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Access to Enantiopure α-Hydrazino Acids for *N*-Amino Peptide Synthesis

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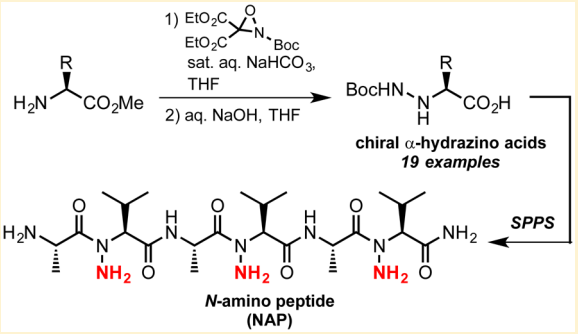
Supporting Information

ABSTRACT: Backbone *N*-methylation of α-peptides has been widely employed to enhance the bioavailability and bioactivity of parent sequences. Heteroatomic peptide amide substituents have received less attention due, in part, to the lack of practical synthetic strategies. Here, we report the synthesis of α-hydrazino acids derived from 19 out of the 20 canonical proteinogenic amino acids and demonstrate their use in the solid-phase synthesis of *N*-amino peptide derivatives.



The introduction of backbone amide substituents has a profound impact on the conformation and proteolytic stability of peptides. Backbone *N*-methylation, for example, has been utilized extensively in peptide structure−activity relationship (SAR) campaigns to probe for bioactive conformations and to improve the bioavailability of lead compounds.[1] From a synthetic standpoint, substitution of a single amide within a sequence represents a subtle modification. However, the resulting increase in *cis* amide rotamer population and removal of a main chain hydrogen-bond donor can give rise to significant conformational heterogeneity. This is particularly evident in peptoids owing to the presence of multiple tertiary amides as well as to the absence of Cα substituents that would otherwise restrict backbone dihedral angles.[2] The development of amide substitution strategies that maintain side-chain functionality while constraining main-chain torsions would thus be of considerable utility in peptidomimetic drug design.

In an effort toward conformationally defined and proteolytically stable peptidomimetics, our group recently developed a class of *N*-amino peptide (NAP) derivatives that are constrained by both covalent and noncovalent interactions.[3] As shown in Figure 1, backbone-aminated peptides retain native Cα substituents, which reduces the number of accessible ϕ and ψ torsions.[4] This feature sets NAPs apart from the related but inherently more flexible glycine-derived *N*-azapeptoids.[5] In contrast to oligomeric *N*-alkylated peptides,[6] the *N*-amino substituent in NAPs also offers a handle for hydrogen bonding or subsequent chemical diversification. Given that ease of synthesis is a major consideration for peptidomimetic SAR studies, we sought a convenient route to diversely substituted α-hydrazino acid building blocks[7] for the assembly of NAPs on solid support. Here, we describe a practical electrophilic amination approach to enantiopure α-hydrazino acids corresponding to 19 canonical proteinogenic amino acids as well as an optimized protocol for their introduction into host peptides.

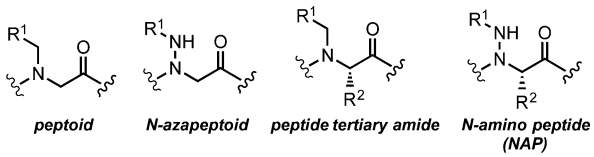


Figure 1. Representative backbone amide modified peptidomimetics.

Peptoids and *N*-azapeptoids are typically prepared via a submonomer approach that relies on displacement of α-halo amides with amine or hydrazine nucleophiles.[5,8] Unfortunately, chiral secondary α-bromo acids and amides are not readily available and may epimerize or undergo elimination during reaction with basic nucleophiles.[3b,9] As an alterantive to on-resin submonomer synthesis, we explored a conventional building block strategy toward NAPs that relied on S_N2 displacement of chiral triflates with *tert*-butylcarbazate (Scheme 1).[3,10] Unlike reactions with α-bromoamides or esters, these reactions proceed rapidly at low temperature with little to no racemization. The triflate intermediates are, in turn, derived from D-amino acids via a diazotization reaction that proceeds with overall retention of stereochemistry.[11] Although convenient for the synthesis of aliphatic α-hydrazino acids, a number of side chains bearing nucleophilic heteroatoms are incompatible with the triflation step. Some acid-labile protecting groups are also unstable under acidic diazotization conditions. Notably, we found that one-pot triflation and substitution reaction of tyrosine derivative **1** afforded Wagner−Meerwein rearrangement product **2**, whose structure was

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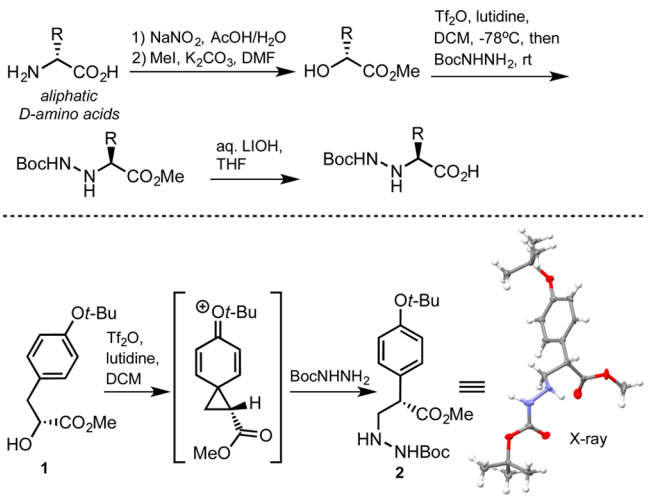
Scheme 1. Cα-Nα Bond Formation Approach to α-Hydrazino Acids

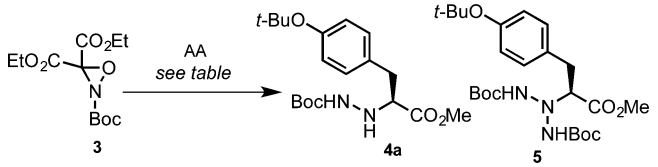


confirmed by X-ray diffraction (Scheme 1).[12] Although this reaction pathway was unique to **1**, the Cα-N bond formation approach toward α-hydrazino acids appeared to impose inherent limitations on substrate scope.

Electrophilic amination represents an attractive method to prepare substituted hydrazines starting from primary and secondary amines. A number of oxaziridine derivatives can rapidly transfer amine or carbamate groups onto nucleophilic heteroatoms under mild conditions, thus allowing for the use of L-amino acids as readily available substrates.[13] Seminal contributions from the labortaories of Collet and Vidal have described *N*-acyloxy oxazirdines effective in aminating zwitterionic amino acid residues.[13c,14] However, the poor solubility of these substrates in organic solvents neccesitates the use of phase-transfer reagents to promote reaction and often affords products in moderate overall yields. The reaction of primary amines with *N*-acyloxaziridines is further complicated by competing diamination as well as the formation of undesired imine adducts. As a result, a protocol involving temporary *N*-benzyl protection of α-amino acids has also been reported.[15] Given the existing methods, we sought to develop a direct route toward α-hydrazino acid building blocks based on each of the canonical proteinogenic amino acids in a form suitable for SPPS.

We first examined the electrophilic amination of H-Tyr(O*t*Bu)-OMe using an *N*-Boc-oxaziridine derivative (**3**, Table 1) recently reported by Armstrong and co-workers.[16] Reagent **3** was previously shown to minimize the formation of imine adducts resulting from reaction of amine substrates with the diethyl ketomalonate byproduct. We employed a streamlined synthesis of **3** that requires only one chromatographic purification, yielding multigram quantities of the shelf-stable oxaziridine in under 48 h starting from *tert*-butyl carbazate.[16,17] The reaction of **3** with the free base of H-Tyr(O*t*Bu)-OMe was equally tolerant of different aprotic solvents as long as excess α-amino ester was employed (entries 1−3). The yield of the desired product decreased when the equivalency of H-Tyr(O*t*Bu)-OMe was reduced (entries 4−6). In these cases, significant formation of **5** was observed, along with the undesired imine adduct. Low yields of **4a** were obtained when H-Tyr(O*t*Bu)-OMe·HCl was used as the substrate, even in the presence of auxiliary bases (entries 7−10). We were pleased to find that a moderate yield of **4a** was achieved when 1:1 THF/H_2O was used as solvent, indicating the suitability of an aqueous reaction medium. By adding excess $NaHCO_3$ to the solvent mixture, the yield of **4a** increased dramatically and diamination was suppressed, even when H-Tyr(O*t*Bu)-OMe·HCl was the limiting reagent (entries 12−16). These aqueous

