Pseudodipeptide Inhibitors of Protein Farnesyltransferase[1]

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A series of pseudodipeptide amides are described that inhibit Ras protein farnesyltransferase (PFTase). These inhibitors are truncated versions of the C-terminal tetrapeptide (CAAX motif) of Ras that serves as the signal sequence for PFTase-catalyzed protein farnesylation. In contrast to CAAX peptidomimetics previously reported, these inhibitors do not have a C-terminal carboxyl moiety, yet they inhibit farnesylation *in vitro* at <100 nM. Despite the absence of the X residue in the CAAX motif, which normally directs prenylation specificity, these pseudodipeptides are greater than 100-fold selective for PFTase over type 1 protein geranylgeranyltransferase.

The *ras* oncogene product Ras p21 plays an important role in cell proliferation, linking cell-surface growth factor receptors to intracellular growth-regulatory pathways.[2] Mutations in Ras proteins can lead to cell transformation and are found in a number of human cancers.[3] For both its normal and cell-transforming activities, Ras must associate with the inner face of the cell membrane. Ras is synthesized *in vivo* as a cytosolic precursor protein that requires a series of posttranslational modifications to promote membrane association. The key modification is S-farnesylation of a cysteine residue contained in a carboxy-terminal tetrapeptide signal sequence of Ras, frequently referred to as a CAAX motif. This modification is catalyzed by protein farnesyltransferase (PFTase) and uses farnesyl pyrophosphate (FPP) as cosubstrate.[4] Subsequent events involve removal of the carboxy-terminal tripeptide adjacent to the farnesylated cysteine and methyl esterification of the now C-terminal farnesylcysteine. Indirect regulation of Ras membrane association and function by the inhibition of PFTase is an attractive approach to developing anticancer agents.[5] The ability of PFTase inhibitors to block tumor growth in a nude mouse explant model has further validated this idea.[6]

A number of PFTase inhibitors have been described that mimic the carboxy-terminal tetrapeptide of the Ras protein (CAAX), the smallest substrate for PFTase. Variations of the backbone of the tetrapeptide, employing amide bond surrogates or peptidomimetics, have been described. One or more amide bonds have been replaced by a reduced amide linkage,[7–9] a trans olefin,[10] or an ether.[6,11] Benzodiazepines[12] and aminobenzoic acids or aminomethylbenzoic acids[13] have been employed as central dipeptide mimics. The most potent inhibitors *in vitro* require a mercapto group at the amino terminus and a carboxylic acid at the carboxy terminus of the tetrapeptide. Unfortunately, the free carboxylate of these inhibitors is associated with relatively poor membrane permeability. Masking the acid as an ester prodrug enables the inhibitors to more readily cross the cell membrane and inhibit farnesylation in intact cells.[12,14] Because of the inherent complexity of devising a prodrug strategy for the intracellular delivery of a carboxylic acid *in vivo*, we have sought to obtain PFTase inhibitors that do not rely on a carboxylic acid for activity.

In this paper we describe a series of pseudodipeptide amide PFTase inhibitors with IC_{50} values in the range of 25–500 nM. These compounds demonstrate that the presence of the carboxyl group is not a requirement for *in vitro* activity in modified CAAX analogs.[15] Furthermore, these pseudodipeptides act as purely competitive inhibitors and are not substrates for PFTase. Prior studies[16] had indicated that the X residue of the CAAX sequence determined whether a protein would be prenylated by PFTase or by the closely related prenyltransferase type 1 protein geranylgeranyltransferase (PGGTase-1). Surprisingly, all of the compounds in the pseudodipeptide amide class, which contain no X residue, possessed much better affinity for PFTase than for PGGTase-1. Finally, compound **32** exhibited modest activity in cell culture. Unfortunately, a more complete analysis of the biological effects of these molecules was limited by their nonspecific cytotoxicity.

