Formation of Urea Dipeptides from Carbonyldiimidazole: Application toward the Protease Inhibitors GE 20372 and MAPI

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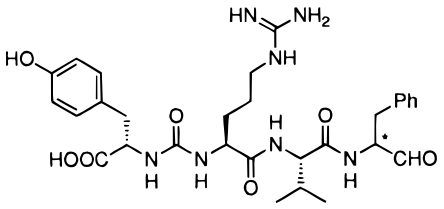
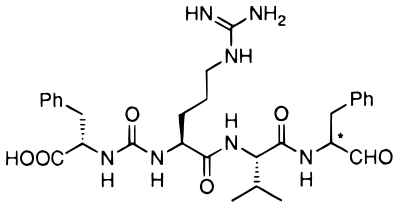
GE 20372 A and B (**1a,b**) are tetrapeptides which were recently isolated and shown to inhibit HIV-protease by Stefanelli and co-workers.[1] Closely related to GE 20372 are the tetrapeptides described as "microbial alkaline protease inhibitors", also termed (*S*)-α- and (*R*)-*β*-MAPI (**2a,b**) which were shown to have similar activity.[2] Both GE 20372 A and B were isolated from a culture broth of a *Streptomyces* species. The structures were elucidated from a combination of high-field NMR and chemical degradations. In this paper, we wish to communicate our results in preparing model systems **14** and **16** incorporating a key feature of the natural product, namely, the carbonyl link between two of the amino acid residues. This effort should aid in the eventual synthesis of both GE 20372 and MAPI.

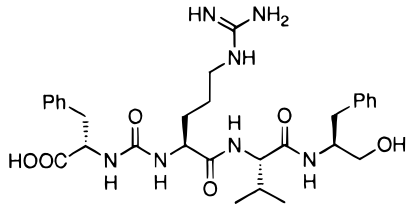


1a GE 20372 A (S at *)
1b GE 20372 B (R at *)



2a α-MAPI (S at *)
2b β-MAPI (R at *)

This family of tetrapeptides has two common features: a terminal aldehyde and a carbonyl link between two of the amino acid residues.[2] Structurally related to the MAPI family is Mer-N5075A (**3**) which was recently isolated from a culture broth of *Streptomyces chromofuscus*.[3] The structure of Mer-N5075A is similar to (*S*)-α-MAPI except for the presence of a terminal alcohol in place of the aldehyde. The researchers obtained IC_{50} values of the tetrapeptides and showed the relative importance of the aldehyde: IC_{50} for Mer-N5075A is 17.8 μM as compared with 1.3 μM for (*S*)-α-MAPI.[4] Other peptide-based protease inhibitors have been synthesized and shown to be highly effective in AIDS therapy as exemplified by Indinavir and Saquinavir.[5]



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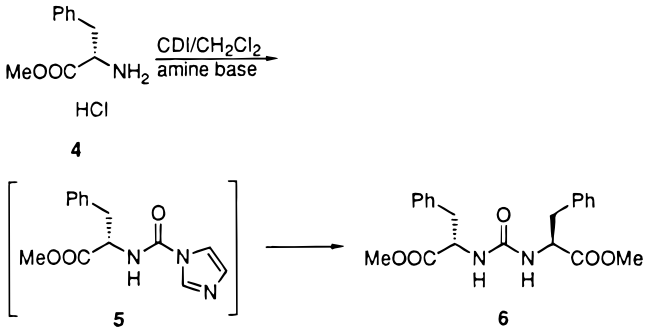
Scheme 1



In on-going work on the synthesis of naturally occurring compounds which inhibit HIV-protease, we were attracted to the GE 20372 family because of the unusual attachment of two of the amino acids. A recent publication has shown the utility of S,S-dimethyl dithiocarbonate in the preparation of unsymmetically substituted ureas.[6] Their method relied on the condensation of an amine with the reagent followed by treatment with LDA to prevent further reactions. The thiocarbamate intermediate was condensed with a different amine to produce a disubstituted urea. Unfortunately, this method could not be employed with amino acids due to the requirement of LDA which would racemize any stereogenic center. Triphosgene has recently been employed in preparing cyclic ureas from a chiral diamine[7] and in preparing simple urea dipeptides.[8] Recently, chiral isocyanates were obtained from protected amino acid derivatives which were incorportated to form various oligoureas.[9]

In initial studies employing *N*,*N*′-carbonyldiimidazole (CDI), we discovered that simple urea dipeptides may be obtained by mixing CDI with an amino acid ester hydrochloride salt in the presence of an amine base (Scheme 1). We studied this reaction extensively by surveying bases and reaction times to find the optimum conditions to form a "urea" dipeptide. We examined several amines such as triethylamine, diisopropylethyl-

† Undergraduate research participants.

