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Synthesis and Application of Carbohydrate-Derived Morpholine Amino Acids†

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The synthesis of series of diversely functionalized ϵ-morpholine amino acids (MAAs, **5a**−**h**) starting from an ϵ-sugar amino acid and following a two-step oxidative glycol cleavage/reductive amination strategy, is described. In an alternative synthetic scheme, diastereoisomerically pure δ-MAAs (**12a**,**b**) were obtained. Oligopeptides containing MAAs were prepared either by direct incorporation of a MAA building block or by subjecting a fully assembled SAA-containing peptide to the two-step glycol cleavage/reductive amination procedure.

Introduction

The design, synthesis, and application of peptidomimetic compounds has been a focal point of research for many years. The generation of a plethora of peptide analogues and their incorporation in oligopeptides has led to the identification of pharmaceutically interesting compounds.[1] As secondary structure is a decisive factor in the functioning of peptides and proteins, scaffolds that restrict the conformational freedom have been applied to provide structural stabilization when incorporated in oligopeptides.[2] Moreover, the incorporation of nonproteinogenic residues can have beneficial effects on metabolic stability, whereas additional functionalities on the molecular framework allow the attachment of potential pharmacophoric groups. Sugar amino acids (SAAs), carbohydrate scaffolds appended with an amine and carboxylic acid moiety, have been employed successfully as nonproteinogenic compounds.[3] SAAs are a structurally and functionally diverse class of peptidomimetics and exist as furanoid, pyranoid, open-chain,[4] and fused-ring systems.[5] Hydroxyl groups that originate from the parent sugar can participate in secondary structure formation. For example, in a recent contribution from our laboratory we revealed that the incorporation of a furanoid SAA into the turn region of gramicidin S (GS) induces an unusual turn structure with a hydroxyl protruding into the turn region of GS causing a disruption in the H-bonding pattern as compared to the native peptide.[6] The free hydroxyl functionalities in SAAs can also be equipped with pharmacophores, thereby increasing their resemblance with native peptide sequences. This principle was elegantly demonstrated by Smith et al. in the synthesis of a potential mammalian ribonuclease reductase inhibitor.[7] In this example, a tetrahydropyran scaffold was adorned with a methylene carboxylate and an isobutyl group that mimic the aspartic acid and leucine side chains, respectively. Next to the decoration of the hydroxyls, another type of derivatization can be envisaged based on oxidative glycol-cleavage of a 1,2-diol functionality on the furan or pyran core structure. The ring structure can subsequently be reinstalled by double-reductive amination of the resulting dialdehyde, resulting in a substituted morpholine. Previously, Du et al. reported the synthesis of morpholinoglycopeptides starting from glycopyranosides.[8a] Inositol triphosphate analogues having substituted amines introduced into the carbacyclic core have been prepared by Malmberg et al.[8b] Further-

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† Dedicated to the memory of our colleague Jacques van Boom, who passed away on July 31, 2004, at the age of 67.

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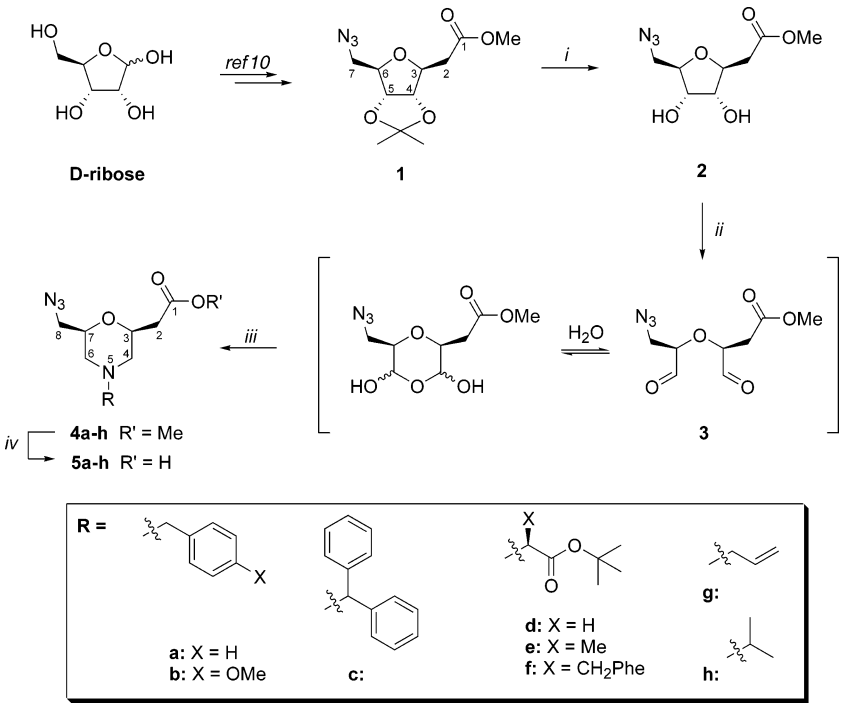
SCHEME 1[a]



[a] Reagents and conditions: (i) 2 M HCl/MeOH (1/3 v/v), 16 h, 82%; (ii) H_5IO_6 (1.5 equiv), THF, 20 min, 94%; (iii) R-NH_2 (1.1 equiv), $NaCNBH_3$ (4.2 equiv), trimethyl orthoformate/MeOH (1/3 v/v), AcOH, 3 Å mol sieves, 16 h, **4a**; 54%, **4b**; 36%, **4c**; 38%, **4d**; 59%, **4e**; 33%, **4f**; 45%, **4g**; 41% and **4h**; 33%; (iv) 1 m NaOH (2 equiv), THF, 4 h, then Amberlite IR-120 (H^+), **5a**; quant, **5b**; 94%, **5c**; quant, **5d**; quant, **5e**; 78%, **5f**; 45%, **5g**; 78% and **5h**; quant.

more, the generation of morpholine derivatives from nucleoside building blocks and their incorporation in oligonucleotide analogues that possess favorable antisense properties has been described.[9]

We herein report the synthesis of a series δ- and ϵ-morpholine amino acids (MAAs) bearing several different moieties on the endocyclic nitrogen, starting from SAA building blocks and following the aforementioned glycol-cleavage/reductive amination-strategy. To demonstrate the versatility of the approach, a single type II′ β-turn of the model peptide GS has been replaced by an ϵ-MAA, both through direct incorporation of an MAA building block and by modification of a SAA-containing GS analogue after complete assembly of the cyclic oligopeptide.

Results and Discussion

The synthesis of a set of ϵ-morpholine amino acids (**5a**−**h**) is outlined in Scheme 1. Starting from D-(+)-ribose, the protected SAA building block **1** was obtained following a high-yielding four-step procedure developed recently in our laboratory.[10] This route entails the installation of the acetonide at the 2,3-diol, Wittig olefination at the anomeric center, mesylation of the remaining hydroxyl functionality, and subsequent introduction of the azide moiety. Removal of the isopropylidene protective group in SAA **1** by acidolysis exposed the *cis*-diol system to give **2** in 82% yield. Glycol cleavage was effected by treatment with periodic acid to afford dialdehyde **3**, together with its corresponding hydrates.[11] The MAA-core structures **4a**−**h** were obtained after slow addition of a solution of the appropriate amine in MeOH, that had been acidified with AcOH to approximately pH = 5 in advance, to a mixture of **3** and $NaCNBH_3$.[12] The yields of the double reductive aminations varied for the benzylic amines (**4a**; 54%, **4b**; 36%, **4c**; 38%), the amino acid derivatives (**4d**; 59%, **4e**; 33%, **4f**; 45%), and the aliphatic amines (**4g**; 41%, **4h**; 33%). Saponification of the methyl ester functionalities in **4a**−**h** produced the free ϵ-morpholine amino acids **5a**−**h**.

To establish whether the above-described approach to ϵ-MAAs is also amenable for δ-MAAs, SAA **7** (Scheme 2), having a similar *cis*-diol system as template **2**, was selected as our next synthetic target. The appropriate precursor **6** was prepared in a five-step procedure, comprising Kiliani ascension[13] of cyclohexylidene-protected D-(+)-ribose, followed by ditosylation, base-catalyzed ring contraction and introduction of the azide, according to the procedure developed by Fleet and coworkers.[14] The *cis*-diol in **7** was unveiled by acidic release of the cyclohexylidene group in **6** (59%). Periodate oxida-

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(11) Glycol cleavage could similarly be effected by sodium periodate although the reaction proceeded sluggishly.

(12) The azide functionality proved to be stable under these reducing conditions as no deterioration of **2** was observed when subjected to the same reaction conditions.

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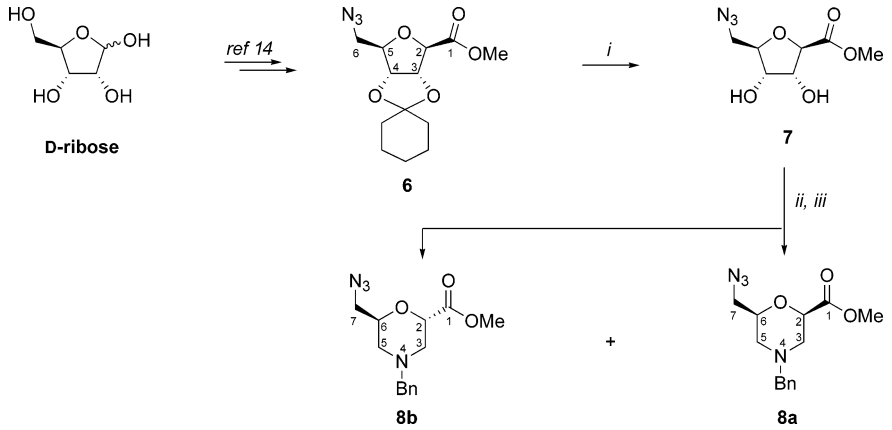
SCHEME 2[a]



[a] Reagents and conditions: (i) 4 M HCl/MeOH (1/4 v/v), 50 °C, 2 h, 59%; (ii) H_5IO_6, THF, 30 min, 95%; (iii) R-NH_2 (1.1 equiv), $NaCNBH_3$ (4.2 equiv), trimethyl orthoformate/MeOH (1/2 v/v), AcOH, 3 Å mol sieves, 16 h, **8a**; 22% and **8b**; 22%.

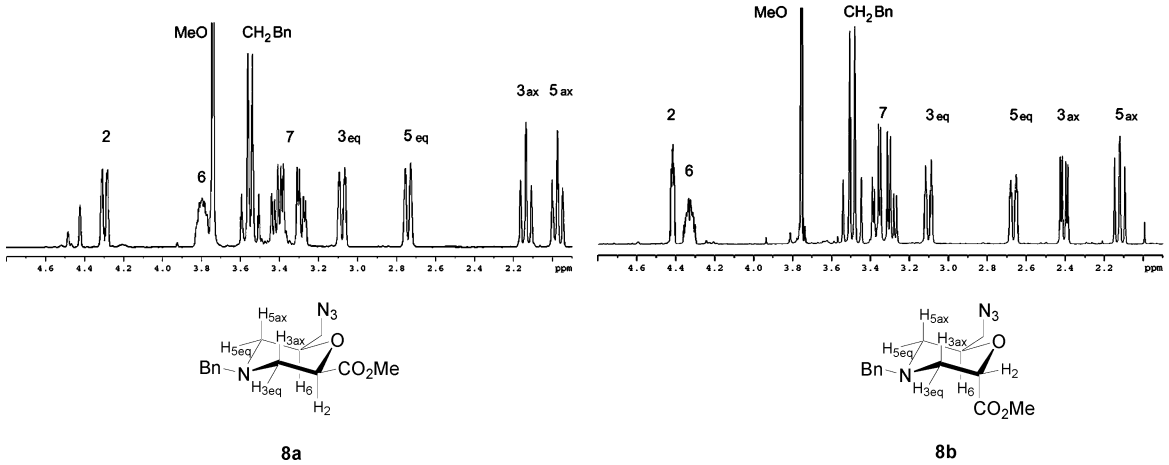


FIGURE 1. Parts of the ^{1}H NMR spectra of **8a** and **8b** (400 MHz, $CDCl_3$).

tion followed directly by reductive amination of the crude dialdehyde furnished, after silica column chromatography, the diastereoisomeric morpholines **8a** and **8b**, both in 22%.

