Submonomer Solution Synthesis of Hydrazinoazapeptoids, a New Class of Pseudopeptides

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The development of oligomeric peptidomimetics is actually the focus of increasing attention.[1] This arises from the very low bioavailability of peptides, which seriously limited their therapeutical applications. Azapeptides,[2] peptoids,[3] and ureapeptoids[4] belong to a new conceptual class of peptidomimetic in which the side chains are carried by nitrogen atoms. Moreover, the potentiality to automate the synthesis of such oligomers by iterative procedures in the solid phase enables the creation of libraries useful for lead-finding in drug discovery.

Our present results come within that general framework. More precisely, we are interested in the synthesis of new kinds of pseudopeptides that we termed hydrazinoazapeptoids by analogy with peptoids. These "hybrid" peptidomimetics combine a C-terminal azaamino acid unit (aza) or an N-substituted azaglycine (Naza) with N^{α}-substituted hydrazinoglycines (N^{α}h) (Figure 1).

Although the chemistry of azaamino derivatives has been widely explored and is well documented,[2] that of hydrazino acids has been the object of much less attention.[5] Recently, some progress has been made in their preparation, although through laborious methods, in particular concerning the synthesis of optically enriched compounds.[6] Nevertheless, only a limited number of side chains seem to be compatible with the chemical methods involved at that time. Moreover, due to the presence of the additional N^{α}, difficulties sometimes occurred during the preparation of hydrazino acids,[6b] and their utilization in pseudopeptides design for which the coupling with amino acids is not always regioselective.[5] This should be the reason why commercially available hydrazinoacids are N^{α} protected.

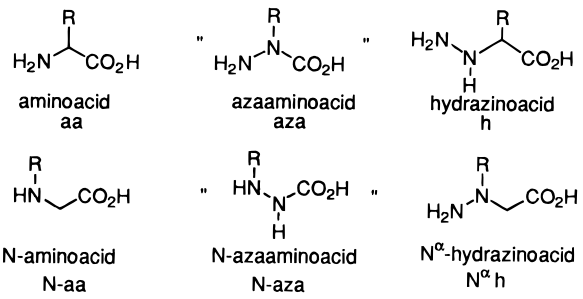

Figure 1. Adopted symbolism for amino acid analogues.

Results and Discussion

In this paper, following our previous research on hydrazinopeptides,[7] we describe a conceptual approach that circumvents these problems by shifting the side chain from the C^{α} to the adjacent N^{α} position, generating in this way N^{α}-substituted hydrazinoglycine. It can be pointed out that one natural compound, the antibiotic negamycin, incorporates one such building block.[8] Our synthetic strategy relies on a sequential process using submonomer methodology. By comparison with the synthesis of peptoids,[3] in our case the displacement of the bromine atom by a monosubstituted alkyl or aralkyl hydrazine can afford two regioisomers in variable proportions. Indeed, it is well-known that the nucleophilicities of the two nitrogens of monosubstituted hydrazines are balanced by both steric and electronic effects of the substituent. As our first goal was the synthesis of N^{α}-substituted hydrazinoglycine, only one regioisomer was desired. Thus, we had to engage in most cases N^{β}-protected hydrazines to avoid alkylation on this atom (step B, Scheme 1). Despite the steric hindrance of these disubstituted hydrazines and the electron-withdrawing effect of the protecting group, substitution takes place in reasonable time in smoothly refluxing chloroform. Typically, a 3-fold excess of hydrazine is used. The reactions are easily followed by ^{1}H NMR, looking for total extinction of the bromomethylene signal. After completion, the crude reaction mixture contains only the expected compound and the remaining hydrazine, which are conveniently separated by chromatography on silica gel. The pseudodipeptides so obtained are orthogonally protected and can thereby be further elongated on the C or N terminal after selective deprotection (Scheme 1).

