Synthesis of Dipeptides by the Photolytic Coupling of Chromium Aminocarbene Complexes with α-Amino Acid Esters. 2. Side Chain Functionalized and α,α-Disubstituted α-Amino Acid Esters and *N*-Methyl- and *N*-Methyl-α,α-dialkyl-α-amino Acid Esters

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Abstract: Photolysis of optically active chromium aminocarbene complex (*R*)-**1** in the presence of functionalized, unprotected α-amino acid esters of serine, cysteine, methionine, and tyrosine led to the production of dipeptides in good yield without competitive coupling at the side chain functional groups. The diesters of aspartic and glutamic acid also coupled efficiently. Even sterically hindered α,α-disubstituted α-amino acids and *N*-methyl- and *N*-methyl-α,α-dialkyl-α-amino acids coupled efficiently to the photogenerated amino acid residue precursor, allowing introduction of these normally difficult-to-couple hindered amino acids into peptides.

Introduction

With the dramatic increase in the development of peptide-based pharmaceuticals,[1] synthetic approaches to this important class of compounds are of substantial current interest.[2] Virtually all chemical syntheses of peptides involve various processes for the incorporation of intact amino acid residues into the growing peptide chain, either in solution or on an insoluble polymer support.[3] Despite its long history, substantial effort continues to be invested in the development of protecting group strategies for these polyfunctional compounds, as well as the development of new peptide-bond-forming (coupling) reagents.[2]

Peptides containing α,α-dialkylated glycines (primarily 2-aminoisobutyric acid, Aib, and D-2-ethylalanine, D-Iva) have been isolated from fungi,[4] and constitute a class of polypeptide antibiotics and ionophores called peptaibols.[5] Introduction of α,α-dialkyl-α-amino acids into peptides results in conformational restrictions which favor certain backbone conformations,[6] as well as enhanced resistance to protease enzymes.[7] Because of their increased steric hindrance, α,α-dialkyl-α-amino acids are often difficult to incorporate into peptides under mild conditions, and a variety of specialized coupling procedures have been developed to overcome these problems. These include the use of strained 3-amino-2*H*-azirines as symmetrical (or racemic) α,α-dialkyl-α-amino acid residue precursors,[8] the use of highly reactive Fmoc amino acid fluorides in solid phase peptide synthesis,[9] and the use of the BOP(1*H*-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate family of peptide coupling agents.[10]

N-Methylated amino acid residues are found in a number of biologically active peptides including the immunosuppressive drug "cyclosporine",[11] the antitumor, antiviral, immunosuppressive cyclodepsipeptides known as didemnins,[12] the antineoplastic agents, dolastatins,[13] and cholecystokinin agonist tetrapeptides.[14] Incorporation of *N*-methylated amino acids into peptides is also difficult,[15] and new methods to couple these compounds have recently been developed.[16]

Recent research in these laboratories has centered on the development of photochemical reactions of chromium ami-

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(2) For recent books on the subject see: (a) Jones, J. H. *The Chemical Synthesis of Peptides*; Oxford Science Publications, Clarendon Press: Oxford, 1991. (b) *Peptides: Design, Synthesis, and Biological Activity*; Basava, C., Anantharamaiah, G. M., Eds.; Birkhäuser: Boston, 1994. The area of peptide synthesis is reviewed annually. See: (c) Elmore, D. T. *Spec. Period. Rep.: Amino Acids Pept.* **1993**, *24*, 81−132.

(3) For an excellent introduction to peptide synthesis see: Bodanszky, M. *Peptide Chemistry: A Practical Textbook*, 2nd ed.; Springer-Verlag: New York, 1993.

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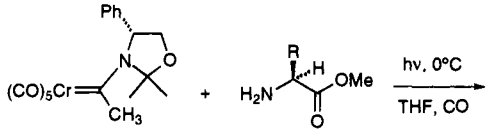
nocarbene complexes[17] for the synthesis of amino acids[18] and peptides.[19] The process is somewhat unconventional in that photogenerated metal-bound ketenes are thought to be the reactive intermediate,[20] and, in peptide synthesis, both the peptide bond and the new stereogenic center on the introduced amino acid residue are formed in the same step. These studies had shown that these reactions were highly selective and, since the "activated" amino acid fragment was in the form of a ketene, relatively insensitive to steric hindrance. These observations suggested that this methodology might be appropriate for the incorporation of side chain functionalized and sterically hindered amino acids into peptides without requiring specialized protection or activation schemes. Below are described studies addressing this question.

Results and Discussion

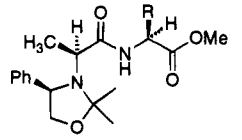
Coupling with Functionalized Amino Acids. Previous studies[19a] had shown that relatively unreactive side chain functional groups such as the hydroxy group of threonine and the indole group of tryptophan did not require protection in the photolytic coupling to optically active chromium carbene complex **1**. The use of amino acids having functional groups normally requiring protection (the OH group of serine, SH group of cysteine, and the *S*-methyl group of methionine) in this reaction proceeded without competitive reaction at the functional group (eq 1) to give dipeptides **3a**–**3f** in fair yield (pure, single diastereoisomer) with good diastereoselectivity (determined by ^{1}H NMR spectra of crude reaction mixtures). As expected, the OH group of tyrosine was also tolerated.



(Eq. 1)

(R)-1

(S)-2 **a** R = CH_2OH (Ser)
b R = CH_2SH (Cys)
c R = $(CH_2)_2SCH_3$ (Met)
d R = p-$HOPhCH_2$ (Tyr)
e R = $(CH_2)_2CO_2CH_3$ (Glu)
f R = $CH_2CO_2CH_3$ (Asp)

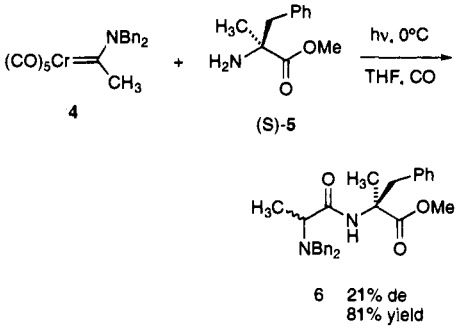


		de (%)	Yield (%)
(R,S,S)-3	**a**	≥95	61
	b	84	37
	c	91	68
	d	88	64
	e	≥95	75
	f	90	64

In the case of cysteine, an additional compound, accounting for roughly 20% of the isolated product, was obtained. Its ^{1}H NMR spectrum showed signals due to both the cysteine and alanine amino acid residues of the dipeptide product, but all sets of peaks were doubled. High-resolution mass spectroscopy confirmed that this compound had the exact mass of the disulfide dimer of the dipeptide, a type of byproduct often encountered in cysteine peptide coupling reactions.[3] The fact that pure cysteine dipeptide **3b** did not oxidatively dimerize under these reaction conditions, in conjunction with the doubling of all NMR signals, suggests this compound is the dimer formed selectively between the major and the minor diastereoisomers of **3b**, although this remains to be confirmed. The reported diastereomeric excess (de) in equation 1 is based on this premise.

The free carboxylic acid groups of glutamic acid and aspartic acid were not tolerated, primarily because of the insolubility of these free amino acids in the reaction solvents. Their corresponding methyl esters underwent clean coupling. Finally, the free amino groups of the basic amino acids (lysine, arginine, histidine), being better nucleophiles than the α-amino group, could not be tolerated.

The photolytic coupling of aminocarbene complexes with α,α-disubstituted α-amino acids was next addressed. To determine the feasibility of this normally difficult coupling, as well as to assess the potential influence of the α,α-disubstituted α-amino acid on the stereochemistry of the newly formed stereogenic center, achiral (dibenzylamino)carbene complex **4** was coupled to (*S*)-α-methylphenylalanine **5** (eq 2). The



(Eq. 2)

reaction proceeded in high chemical yield, but with little diastereoselectivity, as anticipated from previous studies with this same carbene complex and simple optically active α-amino acids.[19a] The efficiency of peptide coupling with the sterically hindered amino acid confirmed the assumption that the photogenerated amino ketene precursor to the new amino acid residue was relatively unhindered, the electrophilic center being the sp carbon of the carbonyl group of the ketene, and thus relatively insensitive to the steric bulk of the nucleophile, in this case the disubstituted amino acid. Similarly, photolysis of (*R*)-carbene complex **1** with a variety of achiral (symmetrical) or optically active α,α-disubstituted α-amino acids produced the corresponding dipeptides **8** in good chemical yield and with high diastereoselectivity (eq 3). In addition, α-alkylated carbene complex (*R*)-**9** coupled efficiently (eq 4).[21]

Previous peptide coupling studies[19a] with complex **1** and simple α-amino acid esters had revealed very modest double diastereoselection,[22] with the (*R*)-carbene complex and the (*S*)-amino acid ester being the "matched" pair. In a similar manner, the (*S*)-carbene complex **1** with (*S*)-α,α-disubstituted α-amino

