Synthesis and Biological Evaluation of the First *N*-Alkyl Cage Dimeric 4-Aryl-1,4-dihydropyridines as Novel Nonpeptidic HIV-1 Protease Inhibitors

Andreas Hilgeroth,*[,†] Michael Wiese,[†] and Andreas Billich[‡]

Department of Pharmacy, Martin-Luther-University Halle-Wittenberg, Wolfgang-Langenbeck-Strasse 4, D-06120 Halle, Germany, and Department of Antiretroviral Therapy, Novartis Forschungsinstitut GmbH, Brunnerstrasse 59, A-1235 Vienna, Austria

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A first series of novel *N*H and *N*-alkyl-substituted cage dimeric 4-aryl-1,4-dihydropyridines **3a**−**f** has been synthesized and evaluated as HIV-1 protease inhibitors in in vitro assays. While the *N*H and *N*-methyl derivatives **3a**,**b**,**e**,**f** were almost inactive with IC_{50} values of about 200 μM, the *N*-Benzyl compounds exhibited stronger activity with an IC_{50} value of 16.2 μM for the presently best compound **3c**. The type of HIV-1 protease inhibition of these novel inhibitors was characterized as competitive. With the increase of observed activity from *N*H and *N*-methyl derivatives to *N*-benzyl compounds, respectively, the binding mode may correspond to that of cyclic and azacyclic ureas showing hydrophobic interactions of the four aromatic residues to the S1/S1′ and S2/S2′ regions of HIV-1 protease.

Introduction

Since the discovery of HIV-1 protease (PR) as a novel target enzyme for the development of HIV-1 protease inhibitors (PI), certain peptidic PIs have been established in HIV therapy combined with nucleoside analogues or reverse transcriptase inhibitors.[1−3] Nevertheless, numerous resistances against the present PIs have been described.[4] The early problems of peptidic PIs, poor oral bioavailability and severe side effects caused by the necessarily high doses of the inhibitors,[1] strengthened the development of nonpeptidic PIs that promised better bioavailability. However, the most potent inhibitors of the first series of cyclic ureas, DMP 323 and DMP 450 (Figure 1), were disappointing in clinical trials with unsatisfying bioavailabilities.[5] The introduction of certain aromatic substituents meanwhile led to derivatives with K_i values in the lower nanomolar and picomolar ranges.[6] The azacyclic urea A-98881, a highly potent inhibitor, is currently being investigated in clinical trials.[7] 4-Hydroxycoumarins have been discovered as a nonpeptidic class of PIs with better oral bioavailability.[8]

Motivated by the present situation that demands innovative lead structures for PIs, we designed *N*-alkyl-substituted cage dimeric 4-aryl-1,4-dihydropyridines **I** with functional groups that are similar to those of cyclic and azacyclic ureas as potential PR inhibitors. Recently we demonstrated by molecular modeling certain conformities in the molecular properties of A-98881 and our cage dimeric target structure **I**, which pointed to a similar binding mode in the active site cavity of PR as was found for A-98881.[9] Requiring only a few reaction steps, the following facile synthesis represents a less expensive alternative for the development of novel nonpeptidic PIs. Several of them have been evaluated regarding their PI activity and the type of inhibition of PR in an in vitro system.

