3,4-Disubstituted γ-Lactam Rings as Conformationally Constrained Mimics of Peptide Derivatives Containing Aspartic Acid or Norleucine

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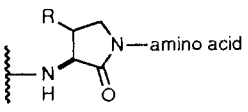
Concise syntheses of carboxylic ester and *n*-propyl-substituted γ-lactam-constrained derivatives **7a,b** and **18a,b**, starting from commercially available *N*-t-Boc-L-Asp(OBz)OH (**4**), are described. Esterification of **4**, followed by regioselective formylation, gave the key intermediate **6** (79%, two steps), which served as a common precursor in both lactam series. Reductive amination of **6** with phenylalanine amide, followed by in situ cyclization of the resulting amino ester, provided the γ-lactam-constrained dipeptide products **7a** (24%) and **7b** (41%). Alkylation of **6** with allyl iodide furnished a mixture of O- and C-allylated products **14** and **15** in 77% and 10% yields, respectively. Thermal Claisen rearrangement of **14** afforded additional **15** (66%), which was then converted to the aldehyde **16** (75%). Reductive amination of **16** with amino acid diester derivative **17** and subsequent lactam closure produced the dipeptide isosteres **18a** (31%) and **18b** (29%). The relative stereochemistry of the lactam ring substituents was determined by ^{1}H NMR using spin–spin decoupling and NOE enhancement experiments. Proof that less than 5% racemization occurred during the preparation of **6** was provided by the independent conversion of **5** to the diastereomeric MTPA esters **11** and **12** and comparison of the ^{1}H NMR spectra of these two compounds to the MTPA ester product mixture of **11** and the enantiomer of **12** derived from **6**. Verification that no additional epimerization of the α-carbon in **6** occurred during any of the subsequent processes leading to **7** or **18** was furnished by HPLC analysis of the crude product mixture resulting from the reductive amination and cyclization of **6** and **16** with the D-enantiomers of phenylalanine amide and **17**, respectively.

Introduction

In recent years, a large number of peptides have been isolated which mediate biological activity by stimulating receptors. An important step in understanding the substrate structure–function relationship for these molecules is based upon knowledge of the conformation a particular peptide adopts when bound to a specific receptor.[1] In conjunction with a program to design mimics of peptide neurotransmitters/neuromodulators, we wished to prepare 3,4-disubstituted γ-lactam-constrained peptide derivatives **1a** and **1b**, which have, attached to the 4-position of the lactam ring, substituents mimicking the natural side chain functionalities of aspartic acid and norleucine, respectively. Local constraints of this type are of interest as a means of limiting the number of conformations available to a peptide analogue,[2] and such restrictions also may result in derivatives with enhanced biologic potency, selectivity, or increased metabolic stability.[3]



1a: R = COOH
b: R = $CH_2CH_2CH_3$

Freidinger and co-workers have previously reported the synthesis and unsubstituted five-, six-, and seven-membered lactam rings,[4] while more recently reports have appeared describing the preparation of α,α′-disubstituted γ-lactam-bridged dipeptide isosteres.[5] For the synthesis of the 3,4-disubstituted lactam-constrained analogues to serve our immediate interests, it was necessary to be able to readily assign the absolute stereochemistry of each center of asymmetry in the molecules. This information would be of critical importance to us in our efforts to define peptide bioactive conformations. As a result, we sought to develop a synthetic process utilizing naturally occurring L-aspartic acid as the chiron[6] for both substituted lactams. Since the relative stereochemistry of the adjacent lactam ring substituents can readily be assigned based upon nuclear Overhauser effects (NOE) observable in the ^{1}H NMR spectrum, a preexisting stereocenter of known absolute configuration would allow for the determination of the center adjacent to it. Thus, our strategy required the development of a synthetic process which would furnish the desired target compounds while maintaining the chiral integrity at the existing stereocenter in the aspartic acid derived starting material.

