# Incorporation of Chromium Aminocarbene Complex-Derived Amino Acids into Soluble Poly(ethylene glycol) (PEG)-Supported Peptides

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Photolysis of optically active chromium aminocarbene complexes in the presence of soluble poly(ethylene glycol) (PEG)-supported peptides (or amino acids) leads to the production of peptides which incorporate chromium aminocarbene complex-derived amino acid residues, in good yields and with good diastereoselectivities. Removal of the oxazolidine auxiliary from the resulting PEG-supported peptides has been achieved in good yields by both oxidative and reductive routes. This photochemical methodology was used to iteratively introduce two amino acid residues to PEG-supported peptides with moderate efficiency.

## Introduction

With the advent of peptide-based pharmaceuticals,[1] the synthesis of small peptides particularly those containing unusual amino acid residues, has become increasingly important.[2] Although solution phase and segment condensation procedures remain popular, most peptide synthesis are carried out on insoluble (Merrifield-like) polymer supports, often in automated devices. Recently, a novel procedure for incorporating amino acid residues into peptides involving the photolysis of optically active chromium aminocarbene complexes with carboxy-protected peptides was reported from these laboratories.[3] In this process, both the peptide bond and the new stereogenic center on the chromium carbene-derived amino acid residue was formed in the same step. Because this procedure allows the facile introduction of natural, unnatural configuration, unnatural side chain, and multiply labeled amino acid residues with equal facility and without the necessity of preforming the free amino acids, it is of use for the introduction of unusual amino acid residues into peptides. Attempts to extend this methodology to Merrifield resin supported peptide synthesis, although successful, proved cumbersome, particularly for iterative introduction of several amino acid residues.[4] The problems lay with the two-phase nature of the reaction and, in particular, with the removal of the chiral auxilliary on the newly introduced amino acid residue while attached to the polystyrene support.

A potential solution to these problems would be to use soluble polymer supports, which enjoy the advantages of both liquid phase and solid phase peptide synthesis, in that the synthesis can be carried out in homogeneous solution, while purification can be effected by precipitation of the polymer peptide.[5] In addition, the solubility properties of the polymer support can enhance the intrinsic solubility of the attached peptide, making peptides of poor solubility accessible by this method. Further, peptides attached to soluble polymers can often be readily characterized by solution spectroscopic techniques such as NMR and infrared spectroscopy,[6] making cleavage from the support for characterization unnecessary.

Poly(ethylene glycol) (PEG) is most often used as a soluble polymer support in peptide synthesis[7] since it has favorable physical and chemical properties for the required manipulations (e.g. ready attachment of the first residue, stability to coupling and deprotection reactions, solubility/insolubility properties, crystallinity in the solid phase for ease of filtration), is inexpensive, and is readily available in a wide range of molecular weights. Experimental results describing the incorporation of chromium aminocarbene complex-derived amino acids into PEG supported amino acids and peptides are reported below.

## Results and Discussion

A series of amino acids and peptides was assembled on soluble PEG 4000 (molecular weight 4700–5200) or 8000 (molecular weight 8800–9500) supports using classical peptide coupling procedures. Thus, Boc-protected glycine, (*S*)-proline, and (*S*)-leucine were activated by addition to dicyclohexylcarbodiimide (DCC), and the resulting symmetrical anhydrides were coupled to the free hydroxyl groups of PEG 4000 in $CH_2Cl_2$ solution using 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as catalyst.[8] Excess acetic anhydride was added to block any remaining free hydroxy groups, and the polymer was precipitated by addition of diethyl ether at 0 °C and washed to remove excess reagents. Dissolution in 1:1 $CH_2Cl_2$/trifluoroacetic acid removed the Boc protecting group, and neutralization with *N*-methylmorpholine gave

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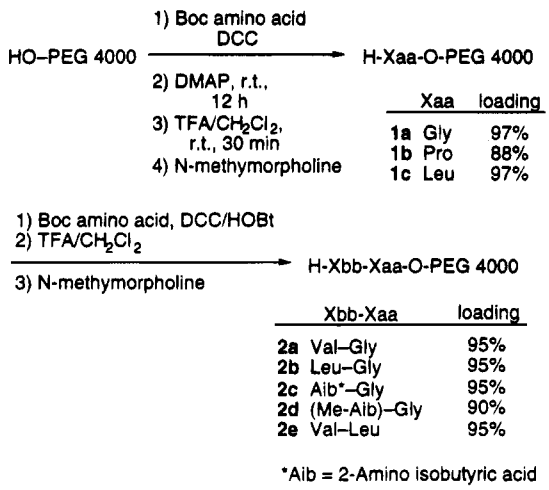
**Scheme 1**




| | Xaa | loading |
|---|---|---|
| **1a** | Gly | 97% |
| **1b** | Pro | 88% |
| **1c** | Leu | 97% |

| | Xbb-Xaa | loading |
|---|---|---|
| **2a** | Val–Gly | 95% |
| **2b** | Leu–Gly | 95% |
| **2c** | Aib*–Gly | 95% |
| **2d** | (Me-Aib)–Gly | 90% |
| **2e** | Val–Leu | 95% |

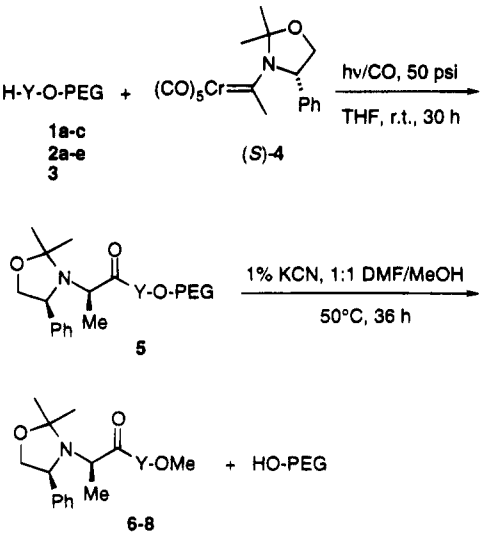
*Aib = 2-Amino isobutyric acid

PEG-bound amino acids **1a**–**c** in excellent yield (Scheme 1), resulting in 88–97% (0.33–0.38 mequiv/g) loading as determined by transesterification cleavage. Solution $^1$H and $^{13}$C NMR spectra of the polymer-supported amino acids were sharp, clean, and characteristic, making spectroscopic monitoring of the various coupling processes routine. PEG-supported glycine **1a** was coupled to (*S*)-valine, (*S*)-leucine, 2-aminoisobutyric acid (Aib), and N-methyl-2-aminoisobutyric acid to give PEG 4000-supported dipeptides **2a**–**d**, with very high efficiency. PEG-bound leucine **1c** was coupled to valine as well to yield PEG 4000-supported dipeptide **2e**, again with high efficiency. By exactly the same procedure the tripeptide **3**, H-Val-Leu-Gly-O-PEG 8000 (0.18 mequiv/g, 95% overall loading) was assembled using higher molecular weight PEG. With these materials in hand, photochemical introduction of chromium aminocarbene complex-derived amino acid residues was next addressed.