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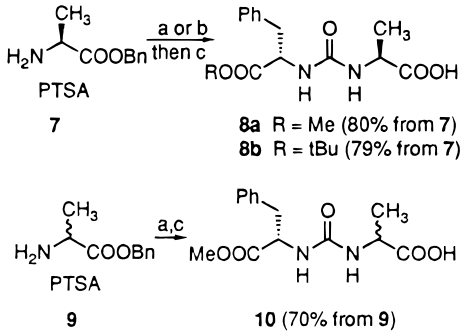
Scheme 2[a]



[a] Conditions: (a) carbonyldiimidazole, CH_2Cl_2, *N*-methylmorpholine, then phenylalanine methyl ester HCl; (b) carbonyldiimidazole, CH_2Cl_2, *N*-methylmorpholine, then phenylalanine *tert*-butyl ester HCl; (c) H_2, Pd−C.

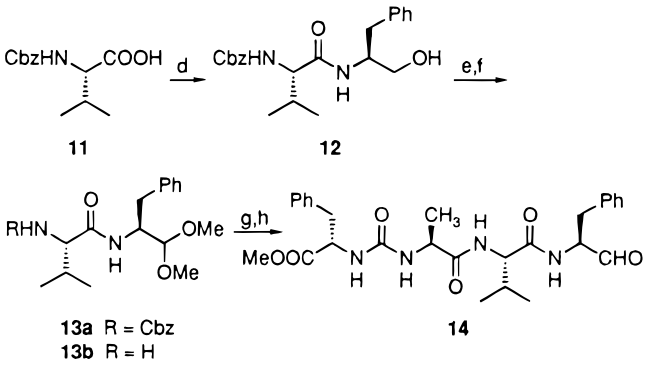
amine, and *N*-methylmorpholine (NMM) and found that NMM gave the best results. The reaction time was particularly important in that stopping the reaction after 1 h we isolated urea dipeptide **6** and imidazole carbamate **5**. We isolated this carbamate by silica gel chromatography and identified it by ^{1}H-NMR and mass spectroscopy. This compound was unstable as it decomposed to the free amino acid ester and imidazole. This result was especially useful in that the intermediate imidazole carbamate **5** was more stable than CDI.

We theorized that we could perform a sequential displacement of the two imidazoles of CDI with two different amino acid esters in order to make an unsymmetrical urea dipeptide. This was exemplified by condensing alanine benzyl ester *p*-toluenesulfonic acid (PTSA) salt (**7**) with CDI and phenylalanine methyl ester hydrochloride in the presence of *N*-methylmorpholine which afforded urea **8a** after hydrogenation of the benzyl ester (Scheme 2). The intermediate urea dipeptide was obtained in ~95% purity; however, we believe the impurity was obtained from the CDI. Reductive removal of the benzyl ester gave acid **8a** as a viscous oil which was easily purified by column chromatography. We discovered that the base is important for preservation of the optical purity of the urea dipeptide. If triethylamine was employed, we observed racemization of the product. *N*-Methylmorpholine gave the best results as no racemization was seen and it was easily removed by a water workup.

The optical purity of the acid **8a** was inferred by comparison with the corresponding diastereomeric acid **10**. Condensing racemic alanine **9** with (*S*)-phenylalanine methyl ester hydrochloride followed by hydrogenation gave **10** as a 1:1 mixture of diastereomers. Examination of both ^{1}H- and ^{13}C-NMR of **10** showed the presence of both diastereomers. The methyl group of alanine was especially useful as it appeared as a mutiplet (1.3 ppm) in the ^{1}H-NMR of **10**, although it appeared as a clean doublet (J = 7 Hz) in the ^{1}H-NMR of **8a**. In the ^{13}C-NMR spectrum of **10**, extra peaks are seen for a number of the carbons; however, **8a** did not show the presence of the other diastereomer in the ^{13}C-NMR spectrum.

