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One-Step Synthesis of Natural Product-Inspired Biaryl Ether-Cyclopeptoid Macrocycles by Double Ugi Multiple-Component Reactions of Bifunctional Building Blocks

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Isonitrile-functionalized biaryl ethers can serve as key building blocks for the highly efficient one-step production of natural product inspired-macrocycles, with six or even twelve new bonds and rings with up to 50 members being formed in total yields of up to 51 %. Aliphatic diamine and diacid tethers give access to two different classes of *N*-substituted biaryl ether cyclopeptides, suitable for library construction. As part of a conceptual work on MiBs (*m*ultiple *m*ulticomponent *m*acrocyclizations/*m*acrocycles *i*ncluding *b*ifunctional *b*uilding *b*locks), the influence of length and type of flexible tethers on the propensity for cyclization is studied.

Introduction

Macrocycles containing biaryl ether moieties in their ring systems are present in many natural products, such as the vancomycin aglycon, K-13, bouvardin, OF4949-III, or biphenomycin-A.[1] These compounds have antibiotic and antitumor properties, and enterprising approaches to their total syntheses and mimetic structures have been described in the last decade.[2,3] Because of the increasing need for potent antibiotics caused by, for example, multiply resistant bacteria, the search for and discovery of new lead candidates and efficient synthetic methods by which to obtain natural product-like or natural product-inspired libraries is an ongoing process (cf. "chemical genetics" and "biology oriented synthesis", BIOS).[2c,2j] Rapid creation of diversity-oriented libraries based on biaryl ether-containing cyclic peptide mimics, in combination with modern high-throughput screening techniques, is desirable for lead discovery.[4] In addition, larger members of the biaryl ether macrocycle class may serve as potential hosts in supramolecular chemistry, utilizing the lipophilic, π-interaction, and thermal stability properties of a biaryl ether moiety.

Results and Discussion

We have investigated a new and efficient approach by which to obtain potentially bioactive cyclopeptide derivatives in very few steps from commercially available substances, through the use of an Ugi-MCR strategy. In contrast with transition metal-catalyzed C–C bond-forming macrocyclization[5] or S_NAr-based cycloetherification[6] approaches to biaryl ether-containing macrocycles, our strategy differs substantially from the known methods in that the combinatorial synthesis of linear precursors and the macrocyclization step are combined in a powerful strategy termed MiB (multiple multicomponent macrocyclization including bifunctional building blocks). Details of the theoretical concept of MiBs, such as directionality, transition state geometries, etc., are discussed elsewhere.[2d] An approach to biaryl ether-containing cyclopeptoids should best be carried out by use of an Ugi-MCR with two different bifunctional substrates, one of them a bisisonitrilo biaryl ether.[3,7] The term peptoid refers in this context to partially *N*-substituted peptides (i.e., it is used in a broader sense then the strictly *N*-substituted polyglycine definition, which excludes additional C_α-substituents).

For our initial study on one-pot syntheses of biaryl ether cyclopeptoids we chose two routes based on the diisonitriles **4** and **11**, each representing a biaryl ether moiety with either an aryl-aryl (Scheme 1) or an aryl-alkyl (Scheme 2) substitution pattern. Each diisocyanide was allowed to react either with an aliphatic diacid or with an aliphatic diamine, complemented with amine/aldehyde or a carboxylic acid/aldehyde, respectively, to form macrocycles containing two dipeptoid units.

The synthesis of the aryl-aryl diisocyanide **4**[8] started from the commercially available bis(4-aminophenyl) ether (**1**). Formylation with ethyl formate was accomplished under reflux conditions after several days; although the reaction time is long, the reaction can be regarded as very mild,

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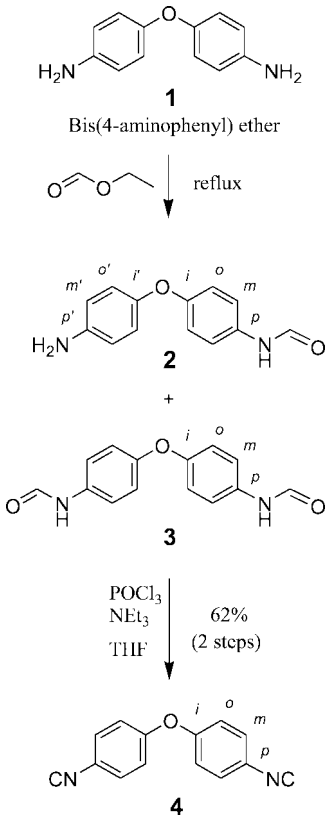


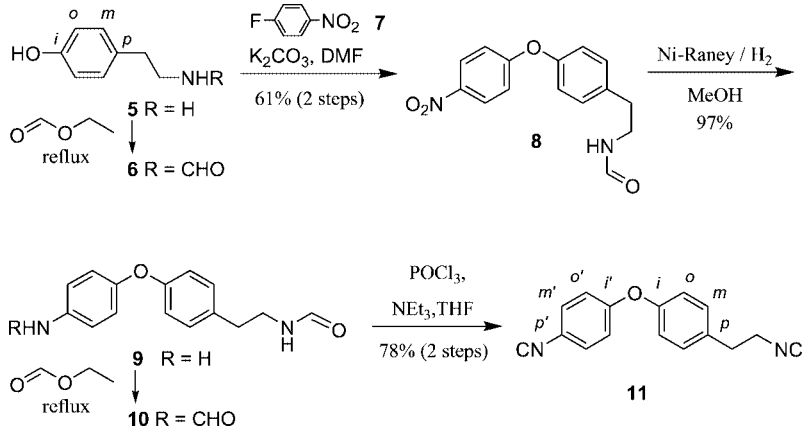
Scheme 1.

with clean conversion being achieved. Even in the case of an incomplete conversion, the presence of residual mono-*N*-formylated intermediate **2** does not disturb the next step, and its separation from the bis-*N*-formyl derivative **3**[9] is not required. Diisocyanide **4** is obtained in acceptable yield (62% overall over two steps, Scheme 1) either from pure **3** or from the mixture of **2** and **3**, by dehydration with phosphorus oxychloride and purification by crystallization.

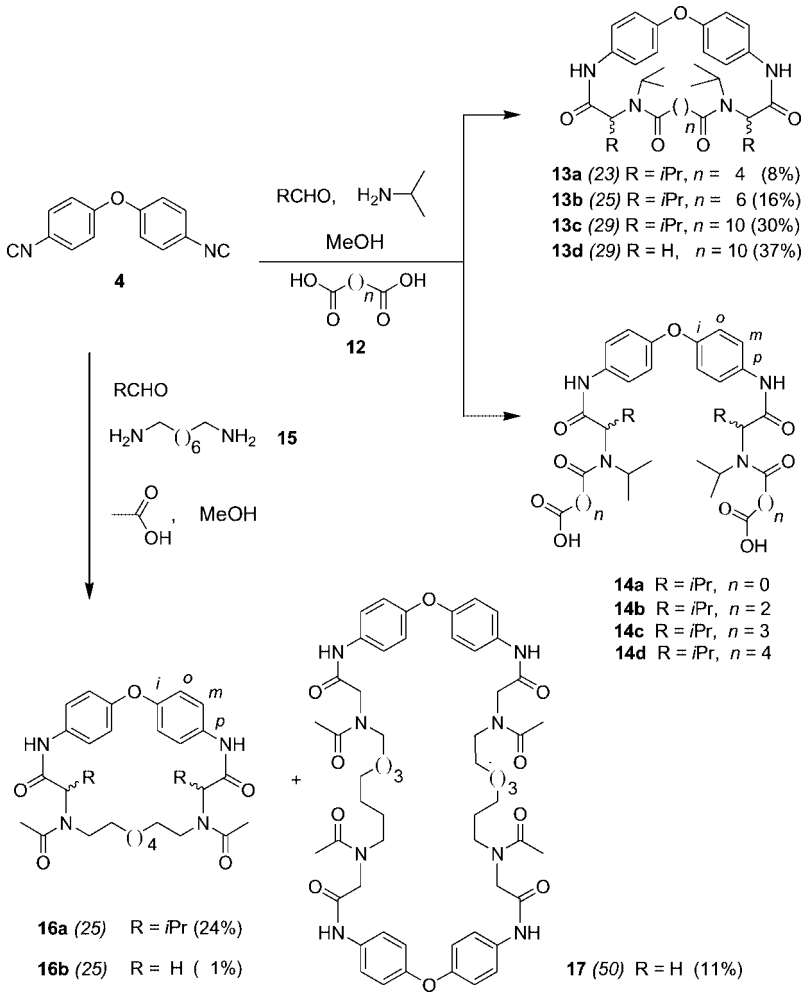
The synthesis of the aryl-alkyl diisocyanide **11** started from tyramine (**5**), which was *N*-formylated[10] to give **6** and coupled to *p*-fluoronitrobenzene (**7**) under basic conditions (K_2CO_3) to yield **8** (61%, two steps). After hydrogenation of **8** with Raney-Ni under hydrogen, **9** was obtained in high yield (97%), *N*-formylated with ethyl formamide to afford **10**, and dehydrated by treatment with phosphorus oxychloride to give the diisocyanide **11** (78%, two steps, Scheme 2).

