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The asymmetric synthesis and conformational analysis of new C_2-symmetric macrocycles derived from head-to-head linked α-amino acids and benzene or pyridine

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Abstract—The synthesis of several novel 15–18-membered macrocycles containing 1,3-disubstituted benzene or 2,6-disubstituted pyridine in a chiral environment is described. The syntheses used a series of di(N^{α}-tosyl-L-alanylamido)alkanes, which could be prepared in good yield. The macrocyclisation reaction with 1,3-di(bromomethyl)benzene or 2,6-di(bromomethyl)pyridine was facilitated by the use of caesium carbonate as base, and NMR and molecular modelling were used to study the preferred conformations of the macrocycles.

1. Introduction

Macrocyclic pyridine-based systems are important in:

- metal chelation and extraction;[1]
- host–guest systems[2] and enzyme mimics;[3]
- antibiotics[4] and natural products such as marine alkaloids.[5]

Our own interest concerns the use of the pyridine moiety as a key catalytic feature of enzyme mimics. This paper reports our work on benzene and pyridine macrocycles, providing results that relate to both the synthetic accessibility and the preferred conformations of macrocyclic pyridine systems.

We identified macrocyclic pyridine derivatives **1** as valuable targets, because the macrocyclic ring substituents might be used to modify the chemistry at the pyridine nitrogen. One feature that we deemed as essential was chirality close to the pyridine nitrogen, and we decided to use α-amino acids as a readily available source of this chirality. These macrocycles are C_2-symmetric, which should ensure that identical chiral environments are present on each face of the macrocycle, regardless of the direction of approach taken by an incoming species, e.g. the attack of a nucleophile on a pyridinium–electrophile intermediate.[6]

It was felt that these macrocycles should also be of moderate size and flexibility, such that the chiral centres are held in close spatial proximity to the pyridine ring at all times, as shown schematically in Fig. 1, but that there should be sufficient space for chemical reactions to occur at the pyridyl nitrogen.

2. Results and discussion

2.1. Synthesis

There are two apparently straightforward approaches to the synthesis of the target molecule **1**, as shown in Scheme 1.

Our initial work followed the more obvious Route **A**, which in theory allows rapid access to a series of differently sized macrocycles simply by changing the diamine cross-linker (X_L) used in the final synthetic step. The early stages of this synthesis proved relatively easy, but the macrocyclisation step could not be achieved under a variety of conditions, and as a result we turned our attentions to Route **B**. This required a new series of head-to-head linked α-amino acids. Thus,

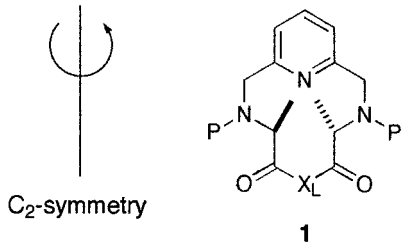

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Figure 1. The C_2-symmetric target molecule **1**; X_L=cross-linker, P=protecting group.

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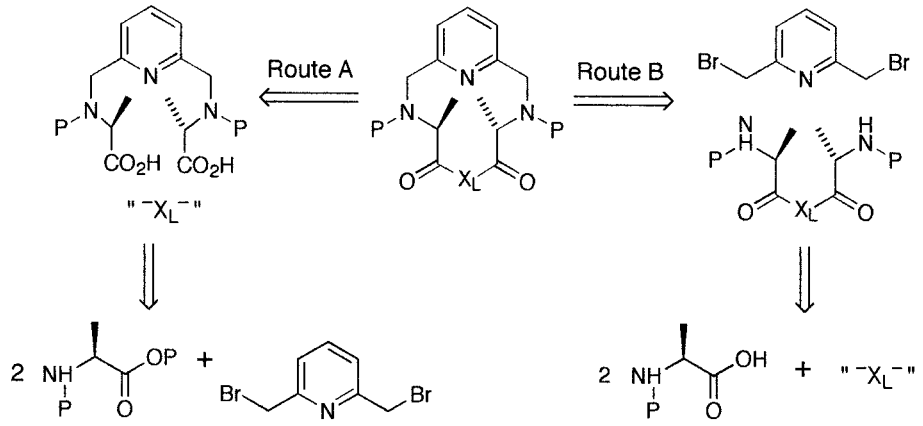
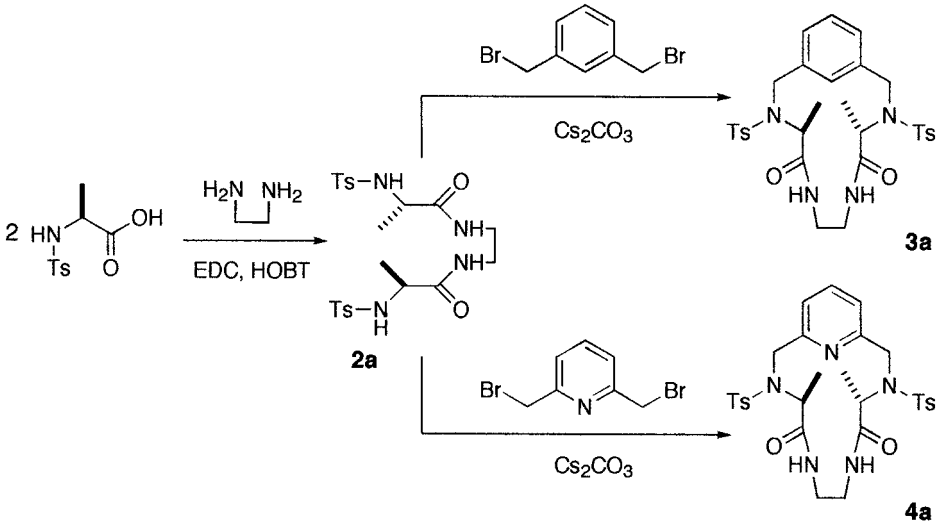
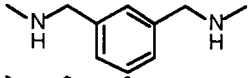
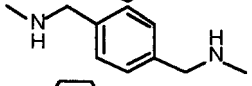
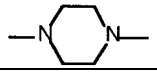


Scheme 1. Retrosynthesis of the target macrocycles.



Scheme 2. Synthesis of the macrocycles **3a** and **4a**.