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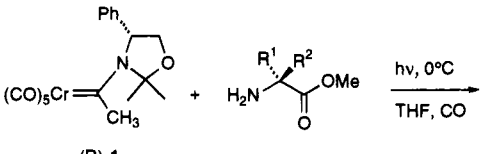
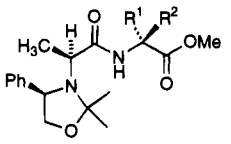
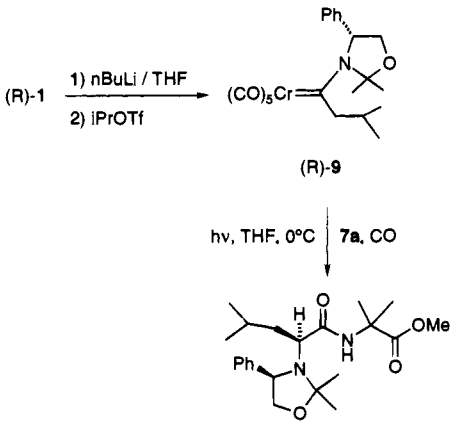


(R)-1 (Eq. 3)

7a $R^1 = R^2 = CH_3$
b $R^1 = R^2 = Ph$
c $R^1 = CH_3$, $R^2 = Bn$
d $R^1 = CH_3$, $R^2 = nPr$
e $R^1 = nPr$, $R^2 = Bn$
f $R^1 = CH_3$, $R^2 = CH_2OH$



	de (%)	Yield (%)
8a	≥95	78
b	≥95	82
c	95	84
d	94	67
e	84	68
f	86	68

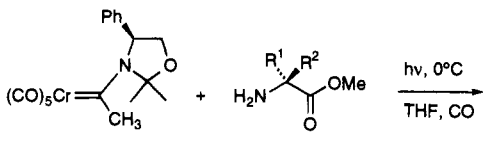


(R)-1 (Eq. 4)

(R)-9

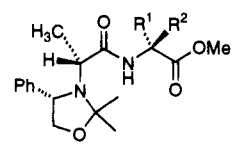
10 ≥95% de, 76% yield

acids was the "mismatched" pair, resulting in slightly lower diastereoselectivity and thus slightly lower yield of the major diastereoisomer, which now contained an (*R*)-alanine N-terminus (eq 5).



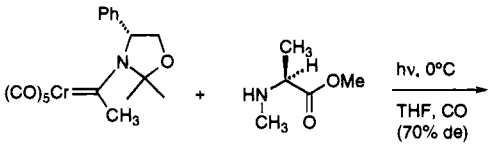
(S)-1 (Eq. 5)

(S)-**7c** $R^1 = CH_3$, $R^2 = Bn$
7d $R^1 = CH_3$, $R^2 = nPr$
7e $R^1 = nPr$, $R^2 = Bn$

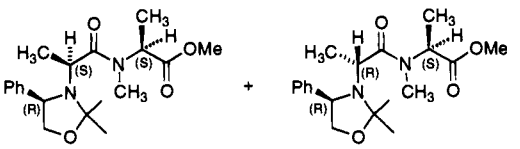


	de (%)	Yield (%)
11	79	76
12	91	71
13	82	53

The final question addressed was the coupling of *N*-methyl-α-amino acids. Photolysis of (*R*)-carbene complex **1** with (*S*)-*N*-methylalanine gave a mixture of two diastereoisomeric dipeptides in isolated yields of 62% and 13%, respectively, and with a diastereoisomeric excess (crude reaction mixture) of 70% (eq 6). The reaction was repeated starting with (*S*)-carbene

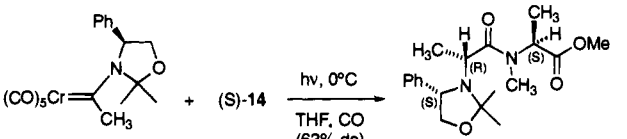


(R)-1 (S)-14 (Eq. 6)

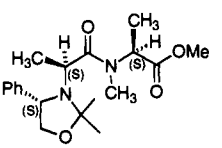


15 (62%) **16** (13%)

complex **1** to give a different set of diastereoisomers (eq 7). To demonstrate that the sets of isomers isolated from each reaction were indeed diastereoisomeric at the newly formed stereogenic center (and not isomers about the peptide bond), the separated

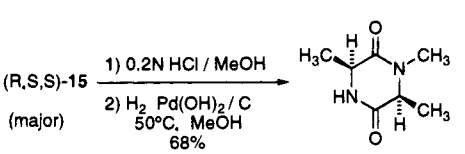


(S)-1 (S)-14 **17** (62%) (Eq. 7)

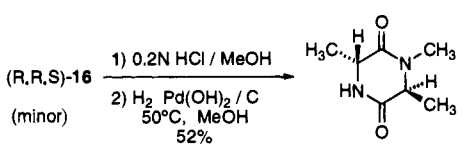


18 (17%)

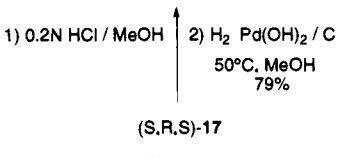
diastereoisomers were converted to their corresponding diketopiperazines (eq 8). The diketopiperazine from the major product from the (*S*)-carbene complex (eq 7) was identical to that from the minor product from the (*R*)-carbene complex (eq 6) and different from the major product from the (*R*)-carbene complex, confirming the stereochemical assignments.



(R,S,S)-**15** (major) **19** (Eq. 8)



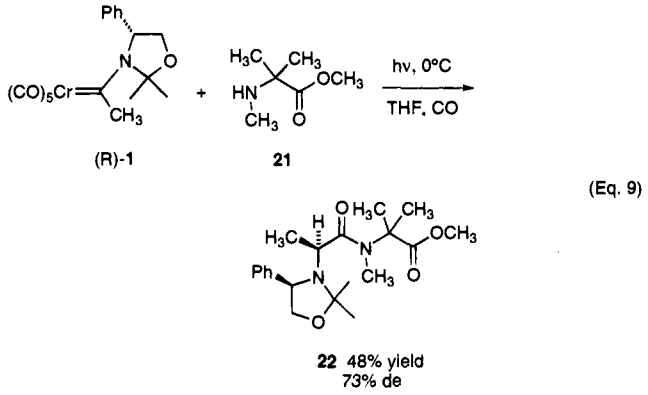
(R,R,S)-**16** (minor) **20**



(S,R,S)-**17** (major)

Finally, photolysis of (*R*)-carbene complex **1** with the very sterically hindered methyl *N*-(methylamino)isobutyrate **21** pro-

duced the dipeptide **22** in 48% yield (purified single diastereoisomer) with reasonable diastereoselectivity (eq 9), under remarkably mild conditions (0 °C, 1.2 equiv of carbene complex **1**).[23]



(R)-1 21

(Eq. 9)

22 48% yield
73% de

In summary, optically active chromium aminocarbene complexes such as **1** and **9** produce highly activated acylating agents for functionalized and sterically hindered amino acid esters upon photolysis, and permit efficient peptide bond formation from these normally difficult to incorporate amino acid residues.

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were obtained on a Bruker ACE-300 NMR spectrometer. NMR spectra were recorded in $CDCl_3$, and chemical shifts are reported in parts per million relative to $CHCl_3$ (7.24 ppm, ^{1}H) or $CDCl_3$ (77.0 ppm, ^{13}C). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Materials. Tetrahydrofuran was predried over CaH_2 and distilled from sodium benzophenone ketyl under a nitrogen atmosphere just prior to use. Pentacarbonyl[(*N*,*N*-dibenzylamino)methylcarbene]chromium(0), **4**,[18a] pentacarbonyl [((5*R* or 5*S*)-1-aza-2,2-dimethyl-3-oxa-5-phenylcyclopent-1-yl)methylcarbene]chromium(0), **1**,[18a] isopropyl triflate,[24] (*S*)-α-methylphenylalanine,[25] (*S*)-α-methylnorvaline,[25] (*S*)-α-propylphenylalanine,[25] (*S*)-α-methylserine,[26] *N*-methyl-(*S*)-alanine methyl ester,[27] and *N*-methyl-2-aminoisobutyric acid[28] were prepared by literature methods.

Serine, cysteine, methionine, tyrosine, and 2-aminoisobutyric acid were converted into the corresponding methyl ester hydrochloride salts as follows: To a −10 °C solution (3.6 M) of thionyl chloride (3.6 equiv) in methanol was added the α-amino acid (1 equiv). After being stirred for 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. Subsequent treatment of the crude material with ether led to the precipitation of the desired α-amino ester hydrochloride salt. Similarly, the dimethyl esters of glutamic acid and aspartic acid were prepared by using a larger excess of thionyl chloride (7.1 equiv). The α,α-disubstituted α-amino acid esters **7b−f** were synthesized by heating the corresponding amino acids at reflux in methanol containing excess thionyl chloride.