Table 1. Screening of α-Amino Ester Amination Conditions



entry	AA	AA (equiv)	conditions	yield of **4a**[a] (%)
1	H-Tyr(O*t*Bu)-OMe	2.0	DCM	98
2	H-Tyr(O*t*Bu)-OMe	2.0	THF	96
3	H-Tyr(O*t*Bu)-OMe	2.0	PhMe	99
4	H-Tyr(O*t*Bu)-OMe	1.2	PhMe	79
5	H-Tyr(O*t*Bu)-OMe	1.0	PhMe	57
6	H-Tyr(O*t*Bu)-OMe	0.5	PhMe	34
7	H-Tyr(O*t*Bu)-OMe·HCl	2.0	PhMe	14
8	H-Tyr(O*t*Bu)-OMe·HCl	2.0	THF	2
9	H-Tyr(O*t*Bu)-OMe·HCl	2.0	PhMe, NEt_3	<1
10	H-Tyr(O*t*Bu)-OMe·HCl	2.0	PhMe, pyridine	5
11	H-Tyr(O*t*Bu)-OMe·HCl	2.0	THF/H_2O (1:1)	48
12	H-Tyr(O*t*Bu)-OMe·HCl	2.0	THF/satd aq $NaHCO_3$	99
13	H-Tyr(O*t*Bu)-OMe·HCl	1.2	THF/satd aq $NaHCO_3$	99
14	H-Tyr(O*t*Bu)-OMe·HCl	1.0	THF/satd aq $NaHCO_3$	98
15	H-Tyr(O*t*Bu)-OMe·HCl	0.5	THF/satd aq $NaHCO_3$	93
16	H-Tyr(O*t*Bu)-OMe·HCl	1.0	PhMe/satd aq $NaHCO_3$	97

[a]Yield determined by HPLC peak integration, fitted to a standard linear regression equation derived from pure **4a**. Reported yields are based on the limiting reagent in each case.

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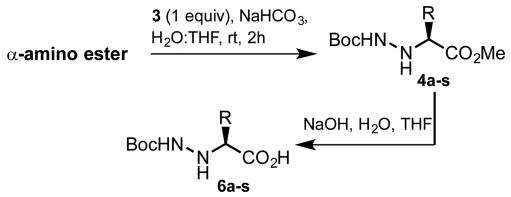
conditions thus obviate the need for excess amino ester or prior neutralization of the substrate hydrochloride salts.

With optimal conditions in hand, we prepared (N^2-Boc)-α-hydrazino acids derived from proteinogenic amino acids using a practical two-step protocol (Table 2). In the majority of

Table 2. Synthesis of α-Hydrazino Acids Derived from Proteinogenic α-Amino Acids



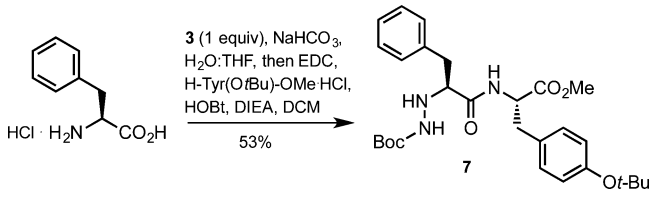
entry	amino ester	yield of 4[a] (%)	yield of 6[a] (%)
1	H-Tyr(*t*-Bu)-OMe·HCl	82	79
2	H-Phe-OMe·HCl	98	95
3	H-Gly-OMe·HCl	47	58
4	H-Ala-OMe·HCl	74	71
5	H-Val-OMe·HCl	80	77
6	H-Leu-OMe·HCl	82	93
7	H-Ile-OMe·HCl	88	91
8	H-Pro-OMe·HCl	76	80
9	H-Lys(Boc)-OMe·HCl	97	86
10	H-Arg(Pbf)-OMe·HCl	88	83
11	H-Trp(Boc)-OMe	73	76[b]
12	H-His(Trt)-OMe·HCl	93	76
13	H-Ser(*t*-Bu)-OMe·HCl	79	71
14	H-Thr(*t*-Bu)-OMe·HCl	94	86
15	H-Asp(*t*-Bu)-OMe·HCl	76	75
16	H-Glu(*t*-Bu)-OMe·HCl	95	95
17	H-Asn(Trt)-OMe	96	89
18	H-Gln(Trt)-OMe	98	83
19	H-Cys(Trt)-OMe	84	59[b]
20	H-Met-OMe·HCl	0	

[a]Isolated yields. [b]2 equiv of LiOH in 1:1 THF/H_2O was employed for hydrolysis.

cases, commercially available and inexpensive α-amino ester hydrochloride salts (bearing acid-labile side chain protecting groups for Fmoc SPPS) were used as substrates. The Cys, Trp, Asn, and Gln subtrates, which are not readily available as hydrochloride salts, were prepared from the corresponding Fmoc-protected derivatives and used in their neutralized amine form. Boc-protected-α-hydrazino ester intermediates were generally obtained in good to excellent yields following purification. One notable exception was the amination of H-Gly-OMe, which afforded **4c** in only 47% isolated yield. However, aGly can be conveniently incorporated into peptides via an alternative submonomer approach owing to the lack of an epimerizable Cα center.[3a] Of the remaining residues, only H-Met-OMe failed to afford the expected α-hydazino ester product.[18] Saponifications proceeded uneventfully to provide (N^2-Boc)-α-hydrazino acids **6a–s**, which are soluble in EtOAc following acidification of the aqueous layer. In most cases trituration of the crude carboxylic acids with hexanes afforded pure products.

It should be noted that the key electrophilic amination reaction proceeds with excellent conversion in a mixture of THF and satd aq $NaHCO_3$ even when the zwitterionic α-amino acids are used as substrates (as determined by LCMS). However, in many cases, we found separation of the (N^2-Boc)-α-hydrazino acid from byproducts to be exceedingly difficult by conventional flash column chromatography. The two-step protocol in Table 2 provides (N^2-Boc)-α-hydrazino ester intermediates (**6**) that are simple to purify, often resulting in higher overall yields relative to direct α-amino acid *N*-amination. Nevertheless, a one-pot amination–coupling protocol could be employed to generate *N*-aminated dipeptide esters. As shown in Scheme 2, the crude N^2-Boc hydrazino

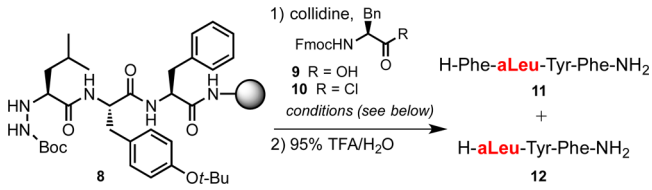
Scheme 2. One-Pot Synthesis of Aminated Dipeptide 7



acid resulting from treatment of H-Phe-OH·HCl with oxaziridine **3** was extracted into DCM and directly coupled to H-Tyr(O*t*Bu)-OMe·HCl to provide **7** in 53% overall yield.

Incorporation of (N^2-Boc)-α-hydrazino acids into growing peptide chains by SPPS can be achieved using HATU/DIEA without protection of the poorly nucleophilic α nitrogen.[3b,19] Optimization of the subsequent Nα acylation step on solid support is shown in Table 3. The use of EDC or HATU as an

Table 3. Optimization of on-Resin Hydrazino Amide Nα Acylation



entry	Phe activation	solvent	temp (°C)	time[a]	**11:12**[b]
1	**9** (10 equiv), EDC (10 equiv)	DMF	45	1 h × 2	<1:99
2	**9** (10 equiv), HATU (10 equiv)	DMF	45	1 h × 2	1:99
3	**10** (10 equiv)	DCM	rt	1 h × 2	51:49
4	**10** (10 equiv)	THF	rt	1 h × 2	94:6
5	**10** (10 equiv)	THF	rt	15 min × 2	82:18
6	**10** (10 equiv)	THF	45	15 min × 2	87:13
7	**10** (10 equiv)	THF	45	1 h × 2	>99:1
8	**9** (10 equiv), BTC (3.3 equiv)	THF	45	15 min × 2	82:18
9	**9** (10 equiv), BTC (3.3 equiv)	THF	rt	1 h × 2	72:28

[a]Reaction time and number of coupling cycles using the indicated conditions. [b]Ratio of HPLC peak areas (λ = 220 nm) from the crude cleavage mixtures.