Chemistry

The general methods used for the preparation of the pseudodipeptides are illustrated in Scheme 1. In method A an amino acid is reductively coupled to *N*-Boc-*S*-tritylcysteinal (prepared by the $LiAlH_4$ reduction of the corresponding *N*-methoxy-*N*-methylamide) using sodium cyanoborohydride to provide **4**. Standard peptide coupling (EDC, HOBt, or BOP-Cl) of **4** with a primary or secondary amine gives **5**. Removal of the Boc and trityl groups with trifluoroacetic acid in the presence of triethylsilane provides **6**. Alternatively (method B), a Boc-amino acid is coupled with a primary or secondary amine using standard peptide-coupling procedures. Cleavage of the Boc group with HCl gives **7** which is reductively coupled with *N*-Boc-*S*-tritylcysteinal to give **5**. Subsequent deprotection provides **6**. Specific examples of each method are described in the Experimental Section.

Structure–Activity Relationships: *In Vitro* Inhibition of PFTase. Inhibition of Ras PFTase *in vitro* was determined by incubating compounds with enzyme purified from bovine brain, [^{3}H]FPP, and recombinant

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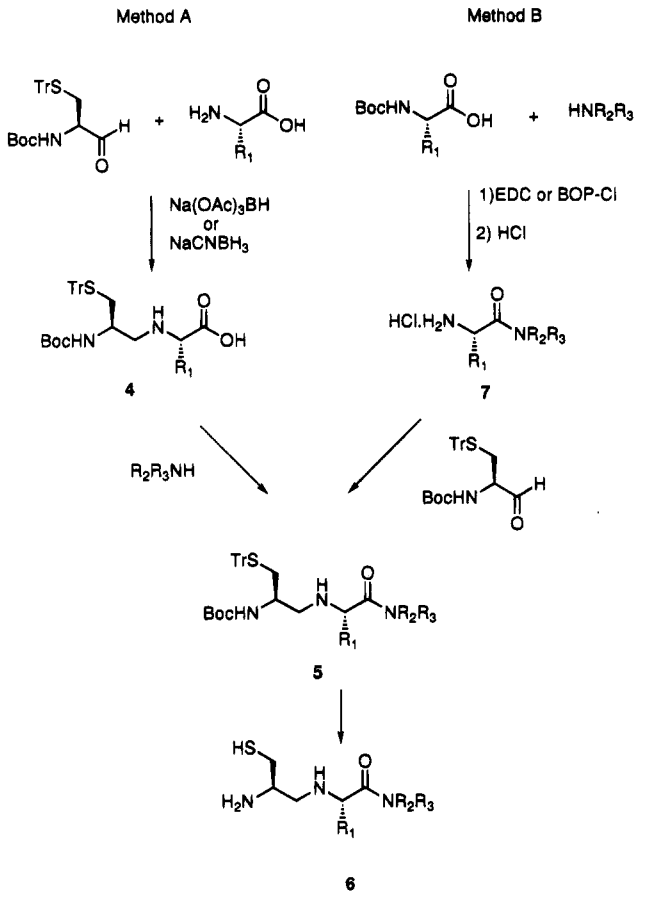
Scheme 1



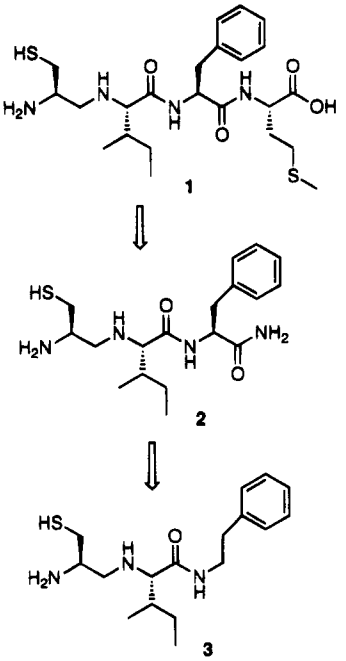
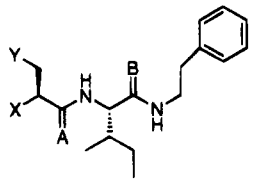


Figure 1.