Table 1. The yields of various diamides prepared using either DCC/HOBT or EDC/HOBT coupling reagents. Both sets of reactions were carried out in THF at room temperature

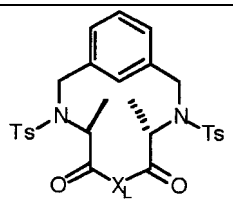
	X_L =	DCC/HOBT yield (%)	EDC/HOBT yield (%)
2a	—$NH(CH_2)_2NH$—	37	80
2b	—$NH(CH_2)_3NH$—	45	75
2c	—$NH(CH_2)_4NH$—	15	90
2d	—$NH(CH_2)_5NH$—	28	89
2e		32	95
2f		—	80
2g		—	89

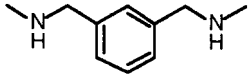
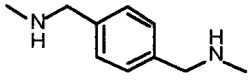
N-tosyl-protected L-alanine[7] was coupled to several α,ω-diamines, using a variety of established amide-forming techniques,[8] to give a series of suitably protected diamides. The synthesis of one such diamide, 1,2-di(N^{α}-tosyl-L-alanyl-amido)ethane **2a**, is shown in Scheme 2.

When dicyclohexylcarbodiimide (DCC) was employed in the synthesis of the diamides, the removal of dicyclohexyl-urea by-product necessitated lengthy chromatography procedures. To avoid this, we opted to use the *N*-ethyl-*N*′-(dimethylamino)propyl carbodiimide (EDC)[9] as the coupling agent. This afforded a water-soluble urea by-product which was easily removed by aqueous washes. As well as simplifying the work-up procedure, this modification also significantly increased the yields of the diamides formed (see Table 1).

In order to investigate the [1+1] macrocyclisation reactions, we decided to carry out model reactions using commercially available 1,3-di(bromomethyl)benzene. We have shown elsewhere[10] in work concerning cyclic hexapeptides that the tosyl (Ts) protecting group is capable of stabilising the deprotonation of the *N*-terminus of an amino acid derivative. This feature of the protecting group allowed us to use

Table 2. The percentage yields for the preparation of the benzene series of 15–18-membered macrocycles



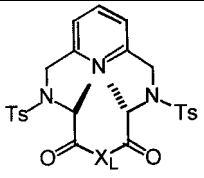
	X_L =	Yield (%)
3a	—$NH(CH_2)_2NH$—	53
3b	—$NH(CH_2)_3NH$—	62
3c	—$NH(CH_2)_4NH$—	32
3d	—$NH(CH_2)_5NH$—	15
3e		22
3f		0

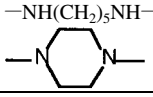
caesium carbonate, a mild base with noted templating effects,[11] to carry out the cyclisation reaction. Thus, equimolar amounts of 1,3-di(bromomethyl)benzene and the diamide **2a** were stirred with 5 equivalents of Cs_2CO_3 in DMF at room temperature for 48 h. After filtration to remove the majority of the sparingly soluble base, and purification by column chromatography, the 15-membered macrocycle **3a** was obtained in good yield (Scheme 2).

This synthetic protocol was followed in the preparation of the related benzene-derived macrocycles, using our series of diamides (X_L) (see Table 2).

The highest yield was obtained for the 16-membered macrocycle **3b**, with yields steadily declining until none of the 19-membered macrocycle **3f** could be isolated. The two aryl diamides showed a related regio-dependence towards the macrocyclisation process; when the two reactive ends of the diamide cross-linker were *para* to one another, the macrocycle could not form. The incidence of polymeric material was noted to increase with increased cross-linker length, probably due to an increase in $\Delta S^{\ddagger}$ for the larger macrocycles, or possibly the reduced efficiency of coordination to the caesium cation (if the latter is acting as a template).

Table 3. The percentage yields for the preparation of the pyridine series of 15–18-membered macrocycles



	X_L =	Yield (%)
4a	—$NH(CH_2)_2NH$—	58
4b	—$NH(CH_2)_3NH$—	51
4c	—$NH(CH_2)_4NH$—	35
4d	—$NH(CH_2)_5NH$—	15
4g		48

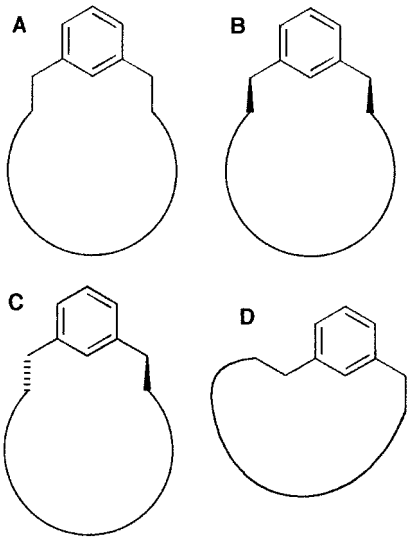


Figure 2. Possible conformations for the macrocycles; **A** planar, **B** saddle, **C** twisted, **D** skewed.

The pyridine-derived macrocycles required the preparation of 2,6-di(bromomethyl)pyridine. This was carried out following Cram's method,[12] although we succeeded in raising the yield from 39% to 78%. The macrocyclisation was carried out under identical reaction conditions to those used for the benzene-derived macrocycles. The yields for the different pyridine macrocycles (Table 3) are very similar to those obtained for the related benzene analogues. Again, the incidence of polymeric material was noted to increase with increased cross-linker length, and little or no macrocyclic material could be isolated cleanly from reactions with the aryl diamides **2e** and **2f**. An interesting result was observed for macrocyclisation with the piperazine-derived cross-linker. We had anticipated a low yield of macrocyclic product **4g** due to a preference for the cross-linker to adopt a chair conformation. The high yield we obtained might be explained by the boat conformation required for the macrocycle formation being stabilised by coordination to the Cs^+ template.

2.2. Preliminary conformational analysis and NMR studies

It is possible to identify four main structural types for these macrocycles, as outlined in Fig. 2. Steric crowding around the central cavity might be expected to preclude the planar conformation **A**, thus leading to a saddle-shaped macrocycle **B**. This saddle shape could effectively abolish the C_2-symmetry which was an important initial design consideration (Fig. 1). Relief of steric crowding could also be achieved by twisting the macrocycle as in **C** which would maintain C_2-symmetry, or by a skewed geometry as in **D**.

