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(3+3)-Cyclocondensation of the enantiopure and racemic forms of *trans*-1,2-diaminocyclohexane with terephthaldehyde. Formation of diastereomeric molecular triangles and their stereoselective solid-state stacking into microporous chiral columns

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Abstract—The non-templated reaction of both the homochiral as well as the racemic form of *trans*-1,2-diaminocyclohexane with terephthaldehyde affords (3+3)-cyclocondensed molecular triangles in practically quantitative yields. The configuration of the diastereomeric products resulting in the individual reactions has been determined by ^{1}H and ^{13}C NMR spectroscopy. Unambiguous proof has been obtained by X-ray crystal structure analysis of both alternative diastereomers, revealing also a stereoselective stacking of the triangles into microporous chiral columns.

1. Introduction

The fascinating architecture of achiral zeolites[1] has inspired the design and synthesis of analogous microporous chiral structures.[2] Recently, large chiral squares possessing unique D_4 symmetry[3–5] have been prepared and some have been shown to exhibit a propensity for columnar solid-state stacking leading to the formation of chiral micropores.[4] In a search for other chiral D_n symmetrical polygons with analogous stacking properties, we focused our attention on the D_3 symmetrical molecular triangles, represented by appropriate (3+3)-cyclocondensed Schiff bases. According to available databases few examples of (3+3)-cyclocondensation between diamines and dicarbonyl compounds have been reported so far, contrasting with several hundreds of known (2+2)-cyclocondensed analogues. Of the known[6a] (3+3)-cyclocondensed compounds, only one could be obtained in the absence of a metal ion template.[6b] Notably, this particular product resulted from the reaction of enantiopure *trans*-1,2-diaminocyclohexane with 2,6-diformylphenol, suggesting an exceptional propensity of this chiral diamine for the formation of (3+3)-cyclocondensed Schiff bases. Supported by model considerations, we chose the reaction of the enantiopure as well as the racemic form of *trans*-1,2-diaminocyclohexane **1** with terephthaldehyde **2** for a systematic study of chiral molecular triangles.

2. Results and discussion

2.1. Synthesis and structural determination of the molecular triangles (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-3 and (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-3

Under a variety of reaction conditions, the individual enantiopure diamines (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1** with terephthaldehyde **2** afforded the (3+3)-cyclocondensed products (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** and (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**, respectively, in practically quantitative yields.

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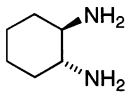
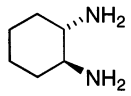


(1R,2R)-1



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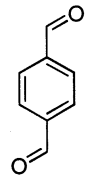
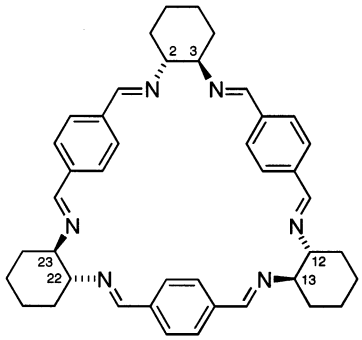
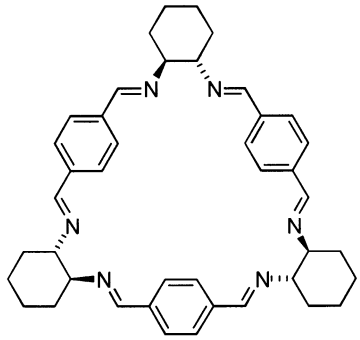