Photolysis of 2 equiv of carbene complex (*S*)-**4** with amino acid-PEG's **1a**–**c**, dipeptide-PEG's **2a**–**e**, and tripeptide-PEG **3** in THF solution under a slight pressure of carbon monoxide resulted in efficient introduction of the (*R*)-alanine residue with good diastereoselectivity. The photochemical reaction was monitored by solution $^1$H-NMR spectroscopy. When complete, the PEG-supported peptide was precipitated by addition of ether at 0 °C and washed with ether to remove soluble impurities. $^1$H and $^{13}$C NMR spectra of the PEG-supported peptides were quite clean, indicating that the coupling was reasonably efficient. The peptides were quantitatively cleaved from the support by transesterification (1% KCN, 1:1 MeOH/DMF, 50 °C, 36 h[9] or DBU/LiBr/MeOH, 25 °C, 4 h[10]), and isolated by precipitation of the PEG from the peptide in solution. Residual traces of PEG were removed by flash chromatography (silica gel, MeOH). The results are summarized in Scheme 2, and roughly paralleled results obtained coupling of amino acids and peptides with chromium aminocarbene complexes in solution.

Thus, PEG-supported glycine (**1a**) and (*S*)-leucine (**1c**), dipeptides Val-Gly (**2a**), Leu-Gly (**2b**), and Val-Leu (**2e**), and tripeptide Val-Leu-Gly (**3**) coupled in good yield and with good to excellent diastereoselectivity. In contrast (*S*)-proline (**1b**) coupled in poor yield and diastereoselectively, just as it did in solution,[3a] while the sterically hindered dipeptide Aib-Gly-O-PEG (**2c**) and *N*-methyl Aib-Gly-O-PEG (**2d**) coupled in fair yield and with reasonable diastereoselectivity, again, as observed for nonpolymer bound systems.[3b] PEG supported tripeptide **3** was also coupled with (*R*) carbene complex **4** to make the tetrapeptide corresponding to **8** having an (*S*)-alanine residue, in comparable yield (79%) and diastereoselectivity (91%). α-Homologated carbene complexes **9a** and **9b**[11] also coupled to leucine-O-PEG (**1c**) installing the (*R*)-homophenylalanine residue (**10a**) and the glutamic acid ester residue (**10b**) in fair yield and diastereoselectivity (Scheme 3).

**Scheme 2**




| | Y | Yield, %[1] | d.e., %[2] | |
|---|---|---|---|---|
| **1a** | Gly | 75 | 92 | **6a** |
| **1b** | Pro | 54 | 52 | **6b** |
| **1c** | Leu | 87 | 95 | **6c** |
| **2a** | Val-Gly | 80 | 88 | **7a** |
| **2b** | Leu-Gly | 82 | 92 | **7b** |
| **2c** | Aib-Gly | 78 | 89 | **7c** |
| **2d** | (Me-Aib)-Gly | 58 | 70 | **7d** |
| **2e** | Val-Leu | 73 | 85 | **7e** |
| **3** | Val-Leu-Gly | 76 | 89 | **8** |

1. Reported yields are for pure, single diastereomers
2. Determined by integration of the relevant peaks in the $^1$H-NMR spectrum of the crude product.

The major impetus for the development of the above methodology was to permit the iterative introduction of amino acid residues into peptides utilizing chromium carbene complex photochemistry. This requires the ability to remove the chiral auxiliary from the nitrogen of the newly installed amino acid while the peptide remains attached to the PEG support and to then couple the newly formed free amino terminus to another chromium carbene complex-derived amino acid. To this end, dipeptide-PEG **2b** was coupled to (*S*)-carbene complex **4** and the resulting N-protected tripeptide was subjected to acetonide hydrolysis, followed by N-debenzylation under either oxidizing ($Pb(OAc)_4$) or reducing ($H_2$, $Pd(OH)_2/C$) conditions to give tripeptide-PEG **11** containing

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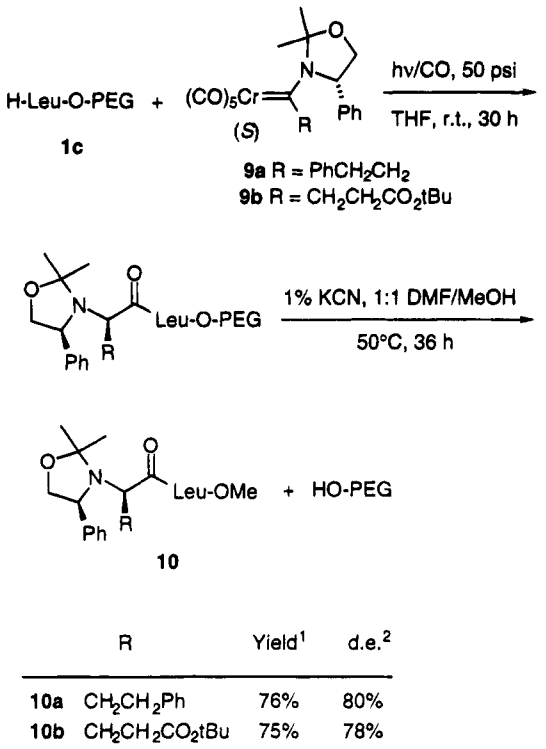
**Scheme 3**




| | R | Yield[1] | d.e.[2] |
|---|---|---|---|
| **10a** | $CH_2CH_2Ph$ | 76% | 80% |
| **10b** | $CH_2CH_2CO_2tBu$ | 75% | 78% |

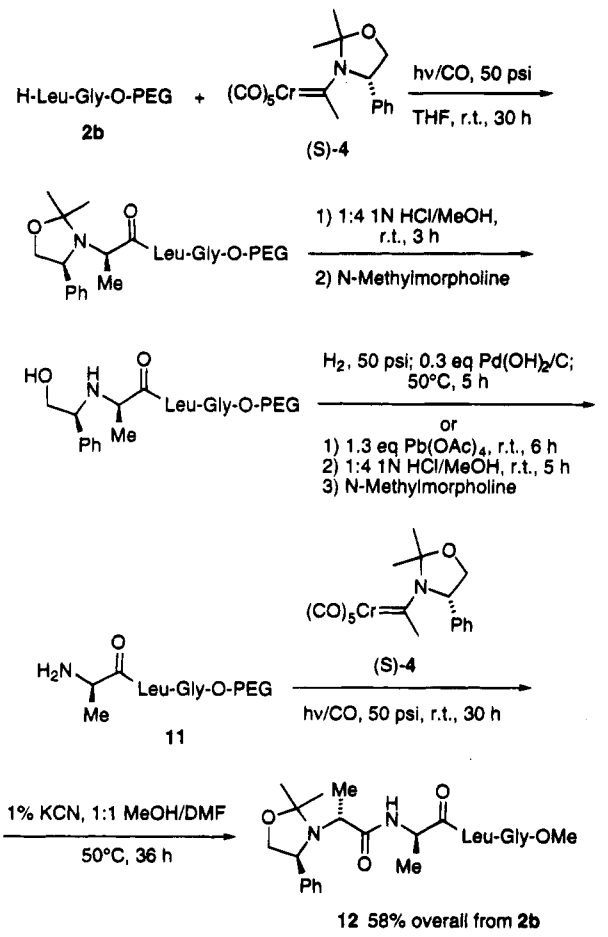
1. Reported yields are for pure, single diastereomers. 2. Determined by integration of the relevant peaks in the $^1$H-NMR spectrum of the crude product.

a chromium carbene complex-derived (*R*)-alanine at the N-terminus. A second cycle of photolytic coupling with (*S*) carbene complex **4** installed a second (*R*)-alanine. Cleavage of the tetrapeptide from the polymer gave crude material that was contaminated with small amounts of other diastereoisomers, which were removed by flash chromatography to give pure tetrapeptide **12** in 58% isolated yield as a single diastereoisomer (Scheme 4). This compares to an 18% overall yield for the same general set of reactions carried out on a classic Merrifield insoluble polymer support.[4] Thus, soluble poly(ethylene glycol) was a superior support for peptide synthesis using chromium aminocarbene complex photochemistry to install unusual amino acid residues, particularly if more than one photochemical coupling cycle is required. Despite this superiority, the failure of this coupling methodology to achieve 100% yield and diastereoselectivity in each step still limits the practical number of amino acid residues introduced into polymer supported peptides, since separation of minor amounts of diastereoisomers at each step is not possible.

