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PAPER

Synthesis of tri-substituted biaryl based trianglimines: formation of C_3-symmetrical and non-symmetrical regioisomers†

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2-Functionalised aromatic monoaldehydes were synthesised in good to excellent yields by reacting 4-bromo-2-fluorobenzaldehyde with different secondary amines and phenol. The Suzuki-coupling reaction of the newly functionalised aromatic monoaldehydes with 4-formylphenylboronic acid afforded the corresponding 2-functionalised-4,4′-biphenyldialdehydes in good yields (47–85%). The [3+3]-cyclocondensation reactions of the 2-functionalised-4,4′-biphenyldialdehydes with (1*R*,2*R*)-1,2-diaminocyclohexane afforded a mixture of regioisomeric C_3-symmetrical and non-symmetrical trianglimines. Reduction of the C_3-symmetrical and the non-symmetrical trianglimines with $NaBH_4$ in a mixture of THF and MeOH afforded the corresponding trianglamines in high yields.

Introduction

Trianglimines form a class of chiral non-racemic macrocycles that are formed in a [3+3]-cyclocondensation reaction between a chiral non-racemic diamine and an aromatic dicarboxaldehyde, in which six new imine bonds are formed in a single reaction. The first member of this class of macrocycles has been introduced by Gawroński a decade ago; more recently the compounds were named trianglimines by our group due to their unique triangular geometry.[1–3] Hexa-amine macrocycles, which constitute reduced versions of their hexa-imine analogues are referred to as trianglamines.[4] Trianglimines combine a series of features and characteristics that make them promising compounds for molecular recognition applications including sensing, chiral recognition, *etc.*, in many cases their potential is much superior if compared to their macrocyclic competitors such as calix[n]-arenes,[5–8] cyclodextrins,[9] cucurbiturils[10,11] or crown ethers.[12] Trianglimines are chiral, and unlike in cyclodextrin chemistry both enantiomers of any derivative are readily available in a pure form and have been reported.[4] Trianglimines are obtained using a modular approach, in which two building blocks are reacted to form macrocyclic compounds with complete control over the size of the macrocycle,[13] electronic properties of the macrocycle and functional groups included.[14] These features make trianglimines in particular attractive for the molecular recognition of small and medium sized organic molecules with complementary functionalities and complementary size to be included in the macrocyclic host by well-designed building blocks.

The [3+3]-cyclocondensation reaction is usually high yielding, with quantitative conversions not uncommon, at relatively high concentrations of the two building blocks. The formation of trianglimines is based on conformational bias rather than on a template effect or high dilution conditions, frequently used in other macrocyclic chemistry.[1] Despite these obviously attractive features of trianglimines, only few applications of trianglimines and their amine analogues in supramolecular chemistry have been reported. Gawroński and others have used trianglimines as organo-catalysts for asymmetric catalysis and they also reported the inclusion of solvent molecules into the trianglimine cavity.[1,15,16] Hodacova[17] reported on the binding of simple aromatic guests in the trianglimine cavity and finally we have reported on chiral recognition of trianglimines binding chiral carboxylic acids and amino acid derivatives.[18] In most of these cases, binding constants were reported with the best values in the region of 10^4 M^{-1}. A second currently existing obstacle in trianglimine and trianglamine chemistry is the poor water solubility. For any attractive application in supramolecular chemistry, host molecules should have satisfactory solubilities in aqueous solution. The imines themselves are of course sensitive to hydrolysis and water stable trianglamines obtained so far, possess water solubilities at neutral pH in low μM region only. In order to overcome these obstacles, in particular unsatisfactory binding constants and water solubilities, novel trianglamine derivatives are urgently required, in which these properties are improved. The strategy to achieve this must include the incorporation of further substituents in one of the trianglimine building blocks that due to their polar nature enhance water solubility and that at the same time offer suitable complementary binding motifs, including salt bridges, hydrogen bond donors and acceptors or further aromatic

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Table 1 Theoretical and experimental molecular weights for both the newly synthesised compounds and the assigned intermediates (ESI-MS, micrOTOF)

Compound / intermediate (Int.)	Molecular formula	Molecular weight (Calcd.)	Molecular weight (*m*/*z*) (Exp.)		Error [ppm]	Yield (%)
6	$C_{14}H_{17}BrN_2O_3$	340.0423	363.0400	$M + Na^+$	2.6	90
8	$C_{15}H_{15}BrN_2O$	318.0368	341.0367	$M + Na^+$	1.7	66
9	$C_{12}H_{16}BrNO_3$	301.0314	324.0326	$M + Na^+$	4.2	94
11	$C_{21}H_{22}N_2O_4$	366.1580	389.1554	$M + Na^+$	1.0	75
12	$C_{20}H_{14}O_3$	302.0943	325.0820	$M + Na^+$	4.8	47
13	$C_{22}H_{20}N_2O_2$	344.1525	367.1598	$M + Na^+$	2.0	85
14	$C_{19}H_{21}NO_4$	327.1471	350.1356	$M + Na^+$	2.0	79
16	$C_{81}H_{96}N_{12}O_6$	1332.7576	1333.7668	$M + H^+$	0.3	10
17	$C_{75}H_{93}N_9O_6$	1215.7249	1216.7305	$M + H^+$	0.1	4
18	$C_{78}H_{72}N_6O_3$	1140.5666	1163.5534	$M + Na^+$	4.0	22
19	$C_{81}H_{96}N_{12}O_6$	1332.7576	1333.4865	$M + H^+$	0.3	35
20	$C_{75}H_{93}N_9O_6$	1216.7322	1216.7292	M^+	2.4	31
21	$C_{78}H_{72}N_6O_3$	1140.5666	1163.5545	$M + Na^+$	1.8	37
22	$C_{84}H_{90}N_{12}$	1267.7482	1267.7439	M^+	3.4	11
23	$C_{28}H_{32}N_4O$	440.2576	441.2758	$M + H^+$	5.0	(Int.)
24	$C_{50}H_{50}N_6O_2$	766.3995	767.4107	$M + H^+$	4.9	(Int.)
25	$C_{56}H_{60}N_8$	844.4941	845.5072	$M + H^+$	2.8	(Int.)
26	$C_{78}H_{84}N_6O_3$	1152.6605	1153.6665	$M + H^+$	1.8	>98
27	$C_{81}H_{108}N_{12}O_6$	1344.8515	1345.8617	$M + H^+$	2.2	>98
28	$C_{78}H_{84}N_6O_3$	1152.6605	1153.6658	$M + H^+$	1.7	>98
29	$C_{75}H_{105}N_9O_6$	1227.8188	1228.8261	$M + H^+$	0.4	>98

groups for the binding of functionalised organic molecules. Within this contribution we present a new synthetic strategy for the introduction of a series of such substituents into novel trianglimines and trianglamines. As core building blocks we have chosen substituted biaryl dicarboxaldehydes. We present a novel functionalisation approach, in which starting from a fluorinated aromatic aldehyde a nucleophilic aromatic substitution reaction introduces a suitable heteroatom substituent. Subsequent Suzuki-coupling methodology,[19] based on our previous work, furnishes a substituted biaryl dialdehyde that serves as a building block for trianglimine synthesis.

Results and discussion

Aromatic nucleophilic substitution reactions of 4-bromo-2-fluorobenzaldehyde (**1**) with secondary amines in DMF have been reported by Nielsen *et al.*[20] We modified this method using alternative nucleophiles such as ethyl piperazine-1-carboxylate (**2**), phenol (**3**), *N*-methyl-2-(pyridin-2-yl)-ethanamine (**4**) and 2,2-dimethoxy-*N*-methylethanamine (**5**) in acetonitrile to afford the corresponding 2-functionalised monoaldehydes (**6–9**) (Scheme 1) in good to excellent yields (62–94%, Table 1). Compound (**7**) has already been reported in the literature.[21–23]

The solid state structure of compound (**6**) based on single crystal X-ray diffraction is shown in Fig. 1. The Suzuki-coupling reaction[19] of the 4-functionalised monoaldehydes (**6–9**) with 4-formylphenylboronic acid (**10**) afforded the newly functionalised 4,4′-biphenyldialdehydes (**11–14**) (Scheme 1) in good yields (47–85%). Compound (**12**) was isolated in low yield (26%) in the case where 0.9 mol% of tetrakis-(triphenylphosphine)-palladium-(0) was used as a catalyst. The yield for compound (**12**) was dramatically improved to (47%) by using 3.0 mol% of the catalyst. With the 2-substituted-4,4′-biphenyldialdehydes (**11–14**) in hand we investigated their behaviour in the [3+3]-cyclocondensation reaction. It is worth noting that compounds (**11–14**) constitute non-symmetric dialdehyde building blocks leading potentially to regioisomeric macrocycles where the reactivity of such non-symmetrical building

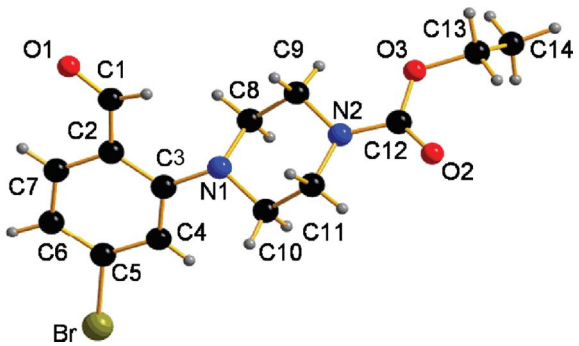
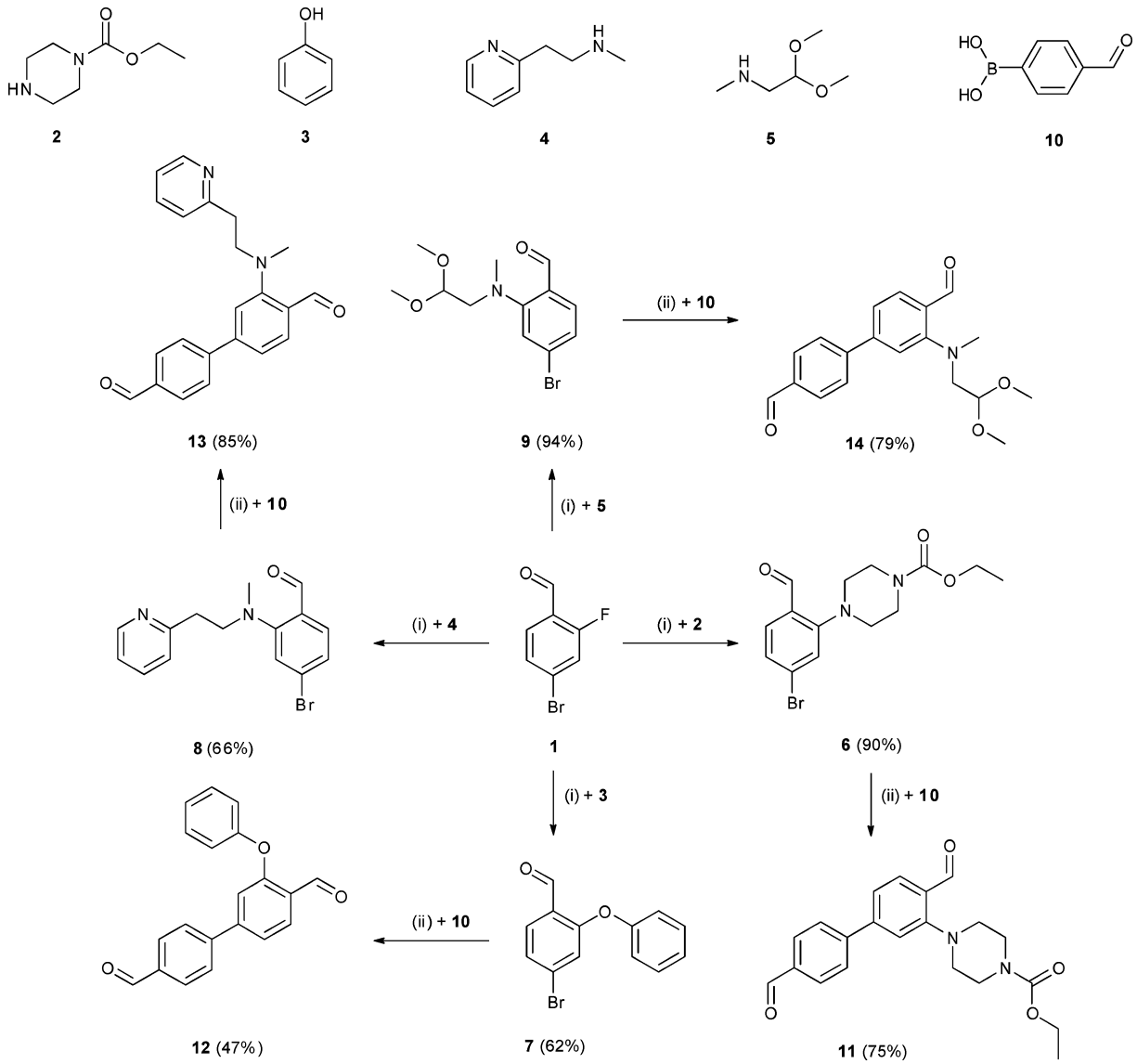


