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Tuning the size of macrocyclic cavities in trianglimine macrocycles

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Received 29th November 2004, Accepted 3rd March 2005
First published as an Advance Article on the web 14th April 2005

The synthesis of aromatic dicarboxaldehydes is described along with their reactivity in the [3 + 3] cyclocondensation reaction with (1*R*,2*R*)-diaminocyclohexane to give trianglimine macrocycles. In particular, the scope and limitation of the reaction with regard to complete control of the cavity size of the macrocycles is discussed producing a total of 11 macrocycles with different cavity sizes ranging from 9 to 23 Å.

Introduction

In recent years macrocyclic compounds have emerged as fascinating and useful synthetic host compounds in host–guest chemistry, molecular recognition and supramolecular chemistry.[1,2] One important requirement for any macrocyclic compound to act as an efficient host is the size of its central cavity, which needs to be complementary in size to any given guest molecule. Control of the size of the central cavity of macrocyclic compounds therefore constitutes a central problem in the design and synthesis of novel macrocyclic compounds. Currently there is no single class of compounds available whose method of synthesis would allow systematic control and variation of the central cavity size. For example, the most popular and readily available macrocycles – the cyclodextrins and calix[*n*]arenes – are only available in reasonable quantities on three sizes each.[3–5] Other classes of macrocycles like the crown ethers are only synthetically available in good yields in the presence of a metal ion templates, and therefore in relatively small sizes. For larger sizes, high dilution conditions need to be employed to access these compounds in moderate yields and along with a series of unwanted by-products.[6]

We believe that size variation and control in the synthesis of macrocycles is not only important in traditional host–guest chemistry but particularly important in the new emerging field of molecular devices and machines.[7] As a working hypothesis for the design of molecular analogues of such macroscopic devices we propose to use the blueprint of the macroscopic devices and directly translate them into the molecular world. Macrocyclic molecules with topologies and shapes analogous to parts found in the equivalent macroscopic devices are therefore urgently required as a molecular toolkit for the construction of molecular devices. The control of cavity sizes within the constituents of the molecular toolkit constitutes a major synthetic challenge, which needs to be addressed urgently. It must be noted that current functioning molecular machines such as molecular motors are complex biomolecules such as ATPase or actin–myosin who perform their mechanical movement by controlled conformational change.[8] Simpler molecular devices, which could act as parts of molecular machines such as molecular gears and bearings could be constructed from a molecular toolkit. Here, at least two complementary building blocks once assembled appropriately will move in a circular motion with respect to one another. As a representative example, Drexler has in detail laid out the theoretical requirements for a molecular bearing, in which the shaft and sleeve are constructed from two conformationally rigid macrocycles complementary in both size and symmetry.[9,10] To allow the realisation of a molecular bearing the synthesis of rigid macrocyclic molecules with a variety of complementary and well defined cavity sizes and symmetries needs to be accomplished. In this paper we report on a class of compounds, trianglimine macrocycles, whose method of synthesis should allow the synthesis of a molecular toolkit for the rational construction of molecular devices, such as a molecular bearing.

Gawronski *et al.* have reported on a class of new *para*- and *meta*-cyclophane polyimine macrocycles formed by a [3 + 3] cyclocondensation reaction.[11] We have reported on significant extensions to this chemistry including the synthesis of macrocycles with ring sizes of 27, 30 and 42 such as **1**–**3**, respectively, in almost quantitative yields.[12–14] Furthermore, we have reported on the scope and limitations of the cyclocondensation reaction, thereby incorporating heterocyclic, oxygen-substituted and other functionalised aromatic building blocks into this new class of macrocycles, which we have named trianglimines,[14,15] This new class of compounds offers great promise as synthetic host compounds in molecular recognition and as components in molecular devices and machines. Diastereomeric structures of this type of macrocycle have recently been reported by the group of Hodacova.[16] Other isolated examples of [3 + 3] cyclocondensation strategies have also been reported.[17,18]

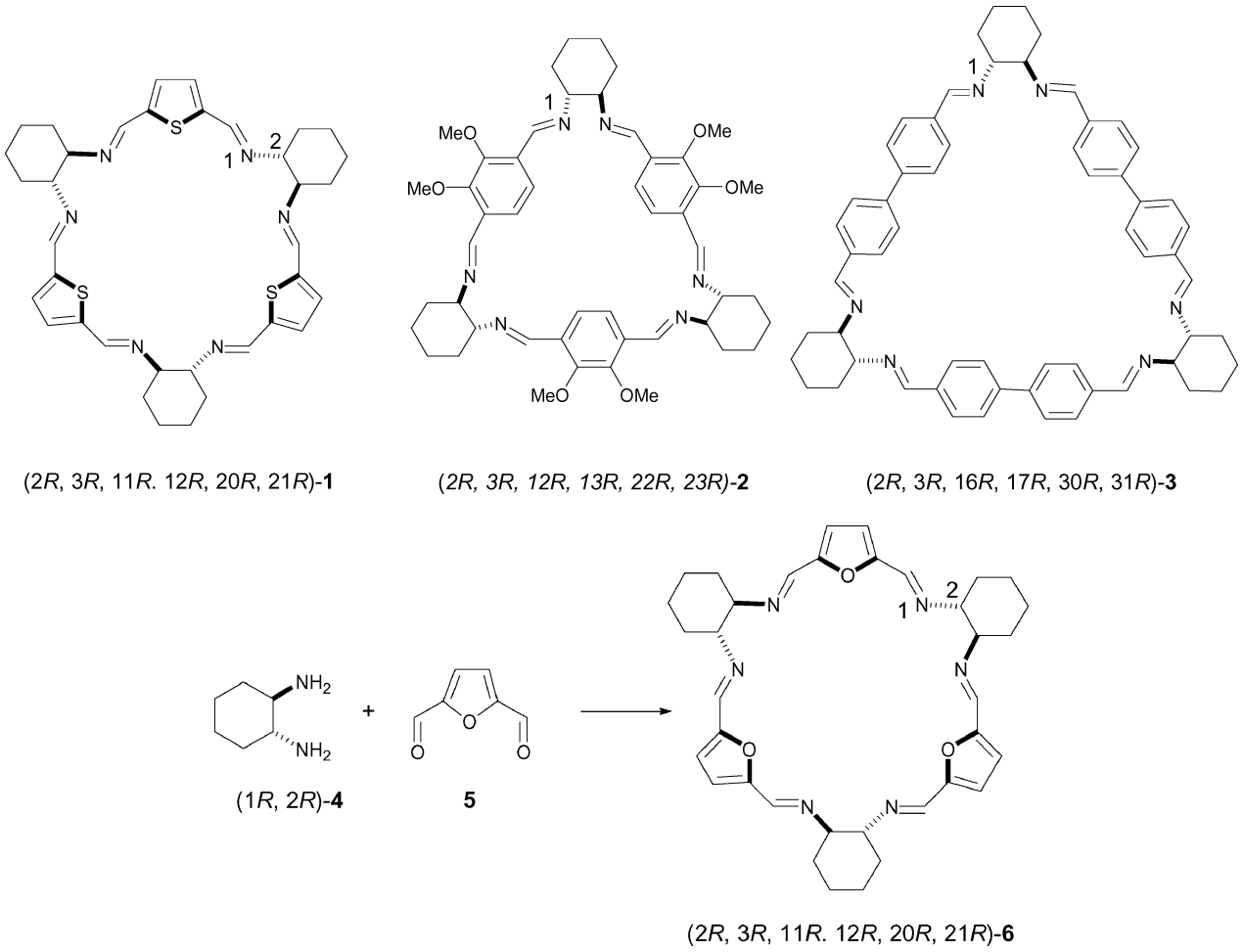
Results and discussion

Trianglimine macrocycles are formed in a [3 + 3] cyclocondensation reaction between enantiomerically pure *trans*-diaminocyclohexane[19] (*e.g.* as in compound **4**) and an aromatic dicarboxaldehyde. In this remarkable reaction, six C=N imine bonds are formed at relatively high concentration of 0.1 M in a variety of solvents of all components due to a conformational bias of the direct macrocyclisation precursor.[11–15] The size of the aromatic dicarboxaldehyde, or more precisely the distance between the two carbonyl carbon atoms, will determine the size of the cavity or central hole of the macrocycle. In this contribution we aim to demonstrate that the macrocyclic cavity or central hole of the trianglimine macrocycle can be tuned with accuracy by choice of the adequate dicarboxaldehyde building blocks.

The smallest aromatic dicarboxaldehyde available is 2,5-diformylfuran **5**.[20] The [3 + 3] cyclocondensation between **5** and diamine **4** yielded the trianglimine **6** in almost quantitative yield (Scheme 1). The ^{1}H-NMR and ^{13}C-NMR spectra show one set of signals for the three repeating units indicating an overall C_3 symmetry of the molecule. The ESI mass spectrum shows a single signal at *m*/*z* 607 corresponding to the molecular ion [M + H].