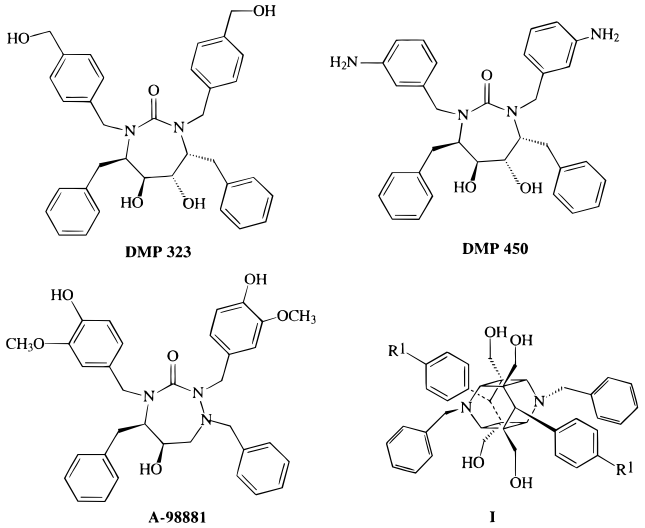

Figure 1. Structures of cyclic and azacyclic ureas DMP 323, DMP 450, and A-98881, respectively, and the general structure of cage dimeric target compounds (with chosen *N*-benzyl substitution) **I** discussed in the text.

Chemistry

Cage dimers **2a**,**c** (Scheme 1) have been synthesized either by solid-state photodimerization reaction of monomeric 4-phenyl-1,4-dihydropyridine (**1a**)[10] in nearly quantitative yields or by solution dimerization reaction of the corresponding monomeric derivative **1c**, which itself was produced by cyclocondensation reaction of benzaldehyde, ethyl propiolate, and benzylamine in acetic acid.[11]

Reduction of the ester groups in the cage compounds **2a**−**d** (Scheme 2) to the alcoholic target structures **3a**−**d** succeeded in excellent yields of about 90% under optimized conditions at −8 °C without any observed dimer fragmentation using lithium aluminum hydride ($LiAlH_4$) in dry THF.

The *N*H alcohols **3e**,**f** could not be obtained from **2e**,**f** [12] by direct ester reduction because the primary

† Martin-Luther-University Halle-Wittenberg.
‡ Novartis Forschungsinstitut GmbH.

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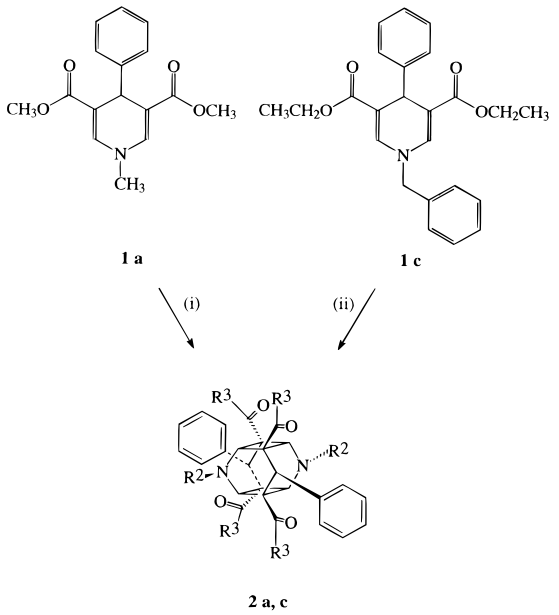
Scheme 1[a]



[a] Reagents and conditions: (i) *hν*, solid state, Ultra-Vitalux lamp; (ii) *hν*, MeOH/THF, Ultra-Vitalux lamp.

proton abstraction led to spontaneous dimer fragmentation into the corresponding monomeric adducts. However, compounds **3e**,**f** (Scheme 3) could be synthesized by *N*-acylation of **2e**,**f** with benzyl chloroformate at room temperature in THF to **4e**,**f**, followed by selective ester group reduction with calcium borohydride at room temperature in THF to **5e**,**f** and finally hydrogenolytical cleavage of the benzylcarbamate moiety.