Fig. 1 Molecular structure of substituted monoaldehyde (**6**); thermal ellipsoids are drawn at 50% probability level. Selected bond lengths (Å) and angles (°) are given in the supplementary information.† Hydrogen atoms are shown as small grey balls.

blocks has never been investigated in trianglimine chemistry and forms an interesting topic. We have previously investigated non-symmetric 2,5-aryl substituted dialdehydes, where no issue of regiochemistry arose, however, diastereomeric compounds with the aromatic ring acting as a stereogenic plane were formed.

Furthermore we have reported on the use of non-symmetric biaryl dialdehydes, in which the [O=C–C_{Ar}–C_{Ar}–C=O] angle was smaller than 180° resulting in [2+2]-cyclocondensation products that form in excellent regioselectivities. Hence compounds (**11–14**) were reacted with (1*R*,2*R*)-1,2-diaminocyclohexane[24] (**15**) in dichloromethane to afford crude macrocyclic products in almost quantitative yields (**16–22**, Fig. 3) each containing mixtures of C_3-symmetrical trianglimines, non-symmetrical regioisomers along with some oligomers (Fig. 2 and 3). An accurate estimation of the regioselectivity was not possible due to signals overlapping in the ^{1}H-NMR spectra. However, a ratio of 1 : 1 for the formation of the C_3-symmetrical and the non-symmetrical regioisomers can be established from the crude integrals. C_3-symmetrical trianglimines (**16–18**) and their non-symmetrical regioisomers (**19–22**) could be separated using column chromatography on pretreated silica gel to give the individual regioisomers in high purity, although low



Scheme 1 *Reagents*, *solvents and conditions*: (i) acetonitrile, K_2CO_3, reflux. (ii) 3.0 mol% of $Pd(PPh_3)_4$, toluene, EtOH, Na_2CO_3, reflux.

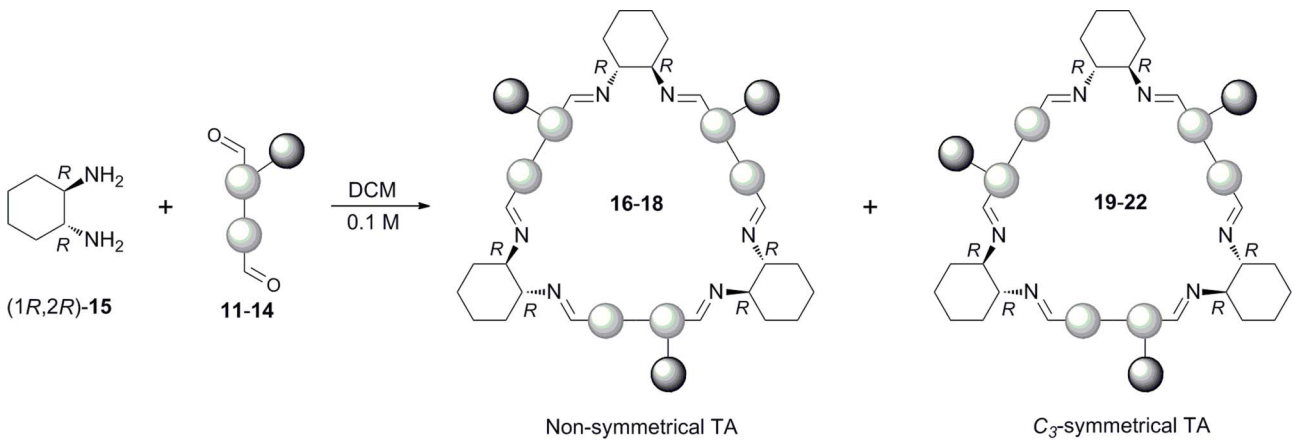


Fig. 2 *Reagents*, *solvents and conditions*: 1.5 mmol of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**), 1.0 mmol of dialdehydes (**11–14**), DCM (0.1 M).

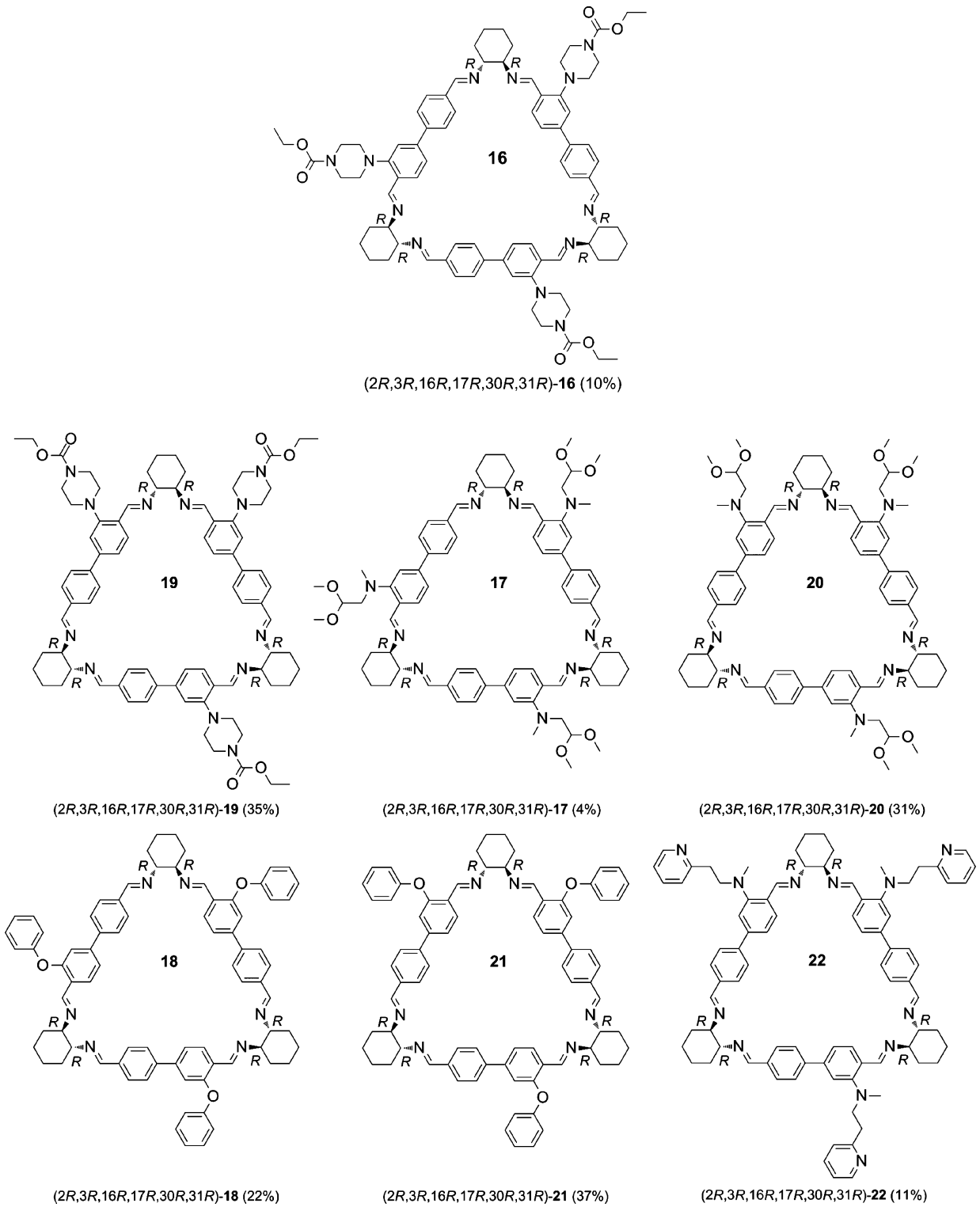


Fig. 3 C_3-symmetrical (**16–18**) and the non-symmetrical (**19–22**) macrocyclisation products from the [3 + 3]-cyclocondensation reaction of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) with dialdehydes (**11–14**).

isolated yield. It is worth noting that in previous work due to their water sensitivity trianglimines were always purified using crystallisation methods, whereas we give here for the first time in trianglimine chemistry an experimental procedure allowing purification by column chromatography. ESI mass spectrum for trianglimine (**20**) showed two peaks at *m*/*z* 1216 and 1238 corresponding to [M+H$^+$]and [M+Na$^+$], respectively (Fig. 4). Fig. 5a represents the ^{1}H-NMR spectrum for a crude mixture of trianglimines (**17**) and (**20**) before being purified by column chromatography (CC). The number of signals corresponding to

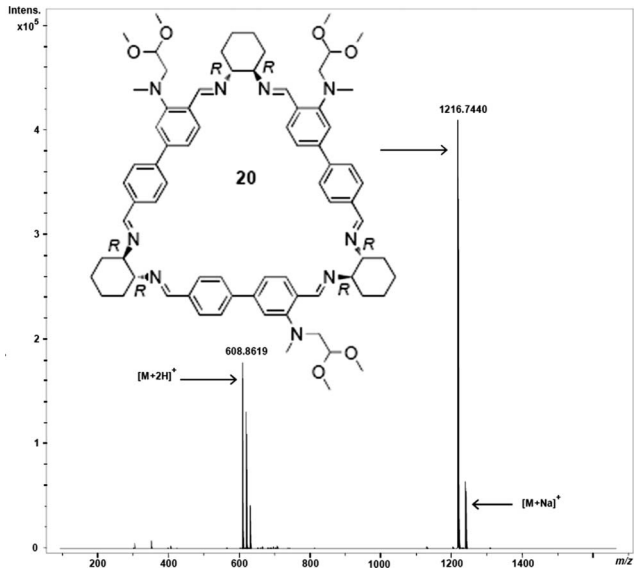


Fig. 4 ESI-MS spectrum for trianglimine (**20**) (micrOTOF, CH_2Cl_2 and MeOH).

