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Rapid synthesis of hydrogen bond templated handcuff rotaxanes†

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The rapid synthesis of hydrogen bond templated handcuff rotaxanes is described. The isolated rotaxanes were characterized by NMR and IR spectroscopies and high resolution mass spectrometry. This report represents a rare demonstration of preparing (2)handcuff [2]rotaxanes by covalently linking separate axes threaded through the rings of a bis-macrocycle by use of the copper catalyzed azide–alkyne cycloaddition (CuAAC) reaction.

Introduction

Demand for synthetic routes that rapidly lead to [2]rotaxanes (a macrocyclic ring trapped on a stoppered axle) and [2]catenanes (two interlocked macrocyclic rings) – the archetypal classes of mechanically interlocked molecule (MIM)¹ – is driven by their deployment in a range of arena including host–guest recognition,² catalysis³ and biological systems⁴ exploiting their unusual three-dimensional molecular structures and (on occasion) controlled motion of their interlocked components. However, by incorporating more interlocked components and/or installing covalent linkages, an exotic range of MIM architectures exists. Amongst these are mechanically interlocked molecular “handcuffs”.⁵ (2)Handcuff [2]rotaxanes consist of an axle threaded through two covalently linked macrocycles. They are typically prepared by stoppering a single axle component passing through both rings of a bis-macrocycle⁶ but have also been synthesized by linking the rings of a [3]rotaxane⁷ and the linking of separate axes passing through each ring of a bis-macrocycle.^{8,9} Hinting at potential nanotechnological applications, the relative motion of the interlocked components of a few (2)handcuff [2]rotaxanes has been studied.^{6a,d,e}

Our group has reported on the rapid synthesis of [2]rotaxanes by copper catalyzed azide–alkyne cycloaddition (CuAAC) stoppering of a hydrogen bond templated pseudorotaxane consisting of a simple aromatic amide azide threading through an isophthalamide macrocycle.^{10,11} We envisioned that adapting such a methodology by use of an analogous bis-macrocycle and a bis-alkyne rather than an alkyne stopper could afford

(2)handcuff [2]rotaxanes in a short synthetic pathway (Fig. 1). This approach would represent an example of one of the rarely used strategies to prepare (2)handcuff [2]rotaxanes, namely covalently linking separate axes passing through each ring of a bis-macrocycle.⁸ Here we report on the successful preparation and characterization of such handcuff rotaxanes.

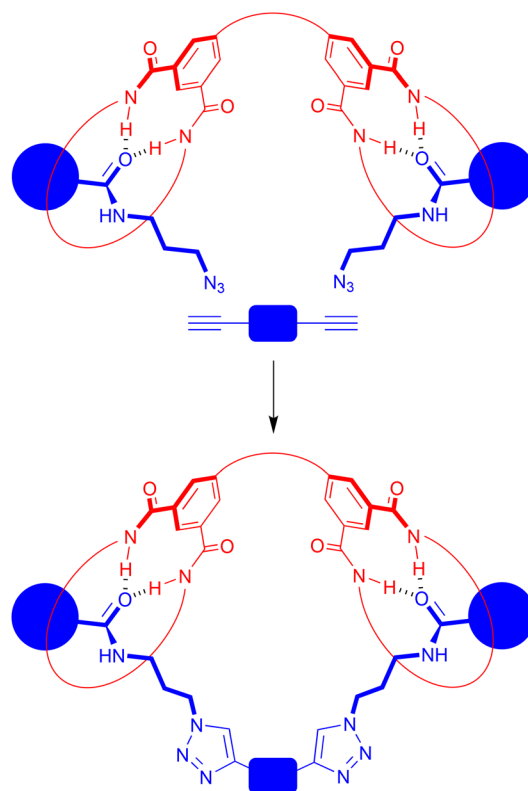


Fig. 1 Schematic representation of the synthesis of a hydrogen bond templated (2)handcuff [2]rotaxane by covalently linking separate amide axes passing through each ring of a bis-isophthalamide bis-macrocycle.

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†Electronic supplementary information (ESI) available: Further detail of synthetic investigations; copies of characterization spectra; crystallographic data for bis-macrocycle **BM2**. CCDC 2343052. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ob00672k>