Preparation of Pentacarbonyl[((5*R*)-1-aza-2,2-dimethyl-3-oxa-5-phenylcyclopent-1-yl)isobutylcarbene]chromium(0) (9). The aminocarbene complex (*R*)-**1** (198 mg, 0.50 mmol) was dissolved in dry THF (2.5 mL), and the solution was cooled to −78 °C. After deoxygenation in vacuo, 470 μL of *n*-butyllithium (0.55 mmol; 1.17 M in hexane) was added dropwise under argon at −78 °C. After 15 min, the clear orange solution was treated with isopropyl triflate (115 mg, 0.60 mmol), was allowed to warm to room temperature, and was stirred for 2 h. Addition of wet ether, drying over magnesium sulfate, and filtration through a short bed of silica gel (elution with ether) afforded an orange-yellow filtrate which was absorbed onto silica gel and dried under reduced pressure. The resulting yellow powder was transferred to a silica gel column, and elution with 9:1 hexanes/EtOAc under argon afforded the desired aminocarbene (90 mg; 41%) as a yellow-orange crystalline solid. ^{1}H NMR: δ 1.01 (d, J = 6.0 Hz, 3H, CH_3), 1.19 (d, J = 5.9 Hz, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 3.02 (m, 3H, CH_2, CH), 4.32 (dd, J = 1.2, 9.4 Hz, 1H, OCH_2), 4.54 (dd, J = 5.3, 9.4 Hz, 1H, OCH_2), 6.06 (d, J = 5.1 Hz, 1H, NCH), 7.33 (m, 5H, ArH).

General Procedure for the Photolysis of Chromium Aminocarbene Complexes with α-Amino Acid Esters. The chromium carbene complex was added as a solid to an oven-dried Pyrex pressure tube (Ace Glass), followed by the α-amino ester dissolved in THF. The solution was rapidly deoxygenated by bubbling argon through for 5 min. The pressure tube was fitted with a pressure head and saturated with CO (three cycles, 60−70 psi of CO) and then pressurized to 60−70 psi and photolyzed using a mercury arc lamp operating at 450 W. 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 as coolant. A water-cooled Pyrex immersion well containing the 450 W Conrad Hanovia lamp was also placed in the cold bath. When the carbene was consumed (TLC; CH_2Cl_2/hexanes, 1:1), the solvent was removed under reduced pressure. A 1:1 EtOAc/hexanes solution of the resulting crude material was exposed to six 20 W Vitalite lamps until the oxidized chromium residues precipitated. Filtration through Celite and concentration under reduced pressure afforded the crude photolysis products.

The free α-amino ester was generated by treatment of the corresponding hydrochloride salt with 2 equiv of Et_3N in THF. After being stirred for 2−12 h, the mixture was filtered through Celite and transferred into the pressure vessel containing the chromium carbene complex.

Coupling of (*R*)-1 with (*S*)-Serine Methyl Ester To Produce 3a. Photolysis (35 h) of (*R*)-**1** (128 mg, 0.32 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-methyl serinate (32 mg, 0.27 mmol) gave 58 mg (61%) of **3a** as a white solid (mp 106−108 °C) after chromatography on silica gel (1:2 hexanes/EtOAc). ^{1}H NMR: δ 1.32 (s, 3H, CH_3), 1.44 (d, J = 7.3 Hz, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.76 (t, J = 6.6 Hz, 1H, OH), 3.44 (m, 3H, C*H*CH_3, C*H*$_2$OH), 3.74 (s, 3H, OCH_3), 3.93 (dd, J = 9.2, 12.3 Hz, 1H, CH_2O), 4.28, 4.35 (m's, 3H, C*H*CH_2, CHPh, CH_2O), 7.26 (m, 3H, ArH), 7.43 (m, 2H, ArH), 7.97 (d, J = 6.9 Hz, 1H, NH). ^{13}C NMR: δ 14.1 (CH_3), 20.9 (CH_3), 27.5 (CH_3), 52.5 (OCH_3), 54.8, 54.9, 60.0 (CH), 63.3, 72.4 (CH_2O), 97.1 (C), 127.7, 128.1, 128.8 (Ph), 142.7 (ipso Ph), 170.5 (C=O), 174.6 (C=O). IR (film): ν 3373 (NH) (OH), 1747 (C=O), 1653 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 61.86; H, 7.37; N, 8.03.

Coupling of (*R*)-1 with (*S*)-Cysteine Methyl Ester To Produce 3b. Photolysis (24 h) of (*R*)-**1** (67 mg, 0.17 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-methyl cysteinate (19 mg, 0.14 mmol) and (*N*,*N*-dimethylamino)pyridine (21 mg, 0.17 mmol) gave 19 mg (37%) of **3b** and 10 mg of the disulfide as colorless oils after chromatography on silica gel (1:1 CH_2Cl_2/EtOAc). The de (84%) was determined by

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(21) The α-carbanion of carbene complex **1** can be alkylated by a variety of reactive electrophiles such as allyl bromide, ethyl bromoacetate, and benzyl bromide, as well as secondary triflates, making a variety of amino acid residues potentially available for this coupling process. Aryl, vinyl, and α-branched analogs of carbene complex **1** have not yet been successfully synthesized, limiting this range.

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integration of the methine quartet (3.44 ppm) of the major diastereoisomer and the CH_2S multiplet (3.02 ppm) of the disulfide. ^1H NMR (major diastereoisomer): δ 1.32 (s, 3H, CH_3), 1.38 (d, J = 7.3 Hz, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.55 (m, 2H, CH_2S), 3.44 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.70 (s, 3H, OCH_3), 3.87 (dd, J = 9.1, 12.1 Hz, 1H, CH_2O), 4.27 (m, 2H, CH_2O, CHPh), 4.54 (dt, J = 5.9, 8.4 Hz, 1H, C*H*CH_2), 7.26 (m, 3H, ArH), 7.40 (m, 2H, ArH), 7.66 (d, J = 8.4 Hz, 1H, NH). ^{13}C NMR: δ 15.2 (CH_3), 21.4 (CH_3), 28.0 (CH_3), 40.1 (CH_2S), 51.1 (CHPh), 52.8 (OCH_3), 55.9 (CH), 60.7 (CH), 72.7 (CH_2O), 97.4 (C), 128.0, 128.2, 129.3 (Ph), 143.4 (ipso Ph), 171.1 (C=O), 174.4 (C=O). IR (film): ν 3366 (NH), 1745 (C=O), 1674 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4S$: C, 58.99; H, 7.15; N, 7.64; S, 8.75. Found: C, 59.03; H, 7.40; N, 7.44; S, 8.53. ^1H NMR (disulfide): δ 1.20 (d, J = 7.1 Hz, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.39 (d, J = 7.3 Hz, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.48 (m, 2H, CH_2S), 3.02 (m, 2H, CH_2S), 3.44 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.63 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.88 (dd, J = 9.1, 12.2 Hz, 1H, CH_2O), 4.28 (m, 3H, CH_2O, CHPh), 4.37 (t, J = 8.0 Hz, 1H, CH_2O), 4.55 (dt, J = 6.1, 8.5 Hz, 1H, C*H*CH_2), 4.69 (m, 2H, C*H*CH_2, CHPh), 7.19–7.41 (m, 11H, ArH, NH), 7.66 (d, J = 8.5 Hz, 1H, NH). ^{13}C NMR: δ 14.8, 18.0 (CH_3), 21.0, 23.5 (CH_3), 27.6, 28.1 (CH_3), 40.0, 40.4 (CH_2S), 50.9, 51.5 (CHPh), 52.5 (OCH_3), 55.4, 56.2 (CH), 60.3, 62.8 (CH), 71.2, 72.3 (CH_2O), 97.1 (C), 126.9, 127.1, 127.6, 127.8, 128.4, 128.8, 129.0 (Ph), 143.3 (ipso Ph), 170.8 (C=O), 174.0 (C=O). IR (film): ν 3332 (NH), 1745 (C=O), 1674 (C=O) cm^{-1}. High-resolution mass measurement calcd for $C_{36}H_{50}N_4O_8S_2$ 730.3070, found 730.3038 (σ = 0.0018).

