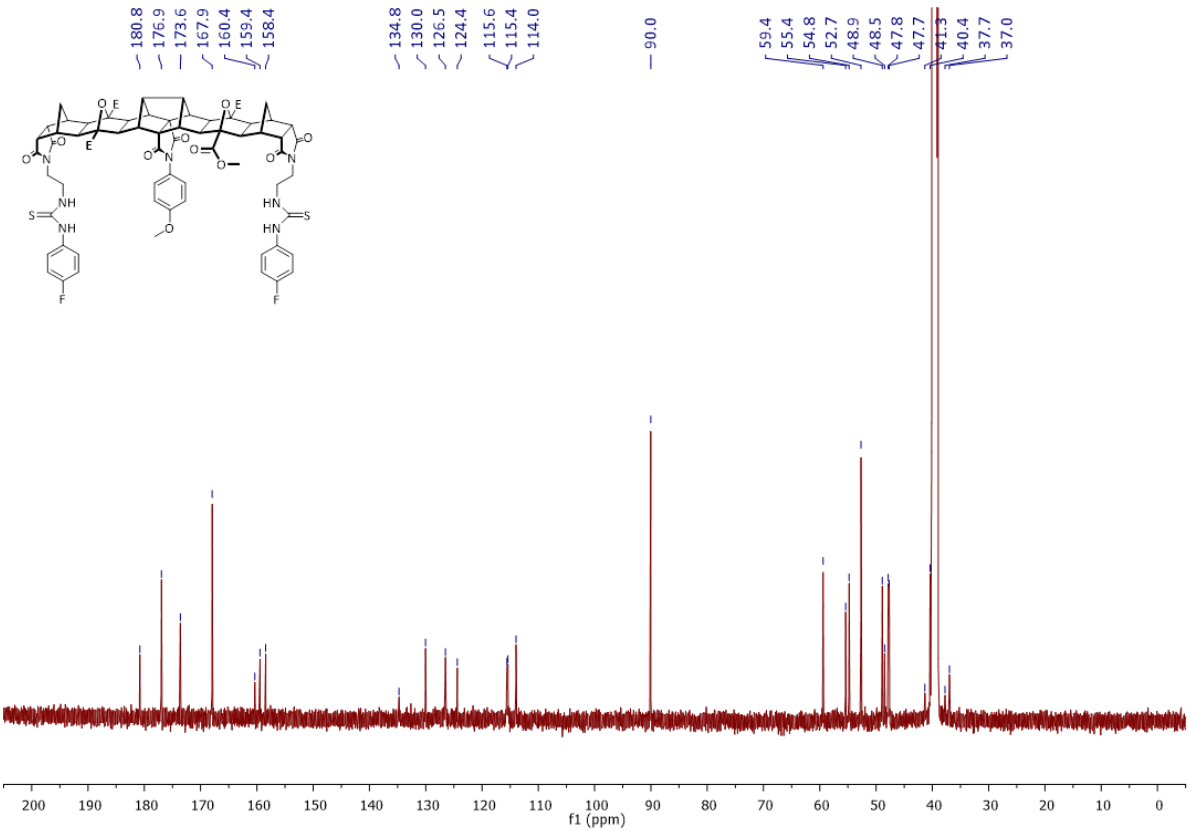
^{13}C NMR (101 MHz, DMSO-d_6) δ 180.8, 176.9, 173.6, 167.9, 160.4, 159.4, 158.4, 134.8, 130.0, 126.5, 124.4, 115.6, 115.4, 114.0, 90.0, 59.4, 55.4, 54.8, 52.7, 48.9, 48.5, 47.7, 41.3, 40.4, 37.7, 37.0.

