Supplementary Material (ESI) for Chemical Communications

A biaryl cross-coupling strategy for functionalisation of benzocrown ethers.

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General techniques.

All reactions involving air or moisture sensitive compounds were carried out under an atmosphere of argon or nitrogen using standard Schlenk equipment and syringe techniques. All glassware was dried in a hot oven (>140 ºC, for at least 12 hours) and cooled in a sealed dessicator over silica gel before assembly.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. THF was freshly distilled from sodium benzophenone ketal under argon. Toluene was freshly distilled from sodium wire under argon. Dichloromethane and acetonitrile were freshly distilled from CaH_2 under argon. DMF was distilled, stored over CaH_2 and degassed before use. *n*-Butyllithium was used as a 2.5 mol dm^3 solution in hexanes, stored under argon. $ZnBr_2$ was dried overnight at 130 ºC under vacuum (0.7 mmHg) before use. Al_2O_3 refers to basic, deactivated Brockmann grade III alumina prepared from Brockman grade I alumina + 6% w/v added water.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV300 or DPX400 spectrometers. ^{1}H Chemical shifts are reported as values in ppm referenced to residual solvent. The following abbreviations are used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, fs = fine splitting. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C spectra were proton decoupled and referenced to solvent. Signals are reported as s, d, t, q, depending on the number of directly attached protons (0, 1, 2, 3, respectively), this being determined by DEPT experiments. Low resolution mass spectra were recorded on a Waters ZMD mass spectrometer, single quadrupole, 2700 autosampler. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focussing mass spectrometer. Values of *m/z* are reported in atomic mass units and the peak intensity relative to the base peak is reported in parenthesis. Infrared spectra were run as neat films on a ThermoNicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absoptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s = strong, m = medium, w = weak and/or br (broad). Melting points were determined using an Electrothermal melting point apparatus and elemental analyses were carried out by Medac Ltd.

Biphenyl-linked benzocrown ethers 4a-c. One-pot preparation using Negishi-coupling.

To a stirred solution of 4-iodobenzocrown ether **1** (n_1 = 1 or 2) (0.5 mmol) in THF (10 mL) at 0 ºC was added ^{i}PrMgCl (0.26 mL of a 2M solution in THF, 0.52 mmol) dropwise over 2 min. The solution was stirred at 0 ºC for 2h before addition of a solution of $ZnBr_2$ (118 mg, 0.525 mmol) in THF (5 mL) dropwise over 5 min. The mixture was stirred at 0 ºC for 45 min further. In a separate flask, a solution of 4-iodobenzocrown ether **3** (n_2 = 1 or 2) (0.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in THF (5 mL) was prepared and stirred at room temperature for 5 min before dropwise addition, at 0 ºC, to the aryl zinc reagent prepared above. The ice bath was immediately removed and the mixture allowed to warm to room temperature before stirring overnight. The mixture was poured onto H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL) before drying over $MgSO_4$ and concentration *in vacuo* to yield crude biaryl products **4a-c**.

4-[4’-benzo-18-crown-6]benzo-18-crown-6 ether (4a).

Purification by column chromatography (99:1 then 98:2 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (245 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 – 6.98 (2H, m), 6.85 (1H, m), 4.18 – 4.09 (4H, m), 3.90 – 3.85 (4H, m), 3.74 – 3.69 (4H, m), 3.68 – 3.64 (4H, m), 3.62 (4H, s). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 149.44 (s), 148.67 (s), 134.85 (s), 120.02 (d), 115.00 (d), 113.90 (d), 71.12 (t), 71.10 (2 × t), 71.07 (t), 71.03 (t), 71.02 (t), 70.01 (t), 69.99 (t), 69.75 (t), 69.65 (t). IR (solid): ν = 2864 (m), 1509 (s), 1100 (s), 794 (m) cm^{-1}. Melting point: 130 °C (CH_2Cl_2). LRMS (ES+): m/z = 640 (M + NH_4^+, 55%), 645 (M + Na^+, 100%). HRMS (ES+): $C_{32}H_{46}O_{12}Na$ requires m/z = 645.2881. Found 645.2870.

4-[4’-benzo-15-crown-5]benzo-15-crown-5 ether (4b).

Purification by column chromatography (99:1 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (245 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 – 6.97 (4H, m), 6.84 (2H, d, *J* = 8.5 Hz), 4.16 – 4.09 (8H, m), 3.88 – 3.84 (8H, m), 3.73 – 3.68 (16H, m). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 149.56 (s), 148.79 (s), 134.87 (s), 120.01 (d), 114.72 (d), 113.68 (d), 71.36 (t), 71.34 (t), 70.86 (t), 70.83 (t), 69.94 (t), 69.91 (t), 69.66 (t), 69.53 (t). IR (solid): ν = 2860 (m, br), 1504 (s) cm^{-1}. Melting point: 164 – 166 °C (CH_2Cl_2). LRMS (ES+): m/z = 290 (M + 2Na^+, 100 %), 557 (M + Na^+, 80%). HRMS (ES+): $C_{28}H_{38}O_{10}Na$ requires m/z = 557.2357. Found 557.2351.

