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Synthesis of bis-(3,5)pyrazolophanes via double cycloadditive macrocyclisation☆

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Abstract—Double cycloadditive macrocyclisation of bis-hydrazonoyl chlorides **5** were performed with bis-allyl ethers **9** and **10**, bis-vinyl ether **14** and bis-propargyl ether **18**. The title compounds having a 18-, 19-, 22- or 24- membered ring annulated to the pyrazole units were obtained with good overall yield.

1. Introduction

Macrocyclic compounds encompasses an astonishing variety of structural types ranging from macrolide antibiotics to crown ethers, cryptands, calixarenes, spherands and so on.[1] Due to their unique complexating ability towards metal cations,[2,3] both natural and synthetic macrocycles have acquired wide interest in the field of host–guest supramolecular chemistry.[3] As a consequence, a number of strategies have been devoted to the synthesis of macrocyclic systems,[4] including that based upon a multiple 1,3-dipolar cycloaddition sequence.[5] This latter approach have been pioniered by Garanti and co-workers in a 1975 paper which describes the formation of macrocyclic compounds using intermolecular followed by intramolecular cycloadditions of nitrile oxides bearing an alkenyl dipolarophile.[6] Our recent contributions in this field is concerned with the use of suitably functionalised nitrilimines as precursors of a variety of (1,5) pyrazolophanes[7] and bis-(3,5) pyrazolophanes.[8] Following the multiple cycloadditive macrocyclisation between bis-nitrile oxides and bifunctional dipolarophiles introduced by Kim and co-workers,[9] we now wish to report a version of the same methodology based upon the double cycloaddition between the bis-hydrazonoyl chlorides **5** and bis-dipolarophiles **9**, **10**, **14** and **18** in the presence of silver carbonate as the basic agent.

2. Results

Bis-hydrazonoyl chlorides **5** were synthesised as depicted in the Scheme 1, following a procedure previously elaborated by us.[10] The corresponding nitrilimines **6** were generated in situ upon treatment of **5** with silver carbonate in dry dioxane at room temperature. Schemes 2 and 3 illustrate the reaction outcomes of intermediates **6** with bis-allyl ethers **9** and **10** and bis-vinyl ether **14**, respectively, while detailed data are collected in Tables 1 and 2. Macrocyclic structures **12**, **13**, **15** and **16** were established through analytical and spectral data. In particular, as far as ^{1}H NMR spectra are concerned, the protons in the 4- and 5- positions of the 4,5-dihydropyrazole rings show resonances which are in perfect agreement with literature data.[11] It must be added that the remaining aliphatic protons give rise to complex overlapping multiplets, as is common for macrocycles.[9] Since all the above macrocyclic products contains two stereocentres, we assigned the chiral structure *rac*-**13** rather than the *meso*-**12** one in the light of the ^{1}H NMR signal of the 4-pyrazolinic protons of **13**, which was splitted in the presence of Eu(hfc)$_3$ [tris(heptafluoropropyl hydroxymethylene-(+)-camphorato(europium-(III)]. This behaviour finds precedents in the literature[7] and just matches that observed in our previous paper for similar bis-(3,5)pyrazolophanes.[8] Furthermore, compound **12d** gave crystals suitable for X-ray diffractometric analysis (Fig. 1),[12] thus demonstrating unambiguously the above assignments.[13] When using the bis-propargyl ether **18** as the dipolarophile (Scheme 4) the intermediate hydrazonoyl chloride **19** was actually isolated when stopping the reaction after 24 h, the latter was further converted to **20**. For the sake of comparison, bis-4,5-dihydro pyrazole macrocycles **12a** and **13a** also gave **20** by oxidation with DDQ.

☆ Supplementary data associated with this article can be found at doi: 10.1016/j.tet.2003.09.088

Keywords: 1,3-dipolar cycloadditions; macrocycles; pyrazoles; bis-nitrilimines.