## Experimental Section

**General Methods.** All manipulations of compounds and solvents were carried out using standard airless techniques. Solvents were degassed and purified by distillation under argon from standard drying reagents. $^1$H NMR chemical shifts are reported in $\delta$ vs $Me_4Si$, assigning the $CDCl_3$ resonance in $^{13}$C spectra to be at 77.00 ppm. Chemical shifts for $^1$H NMR spectra reported in MeOD-$d_4$ are given in ppm relative to methyl pentet at 3.30 ppm. Chemical shifts for $^{13}$C NMR spectra reported in MeOD-$d_4$ are given in ppm relative to the methyl heptet at 49.00 ppm. Column chromatography was performed with ICN 32–63 $\mu$m, 60 Å silica gel using flash column techniques.

**Scheme 4**




*N*-Boc-glycine, *N*-Boc-leucine, *N*-Boc-valine, *N*-Boc-proline, *N*-Boc-2-aminoisobutyric acid,[12a] and *N*-methyl-*N*-Boc-2-aminoisobutyric acid[12] were prepared by literature methods. Chromium aminocarbene complexes (*S*)-**4**, (*R*)-**4**, **9a**, and **9b**[11] were prepared by literature methods. PEG 4000 and PEG 8000 were purchased from Aldrich and J. T. Baker.

**General Procedure for Attachment of α-Carboxy Groups to PEG.** In a separate flask, the Boc-amino acid and DCC dissolved in dry $CH_2Cl_2$ were stirred at room temperature for 30 min, and the resulting DCU precipitate was removed by filtration. The resulting anhydride was transferred to a flask containing the PEG (vacuum dried over $P_2O_5$, 100 °C, 1 torr, overnight). A catalytic amount of DMAP was added, the solution was concentrated under reduced pressure to the concentration of about 40% (w/v), the solution was stirred at room temperature for 12 h, and then the solvent was removed under reduced pressure. An excess of acetic anhydride was added to block the remaining hydroxy groups on the PEG, and the solution was again stirred at room temperature for 8 h followed by vacuum distillation of the solvent. The resulting polymer was dissolved in $CH_2Cl_2$, precipitated with diethyl ether at 0 °C (kept stirring), followed by filtration. This process was repeated three times to afford the PEG-supported Boc amino acid.

**General Procedures for Removal of the Boc Group from the Peptide (or Amino Acid)-PEG.** A solution of the PEG-supported Boc-amino acid (or peptide), in TFA/$CH_2Cl_2$ (1:1 v/v) was stirred under an argon atmosphere at room temperature for 30 to 40 min following by removal of the solvents under reduced pressure. The resulting polymer was precipitated with diethyl ether at 0 °C and redissolved in a minimum amount of $CH_2Cl_2$ (at 40 °C). The solution was neutralized with *N*-methylmorpholine (to pH 7). After remov-

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ing the solvent under reduced pressure, the PEG-supported peptides (or amino acids) with free N-terminal groups were purified by dissolving in a minimum amount of $CH_2Cl_2$, at 40 °C and then precipitating with ether, for three cycles. The polymer was dried under vacuum over $P_2O_5$, at 60 °C overnight. The reaction was monitored by $^1H$ NMR ($\delta$ = 1.4 ppm) and IR ($\nu$ = 1713 $cm^{-1}$) spectroscopy.

**H-Gly-O-PEG 4000 Resin 1a.** The reaction of Boc-glycine (6.80 g, 38.9 mmol), DCC (4.10 g, 19.5 mmol), PEG 4000 (11.2 g, 4.48 mmol), and DMAP (568 mg, 4.65 mmol), in 45 mL of $CH_2Cl_2$, at room temperature for 12 h afforded the PEG-supported Boc-glycine following purification. The resulting polymer was allowed to react in TFA/$CH_2Cl_2$ (55 mL, 1:1 v/v) followed by neutralization and purification to afford the PEG-supported glycine **1a** (10.9 g) as a white powder (0.38 mequiv/g, 97% coupling efficiency). $^1H$ NMR: $\delta$ 7.95 (br s, 2H), 4.35 (m, 2H), 3.96–3.39. $^{13}C$ NMR: $\delta$ 167.4, 73.2, 70.1, 68.2, 64.7, 40.5. IR (film) $\nu$ 3484, 2882, 1753 $cm^{-1}$.

**H-Pro-O-PEG 4000 Resin 1b.** The reaction of Boc-proline (6.88 g, 32.0 mmol), DCC (3.29 g, 16.0 mmol), PEG 4000 (13.9 g, 5.40 mmol), and DMAP (686 mg, 5.60 mmol), in 55 mL of $CH_2Cl_2$, at room temperature for 12 h afforded the PEG-supported Boc-proline following purification. The resulting polymer was allowed to react in TFA/$CH_2Cl_2$ (60 mL, 1:1 v/v) followed by neutralization and purification to afford the PEG-supported proline **1b** (13.0 g) as white powder (0.33 mequiv/g, 88% coupling efficiency). The NMR spectra of this material were broad and uninformative. IR (film): $\nu$ 3460, 2945, 2885, 1749 $cm^{-1}$.

**H-Leu-O-PEG 4000 Resin 1c.** The reaction of Boc-leucine (11.2 g, 48.4 mmol), DCC (4.99 g, 24.2 mmol), PEG 4000 (13.9 g, 5.40 mmol), and DMAP (686 mg, 5.60 mmol), in 55 mL of $CH_2Cl_2$, at room temperature for 12 h afforded the PEG-supported Boc-leucine following purification. The resulting polymer was allowed to react in TFA/$CH_2Cl_2$ (60 mL, 1:1 v/v) followed by neutralization and purification to afford the PEG-supported leucine **1c** (13.0 g) as white powder (0.37 mequiv/g, 97%). $^1H$ NMR: $\delta$ 8.40–8.00 (bs, 2H), 4.31 (m, 1H), 4.00–3.35 (m), 1.74 (m, 3H), 0.92 (m, 6H). $^{13}C$ NMR: $\delta$ 169.6, 70.0, 68.0, 64.5, 51.2, 39.5, 24.1, 22.1, 21.5. IR (film): $\nu$ 3450, 2876, 1780, 1749 $cm^{-1}$.

**General Procedures for Coupling Another Boc-Amino Acid to the Peptide (or the Amino Acid) on PEG.** PEG-supported peptide (or the amino acid) resin, the Boc-amino acid, DCC, and HOBt dissolved in $CH_2Cl_2$ were stirred under an argon atmosphere at room temperature for several hours and monitored by the ninhydrin test.[13] The insoluble DCU was removed by filtration, and the resulting PEG-supported peptide was isolated by precipitation (with $Et_2O$, at 0 °C, three times).

**H-Val-Gly-O-PEG 4000 Resin 2a.** Following the general procedure, the coupling reaction of PEG supported glycine **1a** (5.00 g, 1.90 mmol), Boc-valine (1.35 g, 6.00 mmol), DCC (1.24 g, 6.00 mmol), and HOBt (0.82 g, 6.00 mmol), in 15 mL of $CH_2Cl_2$, for 4 h followed by deprotection (30 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide **2a** (4.70 g) as white powder (0.35 mequiv/g, 95% overall coupling efficiency). $^1H$ NMR: $\delta$ 7.81 (2H), 4.24–2.68, 2.31 (1H), 1.07–0.82 (m, 6H). IR (film): $\nu$ 4017, 3268, 2867, 1754, 1729, 1688 $cm^{-1}$.

