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Carbohydrate-derived conformationally restricted bicyclic dipeptides as potential hetero foldamer building blocks

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ABSTRACT

Starting from carbohydrate precursors, hetero foldamer building blocks featuring diverse amino acid side chains and stereochemistry have been accessed via a multi-step synthetic protocol. These conformationally restricted bicyclic dipeptide building blocks are characterized by a constrained β-lactam ring fused with a pyrrolidine ring carrying a hydroxyethylamine isostere (HEA) on the backbone. These building blocks offer the possibility of developing foldamers with interesting structural architectures, conspicuously different from those classically observed. Furthermore, such hetero-building blocks have the potential to augment the conformational space available for foldamer design with diverse backbone conformations and structural architectures.

1. Introduction

Synthetic oligomers featuring well-defined conformational features, also known as foldamers, have attracted considerable attention from chemists primarily due to the fact that they have considerable potential in the development of oligomers with diverse structural architectures, shapes, and function, quite often closely mimicking the conformational and functional features of native peptides.[1] In order to attain shape diversity of the oligomer backbone, building blocks with diverse structural architectures are being developed. For instance, Fleet et al.[2] and others[3] have reported a huge repertoire of carbohydrate-based foldamer building blocks. Extensive investigations of many of their oligomers have provided a wealth of information regarding conformational propensities[4] and biomedical potential.[5]

Among the numerous foldamers reported to date, hetero foldamers containing amino acid residues of different conformational preferences have gained special status mainly because of two reasons. Firstly, hetero foldamers have been proven to be capable of displaying a unique structural architecture, distinctly different from their homo oligomer counterparts.[6] Secondly, by varying the constitutional ratios of the individual amino acid residues, it would be possible to augment the conformational diversity of the oligomers.[7] For instance, hetero foldamers containing different α, β, and γ residues on the backbone have been shown to adopt helical structures with very different H-bonding patterns.[7a–c]

2. Results and discussion

Herein we report a set of conformationally constrained sugar-derived dipeptide building blocks carrying different amino acid residues at the C-terminus (Fig. 1). These hetero building blocks feature a biomedically important β-lactam core[8–10] armed with a hydroxyethylamine isostere (HEA) on the backbone. It is noteworthy that HEA isosteres are one of the most important peptide transition-state mimics developed so far, and many drug candidates are known to feature this proteolytically stable peptide bond mimic.[11]

The synthesis of the conformationally restricted dipeptide building blocks **1a–d** was straightforward, mainly involving two key steps (Scheme 1).

The use of the mannitol-derived D-glyceraldehyde **3**[12] in the construction of β-lactam **5a–d** via a Staudinger ketene-imine cycloaddition[13] remained an important step in this synthetic protocol. The Staudinger synthesis not only helped us to access the β-lactam as a single diastereomer, but also furnished a vicinal glycol, which was amenable to further functional manipulations

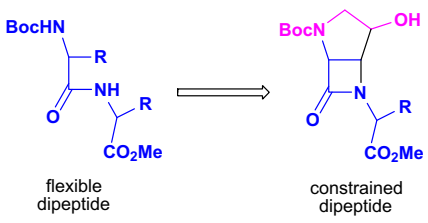

Figure 1. Design strategy of a constrained bicyclic dipeptide heterogeneous foldamer building block with an embedded HEA isostere and a β-lactam core (the dipeptide backbones are highlighted in blue and the HEA moiety in pink).

