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Synthesis of Conformationally Constrained Macrocyclic Analogs of the Potent and Selective CCK-B Antagonist CI-988.

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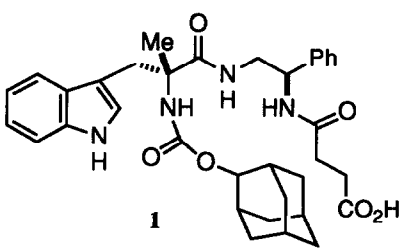
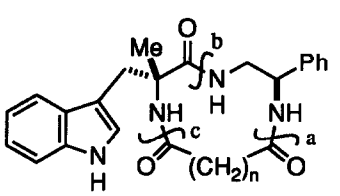
Abstract: A series of conformationally constrained analogs of the potent CCK-B antagonist CI-988 were prepared and evaluated for their CCK-B binding affinity. A macrolactamization reaction leading to the formation of 11 to 14-membered rings was also investigated.

The development of non-peptide agonists and antagonists of the neuropeptide hormone cholecystokinin (CCK) has been of intense interest in recent years.[1] Two types of receptors have been differentiated, designated as CCK-A, located primarily in peripheral sites, and CCK-B, located predominantly in the brain.[2] CCK is believed to be involved in the regulation of several physiological processes, and CCK-B antagonists have demonstrated anxiolytic[3a] and antigastrin[3b] activity in vivo.

Horwell and coworkers[4a] have recently designed and synthesized a series of "peptoid" analogs of the C-terminal octapeptide CCK-26-33, exemplified by CI-988 (**1**), which are potent and selective CCK-B antagonists. The x-ray crystal structure of CI-988 provided evidence of a close through-space proximity of the adamantyl and succinic acid moieties, which was further confirmed in solution by ^{1}H NMR nOe studies.[5] We were interested in designing less complex, conformationally constrained analogs of CI-988 with lower molecular weight and reduced lipophilicity.[4b]



1



2

We postulated that in addition to providing increased lipophilicity, the adamantyl moiety also played a role in orienting CI-988 in the necessary conformation for binding at the CCK-B receptor. We hoped that the conformational constraints imposed by the formation of a medium-sized ring would allow the binding site conformation to be closely mimicked, obviating the need for the bulky adamantyl group. While the succinic acid

sidechain in CI-988 clearly accesses an additional binding site, analogs without this moiety also show excellent CCK-B binding activity.[4a]

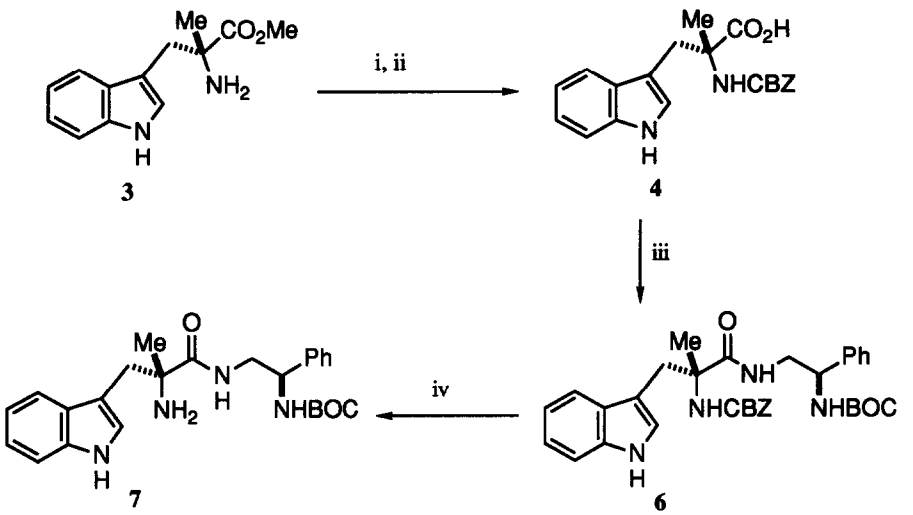
Thus, we designed a series of 11- to 14-membered ring analogs **2** (n=2-5), which were found to overlap the x-ray structure of CI-988 at a number of key points as shown by computer assisted molecular modeling analysis. An array of different sized rings would allow us to probe the tolerance of the binding site and aid in the development of a pharmacophore model. In this paper, we describe the synthesis of these cyclic analogs of CI-988, and also the facility of the macrolactamization with increasing ring size.

As shown in **2**, a macrolactamization could be utilized to construct the final amide bond at points **a**, **b**, or **c**. We selected disconnection **a**, which, being the least hindered site, would presumably facilitate the ring closure.

Chemistry

We believed that the this series of macrocycles could most efficiently be prepared through a common intermediate such as **7**. The synthesis of this key intermediate is described in Scheme I.