4-[4’-benzo-15-crown-5]benzo-18-crown-6 ether (4c).

Purification by column chromatography (99:1 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (219 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 – 6.97 (4H, m), 6.87 – 6.82 (2H, m), 4.18 – 4.08 (8H, m), 3.90 – 3.84 (8H, m), 3.74 – 3.68 (11H, m), 3.68 – 3.64 (5H, m), 3.62 (4H, broad s). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 149.55 (s), 149.45 (s), 148.77 (s), 148.68 (s), 134.90 (s), 134.80 (s), 120.05 (d), 119.96 (d), 115.01 (d), 114.71 (d), 113.98 (d), 113.60 (d), 71.36 (t), 71.34 (t), 71.11 (2 × t), 71.10 (t), 71.08 (t), 71.04 (t), 71.02 (t), 70.85 (t), 70.82 (t), 70.02 (t), 69.99 (t), 69.93 (t), 69.91 (t), 69.79 (t), 69.66 (t), 69.63 (t), 69.53 (t). IR (solid): ν = 1504 (m, br), 938 (m, br) cm^{-1}. Melting point: 122 - 124 °C (CH_2Cl_2). LRMS (ES+): m/z = 312 (M + 2Na^+, 100%), 601 (M + Na^+, 32%). HRMS (ES+): $C_{30}H_{42}O_{11}Na$ requires m/z = 601.2619. Found 601.2614.

4-[3-thiophene]benzo-18-crown-6 ether (5).

To a stirred solution of 4-iodobenzo-18-crown-6 ether (**1**, $n_1 = 2$) (219 mg, 0.5 mmol) in THF (10 mL) at 0 ºC was added ^{i}PrMgCl (0.27 mL of a 2M solution in THF, 0.55 mmol) dropwise over 2 min. The solution was stirred at 0 ºC for 2h before addition of a solution of $ZnBr_2$ (124 mg, 0.55 mmol) in THF (5 mL) dropwise over 5 min. The mixture was stirred at 0 ºC for 1 h further. In a separate flask, a solution of 3-iodothiophene (51 μL, 0.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in THF (5 mL) was prepared and stirred at room temperature for 5 min before dropwise addition, at 0 ºC, to the aryl zinc reagent prepared above. The ice bath was immediately removed and the mixture allowed to warm to room temperature before stirring overnight. The mixture was poured onto H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL) before drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (0.05% MeOH in CH_2Cl_2, basic Al_2O_3) gave the title compound as a white powder (119 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.23 (3H ,m), 7.09 – 7.05 (2H, m), 6.84 (1H, d, *J* = 8.5 Hz), 4.18 – 4.10 (4H, m), 3.90 – 3.85 (4H, m), 3.74 – 3.70 (4H, m), 3.68 – 3.64 (4H, m), 3.62 (4H, s). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 149.46 (s), 148.82 (s), 142.32 (s), 129.94 (s),126.50 (d), 126.26 (d), 119.85 (d), 119.44 (d), 114.96 (d), 113.59 (d), 71.12 (t), 71.11 (t), 71.08 (t), 71.04 (t), 71.02 (t), 70.00 (t), 69.97 (t), 69.76 (t), 69.60 (t). IR (solid): ν = 1506 (m), 1130 (s), 775 (s) cm^{-1}. Melting point: 93 – 95 °C (CH_2Cl_2). LRMS (ES+): m/z = 417 (M + Na^+, 100%). HRMS (ES+): $C_{20}H_{26}O_6S_1Na$ requires m/z = 417.1342. Found 417.1339.

Benzocrown ether(4-boronic acid)s 6a-b.

To a stirred solution of 4-iodobenzocrown ether **1** (n_1 = 1 or 2) (0.5 mmol) in THF (10 mL) at 0 ºC was added ^{i}PrMgCl (0.27 mL of a 2M solution in THF, 0.55 mmol) dropwise over 2 min. The solution was stirred at 0 ºC for 2h before cooling to −78 ºC and addition of trimethyl borate (0.11 mL, 1.0 mmol). The mixture was stirred at room temperature for 2 h before slowly warming to room temperature and stirring overnight. HCl (10 mL of a 2M aqueous solution) was now added and the mixture stirred for 2 h. The mixture was diluted with H_2O (100 mL) and washed with Et_2O (100 mL) before extraction of the aqueous solution with CH_2Cl_2 (6 × 75 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

Benzo-18-crown-6 ether(4-boronic acid) (6a).
The crude solid obtained was washed with boiling hexane and dried *in vacuo* to yield the title compound as a white powder (123 mg, 69 %).

