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The synthesis and conformation of oxygenated trianglimine macrocycles†‡

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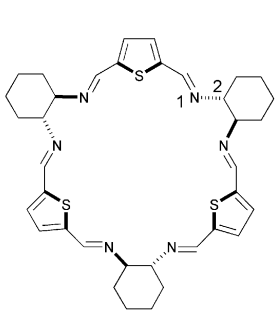
The synthesis of series of D_{2h} and C_{2v} symmetric oxygenated aromatic dicarboxaldehydes, using dilithiation methodology, is described along with their reactivity in the [3 + 3] cyclocondensation reaction with (1*R*,2*R*)-diaminocyclohexane to give oxygenated trianglimine macrocycles. Macrocycles derived from C_{2v} symmetric dialdehydes give macrocycles with a stereogenic aromatic plane with complete diastereocontrol, as a mixture of rotamers.

Introduction

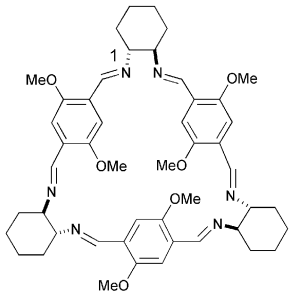
In recent years supramolecular chemistry has emerged as one of the most actively pursued fields of the chemical sciences. Its implications now reach from the basis of molecular recognition in natural systems such as protein substrate interactions to exciting new applications in chemical technology and material sciences.[1,2] Molecular recognition using non-natural receptors of metal cations has reached a high level of maturity and sophistication, and as a consequence is successfully applied on an industrial scale.[3–5] Molecular recognition using non-natural receptors of anions is making rapid progress[6] whereas molecular recognition of small-to-medium sized organic molecules is somehow lagging behind, mainly due to the complexity of the scientific challenge.[1,2] However, a diverse number of potentially useful applications of molecular recognition of small organic molecules using synthetic receptors have been suggested and are being actively pursued.

In order to obtain macrocycles able to bind small organic molecules, particular care needs to be taken to design synthetic macrocyclic systems that comprise a series of desirable requirements, which include the following: (a) they must be easy to synthesise on a large scale and in high yields, (b) they must comprise binding motifs and functional groups suitable for molecular recognition processes and must bind to a variety of guest molecules of interest, (c) they must be soluble in a wide range of solvents, (d) they should be chiral and available in both enantiomeric forms, (e) they should be assembled from readily available building blocks in a modular fashion to allow judicious choice of functionality to be incorporated and to allow the control over overall size and topology, (f) they must be available in various sizes to accommodate different sizes of potential guest molecules, and (g) they must have functionalities that can be further synthetically elaborated to increase versatility in applications and complementarity in the binding process.

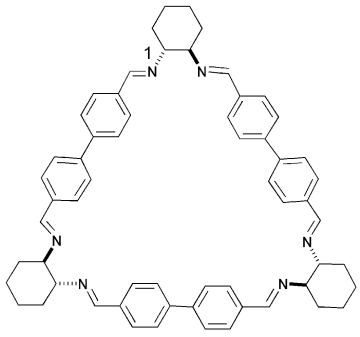
Among the macrocycles most intensely investigated, the calix[*n*]arenes[7–9] and cyclodextrins[10,11] fulfil some of the above criteria. We and others have recently reported on a class of macrocycles which we have named trianglimines,[12–14] which we believe to fulfil all of the above criteria. The first trianglimine macrocycles have been synthesised by Gawronski and co-workers.[15] 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 been reported.[17–20] We have recently reported on significant extensions to this chemistry, synthesising macrocycles with ring sizes of up to 42, such as **1–3** in almost quantitative yields.[12–14]



(2*R*, 3*R*, 11*R*, 12*R*, 20*R*, 21*R*)-**1**



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



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

In this contribution we comment on the scope and limitations of the [3 + 3] cyclocondensation between (1*R*,2*R*)-diaminocyclohexane and various oxygenated aromatic dicarboxaldehydes. In particular we demonstrate that functionalised aromatic dialdehydes as modular building blocks for macrocycles are readily available and can be elaborated into a series of highly substituted trianglimine macrocycles. Furthermore, we introduce for the first time aromatic dialdehydes with a lower symmetry than those published previously and comment on their conformational properties.

† Electronic supplementary information (ESI) available: selected spectra and supplementary experimental procedures. See http://www.rsc.org/suppdata/ob/b4/b414747m/

‡ Dedicated to Professor W. A. Schenk on the occasion of his 60th birthday.

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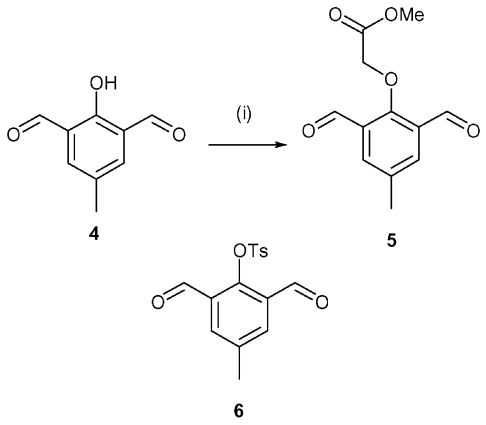
Results and discussion

In order to demonstrate the versatility of the [3 + 3] cyclocondensation of (1*R*,2*R*)-diaminocyclohexane **7** with aromatic dicarboxaldehydes we required a selection of this class of compounds. In this contribution, we choose to focus on oxygenated aromatic dicarboxaldehydes. 1,3-Diformylcresols such as **4** have been used frequently to obtain polyimine macrocycles.[21,22] We synthesised derivatives **5** and **6** from **4** (Scheme 1). [3 + 3] Cyclocondensation between **4** and (1*R*,2*R*)-diaminocyclohexane **7**[23] gave the trianglimine macrocycles **8–10** in satisfactory yields. Compound **8** has been described in the literature previously.[19] In the cyclocondensation reaction with **4** and **6**, trianglimines **8** and **10** were obtained as the only product, whereas in the reaction with **5** a mixture of [2 + 2] cyclocondensation product and trianglimine **9** was obtained (Scheme 2).

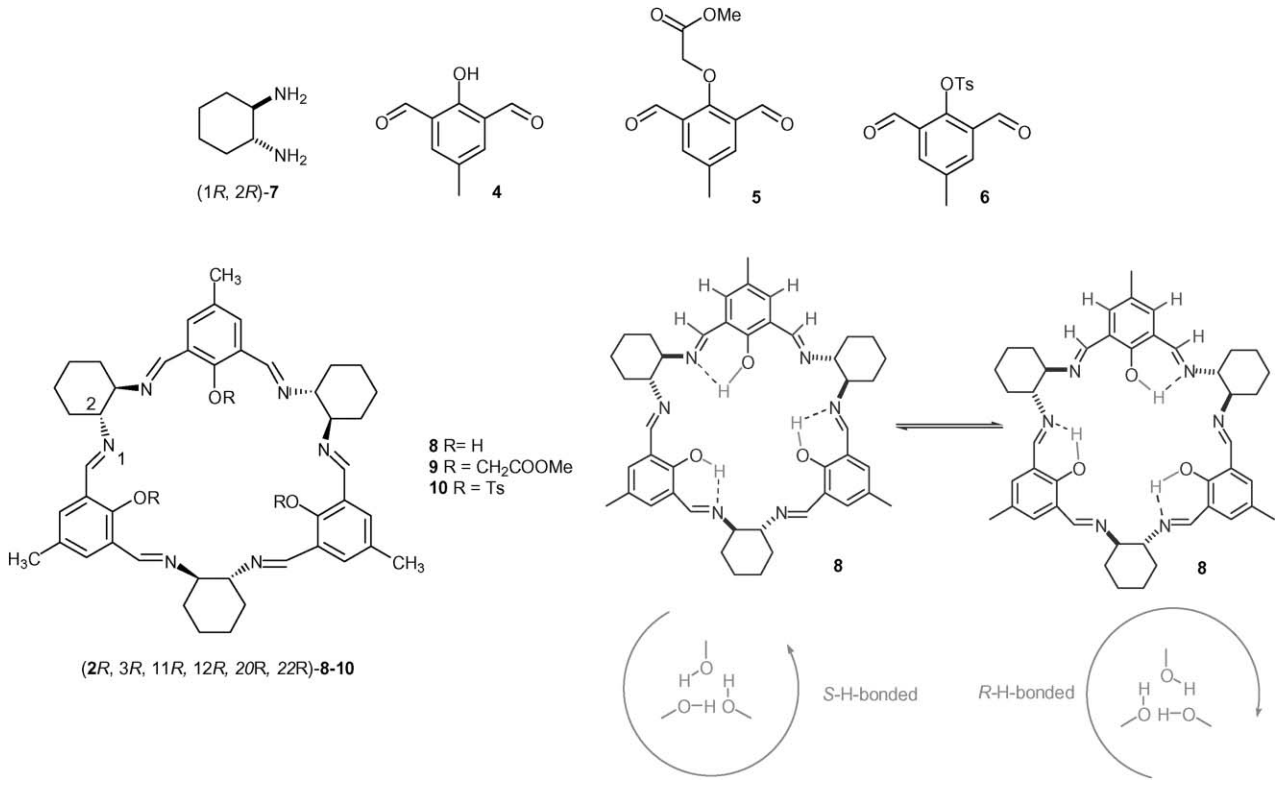


Scheme 1 *Reagents, conditions and yields*: (i) NaH, $BrCH_2COOMe$, DMF.

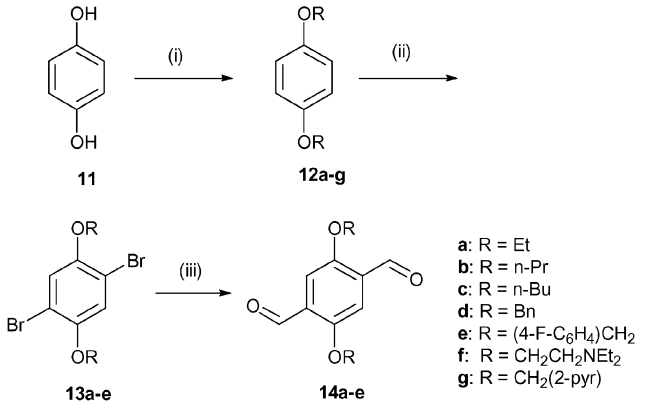
However, we would like to point out an interesting stereochemical feature of **8**, which has not been reported yet. The three phenolic OHs form a hydrogen bond to the lone pair of the neighbouring imine. This arrangement results in the formation of a pair of diastereoisomers, in which the hydrogen bonding array forms a stereogenic element (see Scheme 2). The ^{1}H and ^{13}C-NMR spectra, however show only one set of signals, suggesting that either one diastereoisomer exists in solution or that exchange between the two possible diastereoisomers is fast on the NMR timescale. Similar chiral hydrogen bonding motifs with a hydrogen bonding array as a stereogenic element have been described by Rebek[24] and Böhmer[25] in tetra(ureido)calix[4]arene capsules and by our group in tetra(acrylamido)calix[4]arene capsules.[9]

Next we turned our attention to dialdehydes derived from hydroquinone diethers. Hydroquinone **11** was alkylated using standard conditions[26] with a variety of alkyl halides to give the hydroquinone diethers **12a–g** in excellent yields. Diethers **12a–g** were selectively dibrominated using two equivalents of bromine in buffered acetic acid to give the dibromides **13a–e**, again in excellent yields (Scheme 3). The 1,4-dibromo regiochemistry (as opposed to 1,2 or 1,3) of **13a–e** follows directly from the ^{13}C-NMR spectra and the fingerprint region of the IR-spectra[27] and ultimately by chemical proof in the successful [3 + 3] cyclocondensation reaction. It is worth mentioning that all compounds with a basic nitrogen substituent (*e.g.* **12f,g**) failed to brominate, both under the conditions above and under a series of other bromination conditions.[28] It appears as if protonation of the basic nitrogen creates a positive charge remote from the aromatic nucleus that has a suprising deactivating effect on the electrophilic aromatic substitution reaction. Dibromides **13a–e** were subsequently subjected to our dilithiation procedure[14] giving the aromatic dicarboxaldehydes **14a–e** in good yields (Scheme 3). All yields are summarised in Table 1.

The [3 + 3] cyclocondensation reaction of dialdehydes **14a–e** with diamine **7** gave the trianglimine macrocycles **15a–e**, as expected. The crude yield and conversion of the reaction was excellent, as judged by the crude ^{1}H-NMR spectra of the reaction mixtures. However, isolated yields were, in general, quite poor due to the necessity of repeated recrystallisation to obtain analytically pure material. Crude and isolated yields of all macrocycles are summarised in Table 2.



Scheme 2



Scheme 3 *Reagents and conditions*: (i) RX (for RX see Experimental section), NaOH, DMSO; (ii) Br_2, HOAc, NaOAc; (iii) 1. 2.2 eq. *n*-BuLi, THF; 2. DMF; 3. HCl.

The macrocycles all show the expected spectroscopic features. There is one set of signals for each of the three repeating units in the ^{1}H-NMR and ^{13}C-NMR spectra – see the Supplementary information for the ^{1}H-NMR and ^{13}C-NMR spectra of compound **15a**, together with the signal assignments.† The OCH_2 protons of the two ethyl substituents appear as the AB part of an ABX_3 spin system. From the NMR spectra it can be deduced that the compounds possess overall D_3 symmetry. The mass spectra of compound **15a** show a single molecular ion for the expected mass (see Supplementary information). We recorded both FAB and ESI mass spectra of the compounds and found that generally the ESI mass spectra give more reliable results in the positive ion mode.