Our initial NMR experiments were carried out on the first benzene-derived macrocycle **3a**. The ^1H NMR spectrum revealed that the material was C_2-symmetric on the NMR timescale, with no line-broadening apparent at room temperature. At first sight this would appear to rule out

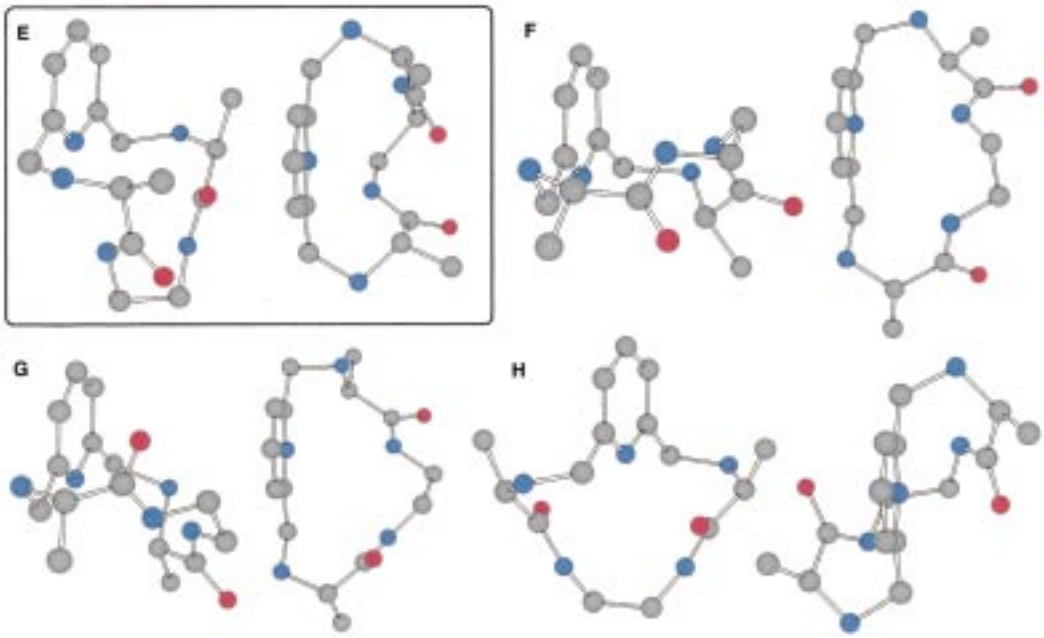


Figure 3. Side and top views of the predicted lowest energy local minima for **4a** (all within 2 kcal mol^{-1}); **E** global minimum, **F** plus 0.41 kcal mol^{-1}, **G** plus 1.05 kcal mol^{-1}, **H** plus 1.58 kcal mol^{-1}.

the proposed conformations **B** and **D**. This benzene-derived macrocycle also presented us with an opportunity to "probe" the cavity using n.O.e. spectroscopy. Several interactions between the aryl proton projecting into the cavity and the alanyl methyl groups demonstrated the proximity of these chiral groups to the 2-position of the benzene ring, and thus further ruled out the conformation **D**. Thus the NMR results appeared to suggest the presence of the C_2-symmetric conformations **A** or **C**.

A positive n.O.e. was also observed between the alanyl methyl groups and the aromatic protons of the tosyl groups, indicating that these groups spent at least some time in close proximity. Because of conformational freedom, the NMR spectra were not conclusive for these macrocycles, and we decided to carry out extensive molecular modelling/conformational analysis in parallel with the NMR studies.

2.3. Molecular modelling and conformational analysis

The smallest pyridine-containing macrocycle **4a** was chosen as a candidate for a careful conformational search using the fast dynamics/Monte Carlo search routine within XED98.[13] A large number of local minima were found to lie close to the predicted global minimum in terms of potential energy. Many of these conformations were the result of duplicates arising when the macrocyclic ring bends to either side of the pyridine ring, or were the result of relatively free rotation of the *N*-sulphonamide groups. The four structures shown in Fig. 3 represent four distinct conformations that the macrocyclic ring itself can adopt, all within 2 kcal mol^{-1} of the predicted global minimum (the *N*-sulphonamide groups have been omitted for clarity). The predicted global minimum **E**, and the related conformations **F** and **G** are all saddle-shaped and therefore not C_2-symmetric. The conformations **F** and **G** are partially skewed off to one edge of the pyridine ring, whilst another low-energy conformation **H** is C_2-symmetric twisted. Crucially, all of these conformations are so close in terms of calculated energy that we can predict that they will all be populated to a significant extent at room temperature. We might also expect the interconversion between these conformations to be relatively easy, and it is possible to envisage "flipping" of the saddle **E** via the intermediacy of **F/G** and **H**. Thus the NMR should indicate a C_2-symmetric, time-averaged structure, as indeed was the case.

In order to confirm that inversion of the macrocycle through a C_2-symmetric intermediate was theoretically possible on the NMR timescale, a long molecular dynamics run was attempted. On short dynamics runs, of several thousand steps, no inversion of the macrocycle was observed (although the *N*-sulphonamide groups could undergo relatively free rotation as expected). The dynamics routine within XED98 uses torsional kinetic energy only, and so cannot be directly related to time, but when using 10 million steps (notionally equivalent to 10 ns), "flipping" of the saddle shape through C_2-symmetric intermediates was observed, even at room temperature. This further supports the conformational search results in terms of the proposed flexibility and average C_2-symmetry of these macrocycles.

3. Conclusions

The benzene- and pyridine-derived macrocycles described above are readily prepared in only two steps, via the formation of head-to-head-linked α-amino acids followed by a [1+1] macrocyclisation. The NMR spectra of these materials suggest that they are C_2-symmetric, but detailed molecular modelling reveals that the macrocycles have substantial conformational freedom and that the apparent symmetry is due to "flipping" of saddle-shaped structures through a C_2-symmetric intermediate.

In more general terms these results show that for antibiotics and other bioactive pyridine-containing macrocyclic structures it may be necessary to consider both saddle and twisted low-energy conformations when attempting to rationalise or predict bioactivity.

For the application of our pyridine-containing systems as enzyme mimics, the conformational freedom of the macrocycle should allow the alanyl methyl groups to provide a chiral environment at the pyridine nitrogen without necessarily blocking reactions at that site, and we are currently investigating the binding and catalysis capabilities of our systems.

4. Experimental

4.1. Molecular modelling

This was performed on a Silicon Graphics O2 (R10k, 195 MHz) using XED98 and the default dielectric constant of 4.

4.1.1. Conformational analysis of macrocycle 4a. Fifty initial fast (high-temperature) torsional dynamics runs generated 255 conformations which were within 10 kcal mol^{-1} of the lowest energy conformation found. Filtration of these conformations based on overlay of the pyridine ring left 77 conformations which were used as starting points in a Monte Carlo-type conformational search. After filtration, XED[13a] addition and careful minimisation (to an accuracy of 0.001 kcal mol^{-1}), 134 conformations were recorded within 10 kcal mol^{-1} of the predicted global minimum. Thirteen conformations were within 2 kcal mol^{-1} of the global minimum, although around half were duplicates caused by the flexing of the macrocycle to either (equivalent) side of the pyridine ring.

4.1.2. Molecular dynamics of macrocycle 4a. This was performed using the torsional dynamics available with XED98. A dynamics run using 10^7 steps at 25°C (notionally equivalent to 10 ns), with a structure being recorded every 10^5 steps, took 10 days to complete.