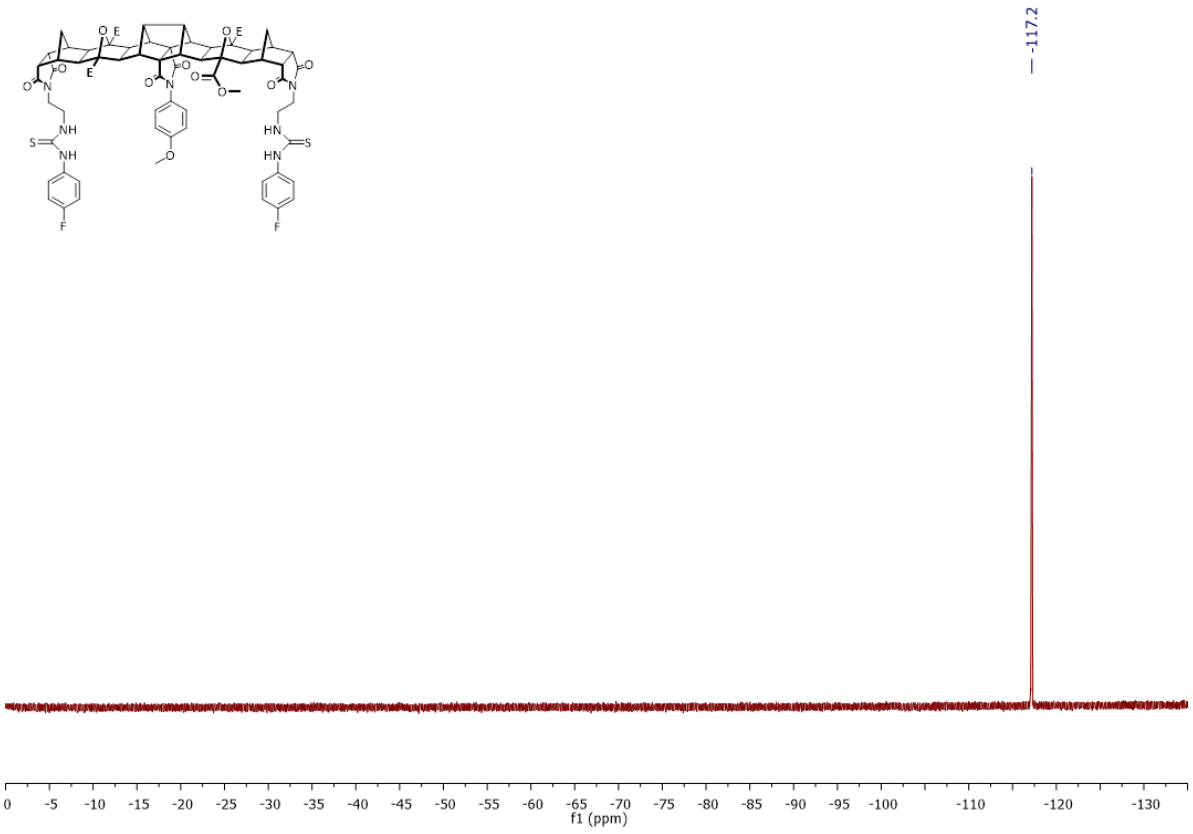
^{19}F NMR (471 MHz, DMSO-d_6) δ -117.2

HRMS (ESI-OrbiTRAP) *m/z*; $[M + H]^+$ Calc. for $C_{69}H_{66}F_2N_7O_{17}S_2$ 1366.3880, found 1366.3953.

mp 304.2 °C (dec)

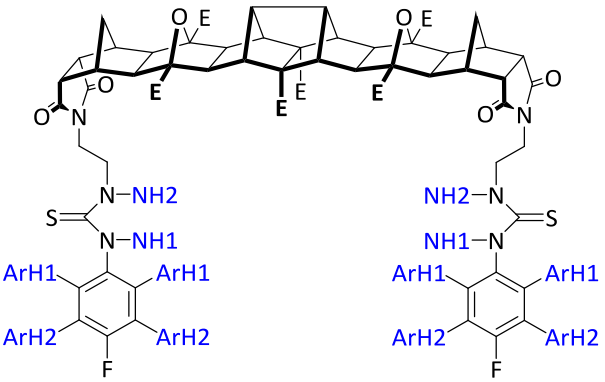

9.58
7.71
7.29
7.28
7.26
7.26
7.24
7.18
7.16
7.15
6.99
6.98
3.80
3.73
3.65
3.59
2.98
2.66
2.50
2.50
2.45
2.41
2.35
2.31
2.29
2.08
1.17
1.16
2.29
2.31
6.55
3.87
2.34
12.64
3.29
3.87
3.74
3.98
2.00
4.05
3.31
3.99
1.92
1.96
f1 (ppm)


180.8
176.9
173.6
167.9
160.4
159.4
158.4
134.8
130.0
126.5
124.4
115.6
115.4
114.0
90.0
59.4
55.4
54.8
52.7
48.9
48.5
47.8
47.7
41.3
40.4
37.7
37.0
f1 (ppm)


-117.2
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-110
-120
-130
f1 (ppm)