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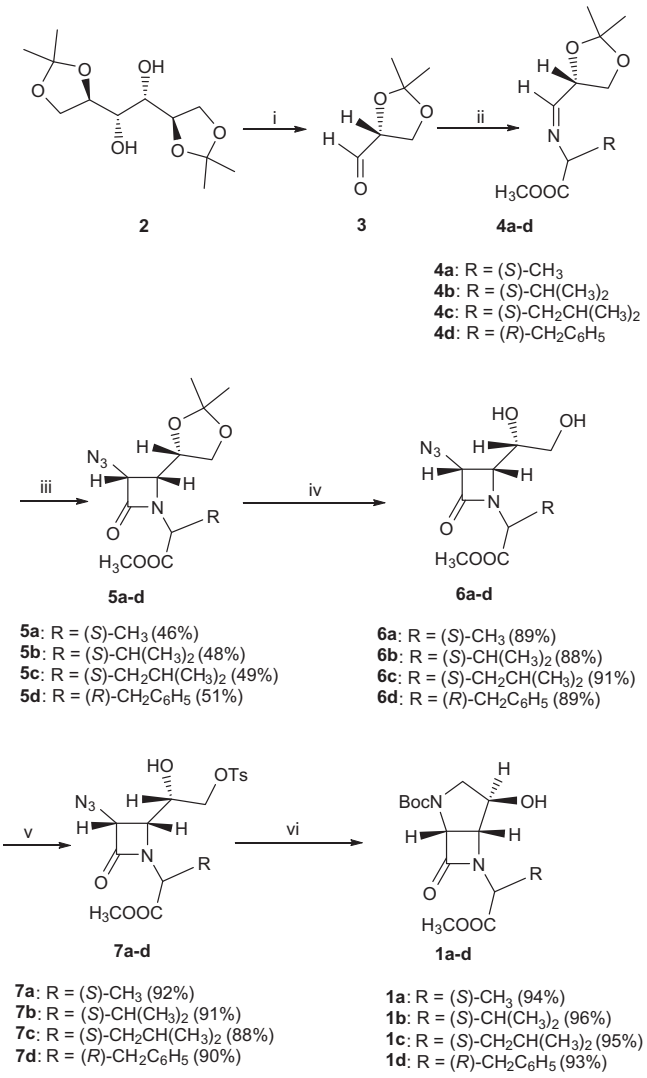

Scheme 1. Reagents and conditions: (i) $NaIO_4$, H_2O, 0 °C, 30 min.; (ii) R-NH_2, H_2O-1,2-dichloroethane, rt, 2 h; (iii) potassium azido acetate, triphosgene, Et_3N, DCM, 0 °C, then rt, 15 h; (iv) PTSA, THF:H_2O, reflux, 16 h; (v) tosyl chloride, Bu_2SnO, Et_3N, DCM, rt, 8 h; (vi) Pd-C, H_2, $(Boc)_2O$, 60 psi, 8 h.

to effect the second key step of cyclization leading to the formation of the constrained building blocks **1a**–**d**. The acetonide protected D-glyceraldehyde **3**, readily available from D-mannitol diacetonide[12] **2** by $NaIO_4$-mediated oxidative cleavage, was converted into the aminoacid-conjugated Schiff bases **4a**–**d**, which without purification, were subjected to the standard Staudinger reaction with azidoacetyl chloride, generated in situ by reacting potassium azido acetate with triphosgene. The *cis*-stereochemistry of the β-lactam was readily indicated by the coupling constants (J = 5–6 Hz), which is characteristic of *cis*-β-lactams.[14] Deprotection of acetonides **5a**–**d** cleanly furnished diols **6a**–**d**, which were then subjected to selective dibutyltin oxide-mediated tosylation[15] to afford the *O*-tosyl derivatives **7a**–**d** in excellent yields. Azide reduction within **7a**–**d** with concomitant Boc protection cleanly afforded the cyclized target building blocks **1a**–**d** in excellent yield (93–96%), without the requirement for special conditions for effecting cyclization.

The conformational characteristics of the heterogeneous dipeptide building blocks **1a**–**d** are clearly evident from the crystal structure of **1a** (Fig. 2).