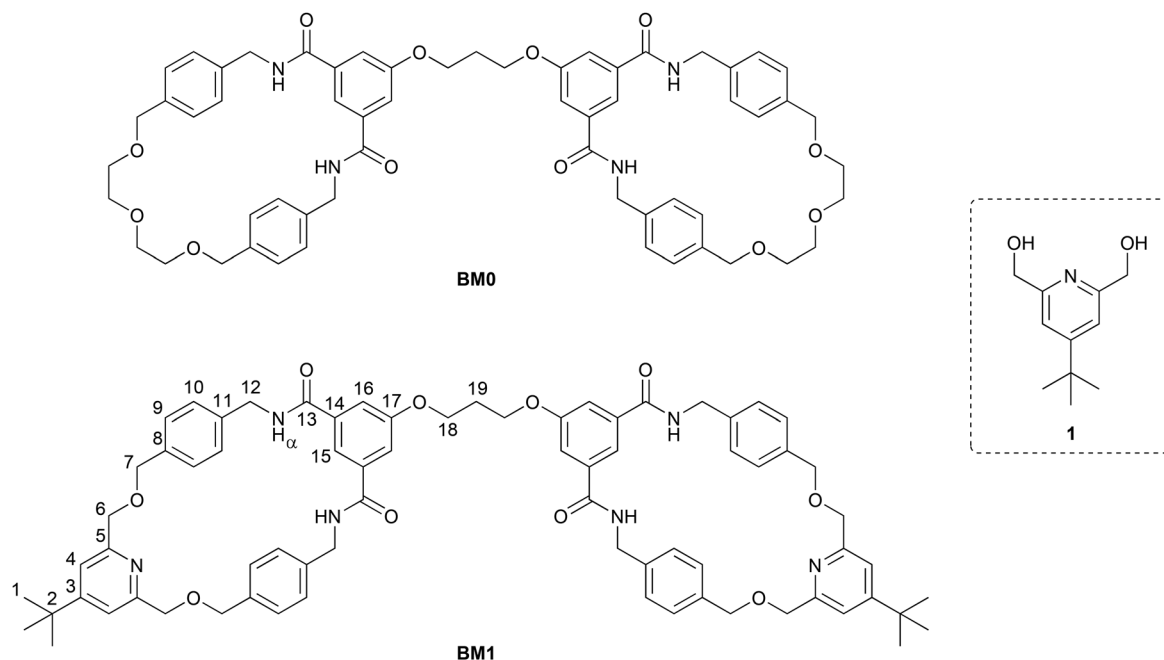


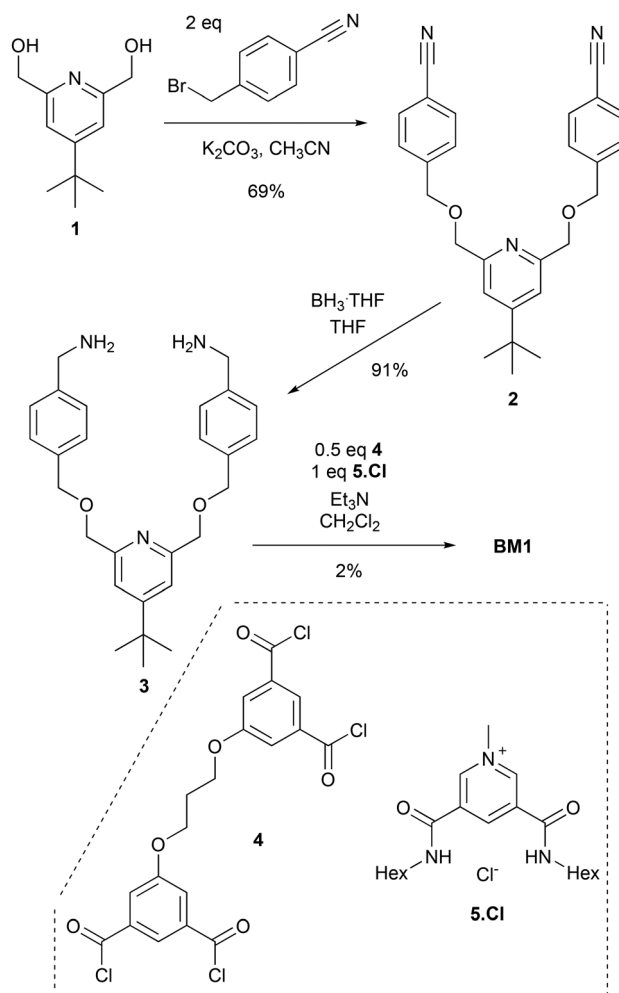
Fig. 2 Structures of bis-macrocycles **BM0** and **BM1** and precursor **1**.

Results and discussion

The design of a suitable bis-macrocycle **BM1**, consisting of two linked isophthalamide macrocycles, is presented in Fig. 2. Initial experiments had indicated that the analogous glycol bis-macrocycle **BM0** was highly insoluble.¹² However, the recent report¹³ of the synthesis of 4-(1,1-dimethylethyl)-2,6-pyridinedimethanol **1**, inspired us to prepare **BM1**, in the hope that the *t*-butyl substituted pyridyl rings would enhance solubility of the bis-macrocycle.

We initially targeted preparation of **BM1** by a “one-pot” double cyclization strategy using a 2:1 ratio of novel bis-amine precursor **3** to tetra-acid chloride unit **4**¹⁴ (Scheme 1). A solution containing equimolar equivalents of bis-amine **2** and methyl pyridinium template **5.Cl**¹⁵ and excess Et₃N in CH₂Cl₂ was prepared. To this solution was added dropwise a solution with 0.5 equivalents of tetra-acid chloride **4** in CH₂Cl₂. Upon aqueous work-up and chromatographic purification, the target bis-macrocycle **BM1** was isolated in a very low 2% yield. A variety of reaction conditions were screened (see ESI, p. S2†), but without any improvement in the yield of **BM1**.