Macrocyclizations were achieved by the envisioned double Ugi-MCRs, ideally under pseudo-dilution conditions.[2b,2d,11] Thus, a solution of the biaryl diisocyanide (**4** or **11**) was slowly added by syringe pump to a reaction mixture containing the other three components. Long-chain aliphatic diamines and diacids served as second bifunctional units to allow ring-closure, resulting in macrocycles with exo- and endocyclic dipeptoid units, respectively (Scheme 3 and Scheme 4). Theoretically, an ideal pseudo-dilution setup would involve simultaneous addition of both bifunctional building blocks; in some combinations[2d] this is even essential. However, after some experience with the combination studies here and for practical reasons, we chose to only add the diisocyanide slowly, because the reaction is speeded up if larger amounts of intermediate iminium salts and acid are present. This is possible with aryl ether isonitriles because the (second) aromatic isocyanide usually reacts more slowly than the first or much more slowly than the aliphatic one, so double-Ugi diacid formation (cf. **14**) and possible tetra-Ugi macrocycle formation (cf. **17**) is intrinsically reduced.

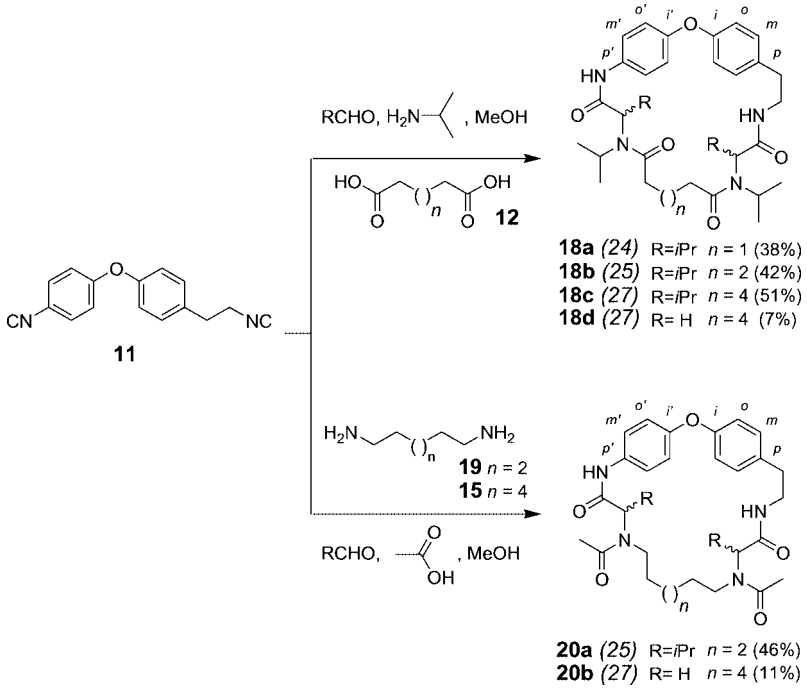
In order to study the importance of tether length, the aryl-aryl diisocyanide **4** was treated with isobutyraldehyde, isopropylamine, and diacids of varying chain length (**12**). Use of the short-chain diacids (oxalic acid, succinic acid, glutaric acid) resulted in acyclic, linear bis-Ugi diacids (**14**, avg. crude yield > 50%; the formation of diacids **14a–d** and sometimes of minor amounts of cyclodimeric tetra-Ugi macrocycles could be unambiguously determined by mass spectrometry, though we performed no further characterization of these products because of our focus on the monomeric macrocyclizations). Attempts to force the cyclisation with glutaric acid by its very slow addition simultaneously with diisocyanide did only result in minute amounts of the monomeric cycle. The reaction is shifted to increased



Scheme 2.



Scheme 3. *Italic* numbers in brackets after the compound number denominate the ring size. **13a**: The macrocycle is isolated as a mixture with a subsequently formed Mannich–Gattermann product (see text).



Scheme 4. *Italic* numbers in brackets after the compound number denominate the ring size.

amounts of the corresponding cyclodimeric MiB – a common product if the cyclomonomer is too strained or the precursor folding is unfavorable (cf., e.g., **17**).[2d,12] Adipic acid (C_6) is a borderline case, with the corresponding 23-membered macrocycle **13a** (n = 4, 8%) being obtained in very low yield. The forced, lengthy reaction causes the subsequent Mannich–Gattermann aminomethylation of one aromatic ring of **13a**, i.e. appending a CH_2NHiPr residue, to give a mixture. The longer-chain diacids, as might be expected, gave increasing yields of the desired cyclomonomeric MiBs, as demonstrated by products **13b** (n = 6, 16%) and **13c** (n = 10, 30%).

The Ugi reaction is not diastereoselective, so the two diastereomers of **13a**–**c** are in all cases formed in almost equal amounts. Although this feature is highly desirable for lead-finding studies, it is inconvenient for method development and analytics, so we investigated the substitution of isobutyraldehyde by paraformaldehyde, a less usual and often not so well behaved aldehyde in Ugi reactions because of its propensities towards polymerization and side reactions. With isopropylamine and dodecandioic acid, however, the reaction proceeded smoothly, affording the glycine-containing cyclopeptoid **13d** in 37% yield, which can be considered very efficient in view of the fact that six new bonds are formed, including a macrocyclization with a very flexible endocyclic C_{10}-alkyl chain.

In a second series utilizing diamines, diisonitrile **4** was treated with isobutyraldehyde, 1,8-octadiamine (**15**), and acetic acid. The resulting 25-membered macrocycle **16a** was obtained in higher yield (24%) than the likewise 25-membered **13b**. Although the diisocyanide/diamine combination is only slightly more efficient than the diisocyanide/diacid one with otherwise equal parameters, this trend was observed in several cases (v.i.). The difference in the product yields of these two combinations is probably a result of the higher configurational flexibility, and thus probably lower ring tension, within the diamine-derived products (e.g., **16a**). Two of the four amide bonds in **16a** are exocyclic, compared to four endocyclic amide bonds in **13a** (Scheme 3, Figure 1).[11] This is important both for strain and for acyclic prefolding, because the *s-trans* amide configuration usually is also preferred in the cyclic MiBs. Furthermore, it also needs to be considered that it is not only the final product that is a limiting factor for the formation of the macrocycles. As discussed earlier,[2d] the formation of the intermediate α adduct is crucial: here the macrocycle is formed initially (Figure 1). Furthermore, conversion of the α adduct into the final product proceeds through a 1,3-*ansa*-like intermediate that should cause additional ring strain in both variations. To form a ring of the same final size when using a diacid, however, requires intermediates with one ring atom fewer than the final macrocycle and, depending on the overall strain and conformational rigidity of the system used, this may result in a disadvantaging of the diacid version, whereas the diamine version does not suffer from smaller intermediates. This, though, is only important for borderline cases: intermediate or product strain becomes less important with increasing length or flexibility of the bifunctional building blocks, and is overruled or even inverted in preference by the increasing statistical disadvantage common to all flexible-chain macrocyclizations.

Treatment of **4** with paraformaldehyde, diamine **15**, and acetic acid gave only a small amount of the expected product **16b** (1%), with the 50-membered macrocycle **17** (11%) containing eight newly formed peptide bonds and having double the molecular mass of **16b** instead being obtained as the main product. Here, 12 building blocks have been engaged in 16 reactions, corresponding to almost 87% for each bond formation (including the macrocyclization).

