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Engineering the Structure of an N-Terminal β-Turn To Maximize Screw-Sense Preference in Achiral Helical Peptide Chains

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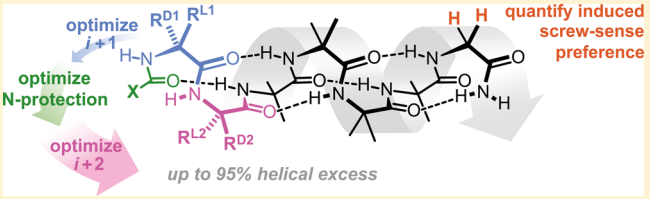
Supporting Information

ABSTRACT: Oligomers of α-aminoisobutyric acid (Aib) are achiral peptides that typically adopt 3_{10} helical conformations in which enantiomeric left- and right-handed conformers are, necessarily, equally populated. Incorporating a single protected chiral residue at the N-terminus of the peptide leads to induction of a screw-sense preference in the helical chain, which may be quantified (in the form of "helical excess") by NMR spectroscopy. Variation of this residue and its N-terminal protecting group leads to the conclusion that maximal levels of screw-sense preference are induced by bulky chiral tertiary amino acids carrying amide protecting groups or by chiral quaternary amino acids carrying carbamate protecting groups. Tertiary L-amino acids at the N-terminus of the oligomer induce a left-handed screw sense, while quaternary L-amino acids induce a right-handed screw sense. A screw-sense preference may also be induced from the second position of the chain, weakly by tertiary amino acids, and much more powerfully by quaternary amino acids. In this position, the L enantiomers of both families induce a right-handed screw sense. Maximal, and essentially quantitative, control is induced by an L-α-methylvaline residue at both positions 1 and 2 of the chain, carrying an N-terminal carbamate protecting group.



INTRODUCTION

Peptide-like oligomers of the achiral amino acid α-aminoisobutyric acid (Aib) adopt stable hydrogen-bonded 3_{10} helical structures[1] with a low barrier to inversion between left- and right-handed screw sense conformations,[2] and the incorporation of Aib into non-natural peptide structures is an important tool in conformational design.[3] Inai has made an extensive study of the solid-state and solution structure of peptides built from repeating achiral chromophore Aib-ΔPhe (*Z*-dehydrophenylalanine) units. $(Aib\text{-}\Delta Phe)_n$ oligomers adopt a 3_{10} helical conformation,[4] which must be racemic in the absence of an external chiral influence. L-Amino acids incorporated either at the N terminus,[5,6] or one residue from the N terminus,[7] or at the C terminus[6] have been shown by CD to induce a screw-sense preference in the oligomer, varying considerably with solvent and residue.[8] Inai also showed that the screw-sense preference of $(Aib\text{-}\Delta Phe)_n$ oligomers responds to binding of a ligand at an N-terminal binding site.[9−11] Ligand binding gives a temperature-dependent response[12] and can compete with screw sense induction from the C terminus.[10] By using cross-linking to slow the inversion of the helix,[13] it was possible to detect the induction of atropisomeric helicity by its slow decay after removal of the chiral influence, and when a contrasting chromophore was incorporated at the C-terminus, communication of helicity through the peptide was detectable.[14] More recently, the group of Yashima has shown that helical oligomers of Aib and its cyclohexyl analogue Ac_6c may communicate information from a chiral residue to a chiral metal center.[15]

Toniolo and co-workers were the first to demonstrate that a single chiral residue is able to influence the global screw sense of a helical pseudopeptide otherwise made from Aib residues,[16] and work in our own laboratories made use of NMR methods to show that the single chiral residue of oligomers **1a−d**, made up principally of achiral Aib and Gly, induces a screw-sense preference that persists over more than 20 residues, or nearly 4 nm (Figure 1).[17] We also demonstrated that this control of

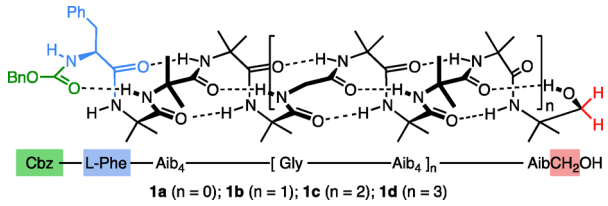


Figure 1. Induced left-handed screw-sense in extended helical oligomers of achiral amino acids.

screw-sense preference can be achieved more readily from the N than from the C terminus.[18] The handedness of the Aib/Gly helices was controlled by the incorporation of a single chiral N-terminal residue, namely Cbz-L-Phe, and the conformational preference of the helix was deduced by the simple technique of measuring anisochronicity (chemical shift difference) between a pair of C-terminal diastereotopic "reporter" protons remote

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from the controlling CbzPhe residue. Under such conditions, each Aib residue communicates absolute helicity to its neighbor with 96.5% fidelity, and anisochronicity may be observed in diastereotopic protons separated by more than 60 bond lengths from the nearest stereogenic center.

Studies using ^{13}C-labeled Aib residues[19] allowed us to quantify the screw-sense preference induced by a small selection of N-terminal amino acids. Although in most peptides L-amino acids induce right-handed helicity, a combination of CD, NMR, and time-dependent DFT calculations have shown that an L configuration at an N-terminal tertiary amino acid induces a left-handed screw sense in the rest of the Aib oligomer, while an L configuration at an N-terminal quaternary amino acid induces a right-handed screw sense.[20−23]

These studies[19] also revealed that even the best-performing controllers studied—CbzPhe and CbzαMv—induce measured screw-sense preferences only of the order of 3:1. We now report the results of an extensive survey of the factors governing screw-sense preference in Aib oligomers more or less closely related to **1a**, with various alternative protected residues placed at the helix terminus. We report the factors favoring high levels of screw-sense control, and by careful choice of the two N-terminal residues, we show that it is possible to direct the achiral portion of the oligomer to adopt complete preference for a single screw-sense.

The development of foldamers—extended molecules with well-organized conformational properties[24,25]—has been driven primarily by the desire to develop nonbiological, stable compounds with valuable biomimetic structural and recognition properties.[26] A wide range of non-natural α-, β-, γ-, and δ-peptides, peptoids, peptide nucleic acids, and various oligomeric aromatic systems have been shown to interact with, or mimic, biological molecules.[27−29] The principles which govern foldamer conformation have been widely studied,[24] and a broad range of structural classes have been characterized, their ground-state conformations usually stabilized by hydrogen bonding, by dipole−dipole interactions, or by aromatic π-stacking.[30]

Many foldamers are helical,[31] either because they are made up of individual chiral monomers or because longer range interactions between monomers within a foldamer sequence favor a helical structure. Indeed, any oligomer with a constant translation and rotation between adjacent monomers will adopt a helical conformation.[32] But a preference for helicity has to be distinguished from a preference for a single screw sense (i.e., *M* vs *P*). For example, polyisocyanides built from achiral monomers adopt rigid, racemic helical structures[33] but can also be formed with a preferred screw sense by using a chiral initiator, terminator, or catalyst to induce a left- or a right-handed screw sense.[34,35] Polyisocyanides undergo only slow helical inversion, and the control achieved in such situations is kinetic in nature.

Helices which can undergo more rapid screw-sense inversion will fall under the thermodynamic control of any stereochemical influence exerted upon them.[36] For foldamers made up of chiral monomers, their absolute screw sense is a direct consequence of those monomers, and this is the situation seen in typical peptides, nucleic acids, and other biopolymers.[37] Side-chain stereochemistry can induce a screw-sense preference in helical foldamers,[38,39] and it has become evident that the stereochemical influence required to provide a high level of screw-sense preference can be very small—even H vs D[40] or circularly polarized light[41] in polyisocyanates,[42] for example. Likewise, not every monomer needs to be chiral for induction to be effective—the principle of "sergeants and soldiers" means that achiral monomers follow suit if chiral monomers are dispersed among them.[39,43−45] A screw-sense preference in a stereolabile helical oligomer or polymer can be induced by coordination to a chiral counterion or other ligand[29,35,46−48] and it is possible to exert measurable levels of thermodynamic control over the global screw-sense preference of helical oligomer with a single terminal chiral controller.[28,49,50]

Instances of long-range (i.e., nanometer-scale[51]) thermodynamic control over screw-sense preference starting from one terminus are still relatively few,[17,52−56] and in cases where a helicity preference has been observed by circular dichroism (CD), the *selectivity* of the control generally remains unquantified. Exceptions include the work of Suginome, in which comparisons with an estimated maximum value of molar ellipticity are used to quantify screw-sense preference.[57] Huc has shown that helical oligo(quinolinamides) adopt predominantly one of the two diastereoisomeric conformations when the terminal residue is made chiral and quantified the preference by NMR;[21] Inai and Yashima used CD to show that noncovalent interactions with the terminal residue of related peptide-based achiral helices[11] or with binding sites spread along the helix[47] can induce some degree of absolute helicity;[48] Feringa has demonstrated that helicity in a polyisocyanate may be controlled by a terminal switching mechanism.[53]

Seminal work on the use of a terminally induced screw-sense preference to achieve a remote, locally measurable chemical effect came from the laboratories of Noe,[58] who showed that the helix-forming properties of paraformaldehyde could propagate the influence of a terminal chiral residue to allow diastereoselectivity at a reaction site up to 10 bonds away. We have recently extended this concept to the use of oligoamide foldamers to control stereoselectivities of reactions up to 60 bonds away.[59]

With switchable controllers, functional mimicry of the conformational changes evident in enzymes, receptors, and other allosteric proteins can be envisaged, and switchable helix inversions have been achieved under the influence of factors such as temperature, solvent polarity, irradiation, and electrochemistry.[41,53,60] Signal transduction can result from conformational changes in artificial molecular structures as a result of a chemical stimulus,[51,54,61] and we have shown that switching the screw sense of a helix by binding a chiral diol to a boronate-based binding site, coupled with local detection of helical screw sense at a remote site, can be used to achieve communication of information over multinanometer distances.[62]

RESULTS AND DISCUSSION

Use of ^{1}H NMR To Quantify Screw-Sense Preference.

As with our previous work,[19] the results reported here rely on the quantification of anisochronicity (chemical shift difference) between a pair of signals arising from a pair of potentially diastereotopic protons CH_AH_B located within the helix. These two ^{1}H nuclei are identical unless they find themselves in a chiral environment (Figure 2). A rapidly inverting configurationally achiral helix (i.e., one built entirely of achiral monomers) is an achiral environment, and the two "reporter" nuclei in such a molecule must be isochronous (Figure 2a). However, if a remote chiral influence succeeds in inducing preferentially one screw sense in the helical oligomer (i.e., $K_{eq} \neq 1$), the symmetry of the local environment of the nuclei will be broken, rendering the reporter nuclei anisochronous (Figure 2b).[63] Provided the chiral influence is located sufficiently far away to avoid direct

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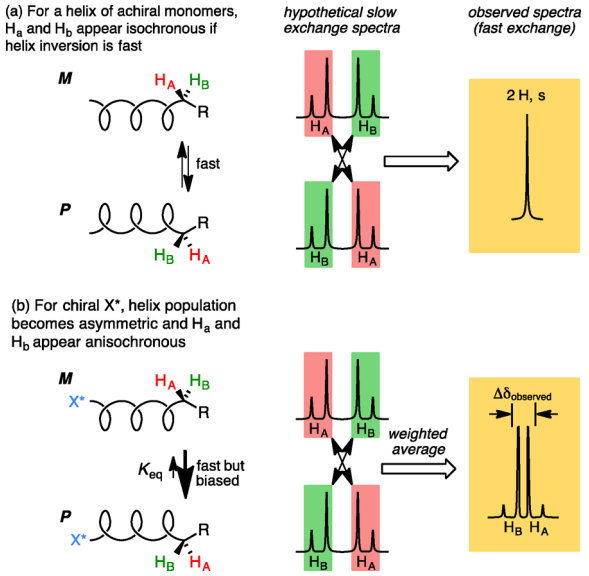


Figure 2. Detection of screw-sense preference by NMR in the fast exchange régime (diagram reproduced from ref 18).

interaction with the reporter nuclei, the degree of anisochronicity results from a weighted average of two pseudoenantiomeric environments and therefore is proportional to the local excess of one screw sense over the other

$$\Delta\delta_{obsd} \propto (K_{eq} - 1)/(K_{eq} + 1)$$

or

$$\Delta\delta_{obsd} \propto ([M] - [P])/([M] + [P])$$

where the expression $([M] - [P])/([M] + [P])$ may be interpreted as "helical excess" (h.e.),[64] given its similarity with the formula for enantiomeric excess (e.e.).

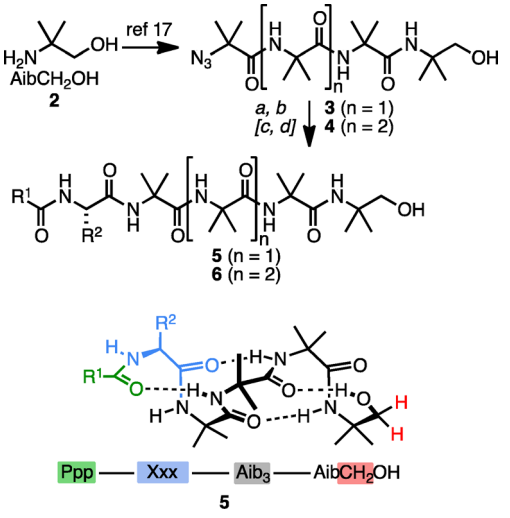
Quantifying the anisochronicity as a chemical shift difference $\Delta\delta$ (most conveniently in ppb) allows the effectiveness of the screw-sense control supplied by X* to be evaluated in a relative sense. In this paper, we use a pair of diastereotopic protons located within a C-terminal glycinamide or C-terminal hydroxymethyl group, which stand clear of the other resonances in the spectrum, to allow ready observation of their anisochronicity. We have used similar methods to compare the effectiveness of screw-sense controllers located at the N and C terminus of an Aib oligomer[18] and to compare the ability of various linking monomers to relay a screw-sense preference from one Aib oligomer to another.[65] We recently reported potential alternative ^{19}F NMR reporters based on β,β'-difluoroAib,[66] but the ready availability of glycinamide or 2-amino-2-methylpropan-1-ol and the ease with which they may be incorporated into peptides make them more suitable for the extensive survey of compounds described in this paper.

Our previous studies with ^{13}C-labeled compounds[19] allowed us to quantify screw-sense preferences, either by line shape analysis of VT ^{13}C NMR spectra or more simply by measuring the anisochronicity (chemical shift separation) at slow exchange $\Delta\delta_{slow}$. Knowing this value allows the magnitude of the h.e. $(= \Delta\delta_{observed}/\Delta\delta_{slow})$ to be determined for any temperature at which the helical inversion is in fast exchange on the NMR time scale. Attempts to apply either of these methods to the temperature-dependent ^{1}H NMR spectra of the compounds in this paper were frustrated by the intrusion of other slow rotational processes in the reporters, which prevented acquisition of simple ^{1}H NMR spectra at the slow exchange limit, and will be reported in full in a future paper. Nonetheless, we have confirmed the validity of using $\Delta\delta$ in glycinamide methylene groups as a means of comparing screw-sense preferences by correlation with the circular dichroism spectra of related thionoglycine-containing compounds.[67] The glycinamide-derived CH_2-containing reporters in particular allow diverse controllers X* to be compared readily, and extrapolation from the few controllers whose conformational preferences have been quantified by ^{13}C NMR methods allows hypothetical slow-exchange chemical shift separations, and hence absolute values for screw-sense preferences, to be estimated.

A further drawback of the ^{1}H NMR method is that it cannot report on whether an *M* or a *P* helix is preferred—in other words, the sign of the screw-sense preference remains unassigned. However, CD studies reported here and elsewhere,[20] correlated with data from enantiomerically enriched isotopically labeled ^{13}C NMR probes, allow the sense of the helical preference to be deduced with confidence in most cases.

