IR (KBr) 3450, 1680 $cm^{-1}$. Anal. Found: C, 81.15; H, 8.35; N, 4.80.

**1,4-Naphthalenedicarbonitrile (NDN) and DMB.** After 16 h (solvent is now a mixture of 100 mL of cyclohexane and 50 mL of benzene), the following adducts were obtained.

**1,6-Dicyano-3,4-dimethyl-7,8-benzobicyclo[4.2.2]deca-3,7,9-triene (24)** (8%): colorless crystals; mp 75–78 °C (from cyclohexane); NMR ($CDCl_3$) δ 7.3–7.7 (AA'BB' system, aromatics), 6.53 (s, H-9 and H-10), 2.9 (2 identical AB systems, methylene groups), 1.45 (s, 2 $CH_3$) groups); IR (KBr) 2230, 1570, 1510, 1390, 1370, 1232, 1222, 850, 792, 750 $cm^{-1}$. Anal. Found: C, 83.25; H, 6.25; N, 10.60. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.25; H, 6.25; N, 10.60.

**3,6-Dicyano-1-methyl-1-(2-propenyl)-2,3-dihydrobenzocyclooctene (22)** (26%): colorless crystals; mp 85–7 °C (from methanol); NMR ($CDCl_3$) δ 9.65 (dd, 1 arom H), 8.3 (dd, 1 arom H), 7.7–7.9 (m, 2 arom H), 7.95 (d, $J$ = 7.5 Hz), and 7.6 (d, H-4 and H-5), 5.2 (s, $=CH_2$), 4.2 (AB system, $CH_2$ at position 2), 1.85 (allylic $CH_3$), 1.67 (s, $CH_3$); IR (KBr) 2215, 1637, 1550, 1510, 905, 895, 832, 778, 768 $cm^{-1}$; UV (cyclohexane) $\lambda_{max}$ 248 nm (log ε 4.37), 3.27 (3.9), 355 (3.85). Anal. Found: C, 82.90; H, 6.10; N, 10.65.

**Other Photochemical Reactions.** Irradiation of both 1-NN or 2-NN in cyclohexane in the presence of 0.1 M 2,5-dimethylfuran (DMFU) for 15 h and workup as above led to complete recovery of the nitrile. The same result was achieved from the irradiation of NDN in cyclohexane or benzene with either CH, DMH, or DMFU. Some results from the irradiation in acetonitrile are also reported in Table I.

**Quantitative Measurements.** Fluorescence spectra were measured by means of an Aminco-Bowman MPF spectrophotometer. Fluorescence intensities and photochemical quantum yield were measured in 1-cm optical path cells after deoxygenation by means of five freeze–degas–thaw cycles. The photochemical reaction was effected with 313-nm radiation (intensity ca. $10^{-7}$ Einstein $min^{-1}$ $cm^{-2}$) obtained from a high-pressure mercury arc (150 W) focused through a quartz lens and filtered by means of an interference filter ($\Delta\lambda_{1/2}$ = 5 nm). Products were assayed by HPLC.

**Acknowledgment.** We thank CNR (Rome) for financial support.

**Registry No.** 1, 116808-76-5; 2, 116907-32-5; 3, 116808-77-6; 4, 116808-78-7; 5, 116808-79-8; 7, 116808-80-1; 8, 116808-81-2; 9, 116908-86-2; 10, 116808-82-3; 11, 116808-83-4; 12, 116808-84-5; 13, 116808-85-6; 15, 116808-86-7; 16, 116808-87-8; 17, 116808-88-9; 18, 116808-89-0; 19, 116808-90-3; 20, 116808-91-4; 22, 116808-92-5; 24, 116808-93-6; DMB, 513-81-5; CH, 592-57-4; DMH, 764-13-6; DMFU, 625-86-5; 1-NN, 86-53-3; 2-NN, 613-46-7; NDN, 3029-30-9.

# Efficient and Versatile Synthesis of Dipeptide Isosteres Containing γ- or δ-Lactams[1]

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Independent five-step syntheses of γ- and δ-lactam-containing dipeptide isosteres, starting from the known compound, (4*S*)-3-(carbobenzyloxy)-4-(phenylmethyl)-5-oxooxazolidine (**3**), are reported. Alkylation of **3** with allyl bromide provided the corresponding 4-allyl-substituted oxazolidinone (**5**), which served as a common intermediate for each lactam series. In general terms, **5** was converted to the homologous aldehydes (**7** and **19**) by manipulating the terminal vinyl group. Reductive amination of the aldehydes with the methyl ester hydrochloride salts of L-alanine, L-phenylalanine, and L-histidine furnished the corresponding amino diesters, which were converted, by thermally induced lactam closures, to the γ- and δ-lactam-containing dipeptide isosteres in 46–59% and 32–33% respective overall yields from **3**. The resulting isosteres were diastereomeric mixtures at the lactam quaternary center. Selective deprotection was accomplished at either terminus by base hydrolysis or catalytic hydrogenolysis. A survey of standard solution phase peptide couplings revealed that addition of appropriately protected amino acid residues could be efficiently carried out at each terminus.

Considerable effort has been expended on the design and synthesis of peptide isosteres, which provide enhanced activity, selectivity, and stability to pharmacologically important peptides.[3] During the course of our work on inhibition of aspartic proteinases, we required a dipeptide isostere for the Phe-His portion of a series of compounds with the general formula **1**. Our specific goal was to maintain the potency while stabilizing the Phe-His amide bond to proteolytic cleavage by the putative enzyme chymotrypsin.[4] Molecular modeling suggested that the Phe-His conformation, as depicted in Figure 1, was important for the maintenance of good binding potency. The syn-periplanar relationship between the histidine NH and the phenylalanine α-methine led us to investigate lactams **2** (eq 1) as suitable dipeptide isosteres. We were further encouraged to pursue the lactams since it is known that amide bonds which are prone to chymotrypsin cleavage are stabilized by methylation of the α-carbon or of the amide nitrogen on either side of the susceptible carboxyl moiety.[5] Both design features are incorporated into the lactam-containing dipeptide isosteres, which suggested this would be a fruitful line of investigation.

A concise synthesis that delivers a *d,l*-mixture at the quaternary lactam center ($n$ = 2) has been recently described.[6] We, however, wished to develop a general synthesis that was capable of producing a single diastereomer

(1) This paper is warmly dedicated to Professor Richard K. Hill on the occasion of his 60th birthday.

(2) Author to whom correspondence should be addressed.

(3) For reviews please see: (a) Fauchere, J.-L. In *Advances in Drug Research*; Testa, B., Ed.; Academic: New York, 1986; Vol. 15, pp 29–69. (b) Goodman, M. *Biopolymers* **1985**, *24*, 137–155. (c) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*(1). (d) Hruby, V. J. *Life Sci.* **1982**, *31*, 189. (e) Spatola, A. F. *Proteins* **1983**, *7*, 267.

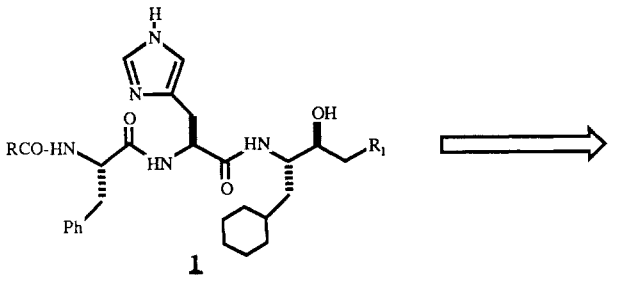
(4) Previous work from our laboratory identified chymotrypsin as the most likely candidate for the proteolysis of the Phe-His amide bond; Rosenberg, S. H.; Plattner, J. J.; Woods, K. W.; Stein, H. H.; Marcotte, P. A.; Cohen, J.; Perun, J. J. *J. Med. Chem.* **1987**, *30*, 1224.

(5) Blow, D. M. In *The Enzymes*; Academic: New York, 1971, Vol. III, Chapter 6, p 185.

(6) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631.

(7) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *79*, 5736.

0022-3263/88/1953-5607$01.50/0 



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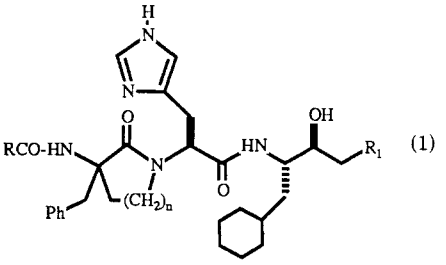


2 (n = 1,2)

at the quaternary center and was amenable to preparing a series of homologous lactams (i.e., where $n$ = 1, 2, 3, ...). Scheme I outlines the general synthetic strategy we developed to meet these criteria. When the synthesis is carried out with the unsubstituted oxazolidinone (**3**, $R_1$ = H), the final lactams are *d,l*-mixtures at the lactam quaternary center. However, when the substituted oxazolidinone (**4**, $R_1$ = Ar) is employed, one may prepare the final lactams enantioselectively.[8]

We elected to initially pursue the *d,l*-synthesis as it was desirable to test both lactam diastereomers. In the following text we will describe how the synthetic strategy in Scheme I was reduced to practice, thus providing a concise and efficient synthesis of dipeptide isosteres containing γ- and δ-lactams. Additionally, model coupling reactions at the carboxyl and nitrogen termini of each dipeptide isostere are described.

**γ-Lactam Synthesis.** Scheme II summarizes the synthesis of the γ-lactam dipeptide isosteres. The known oxazolidinone (**3**) was prepared according to the method of Ben-Ishai[7] from *N*-(carbobenzyloxy)-L-phenylalanine and paraformaldehyde. Via the precedent of Karady,[8] **3** was converted to the corresponding potassium enolate and alkylated with allyl bromide to provide **5**[9] in a 76% yield.[10] Basic hydrolysis, acidification, and treatment with excess diazomethane converted **5** to **6** (91%). The sequence, **3** to **6**, was completed more efficiently (76% overall) by omitting purification of the intermediate **5**. Oxidative cleavage of the terminal olefin with excess ozone and reduction of the ozonide with methyl sulfide provided the aldehyde **7** quantitatively. The aldehyde could be stored under anhydrous conditions in the cold ($T \cong 10$ °C) for up to 2 months before significant decomposition could be detected.

Reductive amination was completed, utilizing a slight modification of the method of Borch.[11] Thus, a methanol solution of aldehyde **7** was treated with the hydrochloride salt of the desired amino acid ester in the presence of anhydrous sodium acetate, sodium cyanoborohydride, and freshly activated 4 Å sieves. The reaction was complete, typically in 1–3 h, to provide the desired amino diesters (**8**, **9**, or **10**) and varying amounts of the corresponding lactams (**11**, **12**, or **13**). The unpurified mixture was converted to a mixture of the diastereomeric lactams (**11–13**) by heating the amino diesters (**8–10**) at 100 °C in equal volumes of dry dimethoxyethane and toluene (concentration, ca. 0.1 M) in the presence of 1-hydroxybenzotriazole[12] (HOBT, 1.0 equiv) in a resealable tube (3–5 h). The overall yields for the sequential reductive aminations and γ-lactam closures are recorded in Table I. Following this five-step procedure, the known oxazolidinone, **3**,[7] was converted to the γ-lactams **11**, **12**, and **13** in 60%, 78%, and 66% overall yields, respectively.