Next we turned our attention to dicarboxaldehydes with a reduced symmetry derived from hydroquinone methyl ether **16**. Note that dicarboxaldehydes **14a–e** possess D_{2h} symmetry, whereas dialdehydes **19a–d** possess the reduced C_{2v} symmetry. As a result we expected trianglimine macrocycles to display two different binding sites, one above a plane formed by any three imine nitrogens and one below a plane formed by any three imine nitrogens, thus offering improved versatility in guest binding. Hydroquinone methyl ether **16** was alkylated using standard conditions,[26] again with a variety of alkyl halides, to give the hydroquinone diethers **17a–d** in excellent yields. Diethers **17a–d** were selectively dibrominated using two equivalents of bromine in buffered acetic acid to give the dibromides **18a–d** in good-to-excellent yields. Dilithiation of dibromides **18a–d** gave the dicarboxaldehydes **19a–d** in good yields (Scheme 4). The yields are summarised in Table 1. All compounds **17a–d**, **19a–d**

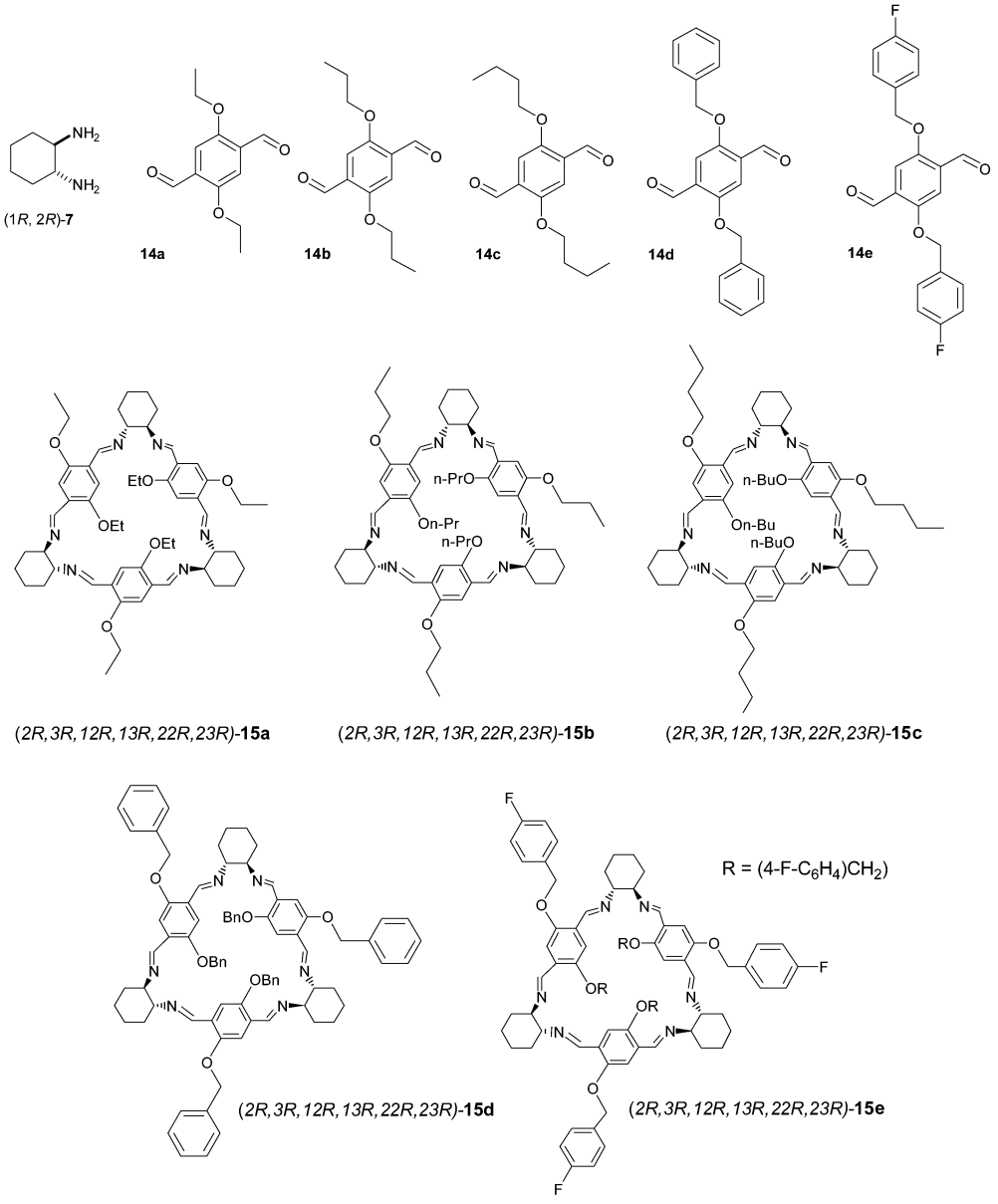


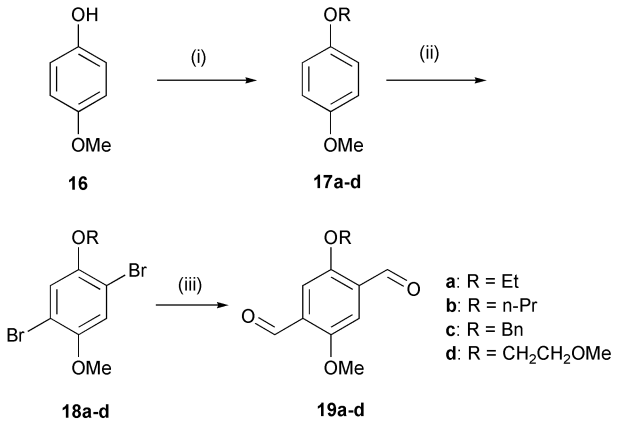
Table 1 Yields of dibromides **13a–e**, **18a–d** and dialdehydes **14a–e**, **19a–d**

Dibromide	R	Yield (%)	Dialdehyde	R	Yield (%)
13a	Et	48	**14a**	Et	64
13b	*n*-Pr	18	**14b**	*n*-Pr	40
13c	*n*-Bu	81	**14c**	*n*-Bu	35
13d	Bn	70	**14d**	Bn	95
13e	(4-F-C_6H_4)CH_2	50	**14e**	(4-F-C_6H_4)CH_2	56
18a	Et	27	**19a**	Et	57
18b	*n*-Pr	88	**19b**	*n*-Pr	96
18c	Bn	80	**19c**	Bn	19
18d	$MeOCH_2CH_2$	81	**19d**	$MeOCH_2CH_2$	62

Table 2 Crude (as judged by ^{1}H-NMR spectra of crude reaction mixtures) and isolated yields of trianglimine macrocycles **15a–e** and **20a–d**

Dialdehyde starting material	R	Trianglimine	Crude yield (%)	Isolated yield (%)
14a	Et	**15a**	82	18
14b	*n*-Pr	**15b**	70	17
14c	*n*-Bu	**15c**	60	32
14d	Bn	**15d**	76	23
14e	(4-F-C_6H_4)CH_2	**15e**	83	29
19a	Et	**20a**	71	8
19b	*n*-Pr	**20b**	86	15
19c	Bn	**20c**	78	13
19d	$MeOCH_2CH_2$	**20d**	78	5

show two non-equivalent aromatic hydrogens in their ^{1}H-NMR spectra and six signals for the non-equivalent carbon atoms in their ^{13}C-NMR spectra, as expected.



Scheme 4 *Reagents and conditions*: (i) RX (for RX see experimental section), NaOH, DMSO; (ii) Br_2, HOAc, NaOAc; (iii) 1. 2.2 eq. *n*-BuLi, THF; 2. DMF; 3. HCl.

[3 + 3] Cyclocondensation between **19a–d** and enantiomerically pure diamine **7** gave the trinaglimine macrocycles **20a–d** in excellent yields, as judged by the ESI mass spectra of the crude reaction mixtures (see Fig. 1), always showing a single molecular ion of the expected mass. Again the crude yields are satisfactory, whereas the isolated yields are moderate due to the need for repeated recrystallisation. Crude and isolated yields are summarised in Table 2.

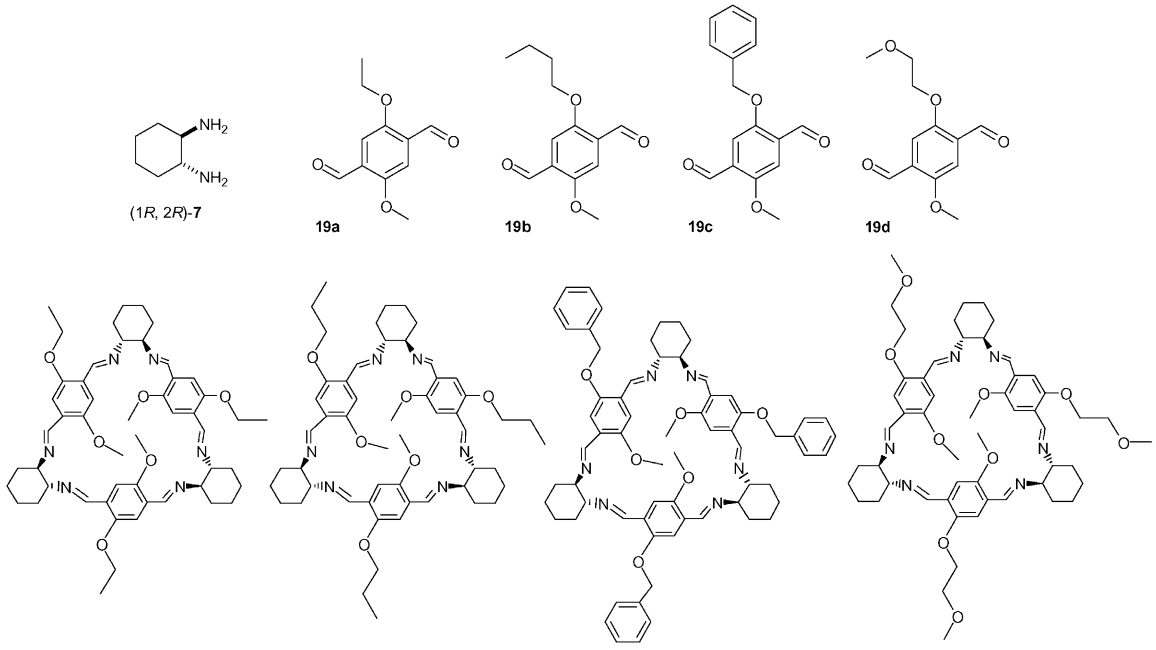
All the NMR spectra of the C_{2v} trianglimines derived from C_{2v} symmetric dialdehydes **20a–d** are distinctively different from those of the D_{3h} symmetric macrocycles **15a–e**, and require detailed discussion. As an example, compound **20c** has been chosen to illustrate all the features of the spectra. In this particular case all the ^{1}H-NMR signals were well separated (see Supplementary information†). The ^{1}H-NMR spectrum of **20c** in $CDCl_3$ clearly shows eight singlets for the imine protons (enlargement **I**), eight AB doublets for the diastereotopic OCH_2 protons (enlargement **II**), and four singlets for the OCH_3 protons (enlargement **III**).

The discussion that follows will be based on a series of previous experimental findings with respect to single crystal X-ray structure analysis of trianglimines reported[15,16] and conformational studies previously undertaken.[14] Furthermore, a series of scenarios need to be considered that take into account all possible isomers that could formed in the [3 + 3] cyclocondensation reaction, along with their theoretically expected spectra.

The reaction between any C_{2v} symmetric dialdehyde **19a–d** and (1*R*,2*R*)-**7** could give a series of isomeric compounds as possible reaction products whose structures are proposed in Fig. 2.

The potential reaction products can be divided into two main groups: the non-C_3 symmetrical isomers **A** and **B** (if X = -OCH_3 and Y = -$OCH_2C_6H_5$) and the C_3 symmetrical isomers **C** and **D**. For each C_3 symmmetric isomer several rotamers are additionally possible (such as **E** and **F** for **C** and **D** respectively), obtained by two different rotation mechanisms, which will be described in detail later.

