Rapid generation of macrocycles with natural-product-like side chains by multiple multicomponent macrocyclizations (MiBs)

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A small parallel library of peptoid macrocycles with natural-product-derived side chains of biological importance was produced by Ugi-type multiple multicomponent macrocyclizations including bifunctional building blocks (Ugi-MiBs). Diverse exocyclic elements of high relevance in natural recognition processes, *i.e.*, all functional amino acid residues (*e.g.*, Cys, Arg, His, Trp) and even sugar moieties, can be introduced in a one-pot process into different types of peptoid-containing macrocyclic skeletons. This is exemplified by the use of a diamine/diisocyanide combination of Ugi-MiBs and *N*-protected α-amino acids or carboxy-functionalized carbohydrates as source for the natural-product-like exocyclic elements. Employed as the acid components of the multiple Ugi reactions, they appear as *N*-amide substituents on the macrocyclic cores. The use of different diamines and diisocyanides allows an easy variation of the *N*- to *C*-directionality and therefore of the position of the exocyclic elements.

Introduction

Natural macrocycles are increasingly important in medicinal chemistry as active principles or as lead structures for drug discovery. Synthetic derivatives are either based on rational design or on privileged structural elements incorporated in combinatorial libraries.[1,2] Apart from the use of natural macrocyclic scaffolds, in medicinal chemistry the cyclization of various skeletons is widely employed with the aim to improve pharmacological properties[3] and to decrease the entropy loss upon binding.[4] This is especially relevant for cyclopeptides, wherein important properties such as bioavailability and enzymatic stability are significantly improved.[1a,3] Cyclization is also used to introduce conformational restrictions into specific peptide sequences that are known to be recognized by biological receptors,[3d,5,6] *e.g.*, RGD-containing peptides.[5]

Natural amino acid-derived macrocycles are of special relevance in the realm of biologically active compounds.[1,7] They may be found either as oligomeric sequences (*e.g.*, cyclopeptides and depsipeptides) or as hybrid skeletons including diverse endocyclic chemical motifs alternating with the peptide sequences. Well-known moieties include the biarylether unit,[1e,k,8] 5,6-membered heterocycles (*e.g.*, oxazole and thiazole)[1e,9] or lipophilic chains (*e.g.*, polyene and phenylene).[1e,2a,10] While endocyclic motifs are known to be important for conformational constrains, rigidity and shape, biological and structural studies have shown that exocyclic elements are relevant for the overall biological profile, such as the recognition and functional elements of macrocycles.[1,2,5,6] This is especially noteworthy in amino acid-derived macrocycles wherein the positioning of the appended functionalities (*i.e.*, side chains or exocyclic residues) is not only influenced by the amino acid configuration but also by the overall conformation of the cavity. In this sense, synthetic macrocyclic skeletons have been devised either to seek desired arrangements of exocyclic functionalities or to impose a specific conformation on oligopeptide chains (*e.g.*, β-turn mimics).[11]

Exocyclic elements that appear frequently in natural macrocycles are α-amino acid side chains, or heterocycles such as oxazoles and thiazoles.[1,2,7–9] Another group, at least as frequent in occurrence, are exocyclic carbohydrates. Each one of these exocyclic motifs usually displays a specific biological role. The function of (for example) exocyclic sugar moieties in macrocycles such as the macrolides and glycopeptide antibiotics is a topic of great interest, as their absence leads to the partial or complete loss of the aglycon bioactivity.[8] It is well-known that the exocyclic sugar units influence the overall recognition and transport (*e.g.*, through higher water solubility) of active macrocycles,[8,12] even in cases where they do not participate in the activation at the target protein itself. It seems also that glycosylation is part of the mechanism of self-protection of the antibiotic-producing bacteria towards further modifications.[8b] The role of the exocyclic amino acids, their side chains as well as the 5-membered heterocycles definitely rests on their participation in the binding to the biological target. Overall, depending on the mode of action of the macrocycle, the exocyclic functionalities can have a higher (protein binding) or lower (membrane activity) importance for the recognition process compared to the endocyclic motifs role.

Herein we report on the use of the Ugi-MiB (MiB = *m*ultiple *m*ulticomponent *m*acrocyclization *i*ncluding *b*ifunctional *b*uilding *b*locks) strategy[13] to generate macrocycles with exocyclic natural product resemblance. Of the various Ugi-MiBs available, the diamine/diisocyanide combination was chosen as it does not generate extra exocyclic elements by itself. Thus, typical natural macrocycle appendages can be incorporated as the acid component. The challenge is to include such side chains, which tend to be

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problematic in the Ugi four-component reaction (Ugi-4CR), but which are at the same time of dominant biological importance as they bear specific recognition elements, *e.g.*, amino, carboxylate, guanidinium, imidazole groups, *etc.*

Results and discussion

The Ugi-MiB approach, *i.e.* a MiB based on multiple Ugi-4CRs, is a versatile strategy towards the rapid creation of macrocycle libraries. It encompasses the use of two building blocks bifunctionalized with Ugi-reactive groups which are allowed to undergo a cyclodimerization process in the presence of the other monofunctional Ugi-components. The resulting scaffolds are macrocycles containing two peptoid moieties and assembled through the formation of 8 new bonds in one pot.[13] Peptoids (*i.e.*, *N*-substituted oligoglycines) are an interesting family of peptidomimetics exhibiting a wide variety of biological activities and often improved pharmacological properties over peptides, such as better bioavailability.[14] Peptoid backbones previously have been incorporated into steroid-based macrocycles and cryptand-type skeletons with the aim of evaluating their molecular and ion pair recognition capabilities.[13a,15]

Recently, the creation of parallel and combinatorial libraries of natural-like macrocycles by Ugi-MiBs has been reported.[16] This issue seems to be especially promising as the method relies on the unification of both cyclization and amide *N*-substitution in order to seek biologically active peptoid-containing macrocycles. These previous studies have focused on structural requirements (*e.g.*, length, flexibility) of the endocyclic moieties essential to achieve a successful double Ugi-4CR-based macrocyclization.[13,16] This article aims to reveal which natural exocyclic elements can be incorporated in a reliable manner by using the diamine/diisocyanide combination of Ugi-MiB, thus addressing one of the many diversity elements that can be varied in one pot.

Initial efforts on the synthesis of natural-product-inspired macrocycles were directed at the incorporation of a biarylether moiety as the endocyclic element.[16a,b] It was shown that diamines that were either too rigid or too short were unable to undergo the ring closure when used as counterparts of the rigid aryl-based diisocyanides (*e.g.*, **6**).[16a,b] Accordingly, it was decided to employ long and more-or-less flexible diamines as counterparts of the previously described diisocyanides **1** and **6**. The use of hetero-functionalized diamines was preferred to aliphatic ones, as the latter not only give lower yields but also are unable to act as binding motifs or control elements, *e.g.*, with metal ions.