activating reagent failed to produce an appreciable amount of desired tetrapeptide **11** after two coupling cycles (entries 1 and 2). Employing the isolated acid chloride derivative of Fmoc-Phe-OH led to significant Nα acylation in the presence of collidine.[20] While the use of DCM as solvent resulted in only moderate coupling efficiency, THF consistently gave high ratios of **11**:**12** (entries 3–7). Optimal conversion involved two sequential 1 h coupling cycles with 10 equiv of Fmoc-Phe-

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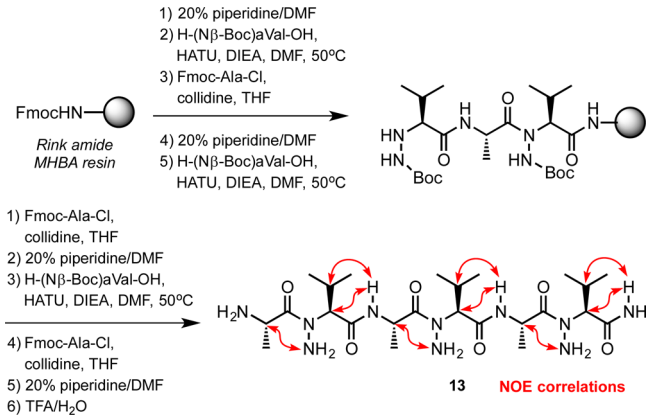
Cl and 30 equiv of collidine in THF at 45 °C. Under these conditions, tetrapeptide **11** was obtained in 64% overall yield (over seven steps) following purification by preparative RP-HPLC. Although formation of Fmoc-Phe-Cl in situ with triphosgene (BTC) was found to be slightly inferior to the use of preformed acid chloride (entries 8 and 9), these conditions are preferred in cases where the coupling partner bears an acid-labile side-chain protecting group (Boc, *t*-Bu, Trt) sensitive to thionyl chloride or oxalyl chloride mediated acid chloride formation.

To further demonstrate the utility of hydrazino acid building blocks in the synthesis of novel pepdidomimetics, we prepared a representative polyaminated sequence on Rink amide MBHA resin as shown in Scheme 3. Treatment of the resin-bound

Scheme 3. Synthesis of Triaminated Peptide 13



hexapeptide with 95:5 TFA/H_2O led to global deptrotection and cleavage from the solid support. Following purification of **13** by RP-HPLC, we compared its NMR spectral data with those of trimethylated analogue **14** (Figure 2). The ^{1}H NMR spectra of **13** in DMSO-d_6 exhibited conformational homogeneity atypical of a polypeptide bearing multiple tertiary amides. The *all-trans* geometry of the amides in **13** was confirmed by the presence of characteristically strong Hα_i/Hβ_i–NαH$_{i+1}$ NOE correlations as well as close contacts between the N^{2}H and Ala Hα protons. In contrast, the ^{1}H NMR spectrum of **14** showed a complex mixture of rotameric forms indicative of largely isoenergetic amide bond geometries. This observation is consistent with calculations predicting a *trans* amide-substantiating effect of the peptide *N*-amino group.[21] Comparison of the NMR spectra for **13** and **14** thus highlights the unique conformational impact of backbone amination relative to *N*-alkylation.

In summary, we have described an efficient protocol for the synthesis of α-hydrazino acids corresponding to 19 of the 20 primary proteinaceous α-amino acids. Electrophilic amination and hydrolysis of L-amino ester hydrochloride salts in aqueous media provides a direct route to enantiopure orthogonally protected building blocks. Suppressed diamination under the optimized conditions circumvents the need to transiently protect the primary amine or to employ excess substrate. We also report an optimized procedure for the assembly of backbone aminated peptides by Fmoc SPPS. These results will thus enable rapid *N*-amino scanning of bioactive peptides as well as the synthesis of NAP-based foldamers with unique conformational preferences.

EXPERIMENTAL SECTION

Solution-Phase Synthesis: General Notes. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen gas using dry solvents. Commercial grade reagents and solvents were used without further purification except where noted. Anhydrous solvents were purchased directly from chemical suppliers. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed using silica gel (60 μm particle size). Reaction progress was judged by TLC analysis (single spot/two solvent systems) using a UV lamp, CAM (ceric ammonium molybdate), ninhydrin, or basic $KMnO_4$ stain(s) for detection purposes. NMR spectra were recorded on a 400, 500, or 600 MHz spectrometer. Proton chemical shifts are reported as δ values relative to residual signals from deuterated solvents (D_2O, $CDCl_3$, CD_3OD, or DMSO-d_6). Three-letter code abbreviations for α-hydrazino acids use the prefix "a" to denote "amino" (i.e, aLeu = N^1-aminoleucine).

***tert*-Butyl (*S*)-2-(2-(4-*tert*-Butoxyphenyl)-3-methoxy-3-oxopropyl)hydrazine-1-carboxylate (2).** 2,6-Lutidine (1.22 g, 11.4 mmol) and Tf_2O (1.39 g, 4.94 mmol) were added to a solution of **1** (0.96 g, 3.80 mmol) in DCM (50 mL) at 0 °C, and the reaction was stirred for 30 min. *tert*-Butyl carbazate (1.01 g, 7.64 mmol) was then added, and the reaction was allowed to warm to rt and stirred 18 h. The reaction was concentrated, diluted with EtOAc, and washed with water, 1 M aq HCl, and brine. Purification by silica gel flash chromatography (40% EtOAc/hexanes) gave **2** as a colorless gum (500 mg, 36% yield): $[\alpha]_D^{20}$ = −24.6 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.01 (s, 1H), 3.75 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.67 (s, 3H), 3.44 (dd, *J* = 12.1, 9.7 Hz, 1H), 3.16 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.43 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 156.7, 154.9, 131.3, 128.4, 124.2, 80.6, 78.5, 54.8, 52.1, 52.0, 49.9, 49.7, 28.8,

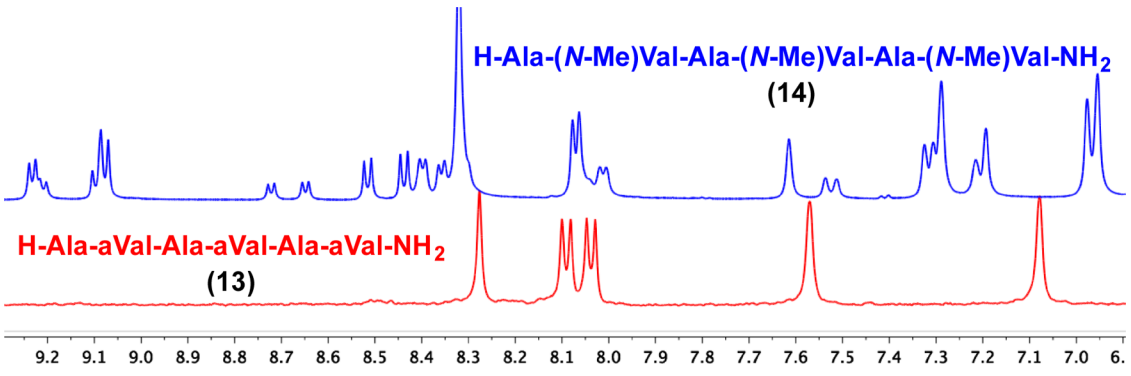


Figure 2. ^{1}H NMR (DMSO-d_6) expansions (amide NH region) showing pronounced conformational heterogeneity for backbone-methylated variant **14** (blue) relative to *N*-amino peptide **13** (red).

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28.7, 28.3, 28.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{31}N_2O_5$ 367.2228, found 367.2230.

