Solid-Phase, Solution, and Segment Condensation Peptide Syntheses Incorporating Chromium Carbene Complex-Derived Nonproteinogenic ("Unnatural") Amino Acid Fragments

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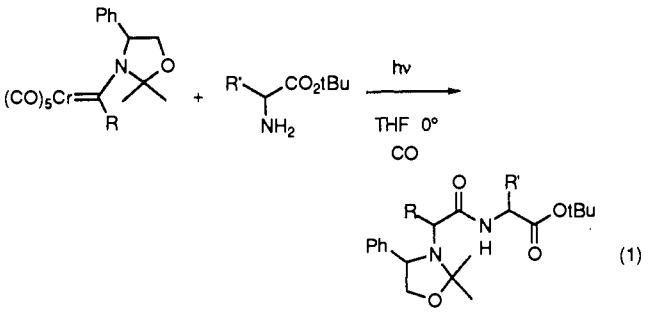
Abstract: Photolysis of optically active chromium aminocarbene complexes in the presence of tripeptide methyl esters gave protected tetrapeptide methyl esters in good yield and with good diastereoselectivity. Photolysis of these same carbene complexes in the presence of Merrifield resin supported amino acids or tripeptides resulted in incorporation of the chromium carbene complex-derived amino acid fragment into the solid-supported peptide. This photochemical methodology could be used iteratively, but it lacked efficiency. The procedure was most effective for segment condensation peptide synthesis. A tripeptide fragment containing two nonproteinogenic amino acids was synthesized by chromium carbene complex photochemistry. This tripeptide was incorporated into a Merrifield resin supported tripeptide, deprotected, and coupled to two more amino acid fragments using classical procedures to produce an octapeptide incorporating the chromium carbene complex-derived amino acid fragment.

Introduction

α-Amino acids occupy a prominent position in current organic chemistry and many new synthetic methods for preparing them have been developed.[1] A major impetus for this activity is to provide routes to nonproteinogenic ("unnatural") amino acids for incorporation into peptides, with the intent of altering the stability, bioavailability, or bioselectivity of these peptides.[2] However the new amino acids are synthesized, they are almost invariably incorporated into peptides by conventional solution phase, solid phase, or segment condensation techniques, which involve starting with the suitably protected, preformed amino acid and coupling it to the growing peptide fragment. While development of new protecting groups and activation groups for this conventional methodology continues unabated, few fundamentally new peptide coupling procedures have been developed.[3]

Over the past several years, research in these laboratories has centered on the development of photochemical reactions of chromium carbene complexes as useful reactions for organic synthesis.[4] The discovery that photolysis of chromium carbenes produced species with ketene-like reactivity[5] permitted the synthesis of a wide range of useful classes of organic compounds by this methodology. Photolysis of aminocarbene complexes in the presence of alcohols permits the efficient synthesis of α-amino acids,[6] optically active glycine,[7] aryl glycines,[8] and multiply ^{13}C-labeled amino acids,[9] giving access to a very wide range of optically active "natural" and "unnatural" amino acids. More importantly, photolysis of chromium aminocarbene complexes in the presence of α-amino acid esters forms dipeptides efficiently (eq 1).[10] This is a remarkable process in that both the peptide bond *and* the new stereogenic center of the carbene complex-derived amino acid fragment are formed in the same step and the "coupling agent" is visible light. This permits the introduction of all of the classes of amino acids mentioned above in peptides *without* having to presynthesize the amino acids themselves.



(1)

60-88% yield
80-96% de

To be truly useful for general peptide synthesis, any new method must be compatible with solid-phase polypeptide synthetic methods, since a vast majority of peptide syntheses are performed in that fashion. Given the transient nature of the photochemically produced, chromium carbene-derived reactive intermediate, having the nucleophilic "trap" in another phase (the solid resin) was perceived to pose a problem. Experiments designed to address this problem are described below.

Results and Discussion

At the outset of these studies, only *di*peptides had been prepared, using single amino acid esters to trap the photogenerated, complexed amino ketenes. To assess the general feasibility of this methodology for polypeptide synthesis, the use of small peptides in solution, rather than single amino acid esters, was examined. The tripeptide HValLeuGlyOMe (**2**) was synthesized by solid phase methods and was photolyzed with (*R*)-carbene complex **1a** and (*S*)-carbene complex **1b** to give fully protected

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(2) For examples, see: (a) Holladay, M.; Nadzan, A. M. *J. Org. Chem.* **1991**, *56*, 3900. (b) Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron* **1991**, *47*, 2389. (c) Knowles, J. R. *Science* **1987**, *236*, 1252.

(3) (a) Kaiser, E. T. *Acc. Chem. Res.* **1989**, *22*, 47. (b) Wieland, T.; Bodanszky, M. *The World of Peptides*; Springer-Verlag: Berlin, 1991. (c) Current developments are reviewed annually In *Amino Acids, Peptides, and Proteins*.

(4) For a limited review, see: Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143.

(5) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.

(6) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.

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(8) Vernier, J. M.; Hegedus, L. S.; Miller, D. B. *J. Org. Chem.* **1992**, *57*, 6914.

(9) Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 87.

(10) Miller, J. R.; Pulley, S. R.; Hegedus, L. S.; DeLombaert, S. *J. Am. Chem. Soc.* **1992**, *114*, 5602.

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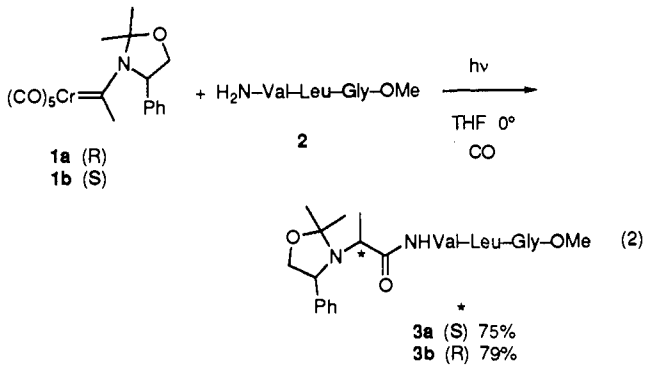
tetrapeptides **3a** and **3b**, respectively, with isolated yields of *single* diastereoisomers of 75–79% and with diastereoisomeric excesses (determined by ^{1}H NMR spectra of the crude reaction mixture) of 85–89% (eq 2).

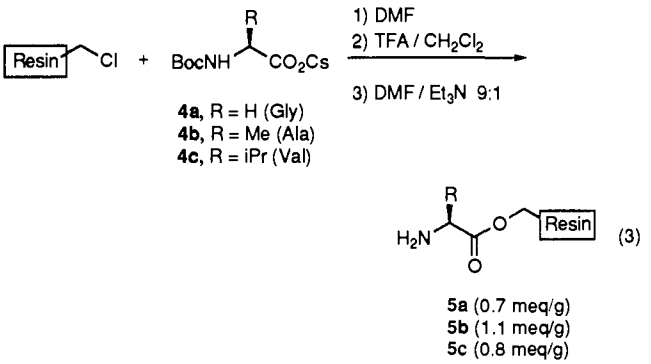


(2)

To verify that the same absolute stereochemistry observed with single amino acid esters as nucleophiles ((*R*)-carbene complexes produced (*S*)-amino acid fragments; (*S*)-carbene complexes produce (*R*)-amino acid fragments) also resulted with tripeptides as nucleophiles, authentic all-(*S*)-tetrapeptide Boc-Ala-Val-Leu-Gly-OMe was prepared by conventional methods and was compared to the material resulting from replacement of the oxazolidine group of **3a** by the Boc group, *via* hydrolysis/hydrogenolysis/di-*tert*-butyl carbonate. The two tetrapeptides were identical in all respects, confirming that the additional stereogenic centers in the tripeptide did not influence the sense of asymmetric induction.

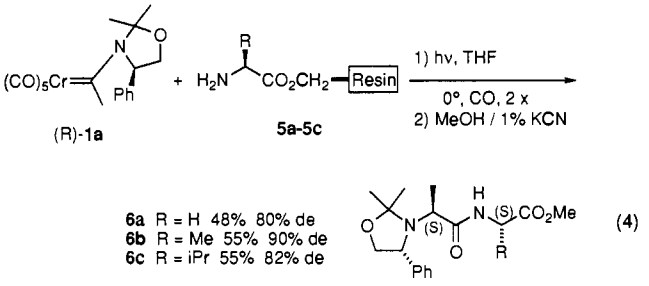
Even at the tetrapeptide stage, the difference between introducing an (*S*)-amino acid fragment and an "unnatural" (*R*)-amino acid fragment became manifest. While the photoreaction to produce the all-(S)-tetrapeptide **3a** remained homogeneous, the one producing the (R,S,S)-tetrapeptide **3b** quickly became heterogeneous, because of the insolubility of **3b** in the reaction medium. This gave impetus for the development of solid-phase methodology.

Three different amino acids were attached to chloromethylated polystyrene (1.2 mequiv/g, 1% crosslinked, 200–400 mesh Bio-Rad) *via* cesium salt esterification (eq 3), and the extent of



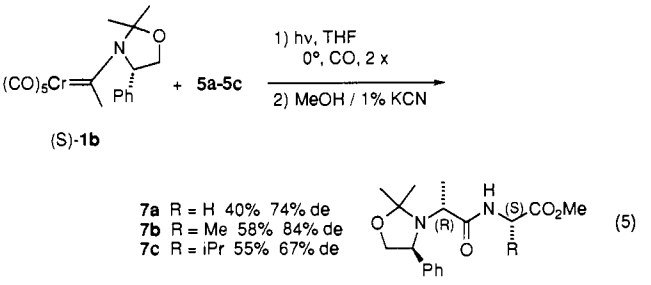
(3)

incorporation was determined both by elemental analysis for nitrogen and, more accurately, by quantitative ninhydrin analysis.[11] Each of these polymer-supported amino acids was photolyzed with 1.3 equiv of (*R*)-carbene complex **1a** in THF at 0 °C under a slight pressure of carbon monoxide for 24 h. At this stage, the ninhydrin test indicated that ≈30% of the free amino groups remained on the resin. An additional 1.3 equiv of **1a** was added and photolysis was continued for an additional 24 h, bringing the total consumption of amino groups to 80–90%. Cleavage of the dipeptide from the resin with methanolic potassium cyanide gave the N-protected (*S,S*)-dipeptides **6a–c** in 48–55% purified yield of single diastereoisomers (eq 4). (These



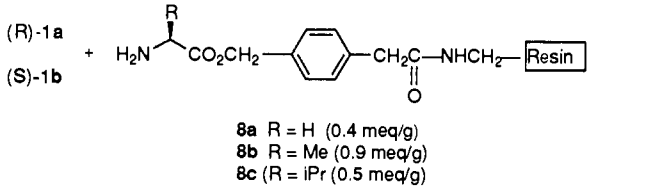
(4)

modest yields reflect, in part, physical loss of the resin during experimental manipulations, since quantitative transfer of these fine particles was difficult.) The diastereoisomeric excess of the crude reaction mixtures (^{1}H NMR spectroscopy) was 71–90%. A similar series of reactions was carried out with (*S*)-carbene complex **1b**, generating the (*R,S*)-dipeptides **7a–c** in comparable yields and with slightly lower diastereoisomeric excess (eq 5). As is typical for all polymer-supported peptides, cleavage of the more sterically hindered **6b**, **6c**, **7b**, and **7c** from the resin required more vigorous conditions than those required for **6a** and **7a** and resulted in some loss of material by racemization of the C-terminal amino acid residue.



(5)

In solid-phase peptide synthesis, the use of a flexible spacer between the polymer backbone and the amino acid residue often improves coupling efficiency.[12] For this reason, the 4-(hydroxymethyl)phenylacetamide (PAM) resin was prepared containing the same three amino acid fragments as those in **4a–c**. Photolysis of (*R*)-**1a** or (*S*)-**1b** in the presence of these resins, followed by release from the resin, gave the dipeptides **6a–c** and **7a–c**, respectively, in yields and with diastereoselectivities comparable to those obtained with the Merrifield resin (eq 6). However, because the peptide was more readily cleaved from the PAM resin, little if any racemization of the C-terminal amino acid was observed.



		Yield	de
1) hv, THF	**6a**	57%	80%
0°, CO, 2 x	**6b**	57%	85%
→	**6c**	53%	73%
	7a	60%	86%
2) MeOH	**7b**	57%	86%
1% KCN	7c	51%	70%

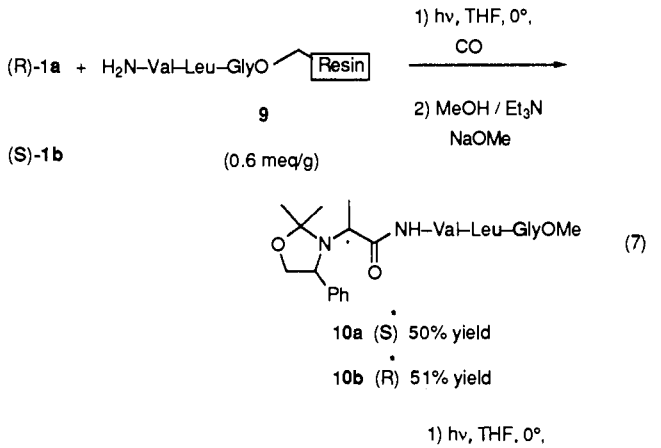
(6)

In solution both the yield and the diastereoselectivity of the photolytic peptide-coupling process improved when tripeptides

(11) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147.

(12) Mitchell, A. R.; Kent, S. B. H.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845.

were used as substrates (eq 2). To probe this effect in solid-supported systems, tripeptides **9** and **11** were photolyzed with carbene complexes **1a** and **1b** to produce tetrapeptides **10a**, **10b**, **12a**, and **12b** (eqs 7 and 8). The reported yields are for purified, single diastereoisomers. The lower yield with tripeptide **11** reflects the difficulty in cleaving the sterically hindered valine residue from the polymer.



