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Efficient Macrocyclization of U-Turn Preorganized Peptidomimetics: The Role of Intramolecular H-Bond and Solvophobic Effects

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Abstract: Simple peptidomimetic molecules derived from amino acids were reacted with *meta*- and *para*-bis(bromomethyl)benzene in acetonitrile to very efficiently yield macrocyclic structures. The cyclization reaction does not require high dilution techniques and seems to be insensitive to the size of the formed macrocycle. The analysis of data obtained by ^{1}H NMR, single-crystal X-ray diffraction, fluorescence measurements, and molecular mechanics indicate that folded conformations can preorganize the system for an efficient cyclization. The role played by intramolecular hydrogen-bonding and solvophobic effects in the presence of folded conformations is analyzed.

Introduction

Much work has been devoted in recent years to the preparation and study of peptidomimetics. The interest on this class of compounds has evolved from different areas of research. The analysis of the molecular basis of structural features in proteins, in particular structural motifs associated with folding, has been one of the main driving forces for this interest.[1] A second factor has been the development of novel receptors in the fields of Molecular Recognition and Supramolecular Chemistry. In this area, molecules containing peptides or peptide-related fragments have found applications in the self-assembly of nanotubes and rosettes,[2a−c] modulation of protein−protein interactions,[2d−e] catalysis [2f−k] cation, and recognition.[2l−n] A third point has been the observation of important biomedical activities of some natural and synthetic peptidomimetics, as has been the case for the synthesis of novel compounds with anti-HIV activities[3a,b] or antibacterial properties.[3c] To stabilize "active" conformations, many of the former examples are based on the preparation of cyclic peptidomimetic structures. In particular, to achieve additional conformational constraints, special attention is focused on the incorporation of aromatic rings into the peptidomimetic backbone. Therefore, different strategies have been described associated to the preparation of cyclic peptides and analogues. For these compounds, the cyclization step is usually the main challenge and their preparation often involves complex synthetic methodologies which require the use of specific reactions, selective protection/deprotection steps and high dilution techniques.[4] Under some circumstances, the use of the appropriate templates, in particular metal cations, can greatly improve cyclization steps.[5] In connection with those approaches, a simple analysis of the structures of some peptidomimetic molecules being able to form *U*-turns, suggests that this preorganization

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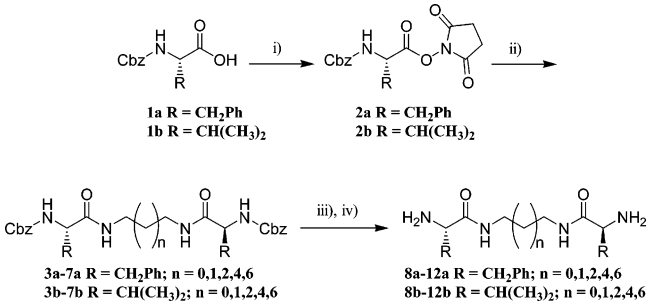
Scheme 1 [a]



[a] (i) DCC, N-hydroxysuccinimide, THF; (ii) $H_2NCH_2(CH_2)_nCH_2NH_2$, DME; (iii) HBr/AcOH; (iv) aq. NaOH

could favor intramolecular processes over the intermolecular ones and provide simple routes for the preparation of macrocyclic peptidomimetic structures. As a matter of fact, the presence of folded conformations found for acyclic peptidomimetics have been associated by us and other groups to the outcome of macrocyclization reactions.[6] The predisposition of different peptidomimetic molecules to fold has been widely studied and several structural units such as urea, amino acids, proline residues, etc., have been associated with the formation of $\beta-\gamma$- or related *U*-turns in peptides or peptidomimetics.[1,7] Here, we report how simple peptidomimetics with C_2 symmetry such as **8**−**12**, show a strong tendency to form folded structures under some conditions and how this can be used advantageously for the synthesis of cyclophane peptidomimetics.

Results and Discussion

Open-chain peptidomimetic molecules **8**−**12** can be easily prepared starting from the corresponding diamines and the N−Cbz protected amino acids **1** through the initial formation of their activated N-hydroxysuccinimide esters **2** (see Scheme 1).[8] Overall yields for the preparation of compounds **8**−**12**, after the final deprotection step, were in the range 60−80%, and did not depend very much on the nature and length of the aliphatic spacer.

Preliminary molecular mechanics calculations on compounds **8**−**10** suggested that folded conformations such as **I** (see Scheme 3) could be prevalent as a result of intramolecular H-bonds and contribute to the appropriate preorganization of the peptidomimetic chain for macrocyclization. Consequently, we evaluated the cyclization reaction shown in the Scheme 2 to test for the preorganization present in those molecules and its dependence on different factors, in particular the amino acid side chain and the length of aliphatic spacer. With this purpose, compounds **8**−**12** were reacted with different bis(bromomethyl)arenes in order to obtain the corresponding cyclic molecules **13**−**22**.

The yields (obtained after chromatographic purification) for the macrocyclization reactions carried out in acetonitrile and using potassium carbonate as a base are shown in Table 1. The reaction can be accelerated by addition of tetrabutylammonium bromide as a phase transfer catalyst but this reagent did not affect the yield of isolated macrocyclic product. The results were quite good for the meta and para substituted aromatic subunits and no significant differences were observed when derivatives of phenylalanine or valine were used. In most cases, yields for the expected product of ca. 80% could be estimated from the crude reaction mixture. The formation of the corresponding 2+2 cyclization compounds was detected in some cases as minor side products. In the case of ortho disubstituted aromatic derivatives the cyclization reactions did not work and 1,2-dihydroisoindol derivatives were obtained, a situation that has been described previously.[9]

Table 1. Yields Obtained for the Cyclization Reaction after Chromatographic Purification

compd	R	n	yield (%)
13a	$-CH_2Ph$	0	65
14a	$-CH_2Ph$	1	61
15a	$-CH_2Ph$	2	66
16a	$-CH_2Ph$	4	65
17a	$-CH_2Ph$	6	52
13b	$-CH(CH_3)_2$	0	49
14b	$-CH(CH_3)_2$	1	61
15b	$-CH(CH_3)_2$	2	69
16b	$-CH(CH_3)_2$	4	52
17b	$-CH(CH_3)_2$	6	55
18a	$-CH_2Ph$	0	63
19a	$-CH_2Ph$	1	52
20a	$-CH_2Ph$	2	63
21a	$-CH_2Ph$	4	67
22a	$-CH_2Ph$	6	55
18b	$-CH(CH_3)_2$	0	64
19b	$-CH(CH_3)_2$	1	56
20b	$-CH(CH_3)_2$	2	65
21b	$-CH(CH_3)_2$	4	60
22b	$-CH(CH_3)_2$	6	65

The good results obtained when the components of the reaction were 1,3- or 1,4-bis(bromomethyl)benzene and the diamines **8**, **9**, and **10** ($n = 0, 1, 2$) could, in a first analysis, be ascribed to the above-mentioned preorganization induced by intramolecular H-bonding as shown in **I** (Scheme 3). Surprisingly, although longer aliphatic chains should disfavor this kind of intramolecular hydrogen-bond formation, and therefore lead to a decrease of the efficiency of macrocycle formation, for compounds **11** and **12**, with aliphatic spacers containing six and eight methylene units respectively, cyclization yields were also good and comparable to those obtained for compounds with shorter aliphatic spacers. Those results prompted us to study in more detail the importance of hydrogen bonding in the possible preorganization.

In first place, ^{1}H NMR experiments were carried out. The chemical shifts observed in $CDCl_3$ and CD_3CN for the signals of the amide protons in compounds **8**−**12** correspond with those expected for strongly hydrogen-bonded systems (see Table 2).

The described chemical shift values were almost insensitive to changes in concentration (see Figure 1) indicating that hydrogen bonding is taking place intramolecularly, as indicated also by the changes observed with temperature.[10] It is noticeable that, both in chloroform and acetonitrile, the amide proton resonances appear at lower ppm values as the length of the

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Table 2. (a) ^{1}H NMR Chemical Shifts for the Amide Protons of Acyclic Compounds **8**−**12** in $CDCl_3$ and CD_3CN

compd	R	n	δ (ppm, $CDCl_3$)	δ (ppm, CD_3CN)
8a	$-CH_2Ph$	0	7.55	7.34
9a	$-CH_2Ph$	1	7.56	7.40
10a	$-CH_2Ph$	2	7.30	7.21
11a	$-CH_2Ph$	4	7.24	7.18
12a	$-CH_2Ph$	6	7.21	7.16
8b	$-CH(CH_3)_2$	0	7.70	7.52
9b	$-CH(CH_3)_2$	1	7.67	7.54
10b	$-CH(CH_3)_2$	2	7.27	7.34
11b	$-CH(CH_3)_2$	4	7.31	7.30
12b	$-CH(CH_3)_2$	6	7.29	7.28

[a] The concentration was 10^{-2} M in all cases.

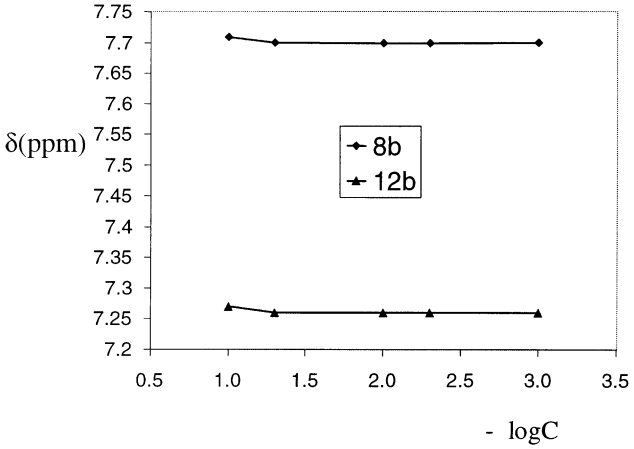
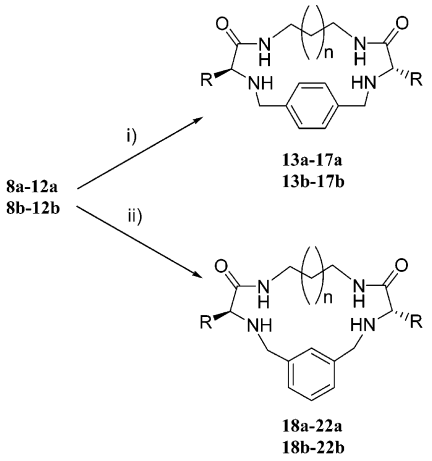


Figure 1. Plot of ^{1}H NMR chemical shift of amide hydrogen atoms of compounds **8b** and **12b** in $CDCl_3$ vs logarithm of concentration (M).

aliphatic spacer increases from ethylenic to butylenic spacers (see the values for **8**−**10**) and remains almost invariable for longer ones (**10**−**12**). These data indicate that intramolecularly hydrogen bonded conformations must be predominant in solution but, according to previous work in this field, they are very unlikely to correspond to folded structures such as **I** (Scheme 3) due to an unfavorable entropy factor.[10] To better understand this behavior the model compounds **24** and **25** were studied (see Scheme 4).

