Solid and Solution Phase Organic Syntheses of Oligomeric Thioureas

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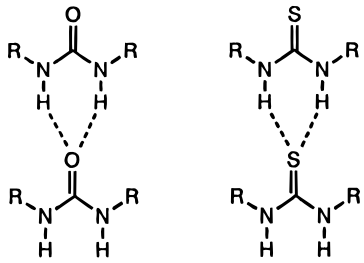
In order to study supramolecular architectures built from unnatural oligomeric and polymeric structures, one must first have an efficient synthetic strategy to produce them. Oligomers built from thiourea groups should form complex secondary and tertiary structures due to the hydrogen-bonding capabilities of the thioureas. Herein, both solution and solid phase synthetic procedures that yield oligomeric thioureas are described. They rely on the coupling of an isothiocyanate with an amine to produce the thiourea linkage. The monomers are derived from simple diamines. Higher yields are achieved using the solid phase method due to the ability to easily monitor the extent of reaction, to use a large excess of reagent, and to perform purification after cleavage from the solid support. A variety of oligomers are given as examples. The procedure is quite general, should be easily extended to complex monomers, and will allow the investigation of intramolecular and intermolecular interactions.

Introduction

Many functional groups have been incorporated into peptidomimetics in order to mimic and replace amides.[1] One group that has been used in such applications and in enzyme inhibitors is the urea group.[2] Ureas have been incorporated into solid phase synthesis schemes[3] and used as switching points for retroinversion peptidomimetics.[4] In quite a novel application, Nowick has used ureas to prepare "molecular scaffolds" for preorganizing peptides and inducing large two-dimensional pleated sheets.[5] Therefore, ureas are finding increased uses in biomimetic chemistry.

The impetus for using ureas in such a variety of applications derives from their hydrogen-bonding capabilities. Each urea oxygen can potentially form two hydrogen bonds to another properly positioned urea. Hydrogen-bonding chains have been found in the crystal structures of ureas,[6] and hence, the incorporation of such groups into unnatural biopolymers may be expected to induce secondary structures, possibly reminiscent of peptide secondary structures.



Thioureas form stronger hydrogen bonds than normal ureas,[7] due to their increased acidity.[8] Furthermore, a thiourea group is susceptible to alkylation to give isouronium salts[9] and facile transformation to the biologically interesting guanidinium functional group.[10] In order to explore such possibilities for higher order structure and exploit the reactivity of thioureas for further functionalization, a synthesis of thiourea oligomers that incorporates distinct monomers in a specific order is necessary. Herein, we describe the solid phase and solution phase syntheses of oligomeric thioureas. We focus on the successes and difficulties of these methods and leave our structural studies to a future paper.

Results and Discussion

A. Retrosynthetic Analysis. A thiourea can be formed by the facile coupling of an isothiocyanate with an amine.[11] Such reactions typically proceed with yields greater than 90% in a period of minutes to a few hours. In order to allow the incorporation of distinct monomers in specific positions in an oligomer, we employed monomers with an isothiocyanate and a protected amine group. The retrosynthesis is shown in Figure 1. The amine protecting group most widely used in peptide synthesis, and therefore easily adapted to our similar

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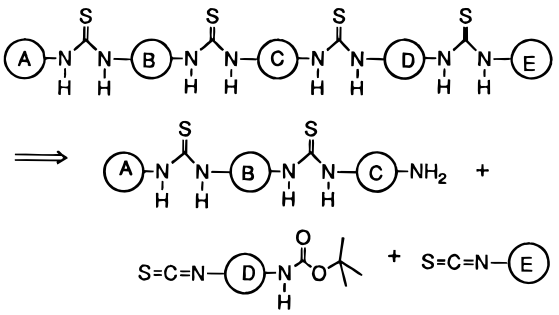

Figure 1. Retrosynthetic analysis of the last few steps for oligomeric thiourea synthesis.

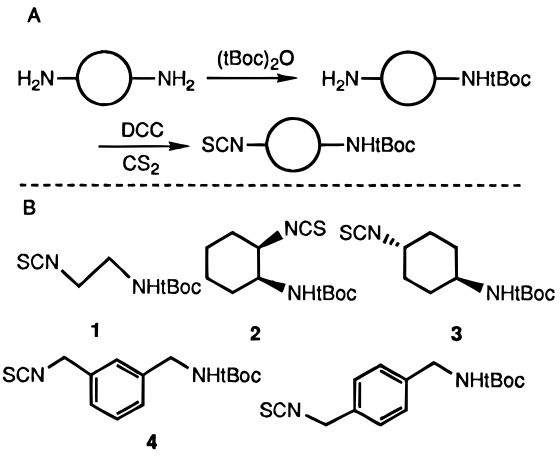

Figure 2. (A) Synthetic route to the monomers. (B) Five monomers synthesized from commercially available diamines.

procedure, is *tert*-butoxycarbonyl (tBoc).[12] After coupling and deprotection of the amine, a new monomer could be introduced, thereby incrementally constructing an oligomer as with peptide synthesis.

B. Monomer Synthesis. To test the feasibility of such an approach, simple monomers that could be rapidly produced from commercially available diamines were the initial targets (Figure 2). Protection of the diamines as the mono tBoc derivatives was achieved employing di-*tert*-butyl dicarbonate as the limiting reagent. Treatment of these monoamine/mono-tBoc compounds with carbon disulfide and dicyclohexylcarbodiimide (DCC) produced isothiocyanates.[13] The commercially available diamines did not allow much molecular diversity of side-chain functional groups, but they did allow proof of concept of the synthetic strategy.

C. Solution Phase Synthesis. The coupling reactions were examined in solution to assess their feasibility for solid phase synthesis (Figure 3). Our initial target (**5**) of the solution phase synthesis incorporated a phenylalanine spacer dipeptide (**6**) that would be the C-terminus of the oligomers produced by the solid phase method (see the next section for a discussion of this specific C-terminus). Although **5** was the target of this initial synthesis, each intermediate tBoc derivative (**7** and **8**) and each amine (**9**−**11**) were also purified and fully characterized. Each monomer was added to a solution of the growing oligomer in dichoromethane (DCM), except for the last coupling which was performed in tetrahydrofuran (THF). The solutions were allowed to stir at ambient temperature, and the products were purified by silica gel chromatography.