Scheme I

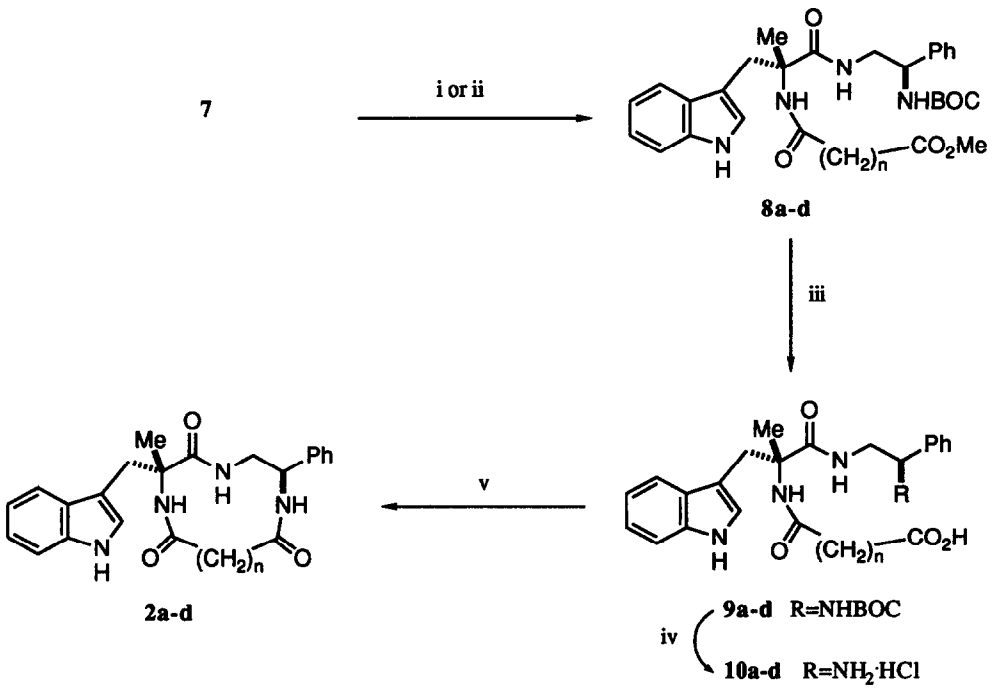


i) benzyl chloroformate, Et_3N, THF, 84%; ii) LiOH, dioxane/H_2O, 99%;
iii) DCC/HOBT, (R)-2-NBOC-phenethylenediamine hydrochloride (**5**), Et_3N, EtOAc, 90%;
iv) H_2, Pd/C, MeOH, 98%.

(R)-α-Methyl tryptophan methyl ester (**3**)[4a] was treated with benzyl chloroformate followed by saponification to provide acid **4**. DCC/HOBT-promoted coupling with the protected diamine **5**[4a] gave amide **6**, which upon hydrogenolysis yielded the desired precursor **7**.

As shown in Scheme II, treatment of amine **7** with the appropriate commercially available acid chloride or acid provided the corresponding esters **8a-d**. Saponification and removal of the BOC protecting group with anhydrous HCl in ethyl acetate afforded the crude amino acid hydrochlorides **10a-d**. The macrolactamizations of **10a-d** were carried out under identical conditions using diphenylphosphoryl azide (DPPA) and excess solid sodium bicarbonate in DMF at high dilution (0.008M).[6]

Scheme II



i) $ClCO(CH_2)_nCO_2Me$, Et_3N/THF (n=2,3); ii) DCC/HOBT, $HO_2C(CH_2)_nCO_2Me$, EtOAc (n=4,5); iii) LiOH, dioxane/H_2O; iv) HCl/EtOAc; v) DPPA, $NaHCO_3$, DMF.

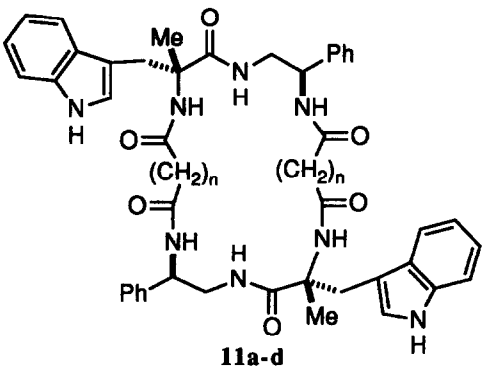
Results and Discussion

As summarized in Table 1, the macrolactamization reactions proceeded more cleanly and provided higher yields of monomeric products with increasing ring size. The cyclization of **10a** afforded a 1:1 mixture of 11-membered ring **2a** and its corresponding 22-membered dimer **11a**. An approximately 2:1 mixture of 12-membered macrocycle **2b** and 24-membered dimer **11b** were produced in the macrolactamization of **10b**. The 13- and 14-membered macrocycles **2c** and **2d** were obtained in good yields with little or no formation of dimeric products. The structural assignments of **2a-d** and their corresponding dimers were confirmed by mass spectral (FAB) analysis.

Table 1

n	Compound	Yield(%)	Compound	Yield(%)
2	**2a**	26	**11a**	27
3	**2b**	53	**11b**	24
4	**2c**	65	**11c**	0
5	**2d**	61	**11d**	6

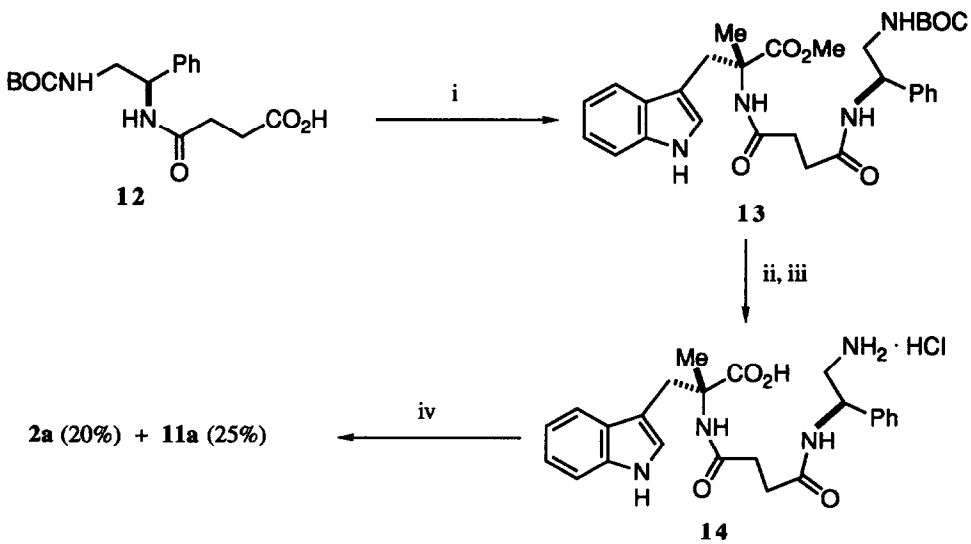
We also attempted to prepare a 10-membered ring analog **2** (n=1) of CI-988. However, using the methodology established in Scheme 2, only the corresponding 20-membered dimer **11** (n=1) was isolated in 20% yield.