For compound **24** ^{1}H NMR experiments discarded intermolecular association and the chemical shift value for the amide protons (6.2 ppm in $CDCl_3$) shows that hydrogen bonding is not so strong as that found for compounds **8**−**12**. On the other hand, in compound **25** the only intramolecular H-bond interaction that can take place connects the lone pair of the amine group and the amide NH. In this case, the chemical shift of the amide protons appears at 7.2 ppm in $CDCl_3$ and dilution experiments indicate the intramolecular nature of the interaction. Therefore, two types of hydrogen bonds would explain the observed spectra of compounds **8**−**12** in $CDCl_3$ and CD_3CN. The first type would involve the two amide groups and result in a folding in the molecule such as in **I** (Scheme 3). Its importance would decrease as the aliphatic spacer becomes longer. The second one involves the amine lone pair and the amide NH. This one must be present in all of the studied peptidomimetics independently of the spacer size and would explain the chemical shift values for the amide proton resonance in the molecules with long aliphatic spacers. Hence, the values reported in Table 2 can be rationalized if it is assumed that for compounds **8** and **9** both types of intramolecular H-bonding take

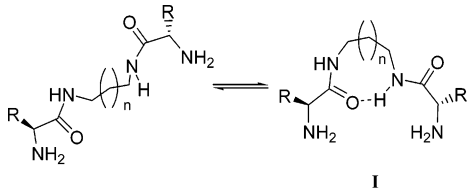
Scheme 2 [a]



a) R = CH_2Ph; n = 0,1,2,4,6
b) R = $CH(CH_3)_2$; n = 0,1,2,4,6

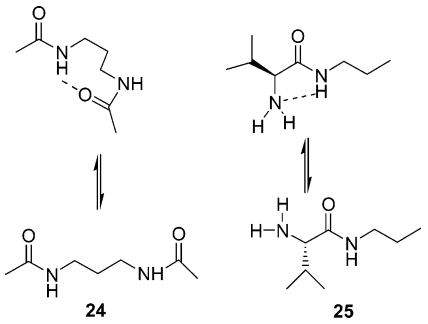
[a] Reagents: (i) *p*-bis(bromomethyl)benzene, CH_3CN, Bu_4NBr, K_2CO_3, reflux 12 h; (ii) *m*-bis(bromomethyl)benzene, CH_3CN, Bu_4NBr, K_2CO_3, reflux 12 h.

Scheme 3



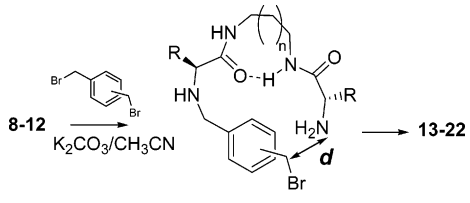
I

Scheme 4



24 **25**

Scheme 5



II

place, whereas for larger compounds **10**−**12** only the last type is present. Consequently, intramolecular hydrogen bonding can be argued as a mean to understand the preorganization that would yield preorganization favorable for the macrocyclization with **8**−**9** but the same case cannot be done for longer molecules **10**−**12**.

Because the key step for the efficiency of the cyclization is the intramolecular reaction of the intermediate species **II** (see Scheme 5) a computational study about the preorganization of such species was performed. It has been shown previously how

Table 3. Average (C−N) Distances between the Primary Amino Group and Bromomethyl Units in Intermediate Compounds (II) (see Scheme 5) Calculated by Molecular Dynamics Simulations[a]

precursor of the intermediate (**II**)	d (Å) in $CHCl_3$	d(Å) in H_2O
8a	10.7	8.2
9a	11.8	9.7
10a	12.5	8.7
11a	13.4	9.0
12a	15.6	8.2
8b	10.7	7.2
9b	13.4	8.7
10b	13.3	7.4
11b	14.7	7.9
12b	15.5	8.3

[a] The molecular dynamics simulations were carried out with MACROMODEL 7.0 (5 ns, AMBER* as force field and GB/SA simulation of solvation).

molecular dynamics simulations can reproduce well the folding induced by intramolecular H-bonding.[11]

The presence of intramolecular H-bonding such as that shown in **II** was studied by analysis of 200 structures sampled during a 5 ns molecular dynamics simulation. It was found, in accordance with related studies described previously,[10a] that hydrogen bonding between the two amido groups in chloroform is only important for the shorter aliphatic species. For the compounds derived from phenylalanine containing spacers with 2, 3, 4, 6, and 8 methylene units the percentage of H-bonded structures found was respectively 25, 10, 7, 1 and 1. Similar results were obtained for the compounds derived from valine. As expected, intramolecular hydrogen bonding was found to be almost negligible when a simulation of water as a solvent was used for the calculations. Additionally, to analyze the ease of the cyclization reaction in these species, the distance between the nitrogen atom of the primary amino group and the carbon atom of the bromomethyl subunit (see distance ***d*** in structure **II**, Scheme 5) was monitored during the MD calculation (see Table 3) both in chloroform and water (acetonitrile parametrization was not available in the molecular mechanics program.)

It can be seen that the average distances were always shorter when a simulation of water was employed as a solvent. The differences are significant, especially for the larger molecules, and a shorter C−N distance should correlate with an increased probability for the intramolecular cyclization reaction. Moreover, the distances distribution was always much narrower for the simulations performed in water where a range of *preferred* distances was found (see as an example Figure 2).

Therefore, the calculations suggest that solvophobic effects seem to be a key issue for the efficiency of macrocyclization and could explain the invariance of the yield with the length of the aliphatic spacer. It can be recalled here that hydrophobic effects are accepted to be the driving force for the protein folding in water which results in *active* conformations.[7b] Solvophobic effects, although not as strong as in water, are expected to be significant in acetonitrile, the solvent used for the studied reactions. As a matter of fact, significant folding of apolar molecules to yield ordered helical structures has been shown

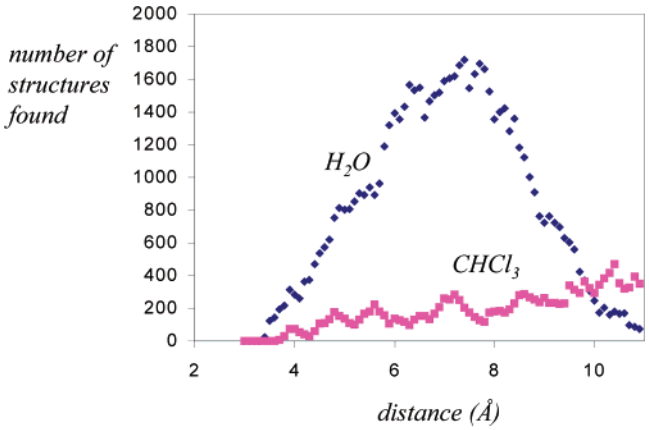


Figure 2. Distribution of distances (see *d* in structure **II**, Scheme 5) found in the molecular dynamics simulations of the intermediate compound derived from **12a** using simulations of chloroform and water as the solvent. (MACROMODEL 7.0, AMBER* as force field and GB/SA simulation of solvation).

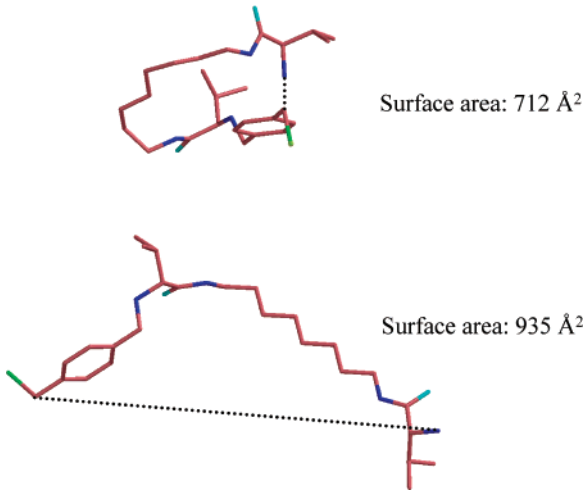


Figure 3. Representative structures found in the MD simulation of intermediate **II** (see Scheme 5) derived from **12b** using simulation of water (up) and chloroform (bottom). (Surface area was calculated with MACROMODEL 7.0 assuming a probe radius of 1.4 Å. The dotted line indicate the atoms whose distance was monitored during the simulation).

to take place in acetonitrile.[12] To illustrate the effect of the solvent in the preorganization, representative molecules from the simulations for the intermediate derived from **12b** in chloroform and in water are shown in Figure 3.

It can be seen that in chloroform the molecule tends to be extended and fully exposed to the solvent. However, in water the molecule tends to fold back and minimize the exposition to the solvent due the presence of hydrophobic subunits.

