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Synthesis of novel enantiomerically pure trianglimine and trianglamine macrocycles

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Abstract—The synthesis of a series trianglimine macrocycles is described using a [3+3] cyclocondensation strategy between a 1,2-diamine and an aromatic dicarboxaldehyde. The novel compounds have been prepared in enantiomerically pure form and their ring sizes range from 30 to 42. © 2002 Published by Elsevier Science Ltd.

1. Introduction

The development of supramolecular chemistry has been driven mainly by the availability of suitable macrocyclic receptors. Once a class of macrocyclic receptors with a unique shape, distinct architecture and set of functional groups becomes widely available from natural or synthetic sources, it begins to inspire the imagination of supramolecular chemists to devise and synthesise novel sophisticated receptors, molecular machines and devices. Starting with Curtis' seminal synthesis of polyaza macrocycles,[1,2] continuing with Pederson's crown ethers and cryptands,[3,4] the cyclodextrins,[5] calix[*n*]arenes,[6–9] and curcubiturils,[10,11] each new class of macrocycle has led to a rapid development of innovative supramolecular chemistry and a considerable advancement in the field. The main requirement for a macrocycle suitable to make an impact on supramolecular chemistry is its ease of synthesis in sufficiently large quantities combined with a unique molecular architecture and a particular set of functional groups that allow further elaboration into more sophisticated structures. Chirality built into any macrocycle offers additional interesting features enabling the macrocycle to be used as a potential receptor for chiral recognition. It should be noted that chiral recognition for the separation of enantiomers might present the most profitable application of macrocyclic chemistry in economic terms.[12]

Gawronski and co-workers[13] have recently introduced a new synthetic strategy for the synthesis of large polyimine *meta*- and *para*-cyclophane type macrocycles using a [3+3] cyclocondensation strategy. Diastereomeric structures of this type of macrocycle have recently been reported by the Hodacova group.[14] Other isolated examples of [3+3] cyclocondensation strategies have been reported.[15] Intrigued by this approach we started investigating the scope and limitation of the concept and would like to report herein significant extensions to Gawronski's basic scheme, synthesising novel exciting and unusual macrocycles. Due to their unique triangular shape we would like to name this new class of macrocycles trianglimines and trianglamines, respectively.

2. Results and discussion

We considered that an extension of the trianglimine cavity in the plane defined by the three nitrogens as well as in the plane of the aromatic moiety would be worth investigating to obtain extended macrocycles in all three dimensions. Hence, we synthesised aromatic 4,4′-diformylbiphenyl **2** using a double lithium bromide exchange and 9,10-diformylanthracene **3**[16] using a published procedure.

The dicarboxaldehydes **2** and **3** were subjected to the macrocyclisation conditions using (1*R*,2*R*)-diaminocyclohexane **1** at 0.1 M concentration in dichloromethane. After heating under reflux for 4 h the macrocycles **4** and **5** could be isolated in good to excellent yields. A variety of linear oligomeric imines by-products were also formed.

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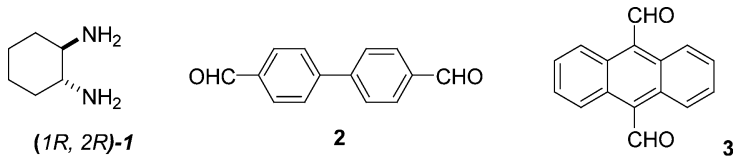
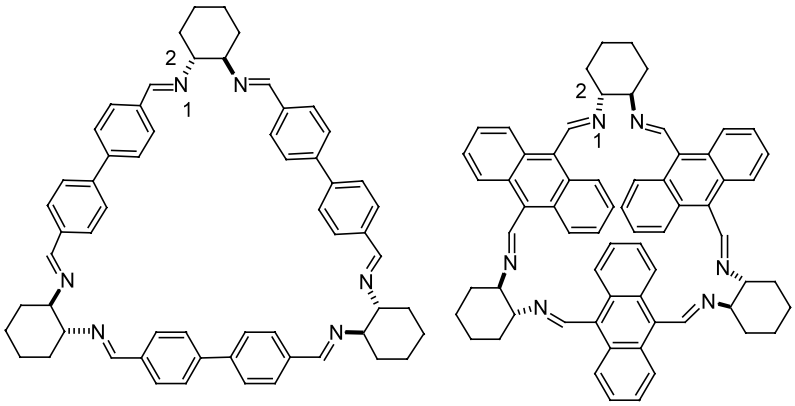