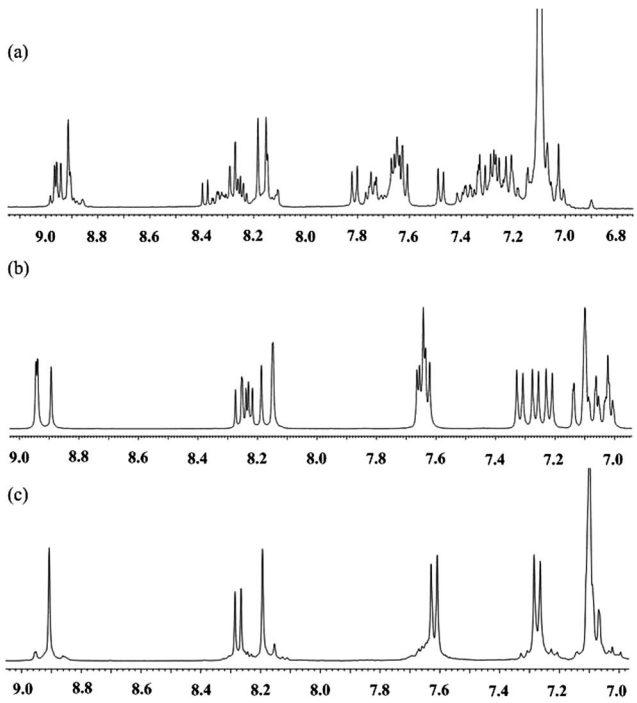


Fig. 5 Expanded ^{1}H-NMR spectra for (a) a crude mixture of trianglimines (**17**) and (**20**) before purification with CC, (b) the non-symmetrical trianglimine (**20**) after purification and (c) the C_3-symmetrical trianglimine (**17**) after purification with CC (C_6D_6, 400 MHz).

the azomethine protons for the C_3-symmetrical trianglimine (**17**) should be two singlets and each signal should have an integration of three. For the non-symmetrical trianglimine (**20**), six different azomethine protons should be recognised. The presence of many signals in the region from δ 8.8 to 9 ppm indicates that the crude mixture contains more than one isomer. Fig. 5b and 5c represent the ^{1}H-NMR spectra for both the non-symmetrical trianglimine (**20**) and its C_3-symmetrical regioisomer (**17**), respectively. The ^{1}H-NMR spectrum for the non-symmetrical trianglimine (**20**) showed four singlets at δ 8.94, 8.93, 8.89 and 8.18 ppm. Each signal had an integration of one. It also showed a broad signal at δ 8.14 ppm with an integration of two corresponding to the six non-equivalent azomethine protons (Fig. 5b). On the other hand the ^{1}H-NMR spectrum for the C_3-symmetrical trianglimine (**17**) showed two set of singlets at δ 8.90 and 8.19 ppm. Each signal had an integration of three corresponding to the six azometine protons (Fig. 5c). Furthermore, the IR spectra for regioisomers (**17**) and (**20**) showed an intense absorption band at ν_{max} 1637 cm^{-1} corresponding to the imine functional groups. In addition, all the protons and carbons could be unambiguously assigned by ^{1}H-^{1}H-COSY, ^{1}H-^{1}H-ROESY, HMBC and HMQC 2D-experiments.

Monitoring the [3+3]-cyclocondensation reactions by direct infusion ESI-MS

Here, we report the use of the high resolution ESI-mass spectrometry as an efficient technique for monitoring the progress of the [3+3]-macrocyclisation reactions. (1*R*,2*R*)-1,2-Diaminocyclohexane (**15**) reacted with dialdehyde (**13**) in dichloromethane at 0.1 M concentration. The mixture was stirred at room temperature for 43 h. Aliquots were taken at different time intervals, diluted and methanol added to the solution before being directly infused to the ESI-TOF-MS. Fascinatingly a total of 15 different reaction intermediates could be detected at different intensities and their appearance and disappearance monitored over the cause of the reaction. This represents to our knowledge the largest number of reaction intermediates ever observed in a single chemical reaction. All intermediates could be assigned on the basis of their high resolution *m*/*z* values. This method does not only allow monitoring of the progress of the reaction, previously not possible by TLC due to the acidic nature of silica plates,[25] but provides an intriguing insight into mechanistic aspects of this unusual reaction. Intermediates (**23**) and (**24**) were for example detected along with both the [2+2]-macrocyclisation product (**25**) and the starting material (**13**) after 3 h from the start of the experiment (Fig. 6). Most of these intermediates were completely consumed in the construction of trianglimine (**22**) after 43 h (Fig. 7). A peak at *m*/*z* 845, corresponding to the [2+2]-cyclocondensation intermediate (**25**) was still observed after that time. We assumed that intermediates (**24**), (**25**) and the final product (**22**) are non-symmetric, but in fact the peaks appearing at *m*/*z* 767, 845 and 1267 can also be related to their symmetrical counterparts. Although the [3+3]-macrocyclisation reaction of dialdehyde (**13**) with (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) had resulted in the formation of the non-symmetrical trianglimine (**22**) along with its C_3-symmetrical regioisomer, we could not succeed in separating the C_3-symmetrical regioisomer because its R_f value was very close to that of the non-symmetrical trianglimine (**22**). The chirality of the newly synthesised trianglimines was confirmed by circular dichromism (CD) spectra (Fig. 8). Trianglimines (**18**) and (**21**) have very similar UV absorption spectra with a slightly increased absorption for the non-symmetrical trianglimine (**21**). Large negative amplitudes were observed for the two regioisomers (**18**) and (**21**) at $\lambda \approx 300$ nm indicating negative Cotton effects.

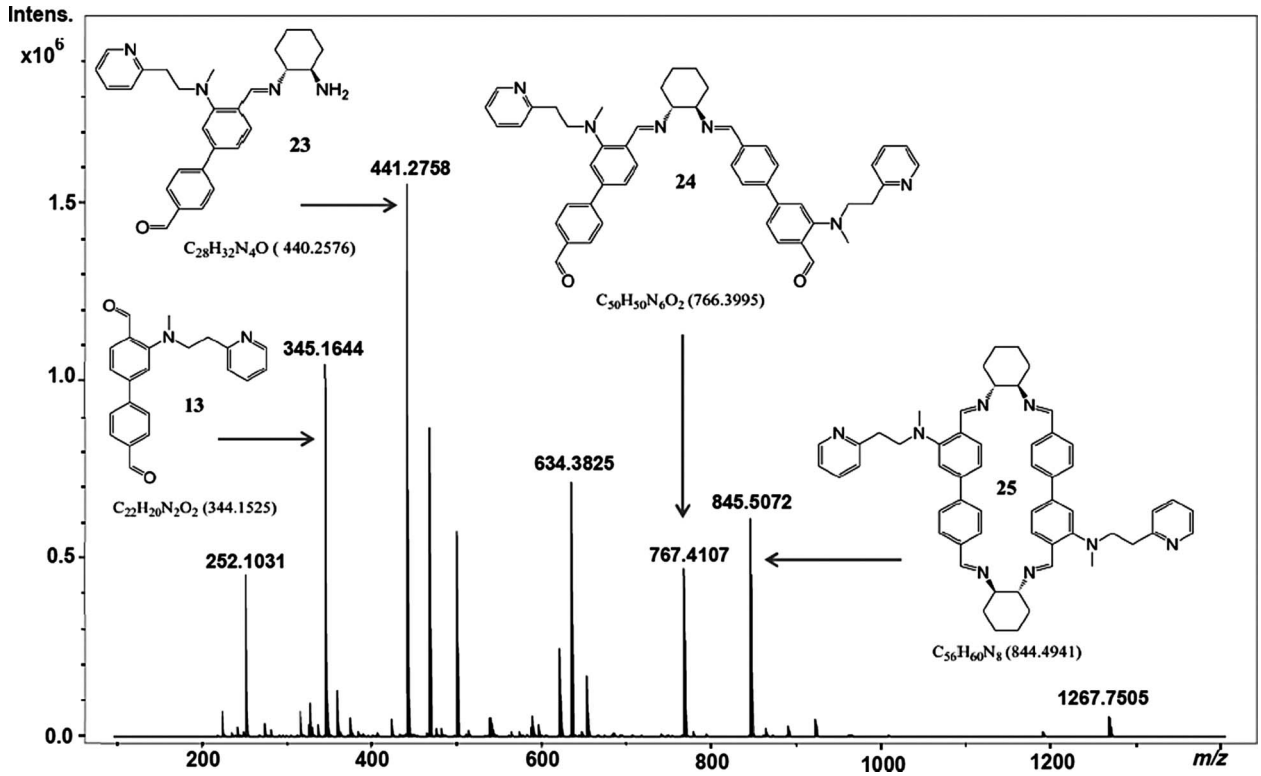


Fig. 6 ESI-MS spectrum for following up the [3+3]-macrocyclisation reaction of diamine (**15**) with dialdehyde (**13**) (micrOTOF, measured after 3 h from the start of the experiment in CH_2Cl_2 and MeOH).