**H-Leu-Gly-O-PEG 4000 Resin 2b.** Following the general procedure, the coupling reaction of PEG supported glycine **1a** (14.0 g, 5.32 mmol), Boc-leucine (3.04 g, 13.1 mmol), DCC (2.71 g, 13.1 mmol), and HOBt (1.77 g, 13.1 mmol), in 30 mL of $CH_2Cl_2$, for 3 h followed by deprotection (80 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide **2b** (13.6 g) as white powder (0.35 mequiv/g, 95% overall coupling efficiency). $^1H$ NMR: $\delta$ 8.95 (br t, 1H), 7.86 (bs, 2H), 4.29–3.34 (m), 1.87 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 0.90 (app t, 6H). $^{13}C$ NMR: $\delta$ 169.3, 168.9, 70.3, 68.6, 63.6, 52.3, 41.3, 39.8, 24.1, 22.8, 21.7. IR (film): $\nu$ 3469–3060, 2885, 1753, 1725, 1689 $cm^{-1}$.

**H-Aib-Gly-O-PEG 4000 Resin 2c.** Following the general procedure, the coupling reaction of the PEG-supported glycine **1a** (2.30 g, 0.87 mmol), 2-(*N*-Boc-amino)isobutyric acid (710 mg, 3.50 mmol), DCC (721 mg, 3.50 mmol), in 7 mL of $CH_2Cl_2$, for 8 h followed by the deprotection (15 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide **2c** (2.25 g) as white powder (0.35 mequiv/g, 95% overall coupling efficiency). $^1H$ NMR: $\delta$ 8.90 (s, 1H), 7.70 (br s, 2H), 4.24–4.07, 3.81–3.31, 1.61 (s, 6H). IR (film): $\nu$ 3424 (br), 2881, 1723, 1654 $cm^{-1}$.

**H-(Me)-Aib-Gly-O-PEG 4000 Resin 2d.** Following the general procedure, the coupling reaction of the PEG supported glycine **1a** (1.60 g, 0.61 mmol), *N*-methyl-*N*-Boc-2-aminoisobutyric acid (500 mg, 2.29 mmol), DCC (472 mg, 2.29 mmol), in 10 mL of $CH_2Cl_2$, for 4 h followed by deprotection (30 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide **2d** (1.55 g) as white powder (0.33 mequiv/g, 90% overall coupling efficiency). $^1H$ NMR: $\delta$ 8.55 (br s, 1H), 7.50 (br s, 1H), 4.40–4.00, 3.91–3.40, 2.75, 2.82, 1.65. IR (film): $\nu$ 3482, 2880, 1751, 1725, 1684 $cm^{-1}$.

**H-Val-Leu-O-PEG 4000 Resin 2e.** Following the general procedure, the coupling reaction of the PEG supported leucine **1c** (3.00 g, 1.11 mmol), Boc-valine (1.21 g, 5.56 mmol), DCC (1.15 g, 5.56 mmol), and HOBt (0.751 g, 5.56 mmol), in 15 mL of $CH_2Cl_2$, for 4 h followed by the deprotection (20 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide **2e** (2.90 g) as white powder (0.35 mequiv/g, 95% overall coupling efficiency). $^1H$ NMR: $\delta$ 8.15 (bs, 2H), 7.09 (br d, 1H), 4.57 (m, 1H), 4.24 (m, 1H), 3.81–3.31, 2.20 (m, 1H), 1.70–1.58 (3H, CH), 1.06–0.81 (m, 12H). IR (film): $\nu$ 3467, 2887, 1743, 1721, 1681 $cm^{-1}$.

**H-Val-Leu-Gly-O-PEG 8000 Resin 3.** Following the general procedure, the reaction of Boc-glycine (2.68 g, 15.3 mmol), DCC (1.58 g, 7.65 mmol), PEG 8000 (15.0 g, 2.92 mmol), and DMAP (388 mg, 3.20 mmol), in 65 mL of $CH_2Cl_2$, at room temperature for 12 h afforded the PEG-supported Boc glycine. The resulting polymer was allowed to react in TFA/$CH_2Cl_2$ (40 mL, 1:1 v/v) followed by neutralization and purification to afford the PEG-supported glycine. Treatment with Boc-leucine (2.12 g, 9.18 mmol), DCC (1.89 g, 9.18 mmol), and HOBt (1.77 g, 13.1 mmol), in 45 mL of $CH_2Cl_2$, for 3 h followed by the deprotection (40 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG-supported dipeptide. Further coupling of valine was done by the same procedure with Boc-valine (1.99 g, 9.18 mmol), DCC (1.89 g, 9.18 mmol) and HOBt (1.24 g, 9.18 mmol), in 45 mL of $CH_2Cl_2$, for 3 h followed by deprotection (40 mL, 50% TFA/$CH_2Cl_2$) afforded the PEG 8000-supported tripeptide resin **3** (13.2 g) (0.18 mequiv/g, 95% overall coupling efficiency) as white powder (vacuum drying over $P_2O_5$, at 60 °C overnight). $^1H$ NMR $\delta$ 7.09 (1H), 6.33 (1H,), 4.46 (1H), 4.25 (2H), 4.00–3.28, 2.20 (1H),1.70–1.54 (3H), 1.02–0.81 (m, 12H). IR (film): $\nu$ 3467, 2887, 1740, 1681 $cm^{-1}$.

**General Procedure for the Photolysis of PEG-Supported Peptides (or Amino Acids) with Chromium Aminocarbene Complexes.** The chromium aminocarbene complex, dissolved in freshly distilled THF, was filtered through Celite directly into a Pyrex (Ace Glass) pressure tube containing a magnetic stir bar and the appropriate amount of PEG-supported peptide (or amino acid), and the mixture was diluted with THF and a minimum amount of $CH_2Cl_2$ (for the purpose of dissolution of the polymer). A pressure head was attached, and the solution was flushed with argon and saturated with CO (50–65 psi). The Pyrex pressure tube was irradiated (stirred at rt, 30 h) with a Conrad Hanovia 7825 medium pressure mercury lamp operating at 450 W, which was placed in a water-cooled Pyrex immersion well. After photolysis, the polymer was isolated by precipitation with diethyl ether (at 0 °C, three times) and the resulting white powder was kept on a vacuum line overnight.

**General Procedure for Cleavage and Purification of the Peptides from the PEG Support by Transesterification.** The PEG-supported peptide dissolved in a solvent mixture of methanol and DMF (1:1 v/v), containing a catalytic amount of KCN (1% w/v) (or 2 equiv of DBU/5 equiv of LiBr, MeOH, 4 h, rt), was stirred at 50 °C for 36 h. (The reaction was monitored by $^1H$ NMR or IR (1748 $cm^{-1}$) spectroscopy.) After cleavage, most of the PEG was removed by precipitation with diethyl ether at 0 °C, the polymer was redissolved in MeOH/$CH_2Cl_2$ 10–50% v/v of MeOH, according to the polarity and solubility of the peptides and reprecipitated a total of five

(13) Moore, S.; Spackman, D. H.; Stein, W. H. *Anal. Chem.* **1959**, *30*, 1185.

times. Traces of remaining PEG were removed by flash chromatography over silica gel with MeOH as solvent, and the crude peptide product was further purified by flash chromatography on silica gel or recrystallization to afford the peptide product.