Firstly, non-C_3 symmetric trianglimines **A** and **B** devoid of any symmetry element need to be considered and a comparison must be made between the theoretically expected ^{1}H-NMR spectrum and the experimentally observed ^{1}H-NMR spectrum. In a non-C_3 symmetric isomer such as **A**, all the protons in the macrocycle can be expected to be non-equivalent. Therefore, six imine, six aromatic and six CHN signals would be expected. Since the overall geometry of any trianglimine features three aromatic rings whose aromatic planes form a perpendicular arrangement,[14–16] two different substituents in a 1,4-position create an element of planar chirality; this situation is similar to the well-known disubstituted arene chromium and iron cyclopentadienyl half-sandwich complexes,[29,30] in which the planes above and below the aromatic ring turn non-equivalent. In the case of the macrocycles, one side of the macrocycle faces the cavity whereas the second one faces the outside of the macrocycle. Keeping this unusual stereochemical feature in mind, further diastereomeric symmetric macrocyclic products (such as **B**, a diastereomer of **A** and **C**, a diastereomer of **D**) become possible, again with an expected set of six non-equivalent imine and aromatic signals for **B** or two non-equivalent imine signals for **D**. To rationalise the above ^{1}H-NMR spectrum (eight signals of similar intensities for the eight non-equivalent imine protons, eight AB doublets for eight sets of diastereotopic non-equivalent benzyl protons and four non-equivalent -OCH_3), a mixture of one non-C_3



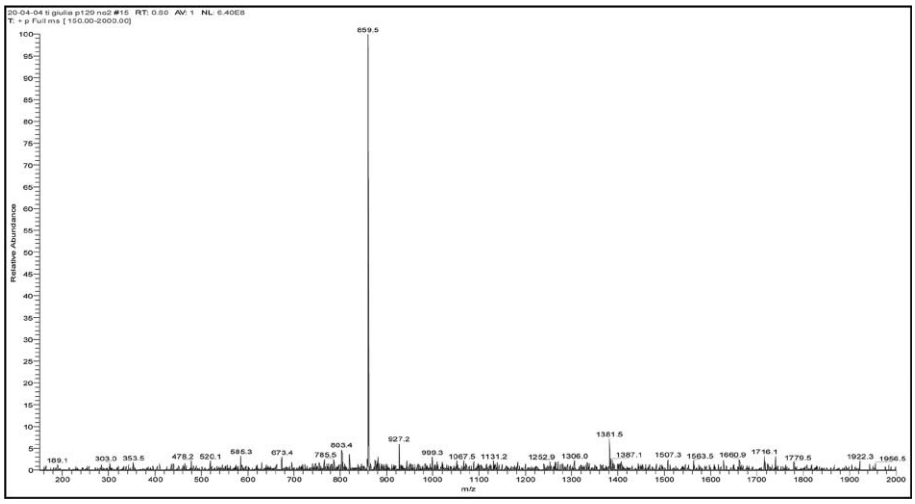


Fig. 1 ESI mass spectrum of compound **20c** (from methanol solution in positive ion mode).

symmetric diastereoisomer, which would account for the six lines for -CH=N and one C_3 symmetric diastereomer, which would account for the remaining two lines, can be postulated. The ^{1}H-NMR spectroscopic data of **20c** could be interpreted in terms of a 3 : 1 mixture of diastereomers with one diastereomeric non-C_3 symmetric isomer as the major component and one C_3 symmetric isomer as the minor component. If these two species are true diastereoisomers (*e.g.* **A** and **B**) as opposed to two diastereomeric rotamers (*e.g.* **D** and **E**) this scenario, although providing a sufficient rationale, seems highly unlikely. Firstly there is no rationale available to account for the high diastereoselection in the cyclisation process. Secondly the ^{1}H–^{1}H NOESY spectrum is in contradiction with this hypothesis since no NOE effect between any of the four non-equivalent -OCH_3 protons themselves or between the -OCH_3 protons and the -$OCH_2C_6H_5$ protons are observed. The existence of a non-C_3 symmetric isomer would require a set of such NOE contacts. A second explanation that fully accounts for the experimentally observed NMR spectra assumes the formation of single C_3 symmetric diastereoisomers that exist in two rotameric forms that interconvert slowly on the NMR timescale. In this case, one rotamer possesses C_3 symmetry, accounting for two imine peaks, and the second rotamer is devoid of any symmetry element, thus accounting for the remaining six imine signals. For any two diastereomeric C_3 symmetric isomers two mechanisms of internal rotation are possible and need to be distinguished. Firstly, simultaneous 180° rotation of the aromatic rings around the two C_{Ar}–C=N bonds produces two distinct rotamers (**C** → **E** or **D** → **F** in Fig. 3). This rotational mechanism has an equivalent in calix[4]arene chemistry;[31,32] in this case, through-annulus rotation of the OR group converts the cone conformation into the alternative conformation. In calix[4]arene chemistry the activation energy for this process depends strongly on the size of the OR substituents, *e.g.* for -OCH_3 the interconversion through rotation is slow on the NMR timescale and distinct rotamers can be observed by ^{1}H-NMR spectroscopy,[33,34] although the rotamers interchange in solution at higher temperature. For upper rim -$OCH_2CH_2CH_3$ substituents, this rotation is frozen and interconversion does not occur in solution even at higher temperature. In the case of trianglimine **20c**, there is no rationale to exclude the simultaneous 180° rotation of the aromatic rings around both C_{Ar}–C=N bonds; the rate of this on the ^{1}H-NMR timescale is so far unknown. This conclusion is based on differential NOE effects observed in **2** showing that both

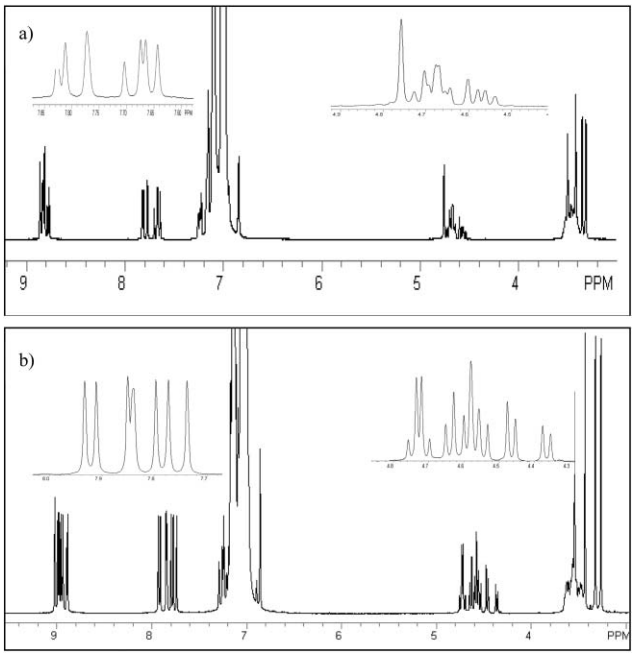


Fig. 2 Expanded region of ^{1}H-NMR spectra of compound **20c** in d_8-toluene at a) 363 K and b) 298 K (500 MHz).

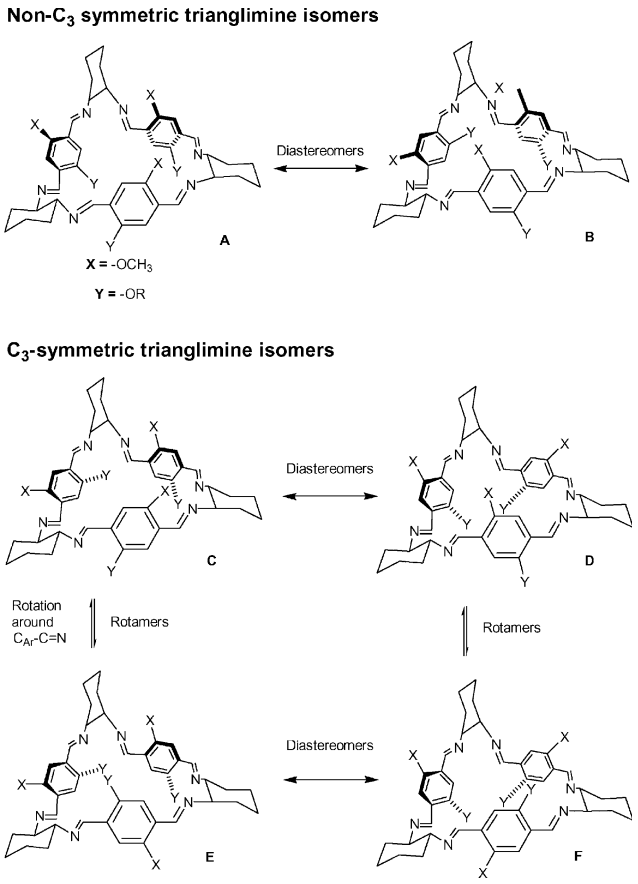


Fig. 3 Hypothetical isomeric products for reaction between **7** and **19a–d**.

rotamers coexist in solution.[14] The presence of rotamers is corroborated by the temperature dependent spectra of **20c** in d_8-toluene (Fig. 2).

As can be seen in Fig. 3, the imine signals, the aromatic signals, the -OCH_2- signals and the methoxy signals broaden at higher temperature, indicating an exchange process. Variation of the line shapes with increased temperature is in agreement with a conformational change rather than chemical interchange of diastereoisomers. Unfortunately we were unable to identify a solvent in which we could observe coalescence of all sets of signals. Furthermore, it is worth noting that the process is strongly solvent dependent. In d_6-DMSO at 363 K no changes in the spectra are apparent. The change of solvent does, however, alter the relative ratio of the two rotamers in solution, with the amount of the minor isomer in the non-polar solvent d_8-toluene being lower than in $CDCl_3$.

In order to rationalise the observed ^{1}H-NMR spectra (room temperature and high temperature) for **20c**, a second rotational mechanism in trianglimines should be considered. This second conformational change would involve simultaneous rotation around both HC–N=C bonds. This rotation, if it occurred three times, would be equivalent to a transformation from a *s-trans* arrangement of the bis-imine moiety to an *s-cis* arrangement (Fig. 4).

No definite spectroscopic information about the energy barrier required for simultaneous rotation around the C_{Ar}–C=N and HC–N=C bonds in trianglimines is currently available. Molecular modelling by Gawronski's group[15] argues in favour of a considerable ground state energy difference between *s-trans* and *s-cis* rotamers with preference for the former (as is found in X-ray structures). However, NOE experiments on a series of heterocyclic trianglimines suggest that in some cases the *s-cis* conformation is more favourable despite unfavourable repulsive lone pair–lone pair interactions.[14] In the hypothesis presented, rotation around the HC–N=C bond is expected to have a low activation barrier and is consequently fast on the NMR timescale. As an analogy, the activation barrier for the rotation process in a structurally related naphthalene imine was reported to be $\Delta G^{\ddagger} = 29.4$ kJ mol^{-1}, and rotation should thus be fast on the NMR time scale for trianglimines **20a–d**.[35]

The NOE data allow a more detailed assignment of the diastereomeric rotamers present in solution as *s-syn-cis*-**20c-I** and *s-syn-cis*-**20c-II** (Fig. 5). There are a series of NOE crosspeaks from the -OCH_3 resonances to the HC=N imine resonances present. However, NOE contacts from the -OCH_2- signals to the -HC=N imine signals are absent. This observation can be rationalised in terms of a *s-syn-cis* conformation dominating in solution. Furthermore, it appears as if the imine lone pair–oxygen lone pair repulsion is more pronounced for the -OMe moiety than for the -OBn moiety. To explain the observed NOE crosspeaks from the -OCH_3 resonances to the HC=N imine resonances and the presence of the C=N lone pair–oxygen lone pair repulsion (as expected according to VSEPR theory), the compound formed must favour the constitution and conformations shown in Fig. 5. The C=N lone pair–oxygen lone pair repulsion seem to be the dominating factor, producing exceptionally high diastereoselectivity in the [3 + 3] cyclocondensation process.

In conclusion, the ^{1}H-NMR spectrum of **20c** with eight signals of similar intensity for the eight non-equivalent imine protons, eight AB doublets for the eight sets of diastereotopic non-equivalent benzyl protons and four non-equivalent -OCH_3 peaks can be rationalised by assuming the presence of a mixture of the C_3 symmetric trianglimine rotamers *s-syn-cis*-**20c-I** and *s-syn-cis*-**20c-II** in a 1 : 3 ratio. Temperature dependent spectra clearly indicate that the two species are exchanging in solution, pointing towards a 1 : 3 mixture in solution at room temperature. The rotational process involves simultaneous rotation around two C_{Ar}–C=N- bonds, as shown in Fig. 6. Similar to calix[4]arene chemistry, a "cone" conformer and an "alternative" conformer are present, which exchange slowly on the NMR timescale.

The spectroscopic data for the other three trianglimines **20a,b,d** agree perfectly with those of **20c** and corroborate the purity and composition of the C_{2v} trianglimines.

In order to confirm the generality and validity of the above argument we decided to synthesise a structurally different C_{2v} symmetric dicarboxaldehyde. Dicarboxaldehyde **22** was obtained after sequential dilithiation in good yields from

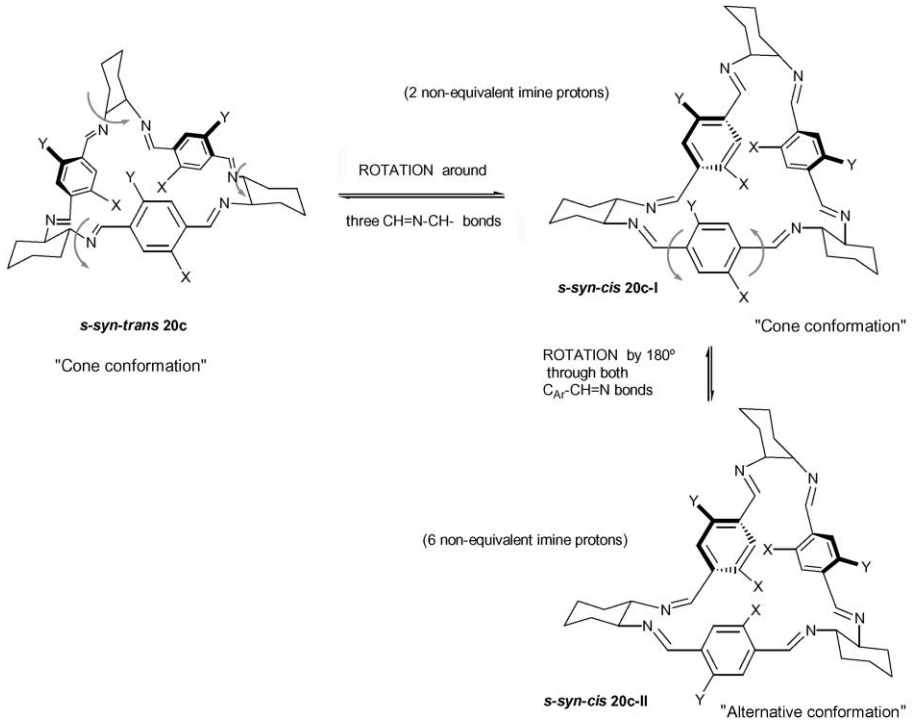


Fig. 4 Mechanism of isomerisation of **20c**.

