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The synthesis of trianglimines: on the scope and limitations of the [3 + 3] cyclocondensation reaction between (1*R*,2*R*)-diaminocyclohexane and aromatic dicarboxaldehydes

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The synthesis of 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 trianglimine macrocycles. The scope and limitations of the cyclocondensation reaction are studied and some comments on the properties of the novel macrocycles are made such as their conformation in solution and temperature dependent dynamic NMR behaviour.

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 materials science.[1,2] Molecular recognition of metal cations using non-natural receptors has reached a high level of maturity and sophistication and, as a consequence, is successfully applied on an industrial scale.[3–5] Molecular recognition of anions using non-natural receptors is making rapid progress,[6] whereas molecular recognition of small to medium sized organic molecules is somehow lingering 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 actively pursued.

Among the most promising applications of molecular recognition are the binding and remediation of environmental toxins from soil, water and food and the binding and removal of undesired trace by-products from the bulk manufacturing of fine chemicals. Moreover, chiral recognition and resolution of enantiomers, the development of sensors and bio-sensors and finally, the design, development and synthesis of nano-gadgets and molecular machines form exciting challenges for supramolecular chemistry for the next decade.[1,2]

In most of these exciting applications, the challenge for any supramolecular scientist is the identification of a host molecule or receptor that binds to a specific guest molecule with a high binding constant and with the required selectivity. In most of the potential applications of supramolecular chemistry mentioned above, it is always the small molecule that defines the scientific problem. The search for supramolecular host guest systems with a commercial impact requires the systematic variation of the synthetic host molecule until a suitable host guest system is discovered. This challenge can be viewed as the reverse to medicinal chemistry. Medicinal chemists rely on supramolecular interactions in the binding of a small drug molecule (guest) to a large receptor molecule (enzyme, receptor or host). We propose to refer to medicinal chemistry as "host centred chemistry", whereas supramolecular chemistry can be described as "guest centred chemistry". Medicinal chemists have to identify a small molecule that binds to a given biological target again with a high binding constant and with high selectivity. In the last decade medicinal chemists have adopted the concept of combinatorial chemistry as an appropriate means to make their quest for matching host guest systems more successful and more efficient.[7] The underlying paradigm of combinatorial chemistry simply states that the more compounds are synthesised and tested, the greater is the likelihood of success in identifying suitable host guest systems. Early experiences and disappointments with this approach have resulted in a slight revision of this paradigm, taking into account that the compounds being synthesised and screened should display molecular diversity. Diversity in this context refers to the compounds being structurally different. Applying this argument to supramolecular chemistry would mean that a large number of synthetic receptors need to be screened against a single guest molecule, which is of particular interest. Therefore, one of the first challenges for supramolecular chemists must be the development of synthetic methodology that allows an efficient synthesis of a large number of synthetic receptors. Secondly, these receptors should display molecular diversity with respect to size, geometry, stereochemistry, electronic properties and functionalities.

Supramolecular chemistry using synthetic receptors has conceptually neglected the combinatorial chemistry concept, with the notable exception of Lehn's and Sander's dynamic combinatorial library approach.[8,9] The main reason for this neglect might be found in the lack of available synthetic methods for the synthesis of large numbers of synthetic, mainly macrocyclic receptors due to inherent difficulties associated with the synthetic procedures such as low yields, restricted availability of templates and high dilution conditions. We conclude that, in order to improve our chances of successfully identifying commercially viable synthetic receptors, synthetic macrocyclic chemists must take on the challenge of developing synthetic methodology allowing the synthesis of large numbers of structurally diverse synthetic receptors. We have started a research programme aimed at developing synthetic methodology that allows the efficient synthesis of a large number of structurally diverse macrocyclic receptors.[10] As target molecules we have chosen calix[*n*]arenes as well as a new class of *para*- and *meta*-cyclophane polyimine macrocycles formed by a [3 + 3] cyclocondensation reaction. This new class of macrocycles, that we have named trianglimines, offers great promise in both generating diversity and small libraries of macrocyclic receptors. The first trianglimine macrocycles have been synthesised by Gawronski and co-workers.[11] Diastereomeric structures of this type of macrocycle have recently been reported by the group of Hodacova.[12] Other isolated examples of [3 + 3] cyclocondensation strategies have been reported.[13,14] We have recently reported on significant extensions to this chemistry,

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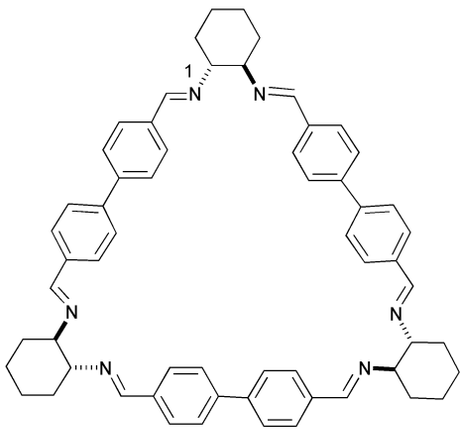
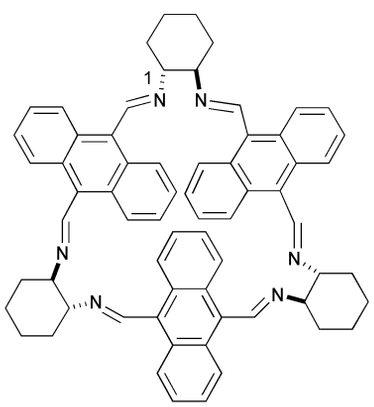
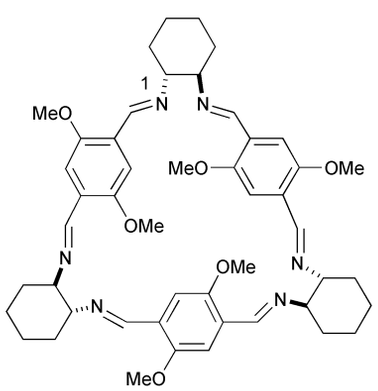


(2*R*, 3*R*, 16*R*, 17*R*, 30*R*, 31*R*)-**1**



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



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

Fig. 1

obtaining macrocycles with ring sizes of up to 42 such as **1**–**3** (Fig. 1) in almost quantitative yields.[15–16]

Within this contribution we would like to comment on the scope and limitations of the [3 + 3] cyclocondensation between (1*R*,2*R*)-diaminocyclohexane and various aromatic dicarboxaldehydes. Part of this work has been reported as a short communication.[12]

Results and discussion

Synthesis of aromatic dicarboxaldehydes

In order to investigate the scope and limitations of the [3 + 3] cyclocondensation of (1*R*,2*R*)-diaminocyclohexane with aromatic dicarboxaldehydes we required a selection of this class of compound. A thorough survey of the literature revealed that only isolated examples of aromatic dicarboxaldehydes have been prepared and no general method for their synthesis was available. Traditionally the formyl group is introduced onto an aromatic or heteroaromatic nucleus using standard electrophilic aromatic substitution reactions.[17] The Vilsmeier–Haack formylation suffers from the disadvantage that only highly electron rich aromatics give sufficiently good results.[17,18] For a one pot diformylation reaction the aromatic iminium ion intermediate is sufficiently deactivated to allow the reaction only in exceptional cases.[18] Other electrophilic formylation reactions such as the Gattermann, Gattermann–Koch or Reimer-Tiemann formylation suffer from similar problems. Additionally electrophilic aromatic formylations usually require drastic reaction conditions and often lack regioselectivity, producing a mixture of positional isomers. The majority of aromatic dicarboxaldehydes synthesised previously were obtained by double oxidation of benzylic alcohols,[19] double reduction of aromatic dinitriles or the Sommelet route using base hydrolysis of the corresponding tetrabromides.[20–24] In this work we report on the synthesis of aromatic dicarboxaldehydes using various directed dilithiation strategies followed by electrophilic quenching with DMF, which offer acceptable solutions to the synthetic problem. Isolated reports on dilithiation reactions have appeared in the literature and are referred to below.

1 Dilithiation by double lithium–bromine exchange

The lithium halogen exchange reaction was discovered by the groups of Wittig[25] and Gilman[26] in 1938 and has proven extremely useful ever since. Dilithiations using a double lithium–halogen exchange were firstly reported by the group of Worden using resorcinole dibromides[27] followed by Snieckus using *O*-carbamate substituted aromatics and *C*-amide substituted thiophene,[28,29] and finally by Nierengarten and co-workers.[30] Di- and tetralithiations have been reported using tetraiodocalix[4]arenes as precursors.[31]

Double lithium–bromine exchange on 1,4-dimethoxy-2,5-dibromobenzene **4a** proceeded smoothly at −78 °C in THF with 3 equivalents of *n*-BuLi to give the dialdehyde **5** after treatment with DMF and 3 M HCl in good yield. Treatment of 3,6-dibromo-*N*-ethylcarbazole **6** gave, under identical conditions, dicarboxaldehyde **7** (Fig. 2). Double lithium bromine exchange on methyl substituted aromatics **14**, **16**, **18** and **20** gave, only in the case of **20** using 5 equivalents of *n*-BuLi, a minute quantity of the desired dialdehyde **21** (see Table 1).

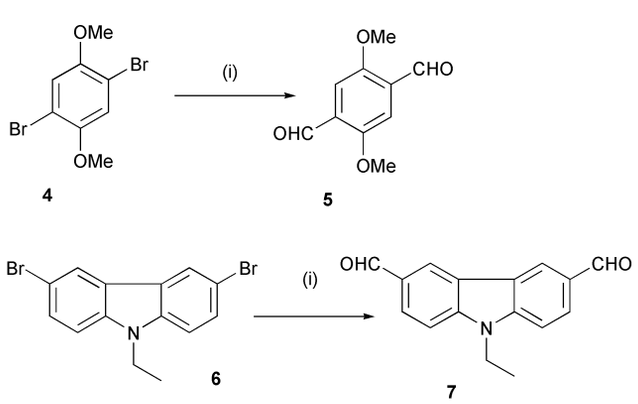


Fig. 2 *Reagents, conditions and yields:* (i) see method A in Table 1.

It is worth noting that double lithiation of fluorinated dibromides failed to yield any dicarboxaldehydes. Surprisingly the first lithium–bromine exchange step, carried out as a control reaction, proceeded smoothly and yielded the monoaldehydes in almost quantitative yields. Addition of more than 1 equivalent of *n*-BuLi however, produced what can only be described as complete and utter decomposition of all materials involved.