Scheme 1 shows the first examples of the creation of natural-product-derived exocyclic appendages based on the use of *N*-protected α-amino acids as the acid components. Paraformaldehyde was always employed as the oxo component to avoid the formation of stereoisomers. The resemblance of these compounds to macrocyclic natural products perfectly illustrates the potential of the method to create libraries amenable to biological screening.

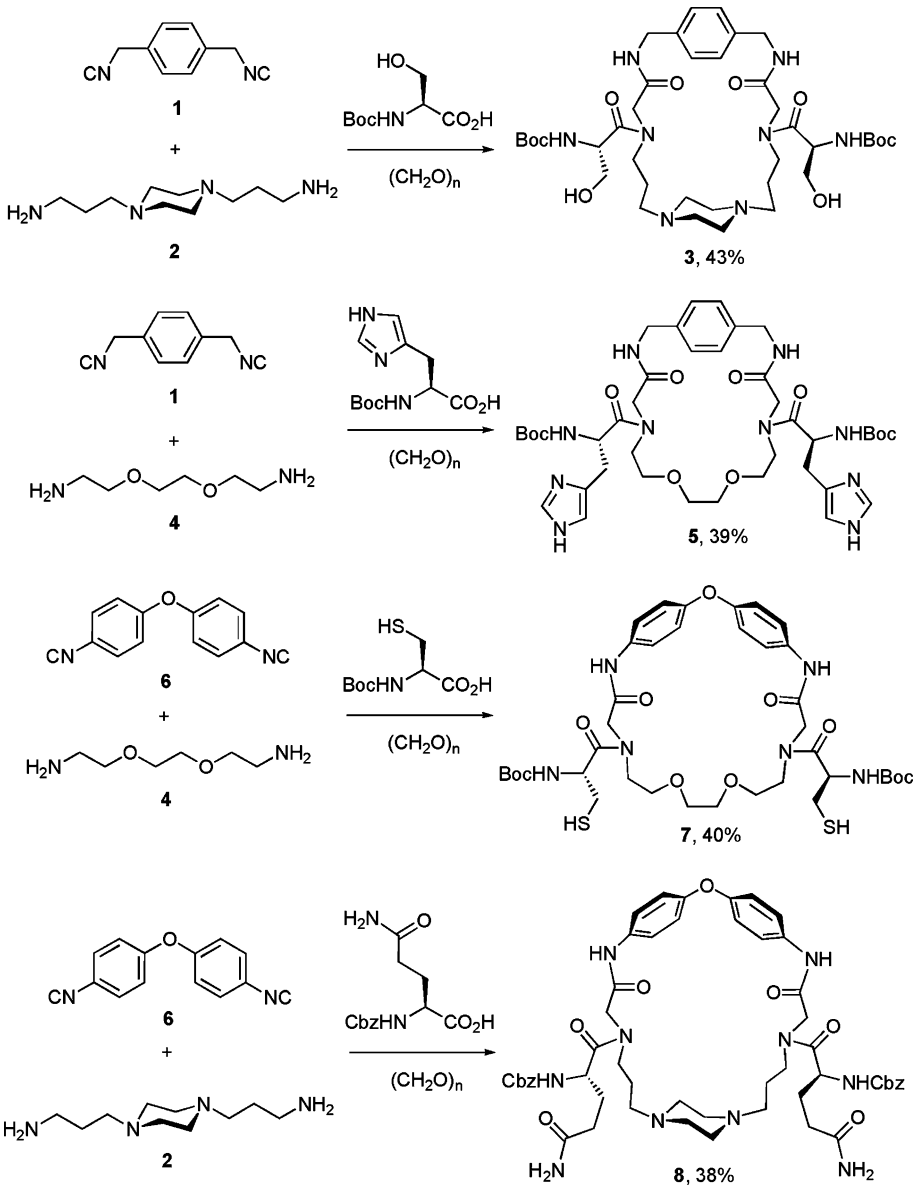
As usual in macrocyclization approaches, experiments were carried out under pseudo-high-dilution conditions. These consisted in the slow addition of the diisocyanide to a stirring mixture of the other components, *i.e.*, the acid and the diimine formed from the diamine and paraformaldehyde. Although this protocol does not ensure high dilution of the diamino building block, the pre-formation of the corresponding iminium species favours a faster completion of the Ugi-4CRs. Similar experiments, wherein the diamine was also slowly added to a solution of paraformaldehyde, were less successful despite the higher dilution of each bifunctional building block. This confirms the advantage of performing the imine-condensation prior to the addition of the other components, a process that is fairly slow at least with paraformaldehyde. Another practical issue to be optimized was the flow rate of addition of the diisocyanide *via* syringe pump. The aim was to achieve a compromise between good yields and short reaction times. Thus, the optimized protocol, which involves reaction times of *ca.* 30 hours, leads to isolated total yields ranging from *ca.* 40 to 50%. Under these conditions, small amounts of acyclic oligomers were sometimes detected by ESI-MS analysis, though they were significantly more polar than the cyclized compounds and easy to separate. Slower addition rates increased the macrocycle yields, but for significant improvements the reaction times required are too long (*i.e.*, several days or weeks) and therefore unsuitable to create macrocycle libraries.

One of the main goals of this study was to explore which α-amino acids could be employed as the acid components in Ugi-MiBs, and if they needed side chain protection or not. Priority was given to natural building blocks possessing recognized binding capabilities derived from the functional groups present in their side chains. The set of α-amino acids shown in Scheme 1 demonstrates that many biologically relevant functional side chains (*i.e.*, those of serine, histidine, glutamine, and cysteine) do not require protection when the amino acid is employed as the acid component in an Ugi-MiB. Of course, Ugi-reactive groups, such as amino groups at the α-position or in the side chain (as in lysine), or any other carboxylic acid group present (as in aspartic and glutamic acid), must be protected to avoid their uncontrolled participation in the Ugi-MiB.

The successful conversion of unprotected cysteine as the acid component is unexpected, as its alternative use as the amino component (*i.e.*, in the *C*-protected form) in the Ugi-4CR is completely ineffective. This latter case is known to be due to the inactivation of the pre-formed imine by formation of a thiazolidine derivative. As the disulfide exchange is a highly useful process for conjugation and in dynamic combinatorial chemistry, this example can be considered as an interesting entry to future applications based on disulfide exchange.