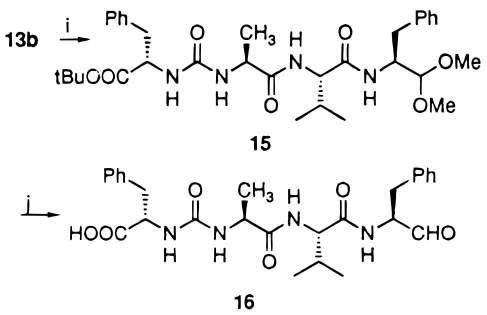
Completion of the model system study required amine **13b** which was prepared from *N*-(benzyloxycarbonyl)valine (**11**)[10] (Scheme 3). Selective coupling of (*S*)-phenylalaninol[11] with **11** yielded amide **12**. Oxidation with the Dess−Martin reagent[12] followed by acetalation[13] (methyl orthoformate/PTSA/methanol) and reductive removal of the benzyloxycarbonyl (Cbz) group gave **13b**. Acid **8a** was coupled with **13b** (DPPA/DMF/TEA), and following deacetalation (TFA) **14** was obtained as a white solid which was further purified by preparative HPLC. Analysis of the spectral data for **16** showed an excellent correlation with GE 20372.

Scheme 3[a]



[a] Conditions: (d) DCC, HOBt, (*S*)-phenylalaninol, CH_2Cl_2 (85%); (e) i. Dess−Martin, CH_2Cl_2 (88%), ii. $HC(OMe)_3$, PTSA, MeOH (61%); (f) H_2/Pd−C (97%); (g) diphenyl phosphorazidate, **8a**, DMF, TEA (60%); (h) TFA (88%).

Scheme 4[a]



[a] Conditions: (i) diphenylphosphorazidate, **8b**, DMF, TEA (60%); (j) TFA (53% as 2,4-DNP).

A closer model system to GE 20372 A was prepared from urea dipeptide **8b** where the carboxylic acid of the phenylalanine portion was blocked as a *tert*-butyl ester[14] (Scheme 4). The acid **8b** was prepared according to our general procedure (CDI condensation of alanine benzyl ester with phenylalanine *tert*-butyl ester followed by hydrogenation). Coupling of **8b** with **13b** (DPPA/DMF/TEA)[15] afforded **15**. Simultaneous deprotection of the ester and acetal (TFA) gave tetrapeptide **16** which we discovered to be unstable. We believe the carboxylic acid racemized the phenylalaninal portion as judged by ^{1}H-NMR analysis. We therefore characterized **16** as a 2,4-DNP derivative after removing the protecting groups and quickly treating the residue with dinitrophenylhydrazine. This problem of racemization may be circumvented in the

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natural product, GE 20372, as the target contains a basic side chain which may form a zwitterion with the terminal carboxylic acid.

We are currently expanding the scope of the preparation of other carbonyl-linked amino acids, such as **8a,b**, in order to eventually synthsize GE 20372, MAPI, and Mer-N5075A. Our efforts will be reported in the future.

Experimental Section

General Methods. All solvents were distilled from calcium hydride prior to use except for tetrahydrofuran (THF) which was distilled from molten potassium and ethyl ether which was distilled from sodium-benzophenone. Methanol and ethanol were distilled from Mg turnings. All reagents were used as obtained from commercial suppliers unless otherwise noted. Thin layer chromatography was performed with glass-backed precoated plates (Si-254F). Column chromatography utilized silica gel 230−400 mesh, 60 Å. The following deuterated solvents and their following internal reference points were used: deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) referenced to TMS (0.000 ppm, ^1H) or chloroform (77.00 ppm, ^{13}C), methanol-d_4 referenced to methanol (3.48 ppm, ^1H; 39.00 ppm, ^{13}C), and DMSO-d_6 referenced to DMSO (2.50 ppm, ^1H; 39.51 ppm, ^{13}C). Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab (Norcross, GA). Mass spectroscopy (FAB) was performed at the Nebraska Center for Mass Spectroscopy.