Survey of N-Terminal-Controlling Residues. We started by surveying the conformational influence of a small selection of chiral N-terminal residues linked to a short Aib oligomer. Trimers **3** or tetramers **4** of Aib were coupled to a C-terminal $AibCH_2OH$ residue **2** by our reported method.[17] This C-terminal hydroxymethyl group was designed to act as a ^{1}H NMR reporter, with the OH group donating a hydrogen bond to an amide carbonyl at the C terminus of the helix, and the CH_2 group providing a pair of diastereotopic reporter protons. It is also reminiscent of the structure of the C-terminal hydroxymethyl substituents characteristic of the peptaibols.[68] The resulting achiral oligomers were capped at the N terminus variously with Cbz-protected L-Phe, Val, Pro, Leu, or Ser to yield tetra- and pentapeptides **5** and **6** (Scheme 1). The Cbz

Scheme 1. Varying the N-Terminal Residue[a]



[a]Reagents:[17] (a) H_2, 10% Pd/C, MeOH; (b) CbzXxxOH, PyBOP, *i*-Pr_2NEt, CH_2Cl_2; (c) H_2, 10% Pd/C, EtOH; (d) *p*-BrC_6H_4COCl, Et_3N, CH_2Cl_2.

protecting group was removed from some of these compounds and replaced with a *p*-bromobenzamide. The anisochronicity in their CH_2OH groups was determined by ^{1}H NMR in CD_3OD and is tabulated in Table 1. Anisochronicity in these AB systems, $\Delta\delta$, was calculated from the formula

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Table 1. Anisochronicity in the Terminal CH_2 Group of 5 and 6: Initial Survey

entry	compd	Ppp =	R^1 =	Xxx =	R^2 =	$\Delta\delta^a$ (ppb) (h.e.,[b] h.e.[c]) (CD_3OD)
1	**5a**	Cbz	BnO	Phe	Bn	166 (−43, −53)
2	**5b**	Cbz	BnO	Val	*i*-Pr	131 (−34, −42)
3	**5c**	Cbz	BnO	Pro		140 (−36, −45)
4	**5d**	Cbz	BnO	Leu	*i*-Bu	102 (−26, −33)
5	**5e**	Cbz	BnO	Ser	CH_2OH	13 (3, 4)
6	**5f**	Cbz	BnO	SerOP	CH_2OSi-*t*-$BuPh_3$	133 (−34, −42)
7	**5g**	*p*-BrBz	*p*-BrC_6H_4	Phe	Bn	236 (−61, −75)
8	**5h**	*p*-BrBz	*p*-BrC_6H_4	Val	*i*-Pr	238 (−61, −76)
9	**5i**	*p*-BrBz	*p*-BrC_6H_4	Leu	*i*-Bu	214 (−55, −68)
10	**6a**	Cbz	BnO	Phe	Bn	156 (−40, −53)
11	**6b**	Cbz	BnO	Val	*i*-Pr	113 (−29, −38)
12	**6c**	*p*-BrBz	*p*-BrC_6H_4	Phe	Bn	210 (−54, −71)
13	**6d**	*p*-BrBz	*p*-BrC_6H_4	Val	*i*-Pr	201 (−52, −68)

[a]Chemical shift separation between the anisochronous peaks arising from diastereotopic protons H_a and H_b in the ^1H NMR spectrum in CD_3OD at 23 °C. [b]Helical excess, as defined in ref 45, measured at the C terminus by comparison with known degree of screw-sense induction by CbzPhe. [c]Inferred helical excess induced by the controller at the N-terminus of the oligomer; see the text for discussion.

$$\nu_0\Delta\delta = [(f_1 - f_3)^2 - J_{AB}{}^2]^{1/2} = [(f_2 - f_4)^2 - J_{AB}{}^2]^{1/2} = [(f_1 - f_4)(f_2 - f_3)]^{1/2}$$

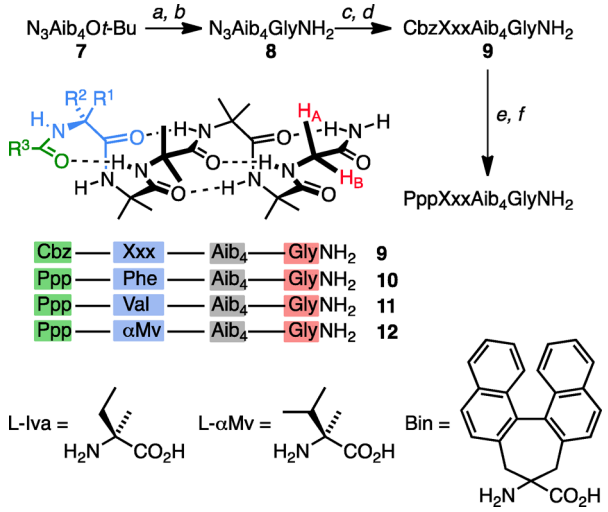
where $f_{1,2,3,4}$ are the observed resonance frequencies in order of the four lines comprising the AB multiplet, J_{AB} is the coupling constant, and ν_0 is the spectrometer frequency. $\Delta\delta$ is conveniently reported in parts per billion (ppb). Methanol was chosen as the solvent because previous studies[17] and further work in progress[69] have confirmed the concentration-independence in CD_3OD of the spectra of closely related compounds.

For comparison between different conformational controllers, a "normalized" value for the degree of screw-sense control, or helical excess (h.e.), is also given in Table 1, in parentheses. The estimated values shown are calculated on the assumption that $\Delta\delta_{observed} \propto$ h.e., extrapolating from the fact that CbzPhe induces a 70:30 screw-sense ratio (i.e., 40% h.e.) when quantified by a probe located at the remote end of an Aib tetramer.[19] The sign of the h.e. is shown as negative for the *M* screw sense and positive for the *P* screw sense and is assigned on the basis that N-terminal tertiary L-amino acids induce *M* helicity and N-terminal quaternary L-amino acids induce *P* helicity.[21,22] Where no sign is shown, the absolute assignment is unsure. The first value in parentheses may be interpreted, for each of the protected N-terminal chiral residues, as the estimated local value of the helical excess measured at the location of the probe, at the C terminus of the helix. The second value—whose arithmetical origin is explained below—takes into account the loss of conformational control experienced by the reporter due to faults occurring in the structure of the helix.[17] This value may be interpreted as the inferred degree of screw-sense control, again measured as h.e., induced at the N terminus and is characteristic of each individual chiral controller.

Phe, Val, and Pro (entries 1−3) all induced similar levels of control, in each case enhanced (though less so for Phe) when the carbamate protecting group Cbz was replaced by the amide *p*-BrBz (entries 7 and 8). β-Branched Leu (entries 4 and 9) performed less well than α-branched Phe or Val. Ser gave very low levels of control, but interestingly, control was improved when the Ser hydroxyl group was protected as a bulky silyl ether (entries 5 and 6). The slightly higher levels of control in **5** compared with the Aib homologated **6** (entries 10−13) are consistent with previous observations[17,19] that h.e. decreases by about 4−5% with each additional Aib residue inserted between controller and reporter (see later discussion).

These initial results gave an indication of the superior control exerted by bulky, branched residues, and a further set of compounds was made, containing both proteinogenic and non-proteinogenic residues, to probe in more detail the dependence of screw-sense control on the size of the alkyl substituents at the N-terminal residue. As shown in Scheme 2, Aib tetramer

Scheme 2. Optimizing the N-Terminal Residue[a]



[a]Reagents: (a) CF_3CO_2H, CH_2Cl_2; (b) Ac_2O, 120°C, then $HGlyNH_2 \cdot HCl$, Et_3N, MeCN, Δ; (c) H_2, 10% Pd/C, MeOH; (d) CbzXxxOH, PyBOP (or EDC/HOBt), *i*-Pr_2NEt, CH_2Cl_2 or CbzXxxF, *i*-Pr_2NEt, CH_2Cl_2; (e) H_2, 10% Pd/C, MeOH; (f) form new protecting group (see the Supporting Information).

tert-butyl ester **7** was deprotected and then coupled at the C-terminus, this time with glycinamide, to provide an NMR reporter. After azide reduction, the N-terminus was capped with one of a range of Cbz-protected tertiary and quaternary amino acids, as shown in Table 2.

As with Table 1, the final column of Table 2 reports the measured value of $\Delta\delta_{observed}$, along with the estimated helical excess at the site of the C-terminal $GlyNH_2$ reporter and at the N-terminal controller. ^{13}C NMR experiments with CbzPhe or Cbzα*M*v as controllers[19] led us to expect that the helical excess at the location of the reporter in oligomers **9d** and **9f** will be −40 and +52% h.e. respectively, implying that the hypothetical maximum peak separation ($\Delta\delta_{slow}$) for $GlyNH_2$ reporter in this position would be ca. 530 ppb. This value has been used to deduce the helical excesses reported throughout Tables 3 and 4.

More bulky, branched amino acids again gave greater control. Methylation of valine was particularly fruitful: *t*-Leu[71] (entry 3) was only marginally better than valine (entry 2), but a much greater improvement in control was seen when valine was replaced by the quaternary amino acid α-methylvaline (entry 6). Likewise, a particularly high level of control was exerted by the

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Table 2. Anisochronicity in the Terminal CH_2 Group of 9: Varying the Controlling Residue

entry	compd	Xxx =	R^1 =	R^2 =	$\Delta\delta^a$ (ppb) (h.e.,[b] h.e.[c]) (CD_3OD)
1	**9a**	Ala	Me	H	79 (−15, −20)
2	**9b**	Val	*i*-Pr	H	142 (−27, −35)
3	**9c**	*t*-Leu	*t*-Bu	H	178 (−34, −44)
4	**9d**	Phe	Bn	H	209 (−40, −52)
5	**9e**	Iva[d]	Me	Et	100 (+19, +25)
6	**9f**	αMv[e]	Me	*i*-Pr	275 (+52, +68)
7	**9g**	Bin[f]	−binaphthyl−		311 (59, 77)
8	**9h**	αMp[g]	Me	Bn	227 (+43, +56)

[a]Chemical shift separation between the anisochronous peaks arising from diastereotopic protons H_a and H_b. [b]Helical excess, as defined in ref 19, measured at the C terminus by comparison with known degree of screw-sense induction by CbzPhe and CbzαMv. [c]Inferred helical excess induced by the controller at the N-terminus of the oligomer; see the text for discussion. [d]L-Isovaline. [e]L-α-Methylvaline. [f](±)-Bin (ref 70). [g]L-(α-Methyl)phenylalanine.

quaternary amino acid Bin[70] (entry 7), employed here in racemic form. In general, circular dichroism studies[20] confirm that the screw-sense preference induced in this series by quaternary amino acids is opposite to that induced by tertiary amino acids: the more bulky of the two substituents prefers the position R^1 in tertiary amino acids but R^2 in quaternary amino acids (see Scheme 2).

Varying N-Terminal Protection. We recently showed that the hydrogen-bonding network at the N-terminus of the oligomer, and the type of β-turn that results, is crucial for the induction of a favored helical conformation.[21] Given the intriguing improvement in selectivity observed in Table 1 on replacing Cbz with *p*-BrBz, we took **9d** and **9f**, hydrogenolyzed them, and reprotected them with a range of N-terminal protecting groups, as shown in Table 3. Observed anisochronicities for the diastereotopic $GlyNH_2$ protons are shown in Table 3, with helical excesses calculated as in Table 2, by reference to the reported values for **9d** = **10a** and **9f** = **12a**.

For phenylalanine derivatives **10**, removal of the Cbz protecting group decreased the degree of control significantly in **10b** (entry 2), but interestingly, reprotection as either an amide (acetamide **10c**, *p*-bromobenzamide **10d**, *m*-nitrobenzamide **10j**) or a urea **10e** (entries 3−5 and 9) gave a higher level of control than the Cbz carbamate protecting group of **10a** = **9d**. The group of compounds **10a−e** was also analyzed in acetonitrile, and using the known +31% h.e. of a related CbzPhe-controlled compound in this solvent[19] to normalize the figures, it was evident that control was consistently slightly weaker in acetonitrile than in methanol. A very high level of control was also observed with the benzoate ester of the hydroxy analogue of phenylalanine[62b] (*O*-benzoyl phenyllactate **10f**) but not its free alcohol **10g** (entries 6,7).

The same trend toward better control with amide- rather than carbamate-protected tertiary amino acids is also true for CbzVal **11a** vs AcVal **11c** or *p*-BrBzVal **11d** (entries 10, 12, and 13). Protection of Val as an *N*-ethyl carbamate **11i**, urea **11j**, or thiourea **11k** (entries 15−17) led to levels of control intermediate between those seen with Cbz and Ac, but protection as a trifluoroacetamide **11h** (entry 14) gave greater control even than the acetamide: **11h** gave the highest stereocontrol

Table 3. Anisochronicity in the Terminal CH_2 Groups of 10 and 11: Varying the N-Terminal Protecting Group

entry	compd	Ppp =	R^3 =	Xxx =	$\Delta\delta^a$ (ppb) (h.e.,[b] h.e.[c]) (CD_3OD)	$\Delta\delta^a$ (ppb) (h.e.,[b] h.e.[c]) (CD_3CN)
1	**9d** = **10a**	Cbz	BnO	Phe	209 (−40, −52)	195 (−31, −41)
2	**10b**		H	Phe	124 (23, 31)	96 (15, 20)
3	**10c**	Ac	Me	Phe	239 (−45, −59)	229 (−36, −48)
4	**10d**	*p*-BrBz	*p*-BrC_6H_4	Phe	295 (−56, −73)	281 (−45, −59)
5	**10e**	PhNHCO	NHPh	Phe	254 (−48, −63)	195 (−31, −41)
6	**10f**	Bz[d]	Ph	Phe	315 (−60, −78)	
7	**10g**	*d*	H	Phe	5 (1, 1)	
8	**10i**	Boc	*t*-BuO	Phe	161 (−30, −40)	
9	**10j**	*m*-NO_2Bz	*m*-$NO_2C_6H_4$	Phe	294 (−56, −73)	
10	**9b** = **11a**	Cbz	OBn	Val	142 (−27, −35)	
11	**11b**		H	Val	92 (17, 23)	
12	**11c**	Ac	Me	Val	225 (−43, −56)	
13	**11d**	*p*-BrBz	*p*-BrC_6H_4	Val	285 (−54, −71)	
14	**11h**	TFA	CF_3	Val	320 (−61, −79)	
15	**11i**	EtOCO	EtO	Val	193 (−37, −48)	
16	**11j**	EtNHCO	EtNH	Val	206 (−39, −51)	
17	**11k**	EtNHCS	EtNH[e]	Val	185 (−35, −46)	
18	**9f** = **12a**	Cbz	OBn	αMv	275 (+52, +68)	
19	**12b**		H	αMv	109 (+21, +27)	
20	**12c**	Ac	Me	αMv	217 (+41, +54)	
21	**12d**	*p*-BrBz	*p*-BrC_6H_4	αMv	126 (+24, +31)	
22	**12h**	TFA	CF_3	αMv	62 (−12, −15)	
23	**12i**	EtOCO	EtO	αMv	252 (+48, +63)	
24	**12j**	EtNHCO	EtNH	αMv	254 (+48, +63)	

[a]Chemical shift separation between the anisochronous peaks arising from diastereotopic protons H_a and H_b in the ^1H NMR spectrum. [b]Helical excess, as defined in ref 19, measured at the C terminus by comparison with known degree of screw-sense induction by CbzPhe and CbzαMv. [c]Inferred helical excess induced by the controller at the N-terminus of the oligomer; see the text for discussion. [d]In these compounds, the N of the N-terminal residue is replaced by O. [e]In this compound, the C═O of the protecting group is replaced by C═S.

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Table 4. Varying the Second Residue of the Chain

entry	compd	Ppp	Yyy =	R^3	R^4	Xxx	R^1	R^2	$\Delta\delta^a$(ppb) (h.e.,[b] h.e.[c])
1	**13a**	Cbz	L-Phe	Bn	H	L-Phe	Bn	H	194 (37, 48)
2	**13b**	Cbz	D-Phe	Bn	H	L-Phe	Bn	H	147 (28, 37)
3	**13c**	N_3	Aib	Me	Me	Val	*i*-Pr	H	266 (−50, −66)
4	**13d**	Cbz	Aib	Me	Me	Val	*i*-Pr	H	79 (+15, +20)
5	**13e**	Ac	Aib	Me	Me	Val	*i*-Pr	H	41 (+8, +10)
6	**13f**	N_3	Aib	Me	Me	αMv	*i*-Pr	Me	211 (+40, +52)
7	**13g**	Cbz	Aib	Me	Me	αMv	*i*-Pr	Me	315 (+60, +78)
8	**13h**	Ac	Aib	Me	Me	αMv	*i*-Pr	Me	327 (+62, +81)
9	**13i**	Cbz	αMv	*i*-Pr	Me	Val	*i*-Pr	H	215 (+41, +53)
10	**13j**	Cbz	αMv	*i*-Pr	Me	*t*-Leu	*t*-Bu	H	153 (+29, +38)
11	**13k**	Cbz	αMv	*i*-Pr	Me	αMv	*i*-Pr	Me	383 (+72, +95)

[a]Chemical shift separation between the anisochronous peaks arising from diastereotopic protons H_a and H_b in the ^{1}H NMR spectrum in CD_3OD at 23 °C. [b]Helical excess, as defined in ref 19, measured at the C terminus by comparison with known degree of screw-sense induction by CbzPhe or CbzαMv (Table 2). [c]Inferred helical excess induced by the controller at the N-terminus of the oligomer; see the text for discussion.

found for any derivative of a single proteinogenic tertiary amino acid residue.