4.2. General synthetic experimental

Melting points were determined on a Riechert microscope hot-stage apparatus, and are uncorrected. Elemental analyses were performed at AstraZeneca Pharmaceuticals, Alderley Park. NMR spectra were recorded on a Bruker AC200 at 200 MHz and a Bruker DPX400 at 400 MHz. Chemical shifts were measured in ppm scale downfield from tetramethylsilane as internal standard. The solvent employed was $CDCl_3$, unless otherwise stated. Infrared spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrophotometer. Optical rotations were recorded on a Bendix-NPL 143D polarimeter at room temperature (20°C) using 2 ml of the solvent cited in the text. FAB mass spectra were recorded on a VG MS9 double sector spectrometer, with argon as the fast atom gas. Analytical TLC was carried out on Merck aluminium sheet silica gel 60 F_{254} plates (thickness 0.2 mm) as the stationary phase. THF was dried by distillation from sodium. Anhydrous DMF was obtained from Aldrich, and was stored under argon. HPLC grade $CHCl_3$, CH_2Cl_2 and MeOH were obtained from Aldrich for use in preparative work. Solvents used for column chromatography were purified by standard procedures.

4.3. General procedure A for the preparation of alkyl and aryl diamides using DCC/HOBT peptide coupling agents

N-Tosyl-L-alanine was dissolved in dry THF with HOBT (1.05 equivalents) and DCC (1.05 equivalents). This solution was stirred at room temperature under argon for 1 h, during which time a white precipitate was formed (DCU). The diamine (0.5 equivalents) was then added, and stirring continued for 24 h. The THF was removed by evaporation, and the residual white solid dissolved in EtOAc (100 ml). The DCU was insoluble in EtOAc, and was removed by filtration, before the solvent was evaporated. The residue was purified by flash chromatography on silica gel, eluted with MeOH/CH_2Cl_2 (1:99) affording the diamide as a white solid.

4.4. General procedure B for the preparation of alkyl and aryl diamides using EDC/HOBT peptide coupling agents

N-Tosyl-L-alanine was dissolved in dry THF with HOBT (1.05 equivalents) and the required diamine (0.5 equivalents). This mixture was stirred at room temperature under an argon atmosphere for 15 min, before the addition of EDC (1.05 equivalents) in a single portion. Further stirring over 6 h afforded a thick white precipitate (EDU). The THF was evaporated, and the residual white solid was taken up into a 1:1 mixture of EtOAc and 1 M HCl (aq) (50 ml). After shaking, the organic layer was washed with 1 M HCl (aq) (1×25 ml), with 1 M NaOH (aq) (2×25 ml) and with sat. brine (2×25 ml). The solvent was then dried over $MgSO_4$, filtered, and evaporated to give the diamide.

4.4.1. Preparation of 1,2-di(N^{α}-tosyl-L-alanylamido)-ethane 2a. General procedure B was followed, using *N*-tosyl-L-alanine (3.48 g, 14.3 mmol), EDC (2.92 g, 15.2 mmol), HOBT (2.94 g, 21.8 mmol), THF (50 ml) and 1,2-diaminoethane (0.49 ml, 7.16 mmol), affording 2.85 g of 1,2-di(N^{α}-tosyl-L-alanylamido)ethane **2a** as a white solid, m.p. 195–196°C (78% yield); R_f 0.09 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.01 (6H, d, 7.0 Hz, α-CH_3), 2.36 (6H, s, Ar–CH_3), 2.84 (4H, d, 6.7 Hz, NH–CH_2–CH_2–NH), 3.62 (2H, m, α-*H*), 7.35 and 7.67 (8H, AB system, 8.2 Hz, Ar–*H*), 7.72 (2H, s, N*H*–CO), 7.82 (2H, d, 8.0 Hz, N*H*–SO_2); ^{13}C NMR (50 MHz) δ: 18.77, 20.86, 37.94, 51.89, 126.53, 129.31, 138.06, 142.52, 171.22; $[\alpha]_D^{20}=-49.3$ (c=1.05, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1}: 3274, 1663, 1541, 1425, 1333, 1239, 1163, 1091, 970, 873, 813, 669, 562; FABMS *m/e* 533 (M+Na; 76%), 511 (M+1; 100%), 286 (26%), 269 (12%), 198 (34%), 155 (34%), 139 (14%), 123 (8%). Found: C 51.5%, H 6.10%, N 10.80%, S12.30%. Calcd: C 51.76%, H 5.88%, N 10.98%, S 12.55% for $C_{22}H_{30}N_4S_2O_6$.

4.4.2. Preparation of 1,3-di(N^{α}-tosyl-L-alanylamido)pro-

pane 2b General procedure B was followed, using *N*-tosyl-L-alanine (2.58 g, 10.6 mmol), EDC (2.16 g, 11.2 mmol), HOBT (1.52 g, 11.2 mmol), THF (40 ml) and 1,3-diaminopropane (0.44 ml, 5.3 mmol), affording 1.21 g of 1,3-di(N^{α}-tosyl-L-alanylamido)propane **2b** as a white solid, m.p. 181.5–182°C (44% yield); R_f 0.17 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (400 MHz) in DMSO-d_6 δ: 1.02 (6H, d, 7.1 Hz, α-CH_3), 1.29 (2H, q, 6.9 Hz, NH–CH_2–CH_2–CH_2–NH), 2.36 (6H, s, Ar–CH_3), 2.84 (4H, dt, 5.3 Hz and 5.3 Hz, NH–CH_2–CH_2–CH_2–NH), 3.64 (2H, dt, 7.5 Hz and 7.5 Hz, α-*H*), 7.34 and 7.65 (8H, AB system, 8.3 Hz, Ar–*H*), 7.75 (2H, br t, N*H*–CO), 7.82 (2H, d, 8.0 Hz, N*H*–SO_2); ^{13}C NMR (50 MHz) in DMSO-d_6 δ: 18.89, 20.86, 28.73, 35.98, 51.87, 126.50, 129.32, 138.09, 142.50, 171.03; $[\alpha]_D^{20}=-73.3$ (c=1.01, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1} (KBr disk) 3251, 1651, 1557, 1435, 1329, 1234, 1163, 1142, 1091, 978, 818, 697, 664, 567; FABMS *m/e* 547 (M+Na; 32%), 525 (M+1; 100%), 300 (18%), 283 (20%), 249 (12%), 239 (10%), 198 (36%), 185 (8%), 176 (12%), 149 (14%). Found: C 52.7%, H 5.90%, N 10.40%. Calcd: C 52.67, H 6.11%, N 10.68% for $C_{23}H_{32}N_4S_2O_6$.

