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Synthesis of Steroid−Biaryl Ether Hybrid Macrocycles with High Skeletal and Side Chain Variability by Multiple Multicomponent Macrocyclization Including Bifunctional Building Blocks

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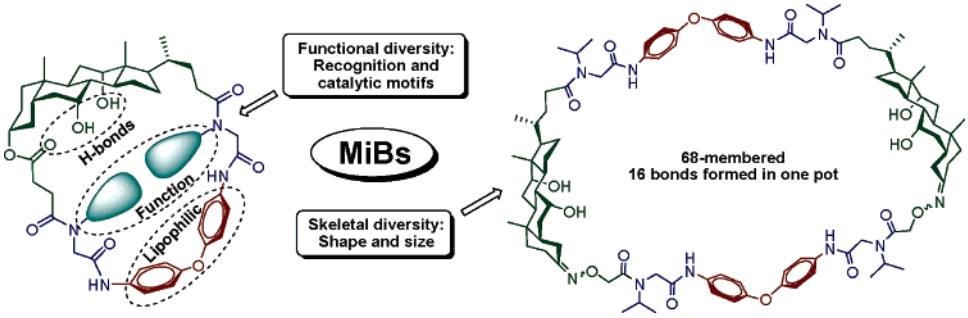

Utilizing the multiple multicomponent macrocyclization including bifunctional building blocks (MiB) strategy, a library of nonracemic, nonrepetitive peptoid-containing steroid−biaryl ether hybrid macrocycles was built. Up to 16 new bonds, including those of the macrocyclization, can be formed in one pot simultaneously while introducing varied elements of diversity. Functional diversity is generated primarily by choosing Ugi-reactive functional building blocks, bearing the respective recognition or catalytic motifs. These appear attached to the peptoid backbone of the macrocyclic cavity, similar to side chains of amino acids found in enzyme active sites. Likewise, skeletal diversity is based on the variation of defined bifunctional building blocks which allow the parallel formation of macrocyclic cavities that are highly diverse in shape and size and thus perspectively in function. This straightforward approach is suitable to generate multifunctional macrocycles for applications in catalysis, supramolecular, or biological chemistry.

Macrocycles are important in areas as diverse as drug development, material science, or supramolecular chemistry. Their remarkable biological and chemical success is based not only on the discovery of naturally occurring macrocycles[1] but also on the chemists' capability to devise strategies toward the synthesis of these compounds.[2] In view of applications toward molecular and ion-pair recognition, macrocycles with nonrepetitive elements are very interesting because they offer varied possibilities to incorporate nonuniform binding motifs from diverse building blocks. They also present a greater synthetic challenge than classical repetitive macrocycles commonly used in supramolecular chemistry (e.g., calixarenes, crown ethers, cyclophanes). Synthetic strategies toward this special class of compounds are of increasing importance, especially considering the prospect of creating multifunctional hybrid skeletons by the assembly of chemically different and differently distributed motifs.

We have recently developed a versatile approach toward peptoid-containing macrocycles based on implementing *m*ultiple *m*ulticomponent *m*acrocyclization(s) *i*ncluding *b*ifunctional *b*uilding *b*locks [MiB(s)] in a one-pot process.[3] Thus, especially the Ugi four-component reaction[4] (Ugi-4CR) was found to allow efficient bidirectional ring-closing reactions from large acyclic precursors.

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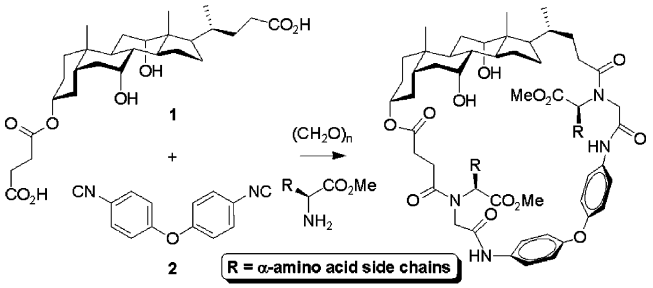
The fascinating scope of this strategy lies in the straightforward assembly of extremely complex molecular entities from simpler and available building blocks as well as in the high level of diversity that can be obtained by varying the nature of the Ugi components taking part in the process. Accordingly, this approach provides collections of structurally diverse macrocycles[4,5] that may be suitable as probes for chemical genetics, bioactivity screenings, drug delivery, or molecular recognition studies. Molecular recognition studies may include catalytic or separation applications derived from selective binding to molecular or ionic guests. Any synthetic approach intended to be applied to these relevant fields must demonstrate the capability of generating diversity within the chosen framework.[6] This may be relatively simple for small and well-studied molecules (usually heterocycles) but not for complex macrocycles. The general tendency to generate diversity in the latter is the variation of appended functionalities in a combinatorial fashion either prior to or after the ring-closure step.[7] Herein, we wish to demonstrate that the MiB strategy allows us to generate diversity for both the appended functionalities (side chains) and the macrocyclic cavity in one pot, including the ring closure itself, thereby representing a promising prospect for combinatorial access to macrocycle libraries.

This paper shows some of the possibilities of side chain and skeletal variation and the diversity that can be achieved by the combination of just two types of bifunctional building blocks: steroidal dicarboxylic acids and the biaryl ether diisocyanide **2**. Steroids represent amenable moieties for macrocycle assembly via MiBs because the resulting hybrid macrocyclic scaffolds may be endowed with the balanced level of preorganization/flexibility required for, e.g., binding to biological targets or surrounding specific guests.[8] Especially, cholic acid derivatives with concave-oriented hydrogen binders have been shown to be important building blocks in supramolecular and pharmaceutical chemistry.[9] Steroidal dicarboxylic acids are readily accessible either from introducing a succinic moiety[10] (e.g., **1**) or by condensation of oxo-derivatives with *O*-(carboxymethyl)-hydroxylamine. Oxo-steroids were prepared according to established procedures[10,11] and allowed a fast access to a variety of diacid building blocks.