Table 1 Yields and conditions for double lithiations

Entry	Substrates	Conditions[a]	Products	Method[b]	Yield[d]
1	**4a**	1.3 eq. *n*-BuLi, −78 °C, THF, 2 h; 2.3 eq. DMF, −78 °C, THF, 30 min; 3.3 M HCl	**5**	A	61
2	**6**	1.4 eq. *n*-BuLi, −78 °C, THF, 2 h; 2.4 eq. DMF, −78 °C, THF, 30 min; 3.3 M HCl	**7**	A	50
3	**14**	See entry 1	**15**	A	0
4	**20**	See entry 1	**21**	A	0
5[c]	**8**	1.5 eq. *n*-BuLi–TMEDA, −78 °C, Et_2O, 2 h; 2.5 eq. DMF, rt, THF, 30 min; 3.3 M HCl	**9**	B	72
6	**4b**	See entry 5	**5**	B	92
7	**10**	See entry 5	**11**	B	76
8	**12**	See entry 5	**13**	B	79
9	**14**	1.1 eq. *n*-BuLi, −78 °C, THF, 30 min; 2.1 eq. DMF, −78 °C, THF, 30 min; 4.3 eq. *n*-BuLi, −78 °C, THF, 2 h; 5.3 eq. DMF, −78 °C, THF, 30 min; 6.3 M HCl	**15**	C	94
10	**14**	1.1 eq. ^{t}BuLi, −78 °C, THF, 30 min; 2.1 eq. DMF, −78 °C, THF, 30 min; 4.3 eq. ^{t}BuLi, −78 °C, THF, 2 h; 5.3 eq. DMF, −78 °C, THF, 30 min; 6.3 M HCl	**15**	C	0[e]
11	**14**	1.1 eq. *sec*-BuLi, −78 °C, THF, 30 min; 2.1 eq. DMF, −78 °C, THF, 30 min; 4.3 eq. *sec*-BuLi, −78 °C, THF, 2 h; 5.3 eq. DMF, −78 °C, THF, 30 min; 6.3 M HCl	**15**	C	65
12	**16**	See entry 9	**17**	C	0[e]
13	**16**	See entry 10	**17**	C	0[e]
14	**16**	See entry 11	**17**	C	71
15	**18**	See entry 9	**19**	C	87
16	**18**	See entry 10	**19**	C	0[e]
17	**20**	See entry 10	**21**	C	79

[a] Further work up as specified in experimental section. [b] Method A (double LiBr-exchange), Method B (double *ortho* lithiation), Method C (sequential dilithiation). [c] Determined as crude ratio by ^{1}H-NMR. [d] Isolated yield (all other materials are starting materials unless otherwise stated). [e] Complete decomposition, no specified product detectable.

2 Dilithiation by double directed *ortho*-metalation

The directed *ortho*-metalation reaction was published one year after the Li–Br exchange reaction, again concomitantly by the groups of Wittig[32] and Gilman.[33] It has been developed into one of the most fundamental methodologies in the functionalisation of aromatic compounds over the last two decades.[34] The dilithiation of aromatics using a double directed *ortho*-lithiation on a single aromatic nucleus has been reported by Snieckus and co-workers using the *O*-carbamate directing group and by Sundberg using the OMe directing group.[35,36] Double *ortho*-lithiation of aromatic compounds with the lithium atoms positioned on separated aromatic nuclei have been reported by König and co-workers in the synthesis of silicon bridged macrocycles[37] and by Warren and Wyatt in a series of papers on the elegant synthesis of homochiral phosphepines.[38,39] The synthesis of a dicarboxaldehyde using this approach was reported by Snieckus using a pyridylformamide as the formyl source, however the yield was low.[40] In our case the double directed *ortho*-lithiation on 1,2- and 1,4-dimethoxybenzene **4b** and **8** as well as on 1,3,5-trimethoxybenzene **10** after treatment with 3 equivalents *n*-BuLi–TMEDA complex for **4b**, and 5 equivalents for **8** in diethyl ether at reflux gave, after quenching with DMF followed by 3 M HCl, the dialdehydes **5**, **9** and **11** in satisfactory yields. Direct comparison of the two methods discussed so far, demonstrates the superiority, both in terms of yield, mildness of conditions and ease of work-up, in the synthesis of **5** using the Li–Br exchange route.

Double directed *ortho* lithiation of biphenyl **12** gave the dicarboxaldehyde **13** in poor yield (Fig. 3).

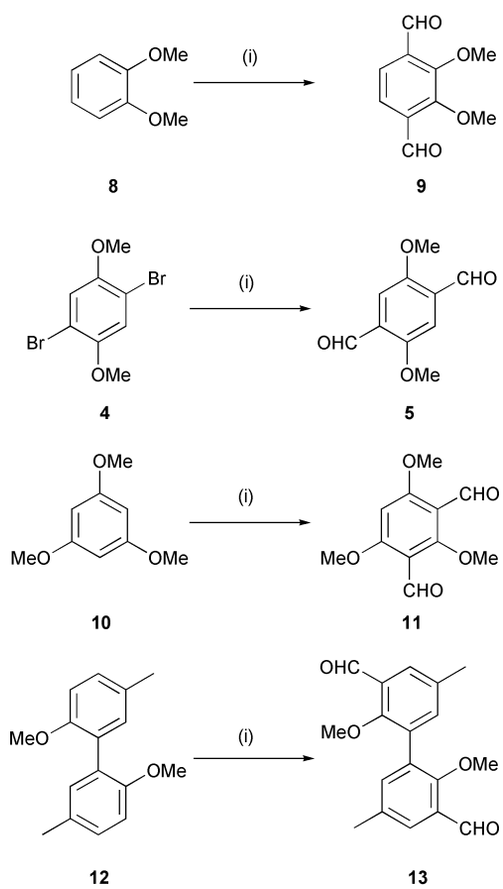


Fig. 3 *Reagents, conditions and yields:* (i) see method B in Table 1.

3 Sequential dilithiation by lithium–bromine exchange

Since a number of substrates failed to undergo the direct double lithiation we reasoned that a sequential route might be beneficial, moving the negatively charged centre away from the central aromatic nucleus and hence reduce any charge–charge repulsion (see Fig. 4).

The sequential route gave dicarboxaldehydes **15**, **17**, **19** and **21** in excellent yields (Fig. 5). Whereas for the previous dilithiation reactions *n*-BuLi was found to be most efficient, for the alkyl substituted dibromides **14**, **16**, **18** and **20** ^{t}BuLi was

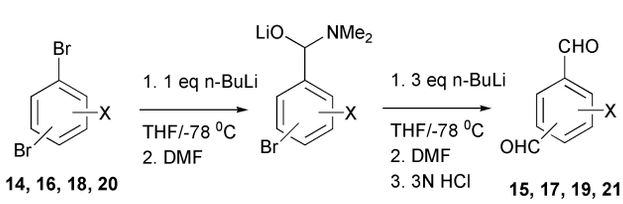


Fig. 4

Table 2 ^{1}H and ^{13}C chemical shifts of *ortho*-methyl groups in aromatic dicarboxaldehydes and reference compounds

Compound	δ_H (ppm)[a]	$\Delta\delta$ (ppm)[b]	δ_C (ppm)[a]	$\Delta\delta$ (ppm)[b]
Toluene	2.31	0	21.4	0
o-Tolaldehyde	2.64	+0.33	19.4	−2.0
15	2.67	+0.36	19.2	−2.2
17	3.04	+0.73	13.8	−8.2
19	2.69	+0.38	15.7	−6.1
21	2.56	+0.25	21.5	+0.1

[a] All spectra were recorded in $CDCl_3$. [b] With regard to toluene as a reference compound.

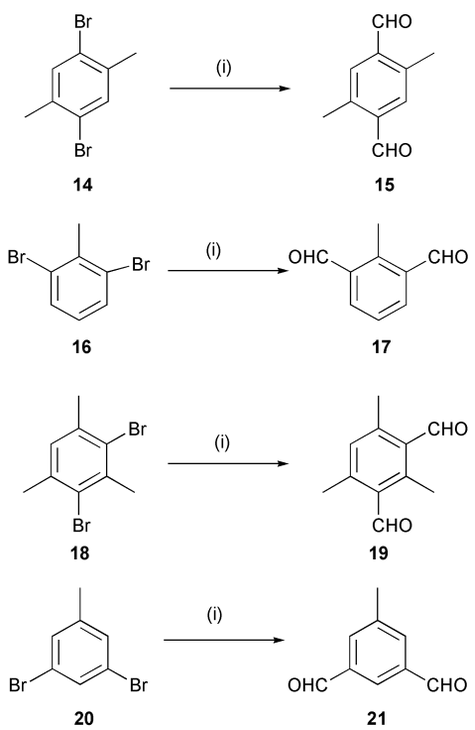


Fig. 5 *Reagents, conditions and yields:* (i) see method C in Table 1.

found to be superior to *n*-BuLi and *sec*-BuLi. Fluorinated dibromides again failed to yield any of the desired products.

All compounds reported either show identical spectroscopic features to the reported materials or in case of new compounds have been fully characterised by ^{1}H-NMR, ^{13}C-NMR, IR-, mass-spectroscopy and elemental analysis.

Careful investigation of the NMR spectra of the dicarboxaldehydes revealed that the C=O moiety has an exceptionally strong influence on the chemical shift of the *ortho*-methyl substituent. A strong upfield shift in the ^{13}C-NMR and a downfield shift in the ^{1}H-NMR resonances is observed, which can be rationalised by taking into account the anisotropy of the C=O π-electrons. Table 2 shows the induced ^{1}H and ^{13}C-shifts of selected compounds.

Synthesis of trianglimines

With the required aromatic dicarboxaldehydes in hand we started investigating the [3 + 3] cyclocondensation reaction. Cyclocondensation between (1*R*,2*R*)-**22** and methyl substituted dialdehydes **15**, **17** and **21** gave, under standard conditions at 0.1 M concentration in dichloromethane, the macrocyclic trianglimines **23**–**25** (Fig. 6). Trianglimine **23** was formed in quantitative yield, whereas compounds **24** and **25** were formed in very good yield along with some "dimeric structures" (according to the crude MS at *m*/*z* 462) and some unidentified by-products (for yields see Table 1). A more detailed description of the selectivity will follow below. The trianglimines could be obtained in analytically pure form after recrystallisation from toluene or ethyl acetate. Dialdehyde **19** failed to give any macrocyclic product. All trianglimines display the predicted spectroscopic features, most importantly one set of NMR signals for the preferred conformation adopted in solution, due to their inherent C_3 or D_3 symmetry. They all show the expected molecular ion in the LSIMS or CI mass spectra. There was no evidence obtained on alternative conformers devoid of any symmetry element.

Next we turned our attention to oxygen substituted aromatic dicarboxaldehydes. Again cyclocondensation between (1*R*,2*R*)-**22** and OMe-substituted dialdehydes **9** and **11** gave, under standard conditions at 0.1 M concentration in dichloromethane, the macrocyclic trianglimines **26** and **27** (Fig. 7). Trianglimine **26** was formed in excellent yield, whereas compound **27** was formed in good yield according to the ^{1}H-NMR spectra of the crude product. In order to obtain analytically pure material, several recrystallisation steps reduced the isolated yields considerably. Compound **26** with a 1,2-di-OMe substitution pattern did display C_3 symmetry in the NMR spectra. Biphenyl dialdehyde **13** yielded trianglimine **28** (Fig. 7) under standard conditions. However in the ^{1}H and ^{13}C-NMR spectra two sets of signals were observed. The LSIMS mass spectra did, however, show a single mass corresponding to the molecular ion of **28**.

Cyclocondensation between (1*R*,2*R*)-**22** and heterocyclic dialdehydes **29** and **30** gave, under standard conditions at 0.1 M concentration in dichloromethane, the macrocyclic trianglimines **31** and **32** (Fig. 8). Both trianglimines were formed in excellent yields. According to molecular modelling at the MM2 level both heterocyclic trianglimines could act as interesting hexadentate ligands for transition metal ions with pyridine N–N distances of 570 pm and thiophene S–S distances of 550 pm.

Cyclocondensation between (1*R*,2*R*)-**22** and 1,3-diformylazulene **33** gave, under standard conditions at 0.05 M concentration in dichloromethane, a mixture of the [2 + 2] **34** and [3 + 3] **35** cyclocondensation products (Fig. 9), which we failed to separate.