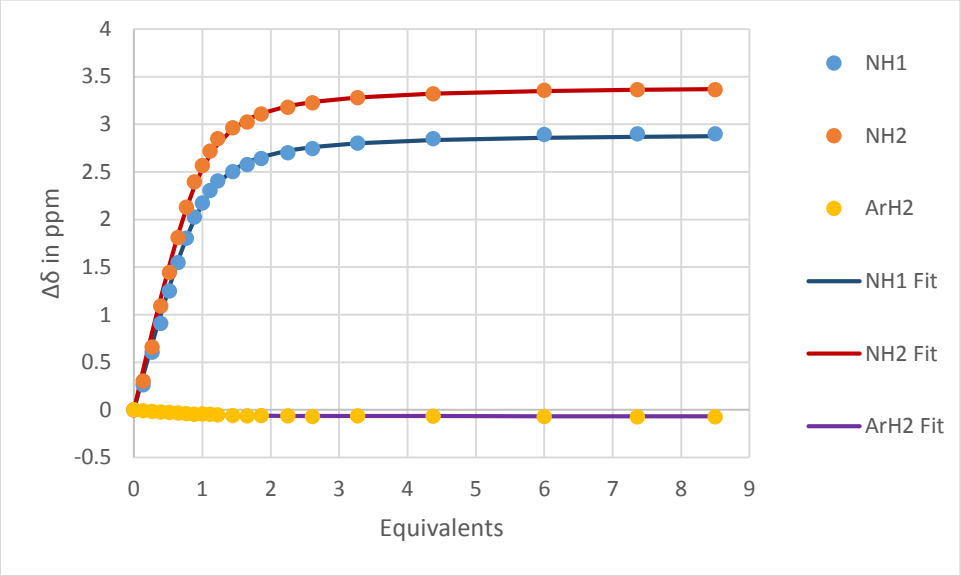
Titrations data

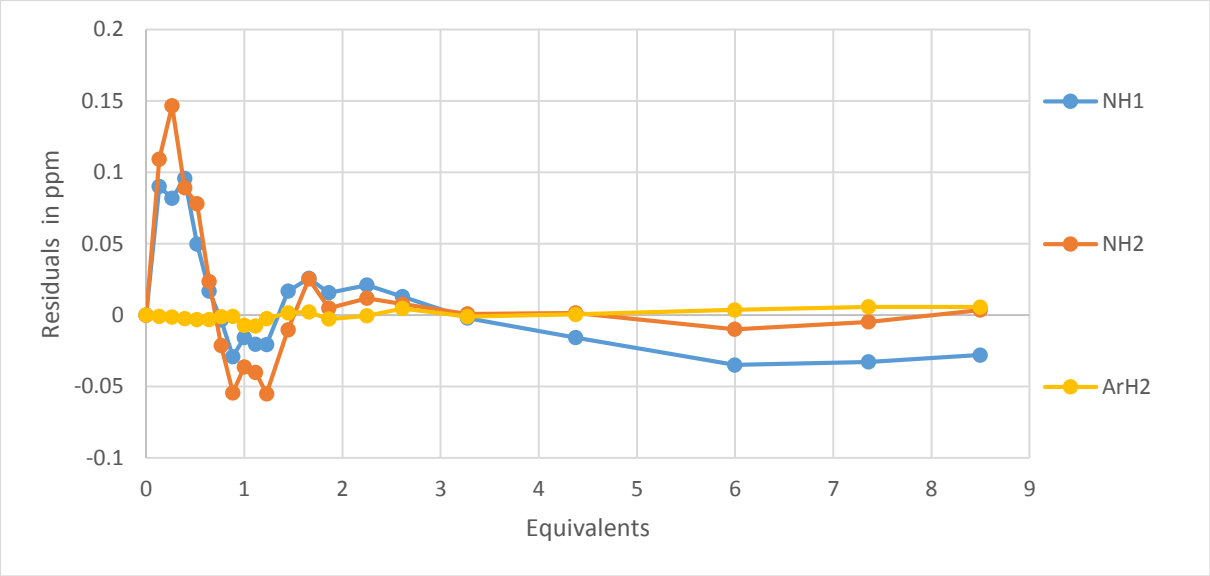
The protons followed in the titration data are as follows NH1 = H5’,5’’; NH2 = H3’,3’’; ArH1 = H7’,7’,7’’,11’,11’’; ArH2 = H8’,8’’,10’,10’’. These signals are represented by the highlighted protons on host **1** below.