The 2,6-*cis* configuration and 2,6-*trans* configuration of **8a** and **8b**, respectively, were established by comparison of the ^{1}H spectra (see Figure 1). The large geminal ($^2J_{3ax,3eq}$ = 11.1 Hz) and vicinal ($^3J_{3ax,2}$ = 11.1 Hz) coupling constants confirmed a *anti*-periplanar relationship between H_{3ax} and H_2 in the case of **8a**. For **8b**, a large geminal ($^2J_{3ax,3eq}$ = 11.6 Hz) and moderate vicinal ($^3J_{3ax,2}$ = 4.1 Hz) coupling constant were observed, indicating a gauche relationship between H_{3ax} and H_2.

The unsuccessful attempts to suppress or circumvent epimerization during the glycol cleavage and ensuing reductive amination, together with the moderate yield and laborious separation, prompted us to select a sequence of reactions that excludes an intermediate β-keto ester. To this end, 2,5-anhydroglucitol **9** (Scheme 3) was prepared following a route described previously by our laboratory and that involves the acidic dehydration of D-(+)-mannitol, acetonation of the 1,3-*cis*-diol system, and consecutive introduction of the primary azide.[15] Acid-catalyzed methanolysis of the isopropylidene group produced triol **10**, which was subjected to glycol cleavage and reductive insertion of benzylamine to give morpholine **11** in 53%. Finally, oxidation of the primary hydroxyl in **11** was examined. We have previously shown that the 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB)-mediated oxidation is a powerful means to chemo- and regioselectively obtain thioglycuronic acids.[16] Gratifyingly, this mild procedure proved effective for the transformation of **11** into δ-MAA **12a**, without affecting the nitrogen of the morpholine, in 61% yield. The C_2-epimer of **12a** was constructed from 2,5-anhydromannitol **14**, which was obtained from D-(+)-glucosamine by nitrous deamination and $NaBH_4$ reduction, as described by Cassel et al.[17] Ensuing selective mesylation of the resulting anhydromannitol **13**[18] and nucleophilic substitution with sodium azide furnished **14** in 45% over two steps. Periodic acid-mediated ring-

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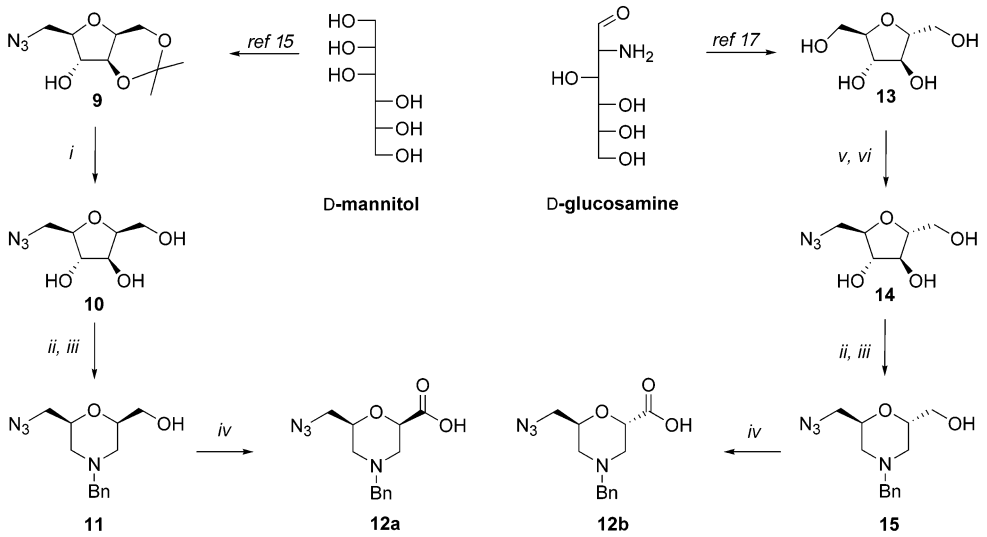
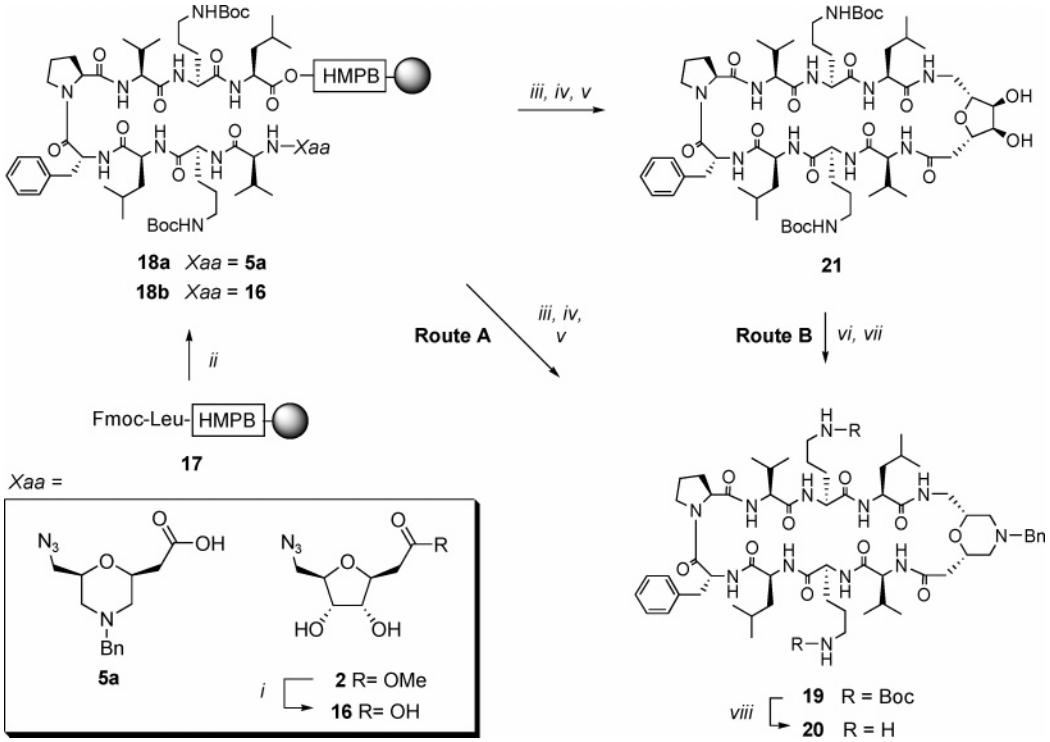
SCHEME 3[a]



[a] Reagents and conditions: (i) TFA/MeOH (1/3 v/v), 1 h, quant; (ii) H_5IO_6, THF, 30 min; (iii) benzylamine (1.1 equiv), $NaCNBH_3$ (4.2 equiv), trimethyl orthoformate/MeOH (1/3 v/v), AcOH, 3 Å mol sieves, 16 h, **11**; 53% and **15**; 52% (two steps); (iv) TEMPO (0.2 equiv), BAIB (2 equiv), DCM, 0 °C, 6 h, **12a**; 61% and **12b**; 68%; (v) MsCl (1.0 equiv), pyridine, −40 °C, 1 h to 0 °C, 16 h; (*vi*) NaN_3 (2.5 equiv), DMF, 70 °C, 48 h, 45% (two steps).

SCHEME 4[a]



[a] Reagents and conditions: (i) 1 M NaOH/THF (1/2 v/v), 3 h, then Amberlite IR-120 (H^+), 98%; (ii) repetitive deprotection piperidine/NMP (1/4 v/v); condensation: Fmoc-aa-OH (3 equiv) or N_3-*Xaa*-OH (2 equiv), BOP (3 equiv), HOBt (3 equiv), DiPEA (3.5 equiv), NMP; (iii) PMe_3 (16 equiv), 1,4-dioxane/H_2O (10/1 v/v); (iv) TFA/DCM (1/99 v/v), 4 × 10 min; (v) PyBOP (5 equiv), HOBt (5 equiv), DiPEA (15 equiv), DMF, 16 h, **19**; 71% and **21**; 63%; (vi) $NaIO_4$ (2 equiv), THF/DMF/H_2O (3/1/1 v/v/v), 16 h; (vii) benzylamine (1.5 equiv), $NaCNBH_3$ (5 equiv), trimethylorthoformate/MeOH (1/2 v/v), AcOH, 16 h, 63% (two steps); (viii) TFA/DCM (1/1 v/v), 30 min, 77%.

opening and reductive amination gave morpholine **15** (52%) that was subjected to TEMPO/BAIB oxidation to provide δ-MAA **12b** in 68%.

At this stage, the application of MAAs as peptidomimetic compounds was explored and ϵ-MAA **5a** was selected for incorporation in GS. Nonapeptide **18a** (Scheme 4) was assembled on 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB) functionalized 4-methylbenzhydrylamine (MBHA) resin **17** using standard Fmoc-based SPPS protocols. The terminal azide in **18a** was subjected

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to Staudinger reduction, and the peptide was released from the solid support by mild acidolysis and subsequently cyclized under highly dilute conditions to give fully protected **19** in 71% (route A).[6] Liberation of the Boc protective groups, followed by HPLC purification, produced peptide **20** in 77%, which was characterized by ^{1}H NMR to reveal that the peptide prevalently adopts a β-sheet secondary structure reminiscent of the native peptide.[19] Encouraged by these results, we decided to examine whether MAA-containing peptidic constructs are also accessible through the glycol cleavage/reductive amination strategy when applied to SAAs that are already embedded in oligopeptide sequences. Thus, saponification of **2** gave SAA **16** in 98%. Following the sequence of reactions as described above for compound **19**, resin-anchored nonapeptide **18b** was constructed through SPPS, from which GS analogue **21** was readily prepared in 63%.[20] Treatment of the *cis*-diol-containing peptide with $NaIO_4$ and reductive amination furnished **19** in 63% (route B), which was deprotected to produce **20**. The MAA-containing GS analogue **20** obtained from both routes were spectroscopically and spectrometrically identical.

In conclusion, ϵ-morpholine amino acids, bearing several different substituents on the nitrogen of the morpholine core structure, were synthesized from furanoid ϵ-SAAs via a two-step oxidative glycol cleavage/reductive amination approach. Diastereoisomeric mixtures of δ-MAAs were obtained when the corresponding furanoid δ-SAAs were subjected to the same sequence of events. To prevent epimerization during oxidative ring opening, an alternative scheme was developed, through which 2,5-anhydroglucitol and 2,5-anhydromannitol were readily transformed into their diastereoisomerically pure δ-MAA counterparts. We further demonstrated that ϵ-MAA-containing GS analogue **19** could be obtained in two ways; by directly employing **5a** as building block or by first preparing GS analogue **21**, featuring ϵ-SAA **16**, which is subsequently subjected to our ring-opening/ring-closing approach.