SCHEME 1. Generation of Peptoid Side Chain Variations during One-Pot MiBs, Exemplified by Using Chiral α-Amino Acids as the Amino Component



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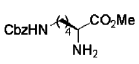
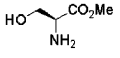
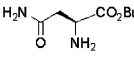
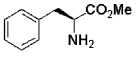
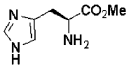
3		39	4		55
5		45	6		37
7		42	8		31

Diisocyanide **2** was obtained via formylation of the corresponding diamine and subsequent dehydration by a standard procedure.[12] In the case of the double Ugi-4CR-based macrocyclization, the symmetric structure of this building block allows us to afford only one regioisomer, thereby facilitating the characterization process. The biaryl ether moiety has received much attention alongside many strategies toward natural product syntheses.[13] Our interest in this chemical motif is due to not only its widespread occurrence in nature[1a] and importance in medicinal chemistry[14] but also the hybrid framework obtained by its combination with cholic acid which comprises a unique macrocyclic cavity containing both hydrophobic inner surfaces and hydrogen-bonding functionalities (i.e., secondary hydroxy groups), respectively. This feature has been recognized to be of high significance for the recognition of biologically relevant molecules, e.g., carbohydrates.[1a,8b]

Scheme 1 highlights the generation of functional diversity based on a single macrocyclic core by altering only the nature of the amino component participating in the Ugi MiB. By selecting proteinogenic α-amino acids, we could show the possibility of introducing natural binding elements found in proteins during the macrocyclization step. The selection presented in Scheme 1 demonstrates that many functional amino acid side chains such as those of serine or histidine do not even require protection. Of course, groups that can interfere with the one-pot macrocycle assembly need to be protected, e.g., carboxylic acids as esters. In principle, any further recognition

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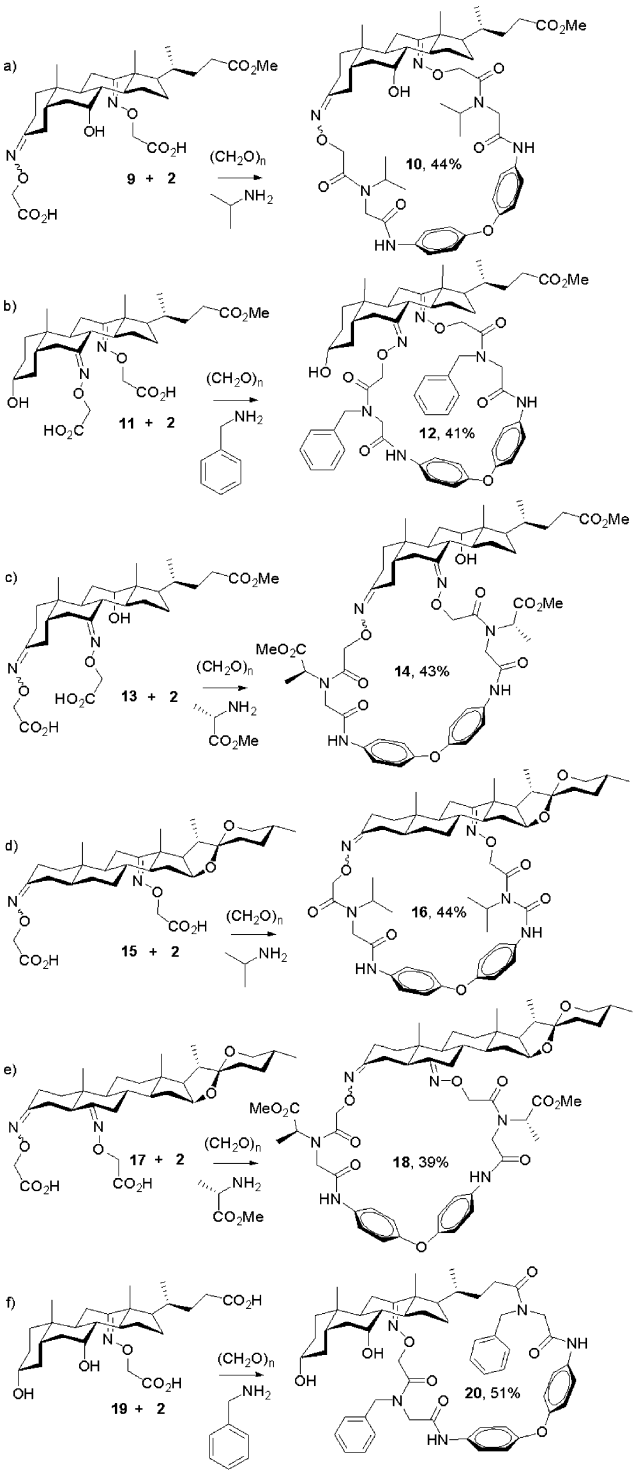
motif of biological, catalytic, or any selection relevance can be introduced if it is compatible with the Ugi-4CR.

Each combination of the MiB building blocks creates a unique binding motif.[3] The diacid/diisocyanide combination is probably the most valuable one toward the synthesis of macrocyclic receptors due to the production of a fully endocyclic peptoid core. This peptoid core may serve as a basic recognition motif, just like a peptide backbone, because of its dual hydrogen-bond-donor/-acceptor capability.