With α-methylvaline, a different trend was seen: conversion to an acetamide **12c** or, even more significantly, a *p*-bromobenzamide **12d** or a trifluoroacetamide **12h** (entries 20−22) by contrast reduced (and in the case of **12h**, inverted: see below) the level of screw-sense control. Alternative carbamate or urea protecting groups in **12i** and **12j** (entries 23 and 24) also gave control slightly weaker than Cbz. As with Phe and Val, lack of N-protection in **12b** gave very poor control (entries 2, 11, 19). In general it seems that control by this quaternary amino acid is maximized by a carbamate protecting group, while control by tertiary amino acids (see also Table 1) is maximized by amide protecting groups.

Steric bulk in carbamates also plays a role: with Phe and Val, the more bulky carbamate O-substituents decrease the control (**10a** vs **10i** and **11i** vs **11a**), while in α-methylvaline the more bulky *O*-benzyl group **12a** gives better control than the less bulky ethyl group of **12i**.

Confirmation of the absolute screw sense preference experienced in the oligomers **10**−**12** shown in Table 2 was provided by CD spectroscopy (Figure 3). The signs of the band at around 207 nm indicate that, as expected,[20,72] oligomers containing the tertiary L-amino acid Val (Figure 3a) display *M* helicity, while oligomers containing the quaternary L-amino acid αMv (Figure 3b) generally display *P* helicity. The exception is the low conformational preference displayed by the trifluoroacetamide-protected **12h**, which is left-handed. These CD traces are characteristic of structures adopting broadly a 3_{10} helical conformation.[20,72]

Optimizing the Structure of the First Helical Turn: The *i*+2 Position. Overall control of screw sense in these oligomers must be dictated by the conformational preference within the first turn of the 3_{10} helix formed by the Aib chain.[21] This turn starts with the N-terminal protecting group (residue *i*), and contains the α-carbon atoms of both the first (*i*+1) and second (*i*+2) residues of the peptide chain (Scheme 3). We hypothesized, therefore, that it should be possible to potentiate the effect of the configuration of the first (*i*+1) residue in the chain by introduction of a chiral residue at the second (*i*+2) position as well.

Pentapeptide **8**[20] was hydrogenated and coupled stepwise with pairs of amino acids, both achiral and chiral, tertiary and quaternary, to yield the Cbz-protected heptapeptides **13a**−**k** (Scheme 3). The anisochronicities measured in their

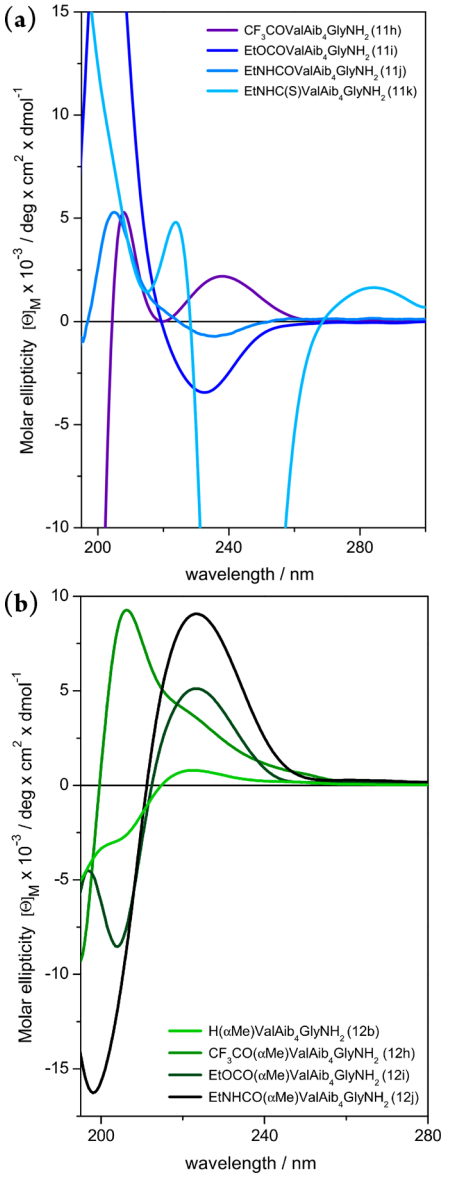

Figure 3. CD spectra of (a) L-Val-capped peptides **11h**−**k** and (b) L-αMv-capped peptides **12bh**−**j**.

C-terminal $GlyCH_2$ groups are reported in Table 4, with helical excesses quoted as before by comparison with the data in

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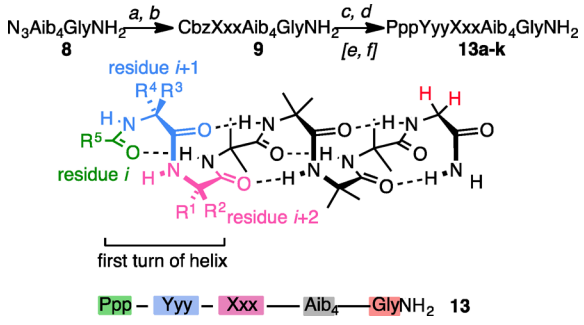
Scheme 3. Two Controlling Amino Acids[a]



[a]Reagents: (a) H_2, 10% Pd/C, MeOH; (b) CbzXxxOH, EDC, HOBt, *i*-Pr_2NEt, CH_2Cl_2 or CbzXxxF, *i*-Pr_2NEt, CH_2Cl_2; (c) H_2, 10% Pd/C, MeOH; (d) N_3AibCl, Et_3N, or CbzYyyOH, EDC, HOBt, *i*-Pr_2NEt, CH_2Cl_2 or CbzYyyF, *i*-Pr_2NEt, CH_2Cl_2; (e) H_2, 10% Pd/C, MeOH; (f) Ac_2O, CH_2Cl_2 (see the Supporting Information).

Tables 2 and 3. The screw-sense preferences of peptides **13** were determined from the sign of the band at 207 nm[20,72] in their CD spectra (Figure 4).

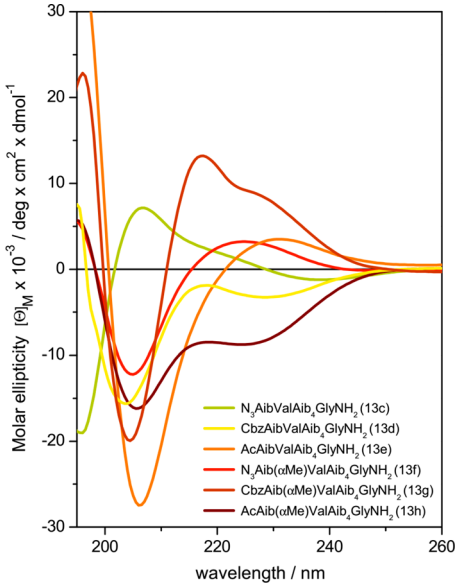


Figure 4. CD spectra of compounds **13c–h**.

Compounds **13a** and **13b** (entries 1 and 2) indicate that two chiral tertiary residues do not increase control beyond that provided by one: indeed, most simple derivatives of Phe in Table 3, entries 1–9, perform better than Cbz-L-Phe-L-Phe or Cbz-L-Phe-D-Phe, presumably because two tertiary residues destabilize the N-terminal β-turn structure. Due to unavoidable contributions from bands arising directly from the chiral aromatic amino acids, it is not clear from the CD spectra of **13a** and **13b** whether the resulting helix is left- or right-handed.

In **13c**, with Val as the second residue of the chain (entry 3), capped with an N_3Aib residue, h.e. is similar, and slightly higher, than that obtained with AcVal at the N-terminus. The lack of hydrogen-bond acceptor in the azide protecting group means that the Val finds itself in the *i*+1 position in both cases, with N_3Aib as residue *i*, effectively functioning as an amide protecting group. However, exchanging N_3Aib for CbzAib (**13d**) or AcAib (**13e**), which must move Val to the *i*+2 position, gave much lower levels of control (entries 4 and 5). CD spectroscopy (Figure 4) indicated that moving Val from the *i*+1 to the *i*+2 position of the first β-turn also inverted the helix from left-handed to the conventionally expected right-handed screw sense:[37] tertiary amino acids induce a left-handed screw sense only when located in the *i*+1 position at the N terminus of an achiral Aib oligomer and not when embedded in the oligomer.[16,20,21]

The ineffectiveness of a tertiary amino acid at the *i*+2 position of the turn was confirmed by the pair of diastereoisomers **13a** and **13b** which showed that $CbzPhe_2$, whatever its relative stereochemistry, gives lower levels of control than CbzPhe (**9d**) (entries 1 and 2). Furthermore, the insertion of a tertiary amino acid at the *i*+2 position failed to potentiate the effect of an αMv substituent at the *i*+1 position: thus, CbzαMvVal **13i** and CbzαMv*t*-Leu **13j** (entries 9 and 10) both performed less well than CbzαMv alone (**9f**). The poor performance exhibited by tertiary amino acids with β-branched hydrophobic side chains (such as Val, Ile, or Phe) embedded within the helix, rather than placed at the N-terminus, may be due to their known propensity to destabilize helical structures[74] while favoring β-sheet formation,[75] because of their increased conformational freedom especially when located at the *i*+2 position of a β-turn.

By contrast, moving a *quaternary* amino acid from the *i*+1 to the *i*+2 position of the turn was not deleterious to h.e. The control achieved with αMv capped with N_3Aib (**13f**, entry 6) was identical with that achieved with αMv protected as an acetamide (**12c**), but replacing the azide with a hydrogen bond acceptor such as carbamate or an amide which moves the αMv to the *i*+2 position (in **13g** and **13h**) increased control significantly (entries 7 and 8). Control from this *i*+2 position was assisted by the quaternary amino acid at the *i*+1 position, which allowed **13g** and **13h** to adopt almost ideal, right-handed 3_{10} helices in the solid state (see discussion below).

Building on this fact, oligomer **13k** was made with a quaternary chiral amino acid at both positions *i*+1 and *i*+2. $Cbz\alpha Mv_2Aib_4GlyNH_2$ **13k** displays anisochronicity in the $GlyNH_2$ protons of 383 ppb, the highest value yet observed, corresponding to a value of 72% h.e. at the C terminus of the oligomer.

Estimating the Effectiveness of the Controller by Extrapolating from Measured h.e. The question remains whether this figure is indeed the highest possible or whether any other controller might surpass the effectiveness of $Cbz\alpha Mv_2$. Anisochronicity ($\Delta\delta$), because of its simple link to the value of helical excess in an ideal helical oligomer, quantifies the scalar value of screw-sense preference *measured at the location of the NMR probe*. However, helical excess can be shown to decay on moving along a helical oligomer,[19] since the chance of a fault (a helix inversion) located in between the controller and reporter increases with oligomer length.[17] The screw-sense preferences we have deduced, expressed as h.e., thus do not represent the degree of control exerted by the controllers themselves, since these are (necessarily) separated from the reporter, usually by four Aib monomers. In order to estimate the control *exerted* by each controller (and therefore how close they each come to achieving maximal control of screw sense), we can assume the observed values of h.e. at the C terminus, $h.e._{obs}$, are related to the induced h.e. at the N terminus, $h.e._0$, by the relationship $h.e._{obs} = h.e._0 \times (2p - 1)^n$ (see ref 17) where *n* is the number of residues and *p* is the fidelity of screw-sense transmission; i.e., $1 - p$ represents the chance of a helix inversion occurring at any residue between the controller and reporter. Our current best estimate of the value of *p* for Aib

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chains in methanol at 23 °C is 0.9735,[19] which corresponds to a 2.65% chance of helix inversion at each residue, or a 5.3% per residue fall in h.e. Assuming that this value is constant at all positions in the chain, we may deduce that the induced control is 1.243 times the observed control in **5** (with a spacing of 3 Aib monomers between controller and reporter, i.e., n = 4) and 1.313 times the observed control in **6** and **9**−**13** (with a spacing of 4 Aib monomers, i.e. n = 5). These values for the estimated control *induced* by each controller are included in Tables 1−4 as the second h.e. value in parentheses, and the Supporting Information contains a spreadsheet showing how both h.e. values were calculated for all compounds reported in this paper.

By this calculation, it appears that the degree of screw-sense control induced by the best controller, CbzαMv$_2$, is almost quantitative (Table 4, entry 11). This conclusion is supported by computational work,[59] which suggests that the lowest energy left-handed helical conformation of the closely related AcαMv$_2$Aib$_4$GlyNH$_2$ is more than 10 kJ mol^{-1} higher in energy than the lowest energy right-handed conformation.[73] The X-ray crystal structure of **13k**[59] shows, like those of **13g** and **13h**, an almost perfect right-handed 3_{10} helix in the solid state (see discussion below).

Structure of the N-Terminal Turn. We assume that the high degree of screw-sense preference displayed by **13k** results from the adoption of an N-terminal type III β-turn consistent with the 3_{10} helical structure, illustrated in Figure 5c.[21] In this

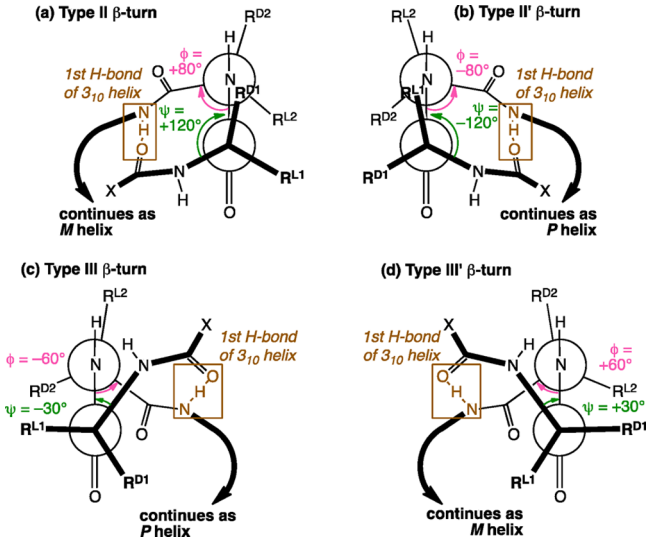

Figure 5. Types of N-terminal β-turns.

conformation, the isopropyl groups of both L-αMv residues in the first turn (ie R^{L1} = R^{L2} = *i*-Pr) adopt the less sterically congested position (perpendicular to the chain for R^{L1}; eclipsing only NH for R^{L2}) and enforce a right-handed helix. Other possible turn structures[76] are illustrated in Figure 5. For any quaternary amino acid at residue i+1, R^{L1} and R^{D1} are both alkyl groups, so type II and II′ turns (Figure 5a,b) are disfavored because of eclipsing interactions between either R^{L1} or R^{D1} and the C−N bond between residues i+1 and i+2. A type III′ β-turn (Figure 5d) is less unfavorable, however, and with a single N-terminal αMv (or other single quaternary residue, as in **9e**−**h**) Figure 5d (and the resulting *M* helix) probably represents the second most populated conformation.

Despite the greater steric difference between the two α substituents in a tertiary L-amino acid, the fact that R^{D1} = H means that the eclipsing interaction in a type II turn (Figure 5a) becomes unimportant and allows the resulting left-handed helical conformer to be populated.[21] The lack of complete control over screw sense observed with tertiary amino acids is unlikely to be due to population of type II′ β-turns (Figure 5b) because of eclipsing interactions experienced by R^{L1}, so it is more likely that a type III β-turn (Figure 5c, R^{D1} = H) makes some contribution to the conformational preference of oligomers carrying N-terminal tertiary amino acids. With a tertiary L-amino acid in the i+2 position (Table 4), the R^{L2} substituent will clearly prefer the uncongested position allowed by both the type II′ and type III turns (Figure 5b,c) so it is likely that the right-handed screw sense adopted by such compounds is due to adoption of one or both of these conformations.