However, our investigation afforded undesired results with regard to other α-amino acid side chains that can interfere with the normal course of the double Ugi-4CR-based macrocyclization. For example, the use of tri-protected arginines (*viz.*, N_{α},N_{δ},N_{ω}-tri-Boc-L-arginine and tri-Cbz-L-arginine), was completely ineffective. No Ugi-product, cyclic or otherwise, could be identified in the reaction crude of the guanidinium carbamates. Considering the mechanism of the Ugi four-component reaction, this failure may have two different reasons:[13b,17] i) the impossibility of the "normal" α-adduct to be formed, or ii) the deviation of the normal Mumm rearrangement by an intramolecular acylation of the guanidinium instead of the nitrogen of the former Ugi-amino component. This second choice seems to be more plausible as the α-adduct is a strong acylating agent[17] and the guanidinium group is a nucleophile, even if protected as the carbamate.

The dominant role of guanidinium groups in many molecular recognition processes of biological relevance required the search for a suitable protection that allows their reliable incorporation into macrocycles *via* the Ugi-MiB. Eventually, it was found



Scheme 1 Ugi-MiB approach towards natural-product-like macrocycles with appended α-amino acids (Ser, His, Cys, Gln).

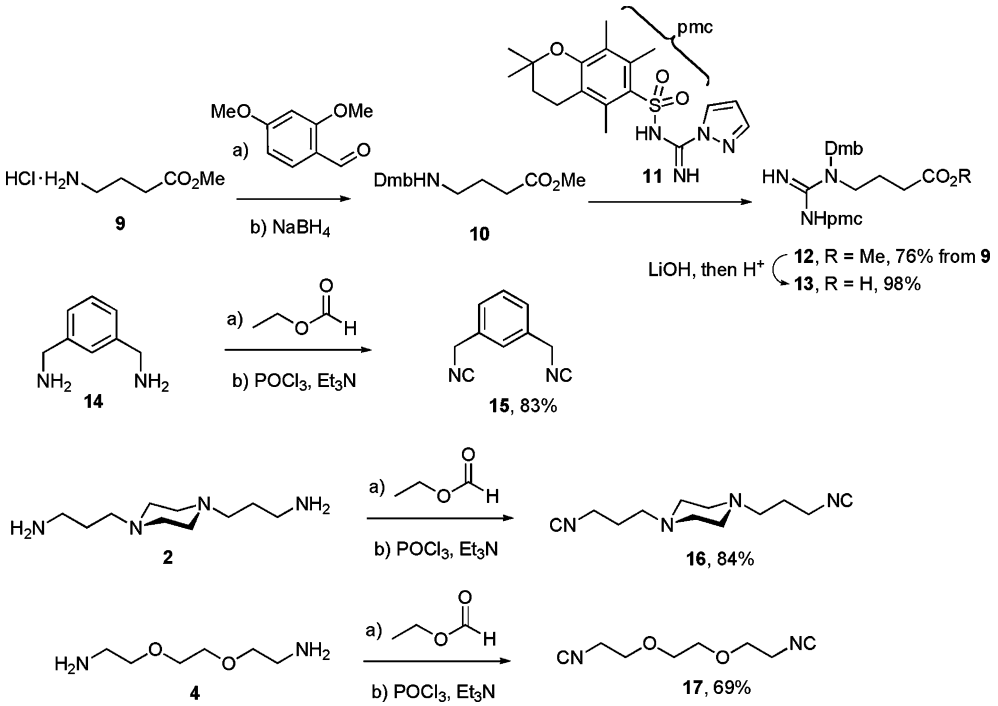
that protection with 2,4-dimethoxybenzyl (Dmb) and 2,2,5,7,8-pentamethylchromane-6-sulfonyl (pmc) at the nucleophilic centers does not affect the normal course of an Ugi-4CR.[18]

As depicted in Scheme 2, a short and practical route was employed to synthesize the guanidinium-containing building block **13** from amino acid **9**. This includes the protection with Dmb of the primary amine followed by formation of the guanidinium group utilizing 1*H*-pyrazole-1-carboxamidine **11** as the guanylating reagent.[19] This pmc-protected reactant (**11**) has been previously described for the guanylation of amines,[20] and proved equally suitable for the synthesis of compound **12** in 76% overall yield from **9**. Finally, methyl ester cleavage under mild conditions afforded acid **13**, which was employed in the double Ugi-4CR-based macrocyclization without further purification.

Scheme 2 shows the syntheses of diisocyanides **15**, **16**, and **17** from commercially available diamino building blocks to enhance the diversity of Ugi-MiB libraries. The straightforward standard procedure of formylation and dehydration for aliphatic amines[21] gave the diisocyanides on a multi-gram scale. Scheme 3 illustrates their use in combination with suitably protected tryptophane and glutamic acid, as well as a guanidinium and a carbohydrate-containing building block.

Macrocycle **19** illustrates access to arginine-like side chains by application of *N*-protected δ-guanidinium butyric acid **13**. The employed protecting groups are also suitable to introduce natural arginine itself, as this amino acid is known to be accessible from ornithine by the same guanylation approach.[19]

Macrocycles **19** and **20** were also designed to exemplify the easy fine-tuning of the positioning of the exocyclic elements derived by variation of the peptoid *N*- to *C*-terminal directionality. The two compounds were obtained from the same type of bifunctional building block core as macrocycles **5** and **3** (*cf.* Scheme 1 *vs.* Scheme 3), respectively, but with the Ugi-reactive functional groups interchanged between the building blocks. This



Scheme 2 Synthesis of mono- and bifunctional building blocks for Ugi-MiBs.