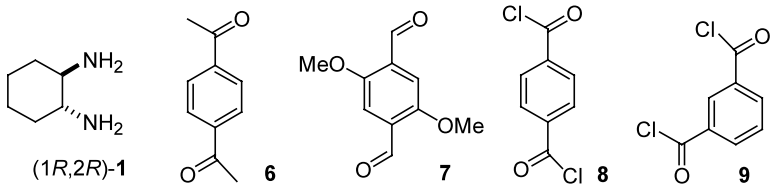
(1*R*, 2*R*)-**1** **2** **3**



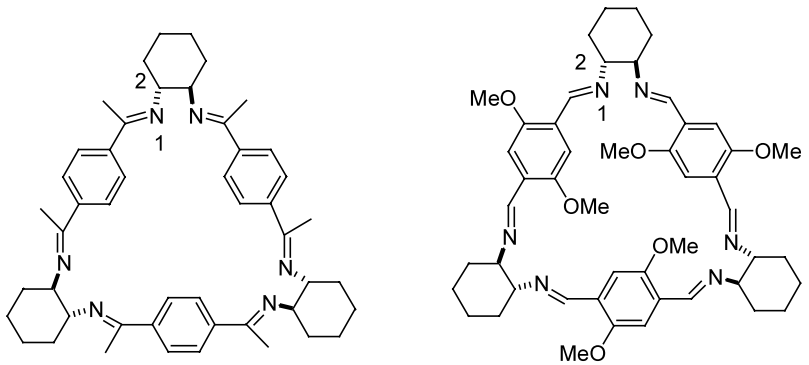
(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-**4** (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-**5**

However, the macrocycles could be isolated after simple crystallisation. The new macrocycles contain a 42-membered ring in the case of **4** and a 30- or 42-membered ring in **5** depending on the formality in counting ring sizes. Both compounds display in an ideal conformation perfect D_3 symmetry. The spectroscopic data support the structure in all aspects. The ^{1}H and ^{13}C NMR spectra show one set of signals as expected for the D_3 symmetry found in the macrocycles **4** and **5**. All signals are observed in the expected range. Interestingly the anthracene protons in compound **5** appear as a ABXY system due to the non-equivalence of the individual protons induced by a tilting of the anthracene plane with respect to the opposing 1,2-diaminocyclohexane moiety or restricted rotation around the C–C=N bonds of the substituted anthracene moiety. The ^{13}C NMR spectrum of **5** shows four CH signals in the aromatic region for identical reasons. At 100°C in DMSO-d_6 no changes of the NMR spectra are observed for compounds **4** and **5**, clearly indicating that anthracene inversion through the middle of the central hole does not take place. The IR spectra show a strong C=N vibration at 1642 cm^{-1} and the aromatic C–C bands indicate the high symmetry of the molecule. Most characteristically the LSIMS mass spectra show the expected molecular ions.