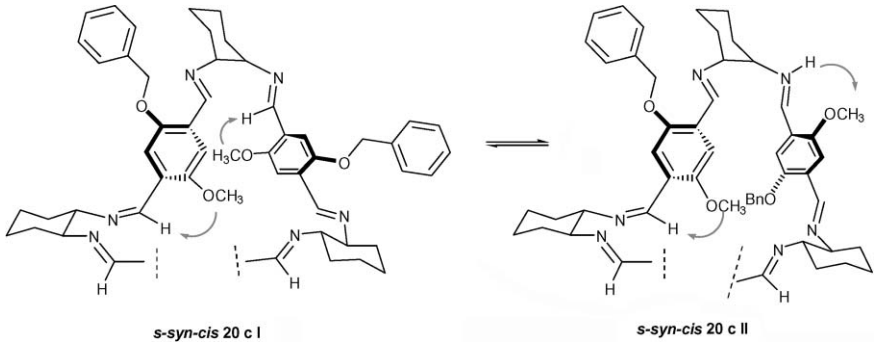


Fig. 5 NOE contacts in compound **20c**.

dibromide **21**. [3 + 3] Cyclocondensation with diamine **7** gave the trianglimine **23** (Scheme 5).

The NMR spectroscopic data of **23** mirror those of **20a–d**. Two triplets can be observed in the ^{1}H-NMR spectra of **23** for the imine protons in $CDCl_3$ that we interpret as originating from eight non-equivalent imine protons with two degenerate imine chemical shifts giving the triplet pattern. Again the spectra show broadening with increase of temperature (see Fig. 6), which is in line with slow exchange of two rotamers on the NMR timescale. The ^{1}H–^{1}H NOESY spectra allow detailed analysis of the conformation of the two rotamers involved, which are depicted in Fig. 7. Exhaustive reduction of **23** with $NaBH_4$ gave trianglamine **24**. In this compound, only one set of broad signals for each of the three repeating units can be observed. This observation can be explained by a reduction of the activation energy for the rotational process due to a lack of imine moieties whose conjugation to the aromatic ring increase the rigidity of the hexa-imine macrocycle, compared to a hexa-amine macrocycle. The reduction is therefore further evidence for the formation of a single diastereoisomer in the [3 + 3] cyclocondensation step of **22**.

Conclusion

In conclusion, we have shown that phenolic aromatic compounds can be transformed in a reliable and efficient synthetic sequence into aromatic dicarboxaldehydes. It is therefore possible to access a wide range of structurally diverse building blocks for [3 + 3] cyclocondensation reactions. The only restriction found is that the functionalities incorporated need to be compatible with the bromination–dilithiation synthetic sequence. All dicarboxaldehydes synthesised underwent [3 + 3] cyclocondensation reaction successfully to give a wide range of highly substituted trianglimine macrocycles. All compounds synthesised are valuable building blocks in organic synthesis and polymer synthesis, and the macrocycles obtained are valuable synthetic receptors for a variety of applications.

Trianglimines obtained from C_{2v} symmetric dicarboxaldehydes were shown to undergo the [3 + 3] cyclocondensation reaction with a high degree of diastereocontrol forming diastereoselectively stereogenic aromatic planes. The trianglimines obtained from C_{2v} symmetric dicarboxaldehydes comprise two distinct binding motifs separated by a plane through any three imine nitrogen atoms, and are proposed to exist as two rotamers in solution, which presumably interconvert by a through-annulus rotation process which is slow on the NMR timescale at room temperature.

Experimental

General

^{1}H and ^{13}C-NMR spectra were recorded on JEOL GSX 270 MHz and Bruker Avance DRX-500 MHz spectrometers.

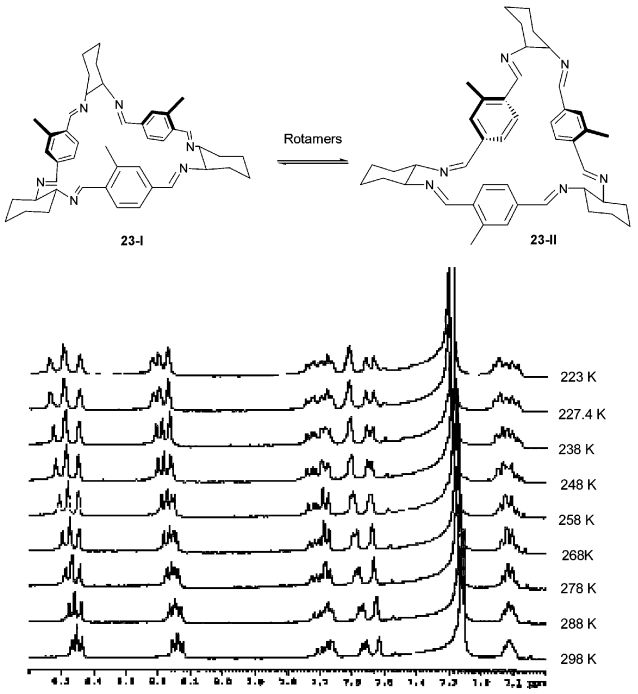
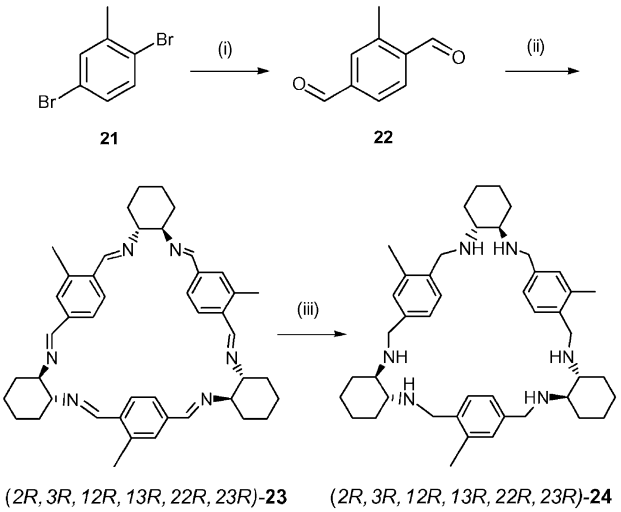


Fig. 6 Variable temperature ^{1}H-NMR spectra of trianglimine **23** in d_6-benzene (500 MHz).



Scheme 5 *Reagents and conditions*: (i) 1. 1.2 eq. *n*-BuLi, THF; 2. DMF, 3. 1.1 eq. *n*-BuLi, 4. DMF, 5. HCl; (ii) (1*R*,2*R*)-**7**, CH_2Cl_2, 0.01 M; (iii) $NaBH_4$, MeOH–THF.

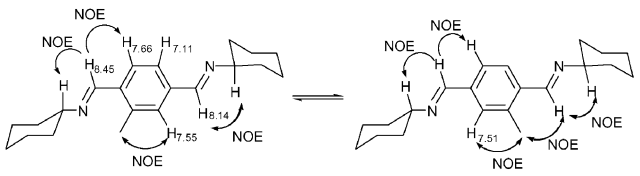


Fig. 7 NOE contacts in trianglimine **23** and structural assignment of two rotamers present in solution for **23**.

Standard Bruker 2-D software was used for spectral processing. Chemical shifts are reported as δ values in ppm relative to TMS ($\delta = 0.00$ ppm) when d_6-DMSO or d_8-toluene were used, or to $CDCl_3$ ($\delta_H = 7.26$ ppm for ^{1}H-NMR and $\delta_C = 77.0$ ppm for ^{13}C-NMR). Coupling constants (J) are quoted in Hz. ^{13}C-NMR data are only quoted for compounds that show sufficient solubility. Peaks assignments in the proton NMR are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet and m = multiplet. For the assignment of NMR signals for trianglimines the first proton/carbon for the first of the three repeating units is quoted.

Microanalyses 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 the inclusion of solvent molecules.[36,37] It is with this in mind that common solvent impurities can be included in the elemental calculation provided there exists corroboration within other spectra. The elemental analysis data, some of which are satisfactory and some are not, are all included. Purity of the compounds with non-satisfactory elemental analysis was demonstrated by ESI mass spectrometry or by accurate mass spectrometry.

Infrared spectra were determined on a Perkin–Elmer 200 spectrometer. Optical rotations were determined on a Bellingham and Stanley ADO 220 polarimeter. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were determined at two concentrations. The mass spectra (m/z) were recorded using a ThermoQuest Finnigan MAT 95 XL spectrometer. ESI-MS spectra were recorded on a ThermoFinnigan DECA CQXP Plus.

Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60 F_{254} silica). All chemicals/reagents were purchased from either Aldrich or Acros Chemical Companies and used without further purification unless stated otherwise. Solvents were dried and purified according to the standard procedures.[38,39] Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. All compounds are named using the IUPAC annulene nomenclature.[40]

The following compounds were prepared according to the published procedures or variations thereof; all compounds were fully characterised. Complete data for these compounds has been omitted from the experimental section, but is available on request.

(*1R,2R*)-Cyclohexane-1,2-diamine **7**,[24] 2-hydroxy-5-methylisophthalaldehyde **4**,[41,42] 6-bis(hydroxymethyl)-4-methyl-1-tosylbenzene,[42] 5-methyl-2-(tosyl)isophthalaldehyde **6**,[42] 1,4-diethoxybenzene **12a**,[43] 1,4-dipropoxybenzene **12b**,[44] 1,4-dibutoxybenzene **12c**,[45] 1,4-dibenzyloxybenzene **12d**,[46] 1,4-bis(2′-diethylaminoethoxy)benzene **12f**,[47] 1,4-bis(2′-pyridylmethoxy)-benzene **12g**,[48] 1-ethoxy-4-methoxybenzene **17a**,[49] 1-benzyloxy-4-methoxybenzene **17c**,[50] 1,4-dibromo-2,5-dipropoxybenzene **18b**,[51] and trianglimine **8**. All full data for novel diethers and dibromides are given in the Supplementary information for this publication.† Only one selected compound from each class is given in this full paper.

2,6-Diformyl-4-methylphenoxy methylacetate 5

A solution of 2-hydroxy-5-methylisophthalaldehyde **4** (0.1 g, 0.61 mmol) in anhydrous DMF (3 ml) was added to a stirred suspension of sodium hydride (NaH) (0.048 g, 1.22 mmol), in anhydrous DMF (2 ml), at room temperature under a dry nitrogen. The solution was stirred for 15 min. Methyl bromoacetate (116 µl, 1.22 mmol) was added to this solution. The reaction mixture was stirred for 3 h at room temperature. The solvent and the excess methyl bromoacetate (bp. 145 °C) were removed under reduced pressure. The residue was recrystallised from diethyl ether to give the *title product* **5** (0.073 g, 51.0%), as a light yellow solid; mp 33–35 °C; IR ν_{max} (solution in $CHCl_3$)/cm^{-1} 1759 (-COO-), 1687 (CHO); ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.41 (2H, s, -C*H*O), 7.89 (2H, s), 4.77 (2H, s, -CH_2-), 3.77 (3H, s, -COOCH_3), 2.40 (3H, s, Ar–CH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 190.17 (-*C*HO), 169.50 (-*C*O-OCH$_3$), 160.74 (C_1), 136.65 (C_4), 135.41 (C_3), 129.54 (C_2), 72.49 (-*C*H$_2$-), 52.47 (-COO-*C*H$_3$), 20.49 (Ar-*C*H$_3$); found (EI) 237.0756 [M + H$^+$], $C_{12}H_{13}O_5$ requires 237.0758; m/z (CI): 237 (100%, M + H$^+$), 222 (15%, M + H$^+$ − CH$_3$), 178 (45%, M + H$^+$ − COCH$_3$); CHN

requires for $C_{12}H_{12}O_5$: C 61.01%, H 5.12%; found: C 55.68%, H 5.07%.