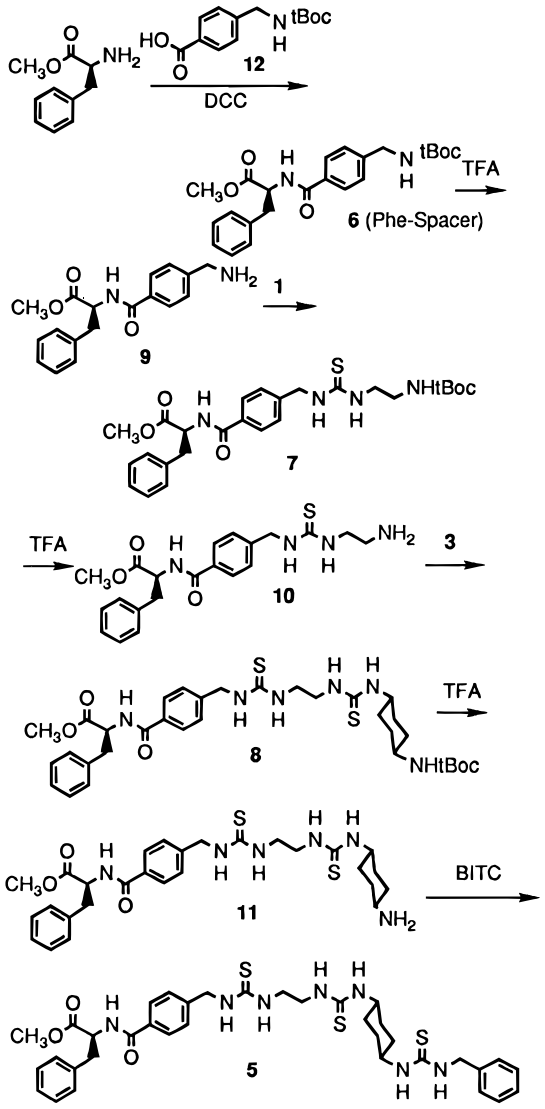

Figure 3. Synthetic route to **5**. BITC, benzyl isothiocyanate.

As the oligomer length increased, the reaction times for the couplings became longer and the yields were poorer. For example, the first coupling typically proceeded in 70−80% yields, the second coupling around 40−50%, and the third coupling near 20%. The decrease in the yields could be attributed to decreasing solubility of the oligomers as their length increased. Although this did not bode well for the coupling efficiencies, we realized that the solid phase method would employ a large excess of monomer, which could be recovered after each reaction. In addition, the analytical ninhydrin test could be used to monitor the solid phase method. Therefore, we proceeded to the synthesis on the solid support.

D. Solid Phase Synthesis. In order to synthesize thioureas on solid support, a few considerations were necessary. The first was the selection of a resin best suited to our synthesis strategy. PAM (phenylacetamidomethyl) resin was chosen since it has been shown to be quite stable to the TFA deprotection conditions for removal of a tBoc group.[14] Use of this resin results in

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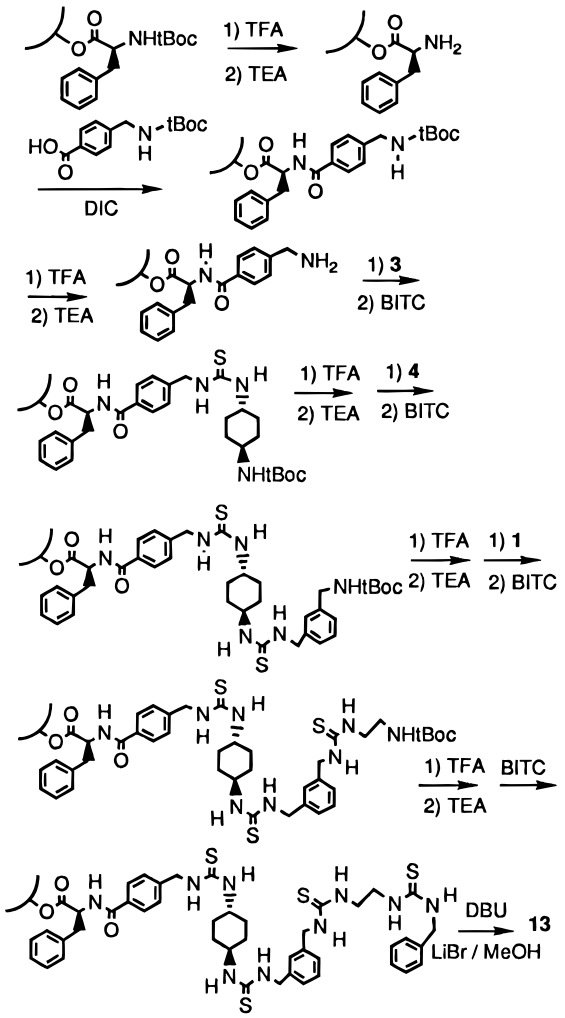

Figure 4. Solid phase synthetic route to **13**. BITC, benzyl isothiocyanate.

the creation of an ester linkage between the growing chain and the solid support.

The second consideration was a concern over a possible Edman-type degradation reaction. The Edman degradation reaction, widely used for polypeptide sequencing,[15] involves the derivitization of an N-terminus of a peptide with an isothiocyanate. The resulting thiourea cyclizes on the adjacent amide bond, resulting in clipping of the terminal amino acid from the polymer. Therefore, attaching a thiourea adjacent to an ester linkage to a solid phase support would be expected to result in a facile cyclization yielding a thiazolone. Indeed, if a monomer was directly attached to an amino acid that was already on the solid support, we found excellent yields of thiazolones during the tBoc deprotection conditions.[16] Therefore, we devised a strategy of spatially removing the growing thiourea chain from the ester bond to the resin via a rigid spacer (**12**, Figure 3); *p*-carboxybenzylamine was chosen since it is commercially available. As expected, incorporation of this spacer into all of the solid phase syntheses eliminated the thiourea cyclization on to the ester that forms the attachment to the resin.

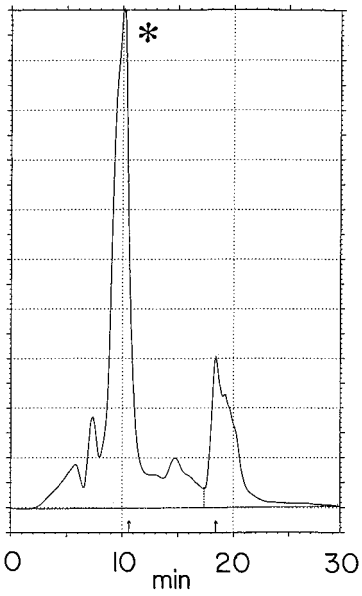

Figure 5. HPLC trace of the crude products from the synthesis of **14**. **14** is indicated with an asterisk. The chromatogram shows the crude reaction mixture on a reverse phase analytical column employing a 1 mL/min follow rate and a gradient over 30 min starting with 25% water in acetonitrile and ending with pure acetonitrile.

The final consideration was the initial linkage to the resin. Either the rigid spacer **12** could be directly attached to the resin, or an amino acid could be used as the attachment point. Although we have demonstrated that derivitization of the resin with the spacer is possible (see below), the yield was low (20%). Since modification of the resin with the first monomer was not a key goal in demonstrating the synthetic methodology for oligomeric ureas, we concentrated upon a commercially available resin with a phenylalanine unit already attached.