This dipeptide foldamer building block **1a**, which readily crystallized from chloroform, features a biomedically significant β-lactam fused with a 5-membered pyrrolidine ring. It is noteworthy that the

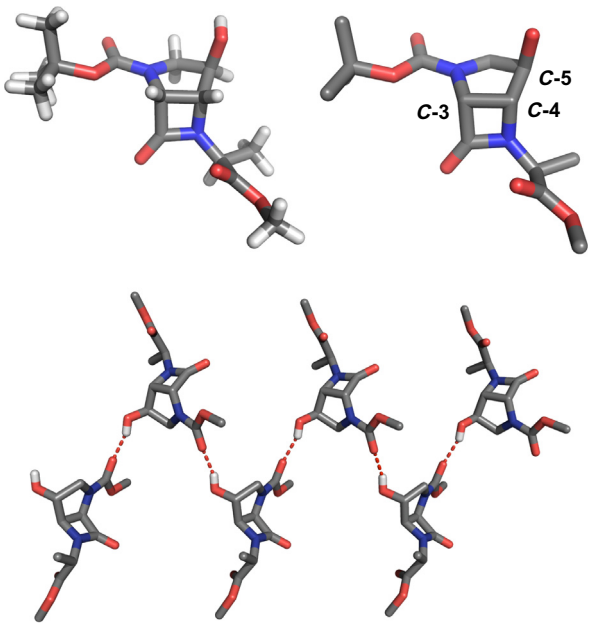

Figure 2. Views of the crystal structure of **1a** with and without hydrogens (top) and self-assembly aided by the *C*-5 hydroxyl group as the H-bonding donor, and ^{t}Boc carbonyl as H-bonding acceptor (bottom). *Note*: ^{t}Boc methyls have been deleted in the self-assembled structure for the sake of clarity.

structural architecture of the pyrrolidine ring displaying the hydroxyl group at *C*-5 is reminiscent of a constrained HEA isostere, as noted earlier.[11] The crystal structure[16] of **1a** also clearly establishes the *cis*-geometry of the *C*-3 and *C*-4 positions of the β-lactam ring. The dipeptide building block **1a** assumes an extended sheet structure in the solid-state, aided by intermolecular hydrogen-bonding interaction between the *C*-5 hydroxyl group of one molecule and the ^{t}Boc carbonyl of another molecule. The hydrogen-bond geometry is characterized by the bond distances d(O···O) = 2.7 Å and d(H···O) = 1.9 Å, and the bond angle (O–H···O) = 162°.

3. Conclusion

In conclusion we have reported on a set of conformationally restricted bicyclic dipeptides derived from readily available carbohydrate precursors through efficient multi-step synthetic protocols. The decoration of the foldamer backbone with biologically relevant moieties such as a rigid fused β-lactam and a hydroxyl ethylamine isostere (HEA) is noteworthy. Oligomers carrying these building blocks are expected to show distinctly different conformational preferences, very different from their homogenous counterparts.

4. Experimental

4.1. (*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde 3

To a chilled solution of $NaIO_4$ (2 equiv) in H_2O, 1,2,5,6-di-isopropylidine-D-mannitol **2** (2 equiv) was added in portions with stirring. After completion of addition, the reaction mixture was stirred for 30 min. The reaction mixture was filtered through a sintered funnel to provide an aqueous solution of the crude product **3**, which was used for subsequent reactions without further purification.

4.2. General procedure for the preparation of azido -lactams 5a–d

To the cooled filtrate of **3**, a solution of amino ester (1 equiv) in 1,2-dichloroethane (EDC) was added. The reaction mixture was

stirred at room temperature for 2 h. The organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with dichloromethane. The combined organic layer containing the Schiff bases **4a–d** was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and re-dissolved in dry dichloromethane cooled at 0 °C. Potassium azido acetate (1 equiv) was added to the above mixture, followed by the sequential addition of Et_3N (6 equiv) and a solution of triphosgene (0.8 equiv) in dry dichloromethane. After stirring for 15 h at room temperature, the reaction mixture was diluted with dichloromethane, sequentially washed with water, saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to furnish crude products **5a–d**, which were then purified by column chromatography.