**δ-Lactam Synthesis.** Our initial attempts to prepare the analogous δ-lactams began with the conversion of **6** to **14**, the homologous aldehyde of **7** (eq 2). Hydroboration of **6** with 9-BBN (1.5 equiv in THF, 12 h, room temperature) and subsequent oxidation (PCC, $CH_2Cl_2$) provided

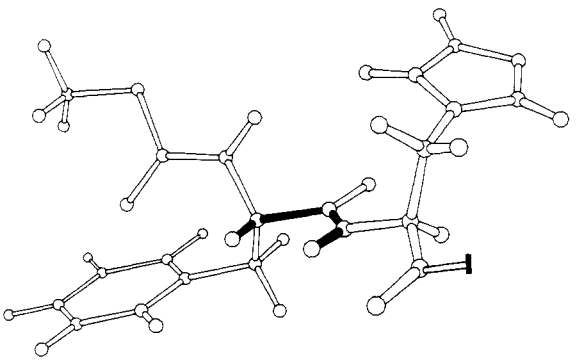
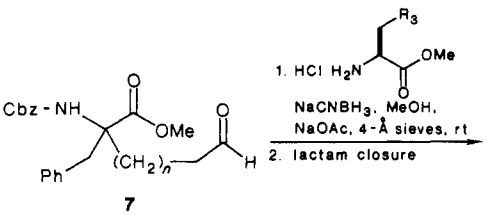


**Figure 1.** Computer-generated partial structure (Boc-Phe-His) of generic inhibitor **1** in the enzyme binding cleft.

**Table I. Overall Yields for Reductive Amination and Lactam Formation**



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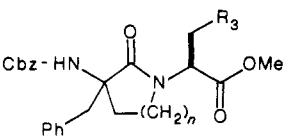


| compd | $n$ | lactam closure method[a] | $R_3$ | yield, % |
|---|---|---|---|---|
| **11** | 1 | A | H | 60 |
| **12** | 1 | A | phenyl | 78 |
| **13** | 1 | A | 4-imidazolyl | 66 |
| **24** | 2 | B | H | 66 |
| **25** | 2 | B | phenyl | 55 |
| **26** | 2 | C | 4-imidazolyl | 60 |

[a] Lactam closure methods: A = 1:1 DME/$PhCH_3$, HOBt, 100 °C; B = NaOAc (10 equiv), MeOH, reflux; C = isopropylamine (5 equiv), MeOH, reflux.

(8) Karady, S.; Amato, J. S.; Weinstock, L M. *Tetrahedron Lett.* **1984**, *25*, 4337.

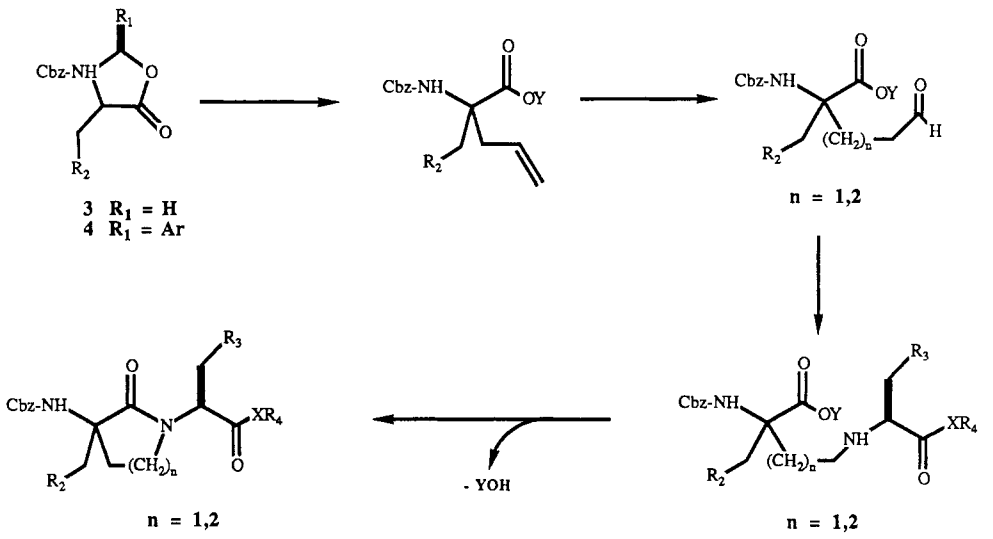
(9) (a) Proton and/or carbon NMR spectra of this compound demonstrated line broadening and/or doubling of signals. This is presumably due to hindered rotation induced by the quaternary center. (b) Refer to the Experimental Section for further details.

(10) Yields reported in the text refer to purified substances obtained after chromatography or recrystallization, unless noted otherwise.

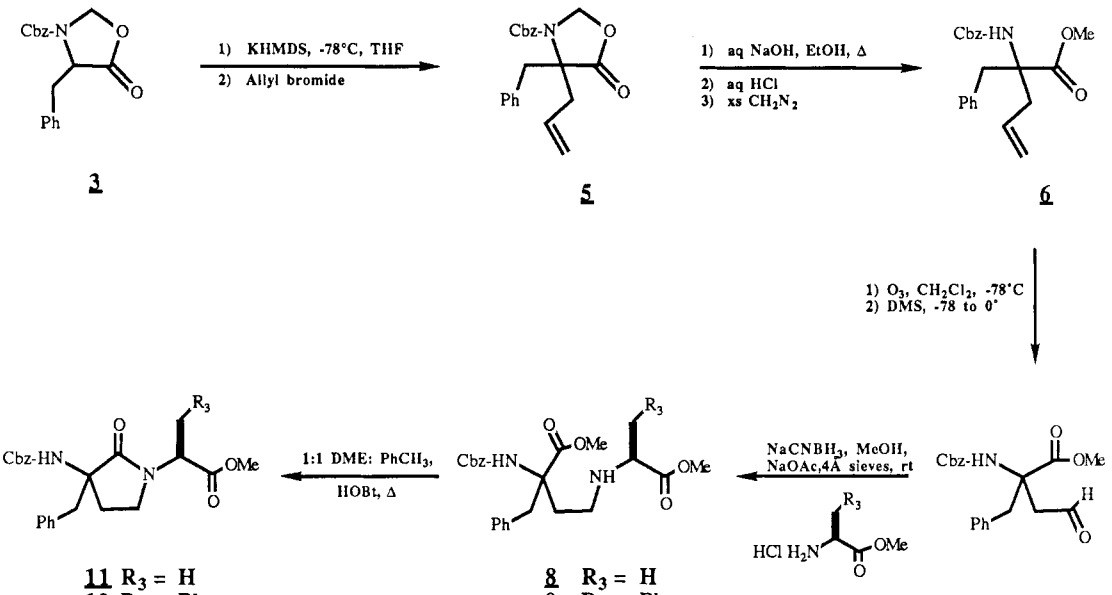
(11) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(12) Qualitative comparison of the time necessary for complete reaction with and without 1-hydroxybenzotriazole (HOBT) indicated that the HOBT catalyzed the lactam closure, giving shorter reaction times (3–5-fold) as compared to the uncatalyzed reactions.

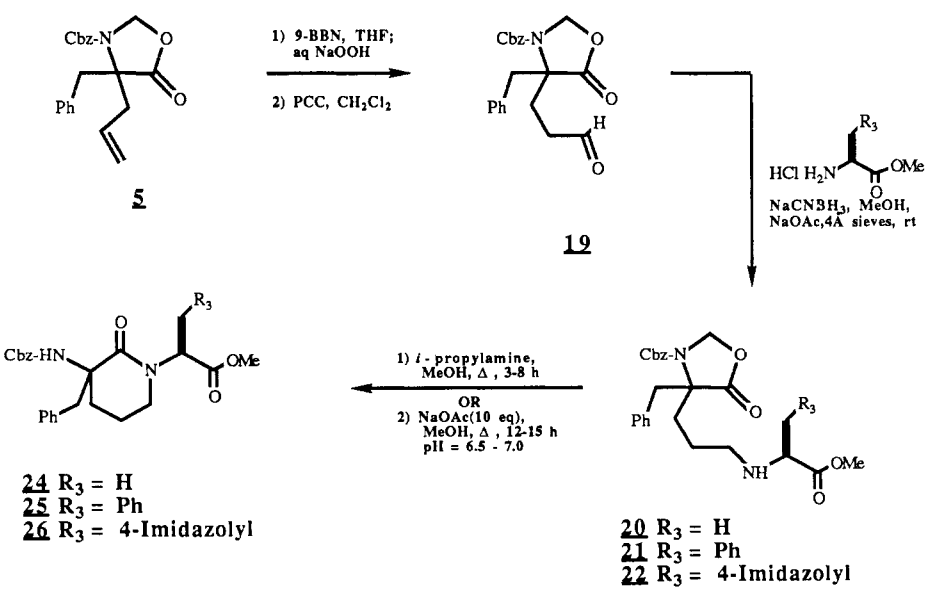
**Scheme I**

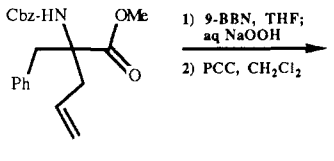



**Scheme II**




**Scheme III**



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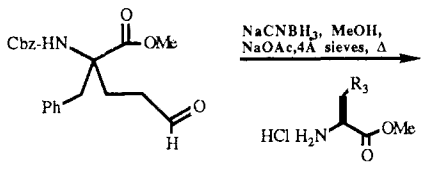
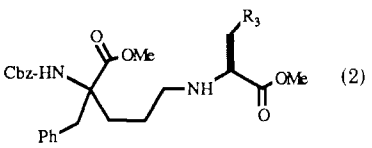



14




(2)

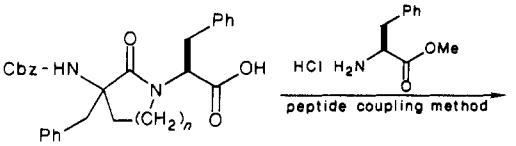
15 $R_3$ = H
16 $R_3$ = Ph

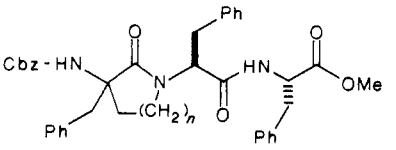
the aldehyde **14**, which, as before, was utilized without further purification. When **14** was submitted to the previously described reductive amination conditions, the desired amino diesters **15** or **16** were formed in modest yields and only after refluxing in methanol for 18 h, in stark contrast to the mild conditions for reductive amination of **7** (room temperature, 1–3 h). This divergence in reactivity appears to be the result of the rapid conversion of **14** to hemiaminal **17**, which is catalyzed by the amino acid ester hydrochloride salt.[13,14] Formation of **17** effectively renders **14** unavailable for reductive amination (except in low equilibrium concentrations) and leads to the observed slow rate for the conversion of **14** to **15** or **16**.[15]

It was clear that temporary blocking of the urethane NH was necessary to mitigate the intramolecular hemiaminal formation during the reductive amination. We turned our attention to the allylated oxazolidinone, **5**, which offered the opportunity to expose the necessary aldehyde in the absence of the urethane NH and, additionally, might serve as the immediate precursor to the lactam closure. This proved to be the case, and after further investigation the chemistry summarized in Scheme III was developed to provide the corresponding δ-lactams.