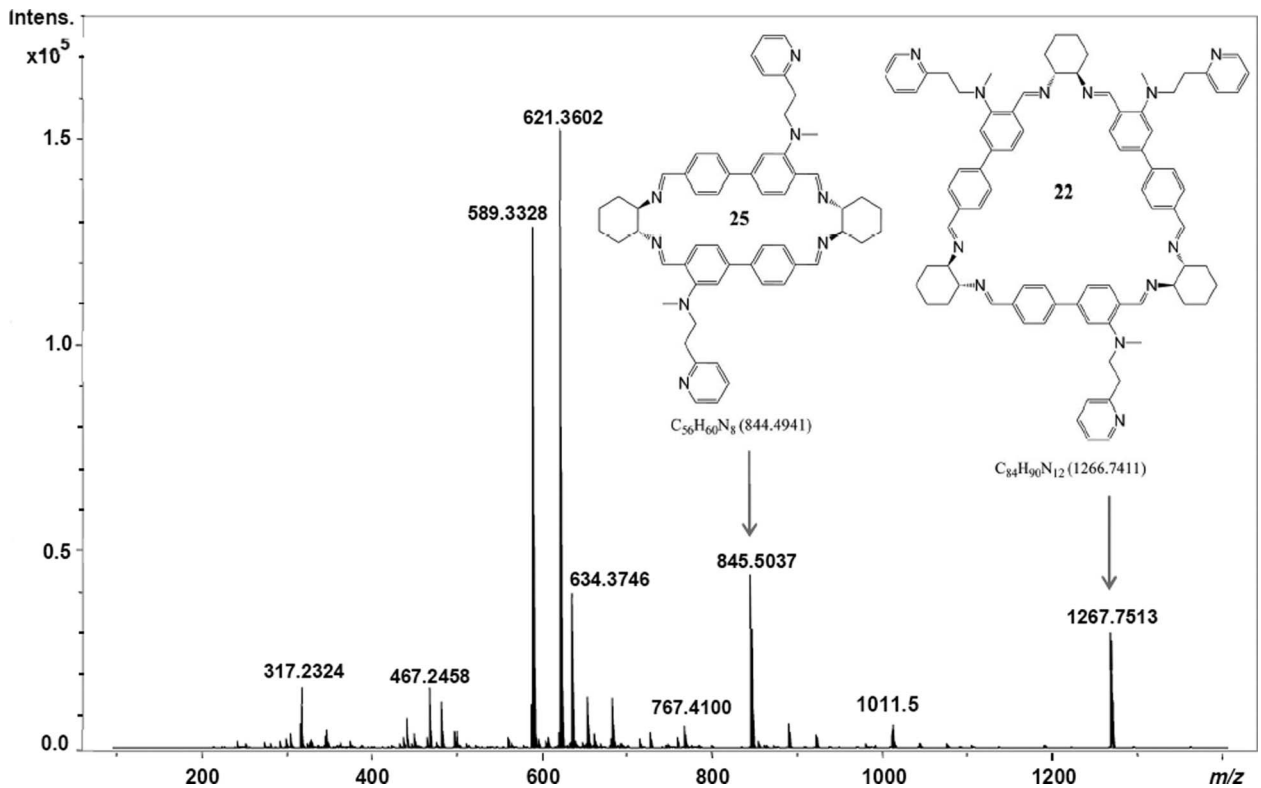


Fig. 7 ESI-MS spectrum for following up the [3+3]-macrocyclisation reaction of diamine (**15**) with dialdehyde (**13**) (micrOTOF, measured after 43 h from the start of the experiment in CH_2Cl_2 and MeOH).

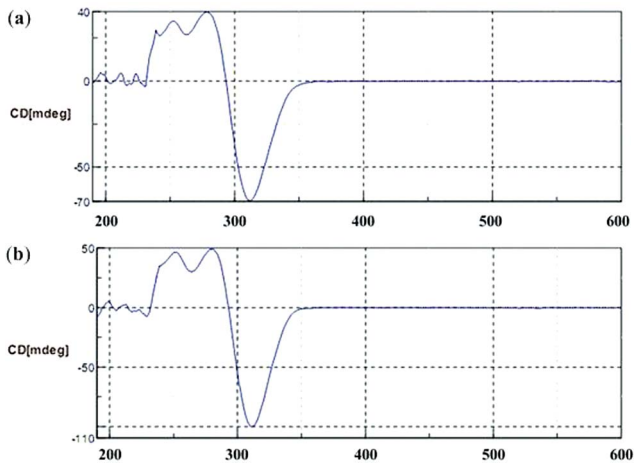


Fig. 8 CD spectra for (a) the C_3-symmetrical trianglimine (**18**) and (b) the non-symmetrical regioisomer (**21**) in $CHCl_3$.

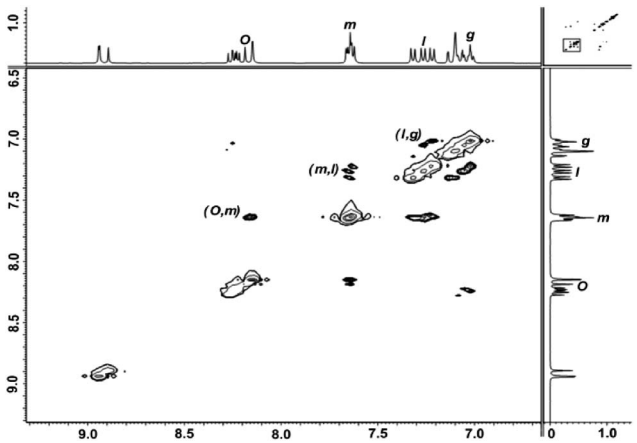


Fig. 9 2D-ROESY spectrum for trianglimine (**20**) showing through space interactions between the aromatic protons ($CDCl_3$, 400 MHz).

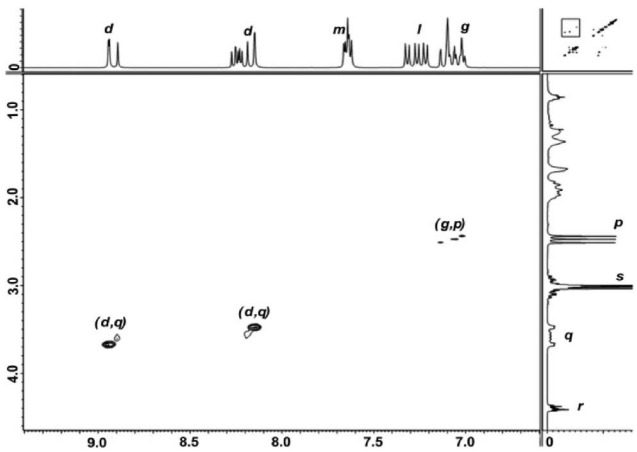


Fig. 10 2D-ROESY spectrum for trianglimine (**20**) showing through space interactions between aromatic and aliphatic protons ($CDCl_3$, 400 MHz).

Regioisomers (**18**) and (**21**) can be distinguishable by their spectral fine structure between 250 and 280 nm.

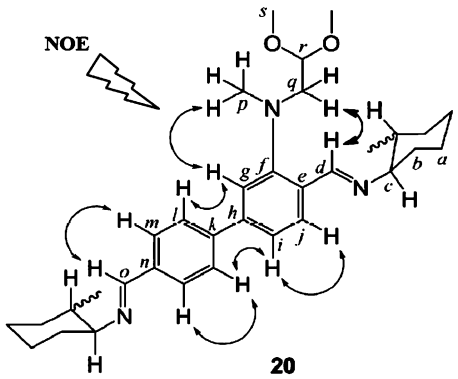


Fig. 11 Conformation structure of trianglimine (**20**).

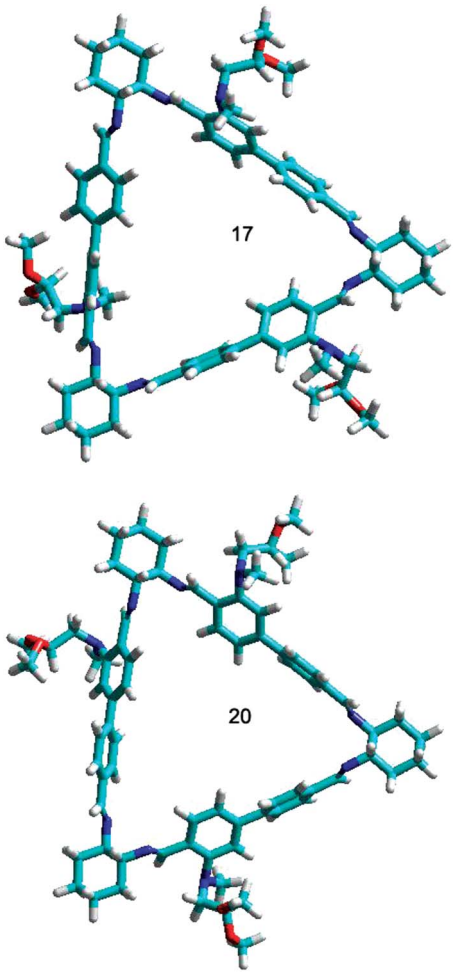


Fig. 12 Computed structures of trianglimines (**17**) and (**20**) using the Polak–Ribiere conjugate gradient with rms 0.007 Kcal/mol.

Equilibration of the C_3-symmetrical trianglimine (16) with its non-symmetrical regioisomer (19)

$$\underset{58\%}{C_3\text{-symmetrical TA} - \mathbf{16}} \xrightleftharpoons{CDCl_3} \underset{42\%}{\text{Non-symmetrical TA-}\mathbf{19}}$$

Surprisingly, trianglimine (**16**) equilibrated with its non-symmetrical regioisomer (**19**) in the NMR tubes during the

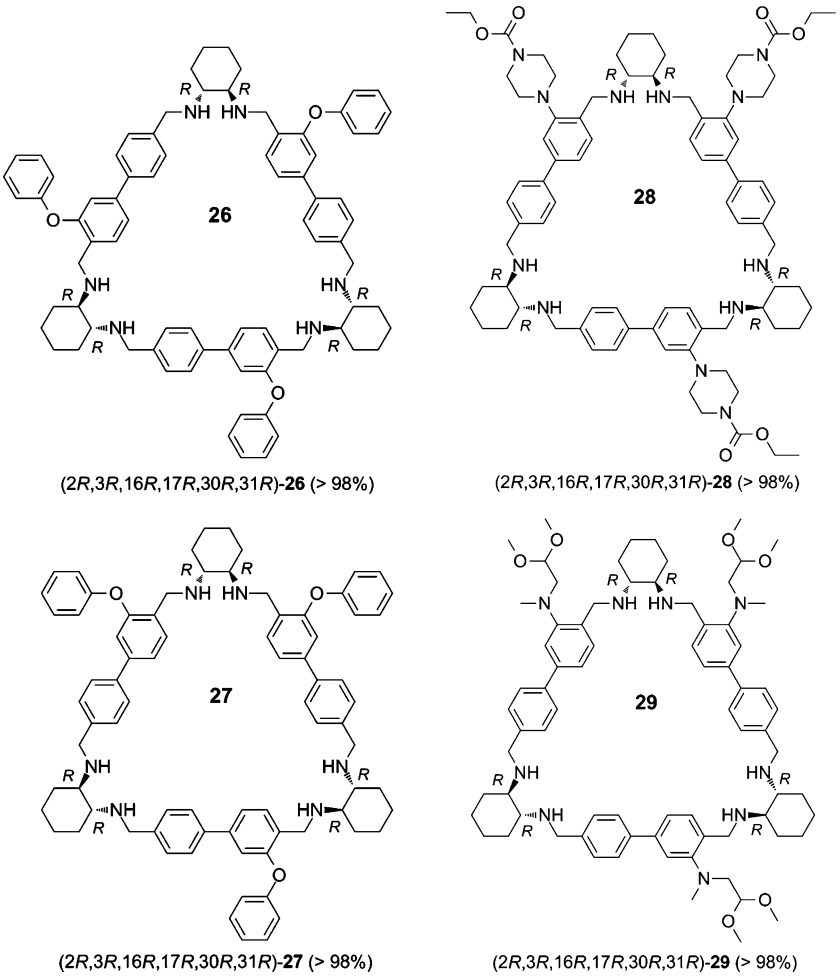


Fig. 13 Reduced trianglamines (**26–29**).

NMR measurements in the case where $CDCl_3$ was the solvent used. On attempts to elucidate the reason behind this equilibration, the ^{1}H-NMR measurements were carried out in different deuterated solvents, such as acetone-d_6, $CDCl_3$ and C_6D_6. Only C_3-symmetrical trianglimines equilibrated with their non-symmetrical regioisomers in $CDCl_3$. This can be attributed to the slight acidity of $CDCl_3$ which facilitates the acid catalysed imine exchange reaction in addition to the fact that the non-symmetrical trianglimine (**19**) is statistically favoured since the arrangements of the building blocks are three times more probable than that with trianglimine (**16**). The ratio of the C_3-symmetrical trianglimine (**16**) to its non-symmetrical regioisomer (**19**) after six days of standing in $CDCl_3$ was estimated from the ^{1}H-NMR integrals and was found to be 58 to 42%, respectively. The ^{1}H-NMR spectrum for the non-symmetrical trianglimine (**19**) showed a doublet signal at δ 6.93 ppm (Ar*H*) and six different signals at δ 8.19, 8.20, 8.23, 8.43, 8.44 and 8.53 ppm corresponding to the imine protons (see supplementary information†). The ^{1}H-NMR spectrum for the C_3-symmetrical trianglimine (**16**) showed a set of two singlet signals at δ 8.23 and 8.50 ppm corresponding to the azomethine protons.