4.2.1. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)propanoate 5a

Viscous liquid. Yield: 2.1 g (46%); $[\alpha]_D^{25} = +160$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3392, 2109, 1769, 1382, 1068, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 4.72 (d, *J* = 5.31 Hz, 1H), 4.41(q, 1H), 4.21–4.12 (m, 2H), 3.93 (dd, *J* = 5.31 Hz, 8.85 Hz, 1H), 3.72 (s, 3H), 3.62 (q, 1H), 1.59 (d, *J* = 7.45 Hz, 3H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 163.9, 109.7, 75.8, 66.3, 63.8, 60.0, 52.3, 51.0, 26.5, 24.9, 16.3; ESI MS: 299.40 $(M+H)^+$, 321.39 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{18}N_4O_5$: C, 48.32; H, 6.08; N, 18.78. Found: C, 48.50; H, 5.89; N, 18.62.

4.2.2. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-3-methylbutanoate 5b

Viscous liquid. Yield: 2.40 g (48%); $[\alpha]_D^{25} = +118$ (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3461, 2110, 1769, 1742, 1675, 1373, 1215, 755; ^1H NMR (200 MHz, $CDCl_3$): δ 4.69 (d, *J* = 5.31 Hz, 1H), 4.26–4.07 (m, 2H), 3.85–3.73 (m, 2H), 3.71 (s, 3H), 3.62–3.53 (m, 1H), 2.63–2.45 (m, 1H), 1.39 (s, 3H), 1.28 (s, 3H), 1.02 (d, *J* = 6.70 Hz, 3H), 0.96 (d, *J* = 6.82 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 163.8, 109.7, 75.8, 66.3, 63.6, 63.2, 60.8, 51.9, 28.9, 26.5, 24.8, 19.8, 19.7; ESI MS: 349.12 $(M+Na)^+$, 365.12 $(M+K)^+$; Anal. Calcd for $C_{14}H_{22}N_4O_5$: C, 51.52; H, 6.79; N, 17.17. Found: C, 51.43; H, 6.61; N, 17.33.

4.2.3. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-4-methylpentanoate 5c

Viscous liquid. Yield: 2.56 g (49%); $[\alpha]_D^{25} = +146$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3026, 2118, 1772, 1742, 1372, 1216, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 4.73 (d, *J* = 5.31 Hz, 1H), 4.36–4.30 (m, 1H), 4.21–4.12 (m, 2H), 3.94–3.87 (m, 1H), 3.71 (s, 3H), 3.63–3.55 (m, 1H), 2.21–2.10 (m, 1H), 1.71–1.51 (m, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 0.94 (d, *J* = 1.14 Hz, 3H), 0.91 (d, *J* = 1.51 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 164.6, 109.7, 75.8, 66.4, 63.7, 60.4, 54.1, 52.3, 38.2, 26.5, 24.9, 24.8, 22.9, 20.7; ESI MS: 363.30 $(M+Na)^+$, 379.30 $(M+K)^+$; Anal. Calcd for $C_{15}H_{24}N_4O_5$: C, 5; H, 7.11; N, 16.46. Found: C, 53.01; H, 6.99; N, 16.65.

4.2.4. (*R*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 5d

Viscous liquid. Yield: 2.93 g (51%); $[\alpha]_D^{25} = +170$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3020, 2110, 1771, 1744, 1602, 1422, 1216, 771; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.19 (m, 5H), 4.65 (dd, *J* = 5.93 Hz, 10.61 Hz, 1H), 4.51 (d, *J* = 5.16 Hz, 1H), 4.10–4.02 (m,1H), 3.81–3.69 (m, 1H) 3.79 (s, 3H), 3.63–3.37 (m, 4H), 1.43 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 163.9, 136.5, 128.6, 128.5, 126.8, 109.6, 75.7, 66.0, 63.3, 59.4, 56.7, 52.5, 34.2, 26.5, 24.7; ESI MS: 375.22 $(M+H)^+$, 397.19 $(M+Na)^+$, 413.18 $(M+K)^+$; Anal. Calcd for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.92; N, 14.96. Found: C, 57.57; H, 6.11; N, 15.08.