1:Naphthalate

Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
1	**1G**	4735	3.7	6

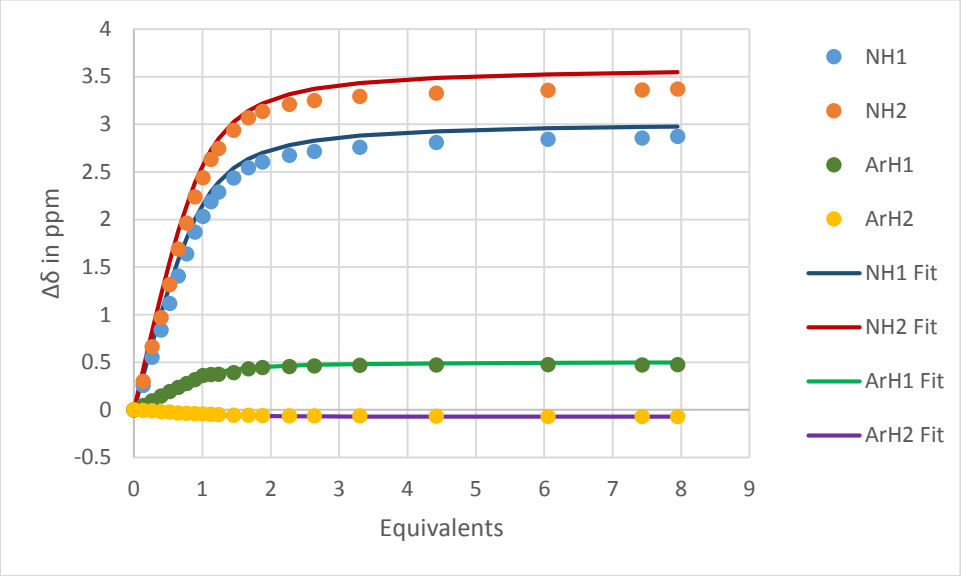


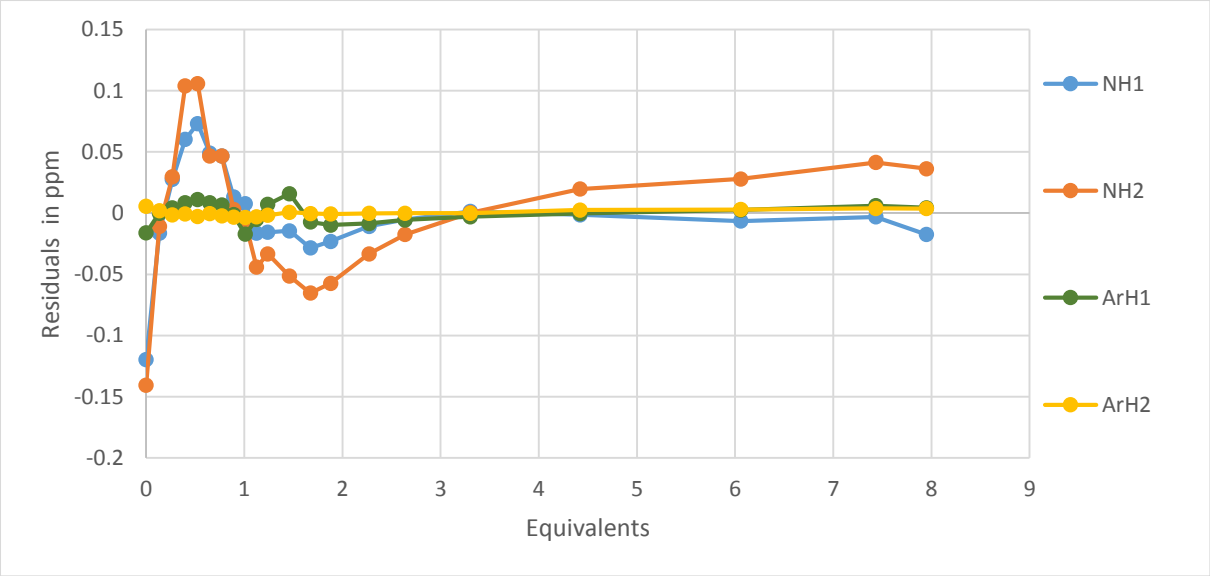


ArH1 omitted due to interference from guest signals

1:Biphenylate

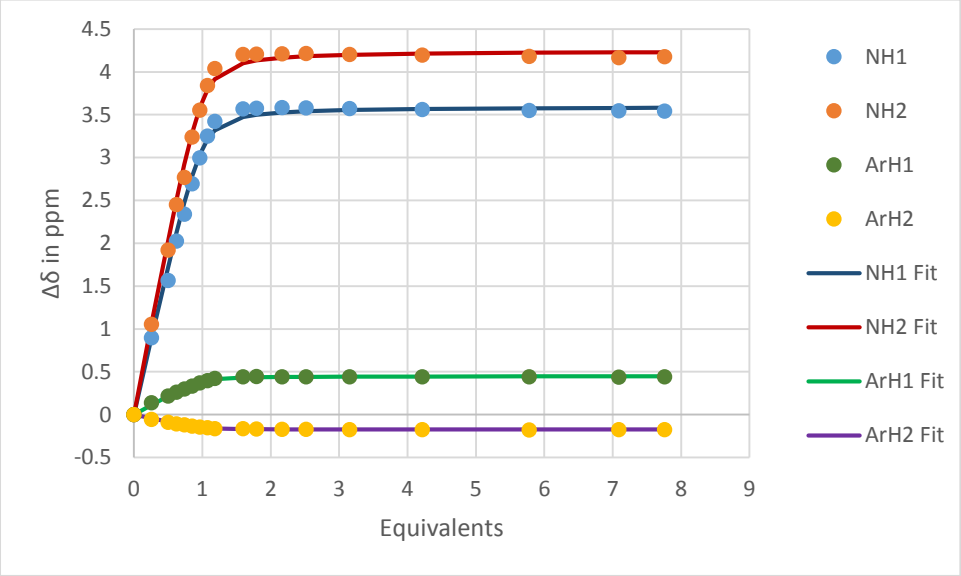
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
1	**2G**	3377	3.5	4

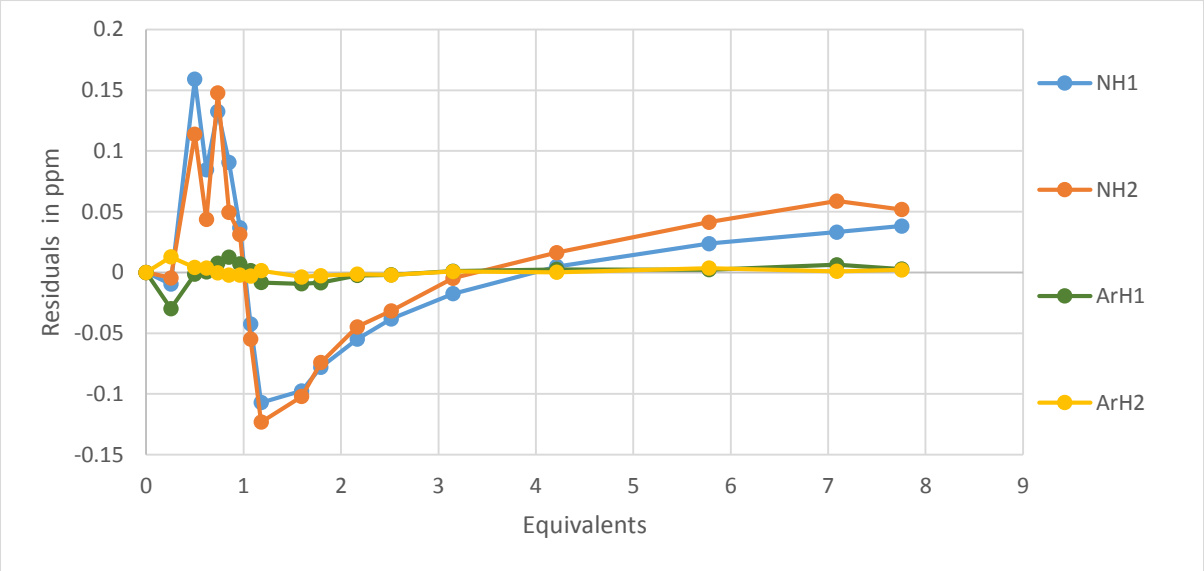




1:Azelate

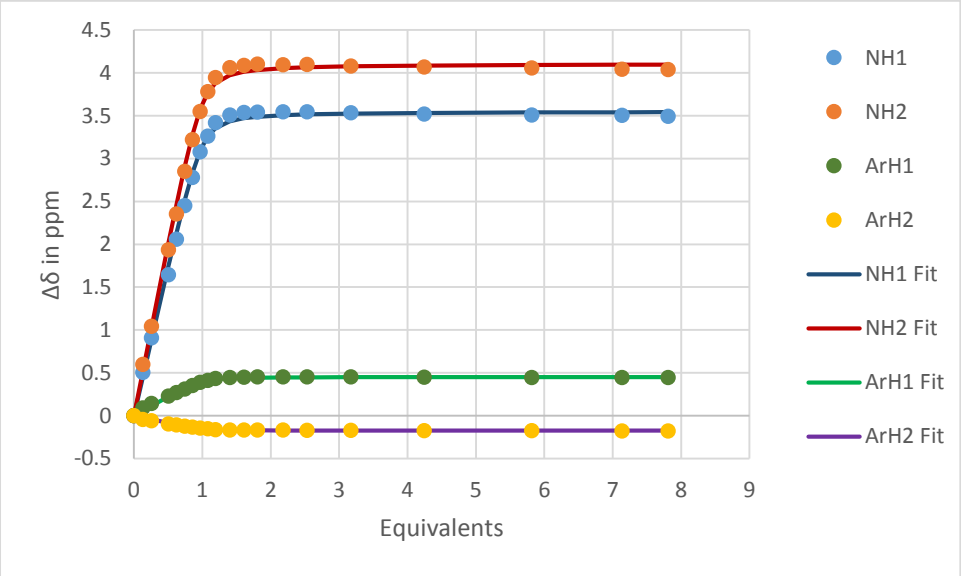
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
1	**3G**	18578	4.3	14

