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PALLADIUM-CATALYZED AMINATION IN THE SYNTHESIS OF MACROBICYCLES INCORPORATING CYCLEN, CYCLAM AND PYRIDINE MOIETIES

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Abstract – Palladium-catalyzed amination was successfully applied to the synthesis of macrobicyclic cryptands comprising cyclen or cyclam and pyridine moieties. Starting bis(halopyridylmethyl) substituted cyclen and cyclam were obtained from protected tetraazamacrocycles in good yields and introduced in the catalytic macrocyclization reactions with a number of polyamines and oxadiamines to give target macrobicycles. The yields of macrobicyclic cryptands were shown to be dependent on the cavity size of starting tetraazamacrocycle, on the nature of halogen atom and substitution pattern in the starting compounds, and on the nature of di- and polyamines. The best yields reached 33%.

INTRODUCTION

Polymacrocyclic compounds derived from tetraazamacrocycles possess several advantages over monomacrocycles, for example, their metal complexes are usually more thermodynamically and kinetically stable. Macropolycyclic compounds containing cyclen (1,4,7,10-tetraazacyclododecane) and cyclam (1,4,8,11-tetraazacyclotetradecane) moieties are known for last decades and can be attributed to different classes of topology: macrobicyclic and macrotricyclic cryptands, macropolycycles of cylindrical shape, macropolycycles incrorporating other macrocyclic structures.

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‡This paper is dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday

The simplest bicyclic compounds based on tetraazamacrocycles are various so-called cross-bridged cyclen and cyclam.[1-3] The introduction of aromatic and heteroaromatic fragments in polymacrocyclic compounds often increases the conformational rigidity of the molecule thus fixing the cavity size.[4] Also, these fragments are crucial in the creation of chemosensors because (hetero)aromatic moieties play the role of chromophores or fluorophores being responsible for the physical response to coordination. The majority of macropolycyclic compounds contain (hetero)aromatic groups linked to nitrogen atoms through methylene or methyne bridges.

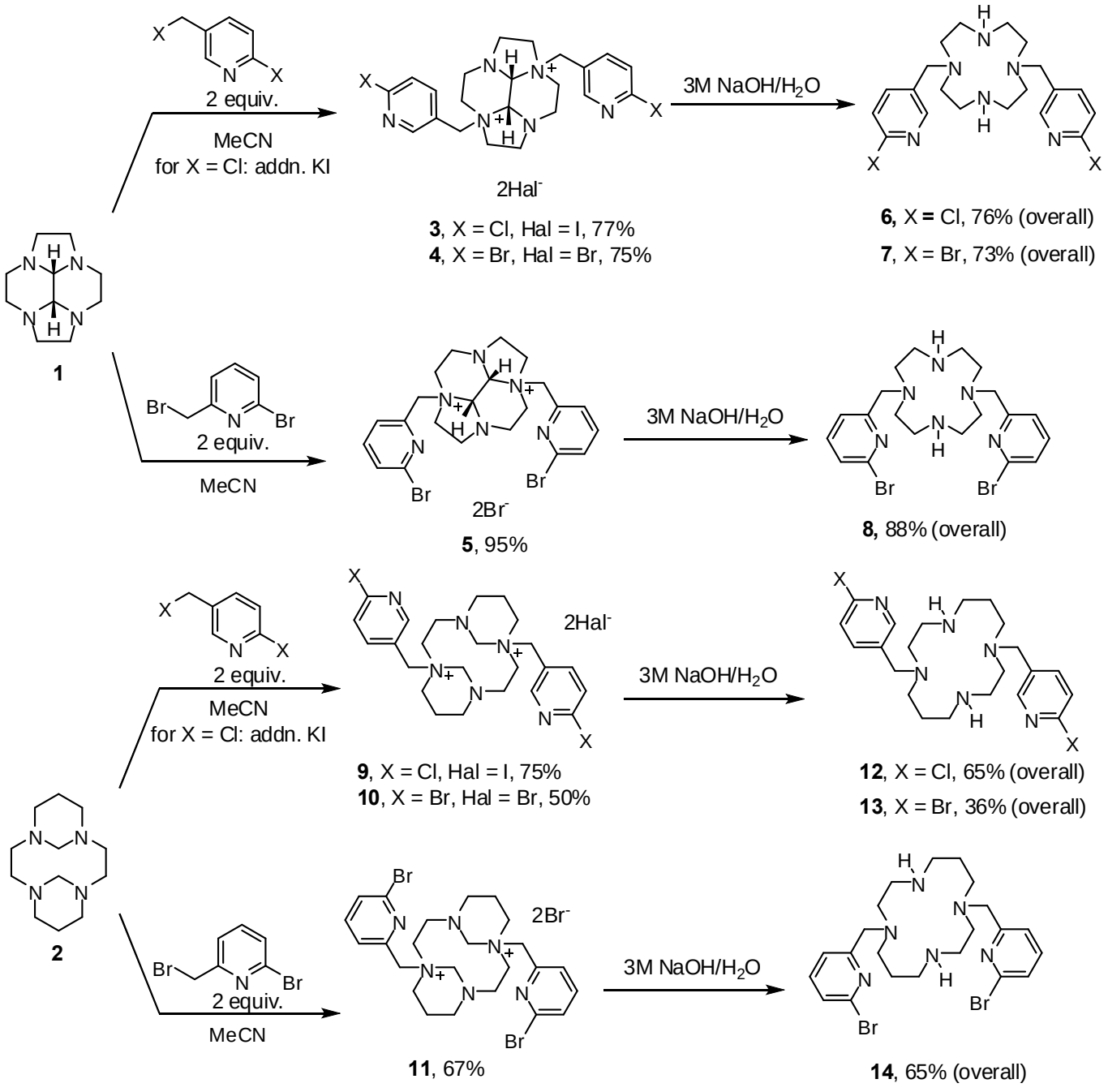
Usually macrobicycles possessing cross-bridged cyclen and cyclam moieties do not contain many donor atoms like nitrogen, oxygen or sulfur in the second cycle,[5-10] however, described are macrobicycles with several donor atoms.[11] Some macrobicycles are formed *via* functionalization of neighboring nitrogen atoms of tetraazamacrocycles.[12-15] Macrotricyclic compounds mainly posses two macrocycles *cis*-fused with the central tetraazamacrocycle.[16-18] The most interesting macrotricycles are actually the cryptands of cylindrical shape and they often contain two cyclen or cyclam fragments arranged in a face-to-face manner *via* two symmetrical aromatic spacers.[19,20] Additional macrocycles may be used as linkers to furnish macropentacyclic structures.[21] Porphirin systems were successfully incorporated into heteropolycyclic systems with cyclen and cyclam.[22-25]

There are several examples of macropolycyclic compounds based on cyclen or cyclam and incorporating pyridine in the macrocyclic moiety. Macrobicycle with cyclam unit with a bridge containing 2,6-disubstituted pyridine was prepared either from 5,12-dioxocyclam[26,27] or from free cyclam.[9] Cryptands of cylindrical shape also may contain two pyridines and two cyclam[20] or cross-bridged cyclam[28] units. Our own interest in these compounds is due to the fact that pyridine incorporated in the macrocyclic system may increase the number of donor sites of the macrocyclic ligand what is important for coordinating cations of heavy and rare earth metals which possess high coordination numbers. Earlier we successfully applied Pd-catalyzed amination to the synthesis of various macrocycles possessing disubstituted benzene,[29] biphenyl,[30] naphthalene,[31] anthracene and anthraquinone,[32] pyridine,[33,34] bipyridine[35] moieties, and recently we have shown the possibility to use this approach for the synthesis of macrobicyclic compounds.[36,37] In this paper we demonstrate how Pd-catalyzed amination works in the synthesis of pyridine-containing macrobicyclic compounds based on cyclen and cyclam.

RESULTS AND DISCUSSION

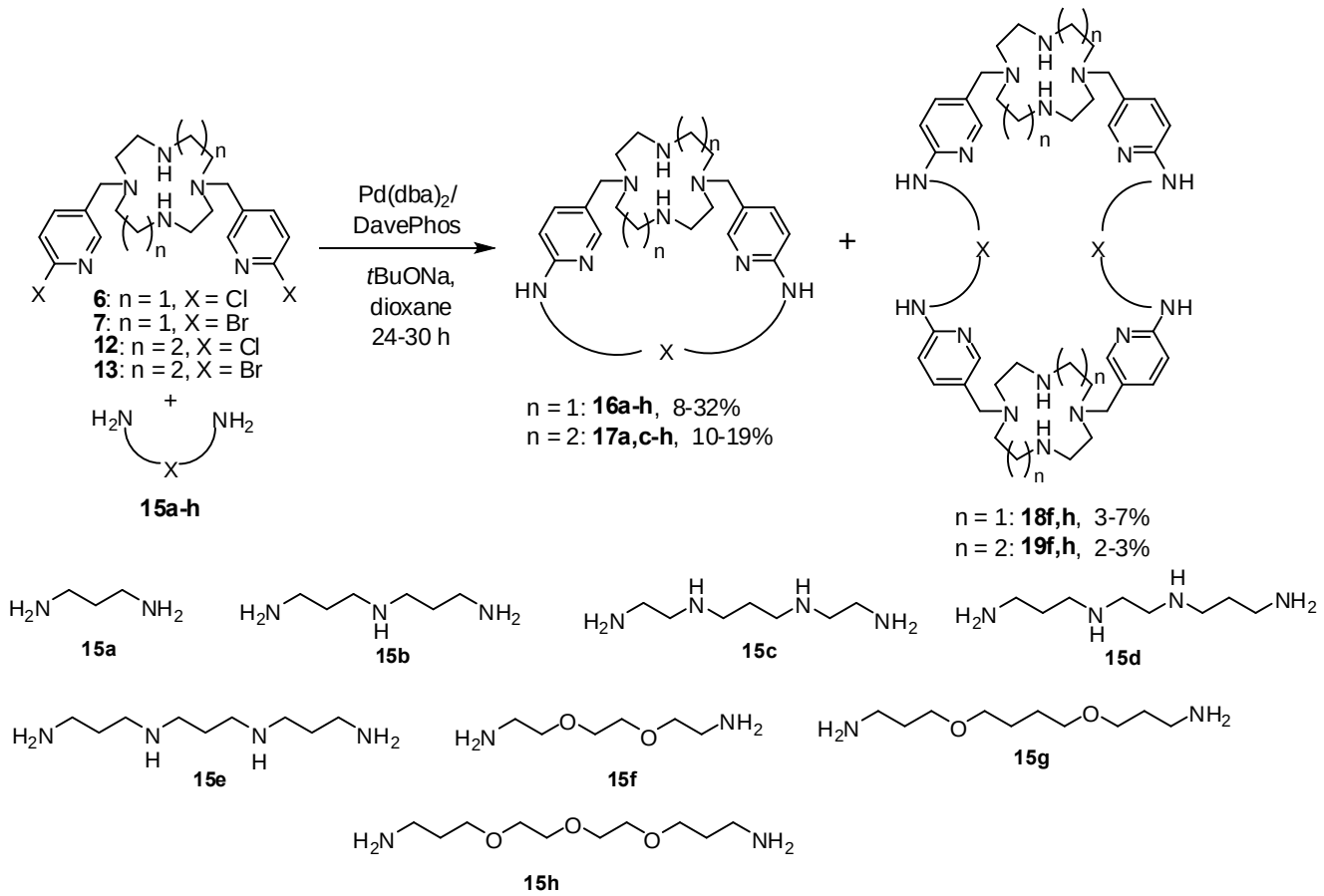
Previously unknown bis(halogenopyridylmethyl) substituted cyclens and cyclams were synthesized using a described procedure[36] from corresponding *cis*-glyoxal-cyclen **1** and formaldehyde-cyclam **2** (Scheme 1). The first step was the reaction of protected tetraazamacrocycles **1** and **2** with 2 equiv. of halogenomethyl halogenopyridines in acetonitrile. Di-salts **3-5** and **9-11** were formed in yields from 48 to 95% and were