Acid 8a. A dichloromethane solution of 1.25 g (7.70 mmol, 1.10 equiv) of *N*,*N*′-carbonyldiimidazole (CDI) was stirred at room temperature before adding *via* cannula a dichloromethane solution of 2.45 g (7.00 mmol) of alanine benzyl ester *p*-toluenesulfonate (**7**) and 3.0 mL (2.50 mmol) of *N*-methylmorpholine (NMM). The reaction mixture was stirred for 5 min before adding a second dichloromethane solution of 1.50 g (7.00 mmol) of phenylalanine methyl ester hydrochloride salt and 3.0 mL (2.50 mmol) of NMM. The entire sequence of events was maintained under a positive pressure of N_2. The resultant reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into a separatory funnel containing dilute aqueous $NaHCO_3$. The organic layer was washed several times with water and dried over Na_2SO_4. Filtration and evaporation of solvent *in vacuo* left a viscous oil which was placed under vacuum for 2 h to remove all traces of NMM. The residue was further purified by column chromatography (75% EtOAc/hexane) to give 2 g of the urea diester as a viscous oil: R_f = 0.60 (75% EtOAc/hexane); ^1H-NMR (CD_3OD) δ 1.3−1.34 (m, 3H), 2.9−3.1 (m, 2H), 3.65 (s, 3H), 4.3 (m, 1H), 4.5 (m, 1H), 5.2 (m, 2H), 7.1−7.3 (m, 10H); ^{13}C-NMR (CD_3OD) δ 173.6, 172.8, 157.9, 136.4, 135.8, 129.0, 128.2, 128.1, 127.8, 127.7, 126.4, 66.3, 54.2, 51.1, 48.6, 37.7, 16.9.

The product was not fully characterized but carried on to the next step as the ^1H-NMR spectrum indicated a purity of about 95%. A methanol solution of the diester and 35 mg of Pd−C was hydrogenated for 40 min. Filtration and evaporation of the solvent *in vacuo* left a viscous oil which was further purified by column chromatography (20% MeOH/chloroform) to give 1.65 g (73% from **7**) of **8a** as a foamy white solid: R_f = 0.50 (20% MeOH/chloroform); $[\alpha]^{24}_D$ +27.6 (*c* 0.81, MeOH); mp 50−53 °C; ^1H-NMR (CD_3OD) δ 1.33 (d, 3H, J = 6.9 Hz), 2.95 (dd, 1H, J = 7.2, 13.8 Hz), 3.05 (dd, 1H, J = 6, 13.8 Hz), 3.6 (s, 3H), 4.2 (q, 1H, J = 7.2 Hz), 4.6 (t, 1H, J = 6 Hz), 7.2 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 177.0, 174.5, 159.6, 137.9, 130.5, 129.6, 128.0, 55.7, 52.7, 49.8, 39.3, 18.8; FAB-HRMS for $C_{14}H_{18}N_2O_5$ 294, found (M + H) *m*/*z* 295.1283 (3.7 ppm deviation).

Acid 8b. This compound was prepared according to the same procedure as **8a**. From 1.52 g (4.30 mmol) of alanine benzyl ester *p*-toluenesulfonate (**7**), 800 mg (4.90 mmol) of CDI, 1.16 g (4.50 mmol) of phenylalanine tert-butyl ester hydrochloride salt, and 1.50 mL (13.0 mmol) of *N*-methylmorpholine was obtained 1.10 g of **8b** (79%) as a white solid: R_f = 0.43 (20% MeOH/chloroform); $[\alpha]^{24}_D$ +22.0 (*c* 0.35, MeOH); mp 55−57 °C; ^1H-NMR (CD_3OD) δ 1.3 (m, 12H), 3.0 (d, 2H, J = 6.6 Hz), 4.2 (q, 1H, J = 7.1 Hz), 4.4 (t, 1H, J = 6.6 Hz), 7.2−7.3 (m, 5H); ^{13}C-NMR (CD_3OD) δ 176.0, 173.0, 159.4, 137.4, 130.5, 129.2, 127.7, 82.7, 56.0, 49.6, 39.4, 28.2, 18.7; FAB-HRMS for $C_{17}H_{24}N_2O_5$ 336.1685, found (M + H) *m*/*z* 337.1757 (1.8 ppm deviation).