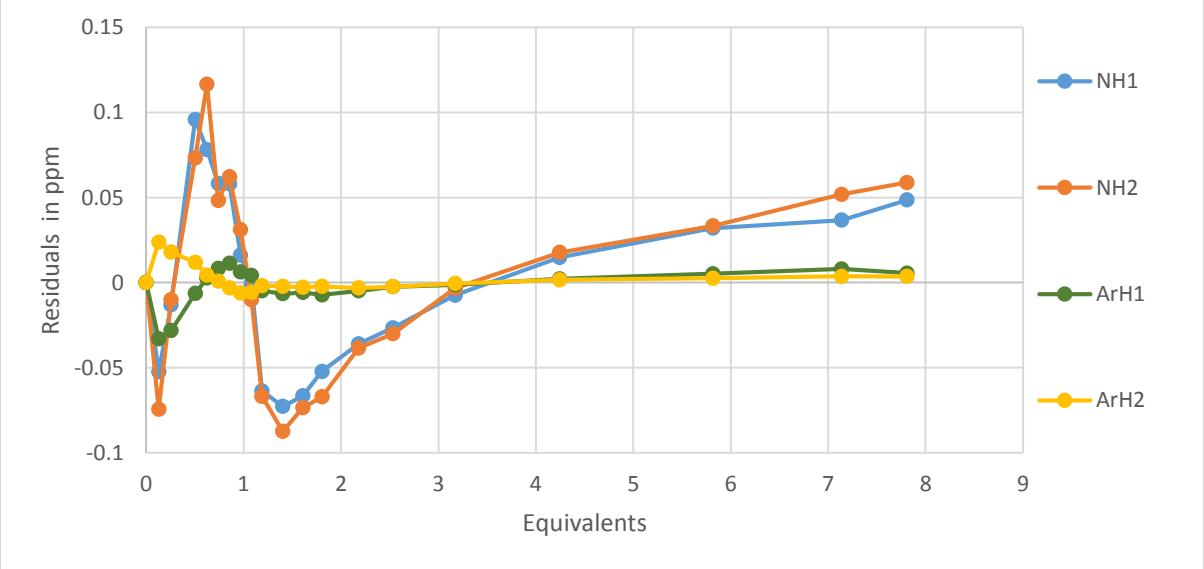




1:Dodecandioate

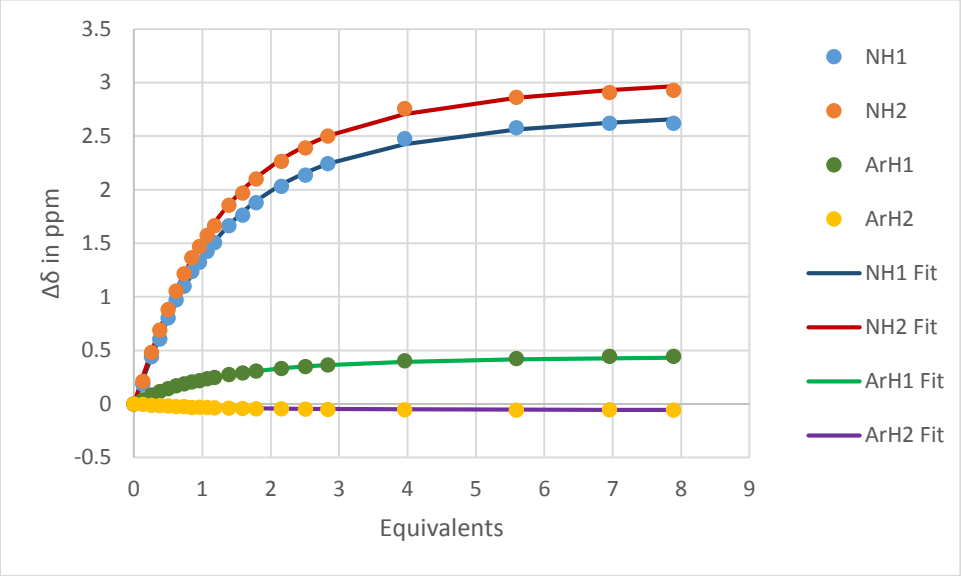
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
1	**4G**	28093	4.4	13