collected as white precipitates. The yields of these compounds were strongly dependent on their solubility in acetonitrile which generally was enough low. In the reactions with 5-(chloromethyl)-2-chloropyridine addition of KI was necessary to increase the rate of the substitution reaction. The second deprotection step proceeded using 3M NaOH solution at 80-90 ^{o}C and was almost quantitative in many cases. Compounds **6**, **7** and **12**, **13** were obtained in order to compare the reactivity of chlorine and bromine atoms in the Pd-catalyzed macrocyclization reactions. Compounds **8** and **14** were made in view of the synthesis of macrobicycles with isomeric 2,6-disubstituted pyridine moieties.



Scheme 1. Synthesis of bis(halogenopyridylmethyl) substituted cyclens and cyclams.

Compounds **6, 7** and **12, 13** were introduced in the Pd-catalyzed amination reactions with a number of polyamines and oxadiamines **15a-h** (Scheme 2). Studied di- and polyamines possess various chain length and contain different number of nitrogen and oxygen atoms. At first a standard catalytic system $Pd(dba)_2$/BINAP (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) was applied in these reactions but it was shown to be inefficient for the synthesis of the target macrocycles though the conversion of starting halogenopyridyl derivatives was quantitative. The use of DavePhos (2-dimethylamino-2'-dicyclohexylphosphino)biphenyl) instead of BINAP was successful for the synthesis of desired macrobicycles. The reactions were run using normally 16 mol% of the catalytic system, in boiling 1,4-dioxane (c = 0.02 M), using *t*BuONa as a base. The reactions were complete in 24-30 h according to ^{1}H NMR spectra of the reaction mixtures. Macrobicycles were isolated using column chromatography on silica gel, the yields are given in Table 1.



Scheme 2. Synthesis of macrobicycles **16**, **17**.

The reaction of bis(6-chloropyrid-3-yl) derivative of cyclen **6** with the shortest 1,3-propanediamine (**15a**) provided only 8% yield of the target macrobicycle **16a** (entry 1), the increase in the polyamine length led to substantially better result in the case of triamine **15b** (29%, entry 2). The reaction of a longer tetraamine **15e** afforded almost the same yield of the cryptand **16e** (27%, entry 5), however, the yields in

the case of two other tetraamines, **15c,d** were notably lower (entries 3, 4), possibly, due to the presence of ethylenediamine fragments in these molecules. These fragments can form more stable 5-member chelates with Pd(0) thus eliminating it from the catalytic cycle and diminishing the yields of the products, the feature already discussed by us in earlier publications.[38] The yields of macrobicycles in the reactions with oxadiamines **15f-h** were among the best (24-32%, entries 6, 8, 9), we also demonstrated that the catalyst loading can be diminished when using 1.5 equiv. of oxadiamine without altering the yield of the macrobicycle (entry 7). The reaction of the bromopyridyl derivative **7** was not advantageous over its chloropyridyl analogue and did not lead to an increase in the product yield (entry 10). Except two examples (entries 7, 10), no cyclic dimers were isolated as by-products in these reactions, in contrast to the results obtained in the reactions with bis(3-bromobenzyl) derivative of cyclen, where cyclic dimers were isolated in the majority of cases.[36,37] This fact is in good correlation with the formation of cyclodimers in the macrocyclization reactions of 1,3-dibromobenzene with polyamines[29] and the absence of such cyclodimers in the macrocyclization reactions with participation of 2,6- and 3,5-dibromopyridines.[33,34]

Table 1. Synthesis of macrobicycles **16**, **17**.

Entry	Halogenopyridyl derivative	Polyamine	Conc., mol/L	Catalyst loading, $Pd(dba)_2$/DavePhos, mol%	Product and yield, %
1	**6**	**15a**	0.02	16/18	**16a**, 8
2	**6**	**15b**	0.02	16/18	**16b**, 29
3	**6**	**15c**	0.02	16/18	**16c**, 16
4	**6**	**15d**	0.02	16/18	**16d**, 15
5	**6**	**15e**	0.02	16/18	**16e**, 27
6	**6**	**15f**	0.02	16/18	**16f**, 32
7	**6**	**15f** (1.5 equiv.)	0.04	8/9	**16f**, 33; **18f**, 7
8	**6**	**15g**	0.02	16/18	**16g**, 24
9	**6**	**15h**	0.02	16/18	**16h**, 24
10	**7**	**15h**	0.035	8/9	**16h**, 21; **18h**, 3
11	**12**	**15a**	0.02	16/18	**17a**, 7
12	**12**	**15c**	0.02	16/18	**17c**, 11
13	**12**	**15d**	0.02	16/18	**17d**, 14
14	**12**	**15e**	0.02	16/18	**17e**, 19

15	**12**	**15f**	0.05	16/18	**17f**, 13
16	**12**	**15f** (1.5 equiv.)	0.02	16/18	**17f**, 17
17	**12**	**15f** (1.5 equiv.)	0.04	8/9	**17f**, 20; **19f**, 2
18	**12**	**15g**	0.02	16/18	**17g**, 10
19	**12**	**15h**	0.02	16/18	**17h**, 19
20	**12**	**15h**	0.04	8/9	**17h**, 19; **19h**, 3
21	**13**	**15h**	0.02	16/18	**17h**, 10

The reactions of bis(chloropyridyl) derivative of cyclam **12** provided macrobicycles **17** in lower yields, and their dependence on the nature of polyamines was not clear. The best yield (19%) of the target cryptand **17h** (entry 19) was observed in the reaction with trioxadiamine **15h** possessing the longest chain. We have already noted that generally bromobenzyl derivatives of cyclam gave poorer yields in macrocyclization reaction than their cyclen analogues,[36] possibly it is due to a better coordination of Pd(0) to cyclam moiety. Application of 1.5 equiv. of oxadiamine **15f** increased the yield of cryptand **17f** (entries 15, 16), and the use of 8 mol% catalyst instead of 16 mol% did not change the yield or even slightly improved it (entries 16 and 17, 19 and 20). We suppose that small excess of polyamine could be favorable in other cases too, however, application of 16 mol% catalyst proved to be important in many other cases. As for the concentration of starting compounds, normally we used 0.02 M solutions, but the increase in the concentration up to 0.035-0.04 M did not affect the yields of the target macrobicycles **16, 17**. The reaction of bromopyridyl analogue **13** with trioxadiamine **15h** was not efficient providing only 10% yield of the desired product **17h** (entry 21). In all above mentioned reactions full conversion of starting halogenopyridyl derivatives **6, 7, 12, 13** was observed, though the conversion of di- and polyamines was not full and sometimes did not exceed 50%, what suggests competing with the reactions other than catalytic amination, which are responsible for moderate or low yields of macrobicycles. Better results achieved with chloropyridyl derivatives **6**, **12** may be explained by a lower reactivity of the chlorine atom in the side reactions which diminish the yields of the amination products. We could not isolate other by-products in these reactions as individual compounds, except above mentioned cyclic dimers, thus we can only suppose that catalytic homo-coupling and hydro-debromination processes took place.

The attempt to use BINAP in the reaction of trioxadiamine with bromopyridyl derivative **13** was useless as no macrobicycle **17h** was formed even in the reaction mixture. Using the same cyclam derivative **13** we tried other donor phosphine ligands: 2-(dicyclohexylphosphino)biphenyl (**L1**), 2-(di*tert*-butylphosphinobiphenyl) (**L2**), several ferrocene-based ligands (**L3-L6**) (Figure 1). We found out that the

use of the ligands **L1**, **L3** and **L4** led to macrobicycle **17h** in 10-12% yields while other ligands did not provide good conversion of starting material.

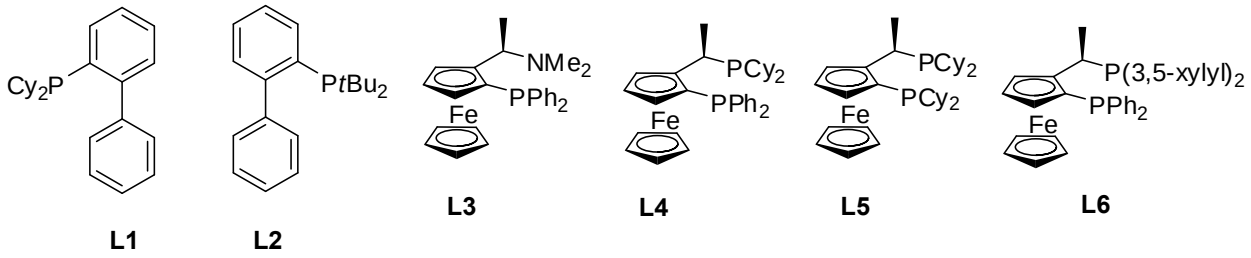
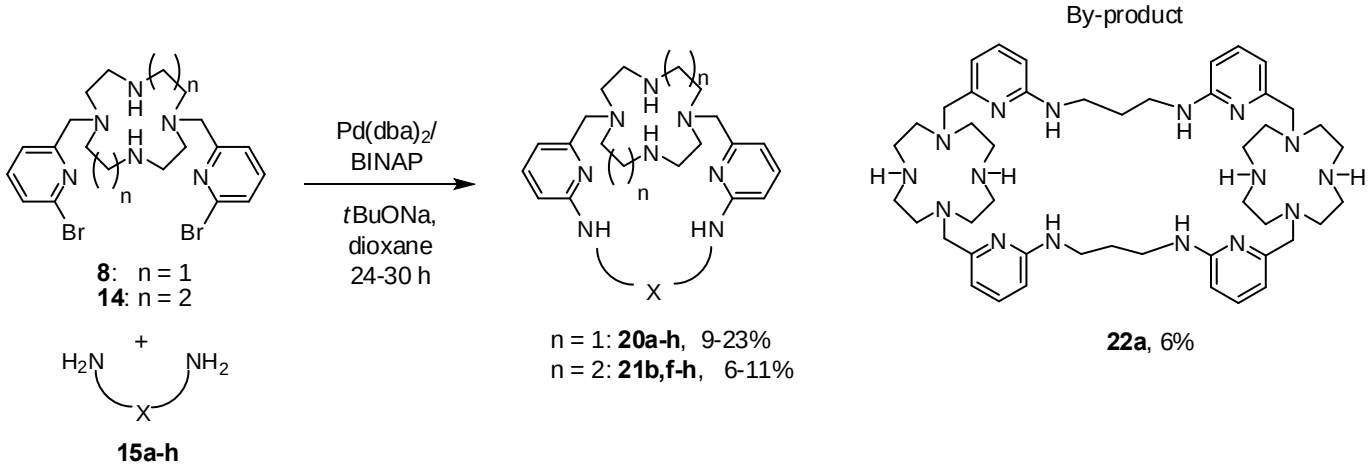


Figure 1. Donor phosphine ligands.

