(275 μL) and the reaction mixture stirred for 3 h at 60 °C. The clear colorless solution was cooled to room temperature, diluted with saturated brine (20 mL), and extracted five times with 20-mL portions of ethyl acetate. The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a white solid that was purified by flash chromatography (ethyl acetate–methanol (9:1)), affording 230 mg of the pure lactone 14 (82.1%): IR (KBr disk) 3413, 1781, 1652 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ 1.58 (s, 1 H, Me), 3.28–3.44 (m, 2 H, 2 H-6′), 3.44–3.53 (m, 1 H, H-5′), 3.64 (m, 1 H, H-4′, after D_2O exchange dd, $J_{4'-5'}$ = 7.1, $J_{4'-3'}$ = 2.9), 3.96 (m, 1 H, H-3′, after exchange with D_2O dd, $J_{3'-4'}$ = 2.9, $J_{2'-3'}$ = 3.5), 4.09 (dd, 1 H, C_6′-OH, $J_{OH-H-6'}$ = 4.4 and 7.8, exchanges with D_2O), 4.32 (d, 1 H, H-1′, $J_{1'-2'}$ = 3.5), 4.63 (t, 1 H, H-2′, $J_{2'-1'}$ = $J_{2'-3'}$ = 3.5), 5.01 (d, 1 H, C_4′-OH, $J_{OH-H-4'}$ = 5.9, exchanges with D_2O), 5.42 (d, 1 H, C_3′-OH, $J_{OH-H-3'}$ = 4.6, exchanges with D_2O), 7.38–7.56 (m, 3 H, *m,p*-ArH), 7.78–7.82 (m, 2 H, *o*-ArH), 8.18 (s, 1 H, NH); ^{13}C NMR ($(CD_3)_2SO$, 75.4 MHz) quaternary carbons δ 175.33, 167.34, 134.34, 60.69, DEPT sequence CH 131.35, 128.19, 127.48, 79.35, 75.48, 74.78, 66.84, 64.97, CH_2 60.81, CH_3 19.32; $[\alpha]_D$ −58.3° (*c* 1.03, MeOH); mp 129–132 °C. Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.12, H, 5.91; N, 4.12.

2-(β-D-Altropyranosyl)-2-amino-(2*R*)-propionic Acid 1′,2′-Lactone Hydrochloride (15). A solution of the lactone 14 (190 mg, 0.56 mmol) in 6 N HCl (4 mL) was heated in an oil bath at 80 °C for 5 h. The solution was cooled to room temperature (benzoic acid precipitated) and extracted with two 5-mL portions of methylene chloride. The aqueous solution was evaporated and maintained under vacuum in a dessicator (P_2O_5) until constant weight to give 142 mg of 15 (94.0%): IR (KBr disk) 3369, 1774; ^1H NMR (D_2O, 300 MHz) δ 1.61 (s, 3 H, Me), 3.66–3.84 (m, 4 H, H-4′, H-5′, 2H-6′), 4.32 (t, 1 H, H-3′, $J_{3'-4'}$ = $J_{3'-2'}$ = 3.1), 4.48 (d, 1 H, H-1 $J_{1'-2'}$ = 2.2), 4.84 (dd, 1 H, H-2′, $J_{2'-1'}$ = 2.2, $J_{2'-3'}$ = 3.1); ^{13}C NMR (D_2O, 75.4 MHz) quaternary carbons δ 176.59, 61.98, DEPT sequence CH 80.78, 75.82, 74.94, 67.03, 65.32, CH_2 62.22, CH_3 18.30; $[\alpha]_D$ −10.1° (*c* 1.40, MeOH); mp 196–198 °C. Anal. Calcd for $C_9H_{16}NO_6Cl\cdot H_2O$: C, 37.57, H, 6.31; N, 4.87. Found: C, 37.71, H, 6.22; N, 4.83.

2-(β-D-Allopyranosyl)-(*R*)-alanine Hydrochloride (12). A solution of the 2*R* lactone 11 (530 mg, 1.40 mmol) in 6 N HCl (10 mL) was heated in an oil bath at 80 °C for 5 h. The solution was cooled to room temperature (benzoic acid precipitated) and extracted with two 10-mL portions of methylene chloride. The aqueous solution was evaporated and maintained under vacuum in a dessicator (P_2O_5) until constant weight to give 382 mg of 12 (94.5%): IR (KBr disk) 3421, 2925, 1729, 1629 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.64 (s, 3 H, Me), 3.47 (dd, 1 H, H-4′, $J_{4'-3'}$ = 2.4, $J_{4'-5'}$ = 10.0), 3.53–3.59 (m, 2 H, H-5′ and one of the H-6′), 3.62 (dd, 1 H, H-2′, $J_{2'-1'}$ = 10.3, $J_{2'-3'}$ = 2.4), 3.80 (dd, 1 H, one of the H-6′, J_{gem} = 15.5, $J_{6'-5'}$ = 10.3), 3.82 (d, 1 H, H-1′, $J_{1'-2'}$ = 10.3), 4.09 (t, 1 H, H-3′, $J_{3'-2'}$ = $J_{3'-4'}$ = 2.4); ^{13}C NMR (D_2O, 75.4 MHz) quaternary carbons δ 173.83, 63.10, DEPT sequence CH 76.89, 76.70, 72.57, 68.75, 67.75, CH_2 62.39, CH_3 21.49; $[\alpha]_D$ −10.4° (*c* 1.06 MeOH); mp 206–210 °C. Anal. Calcd for $C_9H_{18}NO_7Cl\cdot H_2O$: C, 37.36; H, 6.59; N, 4.58. Found: C, 35.26, H, 6.76; N, 4.32.

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Synthesis of α-Benzyl γ-Lactam, α-Benzyl δ-Lactam, and α-Benzylproline Derivatives as Conformationally Restricted Analogues of Phenylalaninamide

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The ready availability of *N*-(trifluoroacetyl)-α-allylphenylalaninamide (4) via a dehydration/hetero-Cope rearrangement/ammonolysis sequence starting with *N*-(trifluoroacetyl)phenylalanine allyl ester made it an attractive intermediate for elaboration into C-α to N- or C-α to N′-bridged products as conformationally restricted phenylalaninamide analogues. Oxidative one-carbon degradation of the side-chain olefin followed by acid-catalyzed silane reduction afforded C-α to N′-bridged γ-lactam. Hydroboration/oxidation of the side-chain olefin provided an intermediate that could be cyclized selectively either to a δ-lactam or a proline analogue depending on choice of dehydrating conditions. For preparation of a target dipeptide containing the α-substituted proline moiety, a preferred route involved N-deprotection of 4 and coupling to Boc-Asp(OBn)-OH to give a dipeptide intermediate, which similarly could be elaborated selectively to either the α-benzyl δ-lactam analogue or the α-benzylproline analogue.