Coupling of (*R*)-1 with (*S*)-Methionine Methyl Ester To Produce 3c. Photolysis (40 h) of (*R*)-**1** (128 mg, 0.32 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-methyl methioninate (44 mg, 0.27 mmol) gave 72 mg (68%) of **3c** as a clear oil after chromatography on silica gel (1:1 hexanes/EtOAc). The de (91%) was determined by integration of the SCH_3 singlet (δ 1.95 ppm major, 2.04 ppm minor). ^1H NMR (major diastereoisomer): δ 1.31 (s, 3H, CH_3), 1.37 (m, 1H, CH_2), 1.42 (d, J = 7.2 Hz, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.79 (m, 2H, CH_2), 1.93 (m, 1H, CH_2), 1.95 (s, 3H, SCH_3), 3.41 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.71 (s, 3H, OCH_3), 3.90 (dd, J = 9.5, 13.4 Hz, 1H, CH_2O), 4.30 (m, 2H, CH_2O, CHPh), 4.42 (dt, J = 4.2, 8.3 Hz, 1H, C*H*CH_2), 7.30 (m, 3H, ArH), 7.41 (m, 2H, ArH), 7.64 (d, J = 8.1 Hz, 1H, NH). ^{13}C NMR: δ 14.9 (CH_3), 15.3 (CH_3), 20.7 (CH_3), 27.4 (CH_3), 29.8 (CH_2), 32.2 (CH_2), 51.1, 52.2, 55.4, 60.1 (CH), 72.5 (CH_2O), 97.2 (C), 127.7, 127.9, 129.0 (Ph), 143.5 (ipso Ph), 172.2 (C=O), 174.1 (C=O). IR (film): ν 3368 (NH), 1743 (C=O), 1673 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_4S$: C, 60.88; H, 7.68; N, 7.10. Found: C, 60.70; H, 7.49; N, 7.01.

Coupling of (*R*)-1 with (*S*)-Tyrosine Methyl Ester To Produce 3d. Photolysis (41 h) of (*R*)-**1** (128 mg, 0.32 mmol) in 6 mL of THF, at 0 °C, containing (*S*)-methyl tyrosinate (53 mg, 0.27 mmol) gave 74 mg (64%) of **3d** as a white solid (mp 148–149 °C) after chromatography on silica gel (2:1 CH_2Cl_2/EtOAc). The de (88%) was determined by integration of the dd's of the benzyl group (δ 2.70 ppm major, 2.82 ppm minor). ^1H NMR (major diastereoisomer): δ 1.19 (d, J = 7.3 Hz, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.39 (dd, J = 8.0, 13.8 Hz, 1H, CH_2Ph), 2.70 (dd, J = 6.1, 13.8 Hz, 1H, CH_2Ph), 3.39 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.68 (s, 3H, OCH_3), 3.80 (m, 1H, CH_2O), 4.26 (m, 2H, CH_2O, CHPh), 4.49 (dt, J = 6.2, 8.1 Hz, 1H, C*H*CH_2), 6.13 (s, 1H, OH), 6.56 (d, J = 8.5 Hz, 2H, ArH), 6.65 (d, J = 8.5 Hz, 2H, ArH), 7.22–7.39 (m, 5H, ArH), 7.55 (d, J = 8.3 Hz, 1H, NH). ^{13}C NMR: δ 15.5 (CH_3), 20.8 (CH_3), 27.3 (CH_3), 37.9 (CH_2Ph), 52.2 (OCH_3), 53.4, 56.0, 60.9 (CH), 72.2 (CH_2O), 97.1 (C), 115.3, 127.1, 127.7, 127.8, 129.0, 130.0 (Ar), 143.4 (ipso Ph), 155.4 (ipso Ar), 172.1 (C=O), 174.8 (C=O). IR (film): ν 3312 (NH) (OH), 1743 (C=O), 1655 (C=O) cm^{-1}. Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.10; N, 6.57. Found: C, 67.37; H, 7.09; N, 6.35.

Coupling of (*R*)-1 with (*S*)-Glutamic Acid Dimethyl Ester To Produce 3e. Photolysis (41 h) of (*R*)-**1** (128 mg, 0.32 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-glutamic acid dimethyl ester (47 mg, 0.27 mmol) gave 83 mg (75%) of **3e** as a colorless oil after chromatography on silica gel (3:4 hexanes/EtOAc). ^1H NMR: δ 1.26 (m, 1H, CH_2), 1.30 (s, 3H, CH_3), 1.42 (d, J = 7.3 Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.62 (m, 1H, CH_2), 1.87 (m, 2H, CH_2), 3.40 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.63 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.91 (m, 1H, CH_2O), 4.31 (m, 3H, CH_2O, CHPh, C*H*CH_2), 7.15–7.42 (m, 5H, ArH), 7.61 (d, J = 8.6 Hz, 1H, NH). ^{13}C NMR: δ 14.7 (CH_3), 20.7 (CH_3), 27.4 (CH_3), 27.7 (CH_2), 29.8 (CH_2), 50.9 (CHPh), 51.5 (OCH_3), 52.2 (OCH_3), 55.2 (CH), 59.9 (CH), 72.4 (CH_2O), 97.1 (C), 127.7, 127.8, 128.9 (Ph), 143.4 (ipso Ph), 172.1 (C=O), 172.8 (C=O), 174.0 (C=O). IR (film): ν 3367 (NH), 1739 (C=O), 1673 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{30}N_2O_6$: C, 62.04; H, 7.45; N, 6.89. Found: C, 61.86; H, 7.28; N, 6.89.

Coupling of (*R*)-1 with (*S*)-Aspartic Acid Dimethyl Ester To Produce 3f. Photolysis (43 h) of (*R*)-**1** (128 mg, 0.32 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-aspartic acid dimethyl ester (43 mg, 0.27 mmol) gave 68 mg (64%) of **3f** as a colorless oil after chromatography on silica gel (1:1 hexanes/EtOAc). The de (90%) was determined by integration of the singlets of the oxazolidine geminal CH_3 groups (δ 1.55 ppm major, 1.43 ppm minor). ^1H NMR (major diastereoisomer): δ 1.33 (s, 3H, CH_3), 1.37 (d, J = 7.2 Hz, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.19 (dd, J = 4.9, 17.2 Hz, 1H, CH_2), 2.76 (dd, J = 4.6, 17.2 Hz, 1H, CH_2), 3.47 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.85 (m, 1H, CH_2O), 4.26 (m, 2H, CH_2O, CHPh), 4.64 (dt, J = 4.7, 9.3 Hz, 1H, C*H*CH_2), 7.20–7.33 (m, 5H,ArH), 7.98 (d, J = 9.4 Hz, 1H, NH). ^{13}C NMR: δ 14.3 (CH_3), 21.1 (CH_3), 27.5 (CH_3), 35.8 (CH_2), 47.8 (CHPh), 51.9 (OCH_3), 52.5 (OCH_3), 55.2 (CH), 60.6 (CH), 72.2 (CH_2O), 97.1 (C), 127.6, 128.0, 128.5 (Ph), 142.0 (ipso Ph), 171.2 (C=O), 171.4 (C=O), 174.0 (C=O). IR (film): ν 3380 (NH), 1738 (C=O), 1675 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.37; H, 7.12; N, 7.17. ^1H NMR (minor diastereoisomer): δ 1.25 (d, J = 7.1 Hz, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.53 (dd, J = 4.6, 17.1 Hz, 1H, CH_2), 2.92 (dd, J = 4.2, 17.4 Hz, 1H, CH_2), 3.57 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.67 (s, 3H, OCH_3), 3.71 (m, 1H, CH_2O), 3.74 (s, 3H, OCH_3), 4.38 (t, J = 8.1 Hz, 1H, CH_2O), 4.57 (m, 1H), 4.76 (m, 1H), 7.21–7.39 (m, 6H, ArH, NH).

Coupling of 4 with (*S*)-α-Methylphenylalanine Methyl Ester To Produce 6. Photolysis (43 h) of **4** (104 mg, 0.25 mmol) in 7 mL of THF , at 0 °C, containing (*S*)-α-methylphenylalanine methyl ester (41 mg, 0.21 mmol) gave 75 mg (81%) of **6** as a clear oil after chromatography on silica gel (2:1 hexanes/EtOAc) (inseparable mixture of diastereoisomers). The de (21%) was determined by integration of the methyl singlets (δ 1.55 ppm major, 1.70 ppm minor). ^1H NMR: δ 1.24, 1.27, 1.29 (d's, J = 7.0 Hz, 3H, C*H*$_3$CH), 1.55 (s, 1.8H, CH_3), 1.70 (s, 1.2H, CH_3), 3.11 (d, J = 13.5 Hz, 0.4H, CH_2Ph), 3.31 (m, 3H, CH, CH_2N), 3.46 (d, J = 13.6 Hz, 0.6H, CH_2Ph), 3.55 (d, J = 13.3 Hz, 1.2H, CH_2N), 3.57 (d, J = 13.5 Hz, 0.8H, CH_2N), 3.71 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.74 (s, 1.8H, OCH_3), 3.81 (s, 1.2H, OCH_3), 6.90–7.25 (m, 15H, ArH), 8.02 (br s, 0.6H, NH), 8.12 (br s, 0.4H, NH). ^{13}C NMR: δ 6.9 (CH_3), 23.3, 23.4 (CH_3), 41.4, 41.6 (CH_2Ph), 52.4, 52.5 (OCH_3), 54.3 (CH_2Ph), 57.7, 57.9 (CH), 60.5, 61.1 (C), 126.8, 127.1, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.5, 129.8 (Ph), 136.2, 136.4 (ipso Ph), 138.6 (ipso Ph), 173.2 (C=O), 174.2, 174.5 (C=O). IR (film): ν 3360 (NH), 1739 (C=O), 1678 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_3$: C, 75.69; H, 7.20; N, 6.30. Found: C, 75.50; H, 7.26; N, 6.18.