Table 1. Backbone Alterations[a]



no.	X	Y	A	B	FPTase[b] IC_{50} (nM)	cytotoxic end point[c] (μM)
3	NH_2	SH	H, H	O	707 ± 98 (3)	10
8[d]	NH_2	SH	O	O	1000 (1)	>100
9[e]	NH_2	SH	H, H	H, H	6000 (1)	10
10	NH_2	SH	O	H, H	9000 (1)	nd
11	H	SH	O	O	>10 000 (1)	10
12	NH_2	H	H, H	O	>10 000 (1)	>100

[a] nd, not determined. [b] Concentration of compound required to reduce the FPTase-catalyzed incorporation of [^{3}H]FPP into recombinant Ha-Ras protein by 50%. The assay protocol is described in ref 16 and used enzyme purified from bovine brain at a concentration of ca. 1 nM. Assay results are reported as concentration ± SEM for the number of determinations shown in parentheses. With one determination, the values are estimated to be reliable within 2-fold. [c] Highest nontoxic concentration for cultured NIH 3T3 cells as assessed by MTT staining. The highest concentration tested in this assay was 100 μM. [d] Anal. ($C_{17}H_{27}N_3O_2S$-CF_3CO_2H) C, H, N: calcd, 9.31; found, 8.81. [e] Isolated and analyzed as the disulfide.

Harvey-Ras protein.[16,17] Total protein was precipitated with acid, and protein-bound FPP was quantitated by scintillation counting. The activity of the compounds is reported as an IC_{50} value, the concentration at which radiolabel incorporation into Ras is reduced by 50% compared to an experiment in which no inhibitor is present. Representative compounds were evaluated as inhibitors of the closely related enzyme PGGTase-1.[16,18] Details of each of these assays are found in the cited literature.

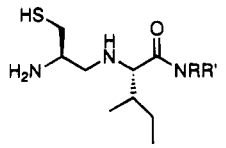
Systematic deletion of elements from the carboxy terminus of the CAAX analog C(ΨCH_2NH)IFM (**1**) (IC_{50} 16 nM), as outlined in Figure 1, led to the phenylalanine amide **2** (IC_{50} 2100 nM) and subsequently to the pseudodipeptide analog **3** (IC_{50} 707 nM). Compound **3** was not a substrate for the enzyme and was 140-fold selective for PFTase versus PGGTase-1.

Using compound **3** as a starting point, the backbone of the dipeptide was altered. The *in vitro* PFTase inhibitory activities of these compounds are tabulated in Table 1. When both amide bonds were present (compound **8**), a 2-fold loss in potency was observed. Reduction of both amide bonds (compound **9**), or only the carboxy-terminal amide bond (compound **10**), decreased activity greater than 10-fold. Unlike the results obtained in the tetrapeptide series,[7] the inhibitory activity of these small dipeptides was always dependent on the presence of both the α-amino group as well as the thiol group. Removal of either of these moieties abolished activity (compounds **11** and **12**).

Using the singly reduced dipeptide template, the carboxy-terminal phenethylamide of **3** was modified as illustrated in Table 2. Truncation of the connecting chain to give the benzamide (compound **13**) and the aniline (compound **14**) improved potency. Lengthening the chain to give the (propylphenyl)amide (compound **15**) also slightly improved potency. Introduction of the polar phenylalaninol (compound **16**) led to a 2-fold potency enhancement. An aromatic moiety appears to be preferred for binding, since the isovalerylamide (compound **17**) was at least 6-fold less active than the aromatic-substituted amides. N-Alkylation of these amides reduced activity. For example, the *N*-methyl-*N*-benzylamide **18** and the *N*-butyl-*N*-benzylamide **19** were 2–3-fold less active than **13**.