Considering the extremely low yield of the final step of the previous synthesis, attention towards an alternative synthesis of bis-macrocycle **BM1**. To begin, equimolar equivalents of bis-amine **3**, methyl pyridinium template **5.Cl**, with excess Et₃N were dissolved in CH₂Cl₂. To this solution was added dropwise a solution of TBDMS-protected 5-hydroxyisophthaloyl chloride **6**¹⁶ in CH₂Cl₂. Upon aqueous work-up and chromatographic purification the TBDMS-protected macrocycle **7** was afforded in a moderate 15% yield. Deprotection of the TBDMS group was performed by reacting macrocycle **7** with excess TBAF,



Scheme 1 Synthesis of bis-macrocycle **BM1**.

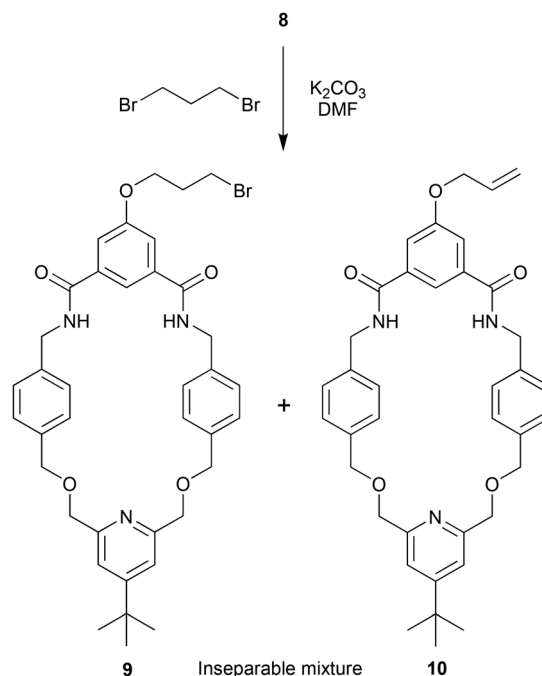


affording the deprotected phenol macrocycle **8** in almost quantitative – 96% – yield (Scheme 2).

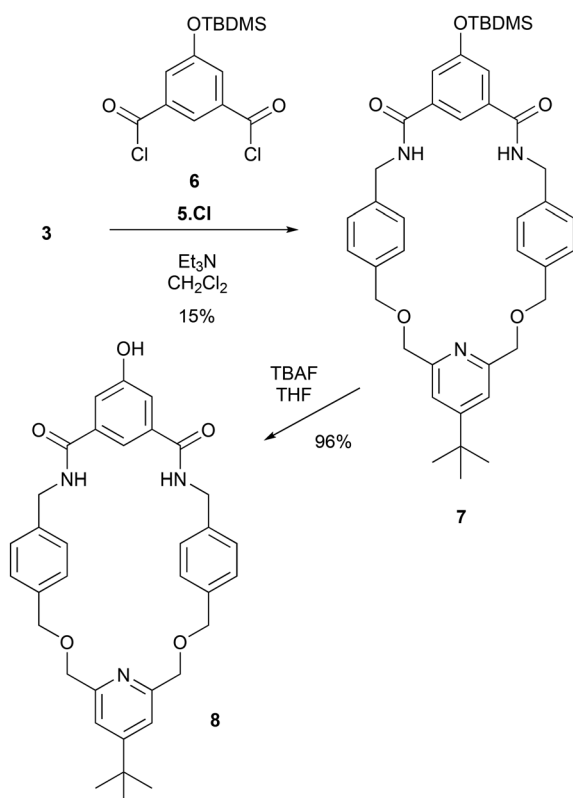
With macrocycle **8** in hand, attempts at the synthesis of the bis-macrocycle **BM1** were undertaken. Phenol macrocycle **8**, 1,3-dibromopropane and K_2CO_3 were added to DMF, the mixture then being heated to 80 °C for 16 hours. Following aqueous work-up and purification by column chromatography it was found the reaction did not afford the desired bis-macrocycle, but a mixture of mono-alkylated **9** and mono-alkylated elimination product **10** (Scheme 3).¹⁷

In response to this setback a new bis-macrocycle **BM2** was targeted (Scheme 4). Phenol macrocycle **8**, diethylene glycol di(*p*-toluenesulfonate) **9**¹⁸ and K_2CO_3 were added to DMF. After heating the reaction to 80 °C for 16 hours, aqueous work-up and chromatographic purification, target **BM2** was isolated in a pleasing 67% yield. A single crystal suitable for X-ray crystallography was grown from a chloroform solution, the solved structure confirming the anticipated bond connectivity (see inset in Scheme 4).