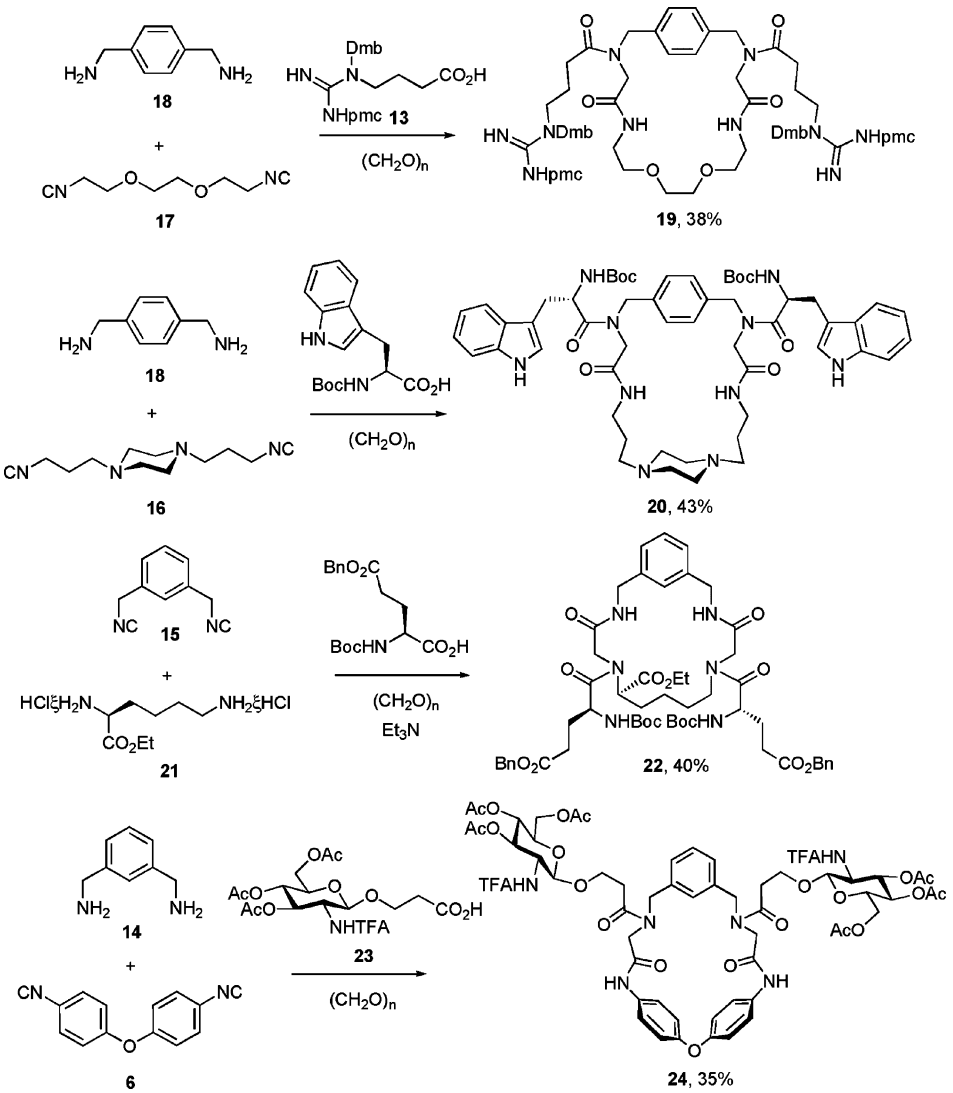
was possible by using diamine **18** (the precursor of diisocyanide **1**) as the counterpart of diisocyanides **16** and **17** (arising from diamines **2** and **4**), thus resulting in macrocycles having the same size, hybridization and functional groups, but in a different orientation and with the appended functionalities attached at different positions. This idea can be used to more rapidly access QSARs of bioactive compounds, as the fine-tuning of the positions of the side chains is available with only very few synthetically related building blocks.

The synthesis of macrocycle **22** highlights the use of natural amino acids not only as exocyclic elements, but here also as part of the endocyclic framework.

The last part of this work deals with the one-pot incorporation of carbohydrate moieties as exocyclic elements of macrocycles. Typical sugar units found in natural macrocycles can have deoxy centers, methyl, or amino or carboxylate substituents along with residual hydroxy groups.[8,12] This feature provides a mixed hydrophilic/hydrophobic nature that seems to be crucial in the delivery and/or recognition of the natural product to the biological target. The incorporation of these natural sugar moieties has been described as a great challenge in total synthesis.[1k] Therefore, rather than devoting much effort to the synthesis of such carbohydrates, our aim is simply to illustrate the possibility of incorporating amino-sugars as exocyclic elements of natural-like macrocycles. To accomplish this, they need to be functionalized with any of the Ugi-reactive groups. To remain in the context of this paper, the protected amino-glucose (GlcN)-derived carboxylic acid **23** was used along with the biaryl ether diisocyanide **6** and diamine **14** in the synthesis of macrocycle **24**. Considering that carbohydrates have been employed as any of the four components of an Ugi-4CR in acyclic systems,[22] their use in the MiB strategy may be devised also for any of the six other principal combinations of Ugi-MiBs.[13]

The lower yield of compound **24** (35%) compared to the earlier macrocycles is not a result of the sugar moiety used. The ring closure step in smaller macrocycles is more problematic with two aryl bifunctional building blocks forming a cyclophane. This was proven by further synthetic studies utilizing the same bifunctional building blocks and simpler acid components under the same pseudo-high-dilution conditions. With the rigid arylene moieties, conditions that are suitable for more flexible diamines now did result in the formation of large amounts of acyclic products. Interestingly, when *p*-xylylenediamine (**18**) was used as the counterpart of diisocyanide **6**, no macrocyclic product could be obtained. This supports previous reports from our laboratory concerning the endocyclic structural requirements needed to succeed with Ugi-MiBs for the assembly of peptoid-containing macrocycles.[13a,16]

The NMR analysis of the macrocycles obtained suggests the existence of various conformers at room temperature. This is typical for peptoid-based compounds, as the *N*-alkylation of the amide bond reduces the energy barrier between the s-*cis* and the s-*trans* configuration, thus allowing easier isomerization. The fact that the appended functional side chains are directly attached to the *N*-substituted amide and not at the α-carbon as in other cyclopeptides may be seen as a unifying concept of the approach presented here. With respect to skeletal mobility, peptoids as (cyclic) peptide mimics are related to *N*-methyl (cyclo)peptides. A recent literature survey revealed that in biologically active macrocycles, methylation is the most common *N*-alkylation reaction used by nature (as well as by medicinal chemists) in order to address physiological stability, lipophilicity, and conformational changes based on amide bond isomerization.[1a] However, an intentional relocation of exocyclic elements with natural binding capabilities to substitute *N*-methylation and side chain at the same time has not yet been explored in detail.



Scheme 3 Ugi-MiB approach towards natural-like macrocycles with appended α-amino acids (Glu, Trp), guanidinium groups (Arg-mimic), and sugar (GlcN) moieties.

This type of macrocycle, available by the MiB method or similar approaches,[1a,5f,13–16] is expected to combine the pharmacological advantages of cyclopeptides and peptoids (*i.e.*, improved bioavailability and physiological stability) in a single structure. Additionally, the occurrence of various low-energy conformations of these macrocyclic frameworks comprises the generation, and therefore screening, of a larger conformational space of exocyclic functionalities compared to those accessible by locating the side chain at an α-carbon atom with predefined stereochemistry. Finally, it must be mentioned that this method is not restricted to macrocycles including *N*-substituted glycines; prochiral oxo-compounds can also be employed with similar success. This gives rise to an even larger chemical space, including all possible stereoisomers.