^{1}H NMR (400 MHz, DMSO, 70 ºC): δ = 7.45 (2H, broad s), 7.39 (1H, d, *J* = 1.3 Hz), 7.36 (1H, dd, *J* = 7.9, 1.3 Hz), 6.91 (1H, d, *J* = 7.9 Hz), 4.12 (4H, m), 3.80 (4H, m), 3.65 (4H, m), 3.60 (4H, m), 3.57 (4H, apparent broad s). ^{13}C NMR (100.5 MHz, DMSO): δ = 150.03 (s), 147.25 (s), 127.77 (d), 125.85 (s [resonance is broad, splitting indistinct]), 118.61 (d), 112.09 (d), 69.89 (t), 69.87 (t), 69.82 (t), 69.80 (t), 68.83 (t), 68.74 (t), 67.99 (t), 67.37 (t). IR (solid): ν = 3350 (w, br), 1346 (s), 1322 (s), 1123 (s, br) cm^{-1}. Melting point: 144 – 146 °C (CH_2Cl_2) (although dehydration of boronic acids takes place at elevated temperature). LRMS (ES+): m/z = 378 (M(^{10}B), + Na^+, 20%), 379 (M(^{11}B), + Na^+, 100%). HRMS (ES+): $C_{16}H_{25}O_8{}^{11}B_1Na$ requires m/z = 379.1535. Found 379.1534.

Benzo-15-crown-5 ether(4-boronic acid) (6b).
The crude solid obtained was washed with boiling hexane and dried *in vacuo* to yield the title compound as a white powder (96 mg, 61 %) containing a ~5% impurity which was not removed following recrystallisation from CH_2Cl_2.

^{1}H NMR (400 MHz, DMSO, 70 ºC): δ = 7.48 (2H broad s), 7.39 – 7.35 (4H, m), 6.91 (1H, d, *J* = 8.0 Hz), 4.81 (4H, m), 3.79 (4H, m), 3.64 (8H, m). ^{13}C NMR (100.5 MHz, DMSO): δ = 150.44 (s), 147.61 (s), 127.96 (d), 119.44 (d), 112.55 (d), 70.45 (2 × t), 69.83 (t), 69.72 (t), 68.97 (t), 68.80 (t), 68.48 (t), 69.06 (t). Note: 4º ^{13}C-B not observed. IR (solid): ν = 3391 (w, br), 1325 (s), 1256 (s), 1132 (s, br) cm^{-1}. HRMS (ES+): $C_{14}H_{21}O_7{}^{11}B_1Na$ requires m/z = 335.1273. Found 335.1268.

Biphenyl-linked benzocrown ethers 4a and 4c. Preparation using Suzuki-coupling.

To a stirred solution of 4-iodobenzo-18-crown-6 ether (109 mg, 0.25 mmol) and $Pd(PPh_3)_4$ (9 mg, 7.5×10^{-3} mmol) in toluene (3 mL) was added Na_2CO_3 (1 mL of a 2M aqueous solution) followed by a solution of benzocrown ether(4-boronic acid) **6a** or **6b** (0.3 mmol) in MeOH (1.5 mL). The mixture was warmed to 80 ºC for 16 h before cooling to room temperature, pouring onto H_2O (100 mL) and extraction with CH_2Cl_2 (100 mL). The organic layer was separated and dried over $MgSO_4$ before concentration *in vacuo*.

4-[4’-benzo-18-crown-6]benzo-18-crown-6 ether (4a).
Purification by column chromatography (99:1 then 98:2 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (123 mg, 79%). ^{1}H and ^{13}C NMR data obtained were in agreement with those reported above for the title compound prepared using Negishi-coupling.

4-[4’-benzo-15-crown-5]benzo-18-crown-6 ether (4c).
Purification by column chromatography (99:1 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (113 mg, 78%). ^{1}H and ^{13}C NMR data obtained were in agreement with those reported above for the title compound prepared using Negishi-coupling.