To get more evidences of the proposed solvent-induced folding, additional experiments were perfomed. First, the reaction to obtain compounds **18a** and **22a** was carried out in dimethylformamide as the solvent. The change of acetonitrile a polar solvent ($\epsilon = 37.5$), that at the same time allows for the presence of fairly strong intramolecular hydrogen bonding interactions, for dimethylformamide, a strongly hydrogen bonding solvent with almost same polarity ($\epsilon = 36.7$), resulted in a significative decrease in reaction yields (due to an important formation of side-products, no starting material was left) both

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for compound **18a** containing a ethylenic spacer (65% yield in acetonitrile, 31% in dimethylformamide) and **22a** containing an octamethylenic spacer (53% yield in acetonitrile, 29% in dimethylformamide). Second, the reaction was performed in tetrahydrofurane, a quite less polar solvent ($\epsilon = 7.6$), where intramolecular hydrogen bonding is expected to be important (the amide proton chemical shift values obtained for compounds **8a** and **12a** in this solvent are comparable to those obtained in chloroform). In this case, the preparation of compounds **18a** and **22a** resulted in poor cyclization yields (<20%). Other experiments using mixtures acetonitrile-water or methanol as solvent resulted in bromide solvolysis as an important side reaction and could not be used to analyze the importance of polarity and hydrogen bonding in the macrocylization. The results in dimethylformamide indicate that the hydrogen-bonding acceptor characteristics of this solvent disfavor the macrocyclization reaction. The strong interaction of the amino and amido groups with this solvent probably disrupts the folded conformations favorable for the cyclization. The chemical shifts of amide protons of compounds **8b** and **12b** in DMF-d_8 were found to be 8.00 and 7.84 respectively, in agreement with a strong hydrogen bonding interaction with this solvent. On the other hand, the low yield for the preparation of **18a** in tetrahydrofurane suggest that hydrogen bonding alone does not preorganize enough the molecule for cyclization. This is supported by the MD simulations in chloroform for the corresponding intermediate **II** (Scheme 5), that shows a poor preorganization as inferred from the distances distribution which was found to be analogous to that shown for **12a** (see Figure 2 and Table 3).

More information regarding the solvophobic contribution to the folding of molecules **13a**−**17a** was obtained by fluorescence studies. It has been shown that variations in fluorescence intensity of different subunits can be used to monitor polarity changes in the environment of protein residues.[13] This prompted us to test the presence of solvophobic interactions by analysis of the intensity of fluorescent emission of 285 nm light (produced after irradiation with 268 nm light) from the phenyl subunits of **13a**−**17a**. As it is shown in Figure 4, when the experiments were carried out in acetonitrile the emission intensity showed a dependence on the length of aliphatic spacer and increased for longer molecules, being noticeable a sharp variation when changing from the ethylenic to the propylenic spacer. This behavior can be ascribed to a less efficient quenching of excited states by the solvent as the molecule becomes more hydrophobic. This should be a consequence of the presence of folded structures that minimize the exposure of hydrophobic units to the solvent (by measurament of NMR relaxation times it was found that unspecific aggregation was not taking place at the concentration used in these experiments). The results measured when a mixture of acetonitrile and water is used as a solvent are also in accordance with a solvophobic folding because in this case the change in emission intensity is even more important. The opposite tendency was obtained when experiments were carried out in chloroform. In this solvent, the decrease of emission intensity with spacer length suggests that the aromatic subunits are, on average, more exposed to the solvent as the aliphatic spacer becomes longer.

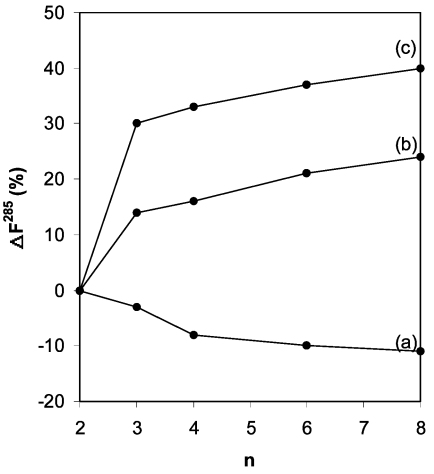

Figure 4. Variation of fluorescence intensity for compounds **13a**−**17a** ("*n*" in the horizontal axis indicates the length of the aliphatic spacer) in chloroform (a), acetonitrile (b) and acetonitrile-water 1:1 (c). The vertical axis values indicate the variation of intensity (percentage) relative to the emission of compound **13a**. Emission was measured at 285 nm after irradiation at 265 nm.

The next stage in the described study was the structural analysis of the of cyclic compounds. Because of the loss of conformational freedom, intramolecular hydrogen bonds are more likely to be found in the cyclic derivatives provided that the size of the macrocycle does not impose strong conformational constraints and the two types of intramolecular H-bond mentioned previously are expected.

The NMR study for the cyclic compounds indicated that the importance of intramolecular hydrogen bonds between the two amido groups cannot be studied properly using as a probe the ^{1}H signals assigned to the amide proton resonance since the two types or intramolecular H-bonds described above affect its chemical shift. Moreover, for the para derivatives aromatic ring shielding effects can be very important. However, the study of the hydrogen atoms corresponding to the methylene attached to the amide nitrogen atom are valuable for those purposes The two nonequivalent geminal protons show increased differences in their chemical shifts as a result of the loss of conformational freedom imposed by the above-mentioned H-bond between amido groups. For example, as can be seen in Figure 5 the signals of *Ha* and *Hb* appear as multiplet in ^{1}H NMR of compound **14b** ($n = 1$). These signals split up into two well separated multiplets for the compound **15b** ($n = 2$). Therefore the presence of an additional carbon in the central spacer eases the conformational constraints of the macrocycle in such a way that amide groups can orient relative to each other in a proper way to yield a stronger intramolecular hydrogen bond becoming more rigid species. For each case the proper assignment of those signals could be confirmed by 2-D NMR experiments.

Assuming that the difference in chemical shift for those protons gives a measure of the amount of intramolecular amide−amide H-bond, the analysis of the graphic in Figure 6 indicates that this interaction is maximum when the spacer is a butylene subunit. For shorter chains the macrocycle is probably too stiff to orient appropriately both amido groups, whereas for longer subunits entropic factors and steric constraints may diminish the stability of this interaction. The analysis of data correspond-

(13) Gibney, B. R., Rabanal, F., Skalicky, J. J., Wand, A. J., Dutton, P. L *J. Am. Chem. Soc.* **1999**, *121*, 4952
(14) (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467. (b) Sheldrick, G. M. SHELX-97: A program for the refinement of crystal structures; University of Göttingen, Germany, 1997.

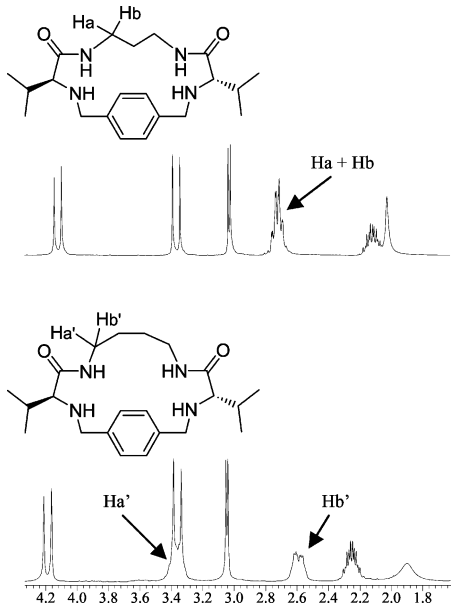

Figure 5. ^{1}H NMR spectra of **14b** (up) and **15b** (down) in $CDCl_3$, 300 MHz.

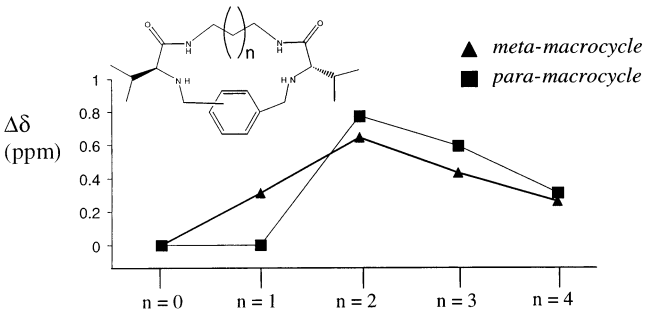

Figure 6. Plot of ^{1}H NMR chemical shift difference found for the geminal protons Ha and Hb (see Figure 5).

ing to molecules with a propylenic spacer reveals, as expected, that meta-macrocycles are more flexible than para-substituted ones as demonstrated by the change in chemical shift differences for the studied geminal protons.

Single-crystals suitable for X-ray analysis were obtained of the compounds **13b** and **18b** by slow diffusion of ether into a solution of the compound in dichloromethane. Their analysis by X-ray diffraction confirmed the structural hypotheses that have been described above. (See Figure 7).

For compound **13b**, the aliphatic spacer and the amide protons are located over the aromatic ring and the carbonyl oxygen atoms are hydrogen bonded with the neighbor molecules in the crystalline packing. Interestingly, one of the amide groups, N-(14), is taking part in a hydrogen bond with the lone pair of N-(17) as described above for the model compound **25**. No other intramolecular hydrogen bond is formed in the crystal presumably due to the constraints imposed by the *para*-substituted spacer. However, for compound **18b**, in addition to different intermolecular hydrogen bonds, three intramolecular ones were found. The first one between the two amido groups, confirming the higher flexibility of the macrocycles with a meta-type spacer, and the other two between the amine lone pairs and the amide hydrogen atoms, again in accordance with the previous discussion.

Conclusions

In conclusion, the present method represents a simple and efficient procedure for the preparation of cyclic peptidomimetics which does not require the use of high dilution techniques or the use of complex synthetic methodologies. The good yields obtained are explained by the existence of a high preorganized intermediate which favors the intramolecular reaction. As evidenced from our experimental results and MD simulations, the folding can be provided by intramolecular H-bonding and solvophobic effects, being the latter important even for the cases were intramolecular H-bonding between amide groups is expected to be present. Therefore, the election of the appropriate solvent is a key issue for the efficiency of the formation of cyclic structures. The best results are obtained in acetonitrile which at the same time provides solvophobic effects and is a weak H-bond acceptor when compared with other polar solvents as DMF. Further work is in progress in order to study the scope of the method and to use this methodology which could be used for the preparation of other structures of interest for catalytic, biomimetic or biological applications.