11a-d

In order to investigate the effect of the final cyclization point on the product distribution, we briefly examined macrolactamization at point **b** for the troublesome 11-membered ring system **2a**. As illustrated in Scheme III, the intermediate ester **13** was prepared by DCC/HOBT-mediated coupling of acid **12** and amine **3**. Saponification followed by deprotection with HCl in ethyl acetate gave the crude amino acid hydrochloride **14** in near quantitative yield. Cyclization using the standard DPPA/$NaHCO_3$ conditions again provided **2a** and **11a** in a nearly 1:1 ratio, in an overall yield similar to the previous ring closure at point **a**. Thus, final cyclization at a more hindered site has little effect on the overall yield and distribution of products.

Scheme III



12 **13** **14**

i) DCC, HOBT, **3**, EtOAc (85%); ii) LiOH, dioxane/H_2O; iii) HCl/EtOAc (95%); iv) DPPA, $NaHCO_3$, DMF.

CCK-B Binding Affinity

The four macrocycles **2a-d** were evaluated for their CCK-B binding activity[7] and found to be inactive. Thus, although these compounds were found to overlap the x-ray structure of CI-988 to a certain extent, it is apparent that they do not possess the structural features required for optimal interactions with the CCK-B receptor. Perhaps the binding site conformation adopted by CI-988 is different from that seen in solution or in the solid state. Alternatively, the rigidity built into these compounds could limit the conformational flexibility which may be necessary to access the CCK-B receptor site.

Conclusion

In conclusion, we have designed and prepared a series of cyclic, conformationally constrained analogs of the potent CCK-B antagonist CI-988. The macrolactamization was found to proceed with greater facility with increasing ring size under identical reaction conditions. These compounds showed no binding affinity in a CCK-B receptor binding assay.

Experimental Section

General.

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Bio-Rad FTS-45 TGA/FTIR spectrophotometer. Proton NMR spectra were determined on a Bruker AM250 spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Mass spectra were obtained by using a VG Masslab Trio-2A, Finnigan TSQ-70, or VG Analytical 7070E/HF mass spectrometer. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Perkin-Elmer 240C elemental analyzer. Optical rotations were determined at 23°C using a Perkin-Elmer 241 polarimeter.

α-Methyl-N-[(phenylmethoxy)carbonyl]-D-tryptophan (4).

To a solution of benzyl chloroformate (8.1mL, 56.8mmol) in THF (200mL) at 0°C was added dropwise over one hour a solution of methyl α-methyl-D-tryptophanate[4] (12.0g, 51.7mmol) in THF (60mL). A solution of triethylamine (8.6mL) in THF (60mL) was then added dropwise over one hour. The mixture was allowed to warm to room temperature and stirred for one hour. After filtration and concentration, the crude product was purified by flash chromatography (2:3 ethyl acetate/hexane). Recrystallization from ethyl acetate/hexane provided 15.8g (84%) of methyl α-methyl-N-[(phenylmethoxy)carbonyl]-D-tryptophanate as a white solid. mp 124-125°C; $[\alpha]_D$ = -60.2 (c 1.022, $CHCl_3$); IR (KBr) 3392, 3362, 2945, 1719, 1699, 1528, 1454, 1256, 1130, 1069, 758 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.52-7.01 (m, 9H), 6.78 (d, J=2Hz, 1H), 5.52 (br s, 1H), 5.15 (d, J=12Hz, 1H), 5.07 (d, J=12Hz, 1H), 3.66 (br s, 3H), 3.52 (br d, J=14Hz, 1H), 3.35 (d, J=14Hz, 1H), 1.68 (s, 3H); MS (CI) m/e 367(8), 366(20), 323(20), 306(31), 259(19), 130(100); Anal. calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65; Found: C, 68.66; H, 5.70; N, 7.45. To a solution of methyl α-methyl-N-[(phenylmethoxy)carbonyl]-D-tryptophanate (15.0g, 40.9mmol) in dioxane (160mL) and water (80mL) was added lithium hydroxide (2.6g, 61.4mmol). The solution was stirred for 24

hours at room temperature. The solution was concentrated, then taken up in water and acidified with 10% HCl to pH 2. The aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford 14.3g (99%) of **4** as a white foam. mp 66-79°C; $[\alpha]_D$ = -39.7 (c 1.037, $CHCl_3$); IR (KBr) 3401, 1711, 1680, 1509, 1457, 1255, 1073, 743 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.06 (br s, 1H), 7.38 (d, J=3Hz, 1H), 7.33-7.00 (m, 8H), 6.80 (d, J=1Hz, 1H), 5.46 (br s, 1H), 5.14 (d, J=12Hz, 1H), 5.08 (d, J=12Hz, 1H), 3.55-3.30 (m, 2H), 1.67 (s, 3H); HRMS (CI) m/e calcd for $C_{20}H_{21}N_2O_4$ (M+H): 353.1501; found: 353.1503; Anal. calcd for $C_{20}H_{20}N_2O_4 \cdot 0.5H_2O$: C, 66.47; H, 5.86; N, 7.75; Found: C, 66.95; H, 5.85; N, 7.37.