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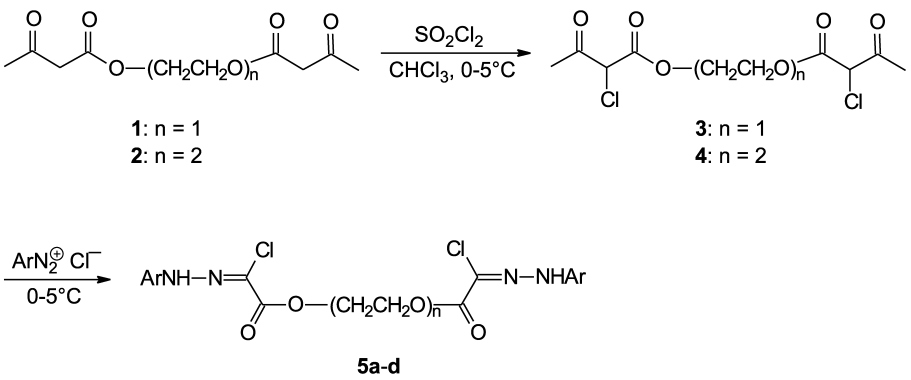
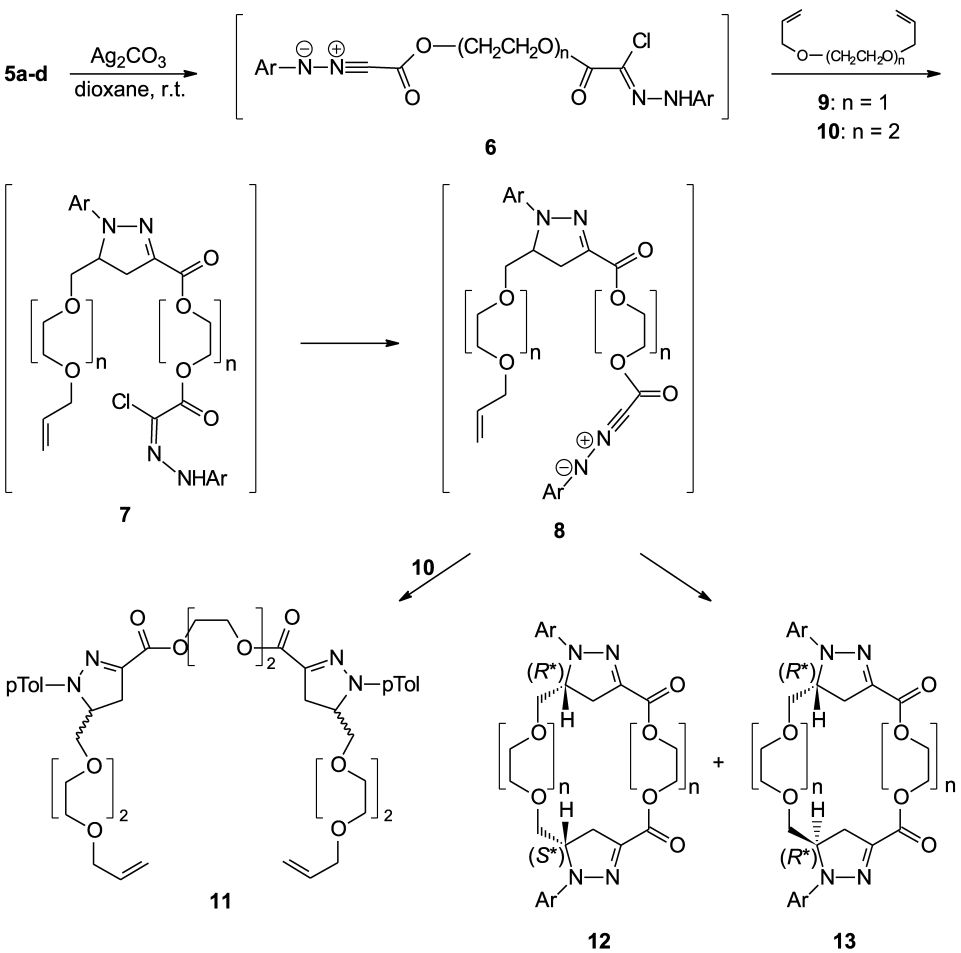


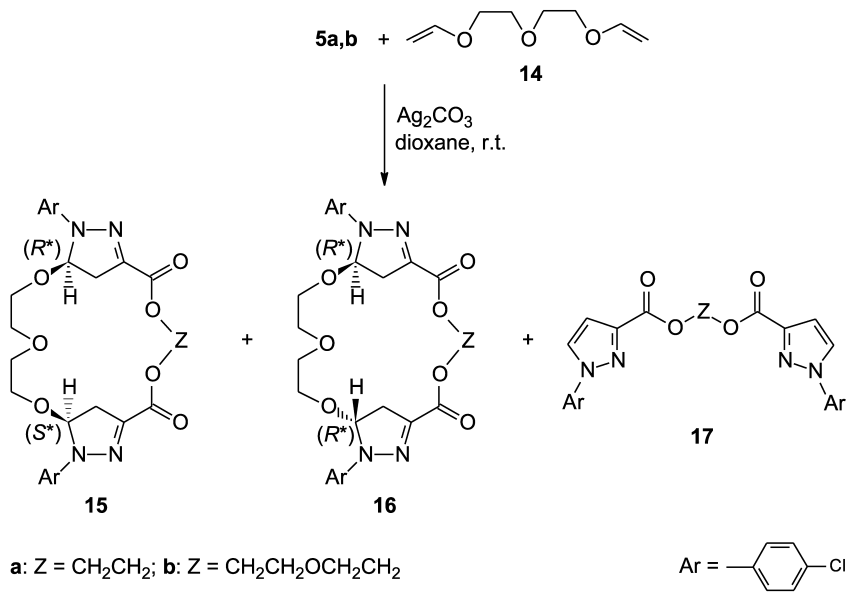
Entry	5a	5b	5c	5d
n	1	2	1	2
Ar	4-Cl-C_6H_4	4-Cl-C_6H_4	4-CH_3-C_6H_4	4-CH_3-C_6H_4

Scheme 1.