Ring contraction under thermodynamic control

As mentioned in the previous sections, macrocyclisation between (1*R*,2*R*)-**22** and dialdehydes **17** and **21** yielded trianglimines **24** and **25** along with small amounts of the [2 + 2] cyclocondensation products **36** and **37** (Fig. 10). It was pointed out earlier that the [3 + 3] cyclocondensation products are formed under kinetic control.[11,16] The origin of this kinetic control can be rationalised by identifying the minimum energy conformation of the direct macrocyclisation precursor, in which one free amine and one free aldehyde functionality are close in space with C=O to N distances of 30–35 pm. Thus the compound is found to be ideally set up for macrocyclisation to give the [3 + 3] cyclocondensation product. The nature of the thermodynamic products of these reactions has however been previously neglected. The appearance of the [2 + 2] cyclocondensation products **36** and **37** points towards these macrocycles as the products of thermodynamic control within the reaction of 1,3-disubstituted dialdehydes. It is worth noting that with 1,4-dialdehydes we have never observed any side products. To test this hypothesis we refluxed solutions of **24** and **25** respectively in dichloromethane for a prolonged period of time. Indeed, in both cases we obtained the [2 + 2] cyclocondensation products **36** and **37** respectively in quantitative yields. Complete conversion of **24** to **36** was observed after 12 h of reflux whereas complete conversion of **25** to **37** required 72 h of reflux. Obviously the position of the Me-substituent has a strong influence on the rate of conversion. Further investigations will be undertaken to study this influence in more detail.

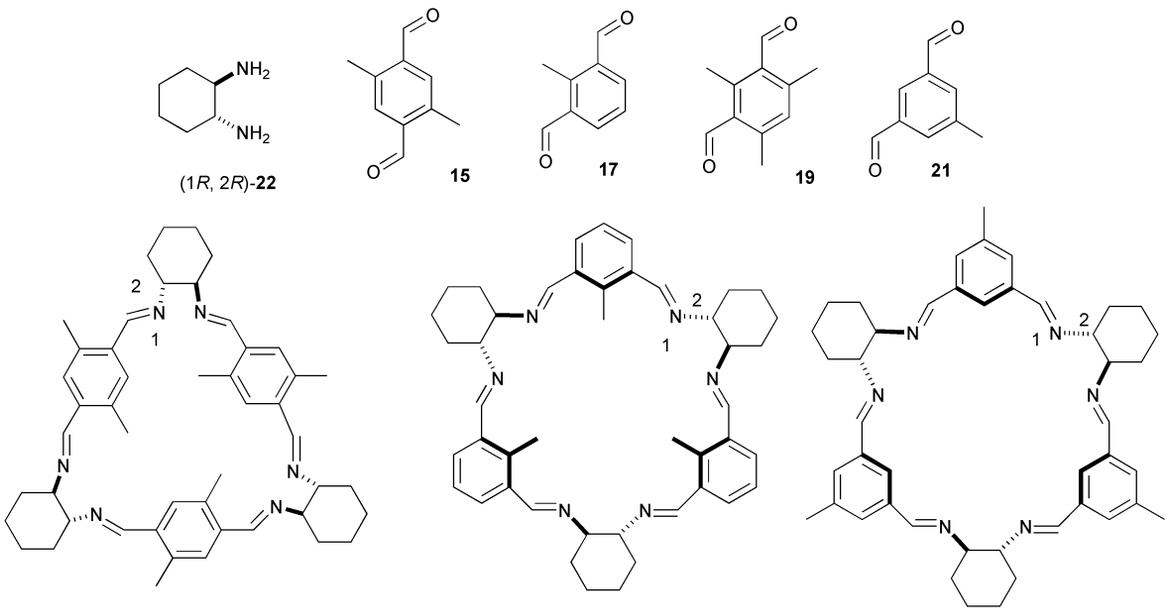


Fig. 6

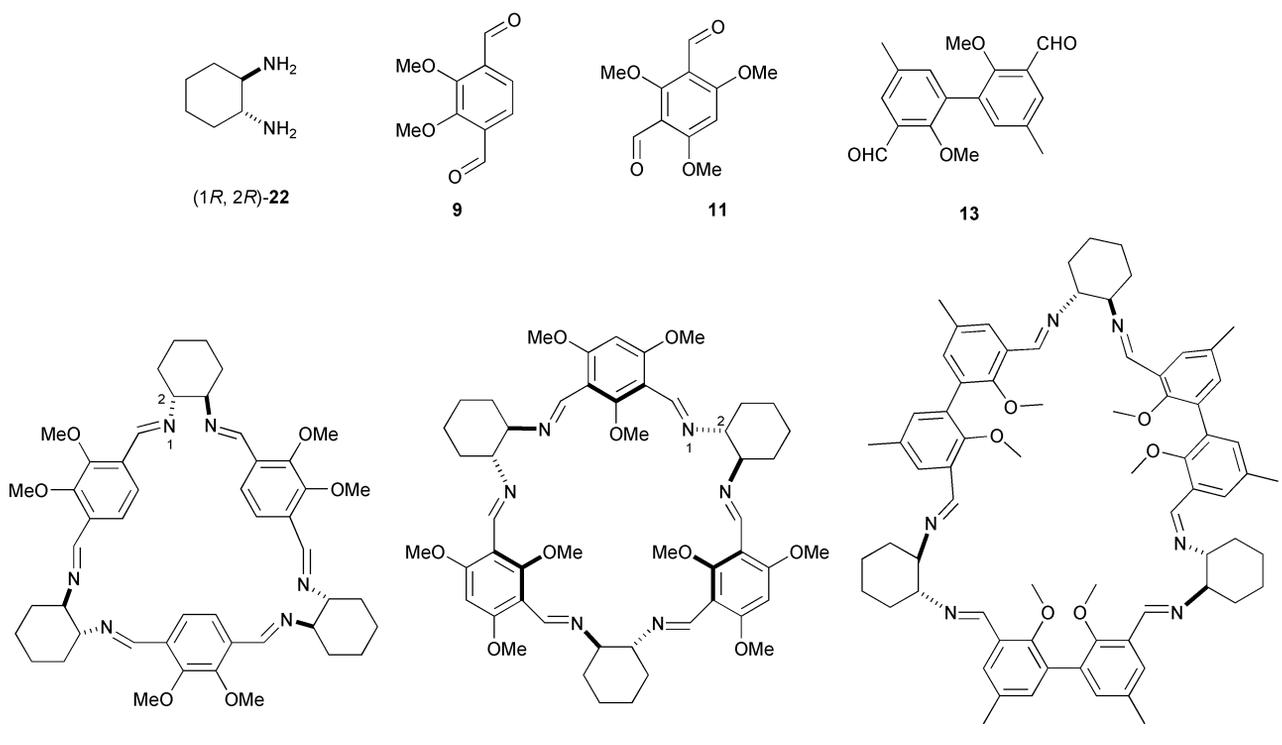
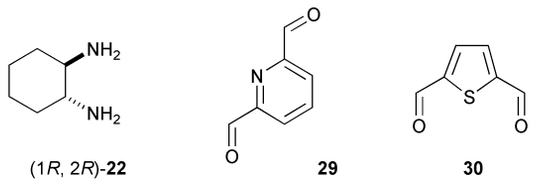


Fig. 7

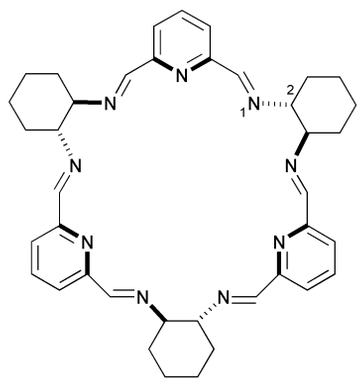
Both compounds **36** and **37** display one set of signals in the ^{1}H and ^{13}C-NMR spectra indicating C_2-symmetry in solution. Furthermore, they are characterised by a single molecular ion found in the CI mass spectra. We conclude that, in the case of 1,3-dicarboxaldehydes, the [3 + 3] cyclocondensation products are formed under kinetic control and the [2 + 2] cyclocondensation products are formed under thermodynamic control using (1*R*,2*R*)-**22**.

Reduction of imines

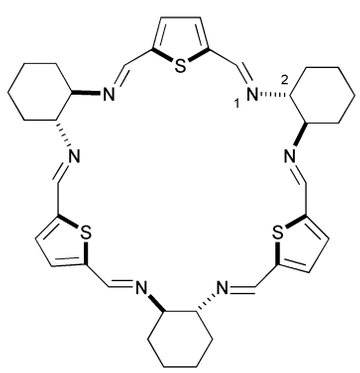
Reduction of the trianglimines **23**–**28** and **31** with $NaBH_4$ in MeOH gave the trianglamines **38**–**43** (Fig. 11) in poor to excellent yields (see Table 3). Due to their additional alkyl or alkoxy groups the novel macrocycles are reasonably soluble in chloroform. Again the macrocycles isolated show NMR spectra that are in agreement with a perfect C_3 symmetric conformation for **39**–**43** and a D_3 symmetric conformation for **38**. Trianglamines **41** and **42** show broad signals in the ^{1}H-NMR spectra, which we attribute to an increased conformational flexibility on the NMR time scale. The LSIMS mass spectra show the expected molecular ions exclusively. Regarding the mass spectral analysis of our novel macrocycles it seems worth mentioning that we initially used LSIMS exclusively with a nitrobenzyl alcohol matrix. Stock solutions for all trianglimines were prepared in chloroform whereas for the trianglamines we used methanol. In the meantime we found that the CI ionisation mode at temperatures between



(1*R*, 2*R*)-**22** **29** **30**

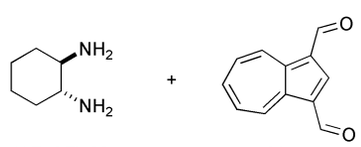


(2*R*, 3*R*, 11*R*. 12*R*, 20*R*, 21*R*)-**31**

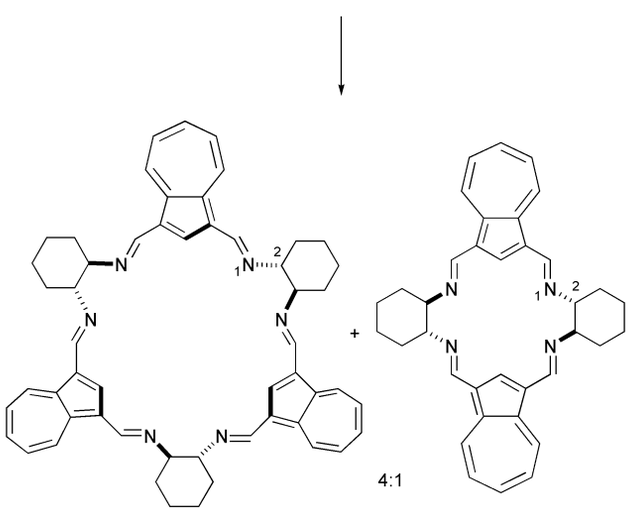


(2*R*, 3*R*, 11*R*. 12*R*, 20*R*, 21*R*)-**32**

Fig. 8



(1*R*, 2*R*)-**22** **33**



(2*R*, 3*R*, 11*R*. 12*R*, 20*R*, 21*R*)-**34** (2*R*, 3*R*, 11*R*, 12 *R*)-**35**

Fig. 9

180 °C and 230 °C gave even more superior results. Regarding the determination of purity we found that CHN analysis can be successfully applied for certain compounds. For other compounds we found that inclusion of solvents, ethyl acetate in particular, lead to unsatisfactory results. In these cases we assessed the purity by HPLC as reported earlier[15] and by accurate mass spectroscopy using CI ionisation and a reference mass of 613.96415.