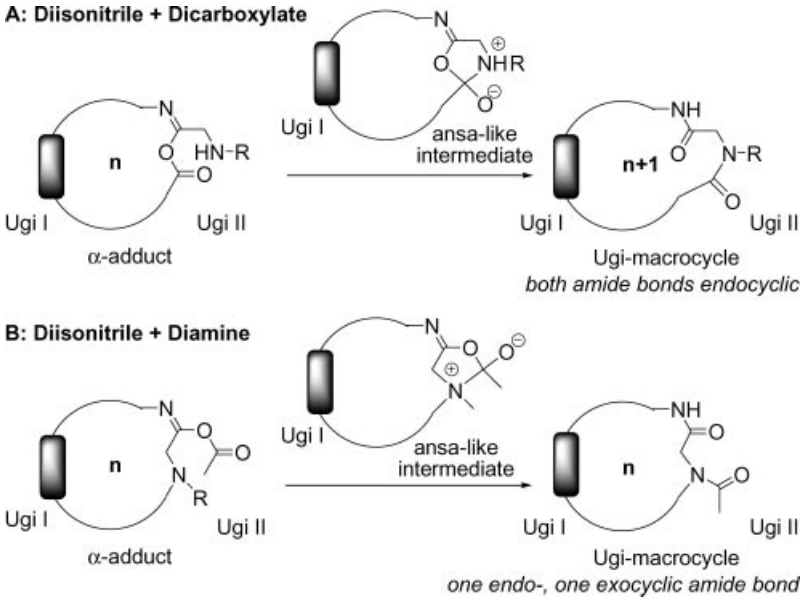


Figure 1. Macrocyclic intermediates, ring strain change, and resulting diamide constitution in MiBs of diisocyanide/diacid vs. diisocyanide/diamine combinations. Boxes represent the first (acyclic) Ugi dipeptide.

The aryl-alkyl diisocyanide **11** (Scheme 4) was treated in the same way as **4** with isobutyraldehyde, isopropylamine, and diacids **12** to produce macrocycles **18a** (n = 1, 38%), **18b** (n = 2, 42%), and **18c** (n = 4, 51%). The aliphatic isocyanide portion reacts more rapidly than the aromatic one. Overall yields in this system are much higher, because the additional ethylene group creates more flexibility in the cycle and lowers the ring tension of the α adduct and the resulting product.[2d]

Treatment of **11** with isobutyraldehyde, acetic acid, and aliphatic diamine **19** provided the macrocycle **20a** in 46% yield (Scheme 4). The ring flexibility of **20a** is higher and ring formation is slightly preferred in comparison with **18b**, for the reasons discussed above (Figure 1), though with increased flexibility these strain-based preferences become less important, or may even invert, with too much flexibility being detrimental. Interestingly, the 27-membered rings **18c** and **20b** appear to retain methanol solvent quite well.

Both conversions of **11** were also performed with paraformaldehyde. With suberic acid, paraformaldehyde, and isopropylamine, compound **18d** was obtained in 7% yield, while with diamine **15**, paraformaldehyde, and acetic acid, macrocycle **20b** was obtained in 11% yield. Obviously, the use of paraformaldehyde decreases the yield in most cases (**16**, **18**, **20**). Although decreased formation or polymerization of the intermediate imine cannot be excluded, the more probable reason is the higher flexibility of the acyclic precursor, thus reducing the propensity towards macrocyclization. This appears most likely because the use of paraformaldehyde can even improve the yield in cases in which macrocyclization is problematic due to very high overall rigidity[11] or strain (cf. **13c** vs. **13d** vs. **14**). Rigidity and strain are factors easily influenced by the Ugi oxo component,[12] and the use of an element such as formaldehyde gives glycine amides, which in such cases avoids putting two sets of vicinal and transannularily interfering α-amino acid side chains (e.g., two isopropyl groups) in a tight macrocycle.

Conclusions

In summary, we have devised a very short and straightforward route to macrocycles containing biaryl ether components through double (and quadruple) Ugi MCRs. The importance of the spans of the bifunctional building blocks, the pseudo-dilution conditions, and the influence of formaldehyde have been discussed. In view of the fact that eight bonds are formed in each double MCR, a total yield of, say, 43% equates to a ca. 90% yield for each bond-forming step, including the macrocyclization.

Experimental Section

General: Reactions were monitored by TLC on 60 F_{254} silica gel (Merck) with detection either by UV light or by charring with 10% H_2SO_4 in EtOH. Solutions were concentrated under reduced pressure at 40 °C. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, Merck). ^{1}H NMR spectra (500, 400 or 300 MHz) and ^{13}C NMR spectra (75.5 or 125.7 MHz) were recorded with VARIAN Inova 500, Mercury 400, and Mercury 300 spectrometers, respectively, at 300 K if not indicated otherwise. δ_H (ppm) and δ_C (ppm) values are referred to the solvent signals: $CDCl_3$ (δ_H = 7.26, δ_C = 77.0), [D_6]DMSO (δ_H = 2.50, δ_C = 39.7) and MeOD (δ_H = 3.30, δ_C = 49.0). EI mass spectrometry was performed on an AMD 402 (AMD Intectra GmbH) instrument. The high-resolution positive ion ESI mass spectra were obtained with a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonics, Billerica, USA) fitted with an Infinity™ cell, a 7.0 Tesla superconducting magnet (Bruker, Karlsruhe, Germany), an RF-only hexapole ion guide, and an external electrospray ion source (Agilent). IR spectra were measured with a Bruker IFS 28 spectrometer. Elemental analyses were performed on a CHNS automatic elemental analyzer Flash EA (ThermoQuest). All compounds for which elemental analytical data are not available were chromatographically homogeneous, and NMR and mass spectroscopic data were in full agreement with the assigned structures.

Bis(4-isocyanophenyl) Ether (4): A mixture of bis(4-aminophenyl) ether (**1**, 10 g, 50 mmol) in ethyl formate (200 mL) was heated at reflux for 5 d. After the starting material had been converted (TLC monitoring), solvent and formed alcohol were removed under reduced pressure and the residue (11.4 g, mixture from **2** and **3**) was dried in vacuo, and then dissolved in THF (350 mL). After addition of NEt_3 (64 mL, 460 mmol), a solution of $POCl_3$ (12 mL, 130 mmol) in THF (50 mL) was added dropwise to the reaction mixture at –60 °C over 2 h, and stirring was continued for 5 h at room temp. The mixture was poured into ice/water and extracted with diethyl ether, and the combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from ethanol gave **4** as light-brown needles (6.8 g, 62%); m.p. 144–145 °C; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.79 (**4**), 0.26 (**3**), and 0.17 (**2**).

Compound 4: ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.39 (m, 4 H, *m*-Ph), 7.01 (m, 4 H, *o*-Ph) ppm. ^{13}C NMR (125.7 MHz; $CDCl_3$): δ = 164.1 (br., NC), 156.5 (*i*-Ph), 128.2 (*m*-Ph), 119.6 (*o*-Ph), 122.3 (br t, *p*-Ph) ppm. IR: $\tilde{\nu}_{(KBr)}$ = 2125 cm^{-1} (NC). EI-MS of $C_{14}H_8N_2O$ (M, 220.1): m/z = 220 $[M]^+$. HRMS of $C_{14}H_8N_2O$ 220.0615; calcd. 220.0637. The diisonitrile is reactive, elemental analysis was varying under normal conditions.

Compound 2: ^{1}H NMR (300 MHz; [D_6]DMSO, δ of minor isomer in brackets): δ = 10.11 (br s, 1 H, NH_{cis}); (10.03) (d, 1 H, NH_{trans}); (8.63) (d, $J_{NH,CHO}$ = 11.3 Hz, 1 H, CHO_{trans}); 8.20 (d, $J_{NH,CHO}$ = 1.9 Hz, 1 H, CHO_{cis}); 7.54 (7.17) (m, 2 H, *m*-Ph); 6.94 (6.94) (m, 2 H, *o*-Ph) ppm. ^{13}C NMR (125.7 MHz; [D_6]DMSO, δ of minor isomer in brackets): δ = 159.7 (163.0) (CHO); 153.0 (153.6) (*i*-Ph); 133.9 (133.9) (*p*-Ph); (121.2), 121.2 (*m*-Ph); (120.0), (119.7), (119.6), (119.1), 119.1 (*o*-Ph) ppm. EI-MS of $C_{14}H_{12}N_2O_3$ (M, 256.1): m/z = 256 $[M]^+$. HRMS of $C_{14}H_{12}N_2Na_1O_3$ [M + Na]: 279.0743; calcd. 279.0740. $C_{14}H_{12}N_2O_3$ (256.26): calcd. C 65.62, H 4.72, N 10.93; found C 65.82, H 4.81, N 10.59.