(2*R*,3*R*,13*R*,14*R*,24*R*,25*R*)-1,4,12,15,23,26-Hexaaza-2,3:13,14:24,25-tributano-8,19,30-trimethyl-7′,18′,29′-tri(2′-oxopropoxy)-6,10:17,21:28,32-trimetheno-2*H*,3*H*,13*H*,14*H*,24*H*,25*H*-hexahydro[33]annulene 8

A solution of 2,6-diformyl-4-methylphenoxy methylacetate **5** (0.07 g, 0.31 mmol) in anhydrous dichloromethane (1.5 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.034 g, 0.31 mmol) in anhydrous dichloromethane (10 ml) at 0 °C. The mixture was stirred at room temperature for 76 h. The solvent was evaporated under reduced pressure. The residue was recrystallised from ethyl acetate–hexane (10 : 1) to give the *title product* **8** (19 mg, 6.0%) as a light brown solid; mp 152 °C; $[a]_D^{25}$ −100.1 (*c* 0.01, $CHCl_3$, 1 dm); IR ν_{max} ($CHCl_3$)/cm^{-1} 1759 (-CO–O-), 1634 (-C=N-); ^{1}H-NMR (500 MHz; $CDCl_3$) δ_H: 8.29 (6H, s, -C*H*=N-), 7.52 (6H, s), 4.38 (3H, d, *J* 8.9, -$CH_AH_BCO_2CH_3$), 4.35 (3H, d, *J* 8.9, -$CH_AH_BCO_2CH_3$), 3.61 (9H, s, -COOC*H*$_3$), 2.48 (9H, s, Ar-C*H*$_3$), 1.72–1.36 (30H + 12H, m, -C*H*$_2$, -C*H*-); ^{13}C-NMR (67.5 MHz; $CDCl_3$) δ_C: 170.14 (-*C*OOCH$_3$), 157.94 (-*C*=N-), 136.51, 133.51, 129.74, 129.59, 75.59 (-*C*H$_2$COOCH$_3$), 75.11 (-OCH$_3$), 52.59 (-*C*H-), 33.49 (-*C*H$_2$-), 24.97 (-*C*H$_2$-), 20.96 (-*C*H$_3$); *m/z* (ESI) 943.4 (75%, M + H$^+$); *m/z* (FAB): 943 (5%, M + H$^+$), 429; CHN requires for $C_{54}H_{66}N_6O_9$·EtOAc: C 67.59%, H 7.18%, N 8.15%; found: C 64.05%, H 6.98%, N 7.72%.

(2*R*,3*R*,13*R*,14*R*,24*R*,25*R*)-1,4,12,15,23,26-Hexaaza-2,3:13,14:24,25-tributano-8,19,30-trimethyl-7′,18′,29′-tri(4-methylbenzene sulfonate)-6,10:17,21:28,32-trimetheno-2*H*,3*H*,13*H*,14*H*,24*H*,25*H*-hexahydro[33]annulene 9

To a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.036 g, 0.31 mmol) in anhydrous dichloromethane (CH_2Cl_2) (1.5 ml) at 0 °C was added a solution of 5-methyl-2-tosyl-isophthalaldehyde **6** (0.1 g, 0.31 mmol) in dichloromethane (1.5 ml). The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from toluene to give the *title product* **9** (0.216 g, 58.5%) as a light yellow powder; mp 160–163 °C; $[a]_D^{25}$ −161.9 (*c* 0.1, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1633 (-C=N-), 1260; ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.06 (3H, s, -C*H*=N-), 7.65 (3H, s, -C*H*=N-), 7.61 (6H, d, *J* 7.7), 7.32 (6H, d, *J* 7.7), 7.25 (3H, s), 7.21 (3H, s), 3.07 (6H, br s, -C*H*–N), 2.47–1.39 (24H, m, -C*H*$_2$); ^{13}C-NMR (67.5 MHz, $CDCl_3$)§ δ_C: 156.08 (-*C*H=N-), 155.52 (-*C*H=N), 131.45, 130.68, 130.68, 129.31, 74.10 (-*C*H–N), 33.46 (-*C*H$_2$-), 33.17 (-*C*H$_2$-), 25.17 (-*C*H$_2$-), 24.88 (-*C*H$_2$-), 21.94 (*C*H$_3$), 20.69 (*C*H$_3$); *m/z* (ESI) 1189.4 (100%, M$^+$); *m/z* (FAB) 1190 (10%, M + H$^+$), 793 (10%, 2/3 M + H$^+$), 483, 388, 317; CHN requires for $C_{66}H_{72}N_6O_9S_3$: C 66.66%, H 6.05%, N 7.06%; found: C 65.58%, H 6.20%, N 6.73%.

1,4-Dibromo-2,5-diethoxybenzene 13a

A solution of bromine (619 µl, 1.92 g, 12.04 mmol) in glacial acetic acid (2 ml) was added to a solution of 1,4-diethoxybenzene **12a** (1 g, 6.02 mmol) and anhydrous potassium acetate (111.6 mg, 1.36 mmol) in glacial acetic acid (15 ml) at 17 °C. The solution was stirred for 2 h at the same temperature. The mixture was poured into distilled water (70 ml). The precipitate was filtered and dried under suction. The residue was recrystallised from CH_2Cl_2 to give the *title compound* **13a** (468 mg, 48.0%) as a light yellow powder; R_f 0.88 [ethyl acetate–hexane (1 : 1)]; mp 118 °C; IR ν_{max} (Nujol)/cm^{-1} 1490 (C=C), 1453, 1269 (C–O), 1030, 924, 777, 455 (C–Br); ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 7.15 (2H, s, -H_3 and -H_6), 4.06 (4H, q, *J* 7.1, -CH_2CH$_3$), 1.4 (6H, t, *J* 7.1, -CH$_2$CH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 150.70 (*C*$_2$–O), 119.26 (*C*$_3$), 111.80 (*C*$_1$–Br), 66.47 (-O*C*H$_2$CH$_3$), 15.33 (-OCH$_2$*C*H$_3$); *m/z* (EI) 325.8/ 323.8/ 321.8 (95%, M^{+81} Br, ^{79}Br), 297.8/ 295.8/ 293.8 (20%, M + H^{+81}Br, ^{79}Br–CH$_2$CH$_3$), 269.8/ 267.8/ 265.8 (100%, M + H$_2^{+81}$Br, ^{79}Br-2 CH$_2$CH$_3$); CHN requires for $C_{10}H_{12}Br_2O_2$: C 37.07%, H 3.73%; found: C 37.61%, H 3.78%.

2,5-Diethoxyterephthalaldehyde 14a

n-Butyllithium (*n*-BuLi) (3.8 ml, 1.6 M in hexane, 6.17 mmol) was added to a solution of 1,4-dibromo-2,5-diethoxybenzene **13a** (400 mg, 1.23 mmol) in anhydrous tetrahydrofuran (THF) (7 ml) at −78 °C under nitrogen. The solution was stirred for 2 h at the same temperature. Anhydrous DMF (480 µl, 6.17 mmol) was added to the reaction mixture. The solution was stirred for 30 min and then allowed to warm to room temperature. Distilled water (4 ml) and a 2 M solution of hydrochloric acid (HCl) (1.5 ml) were added to give a yellow solid. The precipitate was dried under reduced pressure and recrystallised from petroleum ether (40–60 °C) to give the *title compound* **14a** (175 mg, 64.0%) as a yellow powder; R_f 0.78 [ethyl acetate–hexane (1 : 1)]; mp 110 °C; IR ν_{max} (Nujol)/cm^{-1} 1687 (CO), 1480, 1393, 1149; ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.52 (2H, s, -C*H*O), 7.43 (2H, s, -H_3 and -H_6), 4.18 (4H, q, *J* 7.2, -OC*H*$_2$CH$_3$), 1.47 6 (6H, t, *J* 7.2, -OCH$_2$CH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 190.31 (-*C*HO), 155.78 (*C*$_2$ and *C*$_5$), 129.89 (*C*$_1$ and *C*$_4$), 112.27 (*C*$_3$ and *C*$_6$), 65.37 (-O*C*H$_2$CH$_3$), 15.10 (-OCH$_2$*C*H$_3$); found (EI) 223.0956 [M + H$^+$], $C_{12}H_{15}O_4$ requires 223.0965; *m/z* (EI) 223.2 (100%, M + H$^+$), 193 (30%, M$^+$ − CHO), 164 (98%, M$^+$ − 2 CHO); CHN requires for $C_{12}H_{14}O_4$: C 64.85%, H 6.35%; found C 62.68%, H 7.35%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,2)-tributano-7,8′,17,18′,27,28′-hexaethoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]-annulene 15a

A solution of 2,5-diethoxyterephthalaldehyde **14a** (100 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (1.5 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.053 g, 0.45 mmol) in anhydrous CH_2Cl_2 (1.5 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **15a** (0.072 g, 17.7%), as white powder; mp >320 °C $[a]_D^{25}$ −134.6 (*c* 0.05, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1627 (-CH=N-); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.52 (6H, s, -C*H*=N-), 7.27 (6H, s), 3.93 (6H, quintet, J_1 16.5, J_2 7.3, -$CH_AH_BCH_3$), 3.85 (6H, quintet, J_1 16.5, J_2 7.3, -$CH_AH_BCH_3$), 3.37 (6H, m, -N–C*H*-), 1.85–1.45 (24 H, m, -C*H*$_2$-), 1.19 (18H, t, *J* 7.3, -C*H*$_3$); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 157.21 (-*C*H=N), 153.07, 128.33, 111.63, 74.88 (-O*C*H$_2$CH$_3$), 65.33 (-*C*H–N-), 33.30 (-*C*H$_2$-), 25.00 (-*C*H$_2$-), 15.05 (-*C*H$_3$); *m/z* (FAB) 901 (100%, M$^+$); CHN requires for $C_{54}H_{72}N_6O_6$: C 71.97%, H 8.05%, N 9.33%; found: C 70.98%, H 8.05%, N 8.59%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,23-tributano-7,8′,17,18′,27,28′-hexapropoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]-annulene 15b

A solution of 2,5-propoxyterephthalaldehyde **14b** (80 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (2 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.037 g, 0.32 mmol) in anhydrous CH_2Cl_2 (1.5 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **15b** (0.054 g, 17.1%) as a white powder; mp >320 °C; $[a]_D^{25}$ −134.1 (*c* 0.08, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1626 (-CH=N-); δ_H (500 MHz, $CDCl_3$) 8.52 (6H, s, -C*H*=N-), 7.23 (6H, s), 3.81 (6H, dt, J_1 16.3, J_2 7.4, -O-CH_AH_BCH$_2$CH$_3$), 3.71

§ C_q signals for compounds **9**, **19a**, **19c** and **24** were not detectable due to their low solubility in $CDCl_3$.

(6H, dt, J_1 16.3, J_2 6.5, -O-CH$_A$$H_BCH_2CH_3$), 3.37 (6H, m, -N–C$H$-), 1.48 (12H, m, J_1 6.5, J_2 7.4, J_3 7.5, -O-CH$_2$CH_2CH$_3$), 1.86–1.46 (24 H, m, -CH_2-, CH_2-), 0.85 (18H, t, J 7.5, -CH_3); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 156.73 (-CH=N), 152.72, 127.90, 111.06, 74.52 (-OCH$_2$CH$_2$CH$_3$), 70.91 (-CH–N-), 33.04 (-CH$_2$-), 24.74 (-CH$_2$-), 22.75 (-OCH$_2$$CH_2CH_3$), 10.76 (-$CH_3$); m/z (FAB) 985.7 (100%, M + H$^+$); CHN requires for $C_{60}H_{84}N_6O_6$: C 73.14%, H 8.59%, N 8.53%; found: C 72.3%, H 8.71%, N 8.43%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12, 13:22,23-tributano-7,8′,17,18′,27,28′-hexabutoxy-6,9:16,19:26, 29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]-annulene 15c

A solution of 2,5-butoxyterephthalaldehyde **14c** (66 mg, 0.24 mmol) in anhydrous CH$_2$Cl$_2$ (2 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.027 g, 0.24 mmol) in anhydrous CH$_2$Cl$_2$ (1.5 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title compound* **15c** (0.086 g, 32.2%), as a light yellow powder; mp 195 °C; $[a]_D^{25}$ −90.0 (c 0.1, CHCl$_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1628 (-CH=N-); ^{1}H-NMR (500 MHz, CDCl$_3$) δ_H: 8.50 (6H, s, -CH=N-), 7.22 (6H, s), 3.88 (6H, dt, J_1 15.6, J_2 6.6, -OCH_AH$_B$-CH$_2$CH$_2$CH$_3$), 3.72 (6H, dt, J_1 15.6, J_2 6.0, -OCH$_A$$H_B$-CH$_2CH_2CH_3$), 3.36 (6H, m, -N–C$H$-), 1.85 − 1.45 (24H + 12H, m, -CH_2-, CH_2-, -OCH$_2$CH_2CH$_2$CH$_3$), 1.33 (12H, qt, J_1 7.1, J_2 7.5, -OCH$_2$CH$_2$CH_2CH$_3$), 0.90 (18H, t, J 7.5, -CH_3); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 156.90 (-CH=N), 152.75, 127.82, 110.84, 74.38 (-OCH$_2$CH$_2$CH$_2$CH$_3$), 69.03 (-CH–N-), 33.04 (-CH$_2$-), 31.61 (-CH$_2$-), 24.75 (-CH-), 19.49 (-CH$_2$-), 14.12 (-CH$_3$); m/z (FAB) 1069.8 (100%, M + H$^+$); CHN requires for $C_{66}H_{96}N_6O_6$: C 74.12%, H 9.05%, N 7.86%; found: C 73.36%, H 8.99%, N 7.62%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12, 13:22,23-tributano-7,8′,17,18′,27,28′-hexabenzyloxy-6,9:16, 19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro(30)-annulene 15d