Conformational analysis of macrocycles

All NMR spectra of all trianglimine macrocycles show only one set of signals and therefore indicate a high symmetry of the compounds in solution. It seems possible, however that rapid rotation around the N=C–C_{Ar} bonds occurs, which is not directly observed in the NMR spectra. To gain more insight into this likely dynamic process we acquired quantitative NOE-difference data on compounds **3** and **23**. As can be seen in Fig. 12, the 1,4-disubstituted compounds **3** and **23** can adopt two distinct conformations with the 1,4 substituents: *syn* to the N=CH imine proton or *anti* to the N=CH imine proton. The quantitative NOE data are shown in Table 4. A strong NOE from the N=CH imine proton on the substituents in the 1 and 4 positions respectively can be observed. Besides, a much weaker NOE can be observed from the N=CH proton on the aromatic protons H-2 and H-5. We interpret these results in the following way: the conformation **A** with the N=CH *syn* to the CH_3 or OCH_3 moiety respectively is the major conformation adopted by the compounds in solution; conformation **B** with the N=CH proton *anti* to the CH_3 or OCH_3 moiety is the minor conformation adopted in solution. Taking into account basic VSEPR theory, an *anti* relationship between the nitrogen lone pair and the more bulky group on the aromatic nucleus should indeed be expected. More importantly the NOE on both CH_3, H-2 and H-5 clearly indicates that rotation around the N=C–C_{Ar} bonds does occur in solution and that exchange between conformers **A** and **B** is fast on the NMR time scale. It is worth noting that we failed to observe two distinct conformers in the low temperature NMR spectra at −60 °C.

Furthermore, the NMR spectra of biphenyl based trianglimine **28** deserves some comment and interpretation. The ^{1}H and ^{13}C-NMR spectra show two distinct sets of signals in a ratio of 2 : 1. Each set represents a full set of signals representing a biphenyl moiety and a 1,2-cyclohexanediimine moiety. The lines do not broaden in a high temperature ^{1}H NMR spectrum at 100 °C in d_6-DMSO. The LSIMS mass spectrum however, reveals only a single molecular mass *m*/*z* at 1130. Consequently trianglimine **28** must adopt two distinct highly symmetrical conformations in solution, which interconvert slowly on the NMR-time scale. Indeed we could show slow interconversion of the two conformers using 2-D EXSY spectroscopy. From previous investigations we know that rotation around the N=C–C_{Ar} bonds and *anti*–*syn* isomerisation of the two R–N=C–C_{Ar} moieties are fast on the NMR time scale.[11,15–16] Additionally we have never observed formation of (*Z*)-C=N bond isomers. Taking into account the stereogenic nature of the biaryl axis we assign the two conformers as diastereomeric structures *all-(S$_a$)*-**28** and *all-(R$_a$)*-**28** as indicated in Fig. 13. One diastereomer is characterised by an *all-(R)* biaryl axis (three axes with *R* configuration), whereas the second diastereomer is characterised by an *all-(S)* biaryl axis. From molecular models at the MM-2 level however, it seems impossible to assign the major and minor diastereomeric conformers unambiguously by NOE or any other spectroscopic method.

Synthesis and dynamic behaviour of the carbazole based macrocycle

Cyclocondensation between (1*R*,2*R*)-**22** and carbazole dialdehyde **7** gave the [2 + 2] cyclocondensation product exclusively

Table 3 Yields and mass spectroscopic data for trianglimines **23**–**35** and trianglamines **38**–**43**

Entry	Starting material	Product	Crude yield (%)[a]	Isolated yield (%)[b]	*m/z*
1	**15**	**23**	**99**	**97**	721.3
2	**17**	**24**	**80**	**69**	679.4
3	**19**	—	**10**	—	679.4
4	**21**	**25**	**85**[e]	**75**	767.3
5	**9**	**26**	**90**[e]	**25**	817.3
6	**11**	**27**	**70**	**35**	907.3
7	**13**	**28**	**90**	**50**	1130.5
8	**29**	**31**	**95**	**70**	639.5
9	**30**	**32**	**90**	**35**	655.3
10	**33**	**34 + 35**	**90**[e]	—	788.0, 526.4
11	**24**	**36**	**99**	**98**	426
12	**25**	**37**	**99**	**98**	426
13	**23**	**38**	—	**90**	732.6
14	**24**	**39**	—	**94**	690.5
15	**25**	**40**	—	**89**	691.3
16	**26**	**41**	**70**	**15**	831.0
17	**27**	**42**	**65**	**13**	919.0
18	**31**	**43**	—	**90**	652.5
19	**7**	**44**	**90**[e]	**30**	658.4

[a] Determined by ^{1}H-NMR of crude product. [b] After recrystallisation. [c] *m/z* Molecular ion or M + H. [d] By LSIMS; by CI. [e] Mixture of [2 + 2] and [3 + 3] cyclocondensation products.

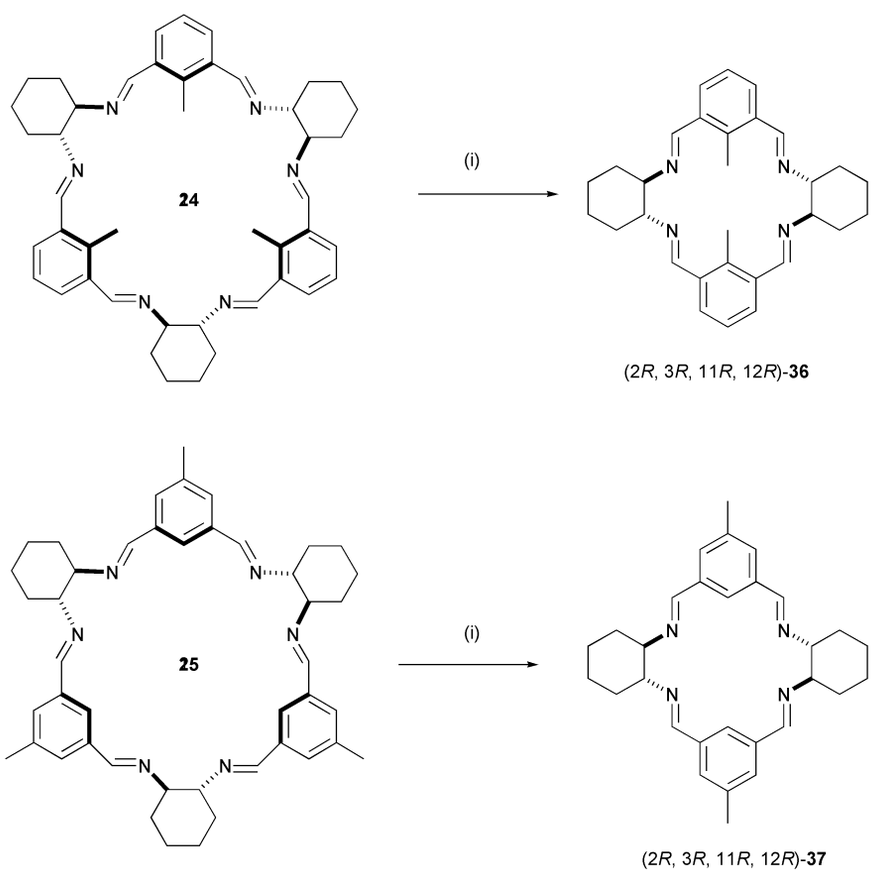


Fig. 10 *Conditions:* (i) reflux in DCM.

(Fig. 14). Careful monitoring of the reaction by ^{1}H-NMR revealed the appearance of a highly symmetric intermediate, which we believe to be the [3 + 3] cyclocondensation product. We failed however to isolate this intermediate. The [2 + 2] cyclocondensation product **44** appears to be thermodynamically favoured over the [3 + 3] cyclocondensation product under the reaction conditions.

Unlike all the other imine macrocycles this compound displayed temperature dependent NMR spectra. In the room temperature spectrum, two sets of signals for the non-equivalent carbazole units are clearly visible. Similarly, the two signals corresponding to the non-equivalent NCH protons coalesce into one signal. Upon an increase in temperature the two sets of signals coalesce into one set of signals. We assign this change of spectra to a ring inversion induced by a concerted rotation around two (N=C)–Ar bonds. This isomerisation is equivalent to a change from a *syn* isomer to an *anti* isomer (illustrated in Fig. 14). NOESY spectra of the isomer preferred at room temperature displayed NOE between the non-equivalent pairs of imine protons (H-5 to H-30 and H-15 to H-20) as well as from H-7′ to the H-5 HC=N of the imine. Molecular models at the MM-2 level for both *syn* and *anti* isomers clearly indicate that these observed NOEs can only occur in the *syn* isomer. We assign the energetically preferred isomer at room temperature to *syn*-**44** with the N–Et moieties in a *syn* arrangement. By estimation of the coalescence temperatures from the temper-

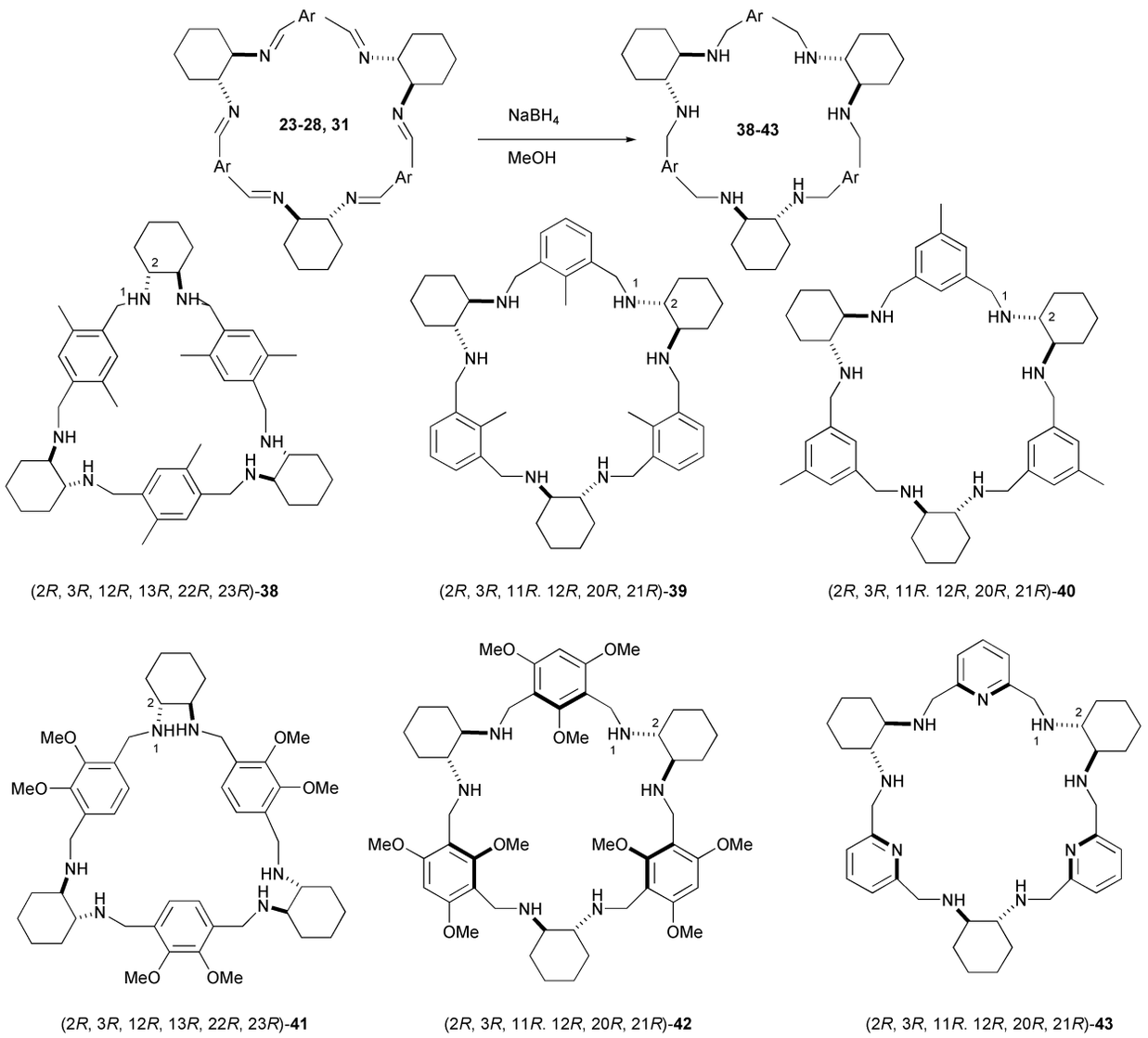


Fig. 11

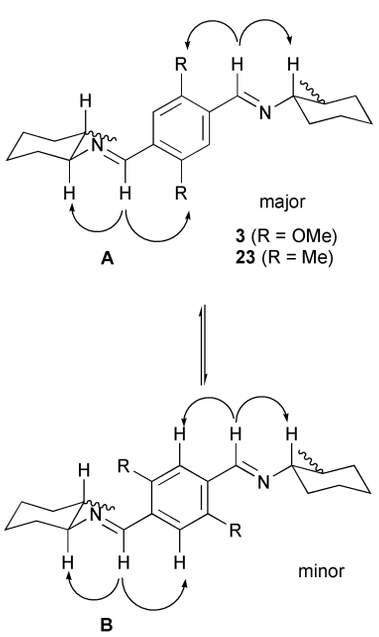


Fig. 12

ature dependent spectra and assuming a simple two-site exchange model[40] we estimate an activation energy of 63 kJ mol^{-1} for the isomerisation process. The reduced tetraamine macrocycle **45** displays broadened lines in its ^{1}H-NMR spectra (Fig 15). A low temperature spectra at −60 °C, however did not show chemically non-equivalent carbazole protons, indicating a rapid ring inversion on the NMR time scale. It appears that the activation energy for the ring inversion of the imine derivative is associated with the rigidity of the four C=N bonds.

Table 4 Quantitative NOE data of compounds **3** and **23**

Compound	R	NOE I	NOE II	NOE III
3	OMe	5.1%	2.8%	0.5%
23	Me	5.0%	4.2%	0.4%

Conclusion

In conclusion, we have developed novel and general synthetic methodology for the synthesis of aromatic dicarboxaldehydes using a variety of dilithiation strategies. All aromatic dialdehydes have successfully undergone macrocyclisation reactions with (1*R*,2*R*)-diaminocyclohexane **22**. In the majority of cases we have obtained trianglimine macrocycles as the product of a [3 + 3] cyclocondensation. All compounds adopt a conformation of the highest possible symmetry in solution. However dynamic interchange of conformations was observed. All the macrocycles synthesised are enantiomerically pure.

Most importantly, due to the generality of our macrocyclisation procedure we are in a position to synthesise

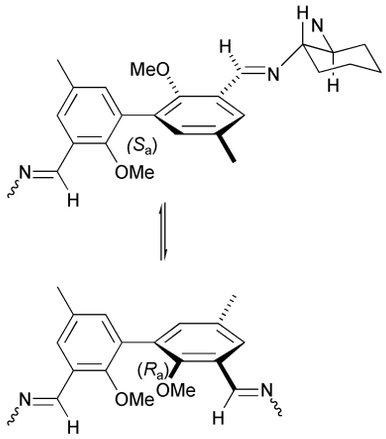


Fig. 13

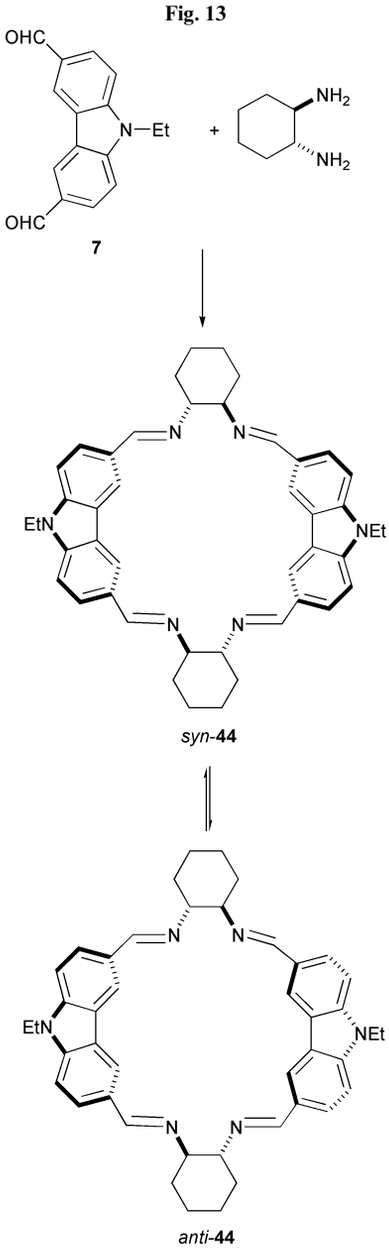


Fig. 14

macrocycles with varying ring sizes and tunable lipophilic cavities. We are in a position to judiciously functionalise the macrocycle and change its electronic properties by variation of the dialdehyde component. Using our macrocyclisation procedure we are approaching our goal of making structurally diverse macrocycles synthetically available in large numbers and in excellent yields, opening up the potential of going combinatorial in macrocyclic chemistry.

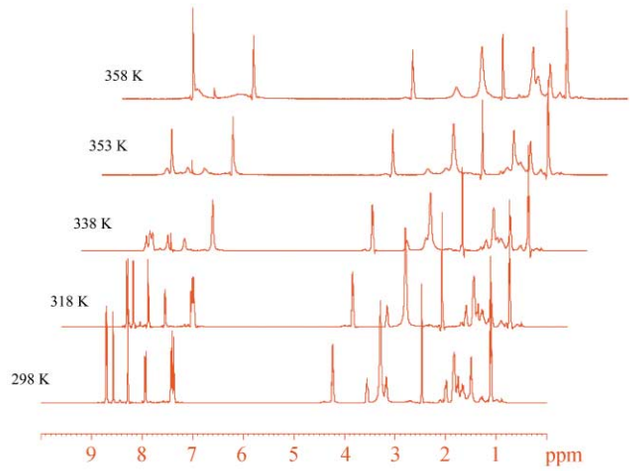


Fig. 15 Temperature dependent ^{1}H NMR spectra (500 MHz) in dmso of compound **44**.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL GSX 270 MHz and a Bruker Avance DRX-500 MHz spectrometer. δ Values are quoted relative to tetramethylsilane ($\delta = 0.00$ ppm) or chloroform (δ = 7.23 ppm) for ^{1}H NMR and relative to chloroform (δ_C = 77.0 ppm) for ^{13}C NMR. Coupling constants (J) are in Hz. 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 inclusion of solvent molecules.[19,20] We have included all elemental analysis data, some of which are satisfactory and some are not. Purity of the compounds with non-satisfactory elemental analysis was demonstrated by HPLC analysis. Future work will reveal the value of elemental analysis in trianglamine and trianglimine chemistry. Infrared spectra were determined on a Perkin-Elmer 200 spectrometer. Optical rotations were determined on a Bellingham and Stanley ADO 220 polarimeter. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were determined at two concentrations at least. The highest concentration is stated in the experimental section. The mass spectra were recorded at the EPSRC National Centre for Mass Spectrometry in Swansea or using a ThermoQuest Finnigan MAT 95XL spectrometer. Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60 F_{254} silica) using 1 : 3 ethyl acetate–hexane as a solvent system. All chemicals/reagents were purchased from 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*)-**22**, 1,3-diformylazulene, 2,6-diformylpyridine and 9-ethyl-2,6-dibromocarbazole were obtained using the published procedures.[16,21,22,41,42,43]

1,4-Dimethoxy-2,5-diformylbenzene (5)[44,45]

n-Butyllithium 2.5 M in hexane (4.8 mL, 12 mmol) was added to a solution of 1,4-dibromo-2,5-dimethoxybenzene (**4**) (1.001 g, 30 mmol) in dry THF (20 mL) at −78 °C under a nitrogen atmosphere and stirred for 2 h at the same temperature. To this solution was added a further portion of dry THF (20 mL). To the reaction mixture was added 3.0 mL (39 mmol) of DMF and the solution was stirred for 60 min and hydrolysed with 10 ml 3 N hydrochloric acid. The reaction mixture was allowed to warm to room temperature. The yellow precipitate was filtered

by suction. After drying *in vacuo*, yellow crystals of the dicarboxaldehyde (**5**) (0.4 g, 60.6%) were obtained. Mp 193–195 °C; ν_{max}(Nujol)/cm^{-1} 1682 (C=O), 1482–1377 (C_{Ar}=C_{Ar}), 1215 (C–O), 877 (isolated Aryl-H); δ_H(270 MHz; $CDCl_3$) 10.5 (2H, s, CHO), 7.5 (2H, s, H-3 and H-6), 4.0 (3H, s, OCH_3); δ_C(270 MHz; $CDCl_3$) 189.6, 156.0, 129.4, 111.1, 56.3; *m*/*z* (EI) 194 (100%, M$^+$), 166 (80%, M-CO); CHN (Found: C, 61.4; H, 5.20. $C_{10}H_{10}O_4$ requires: C, 61.8; H, 5.19%).

9-Ethyl-3,6-diformylcarbazole (7)[44–46]

In the same way as for compound **5** 1 g 9-ethyl-3,6-dibromocarbazole[43] (2.8 mmol) and 8.7 ml *n*-BuLi (1.3 M, 11.3 mmol) gave the dicarboxaldehyde (**7**) as white crystals after recrystallisation from ethanol (351 mg, 50%). Mp 150 °C; ν_{max} (Nujol)/cm^{-1} 1690 (C=O); δ_H(300 MHz; $CDCl_3$) 10.14 (2H, s, CHO), 8.68 (2H, s, H-4 and H-5), 8.09 (2H, d, *J* 8.4, H-2 and H-7), 7.56 (2H, d, *J* 8.4, H-1 and H-8), 4.45 (2H, q, *J* 7.1, NCH_2), 1.40 (3H, t, *J* 7.1, Me); δ_C($CDCl_3$) 191.7, 144.6, 129.9, 128.1, 124.7, 124.5, 109.8, 38.7, 11.1; *m*/*z* (EI) 251.2 (M$^+$, 100%); CHN (Found: C, 75.8; H, 5.10; N, 5.11. $C_{16}H_{13}NO_2$ requires: C, 76.4; H, 5.21; N, 5.57%).