Compound 3: ^{1}H NMR (300 MHz; [D_6]DMSO, δ of minor isomer in brackets): δ = 10.02 (br s, 1 H, NH_{cis}); (9.95) (d, 1 H, NH_{trans}); (8.63) (d, $J_{NH,CHO}$ = 11.0 Hz, 1 H, CHO_{trans}); 8.17 (d, $J_{NH,CHO}$ = 1.9 Hz, 1 H, CHO_{cis}); 7.46 (7.10) (m, 2 H, *m*′-Ph); 6.81 (6.81) (m, 2 H, *o*′-Ph); 6.71 (6.71) (m, 2 H, *o*-Ph); 6.57 (6.57) (m, 2 H, *m*-Ph); 4.85 (br s, 2 H, NH_2) ppm. ^{13}C NMR (125.7 MHz; [D_6]DMSO, δ of minor isomer in brackets): δ = 159.4 (162.7) (CHO); 154.7 (155.4) (*i*-Ph); 146.4 (146.4), 145.0 (145.1) (*i*′-Ph, *p*′-Ph); 132.5 (132.4) (*p*-Ph); 121.0, 120.4 (*m*, *m*′-Ph); (119.9), (117.9), 117.2 (*o*-Ph); 115.2 (*o*′-Ph) ppm. EI-MS of $C_{13}H_{12}N_2O_2$ (M, 228.1): m/z =

228 $[M]^+$. HRMS of $C_{13}H_{12}N_2Na_1O_2$ [M + Na]: 251.0794; calcd. 251.0791. $C_{13}H_{12}N_2O_2$ (228.25): calcd. C 68.41, H 5.30, N 12.27; found C 68.07, H 5.13, N 12.09.

***N*-[2-(4-Hydroxyphenyl)ethyl]formamide (6):** A mixture of tyramine (**5**, 5 g, 36 mmol) in ethyl formate (50 mL) was heated at reflux for 24 h. After the starting material had been converted (tlc monitoring), the solvent and formed alcohol were removed under reduced pressure. Crystallization of the residue from ethanol gave **6** as light brown crystals (4.95 g, 82%). M.p. 96–97 °C; TLC ($CHCl_3$/MeOH 4:1) R_f = 0.47. ^{1}H NMR (400 MHz; [D$_6$]DMSO): δ = 7.94 (br s, 1 H, CHO); 6.98 (m, 2 H, *m*-Ph); 6.65 (m, 4 H, *o*-Ph); 3.23 (dt, $J_{CH_2,CH_2} = J_{CH_2,NH}$ = 7.0 Hz, 2 H, CH_2NH); 2.58 (t, 2 H, CH_2CH$_2$NH) ppm. ^{13}C NMR (125.7 MHz; [D$_6$]DMSO, δ of minor isomer in brackets): δ = 161.3 (164.6) (CHO); 155.6 (*i*-Ph); 129.5 (129.8) (*m*-Ph); 129.4 (128.9) (*p*-Ph); 115.2 (115.2) (*o*-Ph); 39.3 (43.0) (CH_2); 34.3 (36.4) (CH_2) ppm. EI-MS of $C_9H_{11}NO_2$ (M, 165.1): *m*/*z* = 165 $[M]^+$. HRMS of $C_9H_{11}N_1Na_1O_2$ [M + Na]: 188.0685; calcd. 188.0682. $C_9H_{11}N_1O_2$ (165.19): calcd. C 65.44, H 6.71, N 8.48; found C 65.56, H 6.86, N 8.44.

***N*-{2-[4-(4-Nitrophenoxy)phenyl]ethyl}formamide (8):** A mixture of *N*-[2-(4-hydroxyphenyl)ethyl]formamide (**6**, 5 g, 30 mmol), *p*-fluoronitrobenzene (**7**, 3.5 mL, 33 mmol), and K_2CO_3 (5 g) in *N*,*N*-dimethylformamide (35 mL) was stirred for 24 h at room temp. The mixture was poured into ice/water and extracted with chloroform, and the combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from ethanol gave **8** as a light brown solid (6.41 g, 74%). M.p. 96–97 °C; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.37. ^{1}H NMR [400 MHz; $CDCl_3$, δ of minor isomer (15%) in brackets]: δ = 8.20 (m, 3 H, *m*′-Ph, CHO); (7.97) (d, $J_{CHO,NH}$ = 12.1 Hz, 1 H, CHO); 7.29–7.23 (m, 2 H, *m*-Ph); 7.08–6.98 (m, 4 H, *o*-, *o*′-Ph); 5.63 (5.73) (br s, 1 H, NH); 3.61 (dt, $J_{CH_2,CH_2} = J_{CH_2,NH}$ = 6.8 Hz, 2 H, CH_2NH); (3.53) (dt, $J_{CH_2,CH_2} = J_{CH_2,NH}$ = 6.6 Hz, 2 H, CH_2NH); 2.89 (2.87) (t, 2 H, CH_2CH$_2$NH) ppm. ^{13}C NMR (125 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 161.3 (164.5) (CHO); 163.3 (163.2) (*i*′-Ph); 153.3 (153.3) (*i*-Ph); 142.5 (*p*′-Ph); 135.6 (134.6) (*p*-Ph); 130.5 (130.7) (*m*-Ph); 125.9 (*m*′-Ph); 120.7 (120.8), 116.9 (117.0) (*o*-, *o*′-Ph); 39.3 (43.1) (CH_2); 34.9 (36.9) (CH_2) ppm. EI-MS of $C_{15}H_{14}N_2O_4$ (M, 286.1): *m*/*z* = 286 $[M]^+$. HRMS of $C_{15}H_{14}N_2Na_1O_4$ [M + Na]: 309.0849; calcd. 309.0846. $C_{15}H_{14}N_2O_4$ (286.28): calcd. C 62.93, H 4.93, N 9.77; found C 62.68, H 4.97, N 9.80.

***N*-{2-[4-(4-Aminophenoxy)phenyl]ethyl}formamide (9):** A suspension of Raney nickel in water (approx. 2 g wet) was washed with water until the washings remain neutral. After washing with methanol a solution of *N*-{2-[4-(4-nitrophenoxy)phenyl]ethyl}-formamide (**8**, 1.0 g, 3.5 mmol) in methanol (100 mL) was added and the reaction mixture was stirred under hydrogen for 24 h and then filtered through Celite. Concentration of the filtrate gave **9** as a pale yellow syrup (0.87 g, 97%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.25; ^{1}H NMR (300 MHz; [D$_6$]DMSO): δ = 8.04 (br s, 1 H, N*H*CHO); 7.98 (d, $J_{CHO,NH}$ = 1.6 Hz, 1 H, NHC*H*O); 7.13 (m, 2 H, *m*′-Ph); 6.75 (m, 4 H, *o*-, *o*′-Ph); 6.57 (m, 2 H, *m*-Ph); 4.96 (br s, 2 H, NH_2); 3.27 (dt, $J_{CH_2,CH_2} = J_{CH_2,NH}$ = 7.1 Hz, 2 H, CH_2NH); 2.65 (t, 2 H, CH_2CH$_2$NH) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO, δ of minor isomer in brackets): δ = 160.8 (CHO); 157.2 (*i*-Ph); 145.5, 145.2 (*i*-, *p*-Ph); 132.3 (*p*′-Ph); 129.6 (129.9) (*m*′-Ph); 120.7 (*m*-Ph); 116.2, 114.7 (*o*-, *o*′-Ph); 38.9 (42.8) (CH_2); 34.2 (36.3) (CH_2) ppm. $C_{15}H_{16}N_2O_4$ (288.30): calcd. C 70.29, H 6.29, N 10.93; found C 69.74, H 6.39, N 10.75.