Introduction

The incorporation of conformationally restricted residues constitutes an important approach to studying the bioactive conformation of peptides and also offers the potential to discover analogues with improved stability, bioselectivity, and bioavailability. *N*-Methyl amino acids,[1-3] α,α-disubstituted amino acids,[4-8] proline residues[4,9,10] and, more recently, dipeptide lactam derivatives[11-17] and β- and γ-bend mimics[18-24] are common ex-

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(2) Metcalf, G. *Pharm. J.* **1979**, *223*, 356.
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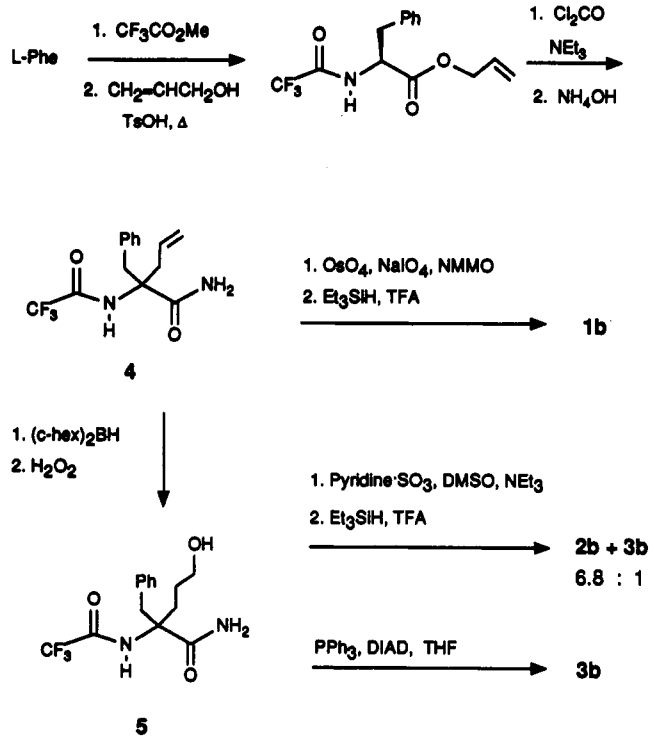
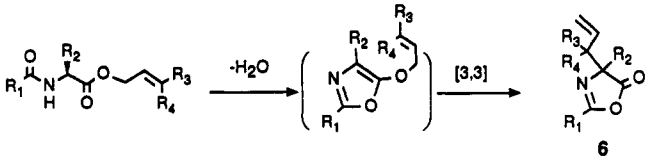
Scheme I[a]



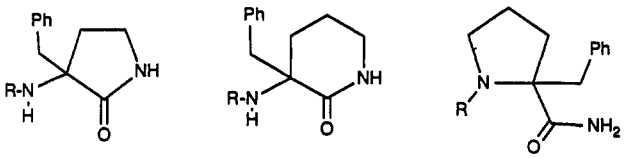
[a] Key: NMMO, *N*-methylmorpholine *N*-oxide; DIAD, diisopropyl azodicarboxylate.

amples of moieties that may be incorporated to influence the local conformation of the peptide. We have recently reported on our efforts in the 3-substituted proline series, wherein the 3-substituents were chosen to mimic potentially important amino acid side-chain moieties.[25] Our finding that *trans*-3-*n*-propyl-L-proline was superior to either proline or norleucine as a replacement for methionine in CCK tetrapeptide analogues has prompted us to examine other conformationally constrained amino acids that retain side-chain functionality.[26] We now wish to described our synthetic studies on a series of constrained analogues of phenylalaninamide, which have as a common

Scheme II



feature the incorporation of a polymethylene bridge extending from the phenylalanine α-carbon to either the nitrogen atom of the C-terminal carboxamide (γ- and δ-lactams, 1 and 2, respectively), or to the α-nitrogen atom



a. R = H
b. R = CF_3CO-
c. R = X-Asp(OBn)-

(proline analogue, 3). A key aspect of this work is the selective elaboration of a single readily available intermediate, *N*-(trifluoroacetyl)-α-allylphenylalaninamide (4), to each of the desired target structures. During the course of this work, other methods for the preparation of α-substituted γ- and δ-lactam dipeptide analogues were reported.[13-15] The work reported here represents an alternative approach to this series of constrained peptides with the present focus on modifications at the C-terminal residue of peptide primary amides and also includes a novel approach to the preparation of peptides containing an α-substituted proline residue.

Results

The synthetic route to **1b–3b** is shown in Scheme I. The introduction of the α-allyl substituent was achieved using procedures described by Steglich and co-workers,[27,28] who found that exposure of various *N*-acyl amino acid allyl esters to appropriate dehydrating conditions effected a tandem dehydration/aza-Cope rearrangement to afford 4-allyloxazalones **6** (Scheme II). For our purposes, it was necessary to establish that this chemistry was effective using a more readily cleaved *N*-acyl group, e.g., trifluoroacetyl. In particular, it was not certain what effect the resulting change in R_1 might have on the known[27,28] propensity for **6** to undergo further [3,3] rearrangement to 2-allyloxazalones. However, good results were obtained when the conditions described in Scheme I were used, and subsequent treatment of the crude **6** (R_1 = CF_3, R_2 = CH_2Ph, R_3 = R_4 = H) with aqueous ammonia followed by chromatography afforded **4** in a 70% overall yield.

Conversion of **4** to γ-lactam **1b** proceeded in a straightforward fashion by one-carbon degradation of the olefinic side chain followed by acid-catalyzed silane reduction (78% overall yield). For elaboration of **4** into δ-lactam and proline derivatives **2b** and **3b**, dehydrative cyclization of the primary alcohol **5** was examined. Precedents in similar α-monosubstituted systems described

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(26) Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. *J. Med. Chem.* **1991**, *34*, 455.
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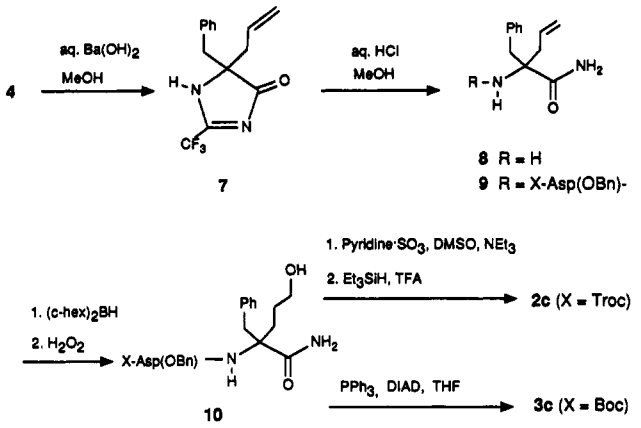
Scheme III[a]



[a] Key: Troc, 2,2,2-trichloroethoxycarbonyl; Boc, *tert*-butoxycarbonyl.

by Nakajima et al.[29] and Olsen et al.[30] led to the expectation that nonselective cyclization would result to afford a mixture of **2b** and **3b**. In fact, as described in the following text, appropriate conditions could be selected that strongly favored either mode of cyclization.