As a further extension to the [3+3] cyclocondensation concept, we attempted the cyclocondensation between (1*R*,2*R*)-**1** and 1,4-diacetylbenzene **6** or 1,4-dimethoxy-2,5-dicarboxaldehyde **7**, respectively. Both carbonyl compounds show a considerably reduced reactivity in comparison to the unsubstituted dialdehydes published by Gawronski and therefore represent more challenging



(1*R*,2*R*)-**1** **6** **7** **8** **9**



(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**10** (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**11**

substrates. After heating the reactants in refluxing dichloromethane for 1 day the [3+3] cyclocondensation between **1** and **6** gave the macrocyclic trianglimine **10** in moderate yield along with a number of trimeric and tetrameric linear condensation products. The longer reaction time in comparison to the trianglimines obtained by Gawronski[8] and Hodacova[9] reflects the decreased reactivity of diketone **6** in comparison to the dialdehydes. After recrystallisation, the macrocycle could be obtained in moderate yield and excellent purity. Reaction of (1*R*,2*R*)-**1** and **7** gave the trianglimine **11** in quantitative yield. The compound was exclusively obtained in a D_3 symmetric conformation as opposed to the alternative conformation devoid of any element of symmetry. The LSIMS mass spectra show exclusively the expected molecular ions.

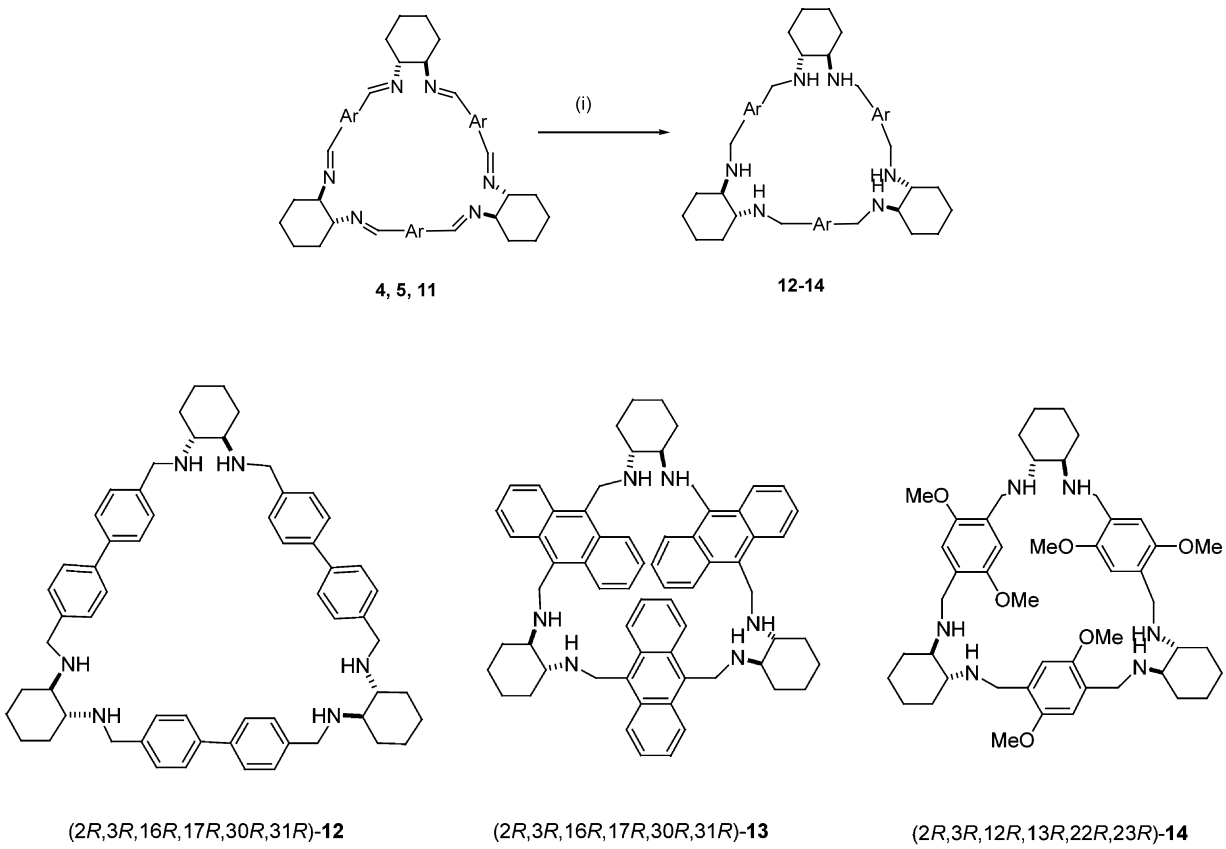
[3+3] Cyclocondensation between (1*R*,2*R*)-**1** and terephthaloylchloride **8** and isophthaloylchloride **9** in dichloromethane using 5% DMAP, NEt_3 or K_2CO_3 resulted in the formation of a white material, displaying an amide C=O band in the infrared spectrum. Due to its complete insolubility in all solvents employed we are unable to assign a definite structure. Similar solubility problems with amides based on enantiomerically pure **5** were reported by Still and co-workers.[17]