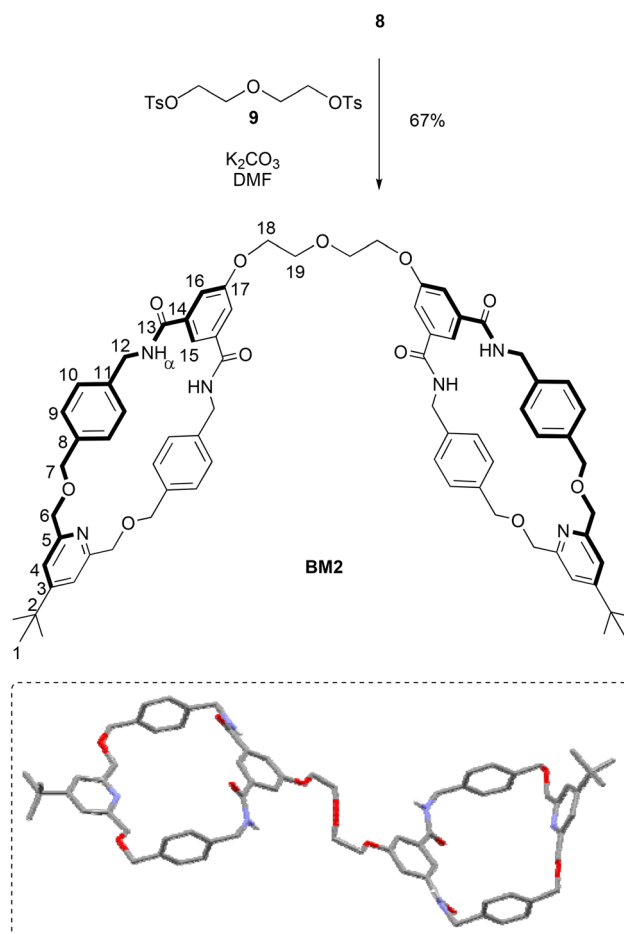
The synthesis of (2)handcuff [2]rotaxanes was then attempted (Scheme 5). This involved dissolving each bis-macrocycle with 2.4 equivalents of azide **10**^{10a} in CH_2Cl_2 and allowing to stir for 10 minutes, so the pseudorotaxane complex could form. Then, 1.2 equivalents of bis-alkyne **11**¹⁹ $Cu(CH_3CN)_4BF_4$, TBTA and DIPEA were added to facilitate the CuAAC reaction, and after stirring overnight, aqueous work-up and chromatographic separation by preparative TLC handcuff rotaxanes **HR1** and **HR2** were isolated in ~30%²⁰ and 15% yields respectively.



Scheme 3 Products **9** and **10** of attempted synthesis of bis-macrocycle **BM1** from macrocycle **8**.

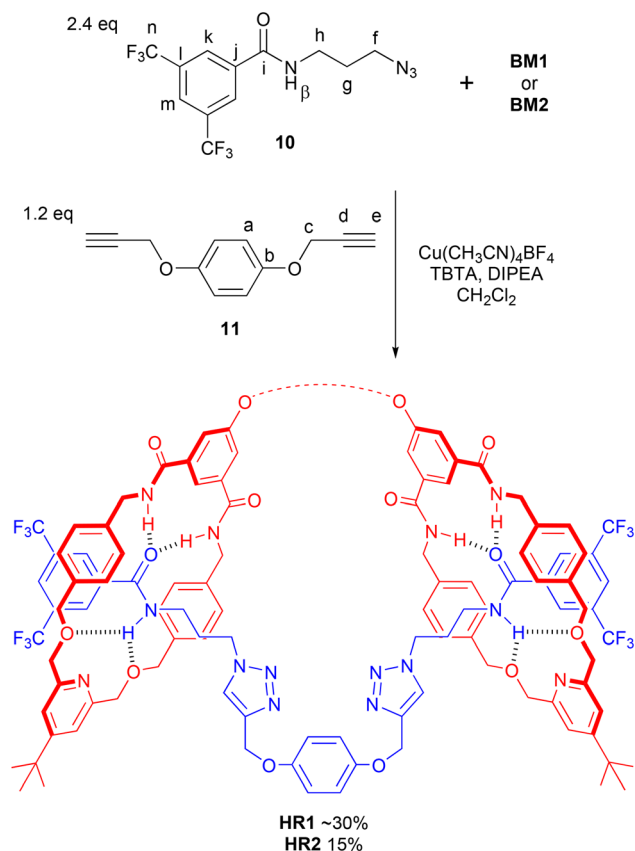


Scheme 2 Synthesis of macrocycle **8**.



Scheme 4 Synthesis of bis-macrocycle **BM2**. Inset: X-ray structure of **BM2**.





Scheme 5 Synthesis of handcuff rotaxanes **HR1** and **HR2**.