Conclusions

The Ugi-MiB strategy proved suitable for the rapid and efficient generation of diverse macrocycles with exocyclic substituents resembling (cyclopeptide) natural products. This was exemplified by the diamino/diisocyanide combination of bifunctional building blocks and the incorporation of natural-product-type side chains as acid components of the Ugi-4CR-based macrocyclizations. The study proved that, with the exception of arginine, all other proteinogenic amino acids containing functional side chains can be introduced as exocyclic elements in one pot. The only structural requirement is that any amino or carboxy functionality that is desired in addition to the reacting functionality, must be protected during the macrocyclization. A solution for the incorporation of arginine-like moieties required a special combination of guanidinium protective groups. Finally, a promising route to the straightforward incorporation of carbohydrate moieties as appended functionalities of macrocycles has been presented.

Experimental

Melting points were determined on a Leica DM LS2 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300.2 MHz and 75.5 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H NMR) and to the solvent signal (^{13}C

NMR). IR spectra were obtained on a Bruker FT-IR spectrometer. High resolution ESI mass spectra were obtained from a Bruker Apex III Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an Infinity™ cell, a 7.0 Tesla superconducting magnet, an RF-only hexapole ion guide and an external electrospray ion source (Agilent, off-axis spray). ESI-MS was recorded on a Finnigan TSQ 7000, LC-Tech Ultra Plus pumps, Linear UV-VIS 200 detector, Sepserve Ultrasep ES RP-18, 5 μm, 1 × 100 mm column, flow 70 μl min^{-1}. Flash column chromatography was carried out using Merck silica gel 60 (0.015–0.040 nm) and analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} aluminium sheets. The solid compounds were recrystallized from selected solvents for the melting point measurements. All commercially available chemicals were used without further purification unless stated differently. Diisocyanides **1** and **6** were obtained as described in refs. 15 and 16. Acid **23** was prepared according to the procedure described in ref. 22*a*.

General procedure for the double Ugi-4CR-based macrocyclizations

A solution of the diamine (0.5 mmol) and paraformaldehyde (1.0 mmol) in MeOH (150 mL) was stirred for 2 h at room temperature. The acid (1.0 mmol) was then added and the stirring continued for 30 min. A solution of the diisocyanide (0.5 mmol) in MeOH (20 mL) was slowly added to the reaction mixture using a syringe pump (flow rate 0.5 mL h^{-1}). After addition was completed, the reaction mixture was stirred for 8 h and concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography.

Macrocycle 3

Diisocyanide **1** (78 mg, 0.5 mmol), diamine **2** (100 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Boc-L-serine (205 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 10 : 1) afforded macrocycle **3** (170 mg, 43%) as a white solid. $R_f = 0.25$ (CH_2Cl_2–MeOH 3 : 1). m.p. (from EtOAc): 172–173 °C. IR (KBr): 3402, 3322, 3073, 2944, 1695, 1682, 1668, 1232, 1217, 1157, 1051. ^{1}H NMR ($CDCl_3$): $\delta = 7.35$ (m, 4H, Ph); 5.67 (m, 1H, N*H*); 5.57 (m, 1H, N*H*); 5.16 (br. s, 2H, N*H*); 4.40–4.37 (m, 4H, CH_2); 4.33 (d, 4H, J= 6.7 Hz, CH_2); 4.27–4.23 (m, 4H, CH_2); 3.64–3.60 (m, 4H, CH_2); 3.39 (m, 4H, CH_2); 2.48–2.44 (m, 8H, CH_2); 2.37 (m, 4H, CH_2); 1.60 (m, 4H, CH_2); 1.43 (s, 18H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$): $\delta = 169.7$, 169.3, 168.9, 168.6, 155.8, 154.0, 137.5, 136.3, 128.5, 128.2, 128.1, 128.0, 80.8, 54.6, 55.6, 52.7, 51.6, 50.5, 46.7, 42.6, 42.1, 39.7, 29.6, 28.8, 28.6, 28.5, 24.8. HRMS (ESI-FT-ICR) m/z: 791.4677 [M + H]$^+$; calcd. for $C_{38}H_{63}O_{10}N_9$: 791.4662.

Macrocycle 5

Diisocyanide **1** (78 mg, 0.5 mmol), diamine **4** (74 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Boc-L-histidine (158 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 10 : 1) afforded the macrocycle **5** (163 mg, 39%) as a white solid. $R_f = 0.41$ (CH_2Cl_2–MeOH 3 : 1). m.p. (from EtOAc): 137–139 °C. IR (KBr): 3336, 2976, 2930, 1698, 1692, 1679, 1653, 1540, 1249, 1166. ^{1}H NMR ($CDCl_3$): $\delta = 7.51$ (s, 2H, C*H*-imid.); 7.28 (s, 4H, C*H*-Ph); 6.82 (s, 1H, C*H*-imid.); 6.79 (s, 1H, C*H*-imid.); 5.49–5.46 (m, 2H, N*H*); 4.69–4.66 (m, 2H, C*H*); 4.26–4.16 (m, 4H, CH_2); 3.61–3.56 (m, 4H, CH_2); 3.39 (m, 4H, CH_2); 3.33–3.31 (m, 4H, CH_2); 3.24–3.20 (m, 4H, CH_2); 3.11 (m, 2H, CH_2); 3.06 (m, 2H, CH_2); 2.96 (dd, 4H, J= 14.4/4.3 Hz, CH_2); 1.43 (s, 18H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$): $\delta = 172.9$, 169.0, 155.0, 138.4, 135.6, 128.2, 128.1, 80.2, 77.4, 69.8, 68.3, 58.2, 53.1, 51.4, 50.7, 48.7, 42.8, 28.4. HRMS (ESI-FT-ICR) m/z: 839.4424 [M + H]$^+$; calcd. for $C_{40}H_{59}O_{10}N_{10}$: 839.4410.

Macrocycle 7

Diisocyanide **6** (110 mg, 0.5 mmol), diamine **4** (74 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Boc-L-cysteine (221 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 15 : 1) afforded the macrocycle **7** (167 mg, 40%) as a white solid. $R_f = 0.43$ (CH_2Cl_2–MeOH 5 : 1). m.p. (from EtOAc–heptane): 183–186 °C. IR (KBr): 3322, 3058, 2971, 1694, 1691, 1641, 1463, 1234, 1209, 1171. ^{1}H NMR ($CDCl_3$): $\delta = 9.38$ (br. s, 2H, N*H*); 9.12 (br. s, 2H, N*H*); 7.63 (d, 2H, $J = 8.8$ Hz, *m*-PhNH); 7.54 (d, 2H, J= 8.9 Hz, *m*-PhNH); 6.97 (d, 2H, $J = 9.0$ Hz, *o*-PhNH); 6.89 (d, 2H, $J = 9.0$ Hz, *o*-PhNH); 5.21 (br. s, 2H, N*H*); 4.51–4.46 (m, 4H, CH_2); 4.22–4.06 (m, 4H, CH_2); 3.78–3.75 (m, 4H, CH_2); 3.53–3.49 (m, 4H, CH_2); 3.76–3.74 (m, 4H, CH_2); 1.44 (s, 18H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$): $\delta = 173.0$, 172.4, 168.3, 166.9, 156.1, 133.6, 133.3, 121.2, 120.6, 119.8, 119.5, 80.8, 70.3, 63.5, 54.2, 53.2, 51.8, 51.4, 47.7, 31.4, 28.8, 28.4, 28.1. HRMS (ESI-FT-ICR) m/z:857.3187 [M + Na]$^+$; calcd. for $C_{38}H_{54}NaO_{11}N_6S_2$: 857.3183.

