Solid Phase Synthesis of β-Peptoids: N-Substituted β-Aminopropionic Acid Oligomers

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A solid-phase organic synthesis method has been developed for the preparation of N-substituted-β-aminopropionic acid oligomers or β-peptoids **1**. Treatment of polymer-bound 4-(benzyloxy)benzyl acrylate **2** with primary amines afforded N-substituted β-alanines **3**. Polymer loadings and product conversions were determined by direct cleavage of resin-bound materials and measurement by ^{1}H NMR with an internal standard. The NMR method was used to establish loading of all resin-bound intermediates including acrylic acid. Acylation with acryloyl chloride followed by Michael addition of primary amines to the acrylamide allowed preparation of di-β-peptoids. By a linear set of seven reactions, trimeric *N*-benzyl-β-aminopropionic acid was prepared in 67% overall yield. Single-bead FT-IR microspectroscopy was used to acquire spectra of the resin bound mono-β-peptoids, di-β-peptoids, and acrylamide intermediates. A combinatorial library of defined mixtures of tri-β-peptoids was prepared by mixing equimolar amounts of the mono-β-peptoid resins and carrying them through two sequences of the acylation−Michael addition. The identity of a sample mixture was determined by LC−MS analysis of the cleavage product.

Introduction

We have developed a solid-phase organic synthesis (SPOS) method for the preparation of β-peptoids **1**, which is suitable for the paralled synthesis of libraries of these unique peptidomimetic structures. The development of SPOS methods for the preparation of combinatorial libraries is a rapidly growing area in discovery research organizations.[1] Whether the intent is to prepare mixtures of compounds or sets of single components, the interest in SPOS lies in the ability to efficiently prepare relatively pure materials for biological testing without the need for extensive purification. The solid phase lends itself toward simultaneous production of sets of compounds using a variety of recently described reactor formats.[2] In the past few years, we have seen an unprecedented growth in nonpeptide-based methods, both solid and solution phase, for the preparation of new compound libraries.[3] Many of the advantages offered by a solid phase have been amply demonstrated for single peptide synthesis such as the ability to employ excess reagents, wash away all soluble byproducts, and carry out multiple reaction steps.[4] In the case of mixtures, SPOS offers the ability to manipulate samples for "pool and split" synthesis, which allows the number of compounds to grow exponentially with each pool and split step.[5]

Peptide-based libraries have allowed the in vitro identification of biologically active sequences such as the opioid peptides;[6] however, these compounds have limitations for pharmaceutical applications due to metabolic instability and poor absorption characteristics. Extensive modification of an active lead would be required for the development of compounds having desired levels of in vivo activity. Recently, efforts have been reported utilizing nonpeptide backbones for the preparation of oligomeric compounds that can potentially overcome these drawbacks such as 3,5-linked pyrrolin-4-ones,[7] vinylogous polypeptides,[8] oligocarbamates and ureas,[9] sulfonopeptides,[10] polyisoxazolines,[11] and N-substituted glycines.[12] Screening of combinatorial libraries of oligo-*N*-(substi-

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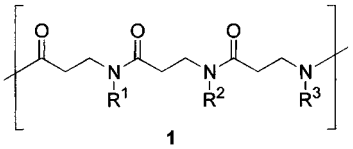
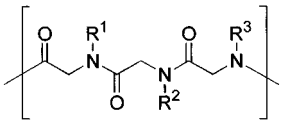
tuted)glycines or "peptoids" has led to the identification of nanomolar ligands for 7-transmembrane G-protein-coupled receptors.[13]

β-Amino acids have been incorporated in fibrinogen receptor antagonists,[14] employed as components of high-affinity SH3 ligands for the Src SH3 domain,[15] used in the synthesis of β-lactam antibiotics[16] and found in meteorites and electron-discharge experiments.[17] Oligomers of β-amino acids (β-peptides) have recently been shown to exhibit residue-controlled secondary structures[18] and to have remarkable stability toward proteases.[19] Until now, β-peptides have been prepared from primary β-amino acids such that oligomers having secondary amides were obtained.[20] The initial targets of our efforts were trimers **1**, which we have named β-peptoids in analogy to the nomenclature used for oligomeric N-substituted glycines or peptoids described by Chiron.[21] The tertiary amides of peptoids provide a backbone structure that is more stable to hydrolysis and less polar than typical peptide amide bonds.[12,21] As a result, libraries of β-peptoids **1** would be expected to have greater metabolic stability and improved absorption properties. We have used SPOS to prepare **1** from the iterative reaction of resin bound acrylate or acrylamides with primary amines, allowing the incorporation of a wide variety of functional groups on nitrogen. In addition, we have developed an NMR method for determination of polymer loading that is faster and more convenient than conventional methods. The NMR method is particularly useful for measurement of volatile substrates such as acrylic acid in which loading cannot easily be established by gravimetric methods or techniques that require the concentration of cleaved material.

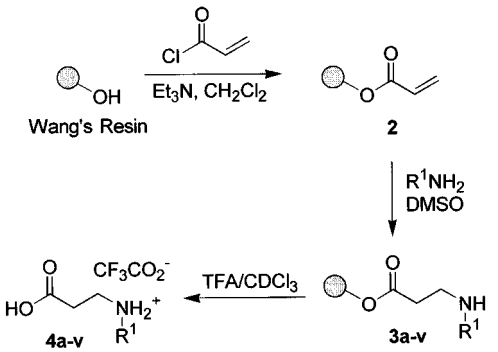


1
β-Peptoid



Peptoid

Scheme 1



Results and Discussion

Oligomeric N-substituted β-aminopropionic acids can be prepared by standard peptide couplings of N-substituted β-amino acids;[20] however, this approach requires the preparation of a significant number of specialized β-amino acids for incorporation into the oligomer. Rather, we have used a two-step approach in which we can take advantage of the ready availability of acrylic acid and primary amines having a wide variety of substituent groups. β-Aminopropionic acids and esters have been prepared by the solution-phase addition of amines to acrylate esters[22] or acrylic acid;[23] however, purification of the monoaddition product is often complicated by the presence of side products obtained from bis-addition. N-Substituted β-alanines have also been prepared from propiolactones and the trimethylsilyl ester of acrylic acid.[24,25] The Michael addition of amines to a resin-bound acrylate appeared to us to be more general than previously reported methods, since an excess of the primary amine could be used, thus reducing the formation of bis-addition side products.[26,27] The purification advantages of solid-phase synthesis allow facile isolation of the monoaddition products.[28] During the course of our studies, Brown et al.[29] reported the Michael addition of amines to acrylate-functionalized (hydroxymethyl)polystyrene resin; however, this linker was used for the synthesis of tertiary amines rather than N-substituted β-alanines. We have previously reported Wang-acrylate resin for the preparation of 5,6-dihydropyrimidine-2,4-

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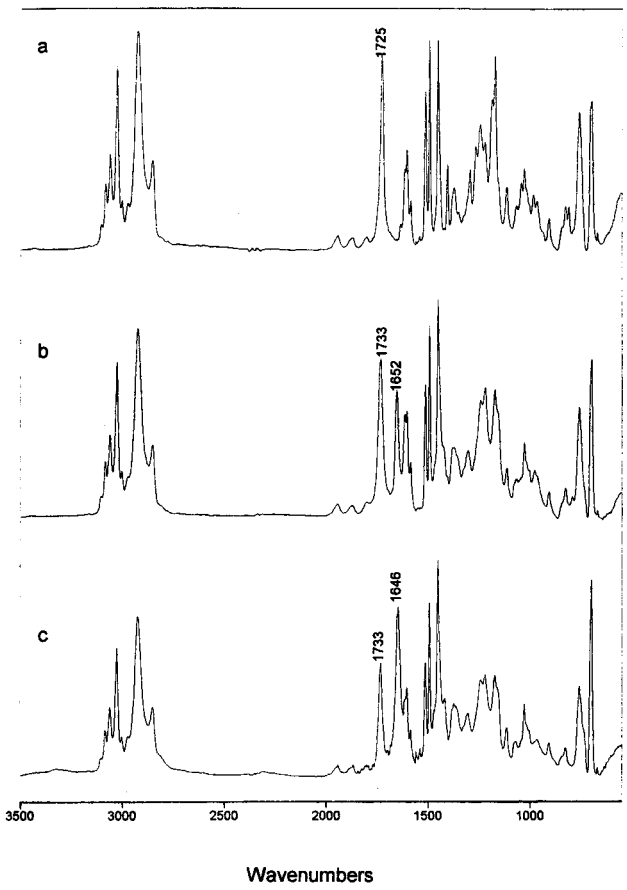

Figure 1. Microspectroscopy FT-IR of a single bead of polymer resin: (a) acrylate resin **2**, (b) acrylamide **R-5**, and (c) trimer resin **R-8**.

diones.[30] Wang's resin provided a means of attaching the acrylic acid as its ester and cleavage of products by treatment with trifluoroacetic acid.[31]

Treatment of Wang's resin with 2 equiv of acryloyl chloride in the presence of excess triethylamine afforded acrylate resin **2** (Scheme 1). Attempts to functionalize Wang's resin directly with acrylic acid and a variety of coupling reagents afforded resins with a lower level of functionalization, although the purity of cleaved acrylic acid was comparable with the acryloyl chloride route as determined by NMR. The polymer-bound acrylate was characterized by single-bead microscopy FT-IR,[32] which showed complete disappearance of the hydroxyl OH stretch and the appearance of a carbonyl stretch at 1725 cm^{-1} (Figure 1a). Loading of **2** was determined only by the NMR cleavage method, since acrylic acid is too volatile for gravimetric determination and lacks a unique atom for elemental analysis. Polymer loading was determined by direct cleavage of a weighed quantity of resin with 1.0 mL of a solution of 9.8 mM hexamethyldisiloxane (HMDS) in TFA/$CDCl_3$ (1:1). Comparison of the integration of specific resonances of the internal standard and product allows a direct measurement of the loading of **2** (0.88 mequiv/g). HMDS was chosen as the internal standard for its solubility in TFA/$CDCl_3$ and the single resonance at 0.42 ppm relative to TMS in this solvent mixture. By comparison, TMS was not soluble in TFA mixtures and due to its volatility did not provide solutions of stable molarity on storage. The stability of the silyl ether in HMDS was of concern, especially considering the acidity of the standard solution. Stability of HMDS was measured by regular preparation of NMR solutions of a weighed amount of 4-hydroxybenzaldehyde, and the solutions were found to maintain constant molarity for at least 2 months. Direct cleavage of **3b** provided an NMR in which the HMDS and *N*-benzylalanine **4b** are clearly identified (Figure 2). Since the cleavage products are not concentrated prior to obtaining the spectrum, any volatile solvent or reagents that inadvertently are present in the resin prior to cleavage will be present. Typically, small amounts of CH_2Cl_2 and acetic acid are detected that are readily removed after concentration of the sample in vacuo.