1,1-Dimethylethyl [R-(R*,R*)]-[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]propyl]amino]-1-phenylethyl]carbamate (6).
To a solution of **4** (15.0g, 42.6mmol) in ethyl acetate (250mL) was added HOBT (8.5g, 55.3 mmol) followed by DCC (10.5g, 51.1mmol). The mixture was stirred at room temperature for 2 hours, and (R)-2-N-BOC-phenethylenediamine hydrochloride (**5**)[4a] (11.6g, 42.6mmol) was added followed by triethylamine (6.5mL, 46.8mmol). The mixture was stirred overnight, then filtered. The filtrate was concentrated and purified by flash chromatography (3:2 ethyl acetate/hexane) to provide 22.0g (90%) of **6** as a white solid. mp 92-104°C; $[\alpha]_D$= -11.3 (c 0.975, $CHCl_3$); IR (KBr) 3360, 2933, 1701, 1668, 1497, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.55 (d, J=8Hz, 1H), 7.40-7.05 (m, 13H), 6.82 (s, 1H), 6.56 (br s, 1H), 5.54 (br s, 1H), 5.32 (s, 1H), 5.09 (s, 2H), 4.75 (m, 1H), 3.64 (m, 1H), 3.47-3.27 (m, 3H), 1.53 (s, 3H), 1.41 (s, 9H); MS (FAB) m/e 571(5), 471(100), 454(35), 341(42), 263(74); Anal. calcd for $C_{33}H_{38}N_4O_5$: C, 69.45; H, 6.71; N, 9.82; Found: C, 69.03; H, 6.67; N, 9.42.

1,1-Dimethylethyl [R-(R*,R*)]-[2-[[2-amino-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-1-phenylethyl]carbamate (7).
To a solution of **6** (11.7g, 20.5mmol) in MeOH (200mL) was added 20% Pd/C (0.5g). The mixture was stirred under a hydrogen balloon for 4 hours. After filtration through Celite, the filtrate was concentrated to afford 8.8g (98%) of **7** as a white powder. mp 90-98°C; $[\alpha]_D$= +32 (c 0.975, $CHCl_3$); IR (KBr) 3339, 2977, 1696, 1653, 1367, 1169 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.71 (m, 1H), 7.63 (d, J=8Hz, 1H), 7.38 (d, J=8Hz, 1H), 7.30-7.00 (m, 7H), 6.91 (br s, 1H), 5.68 (br s, 1H), 4.70 (m, 1H), 3.70-3.45 (m, 2H), 2.81 (d, J=14Hz, 1H), 1.46 (s, 3H), 1.43 (s, 9H), 1.19 (br s, 2H); MS (CI) m/e 437(29), 381(26), 337(75), 320(30, 207(50), 189(48), 173(100), 130(60); Anal. calcd for $C_{25}H_{32}N_4O_4$: C, 68.78; H, 7.39; N, 12.83; Found: C, 68.98; H, 7.64; N, 12.12.

Ethyl [R-(R*,R*)]-4-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-4-oxobutanoate (8a).
To a solution of **7** (2.9g, 6.6mmol) in THF (25mL) at 0°C was added triethylamine (1.4mL, 10.0mmol). Ethyl malonyl chloride (1.0mL, 7.3mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (5:95 MeOH/$CHCl_3$) to give 3.5g (93%) of **8a** as a white powder. mp 186-191°C; $[\alpha]_D$= +22.1 (1.041, MeOH); IR (KBr) 3334, 3325, 2932, 1719, 1695, 1650, 1519, 1169 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.68 (s, 1H), 7.56 (br t, J=6Hz, 1H), 7.41 (d, J=8Hz, 1H), 7.38-7.20 (m, 7H), 7.10-6.90 (m, 3H), 4.65 (m, 1H), 4.06 (q, J=7Hz, 2H), 4.05 (m, 1H), 3.42 (d, J=14Hz, 1H), 3.25 (m, 1H), 3.10 (d, J=14Hz, 1H), 2.51 (m, 2H), 2.35 (m, 2H), 1.35 (s, 9H), 1.19 (t, J=7Hz, 3H), 1.11 (s, 3H); MS (FAB) m/e 565(21), 465(100), 329(40), 301(97), 237(42); Anal. calcd for

$C_{31}H_{40}N_4O_6$: C, 65.94; H, 7.14; N, 9.92; Found: C, 66.30; H, 7.54; N, 10.02.

Methyl [R-(R*,R*)]-5-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-5-oxopentanoate (8b).
To a solution of **7** (2.7g, 6.2mmol) and triethylamine (1.3mL, 9.3mmol) in THF (50mL) at 0°C was added dropwise methyl 4-(chloroformyl)butyrate (0.94mL, 6.8mmol). The mixture was stirred one hour and filtered. The filtrate was concentrated and purified by flash chromatography (3:1 ethyl acetate/hexane) to provide 3.2g (92%) of **8b** as a white powder. mp 82-87°C; $[\alpha]_D$= -7.2 (c 0.991, $CHCl_3$); IR (KBr) 3322, 2978, 1717, 1663, 1521, 1170 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.58 (d, J=7Hz, 1H), 7.41-7.05 (m, 8H), 7.02, (s, 1H), 6.78 (br s, 1H), 6.16 (s, 1H), 5.60 (br s, 1H), 4.79 (m, 1H), 3.67 (m, 1H), 3.64 (s, 3H), 3.37 (m, 3H), 2.30 (m, 2H), 2.11 (m, 2H), 1.87 (m, 2H), 1.68 (s, 3H), 1.42 (s, 9H); MS (FAB) m/e 565(10), 465(100), 329(38), 301(89), 214(23); Anal. calcd for $C_{31}H_{40}N_4O_6$: C, 65.94; H, 7.14; N, 9.92; Found: C, 65.16; H, 7.00; N, 9.72.