4.3. General procedure for the preparation of dihydroxy -lactams 6a–d

A mixture of azido -lactams **5a–d** and PTSA (0.33 equiv) in aq THF was refluxed for 16 h. The reaction mixture was then neutralized with $NaHCO_3$. The residue obtained after removing the solvents under reduced pressure was dissolved in ethyl acetate, washed with brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded **6a–d**, which were purified by column chromatography.

4.3.1. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)propanoate 6a

Viscous liquid. Yield: 1.53 g (89%); $[\alpha]_D^{25} = +164$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3399, 2117, 1753, 1733, 1654, 1637, 1450, 1412, 1021, 770; ^1H NMR (200 MHz, $CDCl_3$): δ 4.71 (d, *J* = 5.06 Hz, 1H), 4.38 (q, 1H), 4.01–3.86 (m, 2H), 3.82–3.78 (m, 1H), 3.76 (s, 3H), 3.73–3.70 (m, 1H), 3.62–3.54 (m, 1H), 2.98(br s, 1H), 1.64(d, *J* = 7.46 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.0, 164.5, 70.6, 63.9, 63.7, 59.2, 52.8, 52.7, 16.1; ESI MS: 259.23 $(M+H)^+$, 281.20 $(M+Na)^+$, 297.20 $(M+K)^+$; Anal. Calcd for $C_9H_{14}N_4O_5$: C, 41.86; H, 5.46; N, 21.70. Found: C, 42.02; H, 5.29; N, 21.57.

4.3.2. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-3-methylbutanoate 6b

Viscous liquid. Yield: 1.54 g (88%); $[\alpha]_D^{25} = +100$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3400, 2117, 1743, 1651, 1408, 1020, 758; ^1H NMR (200 MHz, $CDCl_3$): δ 4.72 (d, *J* = 4.80 Hz, 1H), 3.92–3.80 (m, 4H), 3.74 (s, 3H), 3.74–3.56 (m, 2H), 3.18 (br s, 1H), 2.62–2.44 (m, 1H), 1.02 (d, *J* = 6.57 Hz, 3H), 0.94 (d, *J* = 6.82 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9, 164.4, 70.9, 64.2, 63.5, 63.4, 59.6, 52.4, 29.5, 19.7, 19.4; ESI MS: 287.28 $(M+H)^+$, 309.24 $(M+Na)^+$, 325.25 $(M+K)^+$; Anal. Calcd for $C_{11}H_{18}N_4O_5$: C, 46.15; H, 6.34; N, 19.57. Found: C, 46.29; H, 6.15; N, 19.41.

4.3.3. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-4-methylpentanoate 6c

Viscous liquid. Yield: 1.60 g (91%); $[\alpha]_D^{25} = +150$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3444, 2111, 1765, 1755, 1747, 1270, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 4.70 (d, *J* = 4.67 Hz, 1H), 4.28–4.21 (m, 1H), 3.97–3.91 (m, 2H), 3.86–3.76 (m, 2H), 3.76 (s, 3H), 3.66–3.56 (m, 2H), 2.33–2.14 (m, 1H), 1.73–1.54 (m, 2H), 0.96 (d, *J* = 3.03 Hz, 3H), 0.93 (d, *J* = 2.91 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.1, 164.5, 70.6, 63.8, 63.8, 59.7, 56.0, 52.7, 38.4, 25.1, 22.8, 21.0; ESI MS: 301.30 $(M+H)^+$, 323.26 $(M+Na)^+$, 339.25 $(M+K)^+$; Anal. Calcd for $C_{12}H_{20}N_4O_5$: C, 47.99; H, 6.71; N, 18.66. Found: C, 48.15; H, 6.90; N, 18.47.

