A Solid-Phase Synthetic Route to Unnatural Amino Acids with Diverse Side-Chain Substitutions

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Received October 25, 2001

Reacting imine derivatives of resin-bound amino acids with α,ω-dihaloalkanes provides highly versatile intermediates to racemic α,α-disubstituted amino acids with a wide variety of side-chain functionality. Two strategies were developed to convert the intermediate ω-chloro or ω-bromo derivatives to the desired products. Together, they allow the creation of amino acids with diverse functionalities (ω-chlorides, nitriles, azides, acetates, thioacetates, thioethers, secondary and tertiary aliphatic amines, and anilines) placed at varying chain lengths (2−5) from the α-center of the amino acid.

Introduction

There has been increasing interest in the synthesis and use of unnatural amino acids in the maturing fields of peptide and combinatorial chemistry.[1] In peptides, they are used to alter conformation, activity, stability, and bioavailability.[2] In combinatorial chemistry, they are used as fundamental building blocks to peptidomimetic and small organic molecule libraries.[3] In both areas, the unnatural amino acids are often incorporated via solid-phase chemistry.[4]

To assist this process, we developed UPS (unnatural peptide synthesis) chemistry, which is now a well-documented route to mono- and disubstituted resin-bound unnatural amino acids and peptides.[5−8] In general, UPS is carried out by activating the α carbon for proton abstraction. Such activation is achieved by converting the α-amine function to either a benzophenone imine (for monoalkylation) or to an aldimine (for dialkylation) as shown in Scheme 1. This is followed by alkylation in the presence of a nonionic Schwesinger base[9] and subsequent mild hydrolysis of the imine.

Until recently, our work focused on the introduction, via alkylation reactions, of pre-assembled unnatural side chains.[5,6] It also addressed variations at the carboxy terminus that afforded—in addition to carboxylic acids and amides—esters, aldehydes, and ketones. More sterically hindered aliphatic derivatives and α-aryl derivatives were obtained by a "cationic" variant of this chemistry.

We recognized that the introduction of side chains that could be further derivatized would provide an important entry to a wider range of substituted unnatural amino acids. We first chose to focus on α,α-disubstituted examples,[10] since this would afford the opportunity to simultaneously obtain both natural and diversified un-

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(1) For lead references, see: *Asymmetric Synthesis of Novel Sterically Constrained Amino Acids*; Symposium-in-Print, Hruby, V. J.; Soloshonok, V. A., Eds. *Tetrahedron* **2001**, *57* (30), pp 6329-6650.

(2) For lead references, see: *Peptides 2000: Proceedings of the Twenty-Sixth European Peptide Symposium*; Martinez, J., Fehrentz, J.-A., Eds.; EDK: Paris, 2001.

(3) For lead references, see: *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed., Oxford University Press: Oxford, U.K., 2000.

(4) For lead references, see: Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(5) (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070−6071. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695−3698. (c) O'Donnell, M. J.; Delgado, F.; Domínguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821−828. (d) Scott, W. L.; Delgado, F.; Lobb, K.; Pottorf, R. S.; O'Donnell, M. J. *Tetrahedron Lett.* **2001**, *42*, 2073−2076.

(6) For a recent short review about UPS, see: O'Donnell, M. J.; Scott, W. L. In *Peptides 2000: Proceedings of the Twenty-Sixth European Peptide Symposium*; Martinez, J., Fehrentz, J.-A., Eds.; EDK: Paris, 2001; pp 31−36.

(7) For the application of UPS and related methodologies by others, see: (a) Girdwood, J. A.; Shute, R. E. *Chem. Commun.* **1997**, 2307−2308. (b) Du, X.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5678−5679. (c) Kim, S. W.; Shin, Y. S.; Ro, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1665−1668. (d) Matt, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 1845−1895. (e) Bhandari, A.; Jones, D. G.; Schullek, J. R.; Vo, K.; Schunk, C. A.; Tamanaha, L. L.; Chen, D.; Yuan, Z.; Needels, M. C.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2303−2308. (f) Zhu, Z.; Mckittrick, B. *Tetrahedron Lett.* **1998**, *39*, 7479−7482. (g) Lee, S.-H.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron Lett.* **1998**, *39*, 9469−9472. (h) Huang, X.; Pieczko, M. E.; Long, E. C. *Biochemistry* **1999**, *38*, 2160−2166. (i) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **2000**, *41*, 6371−6375. (j) Ricci, M.; Blakskjaer, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413−12421. (k) Demarcus, M.; Ganadu, M. L.; Mura, G. M.; Porcheddu, A.; Quaranta, L.; Reginato, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 697−706. (l) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742−1746. (m) Miyashita, K.; Iwaki, H.; Tai, K.; Murafuji, H.; Sasaki, N.; Imanishi, T. *Tetrahedron* **2001**, *57*, 5773−5780.

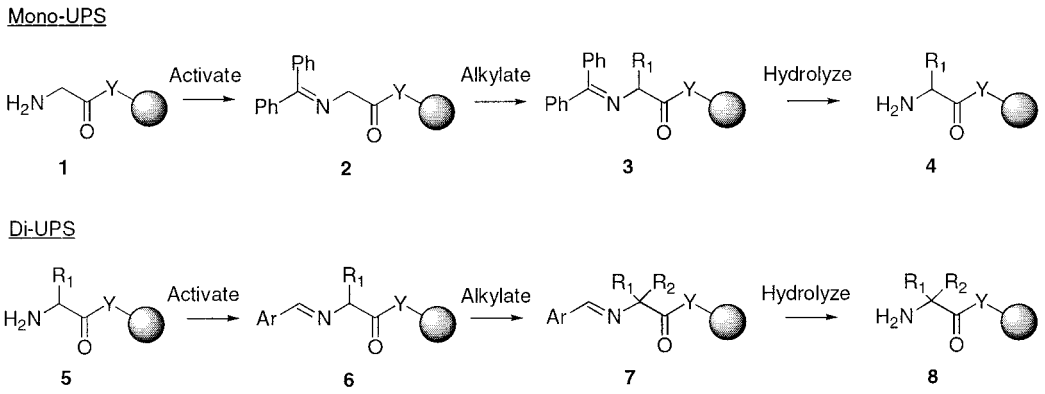
(8) For related applications and reviews concerning the use of benzophenone imines in amino acid and peptide chemistry, see: O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3−15.

(9) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.

(10) For recent reviews concerning the synthesis of α,α-dialkylamino acids, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645−732.

10.1021/jo016236i CCC: $22.00
Published on Web 04/03/2002

Scheme 1. Unnatural Amino Acid and Peptide Synthesis (UPS) for the Preparation of Amino Acid and Peptide Derivatives



natural side chains sprouting from the quaternary α-carbon. In this paper, we report the systematic evaluation of α,ω-dihaloalkanes as alkylating agents to yield key resin-bound racemic intermediates **9**, which were converted to the desired products **10** and **11** (Figure 1).[11,12]

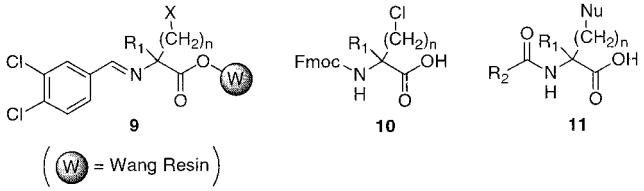
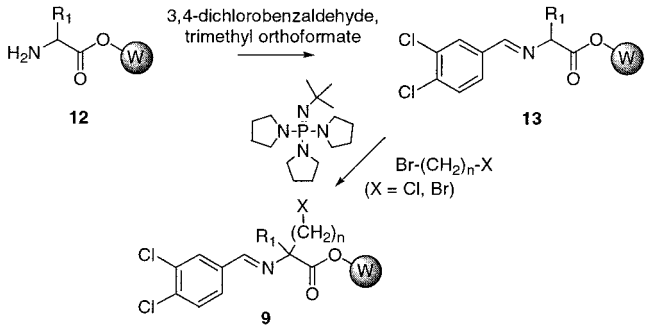


Figure 1. Key resin-bound intermediate **9** and side-chain functionalized unnatural amino acid products **10** and **11**.

Results and Discussion

Synthesis and Characterization of Key Intermediates. We first investigated the synthesis of key resin-bound intermediates **9** by the route outlined in Scheme 2. This involved formation of the aldimine from a resin-bound amino acid and then alkylation with an α,ω-dihaloalkane.