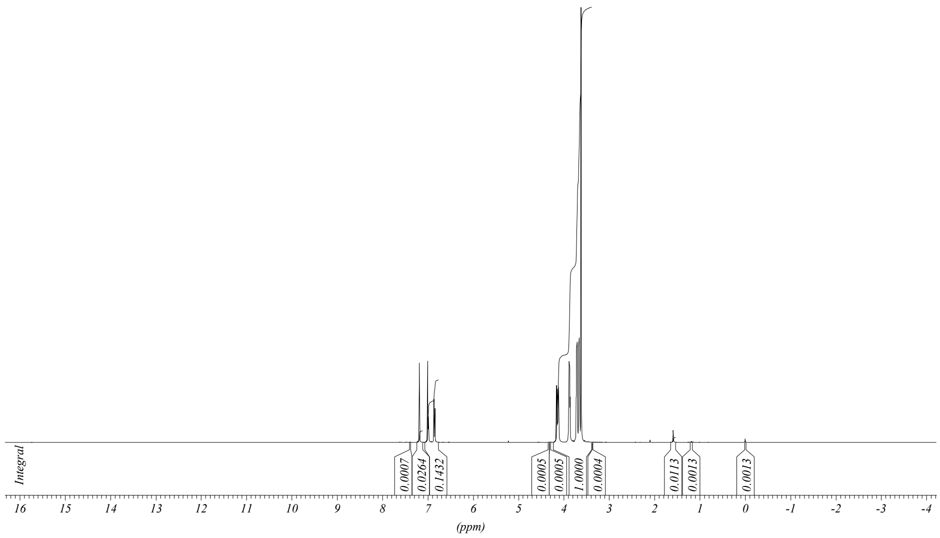
4-[4’-dibenzo-24-crown-8]dibenzo-24-crown-8 ether (10).
To a stirred solution of 4-iodo-dibenzo-18-crown-6 ether (**9**) (115 mg, 0.2 mmol) in THF (5 mL) at 0 ºC was added ^{i}PrMgCl (0.1 mL of a 2M solution in THF) dropwise over 2 min. The solution was stirred at 0

ºC for 2 h before addition of a solution of $ZnBr_2$ (47 mg, 0.21 mmol) in THF (2 mL) dropwise over 3 min. The mixture was stirred at 0 ºC for 45 min further. In a separate flask, a solution of 4-iododibenzo-18-crown-6 ether (**9**) (115 mg, 0.2 mmol) and $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) in THF (2 mL) was prepared and stirred at room temperature for 5 min before dropwise addition, at 0 ºC, to the aryl zinc reagent prepared above. The ice bath was immediately removed and the mixture allowed to warm to room temperature before stirring overnight. The mixture was poured onto H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL) before drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (99:1 CH_2Cl_2:MeOH, basic Al_2O_3) gave the title compound as a white powder (146 mg, 82%).

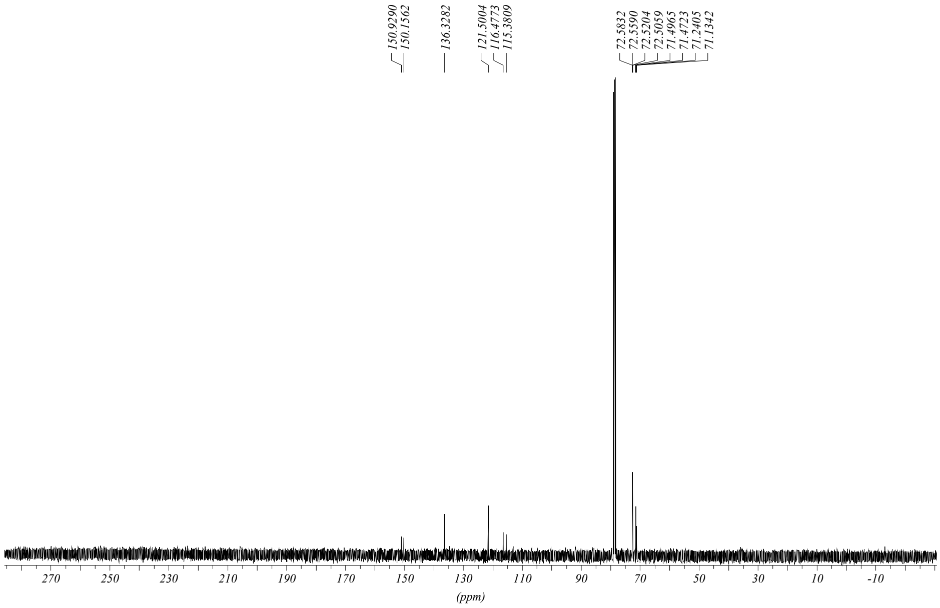
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 – 6.95 (4H, m), 6.87 – 6.78 (10H, m), 4.16 – 4.06 (16H, m), 3.88 – 3.82 (16H, m), 3.78 – 3.74 (16H, broad s). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 149.30 (s), 149.25 (s), 148.53 (s), 134.79 (s), 121.66 (d), 119.95 (d), 114.58 (d), 114.47 (d), 114.45 (d), 113.50 (d), 71.49 (t), 71.48 (t), 70.17 (t), 69.90 (t), 69.83 (t), 69.67 (t), 69.65 (t). IR (solid): ν = 1504 (m), 1258 (s), 1122 (s) cm^{-1}. Melting point: 151 – 152 °C (CH_2Cl_2). LRMS (ES+): m/z = 470 (M + 2Na$^+$, 100%), 917 (M + Na$^+$, 28%). HRMS (ES+): $C_{48}H_{62}O_{16}Na$ requires m/z = 917.3930. Found 917.3933.

4-[4'-benzo-18-crown-6]benzo-18-crown-6 ether (4a).