The reactions of isomeric 3-bromopyrid-2-ylmethyl derivatives of cyclen and cyclam **8** and **14** with polyamines (Scheme 3) were also sensitive to the nature of the phosphine ligand, but in this case only BINAP was efficient, and the use of the donor DavePhos resulted in the formation of a complex mixture of unidentified products according to ^{1}H NMR of the reaction mixtures. All reactions were conducted using 0.05 M concentration of starting compounds to optimize the reaction time. The results of the macrocyclization reactions are presented in Table 2.



Scheme 2. Synthesis of macrobicycles **20**, **21**.

Table 2. Synthesis of macrobicycles **20**, **21**.

Entry	Halogenopyridyl derivative	Polyamine	Product and yield, %
1	**8**	**15a**	**20a**, 20; **22a**, 6
2	**8**	**15b**	**20b**, 23
3	**8**	**15c**	**20c**, 9

4	**8**	**15d**	**20d**, 11
5	**8**	**15e**	**20e**, 16
6	**8**	**15f**	**20f**, 22
7	**8**	**15g**	**20g**, 11
8	**8**	**15h**	**20h**, 18
9	**14**	**15b**	**21b**, 6
10	**14**	**15f**	**21f**, 11
11	**14**	**15g**	**21g**, 6
12	**14**	**15h**	**21h**, 10

It is clearly seen from the table that generally higher yields of cryptands **21** were provided by the use of di- and triamine while the application of tetraamines (entries 3-5) resulted in poorer yields of the target macrobicycles. Moreover, tetraamine **15c** with two ethylenediamine fragments provided notably less yield of **21c** (9%, entry 3) than tetraamine **15e** without such fragments (16%, entry 5). The best yields (23 and 22%) were achieved with triamine **15b** (entry 2) and dioxadiamine **15f** (entry 6), this fact is in a good correlation with the results obtained with bis(6-chloropyrid-3-ylmethyl) substituted cyclen **6** (Table 1). Only in one case, in the reaction with 1,3-diaminopropane, we managed to isolated the cyclic dimer **22a** which is an interesting example of a cylindrically shaped cryptand.

The reactions with the analogous cyclam derivative **14** were not as efficient, and the yields of corresponding macrobicycles **21** did not exceed 11% (entries 9-12). We did not carry out the reactions with more problematic reagents like tetraamines because the results were insufficient even with di- and trioxadimines **15f,h**. Such low yields support an idea that cyclam-based substrates are in general less efficient in the Pd-catalyzed macrocyclization than cyclen derivatives and also they correlate with a similarly low yield of the cryptand in the reaction between isomeric bis(6-bromopyrid-3-ylmethyl) substituted cyclam **13** with trioxadiamine **15h** (Table 1, entry 21).

CONCLUSION

To sum up, we synthesized a series of new bis(halogenopyridylmethyl) substituted cyclens and cyclams, the majority of them were obtained in very good yields. These compounds were introduced into the Pd-catalyzed amination reactions with a number of polyamines and oxadiamines for the synthesis of novel pyridine-containing macrobicyclic cryptands. The reactions were found to be sensitive to the nature of the phosphine ligand: 6-chloropyrid-3-yl and 6-bromopyrid-3-yl derivatives demanded the application of a donor phosphine ligand DavePhos whereas 6-bromopyrid-2-yl derivatives normally reacted when using

BINAP. The best yields of target macrobicyles reached 33% in the case of bis(6-chloropyrid-3-ylmethyl) substituted cyclen. We showed that in some cases the catalyst loading can be diminished, concentration of the starting compounds increased without affecting the yields of macrobicycles. Application of 1.5 equivalents of polyamines can also be helpful for optimizing the yields of these compounds.

EXPERIMENTAL

All chemicals were purchased from Aldrich and Acros companies and used without further purification. *Cis*-glyoxal-cyclen **1** and formaldehyde-cyclam **2** were provided by CheMatech Co. $Pd(dba)_2$ was synthesized according to a known procedure.[39] 2-Chloro-5-chloromethylpyridine, 2-bromo-6-methylpyridine, 2-bromo-5-methylpyridine, di- and polyamines **15a-h**, phosphine ligands were purchased from Aldrich and Acros. 2-Bromo-5-bromomethylpyridine and 2-bromo-6-bromomethylpyridine were synthesized from commercial 2-bromo-5-methylpyridine and 2-bromo-6-methylpyridine by the bromination with NBS in CCl_4 in the presence of AIBN and purified by column chromatography on silica gel (petrol ether – CH_2Cl_2). Commercial 1,4-dioxane was distilled over NaOH and sodium under argon, acetonitrile was distilled over P_2O_5 and CaH_2, dichloromethane and methanol were distilled prior to use. Column chromatography was carried out using silica gel (40-60 mkm) purchased from Fluka. ^{1}H and ^{13}C NMR spectra were registered in $CDCl_3$ using Bruker Avance 400 spectrometer at 400 and 100.6 MHz respectively. Chemical shift values δ are given in ppm and coupling constants *J* in Hz. MALDI-TOF spectra were recorded with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards.

2a,6a-Bis[(6-chloropyridin-3-yl)methyl]decahydro-4a,8a-dizaz-2a,6a-diazoniacyclopenta[*fg*]-acenaphthene diiodide (3). *Cis*-glyoxal-cyclen **1** (20 mmol, 3.88 g) was dissolved in MeCN (70 mL), 2-chloro-5-chloromethylpyridine (40 mmol, 6.48 g) and NaI (40 mmol, 6.0 g) were added, and the reaction mixture was stirred for 32 h at 50-60 ^{o}C and then 60 h at room temperature. The precipitate was filtered off, washed with MeCN (4x30 mL) and dried *in vacuo*. Compound **3** was obtained as a white crystalline powder. Yield 13.96 g (99%). ^{1}H NMR (DMSO-d_6): δ 2.98-3.08 (m, 2H), 3.29 (d, *J* = 12.4 Hz, 2H), 3.40-3.79 (m, 10H), 4.33 (td, *J* = 10.9 Hz, 3.3 Hz, 2H), 5.05 (d, *J* = 13.4 Hz, 2H), 5.18 (s, 2H), 5.30 (d, *J* = 13.4 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 8.30 (dd, *J* = 8.2 Hz, 2.4 Hz, 2H), 8.79 (d, *J* = 2.4 Hz, 2H).

***N*^{1},*N*^{7}-Bis((6-chloropyridin-3-yl)methyl)cyclen (6).** Compound **3** (13.96 g, 19.9 mmol) was dissolved in a water solution of KOH (16 g in 120 mL water) and stirred for 72 h at 80 °C. Aqueous layer was separated from the oily residue, extracted with CH_2Cl_2 (2x40 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **6** was obtained as a slightly beige

crystalline powder, mp 122-124 °C. Yield 6.44 g (76% overall). ^{1}H NMR ($CDCl_3$): δ 2.38 (br.s, 2H), 2.51-2.57 (m, 8H), 2.58-2.65 (m, 8H), 3.53 (s, 4H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.56 (dd, *J* = 8.2 Hz, 2.4 Hz, 2H), 8.26 (d, *J* = 2.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 45.2 (4C), 51.6 (4C), 56.4 (2C), 124.3 (2C), 133.3 (2C), 139.3 (2C), 149.9 (2C), 150.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{20}H_{29}Cl_2N_6$ $[M+H]^+$ 423.1831, found 423.1895.

2a,6a-Bis[(6-bromopyridine-3-yl)methyl]decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]-acenaphthene dibromide (4). *Cis*-glyoxal-cyclene **1** (2.39 mmol, 0.47 g) was dissolved in MeCN (10 mL), 2-bromo-5-bromomethylpyridine (4.78 mmol, 1.2 g) was added, and the reaction mixture was stirred for 48 h at room temperature. The precipitate was filtered off, washed with MeCN (2x10 mL) and dried *in vacuo*. Compound **4** was obtained as white crystalline powder. Yield 0.801 g (48%). ^{1}H NMR (DMSO-d_6): δ 2.96 (q, *J* = 8.2 Hz, 2H), 3.10-3.77 (m, 12H), 4.26 (td, *J* = 10.7 Hz, 3.6 Hz, 2H), 4.94 (d, *J* = 13.6 Hz, 2H), 4.95 (s, 2H), 5.12 (d, *J* = 13.6 Гц, 2H), 7.88 (d *J* = 8.3 Hz, 2H), 8.13 (dd, *J* = 8.3 Hz, 2.0 Hz, 2H), 8.72 (d, *J* = 2.0 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 42.2 (2C), 46.4 (2C), 55.5 (2C), 56.4 (2C), 60.2 (2C), 76.5 (2C), 123.5 (2C), 128.8 (2C), 143.4 (2C), 143.9 (2C), 153.8 (2C).