Substituted β-amino esters **3a**−**v** were obtained by Michael addition of a 6−10-fold excess of the primary amine to **2** in DMSO (Table 1). Reactions of less hindered amines (Table 1, entries a−f, j, and l−n) with **2** were complete within 24 h at rt, while α-branched amines (Table 1, entries g−i, r, t, and u) required longer reaction times or higher temperatures to drive the reaction to completion. Loadings of resins **3a**−**v** were determined by elemental analysis of nitrogen, direct NMR cleavage with HMDS internal standard, and gravimetric determination of cleaved product **4a**−**u**. Addition of mono-BOC-protected 1,3-diaminopropane provided **3m**, which upon cleavage with TFA/H_2O (95:5) provided the deprotected *N*-(3-aminopropyl)-β-alanine **4m**. Similarly, *N*-(3-hydroxy) **4n** was obtained from 3-[(*tert*-butyldimethylsilyl)oxy]propylamine. For resins **3m** and **3n**, cleavage with TFA/water (95:5) was required for removal of the protecting groups, since direct cleavage with TFA/$CDCl_3$ provided the N- and O-protected analogues of **4m** and **4n**, respectively. Nipecotic acid and β-alanine were added to Wang's resin using standard DIC/DMAP peptide-coupling conditions to provide **4o** and **4p**. Elemental analysis of nitrogen is not particularly good for determination of resins with low loading (%N < 0.5%) and led to higher values for **4t**, **4u**, and **4v** compared to either the NMR method or gravimetric determination. In the case of **3t**, the NMR method provided a loading of 0.19 mequiv/g (25% of theory), while no measurable product was found for **3v**. Aniline (entry w) did not add to the acrylate resin under any of the conditions investigated.

Optimization of the reaction conditions for both the Michael addition and the acryloylation steps were necessary prior to obtaining high overall yields for multistep synthesis of N-substituted β-peptoids. Acylation of **3b** with acryloyl chloride provided nearly quantitative conversion to acrylamide **R-5** (Scheme 2). Although addition of benzylamine to acrylate **2** was found to proceed to completion in 24 h at room temperature in DMSO, addition to acrylamide **R-5** required a reaction temperature of 50 °C with 10−25 equiv of amine. The conversion of **R-5** to **6b** was investigated in order to determine standard conditions applicable to a variety of amines (Table 2). Addition of benzylamine in DMF was nearly equivalent to the results in DMSO; however, an impurity was obtained that was identified as the addition of dimethylamine (runs 1 and 2). Dimethylamine impuri-

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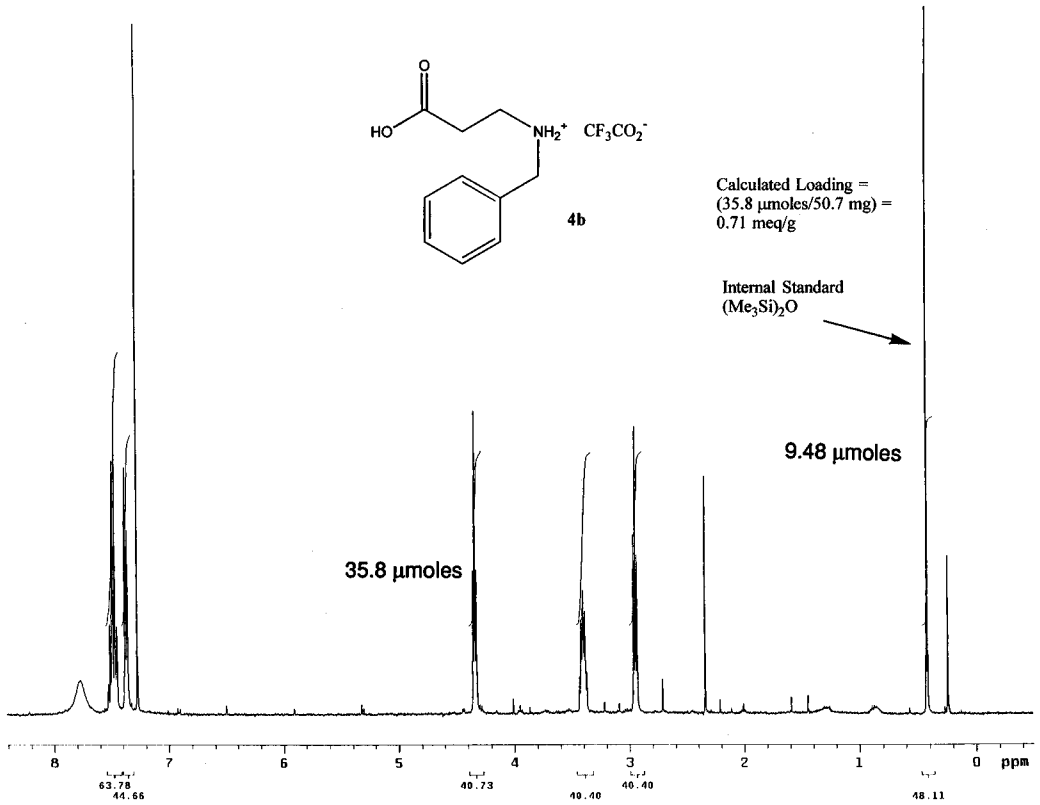
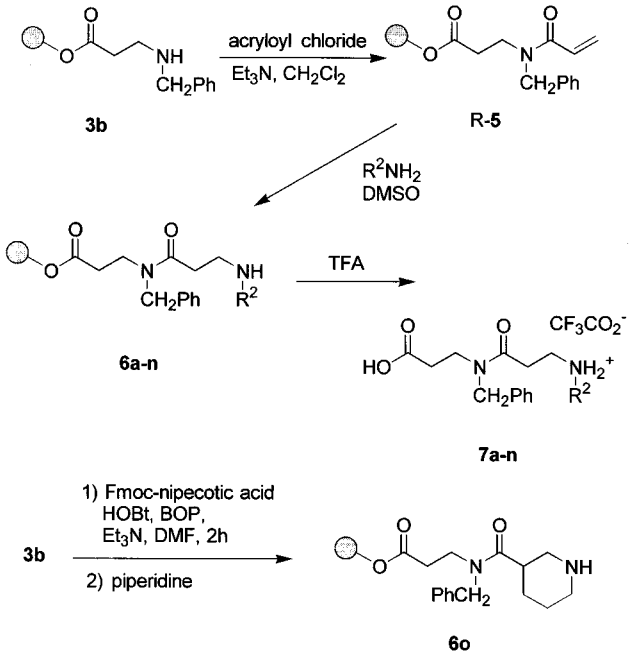


Figure 2. Proton NMR of the direct cleavage product from treatment of 50.7 mg of **3b** with 1.0 mL of 9.48 mM HMDS in TFA/$CDCl_3$ (1:1).

Scheme 2



ties in DMF would be difficult to control and would be more reactive than most of the amines we intended to use in this sequence.[33] Two other solvents, NMP and DCE, were also investigated, but both provided lower conversions to the desired product than DMSO. A number of amines were investigated for possible inclusion in the preparation of a combinatorial library of tri-β-peptoids **1**. Using the standard conditions developed for benzylamine, the crude yields of products obtained by cleavage of the dimers **6a**−**n** were determined (Scheme 2, Table 3). Amines that were not branched at the α position provided the best results (Table 3, entries a, d−i, and k−n), although 1-naphthalenemethylamine required a longer reaction time of 72 h. The branched amines (entries b, c and j) were somewhat slower as evidenced by the lower conversions. Longer 72 h reaction times provided dimers in greater than 95% conversion and these conditions were used for the hindered amines in library synthesis. Two additional β-amino acids, nipecotic acid and β-alanine, were introduced in the tri-β-peptoid library as their Fmoc derivatives using standard peptide coupling methods.[34] Treatment of **3** with the Fmoc-amino acid, HOBt, BOP, and Et_3N in DMF, followed by removal of the Fmoc group with piperidine, afforded the coupled dimers **6o** and **6p**.

Overall yields of trimer **10** for the seven-step reaction sequence from Wang's resin were evaluated (Table 4, Scheme 3) by varying the solvent used for the amine additions (DMF vs DMSO) and the conditions used to acylate the amines (acid chloride vs DIC coupling). The use of DMF in the amine addition reactions (run 1) gave rise to impurities from addition of dimethylamine to both **5** and **8**, as evidenced by LC/MS analysis of the crude reaction mixture. Also present were small amounts of mono- and di-β-peptoids presumably due to incomplete

(33) The use of DMF at room temperature for either solvent washing of acrylate resin **2** or for the capping of the unreacted sites in the resin with DMF/acetic anhydride did not give rise to any measurable addition of dimethylamine by the direct cleavage ^1H NMR method. Presumably, the higher temperatures and longer reaction times employed in the second Michael addition to (*R*)-**5** result in the dimethylamine addition side product.

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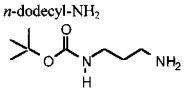
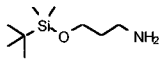
Table 1. Reactions of Primary Amines with Acrylate Resin 2 To Give 3[a]

Entry	R-NH_2	Loading Theor.	EA	NMR	Yield of 4
a	methyl-NH_2	0.83	0.63	0.57	72.9
b	benzyl-NH_2	0.78	0.63	0.79	88%(63%)
c	phenethyl-NH_2	0.77	0.83	0.65	80.5%
d	*p*-methoxybenzyl-NH_2	0.76	0.73	0.63	78.1%
e	allyl-NH_2	0.81	0.81	0.73	75.1%
f	*iso*-butyl-NH_2	0.80	0.86	0.74	87.8%
g	*sec*-butyl-NH_2[b]	0.80	0.79	0.75	85.4%
h	*iso*-propyl-NH_2[b]	0.81	0.82	0.72	95.7%
i	naphthalenemethyl-NH_2[b]	0.75	0.73	0.68	90.0%
j	cyclopropyl-NH_2	0.81	0.83	0.60	74.7%
k	β-alanine ethyl ester[c]	0.77	0.49	0.71	81.8%
l	*n*-dodecyl-NH_2	0.73	0.67	0.62	74.7%
m		0.74	0.71	0.51	>98%[d]
n		0.73	0.70	0.56	55.9%[d]
o	Fmoc-nipecotic acid[e]	0.78	0.76	0.83	>98%
p	Fmoc-β-alanine[e]	0.75	0.55	0.58	77.1%
q	2-methylbutyl-NH_2	0.79	0.86	0.82	98.1%
r	1-methyl-(3-chloro)benzyl-NH_2	0.75	0.89	0.74	>98%
s	cyclohexyl-NH_2	0.78	0.96	0.74	95.4%
t	leucine methyl ester[f]	0.76	0.38	0.19	44.5%
u	diphenylmethyl-NH_2[g]	0.74	0.59	0.41	72.5%
v	phenylalanine methyl ester	0.70	0.31	0	0
w	aniline		0	0	

[a] All conversions of **2** to **3a**−**s** were greater than 95% as determined by ^{1}H NMR. The loading of the resins **3a**−**w** was determined by elemental analysis of nitrogen (EA) and by ^{1}H NMR (NMR). [b] 72 h reaction time. [c] Amine used as HCl salt with an excess of $NaHCO_3$ added to the reaction. [d] Yields of **4m** and **4n** are for the deprotected amine and alcohol, respectively. [e] Products **3o** and **3p** were prepared by standard peptide coupling methods from Wang's resin and Fmoc-amino acid (see Supporting Information). [f] **4t**, 33% conversion. [g] **4u**, 55% conversion.

Table 2. Preparation of Dimer Resin 6b by Michael Addition of Benzylamine to 5

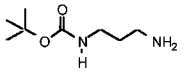
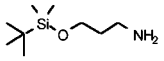
run	reaction condns[a] benzylamine (**b**)	conversion[b] (%)
1	10 equiv of **b**, DMF, 25 °C, 72 h	72[c]
2	25 equiv of **b**, DMF, 50 °C, 24 h	76[d]
3	25 equiv of **b**, DMSO, 50 °C, 24 h	>99
4	25 equiv of **b**, NMP, 50 °C, 24 h	74
5	25 equiv of **b**, DCE, 50 °C, 24 h	60

[a] Solvents: NMP, *N*-methylpyrolidinone; DCE, dichloroethane. [b] Conversion based on reversed-phase HPLC of cleavage products. [c] Further reaction at 50 °C for 18 h led to a 90% conversion. [d] Side product detected and identified as the addition of dimethylamine (impurity in DMF).

reactions at either the amine addition or acylation steps. Therefore, DMSO was chosen as the solvent for amine additions in the preparation of the library. The comparison of acylating conditions (Table 4, runs 2 and 3) showed that the crude product from the DIC-mediated amide formations (Table 4, run 2) contained impurities that appeared to be the result of cross-linking, the

(35) For the DIC-mediated couplings, the apparent mass of the impurity corresponds to a cross-linked product that could arise from initial formation of the expected acrylamide (*R*)-**5** followed by addition of a neighboring secondary amine **3b**. This would constitute a chain-terminating step for both oligomer chains and result in an impurity in the product of $m/z = 412$.

Table 3. Reactions of Amines with Acrylamide Resin 5 To Afford 6a−n[a]

Entry	R-NH_2	Yield (%)	Conversion (%)
a	methyl-NH_2	91	>98
b	benzyl-NH_2	81	>98
c	phenethyl-NH_2	75	>98
d	*p*-methoxybenzyl-NH_2	77	>98
e	allyl-NH_2	80	84
f	*iso*-butyl-NH_2	81	96
g	*sec*-butyl-NH_2[b]	95	56
h	*iso*-propyl-NH_2[b]	86	86
i	naphthalenemethyl-NH_2[b]	84	86
j	cyclopropyl-NH_2	93	77
k	β-alanine ethyl ester[c]	88	>98
l	*n*-dodecyl-NH_2	72	>98
m		93	>98
n		100	91
o	Fmoc-nipecotic acid	83	>98
p	Fmoc-β-alanine	81	>98

[a] Compounds **6o** and **6p** were obtained by standard peptide couplings of the Fmoc-nipecotic acid and Fmoc-β-alanine, respectively to **3b** (see Supporting Information). [b] 72 h reaction time. [c] Amine used as HCl salt with an excess of $NaHCO_3$ added to the reaction.

Table 4. Preparation of Trimer 10 by Seven-Step SPOS from Wang's Resin

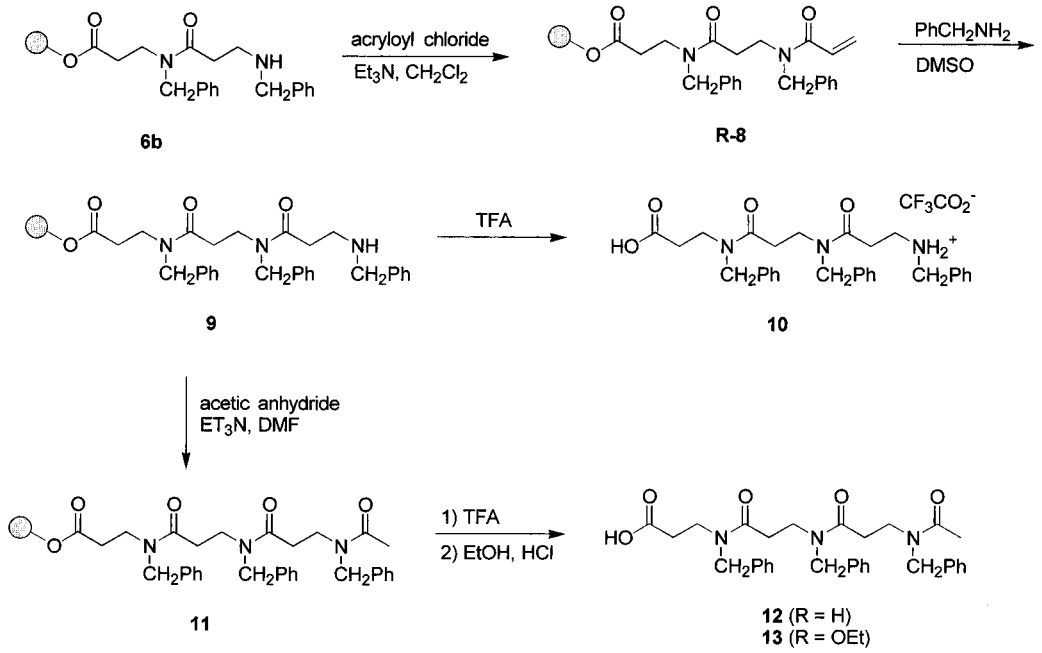
run	addition[a]	acylation[b]	yield[c] (%)	purity[d] (%)
1	DMF	1.5 equiv of acryloyl chloride, 2 equiv of TEA, CH_2Cl_2	73	67
2	DMSO	10 equiv of acrylic acid, 13 equiv of DIC, CH_2Cl_2	54	50
3	DMSO	2 equiv of acryloyl chloride, 3 equiv of TEA, CH_2Cl_2	67	91

[a] Solvent employed for addition of **b** to acrylate resin **2** and acrylamide resins **5** and **8**. [b] Reaction conditions for acylation of resins **3b** and **6b**. TEA, triethylamine; DIC, diisopropylcarbodiimide. [c] Calculated on the basis of recovery of material and the loading of Wang's resin. [d] Based on reversed-phase HPLC.

apparent masses corresponding to products from both 1,2 and 1,4 addition of amines to acrylic acid on acylation of both **3b** and **6b**.[35] In the case of acid chloride-mediated amide bond formation (Table 4, run 3), the cross-linked products were greatly reduced and the overall purity of the tri-β-peptoid **10** for the seven step sequence was >90%. Thus, acryloyl chloride was chosen as the acylating agent in amide bond formation reactions for library synthesis.

Resin-bound products **3**−**9** were identified by a combination of FT-IR microspectroscopy,[32] direct NMR cleavage, and elemental analysis. The microspectroscopy FTIR method allows analysis of a single bead of the resin and eliminates the need to prepare a KBr pellet. As a result, it is much easier to obtain meaningful results in the OH stretch region (3200−3600 cm^{-1}), which is often obscured by adventitious water in the KBr pellet. Conversion to acrylate resin **2** was easily detected by the presence of the carbonyl stretch at 1725 cm^{-1} for the ester group and the loss of the OH stretch vibration of Wang's resin at 3250 cm^{-1} (Figure 1). The acrylamide (*R*)-**5** is detected by the ester carbonyl at 1733 cm^{-1} and the amide at 1652 cm^{-1}. After addition of an amine to **2**, a

Scheme 3

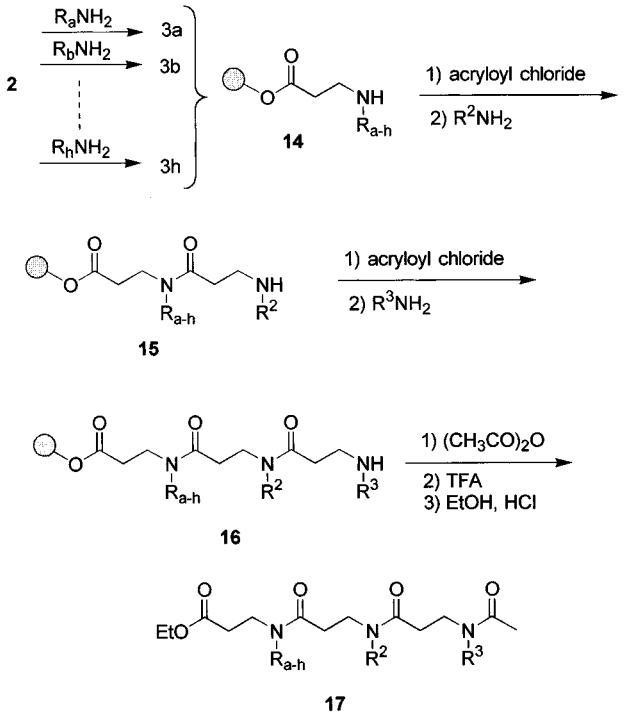


shift in the ester carbonyl stretch from 1725 to 1733 cm^{-1} was observed due to loss of α,β-unsaturation. For trimer **9** we observed a carbonyl stretch for the ester at 1733 cm^{-1} and for the two amides at 1646 cm^{-1}. The amide stretch was nearly twice as intense as that observed for (*R*)-**5** supporting the presence of two amide carbonyl groups.

Intermediates **3**−**9** in the preparation of trimer **10** were cleaved from the resin with TFA−water (95:5) and purified for characterization in the usual manner. *N*-Benzyl-β-alanine **4b** was purified by recrystallization as its TFA salt in 63% yield. The three remaining intermediates (**5**, **7b**, and **8**) and the final product **10** were purified by reversed-phase chromatography. The two conformers for **5** provide sharp ^1H NMR signals (400 MHz) in DMSO solution at room temperature and coalesce at about 75 °C. Diamides from (*R*)-**8** and **9** have, as expected, more than two identifiable conformers in solution. Overall yields were measured for the intermediates **3b**−**9** and for the final product **10** based on the initial loading of the Wang's resin. In a separate run, 10 g of Wang's resin was carried through the seven-step sequence to provide 4.91 g (95%) of the final trimer product **10**. For library synthesis, we prepared a number of acetylated derivatives. Acylation of **9** provided *N*-acetyl **11**, which on cleavage gave the *N*-acetyl trimer **12**, which was further esterified to obtain the *N*-acetyl ethyl ester **13**.

With the availability of 14 amines that can be incorporated into the submonomer synthesis and two amino acids as their Fmoc derivatives, a total of 16 mono-β-peptoids can be used in the synthesis of a trimer library. From the mono-β-peptoid subset a total of 4096 trimer, 256 dimer, and 16 mono-β-peptoids are possible. Since we wished to include intermediates in the synthetic pathway in our final library, there exist an additional 256 acryloyl dimers and 16 acryloyl mono-β-peptoids. The total library of all possible trimers, dimers, mono-β-peptoids, and their intermediates includes 4640 compounds. To display these compounds in a format suitable for our biological screens, we designed a mixture or pooled synthesis consisting a total of eight compounds

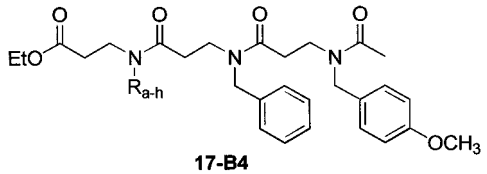
Scheme 4



per individual pool or vessel. For this library, mixtures of eight components require 256 separate mixtures for testing, to accommodate all possible combinations, which were in a 96-well format. The position of a compound in the 96-well plate determines two of the three substitutients of the tri-β-peptoid.

By mixing equimolar amounts of resins at the appropriate stage of synthesis, the final composition of a mixture can be controlled. To obtain final mixtures of eight components, each of the individual resins **3a**−**h** were prepared and equimolar amounts mixed to provide resin mixture **14** (Scheme 4). This mixture was treated with acryloyl chloride to afford the acrylamide followed by treatment with a second amine R_2NH_2 to give **15**. By

Table 5. Analysis of the Eight Components of Mixture 17-B4 by LC/MS[a]



17-B4

entry	R_{a-h}	HPLC retention time (t_R, min)	molecular ion (M + 1)
a	CH_3	10.05	526
b	benzyl	17.38	602
c	phenethyl	18.57	616
d	*p*-methoxybenzyl	16.87	632
e	allyl	13.48	552
f	isobutyl	16.17[b]	568
g	*sec*-butyl	16.17[b]	568
h	isopropyl	14.07	554

[a] The mixture **17-B4** was separated on a Vydac C18 HPLC column (250 × 4.6 cm i.d.) and the eluant analyzed by positive ESI-MS. Flow rate, 1 mL/min; mobile phase, 35% CH_3CN/H_2O with 0.1% TFA in the aqueous phase; after 1 min a linear gradient began at 35% CH_3CN/H_2O reaching 60% CH_3CN/H_2O at 20 min followed by a second linear gradient to 80% CH_3CN/H_2O at 30 min. The mass spectrometer scanned 250−700 Da every 2 s. Listed molecular ion indicates the base peak. The mass spectrum of each compound is included in the Supporting Information. [b] Chromatographic peaks for isomeric entries f and g nearly coelute, although some separation is detected. Since the products have identical mass, absolute assignments of the closely eluting peaks were not made.

employing an excess of the amine, each individual Michael addition reaction can be driven to completion regardless of the relative reactivity of the amine with the individual acrylamide resins. This affords a new mixture of eight resins having amines **a**−**h** at the first position and an individual amine at the second R_2 position of the di-β-peptoid. The sequence of acylation−Michael addition was repeated with a third amine R_3NH_2 to give resin-bound tri-β-peptoid **16**. Individual samples obtained from the library after cleavage from the resin were analyzed by LC/MS and by HPLC to determine the extent of conversion of the dimer precursors **15** to the desired trimers **16**. Acylation of **16** and cleavage from the resin provided the acylated trimeric β-peptoids, which were esterified to provide *N*-acetyl ethyl esters **17**. Evaluation of sample **17-B4** by LC/MS provided separation of all eight components and validation of the expected molecular weights for each product (Table 5). One extra peak was detected in similar concentration to the other eight and tentatively identified based on its molecular weight as a cross-linked product from addition of an amine to two adjacent acrylamide chains on the polymer resin. Since two of the components (Table 5, entries f and g) are isomeric, we could only assign six of the peaks. Clearly, it is advantageous to choose components of different molecular weight in order to allow definitive assignment of all components by LC/MS.

The acylation−Michael addition sequence is amenable to a wide range of compounds and functional types allowing the design of specific β-peptoid libraries with desired functionality. The conditions are compatible with standard solid-phase peptide coupling allowing the incorporation of N-substituted β-alanines in peptides. We have demonstrated the use of this method for the synthesis of a librariy of over 4000 trimeric β-peptoids and their acetylated derivatives. In addition, we have shown the scope of addition of primary amines to polymer-bound acrylates and acrylamides. Investigations into the properties of novel β-peptoids and preparation of libraries of these compounds are in progress.

Experimental Section

General Procedures.[36] Polymer-supported reactions were carried out using flasks fitted with a glass frit at the bottom and a sidearm connected to a needle-valve (Aldrich, Z28,330-4). Prior to carrying out reactions, the polymer-bound starting material was allowed to swell in the reaction solvent for 30−60 min in an inert atmosphere. Wang or *p*-alkoxybenzyl alcohol resin[31] was obtained from Advanced ChemTech (Louisville, KY) and Chem-Impex International (Wood Dale, IL). Preparative and analytical reversed-phase liquid chromatographic separations used aqueous 0.1% TFA/acetonitrile as the eluant. Mass spectra were obtained by positive ion electrospray ionization LC/MS.

FT-IR Microspectroscopy. The samples were prepared for analysis by transferring sample with a stainless steel probe onto a clean microscope slide. A roller knife was then used to flatten the sample. One bead of sample was then transferred onto a KBr chip using a tungsten probe. Each spectrum was recorded at 4 cm^{-1} resolution on a Nicolet 800 Fourier transform interferometer equipped with a Spectra-Tech IR plan microscope. The spectra analyzed clearly showed the expected bands for the polystyrene polymer. The frequencies reported are indicative of the polymer-bound product.

Direct Cleavage of Resins for ^{1}H NMR Analysis and Determination of Polymer Loading. A standard solution 100 mL of 9.8 mM hexamethyldisiloxane (HMDS) in TFA/$CDCl_3$ (1:1) was prepared and used for all of the evaluations of polymeric loading. The molarity of the solution was evaluated over time to determine stability of the stock solution by treating a weighed amount (about 20 mg) of 4-hydroxybenzaldehyde with 1.00 mL of 9.8 mM HMDS. Measurement of the ^{1}H NMR integral of the HMDS peak (0.421 ppm) relative to that of either the aromatic or aldehyde resonances of 4-hydroxybenzaldehyde allowed an independent measure of the molarity of the HMDS solution. For determination of polymer loadings, a weighed amount of polymer (100 mg) was treated with 1.00 mL of 9.8 mM HMDS and allowed to shake for 30 min. The filtrate was collected and the resin washed three times with a minimal amount of $CDCl_3$. The filtrates were combined and placed in an NMR tube for direct evaluation of purity of the cleaved product and measurement of loading of the polymeric resin. Chemical shift of HMDS (0.421 ppm) in this solvent mixture was determined by comparison to added TMS. Loadings by this method are indicated for the cleaved products from resins as NMR loading.

Acrylate−Wang Resin (2). A slurry of 1.0 kg (0.88 mol) of Wang resin and 7.0 L of CH_2Cl_2 in a 12 L three-necked round-bottom flask was stirred with an overhead stirrer for 1 h. The mixture was treated with 0.36 L (2.6 mol) of triethylamine followed by the dropwise addition of 143 mL (1.76 mol) acryloyl chloride over 20 min, maintaining the temperature below 30 °C. After addition was complete, the resin was stirred for an additional 2 h at room temperature. The resin was filtered using a gas dispersion tube and vacuum trap and subsequently washed three times with CH_2Cl_2. The reaction was repeated to ensure completeness using the same amount of reagents and 4 L of CH_2Cl_2. After being stirred for an additional 2 h, the resin was filtered and washed three times with CH_2Cl_2, three times with MeOH, and three times with DMF. Unreacted polymer-bound hydroxyl groups were capped by reaction with acetic anhydride (166 mL, 1.76 mol) and triethylamine (244 mL, 1.76 mol) in DMF (2 L) for 1 h at room temperature. The resin was filtered and washed three times each with DMF, MeOH, and CH_2Cl_2, transferred to a Buchner

(36) Details of the general procedures can be found in the following: Hamper, B. C.; Leschinsky, K. L.; Massey, S. S.; Bell, C. L.; Brannigan, L. H.; Prosch, S. D. *J. Agric. Food Chem.* **1995**, *43*, 219−228. Hamper, B. C.; Kurtzweil, M. L.; Beck, J. P. *J. Org. Chem.* **1992**, *57*, 5680−5686.

funnel, washed three times with Et_2O, and dried in vacuo to yield 1.09 kg of yellow polymeric solid. Theoretical loading: 0.84 mequiv/g FTIR (microscope): 1725 cm^{-1} (C═O). Direct cleavage of 54.2 mg of resin provided an NMR loading of 0.88 mequiv/g: ^1H NMR ($CDCl_3$/TFA) δ 5.74 (m, 2H), 6.20 (dd, J = 16.8, 1.6 Hz, 1H).