The novel imine macrocycles could be reduced in excellent yield using $NaBH_4$ in MeOH to yield the 30-membered hexaamine **14** and the 42-membered hexaamines **12** and **13**. The cyclic hexaamines are surprisingly soluble in both methanol and chloroform. Again the spectroscopic data are in perfect agreement with the proposed structure showing one set of NMR signals as expected for their overall D_3 symmetry (Scheme 1).

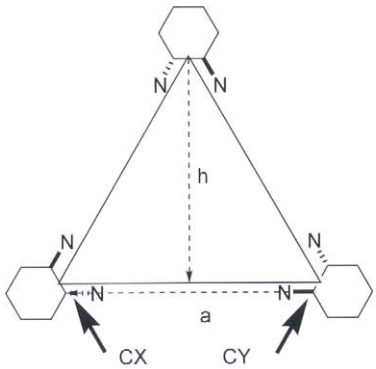
Interestingly compound **12** was obtained as an inclusion compound with one equivalent of MeOH. The ^1H NMR spectra shows a singlet at 3.80 ppm with the correct intensity, which correlates to a carbon signal at 67.1 ppm in the ^1H–^{13}C HSQC spectrum. A coupled ^{13}C spectrum reveals the identity of the signal as a CH_3 group further supporting the inclusion of MeOH.

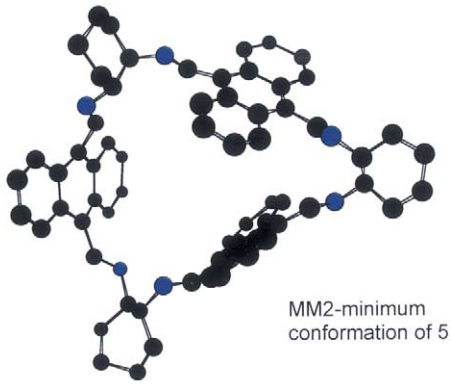
The lines in the ^1H NMR spectra of hexaamines **12**–**14** show considerable line broadening compared to the hexaimines, indicating a higher conformational flexibility and intramolecular mobility. However, no significant changes were observed in low temperature ^1H NMR spectra at −60°C in $CDCl_3$.

The overall molecular architecture of the novel macrocycles is mainly characterised by the dimensions of the central hole. To gain insight into the dimensions of the hole we performed some molecular modelling studies at the MM2 level.[18] Minimisation of the conformation from different starting geometries was undertaken and the size of the hole estimated from a set of three minimum energy conformations found that were within 0.5 kcal/mol strain energy difference of each other. The dimensions of the hole were estimated as averages of the minimum conformations found, resulting in an



Scheme 1. *Reagents and conditions*: (i) $NaBH_4$, MeOH/THF (1:1).





error of approximately ±1%. Attempts are now being made to obtain crystals for X-ray diffraction analysis to support these calculations. In the minimum energy conformation all compounds are approximately triangular shaped with the 1,2-diaminohexane moieties forming the edges of the triangle and the aromatic system forming the base. We estimated the length of the base of the triangles using the through space distance between CX of one 1,2-diaminohexane and CY of the neighbouring 1,2-diaminohexane. The values range from 730 to 1360 pm and are given in Table 1. Furthermore, we estimated the perpendicular height of the triangle by taking the through space distance between the centre of the C(1)–C(2) bond of a 1,2-diaminohexane and the centre of the opposite aromatic anthracene moiety in **5** and **13** or the centre of the central C–C bond in the biphenyl compounds **4** and **12**, respectively. The values range from 930 to 1420 pm in compound **5**. Surprisingly, reduction of the hexaimines results in a decrease in the ring size due to greater conformational flexibility, as experimentally indicated by the line shapes in the ^{1}H NMR spectra. The detailed knowledge of these dimensions should assist us in the design of suitable host guest systems.