Scheme 2. Alkylation of Resin-Bound Amino Acids with α,ω-Dihaloalkanes



As a representative example, commercially available Fmoc-Ala-Wang resin was deprotected in standard fashion (20% piperidine in DMF) to **12** ($R_1 = CH_3$), which was converted to the aldimine **13** by condensation with 3,4-dichlorobenzaldehyde in the presence of trimethyl orthoformate.[5b,13] In the subsequent alkylation step, the chain length in the α,ω-dihaloalkanes used was varied from two to five. In most cases, α-bromo-ω-chloro electrophiles were chosen to permit more selective reactions on the ω-chloro adduct, while limiting side reactions in the alkylation and subsequent transformations. Of particular concern was the potential, if bromine was used in place of chlorine, for premature cyclization on the free amine in **14** (see Scheme 3) when $n = 3$ or 4.[14] An excess of dihalide was used to minimize cross-linking. Alkylations were conducted in NMP using the strong nonionic Schwesinger base, BTPP.[9,15] This base could be used in place of the weaker and more expensive phosphazine base BEMP,[15] the standard base used in our earlier UPS studies,[16] because in this work we do not have to worry

(11) For selected recent reports of the preparation and use of ω-halo-α-amino acid derivatives, see: (a) Lang, I.; Donzé, N.; Garrouste, P.; Dumy, P.; Mutter, M. *J. Pept. Sci.* **1998**, *4*, 72−80. (b) Lundquist, J. T., IV.; Büllesbach, E. E.; Dix, T. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2739−2743. (c) Ciapetti, P.; Mann, A.; Shoenfelder, A.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3843−3846. (d) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347−5350. (e) Sugiyama, H.; Yokokawa, F.; Shioiri, T.; Katagiri, N.; Oda, O.; Ogawa, H. *Tetrahedron Lett.* **1999**, *40*, 2569−2572. (f) Fotouhi, N.; Joshi, P.; Tilley, J. W.; Rowan, K.; Schwinge, V.; Wolitzky, B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1167−1169. (g) Itoh, F.; Yoshioka, Y.; Yukishige, K.; Yoshida, S.; Ootsu, K.; Akimoto, H. *Chem. Pharm. Bull.* **2000**, *48*, 1270−1280. (h) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. *Tetrahedron* **2000**, *56*, 2379−2390. (i) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918. (j) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216−5217. (k) Dexter, C. S.; Hunter, C.; Jackson, R. F. W.; Elliott, J. *J. Org. Chem.* **2000**, *65*, 7417−7421.

(12) For selected examples of nucleophilic displacements of resin-bound alkyl halides, see: (a) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646−10647. (b) Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473−1476. (c) Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. *Org. Lett.* **1999**, *1*, 121−124. (d) Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907−9914. (e) Zaragoza, F.; Stephensen, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 554−556. (f) Ramaseshan, M.; Dory, Y. L.; Deslongchamps, P. *J. Comb. Chem.* **2000**, *2*, 615−623. (g) Gouault, N.; Cupif, J.-F.; Sauleau, A.; David, M. *Tetrahedron Lett.* **2000**, *41*, 7293−7297. (h) Weissberg, A.; Dahan, A.; Portnoy, M. *J. Comb. Chem.* **2001**, *3*, 154−156. (i) Beech, C. L.; Coope, J. F.; Fairley, G.; Gilbert, P. S.; Main, B. G.; Plé, K. *J. Org. Chem.* **2001**, *66*, 2240−2245. (j) Attardi, M. E.; Taddei, M. *Tetrahedron Lett.* **2001**, *42*, 3519−3522.

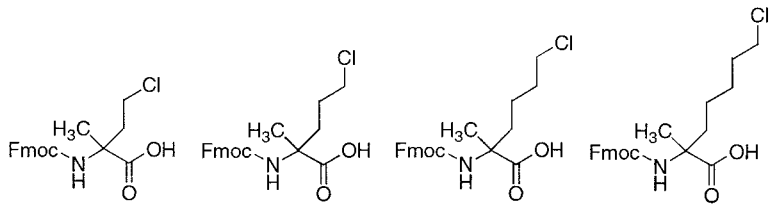
(13) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144−154.

(14) For example, when $n = 3$ we have evidence that the ω-bromo compound cyclized on the relatively unreactive imine nitrogen of **9**.

(15) The following abbreviations are used: BEMP, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; Bzl, benzyl; DIEA, *N*,*N*-diisopropylethylamine; Fmoc, 9-fluorenylmethoxycarbonyl; Fmoc-Cl, 9-fluorenylmethyl chloroformate; HOAc, acetic acid; UPS, unnatural peptide synthesis; TES, triethylsilane; TMOF, trimethyl orthoformate.

(16) For a comparison of the basicities of BTPP and BEMP, see footnote 12 in: O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.

Table 1. Products from Conversion of Key Intermediates to ω-Activated Side Chains

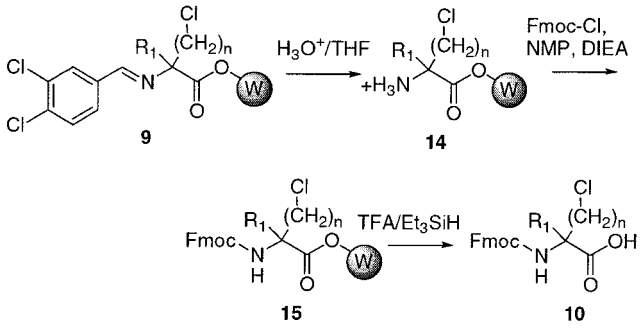


	10a: n = 2	**10b**: n = 3	**10c**: n = 4	**10d**: n = 5
Crude HPLC Purity	85%	67%	89%	88%
Purified Yield	55%[a]	47%	70%	68%

[a] Isolated as the lactone. See text and Scheme 5.

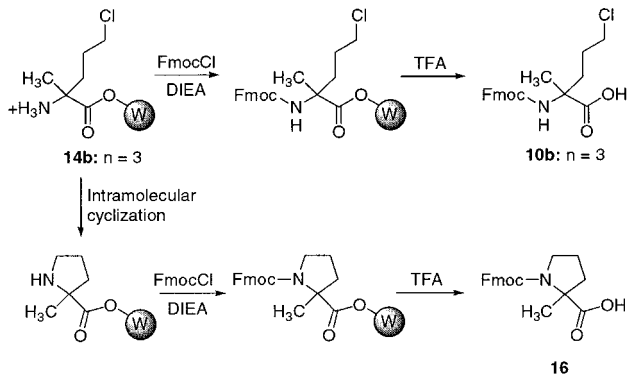
about racemization of preexisting chiral centers remote to the alkylation site.

Scheme 3. Hydrolysis, Acylation, and Cleavage of Resin-Bound Intermediates

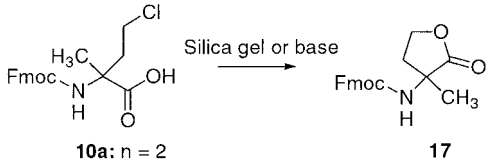


To characterize the products of these alkylations, while at the same time preparing useful side chain reactive intermediates, the resin-bound imine **9** was first hydrolyzed and then converted to the Fmoc amino acid derivatives **10** as outlined in Scheme 3. After hydrolysis of **9** to the resin-bound amine salt **14**, subsequent conversion to the resin-bound Fmoc derivative **15** was carried out using a 10-fold excess of 9-fluorenylmethyl chloroformate (Fmoc-Cl) by an *in situ* neutralization protocol. These conditions were chosen to minimize the competing intramolecular cyclization reaction. Cleavage with TFA/Et_3SiH[17] then gave, for characterization, the N-protected, chloro-substituted amino acid derivatives **10** (Scheme 3 and Table 1), or products derived from **10** or **14** (Schemes 4 and 5). For $n = 4$ and 5, the HPLC purities (UV detection at 220 nm) of the crude products **10c**−**d** were 89 and 88%, with purified, isolated yields of 70 and 68%, respectively. When $n = 3$, the intermediate chloride **14b** rapidly cyclized, and cleaved product **10b** contained 30% (by HPLC) of **16**. The purified yield of **10b** was 47%. If desired, **16** could be isolated in good yield by allowing **14b** to stand at room temperature in the presence of diisopropylethylamine (DIEA) before further treatment with Fmoc-Cl. The pathway leading to **16** is outlined in Scheme 4.

Scheme 4. Formation of Proline Derivatives by Intramolecular Cyclization of 14b ($n = 3$)



Scheme 5. Formation of γ-Lactone 17 by Intramolecular Cyclization of Acid 10a



When $n = 2$, the desired product **10a** was observed in good purity (85%) by LC/MS. However, **10a** partially cyclized during purification.[11c] The mixture of acid and resulting γ-lactone **17** was allowed to stand in chloroform in the presence of DIEA overnight to complete the conversion to the lactone. Subsequent chromatography afforded a 55% isolated yield of **17**. The overall results from these alkylations are summarized in Table 1.

Nucleophilic Displacement Reactions on Activated Resin-Bound Intermediates 9. With the intermediates **9a**−**d** (n = 2−5, respectively) in hand, the substitution of the chloro group with various nucleophiles was investigated. This involved the use of either strategy 1 or strategy 2 as outlined in Scheme 6.

The availability of both these strategies is crucial to the synthesis of a full range of analogues **11**. For example, because of the competing cyclization of intermediate **14b** to the proline analogue **16** (Scheme 4), strategy 2 gives lower yields when $n = 3$. However, strategy 1, which avoids the simultaneous presence of free primary amine and the ω-chloro side chain, can provide **11** (for $n = 3$) in good yield. On the other hand, with primary amine nucleophiles strategy 2 is preferred. It avoids the simultaneous presence, in the acylation step, of a newly introduced ω-amino group and the primary amine of the amino acid. We systematically evaluated both strategies by preparing three series of derivatives using strategy 1 and an additional two series of derivatives using strategy 2.

(17) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739−2742.