4.4.3. Preparation of 1,4-di(N^{α}-tosyl-L-alanylamido)-butane 2c. General procedure B was followed, using *N*-tosyl-L-alanine (5.01 g, 20.6 mmol), EDC (4.15 g, 21.6 mmol), HOBT (2.92 g, 21.6 mmol), THF (50 ml) and 1,4-diaminobutane (1.04 ml, 10.3 mmol), affording 4.99 g of 1,4-di(N^{α}-tosyl-L-alanylamido)butane **2c** as a white solid, m.p. 163–164°C (90% yield). R_f 0.13 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (400 MHz) DMSO-d_6 δ: 1.01 (6H, d, 7.0 Hz, α-CH_3), 1.17 (4H, br s, NH–CH_2–CH_2–CH_2–CH_2–NH), 2.35 (6H, s, Ar–CH_3), 2.84 (4H, br d, NH–CH_2–CH_2–CH_2–CH_2–NH), 3.67 (2H, m, α-*H*), 7.34 and 7.65 (8H, AB system, 8.0 Hz, Ar–*H*), 7.71 (2H, t, 5.4 Hz, N*H*–CO), 7.79 (2H, d, 8.3 Hz, N*H*–SO_2); ^{13}C NMR (50 MHz) in DMSO-d_6 δ: 19.05, 20.88, 26.12, 38.06, 51.80, 126.51, 129.31, 138.18, 142.44, 170.87; $[\alpha]_D^{20}=-39.8$ (c=1.03, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1} (KBr disk) 3310, 3261, 1655, 1560, 1443, 1328, 1230, 1165, 1144, 1091, 990, 816, 662, 568, 547; FABMS *m/e* 561 (M+Na; 6%), 539 (M+1; 10%), 176 (38%), 165 (10%), 149 (14%), 123 (34%). Found: C 53.50%, H 6.3%, N 10.30%, S 12.20%. Calcd: C 53.53%, H 6.31%, N 10.41%, S 11.90% for $C_{24}H_{34}N_4S_2O_6$.

4.4.4. Preparation of 1,5-di(N^{α}-tosyl-L-alanylamido)pentane 2d. General procedure B was followed, using *N*-tosyl-L-alanine (5.04 g, 20.7 mmol), EDC (4.17 g, 21.7 mmol), HOBT (2.96 g, 21.8 mmol), THF (50 ml) and 1,5-diaminopentane (1.21 ml, 10.4 mmol), affording 5.12 g of 1,5-di(N^{α}-tosyl-L-alanylamido)pentane **2d** as a white solid, m.p. 176–177°C (89% yield); R_f 0.23 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (400 MHz) in DMSO-d_6 δ: 1.02 (6H, d, 7.0 Hz, α-CH_3), 1.08 (2H, br s, NH–CH_2–CH_2–CH_2–CH_2–CH_2–NH), 1.21 (4H, quintet, 7.0 Hz, NH–CH_2–CH_2–CH_2–CH_2–CH_2–NH), 2.35 (6H, s, Ar–CH_3), 2.84 (4H, dt, 6.6 Hz and 6.5 Hz, NH–CH_2–CH_2–CH_2–CH_2–CH_2–NH), 3.67 (2H, dq, 7.2 Hz and 7.2 Hz, α-*H*), 7.34 and 7.65 (8H, AB system, 8.1 Hz, Ar–*H*), 7.69 (2H, t, 5.6 Hz, N*H*–CO), 7.79 (2H, d, 8.4 Hz, N*H*–SO_2); ^{13}C NMR (50 MHz) in DMSO-d_6 δ: 19.01, 20.88, 23.48, 28.41, 38.30, 51.81, 126.51, 129.29, 138.19, 142.42, 170.82; $[\alpha]_D^{20}=-51.7$ (c=1.05, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1} (KBr disk) 3413, 3250, 1648, 1617, 1559, 1447, 1331, 1160, 1091, 816, 662, 618; FABMS *m/e* 553 (M+1; 32%), 328 (14%), 306 (26%), 206 (28%), 194 (12%) 178 (12%), 149 (34%), 91 (50%), 55 (100%). Found: C 54.40%, H 6.70%, N 10.10%, S 11.70%. Calcd: C 54.35%, H 6.52%, N 10.14%, S 11.59% for $C_{25}H_{36}N_4S_2O_6$.

4.4.5. Preparation of 1,3-di(N^{α}-tosyl-L-alanylamidomethyl)benzene 2e. General procedure B was followed, using *N*-tosyl-L-alanine (5.04 g, 20.7 mmol), EDC (4.18 g, 21.8 mmol), HOBT (2.93 g, 21.7 mmol), THF (50 ml) and 1,3-di(aminomethyl)benzene (1.36 ml, 13.6 mmol), affording 5.73 g of 1,3-di(N^{α}-tosyl-L-alanylamidomethyl)benzene **2e** as an amorphous white solid, m.p. 191–192°C (94% yield); R_f 0.14 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) in DMSO-d_6 δ: 1.06 (6H, d, 7.1 Hz, α-CH_3), 2.37 (6H, s, Ts–CH_3), 3.75 (2H, m, α-*H*), 4.12 (4H, m, 6.0 Hz, NH–CH_2–Ar), 7.0 (3H, m, Ar–*H*), 7.22 (1H, t, 7.6 Hz, Ar–*H*), 7.35 and 7.68 (8H, AB system, 7.9 Hz, Ar–*H*) 7.89 (2H, d, 4.9 Hz, Ts–N*H*), 8.28 (2H, t, 5.7 Hz, Ar–CH_2–N*H*–CO); ^{13}C NMR (50 MHz) in DMSO-d_6 δ: 18.91, 20.89, 41.92, 51.81, 126.33, 126.00, 126.49, 128.16, 129.34, 138.17, 138.95, 142.47, 171.14; $[\alpha]_D^{20}=-51.5$ (c=1.03, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1} (KBr disk) 3411, 2961, 1734, 1654, 1617, 1534, 1448, 1382, 1337, 1164, 1092, 1018, 960, 876, 815, 662; FABMS *m/e* 587 (M+1; 6%), 467 (4%), 388 (3%), 217 (20%), 131 (25%), 119 (52%), 100 (100%), 89 (15%). Found: C 57.30%, H 5.70%, N 9.40%. Calcd: C 57.33%, H 5.80%, N 9.56% for $C_{28}H_{34}N_4S_2O_6$.