A solution of 2,5-dibenzyloxyterephthalaldehyde **14d** (150 mg, 0.43 mmol) in anhydrous CH$_2$Cl$_2$ (2 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.049 g, 0.43 mmol) in anhydrous CH$_2$Cl$_2$ (1.5 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **15d** (0.126 g, 23.0%), as a white powder; mp 160 °C; $[a]_D^{25}$ −110.1 (c 0.11, CHCl$_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1630 (-CH=N-); ^{1}H-NMR (500 MHz, CDCl$_3$) δ_H: 8.59 (6H, s, -CH=N-), 7.39 (6H, s), 7.32 (12H, d, J 7.5, $H_{2'}$), 7.27 (12H, t, J 7.5, $H_{3'}$), 7.12 (6H, d, J 7.5, $H_{4'}$), 4.82 (6H, d, J 11.0, -OCH_AH$_B$-), 4.53 (6H, d, J 11.0, -OCH$_A$$H_B$-), 3.36 (6H, m, -N–C$H$-), 1.85–1.45 (24H, m, -CH_2-); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 156.54 (-CH=N), 152.68, 136.87, 128.57, 128.05, 128.02, 127.76, 111.23, 74.35 (-OCH$_2$Ph), 71.17 (-CH–N-), 32.92 (-CH$_2$-), 24.67 (-CH$_2$-); m/z (FAB) 1274 (100%, M + H$^+$); CHN requires for $C_{84}H_{84}N_6O_6$·EtOAc: C 77.65%, H 6.75%, N 6.17%; found: C 77.44%, H 6.67%, N 6.15%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12, 13:22,23-tributano-7,8′,17,18′,27,28′-hexa(4-fluorobenzyloxy)-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]annulene 15e

A solution of 2,5-bis(4-fluorobenzyloxy)terephthalaldehyde **14e** (90 mg, 0.235 mmol) in anhydrous CH$_2$Cl$_2$ (3 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.026 g, 0.235 mmol) in anhydrous CH$_2$Cl$_2$ (3 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate–petroleum ether (40–60 °C) (5 : 2), to give the *title product* **15e** (0.094 g, 29.0%) as a white powder; mp 85 °C; $[a]_D^{25}$ −84.21 (c 0.09, CHCl$_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1628 (-CH=N-); ^{1}H-NMR (500 MHz, CDCl$_3$) δ_H: 8.53 (6H, s, -CH=N-), 7.10 (12H, dd, J_1 5.2, J_2 8.2, $H_{2'}$), 7.01 (12H, s, J_1 8.2, J_2 10.6, $H_{3'}$), 6.91 (6H, s), 4.77 (6H, d, J 11.0, -OCH_AH$_B$-), 4.47 (6H, d, J 11.0, -OCH$_A$$H_B$-), 3.35 (6H, m, -N–C$H$-), 1.85–1.45 (24 H, m, -CH_2-); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 165.28 ($C_{4'}$–F, $^1J_{CF}$ 247.1), 156.26 (-CH=N-), 153.04, 132.95 (d, $^4J_{CF}$ 3.2), 129.67 (d, $^3J_{CF}$ 7.5), 119.54, 115.69 (d, $^2J_{CF}$ 16.9), 111.34, 74.28 (-OCH$_2$-(p-F)C$_6$H$_4$), 70.61 (-CH–N-), 32.86 (-CH$_2$-), 24.62 (-CH$_2$-); m/z (FAB) 1382.5 (100%, M + H$^+$); CHN requires for $C_{84}H_{78}F_6N_6O_6$·EtOAc: C 71.86%, H 5.85%, N 5.71%; found: C 68.86%, H 5.69%, N 3.81%.

1-Propoxy-4-methoxybenzene 17b

To dimethyl sulfoxide (30 ml), potassium hydroxide powder (9 g, 161.1 mmol) was added. After stirring for 5 min, 4-methoxyphenol **16** (5g, 40.3 mmol) was added, followed immediately by 1-iodopropane (7.87 ml, 13.72 g, 80.6 mmol) and sodium iodide (30 mg). Stirring was continued for 3 h, after which the mixture was poured into distilled water (50 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed with distilled water (5 × 100 ml), dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The residue was recrystallised from CH$_2$Cl$_2$ to give the *title compound* **17b** (5.40 g, 80.7%) as white needles; R_f 0.81 [ethyl acetate–hexane (1 : 1)]; mp 35 °C; IR ν_{max} (Nujol)/cm^{-1} 1509 (C=C), 1465, 1376, 1228 (O–CH$_2$-), 1043; ^{1}H-NMR (270 MHz, CDCl$_3$) δ_H: 6.83 (2H, d, J 6.1, H_2), 6.77 (2H, d, J 6.1, H_3), 4.90 (2H, t, J 7.4, -OCH_2CH$_2$CH$_3$), 3.76 (3H, s, -OCH_3), 1.77 (2H, sextet, J 7.4, -OCH$_2$CH_2CH$_3$), 1.38 (3H, t, J 7.4, -OCH$_2$CH$_2$CH_3); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 154.38 (C_4–OCH$_3$), 154.01 (C_1–OCH$_2$CH$_2$CH$_3$), 116.08 (C_3–H), 115.27 (C_2–H), 70.72 (-OCH$_2$CH$_2$CH$_3$), 56.27 (-OCH$_3$), 23.17 (-OCH$_2$CH$_2$CH$_3$), 10.98 (-OCH$_2$CH$_2$CH$_3$); m/z (EI) 167 (50%, M + H$^+$), 124 (100%, M + H$^+$ − C$_3$H$_7$); CHN requires for $C_{10}H_{14}O_2$: C 72.26%, H 8.49%; found: C 72.10%, H 8.76%.

1,4-Dibromo-2-ethoxy-5-methoxybenzene 18a

A solution of bromine (678 µl, 2.1 g, 13.2 mmol) in glacial acetic acid (2 ml) was added to a solution of 1-ethoxy-4-methoxybenzene **17a** (1 g, 6.6 mmol) and anhydrous potassium acetate (122 mg, 1.5 mmol) in glacial acetic acid (8 ml) at 17 °C. The solution was stirred for 2 h at the same temperature. The mixture was poured into distilled water (100 ml). The precipitate was filtered and dried under reduced pressure. The residue was recrystallised from petroleum ether to give the *title compound* **18a** (552 mg, 27.0%), as a light yellow powder; R_f 0.88 [ethyl acetate–hexane (1 : 1)]; mp 66 °C; ν_{max} (Nujol)/cm^{-1} 1461 (C=C), 1378, 1359, 1271 (O–CH$_2$-), 1066; ^{1}H-NMR (270 MHz, CDCl$_3$) δ_H: 7.10 (2H, s, -H_3 and -H_6), 4.03 (2H, q, J 7.4, -OCH_2CH$_3$), 3.84 (3H, s, -OCH_3), 1.43 (3H, t, J 7.4, -OCH$_2$CH_3); ^{13}C-NMR (67.5 MHz, CDCl$_3$) δ_C: 155.46 (C_2 or C_5), 152.95 (C_2 or C_5), 120.05 (C_3 or C_6), 118.38 (C_3 or C_6), 112.57 (C_1 or C_4), 110.61 (C_1 or C_4), 64.75 (-OCH$_2$CH$_3$), 56.48 (-OCH$_3$), 14.72 (-OCH$_2$CH$_3$); m/z (CI) 313/311/309 (100%, M + H$^+$ ^{81}Br,^{79}Br), 232.1/230.1 (15%, M + H^{+81}Br − ^{81}Br); m/z (EI) 312/310/308 (70%, M$^+$ ^{81}Br,^{79}Br), 284/282/280 (100%, M + H$^+$ ^{81}Br,^{79}Br − C$_2$H$_5$), 269/267/265 (70%, M + H$_2^{2+}$ ^{81}Br,^{79}Br − OC$_2$H$_5$); CHN requires for $C_9H_{10}Br_2O_2$: C 34.87%, H 3.25%; found: C 34.62%, H 3.18%.

2-Ethoxy-5-methoxyterephthalaldehyde 19a

n-BuLi (4.03 ml, 1.6 M in hexane, 6.45 mmol) was added to a solution of 1,4-dibromo-2-ethoxy-5-methoxybenzene **18a** (400 mg, 1.29 mmol) in anhydrous THF (3 ml) at −78 °C under nitrogen. The solution was stirred for 2 h at the same temperature. Anhydrous DMF (501 µl, 6.45 mmol) was added

to the reaction mixture. The solution was stirred for 30 min and then allowed to warm to room temperature. Distilled water (4 ml) and a 2 M solution of HCl (1.5 ml) were added to give a yellow solid. The precipitate was filtered, dried under reduced pressure and recrystallised from petroleum ether (40–60 °C) to give the *title compound* **19a** (153 mg, 57.1%) as a yellow powder; R_f 0.83 [ethyl acetate–hexane (1 : 1)]; mp 111 °C; IR ν_{max} (Nujol)/cm^{-1} 1682 (CHO), 1464 (C=C), 1384, 1287, 1214 (O–CH_2-), 1041; ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.52 (1H, s, -CHO), 10.49 (1H, s, -CHO), 7.44 (1H, s, H_3 or H_6), 7.43 (1H, s, H_3 or H_6), 4.16 (2H, q, J 7.4, -OCH_2CH$_3$), 3.93 (3H, s, -OCH_3), 1.46 (3H, t, J 7.4, -OCH$_2$CH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$)§ δ_C: 190.68 (-*C*HO), 189.32 (-*C*HO), 112.61 (C_3 or C_6), 111.25 (C_6 or C_3), 65.22 (-O*C*H$_2$CH$_3$), 56.70 (-O*C*H$_3$), 15.11 (-OCH$_2$*C*H$_3$); *m/z* (CI) 209 (70%, M + H$^+$), 180 (100%, M + H$^+$ − CHO); CHN requires for $C_{11}H_{12}O_4$: C 63.45%, H 5.81%; found: C 63.57%, H 7.27%.

2-Propoxy-5-methoxyterephthalaldehyde 19b

n-BuLi (3.84 ml, 1.6 M in hexane, 6.15 mmol) was added to a solution of 1,4-dibromo-2-propoxy-5-methoxybenzene **18b** (400 mg, 1.23 mmol) in anhydrous THF (14 ml) at −78 °C under nitrogen. The solution was stirred for 3 h at the same temperature. Anhydrous DMF (478 µl, 6.15 mmol) was added to the reaction mixture. The solution was stirred for 1 h and then allowed to warm to room temperature. Distilled water (4 ml) and a 2 M solution of HCl (1.5 ml) were added to give a yellow solid. The precipitate was filtered, dried under reduced pressure and recrystallised from petroleum ether (40–60 °C) to give the *title compound* **19b** (261 mg, 95.5%) as a yellow powder; R_f 0.92 [ethyl acetate–hexane (1 : 1)]; mp 112 °C; IR ν_{max} (Nujol)/cm^{-1} 1689 (CHO), 1463 (C=C), 1377, 1291, 1215 (O–CH_2-), 1028; ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.53 (1H, s, -C*H*O), 10.49 (1H, s, -C*H*O), 7.44 (1H, s, H_3 or H_6), 7.43 (1H, s, H_3 or H_6), 4.05 (2H, t, J 7.6, -OCH_2CH$_2$CH$_3$), 3.93 (3H, s, -OCH_3), 1.85 (3H, sextet, J 7.6, -OCH$_2$CH_2CH$_3$), 1.06 (3H, t, J 7.6, -OCH$_2$CH$_2$CH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 190.21 (-*C*HO), 190.15 (-*C*HO), 156.57 (C_2 or C_5), 156.22 (C_2 or C_5), 124.30 (C_1 or C_4), 115.14 (C_1 or C_4), 111.34 (C_3 or C_6), 110.64 (C_3 or C_6), 71.31 (-O*C*H$_2$CH$_2$CH$_3$), 56.76 (-O*C*H$_3$), 22.93 (-OCH$_2$*C*H$_2$*C*H$_3$), 10.99 (-OCH$_2$CH$_2$*C*H$_3$); found (EI) 223.0959, $C_{12}H_{15}O_4$ requires 223.0965; *m/z* (EI) 223 (95%, M + H$^+$), 178 (100%, M$^+$ − [CHO + CH$_3$]), 164 (50%, M$^+$ − 2 CHO), 150 (45%, M$^+$ − [CH$_2$CH$_2$CH$_3$ + CHO]); CHN requires for $C_{12}H_{14}O_4$: C 64.85%, H 6.35%; found: C 65.05%, H 7.01%.

2-Benzyloxy-5-methoxyterephthalaldehyde 19c

n-BuLi (2.50 ml, 1.6 M in hexane, 4.03 mmol) was added to a solution of 1,4-dibromo-2-benzyloxy-5-methoxybenzene **18c** (300 mg, 0.81 mmol) in anhydrous THF (3 ml) at − 78 °C under nitrogen. The solution was stirred for 3 h at the same temperature. Anhydrous DMF (313 µl, 4.03 mmol) was added to the reaction mixture. The solution was stirred for 1 h and then allowed to warm to room temperature. Distilled water (4 ml) and a 2 M solution of HCl (1.5 ml) were added to give a yellow solid. The precipitate was filtered, dried under reduced pressure and recrystallised from petroleum ether (40–60 °C)–ethyl acetate (3 : 1) to give the *title compound* **19c** (40 mg, 18.6%) as a yellow powder; R_f 0.85 [ethyl acetate–hexane (1 : 1)]; mp 133 °C; ν_{max} (Nujol)/cm^{-1} 1679 (CHO), 1457, 1378, 1297 (O–CH_2-), 1131; ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.55 (1H, s, -CHO), 10.49 (1H, s, -CHO), 7.55 (1H, s, -H_3 or -H_6), 7.47 (1H, s, -H_3 or -H_6), 7.43 (2H, d, J 8.8, -$H_{2'}$), 7.37 (2H, dd, J_1 13.5, J_2 8.8, -$H_{3'}$), 7.30 (H, d, J 13.5, -$H_{4'}$), 5.19 (2H, s, -OCH_2Ph), 3.94 (3H, s, -OCH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$)§ δ_C: 189.39 (-*C*HO), 128.99 ($C_{2'}$ or $C_{3'}$ or $C_{4'}$), 128.68 ($C_{2'}$ or $C_{3'}$ or $C_{4'}$), 127.80 ($C_{2'}$ or $C_{3'}$ or $C_{4'}$), 112.65 (C_3 or C_6), 111.11 (C_3 or C_6), 71.42 (-O*C*H$_2$Ph), 56.44 (-O*C*H$_3$). Found (EI) 271.0950 [M + H$^+$], $C_{16}H_{15}O_4$ requires 271.0965; *m/z* (CI) 271 (100%, M + H$^+$), 179 (10%, M$^+$ − C_7H_7); CHN requires for $C_{16}H_{14}O_4$: C 71.10%, H 5.22%; found: C 67.95%, H 5.55%.