Methyl [R-(R*,R*)]-6-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino-6-oxohexanoate (8c).
To a solution of adipic acid monomethyl ester (1.10g, 6.87mmol) in ethyl acetate (50mL) was added HOBT (1.37g, 8.93mmol) followed by DCC (1.70g, 8.24mmol). The mixture was stirred for 2 hours at room temperature, and **7** (3.00g, 6.87mmol) was added and stirring was continued overnight. The mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (4:1 ethyl acetate/hexane) to afford 2.4g (60%) of **8c** as a white solid. mp 88-95°C; $[\alpha]_D$= -1.7 (c 1.062, $CHCl_3$); IR (KBr) 3339, 2937, 1734, 1695, 1663, 1522, 1367, 1170 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.57 (d, J=8Hz, 1H), 7.36 (d, J=8Hz, 1H0, 7.33-7.07 (m, 7H), 7.01 (s, 1H), 6.82 (br s, 1H), 6.20 (s, 1H), 5.63 (d, J=7Hz, 1H), 4.78 (m, 1H), 3.69 (m, 1H), 3.66 (s, 3H), 3.50-3.25 (m, 3H), 2.25 (m, 2H), 2.05 (m, 2H), 1.75-1.30 (m, 4H), 1.61 (s, 3H), 1.41 (s, 9H); HRMS (CI) m/e calcd for $C_{32}H_{43}N_4O_6$ (M+H): 579.3183; found: 579.3171; Anal. calcd for $C_{32}H_{42}N_4O_6 \cdot 0.5\ H_2O$: C, 65.40; H, 7.37; N, 9.53; Found: C, 65.55; H, 7.40; N, 9.44.

Methyl [R-(R*,R*)]-7-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-7-oxoheptanoate (8d).
To a solution of pimelic acid monomethyl ester (1.30g, 7.46mmol) in ethyl acetate (50mL) was added HOBT (1.49g, 9.70mmol) followed by DCC (1.85g, 8.96mmol). The mixture was stirred for 2 hours at room temperature, and **7** (3.26g, 7.46mmol) was added and stirring was continued overnight. The mixture was filtered and the filtrate was concentrated. The crude product was purified by flash chromatography (4:1 ethyl acetate/hexane) to give 2.8g (63%) of **8d** as a white foam. mp 72-80°C; $[\alpha]_D$= -3.0 (c 0.996, $CHCl_3$); IR (KBr) 3359, 2938, 1718, 1696, 1654, 1521, 1457, 1367, 1254, 743 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.59 (d, J=8Hz, 1H), 7.37(d, J=7Hz, 1H), 7.34-7.08 (m, 7H), 7.01 (s, 1H), 6.82 (br s, 1H), 6.17 (s, 1H), 5.60 (d, J=7Hz, 1H), 4.79 (m, 1H), 3.74 (m, 1H), 3.67 (s, 3H), 3.50-3.35 (m, 3H), 2.27 (m, 3H), 2.05 (m, 2H), 1.71-1.20 (m, 5H), 1.62 (s, 3H), 1.41 (s, 9H); HRMS (CI) m/e calcd for $C_{33}H_{45}N_4O_6$ (M+H): 593.3339; found: 593.3359; Anal. calcd for $C_{33}H_{44}N_4O_6\ 0.5\ H_2O$: C, 65.87; H, 7.54; N, 9.31; Found: C, 65.91; H, 7.51; N, 8.87.

General procedure for the hydrolysis of esters 8a-d.

The ester **8a-d** was dissolved in dioxane and water, and LiOH (1.5eq) was added. After stirring 2-3 hours at room temperature, the mixture was concentrated. The residue was taken up in water, acidified with 5% HCl, and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford the crude acid **9a-d** as a white foam.

[R-(R*,R*)]-4-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino-4-oxobutanoic acid (9a).
$[\alpha]_D$= +54.8 (c 0.962, $CHCl_3$); IR (KBr) 3329, 2933, 1716, 1670, 1521, 1457, 1367, 1167 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.65 (s, 1H), 7.59 (m, 1H), 7.43-7.15 (m, 8H), 6.94 (m, 3H), 4.65 (m, 1H), 3.90 (br m, 1H), 3.45-2.80 (m, 2H), 3.43 (d, J=14Hz, 1H), 3.10 (d, J=14Hz, 1H), 2.43 (m, 2H), 2.31 (m, 2H), 1.35 (s, 9H), 1.10 (s, 3H); MS (FAB) m/e 537(25), 437(97), 323(64), 273(100), 237(50); Anal. calcd for $C_{29}H_{36}N_4O_6$: C, 64.91; H, 6.76; N, 10.44; Found: C, 64.26; H, 6.89; N, 10.41.

[R-(R*,R*)]-5-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino-5-oxopentanoic acid (9b).
$[\alpha]_D$= +13.9 (c 1.080, $CHCl_3$); IR (KBr) 3337, 2978, 1696, 1654, 1521, 1368, 1167 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.64 (m, 1H), 7.54 (s, 1H), 7.41 (d, J=8Hz, 1H), 7.35-7.18 (m, 7H), 7.07-6.90 (m, 4H), 4.66 (m, 1H), 3.42 (d, J=14Hz, 1H), 3.26 (m, 2H), 3.10 (d, J=14Hz, 1H), 2.21 (m, 2H), 2.08 (m, 2H), 1.72 (m, 2H), 1.35 (s, 9H), 1.14 (s, 3H); MS (FAB) m/e 551(3), 451(66), 315(34), 287(100), 214(38), 201(39); Anal. calcd for $C_{30}H_{38}N_4O_6$: C, 65.44; H, 6.96; N, 10.17; Found: C, 64.95; H, 6.98; N, 10.23.