Our initial communication related to the preparation of these conformationally constrained peptide derivatives[7] suffered from the fact that 10–15% racemization occurred during the synthetic process, and this complicated the purification scheme required to isolate the desired products. Reported herein are short, convenient syntheses of these two substituted γ-lactam dipeptide isosteres in which racemization at the α-carbon of the amino acid starting material has been minimized. The key step in our synthetic sequence is based upon a report by Danishefsky and co-workers in which the fully protected pyroglutamic acid moiety **2** was regioselectively formylated to produce compound **3** without racemization at the α-carbon (eq 1).[8] We felt that if this regioselective formylation reaction could

(1) Veber, D. F. in *Peptides: Proceedings of the Sixth American Peptide Symposium*; Gross, E., Meinhofer, J., Eds.; Pierce Chemical Co: Rockford, IL, 1979; pp 409–419.
(2) Marshall, G. R.; Gorin, F. A.; Moore, M. L. In *Annual Reports in Medicinal Chemistry*; Clarke, F. H., Ed.; Academic Press: New York, 1978; Vol. 13, pp 227–238.
(3) For reviews, see: (a) Fauchere, J.-I. In *Advances In Drug Research*; Testa, B., Ed.; Academic Press: 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. *J. Life Sci.* **1982**, *31*, 189. (e) Spatola, A. F. *Proteins* **1983**, *7*, 267.
(4) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104.
(5) (a) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631. (b) Zydowsky, T. M.; Dellaria, J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607.
(6) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Permagon: Oxford, 1983.
(7) Garvey, D. S.; May, P. D.; Nadzan, A. M. In *Peptides: Chemistry and Biology: Proceedings of the Tenth American Peptide Symposium*; Marshall, G. R., Ed.; ESCOM: Leiden, 1988; pp 123–125.
(8) (a) Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385. (b) Danishefsky, S.; Morris, J.; Clizbe, L. A. *Heterocycles* **1981**, *15*, 1205.

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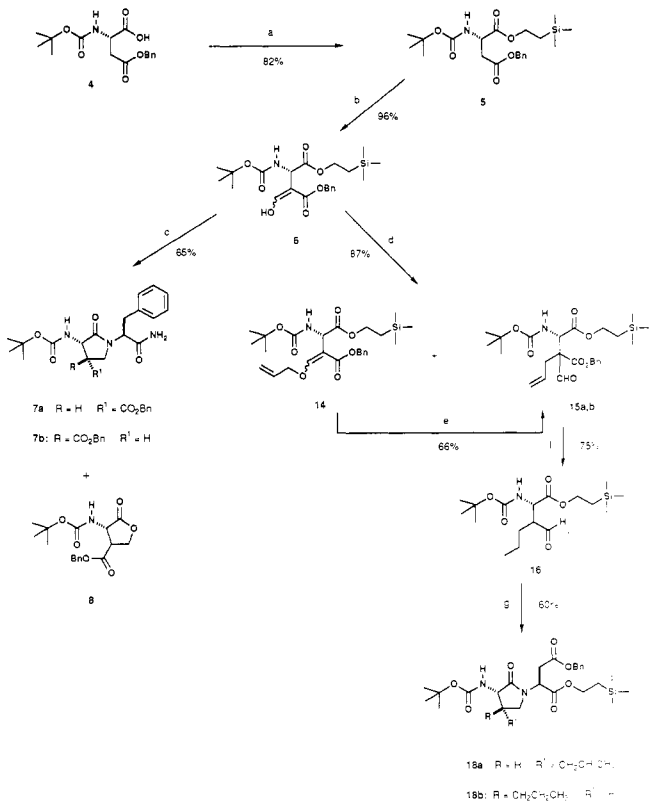
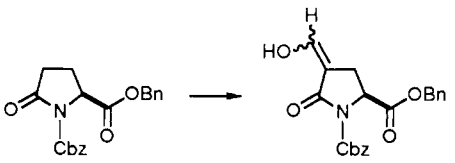
Scheme I[a]



[a] Reagents: (a) EDCI–HCl (1.4 equiv), $TMSCH_2CH_2OH$ (1.2 equiv), DMAP, CH_2Cl_2, 5 h; (b) t-BuOCH[$N(CH_3)_2$]$_2$ (20 equiv), cyclohexane, 40 °C, 18 h; then 5 N HCl, MeOH, 0 °C; (c) $PheNH_2$ (1.1 equiv), $NaBH_3CN$ (2.5 equiv), EtOH, room temperature, 24 h; then 50 °C, 36 h; (d) allyl iodide (1.2 equiv), iPr_2NEt (1.3 equiv), acetone, 16 h; (e) decalin, reflux, 1 h; (f) H_2, 5% Pd/$BaSO_4$, EtOAc, 7 h; (g) HCl–Asp(OBn)OTMSE (17) (1 equiv), NaOAc (1 equiv), $NaBH_3CN$ (2 equiv), EtOH, room temperature, 24 h; then 50 °C, 24 h.

be adapted to a suitably protected aspartic acid derivative, then the preparation of the desired 3,4-disubstituted γ-lactam dipeptides would proceed in a relatively straightforward fashion.