Considering the models that we have tested, and the fact that numerous Boc or Z-protected alkyl and aralkyl

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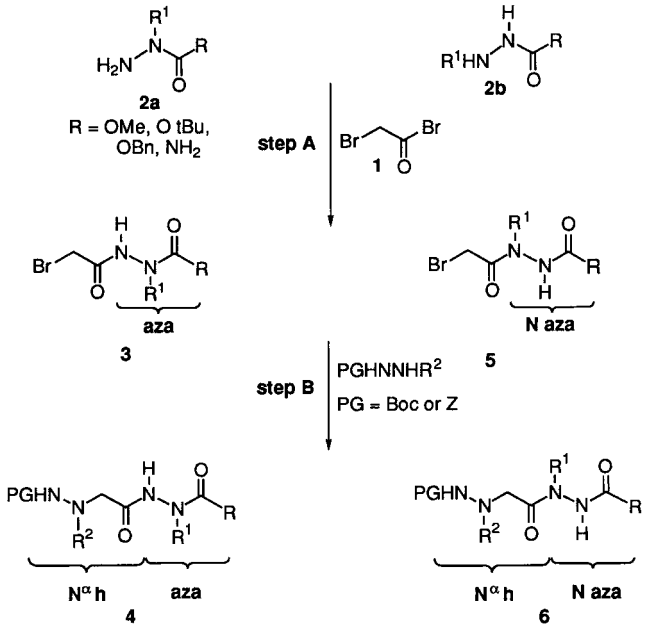
Scheme 1



	R	R^1	R^2
4a	OtBu	H	CH_3
4b	OCH_2Ph	H	$CH(CH_3)CH_2CH_3$
4c	OCH_2Ph	H	$CH_2CH(CH_3)_2$
4d	OtBu	H	CH_2Ph
4e	OCH_3	$CH_2CH(CH_3)_2$	CH_2Ph
4f	OCH_3	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$
4g	OCH_2Ph	H	$CH(CH_3)_2$
4h	OCH_2Ph	H	$CH_2(C_6H_4)OBn$
4i	OCH_2Ph	H	$(CH_2)_2OBn$
4j	OtBu	H	$CH_2C_6H_4pCF_3$
4k	OCH_2Ph	H	$(CH_2)_4NHBoc$
4l	OCH_2Ph	H	$CH_2CH(Ph)_2$
6a	OCH_3	$CH_2CH(CH_3)_2$	CH_2Ph
6b	NH_2	$CH_2CH(CH_3)_2$	CH_2Ph
6c	NH_2	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$

hydrazines are synthetically available,[2a,d,9] it seems consistent to postulate that a large variety of side chains can be introduced, mimicking both proteogenic or non-proteogenic amino acids (Scheme 1).

We have also prepared the pseudopeptide **7** following the same principle. N,N′-Disubstituted benzylcarbazate was easily prepared according to the literature[2c,9] and reacted with bromohydrazide **3** (Scheme 2). This last example further illustrates the great steric tolerance of the substitution step. By this method, it is possible to introduce a methyl substituent on the N^{β} nitrogen that will increase the chemical stability toward peptidases when a peptidic or pseudopeptidic linkage is created on this position.[10]

The repetition of steps A and B leads to superior homologues in a similar way, as illustrated by the synthesis of the three pseudotripeptides **8** (N^{α}hAla-N^{α}-hPhe-azaGly-OtBu), **9** (Boc-N^{α}hVal-N^{α}hPhe-azaGly-OBn), and **10** (Boc-N^{α}hpCF_3Phe-N^{α}hPhe-azaGly-OtBu) (Scheme 3).