***N*-{4-[4-(2-Formylaminoethyl)phenoxy]phenyl}formamide (10):** A mixture of *N*-{2-[4-(4-aminophenoxy)phenyl]ethyl}formamide (**9**, 0.87 g, 3.4 mmol) in ethyl formate (100 mL) was heated at reflux for 24 h. After the starting material had been consumed, solvent and alcohol formed were removed under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **10** as a brown solid (0.88 g, 91%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.20. ^{1}H NMR (400 MHz; MeOD): δ = 8.22 (8.60) (s, 1 H, C_6H_4NHC*H*O); 8.00 (7.75) (s, 1 H, CH_2NHC*H*O); 7.54 (m, 2 H, *m*′-Ph); 7.21 (m, 2 H, *m*-Ph); (7.16) (m, 2 H, *m*-Ph); (6.96) (m, 2 H, *m*-Ph); 6.91 (m, 4 H, *o*,*o*′-Ph); 3.44 (t, J_{CH_2,CH_2} = 7.3 Hz, 2 H, CH_2N); 2.79 (t, 2 H, CH_2CH$_2$N) ppm. ^{13}C NMR (125 MHz; MeOD): δ = 163.6, 161.2 (167.1, 164.7) (CHO); 157.2 (157.1), 155.1 (155.9) (*i*-, *i*′-Ph); 135.1 (135.2), 134.2 (134.5) (*p*-, *p*′-Ph); 131.0 (131.4) (*m*-Ph); 122.5 (121.5) (*m*′-Ph); 120.0 (120.7), 119.6 (119.6) (*o*-, *o*′-Ph); 40.6 (44.5) (CH_2); 35.7 (37.6) (CH_2) ppm. EI-MS of $C_{16}H_{16}N_2O_3$ (M, 284.1): *m*/*z* = 284 $[M]^+$. HRMS of $C_{16}H_{16}N_2Na_1O_3$ [M + Na]: 307.1055; calcd. 307.1053. $C_{16}H_{16}N_2O_3$ (284.31): calcd. C 67.59, H 5.67, N 9.85; found C 67.32, H 5.70, N 9.66.

4-[4-(2-Isocyanoethyl)phenoxy]phenyl Isocyanide (11): A solution of $POCl_3$ (0.6 mL, 6.2 mmol) in THF (10 mL) was added dropwise at –60 °C over 2 h to a mixture of *N*-{4-[4-(2-formylaminoethyl)-phenoxy]phenyl}formamide (**10**, 0.72 g, 2.6 mmol) and NEt_3 (3.5 mL, 25 mmol) in THF (10 mL). Stirring was continued for 5 h at room temp., and the mixture was then poured into ice/water and extracted with diethyl ether. The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated, and **11** was obtained as a dark brown oil (0.55 g, 86%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.73. ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.33 (m, 2 H, *m*′-Ph); 7.24 (m, 2 H, *m*-Ph); 6.97 (m, 4 H, *o*-, *o*′-Ph); 3.63 (t, J_{CH_2,CH_2} = 7.0 Hz, 2 H, CNCH$_2$); 2.98 (t, 2 H,CNCH$_2$CH_2) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 163.2 (br., *C*NC$_{ar}$); 156.6 (t, *C*NCH$_2$); 157.9, 154.7 (*i*-Ph); 132.7 (*p*-Ph); 130.2 (*m*-Ph); 127.8 (*m*′-Ph); 121.0 (br m, *p*′-Ph); 119.9 (*o*-Ph); 118.5 (*o*′-Ph); 43.0 (t, CN*C*H$_2$); 34.9 (CNCH$_2$*C*H$_2$) ppm. IR: $\tilde{\nu}_{(KBr)}$ = 2151 cm^{-1} (–NC); 2130 cm^{-1} (–NC). EI-MS of $C_{16}H_{12}N_2O$ (M, 248.1): *m*/*z* = 248 $[M]^+$. The diisonitrile is reactive, elemental analysis was varying under normal conditions (cf. **4**).

9,10,19,20-Tetraisopropyl-2-oxa-7,10,19,22-tetraazatricyclo[21.2.2.2^{3,6}]nonacosa-1(26),3(29),4,6(28),23(27),24-hexaene-8,11,18,21-tetraone (13b): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and isopropylamine (0.18 mL, 2 mmol) in methanol (130 mL) was stirred for 1 h at room temp., suberic acid (87 mg, 0.5 mmol) was then added, and stirring was continued for another 30 min. Afterwards, a solution of diisonitrile **4** (110 mg, 0.5 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}). The reaction mixture was concentrated under reduced pressure, and column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **13b** as a diastereomeric mixture, isolated as an amorphous solid (50 mg, 16%). TLC (EtOAc) R_f = 0.53. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 10.60, 10.50, 10.42, 10.08 (broad signals, NH); 7.48, 7.35, 7.30, 7.07, 6.99, 6.90 (2), 6.73 (several multiplets from Ar); 4.97 (d, *J* = 11.0 Hz, C*H*CHMe$_2$); 4.12–3.96 (m, NC*H*Me$_2$); 3.17–3.09 (m, C*H*C*H*Me$_2$); 2.67–2.20, 1.80–1.10 (br m, CH_2); 1.40–1.10 [m, NCH(CH_3)$_2$]; 1.07 (d, *J* = 6.2 Hz), 1.06 (d, *J* = 6.3 Hz), 0.98 (d, *J* = 6.3 Hz), 0.87 m, 0.76 (d, *J* = 6.6 Hz) [CHCH(CH_3)$_2$] ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 174.9, 173.0, 172.4, 172.1, 171.3, 171.1, 170.4 (CO); 158.4, 156.8, 154.2 (*i*-Ar); 134.7, 134.3, 130.4 (*p*-Ar); 129.9, 121.3, 120.8, 120.5, 120.0, 119.4 (*o*-, *m*-Ar); 70.3, 57.8 [*C*HCH(CH$_3$)$_2$]; 50.7, 50.5 [N*C*H(CH$_3$)$_2$]; 36.6, 35.6, 35.2 (*C*H$_2$CO); 30.9, 30.5, 30.4, 29.1 (CH_2); 27.6, 27.5, 27.3 (2) (CH*C*HMe$_2$); 26.2, 25.8 (CH_2); 22.7, 22.1, 21.6, 21.5, 21.2, 21.0 (2) [NCH(*C*H$_3$)$_2$]; 20.3, 20.1, 20.0, 19.7, 18.4, 14.2 [CHCH(*C*H$_3$)$_2$] ppm. ESI-MS of $C_{36}H_{52}N_4O_5$ (M,

620.4): *m*/*z* = 621.6 $[M + H]^+$, 643.4 $[M + Na]^+$. HRMS of $C_{36}H_{52}N_4Na_1O_5$ [M + Na]: 643.3830; calcd. 643.3830. $C_{36}H_{54}N_4O_6$ (638.84): calcd. C 67.68, H 8.52, N 8.77; found C 67.13, H 8.33, N 8.65.

9,10,23,24-Tetraisopropyl-2-oxa-7,10,23,26-tetraazatricyclo[25.2.2.$2^{3,6}$]tritriaconta-1(30),3(33),4,6(32),27(31),28-hexaene-8,11,22,25-tetraone (13c): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and isopropylamine (0.18 mL, 2 mmol) in methanol (130 mL) was stirred for 1 h at room temp., dodecanedioic acid (115 mg, 0.5 mmol) was added, and stirring was continued for another 30 min. Afterwards, a solution of diisonitrile **4** (110 mg, 0.5 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}). The reaction mixture was concentrated under reduced pressure, and column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **13c** as a diastereomeric mixture, isolated as an amorphous solid (102 mg, 30%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.31. ^{1}H NMR (500 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 10.60, 10.40 (2 × br, 2 × NH); 7.46 (7.39) (m, 4 H, Ar); (6.90) 6.88 (m, 4 H, Ar); 4.15 (m, 2 H, NC*H*Me$_2$); 3.19 (br., 4 H, C*H*C*H*Me$_2$); 2.65 (m, 2 H), 2.29 (m, 2 H) (CH_2CO); 1.72 (m, 2 H), 1.54 (m, 2 H) (CH_2CH_2CO); 1.34–1.12 [m, 12 H, (CH_2)$_6$]; 1.28 (d, *J* = 6.6 Hz, 6 H), 1.23 (d, *J* = 6.6 Hz, 6 H) [NCH(CH_3)$_2$]; 1.10 (d, *J* = 6.3 Hz, 6 H), 0.90 (d, *J* = 6.3 Hz, 6 H) [CHCH(CH_3)$_2$] ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 175.7, 171.1 (CO); 154.2 (*i*-Ar); 134.3 (*p*-Ar); 120.6, 119.5 (119.7) (*o*-, *m*-Ar); 70.4 (*C*HCHMe$_2$); 50.9 (N*C*HMe$_2$); 35.0 (CH_2CO); 30.0, 29.9 (3), 29.6 (2) [(*C*H$_2$)$_6$]; 27.3 (CH*C*HMe$_2$); 26.5 (*C*H$_2$CH$_2$CO); 21.5, 21.1 [NCH(*C*H$_3$)$_2$]; 20.3, 20.1 [CHCH(*C*H$_3$)$_2$] ppm. FAB MS of $C_{40}H_{60}N_4O_5$ (M, 676.5): *m*/*z* = 676 $[M]^+$. HRMS of $C_{40}H_{60}N_4Na_1O_5$ [M + Na]: 699.4461; calcd. 699.4456. $C_{40}H_{60}N_4O_5$ (676.93): calcd. C 70.97, H 8.93, N 8.28; found C 71.09, H 8.33, N 8.65.