Scheme 6. Summary of Strategies for the Conversion of 9 to Side-Chain Derivatives

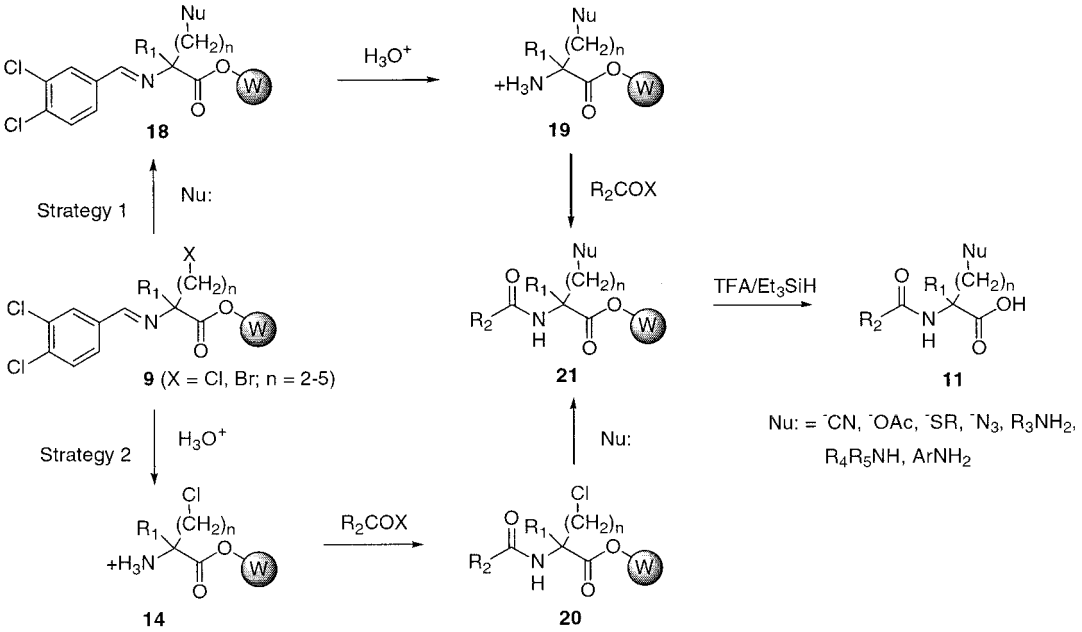
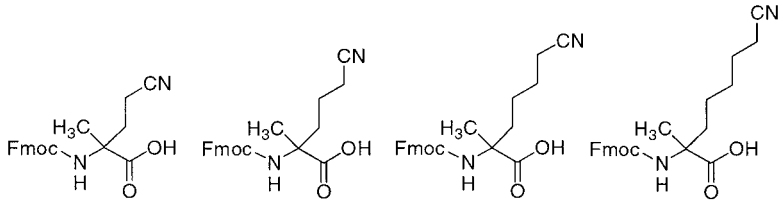


Table 2. Series 1: Preparation of Homologous Nitriles via Strategy 1



	22a: n = 2	**22b**: n = 3	**22c**: n = 4	**22d**: n = 5
Crude HPLC Purity	67%	74%	84%	86%
Purified Yield	30%	52%	66%	66%
Halide Precursor	Br	Cl	Cl	Cl

Strategy 1: Nucleophilic Substitutions on Resin-Bound 9 Before Imine Hydrolysis

The generality of strategy 1 was first examined by preparing three series of side-chain derivatives in which the α-amino group was capped with an Fmoc or acyl group.

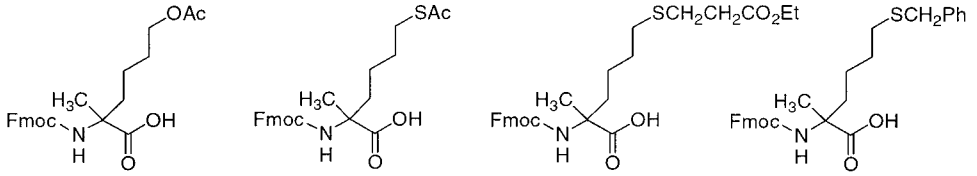
Series 1: Preparation of a Homologous Series of *ω*-Nitrile Derivatives. First prepared were the α-methyl nitrile derivatives **22** in which the length of side chain was varied from $n = 2$ to 5. For cases in which $n = 3-5$, the intermediate **9** was the *ω*-chloride. However, for $n = 2$, the *ω*-bromide was used, since in this case the *ω*-chloride was insufficiently reactive. Standard conditions for the displacement of the halide on **9** were 10 equivalents of tetrabutylammonium cyanide and 10 equivalents of tetrabutylammonium iodide[18] in NMP for 24 h at room temperature. This was followed by acid-catalyzed hydrolysis of the imine, acylation with Fmoc chloride, and TFA cleavage from the resin. The HPLC purity of the crude products **22a**−**d** ranged from 67 to 86%, with isolated, purified yields from 30 to 66% (Table 2).

(18) The inclusion of the tetrabutylammonium iodide was based on our earlier work for activating "unreactive halides" via an in situ Finklestein reaction, see: O'Donnell, M. J.; Lugar, C. W., Pottorf, R. S., Zhou, C.; Scott, W. L.; Cwi, C. L. *Tetrahedron Lett.* **1997**, *38*, 7163−7166. While we did not systematically study the need for this reagent in this work, preliminary studies indicated it gave cleaner products.

Series 2: Displacements with Other Nucleophiles. In a second series, other nucleophiles were examined while maintaining R_1 as methyl and keeping the chain length constant at $n = 4$. Again the α-amino group was capped with an Fmoc group. Four nucleophiles were chosen: acetate, thioacetate, ethyl 3-mercaptopropanoate, and benzyl mercaptide. The displacement of the chloride **9c** ($n = 4$; X = Cl) with acetate (tetrabutylammonium acetate) or thioacetate (thioacetic acid, DIEA) utilized 10 equiv of nucleophile and 10 equiv of tetrabutylammonium iodide in NMP. The acetate was reacted for 24 h at room temperature, but the more reactive thioacetate required only 6 h at room temperature to go to completion. Longer reaction times and/or elevated temperatures led to lower yields, presumably through nucleophilic cleavage of the resin. The two other thiols were less reactive and required the use of 20 equivalents of thiol and DIEA, elevated temperature (85 °C) and longer reaction times (36 h). After the displacement all the intermediates were subjected to acid-catalyzed hydrolysis, acylation with Fmoc-Cl, and TFA cleavage from the resin. The HPLC purity of the crude products **11a**−**d** ranged from 81 to 93%, with isolated, purified yields of 57 to 74% (Table 3).

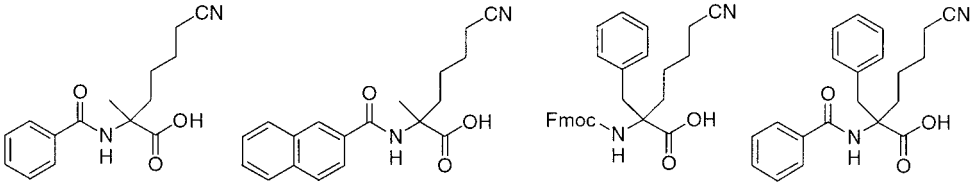
Series 3: R_1 and R_2 Variations. In a third series, the acylating group or starting α-substitutent R_1 was varied while maintaining chain length and functionality. Our previous UPS work had shown that we could perform

Table 3. Series 2: Products from Displacements with Other Nucleophiles via Strategy 1



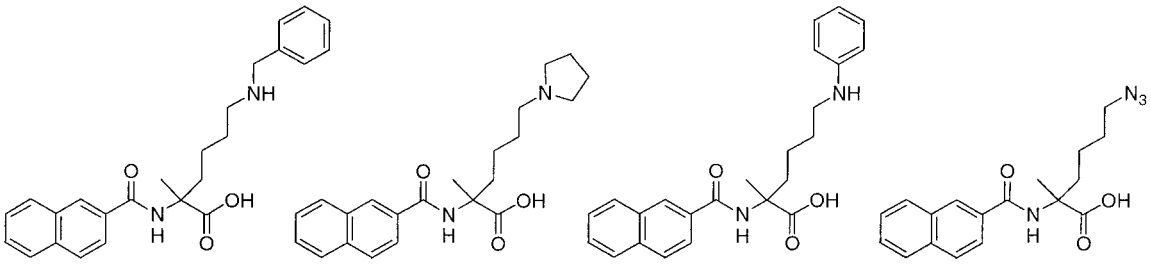
	11a: Nu = $^-$OAc	**11b:** Nu = $^-$SAc	**11c:** Nu = $^-$S(CH$_2$)$_2$CO$_2$Et	**11d:** Nu = $^-$SCH$_2$Ph
Crude HPLC Purity	93%	81%	81%	89%
Purified Yield	74%	59%	57%	62%

Table 4. Series 3: Miscellaneous Products via Strategy 1



	11e	**11f**	**11g**	**11h**
Crude HPLC Purity	83%	77%	93%	88%
Purified Yield	65%	67%	71%	68%

Table 5. Series 4: *ω*-Amino and Azide Derivatives via Strategy 2



	11i	**11j**	**11k**	**11l**
Crude HPLC Purity	86%	90%	89%	87%
Purified Yield	54%	57%	69%	63%