To gain insight into the conformation of macrocycle **6** we recorded a ^{1}H–^{1}H-NOESY spectrum. The complete absence of a nuclear Overhasuer effect (NOE) from the imine protons to

DOI: 10.1039/b417941b



Scheme 1

the aromatic protons in the heterocyclic moiety points towards conformation **B** as the preferred conformation in solution. A strong NOE is observed from the imine protons to the axial cyclohexane protons (see Fig. 1). The same observation is true for thiophene-based macrocycle **1** whose NOE spectra show the same feature.[14] Using Gawronski's nomenclature this conformation can be described as *s-syn*.[11] Molecular modelling at the MM-2 level supports this conformation as the conformation of

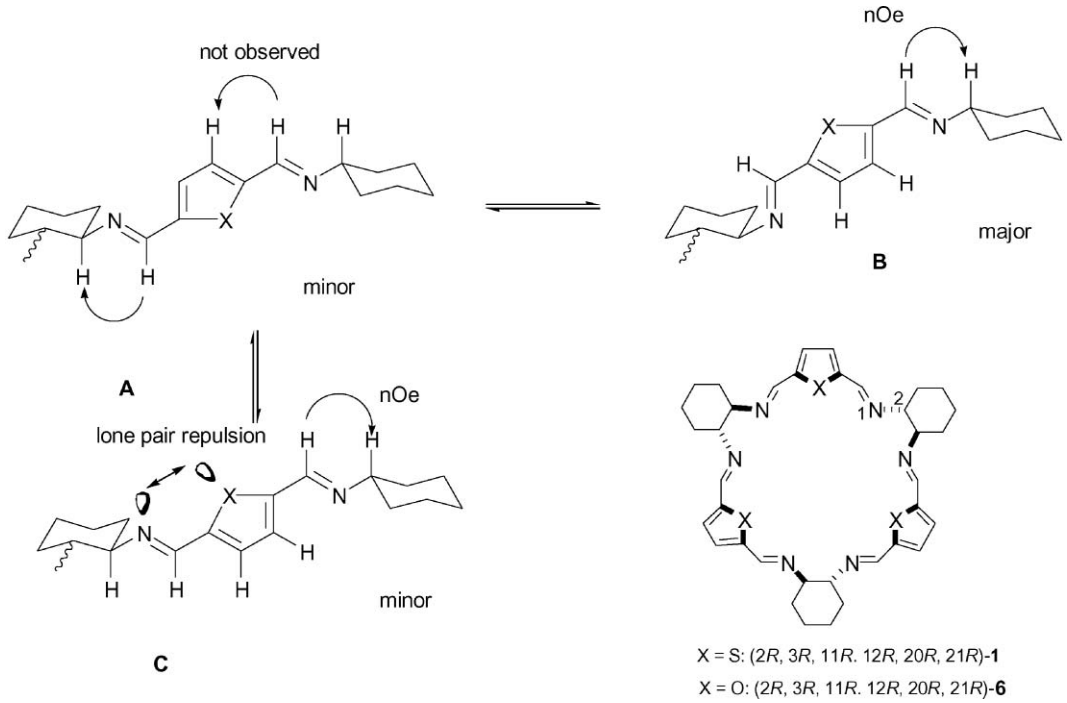
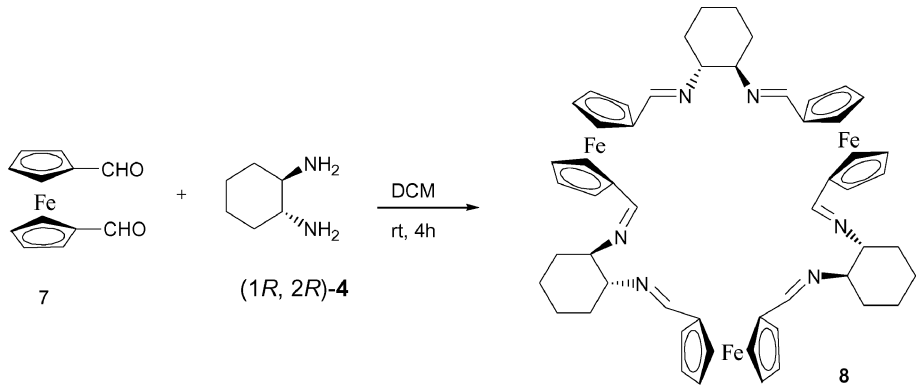


Fig. 1 Observed conformations and NOE influence in trianglimines **6** and **1**.



Scheme 2

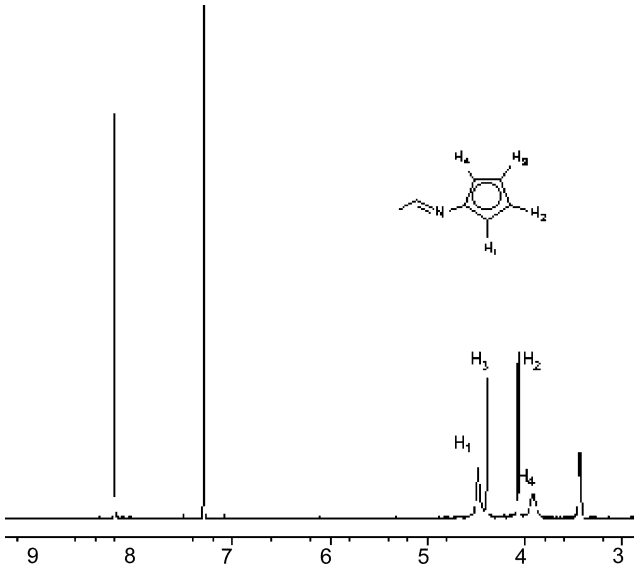


Fig. 2 Expanded ^{1}H-NMR spectrum of ferrocene trianglimine **8** in $CDCl_3$ (500 MHz).

the lowest energy. As a rationale it seems reasonable to assume that repulsion between the imine lone pair at nitrogen and the sp^2-lone pair at oxygen in **6** or sulfur in **1** of the heteroaromatic ring seem to be dominant, enforcing the *s-syn* conformation **B**.

Next we turned our attention to trianglimine macrocycles with intermediate size. As a first example we investigated the reaction between 1,1′-diformylferrocene **7** [21] and diamine **4** (Scheme 2). Ferrocene trianglimine **8** was obtained in 13.8% isolated yield after 45 h of reaction at room temperature in dichloromethane and after repeated recrystallisation.

Despite the apparent complexity of this structure, the trianglimine shows high symmetry in solution. The ^{1}H-NMR spectrum shows one set of signals for the three repeating units. A single imine peak at 8.17 ppm, and four broad singlets at 4.45, 4.36, 4.04 and 3.85 ppm, belonging to the four non-equivalent cyclopentadienyl protons of the ferrocene (Fig. 2) are observed. Apparently, rotation around the C_{Ar}–C=N bonds is slow on the NMR time-scale pointing towards conformational restriction within the macrocycle and resulting in the non-equivalence of the four cyclopentadienyl protons. The [3 + 3] cyclocondensation was confirmed by ESI and FAB mass spectroscopy showing the expected single molecular ion at m/z 961 [M^+ + H] (Fig. 3). The simulated isotope pattern for the macrocycle matches as well the experimental isotope pattern of the macrocycle.

Fig. 4 shows the ^{1}H–^{1}H-NOESY spectrum of the ferrocene trianglimine **8** including the through-space correlation. All protons can be assigned unambigiously. As in the previous trianglimines, the NOE between the imine protons at 8.17 ppm and the H–C–N=C protons of the amine-cyclohexyl moiety at 3.41 ppm is

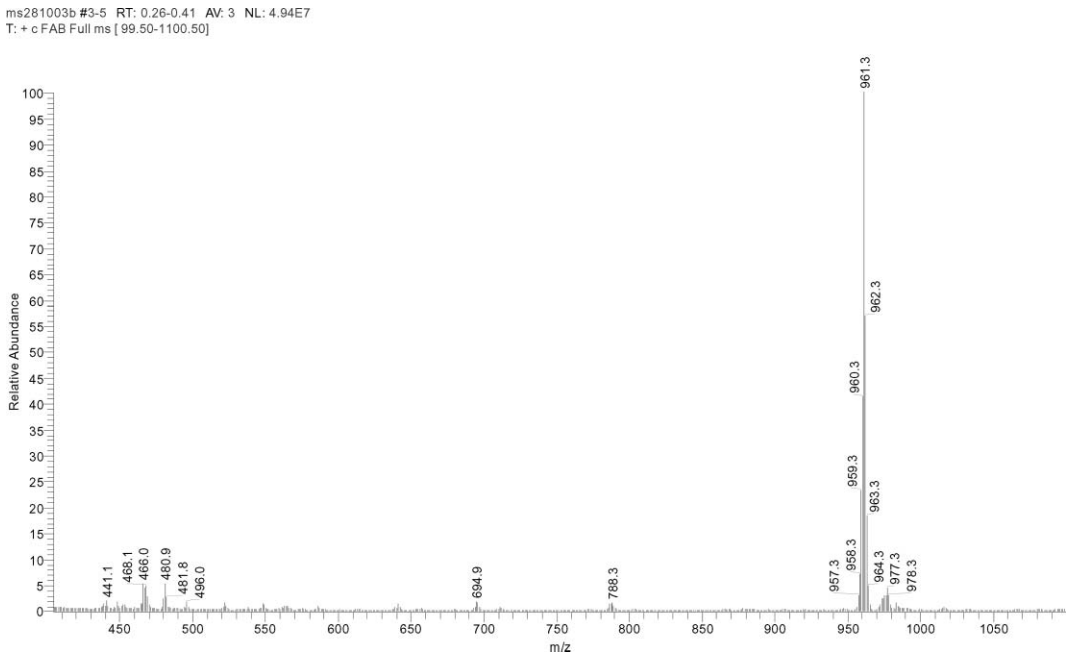


Fig. 3 FAB mass spectrum of ferrocene trianglimine **8** for $C_{54}H_{60}Fe_3N_6$.