***N*′-(Benzyloxycarbonyl)valyl-(*S*)-phenylalaninol (12).** A tetrahydrofuran solution containing 6.60 g (26.0 mmol) of *N*-(benzyloxycarbonyl)valine (**11**), 3.70 g (24.0 mmol) of (*S*)-phenylalaninol, 5.40 g (26.0 mmol) of DCC, and 3.60 g (27.0 mmol) of *N*-hydroxybenzotriazole (HOBt) was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue extracted with EtOAc. Filtration and evaporation of the solution gave a white solid which was further purified by column chromatography (50% EtOAc/hexane) to give 7.90 g (85%) of **12** as a white solid: R_f = 0.15 (50% EtOAc/hexane); mp 151−153 °C; $[\alpha]^{24}_D$ −45.1 (*c* 0.63, MeOH); ^1H-NMR ($CDCl_3$) δ 0.8 (d, 3H, J = 6.6 Hz), 0.9 (d, 3H, J = 6.6 Hz), 2.1 (m, 1H), 2.6 (s, 1H), 2.8 (m, 2H), 3.4−3.6 (m, 2H), 3.9 (dd, 1H, J = 6.3, 8.5 Hz), 4.2 (m, 1H), 5.1 (s, 2H), 5.3 (br d, 1H, J = 7.7 Hz), 6.3 (br d, 1H, J = 7.7 Hz), 7.3−7.1 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 171.7, 156.6, 137.7, 136.2, 129.3, 128.6, 128.3, 128.1, 126.6, 67.2, 63.5, 60.9, 52.8, 36.9, 30.8, 19.2, 17.8, 14.2. Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.71; H, 7.34; N, 7.29. Found: C, 68.58; H, 7.38; N, 7.20.

Amide 13a. A dichloromethane solution of 1.0 g (2.60 mmol) of alcohol **12** and 1.4 g (3.3 mmol, 1.3 equiv) of the Dess−Martin reagent was stirred for 1 h. The reaction was quenched by the addition of a saturated solution of $Na_2S_2O_3$ and $NaHCO_3$. The organic layer was further washed with aqueous $NaHCO_3$ and then dried over Na_2SO_4. Filtration of solvent *in vacuo* left 870 mg (88%) of a pale yellow solid which was not characterized but quickly carried on to the next step: R_f = 0.42 (50% EtOAc/hexane); ^1H-NMR ($CDCl_3$) 0.8 (2d, 6H, J = 6.8 Hz), 2.1 (m, 1H), 3.1 (d, 2H, J = 6.6 Hz), 4.0 (m, 1H), 4.7 (q, 1H, J = 7.4 Hz), 5.1 (s, 2H), 5.2 (br d, 1H, J = 8.8 Hz), 6.4 (br d, 1H, J = 6.6 Hz), 7.1−7.4 (m, 10H), 9.6 (s, 1H).

Into a methanol solution of 220 mg (0.76 mmol) of the aldehyde were added 3.0 mL (27.4 mmol) of methyl orthoformate and 1 mg (catalytic) of *p*-toluenesulfonic acid, and the mixture was heated to reflux for 4 h. The solvent was removed *in vacuo* which left a viscous oil that was further purified by column chromatography to give 590 mg (61%) of **13a** as a white solid: R_f = 0.67 (50% EtOAc/hexane); mp 161−163 °C; $[\alpha]^{24}_D$ −48.0 (*c* 0.5, MeOH); ^1H-NMR ($CDCl_3$) δ 0.8 (d, 3H, J = 6.6 Hz), 0.9 (d, 3H, J = 6.6 Hz), 2.1 (m, 1H), 2.7 (dd, 1H, J = 8.2, 13.7 Hz), 2.9 (dd, 1H, J = 6.3, 13.9 Hz), 3.3 (s, 3H), 3.4 (s, 3H), 3.9 (dd, 1H, J = 7.5, 8.5 Hz), 4.2 (d, 1H, J = 3.3 Hz), 4.4 (m, 1H), 5.1 (s, 2H), 5.2 (br d, 1H, J = 8.2 Hz), 5.9 (br d, 1H, J = 9.3 Hz), 7.1−7.4 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 170.9, 156.3, 137.7, 136.3, 129.3, 128.6, 128.4, 128.2, 128.1, 126.4, 104.5, 67.0, 60.6, 55.6, 55.5, 51.5, 35.7, 31.1, 19.1, 17.7; Anal. Cald for $C_{24}H_{32}N_2O_5$: C, 67.25; H, 7.53; N, 6.54. Found: C, 67.32; H, 7.54; N, 6.56.