Experimental Section

General Procedure for the Preparation of N−Hydroxysuccinimide Esters of Amino Acids. Synthesis of 2a. N−Cbz-L-phenylalanine (25.14 g, 84.0 mmol) and N-hidroxysuccinimide (9.67 g, 84.0 mmol) were dissolved in dry THF at 0 °C. Once a clear solution had been obtained, DCC (17.45 g, 84.6 mmol) in anhydrous THF was added in several aliquots and the resulting solution was stirred at 0−5 °C for 3 h. The dicyclohexylurea formed was filtered off and the filtrate was concentrated to dryness. The crude product was recrystallized from 2-propanol to furnish the pure product. Yield (28.47 g, 86%); mp 143−144 °C; $[\alpha]^{25}_D = -11.1°$ ($c = 0.1$, $CHCl_3$); IR (KBr) 3297, 1814, 1785, 1747, 1679, 1541 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.76$ (br s, 4H), 3.20 (dd, 1H, $J = 14.2$, 6.6 Hz), 3.33 (dd, 1H, $J = 14.2$, 5.6 Hz), 5.00−5.13 (m, 3H), 5.39 (d, 1H, $J = 8.6$ Hz), 7.24−7.38 (m, 10H);

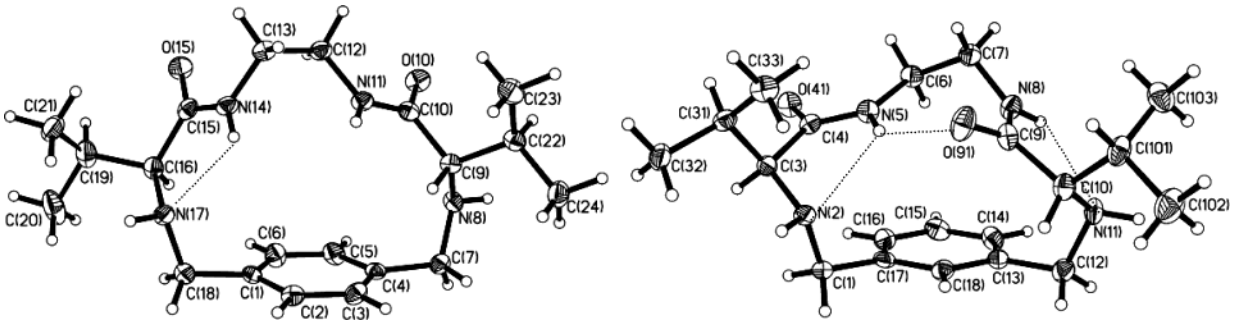

Figure 7. Molecular structure of **13b** (left) and **18b** (right) obtained by X-ray diffraction of single crystals. Dotted lines indicate the intramolecular H-bonds found.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.5, 37.8, 52.9, 67.1, 127.2, 127.9, 128.0, 128.3, 128.5, 129.4, 134.3, 135.7, 155.1, 167.3, 168.6; Anal. Calcd. for $C_{21}H_{20}N_2O_6$: C, 63.6; H, 5.1; N, 7.1. Found: C, 63.5; H, 5.5; N, 7.4.

Synthesis of N−Hidroxysuccinimide Ester of N−Cbz-L-Valine 2b. Yield 87%; mp 119−120 °C; $[\alpha]^{25}_D = -20.1°$ (c = 0.1, $CHCl_3$); IR (KBr) 3360, 1741, 1526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, 6H, J = 7.4 Hz), 1.06 (d, 6H, J = 7.7 Hz), 2.31 (m, 1H), 2.77 (s, 4H), 4.66 (dd, 1H, J = 4.7 Hz), 5.13 (s, 2H), 5.43 (d, 1H, J = 9.5 Hz), 7.28−7.41 (m, 5H);^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 18.7, 25.5, 31.5, 57.4, 67.2, 128.0, 128.1, 128.3, 135.8, 155.6, 167.5, 168.6; Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.6; H, 5.8; N, 7.7. Found: C, 58.1; H, 5.9; N, 8.0.

General Procedure for the Preparation of N−N′-Bis(N−Cbz-L-aminoacyl)diamines. Synthesis of 3a. The N-hydroxysuccinimide ester of N−Cbz-L-phenylalanine (12.00 g, 30.3 mmol) was dissolved in anhydrous DME (150 mL) cooled in an ice bath. Ethylenediamine (0.92 g, 15.3 mmol) dissolved in dry DME (20 mL) was added in several times. The reaction mixture was stirred at room temp for 18 h and then was warmed for 6 h at 40−50 °C. The white solid was filtered off and washed with cold water and cold methanol. Yield (8.79 g, 93%); mp 247−248 °C; IR (KBr) 3310, 3297, 1686, 1666, 1552, 1528 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 40 °C) δ 2.80 (dd, 2H, J = 13.7, 10.1 Hz), 2.99−3.16 (m, 6H), 4.21 (m, 2H), 4.89−5.00 (m, 4H), 7.18−7.31 (m, 22H), 7.90 (br, s 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 40 °C) δ 37.8, 38.4, 56.3, 65.3, 126.1, 127.2, 127.5, 127.9, 128.1, 129.0, 136.9, 137.9, 155.6, 171.2; Anal. Calcd. for $C_{36}H_{38}N_4O_6$: C, 69.4; H, 6.2; N, 9.0. Found: C, 69.3; H, 6.6; N, 8.9.

Synthesis of 4a. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of N−Cbz-phenylalanine (**2a**) and 1,3-diaminopropane. Yield 93%; mp 232−233 °C; IR (KBr) 3298, 1694, 1645, 1537 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 1.47 (m, 2H), 2.78 (dd, 2H, J = 13.4, 10.0 Hz), 2.95−3.07 (m, 6H), 4.20 (m, 2H), 4.95 (s, 4H), 7.18−7.40 (m, 22H), 7.87 (t, 2H, J = 4.8 Hz); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 29.1, 36.3, 37.8, 56.3, 65.3, 126.1, 127.2, 127.5, 127.9, 128.1, 129.0, 136.9, 137.9, 155.5, 170.9; Anal. Calcd. for $C_{37}H_{40}N_4O_6$: C, 69.8; H, 6.3; N, 8.8. Found: C, 69.3; H, 6.6; N, 8.7.

Synthesis of 5a. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-phenylalanine (**2a**) and the 1,4-diaminobutane. Yield 93%; mp 240−241 °C; IR (KBr) 3311, 1690, 1656, 1528 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 50 °C) δ 1.32 (br s, 4H), 2.77 (dd, 2H, J = 13.5, 9.6 Hz), 2.93−3.04 (m, 6H), 4.21 (m, 2H), 4.94 (s, 4H), 7.15−7.33 (m, 22H), 7.79 (t, 2H, J = 5.1 Hz); ^{13}C NMR (75 MHz, $DMSOd_6$, 50 °C) δ 26.3, 37.9, 38.3, 56.2, 65.2, 126.0, 127.1, 127.4, 127.8, 128.0, 128.9, 136.8, 137.8, 155.4, 170.7; Anal. Calcd. for $C_{38}H_{42}N_4O_6$: C, 70.1; H, 6.5; N, 8.6. Found: C, 69.7; H, 6.8; N, 8.9.

Synthesis of 6a. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-phenylalanine (**2a**) and 1,6-diaminohexane. Yield 87%; mp 194−195 °C; IR (KBr) 3306, 1690, 1653, 1536 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 1.17 (bs s, 4H), 1.32 (br s, 4H), 2.74 (dd, 2H, J = 13.4, 10.1 Hz), 2.90−3.07 (m, 6H), 4.19 (m, 2H), 4.93 (s, 4H), 7.18−7.29 (m, 20H), 7.49 (d, 2H, J = 8.6 Hz), 7.96 (br s, 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 26.1, 29.0, 38.0, 38.6, 56.3, 65.3, 126.1, 127.3, 127.5, 127.9, 128.1, 129.1, 137.0, 137.9, 155.6, 170.9; Anal. Calcd. for $C_{40}H_{46}N_4O_6$: C, 70.8; H, 6.8; N, 8.3. Found: C, 71.3; H, 7.1; N, 8.3.

Synthesis of 7a. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-phenylalanine (**2a**) and 1,8-diaminooctane. Yield 97%; mp 202−204 °C; IR (KBr) 3316, 3298, 1687, 1657, 1536 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 1.19 (bs s, 8H), 1.33 (br s, 4H), 2.74 (dd, 2H, J = 13.3, 10.2 Hz), 2.89−3.06 (m, 6H), 4.17 (m, 2H), 4.92 (s, 4H), 7.16−7.31 (m, 20H), 7.50 (d, 2H, J = 8.6 Hz), 8.02 (br s 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 26.3, 28.7, 29.0, 37.9, 38.6, 56.2, 65.2, 126.1, 127.2, 127.5, 127.8, 128.1, 129.0, 136.9, 137.9, 155.5, 170.8; Anal. Calcd. for $C_{42}H_{50}N_4O_6$: C, 71.4; H, 7.1; N, 7.9. Found: C, 71.1; H, 7.4; N, 7.9.

Synthesis of 3b. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-valine (**2b**) and ethylenediamine. Yield 79%; mp 248−249 °C; IR (KBr) 3293, 1691, 1651, 1539 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 0.81 (d, 12H, J = 6.6 Hz), 1.92 (m, 2H), 3.11 (br s, 4H), 3.77 (t, 2H, J = 7.4 Hz), 5.01 (s, 4H), 7.17 (d, 2H, J = 8.4 Hz), 7.33 (br s, 10H), 7.92 (br s, 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 18.4, 19.4, 30.3, 38.4, 60.5, 65.5, 127.6, 127.7, 128.3, 137.1, 156.1, 171.2; Anal. Calcd. for $C_{28}H_{38}N_4O_6$: C, 63.9; H, 7.3; N, 10.6. Found: C, 63.5; H, 7.4; N, 10.5.

Synthesis of 4b. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-valine (**2b**) and 1,3-diaminopropane. Yield 90%; mp 225−226 °C; IR (KBr) 3294, 1691, 1645, 1537 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 0.83 (d, 12H, J = 6.9 Hz), 1.51 (m, 2H), 1.91 (m, 2H), 2.99−3.11 (m, 4H), 3.76 (t, 2H, J = 8.0 Hz), 5.01 (s, 4H), 7.19 (d, 2H, J = 8.4 Hz), 7.28−7.35 (m, 10H), 7.87 (t, 2H, J = 5.0 Hz); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 18.4, 19.4, 29.3, 30.3, 36.4, 60.5, 65.5, 127.6, 128.3, 137.1, 156.0, 171.0; Anal. Calcd. for $C_{29}H_{40}N_4O_6$: C, 64.4; H, 7.5; N, 10.4. Found: C, 64.1; H, 7.4; N, 10.4.