As well as the opposite screw senses induced by tertiary and quaternary amino acids located at the N-terminus of the peptide, another difference in behavior is spotlighted in this paper: the right-handed screw-sense preference associated with the type III β-turn is decreased when a carbamate N-protecting group is replaced by an amide, while the left-handed screw sense preference associated with the type II β-turn is increased when a carbamate is replaced by an amide (Table 3). Among carbamate-protected compounds, the more bulky carbamate *O*-alkyl groups favor the right-handed screw sense associated with the type III β-turn and disfavor the left-handed screw sense associated with the type II β-turn. It is hard to disentangle steric and electronic effects, but in general, it seems that more basic or smaller protecting groups[77] (more powerful hydrogen bond acceptors) favor the formation of the left-handed helix, perhaps by favoring the type II β-turn at the expense of other turn types. The exception is, however, the trifluoroacetamide group of **11h** and **12h**, which, despite having lower carbonyl basicity than all of the other groups,[77] favors left-handed helicity to the greatest extent, perhaps by an alternative hydrogen-bonding interaction.

Although structures in the solid state can be misleading with reference to conformational preferences in solution,[21b] particularly when more than one conformer is populated, the X-ray crystal structures[78] of several compounds reported in this paper and two related structures **14** and **15** were revealing with regard to the accessible conformations in this N-terminal turn. Relevant structures are illustrated in Figure 6a−h.

The X-ray crystal structures of oligomers **9g**, **12j**, **13g**, **13h**, and **13k** containing N-terminal quaternary amino acids (Figure 6a−e) all display well-defined N-terminal type III β-turns, corresponding to the conformation shown in Figure 5c. All show *P* helicity, and even though **9g** is a racemic compound, it crystallizes as a conglomerate, with all molecules in this crystal containing Bin residues with R_a (or *M*) axial chirality. In other words, *M* helicity in the Bin residue appears to induce *P* helicity in the helix.[70]

Oligomers **11i**, **14**, and **15** containing N-terminal tertiary amino acids (Figure 6e−g) display less uniform structures in the solid state. Compound **11i**, which prefers *M* helicity in solution, display the expected N-terminal type II turn illustrated schematically in Figure 5a. Oligomer **14**, which is closely related to **10a**, also shows left-handed helicity, but has an N-terminal turn with dihedral angles lying somewhere between a Type II and a Type III′ structure (Figure 5a,d). Surprisingly, **15**, which is closely related to **11a**, shows a Type III turn at the N-terminus, leading to *P* helicity in the solid state, despite **11a**'s clear *M* helicity in solution. It is worth noting that the ca. 3:1 conformational preference in solution may easily be overturned by stabilization achieved as a result of crystal packing.[65]

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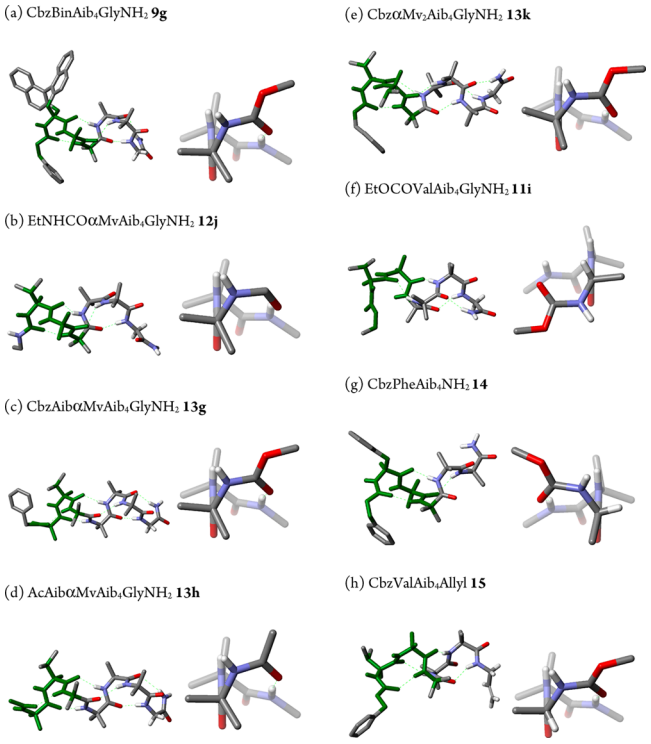

Figure 6. X-ray structures of **9g**, **12j**, **13g**,**h**,**k**, **14**, and **15**. For each compound, the image on the left illustrates the helical structure of the oligomer, with the N-terminal turn highlighted in green. The image on the right illustrates the conformation of the N-terminal turn initiating the helix for comparison with Figure 5, viewing along the C_α–CO bond of the first residue of the helix and showing only those atoms highlighted in green.

CONCLUSION

In conclusion, we find that oligomers of the achiral quaternary amino acid Aib may be induced to adopt a right-handed helix by one, or better two, N-terminal quaternary L-amino acids with a powerful distinction between the two α-substituents (i.e., L-α-methylvaline). N-Terminal tertiary L-amino acids induce left-handed screw sense, with the degree of screw-sense preference increasing with steric bulk. In contrast, in the position i+2, one residue in from the N-terminus, they induce a right-handed screw-sense preference. N-Protecting groups containing more basic carbonyl groups generally shift the screw-sense preference induced by L-amino acids (whether tertiary or quaternary) toward the left-handed helix, possibly by favoring the formation of Type II turns. Taking into account the known decay of helical preference in Aib oligomers, the highest level of screw-sense control observed, induced by Cbz(L-αMv)$_2$, appears to be essentially quantitative.

EXPERIMENTAL SECTION

Procedures for the synthesis of H-Aib$_n$AibCH$_2$OH (n = 3, 4), H-Aib$_4$-AibCH$_2$OTIPS, H-Aib$_4$-GlyNH$_2$, Cbz-Val-Aib$_4$-GlyNH$_2$, Cbz-αMv-Aib$_4$-GlyNH$_2$, and 2-azido-2-methylpropanoyl chloride have been described previously.[17,20,79] Cbz-(±)-Bin-OH, Cbz-αMp-OH, and Cbz-αMv-F were synthesized according to known methods.[70a,80,81] High-resolution mass spectra (HRMS) were recorded using a TOF method and are accurate to ±0.001 Da.

General Procedure 1: PyBOP Coupling of Cbz N-Protected Chiral Amino Acids and N-Terminal Deprotected Aib$_n$ Peptides. A round-bottom flask was charged with 1.0 equiv of PyBOP, 1.0 equiv of the Cbz N-protected amino acid, and 1.0 equiv of the Aib$_n$ peptide fragment in dry CH$_2$Cl$_2$ (10 mL/mmol) and cooled to 0 °C. To the above solution was added 2.0 equiv of i-Pr$_2$NEt via syringe. The mixture was allowed to warm to room temperature and was stirred overnight or until completion (TLC monitoring). Upon completion, the mixture was diluted with EtOAc (20 mL/mmol) and washed with KHSO$_4$ (5% solution, 2 × 5 mL/mmol), NaHCO$_3$ (satd solution, 2 × 5 mL/mmol), and brine (5 mL/mmol), dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using the appropriate mixture of eluents.

General Procedure 2: Cleavage of Cbz and Reprotection of the Resulting Free Amine as a *p*-Bromobenzoate. A round-bottom flask was charged with 1.0 equiv of the Cbz N-protected peptide, 10% Pd/C, and 1 drop of AcOH in EtOH (10 mL/mmol), and the mixture was stirred at room temperature under an atmosphere of H$_2$ (balloon). Upon completion (TLC monitoring), the mixture was filtered under vacuum through a pad of Celite, washing several times with EtOAc. The solvent was removed under reduced pressure, and the resulting deprotected peptide was redissolved in dry CH$_2$Cl$_2$ (6 mL/mmol) and cooled to 0 °C. To the above solution was added 2.0 equiv of i-Pr$_2$NEt dropwise via syringe, followed by 1.1 equiv of a predried (molecular sieves) solution of p-bromobenzoyl chloride in dry CH$_2$Cl$_2$ (4 mL/mmol). The mixture was allowed to warm to room temperature and stirred until completion (TLC monitoring), at which point the mixture was quenched with NaHCO$_3$ (satd solution, 1 mL/mmol). The mixture was diluted with CH$_2$Cl$_2$ (10 mL/mmol) and water (5 mL/mmol), and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL/mmol). The combined organic extracts were washed with NaHCO$_3$ (satd solution, 5 mL/mmol) and brine (5 mL/mmol), dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using the appropriate mixture of eluents.

Cbz-L-Phe-Aib$_3$-AibCH$_2$OH (**5a**). According to general procedure 1, Cbz-L-Phe-OH (224 mg, 0.75 mmol), H-Aib$_3$-AibCH$_2$OH (257 mg, 0.75 mmol), PyBOP (390 mg, 0.75 mmol), and i-Pr$_2$NEt (0.33 mL, 242 mg, 1.87 mmol) in CH$_2$Cl$_2$ (7.5 mL) were used. The crude was purified by by column chromatography (SiO$_2$:EtOAc) to yield Cbz-L-Phe-Aib$_3$-AibCH$_2$OH as a white solid (319 mg, 68%): R_f (SiO$_2$/EtOAc) = 0.22; mp = 198–200 °C; $[\alpha]^{20}_D$ = −15.6 (c = 1.1, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.35–7.21 (m, 12H), 7.06 (s, 1H), 5.09 (A of AB, J = 12.5 Hz, 1H), 5.05 (B of AB, J = 12.5 Hz, 1H), 4.56 (s, 1 H), 4.21 (t, J = 7.5 Hz, 1H), 3.67 (A of AB, J = 11.5 Hz, CH$_2$-OH, 1H), 3.50 (B of AB, J = 11.5 Hz, CH$_2$-OH, 1H), 3.02 (dd, J = 13.5, 8.0 Hz, 1H), 2.95 (dd, J = 13.5, 8.0 Hz, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD$_3$OD) δ 177.4, 176.6, 176.5, 174.3, 158.6, 139.2, 138.1, 130.6, 129.6, 129.5, 129.1, 128.6, 127.9, 69.5, 67.7, 58.3, 58.2, 57.9, 57.6, 56.4, 38.2, 27.1, 26.5, 26.2, 24.7, 24.2, 24.1, 24.0, 23.8 ppm; IR (film) 3319, 2986, 2933, 1664, 1533, 1455, 1385, 1364, 1295, 1259, 1167, 1055 cm^{-1}; MS (ES$^+$, MeOH) 649 ([M + Na]$^+$, 100), 626 ([M + H]$^+$, 75); HRMS (ES$^+$, MeOH) calcd for C$_{33}$H$_{47}$N$_5$O$_7$ + H 626.3548, found 626.3554.

Cbz-L-Val-Aib$_3$-AibCH$_2$OH (**5b**). According to general procedure 1, Cbz-L-Val-OH (260 mg, 1.02 mmol), H-Aib$_3$AibCH$_2$OH (500 mg, 1.02 mmol), PyBOP (540 mg, 1.02 mmol), and i-Pr$_2$NEt (0.36 mL, mg, 2.04 mmol) in CH$_2$Cl$_2$ (10.0 mL) were used. After purification by column chromatography (EtOAc), peptide Cbz-L-Val-Aib$_3$-Aib-CH$_2$OH was obtained as a white solid (570 mg, 96%): R_f (SiO$_2$/EtOAc) = 0.40; mp = 170–172 °C; $[\alpha]^{20}_D$ = −8.5 (c = 1.1, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.35–7.30 (m, 5H), 7.08 (s, 1H), 5.11 (A of AB, J = 13.0 Hz, 1H), 5.09 (B of AB, J = 13.0 Hz, 1H), 3.73 (d, J = 7.5 Hz, 1H), 3.65 (A of AB, J = 11.5 Hz, 1H), 3.52 (B of AB, J = 11.5 Hz, 1H), 2.02 (m, 1H), 1.43 (s, 3H), 1.41 (s, 6H), 1.40 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.32 (s, 6H), 1.01 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.4, 174.4, 173.4, 171.6, 157.1, 135.7, 128.7, 128.6, 128.1, 69.0, 67.6, 62.1, 57.1, 56.9, 56.8, 55.5, 29.7, 25.7, 25.2, 25.1, 24.8, 24.7, 24.1, 24.0, 19.2, 18.5 ppm; IR (film) 3398, 3319, 2974, 1701, 1658, 1530, 1232 cm^{-1}; MS (ES$^+$, MeOH) 600 ([M + Na]$^+$, 100); HRMS (ES$^+$, MeOH) calcd for C$_{29}$H$_{47}$N$_5$O$_7$ + Na 600.3368, found 600.3379.

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*Cbz-L-Pro-Aib$_3$-AibCH$_2$OH (**5c**).* According to general procedure 1, Cbz-L-Pro-OH (157 mg, 0.63 mmol), H-Aib$_3$-AibCH$_2$OH (216 mg, 0.63), PyBOP (328 mg, 0.63 mmol), and *i*-Pr$_2$NEt (0.27 mL, 204 mg, 1.58 mmol) in CH$_2$Cl$_2$ (6.5 mL) were used. After purification by column chromatography (EtOAc), peptide Cbz-L-Pro-Aib$_3$-AibCH$_2$OH was obtained as a white solid (243 mg, 67%): R_f (SiO$_2$/EtOAc) = 0.16; mp = 88−90 °C; $[\alpha]^{20}_D$ = −28.2 (*c* = 1.05, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.67 (brs, 1H), 7.36 (s, 2H), 7.35 (s, 2H), 7.24 (m, 1H), 7.12 (brs, 1H), 7.05 (brs, 1H), 5.16 (A of AB, *J* = 12.5 Hz, 1H), 5.09 (B of AB, *J* = 12.5 Hz, 1H), 4.63 (s, 1H), 4.20 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.66 (A of AB, *J* = 11.5 Hz, 1H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.51 (B of AB, *J* = 11.5 Hz, 1H), 2.21−2.33 (m, 1H), 2.00−2.09 (m, 1H), 1.88−1.95 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.393 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.31 (s, 6H) ppm; ^{13}C NMR (125 MHz, CD$_3$OD) δ 177.3, 176.8, 176.6, 175.0, 156.8, 138.0, 129.7, 129.2, 128.7, 69.5, 68.2, 58.2, 57.9, 57.6, 56.4, 48.2, 31.2, 26.8, 26.3, 26.1, 25.6, 25.0, 24.3, 24.2, 24.1, 23.8 ppm; IR (film) 3323, 2984, 2938, 1671, 1532, 1450, 1422, 1385, 1361, 1218, 1167, 1126 cm^{-1}; MS (ES$^+$, MeOH) 598 [M + Na]$^+$ (100), 576 ([M + H]$^+$, 80). HRMS (ES$^+$, MeOH) calcd for C$_{29}$H$_{45}$N$_5$O$_7$ + Na 598.3211, found 598.3193.

*Cbz-L-Leu-Aib$_3$-AibCH$_2$OH (**5d**).* According to general procedure 1, Cbz-L-Leu-OH (85 mg, 0.32 mmol), H-Aib$_3$-AibCH$_2$OH (110 mg, 0.32), PyBOP (166 mg, 0.32 mmol), and *i*-Pr$_2$NEt (0.11 mL, 83 mg, 0.64 mmol) in CH$_2$Cl$_2$ (3.2 mL) were used. After purification by column chromatography (EtOAc), peptide Cbz-L-Leu-Aib$_3$AibCH$_2$OH was obtained as a white solid (170 mg, 91%): R_f (SiO$_2$/EtOAc) = 0.24; mp = 138−140 °C; $[\alpha]^{20}_D$ = −17.4 (*c* = 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.73 (brs, 1H), 7.36−7.29 (m, 6H), 7.09 (brs, 1H), 5.10 (s, 2H), 4.00 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.64 (A of AB, *J* = 11.5 Hz, 1H), 3.54 (B of AB, *J* = 11.5 Hz, 1H), 1.78−1.67 (m, 2H), 1.60−1.48 (m, 2H), 1.43 (s, 3H), 1.40 (s, 6H), 1.38 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 0.97 (d, *J* = 17.0 Hz, 3H), 0.95 (d, *J* = 17.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CD$_3$OD) δ 177.5, 177.4, 176.6, 176.5, 158.8, 138.3, 129.6, 129.1, 128.6, 69.5, 67.7, 58.3, 57.8, 57.6, 56.5, 55.4, 41.2, 26.6, 26.0, 25.9, 25.7, 25.2, 24.7, 24.5, 24.1, 23.9, 23.3, 22.1 ppm; IR (film) 3318, 3323, 2959, 2483, 1660, 1531, 1470, 1454, 1417, 1380, 1362, 1260, 1049 cm^{-1}; MS (ES$^+$, MeOH) 614 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for C$_{30}$H$_{49}$O$_7$N$_5$ + Na 614.3524, found 614.3502.