Coupling of (*R*)-1 with 2-Aminoisobutyric Acid Methyl Ester To Produce 8a. Photolysis (44 h) of (*R*)-**1** (99 mg, 0.25 mmol) in 4 mL of THF, at 0 °C, containing 2-aminoisobutyric acid methyl ester (25 mg, 0.21 mmol) gave 57 mg (78%) of **8a** as a clear oil after chromatography on silica gel (1:1 hexanes/EtOAc). ^1H NMR: δ 1.15 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.35 (d, J = 7.2 Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.34 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.64 (s, 3H, OCH_3), 3.89 (dt, J = 8.1, 10.2 Hz, 1H), 4.26 (m, 2H), 7.19–7.38 (m, 5H, ArH), 7.65 (br s, 1H, NH). ^{13}C NMR: δ 14.0 (CH_3), 21.0 (CH_3), 23.6 (CH_3), 24.5 (CH_3), 27.6 (CH_3), 52.3 (OCH_3), 55.2, 55.6, 60.0 (CH), 72.3 (CH_2O), 97.0 (C), 127.5, 128.0, 128.7 (Ph), 142.8 (ipso Ph), 173.1 (C=O), 174.9 (C=O). IR (film): ν 3363 (NH), 1737 (C=O), 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.54; H, 8.04; N, 8.04. Found: C, 65.37; H, 7.97; N, 7.97.

Coupling of (*R*)-1 with α,α-Diphenylglycine Methyl Ester To Produce 8b. A solution of the aminocarbene complex (*R*)-**1** (119 mg, 0.30 mmol) in 7 mL of THF containing α,α-diphenylglycine methyl ester (49 mg, 0.20 mmol) was irradiated, at 0 °C, for 3 days. The

crude product was diluted with ethyl acetate and washed with 1 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude dipeptide. Chromatography on silica gel (1:1:0.1 hexanes/EtOAc/CH_2Cl_2) afforded 77 mg (82%) of **8b** as white crystals (mp 137−138 °C). ^1H NMR: δ 1.30 (s, 3H, CH_3), 1.39 (d, J = 7.3 Hz, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.36 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.72 (s, 3H, OCH_3), 3.93 (dd, J = 4.6, 6.8 Hz, 1H, CH_2O), 4.34 (m, 2H, CH_2O, CHPh), 6.88 (m, 2H, ArH), 7.11−7.25 (m, 11H, ArH), 7.46 (m, 2H, ArH), 9.03 (br s, 1H, NH). ^{13}C NMR: δ 13.9 (CH_3), 20.6 (CH_3), 27.5 (CH_3), 53.1 (OCH_3), 55.7 (CHPh), 60.5 (CH), 69.4 ($C(Ph)_2$), 72.6 (CH_2O), 97.1 (C), 127.4, 127.5, 127.6, 127.7, 128.2, 128,3, 128.4, 128.7 (Ph), 138.0 (ipso Ph), 139.6 (ipso Ph), 141.8 (ipso Ph), 172.1 (C=O), 172.4 (C=O). IR (film): ν 3344 (NH), 1733 (C=O), 1682 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{32}N_2O_4$: C, 73.74; H, 6.78; N, 5.93. Found: C, 73.63; H, 6.83; N, 5.88.

Coupling of (*R*)-1 with (*S*)-α-Methylphenylalanine Methyl Ester To Produce 8c. Photolysis (47 h) of (*R*)-**1** (119 mg, 0.30 mmol) in 8 mL of THF, at 0 °C, containing (S)-α-methylphenylalanine (48 mg, 0.25 mmol) gave 89 mg (84%) of **8c** as a clear oil after chromatography on silica gel (4:3 hexanes/EtOAc). The de (95%) was determined by integration of the benzyl singlet (3.03 ppm) of the major diastereoisomer and the benzyl doublet (3.21 ppm) of the minor diastereoisomer. ^1H NMR (major diastereoisomer): δ 1.19 (s, 3H, CH_3), 1.29 (d, J = 7.2 Hz, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.03 (s, 2H, CH_2-Ph), 3.37 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.61 (s, 3H, OCH_3), 3.75 (dd, J = 4.7, 7.0 Hz, 1H, CH_2O), 4.21 (m, 2H, CH_2O, CHPh), 7.01 (m, 2H, ArH), 7.14−7.21 (m, 8H, ArH), 7.50 (br s, 1H, NH). ^{13}C NMR: δ 14.7 (CH_3), 21.0 (CH_3), 21.8 (CH_3), 27.7 (CH_3), 42.5 (CH_2Ph), 52.0 (OCH_3), 55.9 (CHPh), 59.5 (C), 60.7 (CH), 72.2 (CH_2O), 97.0 (C), 126.9, 127.4, 127.6, 128.1, 128.7, 130.0 (Ph), 135.7 (ipso Ph), 142.3 (ipso Ph), 173.4 (C=O), 173.8 (C=O). IR (film): ν 3368 (NH), 1736 (C=O), 1671 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.77; H, 7.54; N, 6.60. Found: C, 70.63; H, 7.69; N, 6.57. ^1H NMR (minor diastereoisomer): δ 1.19 (d, J = 7.2 Hz, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.21 (d, J = 13.5 Hz, 1H, CH_2-Ph), 3.35 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.48 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.59 (dd, J = 5.7, 8.4 Hz, 1H, CH_2O), 3.76 (s, 3H, OCH_3), 4.06 (t, J = 8.1 Hz, 1H, CH_2O), 4.52 (dd, J = 5.9, 7.7 Hz, 1H, CHPh), 6.99 (m, 2H, ArH), 7.14−7.29 (m, 9H, ArH, NH).

Coupling of (*R*)-1 with (*S*)-α-Methylnorvaline Methyl Ester To Produce 8d. Photolysis (47 h) of (*R*)-**1** (126 mg, 0.32 mmol) in 7 mL of THF , at 0 °C, containing (*S*)-α-methylnorvaline methyl ester (39 mg, 0.27 mmol) gave 68 mg (67%) of **8d** as a clear oil after chromatography on silica gel (4:3 hexanes/EtOAc). The de (94%) was determined by integration of the methine quartets (δ 3.35 ppm major, 3.48 ppm minor). ^1H NMR (major diastereoisomer): δ 0.81 (m, 5H, CH_2CH_3), 1.22 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.34 (d, J = 7.3 Hz, 3H, CH_3), 1.47 (m, 1H, C*H*$_2CH_2CH_3$), 1.48 (s, 3H, CH_3), 1.76 (m, 1H, C*H*$_2CH_2CH_3$), 3.35 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.67 (s, 3H, OCH_3), 3.87 (m, 1H, CH_2O), 4.27 (m, 2H, CH_2O, CHPh), 7.25 (m, 3H, ArH), 7.40 (m, 2H, ArH), 7.75 (br s, 1H, NH). ^{13}C NMR: δ 13.9 (CH_3), 14.7 (CH_3), 17.2 (CH_3), 20.8 (CH_3), 22.3 (CH_3), 27.6 (CH_2), 39.5 (CH_2), 52.2 (OCH_3), 55.8 (CHPh), 59.3 (C), 60.4 (CH), 72.4 (CH_2O), 97.1 (C), 127.4, 127.8, 128.8 (Ph), 143.0 (ipso Ph), 173.2 (C=O), 174.4 (C=O). IR (film): ν 3368 (NH), 1738 (C=O), 1674 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.04; H, 8.51; N, 7.44. Found: C, 66.96; H, 8.29; N, 7.45.