Hydroboration of **4** with dicyclohexylborane[31] followed by oxidative workup afforded **5** (68% yield). Use of 9-BBN was less satisfactory, owing to difficulty with separation of the BBN-derived diol from the desired product. For cyclization, a two-step sequence involving oxidation to the aldehyde followed by acid-catalyzed dehydration/silane reduction afforded in 68% combined yield a readily separated mixture of δ-lactam **2b** and proline derivative **3b**, in which **2b** predominated by a ratio of 7:1. In contrast, dehydration under Mitsunobu conditions[32] smoothly produced **3b** as the sole cyclization product in 67% yield. Treatment of **5** with triflic anhydride and NEt_3 at low temperature resulted in a mixture of all possible N- and O-alkylation products. Products **2b** and **3b** were distinguished by comparing the ^1H NMR spectra before and after D_2O exchange, whereby the splitting pattern of the δ methylene resonance simplified for **2b** but not for **3b**. In addition, N-deprotection of **3b** (aqueous $Ba(OH)_2$, MeOH, ambient temperature) gave **3a**, which was independently prepared by α-benzylation of Cbz-Pro-OtBu ($LiN(TMS)_2$, $PhCH_2Br$) followed by conversion to the primary amide and N-deprotection using standard procedures.

The ability to N-deprotect and extend **1b–3b** to dipeptide analogues of Boc-Asp(OBn)-Phe-NH_2 also was examined. For all three analogues, alkaline hydrolysis of the trifluoroacetyl group proceeded readily at room temperature with methanolic $Ba(OH)_2$ although, as expected, the conversion was slower for proline analogue **3b**. As has been found by others in similar systems,[14] the free amino groups of **1a** and **2a** were amenable to acylation under standard peptide coupling conditions. For example, the coupling of Boc-Asp(OBn)-OH to **1a** via the isobutyl carbonic mixed anhydride proceeded in 83% isolated yield. In contrast, **3a** proved resistant to acylation with activated derivatives of aspartic acid, and although a number of methods were attempted,[33] in no case was a usable quantity of the desired dipeptide derivative produced. Therefore, a sequence in which acylation of the amine preceded cyclization to the proline derivative was examined as an alternative approach.

The conversion of **4** to dipeptide alcohol **9** and the selective elaboration of **9** to either **2c** or **3c** is illustrated in Scheme III. Unexpectedly, N-deprotection of **4** was not immediately straightforward. Under alkaline hydrolysis conditions, **4** underwent complete conversion to a product that is tentatively assigned the structure **7** on the basis of results described by Cotton et al.[35] Once **7** was identified, it was subjected to hydrolysis under acidic conditions by treatment with aqueous HCl, which effected clean conversion to the desired amine **8**, isolated in quantitative yield from **4**. Direct exposure of **4** only to the acidic conditions gave no reaction. Reductive cleavage of the trifluoroacetyl group[36] also could be accomplished using $LiBH_4$ in DME or $Ca(BH_4)$ in EtOH/THF, but yields were lower and more variable (50–70%), and these procedures in general did not entirely circumvent the formation of **7** as a byproduct.

Extension of amine **8** to dipeptide **9** proceeded in 75–85% yields under normal mixed anhydride or carbodiimide-mediated coupling conditions. Hydroboration to dipeptide alcohol **10** was accomplished in 54% yield with dicyclohexylborane. Compound **10** was smoothly converted to **3c** in 65–85% yields under standard Mitsunobu conditions; none of the δ-lactam could be observed in the ^1H NMR or TLC of the crude product mixture.

Although the preparation of the δ-lactam dipeptide **2c** is more conveniently accomplished by deprotection and acylation of **2b** as described in the previous text, it was of interest for comparative purposes to examine the extent to which treatment of dipeptide alcohol **10** under the oxidation/reduction protocol also would lead to predominant δ-lactam formation, as had been the case for the simpler alcohol **5**. In particular, this experiment would examine the effect of the *N*-trifluoroacetyl group of **5** vs the less electron-withdrawing amino acyl moiety of **10** on the direction of cyclization, since it was conceivable that the more nucleophilic amide nitrogen might have the effect of increasing the proportion of proline product. For this experiment, N-terminal Troc protection was used, since Boc is marginally stable to the acidic conditions of the silane reduction procedure. In the event, exposure of **10** (X = Troc) to the oxidation/reduction sequence led to exclusive formation of δ-lactam **2c** (X = Troc); the proline derivative (independently prepared using the Mitsunobu conditions) was not detectable in the ^1H NMR or TLC of the crude product mixture.

Discussion

It is of interest to compare the results from the present work with those obtained by others in studies involving

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(33) Attempted coupling methods included the following: symmetrical anhydride (Boc-Asp(OBzl)-OH, 1-(3-[(dimethylamino)propyl]-3-ethylcarbodiimide, CH_2Cl_2); acid chloride ((a) (*Z*)-Asp(Ot-Bu)-OH·DCHA, $SOCl_2$, pyridine, 4-(dimethylamino)pyridine: Matsuda, F.; Itoh, S.; Hattori, N. *Tetrahedron* **1985**, *41*, 3625. (b) Fmoc-Asp(OBzl)-Cl: Carpino, L. A.; Cohen, B. J.; Stephens, K. E.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3734); *N*-(trifluoroacetyl)aspartic anhydride, DMF, 60 °C; (*Z*)-Asp(Ot-Bu)-OH, BOP-Cl.

(34) For other studies involving α-substituted proline derivatives, see: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Thaisrivongs, S.; Pals, D. T.; Lawson, J. A.; Turner, S. R.; Harris, D. W. *J. Med. Chem.* **1987**, *30*, 536. (c) Schollkopf, U.; Wick, R.; Hinrichs, R.; Lange, M. *Liebigs Ann. Chem.* **1988**, 1025. (d) Reference 23. (e) Williams, R. M.; Glinka, T.; Kwast, E.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808.