Preparation of N-Substituted β-Alanine−Wang Resins 3. *N*-Benzyl-β-alanine−Wang Resin (3b) and *N*-Benzyl-β-alanine·TFA Salt (4b). A slurry of acrylate resin **2** (10 g, 8.4 mmol) and 30 mL of anhyd DMSO was prepared in a 250 mL polymer synthesis flask and treated with 5.5 mL (50.4 mmol) of benzylamine. The resin was stirred at rt for 48 h, filtered, and washed three times each with 50 mL of DMF, 50 mL of MeOH, 50 mL of CH_2Cl_2, and 50 mL of Et_2O. The resin was dried in vacuo to yield 10.65 g of **3b**: FTIR (microscope) 1733 cm^{-1} (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{26}H_{27}N_1O_3)_{0.105}$: N, 1.09. Found: N, 0.88. Cleavage of 0.132 g of resin afforded 34.2 mg (quant) of **4b** as a clear oil (lit.[24] mp 182−183 °C (free amine)): ^1H NMR ($CDCl_3$/TFA) δ 2.96 (t, J = 5.7 Hz, 2H), 3.42 (brd s, 2H), 4.35 (brd s, 2H), 7.42 (m, 5H), 7.67 (brd s, 2H); NMR loading: 0.79 mequiv/g.

***N*-Methyl-β-alanine·TFA Salt (4a).** The resin was prepared by addition of anhyd 2 M CH_3NH_2 in DMSO to the acrylate resin **2** by the general method. A yellow-white resin was obtained: IR (KBr) 1733 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{20}H_{23}N_1O_3)_{0.105}$: N, 1.16. Found: N, 0.88. Direct cleavage of 0.0975 g of resin with 1.0 mL of 9.8 mM hexamethyldisiloxane in TFA:$CDCl_3$ (1:1) by the general method and measurement of the ^1H NMR of the collected cleavage solution provided measurement of loading of the resin of 0.57 mequiv/g. Concentration of the combined cleavage filtrates in vacuo gave 14.7 mg (72.9%) of a clear, yellow oil (lit.[37]): ^1H NMR ($CDCl_3$/TFA) δ 2.94 (t, J = 5.6 Hz), 3.00 (t, J = 5.9 Hz), 3.45 (m, 2H), 7.50 (brs, 1H).

***N*-Phenethyl-β-alanine·TFA Salt (4c).** A yellow-white resin was obtained: IR (KBr) 1739, 1734 and 1718 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{27}H_{29}N_1O_3)_{0.105}$: N, 1.08. Found: N, 1.16. Cleavage of 0.127 g of resin afforded 23.8 mg (80.5%) of a clear oil (lit.[38]): ^1H NMR ($CDCl_3$) δ 2.93 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 3.48 (m, 4H), 7.34 (m, 7H).

***N*-(4-Methoxybenzyl)-β-alanine·TFA Salt (4d).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{27}H_{29}N_1O_4)_{0.105}$: N, 1.06. Found: N, 1.02. Cleavage of 0.131 g of resin afforded 25.0 mg (78.1%) of a clear oil: ^1H NMR ($CDCl_3$/TFA) δ 2.96 (t, J = 5.9 Hz, 2H), 3.41 (pent, J = 6.3 Hz, 2H), 3.90 (s, 3H), 4.30 (t, J = 5.4 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.60 (brd s, 2H); HRMS (EI) m/z calcd for $(C_{11}H_{15}NO_3)$ 209.1052, found 209.0994.

***N*-Allyl-β-alanine·TFA Salt (4e).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{22}H_{25}N_1O_3)_{0.105}$: N, 1.13. Found: N, 1.13. Cleavage of 0.138 g of resin afforded 20.1 mg (75.1%) of a clear oil (lit.[39]): ^1H NMR ($CDCl_3$) δ 2.99 (t, J = 5.9 Hz, 2H), 3.43 (m, 2H), 3.80 (m, 2H), 5.60 (m, 2H), 5.90 (m, 1H), 7.44 (brd s, 2H).

***N*-Isobutyl-β-alanine·TFA Salt (4f).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{23}H_{29}N_1O_3)_{0.105}$: N, 1.12. Found: N, 1.17. Cleavage of 0.101 g of resin afforded 18.1 mg (87.8%) of a clear oil (lit.[23] mp 160 °C (free base)): ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 6H), 2.07 (m, 1H), 3.01 (m, 4H), 3.44 (t, J = 6.3 Hz, 2H), 7.27 (brd s, 2H).

***N*-*sec*-Butyl-β-alanine·TFA Salt (4g).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{23}H_{29}N_1O_3)_{0.105}$: N, 1.12. Found: N, 1.11. Cleavage of 0.098 g of resin afforded 17.1 mg (85.4%) of a clear oil: ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3H), 1.41 (d, J = 6.6 Hz, 3H), 1.70 (m, 1H), 1.84 (m, 1H), 3.00 (t, J = 5.9 Hz, 2H), 3.40 (m, 3H), 7.11 (brd s, 2H); HRMS (EI) m/z calcd for $(C_7H_{15}NO_2)$ 145.1103, found 145.1107.

***N*-Isopropyl-β-alanine·TFA Salt (4h).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{22}H_{27}N_1O_3)_{0.105}$: N, 1.13. Found: N, 1.15. Cleavage of 0.099 g of resin afforded 18.4 mg (95.7%) of a clear oil (lit.[40] mp 165−166 °C (free base)): ^1H NMR ($CDCl_3$) δ 1.44 (d, J = 6.6 Hz, 6H), 2.98 (t, J = 6.0 Hz, 2H), 3.43 (m, 2H), 3.57 (m, 1H), 7.10 (brd s, 2H).

***N*-Methyl-1-naphthalene-β-alanine·TFA Salt (4i).** A yellow-white resin was obtained: IR (KBr) 1732 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{30}H_{29}N_1O_3)_{0.105}$: N, 1.05. Found: N, 1.02. Cleavage of 0.126 g of resin afforded 28.9 mg (90.0%) of a clear oil: ^1H NMR ($CDCl_3$) δ 2.94 (t, J = 6.0 Hz, 2H), 3.48 (pent, J = 3.2 Hz, 2H), 4.86 (t, J = 5.5 Hz, 2H), 7.60 (m, 4H), 7.85 (brs, 2H), 7.95 (m, 3H); HRMS (EI) m/z calcd for $(C_{14}H_{15}NO_2)$ 229.1103, found 229.1068.

***N*-Cyclopropyl-β-alanine·TFA Salt (4j).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{22}H_{25}N_1O_3)_{0.105}$: N, 1.13. Found: N, 1.16. Cleavage of 0.136 g of resin afforded 19.8 mg (74.7%) of a clear oil: ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 5.6 Hz, 4H), 2.82 (pent, J = 5.6 Hz, 1H), 2.99 (t, J = 6.0 Hz, 2H), 3.57 (pent, J = 6.2 Hz, 2H), 7.36 (brd s, 2H); HRMS (EI) m/z calcd for $(C_6H_{11}NO_2)$ 129.0790, found 129.0802.

***N*-β-Alanine Ethyl Ester-β-alanine·TFA Salt (4k).** A yellow-white resin was obtained: IR (KBr) 1732 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{24}H_{29}N_1O_5)_{0.105}$: N, 1.08. Found: N, 0.69. Cleavage of 0.100 g of resin afforded 18.9 mg (81.8%) of a clear oil (lit.[41]): ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.2 Hz, 3H), 2.94 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 5.9 Hz, 2H), 3.49 (m, 4H), 4.26 (q, 2H), 7.79 (brd s, 2H).

***N*-Dodecyl-β-alanine·TFA Salt (4l).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{31}H_{45}N_1O_3)_{0.105}$: N, 1.02. Found: N, 0.94. Cleavage of 0.141 g of resin afforded 28.1 mg (74.7%) of a clear oil (lit.[24] mp 82−83 °C (free base)): ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.3 Hz, 3H), 1.28−1.36 (m, 18H), 1.76 (m, 2H), 2.99 (t, J = 6.0 Hz, 2H), 3.21 (m, 2H), 3.46 (m, 2H), 7.27 (brs, 2H).

***N*-(3-Aminopropyl)-β-alanine·Bis-TFA Salt (4m).** A yellow-white resin was obtained: IR (KBr) 1734 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{19}H_{29}N_2O_5)_{0.105}$: N, 2.07. Found: N, 1.98. To 0.146 g of dried resin was added 2.0 mL of 95:5 TFA−water and the slurry agitated for 1 h. The filtrate was collected, the resin was washed with 50:50 TFA−CH_2Cl_2 and twice with CH_2Cl_2, and the combined filtrates were dried in vacuo to afford 42.6 mg (quant = 39.9 mgs) of a clear oil (lit.[42]): ^1H NMR ($CDCl_3$) δ 2.38 (m, 2H), 3.00 (t, J = 5.9 Hz, 2H), 3.37 (m, 4H), 3.50 (m, 2H), 7.09 (brs, 3H), 7.62 (brs, 2H).

***N*-(3-Hydroxypropyl)-β-alanine·TFA Salt (4n).** A yellow-white resin was obtained: IR (KBr) 1732 (C═O). Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{28}H_{41}N_1O_4Si)_{0.105}$: N, 1.02. Found: N, 0.98. To 0.187 g of dried resin was added 2.0 mL of 95:5 TFA−water and the slurry agitated for 1 h. The resin was washed three times with CH_2Cl_2, and the combined filtrates were dried in vacuo to give a mixture of the free hydroxy compound **4n** and its trifluoroacetate derivative. The residue was treated with 5% aqueous HCl for 2 h and the resultant mixture concentrated and dried in vacuo to afford 19.8 mg (55.9%) of a yellow oil (lit.[43] mp 132 °C (free base)): ^1H NMR (DMSO-d_6) δ 1.76 (m, 2H), 2.69 (t, J = 6.6 Hz, 2H), 2.94 (t, J = 7.3 Hz), 3.07 (t, J = 7.3 Hz, 2H), 3.36 (brs, 2H), 3.47 (t, J = 5.9 Hz, 2H), 8.90 (brs, 1H).

***N*-2-Methylbutyl-β-alanine·TFA Salt (4q).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{24}H_{31}N_1O_3)_{0.105}$: N, 1.10. Found: N, 1.21. Cleavage of 0.098 g of resin afforded 20.6 mg (98.1%) of a clear oil: ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H),

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1.30 (m, 1H), 1.45 (m, 1H), 1.84 (m, 1H), 2.99 (m, 3H), 3.14 (m, 1H), 3.45 (m, 2H), 7.27 (brd s, 2H); HRMS (EI) *m/z* calcd for ($C_8H_{17}NO_2$) 159.1259, found 159.1253.

***N*-*β*-Methyl-3-(chlorobenzyl)-*β*-alanine·TFA Salt (4r).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{27}H_{28}N_1O_3Cl)_{0.105}$: N, 1.05. Found: N, 1.25. Cleavage of 0.097 g of resin afforded 31.4 mg (quant) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.77 (d, J = 6.9 Hz, 3H), 2.92 (m, 2H), 3.21 (m, 1H), 3.32 (m, 1H), 4.44 (m, 1H), 7.41 (m, 4H), 7.92 (brd s, 2H); HRMS (EI) *m/z* calcd for ($C_{11}H_{14}NO_2Cl$) 227.0713, found 227.0700.