**Preparation of Dipeptide 6a.** Following the general procedure, photolysis of PEG-supported glycine **1a** (329 mg, 0.125 mmol), and chromium complex (*S*)-**4** (99 mg, 0.250 mmol) in THF (3 mL) and $CH_2Cl_2$ (0.3 mL), at room temperature for 30 h afforded the product (320 mg) as a white powder. Cleavage in a mixture of methanol (2 mL) and DMF (2 mL) containing KCN (35 mg) produced dipeptide **6a** (29 mg, 75%) as a colorless oil after further flash chromatography over silica gel (50% hex/EtOAc). The crude reaction mixture consisted of an 96:4 ratio of two diastereomers (92% de), determined by integration of the *gem*-dimethyl singlets ($\delta$ 1.49 ppm major, 1.55 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.46 (bs, 1H), 7.36–7.14 (m, 5H), 4.29–4.22 (m, 2H), 3.93–3.85 (m, 2H), 3.69 (s, 3H), 3.42 (q, $J$ = 7.1 Hz, 1H), 3.26 (dd, $J$ = 3.8, 18.5 Hz, 1H), 1.49 (s, 3H), 1.35 (d, $J$ = 7.2 Hz, 3H), 1.30 (s, 3H). $^{13}$C NMR: $\delta$ 174.1, 170.1, 141.8, 128.6, 128.0, 127.7, 96.9, 72.1, 60.3, 54.8, 52.2, 40.9, 27.8, 21.5, 14.0. IR (film): $\nu$ 3386, 2979, 1748, 1667 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{17}H_{24}O_4N_2$: M + H = 321.1814. Found: 321.1813 ± 0.0011 ($\Delta$ = −0.6 ppm).

**Preparation of Dipeptide 6b.** Following the general procedure, the photolysis of the PEG-supported proline **1b** (800 mg, 0.264 mmol), and chromium complex (*S*)-**4** (271 mg, 0.680 mmol) dissolved in THF (5 mL) and $CH_2Cl_2$ (0.3 mL), at room temperature for 30 h afforded the product (820 mg) as a white powder. Cleavage in a solvent mixture of methanol (3 mL) and DMF (2 mL) containing KCN (40 mg) produced the dipeptide product **6b** (51 mg, 54%) as a pale yellow oil after further flash chromatography over silica gel (1:1 hex/EtOAc). The crude reaction mixture consisted of an 76:24 ratio of two diastereomers (52% de), determined by integration of the methyl doublets ($\delta$ 1.17 ppm major, 1.11 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.43–7.19 (m, 5H), 5.27 (dd, $J$ = 7.2, 4.1 Hz, 1H), 4.47 (dd, $J$ = 8.4, 4.0 Hz, 1H), 4.33 (app t, $J$ = 7.7 Hz, 1H), 3.72 (s, 3H), 3.75–3.62 (m, 3H), 3.45 (q, $J$ = 7.0 Hz, 1H), 2.17–1.94 (m, 4H), 1.43 (s, 3H), 1.29 (s, 3H), 1.17 (d, $J$ = 7.1 Hz, 3H). $^{13}$C NMR: $\delta$ 175.1, 172.7, 145.4, 128.1, 127.2, 126.9, 95.6, 71.8, 60.5, 58.7, 52.2, 51.5, 46.5, 28.8, 28.0, 25.0, 23.6, 16.7. IR (film): $\nu$ 1746, 1648 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{20}H_{28}O_4N_2$: M + H = 361.2127. Found: 361.2129 ± 0.0007 ($\Delta$ = −0.7 ppm).

**Preparation of Dipeptide 6c.** Following the general procedure, the photolysis of the PEG-supported leucine **1c** (176 mg, 0.065 mmol), and chromium complex (*S*)-**4** (48.0 mg, 0.120 mmol) in THF (1.5 mL) and $CH_2Cl_2$ (0.2 mL), at room temperature for 30 h afforded the product (170 mg) as a white powder. Cleavage in a mixture of methanol (1.5 mL) and DMF (1 mL) containing KCN (20 mg) produced the dipeptide product **6c** (21 mg, 87%) as a pale yellow oil after further flash chromatography over silica gel (50% hex/EtOAc). The crude reaction mixture consisted of an 97.5:2.5 ratio of two diastereomers (95% de), determined by integration of the methylene peaks [$\delta$ 4.23 ppm (3H) major, 4.69 ppm (1H) minor] from the $^1$H NMR spectrum.

If the photolysis was carried out in $CH_2Cl_2$, the combined yield for both diastereomers was 85%, and the crude reaction mixture consisted of a 77:23 ratio of two diastereomers (54% de). $^1$H NMR (major isomer): $\delta$ 7.42–7.20 (m, 6H), 4.35–4.21 (m, 3H), 3.87 (dd, $J$ = 7.7, 5.6 Hz, 1H), 3.65 (s, 3H), 3.43 (q, $J$ = 7.3 Hz, 1H), 1.65–1.48 (m, 3H), 1.47 (s, 3H), 1.37 (d, $J$ = 7.3 Hz, 3H), 1.34 (s, 3H), 0.92 (d, $J$ = 6.3 Hz, 3H), 0.88 (d, $J$ = 6.1 Hz, 3H). $^{13}$C NMR $\delta$ 174.0, 172.5, 141.7, 128.5, 127.8, 127.5, 96.7, 72.2, 60.4, 55.2, 51.8, 50.5, 41.2, 27.6, 24.7, 22.5, 21.8, 20.9, 14.3. IR (film): $\nu$ 3385, 1742, 1673 cm$^{-1}$. Anal. Calcd for $C_{21}H_{32}O_4N_2$: C, 66.99; H, 8.57. Found: C, 67.23; H, 3.26. $^1$H NMR (minor isomer): $\delta$ 7.42–7.14 (m, 5H), 6.66 (d, $J$ = 7.8 Hz, 1H), 4.69 (dd, $J$ = 7.8, 5.4 Hz, 1H), 4.45 (m, 1H), 4.34 (app t, $J$ = 8.1 Hz, 1H), 3.73 (m, 1H), 3.71 (s, 3H), 3.58 (q, $J$ = 7.0 Hz, 1H), 1.83 (m, 1H), 1.67–1.53 (m, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.23 (d, $J$ = 7.2 Hz, 3H), 0.97–0.83 (m, 6H). $^{13}$C NMR: $\delta$ 174.7, 173.1, 144.3, 128.2, 126.9, 126.7, 96.0, 71.0, 62.5, 56.2, 52.0, 50.5, 41.3, 28.0, 24.8, 23.1, 22.5, 21.8, 18.0. IR (film): $\nu$ 3319, 1745, 1658 cm$^{-1}$. Anal. Calcd for $C_{21}H_{32}O_4N_2$: C, 66.99; H, 8.57. Found: C, 66.85; H, 8.56.

**Preparation of Tripeptide 7a.** Following the general procedure, the photolysis of the PEG-supported dipeptide **2a** (255 mg, 0.090 mmol), and chromium complex (*S*)-**4** (85 mg, 0.213 mmol) in THF (2 mL) and $CH_2Cl_2$ (0.2 mL), at room temperature for 30 h afforded the product (252 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (1.5 mL) containing KCN (25 mg) produced the tripeptide product **7a** (30 mg, 80%) as a pale yellow oil after further flash chromatography over silica gel (3:1 hex/EtOAc). The crude reaction mixture consisted of an 94:6 ratio of two diastereomers (88% de), determined by integration of the methyl doublets ($\delta$ 1.46 ppm major, 1.67 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.58 (d, $J$ = 8.0 Hz, 1H), 7.40–7.13 (m, 5H), 5.52 (t, $J$ = 5.4 Hz, 1H), 4.28 (m, 2H), 3.99 (dd, $J$ = 8.1, 5.4 Hz, 1H), 3.87 (m, 1H), 3.72 (m, 2H), 3.71 (s, 3H), 3.47 (q, $J$ = 7.3 Hz, 3H), 2.20 (m, 1H), 1.51 (s, 3H), 1.46 (d, $J$ = 7.3 Hz, 3H), 1.32 (s, 3H), 0.95 (m, 6H). $^{13}$C NMR: $\delta$ 174.5, 170.6, 169.6, 141.9, 128.9, 128.0, 127.5, 96.9, 72.4, 59.8, 58.7, 54.7, 52.0, 40.8, 29.6, 27.9, 20.6, 19.3, 17.7, 13.7. IR (film): $\nu$ 3721–3364, 1754, 1651 cm$^{-1}$. Anal. Calcd for $C_{22}H_{33}O_5N_3$: C, 62.99; H, 7.93. Found: C, 63.08; H, 7.74.