Entry	a	b	c	d
n	1	2	1	2
Ar	4-Cl-C_6H_4	4-Cl-C_6H_4	4-CH_3-C_6H_4	4-CH_3-C_6H_4

Scheme 2.



Scheme 3.

Table 1. Dipolar cycloaddition between bis-hydrazonoyl chlorides **5** and bis-allylethers **9** and **10**

Entry	Time (h)	Products and yields (%)[a]			Yield ratio
		12	**13**	**11**	**12**:**13**
a	72	24	12	–	67:33
b	110	26	17	–	60:40
c	56	31	16	–	66:34
d	96	40	19	7	68:32

[a] Isolated yields.

Table 2. Dipolar cycloaddition between bis-hydrazonoyl chlorides **5a**,**b** and bis-vinylether **14**

Entry	Time (h)	Products and yields (%)[a]			Yield ratio
		15	**16**	**17**	**15**:**16**
a	60	22	22	11	50:50
b	96	24	17	16	58:42

[a] Isolated yields.

As a further stage of our work, we undertook the conformational analysis of cycloadducts *meso*-**12a** and *rac*-**13a** by full optimisation of about 2500 input structures obtained from a MM3 simulated annealing run. The main conformational features are shared by almost all of the optimised conformers, while the most stable conformations are pictured in Figure 2. In both cases the macrocyclic ring is almost planar even if lower part of the cycle (i.e. that containing carbonyl groups) is more rigid than the upper part, which then shows a larger variation among the optimised structures. A summary of the distances between the methylenic hydrogens in the 4-position of the faced 4,5-dihydropyrazole rings is reported in Table 3, where the Boltzmann average approximates the real thermal average as closely as our structure sampling is representative of an equilibrium ensemble.

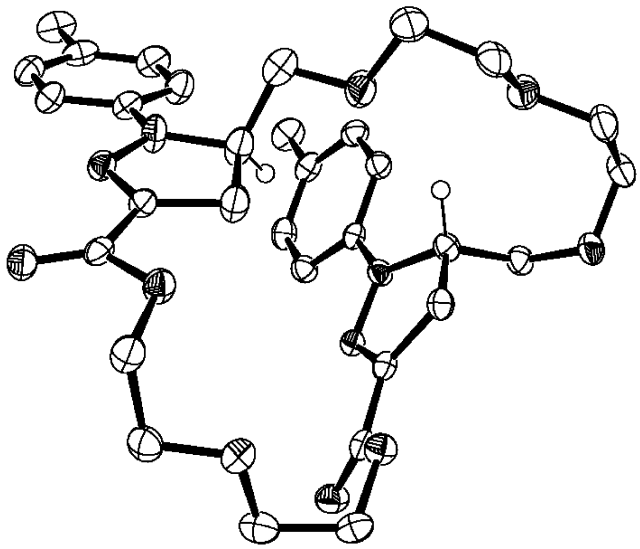
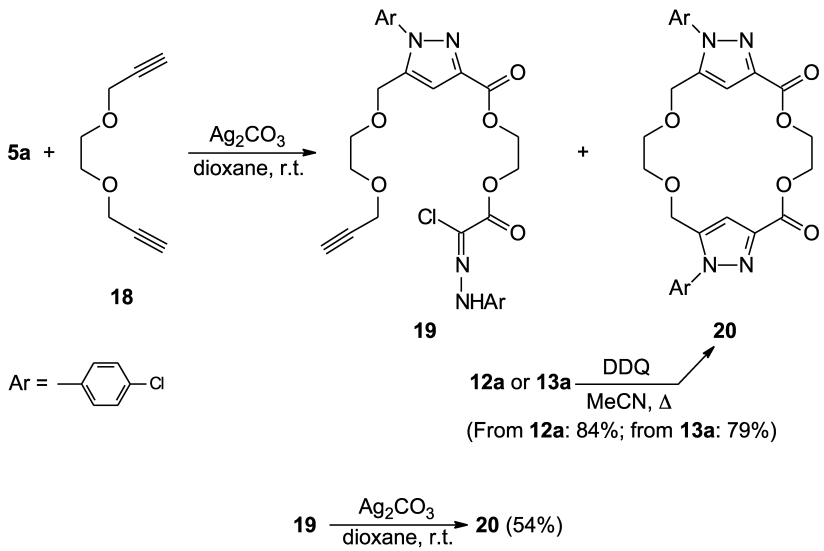


Figure 1. ORTEP*III* plot of **12d** at 90 K. Except those linked to the two stereogenic carbon atoms, hydrogen atoms were omitted for clarity. Ellipsoids at 50% probability level. H atoms not to scale.

3. Discussion

It have been recognised that nitrilimine cycloadditions to monosubstituted ethylenes are controlled from the HOMO of the 1,3-dipole,[14] thus leading to 5-substituted-4,5-dihydropyrazoles.[11] This regioselectivity is just obeyed in both the inter- and the intramolecular cycloaddition sequence leading to the 4,5-dihydropyrazole macrocycles *meso*-**12** and *rac*-**13**. This behaviour can be accounted for by considering that the tether joining the reactive groups in the nitrilimine intermediate **8** is long and flexible enough to allow the formation of the above bridged-ring structures. As far as the diastereoselection is concerned, it can be inferred from Table 1 that the diastereoisomeric ratio *meso*-**12**:*rac*-**13** ranges between 60:40 and 68:32. These low diastereo preferences may be due to the large distance between the first- and the newly- formed stereocentre. The role of silver



Scheme 4.