2-*tert*-Butyl 3,3-Diethyl 1,2-Oxaziridine-2,3,3-tricarboxylate (3). Oxaziridine **3** was prepared by modification of the reported procedure[16,17] as described below. To a solution of *tert*-butyl carbazate (10.0 g, 75.7 mmol) in 60 mL of water and 30 mL of AcOH at 0 °C was added $NaNO_2$ (5.74 g, 83.2 mmol) portionwise over 10 min and the mixture stirred at 0 °C for 30 min. The reaction mixture was then extracted with Et_2O, and the organic layer was washed with water, satd aq $NaHCO_3$, and brine and dried over Na_2SO_4. The filtrate was then cooled to 0 °C, and PPh_3 (19.9 g, 75.7 mmol) was added portionwise over 10 min while stirring. The reaction was then allowed to stir at rt for 45 min. The reaction mixture was filtered, and the residue was washed with Et_2O to afford the *N*-Boc-iminophosphorane as a white solid. In a pressure flask, a solution of the *N*-Boc-iminophosphorane (23.0 g, 60.9 mmol) in 70 mL of dry THF was treated with diethyl ketomalonate (9.29 mL, 60.9 mmol), and the mixture was allowed to stir at 60 °C for 18 h. The reaction mixture was then concentrated and dissolved in warm toluene, and Ph_3PO was precipitated by addition of pentane. This cycle was repeated until no more Ph_3PO precipitated, affording the Boc-iminodiethylmalonate as a light yellow oil which was used in the next step without further purification. To a solution of the *N*-Boc-iminodiethylmalonate in 230 mL of MeCN and 150 mL of water was slowly added a mixture of Oxone (45.0 g, 146 mmol) and $NaHCO_3$ (19.0 g, 226 mmol), and the reaction mixture was allowed to stir for 5 h. Another portion of Oxone (45.0 g, 146 mmol) was then slowly added, and the reaction mixture was allowed to stir for 18 h at rt. The mixture was then poured onto 600 mL of water, extracted with DCM, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography over silica gel (6:2.5:0.5 hexanes/DCM/Et_2O) afforded **3** as a pale yellow oil (7.05 g, 40% yield).

General Procedure for the Synthesis of N^2-Boc-α-hydrazino Esters 4a–s. The α-amino acid methyl ester or α-amino acid methyl ester hydrochloride salt (0.173 mmol) was suspended in a mixture of 2.5 mL of THF and 2.5 mL of satd aq $NaHCO_3$, and the mixture was vigorously stirred for 10 min at rt. After addition of **3** (50.0 mg, 0.173 mmol), the reaction was stirred for 2 h at rt. The reaction was then treated with 50 μL of ethylenediamine. The mixture was absorbed onto 3 g of silica gel and concentrated in vacuo to dryness. The crude materials were purified by silica gel flash chromatography (EtOAc/hexanes) to give **4a–s**.

*H-(N^2-Boc)aTyr(tBu)-OMe (**4a**).* Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4a** as a colorless oil (62 mg, 98% yield): $[\alpha]_D^{20}$ = −5.0 ($CHCl_3$, c = 0.1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.23 (s, 1H), 4.00 (s, 1H), 3.91 (t, J = 6.8 Hz, 1H), 3.64 (s, 3H), 2.98 (dd, J = 13.9, 6.1 Hz, 1H), 2.94–2.88 (m, 1H), 1.39 (s, 9H), 1.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 156.0, 154.3, 131.1, 129.5, 124.2, 80.7, 78.3, 64.3, 51.9, 36.4, 28.8, 28.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{31}N_2O_5$ 367.2228, found 367.2225.

*H-(N^2-Boc)aPhe-OMe (**4b**).*[10] Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4b** as a white solid (41 mg, 82% yield): $[\alpha]_D^{20}$ = −16.6 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 7.23–7.18 (m, 3H), 6.24 (s, 1H), 3.96 (t, J = 6.8 Hz, 1H), 3.89 (s, 1H), 3.68 (s, 3H), 3.05 (dd, J = 13.9, 5.9 Hz, 1H), 2.96 (dd, J = 14.0, 7.3 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 156.1, 136.4, 129.1, 128.6, 126.9, 80.7, 64.1, 52.0, 37.0, 28.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_4$ 295.1652, found 295.1651.

*H-(N^2-Boc)aGly-OMe (**4c**).*[10] Purification by silica gel flash chromatography (30% EtOAc/hexanes) gave **4c** as a white solid (17 mg, 47% yield): mp 74–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 3.83 (s, 1H), 3.72 (s, 3H), 3.63 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 156.2, 80.7, 52.7, 51.9, 28.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{17}N_2O_4$ 205.1183, found 205.1184.

*H-(N^2-Boc)aAla-OMe (**4d**).*[10] Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4d** as a colorless oil (28 mg, 74% yield): $[\alpha]_D^{20}$ = −50.0 ($CHCl_3$, c = 0.1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 3.70 (s, 3H), 3.69–3.64 (m, 1H), 1.41 (s, 9H), 1.28 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 156.3, 80.6, 58.4, 52.0, 28.2, 15.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{19}N_2O_4$ 219.1339, found 219.1338.

*H-(N^2-Boc)aVal-OMe (**4e**).*[13c] Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave **4e** as a colorless oil (34 mg, 80% yield): $[\alpha]_D^{20}$ = −54.6 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (s, 1H), 3.78 (s, 1H), 3.72 (s, 3H), 3.43 (d, J = 5.3 Hz, 1H), 2.18–1.92 (m, 1H), 1.41 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 156.2, 80.7, 69.3, 51.8, 29.9, 28.3, 18.9, 18.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{23}N_2O_4$ 247.1652, found 247.1653.

*H-(N^2-Boc)aLeu-OMe (**4f**).*[10] Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave **4f** as a colorless oil (34 mg, 82% yield): $[\alpha]_D^{20}$ = −50.5 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 3.94 (s, 1H), 3.70 (s, 3H), 3.63 (t, J = 6.9 Hz, 1H), 1.83–1.71 (m, 1H), 1.53–1.44 (m, 2H), 1.41 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 156.1, 80.6, 61.9, 52.0, 39.5, 28.2, 24.9, 22.8, 22.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{25}N_2O_4$ 261.1809, found 261.1813.

*H-(N^2-Boc)aIle-OMe (**4g**).*[3b] Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave **4g** as a colorless oil (37 mg, 88% yield): $[\alpha]_D^{20}$ = −50.7 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 3.89 (s, 1H), 3.70 (s, 3H), 3.50 (d, J = 5.1 Hz, 1H), 1.79–1.71 (m, 1H), 1.55–1.45 (m, 1H), 1.40 (s, 9H), 1.28–1.18 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 156.2, 80.6, 68.24, 51.7, 36.5, 28.2, 25.7, 15.5, 11.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{25}N_2O_4$ 261.1809, found 261.1812.

*H-(N^2-Boc)aPro-OMe (**4h**).* Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4h** as a colorless oil (32 mg, 76% yield): $[\alpha]_D^{20}$ = −79.3 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 3.98 (dd, J = 9.3, 4.2 Hz, 1H), 3.68 (s, 3H), 3.26 (q, J = 7.5 Hz, 1H), 3.13 (td, J = 8.1, 5.2 Hz, 1H), 2.30–2.12 (m, 1H), 1.97–1.74 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 154.7, 80.3, 63.9, 53.0, 51.8, 28.3, 28.0, 22.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{21}N_2O_4$ 245.1496, found 245.1500.

*H-(N^2-Boc)aLys(Boc)-OMe (**4i**).* Purification by silica gel flash chromatography (35% EtOAc/hexanes) gave **4i** as a colorless oil (63 mg, 97% yield): $[\alpha]_D^{20}$ = −17.9 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 4.68 (s, 1H), 4.03 (s, 1H), 3.68 (s, 3H), 3.57 (t, J = 6.4 Hz, 1H), 3.05 (s, 2H), 1.74–1.64 (m, 1H), 1.64–1.54 (m, 1H), 1.49–1.43 (m, 3H), 1.39 (s, 9H), 1.38 (s, 9H), 1.35–1.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 156.2, 156.0, 80.7, 79.0, 63.1, 52.0, 40.0, 29.8, 29.6, 28.4, 28.2, 22.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{34}N_3O_6$ 376.2442, found 376.2453.

*H-(N^2-Boc)aArg(Pbf)-OMe (**4j**).* Purification by silica gel flash chromatography (80% EtOAc/hexanes) gave **4j** as a colorless oil (85 mg, 88% yield): $[\alpha]_D^{20}$ = −54.2 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.43 (s, 1H), 4.12 (s, 1H), 3.70 (s, 3H), 3.49 (dd, J = 10.0, 3.3 Hz, 1H), 3.46–3.39 (m, 1H), 3.16–3.05 (m, 1H), 2.92 (s, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 2.05 (s, 3H), 1.92–1.84 (m, 1H), 1.81–1.72 (m, 1H), 1.66–1.55 (m, 1H), 1.52–1.45 (m, 1H), 1.42 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 158.6, 156.6, 156.0, 138.4, 133.5, 132.3, 124.5, 117.4, 86.3, 81.3, 63.3, 63.0, 52.5, 52.2, 43.2, 28.7, 28.5, 28.4, 28.2, 25.9, 19.5, 19.1, 18.1, 17.7, 12.5, 12.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{42}N_5O_7S$ 556.2799, found 556.2806.