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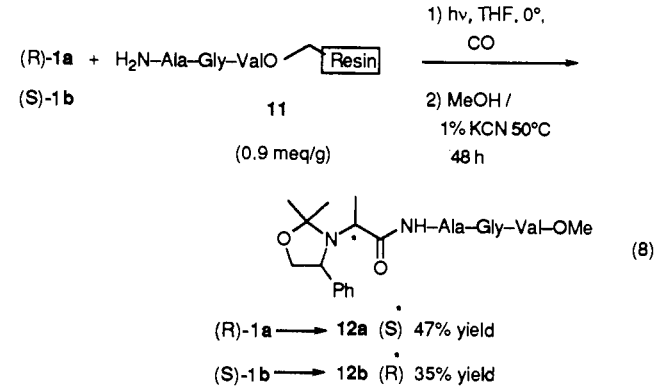
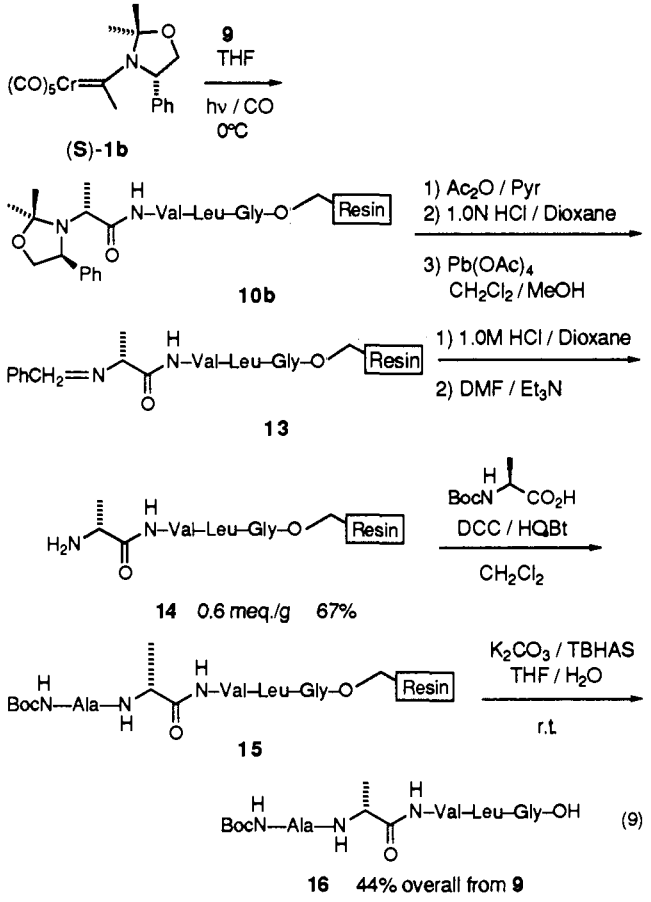


(8)

To be generally useful in peptide synthesis, it is necessary to be able to remove the chiral oxazolidine from the chromium-derived amino acid fragment so that the resulting NH_2 terminus can be coupled to the next amino acid fragment. In solution, this is easily achieved by hydrolysis/hydrogenolysis (Pd/C, H_2). However, polymer-supported, insoluble systems are not directly amenable to heterogeneous catalysis, and hydrogenolysis can cleave the benzyl ester linkage anchoring the peptide to the polymer.[13] Therefore a selective oxidative method of cleavage to remove the chiral auxiliary from the resin-bound peptide was needed. Again, in solution, hydrolysis of the oxazolidine followed by cleavage of the amino alcohol with aqueous periodate[10] efficiently removed the chiral auxiliary, producing the free NH_2 group on the amino terminus of the peptide. However, the hydrophobic nature of the polystyrene support drastically reduced the efficiency of this cleavage, making it useless for polymer-supported peptides. Cleavage of amino alcohols by $Pb(OAc)_4$ in methanol/methylene chloride proved to be the method of choice.[14]

To test this cleavage, polymer-supported tripeptide **9** was photolyzed with (*S*)-carbene complex **1b** to give the resin-bound fully protected tetrapeptide **10b**, in which 84% of the NH_2 groups had reacted in the photolytic coupling step (determined by ninhydrin analysis) (eq 9). The unreacted amino groups were blocked by treatment with acetic anhydride in pyridine. The resin was then suspended in 1.0 N HCl/dioxane and stirred at room temperature for 20 h to hydrolyze the oxazolidine auxiliary. The resin was collected and neutralized with 9:1 DMF/Et_3N and washed successively with DMF/CH_2Cl_2 and MeOH. After



(9)

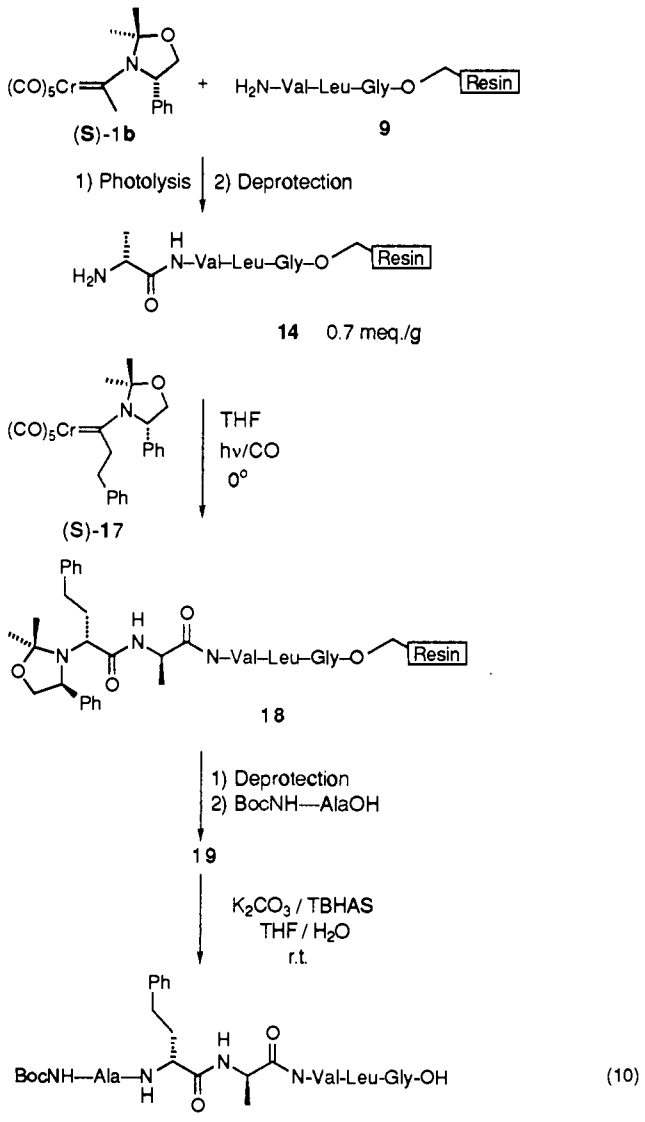
washing, the resin was suspended in 2:1 CH_2Cl_2/MeOH and treated with $Pb(OAc)_4$ to form the intermediate imine **13**. Subsequent hydrolysis with 1 N HCl/dioxane and neutralization gave the free amino tetrapeptide resin **14**, which contained 0.6 mequiv/g of free amine (determined by ninhydrin). Treatment of **14** with BocNH-alanine in the presence of DCC/HOBt in CH_2Cl_2 gave the protected pentapeptide resin **15**. The pentapeptide was released from the resin with tetra-*n*-butylammonium carbonate (TBAC) [prepared *in situ* from potassium carbonate and tetra-*n*-butylammonium hydrogen sulfate (**TBHAS**)][15] to give the N-protected pentapeptide segment **16** in 44% overall yield from **9**.

An attempt to introduce two chromium carbene complex-derived amino acid fragments pointed out the limitations of the methodology for iterative use. Photolysis of (*S*)-**1b** in the presence of **9**, followed by cleavage of the chiral auxiliary, gave the free amino polymer-supported tetrapeptide **14**. The tetrapeptide was then photolyzed in the presence of the homologated homophenylalanine aminocarbene complex (*S*)-**17**. The resulting pentapeptide **18**, which now contained (*R*)-alanine, and (*R*)-homophenylalanine introduced by photolysis, was deprotected and treated with BocNH-alanine to give the fully protected polymer-supported hexapeptide **19**. Releasing the hexapeptide from the resin as the free acid gave the N-protected hexapeptide **20** (eq 10). Unfortunately the crude peptide was contaminated with deletion peptides resulting from incomplete photolytic coupling at the tetra- and pentapeptide stages. After purification, which successfully removed the deletion peptides, the desired hexapeptide was obtained in a disappointing 18% overall yield, based on the starting polymer-supported tripeptide. Deletion peptides are not unique to the photolytic coupling procedure. Conventional solid-phase peptide synthesis is also plagued with this limitation as a result of incomplete conventional coupling steps. Therefore the methodology described above parallels conventional methods in this regard but on a more serious level.

(13) Jones, D. A. *Tetrahedron Lett.* **1977**, 2853. Schlatter, J. M.; Mazur, R. H.; Goodmonson, O. *Tetrahedron Lett.* **1977**, 2851.

(14) Pridgen, L. N.; Mokhallalate, M. K.; Wu, M. J. *J. Org. Chem.* **1992**, *57*, 1237. Gawley, R. E.; Rein, K.; Chenburkar, S. *J. Org. Chem.* **1989**, *54*, 3002.

(15) Anwer, M. K.; Spatola, A. F. *Tetrahedron Lett.* **1992**, *33*, 3121.



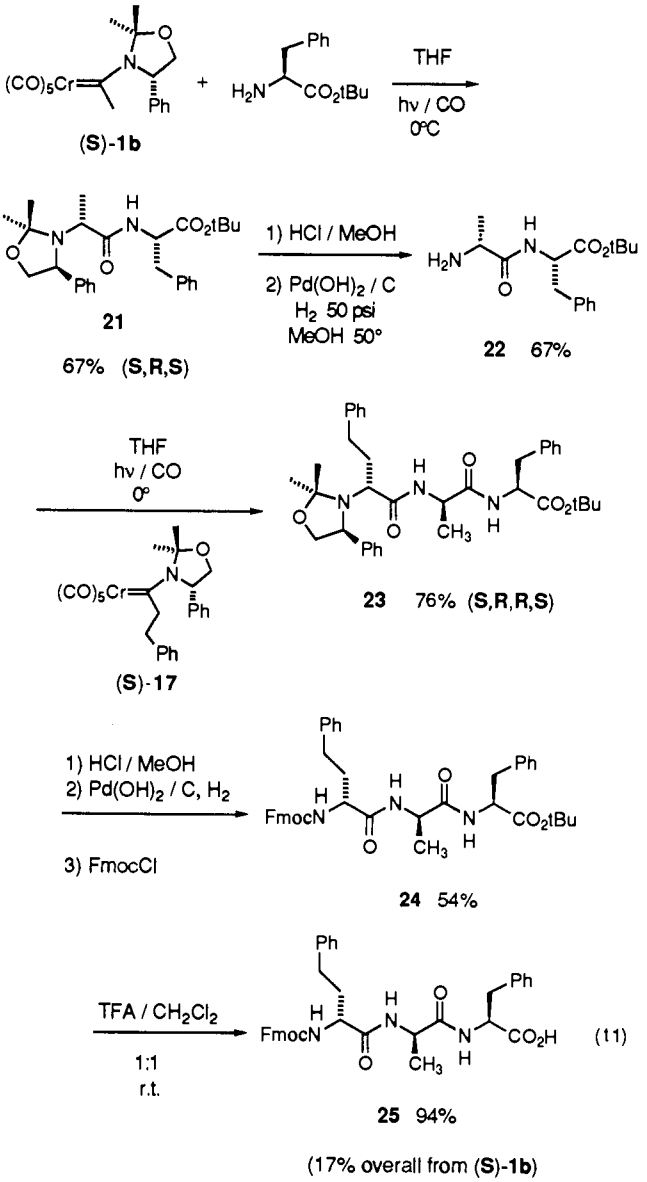
20 18% from 9

The most efficient way to utilize chromium carbene photochemical methods to incorporate unnatural amino acid fragments into peptides proved to be the segment condensation solid-phase method, in which short peptide fragments are synthesized in solution, purified, and then coupled to solid-phase supported peptides. This approach is illustrated in eq 11.

Photolysis of (*S*)-**1b** in the presence of *tert*-butyl phenylalaninate gave the fully protected HAla-(*R*)-Phe-OtBu dipeptide **21**. Hydrolysis/hydrogenolysis of the chiral auxiliary gave the free amino terminal dipeptide **22**, in which the alanine residue has the "unnatural" (*R*) configuration at the newly formed chiral center. Subsequent photolysis of (*S*)-**17** in the presence of **22** gave the fully protected tripeptide **23**, in which the "unnatural" homophenylalanine residue also has the (*R*) configuration at the newly formed stereogenic center.

Before the fully protected tripeptide **23** could be used in a segment condensation reaction with a polymer-supported peptide segment, the chiral auxiliary had to be removed and replaced with an N-terminal protecting group that was stable to conditions necessary for deprotecting the C-terminus. Hydrolysis/hydrogenolysis followed by treatment with 9-fluorenylmethoxy chloroformate (FmocCl)[16] gave the urethane-protected tripeptide **24**. Deprotection of the *tert*-butyl ester gave the N-protected peptide segment **25**, which could be used in segment condensation procedures.