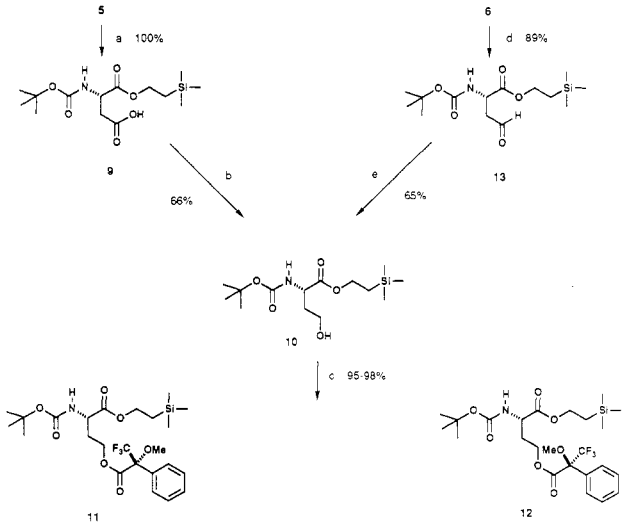


(1)

Results and Discussion

The synthesis of the carboxylic acid substituted lactams is outlined in Scheme I. Esterification of the commercially available protected aspartic acid derivative **4** with (trimethylsilyl)ethanol (EDCI, DMAP) gave the fully protected diester **5** in 86% yield.[9] After numerous attempts in which the formylation reaction temperature, solvent, as well as formamide acetal reagent were independently varied, the optimal conditions for the regioselective formylation were found to be treatment of **5** with 20 equiv of (*tert*-butyloxy)bis(dimethylamino)methane[10] in cyclohexane at 40 °C for 18 h.[11] Acidic hydrolysis of the resulting enamine with aqueous HCl–MeOH gave the desired product **6** as an equilibrium mixture of diastereomeric enols and aldehydes in 96% yield. Compound **6** was then converted directly to two of the desired substituted γ-lactam products by reductive amination with phenylalanine amide, followed by in situ cyclization of the resulting amino ester ($NaBH_3CN$, EtOH, 0 °C, 1 h, then 50 °C, 36 h). This one-pot reaction sequence gave the lactam products **7a** and **7b** in 24% and 41% yields, respectively, as well as a small quantity of lactones **8** (11%) resulting from the direct reduction of the aldehyde functionality in **6** and subsequent cyclization.

Scheme II[a]



[a] Reagents: (a) H_2, 5% Pd/$BaSO_4$, EtOAc, 4.5 h; (b) BH_3–THF (5 equiv), THF, 0 °C, 3.5 h; (c) (*R*)- or (*S*)-MTPA-Cl (2.5 equiv), pyridine (3 equiv), CH_2Cl_2, 0 °C, 2 h; (d) H_2, 5% Pd/$BaSO_4$, EtOAc, 4.5 h; then 60 °C 2 h; (e) BH_3–THF (1.1 equiv), THF, 0 °C, 1.5 h.

Stereochemical assignments of the ring substituents on the constrained lactam dipeptide products were made in the following fashion. After the proton connectivities in the ^1H NMR spectra of **7a** and **7b** were assigned through spin–spin decoupling, NOE difference experiments were carried out. Saturation of the lactam H-3 (δ 4.14) signal in the spectrum of **7a** showed enhancements on the resonances of the carbamate NH (δ 5.03) and the lactam H-4 (δ 3.50) signals, while saturation of the lactam H-3 (δ 3.93) signal in compound **7b** showed only an enhancement of the resonance of the carbamate NH (δ 5.30) signal and not the lactam H-4 (δ 3.48) signal. This data is consistent with our assignment of the relative stereochemistry of substitution on the lactam ring of **7a** as cis and that of **7b** as trans.