***N*-Cyclohexyl-*β*-alanine·TFA Salt (4s).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{25}H_{31}N_1O_3)_{0.105}$: N, 1.09. Found: N, 1.35. Cleavage of 0.135 g of resin afforded 28.6 mg (95.4%) of a clear oil (lit.[24] mp 170−171 °C (free base)): ^{1}H NMR ($CDCl_3$/TFA) d 1.26 (m, 2H), 1.38 (m, 3H), 1.75 (d, J = 13.3 Hz, 2H), 1.93 (d, J = 13.3 Hz, 2H), 2.12 (d, J = 12.0 Hz, 2H), 2.98 (t, J = 5.9 Hz), 3.20 (m, 1H), 3.44 (m, 2H), 7.12 (brs, 2H).

***N*-(Leucine methyl ester)-*β*-alanine·TFA Salt (4t).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{26}H_{33}N_1O_5)_{0.105}$: N, 1.06. Found: N, 0.53. Direct cleavage of 0.1548 g of resin with 1.0 mL of 9.8 mM hexamethyldisiloxane in TFA:$CDCl_3$ (1:1) by the general method and measurement of the ^{1}H NMR of the collected cleavage solution provided measurement of loading of the resin of 0.19 mequiv/g. The NMR indicated a 67:33 ratio of acrylic acid to **4t**. Concentration of the combined cleavage filtrates in vacuo gave 17.1 mg (44.5%) of a clear, yellow oil: ^{1}H NMR ($CDCl_3$/TFA) δ 1.00 (d, J = 6.3 Hz), 1.73−1.93 (m, 3H), 3.06 (m, 2H), 3.54 (brs, 2H), 3.95 (s, 3H), 4.13 (m, 1H), 7.83 (brs, 1H); HRMS (ESI^+) *m/z* calcd for MH^+ ($C_{10}H_{20}NO_4$) 218.1392, found 218.1383.

***N*-(Methyldiphenyl)-*β*-alanine·TFA Salt (4u).** A yellow-white resin was obtained. Anal. Calcd for $(C_8H_8)_{0.895}$ + $(C_{32}H_{31}N_1O_3)_{0.105}$: N, 1.03. Found: N, 0.82. Direct cleavage of 0.1223 g of resin with 1.0 mL of 9.8 mM hexamethyldisiloxane in TFA:$CDCl_3$ (1:1) by the general method and measurement of the ^{1}H NMR of the collected cleavage solution provided measurement of loading of the resin of 0.41 mequiv/g. The NMR indicated a 45:55 ratio of acrylic acid to **4u**. Concentration of the combined cleavage filtrates in vacuo gave 23.9 mg (72.5%) of a clear, yellow oil (lit.[44]): ^{1}H NMR ($CDCl_3$/TFA) δ 2.99 (t, J = 6.0 Hz, 2H), 3.46 (pent, J = 6.2 Hz, 2H), 5.47 (t, J = 6.5 Hz, 1H), 7.43 (m, 10H), 8.17 (brd s, 2H).

***N*-Benzyl-*β*-alanine·TFA Salt.** Polymer-bound *N*-benzyl-*β*-alanine **4b** (1.00 g, 0.77 mmol) was slurried with 10 mL of 95% TFA/H_2O in a 75 mL peptide synthesis flask, and the mixture was agitated for 1 h at rt. The resin was filtered and washed three times with 50% TFA/CH_2Cl_2 and three times with CH_2Cl_2. The combined filtrates were concentrated in vacuo to afford 198 mg of a dark yellow oil (88%). ^{1}H NMR of the crude material showed the desired product with a minor impurity. Recrystallization of the crude from chloroform yielded 142 mg (63%) of an off-white solid: mp 91−96 °C; ^{1}H NMR (acetone-d_6) δ 2.87 (t, J = 6.6 Hz, 2 H), 3.34 (t, J = 6.8 Hz, 2 H), 4.37 (s, 2 H), 7.35−7.45 (m, 3 H), 7.55−7.60 (m, 2 H); ^{13}C NMR (acetone-d_6) δ 30.63, 43.42, 51.60, 129.71, 130.02, 130.87, 132.42, 173.06; MS (FAB) *m/z* 180 (M + 1). Anal. Calcd for $C_{10}H_{13}NO_2$?$C_2H_1F_3O_2$: C, 49.15; H, 4.81; N, 4.78. Found: C, 49.15; H, 4.78; N, 4.72.

***N*-Acryloyl-*N*-benzyl-*β*-alanine−Wang Resin (R-5).** Polymer-bound *N*-benzyl-*β*-alanine **4b** (9.64 g, 7.43 mmol) was placed in a 250 mL solid-phase synthesis flask and treated with 70 mL of CH_2Cl_2. To the stirred slurry was added 3.1 mL of triethylamine (22.3 mmol), followed by dropwise addition of 1.21 mL of acryloyl chloride (14.9 mmol). A slight warming and a darkening of the slurry were noted. After being mixed at rt for 2 h, the resin was filtered and washed three times with 50 mL of CH_2Cl_2. The treatment with acryloyl chloride (1.21 mL, 14.9 mmol) and triethylamine (3.10 mL, 22.3 mmol) in CH_2Cl_2 (70 mL) was repeated and the slurry allowed to stir for an additional 1 h. The resin was filtered and washed three times each with 50 mL of DMF, 50 mL of MeOH, 50 mL of CH_2Cl_2, and 50 mL of Et_2O: IR (microscope) 1733 (C=O, ester) and 1652 cm^{-1} (C=O, amide).

***N*-Acryloyl-*N*-benzyl-*β*-alanine.** Polymer-bound *N*-acryloyl-*N*-benzyl-*β*-alanine **R-5** (1.60 g, 1.18 mmol) was cleaved as described for *N*-benzyl-*β*-alanine·TFA salt to yield 266.8 mg of a dark yellow oil (97% crude yield). Purification by preparative chromatography (reversed-phase C18, 35% CH_3CN/H_2O) yielded 144.8 mg (53%) colorless oil: ^{1}H NMR ($CDCl_3$) mixture of two conformers in ratio of ca. 1:1.8: d 2.53 (t, J = 7.2 Hz, 2 H, minor conformer), 2.67 (t, J = 6.8 Hz, 2 H, major conformer), 3.61 (t, J = 7.4 Hz, 2 H, minor conformer), 3.66 (t, J = 6.8 Hz, 2 H, major conformer), 4.66 (s, 2 H), 5.68 (d, J = 10 Hz, 1 H, major conformer), 5.76 (d, J = 10.8 Hz, 1 H, minor conformer), 6.39 (br t, J = 17.0 Hz, 1 H), 6.51 (dd, J = 10.2, 16.6 Hz, 1 H, major conformer), 6.65 (dd, J = 10.4, 16.8 Hz, 1 H, minor conformer), 7.13−7.35 (m, 5 H), 8.40 (br s, 1 H); ^{13}C NMR ($CDCl_3$) mixture of two conformers δ 32.54, 33.59, 42.67, 43.16, 48.99, 52.24, 126.34, 127.03, 127.20, 127.52, 127.75, 128.03, 128.62, 128.89, 129.33, 129.47, 136.33, 136.84, 166.94, 167.57, 174.40, 175.83; MS (FAB) 234 *m/z* (M + 1). Anal. Calcd for $C_{13}H_{15}NO_3$·0.13 $C_2HF_3O_2$: C, 64.27; H, 6.16; N, 5.66. Found: C, 64.29; H, 6.16; N, 5.51.

General Procedure for Addition of Amines to R-5. A slurry of 0.30 g (0.22 mmol) of resin **R-5** in 2 mL of DMSO was allowed to stir for 30 min. The resin was filtered, treated with 4.5 mmol (20 equiv) of amine in 2 mL of DMSO, and heated to 50 °C for 24 h. After the mixture was allowed to cool, the resin was washed three times each with 3 mL of DMF, 3 mL of MeOH, 3 mL of CH_2Cl_2, and 3 mL of Et_2O and dried in vacuo. A small sample of each resin was submitted for elemental analysis and the remainder (0.20 mmol) treated with 95% TFA/H_2O for 1 h at rt. The resin was washed three times with 50% TFA/CH_2Cl_2, and the combined filtrates were concentrated and dried in vacuo.

General Procedure for Coupling of Fmoc-Protected Amino Acids to 3b. A slurry of 0.30 g (0.22 mmol) of resin **3b** in 2 mL of NMP was allowed to stir for 30 min. The resin was treated with 0.7 mmol (3 equiv) of Fmoc-amino acid, 0.31 g of BOP (0.7 mmol, 3 equiv), 109 mg of HOBt-H_2O (0.7 mmol, 3 equiv), and 0.2 mL of triethylamine (1.4 mmol, 6 equiv). The reaction was allowed to stir for 2 h, filtered, and washed three times each with 3 mL of DMF, 3 mL of MeOH, and 3 mL of DMF. The resin was then treated with 20% piperidine/DMF solution and allowed to stir for 30 min, filtered, washed three times each with 3 mL of DMF, 3 mL of MeOH, 3 mL of CH_2Cl_2, and 3 mL of Et_2O, and dried in vacuo. A small sample of each resin was submitted for elemental analysis and the remainder (0.20 mmol) treated with 95% TFA/H_2O for 1 h at rt. The resin was washed three times with 50% TFA/CH_2Cl_2, and the combined filtrates were concentrated and dried *in vacuo*.

***N*-Methyl-*β*-alaninyl-N-benzyl-*β*-alanine·TFA Salt (7a).** Cleavage of the resin afforded 69 mg (91%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 2.54 (m, 5H), 2.58 and 2.73 (pair of multiplets, 2H), 3.11 (pent, J = 6.0 Hz, 2H), 3.42 (m, 2H), 4.53 and 4.58 (pair of singlets, 2H), 7.25 (m, 5H), 8.50 (brs, 2H); HRMS (EI) *m/z* calcd for ($C_{14}H_{20}N_2O_3$) 264.1474, found 264.1483.

***N*-Phenethyl-*β*-alaninyl-*N*-Benzyl-*β*-alanine·TFA Salt (7c).** Cleavage of the resin afforded 70 mg (75%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 2.50 (m, 2H), 2.60−2.95 (m, 4H), 3.17 (m, 4H), 3.43 (t, J = 7.2 Hz, 2H), 4.53 and 4.59 (pair of singlets, 2H), 7.15−7.55 (m, 10H), 8.70 (br s, 2H); HRMS (EI) *m/z* calcd for ($C_{21}H_{26}N_2O_3$) 354.1943, found 354.1970.