To address the goal of generating intrinsic skeletal diversity rather than only side chain or peptoid backbone moiety variation,[3] we focused on varying the shape and the size of the macrocyclic cavity itself within the steroid−biaryl ether series. Thus, incorporation of carboxylic functions at different positions of the steroidal moiety afforded diacids which allowed the production of a parallel library of geometrically diverse MiB macrocycles. In the eight examples given (Schemes 2 and 3), the endo and exo portions of the steroidal skeleton, i.e., the parts of the steroid outside or within the macrocyclic rim, vary considerably (cf., e.g., compound **20** vs **25**), as well as does the flexibility of each steroidal moiety that is included in each macrocycle (cf., e.g., rigid **10** vs flexible **20**).

Another method to change cavity size and conformation is changing the multiplicity of the macrocyclization. The achievement of 4-fold Ugi-4CR-based macrocycles such as **23** and **26**, from diacids **21** and **24**, respectively, provides significant insight into the requirements to obtain such very large and complex molecular architectures without template support, by forming 16 bonds in one pot. They provide new evidence of a substrate-folding-directed macrocyclization,[15] in this case via multicomponent reactions. It becomes obvious that the conformational preorganization of the acyclic precursor, obtained after the first Ugi-4CR, presents a marked influence on the macrocyclization result. This kinetically driven event is certainly more likely when the two carboxylic acids of the steroidal building blocks are pointing to the same direction or if they are attached close to each other and/or are more rigidly fixed. Thus, if the second building block is long enough to span the distance of its counterpart, and the precursor is able to provide sufficient proximity of the two matching Ugi functional groups, they will react to give the smallest possible macrocyclic ring closure. In contrast to this, a remote positioning of the two carboxylic groups (here: the ones of **21** and **24** in Scheme 3) allows independent Ugi-4CRs to take place in competition with a direct cyclization. The higher oligomer (already based on three Ugi-4CRs) then shows sufficient flexibility to allow cyclization affording 4-fold Ugi-4CR-based macrocycles (i.e., **23** and **26**). The next higher cyclic oligomers (6-fold MiBs), however, were not detected (HR−ESI−FT−ICR). Indeed, a more or less remote position of the carboxylic groups in the steroidal diacids has an influence on the resulting distribution of 2- vs 4-fold MiBs. With **21** (Scheme 3a), the ratio is 3.3 (**22**/**23**), whereas with the more distal diacid **24** (Scheme 3b) it is 1.2 (**25**/**26**); i.e., in contrast to common perception, the larger macrocycle formation is relatively favored with increasing ring size. This is possible because for **24** the oligomerization step is more favored vs cyclization than for **21**. However, the perception of better formation of larger macrocycles is only true in relative terms. The combined macrocycle yield from **21** is 35%, whereas from "larger" **24**, it is 24%, putting the common perception for cyclization propensity back into the place again. This result also indicates that larger amounts of acyclic oligomers could be formed from **24** than from **21**. Interestingly, the overall yield of macrocycles otherwise is quite constant with an average of ca. 45% (Schemes 1 and 2); i.e., an average yield per individual bond formation step including the macrocyclization of ca. 95% is achieved.

SCHEME 2. Diversification of the Cavity Shape Based on Tuning of the Functionalization Site of the Steroidal Moiety[a]



[a] Four-fold MiBs were not detected for these examples by ESI−FT−ICR−MS. For further shapes generated by steroid attachment points variation, see Schemes 1 and 3.

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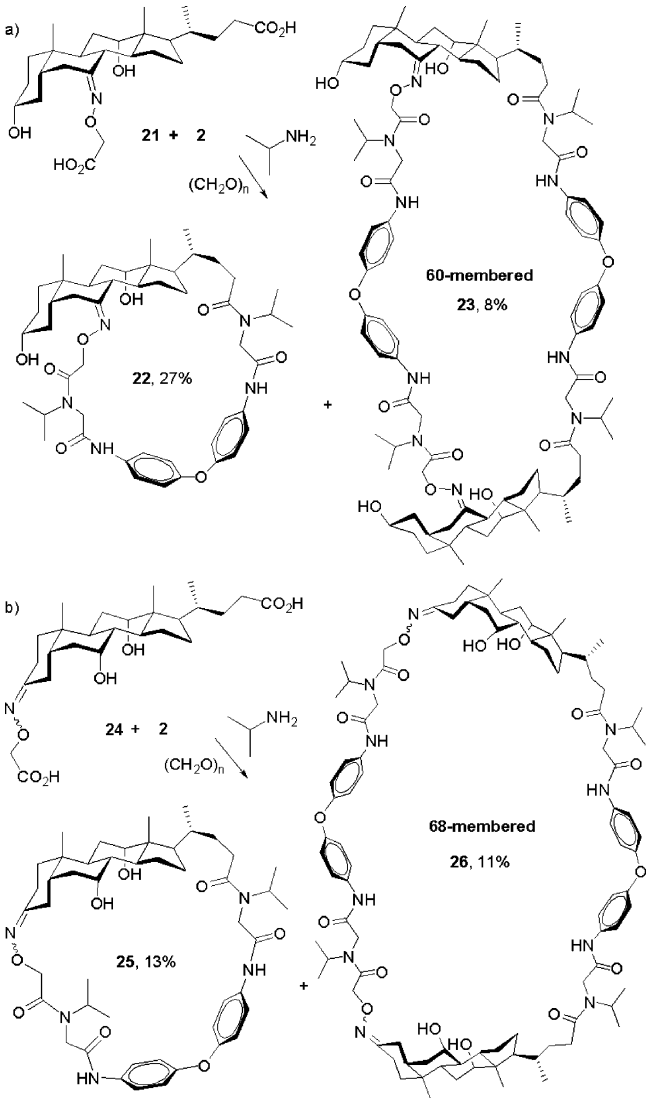
SCHEME 3. Substrate-Folding-Directed Variation of the Cavity Size, Influencing the Multiplicity of MiBs[a]



[a] For **23** and **26**, yields refer to a mixture of head-to-head (H−H) and head-to-tail (H−T) regioisomers, though only H−H isomers are shown.