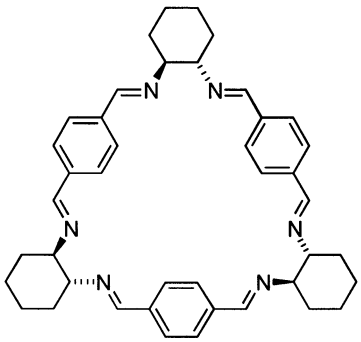
2



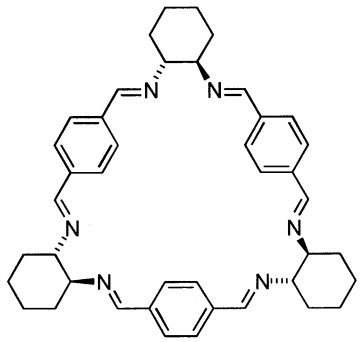
(2R,3R,12R,13R,22R,23R)-3



(2S,3S,12S,13S,22S,23S)-3



(2R,3R,12R,13R,22S,23S)-4



(2S,3S,12S,13S,22R,23R)-4

Identical results have been obtained, in the absence of a template, both in acetonitrile, where the product precipitated from the reaction mixture, and in CH_2Cl_2 or THF, where the product remained in solution. According to GPC analysis, the course of the reaction is unchanged by varying the stoichiometric ratios of the starting materials. Owing to the reversible character of the condensation reaction (vide infra), these results suggest superior thermodynamic stability of the reaction product both in solution and in the solid phase.

The structure of the target product **3** has been determined on the basis of the combined mass spectral and ^1H and ^{13}C NMR evidence. FAB-MS spectra, supported by GPC analysis, demonstrated the cyclotrimeric nature of the product and the symmetry of the Schiff base cyclotrimer was inferred from the ^1H and ^{13}C NMR spectra (vide infra).

2.2. Crystal structure of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-3

A crystal of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** suitable for X-ray diffraction analysis was grown from an acetonitrile–dichloromethane solution. The molecular structure, determined by X-ray crystallography, unambiguously established the expected features of the molecular triangle (Fig. 1).

The crystal packing of the molecular triangles was of particular interest. As seen in Fig. 2, the triangles stack

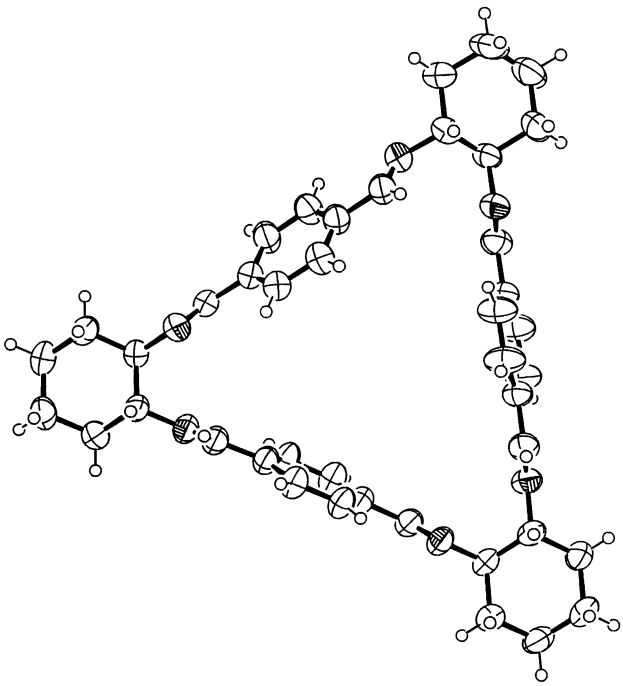


Figure 1. Perspective ORTEP drawing of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**. Thermal ellipsoids are shown at the 50% probability level.

in an eclipsed manner along the crystallographic *b*-axis, giving rise to infinite microporous pillars (columns). The pillars are arranged in a parallel manner along the crystallographic *a*-axis whereas the neighbouring rows of pillars are oriented in an anti-parallel fashion along the *c*-axis.

Simultaneously with our preliminary communication of these results,[7] an independent synthesis and structure determination of **3** was reported by Gawronski et al.[8] However, the crystal structure established by these authors, which is based on a crystal grown from ethyl acetate, differs from our results by the presence of solvent molecules; as a probable consequence of this inclusion, columnar stacking of the molecular triangles did not occur.