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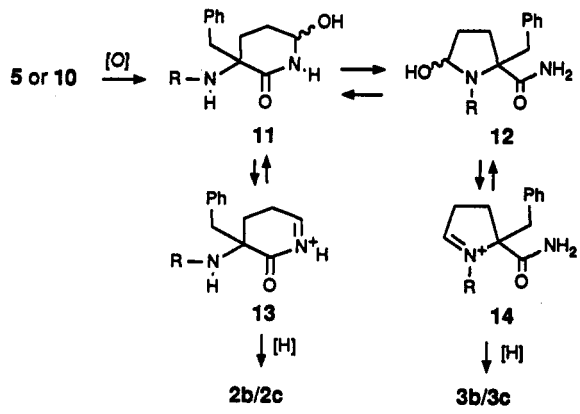
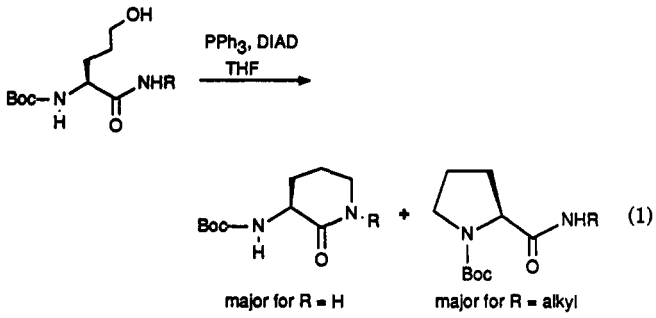
Scheme IV



similar cyclizations of amino acid derivatives bearing ω-functionalized side chains. Nakajima[29] et al. studied the cyclization of a series of Boc-δ-hydroxynorvaline amides under Mitsunobu conditions (eq 1), whereby the primary

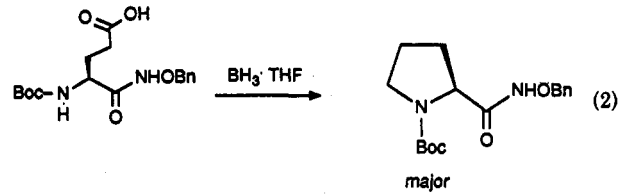


(1)

amide (R = H) cyclized to a mixture in which the δ-lactam predominated over the proline product (2.7:1). Since the formation of five-membered rings is faster than the formation of six-membered rings by an S_N2 process when other factors are equal,[37] the preferred formation of the six-membered ring in the Mitsunobu cyclization of Boc-δ-hydroxynorvalinamide indicates that an opposing bias exists in this case. The importance of steric interactions to the direction of cyclization, as opposed to pK_a differences between the two nucleophilic centers,[38] is supported by the observation that cyclization of secondary amides of Boc-δ-hydroxynorvaline under the same conditions afforded the proline products to the exclusion of δ-lactams.

In the present work, the presence of the additional bulky α-benzyl substituent could potentially create a conformational bias in favor of one mode of cyclization over the other. However, the observation that each mode of cyclization is favored under particular reaction conditions argues against any overwhelming such bias. The finding that primary amides **5** and **10** preferentially cyclized to the proline derivatives under Mitsunobu conditions is consistent with the kinetic preference for five-membered-ring formation, and in the case of **5**, by a lower pK_a for the trifluoroacetamide moiety. For both **5** and especially for **10**, the greater steric congestion about the internal secondary amide nitrogen could in principal have caused δ-lactam formation to be favored but, in contrast to the results of Nakajima, this factor does not appear to have played a major role here.

In contrast to the irreversible S_N2-mediated ring closure under Mitsunobu conditions, initial closure during the oxidation/reduction sequence presumably is a reversible process (Scheme IV). The predominant formation of **2b/2c** over **3b/3c** could reflect either the relative stabilities of the intermediate lactols **11** and **12** or, presuming a rapid equilibrium between the lactols, the relative ease with which each is reduced to product. The greater ability of the six-membered ring of iminium ion **13** to accommodate two sp^2 centers would favor the formation of **2** over **3**, and this factor may account for the results of the present study. However, during work on the synthesis of N^5-hydroxy-L-ornithine from L-glutamic acid, Olsen et al.[30] carried out the borane reduction of Boc-L-Glu-NHOBn (eq 2) and



(2)

obtained, in addition to the expected δ-hydroxynorvaline derivative (19%), a 40% yield of Boc-Pro-NHOBn, presumably via cyclization of the intermediate aldehyde followed by further reduction. Since no mention is made of a possible δ-lactam product, it is assumed that its formation was insignificant relative to that of the proline derivative. Thus, the results from cyclization of **5** and **10** by the oxidation/reduction sequence are in contrast to what might have been anticipated from the literature precedent. Under the assumption that the additional α-benzyl substituent has a minimal effect on the direction of cyclization, in accord with the rationale mentioned previously, then an explanation for the observed discrepancies must lie either in the precise nature of the substituents on the nitrogen atoms or in the difference in reaction conditions. It would be of interest to study these systems in a more controlled fashion with respect to reaction conditions, N-substituents, and the presence or absence of α-substituents.

In summary, key intermediate **4** is efficiently prepared from L-phenylalanine and converted in straightforward fashion to the γ-lactam **1**. Novel observations with respect to the mode of cyclization of alcohols **5** and **10** under different conditions have led to the ability to selectively prepare either δ-lactam or proline derivatives (**2** and **3**, respectively) from a common intermediate. Thus, a novel approach to the preparation of dipeptides containing a C-terminal α-substituted proline unit also has been developed.

Experimental Section

Instrumentation and other analytical procedures were as described previously.[25] THF was distilled from Na/benzophenone; DMSO, CH_2Cl_2, and DMF were dried by storage over 4A molecular sieves; anhydrous CH_3CN was purchased from Aldrich; other solvents were used as purchased unless otherwise indicated. Standard work-up refers to successive washings of an EtOAc solution of the reaction mixture with saturated aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, and brine, drying over anhydrous Na_2SO_4, and evaporation of the filtrate under reduced pressure. Unless otherwise indicated, chromatography was carried out using Merck Silica Gel 60, 230–400 mesh, in either gravity or flash mode.

***N*-(Trifluoroacetyl)-L-phenylalanine.** A suspension of L-phenylalanine (25 g, 152 mmol) in DMF (100 mL) containing NEt_3 (23.3 mL, 182 mmol) and CF_3CO_2Me (15.8 mL, 167 mmol) was stirred at 0 °C and then at ambient temperature overnight. The homogeneous solution was acidified with saturated aqueous $KHSO_4$ then extracted twice with EtOAc. The combined organic phases were washed successively with H_2O and brine and then dried ($MgSO_4$) and concentrated. Recrystallization from

(37) Streitweiser, A.; Heathcock, C. H. *Introduction to Organic Chemistry*; MacMillan: New York, 1976; p 616.
(38) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563 and references cited therein.