4.4.6. Preparation of 1,4-di(N^{α}-tosyl-L-alanylamidomethyl)benzene 2f. General procedure B was followed, using *N*-tosyl-L-alanine (1.90 g, 7.8 mmol), EDC (1.50 g, 7.8 mmol), HOBT (1.07 g, 7.9 mmol), THF (30 ml) and 1,4-di(aminomethyl)benzene (0.48 g, 3.5 mmol), affording 1.56 g of 1,4-di(N^{α}-tosyl-L-alanylamidomethyl)benzene **2f** as an amorphous white solid, m.p. 216–217.5°C; (80% yield); R_f 0.43 in 1:9 MeOH/$CHCl_3$; ^{1}H NMR (200 MHz) δ: 1.12 (6H, d, 7.0 Hz, α-CH_3), 2.35 (6H, s, Ar–CH_3), 4.18 (2H, q, 6.9 Hz, α-*H*), 4.24 (4H, d, 9.0 Hz, Ar–CH_2–N), 7.28 (4H, br s, Ar–*H*), 7.34 and 7.68 (8H, AB system, 7.9 Hz, Ts–*H*), 7.84 (2H, br t, N*H*–CO); ^{13}C NMR (50 MHz) δ: 18.60, 22.98, 43.06, 52.43, 126.72, 129.33, 129.76, 136.51, 143.87, 146.17, 171.76; IR ν_{max} cm^{-1} 3190, 1654, 1562, 1510, 1483, 1432, 1396, 1360, 1124, 823, 755; FABMS *m/e* 587 (M+1; 6%), 452 (8%), 219 (70%), 198 (30%), 150 (100%), 119 (28%), 91 (94%).

4.4.7. Preparation of 1,4-di(N^{α}-tosyl-L-alanyl)piperazine 2g. General procedure B was followed, using *N*-tosyl-L-alanine (2.64 g, 10.2 mmol), EDC (2.06 g, 10.7 mmol), HOBT (1.47 g, 10.6 mmol), THF (40 ml) and piperazine (0.44 g, 5.12 mmol), affording 2.44 g of 1,4-di(N^{α}-tosyl-L-alanyl)piperazine **2g** as a white solid, m.p. 84.5–86°C (89% yield); R_f 0.20 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.25 (6H, d, 7.0 Hz, α-CH_3), 2.42 (6H, s, Ar–CH_3), 2.82 to 3.68 (8H, m, N(CH_2CH_2)$_2$N), 4.22 (2H, m, α-*H*), 5.76 (2H, d, 8.1 Hz, N*H*–SO_2), 7.30 and 7.74 (8H, AB system, 9.0 Hz, Ar–*H*); ^{13}C NMR (50 MHz) δ: 19.79, 21.43, 41.71 and 44.58, 48.37, 127.14, 129.54, 137.04, 143.67, 170.20; IR ν_{max} cm^{-1} 3231, 1734, 1641, 1425, 1337, 1288, 1224, 1164, 1092, 1048, 1013, 968, 816, 758, 666, 558; FABMS

m/e 539 (11%), 538 (21%), 537 (M+1; 52%), 312 (39%), 290 (15%), 197 (49%), 165 (25%), 149 (20%), 124 (30%), 89 (90%), 77 (95%). Found: C 53.30%, H 5.90%, N 10.10%, Calcd: C 53.30%, H 6.01%, N 10.40% for $C_{24}H_{32}N_4S_2O_6$.

4.4.8. Preparation of ethyl cross-linked benzene cyclophane 3a. General procedure was followed, using 1,3-di(bromomethyl)benzene (14.6 mg, 57.0 μmol), [Ts–Ala–$NHCH_2]_2$ **2a** (29.3 mg, 58.0 μmol), Cs_2CO_3 (0.093 g, 0.29 mmol) and DMF (10 ml), affording 19.0 mg of cyclophane **3a** as a colourless foam (53% yield); R_f 0.44 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.12 (6H, d, 7.2 Hz, α-C*H*$_3$), 2.44 (6H, s, Ts–C*H*$_3$), 2.66–2.96 (2H, m, NH–C*H*$_2$–C*H*$_2$–NH), 3.81 and 4.81 (4H, AB system, 14.0 Hz, Ar–C*H*$_2$–N), 4.46 (2H, q, 7.3 Hz, α-*H*), 6.75 (2H, br s, N*H*–SO_2), 7.29 (3H, m, Ar*H*), 7.33 and 7.73 (8H, AB system, 8.0 Hz, Ts–*H*), 7.69 (1H, br s, Ar*H*); ^{13}C NMR (50 MHz) δ: 11.52, 21.49, 40.62, 46.58, 54.11, 126.98, 128.78, 129.14, 129.99, 130.79, 136.72, 136.87, 143.87, 170.84; $[\alpha]_D^{20}$=+28.0 (*c*=1.00, $CHCl_3$); IR ν_{max} cm^{-1} (KBr disk) 3412, 2941, 1674, 1521, 1340, 1157, 1090, 996, 872, 816, 786, 726, 659; FABMS *m/e* 613 (M+1; 14%), 571 (8%), 459 (10%), 302 (8%), 191(14%), 107 (30%), 77 (19%).

4.4.9. Preparation of propyl cross-linked benzene cyclophane 3b. General procedure was followed, using 1,3-di(bromomethyl)benzene (14.5 mg, 57.0 μmol), [Ts–Ala–$NHCH_2]_2CH_2$ **2b** (29.0 mg, 56.0 μmol), Cs_2CO_3 (92 mg, 0.28 mmol) and DMF (10 ml), affording 22.0 mg of cyclophane **3b** as a colourless foam (62% yield); R_f 0.39 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.14 (6H, d, 7.0 Hz, α-C*H*$_3$), 1.21 (2H, m, CH_2–C*H*$_2$–CH_2), 2.42 (6H, s, Ts–C*H*$_3$), 2.52 and 2.94 (4H, 2×m, NH–C*H*$_2$–CH_2–C*H*$_2$–NH), 3.88 and 4.74 (4H, AB system, 15.0 Hz, Ar–C*H*$_2$–N), 4.43 (2H, q, 7.0 Hz, α-*H*), 6.56 (2H, br t, N*H*–SO_2), 7.22 (3H, m, Ar*H*), 7.33 and 7.76 (8H, AB system, 7.9 Hz, Ts–*H*), 7.81 (1H, br s, Ar*H*); ^{13}C NMR (50 MHz) δ: 11.91, 21.48, 28.93, 34.31, 46.58, 54.47, 126.98, 128.51, 129.34, 129.95, 131.98, 136.75, 136.97, 143.75, 169.83; $[\alpha]_D^{20}$=+13.8 (*c*=1.02, $CHCl_3$); IR ν_{max} cm^{-1} (KBr disk) 3385, 2941, 1668, 1534, 1339, 1165, 1098, 729, 659; FABMS *m/e* 626 (M+1; 26%), 549 (8%), 471 (12%), 378 (14%), 249 (10%), 149 (28%), 91 (35%).