*Cbz-L-Ser-Aib$_3$-AibCH$_2$OH (**5e**).* According to general procedure 1, Cbz-L-Ser-OH (189 mg, 0.79 mmol), H-Aib$_3$-AibCH$_2$OH (274 mg, 0.79), PyBOP (414 mg, 0.79 mmol), and *i*-Pr$_2$NEt (0.34 mL, 255 mg, 1.97 mmol) were used. After purification by column chromatography (CH$_2$Cl$_2$/EtOH, 98:2), peptide Cbz-L-Ser-Aib$_3$-AibCH$_2$OH was obtained as a white solid (125 mg, 28%): R_f (SiO$_2$/CH$_2$Cl$_2$/EtOH 98:2) = 0.17; mp = 104−106 °C; $[\alpha]^{20}_D$ = −12.0 (*c* = 0.9, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.91 (brs, 1H), 7.67 (brs, 1H), 7.38−7.29 (m, 7H), 7.07 (brs, 1H), 5.10 (s, 2H), 4.13 (t, *J* = 5.5 Hz, 1H), 3.83 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.76 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.60 (A of AB, *J* = 12.0 Hz, 1H), 3.58 (B of AB, *J* = 12.0 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 6H), 1.40 (s, 3H), 1.36 (s, 3H), 1.36 (s, 3H), 1.32 (s, 6H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.0, 175.1, 174.3, 171.5, 156.6, 136.1, 128.4, 128.3, 128.0, 69.0, 67.1, 62.4, 57.4, 57.1, 56.9, 56.7, 55.6, 25.5, 25.3, 25.2, 25.1, 24.9, 23.9 ppm; IR (film) 3320, 2986, 2940, 1659, 1531, 1457, 1385, 1364, 1266, 1229, 1167, 1059 cm^{-1}; MS (ES$^+$, MeOH) 588 [M + Na]$^+$ (100), 566 [M + H]$^+$ (85); HRMS (ES$^+$, MeOH) calcd for C$_{27}$H$_{43}$N$_5$O$_8$ + H 566.3184, found 566.3180.

*Cbz-L-Ser(OTBDPS)-Aib$_3$-AibCH$_2$OH (**5f**).* Cbz-L-Ser-Aib$_3$-AibCH$_2$OH (31 mg, 0.06 mmol), imidazole (5.0 mg, 0.07 mmol), and DMAP (one crystal) were dissolved in CH$_2$Cl$_2$ (1.0 mL). TBDPSCl (17 μL, 0.07 mmol) was then added and the mixture stirred for 2 days. A mixture of starting material and the two possible monoprotected alcohols was obtained. This mixture was purified by column chromatography (CH$_2$Cl$_2$/EtOH, 98:2) to yield Cbz-L-Ser(OTBDPS)-Aib$_3$-AibCH$_2$OH as a colorless oil (11 mg, 25%): R_f (SiO$_2$/CH$_2$Cl$_2$/EtOH 98:2) = 0.36; $[\alpha]^{20}_D$ = −16.4 (*c* = 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73−7.09 (m, 19H), 5.13 (A of AB, *J* = 12.5 Hz, 1H), 5.08 (B of AB, *J* = 12.5 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 3.95 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.89 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.65 (A of AB, *J* = 11.5 Hz, 1H), 3.52 (B of AB, *J* = 11.5 Hz, 1H), 1.403 (s, 3 H), 1.40 (s, 3H), 1.39 (s, 6H), 1.37 (s, 6H), 1.31 (s, 6H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD$_3$OD) δ 177.4, 176.7, 176.4, 173.0, 158.6, 139.0, 138.2, 136.8, 136.7, 136.6, 134.1, 134.0, 131.2, 131.0, 130.9, 130.5, 130.0, 129.6, 129.3, 129.2, 129.0, 128.9, 128.8, 128.6, 69.5, 67.9, 64.5, 58.4, 58.3, 57.92, 57.9, 56.4, 27.4, 26.8, 26.3, 26.2, 25.0, 24.6, 24.5, 24.1, 23.9 ppm; IR (film) 3310, 2976, 2940, 1665, 1530, 1460, 1384, 1365, 1270, 1230, 1170, 1069 cm^{-1}; MS (ES$^+$, MeOH) 804 [M + H]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for C$_{43}$H$_{61}$N$_5$O$_8$Si + H 804.4368, found 804.4372.

*p-BrBz-L-Phe-Aib$_3$-AibCH$_2$OH (**5g**).* From a solution of the peptide Cbz-L-Phe-Aib$_3$-AibCH$_2$OH (**5a**) (88 mg, 0.14 mmol) and Pd/C (8.8 mg, 10%) in EtOH (1.4 mL) under H$_2$ atmosphere following general procedure 2 (2 h) was obtained the deprotected peptide H-L-Phe-Aib$_3$-AibCH$_2$OH (69 mg, 100%). From a solution of H-L-Phe-Aib$_3$-AibCH$_2$OH (54 mg, 0.11 mmol), *i*-Pr$_2$NEt (38 μL, 28 mg, 0.22 mmol), and *p*-BrBzCl (26 mg, 0.12 mmol) in dry CH$_2$Cl$_2$ (1.1 mL) following general procedure 1 (3 h) and after purification by column chromatography (EtOAc/petroleum ether, 80:20), peptide *p*-BrBz-L-Phe-Aib$_3$-AibCH$_2$OH was obtained as a white solid (46 mg, 64%): R_f (SiO$_2$/EtOAc/petroleum ether 90:10) = 0.16; mp = 124−128 °C; $[\alpha]^{20}_D$ = −24.3 (*c* = 1.2, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (brs, 1H), 7.32 (m, 5H), 7.27−7.25 (m, 2H), 6.99 (brs, 1H), 4.54 (t, *J* = 8.0 Hz, 1H), 3.69 (A of AB, 1 H, *J* = 11.5 Hz, 1H), 3.45 (B of AB, *J* = 11.5 Hz, 1H), 3.17 (d, *J* = 14.0 Hz, 1H), 3.12 (d, *J* = 14.0 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.30 (s, 6H), 1.29 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD$_3$OD) δ 177.4, 176.6, 174.2, 169.4, 138.1, 133.0, 132.9, 130.6, 130.5, 129.6, 128.0, 127.6, 69.5, 58.2, 57.9, 57.7, 56.5, 37.9, 27.5, 27.0, 26.6, 24.2, 23.82, 23.8, 23.6 ppm; IR (film) 3331, 2986, 2927, 1653, 1534, 1420, 1381, 1363, 1228, 1070, 1011 cm^{-1}; MS (ES$^+$ MeOH) 698 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for C$_{32}$H$_{44}$N$_5$O$_6$^{79}Br + Na 696.2367, found 696.2357.

*p-BrBz-L-Val-Aib$_3$-AibCH$_2$OH (**5h**).* From a solution of the peptide Cbz-L-Val-Aib$_3$-AibCH$_2$OH (**5b**) (108 mg, 0.19 mmol) and Pd/C (10.8 mg, 10%) in EtOH (1.8 mL) under H$_2$ atmosphere following general procedure 2 (3 h) was obtained the deprotected peptide H-L-Val-Aib$_3$-AibCH$_2$OH (84 mg, 100%). From a solution of H-L-Val-Aib$_3$-AibCH$_2$OH (84 mg, 0.19 mmol), *i*-Pr$_2$NEt (66 μL, 49 mg, 0.38 mmol), and *p*-BrBzCl (46 mg, 0.21 mmol) in dry CH$_2$Cl$_2$ (1.9 mL) following general procedure 2 (3 h) and after purification by column chromatography (EtOAc/petroleum ether, 80:20), peptide *p*-BrBz-L-Val-Aib$_3$-AibCH$_2$OH was obtained as a white solid (141 mg, 90%): R_f (SiO$_2$/EtOAc/petroleum ether 90:10) = 0.21; mp = 158−160 °C; $[\alpha]^{20}_D$ = −22.9 (*c* = 1.1, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.80 (d, *J* = 8.0 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 6.99 (s, 1 H), 4.01 (d, *J* = 8.5 Hz, 1 H), 3.69 (d, *J* = 11.5 Hz, 1 H), 3.45 (d, *J* = 11.5 Hz, 1 H), 2.17 (m, 1H), 1.47 (s, 3 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 9 H), 1.23 (s, 3 H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3 H) ppm; ^{13}C NMR (100 MHz, CD$_3$OD) δ 177.4, 176.8, 176.7, 174.5, 169.7, 134.0, 132.9, 130.6, 127.6, 69.4, 62.6, 58.2, 57.9, 57.8, 56.4, 30.7, 27.5, 27.0, 26.6, 24.21, 24.2, 23.8, 23.6, 20.3, 19.7 ppm; IR (film) 3333, 2963, 1652, 1538, 1471, 1385, 1362, 1260, 1218, 1055, 1012 cm^{-1}; MS (ES$^+$) 649 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for C$_{28}$H$_{44}$N$_5$O$_6$^{79}Br + Na$^+$ 648.2367, found 648.2352.

*p-BrBz-L-Leu-Aib$_3$-AibCH$_2$OH (**5i**).* From a solution of the peptide Cbz-L-Leu-Aib$_3$-AibCH$_2$OH (**5d**) (85 mg, 0.14 mmol) and Pd/C (8.5 mg, 10%) in EtOH (1.4 mL) under H$_2$ atmosphere following general procedure 2 (5 h) was obtained the deprotected peptide H-L-Leu-Aib$_3$-AibCH$_2$OH (67 mg, 100%). From a solution of H-L-Leu-Aib$_3$-AibCH$_2$OH (67 mg, 0.14 mmol), *i*-Pr$_2$NEt (49 μL, 36 mg, 0.28 mmol), and *p*-BrBzCl (34 mg, 0.15 mmol) in dry CH$_2$Cl$_2$ (1.4 mL) following general procedure 2 (3 h) and after purification by column chromatography (EtOAc/petroleum ether, 80:20) was obtained peptide *p*-BrBz-L-Leu-Aib$_3$-AibCH$_2$OH as a white solid (89 mg, 100%): R_f (SiO$_2$/EtOAc/petroleum ether 80:20) = 0.18; mp = 220−222 °C; $[\alpha]^{20}_D$ = −20.0 (*c* = 1.1, CHCl$_3$); ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.00 (s, 1H), 4.37 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 3.46 (d, *J* = 11.5 Hz, 1H), 1.80 (m, 1H), 1.60 (m, 1H), 1.44 (s, 6H), 1.43 (s, 3H), 1.36 (s, 3H), 1.295 (s, 6H), 1.29 (s, 3H), 1.22 (s, 3H), 1.04

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(d, J = 6.0 Hz, 1H), 1.00 (d, J = 6.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 177.4, 176.7, 175.5, 169.7, 134.0, 132.9, 130.6, 127.6, 69.4, 57.9, 57.7, 56.5, 54.9, 40.7, 27.3, 26.9, 26.4, 26.2, 24.3, 24.1, 24.0, 23.8, 23.4, 22.1 ppm; IR (film) 3411, 2964, 1652, 1537, 1455, 1362, 1386, 1260, 1070 cm^{-1}; MS (ES$^+$) 664 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{29}H_{46}N_5O_6{}^{79}Br$ + Na 662.2524, found 662.2512.

*Cbz-L-Val-Aib$_4$-AibCH$_2$OH (**6b**). (a). Cbz-L-Val-Aib$_4$-AibCH$_2$OTIPS.* From a solution of Cbz-L-Val-OH (35 mg, 0.14 mmol), H-Aib$_4$-AibCH$_2$OTIPS (80 mg, 0.14 mmol), PyBOP (73 mg, 0.14 mmol), and i-Pr$_2$NEt (48 μL, 36 mg, 0.28 mmol), following general procedure 1 and after purification by column chromatography (EtOAc/petroleum ether, 70:30) was obtained peptide Cbz-L-Val-Aib$_4$-AibCH$_2$OTIPS as a white solid (98 mg, 86%): R_f (SiO_2/EtOAc/petroleum ether 70:30) = 0.48; mp = 126−128 °C; $[\alpha]^{20}_D$ = −16.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (brs, 1H) 7.34 (m, 6H), 6.96 (s, 1H), 6.70 (s, 1H), 6.54 (brs, 1H), 5.44 (brs, 1H), 5.12 (A of AB, d, J = 12.5 Hz, 1H), 5.08 (B of AB, d, J = 12.5 Hz, 1H), 3.79 (d, J = 11.0 Hz, 1H), 3.76 (d, J = 9.5 Hz, 1H), 3.70 (t, J = 5.6 Hz, 1H), 2.10 (m, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.44 (s, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (s, 6H), 1.33 (s, 3H), 1.07−1.03 (m, 21 H), 1.01 (d, J = 3.0 Hz, 3H), 0.99 (d, J = 3.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.9, 173.6, 174.2, 171.7, 157.1, 135.8, 128.7, 128.5, 128.1, 69.0, 67.4, 62.1, 57.0, 56.8, 56.7, 54.9, 29.7, 25.8, 24.8, 23.7, 23.6, 25.4, 25.1, 19.2, 18.6, 18.0, 11.9 ppm; IR (film) 3313, 2941, 2865, 1704, 1652, 1664, 1538, 1464, 1384, 1232, 1104 cm^{-1}; MS (ES$^+$) 842 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{42}H_{74}N_6O_8Si$ + H 819.5410, found 819.5424.

(b). Cbz-L-Val-Aib$_4$-AibCH$_2$OH. Cbz-L-Val-Aib$_4$-AibCH$_2$OTIPS (60 mg, 0.073 mmol) was dissolved in HCl (0.6 mL of 1 M solution) and EtOH (1 mL), stirred for 14 h (TLC monitoring), quenched at 0 °C with saturated solution of $NaHCO_3$, and diluted with water (4 mL) and EtOAc (4 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with $NaHCO_3$ (2 × 4 mL) and brine (4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (EtOAc/petroleum ether, 70:30) gave Cbz-L-Val-Aib$_4$-AibCH$_2$OH as a white solid (48 mg, 100%): R_f = 0.21 (SiO_2/EtOAc/petroleum ether 90:10); mp = 170−172 °C; $[\alpha]^{20}_D$ = −3.5 (c = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.81 (s, 1H), 7.80 (s, 1H), 7.56 (s, 1H), 7.37−7.30 (m, 5H), 7.08 (s, 1H), 5.11 (s, 2H), 3.74 (d, J = 7.5 Hz, 1H), 3.65 (A of AB, d, J = 11.5 Hz, 1H), 3.54 (B of AB, d, J = 11.5 Hz, 1H), 2.01 (m, 1H), 1.454 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.42 (s, 6H), 1.40 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.33 (s, 6H), 1.01 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 174.74, 174.70, 174.0, 171.9, 157.1, 136.0, 128.6, 128.5, 128.1, 69.3, 67.3, 57.0, 56.8, 56.7, 55.5, 29.7, 25.7, 25.4, 25.1, 25.0, 24.7, 24.1, 24.0, 19.1, 18.6 ppm; IR (film) 3310, 2974, 2924, 1658, 1530, 1452, 1384, 1356, 1227, 1169, 1049 cm^{-1}; MS (ES$^+$) 663 [M + H]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{33}H_{54}N_6O_8$ + H 663.4076, found 663.4073.

*p-BrBz-L-Phe-Aib$_4$-AibCH$_2$OH (**6c**).* From a solution of the peptide Cbz-L-Phe-Aib$_4$-AibCH$_2$OH (**5a**) (46 mg, 0.065 mmol) and Pd/C (4.6 mg, 10%) in EtOH (0.7 mL) under H_2 atmosphere following general procedure 2 (3 h) was obtained the deprotected peptide H-L-Phe-Aib$_4$-AibCH$_2$OH (36 mg, 95%). From a solution of H-L-Phe-Aib$_4$-AibCH$_2$OH (36 mg, 0.062 mmol), i-Pr$_2$NEt (22 μL, 16 mg, 0.12 mmol), and p-BrBzCl (415 mg, 0.07 mmol) in dry CH_2Cl_2 (0.7 mL) following general procedure 1 (4 h) and after purification by column chromatography (EtOAc/petroleum ether, 80:20) was obtained peptide p-BrBz-L-Phe-Aib$_4$-AibCH$_2$OH as a white solid (35 mg, 74%): R_f (SiO_2/EtOAc/petroleum ether 90:10) = 0.19; mp = 142−144 °C; $[\alpha]^{20}_D$ = −13.5 (c = 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.75 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.33 (m, 5H), 7.262 (brs, 1H), 7.26 (brs, 1H), 7.06 (brs, 1H), 4.54 (t, J = 8.0 Hz, 1H), 3.68 (A of AB, d, J = 11.5 Hz, 1H), 3.47 (B of AB, d, J = 11.5 Hz, 1H), 3.17 (d, J = 14.0 Hz, 1H), 3.13 (d, J = 14.0 Hz, 1H), 1.43 (s, 6H), 1.42 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.314 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.262 (s, 3H), 1.256 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 176.9, 176.7, 177.4, 177.1, 174.2, 169.5, 138.1, 133.9, 132.9, 130.6, 130.5, 129.6, 128.1, 127.7, 69.5, 58.3, 57.9, 57.8, 57.7, 57.6, 56.5, 27.4, 27.0, 26.8, 26.6, 23.83, 23.8, 23.6, 24.4, 24.2, 23.6 ppm; IR (film) 3312, 2976, 2926, 1660, 1520, 1442, 1385, 1355, 1049 cm^{-1}; MS (ES$^+$) [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{36}H_{51}N_6O_7{}^{79}Br$ + Na 781.2895, found 781.2888.