Biological Activity as PR Inhibitors

The in vitro inhibitory activities of the synthesized cage dimers **3a**−**f** against PR have been evaluated as described.[13−15] Saquinavir has been used as reference compound. Due to the poor solubilities of the derivatives **3a**,**b**,**d**−**f**, their IC_{50} values could not be determined directly. They were estimated based on triple inhibitory determinations at 1 μM (**3d**) or 50 μM (for the other compounds) by simultaneous analysis of all dose−response data assuming parallel dose−response curves according to eq 1 using Scientist.[16] The Hill coefficient

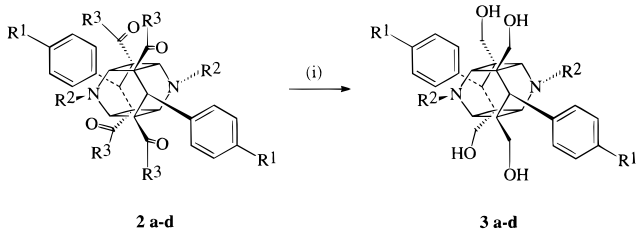
$$\frac{\nu}{\nu_0} = \frac{1}{1 + 10^{(C - I_j \otimes IC_{50,j})}} \qquad (1)$$

of the dose−response curve for **3c** was found to be 1 and was therefore fixed to this value. IC_{50} values are given in Table 1. The determination of K_i followed ref 15.

Results and Discussion

Within the small series of investigated target structures **3a**−**f**, the IC_{50} values of the *N*-methyl and *N*H derivatives (**3a**,**b** and **3e**,**f**) of about 200 μM are comparable to those of the first C_2-symmetric inhibitor A-74702[17] or pepstatin A[18] with IC_{50} > 200 μM proving, those compounds almost inactive. The introduction of the *N*-benzyl substituents mainly increases inhibitory activity up to 16.2 μM for **3c** as the most active compound (cf. Table 1).

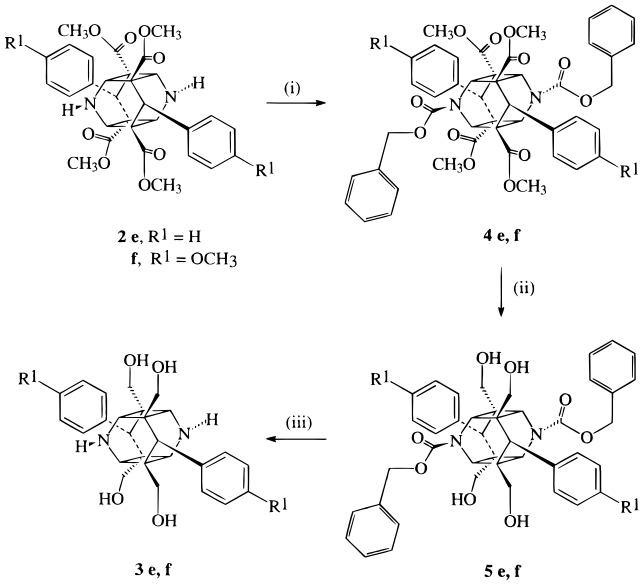
Scheme 2[a]



2	R1	R2	R3
a	H	CH_3	CH_3
b	OCH_3	CH_3	CH_3
c	H	Bzl	C_2H_5
d	OCH_3	Bzl	C_2H_5

[a] Reagents and conditions: (i) $LiAlH_4$, THF, −8 °C.

Scheme 3[a]



[a] Reagents and conditions: (i) BzlOCOCl, THF, rt; (ii) $Ca(BH_4)_2$, THF, rt; (iii) H_2, Pd/C, THF.

Table 1. HIV-1 Protease Inhibition of Cage Dimers **3a**−**f**

compd	IC_{50} (μM)	K_i (μM)
3a	262	nd[a]
3b	195	nd
3c	16.1 ± 1.04	7.8 ± 1
3d	33	nd
3e	227	nd
3f	209	nd

[a] nd, not determined.

Considering the binding mode suggested by us for the cage compound **3d** based on a molecular modeling study,[8] this great difference in activities from *N*H and *N*-methyl substitution to *N*-benzyl substitution can be explained presuming a necessary binding of the inhibitors for high inhibitory activity to both hydrophobic regions S1/S1′ and S2/S2′ of PR as has been shown for the aromatic residues of cyclic and azacyclic ureas.[5,7] In the case of *N*H and *N*-methyl substitutions, respectively, binding to S2/S2′ is not possible as the *N*-substituents do not reach these regions.