Retaining the reduced cysteine and the benzamide, the central amino acid was varied as shown in Table 3 in an effort to explore that binding pocket. With an

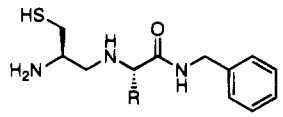
Table 2. Amide Variations[a]



no.	R	R′	FPTase[b] IC_{50} (nM)	GGPTase-1[d] IC_{50} (μM)
3	$(CH_2)_2Ph$	H	707 ± 98 (3)	100
13	CH_2Ph	H	450 ± 130 (2)	86
14	Ph	H	70 ± 17 (3)	nd
15	$(CH_2)_3Ph$	H	350 (1)	nd
16	$CH(CH_2Ph)CH_2OH$	H	370 (1)	nd
17	$(CH_2)_2CH(CH_3)_2$	H	2800 (1)	100
18	CH_2Ph	CH_3	945 ± 55 (2)	nd
19[e]	CH_2Ph	nBu	1300 (1)	nd

[a,b] See corresponding footnotes in Table 1. [d] Inhibition of bovine type 1 geranylgeranyltransferase.[16] Assay results are for single determinations. [e] FAB MS *m/z* 366 (M + 1).

Table 3. Central Amino Acid Variations



no.	R	FPTase[b] IC_{50} (nM)
13	$CH(CH_3)C_2H_5$	370
20	CH_3	2000
21	C_2H_5	1100
22	$(CH_2)_2CH_3$	600
23	$(CH_2)_3CH_3$	900

[b] See corresponding footnote in Table 1.

n-alkyl side chain, activity improved in the series of methyl (**20**), ethyl (**21**), and propyl (**22**). A slight decrease in activity occurred upon further homologation to *n*-butyl (**23**). Best results were obtained with the branched isoleucyl side chain (compound **13**).

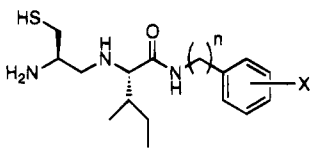
Substitution of the aromatic ring in either the benzamide or anilide series had a marked effect on potency as summarized in Table 4. Substitution in any position was well tolerated. Lipophilic substitution was preferred, especially disubstitution with methyl or chloro groups (compounds **24**–**27** and **30**–**32**). Other polar groups, whether they are electron-donating (compound **28**) or -withdrawing (compound **29**), caused a 10-fold loss of activity.

In all cases tested, the dipeptide analogs were found not to be substrates for PFTase, as determined by a TLC assay for the formation of tritiated products following incubation of the compounds with [^{3}H]FPP in the presence of PFTase.[16] All compounds with an aromatic amide were greater than 150-fold selective for PFTase versus PGGTase-1. Only the aliphatic amide (compound **17**) was less selective (36-fold more selective for PFTase). These results are tabulated in Tables 2 and 4.

Inhibition of Ras Farnesylation in Cell Culture. If farnesyltransferase inhibitors are to be used in cancer chemotherapy, they must be able to penetrate the cell membrane and inhibit posttranslational processing of Ras *in vivo*, without being toxic to normal cells. The cytotoxicity of our compounds was assessed using a viable staining method with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide). The cytotoxic end point is the highest compound concentration tolerated by NIH 3T3 cells in a 48-h assay. NIH 3T3 cells transformed by v-*ras* were used to evaluate the effect of a few of these compounds on the posttranslational processing of Ras in intact cells. The cells were incubated in the presence of the indicated compound or solvent control for 24 h and labeled with [^{35}S]methionine during the final 20 h. Ras was immunoprecipitated from detergent lysates of cell extracts, and the mobility of farnesylated versus nonfarnesylated protein was observed with SDS–polyacrylamide gel electrophoresis. The HMG-CoA reductase inhibitor lovastatin was used as a positive control. Lovastatin at 15 μM gave >90% inhibition of Ras processing.

The majority of these inhibitors was toxic to NIH 3T3 cells. The only exceptions were compounds having polar functional groups attached to the aromatic ring of the C-terminal amide component. The toxicity of the compounds did not appear to be mechanism based since cytotoxicity did not correlate with potency. Thus, the inactive alanine analog **11**, lacking the thiol moiety, was just as cytotoxic as compound **3**. Further evidence that toxicity is not related to PFTase inhibition is provided by studies with other compounds that completely inhibit PFTase without toxicity.[6,7] The cytotoxicity of these analogs limited the maximum concentration at which they could be tested in the Ras-processing assay. However, compound **32** inhibited Ras processing (≈50%) at a concentration of 10 μM, at which dose it was clearly noncytotoxic.