2.3. Interconversion of the diastereomeric triangles 3 and 4

In order to get an insight into the stereochemical requirements of the columnar stacking of molecular triangles, we also wished to examine the crystal structure of the racemic form of **3**. Upon co-crystallisation of the 1:1 mixture of the (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)- and (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-enantiomers of **3**, a suitable specimen was selected at random from the crop of crystals resulting from the dichloromethane–acetonitrile solution and was subjected to X-ray diffraction analysis. Surprisingly, it was established that the molecular structure does not correspond either to the racemic compound (2*RS*,3*RS*,12*RS*,13*RS*,22*RS*,23*RS*)-**3** or to a single enantiomer, (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** or (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**, accountable by the formation of the racemic conglomerate. Instead, the sample was found to represent the diastereomeric pair **4** con-

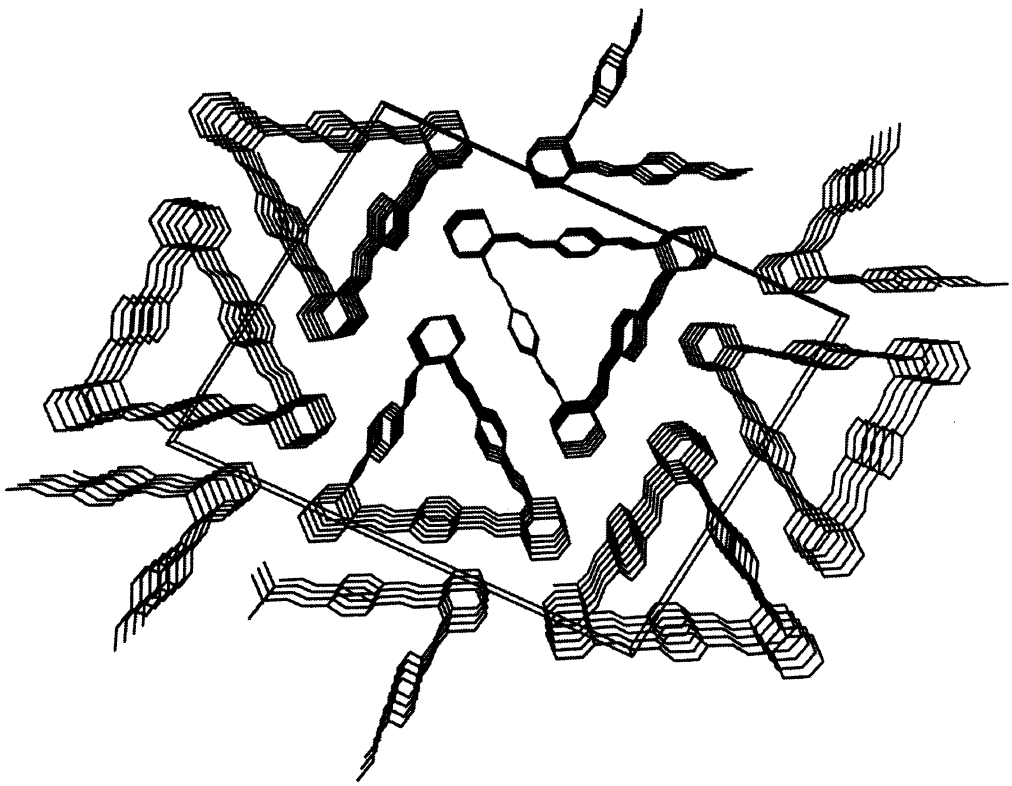


Figure 2. Packing diagram of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** projected down *b*, showing the arrangement of the triangular molecules in pillars.

taining both (1*R*,2*R*)- and (1*S*,2*S*)-diaminocyclohexane units in each molecular triangle (Fig. 3).

