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Multiple Multicomponent Macrocyclizations Including Bifunctional Building Blocks (MiBs) Based on Staudinger and Passerini Three-Component Reactions

Fredy Leon,[†,‡] Daniel G. Rivera,[†,‡] and Ludger A. Wessjohann*[,†]

Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle/Saale, Germany, and Center for Natural Products Study, Faculty of Chemistry, University of Havana, Cuba

wessjohann@ipb-halle.de

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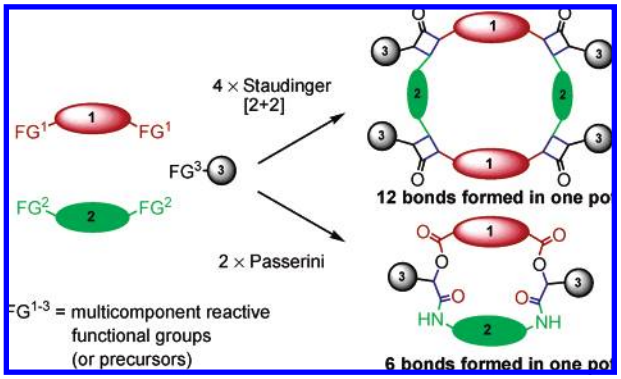

Multiple multicomponent macrocyclizations including bifunctional buildings blocks (MiBs) so far have relied almost exclusively on Ugi reactions. The efficient expansion to non-Ugi-MiBs is exemplified by the synthesis of tetra-β-lactam and bis-α-acyloxy carboxamide macrocycles based on multiple Staudinger and Passerini three-component reactions (3CR), respectively. A recent variation of the Passerini-3CR that involves primary alcohols, isocyanides, and carboxylic acids under oxidative conditions is successfully adapted to this procedure.

Introduction

Macrocycles have received great attention from the scientific community as a result of their widespread occurrence in nature and their astounding applicability in biological and supramolecular chemistry.[1] A key feature of macrocycles is their ability to combine flexibility and conformational preorganization, which makes them a preferred target for the design of new ligands and receptors. Considerable effort has been devoted to the development of new synthetic methodologies that allow a more efficient access to this extremely successful class of compounds. Our group recently developed a diversity-oriented macrocyclization strategy, termed *m*ultiple *m*ulticomponent *m*acrocyclization(s) *i*ncluding *b*ifunctional *b*uilding *b*locks [MiB(s)], which allows the production of constitutionally highly diverse macrocycles in one pot.[2] Several examples have been reported since then, especially on macrocycles with a peptide-like backbone produced by multiple Ugi four-component reactions (Ugi-4CRs). On the basis of this reaction, the concept and methodology for MiBs has been developed, standardized, and extended to generate extremely complex molecules (e.g.,

[†] Leibniz Institute of Plant Biochemistry.
[‡] University of Havana.

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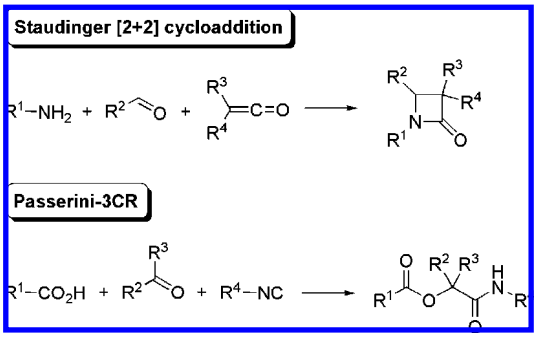
SCHEME 1. Three-Component Reactions: (Top) Staudinger Cycloaddition, (Bottom) Passerini Reaction

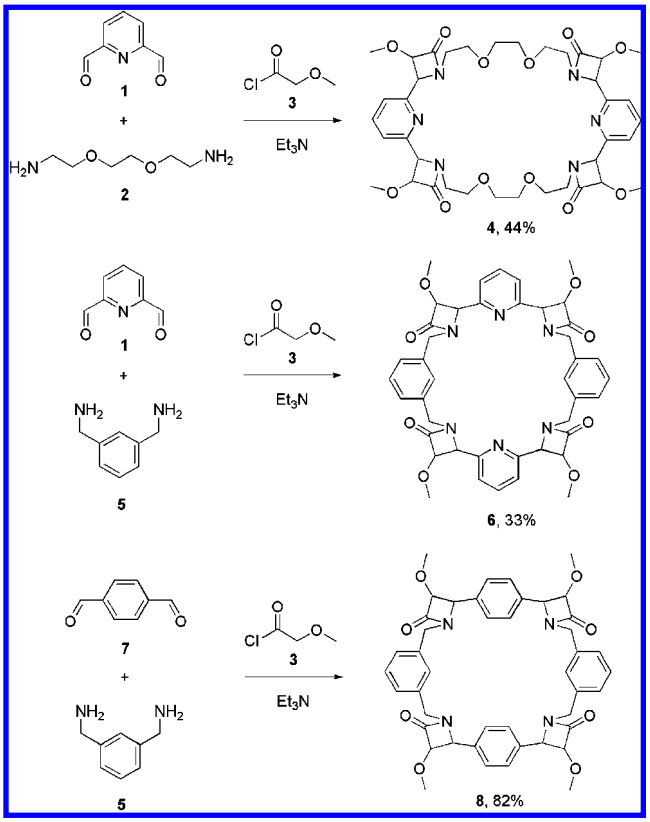


cryptands, cages, and cryptophanes).[2,3] Of course, a limitation to the Ugi-4CR is not intrinsic to the concept of MiBs,[4] therefore we also looked into other multicomponent reactions (MCRs) that might prove useful to access macrocycles in one pot. In this paper we present several examples of the use of Staudinger and Passerini 3-CRs (Scheme 1) to produce β-lactam- and α-acyloxy carboxamide-containing macrocycles via MiBs, i.e., Staudinger-MiBs and Passerini-MiBs.

Natural and synthetic compounds including the β-lactam moiety have been extensively used in the treatment of bacterial diseases.[5] β-Lactams continue to be relevant also in other areas of medicinal chemistry, e.g., trisubstituted β-lactams have been found to be new, potent cholesterol absorption inhibitors,[6] human cytomegalovirus protease inhibitors,[7] and thrombin inhibitors.[8] Also, anticancer activity has been reported recently for this type of compound.[9] The synthesis of macrocycles that contain β-lactams has another interesting aspect. If obtained readily, these complex structures subsequently can be converted into macrocyclic polyamino acids, macrocyclic amides, and macrocyclic azetidines within the diversity-oriented synthesis (DOS) concept.[10a] Despite the long experience with this class of molecules, very few example of macrocycles containing a β-lactam moiety are known.[10]

A second MCR, which through its relation to the Ugi-4CR appears suitable, is the Passerini-3CR. The α-acyloxy carboxamide moiety formed during the Passserini-3CR is also an important target motif in natural product syntheses, as it is found in many biologically relevant macrocycles such as the depsipeptides.[1a,d] The Passerini-3CR has been used previously to install this moiety into acyclic precursors that are later cyclized by another type of ring-closing reaction (e.g., olefin metathesis).[11] However, this MCR has not been employed as the ring-closing reaction itself, so far.

SCHEME 2. Synthesis of Tetra-β-lactam Macrocycles by Staudinger-MiB



Results and Discussion

To implement the MiB methodology based on these non-Ugi-MCRs, the first issue is to select the appropriate bifunctional building blocks that allow the one-pot assembly of the macrocycle with minimal formation of acyclic oligomers. Previous studies of Ugi-MiBs have shown that, in addition to the usual (pseudo) high dilution conditions, the structural features of the building blocks need to be considered. These include structural pre-organization and a suitable reactivity of the MCR-reactive functionalities. Therefore, each MiB may require a specific synthetic protocol to succeed well.

MiBs Based on the Staudinger-3CR. As shown in Scheme 2, the aromatic aldehydes **1** and **7** were selected as dioxo components and condensed with diamines **2** and **5**. In all cases, the diamines were slowly added to the solution of the dialdehydes in dry dichloromethane to allow the formation of the macrocyclic oligoimines. After addition was complete, the reaction mixtures were cooled to −50 °C, treated with triethyl amine and methoxyacetyl chloride in this sequence, and stirred

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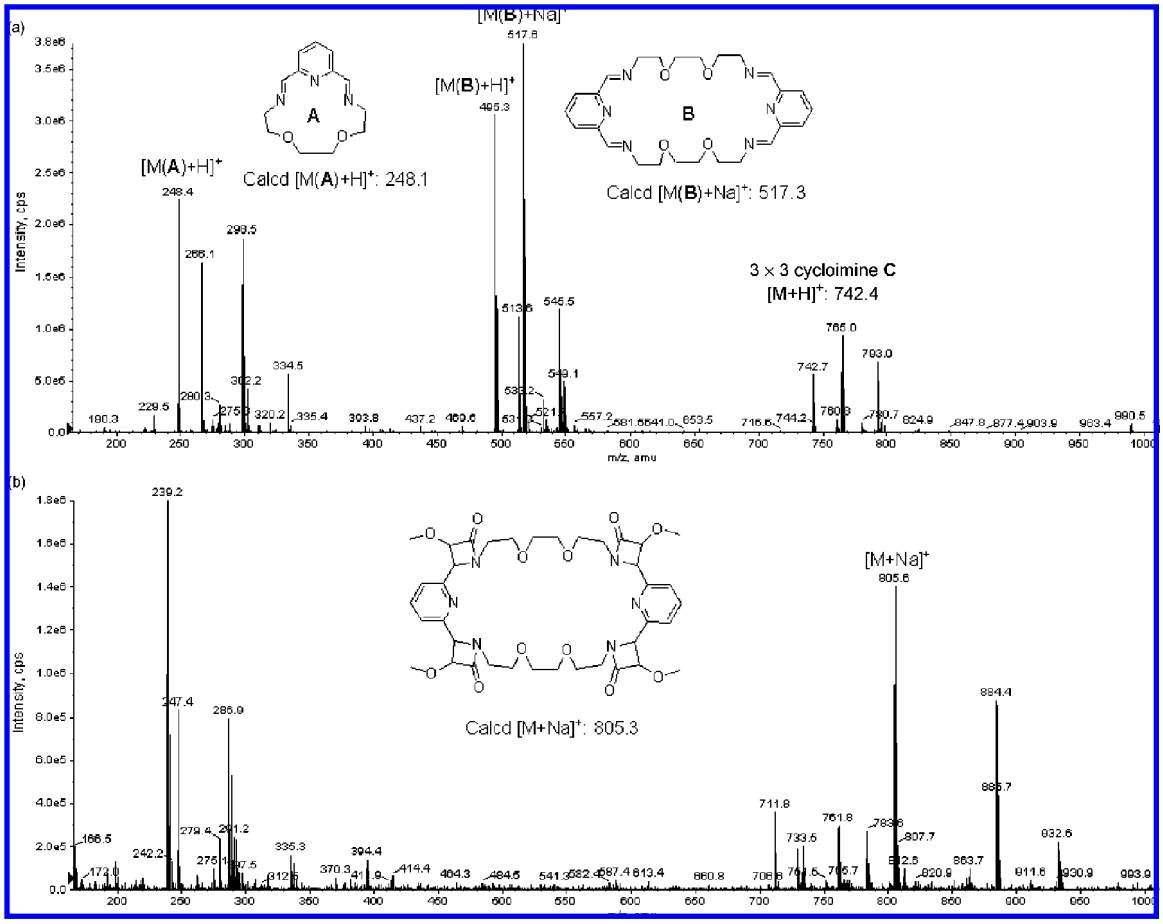

FIGURE 1. ESI-MS spectra (positive ion mode) recorded during the synthesis of macrocycle **4** (Scheme 2): (top) dynamic oligo-imine intermediates after addition of the diamine was completed; (bottom) products after addition of the ketene component.

at room temperature overnight. Macrocycles **4**, **6**, and **8** were obtained in 44%, 33%, and 82% yield, respectively, after purification by column chromatography. Because only moderate high dilution conditions were employed, the structural preorganization of the bifunctional building blocks had a great influence on the macrocyclization outcome. For example, whereas macrocycle **8** was obtained in excellent yield (82%) from the *para*-disubstituted dialdehyde **7**, macrocycle **6** was obtained in only 33% from the pyridine-disubstituted *meta*-dialdehyde **1**. Indeed, the straight structure of **7** favors the formation of the precursor macrocyclic tetraimine and, subsequently, of the tetra-β-lactam macrocycle. Nevertheless, even an overall 33% yield represents an excellent yield per individual bond formation (ca. 92%), considering that 12 new bonds are formed in one pot. This procedure has an important advantage over previously reported schemes,[10] i.e., the whole process occurs in one pot without isolation of the intermediate macrocyclic oligoimines.

Even though several cyclic and acyclic oligomers can be formed from the dynamic system created by the imine exchange,[12] the macrocycles shown were the only compounds detected after workup. Especially interesting is the formation of **4**. After addition of diamine **2** the 1 × 1 and 2 × 2 macrocyclic polyimines **A** and **B** can be observed by ESI-MS (Figure 1), but after the ketene component is added into the system, the equilibrium shifts to the larger cycle. Either the four-membered rings impose strong conformational restrictions that do not allow the formation of a final 1 × 1 macrocycle, a species that could be commonly selected in previous studies using Ugi-MiBs, or the triethylammonium salt formed in the reaction exhibits a templating effect, shifting the composition to the 2 × 2 Schiff base precursor.[12] Interestingly, formation of the next higher oligomer, the larger 3 × 3 cycle, also was detected in minor amounts in the imine intermediate state but also was not found in any of the quenched final products. In principle, such higher homologues of cyclic imines may also be ESI artefacts (clusters of 2 × or 3 × the 1 × 1 Schiff base), but in this case appear unlikely for four reasons: (1) for compounds **6** and **8** a 1 × 1 product would be a very strained *meta*-cyclophane; (2) the dominant product **4** also relates to the 2 × 2 species, which accordingly should be present as a precursor; (3) in similar instances, i.e., Ugi-quenched imine exchange, the Schiff-base ESI distribution is fully reflected in the quenched products;[12a] and finally, (4) specific MS techniques such as variation of the skimmer voltage (FT-ICR) or negative ion mode measurements (when applicable) help to avoid MS-artefacts.[2a]

Stereochemically the Staudinger-3CR is a stereoselective [2 + 2]-cycloaddition, and in the case of monosubstituted ketenes, the *cis*-β-lactam is typically the predominant product. It is well-known that for β-lactams $J_{3,4}$-*cis* is ca. 4.2−6.0 Hz and $J_{3,4}$-*trans* is ca. 2.0−2.5 Hz. The *cis* stereochemistry of all four-membered rings was clearly established for macrocycle **4**

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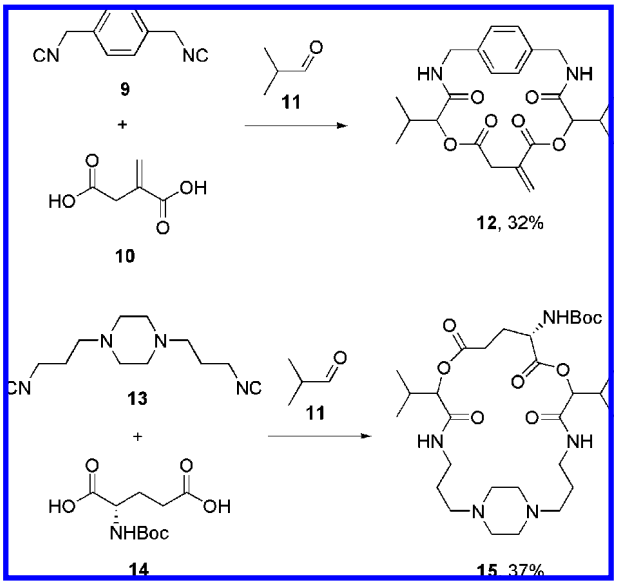
SCHEME 3. MiBs Based on the Passerini-3CR (Classical Procedure)



where the coupling constants are 4.8 and 4.6 Hz. Similar values were found for the macrocycles **6** and **8**. According to this and the C_2-symmetry of the obtained molecules, we can expect a maximum of four diastereoisomers to be produced, and the related signal sets can be seen in the ^{13}C NMR spectra in some instances. Isolation of a single stereoisomer, however, was not possible by simple column chromatography.

MiBs Based on the Passerini-3CR. Similarly to Ugi-MiBs, Passerini-MiBs are very amenable for generating a high level of skeletal diversity with low synthetic cost. This is due to the variable combinations of bifunctional building blocks that can be implemented based on a variation of the Passerini-reactive functional groups attached to the same building block core. As a result of the three-component character of this reaction, also three different combinations of bifunctional building blocks are possible, i.e., diacid/diisocyanide, diacid/dialdehyde, and dialdehyde/diisocyanide.

In Scheme 3, the synthesis of depsipeptide-like macrocycles is exemplified with the diacid/diisocyanide combination of Passerini-MiBs. Accordingly, the structurally varied macrolactones **12** and **15** were produced from commercial or easily available starting materials. As previously shown, diisocyanides are readily available from commercial diamines via formylation and subsequent dehydration of the corresponding diformamides.[2c,3] The easy access to this type bifunctional building blocks has proven suitable not only to produce libraries of peptoid-containing macrocycles but also toward other natural product-like macrocycles such as, e.g., oxazole-containing macrocycles.[4]

These first examples of Passerini-MiBs were performed by employing the same type of pseudo-high-dilution protocols previously used for Ugi-MiBs. That is, high dilution was mimicked by adding slowly over several hours (via syringe pump) the two bifunctional building blocks to a solution of the aldehyde at "normal" concentration. Compounds **12** and **15** were obtained in moderate yields by this procedure. It should be noted though that the ester bond from Passerini reactions is quite flexible, which decreases the cyclization propensity compared to that of amides and that significant molecular complexity is created in one pot, with the formation of six new covalent bonds. Improvements of the reaction yields are possible if higher dilution, longer reaction times, or slower addition rates are applied, but then the conditions are certainly not suitable to produce larger macrocycle libraries. As expected, the use of prochiral isobutyraldehyde leads to diastereomeric mixtures as a result of the stereochemically unselective nature of the Passerini-3CR (see Supporting Information).

For the other two possible Passerini-MiB combinations (i.e., diacid/dialdehyde and dialdehyde/diisocyanide), dialdehydes were required. With the stable aromatic aldehydes, the Passerini reaction is rather slow, whereas enolizable aliphatic aldehydes often give side reactions under the acidic conditions required. Thus, an elegant modification of the Passerini-3CR recently reported by Zhu and co-workers[13] was probed. This versatile procedure uses (mono)alcohols oxidized in situ to form (mono)-aldehydes that are not commercially available or that are very difficult to synthesize as building blocks. An extension of this protocol to the synthesis of macrocycles with in situ-generated dialdehydes is even more demanding: reaction times are longer, and dialdehydes are even more misbehaved based on their fast intramolecular reactions. However, after some adaption to the MiB approach, compounds **18** and **20** could be synthesized by the first MiB-application of the oxidative Passerini reaction. Commercially available triethylene glycol (**16**) was selected as the diol component as illustrated in Scheme 4 and used to probe the diacid/dialdehyde and diisocyanide/dialdehyde combinations. The original conditions for the oxidative Passerini-3CRs (isocyanide/alcohol/acid/IBX = 1:1.5:1.5:2.0) were adjusted for bifunctional building blocks and for pseudo-high-dilution conditions to enable the formation of macrocycles based on a double Passerini-3CR process (see Experimental Section).

The easy implementation of all combinations of Passerini-MiBs even with rather flexible building blocks supports the great potential of this concept toward the diversity-oriented synthesis of macrocycles.[2] It is now evident that the facile access to structurally diverse macrocyclic scaffolds is possible not only by tuning the combination of bifunctional building blocks used for each MCR but also by using different kinds of MCRs, isonitrile-based or not. For example, compound **18** is a bis-macrolactam bearing acyloxy functionalities appended to the macrocyclic skeleton, whereas compound **20** is a bis-macrolactone having exocyclic amide groups.

Conclusions

It was shown that the MiB-approach to macrocycles is limited to neither Ugi-type nor isonitrile-based MCRs. The versatility and wide scope of the MiB methodology to produce complex macrocyclic structures in one pot and in a straightforward manner with multiple functional groups was successfully extended to multiple Staudinger-3CRs and Passerini-3CRs. In case of the tetra-β-lactam macrocycles, 12 bonds (three per β-lactam ring) are formed in one step with overall yields between 33% and 82% including the macrocyclization. Also, this reaction can be used for the generation of imine-exchange-based dynamic combinatorial libraries.[12a] The use of the more easily available alcohols in the Passerini reaction increases the possibilities of this reaction to access difficult frameworks, potentially including such not available otherwise because the corresponding aldehydes lack stability.

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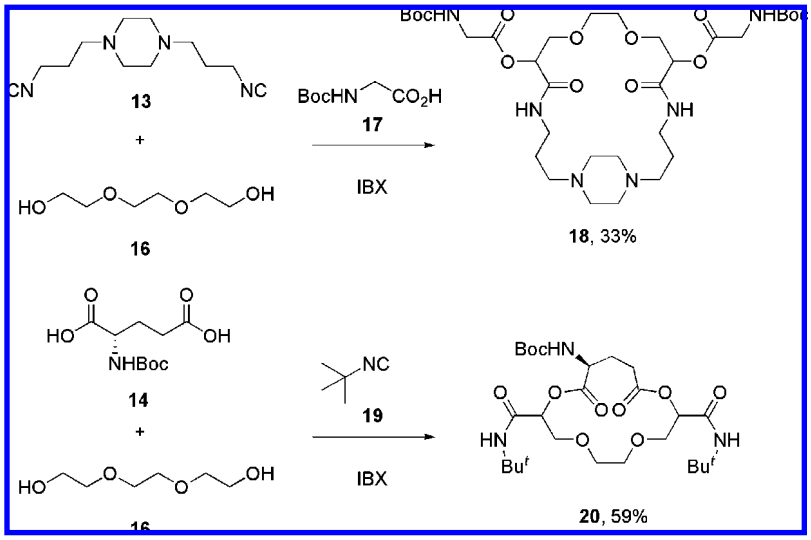
SCHEME 4. MiBs Based on the Passerini-Zhu-3CR That Involves Diols and (Di)isocyanides or (Di)acids under Oxidative Conditions[a]



[a] Reactions were conducted in THF and kept between 35 °C and 40 °C. IBX: 2-iodoxybenzoic acid.

Experimental Section

General Procedure for the Synthesis of Staudinger-3CR-Based Macrocycles (4, 6, and 8). To a stirred mixture of dialdehyde (1.5 mmol) in CH_2Cl_2 (100 mL) and activated 4 Å molecular sieve (600 mg) was slowly added the diamine (1.5 mmol) in 50 mL CH_2Cl_2 using a syringe pump (flow rate 1.2 mL/h). After addition was completed, the mixture was cooled to −50 °C, and Et_3N (2.5 mL, 18 mmol) and methoxyacetyl chloride (6 mmol) were added in this sequence. The resulting mixture was left overnight to warm to room temperature, and the molecular sieve was filtered off through a pad of celite and rinsed thoroughly with CH_2Cl_2. The combined filtrates were washed with 1 M HCl, water, dried with Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography.

Compound 4 (Mixture of *cis*-Lactam Diastereomers). Dialdehyde **1** (300 mg, 2.22 mmol), diamine **2** (325 μL, 2.22 mmol), triethylamine (3.7 mL, 26.3 mmol), and methoxyacetyl chloride (0.82 mL, 8.88 mmol) were reacted according to the general procedure for the synthesis of Staudinger-3CR-based macrocycles described above. Flash column chromatography purification (CH_2Cl_2/MeOH 25:1; 25 g of silica) afforded tetralactam macrocycle **4** (382 mg, 44%) as a brown oil. R_f = 0.48 (CH_2Cl_2/MeOH 8:1). IR (ATR, cm^{-1}): ν = 3025, 2967, 2925, 1747, 1600, 1456, 1116, 1025. ^1H NMR ($CDCl_3$) δ 7.79 ,7.75, 7.69 (t, 2H, J = 7.7 Hz, Py), 7.35 (d, 1H, J = 7.5 Hz, Py); 7.31−7.26 (m, 3H, Py); 5.04 (d, 1H, J = 4.8 Hz, C*H*); 5.03 (d, 1H, J = 4.8 Hz, C*H*); 5.01 (d, 1H, J = 4.8 Hz, C*H*); 5.00 (d, 1H, J = 4.8 Hz, C*H*); 4.79 (d, 1H, J = 4.6 Hz, C*H*); 4.78 (d, 1H, J = 4.6 Hz, C*H*); 4.75 (d, 1H, J = 4.6 Hz, C*H*); 4.73 (d, 1H, J = 4.6 Hz, C*H*); 3.70−3.15 (m, 24H, 12 × CH_2); 3.10 (s, 3H, CH_3O); 3.08 (s, 3H, CH_3O); 3.07 (s, 3H, CH_3O); 3.06 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$) δ 171.6, 169.6, 167.18, 167.16, 167.13, 167.11, 155.1, 154.9, 154.82, 154.81, 136.5, 136.4, 136.3, 121.7, 121.6, 121.55, 121.5, 86.0, 85.95, 85.9, 71.9, 71.8, 70.1, 70.0, 69.9, 69.8, 69.7, 69.4, 68.5, 68.4, 68.2, 68.1, 64.2, 64.0, 59.3, 59.2, 58.3, 58.26, 58.2, 40.7, 40.5, 40.4, 38.6. HRMS (ESI-FT-ICR) *m/z*: 805.3372 $[M + Na]^+$; calcd for $C_{38}H_{50}O_{12}N_6Na$ 805.3379.

Compound 6 (Mixture of *cis*-Lactam Diastereomers). Dialdehyde **1** (485 mg, 3.59 mmol), diamine **5** (235 μL, 3.59 mmol), triethylamine (2.3 mL, 16.4 mmol), and methoxyacetyl chloride (495 μL, 5.38 mmol) were reacted according to the general procedure for the synthesis of Staudinger-3CR-based macrocycles described above. Flash column chromatography purification (CH_2Cl_2/MeOH 40:1; 50 g of silica) afforded tetralactam macrocycle **6** (449 mg, 33%) as a brown solid. R_f = 0.5 (CH_2Cl_2/MeOH 16:1). IR (ATR, cm^{-1}): ν = 3052, 2924, 1754, 1459, 1395, 1348, 1212, 1041. ^1H NMR ($CDCl_3$) δ 7.77−7.69 (m, 2H, 2×C*H*); 7.41−7.28 (m, 4H, 4×C*H*); 7.34−7.27 (m, 4H, 4 × C*H*); 6.93−6.45 (m, 4H, 4 × C*H*); 4.95−4.88 (m, 4H, 4 × C*H*); 4.86−4.81 (m, 4H, 4 × C*H*); 4.79−4.70 (m, 4H, 2 × CH_2); 4.68−4.57 (m, 4H, 2 × CH_2); 3.06 (s, 3H, CH_3O); 3.05 (s, 3H, CH_3O); 3.03 (s, 3H, CH_3O); 2.99 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$) δ 166.8, 166.3, 166.1, 166.0, 165.7, 154.4, 154.1, 154.0, 136.4, 136.1, 135.6 135.2, 134.4, 134.3, 134.2, 131.7, 130.2, 130.1, 129.6, 129.5, 129.3, 128.7, 128.4, 127.6, 127.0, 126.8, 122.2, 122.1, 121.7, 121.2, 121.0, 120.9, 86.2, 86.1, 86.0, 85.9, 85.8, 63.2, 62.9, 62.6, 62.5, 62.1, 61.9, 61.5, 58.7, 58.5, 58.4, 58.3, 58.2, 58.18, 58.15, 44.7, 44.6, 44.5, 44.4, 44.3. HRMS (ESI-FT-ICR) *m/z*: 781.2934 $[M + Na]^+$; calcd for $C_{42}H_{42}O_8N_6Na$ 781.2956. Anal. Found: C 66.8 H 5.9 N 11.3. Calcd: C 66.5 H 5.6 N 11.1.

Compound 8 (Mixture of *cis*-Lactam Diastereomers). Dialdehyde **7** (100 mg, 0.75 mmol), diamine **5** (100 μL, 0.75 mmol), triethylamine (1.3 mL, 8.95 mmol), and methoxyacetyl chloride (275 μL, 2.98 mmol) were reacted according to the general procedure for the synthesis of Staudinger-3CR-based macrocycles described above. Flash column chromatography purification (CH_2Cl_2/MeOH 32:1; 7 g of silica) afforded tetralactam macrocycle **8** (231 mg, 82%) as a brown solid. R_f = 0.44 (CH_2Cl_2/MeOH 16:1). IR (ATR, cm^{-1}) ν = 3060, 2930, 1751, 1436, 1399, 1209, 1145, 1095, 1036. ^1H NMR ($CDCl_3$) δ 7.38−7.26 (m, 4H, 4 × C*H*-Ph); 7.22−7.19 (d, 8H, J = 8.6 Hz, 8 × C*H*-Ph); 7.06, 6.89, 6.87, 6.63, 6.53, 6.46, 6.31 (s, 4H, C*H*-Ph); 4.78 (m, 2H, 2 × C*H*); 4.72 (d, 2H, J = 4.8 Hz, 2 × C*H*); 4.63 (d, 2H, J = 4.1 Hz, 2 × C*H*); 4.61 (m, 2H, 2 × C*H*); 4.55 (d, 2H, J = 4.1 Hz, 2 × C*H*); 4.43−4.36 (m, 1H, C*H*); 4.26−4.21 (m, 1H, C*H*); 3.86−3.62 (m, 4H, 4 × C*H*); 3.15 (s, 3H, CH_3O); 3.09 (s, 3H, CH_3O); 3.02 (s, 3H, CH_3O); 3.00 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$) δ 166.6, 166.5, 166.4, 166.0, 165.9, 135.2, 134.8, 134.5, 134.4, 134.1, 134.0, 133.8, 133.7, 133.6, 130.0, 129.9, 129.6, 129.3, 129.2, 128.5, 128.4, 128.3, 128.0, 127.6, 86.1, 86.0, 85.8, 85.5, 85.4, 62.3, 61.4, 61.0, 60.8, 60.7, 60.5, 60.2, 58.3, 58.2, 58.1, 58.0, 57.9, 45.5, 44.1, 44.0, 43.8, 43.7. HRMS (ESI-FT-ICR) *m/z*: 779.3045 $[M + Na]^+$; calcd for $C_{44}H_{44}O_8N_4Na$ 779.3051. Anal. Found: C 70.2 H 6.2 N 7.9. Calcd: C 69.8 H 5.9 N 7.4.

General Procedure for the Synthesis of Passerini-3CR-Based Macrocycles (12 and 15). Solutions of diacid (1.5 mmol) and of

diisocyanide (1.5 mmol) in 50 mL CH_2Cl_2 each were slowly added in parallel by a syringe pump (flow rate 0.6 mL/h) to isobutyraldehyde (3 mmol) in 100 mL of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred overnight and then concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica eluting with CH_2Cl_2/MeOH/NEt_3 to afford the corresponding macrocycles.

Compound 12 (Diastereomeric Mixture). Diacid **10** (416.5 mg, 3.2 mmol), diisocyanide **9** (500 mg, 3.2 mmol), and isobutyraldehyde (0.88 mL, 9.6 mmol) were reacted according to the general procedure for the synthesis of Passerini-3CR-based macrocycles described above. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1; 20 g of silica) afforded bis-Passerini-macrocycle **12** (436 mg, 32%) as a white solid. $R_f = 0.4$ (CH_2Cl_2/MeOH 8:1). IR (ATR, cm^{-1}): ν = 3308, 3089, 2967, 2930, 1728, 1662, 1540, 1436, 1321, 1141, 1001. ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 2H, C*H*-Ph); 7.18 (m, 2H, C*H*-Ph); 6.46 (d, 1H, J = 19.9 Hz, CH_2); 6.00 (m, 1H N*H*); 5.85 (m, 1H N*H*); 5.76 (d, 1H, J = 21.0 Hz, CH_2); 5.23−5.15 (m, 1H, C*H*); 4.8−4.74 (m, 1H, C*H*); 4.62−4.57 (m, 1H, CH_2); 4.54−4.50 (m, 1H, CH_2); 4.34−4.28 (m, 1H, CH_2); 4.15 (dd, 1H, J = 13.7/4.8 Hz, CH_2); 4.01 (dd, 1H, J = 13.7/4.8 Hz, CH_2); 3.55−3.50 (m, 1H, CH_2); 3.43−3.38 (m, 1H, CH_2); 2.44 (m, 1H, C*H*); 2.30 (m, 1H, C*H*); 1.02 (d, 3H, J = 6.8 Hz, (CH_3)$_2$C*H*); 0.99 (d, 3H, J = 6.8 Hz, (CH_3)$_2$C*H*); 0.95 (d, 3H, J = 6.8 Hz, (CH_3)$_2$C*H*); 0.91 (d, 3H, J = 6.8 Hz, (CH_3)$_2$C*H*). ^{13}C NMR ($CDCl_3$) δ 172.1, 172.0, 169.7, 169.0, 168.7, 168.5, 164.9, 164.7, 138.2, 138.1, 137.8, 137.2, 132.7, 131.3, 131.1, 130.6, 130.5, 128.9, 128.8, 128.7, 128.6, 127.82, 127.8, 81.0, 80.9, 80.1, 78.6, 52.3, 43.7, 43.1, 43.0, 42.7, 37.6, 34.4, 30.5, 29.9, 29.6, 19.2, 19.0, 18.7, 17.9, 17.8, 16.5. HRMS (ESI-FT-ICR) *m/z*: 453.1991 [M + Na]$^+$; calcd for $C_{23}H_{30}O_6N_2Na$ 453.1996. Anal. Found: C 64.6 H 7.5 N 6.9. Calcd: C 64.2 H 7.0 N 6.5.

Compound 15 (Diastereomeric Mixture). Diacid **14** (500 mg, 2.02 mmol), diisocyanide **13** (445 mg, 2.02 mmol), and isobutyraldehyde (0.55 mL, 6.06 mmol) were reacted according to the general procedure for the synthesis of Passerini-3CR-based macrocycles described above. Flash column chromatography purification (CH_2Cl_2/MeOH 30:1; 40 g of silica) afforded macrocycle **15** (456 mg, 37%) as a brown oil. $R_f = 0.29$ (CH_2Cl_2/MeOH 10:1). IR (ATR, cm^{-1}): ν = 3305, 2976, 2937, 1736, 1709, 1666, 1391, 1367, 1167, 1051. ^{1}H NMR ($CDCl_3$) δ 5.96 (m, 1H, N*H*); 5.60 (m, 1H, N*H*); 5.05−5.00 (m, 1H, C*H*); 4.95−4.91 (m, 1H, C*H*); 4.83 (dd, 1H, J = 10.6/3.5 Hz, C*H*); 4.13−4.06 (m, 2H, CH_2); 3.76−3.70 (m, 2H, CH_2); 3.64 (m, 2H, CH_2); 1.45 (s, 3H, (CH_3)$_3$C); 1.43 (s, 3H, (CH_3)$_3$C); 0.97−0.92 (m, 12H, 4 × CH_3). ^{13}C NMR ($CDCl_3$) δ 174.1, 172.2, 172.1, 171.9, 171.0, 169.5, 169.1, 169.0, 168.9, 168.7, 168.3, 155.5, 155.4, 80.8, 80.5, 80.4, 79.5, 79.0, 78.7, 77.2, 60.2, 54.5, 53.4, 52.6, 52.1, 51.5, 30.9, 30.8, 30.5, 30.4, 30.2, 28.4, 28.36, 28.3, 19.3, 19.1, 19.0, 18.9, 18.8, 18.6, 17.4, 17.1, 16.8, 16.6, 16.4. HRMS (ESI-FT-ICR) *m/z*: 612.3960 [M + H]$^+$; calcd for $C_{30}H_{54}O_8N_5$ 612.3967.

Passerini-3CR-Based Macrocycle Synthesis using IBX/Alcohol as Aldehyde Substitute (Synthesis of Macrocycle 18). *tert*-Butoxycarbonylglycine (700 mg, 3.99 mmol) and IBX (1.50 g, 5.35 mmol) in THF (150 mL) were warmed to 40 °C under stirring. Triethylene glycol (270 μL, 2.0 mmol) in 50 mL of THF and 1,4-bis(3-isocyanopropyl)piperazine (293 mg, 1.33 mmol) in 50 mL of THF were slowly added in parallel by syringe pump (flow rate 0.6 mL/h). After complete addition, the heterogeneous mixture was stirred for 16 h, diluted with CH_2Cl_2, and filtered through a pad of celite. The filtrate was evaporated to dryness. The crude oil was dissolved in 200 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ solution and water, and concentrated using a rotavap. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1; 50 g of silica) afforded **18** (248 mg, 26%) as a brown oil (diastereomeric mixture). $R_f = 0.15$ (CH_2Cl_2/MeOH 8:1). IR (ATR, cm^{-1}): ν = 3300, 2970, 2952, 1728, 1675, 1360, 1154, 1016. ^{1}H NMR ($CDCl_3$) δ 5.30 (m, 2H, 2 × C*H*); 4.00 (m, 2H, 2 × CH_2); 3.92 (m, 2H); 3.80−3.56 (m, 8H, 4 × CH_2); 3.38 (m, 2H, 2 × CH_2); 3.1−2.6 (m, 8H, 4 × CH_2); 1.94−1.72 (m, 4H, 2 × CH_2); 1.44 (s, 9H, (CH_3)$_3$C); 1.43 (s, 9H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$) δ 174.4, 170.4, 155.8, 80.3, 80.0, 79.3, 73.8, 70.1, 53.4, 52.3, 50.1, 43.6, 42.8, 42.3, 28.4, 24.5. HRMS (ESI-FT-ICR) *m/z*: 717.4021 [M + H]$^+$; calcd for $C_{32}H_{56}O_{12}N_6$ 717.4029.

Synthesis of Macrocycle 20 (Diastereomeric Mixture). A mixture of *tert*-butoxycarbonylglutamic acid (494 mg, 2.0 mmol) and IBX (1.5 g, 5.35 mmol) in THF (150 mL) was warmed to 40 °C under stirring. Triethylene glycol (270 μL, 2.0 mmol) in 50 mL of THF and *tert*-butyl isocyanide (305 μL, 2.66 mmol) in 50 mL of THF were slowly added in parallel by syringe pump (flow rate 0.6 mL/h). After complete addition, the heterogeneous mixture was stirred for 16 h, diluted with CH_2Cl_2, and filtered through a pad of Celite. The filtrate was evaporated to dryness. The crude oil was dissolved in 200 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ solution and water, and concentrated using a rotavap. Flash column chromatography purification (CH_2Cl_2/MeOH 20:1; 50 g of silica) afforded **20** (668 mg, 59%) as a brown oil. $R_f = 0.48$ (CH_2Cl_2/MeOH 8:1). IR (ATR, cm^{-1}): ν = 3303, 2969, 2930, 1713, 1670, 1426, 1162. ^{1}H NMR ($CDCl_3$) δ 6.27 (br. s, 1H, N*H*); 6.06 (br. s, 1H, N*H*); 5.30 (dd, 1H, J = 5.4/3.0 Hz, C*H*); 5.22 (dd, 1H, J = 5.5/4.4 Hz, C*H*); 5.15 (d, 1H, J = 6.9 Hz, C*H*); 3.88−3.82 (m, 2H, CH_2); 3.79−3.76 (m, 2H, CH_2); 3.64−3.56 (m, 4H, 2 × CH_2); 2.58−2.47 (m, 1H, CH_2); 2.36−2.26 (m, 1H, CH_2); 2.04−1.91 (m, 2H, CH_2); 1.44 (s, 9H, (CH_3)$_3$C); 1.37 (s, 9H, (CH_3)$_3$C); 1.36 (s, 9H, (CH_3)$_3$C). ^{13}C NMR ($CDCl_3$) δ 171.5, 171.4, 171.0, 166.5, 166.4, 166.2, 165.9, 155.3, 80.5, 77.2, 74.0, 73.9, 70.7, 70.6, 70.4, 70.0, 69.8, 62.3, 53.7, 51.7, 51.6, 31.0, 29.8, 28.8, 28.7, 28.6, 28.4, 28.3. HRMS (ESI-FT-ICR) *m/z*: 582.2983 [M + Na]$^+$; calcd for $C_{26}H_{45}O_{10}N_3Na$ 582.2997.

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Supporting Information Available: Selected NMR and HR-FT-ICR spectra and HPLC analysis of final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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