Macrocycle 8

Diisocyanide **6** (110 mg, 0.5 mmol), diamine **2** (100 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Cbz-L-glutamine (280 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 10 : 1) afforded **8** (191 mg, 38%) as a white solid. $R_f = 0.21$ (CH_2Cl_2–MeOH 3 : 1). m.p. (from MeOH): 207–208 °C. IR (KBr): 3317, 3064, 2953, 1697, 1693, 1635, 1467, 1248, 1211, 1168. ^{1}H NMR ($CDCl_3$): $\delta = 9.72$ (br. s, 1H, N*H*); 9.58 (br. s, 1H, N*H*); 7.66 (d, 2H, $J = 8.8$ Hz, *m*-PhNH); 7.57 (d, 2H, J = 8.9 Hz, *m*-PhNH); 7.35 (m, 10H, Ph-Cbz); 6.94 (d, 2H, $J = 9.2$ Hz, *o*-PhNH); 6.87 (d, 2H, $J = 9.1$ Hz, *o*-PhNH); 5.50 (br. s, 2H, N*H*); 5.10 (m, 4H, CH_2); 4.94–4.89 (m, 2H, CH_2); 4.60–4.56 (m, 2H, CH_2); 4.37–4.31 (m, 4H, CH_2); 4.21–4.18 (m, 2H, CH_2); 4.05 (m, 2H, CH_2); 3.71–3.64 (m, 4H, CH_2); 3.20 (m, 4H, CH_2); 2.40–2.21 (m, 8H, CH_2); 1.60 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 173.8$, 172.6, 168.1, 166.9, 156.6, 156.2, 136.4, 130.1, 128.4, 128.0, 122.3, 121.7, 120.5, 120.1, 66.6, 55.0, 53.6, 52.3, 52.2, 51.4, 40.0, 31.8, 29.6, 22.6, 22.4, 14.0. HRMS (ESI-FT-ICR) m/z: 1105.4767 [M + H]$^+$; calcd. for $C_{52}H_{65}O_{11}N_{10}$: 1105.4761.

N-Protected δ-guanidinium butyric ester 12 and acid 13

A solution of methyl 4-aminobutanoate hydrochloride **9** (306 mg, 2.0 mmol), Et_3N (0.28 mL, 2.0 mmol) and 2,4-dimethoxybenzaldehyde (276 mg, 1.7 mmol) in MeOH (20 mL) was stirred

for 2 h at room temperature. $NaBH_4$ (114 mg, 3.0 mmol) was added to the reaction mixture in small portions and the reaction mixture was stirred for additional 2 h. The solution was diluted with diethyl ether (20 mL) and treated carefully with 10% aqueous NaOH (10 mL). Then the organic layer was separated, washed with water (2 × 10 mL) and brine (10 mL) and dried over anhyd. Na_2SO_4 to afford the amine **10**. A solution of this crude product in DMF (2.5 mL) was treated with *N*-pmc-1-*H*-pyrazole-1-carboxamidine **11** (800 mg, 2.1 mmol) and the reaction mixture was stirred at 130 °C for 24 h in a sealed tube. After cooling to room temperature, the solution was diluted with EtOAc (30 mL), washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), dried over anhyd. Na_2SO_4 and concentrated under pressure to furnish a crude product. Flash column chromatography purification (*n*-hexane–EtOAc 1 : 1) afforded the pure compound **12** (874 mg, 76%) as a white solid. m.p. (from CH_2Cl_2–*n*-hexane): 145–146 °C. ^{1}H NMR ($CDCl_3$): $\delta = 7.01$ (d, 1H, $J = 8.4$ Hz, C*H*); 6.61 (br. s, 1H, N*H*); 6.41 (s, 1H, C*H*); 6.34 (d, 1H, $J = 7.2$ Hz, C*H*), 4.41 (s, 2H); 3.77 (s, 3H, CH_3O); 3.76 (s, 3H, CH_3O); 3.64 (s, 3H, CH_3O); 3.29 (m, 2H, CH_2); 2.61 (t, 2H, $J = 6.8$ Hz, CH_2); 2.57(s, 3H, CH_3); 2.56 (s, 3H, CH_3); 2.26 (t, 2H, $J = 6.6$ Hz, CH_2); 2.09 (s, 3H, CH_3); 1.80 (m, 2H, CH_2); 1.30 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 173.2$, 160.4, 157.6, 155.4, 153.0, 135.3, 134.6, 133.9, 130.0, 123.6, 117.6, 104.2, 98.4, 73.4, 60.3, 55.4, 51.8, 46.6, 45.6, 32.9, 30.4, 30.3, 26.8, 22.4, 21.4, 18.5, 17.5, 14.3, 12.0. HRMS (ESI-FT-ICR) *m*/*z*: 598.2571 [M + Na]$^+$; calcd. for $C_{29}H_{41}N_3NaO_7S$: 598.2567.