This "unnatural" tripeptide fragment was next coupled to the polymer-supported tripeptide segment of **9** using conventional

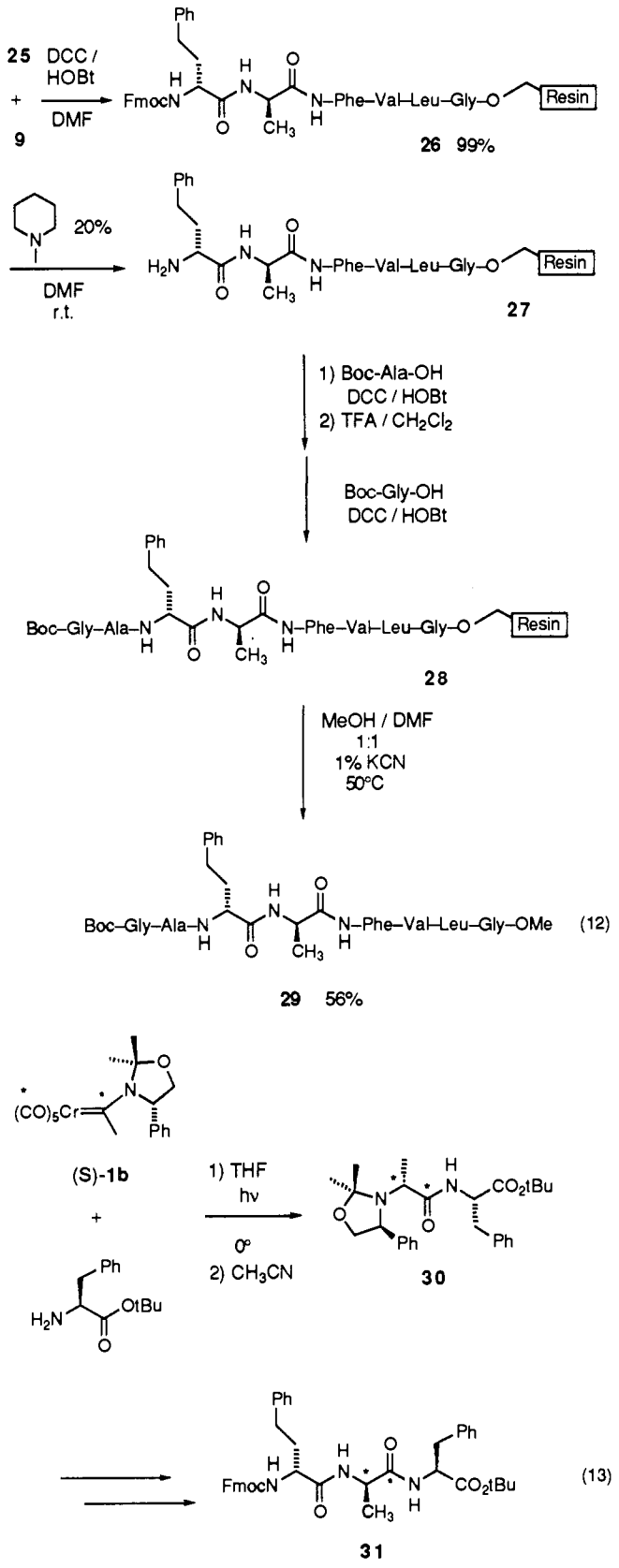


DCC/HOBt solid-phase coupling methodology (eq 12). *N,N*-Dimethylformamide was necessary as a solvent because of the low solubility of the Fmoc derivative **25**. Ninhydrin analysis of the resin after the coupling reaction indicated a 99% coupling efficiency between the peptide segment **25** and the polymer-supported tripeptide **9**. The Fmoc group was cleaved by suspending the resin in 20% *N*-methylpiperidine in DMF to give the free amino terminal hexapeptide **27** attached to the polymer support. Conventional solid-phase coupling methodology was then used to extend the peptide chain to the polymer-supported octapeptide **28**. The octapeptide was released from the resin as the methyl ester to give the fully protected octapeptide **29** in 56% overall yield based on the amount of starting tripeptide attached to the polymer-supported **9**.

Specific introduction of ^{13}C-labeled amino acid residues into peptides is useful in NMR investigation of mechanisms of action.[17] By starting with ^{13}C-enriched chromium hexacarbonyl, ^{13}C-enriched (*S*)-carbene complex **1b** was synthesized.[9] Photolysis in the presence of (*S*)-*tert*-butyl phenylalaninate gave the ^{13}C-enriched, fully protected dipeptide **30** (corresponding to **21**) (eq 13). The ^{13}C-enriched positions in the ^{13}C-spectrum appeared

(16) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

(17) London, R. E. NMR of ^{13}C-enriched Amino Acids and Peptides. In *NMR Spectroscopy: New Methods and Applications*; Levy, G. C., Ed.; ACSSymposium Series 191; American Chemical Society: Washington, DC, 1982; pp 119–155. Separovic, F.; Smith, R.; Yannoni, C. S.; Cornell, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 8324.



as intense doublets (δ 173.5 (^{13}CO), 54.95 (^{13}CHCH$_3$), J = 54.6 Hz) flanking a singlet, which corresponds to the ^{12}C–^{13}C isotopomer resulting from incomplete labeling. The labeled dipeptide was converted to the fully protected labeled tripeptide segment **31** using the methodology described above for the synthesis of **24** (eq 11). By this procedure, multiply labeled peptide segments for incorporation into larger peptides can readily be prepared.

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. Spectroscopic measurements utilized the following instrumentation: 300 MHz ^{1}H-NMR and 75 MHz ^{13}C-NMR were obtained on a Bruker ACE 300 NMR spectrometer. ^{1}H-NMR chemical shifts are reported in δ 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 the methyl pentet at 3.30 ppm. Chemical shifts for ^{1}H-NMR spectra reported in DMSO-d_6 are given in ppm relative to the methyl pentet at 2.49 ppm. Chemical shifts for ^{1}H-NMR spectra reported in acetone-d_6 are given in ppm relative to Me_4Si at 0.00 ppm. Chemical shifts for ^{13}C-NMR spectra reported in MeOD-d_4 and DMSO-d_6 are given in ppm relative to the methyl heptet at 49.00 and 39.50 ppm, respectively. High-resolution fast atom bombardment mass spectra were obtained from the Midwest Center for Mass Spectrometry, Department of Chemistry, Lincoln, NE 68588. Radial-layer chromatography was performed using glass plates with silica gel 60 PF_{254} (with gypsum, E. Merck Science), and column chromatography was performed with ICN 32–63 μm, 60 A silica gel using flash column techniques. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. In the case of photolysis at 0 °C the pressure tube was immersed in a Neslab Agitainer B Magnetic Stirring Insulated Container used in combination with a Lauda RM 20 circulating cooler with ethylene glycol at –8 °C as coolant. A water-cooled Pyrex immersion well was placed in the center of the cold bath containing the Conrad Hanovia lamp. *N*-tBoc-glycine, *N*-tBoc-alanine, *N*-tBoc-valine, and *N*-tBoc-leucine were prepared by literature methods.[18]

Preparation of Tripeptide 2. The tripeptide bound to a Bio-Rad SX-I polystyrene (see **9** below) resin (1.2 g, 0.9 mequiv/g, 1.0 mmol) was suspended in a 5- mL solution of 1 N, *N*-methylpiperidine/MeOH containing a catalytic amount of $NaOCH_3$ (2 mg, 0.03 mmol). The suspension was stirred at room temperature for 20 h. The resin was collected by filtration through a sintered glass funnel and washed with CH_2Cl_2 (2 × 10 mL) and MeOH (2 × 10 mL). A small sample of the resin was checked by IR (KBr pellet) for complete cleavage, determined by the loss of the ester CO absorption at 1750 cm^{-1}. The filtrate was concentrated *in vacuo* to give a yellow oil. Radial chromatography (5% MeOH/CH_2Cl_2) gave 265 mg (85%) of **2** as a clear oil.

^{1}H-NMR: δ 7.75 (d, J = 8.5 Hz, 1H, N*H*), 6.97 (bs, 1H, N*H*), 4.50 (m, 1H, C*H*CH$_2$(CH$_3$)$_2$), 4.00 (d, J = 5.5 Hz, 2H, C*H*$_2$NH), 3.74 (s, 3H, OC*H*$_3$), 3.31 (d, J = 4.0 Hz, 1H, C*H*NH$_2$), 2.31 (m, 1H, C*H*(CH$_3$)$_2$), 1.67 (m, 5H, C*H*(CH$_3$)$_2$, C*H*$_2$CH(CH$_3$)$_2$, N*H*$_2$), 0.99 (d, J = 6.9 Hz, 3H, (C*H*$_3$)$_2$CH), 0.95 (d, J = 6.2 Hz, 3H, (C*H*$_3$)$_2$CH), 0.91 (d, J = 6.2 Hz, 3H, (C*H*$_3$)$_2$CH), 0.83 (d, J = 6.9 Hz, 3H, (C*H*$_3$)$_2$CH). ^{13}C-NMR: δ 174.9 (CO), 172.5 (CO), 170.1 (CO), 59.98 (CH), 52.16 (OCH$_3$), 50.90 (CH), 40.99 (CH$_2$), 40.26 (CH$_2$), 30.67 (CH), 24.66 (CH), 22.90 (CH$_3$), 21.76 (CH$_3$), 19.53 (CH$_3$), 16.04 (CH$_3$). IR (film): ν 3302 (NH), 1755 (CO), 1651 (CO) cm^{-1}. Analysis was performed on the Boc NH-alanine tetrapeptide (see below).

Coupling of (*R*)-1a with 2 To Give 3a. Photolysis (24 h) of (*R*)-**1a** (97 mg, 0.25 mmol) in 4 mL of THF, at 0 °C, containing **2** (62 mg, 0.20 mmol) gave 80 mg (75%) of **3a** as a single diastereomer after radial chromatography (70:30 EtOAc/hexanes, R_f = 0.30). The crude reaction mixture consisted of a 91:9 ratio of diastereomers (82% de) determined by integration of the CH$_3$ doublets (δ 0.48 ppm ma*J*or, 1.19 ppm minor).

^{1}H-NMR: δ 7.56 (d, J = 7.8 Hz, 1H, N*H*), 7.46–7.22 (m, 5H, Ar*H*), 6.71 (t, J = 4.9 Hz, 1H, N*H*), 6.38 (d, J = 8.3 Hz, 1H, N*H*), 4.50 (m, 1H, C*H*CH$_2$(CH$_3$)$_2$), 4.32 (m, 2H, C*H*Ph, C*H*$_2$O), 4.02 (d, J = 5.4 Hz, 1H, C*H*$_2$NH), 4.01 (d, J = 5.4 Hz, 1H, CH$_2$NH), 3.87 (m, 2H, C*H*CH(CH$_3$)$_2$, C*H*$_2$O), 3.74 (s, 3H, OC*H*$_3$), 3.47 (quart, J = 7.3 Hz, 1H, C*H*CH$_3$), 1.74–1.47 (m, 4H, C*H*(CH$_3$)$_2$, C*H*$_2$C*H*(CH$_3$)$_2$), 1.44 (s, 3H, C*H*$_3$), 1.38 (d, J = 7.3 Hz, 3H, C*H*$_3$CH), 1.33 (s, 3H, C*H*$_3$), 0.90 (app t, J = 6.7 Hz, 6H, (C*H*$_3$)$_2$CH), 0.77 (d, J = 6.7 Hz 3H, (C*H*$_3$)$_2$CH), 0.53 (d, J = 6.7 Hz, 3H, (C*H*$_3$)$_2$CH). ^{13}C-NMR: δ 175.0 (CO), 172.0 (CO), 171.1 (CO), 170.0 (CO), 143.4, 129.1, 127.7, 127.6 (Ar), 97.03 ((CH$_3$)$_2$*C*), 72.42 (CH$_2$O), 60.80 (CH), 58.91 (CH), 56.27 (CH), 52.26 (OCH$_3$), 51.25 (CH), 41.10 (CH$_2$), 40.59 (CH$_2$), 31.00 (CH), 27.37 (CH$_3$), 24.63 (CH), 23.02 (CH$_3$), 21.64 (CH$_3$), 20.62 (CH$_3$), 18.96 (CH$_3$), 18.42 (CH$_3$), 15.84 (CH$_3$). IR (film): ν 3291 (NH), 1752 (CO), 1640 (CO) cm^{-1}. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 63.13; H, 8.27; N, 10.52. Found: C, 62.97; H, 8.02; N, 10.34.

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Coupling of (*S*)-1b with 2 To Give 3b. Photolysis (24 h) of (*S*)-**1b** (97 mg, 0.25 mmol) in 4 mL of THF, at 0 °C, containing **2** (62 mg, 0.20 mmol) gave 84 mg (79%) of a white solid (mp = 210–212 °C) as a single diastereomer after radial chromatography (70:30 EtOAc/hexane, R_f = 0.30). The crude reaction mixture consisted of a 94:6 ratio of two diastereomers (89%) determined by integration of the CH_3 doublets (0.84 ppm major, 1.18 ppm minor).

^{1}H-NMR: δ 7.57 (d, J = 5.4 Hz, 1H, NH), 7.49–7.24 (m, 5H, ArH), 6.98 (t, J = 5.4 Hz, 1H, NH), 5.21 (d, J = 8.6 Hz, 1H, NH), 4.37 (m, 3H, CH, CH_2O, CHPh), 4.04 (dd, J = 6.5, 17.8 Hz, 1H, CH_2NH), 3.94 (dd, J = 8.9, 12.2 Hz, 1H, CH_2O), 3.83 (dd, J = 6.5, 17.8 Hz, 1H, CH_2NH), 3.74 (s, 3H, OCH_3), 3.69 (dd, J = 5.5, 7.3 Hz, 1H, $CHCH(CH_3)_2$), 3.46 (quart, J = 7.3 Hz, 1H, $CHCH_3$), 1.88 (hex, J = 6.9 Hz, 1H, $CH(CH_3)_3$), 1.76 (m, 1H, $CH_2CH(CH_3)_2$), 1.50 (s, 3H, CH_3), 1.43 (d, J = 7.3 Hz, 3H, CH_3CH), 1.38 (m, 2H, $CH_2CH(CH_3)_2$), 1.34 (s, 3H, CH_3), 0.94 (m, 9H, $(CH_3)_2CH$), 0.84 (d, J = 6.4 Hz, 3H, $(CH_3)_2CH$). ^{13}C-NMR: δ 175.8 (CO), 172.1 (CO), 170.6 (CO), 170.0 (CO), 142.9, 129.2, 128.0, 127.9 (Ar), 97.09 ($C(CH_3)_2$), 72.52 (CH_2O), 60.75 (CH), 59.82 (CH), 55.04 (CH), 52.10 (OCH_3), 50.99 (CH), 41.08 (CH_2), 39.62 (CH_2), 29.66 (CH), 27.82 (CH_3), 24.50 (CH), 23.07 (CH_3), 21.30 (CH_3), 20.69 (CH_3), 19.40 (CH_3), 18.86 (CH_3), 13.99 (CH_3). IR (film): ν 3290 (NH), 1757 (CO), 1642 (CO) cm^{-1}. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 63.13; H, 8.27; N, 10.52. Found: C, 62.88; H, 8.17; N, 10.39.