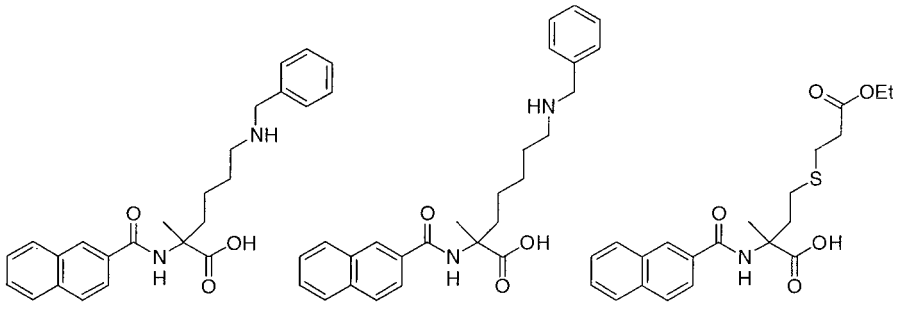
analogous alkylation chemistry on a wide variety of naturally occurring resin-bound amino acids,[5b,6,8] and we chose phenylalanine as an example to demonstrate that the transformations reported in this work could also accept other substituents at the α-position. For the nucleophilic displacements, conditions previously described were used to convert **9c** (R_1 = methyl; n = 4; X = Cl) or **9e** (R_1 = benzyl; n = 4; X = Cl) to the cyanide adducts, followed by hydrolysis of the imine intermediate. Acylations were done with benzoyl chloride, 2-naphthoyl chloride, or Fmoc-Cl (10 equiv of acid chloride and 20 equiv of DIEA in NMP), followed by TFA cleavage from the resin. The HPLC purities of the crude products **11e**−**h** were from 77 to 93%, and isolated, purified yields were from 65 to 71%. These results are summarized in Table 4.

Strategy 2: Nucleophilic Substitutions after Hydrolysis and Acylation of Resin-Bound 9

Series 4: Preparation of *ω*-Amine and Azide Derivatives. As discussed previously (Scheme 6), strategy 2 enables the formation of *ω*-substituted secondary amines by displacement of the halide after the α-amino group has been converted to an acylated derivative. Strategy 1 would have required additional protection/deprotection steps to accomplish this regioselectively. Strategy 2 also provides an alternative route to *ω*-azide and tertiary amino derivatives. In series 4, using this second strategy, four representative nitrogen nucleophiles (primary amine, secondary amine, aniline, and azide) were examined. The R_1 group was methyl, n = 4, and all the intermediates were acylated with a 2-naphthoyl group. All displacements were done in the presence of tetrabutylammonium iodide over a 24 h period. The azide derivative could be prepared at room temperature using tetrabutylammonium azide (10 equiv). However, reactions with benzylamine (20 equiv), pyrrolidine (20 equiv) and aniline (50 equiv) all required elevated temperature (85 °C for benzylamine and aniline, and 60 °C for pyrrolidine). The HPLC purity of the crude products **11i**−**l** was between 86 and 90%, with isolated, purified yields of 54 to 69% (Table 5).

Series 5. Miscellaneous Amines and Thioethers Obtained by Strategy 2. Finally, we attempted to prepare, by strategy 2, a series of secondary amine derivatives in which the length of side chain was 2, 4, and 5. Nucleophilic displacements of the chloride worked well for n = 4 or 5. Reactions with benzylamine (20 equiv) to yield **11i** and **11m** were done at 85 °C over a 24 h

Table 6. Series 5: Miscellaneous Amines and Thioethers Obtained via Strategy 2



	11i	**11m**	**11n**
Crude HPLC Purity	86%	89%	74%
Purified Yield	54%	55%	42%

period in the presence of tetrabutylammonium iodide. When we tried to displace the ω-chloride, $n = 2$, with benzylamine the desired product was not obtained. Starting material was not recovered. We believe there is a competing intramolecular cyclization, but have not further characterized the reaction products. However, the thioether **11n** could be prepared with acceptable HPLC purity and purified yield by displacing the ω-chloride ($n = 2$) using a large excess of ethyl 3-mercaptopropanoate (50 equiv) in the presence of DIEA (50 equiv) and tetrabutylammonium iodide at 85 °C for 24 h. The HPLC purity of the crude products **11i**, **11m**, and **11n**, was between 74 and 89%, with isolated, purified yields of 42 to 55% (Table 6).

Conclusions

In summary, reacting imine derivatives of resin-bound amino acids with α,ω-dihaloalkanes allows access to novel α,α-disubstituted amino acids with a wide variety of side chain diversity. Two strategies were developed to convert the intermediate chloro or bromo derivatives to the desired products. Together, they allow the creation of amino acids with diverse functionalities (ω-chlorides, nitriles, azides, acetates, thioacetates, thioethers, secondary and tertiary aliphatic amines, and anilines) placed at varying chain lengths (2−5) from the α-center. The halide intermediates can also participate in intramolecular cyclization reactions to produce proline and lactone derivatives. A more systematic exploration of these cyclizations in the preparation of analogous cyclic compounds is currently under investigation.

Experimental Section

General Methods. All reactions and washes were conducted at ambient temperature unless indicated otherwise. Fmoc-Ala-Wang-resin (0.84 mmol/g), Fmoc-Phe-Wang-resin (1.0 mmol/g), and 9-fluorenylmethyl chloroformate were obtained from NovaBiochem. BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane) and tetrabutylammonium iodide were purchased from Fluka. Tetrabutylammonium azide was obtained from TCI America. Manual solid-phase organic syntheses at 25 °C were carried out in polypropylene syringes equipped with a porous polypropylene disk at the bottom purchased from Torviq (Catalog No. SF-0250, SF-0500, and SF-2000). Solid-phase reactions at higher temperatures were carried out in Pyrex brand tubes with Teflon fluorocarbon resin-faced rubber-lined caps purchased from Fisher Scientific (Catalog No. 14-933A and 14-933C). Silica gel flash chromatography was performed with silica gel 60 (230−400 mesh) from Silicycle. Analytical HPLC was performed using a Waters C_{18} reversed-phase column (3.9 × 150 mm) on a Varian 9010 instrument, and linear gradients of 0.1% TFA in CH_3CN and 0.1% aqueous TFA were run at 1.0 mL/min flow rate from 0:1 to 1:0 over 25 min. UV detection was at 220 nm. NMR analyses were performed using a GE QE 300 MHz NMR. Chemical shifts (δ) are in ppm. Electrospray ionization mass spectrometry was conducted using a PESciex API III triple stage quadrupole mass spectrometer operated in the positive-ion detection mode. High-resolution mass spectrometry was run in the FAB mode. The yields of final compounds, after chromatographic purification, are calculated on the basis of the initial loading of the starting Wang resins and are the overall yields of all reaction steps starting from these resins.

Comment on the Compiled Spectral Data. For several compounds, too few or too many ^{13}C resonances were observed. These examples (eight spectra in total) can be classified in three categories. (a) For compound **17**, one of the quaternary carbons of the Fmoc system gave separated signals (δ 145.1 and 145.3) because of nonequivalency. This also happened for compound **11d** (δ 145.3 and 145.4). (b) For compound **22a**, the peak corresponding to the CN group overlapped with a CH aromatic (δ 120.9), and also one of the CH aromatics (δ 128.8 and 128.8) and one of the quaternary carbons (δ 145.2 and 145.4) of the Fmoc system were nonequivalent. For compound **11g**, one of the CH aromatics (δ 125.0 and 125.1) and one of the quaternary carbons (δ 143.8 and 143.9) of the Fmoc system were nonequivalent. (c) For compounds **11f**, **11l**, and **11n** too few ^{13}C resonances were observed because of overlap of one of the CH aromatic signals. For compound **11k**, two CH aromatic signals overlapped.

General Procedures for Parallel Solid-Phase Reactions. Manual solid-phase organic syntheses at 25 °C were carried out in polypropylene syringes (disposable reaction vessels) equipped with porous polypropylene disks at the bottom. Syringes of variable volume were used based on the quantity of initial dried resin (e.g., 3 mL syringes for 100 mg of resin, 5 mL syringes for 200 mg of resin, and 20 mL syringes for 1 g of resin). Typically, the syringe was charged with resin and then the solvent used in the following reaction was added to create a slurry. The resin beads were washed with this solvent (3 mL of solvent per 1 mL of swollen resin). The mixture was stirred using a capillary tube for a given time, and after finishing the treatment, the solvent was removed by filtration using a vacuum system.

Introduction of Reagents. Prior to the addition of reagents, the bottom part of the syringe was capped using a septum, then solvents and reagents were added. After manual stirring with a capillary tube for 2 min, the plunger was placed at the top of the syringe. Removal of the septum allowed for modification of the volume of the reaction vessel by moving the plunger to the desired position. After putting back the septum, the reaction vessel was mixed by gentle rotation using a rotary evaporator or mechanical stirrer.

Higher Temperature Reactions. Solid-phase reactions at higher temperatures (from 60 to 85 °C) were carried out in Pyrex brand tubes with Teflon fluorocarbon resin-faced rubber-

lined caps. In these experiments, after the resin was washed using the syringe system as above, the resin was transferred to the glass tube using the total amount of solvent needed for the reaction. Then, reagents were added, and after the cap was replaced, the reaction vessel was placed in a sand bath for the given time with occasional manual agitation. After the reaction was completed, the reaction mixture was transferred to a syringe and treated as above.

Strategy 1

Preparation of the 3,4-Dichlorobenzaldehyde Imine of Ala-Wang Resin. In a 20 mL syringe, Fmoc-Ala-Wang-resin (1.0 g, 0.84 mmol/g) was washed with CH_2Cl_2 (3 × 15 mL, 1 min each) and DMF (3 × 15 mL, 1 min each) and then treated with piperidine−DMF (1:4, 3 × 15 mL, 5 min each), followed by washings with DMF (6 × 15 mL, 0.5 min each). 3,4-Dichlorobenzaldehyde (2.21 g, 15 equiv) was dissolved in NMP−TMOF (1:2, 10 mL total) and added to the resin, and the reaction was allowed to proceed for 24 h with rotation. The resultant resin-bound Schiff base product (theoretical loading of 0.89 mmol/g) was washed with NMP (6 × 15 mL, 0.5 min each), THF (6 × 15 mL, 0.5 min each), and CH_2Cl_2 (4 × 15 mL, 0.5 min each) and finally dried under argon.

Alkylation of the Benzaldehyde Imine of Ala-Wang Resin with an α,ω-Dihaloalkane. In a 5 mL syringe, resin-bound Schiff base (0.200 g, 0.89 mmol/g, 178 μmol) was washed with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). The α,ω-dihaloalkane (10 equiv) in NMP (2.0 mL) and BTPP (545 μL, 10 equiv) were added, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each) and CH_2Cl_2 (4 × 4 mL, 0.5 min each).

Nucleophilic Displacement of the Halide. The resin-bound imine (178 μmol) was swollen with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). Tetrabutylammonium iodide (657 mg, 10 equiv) and tetrabutylammonium cyanide (478 mg, 10 equiv) were individually dissolved in NMP (1.5 mL each), and both solutions were combined and added to the resin. The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each) and CH_2Cl_2 (6 × 4 mL, 0.5 min each). **Note:** an alternative experimental procedure consisted of addition of solid tetrabutylammonium iodide (657 mg, 10 equiv) to the dried resin, and further addition of a solution of tetrabutylammonium cyanide (478 mg, 10 equiv) in NMP (3 mL). Equivalent results were obtained using either procedure.

Hydrolysis of the Imine in the Resin-Bound Alkylated Products. The resin-bound imine (178 μmol) was washed with THF (6 × 4 mL, 0.5 min each) and THF−H_2O (3:1, 3 × 4 mL, 1 min each). THF-1 N HCl (2:1, 5 mL) was added, and the reaction mixture was rotated for 4 h. The resin was filtered and washed with THF (6 × 4 mL, 0.5 min each), CH_2Cl_2 (6 × 4 mL, 0.5 min each), and NMP (6 × 4 mL, 0.5 min each).

Acylation of Resin-Bound Product with Fmoc-Cl. The resin-bound amine (178 μmol) was washed with CH_2Cl_2 (4 × 4 mL, 0.5 min each), and NMP (4 × 4 mL, 0.5 min each). Fmoc-Cl (460 mg, 10 equiv) was dissolved in NMP (2 mL), added to the resin, and the acylation was started by addition of DIEA (605 μL, 20 equiv). The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), THF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Cleavage of the Product from the Resin and Final Purification. The resin was cleaved with TFA−triethylsilane (TES) (95:5, 2 × 5 mL, 1 × 2 h, + 1 × 30 min). The filtrates from the cleavage reaction were collected, combined with the TFA-CH_2Cl_2 washes (1:3, 2 × 5 mL, 2 min each) of the resin, and evaporated under a stream of argon. The crude residues were redissolved in $CHCl_3$ (1.5 mL) and purified over silica gel with $CHCl_3$−THF−HOAc (92:8:1) to elute the final compounds. After removal of the solvent from the desired fractions, in most cases the purified products were redissolved in the minimum amount of benzene and precipitated by addition of cold pentane to obtain, after centrifugation/decantation, solid material.

4-Cyano-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylbutanoic Acid (22a). Prepared as described above, using 1,2-dibromoethane (154 μL, 10 equiv) in the alkylation step to provide an amorphous white solid (19.4 mg, 30% isolated yield) following purification. Initial HPLC purity 67%, t_R = 10.6 min; ^{1}H NMR (CD_3OD) δ 1.47 (s, 3H), 2.16−2.50 (m, 4H), 4.26 (t, *J* = 6.3 Hz, 1H), 4.38−4.52 (m, 2H), 7.28−7.48 (m, 4H), 7.71 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (CD_3OD) δ 12.6, 23.5, 32.7, 48.6, 59.4, 67.4, 120.9, 126.2, 128.1, 128.8, 128.8, 142.7, 145.2, 145.4, 157.3, 176.6; IR (cm^{-1}) 2253, 1716, 1504, 1452, 1077; HRMS *m/z* calcd for $C_{21}H_{20}N_2O_4Na$ 387.1321 for ($M + Na^+$), found 387.1341.

5-Cyano-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylpentanoic Acid (22b). Prepared as described above, using 1-bromo-3-chloropropane (176 μL, 10 equiv) in the alkylation step to provide an amorphous white solid (35.0 mg, 52% isolated yield) following purification: initial HPLC purity 74%; t_R = 11.4 min; ^{1}H NMR (CD_3OD) δ 1.35−1.70 (m, 2H), 1.49 (s, 3H), 1.92−2.12 (m, 2H), 2.36−2.52 (m, 2H), 4.25 (t, *J* = 6.3 Hz, 1H), 4.33−4.51 (m, 2H), 7.31−7.46 (m, 4H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 17.4, 21.4, 23.5, 36.6, 48.6, 59.9, 67.3, 120.8, 120.9, 126.1, 128.1, 128.7, 142.6, 145.3, 157.1, 177.2; IR (cm^{-1}) 3413, 3028, 2948, 2250, 1716, 1656, 1505, 1452, 1355, 1249, 1082; HRMS *m/z* calcd. for $C_{22}H_{22}N_2O_4Na$ 401.1477 for ($M + Na^+$), found 401.1481.

6-Cyano-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylhexanoic Acid (22c). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step to provide an amorphous white solid (46.1 mg, 66% isolated yield) following purification: initial HPLC purity 84%; t_R = 12.1 min; ^{1}H NMR (CD_3OD) δ 1.30−1.56 (m, 2H), 1.51 (s, 3H), 1.56−1.70 (m, 2H), 1.86−2.00 (m, 2H), 2.38−2.52 (m, 2H), 4.24 (t, *J* = 5.7 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 2H), 7.30−7.45 (m, 4H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (CD_3OD) δ 17.2, 23.4, 24.1, 26.5, 36.8, 48.5, 60.2, 67.4, 120.9, 121.0, 126.2, 128.2, 128.7, 142.6, 145.4, 157.2, 177.4; IR (cm^{-1}) 3414, 3023, 2946, 2872, 2250, 1714, 1505, 1452, 1249, 1086; HRMS *m/z* calcd for $C_{23}H_{25}N_2O_4$ 393.1814 for ($M + H^+$), found 393.1808.

7-Cyano-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylheptanoic Acid (22d). Prepared as described above using 1-bromo-5-chloropentane (236 μL, 10 equiv) in the alkylation step to provide an amorphous white solid (47.8 mg, 66% isolated yield) following purification: initial HPLC purity 86%; t_R = 12.4 min; ^{1}H NMR (CD_3OD) δ 1.22−1.40 (m, 2H), 1.40−1.56 (m, 2H), 1.50 (s, 3H), 1.59−1.71 (m, 2H), 1.88−1.98 (m, 2H), 2.44 (t, *J* = 6.9 Hz, 2H), 4.25 (t, *J* = 6.6 Hz, 1H), 4.38 (d, *J* = 6.6 Hz, 2H), 7.30−7.48 (m, 4H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 17.2, 23.4, 24.2, 26.3, 29.7, 37.5, 48.5, 60.4, 67.4, 120.9, 121.1, 126.2, 128.1, 128.7, 142.6, 145.4, 157.1, 177.6; IR (cm^{-1}) 3416, 3068, 3022, 2968, 2943, 2249, 1714, 1505, 1452, 1355, 1242, 1089, 1044; HRMS *m/z* calcd for $C_{24}H_{27}N_2O_4$ 407.1971 for ($M + H^+$), found 407.1967.

9*H*-Fluoren-9-ylmethyl [3-Tetrahydro-1-methyl-2-oxo-3-furanyl]carbamate (17). Prepared as described above, using 1-bromo-2-chloroethane (149 μL, 10 equiv) for the alkylation step. The step involving displacement of the halide with a nucleophile was omitted. After cleavage from the resin, initial attempts to purify the chloro derivative by silica gel chromatography were not successful because of partial formation of the homoserine lactone derivative. Cyclization was completed by stirring a chloroform solution containing the mixture of both products in the presence of an excess of DIEA for 24 h at 25 °C. The crude cyclization product was then purified over silica gel with $CHCl_3$−THF (95:5) to provide the final compound as a white solid (33.0 mg, 55% isolated yield). Initial HPLC purity [(85%, corresponding to N^{α}-(9-fluorenylmethoxycarbonyl)-α′-(2-chloroethyl)alanine)]: t_R = 11.4 min; mp 156−158 °C; ^{1}H NMR (CD_3OD) δ 1.47 (s, 3H), 2.12−2.26 (m, 1H), 2.72−2.84 (m, 1H), 4.24 (t, *J* = 6.3 Hz, 1H), 4.40 (d,

J = 6.3 Hz, 2H), 4.28−4.50 (m, 2H), 7.31−7.46 (m, 4H), 7.68 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 6.6 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H); ^{13}C NMR (CD_3OD) δ 22.5, 34.9, 57.2, 58.7, 66.2, 67.8, 120.9, 126.2, 128.2, 128.8, 142.6, 145.1, 145.3, 157.2, 180.2; IR (cm^{-1}) 3445, 3415, 3068, 3012, 1781, 1722, 1504, 1273, 1230, 1084, 1023; HRMS m/z calcd for $C_{20}H_{20}NO_4$ 338.1392 for (M + H^+), found 338.1411.