*H-(N^2-Boc)aTrp(Boc)-OMe (**4k**).* Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4k** as a colorless oil (53 mg, 73% yield): $[\alpha]_D^{20}$ = −2.5 ($CHCl_3$, c = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.38–7.15 (m, 3H), 6.21 (s, 1H), 4.01 (t, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.14 (dd, J = 15.0, 5.4 Hz, 1H), 3.05 (dd, J = 15.1, 7.3 Hz, 1H), 1.64 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 156.2, 149.6, 135.5, 130.3, 124.5, 124.1, 122.5, 118.7,

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115.4, 115.3, 83.5, 80.7, 62.8, 52.2, 28.2, 26.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{32}N_3O_6$ 434.2286, found 434.2277.

*H-(N²-Boc)aHis(Trt)-OMe (**4l**).* Purification by silica gel flash chromatography (80% EtOAc/hexanes) gave **4l** as a colorless oil (85 mg, 93% yield): $[\alpha]_D^{20} = -4.2$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 1.4 Hz, 1H), 7.32−7.28 (m, 9H), 7.15−7.06 (m, 6H), 6.59 (d, J = 1.4 Hz, 1H), 6.41 (s, 1H), 4.58 (s, 1H), 3.97−3.87 (m, 1H), 3.62 (s, 3H), 3.00 (dd, J = 14.7, 5.0 Hz, 1H), 2.90 (dd, J = 14.7, 6.8 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.01, 156.01, 142.4, 138.6, 136.5, 129.8, 128.0, 119.4, 80.2, 75.2, 63.0, 51.9, 29.5, 28.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{31}H_{35}N_4O_4$ 527.2653, found 527.2658.

*H-(N²-Boc)aSer(tBu)-OMe (**4m**).*[3b] Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4m** as a colorless oil (40 mg, 79% yield): $[\alpha]_D^{20} = -39.9$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 5.63 (s, 1H), 3.79−3.64 (m, 1H), 3.72 (s, 3H), 3.69−3.57 (m, 2H), 1.41 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 156.1, 80.9, 73.5, 63.6, 60.8, 52.1, 28.2, 27.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{27}N_2O_5$ 291.1915, found 291.1924.

*H-(N²-Boc)aThr(tBu)-OMe (**4n**).* Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave **4n** as a colorless oil (49 mg, 94% yield): $[\alpha]_D^{20} = -64.3$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.13 (s, 1H), 4.03−3.93 (m, 1H), 3.69 (s, 3H), 3.42 (s, 1H), 1.40 (s, 9H), 1.27 (d, J = 6.2 Hz, 3H), 1.08 (s, 9H);^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 156.0, 80.2, 73.9, 69.4, 67.5, 51.9, 28.3, 28.2, 20.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{29}N_2O_5$ 305.2071, found 305.2077.

*H-(N²-Boc)aAsp(tBu)-OMe (**4o**).* Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4o** as a colorless oil (42 mg, 76% yield): $[\alpha]_D^{20} = -8.9$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.06 (s, 1H), 3.87 (t, J = 5.7 Hz, 1H), 3.73 (s, 3H), 2.72 (d, J = 5.5 Hz, 2H), 1.42 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 169.8, 156.1, 81.5, 80.9, 59.6, 52.3, 36.4, 28.2, 28.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{27}N_2O_6$ 319.1864, found 319.1865.

*H-(N²-Boc)aGlu(tBu)-OMe (**4p**).* Purification by silica gel flash chromatography (25% EtOAc/hexanes) gave **4p** as a colorless oil (54 mg, 95% yield): $[\alpha]_D^{20} = -7.6$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 4.06 (s, 1H), 3.71 (s, 3H), 3.63 (t, J = 6.3 Hz, 1H), 2.35−2.28 (m, 2H), 2.08−1.96 (m, 1H), 1.94−1.82 (m, 1H), 1.40 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 172.4, 156.1, 80.7, 80.5, 62.2, 52.1, 31.4, 28.2, 28.0, 25.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{29}N_2O_6$ 333.2020, found 333.2027.

*H-(N²-Boc)aAsn(Trt)-OMe (**4q**).* Purification by silica gel flash chromatography (35% EtOAc/hexanes) gave **4q** as a colorless oil (83 mg, 96% yield): $[\alpha]_D^{20} = -16.8$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.37−7.12 (m, 15H), 6.61 (s, 1H), 3.92 (t, J = 5.2 Hz, 1H), 3.86 (s, 1H), 3.69 (s, 3H), 2.80 (d, J = 5.2 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 168.9, 156.1, 144.5, 128.7, 127.8, 126.9, 81.2, 70.7, 60.0, 52.6, 37.0, 28.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{34}N_3O_5$ 504.2493, found 504.2494.

*H-(N²-Boc)aGln(Trt)-OMe (**4r**).* Purification by silica gel flash chromatography (35% EtOAc/hexanes) gave **4r** as a white solid (87 mg, 98% yield): mp 98−102 °C; $[\alpha]_D^{20} = -2.5$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.10 (m, 15H), 6.94 (s, 1H), 6.35 (s, 1H), 3.76 (s, 1H), 3.69 (s, 3H), 3.54 (dd, J = 7.8, 4.4 Hz, 1H), 2.46 (t, J = 6.7 Hz, 2H), 2.22−2.11 (m, 1H), 1.90−1.70 (m, 1H), 1.36 (s, 9H);^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 171.3, 156.1, 144.7, 127.8, 126.9, 80.7, 70.4, 62.2, 52.2, 33.3, 28.3, 24.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{36}N_3O_5$ 518.2650, found 518.2645.

*H-(N²-Boc)aCys(Trt)-OMe (**4s**).* Purification by silica gel flash chromatography (20% EtOAc/hexanes) gave **4s** as a colorless oil (72 mg, 84% yield): $[\alpha]_D^{20} = -21.1$ ($CHCl_3$, $c = 1.0$);Yield =84%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.34 (m, 6H), 7.33−7.15 (m, 9H), 6.07 (s, 1H), 4.05 (s, 1H), 3.67 (s, 3H), 3.47 (s, 1H), 2.53 (d, J = 5.4 Hz, 2H), 1.41 (s, 9H);^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 156.1, 144.4, 129.6, 127.9, 126.7, 80.8, 66.8, 61.9, 52.2, 32.2, 28.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_4S$ 493.2156, found 493.2142.

General Procedure for the Synthesis of (N²-Boc)-α-hydrazino Acids 6a−s. Compounds **4a−s** were dissolved in 1.5 mL of THF and 1.5 mL of 1.0 M aq NaOH, and the mixtures were stirred for 1−4 h at rt. The reaction mixture was diluted with water (10 mL) and washed with Et_2O, and the aqueous layer was acidified to pH 1 with 1 M aq HCl. The aqueous solution was extracted with EtOAc, the organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give the corresponding *N*-hydrazo amino acid. In the case of **4k** and **4o**, 2 equiv of LiOH was used for hydrolysis in place of 1 M aquiv NaOH. The crude materials were purified by either silica gel flash chromatography (MeOH/DCM) or trituration with hexanes to give **6a−s**.

*H-(N²-Boc)aTyr(tBu)-OH (**6a**).* Purification by trituration with hexanes gave **6a** as a white solid (45 mg, 95% yield): mp 118−120 °C; $[\alpha]_D^{20} = -2.0$ ($CHCl_3$, $c = 1.0$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.1 Hz, 2H), 3.64 (t, J = 6.3 Hz, 1H), 2.79 (dd, J = 6.3, 2.8 Hz, 2H), 1.36 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 156.7, 153.8, 132.7, 130.3, 123.7, 79.1, 78.0, 64.3, 35.8, 29.0, 28.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{29}N_2O_5$ 353.2071, found 353.2078.

*H-(N²-Boc)aPhe-OH (**6b**).*[22] Purification by trituration with hexanes gave **6b** as a white solid (26 mg, 79% yield); mp 184−188 °C; $[\alpha]_D^{20}$ = −6.0° (MeOH, c = 0.1); ^1H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.35−7.09 (m, 5H), 3.67 (t, J = 6.2 Hz, 1H), 2.84 (d, J = 6.4 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.7, 156.7, 138.2, 129.8, 128.5, 126.7, 79.1, 64.2, 36.5, 28.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{20}N_2NaO_4$ 303.1315, found 303.1330.