Experimental Section

General Methods. Reactions were monitored by TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by spraying with 20% H_2SO_4 in EtOH, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L), and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid or by spraying with a solution of ninhydrin (3 g/L) in EtOH/AcOH (20/1 v/v), followed by charring at ~150 °C. Column chromatography was performed on Fluka silica gel (0.04−0.063 mm) and size-exclusion chromatography on Sephadex LH-20. For LC/MS analysis, an HPLC system (detection simultaneously at 214 and 254 nm) equipped with an analytical C_{18} column (4.6 mm i.d. × 250 mm, 5 μm particle size) in combination with buffers A (H_2O), B (MeCN), and C (0.5% aq TFA) and coupled to a mass instrument with a custom-made electronspray interface (ESI) was used. For reversed-phase HPLC purification of the peptides, an automated HPLC system supplied with a semipreperative C_{18} column (10.0 mm i.d. × 250 mm, 5 μm particle size) was used. The applied buffers were A (H_2O), B (MeCN), and C (1.0% aq TFA).

Methyl 3,6-Anhydro-7-azido-2,7-dideoxy-D-*allo*-heptonate (2). To a mixture of methyl ester **1** (5.03 g, 18.56 mmol) in MeOH (75 mL) was added 2 M aq HCl (25 mL), and the solution was stirred overnight. After being neutralized with 1 M aq NaOH (50 mL), the mixture was partially concentrated and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Silica gel column chromatography (50% → 100% EtOAc in light PE) yielded the title compound as a clear oil (3.52 g, 15.25 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (ddd, 1H, H_3, $J_{3,2a} = J_{3,2b}$ = 6.5 Hz, $J_{3,4}$ = 6.3 Hz), 4.06 (dd, 1H, H_5, $J_{5,6}$ = 5.4 Hz, $J_{5,4}$= 6.3 Hz), 4.00 (dd, 1H, H_6, $J_{6,7}$ = 4.3 Hz, $J_{6,5}$ = 5.4 Hz), 3.95 (dd, 1H, H_4, $J_{4,5} = J_{4,3}$ = 6.3 Hz), 3.57 (dd, 1H, H_{7a}, $J_{7a,6}$ = 3.4 Hz, $J_{7a,7b}$ = 13.3 Hz), 3.31 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.3 Hz, $J_{7b,7a}$ = 13.3 Hz), 2.77 (dd, 1H, H_{2a}, $J_{2a,3}$ = 6.5 Hz, $J_{2a,2b}$ = 16.3 Hz), 2.69 (dd, 1H, H_{2b}, $J_{2b,3}$ = 6.5 Hz, $J_{2b,2a}$ = 16.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C_1), 82.8 (C_6), 79.1 (C_3), 74.6 (C_4), 72.1 (C_5), 52.1 (C_7), 52.0 (OMe), 37.9 (C_2). ATR-IR (thin film) 3396.4, 2956.2, 2098.4, 1728.1, 1438.8, 1400.2, 1274.9, 1172.6, 1097.4, 1037.6, 987.5, 910.3, 850.5, 829.3, 731.0 cm^{-1}. $[\alpha]^{23}_D$ = +80.4 (c = 1.0, CH_2Cl_2). MS (ESI): m/z = 232.1 $[M + H]^+$, 253.8 $[M + Na]^+$, 463.0 $[2M + H]^+$.

Methyl 3,7-Anhydro-5-aza-8-azido-5-benzyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4a). Clear oil (668 mg, 2.2 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5H, H_{ar}), 4.07 (m, 1H, H_3), 3.82 (m, 1H, H_7), 3.67 (s, 3H, OMe), 3.54 (d, 1H, CH_2 Bn, $J_{CHa,CHb}$ = 13.1 Hz), 3.47 (d, 1H, CH_2 Bn, $J_{CHb,CHa}$ = 13.1 Hz), 3.24 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.6 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.10 (dd, 1H, H_{8b}, $J_{8b,7}$ = 3.9 Hz, $J_{8b,8a}$ = 12.9 Hz), 2.81 (ddd, 1H, H_{4eq}, $J_{4eq,6eq} = J_{4eq,3}$ = 1.9 Hz, $J_{4eq,4ax}$ = 10.9 Hz), 2.67 (ddd, 1H, H_{6eq}, $J_{6eq,4eq} = J_{6eq,7}$ = 2.0 Hz, $J_{6eq,6ax}$ = 10.9 Hz), 2.53 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.7 Hz, $J_{2a,2b}$ = 15.3 Hz), 2.38 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.3 Hz, $J_{2a,2b}$ = 15.3 Hz), 1.88 (dd, 1H, H_{6ax}, $J_{6ax,6eq} = J_{6ax,7}$ = 10.7 Hz), 1.87 (dd, 1H, H_{4ax}, $J_{4ax,4eq} = J_{4ax,3}$ 10.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_1), 137.3 (C_q Bn), 129.0 128.3 128.1 127.2 (CH_{ar}), 75.2 (C_7), 72.5 (C_3), 62.8 (CH_2 Bn), 57.2 (C_4), 54.6 (C_6), 52.7 (C_8), 51.7 (OMe), 38.6 (C_2). ATR-IR (thin film) 2094.6, 1735.8, 1454.2, 1436.9, 1348.1, 1330.8, 1288.4, 1251.7, 1213.1, 1168.8, 1149.5, 1110.9, 1056.9, 1028.0, 999.1, 956.6, 920.0, 742.5, 700.1 cm^{-1}. $[\alpha]^{23}_D$ = −7.4 (c = 1.0, CH_2Cl_2). MS (ESI): m/z = 305.0 $[M + H]^+$, 327.1 $[M + Na]^+$.

Methyl 3,7-Anhydro-5-aza-8-azido-5-*p*-methoxybenzyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4b). Clear oil (358 mg, 1.12 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, 2H, H_{ar}, J = 8.6 Hz), 6.85 (d, 2H, H_{ar}, J = 8.6 Hz), 4.06 (m, 1H, H_3), 3.79 (m, 4H, H_7, Me PMB), 3.67 (s, 3H, OMe), 3.50 (d, 1H, CH_2 PMB, $J_{CHa,CHb}$ = 12.8 Hz), 3.40 (d, 1H, CH_2 PMB, $J_{CHb,CHa}$ = 12.8 Hz), 3.25 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.8 Hz, $J_{8a,8b}$ = 12.8 Hz), 3.10 (dd, 1H, H_{8b}, $J_{8b,7}$ = 3.8 Hz, $J_{8b,8a}$ = 12.8 Hz), 2.80 (ddd, 1H, H_{4eq}, $J_{4eq,6eq} = J_{4eq,3}$ = 1.8 Hz, $J_{4eq,4ax}$ = 11.1 Hz), 2.66 (ddd, 1H, H_{6eq}, $J_{6eq,4eq} = J_{6eq,7}$ = 1.8 Hz, $J_{6eq,6ax}$ = 11.1 Hz), 2.53 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.8 Hz, $J_{2a,2b}$ = 15.4 Hz), 2.39 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.3 Hz, $J_{2a,2b}$ = 15.4 Hz), 1.85 (dd, 1H, H_{6ax}, $J_{6ax,6eq} = J_{6ax,7}$ = 10.8 Hz), 1.84 (dd, 1H, H_{4ax}, $J_{4ax,4eq} = J_{4ax,3}$ = 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_1), 158.7 (C_q PMB), 130.1 (CH_{ar}), 129.2 (C_q PMB), 113.6 (CH_{ar}), 75.1 (C_7), 72.5 (C_3), 62.1 (CH_2 PMB), 57.1 (C_4), 55.1 (Me PMB), 54.5 (C_6), 52.7 (C_8), 51.7 (OMe), 38.6 (C_2). ATR−IR (thin film) 2094.6, 1735.8, 1510.2, 1436.9, 1346.2, 1244.0, 1170.7, 1109.0, 1056.9, 1033.8, 817.8 cm^{-1}. $[\alpha]^{23}_D$ = −5.0 (c = 1.0, $CHCl_3$). MS (ESI): m/z = 355.2 $[M + H]^+$, 357.0 $[M + Na]^+$.

Methyl 3,7-Anhydro-5-aza-8-azido-5-benzhydryl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4c). Clear oil

(19) Upon perusal of the acquired data reported in the Experimental Section, it was found that the coupling constants ($^3J_{NH,H\alpha}$) and chemical shift perturbation ($\Delta\delta H_\alpha$) for the proteinogenic residues in peptide **20** follow a similar trend compared to native GS. These distinctive features validate a β-sheet conformation in GS analogues, as we have previously observed: Grotenbreg, G. M.; Kronemeijer, M.; Timmer, M. S. M.; El Oualid, F.; van Well, R. M.; Verdoes, M.; Spalburg, E.; van Hooft, P. A. V.; de Neeling, A. J.; Noort, D.; van Boom, J. H.; van der Marel, G. A.; Overkleeft H. S.; Overhand, M. *J. Org. Chem.*, in press.

(20) To facilitate the characterization of GS analogue **21**, a small aliquot was deprotected and purified by reversed-phase HPLC to produce the unprotected peptide in 69% yield.

(95 mg, 0.25 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 10H, H_{ar}), 4.22 (s, 1H, $HCPh_2$), 4.13 (m, 1H, H_3), 3.87 (m, 1H, H_7), 3.63 (s, 3H, OMe), 3.16 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.8 Hz, $J_{8a,8b}$ = 13.0 Hz), 3.01 (dd, 1H, H_{8b}, $J_{8b,7}$ = 3.5 Hz, $J_{8b,8a}$ = 13.0 Hz), 2.79 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 2.0 Hz, $J_{4eq,4ax}$ = 11.3 Hz), 2.66 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 2.0 Hz, $J_{6eq,6ax}$ = 11.3 Hz), 2.46 (dd, 1H, H_{2a}, $J_{2a,3}$ = 8.4 Hz, $J_{2a,2b}$ = 15.1 Hz), 2.30 (dd, 1H, H_{2b}, $J_{2b,3}$ = 4.8 Hz, $J_{2a,2b}$ = 15.1 Hz), 1.79 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.1 Hz), 1.74 (dd, 1H, H_{4ax}, $J_{4ax,3}$ = 10.5 Hz, $J_{4ax,4eq}$ = 11.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_1), 141.7 (C_q Ph), 128.6, 127.8, 127.1 (CH_{ar}), 76.0 (CH Ph_2), 75.4 (C_7), 72.7 (C_3), 55.9 (C_4), 53.5 (C_6), 52.7 (C_8), 51.7 (OMe), 38.6 (C_2). ATR−IR (thin film) 2094.6, 1735.8, 1490.9, 1450.4, 1436.9, 1282.6, 1251.7, 1168.8, 1110.9, 1055.0, 1028.0, 763.8, 746.4, 705.9 cm^{-1}. $[\alpha]^{23}_D$ = −2.4 (*c* = 1.0, $CHCl_3$). MS (ESI): *m/z* = 381.1 $[M + H]^+$, 403.1 $[M + Na]^+$.

Methyl 3,7-Anhydro-5-aza-8-azido-5-(*tert*-butylglycinyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4d). Clear oil (87 mg, 0.266 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.11 (m, 1H, H_3), 3.87 (m, 1H, H_7), 3.69 (s, 3H, OMe), 3.28 (dd, 1H, H_{8a}, $J_{7,8a}$ = 6.5 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.17 (dd, 1H, H_{8b}, $J_{7,8b}$ = 4.1 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.14 (m, 2H, H_α Gly), 2.88 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.7 Hz, $J_{4eq,4ax}$ = 10.9 Hz), 2.80 (ddd, 1H, H_{6eq}, $J_{6eq,7}$ = $J_{6eq,4eq}$ = 1.7 Hz, $J_{6eq,6ax}$ = 10.9 Hz), 2.56 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.5 Hz, $J_{2a,2b}$ = 15.3 Hz), 2.43 (dd, 1H, H_{2b}, $J_{2b,\ 3}$ = 5.6 Hz, $J_{2a,2b}$ = 15.3 Hz), 2.15 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.9 Hz), 2.12 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.9 Hz), 1.47 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 169.1 (C_1, C=O *t*-Bu), 81.3 (C_q *t*-Bu), 75.0 (C_7), 72.4 (C_3), 59.5 (C_α Gly), 56.5 (C_4) 54.1 (C_6), 52.6 (C_8), 51.7 (OMe), 38.5 (C_2), 28.0 (CH_3 *t*-Bu). ATR-IR (thin film) 2098.4, 1735.8, 1442.7, 1365.5, 1218.9, 1149.5, 1064.6 cm^{-1}. $[\alpha]^{23}_D$ = −4.4 (*c* = 1.0, CH_2Cl_2). HRMS: calcd for $C_{14}H_{24}N_4O_5H$ 329.18195, found 329.18140.