LiOH (233 mg, 3.7 mmol) was added to a solution of ester **12** (850 mg, 1.48 mmol) in THF–H_2O (2 : 1, 50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then acidified with 10% aq. $NaHSO_4$ to pH 3. The resulting phases were separated and the aqueous phase was further extracted with EtOAc (2 × 60 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the acid **13** (814 mg, 98%) as a white solid. The product (identified by ESI-MS) was used in the macrocyclization without further purification and characterization.

m,*m*′-Diisocyanoxylene (15)

A solution of *m*-xylylenediamine **14** (3.0 g, 22.0 mmol) in ethyl formate (200 mL) was stirred at reflux for 20 h. The resulting precipitate was filtered under reduced pressure, washed with cold EtOAc (2 × 30 mL) and dried at 60 °C to furnish the corresponding diformamide. This product was dissolved in 150 mL of dry CH_2Cl_2, then Et_3N (40 mL) was added and the solution was cooled to −60 °C. A solution of $POCl_3$ (6.6 mL, 72 mmol) in 30 mL of CH_2Cl_2 was added dropwise under argon atmosphere and the resulting reaction mixture was stirred overnight at room temperature. The mixture was poured into cold water (200 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), then dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2) to afford the diisocyanide **15** (2.84 g, 83%) a pale yellow oil. $R_f = 0.58$ (CH_2Cl_2). IR (ATR, cm^{-1}): 2123. ^{1}H NMR ($CDCl_3$): $\delta = 7.45$ (t, 1H, $J = 6.6$ Hz, C*H*-Ph); 7.35 (d, 2H, $J = 6.8$ Hz, C*H*-Ph); 7.32 (s, 1H, C*H*-Ph); 4.68 (s, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 157.8$, 157.8, 133.0, 129.5, 126.5, 124.6, 45.3, 45.1. ESI-MS *m*/*z*: 156.8 [M + H]$^+$; calcd. for $C_{10}H_9N_2$: 157.0. The compound should be stored at 4 °C to avoid decomposition.

1,4-Bis(3-isocyanopropyl)piperazine (16)

Diamine **2** (3.6 g, 22.0 mmol) was treated in a similar way as described for the synthesis of **15** to afford the diisocyanide **16** (4.01 g, 84%) as a pale yellow solid. $R_f = 0.37$ (CH_2Cl_2–MeOH 10 : 1). m.p. (from EtOH): 79–81 °C. IR (KBr, cm^{-1}): 2814, 2153, 1462, 1283, 1159, 1143. ^{1}H NMR ($CDCl_3$): $\delta = 3.47$ (tt, 4H, $J =$ 6.6/1.9 Hz, CH_2); 2.47 (t, 4H, $J = 6.8$ Hz, CH_2); 2.46 (m, 8H, CH_2); 3.47 (qt, 4H, $J = 6.7/2.0$ Hz, CH_2). ^{13}C NMR ($CDCl_3$): $\delta =$ 155.7, 155.6, 54.4, 53.1, 39.6, 39.5, 39.4, 26.5. HRMS (ESI-FT-ICR) *m*/*z*: 243.1578 [M + Na]$^+$; calcd. for $C_{12}H_{20}NaN_4$: 243.1580.

1,8-Diisocyano-3,6-dioxaoctane (17)

Diamine **4** (5 g, 24 mmol) was treated in a similar way as described for the synthesis of **15** to afford the diisocyanide **17** (3.91 g, 69%) as a pale brown oil. $R_f = 0.47$ (CH_2Cl_2–MeOH 10 : 1). IR (ATR, cm^{-1}): 2927, 2151, 1254, 1206, 1178, 1159, 1103. ^{1}H NMR ($CDCl_3$): $\delta =$ 3.74–3.71 (m, 8H, CH_2); 3.60 (t, 4H, $J = 5.8$ Hz, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 157.0$, 156.9, 70.7, 68.6, 41.9, 41.8, 41.7. HRMS (ESI-FT-ICR) *m*/*z*: 191.0788 [M + Na]$^+$; calcd. for $C_8H_{12}NaN_2O_2$: 191.0790. The compound should be stored at 4 °C to avoid decomposition.

Macrocycle 19

Diisocyanide **17** (84 mg, 0.5 mmol), diamine **18** (68 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-protected *δ*-guanidinium butyric acid **13** (561 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 15 : 1) afforded the macrocycle **19** (276 mg, 38%) as a pale yellow solid. $R_f = 0.43$ (CH_2Cl_2–MeOH 10 : 1). m.p. (from EtOAc): 187–190 °C. IR (KBr): 3021, 2918, 2850, 1728, 1626, 1541, 1506, 1463, 1258, 1209, 1107, 759. ^{1}H NMR ($CDCl_3$): $\delta = 7.26$ (m, 4H, C*H*-Ph); 7.01 (d, 1H, $J = 8.4$ Hz, C*H*-Ph); 6.43 (s, 2H, C*H*); 6.37 (m, 2H, $J = 7.2$ Hz, C*H*-Ph), 5.37–5.32 (m, 2H, N*H*); 4.47–4.42 (s, 4H); 4.32–4.25 (m, 4H); 3.78 (s, 6H, CH_3O); 3.76 (s, 6H, CH_3O); 3.62–3.57 (m, 4H); 3.39–3.28 (m, 6H); 3.31–3.27 (m, 4H, CH_2); 3.25–3.20 (m, 4H, CH_2); 3.06–2.07 (m, 4H, CH_2); 2.62–2.60 (m, 4H); 2.56 (s, 6H, CH_3); 2.54 (s, 6H, CH_3); 2.31–2.28 (m, 4H); 2.11 (s, 6H, CH_3); 1.31 (s, 12H, CH_3). ^{13}C NMR ($CDCl_3$): $\delta =$ 171.7, 170.9, 169.7, 169.6, 169.3, 160.4, 160.2, 157.8, 155.3, 153.4, 153.2, 138.7, 135.9, 135.4, 134.1, 133.7, 131.2, 128.4, 128.2, 123.4, 123.3, 117.7, 177.5, 104.2, 98.2, 73.6, 60.1, 55.8, 51.6, 50.5, 48.7, 46.8, 45.3, 42.9, 33.1, 30.7, 30.5, 26.9, 22.5, 21.2, 18.7, 18.6, 17.5, 17.3, 14.3, 14.2, 12.2, 12.1. HRMS (ESI-FT-ICR) *m*/*z*: 1473.6825 [M + Na]$^+$; calcd. for $C_{74}H_{102}N_{10}NaO_{16}S_2$: 1473.6812.

Macrocycle 20

Diisocyanide **16** (110 mg, 0.5 mmol), diamine **18** (68 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Boc-L-tryptophan (304 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH–Et_3N 10 : 1 : 0.1) afforded