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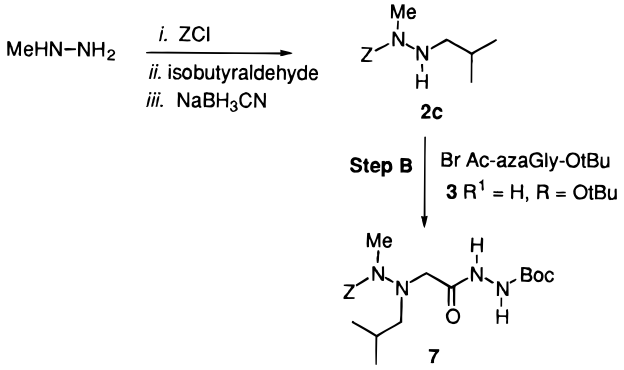
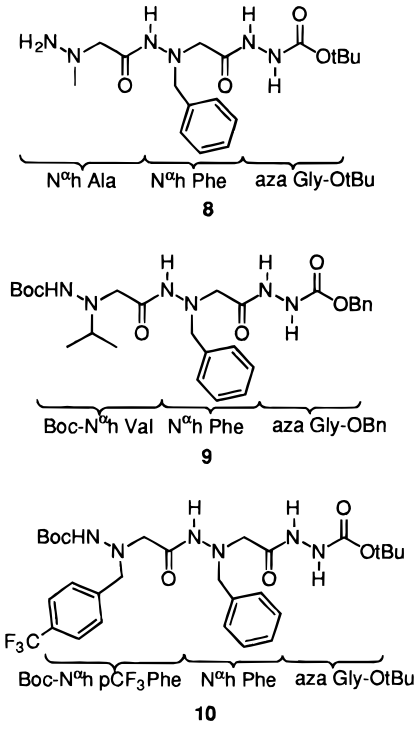
Scheme 2



Scheme 3



As bromohydrazides, which are our building blocks, are simply obtained by reacting a carbazate with bromoacetyl bromide, chemical variations can also be introduced on this part of our pseudopeptides. The synthesis of both pseudodipeptides **4e** (Boc-N^{α}hPhe-azaLeu-OMe) and **6a** (Boc-N^{α}hPhe-NazaLeu-OMe) (Scheme 1) clearly shows that the relative positions of the two side chains can be easily modulated in this way. The compounds prepared are new pseudopeptidic variations of the Phe-Leu terminal dipeptide from leucine-enkephaline.

Conclusion

These preliminary results demonstrate that the manipulation of the flexible chemistry of hydrazine constitutes a simple way to combine special kinds of azaamino acids and hydrazino acids where the side chains are introduced in unusual positions. Hybrid pseudopeptides with nitrogen-enriched peptidic backbones are obtained. These atoms can carry various side chains, allowing the iterative construction of elaborated peptidomimetics. In considering the related peptoids, the present compounds can be regarded as hydrazinoazapeptoids. In addition to the synthesis of oligomeric derivatives, such building

blocks can be integrated in peptidic fragments or combined with other amino acids' analogues, increasing the diversity of peptidomimetics.

Experimental Section

NMR spectra were run at 200, 300 (^{1}H), or 75.5 MHz (^{13}C). HR-MS were obtained from the Centre Régional de Mesures Physiques de l'Ouest, using an MS/MS mass spectrometer ZAB Spec TOF. Infrared spectra were recorded on an FT-IR spectrometer as suspensions in KBr. Elemental analyses were performed by the analytical laboratory, CNRS (Lyon).

Boc- or Z-protected alkyl or aralkyl hydrazines **2b** and **2c** were prepared according to literature procedures by reduction of Boc- or Z-protected hydrazones, derived from the reaction of Boc- or Z-carbazate with either aldehyde or ketone.[9,11] Carbomethoxylation of **2a** with MocCl and deprotection by HCl afforded **2b**.

Step A. To a stirred and cooled (0 °C) solution of N-protected hydrazine (30 mmol, 3 equiv) in methylene chloride (20 mL) and pyridine (30 mmol, 3 equiv) was added the bromo acetyl bromide (10 mmol, 1 equiv) in methylene chloride (5 mL). The reaction mixture was stirred over a period of 6 h and washed three times with water (50 mL). The organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product slowly precipitated.

BrCH$_2$CO-azaGly-OtBu (**3**, R^1 = H, R = OtBu): yield 94%; mp 77 °C; IR (KBr) 3500−3100, 1723, 1706, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 3.97 (s, 2H), 7.03 (s br, 1H), 8.75 (s br, 1H). Anal. Calcd for $C_7H_{13}N_2O_3Br$: C, 33.20; H, 5.14; N, 11.07; Br, 31.62. Found: C, 33.07; H, 5.10; N, 10.78; Br, 31.44.