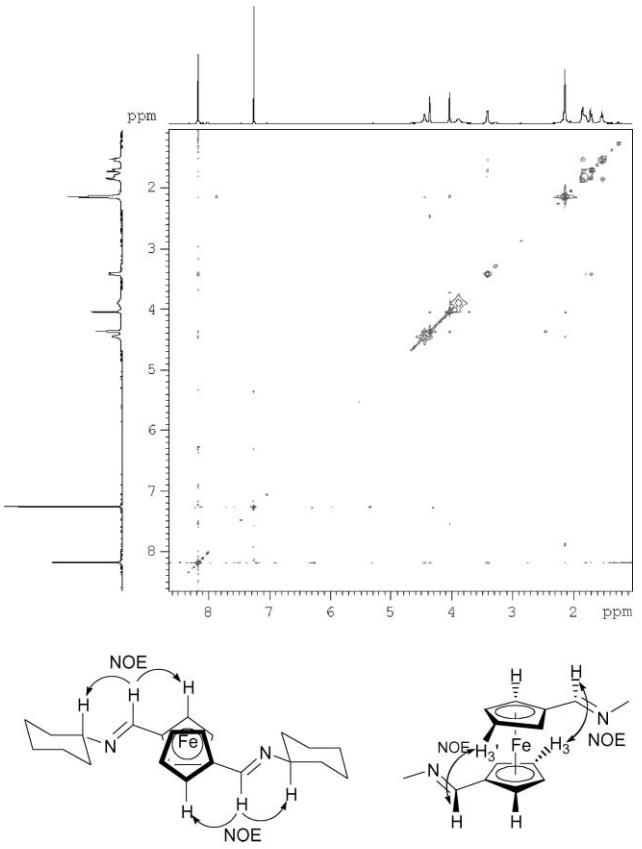


Fig. 4 ^{1}H–^{1}H-NOESY spectrum of ferrocene trianglimine **8** and illustration of the through-space correlation between protons.

observed. Simultaneously, these two protons correlate with the cyclopentadienyl protons (H_1, 4.45 ppm), as expected. The ^{1}H–^{1}H-NOESY spectrum also shows correlation between the previously mentioned protons and other hydrogen of the cyclopentadienyl ring. Since ^{1}H–^{1}H-NOESY spectroscopy can determine through-space correlation up to 5 Å, and the distance between the two cyclopentadienyl rings is reported to be about 3.3 Å, the interactions observed are between protons of the two counterpart cyclopentadienyl rings of each of the three repeating units.

Next we turned our attention to macrocycles whose cavity size would fall in between 30-annulene **2** and 42-annulene **3**. To obtain compounds of this intermediate size we turned to dimethoxynaphthalene dicarboxaldehydes as the required building blocks. The naphthalene dicarboxaldehydes were synthesised using our dilithiation methodology recently reported.[14,15] Using either double lithium bromide exchange or a double directed ortholithiation we obtained the required naphthalene dicarboxaldehydes **10**, **12** and **13** in moderate yields (Scheme 3). Dilithiation of 2,7-dimethoxynaphthalene yielded a mixture of regioisomeric dialdehydes **12** and **13**. Only **12** could be isolated in its analytically pure form, whereas **13** was obtained as mixture containing 10% of **12**. The spectroscopic data fully support their structures. Compounds **11** and **14** have been reported in the literature,[22–24] however, without complete spectroscopic characterisation. The complete data are given in the Experimental section.

With the naphthalene dicarboxaldehydes in hand we attempted the macrocyclisation reaction using diamine **4**. In each case the trianglimine macrocycles **14** and **15** were obtained in good yields as judged by the crude ^{1}H-NMR spectra. In order to obtain analytically pure material repeated recrystallisation was necessary, reducing the isolated yields considerably.

The ESI mass spectra (not shown) of compounds **14** and **15** show a single molecular ion at *m/z* 967. The ^{1}H-NMR spectrum of **14** exhibits one set of signals for each of the three repeating units. One peak is observed for the imine protons at 8.64 ppm and another single peak for the methoxy protons at 3.71 ppm. The ^{1}H–^{1}H-NOESY experiments showed the through-space interaction between both methoxy protons with the imine protons (Fig. 5).

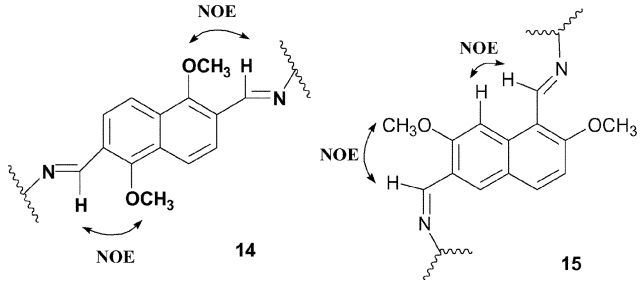
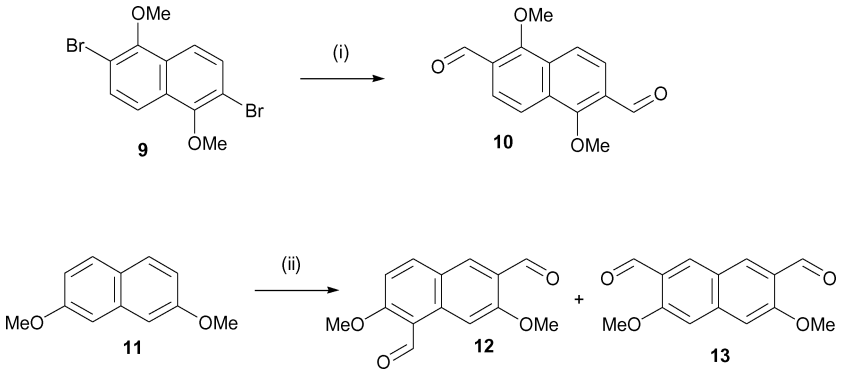


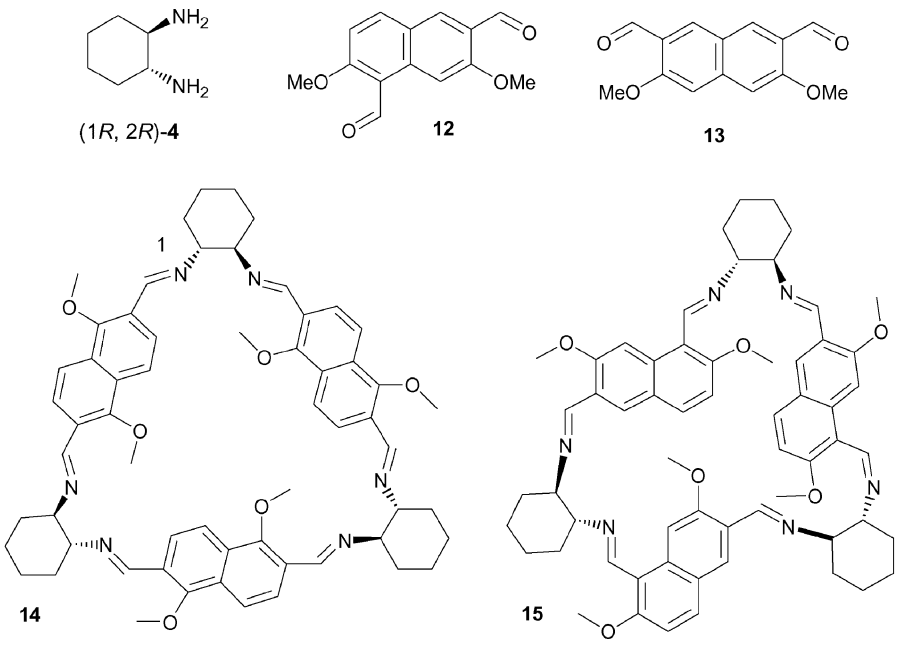
Fig. 5 The NOE data and overall conformation of macrocycles **14** and **15**.

This trianglimine can be compared with previously reported trianglimine **2** [11] due to the similar orientation of the methoxy groups in relation to the proton of the imine. Again it appears that the repulsive interaction between the imine lone pair and the oxygen lone pair is responsible for the observed preferred conformation in solution. The ^{1}H-NMR spectrum of trianglimine **15** is more complex than that of **14** due to a reduced symmetry of the dialdehyde building block (not D_{2h} like **10** but C_s for **12**). The spectroscopic data showed two signals for the non-equivalent imine protons at 9.01 and 8.84 ppm. The methoxy protons also appear as two sets of signals at 3.93 and 3.86 ppm respectively.