A complete synthetic route for one oligomer (**13**) is shown in Figure 4. The procedure starts with a deprotection of the terminal tBoc on the phenylalanine, followed by a coupling of the rigid spacer to the resulting amine using diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole hydrate (HOBT), and then another tBoc deprotection. At this point, the monomers are added incrementally, each time followed by a tBoc deprotection. The trifluoroacetic acid (TFA) deprotection solution included 1,2-ethanedithiol or thioanisole as a *tert*-butyl cation scavenger. The coupling reactions typically required 3 d at 45 °C and were followed with the qualitative ninhydrin test.[17] After the reaction was found to be complete, a solution of benzyl isothiocyanate (or acetic anhydride) was added to cap any remaining amines on the growing oligomers. Though the final oligomers were likewise capped with this same reagent, capping with other isothiocyanates could increase diversity. Clipping of the oligomers from the resin was performed with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and LiBr in MeOH.[18] When the oligomers were sufficiently soluble, purification could either be performed by flash silica gel chromatography or HPLC on semipreparative silica or reverse phase columns. Figure 5 shows a typical HPLC trace

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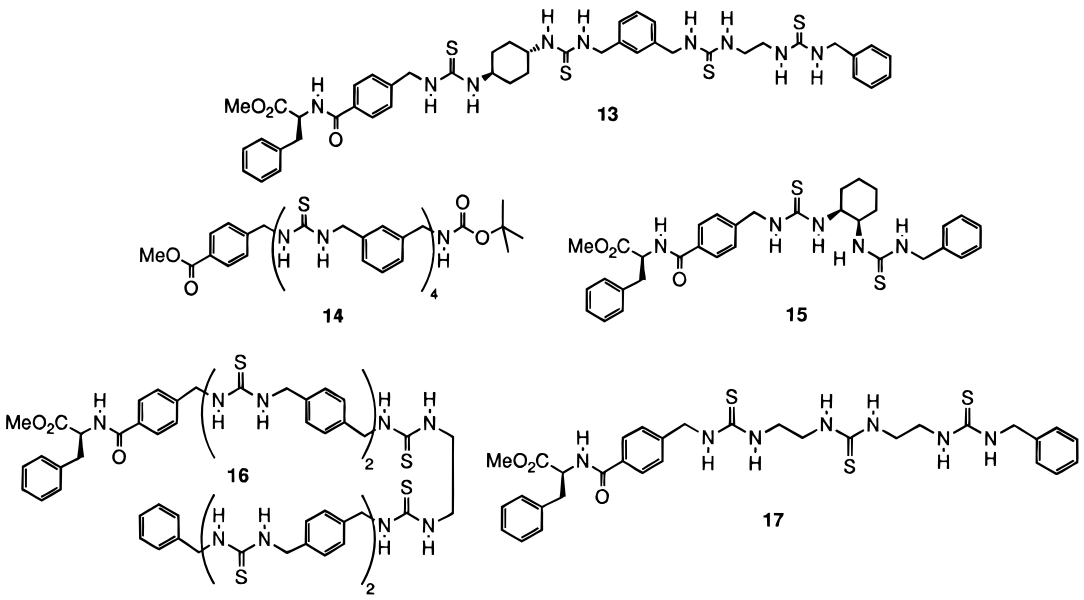

Figure 6. Oligomers produced using the solid phase method.

for a crude reaction mixture obtained directly after cleavage from the resin. When the oligomers were found to be too insoluble for chromatography, repeated washing and precipitation from hot methanol was found to be sufficient for greater than 80−90% purification. The yields of the oligomers are good (20−50%), but not quite as good as those routinely found for the solid phase organic synthesis of peptides. We estimate that the yields of the individual couplings steps to form the thiourea linkages are near 90%.

Figure 6 shows a variety of oligomers produced using this method. As can be seen with structure **14**, one does not require an amino acid C-terminus, but the rigid spacer is required. In addition, thioureas can be efficiently formed with amines or isothiocyanates attached to both primary and secondary carbons, as demontrated in the synthesis of **13** and **15**. As shown by **16**, quite long oligomers, incorporating six thioureas, are accessible. Unfortunately, the solubility of these molecules becomes quite low once four or more thioureas are included. Thus, the high insolubility of **16** prevented conventional characterization. Although a ^{1}H NMR in DMSO-d_6 indicated that all the appropriate resonances were present, and in the correct ratios, neither ^{13}C NMR nor MS analysis was successful. All the oligomers are highly hygroscopic and have a strong tendency to retain solvents such as alcohols, ether, and ethyl acetate, making the ability to obtain correct C, H, N analyses nearly impossible. Finally, it should be noted that NMR spectra of the oligomers are temperature dependent, indicating significant conformational restriction. Differing conformations likely result from a combination of the well-documented restriction to rotation of the C−N bonds of thioureas[19] and intramolecular hydrogen bonds which induce secondary structure. We are currently exploring further derivitization of the thioureas to other functional groups and are examining monomers with side chains for future supramolecular receptor and catalyst designs.

Summary

An efficient methodology for the solid phase synthesis of oligomeric thioureas has been developed. The method builds upon the well-known procedure to produce peptides. Besides the advantages of monitoring the reactions, pushing them to completion with the use of excess reagents, and the subsequent simple isolation of the final support-bound thiourea products, the method should also benefit from the remarkable encoding strategies and bead identification methods developed for solid phase syntheses.[20] The disadvantages are that a rigid spacer is required to separate the growing chain from the solid support and that longer oligomers are quite insoluble and difficult to characterize by conventional methods.

Experimental Section

General Information. ^{1}H and ^{13}C NMR spectra and low-resolution and high-resolution mass spectra were measured at the spectral facilities on the campus of the University of Texas. Elemental analyses were performed by Atlantic Microlab, Inc. All chromatographic separations were carried out with 40 μm silica gel from Scientific Adsorbents Inc. High-performance liquid chromatography was performed with Prep-Pak silica column packing.