Et_2O/hexanes afforded 32 g (99%) of fine needles: mp 119–120 °C (lit.[39] mp 120–121 °C); $[\alpha]^{23}_D$ = +16° (c 2.05, EtOH) lit. $[\alpha]^{23}_D$ = +16° (2%, EtOH); ^1H NMR ($CDCl_3$) δ 3.22 (dd, J = 6 and 15 Hz, 1 H), 3.31 (dd, J = 6 and 14 Hz, 1 H), 4.93 (m, 1 H), 6.72 (br d, J = 7 Hz, 1 H), 7.13 (m, 2 H), 7.32 (m, 3 H); MS (DCI/NH_3) m/e 279 (M + NH_4^+, 100), 262 (M + H^+, 7).

***N*-(Trifluoroacetyl)-L-phenylalanine Allyl Ester.** A mixture of the previous acid (7.6 g, 29.1 mmol), TsOH·H_2O (0.55 g, 2.9 mmol), allyl alcohol (7.9 mL, 116 mmol), and toluene (100 mL) was heated at reflux for 4 h with azeotropic removal of water using a Dean-Stark apparatus. The cooled reaction mixture was diluted with EtOAc, washed successively with saturated aqueous $NaHCO_3$ and brine, and then dried and concentrated. Recrystallization from EtOH/H_2O afforded 6.7 g (76%) of off-white needles: mp 44–45 °C; $[\alpha]^{23}_D$ = +68.0 (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.21 (m, 2 H), 4.17 (m, J_1 = 6 Hz, 2 H), 4.90 (dd, J = 6, 16 Hz, 1 H), 5.36 (m, 2 H), 5.89 (m, 1 H), 6.73 (br d, 1 H), 7.09 (m, 2 H), 7.30 (m, 3 H); MS (DCI/NH_3) m/e 319 (M + NH_4^+, 100). Anal. Calcd for $C_{14}H_{14}NO_3F_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.65; H, 4.65; N, 4.64.

***N*-(Trifluoroacetyl)-α-allylphenylalaninamide (4).** *Caution: This procedure should be carried out in a well-ventilated hood.* To a solution of the previous ester (4.24 g, 14.1 mmol) and NEt_3 (10 mL, 72 mmol) in anhydrous CH_3CN (50 mL) at 0 °C under N_2 was added a solution of phosgene in toluene (32 mL, nominal concentration 12.5%, ca. 32 mmol) dropwise over 0.5 h. Stirring was continued for an additional 2 h at 0 °C, and then the mixture was poured onto ice–water and extracted with EtOAc. The organic layer was washed successively with H_2O and brine then concentrated. The residue was dissolved in 200 mL of THF, of which a 150-mL portion was treated with 10 mL of concd NH_4OH followed by stirring at ambient temperature overnight. After concentration, the residue was subjected to standard workup. Chromatography (1:2 to 1:1 EtOAc/hexanes) afforded 2.8 g of nearly pure product, which was crystallized from Et_2O/hexanes to give 2.21 g (70%) of colorless crystals: R_f (10% MeOH/$CHCl_3$) 0.50; mp 124–125 °C; ^1H NMR ($CDCl_3$) δ 2.56 (dd, J = 6, 14 Hz, 1 H), 3.12 (d, J = 14 Hz, 1 H), 3.43 (dd, J = 8, 14 Hz, 1 H), 3.72 (d, J = 14 Hz, 1 H), 5.20 (m, 2 H), 5.12 (m, 1 H), 5.80 (br m, 2 H), 7.12 (m, 2 H), 7.28 (m, 3 H), 7.62 (br s, 1 H); MS (DCI/NH_3) m/e 318 (M + NH_4^+, 100), 301 (M + H^+, 5). Anal. Calcd for $C_{14}H_{15}N_2O_2F_3$: C, 56.00; H, 5.04; N, 9.33. Found: C, 55.73; H, 5.02; N, 9.33.

3-Benzyl-2-oxo-3-(trifluoroacetamido)pyrrolidine (1b). A solution of 4 (293 mg, 0.97 mmol) and NMMO (144 mg, 1.07 mmol) in CH_3CN (16 mL) and H_2O (8 mL) was treated with 2.5% OsO_4 in toluene (0.13 mL, 0.01 mmol) followed by solid $NaIO_4$ (829 mg, 3.88 mmol). The mixture was stirred at ambient temperature for 3 days, diluted with EtOAc, washed successively with H_2O, saturated aqueous $NaHCO_3$, and brine, and then dried (Na_2SO_4), concentrated, filtered through Celite, and again concentrated to afford 348 mg of crude hydroxy lactam. A solution of the hydroxy lactam, Et_3SiH (0.31 mL, 1.95 mmol), and TFA (0.94 mL) in CH_2Cl_2 (4 mL) was allowed to stand under a $CaSO_4$ drying tube at ambient temperature for 18 h then concentrated. The residue in EtOAc was washed successively with H_2O, 10% aqueous Na_2CO_3, and brine, then dried (Na_2SO_4), and concentrated. Crystallization of the residue from Et_2O/hexanes afforded 230 mg (78%) of fine needles: mp 130–131 °C; ^1H NMR ($CDCl_3$) δ 2.48 (m, 2 H), 2.85 (m, 1 H), 3.11–3.25 (m, 3 H), includes 3.13 (d, J = 12 Hz, 1 H) and 3.21 (d, J = 12 Hz, 1 H), 5.82 (br s, 1 H), 6.99 (br s, 1 H), 7.22 (m, 1 H), 7.30 (m, 1 H); MS (DCI/NH_3) m/e 304 (M + NH_4^+, 100), 287 (M + H^+, 85). Anal. Calcd for $C_{13}H_{13}N_2O_2F_3$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.28; H, 4.59; N, 9.70.

***N*-(Boc-Asp(OBn))-3-amino-3-benzyl-2-oxopyrrolidine (1c, X = Boc).** A solution of **1b** (75 mg, 0.26 mmol) in MeOH (3 mL) and saturated aqueous $Ba(OH)_2$ (3 mL, 0.53 mmol) was stirred for 18 h then concentrated. The remaining aqueous solution was saturated with NaCl and extracted four times with EtOAc, then the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered through Celite, and evaporated to 50 mg (quantitative) of **1a**: ^1H NMR ($CDCl_3$) δ 1.90 (m, 1 H), 2.31 (m, 1 H), 2.67 (m, 1 H), 2.80 (d, J = 13 Hz, 1 H), 2.98 (d, J = 13 Hz, 1 H), 3.16 (m, 1 H), 5.46 (br s, exchangeable), 7.27 (m, 5 H); MS (DCI/NH_3) m/e 208 (M + NH_4^+, 100), 191 (M + H^+, 83).