In conclusion, we have demonstrated that both functional side chain and skeletal diversity can be generated via MiBs in one pot, including the macrocyclic ring closure. The first is possible by choosing Ugi-reactive building blocks containing specific functional motifs, like amino acid side chains that appear appended to the peptoid backbone. The latter can be achieved by the selection of building blocks that allows access to geometrically diverse cavities or by modification of the macrocycle size by substrate-folding-directed macrocyclization. We believe that not only binding properties can be tuned in MiBs but also the combination with catalytically active appendices (e.g., the acid/base moieties shown in Scheme 1) can provide enzyme-like selective transformations in the future.

Experimental Section

General Procedure for the Ugi-4CR-Based Multiple Macrocyclizations. A solution of paraformaldehyde (2.5 mmol) and the amino component (2.5 mmol) in MeOH (250 mL) was stirred for 1 h at room temperature (when an α-amino acid alkyl ester hydrochloride was used, 2.5 mmol of NEt_3 was added to allow better formation of the corresponding imine). The steroidal diacid (0.5 mmol) was added, and the stirring was continued for 30 min. A solution of diisocyanide **2** (0.5 mmol) in MeOH (10 mL) was slowly added to the reaction mixture using a syringe pump (flow rate 0.2 mL h^{-1}). After addition was complete, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash column chromatography on silica gel with CH_2Cl_2/MeOH (20:1) to afford the corresponding macrocycles, which were recrystallized from selected solvents.

Macrocycle 3: mp (from MeOH) 197−199 °C; IR (KBr, cm^{-1}) 3515, 3431, 3222, 2956, 2870, 1726, 1659, 1644, 1500, 1217, 1172; ^{1}H NMR ($CDCl_3$) δ = 8.87 (m, 2H), 7.44 (m, 2H), 7.42 (d, 2H), 7.32 (m, 10H), 6.85 (m, 4H, *o*,*o*′-PhNH), 5.11 (m, 2H), 4.44 (m, 1H, H-3β), 4.26 (m, 2H), 4.17 (m, 2H), 4.10 (m, 2H), 3.84 (m, 1H), 3.81 (m, 1H), 3.67 (s, 6H), 3.24 (m, 4H), 0.93 (s, 3H), 0.83 (d, 3H, J = 6.4 Hz), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 176.0, 175.2, 172.9, 171.2, 169.4, 168.7, 157.0, 156.7, 136.5, 136.2, 128.5, 128.1, 127.8, 153.5, 133.4, 121.6, 121.3, 119.7, 119.5, 77.3, 68.2, 68.0, 66.7, 53.0, 52.5, 52.4, 49.8, 49.4, 49.1, 46.8, 46.5, 46.0, 45.8, 45.3, 43.3, 43.1, 41.5, 41.0, 39.9, 39.5, 35.1, 34.7, 34.6, 33.8, 30.4, 32.8, 30.8, 29.8, 29.6, 28.3, 26.1, 23.9, 22.0, 17.5, 12.8; HRMS (ESI−FT−ICR) *m*/*z* 1363.6725 [M + Na]$^+$, calcd for $C_{74}H_{96}NaO_{17}N_6$ 1363.6728. Anal. found: C, 66.4; H, 7.5; N, 6.6. Calcd: C, 66.25; H, 7.2; N, 6.3.

Macrocycle 4: mp (from MeOH) 188−189 °C; IR (KBr, cm^{-1}) 3521, 3334, 3290, 2942, 2872, 1726, 1691, 1661, 1499, 1219; ^{1}H NMR ($CDCl_3$) δ = 10.35 (m, 1H), 10.08 (m, 1H), 7.69 (d, 2H, J = 9.2 Hz), 7.61 (d, 2H, J = 9.2 Hz), 7.05 (m, 2H, J = 9.2 Hz), 6.98 (m, 2H, J = 8.9 Hz), 4.52 (m, 1H), 4.27 (d, 1H, J = 18.5 Hz), 4.26 (d, 1H, J = 18.5 Hz), 4.15−4.07 (m, 2H), 4.05 (d, 1H, J = 18.3 Hz), 3.99 (d, 1H, J = 18.7 Hz), 3.86 (s, 6H), 3.83 (m, 1H), 3.75 (m, 1H), 1.53 (d, 3H, J = 7.2 Hz), 1.50 (d, 3H, J = 6.8 Hz), 0.87 (s, 3H), 0.87 (d, 3H, J = 6.8 Hz), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 175.3, 174.4, 172.4, 172.3, 171.8, 167.5, 166.8, 154.9, 154.2, 133.6, 133.2, 122.2, 121.8, 121.7, 120.6, 75.3, 72.6, 68.0, 57.5, 53.7, 53.5, 53.4, 51.6, 46.7, 46.6, 46.5, 41.9, 41.5, 39.8, 35.3, 35.2, 35.0, 34.6, 31.6, 30.6, 29.4, 28.6, 27.4, 26.8, 26.5, 23.3, 22.8, 21.9, 14.9, 14.4, 12.7; HRMS (ESI−FT−ICR) *m*/*z* 981.4834 [M + Na]$^+$, calcd for $C_{52}H_{70}NaO_{13}N_4$ 981.4831. Anal. found: C, 63.9; H, 8.2; N, 5.6. Calcd: C, 64.3; H, 8.5; N, 5.8.