*H-(N²-Boc)aGly-OH (**6c**).*[23] Purification by trituration with hexanes gave **6c** as a white solid (18 mg, 58% yield): mp 136−140 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H), 3.39 (s, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.4, 156.7, 79.1, 52.7, 28.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_7H_{15}N_2O_4$ 191.1032, found 191.1024.

*H-(N²-Boc)aAla-OH (**6d**).*[14b] Purification by trituration with hexanes gave **6d** as a white solid (14 mg, 71% yield): mp 94−98 °C; $[\alpha]_D^{20} = -29.6$ ($CHCl_3$, $c = 1.0$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 3.45 (q, J = 6.9 Hz, 1H), 1.37 (s, 9H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.0, 156.8, 79.1, 57.8, 28.6, 16.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{17}N_2O_4$ 205.1183, found 205.1190.

*H-(N²-Boc)aVal-OH (**6e**).*[14b] Purification by silica gel flash chromatography (0−10% MeOH/DCM) gave **6e** as a white solid (23 mg, 77% yield): mp 62−66 °C; $[\alpha]_D^{20} = -25.6$ ($CHCl_3$, $c = 1.0$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 3.14 (d, J = 5.0 Hz, 1H), 1.92−1.81 (m, 1H), 1.36 (s, 9H), 0.89 (d, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 156.8, 79.0, 68.9, 29.9, 28.6, 19.2, 19.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{10}H_{20}N_2NaO_4$ 255.1315, found 255.1326.

*H-(N²-Boc)aLeu-OH (**6f**).*[3b] Purification by trituration with hexanes gave **6f** as a white solid (35 mg, 93% yield): mp 94−96 °C; $[\alpha]_D^{20}$ = −29.2 ($CHCl_3$, c = 1.0); ^1H NMR (500 MHz, DMSO-d_6) δ 8.09 (s, 1H), 3.40 (t, J = 6.9 Hz, 1H), 1.73 (dt, J = 13.4, 6.7 Hz, 1H), 1.36 (s, 9H), 1.36−1.31 (m, 2H), 0.86 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.3, 156.7, 79.0, 61.4, 28.6, 24.7, 23.1, 22.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{23}N_2O_4$ 247.1652, found 247.1655.

*H-(N²-Boc)alle-OH (**6g**).*[24] Purification by trituration with hexanes gave **6g** as a white solid (76 mg, 91% yield): mp 94−96 °C; $[\alpha]_D^{20}$ = −19.4 ($CHCl_3$, c = 1.0); ^1H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H), 3.24 (d, J = 4.7 Hz, 1H), 1.72−1.55 (m, 1H), 1.50−1.38 (m, 1H), 1.35 (s, 9H), 1.26−1.15 (m, 1H), 0.85 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 156.7, 79.0, 67.4, 36.4, 28.6, 25.7, 15.8, 12.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{23}N_2O_4$ 247.1652, found 247.1659.

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H-(N²-Boc)aPro-OH (**6h**).[14b] Purification by trituration with hexanes gave **6h** as a white solid (21 mg, 80% yield): mp 128−130 °C; $[\alpha]_D^{20}$ = −20.4 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.35 (s, 1H), 3.53 (dd, *J* = 9.3, 5.4 Hz, 1H), 3.09−2.99 (m, 1H), 2.93−2.77 (m, 1H), 2.10−1.96 (m, 1H), 1.84−1.69 (m, 2H), 1.69−1.56 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.6, 155.8, 79.4, 66.1, 54.7, 28.5, 28.2, 22.8; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{19}N_2O_4$ 231.1339, found 231.1341.

H-(N²-Boc)aLys(Boc)-OH (**6i**). Purification by trituration with hexanes gave **6i** as a white solid (45 mg, 86% yield): mp 94−98 °C; $[\alpha]_D^{20}$ = −27.7 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 6.72 (d, *J* = 5.6 Hz, 1H), 3.34 (t, *J* = 6.0 Hz, 1H), 2.86 (q, *J* = 6.3 Hz, 2H), 1.53−1.45 (m, 2H), 1.45−1.39 (m, 2H), 1.36 (s, 9H), 1.35 (s, 9H), 1.33−1.29 (m, 1H), 1.26−1.18 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7, 156.7, 156.0, 79.0, 77.7, 62.7, 30.3, 29.9, 28.7, 28.6, 22.9; HRMS (ESI-TOF) *m*/*z* [M + K]$^+$ calcd for $C_{16}H_{31}KN_3O_6$ 400.1844, found 400.1859.

H-(N²-Boc)aArg(Pbf)-OH (**6j**). Purification by trituration with hexanes gave **6j** as a white solid (73 mg, 83% yield): mp 86−90 °C; $[\alpha]_D^{20}$ = −29.9 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (s, 1H), 6.83 (s, 1H), 6.43 (s, 1H), 3.29 (t, *J* = 5.0 Hz, 1H), 3.00 (d, *J* = 6.2 Hz, 2H), 2.94 (s, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 1.99 (s, 3H), 1.55−1.42 (m, 4H), 1.39 (s, 6H), 1.35 (s, 9H);^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 157.9, 156.5, 137.7, 134.6, 131.9, 124.7, 116.7, 86.7, 79.6, 79.2, 42.9, 28.8, 28.6, 19.4, 18.0, 12.7; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{40}N_5O_7S$ 542.2643, found 542.2668.

H-(N²-Boc)aTrp(Boc)-OH (**6k**). Purification by trituration with hexanes gave **6k** as a white solid (41 mg, 76% yield): mp 66−70 °C; $[\alpha]_D^{20}$ = −3.7 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.62 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 3.76 (t, *J* = 6.2 Hz, 1H), 2.94 (d, *J* = 6.1 Hz, 2H), 1.61 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.9, 156.8, 149.5, 135.0, 130.9, 124.7, 124.5, 122.8, 119.7, 117.0, 115.1, 83.9, 79.1, 62.6, 28.6, 28.2, 25.9; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_6$ 420.2129, found 420.2141.

H-(N²-Boc)aHis(Trt)-OH (**6l**). Purification by silica gel flash chromatography (0−10% MeOH/DCM) gave **6l** as a white solid (31 mg, 76% yield): mp 76−80 °C; $[\alpha]_D^{20}$ = +10.1 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.22 (s, 1H), 7.67 (s, 1H), 7.45−7.32 (m, 9H), 7.14−7.02 (m, 6H), 6.88 (s, 1H), 3.63 (t, *J* = 6.3 Hz, 1H), 2.88−2.68 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.7, 156.9, 142.2, 137.5, 135.6, 129.7, 129.6, 128.9, 128.7, 128.6, 120.0, 79.7, 79.2, 75.7, 62.9, 28.6; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{33}N_4O_4$ 513.2496, found 513.2517.

H-(N²-Boc)aSer(tBu)-OH (**6m**).[3b] Purification by trituration with hexanes gave **6m** as a white solid (26 mg, 71% yield): mp 114−116 °C; $[\alpha]_D^{20}$ = −13.6 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 3.52−3.35 (m, 3H), 1.36 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.8, 156.6, 79.1, 73.1, 63.8, 61.4, 28.6, 27.6; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{25}N_2O_5$ 277.1758, found 277.1768.

H-(N²-Boc)aThr(tBu)-OH (**6n**). Purification by trituration with hexanes gave **6n** as a white solid (37 mg, 86% yield): mp 116−118 °C; $[\alpha]_D^{20}$ = −45.2 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 3.86−3.73 (m, 1H), 3.33 (s, 1H), 1.36 (s, 9H), 1.11 (s, 9H), 1.08 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.2, 156.6, 79.0, 73.9, 69.0, 67.3, 28.6, 28.5, 20.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{27}N_2O_5$ 291.1915, found 291.1923.

H-(N²-Boc)aAsp(tBu)-OH (**6o**). Purification by trituration with hexanes gave **6o** as a white solid (14 mg, 75% yield): mp 114−118 °C; $[\alpha]_D^{20}$ = −6.2 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 3.66 (t, *J* = 6.4 Hz, 1H), 2.58−2.38 (m, 2H), 1.37 (s, 18H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.2, 173.1, 172.5, 170.1, 156.8, 80.4, 79.2, 59.4, 36.8, 35.6, 28.6, 28.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{25}N_2O_6$ 305.1707, found 305.1715.