After six days of standing in $CDCl_3$, the ^{1}H-NMR spectrum for the C_3-symmetrical trianglimine (**16**) showed a doublet signal at δ 6.93 ppm related to the non-symmetrical trianglimine (**19**) (Ar*H*). It also showed many aldehydic signals in the region from δ 10.02 to 10.07 ppm and δ 10.32 to 10.36 ppm. The singlet signals appearing at δ 10.07 and 10.36 ppm are related to the two aldehydic protons of dialdehyde (**11**). In addition, all the assigned signals corresponding to the azomethine protons for both the C_3-symmetrical trianglimine (**16**) and its non-symmetrical regioisomer (**19**) were observed at δ 8.18, 8.20, 8.23, 8.43, 8.44, 8.50 and 8.53 ppm indicating clearly an equilibration between the two isomers.

Conformational analysis for the non-symmetrical trianglimine (20)

The two-dimensional ^{1}H-^{1}H-ROESY experiments confirmed both the regiochemistry and the stereochemistry for all of the newly synthesised trianglimines (*e.g.*, trianglimine **20**). The ^{1}H-^{1}H-ROESY spectrum for compound (**20**) showed through space interactions between the methylene protons (*q*) and the azomethine proton (*d*) (Fig. 9–11). It can be concluded from the observed nOe effects that trianglimine (**20**) adopts a conformation in solution in which the 2-biaryl substituent is placed *syn*- to the imine (*H*C═N) group and *anti*- to the nitrogen lone pairs. Structures of trianglimines (**17**) and (**20**) were optimised with Hyperchem[26] software (Release 8.0) using MM+ molecular mechanics along with the semi-empirical molecular orbital PM3 method (Parametic Method 3,

Fig. 12).[27] The structures were minimised using the Polak–Ribiere conjugate gradient with rms 0.007 Kcal/mol. Reaching a gradient of 0.007 Kcal/mol took 28 h of calculations for the C_3-symmetrical trianglimine (**17**) and 30 h for its non-symmetrical regioisomer (**20**). The total energies for trianglimines (**17**) and (**20**) were found to be exactly identical with a value of –497.56 a.u.

The results from the computational calculations were found to be in accordance with both the conformational structures suggested by the 2D-ROESY experiments and the previously reported X-ray data.[28]

Reduction of trianglimines (18–21)

Trianglimines (**18 - 21**) $\xrightarrow[THF/MeOH]{NaBH_4}$ Trianglamines (**26 - 29**)

Trianglimines (**18–21**) were reduced by sodium borohydride ($NaBH_4$) in a mixture of THF and MeOH to the corresponding trianglamines (**26–29**) in excellent yields without needing further purification (Fig. 13). The ^{1}H-NMR spectrum for trianglamine (**27**) showed multiplet signals at δ 3.94–4.00 and 3.63–3.72 (J = 13.2) ppm corresponding to -CH_ACH$_B$N and -CH$_A$CH_BN in the AB spin system. It also showed a broad multiplet at δ 2.08–2.31 ppm with an integration of 18 corresponding to the twelve methylene protons (-CH_2-) of the cyclohexyl group and the six (-NH-) protons. On the other hand, the IR spectrum showed a broad absorption band at ν = 3286 cm^{-1} corresponding to the (-NH-) groups.

Conclusion

In conclusion, we have shown an efficient procedure for synthesising functionalised aromatic dialdehydes in excellent yields using nucleophilic aromatic substitution reactions along with the Suzuki-coupling methodology. The newly functionalised dialdehydes successfully underwent [3+3]-cyclocondensation reactions to give C_3-symmetrical trianglimines along their non-symmetrical regioisomers, which were separated and purified efficiently using column chromatography. Computational calculations at the PM3 level showed great flexibility of the newly synthesised trianglimines due to the free rotations around the C_9–C_{10}, C_{23}–C_{24} and C_{37}–C_{38} single bonds. The C_3-symmetrical trianglimines showed dynamic interchange to the non-symmetrical regioisomers in $CDCl_3$ during the NMR measurements. All the synthesised trianglimine and trianglamine regioisomers are enantiomerically pure and can serve as good receptors for different guests. Although the water solubility for the newly synthesised trianglamines was not enhanced in a satisfactory way by the introduction of the substituents chosen in this work, we still believe that a careful choice of the substituents which possess functional groups capable of forming hydrogen bonds or salt bridges can lead to a dramatic improvement in the solubility of this class of macrocycle, leading to potential applications. We showed that the ESI-MS instrument can be used as an efficient technique for monitoring the progress of the [3+3]-macrocyclisation reaction providing vital information about the reactive intermediates participating in the formation of the final product.

Experimental

Ethyl 4-(5-bromo-2-formylphenyl)-piperazine-1-carboxylate (6)

To a stirred solution of 4-bromo-2-fluorobenzaldehyde (**1**) (2.02 g, 10 mmol) in acetonitrile (20 mL), K_2CO_3 (4.07 g, 29.5 mmol) and ethyl *N*-piperazinecarboxylate (**2**) (2.2 mL, 14.79 mmol) was added. The mixture was stirred at 100 °C for 48 h. The solvent was evaporated under vacuum. Water was added to the crude product and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O, dried with Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by column chromatography (petroleum ether : ethylacetate, 9 : 1, the polarity was increased gradually to 7 : 3 after receiving the first fraction of impurities) to give the title compound (**6**) as a yellow solid (3.06 g, 90%); mp 95–96 °C; R_f (0.6, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1686 (br, N(C═O)O and H(C═O)); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.20 (1H, s, CHO), 7.62 (1H, dd, J = 8.2, ArH), 7.24 (1H, d, J = 8.2, ArH), 7.19 (1H, s, ArH), 4.14 (2H, q, CH_2CH$_3$), 3.64 (4H, t, J = 4.5, CH_2N-), 3.01 (4H, t, J = 4.1, CH_2N-), 1.25 (3H, m, CH$_2$CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 189.91, 155.78, 155.48, 132.00, 130.08, 127.46, 126.38, 122.76, 61.70, 53.57, 43,72, 14.74; MS (ESI-MS, micrOTOF) m/z (Calcd. 340.0423; exp. 363.0400, M + Na$^+$, 100%). A crystal structure was obtained and solved.[19]

4-Bromo-2-phenoxybenzaldehyde (7)

To a stirred solution of 4-bromo-2-fluorobenzaldehyde (**1**) (4.0 g, 19.7 mmol) in acetonitrile (20 mL), K_2CO_3 (8.18 g, 59.3 mmol) and phenol (**3**) (2.32 g, 24.7 mmol) was added. The mixture was stirred at 100 °C for 48 h. The solvent was evaporated under vacuum. Water was added to the crude product and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O, dried with Na_2SO_4 and evaporated under vacuum. The crude compound was purified by column chromatography (petroleum ether : ether, 9.7 : 0.3 mL) to give the title compound (**7**) as a pale yellow solid (3.68 g, 62%); mp 86–87 °C; R_f (0.9, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1676 (C═O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.46 (1H, s, CHO), 7.77 (1H, d, J = 8.4, ArH), 7.41 (2H, t, J = 8.4, ArH), 7.21–7.29 (2H, m, ArH), 7.08 (2H, d, J = 8.4, ArH), 6.99 (1H, s, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 188.39, 160.51, 155.44, 130.46, 130.27, 129.69, 126.66, 125.44, 125.22, 121.09, 119.95; MS (APCI-MS, HCTultra) m/z (Calcd. 275.9; exp. 276.9, M + H$^+$, 100%).

4-Bromo-2-[methyl-(2-pyridin-2-yl)-ethylamino]-benzaldehyde(8)

To a stirred solution of 4-bromo-2-fluorobenzaldehyde (**1**) (4.0 g, 19.7 mmol) in acetonitrile (20 mL), K_2CO_3 (8.14 g, 59 mmol) and *N*-methyl-2-(pyridin-2-yl)-ethanamine (**4**) (2.7 mL, 19.8 mmol) was added. The mixture was stirred at 100 °C for 48 h. The solvent was evaporated under vacuum. Water was added to the crude product and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O, dried with Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by column chromatography (petroleum ether : ethylacetate, 8 : 2) to give the title compound (**8**) as a yellow oil (4.43 g, 66%); R_f (0.17, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1682 (C═O), 1580 (C═N); ^{1}H-NMR (400 MHz,

$CDCl_3$) δ_H 9.92 (1H, s, C*H*O), 8.41 (1H, m, Ar*H*), 7.44–7.51 (2H, m, Ar*H*), 7.12 (1H, s, Ar*H*), 6.99–7.05 (3H, m, Ar*H*), 3.51 (2H, m, CH_2N-), 2.99 (2H, m, CH_2CH_2), 2.86 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 190.16, 158.98, 155.99, 149.45, 136.41, 131.66, 129.56, 126.76, 124.56, 123.30, 122.77, 121.58, 57.58, 42.40, 36.03; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 318.0368; exp. 341.0367, M + Na^+, 100%).

4-Bromo-2-[(2,2-dimethoxyethyl)-methylamino]-benzaldehyde (9)

To a stirred solution of 4-bromo-2-fluorobenzaldehyde (**1**) (4.0 g, 19.7 mmol) in acetonitrile (20 mL), K_2CO_3 (8.14 g, 59 mmol) and 1,1-dimethoxy-*N*-methylethanamine (**5**) (2.5 mL, 19.78 mmol) was added. The mixture was stirred at 100 °C for 48 h. The solvent was evaporated under vacuum. Water was added to the crude product and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O, dried with Na_2SO_4 and evaporated under vacuum. The crude mixture was purified by column chromatography (petroleum ether was used as an eluent for the first fraction of impurities and then a mixture of petroleum ether and ethylacetate was used to get the target product, 7 : 3 mL) to give the title compound (**9**) as a yellow oil (5.66 g, 94%); R_f (0.67, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1738 (C═O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.12 (1H, s, C*H*O), 7.54 (1H, d, *J* = 8.2, Ar*H*), 7.21 (1H, s, Ar*H*), 7.10 (1H, d, *J* = 8.2, Ar*H*), 4.51 (1H, m, CH_2CH), 3.23–3.25 (8H, m, 2 -OCH_3, CH_2CH), 2.92 (3H, s,-NCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 190.25, 156.02, 132.04, 129.60, 126.67, 124.72, 122.98, 102.41, 59.16, 53.72, 42.96; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 301.0314; exp. 324.0326, M + Na^+, 100%).