^{1}H NMR (400 MHz, $CDCl_3$):

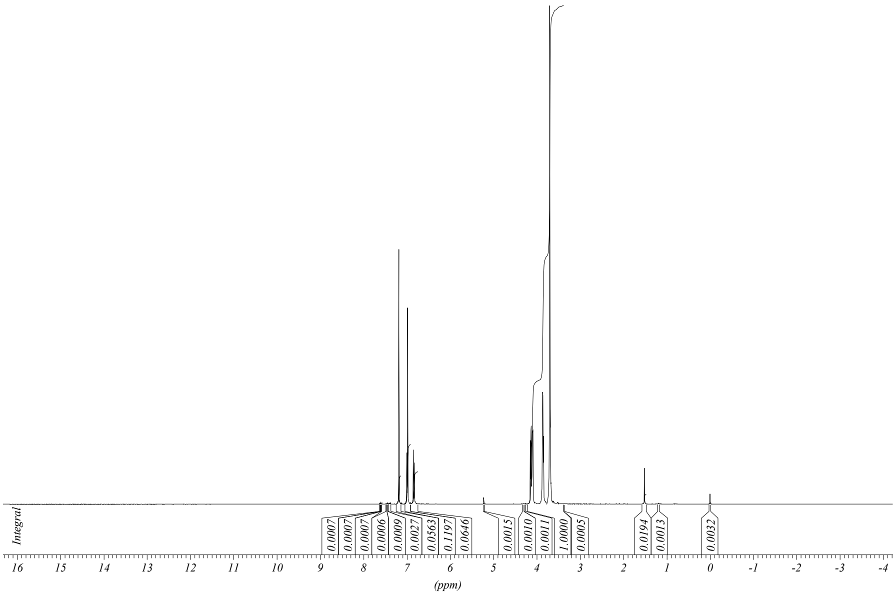


^{13}C NMR (100.5 MHz, $CDCl_3$):

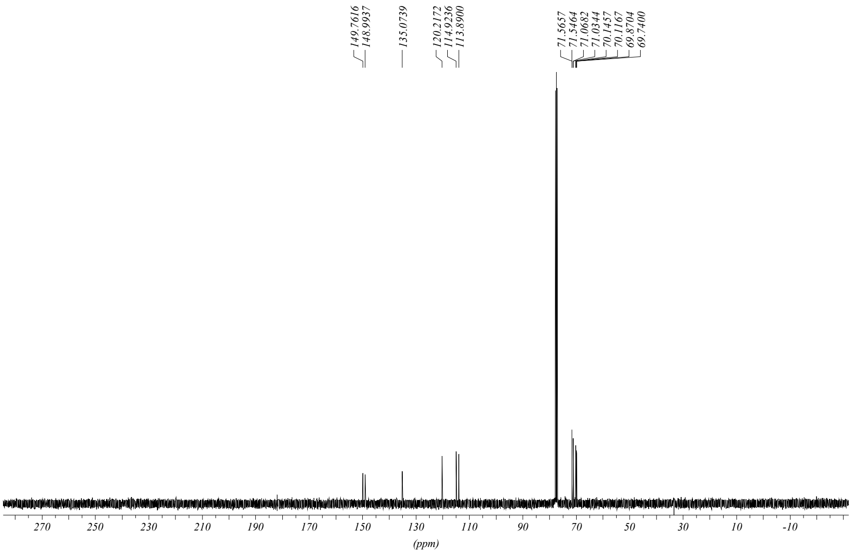


4-[4’-benzo-15-crown-5]benzo-15-crown-5 ether (4b).

^{1}H NMR (400 MHz, $CDCl_3$):

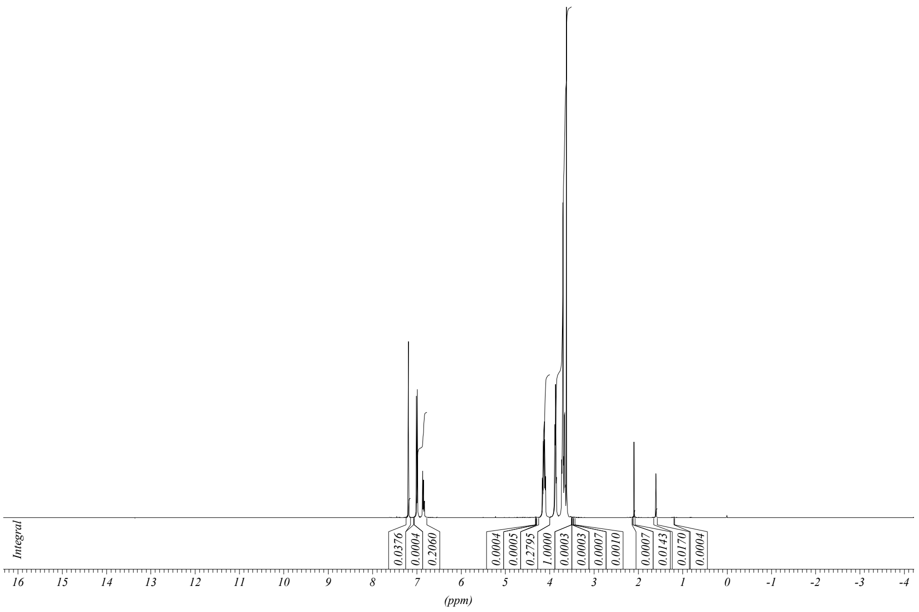


^{13}C NMR (100.5 MHz, $CDCl_3$):