In order to explain formation of the 'misfit' diastereomer **4** under these crystallisation conditions, we carried out an independent synthesis. Contrary to the Polish authors[8] claims that no defined cyclic product could be obtained from the reaction of the racemic form of the starting diamine (1*RS*,2*RS*)-**1** with the dialdehyde **2**, we established via NMR analysis the concurrent formation of both diastereomers (diastereomeric pairs), **3** and **4**, as the sole products of the condensation.

2.4. NMR analysis of the diastereomeric mixture 3 and 4

The ^{1}H and ^{13}C NMR spectra of the triangles (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** and (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**, prepared from the enantiopure diamines (1*R*,2*R*)-**1** or (1*S*,2*S*)-**1**, respectively, exhibit the expected number of signals (one for N=C-H as well as for the aromatic protons) corresponding to D_3 symmetry of the molecules (Fig. 4a). In contrast, the product obtained from the racemic diamine (1*RS*,2*RS*)-**1** gave more complex spectra (Fig. 4b). In addition to the signals corresponding to the enantiomeric pair **3**, these spectra contain an additional set of signals that can be assigned to the diastereomer **4**. The lower symmetry of the triangle **4** (C_2 symmetry) accounts for the three signals for N=C-H as well as for the aromatic protons in the ^{1}H NMR spectrum (and for three signals for each carbon atom in the ^{13}C NMR spectrum) instead of one found for the diastereoisomer **3**. All the signals are summarised in Table 1.

The signals of the individual enantiomers could be resolved in the ^{1}H NMR spectra upon addition of the optically-active shift reagent tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato] europium(III) (Eu(HFC)$_3$). The enantiomeric pair **3** showed the doubling of signals of both N=C-H as well as aromatic protons. Assignment of the signals belonging to the enantiomer (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** was achieved by the addition of this enantiomer in the pure form to the analysed Eu(HFC)$_3$-complexed racemic sample, leading to an increase in intensity of the corresponding signals (Fig. 4c).

A similar doubling of signals can be observed upon complexation with Eu(HFC)$_3$ in the ^{1}H NMR spectrum of the other enantiomeric pair **4** (Fig. 4d). For the assignment of signals to the individual enantiomers of **4**, we have employed the product obtained from the enantiomerically enriched racemic diamine (1*RS*,2*RS*)-**1**. Interestingly, in both enantiomeric pairs **3** and **4**, the signals of the isomers with a prevailing (*R*)-configuration ((2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** or (2*R*,3*R*,12*R*,13*R*,22*S*,23*S*)-**4**) appear at a higher field (except for the -CH=N signal of **4** appearing at the lowest field).

Attempts to resolve signals of the individual enantiomers in ^{13}C NMR spectra analogously were unsuccessful, probably due to a combination of very small chemical shift differences and line broadening effects.

Eu(HFC)$_3$ was also employed to determine the composition of the stereoisomeric mixture arising from the equilibration of the racemate **3**. It was found that the resulting mixture contains all four possible stereoisomers of **3** and **4** corresponding approximately to a 1:1:1:1 ratio.

2.5. Mechanism of the diastereomeric conversion

A gradual appearance of the 'misfit' diastereomer **4** arising from the crystallisation of racemate **3** could be monitored by NMR (vide supra). In the initial experiments, we observed irreproducible, and sometimes very low rates, of the conversion **3**→**4**. Presumably, amines present in varying amounts in the individual crystallisation experiments are responsible for controlling the rate of the diastereomeric conversion. The diamine **1** was found to be an efficient catalyst, allowing a reproducible rapid conversion.

On the strength of this experimental evidence, the diastereomeric conversion, which may also take place during the course of the (3+3)-cyclocondensation from the racemic amine **1**, can be rationalised in terms of a series of reversible addition–elimination reactions (Scheme 1).