***N*^{1},*N*^{7}-Bis((6-bromopyridin-3-yl)methyl)cyclen (7)**. Compound **4** (1.15 mmol, 0.801 g) was dissolved in a water solution of KOH (3.4 g in 20 mL water) and stirred for 48 h at 80 °C. Aqueous layer was separated from the oily residue, extracted with CH_2Cl_2 (2x40 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **6** was obtained as a yellowish glassy compound. Yield 0.585 g (48% overall). ^{1}H NMR ($CDCl_3$): δ 2.60-2.68 (m, 16H), 3.60 (s, 4H), 7.47-7.57 (m, 4H), 8.28 (s, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 45.6 (4C), 51.6 (4C), 56.9 (2C), 128.2 (2C), 133.7 (2C), 139.2 (2C), 141.1 (2C), 150.3 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{20}H_{29}Br_2N_6$ $[M+H]^+$ 511.0820, found 511.0776.

2a,6a-Bis[(6-bromopyridin-2-yl)methyl]decahydro-4a,8a-diaza-2a,6a-diazoniacyclopenta[*fg*]-acenaphthene dibromide (5). *Cis*-glyoxal-cyclen **1** (0.848 g, 4.37 mmol) was dissolved in MeCN (15 mL) and 2-bromo-6-bromomethylpyridine (2.19 g, 8.7 mmol) was added. The reaction mixture was stirred for 72 h at 40-50 °C. The precipitate was filtered off, washed with MeCN (2x30 mL) and dried *in vacuo*. Compound **5** was obtained as a white crystalline powder. Yield 2.89 g (95%). ^{1}H NMR (DMSO-d_6): δ 2.95 (t, *J* = 8.6 Hz, 2H), 3.21-3.41 (m, 4H), 3.43-3.50 (m, 2H), 3.60 (d, *J* = 13.1 Hz, 2H), 3.76 (td, *J* = 13.0 Hz, 3.4 Hz, 2H), 3.89 (dt, *J* = 12.1 Hz, 7.6 Hz, 2H), 4.38 (td, *J* = 11.1 Hz 3.3 Hz, 2H), 4.90 (s, 2H), 4.94 (d, *J* = 13.5 Hz, 2H), 5.14 (d, *J* = 13.5 Hz, 2H), 7.83-7.88 (m, 4H), 7.98 (t, *J* = 7.8 Hz, 2H). ^{13}C

NMR (DMSO-d_6): δ 42.9 (2C), 46.2 (2C), 56.6 (2C), 60.3 (2C), 61.5 (2C), 71.2 (2C), 126.9 (2C), 130.4 (2C), 141.0 (2C), 142.2 (2C), 147.9 (2C).

***N*[1],*N*[7]-Bis((6-bromopyridin-2-yl)methyl)cyclen (8)**. Compound **5** (4.15 mmol, 2.89 g) was dissolved in a water solution of KOH (3.4 g in 25 mL water) and stirred for 48 h at 80 °C. Aqueous layer was separated from the oily residue, extracted with CH_2Cl_2 (2x40 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **8** was obtained as a beige powder. Yield 1.97 g (88% overall). ^{1}H NMR ($CDCl_3$): δ 2.84-2.90 (m, 8H), 2.90-2.97 (m, 8H), 3.78 (s, 4H), 7.32-7.42 (m, 4H), 7.48-7.54 (m, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 45.1 (4C), 52.1 (4C), 60.8 (2C), 121.8 (2C), 126.4 (2C), 138.7 (2C), 141.4 (2C), 161.2 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{20}H_{29}Br_2N_6$ $[M+H]^+$ 511.0820, found 511.0856.

1,8-Bis[(6-chloropyridin-3-yl)methyl]-4,11-diaza-1,8-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane diodide (9). Formaldehyde-cyclam **2** (4.48 g, 20 mmol) was dissolved in MeCN (135 mL), 2-chloro-5-chloromethylpyridine (6.48 g, 40 mmol) and NaI (6.0 g, 40 mmol) were added. The reaction mixture was stirred for 48 h at room temperature. The precipitate was filtered off, washed with MeCN (2x30 mL) and dried *in vacuo*. Compound **9** was obtained as a white crystalline powder. Yield 11.03 g (75%). ^{1}H NMR (DMSO-d_6): δ 1.73 (d, *J* = 10.3 Hz, 2H), 2.38 (d, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 15.4 Hz, 4H), 3.13 (br.s, 2H), 3.30 (br.s, 4H), 4.41 (t, *J* = 13.5 Hz, 4H), 4.74 (s, 4H), 5.37 (d, *J* = 9.4 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 2H), 8.63 (br.s, 2H) (4 aliphatic protons are overlapped by the signal of HDO).

***N*[1],*N*[8]-Bis((6-chloropyridin-3-yl)methyl)cyclam (12)**. Compound **9** (11.03 g, 15.1 mmol) was dissolved in a water solution of KOH (30 g in 180 mL) and stirred at 90 °C for 24 h. Aqueous layer was separated from the oily residue, extracted with CH_2Cl_2 (3x50 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **12** was obtained as a slightly beige crystalline powder, mp 128-130 °C. Yield 5.21 g (58% overall). ^{1}H NMR ($CDCl_3$): δ 1.80 (quintet, *J* = 4.9 Hz, 4H), 2.45-2.55 (m, 8H), 2.65-2.73 (m, 8H), 3.64 (s, 4H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.57 (dd, *J* = 8.1 Hz, 2.4 Hz, 2H), 8.30 (d, *J* = 2.4 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 47.4 (2C), 49.6 (2C), 51.1 (2C), 54.0 (2C), 54.3 (2C), 123.8 (2C), 131.9 (2C), 139.7 (2C), 150.2 (2C), 150.3 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{22}H_{33}Cl_2N_6$ $[M+H]^+$ 451.2144, found 451.2093.

1,8-Bis[(6-bromopyridin-3-yl)methyl]-4,11-diaza-1,8-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane dibromide (10). Formaldehyde-cyclam **2** (1.25 g, 5.6 mmol) was dissolved in MeCN (40 mL) and 2-

bromo-5-bromomethylpyridine (2.81 g, 11.2 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The precipitate was filtered off, washed with MeCN (2x30 mL) and dried *in vacuo*. Compound **10** was obtained as white crystalline powder. Yield 2.05 g (50%). ^{1}H NMR (DMSO-d_6): δ 1.72 (d, *J* = 7.8 Hz, 2H), 2.39 (d, *J* = 7.0 Hz, 4H), 2.76 (d, *J* = 15.3 Hz, 2H), 2.86 (d, *J* = 14.8 Hz, 2H), 3.34 (br.s, 6H), 3.44 (d, *J* = 9.5 Hz, 2H), 3.62 (t, *J* = 14.5 Hz, 2H), 4.44 (t, *J* = 13.7 Hz, 2H), 4.82 (q, *J* = 13.3 Hz, 4H), 5.42 (d, *J* = 9.6 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 2H), 8.06 (dd, *J* = 8.3 Hz, 2.4 Hz, 2H), 8.67 (d, *J* = 2.4 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 19.1 (2C), 46.7 (2C), 48.1 (2C), 50.5 (2C), 57.8 (2C), 58.0 (2C), 75.7 (2C), 123.2 (2C), 128.3 (2C), 143.4 (2C), 143.9 (2C), 154.2 (2C).

***N*^{1},*N*^{8}-Bis((6-bromopyridin-3-yl)methyl)cyclam (13)**. Compound **10** (2.05 g, 2.8 mmol) was dissolved in a water solution of KOH (6.3 g in 37 mL) and stirred at 80 °C for 48 h. Aqueous layer was separated from the oily residue, extracted with CH_2Cl_2 (2x40 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **13** was obtained as a yellow oil. Yield 1.1 g (36% overall). ^{1}H NMR ($CDCl_3$): δ 1.72 (br.s, 4H), 2.39-2.47 (m, 8H), 2.57-2.65 (m, 8H), 3.55 (s, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.42 (dd, *J* = 8.1 Hz, 2.1 Hz, 2H), 8.22 (d, *J* = 2.1 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.6 (2C), 47.2 (2C), 49.5 (2C), 50.9 (2C), 53.9 (2C), 54.2 (2C), 127.5 (2C), 132.3 (2C), 139.3 (2C), 140.6 (2C), 150.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{22}H_{33}Br_2N_6$ $[M+H]^+$ 539.1133, found 539.1187.

1,8-Bis[(6-bromopyridin-2-yl)methyl]-4,11-diaza-1,8-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane dibromide (11). Formaldehyde-cyclam **2** (0.891 g, 3.95 mmol) was dissolved in MeCN (25 mL) and 2-bromo-6-bromomethylpyridine (1.99 g, 7.9 mmol) was added. The reaction mixture was stirred for 72 h at room temperature. The precipitate was filtered off, washed with MeCN (2x30 mL) and dried *in vacuo*. Compound **11** was obtained as white crystalline powder. Yield 1.93 g (67%). ^{1}H NMR (DMSO-d_6): δ 1.75 (d, *J* = 14.4 Hz, 2H), 2.32 (br.s, 2H), 2.45 (d, *J* = 11.5 Hz, 2H), 2.80 (d, *J* = 14.6 Hz, 2H), 2.99 (d, *J* = 15.1 Hz, 2H), 3.14 (br.s, 2H), 3.33-3.38 (m, 2H), 3.45-3.63 (m, 6H), 4.33 (t, *J* = 13.7 Hz, 2H), 4.73 (d, *J* = 13.4 Hz, 2H), 4.88 (d, *J* = 13.3 Hz, 2H), 5.42 (d, *J* = 9.2 Hz, 2H), 7.80-7.85 (m, 4H), 7.93 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 19.2 (2C), 47.1 (2C), 50.8 (2C), 59.2 (2C), 60.7 (2C), 76.8 (2C), 127.7 (2C), 129.4 (2C), 140.7 (2C), 141.2 (2C), 149.4 (2C), two aliphatic carbon atoms are overlapped by CD_3 multiplet.

***N*^{1},*N*^{8}-Bis((6-bromopyridin-2-yl)methyl)cyclam (14)**. Compound **11** (1.93 g, 2.65 mmol) was dissolved in a water solution of KOH (8.9 g in 53 mL) and stirred at 80 °C for 48 h. Aqueous layer was separated

from the oily residue, extracted with CH_2Cl_2 (2x40 mL), organic phases were combined and dried over Na_2SO_4. Solvent was evaporated *in vacuo* and compound **14** was obtained as a yellowish glassy compound. Yield 1.39 g (65% overall). ^{1}H NMR ($CDCl_3$): δ 1.79 (quintet, *J* = 5.0 Hz, 4H), 2.54 (t, *J* = 5.6 Hz, 4H), 2.61-2.65 (m, 4H), 2.66-2.73 (m, 8H), 3.73 (s, 4H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), NH protons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{22}H_{33}Br_2N_6$ $[M+H]^+$ 539.1133, found 538.1097.