Coupling of 2 with N-*t*Boc-(L)-alanine To Give Boc-NH-Ala-Val-Leu-Gly-OMe. To a solution of *N*-*t*Boc-L-alanine (211 mg, 1.1 mmol) in 1.5 mL of CH_2Cl_2, at room temperature was added a solution of dicyclohexylcarbodiimide (DCC) (109 mg, 0.53 mmol) in 1 mL of CH_2Cl_2. The mixture was stirred for 30 min followed by filtration through a sintered glass funnel to remove the dicyclohexylurea (DCU). The filtrate was concentrated *in vacuo* to give the symmetrical anhydride as a white solid. The anhydride was dissolved in 4 mL of CH_2Cl_2 containing **2** (160 mg, 0.53 mmol) and stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo* to give a white solid. The residue was dissolved in 30 mL of EtOAc and washed with 5% aqueous $NaHCO_3$ (3 × 10 mL), followed by brine (1 × 10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave the crude tetrapeptide (240 mg, 96%). An unoptimized recrystallization from CH_2Cl_2/hexanes gave 160 mg (64%) of the protected tetrapeptide as a white powder (mp 223 °C).

^{1}H-NMR: δ 7.22 (brs, 1H, NH), 6.86 (m, 2H, NH), 5.02 (d, J = 4.4 Hz, 1H, NH), 4.57 (m, 1H, $HNCHCH(CH_3)_2$), 4.19 (m, 2H, $CHCH_3$, $CHCH_2$), 4.09 (dd, J = 5.9, 18.0 Hz, 1H, $NHCH_2$), 3.93 (dd, J = 5.4, 18.0 Hz, 1H, $NHCH_2$), 3.72 (s, 3H, OCH_3), 2.31 (m, 1H, $CHCH(CH_3)_2$), 1.80 (m, 1H, $CH_2CH(CH_3)_2$), 1.64 (m, 2H, $CH_2CH(CH_3)_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.38 (d, J = 7.2 Hz, 3H, CH_3CH), 0.99 (d, J = 6.9 Hz, 3H, $CH(CH_3)_2$), 0.93 (m, 9H, $CH(CH_3)_2$). ^{13}C-NMR: (MeOD-d_4, reference 49.00 ppm) δ 176.1 (CO), 175.0 (CO), 173.3 (CO), 171.4 (CO), 157.8 (CO), 80.69 ($OC(CH_3)_3$), 60.13 (CH), 52.86 (OCH_3), 52.54 (CH), 51.76 (CH), 41.81 (CH_2), 32.03 (CH), 28.72 ($C(CH_3)_3$), 25.74 (CH), 23.40 (CH_3), 21.95 (CH_3), 19.71 (CH_3), 18.59 (CH_3), 17.92 (CH_3). IR (KBr): ν 3284 (NH), 1758 (CO), 1666 (CO), 1641 (CO) cm^{-1}. Anal. Calcd for $C_{22}H_{40}N_4O_7$: C, 55.93; H, 8.47; N, 11.86. Found: C, 55.90; H, 8.37; N, 11.75.

Preparation of the Protected Tetrapeptide Derived from (*R*)-1a. To a solution of the free N-terminal tetrapeptide (17 mg, 0.05 mmol) (see below) in 1.5 mL of 2:1 H_2O/THF, containing potassium carbonate (14 mg, 0.10 mmol), was added a solution of di-*tert*-butyl dicarbonate in 0.5 mL of THF. The mixture was stirred for 4 h at room temperature, diluted with H_2O, and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. The crude residue was compared to the material obtained by classical coupling procedures and found to be identical.

General Procedure for Reductive Removal of the Oxazolidine Chiral Auxiliary. The oxazolidine protected peptide was stirred in 5 mL of a 1:3 mixture of 0.2 N HCl/MeOH until the starting material was consumed (TLC, 70:30 EtOAc/hexanes, I_2 stain). The MeOH was removed *in vacuo*, and the aqueous residue was neutralized with 5 mL of 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to leave the crude amino alcohol. This was dissolved in MeOH (5 mL) and added to a pressure tube containing 30 mol % $Pd(OH)_2$/C. The reaction was pressurized to 50 psi with hydrogen and heated to 50 °C in an oil bath. After hydrogenation was complete (TLC, 10% acetone/EtOAc, $KMnO_4$ stain), the black slurry was stirred for 1 h under 50 psi of CO followed by removal of the $Pd(OH)_2$/C by filtration through Celite. The filter cake was washed with MeOH and EtOAc, and the filtrate was concentrated *in vacuo* to give the crude amine.

General Procedure for Oxidative Removal of the Oxazolidine Chiral Auxiliary. A solution of the peptide (0.4 mmol) in 10 mL of 1:4 0.2 N HCl/MeOH was allowed to stir at room temperature for 2 h. The MeOH was removed *in vacuo*, and 10 mL of 5% aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to leave the crude amino alcohol. The crude amino alcohol was dissolved in 6 mL of a 1:2 0.2 N HCl/CH_2Cl_2 solution followed by the addition of $NaIO_4$ (0.8 mmol). After being stirred at room temperature for 8 h, the mixture was diluted with 5% aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL), followed by EtOAc (2 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to leave a mixture of the amine and imine. This mixture was dissolved in 1:1 MeOH/0.2 N HCl and stirred at room temperature for 3 h. The MeOH was removed *in vacuo* and the aqueous residue neutralized with 10 mL of 5% aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, dried with $MgSO_4$, and concentrated *in vacuo* to leave the crude amine. To a solution of the crude amine in 8 mL of 1:2 THF/H_2O was added potassium carbonate (0.8 mmol) and a solution of di-*tert*-butyl dicarbonate in 1 mL of THF. The mixture was stirred at room temperature for 5 h and then diluted with H_2O (5 mL) and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (1:3 EtOAc/hexanes) gave the carbamate.

Quantitative Ninhydrin Analysis of Solid-Phase Peptide Synthesis. The ninhydrin assay does not work with N-terminal secondary amino acids and is unreliable with N-terminal tryptophanes.[19]

Reagents used were as follows: (A) 40 g of 100% phenol in 10 mL of absolute ethanol, (B) 0.2 mM potassium cyanide (KCN) in pyridine, (C) 500 mg ninhydrin in 10 mL of absolute ethanol, (D) 0.5 M tetraethylammonium bromide in CH_2Cl_2.

Procedure followed is outlined in steps 1-7: (1) Resin (2–5 mg) was added to a 10 × 70 mm test tube and treated with (a) 2 drops of reagent A, (b) 4 drops of reagent B, and (c) 3 drops of reagent C. (2) The test tube was heated in an oil bath at 100 °C for 5 min. (3) The sample was cooled to room temperature and diluted with 60% EtOH to a volume of 2 mL. (4) The sample was filtered through a Pasteur pipet plugged with glass wool and was washed twice (0.5 mL each) with reagent D into a glass vial. (5) The purple solution was diluted with 60% EtOH to a total volume of 6 mL. (6) 50 μL of the sample from step 5 was diluted with 60% EtOH to a volume of 3 mL. (7) The absorbance was measured at 570 nm versus a 60% EtOH blank, and the μmol of NH_2 was calculated according to the following equation:

$$\mu\text{mol of } NH_2/\text{gram} = \frac{A_{570}(60)(6)}{(1.5 \times 10^4) \times \text{wt in mg}} \times 10^6$$

The factor 60 represents the dilution factor from step 6. The value obtained from step 7 represents the number of milliequivalents of amine terminus per gram of resin. This value was used to determine the stoichiometry for subsequent carbene photoreactions.

General Procedure for the Preparation of Polymer-Supported C-Terminal Amino Acids (Merrifield's Resin). A DMF (10 mL per gram of polymer) suspension of chloromethylated polystyrene, containing the *N*-*tert*-butoxycarbonyl-protected cesium salt of the amino acid,[20] was stirred for 16 h at 50 °C. The polymer-supported Boc amino acid was collected by filtration (sintered glass funnel) and washed with DMF/H_2O (9:1 v/v), DMF, and CH_2Cl_2, respectively. The resin was suspended in 50% TFA/CH_2Cl_2 and stirred for 30 min at room temperature. The polymer-supported ammonium salt was suspended in 9:1 DMF/Et_3N (2 × 5 min) and washed with DMF, CH_2Cl_2, and MeOH. The resin was dried under reduced pressure at 70 °C, and quantitative ninhydrin analysis on a small sample (2–3 mg) gave the mequiv/g of amino groups attached to the polymer support.

Polymer-Supported Glycine 5a. The *N*-(*tert*-butoxycarbonyl)glycine cesium salt (0.5 g, 2.8 mmol) and chloromethylated polystyrene (2% DVB, 0.9 mequiv/g) (3.2 g, 2.8 mmol) were allowed to react according to the above general procedure to give 3.0 g (95%) of **5a** (0.8 mequiv/g). IR (KBr): ν 3392 (NH), 1735 (CO) cm^{-1}. Anal. Calcd: N, 1.24. Found: N, 1.26.

Polymer-Supported (*S*)-Alanine 5b. The *N*-(*tert*-butoxycarbonyl)-(*S*)-alanine cesium salt (1.7 g, 5.3 mmol) and chloromethylated

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polystyrene (1% DVB, 1.2 mequiv/g) (2.2 g, 2.7 mmol) were allowed to react according to the above general procedure to give 2.2 g (95%) of **5b** (1.0 mequiv/g). IR (KBr): ν 3368 (NH), 1736 (CO) cm^{-1}. Anal. Calcd: N, 1.55. Found: N, 1.43.

Polymer-Supported (*S*)-Valine 5c. The *N*-(*tert*-butoxycarbonyl)-(*S*)-valine cesium salt (1.2 g, 3.5 mmol) and chloromethylated polystyrene (2% DVB, 0.9 mequiv/g) (3.2 g, 2.9 mmol) were allowed to react according to the above general procedure to give 3.3 g (95%) of **5c** (0.8 mequiv/g). IR (KBr): ν 3381 (NH), 1733 (CO) cm^{-1}. Anal. Calcd: N, 1.19. Found: N, 1.02.

General Procedure for Photolysis of Polymer-Supported Amino Acids with Chromium Aminocarbene Complexes. The chromium aminocarbene complex (1.3 equiv) was dissolved in a minimal amount of dry THF (1–2 mL) and filtered through Celite directly into an oven-dried Pyrex (Ace Glass) pressure tube, containing a magnetic stir bar and the appropriate polymer-supported amino acid or peptide (300 mg). The reaction mixture was diluted to 5 mL with THF (necessary to maintain efficient stirring), and saturated with CO (3 × 50 psi). In the case of photolysis at 0 °C with stirring, the tube was immersed in a Neslab Agitainer B Magnetic Stirring Insulated Container used in combination with a Lauda RM 20 circulating cooler, to maintain a constant 0 °C in the insulated container. In the center of the insulated container was a water cooled Pyrex immersion well containing a Conrad Hanovia 7825 medium-pressure mercury arc lamp operating at 450 W. The reaction mixture was irradiated for 24 h, and then the resin was collected by filtration and washed with DMF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), and MeOH (2 × 5 mL). The polymer-supported amino acid or peptide was transferred back to a pressure tube, and the general procedure was repeated for an additional 24 h. Efficient stirring must be maintained during photolysis to maximize the contact between the polymer-supported amino acid or peptide and the soluble chromium aminocarbene complex.

Preparation of Dipeptide 6a. Photolysis of (*R*)-**1a** (108 mg, 0.27 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) glycine **5a** (0.7 mequiv/g) (300 mg, 0.21 mmol) according to the general procedure described above gave the polymer-supported dipeptide as a yellow solid (IR 1676 cm^{-1}). After photolysis, the resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 24 h at room temperature. The resin was collected by filtration and washed with CH_2Cl_2 (2 × 5 mL) and MeOH (2 × 5 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy by monitoring the disappearance of the ester CO absorption at 1740 cm^{-1}. When necessary the cleavage conditions were repeated to completely release the dipeptide from the polymer support. The combined filtrates were diluted with EtOAc (50 mL), filtered through a 0.5-in. pad of silica gel to remove the KCN, and concentrated *in vacuo* to give the crude dipeptide. Radial chromatography (1:1 EtOAc/Hexanes, R_f = 0.25) gave 32 mg (48%) of **6a** as a colorless oil. The crude reaction mixture consisted of a 90:10 ratio of two diastereomers (80% de), determined by integration of the geminal-dimethyl singlets (1.53 ppm major, and 1.49 ppm minor).

^{1}H-NMR: (major) δ 7.50 (bs, 1H, NH), 7.40–7.21 (m, 5H, ArH), 4.29 (m, 2H, C*H*Ph, CH_2O), 3.94 (m, 2H, CH_2O, CH_2NH), 3.74 (s, 3H, OCH_3), 3.47 (q, J = 7.2 Hz, 1H, $CHCH_3$), 3.31 (dd, J = 3.8, 18.5 Hz, 1H, CH_2NH), 1.53 (s, 3H, CH_3), 1.39 (d, J = 7.2 Hz, 1H, CH_3CH), 1.34 (s, 3H, CH_3). ^{13}C-NMR: δ 174.1 (CO), 170.1 (CO), 141.8, 128.6, 128.0, 127.7 (Ar), 96.91 ($C(CH_3)_2$), 72.12 (CH_2O), 60.30 (CH), 54.81 (CH), 52.17 (OCH_3), 40.88 (CH_2), 27.77 (CH_3), 21.50 (CH_3), 14.02 (CH_3). IR (film): ν 3384 (NH), 1751 (CO), 1674 (CO) cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_2O_4$: C, 63.77; N, 7.49; N, 8.75. Found: C, 63.84; H, 7.46; N, 8.59.

^{1}H-NMR: (minor) δ 7.41–7.20 (m, 5H, ArH), 6.70 (bs, 1H, NH), 4.45 (m, 1H, CHPh), 4.37 (app t, J = 8.1 Hz, 1H, CH_2O), 3.98 (dd, J = 6.0,18.4 Hz, 1H, CH_2NH), 3.74 (m, 4H, OCH_3, CH_2O), 3.60–3.48 (m, 2H, $CHCH_3$, CH_2NH), 1.49 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.29 (d, J = 7.1 Hz, 3H, CH_3CH). IR (film): ν 3319 (NH), 1753 (CO), 1663 (CO) cm^{-1}.