10,23-Diisopropyl-2-oxa-7,10,23,26-tetraazatricyclo[25.2.2.2^{3,6}]tritriaconta-1(30),3(33),4,6(32),27(31),28-hexaene-8,11,22,25-tetraone (13d): A mixture of paraformaldehyde (120 mg, 4 mmol), isopropylamine (0.36 mL, 4 mmol) and sodium sulfate (2 g) in methanol (40 mL) was stirred for 2 h at room temp., methanol (130 mL) and dodecanedioic acid (230 mg, 1 mmol) were then added, and stirring was continued for another 30 min. Afterwards, a solution of diisonitrile **4** (220 mg, 1 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}) and the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **13d** as an amorphous solid (220 mg, 37%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.60. ^{1}H NMR (500 MHz; [D$_6$]DMSO, δ of minor isomer in brackets): δ = 10.05 (9.52) (br., 2 H, 2 × NH); 7.50 (m, 4 H, Ar); 6.91 (m, 4 H, Ar); 4.71 (4.15) (m, 2 H, C*H*Me$_2$); 4.00 (3.80) (s, 4 H, 2 × NCH_2CO); (2.36) 2.03 (m, 4 H, CH$_2$C*H*$_2$CO); 1.42 (m, 4 H, C*H*$_2$CH$_2$CO); 1.20–1.00 [m, 24 H, (CH$_2$)$_6$, 4 × Me] ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 172.2, 168.1 (CO); 153.9 (*i*-Ar); 134.0 (*p*-Ar); 121.3, 121.2, 119.9, 119.2, 118.6 (*o*-, *m*-Ar); 47.6, 45.2, 44.6, 43.8 (N*C*H$_2$CO, *C*HMe$_2$); 32.7, 31.9, 29.6, 29.1, 28.9, 25.0, 24.7, 20.7, 19.6 [(CH$_2$)$_6$, 4 × Me] ppm. ESI-MS of $C_{34}H_{48}N_4O_5$ (M, 592.7): *m*/*z* = 593.7 $[M + H]^+$, 615.6 $[M + Na]^+$. HRMS of $C_{34}H_{48}N_4O_5Na$ [M + Na]: 615.3511; calcd. 615.3517. $C_{34}H_{48}N_4O_5$ (592.77): calcd. C 68.89, H 8.16, N 9.45; found C 69.00, H 8.36, N 9.51.

10,19-Diacetyl-9,20-diisopropyl-2-oxa-7,10,19,22-tetraazatricyclo-[21.2.2.2^{3,6}]nonacosa-1(26),3(29),4,6(28),23(27),24-hexaene-8,21-dione (16a): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and 1,8-diaminooctane (**15**, 144 mg, 1 mmol) in methanol (30 mL) was stirred for 1 h at room temp., acetic acid (0.12 mL, 2 mmol) was then added, and stirring was continued for another 30 min. After addition of methanol (100 mL), a solution of diisonitrile **4** (110 mg, 0.5 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}) and the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **16a** as a diastereomeric mixture, isolated as an amorphous solid (72 mg, 24%). TLC ($CHCl_3$/MeOH 95:5) R_f = 0.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (br., NH); 7.44 (m, 4 H, Ar); 6.87 (m, 4 H, Ar); 4.20 (br., 2 H, CHN); 3.27 (br., 4 H, 2 × C*H*$_2$NAc); 2.60 (br., 2 H, 2 × C*H*Me$_2$); 2.16, 2.14 (2 × s, 6 H, 2 × Ac); 2.00–1.05 [br m, 12 H, (C*H*$_2$)$_6$]; 1.03, 0.86 (2 × d, *J* = 6.5 Hz, 12 H, 4 × CH$_3$) ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$): δ = 172.6, 172.5, 168.9 (CO); 153.3 (*i*-Ar); 133.4 (*p*-Ar); 121.2, 121.1, 119.0, 118.9 (*o*-, *m*-Ar); 63.0 (br., *C*HN); 48.0 (br., NCH$_2$); 37.9, 33.9, 30.4 (br), 29.3, 29.1 (2), 29.0 (br) [(*C*H$_2$)$_6$]; 26.9 (br), 20.0, 19.1 (br) [*C*HMe$_2$, CH(*C*H$_3$)$_2$, CO*C*H$_3$] ppm. FAB MS of $C_{34}H_{48}N_4O_5$ (M, 592.4): *m*/*z* = 592 $[M]^+$. HRMS of $C_{34}H_{48}N_4Na_1O_5$ [M + Na]: 615.3530; calcd. 615.3517. M + H_2O, $C_{34}H_{50}N_4O_6$ (610.78): calcd. C 66.86, H 8.25, N 9.17 and $C_{34}H_{48}N_4O_5$ (592.77): calcd. C 68.89, H 8.16, N 9.45; found C 66.05, H 8.16, N 9.45.

10,19-Diacetyl-2-oxa-7,10,19,22-tetraazatricyclo[21.2.2.2^{3,6}]nonacosa-1(26),3(29),4,6(28),23(27),24-hexaene-8,21-dione (16b): A mixture of paraformaldehyde (60 mg, 2 mmol), 1,8-diaminooctane (**15**, 144 mg, 1 mmol), and sodium sulfate (2 g) in methanol (30 mL) was stirred for 2 h at room temp., methanol (100 mL) and acetic acid (0.12 mL, 2 mmol) were then added, and stirring was continued for another 30 min. Afterwards, a solution of diisonitrile **4** (220 mg, 1 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}), and the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **16b** as an amorphous solid (4.3 mg, 1%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.30. ^{1}H NMR (500 MHz; [D$_6$]DMSO): δ = 10.20 (br., 1 H, NH); 9.65 (br., 1 H, NH); 7.38 (br., 4 H, Ar); 7.00 (br., 4 H, Ar); 4.10–3.90 (br., 4 H, 2 × COCH$_2$); 3.15 (br., 4 H, 2 × CH$_2$C*H*$_2$N); 2.00 (br s, 6 H, 2 × Ac); 1.40–0.90 (br m, 12 H, 6 × CH$_2$); (at 120 °C): δ = 9.40 (br., 2 H, NH); 7.36 (m, 4 H, Ar); 6.98 (m, 4 H, Ar); 3.95 (s, 4 H, 2 × COCH$_2$); 3.20 (t, *J* = 7.0 Hz, 4 H, 2 × CH$_2$C*H*$_2$N); 2.03 (s, 6 H, 2 × Ac); 1.30 (br s, 4 H, 2 × CH$_2$); 1.03 (br s, 8 H, 4 × CH$_2$) ppm. ^{13}C NMR (125 MHz; [D$_6$]DMSO): δ = 170.5, 170.0, 167.2 (CO); 152.5, 152.3, 151.8 (*i*-Ar); 139.3, 134.4, 134.2 (*p*-Ar); 128.0, 124.8, 120.8 (2), 118.5 (*o*-, *m*-Ar); 51.5, 49.5, 49.0, 46.2 (NCH$_2$); 35.0–20.0 (several signals from CH$_2$ and CH$_3$); (at 120 °C): δ = 169.6, 168.0 (CO); 155.6 (*i*-Ar); 133.5 (*p*-Ar); 123.9 (br), 119.7 (br) (*o*-, *m*-Ar); 35.0–20.0 (several broad signals) ppm. ESI-MS of $C_{28}H_{36}N_4O_5$ (M, 508.6): *m*/*z* = 509.3 $[M + H]^+$, 531.4 $[M + Na]^+$. HRMS of $C_{28}H_{36}N_4O_5Na$ [M + Na]: 531.2579; calcd. 531.2578.