To a solution of Boc-Asp(OBn)-OH (121 mg, 0.38 mmol) and *N*-methylmorpholine (0.041 mL, 0.38 mmol) in CH_2Cl_2 (2 mL) at −15 °C was added isobutyl chloroformate (0.047 mL, 0.36 mmol). The mixture was stirred for 5 min, treated with a solution of **1c** (48 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), allowed to warm to ambient temperature and stir overnight then concentrated. The residue was subjected to standard workup followed by chromatography (1.5% MeOH/$CHCl_3$) to afford 103 mg (83%) of the dipeptide as a mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.28–2.47 (m, 2 H), 2.60–2.78 (m, 2 H), 3.00–3.15 (m, 4 H), 4.54 (m, 1 H), 5.11 (dd, J = 2, 12 Hz, 1 H), 5.17 (dd, J = 3, 12 Hz, 1 H), 5.55–5.65 (m, 2 H), 7.08 (m, 1 H), 7.22–7.38 (m, 10 H); MS (DCI/NH_3) m/e 513 (M + NH_4^+, 100), 496 (M + H^+, 10).

***N*-(Trifluoroacetyl)-α-(3-hydroxy-*n*-propyl)phenylalaninamide (5).** A suspension of dicyclohexylborane in THF was prepared by addition of cyclohexene (0.31 mL, 3.1 mmol) to 1.0 M BH_3/THF (1.5 mL, 1.5 mmol) at 0 °C under N_2, followed by stirring at 0 °C for 0.25 h. Approximately half of the resultant suspension (ca. 0.7 mmol) was transferred by syringe to a prechilled flask containing 4 (153 mg, 0.51 mmol). After being stirred for 5 min at 0 °C and at ambient temperature for 1.5 h, the mixture was diluted with pH 7 phosphate buffer (10 mL) and 95% EtOH (5 mL) then treated with 30% H_2O_2 (2 mL). After being stirred at ambient temperature overnight, the solution was concentrated and the resulting aqueous mixture was extracted twice with EtOAc. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine and then dried (Na_2SO_4) and evaporated to 200 mg of crude product. Chromatography (2:3 Me_2CO/hexanes) afforded 111 mg (68%) of a foam: ^1H NMR ($CDCl_3$) δ 1.50 (m, 2 H), 1.95 (m, 1 H), 2.83 (m, 1 H), 3.12 (d, J = 14 Hz, 1 H), 3.55–3.78 (m, 2 H), 3.68 (d, J = 14 Hz, 1 H), 5.72 (br s, 1 H), 6.02 (br s, 1 H), 7.11 (m, 2 H), 7.28 (m, 3 H), 7.80 (s, 1 H); MS (FAB$^+$) m/e 319 (M + H^+, 20), 302 (100). Anal. Calcd for $C_{14}H_{17}N_2O_3F_3$·0.1 Me_2CO: C, 52.99; H, 5.47; N, 8.64. Found: C, 52.76; H, 5.48; N, 8.38.

Conversion of 5 to 3-Benzyl-2-oxo-3-(trifluoroacetamido)piperidine (2b) and *N*-(Trifluoroacetyl)-α-benzylprolinamide (3b) by the Oxidation/Reduction Sequence. To a rapidly stirred solution of **5** (130 mg, 0.41 mmol) and NEt_3 (0.34 mL, 2.46 mmol) in anhydrous DMSO (1 mL) was added over 3 min a solution of pyridine/sulfur trioxide complex (261 mg, 1.64 mmol) in DMSO (3 mL). After 20 min, the mixture was subjected to standard workup. The crude hydroxy lactam (130 mg) was treated with Et_3SiH/TFA and subsequent workup as described for preparation of **1b** to afford 140 mg of crude product. ^1H NMR indicated a 7:1 mixture of **2b** to **3b**. Chromatography (0.5% MeOH/$CHCl_3$) afforded 76 mg (62%) of **2b**: R_f (10% MeOH/$CHCl_3$) 0.61; mp 143–144 °C; ^1H NMR ($CDCl_3$) δ 1.87–2.05 (m, 2 H), 2.15 (m, 1 H), 2.75 (dt, J = 4.5, 13.5 Hz, 1 H), 3.20 (d, J = 14 Hz, 1 H), 3.30–3.50 (m, 2 H), 3.43 (d, J = 14 Hz, 1 H), 5.80 (br m, 1 H), 7.12 (m, 2 H), 7.20 (br s, 1 H), 7.30 (m, 3 H). In the presence of D_2O, the pattern at δ 3.30–3.50 simplified. MS (DCI/NH_3) 318 (M + NH_4^+, 100), 301 (M + H^+, 55). Anal. Calcd for $C_{14}H_{15}N_2O_2F_3$: C, 56.00; H, 5.04; N, 9.33. Found: C, 55.82; H, 5.11; N, 9.19.

There also was obtained 7 mg (6%) of **3b**: R_f (10% MeOH/$CHCl_3$) 0.48; ^1H NMR ($CDCl_3$) δ 1.43 (m, 1 H), 1.80 (m, 1 H), 2.08 (m, 1 H), 2.43 (m, 1 H), 3.16 (m, 1 H), 3.18 (d, J = 14 Hz, 1 H), 3.72 (m, 1 H), 3.82 (d, J = 14 Hz, 1 H), 5.45 (br s, 1 H), 6.55 (br s, 1 H), 7.11 (m, 2 H), 7.30 (m, 3 H); MS (DCI/NH_3) 318 (M + NH_4^+, 100), 301 (M + H^+, 20).

Conversion of 5 to 3b under Mitsunobu Conditions. A solution of **5** (46 mg, 0.14 mmol) and PPh_3 (76 mg, 0.29 mmol) in anhydrous THF under N_2 was treated with DIAD (0.057 mL, 0.29 mmol). After being stirred at ambient temperature for 24 h, the solution was concentrated, and then the residue was subjected to standard workup to afford 194 mg of crude product. A 161-mg protion was chromatographed (3% MeOH/$CHCl_3$) to yield 23 mg (67%) of **3b**: mp 183–184.5 °C; MS (DCI/NH_3) m/e 318 (M + NH_4^+, 18), 301 (M + H^+, 100), 256 (30). The NMR spectrum was identical with that described previously for **3b**. Anal. Calcd for $C_{14}H_{15}N_2O_2F_3$·0.2 H_2O: C, 55.34; H, 5.11; N, 9.22. Found: C, 55.26; H, 5.10; N, 8.97.