Table 4. Aromatic Ring Substitution[a]



		n = 1				*n* = 0		
X	no.	FPTase[b] IC_{50} (nM)	GGTase-1[d] IC_{50} (μM)	cytotoxic end point[c] (μM)	no.	FPTase[b] IC_{50} (nM)	GGTase-1[d] IC_{50} (μM)	cytotoxic end point[c] (μM)
2,4-diMe	**24**	120 (1)	30	10	**30**[e]	60 ± 20 (2)	nd	5
2,4-diCl	**25**	97 ± 18 (5)	10	10				
2,3-diCl	**26**	23 ± 3.5 (3)	6.8	5				
3-Me	**27**	1000 (1)	nd	25	**31**	46 ± 2 (3)	6.2	25
2,3-diMe					**32**	40 ± 8 (4)	8.2	10
4-OMe	**28**	660 (1)	nd	50				
4-SO_2NH_2	**29**	400 (1)	21	100				

[a–d] See corresponding footnotes in Tables 1 and 2. [e] Isolated and analyzed as the disulfide derivative.

Conclusions

Known CAAX analog farnesyltransferase inhibitors were truncated to eliminate the X residue and still retained *in vitro* potency as enzyme inhibitors. A carboxyl moiety was not an essential element for good inhibition in these pseudodipeptide amides which possess *in vitro* potencies in the range of 25–500 nM. Although it has been reported that prenylation selectivity is determined by the X residue of the CAAX box, this residue was eliminated from these potent inhibitors without losing selectivity for PFTase versus PGGTase-1. In general, the dipeptides exhibited marked non-mechanism-based cytotoxicity which limits their usefulness in further cell-based studies. These results open new opportunities for exploring the structure–activity relationships of modified CAAX analogs.

Experimental Section

Solvents and reagents were obtained from commercial suppliers and used as received. Simple peptides used as synthetic intermediates were prepared using standard solution-phase methods and are not described in detail. Reactions were generally conducted under an argon atmosphere using magnetic stirring. Standard workup was performed with an organic solvent, washing as appropriate with 10% citric acid, saturated sodium bicarbonate solution, and brine. The organic solutions were dried over sodium sulfate, and the solvent was removed on a rotary evaporator. Chromatography was performed on silica gel (230–400 mesh) at ca. 5 psig. Preparative reverse-phase HPLC was performed on a Waters 3000 instrument using either C-18 Vydac or PrepPak columns. Products and intermediates were characterized by 300-MHz ^{1}H NMR. Final products were also characterized by combustion analyses. Observed values are within 0.4% of calculated values for the compound formulae shown. The following examples are illustrative of the procedures employed.

Method A. Preparation of *N*-(2(*R*)-Amino-3-mercaptopropyl)-*N*-phenethylisoleucine Amide (3). *N*-Boc-*S*-tritylcysteinal[7] (6.71 g, 0.015 mol), isoleucine (1.97 g, 0.015 mol), and 3 Å molecular sieves (6 g) were suspended in absolute EtOH (150 mL) at ambient temperature and treated with sodium cyanoborohydride (0.47 g, 0.0075 mol). After stirring overnight, the mixture was filtered, the solvent evaporated, and the residue partitioned between EtOAc and aqueous sodium bicarbonate solution. Standard workup and chromatography (5–10% methanol in methylene chloride) gave 2.1 g (26%) of *N*-[2(*R*)-[(*tert*-butoxycarbonyl)amino]-3-[(triphenylmethyl)thio]propyl]isoleucine (**4**; R_1= *sec*-butyl): ^{1}H NMR δ 7.2–7.5 (15H, m), 3.63–3.73 (1H, m), 3.35 (1H, d, J = 3 Hz), 3.02 (1H, dd, J = 3, 12 Hz), 2.69 (1H, br t, J = 12 Hz), 2.45 (1H, dd, J = 6, 12 Hz), 2.31 (1H, dd, J = 6, 12 Hz), 1.8–1.9 (1H, m), 1.52–1.7 (1H, m), 1.47 (9H, s), 1.22–1.3 (1H, m), 0.9–1.15 (6H, m).