3. Conclusion

In conclusion we have developed a facile synthesis of enantiomerically pure novel 30- and 42-membered hexaimine and hexaamine macrocycles. The new macrocycles have an intriguing structure and their functionalities are perfectly suited for further synthetic elaboration. Studies on the extension of the synthetic principle involving the elaboration and host guest chemistry of these compounds are currently under investigation.

We hope that this new class of macrocycles will inspire the imagination of supramolecular chemists to devise new classes of selective receptors and molecular machines and devices.

Table 1. Dimensions of size of the central hole in trianglimines and trianglamines **4**, **5**, **12** and **13** derived from MM2 structure minimisation

Compound	Height h (pm)	A (d CX−CY) (pm)
4	1420±15	1360±15
5	950±10	730±10
12	1410±15	1320±15
13	930±10	720±10

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a JEOL GSX 270 MHz and a Bruker Avance DRX-500 MHz spectrometer. δ values are quoted relative to teramethylsilane ($\delta=0.00$ ppm) or chloroform ($\delta=7.23$ ppm) for ^{1}H NMR and relative to chloroform ($\delta_C=77.0$ ppm) for ^{13}C NMR. Coupling constants J are in Hz. Microanalysis were carried out using a Leeman CE 440 automatic elemental analyser. It should be noted that elemental analysis has often been criticised by other authors as an inappropriate criterion for purity in synthetic macrocyclic chemistry due to inclusion of solvent molecules.[19,20] We have included all elemental analysis data, of which some are satisfactory and others are not. The purity of the compounds with non-satisfactory elemental analysis was demonstrated by HPLC analysis. Future work will reveal the value of elemental analysis in trianglamine and trianglimine chemistry. Infrared spectra were determined on a Perkin Elmer 200 Spectrometer. Optical rotations were determined on a Bellingham+Stanley ADO 220 polarimeter. Optical rotations were determined at least two concentrations. The highest concentration is stated in Section 4. The mass spectra were recorded at the EPSRC National Centre for Mass Spectrometry in Swansea or using a ThermoQuest Finnagan MAT 95XL spectrometer. Thin-layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60 F_{254} silica) using 1:3 ethyl acetate:hexane as a solvent system. All chemicals/reagents were purchased from the Aldrich Chemical Company. Solvents were dried using the usual procedures and reagents used without further purification unless stated otherwise. 9,10-Diformylanthracene, 4,4′-diformylbiphenyl and (1*R*,2*R*)-**1** were obtained by the published procedures.[16,21,22]

4.2. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(2,3:16,17:30,31)-tributano-(6,9:10,13:20,23:24,27:34,37:38,41)-hexaetheno-(2*H*,3*H*,16*H*,17*H*,30*H*,31*H*)-hexahydro-(42)-annulene, 4