**Preparation of Tripeptide 7b.** Following the general procedure, the photolysis of the PEG-supported dipeptide **2b** (850 mg, 0.297 mmol), and chromium complex (*S*)-**4** (235 mg, 0.594 mmol) in THF (5 mL) and $CH_2Cl_2$ (0.8 mL), at room temperature for 30 h afforded the product (850 mg) as a white powder. Cleavage in methanol (2.5 mL) and DMF (2 mL) containing KCN (50 mg) produced the tripeptide **7b** (102 mg, 81%) as a pale yellow oil after further flash chromatography over silica gel (10:9:1 of hex/EtOAc/MeOH). The crude reaction mixture consisted of an 96:4 ratio of two diastereomers (92% de), determined by integration of the methyl doublets ($\delta$ 1.43 ppm major, 1.35 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.35–7.13 (m, 6H), 5.75 (t, $J$ = 5.3 Hz, 1H), 4.25 (m, 2H), 4.02 (m, 1H), 3.85 (dd, $J$ = 12.5, 9.2 Hz, 1H), 3.79 (dd, $J$ = 18.2, 5.0 Hz, 1H), 3.67 (s, 3H), 3.59 (dd, $J$ = 18.1, 5.0 Hz, 1H), 3.41 (q, $J$ = 7.2 Hz, 1H), 1.63–1.50 (m, 3H), 1.43 (d, $J$ = 7.3 Hz, 3H), 1.41 (s, 3H), 1.27 (s, 3H), 0.88 (d, $J$ = 6.3 Hz, 3H), 0.79 (d, $J$ = 6.2 Hz, 3H). $^{13}$C NMR: $\delta$ 174.7, 171.4, 169.8, 142.7, 129.1, 128.0, 127.9, 97.1, 72.5, 59.9, 55.0, 52.2, 51.8, 41.0, 39.9, 27.6, 24.9, 23.1, 21.5, 20.8, 14.3. IR (film): $\nu$ 3500–3200, 1755, 1659 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{23}H_{35}O_5N_3$: M + H = 434.2655. Found: 434.2678 ± 0.0023 ($\Delta$ = −5.6 ppm).

**Preparation of Tripeptide 7c.** Following the general procedure, the photolysis of the PEG-supported dipeptide **2c** (400 mg, 0.140 mmol), and chromium complex (*S*)-**4** (117 mg, 0.290 mmol) in THF (3.5 mL) and $CH_2Cl_2$ (0.4 mL), at room temperature for 30 h afforded the product (403 mg) as white powder. Cleavage in methanol (2 mL) and DMF (2 mL) containing KCN (30 mg) produced the tripeptide **7c** (45 mg, 78%) as a pale yellow oil after further flash chromatography over silica gel (2:1 hex/EtOAc). The crude reaction mixture consisted of an 94:6 ratio of two diastereomers (88% de), determined by integration of the methyl doublets ($\delta$ 1.43 ppm major, 1.65 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.55 (s, 1H), 7.41–7.20 (m, 5H), 6.44 (t, $J$ = 6.8 Hz, 1H), 4.34 (m, 2H), 3.94 (dd, $J$ = 6.7, 3.1 Hz, 1H), 3.81 (app d, $J$ = 5.3 Hz, 2H), 3.71 (s, 3H), 3.38 (q, $J$ = 7.3 Hz, 1H), 1.49 (s, 3H), 1.43 (d, $J$ = 7.3 Hz, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H). $^{13}$C NMR $\delta$ 174.1, 173.8, 170.0, 142.6, 128.9, 127.9, 127.7, 96.9, 72.2, 59.5, 56.4, 55.0, 52.0, 41.1, 27.5, 24.9, 24.3, 20.7, 13.5. IR (film): $\nu$ 3340, 1754, 1659 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{21}H_{31}O_5N_3$: M + H = 406.2342. Found: 406.2368 ± 0.0013 ($\Delta$ = −5.5 ppm).

**Preparation of Tripeptide 7d.** Following the general procedure, the photolysis of the PEG-supported dipeptide **2d** (470 mg, 0.155 mmol), and chromium complex (*S*)-**4** (154 mg, 0.390 mmol) in THF (4 mL) and $CH_2Cl_2$ (0.3 mL), at room temperature for 30 h afforded the product (465 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (2 mL) containing KCN (30 mg) produced the tripeptide product **7d** (38 mg, 58%) as a pale yellow oil after further flash chromatography over silica gel (1:2:4 MeOH/hex/EtOAc). The crude

reaction mixture consisted of an 85:15 ratio of two diastereomers (70% de), determined by integration of the methyl singlets ($\delta$ 1.56 ppm major, 1.43 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.38−7.16 (m, 5H), 5.50 (br t, 1H), 4.53 (dd, $J$ = 8.6, 5.4 Hz, 1H), 4.31 (app t, $J$ = 8.4 Hz, 1H), 4.04 (q, $J$ = 6.5 Hz, 1H), 3.77 (m, 2H), 3.68 (s, 3H), 3.62 (dd, $J$ = 8.2, 5.5 Hz, 1H), 3.25 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.26 (d, $J$ = 6.4 Hz, 3H), 1.11 (s, 3H). $^{13}$C NMR: $\delta$ 174.6, 172.4, 170.7, 145.3, 128.4, 126.8, 126.1, 97.4, 71.1, 61.8, 60.8, 55.5, 52.0, 41.1, 30.3, 28.3, 23.5, 23.1, 22.8, 14.2. IR (film) $\nu$ 3854, 1734, 1670 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{22}H_{28}O_5N_3$: M + H = 420.2498. Found: 420.2509 ± 0.0006 ($\Delta$ = −2.6 ppm).

**Preparation of Tripeptide 7e.** Following the general procedure, the photolysis of the PEG-supported dipeptide **2e** (400 mg, 0.140 mmol), and chromium complex (*S*)-**4** (119 mg, 0.300 mmol) in THF (3.5 mL) and $CH_2Cl_2$ (0.4 mL), at room temperature for 30 h afforded the product (403 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (2 mL) containing KCN (25 mg) produced the tripeptide product **7e** (30 mg, 80%) as a pale yellow oil after further flash chromatography over silica gel (1:1 hex/EtOAc). The crude reaction mixture consisted of an 95.5:4.5 ratio of two diastereomers (91% de), determined by integration of the methine peaks ($\delta$ 2.04 ppm major, 2.25 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.66 (d, $J$ = 7.8 Hz, 1H), 7.41−7.18 (m, 5H), 5.97 (d, $J$ = 7.7 Hz, 1H), 4.41 (m, 1H), 4.26 (m, 2H), 3.86 (m, 2H), 3.72 (s, 3H), 3.47 (q, $J$ = 7.2 Hz, 1H), 2.04 (hep, $J$ = 6.8 Hz, 1H), 1.65−1.55 (m, 3H), 1.51 (s, 3H), 1.36 (d, $J$ = 7.3 Hz, 3H), 1.34 (s, 3H), 0.98−0.87 (m, 12H). $^{13}$C NMR $\delta$ 174.7, 173.0, 170.2, 141.4, 128.9, 128.1, 127.8, 97.0, 72.6, 60.7, 58.9, 55.3, 52.2, 50.7, 41.1, 30.3, 28.0, 24.7, 22.7, 22.0, 21.0, 19.2, 18.5, 14.2. IR (film): $\nu$ 3308, 1745, 1652 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{26}H_{41}O_5N_3$: M + H = 476.3124. Found: 476.3117 ± 0.0014 ($\Delta$ = 0.5 ppm).