The sequence began with the hydroboration of **5** (1.5 equiv of 9-BBN in THF, 12 h, room temperature) to give the alcohol (**18**, 74%), and subsequent oxidation of the alcohol (PCC, $CH_2Cl_2$) furnished the unpurified aldehyde **19** in an 80% yield. Submission of **19** to reductive amination with the methyl ester hydrochloride salts of L-alanine, L-phenylalanine, and L-histidine resulted in the smooth conversion to the desired amino diesters **20**, **21**, and **22** (1–3 h, 25 °C).

**Table II. Yields for C-Terminal Coupling to the Dipeptide Isosteres**

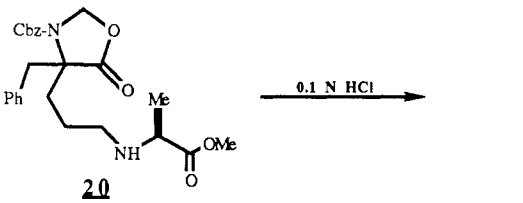


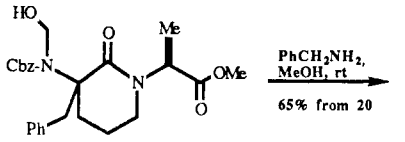

| starting material | product | n | coupling method[a] | yield, % |
|---|---|---|---|---|
| 29 | 31 | 1 | A | 83 |
| 29 | 31 | 1 | B | 88 |
| 29 | 31 | 1 | C | 66 |
| 30 | 32 | 2 | B | 73 |
| 30 | 32 | 2 | C | 70 |

[a] Coupling methods: A = mixed anhydride; B = water-soluble carbodiimide; C = BOP-Cl.

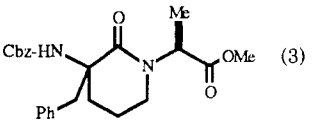
Attempts to close the amino diesters **20** or **21** to the corresponding δ-lactams under the previously described conditions (1:1 DME/$PhCH_3$, 1.0 equiv of HOBT, 100 °C) gave no reaction after extended reaction times. There was good precedent from the recent work of Schollkopf[16] that acid catalysis might lead to the desired lactam closure. Exposure of **20** to aqueous hydrochloric acid (0.1 N) following by deformylation of **23** with benzylamine in methanol lead to an excellent overall yield of the diastereomeric lactams **24** (65%) (eq 3). However, this proved




20




23




(3)

24

not to be a general method, and little or no lactam was formed when **21** was exposed to a variety of aqueous and anhydrous acidic media.

At this juncture, a survey of amine bases was undertaken, and much to our delight it was discovered that primary amines, such as benzylamine or isopropylamine

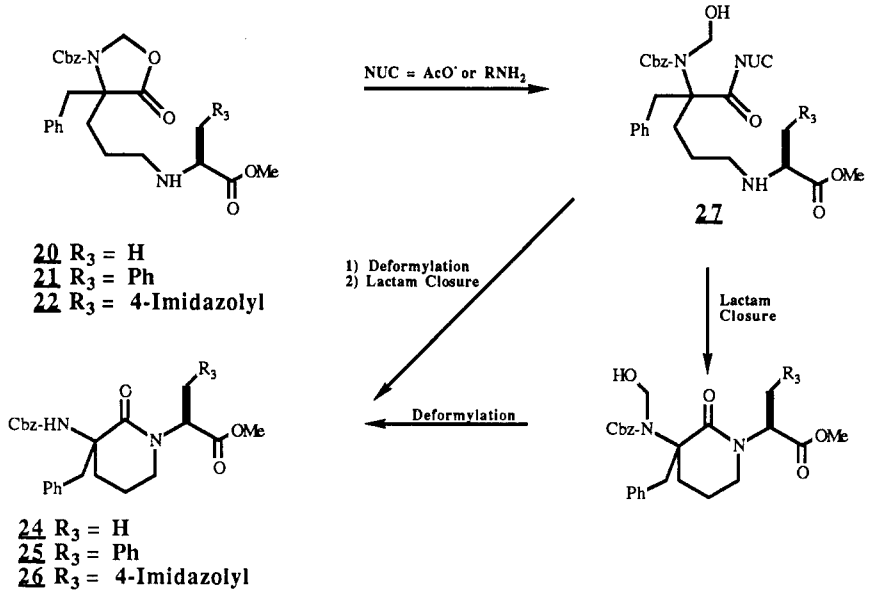
(13) Formation of hemiaminals from secondary amides and formaldehyde equivalents is known to occur under acid catalysis: Saugg, H. E.; Martin, W. B. In *Organic Reactions*; Cope, A. C., Ed.; Robert E. Krieger: Huntington, NY, 1978; Vol. 14, pp 52–269; especially Table XX, p 174.

(14) To substantiate this suggestion an $^1H$ NMR spectrum of **14** in $CDCl_3$ was obtained; subsequently, a single crystal of *p*-toluenesulfonic acid was added to the same solution which resulted in the complete and immediate consumption of the aldehyde absorption at δ 9.24. Analysis of the same solution by TLC (5% methanol/chloroform) indicated two spots $R_f$ 0.64 and 0.52. The more mobile spot ($R_f$ 0.64) had the same $R_f$ as **14**. These results are consistent with the formation of the cyclic hemiaminal **17**, as a pair of diastereomers, which is undoubtedly facilitated by the intramolecular disposition of the two reactive functionalities.

(15) Amino diesters **15** and **16** were submitted to the conditions for γ-lactam closure (1:1 DME/$PhCH_3$, HOBT, 100 °C). In each instance the reactions could not be driven to completion, the yields were low, and the resulting δ-lactams were enriched in one of the diastereomers. This provided additional cause to seek an alternative route to the δ-lactams.

(16) Schollkopf, U.; Busse, U.; Lonsky, R.; Hinrichs, R. *Justus Liebigs. Ann. Chem.* **1986**, 2150.

**Scheme IV**



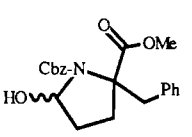

20 $R_3$ = H
21 $R_3$ = Ph
22 $R_3$ = 4-Imidazolyl

24 $R_3$ = H
25 $R_3$ = Ph
26 $R_3$ = 4-Imidazolyl

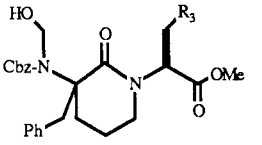
(5 equiv) catalyzed the lactam closure of amino diesters **20**, **21**, and **22**. Further experimentation revealed that excess sodium acetate (10 equiv) in refluxing methanol (the apparent pH of the solution was adjusted to 6.5–7 with glacial acetic acid (1–3 drops) as judged by spotting the reaction mixture on moist pH paper) also led to efficient lactam formation from **20** and **21**. The sodium acetate catalyzed lactam closure provided lower yields of **26** (vide infra) as compared to the isopropylamine catalyzed closure. Yields for the conversion of aldehyde **19** to the corresponding δ-lactams are tabulated in Table II. Thus, starting from the known oxazolidinone **3**,[7] the corresponding δ-lactams, **24**, **25**, and **26**, were prepared in five steps in 32–33% overall yields.

The divergence in the susceptibility of amino diesters **8–10**, **15**, **16**, and **20–22** implies that intermediates **20–22** are converted to the corresponding lactams via a different mechanism from that available to the amino diesters **8–10**, **15**, and **16**. Since **20–22** are not converted to the corresponding lactams by heating in the presence of HOBT, it is reasonable to assume that these compounds do not suffer direct intramolecular attack by the secondary amine. Scheme IV summarizes a reasonable alternative reaction sequence, which leads to lactam closure. The first step involves the addition of an external nucleophile (a primary amine or sodium acetate) to open the oxazolidinone ring to the acyclic intermediate **27**, which subsequently suffers nucleophilic displacement of NUC by the intramolecular secondary amine. Deformylation could occur either prior to or after lactam closure.

There is ample precedent for the susceptibility of oxazolidinones to the addition of external nucleophiles such as ammonia,[7,17a] benzylamine,[7] and hydrazine;[17a] it is also known that excess unhindered amine leads to deformylation after initial addition to the oxazolidinone.[7] These observations support the suggested reaction sequence for the formation of the δ-lactams. Further chemical evidence has been secured by isolating significant amounts (30–40%) of **28**[18] when the sodium acetate catalyzed lactam closure on **22** is terminated after short reaction times (30 min). Apparently the approach of the secondary amine to the oxazolidinone carbonyl is unfavorable (for unknown reasons); lactam closure in the δ-lactam series is possible only from the acyclic intermediate **27**.[17b]




17

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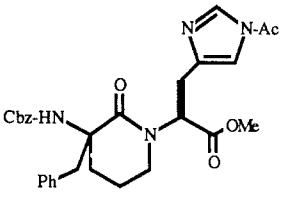



28

**Amino Acid Couplings to the Carboxyl and Nitrogen Termini of the Dipeptide Isosteres.** A series of experiments was undertaken to elucidate conditions for the selective deprotection of the carboxyl or nitrogen protecting group and to investigate the ease of coupling at each terminus. A single diastereomer[19] of the γ- or δ-lactam-containing Phe-Phe (**12** and **25**) isosteres was used for the model peptide coupling reactions to *N*-*t*-Boc-L-phenylalanine and the hydrochloride salt of methyl L-phenylalaninate.

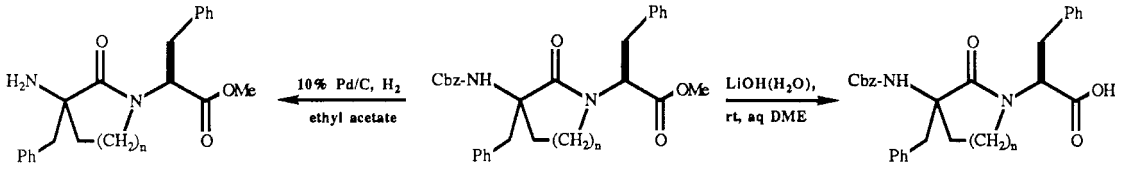
Esters **12a** and **25b** were deprotected with lithium hydroxide in aqueous dimethoxyethane (Scheme V) to provide the corresponding acids **29** and **30** (95–100% unpurified yields). The acids were submitted to coupling with

(17) (a) Itoh, M. *Chem. Pharm. Bull.* **1969**, *17*, 1679. (b) Compare these results to those of Baldwin and Lee where a bicyclic γ-lactam was prepared by a similar strategy. In this case closure of the γ-lactam occurs without the apparent intervention of an external nucleophile. However, the α-carbon is not quaternary. See: Baldwin, J. E.; Lee, E. *Tetrahedron* **1986**, *42*(23), 6551.