Methyl 3,7-Anhydro-5-aza-8-azido-5-(*tert*-butyl-L-alaninyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4e). Clear oil (110 mg, 0.43 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (m, 1H, H_3), 3.81 (m, 1H, H_7), 3.69 (s, 3H, OMe), 3.29 (dd, 1H, H_{8a}, $J_{7,8a}$ = 6.6 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.19 (q, 1H, H_α Ala, $J_{\alpha,\beta}$ = 7.1 Hz), 3.14 (dd, 1H, H_{8b}, $J_{7,8b}$ = 4.2 Hz, $J_{8a,8b}$ = 12.9 Hz), 2.85 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 2.0 Hz, $J_{4eq,4ax}$ = 10.9 Hz), 2.73 (ddd, 1H, H_{6eq}, $J_{6eq,7}$ = $J_{6eq,4eq}$ = 1.9 Hz, $J_{6eq,6ax}$ = 10.9 Hz), 2.56 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.6 Hz, $J_{2a,2b}$ = 15.4 Hz), 2.42 (dd, 1H, H_{2b}, $J_{2b,\ 3}$ = 5.6 Hz, $J_{2a,2b}$ = 15.4 Hz), 2.33 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.7 Hz), 2.21 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.7 Hz), 1.47 (s, 9H, *t*-Bu), 1.26 (d, 3H, H_β Ala, $J_{\alpha,\beta}$ = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 171.0 (C_1, C=O *t*-Bu), 81.1 (C_q *t*-Bu), 75.3 (C_7), 72.9 (C_3), 62.7 (C_α Ala), 52.7 (C_6, C_8), 51.7 (OMe), 51.6 (C_4), 38.5 (C_2), 28.0 (CH_3 *t*-Bu), 14.5 (C_β Ala). ATR-IR (thin film): 2098.4, 1722.3, 1436.9, 1367.4, 1350.1, 1255.6, 1318.0, 1145.6, 1114.8, 1091.6, 1062.7, 1049.2, 993.3, 952.8, 881.4, 846.7 cm^{-1}. $[\alpha]^{23}_D$ = −23.2 (*c* = 1.0, CH_2Cl_2). MS (ESI): *m/z* = 343.1 $[M + H]^+$, 365.2 $[M + Na]^+$.

Methyl 3,7-Anhydro-5-aza-8-azido-5-(*tert*-butyl-L-phenylalaninyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4f). Clear oil (103 mg, 0.25 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (m, 5H, CH_{ar}), 3.98 (m, 1H, H_3), 3.76 (m, 1H, H_7), 3.70 (s, 3H, OMe), 3.33 (dd, 1H, H_α, $J_{\alpha,\beta b}$ = 6.6 Hz, $J_{\alpha,\beta a}$ = 9.1 Hz), 3.27 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.8 Hz, $J_{8a,8b}$ = 13.0 Hz), 3.10 (dd, 1H, H_{8b}, $J_{8b,7}$ = 4.1 Hz, $J_{8b,8a}$ = 13.0 Hz), 3.00 (m, 2H, H_{4eq}, $H_{\beta a}$), 2.89 (dd, 1H, $H_{\beta b}$, $J_{\beta b,\alpha}$ = 6.6 Hz, $J_{\beta b,\beta a}$ = 13.4 Hz), 2.69 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 2.0 Hz, $J_{6eq,6ax}$ = 11.1 Hz), 2.57 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.7 Hz, $J_{2a,2b}$ = 15.4 Hz), 2.45 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.5 Hz, $J_{2b,2a}$ = 15.4 Hz), 2.40 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.7 Hz), 1.81 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.8 Hz), 1.35 (s, 9H, CH_3 *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.2 (C_1, C=O *t*-Bu), 137.8 (C_q Ph), 129.6, 129.4, 129.2, 128.2, 126.3 (CH_{ar}), 81.4 (CH_q *t*-Bu), 75.4 (C_7), 72.9 (C_3), 69.6 (CH_α), 53.9 (C_6), 52.5 (C_8), 51.7 (OMe), 51.2 (C_4), 38.4 (C_2), 35.3 (C_β), 28.1 (CH_3 *t*-Bu). ATR-IR (thin film): 2098.4, 1422.3, 1367.4, 1288.4, 1253.6, 1145.6, 1112.9, 1064.6, 844.8, 742.5, 700.1 cm^{-1}. $[\alpha]^{23}_D$ = −13.6 (*c* = 1.0, $CHCl_3$). MS (ESI): *m/z* = 419.2 $[M + H]^+$, 441.2 $[M + Na]^+$. HRMS: calcd for $C_{21}H_{30}N_4O_5H$ 419.22890, found 419.22794.

Methyl 3,7-Anhydro-5-aza-8-azido-5-allyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4g). Clear oil (121 mg, 0.48 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1H, CH All), 5.19 (m, 2H, CH_2 All), 4.05 (m, 1H, H_3), 3.82 (m, 1H, H_7), 3.69 (s, 3H, OMe), 3.23 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.6 Hz, $J_{8a,8b}$ = 13.0 Hz), 3.11 (dd, 1H, H_{8b}, $J_{7,8b}$ = 4.1 Hz, $J_{8b,8a}$ = 13.0 Hz), 3.00 (m, 2H, CH_2 All), 2.86 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.9 Hz, $J_{4eq,4ax}$ = 11.2 Hz), 2.75 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 1.9 Hz, $J_{6eq,6ax}$ = 11.2 Hz), 2.56 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.7 Hz, $J_{2a,2b}$ = 15.4 Hz), 2.43 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.8 Hz, $J_{2b,2a}$ = 15.4 Hz), 1.85 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.9 Hz), 1.81 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_1), 134.2 (CH All), 118.6 (CH_2 All), 75.1 (C_7), 72.5 (C_3), 61.7 (CH_2 All), 57.2 (C_4), 54.7 (C_6), 52.8 (C_8), 51.8 (OMe), 38.7 (C_2). ATR−IR (thin film) 2098.4, 1735.8, 1434.9, 1342.4, 1288.4, 1172.6, 1110.9, 1064.6, 995.2, 925.8 cm^{-1}. $[\alpha]^{23}_D$ = −12.8 (*c* = 1.0, CH_2Cl_2). MS (ESI): *m/z* = 255.0 $[M + H]^+$. HRMS: calcd for $C_{11}H_{18}N_4O_3H$ 255.14517, found 255.14462.

Methyl 3,7-Anhydro-5-aza-8-azido-5-isopropyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonate (4h). Clear oil (110 mg, 0.43 mmol, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (m, 1H, H_3), 3.75 (m, 1H, H_7), 3.63 (s, 3H, OMe), 3.23 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.4 Hz, $J_{8a,\ 8b}$ = 12.9 Hz), 3.11 (dd, 1H, H_{8b}, $J_{7,8b}$ = 4.2 Hz, $J_{8a,8b}$ = 12.9 Hz), 2.75 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.9 Hz, $J_{4eq,4ax}$ = 11.1 Hz), 2.63 (m, 2H, H_{6eq}, CH *i*-Pr), 2.51 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.4 Hz, $J_{2a,2b}$ = 15.3 Hz), 2.37 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.7 Hz, $J_{2b,2a}$ = 15.3 Hz), 1.99 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.7 Hz), 1.95 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.7 Hz), 0.99 (s, 3H, CH_3 *i*-Pr), 0.97 (s, 3H, CH_3 *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C_1), 75.2 (C_7), 73.9 (C_3), 54.5 (CH *i*-Pr), 52.9 (C_4, C_8), 51.8 (OMe), 50.4 (C_6), 38.7 (C_2), 18.1 (CH_3 *i*-Pr), 18.0 (CH_3 *i*-Pr). ATR−IR (thin film) 2098.4, 1737.7, 1436.9, 1350.1, 1257.5, 1168.8, 1109.0, 1060.8, 999.1 cm^{-1}. $[\alpha]^{23}_D$ = −14.6 (*c* = 1.0, CH_2Cl_2). MS (ESI): *m/z* 257.2 $[M + H]^+$, 279.0 $[M + Na]^+$.

3,7-Anhydro-5-aza-8-azido-5-benzyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5a). Clear oil (102 mg, 0.35 mmol, quant). ^{1}H NMR (400 MHz, MeOD): δ = 7.22 (m, 5H, H_{ar}), 3.93 (m, 1H, H_3), 3.67 (m, 1H, H_7), 3.45 (d, 1H, CH_2 Bn, $J_{CHa,CHb}$ = 12.8 Hz), 3.39 (d, 1H, CH_2 Bn, $J_{CHb,CHa}$ = 12.8 Hz), 3.13 (m, 2H, H_8), 2.84 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 2.0 Hz, $J_{4eq,4ax}$ = 11.3 Hz), 2.62 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 2.0 Hz, $J_{6eq,6ax}$ = 11.1 Hz), 2.35 (dd, 1H, H_{2a}, $J_{2a,3}$ = 6.3 Hz, $J_{2a,2b}$ = 14.4 Hz), 2.13 (dd, 1H, H_{2b}, $J_{2b,3}$ = 7.3 Hz, $J_{2a,2b}$ = 14.4 Hz), 1.79 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.0 Hz), 1.74 (dd, 1H, H_{4ax}, $J_{4ax,3}$ = 10.3 Hz, $J_{4ax,4eq}$ = 11.3 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 177.4 (C_1), 136.8 (C_q Bn), 129.0, 127.8, 126.9 (CH_{ar}), 74.4 (C_7), 73.7 (C_3), 62.6 (CH_2 Bn), 57.5 (C_4), 54.5 (C_6), 52.6 (C_8), 42.2 (C_2). ATR-IR (thin film): 3033.8, 2786.9, 2933.5, 2380.0, 2100.3, 1569.9, 1494.7, 1398.3, 1361.7, 1296.1, 1191.9, 1107.1, 1051.1, 1028.0, 925.8, 742.5, 698.2 cm^{-1}. $[\alpha]^{23}_D$ = +16.0 (*c* = 1.0, MeOH). MS (ESI): *m/z* = 290.8 $[M + H]^+$, 313.0 $[M + Na]^+$.

3,7-Anhydro-5-aza-8-azido-5-*p*-methoxybenzyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5b). Clear oil (117 g, 0.37 mmol, 94%). ^{1}H NMR (400 MHz, MeOD): δ = 7.14 (d, 2H, H_{ar}, *J* = 8.5 Hz), 6.76 (d, 2H, H_{ar}, *J* = 8.5 Hz), 3.92 (m, 1H, H_3), 3.67 (m, 1H, H_7), 3.64 (s, 3H, OMe), 3.48 (m, 2H, CH_2 PMB), 3.15 (m, 2H, H_8), 2.86 (ddd, 1H, H_{4eq}, $J_{4eq,3}$ = 1.5 Hz, $J_{4eq,6eq}$ = 2.0 Hz, $J_{4eq,4ax}$ = 11.4 Hz), 2.69 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 2.0 Hz, $J_{6eq,6ax}$ = 11.4 Hz), 2.33 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.0 Hz, $J_{2a,2b}$ = 15.0 Hz), 2.21 (dd, 1H, H_{2b}, $J_{2b,3}$ = 6.3 Hz, $J_{2a,2b}$ = 15.0 Hz), 1.93 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.4 Hz), 1.87 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 11.4 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 176.3 (C_1), 160.9 (C_q PMB), 132.2 (CH_{ar}), 128.5 (C_q PMB), 114.9 (CH_{ar}), 75.7 (C_7), 74.0 (C_3), 63.0 (CH_2 PMB), 57.8 (C_4), 55.7 (Me PMB), 55.2 (C_6), 53.9 (C_8), 41.4 (C_2). ATR−IR (thin film) 2098.4, 1705.0, 1612.4, 1512.1, 1404.1, 1242.1,

1180.4, 1110.9, 1033.8, 817.8, 732.9 cm^{-1}. $[\alpha]^{23}_D = +20.0$ (c = 1.0, $CHCl_3$). MS (ESI): m/z = 321.1 $[M + H]^+$, 343.0 $[M + Na]^+$. HRMS: calcd for $C_{15}H_{20}N_4O_4H$ 321.15573, found 321.15512.