5-Chloro-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylpentanoic Acid (10b). Prepared as described above, using 1-bromo-3-chloropropane (176 μL, 10 equiv) for the alkylation step. The step involving displacement of the halide with a nucleophile was omitted. The crude residue was purified over silica gel with CH_2Cl_2−EtOAc−HOAc (95:5:1) to provide an amorphous white solid (32.4 mg, 47% isolated yield): initial HPLC purity 67%, t_R = 11.9 min; ^{1}H NMR (CD_3OD) δ 1.50 (s, 3H), 1.60−1.86 (m, 2H), 1.95−2.15 (m, 2H), 3.48−3.64 (m, 2H), 4.26 (t, J = 6.6 Hz, 1H), 4.39 (d, J = 6.6 Hz, 2H), 7.31−7.46 (m, 4H), 7.70 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 23.5, 28.6, 35.2, 45.6, 48.5, 60.0, 67.4, 120.9, 126.2, 128.1, 128.7, 142.6, 145.3, 157.1, 177.4; IR (cm^{-1}) 2935, 1691, 1478, 1452, 1414, 1354, 1287, 1206, 1046; HRMS m/z calcd for $C_{21}H_{22}NO_4NaCl$ 410.1135 for (M + Na^+), found 410.1107.

6-Chloro-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylhexanoic Acid (10c). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) for the alkylation step. The step involving displacement of the halide with a nucleophile was omitted. The crude residue was purified over silica gel with CH_2Cl_2−EtOAc−HOAc (97:3:1) to provide a pale yellow solid (50.1 mg, 70% isolated yield): initial HPLC purity 89%; t_R = 13.5 min; mp 138−140 °C; ^{1}H NMR (CD_3OD) δ 1.34−1.60 (m, 2H), 1.51 (s, 3H), 1.73−1.85 (m, 2H), 1.89−2.01 (m, 2H), 3.53−3.65 (m, 2H), 4.25 (t, J = 6.6 Hz, 1H), 4.37 (d, J = 6.6 Hz, 2H), 7.31−7.46 (m, 4H), 7.70 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.4, 32.2, 35.6, 44.5, 47.2, 59.7, 66.6, 120.2, 124.5, 127.1, 127.5, 141.4, 143.8, 154.7, 178.8; IR (cm^{-1}) 3418, 2943, 2865, 1715, 1506, 1452, 1246, 1225, 1084; HRMS m/z calcd for $C_{22}H_{25}ClNO_4$ 402.1472 for (M + H^+), found 402.1471.

7-Chloro-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylheptanoic Acid (10d). Prepared as described above, using 1-bromo-5-chloropentane (236 μL, 10 equiv) for the alkylation step. The step involving displacement of the halide with a nucleophile was omitted. The crude residue was purified over silica gel with CH_2Cl_2−EtOAc−HOAc (97:3:1) to provide a pale yellow solid (50.3 mg, 68% isolated yield): initial HPLC purity 88%; t_R = 14.1 min; mp 126−128 °C; ^{1}H NMR (CD_3OD) δ 1.24−1.42 (m, 2H), 1.42−1.56 (m, 2H), 1.50 (s, 3H), 1.73−1.85 (m, 2H), 1.85−1.97 (m, 2H), 3.56 (t, J = 6.6 Hz, 2H), 4.24 (t, J = 6.6 Hz, 1H), 4.37 (d, J = 6.6 Hz, 2H), 7.31−7.46 (m, 4H), 7.70 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 23.3, 23.4, 26.7, 32.3, 36.4, 44.8, 47.3, 59.8, 66.6, 120.0, 124.9, 127.1, 127.7, 141.4, 143.8, 154.8, 178.9; IR (cm^{-1}) 3418, 3069, 3012, 2943, 2865, 1714, 1506, 1452, 1242, 1087, 1044; HRMS m/z calcd for $C_{23}H_{27}ClNO_4$ 416.1629 for (M + H^+), found 416.1642.

6-(Acetyloxy)-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino]-2-methylhexanoic Acid (11a). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step, and tetrabutylammonium acetate (535 mg, 10 equiv) instead of tetrabutylammonium cyanide for the nucleophilic displacement of the halide, to provide an amorphous white solid (56.0 mg, 74% isolated yield) following purification: initial HPLC purity 93%; t_R = 12.5 min; ^{1}H NMR (CD_3OD) δ 1.25−1.50 (m, 2H), 1.51 (s, 3H), 1.60−1.70 (m, 2H), 1.90−2.05 (m, 2H), 2.01 (s, 3H), 4.00−4.14 (m, 2H), 4.24 (t, J = 6.3 Hz, 1H), 4.36 (d, J = 6.3 Hz, 2H), 7.31−7.46 (m, 4H), 7.69 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 20.8, 21.4, 23.4, 29.7, 37.4, 48.5, 60.4, 65.4, 67.5, 120.9, 126.4, 128.2, 128.8, 142.6, 145.3, 157.1, 173.0, 177.5; IR (cm^{-1}) 3417, 3029, 2956, 1721, 1505, 1452, 1367, 1251, 1194, 1106, 1094, 1043; HRMS m/z calcd for $C_{24}H_{28}NO_6$ 426.1917 for (M + H^+), found 426.1937.

6-(Acetylthio)-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino]-2-methylhexanoic Acid (11b). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step, with thioacetic acid (127 μL, 10 equiv) and DIEA (302 μL, 10 equiv) instead of tetrabutylammonium cyanide for the nucleophilic displacement of the halide (6 h), to provide an amorphous pale yellow solid (46.4 mg, 59% isolated yield) following purification: initial HPLC purity 81%, t_R = 13.2 min; ^{1}H NMR (CD_3OD) δ 1.26−1.44 (m, 2H), 1.50 (s, 3H), 1.52−1.64 (m, 2H), 1.86−1.98 (m, 2H), 2.29 (s, 3H), 2.90 (t, J = 6.6 Hz, 2H), 4.26 (t, J = 6.3 Hz, 1H), 4.37 (d, J = 6.3 Hz, 2H), 7.32−7.46 (m, 4H), 7.71 (d, J = 6.6 Hz, 2H), 7.84 (d, J = 7.2 Hz, 2H); ^{13}C NMR (CD_3OD) δ 23.4, 24.1, 29.7, 30.4, 30.7, 37.2, 48.5, 60.4, 67.5, 120.9, 126.2, 128.2, 128.7, 142.6, 145.4, 157.1, 177.6, 197.6; IR (cm^{-1}) 3416, 3010, 2937, 1714, 1688, 1505, 1452, 1243, 1107, 1082; HRMS m/z calcd for $C_{24}H_{27}NO_5SNa$ 464.1508 for (M + Na^+), found 464.1501.

6-(Ethyl 3-mercaptopropionate)-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino]-2-methylhexanoic Acid (11c). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step and ethyl 3-mercaptopropionate (455 μL, 20 equiv) and DIEA (605 μL, 20 equiv) instead of tetrabutylammonium cyanide for the nucleophilic displacement of the halide (using a glass vessel and heating at 85 °C for 36 h with occasional agitation), to provide an amorphous white solid (50.7 mg, 57% isolated yield) following purification: initial HPLC purity 81%; t_R = 13.6 min; ^{1}H NMR (CD_3OD) δ 1.27 (t, J = 7.2 Hz, 3H), 1.32−1.46 (m, 2H), 1.51 (s, 3H), 1.52−1.68 (m, 2H), 1.86−1.98 (m, 2H), 2.50−2.64 (m, 4H), 2.75 (t, J = 6.6 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.25 (t, J = 6.3 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 7.30−7.46 (m, 4H), 7.70 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 23.4, 24.1, 27.9, 30.6, 32.6, 35.9, 37.3, 48.5, 60.4, 61.7, 67.5, 120.9, 126.2, 128.2, 128.8, 142.6, 145.3, 157.1, 173.8, 177.6; IR (cm^{-1}); 3416, 3028, 2986, 2942, 1719, 1505, 1452, 1245, 1080; HRMS m/z calcd. for $C_{27}H_{33}NO_6SNa$ 522.1926 for (M + Na^+), found 522.1939.