To verify that indeed no significant amount of racemization occurred during the formylation process, the ester **5** was converted to the α-methoxy-α-(trifluoromethyl)-phenacetyl (MTPA) esters[12] **11** and **12** while the aldehyde

(9) Yields reported in the text refer to purified substances obtained after chromatography or recrystallization.

(10) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffman, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

(11) With the aspartic acid derived substrates, the formylation conditions reported by Danishefsky (ref 8), as well as a number of others we attempted, all resulted in significant amounts of racemization. Although a rigorous systematic study was not done, some trends were observed. Other formamide acetal reagents gave inferior results; however, with a particular formamide acetal reagent, performing the reaction at higher temperature or with an aspartic acid derivative having a sterically smaller ester protecting group on the α-carboxylate generally resulted in greater amounts of racemized product. The propensity for the substrate to racemize appeared to be particularly sensitive to the reaction solvent, with the level of racemization increasing dramatically when the reaction was performed in a polar solvent such as DMF.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

6 was independently transformed into 11 and the enantiomer of 12 (*enan*-12) via the the sequence of reactions summarized in Scheme II. The benzyl ester of compound 5 was removed (H_2, 5% $Pd/BaSO_4$), and the resulting carboxylic acid 9 was then reduced with BH_3·THF to the alcohol 10 (66%, two steps). The diastereomeric MTPA esters 11 and 12 were then prepared by acylation of the alcohol 10 with (*R*)-MTPA-Cl and (*S*)-MTPA-Cl, respectively. In many of the solvents tested there were no discernable differences in the 300-MHz ^1H NMR spectra of compounds 11 and 12 and their ^{19}F NMR spectra were superimposable; however, we were gratified to find that in deuteriobenzene there was a chemical shift difference in the ^1H NMR spectrum of the finely split doublet which corresponded to the methyl ether substituent of each diastereomer.[13]

Having found a suitable method for determining the extent of racemization which might have occurred during the formylation step, we proceeded to appropriately derivitize the formylation product 6. Catalytic hydrogenation of 6 gave the free acid which upon further heating decarboxylated to produce aldehyde 13 (89%). Reduction of 13 with BH_3·THF followed by acylation of the resulting alcohol with (*R*)-MPTA-Cl gave esters 11 and *enan*-12 in approximately a 20:1 ratio as determined by ^1H NMR analysis.[14] Therefore, from this result it was concluded that the formylation process to produce 6 proceeded with less than 5% racemization at the α-carbon.

Compound 6 also was utilized for the preparation of the *n*-propyl-substituted lactam constrained dipeptide isosteres as shown in Scheme I. Alkylation of 6 with allyl bromide (iPr_2NEt, acetone) gave approximately a 9:1 mixture of O-alkylated to C-alkylated products 14 and **15a,b** (1:1 mixture of diastereoisomers) in 87% combined yield. The C-alkylated adducts **15a,b** were separated from the allyl enol ether 14, and then 14 was subject to thermal Claisen rearrangement (decalin, reflux, 1 h) to produce a mixture of the diastereomeric aldehydes **15a** and **15b** (1:7 mixture by ^1H NMR) in a combined yield of 66%. These aldehydes were not normally separated at this stage but rather carried on as a mixture to the constrained dipeptide products which were readily separable by column chromatography. Catalytic hydrogenation of 15 (H_2, $Pd/BaSO_4$) gave a mixture of aldehydes 16 in 75% yield. Reductive amination of a 1:1 diastereomeric mixture of 16 with HCl·H_2NAsp(OBz)OTMSE (17), followed by in situ cyclization of the resulting amino ester ($NaBH_3CN$, EtOH, NaOAc, room temperature, 24 h, then 50 °C, 24 h), gave the substituted lactams **18a** and **18b** in 31% and 29% yields, respectively.

As described previously, the relative stereochemistry of the lactam substituents was assigned based upon the results of spin–spin decoupling and NOE difference experiments. Saturation of the lactam H-3 (δ 4.23) signal in the spectrum of **18a** showed an enhancement of the resonance corresponding to the lactam H-4 (δ 2.56) signal, indicative of **18a** being the cis substituted isomer. When the lactam H-3 (δ 3.98) signal in the spectrum of **18b** was saturated, there was no NOE enhancement of the lactam H-4 (δ 2.13) signal, thus supporting the assignment of **18b** as that of the trans-substituted product.