Supplies. Merrifield and PAM resins with Boc-Phe attached were purchased from Peptides International Inc. TFA,

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DCC, DMF, DBU, benzyl isothiocyanate, 1,2-ethanedithiol, HBOT (Aldrich), LiBr (Janssen), ethyldiisopropylamine (EDA), DIC, and CS_2 (Fluka) were purchased from commercial sources. THF was distilled from sodium benzophenone ketyl radical. DCM and EDA were refluxed and distilled from calcium hydride. Compound **1** was synthesized by a literature procedure.[21]

Monomer Syntheses. (1) *cis*-2-[[(1,1-Dimethylethoxy)-carbonyl]amino]cyclohexylamine. In a 50-mL round-bottom flask was placed a solution of di-*tert*-butyl dicarbonate (2.05 g, 9.39 mmol) in chloroform (5.0 mL) under an atmosphere of Ar. To this was added a solution of *cis*-1,2-diaminocyclohexane (2.15 g, 18.8 mmol) in chloroform (20 mL) over a period of 6 h. The solution was stirred an additional 5 h. The chloroform was removed under reduced pressure. The resulting yellow oil was redissolved in DCM (30 mL) and washed with a saturated aqueous solution of sodium carbonate (3 × 50 mL). The DCM solution was collected, dried, and concentrated. The resulting oil was purified by flash chromatography (DCM/ammonia saturated methanol, 9:1) to yield 1.58 g of a yellow oil (79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (br, 1 H), 3.57 (br, 1 H), 2.98 (m, 1 H), 1.42 (s, 9 H), 1.20−1.63 (m, 10 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.67, 78.98, 51.64, 49.89, 32.04, 28.38, 27.97, 22.95, 20.81; HRMS (CI$^+$ *m*/*z*) calcd for $C_{11}H_{23}N_2O_2$ (M + H$^+$) 215.1760, obsd 215.1773.

(2) *cis*-2-[[(1,1-Dimethylethoxy)carbonyl]amino]cyclohexyl Isothiocyanate (2). In a 100-mL round-bottom flask under Ar was placed dicyclohexylcarbodiimide (1.44 g, 7.00 mmol), carbon disulfide (2.87 mL, 47.7 mmol), and THF (30 mL). The solution was cooled to −5 °C. To this was added a solution of *cis*-2-[[(1,1-dimethylethoxy)carbonyl]amino]cyclohexylamine (1.50 g, 7.00 mmol) in THF (20 mL) over a period of 30 min. This mixture was allowed to stir at ambient temperature for 15 h. THF was removed under reduced pressure, and the resulting white solid was resuspended in diethyl ether (30 mL) and filtered. The filtrate was concentrated to give a white solid which was further purified by flash chromatography (hexanes/ethyl acetate, 3:1) to afford 1.51 g of a white crystalline material (84%): mp 95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, 1 H), 4.23 (br, 1 H), 3.61 (m, 1 H), 2.05 (m, 1 H), 1.82−1.24 (m, 7 H), 1.45 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.81, 132.48, 79.85, 58.60, 51.66, 30.73, 28.28, 27.41, 24.27, 19.64; HRMS (CI$^+$ *m*/*z*) calcd for $C_{12}H_{21}N_2O_2S$ (M + H$^+$) 257.1324, obsd 257.1325. Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.05; H, 7.84; N, 10.89. Found: C, 56.10; H, 7.80; N, 10.87.

(3) *trans*-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-cyclohexylamine. In a 500-mL round-bottom flask under Ar was placed *trans*-1,4-diaminocyclohexane (10.0 g, 87.6 mmol) and chloroform (200 mL). To this was added over a period of 3 h a solution of di-*tert*-butyl dicarbonate (9.56 g, 43.8 mmol) in chloroform (150 mL). The milky white suspension was stirred for 15 additional h. The chloroform was removed under reduced pressure. To the white residue was added DCM (150 mL) and a saturated aqueous solution of sodium carbonate (200 mL). The layers were separated, and the organic layer was washed with the sodium carbonate solution (2 × 100 mL). The DCM solution was collected, dried (Na_2SO_4), and concentrated *in vacuo* to a white solid. Flash chromatography (DCM/ammonia saturated methanol, 9:1) furnished 7.24 g of white powder (77%): mp 74.5−75.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (br, 1 H), 3.30, br, 1 H), 2.52 (m, 1 H), 1.91 (d, 2 H), 1.78 (br, 4 H), 1.36 (s, 9 H), 1.10 (m, 4 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.70, 77.71, 48.99, 48.24, 34.33, 31.12, 27.61; HRMS (CI$^+$ *m*/*z*) calcd for $C_{11}H_{23}N_2O_2$ (M + H$^+$) 215.1760, obsd 215.1755.

(4) *trans*-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-cyclohexyl Isothiocyanate (3). To a solution of dicyclohexylcarbodiimide (7.00 g, 32.7 mmol) and carbon disulfide (13.4 mL, 223 mmol) in THF (50 mL) was added a solution of *trans*-4-[[(1,1-dimethylethoxy)carbonyl]amino]cyclohexylamine (5.08 g, 23.7 mmol) in THF (20 mL) over a period of 30 min at −5 °C. This solution was allowed to warm to room temperature and stirred for an additional 21 h under Ar. The reaction mixture was concentrated to an orange solid and resuspended in diethyl ether (200 mL). The suspension was filtered, and the filtrate was concentrated to an orange solid. This solid was further purified by flash chromatography (hexanes/ethyl acetate, 3:1) to afford 6.31 g of colorless needles (75%): mp 114.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (br, 1 H), 3.54 (m, 1 H), 3.43 (br, 1 H), 2.06 (m, 4 H), 1.62 (ddd, 2 H), 1.42 (s, 9 H), 1.18 (ddd, 2 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.99, 130.58, 79.35, 54.75, 47.83, 31.83, 30.56, 28.28; HRMS (CI$^+$ *m*/*z*) calcd for $C_{12}H_{21}N_2O_2S$ (M + H$^+$) 257.1324, obsd 257.1324. Anal. Calcd for $C_{12}H_{20}N_2O_2S$: C, 56.05; H, 7.84; N, 10.89. Found: C, 56.16; H, 7.86; N, 10.89.

(5) 3-[(1,1-Dimethylethoxy)carbonyl]amino]benzyl-amine. Di-*tert*-butyl dicarbonate (8.27 g, 37.9 mmol) in chloroform (80 mL) was added dropwise over a period of 2 h to a solution of *m*-xylylenediamine (10.0 mL, 75.8 mmol) in chloroform (15 mL). The mixture was stirred 20 h under Ar. The chloroform was removed *in vacuo*, and a saturated, aqueous solution of sodium carbonate (200 mL) and DCM (200 mL) were added. The layers were separated and the aqueous layer was extracted with DCM (3 × 150 mL). The extracts were combined, dried (Na_2SO_4), and concentrated to a yellow oil. Further purification by flash chromatography (DCM/ammonia saturated methanol, 9:1) afforded 4.54 g of an opaque oil (52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, 1 H), 7.12 (m, 3 H), 5.23 (br, 1 H), 4.23 (d, 2 H), 3.77 (s, 2 H), 1.53 (s, 2 H), 1.41 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.80, 143.35, 139.12, 128.53, 125.78, 125.65, 125.92, 79.13, 46.11, 44.37, 28.22; HRMS (CI$^+$ *m*/*z*) calcd for $C_{13}H_{21}N_2O_2$ (M + H$^+$) 237.1603, obsd 237.1605.