(18) $^1$H NMR spectrum of **28** as a 1:1 mixture of diastereomers shows a shift in the imidazole methines from δ 7.62 and 7.43 for **26a** and **26b** to δ 7.50, and from δ 6.91 and 6.84 for **26a** and **26b** to δ 6.98 and 7.0 for **28**; the methyl ester signals for **26a** and **26b** are at δ 3.78 and 3.77 while **28** has methyl ester signals at δ 3.68, 3.67, and 3.65; finally the acetyl methyls appear as broad singlets at δ 3.04 and 2.98. MS analysis (CI) gave an $(M + H)^+$ 533 consistent with **28**. Finally the acetyl group could be removed by treating **28** with $Na_2CO_3$ in methanol at 40 °C to give **26a** and **26b**.

(19) The diastereomers at the lactam quaternary center for the Phe-Phe isosteres were easily separable by chromatographic methods.

**Scheme V**

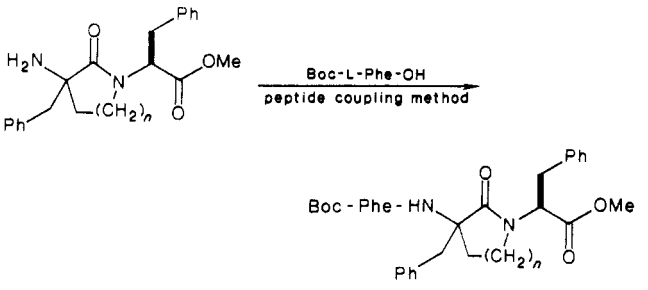



33 n = 1(92%)
34 n = 2(88%)

12a n = 1
25b n = 2

29 n = 1
30 n = 2
(95-100%)

**Table III. Yields for N-Terminal Coupling to the Dipeptide Isosteres**




| starting material | product | n | coupling method[a] | yield, % |
|---|---|---|---|---|
| 33 | 35 | 1 | A | 84 |
| 33 | 35 | 1 | B | 68 |
| 33 | 35 | 1 | C | 92 |
| 34 | 36 | 2 | B | 80 |
| 34 | 36 | 2 | C | 80 |

[a] Coupling methods: A = mixed anhydride; B = water-soluble carbodiimide; C = BOP-Cl.

the hydrochloride salt of methyl L-phenylalanine by using standard peptide coupling methods (mixed anhydride, water-soluble carbodiimide, and BOP-Cl[20]) to provide the tripeptide isosteres **31** and **32**. Yields for the carboxyl-terminal couplings (Table II) varied from good to excellent and appeared to be substrate dependent.[21]

Deprotection of the carbobenzyloxy-protecting group was achieved easily by hydrogenolysis (10% Pd/C, ethyl acetate, $H_2$) of **12** and **25** to provide **33** and **34** (Scheme V) in 92% and 88% yields, respectively. The hindered amines were coupled to *N*-*t*-Boc-L-phenylalanine under standard peptide coupling conditions to provide the tripeptide isosteres **35** and **36**. Yields (see Table III) for coupling to the hindered N-termini of **33** and **34** were also good to excellent and demonstrated some substrate dependence.[21]

## Conclusions

We have presented a general five-step synthesis of γ- and δ-lactam-containing dipeptide isosteres, which provides the final compounds in good overall yields (46–59% and 32–33%, respectively) from oxazolidinone **3**. The synthetic scheme is versatile in that the final lactam-containing isosteres can be obtained as a *d,l*-mixture at the lactam quaternary center, as presented in the paper or by following a literature procedure;[8] it is anticipated that an enantioselective synthesis can also be achieved. The lactam-containing dipeptide isosteres are orthogonally protected at the termini, making it possible to selectively deprotect either terminus. Standard peptide coupling methods can then be employed to efficiently add other amino acid residues at either terminus. Finally, these dipeptide isosteres mitigate chymotrypsin-catalyzed proteolysis[22,23] when substituted for the Phe-His portion of compounds such as **1**.

## Experimental Section

Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz). Chemical shifts are reported as δ values (ppm) relative to $Me_4Si$ as the internal standard. A few intermediates displayed time-dependent behavior in the corresponding $^1H$ NMR and/or $^{13}C$ NMR spectra; compounds displaying this behavior have been indicated appropriately in their NMR spectral characterization, and where possible fractions of protons have been reported. A variable-temperature experiment was carried out on a General Electric GN-300 (300 MHz, $^1H$ NMR; 75.5 MHz, $^{13}C$ NMR) to obtain a nearly time-averaged spectra on **5**. Similar observations have been reported by Karady.[8] Mass spectra were obtained with Hewlett Packard HP5985 (CI, EIO, Varian CH7 (EI) and Dratos MS50 (FAB, HRMS) spectrometers. Elemental analysis and the above determinations were performed by the Analytical Research Department at Abbott Laboratories, Abbott Park and North Chicago.

Thin-layer chromatography (TLC) was carried out with E. Merck precoated silica gel F-254 plates (thickness, 0.25 mm). Chromatographic purification was carried out by either medium-pressure liquid chromatography (MPLC) employing columns packed with EM Silica gel 60 (40–63 μm) at 30–50 psi or by forced-air chromatography (FAC), employing the previously described silica gel at 5–10 psi of air pressure.

Protected amino acids were purchased from Bachem (Torrance, CA). Tetrahydrofuran was distilled from sodium/benzophenone ketyl, and dichloromethane was distilled from $P_2O_5$. Absolute methanol was stored over freshly activated 4 Å sieves under an $N_2$ atmosphere at least 24 h prior to use. All other solvents and reagents were reagent grade and used without further purification.

**(4*S*)-3-(Benzyloxycarbonyl)-4-(phenylmethyl)-5-oxooxazolidine (3).** Via the procedure of Ben-Ishai,[7] *N*-Cbz-L-phenylalanine (10.0 gm, 33.4 mmol), paraformaldehyde (3.0 gm, 100.2 mmol), and *p*-toluenesulfonic acid (0.64 gm, 3.3 mmol) were suspended in toluene (150 mL). The reaction was brought to reflux, and water was removed azeotropically through the agency of a Dean–Stark trap until collection of water ceased (0.5–2.0 h). After cooling, the reaction mixture was diluted with ethyl ether, washed (1×, saturated aqueous $NaHCO_3$; 1×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to provide a solid after cooling. Recrystallization from ethyl acetate/hexanes provided, after the collection of two crops, the pure title compound **3** (9.26 g, 89%). **3**: mp 85.5–86.5 °C; $^1H$ NMR ($CDCl_3$, TMS) δ ca. 7.4 (br s, 5 H), ca. 7.24 (m, 3 H), 7.07 (br s, 2 H), 5.1–5.37 (br m, 3 H), 4.56 (br s, 1 H), 4.24 (br d, $J$ = 3.5 Hz), 3.02–3.52 (m, 2 H); MS (CI) $(M + NH_4)^+$ 329, $(M + H)^+$ 312. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.33; H, 5.48; N, 4.40.

**(4*S*,*R*)-3-(Benzyloxycarbonyl)-4-(phenylmethyl)-4-[1-(2-propenyl)]-5-oxooxazolidine (5).** A 250-mL round-bottom flask

(20) Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342.
(21) Comparison of the $^1H$ NMR spectra of the final coupling products, from each method, revealed no indication of racemization within the detection limits of this method (estimated to be ±5%).
(22) Unpublished results Dr. P. Marcotte.
(23) Incorporation of a γ-lactam-containing dipeptide isostere into the general structure **2** provided compounds that suffered no detectable cleavage by chymotrypsin after 6 h in an in vitro assay. Further work along these lines will be published elsewhere.

was charged with **3** (5.32 g, 17.1 mmol), THF (40 mL), and a magnetic stir bar. The flask was fit with a septum and a gas outlet and cooled to −78 °C while flushing with $N_2$. To the flask was added via syringe sodium hexamethyldisilyl amide (36.6 mL, 18.8 mmol, 0.5 M solution in toluene); the resulting solution was stirred 0.5 h at −78 °C. The allyl bromide (2.22 mL, 25.6 mmol) was passed through a neutral alumina pad just prior to addition as a single neat portion to the enolate solution. Reaction progress was monitored by the TLC for disappearance of **3**; the reaction was quenched with saturated aqueous $NH_4Cl$ after being judged complete (1–2 h). The quenched mixture was partitioned between brine and ethyl ether. The organic layer was washed (1×, brine), dried ($Na_2SO_4$), and concentrated in vacuo to provide a free-flowing light brown liquid. Purification by plug filtration through a pad of silica gel (100 g: 20% ethyl acetate/hexanes; 20-mL fractions) provded the pure title compound, **5** (4.56 g, 76%), as a colorless thick oil. **5**: $^1H$ NMR ($CDCl_3$, TMS; at room temperature the spectrum was a mixture of two rotamers (~2:1), fractions of protons will be reported where possible) δ 7.3–7.55 (m, 8 H), 7.1–7.25 (m, 5 H), 7.0–7.05 (m, 2 H), ca. 6.93 (m, 1 H), 5.47–5.7 (m, 1 H), 5.4 (*AB*, $J$ = 12.5 Hz, $^1/_3$ H), 5.33 (*AB*, $J$ = 12.5 Hz, $^1/_3$ H), 5.31 (*AB*, $J$ = 12 Hz, $^2/_3$ H), 5.05–5.22 (m, 2 H), 5.12 (*AB*, $J$ = 12 Hz, $^2/_3$ H), 5.0 (d, $J$ = 4.0 Hz, $^1/_3$ H), 4.96 (d, $J$ = 3.6 Hz, $^2/_3$ H), 4.24 (d, $J$ = 4.0 Hz, $^1/_3$ H), 4.13 (d, $J$ = 3.5 Hz, $^2/_3$ H), 3.53 (*AB*, $J$ = 13.5 Hz, $^2/_3$ H), 3.27 (*AB*, $J$ = 13.5 Hz, $^1/_3$ H), 3.23 (dd, $J$ = 13.5, 8.0 Hz, $^2/_3$ H), 3.06 (*AB*, $J$ =13.5 Hz, 1 H), 2.97 (dd, $J$ = 13.5, 8.0 Hz, $^1/_3$ H), 2.67 (dd, $J$ = 13.5, 7.5 Hz, 1 H). A variable-temperature $^1H$ NMR experiment in DMSO-$d_6$ revealed that at 150 °C almost all of the signals were time averaged: $^1H$ NMR (DMSO-$d_6$, TMS, 150 °C) δ 7.30–7.43 (m, 4 H), 7.13–7.23 (m, 4 H), 6.95–7.05 (m, 2 H), 5.55–5.70 (m, 1 H), 5.27 (*AB*, $J$ = 12.0 Hz, 1 H), 5.18 (*AB*, $J$ = 12.0 Hz, 1 H), 5.0–5.15 (m, 2 H), 5.0 (d, $J$ = 4.0 Hz, 1 H), 4.3 (d, $J$ = 4.0 Hz, 1 H), 3.41 (*AB*, $J$ = 14.5 Hz, 1 H), 3.08 (dd, $J$ = 14.5, 8.0 Hz, 1 H), 3.02 (*AB*, $J$ = 14.5 Hz, 1 H), 2.62 (dd, $J$ = 14.5, 8.0 Hz, 1 H); MS (EI) ($M^+$) 351 [weak], (M − $CH_2CHCH_2$)$^+$ 310. Anal. Calcd for $C_{21}H_{21}NO_4 \cdot 0.25H_2O$: C, 70.92; H, 6.09; N, 3.94. Found: C, 70.69; H, 6.07; N, 3.94.