1,2-Dimethoxy-3,6-diformylbenzene (9)[47]

TMEDA (5 eq., 1.36 mL, 9 mmol) was added to a solution of 1,2-dimethoxybenzene (**8**) (0.23 mL, 1.8 mmol) in diethyl ether (6 mL). The mixture was cooled in an ice bath (0 °C). *n*-Butyllithium 2.5 M in hexane (3.6 mL, 9 mmol) was added slowly over 1–2 min. The lithiation mixture was stirred during reflux for 10 h. During the metalation period a tannish-yellow precipitate was formed which was assumed to be the intermediate lithium salts.

At the end of the metalation, DMF (0.70 mL, 9 mmol) was added to the mixture, and the reaction was carried out for 30 min. Finally, the reaction mixture was allowed to warm to room temperature and hydrolysed with 10 ml water and 2 ml of 3 N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with 3 × 15 mL diethyl ether. The extract was dried over Na_2SO_4, and recrystallised from petrol ether, leading to the dicarboxaldehyde (**9**) as a yellow solid (154 mg, 45%). Mp 80 °C; ν_{max} (Nujol)/cm^{-1} 1689 (C=O); δ_H(300 MHz; $CDCl_3$) 10.44 (2H, s, CHO), 7.63 (2H, s, H-3 and H-6), 4.05 (6H, s, OMe); δ_C($CDCl_3$) 189.5, 156.9, 134.4, 123.1, 62.9; *m*/*z* (EI) 189.5 (M$^+$, 100%); CHN (Found: C, 61.6; H, 5.21. $C_{10}H_{10}O_4$ requires: C, 61.8; H, 5.19%).

1,3,5-Trimethoxy-2,4-diformylbenzene (11)

In the same way as for compound (**9**) 1,3,5-trimethoxybenzene (504 mg, 3 mmol), 2.3 ml TMEDA (15 mmol) and 6 ml *n*-BuLi (2.5 M, 15 mmol) gave the dicarboxaldehyde (**11**) as a yellow solid (513 mg, 74%). Mp 70 °C; ν_{max} (Nujol)/cm^{-1} 1680 (C=O); δ_H(300 MHz; $CDCl_3$) 10.32 (2H, s, CHO), 6.27 (1H, s, H-6), 4.00 (9H, s, OMe); δ_C($CDCl_3$) 187.4, 167.5, 112.9, 91.1, 65.2, 56.6; *m*/*z* (EI) 225.2 (M$^+$ + H, 100%); CHN (Found: C, 61.6; H, 5.21. $C_{11}H_{12}O_5$ requires: C, 58.9; H, 5.39%).

1,1′-Dimethoxy-2,2′-diformyl-4,4′-dimethylbiphenyl (13)

TMEDA (5 eq., 0.77 mL, 5.15 mmol) was added to a solution of 1,1′-dimethoxy-4,4′-dimethylbiphenyl (**12**) (250 mg, 1.03 mmol) in diethyl ether (4 mL). The solution was cooled in an ice bath at 0 °C. *n*-Butyllithium (1.6 M in hexane, 3.21 mL, 5.15 mmol) was added slowly. The lithiation mixture was stirred in reflux for 10 h. During the metalation period a tannish-yellow precipitate was formed which was assumed to be the intermediate lithium salts. At the end of the metalation, DMF (0.4 ml, 5.15 mmol) was added to the mixture, and the reaction was stirred for 30 min. The reaction mixture was warmed to room temperature and hydrolysed with water and a few drops of 3 N hydrochloric acid were added. The organic layer was separated and the aqueous layer was extracted with three 15 mL portions of diethyl ether. The extract was dried over Na_2SO_4, and recrystallised from petrol ether, leading to the title product as a yellow solid (9 mg, 30.5%). Mp 80 °C; ν_{max} (Nujol)/cm^{-1} 1694 (C=O); δ_H(300 MHz; $CDCl_3$) 10.41 (2H, s, CHO), 7.72 (2H, s, H-5), 7.43 (2H, s, H-3), 3.57 (6H, s, OMe), 2.41 (6H, s, Me); δ_C($CDCl_3$) 190.4, 159.1, 138.5, 134.3, 131.7, 129.3, 128.9, 63.6, 20.9; *m*/*z* (EI) 298.2 (M$^+$, 90%); CHN (Found: C, 71.9; H, 5.99. $C_{18}H_{18}O_4$ requires: C, 72.5; H, 6.08%).

1,4-Diformyl-2,5-dimethylbenzene (15)[44,48]

To a solution of 1.056 g of 1,4-dibromo-2,5-dimethylbenzene (**14**) (4.0 mmol) in 25 ml THF at −78 °C was slowly added 4.7 ml of a 1.7 M solution of ^{t}BuLi (8 mmol) and stirred for 30 minutes at that temperature. To the solution was added 0.3 ml DMF (296 mg, 4 mmol). The solution was stirred for a further 30 minutes, 9.4 ml of a 1.7 M solution of ^{t}BuLi in pentane (16 mmol) was slowly added, the solution was stirred a further 1 h, 0.9 ml of DMF was added and the solution allowed to warm to room temperature. 20 ml 2 M HCl was added to the mixture followed by 50 ml diethyl ether. The organic phase was separated and the aqueous phase washed twice with 20 ml diethyl ether. The organic extracts were combined, dried over Na_2SO_4, filtered and removed *in vacuo*. The white residue was recrystallised from petrol ether to give the title compound (**15**) (557 mg, 85%) as a white solid. Mp 55–56 °C; ν_{max} (Nujol)/cm^{-1} 1692 (C=O); δ_H(300 MHz; $CDCl_3$) 10.31 (2H, s, CHO), 7.82 (2H, s, H-3 and H-6), 2.67 (6H, s, Me); δ_C($CDCl_3$) 192.6, 138.6, 137.3, 135.1, 19.2; *m*/*z* (EI) 163.2 (M$^+$ + H, 100%); CHN (Found: C, 61.6; H, 5.21. $C_{10}H_{10}O_2$ requires: C, 74.1; H, 6.21%).

1,3-Diformyl-2-methylbenzene (17)[44,49]

In the same way as for compound (**15**) 1 g 1,3-dibromo-2-methylbenzene (4 mmol) gave the title compound as a light yellow solid. Mp 48 °C; ν_{max} (Nujol)/cm^{-1} 1692 (C=O); δ_H(500 MHz; $CDCl_3$) 10.49 (2H, s, CHO), 8.09 (2H, d, *J* 8.1, H-4 and H-6), 7.57 (1H, t, *J* 8.1, H-5), 3.04 (3H, s, Me); δ_C($CDCl_3$) 191.1, 143.2, 136.7, 135.9, 127.1, 13.8; *m*/*z* (EI) 149.1 (M$^+$ + H, 100%); CHN (Found: C, 61.6; H, 5.21. $C_9H_8O_2$ requires: C, 73.0; H, 5.44%).

1,3,5-Trimethyl-2,4-diformylbenzene (19)[44,50]

In the same way as for compound (**15**) 1 g 1,3,5-trimethyl-2,4-dibromobenzene (3.6 mmol) gave the title compound as a light brown solid. Mp 62–64 °C; ν_{max} (Nujol)/cm^{-1} 1694 (C=O); δ_H(300 MHz; $CDCl_3$) 10.43 (2H, s, CHO), 6.98 (1H, s, H-6), 2.69 (3H, s, Me), 2.50 (6H, s, Me); δ_C($CDCl_3$) 193.7, 145.4, 133.5, 132.9, 130.9, 21.3, 15.7; *m*/*z* (EI) 177.0 (M$^+$ + H, 100%); CHN (Found: C, 75.2; H, 6.88. $C_{11}H_{12}O_2$ requires: C, 75.0; H, 6.86%).

1,3-Diformyl-5-methylbenzene (21)

In the same way as for compound (**15**) 1 g 1,3-dibromo-5-methylbenzene (4 mmol) gave the title compound as a white solid. Mp 95–98 °C; ν_{max} (Nujol)/cm^{-1} 1690 (C=O); δ_H(500 MHz; $CDCl_3$) 10.12 (2H, s, CHO), 8.21 (1H, s, H-2), 7.99 (2H, s, H-4 and H-6), 2.56 (3H, s, Me); δ_C($CDCl_3$) 191.7, 140.7, 137.5, 135.6, 129.2, 21.5; *m*/*z* (EI) 149.1 (M$^+$ + H, 100%); CHN (Found: C, 61.6; H, 5.21. $C_9H_8O_2$ requires: C, 73.0; H, 5.44%).

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

A solution of 342 mg (1*R*,2*R*)-diaminocyclohexane **22** (3 mmol) and 486 mg 1,4-diformyl-2,5-dimethylbenzene (**15**)

(3 mmol) in 30 ml of dichloromethane was stirred at room temperature for 6 hours. The solvent was removed *in vacuo* and the white residue recrystallised from ethyl acetate to give the trianglimine (**23**) (700 mg, 97%) as a white powder. Mp over 200 °C; $[a]_D^{25}$ +221 ($CHCl_3$, c = 0.1); ν_{max}(Nujol)/cm^{-1} 1636 (C=N), 1606–1463 (C_{Ar}=C_{Ar}), 815; δ_H(500 MHz; $CDCl_3$) 8.43 (6H, s, N=CH), 7.51 (6H, s, Ar), 3.41 (6H, m, CHN=C), 2.51–2.30 (m, 12H, CH_2), 2.31 (18H, s, Me), 1.49–1.86 (24H, m, CH_2); δ_C(125 MHz; $CDCl_3$) 159.3, 135.9, 135.3, 128.7, 75.1, 33.2, 24.9, 18.5; *m*/*z* (LSIMS) 721.4 (M^+ + H); CHN (Found: C, 79.6; H, 8.39; N, 11.66. $C_{48}H_{60}N_6$ requires: C, 80.0; H, 8.21; N, 11.2%).

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

In the same way as for compound (**23**) 342 mg (1*R*,2*R*)-diaminocyclohexane (**22**) (3 mmol) and 444 mg (3 mmol) 1,3-diformyl-2-methylbenzene (**17**) gave trianglimine (**24**) (469 mg, 67%) as a white powder. Mp 216–218 °C; $[a]_D^{25}$ +201 ($CHCl_3$, c = 0.1); ν_{max} (Nujol)/cm^{-1} 1642 (C=N); δ_H(500 MHz; $CDCl_3$) 8.28 (6H, s, CH=N), 7.48 (6H, d, *J* 8.0, Ar–H), 7.10 (3H, t, *J* 8.0 Ar–H), 3.36 (4H, m, N=CH), 2.31 (9H, s, Me), 1.29–2.12 (18H, m, CH_2); δ_C($CDCl_3$) 162.3, 136.9, 130.3, 126.3, 125.5, 74.5, 32.8, 25.0, 21.5; *m*/*z* (LSIMS) 679.4 (M^+ + H); CHN (Found: C, 79.6; H, 8.09; N, 11.9. $C_{48}H_{60}N_6$ requires: C, 79.6; H, 8.02; N, 12.4%).