Typical procedure for the synthesis of macrobicycles 16, 17, 20, 21.

A two-neck flask (25 mL) flushed with dry argon, equipped with a magnetic stirrer and condenser was charged with cyclen or cyclam derivatives **6-8**, **12-14** (0.25 mmol), $Pd(dba)_2$ (16 mol%), DavePhos or BINAP (18 mol%), and absolute dioxane (12 mL). The mixture was stirred for 2 min, then appropriate amine **15a-h** (0.25 mmol) and sodium *tert*-butoxide (0.6 mmol) were added. The reaction mixture was refluxed for 24 h, after cooling to room temperature the residue was filtered off, dioxane evaporated *in vacuo*, and the residue was analyzed by NMR spectroscopy. Column chromatography was carried out using a sequence of eluents: CH_2Cl_2, CH_2Cl_2-MeOH 20:1 – 3:1, CH_2Cl_2-MeOH-NH_3aq 100:20:1 – 10:4:1.

1,5,7,11,13,17,20,25-Octaazatetracyclo[15.5.5.2^{3,6}.2^{12,15}]hentriaconta-3,5,12,14,28,30-hexaene (16a) was synthesized from compound **6** (0.5 mmol, 212 mg) and diamine **15a** (0.5 mmol, 37 mg) in the presence of $Pd(dba)_2$ (46 mg, 16 mol%), DavePhos (36 mg, 18 mol%), *t*BuONa (1.2 mmol, 116 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 18 mg (8%). ^{1}H NMR ($CDCl_3$): δ 1.91 (quintet, *J* = 7.4 Hz, 2H), 2.38-2.45 (m, 4H), 2.63-2.71 (m, 4H), 2.74-2.82 (m, 4H), 2.95-3.03 (m, 4H), 3.36 (t, *J* = 7.1 Hz, 4H), 3.54 (s, 4H), 5.15 (br.s, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 8.5 Hz, 2.1 Hz, 2H), 7.96 (d, *J* = 2.1 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.2 (1C), 39.7 (2C), 47.4 (4C), 51.3 (4C), 59.5 (2C), 107.6 (2C), 122.9 (2C), 138.9 (2C), 147.8 (2C), 157.8 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{23}H_{37}N_8$ $[M+H]^+$ 425.3141, found 425.3100.

1,5,7,11,15,17,21,24,29-Nonaazatetracyclo[19.5.5.2^{3,6}.2^{16,19}]pentatriaconta-3,5,16,18,32,34-hexaene (16b) was synthesized from compound **6** (0.25 mmol, 106 mg) and triamine **15b** (0.25 mmol, 33 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 36 mg (29%). ^{1}H NMR ($CDCl_3$): δ 1.79 (quintet, *J* = 5.9 Hz, 4H), 2.53-2.70 (m, 16H), 2.80 (t, *J* = 5.2 Hz, 4H), 3.43 (t, *J* = 6.5 Hz, 4H), 3.47 (s, 4H), 5.73 (br.s, 2H), 6.67 (d, *J* = 8.5 Hz, 2H), 7.41 (dd, *J* = 8.5 Hz, 2.1

Hz, 2H), 7.96 (d, *J* = 2.1 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.9 (2C), 42.5 (2C), 46.3 (4C), 48.9 (2C), 52.3 (4C), 58.8 (2C), 107.6 (2C), 123.0 (2C), 138.1 (2C), 147.8 (2C), 158.6 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{44}N_9$ $[M+H]^+$ 482.3720, found 482.3687.

1,5,7,10,14,17,19,23,26,31-Decaazatetracyclo[21.5.5.2^{3,6}.2^{18,21}]heptatriaconta-3,5,18,20,34,36-hexaene (16c) was synthesized from compound **6** (0.25 mmol, 106 mg) and tetraamine **15c** (0.25 mmol, 40 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 21 mg (16%). ^{1}H NMR ($CDCl_3$): δ 1.87 (br.s, 2H), 2.50-2.80 (m, 16H), 2.90-2.98 (m, 8H), 3.47 (s, 4H), 3.52 (br.s, 4H), 5.87 (br.s, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.92 (br.s, 2H), four NH protons were not assigned. ^{13}C NMR (CD_3OD): δ 26.0 (1C), 41.4 (2C), 47.8 (4C), 50.1 (2C), 52.9 (4C), 59.9 (2C), 110.7 (2C), 124.8 (2C), 140.2 (2C), 148.7 (2C), 159.9 (2C), two aliphatic carbon atoms are overlapped by CD_3 multiplet. HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{47}N_{10}$ $[M+H]^+$ 511.3985, found 511.3947.

1,5,7,11,14,18,20,24,27,32-Decaazatetracyclo[22.5.5.2^{3,6}.2^{19,22}]octatriaconta-3,5,19,21,35,37-hexaene (16d) was synthesized from compound **6** (0.25 mmol, 106 mg) and tetraamine **15d** (0.25 mmol, 44 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. In the second experiment the reaction with the same amounts of starting compounds, catalyst and base was conducted in 5 mL dioxane. As the ^{1}H NMR spectra of both reaction mixtures were identical, the chromatography of combined reactions mixtures was carried out. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 40 mg (15%). ^{1}H NMR ($CDCl_3$): δ 1.85 (quintet, *J* = 5.8 Hz, 4H), 2.55-2.70 (m, 16H), 2.80 (t, *J* = 6.5 Hz, 4H), 2.81 (s, 4H), 3.40 (t, *J* = 6.1 Hz, 4H), 3.43 (s, 4H), 6.58 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.92 (d, *J* = 2.0 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.3 (2C), 40.7 (2C), 46.4 (4C), 47.7 (2C), 48.4 (2C), 51.7 (4C), 58.4 (2C), 108.0 (2C), 122.5 (2C), 130.1 (2C), 147.9 (2C), 158.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{49}N_{10}$ $[M+H]^+$ 525.4142, found 525.3989.

1,5,7,11,15,19,21,25,28,33-Decaazatetracyclo[23.5.5.2^{3,6}.2^{20,23}]nonatriaconta-3,5,20,22,36,38-hexaene (16e) was synthesized from compound **6** (0.25 mmol, 106 mg) and tetraamine **15e** (0.25 mmol, 47 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 37 mg (27%). ^{1}H NMR ($CDCl_3$): δ 1.76 (quintet, *J* = 6.2 Hz, 2H), 1.81 (quintet, *J* = 5.9 Hz, 4H), 2.50-2.70 (m, 16H),

2.77 (t, *J* = 6.4 Hz, 4H), 2.80 (t, *J* = 6.0 Hz, 4H), 3.38-3.42 (m, 8H), 6.55 (d, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 8.5 Hz, *J* = 1.7 Hz, 2H), 7.90 (br.s, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.3 (3C), 40.9 (2C), 45.9 (4C), 47.7 (2C), 48.3 (2C), 51.8 (4C), 57.8 (2C), 108.1 (2C), 122.7 (2C), 138.1 (2C), 148.0 (2C), 158.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{29}H_{51}N_{10}$ $[M+H]^+$ 539.4298, found 539.4275.

11,16-Dioxa-1,5,7,20,22,26,29,34-octaazatetracyclo[24.5.5.2^{3,6}.2^{21,24}]tetraconta-3,5,21,23,37,39-hexaene (16f) was synthesized from compound **6** (0.25 mmol, 106 mg) and dioxadiamine **15f** (0.25 mmol, 37 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:2 – 100:20:3, pale-beige crystalline powder, mp 194-196 °C. Yield 39 mg (32%). In the second experiment (scale-up), compound **16f** was synthesized using compound **6** (5 mmol, 2.115 g) and dioxadiamine **15f** (7.5 mmol, 1.1 g) in the presence of $Pd(dba)_2$ (245 mg, 8 mol%), DavePhos (177 mg, 9 mol%), *t*BuONa (15 mmol, 1.44 g) in 125 mL dioxane.. Yield 821 mg (33%). ^{1}H NMR ($CDCl_3$): δ 2.47 (br.s, 4H), 2.67 (br.s, 4H), 2.75 (br.s, 4H), 2.99 (br.s, 4H), 3.52 (q, *J* = 4.6 Hz, 4H), 3.56 (s, 4H), 3.69 (s, 4H), 3.73 (t, *J* = 5.0 Hz, 4H), 5.14 (s, 2H), 6.59 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 8.5 Hz, 1.9 Hz, 2H), 7.97 (d, *J* = 1.9 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 41.6 (2C), 47.3 (4C), 51.4 (4C), 59.4 (2C), 69.3 (2C), 70.1 (2C), 108.4 (2C), 123.2 (2C), 138.2 (2C), 148.0 (2C), 158.2 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{43}N_8O_2$ $[M+H]^+$ 499.3509, found 499.3360.

10,13,37,40-Tetraoxa-1,5,7,16,18,22,25,28,32,34,43,45,49,52,57,66-hexadecaazaheptacyclo-[47.5.5.5^{22,28}.2^{3,6}.2^{17,20}.2^{30,33}.2^{44,47}]doheptaconta-3,5,17,19,30,32,44,46,60,62,69,71-dodecaene (18f) was isolated as the second product in the scaled-up synthesis of compound **16f**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 185 mg (7%). ^{1}H NMR ($CDCl_3$): δ 2.45-2.65 (m, 32H), 3.33-3.64 (m, 32H), 4.93 (br.s, 4H), 6.48 (d, *J* = 8.4 Hz, 4H), 7.29 (d, *J* = 8.4 Hz, 4H), 7.87 (br.s, 4H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 41.4 (4C), 45.5 (8C), 51.5 (8C), 57.1 (4C), 69.7 (4C), 69.9 (4C), 107.9 (4C), 122.8 (4C), 138.1 (4C), 147.7 (4C), 158.1 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{52}H_{85}N_{16}O_4$ $[M+H]^+$ 997.6940, found 997.6872.

10,13-Dioxa-1,5,7,16,18,22,25,30-octaazatetracyclo[20.5.5.2^{3,6}.2^{17,20}]hexatriaconta-3,5,17,19,33,35-hexaene (16g) was synthesized from compound **6** (0.25 mmol, 106 mg) and dioxadiamine **15g** (0.25 mmol, 51 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1 – 100:20:2, pale-yellow glassy

compound. Yield 33 mg (24%). ^{1}H NMR ($CDCl_3$): δ 1.65-1.70 (m, 4H), 1.87 (quintet, *J* = 5.4 Hz, 4H), 2.65-2.75 (m, 16H), 3.41-3.46 (m, 8H), 3.47 (s, 4H), 3.57 (t, *J* = 5.2 Hz, 4H), 5.21 (br.s, 2H), 6.48 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.91 (br.s, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.9 (2C), 29.1 (2C), 40.9 (2C), 46.9 (4C), 51.7 (4C), 58.5 (2C), 70.1 (2C), 71.1 (2C), 107.3 (2C), 122.6 (2C), 138.4 (2C), 148.1 (2C), 158.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{51}N_8O_2$ $[M+H]^+$ 555.4135, found 554.4079.