The novel handcuff rotaxanes were characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy and electrospray high resolution mass spectrometry. The ^1H NMR spectra of handcuff rotaxane **HR2**, along with those of bis-macrocycle **BM2** and non-threaded axle **Ax**²¹ for comparison are shown in Fig. 3. Upon studying the stacked spectra, evidence for the formation of handcuff rotaxane is observed. The upfield shift and splitting of aromatic protons 9 and 10 in the interlocked molecule compared to non-interlocked bis-macrocycle **BM2** is consistent with the axle passing between the aromatic rings of each macrocyclic ring. The downfield shift of proton 15 and the amide protons α of the bis-macrocycle in the handcuff rotaxane are indicative of interactions with a hydrogen bond acceptor on the threaded axle. In addition, the splitting of protons 7 and 12 arises from the desymmetrization caused by the axle component threaded through the two macrocyclic cavities. The interlocked architecture of the handcuff rotaxane **HR2** was further supported by multiple through-space correlations between signals arising from protons in the two components as observed in the ^1H - ^1H ROESY NMR spectrum (see ESI, p. S20†). In addition, the molecular ion peak for the target rotaxane is also observed in the electrospray HRMS (see ESI, p. S19†). Similar observations and conclusions regarding the formation of handcuff rotaxane **HR1** can also be seen by, *e.g.*, comparing its spectra with its analogous bis-macrocycle **BM1** and axle **Ax** (see ESI, pp. S15–S17 and S23†).

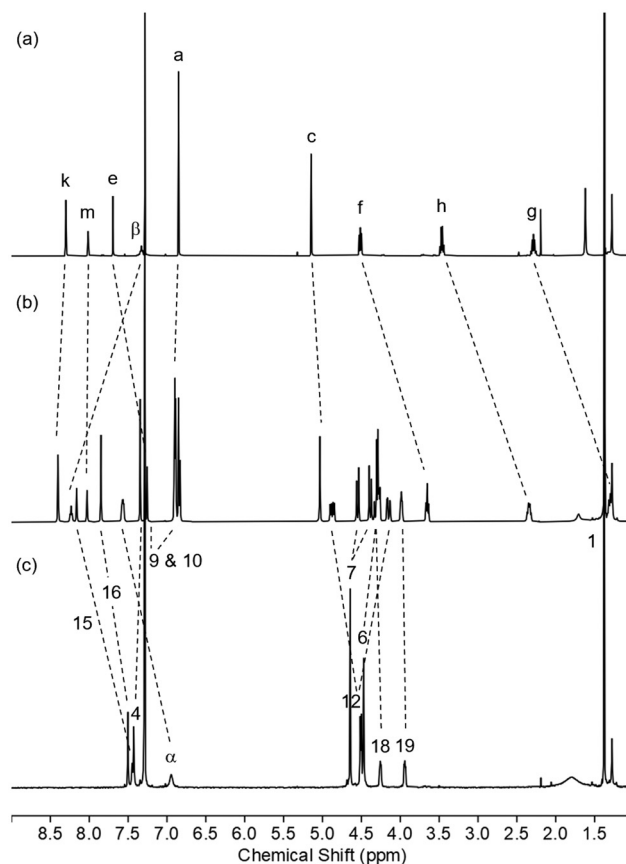


Fig. 3 ^1H NMR spectra of (a) axle **Ax**, (b) handcuff rotaxane **HR2** and (c) bis-macrocycle **BM2** (CDCl_3 , 400 MHz, 298 K). For atom labels see Schemes 4 and 5.

Conclusions

We have successfully synthesized novel hydrogen bond templated (2)handcuff [2]rotaxanes by a rare application of the strategy to covalently link axles threaded through each ring of a bis-macrocycle. Indeed, careful comparison to the only previously reported example of this synthetic strategy to prepare (2)handcuff [2]rotaxanes,⁸ reveals a unique feature of our design – namely the use of a separate molecule to link the two axle components. Successful preparation of the rotaxanes was confirmed by NMR spectroscopy and electrospray HRMS. Investigations into deploying our hydrogen bond templation methodologies to prepare – and functionally deploy – exotic interlocked structures are continuing in our laboratories.

Experimental

General information

All reagents and solvents were used as obtained from commercial suppliers, unless otherwise stated. Dry solvents, Et_3N and DIPEA were purchased dry and stored under an



inert atmosphere. $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$ was stored in a desiccator over P_4O_{10} . Petrol refers to the fractions of petroleum that boil between 40 °C and 60 °C. Deionized water was used in all cases. All aqueous solutions are saturated unless otherwise stated.

Silica gel with a 60 Å particle size was used as the stationary phase for column chromatography. Analytical TLC was used to monitor the progress of column chromatography, with analytical TLC plates examined under short wavelength (254 nm) UV light or staining with potassium permanganate and/or phosphomolybdic acid solutions. Preparatory TLC was carried out on silica gel possessing a fluorescent indicator to allow for examination with short wavelength UV light.