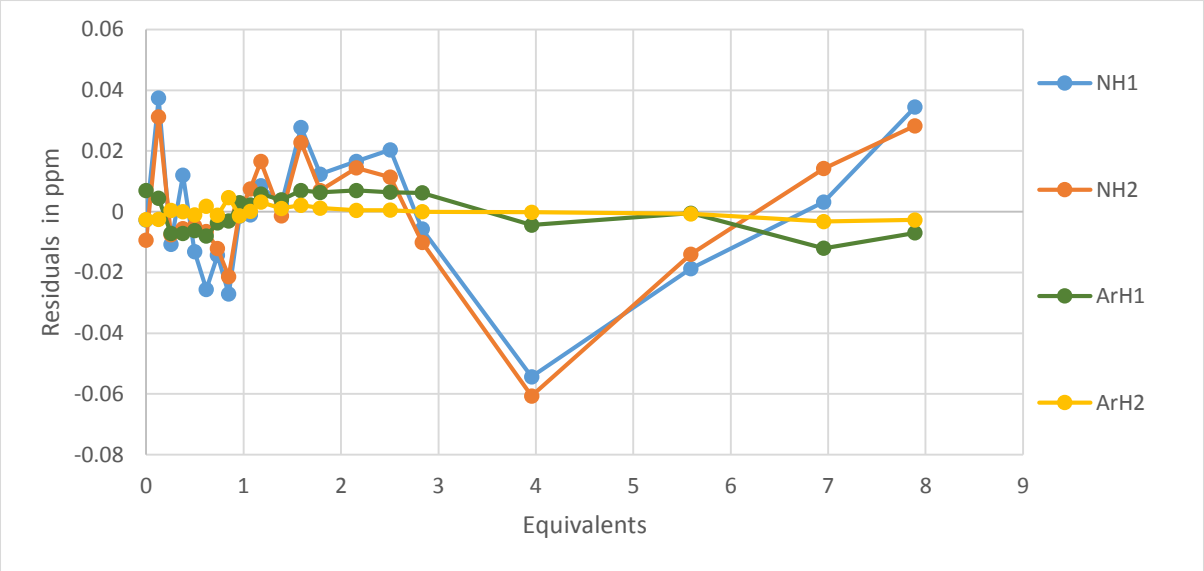




2:Naphthalate

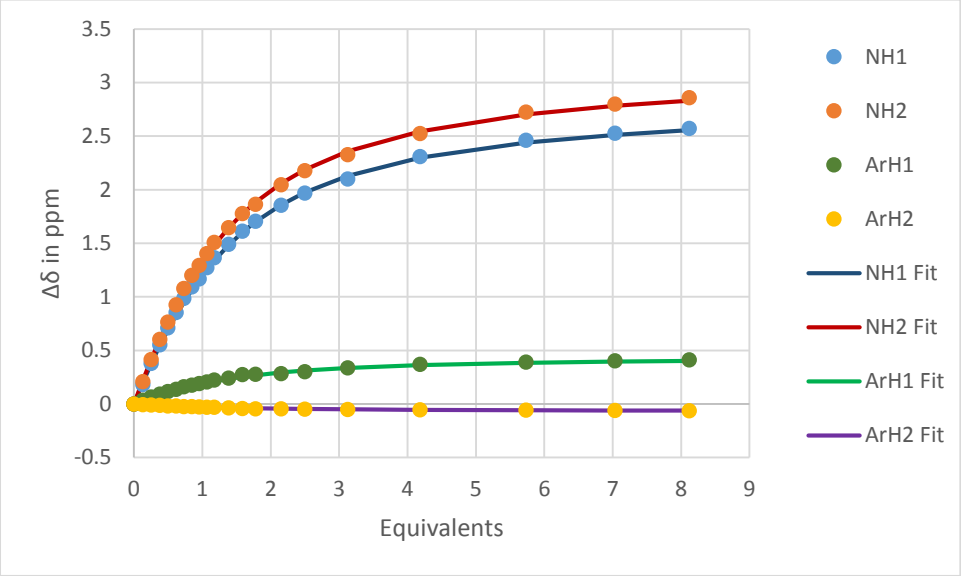
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
2	**1G**	679	2.8	1