It is worth pointing out that in the case of compound **15** the aromatic ring system corresponds to a stereogenic plane with non-equivalence created by the non-equivalence of the inside and outside of the macrocycle.[15] Hence in case



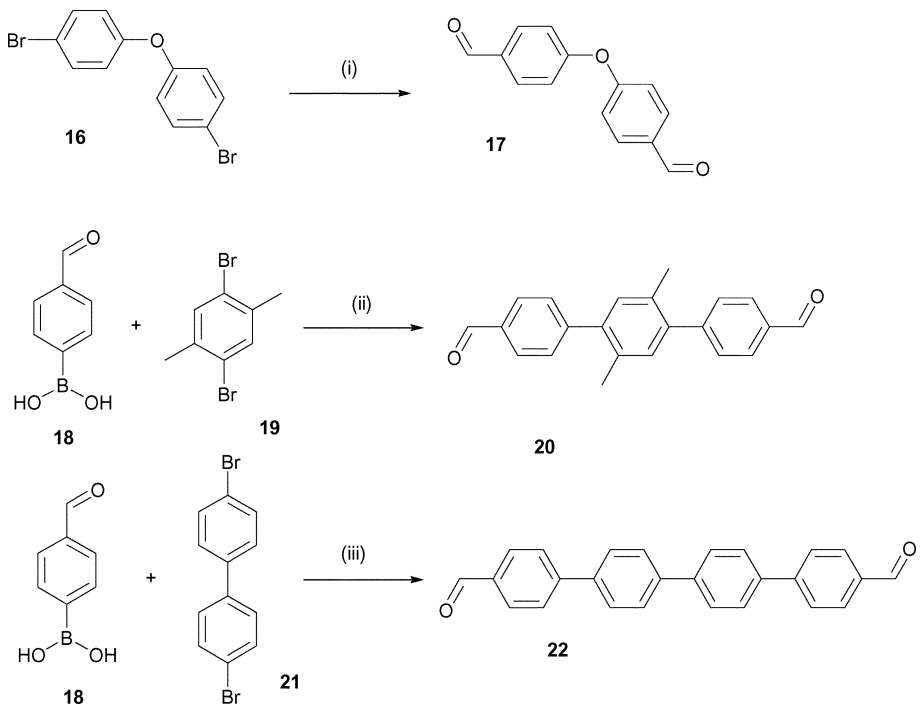
Scheme 3 *Reagents and conditions*: (i) 1) 3 equiv. n-BuLi, THF, −78 °C; 2) DMF; 3) 3 M HCl; (ii) 1) 3 equiv. n-BuLi/TMEDA, diethyl ether, reflux 3h; 2) DMF; 3) 3 M HCl.



of compounds **15**, two disatereomeric compounds could be expected as products of the macrocyclisation reaction. Since only a single diastereomer is observed by NMR spectroscopy as the product of the reaction, the reaction proceeds with exceptionally high diastereoselectivity. The NOE data allow assignment of the diastereomer obtained, which is shown in Fig. 5.

After successful synthesis of the naphthalene-based trianglimines we decided to investigate the formation of trianglimines with larger cavity sizes than those reported so far.[11,13] The largest compound we have reported on so far is 42-annulene **3** derived from a 4,4′-diformyl biaryl dicarboxaldehyde. To increase the distance between the two aldehyde functionalities in an aromatic dicarboxaldehyde we first synthesised diphenyl ether dicarboxaldehyde **17** using a double lithium bromide exchange reaction (Scheme 4). Terphenyldialdehyde **20** was obtained using a Suzuki coupling methodology from 4-formylboronic acid **18**, and quadphenyldialdehyde **22** was again obtained using a Suzuki coupling methodology. The synthesis of other aromatic terphenyldialdehydes has been reported using Suzuki coupling methodology.[25] However, the catalytic system reported failed in our hands, so that after some optimisation compound **20** using $Pd(PPh_3)_4$ and Na_2CO_3 as a base in DMF and **22** using palladium on charcoal in ethanol could be obtained.

In case of diphenyldicarboxaldehyde **17** we could obtain crystals suitable for single crystal X-ray structure determination (Fig. 6). Suprisingly, a search through the Cambridge Crystallographic Database revealed that there has only been one structure of an aromatic dicarboxaldehyde yet reported.[26] In terms of bond lengths and angles the structure shows no unexpected or unusual features. In terms of the macrocyclisation reactions and the conformations of macrocycles adopted in solution it seems remarkable that the two C=O units occupy an *s-trans*



Scheme 4 *Reagents and conditions*: (i) 1) 3 equiv. n-BuLi, THF, −78 °C; 2) DMF; 3) 3 M HCl; (ii) $Pd(PPh_3)_4$ 5 mol%, Na_2CO_3, DMF; (iii) Pd/C 5 mol%, Na_2CO_3/EtOH.

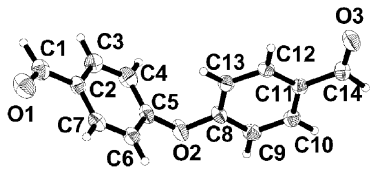


Fig. 6 Molecular structure of dialdehyde **17**; thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) and angles (°): O(1)–C(1) 1.207(3), C(1)–C(2) 1.477(3), O(2)–C(5) 1.399(2), O(2)–C(8) 1.384(2), O(3)–C(14) 1.220(3); C(5)–O(2)–C(8) 117.87(15).

configuration in the crystal. The same *s-trans* conformation in a related bisimine has been used to rationalise the selectivity of the macrocyclisation reaction.[11,14]

With the new dialdehydes in hand we attempted again the [3 + 3] cyclocondensation reaction using diamine **4**. In the case of **17** we could obtain only the [2 + 2] cyclocondensation product **23** as the single product of the reaction as judged by the ESI mass spectrum. In the case of dialdehydes **20** and **22** we could obtain the [3 + 3] cyclocondenstion products **24** and **25** as the only products of the reaction in good yields after prolonged reaction times. Whereas completion of the cyclocondensation reaction at 0.1 M concentration occurs within 3 h using, for example, terephthalaldehyde, in the cases of dialdehydes **20**, a time of 5 days at reflux is required to complete the reaction. It is worth noting that a ^{1}H-NMR spectrum along with an ESI or LSIMS mass spectrum of the crude mixture of the reaction between **22** and **4** shows after 24 h the presence of 10% [2 + 2] cyclocondensation product, which disappears after 5 days of further reaction at the expense of the [3 + 3] cyclocondensation product. For **22**, two weeks at reflux are required to obtain **25** along with some polymeric by-products. The spectroscopic data are as expected. It is worth noting that compounds **24** and **25** show a low solubility in most organic solvents.

Reduction of macrocycles

As reported previously the new trianglamine macrocycles can be reduced to give hexa-amines or trianglamines using sodium borohydride.[11–15] We attempted reduction of macrocycle **6** and reduction of naphthalene-based trianglimines **14** and **15**. The trianglamines **26**–**28** (Fig. 7) could be obtained in good yields. They all show broadened signals in their ^{1}H-NMR spectra due to

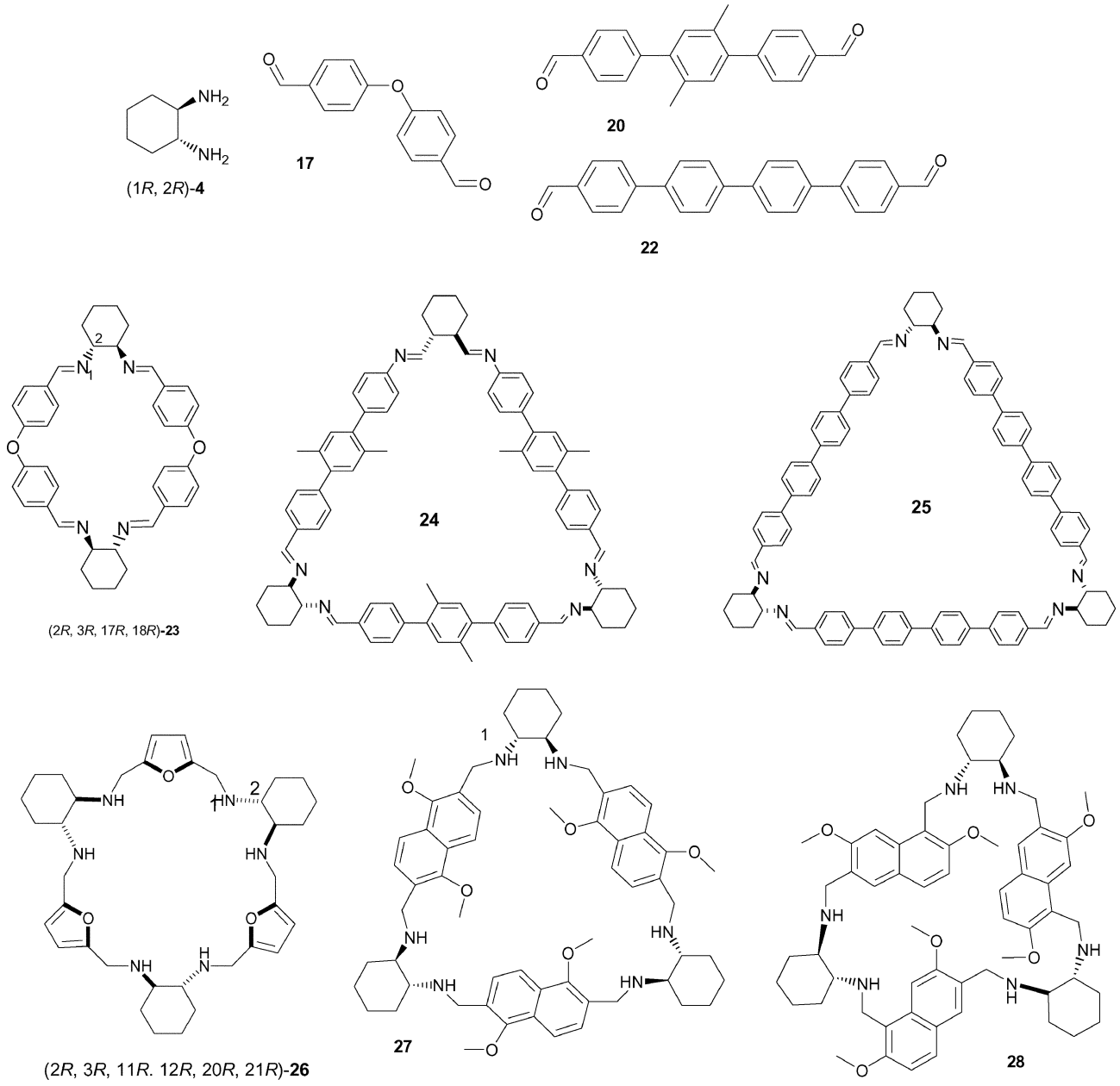


Fig. 7 Reduction of trianglimines to give trianglamines **26**–**28**.