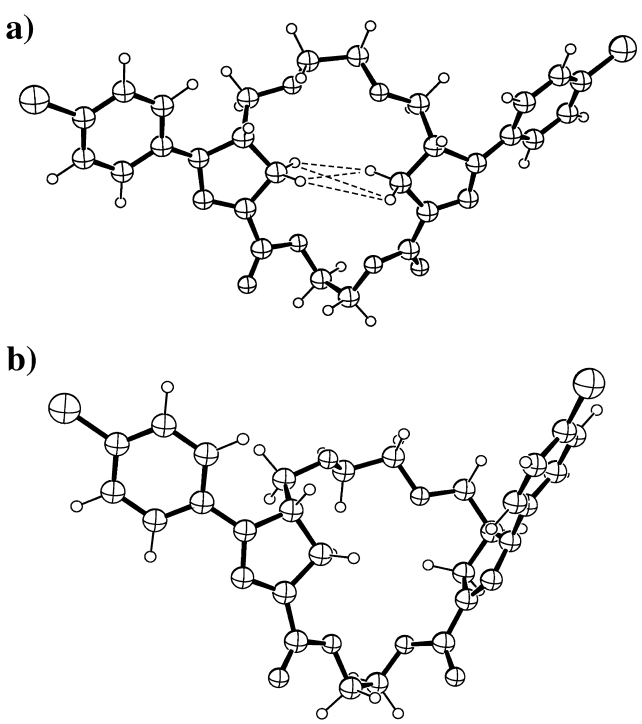


Figure 2. The two most stable confomers of *meso*-**12a** (a) and *rac*-**13a** (b) among those obtained by full geometry optimisation of ~2500 input structures at the AM1 level. Dashed lines denote the interannular distances summarised in Table 3 and discussed in the text; for the sake of clarity they have been drawn only for *meso*-**12a**.

Table 3. Computed interannular distances between the hydrogens in the 4-positions of the facing 4,5-dihydropyrazole rings of cycloadducts *meso*-**12a** and *rac*-**13a**

	meso-**12a**				*rac*-**13a**			
Minimum	2.61	1.77	1.97	1.70	4.52	2.80	2.80	2.12
Maximum	5.15	4.91	5.25	3.45	6.72	5.08	5.45	3.79
Mean	4.27	3.75	3.56	2.48	5.13	3.82	4.01	2.78
Std. Dev.[a]	0.57	0.49	0.78	0.31	0.29	0.32	0.59	0.36
Boltzmann average[b]	3.72	3.38	2.69	2.14	5.22	3.82	3.85	2.58

[a] Standard deviation from the mean.
[b] Thermal Boltzmann average.

carbonate as the choice basic agent for the efficient synthesis of pyrazole macrocycles is of interest. Its low solubility in dioxane determines the slow generation of the nitrilimine **6** which leads to the cycloadducts *meso*-**12** and *rac*-**13** via the labile hydrazonoyl chloride **7**. Conversely, in a control experiment (see Section 5), the reaction between bis-hydrazonyl chloride **5a** and bis-allyl ether **9** in the presence of triethylamine gave no characterisable product, but only tarry material.

The above considerations can also be applied to the formation of macrocycles *meso*-**15** and *rac*-**16**. The latter, however, showed a marked lability towards acidic species giving the bis-pyrazole derivatives **17** by extrusion of ethylene glycol(s), in close analogy with the behaviour of 5-alkoxy-4,5-dihydropyrazoles.[15]

Due to the presence of bulky aryl groups and of planar units, the macrocycle adopts conformations in which the hydrogens in the 4- position of the two 4,5-dihydropyrazole rings face each other. These interannular hydrogen–hydrogen distance are rather short, particularly in *meso*-**12a** because the coplanar arrangement of the pyrazole rings. Moreover, in *meso*-**12a** the Boltzmann-average distances are about one standard deviation shorter than the mean distances, indicating that more stable conformers have shorter hydrogen–hydrogen distances. Conversely, in *rac*-**13a** the Boltzmann-average distances are close to the mean distances, thus showing that more stable conformer have longer hydrogen–hydrogen distances.

4. Conclusions

The described double cycloadditive macrocyclisation involving the bis-hydrazonoyl chlorides **5** deserves some interesting features: (i) the overall yield of the resulting 4,5-dihydropyrazole macrocycles is worthy of note, and (ii) due to the availability and the low cost of the starting materials, the present approach constitutes a valuable entry for the multi-gram synthesis of a variety of bis-(3,5) pyrazolophanes.

5. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz.

Compounds **1**,[16] **2**,[16] **9**,[17] **10**[17] and **18**[18] are known in the literature. Compound **14** was used as supplied from Aldrich.