Compound **4** (R_1 = *sec*-butyl) (0.108 g, 0.2 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) (0.042 g, 0.22 mmol), and 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HOOBt) (0.036 g, 0.22 mmol) were dissolved in EtOAc (2 mL)–$CHCL_3$ (2 mL) and stirred at ambient temperature for 0.5 h. To this yellow solution were added phenethylamine (0.028 mL, 0.22 mmol) and diisopropylethylamine (0.038 mL, 0.22 mmol), and stirring was continued for 48 h. After concentration to dryness and standard workup, chromatography (EtOAc:hexane, 1:3) gave 0.09 g (69%) of *N*-[2(*R*)-[(*tert*-butyloxycarbonyl)amino]-3-[(triphenylmethyl)thio]propyl]-*N*-phenethylisoleucine amide: ^{1}H NMR ($CDCl_3$) δ 7.1–7.4 (2H, m), 4.5–4.55 (1H, m), 3.56–3.68 (1H, m), 3.43–3.55 (2H, m), 2.7–2.9 (3H, m), 2.4–2.5 (1H, m), 2.2–2.4 (3H, m), 1.6–1.75 (1H, m), 1.44 (9H, s), 1.0–1.1 (6H, m).

N-[2(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3-[(triphenylmethyl)thio]propyl]-*N*-phenethylisoleucine amide (0.09 g, 0.14 mmol) was dissolved in CH_2Cl_2 (3 mL) and CF_3CO_2H (1 mL) at ambient temperature, treated with triethylsilane (0.089 mL, 0.56 mmol), and stirred for 3 h. The reaction mixture was concentrated, partitioned between EtOAc and aqueous saturated $NaHCO_3$ solution, and the organic layer was separated, washed with brine, and dried (Na_2SO_4). Filtration, concentration, and then trituration with hexane provided 0.02 g (44%) of compound **3**: mp 69–73 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H), 7.07 (t, 1H, J = 4 Hz), 3.5–3.6 (m, 2H), 3.0–3.1 (m, 1H), 2.75–2.9 (m, 4H), 2.4–2.65 (m, 3H), 1.7–1.8 (m, 1H), 1.4–1.5 (m, 1H), 1.0–1.2 (m, 1H), 0.8–0.95 (m, 6H); FAB MS m/z 324 (M + 1). Anal. ($C_{17}H_{29}N_3OS$) C, H, N.

Compounds **3** (21%), **13** (17%), **15** (14%), **16** (23%), **17** (41%), **18** (21%), **19** (7%), **24** (40%), **25** (39%), **26** (28%), **27** (27%), **28** (27%), and **29** (33%) were prepared in this manner. Percent yields represent that of the final coupling followed by deprotection.

Preparation of *N*-[2(*R*)-Amino-3-mercaptopropyl]-*N*-phenylisoleucine Amide (14). To a solution of aniline (0.015 g, 0.16 mmol) and diisopropylethylamine (0.42 g, 0.32 mmol) in CH_2Cl_2 (3 mL) was added compound **4** (R_1 = *sec*-butyl) (0.84 g, 0.15 mmol) followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (0.42 g, 0.165 mmol) with stirring under argon at ambient temperature. After stirring for 20 h, standard workup followed by chromatography (15% EtOAc–hexane) gave 0.72 g (76%) of *N*-[2(*R*)-[(*tert*-butyloxycarbonyl)-amino]-3-[(triphenylmethyl)thio]propyl]-*N*-phenylisoleucine amide as a pale yellow gum; FAB MS m/z 638 (M + 1). This gum (0.07 g, 0.11 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (2 mL) at ambient temperature, treated with triethylsilane (0.2 mL, 1.2 mmol), and stirred for 2 h. The reaction mixture was concentrated and partitioned between hexane and 0.1% aqueous TFA solution, and the aqueous layer was separated and lyophilized to give 0.04 g (61%) of compound **14**: ^{1}H NMR (CD_3OD) δ 7.56–7.6 (2H, m), 7.3–7.6 (2H, m), 7.1–7.16 (1H, m), 3.4–3.48 (1H, m), 3.08 (1H, dd, J = 5, 14 Hz), 2.79–2.92 (3H, m), 1.72–1.86 (2H, m), 1.24–1.31 (1H, m), 1.03 (3H, d, J = 7 Hz), 0.96 (3H, t, J = 7 Hz); FAB MS m/z 296 (M + 1). Anal. ($C_{15}H_{25}N_3OS{\cdot}2.6CF_3CO_2H$) C, H, N.