*p-BrBz-L-Val-Aib$_4$-AibCH$_2$OH (**6d**).* From a solution of the peptide Cbz-L-Val-Aib$_4$-AibCH$_2$OH (**5b**) (86 mg, 0.13 mmol) and Pd/C (10.3 mg, 10%) in EtOH (1.3 mL) under H_2 atmosphere following general procedure 2 (3 h) was obtained the deprotected peptide L-Val-Aib$_4$-AibCH$_2$OH (69 mg, 100%). From a solution of H-L-Val-Aib$_4$-AibCH$_2$OH (69 mg, 0.13 mmol), i-Pr$_2$NEt (45 μL, 34 mg, 0.26 mmol), and p-BrBzCl (28 mg, 0.13 mmol) in dry CH_2Cl_2 (1.3 mL) following general procedure 1 (5 h) and after purification by column chromatography (EtOAc/petroleum ether, 80:20) was obtained peptide p-BrBz-L-Val-Aib$_4$-AibCH$_2$OH as a white solid (57 mg, 62%): R_f (SiO_2/EtOAc/petroleum ether 80:20) = 0.19; mp = 150−152 °C; $[\alpha]^{20}_D$ = −23.3 (c = 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (s, 1H), 7.80 (s, 1 H), 7.70 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.05 (brs, 1H), 4.02 (d, J = 9.0 Hz, 1H), 3.68 (A of AB, d, J = 11.5 Hz, 1H), 3.48 (B of AB, d, J = 11.5 Hz, 1H), 2.17 (m, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.44 (s, 6H), 1.43 (s, 3H), 1.32 (s, 3H), 1.31 (s, 6H), 1.30 (s, 3H), 1.25 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 177.4, 177.2, 177.0, 176.8, 174.5, 169.8, 134.0, 132.9, 130.6, 127.6, 69.5, 62.6, 58.4, 57.9, 57.8, 56.5, 30.7, 27.4, 27.0, 26.9, 26.8, 26.6, 24.4, 24.2, 23.93, 23.9, 23.8, 23.6, 20.3, 19.7 ppm; IR (film) 3313, 2979, 2930, 1654, 1591, 1535, 1470, 1384, 1363, 1229, 1171, 1060, 1012 cm^{-1}; MS (ES$^+$, MeOH) 733 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{32}H_{51}N_6O_7{}^{79}Br$ + Na 733.2895, found 733.2902.

*Cbz-t-Leu-Aib$_4$-GlyNH$_2$ (**9c**).* According to t general procedure 1, 40 mg (0.096 mmol) of H-Aib$_4$-GlyNH$_2$, 28 mg of Cbz-t-Leu-OH (0.11 mmol), and 55 mg (0.11 mmol) of PyBOP in 2.5 mL of dichloromethane were used. Purification by column chromatography (EtOAc/EtOH, 99:1) gave Cbz-t-Leu-Aib$_4$-GlyNH$_2$ as a colorless oil that crystallized on standing (27 mg, 0.04 mmol, 42%): R_f (SiO_2/CH_2Cl_2/EtOH) 95:5 = 0.15/ $[\alpha]_D$ = −16.0 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.38−7.28 (m, 5H), 7.53 (brs, 1H), 7.90 (brs, 1H), 8.05 (brs, 1H), 5.12 (s, 2H), 3.92 (A of AB, d, J = 17.0 Hz, 1H), 3.80 (s, 1H), 3.74 (B of AB, d, J = 17.0 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H), 1.42 (s, 6H), 1.41 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.2, 178.0, 176.7, 175.4, 173.8, 159.0, 138.2, 129.6, 129.2, 128.8, 67.8, 65.4, 58.3, 58.2, 57.9, 57.8, 43.8, 34.3, 27.2, 26.4, 24.9, 24.5, 24.4, 24.3, 26.1, 26.0 ppm; IR (film) 3302, 2982, 1659, 1531, 1384, 1363, 1228 cm^{-1}; MS (ES$^+$, MeOH) 684 ([M + Na]$^+$, 100), 662 ([M + H]$^+$, 8); HRMS (ES$^+$, MeOH) calcd for $C_{32}H_{51}N_7O_8$ + H 662.3872, found 662.3879.

*Cbz-(±)-Bin-Aib$_4$-GlyNH$_2$ (**9g**).* Cbz-(±)-Bin-OH (30 mg, 0.06 mmol) was dissolved in DCM (0.7 mL) and cooled to 0 °C. Cyanuric fluoride (53 μL, 0.62 mmol) and pyridine (10 μL, 0.12 mmol) were added, and the mixture was stirred at 0 °C for 1 h. The reaction was allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with ice-cold water (3 × 2.5 mL), dried ($MgSO_4$), filtered, and concentrated to give Cbz-(±)-Bin-F, which was used immediately without further purification.

Crude Cbz-(±)-Bin-F was dissolved in MeCN (3 mL), and H-Aib$_4$-GlyNH$_2$ (13 mg, 0.03 mmol) was added. DIPEA (6 μL, 0.03 mmol) was added dropwise and the reaction stirred at room temperature for 24 h. The mixture was diluted with EtOAc (10 mL), washed with 5% $KHSO_4$ (2 × 1 mL), satd $NaHCO_3$ (2 × 1 mL), and brine (1 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/MeOH 99:1−95:5) gave Cbz-(±)-Bin-Aib$_4$-GlyNH$_2$ as a white solid (23 mg, 0.03 mmol, 84%): R_f (SiO_2/CH_2Cl_2/MeOH) 95:5 = 0.29; ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (s, 1H), 8.08 (t, X of ABX, J = 6.0 Hz, 1H), 7.98−7.85 (m, 6H), 7.80 (s, 1H), 7.70 (s, 1H), 7.49−7.19 (m, 12H), 5.27 (B of AB, d, J = 12.5 Hz, 1H), 5.20 (A of AB, d, J = 13.0 Hz, 1H), 3.95 (dd, B of ABX, J = 17.5 7.0 Hz, 1H), 3.64 (dd, A of ABX, J = 17.5, 5.5 Hz, 1H), 3.22 (B of AB, d, J= 14.0 Hz, 1H), 3.08−2.97 (m, B and A of AB), 2.62 (d, B of AB, J = 13.0 Hz), 1.55 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H),

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1.21 (s, 3H), 1.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 178.2, 178.2, 178.1, 177.1, 175.5, 174.9, 158.8, 138.9−126.4, 79.6, 71.6, 68.0, 58.3, 58.1 (overlapping signals), 43.8, 42.7, 27.0, 26.9, 26.5, 26.4, 24.5, 24.0, 23.9, 23.8 ppm; MS (ES^+, MeOH) 885 ($[M + H]^+$, 10), 902 ($[M + NH_4]^+$, 100), 907 ($[M + Na]^+$, 50); HRMS (ES^+, MeOH) calcd for $C_{50}H_{57}N_7O_8$ + H 884.4342, found 884.4317.

*Cbz-L-αMp-Aib$_4$-GlyNH$_2$ (**9h**).* Cbz-L-αMp-OH (76 mg, 0.24 mmol) was dissolved in DCM (3 mL) and cooled to 0 °C. TFFH (96 mg, 0.36 mmol) and pyridine (20 μL, 0.24 mmol) were added, the cooling bath was removed, and the reaction was stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with ice-cold water (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated to give Cbz-L-αMp-F, which was used immediately without further purification.

Crude Cbz-L-αMp-F was dissolved in CH_2Cl_2 (2 mL) and H-Aib$_4$-GlyNH$_2$ (50 mg, 0.12 mmol) added. DIPEA (42 μL, 0.24 mmol) was added dropwise and the reaction stirred at room temperature for 5 d. The solvents were removed, and the residue was redissolved in EtOAc (15 mL), washed with 5% $KHSO_4$ (2 × 10 mL), satd $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2−94:6) gave Cbz-L-αMp-Aib$_4$-GlyNH$_2$ as a white solid (46 mg, 0.065 mmol, 54%): R_f (SiO_2/CH_2Cl_2/MeOH) 95:5 = 0.12; mp = 140−142 °C; $[\alpha]_D$ = −81.6 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.06 (brs, 1H), 7.93 (brs, 1H), 7.86 (brs, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.39 (t, J = 7.0 Hz, 2H), 7.39 (t, J = 7.0 Hz, 1H), 7.25−7.20 (m, 3H), 7.06−7.05 (m, 2H), 5.21 (A of AB, d, J = 12.5 Hz, 1H), 5.18 (B of AB, d, J = 12.5 Hz, 1H), 3.95 (A of AB, d, J = 17.5 Hz, 1H), 3.72 (B of AB, d, J = 17.5 Hz, 1H), 3.31 (m, 1H, overlaid with solvent signal), 3.01 (d, J = 13.5 Hz, 1H), 1.513 (s, 3H), 1.505 (s, 3H), 1.49 (s, 3H), 1.433 (s, 3H), 1.426 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.2, 178.1, 178.0, 177.0, 176.8, 175.4, 158.0, 138.7, 137.7, 132.0, 129.6, 129.2, 129.1, 129.0, 127.0, 67.8, 60.5, 58.2, 58.0, 57.8, 57.7, 43.7, 41.2, 26.53, 26.50, 26.43, 26.35, 24.7, 24.2, 24.1, 23.9, 23.4 ppm; IR (film) 3298, 2985, 1652, 1526, 1454, 1383, 1362, 1266, 1226 cm^{-1}; MS (ES^+, MeOH) 710 ($[M + H]^+$, 100), 732 ($[M + Na]^+$, 60); HRMS (ES^+, MeOH) calcd for $C_{36}H_{51}N_7O_8$ + Na 732.3697, found 732.3666.

*Boc-L-Phe-Aib$_4$-GlyNH$_2$ (**10i**).* According to general procedure 1, Boc-L-Phe-OH (96 mg, 0.36 mmol), H-Aib$_4$-GlyNH$_2$ (50 mg, 0.12 mmol), PyBOP (187 mg, 0.36 mmol), and i-Pr$_2$NEt (0.157 mL, 116 mg, 0.90 mmol) in CH_2Cl_2 (5 mL) were used. Purification by column chromatography (SiO_2/CH_2Cl_2/MeOH; 9:1) gave Boc-L-Phe-Aib$_4$-GlyNH$_2$ as a white solid (60 mg, 76%): R_f (SiO_2/CH_2Cl_2/MeOH) 9:1 = 0.35; mp = 236−237 °C; $[\alpha]^{20}_D$ = −10.8 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (t, J = 6.0 Hz, 1H), 7.98 (s, 1H), 7.95 (s, 2H), 7.82 (s, 1H), 7.35−7.19 (m, 5H), 4.17 (t, J = 7.5 Hz, 1H), 3.90 (A of AB, d, J = 17.5 Hz, 1H), 3.75 (B of AB, d, J = 17.5 Hz, 1H), 3.04 (dd, J = 13.5, 8.5 Hz, 1H), 2.92 (dd, J = 13.5, 8.5 Hz, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H), 1.45 (s, 9H), 1.434 (s, 3H), 1.426 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.1, 177.8, 176.6, 175.4, 174.4, 158.1, 138.3, 130.5, 129.5, 127.9, 80.9, 58.2, 58.0, 57.8, 57.5, 43.7, 38.4, 28.8, 26.2, 26.2, 26.1, 26.03, 26.01, 26.0, 25.8, 25.1, 24.6, 24.4 ppm; IR (film) 3294, 2984, 1649, 1529, 1418, 1363, 1226, 1167 cm^{-1}; MS (ES^+, MeOH) 684 ($[M + Na]^+$, 100); HRMS (ES^+, MeOH) calcd for $C_{32}H_{51}N_7O_8$ + H 662.3872, found 662.3865.

*m-NO$_2$Bz-L-Phe-Aib$_4$-GlyNH$_2$ (**10j**).* To an ice-cooled mixture of m-nitrobenzoic acid (148 mg, 0.88 mmol) and HOAt (120 mg, 0.88 mmol) in CH_2Cl_2 (2 mL) was added EDC (155 μL, 136 mg, 0.88 mmol). After 10 min, this solution was added to a solution of H-L-Phe-Aib$_4$-GlyNH$_2$ (**10b**) (249 mg, 0.44 mmol) and i-Pr$_2$NEt (38 μL, 28 mg, 0.22 mmol) in CH_2Cl_2 (3 mL). The mixture was allowed to warm to room temperature and stirred for 24 h, after which the solvent was evaporated. The residue was taken up in EtOAc (20 mL) and washed with $KHSO_4$ (5% solution, 3 × 5 mL), $NaHCO_3$ (sat. solution, 3 × 5 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 90:10) to give pure m-NO_2Bz-L-Phe-Aib$_4$-GlyNH$_2$ as a white solid (287 mg, 92%): R_f (SiO_2/CH_2Cl_2/MeOH) = 0.55; mp = 265−267 °C; $[\alpha]^{20}_D$ = −13.2 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.72 (t, J = 2.0 Hz, 1H), 8.43 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 8.23 (ddd, J = 8.0, 1.5, 1.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.39−7.22 (m, 5H), 4.61 (t, J = 8.0 Hz, 1H), 3.96 (A of AB, d, J = 17.5 Hz, 1H), 3.66 (B of AB, d, J = 17.5 Hz, 1H), 3.24−3.15 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.37 (s, 6H), 1.31 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.0, 177.81, 177.79, 176.7, 175.3, 174.0, 168.1, 149.7, 138, 136.6, 134.6, 131.2, 130.6, 129.6, 128.0, 127.5, 123.6, 58.1, 58.0, 57.9, 57.7, 57.6, 43.7, 37.9, 26.7, 26.6, 26.5, 24.4, 23.9, 23.8, 23.6 ppm; IR (film) 3328, 2987, 1643, 1536, 1412, 1348, 1227, 1077 cm^{-1}; MS (ES^+, MeOH) 711 ($[M + H]^+$, 25), 734 ($[M + H]^+$, 100).

*H-L-Val-Aib$_4$-GlyNH$_2$ (**11b**).* A round-bottom flask was charged with of Cbz-L-Val-Aib$_4$-GlyNH$_2$ (**9b**) (30 mg, 0.046 mmol), 10% Pd/C (6 mg, 20%), and MeOH (3 mL), and the mixture was stirred at room temperature under an atmosphere of H_2 (balloon) until completion (TLC monitoring). Upon completion the mixture was filtered under vacuum through a pad of Celite, washing several times with MeOH. The solvent was removed under reduced pressure, and H-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (23 mg, 0.046 mmol, 99%): mp 234−236 °C; $[\alpha]_D^{20}$ = −3.6 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.88 (d, A of AB, J = 17.5 Hz, 2H), 3.78 (d, B of AB, J = 17.5 Hz, 2H), 3.38 (d, J = 5.5 Hz, 1H), 2.11 (m, 1H), 1.56−1.38 (m, 24H), 1.04 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.2, 178.1, 177.9, 176.5, 175.6, 174.3, 60.8, 58.3, 58.2, 58.0, 57.8, 43.9, 32.9, 26.1−25.7 (overlapping signals), 25.3, 25.0, 24.9, 24.8, 19.8, 17.8 ppm; IR (film) 3304, 2981, 1644, 1526, 1416, 1362, 1219, 599 cm^{-1}; MS (ES^+, MeOH) 514 $[M + H]^+$, 536 $[M + Na]^+$ 100); HRMS (ES^+, MeOH) calcd for $C_{23}H_{43}N_7O_6$ + H 514.3348, found 514.3357.