4.3.4. (*R*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1,2-dihydroxyethyl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 6d

Viscous liquid. Yield: 1.58 g (89%); $[\alpha]_D^{25} = +118$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 2116, 1764, 1739, 1399, 1215, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 4.82–4.74 (m, 1H), 4.43 (d, *J* = 5.31 Hz, 1H), 3.83–3.79 (m, 1H), 3.75 (s, 3H), 3.72–3.62 (m, 3H), 3.59–3.39 (m, 2H), 3.37–3.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.7, 165.4, 136.0, 128.6, 128.4, 127.1, 70.8, 63.5, 63.2, 58.3, 56.3, 52.8, 34.5; ESI MS: 335.15 $(M+H)^+$, 357.15 $(M+Na)^+$, 373.14 $(M+K)^+$; Anal. Calcd for $C_{15}H_{18}N_4O_5$: C, 53.89; H, 5.43; N, 16.76. Found: C, 54.05; H, 5.30; N, 16.58.

4.4. General procedure for the preparation of tosyl -lactams 7a–d

To a solution of dihydroxy -lactams **6a–d** (1 equiv) dissolved in dry dichloromethane, dibutyltin oxide (1 equiv) was added and the reaction mixture was stirred for 5 min at room temperature.

After cooling the reaction mixture to 0 °C, Et_3N (1.1 equiv) and tosyl chloride (1.05 equiv) were added. After the addition was completed, the reaction mixture was allowed to stir at room temperature for 6 h, diluted with dichloromethane, washed sequentially with water and saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude products **7a–d**, which were then purified by column chromatography.

4.4.1. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1-hydroxy-2-(tosyl oxy)ethyl)-4-oxoazetidin-1-yl)propanoate 7a

Viscous liquid. Yield: 1.90 g (92%); $[\alpha]_D^{25} = +154$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3400, 2114, 1743, 1652, 1632, 1407, 1176, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.34 Hz, 2H), 7.38 (d, *J* = 7.96 Hz, 2H), 4.60 (d, *J* = 4.80 Hz, 1H), 4.30 (q, 1H), 4.09–4.08 (m, 2H), 4.01–3.92 (m, 2H), 3.88–3.84 (m, 1H), 3.74 (s, 3H), 2.43 (s, 3H), 1.62 (d, *J* = 7.45 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.8, 163.9, 145.4, 131.7, 129.6, 127.9, 71.2, 68.4, 63.6, 58.4, 52.8, 52.7, 21.5, 16.0; ESI MS: 413.41 $(M+H)^+$, 435.41 $(M+Na)^+$, 451.31 $(M+K)^+$; Anal. Calcd for $C_{16}H_{20}N_4O_7S$: C, 46.60; H, 4.89; N, 13.58. Found: C, 46.79; H, 5.12; N, 13.39.

4.4.2. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1-hydroxy-2-(tosyl oxy)ethyl)-4-oxoazetidin-1-yl)-3-methylbutanoate 7b

Viscous liquid. Yield: 1.82 g (91%); $[\alpha]_D^{25} = +96$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3455, 2114, 1764, 1661, 1359, 1176, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.34 Hz, 2H), 7.37 (d, *J* = 7.96 Hz, 2H), 4.62 (d, *J* = 4.80 Hz, 1H), 4.12–4.06 (m, 2H), 3.95–3.84 (m, 2H), 3.80–3.73 (m, 2H), 3.71(s, 3H), 2.54–2.32 (m, 1H), 2.42 (s, 3H), 0.98 (d, *J* = 6.57 Hz, 3H), 0.91 (d, *J* = 6.69 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 163.9, 145.2, 131.9, 129.8, 127.8, 70.9, 68.8, 63.8, 63.2, 58.6, 52.3, 29.6, 21.4, 19.6, 19.3; ESI MS: 441.43 $(M+H)^+$, 463.44 $(M+K)^+$; Anal. Calcd for $C_{18}H_{24}N_4O_7S$: C, 49.08; H, 5.49; N, 12.72. Found: C, 48.92; H, 5.61; N, 12.51.