To characterize the type of inhibition, the best inhibitor of this first series of *N*-alkyl derivatives **3c** has been selected. The Lineweaver−Burk plot for **3c** obviously

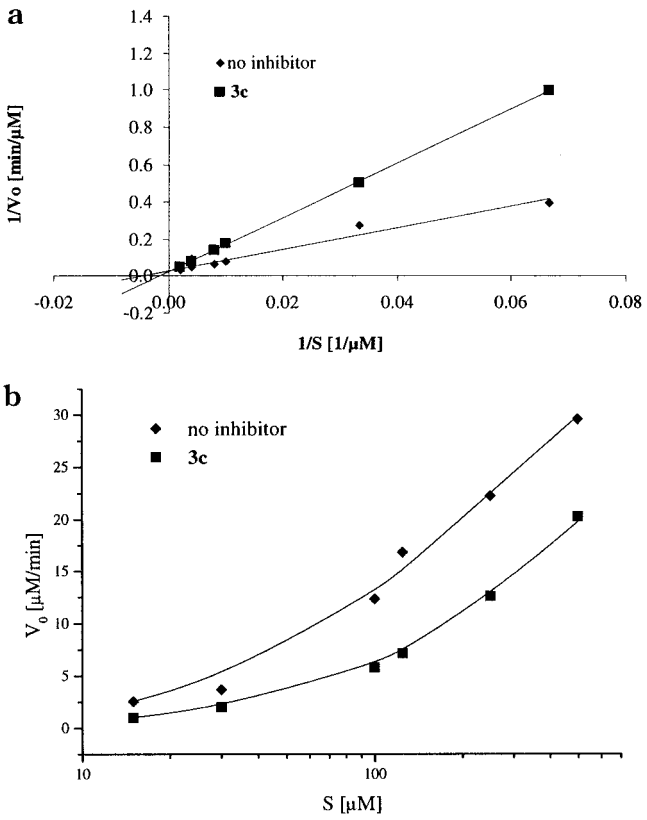


Figure 2. (a) Lineweaver−Burk plot for inhibitor **3c**. The substrate concentration was varied in the range of 15−500 μM. Measurements were conducted in the absence or presence of inhibitor **3c** at a fixed concentration of 15 μM. From linear fits of the data the parameters V_{max} and $K_{m/app}$ were calculated with V_{max} [μM/min] = 37 and K_m [μM] = 214 for the uninhibited reaction and V_{max} [μM/min] = 46 and K_{app} [μM] = 670, respectively, for the inhibited reaction. The determined K_i value of 7.0 μM corresponds well to the one given in Table 1. (b) Simultaneous analysis of both dose−response curves by nonlinear regression analysis yielded values of 44.0 (±2.4) μM/min for V_{max}, K_m = 240 (±28) μM and K_i = 9.55 (±1.03) μM.

shows that **3c** is a competitive inhibitor of PR with a decrease of K_m and a nearly unchanged V_{max} for the substrate hydrolysis of the inhibited reaction compared to the uninhibited one as demonstrated in Figure 2.

Comparing the inhibitory activity to the first representatives in the class of 4-hydroxycoumarins (Warfarin) with an $IC_{50} \sim 30$ μM[8] and phenprocoumon ($K_i = 1$ μM)[8] the cage dimers developed by us having a K_i value of 7−9 μM and an IC_{50} of 16.1 μM for **3c** can actually be classified as an innovative, promising new class of nonpeptidic PIs.

Experimental Section

General. Commercial reagents were used without further purification. ^{1}H NMR (400 or 500 MHz) spectra were recorded using tetramethylsilane as internal standard. TLC was performed on E. Merck 5554 silica gel plates. Mass spectra were measured with an AMD 402 mass spectrometer. Elemental analysis was performed using a Leco CHNS-932 apparatus.

The synthesis of compounds **2b**,**d** was recently reported; see ref 11.