(39) Panetta, C. A.; Casanova, T. G. *J. Org. Chem.* **1970**, *35*, 4275.

α-Benzylprolinamide (3a). A solution of trifluoroacetamide **3b** (3 mg, 0.01 mmol) in MeOH (0.5 mL) and saturated aqueous $Ba(OH)_2$ (0.55 mL) was stirred under N_2 for 48 h and then partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc (2X), and then the combined organic extracts were dried (Na_2SO_4) and evaporated to 2 mg of **3c**: ^1H NMR ($CDCl_3$) δ 1.73 (m, 2 H), 1.90 (m, 1 H), 2.22 (m, 1 H), 2.72 (d, J = 13 Hz, 1 H), 2.90 (m, 1 H), 3.02 (m, 1 H), 3.49 (d, J = 13 Hz, 1 H), 5.31 (br m, 1 H), 7.20 (m, 2 H), 7.29 (m, 3 H), 7.49 (br m, 1 H); MS (DCI/NH_3) m/e 205 (M + H^+, 100). A product with identical spectroscopic properties was obtained from Cbz-Pro-OtBu by alkylation (LiN(TMS)$_2$, THF, then $PhCH_2Br$), ester cleavage (TFA/CH_2Cl_2), conversion to the primary amide [$(ClCO)_2$, DMF (cat.), CH_2Cl_2, then concd NH_4OH], and hydrogenolysis (HCO_2NH_4, Pd/C, MeOH) in 58% overall yield.

***N*-(Boc-Asp(OBn))-3-amino-3-benzyl-2-oxopiperidine (2c, X = Boc).** A solution of **2b** (59 mg, 0.20 mmol) in MeOH (2 mL) and saturated aqueous $Ba(OH)_2$ (2.2 mL) was stirred at ambient temperature for 18 h. The methanol was evaporated, and the aqueous residue was diluted with brine and extracted four times with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated to 38 mg of the free amine, which was dissolved in DMF (4 mL) together with Boc-Asp(OBn)-OH (97 mg, 0.3 mmol) and HOBt·H_2O (46 mg, 0.3 mmol). The solution was cooled to 0 °C, treated with 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (57 mg, 0.3 mmol), then allowed to warm to ambient temperature and stir overnight. Standard workup afforded 102 mg of crude product, which was chromatographed (1.5% MeOH/$CHCl_3$) to yield 19 mg of the more mobile isomer, 40 mg of a mixture of isomers, and 9 mg of the less mobile isomer (combined yield, 67%). More mobile isomer: R_f (10% MeOH/$CHCl_3$) 0.53; NMR ($CDCl_3$) δ 1.45 (2 s, 9 H), 1.95 (m, 1 H), 2.29–2.79 (m, 4 H), 2.95–3.19 (m, 4 H), 3.75 (m, 1 H), 4.52 (m, 1 H), 5.13 (m, 2 H), 5.49 (m) and 5.59 (m) (total 2 H), 7.06 (m, 1 H), 7.21–7.38 (m, 10 H); MS (DCI/NH_3) m/e 510 (M + H^+, 100), 496 (38), 454 (MH–C_4H_8, 30).

Less mobile isomer: R_f (10% MeOH/$CHCl_3$) 0.49; NMR ($CDCl_3$) δ 1.42 (s with shoulder, 9 H), 1.78 (m, 2 H), 2.19 (m, 2 H), 2.71 (dd, J = 6, 17 Hz, 1 H), 2.95–3.09 (m, 2 H, includes 3.02, d, J = 14 Hz), 3.18–3.31 (m, 2 H, includes 3.28, d, J = 14 Hz), 3.43 (m, 1 H), 4.51 (m, 1 H), 5.10 and 5.14 (2 s, 2 H), 5.50 and 5.59 (m, total 1 H), 5.75 (m, 1 H), 7.10 (m, 1 H), 7.21 (m, 2 H), 7.35 (m, 8 H); MS (DCI/NH_3) m/e 510 (M + H^+, 100), 454 (MH–C_4H_8, 40).

α-Allylphenylalaninamide (8). A solution of **4** (500 mg, 1.67 mmol) in MeOH (13 mL) and saturated aqueous $Ba(OH)_2$ (13 mL, ca. 2.3 mmol) was stirred at ambient temperature overnight. The methanol was evaporated, the residual aqueous phase was extracted with EtOAc (4X), and then the EtOAc was evaporated to afford **7**: R_f (10% MeOH/$CHCl_3$) 0.81; ^1H NMR ($CDCl_3$) 1.90 (broad), 2.68 (t, J = 7.5 Hz, 2 H), 3.08 (d, J = 13 Hz, 1 H), 3.19 (d, J = 13 Hz, 1 H), 5.09–5.24 (m, 2 H), 5.60 (m, 1 H), 7.12 (m, 2 H), 7.21 (m, 2 H), 7.28 (m, 1 H).

The residue was dissolved in MeOH (10 mL) and 3 N HCl (10 mL) and allowed to stand at ambient temperature overnight, and then the solution was concentrated. An equal volume of EtOAc was added to the residual aqueous solution, and the pH was adjusted to 10–11 by cautious addition of solid Na_2CO_3. The layers were separated, the aqueous phase was extracted with EtOAc (3 X), and then the combined organic extracts were dried (Na_2SO_4) and evaporated to 340 mg (100%) of a colorless solid: mp 120–121 °C; R_f (10% MeOH/$CHCl_3$) 0.51; ^1H NMR ($CDCl_3/D_2O$) δ 2.19 (dd, J = 9, 13 Hz, 1 H), 2.65 (d, J = 14 Hz, 1 H), 2.80 (dd, J = 7, 13 Hz, 1 H), 3.36 (d, J = 14 Hz, 1 H), 5.10–5.21 (m, 2 H), 5.81 (m, 1 H), 7.20 (m, 2 H), 7.30 (m, 3 H); MS (DCI/NH_3) m/e 205 (M + H^+, 100). Anal. Calcd for $C_{12}H_{16}N_2O·0.4\ H_2O$: C, 68.15; H, 8.01; N, 13.25. Found: C, 67.84; H, 7.63; N, 13.01.