Coupling of (*R*)-1 with (*S*)-α-Propylphenylalanine Methyl Ester To Produce 8e. Photolysis (47 h) of (*R*)-**1** (55 mg, 0.14 mmol) in 2 mL of THF, at 0 °C, containing (*S*)-α-propylphenylalanine methyl ester (21 mg, 0.09 mmol) gave 28 mg (68%) of **8e** as a clear oil after chromatography on silica gel (4:3 hexanes/EtOAc). The de (84%) was determined by integration of the singlet of the methoxy group (δ 3.65 ppm major, 3.80 ppm minor). ^1H NMR (major diastereoisomer): δ 0.82 (t, J = 7.2 Hz, 3H, CH_3), 1.06 (m, 2H, C*H*$_2CH_3$), 1.30 (d, J = 7.0 Hz, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.66 (ddd, J = 4.7, 11.8, 13.5 Hz, 1H, C*H*$_2CH_2CH_3$), 1.99 (ddd, J = 4.8, 11.8, 13.6 Hz, 1H, C*H*$_2CH_2CH_3$), 3.11 (s, 2H, CH_2Ph), 3.39 (q, J = 7.3Hz, 1H, C*H*CH_3), 3.65 (s, 3H, OCH_3), 3.74 (dd, J = 6.1, 8.2 Hz, 1H, CH_2O), 4.23 (m, 2H, CHPh, CH_2O), 6.87 (m, 2H, ArH), 7.11 (m, 6H, ArH), 7.31 (m, 2H, ArH), 7.67 (br s, 1H, NH). ^{13}C NMR: δ 14.0 (CH_3), 15.4 (CH_3), 17.4 (CH_3), 21.0 (CH_3), 27.9 (CH_2), 36.4 (CH_2), 40.3 (CH_2-Ph), 52.0 (OCH_3), 56.7 (CHPh), 61.3 (CH), 64.2 (C), 72.4 (CH_2O), 97.1 (C), 126.7, 127.5, 127.6, 128.0, 128.7, 129.8 (Ph), 136.1 (ipso Ph), 142.5 (ipso Ph), 173.5 (C=O), 173.6 (C=O). IR (film): ν 3365 (NH), 1738 (C=O), 1671 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{36}N_2O_4$: C, 71.70; H, 7.96; N, 6.19. Found: C, 71.78; H, 8.09; N, 6.25. ^1H NMR (minor diastereoisomer): δ 0.92 (t, J = 7.3 Hz, 3H, CH_3), 1.13 (d, J = 7.3 Hz, 3H, CH_3), 1.21 (m, 2H, C*H*$_2CH_3$), 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.83 (ddd, J = 4.8, 13.6, 16.4 Hz, 1H, C*H*$_2CH_2CH_3$), 2.43 (ddd, J = 4.3, 13.3, 16.7 Hz, 1H, C*H*$_2CH_2CH_3$), 3.21 (d, J = 13.6 Hz, 1H, CH_2Ph), 3.49 (q, J = 7.3 Hz, 1H, C*H*CH_3), 3.62 (m, 1H, CH_2O), 3.58 (d, J = 13.6 Hz, 1H, CH_2Ph), 3.80 (s, 3H, OCH_3), 4.14 (t, J = 7.9 Hz, 1H, CH_2O), 4.64 (dd, J = 5.4, 7.3 Hz, 1H, CHPh), 6.95 (m, 2H, ArH), 7.06 (br s, 1H, NH), 7.20 (m, 8H, ArH).

Coupling of (*R*)-1 with (*S*)-α-Methylserine Methyl Ester To Produce 8f. Photolysis (24 h) of (*R*)-**1** (36 mg, 0.09 mmol) in 2 mL of THF, at 0 °C, containing (*S*)-α-methylserine methyl ester (10 mg, 0.07 mmol) gave 17 mg (68%) of **8f** as white crystals (mp 129−131 °C) after chromatography on silica gel (1:2 hexanes/EtOAc). The de (86%) was determined by integration of the CH_2O dd (3.90 ppm) of the major diastereoisomer and the CHPh dd (4.53 ppm) of the minor diastereoisomer. ^1H NMR (major diastereoisomer): δ 1.29 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.38 (d, J = 7.3 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.16 (t, J = 6.7 Hz, 1H, OH), 3.39 (m, 2H, C*H*CH_3, C*H*$_2$OH), 3.72 (s, 3H, OCH_3), 3.74 (m, 1H, C*H*$_2$OH), 3.90 (dd, J = 9.7, 12.3 Hz, 1H, CH_2O), 4.27 (m, 2H, CHPh, CH_2O), 7.24 (m, 3H, ArH), 7.41 (m, 2H, ArH), 8.20 (br s, 1H, NH). ^{13}C NMR: δ 14.0 (CH_3), 19.4 (CH_3), 21.1 (CH_3), 27.6 (CH_3), 52.8 (OCH_3), 55.4, 60.3, 61.8, 66.9, 72.4 (CH_2O), 97.0 (C), 127.8, 128.2, 128.7 (Ph), 142.1 (ipso Ph), 173.3 (C=O), 174.6 (C=O). IR (film): ν 3363 (NH) (OH), 1738 (C=O), 1659 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.66; H, 7.69; N, 7.69. Found: C, 62.72; H, 7.49; N, 7.71.

Coupling of (*R*)-9 with 2-Aminoisobutyric Acid Methyl Ester To Produce 10. Photolysis (2 days) of (*R*)-**9** (124 mg, 0.28 mmol) in 5 mL of THF, at 0 °C, containing 2-aminoisobutyric acid methyl ester (27 mg, 0.23 mmol) gave 68 mg (76%) of **10** as a clear oil after chromatography on silica gel (3:1:0.1 hexanes/EtOAc/CH_2Cl_2). ^1H NMR: δ 0.90 (d, J = 6.5 Hz, 3H, CH_3), 0.96 (d, J = 6.5 Hz, 3H, CH_3), 1.16 (s, 6H, CH_3), 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.51 (m, 1H, CH_2), 1.64 (m, 1H, CH_2), 1.78 (m, 1H, CH), 3.27 (t, J = 7.0 Hz, 1H, C*H*CH_2), 3.63 (s, 3H, OCH_3), 3.87 (m, 1H), 4.25 (m, 2H), 7.24 (m, 4H, ArH, NH), 7.40 (m, 2H, ArH). ^{13}C NMR: δ 21.7 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 23.8 (CH_3), 24.6 (CH_3), 25.7 (CH_3), 28.0 (CH_2), 39.7 ($CH(CH_3)_2$), 52.2 (OCH_3), 55.5 (C), 58.1 (CHPh), 60.3 (CH), 72.1 (CH_2O), 96.6 (C), 127.4, 128.9 (Ph), 144.5 (ipso Ph), 173.7 (C=O), 174.7 (C=O). IR (film): ν 3385 (NH), 1739 (C=O), 1672 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.71; H, 8.71; N, 7.18. Found: C, 67.63; H, 8.58; N, 7.20.

Coupling of (*S*)-1 with (*S*)-α-Methylphenylalanine Methyl Ester To Produce 11. Photolysis (2 days) of (*S*)-**1** (119 mg, 0.30 mmol) in 8 mL of THF, at 0 °C, containing (*S*)-α-methylphenylalanine methyl ester (48 mg, 0.25 mmol) gave 81 mg (76%) of **11** as white crystals (mp 92.5−93.5 °C) after chromatography on silica gel (4:3 hexanes/EtOAc). The de (79%) was determined by integration of the doublet of the benzyl group (δ 2.96 ppm major, 3.38 ppm minor). ^1H NMR (major diastereoisomer): δ 1.01 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.39 (d, J = 7.3 Hz, 3H, CH_3), 2.96 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.21 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.58 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.78 (s, 3H, OCH_3), 3.82 (dd, J = 4.8, 6.5 Hz, 1H, CH_2O), 4.20 (m, 2H, CH_2O, CHPh), 6.91 (m, 2H, ArH), 7.16 (m, 6H, ArH), 7.31 (m, 2H, ArH), 8.12 (br s, 1H, NH). ^{13}C NMR: δ 13.0 (CH_3), 21.3 (CH_3), 22.7 (CH_3), 27.0 (CH_3), 41.0 (CH_2Ph), 52.3 (OCH_3), 55.1 (CHPh), 60.1 (CH), 61.2 (C), 72.2 (CH_2O), 96.7 (C), 126.6, 127.5, 128.0, 128.2, 128.6, 129.3 (Ph), 136.8 (ipso Ph), 140.8 (ipso Ph), 172.7 (C=O), 174.1 (C=O). IR (film): ν 3350 (NH), 1739 (C=O), 1672 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.77; H, 7.54; N, 6.60. Found: C, 71.00; H, 7.74; N, 6.59. ^1H NMR (minor diastereoisomer): δ 1.19 (d, J = 7.2 Hz, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.25 (d, J = 13.5 Hz, 1H, CH_2Ph), 3.38 (d, J = 13.6 Hz, 1H, CH_2Ph), 3.52 (q, J = 7.2 Hz, 1H, C*H*CH_3), 3.61 (dd, J = 5.5, 8.4 Hz, 1H, CH_2O), 3.77 (s, 3H, OCH_3), 4.21 (t, J = 8.0

Hz, 1H, CH_2O), 4.40 (dd, J = 5.5, 7.7 Hz, 1H, CHPh), 7.01 (m, 3H, ArH, NH), 7.15−7.29 (m, 8H, ArH).