Amine 13b. A methanol solution of 340 mg (0.785 mmol) of acetal **13a** and 30 mg of Pd−C was hydrogenated in a Parr hydrogenator for 2 h. Filtration and removal of solvent *in vacuo* gave 224 mg (97%) of **13b** as a white solid: R_f = 0.06 (50% EtOAc/hexane); ^1H-NMR ($CDCl_3$) δ 0.75 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.6 Hz), 1.8 (m, 1H), 2.7 (m, 1H), 2.9 (m, 2H), 4.2 (d, 1H, J = 4.4 Hz), 3.42, 3.40 (2s, 6H), 4.25 (m, 1H), 7.2 (m, 5H); ^{13}C (CD_3OD) δ 175.2, 138.3, 128.9, 127.9, 125.9, 105.2, 60.1, 54.6, 54.1, 51.5, 34.9, 31.6, 18.4, 16.0. This compound was not fully characterized but quickly carried on to the next step.

Tetrapeptide 14. A dimethylformamide solution of 230 mg (0.790 mmol) of **8a**, 223 mg (0.760 mmol) of **13b**, 379 mg (1.38 mmol) of diphenyl phosphorazidate, and 0.3 mL (2.16 mmol) of triethylamine was stirred at 0 °C for 4 h and then warmed to room temperature overnight. The solution was poured into a separatory funnel containing water and ethyl acetate. The organic layer was washed with several portions of water and dried over Na_2SO_4. Filtration and evaporation of solvent *in vacuo* left a solid which was further purified by column chromatography (10% MeOH/chloroform) to give 258 mg (60%) of the tetrapeptide acetal **14** as a white solid: R_f = 0.24 (50% EtOAc/hexane); mp 225−226 °C; $[\alpha]^{24}_D$ −21.1 (*c* 0.18, MeOH), ^1H-NMR (DMSO-d_6) δ 0.7 (dd, 6H, $J \approx 2$, 6.8 Hz), 1.0 (d, 3H, J = 7.1 Hz), 1.8 (m, 1H), 2.6 (dd, 1H, J = 10, 14 Hz), 2.8−2.9 (m, 3H), 3.2 (s, 3H), 3.3 (s, 3H), 3.6 (s, 3H), 4.0−4.1 (m, 4H), 4.3 (q, 1H, J = 7.8 Hz), 6.4 (br d, 2H, J = 7.7 Hz), 7.1−7.3 (m, 10H), 7.6 (br d, 1H, J = 9.3 Hz), 7.8 (br d, 1H, J = 8.8 Hz); ^{13}C-NMR (DMSO-d_6) δ 172.8, 172.5, 170.3, 156.7, 138.6, 136.9, 129.1, 128.9, 128.2, 127.9, 126.5, 125.8, 104.9, 57.6, 55.1, 54.0, 51.6, 51.2, 48.4, 37.5, 34.4, 30.6, 19.1, 18.9, 17.9. Anal. Calcd for

$C_{30}H_{42}N_4O_7$: C, 63.14; H, 7.42; N, 9.82. Found: C, 63.24; H, 7.46; N, 9.76.

A trifluoroacetic acid solution containing 256 mg (0.45 mmol) of the tetrapeptide acetal **14** was stirred at 0 °C for 4 h. The solvent was removed *in vacuo* and the residue extracted with chloroform and washed with several portions of aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4. Filtration and evaporation of solvent *in vacuo* left a light tan solid which was initially purified by column chromatography (10% MeOH/chloroform) and then further purified by preparative HPLC (90:10 acetonitrile: water, 4 mL/min; 220 nm, C-18 preparative column; t_R = 20 min) to give 207 mg (88%) of **14** as a white solid: R_f = 0.45 (10% MeOH/chloroform); mp 205−207 °C; $[\alpha]^{24}_D$ −32.8 (*c* 0.20, MeOH); ^{1}H-NMR (DMSO-d_6) δ 0.8 (t, 6H, J = 6.5 Hz), 1.1 (d, 1H, J = 7.2 Hz), 1.9−2.2 (m, 1H), 2.8−3.0 (m, 3H), 3.1 (dd, 1H, J = 5.0, 14.8 Hz), 3.6 (s, 3H), 4.5 (m, 2H), 4.7 (m, 2H), 6.4 (br d, 2H, J = 7.8 Hz), 7.2−7.3 (m, 10H), 7.6 (br d, 1H, J = 8.7 Hz), 8.4 (br d, 1H, J = 7.8 Hz), 9.4 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 201.3, 174.2, 174.1, 172.7, 158.1, 138.8, 138.2, 130.4, 130.3, 129.6, 129.5, 127.9, 127.6, 60.8, 58.6, 55.3, 53.0, 49.7, 38.8, 34.6, 31.8, 20.5, 20.3, 19.1; FAB-HRMS for $C_{28}H_{36}N_4O_6$ 524.2635, found (M + H) m/z 525.2718 (−1.0 ppm deviation).