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tris(2′-methyl)-propeno-(2*H*,3*H*,11*H*,12*H*,20*H*,21*H*)-hexahydro-(27)-annulene (25)

In the same way as for compound (**23**) 342 mg (1*R*,2*R*)-diaminocyclohexane (**22**) (3 mmol) and 444 mg (3 mmol) 1,3-diformyl-5-methylbenzene (**21**) gave trianglimine (**25**) (510 mg, 75%) as a white powder. Mp 212 °C; $[a]_D^{25}$ +220 ($CHCl_3$, c = 0.1); ν_{max} (Nujol)/cm^{-1} 1642 (C=N); δ_H(500 MHz; $CDCl_3$) 8.32 (6H, s, CH=N), 7.84 (3H, br s, Ar–H), 7.31 (6H, br s Ar–H), 3.43 (6H, m, N=CH), 2.36 (9H, s, Me), 1.52–2.03 (18H, m, CH_2); δ_C($CDCl_3$) 162.3, 136.9, 130.3, 126.3, 125.5, 74.5, 32.8, 25.0, 21.5; *m*/*z* (LSIMS) 679.4 (M^+ + H); CHN (Found: C, 79.5; H, 8.05; N, 11.9. $C_{48}H_{60}N_6$ requires: C, 79.6; H, 8.02; N, 12.4%).

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

250 mg (1.28 mmol) of 1,2-dimethoxy-3,6-diformylbenzene in dichloromethane (6 ml) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (**22**) (140 mg, 1.28 mmol) in dichloromethane (6 ml) at rt and stirred for 3 hours under reflux. The solvent was evaporated and the title compound was obtained after recrystallisation from ethyl acetate as a white powder (256 mg, 25%). Mp. 70 °C; $[a]_D^{25}$ −313.8 ($CHCl_3$, c = 0.1); ν_{max} (Nujol)/cm^{-1} 1635 (C=N); δ_H(500 MHz; $CDCl_3$) 8.35 (6H, s, N=CH), 7.42 (6H, s, CH_{Ar}), 3.50 (18H, s, OMe), 3.35 (6H, m, CHN), 1.45–1.80 (24H, m, CH_2); δ_C($CDCl_3$) 159.3, 156.1, 134.9, 124.7, 77.2, 69.4, 35.4, 27.0; *m*/*z* (LSIMS) 817.3; CHN (Found: C, 68.7; H, 6.43; N, 6.67. $C_{48}H_{60}N_6O_6$ requires: C, 45.85; H, 4.55; N, 10.49%).

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

A solution of 30 mg (0.133 mmol) of 1,3,5-trimethoxy-2,4-diformylbenzene (**11**) in dichloromethane (1.5 ml) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (**22**) (15 mg) in 1.33 ml of dichloromethane at rt and stirred for 3 hours under reflux. The solvent was evaporated and the title compound was obtained after recrystallisation from ethyl acetate as a white powder. Mp 100 °C; $[a]_D^{25}$ −200 ($CHCl_3$, c = 0.04); ν_{max} (Nujol)/cm^{-1} 1642 (C=N); δ_H(300 MHz; $CDCl_3$) 8.71 (6H, s, N=CH), 8.39 (3H, s, CH_{Ar}), 3.61 (6H, m, NCH), 3.24 (12H, s, OCH_3), 3.21 (24H, s, OCH_3), 1.51–2.03 (24H, m, CH_2); δ_C($CDCl_3$) 155.3, 90.7, 90.3, 56.2, 56.1, 33.6, 25.5, 25.1, 24.9; *m*/*z* (LSIMS) 907.2; CHN (Found: C, 57.5; H, 6.79; N, 8.25%. $C_{51}H_{66}N_6O_9$ requires: C, 45.85; H, 4.55; N, 9.26%).

(2*R*,3*R*,14*R*,15*R*,26*R*,27*R*)-1,4,13,16,25,28-Hexaaza-(2,3:14,16:26,27)-tributano-(6,8:9,11:18,20:21,23:30,32:33,35)-hexakis(2-methoxy-4-methylpropeno)-(2*H*,3*H*,14*H*,15*H*,26*H*,27*H*)-hexahydro-(36)-annulene (28)

In the same way as for compound (**27**) 114 mg (1*R*,2*R*)-diaminocyclohexane (**22**) (1 mmol) and 300 mg 1,1′-dimethoxy-2,2′-diformyl-4,4′-dimethylbiphenyl (**13**) (1 mmol) in 10 ml dichloromethane gave after repeated recrystallisation from ethyl acetate the trianglimine (**28**) as a white solid (377 mg, 50%) as a 3 : 1 mixture of diastereomers. Mp 70 °C; $[a]_D^{25}$ +250 ($CHCl_3$, c = 0.1); ν_{max} (Nujol)/cm^{-1} 1635 (C=N); δ_H(500 MHz; $CDCl_3$) 8.58 (6H, s, HC=N, minor isomer), 8.45 (6H, s, HC=N, major isomer), 7.64 (6H, s, Ar–H, minor isomer), 7.54 (6H, s, Ar–H, major isomer), 7.17 (6H, s, Ar–H, major isomer), 6.99 (6H, s, Ar–H, minor isomer), 3.47 (6H, m, HCN, both isomers), 3.29 (9H, s, OMe, minor isomer), 2.84 (9H, s, OMe, major isomer), 2.23 (9H, s, Me, major isomer), 2.18 (9H, s, Me, minor isomer), 1.21–1.93 (24H, m, CH_2, both isomers); δ_C($CDCl_3$) 158.7, 157.3, 134.3, 129.2, 127.5, 73.2, 61.4, 33.0, 24.7, 24.5 and 20.8 (sample very weak and no second diastereomer and quarternary carbons observed and assigned); *m*/*z* (LSIMS) 1130.5 (M + 2H); CHN (Found: C, 76.7; H, 7.55; N, 7.5. $C_{72}H_{84}N_6O_6$ requires: C, 76.6; H, 7.50; N, 7.44%).

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,7,10,13,16,19,22,25-Nonaaza-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tripropeno-(2*H*,3*H*,11*H*,12*H*,20*H*,21*H*)-hexahydro-(27)-annulene (31)

180 mg (1.33 mmol) of 2,6-diformylpyridine in dichloromethane (6.5 ml) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (150 mg, 1.33 mmol) in dichloromethane (6 ml) and stirred for 3 hours under reflux. The solvent was evaporated and the title compound was obtained after recrystallisation from ethyl acetate as a light brown powder (69.9 mg, 70%). Mp 180 °C; $[a]_D^{25}$ −56.8 ($CHCl_3$, c = 0.21); ν_{max} (Nujol)/cm^{-1} 1642 (C=N); δ_H(270 MHz; $CDCl_3$) 8.22 (6H, s, N=CH), 7.79 (9H, m, CH_{Ar}), 3.45 (6H, m, NCH), 1.46–1.84 (24H, m, CH_2); δ_C($CDCl_3$) 161.2, 154.3, 136.8, 123.8, 76.7, 33.1, 24.7; *m*/*z* (CI) 639.4 (M^+, 100%); CHN (Found: C, 69.7; H, 6.64; N, 18.34. $C_{39}H_{45}N_9$ requires: C, 73.2; H, 7.09; N, 19.70%).

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-7,16,25-trithia-(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 (32)

50 mg (0.356 mmol) of 2,5-thiophenedicarboxaldehyde (**30**) in dichloromethane (2 ml) was added to a solution of (1*R*,2*R*)-diaminocyclohexane (**22**) (0.04 g, 0.356 mmol) in dichloromethane (3 ml) and stirred for 3 hours under reflux. The solvent was evaporated and the title compound was obtained after recrystallisation from ethyl acetate (82 mg, 35.2%). Mp 220 °C; $[a]_D^{25}$ (could not be determined due to low solubility); ν_{max} (Nujol)/cm^{-1} 1634 (C=N); δ_H(300 MHz; $CDCl_3$), 9.92 (6H, s, N=CH), 8.06 (6H, s, Ar–H), 3.32 (6H, m, NCH), 1.52–1.83 (24H, m, CH_2); δ_C($CDCl_3$) 153.5, 128.4,

76.8, 32.9, 24.6 (quaternary Ar–C could not be detected due to low solubility); *m/z* (CI) Found: 655.269 (M + H). $C_{36}H_{43}N_6S_3$ requires: 655.2706.

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tris(cycloheptatrieno)-(2*H*,3*H*,11*H*,12*H*,20*H*,21*H*)-hexahydro-(27)-annulene (34) and (2*R*,3*R*,11*R*,12*R*)-1,4,10,13-tetraaza-(2,3:11,12)-dibutano-(6,8:15,17)-bis(cycloheptatrieno)-(2*H*,3*H*,11*H*,12*H*)-tetrahydro-(18)-annulene (35)

In the same way as for compound (**27**) 228 mg (1*R*,2*R*)-diaminocyclohexane (**22**) (2 mmol) and 368 mg 1,3-diformylazulene (2 mmol) in 20 ml dichloromethane gave an inseparable 4 : 1 mixture of trianglimine (**34**) and macrocycle (**35**) as a black glassy solid. Mp 180–183 °C; $[\alpha]_D^{25}$ (could not be determined since solution completely absorbs polarised light); ν_{max} (Nujol)/cm^{-1} 1644 (C=N); δ_H(500 MHz; d_6-DMSO) 9.00 (6H, d, *J* 9.7, Ar–H, trimer), 8.58 (6H, s, HC=N, trimer), 8.49 (4H, s, HC=N, dimer), 8.27 (2H, s, Ar–H, dimer), 8.19 (4H, d, *J* 9.7, Ar–H, dimer), 8.09 (3H, s, Ar–H, trimer), 7.47 (2H, t, *J* 9.7, Ar–H, dimer), 7.11 (6H, t, *J* 9.7, Ar–H, trimer), 6.56 (4H, t, *J* 9.7, Ar–H, dimer), 6.33 (3H, t, *J* 9.7, Ar–H, trimer), 3.50 (4H, m, HCN, dimer), 3.44 (6H, m, HCN, trimer), 1.12–2.15 (24H, m, CH_2, dimer and trimer); *m/z* (LSIMS) 788.0 (M + H, trimer, 80%), 526.4 (M, 20%, dimer); CHN (Found: C, 81.8; H, 7.63; N, 10.6. $C_{59}H_{60}N_6$ requires: C, 81.1; H, 7.43; N, 9.24%).

(2*R*,3*R*,11*R*,12*R*)-1,4,10,13-Tetraaza-7,16-dimethyl-(2,3:11,12)-dibutano-(6,8:15,17)-dipropeno-(2*H*,3*H*,11*H*,12*H*)-tetrahydro-(18)-annulene (36)

A solution of 50 mg (0.74 mmol) of trianglimine (**24**) in 5 ml dichloromethane was heated under reflux for 12 hours. The solvent was removed *in vacuo* and the residue recrystallised from ethyl acetate–toluene (1 : 1) to give the title compound as a white powder (50 mg, 99%). Mp 206–208 °C; $[\alpha]_D^{25}$ +196 ($CHCl_3$, *c* = 0.1); ν_{max} (Nujol)/cm^{-1} 1640 (C=N); δ_H(500 MHz; $CDCl_3$) 8.36 (4H, s, CH=N), 7.50 (4H, d, *J* 8.0, Ar–H), 7.12 (2H, t, *J* 8.0, Ar–H), 3.35 (4H, m, N=CH), 2.29 (6H, s, Me), 1.26–2.17 (12H, m, CH_2); δ_C($CDCl_3$) 162.3, 136.9, 130.3, 126.3, 125.5, 74.5, 32.8, 25.0, 21.5; *m/z* (CI) 425 (M + H); CHN (Found: C, 79.8; H, 8.03; N, 12.4. $C_{30}H_{36}N_4$ requires: C, 79.6; H, 8.02; N, 12.4%).