Table 1 Yields and selected spectroscopic data for macrocycles **6**, **8**, **14**, **15**, **22**–**25**

Compound	Crude yield (%)[a]	Isolated yield (%)	*H*C=N δ_H [b]	HC=N δ_C [c]	MS *m*/*z* [d]
6	90	14	8.22	152.8	607
8	74	13	8.12	160.0	961
14	85	14	8.64	157.3	967
15	80	18	9.01, 8.72	158.3, 158.2	967
24	88	86	8.21	161.1	1178
25	70	35	8.11	160.8	1323

[a] As judged by ^{1}H-NMR spectrum of crude reaction mixture. [b] 500 MHz in $CDCl_3$. [c] 125 MHz in $CDCl_3$. [d] ESI-MS in MeOH solution showing [M + H].

increased conformational flexibility or aggregation in solution. The observed ESI mass spectra confirm the synthesis of all trianglamines due to appearance of the expected molecular ion (see Table 1, Fig. 8). Surprisingly additional molecular ions are apparent in the ESI mass spectra of trianglamine **14**, which can be attributed to a sodium adduct of a host guest complex with $NaBH_4$ at *m*/*z* 1029.

Estimation of size

The main aim of this contribution is to illustrate clearly that trianglimine macrocycles can be synthesised with a large variety of defined sizes of their central hole or cavity. The overall molecular architecture of the novel macrocycles is mainly characterised by the dimensions of their central hole or cavity. To gain insight into these dimensions we performed some molecular modelling studies at the MM-2 level.[27] 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^{-1} strain energy difference of each other. Starting geometries that were in good agreement with the NOE spectroscopic data were chosen exclusively. The dimensions of the hole size were estimated as an average of the minimum conformations found, resulting in an error of approximately ±5%. With increasing ring size the error increases. Attempts are made to obtain crystals for single X-ray diffraction to support the calculations. In the minimum energy conformation all compounds are approximately triangular shaped with the 1,2-diaminohexane moieties forming the edges of the equilateral triangle and the aromatic system forming the base of the triangle. We estimated the length of the base of the triangles using the through-space distance between CX of one the 1,2-diaminohexanes and CY of the next neighbour 1,2-diaminohexane. The values range

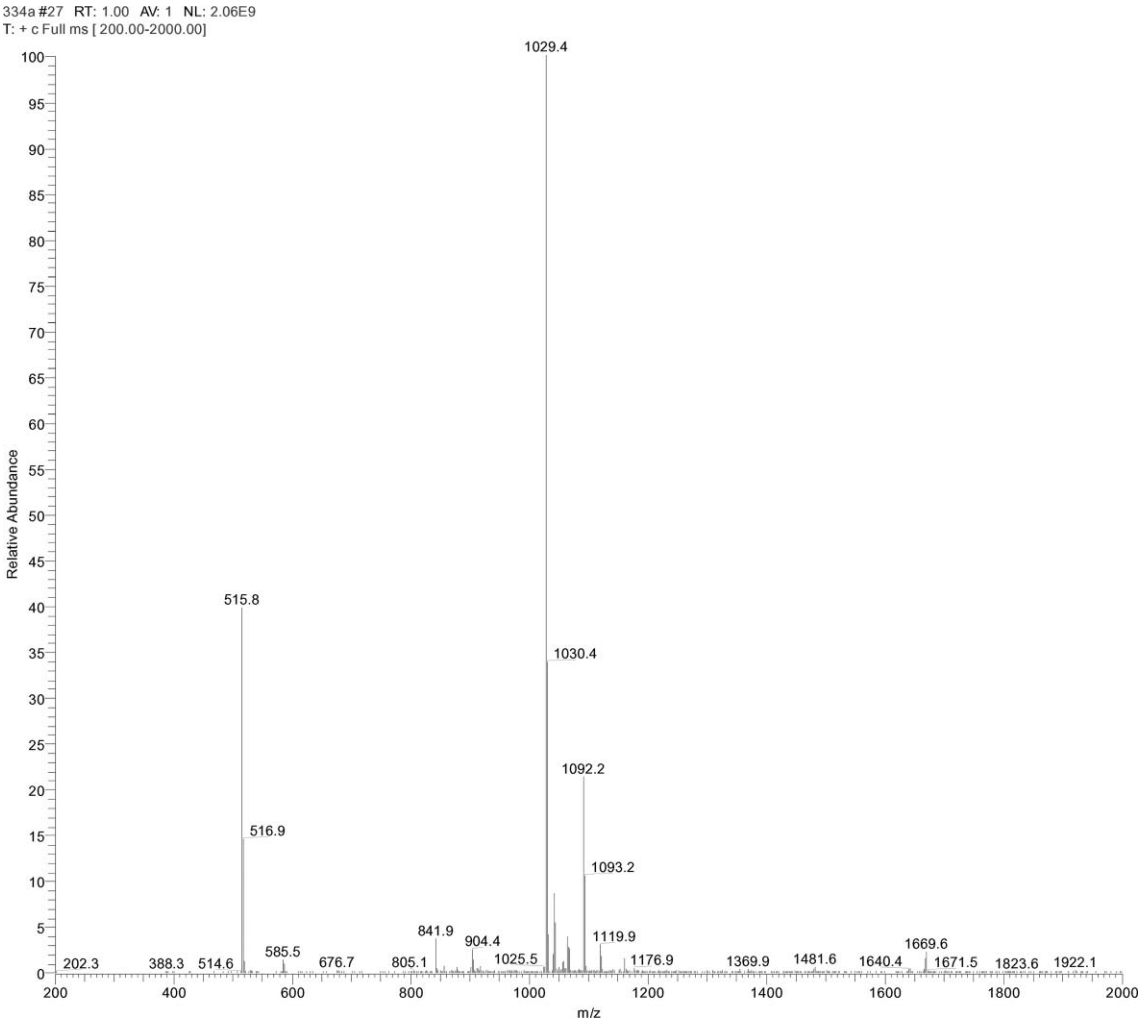
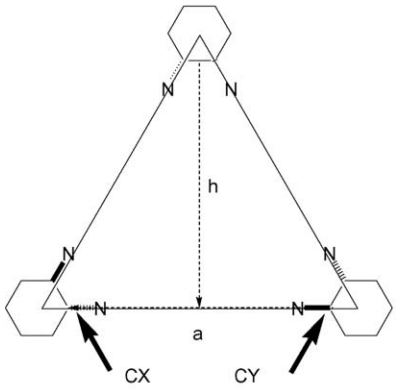
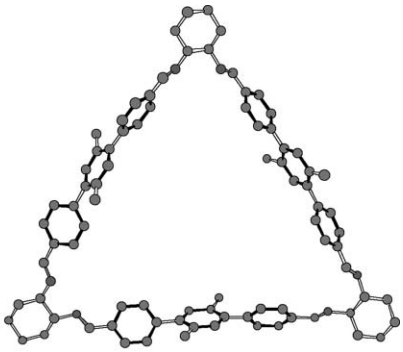


Fig. 8 ESI mass spectrum of trianglamine **26**.





MM2-minimum conformation of **24**

Table 2 Estimated dimensions of central hole sizes of trianglimines

Compound	Height, h/Å	Base length, a/Å[a]	$A(d$CX–CY)/Å
6	9.0 ± 0.4	10.4	8.9 ± 0.4
1	9.9 ± 0.5	11.4	9.7 ± 0.5
2	10.6 ± 0.5	12.2	10.8 ± 0.6
3	13.5 ± 0.7	15.6	14.4 ± 0.6
14	12.6 ± 0.6	14.5	12.9 ± 0.6
15[b]	11.1 ± 0.6	12.8	10.9 ± 0.6
24	17.5 ± 0.8	20.2	19.0 ± 0.8
25	20.7 ± 1.0	23.9	22.8 ± 1.0
8[c]	10.5	12.1	11.6 ± 0.6

[a] Base length calculated from h using $a^2 = h^2 + (a/2)^2$. [b] Irregular triangle: only one value for h stated. [c] Model incompatible with MM-2 minimisation; stick model was used.

from 9 to 23 Å and are given in Table 2. Furthermore, we estimated the perpendicular height of the triangle by taking the through-space distance between the centre of the C1–C2 bond of a 1,2-diaminohexane and the centre of the opposite aromatic moiety. Table 2 shows the dimensions of size of the central hole in trianglimines **1**–**3**, **6**, **8**, **14**, **15**, **24** and **25** derived from MM-2 structure minimisation. It is worth mentioning that the distance CX and CY is a molecular parameter that does not coincide with the actual base length of an ideal equilateral triangle. Therefore the base length a was additionally calculated from the height h. As can be seen from the values in Table 2, for larger macrocycles the CX–CY distance approaches the actual base length a, whereas for the smaller compounds such as **1** and **6** the CX–CY distance deviates more strongly from the base length a. A further set of three compounds with different sizes have been reported by our group, extending the number of compounds with various sizes to a total of eleven.[11–13] The modular approach for trianglimine synthesis should in the future allow the synthesis of further macrocycles containing any desired ring size.