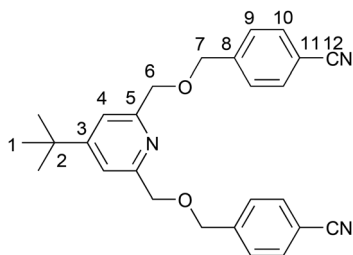
IR spectra were recorded on an Agilent Technologies Cary 640 FTIR spectrometer. NMR spectra were recorded on a Bruker AVANCE III 400 at 298 K (unless otherwise stated). Mass spectra were recorded on a Shimadzu LCMS IT ToF instrument at Lancaster University and Bruker Compact ToF coupled to an Agilent 1260 Infinity LC at the University of York. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected.

4-(1,1-Dimethylethyl)-2,6-pyridinedimethanol **1**,¹³ tetra-acid chloride **4**,¹⁴ methyl pyridinium chloride template **5.Cl**,¹⁵ acid chloride **6**,¹⁶ diethylene glycol di(*p*-toluenesulfonate) **9**,¹⁸ azide **10**,^{10a} bis-alkyne **11**¹⁹ and axle **Ax**²¹ were synthesized by adaptation of previously reported procedures.

Experimental procedures

Bis-nitrile 2

4-(1,1-Dimethylethyl)-2,6-pyridinedimethanol **1** (7.17 g, 36.7 mmol) was dissolved in dry THF (100 mL) under argon and cooled to 0 °C. NaH (5.15 g, 128.7 mmol, 60% dispersion in mineral oil) was added portion wise and left to stir until foaming subsided. 4-(Bromomethyl)benzonitrile (18.0 g, 91.9 mmol) was then added and the reaction warmed to room temperature and stirred under argon for 18 hours. The reaction was then quenched with water and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (EtOAc/Petrol 1 : 1) to afford the *title product* as a yellow solid (10.7 g, 69%).

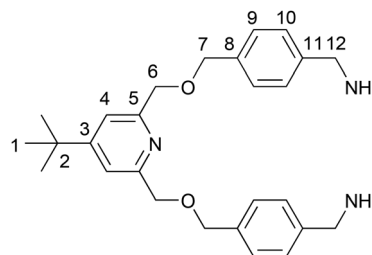


R_f : 0.22 [EtOAc/Petrol 1 : 1]. **m.p.** 85–87 °C. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 2961 (C–H), 2230 (C≡N), 1604 (C–O), 1347 (C–O), 1123 (C–H). δ_{H} (400 MHz, CDCl_3): 7.67 (4H, d, J = 8.2 Hz, H^{10}),

7.51 (4H, d, J = 8.2 Hz, H^9), 7.39 (2H, s, H^4), 4.72 (4H, s, H^7), 4.69 (4H, s, H^6), 1.34 (9H, s, H^1). δ_{C} (100 MHz, CDCl_3): 161.8 (C^3), 157.1 (C^5), 143.6 (C^8), 132.2 (C^{10}), 127.8 (C^9), 118.7 (C^{12}), 117.4 (C^4), 111.4 (C^{11}), 73.8 (C^6), 71.9 (C^7), 34.9 (C^2), 30.6 (C^1). m/z (ESI): 448.1982 [$\text{M} + \text{Na}$]⁺, $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_2$ requires 448.1995.

Bis-amine 3

Bis-nitrile **2** (1.00 g, 2.35 mmol) was dissolved in dry THF (20 mL) under nitrogen and cooled to 0 °C. $\text{BH}_3\cdot\text{THF}$ (1 M in THF, 13 mL, 11.7 mmol) was added dropwise, then the reaction was allowed to stir for 1 hour. The reaction was then warmed to 70 °C and stirred for a further 18 hours. Upon cooling to room temperature, the reaction was quenched with conc. HCl (4 mL). All volatiles were then removed under reduced pressure to afford a white solid. The crude material was re-dissolved in water (50 mL) and washed with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 12 with 10% NaOH (aq.) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo* to afford the *title product* (925 mg, apparent yield 91%) as a light green oil. NMR spectral analysis reveals some impurities, but material taken on without further purification.



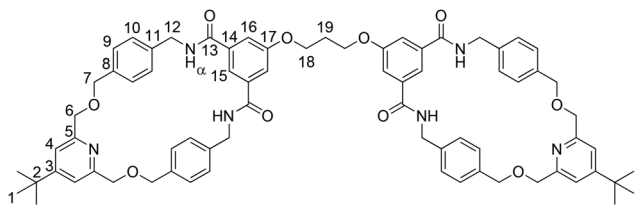
$\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 2957 (C–H), 2857 (C–H), 2372 (N–H), 1604 (C–O), 1347 (C–O), 1097 (C–O). δ_{H} (400 MHz, CDCl_3): 7.41–7.36 (6H, m, H^4 & H^9), 7.32 (4H, d, J = 8.2 Hz, H^{10}), 4.66 (4H, s, H^6), 4.65 (4H, s, H^7), 3.88 (4H, s, H^{12}), 1.34 (9H, s, H^1). δ_{C} (100 MHz, CDCl_3): 161.4 (C^3), 157.6 (C^5), 142.9 (C^{11}), 136.5 (C^8), 128.2 (C^9), 127.1 (C^{10}), 117.1 (C^4), 73.2 (C^6), 72.7 (C^7), 46.3 (C^{12}), 34.9 (C^2), 30.6 (C^1). m/z (ESI): 456.2619 [$\text{M} + \text{Na}$]⁺, $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_2$ requires 456.2621.