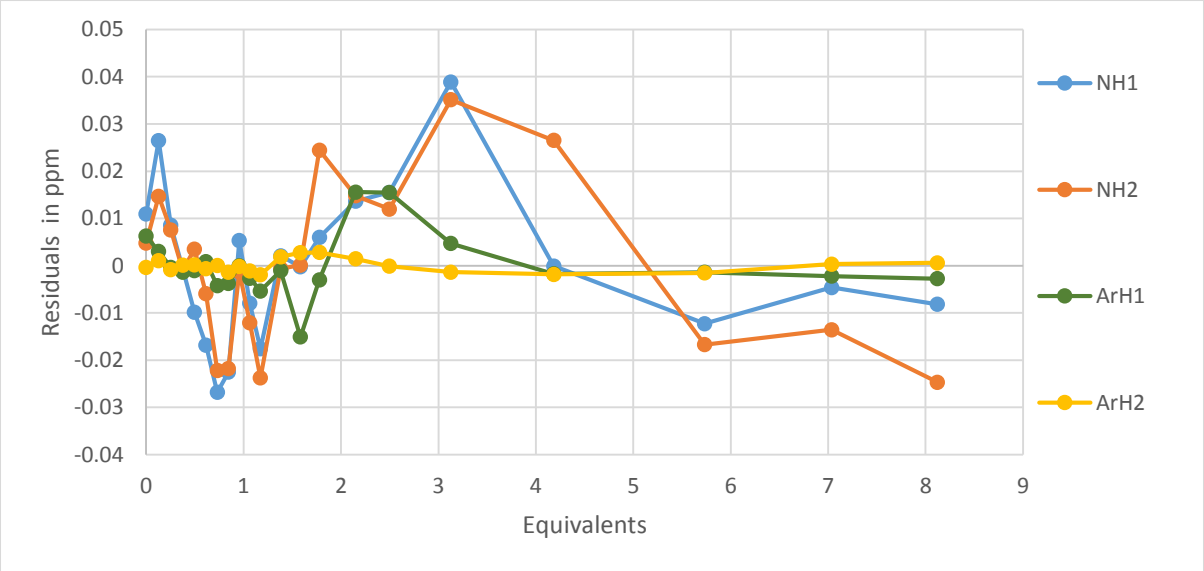




2:Biphenylate

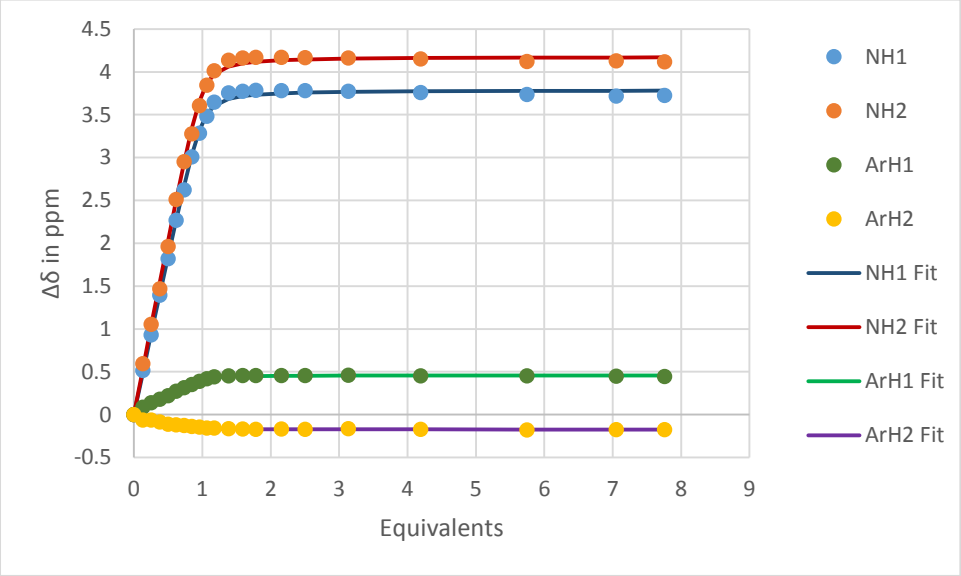
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
2	**2G**	508	2.7	1

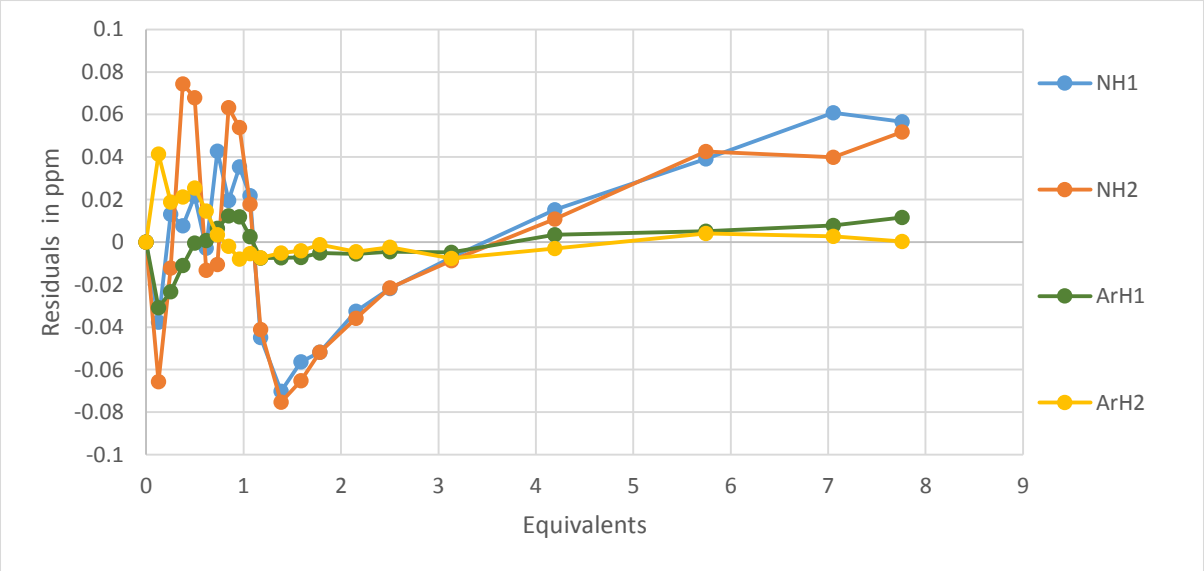




2:Azelate

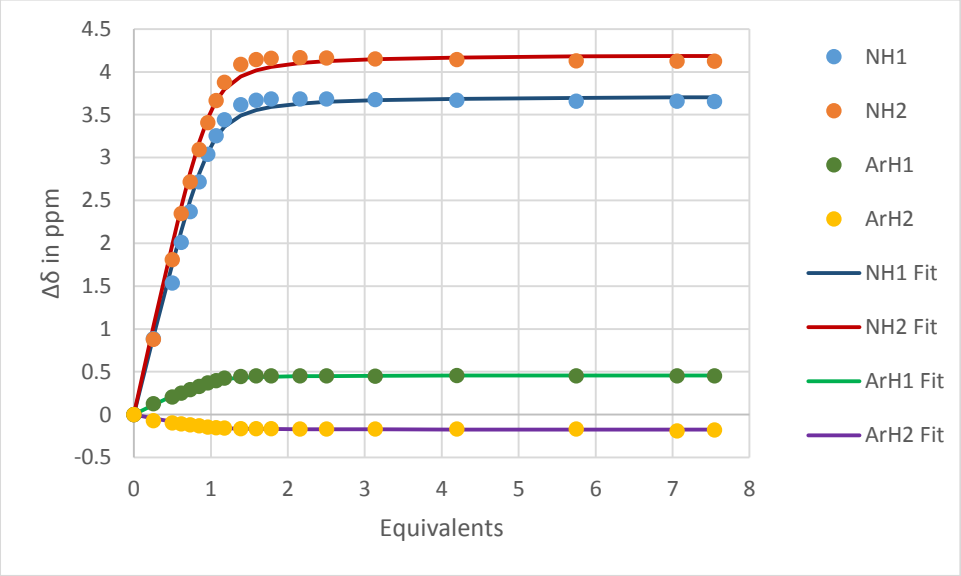
Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
2	**3G**	34641	4.5	12