Compounds **30** (11%), **31** (23%), and **32** (8%) were prepared in this manner. Percent yields represent that of the final coupling followed by deprotection.

Method B. Preparation of *N*-[2(*R*)-Amino-3-mercaptopropyl]-*N*-benzylalanine Amide (20). *N*-(*tert*-Butoxycarbonyl)-L-alanine (0.377 g, 2.0 mmol), HOBt (0.283 g, 2.1 mmol), and EDC (0.420 g, 2.2 mmol) were dissolved in 5 mL of DMF and treated with benzylamine (0.23 mL, 2.1 mmol) followed by triethylamine (0.28 mL, 1.9 mmol). The mixture was stirred overnight, and the solvent was evaporated. Standard workup gave 0.498 g of *N*-(*tert*-butoxycarbonyl)-*N*-benzylalanine amide as a waxy solid: ^{1}H NMR ($CDCl_3$) δ 7.3 (5H, m) 6.54 (1H, br s), 5.00 (1H, br s), 4.44 (2H, m), 4.18 (1H, m), 1.41 (9H, s), 1.38 (3H, d, J = 7 Hz).

This product was dissolved in ethyl acetate and cooled to −50 °C, and the solution was saturated with HCl gas. The mixture was stirred until TLC analysis indicated the complete consumption of the starting material. The solvent was evaporated at room temperature to afford the solid hydrochloride salt (0.183 g, 0.85 mmol) which was dissolved in 3 mL of CH_3OH and treated with *N*-Boc-*S*-tritylcysteinal (0.229 g, 0.57 mmol). Sodium cyanoborohydride (95%, 0.019 g, 0.28 mmol) was added, and the mixture was stirred overnight. Standard workup and chromatography (2% methanol in methylene chloride) gave 0.106 g of *N*-[2(*R*)-[(*tert*-butoxycarbonyl)amino]-3-(triphenylmethyl)thio]propyl]-*N*-benzylalanine amide as a foamy solid: ^{1}H NMR ($CDCl_3$) δ 7.3 (20H, m), 4.8 (1H, br s), 4.4 (2H, m), 3.65 (1H, br s), 2.8 (2H, br s), 2.4 (2H, m), 1.5 (12H, m).

N-[2(*R*)-[(*tert*-Butoxycarbonyl)amino]-3-(triphenylmethyl)-thio]propyl]-*N*-benzylalanine amide (0.103 g, 0.18 mmol) was dissolved in 6 mL of 25% TFA in CH_2Cl_2, and triethylsilane (0.073 mL, 0.45 mmol) was added. After 1 h the solvent was evaporated, and the residue was triturated with hexane. The hexane insoluble product was purified by reverse-phase HPLC (Waters C-18 column, 93:7:0.1 H_2O:CH_3CN:TFA) and lyophilized to give 0.043 g of compound **20**: mp 61–68 °C; ^{1}H NMR (CD_3OD) δ (5H, m), 4.42 (2H, s), 3.78 (1H, q, J = 3.6 Hz), 3.55 (1H, m), 3.22 (1H, dd, J = 6, 13 Hz), 3.12 (1H, dd, J

= 6, 13 Hz), 2.90 (2H, m), 1.48 (3H, d, J = 7 Hz). Anal. ($C_{13}H_{21}N_3OS \cdot 2CF_3CO_2H \cdot 0.57H_2O$) C, H, N.

Compounds **2** (26%), **8** (59%), **9** (15%), **10** (61%), **11** (61%), **12** (28%), **20** (16%), **21** (21%), **22** (23%), and **23** (7%) were prepared in this manner. Percent yields represent that of the final reductive alkylation followed by deprotection.

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