Protected Tetrapeptide 15. This compound was prepared according to the same procedure as for **14**. From 270 mg (0.80 mmol) of acid **8b**, 200 mg (0.67 mmol) of amine **13b**, 250 mg (0.90 mmol) of diphenyl phosphorazidate, and 0.1 mL (1.00 mmol) of triethylamine was obtained a white solid which was further purified by column chromatography (10% MeOH/chloroform) to give 240 mg (60%) of **15** as a white solid: R_f = 0.66 (10% MeOH/chloroform); mp 229−230 °C dec; $[\alpha]^{24}_D$ −23.6 (*c* 0.20, MeOH); ^{1}H-NMR (CD_3OD) δ 0.8 (2d, 6H, J = 6.6 Hz), 1.2 (d, 3H, J = 7.1 Hz), 1.4 (s, 9H), 1.95 (m, 1H), 2.65 (dd, 1H, J = 9.3, 14.3 Hz), 2.9 (m, 3H), 3.4 (2s, 6H), 4.1 (d, 1H, J = 6.6 Hz), 4.1−4.3 (m, ∼3H), 4.4 (t, 1H, J = 4.4 Hz), 7.2−7.4 (m, 10H); ^{13}C-NMR (CD_3OD) δ 174.1, 171.6, 158.1, 138.1, 136.6, 129.1, 128.8, 127.9, 127.9, 127.8, 126.3, 125.7, 105.0, 81.4, 58.6, 54.7, 54.4, 53.9, 51.9, 49.3, 37.9, 34.7, 30.5, 26.7, 18.1, 17.2, 16.9. Anal. Calcd for $C_{33}H_{48}N_4O_7$: C, 64.68; H, 7.90; N, 9.14. Found: C, 64.61; H, 7.89; N, 9.15.

Tetrapeptide 16. A trifluoroacetic acid solution of **15** (230 mg, 0.380 mmol) was stirred at 0 °C for 2 h. The solvent was removed *in vacuo* leaving a white solid which was first washed with water and then ether. The solid was placed under vacuum for 2 h. The crude product was treated with a saturated solution of 2,4-DNP to give 140 mg (53% from **15**) of a pale orange solid: R_f = 0.14 (25% MeOH/chloroform); mp 215 °C (dec.); $[\alpha]^{24}_D$ −16.6 (*c* 0.3, DMSO); ^{1}H-NMR (DMSO-d_6) δ 0.75 (2d, 6H, J = 6.6 Hz), 1.0 (d, 3H, J = 7.2 Hz), 1.95 (m, 1H), 2.8−3.1 (m, 4H), 4.1 (m, 2H), 4.25 (m, 1H), 4.8 (m, 1H), 6.2 (d, 1H, J = 8.2 Hz), 6.4 (d, 1H, J = 7.7 Hz), 7.1−7.25 (m, 10H), 7.6 (d, 1H, J = 8.8 Hz), 7.8 (d, 1H, J = 9.3 Hz), 8.0 (d, 1H, J = 4.9 Hz), 8.3 (m, 2H), 8.8 (d, 1H, J = 2.7 Hz); ^{13}C-NMR (DMSO-d_6) δ 175.0, 174.1, 171.8, 158.3, 153.8, 146.1, 138.9, 138.6, 138.2, 130.8, 130.5, 129.5, 129.4, 127.7, 127.6, 124.3, 107.9, 58.8, 55.2, 52.8, 49.8, 38.8, 31.9, 28.9, 20.6, 20.2, 19.2; FAB-HRMS for $C_{33}H_{38}N_8O_9$ 690.2761, found (M + Na) m/z 713.2648 (1.5 ppm deviation).

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Supporting Information Available: Spectra for compounds **8**, **14**, and **16** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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