5.1. General procedure for the preparation of bis-2-chloroacetoacetates 3 and 4

A solution of sulfuryl chloride (2.84 g, 28.5 mmol) in dry chloroform (25 mL) was slowly added (30 min) to a solution of **1** or **2** (12.0 mmol) in dry chloroform (50 mL), and keeping the temperature in the range 0–5°C. After 4 h at room temperature, the organic solution was washed with 5% aqueous sodium hydrogen carbonate (2×25 mL). The organic layer was washed with water (2×25 mL) and dried over sodium sulfate. The solvent was removed affording bis-2-chloroacetoacetates **3** and **4** as undistillable thick oils which were used without further purification.

5.1.1. Compound 3. 3.41 g, 95%. Pale yellow oil; IR (nujol) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (6H, s), 4.48 (4H, s), 4.80 (2H, s); MS *m/z* 298 (M^+). Anal. calcd for $C_{10}H_{12}Cl_2O_6$: C, 40.16; H, 4.04. Found: C, 40.22; H, 4.09.

5.1.2. Compound 4. 2.80 g, 68%. Pale yellow oil; IR (nujol) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (6H, s), 4.25–4.57 (8H, m), 4.86 (2H, s); MS *m/z* 342 (M^+). Anal. calcd for $C_{12}H_{16}Cl_2O_7$: C, 42.00; H, 4.70. Found: C, 41.94; H, 4.64.

5.2. General procedure for the preparation of bis-hydrazonoyl chlorides 5

A solution of **3** or **4** (8.0 mmol) in methanol (8 mL) was added to a cold aqueous solution of the appropriate aryldiazonium chloride (16.0 mmol) with vigorous stirring and ice-cooling. During the addition, the pH was adjusted to 5 by adding sodium acetate. The mixture was allowed to stand overnight with stirring at room temperature and was then extracted with diethyl ether (2×75 mL). The organic layer was washed firstly with 5% sodium hydrogen-carbonate (2×25 mL), then with water (2×75 mL), and dried over sodium sulfate. Evaporation of the solvent gave a solid and subsequent recrystallisation gave the bis-hydrazonoyl chlorides **5** in the pure state.

5.2.1. Compound 5a. 2.40 g, 61%. Pale yellow powder; mp 148–150°C (from diisopropyl ether); IR (nujol) 3280, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.57 (4H, s), 6.88–7.60 (8H, m), 8.36 (2H, br s); MS *m/z* 492 (M^++2). Anal. calcd for $C_{18}H_{14}Cl_4N_4O_4$: C, 43.93; H, 2.87; N, 11.38. Found: C, 43.98; H, 2.92; N, 11.44.

5.2.2. Compound 5b. 1.99 g, 51%. Pale yellow powder; mp 115–120°C (from diisopropyl ether); IR (nujol) 3270, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.06 (4H, t, *J*=5.0 Hz), 4.55 (4H, t, *J*=5.0 Hz), 6.86–7.65 (8H, m), 8.35 (2H, br s); MS *m/z* 536 (M^++2). Anal. calcd for $C_{20}H_{18}Cl_4N_4O_5$: C, 44.80; H, 3.38; N, 10.45. Found: C, 44.85; H, 3.42; N, 10.50.

5.2.3. Compound 5c. 2.96 g, 83%. White powder; mp 116–118°C (from hexane–benzene); IR (nujol) 3280, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.27 (6H, s), 4.62 (4H, s), 7.00–7.26 (8H, m), 8.35 (2H, br s); MS *m/z* 450 (M^+). Anal. calcd for $C_{20}H_{20}Cl_2N_4O_4$: C, 53.23; H, 4.47; N, 12.41. Found: C, 53.28; H, 4.51; N, 12.49.

5.2.4. Compound 5d. 2.96 g, 75%. White powder; mp 96–98°C (from hexane–benzene); IR (nujol) 3270, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.39 (6H, s), 3.90 (4H, t, *J*=5.0 Hz), 4.47 (4H, t, *J*=5.0 Hz), 7.10–7.30 (8H, m), 8.26 (2H, br s); MS *m/z* 494 (M^+). Anal. calcd for $C_{22}H_{24}Cl_2N_4O_5$: C, 53.34; H, 4.88; N, 11.31. Found: C, 53.38; H, 4.92; N, 11.37.

5.3. General procedure for the dipolar cycloaddition between bis-hydrazonoyl chlorides 5 and bis-allyl ethers 9 and 10

A solution of the bis-hydrazonyl chlorides **5** (5.0 mmol) and bis-allylethers **9** or **10** (5.0 mmol) in dry dioxane (250 mL) was treated with silver carbonate (2.76 g, 10.0 mmol) and stirred in the dark at room temperature for the time indicated in Table 1. The undissolved material was then filtered off, the solvent evaporated, and the residue chromatographed on a silica gel column with ethyl acetate–hexane 1:2. Major cycloadducts *meso*-**12** were eluted first, followed by minor *rac*-**13** and **11**.