BrCH$_2$CO-azaGly-OBn (**3**, R^1 = H, R= OCH_2Ph): yield 80%; mp 98 °C; IR (Nujol) 3330, 3250, 1720, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 2H), 5.19 (s, 2H), 6.88 (s br, 1H), 7.37 (m, 5H), 8.25 (s br, 1H). Anal. Calcd for $C_{10}H_{11}N_2O_3Br$: C, 41.81; H, 3.83; N, 9.76; Br, 27.87. Found: C, 41.54; H, 3.91; N, 9.59; Br, 27.45.

BrCH$_2$CO-azaLeu-OMe (**3**, R^1 = $CH_2CH(CH_3)_2$, R = OCH_3): yield 99%; oil; IR (Nujol) 3250, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 6H, J = 6.5 Hz), 1.9 (m, 1H), 3.35 (d, 2H, J = 7.5 Hz), 3.75 (s, 3H), 3.88 (s, 2H), 7.09 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9 (q, J = 126 Hz), 26.4 (t, J = 154 Hz), 26.9 (d, J = 126 Hz), 53.6 (q, J = 143 Hz), 56.8 (t, J = 140 Hz), 155 (s), 163 (s). Anal. Calcd for $C_8H_{15}N_2O_3Br$: C, 35.95; H, 5.62; N, 10.49; Br, 25.96. Found: C, 35.96; H, 5.56; N, 10.47; Br, 25.87.

BrCH$_2$CO-NazaLeu-OMe (**5**, R^1 = $CH_2CH(CH_3)_2$, R = OCH_3): yield 80%; mp 108 °C; IR (Nujol) 3250, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$)[11] δ 0.93 (d, 6H, J = 6.7 Hz), 1.95 (m, 1H), 3.41 (br, 2H), 3.79 (s, 3H), 3.89 (s, 2H), 8.55 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3 (q, J = 126 Hz), 26.9 (d, J = 154 Hz), 28.1 (t, J = 131 Hz), 53.2 (q, J = 148 Hz), 55.7 (t, J = 140 Hz), 156.6 (s), 169.5 (s). Anal. Calcd for $C_8H_{15}N_2O_3Br$: C, 35.95; H, 5.62; N, 10.49; Br, 25.96. Found: C, 35.91; H, 5.52; N, 10.50; Br, 25.78.

BrCH$_2$CO-NazaLeu-NH$_2$ (**5**, R^1 = $CH_2CH(CH_3)_2$, R = NH_2): yield 54%; mp 168 °C; IR (KBr) 3367, 3191, 1712, 1665, 1623 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.85 (br, 6H), 1.88 (m, 1H), 2.82 (dd, 1H, J = 10.5, 6.8 Hz), 3.69 (dd, 1H, J = 10.5, 6.8 Hz), 3.91 (d, 1H, J = 12.8 Hz), 4.21 (d, 1H, J = 12.8 Hz), 6.21 (s, 2H), 8.58 (s, 1H). Anal. Calcd for $C_7H_{14}N_3O_2Br$: C, 33.33; H, 5.56; N, 16.67; Br, 31.75. Found: C, 33.34; H, 5.65; N, 16.92; Br, 31.44.

Step B. To a stirred solution of N-protected hydrazine (20 mmol, 3 equiv) in chloroform (12 mL) was added slowly the α-bromo hydrazide **3** (10 mmol, 1 equiv) in chloroform (5 mL). The reaction mixture was refluxed over a period of 12 h and, after cooling, washed once with $NaHCO_3$ 1 N (30 mL) and twice with water (30 mL). The organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromathography (hexane−EtOAc as eluent 1:1).

N$^\alpha$hAla-azaGly-OtBu (4a): yield 70%; mp 101 °C; IR (Nujol) 3340, 3310, 1730, 1705, 1680, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.50 (s, 3H), 3.00 (s br, 2H), 3.25 (s, 2H), 6.75 (s br, 1H), 8.40 (s br, 1H). Anal. Calcd for $C_8H_{18}N_4O_3$: C, 44.03; H, 8.26; N, 25.69. Found: C, 43.92; H, 8.03; N, 25.53.