Bis-macrocycle BM1

To a solution of bis-amine **3** (750 mg, 1.73 mmol) and methyl-pyridinium template **5.Cl** (662 mg, 1.73 mmol) in dry CH_2Cl_2 (50 mL) under argon was added Et_3N (1.20 mL, 8.65 mmol), followed immediately by a dropwise solution of tetra-acid chloride **4** (350 mg, 0.86 mmol) in dry CH_2Cl_2 (20 mL). The reaction was stirred for 1.5 hours at room temperature, then washed with 10% citric acid (2 × 50 mL) and brine (1 × 50 mL). The reaction mixture was then dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98 : 2), followed by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$



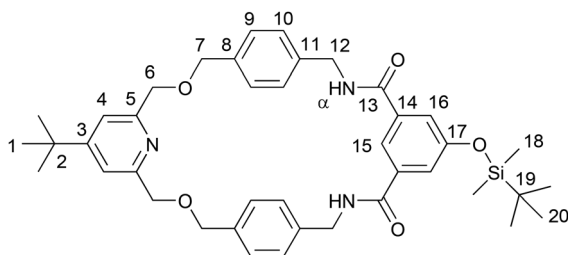
98:2–96:4) to afford the *title product* as a colourless film (18 mg, 2%).



R_f: 0.32 [CH₂Cl₂/CH₃OH 98 : 2]. $\nu_{\max}/\text{cm}^{-1}$ (neat): 3330 (N–H), 2922 (C–H), 2860 (C–H), 1645 (C=O), 1515 (C–O), 1066 (C–O). δ_{H} (400 MHz, CDCl₃): 7.57 (4H, s, H¹⁶), 7.42 (2H, s, H¹⁵), 7.36 (4H, s, H⁴), 7.29 (16H, s, H⁹ & H¹⁰), 6.93 (4H, bs, H^α), 4.64 (8H, s, H⁷), 4.55 (8H, d, *J* = 5.4 Hz, H¹²), 4.40 (8H, s, H⁶), 4.22 (4H, t, *J* = 5.5 Hz, H¹⁸), 2.26 (2H, bs, H¹⁹), 1.36 (18H, s, H¹). δ_{C} (100 MHz, CDCl₃): 166.7 (C¹³), 161.5 (C³), 159.2 (C¹⁷), 157.1 (C⁵), 137.5 (C¹¹), 137.0 (C⁸), 136.2 (C¹⁴), 128.9 (C⁹), 128.6 (C¹⁰), 117.3 (C⁴), 116.8 (C¹⁶), 116.5 (C¹⁵), 72.2 (C⁷), 71.7 (C⁶), 64.4 (C¹⁸), 44.2 (C¹²), 34.9 (C²), 30.6 (C¹), 29.0 (C¹⁹). **m/z** (ESI): 1199.5873 [M + H]⁺, C₇₃H₇₉N₆O₁₀ requires 1199.5852.

TBDMS-protected macrocycle 7

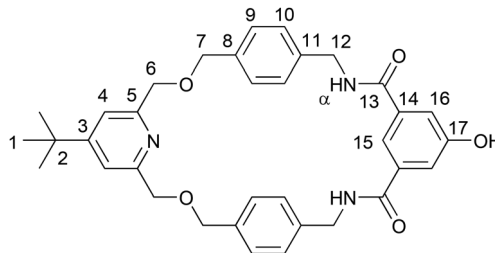
To a solution of bis-amine 3 (860 mg, 1.98 mmol) and methylpyridinium template 5.Cl (758 mg, 1.98 mmol) in dry CH₂Cl₂ (60 mL) under argon was added Et₃N (0.68 mL, 4.95 mmol), followed immediately by a dropwise solution of TBDMS-protected acid chloride 6 (589 mg, 1.99 mmol) in dry CH₂Cl₂ (20 mL). The reaction was stirred for 1.5 hours at room temperature, then washed with 0.5 M HCl (2 × 40 mL) and brine (1 × 40 mL). The reaction mixture was then dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (CH₂Cl₂/CH₃OH 98 : 2) to afford the *title product* as a colourless solid (240 mg, 17%).