Macrocycle 5: mp (from MeOH) 245−247 °C; IR (KBr, cm^{-1}) 3529, 3414, 3294, 2947, 2871, 1725, 1698, 1661, 1500, 1212, 1106, 1056; ^{1}H NMR ($CDCl_3$) δ = 9.89 (m, 1H), 9.78 (m, 1H), 7.65 (d, 2H, J = 9.0 Hz), 7.60 (d, 2H, J = 8.9 Hz), 7.00 (m, 2H, J = 9.1 Hz), 6.94 (m, 2H, J = 9.0 Hz), 4.55 (m, 1H, H-3β), 4.25−4.23 (m, 2H), 4.17−4.15 (m, 2H), 4.11−4.08 (m, 2H), 3.78 (s, 3H), 3,75 (s, 3H), 3.84 (m, 1H), 3.78 (m, 1H), 3.67−3.62 (m, 4H), 0.93 (s, 3H), 0.86 (d, 3H, J = 6.2 Hz), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 175.5, 174.9, 172.7, 171.1, 171.0, 168.9, 167.8, 154.5, 154.2, 133.9, 133.4, 122.0, 121.9, 121.6, 120.9, 75.1, 71.8, 68.7, 63.3, 63.1, 56.9, 52.9, 53.7, 53.5, 51.9, 46.8, 45.8, 45.5, 42.2, 41.7, 39.9, 35.8, 35.5, 35.2, 34.3, 31.8, 30.5, 29.5, 28.7, 27.2, 27.0, 26.7, 23.1, 22.7, 22.0, 15.1, 14.3, 12.9; HRMS (ESI−FT−ICR) *m*/*z* 1013.4739 [M + Na]$^+$, calcd for $C_{52}H_{70}NaO_{15}N_4$ 1013.4737. Anal. found: C, 63.5; H, 7.9; N, 5.8. Calcd: C, 63.0; H, 7.1; N, 5.65.

Macrocycle 6: mp (from EtOAc) 267−268 °C; IR (KBr, cm^{-1}) 3528, 3459, 3325, 3286, 2980, 2870, 1729, 1686, 1668, 1499, 1205; ^{1}H NMR ($CDCl_3$) δ = 9.14 (m, 1H), 8.64 (m, 1H), 7.51 (d, 2H, J = 8.9 Hz), 7.42 (d, 2H, J = 8.8 Hz), 6.91 (m, 4H), 6.66 (m, 4H), 4.54 (m, 1H), 4.34 (m, 2H), 4.15−4.09 (m, 4H), 4.02 (m, 1H), 3.98 (m, 1H), 1.48 (s), 0.89 (s, 3H), 0.87 (d, 3H, J = 0.7 Hz), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 173.8, 173.7, 172.1, 171.2, 171.0, 168.3, 167.9, 170.2, 170.0, 154.7, 154.1, 133.9, 133.7, 122.0, 121.6, 121.3, 120.8, 82.1, 82.0, 75.2, 71.7, 68.8, 57.1, 52.4, 51.6, 50.8, 46.7, 46.4, 45.9, 42.1, 41.4, 40.1, 35.2, 35.0, 34.8, 34.3, 31.9, 30.9, 29.6, 28.9, 28.3, 28.1, 27.9, 26.6, 26.4, 22.9, 20.5, 14.9, 12.9; HRMS (ESI−FT−ICR) *m*/*z* 1151.5897 [M + Na]$^+$, calcd for $C_{60}H_{84}$-

$NaO_{15}N_6$ 1151.5894. Anal. found: C, 62.5; H, 7.2; N, 7.8. Calcd. C, 62.0; H, 6.9; N, 8.0.

Macrocycle 7: mp (from MeOH) 289−292 °C; IR (KBr, cm^{-1}) 3445, 3321, 3092, 3008, 2951, 2865, 1728, 1698, 1656, 1502, 1219, 1056; ^1H NMR ($CDCl_3$) δ = 8.93 (m, 2H), 7.43 (m, 2H), 7.39 (d, 2H), 7.23−7.21 (m, 10H), 6.89 (m, 2H), 6.83 (m, 2H), 4.50 (m, 1H), 4.39 (m, 2H), 4.19−4.11 (m, 4H), 3.87 (m, 1H), 3.81 (m, 1H), 3.68, 3.66 (s, 6H), 0.96 (s, 3H), 0.82 (d, 3H, J = 5.9 Hz), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 175.2, 175.0, 172.7, 171.8, 170.7, 169.0, 168.8, 153.5, 135.4, 133.4, 129.4, 128.8, 127.1, 121.4, 121.1, 120.0, 119.6, 119.5, 75.9, 68.6, 68.2, 53.2, 52.8, 52.6, 49.6, 49.3, 48.8, 46.6, 46.2, 46.1, 45.9, 45.5, 44.2, 44.0, 43.3, 43.1, 41.2, 41.0, 39.6, 39.3, 35.1, 34.3, 34.1, 33.4, 30.8, 32.7, 30.6, 29.9, 29.8, 28.3, 26.0, 23.7, 21.7, 17.2, 13.1; HRMS (ESI−FT−ICR) *m/z* 1133.5438 $[M + Na]^+$, calcd for $C_{64}H_{78}NaO_{13}N_4$ 1133.5435. Anal. found: C, 69.55; H, 7.3; N, 5.4. Calcd: C, 69.2; H, 7.1; N, 5.0.

Macrocycle 8: mp (from MeOH) 202−203 °C; IR (KBr, cm^{-1}) 3521, 3334, 3009, 2939, 2871, 1728, 1666, 1641, 1506, 1168; ^1H NMR ($CDCl_3$) δ = 9.15 (m, 1H), 8.72 (m, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.41 (d, 2H, J = 8.4 Hz), 7.34 (m, 2H), 6.88 (m, 4H), 6.71 (m, 2H), 4.54 (m, 1H), 4.47 (m, 2H), 4.21−4.18 (m, 2H), 4.17−4.15 (m, 2H), 4.07 (m, 1H), 3.97 (m, 1H), 3.71 (s, 6H), 1.06 (d, 3H, J = 6.4 Hz), 0.89 (s, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 175.2, 174.8, 173.1, 172.9, 168.6, 168.2, 153.5, 133.5, 139.2, 135.7, 117.0, 116.9, 121.5, 121.3, 119.2, 118.9, 77.2, 71.0, 68.4, 55.2, 53.8, 52.7, 52.5, 52.0, 52.3, 52.0, 49.3, 47.0, 46.6, 46.0, 46.4, 45.8, 41.8, 41.4, 41.2, 39.4, 35.4, 35.0, 34.8, 34.4, 34.1, 32.8, 31.4, 30.3, 29.2, 28.2, 26.5, 23.1, 19.6, 17.3, 12.7; HRMS (ESI−FT−ICR) *m/z* 1113.5279 $[M + Na]^+$, calcd for $C_{58}H_{74}NaO_{13}N_8$ 1113.5277. Anal. found: C, 64.0; H, 7.0; N, 10.7. Calcd: C, 63.8; H, 6.8; N, 10.3.