H-(N²-Boc)aGlu(tBu)-OH (**6p**). Purification by trituration with hexanes gave **6p** as a sticky foam (44 mg, 95% yield): $[\alpha]_D^{20}$ = −1.5 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 3.36 (t, *J* = 6.1 Hz, 1H), 2.42−2.29 (m, 1H), 2.29−2.17 (m, 1H), 1.83−1.63 (m, 2H), 1.37 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 172.3, 156.7, 79.9, 79.0, 61.7, 31.3, 28.5, 28.2, 25.7; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}N_2O_6$ 319.1864, found 319.1878.

H-(N²-Boc)aAsn(Trt)-OH (**6q**). Purification by silica gel flash chromatography (0−10% MeOH/DCM) gave **6q** as a white solid (171 mg, 89% yield): mp 69−100 °C; $[\alpha]_D^{20}$ = −1.5 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.24 (s, 1H), 7.49−7.09 (m, 15H), 3.66 (t, *J* = 5.8 Hz, 1H), 2.65 (dd, *J* = 15.4, 6.2 Hz, 1H), 2.40 (dd, *J* = 15.4, 5.6 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.1, 169.1, 156.3, 144.9, 128.6, 127.4, 126.3, 78.8, 69.4, 59.4, 36.7, 28.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{32}N_3O_5$ 490.2337, found 490.2345.

H-(N²-Boc)aGln(Trt)-OH (**6r**). Purification by silica gel flash chromatography (0−10% MeOH/DCM) gave **6r** as a white solid (138 mg, 83% yield): mp 68−72 °C; $[\alpha]_D^{20}$ = −6.8 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.40−7.07 (m, 15H), 3.40−3.27 (m, 1H), 2.48−2.40 (m, 1H), 2.35−2.21 (m, 1H), 1.83−1.60 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 172.8, 158.3, 145.0, 128.5, 127.4, 126.3, 78.7, 69.2, 62.0, 32.2, 28.2, 26.1; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{34}N_3O_5$ 504.2493, found 504.2503.

H-(N²-Boc)aCys(Trt)-OH (**6s**). Purification by silica gel flash chromatography (0−10% MeOH/DCM) gave **6s** as a pale yellow solid (60 mg, 76% yield): mp 58−62 °C; $[\alpha]_D^{20}$ = −8.7 ($CHCl_3$, *c* = 1.0); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.41−7.16 (m, 15H), 3.30 (t, *J* = 6.5 Hz, 1H), 2.36 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.29 (dd, *J* = 12.0, 5.8 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.7, 156.7, 144.8, 129.6, 128.4, 127.2, 79.1, 66.4, 62.3, 32.6, 28.6; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{30}N_2NaO_4S$ 501.1818, found 501.1836.

Boc-aPhe-Tyr(O*t*Bu)-OMe (7). To a stirred biphasic solution of H-Phe-OH·HCl (100 mg, 0.61 mmol) in 7.5 mL of THF and 7.5 mL of satd aq $NaHCO_3$ was added the oxaziridine **3** (155 μL, 0.61 mmol) and the reaction mixture was allowed to stir for 1 h. Ethylenediamine (155 μL, 2.32 mmol) was then added and the reaction mixture was stirred for additional 5 min to eliminate the diethylketomalonate side-product. The reaction mixture was acidified to pH = 1 to 2 using 1 M aq. HCl, extracted with DCM and dried over Na_2SO_4. The DCM layer was then transferred to a 100 mL round-bottom flask and treated with H-Tyr(O*t*Bu)-OMe·HCl (348 mg, 1.21 mmol), HOBt (14 mg, 0.1 mmol), DIEA (632 μL, 3.63 mmol), and EDC·HCl (128 mg, 0.67 mmol), and the reaction mixture was allowed to stir for 18 h. The reaction was then washed with 1 M aq. HCl, satd aq $NaHCO_3$, and brine, and dried over Na_2SO_4. The organic layer was filtered, concentrated, then purified by flash chromatography over silica gel (40% EtOAc/Hexanes) affording **7** as a white foam (165 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 0.5H), 7.31−7.13 (m, 5.5H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.04 (s, 1H), 4.78 (s, 1H), 3.95 (s, 1H), 3.66 (s, 4H), 3.10−2.88 (m, 3H), 2.58 (t, *J* = 11.8 Hz, 1H), 1.48−1.24 (ss, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.0, 154.3, 136.4, 130.9, 129.6, 129.1, 128.8, 127.1, 124.2, 80.9, 78.4, 66.0, 53.0, 52.2, 37.6, 37.1, 28.8, 28.2; HRMS (ESI-TOF) (*m*/*z*) [M + H]$^+$ calcd for $C_{28}H_{40}N_3O_6$ 514.2912, found 514.2910.

Solid-Phase Peptide Synthesis. Solid-phase peptide synthesis was carried out on Fmoc-capped polystyrene rink amide MBHA resin (100−200 mesh). Dry resin was washed with DMF 3× and allowed to swell in DMF for 2 h prior to use. All reactions were carried out using gentle agitation. Fmoc deprotection steps were carried out by treating the resin with a solution of 20% piperidine/DMF (15 min × 2). Coupling of Fmoc-protected amino acids as well as (*N*²-Boc)hydrazino acids was effected using 5 equiv of HATU (0.5 M in DMF), 10 equiv of DIEA (1.0 M in DMF), and 5 equiv of the

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carboxylic acid in DMF at 50 °C (1 h). Coupling of residues N-terminal to the hydrazino acids was carried out with 30 equiv of collidine and 10 equiv of preformed Fmoc amino acid chloride in THF at 45 °C (2 × 1 h). After each reaction, the resin was washed with DMF 3×. Peptides were cleaved from the resin by incubating with gentle stirring in 95:5 TFA/H_2O or 45:45:10 TFA/DCM/TES at rt for 4 h. The cleavage mixture was filtered, and the resin was rinsed with additional cleavage solution. The filtrate was concentrated to remove the bulk of the TFA, and the remaining residue was treated with 8 mL of cold Et_2O to induce precipitation. The mixture was centrifuged, and the supernatant was removed. The remaining solid was washed two more times with Et_2O and dried under vacuum. Peptides were analyzed and purified on C12 RP-HPLC columns (preparative: 4 μm, 90 Å, 250 × 21.2 mm; analytical: 4 μm, 90 Å, 150 × 4.6 mm) using linear gradients of MeCN/H_2O (with 0.1% formic acid) and then lyophilized to afford white powders. All peptides were characterized by LCMS (ESI), HRMS (ESI-TOF), and ^{1}H NMR.

*H-Phe-aLeu-Tyr-Phe-NH$_2$ (**11**).* Purification by RP-HPLC (10−90% MeCN/H_2O with 0.1% HCO_2H) gave **11** as an amorphous white solid (39 mg, 64% overall yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.28−7.13 (m, 10H), 7.08 (s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 4.99 (dd, J = 11.4, 3.7 Hz, 1H), 4.60 (dd, J = 7.5, 4.4 Hz, 1H), 4.57 (s, 1H), 4.48−4.37 (m, 2H), 3.07−2.96 (m, 2H), 2.91−2.77 (m, 3H), 2.67 (dd, J = 14.1, 9.4 Hz, 1H), 1.86−1.74 (m, 1H), 1.48−1.34 (m, 2H), 0.89 (d, J = 5.8 Hz, 3H), 0.83 (d, J = 5.7 Hz, 3H);^{13}C NMR (126 MHz, DMSO-d_6) δ 173.0, 172.2, 171.7, 171.2, 156.3, 138.2, 136.7, 130.4, 129.9, 129.7, 128.7, 128.5, 128.2, 127.1, 126.7, 115.4, 55.1, 54.8, 54.2, 52.4, 38.1, 37.3, 36.8, 36.4, 24.8, 23.6, 21.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{33}H_{43}N_6O_5$ 603.3289, found 603.3297.

*H-Ala-aVal-Ala-aVal-Ala-aVal-NH$_2$ (**13**).* Purification by RP-HPLC (5−40% MeCN/H_2O with 0.1% HCO_2H) gave **13** as an amorphous white solid (20 mg, 17% overall yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.09 (m, 2H), 7.61 (s, 1H), 7.12 (s, 1H), 5.09 (m, 2H), 4.82−4.54 (m, 7H), 4.49 (d, J = 10.8 Hz, 1H), 4.31 (m, 1H), 2.29−2.04 (m, 3H), 1.17 (m, 10H), 1.05−0.63 (m, 19H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 174.0, 174.0, 172.9, 170.2, 170.0, 165.3, 62.0, 61.8, 61.7, 46.6, 45.1, 45.1, 25.7, 25.6, 25.2, 19.6, 19.5, 19.4, 18.9, 18.7, 18.7, 17.9, 16.7, 16.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{48}N_{10}O_6$ 572.3753, found 572.3758.