4.4.10. Preparation of butyl cross-linked benzene cyclophane 3c. General procedure was followed, using 1,3-di(bromomethyl)benzene (33.7 mg, 132 μmol), [Ts–Ala–$NH(CH_2)_2]_2$ **2c** (71.0 mg, 129 μmol), Cs_2CO_3 (21.4 mg, 660 μmol) and DMF (15 ml), affording 27.0 mg of cyclophane **3c** as a colourless foam (32% yield); R_f 0.37 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 0.75 (4H, m, NH–CH_2–C*H*$_2$), 1.12 (6H, d, 6.9 Hz, α-C*H*$_3$), 2.45 (6H, s, Ts–C*H*$_3$), 2.67 and 3.22 (4H, 2×m, NH–C*H*$_2$–CH_2), 3.94 and 4.73 (4H, AB system, 15.9 Hz, Ar–C*H*$_2$–N), 4.38 (2H, q, 7.07 Hz, α-*H*), 6.19 (2H, m, N*H*–CO), 7.29–7.45 (3H, m, Ar*H*), 7.36 and 7.73 (8H, AB system, 8.3 Hz, Ts–*H*), 7.59 (1H, br s, Ar*H*); ^{13}C NMR (50 MHz) δ: 12.09, 20.71, 25.27, 38.79, 47.03, 55.52, 127.19, 128.45, 128.89, 129.80, 130.05, 135.93, 137.14, 144.19, 169.85; $[\alpha]_D^{20}$=+53.1 (*c*=0.96, $CHCl_3$); IR ν_{max} cm^{-1} (KBr disk) 3420, 2925, 1677, 1526, 1337, 1157, 1090, 727, 660; FABMS *m/e* 641 (M+1; 25%), 485 (14%), 469 (6%), 391 (8%), 329 (4%), 289 (25%), 272 (6%), 165 (18%), 149 (36%), 105 (80%), 55 (100%).

4.4.11. Preparation of pentyl cross-linked benzene cyclophane 3d. General procedure was followed, using 1,3-di(bromomethyl)benzene (29.0 mg, 114 μmol), [Ts–Ala–$NH(CH_2)_2]_2CH_2$ **2d** (63.0 mg, 1.17 μmol), Cs_2CO_3 (0.186 g, 573 μmol) and DMF (15 ml), affording 12.0 mg of cyclophane **3d** as a colourless foam (15% yield); R_f 0.25 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 0.85 (2H, m, NH–C*H*$_2$–CH_2–CH_2), 1.14 (6H, d, 7.0 Hz, α-C*H*$_3$), 1.32 (4H, quintet, 6.8 Hz, NH–CH_2–C*H*$_2$–CH_2), 2.36 (6H, s, Ts–C*H*$_3$), 2.58 and 3.20 (4H, 2×m, NH–C*H*$_2$–CH_2–CH_2), 4.06 and 4.56 (4H, AB system, 15.2 Hz, Ar–C*H*$_2$–N), 4.42 (2H, q, 7.0 Hz, α-*H*), 6.36 (2H, br s, N*H*–CO), 7.34 and 7.76 (8H, AB system, 8.4 Hz, Ts–*H*), 7.40 (3H, m, Ar*H*), 7.72 (1H, br s, Ar*H*); FABMS *m/e* 677 (M+Na; 8%), 655 (11%), 391 (6%), 259 (6%), 193 (8%), 165 (18%), 123 (40%), 109 (62%).

4.4.12. Preparation of *m*-xylyl cross-linked benzene cyclophane 3e. General procedure was followed, using 1,3-di(bromomethyl)benzene (32.0 mg, 1.24 μmol), 1,3-di[Ts–Ala–$NHCH_2]_2$-benzene **2e** (73.2 mg, 125 μmol). Cs_2CO_3 (0.73 g, 625 μmol) and DMF (20 ml), affording 18.7 mg of cyclophane **3e** as a colourless foam (22% yield); R_f 0.22 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.18 (6H, d, 7.24 Hz, α-C*H*$_3$), 2.42 (6H, s, Ts–C*H*$_3$), 3.89 and 4.52 (4H, AB system, 14.1 Hz, Ar–C*H*$_2$–NH), 3.95 and 4.44 (4H, 2×d, Ar–C*H*$_2$–N), 4.38 (2H, q, 7.1 Hz, α-*H*), 6.55–7.24 (10H, m, Ar–*H*+N*H*–CO), 7.31 and 7.67 (8H, AB system, 8.4 Hz, Ts–*H*); ^{13}C NMR (50 MHz) δ: 13.15, 21.51, 43.90, 47.98, 56.61, 127.30, 127.69, 127.72, 127.85, 127.98, 128.35, 128.74, 144.22, 170.08; FABMS *m/e* 689 (M+1; 12%), 533 (6%), 464 (5%), 290 (10%), 274 (8%), 206 (10%), 167 (30%), 149 (50%).

4.4.13. Preparation of ethyl cross-linked pyridine cyclophane 4a. General procedure was followed, using 2,6-di(bromomethyl)pyridine (28.0 mg, 109 μmol), [Ts–Ala–$NHCH_2]_2$ **2a** (56.0 mg, 107 μmol), Cs_2CO_3 (0.178 g, 548 μmol) and DMF (20 ml), affording 39.0 mg of cyclophane **4a** as a colourless foam (58% yield); R_f 0.35 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) in DMSO-d_6 δ: 1.14 (6H, d, 7.1 Hz, α-C*H*$_3$), 2.39 (6H, s, Ar–C*H*$_3$), 3.08 (4H, br s, NH–C*H*$_2$–C*H*$_2$–NH), 4.18 (2H, q, 7.1 Hz, α-*H*), 4.27 (4H, AB system, 13.0 Hz, Ar–C*H*$_2$), 7.37 and 7.73 (8H, AB system, 7.8 Hz, Ts–*H*), 7.40 (2H, d, 6.5 Hz, py–*H*), 7.81 (1H, t, 7.0 Hz, py–*H*), 8.02 (2H, br s, CO–N*H*–CH_2); ^{13}C NMR (60 MHz) in DMSO-d_6 δ: 15.07, 20.90, 50.57, 54.84, 57.56, 122.38, 127.29, 129.52, 136.72, 137.58, 143.23, 156.21, 169.61; $[\alpha]_D^{20}$=−40.6 (*c*=0.64, CH_2Cl_2); IR ν_{max} cm^{-1} (KBr disk) 3426, 2924, 1670, 1596, 1522, 1338, 1156, 1090, 879, 789, 659; FABMS *m/e* 636 (M+Na; 72%), 614 (M+1; 100%), 480 (10%), 458 (26%), 307 (8%), 289 (8%), 176 (16%), 163 (12%). Elemental composition by FABMS *m/e* 614.2114 for $C_{29}H_{36}N_5O_6S_2$: Calcd 614.2107.