*Tfa-L-Val-Aib$_4$-GlyNH$_2$ (**11h**).* EDC (11 μL, 0.12 mmol) was added to a suspension of TFA (9.3 μL, 0.12 mmol) and HOAt (16.3 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), and the mixture was cooled to 0 °C. A solution of H-Val-Aib$_4$-GlyNH$_2$ (**11b**) (31 mg, 0.06 mmol) in 1 mL of anhydrous DMF was added to the previous solution, and the mixture was allowed to warm to room temperature and was stirred for 24 h. The solvent was evaporated and the residue purified by column chromatography (CH_2Cl_2/MeOH, 90:10) to give Tfa-L-Val-Aib$_4$-GlyNH$_2$ as a white solid (17 mg, 0.08 mmol, 65%): R_f (SiO_2/$CHCl_3$/MeOH 90:10) = 0.40; mp 267−269 °C; $[\alpha]_D^{20}$ = −35.6 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 3.99 (A of AB, d, J = 17.5 Hz, 1H), 3.94 (B of AB, d, J = 9.0 Hz, 1H), 3.66 (d, J = 17.5 Hz, 1H), 2.13 (m, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H), 1.44 (s, 6H + 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (126 MHz, MeOD) δ 178.0, 177.9, 177.7, 176.5, 175.4, 173.1, 159.6 (t, J = 37.8 Hz), 117.4 (q, J = 287 Hz), 62.2, 58.2, 58.0, 57.9, 57.8, 43.7, 30.6, 26.9, 26.8, 26.5 (overlapping signals), 24.3, 23.7, 23.6, 23.4, 19.9, 19.4 ppm; IR (film) 3300, 2984, 2933, 2361, 1651, 1530, 1382, 1209, 1166 cm^{-1}; MS (ES^+, MeOH) 610 ($[M + H]^+$, 35); HRMS (ES^+, MeOH) calcd for $C_{25}H_{42}N_7O_7F_3$ + Na 632.2996, found 632.3003.

*EtOCO-L-Val-Aib$_4$-GlyNH$_2$ (**11i**).* Ethyl chloroformate (11.4 μL, 0.12 mmol) was added dropwise to a suspension of H-Val-Aib$_4$-GlyNH$_2$ (**11b**) (20 mg, 0.039 mmol) and NEt_3 (26 μL, 0.2 mmol) in CH_2Cl_2 (3 mL) maintained at −20 °C. The homogeneous mixture was allowed to warm to room temperature and allowed to stir for 24 h, and then the solvent was removed in vacuo. The residue was diluted with EtOAc (10 mL) and washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (sat. solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography ($CHCl_3$/MeOH, 99:1), and EtOCO-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (20 mg, 0.034 mmol, 87%): R_f (SiO_2/$CHCl_3$/MeOH 95:5) = 0.40; mp 241−243 °C; $[\alpha]_D^{20}$ = −26.0 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 4.17−4.01 (m, 2H), 3.92 (A of AB, d, J = 17.5 Hz, 1H), 3.73 (B of AB, d, J = 7.5 Hz, 1H), 3.73 (d, J = 5.0 Hz, 1H), 2.06−1.92 (m, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H), 1.45 (s, 6H), 1.435 (s, 3H), 1.43 (s, 6H), 1.40 (s, 3H), 1.25 (t, J = 7.1 Hz, 2H), 1.01 (t, J = 5.5 Hz, 3H), 1.00 (t, J = 5.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.2, 178.1, 178.0, 176.9, 175.5, 175.0, 159.5, 62.7, 62.2, 58.3, 58.1, 57.9, 57.8, 43.8, 31.4, 26.6−26.2 (overlapping

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signals), 24.9, 24.5, 24.4, 24.3, 24.2, 19.8, 19.4, 15.2 ppm; IR (film) 3307, 2984, 2415, 1705, 1647, 1468, 1417, 1227, 1033 cm^{-1}; MS (ES^+, MeOH) 608 $[M + Na]^+$ (100); HRMS (ES^+, MeOH) calcd for $C_{26}H_{47}N_7O_8$ + Na 608.3378, found 608.3388.

*EtNHCO-L-Val-Aib$_4$-GlyNH$_2$ (**11j**).* Ethyl isocyanate (61 μL, 0.39 mmol) was added dropwise to a suspension of H-Val-Aib$_4$-GlyNH$_2$ (**11b**) (40 mg, 0.078 mmol) and *i*-Pr$_2$NEt (95 μL, 0.55 mmol) in THF (3 mL) maintained at 0 °C. The mixture was allowed to warm to room temperature, and 300 μL of anhydrous DMF was added to help solubilization as well as few crystals of DMAP. The solution was allowed to stir for 24 h, and then the solvent was removed in vacuo. Et_2O was added (5 mL) to remove DMF by decanting the insoluble material. The process was repeated three times, and then the solids were filtered and washed with more Et_2O. EtNHCO-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (44 mg, 0.076 mmol, 97%): R_f (SiO_2/$CHCl_3$/MeOH 90:10) = 0.2; mp 221−223 °C; $[\alpha]_D^{20}$ = −25.6 (*c* = 1.0, MeOH/CH_2Cl_2 1:1); ^{1}H NMR (400 MHz, MeOD) δ 3.93 (A of AB, d, *J* = 17.5 Hz, 1H), 3.78 (d, *J* = 7.5 Hz, 1H), 3.72 (B of AB, d, *J* = 17.5 Hz, 1H), 3.24−3.06 (m, 2H), 1.96 (m, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.425 (s, 3H), 1.40 (s, 3H), 1.10 (t, *J* = 7.0 Hz, 3H), 1.01 (dd, *J* = 7.0, 1.5 Hz, 6H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.3, 178.3, 178.2, 177.0, 175.7, 175.5, 161.2, 61.6, 58.4, 58.2, 57.90, 57.9, 57.7, 43.8, 40.3, 35.9, 31.7, 26.6−26.3 (overlapping signals), 24.9, 24.5, 24.4, 24.3, 19.9, 19.2, 16.0 ppm; IR (film) 3409, 3299, 2986, 1657, 1566, 1529, 1384, 1224, 631 cm^{-1}; MS (ES^+, MeOH) 607 $[M + Na]^+$ (100); HRMS (ES^+, MeOH) calcd for $C_{26}H_{48}N_8O_7$ + Na 607.3551, found 607.3538.

*EtNHCS-L-Val-Aib$_4$-GlyNH$_2$ (**11k**).* Ethyl isothiocyanate (68 μL, 0.39 mmol) was added dropwise to a suspension of H-Val-Aib$_4$-GlyNH$_2$ (**11b**) (40 mg, 0.078 mmol) and *i*-Pr$_2$NEt (95 μL, 0.55 mmol) in CH_2Cl_2 (3 mL) maintained at 0 °C. The mixture was allowed to warm to room temperature, and 300 μL of anhydrous DMF was added to help solubilization as well as few crystals of DMAP. The solution ws allowed to stir for 24 h, and then the solvent was removed in vacuo. Et_2O was added (5 mL) to remove DMF by decanting the insoluble material. The process was repeated three times, and then the solids were dissolved in CH_2Cl_2 (1 mL) and petroleum ether was added until turbidity appeared. EtNHCS-L-Val-Aib$_4$-GlyNH$_2$ was collected by filtration as a white solid (41 mg, 0.068 mmol, 87%): R_f (SiO_2/$CHCl_3$/MeOH 90:10) = 0.45; mp 180−182 °C; $[\alpha]_D^{20}$ = −54.4 (*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 4.44 (d, *J* = 7.0 Hz, 1H), 3.92 (A of AB, d, *J* = 17.5 Hz, 1H), 3.73 (B of AB, d, *J* = 17.5 Hz, 1H), 3.51 (brs, 2H), 2.10 (m, 1H), 1.51 (s, 3H), 1.44 (s, 6H), 1.43 (s, 6H), 1.425 (s, 3H), 1.42 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.03 (dd, *J* = 7.0, 4.5 Hz, 6H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.3, 178.2, 178.1, 177.0, 176.7, 175.6, 174.9, 108.4, 58.4, 58.4, 58.2, 58.2, 58.1, 57.9, 44.0, 43.9, 40.3, 31.8, 26.8−26.4 (overlapping signals), 25.0, 24.6, 24.5, 24.4, 20.0, 14.9 ppm; IR (film) 3316, 2978, 1650, 1530, 1288, 1219, 586 cm^{-1}; MS (ES^+, MeOH) 623 $[M + Na]^+$ (100); HRMS (ES^+, MeOH) calcd for $C_{26}H_{48}N_8O_6S$ + Na 623.3310, found 623.3322.

*H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**).* A round-bottom flask was charged with of Cbz-L-αMv-Aib$_4$-GlyNH$_2$ (**9f**) (30 mg, 0.046 mmol), 10% Pd/C (6 mg, 20%), and MeOH (3 mL), and the mixture was stirred at room temperature under an atmosphere of H_2 (balloon) until completion (TLC monitoring). Upon completion, the mixture was filtered under vacuum through a pad of Celite, washing several times with MeOH. The solvent was removed under reduced pressure and H-L-αMv-Aib$_4$-GlyNH$_2$ was obtained as a white solid (23 mg, 0.046 mmol, 99%): mp 244−245 °C; $[\alpha]_D^{20}$ = +5.2 (*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.87 (A of AB, d, *J* = 17.5 Hz, 1H), 3.75 (B of AB, d, *J* = 17.5 Hz, 1H), 2.07 (m, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.23 (s, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, MeOD) δ 179.9, 178.2, 178.2, 177.9, 176.9, 175.5, 61.5, 58.3, 58.2, 57.8, 57.5, 43.9, 36.5, 26.1, 26.1−26.0 (overlapping signals), 25.4, 25.3, 25.1, 25.0, 24.8, 24.6, 18.1, 16.5 ppm; IR (film) 3306, 1646, 1523, 1416, 1362, 1225 cm^{-1}; MS (ES^+, MeOH) 550 $[M + Na]^+$ (100); HRMS (ES^+, MeOH) calcd for $C_{24}H_{45}N_7O_6$ + Na 550.3324, found 550.3324.

*Tfa-L-αMv-Aib$_4$-GlyNH$_2$ (**12h**).* Trifluoroacetic anhydride (38 μL, 0.27 mmol) was added dropwise to a suspension of H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**) (72 mg, 0.14 mmol) and *i*-Pr$_2$NEt (237 μL, 1.36 mmol) in CH_2Cl_2 (4 mL) maintained at −20 °C. The mixture was allowed to warm to room temperature with stirring overnight, and then the solvent was removed in vacuo. The residue was diluted with EtOAc (10 mL), washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (sat. solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography (CH_2Cl_2/MeOH, 95:5), and Tfa-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (40 mg, 0.13 mmol, 47%): R_f (SiO_2/CH_2Cl_2/MeOH 95:5) = 0.35; mp 235−236 °C; $[\alpha]_D^{20}$ = +13.2 (*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.87 (A of AB, d, *J* = 17.5 Hz, 1H), 3.79 (B of AB, d, *J* = 17.5 Hz, 1H), 2.21 (m, 1H), 1.53 (s, 3H), 1.51 (s, 6H), 1.46 (s, 3H), 1.45 (s, 3H + 3H), 1.44 (s, 6H), 1.42 (s, 3H), 1.01 (t, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (126 MHz, MeOD) δ 178.2, 178.1, 178.1, 176.8, 175.5, 174.1, 159.3 (q, *J* = 37.2 Hz), 117.4 (q, *J* = 287.0 Hz), 65.3, 58.5, 58.3, 58.1, 58.0, 43.9, 35.9, 26.0, 25.7, 25.5, 25.3, 25.2−25.0 (overlapping signals), 18.2, 18.00, 17.9 ppm; IR (film) 3285, 2986, 1653, 1531, 1383, 1220, 1174, 660 cm^{-1}; MS (ES^-, MeOH) 622 $[M - 1]^-$ (100); HRMS (ES^-, MeOH) calcd for $C_{26}H_{44}N_7O_7F_3$ − H 622.3181, found 622.3183.

*EtOCO-L-αMv-Val-Aib$_4$-GlyNH$_2$ (**12i**).* Ethyl chloroformate (30 μL, 0.32 mmol) was added dropwise to a suspension of H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**) (85 mg, 0.16 mmol) and *i*-Pr$_2$NEt (270 μL, 1.6 mmol) in CH_2Cl_2 (4 mL) maintained at −20 °C. The mixture was allowed to warm to room temperature with stirring overnight, and then the solvent was removed in vacuo. The residue was diluted with EtOAc (10 mL), washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (sat. solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography (CH_2Cl_2/MeOH, 93:7), and Tfa-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (50 mg, 0.08 mmol, 52%): R_f (SiO_2/$CHCl_3$/MeOH 90:10) = 0.65; mp 232−233 °C; $[\alpha]_D^{20}$ = +26.4 (*c* = 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 8.11 (brs, 2H), 8.05 (brs, 1H), 7.99 (brs, 1H), 7.91 (brs, 1H), 7.90 (brs, 1H), 4.13 (tt, *J* = 7.5, 3.5 Hz, 2H), 3.96 (A of AB, d, *J* = 17.5 Hz, 1H), 3.71 (B of AB, d, *J* = 17.5 Hz, 1H), 2.00 (dt, *J* = 13.5, 7.0 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.46 (s, 6H), 1.45 (s, 3H), 1.44 (s, 3H), 1.39 (s, 6H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, MeOD) δ 178.4, 178.2, 178.1, 177.3, 176.1, 175.5, 158.6, 64.0, 62.3, 58.3, 58.2, 58.0, 58.0, 43.9, 36.4, 26.8−26.7 (overlapping signals), 24.8, 24.2, 18.6, 18.1, 17.8, 15.2 ppm; IR (film) 3293, 2984, 2414, 1642, 1418, 1379, 1217, 670 cm^{-1}; MS (ES^+, MeOH) 622 $[M + Na]^+$ (100); HRMS (ES^+, MeOH) calcd for $C_{27}H_{49}N_7O_8$ + Na 622.3535, found 622.3530.

*EtNHCO-L-αMv-Aib$_4$-GlyNH$_2$ (**12j**).* Ethyl isocyanate (38 μL, 0.48 mmol) was added dropwise to a suspension of H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**) (69 mg, 0.13 mmol) and *i*-Pr$_2$NEt (85 μL, 0.48 mmol) in CH_2Cl_2 (4 mL) maintained at −20 °C, followed by DMAP (8 mg, 0.07 mmol). The mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed in vacuo, and then the residue was diluted with EtOAc (10 mL), washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (satd solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography (CH_2Cl_2/MeOH, 9:1), and EtNHCO-L-αMv-Aib$_4$-GlyNH$_2$ was obtained as a white solid (50 mg, 0.08 mmol, 64%): R_f (SiO_2/CH_2Cl_2/MeOH 90:10) = 0.40; mp 237−238 °C; $[\alpha]_D^{20}$ = +32.4 (*c* = 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 8.41 (s, 1H), 8.14 (s, 1H), 7.82 (s, 1H), 3.97 (A of AB, d, *J* = 17.3 Hz, 1H), 3.71 (B of AB, d, *J* = 17.5 Hz, 1H), 3.17 (qd, *J* = 7.0, 5.0 Hz, 2H), 2.05−1.92 (m, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.46 (s, 6H), 1.455 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.37 (d, *J* = 8.5 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.7, 178.2, 178.2, 177.6, 177.2, 175.5, 160.3, 63.2, 58.3, 58.1, 57.9, 57.7, 43.9, 36.7, 35.8, 27.0, 26.9 (overlapping signals), 26.8, 24.7, 24.2, 24.0, 18.0, 17.6, 16.1 ppm; IR (film) 3339, 2978, 2462, 1633, 1527, 1418, 1222, 609 cm^{-1};

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MS (ES$^+$, MeOH) 621 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{27}H_{50}N_8O_7$ + Na 621.3695, found 621.3693.

*N_3Aib-L-Val-Aib$_4$-GlyNH$_2$ (**13c**).* A solution of freshly distilled 2-azido-2-methylpropanoyl chloride (31 mg, 0.21 mmol) in CH_2Cl_2 (200 μL) was added dropwise to a suspension of H-L-Val-Aib$_4$-GlyNH$_2$ (**11b**) (80 mg, 0.16 mmol) and triethylamine (45 μL, 0.32 mmol) in CH_2Cl_2 (2 mL) maintained at −20 °C. The mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed in vacuo, and then the residue was diluted with EtOAc (10 mL), washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (sat. solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using column chromatography ($CHCl_3$/MeOH, 98:2 to 95:5), and N_3Aib-L-Val-Aib$_4$-GlyNH$_2$ was obtained as a white solid (64 mg, 0.10 mmol, 64%): R_f (SiO_2/$CHCl_3$/MeOH 98:2) = 0.40; mp 228−230 °C; $[\alpha]_D^{20}$ = −28.0 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 3.99 (d, J = 7.5 Hz, 1H), 3.96 (A of AB, d, J = 17.5 Hz, 1H), 3.70 (B of AB, d, J = 17.5 Hz, 1H), 2.17−2.06 (m, 1H), 1.53 (s, 3H), 1.51 (s, 6H), 1.50 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.44 (s, 6H), 1.38 (s, 3H), 1.01 (d, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.2, 178.2, 178.0, 176.7, 175.5, 175.2, 173.8, 65.4, 60.9, 58.4, 58.3, 58.2, 58.2, 57.9, 57.9, 43.8, 31.8, 26.8, 26.7, 26.5, 26.3 (overlapping signals), 25.1, 25.0, 24.7, 24.3, 24.2, 24.1, 19.8, 19.4 ppm; IR (film) 3283, 2928, 2112, 1652, 1526, 1384, 1224, 647 cm^{-1}; MS (ES$^+$, MeOH) 647 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{27}H_{48}N_{10}O_7$ + Na 647.3600, found 647.3577.