**Preparation of Tetrapeptide 8.** Following the general procedure, the photolysis of the PEG-supported tripeptide **3** (1.00 g, 0.184 mmol), and chromium complex (*S*)-**4** (137 mg, 0.346 mmol) in THF (5 mL) and $CH_2Cl_2$ (0.5 mL), at room temperature for 30 h afforded the product (995 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (2 mL), containing KCN (35 mg) produced the tetrapeptide product **8** (74 mg, 76%; mp: 208−211 °C) as white needles after further flash chromatography over silica gel (10% MeOH/$CH_2Cl_2$) and recrystallization (1:1 hex/EtOAc). The crude reaction mixture consisted of an 94.5:5.5 ratio of two diastereomers (89% de), determined by integration of the methyl doublets ($\delta$ 0.84 ppm major, 1.18 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.58 (d, $J$ = 5.5 Hz, 1H, NH), 7.49−7.23 (m, 5H), 7.00 (t, $J$ = 5.4 Hz, 1H), 5.33 (d, $J$ = 8.6 Hz, 1H), 4.42 (m, 1H), 4.31 (m, 2H), 4.03 (dd, $J$ = 17.8, 5.7 Hz, 1H), 3.93 (dd, $J$ = 12.2, 9.2 Hz, 1H), 3.84 (dd, $J$ = 17.8, 5.6 Hz, 1H), 3.81 (s, 3H), 3.73 (m, 1H), 3.46 (q, $J$ = 7.2 Hz, 1H), 1.87 (m, 1H), 1.74 (m, 1H), 1.50 (s, 3H), 1.42 (d, $J$ = 7.3 Hz, 3H), 1.38 (m, 2H), 1.34 (s, 3H), 0.93 (m, 9H), 0.84 (d, $J$ = 6.4 Hz, 3H). $^{13}$C NMR: $\delta$ 175.9, 172.1, 170.6, 170.0, 142.9, 129.2, 128.0, 127.9, 97.1, 72.5, 60.8, 59.8, 55.0, 52.1, 51.0, 41.1, 39.6, 29.7, 27.8, 24.5, 23.1, 21.3, 20.7, 19.4, 18.9, 14.0. IR (film): $\nu$ 3287, 1758, 1642 cm$^{-1}$. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 63.13; H, 8.27. Found: C, 63.29; H, 8.30.

**Preparation of Tetrapeptide 8′.** Following the general procedure, the photolysis of the PEG-supported tripeptide **3** (1000 mg, 0.184 mmol), and chromium complex (*R*)-**4** (137 mg, 0.346 mmol) in THF (5 mL) and $CH_2Cl_2$ (0.4 mL), at room temperature for 30 h afforded the product (997 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (2 mL), containing KCN (35 mg) produced the tetrapeptide product **8′** (77 mg, 79%; mp: 208−213 °C) as white needles after further flash chromatography over silica gel (10% MeOH/$CH_2Cl_2$) and recrystallization (1:1 hex/EtOAc). The crude reaction mixture consisted of an 95.5:4.5 ratio of two diastereomers (91% de), determined by integration of the methyl doublets ($\delta$ 0.45 ppm major, 1.15 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.66 (d, $J$ = 9.0 Hz, 1H), 7.47−7.21 (m, 6H), 6.99 (t, $J$ = 5.4 Hz, 1H), 4.54 (m, 1H), 4.32 (m, 2H), 4.07 (d, $J$ = 5.1 Hz, 1H), 4.01 (m, 1H), 3.86 (dd, $J$ = 6.9, 3.9 Hz, 1H), 3.72 (s, 3H), 3.45 (q, $J$ = 7.3 Hz), 1.71−1.50 (m, 4H), 1.42 (s, 3H), 1.40 (d, $J$ = 7.3 Hz, 3H), 1.32 (s, 3H), 0.88 (app t, $J$ = 6.2 Hz, 6H), 0.75 (d, $J$ = 6.7 Hz, 3H), 0.45 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR: $\delta$ 174.8, 172.1, 171.2, 169.9, 143.3, 129.0, 127.5, 127.4, 97.0, 72.4, 60.8, 58.7, 56.2, 52.2, 51.2, 41.0, 40.1, 31.1, 27.3, 24.5, 22.9, 21.6, 20.5, 18.9, 18.4, 15.8. IR (film) $\nu$ 3287, 1756, 1642 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{28}H_{44}N_4O_6$: M + H = 533.3339. Found: 533.3317 ± 0.0010 ($\Delta$ = 4.1 ppm).

**Preparation of Dipeptide 10a.** Following the general procedure, the photolysis of the PEG-supported leucine **1c** (210 mg, 0.077 mmol), and chromium complex **9a** (71 mg, 0.146 mmol) in THF (2 mL) and $CH_2Cl_2$ (0.2 mL), at room temperature for 30 h afforded the product (208 mg) as a white powder. Cleavage in methanol (1.5 mL) and DMF (1.5 mL) containing KCN (20 mg) produced the dipeptide product **10a** (26 mg, 76%) as a pale yellow oil after further flash chromatography over silica gel (2:1 hex/EtOAc). The crude reaction mixture consisted of an 90:10 ratio of two diastereomers (80% de), determined by integration of the *gem*-dimethyl singlets ($\delta$ 1.45 ppm major, 1.38 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.38−7.16 (m, 10H), 6.86 (d, $J$ = 7.2 Hz, 1H), 4.33−4.29 (dd, $J$ = 7.4, 5.1 Hz, 1H), 4.25−4.16 (m, 2H), 3.85 (dd, $J$ = 8.3, 5.1 Hz, 1H), 3.63 (s, 3H), 3.29 (dd, $J$ = 8.6, 4.87 Hz, 1H), 2.82 (m, 1H), 2.68 (m, 1H), 2.17 (m, 1H), 1.94 (m, 1H), 1.55−1.47 (m, 2H), 1.44 (s, 3H), 1.32 (m, 1H), 1.20 (s, 3H), 0.90 (d, $J$ = 6.3 Hz, 3H), 0.87 (d, $J$ = 6.2 Hz, 3H). $^{13}$C NMR: $\delta$ 173.6, 172.6, 142.5, 141.4, 128.6, 128.4, 127.6, 127.5, 127.0, 125.8, 96.5, 72.0, 60.5, 59.1, 51.8, 50.4, 40.9, 34.1, 31.7, 27.9, 24.7, 22.5, 21.7, 21.5. IR (film): $\nu$ 3385, 3061, 3026, 2955, 1743, 1674 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{28}H_{38}O_4N_2$: M + H = 467.2910. Found: 467.2931 ± 0.0021 ($\Delta$ = −3.0 ppm).