Boc-N$^\alpha$hIle-azaGly-OBn (4b): yield 80%; mp 110 °C; IR (KBr) 3250, 1750, 1712, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz), 0.95 (d, 3H, J = 6.5 Hz), 1.20 (m, 2H), 1.40 (s, 9H), 2.70 (m, 1H), 3.40 (s, 2H), 5.10 (s, 2H), 5.85 (s br, 1H), 6.35 (s br, 1H), 7.30 (m, 5H), 10.00 (s br, 1H); HR-MS FAB m/z for $C_{19}H_{30}N_4O_5$ calcd 497.2012 (M + H$^+$), obsd 497.2020. Anal. Calcd: C, 57.87; H, 7.61; N, 14.21. Found: C, 58.10; H, 7.79; N, 14.40.

Boc-N$^\alpha$hLeu-azaGly-OBn (4c): yield 54%; mp 128 °C; IR (KBr) 3250−3100, 1732, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 6H, J = 6.4 Hz), 1.43 (s, 9H), 1.68 (m, 1H), 2.53 (d, 2H, J = 6.9 Hz), 3.49 (s, 2H), 5.16 (s, 2H), 5.54 (s br, 1H), 6.49 (s br, 1H), 7.35 (m, 5H), 9.84 (s br, 1H); HR-MS FAB m/z for $C_{19}H_{30}N_4O_5$ calcd 395.2294 (M + H$^+$), obsd 395.2295. Anal. Calcd: C, 57.87; H, 7.61; N, 14.21. Found: C, 58.17; H, 7.61; N, 14.14.

H-N$^\alpha$hPhe-azaGly-OtBu (4d): yield 75%; mp 140 °C; IR (KBr) 3291, 3191, 3152, 1732, 1690, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.55 (s br, 2H), 3.28 (s, 2H), 3.73 (s, 2H), 6.65 (s br, 1H), 7.30 (s, 5H), 8.60 (s br, 1H). Anal. Calcd for $C_{14}H_{22}N_4O_3$: C, 57.14; H, 7.48; N, 19.05. Found: C, 57.06; H, 7.61; N, 18.91.

Boc-N$^\alpha$hPhe-azaLeu-OMe (4e): yield 44%; mp 114 °C; IR (Nujol) 3250, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 6H, J = 6.5 Hz), 1.35 (s, 9H), 1.9 (m, 1H), 3.33 (d, 2H, J = 7.3 Hz), 3.47 (s, 2H), 3.67 (s, 3H), 3.95 (s, 2H), 5.79 (s br, 1H), 7.35 (m, 5H), 9.86 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 19.96 (q, J = 125 Hz), 26.67 (d, J = 129 Hz), 28.13 (q, J = 127 Hz), 53.26 (q, J = 147 Hz), 56.93 (t, J = 147 Hz), 59.35 (t, J = 137 Hz), 63.31 (t, J = 137 Hz), 80.92 (s), 128.09 (d, J = 161 Hz), 128.53 (d, J = 160 Hz), 129.55 (d, J = 158 Hz), 135.16 (s), 156.17 (s), 156.56 (s), 168.68 (s); HR-MS FAB m/z for $C_{20}H_{33}N_4O_5$ calcd 409.2451 (M + H$^+$), obsd 409.2456. Anal. Calcd: C, 58.68; H, 8.07; N, 13.69. Found: C, 58.76; H, 8.10; N, 13.63.

Boc-N$^\alpha$hLeu-azaLeu-OMe (4f): yield 42%; mp 93 °C; IR (Nujol) 3206, 1711, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 6H), 0.92 (d, J = 6.6 Hz, 6H), 1.37 (s, 9H), 1.65 (m, 1H), 1.82 (m, 1H), 2.47 (d, J = 7.5 Hz, 2H), 3.27 (d, J = 7 Hz, 2H), 3.38 (s, 2H), 3.62 (s, 3H), 5.52 (s br, 1H), 9.89 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.30 (q, J = 125 Hz), 20.90 (q, J = 125 Hz), 26.88 (d, J = 124 Hz), 27.07 (d, J = 124 Hz), 28.58 (q, J = 126.5 Hz), 53.57 (q, J = 147 Hz), 57.40 (t, J = 136 Hz), 62.06 (t, J = 133 Hz), 68.54 (t, J = 130 Hz), 81.18 (s), 156.64 (s), 156.95 (s), 169.21 (s); HR-MS FAB m/z for $C_{17}H_{34}N_4O_5$ calcd 375.2607 (M + H$^+$), obsd 375.2603. Anal. Calcd: C, 54.54; H, 9.10; N, 14.97. Found: C, 54.32; H, 9.22; N, 15.15.