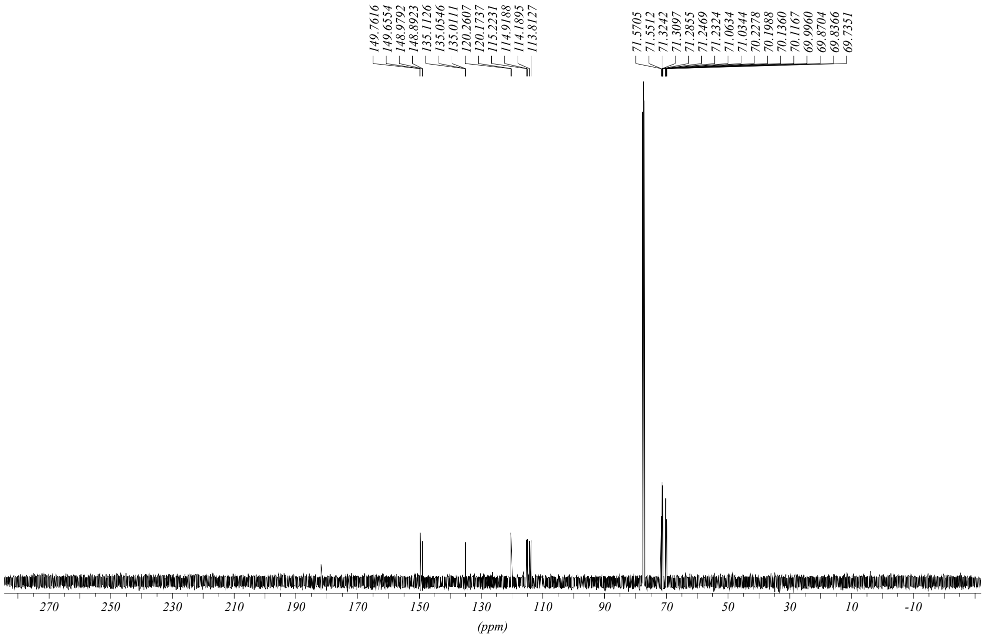


4-[4’-benzo-15-crown-5]benzo-18-crown-6 ether (4c).

^{1}H NMR (400 MHz, CDCl$_3$):

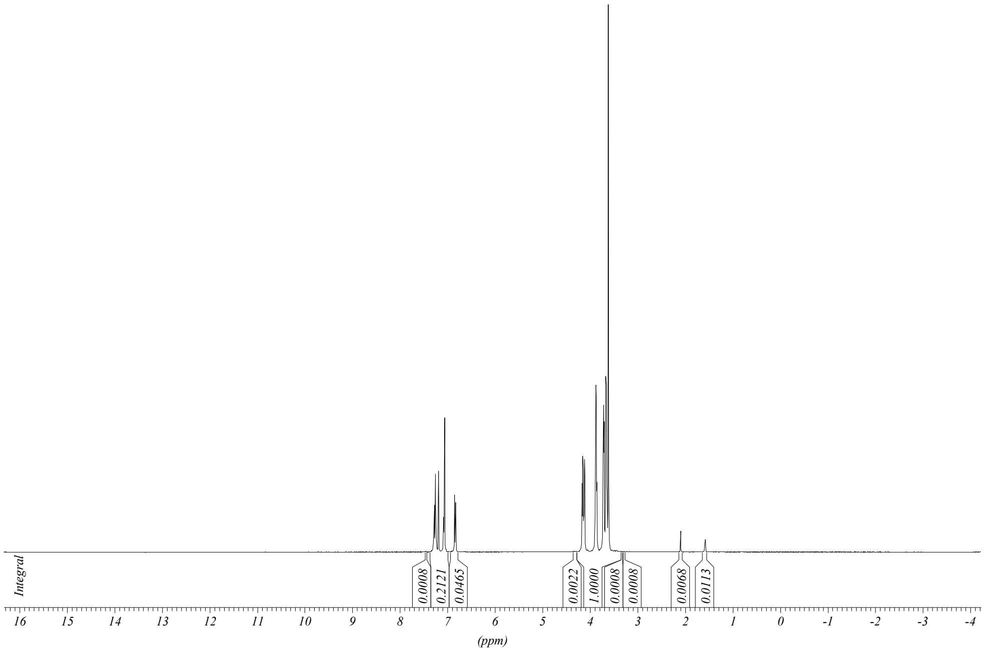


^{13}C NMR (100.5 MHz, CDCl$_3$):