***N*-(4-Methoxybenzyl)-*β*-alaninyl-*N*-Benzyl-*β*-alanine·TFA Salt (7d).** Cleavage of the of resin afforded 75 mg (77%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 2.40−2.59 (m, 4H), 3.00−3.17 (m, 2H), 3.40 (t, J = 7.2 Hz, 2H), 3.73 and 3.74 (pair of singlets, 3H), 4.03−4.20 (m, 2H), 4.52 and 4.56 (pair of singlets, 2H), 6.96 (m, 2H), 7.17−7.50 (m, 5H), 8.81 (br s, 2H); HRMS (EI) *m/z* calcd for ($C_{21}H_{26}N_2O_4$) 370.1892, found 370.1841.

***N*-Allyl-*β*-alaninyl-*N*-benzyl-*β*-alanine·TFA Salt (7e).** Cleavage of the resin afforded 65 mg (80%) of a clear oil: ^{1}H

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NMR (DMSO-d_6/TFA) δ 2.46 (m, 2H), 2.75 and 2.90 (multiplets, 2H), 3.10 (m, 2H), 3.42 (t, J = 7.5 Hz), 3.58 (m, 2H), 4.53 and 4.71 (pair of singlets, 2H), 5.30−5.50 (m, 2H), 5.75−5.95 (m, 1H), 7.15−7.55 (m, 5H), 8.80 (br s, 2H); HRMS (EI) m/z calcd for ($C_{16}H_{22}N_2O_3$) 290.1630, found 290.1632.

***N*-Isobutyl-β-Alaninyl-*N*-benzyl-β-alanine·TFA Salt (7f).** Cleavage of the resin afforded 68 mg (81%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 0.86−0.93 (m, 6H), 1.92 (m, 1H), 2.38−2.95 (m, 6H), 3.12 (m, 2H), 3.42 (t, J = 7.3 Hz, 2H), 4.53 and 4.58 (pair of singlets, 2H), 7.12−7.55 (m, 5H), 8.43 (br s, 2H); HRMS (EI) m/z calcd for ($C_{17}H_{26}N_2O_3$) 306.1943, found 306.1933.

***N*-*sec*-Butyl-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7g).** Cleavage of the resin afforded 69 mg (82%) of a clear oil: ^{1}H NMR ($CDCl_3$/TFA) δ 1.04 (m, 3H), 1.41 (m, 3H), 1.68 (m, 1H), 1.84 (m, 1H), 2.74 (brs, 2H), 3.02 and 3.14 (pair of multiplets, 2H), 3.24−3.44 (m, 3H), 3.72 and 3.79 (pair of triplets, 2H, J = 6.4 Hz), 4.64 (s, 2H), 7.12−7.40 (m, 5H); ^{1}H NMR (DMSO-d_6/TFA) δ 0.87 (q, J = 6.0 Hz, 3H), 1.17 (t, J = 7.5 Hz), 1.45 (m, 1H), 1.70 (m, 1H), 2.50 (m, 2H), 2.72 and 2.83 (pair of multiplets, 2H), 3.08 (m, 2H), 3.43 (t, J = 7.2 Hz, 2H), 4.53 and 4.58 (pair of singlets, 2H), 7.12−7.55 (m, 5H), 8.40 (br s, 2H); HRMS (EI) m/z calcd for ($C_{17}H_{26}N_2O_3$) 306.1943, found 306.1924.

***N*-Isopropyl-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7h).** Cleavage of the resin afforded 70 mg (86%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 1.19 (t, J = 7.5 Hz, 6H), 2.38−2.60 (m, 2H), 2.72 and 2.85 (pair of multiplets, 2H), 3.10 (m, 2H), 3.28 (m, 1H), 3.43 (t, J = 7.3 Hz), 4.53 and 4.57 (pair of singlets, 2H), 7.18−7.55 (m, 5H), 8.41 (br s, 2H); HRMS (EI) m/z calcd for ($C_{16}H_{24}N_2O_3$) 292.1787, found 292.1786.

***N*-Methyl-1-naphthalene-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7i).** The reaction of **5** with 1-naphthylenemethylamine was carried out for 72 h. Cleavage of the resin afforded 92.5 mg (83%) of a clear oil: ^{1}H NMR ($CDCl_3$/TFA) δ 2.67 (t, 2H, J = 6.7 Hz), 2.96 and 3.18 (pair of triplets, 2H, J = 5.0 Hz), 3.47 and 3.61 (pair of singlets, 2H), 3.66 and 3.72 (pair of triplets, 2H, J = 6.6 Hz), 4.58 (s, 2H), 4.84 (m, 2H), 7.06 (m, 2H), 7.26−7.35 (m, 4H), 7.49−7.64 (m, 6H), 7.88 (brs, 2H), 7.96−8.02 (m, 2H); (DMSO-d_6/TFA) δ 2.46 (m, 2H), 2.78 and 2.94 (pair of triplets, J = 6.6 Hz, 2H), 3.31 (m, 2H), 3.44 (m, 2H), 4.53 and 4.57 (pair of singlets, 2H), 4.66 (m, 2H), 7.19−7.70 (m, 10H), 7.90−8.25 (m, 3H), 9.00 (br s, 2H); HRMS (EI) m/z calcd for ($C_{24}H_{26}N_2O_3$) 390.1943, found 390.1941.

***N*-Cyclopropyl-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7j).** Cleavage of the resin afforded 39.1 mg (93%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 0.61−0.80 (m, 4H), 2.40−2.53 (m, 2H), 2.65 (m, 1H), 2.70 and 2.89 (pair of triplets, J = 6.3 Hz, 2H), 3.23 (m, 2H), 3.45 (m, 2H), 4.53 and 4.57 (pair of singlets, 2H), 7.15−7.50 (m, 5H), 8.65 (br s, 2H); HRMS (EI) m/z calcd for ($C_{16}H_{22}N_2O_3$) 290.1630, found 290.1618.

***N*-β-(Alanine ethyl ester)-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7k).** Cleavage of the resin afforded 42.9 mg (88%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 1.15−1.25 (m, 3H), 2.40−2.97 (m, 6H), 3.10−3.35 (m, 4H), 3.46 (m, 2H), 4.12 (m, 2H), 4.57 and 4.62 (pair of singlets, 2H), 7.20−7.60 (m, 5H), 8.58 (br s, 2H); HRMS (EI) m/z calcd for ($C_{18}H_{26}N_2O_5$) 350.1841, found 350.1869.

***N*-Dodecyl-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7l).** Cleavage of the resin afforded 87 mg (72%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 0.84 (t, J = 6.7 Hz, 3H), 1.23 (brs, 18H), 1.57 (m, 2H), 2.48 (m, 2H), 2.75 (m, 1H), 2.90 (m, 3H), 3.16 (m, 2H, 3.46 (t, J = 7.3 Hz, 2H), 4.56 and 4.60 (pair of singlets, 2H), 7.22−7.48 (m, 5H), 8.60 (brs, 2H); HRMS (EI) m/z calcd for ($C_{25}H_{42}N_2O_3$) 418.3195, found 418.3220.

***N*-(3-Aminopropyl)-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7m).** Cleavage of the resin afforded 52.3 mg (93%) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 1.88 (m, 2H), 2.42−2.73 (m, 2H), 2.88 (m, 2H), 2.97 (m, 2H), 3.12 (m, 2H), 3.44 (t, J = 6.3 Hz, 2H), 4.57 and 4.62 (pair of singlets, 2H), 7.20−7.50 (m, 5H), 8.00 (br s, 3H), 8.68 (br s, 2H); HRMS (EI) m/z calcd for ($C_{16}H_{25}N_3O_3$) 307.1896, found 307.1881.

***N*-(3-Hydroxypropyl)-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7n).** Cleavage of the resin afforded 91 mg (quant) of a clear oil: ^{1}H NMR (DMSO-d_6/TFA) δ 1.70 (m, 2H), 2.47 (m, 2H), 2.72 and 2.88 (pair of multiplets, 2H), 2.95 (m, 2H), 3.11 (m, 2H), 3.45 (m 4H), 4.53 and 4.58 (pair of singlets, 2H), 7.10−7.44 (m, 5H), 8.30 (brs, 3H), 8.85 (brs, 2H); HRMS (EI) m/z calcd for ($C_{16}H_{24}N_2O_3$) 308.1736, found 308.1724.

Nipicotyl-*N*-benzyl-β-alanine·TFA Salt (7o). The entire quantity of resin was treated with TFA as described above to give 80 mg of crude **7o** as a dark yellow oil (83%). Purification by RP HPLC yielded 54.6 mg of pure **7o** as a colorless oil (57%): ^{1}H NMR ($CDCl_3$/TFA) δ 1.86 (m, 4H), 2.50−2.95 (m, 2H), 3.05−3.90 (m, 7H), 4.22−5.3 (m, 3H), 7.10−7.50 (m, 5 H), 8.00 (brs, 2H); HRMS (ESI) m/z calcd for ($C_{16}H_{22}N_2O_3$ + H) 291.1709, found 291.1721.

***β*-Alaninyl-*N*-benzyl-β-alanine·TFA Salt (7p).** A 150 mg quantity of resin was treated with TFA as described above to give 28 mg of crude **7p** as a dark yellow oil (81%). Purification by RP HPLC yielded 14.3 mg of pure **7p** as a colorless oil (41%): ^{1}H NMR ($CDCl_3$/TFA) δ 2.70−3.33 (m, 4H), 3.40−3.95 (m, 4H), 4.35 and 4.67 (pair of singlets, 2H), 7.14 (brs, 2 H), 7.30−7.50 (m, 5 H), HRMS (ESI) m/z calcd for ($C_{13}H_{18}N_2O_3$ + H) 251.1396, found 251.1375.

***N*-Benzyl-β-alaninyl-*N*-benzyl-β-alanine−Wang Resin (6b).** Polymer-bound acrylamide **5** (7.016 g, 5.19 mmol) was placed in a 100 mL two-necked polymer synthesis flask with an overhead stirrer and an N_2 inlet. Dry DMSO (20 mL) was added followed by 3.4 mL (31.2 mmol) benzylamine. The flask was immersed in an oil bath and heated to maintain a solution temperature of 50 °C for 48 h. After the mixture was allowed to cool, the resin was filtered and washed three times each with 50 mL of DMF, 50 mL of MeOH, 50 mL of CH_2Cl_2, and 50 mL of Et_2O. The resin was dried in vacuo to yield 7.07 g of polymer-bound product **6b**: IR (microscope) 1733 (C═O, ester), 1648 cm^{-1} (C═O, amide). Found: N, 1.84. Calcd loading: 0.657 mmol/g.