Conclusion

In conclusion, we have shown that by choosing aromatic dialdehydes of different sizes we are able to fully control the overall size of the central hole of a trianglimine macrocycles. Compounds with central hole sizes ranging from 9 to 23 Å have been obtained. In all our trianglimine publications we have been able to produce a total of 11 compounds with different central hole sizes covering the low nanometer spectrum in various increments. This achievement opens the way for the construction of molecular machines and assemblies with well designed macrocycles who are complementary in size to one another and other components of interest for molecular machines.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GSX 270 MHz and a Bruker Avance DRX-500 MHz spectrometer. All δ values are quoted relative to tetramethylsilane ($\delta = 0.00$ ppm) or chloroform ($\delta = 7.26$ ppm) for ^{1}H-NMR and relative to chloroform ($\delta = 77.0$ ppm) for ^{13}C-NMR. Coupling constants J are in Hz. ^{1}H–^{1}H-NOESY spectra were recorded using a pulsed gradient sequence[28] using a mixing time of 400 ms. Samples were degassed using dry nitrogen before the acquisition of spectra. Microanalysis measurements 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.[29] We have included all elemental analysis data, of which some are satisfactory and others are not. Purity of the compounds with non-satisfactory elemental analysis was further demonstrated by ^{13}C-NMR spectroscopy[30] and HPLC analysis using the reported method using a Varian Pro Star HPLC system with a 250 × 4.60 mm 5 μm ODS Phenomenex analytical column.[12] Future work will reveal the value of elemental analysis in trianglamine and trianglimine chemistry. Infrared spectra were determined on a Perkin Elmer 2000 spectrometer. Optical rotations were determined on a Bellingham + Stanley ADO 220 polarimeter. Optical rotations were determined at two concentrations. The higher concentration is stated in the Experimental section. The mass spectra were recorded using a ThermoQuest Finnagan MAT 95XL spectrometer (CI and LSIMS) or a Finnigan DECAQplus for ESI spectra. All ESI spectra were recorded from a 0.001 M solution in methanol at a cone temperature of 698 K, a cone voltage of 3.3 kV in the positive ion mode. Thin layer chromatography (TLC) was carried out on commercially available precoated plates (Merck Kieselgel 60 F254 silica) using 1 : 3 ethyl acetate–hexane as the solvent system. All chemicals/reagents were purchased from either Aldrich or ACROS Chemical Companies. Solvents were dried using the usual procedures and reagents used without further purification unless stated otherwise. (1*R*, 2*R*)-**4**, 1,3-diformylfuran, 1,1′-diformylferrocene, 2,7-dimethoxynaphthalene and 4-formylbenzeneboronic acid were obtained by the published procedures.[19–24]

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexa-aza-(7,16,25)-trioxo-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-trietheno-(2*H*,3*H*,11*H*,12*H*,20*H*,21*H*)-hexahydro-(27)-annulene 6

2,5-Diformylfuran **5** 20 mg (0.16 mmol) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **4** (9 mg, 0.16 mmol) in dichloromethane (3 ml) and stirred for 4 h at room temperature. The solvent was evaporated and after recrystallisation from ethyl acetate the title compound **6** was obtained as a brown oil (14 mg, 14%); ($[\alpha]_D^{25}$ could not be determined due to the sample

being opaque); ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H 8.22 (6H, s, N=C*H*), 6.86 (12H, s, Ar–*H*), 3.54 (6H, m, C*H*–N), 1.5–1.8 (24H, m, CH_2); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 152.8, 114.9, 33.9, 33.15, 24.5 (quartenary Ar–C could not be detected due to low solubility); MS (CI) *m/z* 607 (M^+ + H, 100%), MS (ESI) *m/z* 607.3 (M + H, 100%), accurate mass $C_{36}H_{43}N_6O_3$ (M + H) requires 607.3397, found: 607.334.

Ferrocene trianglimine 8

1,1′-Diformylferrocene **7** (50 mg, 0.21 mmol) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **4** (23 mg, 0.21 mmol) in dichloromethane (3 ml) and stirred for 45 h at room temperature. The solvent was evaporated and recrystallised from ethyl acetate to give the title compound **8** as a brown powder (2.8 mg, 13%); mp > 250 °C; ($[\alpha]_D^{25}$ could not be determined due to the sample being opaque); ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H 8.12 (6H, s, N=C*H*), 4.45 (6H, s, Ar–*H*), 4.36 (6H, s, Ar–H), 4.02 (6H, s, Ar–*H*), 3.90 (6H, s, Ar–*H*), 2.86 (6H, m, C*H*–N), 1.5–1.78 (24H, m, CH_2); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 160.0, 83.6, 76.8, 73.4, 70.2, 33.9, 25.5; MS (FAB) *m/z* 961 (M^+ + H, 100%); CHN requires for $C_{54}H_{60}Fe_3N_6$: C 67.5, H 5.7, N 8.8%. Found: C 67.4, H 5.4, N 8.5%.

1,5-Dimethoxy-2,6-dibromonaphthalene 9 [23,31]

DMSO (1.8 ml) was added to powdered KOH (420 mg, 56 mmol). After stirring for 5 min, 1,5-dihydroxy-2,6-dibromonaphthalene (298 mg, 0.93 mmol) was added followed immediately by iodomethane (0.46 ml, 7.49 mmol). The reaction mixture was stirred for 6 h at room temperature, after which time 15 ml of H_2O was added. The precipitate was filtered and dried under vacuum to give the title compound **9** as a brown powder (0.2 g, 61%); mp 250 °C; IR ν_{max}(Nujol)/cm^{-1} 700; ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* 8.8, Ar–*H*), 7.62 (2H, d, *J* 8.8, Ar–*H*), 3.99 (6H, s, –OCH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 153.6 (C_1 and C_5), 131.3 (C_7 and C_3), 129.8 (C_9 and C_{10}), 119.6 (C_8 and C_4), 113.7 (C_2 and C_6), 41.1 (C_1 and C_5); MS (EI) *m/z* 344/346/348 (M^+, 100%).

1,5-Dimethoxy-2,6-diformylnaphthalene 10

n-Butyllithium 2.5 M in hexane (1.25 ml, 2 mmol) was added to a solution of 1,5-dimethoxy-2,6-dibromonaphthalene **9** (170 mg, 0.5 mmol) in dry THF (5 ml) at −78 °C under a nitrogen atmosphere and stirred for 2 h at the same temperature. To the reaction mixture DMF (0.15 ml, 2 mmol) was added and the solution was stirred for 30 min. The reaction mixture was allowed to warm to room temperature, and 3 ml of 3 M hydrochloric acid was added. The precipitate was filtered and dried under vacuum to give the title compound **10** as a yellow powder (16 mg, 13%), mp 180 °C; IR ν_{max}(Nujol)/cm^{-1} 1672 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 10.61 (2H, s, C*H*O), 8.08 (2H, d, *J* 8.7, Ar–*H*), 7.96 (2H, d, *J* 8.7, Ar–*H*), 4.14 (6H, s, –OCH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 189.6, 150.0, 124.1, 123.8, 119.8, 117.4, 66.1; MS (EI) *m/z* 245 (M^+ + H, 100%); CHN requires for $C_{14}H_{10}O_4$: C 68.8, H 4.9%. Found: C 68.5, H 4.7%.

2,7-Dimethoxynaphthalene 11 [24,31]

DMSO (12 ml) was added to powdered KOH (2.80 g, 50 mmol). After stirring for 5 min, 2,3-dihydroxynaphthalene (1 g, 6.24 mmol) was added followed immediately by iodomethane (1.55 ml, 25 mmol). The reaction mixture was stirred for 24 h at room temperature, after which time 15 ml of H_2O was added. The precipitate was filtered and dried under vacuum to give the title compound **11** as a yellow powder (0.8 g, 68%); mp 139 °C; IR ν_{max}(Nujol)/cm^{-1} 1627, 1228; ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.65 (2H, d, *J* 9, $H_{4,5}$), 7.06 (2H, s, $H_{1,8}$), 6.99 (2H, d, *J* 8.8, $H_{3,6}$), 3.91 (6H, s, –OCH_3); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 158.4 (C_2, C_7), 135.6 (C_9), 129.3 (C_4, C_5), 124.5 (C_{10}), 116.2 (C_3, C_6), 105.4 (C_1, C_8), 55.4 (–OCH_3); MS (CI) *m/z* 189 (M^+ + H, 100%).

1,6-Diformyl-2,7-dimethoxynaphthalene 12

TMEDA (0.8 ml, 5.31 mmol) was added to a solution of 2,7-dimethoxynaphthalene **11** (250 mg, 1.33 mmol) in diethyl ether (10 ml) at 0 °C. *n*-Butyllithium 1.6 M in hexane (3.32 ml, 5.31 mmol) was added slowly over 1 min. The lithiation mixture was stirred at room temperature for 6 h. DMF (0.41 ml, 5.31 mmol) was added to the mixture and the reaction was stirred for 30 min. The mixture reaction was warmed to room temperature and 7 ml of 3 M hydrochloric acid was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 15 ml). The extract was dried over Na_2SO_4 and recrystallised from petroleum ether to give the title compound **12** as a white powder (8.5 mg, 44%); mp 140 °C; IR ν_{max}(Nujol)/cm^{-1} 1680 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 10.84 (1H, s, C*H*O), 10.52 (1H, s, C*H*O), 8.90 (1H, s, H_8), 8.24 (1H, s, H_5), 8.08 (1H, d, *J* 9, H_4), 7.17 (1H, d, *J* 9, H_3), 4.07 (3H, s, –OCH_3), 4.06 (3H, s, –OCH_3); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ_C 191.6, 189.7, 166.5, 161.3, 139.6, 136.6, 130.7, 124.0, 122.9, 115.3, 110.7, 104.1, 56.5, 55.8; MS (CI) *m/z* 244.1 (M^+, 100%); CHN requires for $C_{14}H_{10}O_4$: C 68.8, H 4.9%. Found: C 68.5, H 5.4%. Accurate mass: requires 244.0730. Found 244.075 (R_f 0.3).