**Preparation of Dipeptide 10b.** Following the general procedure, the photolysis of the PEG-supported leucine **1c** (400 mg, 0.150 mmol), and chromium complex **9b** (153 mg, 0.300 mmol) in THF (2.5 mL) and $CH_2Cl_2$ (0.2 mL), at room temperature for 30 h afforded the product (402 mg) as a white powder. Cleavage in methanol (2 mL) and DMF (1.5 mL) containing KCN (20 mg) produced the dipeptide product **10b** (55 mg, 75%) as a pale yellow oil after further flash chromatography over silica gel (4:1 hex/EtOAc). The crude reaction mixture consisted of an 89:11 ratio of two diastereomers (78% de), determined by integration of the methine peaks ($\delta$ 3.30 ppm major, 3.42 ppm minor) from the $^1$H NMR spectrum. $^1$H NMR: $\delta$ 7.43−7.23 (m, 5H), 6.90 (d, $J$ = 7.5 Hz, 1H), 4.36 (dd, $J$ = 7.5, 5.3 Hz, 1H), 4.26 (dd, $J$ = 8.5, 7.6 Hz, 1H), 4.18 (m, 1H), 3.86 (dd, $J$ = 8.4, 5.3 Hz, 1H), 3.65 (s, 3H), 3.30 (dd, $J$ = 8.6, 5.5 Hz, 1H), 2.48 (m, 1H), 2.32 (m, 1H), 2.01 (m, 2H), 1.61−1.21 (m, 3H), 1.48 (s, 3H), 1.44 (s, 9H), 1.37 (s, 3H), 0.90 (d, $J$ = 6.4 Hz, 3H), 0.87 (d, $J$ = 6.2 Hz, 3H). $^{13}$C NMR: $\delta$ 173.5, 172.8, 172.5, 142.7, 128.8, 127.8, 127.7, 96.7, 80.3, 72.2, 60.7, 59.2, 52.0, 50.6, 41.2, 33.5, 28.1, 28.0, 25.4, 24.9, 22.7, 21.9, 21.8. IR (film): $\nu$ 3390, 1729, 1677 cm$^{-1}$. Mass (HR FAB): Calcd for $C_{27}H_{42}O_6N_2$: M + H = 491.3121. Found: 491.3122 ± 0.0017 ($\Delta$ = −0.2 ppm).

**Oxidative Removal of the Oxazolidine Chiral Auxiliary of the Peptide on PEG and Preparation of 11.** The PEG-supported tripeptide (D)-Ala-Leu-Gly with the oxazolidine auxiliary at the N-terminus (1.00 g, 0.34 mmol) (from the photolysis of **2b** and (*S*)-**4**) dissolved in 10 mL of 1:4 (v/v) 1 N HCl/MeOH was allowed to stir at room temperature for 3 h, followed by removal of the solvent *in vacuo*. The polymer was precipitated with diethyl ether at 0 °C followed by neutralization of the polymer solution with *N*-methylmorpholine. Removal of the solvent under reduced pressure and precipitation with diethyl ether at 0 °C for three times (the solvent was 1:1 MeOH/$CH_2Cl_2$) gave 930 mg of acetonide-hydrolysis product.

The resulting polymer (500 mg, 0.18 mmol) dissolved in 5 mL of MeOH was cooled to 0 °C in an ice bath, and $Pb(OAc)_4$ (109 mg, 0.23 mmol) was added. The mixture was warmed to the room temperature, stirred for 6 h, and then filtered through Celite, and the Celite was washed with 1:1 MeOH/$CH_2Cl_2$. The filtrate was collected, and the polymer was purified by precipitation with diethyl ether at 0 °C three times (1:1 MeOH/$CH_2Cl_2$). The resulting polymer was dissolved in 1:4 1 N HCl/MeOH and stirred at room temperature for 5 h. The solvent was removed *in vacuo*, and the polymer was

purified by precipitation with diethyl ether at 0 °C followed by neutralization with *N*-methylmorpholine. Further precipitation and isolation as above afforded the PEG-supported tripeptide **11** with a free amino group at the N-terminus (456 mg, vacuum dried over $P_2O_5$ at 60 °C overnight) as a white powder. The reaction was monitored by $^1H$ NMR ($\delta$ 7.2–7.6 ppm) for completion of the deprotection. IR (film): $\nu$ 3380, 2886, 1745, 1673 $cm^{-1}$.

**Reductive Removal of the Oxazolidine Chiral Auxiliary of the Peptide on PEG and Preparation of 11.** The acetonide hydrolysis product made as above (500 mg, 0.18 mmol) was dissolved in MeOH (4 mL) and transferred into a pressure tube containing the Pearlman's catalyst $Pd(OH)_2/C$ (75 mg, 0.053 mmol). The mixture was flushed with argon (three times), pressurized to 50 psi with $H_2$, heated to 50 °C in an oil bath, and kept stirring at this temperature for 5 h. After hydrogenation was completed, the black slurry was stirred for 1 h more under 50 psi of CO at room temperature followed by removal of the $Pd(OH)_2/C$ by filtration through Celite. The filter cake was washed with 3 mL of MeOH and 3 mL of $CH_2Cl_2$, and the filtrate was concentrated *in vacuo*. Precipitation with $Et_2O$ at 0 °C from a 2:1 $CH_2Cl_2$/MeOH solvent mixture three times afforded the PEG-supported tripeptide with a free amino group at the N-terminus **11** (460 mg, vacuum dried over $P_2O_5$ at 60 °C overnight) as a white powder. The reaction was monitored by $^1H$ NMR ($\delta$ 7.2–7.6 ppm) for completion of the deprotection.

The compound was identical to **11** produced by oxidative methods.

**Preparation of Tetrapeptide 12.** Following the general procedure, the photolysis of the PEG-supported tripeptide **11** (360 mg, 0.120 mmol), and chromium complex (*S*)-**4** (100 mg, 0.250 mmol) in THF (3 mL) and $CH_2Cl_2$ (0.3 mL), at room temperature for 30 h afforded the product (350 mg) as a white powder. Cleavage in methanol (1.5 mL) and DMF (1.5 mL) containing KCN (20 mg) produced the tetrapeptide product **12** (36 mg, 58% overall from **2b**) as a pale yellow oil after further flash chromatography over silica gel (2:2:1 hex/EtOAc/MeOH). $^1H$ NMR: $\delta$ 7.48–7.25 (m, 6H), 6.98 (bs, 1H), 6.61 (d, $J$ = 8.6 Hz, 1H), 4.48 (m, 1H), 4.32 (m, 2H), 4.00 (m, 4H), 3.76 (s, 3H), 3.54 (q, $J$ = 7.2 Hz, 1H), 1.78 (m, 2H), 1.62 (m, 1H), 1.52 (s, 3H), 1.45 (d, $J$ = 7.2 Hz, 3H), 1.36 (s, 3H), 0.99 (d, $J$ = 6.9 Hz, 3H), 0.96 (d, $J$ = 6.5 Hz, 3H), 0.93 (d, $J$ = 6.4 Hz, 3H). $^{13}C$ NMR: $\delta$ 174.8, 172.2, 172.1, 170.2, 142.7, 128.9, 127.9, 127.8, 97.1, 72.9, 59.8, 54.6, 52.2, 51.5, 48.9, 41.1, 40.4, 27.7, 24.8, 23.0, 21.6, 21.1, 16.7, 13.7. IR (film): $\nu$ 3298, 1754, 1646 $cm^{-1}$. Mass (HR FAB): Calcd for $C_{26}H_{40}O_6N_4$: M + H = 505.3026. Found: 505.3039 ± 0.0006 ($\Delta$ = −2.5 ppm).

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**Supporting Information Available:** Copies of $^1H$ and $^{13}C$ NMR spectra (20 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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