Preparation of Dipeptide 6b. Photolysis of (*R*)-**1a** (169 mg, 0.43 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) (*S*)-alanine **5b** (1.1 mequiv/g) (300 mg, 0.33 mmol) according to the general procedure described above gave the polymer-supported dipeptide as a yellow solid (IR 1662 cm^{-1}). After photolysis, the resin was suspended in 10 mL of MeOH/DMF (8:2 v/v), containing 100 mg of KCN, and stirred for 18 h at 40 °C. The procedure for isolating the crude dipeptide was as described for the isolation of crude dipeptide **6a**. Radial chromatography (33% EtOAc/hexanes, R_f = 0.12) gave 61 mg (55%) of **6b** as a colorless oil. The crude reaction mixture consisted of a 95:5 ratio of two diastereomers (90% de), determined by integration of the methyl doublets (1.19 ppm minor, 0.90 ppm major). The final product was contaminated with **6b**, in which the C-terminal alanine residue was epimerized (20%).

^{1}H-NMR: (major) δ 7.61 (d, J = 7.7 Hz, 1H, NH), 7.40 (m, 2H, ArH), 7.32–7.20 (m, 3H, ArH), 4.30 (m, 3H, CHPh, CH_2O, $CHCH_3$), 3.94 (dd, J = 2.3, 5.7 Hz, 1H, CH_2O), 3.72 (s, 3H, OCH_3), 3.43 (q, J = 7.3 Hz, 1H, $CHCH_3$), 1.52 (s, 3H, CH_3), 1.43 (d, J = 7.3 Hz, 3H, CH_3CH), 1.31 (s, 3H, CH_3), 0.90 (d, J = 7.2 Hz, 3H, CH_3CH). ^{13}C-NMR: δ 173.4 (CO), 173.2 (CO), 143.0, 128.8, 127.9, 127.6 (Ar), 97.07 ($C(CH_3)_2$), 72.37 (CH_2O), 59.90 (CH), 54.88 (CH), 52.17 (OCH_3), 47.46 (CH), 27.57 (CH_3), 20.96 (CH_3), 17.76 (CH_3), 14.18 (CH_3). IR (film): ν 3376 (NH), 1742 (CO), 1671 (CO) cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.69; H, 7.78; N, 8.38. Found: C, 64.81; H, 7.57; N, 8.38.

^{1}H-NMR: (minor) δ 7.41–7.21 (m, 5H, ArH), 6.81 (d, J = 6.3 Hz, 1H, NH), 4.51 (dd, J = 4.7, 7.5 Hz, 1H, CHPh), 4.40 (m, 2H, CH_2O, $CHCH_3$), 3.74 (s, 3H, OCH_3), 3.72 (m, 1H, CH_2O), 3.58 (q, J = 7.2 Hz, 1H, $CHCH_3$), 1.48 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.18 (d, J = 7.2 Hz, 3H, CH_3CH). IR (film): ν 3316 (NH), 1743 (CO), 1654 (CO) cm^{-1}.

Preparation of Dipeptide 6c. Photolysis of (*R*)-**1a** (123 mg, 0.31 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) (*S*)-valine **5c** (0.8 mequiv/g) (300 mg, 0.24 mmol) according to the general procedure described above gave the polymer-supported dipeptide as a yellow solid (IR 1676 cm^{-1}). After photolysis, the resin was suspended in 10 mL of MeOH/DMF (8:2 v/v), containing 100 mg of KCN, and stirred for 24 h at 70 °C. The procedure for isolating the crude dipeptide was as described for the isolation of crude dipeptide **6a**. Radial chromatography (33% EtOAc/hexanes, R_f = 0.13) gave 48 mg (55%) of **6c** as a colorless oil. The crude reaction mixture consisted of a 91:9 ratio of two diastereomers (82% de), determined by integration of the methines (3.86 ppm major, 4.68 ppm minor).

^{1}H-NMR: (major) δ 7.54 (d, J = 8.6 Hz, 1H, NH), 7.44 (m, 2H, ArH), 7.35- 7.21 (m, 3H, ArH), 4.37–4.23 (m, 3H, CH_2O, CHPh, C*H*NH), 3.86 (dd, J = 4.4, 7.5 Hz, 1H, CH_2O), 3.72 (s, 3H, OCH_3), 3.47 (q, J = 7.3 Hz, 1H, $CHCH_3$), 1.77 (m, 1H, $CH(CH_3)_2$), 1.50 (s, 3H, CH_3), 1.39 (d, J = 7.3 Hz, 3H, CH_3CH), 1.35 (s, 3H, CH_3), 0.70 (d, J = 6.8 Hz, 3H, $(CH_3)_2CH$), 0.59 (d, J = 6.8 Hz, 3H, $(CH_3)_2CH$). ^{13}C-NMR: δ 174.7 (CO), 172.2 (CO), 143.7, 129.0, 127.6, 127.5 (Ar), 97.22 ($C(CH_3)_2$), 72.41 (CH_2O), 60.95 (CH), 57.23 (CH), 56.44 (CH), 51.83 (OCH_3), 31.25 (CH), 27.49 (CH_3), 20.72 (CH_3), 18.70 (CH_3), 18.09 (CH_3), 16.05 (CH_3). IR (film): ν 3374 (NH), 1741 (CO), 1675 (CO) cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.32; H, 8.28; N, 7.73. Found: C, 66.25; H, 8.25; N, 7.66.

^{1}H-NMR: (minor) δ 7.43–7.22 (m, 5H, ArH), 7.13 (bs, 1H, NH), 4.68 (m, 1H, C*H*NH), 4.48 (m, 2H, CH_2O, CHPh), 3.76 (s, 3H, OCH_3), 3.71 (m, 2H, CH_2O, $CHCH_3$), 2.16 (m, 1H, $CH(CH_3)_2$), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.27 (m, 6H, CH_3CH), 0.90 (d, J = 6.8 Hz, 3H, $(CH_3)_2CH$), 0.88 (d, J = 6.8 Hz, 3H, $(CH_3)_2CH$). IR (film): ν 3320 (NH), 1743 (CO), 1656 (CO) cm^{-1}.

Preparation of Dipeptide 7a. Photolysis of (*S*)-**1b** (108 mg, 0.27 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) glycine **5a** (0.7 mequiv/g) (300 mg, 0.21 mmol) according to the general procedure described above gave 27 mg (40%) of **7a** as a colorless oil after radial chromatography. The crude reaction mixture consisted of an 87:13 ratio of two diastereomers (74% de), determined by integration of the geminal-dimethyl singlets (1.53 ppm major, 1.49 ppm minor). This was identical in all respects to the enantiomer **6a**.

Preparation of Dipeptide 7b. Photolysis of (*S*)-**1b** (169 mg, 0.43 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) (*S*)-alanine **5b** (1.1 mequiv/g) (300 mg, 0.33 mmol) according to the general procedure described above gave the polymer-supported dipeptide as a yellow solid (IR 1666 cm^{-1}). After photolysis, the resin was suspended in 10 mL of MeOH/DMF (8:2 v/v), containing 100 mg of KCN, and stirred for 18 h at 40 °C. The procedure for isolating the crude dipeptide was as described for the isolation of crude dipeptide **6a**. Radial chromatography (33% EtOAc/hexanes, R_f = 0.12) gave 64 mg (58%) of **7b** as a colorless oil. The crude reaction mixture consisted of a 92:8 ratio of two diastereomers (84% de), determined by integration of the methines (4.06 ppm major, 4.55 ppm minor). The final product was contaminated with **7b**, in which the C-terminal alanine residue was epimerized (19%).

^{1}H-NMR: (major) δ 7.62 (d, J = 5.3 Hz, 1H, NH), 7.40 (m, 2H, ArH), 7.33–7.18 (m, 3H, ArH), 4.34–4.23 (m, 2H, CHPh, CH_2O), 4.14 (pent, J = 7.0 Hz, 1H, CH_3CHNH), 3.86 (dd, J = 6.1, 7.8 Hz, 1H, CH_2O), 3.72 (s, 3H, OCH_3), 3.44 (q, J = 7.3 Hz, 1H, $CHCH_3$), 1.51 (s, 3H, CH_3), 1.35 (d, J = 7.2 Hz, 3H, CH_3CH), 1.35 (s, 3H, CH_3), 1.30 (d, J = 7.1 Hz, 3H, CH_3CH). ^{13}C-NMR: δ 173.9 (CO), 173.0 (CO),

141.4, 128.5, 128.1, 127.6 (Ar), 96.83 ($C(CH_3)_2$), 72.25 (CH_2O), 60.81 (CH), 55.34 (CH), 52.24 (OCH_3), 47.93 (CH), 27.83 (CH_3), 21.39 (CH_3), 18.19 (CH_3), 14.32 (CH_3). IR (film): ν 3383 (NH), 1740 (CO), 1674 (CO) cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.69; H, 7.78; N, 8.38. Found: C, 64.81; H, 7.63; N, 8.30.

^{1}H-NMR: (minor) δ 7.40 (m, 2H, ArH), 7.33–7.20 (m, 3H, ArH), 6.83 (d, J = 6.3 Hz, 1H, NH), 4.60 (dd, J = 5.6, 7.7 Hz, 1H, CHPh), 4.39–4.30 (m, 2H, CH_2O, $CHCH_3$), 3.73 (m, 4H, OCH_3, CH_2O), 3.53 (q, J = 7.2 Hz, 1H, $CHCH_3$), 1.47 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (d, J = 7.1 Hz, 3H, CH_3CH), 1.24 (d, J = 7.2 Hz, 3H, CH_3CH). IR (film): ν 3319 (NH), 1745 (CO), 1659 (CO) cm^{-1}.

Preparation of Dipeptide 7c. Photolysis of (*S*)-**1b** (123 mg, 0.31 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) (*S*)-valine **5c** (0.8 mequiv/g) (300 mg, 0.24 mmol) according to the general procedure described above gave the polymer-supported dipeptide as a yellow solid (IR 1673 cm^{-1}). After photolysis, the resin was suspended in 10 mL of MeOH/DMF (8:2 v/v), containing 100 mg of KCN, and stirred for 48 h at 65 °C. The procedure for isolating the crude dipeptide was as described for the isolation of crude dipeptide **6a**. Radial chromatography (30% EtOAc/hexanes, R_f = 0.24) gave 41 mg (47%) of **7c** as a colorless oil. The crude reaction mixture consisted of an 85:15 ratio of two diastereomers (70% de), determined by integration of the geminal-dimethyl singlets (1.53 ppm major, 1.47 ppm minor).

^{1}H-NMR: (major) δ 7.61 (d, J = 8.2 Hz, 1H, NH), 7.39 (m, 2H, ArH), 7.28–7.18 (m, 3H, ArH), 4.36–4.19 (m, 3H, CH_2O, CHPh, $CHNH$), 3.85 (dd, J = 6.8, 7.9 Hz, 1H, CH_2O), 3.68 (s, 3H, OCH_3), 3.45 (q, J = 7.3 Hz, 1H, $CHCH_3$), 2.09 (m, 1H, $CH(CH_3)_2$), 1.53 (s, 3H, CH_3), 1.36 (d, J = 7.1 Hz, 3H, CH_3CH), 1.35 (s, 3H, CH_3), 0.91 (d, J = 6.9 Hz, $(CH_3)_2CH$), 0.88 (d, J = 6.9 Hz, 3H, $(CH_3)_2CH$). ^{13}C-NMR: δ 174.1 (CO), 171.7 (CO), 140.7, 128.6, 128.2, 127.7 (Ar), 96.77 ($C(CH_3)_2$), 72.44 (CH_2O), 60.83 (CH), 57.16 (CH), 55.16 (CH), 51.81 (OCH_3), 31.26 (CH), 28.09 (CH_3), 21.20 (CH_3), 18.71 (CH_3), 18.18 (CH_3), 13.93 (CH_3). IR (film): ν 3385 (NH), 1739 (CO), 1677 (CO) cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.32; H, 8.28; N, 7.73. Found: C, 66.14; H, 8.18; N, 7.75.

^{1}H-NMR: (minor) δ 7.42–7.20 (m, 5H, ArH), 6.75 (d, J = 7.1 Hz, 1H, NH), 4.71 (dd, J = 5.6, 8.0 Hz, 1H, $CHNH$), 4.38 (m, 2H, CHPh, CH_2O), 3.74 (m, 4H, CH_2O, OCH_3), 3.62 (q, J = 7.2 Hz, 1H, $CHCH_3$), 2.19 (m, 1H, $CH(CH_3)_2$), 1.50 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.22 (d, J = 8.0 Hz, 3H, CH_3CH), 0.96 (d, J = 6.9 Hz, 3H, $(CH_3)_2CH$), 0.95 (d, J = 6.9 Hz, 3H, $(CH_3)_2CH$). IR (film): ν 3333 (NH), 1743 (CO), 1660 (CO) cm^{-1}.

Polymer-Supported Glycine PAM Resin 8a. A CH_2Cl_2 (40 mL) suspension of the hydroxy PAM resin[21] (1.0 mequiv/g) (3.0 g, 3.0 mmol), containing *N*-(*tert*-butoxycarbonyl)glycine (1.1 g, 6.0 mmol), DCC (1.33 g, 6.0 mmol), and DMAP (73 mg, 6.0 mmol), was stirred for 8 h at room temperature. The polymer-supported Boc amino acid was collected by filtration and washed with DMF (3 × 10 mL), CH_2Cl_2 (3 × 10 mL), and MeOH (2 × 10 mL). The resin was suspended in 1:1 Ac_2O/pyridine and stirred for 1 h at room temperature. The resin was collected, washed, and suspended in 1:1 TFA/CH_2Cl_2 and stirred for 30 min at room temperature. The polymer-supported ammonium salt was collected and washed with CH_2Cl_2 (2 × 30 mL) and then treated with DMF/Et_3N (9:1 v/v, 2 × 30 mL, 2 × 10 min). The resin was collected and washed with DMF (2 × 30 mL), CH_2Cl_2 (2 × 30 mL), and MeOH (2 × 30 mL), and dried under reduced pressure at 70 °C to give **8a** (0.4 mequiv/g). IR (KBr): ν 3389 (NH), 3313 (NH), 1741 (CO), 1665 (CO) cm^{-1}.