4.4.3. (*S*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1-hydroxy-2-(tosyl oxy)ethyl)-4-oxoazetidin-1-yl)-4-methylpentanoate 7c

Viscous liquid. Yield: 1.72 g (88%); $[\alpha]_D^{25} = +112$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3300, 2116, 1771, 1744, 1599, 1262, 768; ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.34 Hz, 2H), 7.39 (d, *J* = 7.96 Hz, 2H), 4.62 (d, *J* = 5.05 Hz, 1H), 4.24–4.16 (m, 1H), 4.12–4.10 (m, 2H), 4.05–3.97 (m, 1H), 3.97 (q, 1H), 3.75 (s, 3H), 3.72–3.66 (m, 1H), 2.45 (s, 3H), 2.29–2.13 (m, 1H), 1.74–1.51 (m, 2H), 0.95 (d, *J* = 1.77 Hz, 3H), 0.92 (d, *J* = 1.39 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.0, 164.1, 145.1, 131.8, 130.0, 127.9, 71.2, 68.5, 63.5, 58.9, 55.9, 52.8, 38.3, 25.0, 22.8, 21.6, 21.0; ESI MS: 477.15 $(M+Na)^+$; Anal. Calcd for $C_{19}H_{26}N_4O_7S$: C, 50.21; H, 5.77; N, 12.33. Found: C, 50.35; H, 5.95; N, 12.04.

4.4.4. (*R*)-Methyl 2-((2*R*,3*R*)-3-azido-2-((*S*)-1-hydroxy-2-(tosyl oxy)ethyl)-4-oxoazetidin-1-yl)-3-phenylpropanoate 7d

Viscous liquid. Yield: 1.70 g (90%); $[\alpha]_D^{25} = +124$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3420, 2114, 1772, 1764, 1738, 1641, 1216, 769; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80–7.75 (m, 2H), 7.38–7.20 (m, 7H), 4.80–4.72 (m, 1H), 4.29 (d, *J* = 4.80 Hz, 1H), 4.04–4.03 (m, 2H), 3.81–3.77 (m, 1H), 3.75 (s, 3H), 3.73–3.70 (m, 2H), 3.43–3.18 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 164.9, 145.2, 135.9, 131.8, 129.8, 128.6, 128.4, 127.8, 127.0, 70.4, 68.4, 63.3, 57.3, 56.1, 52.8, 34.4, 21.4; ESI MS: 511.39 $(M+Na)^+$, 527.33 $(M+K)^+$; Anal. Calcd for $C_{22}H_{24}N_4O_7S$: C, 54.09; H, 4.95; N, 11.47. Found: C, 53.91; H, 5.08; N, 11.59.

4.5. General procedure for the preparation of the β-lactam foldamer building blocks 1a–d

To a solution of **7a–d** (1 equiv) in ethyl acetate, 10% Pd-C, Et_3N (1.2 equiv) and Boc anhydride (1.1 equiv) were added. The reaction mixture was hydrogenated at 60 psi for 4 h. The reaction mixture was filtered over a Celite pad and washed several times with ethyl acetate. The combined ethyl acetate washings were washed sequentially with saturated $KHSO_4$, and brine solutions and the organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude **1a–d**, which were then purified by column chromatography.

4.5.1. (1*R*,4*R*,5*R*)-*tert*-Butyl 4-hydroxy-6-((*S*)-1-methoxy-1-oxopropan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 1a

White solid. Yield: 0.99 g (94%); mp: 143–145 °C; $[\alpha]_D^{25} = +180$ (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3368, 1752, 1733, 1684, 1655, 1420, 1024; ^1H NMR (400 MHz, $CDCl_3$): δ 5.20 (br s, 1H), 4.45 (q, 1H), 4.30 (d, *J* = 3.02 Hz, 1H), 4.28 (d, *J* = 3.51 Hz, 1H), 4.02–3.99 (m, 1H), 3.74 (s, 3H), 3.52 (dd, *J* = 3.26 Hz, 13.05 Hz, 1H), 3.16 (br s, 1H), 1.49 (d, *J* = 7.45 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 165.3, 165.3, 154.1, 81.0, 69.8, 67.5, 63.6, 52.6, 52.4, 49.9, 28.2, 16.6; ESI MS: 315.33 $(M+H)^+$, 337.29 $(M+Na)^+$, 353.28 $(M+K)^+$; Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.57; H, 6.99; N, 9.09.