To verify that no additional epimerization of the α-carbon in compound 6 occurred during any of the subsequent reactions leading to the products 7 and 18, the following set of experiments were performed. First, we prepared the D-enantiomers of phenylalanine amide and the aspartic acid diester derivative 17. D-Phenylalanine amide was reacted with aldehyde 6 and the enantiomer of 17 with aldehyde 16 under the reductive amination, cyclization conditions described previously. HPLC analysis of the crude reaction mixtures showed that in each instance the major lactam-constrained dipeptide products had significantly different retention times than those of **7a,b** or **18a,b**. Furthermore, if additional epimerization of the chiral carbon in question had occurred, then we would have expected to observe major peaks in the chromatograms with retention times corresponding to **7a** and **7b** or **18a** and **18b** since enantiomers of these dipeptide products would have been formed in the process. The results of this study indicated that the absolute configuration of the α-carbon in 6 remained intact. The chromatogram peaks with retention times equal to those of **7a** and **7b** or **18a** and **18b** were still very minor components comprising less than 5% of the total product mixture in each case.

Conclusion

In summary, we have presented short and efficient syntheses of carboxylic ester and *n*-propyl-substituted lactam-constrained dipeptide isosteres which, after ester deprotection, may serve as conformationally restricted mimics of aspartic acid and norleucine containing peptides, respectively. The method for the preparation of these substituted lactam analogues utilizes the readily available, optically pure aspartic acid derivative 4 as the starting material, and maintains in greater than 90% ee the absolute chirality of the amino acid precursor as well as allows for the introduction of additional centers of asymmetry with little or no racemization. Since the resulting constrained dipeptide isosteres have been designed with orthogonal protecting groups, they are suitable substrates for incorporation into larger peptides using standard deprotection and peptide coupling techniques.

Finally, it is envisioned that the highly functionalized, differentially protected, formylated aspartic acid derivative 6 can serve as a synthetic precursor for a wide variety of other constrained or novel amino acid derived products. Other applications utilizing this versatile intermediate will be reported in due course.

Experimental Section

Proton magnetic resonance spectra were obtained in a Nicolet QE-300 (300 MHz) and a General Electric GN-300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Spin–spin decoupling and NOE difference spectra were obtained on a General Electric GN-500 (500 MHz) instrument. Mass spectra were obtained with Hewlett-Packard HP5965 (Cl) and Kratos MS50 (FAB, HRMS) spectrometers. Elemental analyses and the above determinations were performed by the Analytical Research Department, Abbott Laboratories.

Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Preparative thin-layer chromatography (PTLC) was carried out using Analtech 20 × 20 cm precoated silica gel GF plates (thickness 1.00 mm). Column chromatography was carried out using Merck silica gel 60, 70–230 mesh. High-pressure liquid chromatography (HPLC) was performed on a 3.9 mm × 30 cm, 10-μm Waters Porasil normal-phase silica gel column at a flow rate of 1 mL/min utilizing UV absorbance at 254 nm for peak detection.

Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. Optical rotation data was obtained on a Perkin-Elmer Model 241 polarimeter. Protected amino acids were purchased from Bachem (Torrance, CA) or Chemical Dynamics Corp. (S. Plainfield, NJ). Anhydrous solvents

(13) The fine splitting observed in the spectra appears to be due to rotational isomerism. Spectra obtained at an elevated probe temperature (75 °C) show a broad singlet.

(14) Although the minor MTPA ester product derived from 6 is the enantiomer of compound 12, this is inconsequencial for the purpose of ^1H NMR spectra comparison.

were purchased from Aldrich (Milwaukee, WI), and reactions requiring anhydrous solvents were performed under a nitrogen atmosphere.