Coupling of (*S*)-1 with (*S*)-α-Methylnorvaline Methyl Ester To Produce 12. Photolysis (48 h) of (*S*)-**1** (119 mg, 0.30 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-α-methylnorvaline methyl ester (36 mg, 0.25 mmol) gave 67 mg (71%) of **12** as a clear oil after chromatography on silica gel (4:3 hexanes/EtOAc). The de (91%) was determined by integration of the methine quartets of the newly formed stereogenic center (δ 3.33 ppm major, 3.50 ppm minor). ^{1}H NMR (major diastereoisomer): δ 0.80 (m, 4H, CH_2CH_3), 1.03 (m, 1H, CH_2-CH_3), 1.11 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.36 (d, J = 7.3 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.55 (m, 1H, CH_2CH$_2$CH$_3$), 2.11 (m, 1H, CH_2CH$_2$CH$_3$), 3.33 (q, J = 7.2 Hz, 1H, CHCH$_3$), 3.71 (s, 3H, OCH_3), 3.90 (dd, J = 9.6, 11.9 Hz, 1H, CH_2O), 4.26 (m, 2H, CH_2O, CHPh), 7.21 (m, 3H, ArH), 7.39 (m, 2H, ArH), 8.11 (br s, 1H, NH). ^{13}C NMR: δ 13.5 (CH_3), 13.8 (CH_3), 17.5 (CH_3), 21.0 (CH_3), 22.5 (CH_3), 27.6 (CH_2), 37.7 (CH_2), 52.3 (OCH_3), 55.0 (CHPh), 59.8 (C), 60.1 (CH), 72.4 (CH_2O), 96.8 (C), 127.5, 128.4 (Ph), 141.7 (ipso Ph), 172.6 (C=O), 174.9 (C=O). IR (film): ν 3352 (NH), 1736 (C=O), 1674 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.04; H, 8.51; N, 7.44. Found: C, 67.02; H, 8.24; N, 7.48. ^{1}H NMR (minor diastereoisomer): δ 0.86 (t, J = 7.2 Hz, 3H, CH_3), 1.03 (m, 1H, CH_2CH$_3$), 1.07 (m, 1H, CH_2CH$_3$), 1.20 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.46 (d, J = 4.5 Hz, 3H, CH_3), 1.69 (ddd, J = 5.0, 13.6, 18.3, 1H, CH_2CH$_2$CH$_3$), 2.02 (ddd, J = 4.6, 12.2, 16.3, 1H, CH_2CH$_2$CH$_3$), 3.50 (q, J = 7.2 Hz, 1H, CHCH$_3$), 3.71 (s, 3H, OCH_3), 3.71 (m, 1H, CH_2O), 4.34 (t, J = 8.1 Hz, 1H, CH_2O), 4.62 (dd, J = 4.9, 7.4 Hz, 1H, CHPh), 6.98 (br s, 1H, NH), 7.18−7.40 (m, 5H, ArH).

Coupling of (*S*)-1 with (*S*)-α-Propylphenylalanine Methyl Ester To Produce 13. Photolysis (49 h) of (*S*)-**1** (43 mg, 0.11 mmol) in 2 mL of THF, at 0 °C, containing (*S*)-α-propylphenylalanine methyl ester (16 mg, 0.07 mmol) gave 17 mg (53%) of **13** as a clear oil after chromatography on silica gel (2:1 hexanes/EtOAc). The de (82%) was determined by integration of the singlets of the oxazolidine geminal CH_3 groups (δ 1.18 ppm major, 1.21 ppm minor). ^{1}H NMR (major diastereoisomer): δ 0.24 (m, 1H, CH_2CH$_3$), 0.42 (m, 1H, CH_2CH$_3$), 0.61 (t, J = 7.2 Hz, 3H, CH_3), 0.80 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.39 (d, J = 7.3 Hz, 3H, CH_3), 1.62 (ddd, J = 4.5, 12.7, 17.2 Hz, 1H, CH_2CH$_2$CH$_3$), 2.23 (ddd, J = 4.6, 12.5 , 17.3 Hz, 1H, CH_2CH$_2$CH$_3$), 3.04 (d, J = 13.6 Hz, 1H, CH_2Ph), 3.20 (q, J = 7.3 Hz, 1H, CHCH$_3$), 3.66 (d, J = 13.6 Hz, 1H, CH_2Ph), 3.74 (dd, J = 5.6, 7.8 Hz, 1H, CH_2O), 3.82 (s, 3H, OCH_3), 4.19 (m, 2H, CHPh, CH_2O), 6.93 (m, 2H, ArH), 7.16 (m, 6H, ArH), 7.34 (m, 2H, ArH), 8.07 (br s, 1H, NH). ^{13}C NMR: δ 13.7 (CH_3), 13.9 (CH_3), 17.3 (CH_3), 20.8 (CH_3), 26.8 (CH_2), 37.8 (CH_2), 40.8 (CH_2Ph), 52.3 (OCH_3), 56.0 (CHPh), 60.6 (CH), 66.0 (C), 72.6 (CH_2O), 97.1 (C), 126.7, 127.2, 128.2, 128.7, 129.5 (Ph), 136.8 (ipso Ph), 142.0 (ipso Ph), 173.2 (C=O), 173.7 (C=O). IR (film): ν 3348 (NH), 1737 (C=O), 1669 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{36}N_2O_4$: C, 71.70; H, 7.96; N, 6.19. Found: C, 71.85; H, 8.06; N, 6.21. ^{1}H NMR (minor diastereoisomer): δ 0.83 (t, J = 7.2 Hz, 3H, CH_3), 1.05 (m, 2H, CH_2CH$_3$), 1.18 (d, J = 3.4 Hz, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.76 (m, 1H, CH_2CH$_2$CH$_3$), 2.43 (m, 1H, CH_2CH$_2$CH$_3$), 3.23 (d, J = 13.7 Hz, 1H, CH_2Ph), 3.57 (m, 2H, CHCH$_3$, CH_2O), 3.68 (d, J = 13.7 Hz, 1H, CH_2Ph), 3.83 (s, 3H, OCH_3), 4.13 (t, J = 7.9 Hz, 1H, CH_2O), 4.26 (dd, J = 5.5, 7.4 Hz, 1H, CHPh), 7.01 (m, 2H, ArH), 7.22 (m, 8H, ArH), 7.36 (br s, 1H, NH).

Coupling of (*R*)-1 with *N*-Methyl-(*S*)-alanine Methyl Ester To Produce 15 and 16. Photolysis (74 h) of (*R*)-**1** (312 mg, 0.79 mmol) in 8 mL of THF, at 0 °C, containing *N*-methyl-(*S*)-alanine methyl ester (77 mg, 0.66 mmol) gave 142 mg (62%) of **15** as white crystals (mp 112−113 °C) and 30 mg (13%) of **16** as a clear oil after chromatography on silica gel (1:1 hexanes/EtOAc). The de (71%) was determined by integration of the singlet of the *N*-methyl group (δ 3.06 ppm major, 2.91 ppm minor). ^{1}H NMR (major diastereoisomer): δ 1.04 (d, J = 7.3 Hz, 3H, CH_3), 1.28 (d, J = 6.4 Hz, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 3.68 (dd, J = 5.4, 8.3 Hz, 1H, CH_2O), 4.04 (q, J = 6.3 Hz, 1H, CHCH$_3$), 4.25 (t, J = 8.2 Hz, 1H, CH_2O), 4.45 (dd, J = 5.3, 8.0 Hz, 1H, CHPh), 4.85 (q, J = 7.3 Hz, 1H, CHCH$_3$), 7.13−7.28 (m, 5H, ArH). ^{13}C NMR: δ 13.8 (CH_3), 14.3 (CH_3), 23.8 (CH_3), 28.3 (CH_3), 30.7 (CH_3), 51.9, 52.0, 53.5, 60.8 (CH), 71.1 (CH_2O), 97.1 (C). 126.5, 128.0 (Ph), 144.7 (ipso Ph), 172.2 (C=O), 172.6 (C=O). IR (film): ν 1742 (C=O), 1649 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.54; H, 8.04; N, 8.04. Found: C, 65.61; H, 8.22; N, 8.25. ^{1}H NMR (minor diastereoisomer): δ 1.09 (d, J = 7.2 Hz, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.32 (d, J = 7.3 Hz, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.91 (s, 3H, NCH_3), 3.67 (s, 3H, OCH_3), 3.70 (dd, J = 4.1, 8.2 Hz, 1H, CH_2O), 3.83 (q, J = 6.6 Hz, 1H, CHCH$_3$), 4.33 (t, J = 7.5 Hz, 1H, CH_2O), 5.13 (q, J = 7.3 Hz, 1H, CHCH$_3$), 5.30 (dd, J = 3.9, 7.1 Hz, 1H, CHPh), 7.17−7.42 (m, 5H, ArH).