Ethyl 4-[4,4′-diformyl-(1,1′-biphenyl)-3-yl]-piperazine-1-carboxylate (11)

To a stirred solution of ethyl 4-(5-bromo-2-formylphenyl)-piperazine-1-carboxylate (**6**) (3.0 g, 8.82 mmol) in toluene (20 mL) under nitrogen atmosphere, $Pd(PPh_3)_4$ (0.4 g, 0.35 mmol, 3.0 mol%) and an aqueous solution of Na_2CO_3 (10 mL, 2mol L^{-1}) was added. The mixture was stirred vigorously and then 4-formylphenylboronic acid (**10**) (1.32 g, 8.8 mmol) in 15 mL of ethanol was added. The mixture was refluxed overnight under vigorous stirring. The organic phase was extracted with Na_2CO_3 solution (2 × 50 mL) and 10 mL brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether : ethylacetate, 8 : 2 mL) to give the title compound (**11**) as a yellow solid (2.43 g, 75%); mp 139–140 °C; R_f (0.28, petroleum ether : ethyl-acetate, 7 : 3); IR ν_{max}/cm^{-1} 1684 (br, N(C═O)O, H(C═O)); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.36 (1H, s, C*H*O), 10.07 (1H, s, C*H*O), 7.97 (2H, d, *J* = 8.2, Ar*H*), 7.92 (1H, d, *J* = 7.7, Ar*H*), 7.74 (2H, d, *J* = 7.7, Ar*H*), 7.40 (1H, dd, *J* = 7.7, Ar*H*), 7.30 (1H, s, Ar*H*), 4.17 (2H, q, CH_2CH_3), 3.71 (4H, m, CH_2N-), 3.12 (4H, m, CH_2N-), 1.28 (3H, m, CH_2CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.76, 190.55, 155.63, 146.42, 145.91, 136.10, 131.35, 130.40, 128.37, 128.05, 122.23, 118.29, 61.72, 53.77, 43.88, 14.76; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 366.1580; exp. 389.1554, M + Na^+, 100%).

3-Phenoxybiphenyl-4,4′-dicarbaldehyde (12)

To a stirred solution of 4-bromo-2-phenoxybenzaldehyde (**7**) (3.0 g, 10.9 mmol) in toluene (20 mL) under nitrogen atmosphere, $Pd(PPh_3)_4$ (0.32 g, 0.28 mmol, 3.0 mol%) and an aqueous solution of Na_2CO_3 (10 mL, 2mol L^{-1}) was added. The mixture was stirred vigorously and then 4-formylphenylboronic acid (**10**) (1.62 g, 10.8 mmol) in 15 mL ethanol was added. The mixture was refluxed overnight under vigorous stirring. The organic phase was extracted with Na_2CO_3 solution (2 × 50 mL) and 10 mL brine. The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether : ethylacetate, 8 : 2 mL) to give the title compound (**12**) as a pale yellow solid (1.54 g, 47%); mp 100–101 °C; R_f (0.74, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1733 (C═O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.52 (1H, s, C*H*O), 10.01 (1H, s, C*H*O), 8.01 (1H, d, *J* = 7.7, Ar*H*), 7.90 (2H, d, *J* = 7.7, Ar*H*), 7.63 (2H, d, *J* = 7.7, Ar*H*), 7.38–7.44 (3H, m, Ar*H*), 7.10–7.21 (4H, m, Ar*H*);^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.66, 188.88, 160.35, 156.33, 147.21, 145.09, 136.19, 130.37, 130.09, 129.28, 127.97, 126.47, 124.68, 122.50, 119.44, 117.32; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 302.0943; exp. 325.0820, M + Na^+, 100%).

3-[Methyl-(2-pyridin-2-yl)-ethylamino]-1,1′-biphenyl-4,4′-dicarbaldehyde (13)

To a stirred solution of 4-bromo-2-[methyl-(2-pyridin-2-yl)-ethylamino]-benzaldehyde (**8**) (3.02 g, 9.49 mmol) in toluene (20 mL) under nitrogen atmosphere, $Pd(PPh_3)_4$ (0.33 g, 0.28 mmol, 3.0 mol%) and an aqueous solution of Na_2CO_3 (10 mL, 2mol L^{-1}) was added. The mixture was stirred vigorously and then 4-formylphenylboronic acid (**10**) (1.56 g, 10.4 mmol) in 15 mL ethanol was added. The mixture was refluxed overnight under vigorous stirring. The organic phase was extracted with Na_2CO_3 solution (2 × 50 mL) and 10 mL brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether : ethylacetate, 7 : 3 then the polarity was increased to 6 : 4) to give the title compound (**13**) as a yellow oil (2.8 g, 85%); R_f (0.28, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1697 and 1676 (C═O), 1596 (C═N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.12 (1H, s, C*H*O), 10.05 (1H, s, C*H*O), 8.48 (1H, m, Ar*H*), 7.95 (2H, d, *J* = 8.2, Ar*H*), 7.83 (1H, d, *J* = 8.2,Ar*H*), 7.74 (2H, d, *J* = 8.2, Ar*H*), 7.53 (1H, ddd,, *J* = 7.7, Ar*H*), 7.30 (1H, s, Ar*H*), 7.24–7.26 (1H, m, Ar*H*), 7.06–7.10 (2H, m, Ar*H*), 3.64 (2H, m, CH_2N-), 3.10 (2H, m, CH_2CH_2), 3.01 (3H, s, CH_3N); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.83, 190.91, 159.27, 155.83, 149.46, 146.27, 145.76, 136.50, 135.95, 131.05, 130.33, 128.05, 123.37, 121.58, 120.65, 118.68, 57.60,42.97, 36.19; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 344.1525; exp. 367.1598, M + Na^+, 100%).

3-[(2,2-Dimethoxyethyl)-methylamino]-1,1′-biphenyl-4,4′-dicarbaldehyde (14)

To a stirred solution of 4-bromo-2-[(2,2-dimethoxyethyl)-methylamino]-benzaldehyde (**9**) (3.0 g, 9.9 mmol) in toluene (20 mL) under nitrogen atmosphere, $Pd(PPh_3)_4$ (0.35 g, 0.3 mmol, 3.0 mol%) and an aqueous solution of Na_2CO_3 (10 mL, 2 mol L^{-1}) was added. The mixture was stirred vigorously and then

4-formylphenylboronic acid (**10**) (1.49 g, 9.9 mmol) in 15 mL ethanol was added. The mixture was refluxed overnight under vigorous stirring. The organic phase was extracted with Na_2CO_3 solution (2 × 50 mL) and 10 mL brine. The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether : ethylacetate, 9 : 1 mL) to give the title compound (**14**) as a yellow oil (2.58 g, 79%); R_f (0.37, petroleum ether : ethylacetate, 7 : 3); IR ν_{max}/cm^{-1} 1697, 1678 (C═O), ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 10.31 (1H, s, C*H*O), 10.06 (1H, s, C*H*O), 7.96 (2H, d, *J* = 8.2, Ar*H*), 7.86 (1H, d, *J* = 7.7, Ar*H*), 7.75 (2H, d, *J* = 7.7, Ar*H*), 7.34 (1H, s, Ar*H*), 7.29 (1H, d, *J* = 8.2, Ar*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 191.80, 190.96, 155.93, 146.21, 145.84, 135.99, 131.35, 130.35, 128.04, 127.79, 120.80, 118.90, 102.58, 59.20, 53.72, 43.46; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 327.1471; exp. 350.1356, M + Na$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,35)-tri-*N*-piprazinocarboxylate-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(2*H*,3*H*,16*H*,17*H*, 30*H*,31*H*)-hexahydro-[42]-annulene (16)

Dialdehyde (**11**) (1.15 g, 3.14 mmol) in dichloromethane (16 mL) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) (540 mg, 4.74 mmol) in dichloromethane (16 mL). The mixture was stirred at room temperature for 72 h. The solvent was removed under vacuum. The crude mixture was purified by column chromatography (petroleum ether : ethylacetate : triethylamine, 7 : 2: 1 mL) to give the title compound (**16**) as a yellow solid (140 mg, 10%); mp > 150 °C; IR ν_{max}/cm^{-1} 1687 (N(C═O)O), 1638 (C═N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.49 (3H, s, N═C*H*), 8.22 (3H, s, -N═C*H*), 7.80–7.85 (1H, m, Ar*H*), 7.70 (2H, d, *J* = 8.2, Ar*H*), 7.60 (6H, d, *J* = 8.2, Ar*H*), 7.44 (6H, d, *J* = 8.2, Ar*H*), 7.14–7.21 (4H, m, Ar*H*), 7.05 (2H, s, Ar*H*), 4.08–4.17 (6H, m, CH_2CH$_3$), 3.35–3.62 (18H, m, -NCH_2, *H*CN), 2.75–2.98 (12H, br, m, -NCH_2), 1.86 (18H, br, m, CH_2), 1.49 (6H, br, m, CH_2), 1.21–1.32 (9H, m, CH_3CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 160.35, 158.57, 155.54, 152.73, 142.82, 142.32, 135.56, 129.09, 128.54, 126.99, 121.93, 117.70, (74.83, 74.76), 61.49, 45.95, 44.95, 44.00, 32.76, 24.57, (14.94, 14.79); MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1332.7576; exp. 1333.7668, M+H$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4, 15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,35)-tri-(2,2-dimethoxy-*N*-methylethanamino)-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(2*H*,3*H*,16*H*,17*H*,30*H*,31*H*)-hexahydro-[42]-annulene (17)

Dialdehyde (**14**)(1.73 g, 5.29 mmol) in dichloromethane (26 mL) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) (906 mg, 7.95 mmol) in dichloromethane (26 mL). The mixture was stirred at room temperature for 50 h. The crude product was purified by column chromatography (petroleum ether : ethylacetate : triethylamine, 8 : 1 : 1) to give the title compound (**17**) as a yellow solid (90 mg, 4%); mp > 115 °C; IR ν_{max}/cm^{-1} 1637 (C═N); ^{1}H-NMR (400 MHz, C_6D_6) δ_H 8.90 (3H, s, -N═C*H*), 8.27 (3H, d, *J* = 7.7, Ar*H*), 8.19 (3H, s, -N═C*H*), 7.61 (6H, d, *J* = 8.7, Ar*H*), 7.27 (6H, d, *J* = 8.2, Ar*H*), 7.60–7.09 (6H, m, Ar*H* overlapping with C_6D_6 signals), 4.38 (3H, m, CH_2C*H*), 3.52–3.65 (6H, m, *H*CN), 2.91–3.10 (24, m, CH_3, -NCH_2), 2.48 (9H, s, CH_3), 1.83–2.00 (16H, br, m, CH_2), 1.66–1.69 (8H, br, m, CH_2); ^{13}C-NMR (100 MHz, C_6D_6) δ_C 159.65, 158.34, 153.74, 142.47, 142.21, 135.97, 129.94, 128.79, 128.69, 126.87, 121.50, 119.07, 102.66, (75.31, 77.21) 58.00, (52.65, 52.61), 43.79, (33.38, 33.18), 24.74; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1215.7249; exp. 1216.7305, M + H$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,35)-triphenoxy-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(2*H*,3*H*,16*H*,17*H*,30*H*,31*H*)-hexahydro-[42]-annulene (18)