***N*-(Boc-Asp(OBn))-α-allylphenylalaninamide (9, X = Boc).** A mixed carbonic anhydride procedure analogous to that described for the preparation of **1c (X = Boc)** was used to convert **8** (270 mg, 1.32 mmol) to the title compound. The crude product (780 mg) was crystallized from Et_2O/hexanes to afford 460 mg (67%) of a ca. 1:1 mixture of diastereomers: mp 102–108 °C; ^1H NMR ($CDCl_3$) δ 1.39 (s) and 1.41 (s) (total 9 H), 2.45 (m, 0.5 H), 2.59 (m, 0.5 H), 2.73–2.90 (m, 1 H), 2.90–3.10 (m, 1 H), 3.13 (d, J = 14 Hz, 0.5 H), 3.22 (d, J = 14 Hz, 0.5 H), 3.45 (d, J = 14 Hz, 0.5 H), 3.58 (d, J = 14 Hz, 0.5 H), 4.38 (m, 1 H), 5.05–5.20 (m, 4 H), 5.22 (br m, 1 H), 5.39 (br m, 1 H), 5.72 (m, 1 H), 6.52 (br m, 1 H), 6.70 (br s, 0.5 H), and 6.80 (br s, 0.5 H), 7.15 (m, 2 H), 7.22–7.40 (m, 8 H); MS (FAB) m/e 510 (M + H^+, 80), 437 (100). Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.25. Found: C, 65.65; H, 6.94; N, 8.15. An additional 112 mg (16%) of the product was obtained by chromatography of the mother liquors (2% MeOH/$CHCl_3$).

***N*-(Boc-Asp(OBn))-α-(3-hydroxy-*n*-propyl)phenylalaninamide (10).** To a solution 1.0 M BH_3 in THF (1.44 mL, 1.44 mmol) at 0 °C under N_2 was added cyclohexene (0.29 mL, 2.88 mmol) by syringe, and the mixture was stirred for 0.5 h, during which time a white precipitate formed. A prechilled (0 °C) solution of **9** (480 mg, 0.92 mmol) in anhydrous THF (4 mL) was added, and stirring was continued for 2 h at 0 °C and then at room temperature overnight. Workup as described for isolation of **5** afforded 514 mg of crude product, which was chromatographed (1:1 hexanes/Me_2CO) to yield 266 mg (54%) of a colorless solid: mp 75–79 °C. ^1H NMR ($CDCl_3$) indicated a nearly 1:1 mixture of diastereomers δ 1.37 and 1.40 (s, total 9 H), 1.50–1.71 (m, 2 H), 1.92–2.12 (m) and 2.13–2.27 (m) (total 2 H), 2.71–2.88 (overlapping dd's, J = 6, 18 Hz and J = 5, 16 Hz, total 1 H), 3.10 (dd, J = 4.5, 17 Hz, 1 H), 3.25–3.48 (m, 2 H), 3.61 (m, 2 H), 4.40 (m, 1 H), 5.10 and 5.12 (s, total 2 H), 5.32 (br m, 1 H), 5.45 (br t, J = 9 Hz, 1 H), 6.42 (br m, 1 H), 7.12 (m, 2 H), 7.16–7.40 (m, 8 H); MS (DCI/NH_3) m/e 545 (M + NH_4^+, 75), 528 (M + H^+, 100). Anal. Calcd for $C_{28}H_{37}N_3O_7·0.1\ H_2O$: C, 63.52; H, 7.08; N, 7.94. Found: C, 63.21; H, 7.03; N, 7.68.

***N*-((Boc-Asp(OBn))-α-benzylprolinamide (3c, X = Boc).** Starting with **10** (171 mg, 0.32 mmol), Mitsunobu reaction and workup conditions analogous to those described for conversion of **5 to 3b** were employed. The product was purified by radial thin-layer chromatography on silica gel (2-mm thickness, hexanes/Me_2CO (3:1 to 1:1)), which afforded 36 mg (21%) of the more mobile isomer, 73 mg (43%) of a mixture of diastereomers, and 35 mg (21%) of the less mobile isomer. More mobile isomer: R_f (1:1 hexanes/Me_2CO) 0.44; $[\alpha]^{25}_D$ = −87.7° (c 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$/MeOH-d_4) δ 1.21 (m, 1 H), 1.43 (s, 9 H), 1.73 (m, 1 H), 2.20 (m, 2 H), 2.68 (dd, J = 7.5, 16.5 Hz, 1 H), 2.80 (dd, J = 6, 16.5 Hz, 1 H), 3.16 (m, 1 H), 3.24 (d, J = 13.5 Hz, 1 H), 3.78 (d, J = 13.5 Hz, 1 H), 3.86 (m, 1 H), 4.63 (m, 1 H), 5.16 (s, 2 H), 7.11 (m, 2 H), 7.22–7.30 (m, 4 H), 7.36 (m, 4 H); HRMS calcd for $C_{28}H_{36}N_3O_6$ 510.2604, found 510.2604.

Less mobile isomer: R_f (1:1 hexanes/Me_2CO) 0.40; $[\alpha]^{25}_D$ = +44.0° (c 2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$/MeOH-d_4) δ 1.13 (m, 1 H), 1.49 (s, 9 H), 1.68 (m, 1 H), 2.20 (m, 2 H), 2.72 (dd, J = 4, 17 Hz, 1 H), 3.13 (dd, J = 10.5, 17 Hz, 1 H), 3.21 (d, J = 14 Hz, 1 H), 3.30 (m, 1 H), 3.70–3.83 (m, 2 H, includes 3.80, d, J = 14 Hz, 1 H), 4.88 (m, 1 H), 5.12 (m, 2 H), 7.13 (m, 2 H), 7.20–7.33 (m, 4 H), 7.36 (m, 4 H); HRMS found 510.2599.

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Registry No. **1a**, 133230-46-3; **1b**, 133230-45-2; **1c** (X = BOC, diastereomer-1), 133230-47-4; **1c** (X = BOC, diastereomer-2), 133230-48-5; **2b**, 133270-15-2; **2c** (X = BOC, diastereomer-1), 133230-52-1; **2c** (X = BOC, diastereomer-2), 133230-53-2; **3a**, 133230-51-0; **3b**, 133230-50-9; **3c** (X = BOC, diastereomer-1), 133230-60-1; **3c** (X = BOC, diastereomer-2), 133230-61-2; **4**, 133230-44-1; **5**, 133230-49-6; **7**, 133230-54-3; **8**, 133230-55-4; **9** (X = BOC, diastereomer-1), 133230-56-5; **9** (X = BOC, diastereomer-2), 133230-57-6; **10** (X = BOC, diastereomer-1), 133230-58-7; **10** (X = BOC, diastereomer-2), 133230-59-8; H-Phe-OH, 63-91-2; CF_3COOMe, 431-47-0; CF_3CO-Phe-OH, 350-09-4; CF_3CO-Phe-$OCH_2CH{=}CH_2$, 133230-43-0; BOC-Asp(OBn)-OH, 7536-58-5.