*Cbz-Aib-L-Val-Aib$_4$-GlyNH$_2$ (**13d**).* EDC·HCl (29 mg, 0.12 mmol) was added to a cold (0 °C) suspension of H-L-Val-Aib$_4$-GlyNH$_2$ (**11b**) (22 mg, 0.04 mmol), Cbz-Aib-OH (30 mg, 0.12 mmol), and HOAt (17 mg, 0.12 mmol) in CH_2Cl_2 (1 mL). i-Pr_2NEt (30 μL, 0.2 mmol) was added, and the resulting clear solution was allowed to warm to room temperature and stirred for 3 days. The solvent was removed in vacuo, and then the residue was diluted with EtOAc (10 mL), washed with $KHSO_4$ (5% solution, 3 × 2 mL), $NaHCO_3$ (sat. solution, 3 × 2 mL), and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography ($CHCl_3$/MeOH, 95:5 to 9:1) to give Cbz-Aib-L-Val-Aib$_4$-GlyNH$_2$ as a white solid (22 mg, 0.03 mmol, 75%): R_f (SiO_2/$CHCl_3$/MeOH 95:5) = 0.40; mp 143−145 °C; $[\alpha]_D^{20}$ = +9.6 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.46−7.22 (m, 5H), 5.12 (A of AB, d, J = 12.5 Hz, 1H), 5.08 (B of AB, d, J = 12.5 Hz, 1H), 3.87 (A of AB, d, J = 17.5 Hz, 1H), 3.77 (B of AB, d, J = 17.5 Hz, 1H), 3.77 (d, J = 7.0 Hz, 1H), 2.13−2.01 (m, 1H), 1.50 (s, 6H), 1.45 (s, 6H), 1.44 (s, 6H), 1.43 (s, 6H), 1.42 (s, 6H), 0.95 (d, J = 5.0 Hz, 3H), 0.93 (d, J = 5.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.2, 178.2, 177.0, 175.5, 174.1, 173.9, 157.9, 138.4, 129.7, 129.3, 128.9, 67.8, 62.6, 58.4, 58.3, 58.2, 57.9, 57.9, 57.8, 43.9, 30.8, 26.3−25.9 (overlapping signals), 25.3, 25.3, 25.0, 24.9, 19.8, 19.7 ppm; IR (film) 3297, 2915, 2848, 1653, 1527, 1466, 1381, 1260, 1083, 718 cm^{-1}; MS (ES$^+$, MeOH) m/z = 755 ([M + Na]$^+$, 100); HRMS (ES$^+$, MeOH) calcd for $C_{35}H_{56}N_8O_9$Na [M + Na]$^+$ 755.4068, found 755.4062.

*Ac-Aib-L-Val-Aib$_4$-GlyNH$_2$ (**13e**).* Pd/C (3 mg, 20%) was carefully added to a solution of Cbz-Aib-L-Val-Aib$_4$-GlyNH$_2$ (**13d**) (17 mg, 0.023 mmol) in acetic anhydride (3 mL), and the mixture was stirred at room temperature under an atmosphere of H_2 (balloon) until completion (TLC monitoring). Upon completion the mixture was filtered under vacuum through a pad of Celite, washing several times with EtOAc. The solvent was removed under reduced pressure and the residue purified by colum chromatography ($CHCl_3$:MeOH, 95:5 to 9:1) to give Ac-Aib-L-Val-Aib$_4$-GlyNH$_2$ as a white solid (16 mg, 0.022 mmol, 95%): R_f (SiO_2/CH_2Cl_2/MeOH 90:10) = 0.40; mp 268−269 °C; $[\alpha]_D^{20}$ = −3.6 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 3.86 (A of AB, d, J = 17.5 Hz, 1H), 3.81 (d, J = 7.5 Hz, 1H), 3.80 (B of AB, d, J = 17.5 Hz, 1H), 2.17−2.07 (m, 1H), 1.99 (s, 3H), 1.51 (s, 3H), 1.505 (s, 3H), 1.465 (s, 6H), 1.46 (s, 6H), 1.45 (s, 3H), 1.445 (s, 6H + 3H), 1.43 (s, 3H), 1.00 (d, J = 6.0 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.3, 178.1, 177.8, 177.1, 175.6, 174.0, 173.2, 62.4, 58.4, 58.2, 57.9, 57.8, 57.8, 43.9, 30.9, 26.2, 25.69−25.1 (overlapping signals), 23.3, 19.9, 19.8 ppm; IR (film) 3293, 2982, 1646, 1528, 1416, 1363, 1222, 661 cm^{-1}; MS (ES$^+$, MeOH) 663 [M + Na]$^+$ (100); HRMS (ES$^+$, MeOH) calcd for $C_{29}H_{52}N_8O_8$ + Na 663.3800, found 663.3789.

*N_3Aib-L-αMv-Aib$_4$-GlyNH$_2$ (**13f**).* Peptide **13f** was synthesized following the same procedure described for peptide **13c** using peptide H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**) as the starting material. The crude product was purified by column chromatography ($CHCl_3$/MeOH, 95:5 to 97:3) to give N_3Aib-L-αMv-Aib$_4$-GlyNH$_2$ as a white powder (56% yield): R_f (SiO_2/CH_2Cl_2/MeOH 97:3) = 0.50; mp 130−133 °C; $[\alpha]_D^{20}$ = +6.5 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 8.14 (brs, 1H), 7.92 (brs, 1H), 7.92 (brs, 1H), 7.80 (brs, 1H), 3.94 (A of AB, d, J = 17.5 Hz, 1H), 3.72 (B of AB, d, J = 17.5 Hz, 1H), 2.23−2.08 (m, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.505 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H) 1.04 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 176.0, 175.8, 174.3, 173.3, 173.0, 172.6, 64.2, 62.5, 57.1, 56.8, 56.7, 43.2, 35.1, 26.4−26.0 (overlapping signals), 24.4, 24.1, 23.8, 17.1, 17.1, 16.4 ppm; IR (film) 2981, 2114, 1651, 1525 1382, 1362, 1224, 655 cm^{-1}; MS (ES$^+$, MeOH) m/z = 661 ([M + Na]$^+$, 100); HRMS (ES$^+$, MeOH) calcd for $C_{28}H_{50}N_{10}O_7$Na [M + Na]$^+$ 661.3762, found 661.3749.

*Cbz-Aib-L-αMv-Aib$_4$-GlyNH$_2$ (**13g**).* Peptide **13g** was synthesized following the same procedure described for peptide **13d** using peptide H-L-αMv-Aib$_4$-GlyNH$_2$ (**12b**) as the starting material. The crude product was purified by column chromatography ($CHCl_3$/MeOH, 99:1 to 95:5) to give Cbz-Aib-L-αMv-Aib$_4$-GlyNH$_2$ as a white powder (38% yield): R_f (SiO_2/CH_2Cl_2/MeOH 95:5) = 0.40; mp 231−232 °C; $[\alpha]_D^{20}$ = +48.0 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 8.06 (brs, 1H), 7.77 (brs, 1H), 7.48 (brs, 1H), 7.44−7.28 (m, 5H), 5.17 (A of AB, d, J = 12.5 Hz, 1H), 5.06 (B of AB, d, J = 12.5 Hz, 1H), 3.99 (d, J = 17.5 Hz, 3H), 3.68 (d, J = 17.5 Hz, 3H), 1.85−1.70 (m, J = 13.0, 6.5 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.455 (s, 3H), 1.45 (s, 6H), 1.44 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 0.87 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, MeOD) δ 178.4, 178.2, 178.2, 177.7 177.6, 177.2, 175.6, 158.2, 138.4, 129.8, 129.4, 129.4, 68.0, 63.7, 63.7, 58.3, 58.2, 58.1, 57.9, 44.0, 43.9, 36.6, 27.3−27.0 (overlapping signals), 26.5, 24.5, 24.2, 24.0−23.9 (overlapping signals), 19.6, 18.2, 17.7 ppm; IR (film) 3311, 2982, 2937, 1646, 1522, 1414, 1262, 1221, 1081, 744 cm^{-1}; MS (ES$^+$, MeOH) m/z = 769 ([M + Na]$^+$, 100); HRMS (ES$^+$, MeOH) calcd for $C_{36}H_{58}N_8O_9$ [M + Na]$^+$ 769.4224, found 769.4219.

*Ac-Aib-L-αMv-Aib$_4$-GlyNH$_2$ (**13h**).* Peptide **13h** was synthesized following the same procedure described for peptide **13e** using peptide N_3Aib-L-αMv-Aib$_4$-GlyNH$_2$ (**13f**) as the starting material. The crude product was purified by column chromatography ($CHCl_3$/MeOH, 99:1 to 95:5) to give Ac-Aib-L-αMv-Aib$_4$-GlyNH$_2$ as a white powder (94% yield): R_f (SiO_2/$CHCl_3$:MeOH 90:10) = 0.45; mp 271−272 °C; $[\alpha]_D^{25}$ = +51.6 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 4.00 (A of AB, dd, J = 17.5, 5.5 Hz, 1H), 3.67 (B of AB, dd, J = 17.5, 5.5 Hz, 1H), 2.08−1.96 (m, 4H), 1.52 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.46 (s, 6H), 1.45 (s, 6H), 1.45 (s, 3H), 1.41 (s, 3H), 0.97 (d, J = 1.5 Hz, 3H), 0.95 (d, J = 1.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, MeOD) δ 178.3, 178.1, 178.0, 177.5, 176.5, 175.4, 174.1, 173.3, 63.7, 58.2, 58.1, 58.0, 57.8, 43.8, 36.4, 27.1−26.9 (overlapping signals), 26.3, 24.4, 24.1, 23.9, 23.8, 23.8, 23.1, 20.3, 18.1, 17.7 ppm; IR (film) 3276, 2983, 1642, 1532, 1419, 1379, 1220, 683 cm^{-1}; MS (ES$^+$, MeOH) m/z = 677 ([M + Na]$^+$, 100), 655 ([M + H]$^+$, 70); HRMS (ES$^+$, MeOH) calcd for $C_{30}H_{54}N_8O_8$ + Na [M + Na]$^+$ 677.3957, found 677.3948.

*Cbz-L-αMv-L-Val-Aib$_4$-GlyNH$_2$ (**13i**).* Cbz-L-αMv-OH (149 mg, 0.56 mmol) was dissolved in DCM (4 mL) and cooled to 0 °C. TFFH (222 mg, 0.84 mmol) and pyridine (45 μL, 0.56 mmol) were added, the cooling bath removed, and the reaction stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with ice-cold water (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated to give Cbz-L-αMv-F, which was used immediately without further purification.

Crude Cbz-L-αMv-F was dissolved in CH_2Cl_2 (6 mL) and H-L-Val-Aib$_4$GlyNH$_2$ (**11b**) (115 mg, 0.22 mmol) added. DIPEA (97 μL, 0.56 mmol) was added dropwise and the reaction stirred at room

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temperature for 5 d. The solvents were removed, and the residue was redissolved in EtOAc (20 mL), washed with 5% $KHSO_4$ (2 × 15 mL), satd $NaHCO_3$ (2 × 15 mL), and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (CH_2Cl/MeOH 98:2−95:5) gave Cbz-L-αMv-Val-Aib_4-$GlyNH_2$ as a white solid (141 mg, 0.19 mmol, 83%): R_f (SiO_2/CH_2Cl_2/MeOH) 95:5 = 0.18; mp = 127−130 °C; $[\alpha]_D$ + 27.6 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ 8.11 (t, *J* = 6.0 Hz, 1H), 7.95 (brs, 1H), 7.93 (brs, 1H), 7.65 (brs, 1H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.0 Hz, 1H), 5.16 (A of AB, d, *J* = 12.5 Hz, 1H), 5.11 (B of AB, d, *J* = 12.5 Hz, 1H), 3.94 (A of AB, d, *J* = 17.5 Hz, 1H), 3.77 (d, *J* = 6.5 Hz, 1H), 3.72 (B of AB, d, *J* = 17.5 Hz, 1H), 2.05 (m, 2H), 1.513 (s, 3H), 1.508 (s, 3H), 1.48 (s, 3H), 1.453 (s, 3H), 1.448 (s, 3H), 1.441 (s, 3H), 1.437 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.2, 178.1, 177.0, 176.9, 176.8, 175.4, 173.7, 158.2, 138.2, 129.6, 129.2, 128.8, 67.9, 64.4, 63.1, 58.29, 58.27, 58.2, 58.1, 57.9, 57.80, 57.78, 57.74, 57.72, 43.7, 36.5, 30.6, 26.6−26.4 (overlapping signals), 24.7, 24.12, 24.08, 19.6, 19.5, 18.3, 18.0, 17.5 ppm; IR (film) 3296, 2977, 1652, 1526, 1455, 1384, 1362, 1257, 1227, 1171 cm^{-1}; MS (ES^+, MeOH) 783 ($[M + Na]^+$, 100); HRMS (ES^+, MeOH) calcd for $C_{37}H_{60}N_8O_9$ + H 761.4557, found 761.4536.

*Cbz-L-αMv-t-Leu-Aib_4-$GlyNH_2$ (**13j**).* Cbz-L-αMv-OH (123 mg, 0.46 mmol) was dissolved in DCM (4 mL) and cooled to 0 °C. TFFH (184 mg, 0.70 mmol) and pyridine (38 μL, 0.46 mmol) were added, the cooling bath was removed, and the reaction was stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with ice-cold water (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated to give Cbz-L-αMv-F, which was used immediately without further purification.

Crude Cbz-L-αMv-F was dissolved in CH_2Cl_2 (6 mL) and H-L-*t*-Leu-Aib_4GlyNH_2 (prepared by quantitative hydrogenolysis of peptide **9c** with Pd/C and H_2 in MeOH, 98 mg, 0.19 mmol) added. DIPEA (80 μL, 0.46 mmol) was added dropwise and the reaction stirred at room temperature for 5 d. The solvents were removed, and the residue was redissolved in EtOAc (20 mL), washed with 5% $KHSO_4$ (2 × 15 mL), satd $NaHCO_3$ (2 × 15 mL), and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (CH_2Cl_2/MeOH; 95:5) gave Cbz-L-αMv-*t*-Leu-Aib_4-$GlyNH_2$ as a white solid (107 mg, 0.14 mmol, 74%): R_f (SiO_2/CH_2Cl_2/MeOH) 90:10 = 0.42; mp = 142−145 °C; $[\alpha]_D$ + 25.5 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ 7.92 (brs, 1H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.0 Hz, 1H), 5.20 (A of AB, d, *J* = 12.5 Hz, 1H), 5.07 (B of AB, d, *J* = 12.5 Hz, 1H), 3.91 (A of AB, d, *J* = 17.5 Hz, 1H), 3.75 (B of AB, d, *J* = 17.5 Hz, 1H), 3.73 (s, 1H), 2.13 (sept, *J* = 7.0 Hz, 1H), 1.51 (s, 6H), 1.47 (s, 3H), 1.46 (s, 3H), 1.44 (s, 6H), 1.43 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 0.99−0.98 (m, 12H), 0.94 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 178.1, 178.01, 177.95, 176.9, 176.5, 175.4, 172.7, 158.4, 138.1, 129.6, 129.2, 129.0, 67.9, 65.6, 64.7, 58.2, 58.1, 57.83, 57.79, 43.7, 36.2, 33.5, 27.3, 30.6, 26.3, 26.2, 26.1, 26.0, 24.9, 24.5, 24.4, 18.5, 17.9, 17.4 ppm; IR (film) 3303, 2975, 1653, 1526, 1456, 1383, 1362, 1258, 1226, 1170 cm^{-1}; MS (ES^+, MeOH) 797 ($[M + Na]^+$, 100);HRMS (ES^+, MeOH) calcd for $C_{38}H_{62}N_8O_9$ + H 775.4713, found 775.4704.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds, X-ray data, and an interactive spreadsheet summarizing calculations of chemical shift differences and helical excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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