3. Conclusion

A simple approach leading to molecular triangles with chiral intra-annular cavities, which rests on the unique propensity of *trans*-1,2-diaminocyclohexane **1** to (3+3)-cyclocondensation reactions with a rod-like aromatic

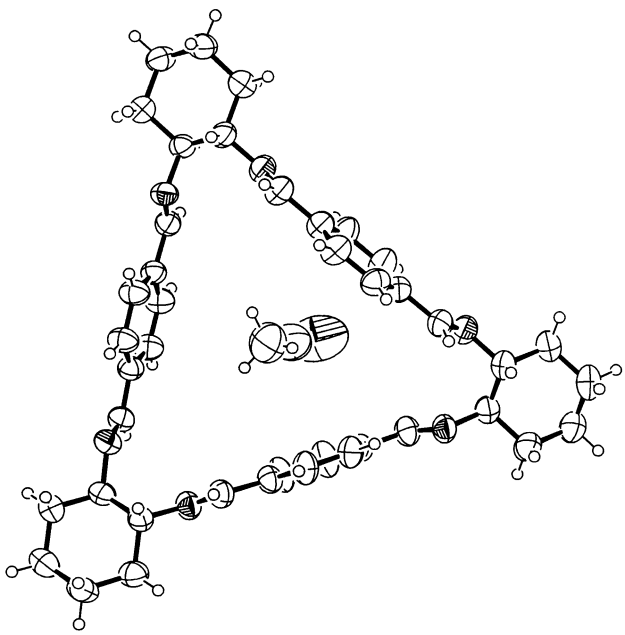


Figure 3. Perspective ORTEP drawing of **4** (only one enantiomer is shown). Thermal ellipsoids are shown at the 50% probability level.

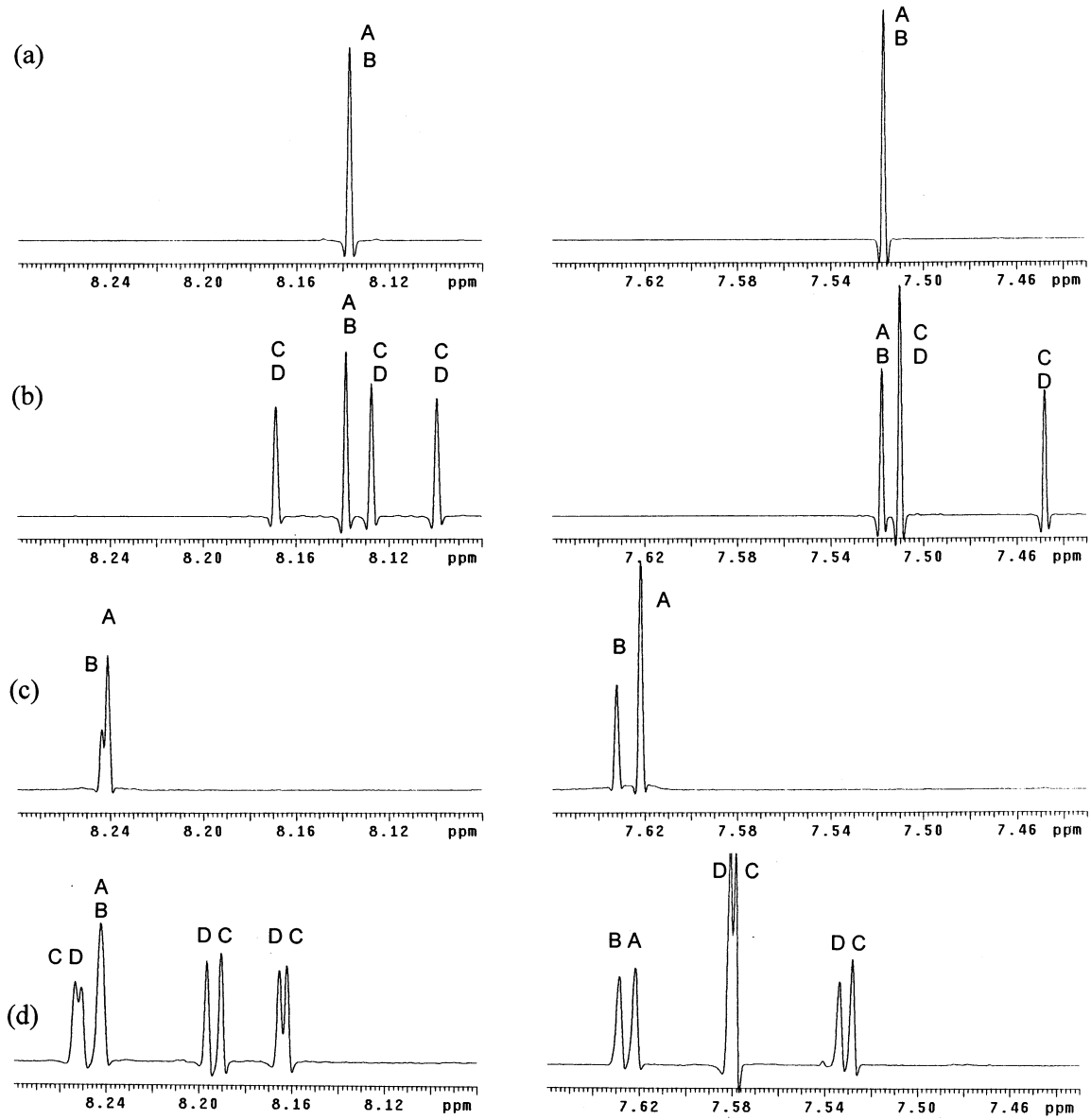
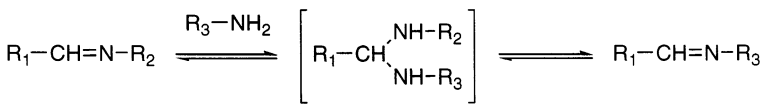