Dialdehyde (**12**) (1.2 g, 3.97 mmol) in dichloromethane (19.9 mL) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) (679 mg, 5.96 mmol) in dichloromethane (19.9 mL). The mixture was stirred at room temperature for 8 h. The solvent was evaporated under vacuum. The crude mixture was purified by column chromatography (petroleum ether : diethylether : triethylamine, 5 : 4: 1 mL) to give the title compound (**18**) as a pale yellow solid (344 mg, 22%); mp > 250 °C; IR ν_{max}/cm^{-1} 1637 (C═N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.51 (3H, s, -N═C*H*), 8.14 (3H, s, -N═C*H*), 7.93 (3H, d, *J* = 8.2, Ar*H*), 7.52 (6H, d, *J* = 8.2, Ar*H*), 7.35 (6H, d, *J* = 8.2, Ar*H*), 7.20–7.28 (5H, m, Ar*H*), 6.94–6.99 (8H, m, Ar*H*), 6.66–6.80 (8H, m, Ar*H*), 3.35 (6H, br, m, *H*CN), 1.83 (18H, br, m, CH_2), 1.46 (6H, br, m, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 170.03, 160.59, 157.57, 156.49, 143.58, 141.12, 135.83, 129.80, 128.47, 127.88, 126.97, 126.83, 123.23, 122.35, 118.05, 117.61, (74.40, 74.13), 32.72, 24.52; MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1140.5666; exp. 1140.5534, M$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-tri-*N*-piprazinocarboxylate-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(2*H*,3*H*,16*H*,17*H*,30*H*,31*H*)-hexahydro-[42]-annulene (19)

Dialdehyde (**11**) (1.15 g, 3.14 mmol) in dichloromethane (16 mL) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) (537 mg, 4.71 mmol) in dichloromethane (16 mL). The mixture was stirred at room temperature for 72 h. The solvent was removed under vacuum. The crude mixture was purified by column chromatography (petroleum ether : ethylacetate : triethylamine, 7 : 2: 1 mL) to give the title compound (**19**) as a pale yellow solid (430 mg, 35%); mp > 200 °C; IR ν_{max}/cm^{-1} 1691 (N(C═O)O), 1638 (C═N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.53 (1H, s, -N═C*H*), 8.43 (1H, s, -N═C*H*), 8.42 (1H, s, -N═C*H*), 8.22 (1H, s, -N═C*H*), 8.19 (1H, s, -N═C*H*), 8.18 (1H, s, -N═C*H*), 7.83–7.86 (2H, m, Ar*H*), 7.75 (1H, d, *J* = 8.2, Ar*H*), 7.57–7.60 (6H, m, Ar*H*), 7.42–7.45 (6H, m, Ar*H*), 7.17–7.25 (3H, m, Ar*H*), 7.06 (1H, s, Ar*H*), 6.90–6.93 (2H, m, Ar*H*), 4.12–4.18 (6H, m, CH_2CH$_3$), 3.72 (2H, br, m, CH_2N-), 3.50 (6H, br, m, *H*CN), 3.36–3.41 (10H, m, CH_2N-), 2.76 (4H, br, m, CH_2N-), 2.53 (4H, br, m, CH_2N-), 2.43 (4H, br, m, CH_2N-), 1.85 (18H, br, m, CH_2), 1.48 (6H, br, m, CH_2), 1.23–1.28 (9H, m, CH$_2$CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C (160.59, 160.48, 160.27), (158.36, 157.86, 157.76), (155.54, 155.48, 155.42), (152.84, 153.68), (143.44, 143.22, 142.84), (142.38, 142.12), (135.63, 135.57, 135.46), (129.10,

128.98), (128.60, 128.51, 128.44), (128.41, 128.33, 128.27), (127.26, 127.14, 126.96), (122.11, 121.97), (118.18, 118.03, 117.82), (75.25, 75.14, 75.01, 74.82, 74.66, 74.38), (61.53, 61.50, 61.45), (52.53), (43.98), (32.98, 32.83, 32.73, 32.61), (24.60), (14.87, 14.82); MS (ESI-MS, micrOTOF) *m/z* (Calcd. 1332.7576; exp. 1333.4865, M + H^+, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-tri-(2,2-dimethoxy-*N*-methylethanamino)-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*2H*,*3H*,*16H*,*17H*,*30H*,*31H*)-hexahydro-[42]-annulene (20)

Yellow solid (680 mg, 31%); mp > 125 °C; IR ν_{max}/cm^{-1} 1637 (C═N); ^{1}H-NMR (400 MHz, C_6D_6) δ_H 8.94 (1H, s, -N═C*H*), 8.93 (1H, s, -N═C*H*), 8.89 (1H, s, -N═C*H*), 8.21–8.27 (3H, m, Ar*H*), 8.18 (1H, s, -N═C*H*), 8.14 (2H, br, s, -N═C*H*), 7.62–7.66 (6H, m, Ar*H*), 7.31 (2H, d, *J* = 8.2, Ar*H*), 7.26 (2H, d, *J* = 8.2, Ar*H*), (2H, d, *J* = 8.2, Ar*H*), 7.00–7.13 (6H, m, Ar*H*), 4.36–4.42 (3H, m, CH_2CH), 3.46–3.68 (6H, m, CH_2), 3.00–3.03 (24H, m, CH_3, -NCH_2) 2.51 (3H, s, CH_3), 2.47 (3H, s, CH_3), 2.43 (3H, s, CH_3), 1.82–1.99 (12H, br, m, CH_2), 1.67 (6H, br, m, CH_2), 1.36 (6H, br, m, CH_2); ^{13}C-NMR (100 MHz, C_6D_6) δ_C (159.78, 159.69, 159.60), (158.42, 158.22, 158.17), (153.87, 153.82, 153.77), (142.43, 142.36, 142.31), (136.01, 135.88, 135.84), (130.00, 129.91), (128.88, 128.73, 128.58), (126.97, 126.86), (121.45), (119.25, 119.21, 119.11), (102.78, 102.69), (75.62, 75.57), (75.24), (74.76), (58.08, 58.04, 57.94), (52.77, 52.70, 52.61), (44.01, 43.95, 43.87), (33.34, 33.14), (24.74); MS (ESI-MS, micrOTOF) *m/z* (Calcd. 1215.7322; exp. 1216.7292, M+H^+, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-triphenoxy-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*2H*,*3H*,*16H*,*17H*,*30H*,*31H*)-hexahydro-[42]-annulene (21)

Yellow solid (564 g, 37%); mp > 135 °C (decomposition); IR ν_{max}/cm^{-1} 1637 (C═N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.57 (1H, s,-N═C*H*), 8.55 (1H, s, -N═C*H*), 8.54 (1H, s, -N═C*H*), 8.18 (1H, s, -N═C*H*), 8.15 (1H, s, -N═C*H*), 8.14 (1H, s, -N═C*H*), 7.94–7.97 (3H, m, Ar*H*), 7.53–7.57 (6H, m, Ar*H*), 7.34–7.42 (6H, m, Ar*H*), 7.22–7.31 (6H, m, Ar*H*), 6.99–7.11 (7H, m, Ar*H*), 6.91 (1H, s, Ar*H*), 6.75–6.86 (5H, m, Ar*H*), 6.69 (2H, d, *J* = 8.2, Ar*H*), 3.37 (6H, m, br, *H*CN), 1.85 (18H, m, br, CH_2), 1.47 (6H, m, br, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C (160.62, 160.53), (157.78, 157.65, 157.45), (156.49), (143.63, 143.58), (141.23, 141.18), (135.93, 135.85, 135.78), (130.00, 129.95, 129.80), (128.54, 128.47), (128.23), (127.92), (127.17, 127.06), (126.86), (123.28, 123.19, 123.13), (122.51, 122.37, 122.26), (118.18), (117.70, 117.60), (74.45, 74.36, 74.32, 74.26, 74.20, 74.05), (32.78, 32.71), (24.57); MS (ESI-MS, micrOTOF) *m/z* (Calcd. 1140.5666; exp. 1163.5545, M+Na^+, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-tri-[*N*-methyl-2-(pyridin-2-yl)-ethanamino]-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*2 H*,*3H*,*16H*,*17H*,*30H*,*31H*)-hexahydro-[42]-annulene (22)

Dicarbaldehyde (**13**) (2.3 g, 6.69 mmol) in dichloromethane (33.4 mL) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**15**) (1.14 g, 10.03 mmol) in dichloromethane (33.4 mL). The mixture was stirred at room temperature for 96 h. The crude product was purified by column chromatography (petroleum ether : ethylacetate : triethylamine, 7 : 2 : 1) to give the title compound (**22**) as a yellow solid (310 mg, 11%); mp > 125 °C; IR ν_{max}/cm^{-1} 1637; ^{1}H-NMR (400 MHz, C_6D_6) δ_H 8.66–8.69 (3H, br, m, -N═C*H*), 8.41–8.43 (3H, br, m, -N═C*H*), 8.14–8.26 (6H, m, Ar*H*), 7.62–7.68 (6H, m, Ar*H*), 7.24–7.28 (6H, m, Ar*H*), 6.95–7.04 (9H, m, Ar*H*), 6.58–6.71 (6H, m, Ar*H*), 3.48–3.55 (6H, m, CH_2), 3.13–3.23 (6H, m, -NCH_2), 2.77–2.84 (6H, m, CH_2CH_2), 2.34–2.41 (9H, m, CH_3), 1.86–1.95 (12H, br, m, CH_2), 1.68 (6H, br, m, CH_2), 1.37 (6H, br, m, CH_2); ^{13}C-NMR (100 MHz, C_6D_6) δ_C (160.25), (159.83, 159.76, 159.67), (158.34, 158.20, 158.18), (153.65, 153.58, 153.50), (149.42), (142.49, 142.42), (135.87, 135.82, 135.79), (135.54, 135.50, 135.47), (130.16, 130.13, 130.09), (128.68, 128.63, 128.53), (127.06, 127.04, 126.96), (123.08, 122.97), (121.34),(120.85), (119.26, 119.18, 119.10), (75.61, 75.53), (75.34, 75.27), (74.80), (56.09), (43.27, 43.22, 43.19), (36.65, 36.63, 36.53), (33.36, 33.21, 33.16), (24.84, 24.78, 24.70); MS (ESI-MS, micrOTOF) *m/z* (Calcd. 1267.7482; exp. 1267.7439, M $^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,35)-triphenoxy-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*1H*,*2H*,*3H*,*4H*,*5H*,*14H*,*15H*,*16H*, *17H*,*18H*,*19H*,*28H*,*29H*,*30H*,*31H*,*32H*,*33H*,*42H*)-octadecahydro-[42]-annulene (26)