2-(2′-Methoxyethoxy)-5-methoxyterephthalaldehyde 19d

n-BuLi (2.50 ml, 1.6 M in hexane, 4.03 mmol) was added to a solution of 1,4-dibromo-2-benzyloxy-5-methoxybenzene **18d** (300 mg, 0.81 mmol) in anhydrous THF (3 ml) at −78 °C under nitrogen. The solution was stirred for 3 h at the same temperature. Anhydrous DMF (313 µl, 4.03 mmol) was added to the reaction mixture. The solution was stirred for 1 h and then allowed to warm to room temperature. Distilled water (4 ml) and a 2 M solution of HCl (1.5 ml) were added to give a yellow solid. The precipitate was filtered, dried under reduced pressure and recrystallised from petroleum ether (40–60 °C)–ethyl acetate (3 : 1) to give the *title compound* **19d** (120 mg, 62.2%) as a yellow powder; R_f 0.65 [ethyl acetate–hexane (1 : 1)]; mp 85 °C; IR ν_{max} (Nujol)/cm^{-1} 1683 (CHO), 1457 (C=C Ar), 1375, 1287 (O–CH_2-); ^{1}H-NMR (270 MHz, $CDCl_3$) δ_H: 10.43 (1H, s, -C*H*O), 10.37 (1H, s, -C*H*O), 7.33 (1H, s, -H_3 or -H_6), 7.27 (1H, s, -H_3 or -H_6), 4.20 (2H, AA′ part of AA′XX′ system, N 16.6, -OCH_2CH$_2$-OCH$_3$ or -OCH$_2$CH_2-OCH$_3$), 3.89 (3H, s, Ph–OCH_3), 3.83 (2H, XX′ part of AA′XX′ system, N 17.6, -OCH_2CH$_2$–OCH$_3$ or -OCH$_2$CH_2–OCH$_3$), 3.79 (3H, s, -OCH$_2$CH$_2$–OCH_3); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 190.08 (-CHO), 189.98 (-CHO), 156.63 (C_2 or C_5), 155.77 (C_2 or C_5), 130.21 (C_1 or C_4), 129.89 (C_1 or C_4), 112.93 (C_3 or C_6), 111.40 (C_3 or C_6), 71.32 (-OCH$_2$*C*H$_2$OCH$_3$), 69.40 (-O*C*H$_2$CH$_2$OCH$_3$), 59.79 (-OCH$_2$CH$_2$O*C*H$_3$), 56.72 (-O*C*H$_3$). Found (EI) 238.0828 [M$^+$], $C_{12}H_{14}O_5$ requires 238.0836; *m/z* (EI) 239 (100%, M + H$^+$), 209 (10%, M$^+$ − CHO), 180 (25%, M + H$^+$ − 2 CHO); CHN requires for $C_{12}H_{14}O_5$: C 60.50%, H 5.92%; found: C 57.89%, H 6.44%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,23-tributano-7,17,27-triethoxy-8′,18′,28′-trimethoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]annulene 20a

A solution of 2-ethoxy-5-methoxyterephthalaldehyde **19a** (100 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (3 ml) was added to a solution of (1*R*,2*R*) diaminocyclohexane **7** (0.055 g, 0.48 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **20a** (0.034 g, 8.2%), as a mixture of rotamers (2 : 1); mp >320 °C; $[\alpha]_D^{25}$ −416.67 (*c* 0.01, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1630 (-CH=N-); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.578 (1H, s, -C*H*=N-, 1st rotamer), 8.572 (1H, s, -C*H*=N-, 1st rotamer), 8.563 (1H, s, -C*H*=N-, 1st rotamer), 8.558 (1H, s, -C*H*=N-, 1st rotamer), 8.553 (1H, s, -C*H*=N-, 1st rotamer), 8.549 (1H, s, -C*H*=N-, 1st rotamer), 8.530 (3H, s, -C*H*=N-, 2nd rotamer), 8.526 (3H, s, -C*H*=N-, 2nd rotamer), 7.32 (3H + 3H, m, 1st rotamer), 7.29 (3H + 3H, m, 2nd rotamer), 3.93 (6H, m, -OCH_AH_BCH$_3$, 1st rotamer), 3.87 (6H, m, -OCH_AH_BCH$_3$, 2nd rotamer), 3.72 (9H, s, -OCH_3, 1st rotamer), 3.70 (9H, s, -OCH_3, 2nd rotamer), 3.37 (6H + 6H, m, -N–C*H*-, 1st and 2nd rotamers), 1.85–1.45 (24 H + 24 H, m, -CH_2-, 1st and 2nd rotamers), 1.26 (9H, dd, J_1 10.2, J_2 7.1, -CH_3, 1st rotamer), 1.21 (9H, t, J_1 15.8, J_2 8.1, -CH_3, 2nd rotamer); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 157.23 (-*C*H=N-, 1st rotamer), 157.14 (-*C*H=N-, 2nd rotamer), 153.68 1st rotamer), 153.60 (2nd rotamer), 153.11 (1st rotamer), 152.74 (2nd rotamer), 128.43 (1st rotamer), 128.37 (2nd rotamer), 127.38 (1st rotamer), 126.82 (2nd rotamer), 111.74 (1st rotamer), 111.70 (2nd rotamer), 110.15 (1st rotamer), 110.06 (2nd rotamer) 74.83 (-O*C*H$_2$CH$_3$ or -*C*H–N-, 1st rotamer), 74.77 (-O*C*H$_2$CH$_3$ or -*C*H–N-, 2nd rotamer) 65.44 (-O*C*H$_2$CH$_3$ or -*C*H–N-, 1st rotamer), 65.36 (-O*C*H$_2$CH$_3$ or -*C*H–N-, 2nd rotamer), 56.56 (-O*C*H$_3$, 1st rotamer), 56.51 (-O*C*H$_3$, 2nd rotamer), 33.34 (-*C*H$_2$-, 1st rotamer), 33.25 (-O*C*H$_3$, 2nd rotamer), 25.01 (-*C*H$_2$-, 1st rotamer), 24.95 (-*C*H$_2$-, 2nd rotamer), 15.20 (-*C*H$_3$, 1st rotamer),

15.15 (-CH_3, 2nd rotamer); *m/z* (FAB) 860 (100%, M + H^+); CHN requires for $C_{51}H_{66}N_6O_6 \cdot \frac{1}{2}$EtOAc: C 70.42%, H 7.75%, N 9.30%; found: C 69.19%, H 8.43%, N 9.13%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,23-tributano-7,17,27-trimethoxy-8′,18′,28′-tripropoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]annulene 20b

A solution of 2-ethoxy-5-methoxyterephthalaldehyde **19b** (120 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (3 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.061 g, 0.54 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **20b** (74 mg, 15.20%) as mixture of rotamers (1 : 1); mp >320 °C; $[\alpha]_D^{25}$ −200.1 (*c* 0.01, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1633 (-CH=N-); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.62 (1H, s, -C*H*=N-, 1st rotamer), 8.58 (1H, s, -C*H*=N-, 1st rotamer), 8.57 (1H, s, -C*H*=N-, 1st rotamer), 8.56 (1H, s, -C*H*=N-, 1st rotamer), 8.55 (1H, s, -C*H*=N-, 1st rotamer), 8.55(1H, s, -C*H*=N-, 1st rotamer), 8.51 (3H, s, -C*H*=N-, 2nd rotamer), 8.51 (3H, s, -C*H*=N-, 2nd rotamer), 7.29–7.27 (6H + 6H, m, 1st and 2nd rotamers), 3.89 (6H, m, -OCH_2CH$_2$CH$_3$, 1st rotamer), 3.86 (6H, m, -OCH_2CH$_2$CH$_3$, 2nd rotamer), 3.73 (9H, s, -OCH$_3$, 1st rotamer), 3.70 (9H, s, -OCH$_3$, 2nd rotamer), 3.36 (6H + 6H, m, -N-C*H*-, 1st and 2nd rotamers), 1.85–1.45 (48H + 12H, m, -CH_2-, -CH$_2$CH_2CH$_3$, 1st and 2nd rotamers), 0.95 (9H, t, *J* 7.3, -CH_3, 1st rotamer), 0.89 (9H, t, *J* 7.3, -CH_3, 2nd rotamer); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 157.20 (-*C*H=N-, 1st rotamer), 157.08 (-*C*H=N-, 2nd rotamer), 153.73 (1st rotamer), 153.65 (2nd rotamer), 153.32 (1st rotamer), 153.29 (2nd rotamer), 128.38 (1st rotamer), 128.16 (2nd rotamer), 127.97 (1st rotamer), 127.92 (2nd rotamer), 111.73 (1st rotamer), 111.42 (2nd rotamer), 110.67 (1st rotamer), 110.13 (2nd rotamer), 74.61 (-O*C*H$_2$CH$_2$CH$_3$ or -*C*H-N-, 1st rotamer), 74.28 (-O*C*H$_2$CH$_2$CH$_3$ or -*C*H-N-, 2nd rotamer), 71.05 (-O*C*H$_2$CH$_2$CH$_3$ or -*C*H-N-, 1st rotamer), 70.91 (-O*C*H$_2$CH$_2$CH$_3$ or -*C*H-N-, 2nd rotamer), 56.29 (-OCH$_3$, 1st rotamer), 56.16 (-OCH$_3$, 2nd rotamer), 33.03 (-*C*H$_2$-, 1st rotamer), 32.90 (-*C*H$_2$-, 2nd rotamer), 25.07 (-OCH$_2$*C*H$_2$CH$_3$, 1st rotamer), 24.65 (-OCH$_2$*C*H$_2$CH$_3$, 2nd rotamer), 22.76 (-*C*H$_2$-, 1st rotamer), 22.73 (-*C*H$_2$-, 2nd rotamer), 11.08 (-*C*H$_3$, 1st rotamer), 10.72 (-*C*H$_3$, 2nd rotamer); *m/z* (FAB) 902 (100%, M + H^+); CHN requires for $C_{54}H_{72}N_6O_6 \cdot$EtOAc: C 70.43%, H 8.08%, N 8.49%; found: C 70.73%, H 8.10%, N 8.61%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,23-tributano-7,17,27-tribenzyloxy-8′,18′,28′-trimethoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]annulene 20c