Figure 4. Sections of the ^{1}H NMR spectra of molecular triangles in $CDCl_3$ (-CH=N protons on the left and aromatic protons on the right). Capitals A–D refer to individual stereoisomers: A: (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**; B: (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**; C: (2*R*,3*R*,12*R*,13*R*,22*S*,23*S*)-**4**; D: (2*S*,3*S*,12*S*,13*S*,22*R*,23*R*)-**4**. (a) A and B were prepared from the enantiopure diamines (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1**, respectively; (b) a mixture of A, B, C and D was obtained from the racemic diamine (1*RS*,2*RS*)-**1**; (c) a 2:1 mixture of A and B after addition of $Eu(HFC)_3$; substrate/$Eu(HFC)_3$ molar ratio 2:1; (d) same solution as in (b) after addition of $Eu(HFC)_3$; substrate/$Eu(HFC)_3$ molar ratio 2:1.



Scheme 1.

dialdehyde (terephthaldehyde), has been explored. Two distinct diastereomers of the molecular triangle, **3** and **4**, differing by symmetry (D_3 versus C_2) and also by the propensity to columnar stacking in the solid state, have been found to arise from the homochiral and racemic forms of the starting diamine **1**.

4. Experimental

4.1. General

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a

Varian UNITY 500 instrument (^{1}H at 499.9 MHz; ^{13}C at 125.7 MHz) in $CDCl_3$ and are referenced to an internal TMS standard (^{1}H) or $CDCl_3$ (^{13}C; $\delta(CDCl_3)=77.0$). Structural assignment of proton signals is based on characteristic chemical shifts, multiplicity and the intensity of individual signals. Carbon signals were assigned using ^{1}H–^{13}C correlated HMQC spectra. For the resolution of enantiomers in NMR spectra, a stepwise addition of Eu(HFC)$_3$ to a solution of the enantiomeric mixture in $CDCl_3$ was used. Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument using the FAB (Xe, 8 kV) technique. GPC analyses were performed on an ECOM HPLC chromatograph with a UV detector operating at 254 nm using a Eurogel SEG100 (Knauer) column (300×8 mm; particle size 6 μm) and tetrahydrofuran as the mobile phase (flow rate: 0.5 ml min^{-1}).