5.3.1. Compound *meso*-12a. 0.67 g, 24%. Pale yellow needles; mp 97–100°C (from diisopropyl ether); IR (nujol) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.18 (2H, dd, *J*=18.2, 6.5 Hz), 3.23 (2H, dd, *J*=18.2, 11.6 Hz), 3.37–3.54 (8H, m), 4.40–4.70 (6H, m), 7.10–7.30 (8H, m); MS *m/z* 560 (M^+). Anal. calcd for $C_{26}H_{26}Cl_2N_4O_6$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.66; H, 4.65; N, 10.07.

5.3.2. Compound *meso*-12b. 0.84 g, 26%. Yellow prisms; mp 154–156°C (from diisopropyl ether–dichloromethane); IR (nujol) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.21 (2H, dd, *J*=17.9, 7.6 Hz), 3.30 (2H, dd, *J*=17.9, 11.5 Hz), 3.40–3.80 (16H, m), 4.49 (2H, dd, *J*=13.7, 6.3 Hz), 4.58 (2H, dd, *J*=13.7, 5.3 Hz), 4.66 (2H, dddd, *J*=11.5, 7.6, 6.3, 5.3 Hz), 7.00–7.30 (8H, m); MS *m/z* 648 (M^+). Anal. calcd for $C_{30}H_{34}Cl_2N_4O_8$: C, 55.48; H, 5.28; N, 8.63. Found: C, 55.52; H, 5.31; N, 8.69.

5.3.3. Compound *meso*-12c. 0.81 g, 31%. Yellow needles; mp 95–97°C (from ethanol); IR (nujol) 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.29 (6H, s), 3.20 (2H, dd, *J*=17.6, 6.7 Hz), 3.31 (2H, dd, *J*=17.6, 11.4 Hz), 3.40–3.80 (8H, m), 4.30–4.50 (6H, m), 6.95–7.10 (8H, m); MS *m/z* 520 (M^+). Anal. calcd for $C_{28}H_{32}N_4O_6$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.66; H, 6.16; N, 10.81.

5.3.4. Compound *meso*-12d. 1.22 g, 40%. Yellow prisms; mp 152–155°C (from diisopropylether–dichloromethane);

IR (nujol) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (6H, s), 3.19 (2H, dd, J=18.0, 7.8 Hz), 3.31 (2H, dd, J=18.0, 11.8 Hz), 3.40–3.80 (16H, m), 4.32 (2H, dd, J=13.1, 6.7 Hz), 4.52 (2H, dd, J=13.1, 5.3 Hz), 4.68 (2H, dddd, J=11.8, 7.8, 6.7, 5.3 Hz), 6.90–7.00 (8H, m); MS m/z 608 (M^+). Anal. calcd for $C_{32}H_{40}N_4O_8$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.18; H, 6.65; N, 9.25.

5.3.5. Compound *rac*-13a. 0.37 g, 12%. Pale yellow powder; mp 250–251°C (from diisopropyl ether); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (2H, dd, J=18.0, 6.9 Hz), 3.30 (2H, dd, J=18.0, 11.5 Hz), 3.35–3.58 (8H, m), 4.40 (2H, dd, J=13.0, 7.8 Hz), 4.67 (2H, dddd, J=11.5, 7.8, 6.9, 6.4 Hz), 4.78 (2H, dd, J=13.0, 6.4 Hz), 7.05–7.20 (8H, m); MS m/z 560 (M^+). Anal. calcd for $C_{26}H_{26}Cl_2N_4O_6$: C, 55.62; H, 4.67; N, 9.98. Found: C, 55.60; H, 4.70; N, 10.05.

5.3.6. Compound *rac*-13b. 0.55 g, 17%. Yellow powder; mp 167–170°C (from diisopropyl ether–dichloromethane); IR (nujol) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (2H, dd, J=18.5, 8.1 Hz), 3.30 (2H, dd, J=18.5, 11.6 Hz), 3.33–3.67 (16H, m), 4.25 (2H, dd, J=12.8, 7.7 Hz), 4.40 (2H, dddd, J=11.6, 8.1, 7.7, 6.0 Hz), 4.66 (2H, dd, J=12.8, 6.0 Hz), 7.00–7.20 (8H, m); MS m/z 648 (M^+). Anal. calcd for $C_{30}H_{34}Cl_2N_4O_8$: C, 55.48; H, 5.28; N, 8.63. Found: C, 55.44; H, 5.25; N, 8.66.

5.3.7. Compound *rac*-13c. 0.42 g, 16%. Pale yellow powder; mp 160–162°C (from diisopropylether); IR (nujol) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (6H, s), 3.16 (2H, dd, J=17.8, 6.4 Hz), 3.25 (2H, dd, J=17.8, 12.0 Hz), 3.32–3.87 (12H, m), 4.60–4.70 (2H, m), 6.99–7.12 (8H, m); MS m/z 520 (M^+). Anal. calcd for $C_{28}H_{32}N_4O_6$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.22; N, 10.83.