[R-(R*,R*)]-6-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino-6-oxohexanoic acid (9c).
mp 108-121°C; $[\alpha]_D$= +44.9 (c 0.986, $CHCl_3$); IR (KBr) 3337, 2934, 1695, 1663, 1518, 1168, 745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.57 (d, J=8Hz, 1H), 7.36 (d, J=8Hz, 1H), 7.33-7.05 (m, 8H), 6.99 (s, 1H), 6.85 (m, 1H), 6.25 (br s, 1H), 5.60 (m, 1H), 4.78 (m, 1H), 3.71 (m, 1H), 3.60-3.15 (m, 3H), 2.28 (m, 2H), 2.08 (m, 2H), 1.60 (m, 7H), 1.50-1.10 (m, 9H); HRMS (CI) m/e calcd for $C_{31}H_{41}N_4O_6$ (M+H): 565.3026; found: 565.2990; Anal. calcd for $C_{31}H_{40}N_4O_6 \cdot 0.5H_2O$: C, 64.90; H, 7.20; N, 9.77; Found: C, 65.31; H, 7.16; N, 9.32.

[R-(R*,R*)]-7-[[2-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino-7-oxoheptanoic acid (9d).
mp 98-112°C; $[\alpha]_D$= +26.1 (c 1.006, $CHCl_3$); IR (KBr) 3338, 2934, 1696, 1663, 1517, 1168, 745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.83 (m, 1H), 7.61 (m, 1H), 7.55-7.10 (m, 7H), 6.96 (s, 1H), 6.38 (m, 1H), 6.12 (br s, 1H), 4.82 (m, 1H), 3.73 (m, 1H), 3.44(d, J=14Hz, 1H), 3.38-2.90 (m, 2H), 2.40-1.85 (m, 4H), 1.80-1.45 (m, 5H), 1.40 (br s, 3H), 1.29 (br s, 9H), 0.69 (m, 1H); HRMS (CI) m/e calcd for $C_{32}H_{43}N_4O_6$ (M+H): 579.3183; found: 579.3201; Anal. calcd for $C_{32}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 65.40; H, 7.37; N, 9.53; Found: C, 65.46; H, 7.27; N, 8.98.

General procedure for the preparation of amino acid hydrochlorides 10a-d by deprotection of acids 9a-d.

The acid **9a-d** was dissolved in ethyl acetate and treated with a 3M solution of anhydrous HCl in ethyl acetate.[6d] The mixture was stirred for 2-3 hours at room temperature. The resulting suspension was concentrated and dried in vacuo to provide the crude amino acid hydrochloride **10a-d** as a powder.

[R-(R*,R*)]-4-[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-4-oxobutanoic acid monohydrochloride (10a).
$[\alpha]_D$= -7.1 (c 1.120, MeOH); IR (KBr) 3285, 3051, 2937, 1718, 1653, 1522, 746 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.09 (s, 1H), 7.99 (m, 1H), 7.58-7.25 (m, 8H), 7.10-6.90 (m, 4H), 4.41 (m, 1H), 3.57 (m, 1H), 3.38 (m, 1H), 3.35 (d, J=14Hz, 1H), 3.10 (d, J=14Hz, 1H), 2.58-2.25 (m, 4H), 1.14 (s, 3H); MS (CI) m/e 437(16), 419(84), 313(36), 289(53), 225(91), 130(100), 101(69); Anal. calcd for $C_{24}H_{28}N_4O_4$·HCl: C, 60.95; H, 6.18; N, 11.85; Found: C, 60.65; H, 6.60; N, 11.11.

[R-(R*,R*)]-5-[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-5-oxopentanoic acid monohydrochloride (10b).
$[\alpha]_D$= -12.1 (c 1.029, MeOH); IR (KBr) 3386, 3286, 3039, 2938, 1717, 1653, 1522 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.45 (br s, 1H), 8.05 (s, 2H), 7.55-7.28 (m, 7H), 7.10-6.88 (m, 3H), 4.42 (m, 1H), 3.60 (m, 2H), 3.42 (m, 1H), 3.34 (d, J=14Hz, 1H), 3.11(d, J=14Hz, 1H), 2.30-2.12 (m, 4H), 1.76(m, 2H), 1.18 (s, 3H); MS (CI) m/e 451(2), 433(12), 304(8), 268(9), 158(12), 130(100), 85(47); Anal. calcd for $C_{25}H_{30}N_4O_4$·HCl·H_2O: C, 59.46; H, 6.59; N, 11.09; Found: C, 59.88; H, 6.86; N, 10.76.

[R-(R*,R*)]-6-[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-6-oxohexanoic acid monohydrochloride (10c).
$[\alpha]_D$= -14.9 (c 0.911, MeOH); IR (KBr) 3399, 3053, 2939, 1718, 1653, 1522 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.10 (br m, 3H), 8.05 (s, 2H), 7.55-7.28 (m, 7H), 7.08-6.90 (m, 3H), 4.39 (t, J=7Hz, 1H), 3.57 (m, 1H), 3.40 (m, 2H), 3.33 (d, J=14Hz, 1H), 3.11 (d, J=14Hz, 1H), 2.23 (m, 2H), 2.11 (m, 2H), 1.51 (m, 4H), 1.19 (s, 3H); MS (CI) m/e 465(1), 447(3), 317(2), 130(4), 85(100); Anal. calcd for $C_{26}H_{32}N_4O_4$·HCl·0.75H_2O: C, 60.69; H, 6.76; N, 10.89; Found: C, 61.02; H, 6.64; N, 10.44.