4.1.1. Synthesis of (−)-(2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-3

4.1.1.1. Method A. To a solution of diamine (1*R*,2*R*)-**1** (2.17 g, 19.0 mmol) in acetonitrile (120 ml) a solution of terephthaldehyde (2.55 g, 19.0 mmol) in acetonitrile (60 ml) was added. The reaction mixture was stirred overnight at room temperature. The white precipitate was isolated (3.86 g) and re-crystallised from a CH_2Cl_2–CH_3CN mixture giving colourless crystals (3.47 g, 86%). Mp: >300°C (dec.). $[\alpha]_D$ −304.5 ($c=1$, CH_2Cl_2). For $C_{42}H_{48}N_6$ (636.9) calculated: 79.21% C, 7.60% H, 13.20% N; found: 78.96% C, 7.70% H, 13.20% N.

4.1.1.2. Method B. Tetrahydrofuran solutions of diamine (1*R*,2*R*)-**1** (5.68 g, 49.7 mmol, in 60 ml THF) and dialdehyde **2** (6.67 g, 49.7 mmol, in 120 ml THF) were mixed together and stirred overnight at room temperature. The solvent was evaporated and the residue was crystallised from a CH_2Cl_2–CH_3CN mixture giving the colourless microcrystalline material (9.50 g, 90%). Mp: >300°C (dec.). $[\alpha]_D$ −304.4 ($c=1$, CH_2Cl_2). For $C_{42}H_{48}N_6$ (636.9) calculated: 79.21% C, 7.60% H, 13.20% N; found: 79.18% C, 7.74% H, 13.19% N.

The products obtained by both Methods A and B possessed the same NMR and MS spectra and exhibited only a single peak in GPC analysis ($t_R=18.5$ min). FAB-MS (matrix: thioglycerol/glycerol 3:1): m/z 637 ([M+H]$^+$).

4.1.2. Synthesis of (+)-(2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-3

Prepared from (1*S*,2*S*)-*trans*-diaminocyclohexane by Method A in 78% yield. Mp: >300°C (dec.). $[\alpha]_D$ +300.9 ($c=1$, CH_2Cl_2). FAB-MS and NMR spectra were identical with those of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**.

4.1.3. Synthesis of a diastereomeric mixture of 3 and 4

To a solution of the racemic diamine **1** (0.228 g, 2.0 mmol) in acetonitrile (80 ml) a solution of **2** (0.268 g, 2.0 mmol) in acetonitrile (40 ml) was added dropwise over a 30 min period. After stirring overnight at room temperature, a mixture of **3** and **4** was isolated as a white precipitate (0.349 g, 82%). The ratio (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**:(2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**:(2*R*,3*R*,12*R*,13*R*,22*S*,23*S*)-**4**:(2*S*,3*S*,12*S*,13*S*,22*R*,23*R*)-**4**≅1:1:3:3 was determined by the NMR analysis. The GPC analysis revealed only a single peak, which had a t_R identical with that of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**. FAB-MS: m/z 637 ([M+H]$^+$). For $C_{42}H_{48}N_6$ (636.9) calculated: 79.21% C, 7.60% H, 13.20% N; found: 79.40% C, 7.90% H, 13.11% N.

4.1.4. Equilibration of 3

To a 1:1 mixture of (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3** (0.020 g, 0.0314 mmol) and (2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3** (0.020 g, 0.0314 mmol) in dichloromethane (50 ml), (*RS*,*RS*)-**1** (0.0005 g, 0.0044 mmol) was added and the mixture was stirred at room temperature. Samples were taken and analysed by

Table 1. Proton and carbon-13 NMR data of the diastereomeric cyclic trimers **3** and **4** in $CDCl_3$

^{1}H NMR					
Compound	-CH=N-	Aromatic protons	Alicyclic protons		
			>CH-N	-CH_2-	-CH_2-
3	8.138	7.510	3.36 m	1.82 m	1.82 m; 1.47 m
3+**4**	8.138	7.518	3.26–3.42 m	1.84 m	1.84 m
	8.169, 8.128	7.510 (2)	*	*	*
	8.100	7.448			