Boc-N$^\alpha$hVal-azaGly-OBn (4g): yield 72%; oil; IR (KBr) 3652−3121, 1748−1634 cm^{-1}; ^{1}H NMR ($CDCl_3$)[12] δ 0.96 (d, 6H, J = 6.1 Hz), 1.39 (s, 9H), 3 (m, 1H), 3.38 (s, 2H), 5.08 (s, 2H), 5.75 (s br, 1H), 6.55 (s br, 1H), 9.96 (s br, 1H). For elemental analysis the hydrazinopeptoide **4g** was deprotected.

Boc-N$^\alpha$hVal-NHNH$_2$: yield 68%; mp 108 °C; IR (KBr) 3376, 3324, 3220, 3127, 1702, 1680, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$)[12] δ 1.14 (d, 6H, J = 6.5 Hz), 1.53 (s, 9H), 3.15 (m, 1H), 3.48 (s, 2H), 3.93 (s br, 2H), 5.75 (s br, 1H), 9.46 (s br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2 (q, J = 125 Hz), 28.6 (q, J = 126 Hz), 57.3 (d, J = 135 Hz), 58.5 (t, J = 141 Hz), 81.2 (s), 156.9 (s), 170.3 (s). Anal. Calcd for $C_{10}H_{22}N_4O_3$: C, 48.78; H, 8.94; N, 22.77. Found: C, 48.80; H, 8.69; N, 23.03.

Boc-N$^\alpha$hTyr(Bzl)-azaGly-OBn (4h): yield 94%; mp 60 °C; IR (KBr) 3400−3100, 1750−1680, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 3.42 (s, 2H), 3.80 (s, 2H), 4.98 (s, 2H), 5.08 (s, 2H), 5.61 (s br, 1H), 6.40 (s br, 1H), 7.02 (AB, J = 8.5 Hz, 4H), 7.22−7.40 (m, 5H), 9.70 (s br, 1H); HR-MS FAB m/z for $C_{29}H_{34}N_4O_6$ calcd 535.2557 (M + H$^+$), obsd 535.2554. Anal. Calcd: C, 65.17; H, 6.37; N, 10.48. Found: C, 65.00; H, 6.35; N, 10.24.

Boc-N$^\alpha$h-homoSer(Bzl)-azaGly-OBn (4i): yield 53%; mp 90 °C; IR (KBr) 3277, 1747, 1698, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 9H), 3.3 (t br, 2H), 3.83 (s, 2H), 3.87 (t br, 2H), 4.74 (s, 2H), 5.36 (s, 2H), 6.83 (s br, 1H), 7.00 (s br, 1H), 7.55 (m, 10H), 10.1 (s br, 1H); HR-MS FAB m/z for $C_{24}H_{32}N_4O_6$ calcd 473.2400 (M + H$^+$), obsd 473.2384. Anal. Calcd: C, 61.02; H, 6.78; N, 11.86. Found: C, 60.76; H, 7.10; N, 11.92.

(11) Han, H. H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2339−2344.

(12) These values were obtained at 55 °C (78 °C for **7**) as the room temperature spectrum is poorly resolved because of partial coalescence of most of the signals.

Boc-N$^{\alpha}$hpCF$_3$Phe-azaGly-OBn (4j): yield 70%; mp 139−143 °C; IR (KBr) 3300, 1758, 1702, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 3.58 (s, 2H), 4.01 (s, 2H), 5.17 (s, 2H), 5.9 (s br, 1H), 6.6 (s br, 1H), 7.35 (s, 5H), 7.56 (AB, J = 7.7 Hz, 4H), 9.8 (s br, 1H); HR-MS FAB m/z for $C_{23}H_{27}N_4O_5F_3$ calcd 395.2294 (M + H$^+$), obsd 395.2299. Anal. Calcd: C, 55.65; H, 5.44; N, 11.29; F, 11.43. Found: C, 55.40; H, 5.71; N, 11.50; F, 11.67.