3,7-Anhydro-5-aza-8-azido-5-benzhydryl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5c). White solid (109 mg, 0.30 mmol, quant). ^1H NMR (400 MHz, MeOD): δ = 7.17 (m, 10H, H_{ar}), 4.08 (s, 1H, $HCPh_2$), 3.95 (m, 1H, H_3), 3.64 (m, 1H, H_7), 2.92 (m, 2H, H_8), 2.72 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.9 Hz, $J_{4eq,4ax}$ = 11.2 Hz), 2.54 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 1.9 Hz, $J_{6eq,6ax}$ = 11.0 Hz), 2.23 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.2 Hz, $J_{2a,2b}$ = 15.2 Hz), 2.04 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.8 Hz, $J_{2a,2b}$ = 15.2 Hz), 1.61 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.0 Hz), 1.56 (dd, 1H, H_{4ax}, $J_{4ax,3}$ = 10.5 Hz, $J_{4ax,4eq}$ = 11.2 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 177.5 (C_1), 143.5 (C_q Ph), 129.6, 129.0, 128.1 (CH_{ar}), 77.6 (CH Ph_2), 76.2 (C_7), 74.8 (C_3), 57.7 (C_4), 55.1 (C_6), 54.0 (C_8), 42.0 (C_2). ATR−IR (thin film) 2098.4, 1712.7, 1581.5, 1450.4, 1265.2, 1110.9, 1056.9, 933.5, 732.9, 702.0 cm^{-1}. $[\alpha]^{23}_D = +23.8$ (c = 1.0, $CHCl_3$). MS (ESI): m/z = 367.2 $[M + H]^+$, 389.3 $[M + Na]^+$. HRMS: calcd for $C_{20}H_{22}N_4O_3H$ 367.17647, found 367.17575.

3,7-Anhydro-5-aza-8-azido-5-(*tert*-butylglycinyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5d). Clear oil (61 mg, 0.19 mmol, quant). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.04 (m, 1H, H_3), 3.83 (m, 1H, H_7), 3.22 (dd, 1H, H_{8a}, $J_{8,7}$ = 6.1 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.16 (dd, 1H, H_{8b}, $J_{8b,7}$ = 4.3 Hz, $J_{8b,8a}$ = 12.9 Hz), 3.15 (d, 1H, H_α Gly, $J_{\alpha a,\alpha b}$ = 16.7 Hz), 3.09 (d, 1H, H_α Gly, $J_{\alpha b,\alpha a}$ = 16.7 Hz), 2.90 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.8 Hz, $J_{4eq,4ax}$ = 11.0 Hz), 2.82 (ddd, 1H, H_{6eq}, $J_{6eq,7}$ = $J_{6eq,4eq}$ = 1.8 Hz, $J_{6eq,6ax}$ = 11.0 Hz), 2.50 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.1 Hz, $J_{2a,2b}$ = 15.5 Hz), 2.36 (dd, 1H, H_{2b}, $J_{2b,3}$ = 6.0 Hz, $J_{2a,2b}$ = 15.5 Hz), 2.17 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.0 Hz), 2.12 (dd, 1H, H_{4ax}, $J_{4ax,3}$ = $J_{4ax,4eq}$ = 11.0 Hz), 1.39 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C_1), 168.7 (C=O *t*-Bu), 81.7 (C_q *t*-Bu), 74.5 (C_7), 72.0 (C_3), 59.0 (C_α Ala), 56.0 (C_4), 53.7 (C_6), 52.6 (C_8), 38.7 (C_2), 28.0 (CH_3 *t*-Bu). ATR-IR (thin film) 2977.9, 2098.4, 1728.1, 1367.4, 1288.4, 1222.8, 1149.5, 1110.9, 1058.8, 914.2, 842.8, 731.0 cm^{-1}. $[\alpha]^{23}_D = +7.8$ (c = 1.0, $CHCl_3$). MS (ESI): m/z = 315.0 $[M + H]^+$, 337.3 $[M + Na]^+$. HRMS: calcd for $C_{13}H_{23}N_4O_5H$ 315.16630, found 315.15637.

3,7-Anhydro-5-aza-8-azido-5-(*tert*-butyl-L-alaninyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5e). White solid (57 mg, 0.17 mmol, 78%). ^1H NMR (400 MHz, MeOD): δ = 3.86 (m, 1H, H_3), 3.67 (m, 1H, H_7), 3.17 (d, 2H, H_8, $J_{8,7}$ = 5.0 Hz), 3.19 (q, 1H, H_α Ala, $J_{\alpha,\beta}$ = 7.1 Hz), 2.84 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 2.0 Hz, $J_{4eq,4ax}$ = 11.3 Hz), 2.68 (ddd, 1H, H_{6eq}, $J_{6eq,7}$ = $J_{6eq,4eq}$ = 2.0 Hz, $J_{6eq,6ax}$ = 11.0 Hz), 2.36 (dd, 1H, H_{2a}, $J_{2a,3}$ = 6.8 Hz, $J_{2a,2b}$ = 15.1 Hz), 2.24 (dd, 1H, H_{2b}, $J_{2b,3}$ = 6.6 Hz, $J_{2a,2b}$ = 15.1 Hz), 2.21 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.9 Hz), 2.04 (dd, 1H, H_{4ax}, $J_{4ax,3}$ = 10.3 Hz, $J_{4ax,4eq}$ = 11.3 Hz), 1.41 (s, 9H, *t*-Bu), 1.26 (d, 3H, H_β Ala, $J_{\beta,\alpha}$ = 7.1 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 175.2 (C_1), 172.1 (C=O *t*-Bu), 80.9 (C_q *t*-Bu), 74.8 (C_7), 73.4 (C_3), 62.9 (C_α Ala), 52.5, 52.2, 52.1 (C_4, C_6, C_8), 40.1 (C_2), 26.9 (CH_3 *t*-Bu), 13.4 (C_β Ala). ATR-IR (thin film): 2098.4, 1722.3, 1581.5, 1367.4, 1255.6, 1218.9, 1145.6, 1089.7, 1031.8, 991.3, 846.7 cm^{-1}. $[\alpha]^{23}_D = -3.6$ (c = 1.0, MeOH). MS (ESI): m/z = 243.0 $[M + H]^+$.

3,7-Anhydro-5-aza-8-azido-5-(*tert*-butyl-L-phenylalaninyl)-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5f). White solid (55 mg, 0.14 mmol, 45%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 5H, CH_{ar}), 4.00 (m, 1H, H_3), 3.79 (m, 1H, H_7), 3.38 (dd, 1H, H_α, $J_{\alpha,\beta b}$ = 6.1 Hz, $J_{\alpha,\beta a}$ = 9.4 Hz), 3.28 (dd, 1H, H_{8a}, $J_{8a,7}$ = 6.3 Hz, $J_{8a,8b}$ = 12.9 Hz), 3.15 (dd, 1H, H_{8b}, $J_{8b,7}$ = 4.3 Hz, $J_{8b,8a}$ = 12.9 Hz), 3.01 (m, 2H, H_{4eq}, $H_{\beta a}$), 2.91 (dd, 1H, $H_{\beta b}$, $J_{\beta b,\alpha}$ = 6.1 Hz, $J_{\beta b,\beta a}$ = 13.3 Hz), 2.75 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 1.8 Hz, $J_{6eq,6ax}$ = 11.1 Hz), 2.60 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.7 Hz, $J_{2a,2b}$ = 15.7 Hz), 2.50 (dd, 1H, H_{2b}, $J_{2b,3}$ = 5.7 Hz, $J_{2b,2a}$ = 15.7 Hz), 2.41 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 10.9 Hz), 2.33 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 10.9 Hz), 1.34 (s, 9H, CH_3 *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (C_1), 170.2 (C=O *t*-Bu), 137.6 (C_q Ph), 129.3, 128.2, 126.4 (CH_{ar}), 81.6 (CH_q *t*-Bu), 75.2 (C_7), 72.6 (C_3), 69.5 (CH_α), 53.6 (C_6), 52.6 (C_8), 51.1 (C_4), 38.5 (C_2), 35.3 (C_β), 28.0 (CH_3 *t*-Bu). ATR-IR (thin film) 2098.4, 1720.4, 1450.4, 1365.5, 1257.5, 1149.5, 840.9 cm^{-1}. $[\alpha]^{23}_D = -8.8$ (c = 1.0, CH_2Cl_2). HRMS: calcd for $C_{20}H_{29}N_4O_5H$ 405.21325, found 405.21136.

3,7-Anhydro-5-aza-8-azido-5-allyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5g). White solid (45 mg, 0.19 mmol, 78%). ^1H NMR (400 MHz, MeOD): δ= 5.81 (m, 1H, CH All), 5.24 (m, 2H, CH_2 All), 4.01 (m, 1H, H_3), 3.77 (m, 1H, H_7), 3.22 (m, 2H, H_8), 3.18 (m, 2H, CH_2 All), 3.05 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.7 Hz, $J_{4eq,4ax}$ = 11.6 Hz), 2.91 (ddd, 1H, H_{6eq}, $J_{6eq,4eq}$ = $J_{6eq,7}$ = 1.7 Hz, $J_{6eq,6ax}$ = 11.6 Hz), 2.41 (dd, 1H, H_{2a}, $J_{2a,3}$ = 7.0 Hz, $J_{2a,2b}$ = 15.5 Hz), 2.34 (dd, 1H, H_{2b}, $J_{2b,3}$ = 6.1 Hz, $J_{2b,2a}$ = 15.5 Hz), 2.10 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.2 Hz), 2.03 (dd, 1H, H_{4ax}, $J_{4ax,4eq}$ = $J_{4ax,3}$ = 11.1 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 175.5 (C_1), 132.6 (CH All), 121.9 (CH_2 All), 75.4 (C_7), 73.4 (C_3), 61.9 (CH_2 All), 57.2 (C_4), 54.7 (C_6), 53.7 (C_8), 40.5 (C_2). ATR-IR (thin film) 2094.6, 1705.0, 1573.8, 1423.4, 1296.1, 1188.1, 1110.91051.1, 999.1, 927.7, 819.7 cm^{-1}. $[\alpha]^{23}_D = +12.0$ (c = 1.0, MeOH). HRMS: calcd for $C_{10}H_{16}N_4O_3H$ 241.12952, found 241.12821.