Synthesis of 5b. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-valine (**2b**) and 1,4-diaminobutane. Yield 79%; mp 240−241 °C; IR (KBr) 3294, 1691, 1646, 1537 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 0.81 (d, 12H, J = 6.3 Hz), 1.37 (br s, 4H), 1.90 (m, 2H), 2.99−3.05 (m, 4H), 3.78 (t, 2H, J = 6.9 Hz), 5.01 (s, 4H), 7.14 (d, 2H, J = 8.4 Hz), 7.33 (br s, 10H), 7.86 (br s, 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 18.4, 19.4, 26.7, 30.5, 38.3, 60.5, 65.5, 127.6, 127.7, 128.3, 137.1, 156.0, 170.8; Anal. Calcd. for $C_{30}H_{42}N_4O_6$: C, 65.0; H, 7.6; N, 10.1. Found: C, 65.4; H, 8.0; N, 10.2.

Synthesis of 6b. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-valine (**2b**) and 1,6-diaminohexane. Yield 73%; mp 223−224 °C; IR (KBr) 3292, 1690, 1648, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 0.82 (d, 12H, J = 6.6 Hz), 1.22 (br s, 4H),1.35 (br s, 4H), 1.90 (m, 2H), 2.94−3.09 (m, 4H), 3.77 (t, 2H, J = 9.0 Hz), 5.01 (s, 4H), 7.15 (d, 2H, J = 8.4 Hz), 7.28−7.33 (m, 10H), 7.83 (br s, 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 18.4, 19.3, 26.2, 29.1, 30.4, 38.5, 60.5, 65.4, 127.6, 127.7, 128.3, 137.1, 156.0, 170.8; Anal. Calcd. for $C_{32}H_{46}N_4O_6$: C, 66.0; H, 8.0; N, 9.6. Found: C, 66.0; H, 8.1; N, 9.6.

Synthesis of 7b. This compound was obtained as described above starting from the N-hydroxysuccinimide ester of the N−Cbz-L-valine (**2b**) and 1,8-diaminooctaane. Yield 86%; mp 207−208 °C; IR (KBr) 3297, 1691, 1649, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $DMSOd_6$, 30 °C) δ 0.81 (d, 12H, J = 6.3 Hz), 1.20 (br s, 8H), 1.25 (br s, 4H), 1.89 (m, 2H), 2.95−3.08 (m, 4H), 3.76 (t, 2H, J = 8.0 Hz), 5.00 (s, 4H), 7.13 (d, 2H, J = 8.4 Hz), 7.33 (br s, 10H), 7.81 (br s, 2H); ^{13}C NMR (75 MHz, $DMSOd_6$, 30 °C) δ 18.4, 19.4, 26.4, 28.8, 29.1, 30.4, 38.5, 60.4, 65.4, 127.6, 127.7, 128.3, 137.1, 156.0, 170.8; Anal. Calcd. for $C_{34}H_{50}N_4O_6$: C, 66.9; H, 8.3; N, 9.2. Found: C, 66.8; H, 8.4; N, 9.3.

General Procedure for the Deprotection of N−Cbz Groups. Synthesis of 8a. N,N′-bis(N−Cbz-L-phenylalanyl)-1,2-diaminoethane (**3a**) (8.01 g, 12.9 mmol) were added to HBr/AcOH (33%) (20 mL) and the mixture was stirred at room temp. until CO_2 evolution ceased. At this point, diethyl ether was added to the clear solution, which led to the deposition of a white precipitate. This was filtered off, washed with additional ether and dissolved in distilled water, the resulting solution was extracted with chloroform (30 mL, 3×). Solid NaOH was then added up to a pH value of 12 and the resulting solution was saturated with NaCl and extracted with chloroform (30 mL, 3×). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to obtain a white solid. Yield (3.8 g, 84%); mp 118−119 °C; $[\alpha]_D^{25}$ =

−86.9 ° (c = 0.1, $CHCl_3$); IR (KBr) 3358, 3299, 1655, 1529 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 4H), 2.66 (dd, 2H, J = 13.7, 9.3 Hz), 3.19 (dd, 2H, J = 13.7, 4.2 Hz), 3.32 (m, 4H), 3.55 (dd, 2H, J = 9.2, 4.3 Hz), 7.17−7.30 (m, 10H), 7.55 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1, 40.9, 56.2, 126.3, 128.2, 128.8, 137.4, 174.7; ESI-MS m/z = 355.1 (M + H^+), 377.1 (M + Na^+); Anal. Calcd. for $C_{20}H_{26}N_4O_2$: C, 67.8; H, 7.4; N, 15.8. Found: C, 67.9; H, 7.8; N, 16.0.

Synthesis of 9a. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-phenylalanyl)-1,3-diaminopropane (**4a**). Yield 91%; mp 121−122 °C; $[\alpha]_D^{25}$ = −85.3° (c = 0.1, $CHCl_3$); IR (KBr) 3345, 3302, 1651, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 4H), 1.57 (m, 2H), 2.69 (dd, 2H, J = 13.7, 9.3 Hz), 3.13−3.24 (m, 6H), 3.57 (dd, 2H, J = 9.0, 3.9 Hz), 7.18−7.31 (m, 10H), 7.56 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 29.5, 35.5, 41.0, 56.5, 126.5, 128.4, 129.0, 137.6, 174.4; ESI-MS m/z = 369.1 (M + H^+), 391.1 (M + Na^+), 407.1 (M + K^+); Anal. Calcd. for $C_{21}H_{28}N_4O_2$: C, 68.4; H, 7.7; N, 15.2. Found: C, 68.5; H, 8.0; N, 15.4.

Synthesis of 10a. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-phenylalanyl)-1,4-diaminobutane (**5a**). Yield 90%; mp 134−135 °C; $[\alpha]_D^{25}$ = −86.1° (c = 0.1, $CHCl_3$); IR (KBr) 3358, 3303, 1648, 1534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 4H), 1.26 (m, 4H), 2.47 (dd, 2H, J = 13.7, 9.3 Hz), 3.02 (m, 6H), 3.36 (dd, 2H, J = 9.2, 4.0 Hz), 6.98−7.16 (m, 10H), 7.30 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 38.6, 41.0, 56.4, 126.6, 128.5, 129.1, 137.7, 173.9; ESI-MS m/z = 383.0 (M + H^+), 405.0 (M + Na^+), 421.0 (M + K^+); Anal. Calcd. for $C_{22}H_{30}N_4O_2$: C, 69.1; H, 7.9; N, 14.7. Found: C, 69.2; H, 8.1; N, 14.9.

Synthesis of 11a. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-phenylalanyl)-1,6-diaminohexane (**6a**). Yield 88%; mp 131−132 °C; $[\alpha]_D^{25}$ = −80.4° (c = 0.1, $CHCl_3$); IR (KBr) 3365, 3289, 1650, 1628, 1547, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27−1.48 (m, 12H), 2.66 (dd, 2H, J = 13.7, 9.3 Hz), 3.18−3.26 (m, 6H), 3.56 (dd, 2H, J = 9.3, 4.2 Hz), 7.18−7.32 (m, 12H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 26.3, 29.4, 38.8, 41.0, 56.4, 126.6, 128.5, 129.1, 137.8, 173.9; ESI-MS m/z = 411.1 (M + H^+) 433.1 (M + Na^+), 206.2 (M + 2H^+); Anal. Calcd. for $C_{24}H_{34}N_4O_2$: C, 70.2; H, 8.3; N, 13.7. Found: C, 70.5; H, 8.2; N, 13.8.

Synthesis of 12a. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-phenylalanyl)-1,8-diaminooctane (**7a**). Yield 92%; mp 114−115 °C; $[\alpha]_D^{25}$ = −70.1° (c =0.1, $CHCl_3$); IR (KBr) 3309, 1643, 1535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (br s, 12H), 1.45 (m, 4H), 2.67 (dd, 2H, J = 13.7, 9.3 Hz), 3.19−3.29 (m, 6H), 3.58 (dd, 2H, J = 9.4, 4.0 Hz), 7.18−7.33 (m, 12H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 26.9, 29.2, 29.6, 39.0, 41.1, 56.5, 126.6, 128.5,129.2, 137.9, 173.8; ESI-MS m/z = 439.1 (M + H^+), 461.0 (M + Na^+), 219.9 (M + 2H^+); Anal. Calcd. for $C_{26}H_{38}N_4O_2$: C, 71.2; H, 8.7; N, 12.8. Found: C, 71.3; H, 8.6; N, 12.7.

Synthesis of 8b. This compound was obtained as described above starting N,N′-bis(N−Cbz-L-valinyl)-1,2-diaminoethane (**3b**). Yield 91%; mp 136−137 °C; $[\alpha]_D^{25}$ = −66.1° (c =0.01, $CHCl_3$); IR (KBr) 3289, 1643, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, 6H, J = 7.1 Hz), 0.90 (d, 6H, J = 6.8 Hz), 1.26 (s, 4H), 2.15 (m, 2H), 3.13 (d, 2H, J = 4.2 Hz), 3.33 (m, 4H), 7.69 (br s, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 16.1, 19.6, 30.9, 39.4, 60.1, 175.2; ESI-MS m/z = 259.0 (M + H^+), 281.1 (M + Na^+); Anal. Calcd. for $C_{12}H_{26}N_4O_2$: C, 55.8; H, 10.1; N, 21.7. Found: C, 55.2; H, 10.1; N, 21.5.

Synthesis of 9b. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-valinyl)-1,3-diaminopropane (**4b**). Yield 89%; mp 100−101 °C; $[\alpha]_D^{25}$ = −54.5° (c = 0.1, $CHCl_3$); IR (KBr) 3298, 1651, 1538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (d, 6H, J = 7.0 Hz), 0.80 (d, 6H, J = 6.8 Hz), 1.23 (s, 4H), 1.45 (m, 2H), 2.04 (m, 2H), 3.01 (d, 2H, J = 4.2 Hz), 3.11 (m, 4H), 7.58 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 15.8, 19.2, 29.3, 30.6, 35.1, 59.8, 174.3; ESI-MS m/z = 273.1 (M + H^+), 295.1 (M + Na^+); Anal. Calcd for $C_{13}H_{28}N_4O_2$: C, 57.3; H, 10.4; N, 20.6. Found: C, 57.2; H, 10.5; N, 20.6.