[R-(R*,R*)]-7-[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]-7-oxoheptanoic acid monohydrochloride (10d).
$[\alpha]_D$= -9.9 (c 0.962, MeOH); IR (KBr) 3393, 3267, 3053, 2940, 1711, 1653, 1522, 1458 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.05 (m, 2H), 7.55-7.28 (m, 8H), 7.10-6.90 (m, 3H), 4.43 (t, J=6Hz, 1H), 3.60 (m, 1H), 3.50 (br m, 3H), 3.42 (m, 1H), 3.34 (d, J=14Hz, 1H), 3.12 (d, J=14Hz, 1H), 2.22 (t, J=7Hz, 2H), 2.10 (m, 2H), 1.60-1.45 (m, 4H), 1.26 (m,2H), 1.20 (s, 3H); MS (CI) m/e 479(1), 461(4), 331(2), 130(5), 85(100); Anal. calcd for $C_{27}H_{34}N_4O_4$ HCl·0.5H_2O: C, 61.88; H, 6.92; N, 10.69; Found: C, 61.57; H, 6.71; N, 10.56.

General procedure for the macrolactamizations of 10a-d with diphenylphosphoryl azide (DPPA).[6d]

To a 0.008M solution of the crude amino acid hydrochloride **10a-d** in dry DMF at 0°C was added solid sodium bicarbonate (5eq). DPPA (1.5eq) was added dropwise and the solution was allowed to warm slowly to room temperature and stirred for 72 hours. Water was added and the mixture was concentrated. The mixture was extracted three times with $CHCl_3$, and the combined organic extracts were washed with water, brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (5-10% MeOH:$CHCl_3$) to give the products **2a-d** and **11a-d** in the yields shown in Table 1.

[2R-(2R*,6R*)]-2-(1H-Indol-3-ylmethyl)-2-methyl-6-phenyl-1,4,7-triazacycloundecan-3,8,11-trione (2a).
mp 222-232°C; $[\alpha]_D$= -25.9 (c 0.864, 1:1 MeOH:$CHCl_3$); IR (KBr) 3390, 2937, 1670, 1654, 1533, 1497, 1458, 745 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.45 (s, 1H), 8.04 (d, J=10Hz, 1H), 7.55-7.20 (m, 7H), 7.17 (d, J=2Hz, 1H), 7.01 (m, 2H), 6.75 (d, J=7Hz, 1H), 5.32 (m, 1H), 3.37 (m, 1H), 3.17 (dd, J=13 and 4Hz, 1H), 3.10 (d, J=14Hz, 1H), 3.00 (d, J=14Hz, 1H), 2.67 (m, 2H), 2.26 (m, 2H), 1.35 (s, 3H); HRMS (EI) m/e calcd for $C_{24}H_{26}N_4O_3$: 418.2005; found: 418.1987; Anal. calcd for $C_{24}H_{26}N_4O_3 \cdot H_2O$: C, 66.04; H, 6.47; N, 12.84; found: C, 66.36; H, 6.34; N, 12.92.

[2R-(2R*,6R*13R*,17R*)]-2,13-bis(1H-Indol-3-ylmethyl)-2,13-dimethyl-6,17-diphenyl-1,4,7,12,15,18-hexaazacyclodocosan-3,8,11,14,19,22-hexaone (11a).
$[\alpha]_D$= -41.9 (c 0.697, 1:1 MeOH:$CHCl_3$); IR (KBr) 3403, 3319, 1654, 1522 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.80 (s, 2H), 8.71 (d, J=8Hz, 2H), 7.93 (s, 2H), 7.85 (m, 2H), 7.47 (m, 4H), 7.38 (m, 4H), 7.27 (m, 4H), 7.12 (d, J=8Hz, 2H), 6.98 (t, J=8Hz, 2H), 6.85 (t, J=8Hz, 2H), 6.74 (s, 2H), 5.55 (m, 2H), 3.35 (m, 2H), 3.11 (m, 4H), 2.83 (d, J=14Hz, 2H), 2.60 (m, 4H), 2.31 (m, 2H), 2.12 (m, 2H), 1.17 (s. 6H); HRMS (FAB) m/e calcd for $C_{48}H_{53}N_8O_6$ (M+H): 837.4088; found: 837.4154; Anal. calcd for $C_{48}H_{52}N_8O_6 \cdot 4H_2O$: C, 63.42; H, 6.65; N, 12.33; found: C, 63.08; H, 6.02; N, 11.97.

[2R-(2R*,6R*)]-2-(1H-Indol-3-ylmethyl)-2-methyl-6-phenyl-1,4,7-triazacyclododecan-3,8,12-trione (2b).
mp 282-286°C; $[\alpha]_D$=+15.6 (c 1.030, DMF); IR (KBr) 3384, 3297, 2936, 1670, 1652, 1647, 1521, 1263, 1093, 739 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.90 (s,1H), 7.99 (s, 1H), 7.91 (d, J=6Hz, 1H), 7.59 (m, 1H), 7.43-7.19 (m, 7H), 7.07-6.88 (m, 3H), 4.60 (m, 1H), 3.65 (m, 1H), 3.63 (d, J=14Hz, 1H), 2.96 (d, J=14Hz, 1H), 2.73 (m, 1H), 2.30-1.95 (m, 4H), 1.62 (m, 1H), 1.16 (s, 3H); HRMS (EI) m/e calcd for $C_{25}H_{28}N_4O_3$: 432.2161; found: 432.2156; Anal. calcd for $C_{25}H_{28}N_4O_3 \cdot H_2O$: C, 66.65; H, 6.71; N, 12.44; Found: C, 66.68; H, 6.25; N, 12.37.