Z-N$^{\alpha}$hLys(Boc)-azaGly-OBn (4k): yield 51%; mp 66 °C; IR (KBr) 3400−3200, 1745, 1702, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.52 (m, 4H), 2.78 (t br, 2H), 3.10 (t br, 2H), 3.51 (s, 2H), 4.76 (s br, 1H), 5.09 (s, 2H), 5.15 (s, 2H), 6.20 (s br, 1H), 6.70 (s br, 1H), 7.35 (m, 10H), 9.50 (s br, 1H). HR-MS FAB m/z for $C_{27}H_{37}N_5O_7$ calcd 544.2771 (M + H$^+$), obsd 544.2793. Anal. Calcd for $C_{27}H_{37}N_5O_7 \cdot 0.5C_4H_{10}O$: C, 60.00; H, 7.24; N, 12.07. Found: C, 59.78; H, 6.90; N, 12.63.

Boc-N$^{\alpha}$h(diPhenylmethyl)Ala-azaGly-OBn (4l): yield 61%; mp 64 °C; IR (KBr) 3400−3100, 1740−1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.4 (d br, 2H), 3.52 (s, 2H), 4.10 (t, 1H, J = 7.6 Hz), 5.07 (s, 2H), 5.82 (s br, 1H), 6.10 (s br, 1H), 7.15 (m, 15H), 8.68 (s br, 1H); HR-MS FAB m/z for $C_{29}H_{34}N_4O_5$ calcd 519.2607 (M + H$^+$), obsd 519.2608. Anal. Calcd: C, 67.18; H, 6.57; N, 10.81. Found: C, 66.67; H, 6.77; N, 10.67.

Boc-N$^{\alpha}$hPhe-NazaLeu-OMe (6a): yield 40%; mp 110 °C; IR (KBr) 3291, 3174, 1744, 1702, 1655 cm^{-1}; ^{1}H NMR[13] ($CDCl_3$) δ 0.9 (d, 6H, J = 6.6 Hz), 1.3 (s, 9H), 1.9 (m, 1H), 3.4 (br, 2H), 3.5 (br, 2H), 3.7 (s, 3H), 3.9 (s, 2H), 6.3 (s br, 1H), 7.3 (m, 5H), 8.9 (s br, 1H); HR-MS FAB m/z for $C_{20}H_{31}N_4O_5$ calcd 409.2451 (M + H$^+$), obsd 409.2467. Anal. Calcd: C, 58.97; H, 7.62; N, 13.76. Found: C, 58; H, 7.84; N, 13.77.

Boc-N$^{\alpha}$hPhe-NazaLeu-NH$_2$ (6b): yield 40%; mp 150 °C; IR (KBr) 3413, 3284, 3220, 3195, 1723, 1686, 1655 cm^{-1}; ^{1}H NMR[13] ($CDCl_3$) δ 0.9 (d, 6H, J = 6.7 Hz), 1.3 (s, 9H), 2 (m, 1H), 3.4 (br, 2H), 3.6 (br, 2H), 3.9 (br, 2H), 5.2 (s br, 2H), 6.1 (s br, 1H), 7.3 (m, 5H), 8.4 (s br, 1H); HR-MS FAB m/z for $C_{19}H_{31}N_5O_4$ calcd 394.2454 (M + H$^+$), obsd 394.2448. Anal. Calcd: C, 58.02; H, 7.89; N, 17.81. Found: C, 58.10; H, 7.96; N, 17.84.

Boc-N$^{\alpha}$hLeu-NazaLeu-NH$_2$ (6c): yield 42%; mp 138 °C; IR (KBr) 3342, 3195, 1723, 1680, 1665, 1619 cm^{-1}; ^{1}H NMR[13] ($CDCl_3$) δ 0.96 (d, 6H, J = 6.6 Hz), 0.97 (d, 6H, J = 6.7 Hz), 1.47 (s, 9H), 1.82 (m, 1H), 2.01 (m, 1H), 2.53 (d br, 2H, J = 6.7 Hz), 3.47 (br, 2H), 3.58 (br, 2H), 5.37 (s br, 2H), 6.24 (s br, 1H), 8.69 (s br, 1H); HR-MS FAB m/z for $C_{16}H_{33}N_5O_4$ calcd 360.2611 (M + H$^+$), obsd. 360.2600. Anal. Calcd: C, 53.48; H, 9.19; N, 19.50. Found: C, 53.27; H, 9.23; N, 19.39.