To a solution of 4,4′-diformylbiphenyl (0.42 g, 2.0 mmol) in dichloromethane (2.0 mL) was added a solution of (1*R*,2*R*)-diaminocyclohexane (0.23 g, 2.0 mmol) in dichloromethane (3.0 mL) at room temperature and the mixture was stirred under reflux for 4 h. The solvent was evaporated and the *trianglimine* **4** was obtained after recrystallisation from ethyl acetate as a white solid (0.55 g, 32%). Mp >200°C; $[\alpha]_D^{25}$ +250 ($CHCl_3$, $c=0.1$); IR ν_{max} (Nujol)/cm^{-1}: 1636 (C=N), 1606–1463 (C_{Ar}=C_{Ar}), 815; ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 8.1 (1H, s, N=CH), 7.52–7.49 (2H, d, *J* 7.8, Ph), 7.41–7.38 (2H, d, *J* 8.4, Ph), 3.3 (1H, s, CH–N), 1.8–1.2 (4H, m, CH_2); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 160.9, 142.0, 135.6, 128.3, 127.0, 73.9, 32.6, 24.4; CHN calcd: C, 83.3; H, 6.99; N, 9.71; found: C, 77.6; H, 6.8; N, 8.8%; MS (LSIMS): $C_{60}H_{60}N_6$ (*m*/*z* 866.3, M+H).

4.3. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(2,3:12,13:22,23)-tributano-(6,9:16,19:26,29)-tribenzo-(6′,9′:16′,19′:26′,29′)-tributadieno (2*H*,3*H*,12*H*,13*H*,22*H*,23*H*)-hexahydro-(30)-annulene, 5

To a solution of 9,10-diformylanthracene (0.30 g, 1.3 mmol) in dichloromethane (5.0 mL) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (0.14 g, 1.3 mmol) in dichloromethane (1.5 mL) at rt and stirred under reflux for 3 h. The solvent was evaporated and the *trianglimine* **5** was obtained after recrystallisation from ethyl acetate as an orange solid (0.32 g, 80%). Mp over 200°C; $[\alpha]_D^{25}$ −242 (*c* 0.2, CH_2Cl_2, 1-dm); IR ν_{max} (Nujol)/cm^{-1}: 1632 (C=N), 1463–1377 (C_{Ar}=C_{Ar}), 755–722 (Ar, C–H); ^{1}H NMR (270 MHz; $CDCl_3$) δ_H: 8.21 (1H, s, N=CH), 7.3 (1H, s, H_{Ar}), 3.7 (3H, s, CH_3), 3.4 (1H, s, CH–N), 2.0–1.5 (4H, m, CH_2); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C: 160.8, 130.4, 129.4, 126.3, 126.2, 126.0, 125.1, 76.6, 33.6, 24.7; CHN calcd: C, 84.6; H, 6.5; N, 8.9; found: C, 84.1; H, 6.7; N, 8.7%; MS (LSIMS) $C_{66}H_{60}N_6$ (*m*/*z* 938.3, M+H).

4.4. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(5,10,15,20,25,30)-hexamethyl-(2,3:12,13:22,23)-tributano-(6,9:16,19:26,29)-trietheno-(2*H*,3*H*,12*H*,13*H*,22*H*,23*H*)-hexahydro-(30)-annulene, 10

(1*R*,2*R*)-Diaminocyclohexane (0.5 g, 4.37 mmol) in dichloromethane (5 mL) was added at 0°C a solution of 1,4-diacetylbenzol (0.7 g, 4.37 mmol) in dichloromethane (8 mL). The mixture was stirred under reflux for 24 h, the solvent was evaporated to yield the *trianglimine* **10** after repeated recrystallisation from ethyl acetate as a golden powder (264 mg, 28%), mp 90°C; $[\alpha]_D^{20}$ −190 (*c* 0.2, $CHCl_3$, 2-dm); ^{1}H NMR (270 MHz, $CDCl_3$) δ_H: 1.40 (m, 2H), 1.68 (m, 6H), 2.09 (s, 3H), 3.70 (m, 2H), 7.95 (s, 4H); ^{13}C (67.5, $CDCl_3$) δ_C 163.3, 128.5, 126.6, 65.5, 32.0, 24.8, 16.4; IR *v* 1631 cm^{-1}; CHN calcd: C, 80; H, 8.33; N, 11.66; found: C, 75.82; H, 8.18; N, 10.23%; MS (LSIMS) $C_{48}H_{60}N_6$ (*m*/*z* 720.3, M).