2-[[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino]-2-methyl-6-[(phenylmethyl)thio]hexanoic Acid (11d). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step, and benzyl mercaptan (420 μL, 20 equiv) and DIEA (605 μL, 20 equiv) instead of tetrabutylammonium cyanide for the nucleophilic displacement of the halide (using a glass vessel and heating at 85 °C for 36 h with occasional agitation), to provide an amorphous white solid (54.0 mg, 62% isolated yield) following purification: initial HPLC purity 89%; t_R = 14.5 min; ^{1}H NMR (CD_3OD) δ 1.20−1.42 (m, 2H), 1.49 (s, 3H), 1.44−1.64 (m, 2H), 1.80−1.96 (m, 2H), 2.36−2.50 (m, 2H), 3.71 (s, 2H), 4.25 (t, J = 6.0 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 7.18−7.46 (m, 9H), 7.69 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H); ^{13}C NMR (CD_3OD) δ 23.5, 24.1, 30.3, 32.0, 36.9, 37.3, 48.5, 60.4, 67.4, 120.9, 126.2, 127.8, 128.1, 128.7, 129.4, 129.9, 140.2, 142.6, 145.3, 145.4, 157.1, 177.8; IR (cm^{-1}) 1715, 1602, 1505, 1452, 1240, 1080; HRMS m/z calcd for $C_{29}H_{32}NO_4S$ 490.2052 for (M + H^+), found 490.2044.

2-(Benzoylamino)-6-cyano-2-methylhexanoic Acid (11e). Prepared as described above, using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step, and benzoyl chloride (207 μL, 10 equiv) instead of Fmoc-Cl during the acylation step, to provide a white solid (31.7 mg, 65% isolated yield) following purification: initial HPLC purity 83%; t_R = 6.7 min; mp 144−146 °C; ^{1}H NMR (CD_3OD) δ 1.42−1.61 (m, 2H), 1.66 (s, 3H), 1.62−1.76 (m, 2H), 2.14 (t, J = 8.1 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 7.45−7.63 (m, 3H), 7.80−7.88 (m, 2H), 8.27 (broad, 1H); ^{13}C NMR (CD_3OD) δ 17.2, 23.2, 24.3, 26.6, 36.6, 60.8, 121.0, 128.3, 129.6, 132.7, 135.9, 169.7, 177.3. IR (cm^{-1}) 3011, 2943, 2526, 2250, 1718, 1660, 1517, 1451, 1417; HRMS m/z calcd for $C_{15}H_{18}N_2O_3Na$ 297.1215 for (M + Na^+), found 297.1214.

6-Cyano-2-methyl-2-[(2-naphthalenylcarbonyl)amino]-hexanoic Acid (11f). Prepared as described above using 1-bromo-4-chlorobutane (206 μL, 10 equiv) in the alkylation step and 2-naphthoyl chloride (339 mg, 10 equiv) instead of Fmoc-Cl during the acylation step to provide a white solid (38.7 mg, 67% isolated yield) following purification: initial HPLC purity 77%; t_R = 9.4 min; mp 169−171 °C; ^{1}H NMR (CD_3OD)

δ 1.43−1.78 (m, 4H), 1.69 (s, 3H), 2.18 (t, J = 8.4 Hz, 2H), 2.50 (t, J = 6.9 Hz, 2H), 7.54−7.68 (m, 2H), 7.84−8.06 (m, 4H), 8.40 (s, 1H); ^{13}C NMR (CD_3OD) δ 17.2, 23.2, 24.3, 26.6, 36.7, 60.9, 121.0, 124.9, 127.8, 128.8, 128.8, 129.3, 130.0, 133.1, 134.0, 136.3, 169.8, 177.4; IR (cm^{-1}) 3356, 3331, 2946, 2251, 1714, 1704, 1649, 1527, 1500, 1307, 779; HRMS *m/z* calcd for $C_{19}H_{20}N_2O_3Na$ 347.1372 for ($M + Na^+$), found 347.1379.

2-(4-Cyanobutyl)-2-[[(9*H*-fluoren-9-ylmethoxy)carbonyl]-amino]benzenepropanoic Acid (11g). Prepared as described above starting from Fmoc-Phe-Wang resin (0.200 g, 1.0 mmol/g) and using 1-bromo-4-chlorobutane (231 μL, 10 equiv) in the alkylation step to provide a white solid (66.5 mg, 71% isolated yield) following purification: initial HPLC purity 93%; t_R = 13.4 min; mp 188−190 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.19−1.36 (m, 1H), 1.38−1.54 (m, 1H), 1.58−1.74 (m, 2H), 1.86−2.02 (m, 1H), 2.24−2.42 (m, 2H), 2.50−2.64 (m, 1H), 3.09 (d, J = 13.5 Hz, 1H), 3.58 (d, J = 13.5 Hz, 1H), 4.24 (t, J = 6.6 Hz, 1H), 4.33 (dd, J_1=6.6 Hz, J_2=10.8 Hz, 1H), 4.56 (dd, J_1=6.6 Hz, J_2=10.8 Hz, 1H), 7.02−7.10 (m, 2H), 7.14−7.22 (m, 3H), 7.26−7.38 (m, 4H), 7.55 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 16.8, 23.2, 24.9, 34.4, 41.1, 47.3, 64.7, 66.3, 119.4, 119.9, 125.0, 125.1, 126.8, 127.0, 127.7, 128.2, 129.7, 136.0, 141.3, 143.8, 143.9, 154.3, 174.4; IR (cm^{-1}) 3410, 3027, 2947, 2251, 1712, 1504, 1451, 1217, 1080; HRMS *m/z* calcd for $C_{29}H_{28}N_2O_4Na$ 491.1947 for ($M + Na^+$), found 491.1958.

2-(Benzoylamino)-2-(4-cyanobutyl)benzenepropanoic Acid (11h). Prepared as described above starting from Fmoc-Phe-Wang resin (0.200 g, 1.0 mmol/g) using 1-bromo-4-chlorobutane (231 μL, 10 equiv) in the alkylation step and benzoyl chloride (232 μL, 10 equiv) instead of Fmoc-Cl during the acylation step to provide a white solid (47.6 mg, 68% isolated yield) following purification: initial HPLC purity 88%; t_R = 9.8 min; mp 124−126 °C; ^{1}H NMR (CD_3OD) δ 1.42−1.58 (m, 2H), 1.62−1.76 (m, 2H), 2.00−2.12 (m, 1H), 2.47 (t, J = 6.9 Hz, 2H), 2.48−2.60 (m, 1H), 3.37 (d, J = 13.8 Hz, 1H), 3.67 (d, J = 13.8 Hz, 1H), 7.12−7.20 (m, 2H), 7.20−7.26 (m, 3H), 7.42−7.52 (m, 2H), 7.52−7.60 (m, 1H), 7.64 (s, 1H), 7.71 (d, J = 6.6 Hz, 2H); ^{13}C NMR (CD_3OD) δ 17.2, 24.4, 26.4, 35.1, 40.9, 66.4, 121.0, 127.9, 128.0, 129.2, 129.8, 131.0, 132.8, 136.2, 137.7, 169.4, 175.9; IR (cm^{-1}) 3403, 3032, 2945, 2251, 1725, 1660, 1518, 1488; HRMS *m/z* calcd for $C_{21}H_{23}N_2O_3$ 351.1709 for ($M + H^+$), found 351.1717.

Strategy 2

Preparation of the 3,4-Dichlorobenzaldehyde Imine of Ala-Wang Resin. Described previously for strategy 1 (168 μmol scale).

Alkylation of the Benzaldehyde Imine of Ala-Wang Resin with an α,ω-Dihaloalkane. Described previously for strategy 1 (168 μmol scale).

Hydrolysis of the Imine in Resin-Bound Alkylated Products. Described previously for strategy 1 (168 μmol scale).

Acylation of Resin-Bound Product with 2-Naphthoyl Chloride. The resin-bound amine (168 μmol) was washed with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). 2-Naphthoyl chloride (320 mg, 10 equiv) was dissolved in NMP (1.8 mL), added to the resin, and the acylation was started by the addition of DIEA (570 μL, 20 equiv). The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), THF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Nucleophilic Displacement of the Halide. The resin bound amide (168 μmol) was swollen with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). Nucleophilic displacement of the halide was carried out in a glass vessel by adding tetrabutylammonium iodide (620 mg, 10 equiv) to the resin in NMP (2 mL), followed by the addition of benzylamine (370 μL, 20 equiv). The reaction mixture was heated at 85 °C for 24 h with occasional agitation. The resin was then washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), THF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Cleavage of the Product from the Resin and Final Purification. The resin was cleaved with TFA−TES (95:5, 2 × 5 mL, 1 × 2 h, + 1 × 30 min). The filtrates from the cleavage reaction were collected, combined with the TFA−CH_2Cl_2 washes (1:3, 2 × 5 mL, 2 min each) of the resin, and evaporated under a stream of argon. The crude residue was purified using reversed-phase chromatography (19 × 100 mm symmetry column) and elution with a linear 10−50% gradient of 0.1% TFA of CH_3CN into 0.1% aqueous TFA at 20 mL/min for 11 min.