**(2*R*,*S*)-Methyl 2-[(Benzyloxycarbonyl)amino]-2-(phenylmethyl)pent-4-enoate (6).** A 100-mL round-bottom flask was charged with a magnetic stir bar, **5** (4.28 g, 12.2 mmol), 95% ethanol (50 mL), water (10 mL), and sodium hydroxide (0.97 g, 24.4 mmol). The reaction was refluxed under $N_2$ for 1 h, cooled, and concentrated in vacuo, and the resulting slurry was poured into excess 10% aqueous HCl. The aqueous solution was extracted with ethyl ether (2×). The combined organic layers were washed (2×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to ~100 mL. The ethereal solution was cooled to 0 °C and treated with excess diazomethane (1.5 equiv, prepared according to Arndt[24] from 1-methyl-3-nitro-1-nitrosoguanidine (2.69 g, 18.3 mmol)) and slowly warmed to room temperature over 1 h. Glacial acetic acid was added dropwise until the ecess diazomethane was consumed. The resulting solution was concentrated in vacuo and chased with toluene (2×, 150 mL) to provide a light brown liquid. Filtration through a short silica gel column (100 g; 20% ethyl acetate/hexane; 100-mL fractions) provided the pure title compound, **6** (3.91 g, 91%).

The title compound was more efficiently prepared from **3** without purification of any intermediates. Via the previously described procedures, **3** (7.0 g, 22.48 mmol) was converted to **6** (6.0 g, 76% overall yield). **6**: $^1H$ NMR ($CDCl_3$, TMS) δ 7.33–7.42 (m, 5 H), 7.14–7.22 (m, 3 H), 6.90–6.97 (m, 2 H), 5.53–5.70 (m, 2 H), 5.2 (*AB*, $J$ = 12 Hz, 1 H), 5.05–5.15 (m, 2 H), 5.07 (*AB*, $J$ = 12 Hz, 1 H), 3.75 (s, 3 H), 3.6 (br *AB*, $J$ = 13.5 Hz, 1 H), 3.23 (dd, $J$ = 15, 7.5 Hz, 1 H), 3.12 (*AB*, $J$ = 13.5 Hz, 1 H), 2.62 (dd, $J$ = 15, 8.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, TMS) δ 172.6, 154.2, 136.6, 135.8, 132.0, 129.6, 128.4, 128.1, 128.0, 126.8, 119.1, 66.2, 65.1, 58.2, 52.5, 40.6, 39.8, 25.2, 18.3; MS (EI) (M + H)$^+$ 353 (weak), (M − $C_3H_5$)$^+$ 312. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.40; H, 6.59; N, 3.96.

**(2*R*,*S*)-Methyl 2-[(Benzyloxycarbonyl)amino]-2-(formylmethyl)-3-phenylpropanoate (7).** A 250-mL round-bottom flask was charged with **6** (0.619 g, 1.75 mmol), dichloromethane (20 mL), and a magnetic stir bar. The reaction solution was cooled to −78 °C, and ozone was bubbled into the solution until a light blue color persisted. The excess ozone was purged from the reaction with $N_2$ until the blue color was removed. Excess methyl sulfide (390 μL, 5.25 mmol) was added to the −78 °C solution, the cooling bath was removed, and the reaction mixture was warmed to ~0 °C. Concentration in vacuo and drying under high vacuum to a constant weight provided the title compound **7** (0.69 g, 110%). The unpurified aldehyde was used without further purification and could be stored in the freezer ($T \simeq 10$ °C) for up to 2 months. **7**: $^1H$ NMR ($CDCl_3$, TMS)[9a] δ 9.73 (s, 0.1 H), 9.67 (s, 0.9 H), 7.33–7.43 (m, 5 H), 7.13–7.22 (m, 3 H), 6.85–6.92 (m, 2 H), 5.77–5.87 (m, 1 H), 3.94 (br *AB*, $J$ = 18 Hz, 0.9 H), 3.72–3.80 (m, 3.2 H), 3.6 (br *AB*, $J$ = 13.5 Hz, 0.9 H), 3.11 (br *AB*, $J$ = 18 Hz, 0.9 H), 2.97–3.13 (m, 0.2 H), 2.97 (br *AB*, $J$ = 13.5 Hz, 0.9 H); MS (EI) (M + H)$^+$ 356 (weak).

**(4*S*,*R*)-3-(Benzyloxycarbonyl)-4-(phenylmethyl)-4-[1-(3-hydroxypropyl)]-5-oxooxazolidine (18).** Alkene **5** (3.5 g, 10 mmol) was dissolved in dry THF (80 mL) and then treated with 9-BBN (0.5 M in THF, 30 mL, 15 mmol). After the mixture was stirred overnight at 25 °C, excess 9-BBN was quenched by the dropwise addition of water (1 mL). The reaction flask was then immersed in a 25 °C water bath followed by the concurrent and dropwise addition of 3 N NaOH (30 mL, 90 mmol) and 30% $H_2O_2$ (30 mL). Stirring was continued for 10 min after the addition was completed, after which the solution was saturated with solid NaCl. The layers were separated, and the aqueous layer was extracted with ether (3×, 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×, 25 mL) and brine (1×, 50 mL), dried ($Na_2SO_4$), and concentrated in vacuo to afford a light yellow oil (5.6 g). Flash chromatography (2.5% MeOH/$CHCl_3$, 100 g sg; 6-mL fractions) afforded the alcohol in fractions 26–39 as a light yellow oil. A second flash column (50% EA/hex, 100 g sg; 8-mL fractions) gave the desired product in fractions 37–50 to afford **18** as a colorless oil, which solidified upon storage in a refrigerator (2.7 g, 74%). **18**: $^1H$ NMR[9a] ($CDCl_3$, TMS) δ 6.9–7.55 (m, 10 H), 5.38 (*AB*, $J$ =12 Hz, 0.40 H), 5.36 (*AB*, $J$ =12.5 Hz, 0.60 H), 5.33 (*AB*, $J$ = 12 Hz, 0.40 H), 5.07 (d, $J$ = 4.0 Hz, 0.40 H), 5.06 (*AB*, $J$ = 12.5 Hz, 0.60 H), 5.03 (d, $J$ = 3.5 Hz, 0.60 H), 4.17 (d, $J$ = 4.0 Hz, 0.40 H), 3.97 (d, $J$ = 3.5 Hz, 0.60 H), 3.66 (t, $J$ = 6.5, 6.5 Hz, 1.2 H), 3.55 (dt, $J$ = 6.5, 6.5, 2.0 Hz, 0.8 H), 3.52 (*AB*, $J$ = 13.0 Hz, 0.6 H), 3.26 (*AB*, $J$ = 13.0 Hz, 0.4 H), 3.04 (*AB*, $J$ =13.0 Hz, 1.0 H), 2.57 (ddd, $J$ =14.0, 11.5, 5.5 Hz, 0.60 H), 2.33 (ddd, $J$ = 14.0, 11.5, 5.5 Hz, 0.40 H), 2.24 (tq, $J$ =14.5, 14.5, 5.5, 5.5, 5.5 Hz, 1 H), 1.3–1.65 (m, 3 H); MS (CI) (M + $NH_4$)$^+$ 387, (M + H)$^+$ 370.

**(4*S*,*R*)-3-(Benzyloxycarbonyl)-4-(phenylmethyl)-4-[2-(formylethyl)]-5-oxooxazolidine (19).** Alcohol **18** (1.0 g, 2.7 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and added to a vigorously stirred mixture of PCC (1.5 g, 7.0 mmol) and 4-Å molecular sieves (4 g) in $CH_2Cl_2$ (100 mL). Additional portions of PCC (0.75 g, 3.5 mmol) were added after 30 and 45 min. After 1 h total reaction time, the mixture was poured into 200 mL of moist ether. The reaction flask was rinsed with ether (4×, 50 mL), and the combined ether solution was filtered through Celite and concentrated in vacuo to afford a dark semisolid. The crude product was suspended in $CH_2Cl_2$ and filtered through a 4-in. column of Florisil. The filtrate (200 mL) was concentrated in vacuo to afford a light yellow oil, which was used without further purification (0.8 g, 80%). **19**: $^1H$ NMR[9a] ($CDCl_3$, TMS) δ 9.70 (s, 0.70 H), 9.62 (s, 0.30 H), 6.85–7.53 (m, 10 H), 5.28–5.40 (m, 1.3 H), 4.94–5.10 (m, 1.7 H), 4.08 (d, $J$ = 4.0 Hz, 0.30 H), 4.02 (d, $J$ = 3.5 Hz, 0.70 H), 3.57 (*AB*, $J$ = 13.0 Hz, 0.70 H), 3.28 (*AB*, $J$ = 13.0 Hz, 0.30 H), 3.06 (*AB*, $J$ = 13.0 Hz, 1.0 H), ca. 2.87 (br m, 0.70 H), ca. 2.62 (br m, 0.30 H), 2.24–2.46 (m, 3 H); MS (CI) (M + $NH_4$)$^+$ 385, (M + H)$^+$ 368.

**General Procedures for Reductive Amination of Aldehydes 7 and 19.** An adaptation of the procedure of Borch[11] was followed for the reductive amination step. A flask was charged with aldehyde (1.0 equiv), the desired amino acid methyl ester hydrochloride salt (1.0 equiv), anhydrous sodium acetate (2.0 equiv), freshly activated 4-Å molecular sieves (1 g/mmol aldehyde), and a magnetic stir bar in absolute methanol ($C \simeq 0.25$ M). The sodium cyanoborohydride (2.0 equiv) was added in a single portion, and the reaction was stirred at room temperature until the aldehyde was consumed (1–3 h). Excess 10% aqueous HCl

(24) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 165, note 3.

was added to carefully adjust to pH ≅2 (according to wet litmus paper) to destroy excess sodium cyanoborohydride. The aqueous layer was adjusted to pH ≅10 with saturated aqueous $Na_2CO_3$ and extracted with ethyl acetate (2×). The combined organic layers were washed (2×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to provide the unpurified reductive amination product (in most cases for the γ-lactam series some of the final diastereomeric lactams were also present). The amino diester intermediates could be purified by chromatographic methods if desired; however, higher overall yields were obtained by converting the unpurified amino diesters to the final lactams.

**Lactam Closure Method A.** The amino diesters (1.0 equiv) and HOBT (1.0 equiv) were taken up in a 1:1 (v/v) solution of dry toluene/dimethoxyethane ($C \cong 0.1$ M) and heated at 100 °C in a resealable tube until the starting materials were consumed (3–8 h) as judged by TLC. The volatiles were removed in vacuo, and the resulting slurry taken up in ethyl acetate, washed (1×, saturated aqueous $Na_2CO_3$; 1×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to provide a 1:1 diastereomeric mixture of the unpurified lactams. Purification by silica gel chromatography using the noted solvent system provided the purified lactams. Where possible the diastereomeric lactams were separated; unless noted otherwise, the final lactams were isolated as a 1:1 mixture at the lactam quaternary center in the noted yield.