Macrocycle 10: mp (from CH_3CN) 266−268 °C; IR (KBr, cm^{-1}) 3494, 3274, 3205, 2975, 2948, 2869, 1741, 1698, 1677, 1641, 1500, 1215, 1169; ^1H NMR ($CDCl_3$) δ = 8.90 (m, 2H), 7.42 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 8.4 Hz), 6.85 (d, 2H, J = 9.2 Hz), 6.81 (d, 2H, J = 8.8 Hz), 4.76−4.63 (m, 4H), 4.33 (m, 2H), 4.20 (m, 2H), 3.94 (m, 2H), 3.90 (m, 1H), 3.67 (s, 3H), 1.28−1.19 (m, 12H), 0.98 (d, 3H, J = 6.4 Hz), 0.93 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 174.8, 171.0, 168.1, 167.8, 166.0, 163.0, 162.8, 155.0, 154.2, 133.6, 133.4, 121.2, 120.5, 119.6, 119.3, 72.6, 71.1, 67.8, 52.0, 51.5, 50.0, 49.5, 49.0, 48.7, 47.5, 45.8, 42.0, 39.1, 37.0, 35.6, 34.2, 33.8, 31.6, 30.5, 29.2, 27.4, 26.9, 23.4, 22.0, 20.9, 20.7, 20.6, 19.8, 12.3; HRMS (ESI−FT−ICR) *m/z*: 949.5041 $[M + Na]^+$, calcd for $C_{51}H_{70}NaN_6O_{10}$ 949.5045. Anal. found: C, 66.5; H, 7.6; N, 9.0. Calcd. C, 66.1; H, 7.6; N, 9.1.

Macrocycle 12: mp (from CH_3OH) 236−237 °C; IR (KBr, cm^{-1}) 3434, 3327, 3054, 3025, 2978, 2939, 2870, 1738, 1619, 1648, 1502, 1206, 1170; ^1H NMR ($CDCl_3$) δ = 8.95 (m, 2H), 7.44 (d, 2H, J = 8.6 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.27 (m, 10H), 6.88 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.8 Hz), 4.66 (m, 2H), 4.61 (m, 2H), 4.38 (m, 4H), 4.31−4.26 (m, 4H), 3.66 (s, 3H), 3.55 (m, 1H), 1.12 (s, 3H), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 175.9, 171.4, 169.9, 168.4, 167.8, 162.9, 162.7, 155.1, 154.5, 137.4, 133.8, 133.5, 128.4, 127.8, 127.1, 121.1, 120.8, 119.8, 119.7, 72.5, 71.8, 70.2, 52.5, 51.7, 48.9, 48.8, 45.1, 43.8, 43.7, 42.7, 37.6, 37.8, 35.8, 32.1, 31.9, 30.5, 29.8, 28.7, 26.4, 22.1, 21.7, 19.5, 12.7; HRMS (ESI−FT-ICR) *m/z* 1045.5055 $[M + Na]^+$, calcd for $C_{59}H_{70}NaN_6O_{10}$ 1045.5052. Anal. found: C, 69.4; H, 6.7; N, 8.5. Calcd: C, 69.25; H, 6.9; N, 8.2.

Macrocycle 14: mp (from CH_3OH) 266−268 °C; IR (KBr, cm^{-1}) 3512, 3336, 3290, 2940, 2868, 1725, 1689, 1661, 1502, 1221; ^1H NMR ($CDCl_3$) δ = 8.95 (m, 1H), 8.89 (m, 1H), 7.42 (d, 2H, J = 9.0 Hz), 7.40 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 9.0 Hz), 6.84 (d, 2H, J = 8.6 Hz), 4.58 (m, 4H), 4.55 (m, 4H), 4.13−4.08 (m, 2H), 4.28 (m, 2H), 4.24 (m, 2H), 4.13−4.08 (m, 2H), 3.98 (m, 1H), 3.77 (s, 3H), 3.66 (s, 6H), 1.51 (m, 6H), 0.97 (d, 3H, J = 6.7 Hz), 0.94 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 176.2, 175.4, 174.8, 172.0, 171.6, 168.8, 167.9, 162.9, 161.8, 155.1, 154.6, 133.5, 133.0, 121.8, 121.4, 121.1, 120.7, 72.0, 71.6, 68.7, 53.5, 53.1, 52.7, 51.4, 45.1, 43.6, 43.7, 42.1, 37.6, 37.4, 37.2, 35.1, 32.8, 31.9, 30.3, 29.7, 28.4, 26.7, 22.5, 22.2, 21.9, 21.4, 19.3, 12.7; HRMS (ESI−FT−ICR) *m/z* 1015.5033 $[M + H]^+$, calcd for $C_{53}H_{71}N_6O_{14}$ 1015.5023. Anal. found: C, 62.7; H, 6.95; N, 8.2. Calcd: C, 62.4; H, 6.7; N, 8.3.