(6) 3-[[(1,1-Dimethylethoxy)carbonyl]amino]benzyl Isothiocyanate (4). A solution of 3-[(1,1-dimethylethoxy)-carbonyl]amino]benzylamine (4.43 g, 18.8 mmol) in THF (100 mL) was added dropwise over a period of 30 min to a solution of 1,3-dicyclohexylcarbodiimide (3.88 g, 18.8 mmol) and carbon disulfide (7.70 mL, 128 mmol) in THF (60 mL) at −5 °C. The reaction mixture was allowed to warm with stirring to room temperature over 20 h. THF was removed *in vacuo* and diethyl ether (300 mL) was added. The white precipitate was filtered, and the filtrate was collected and concentrated to a yellow oil. This oil was further purified by flash chromatography (hexanes/ethyl acetate, 3:1) to yield 4.12 g of a white solid (79%): mp 43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 1 H), 7.24 (m, 3 H), 4.89 (br, 1 H), 4.71 (s, 2 H), 4.32 (d, 2 H), 1.47 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.81, 139.95, 134.49, 132.45, 129.15, 127.24, 125.65, 79.56, 48.48, 44.26, 28.31; HRMS (CI$^+$ *m*/*z*) calcd for $C_{14}H_{19}N_2O_2S$ (M + H$^+$) 279.1167, obsd 279.1167. Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.52; H, 6.56; N, 10.16.

(7) 4-[[(1,1-Dimethylethoxy)carbonyl]amino]benzyl-amine. Di-*tert*-butyl dicarbonate (9.17 g, 42.0 mmol) in chloroform (200 mL) was added dropwise over a period of 2.5 h to a solution of *p*-xylylenediamine (11.90 g, 87.4 mmol) in chloroform (100 mL). The mixture was stirred 17 h under Ar. A chalky, white precipitate formed. This solid was filtered and washed in cold chloroform (4 °C, 100 mL). The organic fractions were combined, and the chloroform was removed *in vacuo*. To this was added water (200 mL) and DCM (200 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 150 mL). The extracts were combined, dried (Na_2SO_4), and concentrated to an oil containing white solids. To the oil was added chloroform (25 mL), and the solution was left on ice for 1 h. The solution was filtered, and the white precipitate washed with chloroform (4 °C, 100 mL). The precipitates were combined and resuspended in chloroform (500 mL). The solution was refluxed under argon for 15 min and then allowed to slowly cool. The solution was placed on ice for 1 h, and the precipitated product (5.10 g, 51%) collected by filtering: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.05 (m, 4 H), 5.70 (br, 1 H), 4.06 (d, 2 H), 3.62 (t, 2 H), 1.33 (s, 2 H), 1.30 (s, 9 H); ^{13}C {^{1}H} NMR (62 MHz, $CDCl_3$) δ 155.62, 137.93, 130.70, 127.46, 127.10, 79.40, 45.97, 44.18, 28.17; HRMS (CI$^+$ *m*/*z*) calcd for $C_{13}H_{21}N_2O_2$ (M + H$^+$) 237.1603, obsd 237.1605.

(21) Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C.-Y.; Anslyn, E. V. *J. Am. Chem. Soc.* **1993**, *115*, 10042.

(8) 4-[[(1,1-Dimethylethoxy)carbonyl]amino]benzyl Isothiocyanate. A solution of 4-[(1,1-dimethylethoxy)carbonyl]-amino]benzylamine (5.10 g, 21.6 mmol) in THF (130 mL) was added dropwise over a period of 2 h to a solution of 1,3-dicyclohexylcarbodiimide (4.54 g, 22.0 mmol) and carbon disulfide (9.0 mL, 149.6 mmol) in THF (80 mL) at −5 °C. The reaction mixture was allowed to warm with stirring to room temperature over 24 h. The THF was removed *in vacuo*, and diethyl ether (400 mL) was added. The precipitate was filtered, and the filtrate was collected and concentrated to a slightly yellow oil. This oil was further purified by flash chromatography (hexanes/DCM, 4:1) to yield 5.23 g of a white solid (87%): mp 74 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31−7.24 (m, 4 H), 4.90 (br, 1 H), 4.68 (s, 2 H), 4.30 (d, 2 H), 1.45 (s, 9 H); ^{13}C {^{1}H} NMR (62.5 MHz, $CDCl_3$) δ 155.83, 139.38, 133.24, 127.91, 127.10, 79.62, 48.38, 44.19, 28.35; HRMS (CI^+ *m/z*) calcd for $C_{14}H_{19}N_2O_2S$ (M + H^+) 279.1167, obsd 279.1157.

Spacer Synthesis. 4-[[(1,1-Dimethylethoxy)carbonyl]-aminomethyl]benzoic Acid (12). Di-*tert*-butyl dicarbonate (19.1 g, 87.3 mmol) was added dropwise over a period of 1 h to 4-(aminomethyl)benzoic acid (12.0 g, 79.4 mmol) in a solution of sodium hydroxide (3.18 g, 79.5 mmol), water (20 mL), and *tert*-butyl alcohol (30 mL). The mixture was stirred 18 h. Water (200 mL) was added to the mixture, and it was extracted with hexanes (3 × 75 mL). The aqueous layer was cooled with the addition of ice (100 g) and then acidified with sulfuric acid to pH 2. The cold aqueous layer was quickly extracted with ethyl acetate (2 × 100 mL). The organic layers were combined and dried, and the solvent was removed *in vacuo* to yield 18.31 g of a white powder (92%): mp 158.5 °C; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.96 (d, 2 H), 7.36 (d, 2 H), 4.89 (br, 2 H), 4.28 (br, 2 H), 1.4 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, methanol-d_4) δ 169.67, 155.23, 146.65, 130.91, 130.56, 127.97, 80.35, 44.75, 28.74; HRMS (CI^+ *m/z*) calcd for $C_{13}H_{18}NO_4$ (M + H^+) 252.1236, obsd 252.1240.