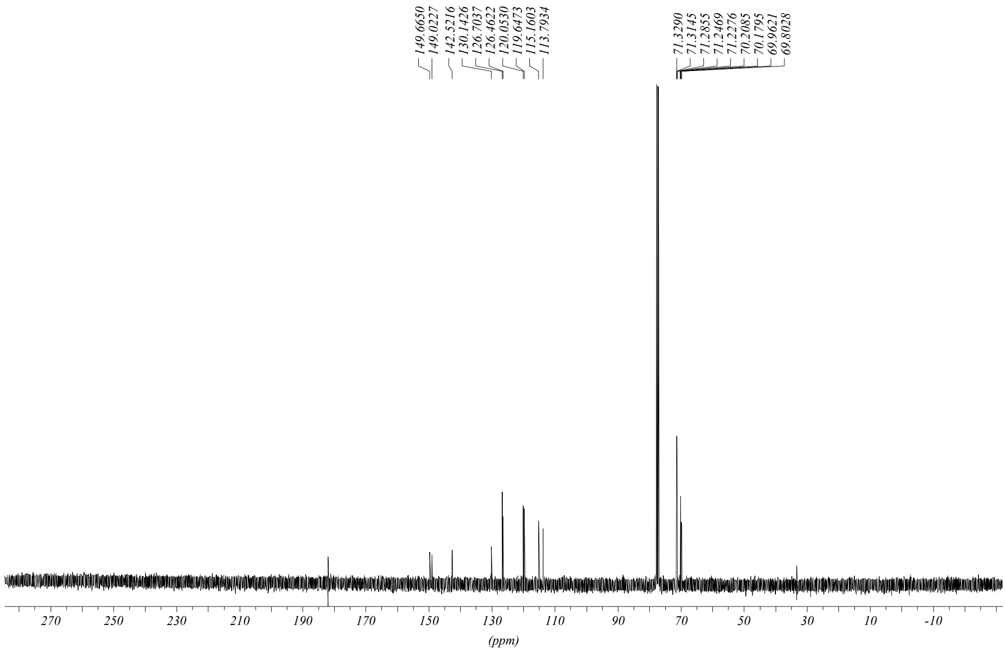


4-[3-thiophene]benzo-18-crown-6 ether (5).

^{1}H NMR (400 MHz, $CDCl_3$):

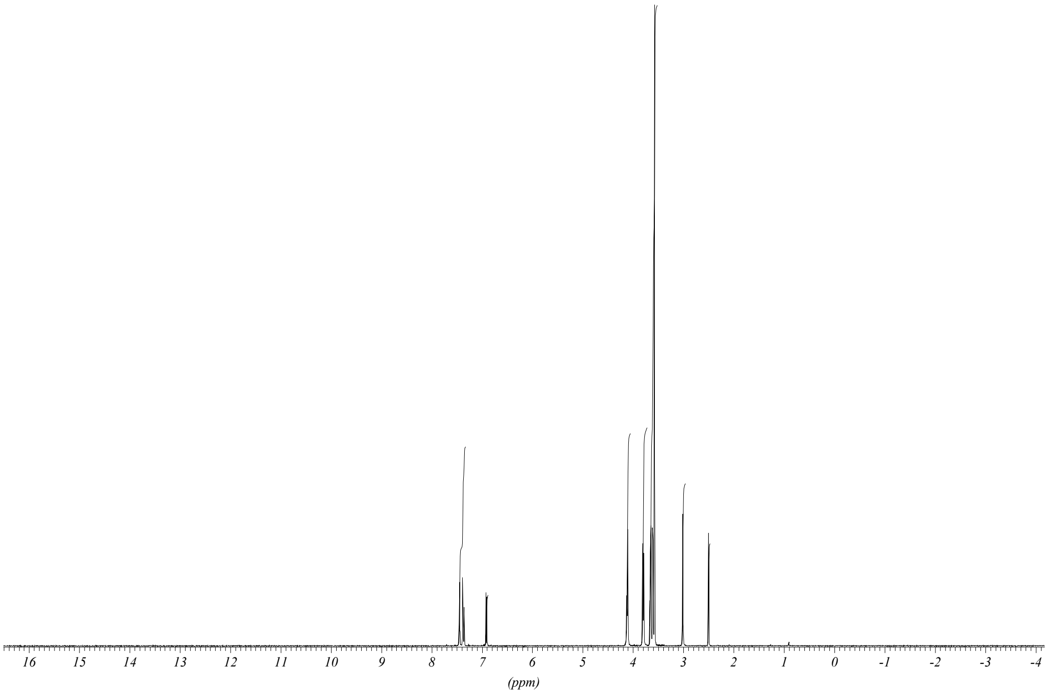


^{13}C NMR (100.5 MHz, $CDCl_3$):