Macrocycle 16: mp (from CH_3CN) 228−230 °C; IR (KBr, cm^{-1}) 3288, 3076, 2928, 2872, 1697, 1649, 1610, 1500, 1216, 1179, 1079, 980, 912; ^1H NMR ($CDCl_3$) δ = 9.61 (m, 1H), 9.18 (m, 1H), 7.53 (m, 2H), 7.19 (m, 2H), 6.90 (m, 2H), 6.79 (m, 2H), 4.84 (m, 2H), 4.74 (m, 2H), 4.37 (m, 1H), 4.17−3.92 (m, 4H), 3.80−3.77 (m, 2H), 1.34 (d, 6H, J = 6.0 Hz), 1.26 (d, 6H, J = 6.3 Hz), 1.06 (d, 3H, J = 6.4 Hz), 0.90 (s, 3H), 0.86 (s, 3H), 0.80 (d, 3H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ = 172.4, 171.0, 169.6, 167.8, 164.0, 163.2, 155.3, 134.3, 132.7, 121.4, 120.4, 119.7, 119.2, 109.3, 79.9, 71.7, 71.5, 66.8, 56.0, 51.6, 48.9, 47.9, 46.8, 45.3, 42.0, 36.3, 34.2, 33.9, 31.4, 30.7, 30.2, 28.7, 20.9, 17.6, 17.1, 13.2, 10.6; HRMS (ESI−FT−ICR) *m/z* 959.5259 $[M + Na]^+$, calcd for $C_{53}H_{72}NaO_9N_6$ 959.5253. Anal. found: C, 63.9; H, 8.1; N, 5.6. Calcd: C, 64.3; H, 8.5; N, 5.8.

Macrocycle 18: mp (from CH_3OH) 217−220 °C; IR (KBr, cm^{-1}) 3516, 3342, 3292, 2947, 2868, 1725, 1690, 1666, 1500, 980, 912; ^1H NMR ($CDCl_3$) δ = 8.97 (m, 1H), 9.35 (m, 1H), 7.50 (m, 2H), 7.31 (m, 2H), 6.94 (m, 2H), 6.82 (m, 2H), 4.65 (m, 2H), 4.58 (m, 2H), 4.39 (m, 1H), 4.22−4.17 (m, 4H), 4.16−4.10 (m, 2H), 3.77 (s, 6H), 1.50 (d, 3H, J = 7.1 Hz), 1.48 (d, 3H, J = 6.8 Hz), 1.05 (d, 3H, J = 6.3 Hz), 0.92 (s, 3H), 0.89 (s, 3H), 0.78 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 175.4, 174.9, 172.0, 171.2, 169.8, 168.3, 165.1, 164.7, 155.2, 155.0, 134.8, 132.3, 121.2, 120.8, 119.6, 119.4, 109.3, 80.2, 71.2, 70.7, 66.8, 61.8, 55.8, 44.7, 42.2, 41.5, 40.8, 39.5, 34.1, 31.7, 31.2, 30.1, 28.7, 26.8, 26.2, 22.2, 21.9, 21.1, 17.2, 16.6, 14.5, 13.9; HRMS (ESI−FT−ICR) *m/z* 1047.5059 $[M + Na]^+$, calcd for $C_{55}H_{72}NaO_{13}N_6$ 1047.5055. Anal. found: C, 64.2; H, 7.3; N, 8.0. Calcd: C, 64.4; H, 7.1; N, 8.2.

Macrocycle 20: mp (from CH_3CN) 245−246 °C; IR (KBr, cm^{-1}) 3434, 3056, 3019, 2937, 2871, 1728, 1666, 1604, 1213, 1172; ^1H NMR ($CDCl_3$) δ = 9.45 (m, 1H), 9.36 (m, 1H), 7.41 (m, 2H), 7.36 (m, 2H), 7.23 (m, 10H), 6.98 (m, 2H), 6.84 (m, 2H), 4.57 (m, 2H), 4.42 (m, 4H), 4.37 (m, 2H), 4.33 (m, 2H), 3.92 (m, 1H), 3.79 (m, 1H), 0.97 (s, 3H), 0.92 (d, 3H, J = 6.2 Hz), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 174.7, 171.0, 169.1, 167.8, 161.9, 160.2, 155.0, 154.9, 137.1, 134.6, 134.0, 128.2, 127.8, 127.4, 120.5, 120.2, 119.7, 118.9, 71.1, 70.9, 70.2, 68.2, 47.5, 47.3, 45.6, 43.5, 42.8, 41.7, 36.6, 35.8, 35.2, 34.3, 33.9, 32.9, 31.8, 30.4, 28.4, 19.1, 16.1, 12.3; HRMS (ESI−FT−ICR) *m/z* 960.4882 $[M + Na]^+$, calcd for $C_{56}H_{67}NaO_8N_5$ 960.4887. Anal. found: C, 71.5; H, 7.0; N, 7.9. Calcd: C, 71.7; H, 7.2; N, 7.4.

Macrocycle 22: mp (from acetone) 214−216 °C; IR (KBr, cm^{-1}) 3434, 3273, 3006, 2972, 2954, 2869, 1735, 1701, 1695, 1649, 1499, 1212; ^1H NMR ($CDCl_3$) δ = 9.40 (m, 1H), 9.25 (m, 1H), 7.43 (m, 2H), 7.34 (m, 2H), 6.92 (m, 2H), 6.80 (m, 2H), 4.74−4.70 (m, 2H), 4.54 (m, 2H), 4.40 (m, 2H), 4.00 (m, 2H), 3.86 (m, 1H), 3.70 (m, 1H), 1.27−1.25 (m, 12H), 0.95 (s, 3H), 0.88 (s, 3H), 0.87 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ = 175.8, 170.9, 168.5, 166.0, 160.0, 155.0, 154.9, 134.6, 134.0, 120.4, 120.3, 119.4, 118.9, 71.6, 71.5, 69.2, 50.2, 47.5, 47.3, 45.6, 43.5, 42.8, 41.7, 36.6, 34.3, 33.9, 32.9, 31.8, 30.4, 28.4, 22.0, 21.5, 21.3, 20.9, 20.2, 19.3, 16.8, 12.9; HRMS (ESI−FT−ICR) *m/z* 864.4855 $[M + Na]^+$, calcd for $C_{48}H_{67}NaO_8N_5$ 864.4881. Anal. found: C, 68.1; H, 8.0; N, 8.1. Calcd: C, 68.5; H, 8.0; N, 8.3.