2-Methyl-2-[(2-naphthalenylcarbonyl)amino]-6-[(phenylmethyl)amino]hexanoic Acid (11i). Prepared as described above using 1-bromo-4-chlorobutane (194 μL, 10 equiv) in the alkylation step to provide a solid (47.0 mg, 54% isolated yield) following purification. The pure product was isolated as the trifluoroacetate salt: initial HPLC purity 86%; t_R = 9.5 min; mp 94−96 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.18−1.44 (m, 2H), 1.56−1.72 (m, 2H), 1.68 (s, 3H), 1.82−1.98 (m, 1H), 2.30−2.44 (m, 1H), 2.85 (t, J = 7.2 Hz, 2H), 3.70 (broad, 3H), 4.02 (s, 2H), 7.26−7.38 (m, 5H), 7.48−7.58 (m, 2H), 7.74−7.92 (m, 4H), 8.27 (s, 1H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 21.2, 22.9, 25.5, 35.3, 46.4, 51.1, 60.2, 123.3, 126.7, 127.5, 127.6, 127.7, 128.3, 128.9, 129.0, 129.4, 129.7, 130.2, 131.4, 132.5, 134.7, 167.3, 176.6; IR (cm^{-1}) 1670, 1628, 1519, 1503, 1207, 1142; HRMS *m/z* calcd. for $C_{25}H_{29}N_2O_3$ 405.2178 for ($M + H^+$), found 405.2181.

2-Methyl-2-[(2-naphthalenylcarbonyl)amino]-6-pyrrolidinohexanoic Acid (11j). Prepared as described above, using 1-bromo-4-chlorobutane (194 μL, 10 equiv) in the alkylation step, and pyrrolidine (280 μL, 20 equiv) instead of benzylamine for the nucleophilic displacement of the halide at 60 °C for 24 h, to provide a solid (46.2 mg, 57% isolated yield) following purification. The pure product was isolated as the trifluoroacetate salt: initial HPLC purity 90%; t_R = 8.6 min; mp 148−150 °C; ^{1}H NMR (CD_3SOCD_3) δ 1.20−1.42 (m, 2H), 1.48 (s, 3H), 1.56−1.72 (m, 2H), 1.74−2.14 (m, 6H), 2.88−3.04 (m, 2H), 3.00−3.18 (m, 4H), 7.55−7.68 (m, 2H), 7.86−8.08 (m, 4H), 8.45 (d, J = 5.1 Hz, 1H), 9.50 (broad, 1H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 21.4, 23.0, 23.2, 25.2, 34.8, 53.7, 55.2, 60.3, 123.4, 126.7, 127.4, 127.6, 127.7, 128.4, 128.9, 131.6, 132.6, 134.8, 166.9, 176.6; IR (cm^{-1}): 1661, 1517, 1503, 1451, 1196, 1141; HRMS *m/z* calcd for $C_{22}H_{29}N_2O_3$ 369.2178 for ($M + H^+$), found 369.2190.

2-Methyl-2-[(2-naphthalenylcarbonyl)amino]-6-anilinohexanoic Acid (11k). Prepared as described above using 1-bromo-4-chlorobutane (194 μL, 10 equiv) in the alkylation step and aniline (765 μL, 50 equiv) instead of benzylamine for the nucleophilic displacement of the halide. After cleavage from the resin, the crude product was purified by silica gel flash chromatography with $CHCl_3$−THF−HOAc (80:20:1) to provide an oil (45.5 mg, 69% isolated yield): initial HPLC purity 89%, t_R = 9.2 min; ^{1}H NMR (CD_3OD) δ 1.42−1.60 (m, 2H), 1.62−1.76 (m, 2H), 1.70 (s, 3H), 2.10−2.28 (m, 2H), 3.13 (t, J = 7.2 Hz, 2H), 6.62−6.72 (m, 1H), 6.68 (d, J = 8.1 Hz, 2H), 7.12 (dd, J_1=7.2 Hz, J_2=8.1 Hz, 2H), 7.54−7.66 (m, 2H), 7.82−8.06 (m, 4H), 8.38 (s, 1H); ^{13}C NMR (CD_3OD) δ 22.8, 23.2, 30.3, 37.5, 45.2, 61.3, 114.6, 118.6, 124.9, 127.8, 128.7, 128.8, 129.3, 130.0, 133.2, 134.0, 136.3, 149.6, 169.6, 177.8; IR (cm^{-1}) 3409, 3009, 2940, 2864, 1715, 1657, 1604, 1516, 1503, 1450; HRMS *m/z* calcd for $C_{24}H_{27}N_2O_3$ 391.2022 for ($M + H^+$), found 391.1989.

6-Azido-2-methyl-2-[(2-naphthalenylcarbonyl)amino]-hexanoic Acid (11l). Prepared as described above using 1-bromo-4-chlorobutane (194 μL, 10 equiv) in the alkylation step. Nucleophilic displacement of the halide was carried out in a syringe by adding tetrabutylammonium iodide (620 mg, 10 equiv) to the dried resin bound amide (168 μmol), followed by the addition of a solution of tetrabutylammonium azide (478 mg, 10 equiv) in NMP (3 mL). The reaction mixture was rotated for 24 h at 25 °C. The resin was then filtered and washed with NMP (4 × 4 mL, 0.5 min each), CH_2Cl_2 (4 × 4 mL, 0.5 min each), and NMP (4 × 4 mL, 0.5 min each). A second nucleophilic displacement (24 h) by the same procedure

as described above was then carried out. After cleavage from the resin, the crude residue was purified over silica gel with $CHCl_3$−THF−HOAc (92:8:1) to provide an amorphous white solid (36.0 mg, 63% isolated yield): initial HPLC purity 87%; t_R = 10.6 min; ^{1}H NMR (CD_3OD) δ 1.40−1.58 (m, 2H), 1.69 (s, 3H), 1.60−1.74 (m, 2H), 2.16 (t, J = 8.4 Hz, 2H), 3.32−3.38 (m, 2H), 7.56−7.68 (m, 2H), 7.86−8.06 (m, 4H), 8.40 (s, 1H), 8.45 (broad, 1H); ^{13}C NMR (CD_3OD) δ 22.4, 23.1, 30.0, 37.1, 52.2, 61.1, 124.9, 127.8, 128.8, 128.8, 129.3, 130.0, 133.1, 134.0, 136.3, 169.7, 177.5; IR (cm^{-1}) 3409, 2942, 2868, 2100, 1716, 1658, 1519, 1503, 1450; HRMS m/z calcd for $C_{18}H_{21}N_4O_3$ 341.1614 for (M + H$^+$), found 341.1624.

2-Methyl-2-[(2-naphthalenylcarbonyl)amino]-7-[(phenylmethyl)amino]heptanoic Acid (11m). Prepared as described above using 1-bromo-5-chloropentane (221 μL, 10 equiv) in the alkylation step to provide a solid (49.2 mg, 55% isolated yield) following purification. The pure product was isolated as the trifluoroacetate salt: initial HPLC purity 89%; t_R = 9.9 min; mp 87−89 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.08−1.40 (m, 4H), 1.52−1.66 (m, 2H), 1.68 (s, 3H), 1.78−1.94 (m, 1H), 2.28−2.44 (m, 1H), 2.79 (t, J = 7.5 Hz, 2H), 3.79 (broad, 2H), 4.00 (s, 2H), 7.25−7.40 (s, 5H), 7.46−7.58 (m, 2H), 7.74−7.92 (m, 4H), 8.27 (s, 1H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 22.9, 23.3, 25.2, 25.8, 35.4, 46.4, 50.9, 60.4, 123.3, 126.7, 127.4, 127.6, 127.7, 128.4, 128.9, 129.1, 129.4, 129.7, 130.2, 131.5, 132.5, 134.7, 167.2, 176.7; IR (cm^{-1}) 1672, 1519, 1503, 1201, 1142; HRMS m/z calcd for $C_{26}H_{31}N_2O_3$ 419.2335 for (M + H$^+$), found 419.2343.

4-(Ethyl 3-mercaptopropionate)-2-methyl-2-[(2-naphthalenylcarbonyl)amino]butanoic Acid (11n). Prepared as described above using 1-bromo-2-chloroethane (140 μL, 10 equiv) in the alkylation step and DIEA (1.43 mL, 50 equiv) and ethyl 3-mercaptopropionate (1.07 mL, 50 equiv) instead of benzylamine for the nucleophilic displacement of the halide. After cleavage from the resin, the crude product was purified by silica gel flash chromatography with $CHCl_3$−THF−HOAc (92:8:1) to provide an amorphous white solid (28.5 mg, 42% isolated yield): initial HPLC purity 74%; t_R = 10.7 min; ^{1}H NMR (CD_3OD) δ 1.22 (t, J = 6.9 Hz, 3H), 1.70 (s, 3H), 2.36−2.50 (m, 2H), 2.50−2.72 (m, 4H), 2.82 (t, J = 6.9 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 7.56−7.68 (m, 2H), 7.86−8.06 (m, 4H), 8.41 (s, 1H), 8.49 (broad, 1H); ^{13}C NMR (CD_3OD) δ 14.4, 23.4, 27.4, 27.8, 35.8, 37.6, 60.9, 61.7, 124.9, 127.8, 128.8, 128.8, 129.3, 130.0, 133.0, 134.0, 136.3, 169.7, 173.7, 177.0; IR (cm^{-1}) 3406, 2987, 1726, 1658, 1519, 1503, 1449, 1223, 1192; HRMS m/z calcd for $C_{21}H_{26}NO_5S$ 404.1532 for (M + H$^+$), found 404.1541.

Acknowledgment. We gratefully acknowledge the financial support of Eli Lilly Research Laboratories and the National Institutes of Health (GM 28193).

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JO016236I