11,14,17-Trioxa-1,5,7,21,23,27,30,35-octatetracyclo[25.5.5.2^{3,6}.2^{22,25}]hentetraconta-3,5,22,24,38,40-hexaene (16h) was synthesized from compound **6** (0.25 mmol, 106 mg) and trioxadiamine **15h** (0.25 mmol, 55 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1 – 100:20:2, pale-yellow glassy compound. Yield 35 mg (24%). In the second experiment, compound **16h** was synthesized using compound **7** (1.75 mmol, 898 mg) and trioxadiamine **15h** (1.75 mmol, 386 mg) in the presence of $Pd(dba)_2$ (80 mg, 8 mol%), DavePhos (62 mg, 9 mol%), *t*BuONa (5.25 mmol, 504 mg) in 50 mL dioxane. Yield 209 mg (21%). ^{1}H NMR ($CDCl_3$): δ 1.88 (quintet, *J* = 5.8 Hz, 4H), 2.68-2.75 (m, 16H), 3.44 (q, *J* = 5.3 Hz, 4H), 3.50 (s, 4H), 3.59-3.64 (m, 8H), 3.65-3.69 (m, 4H), 5.32 (br.s, 2H), 6.48 (d, *J* = 8.5 Hz, 2H), 7.38 (dd, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.92 (br.s, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.8 (2C), 40.0 (2C), 47.2 (4C), 51.7 (4C), 59.0 (2C), 69.5 (2C), 70.0 (2C), 70.3 (2C), 107.5 (2C), 122.5 (2C), 138.3 (2C), 148.1 (2C), 158.5 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{51}N_8O_3$ $[M+H]^+$ 571.4084, found 571.4071.

11,14,17,43,46,49-Hexaoxa-1,5,7,21,23,27,30,33,37,39,53,55,59,62,67,76-hexadecaazaheptacyclo-[57.5.5.5^{27,33}.2^{3,6}.2^{22,25}.2^{35,38}.2^{54,57}]dooctaconta-3,5,22,24,35,37,54,56,70,72,79,81-dodecaene (18h) was isolated as the second product in the synthesis of compound **16f** from cyclen derivative **7**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:2, pale-yellow glassy compound. Yield 35 mg (3%). ^{1}H NMR ($CDCl_3$): δ 1.83 (quintet, *J* = 6.0 Hz, 8H), 2.51-2.66 (m, 32H), 3.35 (s, 8H), 3.37 (br.s, 8H), 3.52-3.62 (m, 24H), 5.26 (br.s, 4H), 6.46 (d, *J* = 8.6 Hz, 4H), 7.32 (dd, *J* = 8.6 Hz, 1.7 Hz, 4H), 7.87 (br.s, 4H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.0 (4C), 39.7 (4C), 45.4 (8C), 51.3 (8C), 56.8 (4C), 69.4 (4C), 70.0 (4C), 70.4 (4C), 107.4 (4C), 122.2 (4C), 138.2 (4C), 148.0 (4C), 158.3 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{60}H_{101}N_{16}O_6$ $[M+H]^+$ 1141.8090, found 1141.8163.

1,5,7,11,13,17,20,26-Octaazatetracyclo[15.6.6.2^{3,6}.2^{12,15}]tritriaconta-3,5,12,14,30,32-hexaene (17a) was synthesized from compound **12** (0.5 mmol, 226 mg) and diamine **15a** (0.5 mmol, 37 mg) in the

presence of $Pd(dba)_2$ (46 mg, 16 mol%), DavePhos (36 mg, 18 mol%), *t*BuONa (1.2 mmol, 116 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 15 mg (7%). ^{1}H NMR ($CDCl_3$): δ 1.73 (br.s, 2H), 1.82 (br.s, 2H), 1.87 (quintet, *J* = 6.3 Hz, 2H), 2.31-2.81 (m, 16H), 3.10 (d, *J* = 13.0 Hz, 2H), 3.26 (dq, *J* = 13.0 Hz, 5.4 Hz, 2H), 3.44 (d, *J* = 13.0 Hz, 2H), 3.45-3.53 (m, 2H), 4.72 (t, *J* = 6.0 Hz, 2H), 6.22 (d, *J* = 8.5 Hz, 2H), 7.25 (dd, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.86 (d, *J* = 2.0 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.8 (2C), 29.7 (1C), 39.0 (2C), 48.9 (2C), 49.6 (2C), 53.5 (2C), 53.7 (2C), 57.6 (2C), 106.6 (2C), 123.1 (2C), 138.7 (2C), 148.3 (2C), 158.2 (2C). MS (MALDI-TOF) *m/z* calcd for $C_{25}H_{41}N_8$ $[M+H]^+$ 453.34, found 453.30.

1,5,7,10,14,17,19,23,26,32-Decaazatetracyclo[21.6.6.2^{3,6}.2^{18,21}]nonatriaconta-3,5,18,20,36,38-hexaene (17c) was synthesized from compound **12** (0.25 mmol, 113 mg) and tetraamine **15c** (0.25 mmol, 40 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 16 mg (11%). ^{1}H NMR ($CDCl_3$): δ 1.69 (br.s, 2H), 1.77 (br.s, 4H), 2.30-2.85 (m, 24H), 3.26 (br.s, 4H), 3.40 (br.s, 4H), 5.51 (br.s, 2H), 6.20 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.90 (br.s, 2H), four NH protons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{29}H_{51}N_{10}$ $[M+H]^+$ 539.4298, found 539.4275.

1,5,7,11,14,18,20,24,27,33-Decaazatetracyclo[22.6.6.2^{3,6}.2^{19,22}]tetraconta-3,5,19,21,37,39-hexaene (17d) was synthesized from compound **12** (0.5 mmol, 226 mg) and tetraamine **15d** (0.5 mmol, 86 mg) in the presence of $Pd(dba)_2$ (46 mg, 16 mol%), DavePhos (36 mg, 18 mol%), *t*BuONa (1.2 mmol, 116 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 40 mg (14%). ^{1}H NMR (CD_3OD): δ 1.81-1.94 (m, 8H), 2.40-2.98 (m, 24H), 3.38 (t, *J* = 6.4 Hz, 4H), 3.52 (s, 4H), 6.56 (d, *J* = 8.5 Hz, 2H), 7.44 (dd, *J* = 8.5 Hz, 2.2 Hz, 2H), 7.96 (d, *J* = 2.2 Hz, 2H), NH protons were not assigned. ^{13}C NMR (CD_3OD): δ 25.5 (2C), 29.0 (2C), 39.6 (2C), 46.6 (2C), 47.7 (2C), 48.0 (2C), 50.2 (2C), 52.0 (2C), 56.2 (2C), 110.1 (2C), 121.9 (2C), 140.9 (2C), 149.0 (2C), 160.1 (2C), two aliphtaic carbon atoms are overlapped by CD_3 multiplet. MS (MALDI-TOF) *m/z* calcd for $C_{30}H_{53}N_{10}$ $[M+H]^+$ 552.46, found 552.39.

1,5,7,11,15,19,21,25,28,34-Decaazatetracyclo[23.6.6.2^{3,6}.2^{20,23}]hentetraconta-3,5,20,22,38,40-hexaene (17e) was synthesized from compound **12** (0.25 mmol, 113 mg) and tetraamine **15e** (0.25 mmol, 47 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 27 mg

(19%). ^{1}H NMR ($CDCl_3$): δ 1.73-1.84 (m, 10H), 2.40-2.55 (m, 8H), 2.55-2.67 (m, 8H), 2.70 (t, *J* = 5.9 Hz, 4H), 2.76 (t, *J* = 5.9 Hz, 4H), 3.33 (t, *J* = 6.0 Hz, 4H), 3.37 (s, 4H), 4.95 (br.s, 2H), 6.35 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz,. 2H), 7.93 (br.s, 2H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 24.9 (3C), 28.3 (2C), 40.1 (2C), 47.1 (2C), 47.8 (2C), 48.4 (2C), 49.2 (2C), 51.3 (2C), 51.8 (2C), 56.2 (2C), 107.7 (2C), 121.1 (2C), 138.8 (2C), 148.5 (2C), 158.3 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{31}H_{55}N_{10}$ $[M+H]^+$ 567.4611, found 567.4661.

10,13-Dioxa-1,5,7,16,18,22,25,31-octaazatetracyclo[20.6.6.2^{3,6}.2^{17,20}]octatriaconta-3,5,17,19,35,37-hexaene (17f) was synthesized from compound **12** (0.25 mmol, 113 mg) and dioxadiamine **15f** (0.25 mmol, 37 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 17 mg (13%). In the second experiment (scale-up), compound **17f** was synthesized using compound **12** (5 mmol, 2.255 g) and dioxadiamine **15f** (7.5 mmol, 1.1 g) in the presence of $Pd(dba)_2$ (245 mg, 8 mol%), DavePhos (177 mg, 9 mol%), *t*BuONa (15 mmol, 1.44 g) in 125 mL dioxane. Yield 525 mg (20%). ^{1}H NMR ($CDCl_3$): δ 1.76 (br.s, 4H), 2.57 (br.s, 8H), 2.67 (br.s, 8H), 3.29 (br.s, 4H), 3.48 (s, 4H), 3.61 (s, 4H), 3.65 (br.s, 4H), 4.91 (t, *J* = 5.3 Hz, 2H), 6.24 (d, *J* = 8.4 Hz, 2H), 7.26 (dd, *J* = 8.4 Hz, 2.1 Hz, 2H), 7.93 (d, *J* = 2.1 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 41.6 (2C), 48.7 (2C), 49.7 (2C), 52.9 (2C), 53.3 (2C), 57.3 (2C), 69.4 (2C), 70.0 (2C), 108.5 (2C), 122.8 (2C), 138.8 (2C), 148.3 (2C), 158.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{47}N_8O_2$ $[M+H]^+$ 527.3822, found 527.3809.