A solution of 2-benzyloxy-5-methoxyterephthalaldehyde **19c** (120 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (3 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.061 g, 0.54 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate–petroleum ether (40–60°) (1 : 1) to give the *title product* **20c** (38 mg, 12.5%), as a mixture of rotamers; mp 225 °C; $[\alpha]_D^{25}$ −217.19 (*c* 0.02, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1631 (-CH=N-); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.65 (1H, s, -C*H*=N-1st rotamer), 8.62 (1H, s, -C*H*=N-, 1st rotamer), 8.61 (1H, s, -C*H*=N-, 1st rotamer), 8.59 (1H, s, -C*H*=N-, 1st rotamer), 8.59 (1H, s, -C*H*=N-, 1st rotamer), 8.59(1H, s, -C*H*=N-, 1st rotamer), 8.54 (3H, s, -C*H*=N-, 2nd rotamer), 8.54 (3H, s, -C*H*=N-, 2nd rotamer), 7.49 (1H, s, 1st rotamer), 7.47 (1H, s, *Ar*, 1st rotamer), 7.46 (1H, s, *Ar*, 1st rotamer), 7.43 (1H, s, *Ar*, 1st rotamer), 7.42 (1H, s, *Ar*, 1st rotamer), 7.41 (1H, s, *Ar*, 1st rotamer), 7.38–7.31 (15H + 15H, m, -C$_6H_5$, 1st and 2nd rotamers), 7.21 (3H, s, *Ar*, 2nd rotamer), 7.19 (3H, s, *Ar*, 2nd rotamer), 5.02 (1H, d, *J* 11.3, -CH_ACH$_B$Ph, 1st rotamer), 4.98 (1H, d, *J* 11.3, -CH$_A$CH_BPh, 1st rotamer), 4.93 (1H, d, *J* 11.1, -CH_ACH$_B$Ph, 1st rotamer), 4.90 (1H, d, *J* 11.1, -CH$_A$CH_BPh, 1st rotamer), 4.89 (1H, d, *J* 11.2, -CH_ACH$_B$Ph, 1st rotamer), 4.88 (1H, d, *J* 11.2, -CH$_A$CH_BPh, 1st rotamer), 4.76 (3H, s, *J* 11.0, -CH_ACH$_B$Ph, 2nd rotamer), 4.74 (1H, d, *J* 11.0, -CH$_A$CH_BPh, 2nd rotamer), 3.76 (3H, s, -OCH_3, 1st rotamer), 3.67 (3H, s, -OCH_3, 1st rotamer), 3.62 (3H, s, -OCH_3, 1st rotamer), 3.55 (9H, s, -OCH_3, 2nd rotamer), 3.36 (6H + 6H, m, -N–C*H*-, 1st and 2nd rotamers), 1.87 − 1.28 (24H + 24H, m, -CH_2-, 1st and 2nd rotamers); ^{1}H-NMR (500 MHz, d_8-toluene) δ_H: 9.02 (1H, s, -C*H*=N-, 1st rotamer), 9.02 (1H, s, -C*H*=N-, 1st rotamer), 8.99 (1H, s, -C*H*=N-, 1st rotamer), 8.97 (1H, s, -C*H*=N-, 1st rotamer), 8.96 (1H, s, -C*H*=N-, 1st rotamer), 8.94 (1H, s, -C*H*=N-, 1st rotamer), 8.90 (3H, s, -C*H*=N-, 2nd rotamer), 8.89 (3H, s, -C*H*=N-, 2nd rotamer), 7.93 (1H, s, -*Ar*, 1st rotamer), 7.91 (1H, s, -*Ar*, 1st rotamer), 7.85 (1H, s, -*Ar*, 1st rotamer), 7.84 (3H, s, -*Ar*, 2nd rotamer), 7.82 (3H, s, -*Ar*, 2nd rotamer), 7.79 (1H, s, -*Ar*, 1st rotamer), 7.77 (1H, s, -*Ar*, 1st rotamer), 7.74 (1H, s, -*Ar*, 1st rotamer), 7.25–6.67 (15H + 15H, m, -C$_6H_5$, 1st and 2nd rotamers), 4.75 (3H, d, *J* 11.9, -OCH_AH$_B$Ph, 2nd rotamer), 4.71 (3H, d, *J* 11.9, -OCH$_A$H$_B$Ph, 2nd rotamer), 4.64 (1H, d, *J* 11.7, -OCH_ACH$_B$Ph, 1st rotamer), 4.59 (1H, d, *J* 11.7, -OCH$_A$CH_BPh, 1st rotamer), 4.57 (1H, d, *J* 10.9, -OCH_ACH$_B$Ph, 1st rotamer), 4.54 (1H, d, *J* 10.9, -OCH$_A$CH_BPh, 1st rotamer), 4.47 (1H, d, *J* 11.6, -OCH_ACH$_B$Ph, 1st rotamer), 4.37 (1H, d, *J* 11.6, -OCH$_A$CH_BPh, 1st rotamer), 3.54 (9H, s, -OCH_3, 2nd rotamer), 3.43 (3H, s, -OCH_3, 1st rotamer), 3.33 (3H, s, -OCH_3, 1st rotamer), 3.27 (3H, s, -OCH_3, 1st rotamer), 2.21–0.64 (24H + 24H, m, -CH_2-, 6H + 6H, m, -C*H*-N, m, 1st and 2nd rotamers); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ_C: 157.15 (-*C*H=N-, 1st rotamer), 156.64 (-*C*H=N-, 2nd rotamer), 154.09 (1st rotamer), 154.03 (2nd rotamer), 152.94 (1st rotamer), 152.84 (20nd rotamer), 137.61 (1st rotamer), 136.87 (2nd rotamer), 129.17 (1st rotamer), 129.07 (2nd rotamer), 128.64 (1st rotamer), 128.59 (2nd rotamer), 128.51 (1st rotamer), 128.27 (2nd rotamer), 128.16 (1st rotamer), 128.11 (2nd rotamer), 112.18 (1st rotamer), 111.50 (2nd rotamer), 110.66 (1st rotamer), 110.56 (2nd rotamer), 74.86 (-O*C*H$_2$Ph or *C*H-N-, 1st rotamer), 74.61 (-O*C*H$_2$Ph or *C*H–N-, 2nd rotamer), 72.01 (-O*C*H$_2$Ph or -*C*H–N-, 1st rotamer), 71.60 (-O*C*H$_2$Ph or -*C*H-N-, 2nd rotamer), 56.61 (-*C*H$_2$-, 1st rotamer), 56.41 (-*C*H$_2$-, 2nd rotamer), 32.34 (-*C*H$_2$-, 1st rotamer), 33.17 (-*C*H$_2$-, 2nd rotamer), 24.98 (-*C*H$_3$, 1st rotamer), 24.95 (-*C*H$_3$, 2nd rotamer); *m/z* (FAB) 1045 (100%, M^+); CHN requires for $C_{66}H_{72}N_6O_6 \cdot$EtOAc: C 74.20%, H 7.06%, N 7.41%; found: C 74.63%, H 7.10%, N 7.71%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*-1,4,11,14,21,24-Hexaaza-2,3:12,13:22,23-tributano-7,17,27-tri(2′-methoxyethoxy)-8′,18′,28′-trimethoxy-6,9:16,19:26,29-trietheno-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*)-hexahydro[30]annulene 20d

A solution of 2-methoxy-5-(2′-methoxyethoxy)terephthalaldehyde **19d** (120 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (3 ml) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine **7** (0.048 g, 0.42 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred at room temperature for 3 h and the solvent evaporated. The residue was recrystallised from ethyl acetate to give the *title product* **20d** (20 mg, 5.0%), as mixture of rotamers (3 : 1); mp 190 °C; $[\alpha]_D^{25}$ −500.1 (*c* 0.01, $CHCl_3$, 1 dm); IR ν_{max} (Nujol)/cm^{-1} 1635 (-CH=N-); ^{1}H-NMR (500 MHz, $CDCl_3$) δ_H: 8.612 (3H, s, -C*H*=N-, 2nd rotamer), 8.610 (1H, s, -C*H*=N-, 1st rotamer), 8.58 (3H, s, -C*H*=N-, 2nd rotamer), 8.57 (1H, s, -C*H*=N-, 1st rotamer), 8.55 (1H, s, -C*H*=N-, 1st rotamer), 8.53 (1H, s, -C*H*=N-, 1st rotamer), 8.51 (1H, s, -C*H*=N-, 1st rotamer), 8.48 (1H, s, -C*H*=N-, 1st rotamer), 7.30 (6H + 6H, m, 1st and 2nd rotamers), 4.03 (6H + 6H, m, -OCH$_2$-CH_2OCH$_3$, 1st and 2nd rotamers), 3.73 (6H + 6H, m, -OCH_2-CH$_2$OCH$_3$, 1st and 2nd rotamers), 3.37 (6H + 6H, m, -N-C*H*-, 1st and 2nd rotamers), 3.31 (9H + 9H, s, -OCH_3, 1st and 2nd rotamer), 1.88 − 1.18 (24H + 24H, m, -CH_2-1st and 2nd rotamer); ^{13}C-NMR (67.5 MHz, $CDCl_3$)§ δ_C: 157.15

(-*C*H=N-, 1st rotamer), 156.49 (-*C*H=N-, 2nd rotamer), 136.91 (1st rotamer), 136.47 (2nd rotamer), 132.56 (1st rotamer), 132.54 (2nd rotamer), 72.59 (-*C*H-N-, 1st rotamer), 71.66 (-*C*H–N-, 2nd rotamer), 69.34 (-O*C*$H_2$$CH_2$$OCH_3$, 1st rotamer), 69.24 (-O*C*$H_2$$CH_2$$OCH_3$, 2nd rotamer), 60.19 (-$OCH_2$*C*$H_2$$OCH_3$, 1st rotamer), 59.59 (-$OCH_2$*C*$H_2$$OCH_3$, 2nd rotamer), 55.33 (-$CH_2CH_2O$*C*$H_3$ or -O*C*H_3, 1st rotamer), 54.31 (-CH_2CH_2O*C*H_3 or -O*C*H_3, 2nd rotamer), 51.39 (-CH_2CH_2O*C*H_3 or -O*C*H_3, 1st rotamer), 51.08 (-CH_2CH_2O*C*H_3 or -O*C*H_3, 2nd rotamer), 33.44 (-*C*H_2-, 1st rotamer), 33.19 (*C*H_2-, 2nd rotamer), 25.07 (-*C*H_2-, 1st rotamer), 25.01 (-*C*H_2-, 2nd rotamer); *m/z* (FAB) 950 (75%, M + H)$^+$; CHN requires for $C_{54}H_{74}N_6O_6$·EtOAc: C 67.15%, H 7.91%, N 8.10%; found: C 67.15%, H 7.81%, N 7.98%.

1,4-Diformyl-2-methylbenzene 22

tert-Butyllithium (1.7 M in hexane, 4.26 ml, 7.25 mmol) was added to a solution of 2,5-dibromotoluene **21** (1 ml, 7.25 mmol) in dry THF (10 ml) at −78 °C under nitrogen and stirred for 2 h at the same temperature. DMF (0.56 ml, 7.25 mmol) was added to the reaction mixture at the same temperature and the solution stirred for 30 min. Then, 12.79 ml (21.79 mmol) of *tert*-butyllithium (1.7 M in hexane) was added. After 30 min, DMF (1.58 ml, 21.75 mmol) was added, and the mixture was stirred for 30 min. The mixture was allowed to warm to room temperature, and 15 ml of 3 N hydrochloric acid was added. The precipitate was filtered, recrystallised from petroleum ether and dried *in vacuo* to give the *title product* **22** as a light red powder (1.07 g, 99%); R_f 0.7 (EtOAc); mp 45 °C; IR ν_{max}(Nujol)/cm^{-1} 1699 (C=O);^{1}H-NMR (500 MHz; $CDCl_3$) δ_H 10.38 (1H, s, C*H*O), 10.08 (1H, s, C*H*O), 7.97 (1H, d, *J* 7.8, H_5), 7.86 (1H, d, *J* 7.8, H_4), 7.78 (1H, s, H_3), 2.76 (3H, s, -CH_3);^{13}C-NMR (67.8 MHz; $CDCl_3$) δ_C 192.8 (C_4-*C*HO), 192.5 (C_1-*C*HO), 133.4 (C_4), 132.8 (C_1), 127.9 (C_2), 19.9 (-*C*H_3) (quaternary Ar-C not detected); MS (EI) *m/z* 148 (M$^+$, 100%). Accurate mass requires for $C_9H_8O_2$: 148.0519; found 148.0523.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-8,18,27-trimethyl-2,3:12,13:22,23-tributano-6,9:16,19:26,29-tripropano-2*H*,3*H*,12*H*,13*H*,22*H*,23*H*-hexahydro[30]annulene 23

1,4-Diformyl-2-methylbenzene **22** (56 mg, 0.37 mmol) was added to a solution of (1*R*,2*R*)-diaminocyclohexane **7** (43 mg, 0.37 mmol) in dichloromethane (3.78 ml) and stirred for 3 h at room temperature. The solvent was evaporated and the residue was recrystallised from ethyl acetate to give the *title product* **23** as a pale yellow powder (120 mg, 46%); R_f 0.4 (EtOAc); mp >250 °C; $[\alpha]_D^{25}$ −361 (*c* 0.03, CH_2Cl_2, 1 dm); IR ν_{max}(Nujol)/cm^{-1} 1643 (C=N); ^{1}H-NMR (500 MHz; $CDCl_3$) δ_H 8.45 (6H, t, N=C*H*), 8.14 (6H, dd, N=C*H*), 7.66 (6H, m, Ar-*H*), 7.55 (6H, d, Ar-*H*), 7.51 (3H, s, Ar-*H*), 7.11 (3H, broad, Ar-*H*), 3.36 (12H, broad, C*H*-N), 2,43 (18H, s, -CH_3), 1.85–1.47 (48H, m, CH_2); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 161.0, 160.9, 54.7, 33.0, 24.9, 19.15 (the signals of the other rotamer overlap); MS (CI) *m/z* 679 (M$^+$, 100%). Accurate mass requires for $C_{25}H_{55}N_6$: 679.4483; found 679.447; CHN requires C 79.6%, H 8.0%, N 12.3%; found: C 78.4%, H 8.2%, N 12.2%.

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-8,18,27-trimethyl-2,3:12,13:22,23-tributano-6,9:16,19:26,29-tripropano-1*H*,2*H*,3*H*,4*H*,5*H*,10*H*,11*H*,12*H*,13*H*,14*H*,15*H*,20*H*,21*H*,22*H*,23*H*,24*H*,25*H*,30*H*-octadecahydro[30]annulene-24

Macrocycle **23** (35 mg, 0.51 mmol), and $NaBH_4$ (39 mg, 1.02 mmol) were stirred for 3 h in 6 ml of THF–MeOH (1 : 1) at room temperature. Chloroform (10 ml) andl water (10 ml) were added and the phases separated. The organic phase was dried over Na_2SO_4, filtered and removed *in vacuo*. The residue was recrystallised from hot toluene to give the title product **24** as a white powder; mp 185 °C; $[\alpha]_D^{25}$ −200 (*c* 0.01, $CHCl_3$, 1 dm); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.27 (6H, d, *J* 8.0, Ar-*H*), 7.22 (6H, d, *J* 7.0, Ar-*H*), 7.75 (6H, d, J 7.0, Ar-*H*), 7.18 (3H, s, Ar-*H*), 7.15 (3H, s, Ar-*H*), 7.12 (3H, s, Ar-*H*), 3.88 and 3.56 (36H, AB system, *J* 13.5, -CH_AH_BN), 2.28 (18H, broad, C*H*-N), 2.12–1.18 (90H, m, CH_2, N*H*); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ_C 139.7, 137.4, 136.5, 130.0, 128.7, 125.5, 50.7, 48.9, 31.8, 25.8, 19.2; MS (ESI) *m/z* 691 (M$^+$, 100%), 754.6 (M$^+$ + $NaBH_4$ + Na, 97%), 761.8 (M$^+$ + THF, 80%).

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