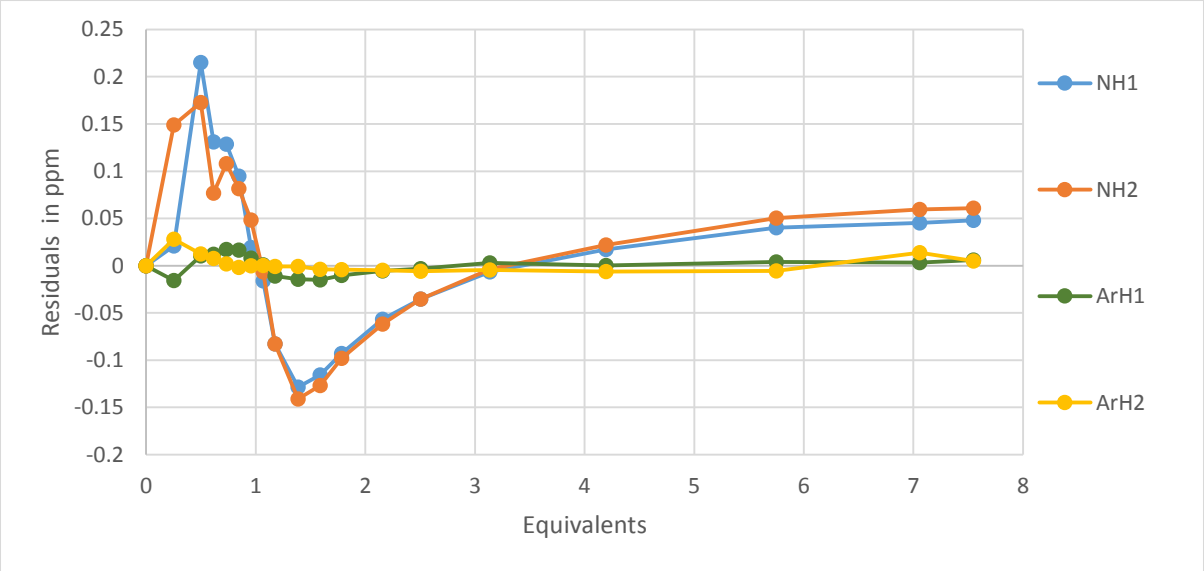




2:Dodecandioate

Host	Guest	$K_{1:1}$	Log_{10} $K_{1:1}$	Error %
2	**4G**	135.05	4.1	14





References

(1) Ahmad, N.; Levison, J. J.; Robinson, S.; Uttley, M.; Wonchoba, E.; Parshall, G. Complexes of ruthenium, osmium, rhodium, and iridium containing hydride carbonyl, or nitrosyl ligands. *Inorganic Syntheses, Volume 15* **2007**, 45.

(2) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. Anhydrous tert-butyl hydroperoxide in toluene: the preferred reagent for applications requiring dry TBHP. *The Journal of Organic Chemistry* **1983,** *48* (20), 3607.

(3) http://supramolecular.org (accessed 15th May, 2016).

(4) P. Thordarson, Chem. Soc. Rev. 2011, 40, 1305–1323.

(5) Rigaudy, J.; Klesney, S. Nomenclature of organic chemistry: sections A, B, C, D, E, F and H-1979 ed. **1979**.

(6) McNeil, D.; Vogt, B.; Sudol, J.; Theodoropulos, S.; Hedaya, E. Multiple cycloaddition reaction of 9, 10-dihydrofulvalene. New approach to 3, 4, 7-methenocyclopenta [a] pentalene derivatives. *Journal of the American Chemical Society* **1974,** *96* (14), 4673.

(7) Paquette, L. A.; Wyvratt, M. J. Domino Diels-Alder reactions. I. Applications to the rapid construction of polyfused cyclopentanoid systems. *Journal of the American Chemical Society* **1974,** *96* (14), 4671.

(8) Taylor, R.; Pelter, M.; Paquette, L. Domino Diels-Alder reaction-3, 3a, 3b, 4, 6a, 7a-hexanhydro-3, 4, 7-metheno-7H-cyclopenta [A] pentalene-7, 8-dicarboxylic acid-(3, 4, 7-metheno-7H-cyclopenta [A] pentalene-7, 8-dicarboxylic acid, 3, 3a, 3b, 4, 6a, 7a-hexahydro). *Organic Synthesis*, **1990,** *68*, 198.

(9) Johnstone, M. D.; Schwarze, E. K.; Clever, G. H.; Pfeffer, F. M. Modular Synthesis of Linear Bis-and Tris-monodentate Fused [6] Polynorbornane-Based Ligands and their Assembly into Coordination Cages. *Chemistry–A European Journal* **2015,** *21* (10), 3948.

(10) Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe. VII. Mitteilung.(Mitbearbeitet von den Harren Ernst Petersen und Franz Querberitz.). *Justus Liebigs Annalen der Chemie* **1930,** *478* (1), 137.

(11) Barker, P. L.; Gendler, P. L.; Rapoport, H. Acylation of dibasic compounds containing amino amidine and aminoguanidine functions. *The Journal of Organic Chemistry* **1981,** *46* (12), 2455.

(12) Pfeffer, F. M.; Gunnlaugsson, T.; Jensen, P.; Kruger, P. E. Anion recognition using preorganized thiourea functionalized [3] polynorbornane receptors. *Organic letters* **2005,** *7* (24), 5357.