the macrocycle **20** (213 mg, 43%) as a light yellow solid. R_f = 0.33 (CH_2Cl_2–MeOH–Et_3N 5 : 1 : 0.1). m.p. (from EtOAc): 174–175 °C. IR (KBr): 3313, 3011, 2941, 1652, 1540, 1457, 1254, 1215, 1166, 1011, 750. ^{1}H NMR ($CDCl_3$): δ = 9.54 (br. s, 1H, N*H*); 8.94 (br. s, 1H, N*H*); 7.77–7.74 (m, 2H, C*H*-indole); 7.59–7.56 (m, 2H, C*H*-indole); 7.43 (d, 2H, J = 7.3 Hz, C*H*-Ph); 7.32 (d, 2H, J = 7.4 Hz, C*H*-Ph); 7.15–7.00 (m, 6H, C*H*-indole); 6.56 (m, 1H, N*H*); 6.29 (m, 1H, N*H*); 5.64 (br. s, 1H, N*H*); 5.48 (br. s, 1H, N*H*); 5.38–5.33 (m, 2H, CH_2); 5.24–5.18 (m, 2H, CH_2); 4.83–4.80 (m, 4H, CH_2); 4.59–4.54 (m, 2H, CH_2); 4.48–4.45 (m, 2H, CH_2); 4.39–4.34 (m, 2H, C*H*); 4.22–4.08 (m, 4H, CH_2); 3.36–3.28 (m, 4H, CH_2); 1.47, 1.44, 1.43 (s, 18H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$): δ = 172.9, 172.3, 171.5, 170.7, 155.3, 155.0, 136.1, 134.9, 130.8, 129.8, 129.6, 129.1, 128.7, 128.4, 128.1, 127.2, 127.0, 126.5, 123.8, 123.5, 121.6, 121.4, 119.6, 119.2, 118.7, 117.6, 111.5, 111.2, 109.8, 109.6, 105.5, 80.6, 80.4, 77.2, 61.3, 58.4, 56.5, 56.1, 55.4, 54.9, 52.6, 52.0, 50.8, 47.5, 46.2, 37.4, 29.7, 29.4, 28.6, 28.5, 28.4, 23.3, 18.5. HRMS (ESI-FT-ICR) m/z: 989.5599 [M + H]$^+$; calcd. for $C_{55}H_{73}O_8N_{10}$: 989.5607.

Macrocycle 22

Diisocyanide **15** (78 mg, 0.5 mmol), L-lysine ethyl ester dihydrochloride (124 mg, 0.5 mmol), Et_3N (0.128 mL, 1 mmol), paraformaldehyde (30 mg, 1 mmol), and *N*-Boc-L-glutamic acid 5-benzyl ester (337 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 15 : 1) afforded the macrocycle **22** (206 mg, 40%) as a white solid. R_f = 0.33 (CH_2Cl_2–MeOH 10 : 1). m.p. (from *n*-hexane–CH_2Cl_2): 82–84 °C. IR (KBr): 2979, 2944, 1732, 1697, 1654, 1522, 1454, 1248, 1167, 1029, 751. ^{1}H NMR ($CDCl_3$): δ = 7.88 (m, 1H, N*H*); 7.79 (m, 1H, N*H*); 7.35 (m, 5H, Bn); 7.34–7.33 (m, 6H, Bn + C*H*-Ph); 7.23 (s, 1H, C*H*-Ph); 7.19 (d, 2H, J = 6.9 Hz, C*H*-Ph); 5.32 (d, 1H, J = 8.0 Hz, N*H*); 5.25 (d, 1H, J = 7.9 Hz, N*H*); 5.15 (m, 2H, CH_2-Bn); 5.11 (m, 2H, CH_2-Bn); 4.89–4.86 (m, 1H, C*H*); 4.72–4.67 (m, 1H, C*H*); 4.50–4.40 (m, 3H, CH_2 + C*H*); 4.18–4.07 (m, 4H, CH_2); 2.55–2.44 (m, 4H, CH_2); 1.44 (s, 9H, (CH_3)$_3$C); 1.40 (s, 9H, (CH_3)$_3$C); 1.21 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ = 173.2, 172.7, 170.7, 168.4, 168.3, 167.9, 167.6, 156.4, 156.1, 138.9, 138.4, 135.5, 128.4, 128.2, 128.1, 128.0, 80.4, 80.1, 66.6, 61.9, 61.5, 58.0, 50.8, 50.0, 49.3, 43.7, 43.4, 43.0, 29.6, 29.2, 28.6, 28.4, 28.3, 27.2, 26.9, 23.4, 14.2. HRMS (ESI-FT-ICR) m/z: 1051.5008 [M + Na]$^+$; calcd. for $C_{54}H_{72}O_{14}NaN_6$: 1051.4999.

Macrocycle 24

Diisocyanide **6** (110 mg, 0.5 mmol), diamine **14** (68 mg, 0.5 mmol), paraformaldehyde (30 mg, 1 mmol), and the aminosugar-derived acid **23** (489 mg, 1 mmol) were reacted according to the general macrocyclization procedure. Flash column chromatography purification (CH_2Cl_2–MeOH 10 : 1) afforded the macrocycle **24** (232 mg, 35%) as a pale brown solid. R_f = 0.37 (CH_2Cl_2–MeOH 5 : 1). m.p. (from EtOAc): 231–233 °C. ^{1}H NMR ($CDCl_3$): δ = 9.65 (br. s, 1H, N*H*); 9.54 (br. s, 1H, N*H*); 7.63 (d, 2H, J = 8.9 Hz, *m*-PhNH); 7.54 (d, 2H, J = 8.9 Hz, *m*-PhNH); 6.92 (d, 2H, J = 9.1 Hz, *o*-PhNH); 6.84 (d, 2H, J = 9.0 Hz, *o*-PhNH); 7.31 (t, 1H, J = 7.6 Hz, C*H*-Ph); 7.29 (s, 1H, C*H*-Ph); 7.19 (d, 2H, J = 7.2 Hz, C*H*-Ph); 5.27 (t, 2H, J = 9.9 Hz, C*H*); 5.00 (t, 2H, J = 9.4 Hz, C*H*); 4.75 (d, J = 8.5 Hz, 2H, C*H*); 4.54–4.49 (m, 4H, CH_2); 4.30 (dd, 2H, J = 12.3/4.5 Hz, C*H*); 4.13 (dd, 2H, J = 12.4/2.3 Hz, C*H*); 4.04 (td, 2H, J = 10.1/5.9 Hz, C*H*); 3.84–3.79 (m, 4H, CH_2); 2.57–2.54 (m, 4H, CH_2); 2.06 (s, 6H, CH_3CO); 2.00 (s, 6H, CH_3CO); 1.96 (s, 6H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ = 173.1, 172.6, 171.8, 171.1, 170.8, 169.1, 168.4, 157.7 (q, J = 38 Hz), 157.4 (q, J = 38 Hz), 143.8, 136.3, 130.2, 128.3, 128.2, 128.0, 127.9, 115.5 (q, J = 288 Hz), 114.8 (q, J = 288 Hz), 101.3, 101.2, 73.5, 73.1, 69.9, 66.8, 63.2, 55.9, 45.9, 44.2, 40.9, 35.7, 20.9, 20.6, 20.4. HRMS (ESI-FT-ICR) m/z: 1349.3819 [M + Na]$^+$; calcd. for $C_{58}H_{64}NaF_6O_{23}N_6$: 1349.3818.

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