Solution Synthesis. (1) L-Phenylalanine, *N*-4-[[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]benzoyl]-, Methyl Ester (6). A solution of L-phenylalanine methyl ester hydrochloride (3.90 g, 18.0 mmol) in water (40 mL) was treated with a solution of potassium carbonate (5.0 g, 36.2 mmol) in water (15 mL). This aqueous solution was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate layers were combined, dried over anhydrous sodium sulfate, and concentrated to an oil under reduced pressure. To this residue was added DCM (50 mL) and 4-[[(1,1-dimethylethoxy)carbonyl]aminomethyl]-benzoic acid (4.69 g, 18.7 mmol) in DMF (5 mL) followed by diisopropylcarbodiimide (2.82 mL, 18.0 mmol). The solution was stirred under Ar for 18 h. To the mixture was added DCM (50 mL), and the solution was filtered through Celite. The filtrate was washed with saturated, aqueous sodium bicarbonate solution (2 × 50 mL) and a saturated, aqueous solution of ammonium chloride solution (2 × 50 mL). The DCM solution was evaporated *in vacuo* to give a white solid (5.7 g) which was purified by flash chromatography (DCM/ethyl acetate, 3:1) to give 2.72 g of a white solid (52%): mp 129.5−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 2 H), 7.28 (m, 5 H), 7.11 (d, 2 H), 6.59 (d, 1 H), 5.07 (dd, 1 H), 4.98 (br, 1 H), 4.34 (d, 2 H), 3.71 (s, 3 H), 3.28 (dd, 1 H), 3.21 (dd, 1 H), 1.45 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.01, 166.44, 155.86, 143.04, 135.71, 132.67, 129.28, 128.60, 127.36, 127.30, 127.17, 79.74, 53.44, 52.48, 44.16, 37.79, 28.35; HRMS (CI^+ *m/z*) calcd for $C_{23}H_{29}N_2O_5$ (M + H^+) 413.2076, obsd 413.2075. Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 64.42; H, 6.79; N, 6.76.

(2) L-Phenylalanine, *N*-[4-(Aminomethyl)benzoyl]-, Methyl Ester (9). To **6** (1.45 g, 3.52 mmol) in a 50-mL round-bottom flask was added a solution of TFA (15 mL) and water (5 mL). The solution was stirred 1 h. The water and TFA were evaporated *in vacuo*. To the resulting glassy solid was added a 75 mL solution of ammonium hydroxide (pH 12, 1 M NaCl). This was extracted with DCM (3 × 50 mL), dried over anhydrous sodium sulfate, and concentrated to 0.81 g of a white amorphous solid (93%): mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 2 H), 7.27 (m, 5 H), 7.13 (d, 2 H), 6.18 (d, 1 H), 5.03 (dd, 1 H), 3.88 (s, 2 H), 3.75 (s, 3 H), 3.28 (dd, 1 H), 3.20 (dd, 1 H), 2.99 (br, 2 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.07, 166.64, 145.45, 135.80, 132.41, 129.24, 128.54, 127.37, 127.30, 127.11, 53.51, 52.41, 45.45, 37.71; HRMS (CI^+ *m/z*) calcd for $C_{18}H_{21}N_2O_3$ (M + H^+) 313.1552, obsd 313.1550.

(3) L-Phenylalanine, *N*-[4-[[[[2-[[(1,1-Dimethylethoxy)-carbonyl]amino]ethyl]amino]thioxomethyl]amino]-methyl]benzyoyl]-, Methyl Ester (7). To a solution of **9** (1.44 g, 3.70 mmol) in DCM (50 mL) was added the isothiocyanate **1** (0.84 g, 4.4 mmol). The solution was stirred 4 days at room temperature. The DCM was evaporated *in vacuo*. The solid was purified by flash chromatography (DCM/ethyl acetate, 2:1) to give 1.11 g of a white fluffy solid (79%): mp 68−72 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2 H), 7.16 (m, 1 H), 5.43 (br, 1 H), 4.89 (dd, 13.2 Hz, 1 H), 4.60 (br, 2 H), 3.65 (s, 3 H), 3.48 (br 2 H), 3.16 (br, 4 H), 1.32 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 182.59 (br), 171.93, 167.09, 156.76, 141.95 (br), 135.79, 132.31, 129.93, 128.39, 127.36, 127.04, 126.91, 79.48, 53.73, 52.20, 47.42 (br), 44.57 (br), 39.89 (br), 37.38, 28.13; HRMS (CI^+ *m/z*) calcd for $C_{26}H_{34}N_4O_5S$ (M + H^+) 515.2328, obsd 515.2310.

(4) L-Phenylalanine, *N*-[4-[[[[(2-Aminoethyl)amino]-thioxomethyl]amino]methyl]benzyoyl]-, Methyl Ester (10). To **7** (0.80 g, 1.6 mmol) in a 25-mL round-bottom flask was added a solution of TFA (9 mL) and water (3 mL). The solution was stirred at room temperature for 1 h. TFA and water were removed *in vacuo*. To the resulting glassy solid was added a solution of ammonium hydroxide (pH 12, 1 M NaCl), and the solution was extracted with DCM (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to afford 0.44 g of a white amorphous solid (68%): mp 95−100 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 2 H), 7.36 (br, 1 H), 7.27 (br, 1 H), 7.13 (m, 7 H), 7.04 (br, 1 H), 4.90 (d, 1 H), 4.64 (br, 2 H), 3.65 (s, 3 H), 3.5−3.2 (br, 2 H), 3.42 (br, 2 H), 3.16 (m, 2 H), 2.99 (br, 2 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 183.01 (br), 172.04, 167.32, 142.38 (br), 135.88, 132.15, 128.94, 128.40, 127.26, 127.05, 126.92, 53.85, 52.27, 47.49 (br), 45.64 (br), 40.61 (br), 37.38; HRMS (FAB *m/z*) calcd for $C_{21}H_{26}N_4O_3S$ (M + H^+) 415.1804, obsd 415.1825.

(5) L-Phenylalanine, *N*-[4-[[[[2-[[[4-[[(1,1-Dimethyl-ethoxy)carbonyl]aminocyclohexyl]amino]thioxomethyl]]-amino]ethyl]amino]thioxomethyl]amino]methyl]benz-yoyl]-, Methyl Ester, *trans* (8). To a solution of **10** (0.40 g, 0.96 mmol) in DCM (50 mL) was added isothiocyanate **3** (0.27 g, 1.06 mmol). The solution was stirred 7 d at room temperature. The DCM was removed under reduced pressure, and the residue was purified by flash chromatography (DCM/ethyl acetate, 1:2) to give 0.33 g of a white solid (50%): mp = 132−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2 H), 7.38 (br, 2 H), 7.16 (m, 7 H), 7.07 (d, 2 H), 7.04 (br, 1 H), 6.8 (br, 1 H), 4.90 (q, 2 H), 4.64 (br, 2 H), 4.51 (d, 1 H), 3.65 (s, 3 H), 3.5−3.3 (br, 4 H), 3.16 (m, 4 H), 1.87 (br, 3 H), 1.33 (s, 9 H), 1.11 (m, 3 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 184−178 (br, 2 C), 171.95, 167.46, 155.24, 142.17 (br), 135.82, 132.15, 128.38, 128.41, 127.40, 127.05, 126.94, 79.09, 53.85, 52.29, 48.68, 47.41 (br), 44−41 (br, 3 C), 37.31, 31.48, 30.94, 28.21; HRMS (FAB *m/z*) calcd for $C_{33}H_{47}N_6O_5S_2$ (M + H^+) 671.3049, obsd 617.3059.