To a stirred solution of trianglimine (**18**) (125 mg, 0.11 mmol) in THF–MeOH (1 : 1, 20 mL) solid $NaBH_4$ (36.5 mg, 0.96 mmol) was gradually added and the solution was stirred for 5 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 and water. The organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the title compound (**26**) as a pale yellow solid (>98%) which required no further purification; mp > 180 °C; IR ν_{max}/cm^{-1} 3289 (NH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.48 (8H, t, *J* = 7.7, Ar*H*), 7.38 (8H, d, *J* = 8.2, Ar*H*), 7.20–7.25 (8H, m, Ar*H*), 7.14 (3H, s, Ar*H*), 6.99 (3H, m, Ar*H*), 6.92 (6H, d, *J* = 7.7, Ar*H*), 3.94–3.98 (6H, m, AB system, -CH_ACH_BN), 3.63–3.74 (6H, m, AB system, *J* = 12.8, CH_ACH_BN-), 2.18–2.34 (18H, m, CH_2, -N*H*), 1.73 (6H, br, s, *CH*N-), 1.18–1.27 (6H, br, m, CH_2), 1.03–1.08 (6H, br, m, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 157.70, 155.18, 141.34, 140.42, 138.79, (130.97, 130.64), 129.87, 128.63, 126.98, 122.91, 122.44, (118.02, 117.78), (61.02, 60.97), 50.50, (31.52, 31.37), (25.22, 25.10); MS (ESI-MS, micrOTOF) *m/z* (Calcd. 1152.6605; exp. 1153.6665, M + H^+, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-triphenoxy-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*1H*,*2H*,*3H*,*4H*,*5H*,*14H*,*15H*,*16H*, *17H*,*18H*,*19H*,*28H*,*29H*,*30H*,*31H*,*32H*,*33H*,*42H*)-octadecahydro-[42]-annulene (27)

To a stirred solution of trianglimine (**21**) (125 mg, 0.11 mmol) in THF–MeOH (1 : 1, 10 mL) solid $NaBH_4$ (36.5 mg, 0.96 mmol) was gradually added and the solution was stirred for 5 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 and water. The organic extracts were dried over

$MgSO_4$, filtered and evaporated under reduced pressure to give the title compound (**27**) as a pale yellow solid (>98%) which required no further purification; mp > 110 °C; IR ν_{max}/cm^{-1} 3286 (NH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.53 (2H, dd, $J = 7.7$, Ar*H*), 7.46–7.49 (6H, m, Ar*H*), 7.29–7.38 (12H, m, Ar*H*), 7.20–7.25 (8H, m, Ar*H*), 7.12–7.15 (3H, m, Ar*H*), 6.97–7.02 (4H, m, Ar*H*), 6.91–6.92 (6H, d, $J = 7.3$, Ar*H*),3.94–4.00 (6H, m, AB system, -CH_ACH_BN), 3.63–3.72 (6H, m, AB system, J = 13.2, -CH_ACH_BN), 2.08–2.31 (18H, m, CH_2, N*H*), 1.96–1.74 (6H, br, s, C*H*N), 1.26 (6H, br, m, CH_2), 1.05–1.07 (6H, br, m, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C (157.57, 157.54), (155.23, 155.20, 155.16), (141.49, 141.45, 141.39), (140.25), (138.81), (135.87), (130.96), (130.69), (129.87), (128.66, 128.49), (127.00, 127.03), (125.62), (122.96), (122.53, 122.47), (118.04, 118.02, 117.98), (117.72, 117.69, 117.61), (60.99, 60.92, 60.86, 60.81), (50.45), (31.43, 31.14, 31.02), (25.14, 25.02); MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1152.6605; exp. 1153.6658, M+H$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-tri-*N*-piprazinocarboxylate-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(*1H*,*2H*,*3H*,*4H*,*5 H*,*14H*,*15H*,*16H*,*17H*, *18H*,*19H*,*28H*,*29H*,*30H*,*31H*,*32H*,*33H*,*42H*)-octadecahydro-[42]-annulene (28)

To a stirred solution of trianglimine (**19**) (111 mg, 0.083 mmol) in THF–MeOH (1 : 1, 10 mL) solid $NaBH_4$ (32 mg, 0.83 mmol) was gradually added and the solution was stirred for 5 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 and water. The organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the title compound (**28**) as a pale yellow solid (>98%) which required no further purification; mp > 110 °C; IR ν_{max}/cm^{-1} 3293 (NH), 1686 (N(C═O)O);^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.50–7.56 (6H, m, Ar*H*), 7.45 (2H, d, $J = 7.79$, Ar*H*), 7.41 (3H, d, $J = 7.79$, Ar*H*), 7.29–7.38 (7H, m, Ar*H*), 7.27 (1H, s, Ar*H*), 7.25 (3H, s, Ar*H*), 3.96–4.71 (12H, m, AB system, $J = 13.28$, -CH_ACH_BN), 3.49–3.69 (18H, m, CH_2N, *H*CN), 2.90–2.95 (12H, br, m, CH_2N), 2.24–2.33 (12H, br, m, CH_2), 2.02 (6H, br, s, CH$_2$N*H*), 1.78 (6H, br, s, CH$_2$), 1.17–1.25 (15H, m, CH_3CH$_2$, CH$_3$CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C (155.68, 155.65), (151.76, 151.72), (140.72), (140.19, 140.15, 140.07), (139.55, 139.53, 139.50), (134.79, 134.74), (130.61, 130.58, 130.48), (128.55), (127.09, 127.05, 127.02), (123.02), (121.39), (122.93), (118.84), (61.60, 61.53, 61.42), (61.14, 61.01, 60.94), (52.76), (50.66, 50.61, 50.58), (44.30), (31.53), (25.18), (14.77); MS (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1344.8515; exp. 1345.8617, (ESI-MS, micrOTOF) *m*/*z* (Calcd. 1344.8515; exp. 1345.8617, M+ H$^+$, 100%).

(2*R*,3*R*,16*R*,17*R*,30*R*,31*R*)-(1,4,15,18,29,32)-Hexaza-(2,3 : 16,17 : 30,31)-tributano-(7,21,40)-tri-(2,2-dimethoxy-*N*-methylethanamino)-(6,9 : 10,13 : 20,23 : 24,27 : 34,37 : 38,41)-hexa-etheno-(1 H, 2*H*,3*H*,4H,5H,14H,15H,16H,17H, 18H,19H,28H,29*H*,30*H*,31*H*,32*H*,33*H*,42H)-octadecahydro-[42]-annulene (29)

To a stirred solution of trianglimine (**20**) (207 mg, 0.17 mmol) in THF–MeOH (1 : 1, 10 mL) solid $NaBH_4$ (65 mg, 1.7 mmol) was gradually added and the solution was stirred for 5 h at room temperature. After removal of solvents the residue was extracted with CH_2Cl_2 and water, the organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the title compound (**29**) as a yellow oil (>98%) which required no further purification, ^{1}H-NMR (400 MHz, C_6D_6) δ_H 7.49–7.54 (8H, m, Ar*H*), 7.37–7.40 (9H, m, Ar*H*), 7.23–7.28 (1H, m, Ar*H*), 7.09 (2H, s, Ar*H*), 4.45–4.47 (3H, m, CH$_2$C*H*), 4.11–4.19 (3H, m, AB system, J = 12.82,-CH_ACH$_B$N), 3.76–3.87 (6H, m, *H*CN), 3.53–3.58 (3H, m, AB system, -CH$_A$CH_BN), 3.13–3.21 (6H, m, CH_2CH), 3.03 (18H, s, OCH_3), 2.64 (9H, s, NCH_3), 2.01–2.37 (18H, m, CH_2, N*H*), 1.56–1.62 (6H, m, CH_2), 1.24 (6H, br, s, CH_2); ^{13}C-NMR (100 MHz, C_6D_6) δ_C (152.47), (140.59, 140.56, 140.50, 140.41), (140.08, 140.04, 140.00), (135.47), (130.57, 130.49), (128.65, 128.52), (127.15, 127.06), (125.55), (122.65, 122.53), (119.99, 119.92), (102.71), (77.65), (61.74), (60.97, 60.90), (58.04), (52.45), (43.53), (31.52, 31.36), (25.35, 25.17); MS (ESI-MS, micrOTOF) *m*/*z*(Calcd. 1227.8188; exp. 1228.8261, M$^+$+H$^+$, 100%).

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Notes and references

1 J. Gawroński, H. Kolbon, M. Kwit and A. Katrusiak, *J. Org. Chem.*, 2000, **65**, 5768.
2 N. Kuhnert, A. Lopez-Periago and G. Rossignolo, *Org. Biomol. Chem.*, 2005, **3**, 524.
3 N. Kuhnert, A. Lopez-Periago and G. Rossignolo, *Org. Biomol. Chem.*, 2003, **1**, 1157.
4 N. Kuhnert and A. Lopez-Periago, *Tetrahedron Lett.*, 2002, **43**, 3329.
5 C. Gutsche, *Calixarenes in Monographs in Supramolecular Chemistry*, ed. J. Stoddart, Royal Society of Chemistry, Cambridge, 1989.
6 Gutsche, *Calixarenes Revisited in Monographs in Supramolecular Chemistry*, ed. J. Stoddart, Royal Society of Chemistry, Cambridge, 1998.
7 V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713.
8 A. Danil de Namor, R. Cleverley and M. Zapata-Ormachea, *Chem. Rev.*, 1998, **98**, 2495.
9 For cyclodextrins see special edition of Chemical Review, edition 5, 1998.
10 J. Kim, I. Jung, S. Kim, E. Lee, K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 540.
11 S. Kim, I. Jung, E. Lee, J. Kim, S. Sakamoto, K. Yamaguchi and K. Kim, *Angew. Chem., Int. Ed.*, 2001, **40**, 2119.
12 C. Pederson, *J. Am. Chem. Soc.*, 1967, **89**, 7017.
13 N. Kuhnert, N. Burzlaff, C. Patel and A. Lopez-Periago, *Org. Biomol. Chem.*, 2005, **3**, 1911.
14 N. Kuhnert, A. Lopez-Periago and G. Rossignolo, *Org. Biomol. Chem.*, 2005, **3**, 524.
15 J. Gajewy, M. Kwit and J. Gawroński, *Adv. Synth. Catal.*, 2009, **351**, 1.
16 K. Tanaka and S. Hachiken, *Tetrahedron Lett.*, 2008, **49**, 2533.
17 M. Chadim, M. Budesinsky, J. Hodacova, J. Zavada and P. Junk, *Tetrahedron: Asymmetry*, 2001, **12**, 127.
18 N. Kuhnert, D. Marsh and D. Nicolau, *Tetrahedron: Asymmetry*, 2007, **18**, 1648.

19 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
20 S. Nielsen, M. Larsen, T. Boesen, K. Schønning and H. Kromann, *J. Med. Chem.*, 2005, **48**, 2667.
21 Y. Yamaguchi, T. Yanase, S. Muto and A. Itai, *US Pat. Appl. Publ.*, 20090312315, 2009.
22 Y. Yamaguchi, T. Yanase, S. Muto and A. Itai, *US Pat. Appl. Publ.*, 2009125606, 2009.
23 K. Hattori, Y. Tomishita and M. Imanishi, *PCT Int. Appl.*, 2004002939, 2004.
24 H. Smith, J. Neegaard, E. Burrows and F. Chen, *J. Am. Chem. Soc.*, 1974, **96**, 2908.
25 M. Smith and J. March, in *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, John Wiley & Sons, Ltd., Chichester, UK, 5th edn, 2001, pp. 1177.
26 Molecular modeling was carried out using Hyperchem software (Release 8.0). Hypercube, Inc., 1115 NW 4th Street, Gaineville, F1 32601 USA. Trial, version from http://www.hypercube.com.
27 J. Stewart, *J. Comput. Chem.*, 1989, **10**(209), 221.
28 J. Cannadine, J. Corden, W. Errington, P. Moore and M. Wallbridge, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1996, **C52**, 1014.
29 G. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **A64**, 112.