R_f: 0.41 [CH₂Cl₂/CH₃OH 98 : 2]. **m.p.** 145–147 °C. $\nu_{\max}/\text{cm}^{-1}$ (neat): 3300 (N–H), 2952 (C–H), 2857 (C–H), 1649 (C–O), 1101 (C–O), 836 (Si–C). δ_{H} (400 MHz, CDCl₃): 7.52 (2H, d, *J* = 1.3 Hz, H¹⁶), 7.41 (3H, app s, H⁴ & H¹⁵), 7.32 (8H, s, H⁹ & H¹⁰), 6.41 (2H, bs, H^α), 4.67 (4H, s, H⁷), 4.58 (4H, d, *J* = 5.6 Hz, H¹²), 4.45 (4H, s, H⁶), 1.37 (9H, s, H¹), 1.02 (9H, s, H²⁰), 0.27 (6H, s, H¹⁸). δ_{C} (100 MHz, CDCl₃): 166.3 (C¹³), 162.1 (C³), 156.5 (C¹⁷), 137.5 (C¹¹), 137.1 (C⁸), 136.3 (C¹⁴), 129.0 (C⁹), 128.7 (C¹⁰), 122.4 (C¹⁶), 117.5 (C⁴), 116.4 (C¹⁵), 72.2 (C⁷), 71.5 (C⁶), 44.2 (C¹²), 35.0 (C²), 30.6 (C¹), 25.6 (C²⁰), 18.1 (C¹⁹), –4.3 (C¹⁸). **m/z** (ESI): 716.3511 [M + Na]⁺, C₄₁H₅₁N₃NaO₅Si requires 716.3490.

Phenol macrocycle 8

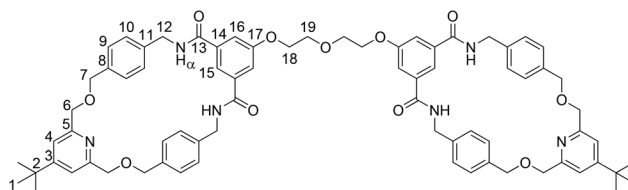
To a solution of TBDMS-protected macrocycle 7 (260 mg, 0.353 mmol) in dry THF (10 mL) was added TBAF (185 mg, 0.706 mmol). The reaction was stirred at room temperature for 2 hours then quenched with the addition of NH₄Cl (aq.). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (CH₂Cl₂/CH₃OH 98 : 2–95 : 5) to afford the *title product* as a colourless solid (196 mg, 96%).



R_f: 0.28 [CH₂Cl₂/CH₃OH 98 : 2]. **m.p.** 178–180 °C. $\nu_{\max}/\text{cm}^{-1}$ (neat): 3552 (N–H), 3281 (O–H), 2927 (C–H), 2338 (C–H), 1651 (C=O), 1101 (C–O). δ_{H} (400 MHz, 1 : 1 CDCl₃/CD₃OD): 7.52 (1H, t, *J* = 1.5 Hz, H¹⁵), 7.48 (2H, d, *J* = 1.5 Hz, H¹⁶), 7.42 (2H, s, H⁴), 7.31 (8H, s, H⁹ & H¹⁰), 4.65 (4H, s, H⁷), 4.55 (4H, s, H¹²), 4.41 (4H, s, H⁶), 1.36 (9H, s, H¹). δ_{C} (100 MHz, 1 : 1 CDCl₃/CD₃OD): 167.7 (C¹³), 162.3 (C³), 157.8 (C¹⁷), 156.8 (C⁵), 137.7 (C¹¹), 136.6 (C⁸), 135.7 (C¹⁴), 128.6 (C⁹), 128.1 (C¹⁰), 118.0 (C⁴), 117.8 (C¹⁶), 115.4 (C¹⁵), 72.1 (C⁷), 71.2 (C⁶), 43.6 (C¹²), 34.8 (C²), 30.1 (C¹). **m/z** (ESI): 602.2638 [M + Na]⁺, C₃₅H₃₇N₃NaO₅ requires 602.2625.

Bis-macrocycle BM2

To a solution of phenol macrocycle 8 (50 mg, 0.086 mmol) in dry DMF (5 mL) was added K₂CO₃. The solution was stirred for 5 minutes then diethylene glycol di(*p*-toluenesulfonate) 9 (18 mg, 0.043 mmol) was added. The reaction was heated at 80 °C under argon for 16 hours. The reaction was then cooled to room temperature and excess DMF removed *in vacuo*. The crude residue was dissolved in CH₂Cl₂ (15 mL) and washed with water (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (CH₂Cl₂/CH₃OH 98 : 2–96 : 4) to afford the *title product* as a colourless solid (35 mg, 67%).



R_f: 0.35 [CH₂Cl₂/CH₃OH 98 : 2]. **m.p.** 156–158 °C. $\nu_{\max}/\text{cm}^{-1}$ (neat): 3296 (N–H), 2968 (C–H), 2853 (C–H), 1647 (C=O), 1535 (C–O), 1101 (C–O). δ_{H} (400 MHz, CDCl₃): 7.45 (4H, s, H¹⁶), 7.41 (2H, s, H¹⁵), 7.36 (4H, s, H⁴), 7.30–7.23 (16H, m, H⁹ & H¹⁰),



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Data availability

Underlying data for this paper are provided in the Experimental section and ESI.† Electronic copies of NMR spectra (including fid files) will be available upon publication from: <https://doi.org/10.17635/lancaster/researchdata/663>. Crystallographic data for **BM2** has been deposited at CCDC (<https://ccdc.cam.ac.uk>) under structure number 2343052.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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