(2*R*,3*R*,11*R*,12*R*)-1,4,10,13-Tetraaza-(2,3:11,12)-dibutano-(6,8:15,17)-bis(2′-methylpropeno)-(2*H*,3*H*,11*H*,12*H*)-tetrahydro-(18)-annulene (37)

In the same way as for compound (**36**) 50 mg (0.74 mmol) of trianglimine (**25**) gave after 72 hours under reflux the title compound as a white powder (50 mg, 99%). Mp 188 °C; $[\alpha]_D^{25}$ +181 ($CHCl_3$, *c* = 0.1); ν_{max} (Nujol)/cm^{-1} 1641 (C=N); δ_H(500 MHz; $CDCl_3$) 8.18 (4H, s, CH=N), 7.74 (2H, br s, Ar–H), 7.36 (4H, br s Ar–H), 3.43 (4H, m, N=CH), 2.28 (6H, s, Me), 1.50–2.08 (18H, m, CH_2); δ_C($CDCl_3$) 160.5, 138.9, 136.8, 126.3, 125.4, 74.9, 33.5, 24.9, 21.4; *m/z* (CI) (Found: 453.2942 (M + H). $C_{30}H_{30}N_4$ requires: 453.2940).

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-(7,8′,17,18′,27,28′)-hexamethyl-(2,3:12,13:22,23)-tributano-(6,9:16,19:26,29)-trietheno-(1*H*,2*H*,3*H*,4*H*,5*H*,10*H*,11*H*,12*H*,13*H*,14*H*,15*H*,20*H*,21*H*,22*H*,23*H*,24*H*,25*H*,29*H*)-octadecahydro-(30)-annulene (38)

To a solution of 100 mg (1.3 mmol) trianglimine (**23**) in 5 ml THF–MeOH (1 : 1) was slowly added 30 mg (7.9 mmol) of $NaBH_4$ at 0 °C. The solution was stirred for 2 hours at this temperature. To the solution was added 10 ml of H_2O and 10 ml of chloroform. The organic phase was separated and the aqueous phase was extracted with 2 × 10 ml chloroform. The organic extracts were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The residue was recrystallised from toluene to give the trianglamine (**38**) as a white solid. Mp 195–198 °C; $[\alpha]_D^{25}$ +190 ($CHCl_3$, *c* = 0.1); ν_{max} (Nujol)/cm^{-1} 3331 (N–H); δ_H(500 MHz; $CDCl_3$) 7.07 (6H, s, Ar–H), 3.85 (6H, d, *J* 12.9, CH_AH_BN), 3.55 (6H, d, *J* 12.9, CH_AH_BN), 2.28 (18H, s, Me), 1.01–1.86 (36H, CH_2, CHN and NH); δ_C($CDCl_3$) 137.4, 133.9, 130.5, 61.9, 49.0, 32.0, 25.6, 18.9; *m/z* (CI) (Found: 732.583. $C_{48}H_{72}N_6$ requires: 732.5818).

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-(7,16,25)-trimethyl-(2,3:11,12:20,21)-tributano-(6,8:15,17,24,26)-tripropeno-(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 (39)

In the same way as for compound (**38**) 100 mg trianglimine (**23**) (1.47 mmol) and 34 mg $NaBH_4$ (8.8 mmol) gave the trianglamine (**39**) as a colourless oil that turned solid upon standing (95 mg, 94%). Mp 182–184 °C; $[\alpha]_D^{25}$ +192 ($CHCl_3$, *c* = 0.1); ν_{max} (Nujol)/cm^{-1} 3334 (N–H); δ_H(500 MHz; $CDCl_3$) 7.10 (6H, d, *J* 8.1, Ar–H), 7.02 (3H, t, *J* 8.1, Ar–H), 3.78 (6H, d, *J* 12.9, CH_AH_BN), 3.55 (6H, d, *J* 12.9, CH_AH_BN), 2.17 (18H, s, Me), 0.96–1.86 (36H, CH_2, CHN and NH); δ_C($CDCl_3$) 137.2, 133.9, 130.5, 128.2, 62.2, 49.1, 32.1, 25.6, 18.9; *m/z* (CI) (Found: 690.535 (M^+). $C_{45}H_{66}N_6$ requires: 690.5349).

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tris(2-methylpropeno)-(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 (40)

In the same way as for compound (**38**) 60 mg of trianglimine (**24**) (0.88 mmol) and 20 mg $NaBH_4$ (5.3 mmol) gave the trianglamine (**40**) as a white solid (54 mg, 89%). Mp over 200 °C; $[\alpha]_D^{25}$ −192 ($CHCl_3$, *c* = 0.1); ν_{max}(Nujol)/cm^{-1} 3420 (br, NH), 1604, 1463, 815; δ_H(500 MHz; $CDCl_3$) 7.11 (3H, s, CH), 6.97 (6H, s, CH), 3.79 (6H, d, *J* 13.1, CH_AH_BN), 3.56 (6H, d, *J* 13.1, CH_AH_BN), 2.29 (9H, s, Me), 2.13 (6H, br s, exchanges with D_2O, NH), 2.03 (6H, m, CHN), 1.20–1.88 (24H, m, CH_2); δ_C(125 MHz; $CDCl_3$) 141.8, 138.2, 127.9, 124.9, 61.4, 51.4, 32.2, 25.7, 21.7; *m/z* (CI) 691.2 (M + H); CHN (Found: C, 77.6; H, 9.81; N, 11.9. $C_{45}H_{66}N_6$ requires: C, 78.2; H, 9.63; N, 12.2%).

(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-1,4,11,14,21,24-Hexaaza-(7,8,17,18,27,28)-hexamethoxy-(2,3:12,13:22,23)-tributano-(6,9:16,19:26,29)-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-(30)-annulene (41)

Trianglimine (**26**) (0.1 g, 0.16 mmol), was dissolved in 2 ml of THF–MeOH (1 : 1) at 0 °C. $NaBH_4$ (0.12 g, 3.21 mmol) was added slowly. After the addition the reaction was stirred for 2 h at rt. Finally the solvent was removed and the solid was extracted with dichloromethane and water. The solvent was evaporated to give the trianglamine (**41**) (20 mg, 15%) as an oil. $[\alpha]_D^{25}$ −200 ($CHCl_3$, *c* = 0.1); ν_{max} (Nujol)/cm^{-1} 3415 (N–H); δ_H(300 MHz; $CDCl_3$) 6.93 (6H, s, Ar–H), 3.77 (18H, s, CH_3O), 3.52 (12H, AB quartet, *J* 13.3, CH_AH_BN), 0.95–2.08 (36H, m, CHN, CH_2 and NH); δ_C($CDCl_3$) 152.3, 124.6, 77.7, 61.3, 46.1, 32.1, 31.7, 25.5; *m/z* (CI) 831.0 (M + 3H); $C_{48}H_{72}N_6O_6$ requires: 828.5508, found: 828.54419.

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,10,13,19,22-Hexaaza-(7,16,25)-trimethoxy-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tris(1′,3′-dimethoxypropeno)-(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 (42)

Trianglimine (**27**) (16 mg, 0.02 mmol), was dissolved in 0.6 ml

of THF–MeOH (1 : 1) at 0 °C. Gradually $NaBH_4$ (15.54 mg, 0.411 mmol) was added slowly. After the addition the reaction was stirred for 2 h at rt. Finally the solvent was removed and the solid was extracted with dichloromethane and water. The solvent was evaporated to give the trianglamine (**42**) as a yellow oil (2 mg 13%). $[\alpha]_D^{25}$ −200 ($CHCl_3$, $c = 0.1$); ν_{max} (Nujol)/cm^{-1} 3320 (N–H); δ_H(300 MHz; $CDCl_3$) 6.14 (6H, s, Ar–H), 3.74 and 3.72 (12H, AB quartet, J 12.7, CH_AH_BN), 3.66 (9H, s, OMe), 3.62 (18H, s, OMe), 1.51–2.05 (36H, m, CHN, CH_2 and NH); δ_C($CDCl_3$) 157.5, 128.3, 124.3, 123.7, 123.6, 72.0, 62.8, 59.5, 58.9, 36.2, 33.5; m/z (CI) 919.9 (M + H); $C_{58}H_{78}N_6O_9$ requires: 918.5825, found: 918.95619.

(2*R*,3*R*,11*R*,12*R*,20*R*,21*R*)-1,4,7,10,13,16,19,22,25-Nonaaza-(2,3:11,12:20,21)-tributano-(6,8:15,17:24,26)-tripropeno-(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 (43)

In the same way as for compound (**38**) 60 mg trianglimine (0.94 mmol) (**31**) and 22 mg $NaBH_4$ (5.6 mmol) gave the trianglamine (**43**) as a white powder (55 mg, 90%). Mp 60 °C; $[\alpha]_D^{25}$ −240 ($CHCl_3$, $c = 0.05$); ν_{max} (Nujol)/cm^{-1} 3340 (N–H, br); δ_H(300 MHz; $CDCl_3$) 7.55 (6H, m, br, Ar–H), 7.04 (3H, m, br, Ar–H), 3.80 and 3.73 (12H, AB quartet, J 12.9, CH_AH_BN), 0.71–2.42 (36H, CHN, CH_2 and NH); δ_C($CDCl_3$) 137.0, 135.1, 120.3, 61.6, 52.7, 31.7, 25.2; m/z (EI) 651.4735 (M^+). $C_{39}H_{57}N_9$ requires: 651.4731.

(2*R*,3*R*,17*R*,18*R*)-1,4,10,16,18,25-Hexaaza-10,25-diethyl-(2,3:17,18)-dibutano-(6:9:11:14,21:24:26:29)-dibutadieno-(2*H*,3*H*,17*H*,18*H*)-tetrahydro-(30)-annulene (44)

40 mg (0.59 mmol) 3,6-dibromo-*N*-ethylcarbazole in dichloromethane (2 ml) was added to a solution of 18.20 mg (0.59 mmol) of (1*R*,2*R*)-diaminocyclohexane (**22**) in dichloromethane (2 ml) at rt and stirred for 3 hours under reflux. The solvent was evaporated and the title compound was obtained after recrystallisation from ethyl acetate as a white powder (45 mg, 30%). Mp 250 °C; $[\alpha]_D^{25}$ −295.5 (CH_2Cl_2, $c = 0.044$); ν_{max} (Nujol)/cm^{-1} 1620 (C=N); δ_H(500 MHz; $CDCl_3$) 8.73 (2H, s, N=CH), 8.48 (2H, s N=CH), 8.24 (2H, s, H-7′, H23′), 8.18 (2H, s, H-13′, H-22′), 7.09 (4H, t, J 8.6, H-8, H-12, H-23, H-27), 6.82 (2H, d, J 8.6, H-13, H-28), 3.99 (4H, q, J 7.1, NCH_2), 3.74 (2H, m, NCH), 3.40 (2H, m, NCH), 2.06 (2H, m), 1.20–1.92 (14H, m), 0.99 (6H, t, J 7.1, CH_3); δ_C($CDCl_3$) 162.9, 161.5, 141.5, 141.0, 128.4, 128.3, 123.8, 123.6, 117.3, 109.3, 107.7, 75.9, 72.9, 37.1, 33.8, 32.7, 24.1, 24.9, 13.1; m/z (LSIMS) 658.4 (M^+); CHN (Found: C, 71.4; H, 8.17; N, 9.97. $C_{44}H_{46}N_6$ requires: C, 80.0; H, 7.04; N, 12.76%).

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