10,19,35,44-Tetraacetyl-2,27-dioxa-7,10,19,22,32,35,44,47-octaazapentacyclo[42.2.2.2^{3,6}.2^{23,26}.2^{28,31}]octapentaconta-1(51),3(54),4,6(53),23,25,28,30,48(52),49,55,57-dodecaene-8,21,33,46-tetraone (17): Amorphous solid (55 mg, 11%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.20. ^{1}H NMR (500 MHz; [D$_6$]DMSO, room temp.): δ = 10.20 (br., 2 H, NH); 9.95 (br., 2 H, NH); 7.58 (br., 8 H, Ar); 6.96 (br., 8 H, Ar); 4.15 (s, 4 H, 2 × COCH$_2$); 4.05 (s, 4 H, 2 × COCH$_2$); 3.40–3.20 (2 × t, 8 H, 2 × CH$_2$C*H*$_2$N); 2.20–1.90 (4 × s, 12 H, 4 × Ac); 1.60–1.20 (br m, 24 H, 12 CH$_2$) ppm. ^{13}C NMR (125 MHz; [D$_6$]DMSO, room temp.): δ = 170.4 (2), 169.9, 167.2 (2) (CO); 152.7, 152.6, 152.5, 152.4, 151.5 (*i*-Ar); 139.2, 134.6, 134.5, 134.2 (2) (*p*-Ar); 128.0, 124.9, 120.8, 120.7, 118.8, 118.7 (*o*-, *m*-Ar); 51.7 (br), 49.6, 49.0, 46.4 (br) (NCH$_2$); 35.0–20.0 (several signals from CH$_2$ and CH$_3$) ppm. ESI-MS of $C_{56}H_{72}N_8O_{10}$ (M, 1017.2): *m*/*z* =

1039.7 [M + Na]$^+$. HRMS of $C_{56}H_{72}N_8O_{10}Na$ [M + Na]: 1039.5280; calcd. 1039.5264.

9,10,16,17-Tetraisopropyl-2-oxa-7,10,16,19-tetraazatricyclo[20.2.2.2^{3,6}]octacosa-1(25),3(28),4,6(27),22(26),23-hexaene-8,11,15,18-tetraone (18a): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and isopropylamine (0.18 mL, 2 mmol) in methanol (130 mL) was stirred for 1 h at room temp., glutaric acid (66 mg, 0.5 mmol) was then added, and stirring was continued for another 30 min. Afterwards, a solution of 4-[4-(2-isocyanoethyl)phenoxy]phenyl isocyanide (**11**, 124 mg, 0.5 mmol) in methanol (20 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}), and the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **18a** as a diastereomeric mixture, isolated as an amorphous solid (116 mg, 38%). TLC (EtOAc) R_f = 0.31. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 10.53, 10.21 (2 broad signals, ArN*H*); 8.29–7.95 (5 broad signals, CH_2N*H*); 7.48–6.74 (several multiplets, Ar); 5.06 (d, *J* = 11.0 Hz, C*H*CHMe$_2$); 4.18–3.75 (m), 3.42 (m), 3.20–2.00 (several multiplets, C*H*C*H*Me$_2$, NC*H*Me$_2$, CH_2); 1.90–0.70 (several multiplets from Me) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 174.5, 174.0; 173.8, 173.3, 173.1, 172.8, 171.9, 171.5, 171.4, 171.3, 171.1, 170.9 (CO); 158.5, 157.0, 156.7, 156.3 (2), 156.1 (*i*-Ar); 135.1, 134.4, 134.2, 132.3, 130.7 (*p*-Ar); 130.5, 130.3, 130.1, 130.0, 129.9, 129.8, 123.2, 120.9, 120.6, 120.5, 119.9, 118.3, 116.7 (*o*-, *m*-Ar); 70.4 (br), 68.7 (br), 68.4 (br), 68.3, 61.2, 61.1, 58.0 (br., CO*C*HN); 51.0 (br), 50.1 (br), 50.0, 49.6, 47.6, 47.2, 45.4 (br) (N*C*HMe$_2$); 41.0, 40.8, 40.3, 40.2, 35.5, 35.2 (2), 35.1, 34.9, 34.7, 34.4, 33.6, 32.6, 32.0 (CH_2); 28.3, 28.1, 27.4 (br), 27.0 (br), 26.6, 26.4 (CH*C*HMe$_2$); 22.6–18.5 (several signals from Me) ppm. ESI-MS of $C_{35}H_{50}N_4O_5$ (M, 606.4): *m*/*z* = 607.4 [M + H]$^+$, 629.3 [M + Na]$^+$. HRMS of $C_{35}H_{50}N_4Na_1O_5$ [M + Na]: 629.3656; calcd. 629.3673.

9,10,19,20-Tetraisopropyl-2-oxa-7,10,19,22-tetraazatricyclo[23.2.2.2^{3,6}]hentriaconta-1(28),3(31),4,6(30),25(29),26-hexaene-8,11,18,21-tetraone (18c): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and isopropylamine (0.18 mL, 2 mmol) in methanol (130 mL) was stirred for 1 h at room temp., octanedioic acid (87 mg, 0.5 mmol) was then added, and stirring was continued for another 30 min. Afterwards, a solution of 4-[4-(2-isocyanoethyl) phenoxy]phenyl isocyanide (**11**, 124 mg, 0.5 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}), and the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **18c** as a diastereomeric mixture, isolated as an amorphous solid (165 mg, 51%) that can contain methanol. TLC (EtOAc) R_f = 0.39. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 10.56, 8.26 (2 × br, 2 × NH); 7.45 (m, 2 H, Ar); 7.13 (m, 2 H, Ar); 6.91 (m, 4 H, Ar); 4.10–3.90 (br m, 4 H, CHN); 3.10–2.10 (broad signals, 10 H, NCH_2, 2 × $COCH_2$, C*H*$_2$Ar, 2 × C*H*Me$_2$); 1.90–1.10 [broad signals, 8 H, (C*H*$_2$)$_4$]; 1.26 (d, *J* = 6.6 Hz, 6 H, Me); 1.15 (d, *J* = 6.5 Hz, 3 H, Me); 1.08 (d, *J* = 6.2 Hz, 6 H, Me); 1.02 (d, *J* = 6.5 Hz, 3 H, Me); 0.88 (d, *J* = 6.2 Hz, 3 H, Me); 0.74 (d, *J* = 6.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$): δ = 174.8, 173.7, 173.2 (br), 170.9 (CO); 155.7, 154.2 (*i*-, *i*′-Ar); 134.7, 133.6 (*p*-, *p*′-Ar); 130.1, 120.7, 119.7, 118.6 (*o*-, *o*′-, *m*-, *m*′-Ar); 70.1, 68.5 62.1 (br., CO*C*HN); 50.6, 49.9 (N*C*HMe$_2$); 40.3, 35.3, 34.3, 30.3, 29.5, 25.8, 25.7 (CH_2); 27.5, 26.5 (CH*C*HMe$_2$); 21.5, 21.1, 20.6, 20.4, 20.3 (2), 20.0 (2) (Me) ppm. EI-MS of $C_{38}H_{57}N_4O_5$ (M, 648.4): *m*/*z* = 648 [M]$^+$. HRMS of $C_{38}H_{58}N_4O_5$ [M + H]: 649.4314; calcd. 649.4323. M+MeOH; $C_{39}H_{60}N_4O_6$ (680.92): calcd. C 68.79, H 8.88, N 8.23; found C 69.03, H 8.76, N 8.41.