3,7-Anhydro-5-aza-8-azido-5-isopropyl-2,4,5,6,8-pentadeoxy-D-*glycero*-D-*allo*-octonic Acid (5h). White solid (53 mg, 0.22 mmol, quant). ^1H NMR (400 MHz, MeOD): δ = 4.04 (m, 1H, H_3), 3.81 (m, 1H, H_7), 3.27 (m, 2H, H_8), 3.15 (ddd, 1H, H_{4eq}, $J_{4eq,6eq}$ = $J_{4eq,3}$ = 1.7 Hz, $J_{4eq,4ax}$ = 11.6 Hz), 2.99 (m, 2H, H_{6eq}, CH *i*-Pr), 2.42 (dd, 1H, H_{2a}, $J_{2a,3}$ = 6.3 Hz, $J_{2a,2b}$ = 15.2 Hz), 2.36 (dd, 1H, H_{6ax}, $J_{6ax,6eq}$ = $J_{6ax,7}$ = 11.2 Hz), 2.30 (m, 2H, H_{4ax}, H_{2b}), 1.14 (s, 3H, CH_3 *i*-Pr), 1.11 (s, 3H, CH_3 *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0 (C_1), 75.1 (C_7), 73.9 (C_3), 58.0 (CH *i*-Pr), 53.7, 53.5 (C_4, C_8), 51.0 (C_6), 42.2 (C_2), 17.8 (CH_3 *i*-Pr). ATR−IR (thin film)) 3375.2, 1211.9, 1733.9, 1635.5, 1575.7, 1398.3, 1107.1, 1020.3 cm^{-1}. $[\alpha]^{23}_D = +11.2$ (c = 1.0, MeOH). MS (ESI): m/z = 243.0 $[M + H]^+$. HRMS: calcd for $C_{10}H_{18}N_4O_3H$ 243.14517, found 243.14368.

Methyl 2,5-Anhydro-6-azido-6-deoxy-D-allonate (7). Cyclohexylidene-protected **6** (1.45 g, 4.88 mmol) was dissolved in MeOH (20 mL) and treated with 4 M aq HCl (5 mL). The solution was stirred 2 h at 50 °C and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification by silica column chromatography (50% → 100% EtOAc in light PE) gave diol **7** as a clear oil (628 mg, 2.88 mmol, 59%). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.44 (d, 1H, H_2, $J_{2,3}$ = 4.4 Hz), 4.43 (dd, 1H, H_3, $J_{3,4}$ = $J_{3,2}$= 4.4 Hz), 4.09 (m, 2H, H_4, H_5), 3.80 (s, 3H, OMe), 3.60 (dd, 1H, H_{6a}, $J_{6a,5}$ = 3.3 Hz, $J_{6a,6b}$ = 13.5 Hz), 3.45 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.7 Hz, $J_{7b,7a}$ = 13.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3 (C_1), 82.4, 81.9 (C_2, C_5), 74.0, 72.2 (C_4, C_5), 52.6 (OMe), 52.1 (C_6). MS (ESI): m/z = 218.1 $[M + H]^+$, 239.9 $[M + Na]^+$.

Methyl 2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*ribo*-heptonate (8a). Diol **7** (109 mg, 0.47 mmol) was treated as described in the general procedure for glycol cleavage and reductive amination (Supporting Information). Silica gel column chromatography of the resulting mixture (10% EtOAc in light PE) first gave **8b** (32 mg, 0.11 mmol, 22%). Upon further elution of the column (10% → 15% EtOAc in light PE), the lower running title compound **8a** (31 mg, 0.11 mmol, 22%) was obtained as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H, H_{ar}), 4.30 (dd, 1H, H_2, $J_{2,3eq}$ = 2.7 Hz, $J_{2,3ax}$ = 10.9 Hz), 3.80 (m, 1H, H_6), 3.58 (d, 1H, CH_2 Bn, $J_{CHa,CHb}$ = 12.9 Hz), 3.52 (d, 1H, CH_2 Bn, $J_{CHb,CHa}$ = 12.9 Hz), 3.42 (dd, 1H, H_{7a}, $J_{7a,6}$ = 6.3 Hz, $J_{7a,7b}$ = 12.9 Hz), 3.29 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.8 Hz, $J_{7b,7a}$ = 12.9 Hz), 3.08 (ddd, 1H, H_{3eq}, $J_{3eq,5eq}$ = 1.7 Hz, $J_{3eq,2}$ = 2.7 Hz, $J_{3eq,3ax}$ = 11.0 Hz), 2.74 (ddd, 1H, H_{5eq}, $J_{5eq,3eq}$ = $J_{5eq,6}$ = 1.7 Hz, $J_{5eq,5ax}$ = 11.1 Hz), 2.14 (dd, 1H, H_{3ax}, $J_{3ax,3eq}$ = $J_{3ax,2}$ = 11.0 Hz), 1.97 (dd, 1H, H_{5ax}, $J_{5ax,5eq}$ = $J_{5ax,6}$ = 11.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6 (C_1), 136.9 (C_q Bn), 129.0, 128.4, 127.8, 127.4 (CH_{ar}), 75.1 (C_2), 74.9 (C_6), 62.8 (CH_2 Bn), 54.5 (C_5), 54.2 (C_3), 52.7 (C_7), 52.2 (OMe). ATR-IR (thin film) 2098.4, 1759.0,

1288.4, 1203.5, 1118.6, 1064.6, 740.6, 702.0 cm^{-1}. $[\alpha]^{23}_D = -7.6$ ($c = 1.0$, CH_2Cl_2). HRMS: calcd for $C_{14}H_{18}N_4O_3H$ 291.14517, found 291.14508.

Methyl 2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*arabino*-heptonate (8b). Clear oil (32 mg, 0.11 mmol, 22%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H, H_{ar}), 4.42 (dd, 1H, H_2, $J_{2,3eq}$ = 2.2 Hz, $J_{2,3ax}$ = 4.1 Hz), 4.33 (m, 1H, H_6), 3.52 (d, 1H, CH_2 Bn, $J_{CHa,CHb}$ = 13.3 Hz), 3.46 (d, 1H, CH_2 Bn, $J_{CHb,CHa}$ = 13.3 Hz), 3.37 (dd, 1H, H_{7a}, $J_{7a,6}$ = 4.5 Hz, $J_{7a,7b}$ = 13.0 Hz), 3.29 (dd, 1H, H_{7b}, $J_{7b,6}$ = 5.8 Hz, $J_{7b,7a}$ = 13.0 Hz), 3.10 (ddd, 1H, H_{3eq}, $J_{3eq,5eq} = J_{3eq,2}$ = 2.2 Hz, $J_{3eq,3ax}$ = 11.6 Hz), 2.74 (ddd, 1H, H_{5eq}, $J_{5eq,6}$ = 1.7 Hz, $J_{5eq,3eq}$ = 2.2 Hz, $J_{5eq,5ax}$ = 11.2 Hz), 2.41 (dd, 1H, H_{3ax}, $J_{3ax,2}$ = 4.1 Hz, $J_{3ax,eq}$ = 11.6 Hz), 1.97 (dd, 1H, H_{5ax}, $J_{5ax,6}$ = 9.9 Hz, $J_{5ax,5eq}$ = 11.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (C_1), 137.2 (C_q Bn), 128.7, 128.2, 127.3 (CH_{ar}), 72.6 (C_2), 70.9 (C_6), 62.6 (CH_2 Bn), 54.9 (C_5), 53.5 (C_3), 52.7 (C_7), 51.9 (OMe). ATR-IR (thin film) 2098.4, 1743.5, 1272.9, 1203.5, 1126.4, 1026.1, 740.6, 702.0 cm^{-1}. $[\alpha]^{23}_D$ = +49.6 ($c = 1.0$, CH_2Cl_2). HRMS: calcd for $C_{14}H_{18}N_4O_3H$ 291.14517, found 291.14456.

2,5-Anhydro-6-azido-6-deoxy-D-glucitol (10). Azide **9** (98 mg, 0.43 mmol) was dissolved in MeOH (3 mL), and TFA (1 mL) was added. The mixture was stirred for 1 h, and all solvents were removed in vacuo. Residual traces of acid were removed by repeated coevaporation with toluene to furnish the title compound **10** (83 mg, 0.43 mmol) quantitatively as a clear oil. ^1H NMR (400 MHz, MeOD): δ = 3.96 (m, 2H, H_2, H_3), 3.80 (dd, 1H, H_4, $J_{4,3}$ = 1.9 Hz, $J_{4,5}$ = 3.6 Hz), 3.71 (m, 2H, H_5, H_{1a}), 3.64 (dd, 1H, H_{1b}, $J_{1b,2}$ = 5.7 Hz, $J_{1b,1a}$ = 11.7 Hz), 3.36 (dd, 1H, H_{6a}, $J_{6a,5}$ = 6.5 Hz, $J_{6a,6b}$ = 12.8 Hz), 3.32 (dd, 1H, H_{6b}, $J_{6b,5}$ = 5.1 Hz, $J_{6b,6a}$ = 12.8 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 85.2 (C_5), 82.9 (C_2), 80.7 (C_4), 78.8 (C_3), 61.8 (C_1), 53.8 (C_6). ATR−IR (thin film) 3357.4, 3103.3, 2924.5, 2104.2, 1635.5, 1338.5, 1280.6, 1045.3, 974.0, 923.8 cm^{-1}. $[\alpha]^{23}_D$ = +49.0 (c = 1.0, MeOH). MS (ESI): m/z = 190.0 $[M + H]^+$, 212.0 $[M + Na]^+$.

2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*ribo*-heptitol (11). Triol **10** (693 mg, 3.5 mmol) was subjected to glycol cleavage and reductive amination, as described in the general procedure (Supporting Information), to deliver **11** (486 mg, 1.85 mmol, 53%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5H, H_{ar}), 3.87 (m, 1H, H_6), 3.76 (m, 1H, H_2), 3.65 (dd, 1H, H_{1a}, $J_{1a,2}$ = 3.6 Hz, $J_{1a,1b}$ = 11.6 Hz), 3.55 (dd, 1H, H_{1b}, $J_{1b,2}$ = 6.3 Hz, $J_{1b,1a}$ = 11.6 Hz), 3.53 (s, 2H, CH_2 Bn), 3.28 (dd, 1H, H_{7a}, $J_{7a,6}$ = 6.3 Hz, $J_{7a,7b}$ = 12.9 Hz), 3.22 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.1 Hz, $J_{7b,7a}$ = 12.9 Hz), 2.72 (ddd, 2H, H_{3eq}, H_{5eq}, $J_{3eq,5eq} = J_{3eq,2} = J_{5eq,3eq} = J_{5eq,6}$ = 1.7 Hz, $J_{3eq,3ax} = J_{5eq,5ax}$ = 10.6 Hz), 1.98 (dd, 1H, H_{3ax}, $J_{3ax,3eq} = J_{3ax,2}$ = 11.0 Hz), 1.95 (dd, 1H, H_{5ax}, $J_{5ax,5eq} = J_{5ax,6}$ 11.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.7 (C_q Bn), 129.2, 128.4, 127.4 (CH_{ar}), 76.3 (C_2), 75.2 (C_6), 64.0 (C_1), 63.1 (CH_2 Bn), 55.0 (C_5), 53.8 (C_3), 53.0 (C_7). ATR−IR (thin film) 3386.8, 2923.9, 2877.6, 2098.4, 1450.4, 1288.4, 1118.6, 1064.6, 918.1 cm^{-1}. $[\alpha]^{23}_D$ = +2.0 ($c = 1.0$, CH_2Cl_2). HRMS: calcd for $C_{13}H_{18}N_4O_2H$ 263.15025, found 263.14951.