4.5.2. (1*R*,4*R*,5*R*)-*tert*-Butyl 4-hydroxy-6-((*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 1b

White solid. Yield: 1.03 g (96%); mp: 76–78 °C; $[\alpha]_D^{25} = +110$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 1740, 1697, 1416, 1165, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 5.12 (br s, 1H), 4.31 (br s, 1H), 4.23 (d, *J* = 3.92 Hz, 1H), 4.02–3.92 (m, 2H), 3.71 (s, 3H), 3.61 (br s, 1H), 3.51 (dd, *J* = 3.54 Hz,13.01 Hz, 1H), 2.24–2.06 (m, 1H), 1.43 (s, 9H), 0.98 (d, *J* = 6.69 Hz, 3H), 0.92 (d, *J* = 6.70 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 166.0, 153.9, 80.8, 69.2, 67.2, 64.8, 61.5, 52.6, 52.0, 30.0, 28.1, 19.5, 19.1; ESI MS: 343.54 $(M+H)^+$, 365.47 $(M+Na)^+$, 381.47 $(M+K)^+$; Anal. Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.97; H, 7.84; N, 8.28.

4.5.3. (1*R*,4*R*,5*R*)-*tert*-Butyl 4-hydroxy-6-((*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 1c

White solid. Yield: 1.03 g (95%); mp: 66–68 °C; $[\alpha]_D^{25} = +125$ (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3422, 1763, 1742, 1685, 1420, 1216, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 5.24 (br s, 1H), 4.41 (d, *J* = 7.58 Hz, 1H), 4.33–4.27 (m, 2H), 4.07 (d, *J* = 12.89 Hz, 1H), 3.75 (s, 3H), 3.57 (dd, *J* = 3.53 Hz, 13.01 Hz, 1H), 2.49 (br s, 1H), 1.80–1.53 (m, 3H), 1.48 (s, 9H), 0.98 (d, *J* = 0.76 Hz, 3H), 0.94 (d, *J* = 0.69 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.6, 165.8, 153.9, 80.7, 69.1, 67.1, 64.0, 53.0, 52.5, 52.3, 39.0, 28.0, 24.7, 22.5, 21.1; ESI MS: 379.46 $(M+Na)^+$, 395.46 $(M+K)^+$; Anal. Calcd for $C_{17}H_{28}N_2O_6$: C, 57.29; H, 7.92; N, 7.86. Found: C, 57.37; H, 7.88; N, 7.74.

4.5.4. (1*R*,4*R*,5*R*)-*tert*-Butyl 4-hydroxy-6-((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)-7-oxo-2,6-diazabicyclo[3.2.0]heptane-2-carboxylate 1d

White solid. Yield: 0.94 g (93%); mp: 122–124 °C; $[\alpha]_D^{25} = +190$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3443, 1764, 1744, 1644, 1216, 772; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 5.00 (br s,1H), 4.50–4.42 (m, 1H), 4.05 (d, *J* = 3.28 Hz, 1H), 4.00 (d, *J* = 3.54 Hz, 1H), 3.79–3.74(m, 1H), 3.74 (s, 3H), 3.37–3.14 (m, 3H), 3.08–3.00 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.2, 165.8, 153.9, 136.1, 128.7, 128.4, 127.7, 80.7, 68.9, 67.0, 63.4, 56.4, 52.6, 52.4, 35.0, 28.1; ESI MS: 413.31 $(M+Na)^+$, 429.31 $(M+K)^+$; Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.38; H, 6.90; N, 6.99.

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