5.3.8. Compound *rac*-13d. 0.58 g, 19%. Yellow powder; mp 165–167°C (from diisopropylether–dichloromethane); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (6H, s), 3.14 (2H, dd, J=17.9, 7.1 Hz), 3.26 (2H, dd, J=17.9, 11.9 Hz), 3.50–3.90 (16H, m), 4.35–4.45 (4H, m), 4.60–4.70 (2H, m), 7.00–7.20 (8H, m); MS m/z 608 (M^+). Anal. calcd for $C_{32}H_{40}N_4O_8$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.20; H, 6.66; N, 9.27.

5.3.9. Compound 11. 0.28 g, 7%. Pale yellow powder; mp 61–63°C (from diisopropylether); IR (nujol) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (6H, s), 3.12 (2H, dd, J=17.6, 7.3 Hz), 3.21 (2H, dd, J=17.6, 11.6 Hz), 3.30–3.90 (24H, m), 4.30–4.40 (10H, m), 5.11 (2H, dd, J=10.5, 1.8 Hz), 5.20 (2H, dd, J=17.6, 1.8 Hz), 5.75–5.90 (2H, m), 6.9–7.00 (8H, m); MS m/z 794 (M^+). Anal. calcd for $C_{42}H_{58}N_4O_{11}$: C, 63.46; H, 7.35; N, 7.05. Found: C, 63.50; H, 7.38; N, 7.12.

5.3.10. Reaction between bis-hydrazonoyl chloride 5a and bis-allyl ether 10 in the presence of triethylamine. A solution of the bis-hydrazonoyl chloride **5a** (1.22 g, 2.5 mmol) and bis-vinylether **12** (0.36 g, 2.5 mmol) in dry dioxane (125 mL) was treated with triethylamine (1.52 g, 15.0 mmol) and refluxed for 3 h. The solvent was evaporated, and then the residue was chromatographed on a silica gel column with ethyl acetate–hexane–triethylamine 1:1. No characterisable products were isolated.

5.4. General procedure for the dipolar cycloaddition between bis-hydrazonoyl chlorides 5a,b and bis-vinyl ethers 14

A solution of the bis-hydrazonoyl chloride **5a** or **5b** (5.0 mmol) and bis-vinylether **14** (0.57 g, 5.0 mmol) in dry dioxane (250 mL) was treated with silver carbonate (4.14 g, 15.0 mmol) and stirred in the dark at room temperature for the time indicated in Table 2. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with ethyl acetate–hexane–triethylamine 49:49:2. Bis-pyrazoles **17** were eluted first, followed by major cycloadducts *meso*-**15** and minor *rac*-**16**.

5.4.1. Compound 17a. 0.26 g, 11%. White needles; mp 150–151°C (from diisopropyl ether–dichloromethane); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (4H, s), 6.95 (2H, d, J=2.5 Hz), 7.40–7.70 (8H, m), 7.95 (2H, d, J=2.5 Hz); MS m/z 470 (M^+). Anal. calcd for $C_{22}H_{16}Cl_2N_4O_4$: C, 56.07; H, 3.42; N, 11.89. Found: C, 56.11; H, 3.44; N, 11.95.

5.4.2. Compound 17b. 0.41 g, 16%. White needles; mp 109–111°C (from diisopropyl ether–dichloromethane); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (4H, t, J=5.3 Hz), 4.50 (4H, t, J=5.3 Hz), 6.95 (2H, d, J=2.5 Hz), 7.40–7.70 (8H, m), 7.90 (2H, d, J=2.5 Hz); MS m/z 514 (M^+). Anal. calcd for $C_{24}H_{20}Cl_2N_4O_5$: C, 55.93; H, 3.91; N, 10.87. Found: C, 55.98; H, 3.87; N, 10.93.

5.4.3. Compound *meso*-15a. 0.63 g, 22%. Pale yellow needles; mp 90–91°C (from diisopropyl ether–dichloromethane); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (2H, dd, J=19.4, 2.7 Hz), 3.33 (2H, dd, J=19.4, 8.7 Hz), 3.40–3.50 (8H, m), 4.42–4.70 (2H, ddd, J=11.4, 7.4, 2.8 Hz), 4.63 (2H, ddd, J=11.4, 7.4, 2.8 Hz), 5.82 (2H, dd, J=8.7, 2.7 Hz), 7.20–7.30 (8H, m); MS m/z 576 (M^+). Anal. calcd for $C_{26}H_{26}Cl_2N_4O_7$: C, 54.08; H, 4.54; N, 9.70. Found: C, 54.12; H, 4.57; N, 9.76.

5.4.4. Compound *meso*-15b. 0.75 g, 24%. Yellow needles; mp 156–158°C (from diisopropylether); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.13 (2H, dd, J=19.4, 3.2 Hz), 3.18 (2H, dd, J=19.4, 8.2 Hz), 3.40–3.60 (12H, m), 4.30–4.60 (4H, m), 5.45 (2H, dd, J=8.2, 3.2 Hz), 7.15–7.30 (8H, m); MS m/z 620 (M^+). Anal. calcd for $C_{28}H_{30}Cl_2N_4O_8$: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.15; H, 4.91; N, 9.08.