Polymer-Supported (*S*)-Alanine PAM Resin 8b. A CH_2Cl_2 (40 mL) suspension of the hydroxy PAM resin (1.0 mequiv/g) (1.5 g, 1.5 mmol), containing *N*-(*tert*-butoxycarbonyl)-(*S*)-alanine (570 mg, 3.0 mmol), DCC (620 mg, 3.0 mmol), and DMAP (370 mg, 3.0 mmol), was stirred for 16 h at room temperature. The *tert*-butoxycarbonyl was removed and the resin neutralized according to the procedure described above to give 1.6 g of **8b** (0.9 mequiv/g). IR (KBr): ν 3398 (NH), 3308 (NH), 1734 (CO), 1664 (CO) cm^{-1}. Anal. Calcd: N, 2.67. Found: N, 2.75.

Polymer-Supported (*S*)-Valine PAM Resin 8c. A CH_2Cl_2 (30 mL) suspension of the hydroxy PAM resin (1.0 mequiv/g) (3.4 g, 3.4 mmol), containing *N*-(*tert*-butoxycarbonyl)-(*S*)-valine (960 mg, 4.4 mmol) and carbonyldiimidazole (CDI) (660 mg, 4.1 mmol), was stirred for 8 h at room temperature. The *tert*-butoxycarbonyl was removed and the resin neutralized according to the procedure described above to give 3.1 g of **8c** (0.5 mequiv/g). IR (KBr): ν 3531–3235 (NH), 1737 (CO), 1670 (CO) cm^{-1}. Anal. Calcd: N, 2.60. Found: N, 2.01.

Synthesis of Dipeptides 6a–c and 7a–c Using PAM-Supported Amino Acids. Photolysis of (*R*)-**1a** (59 mg, 0.14 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) glycine **8a** (0.4 mequiv/g) (300 mg, 0.11 mmol) gave 20 mg (57%) of **6a** after the dipeptide was released from the resin and purified by radial chromatography.

Photoylsis of (*R*)-**1a** (128 mg, 0.32 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) (*S*)-alanine **8b** (0.9 mequiv/g) (300 mg, 0.27 mmol) gave the dipeptide as a yellow solid. After photolysis, the PAM resin was suspended in 10 mL of MeOH/DMF (8:2 v/v), containing 100 mg of KCN, and stirred for 24 h at room temperature. The crude dipeptide was isolated as described for the isolation of crude dipeptide **6a**. Radial chromatography gave 48 mg (53%) of **6b** as a colorless oil. The crude reaction mixture consisted of a 92:8 ratio of two diastereomers (85% de). In the case of cleavage from the PAM resin, C-terminal epimerization was ~5%.

Photoylsis of (*R*)-**1a** (68 mg, 0.17 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) (*S*)-valine **8c** (0.5 mequiv/g) (300 mg, 0.14 mmol) gave the dipeptide as a yellow solid. After photolysis, the PAM resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 24 h at 50 °C. The crude dipeptide was isolated as described for the isolation of crude dipeptide **6a**. Radial chromatography gave 29 mg (57%) of **6c** as a colorless oil. The crude reaction mixture consisted of an 85:15 ratio of two diastereomers (70% de), determined by integration of the methyl doublets (1.39 ppm major, 1.27 ppm minor).

Photolysis of (*S*)-**1b** (59 mg, 0.14 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) glycine **8a** (0.4 mequiv/g) (300 mg, 0.11 mmol) gave 21 mg (57%) of **7a** after the dipeptide was released from the resin and purified by radial chromatography. This material was identical to the enantiomeric material obtained from (*R*)-**1a** in all respects.

Photolysis of (*S*)-**1b** (128 mg, 0.32 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) (*S*)-alanine **8b** (0.9 mequiv/g) (300 mg, 0.27 mmol) gave the dipeptide as a yellow solid. After photolysis, the PAM resin was suspended in 10 mL of MeOH/DMF (1:1 v/v), containing 100 mg of KCN, and stirred for 24 h at room temperature. The crude dipeptide was isolated as described for the isolation of crude dipeptide **6a**. Radial chromatography gave 51 mg (57%) of **7b** as a colorless oil. The crude reaction mixture consisted of a 93:7 ratio of two diastereomers (86% de). In the case of cleavage from the PAM resin, C-terminal epimerization was ~5%.

Photolysis of (*S*)-**1b** (68 mg, 0.17 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (PAM resin) (*S*)-valine **8c** (0.5 mequiv/g) (300 mg, 0.14 mmol) gave the dipeptide as a yellow solid. After photolysis, the PAM resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 24 h at 70 °C. The crude dipeptide was isolated as described for the isolation of crude dipeptide **6a**. Radial chromatography gave 26 mg (51%) of **7c** as a colorless oil. The crude reaction mixture consisted of an 85:15 ratio of two diastereomers (70% de), determined by integration of the geminal-dimethyl singlets (1.53 ppm major, 1.47 ppm minor).

Polymer-Supported H_2N-Val-Leu-Gly-O-Merrifield Resin 9. A CH_2Cl_2 (100 mL) suspension of polymer-supported glycine **5a** (8.8 g, 6.3 mmol), containing *N*-(*tert*-butoxycarbonyl)-(*S*)-leucine (3.8 g, 16 mmol), DCC (3.5 g, 16 mmol), and HOBt (2.2 g, 16 mmol), was stirred for 2 h at room temperature. The resin was collected by filtration and washed with DMF (2 × 100 mL), CH_2Cl_2 (2 × 100 mL), and MeOH (2 × 100 mL). The resin was suspended in 1:1 TFA/CH_2Cl_2 (100 mL) and stirred for 30 min at room temperature. The polymer-supported H_3N-Leu-Gly-O-dipeptide was collected and washed with CH_2Cl_2 (2 × 100 mL), neutralized with 9:1 DMF/Et_3N (100 mL, 2 × 10 min), and washed with DMF, CH_2Cl_2, and MeOH. This process was repeated with *N*-(*tert*-butoxycarbonyl)-(*S*)-valine (2.6 g, 13 mmol) to give **9** (0.8 mequiv/g). IR (KBr): ν 3324 (NH), 1751(CO), 1655 (CO) cm^{-1}. Anal. Calcd: N, 3.81. Found: N, 3.39.

Polymer-Supported H_2N-Ala-Gly-Val-O-Merrifield Resin 11. A CH_2Cl_2 (50 mL) suspension of polymer-supported (*S*)-valine **5c** (4.4 g, 4.7 mmol), containing *N*-(*tert*-butoxycarbonyl)glycine (1.6 g, 9.4 mmol) and DCC (1.9 g, 9.4 mmol), was stirred for 2 h at room temperature. The resin was collected by filtration and washed with DMF (2 × 50 mL), CH_2Cl_2 (2 × 50 mL), and MeOH (2 × 50 mL). The resin was suspended in 1:1 TFA/CH_2Cl_2 (50 mL) and stirred for 30 min at room temperature. The polymer-supported H_3N-Gly-Val-O-dipeptide was collected and washed with CH_2Cl_2 (2 × 100 mL), neutralized with 9:1 DMF/Et_3N (50 mL, 2 × 10 min), and then washed with DMF, CH_2Cl_2, and MeOH. This process was repeated with *N*-(*tert*-butoxycarbonyl)-(*S*)-alanine (2.6 g, 13 mmol) to give **11** (0.9 mequiv/g). IR (KBr): ν 3335 (NH), 1736 (CO), 1657 (CO) cm^{-1}. Anal. Calcd: N, 3.97. Found: N, 4.01.

Preparation of Tetrapeptide 10a. Photolysis of (*R*)-**1a** (128 mg, 0.32 mmol), in 5 mL of THF, at 0 °C, containing the polymer-supported

(Merrifield's resin) tripeptide **9** (0.8 mequiv/g) (300 mg, 0.24 mmol) according to the above general procedure gave the polymer-supported tetrapeptide as a yellow solid. After photolysis the resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 48 h at room temperature. The resin was collected by filtration and washed with CH_2Cl_2 (2 × 5 mL) and MeOH (2 × 5 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy by monitoring the disappearance of the ester CO absorption at 1736 cm^{-1}. The filtrate was diluted with EtOAc (50 mL), filtered through a 0.5-in. pad of silica gel to remove the KCN, and concentrated *in vacuo* to give the crude peptide. Radial chromatography (70:30 EtOAc/hexanes, R_f = 0.18) gave 64 mg (50%) of **10a** as a colorless oil. The diastereomeric excess could not be determined from the crude reaction mixture. However, **10a** was isolated as a single diastereomer. This material was identical to the material isolated from photolysis in solution.

Preparation of 10b. Photolysis of (*S*)-**1b** (78 mg, 0.20 mmol), in 5 mL of THF, at 0 °C, containing the polymer-supported (Merrifield's resin) tripeptide **9** (0.6 mequiv/g) (300 mg, 0.18 mmol) according to the above general procedure gave the polymer-supported tetrapeptide as a yellow solid. After photolysis the resin was suspended in 1 M Et_3N in MeOH (5 mL), containing 4 mg of $NaOCH_3$, and stirred for 24 h at room temperature. The resin was collected by filtration and washed with CH_2Cl_2 (2 × 5 mL) and MeOH (2 × 5 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy by monitoring the disappearance of the ester CO absorption at 1730 cm^{-1}. The filtrate was diluted with EtOAc (50 mL), filtered through a 0.5-in. pad of silica gel to remove the oxidized chromium residues, and concentrated *in vacuo* to give the crude peptide. Radial chromatography (70:30 EtOAc/hexanes, R_f = 0.15) gave 49 mg (51%) of **10b** as a white solid (mp = 210–212 °C). The crude reaction mixture consisted of a 94:6 ratio of two diastereomers (88% de), determined by integration of the methyl doublets (0.84 ppm major, 1.19 ppm minor). This material was identical to the material isolated from photolysis in solution.

Preparation of Tetrapeptide 12a. Photolysis of (*R*)-**1a** (143 mg, 0.36 mmol), in 5 mL of THF, at 0 °C, containing the polymer-supported (Merrifield's resin) tripeptide **11** (0.9 mequiv/g) (300 mg, 0.28 mmol) according to the above general procedure gave the polymer-supported tetrapeptide as a yellow solid. After photolysis the resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 48 h at 50 °C. The resin was collected by filtration and washed with CH_2Cl_2 (2 × 10 mL) and MeOH (1 × 5 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy by monitoring the disappearance of the ester CO absorption at 1735 cm^{-1}. The filtrate was diluted with Et_2O (50 mL), filtered through a 0.5-in. pad of silica gel to remove the KCN, and concentrated *in vacuo* to give the crude peptide. Radial chromatography (5% MeOH/CH_2Cl_2, R_f = 0.25) gave 65 mg (47%) of **12a** as a clear oil. The diastereomeric excess could not be determined from the crude reaction mixture. However, **12a** was isolated as a single diastereomer.

^{1}H-NMR: δ 7.50 (d, *J* = 6.9 Hz, 1H, NH), 7.42–7.22 (m, 5H, ArH), 6.77 (m, 2H, NH), 4.47 (dd, *J* = 5.4,8.5 Hz, 1H, C*H*CH(CH_3)$_2$), 4.30 (m, 2H, CHPh, CH_2O), 3.95 (m, 3H, CH_2O, CH_2N, C*H*CH_3), 3.78 (dd, *J* = 5.2, 16.7 Hz, 1H, CH_2NH), 3.72 (s, 3H, OCH_3), 3.47 (q, *J* = 7.2 Hz, 1H, C*H*CH_3), 2.15 (m, 1H, C*H*(CH_3)$_2$), 1.50 (s, 3H, CH_3), 1.43 (d, *J* = 7.2 Hz, 3H, CH_3CH), 1.33 (s, 3H, CH_3), 0.97 (d, *J* = 7.0 Hz, 3H, CH_3CH), 0.92 (d, *J* = 7.0 Hz, 3H, (CH_3)$_2$CH), 0.89 (d, *J* =7.0 Hz, 3H, (CH_3)$_2$CH). ^{13}C-NMR: δ 174.4 (CO), 172.5 (CO), 172.2 (CO), 168.8 (CO), 142.7, 128.9, 128.0, 127.8 (Ar), 97.05 (*C*(CH_3)$_2$), 72.30 (CH_2O), 59.78 (CH), 57.32 (CH), 54.68 (CH), 52.05 (OCH_3), 48.80 (CH), 43.16 (CH_2), 30.94 (CH), 27.75 (CH_3), 21.13 (CH_3), 18.91 (CH_3), 17.92 (CH_3), 16.97 (CH_3), 13.70 (CH_3). IR (film): ν 3309 (NH), 1744 (CO), 1651 (CO) cm^{-1}. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 61.22; H, 7.76; N, 11.43. Found: C, 61.06; H, 7.78; N, 11.20.

Preparation of Tetrapeptide 12b. Photolysis of (*S*)-**1b** (143 mg, 0.36 mmol) in 5 mL of THF, at 0 °C, containing the polymer-supported (Merrifield's resin) tripeptide **11** (0.9 mequiv/g) (300 mg, 0.28 mmol) according to the above general procedure gave the polymer-supported tetrapeptide as a yellow solid. After photolysis the resin was suspended in 10 mL of MeOH, containing 100 mg of KCN, and stirred for 48 h at 50 °C. The resin was collected by filtration and washed with CH_2Cl_2 (2 × 10 mL) and MeOH (1 × 5 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy by monitoring the disappearance of the ester CO absorption at 1735 cm^{-1}. The filtrate was diluted with Et_2O (50 mL), filtered through a 0.5-in. pad of silica gel to remove the KCN, and concentrated *in vacuo* to give the crude peptide. Radial chromatography (3% MeOH/CH_2Cl_2, R_f = 0.22) gave 34 mg (25%) of **12b** as a clear oil. A second fraction was isolated (12 mg) that was a mixture of the major diastereomer **12b** and a minor diastereomer in an 85:15 ratio, determined by integration of the glycine methylene (3.55 ppm major, 3.23 ppm minor).