***N*-Benzyl-β-alaninyl-*N*-benzyl-β-alanine·TFA Salt (7b).** Polymer-bound dimer **6b** (1.39 g, 0.912 mmol) was cleaved as described for *N*-benzyl-β-alanine·TFA salt to yield 395.9 mg of a dark yellow oil (95.9% crude yield). Purification by preparative chromatography (reversed-phase C18, 35% CH_3CN/H_2O) yielded 75 mg (18%) of a colorless oil: ^{1}H NMR (acetone-d_6) mixture of two conformers in ratio of 1:1.16: δ 2.56 (t, J = 7.2 Hz, 2 H, minor conformer), 2.63 (t, J = 7.0 Hz, 2 H, major conformer), 3.04 (t, J = 5.8 Hz, 2 H, minor conformer), 3.21 (t, J = 6.0 Hz, 2 H, major conformer), 3.35−3.45 (m, 2 H), 3.53−3.62 (m, 2 H), 4.41, 4.44 (2 s, 2 H), 4.64, 4.67 (2 s, 2 H), 7.25−7.65 (m, 12 H), 9.37 (br s, 1 H); ^{13}C NMR (acetone-d_6) mixture of two conformers δ 32.50, 33.04, 43.18, 43.34, 44.29, 48.24, 51.64, 52.09, 127.69, 128.02, 128.35, 128.59, 129.28, 129.63, 129.82, 130.10, 130.81, 130.84, 132.46, 137.70, 138.36, 172.09, 172.93, 173.34; MS (FAB) m/z 369 (M + H), 391 (M + Na). Anal. Calcd for $C_{20}H_{24}N_2O_3$·1.13 $C_2HF_3O_2$: C, 56.95; H, 5.39; N, 5.97. Found: C, 56.97; H, 5.76; N, 5.57.

***N*-Acryloyl-*N*-benzyl-β-alaninyl-*N*-benzyl-β-alanine−Wang Resin (R-8).** Resin **6b** (5.56 g, 3.65 mmol) was placed in a 250 mL solid-phase synthesis flask and treated with 40 mL of CH_2Cl_2. The stirred slurry was treated with 1.60 mL (11.5 mmol) of triethylamine followed by the dropwise addition of 0.62 mL (7.67 mmol) of acryloyl chloride. After being stirred for 2 h, the resin was filtered, washed three times with 50 mL of CH_2Cl_2, and retreated with a solution with 1.60 mL (11.5 mmol) of triethylamine and 0.62 mL (7.67 mmol) acryloyl chloride in CH_2Cl_2. The mixture was allowed to stir for 1 h, filtered, and washed three times each with 50 mL of DMF, 50 mL of MeOH, 50 mL of CH_2Cl_2, and 50 mL of Et_2O: IR (microscope) 1733 (C═O, ester), 1650 cm^{-1} (C═O, amide).

***N*-Acryloyl-*N*-benzyl-β-alaninyl-*N*-benzyl-β-alanine (8).** Polymer-bound *N*-acryloyl-*N*-benzyl-β-alaninyl-*N*-benzyl-β-alanine **R-8** (1.757 g, 1.11 mmol) was cleaved as described for *N*-benzyl-β-alanine·TFA salt to yield 441.2 mg of a dark yellow oil (100% crude yield). Purification by preparative chromatography (reversed-phase C18, 40% CH_3CN/H_2O) yielded 204 mg (47%) colorless oil: ^{1}H NMR ($CDCl_3$) mixture of several conformers d 2.36−2.87 (m, 4 H), 3.36−3.77 (m, 4 H), 4.44−4.71 (m, 4 H), 5.65−5.80 (m, 1 H), 6.32−6.78 (m, 2 H), 7.05−7.42 (m, 10 H), 8.05 (br s, 1 H); MS (FAB) m/z 401 (M + Li),

408 (M + 2 Li). Anal. Calcd for $C_{23}H_{26}N_2O_4 \cdot 0.27C_2HF_3O_2$: C, 66.51; H, 6.23; N, 6.59. Found: C, 66.48; H, 6.54; N, 6.55.

***N*-Benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine−Wang Resin (9).** Polymer-bound acryl amide **R-8** (3.93 g, 2.48 mmol) was reacted with benzylamine (1.74 mL, 2.64 mmol) in dry DMSO (16 mL) as described for **6b**. Yield of crude polymer-bound product was 3.94 g: IR (microscope) 1733 (C═O, ester), 1646 cm^{-1} (C═O, amide).

***N*-Benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine·TFA Salt (10).** Polymer-bound *N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine **9** (1.50 g, 0.77 mmol) was cleaved as described for *N*-benzyl-*β*-alanine·TFA salt to yield 537 mg of a dark yellow oil. Purification by preparative chromatography (reversed-phase C18, 40% CH_3CN/H_2O) yielded 145 mg (31%) of a colorless oil: ^{1}H NMR (acetone-d_6) mixture of several conformers δ 2.50−2.71 (m, 3 H), 2.87−3.05 (m, 2 H), 3.20−3.32 (m, 1 H), 3.33−3.69 (m, 6 H), 4.37−4.72 (m, 6 H), 7.14−7.66 (m, 15 H), 9.24 (br s, 1 H); MS (FAB) *m*/*z* 502 (M + H), 524 (M + Na). Anal. Calcd for $C_{30}H_{35}N_3O_4 \cdot 1.47C_2HF_3O_2$: C, 59.12; H, 5.49; N, 6.28. Found: C, 59.45; H, 5.59; N, 5.88.

***N*-Acetyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine (12).** Polymer-bound *N*-benzyl trimer **9** (2.20 g, 1.30 mmol) was reacted with triethylamine (1.81 mL, 13 mmol) and acetic anhydride (1.23 mL, 13 mmol) in DMF (15 mL) for 3 h at rt in a peptide synthesis flask. Subsequently, the resin was drained and washed with DMF (3 × 20 mL), MeOH (3 × 20 mL), CH_2Cl_2 (3 × 20 mL), and Et_2O (3 × 20 mL). The resin was dried in vacuo, and the product was cleaved from the polymer by reaction with 20 mL of 95% TFA/H_2O as described for *N*-benzyl-*β*-alanine·TFA salt to give 714 mg of crude *N*-acetyltrimer as a dark yellow oil (100%). Purification by preparative RP HPLC (50% B isocratic) yielded 316 mg (52%) of a pure colorless, viscous oil: analytical RP HPLC (20−70% B) t_R = 8.4 min; ^{1}H NMR ($CDCl_3$) δ 2.14−2.31 (m, 3 H), 2.42−2.86 (m, 6 H), 3.37−3.75 (m, 6 H), 4.37−4.67 (m, 6 H), 7.02−7.39 (m, 15 H), 7.83 (br s, 1 H); MS (FAB) *m*/*z* 544 (M + H), 566 (M + Na). Anal. Calcd for $C_{32}H_{37}N_3F_3O_5 \cdot 1.31C_2HF_3O_2$: C, 59.98; H, 5.57; N, 6.06. Found: C, 59.98; H, 5.69; N, 5.99.

***N*-Acetyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine, Ethyl Ester (13).** *N*-Acetyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-benzyl-*β*-alanine (**12**) (107 mg, 0.20 mmol) was dissolved in 3 mL of ethanol saturated with HCl and placed in a capped 4 dram vial. The vial was placed in a heating block at 80 °C for 30 min and then cooled to rt. The sample was concentrated under a stream of nitrogen yielding 83 mg of a dark yellow oil. Purification by flash chromatography (ethyl acetate) yielded 35 mg (31%) of a colorless oil: ^{1}H NMR ($CDCl_3$) mixture of several conformers δ 2.50−2.71 (m, 3 H), 2.87−3.05 (m, 2 H), 3.20−3.32 (m, 1 H), 3.33−3.69 (m, 6 H), 4.37−4.72 (m, 6 H), 7.14−7.66 (m, 15 H), 9.24 (br s, 1 H); HRMS (ESI) *m*/*z* calcd for ($C_{34}H_{41}N_3O_5$ + H) 572.3127, found 572.3127.

Mixture Synthesis: Preparation of *N*-Acetyl-*N*-(4-methoxybenzyl)-*β*-alaninyl-*N*-benzyl-*β*-alaninyl-*N*-substituted-*β*-alanine, Ethyl Ester (17-B4). Equimolar amounts (1 mmol each) of eight resins **3a**−**h** were weighed based on the calculated NMR loadings (Table 1) and the resultant 13.1 g (8 mmol) of mixture **14** suspended in 100 mL of CH_2Cl_2. The slurry was treated with 3.3 mL (24 mmol) of triethylamine followed by dropwise addition of 1.3 mL (16 mmol) of acryloyl chloride. After being mixed for 2 h at rt, the resin was filtered and washed three times with 50 mL of CH_2Cl_2. The treatment with acryloyl chloride and triethylamine was repeated in 70 mL of CH_2Cl_2. After 1 h, the resin was filtered and washed three times each with 50 mL of CH_2Cl_2, MeOH, DMF, and DMSO. The resin was treated with 5.2 mL (48 mmol) of benzylamine following the procedure for preparation of **6b** to give 14.4 g (0.55 mequiv/g) of polymer-bound product **15**: IR (microscopy) 1733 (C═O, ester), 1648 (C═O, amide). A 300 mg (0.16 mmol) quantity of **15** was placed in a 15 mL polymer synthesis vessel and treated sequentially with acryloyl chloride and 4-methoxybenzylamine by the standard method to give the trimer resin **16**. Resin **16** was treated twice with 2.5 mL of DMF, 0.9 mL (0.65 g, 6.5 mmol) of triethylamine, and 0.6 mL (0.65 g, 6.4 mmol) of acetic anhydride for 1 h each. The resin was washed three times each with 3 mL of DMF, MeOH, and CH_2Cl_2 and allowed to air dry. Cleavage and esterification with EtOH was carried as described for **13** to provide a mixture of eight trimeric *β*-peptoids **17-B4**. The mixture was analyzed by LC/MS (Table 5).

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Supporting Information Available: Description of the preparation of the NMR cleavage solution, measurement of resin loading, resins **3o** and **3p**, and ^{1}H NMR spectra for **4d**,**g**, **i**,**j**,**q**,**r**,**t**, **7a**,**c**−**p**, and **13** together with the LC-MS data for each of the products from **17-B4** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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