10,19-Diisopropyl-2-oxa-7,10,19,22-tetraazatricyclo[23.2.2.2^{3,6}]hentriaconta-1(28),3(31),4,6(30),25(29),26-hexaene-8,11,18,21-tetraone (18d): A mixture of paraformaldehyde (60 mg, 2 mmol), isopropylamine (0.18 mL, 2 mmol), and sodium sulfate (2 g) in methanol (40 mL) was stirred for 2 h at room temp., methanol (130 mL) and octanedioic acid (174 mg, 1 mmol) were then added, and stirring was continued for another 30 min. Afterwards, a solution of 4-[4-(2-isocyanoethyl)phenoxy]phenyl isocyanide (**11**, 248 mg, 1 mmol) in methanol (20 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}), and the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **18d** as an amorphous solid (40 mg, 7%). TLC ($CHCl_3$/MeOH 9:1) R_f = 0.72. ^{1}H NMR (300 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = (9.50) 9.34 (br., NH); (7.48) 7.44 (m, 2 H, Ar); 7.09 (7.02) (m, 2 H, Ar); 6.92 (m, 4 H, Ar); 4.19 (m, 1 H, C*H*Me$_2$); 4.08 (s, 2 H, $COCH_2$N); 3.98 (m, 1 H, C*H*Me$_2$); 3.86 (s, 2 H, $COCH_2$N); 2.74 (t, 2 H, C*H*$_2$Ar); 2.51, 2.23 (2 × t, 4 H, 2 × $COCH_2$); 1.80–1.00 [br m, 8 H, (C*H*$_2$)$_4$]; 1.27 (d, *J* = 6.7 Hz, 6 H, Me); 1.15 (d, *J* = 6.7 Hz, 6 H, Me) ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 174.5, (173.9), 173.2, 170.7, 168.5, (167.2) (CO); (156.1), 155.9, (154.3), 154.0 (*i*-, *i*′-Ar); 134.2, (134.1), 133.4 (132.3) (*p*-, *p*′-Ar); 130.1, (129.9), (121.0), 120.4, (119.8), 119.5, 118.9 (*o*-, *o*′-, *m*-, *m*′-Ar); 49.8, (48.8), 48.7 (*C*HMe$_2$); 46.7, 45.8, 40.5, (40.4), 34.7, (33.7), 33.5, 33.0, 30.3, (29.5), 29.4, 26.1, (25.4), 25.3 (CH_2); 21.1, (20.8), 20.7, (20.4) (Me) ppm. ESI-MS of $C_{32}H_{44}N_4O_5$ (M, 564.7): *m*/*z* = 565.5 [M + H]$^+$, 587.3 [M + Na]$^+$. HRMS of $C_{38}H_{58}N_4O_5$ [M + H]: 565.3375; calcd. 565.3385. $C_{32}H_{44}N_4O_5$ (564.72): calcd. C 68.06, H 7.85, N 9.92; found C 68.03, H 7.95, N 9.97.

10,17-Diacetyl-9,18-diisopropyl-2-oxa-7,10,17,20-tetraazatricyclo-[21.2.2.2^{3,6}]nonacosa-1(26),3(29),4,6(28),23(27),24-hexaene-8,19-dione (20a): A solution of isobutyraldehyde (0.19 mL, 2 mmol) and 1,6-diaminohexane (**19**, 116 mg, 1 mmol) in methanol (30 mL) was stirred for 1 h at room temp., acetic acid (0.12 mL, 2 mmol) was then added, and stirring was continued for another 30 min. After addition of methanol (100 mL), a solution of 4-[4-(2-isocyanoethyl) phenoxy]phenyl isocyanide (**11**, 124 mg, 0.5 mmol) in methanol (10 mL) was slowly added to the reaction mixture by syringe pump (flow rate 0.1 mL h^{-1}), and the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **20a** as a diastereomeric mixture, isolated as an amorphous solid (136 mg, 46%). TLC ($CHCl_3$/MeOH 95:5) R_f = 0.49. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.50 (m, 2 H, Ar); 7.04 (m, 2 H, Ar); 6.94 (m, 2 H, Ar); 6.83 (m, 2 H, Ar); 4.80 (br., 2 H, CHN); 3.80 (br., 2 H, NCH_2); 3.30 (br., 4 H, 2 × C*H*$_2$NAc); 2.95–2.30 (br m, 4 H, C*H*$_2$Ar, 2 × C*H*Me$_2$); 2.19, 1.78 (2 × s, 6 H, 2 × Ac); 1.60–1.10 [br m, 8 H, (C*H*$_2$)$_4$]; 1.05, 0.92, 0.84, 0.78 (4 × d, *J* = 6.6 Hz, 12 H, 4 × CH_3) ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$): δ = 172.4, 172.1, 170.6, 169.3 (br) (CO); 156.9, 154.0 (*i*-, *i*′-Ar); 134.1, 133.3 (*p*-, *p*′-Ar); 129.4, 120.7, 120.5, 118.7 (*o*-, *o*′-, *m*-, *m*′-Ar); 62.1 (br., *C*HN); 48.2, 44.4 (2 × br, NCH_2); 37.9, 33.9, 30.4 (br), 29.1, 27.9, 26.7, 25.7 (br) [(C*H*$_2$)$_4$, *C*HMe$_2$]; 26.4, 22.0, 20.0, 19.9, 19.7, 18.5 (br) (CH*C*H$_3$, CO*C*H$_3$) ppm. EI-MS of $C_{34}H_{48}N_4O_5$ (M, 592.4): *m*/*z* = 592 [M]$^+$. HRMS of $C_{34}H_{49}N_4O_5$ [M + H]: 593.3696; calcd. 593.3697.

10,19-Diacetyl-2-oxa-7,10,19,22-tetraazatricyclo[23.2.2.2^{3,6}]hentriaconta-1(28),3(31),4,6(30),25(29),26-hexaene-8,21-dione (20b): A mixture of paraformaldehyde (60 mg, 2 mmol), 1,8-diaminooctane (**15**, 144 mg, 1 mmol) and sodium sulfate (2 g) in methanol (40 mL) was stirred for 2 h at room temp., methanol (130 mL) and acetic acid (0.12 mL, 2 mmol) were then added, and stirring was continued for another 30 min. Afterwards, a solution of 4-[4-(2-isocyanoethyl)phenoxy]phenyl isocyanide (**11**, 248 mg, 1 mmol) in methanol (20 mL) was slowly added to the reaction mixture by syringe pump

(flow rate 0.1 mL h^{-1}), and the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography of the residue on silica ($CHCl_3$/MeOH 9:1) gave **20b** as an amorphous solid (62 mg, 11%) that can contain methanol. TLC ($CHCl_3$/MeOH 9:1) R_f = 0.37. ^{1}H NMR (300 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 9.30 (9.11) (s, NH); 7.45 (m, 2 H, Ar); 7.05 (m, 2 H, Ar); 6.91 (m, 2 H, Ar); 6.83 (m, 2 H, Ar); (4.12) 4.10, 3.83 (2 × s, 4 H, $COCH_2N$); 3.50 (m, 4 H), (3.06) 2.98 (t, 2 H), 2.80 (t, 2 H) ($ArCH_2$, 3 × NCH_2); 2.21, 1.95 (2 × s, 6 H, 2 × Me); 1.75–1.00 [brm, 12 H, $(CH_2)_6$] ppm. ^{13}C NMR (75.5 MHz; $CDCl_3$, δ of minor isomer in brackets): δ = 172.6, 171.0, (170.9), 169.2, (168.6), 186.4, (167.8) (CO); (156.9), 156.4, 153.3 (*i*-, *i*′-Ar); 133.5, 133.2, (132.6) (*p*-, *p*′-Ar); 129.9, (121.8), 121.4, 119.8, (118.7), 118.1 (*o*-, *o*′-, *m*-, *m*′-Ar); (58.4), 54.2, (52.5), 52.4, (52.0), 50.9, 50.2, (46.6), (40.4), 39.5 (NCH_2); (34.1), 34.0, 30.2, (29.9), (29.5), 29.1, 28.9, 28.4, (27.5), (27.0), 26.7, 26.5 (CH_2); 21.9, 21.1 (2 × Me) ppm. ESI-MS of $C_{30}H_{40}N_4O_5$ (M, 536.3): *m*/*z* = 537.5 [M + H]$^+$, 559.4 [M + Na]$^+$. HRMS of $C_{30}H_{40}N_4O_5Na$ [M + Na]: 559.2887; calcd. 559.2891. M + MeOH, $C_{31}H_{44}N_4O_6$ (568.70): calcd. C 65.47, H 7.80, N 9.85; found C 65.33, H 7.40, N 9.85.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of diisonitriles **4** and **11** and an X-ray based representation of macrocycle **18d**.

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