^{1}H-NMR: (major) δ 7.49 (d, *J* = 6.0 Hz, 1H, NH), 7.44–7.23 (m, 5H, ArH), 6.70 (d, *J* = 8.7 Hz, 1H, NH), 5.64 (t, *J* = 5.7 Hz, 1H, NH), 4.46 (dd, *J* = 5.4, 8.9 Hz, C*H*CH(CH_3)$_2$), 4.32 (m, 2H, CH_2O, CHPh), 4.05 (pent, *J* = 7.1 Hz, 1H, C*H*CH_3), 3.95 (dd, *J* = 3.0, 6.3 Hz, 1H, CH_2O), 3.82 (dd, *J* = 6.5,16.6 Hz, 1H, CH_2NH), 3.73 (s, 3H, OCH_3), 3.56 (dd, *J* = 6.5, 16.6 Hz, 1H, CH_2NH), 3.45 (q, *J* = 7.4 Hz, 1H, C*H*CH_3), 2.15 (hext, *J* = 5.6 Hz, 1H, C*H*(CH_3)$_2$), 1.49 (s, 3H, CH_3), 1.45 (d, *J* = 7.3 Hz, 3H, CH_3CH), 1.34 (s, 3H, CH_3), 1.28 (d, *J* =7.2 Hz, 3H, CH_3CH), 0.92 (d, *J* = 6.8 Hz, (CH_3)$_2$CH), 0.89 (d, *J* = 6.8 Hz, 3H, (CH_3)$_2$CH). ^{13}C-NMR: δ 174.6 (CO), 172.2 (CO), 172.0 (CO), 168.7 (CO), 142.5, 129.1, 128.1, 128.0 (Ar), 96.98 (*C*(CH_3)$_2$), 72.36 (CH_2O), 59.70 (CH), 57.26 (CH), 54.67 (CH), 52.04 (OCH_3), 49.69 (CH), 43.27 (CH_2), 30.86 (CH), 27.59 (CH_3), 20.87 (CH_3), 18.91 (CH_3), 17.91 (CH_3), 17.34 (CH_3), 13.86 (CH_3). IR (film): ν 3322 (NH), 1738 (CO), 1652 (CO) cm^{-1}. Anal. Calcd for $C_{28}H_{44}N_4O_6$: C, 61.22; H, 7.76; N, 11.43. Found: C, 61.46; H, 7.90; N, 11.10.

General Procedure for the Oxidative Cleavage of the Oxazolidine Chiral Auxiliary from the Polymer-Supported Peptide. After photoylsis, the polymer-supported tetrapeptide **10b** was suspended in 1:1 Ac_2O/pyridine (5 mL) and stirred for 3 h at room temperature. The resin was collected by filtration, washed with DMF (2 × 10 mL), CH_2Cl_2 (2 × 10 mL), and MeOH (2 × 10 mL), and then transferred to a round bottom flask. The resin was suspended in 4:1 dioxane/1 N HCl (6 mL) and stirred for 12 h at room temperature to hydrolyze the oxazolidine ring. The resin was then collected by filtration, washed with dioxane (2 × 10 mL), and neutralized with 9:1 DMF/Et_3N (2 × 5 mL, 5 min each). The resin was then washed with DMF (2 × 10 mL), CH_2Cl_2 (2 × 10 mL), MeOH (2 × 10 mL) and suspended in 2:1 CH_2Cl_2/MeOH (6 mL), containing $Pb(OAc)_4$ (1.1 equiv), followed by stirring for 5 h at room temperature. After the resin was collected and washed, the resulting polymer-supported imine **13** was suspended in 4:1 dioxane/1 N HCl and stirred for 5 h at room temperature. After hydrolysis, the resin was washed with dioxane (2 × 10 mL), neutralized with 9:1 DMF/Et_3N (2 × 5 mL, 5 min each), and washed with DMF, CH_2Cl_2, and MeOH. Quantitative ninhydrin analysis on a small sample (2–5 mg) of the resin gave the amount of amino groups on the polymer support after the auxiliary was removed.

Preparation of Pentapeptide 16. Photolysis of (*S*)-**1b** (128 mg, 0.32 mmol) in 5 mL of THF, at 0 °C, containing polymer-supported (Merrifield's resin) tripeptide **9** (0.9 mequiv/g) (300 mg, 0.28 mmol), according to the general procedure described above, gave the resin-bound tetrapeptide **10b** as a yellow solid. Ninhydrin analysis indicated 0.14 mequiv/g of unreacted amino groups. The oxazolidine chiral auxiliary was removed according to the general procedure described above to give the free N-terminal tetrapeptide **14** (0.6 mequiv/g). The tetrapeptide **14** was suspended in 3 mL of CH_2Cl_2, containing Boc-NH-alanine (102 mg, 0.54 mmol), DCC (111 mg, 0.54 mmol), and HOBt (73 mg, 0.54 mmol) and then stirred for 3 h at room temperature. The resin was collected by filtration and washed with DMF (2 × 10 mL), CH_2Cl_2 (2 × 10 mL), and MeOH (2 × 10 mL) to give the polymer-supported N-Boc-protected pentapeptide **15**. The resin was suspended in 3:1 THF/saturated aqueous K_2CO_3 (20 mL), containing tetra-*n*-butylammonium hydrogen sulfate (TBHAS),[15] and stirred for 36 h at room temperature. The reaction mixture was diluted with H_2O (10 mL), and the resin was collected by filtration and then washed with H_2O (1 × 5 mL), and EtOAc (2 × 10 mL). The extent of cleavage from the polymer support was checked by IR spectroscopy and was complete. The filtrate was concentrated *in vacuo* to remove the orgainc layer, and the resulting aqueous phase was acidified to pH = 1 with solid potassium hydrogen sulfate ($KHSO_4$). The aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with 1 N HCl (1 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 86 mg (60%) of crude N-terminal-protected pentapeptide **16**. The crude peptide was dissolved in 19:1 $CHCl_3$/AcOH and applied to the top of a silica gel column (1 × 15 cm). Flash chromatography (90:8:2 $CHCl_3$/MeOH/AcOH, R_f = 0.12) gave 63 mg (44%) of **16** as a white solid (mp = 184–186 °C).

^{1}H-NMR (MeOD-d_4): δ 4.44 (m, 1H, C*H*CH(CH_3)$_2$), 4.34 (q, J = 7.4 Hz, 1H, C*H*CH_3), 4.13 (q, *J* = 6.4 Hz, 1H, C*H*CH_3), 4.05 (m, 2H, C*H*CH_2CH(CH_3)$_2$, CH_2NH), 3.93 (d, *J* = 17.7 Hz, 1H, CH_2CO_2H), 3.84 (d, *J* = 17.7 Hz, 1H, CH_2NH), 2.19 (m, 1H, C*H*(CH_3)$_2$), 1.66 (m, 3H, CH_2C*H*(CH_3)$_2$, CH_2CH(CH_3)$_2$), 1.44 (s, 9H, (CH_3)$_3$), 1.35 (d, *J* = 7.1 Hz, 3H, CH_3CH), 1.29 (d, *J* = 7.1 Hz, 3H, CH_3CH), 0.93 (m, 12H, (CH_3)$_2$CH). ^{13}C-NMR (DMSO-d_6): δ 172.3 (CO), 172.2 (CO), 172.1 (CO), 171.0 (CO), 170.5 (CO), 155.0 (CO), 78.12 (*C*(CH_3)$_3$),

57.43 (CH), 50.74 (CH), 49.84 (CH), 48.27 (CH), 40.83 (CH_2), 40.65 (CH_2), 30.36 (CH), 28.13 ((CH_3)$_3$), 24.05 (CH), 22.99 (CH_3), 21.53 (CH_3), 19.17 (CH_3), 18.72 (CH_3), 18.10 (CH_3), 17.75 (CH_3). IR (KBr): ν 3698–2374 (OH, NH), 1715 (CO), 1648 (CO) cm^{-1}. High-resolution FAB mass spec. Calcd for $C_{24}H_{44}N_5O_8$: [M + H] = 530.3190. Found: [M + H] = 530.3208.

Preparation of Hexapeptide 20. Photoylsis of (*S*)-**17** (prepared by literature methods)[6,10] (110 mg, 0.23 mmol) in 5 mL of THF, at 0°C, containing the polymer-supported tetrapeptide **14** (see above) (0.7 mequiv/g), according to the general procedure described above, gave the resin bound pentapeptide **18** as a yellow solid. Ninhydrin analysis indicated 0.14 mequiv/g of unreacted amino groups. The oxazolidine auxiliary was removed according to the general procedure described above to give the free N-terminal pentapeptide (0.4 mequiv/g). The free amino pentapeptide was coupled with Boc-alanine (DCC/HOBt), and the resulting hexapeptide was released from the polymer support as the free C-terminal N-protected hexapeptide **20** (see above). The crude peptide was dissolved in 19:1 $CHCl_3$/AcOH and applied to the top of silica gel column (1 × 15 cm). Flash chromatography (90:8:2 $CHCl_3$/MeOH/AcOH, R_f = 0.14), followed by recrystallization from MeOH gave 34 mg (18% calculated from the starting NH_2 content of **9**) of **20**.

^{1}H-NMR (DMSO-d_6): δ 8.06 (d, J = 7.9 Hz,1H, NH), 7.95 (m, 3H, NH), 7.85 (d, J = 9.0 Hz, 1H, NH), 7.24 (m, 2H, ArH), 7.15 (m, 3H, ArH), 7.00 (d, J = 7.2 Hz, 1H, NH), 4.34 (m, 3H, CH), 4.16 (app t, J = 6.7 Hz, 1H, CH), 3.96 (app t, J = 7.4 Hz, 1H, CH), 3.72 (dd, J = 5.9, 17.6 Hz, 1H, CH_2NH), 3.62 (dd, J = 5.4, 17.6 Hz, 1H, CH_2NH), 2.49 (m, 2H, CH_2Ph), 1.97 (m, 2H, CH_2CH_2Ph, CH(CH_3)$_2$), 1.77 (m, 1H, CH_2CH_2Ph), 1.55 (m, 1H, CH_2CH(CH_3)$_2$), 1.43 (m, 2H, CH_2CH(CH_3)$_2$), 1.36 (s, 9H, (CH_3)$_3$), 1.20 (m, 6H, CH_3CH), 0.78 (m, 12H, (CH_3)$_2$CH). ^{13}C-NMR (DMSO-d_6): δ 172.8 (CO), 172.2 (CO), 172.1 (CO), 170.9 (CO), 170.5 (CO), 155.1 (CO), 141.4, 128.2, 125.7 (Ar), 78.09 (C(CH_3)$_3$), 57.32 (CH), 51.67 (CH), 50.76 (CH), 50.07 (CH), 48.36 (CH), 40.68 (CH_2), 34.01 (CH_2), 31.18 (CH_2), 30.44 (CH), 28.13 ((CH_3)$_3$), 24.01 (CH), 22.91 (CH_3), 21.41 (CH_3), 19.15 (CH_3), 18.41 (CH_3), 18.10 (CH_3), 17.68 (CH_3). IR (KBr): ν 3623–2368 (OH, NH), 1714 (CO), 1684 (CO) cm^{-1}. High-Resolution mass spec. Calcd for $C_{34}H_{55}N_6O_9$: [M + H] = 691.4031. Found: [M + H] = 691.4035.

Preparation of Dipeptide 22. The general hydrolysis/hydrogenolysis procedure was applied to **21** (390 mg, 0.86 mmol).[10] The crude amine was dissolved in 10 mL of MeOH, containing 2 equiv of HCl (prepared by the addition of 2 equiv of AcCl to dry MeOH), and stirred for 30 min at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in H_2O (15 mL) and washed with Et_2O (2 × 15 mL). The aqueous layer was neutralized with 10% $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give 168 mg (67%) of **22** as a clear oil.

^{1}H-NMR: δ 7.55 (d, J = 8.3 Hz, 1H, NH), 7.31–7.16 (m, 5H, ArH), 4.72 (m, 1H, CHCH$_2$), 3.47 (q, J = 7.0 Hz, 1H, CHCH$_3$), 3.11 (d, J = 6.2 Hz, 1H, CHCH_2Ph), 3.10 (d, J = 6.2 Hz, 1H, CHCH_2Ph), 1.82 (bs, 2H, NH_2), 1.41 (s, 9H, (CH_3)$_3$), 1.31 (d, J = 6.9 Hz, 3H, CH_3CH). ^{13}C-NMR: δ 175.1 (CO), 170.6 (CO), 136.4, 129.4,128.2, 126.8 (Ar), 82.01 (C(CH_3)$_3$), 53.14 (CH), 50.58 (CH), 38.03 (CH_2), 27.88 ((CH_3)$_3$), 21.44 (CH_3). IR (film): ν 3316 (NH), 1731 (CO), 1666 (CO) cm^{-1}.

Preparation of Tripeptide 23. Photolysis (36 h) of (*S*)-**17** (770 mg, 1.6 mmol) in 17 mL of THF, at 0 °C, containing **22** (421 mg, 1.4 mmol) gave 650 mg (76%) of **23** as a white foam after chromatography (25% EtOAc/hexanes, R_f = 0.13). The crude reaction mixture consisted of a 95:5 ratio of two diastereomers (90% de), determined by integration of the methine dd (4.83 ppm minor, 4.69 ppm major).

^{1}H-NMR: δ 7.38–7.12 (m, 16H, ArH, NH), 6.40 (d, J = 7.6 Hz, 1H, NH), 4.69 (dd, J = 6.0,13.7 Hz, 1H, CHCH$_2$Ph), 4.25 (m, 2H, CH_2O, CHPh), 4.07 (pent, J = 7.2 Hz, 1H, CHCH$_3$), 3.90 (dd, J = 8.3, 12.2 Hz, 1H, CH_2O), 3.23 (dd, J = 4.5, 8.3 Hz, 1H, CHCH$_2$CH$_2$Ph), 3.06 (d, J = 5.9 Hz, 2H, CHCH_2Ph), 2.97 (m, 1H, CH_2CH_2Ph), 2.73 (m, 1H, CH_2CH_2Ph), 2.31 (m, 1H, CH_2CH$_2$Ph), 1.93 (m, 1H, CH_2CH$_2$Ph), 1.40 (s, 9H, (CH_3)$_3$), 1.37 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 0.78 (d, J = 7.1 Hz, 3H, CH_3CH). ^{13}C-NMR: δ 173.8 (CO), 171.4 (CO), 170.2 (CO), 143.2, 141.6, 136.1, 129.6, 129.0, 128.6, 128.5, 128.3, 127.7, 126.9, 126.1 (Ar), 96.88 (C(CH_3)$_2$), 82.26 (C(CH_3)$_3$), 72.16 (CH_2O), 60.25 (CH), 58.56 (CH), 53.33 (CH), 48.22 (CH), 37.95 (CH_2), 34.81 (CH_2), 31.96 (CH_2), 28.00 (CH_3), 27.94 ((CH_3)$_3$), 21.68 (CH_3), 17.15 (CH_3). IR (film): ν 3365 (NH), 3309 (NH), 1730 (CO), 1651 (CO) cm^{-1}. Anal. Calcd for $C_{37}H_{48}N_3O_5$: C, 72.33; H, 7.81; N, 6.84. Found: C, 72.11; H, 7.84; N, 6.89.