5.4.5. Compound *rac*-16a. 0.63 g, 22%. Pale yellow powder; mp 164–166°C (from diisopropyl ether–dichloromethane); IR (nujol) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.15 (2H, dd, J=19.4, 3.1 Hz), 3.27 (2H, dd, J=19.4, 8.7 Hz), 3.40–3.50 (8H, m), 4.55 (2H, t, J=10.0 Hz), 4.61 (2H, t, J=10.0 Hz), 5.82 (2H, dd, J=8.7, 3.1 Hz), 7.20–7.30 (8H, m); MS m/z 576 (M^+). Anal. calcd for $C_{26}H_{26}Cl_2N_4O_7$: C, 54.08; H, 4.54; N, 9.70. Found: C, 54.14; H, 4.56; N, 9.78.

5.4.6. Compound *rac*-16b. 0.53 g, 17%. Yellow powder; mp 150–152°C (from diisopropylether); IR (nujol) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (2H, dd, J=19.5, 3.7 Hz), 3.32 (2H, dd, J=19.5, 8.8 Hz), 3.40–3.60 (12H,

m), 4.40–4.55 (4H, m), 5.94 (2H, dd, J=8.8, 3.7 Hz), 7.20–7.30 (8H, m); MS m/z 620 (M^+). Anal. calcd for $C_{28}H_{30}Cl_2N_4O_8$: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.07; H, 4.90; N, 9.10.

5.4.7. Dipolar cycloaddition between bis-hydrazonoyl chloride 5a and bis-propargyl ether 18. A solution of the bis-hydrazonoyl chloride **5a** (2.46 g, 5.0 mmol) and bis-propargylether **18** (0.69 g, 5.0 mmol) in dry dioxane (250 mL) was treated with silver carbonate (2.76 g, 10.0 mmol) and stirred in the dark at room temperature. After 48 h silver carbonate (2.76 g, 10.0 mmol) was added again and the mixture was stirred for 72 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethyl ether–hexane 5:1. First fractions contained the hydrazonoyl chloride **19** (0.24 g, 8%). Undistillable orange oil; IR (nujol) 3280, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (1H, t, J=2.4 Hz), 3.50–3.60 (4H, m), 4.17 (2H, d, J=2.4 Hz), 4.54–4.78 (6H, m), 6.96 (1H, s), 7.10–7.40 (8H, m), 8.35 (1H, br s); MS m/z 592 (M^+). Anal. calcd for $C_{26}H_{23}Cl_3N_4O_6$: C, 52.59; H, 3.90; N, 9.43. Found: C, 52.63; H, 3.88; N, 9.48.

Further elution gave **20** (0.39 g, 14%). Pale yellow solid; mp 110–112°C (from diisopropyl ether); IR (nujol) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40–3.60 (4H, m), 4.50–4.80 (8H, m), 6.95 (2H, s), 7.15–7.30 (8H, m); MS m/z 556 (M^+). Anal. calcd for $C_{26}H_{22}Cl_2N_4O_6$: C, 56.03; H, 3.98; N, 10.05. Found: C, 56.08; H, 4.02; N, 10.11.

5.4.8. Intramolecular cycloaddition of hydrazonoyl chloride 19. A solution of the hydrazonoyl chloride **19** (0.24 g, 0.4 mmol) in dry acetonitrile (24 mL) was treated with silver carbonate (0.28 g, 1.0 mmol) and stirred in the dark at room temperature for 96 h. The undissolved material was filtered off and washed with acetonitrile (2×15 mL). The solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethyl ether giving **20** (0.12 g, 54%).

5.4.9. DDQ oxidation of cycloadducts 12a and 13a. A solution of **12a** or **13a** (0.28 g, 0.5 mmol) and DDQ (0.57 g, 2.5 mmol) in dry benzene (50 mL) was refluxed for 16 h. The crude was taken up with dichloromethane (100 mL), the undissolved tarry material was filtered off and the solvent was evaporated at reduced pressure. The residue was chromatographed on a silica gel column with diethyl ether giving **20** (0.23 g, 84% from **12a**; 0.22 g, 79% from **13a**).

5.5. Computational details

In order to generate a large non-biased number of input structures for the subsequent optimisation of macrocycles *meso*-**12a** and *rac*-**13a** we proceeded as follows. A guess structure was optimised with the MM3 force field as implemented in the Hyperchem Release 2 package. This structure was used as input for a molecular dynamic run carried out with the same force-field and software as before. The details of the dynamic run are as follows: starting temperature=1 K raised to 300 K in 10 ps; constant temperature run for 250 ps with time step for dynamics=1 fs; macrocycle structures were collected every 100 fs. Therefore, 2500 input structures were collected for each macrocycle. Each of these was fully optimised at the AM1 level by means of the Gaussian98[19] package. Thermally-averaged intramolecular distances were obtained from the AM1-computed distances and energies and the Boltzmann distribution.

6. Supplementary Material

Two colour figures in which the 14 most stable conformers of *meso*-**12a** and *rac*-**13a** are superimposed are available as Supplementary Material.

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