**Lactam Closure Method B.** The desired amino diesters (1.0 equiv) and anhydrous sodium acetate (10 equiv) were placed in an oven-dried resealable tube and suspended in absolute methanol (0.1–0.3 M). The pH of the resulting solution was adjusted to ≈6.5–7.0 (as judged by spotting on wet litmus paper) by adding glacial acetic acid (typically 1–3 drops). The tube was sealed and heated at 105 °C (5–12 h) until the reaction was complete as judged by TLC. The reaction was cooled, and the volatiles were removed in vacuo. The resulting semisolid was suspended in ethyl acetate (200 mL) and washed (2×, saturated aqueous $NaHCO_3$; 2×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to provide the unpurified lactams. Final purification was achieved chromatographically as described in method A.

**Lactam Closure Method C.** The desired amino diesters (1.0 equiv) and isopropylamine (5.0 mmol) were refluxed in absolute methanol (0.1 M) under $N_2$ until the reaction was judged complete by TLC analysis (2.5–4.0 h). After cooling, the volatiles were removed in vacuo to afford the unpurified lactams. Final purification was achieved chromatographically as described in method A.

**(2*S*)-Methyl 2-[3(*R*,*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]propionate (11).** Via the general procedure, aldehyde **7** (209 mg, 0.588 mmol) was reductively aminated with the hydrochloride salt of methyl L-alaninate (82.1 mg, 0.588 mmol). The resulting amino diesters (**8**, 219.3 mg) were converted to the corresponding lactams (**11**) via method A. Purification by FAC (16 g sg, column packed in dichloromethane, eluant was 1% methanol/chloroform) provided a 1:1 diastereomeric mixture of the title compound **11** (143.9 mg, 60% overall yield from **7**) as a thick, colorless oil. **11**: $^1$H NMR ($CDCl_3$, TMS) δ 7.08–7.40 (m, 10 H), 5.67 (br s, 0.5 H), 5.39 (br s, 0.5 H), 5.0–5.25 (m, 2 H), 4.88 (br q, $J$ = 7.5, 7.5, 7.5 Hz, 0.5 H), 4.75 (br q, $J$ = 7.5, 7.5, 7.5 Hz, 0.5 H), 3.72 (s, 1.5 H), 3.68 (br s, 1.5 H), 2.98–3.35 (m, 3 H), 2.5–2.73 (m, 3 H), 1.03 (br d, $J$ = 7.5 Hz, 3 H); MS (CI) $(M + NH_4)^+$ 428 [weak], $(M + H)^+$ 411.

After the product stood for 6 months, partial solidification was noted. Trituration with ethyl ether provided a single pure diastereomer. The mother liquors were enriched in the other diastereomer; however, conditions to obtain the remaining diastereomer as a single pure compound could not be identified). The crystalline diastereomer was characterized as follows: **11** (crystalline diastereomer); $^1$H NMR ($CDCl_3$, TMS) δ 7.15–7.40 (m, 10 H), 5.62 (br s, 1 H), 5.17 (br *AB*, $J$ = 12 Hz, 1 H), 5.08 (br *AB*, $J$ = 12 Hz, 1 H), 4.75 (q, $J$ = 7.5, 7.5, 7.5 Hz, 1 H), 3.68 (s, 3 H), 3.27 (br *AB*, $J$ = 12 Hz, 1 H), 3.12 (t, $J$ = 9.0, 9.0 Hz, 1 H), 3.04 (*AB*, $J$ = 12.0 Hz, 1 H), 2.7 (br dd, $J$ = 12.5, 6.0 Hz, 1 H), 2.48 (br q, $J$ = 9.0, 9.0, 9.0 Hz, 1 H), 2.23 (br q, $J$ = 9.0, 9.0, 9.0 Hz), 1.03 (d, $J$ = 7.5 Hz, 3 H). Anal. Calcd for $C_{23}H_{26}N_2O_5 \cdot 0.25H_2O$: C, 66.57; H, 6.44; N, 6.75. Found: C, 66.89; H, 6.40; N, 6.76.

**(2*S*)-Methyl 2-[3(*R*)- and 3(*S*)-[(Benzyloxycarbonyl)-amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionate (12a and 12b).** Via the general procedure, aldehyde **7** (779 mg, 2.19 mmol) was reductively aminated with the hydrochloride salt of methyl L-phenylalaninate (472.7 mg, 2.19 mmol). The resulting amino diesters (**9**, 1.17 g) were converted to the corresponding lactams **12** via method A, which were partially separable by MPLC (75 g sg, 30% ethyl acetate/hexanes) to provide in order of elution: pure more mobile diastereomer **12a** (375 mg, 35%), mixed fractions (74 mg, 7%), pure less mobile isomer **12b** (383 mg, 36%) [total yield 832 mg, 78%]. **12a**: $^1$H NMR ($CDCl_3$, TMS) δ 7.03–7.40 (m, 15 H), 5.29 (br s, 1 H), 5.10 (*AB*, $J$ =12.5 Hz, 1 H), 5.07 (t, $J$ = 8 Hz, 1 H), 5.01 (*AB*, $J$ = 12.5, 1 H), 3.63 (s, 3 H), 2.83–3.35 (m, 6 H), 2.52 (d, d, $J$ = 12.5, 6.0 Hz, 1 H), 2.15 (d, t, $J$ = 12.5, 6.0, 6.0 Hz, 1 H); MS (CI), $(M + NH_4)^+$ 504 (weak), $(M + H)^+$ 487. Anal. Calcd for $C_{29}H_{30}N_2O_5 \cdot 0.25H_2O$: C, 70.93; H, 6.25; N, 5.70. Found: C, 70.69; H, 6.22; N, 5.70. **12b**: $^1$H NMR ($CDCl_3$, TMS) δ 7.05–7.40 (m, 13 H), ca. 6.73 (m, 2 H), 5.37 (s, 1 H), 5.12 (*AB*, $J$ =12.5 Hz, 1 H), 5.03 (t, $J$ = 8.0, 8.0 Hz, 1 H), 5.01 (*AB*, $J$ = 12.5 Hz, 1 H), 3.70 (s, 3 H), 3.40 (br t, $J$ = 6.0, 6.0 Hz, 1 H), 3.25 (d, d, $J$ = 14.5, 4.5 Hz, 1 H), 3.03 (br q, $J$ = 7.0, 7.0, 7.0 Hz, 1 H), 2.75–2.88 (m, 2 H), 2.5–2.65 (m, 2 H), 2.40 (br q, $J$ = 10.5, 10.5, 10.5 Hz, 1 H); MS (CI) same as isomer **12a**. Anal. Calcd for $C_{29}H_{30}N_2O_5 \cdot 0.25H_2O$: C, 70.93; H, 6.25; N, 5.70. Found: C, 70.81; H, 6.28; N, 5.77.

**(2*S*)-Methyl 2-[3(*R*,*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-(4-imidazolyl)-propionate (13).** Via the general procedure, aldehyde **7** (217 mg, 0.611 mmol) was reductively aminated with the bis(hydrochloride salt) of methyl L-histidinate (148 mg, 0.611 mmol). The resulting amino diesters (**10**, 230 mg) were converted to the corresponding lactams **13** via method A. Purification was achieved by FAC (16 g sg, 5% methanol/chloroform) to provide a 1:1 diastereomeric mixture of the lactams **13** (192.5 mg, 66%) overall yield from **7**. Conditions to chromatographically fractionate the diastereomers could not be identified. A center cut fraction provided a sample for elemental analysis. **13**: $^1$H NMR ($CD_3OD$, TMS) δ 7.56 (s, 0.5 H), 7.48 (s, 0.5 H), 7.13–7.42 (m, 9 H), 6.98 (br s, 1 H), 6.88 (s, 0.5 H), 6.82 (br s, 0.5 H), 4.67–4.78 (obscured by HOD), 5.12 (br *AB*, $J$ = 12 Hz, 1 H), 5.07 (*AB*, $J$ = 12 Hz, 0.5 H), 5.03 (*AB*, $J$ = 12 Hz, 0.5 H), 3.76 (br s, 1.5 H), 3.68 (s, 1.5 H), 2.73–3.85 (m, 6 H), ca. 2.43 (br m, 2 H); MS (CI) $(M + H)^+$ 477. Anal. Calcd for $C_{26}H_{28}N_4O_5 \cdot 0.75H_2O$: C, 63.73; H, 6.07; N, 11.43. Found: C, 63.43; H, 5.76; N, 11.08.

**(2*S*)-Methyl 2-[3(*R*,*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-piperidinyl]propionate (24).** Via the general procedures, aldehyde **19** (350 mg, 0.95 mmol) was reductively aminated with the hydrochloride salt of methyl L-alaninate (130 mg, 0.95 mmol). The resulting amino diesters (**20**, 460 mg) were converted to the corresponding lactams **24** by lactam closure method B. Purification by MPLC (75 g sg; 40% ethyl acetate/hexanes) afforded lactams **24** (264.5 mg, 66% yield from **19**) as an inseparable 1:1 diastereomeric mixture, which solidified upon standing. No attempt was made to separate the diastereomers by recrystallization. **24**: $^1$H NMR ($CDCl_3$, TMS) δ 7.06–7.40 (m, 10 H), 5.70 (br s, 0.5 H), 5.52 (br s, 0.5 H), 5.23 (q, $J$ = 7.5, 7.5, 7.5 Hz, 0.5 H), 5.13 (*AB*, $J$ = 11.5 Hz, 0.5 H), 5.11 (*AB*, $J$ = 12.0 Hz, 0.5 H), 5.04 (br *AB*, $J$ = 11.5 Hz, 0.5 H), 5.01 (br *AB*, $J$ = 12.0 Hz, 0.5 H), 4.91 (q, $J$ = 7.5, 7.5, 7.5 Hz, 0.5 H), 3.73 (s, 1.5 H), 3.71 (s, 1.5 H), 3.0–3.43 (m, 4 H), 2.25–2.53 (m, 2 H), 1.70–1.89 (m, 2 H), 1.43 (br d, $J$ = 7.5 Hz, 1.5 H), 1.34 (d, $J$ = 7.5 Hz, 1.5 H); MS (CI) $(M + H)^+$ 425. Anal. Calcd for $C_{24}H_{28}N_2O_5 \cdot 0.20H_2O$: C, 67.34; H, 6.69; N, 6.54. Found: C, 67.06; H, 6.54; N, 6.55.