4.4.14. Preparation of propyl cross-linked pyridine cyclophane 4b. General procedure C was followed,

using 2,6-di(bromomethyl)pyridine (20.8 mg, 81.3 μmol), [Ts–Ala–NHCH$_2$]$_2$CH$_2$ **2b** (42.0 mg, 82 μmol), Cs_2CO_3 (0.132 g, 407 μmol) and DMF (20 ml), affording 26.0 mg of cyclophane **4b** as a white solid, m.p. 96.5–97.5°C (51% yield); R_f 0.37 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.06 (6H, d, 7.0 Hz, α-CH_3), 1.70 (2H, br quintet, NH–CH$_2$–CH_2–CH$_2$–NH), 2.24 (6H, s, Ar–CH_3), 3.10 (4H, br s, NH–CH_2–CH$_2$–CH_2–NH), 4.02 and 4.18 (4H, AB system, 16.0 Hz, Ar–CH_2), 4.20 (2H, q, 7.0 Hz, α-*H*), 7.13 and 7.56 (8H, AB system, 9.0 Hz, Ts–*H*), 7.22 (2H, d, 8.5 Hz, py–*H*), 7.55 (1H, t, 8.5 Hz, py–*H*), 8.10 (2H, br t, CO–N*H*–CH$_2$); ^{13}C NMR (60 MHz) δ: 14.23, 21.12, 25.30, 35.161, 50.77, 57.56, 123.44, 127.18, 129.62, 135.78, 138.04, 143.92, 156.21, 170.91; IR ν_{max} cm^{-1} (KBr disk) 3402, 2937, 1668, 1596, 1526, 1455, 1337, 1157, 1090, 790, 659; FABMS *m/e* 628 (M+1; 68%), 472 (26%), 392 (8%), 318 (8%), 190 (15%), 149 (34%), 133 (25%).

4.4.15. Preparation of butyl cross-linked pyridine cyclophane 4c. General procedure was followed, using 2,6-di(bromomethyl)pyridine (37.8 mg, 147 μmol), [Ts–Ala–NH(CH$_2$)$_2$]$_2$ **2c** (79.0 mg, 150 μmol), Cs_2CO_3 (0.239 g, 735 μmol) and DMF (25 ml), affording 33.0 mg of cyclophane **4c** as a colourless foam (35% yield); R_f 0.38 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (200 MHz) δ: 1.00 (4H, m, NH–CH$_2$–CH_2–CH_2–CH$_2$–NH), 1.13 (6H, d, 7.1 Hz, α-CH_3), 2.39 (6H, s, Ar–CH_3), 2.89 (4H, m, NH–CH_2–CH$_2$–CH$_2$–CH_2–NH), 4.22 and 4.44 (4H, AB system, 16.9 Hz, Ar–CH_2), 4.36 (2H, q, 7.1 Hz, α-*H*), 7.35 (2H, d, 7.8 Hz, 2-*H*), 7.41 and 7.76 (8H, AB system, 8.1 Hz, Ts–*H*), 7.53 (1H, br t, py–*H*); FABMS *m/e* 664 (M+Na; 42%), 642 (M+1; 100%), 486 (36%), 344 (14%), 190 (12%).

4.4.16. Preparation of pentyl cross-linked pyridine cyclophane 4d. General procedure was followed, using 2,6-di(bromomethyl)pyridine (47.0 mg, 181 μmol), [Ts–Ala–NH(CH$_2$)$_2$]$_2$CH$_2$ **2d** (0.101 g, 184 μmol), Cs_2CO_3 (0.297 g, 9.16 μmol) and DMF (25 ml), affording 18.0 mg of cyclophane **4d** as a colourless foam (15% yield) (oil). R_f 0.41 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (400 MHz) in DMSO-d$_6$ δ: 1.04 (2H, m, NH–CH$_2$–CH$_2$–CH_2–CH$_2$–CH$_2$–NH), 1.16 (6H, d, 7.04 Hz, α-CH_3), 1.28 (4H, quintet (tt.), 6.5 Hz, NH–CH$_2$–CH_2–CH$_2$–CH_2–CH$_2$–NH), 2.38 (6H, s, Ar–CH_3), 2.91 and 3.16 (4H, AB system, NH–CH_2–CH$_2$–CH$_2$–CH$_2$–CH_2–NH), 4.22 and 4.48 (4H, AB system, 16.7 Hz, Ar–CH_2), 4.35 (2H, q, 7.1 Hz, α-*H*), 7.35 (2H, m, 2-*H*), 7.35 and 7.75 (8H, AB system, 8.3 Hz, Ts–*H*), 7.81 (1H, t, 7.8 Hz, py–*H*), 7.98 (2H, t, 9.2 Hz, CO–N*H*–CH$_2$); ^{13}C NMR (60 MHz) in DMSO-d$_6$ δ: 15.71, 20.93, 23.46, 27.91, 50.44, 54.75, 57.25, 121.40, 127.28, 129.64, 136.52, 137.60, 143.54, 156.65, 169.65, 169.07; FABMS *m/e* 678 (M+Na; 20%), 656 (M+1; 32%), 500 (8%), 289 (14%), 193 (12%), 165 (16%).

4.4.17. Preparation of piperazine cross-linked pyridine cyclophane 4g. General procedure was followed, using 2,6-di(bromomethyl)pyridine (29.0 mg, 112 μmol), 1,4-di(N^{α}-tosyl-L-alanyl)piperazine **2g** (61.1 mg, 114 μmol), Cs_2CO_3 (0.185 g, 571 μmol) and DMF (20 ml), affording 35 mg of cyclophane **4g** as a colourless foam (48% yield); R_f 0.37 in MeOH/$CHCl_3$ (5:95); ^{1}H NMR (400 MHz) in DMSO-d$_6$ δ: 1.26 (6H, d, 7.0 Hz, α-CH_3), 2.36 (6H, s, Ts–*H*), 3.28 (td.), 3.46, 4.08 and 4.32 (8H, 4×m, piperazine–*H*), 3.72 and 4.18 (4H, AB system, 16.2 Hz, Ar–CH_2–N), 4.88 (2H, q, 7.0 Hz, α-*H*), 7.12 and 7.28 (8H, AB system, 8.1 Hz, Ts–*H*), 7.16 (2H, br d, py–*H*3,5), 7.56 (1H, t, 6.0 Hz, py–*H*4); ^{13}C NMR (60 MHz) δ: 14.57, 21.83, 39.14, 45.39, 50.04, 55.44, 123.74, 128.03, 129.64, 136.59, 137.07, 144.24, 156.87, 169.57: $[\alpha]_D^{20}$=+158.8 (*c*=1.00, MeOH/$CHCl_3$ (1:9)); IR ν_{max} cm^{-1} (KBr disk) 3449, 2925, 1648, 1595, 1458, 1338, 1226, 1158, 1089, 1011, 886, 813, 747, 688; FABMS *m/e* 640 (M+1; 16%), 484 (12%), 344 (26%), 303 (12%), 190 (32%), 145 (80%), 91 (100%); Elemental composition by FABMS *m/e* 640.2259 for $C_{31}H_{38}N_5O_6S_2$: Calcd 640.2263.

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