(2*R*,3*R*,14*R*,15*R*,26*R*,27*R*)-(1,4,11,13,16,25,28)-Hexa-aza-(7,10,19,22,31,34)-hexamethoxy-(2,3:14,15:26,27)-tributano-(6,9:8,11:18,21:20,23:30,33:32,35)-hexaetheno-(2*H*,3*H*,14*H*,15*H*,26*H*,27*H*)-hexahydro-(36)-annulene 14

1,5-Dimethoxy-2,6-diformylnaphthalene **10** (16 mg, 0.06 mmol) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **4** (7.5 mg, 0.06 mmol) in dichloromethane (3 ml) and stirred for 4 h at room temperature. The solvent was evaporated and recrystallised from ethyl acetate to give the title compound **14** as a brown powder (9 mg, 14%); mp > 250 °C; ($[\alpha]_D^{25}$ could not be determined due to the sample being opaque); IR ν_{max}(Nujol)/cm^{-1} 1636 (C=N); HPLC (R_f 3.5–3.6 min, $CHCl_3$–$BuNH_2$ 9 : 1, UV detection at 300 nm); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.64 (6H, s, N=C*H*), 7.88 (6H, d, *J* 8.8, Ar–*H*), 7.63 (6H, d, *J* 8.8, Ar–*H*), 3.71 (18H, s, –OCH_3), 3.51 (6H, broad, C*H*–N), 1.88–1.42 (24H, m, CH_2); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C 157.3, 153.1, 124.1, 118.6, 75.3, 64.2, 33.0, 27.7; MS (FAB) *m/z* 967 (M^+, 100%); accurate mass requires for $C_{60}H_{67}N_6O_6$ [M + H] 967.5122, found 967.510;[32] CHN requires for $C_{60}H_{66}N_6O_6$: C 74.5, H 6.8, N 8.6%. Found: C 72.5, H 6.1, N 7.5%.

(2*R*,3*R*,13*R*,14*R*,24*R*,25*R*)-(1,4,12,15,23,26)-Hexa-aza-(7′,18′,29′)-trimethoxy-(6,9:17,20:28,31)-trietheno-(8,10:19,21:30,32)-tris(tri-3-methoxy)propeno-(2*H*,3*H*,13*H*,14*H*,24*H*,25*H*)-hexahydro-(33)-annulene 15

2,7-Dimethoxy-1,6-diformylnaphthalene **12** (5.5 mg, 0.02 mmol) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **4** (2.6 mg, 0.02 mmol) in dichloromethane (1 ml) and stirred for 4 h at room temperature. The solvent was evaporated and recrystallised from ethyl acetate to give the title compound **15** as a yellow oil (4 mg, 18%); IR ν_{max}(Nujol)/cm^{-1} 1636 (C=N); $[\alpha]_D^{25}$ 275° (*c* 0.04, CH_2Cl_2, 1 dm); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 9.01 (3H, s, N=C*H*), 8.84 (3H, s, N=C*H*), 8.72 (3H, s, Ar–*H*), 8.14 (3H, s, Ar–*H*), 7.63 (3H, d, *J* 9, Ar–*H*), 6.90 (3H, d, *J* 9, Ar–*H*), 3.93 (9H, s, –OCH_3), 3.86 (9H, s, –OCH_3), 3.52 (6H, s, C*H*–N), 1.86–1.51 (24H, m, CH_2); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C 158.3, 158.2, 155.9, 134.7, 133.4, 127.3, 124.3, 116.2, 110.8, 110.5, 104.0, 76.4, 76.1, 55.5, 55.4, 33.5, 33.4, 24.8; MS (LSIMS) *m/z* 967 (M^+, 100%).

4,4′-Diformylphenyl ether 17

n-Butyllithium 1.6 M in hexane (6.9 ml, 11 mmol) was added to a solution of of bis-4,4′-dibromophenyl ether (1.45 g, 4.42 mmol) in dry THF (10 ml) at −78 °C under a nitrogen atmosphere

and stirred for 2 h at the same temperature. To the reaction mixture DMF (0.85 ml, 11 mmol) was added and the solution was stirred 30 min. The reaction mixture was allowed to warm to room temperature, and 7 ml of 3 M hydrochloric acid was added. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 × 15 ml). The extract was dried over Na_2SO_4, filtered, the solvents were removed under vacuum and the solids were recrystallised from petroleum ether to give the title compound **17** as colourless crystals (0.27 g, 27%); mp 140 °C; IR ν_{max}(Nujol)/cm^{-1} 1676 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 9.98 (2H, s, C*H*O), 7.92 (4H, d, *J* 8.6, Ar–*H*), 7.18 (4H, d, *J* 8.6, Ar–*H*); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 190.8, 161.2, 132.3, 132.2, 119.6; MS (CI) *m*/*z* 227 (M^+, 100%); CHN requires for $C_{14}H_{10}O_3$: C 74.3, H 4.4%. Found: C 74.2, H 4.3%.

Crystal structure determination of 17. A single crystal of **17** was mounted with Paratone-N on a glass fibre. A modified Siemens P4-Diffractometer was used for data collection (graphite monochromator, Mo-Kα radiation, $\lambda = 0.71073$ Å, scan rate 4–30 ° min^{-1} in ω). The structure was solved by using direct methods and refined with full-matrix least-squares against F^2 {Siemens SHELX-97}.[33] A weighting scheme was applied in the last steps of the refinement with $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ and $P = [2F_c^2 + \mathrm{Max}(F_o^2,0)]/3$. The protons of the aldehyde groups were found and refined free. All other hydrogen atoms were included in their calculated positions and refined in a *riding model*. Crystal data: $C_{14}H_{10}O_3$, $M = 226.22$, monoclinic, $a = 12.543(6)$, $b = 7.122(3)$, $c = 12.956(6)$ Å, $\beta = 102.40(3)°$, $V = 1130.4(9)$ Å^3, $T = 188(2)$ K, space group $P2_1/n$ (no. 4), $Z = 4$, μ(Mo-Kα) = 0.094 mm^{-1}, $D_c = 1.329$ g cm^{-3}, 2834 reflections measured, 2450 unique ($R_{int} = 0.0456$) which were used in all calculations, 1760 observed ($>2\sigma I$), R_1 (obsd.) = 0.0507, R_1 (overall) = 0.0755, wR_2 (obsd.) = 0.1259, wR_2 (overall) = 0.1419. The structure pictures were prepared with the program Diamond 2.1e.[34]

CCDC reference number 249596. See http://www.rsc.org/suppdata/ob/b4/b417941b/ for crystallographic data in CIF or other electronic format.

4,4″-Diformyl-2′,5′-dimethyl-1,1′.4′,1″-terphenyl 20

4-Formylboronic acid (75 mg, 0.54 mmol) was added to a degassed solution of 1,4-dibromo-2,5-dimethylbenzene (70 mg, 0.27 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), Na_2CO_3 (212 mg, 20 mmol) in 25 ml of toluene and 5 ml methanol. The solution was heated under reflux for 12 h. The organic phase was extracted with Na_2CO_3 solution (2 × 50 ml), 50 ml NH_4OH solution and 10 ml brine. The organic phase was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The crude product was purified by column chromatography (EtOAc–CH_2Cl_2 1 : 2) to give the title compound **20** as a light brown powder (14 mg, 74%); mp 190–193 °C; IR ν_{max}(Nujol)/cm^{-1} 1665 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 9.87 (2H, s, O=C*H*), 7.67 (4H, d, *J* 8.2, ArH), 7.29 (4H, d, *J* 8.3, ArH), 7.15 (2H, s, ArH), 2.35 (6H, s, Me); ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C 192.5, 159.7, 132.1, 130.8, 130.4, 130.0, 129.7, 121.2, 19.9; MS (CI) *m*/*z* 315 (M^+ + H, 100%), 286 (M − CO, 24%), 257 (M − C_2O_2H, 12%); CHN requires for $C_{22}H_{18}O_2$: C 84.1, H 5.77%. Found: C 84.0, H 5.88%.

Bis-(4-formylbenzene)-4,4′-biaryl 22

4-Formylboronic acid (300 mg, 2 mmol) and 4,4′-dibromobiphenyl (320 mg, 1 mmol) were added to a suspension of Na_2CO_3 (424 mg, 4 mmol) Pd/C (5%, 300 mg) in 15 ml ethanol. The solution was refluxed for 48 h and filtered through Celite. The solvent was removed under vacuum, dissolved in 30 ml CH_2Cl_2 and extracted with 20 ml NH_4Cl solution and 20 ml brine. The organic phase was separated, dried over $MgSO_4$, filtered and the solvent removed under vacuum. The crude product was recrystallised from ethanol to give the title compound **22** as a white powder (486 mg, 67%); mp 199–201 °C; IR ν_{max}(Nujol)/cm^{-1} 1667 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 10.09 (2H, s, O=C*H*), 8.0 (4H, d, *J* 8.3, ArH), 7.80 (4H, d, *J* 8.1, ArH), 7.55 (4H, d, *J* 8.3, ArH), 7.41 (4H, d, *J* 8.2, ArH); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C MS (EI) *m*/*z* 363 (M^+ + H, 100%), 334 (M − CHO, 13%);. CHN requires for $C_{26}H_{18}O_2$: C 86.2, H 5.01%. Found: C 86.0, H 5.08%.