***N*-(*tert*-Butyloxycarbonyl)-L-aspartic Acid β-Benzyl-α-(trimethylsilyl)ethyl Diester (5).** To a solution of **4** (3.49 g, 10.8 mmol), (trimethylsilyl)ethanol (1.53 g, 13.0 mmol), and 4-(dimethylamino)pyridine in CH_2Cl_2 (30 mL) was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (2.87 g, 15 mmol), and the solution was stirred at room temperature for 5 h. The reaction mixture was diluted with additional CH_2Cl_2 (20 mL), and then the organic phase was washed with 1 N HCl (20 mL) followed by saturated $NaHCO_3$–brine, 1:1 (20 mL). Drying ($NaSO_4$), followed by concentration in vacuo, gave a yellow oil, which was purified by column chromatography (EtOAc/hexane, 1:4) to yield 3.74 g (82%) of **5** as a colorless oil, which solidified on standing: mp 34 °C; $[\alpha]^{23}_D$ +17.1° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.28 (s, 9 H), 0.95 (m, 2 H), 1.45 (s, 9 H), 2.86 (dd, 1 H, *J* = 6.9, 4.8 Hz), 3.05 (dd, 1 H, *J* = 16.9, 4.8 Hz), 4.18 (m, 2 H), 4.55 (dt, 1 H, *J* = 8.4, 4.8 Hz), 5.13 (s, 2 H), 5.48 (d, 1 H, *J* = 8.4 Hz), 7.30–7.40 (m, 5 H); MS (CI) $(M + H)^+$ 424, $(M + NH_4)^+$ 441. Anal. Calcd for $C_{21}H_{33}NO_6Si$: C, 59.5; H, 7.9; N, 3.3. Found: C, 59.8; H, 7.9; N, 3.3.

4-Oxo-4-(benzyloxy)-3-(hydroxymethylene)-2(*S*)-((*tert*-butyloxycarbonyl)amino)butanoic Acid (Trimethylsilyl)-ethyl Ester (6). To a solution of **5** (1.82 g, 4.29 mmol) in anhydrous cyclohexane (20 mL) under N_2 was added freshly distilled *tert*-butoxybis(dimethylamino)methane[10] (14.7 g, 84 mmol), and the reaction mixture was maintained at 40 °C for 18 h. After the reaction mixture was allowed to cool to room temperature, the mixture was added to a rapidly stirred 0 °C solution of methanol (250 mL) containing 5 N HCl (34 mL). Stirring at room temperature was continued for 5 min, and then the reaction mixture was concentrated in vacuo. The aqueous residue was extracted with EtOAc (3 × 30 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. This material was purified by column chromatography (EtOAc/hexane, 1:2 → 2:1) to yield 1.86 g (96%) of the formylated derivative **6** as a pale yellow oil: MS (FAB) $(M + H)^+$ 452. Anal. Calcd for $C_{22}H_{33}NO_7Si$: C, 58.5; H, 7.4; N, 3.1. Found: C, 58.4; H, 7.3; N, 3.1.

3-Phenyl-2(*S*)-(3(*S*)-((*tert*-butyloxycarbonyl)amino)-4(*R* and *S*)-(carbobenzyloxy)-2-oxo-1-pyrrolidinyl)propionamide (7a,b). To a solution of **6** (133 mg, 0.29 mmol), phenylalanine amide (54 mg, 0.32 mmol), and acetic acid (20 mg, 0.32 mmol) in absolute ethanol (2.5 mL) was added $NaBH_3CN$ (45 mg, 0.71 mmol). The reaction mixture was stirred at room temperature for 24 h and then at 50 °C for 36 h. After concentrating in vacuo, the residual oil was taken up in EtOAc (20 mL) and then washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4) and then concentrated in vacuo to give a colorless oil, which was purified by column chromatography ($CHCl_3/CH_3CN$, 2:1) to yield 34 mg (24%) of the more mobile diastereomer **7a** as a white solid, 59 mg (41%) of the less mobile diastereoisomer **7b** as a white solid, and 11 mg (11%) of a diastereomeric mixture of lactones **8** as a colorless oil.

Cis isomer 7a: mp 165–168 °C; $[\alpha]^{22}_D$ −15.7° (*c* = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 2.83 (dd, 1 H, *J* = 15.5, 12.3 Hz), 3.34 (dd, 1 H, *J* = 10.4, 6.0 Hz), 3.53 (m, 2 H), 3.70 (dd, 1 H, *J* = 15.5, 4.5 Hz), 4.14 (m, 1 H), 5.03 (d, 1 H, *J* = 5.4 Hz), 5.11 (d, 1 H, *J* = 12.1 Hz), 5.14 (d, 1 H, *J* = 12.1 Hz), 5.18 (dd, 1 H, *J* = 12.3, 4.5 Hz), 5.32 (br s, 1 H), 7.14–7.40 (m, 11 H); MS (CI) $(M + H)^+$ 482. