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# Synthesis of Macrocycles Derived from Substituted Triazines

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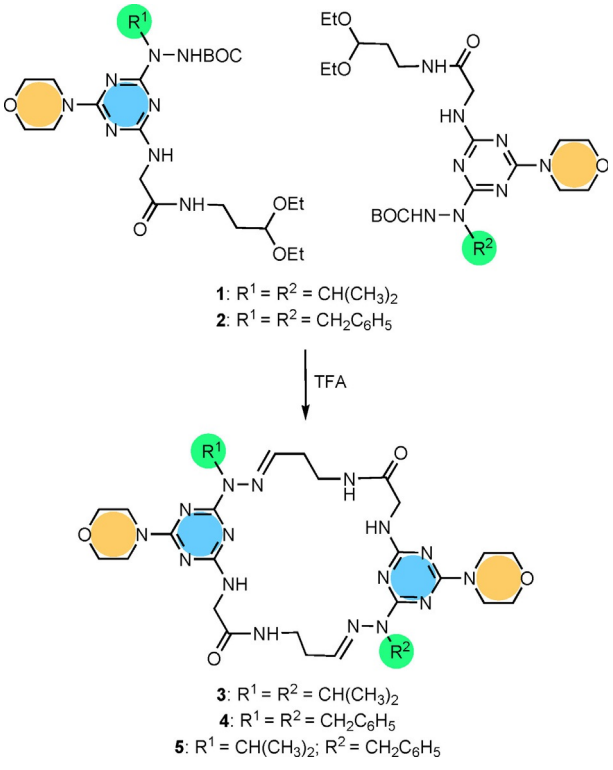
A triazine ring derivatized with morpholine, an *N*-alkyl-*N*′-BOC-hydrazine (alkyl = isopropyl or benzyl) and the diethylacetal of glycinylpropionaldehyde undergoes spontaneous dimerization in good yields upon acid-catalyzed deprotection. The resulting 24-member macrocycles can be characterized by NMR spectroscopy, mass spectrometry, and single crystal X-ray diffraction. In the solid state, both homodimers adopt a taco-like conformation. Although each shows π–π stacking between the triazine rings, different patterns of hydrogen bonds emerge. The crystal structure of the isopropyl dimer shows that it includes two molecules of trifluoracetic acid per macrocycle. The trifluoroacetate anion charge balances the protonated triazines, which engage in bifurcated hydrogen bonds with the carbonyl acceptor of the distant glycine. This carbonyl also forms a hydrogen bond with the NH of the proximate glycine. The crystal structure of the benzyl derivative does not include trifluoracetic acid. Instead, two hydrogen bonds form, each between a glycine NH and the lone pair of the C=N nitrogen of the hydrazine group. In the solid state, both molecules present the alkyl side chains and morpholine groups in close proximity. A heterodimer is accessible in approximately statistical yields—along with both homodimers—by mixing the two protected monomers prior to subjecting them to deprotection.

## Introduction

Macrocycles—both naturally occurring and synthetic—have captured the attention of chemists for decades for reasons of biological activity,[1] interesting topologies[2] that can be incorporated into molecular machines,[3] devices[4] and sensors,[5] and as testing grounds for the limits of synthetic methodology.[6] Whereas some classes of macrocycles, including cyclodextrins,[7] calixarenes[8] and related constructions,[9] are amenable to facile synthesis, most present challenges. Thus, macrocyclization has been probed by using template-directed strategies[10] and a variety of synthetic methods[11,12] including stapling[13] or the incorporation of labile covalent bonds such as the formation of disulfides,[14] imines,[15] and hydrazones[16] to take advantage of self-assembly.[17] Herein, we report the fortuitous and selective macrocyclization of substituted triazines containing both a protected hydrazine group and masked aldehyde. Upon acid-catalyzed deprotection of **1** or **2**, dimerization yields 24-membered rings **3** or **4**, respectively (Scheme 1). Characterization of these macrocycles is afforded by $^{1}$H and $^{13}$C NMR spectroscopies, mass spectrometry, LC-MS, HPLC, and single-crystal X-ray diffraction. A mixture containing heterodimer **5** can also be accessed (vide infra).




**Scheme 1.** Strategy for macrocyclization.

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## Results and Discussion

### Synthesis of precursors 1 and 2

Compositional differences between **1** and **2** rest on the choice of alkyl group on the hydrazine residue. *N*-Isopropyl-*N*′-BOC-hydrazine[18] (for **1**) and *N*-benzyl-*N*′-BOC-hydrazine[19] (for **2**) were prepared starting with *tert*-butyl carbazate. Following 12 hours' incubation with an excess of either acetone or benzaldehyde in ether at room temperature, the solvent was removed. The residues were redissolved in anhydrous tetrahydrofuran, and sodium cyanoborohydride was added. For the isopropyl derivative, acetic acid was added at low temperature, and, following warming, the reaction mixture stirred for 30 hours. For the benzyl derivative, toluene sulfonic acid and bromocresol green were used at room temperature for 2 hours.

The syntheses of precursors **1** and **2** takes advantage of the stepwise substitution of cyanuric chloride (Scheme 2). First, the appropriate alkylated *tert*-butylcarbazate is added to cyanuric chloride. Morpholine is then added at room temperature to yield **6** or **7**. Microwave irradiation is employed to facilitate substitution with ethyl glycinate to yield intermediate **8** or **9**.[20] Following saponification[21] of each to **10** or **11**, EDC-mediated couplings[22] with 1-amino-3,3-diethyoxypropane completes the syntheses. In summary, **3** and **4** are obtained as a white solids in five steps with overall yields of 38 and 35%, respectively. The detailed characterization of these intermediates is provided below and spectra of the intermediates appear in the Supporting Information.

### Synthesis and characterization of macrocycles 3 and 4

Dissolution of **1** or **2** in a 1:1 mixture of dichloromethane and trifluoroacetic acid (TFA)[23] followed by stirring for 12 hours yields macrocycles **3** or **4**, respectively. To purify these materials, the solvent is removed, and the residues are resuspended in hexanes. The suspension is pelleted by centrifugation to give **3** in 88% yield. Pelleting by centrifugation followed aluminium oxide gel chromatography yields **4** in 93% yield. These macrocycles were characterized by MS, $^{1}$H and $^{13}$C NMR spectroscopies, LC-MS, HPLC, and single-crystal X-ray diffraction. The appearance of signals in the $^{1}$H NMR corresponding to the methyne –N=CH– between 7.5 and 8.0 ppm is indicative of hydrazone formation.

### Solid-state structures of 3 and 4

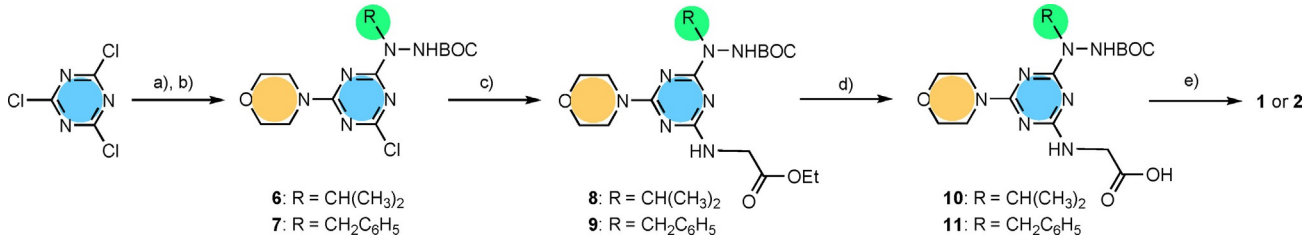
The crystal structures of **3** and **4** are detailed in Figures 1–3, and crystallographic data appear in Table S1 in the Supporting Information. Briefly, the structure of **3** was solved and refined in the triclinic space group *P*-1, with $Z=2$. Each macrocycle cocrystallizes with two molecules of TFA. The basicity of the triazine ($pK_a \approx 5$) leads to disproportionation of TFA. Protonation of the triazine occurs on the nitrogen opposite the morpholine substituent. For **3**, This proton and the NH of adjacent glycine residue form a bifurcated hydrogen bond with the carbonyl group of the distant glycine as shown schematically in Figure 1.

This network of hydrogen bonds forms the bottom of the "taco". The sidewalls are created by π–π stacking of the triazine rings. Edge and side views are provided in Figure 2A and B (with the trifluoroacetate anions omitted for clarity), which reveal the taco-like shape of the macrocycle in the solid state. The figure also reveals that the substituents—the isopropyl groups and morpholine rings—occupy the top edge of the structure in close proximity (indicated with a purple arc in Figure 1). Figure 3 shows the thermal ellipsoids for **3**.

Unlike **3**, macrocycle **4** does not co-crystallize with TFA. Still, this neutral molecule adopts a similar taco-like shape, as shown in Figure 2. Briefly, macrocycle **4** crystallizes in the monoclinic space group $P2_1/c$ with $Z=2$. Two symmetric hydrogen bonds were identified with the –C=N– nitrogen acting as the acceptor and the proximate NH of the glycinamide donating the hydrogen. These interactions are illustrated in Figure 1B. The crystal structure of **4** shows less π–π stacking of the triazines that create the side walls of the taco than **3**, but as before, the substituents—both benzyl groups and both morpholines—are clustered along the upper rim of the architecture. Figures 2B and 3B provide edge and side views as well as thermal ellipsoids derived from the solid-state structure.

### Heterodimer 5

To complete this preliminary study, a 1:1 mixture of **1** and **2** was dissolved in dichloromethane/TFA (1:1). After 12 hours of stirring, the solvent was removed, and the residue was resuspended in hexanes. A pellet obtained by centrifugation was analyzed by NMR spectroscopy and mass spectrometry. All three expected products were identified; **3**, **4**, and **5** in ratios that approximate the statistical expectation. That is, the mix-




**Scheme 2.** Facile synthesis of the protected precursors. a) *N*-alkyl-*tert*-butylcarbazate, (0.95 equiv), DIPEA (3.5 equiv), anhydrous THF, 0 °C, 2 h; b) morpholine (1.05 equiv), RT, 12 h; c) glycine ethyl ester hydrochloride (3 equiv), DIPEA (3.5 equiv), 1,4-dioxane, microwave, 90 °C, 3 h; d) NaOH (3 equiv), MeOH/$H_2O$/THF (1:1:1, *v*/*v*/*v*), RT, 12 h; e) 1-amino-3,3-diethoxypropane (1.2 equiv), EDC·HCl (1.5 equiv), HOBt (1.5 equiv), DIPEA (3 equiv), RT, 12 h.

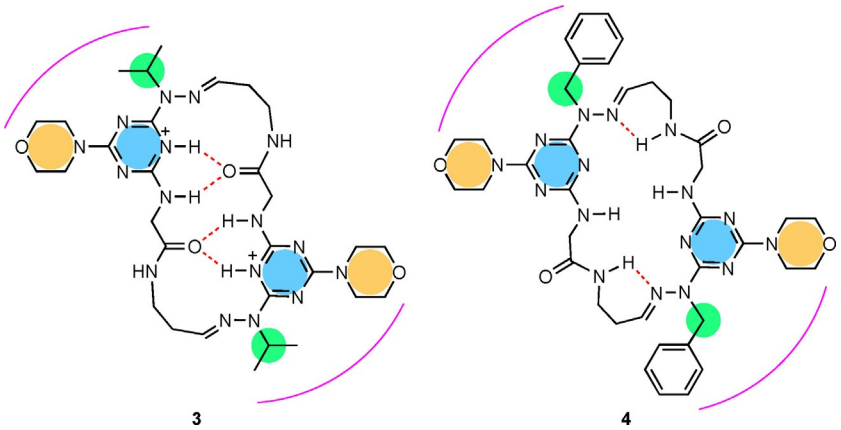



**Figure 1.** The pattern of hydrogen bonds formed in the solid-state structures of A) **3** and B) **4**. The purple arcs identify groups at the top edges of the "tacos". Hydrogen bonds are indicated with dotted red lines.

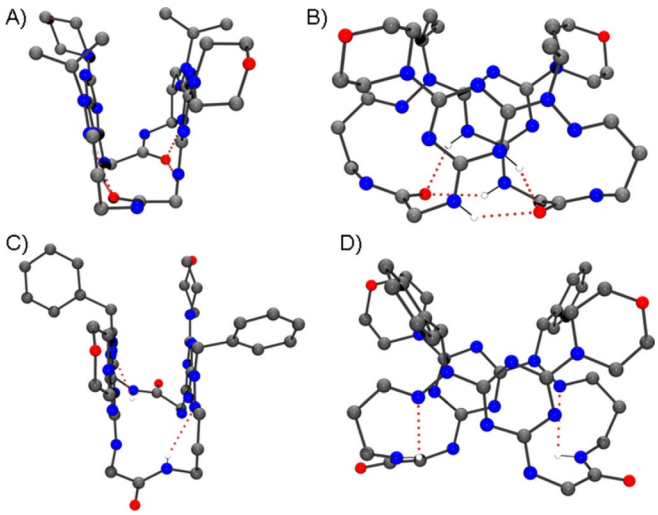



**Figure 2.** Solid-state structures of **3** (top) and **4** (bottom) shown from the edge (left) and side (right) with hydrogen bonds shown as dotted red lines.

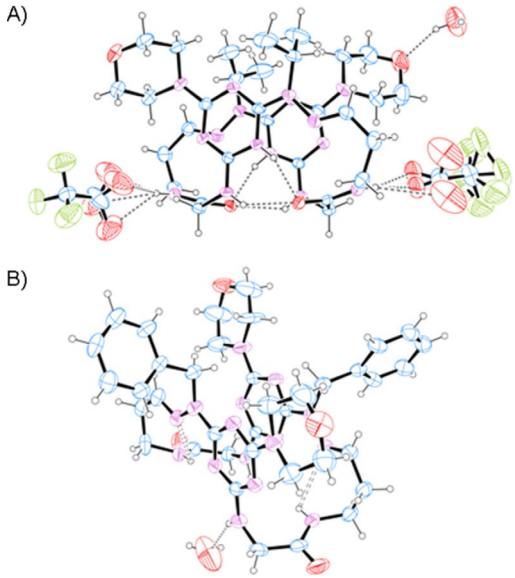



**Figure 3.** Thermal ellipsoids from the solid-state structures of A) **3** and B) **4**.

ture appeared to be 50% **3**+**4** and 50% **5**. Slight deviation from the expected 1:2:1 ratio is attributed to the different solubility of these materials in hexanes. The trace from LC-MS and the corresponding mass spectra are shown in Figure 4.

## Conclusion

The fortuitous dimerization of monomers **1** and **2** to form macrocyclic dimers offers a route to compositional diversity. In addition to being readily accessible by synthesis, the protected monomers offer three sites for manipulation: the substituent on the triazine ring (here, morpholine), the *N*-alkyl substituent on the hydrazine group (here, isopropyl or benzyl), and the choice of amino acid (here, glycine). The scope and limitations of substitution at these positions remains to be determined in terms of both ready access to macrocyclization and conservation of shape.

## Experimental Section

**General procedure:** All reagents and solvents were obtained from commercial sources and used as received, unless noted otherwise. NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer. $^{1}$H NMR chemical shifts were referenced to $CDCl_3$ (7.26 ppm), $D_2O$ (4.80 ppm), $CD_3OD$ (3.31 ppm), and [$D_6$]DMSO (2.55 ppm). $^{13}$C NMR chemical shifts were referenced to $CDCl_3$ (77.23 ppm), $CD_3OD$ (49.86 ppm), and [$D_6$]DMSO (39.52 ppm). High-resolution mass spectra were recorded on an Agilent Technologies 6224 TOF LC/MS system.

***tert*-Butyl 2-benzylhydrazonecarboxylate:** The procedure follows a known synthesis.[18] Freshly distilled benzaldehyde (6.30 g, 59.4 mmol) was added to a stirred solution of *tert*-butylcarbazate (6.00 g, 45.5 mmol) in $Et_2O$ (30 mL) at RT. After 12 h, the precipitate was filtered, washed with cold $Et_2O$, and dried under vacuum to yield as a white solid (8.23 g, 77%). $^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 8.13 (s, 1H), 7.73–7.65 (m, 2H), 7.39–7.34 (m, 3H), 1.56 ppm (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 152.5, 143.7, 133.9, 129.8, 128.6, 127.2, 81.5, 28.3 ppm.

***tert*-Butyl-2-benzylidenehydrazine-1-carboxylate:** The procedure follows a known synthesis.[19] $NaBH_3CN$ (2.82 g, 44.9 mmol) was slowly added to a stirred solution of *tert*-butyl-2-benzylidenehydra-

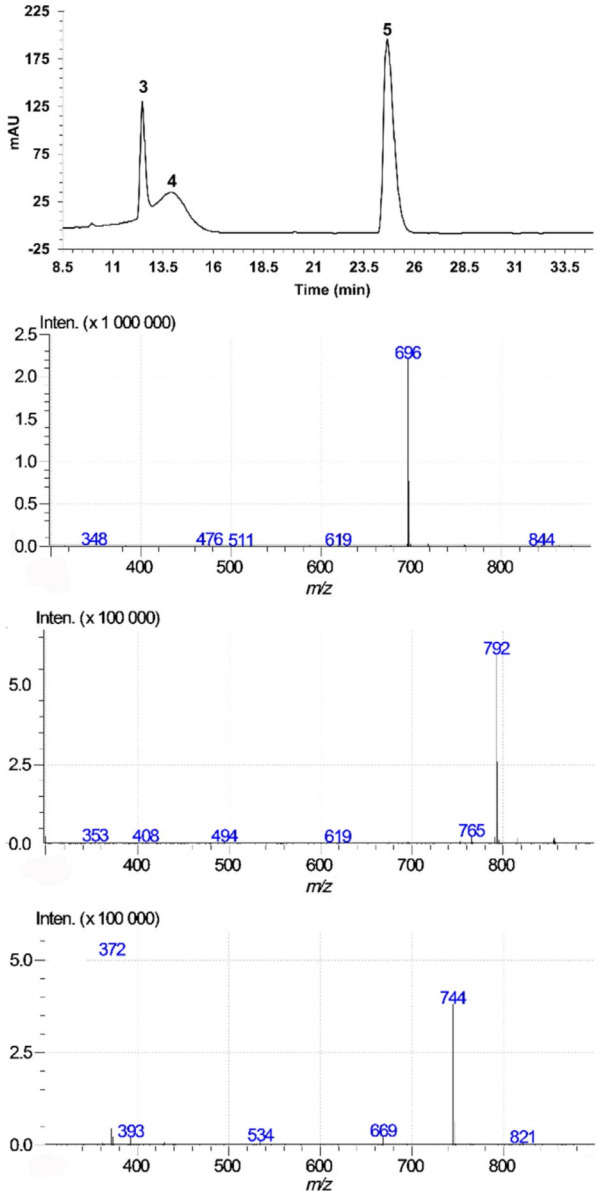



**Figure 4.** A) The chromatography trace of the reaction yielding **5** and the mass spectra of macrocycles B) **3**, C) **4**, and D) **5** obtained by LC-MS.

zone-1-carboxylate (4.00 g, 18.0 mmol) in dry THF (40 mL) at 0 °C. Acetic acid (27.0 mL, 471.1 mmol) was then added, and the mixture was stirred for 18 h at room temperature. An additional amount of $NaBH_3CN$ (2.82 g, 44.9 mmol) was added, and the reaction mixture was stirred for 12 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with sat. $NaHCO_3$ (100 mL) and ethyl acetate (2×100 mL). The organic layer was collected and concentrated in vacuo. The crude product was dissolved in a mixture of methanol (35 mL) and aqueous NaOH (35 mL, 1 M), and this mixture was stirred at room temperature for 12 h. Following concentration, the product was extracted with $H_2O$ (100 mL) and ethyl acetate (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, hexanes/EtOAc 2:1→1:1) to afford compound **1b** (3.13 g, 78%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.54–7.22 (m, 5H), 4.01 (s, 2H), 1.49 ppm (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 156.7, 137.6, 129.0, 128.5, 127.5, 80.6, 55.8, 28.4 ppm.

***tert*-Butyl 2-isopropylhydrazonecarboxylate:** The procedure follows a known synthesis.[18] Acetone (12.8 mL, 172.1 mmol) was added to a stirred solution of *tert*-butylcarbazate (6.00 g, 45.5 mmol) in $Et_2O$ (24 mL), and the mixture was stirred at room temperature for 12 h. The solvent was removed by rotary evaporation under reduced pressure, and the crude product was purified by flash column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 10:1) to afford a white solid (7.22 g, 92%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.04 (s, 3H), 1.82 (s, 3H), 1.51 ppm (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 152.9, 149.9, 80.9, 28.3, 25.4, 16.0 ppm.

***tert*-Butyl 2-isopropylhydrazinecarboxylate:** The procedure follows a known synthesis.[19] $NaBH_3CN$ (1.47 g, 23.2 mmol) and catalytic bromocresol green were added to a stirred solution of *tert*-butyl 2-isopropylhydrazonecarboxylate (4.00 g, 23.2 mmol) in dry THF (150 mL), then a solution of *p*-toluenesulfonic acid (4.41 g, 23.2 mmol) in dry THF (12 mL) was added dropwise over 1 h. The reaction mixture was maintained between pH 3.5–5.0. After an additional 1 h of stirring, the solvent was removed by rotary evaporation under reduced pressure and extracted with sat. $NaHCO_3$ (100 mL) and ethyl acetate (2×100 mL). The organic layer was collected and concentrated in vacuo. The crude product was dissolved in a mixture of methanol (70 mL) and aqueous NaOH (28 mL, 1 M), and the solution was stirred at room temperature for 2 h. Following concentration, the product was extracted with $H_2O$ (100 mL) and ethyl acetate (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 20:1) to afford a white solid (2.87 g, 71%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.14 (septet, $J$ = 6.3 Hz, 1H), 1.47 (s, 9H), 1.04 ppm (d, $J$ = 6.3 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 156.9, 80.4, 50.7, 28.4, 20.6 ppm.

**Monomer 1**: EDC·HCl (0.49 g, 2.5 mmol), 1-hydroxy-1*H*-benzotriazole (HOBt; 0.39 g, 2.5 mmol), and *N*,*N*-diisopropylethylamine (DIPEA; 0.54 mL, 5.1 mmol) were added to a stirred solution of **10** (0.70 g, 1.7 mmol) in anhydrous THF (6.8 mL). The reaction mixture was stirred for 10 min under argon. 1-Amino-3,3-diethoxypropane (0.28 mL, 2.0 mmol) was then added, and the mixture was stirred at room temperature for 12 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 20:1→9:1) to afford compound **1** (0.72 g, 78%) as clear solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.00–4.80 (m, 1H), 4.57–4.45 (m, 1H), 4.10–3.92 (m, 1H), 3.86–3.56 (m, 11H), 3.55–3.25 (m, 4H), 1.88–1.72 (m, 2H), 1.56–1.36 (m, 9H), 1.27–1.09 ppm (m, 12H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 170.2, 166.2, 165.1, 156.7, 102.6, 81.4, 66.8, 62.0, 48.0, 45.1, 43.6, 35.3, 33.0, 28.2, 19.5, 15.3 ppm; HRMS (ESI) *m/z* calcd for $C_{24}H_{45}N_8O_6$: 541.3462 $[M+H]^+$; found: 541.3573.

**Monomer 2**: EDC·HCl (0.38 g, 1.9 mmol), HOBt (0.30 g, 1.9 mmol), and DIPEA (0.57 mL, 3.3 mmol) were added to a stirred solution of **11** (0.60 g, 1.3 mmol) in anhydrous THF (5.2 mL). The mixture was stirred for 10 min under argon. 1-Amino-3,3-diethoxypropane (0.21 mL, 1.5 mmol) was then added, and the mixture was stirred at RT for 12 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 20:1→9:1) to afford monomer **2** (0.59 g, 77%) as clear solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.42–7.24 (m, 5H), 5.07–4.85 (m, 2H),

4.56–4.44 (m, 1H), 4.13–3.87 (m, 2H), 3.83–3.57 (m, 10H), 3.55–3.25 (m, 4H), 1.89–1.74 (m, 2H), 1.46 (s, 9H), 1.19 ppm (t, $J=6.7$ Hz, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=170.0$, 167.0, 166.6, 165.1, 155.8, 137.8, 128.6, 128.4, 127.3, 102.2, 81.0, 66.8, 61.9, 52.4, 45.1, 43.6, 35.3, 29.7, 28.2, 15.3 ppm; HRMS (ESI) *m/z* calcd for $C_{28}H_{45}N_8O_6$: 589.3462 $[M+H]^+$; found: 589.3616.

**Macrocycle 3:** TFA (2.2 mL) was added to a stirred solution of **1** (0.20 g, 0.37 mmol) in $CH_2Cl_2$ (2.2 mL). The mixture was stirred for 12 h at room temperature. The solvent was removed by rotary evaporation under reduced pressure and subjected to centrifugation after suspension first with hexanes (2×10 mL) then with $Et_2O$ (2×10 mL). The precipitate was filtered and dried to afford macrocycle **3** (0.11 g, 88%) as a white powder. $^1$H NMR ($CD_3OD$, 400 MHz): $\delta=7.86$ (t, $J=2.7$ Hz, 2H), 5.20–4.80 (m, 2H) 4.36–4.29 (m, 2H), 4.23–4.18 (m, 2H), 4.01–3.81 (m, 10H), 3.80–3.64 (m, 10H), 3.11–2.95 (m, 2H), 2.81–2.69 (m, 2H), 1.56–1.36 ppm (m, 12H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=171.3$, 161.2, 155.1, 153.5, 148.2, 66.1, 54.4, 45.0, 43.4, 32.4, 19.5, 17.9 ppm; HRMS (ESI) *m/z* calcd for $C_{30}H_{49}N_{16}O_4$: 697.4123 $[M+H]^+$; found: 697.4300.

**Macrocycle 4:** TFA (1.5 mL) was added to a stirred solution of **2** (0.15 g, 0.25 mmol) in $CH_2Cl_2$ (1.5 mL). The mixture was stirred for 12 h at room temperature. The solvent was removed by rotary evaporation under reduced pressure and subjected to centrifugation after suspension in hexanes (2×10 mL) then $Et_2O$ (2×10 mL). The precipitate was filtered, dried, and purified by alumina flash column chromatography ($Al_2O_3$, $CH_2Cl_2$/MeOH 9:1) to afford macrocycle **4** (92 mg, 93%) as a white powder. $^1$H NMR ($CD_3OD$, 400 MHz): $\delta=7.5$ (s, 2H), 7.40–7.22 (m, 10H), 5.40–5.25 (m, 4H), 4.33–4.20 (m, 4H), 4.00–3.63 (m, 20H), 2.68–2.58 ppm (m, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=171.1$, 161.6, 146.1, 133.7, 128.8, 127.7, 126.3, 66.1, 45.1, 44.9, 43.2 33.3, 32.0 ppm; HRMS (ESI) *m/z* calcd for $C_{38}H_{49}N_{16}O_4$: 793.4123 $[M+H]^+$; found: 793.4374.

**Heterodimer 5**: TFA (0.5 mL) was added to a stirred solution of **2** (30 mg, 0.05 mmol) and **1** (27 mg, 0.05 mmol) in $CH_2Cl_2$ (0.5 mL). The mixture was stirred for 12 h at room temperature. The solvent was removed by rotary evaporation under reduced pressure. The residue was suspended in hexanes and subjected to centrifugation to produce a pellet (2×10 mL). The procedure was repeated with $Et_2O$ (2×10 mL). The precipitate was filtered and dried to afford a total yield of 77% in which macrocycle **3** (1.7 mg, 12%), macrocycle **4** (5.4 mg, 38%) and macrocycle **5** (7.2 mg, 50%) were formed as a white powder. $^1$H NMR ($CD_3OD$, 400 MHz): $\delta=7.90$–7.84 (m, 1H), 7.57–7.52 (m, 1H), 7.42–7.22 (m, 5H), 5.40–5.24 (m, 2H), 5.10–4.95 (m, 1H), 4.35–4.24 (m, 2H), 4.23–4.15 (m, 2H), 4.00–3.60 (m, 20H), 2.81–2.74 (m, 2H), 2.67–2.60 (m, 2H), 1.51–1.41 ppm (m, 6H); HRMS (ESI) *m/z* calcd for $C_{34}H_{49}N_{16}O_4$: 745.4123 $[M+H]^+$; found: 745.4440.

**Compound 6:** *tert*-Butyl 2-isopropylhydrazinecarboxylate (1.00 g, 5.7 mmol) and DIPEA (2.97 mL, 17.1 mmol) were added to a stirred solution of cyanuric chloride (1.11 g, 6.0 mmol) in THF (38 mL) at 0 °C. After 2 h, morpholine (0.54 mL, 6.3 mmol) was added, and the mixture was stirred for 12 h at room temperature. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, hexanes/EtOAc 4:1) to afford compound **6** (1.63 g, 77%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=5.02$–4.75 (m, 1H), 3.95–3.55 (m, 8H), 1.56–1.34 (m, 9H), 1.19 ppm (d, $J=6.4$, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=169.7$, 165.9, 164.5, 156.4, 81.5, 66.7, 48.8, 43.7, 28.1, 19.5 ppm; HRMS (ESI) *m/z* calcd for $C_{15}H_{26}ClN_6O_3$: 373.1755 $[M+H]^+$; found: 373.1775.

**Compound 7**: *tert*-Butyl-2-benzylidenehydrazine-1-carboxylate (1.00 g, 4.5 mmol) and DIPEA (2.35 mL, 13.5 mmol) were added to a stirred solution of cyanuric chloride (0.87 g, 4.7 mmol) in THF (50 mL) at 0 °C. After 2 h, morpholine (0.43 mL, 5.0 mmol) was added, and the mixture was stirred for 12 h at room temperature. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, hexanes/EtOAc 4:1→2:1) to afford compound **7** (1.47 g, 78%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=7.40$–7.25 (m, 5H), 5.10–4.85 (m, 2H), 3.90–3.57 (m, 8H), 1.55–1.30 ppm (m, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=170.3$, 167.1, 164.5, 155.5, 136.7, 128.6, 128.1, 127.7, 81.9, 66.7, 53.4, 43.9, 28.2 ppm; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}ClN_6O_3$: 421.1755 $[M+H]^+$; found: 421.1800.

**Compound 8**: Glycine ethyl ester hydrochloride (1.13 g, 8.1 mmol) and DIPEA (2.12 mL, 12.2 mmol) were added to a stirred solution of **6** (1.00 g, 2.7 mmol) in 1,4-dioxane (17 mL). The mixture was stirred in a CEM 300 W microwave in dynamic mode at 90 °C for 4 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, hexanes/EtOAc 2:1) to afford compound **8** (0.86 g, 73%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=4.98$–4.80 (m, 1H), 4.23 (q, $J=7.1$ Hz, 2H), 4.17–4.05 (m, 2H), 3.83–3.61 (m, 8H), 1.60–1.33 (m, 9H), 1.29 (t, $J=7.1$ Hz, 3H), 1.16 ppm (d, $J=5.4$, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=170.8$, 166.2, 166.1, 165.2, 156.9, 80.6, 66.8, 61.2 47.8, 43.5, 43.1, 28.3, 19.5, 14.2 ppm; HRMS (ESI) *m/z* calcd for $C_{19}H_{34}N_7O_5$: 440.2621 $[M+H]^+$; found: 440.2686.

**Compound 9**: Glycine ethyl ester hydrochloride (1.00 g, 7.2 mmol) and DIPEA (1.88 mL, 10.8 mmol) were added to a stirred solution of **7** (1.00 g, 2.4 mmol) in 1,4-dioxane (15 mL). The mixture was stirred in a CEM 300 W microwave in dynamic mode at 90 °C for 4 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The organic layer was collected, dried over $Na_2SO_4$, and filtered. Following concentration, the crude product was purified by flash column chromatography ($SiO_2$, hexanes/EtOAc 2:1) to afford compound **9** (0.74 g, 63%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=7.38$–7.20 (m, 5H), 5.10–4.75 (m, 2H), 4.30–3.95 (m, 4H), 3.81–3.55 (m, 8H), 1.57–1.29 (m, 9H), 1.30–1.15 ppm (m, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=170.7$, 167.1, 166.2 165.2, 155.8, 138.0, 128.7, 128.3, 127.2, 80.9, 66.8, 61.1, 52.5, 43.5, 43.1, 44.5, 28.2, 14.2 ppm; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}N_7O_5$: 488.2621 $[M+H]^+$; found: 488.2714.

**Compound 10:** NaOH (0.23 g, 5.6 mmol) was added to a stirred solution of **8** (0.80 g, 1.8 mmol) in MeOH/$H_2O$/THF (1:1:1, 8 mL). The mixture was stirred at RT for 12 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The aqueous layer was collected, and $CH_2Cl_2$ (50 mL) was added. The solution was then acidified to pH 3 with acetic acid at 0 °C. After extraction, the aqueous layer was washed with $CH_2Cl_2$ (100 mL), and the combined organic layers were collected, dried over $Na_2SO_4$, and filtered. Following concentration under reduced pressure, compound **10** was obtained in quantitative yields as a white solid. Compound **10** was

carried on to the next step without further purification. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 4.79$ (quint, $J = 6.4$ Hz, 1H), 4.15–3.65 (m, 10H), 1.46 (s, 9H), 1.22 ppm (d, $J = 5.8$, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 175.5$, 162.3, 157.7, 155.8, 155.6, 81.4, 66.6, 50.2, 44.8, 44.4, 28.1, 19.4 ppm; HRMS (ESI) *m/z* calcd for $C_{17}H_{30}N_7O_5$: 412.2308 $[M+H]^+$; found: 412.2354.

**Compound 11**: NaOH (0.18 g, 4.3 mmol) was added to a stirred solution of **9** (0.70 g, 1.4 mmol) in MeOH/$H_2O$/THF (1:1:1, 6 mL). The mixture was stirred at RT for 12 h. The solvent was removed by rotary evaporation under reduced pressure and extracted with $H_2O$ (100 mL) and $CH_2Cl_2$ (2×100 mL). The aqueous layer was collected, and $CH_2Cl_2$ (50 mL) was added. The solution was then acidified to pH 3 with acetic acid at 0 °C. After extraction, the aqueous layer was washed with $CH_2Cl_2$ (100 mL), and the combined organic layers were collected, dried over $Na_2SO_4$, and filtered. Following concentration under reduced pressure, compound **11** was obtained in quantitative yields as a white solid. Compound **11** was carried on to the next step without further purification. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 7.39$–7.25 (m, 5H), 5.20–4.70 (m, 2H), 4.11–3.60 (m, 10H), 1.45 ppm (s, 9H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta =$ 172.8, 162.3, 159.0, 156.1, 155.1, 135.5, 128.7, 128.2, 127.9, 81.6, 66.6, 53.3, 44.8, 44.5, 28.2 ppm; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}N_7O_5$: 460.2308 $[M+H]^+$; found: 460.2381.

**X-ray diffraction analysis:** Colorless single crystals of compounds **3** and **4** were grown at room temperature by slow evaporation of a water, methanol, and TFA mixture. The X-ray diffraction data sets of both compounds were collected at room temperature on a Bruker D8 Quest diffractometer equipped with a Photon 100 CMOS detector with $K_\alpha$ radiation ($\lambda = 0.71073$ Å). A suitable crystal of each compound was mounted on the goniometer head by using Paratone-N oil on the tip of a MiTeGen MicroLoops LD, 50 mm away from the detector. An exposure time of 15 s was selected in shutter-less mode with a scan angle of 0.75° per frame with the generator operating at 50 kV and 30 mA. The Bragg intensities of data sets consisting of $\omega$ and $\phi$ scans were indexed by using the APEX3 package;[24] data reduction and absorption corrections were carried out with the SAINT[25] and SADABS[26] packages, respectively. The space group was determined by using XPREP[24] through analysis of the Laue symmetry and systematic absences. Structures were solved by the intrinsic phasing method with SHELXT[27] software. Solving each compound with the best figure of merit revealed the coordinates of all non-hydrogen atoms, which were refined by using the SHELXL[28] program embedded in the OLEX2 package.[29] The hydrogen atoms were located by difference Fourier analysis, and, during structure refinement, the atomic displacement parameters of the hydrogen atoms were treated isotropically; non-hydrogen atoms were anisotropically refined by using the full-matrix least-squares procedure on $F^2$ (using all data). Hydrogen atoms attached to carbon atoms were allowed to ride on their carrying atoms, whereas those attached to heteroatoms were refined freely.

The asymmetric unit of **3** contains two TFA anions with multiple disorders. During the refinement of these disorders, the sum of the occupancies of the two disordered parts was fixed to unity. The disordered atoms of both TFA moieties overlap; this resulted in pathological displacement ellipsoids. This correlation of the thermal parameters was avoided by constraining the atomic displacement parameters (ADPs) of both parts to be equal during refinement. The occupancies of the two components were refined, yielding an approximately 0.388(6):0.612(6) ratio. Details of the data collection and statistics for structure refinement of both compounds are given in Table S1.

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## Conflict of Interest

*The authors declare no conflict of interest.*

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