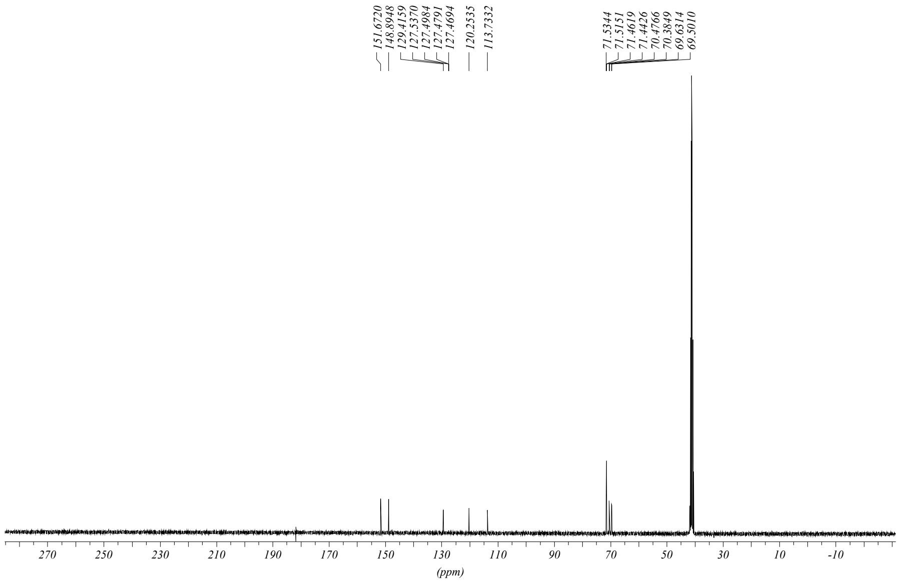


Benzo-18-crown-6 ether(4-boronic acid) (6a).

^{1}H NMR (400 MHz, DMSO, 70 ºC):

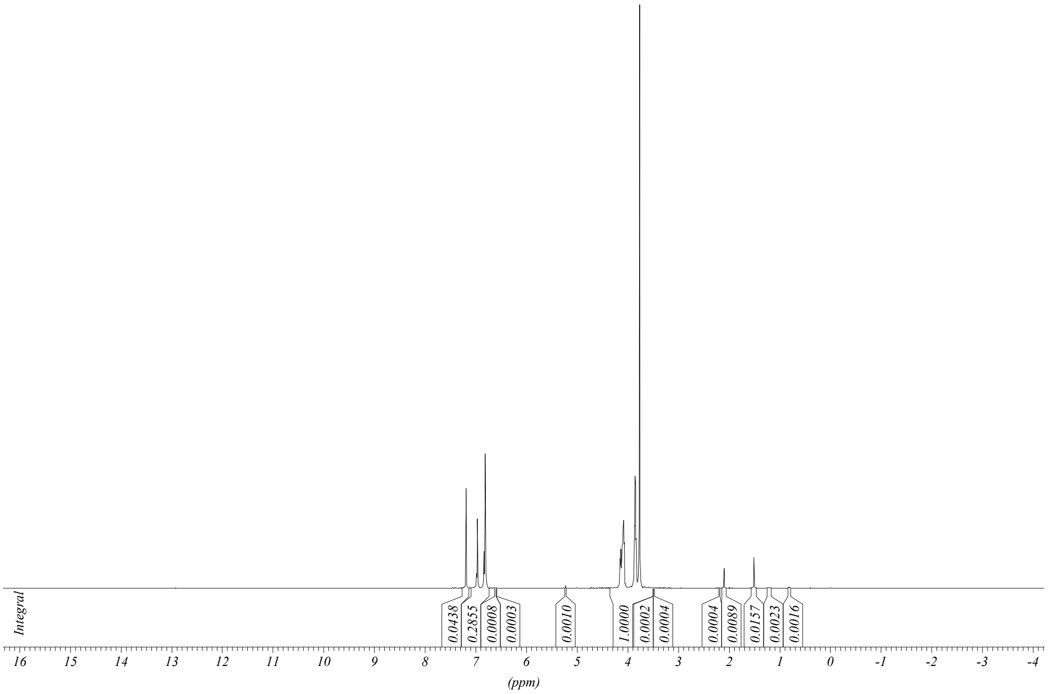


^{13}C NMR (100.5 MHz, DMSO):



4-[4'-dibenzo-24-crown-8]dibenzo-24-crown-8 ether (10).

^{1}H NMR (400 MHz, CDCl$_3$):



^{13}C NMR (100.5 MHz, CDCl$_3$):