Macrocycle 23: Mixture of regiomers; IR (KBr, cm^{-1}) 3434, 2939, 2871, 1738, 1659,1644, 1639, 1172; ^1H NMR ($CDCl_3$) δ = 9.74 (m, 1H), 9.61 (m, 1H), 9.25 (m, 2H), 7.70 (d, 1H, J = 9.1 Hz), 7.46 (d, 1H, J = 8.6 Hz), 7.39 (m, 2H, J = 8.9 Hz), 6.95 (m, 1H, J = 8.8 Hz), 6.86 (m, 1H, J = 9.0 Hz), 6.80 (m, 2H, J = 9.2 Hz), 4.73−4.70 (m, 4H), 4.18−3.98 (m, 8H), 3.84−3.82 (m, 2H), 3.57 (m, 1H), 1.28−1.25 (m, 24H), 1.02 (s, 6H), 0.97 (m, 6H), 0.78 (s, 6H); ^{13}C NMR ($CDCl_3$) δ = 172.3, 171.9, 171.2, 169.8, 169.6, 169.4, 168.9, 165.2, 163.2, 155.8, 155.6, 155.3, 155.2, 134.5, 134.3, 134.2, 121.1, 120.7, 120.5, 120.4, 120.2, 119.8, 119.5, 72.6,

72.1, 70.8, 70.5, 68.4, 68.2, 21.7, 20.6, 19.2, 18.9, 12.3, 12.1; HRMS (ESI−FT−ICR) *m*/*z* 1684.0095 $[M + H]^+$, calcd for $C_{96}H_{134}NaO_{16}N_{10}$ 1684.0097.

Macrocycle 25: mp (CH_3OH) 222−223 °C; IR (KBr, cm^{-1}) 3431, 3256, 3009, 2970, 2959, 2870, 1738, 1712, 1696, 1651, 1499, 1217, 1178; ^1H NMR ($CDCl_3$) δ = 9.24 (m, 1H), 9.18 (m, 1H), 7.49 (d, 2H, J = 9.0 Hz), 7.30 (m, 2H, J = 9.0 Hz), 6.96 (m, 2H, J = 8.8 Hz), 6.90 (m, 2H, J = 9.0 Hz), 4.82 (m, 2H), 4.74 (m, 2H), 4.25−4.21 (m, 2H), 4.18−4.14 (m, 2H), 4.03 (m, 1H), 4.00 (m, 1H), 3.95 (m, 2H), 1.30−1.28 (m, 12H), 1.21 (s, 3H), 1.03 (d, 3H, J = 5.9 Hz), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ = 171.2, 169.9, 169.3, 168.7, 163.2, 156.1, 155.4, 134.8, 134.4, 121.3, 120.9, 120.3, 119.3, 71.6, 70.9, 67.9, 54.7, 53.7, 50.5, 50.2, 47.8, 46.5, 46.1, 41.2, 39.6, 39.5, 38.7, 35.6, 34.8, 33.9, 33.2, 30.0, 28.5, 23.7, 21.8, 21.3, 20.6, 18.9, 11.8; HRMS (ESI−FT−ICR) *m*/*z* 864.4882 $[M + Na]^+$, calcd for $C_{48}H_{67}NaO_8N_5$ 864.4881. Anal. found: C, 68.1; H, 8.0; N, 8.1. Calcd: C, 68.5; H, 8.0; N, 8.3.

Macrocycle 26: Mixture of regiomers; IR (KBr, cm^{-1}) 3441, 3243, 3004, 2971, 2866, 1734, 1730, 1712, 1699, 1658, 1499, 1212, 1174; ^1H NMR ($CDCl_3$) δ = 9.69 (m, 2H, N*H*CO), 9.37 (m, 1H), 7.66 (d, 1H, J = 8.9 Hz), 7.58 (d, 1H, J = 8.8 Hz), 7.41 (m, 1H, J = 8.9 Hz), 7.38 (m, 1H, J = 8.9 Hz), 6.91 (m, 1H, J = 8.8 Hz), 6.87 (m, 1H, J = 8.7 Hz), 6.82−6.80 (m, 2H, J = 8.9 Hz), 4.69−4.66 (m, 4H), 4.23−4.02 (m, 8H), 3.84−3.82 (m, 2H), 3.79 (m, 2H), 1.33−1.27 (m, 24H), 1.15 (s, 6H), 1.00 (m, 6H), 0.71 (s, 6H); ^{13}C NMR ($CDCl_3$) δ = 173.0, 172.5, 172.1, 170.3, 169.8, 169.6, 163.7, 163.5, 155.5, 155.2, 155.1, 154.8, 135.7, 134.9, 134.6, 121.0, 120.5, 120.7, 120.3, 120.0, 119.9, 119.2, 70.6, 70.2, 68.3, 68.1, 67.9, 67.5, 21.3, 20.2, 19.8, 19.5, 18.3, 13.1, 12.7; HRMS (ESI−FT−ICR) *m*/*z* 1684.0096 $[M + H]^+$, calcd for $C_{96}H_{134}NaO_{16}N_{10}$ 1684.0097.

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Supporting Information Available: Experimental procedures for the preparation of building blocks. NMR and HR−ESI−FT−ICR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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