Synthesis of 10b. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-valinyl)-1,4-diaminobutane (**5b**). Yield 95%; mp 109−110 °C; $[\alpha]_D^{25}$ = −48.4° (c = 0.1, $CHCl_3$); IR (KBr) 3294, 1641, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (d, 6H, J = 6.8 Hz), 0.85 (d, 6H, J = 7.1 Hz), 1.39−1.43 (m, 8H), 2.08 (m, 2H), 3.05 (d, 2H, J = 4.2 Hz), 3.14 (m, 4H), 7.27 (br s, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 16.2, 19.5, 27.0, 30.9, 38.4, 60.2, 174.1; ESI-MS m/z = 143.2 (M + 2H^+); Anal. Calcd. for $C_{14}H_{30}N_4O_2$: C, 58.7; H, 10.6; N, 19.6. Found: C, 58.9; H, 10.8; N 19.7.

Synthesis of 11b. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-valinyl)-1,6-diaminohexane (**6b**). Yield 92%; mp 101−102 °C; $[\alpha]_D^{25}$ = −45.6° (c = 0.1, $CHCl_3$); IR (KBr) 3366, 3286, 1640,1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, 6H, J = 7.1 Hz), 0.84 (d, 6H, J = 6.8 Hz), 1.20 (br s, 8H), 1.37 (m, 4H), 2.11 (m, 2H), 3.03−3.12 (m, 6H), 7.31 (br s, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 15.9, 19.5, 26.2, 29.3, 30.7, 38.4, 59.9, 173.9; ESI-MS m/z = 315.3 (M + H^+); Anal. Calcd. for $C_{16}H_{34}N_4O_2$: C, 61.1; H, 10.9; N, 17.8. Found: C, 61.3; H, 11.2; N, 17.9.

Synthesis of 12b. This compound was obtained as described above starting from N,N′-bis(N−Cbz-L-valinyl)-1,8-diaminooctane (**7b**). Yield 94%; mp 103−104 °C; $[\alpha]_D^{25}$ = −43.7° (c = 0.1, $CHCl_3$); IR (KBr) 3285, 1645, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, 6H, J = 6.8 Hz), 0.89 (d, 6H, J = 7.1 Hz), 1.21 (s, 8H), 1.38−1.43 (m, 8H), 2.17 (m, 2H), 3.09−3.18 (m, 6H), 7.30 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 19.6, 26.7, 29.0, 29.5, 30.7, 38.8, 60.0, 174.0; ESI-MS m/z = 172.2 (M + 2H^+); Anal. Calcd. for $C_{18}H_{38}N_4O_2$: C, 63.1; H, 11.2; N, 16.4. Found: C, 63.3; H, 11.6; N, 16.3.

General Procedure for the Preparation of the para-Macrocycles. Synthesis of 13a (Method a). Compound **8a** (0.507 g, 1.43 mmol), anhydrous K_2CO_3 (1.97 g, 14.3 mmol) and 1,4-bis(bromomethyl)-benzene (0.377 g, 1.43 mmol) were placed in a flask containing dry CH_3CN (175 mL) and the mixture was refluxed for 24 h under argon atmosphere. The reaction was filtered and the solvent evaporated under reduced pressure. The product was purified by silica flash chromatography using MeOH/CH_2Cl_2 (1:40) as the eluent to yield a white solid (**13a**). Yield (0.360 g, 55%); mp 77−80 °C; $[\alpha]_D^{25}$ = −32.5° (c = 0.01, $CHCl_3$); IR (KBr) 3376, 1655, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (br s, 2H), 2.62 (dd, 2H, J = 13.4, 9.0 Hz), 3.03 (m, 4H), 3.10 (d, 2H, J = 13.1 Hz), 3.21−3.32 (m, 4H), 3.82 (d, 2H, J = 13.2 Hz), 6.52 (br s, 2H), 7.03 (dd, 2H, J = 7.9, 1.7 Hz), 7.13 (dd, 2H, J = 7.5, 1.5 Hz), 7.17−7.30 (m, 10H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 39.1, 39.5, 54.4, 64.4, 126.4, 128.3, 128.5, 128.6, 129.0, 137.1, 139.0, 174.5; ESI-MS m/z = 457.7 (M + H^+); Anal. Calcd. for $C_{28}H_{32}N_4O_2$•1/2 H_2O C, 72.2; H, 7.1; N, 12.0. Found: C, 72.3; H, 7.5; N, 11.7.

Synthesis of 13a. Method b. Compound **8a** (0.521 g, 1.47 mmol), anhydrous K_2CO_3 (2.041 g, 14.8 mmol), tetrabutylammonium bromide (0.245 g, 0.76 mmol) and 1,4-bis(bromomethyl)benzene (0.388 g, 1.47 mmol) were placed in a flask containing dry CH_3CN (175 mL) and the mixture was refluxed for 12 h under argon atmosphere. The reaction was filtered and the solvent evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ (50 mL) and extracted with aqueous NaOH 0.01M (50 mL, 3×). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by silica flash chromatography using MeOH/CH_2Cl_2 (1:40) as the eluent to give 0.436 of **13a** as a white solid. Yield 65%; mp 77−80 °C; $[\alpha]_D^{25}$ = −32.5° (c = 0.01, $CHCl_3$); IR (KBr) 3376, 1655, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (br s, 2H), 2.62 (dd, 2H, J = 13.4, 9.0 Hz), 3.03 (m, 4H), 3.10 (d, 2H, J = 13.1 Hz), 3.21−3.32 (m, 4H), 3.82 (d, 2H, J = 13.2 Hz), 6.52 (br s, 2H), 7.03 (dd, 2H, J = 7.9, 1.7 Hz), 7.13 (dd, 2H, J = 7.5, 1.5 Hz), 7.17−7.30 (m, 10H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 39.1, 39.5, 54.4, 64.4, 126.4, 128.3, 128.5, 128.6, 129.0, 137.1, 139.0, 174.5; ESI-MS m/z = 457.7 (M + H^+); Anal. Calcd. for $C_{28}H_{32}N_4O_2$•1/2 H_2O C, 72.2; H, 7.1; N, 12.0. Found: C, 72.3; H, 7.5; N, 11.7.

Synthesis of 14a (Method a). This compound was obtained as described above starting from **9a**. Yield 61%; mp 212−213 °C; $[\alpha]_D^{25}$

= −58.5° (c = 0.01, $CHCl_3$); IR (KBr) 3348, 3302, 1648, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (m, 2H), 2.06 (br s, 2H), 2.55 (dd, 2H, J = 14.0, 10.6 Hz), 2.75 (m, 4H), 3.18 (d, 2H, J = 14.2 Hz), 3.27 (dd, 2H, J = 14.2, 3.4 Hz), 3.44 (dd, 2H, J = 10.5, 3.6 Hz), 3.88 (d, 2H, J = 14.2 Hz), 6.64 (t, 2H, J = 5.5 Hz), 7.09−7.36 (m, 14H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 28.4, 36.1, 40.1, 54.5, 66.9, 126.8, 128.5, 128.7, 128.8, 129.0, 137.2, 139.4, 173.9; ESI-MS m/z = 471.2 (M + H^+), 509.2 (M + K^+); Anal. Calcd. for $C_{29}H_{34}N_4O_2$: C, 74.0; H, 7.3; N, 11.9. Found: C, 73.7; H, 7.7; N, 11.5.

Synthesis of 14a (Method b). Yield 58%.

Synthesis of 15a (Method a). This compound was obtained as described above starting from **10a**. Yield 66%; mp 149−151 °C; $[\alpha]_D^{25}$ = −83.9° (c = 0.01, $CHCl_3$); IR (KBr) 3328, 3308, 1651, 1637, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 4H), 1.96 (br s, 2H), 2.61 (m, 4H), 3.20 (d, 2H, J = 14.7 Hz), 3.27−3.46 (m, 6H), 3.90 (d, 2H, J = 14.7 Hz), 7.01 (dd, 2H, J = 7.7, 4.0 Hz), 7.14−7.35 (m, 14H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 25.9, 38.4, 39.4, 52.8, 65.3, 126.7, 127.7, 128.6, 128.7, 137.4, 139.3, 173.2; ESI-MS m/z = 485.5 (M + H^+), 507.5 (M + Na^+); Anal. Calcd. for $C_{30}H_{36}N_4O_2$: C, 74.4; H, 7.5; N, 11.6. Found: C, 74.2; H, 7.8; N, 11.3.

Synthesis of 16a (Method a). This compound was obtained as described above starting from **11a**. Yield 65%; mp 121−123 °C; $[\alpha]_D^{25}$ = −100.4° (c = 0.01, $CHCl_3$); IR (KBr) 3310, 1661, 1646, 1538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (m, 8H), 1.86 (br s, 2H), 2.69 (dd, 2H, J = 13.9, 10.0 Hz), 2.79 (m, 2H), 3.28−3.43 (m, 8H), 3.81 (d, 2H, J = 14.4 Hz), 7.17−7.35 (m, 16H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 26.3, 28.9, 38.3, 39.2, 52.5, 64.5, 126.6, 127.3, 128.5, 128.7, 137.3, 138.5, 173.0; ESI-MS m/z = 513.5 (M + H^+); Anal. Calcd. for $C_{32}H_{40}N_4O_2$: C, 75.0; H, 7.9; N, 10.9. Found: C, 74.6; H, 8.2; N, 10.5.

Synthesis of 17a (Method a). This compound was obtained as described above starting from (**12a**). Yield 52%; mp 182−184 °C; $[\alpha]_D^{25}$ = −103.8° (c = 0.01, $CHCl_3$); IR (KBr) 3304, 1644, 1544 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (br, s 8H), 1.42 (m, 4H), 1.79 (br, s 2H), 2.77 (dd, 2H, J = 13.9, 9.3 Hz), 3.06 (m, 2H), 3.28 (dd, 2H, J = 13.8, 3.8 Hz), 3.34−3.48 (m, 6H), 3.69 (d, 2H, J = 13.4 Hz), 7.11−7.34 (m, 14H), 7.43 (t, 2H, J = 5.4 Hz); ^{13}C NMR (75 MHz,$CDCl_3$) δ 26.5, 29.0, 29.3, 38.1, 38.7, 52.1, 63.4, 126.6, 127.6, 128.5, 128.8, 137.2, 138.3, 172.8; ESI-MS m/z = 541.6 (M + H^+), 575.7 (M + Cl^-); Anal. Calc for $C_{34}H_{44}N_4O_2$: C, 75.5; H, 8.2; N, 10.4;. Found: C, 75.9; H, 8.4; N, 10.2.