4.5. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(2,3:12,13:22,23)-tributano-(7,8′,17,18′,27,28′)-hexamethoxy-(6,9:16,19:26,29)-trietheno-(2*H*,3*H*,12*H*,13*H*,22*H*,23*H*)-hexahydro-(30)-annulene, 11

To a solution of 2,5-diformyl-1,4-dimethoxybenzene (0.2 g, 0.001 mol) in dichloromethane (1.5 mL) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (0.1 g, 0.001 mol) in dry dichloromethane (1 mL) at 0°C and the mixture was stirred for 3 h at room temperature. The solvent was evaporated to give the *trianglimine* **11** after recrystallisation from ethyl acetate as white needles (0.26 g, 90%). Mp over 200°C; $[\alpha]_D^{25}$ +442.4° (*c* 0.2, CH_2Cl_2, 1-dm); IR ν_{max} (Nujol)/cm^{-1}: 1630 (C=N), 1489–1378 (C_{Ar}=C_{Ar}); ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 8.4 (1H, s, N=CH), 7.2 (1H, s, C_{Ar}–H), 3.6 (3H, s, CH_3), 3.3 (1H, s, CH–N), 1.9–1.2 (4H, m, CH_2); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 155.6, 132.1, 123.8, 100.5, 82.3, 46.8, 29.1, 23.4; CHN calcd: C, 70.5; H, 7.4; N, 10.3; found: C, 63.7; H, 7.7; N, 8.3%; MS (LSIMS) $C_{48}H_{60}N_6O_6$ (*m*/*z* 817.4 M+H).

4.6. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(2,3:16,17:30,31)-tributano-(6,9:10,13:20,23:24,27:34,37:38,41)-hexaetheno-(1*H*,2*H*,3*H*,4*H*,5*H*,14*H*,15*H*,16*H*,17*H*-18*H*,19*H*,28*H*,29*H*,30*H*,31*H*,32*H*,33*H*,42*H*)-duodecahydro-(42)-annulene, 12

To a stirred solution of compound **4** (0.127 g, 0.15 mmol) in tetrahydrofuran–methanol (1:1, 3 mL) was added $NaBH_4$ (0.05 g, 3.1 mmol), and the solution was stirred for 2 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 (3×15 mL) and water (10 mL), the organic extracts were dried over $MgSO_4$, and the residue after evaporation of the solvents gave the *trianglamine* **12** after recrystallisation from toluene (0.05 g, 40%) a white solid. Mp over 200°C; $[\alpha]_D^{25}$ −227.3 (*c* 0.1, CH_2Cl_2, 1-dm); IR ν_{max} (Nujol)/cm^{-1}: 1460–1377 (C_{Ar}=C_{Ar}) 799–722; ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 7.22–7.61 (m, br, 8H, Ar) 3.99 (d, $J=12.4$ Hz, CH_AH_BN), 3.80 (s, MeOH), 3.42 (d, $J=12.4$ Hz, CH_AH_BN), 2.11 (m, 2H, CHN), 1.80 (m, 4H, CH_2), 1.15 (m, 4H, CH_2); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 140.1, 139.8, 128.1, 127.3, 67.1, 62.3, 43.5, 32.3, 25.2; CHN calcd (for $C_{60}H_{72}N_6$+H_3COH): C, 80.6; H, 8.42; N, 9.24; found: C, 79.1; H, 8.30; N, 9.30%; MS (LSIMS) $C_{60}H_{72}N_6$ (*m*/*z* 877.3 M+1).