10,13,38,41-Tetraoxa-1,5,7,16,18,22,25,29,33,35,44,46,50,53,59,69-hexadecaazaheptacyclo-[48.6.6.6^{22,29}.2^{3,6}.2^{17,20}.2^{31,34}.2^{45,48}]hexaheptaconta-3,5,17,19,31,33,45,47,63,65,73,75-dodecaene (19f) was isolated as the second product in the scaled-up synthesis of compound **17f**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 47 mg (2%). ^{1}H NMR ($CDCl_3$): δ 1.59 (quintet, *J* = 5.0 Hz, 8H), 2.30-2.45 (m, 16H), 2.51-2.61 (m, 16H), 3.34 (t, *J* = 5.1 Hz, 8H), 3.50-3.55 (m, 24H), 4.88 (t, *J* = 5.5 Hz, 4H), 6.16 (d, *J* = 8.5 Hz, 4H), 7.17 (d, *J* = 8.5 Hz, 4H), 7.84 (br.s, 4H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.2 (4C), 41.1 (4C), 47.9 (4C), 49.7 (4C), 53.4 (4C), 54.0 (4C), 56.4 (4C), 69.1 (4C), 69.6 (4C), 108.0 (4C), 122.4 (4C), 138.4 (4C), 147.8 (4C), 157.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{56}H_{93}N_{16}O_4$ $[M+H]^+$ 1053.7566, found 1053.7622.

10,15-Dioxa-1,5,7,18,20,24,27,33-octaazatetracyclo[22.6.6.2^{3,6}.2^{19,22}]tetraconta-3,5,19,21,37,39-hexaene (17g) was synthesized from compound **12** (0.25 mmol, 113 mg) and dioxadiamine **15g** (0.25

mmol, 51 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:1-100:20:3, pale-yellow glassy compound. Yield 15 mg (10%). ^{1}H NMR ($CDCl_3$): δ 1.59-1.64 (m, 4H), 1.82 (quintet, *J* = 5.9 Hz, 4H), 1.84 (quintet, *J* = 5.6 Hz, 4H), 2.50-2.55 (m, 4H), 2.60-2.65 (m, 4H), 2.71 (t, *J* = 5.1 Hz, 4H), 2.73-2.77 (m, 4H), 3.36 (q, *J* = 5.9 Hz, 4H), 3.37-3.41 (m, 8H), 3.49 (t, *J* = 5.5 Hz, 4H), 4.95 (t, *J* = 5.1 Hz, 2H), 6.31 (d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 8.5 Hz, 2.1 Hz, 2H), 7.94 (d, *J* = 2.1 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.0 (2C), 26.5 (2C), 29.3 (2C), 41.7 (2C), 48.0 (2C), 49.0 (2C), 51.3 (2C), 51.5 (2C), 56.5 (2C), 69.5 (2C), 70.9 (2C), 106.8 (2C), 121.4 (2C), 138.9 (2C), 148.9 (2C), 158.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{55}N_8O_2$ $[M+H]^+$ 583.4448, found 583.4391.

10,13,16-Trioxa-1,5,7,19,21,25,28,34-octaazatetracyclo[23.6.6.2^{3,6}.2^{20,23}]hentetraconta-3,5,20,22,38,40-hexaene (17h) was synthesized from compound **12** (0.25 mmol, 113 mg) and trioxadiamine **15h** (0.25 mmol, 55 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), DavePhos (18 mg, 18 mol%), *t*BuONa (0.6 mmol, 58 mg) in 12 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 28 mg (19%). In the second experiment (scale-up), compound **17h** was synthesized using compound **12** (4 mmol, 1.804 g) and trioxadiamine **15h** (4 mmol, 880 mg) in the presence of $Pd(dba)_2$ (183 mg, 8 mol%), DavePhos (142 mg, 9 mol%), *t*BuONa (12 mmol, 1.152 g) in 100 mL dioxane. Yield 455 mg (19%). ^{1}H NMR ($CDCl_3$): δ 1.81 (quintet, *J* = 5.8 Hz, 8H), 2.49-2.54 (m, 4H), 2.59-2.64 (m, 4H), 2.69-2.76 (m, 8H), 3.19 (br.s, 2H), 3.33 (q, *J* = 6.1 Hz, 4H), 3.36 (s, 4H), 3.54 (t, *J* = 5.6 Hz, 4H), 3.54-3.57 (m, 4H), 3.59-3.62 (m, 4H), 5.02 (t, *J* = 5.4 Hz, 2H), 6.26 (d, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 8.5 Hz, 1.9 Hz, 2H), 7.93 (d, *J* = 1.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 25.1 (2C), 29.1 (2C), 40.0 (2C), 48.0 (2C), 49.5 (2C), 51.6 (2C), 52.1 (2C), 56.3 (2C), 69.5 (2C), 70.1 (2C), 70.3 (2C), 106.8 (2C), 121.4 (2C), 139.0 (2C), 148.8 (2C), 158.3 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{55}N_8O_3$ $[M+H]^+$ 599.4397, found 598.4342.

11,14,17,44,47,50-Hexaoxa-1,5,7,21,23,27,30,34,38,40,54,56,60,63,69,79-hexadecaazaheptacyclo-[58.6.6.6^{27,34}.2^{3,6}.2^{22,25}.2^{36,39}.2^{55,58}]hexaoctaconta-3,5,22,24,36, 38,55,57,73,75,83,85-dodecaene (19h) was isolated as the second product in the scaled-up synthesis of compound **17h**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 73 mg (3%). ^{1}H NMR ($CDCl_3$): δ 1.71-1.79 (m, 16H), 2.37-2.67 (m, 32H), 3.27 (br.s, 8H), 3.40-3.62 (m, 32H), 5.05 (br.s, 4H), 6.27 (d, *J* = 8.5 Hz, 4H), 7.29 (d, *J* = 8.5 Hz, 4H), 7.86 (br.s, 4H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.1 (4C), 28.98 (4C), 41.3 (4C), 44.7 (4C), 47.2 (4C), 50.9 (4C), 51.4 (4C), 54.6 (4C), 69.2 (4C), 69.8 (4C), 70.2 (4C), 106.6 (4C), 120.1 (4C), 138.6 (4C), 148.5 (4C), 158.0 (4C). HRMS (MALDI-TOF) *m/z* calcd

for $C_{64}H_{109}N_{16}O_6$ $[M+H]^+$ 1197.8716, found 1197.8597.

1,8,12,19,22,27,30,31-Octaazatetracyclo[17.5.5.1^{3,7}.1^{13,17}]hentriaconta-3(31),4,6,13(30),14,16-hexaene (20a) was synthesized from compound **8** (0.25 mmol, 128 mg) and diamine **15a** (0.25 mmol, 19 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 21 mg (20%). ^{1}H NMR ($CDCl_3$): δ 1.84 (br.s, 2H), 2.68-2.73 (m, 16H), 3.38 (br.s, 4H), 3.67 (s, 4H), 5.79 (br.s, 2H), 6.29 (d, *J* = 8.2 Hz, 2H), 6.43 (d, *J* = 7.3 Hz, 2H), 7.35 (dd, *J* = 8.2 Hz, 7.3 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.2 (1C), 40.8 (2C), 46.3 (4C), 51.8 (4C), 62.3 (2C), 105.0 (2C), 112.6 (2C), 138.3 (2C), 156.2 (2C), 159.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{23}H_{37}N_8$ $[M+H]^+$ 425.3141, found 425.3110.

1,8,12,19,22,25,32,36,43,46,51,54,55,58,61,62-Hexadecaazaheptacyclo-[41.5.5.5^{19,25}.1^{3,7}.1^{13,17}.1^{27,31}.1^{37,41}]dohexaconta-3(62),4,6,13(61),14,16,27(55),28,30,37(54),38,40-dodecaene (22a) was isolated as the second product in the synthesis of compound **20a**. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 6 mg (6%). ^{1}H NMR ($CDCl_3$): δ 2.07 (quintet, *J* = 5.5 Hz, 4H), 2.57-3.02 (m, 32H), 3.48 (t, *J* = 5.7 Hz, 8H), 3.67 (s, 8H), 5.94 (br.s, 4H), 6.54 (d, *J* = 7.3 Hz, 4H), 6.57 (d, *J* = 8.6 Hz, 4H), 7.44 (t, *J* = 7.9 Hz, 4H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 27.9 (2C), 46.0 (4C), 46.5 (8C), 51.8 (8C), 64.0 (4C), 107.1 (4C), 114.6 (4C), 138.2 (4C), 155.5 (4C), 159.6 (4C). HRMS (MALDI-TOF) *m/z* calcd for $C_{46}H_{73}N_{16}$ $[M+H]^+$ 849.6204, found 849.6282.

1,8,12,16,23,26,31,34,35-Nonaazatetracyclo[21.5.5.1^{3,7}.1^{17,21}]pentatriaconta-3(35),4,6,17(34),18,20-Hexaene (20b) was synthesized from compound **8** (0.25 mmol, 128 mg) and triamine **15b** (0.25 mmol, 33 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 27 mg (23%). ^{1}H NMR ($CDCl_3$): δ 1.67 (quintet, *J* = 5.4 Hz, 4H), 2.55-2.70 (m, 20H), 3.25 (br.s, 4H), 3.56 (s, 4H), 5.27 (br.s, 2H), 6.21 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H), three NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.4 (2C), 40.5 (2C), 45.2 (4C), 47.2 (2C), 52.4 (4C), 61.3 (2C), 104.4 (2C), 111.9 (2C), 138.0 (2C), 157.3 (2C), 159.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{44}N_9$ $[M+H]^+$ 482.3720, found 482.3677.

1,8,11,15,18,25,28,33,36,37-Decaazatetracyclo[23.5.5.1^{3,7}.1^{19,23}]heptatriaconta-3(37),4,6,19(36),20,22-

hexaene (20c) was synthesized from compound **8** (0.25 mmol, 128 mg) and tetraamine **15c** (0.25 mmol, 40 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 11 mg (9%). ^{1}H NMR ($CDCl_3$): δ 1.55 (br.s, 2H), 2.20-2.85 (m, 24H), 3.24 (br.s, 4H), 3.51 (s, 4H), 6.20 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), NH protons were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{27}H_{47}N_{10}$ $[M+H]^+$ 511.3985, found 511.3929.

1,8,12,15,19,26,29,34,37,38-Decaazatetracyclo[24.5.5.1^{3,7}.1^{20,24}]octatriaconta-3(38),4,6,20(37),21,23-hexaene (20d) was synthesized from compound **8** (0.25 mmol, 128 mg) and tetraamine **15d** (0.25 mmol, 44 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 15 mg (11%). ^{1}H NMR ($CDCl_3$): δ 1.61 (quintet, *J* = 6.1 Hz, 4H), 2.44-2.90 (m, 24H), 3.15 (br.s, 4H), 3.59 (s, 4H), 6.15 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.1 (2C), 40.8 (2C), 45.3 (4C), 47.3 (2C), 48.4 (2C), 52.1 (4C), 60.8 (2C), 103.6 (2C), 111.4 (2C), 138.0 (2C), 157.6 (2C), 159.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{49}N_{10}$ $[M+H]^+$ 525.4142, found 525.4159.