Diethyl 1-Benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (1c). Ethyl propiolate (1.96 g, 20 mmol), benzaldehyde (1.06 g, 10 mmol), and benzylamine (1.07 g, 10 mmol) were heated in 1 mL of glacial acetic acid on a steam bath for 15 min. The reaction mixture was then poured into ice−water from which 2.8 g (72%) of **1c** crystallized on stirring: ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 7 Hz, 6H), 4.08 (q, 7 Hz, 4H), 4.46 (s, 2H), 4.91 (s, 1H), 7.09−7.73 (m, 12H); ESI-MS *m*/*z* 392 (M + H$^+$). Anal. ($C_{24}H_{25}NO_4$) C, H, N.

Tetramethyl 3,9-Dimethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,5,7,11-tetracarboxylate (2a). Crystalline **1a** (1.0 g, 1.74 mmol) with a layer thickness of 1 mm was irradiated as recently described.[11] After 6 days the reaction product was dissolved in boiling toluene from which 0.90 g (90%) of **2a** crystallized on cooling: ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 6H), 3.52 (s, 12H), 4.11 (4H), 4.16 (2H), 7.10−7.22 (m, 10H); ESI-MS *m*/*z* 597 (M + Na$^+$). Anal. ($C_{32}H_{34}N_2O_4$) C, H, N.

Tetraethyl 3,9-Dibenzyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,5,7,11-tetracarboxylate (2c). 1c (0.40 g, 0.51 mmol) was dissolved in 40 mL of methanol/THF under stirring. The solution was irradiated in a quartz flask with an Ultra-Vitalux lamp from a distance of 60 cm for about 4 weeks. During the irradiation compound **2c** crystallized from the solution finally yielding 0.28 g (70%) as white crystals: ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 7.0 Hz, 12H), 3.96 (q, 7.0 Hz, 8H), 4.26 (s, 4H), 4.27 (s, 2H), 7.05−7.31 (m, 24H); ESI-MS *m*/*z* 783 (M + H$^+$). Anal. ($C_{48}H_{50}N_2O_8$) C, H, N.

Representative Procedure for the Ester Reduction of Compounds 2a−d to Alcohols 3a−d: 1,5,7,11-Tetrahydroxymethyl-3,9-dimethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (3a). 2a (0.04 g, 0.7 mmol) was dissolved in dry THF and the solution was cooled to −8 °C. Then a solution of lithium aluminum hydride (1.4 mL, 1.4 mmol) in THF (1 M) was added. After 2 h the reaction mixture was hydrolyzed with 2 mL of a solution of potassuim hydroxide (20%) at 0 °C. The water layer was then extracted with 100 mL of chloroform three times. The combined extracts were dried over sodium sulfate. On reducing the extraction volume the crude compound **3a** crystallized and was recrystallized from methanol/water yielding 0.28 g (88%) of pure **3a** as white powder: ^{1}H NMR (DMSO-d_6) δ 2.73 (s, 4H), 2.76 (s, 6H), 3.04 (dd, after D_2O addition d, 10.6 Hz, 4.9 Hz, 4H), 3.19 (dd, after D_2O addition d, 10.6 Hz, 4.9 Hz, 4H), 3.59 (s, 2H), 4.30 (t, 4.9 Hz, 4H, exchangeable), 7.07−7.81 (m, 10H); ESI-MS *m*/*z* 463 (M + H$^+$). Anal. ($C_{28}H_{34}N_2O_4 \cdot 1.5H_2O$) C, H, N.

1,5,7,11-Tetrahydroxymethyl-3,9-dimethyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]-dodecane (3b): yield 0.029 g (89%); ^{1}H NMR (DMSO-d_6) δ 2.69 (s, 4H), 2.74 (s, 6H), 3.02 (dd, after D_2O addition d, 10.4 Hz, 4.6 Hz, 4H), 3.18 (dd, after D_2O addition d, 10.4 Hz, 4.6 Hz, 4H), 3.52 (s, 2H), 3.70 (s, 6H), 4.24 (t, 4.6 Hz, 4H, exchangeable), 6.68−7.70 (m, 8H); ESI-MS *m*/*z* 523 (M + H$^+$). Anal. ($C_{30}H_{38}N_2O_6 \cdot 0.5H_2O$) C, H, N.