Coupling of (*S*)-1 with *N*-Methyl-(*S*)-alanine Methyl Ester To Produce 17 and 18. Photolysis (57 h) of (*S*)-**1** (332 mg, 0.84 mmol) in 9 mL of THF, at 0 °C, containing *N*-methyl-(*S*)-alanine methyl ester (82 mg, 0.70 mmol) gave 152 mg (62%) of **17** and 41 mg (17%) of **18** as clear oils after chromatography on silica gel (4:3 hexanes/EtOAc). The major diastereoisomer existed as an inseparable mixture of cis and trans rotamers about the C−N bond (ratio 7:3). The de (63%) was determined by integration of the singlet of the *N*-methyl group (δ 2.44, 3.14 ppm major, 2.89 ppm minor). ^{1}H NMR (major diastereoisomer): δ 1.16 (s, 0.9H, CH_3), 1.18 (d, J = 7.2 Hz, 2.1H, CH_3), 1.18 (s, 0.9H, CH_3), 1.24 (d, J = 7.1 Hz, 0.9H, CH_3), 1.30 (d, J = 6.4 Hz, 0.9H, CH_3), 1.35 (s, 2.1H, CH_3), 1.42 (d, J = 4.7 Hz, 2.1H, CH_3), 1.46 (s, 2.1H, CH_3), 2.44 (s, 0.9H, NCH_3), 3.14 (s, 2.1H, NCH_3), 3.59 (s, 2.1H, OCH_3), 3.64 (dd, J = 6.1, 8.2 Hz, 0.7H, CH_2O), 3.68 (s, 0.9H, OCH_3), 3.76 (dd, J = 4.9, 8.5 Hz, 0.3H, CH_2O), 3.87 (q, J = 6.4 Hz, 0.3H, CHCH$_3$), 4.00 (q, J = 6.5 Hz, 0.7H, CHCH$_3$), 4.20 (m, 1H), 4.38 (m, 1H), 4.71 (q, J = 7.2 Hz, 0.7H, CHCH$_3$), 5.09 (q, J = 7.0 Hz, 0.3H, CHCH$_3$), 7.11−7.33 (m, 5H, ArH). ^{13}C NMR: δ 13.8 (CH_3), 14.8, 15.5 (CH_3), 23.0, 24.1 (CH_3), 28.1, 28.3 (CH_3), 32.1 (CH_3), 51.8, 52.2, 52.4, 53.2, 53.6, 54.8, 59.8, 62.1 (CH), 71.0 (CH_2O), 96.7, 97.1 (C), 126.4, 126.7, 127.0, 127.8, 128.0 (Ph), 143.9, 144.5 (ipso Ph), 171.6, 171.9 (C=O), 172.3, 172.4 (C=O). IR (film): ν 1744 (C=O), 1651 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.54; H, 8.04; N, 8.04. Found: C, 65.80; H, 7.79; N, 8.16. ^{1}H NMR (minor diastereoisomer): δ 1.12 (d, J = 7.1 Hz, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.34 (d, J = 7.3 Hz, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.89 (s, 3H, NCH_3), 3.64 (s, 3H, OCH_3), 3.71 (dd, J = 4.1, 8.1 Hz, 1H, CH_2O), 3.82 (q, J = 7.0 Hz, 1H, CHCH$_3$), 4.30 (t, J = 7.4 Hz, 1H, CH_2O), 5.13 (q, J = 7.3 Hz, 1H, CHCH$_3$), 5.28 (dd, J = 4.2, 7.1 Hz, 1H, CHPh), 7.24 (m, 3H, ArH), 7.40 (m, 2H, ArH).

Coupling of (*R*)-1 with *N*-Methyl-2-aminoisobutyric Acid Methyl Ester To Produce 22. Photolysis (42 h) of (*R*)-**1** (166 mg, 0.42 mmol) in 5 mL of THF, at 0 °C, containing *N*-methyl-2-aminoisobutyric acid methyl ester (46 mg, 0.35 mmol) gave 61 mg (48%) of **22** as a white solid (mp 128−129 °C) after chromatography on silica gel (1:1:0.1 hexanes/EtOAc/CH_2Cl_2). The de (73%) was determined by integration of the singlet of the *N*-methyl group (δ 3.15 ppm major, 2.93 ppm minor). ^{1}H NMR (major diastereoisomer): δ 0.98 (s, 3H, CH_3), 1.17 (d, J = 6.5 Hz, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.15 (s, 3H, NCH_3), 3.46 (s, 3H, OCH_3), 3.62 (dd, J = 5.6, 8.3 Hz, 1H, CH_2O), 3.95 (q, J = 6.5 Hz, 1H, CHCH$_3$), 4.23 (t, J = 8.3 Hz, 1H, CH_2O), 4.40 (dd, J = 5.5, 8.1 Hz, 1H, CHPh), 7.14−7.29 (m, 5 H, ArH). ^{13}C NMR: δ 15.1 (CH_3), 21.5 (CH_3), 23.0 (CH_3), 23.3 (CH_3), 28.0 (CH_3), 29.6 (CH_3), 51.6 (OCH_3), 55.8, 60.5, 61.8 (CH), 71.1 (CH_2O), 97.2 (C), 126.4, 126.6, 128.0 (Ph), 144.9 (ipso Ph), 171.6 (C=O), 174.5 (C=O). IR (film): ν 1742 (C=O), 1646 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.32; H, 8.28; N, 7.73. Found: C, 66.11; H, 8.20; N, 7.56. ^{1}H NMR (minor diastereoisomer): δ 1.08 (d, J = 7.1 Hz, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.93 (s, 3H, NCH_3), 3.63 (s, 3H, OCH_3), 3.70 (dd, J = 3.8, 8.1 Hz, 1H, CH_2O), 3.77 (q, J = 7.1 Hz, 1H, CHCH$_3$), 4.29 (t, J = 8.3 Hz, 1H, CH_2O), 5.22 (dd, J = 3.8, 6.9 Hz, 1H, CHPh), 7.19−7.40 (m, 5 H, ArH).

General Procedure for the Synthesis of Diketopiperazines. The oxazolidine-protected dipeptide was stirred in a 1:1:1 mixture of THF/MeOH/0.2 N HCl (0.04 M solution) until the starting material was consumed (TLC, 1:1 EtOAc/hexanes). The reaction mixture was concentrated *in vacuo*, and the residue was neutralized with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 × 15 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 methanol and added to a pressure tube containing one weight equivalent of $Pd(OH)_2$/C. The reaction was pressurized to 50 psi with hydrogen and heated to 50 °C in an oil bath. After the

hydrogenation was complete (6−7 h), 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 methanol and ethyl acetate, and the filtrate was concentrated in vacuo to give the crude diketopiperazine.

Synthesis of 19. The above general procedure was applied to protected dipeptide **15** (70 mg, 0.20 mmol). Chromatography on silica gel (5% $MeOH/CH_2Cl_2$) afforded 21 mg (68%) of **19** as a clear oil. ^1H NMR: δ 1.47 (d, J = 7.1 Hz, 3H, CH_3), 1.51 (d, J = 7.0 Hz, 3H, CH_3), 2.93 (s, 3H, NCH_3), 3.83 (q, J = 7.0 Hz, 1H, C*H*CH_3), 4.04 (dq, J = 3.0, 6.9 Hz, 1H, C*H*CH_3), 7.46 (br s, 1H, NH). ^{13}C NMR: δ 18.9 (CH_3), 22.1 (CH_3), 32.2 (CH_3), 51.3 (CH), 57.7 (CH), 166.7 (C=O), 169.1 (C=O). IR (film): ν 3216 (NH), 1646 (C=O) cm^{-1}.

Synthesis of 20. The above general procedure was applied to protected dipeptide **17** (104 mg, 0.30 mmol). Chromatography on silica gel (5% $MeOH/CH_2Cl_2$) afforded 37 mg (79%) of **20** as a clear oil. ^1H NMR: δ 1.43 (d, J = 3.4 Hz, 3H, CH_3), 1.45 (d, J = 3.3 Hz, 3H, CH_3), 2.92 (s, 3H, NCH_3), 3.83 (q, J = 6.8 Hz, 1H, C*H*CH_3), 4.02 (q, J = 6.9 Hz, 1H, C*H*CH_3), 7.67 (br s, 1H, NH). ^{13}C NMR: δ 16.9 (CH_3), 18.1 (CH_3), 32.2 (CH_3), 49.5 (CH), 58.6 (CH), 167.0 (C=O), 170.0 (C=O). IR (film): ν 3095 (NH), 1661 (C=O) cm^{-1}.

According to the general procedure, diketopiperazine **20** (14 mg, 52%) was also obtained by deprotection of dipeptide **16** (59 mg, 0.17 mmol). This material was identical in all respects to that from dipeptide **17**.

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