(6) L-Phenylalanine, *N*-[4-[[[[[[2-[[[(4-Aminocyclo-hexyl)amino]thioxomethyl]]amino]ethyl]amino]thi-oxomethyl]amino]methyl]benzyoyl]-, Methyl Ester, *trans* (11). To **8** (0.15 g, 0.22 mmol) in a 25-mL round-bottom flask was added a solution of TFA (1.5 mL) and water (0.5 mL). The solution was stirred at room temperature for 1 h. TFA and water were removed in *vacuo*. To the resulting glassy solid was added a solution of ammonium hydroxide (pH 12, 1 M NaCl). The aqueous solution was decanted, and the residue was dissolved in THF, dried (Na_2SO_4), and concentrated under reduced pressure to afford 0.13 g of a clear glassy solid (98%): mp 130 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (d, 1 H), 8.05 (br, 1 H), 7.81 (br 1 H), 7.73 (d, 2 H), 7.43 (br, 2 H), 7.32 (d, 2 H), 7.25 (m, 3 H), 7.15 (m, 2 H), 4.65 (m, 5 H), 3.62 (s, 3 H), 3.50 (br, 4 H), 3.12 (dd, 2 H), 2.94 (br, 2 H), 1.89, (br, 3 H), 1.32 (m, 3, H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 184−178 (br, 2 C), 172.10, 166.11, 142.96 (br), 137.63, 132.10, 128.98, 128.14, 127.27, 126.83, 126.38, 54.17, 51.85, 48.41, 46.5 (br), 44−41 (br, 3 C), 36.19, 29.68, 29.00; HRMS (FAB *m/z*) calcd for $C_{28}H_{39}N_6O_3S_2$ (M + H^+) 571.2525, obsd 571.2524.

(7) L-Phenylalanine, *N*-[4-[[[[[2-[[[[4-[(Phenylmethyl)-amino]thioxymethyl]amino]cyclohexyl]amino]thioxo-methyl]]amino]ethyl]amino]thioxomethyl]amino]methyl]-benzyoyl]-, Methyl Ester, *trans* (5). To a solution of **11** (0.15 g, 0.22 mmol) in THF (10 mL) was added benzyl isothiocyanate (0.034 mL, 0.26 mmol). The solution was stirred 21 days at room temperature. The solvent was removed under reduced pressure, and the residue was purified by reverse phase HPLC. A gradient from 50% acetonitrile and water to 100% acetonitrile over 30 min was employed with a flow rate of 45 mL/per min to elute the product at 20 min. A clear glassy solid (0.030 g, 19%) was isolated: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 1 H), 7.54 (d, 2 H), 7.24 (br, 9 H), 7.12 (d, 2 H), 6.92 (br, 3 H), 6.30 (br, 2 H), 6.29 (br, 2 H), 4.87 (m, 1, H), 4.84 (br, 2 H), 4.67 (br, 2 H), 3.85, (br, 2 H), 3.72 (s, 3 H), 3.6−3.4 (br, 4 H), 3.33 (br, 2 H), 3.18 (br, 2 H), 1.96, (br, 3 H), 1.15 (br, 3 H); ^{13}C {^{1}H} NMR (125 MHz, acetonitrile-d_3) δ 183 (br, 3 C), 173.08, 167.73, 144 (br), 140 (br), 138.27, 133.61, 130.25, 129.42, 129.38, 128.30, 128.24, 127.99, 127.76, 125.72, 55.21, 53.02 (br), 52.85, 48.18 (br, 2C), 46.5 (br), 45−43 (br, 3 C), 37.98, 31.76, 30.34, 29.43; HRMS (FAB *m/z*) calcd for $C_{36}H_{45}N_7O_3S_3$ ($M + H^+$) 720.2824, obsd 720.2814

General Protocol for Solid Phase Synthesis. The solid phase resins were stored and weighed in a drybox. The resin, 0.5−1.0 g of 0.25−0.5 mequiv/g, was suspended in a reaction chamber in 80 mL of DCM under inert atmosphere. The resin was allowed to swell in the solvent for at least 1 h. The solvent was removed from the chamber by application of N_2 pressure, and 80 mL of a fresh 1:1:3 solution of TFA/1,2-ethanedithiol/DCM (solution A) was added. In the synthesis of **14**, a 9:9:2 ratio of TFA/DCM/thioanisole was used. The resulting solution was allowed to shake for 30 min, followed by removal of the solvents and reagents by N_2 pressure. The resin was then washed twice with 80 mL of 10% EDA solution in DCM. The resin was then washed six times with 80 mL of DCM. A small amount of the resin would be removed at this point and subjected to the ninhydrin test.[17] When the ninhydrin test indicated that the reaction was incomplete, another cycle of TFA and EDA treatment was repeated. After deprotection of the first tBoc group, a spacer (**12**) was added so that an Edman degradation reaction would not occur (see the Results and Discussion section).

The spacer was added using procedures similar to those involved with peptide synthesis.[12] For each 1 g of resin, 0.4 g (2.96 mmol) of HOBT, 0.45 g (1.6 mmol) of **12**, and 0.45 mL (2.9 mmol) of DIC were used. To a solution of the HOBT in a 5-mL solution of 3:1 MeOH/DCM was added a solution of **12** and DIC also dissolved in 5 mL of 3:1 MeOH/DCM. An additional 5 mL of DCM was added. The mixture was filtered and added to the resin in the solid phase reaction vessel. The vessel was allowed to shake at 45 °C for 24 h. A ninhydrin test was performed every 24 h to monitor the extent of reaction. Typically 3 d was required. When the ninhydrin test indicated that the reaction was incomplete, a fresh solution of HOBT, DIC, and **12** was added. After the reaction reached completion, the solution was removed from the resin with N_2 pressure and the resin was washed three times with 80 mL of 1:5 MeOH/DCM solution, followed by three washes with 80 mL of DCM. Any remaining free amines were capped with benzyl isothiocyanate (or acetic anhydride) as described below. The tBoc group was removed from the spacer as described above.

After removal of the tBoc group, the desired monomer was added. Addition of the monomer was accomplished by first dissolving 10 equiv of monomer in 80 mL of DCM. If the monomer was insoluble, MeOH was added to enhance solubility. The reaction vessel was sealed and allowed to shake in an oven at 45 °C for 24 h. At the beginning of the reaction, the resin was found to coat the inside of the vessel, but when the coupling was complete, the resin would be fully suspended in solution. A small amount of the resin was removed and subjected to the ninhydrin test. If the reaction was incomplete, the vessel was stirred for another 24 h, or in some cases, another treatment with the monomer was performed. Typically, 2−4 d was required for complete reaction. The solution of monomer was removed with N_2 pressure, and the monomer was recovered by solvent evaporation and sometimes repurified with flash silica gel chromatography (as described in the monomer synthesis section). The resin was washed three times with 80 mL of DCM. In the synthesis of **14**, the resin was also washed with DMF and MeOH in between the washings with DCM. A solution of 10 equiv of benzyl isothiocyanate was added to cap any remaining free amine groups. In the synthesis of **14**, 10 equiv of acetic anhydride was used. The reaction was shaken for 30 min at 45 °C, and again the resin was washed three times with 80 mL of DCM. At this point the same deprotection conditions as described above with solution A were applied. The next desired monomer was added as described above. The deprotection and elongation steps were repeated until the desired oligomer had been produced on the resin.