3,9-Dibenzyl-1,5,7,11-tetrahydroxymethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (3c): yield 0.029 g (92%); ^{1}H NMR (DMSO-d_6) δ 2.95 (s, 4H), 3.06 (dd, after D_2O addition d, 10.5 Hz, 4.4 Hz, 4H), 3.16 (dd, after D_2O addition d, 10.5 Hz, 4.4 Hz, 4H), 3.66 (s, 2H), 4.13 (s, 4H), 4.41 (t, 4.4 Hz, 4H, exchangeable), 7.03−7.79 (m, 20H); ESI-MS *m*/*z* 615 (M + H$^+$). Anal. ($C_{40}H_{42}N_2O_4 \cdot 0.5H_2O$) C, H, N.

3,9-Dibenzyl-1,5,7,11-tetrahydroxymethyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]-dodecane (3d): yield 0.027 g (87%); ^{1}H NMR (DMSO-d_6) δ 2.92 (s, 4H), 3.06 (dd, after D_2O addition d, 10.5 Hz, 4.0 Hz, 4H), 3.20 (dd, after D_2O addition d, 10.5 Hz, 4.0 Hz, 4H), 3.60 (s, 2H), 3.70 (s, 6H), 4.11 (s, 4H), 4.43 (t, 4.4 Hz, 4H, exchangeable), 6.49−7.67 (m, 18H); FD-MS *m*/*z* 675 (M$^+$). Anal. ($C_{42}H_{46}N_2O_6$) C, H, N.

Representative Procedure for the Hydrogenolytical Cleavage of *N*-Benzyloxycarbonyl Substituents in Compounds 5e,f to *N*H Derivatives 3e,f: 1,5,7,11-Tetrahydroxymethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (3e). Compound **5e** (0.04 g, 0.05 mmol) was dissolved im 25 mL of THF. After the addition of Pd/C (10%) (20 mg, 0.02 mmol) the suspension was shaken under hydrogen atmosphere for 1 week. Then the solution was filtered and the residue was washed several times with warm methanol. The methanolic extracts were evaporated to dryness. The remaining white powder was recrystallized from

methanol/water yielding 0.017 g (69%) of **3e**: ^{1}H NMR (DMSO-d_6) δ 2.91 (s, 4H), 2.94 (dd, after D_2O addition d, 10.4 Hz, 4.9 Hz, 4H), 3.17 (dd, after D_2O addition d, 10.4 Hz, 4.9 Hz, 4H), 3.30 (s, 2H), 4.11 (t, 4.9 Hz, 4H, exchangeable), 7.09−8.32 (m, 10H); *N*H signals were covered by the water signal of DMSO; ESI-MS *m*/*z* 435 ($M + H^+$). Anal. ($C_{26}H_{30}N_2O_4 \cdot 2H_2O$) C, H, N.

1,5,7,11-Tetrahydroxymethyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (3f): yield 0.017 g (65%); ^{1}H NMR (DMSO-d_6) δ 2.97 (s, br, 4H), 3.28 (d, br, 15 Hz, 4H), 3.56 (s, br, 2H), 3.58 (d, br, 15 Hz, 4H), 3.73 (s, 6H), 3.75 (s, 2H), 4.62, 4.71 (2 × s, br, 4H, exchangeable), 6.72−7.14 (m, 8H); ESI-MS *m*/*z* 495 ($M + H^+$). Anal. ($C_{28}H_{34}N_2O_6$) C, H, N.