Synthesis of 13b (Method a). This compound was obtained as described above starting from **8b**. Yield 49%; mp 182−183 °C; $[\alpha]_D^{25}$ = 26.0° (c = 0.01, $CHCl_3$); IR (KBr) 3340, 3325, 3308, 1661, 1650, 1631, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, 6H, J = 7.1 Hz), 1.03 (d, 6H, J = 7.1 Hz), 1.94 (s, 2H), 2.40 (m, 2H), 2.94 (d, 2H, J = 3.7 Hz), 3.11 (m, 4H), 3.41 (d, 2H, J = 12.9 Hz), 4.13 (d, 2H, J = 12.9 Hz), 6.64 (br s, 2H), 7.14 (dd, 2H, J = 7.8, 1.7 Hz), 7.23 (dd, 2H, J = 7.7, 1.6 Hz); ^{13}C NMR (75 MHz,$CDCl_3$) δ 16.6, 19.8, 31.1, 39.3, 55.5, 68.6, 129.1, 129.4, 139.6, 175.1; ESI-MS m/z = 361.2 (M + H^+), 395.1 (M + Cl^-); Anal. Calcd. for $C_{20}H_{32}N_4O_2$: C, 66.6; H, 9.0; N, 15.5. Found: C,66.8; H, 8.8; N,15.6.

Synthesis of 14b (Method a). This compound was obtained as described above starting from **9b**. Yield 61%; mp 223−224 °C; $[\alpha]_D^{25}$ = 16.1° (c = 0.01, $CHCl_3$); IR (KBr) 3345, 3320, 3302, 1662, 1649, 1637, 1544, 1527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 6H, J = 7.1 Hz), 1.01 (d, 6H, J = 7.1 Hz), 1.16 (m, 2H), 2.03 (s, 2H), 2.12 (m, 2H), 2.72 (m, 4H), 3.03 (d, 2H, J = 4.2 Hz), 3.37 (d, 2H, J = 13.9 Hz), 4.12 (d, 2H, J = 13.7 Hz), 6.67 (m, 2H), 7.17 (br s, 4H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.6, 19.8, 31.4, 36.1, 55.2, 71.4, 128.9, 139.6, 173.7; ESI-MS m/z = 375.7 (M + H^+); Anal. Calcd. for $C_{21}H_{34}N_4O_2$: C, 67.4; H, 9.2; N, 15.0. Found: C, 67.5; H, 9.0; N, 15.0.

Synthesis of 15b (Method a). This compound was obtained as described above starting from **10b**. Yield 45%; mp 185−186 °C; $[\alpha]_D^{25}$ = 11.4° (c = 0.01, $CHCl_3$); IR (KBr) 3301, 1636, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 6H, J = 6.5 Hz), 0.92 (m, 4H), 1.04 (d, 6H, J = 7.1 Hz), 1.88 (br s, 2H), 2.25 (m, 2H), 2.59 (m, 2H), 3.04 (d, 2H, J = 3.9 Hz), 3.34−3.39 (m, 4H), 4.19 (d, 2H, J = 14.6 Hz), 7.04 (m, 2H), 7.21 (s, 4H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.2, 19.9, 26.1, 31.1, 38.3, 53.7, 69.7, 128.0, 139.6, 173.2; ESI-MS m/z = 389.5 (M + H^+), 423.3 (M + Cl^-); Anal. Calcd. for $C_{22}H_{36}N_4O_2$: C, 68.0; H, 9.3; N, 14.4. Found: C, 68.1; H, 9.2; N, 14.3.

Synthesis of 15b (Method b). Yield 69%.

Synthesis of 16b (Method a). This compound was obtained as described above starting from **11b**. Yield 52%; mp 216−217 °C; $[\alpha]_D^{25}$ = −14.1° (c = 0.01, $CHCl_3$); IR (KBr) 3303, 1633, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, J = 7.1 Hz), 0.94−1.16 (m, 14H), 1.75 (s, 2H), 2.18 (m, 2H), 2.73 (m, 2H), 2.98 (d, 2H, J = 3.9 Hz), 3.32 (m, 2H), 3.47 (d, 2H, J = 14.4 Hz), 4.04 (d, 2H, J = 14.2 Hz), 7.14 (m, 2H), 7.23 (s, 4H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.4, 19.8, 26.5, 29.2, 31.1, 38.3, 53.6, 69.1, 127.5, 138.9, 173.1; ESI-MS m/z = 417.5 (M + H^+), 451.4 (M + Cl^-); Anal. Calcd. for $C_{24}H_{40}N_4O_2$: C, 69.2; H, 9.7; N, 13.5. Found: C, 69.4; H, 9.6; N,13.4.

Synthesis of 17b (Method a). This compound was obtained as described above starting from **12b**. Yield 55%; mp 212−214 °C; $[\alpha]_D^{25}$ = −27.1° (c = 0.01, $CHCl_3$); IR (KBr) 3319, 1628, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, J = 6.8 Hz), 1.04 (d, 6H, J = 6.8 Hz), 1.26 (br s, 8H), 1.45 (m, 4H), 1.62 (br s, 2H), 2.22 (m, 2H), 3.01 (d, 2H, J = 4.2 Hz), 3.09 (m, 2H), 3.41 (m, 2H), 3.57 (d, 2H, J = 13.4 Hz), 3.91 (d, 2H, J = 13.2 Hz), 7.28 (s, 4H), 7.46 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 17.5, 19.8, 26.8, 29.3, 29.5, 31.2, 38.1, 53.4, 68.4, 127.8, 138.8, 173.0 ESI-MS m/z = 445.6 (M + H^+),479.5 (M + Cl^-); Anal. Calcd. for $C_{26}H_{44}N_4O_2$: C, 70.2; H, 10.0; N, 12.6. Found: C, 70.6; H, 10.0; N, 12.2.

General Procedure for the Preparation of the meta-Macrocycles. Synthesis of 18a (Method b). Compound **8a** (0.546 g, 1.54 mmol), anhydrous K_2CO_3 (2.13 g, 15.41 mmol), tetrabutylammonium bromide (0.260 g, 0.81 mmol) and 1,3-bis(bromomethyl)benzene (0.406 g, 1.54 mmol) were placed in a flask containing dry CH_3CN (175 mL) and the mixture was refluxed for 12 h under argon atmosphere. The reaction was filtered and the solvent evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ (50 mL) and extracted with aqueous NaOH 0.01 M (50 mL, 3×). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by silica flash chromatography using MeOH/CH_2Cl_2 (1:40) as the eluent to give a white solid (**18a**)**.** Yield (0.445 g, 63%); mp 157−158 °C; $[\alpha]_D^{25}$ = −80.1° (c = 0.01, $CHCl_3$); IR (KBr) 3328, 3302, 1648, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (br s, 2H), 2.75 (dd, 2H, J = 13.9, 9.5 Hz), 3.12−3.28 (m, 6H), 3.33 (d, 2H, J = 13.2 Hz), 3.42 (dd, 2H, J = 9.4, 3.8 Hz), 3.82 (d, 2H, J = 13.4 Hz), 6.97 (d, 2H, J = 7.6 Hz), 7.16−7.36 (m, 12H), 7.42 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 39.0, 53.7, 64.5, 126.8, 127.3, 128.4, 128.5, 128.6, 128.9, 137.2, 139.9, 174.4; ESI-MS m/z = 457.5 (M + H^+), 479.4 (M + Na^+); Anal. Calcd. for $C_{28}H_{32}N_4O_2$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.8; H, 7.1; N, 12.1.

Synthesis of 19a (Method b). This compound was obtained as described above starting from **9a**. Yield 53%; mp 197−199 °C; $[\alpha]_D^{25}$ = −67.3° (c = 0.01, $CHCl_3$); IR (KBr) 3325, 3306, 1629, 1545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (m, 2H), 2.16 (br s, 2H), 2.84 (dd, 2H, J = 13.9, 8.8 Hz), 3.06−3.32 (m, 6H), 3.46 (m, 4H), 3.82 (d, 2H, J = 13.9 Hz), 6.99 (d, 2H, J = 7.3 Hz), 7.17−7.34 (m, 12H), 7.43 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 36.7, 38.5, 52.4, 63.5, 126.8, 126.8, 127.2, 128.5, 128.6, 129.0, 137.1, 140.0, 173.6; ESI-MS m/z = 471.6 (M + H^+), 236.4 (M + $2H^+$); Anal. Calcd. for $C_{29}H_{34}N_4O_2$: C, 74.0; H, 7.3; N, 11.9. Found: C, 73.9; H, 7.3; N, 11.6.

Synthesis of 20a (Method b). This compound was obtained as described above starting from **10a**. Yield 63%; mp 211−213 °C; $[\alpha]_D^{25}$ = −151.5° (c = 0.01, $CHCl_3$); IR (KBr) 3329, 3309, 1650, 1638, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (br s, 4H), 1.64 (br s, 2H), 2.70 (dd, 2H, J = 13.9, 9.8 Hz), 2.96 (m, 2H), 3.26 (dd, 2H, J = 13.9, 3.7 Hz), 3.40−3.45 (m, 4H), 3.57−3.69 (m, 4H), 6.94 (d, 2H, J = 7.6 Hz), 7.14−7.33 (m, 12H), 7.44 (dd, 2H, J = 7.3, 2.7 Hz); ^{13}C NMR (75 MHz,$CDCl_3$) δ 26.8, 38.2, 39.0, 52.8, 64.0, 126.6, 126.8, 127.9,

128.5, 128.6, 128.8, 137.2, 139.9, 173.2; ESI-MS m/z = 485.7 (M + H^+), 243.4 (M + $2H^+$); Anal. Calcd. for $C_{30}H_{36}N_4O_2$: C, 74.4; H, 7.5; N, 11.6. Found: C, 74.2; H, 7.4; N, 11.2.