*H-Ala-(N-Me)Val-Ala-(N-Me)Val-Ala-(N-Me)Val-NH$_2$ (**14**).* Purification by RP-HPLC (5−40% MeCN/H_2O with 0.1% HCO_2H) gave **14** as an amorphous white solid (9 mg, 8% overall yield): ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ 9.23 (m, 0.2H), 9.10 (m, 0.3H), 8.73 (d, J = 6.7 Hz, 0.05H), 8.66 (d, J = 6.7 Hz, 0.06H), 8.53 (d, J = 7.7 Hz, 0.13H), 8.49−8.23 (m, 1.4H), 8.05 (m, 0.6H), 7.63 (s, 0.2H), 7.54 (d, J = 11.9 Hz, 0.1H), 7.38−7.26 (m, 0.6H), 7.22 (d, J = 10.9 Hz, 0.3H), 6.98 (d, J = 11.0 Hz, 0.6H), 5.02−4.80 (m, 0.7H), 4.80−4.46 (m, 4H), 4.22−3.84 (m, 2H), 3.00 (m, 5H), 2.85−2.61 (m, 4H), 2.26−1.98 (m, 3H), 1.29−1.06 (m, 9H), 0.96−0.67 (m, 18H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 174.2, 173.8, 173.0, 172.9, 172.7, 172.6, 172.4, 172.3, 171.6, 170.8, 170.0, 170.0, 169.5, 169.4, 169.3, 168.9, 168.3, 165.3, 64.4, 64.3, 64.0, 63.6, 63.4, 63.3, 61.0, 60.9, 60.8, 60.6, 60.5, 46.2, 46.1, 46.1, 44.9, 44.8, 44.5, 44.3, 44.2, 44.1, 30.3, 30.3, 30.2, 30.1, 30.0, 28.7, 28.5, 27.0, 26.9, 26.8, 26.7, 26.6, 26.5, 26.4, 26.3, 26.2, 26.2, 26.1, 21.0, 20.7, 19.7, 19.6, 19.6, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.9, 18.7, 18.6, 17.9, 17.8, 17.1, 17.0, 16.9, 16.8, 16.8, 16.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{51}N_7O_6$ 569.3895, found 569.3908.

Determination of HPLC Yields for 4a. H-Tyr(*t*-Bu)-OMe or H-Tyr(*t*-Bu)-OMe·HCl was added to a solution of **3** (10 mg, 0.035 mmol) in 1 mL of solvent (35 mM as final concentration) ,and base was added as needed. The reaction was stirred for 2 h at rt and treated with 10 μL of ethylenediamine. The reaction was concentrated and the crude material dissolved in 20 mL of MeCN. The crude solution (10 μL) was analyzed by HPLC to measure product peak area at 220 nm. HPLC yield was calculated by fitting data to an experimentally derived linear regression equation using standard concentrations of pure **4a**.

Determination of HPLC Peak Ratio for 11 and 12. Cleavage solutions containing crude peptides (0.025 mmol) were dissolved in 10 mL of 1:1 water/MeCN. A 5 μL aliquot of the crude solution for each entry was analyzed by HPLC to measure relative peak areas at 220 nm for **11** and **12**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02718.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

X-ray diffraction data for compound **2** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chatterjee, J.; Gilon, C.; Hoffman, A.; Kessler, H. *Acc. Chem. Res.* **2008**, *41*, 1331−1342. (b) Chatterjee, J.; Rechenmacher, F.; Kessler, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 254−269. (c) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Curr. Med. Chem.* **2004**, *11*, 2799−2822.

(2) (a) Rosales, A. M.; Murnen, H. K.; Kline, S. R.; Zuckermann, R. N.; Segalman, R. A. *Soft Matter* **2012**, *8*, 3673−3680. (b) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K. *Proc. Natl. Acad. Sci. U. S. A.* **1992**, *89*, 9367−9371. (c) Bradley, E. K.; Kerr, J. M.; Richter, L. S.; Figliozzi, G. M.; Goff, D. A.; Zuckermann, R. N.; Spellmeyer, D. C.; Blaney, J. M. *Mol. Diversity* **1997**, *3*, 1−15.

(3) (a) Kang, C. W.; Sarnowski, M. P.; Ranatunga, S.; Wojtas, L.; Metcalf, R. S.; Guida, W. C.; Del Valle, J. R. *Chem. Commun.* **2015**, *51*, 16259−16262. (b) Kang, C. W.; Ranatunga, S.; Sarnowski, M. P.; Del Valle, J. R. *Org. Lett.* **2014**, *16*, 5434−5437.

(4) For the first example of *N*-amino peptide derivatives based on aGly building blocks, see: Niedrich, H.; Knobloch, W. *J. Prakt. Chem.* **1962**, *17*, 263−272.

(5) (a) Sarma, B. K.; Kodadek, T. *ACS Comb. Sci.* **2012**, *14*, 558−564. (b) Kanta Sarma, B.; Yousufuddin, M.; Kodadek, T. *Chem. Commun.* **2011**, *47*, 10590−10592. (c) Liu, F.; Stephen, A. G.; Adamson, C. S.; Gousset, K.; Aman, M. J.; Freed, E. O.; Fisher, R. J.; Burke, T. R., Jr. *Org. Lett.* **2006**, *8*, 5165−5168.

(6) Gao, Y.; Kodadek, T. *Chem. Biol.* **2013**, *20*, 360−369.

(7) Vidal, J. In *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH, 2009; p 35−92.

(8) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646−10647.

(9) Niedrich, H.; Grupe, R. *J. Prakt. Chem.* **1965**, *27*, 108−112.

(10) Hoffman, R. V.; Kim, H. O. *Tetrahedron Lett.* **1990**, *31*, 2953−2956.

(11) (a) Winitz, M.; Bloch-Frankenthal, L.; Izumiya, N.; Birnbaum, S. M.; Baker, C. G.; Greenstein, J. P. *J. Am. Chem. Soc.* **1956**, *78*, 2423−2430. (b) Deechongkit, S.; You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 497−500.

(12) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863−3870.

DOI: 10.1021/acs.joc.6b02718
J. Org. Chem. 2017, 82, 1833−1841

(13) (a) Andreae, S.; Schmitz, E. *Synthesis* **1991**, *1991*, 327−341. (b) Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. *Chem. Rev.* **2014**, *114*, 8016−8036. (c) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A.; Aubry, A. *Chem. - Eur. J.* **1997**, *3*, 1691−1709.
(14) (a) Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1991**, *0*, 435−437. (b) Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791−4793. (c) Vidal, J. l.; Hannachi, J.-C.; Hourdin, G. n. l.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845−8848.
(15) Hannachi, J. C.; Vidal, J.; Mulatier, J. C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367−2373.
(16) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713−716.
(17) Cali, P.; Begtrup, M. *Synthesis* **2002**, *2002*, 63−66.
(18) Although not observed in the case of the H-Met-OH substrate, reaction of **3** with unhindered sulfides to form sulfimides has been reported previously: Armstrong, A.; Cooke, R. S. *Chem. Commun.* **2002**, 904−905.
(19) Gardner, B.; Nakanishi, H.; Kahn, M. *Tetrahedron* **1993**, *49*, 3433−3448.
(20) (a) Killian, J. A.; Van Cleve, M. D.; Shayo, Y. F.; Hecht, S. M. *J. Am. Chem. Soc.* **1998**, *120*, 3032−3042. (b) Lecoq, A.; Marraud, M.; Aubry, A. *Tetrahedron Lett.* **1991**, *32*, 2765−2768.
(21) Aleman, C. *J. Phys. Chem. A* **2002**, *106*, 1441−1449.
(22) Achiwa, K.; Yamada, S. *Tetrahedron Lett.* **1975**, *16*, 2701−2704.
(23) Kaneko, T.; Willner, D.; Monkovic, I.; Knipe, J. O.; Braslawsky, G. R.; Greenfield, R. S.; Vyas, D. M. *Bioconjugate Chem.* **1991**, *2*, 133−141.
(24) Amour, A.; Collet, A.; Dubar, C.; Reboudravaux, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 297−304.

DOI: 10.1021/acs.joc.6b02718
J. Org. Chem. 2017, 82, 1833−1841