Z-N$^{\beta}$Me-N$^{\alpha}$hLeu-azaGly-OtBu (7): yield 40%; mp 121 °C; IR (KBr) 3228, 3141, 1732, 1698 cm^{-1}; ^{1}H NMR[12] (C_6D_6) δ 0.83 (d, 6H, J = 5.3 Hz), 1.38 (m, 1H), 1.39 (s, 9H), 2.21 (d, 2H, J = 4.8 Hz), 2.54 (s, 3H), 3.21 (s, 2H), 5.10 (s, 2H), 6.28 (s br, 1H), 7.16 (m, 5H), 9.45 (s br, 1H); HR-MS FAB m/z for $C_{20}H_{32}N_4O_5$ calcd 409.2451 (M + H$^+$), obsd 409.2463. Anal. Calcd: C, 58.82; H, 7.84; N, 13.73. Found: C, 58.57; H, 7.93; N, 13.77.

Reiteration of Steps A and B. H-N$^{\alpha}$hAla-N$^{\alpha}$hPhe-azaGly-OtBu (8): yield 78%; mp 104 °C; IR (KBr) 3334, 3228, 1715, 1665 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 1.45 (s, 9H), 2.30 (s, 3H), 3.00 (s, 2H), 3.58 (s, 2H), 4.13 (s, 2H), 7.40 (s, 5H), 8.80 (s br, 1H), 9.25 (s br, 1H), 9.80 (s br, 1H); HR-MS FAB m/z for $C_{17}H_{28}N_6O_4$ calcd 381.2250 (M + H$^+$), obsd 381.2268. Anal. Calcd for $C_{17}H_{28}N_6O_4$, 2HCl: C, 45.03; H, 6.62; N, 18.54. Found: C, 45.44; H, 6.24; N, 18.06.

Z-N$^{\alpha}$hVal-N$^{\alpha}$hPhe-azaGly-OtBu (9): yield 40%; mp 136 °C; IR (KBr) 3500−3100, 1760−1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 6H, J = 6.5 Hz), 1.41 (s, 9H), 3.03 (m, 1H), 3.32 (s, 2H), 3.54 (s, 2H), 3.93 (s, 2H), 5.10 (s, 2H), 5.88 (s br, 1H), 6.20 (s br, 1H), 7.38 (m, 10H), 9.35 (s br, 1H), 9.68 (s br, 1H); HR-MS FABm/z for $C_{27}H_{38}N_6O_6$ calcd 543.2931 (M + H$^+$), obsd 543.2930. Anal. Calcd: C, 59.78; H, 7.01; N, 15.50. Found: C, 59.64; H, 6.96; N, 15.80.

Boc-N$^{\alpha}$hpCF$_3$Phe-N$^{\alpha}$hPhe-azaGly-OtBu (10): yield 57%; mp 90 °C; IR (KBr) 3510−3260, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.43 (s, 9H), 3.42 (s, 2H), 3.54 (s, 2H), 3.95 (s, 2H), 3.98 (s, 2H), 5.81 (s br, 1H), 6.24 (s br, 1H), 7.35 (m, 5H), 7.53 (AB, 4H, J = 8.25 Hz), 9.30 (s br, 1H), 9.74 (s br, 1H); HR-MS FAB m/z for $C_{29}H_{39}N_6O_6F_3$ calcd 625.2961 (M + H$^+$), obsd 625.2967. Anal. Calcd: C, 55.77; H, 6.25; N, 13.46; F, 9.13. Found: C, 55.53; H, 6.36; N, 13.55; F, 8.92.

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(13) The title compound is present in two rotameric forms in solution; the data of only the major compound are reported.