[2R-(2R*,6R*14R*,18R*)]-2,14-bis(1H-Indol-3-ylmethyl)-2,14-dimethyl-6,18-diphenyl-1,4,7,13,16,19-hexaazacyclotetracosan-3,8,12,15,20,24-hexaone(11b).
mp 186-199°C; $[\alpha]_D$= -12.6 (c 0.772, 1:1 MeOH:$CHCl_3$); IR (KBr) 3314, 2935, 1654, 1522, 745 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.90 (s, 2H), 7.92 (d, J=7Hz, 2H), 7.75 (s, 2H), 7.60-7.40 (m, 4H), 7.40-7.20 (m, 12H), 7.15-6.90 (m, 6H), 4.89 (m, 2H), 3.70 (m, 2H), 3.53 (d, J=14Hz, 2H), 3.07 (m, 2H), 3.06

(d, J=14Hz, 2H), 2.45-1.90 (m, 12H), 1.18 (s, 6H); HRMS (FAB) m/e calcd for $C_{50}H_{57}N_8O_6$ (M+H): 865.4401; found: 865.4420; Anal. calcd for $C_{50}H_{56}N_8O_6 \cdot H_2O$: C, 68.01; H, 6.62; N, 12.69; Found: C, 67.60; H, 6.65; N, 12.80.

[2R-(2R*,6R*)]-2-(1H-Indol-3-ylmethyl)-2-methyl-6-phenyl-1,4,7-triazacyclotridecan-3,8,13-trione (2c).
mp 173-182°C; $[\alpha]_D$= -47.7 (c 0.916, 1:1 MeOH:$CHCl_3$); IR (KBr) 3380, 3314, 2937, 1653, 1522, 1457, 743 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.99 (d, J=8Hz, 1H), 7.90 (s, 1H), 7.45 (d, J=8Hz, 1H), 7.38-7.20 (m, 6H), 7.17-6.90 (m, 4H), 4.73 (m, 1H), 3.29 (d, J=14Hz, 1H), 3.20 (m, 2H0, 3.07 (d, J=14Hz, 1H), 2.44-2.23 (m, 2H), 1.89 (m, 2H), 1.68 (m, 4H), 1.28 (s, 3H); HRMS (EI) m/e calcd for $C_{26}H_{30}N_4O_3$: 446.2318; found: 446.2323; Anal. calcd for $C_{26}H_{30}N_4O_3 \cdot 0.5H_2O$: C, 68.55; H, 6.86; N, 12.30; Found: C, 69.11; H, 6.91; N, 11.82.

[2R-(2R*,6R*)]-2-(1H-Indol-3-ylmethyl)-2-methyl-6-phenyl-1,4,7-triazacyclotetradecan-3,8,14-trione (2d).
mp 170-181°C; $[\alpha]_D$= -55.7 (c 0.978, MeOH); IR (KBr) 3314, 2932, 1683, 1522, 1458, 744 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.20 (d, J=7Hz, 1H), 7.90 (s, 1H), 7.45 (d, J=7Hz, 1H), 7.39-7.20 (m, 6H), 7.15 (m, 1H), 7.10-6.90 (m, 3H), 4.59 (m, 1H), 3.52 (d, J=14Hz, 1H), 3.50 (m, 1H), 3.07 (d, J=14Hz, 1H), 2.97 (m, 1H), 2.30-1.95 (m, 4H), 1.75-1.30 (m, 6H), 1.22 (s, 3H); HRMS (EI) m/e calcd for $C_{27}H_{32}N_4O_3$: 460.2474; found: 460.2462; Anal. calcd for $C_{27}H_{32}N_4O_3 \cdot 0.5H_2O$: C, 69.06; H, 7.08; N, 11.93; Found: C, 69.18; H, 7.15; N, 11.63.

[2R-(2R*,6R*16R*,20R*)]-2,16-bis(1H-Indol-3-ylmethyl)-2,16-dimethyl-6,20-diphenyl-1,4,7,15,18,21-hexaazacyclooctacosan-3,8,14,17,22,28-hexaone (11d).
mp 170-182°C; $[\alpha]_D$= -11.5 (c 0.435, MeOH); IR (KBr) 3395, 3304, 1653, 1522, 1458, 746 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.90 (s, 2H), 7.85 (d, J=7Hz, 2H), 7.44 (m, 4H), 7.35-7.17 (m, 12H), 7.04-6.90 (m, 6H), 4.88 (m, 2H), 3.75 (m, 2H), 3.51 (d, J=14Hz, 2H), 3.07 (d, J=14Hz, 2H), 3.05 (m, 2H), 2.38-2.04 (m, 8H), 1.75-1.50 (m, 8H), 1.33 (m, 4H), 1.17 (s, 6H); HRMS (FAB) m/e calcd for $C_{54}H_6N_8O_6$(M+H): 921.5027; found: 921.5094; Anal. calcd for $C_{54}H_{64}N_8O_6 \cdot H_2O$: C, 69.06; H, 7.08; N, 11.93; Found: C, 68.73; H, 6.99; N, 11.78.

[2R-(2R*,6R*12R*,16R*)]-2,12-bis(1H-Indol-3-ylmethyl)-2,12-dimethyl-6,16-diphenyl-1,4,7,11,14,17-hexaazacycloeicosan-3,8,10,13,18,20-hexaone (11, n=1).
mp 190-198°C; $[\alpha]_D$= -76.2 (c 0.818, 1:1 MeOH:$CHCl_3$); IR (KBr) 3314, 1654, 1522, 1458, 745 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 10.85 (s, 2H), 8.21 (s, 2H), 8.06 (d, J=8Hz, 2H), 7.97 (m, 2H), 7.45-7.18 (m, 16H), 6.99 (t, J=7Hz, 2H), 6.88 (t, J=7Hz, 2H), 5.04 (m, 2H), 3.55-3.10 (m, 8H), 3.13 (d, J=15Hz, 2H), 3.03 (d, J=15Hz, 2H), 1.28 (s, 6H); HRMS (FAB) m/e calcd for $C_{46}H_{49}N_8O_6$: 809.3775; found: 809.3734; Anal. calcd for $C_{46}H_{48}N_8O_6 \cdot H_2O$: C, 66.81; H, 6.09; N, 13.55; Found: C, 66.61; H, 5.88; N, 13.16.

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