4.7. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1:4:15:18:29:32-Hexaaza-(2,3:12,13:22,23)-tributano-(6,9:16,19:26,29)-tribenzo-(6′,9′:16′,19′:26′,29′)-tributadieno-(1*H*,2*H*,3*H*,4*H*,5*H*,10*H*,11*H*,12*H*,13*H*,14*H*,20*H*,21*H*,22*H*,23*H*,24*H*,25*H*)-duodecahydro-(30)-annulene, 13

To a stirred solution of compound **5** (0.127 g, 0.15 mmol) in tetrahydrofuran–methanol (1:1, 4 mL) gradually was added solid $NaBH_4$ (0.05 g, 3.1 mmol), and the solution was stirred for 2 h at room temperature. After removal of solvents the residue was extracted three times with 15 mL CH_2Cl_2 and 10 mL water, the organic extracts were dried over $MgSO_4$, and the residue after evaporation of the solvents gave the *trianglamine* **13** after recrystallisation from toluene (113 mg, 88%) as a

yellow solid. Mp 147°C; $[\alpha]_D^{25}$ +212.6 (*c* 0.1, CH_2Cl_2, 1-dm); IR ν_{max} (Nujol)/cm^{-1}: 1462–1377 (C_{Ar}=C_{Ar}), 755–722); ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 8.02–6.94 (m, br, 4H, Ar), 4. 88 (d, J=12.3 Hz, CH_AH_BN), 4.56 (d, J=12.3 Hz, CH_AH_BN), 1H, CH, 2.17 (m, 2H, CHN), 1.85 (4H, m, CH_2), 1.29 (4H, m, CH_2); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 132.1, 130.0, 125.4, 125.0, 124.9, 124.7, 62.3, 43.5, 32.3, 25.3; CHN calcd: C, 83.5; H, 7.6; N, 8.9; found: C, 83.7; H, 7.9; N, 8.2%; MS (LSIMS) $C_{66}H_{72}N_6$ (*m*/*z* 949.4 M+H).

4.8. (2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-1,4,15,18,29,32-Hexaaza-(2,3:12,13:22,23)-tributano-(7,8′,17,18′,27,28′)-hexamethoxy-(6,9:16,19:26,29)-trietheno-(1*H*,2*H*,3*H*,4*H*,5*H*,10*H*,11*H*,12*H*,13*H*,14*H*,20*H*,21*H*,22*H*,23*H*,24*H*,25*H*)-duodecahydro-(30)-annulene, 14

To a stirred solution of compound **11** (0.127 g, 0.15 mmol) in tetrahydrofuran–methanol (1:1, 3 mL) gradually was added solid $NaBH_4$ (0.05 g, 1.2 mmol), and the solution was stirred for 2 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 (3×15 mL) and water (10 mL), the organic extracts were dried over $MgSO_4$, and the residue after evaporation of the solvents gave the *trianglamine* **14** (0.1 g, 80%). Mp 165°C; $[\alpha]_D^{25}$ −219.8° (*c* 0.2, CH_2Cl_2, 1-dm); IR ν_{max} (Nujol)/cm^{-1}: 1460, 1378; ^{1}H NMR (270 MHz; $CDCl_3$) δ_H (6.74, 1H, s), 3.81 (d, J=12.6 Hz, 1H, CH_AH_BN), 3.59 (3H, s, OCH_3), 3.56 (d, J=12.6 Hz, 1H, CH_AH_BN), 2.12 (m, 2H, CHN) 1.76 (m, 4H), 1.81 (m, 4H); ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 151.6, 128.0, 112.8, 60.8, 55.0, 45.8, 31.2, 25.1; CHN calcd: C, 69.5; H, 8.7; N, 10.0; found: C, 69.4; H, 8.7; N, 9.0%; MS (LSIMS) $C_{48}H_{72}N_6O_6$ (*m*/*z* 829.3 M+H).

4.9. HPLC conditions for purity analysis of macrocycles

HPLC was carried out using a Spectra Physics SP 8800 ternary HPLC pump coupled to a Kontron LC 780 UV detector. A Spherisorb 50 DS2 column with dimensions of 15 cm×4.7 mm was used. As a solvent system 65% ethyl acetate, 25% acetonitrile and 10% chloroform was used prior to washing the column with 90% chloroform 10% *n*-butylamine. The UV detector was used at 270 nm.

Retention time for compound **10**: 2.8 min. Retention for compound **12**: 4.56 min.

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