General Procedure for *N*-Acylation of *N*H Cage Dimers 2e,f with Benzyl Chloroformate to 4e,f: Tetramethyl 3,9-Dibenzyloxycarbonyl-6,12-diphenyl-3,9-diazahexacyclo-[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,5,7,11-tetracarboxylate (4e). Compound **2e** (0.04 g, 0.07 mmol) was dissolved in 40 mL of THF at 40 °C. Under stirring benzyl chloroformate (0.119 g, 0.7 mol) was added to the solution at room temperature and stirring continued overnight. Then the solution volume was reduced by evaporation in vacuo compound **4e** precipitated with a yield of 0.053 g (89%): ^{1}H NMR ($CDCl_3$) δ 3.57, 3.55, 3.46 (3 × s, br, 24 H of two rotamers), 3.81 (s, 4H), 5.27 (s, br, 4H), 5.33 (s, br, 4H), 5.66, 5.56 (2 × s, br, 8H), 6.87−7.33 (m, 40H); ESI-MS *m*/*z* 837 ($M + Na^+$). Anal. ($C_{46}H_{42}N_2O_{12}$) C, H, N.

Tetramethyl 3,9-dibenzyloxycarbonyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,5,7,11-tetracarboxylate (4f): yield 0.047 g (85%); ^{1}H NMR ($CDCl_3$) δ 3.41, 3.46 (2 × s, 24H), 3.51, 3.53, 3.65 (3 × s, 12H), 3.71 (s, 4H), 3.26 (s, br, 4H), 5.32 (s, br, 4H), 5.50, 5.59 (2 × s, br, 8H), 6.48−7.34 (m, 36H); ESI-MS *m*/*z* 913 ($M + K^+$). Anal. ($C_{48}H_{46}N_2O_{14}$) C, H, N.

General Procedure for the Ester Reduction of Cage Compounds 4e,f to Alcoholic Derivatives 5e,f: 3,9-Dibenzyloxycarbonyl-1,5,7,11-tetrahydroxymethyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (5e). Compound **4e** (0.04 g, 0.05 mmol) was dissolved in 25 mL of a suspension of 0.027 g (0.5 mmol) of freshly prepared calcium borohydride in THF.[19] The mixture was stirred for about 4 weeks at room temperature. Then 2.5 mL of ice−water was added at 0 °C and the excess of calcium borohydride was hydrolyzed by the dropwise addition of hydrochloric acid (10%). The solution was kept stirring for 1 h at 0 °C and then extracted with 100 mL of chloroform three times. After drying over sodium sulfate for 30 min the solution was filtered. After evaporation to dryness in vacuo the residue was recrystallized from methanol/water yielding 0.031 g (89%) of **5e** as a white powder: ^{1}H NMR (DMSO-d_6) δ 3.02−3.07 (m, 12H), 3.41−3.44 (m, 8H), 4.40, 4.44, 4.50 (3 × s, 8H), 4.63, 4.66, 4.69, 4.71 (4 × t, 13 Hz, 8H, exchangeable), 5.11 (d, 13.0 Hz, 4H), 5.28 (d, 13.0 Hz, 4H), 6.88−7.39 (m, 40H); ESI-MS *m*/*z* 741 ($M + K^+$). Anal. ($C_{42}H_{42}N_2O_8$) C, H, N.

3,9-Dibenzyloxycarbonyl-1,5,7,11-tetrahydroxymethyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo-[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane (5f): yield 0.032 g (93%); ^{1}H NMR (DMSO-d_6) δ 3.00 (s, 4H), 3.01−3.06 (m, 8H), 3.50−3.51 (m, 8H), 3.68 (s, 12H), 4.40, 4.42, 4.47 (3 × s, 8H), 4.57, 4.61, 4.63, 4.65 (4 × t, 2.0 Hz, 8H, exchangeable), 5.09 (d, 13.2 Hz, 4H), 5.30 (d, 13.2 Hz, 4H), 6.42−7.39 (m, 36H); ESI-MS *m*/*z* 801 ($M + K^+$). Anal. ($C_{44}H_{46}N_2O_{10}$) C, H, N.

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