(2*R*,3*R*,17*R*,18*R*)-1,4,16,19-Hexa-aza-(2,3:17,18)-dibutano-(6,9:11,14:21,24:26,29)-tetraethene-10,25-dioxo-(2*H*,3*H*,17*H*,18*H*)- tetrahydro-(30)-annulene 23

4,4′-Bis(formyl)phenyl ether **17** (70 mg, 0.31 mmol) in dichloromethane (1.0 ml) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **4** (35 mg, 0.31 mmol) in dichloromethane (1.0 ml) and stirred for 24 h at room temperature. The solvent was evaporated and the title compound **23** was obtained as a white powder (80 mg, 42%); mp 120 °C (decomposition); IR ν_{max}(Nujol)/cm^{-1} 1636 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.33 (4H, s, N=C*H*), 7.73 (8H, d, *J* 8.6, Ar–*H*), 7.04 (8H, d, *J* 8.6, Ar–*H*), 2.9 (4H, m, C*H*–N), 1.91–1.65 (16H, m, C*H*$_2$); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 160.0, 130.1, 129.8, 119.1, 74.0, 33.8, 25.3, 25.0; MS (FAB) *m*/*z* 609.7 (M^+ + H, 100%); CHN requires for $C_{40}H_{40}N_4O_2$: C 78.9, H 6.6, N 9.2%. Found: C 77.4, H 6.6, N 9.0%.

(2*R*,3*R*,20*R*,21*R*,38*R*,39*R*)-1,4,19,22,37,40-Hexa-aza-(2,3:20,21:38,39)-tributano-11,12′,29,30′,47,48′-hexamethyl-(6,9:10,13:14,17:24,27:28,31:42,45:46,49:50,53)-nonaetheno-(2*H*,3*H*,20*H*,21*H*,38*H*,39*H*)-hexahydro-(54)-annulene 24

A solution of 4,4″-diformyl-2′,5′-dimethyl-1,1′.4′,1″-terphenyl **20** (157 mg, 0.5 mmol) and of (1*R*,2*R*)-diaminocyclohexane **4** (56 mg, 0.5 mmol) in 50 ml CH_2Cl_2 was stirred for 6 days at room temperature. The solvent was removed under vavuum and the crude product recrystallised from EtOAc to give the title compound **24** as a white solid (4 mg, 18%); mp over 300 °C; IR ν_{max}(Nujol)/cm^{-1} 1638 (C=N); $[\alpha]_D^{25}$ −185° (*c* 0.04, CH_2Cl_2, 1 dm); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.21 (6H, s, N=C*H*), 7.58 (12H, d, *J* 8.1, ArH), 7.23 (12H, d, *J* 8.1, ArH), 6.99 (6H, s, ArH), 3.38 (6H, m, br, *H*CN), 2.15 (18H, s, Me), 1.82 (12H, m, br, CH_2), 1.48 (6H, m, br, CH_2); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C 161.1, 148.3, 140.6, 135.2, 132.7, 131.8, 129.7, 127.5, 74.3, 33.3, 24.8, 20.0; MS (LSIMS) *m*/*z* 1178 (M^+, 100%); CHN requires for $C_{84}H_{84}N_6$: C 85.7, H 7.19, N 7.14%. Found: C 86.1, H 7.05, N 7.02%.

(2*R*,3*R*,24*R*,25*R*,46*R*,47*R*)-1,4,23,26,45,48-Hexa-aza-(2,3:24,25:46,47)-tributano-(6,9:10,13:14,17:18,21:28,31:32,35:36,39:40,43:50,53:54,57:58,61:62,65)-duodecaetheno-(2*H*,3*H*,24*H*,25*H*,46*H*,47*H*)-hexahydro-(66)-annulene 25

In the same way as for compound **24**, bis-(4-formylbenzene)-4,4′-biaryl **22** (180 mg, 0.5 mmol) and (1*R*,2*R*)-diaminocyclohexane **4** (56 mg, 0.5 mmol) in 50 ml CH_2Cl_2 gave after 10 days of stirring at room temperature, size exclusion chromatography (Sephadex, eluent CH_2Cl_2) and recrystallisation from ethyl acetate the title compound **25** as a white powder (132 mg, 57%); mp over 300 °C; IR ν_{max}(Nujol)/cm^{-1} 1638 (C=N); $[\alpha]_D^{25}$ −188° (*c* 0.005, CH_2Cl_2, 1 dm); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 8.11 (6H, s, N=C*H*), 7.72 (12H, d, *J* 8.0, ArH), 7.51 (12H, d, *J* 7.8, ArH), 7.40 (24H, m, ArH), 3.38 (6H, m, br, *H*CN), 2.15 (18H, s, Me), 1.82 (12H, m, br, CH_2), 1.48 (6H, m, br, CH_2); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C 161.1, 148.3, 140.6, 135.2, 132.7, 131.8, 129.7, 127.5, 74.3, 33.3, 24.8, 20.0 (quartenary Cs could not be detected due to low solubility); MS (ESI) *m*/*z* 1321.7 (M + H, 100%); CHN requires for $C_{96}H_{84}N_6$: C 87.2, H 6.41, N 6.36%. Found: C 86.9, H 6.39, N 6.44%.

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexa-aza-(7,16,25)-trioxo-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-trietheno-(1*H*,2*H*,3*H*,4*H*,5*H*,9*H*,10*H*,11*H*,12*H*,13*H*,14*H*,18*H*,19*H*,20*H*,21*H*,22*H*,23*H*,27*H*)-octadecahydro-(27)-annulene 26

Trianglamine **6** (0.11 mg, 0.18 mmol) and $NaBH_4$ (21 mg, 0.56 mmol) were dissolved in 10 ml of THF–MeOH (1 : 1) and stirred for 2 h at room temperature. The solvent was removed under vacuum, 5 ml chloroform and 5 ml water added and the organic phase separated. The organic phase was dried over Na_2SO_4, filtered and removed under vacuum. The residue was recrystallised from toluene to give the title compound **26** as a brown oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 6.06 (6H, broad, Ar–*H*), 3.44–3.88 (18H, broad, C*H*$_2$N, C*H*–N), 2.17–0.97 (30H, broad, –C*H*$_2$, N*H*); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 115.0, 107.4, 60.67, 43.7, 31.6, 25.1; MS (LSIMS) *m*/*z* 619.5 ($M^+ + H$, 100%).

(2*R*,3*R*,13*R*,14*R*,24*R*,25*R*)-(1,4,12,15,23,26)-Hexa-aza-(7′,18′,29′)-trimethoxy-(6,9:17,20:28,31)-trietheno-(8,10:19,21:30,32)-tris(tri-3-methoxy)propeno-(1*H*,2*H*,3*H*,4*H*,5*H*,11*H*,12*H*,13*H*,14*H*,15*H*,16*H*,22*H*,23*H*,24*H*,25*H*,26*H*,27*H*,33*H*)-octadecahydro-(33)-annulene 28

In the same way as for macrocycle **26**, macrocycle **15** (less than 3 mg) and $NaBH_4$ in 2 ml of THF–MeOH (1 : 1) gave macrocycle **28** as a dark yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.35 (12H, broad, Ar–*H*), 4.00–3.30 (34H, broad, C*H*$_2$N, OC*H*$_3$, C*H*–N), 1.19–1.9 (28H, broad, C*H*$_2$, N*H*); MS (ESI) *m*/*z* 1042 ($M^+ + H + NaBH_4 + Na$, 100%), 1056 ($M^+ + H + 2NaBH_4$, 55%).

(2*R*,3*R*,14*R*,15*R*,26*R*,27*R*)-(1,4,11,13,16,25,28)-Hexa-aza-(7,10,19,22,31,34)-hexamethoxy-(2,3:14,15:26,27)-tributano-(6,9:8,11:18,21:20,23:30,33:32,35)-hexaetheno-(1*H*,2*H*,3*H*,4*H*,5*H*,14*H*,15*H*,26*H*,27*H*)-octadecahydro-(36)-annulene 27

In the same way as for macrocycle **26**, macrocycle **14** (6 mg, 6.21×10^{-3} mmol) and $NaBH_4$ (4 mg, 0.12 mmol) in 2 ml of THF–MeOH (1 : 1) gave macrocycle **27** as brown oil; ($[\alpha]_D^{25}$ could not be determined due to the sample being opaque); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H 7.40 (6H, d, *J* 7.5, Ar–*H*), 6.85 (6H, d, *J* 7.5, Ar–*H*), 4.28 and 4.03 (12H, AB system, *J* 12.0, –CH_AH$_B$N), 3.85 (8H, s, OC*H*$_3$), 3.72 (6H, broad, C*H*–N), 1.19–1.9 (28H, m, –C*H*$_2$, N*H*); MS (LSIMS) *m*/*z* 1049.6 (M^+ + THF, 100%), 979.7 ($M^+ + H$, 50%).

Acknowledgements

We would like to thank the European Union for financial support (project "Pesticide"; No. ICA2-CT-2000-10002). Furthermore I would like to express my gratitude to Professor M. N. Clifford for help with ESI mass spectrometry, Mr J. Bloxsidge, Ms J. Peters, Ms N. Walker and Mr R. Chaundy for providing excellent technical support at Chemistry at Surrey.

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