**(2*S*)-Methyl 2-[3(*R*)- and 3(*S*)-[(Benzyloxycarbonyl)-amino]-3-(phenylmethyl)-2-oxo-1-piperidinyl]-3-phenylpropionate (25a and 25b).** Via the general procedure, aldehyde **19** (800 mg, 2.18 mmol) was reductively aminated with the hydrochloride salt of methyl L-phenylalinate (470 mg, 2.18 mmol). The resulting amino diesters (**21**, 1.0 g) were converted to the corresponding lactams **25** by lactam closure method B. Purification by MPLC (75 g sg; 25% ethyl acetate/hexanes) afforded the separated diastereomeric lactams as colorless foams in the order of elution **25a** (299 mg) and **25b** (305 mg) for an overall yield of 55% from **19**. **25a**: $^1$H NMR ($CDCl_3$, TMS) δ 7.07–7.42 (m, 10 H), 5.39 (br s, 1 H), 5.07 (br *AB*, $J$ = 12.0 Hz, 1 H), 5.05 (dd, $J$ = 6.0, 3.5 Hz, 1 H), 4.98 (*AB*, $J$ = 12.0 Hz, 1 H), 3.71 (s, 3 H),

3.38 (*ABX*, $J$ = 14.5, 6.0 Hz, 1 H), ca. 3.35 (m, 1 H), 3.20 (*AB*, $J$ = 13.0 Hz, 1 H), 3.07 (*AB*, $J$ = 13.0 Hz, 1 H), 2.97–3.07 (m, 2 H), 2.15–2.33 (m, 2 H), 1.63–1.72 (m, 2 H); MS (CI) $(M + H)^+$ 501. Anal. Calcd for $C_{30}H_{32}N_2O_5 \cdot 0.5H_2O$: C, 70.71; H, 6.53; N, 5.30. Found: C, 70.71; H, 6.51; N, 5.45. **25b**: $^1$H NMR ($CDCl_3$, TMS) δ 7.10–7.40 (m, 8 H), 6.73–6.80 (m, 2 H), 5.57 (br s, 1 H) 5.15 (br dd, $J$ = 11.5, 5.5 Hz, 1 H), 5.10 (*AB*, $J$ = 12.5 Hz, 1 H), 4.98 (*AB*, $J$ = 12.5 Hz, 1 H), 3.76 (s, 3 H), 3.40 (dd, $J$ = 15.0, 5.5 Hz, 1 H), 3.20–3.32 (m, 2 H), 3.07 (dd, $J$ = 15.0, 11.5 Hz, 1 H), 2.94 (br *AB*, $J$ = 14.0 Hz, 1 H), 2.74 (*AB*, $J$ = 14.0 Hz, 1 H), 2.15–2.40 (m, 2 H), 2.23–2.34 (m, 2 H); MS (CI) $(M + H)^+$ 501. Anal. Calcd for $C_{30}H_{32}N_2O_5 \cdot 1.0H_2O$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.35; H, 6.28; N, 5.63.

**(2*S*)-Methyl 2-[3(*R*)- and 3(*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-piperidinyl]-3-(4-imidazolyl)propionate (26a and 26b).** Via the general procedure, aldehyde **19** (580 mg, 1.6 mmol) was reductively aminated with the bis(hydrochloride salt) of methyl L-histidinate (383 mg, 1.58 mmol). The resulting amino diesters (**22**, 77%) were converted to the corresponding lactams **26a** and **26b** following lactam closure method C. Purification by MPLC (75 g sg, 2.5% methanol/chloroform) afforded the separated diastereomeric lactams as colorless foams, in the order of elution, **26a** (241.5 mg) and **26b** (230.0 mg) for an overall yield of 60% from **19**. Lactam closure via method B was also performed with amino diesters **22** (156 mg, 0.30 mmol) and provided, after chromatographic purification as described above, lactams **26a** and **26b** in an overall 45% yield from **19**. **26a**: $^1$H NMR ($CDCl_3$, TMS) δ 7.62 (br s, 1 H), 7.28–7.40 (m, 8 H), 7.14–7.20 (m, 2 H), 6.91 (br s, 1 H), 5.37 (br s, 1 H), 5.10 (*AB*, $J$ = 12 Hz, 1 H), 5.02 (*AB*, $J$ = 12 Hz, 1 H), 3.78 (s, 3 H), 3.33–3.78 (m, 4 H), 3.19 (*AB*, $J$ = 14.5 Hz, 1 H), ca. 3.15 (br m, 1 H), 3.02 (*AB*, $J$ = 14.5 Hz, 1 H), 2.27 (dt, $J$ = 14.5, 14.5, 4.0 Hz, 1 H), 1.90–2.18 (br m, 2 H), 1.7–1.8 (br m, 1 H); MS (CI) $(M + H)^+$ 491; exact mass calcd for $C_{27}H_{31}N_4O_5$ $(M + H)^+$ 491.2294, found 491.2294. **26b**: $^1$H NMR ($CDCl_3$, TMS) δ 7.43 (br s, 1 H), 7.27–7.43 (m, 8 H), 7.13–7.20 (m, 2 H), 6.84 (br s, 1 H), 5.48 (br s, 1 H), 5.31 (dd, $J$ = 9.5, 4.5 Hz, 1 H), 5.10 (*AB*, $J$ = 12.0 Hz, 1 H), 5.03 (*AB*, $J$ = 12.0 Hz, 1 H), 3.77 (s, 3 H), 3.41 (*ABX*, $J$ = 15.5, 5.0 Hz, 1 H), ca. 3.35 (m, 1 H), 3.28 (*AB*, $J$ = 13.0 Hz, 1 H), 3.1–3.21 (m, 2 H), 3.06 (*AB*, $J$ = 13.0 Hz, 1 H), 2.17–2.30 (m, 2 H), 1.77–1.88 (m, 2 H); MS (CI) $(M + H)^+$ 491; exact mass calcd for $C_{27}H_{31}N_4O_5$ $(M + H)^+$ 491.2294, found 491.2294.

**2(*S*)-[3(*R*)- or 3(*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionic Acid (29).** The more mobile isomer of the γ-lactam-containing Phe-Phe isostere, **12a** (161.9 mg, 0.333 mmol), was dissolved in dimethoxyethane (1.3 mL), and $H_2O$ was added until the solution remained cloudy (~0.6 mL). The resulting solution was cooled to 0 °C under $N_2$, and $LiOH \cdot H_2O$ (14.6 mg, 0.349 mmol) was added in a single portion. The cooling bath was removed, and the reaction stirred for 1 h, at which time complete hydrolysis was noted by TLC. The pH was adjusted to ~2.0 by adding 10% aqueous HCl, and the resulting solution was extracted (2×, ethyl acetate). The combined organic extracts were washed (1×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo to provide the title compound (**29**, 162.3 mg, 103% unpurified) as an off-white foam. This substance was carried on without further purification. **29**: $^1$H NMR ($CDCl_3$, TMS) δ 8.73 (br s, 1 H), 7.0–7.4 (m, 16 H), 5.5 (br s, 1 H), 5.02–5.13 (m, 2 H), 4.98 (*AB*, $J$ = 12 Hz, 1 H), 3.35 (dd, $J$ = 14.0, 6.0 Hz, 1 H), 3.20 (t, $J$ = 9.0, 9.0 Hz, 1 H), 2.90–3.10 (m, 3 H), 2.46 (br dd, $J$ = 12.0, 5.0 Hz, 1 H), 2.17 (br q, $J$ = 9.5, 9.5, 9.5 Hz, 1 H).

**2(*S*)-[3(*R*)- or 3(*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-piperidinyl]-3-phenylpropionic Acid (30).** Via the procedure described for the conversion of **12a** to **29**, lactam ester **25b** (130 mg, 0.26 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (10.9 mg, 0.26 mmol) to provide acid **30** (120 mg, 95%) as a colorless foam. **30**: $^1$H NMR ($CDCl_3$, TMS) δ 7.2–7.4 (m, 13 H), ca. 7.90 (m, 2 H), 5.53 (br m, 1 H), 5.50 (br s, 1 H), 5.08 (*AB*, $J$ = 12.0 Hz, 1 H), 4.98 (*AB*, $J$ = 12.0 Hz, 1 H), 3.48 (br dd, $J$ = 15.0, 5.5 Hz, 1 H), 3.26 (m, 2 H), 3.07 (dd, $J$ = 15.0, 11.5 Hz, 1 H), 2.84 (*AB*, $J$ = 14.5 Hz, 1 H), 2.77 (*AB*, $J$ = 14.5 Hz, 1 H), 2.05–2.13 (m, 2 H), 1.73–1.83 (m, 1 H), 1.58 (septet, $J$ = 7.0, 7.0, 7.0, 7.0, 7.0, 7.0 Hz, 1 H); MS (FAB) $(M + H)^+$ = 487.

**(2*S*)-Methyl 2-[3(*R*)- or 3(*S*)-Amino-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionate (33).** The less mobile isomer of the Phe-Phe dipeptide isostere (**12b**, 370 mg, 0.760 mmol) was added in 4:1 ethyl acetate/methanol (5 mL) to a suspension of 10% Pd/C (400 mg) in ethyl acetate (2 mL). The suspension was stirred under 1 atm of $H_2$(g) at room temperature for 1 h when an additional portion of 10% Pd/C was added (400 mg) after purging the reaction atmosphere with $N_2$. The resulting suspension was stirred 2.5 h at room temperature under 1 atm of $H_2$ when the reaction was judged to be complete by TLC (**29**, $R_f$ 0.90; **33**, $R_f$ 0.29 in 5% methanol/chloroform). After the reaction was flushed with $N_2$, the solution was filtered through a Celite pad, and the filter cake was rinsed thoroughly with ethyl acetate. The combined filtrates were concentrated in vacuo to provide the title compound, **33** (246.4 mg, 92% yield), as a light yellow viscous oil, which was utilized without further purification. **33**: $^1$H NMR ($CDCl_3$, TMS) δ 7.17–7.33 (m, 8 H), 6.98–7.05 (m, 2 H), 5.10 (dd, $J$ = 10.5, 6.0 Hz, 1 H), 3.71 (s, 3 H), 3.34 (dt, $J$ = 9.0, 9.0, 3.0 Hz, 1 H), 3.28 (dd, $J$ = 15, 6.5 Hz, 1 H), 2.97 (dt, $J$ = 9.5, 8.0 Hz, 1 H), 2.86 (dd, $J$ = 15.0, 10.0 Hz, 1 H), 2.51 (*AB*, $J$ = 13.5 Hz, 1 H), 2.32 (*AB*, $J$ = 13.5 Hz, 1 H), 2.03 (ddd, $J$ = 13.5, 7.0, 3.0 Hz, 1 H), 1.70 (dt, $J$ = 14.5, 8.0, 8.0 Hz, 1 H), 1.64 (br s, 2 H); MS (CI) $(M + H)^+$ 353.

**(2*S*)-Methyl 2-[3(*R*)- or 3(*S*)-Amino-3-(phenylmethyl)-2-oxo-1-piperidinyl]-3-phenylpropionate (34).** Via the procedure for the conversion of **12b** to **33**, the less mobile dipeptide lactam **25b** (170 mg, 0.34 mmol) was hydrogenolyzed to provide **34** (104 mg, 84%) as a pale yellow oil. **34**: $^1$H NMR ($CDCl_3$, TMS) δ 7.1–7.35 (m, 10 H), 4.97 (dd, $J$ = 11.5, 5.0 Hz, 1 H), 3.75 (s, 3 H), 3.39 (*ABX*, $J$ = 15, 5.5 Hz, 1 H), ca. 3.17 (m, 1 H), 3.01 (*AB*, $J$ = 14.5 Hz, 1 H), 3.00 (*ABX*, $J$ = 15, 11.5 Hz, 1 H), ca. 2.83 (m, 1 H), 2.77 (*AB*, $J$ = 14.5 Hz, 1 H), 1.32–1.82 (m, 6 H).