Synthesis of 21a (Method b). This compound was obtained as described above starting from **11a**. Yield 67%; mp 200−202 °C; $[\alpha]_D^{25}$ = −134.6° (c = 0.01, $CHCl_3$); IR (KBr) ν 3312, 1635, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35−1.57 (m, 10H), 2.68 (dd, 2H, J = 13.9, 10.0 Hz), 3.04 (m, 2H), 3.28 (dd, 2H, J = 13.9, 3.4 Hz), 3.42 (dd, 2H, J = 9.9, 3.5 Hz), 3.50−3.61 (m, 6H), 6.89 (d, 2H, J = 7.6 Hz), 7.14−7.36 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 29.4, 38.0, 39.1, 52.9, 64.0, 126.4, 126.7, 127.4, 128.5, 128.6, 128.7, 137.1, 139.4, 172.8; ESI-MS m/z = 513.6 (M + H^+); Anal. Calcd. for $C_{32}H_{40}N_4O_2$: C, 75.0; H, 7.9; N, 10.9. Found: C, 74.8; H, 7.9; N, 10.6.

Synthesis of 22a (Method b). This compound was obtained as described above starting from **12a**. Yield 55%; mp 207−208 °C; $[\alpha]_D^{25}$ = −100.4° (c = 0.01, $CHCl_3$); IR (KBr) 3347, 3280, 1650, 1528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (br s, 4H), 1.43−1.66 (m, 10H), 2.69 (dd, 2H, J = 13.67, 9.76 Hz), 3.09 (m, 2H), 3.27 (dd, 2H, J = 13.92, 3.18 Hz), 3.36 (dd, 2H, J = 9.77, 3.67 Hz), 3.45−6.65 (m, 6H), 6.72 (d, 2H, J = 7.81 Hz), 7.07−7.34 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.45, 29.16, 29.27, 38.36, 39.34, 52.65, 63.54, 126.08, 126.77, 127.48, 128.62, 128.93, 137.33, 139.24, 172.96; ESI-MS m/z = 541.5 (M + H^+), 563.5 (M + Na^+), 579.5 (M + K^+); Anal. Calcd. for $C_{34}H_{44}N_4O_2$: C, 75.5; H, 8.2; N, 10.4. Found: C, 75.0; H, 8.6; N, 10.4.

Synthesis of 18b (Method b). This compound was obtained as described above starting from **8b**. Yield 64%; mp 156−157 °C; $[\alpha]_D^{25}$ = −27.9° (c = 0.01, $CHCl_3$); IR (KBr) 3314, 1650, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 6H, J = 6.8 Hz), 0.97 (d, 6H, J = 6.8 Hz), 1.83 (br s, 2H), 2.12 (m, 2H), 2.97 (d, 2H, J = 4.2 Hz), 3.07 (m, 4H), 3.45 (d, 2H, J = 13.2 Hz), 4.03 (d, 2H, J = 13.2 Hz), 7.02 (d, 2H, J = 7.3 Hz), 7.17 (t, 1H, J = 7.1 Hz), 7.27 (s, 1H), 7.32 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.7, 31.3, 39.0, 54.8, 69.2, 127.2, 128.2, 128.7, 140.2, 174.5; ESI-MS m/z = 361.4 (M + H^+); Anal. Calcd. for $C_{20}H_{32}N_4O_2$: C, 66.6; H, 9.0; N, 15.5. Found: C, 66.4; H, 9.5; N, 15.2.

Synthesis of 19b (Method b). This compound was obtained as described above starting from **9b**. Yield 56%; mp 225−226 °C; $[\alpha]_D^{25}$ = 22.2° (c = 0.01, $CHCl_3$); IR (KBr) ν 3343, 3313, 1636, 1545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, J = 6.8 Hz), 0.97 (d, 6H, J = 7.1 Hz), 1.53 (m, 2H), 1.85 (br s, 2H), 2.09 (m, 2H), 2.93−3.02 (m, 4H), 3.31 (m, 2H), 3.44 (d, 2H, J = 13.4 Hz), 3.99 (d, 2H, J = 13.7 Hz), 7.06 (d, 2H, J = 8.1 Hz), 7.20 (t, 1H, J = 6.8 Hz), 7.27 (s, 1H), 7.38 (t, 2H, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.6, 28.6, 31.2, 35.5, 53.7, 68.8, 126.8, 127.8, 128.5, 140.4, 173.6; ESI-MS m/z = 375.5 (M + H^+); Anal. Calcd. for $C_{21}H_{34}N_4O_2$: C, 67.4; H, 9.2; N, 15.0. Found: C, 67.2; H, 9.4; N, 15.0.

Synthesis of 20b (Method b). This compound was obtained as described above starting from **10b**. Yield 65%; mp 237−238 °C; $[\alpha]_D^{25}$ = −94.3° (c = 0.01, $CHCl_3$); IR (KBr) 3301, 1636, 1543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, J = 6.8 Hz), 1.02 (d, 6H, J = 6.8 Hz), 1.57 (br s, 6H), 2.15 (m, 2H), 2.95−3.04 (m, 4H), 3.51−3.64 (m, 4H), 3.88 (d, 2H, J = 12.9 Hz), 7.15 (d, 2H, J = 6.8 Hz), 7.28 (t, 1H, J = 6.8 Hz), 7.39 (s, 1H), 7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.7, 26.9, 31.1, 38.1, 53.9, 68.8, 126.7 128.6, 128.6, 140.3 173.3; ESI-MS m/z = 389.5 (M + H^+), 423.5 (M + Cl^-); Anal. Calcd. for $C_{22}H_{36}N_4O_2$: C, 68.0; H, 9.3; N, 14.4. Found: C, 68.5; H, 9.5; N, 14.4.

Synthesis of 21b (Method b). This compound was obtained as described above starting from **11b**. Yield 60%; mp 240−242 °C; $[\alpha]_D^{25}$ = −60.8° (c = 0.01, $CHCl_3$); IR (KBr) 3305, 1632, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 6H, J = 6.8 Hz), 1.00 (d, 6H, J = 7.1 Hz), 1.40−1.54 (m, 10H), 2.12 (m, 2H), 3.00−3.10 (m, 4H), 3.52 (m, 2H), 3.59 (d, 2H, J = 12.5 Hz), 3.76 (d, 2H, J = 12.5 Hz), 7.18−7.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 19.7, 26.7, 29.7, 31.3, 37.9, 54.0, 68.9, 126.9, 128.2, 128.8, 140.0, 172.9; ESI-MS m/z = 417.5 (M + H^+), 439.5 (M + Na^+), 453.4 (M+ HCl + H^+); Anal. Calcd. for $C_{24}H_{40}N_4O_2$: C, 69.2; H, 9.7; N, 13.5. Found: C, 69.3; H, 10.0; N, 13.3.

Synthesis of 22b (Method b). This compound was obtained as described above starting from **12b**. Yield 65%; mp 222−223 ° C; $[\alpha]_D^{25}$ = −47.3 ° (c 0.01, $CHCl_3$); IR (KBr) 3322, 3297, 1628, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, J = 6.8 Hz), 1.00 (d, 6H, J = 7.1 Hz), 1.31−1.55 (m, 14H), 2.15 (m, 2H), 2.98 (d, 2H, J = 4.4 Hz), 3.14 (m, 2H), 3.41 (m, 2H), 3.72 (s, 4H), 7.19−7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.7, 26.5, 29.2, 29.3, 31.4, 38.3, 53.7, 68.6, 126.5, 127.8, 128.8, 139.9, 172.9; ESI-MS m/z = 445.4 (M + H^+), 467.4 (M + Na^+); Anal. Calcd for $C_{26}H_{44}N_4O_2$: C, 70.2; H, 10.0; N, 12.6. Found: C, 69.8; H, 10.2; N, 12.3.

Fluorescence Measurements. Steady-state fluorescence measurements were carried out in a VARIAN Cary Eclipse Fluorescence Spectrophotometer equipped with a xenon flash lamp in a rectangular quartz cell with an optical path of 10 mm. The concentration of the samples was 10^{-3} M and emission intensity was measured at 285 nm after excitation at 268 nm.

Molecular Mechanics Calculations. Monte Carlo conformational search and molecular dynamics studies were performed with MACROMODEL 7.0 using AMBER* as the force field and GB/SA simulation of chloroform as solvent.The Monte Carlo conformational search involved the modification of the torsional angles automatically setup by the program and convergence was obtained after performing 2 cycles of 1000 steps departing from different conformers in each case and using simulation of chloroform. The global minima obtained in this way were used as starting structures for the molecular dynamics calculations which were carried out using the following conditions: simulation temperature = 300 K, length of simulation = 5 ns with 1.5 fs steps, SHAKE was used to constraint the length of bonds to hydrogen and 200 structures were sampled to analyze the percentage of hydrogen-bonded structures.

Crystal Structure Analysis. Compound 13b. $C_{20}H_{32}N_4O_2$, orthorhombic, space group $P2_12_12_1$, a = 6.4222(4), b = 15.171(1), c = 20.007(2) Å, V = 1949.3(3) $Å^3$, Z = 4, μ = 0.081 mm^{-1}, $\rho_{calc.}$ = 1.228 gcm^{-1}, Siemens-SMART-CCD-three-circle diffractometer, Mo Kα-radiation, 2θ-range = 3.36−54.20°, 27875 reflections collected, 4256 independent reflections (R_{int}= 0.077), empirical absorption correction (SADABS, Sheldrick, 1996), structure solution with SHELXS-90,[13a] refinement on F^2 with SHELXL-97,[13b] R1[$I > 2\sigma(I)$]= 0.064, wR2 = 0.119, data-parameter-ratio = 17.0, max. peak in final electron density map = 0.25 e $Å^3$.

Compound 18b. $C_{20}H_{32}N_4O_2$, monoclinic, space group $P2_1$, a = 10.1580(6), b = 18.8852(15), c = 10.8306(6) Å, β = 92.105(5)°, V = 2076.3(2) $Å^3$, Z = 4, μ = 0.076 mm^{-1}, $\rho_{calc.}$ = 1.153 gcm^{-1}, STOE-IPDS−II-two-circle diffractometer, Mo Kα-radiation, 2θ-range = 3.76−53.96°, 20 452 reflections collected, 8830 independent reflections (R_{int}= 0.047), structure solution with SHELXS-90, refinement on F^2 with SHELXL-97, R1[$I > 2\sigma(I)$]= 0.038, wR2 = 0.066, data-parameter-ratio = 17.6, max. peak in final electron density map = 0.16 e $Å^3$.

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Supporting Information Available: X-ray crystallographic data (.cif files) for the compounds **13b** and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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