1,8,12,16,20,27,30,35,38,39-Decaazatetracyclo[25.5.5.1^{3,7}.1^{21,25}]nonatriaconta-3(39),4,6,21(38),22,24-hexaene (20e) was synthesized from compound **8** (0.25 mmol, 128 mg) and tetraamine **15e** (0.25 mmol, 47 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 22 mg (16%). ^{1}H NMR ($CDCl_3$): δ 1.68 (br.s, 6H), 2.47-2.81 (m, 24H), 3.18 (br.s, 4H), 3.57 (s, 4H), 5.22 (br.s, 2H), 6.21 (d, *J* = 8.2 Hz, 2H), 6.60 (d, *J* = 6.8 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), four NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 28.0 (1C), 28.8 (2C), 40.6 (2C), 45.0 (4C), 47.5 (2C), 49.2 (2C), 52.0 (4C), 60.7 (2C), 104.2 (2C), 111.7 (2C), 137.9 (2C), 157.1 (2C), 159.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{29}H_{51}N_{10}$ $[M+H]^+$ 539.4298, found 539.4275.

11,14-Dioxa-1,8,17,24,27,32,35,36-octaazatetracyclo[22.5.5.1^{3,7}.1^{18,22}]hexatriaconta-3(36),4,6,18(35),19,21-hexaene (20f) was synthesized from compound **8** (0.25 mmol, 128 mg) and dioxadiamine **15f** (0.25 mmol, 37 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:2, pale-yellow glassy compound. Yield 27 mg (22%). ^{1}H NMR ($CDCl_3$): δ 2.74-2.79 (m, 8H), 2.82-2.87 (m, 8H), 3.37 (q, *J* = 5.1 Hz, 4H), 3.58 (s, 4H), 3.63 (t, *J* = 5.4 Hz, 4H), 3.64 (s, 4H), 5.75 (br.s, 2H), 6.28 (d, *J* =

7.1 Hz, 2H), 6.42 (d, *J* = 7.1 Hz, 2H), 7.33 (dd, *J* = 8.3 Hz, 7.3 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 41.8 (2C), 46.0 (4C), 51.8 (4C), 61.6 (2C), 69.5 (2C), 70.0 (2C), 104.9 (2C), 112.2 (2C), 138.2 (2C), 156.5 (2C), 159.2 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{26}H_{43}N_8O_2$ $[M+H]^+$ 499.3509, found 499.3540.

11,16-Dioxa-1,8,20,27,30,35,38,39-octaazatetracyclo[25.5.5.1^{3,7}.1^{21,25}]nonatriaconta-3(39),4,6,21(38),22,24-hexaene (20g) was synthesized from compound **8** (0.25 mmol, 128 mg) and dioxadiamine **15g** (0.25 mmol, 51 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 15 mg (11%). ^{1}H NMR ($CDCl_3$): δ 1.57-1.61 (m, 4H), 1.80 (quintet, *J* = 6.0 Hz, 4H), 2.75-2.80 (m, 8H), 2.89-2.92 (m, 8H), 3.24 (q, *J* = 5.9 Hz, 4H), 3.37-3.41 (m, 4H), 3.44 (t, *J* = 5.8 Hz, 4H), 3.65 (s, 4H), 5.59 (t, *J* = 5.1 Hz, 4H), 6.24 (d, *J* = 8.3 Hz, 2H), 6.40 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 26.3 (2C), 29.3 (2C), 40.0 (2C), 45.9 (4C), 52.0 (4C), 61.3 (2C), 68.4 (2C), 70.7 (2C), 104.0 (2C), 112.2 (2C), 138.2 (2C), 156.7 (2C), 159.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{51}N_8O_2$ $[M+H]^+$ 555.4135, found 555.4081.

11,14,17-Trioxa-1,8,21,28,31,36,39,40-octaazatetracyclo[26.5.5.1^{3,7}.1^{22,26}]tetraconta-3(40),4,6,22(39),23,25-hexaene (20h) was synthesized from compound **8** (0.25 mmol, 128 mg) and trioxadiamine **15h** (0.25 mmol, 55 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:20:3, pale-yellow glassy compound. Yield 26 mg (18%). ^{1}H NMR ($CDCl_3$): δ 1.79 (quintet, *J* = 6.1 Hz, 4H), 2.86-2.93 (m, 16H), 3.24 (br.s, 4H), 3.48 (t, *J* = 5.9 Hz, 4H), 3.49-3.52 (m, 4H), 3.57-3.61 (m, 4H), 3.63 (s, 4H), 5.69 (br.s, 2H), 6.30 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 29.1 (2C), 39.7 (2C), 45.4 (4C), 51.5 (4C), 61.1 (2C), 68.8 (2C), 70.2 (2C), 70.6 (2C), 104.8 (2C), 111.5 (2C), 138.5 (2C), 155.8 (2C), 159.4 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{30}H_{51}N_8O_3$ $[M+H]^+$ 571.4084, found 571.4071.

1,8,12,16,23,26,32,36,37-Nonaazatetracyclo[21.6.6.1^{3,7}.1^{17,21}]heptatriaconta-3(37),4,6,17(36),18,20-hexaene (21b) was synthesized from compound **14** (0.25 mmol, 135 mg) and triamine **15b** (0.25 mmol, 33 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 10:4:1, pale-yellow glassy compound. Yield 8 mg (6%). ^{1}H NMR ($CDCl_3$): δ 1.76 (quintet, *J* = 6.0 Hz, 4H), 1.82 (quintet, *J* = 5.0 Hz, 4H), 2.56 (t, *J* = 5.1

Hz, 4H), 2.68-2.81 (m, 16H), 3.27 (br.s, 4H), 3.74 (s, 4H), 6.16 (d, *J* = 8.5 Hz, 2H), 6.33 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.7 (2C), 29.0 (2C), 41.1 (2C), 47.3 (2C), 47.4 (2C), 49.0 (2C), 51.9 (2C), 53.8 (2C), 59.0 (2C), 103.8 (2C), 112.5 (2C), 137.6 (2C), four quaternary carbon atoms were not assigned. HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{48}N_9$ $[M+H]^+$ 510.4033, found 510.3989.

11,14-Dioxa-1,8,17,24,27,33,37,38-octaazatetracyclo[22.6.6.1^{3,7}.1^{18,22}]octatriaconta-3(38),4,6,18(37),19,21-hexaene (21f) was synthesized from compound **14** (0.25 mmol, 135 mg) and dioxadiamine **15f** (0.25 mmol, 37 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 15 mg (11%). ^{1}H NMR ($CDCl_3$): δ 1.85 (br.s), 2.57 (t, *J* = 5.1 Hz, 4H), 2.72-2.87 (m, 12H), 3.39 (q, *J* = 5.5 Hz, 4H), 3.42 (s, 4H), 3.63 (s, 4H), 3.70 (t, *J* = 5.5 Hz, 4H), 5.57 (br.s, 2H), 6.21 (d, *J* = 8.3 Hz, 2H), 6.40 (d, *J* = 7.1 Hz, 2H), 7.28 (t, J = 7.7 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.0 (2C), 42.1 (2C), 47.4 (2C), 49.3 (2C), 52.2 (2C), 52.8 (2C), 58.9 (2C), 69.7 (2C), 70.4 (2C), 104.2 (2C), 112.9 (2C), 137.7 (2C), 156.0 (2C), 159.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{28}H_{47}N_8O_2$ $[M+H]^+$ 527.3822, found 527.3751.

12,17-Dioxa-1,8,21,28,31,37,41,42-octaazatetracyclo[26.6.6.1^{3,7}.1^{22,26}]dotetraconta-3(42),4,6,22(41),23,25-hexaene (21g) was synthesized from compound **14** (0.25 mmol, 135 mg) and dioxadiamine **15g** (0.25 mmol, 51 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-yellow glassy compound. Yield 9 mg (6%). ^{1}H NMR ($CDCl_3$): δ 1.62 (br.s, 4H), 1.81 (quintet, *J* = 6.0 Hz, 4H), 1.84 (br.s, 4H), 2.60 (t, *J* = 5.0 Hz, 4H), 2.75-2.89 (m, 12H), 3.26 (q, *J* = 5.9 Hz, 4H), 3.38-3.47 (m, 8H), 3.48 (s, 4H), 5.59 (br.s, 2H), 6.18 (d, *J* = 8.3 Hz, 2H), 6.41 (d, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.7 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 25.0 (2C), 26.5 (2C), 29.5 (2C), 40.1 (2C), 47.4 (2C), 48.3 (2C), 52.1 (2C), 52.2 (2C), 54.8 (2C), 68.6 (2C), 70.7 (2C), 103.9 (2C), 112.0 (2C), 137.8 (2C), 156.6 (2C), 159.0 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{55}N_8O_2$ $[M+H]^+$ 583.4448, found 583.4406.

12,15,18-Trioxa-1,8,22,29,32,38,42,43-octaazatetracyclo[27.6.6.1^{3,7}.1^{23,27}]tritetraconta-3(43),4,6,23(42),24,26-hexaene (21h) was synthesized from compound **14** (0.25 mmol, 135 mg) and trioxadiamine **15h** (0.25 mmol, 55 mg) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%), *t*BuONa (0.75 mmol, 72 mg) in 5 mL dioxane. Eluent CH_2Cl_2-MeOH-NH_3aq 100:25:5, pale-

yellow glassy compound. Yield 15 mg (10%). ^{1}H NMR ($CDCl_3$): δ 1.78 (quintet, *J* = 6.0 Hz, 4H), 1.87 (br.s, 4H), 2.62 (t, *J* = 5.1 Hz, 4H), 2.79-2.84 (m, 4H), 2.85-2.90 (m, 4H), 2.93-2.97 (m, 4H), 3.23 (q, *J* = 5.9 Hz, 4H), 3.49 (s, 4H), 3.52 (t, *J* = 5.9 Hz, 4H), 3.53-3.56 (m, 4H), 3.59-3.62 (m, 4H), 5.38 (br.s, 2H), 6.19 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$): δ 24.5 (2C), 29.1 (2C), 39.9 (2C), 47.3 (2C), 48.3 (2C), 51.7 (2C), 52.3 (2C), 59.7 (2C), 69.2 (2C), 70.2 (2C), 70.5 (2C), 104.3 (2C), 112.2 (2C), 137.8 (2C), 156.2 (2C), 159.1 (2C). HRMS (MALDI-TOF) *m/z* calcd for $C_{32}H_{55}N_8O_3$ $[M+H]^+$ 599.4397, found 599.4436.

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