Preparation of Tripeptide 24. The general hydrolysis/hydrogenolysis procedure was applied to **23** (80 mg, 0.14 mmol). The crude amine was dissolved in 2 mL of 2:1 aqueous 10% $NaHCO_3$/THF and cooled to 0 °C. The reaction mixture was treated with 0.5 mL of THF, containing 9-fluorenylmethyl chloroformate (72 mg, 0.28 mmol), and the reaction was warmed to room temperature. After being stirred for 8 h at room temperature, the reaction mixture was diluted with H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude protected tripeptide. Radial chromatography (33% EtOAc/hexanes, R_f = 0.25) gave 51 mg (54%) of **24** as a white solid (mp = 179–181 °C).

^{1}H-NMR: δ 7.76 (m, 2H, ArH), 7.59 (m, 2H, ArH), 7.42–7.11 (m, 14H, ArH), 6.52 (d, J = 7.5 Hz, 1H, NH), 6.48 (d, J = 7.0 Hz, 1H, NH), 5.41 (d, J = 8.0 Hz, 1H, NH), 4.71 (q, J = 6.1 Hz, 1H, CH), 4.43 (m, 3H, CH_2O, CH), 4.20 (m, 2H, CH), 3.12 (dd, J = 6.3, 13.9 Hz, 1H, CH_2Ph), 3.03 (dd, J = 6.1, 13.8 Hz, 1H, CH_2Ph), 2.65 (m, 2H, CH_2CH_2Ph), 2.11 (m, 1H, CH_2CH_2Ph), 1.95 (m, 1H, CH_2CH_2Ph), 1.38 (s, 9H, (CH_3)$_3$), 1.29 (d, J = 7.0 Hz, 3H, CH_3CH). ^{13}C-NMR: δ 171.3 (CO), 170.4 (CO), 156.2 (CO), 143.9, 143.7, 141.2, 140.7, 136.0, 129.4, 128.4, 128.3, 127.7, 127.0, 126.9, 126.0, 125.0, 119.9 (Ar), 82.37 (C(CH_3)$_3$), 67.03 (OCH_2), 54.50 (CH), 53.55 (CH), 48.78 (CH), 47.08 (CH), 38.17 (CH_2), 34.73 (CH_2), 31.63 (CH_2), 27.83 ((CH_3)$_3$), 18.76 (CH_3). IR (film): ν 3291 (NH), 1731 (CO), 1694 (CO), 1640(CO) cm^{-1}. Anal. Calcd for $C_{41}H_{45}N_3O_6$: C, 72.91; H, 6.66; N, 6.22. Found: C, 72.74; H, 6.86; N, 6.20.

Preparation of Tripeptide 25. The fully protected tripeptide **24** (195 mg, 0.20 mmol) was dissolved in 4 mL of 1:1 TFA/CH_2Cl_2 and stirred for 3 h at room temperature. The solvent was removed under reduced pressure, and the residue was treated with toluene and evaporated to dryness (repeated three times) to give 168 mg (94%) of **25** as a sparingly soluble white solid.

^{1}H-NMR (acetone-d_6): δ 7.87 (m, 2H, ArH), 7.73 (m, 2H, ArH), 7.54–7.17 (m, 16H, ArH, NH), 6.85 (d, J = 7.4 Hz, 1H, NH), 4.72 (m, 1H, CH), 4.47–4.17 (m, 5H, CH_2, CH), 3.23 (dd, J = 5.1, 13.9 Hz, 1H, CHCH_2Ph), 3.02 (dd, J = 5.1, 13.9 Hz, 1H, CHCH_2Ph), 2.72 (m, 2H, CH_2CH_2Ph), 2.13–1.94 (m, 2H, CH_2CH_2Ph), 1.20 (d, J = 7.1 Hz, 3H, CH_3CH).

Preparation of Octapeptide 29. The *N*-Fmoc-tripeptide **25** (284 mg, 0.46 mmol) was dissloved in 6 mL of DMF, containing HOBt (62 mg, 0.46 mmol), followed by the addition of polymer-supported tripeptide **9** (0.9 mequiv/g) (390 mg, 0.35 mmol). The suspension was stirred for 15 min at room temperature to make sure **25** was in solution. The reaction mixture was treated with 1 mL of DMF, containing DCC (95 mg, 0.46 mmol), and stirred for 14 h at room temperature. The resin was collected by filtration and washed with DMF (2 × 10 mL), CH_2Cl_2 (2 × 10 mL), and MeOH (2 × 10 mL). Ninhydrin analysis indicated 99% complete coupling. The protected hexapeptide was suspended in 10 mL of DMF and stirred for 15 min, and the DMF was decanted away from the resin. The resin was suspended in 20% v/v piperidine/DMF and stirred for 30 min at room temperature, and the solution was decanted away from the resin. The deprotection procedure was repeated twice with fresh reagents. The resin was collected by filtration and washed with DMF, CH_2Cl_2, and MeOH to give the N-terminal amino hexapeptide **27**. Ninhydrin analysis indicated 0.6 mequiv/g of hexapeptide attached to the polymer support. Hexapeptide **27** was elongated by classical DCC/HOBt coupling procedures with Boc-alanine, followed by Boc-glycine, to give the N-Boc-protected octapeptide **28** attached to the polymer support. The octapeptide resin was suspended in 10 mL of MeOH/DMF (1:1), containing 100 mg of KCN, and stirred for 24 h at 50 °C. The resin was collected by filtration and then washed with DMF, CH_2Cl_2, and MeOH. IR spectroscopy indicated cleavage was complete. The filtrate was diluted with 10% MeOH/CH_2Cl_2 (10 mL), filtered through a 0.5-in. pad of silica gel to remove the KCN, and concentrated *in vacuo* to a volume of 5 mL. The concentrated filtrate was treated with 100 mL of Et_2O and stored at –20 °C for 12 h. The resulting precipitate was collected by filtration and dried under vacuum to give 229 mg (72%) of the crude octapeptide **29** as a cream-colored solid. Recrystallization of the crude peptide from MeOH gave 180 mg (56%) of **29** as a white powder.

^{1}H-NMR (DMSO-d_6): δ 8.31 (t, J = 5.6, 1H, NH), 8.21 (d, J = 7.7 Hz, 1H, NH), 7.94 (m, 5H, NH), 7.27–7.13 (m, 10H, ArH), 6.87 (t, J = 5.7, 1H, NH), 4.57 (m, 1H, CH), 4.39–4.12 (m, 6H, CH), 3.86 (dd, J = 5.9, 17.4 Hz, 1H, CH_2NH), 3.77 (dd, J = 5.9, 17.4 Hz, 1H, CH_2NH), 3.59 (m, 5H, OCH_3, CH_2NH), 2.97 (m, 1H, CHCH_2Ph), 2.72 (m, 1H, CHCH_2Ph), 2.53 (m, 2H, CH_2Ph), 1.94 (m, 2H, CH(CH_3)$_2$, CH_2CH_2Ph), 1.74 (m, 1H, CH_2CH_2Ph), 1.63 (m, 1H, CH_2CH(CH_3)$_2$), 1.45 (m, 2H, CH_2CH(CH_3)$_2$), 1.34 (s, 9H, (CH_3)$_3$), 1.22 (d, J = 9.9 Hz, 3H, CH_3CH), 0.97 (d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), 0.88 (d, J = 6.4 Hz, 3H, (CH_3)$_2$CH), 0.80 (m, 6H, (CH_3)$_2$CH). ^{13}C-NMR (DMSO-d_6): δ 171.9 (CO), 171.4 (CO), 170.6 (CO), 170.2 (CO), 170.0 (CO), 169.6 (CO), 168.6 (CO),

155.3 (CO), 140.9, 137.2, 128.8, 127.8, 127.7, 127.3, 125.6, 125.2 (Ar), 77.50 ($C(CH_3)_3$), 57.26 (CH), 52.99 (CH), 51.53 (CH), 51.11 (CH), 50.13 (CH), 47.90 (CH), 47.52 (CH), 42.65 (CH_2), 40.48 (CH_2), 39.99 (CH_2), 36.83 (CH_2), 33.26 (CH_2), 30.91 (CH_2), 29.94 (CH), 27.63 (($CH_3)_3$), 23.56 (CH), 22.45 (CH_3), 21.14 (CH_3), 18.66 (CH_3),18.02 (CH_3), 17.67 (CH_3), 17.56 (CH_3). IR (KBr): ν 3287 (NH), 1745 (CO), 1638 (CO) cm^{-1}. High-resolution mass spec. Calcd for $C_{46}H_{69}N_8O_{11}$: [M + H] = 909.5086. Found: [M + H] = 909.5073.

Preparation of Labeled Dipeptide 30. The ^{13}C-labelled (*S*)-**1b** carbene complex (200 mg, 0.50 mmol) and (*S*)-*tert*-butyl phenylalaninate (92 mg, 0.42 mmol) were dissolved in 6 mL of THF, deoxygenated for 5 min, and photolyzed in a sealed tube for 27 h. After photolysis, the reaction mixture was treated with acetonitrile (10 mL) and stirred for 10 min at room temperature to convert the $(THF)_2Cr(^{13}CO)_4$ complex to the more stable $(CH_3CN)_2Cr(^{13}CO)_4$ complex. The solvents were removed *in vacuo*, and flash chromatography (1:1 CH_2Cl_2/hexanes) gave the $(CH_3CN)_2Cr(^{13}CO)_4$ complex as a yellow solid and the crude ^{13}C-labeled dipeptide **30**. Radial chromatography (25% EtOAc/hexanes, R_f = 0.20) gave 106 mg (55%) of **30** as a colorless oil. The crude reaction mixture consisted of a 75:25 ratio of two diastereomers (50% de), determined by integration of the NH doublets (7.65 ppm major, 6.81 ppm minor).

^1H-NMR: δ 7.65 (d, J = 5.9 Hz, 1H NH), 7.36–7.11 (m, 10H, ArH), 4.29 (m, 2H, CHPh, $CHCH_2Ph$), 4.18 (t, J = 7.8 Hz,1H, CH_2O), 3.78 (t, J = 7.7 Hz, 1H, CH_2O), 3.34 (dm, J = 129.0 Hz, $^*CO^*CHCH_3$), 3.34 (m, $^*COCHCH_3$, monolabeled), 3.10 (dd, J = 6.5, 13.8 Hz, 1H, CH_2Ph), 3.02 (dd, J = 6.5, 13.8 Hz, 1H, CH_2Ph), 1.43 (s, 9H, $(CH_3)_3$), 1.33 (m, 3H, $CH_3{}^*CH$), 1.29 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). ^{13}C-NMR: δ 173.5 (d, J = 54.6 Hz, $^*CH^*CO$), 173.5 (s, $^*CO$), 170.2 (CO), 139.9, 136.5, 129.5, 128.5, 128.4, 128.2, 127.7, 126.8 (Ar), 96.64 ($C(CH_3)_2$), 82.02 ($C(CH_3)_3$), 72.31 (CH_2O), 60.96 (CH), 54.95 (d, J = 54.6, $^*CH^*CO$), 54.95 (s, $^*CHCO$), 53.67 (CH), 37.57 (CH_2), 27.96 (($CH_3)_3$), 27.71 (CH_3), 21.58 (CH_3), 13.56 (d, J = 17.9 Hz, $CH_3{}^*CH$), 13.56 (s, CH_3CH). IR (film): ν 3385 (NH), 1729 (CO), 1672 (CO), 1630 ($^*CO$) cm^{-1}.

Preparation of Tripeptide 31. The fully protected ^{13}C-labeled dipeptide **30** (100 mg, 0.22 mmol) was converted to the protected ^{13}C-labeled tripeptide **31** (37 mg, 25% overall from **30**), following the the experimental details given above for the formation of **24** from **21**. The yields for each step were comparable to those for the unlabeled scheme as expected.

^1H-NMR: δ 7.76 (m, 2H, ArH), 7.59 (m, 2H, ArH), 7.42–7.11 (m, 14H, ArH), 6.53 (bs, 2H, NH), 5.47 (bs, 1H, NH), 4.71 (m, 1H, CH), 4.43 (m, 3H, $^*CH$, CH_2O), 4.21 (m, 2H, CH), 3.12 (dd, J = 6.3, 13.9 Hz, 1H, CH_2Ph), 3.03 (dd, J = 6.3, 13.9 Hz, 1H, CH_2Ph), 2.65 (m, 2H, CH_2CH_2Ph), 2.11 (m, 1H, CH_2CH_2Ph), 1.95 (m, 1H, CH_2CH_2Ph), 1.37 (s, 9H, $(CH_3)_3$), 1.28 (bs, 3H, $CH_3{}^*CH$). ^{13}C-NMR: δ 171.2 (d, J = 52.8 Hz, $^*CO^*CH$), 171.2 (s, $^*COCH$), 170.4 (CO), 156.2 (CO), 143.8, 143.7, 141.3, 140.7, 136.0, 129.5, 128.5, 128.4, 128.3, 127.7, 127.1, 127.0, 126.1, 125.1, 120.0 (Ar), 82.48 ($C(CH_3)_3$), 67.07 (OCH_2), 54.58 (CH), 53.58 (CH), 48.78 (d, J = 52.8 Hz, $^*CO^*CH$), 48.78 (s, CO^*CH), 47.13 (CH), 38.09 (CH_2), 34.56 (CH_2), 31.63 (CH_2), 27.89 (($CH_3)_3$, 18.62 (d, J = 16.7 Hz, $CH_3{}^*CH$), 18.62 (s, CH_3CH). IR (film): ν 3292 (NH), 1729 (CO), 1704 (CO), 1646(CO), 1622 ($^*CO$) cm^{-1}.

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