For problematic couplings, the reaction vessel was placed in an 80 °C water bath for 12 h. However, this caused the monomers to slowly decompose so that their reisolation was difficult. Another method to increase coupling rates was sonication. When the resin is sonicated, the DCM should be added to the reaction vessel so that very little air remains. Otherwise the resin would cluster away from the solvent during sonication.

After the desired sequence of monomers had been added, the resin was washed three times with 80 mL of DCM. The resin was then transferred to an oven-dried round-bottom flask, and all the solvent was removed *in vacuo*. The dried resin was then taken into a drybox, and for each 100 mg of resin, a 1-mL solution of 25 mg (0.288 mmol) of anhydrous LiBr in MeOH was added. The MeOH was added slowly to avoid having the resin stick to the glass walls of the round bottom flask. Next, 18 μL (0.12 mmol) of DBU/100 mg of resin was added. The mixture was gently stirred for at least 4 h. If aggregation of the resin persisted, more of the LiBr/MeOH solution was added. After completion of the cleavage from the resin, the reaction was removed from the drybox.

The resin was filtered and washed with 10 mL of EtOAc, 10 mL of 1 N HCl, and then with 20−30 mL of EtOAc. The washes were combined and extracted with water. Depending upon the oligomer, a stringy precipitate (the product) would form during the extractions. This precipitate was collected. The organic layer was dried with $MgSO_4$ and concentrated by rotary evaporation, and the resulting solid was combined with the precipitate from the extraction. The combined residue dried *in vacuo*. If the oligomer was sufficiently soluble, purification was done by reverse phase chromatography. Otherwise purification involved repeated precipitation from hot MeOH.

L-Phenylalanine, *N*-[4-[[[[[4-[[[[[3-(10-Phenyl-3,8-dithioxo-2,4,7,9-tetrazadec-1-yl) phenyl]methyl]amino]thioxomethyl]amino]cyclohexyl]amino]thioxomethyl]amino]-methyl]benzoyl]-, Methyl Ester, *trans* (13). This was synthesized using the solid phase methodology: yield 40%; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.78 (d, 1 H), 8.0 (d, 1 H), 7.73 (br, 6 H), 7.23 (m, 18 H), 4.63 (br, 8 H), 4.15 (d, 1 H), 3.62 (s, 3 H), 3.72 (m, 2 H), 3.12 (m 4 H), 2.37 (m, 2 H), 1.95 (br, 8 H); ^{13}C {^{1}H} NMR (75 MHz, DMSO-d_6) δ 172.22, 166.24, 139.24, 137.73, 129.31, 129.08, 128.48, 127.78, 127.36, 127.29, 126.77, 126.48, 125.77, 59.77, 54.28, 51.95, 47.89, 37.27, 31.67, 30.88, 29.49, 25.93, 23.35; HRMS (FAB^+ *m/z*) calcd for $C_{45}H_{56}N_9O_3S_4$ ($M + H^+$) 898.3389, found 898.3414.

Benzoic Acid, 4-[[[[[[3-[[[[[[3-[[[[[[3-[[[[[3-[[[(1,1-Dimethylethoxy) carbonyl]amino]methyl]phenyl]methyl]-amino]thioxomethyl]amino]methyl]phenyl]methyl]-amino]thioxomethyl]amino]phenyl]methyl]amino]thioxomethyl]amino]methyl]phenyl]methyl]-amino]thioxomethyl]amino]methyl]-, Methyl Ester (14). This was synthesized using the solid phase methodology: yield 22%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.0 (br, 8 H), 7.95 (d, 1 H), 7.22 (m, 20 H), 4.77 (br, 2 H), 4.65 (br, 16 H), 4.08 (d, 1 H), 3. 81 (s, 3 H), 1.38 (s, 9 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.85, 166.16, 139.25, 139.33, 137.53, 129.43, 129.18, 128.29, 129.49, 128.11, 127.55, 127.23, 126.29, 125.82, 114.13, 59.75, 52.08, 52.01, 47.08 (br), 42.61, 42.34, 28.25, 20.72, 14.05; HRMS (FAB^- *m/z*) calcd for $C_{50}H_{58}N_9O_4S_4$ ($M - H^+$) 976.3494, found 976.3407.

L-Phenylalanine, *N*-[4-[[[[[2-[[[(Phenylmethyl)amino]-thioxomethyl]amino]cyclohexyl]amino]thioxomethyl]-amino]methyl]benzyoyl]-, Methyl Ester, *cis* (15). This was synthesized using the solid phase methodology: yield 63%; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.25 (d, 2 H), 8.18 (d, 1 H) 7.82 (m, 14 H), 7.4 (br, 1 H), 7.0 (br, 1 H), 5.40 (m, 1 H), 5.24 (m, 2 H), 4.23 (s, 3 H), 3.72 (m, 1 H), 2.37 (m, 2 H), 1.95 (br, 8 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.93, 135.81, 136.72, 133.62, 129.83, 128.89, 128.79, 128.00, 127.86, 127.65, 127.57, 61.35, 57.45, 54.24, 53.61, 47.86, 47.77, 43.33 (br), 37.61; HRMS (CI$^+$ *m*/*z*) calcd for $C_{33}H_{40}N_5O_3S_2$ (M + H$^+$) 618.2582, found 618.2572.

L-Phenylalanine, *N*-[4-(15-phenyl-3,8,13-thithioxo-2,4,7,9,12,14-hexaazapentadec-1-yl) benzoyl]-, Methyl Ester (17). This was synthesized using the solid phase methodology: yield 75%; ^{1}H NMR (250 MHz, CD_3CN) δ 7.63 (d, 2 H), 7.25 (m, 14 H), 6.8 (b, 6 H), 4.79 (m, 1 H), 4.69 (b, 2 H), 4.65 (br, 2 H), 3.67 (s, 3 H), 3.47 (br, 8 H), 3.26 (m, 2 H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 184.5, 173.3, 167.8, 138.1, 133.7, 130.5, 129.5, 128.4, 128.3, 128.2, 127.9, 55.5, 52.8, 49.2 (br), 44.0 (br); HRMS (FAB$^+$ *m*/*z*) calcd for $C_{32}H_{40}N_7O_3S_3$ (M + H$^+$) 666.2355, found 666.2346.

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Supporting Information Available: The ^{1}H NMR spectra of new compounds **13**−**17** lacking combustion data (5 pages). The 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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