2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*ribo*-heptonic Acid (12a). To a vigorously stirred solution of morpholine **11** (79 mg, 0.30 mmol) in DCM (1 mL) and water (0.5 mL), that was cooled to 0 °C, were added TEMPO (9.4 mg, 0.06 mmol, 0.2 equiv) and BAIB (193 mg, 0.6 mmol, 2 equiv). After 6 h, the reaction was quenched with MeOH and the mixture was evaporated to dryness. Silica gel column chromatography (0% → 10% of a mixture of *n*-BuOH/AcOH/water (1/1/1 v/v/v) in EtOAc) provided **12a** as a clear oil (50 mg, 0.18 mmol, 61%). ^1H NMR (400 MHz, MeOD): δ = 7.38 (m, 5H, H_{ar}), 4.24 (m, 1H, H_2), 3.96 (m, 2H, CH_2 Bn), 3.87 (m, 1H, H_6), 3.41 (m, 3H, H_7, H_{3eq}), 3.06 (d, 1H, H_{5eq}, $J_{5eq,5ax}$ = 11.4 Hz), 2.51 (dd, 1H, H_{3ax}, $J_{3ax,3eq} = J_{3ax,2}$ = 11.4 Hz), 2.43 (dd, 1H, H_{5ax}, $J_{5ax,5eq} = J_{5ax,6}$ = 11.2 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 173.1 (C_1), 134.3 (C_q Bn), 131.4, 129.8 (CH_{ar}), 75.7 (C_2), 74.7 (C_6), 62.9 (CH_2 Bn), 54.7, 54.4 (C_3, C_5), 53.4 (C_7). IR (thin film) 2100.3, 1608.5, 1456.2, 1373.2, 1274.9, 1120.6, 1053.1, 999.1, 862.1, 754.1, 698.2 cm^{-1}. $[\alpha]_D$ = +4.8 ($c = 1.0$, MeOH). HRMS: calcd for $C_{13}H_{17}N_4O_3H$ 277.12952, found 277.12817.

2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*arabino*-heptonic Acid (12b). Compound **15** (95 mg, 0.36 mmol) was treated following the same procedure as for **11**, to deliver MAA **12b** (68 mg, 0.24 mmol, 68%) as a clear oil. ^1H NMR (400 MHz, MeOD): δ = 7.36 (m, 5H, H_{ar}), 4.30 (1H, H_2, $J_{2,3eq}$ = 3.2 Hz, $J_{2,3ax}$ = 4.1 Hz), 4.24 (m, 1H, H_6), 3.69 (d, 1H, CH_2 Bn, $J_{CHa,CHb}$ = 13.1 Hz), 3.65 (d, 1H, CH_2 Bn, $J_{CHb,CHa}$ = 13.1 Hz), 3.37 (dd, 1H, H_{7a}, $J_{7a,6}$ = 4.7 Hz, $J_{7a,7b}$ = 13.0 Hz), 3.30 (dd, 1H, H_{7b}, $J_{7b,6}$ = 5.5 Hz, $J_{7b,7a}$ = 13.0 Hz), 3.16 (ddd, 1H, H_{3eq}, $J_{3eq,5eq}$ = 1.7 Hz, $J_{3eq,2}$ = 3.2 Hz, $J_{3eq,3ax}$ = 11.8 Hz), 2.75 (ddd, 1H, H_{5eq}, $J_{5eq,3eq}$ = 1.7 Hz, $J_{5eq,6}$ = 2.6 Hz, $J_{5eq,5ax}$ = 11.6 Hz), 2.61 (dd, 1H, H_{3ax}, $J_{3ax,2}$ = 4.3 Hz, $J_{3ax,3eq}$ = 11.8 Hz), 2.35 (dd, 1H, H_{5ax}, $J_{5ax,6}$ = 9.3 Hz, $J_{5ax,5eq}$ = 11.6 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 175.7 (C_1) 136.2 (C_q Bn), 130.8, 129.6, 129.1 (CH_{ar}), 73.7, (C_2), 71.6 (C_6), 63.3 (CH_2 Bn), 55.2 (C_5), 54.5 (C_3), 53.4 (C_7). ATR−IR (thin film) 2098.4, 1716.5, 1602.7, 1456.2, 1396.4, 1274.9, 1213.1, 1120.6, 752.2, 700.1 cm^{-1}. $[\alpha]^{23}_D$ = +12.8 ($c = 0.1$, MeOH). MS (ESI): m/z = 277.0 $[M + H]^+$, 298.9 $[M + Na]^+$. HRMS: calcd for $C_{13}H_{17}N_4O_3H$ 277.12952, found 277.12799.

2,5-Anhydro-6-azido-6-deoxy-D-mannitol (14). Anhydromannitol **13** (6.65 g, 20 mmol) was mesylated as described by Guthrie et al.[18] The mesylate (2.20 g, 9.1 mmol) was subsequently dissolved in DMF (50 mL), NaN_3 (1.47 g, 22.7 mmol, 2.5 equiv) was added, and the mixture was stirred at 70 °C for 48 h. Evaporation of the volatiles and silica column chromatography (0% → 10% of MeOH in EtOAc) produced **14** (1.73 g, 9.1 mmol, 45% over two steps) as a clear oil. ^1H NMR (400 MHz, MeOD): δ= 3.94 (dd, 1H, H_3, $J_{3,2} = J_{3,4}$ = 6.1 Hz), 3.89 (dd, 1H, H_4, $J_{4,3} = J_{4,5}$ = 6.1 Hz), 3.84 (m, 1H, H_5), 3.76 (m, 1H, H_2), 3.65 (dd, 1H, H_{1a}, $J_{1a,2}$ = 3.4 Hz, $J_{1a,1b}$ = 11.9 Hz), 3.55 (dd, 1H, H_{1b}, $J_{1b,2}$ = 4.9 Hz, $J_{1b,1a}$ = 11.9 Hz), 3.42 (dd, 1H, H_{6a}, $J_{6a,5}$ = 3.6 Hz, $J_{6a,6b}$ = 13.1 Hz), 3.28 (dd, 1H, H_{6b}, $J_{6b,5}$ = 5.6 Hz, $J_{6b,6a}$ = 13.1 Hz). ^{13}C NMR (100 MHz, MeOD): δ = 84.9 (C_2), 83.4 (C_5), 79.2 (C_4), 78.2 (C_3), 63.0 (C_1), 53.3 (C_6). ATR-IR (thin film) 3357.8, 2923.9, 2104.2, 1645.2, 1440.7, 1280.6, 1109.0, 1045.3, 933.5 cm^{-1}. $[\alpha]^{23}_D$ = +73.4 ($c = 1.0$, MeOH). MS (ESI): m/z = 190.0 $[M + H]^+$, 212.1 $[M + Na]^+$.

2,6-Anhydro-4-aza-7-azido-4-benzyl-3,4,5,7-tetradeoxy-D-*glycero*-D-*arabino*-heptitol (15). Triol **14** (280 mg, 1.4 mmol) was subjected to glycol cleavage and reductive amination, as described in the general procedure (Supporting Information), to obtain title compound **15** (191 mg, 0.73 mmol, 52%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5H, H_{ar}), 4.16 (m, 1H, H_6), 3.92 (m, 1H, H_2), 3.84 (dd, 1H, H_{1a}, $J_{1a,2}$ = 5.8 Hz, $J_{1a,1b}$ = 11.6 Hz), 3.74 (dd, 1H, H_{1b}, $J_{1b,2}$ = 3.4 Hz, $J_{1b,1a}$ = 11.6 Hz), 3.61 (dd, 1H, H_{7a}, $J_{7a,6}$ = 7.3 Hz, $J_{7a,7b}$ = 12.9 Hz), 3.47 (s, 2H, CH_2 Bn), 3.27 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.8 Hz, $J_{7b,7a}$ = 12.9 Hz), 2.58 (dd, 1H, H_{3a}, $J_{3a,2}$ = 3.4 Hz, $J_{3a,3b}$ = 11.4 Hz), 2.53 (dd, 1H, H_{5a}, $J_{5a,6}$ = 3.4 Hz, $J_{5a,5b}$ = 11.6 Hz), 2.47 (dd, 1H, H_{3b}, $J_{3b,2}$ = 5.6 Hz, $J_{3b,3a}$ = 11.4 Hz), 2.32 (dd, 1H, H_{5b}, $J_{5b,6}$ = 6.1 Hz, $J_{5b,5a}$ = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (C_q Bn), 128.9, 128.5, 127.4 (CH_{ar}), 71.3, 71.2 (C_2, C_6), 64.8 (C_1), 63.1 (CH_2 Bn), 54.4 (C_3), 54.2 (C_5), 51.8 (C_7). IR (thin film) 3384.5, 2936.2, 2094.6, 1454.2, 1265.2, 1149.6, 1112.9, 1053.1, 912.3, 742.5, 698.2 cm^{-1}. $[\alpha]^{23}_D$ = +3.8 ($c = 1.0$, CH_2Cl_2). HRMS: calcd for $C_{13}H_{18}N_4O_2H$ 263.15025, found 263.15015.

3,6-Anhydro-7-azido-2,7-dideoxy-D-*allo*-heptonic Acid (16). To a solution of ester **2** (350 mg, 1.52 mmol) in THF (4 mL) was added 1 M aq NaOH (2 mL). The mixture was neutralized after 3 h with Amberlite IR-120 (H^+), filtered, and concentrated. Purification by silica column chromatography (0% → 2% AcOH in EtOAc) furnished **16**, as a clear oil (323 mg, 1.49 mmol, 98%). ^1H NMR (400 MHz, CD_3OD): δ = 4.16 (ddd, 1H, H_3, $J_{3,2a}$ = 4.9 Hz, $J_{3,4}$ = 5.3 Hz, $J_{3,2b}$ = 8.4 Hz), 3.96 (m, 2H, H_5, H_6), 3.84 (dd, 1H, H_4, $J_{4,3}$ = 5.3 Hz, $J_{4,5}$ = 5.4 Hz), 3.51 (dd, 1H, H_{7a}, $J_{7a,6}$ = 3.1 Hz, $J_{7a,7b}$ = 13.2 Hz), 3.29 (dd, 1H, H_{7b}, $J_{7b,6}$ = 4.4 Hz, $J_{7b,7a}$ = 13.2 Hz), 2.67 (dd, 1H, H_{2a},

$J_{2a,3}$ = 4.9 Hz, $J_{2a,2b}$ = 15.7 Hz), 2.50 (dd, 1H, H_{2b}, $J_{2b,3}$ = 8.4 Hz, $J_{2b,2a}$ = 15.7 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ = 174.6 (C_1), 83.9 (C_6), 81.2 (C_3), 75.7 (C_4), 73.0 (C_5), 53.5 (C_7), 39.4 (C_2). ATR-IR (thin film): 3434.6, 2927.7, 2100.3, 1706.9, 1406.0, 1272.9, 1180.4, 1097.4, 1033.8, 977.8, 912.3, 827.4, 748.3 cm^{-1}. $[\alpha]^{23}_D$ +54.4 (c = 1.0, MeOH). MS (ESI): m/z 217.9 $[M + H]^+$, 241.0 $[M + Na]^+$, 435.1 $[2M + H]^+$, 457.1 $[2M + Na]^+$. HRMS: calcd for $C_7H_{11}N_3O_5H$ 218.07715, found 218.07724.

***cyclo*-[MAA-Val-Orn(Boc)-Leu-^{D}Phe-Pro-Val-Orn-Leu] (19). Route A.** Fmoc-based solid-phase peptide synthesis was performed as described previously,[6] starting with preloaded resin **17** (100 μmol), with a final coupling of **5a** (64 mg, 0.2 mmol, 2 equiv), BOP (132 mg, 0.3 mmol, 3 equiv), HOBt (41 mg, 0.3 mmol, 3 equiv), and DiPEA (58 μL, 0.35 mmol, 3.5 equiv) in NMP (2 mL), to ultimately furnish the title compound **19** (96 mg, 71 μmol, 71%) as a white amorphous solid.