^{13}C NMR						
Compound	-CH=N-	Aromatic carbons		Alicyclic carbons		
		1,4	2,3,5,6	>CH-N	-CαH_2-	-CβH_2-
3	160.19	137.74	127.99	74.40	32.72	24.44
3+**4**	160.19	137.74	127.99	74.40	32.72	24.44
	160.93	137.74	128.16	75.13	32.80 (2)	24.51
	160.48	137.70	128.04	74.51	32.44	24.47 (2)
	160.43	137.66	127.89	73.83		

* Overlapping multiplets.

NMR at regular intervals until the ratio of **3**:**4** remained constant. The resulting mixture contained the individual stereoisomers in an approximate ratio (2*R*,3*R*,12*R*,13*R*,22*R*,23*R*)-**3**:(2*S*,3*S*,12*S*,13*S*,22*S*,23*S*)-**3**:(2*R*,3*R*,12*R*,13*R*,22*S*,23*S*)-**4**:(2*S*,3*S*,12*S*,13*S*,22*R*,23*R*)-**4** ≅ 1:1:1:1.

4.2. X-Ray structural analysis

For compounds **3** and **4** a hemisphere of data was collected (epoxy mounted specimens) at room temperature on a Bruker SMART CCD diffractometer using the omega scan mode yielding a total of N_{tot} reflections, which reduced to N unique data with $F_o > 4\sigma(F_o)$ being considered observed. Data were corrected for absorption using the program SADABS.[9] The structures were solved using direct methods in SHELXS-86[10] and refined (refinement by full-matrix least-squares techniques on F^2) using SHELXL-97-2.[11] All non-hydrogen atoms were located and were refined with anisotropic thermal parameters. All hydrogen atoms were placed in calculated positions (riding model) and were not refined.

4.2.1. Crystal/refinement data. Compound **3**: $C_{42}H_{48}N_6$; M 636.86; monoclinic space group C_2 (no. 5); a 31.360(3), b 5.3347(5), c 23.933(3) Å; β 100.518(2)°; V 3936.6(7) Å^3; D_c ($Z=4$) 1.075 g cm^{-3}; $F(000)$ 1368; μ_{Mo} 0.064 mm^{-1}; specimen: 0.60×0.50×0.15 mm; N_{tot} 9027, N 4539; $R_{(int)}=0.0291$, R_1 0.039, wR_2 (all data) 0.113.

Compound **4**: $C_{42}H_{48}N_6$; M 636.86; monoclinic space group $P2_1/c$ (no. 14); a 10.327(5), b 16.308(8), c 24.298(12) Å; β 92.386(12)°; V 4089(3) Å^3; D_c ($Z=4$) 1.035 g cm^{-3}; $F(000)$ 1368; μ_{Mo} 0.062 mm^{-1}; specimen: 0.15×0.14×0.10 mm; N_{tot} 15486, N 5751; $R_{(int)}=0.2179$, R_1 0.097, wR_2 (all data) 0.366.

4.3. IUPAC nomenclature of the diastereomeric pairs 3 and 4

Compound **3**: (2*RS*,3*RS*,12*RS*,13*RS*,22*RS*,23*RS*)-1,4,11,14,21,24-Hexaaza-(2,3:12,13:22,23)-tributeno-(6,9:16,19:26,29)-trietheno-2*H*,3*H*,12*H*,22*H*,23*H*-(30)-annulene.

Compound **4**: (2*RS*,3*RS*,12*RS*,13*RS*,22*SR*,23*SR*)-1,4,11,14,21,24-Hexaaza-(2,3:12,13:22,23)-tributeno-(6,9:16,19:26,29)-trietheno-2*H*,3*H*,12*H*,22*H*,23*H*-(30)-annulene.

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