**General Procedures for Protected Amino Acid Couplings to the Dipeptide Isosteres. Method A: Mixed Anhydride.** The desired acid (1.0 equiv) was dissolved in dry dichloromethane (0.25 M) and *N*-methylmorpholine was added (1.05 equiv). The resulting solution was cooled to −23 °C ($CCl_4$/dry ice), and isobutyl chloroformate (1.05 equiv) was added neat. After 2 min the desired amine or amine hydrochloride salt was added (1.0 equiv) [when the amine was hydrochloride salt was employed an additional 1.05 equiv of *N*-methylmorpholine was added subsequently]. The reaction was stirred 2 h at −23 °C, warmed to room temperature over ~1 h, and quenched by pouring into 10% aqueous HCl. The resulting two-phased mixture was extracted (2×, EtOAc). The combined organic extracts were washed (1×, saturated aqueous $NaHCO_3$; 1×, brine), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The unpurified substance was chromatographically purified by employing the noted method and solvent system to provide the final tripeptide analogues.

**Method B: Water-Soluble Carbodiimide.** To a dry dimethylformamide solution (0.25 M) of the desired acid (1.0 equiv) at −23 °C ($CCl_4$/dry ice) was added, sequentially, the desired amine or amine hydrochloride salt (1.0 equiv), *N*-methylmorpholine (1.05 equiv for amines, 2.10 equiv for amine hydrochloride salts), 1-hydroxybenzotriazole (HOBT) (3.0 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.0 equiv). The resulting mixture was stirred 2 h at −23 °C, the cooling bath was removed, and the mixture was stirred at room temperature overnight (~18 h). The reaction was quenched and processed as described in method A to provide the purified final tripeptide analogues.

**Method C: BOP-Cl.**[20] The desired acid (1.0 equiv) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (1.0 equiv) were suspended in dry dichloromethane (0.10 M) and cooled to 0 °C. To this suspension was added sequentially triethylamine (3.3 equiv) and the desired amine or amine hydrochloride (1.0 equiv) [an additional 1.1 equiv of triethylamine was added when the amine hydrochloride was employed]. The reaction was stirred 2 h at 0 °C, the cooling bath was removed, and the mxiture was stirred overnight at room temperature (~18 h). The reaction was quenched and processed as described in method A to provide the desired tripeptide analogue.

**Methyl [2(*S*)-[3(*R*)- or 3(*S*)-[(Benzyloxycarbonyl)amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionyl]-L-phenylalaninate (31).** Via method A for peptide coupling, **29** (42.0 mg, 88.9 μmol) and methyl L-phenylalaninate hydrochloride (19.2 mg, 88.9 μmol) were coupled to provide the pure title compound (**31**, 46.6 mg, 83% yield) after purification

by MPLC (75 g sg, 40% ethyl acetate/hexane). **31**: $^1$H NMR ($CDCl_3$, TMS) $\delta$ 7.03–7.40 (m, 20 H), 6.87 (d, $J$ = 7.0 Hz, 1 H), 5.13 (br s, 1 H), 5.06 (*AB*, $J$ = 12 Hz, 1 H), 4.97 (*AB*, $J$ = 12 Hz, 1 H), 4.73 (br q, $J$ = 7.0, 7.0, 7.0 Hz, 1 H), 4.45 (br t, $J$ = 7.0, 7.0 Hz, 1 H), 3.64 (s, 3 H), 3.17–3.38 (m, 3 H), 3.14 (*ABX*, $J$ = 14.0, 7.0 Hz, 1 H), 2.96 (*ABX*, $J$ = 14.0, 8.5 Hz, 1 H), 2.89 (*AB*, $J$ = 14.5 Hz, 1 H), 2.72 (*AB*, $J$ = 14.5 Hz, 1 H), 2.64–2.75 (m, 1 H), 2.24 (br t, $J$ = 6.0, 6.0 Hz, 2 H); MS (CI) $(M + NH_4)^+$ 651 [weak], $(M + H)^+$ 634. Anal. Calcd for $C_{38}H_{39}N_3O_6 \cdot 0.5H_2O$: C, 71.01; H, 6.27; N, 6.53. Found: C, 71.04; H, 6.15; N, 6.45.

Via peptide coupling method B, **29** (62.5 mg, 132 $\mu$mol) and methyl L-phenylalaninate hydrochloride (28.5 mg, 132 $\mu$mol) were coupled to provide **31** (73.3 mg, 88% yield) after purification by MPLC as described above.

Via peptide coupling method C, **29** (41.6 mg, 88.0 $\mu$mol) and methyl L-phenylalaninate hydrochloride were coupled to provide **31** (36.6 mg, 66% yield) after purification by MPLC as described above. The $^1$H NMR spectra of the tripeptide analogue, **31**, derived from the three coupling methods were identical in all respects. No discernable sign of racemization was observed by high-field $^1$H NMR analysis.

**Methyl [2(*S*)-[3(*R*)- or 3(*S*)-[(Benzyloxycarbonyl)-amino]-3-(phenylmethyl)-2-oxo-1-piperidinyl]-3-phenylpropionyl]-L-phenylalaninate (32).** Via method B for peptide coupling, acid **30** (63 mg, 0.13 mmol) and the hydrochloride salt of methyl L-phenylalinate were coupled. The resulting tripeptide analogue was purified by MPLC (75 g sg, 35% ethyl acetate/hexanes) to afford the title compound, **32** (61 mg, 73% yield) as a colorless oil, which upon scratching yielded a colorless solid. **32**: $^1$H NMR ($CDCl_3$, TMS) $\delta$ 7.12–7.40 (m, 18 H), ca. 6.88 (m, 2 H), 5.81 (dd, $J$ = 11.5, 6.0 Hz, 1 H), 5.28 (br s, 1 H), 5.09 (*AB*, $J$ = 12 Hz, 1 H), 5.03 (*AB*, $J$ = 12 Hz, 1 H), ca. 4.97 (m, 1 H), 3.72 (s, 3 H), 3.40 (*ABX*, $J$ = 15, 6.0 Hz, 1 H), 3.30 (*ABX*, $J$ = 13.5, 5.0 Hz, 1 H), 3.02 (*ABX*, $J$ = 13.5, 11.5 Hz, 1 H), ca. 2.87 (m, 1 H), 2.83 (*ABX*, $J$ = 15, 11.5 Hz, 1 H), 2.72 (*AB*, $J$ = 13.5 Hz, 1 H), 2.45 (*AB*, $J$ = 13.5 Hz, 1 H), 2.34 (dt, $J$ = 7.5, 7.5, 4.5 Hz, 1 H), 1.8–1.93 (m, 2 H), 1.3–1.5 (m, 3 H); MS (CI) $(M + H)^+$ 648. Anal. Calcd for $C_{39}H_{41}N_3O_6$: C, 72.31; H, 6.38; N, 6.49. Found: C, 72.20; H, 6.65; N, 6.41.

Via the general method C for peptide coupling, acid **30** (58 mg, 0.119 mmol) was coupled to the hydrochloride salt of methyl L-phenylalaninate (25.7 mg, 0.119 mmol). Purification of the resulting tripeptide analogue was carried out by MPLC, as described above, to afford the title compound **32** (54 mg, 70% yield), which was identical with the previous sample by $^1$H NMR analysis.

**(2*S*)-Methyl 2-[3(*R*)- or 3(*S*)-[[*N*-(*tert*-Butyloxycarbonyl)-L-phenylalaninyl]amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionate (35).** Via peptide coupling method A, amine **33** (36.0 mg, 102 $\mu$mol) and *N*-*t*-Boc-L-phenylalanine (27.0 mg, 102 $\mu$mol) were coupled to provide the title compound, **35** (51.6 mg, 84% yield), after purification by MPLC (75 g sg, 40% ethyl acetate/hexanes).

By peptide coupling method B, amine **33** (41.1 mg, 117 $\mu$mol) and *N*-*t*-Boc-L-phenylalanine (30.9 mg, 117 $\mu$mol) were coupled to provide the title compound, **35** (47.8 mg, 68% yield), after MPLC purification as described above.

By peptide coupling method C, amine **33** (42.6 mg, 121 $\mu$mol) and *N*-*t*-Boc-L-phenylalanine (32.1 mg, 121 $\mu$mol) were coupled to provide the title compound, **35** (66.8 mg, 92% yield), after MPLC purification as described above. **35**: $^1$H NMR ($CDCl_3$, TMS) $\delta$ 7.13–7.33 (m, 13 H), 6.78–6.85 (m, 2 H), 6.39 (br s, 1 H), (dd, $J$ = 9.5, 7.0 Hz, 1 H), 4.95–5.03 (m, 1 H), 4.34 (br m, 1 H), 3.69 (s, 3 H), 3.38 (br t, $J$ = 9.5, 9.5 Hz, 1 H), 3.17 (dd, $J$ = 14.5, 7.0 Hz, 1 H), 2.93–3.08 (m, 2 H), 2.88 (dt, $J$ = 9.5, 9.5, 7.0 Hz, 1 H), 2.71 (dd, $J$ = 15, 12 Hz, 1 H), 2.48–2.68 (m, 3 H), 2.31 (dt, $J$ = 13.0, 9.5, 9.5 Hz, 1 H), 1.37 (s, 9 H); MS (CI) $(M + NH_4)^+$ 617 [weak], $(M + H)^+$ 600. Anal. Calcd for $C_{35}H_{41}N_3O_6 \cdot 1.5H_2O$: C, 67.04; H, 7.08; N, 6.70. Found: C, 66.97; H, 6.74; N, 6.57.

The tripeptide analogues, **35**, obtained from the three peptide coupling methods proved to be virtually identical by high-field $^1$H NMR analysis and gave no indication of racemization in any case.

**(2*S*)-Methyl 2-[3(*R*)- or 3(*S*)-[[*N*-(*tert*-Butyloxycarbonyl)-L-phenylalaninyl]amino]-3-(phenylmethyl)-2-oxo-1-pyrrolidinyl]-3-phenylpropionate (36).** Via peptide coupling method B, amine **34** (49 mg, 0.134 mmol) and *N*-*t*-Boc-L-phenylalanine were coupled to provide the title compound **36** (65 mg, 80%) as a colorless foam after purification by MPLC (75 g sg, 33% ethyl acetate/hexanes).

Via peptide coupling method C, amine **34** (47 mg, 0.13 mmol) and *N*-*t*-Boc-L-phenylalanine were coupled to provide the title compound **36** (65 mg, 80%) as a colorless foam after purification by MPLC as described above. **36**: $^1$H NMR ($CDCl_3$, TMS) $\delta$ 7.18–7.38 (m, 15 H), ca. 6.89 (m, 2 H), 6.13 (br s, 1 H), 5.05 (dd, $J$ = 9.0, 6.0 Hz, 1 H), ca. 5.05 (m, 1 H), ca. 4.18 (br m, 1 H), 3.72 (s, 3 H), 3.38 (*ABX*, $J$ = 14.5, 6.5 Hz, 1 H), ca. 3.33 (m, 1 H), 3.23 (*AB*, $J$ = 12.5 Hz, 1 H), 2.95–3.13 (m, 5 H), ca. 2.18 (br m, 1 H), 2.03 (dt, $J$ = 14.5, 7.5 Hz, 1 H), 1.39 (s, 9 H); MS (CI) $(M + H)^+$ 614. Anal. Calcd for $C_{36}H_{43}N_3O_6 \cdot 0.25H_2O$: C, 69.94; H, 7.09; N, 6.80. Found: C, 69.92; H, 7.17; N, 6.70.

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