Route B. Boc-protected GS analogue **21** (50 mg, 40 μmol) was dissolved in THF (7.5 mL) and DMF (2.5 mL), and a solution of sodium periodate (17 mg, 80 μmol, 2 equiv) in water (2.5 mL) was added. Stirring was continued overnight, after which the milky suspension was concentrated and partitioned between water and chloroform. The water layer was extracted with chloroform (2×), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to quantitatively produce the crude dialdehyde (50 mg, 40 μmol). Subsequently, the dialdehyde (25 mg, 20 μmol) was dissolved in MeOH (4 mL) and trimethyl orthoformate (2 mL) and $NaCNBH_3$ (7 mg, 100 μmol, 5 equiv) was added. To this mixture was added a solution of benzylamine (3.2 μL, 30 μmol, 1.5 equiv) in MeOH (0.5 mL), trimethyl orthoformate (0.2 mL), and DMF (0.2 mL) that had been acidified to pH = 5 with AcOH in advance. After stirring overnight, all solvents were evaporated and the mixture was applied to a size exclusion column that was eluted with MeOH, to yield the title compound **19** (17 mg, 12 μmol, 63%) as white amorphous solid.

***cyclo*-[MAA-Val-Orn-Leu-^{D}Phe-Pro-Val-Orn-Leu] (20).** A mixture of MAA-containing **19** (17 mg, 12 μmol) in DCM (2 mL) was cooled to 0 °C, treated with TFA (2 mL), and stirred for 30 min. The solvents were evaporated, and the crude mixture was analyzed by LC/MS (t_R 12.74 min (linear gradient 05 → 90% B in 20 min.; m/z = 1144.0 $[M + H]^+$, 572.7 $[M + H]^{2+}$) followed by semipreparative RP-HPLC purification (linear gradient of 3.0 CV; 35 → 55% B; t_R 2.2 CV), to produce **20** (10.6 mg, 9.3 μmol) in 77% after lyophilization of the pooled fractions. ^1H NMR (600 MHz, CD_3OH): δ = 8.86 (d, 1H, NH ^{D}Phe$_5$, $J_{NH,H\alpha}$ = 3.8 Hz), 8.65 (d, 1H, NH$_\alpha$ Orn$_8$, $J_{NH,H\alpha}$ = 8.2 Hz), 8.56 (d, 1H, NH$_\alpha$ Orn$_3$, $J_{NH,H\alpha}$ = 8.9 Hz), 8.48 (d, 1H, NH Leu$_4$, $J_{NH,H\alpha}$ = 8.7 Hz), 8.21 (d, 1H, NH Leu$_9$, $J_{NH,H\alpha}$ = 8.4 Hz), 7.89 (d, 1H, NH Val$_7$, $J_{NH,H\alpha}$ = 7.1 Hz), 7.83 (t, 1H, NH MAA$_1$, $J_{NH,8}$ = 5.8 Hz), 7.47−7.45 (m, 5H, H_{ar}), 7.39 (d, 1H, NH Val$_2$, $J_{NH,H\alpha}$ = 8.3 Hz), 7.31−7.23 (m, 5H, H_{ar}), 4.98 (m, 1H, H_α Orn$_3$), 4.63 (m, 1H, H_α Leu$_4$), 4.53 (m, 1H, H_α ^{D}Phe$_5$), 4.43 (m, 2H, H_α Leu$_9$, H_α Orn$_8$), 4.35 (m, 2H, H_α Pro$_6$, H_α Val$_2$), 4.23 (m, 2H, CH_2 Bn), 4.11 (m, 1H, H_3 MAA$_1$), 3.93 (m, 1H, H_7 MAA$_1$), 3.88 (m, 1H, H_α Val$_7$), 3.71 (m, 1H, $H_{\delta d}$ Pro$_6$), 3.36 (m, 1H, H_{8d} MAA$_1$), 3.32 (m, 2H, H_{4d}, H_{6d} MAA$_1$), 3.07 (m, 2H, $H_{\beta d}$ ^{D}Phe$_5$, H_{8u} MAA$_1$), 2.98 (m, 5H, H_δ Orn$_3$, H_δ Orn$_8$, $H_{\beta u}$ ^{D}Phe$_5$), 2.75 (m, 1H, H_{4u} MAA$_1$), 2.67 (m, 1H, H_{6u} MAA$_1$), 2.53 (m, 2H, H_{2d} MAA$_1$, $H_{\delta u}$ Pro$_6$), 2.30 (m, 1H, H_β Val$_7$), 1.95 (m, 3H, H_β Val$_2$, $H_{\beta d}$ Pro$_6$, $H_{\beta d}$ Orn$_8$), 1.88 (m, 1H, $H_{\beta d}$ Orn$_3$), 1.75 (m, 5H, $H_{\beta u,\gamma}$ Orn$_3$, H_γ Orn$_8$), 1.72 (m, 2H, $H_{\beta u,\gamma d}$ Pro$_6$), 1.67 (m, 1H, $H_{\beta u}$ Orn$_3$), 1.66 (m, 1H, $H_{\beta u}$ Orn$_8$), 1.65 (m, 1H, $H_{\gamma u}$ Pro$_6$), 1.64 (m, 3H, $H_{\beta,\gamma}$ Leu$_9$), 1.56 (m, 2H, $H_{\beta d,\ \gamma}$ Leu$_4$), 1.41 (m, 1H, $H_{\beta u}$ Leu$_4$), 0.97 (m, 3H, $H_{\gamma d}$ Val$_7$), 0.93 (m, 6H, H_γ Val$_2$), 0.90 (m, 9H, H_δ Leu$_4$, $H_{\gamma u}$ Val$_7$), 0.84 (m, 6H, H_δ Leu$_9$). HRMS: calcd for $C_{60}H_{94}N_{12}O_{10}H$ 1143.72886, found 1143.72632.

***cyclo*-[SAA-Val-Orn(Boc)-Leu-^{D}Phe-Pro-Val-Orn-Leu] (21).** In a similar scheme described in route A, preloaded resin **17** (100 μmol) was elongated in a stepwise fashion, with a final condensation of SAA **16** (44 mg, 0.2 mmol, 2 equiv), BOP (132 mg, 0.3 mmol, 3 equiv), HOBt (41 mg, 0.3 mmol, 3 equiv), and DiPEA (58 μL, 0.35 mmol, 3.5 equiv) in NMP (3 mL), to ultimately obtain the title peptide **21** (80 mg, 63 μmol, 63%) as an off-white amorphous solid. An aliquot of **21** (14 mg, 11.0 μmol) was then dissolved in DCM (2 mL) and cooled to 0 °C, and TFA (2 mL) was added slowly. After the mixture was stirred for 30 min, the volatiles were removed in vacuo and the crude peptide was analyzed by LC/MS (t_R 14.71 min (linear gradient 10 → 90% B in 20 min; m/z = 1070.8 $[M + H]^+$, 536.1 $[M + H]^{2+}$), purified by RP-HPLC (linear gradient of 3.0 CV; 40→50% B; t_R = 1.9 CV) and the combined fractions were lyophilizated to furnish the unprotected peptide (8.1 mg, 7.6 μmol, 69%) as an amorphous white powder. ^1H NMR (600 MHz, CD_3OH): δ = 8.90 (d, 1H, NH ^{D}Phe$_5$, $J_{NH,H\alpha}$ = 3.5 Hz), 8.68 (d, 1H, NH$_\alpha$ Orn$_3$, $J_{NH,H\alpha}$ = 8.1 Hz), 8.62 (d, 1H, NH Leu$_4$, $J_{NH,H\alpha}$ = 9.4 Hz), 8.61 (d, 1H, NH$_\alpha$ Orn$_8$, $J_{NH,H\alpha}$ = 8.9 Hz), 8.56 (d, 1H, NH Leu$_9$, $J_{NH,H\alpha}$ = 8.9 Hz), 8.07 (t, 1H, NH SAA$_1$, $J_{NH,7}$ = 6.1 Hz), 7.86 (bs, 2H, NH$_\delta$ Orn$_{3,8}$), 7.74 (d, 1H, NH Val$_7$, $J_{NH,H\alpha}$ = 8.6 Hz), 7.55 (d, 1H, NH Val$_2$, $J_{NH,H\alpha}$ = 8.5 Hz), 7.38−7.21 (m, 5H, H_{ar}), 4.98 (m, 1H, H_α Orn$_3$), 4.71 (m, 1H, H_α Orn$_8$), 4.65 (m, 1H, H_α Leu$_4$), 4.56 (m, 1H, H_α Leu$_9$), 4.51 (m, 1H, H_α ^{D}Phe$_5$), 4.34 (m, 1H, H_α Pro$_6$), 4.24 (m, 1H, H_α Val$_2$), 4.06 (m, 1H, H_α Val$_7$), 3.95 (m, 2H, H_3, H_6 SAA$_1$), 3.86 (dd, 1H, H_5 SAA$_1$, $J_{5,4}$ = 5.2 Hz, $J_{5,6}$ = 3.0 Hz), 3.78 (dd, 1H, H_4 SAA$_1$, $J_{4,5}$ = 5.2 Hz, $J_{4,3}$ = 6.5 Hz), 3.72 (m, 1H, $H_{\delta d}$ Pro$_6$), 3.36 (m, 1H, H_{7d} SAA$_1$), 3.31 (m, 1H, H_{7u} SAA$_1$), 3.07 (dd, 1H, $H_{\beta d}$ ^{D}Phe$_5$, $J_{\beta d,\beta u}$ = 12.6 Hz, $J_{\beta d,\alpha}$ = 5.0 Hz), 3.02 (m, 1H, $H_{\delta d}$ Orn$_3$), 2.98 (m, 1H, $H_{\delta d}$ Orn$_8$), 2.96 (m, 3H, $H_{\delta u}$ Orn$_3$, $H_{\delta u}$ Orn$_8$, $H_{\beta u}$ ^{D}Phe$_5$), 2.50 (m, 3H, H_2 SAA$_1$, $H_{\delta u}$ Pro$_6$), 2.28 (m, 1H, H_β Val$_7$), 1.99 (m, 3H, $H_{\beta d}$ Pro$_6$, $H_{\beta d}$ Orn$_3$, H_β Val$_2$), 1.83 (m, 1H, $H_{\beta d}$ Orn$_8$), 1.74 (m, 2H, H $_\gamma$ Orn$_3$), 1.71 (m, 2H, $H_{\beta u,\ \gamma d}$ Pro$_6$), 1.67 (m, 1H, $H_{\beta u}$ Orn$_3$), 1.66 (m, 2H, H_γ Orn$_8$), 1.64 (m, 3H, $H_{\beta,\ \gamma}$ Leu$_9$), 1.59 (m, 1H, $H_{\gamma u}$ Pro$_6$), 1.56 (m, 2H, $H_{\beta d,\ \gamma}$ Leu$_4$), 1.39 (m, 1H, $H_{\beta u}$ Leu$_4$), 0.95 (m, 3H, $H_{\gamma d}$ Val$_7$), 0.94 (m, 3H, $H_{\gamma d}$ Val$_2$), 0.92 (m, 3H, $H_{\gamma u}$ Val$_2$), 0.90 (m, 6H, H_δ Leu$_4$), 0.88 (m, 3H, $H_{\gamma u}$ Val$_7$), 0.86 (m, 6H, H_δ Leu$_9$). ATR-IR (thin film): 3278.1, 3071.9, 2959.2, 2935.6, 2873.4, 1669.8, 1636.5, 1539.2, 1464.7, 1456.7, 1437.0, 1203.7, 1182.7, 1135.0, 1033.3, 1020.8, 837.1, 800.1, 722.6, 702.5 cm^{-1}. HRMS: calcd for $C_{53}H_{87}N_{11}O_{12}H$ 1079.6608, found 1070.6521.

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Supporting Information Available: General experimental methods and copies of ^1H and ^{13}C NMR spectra as well as 2D NMR spectra of compounds **4a**, **8a**,**b**, **12a**,**b**, **20**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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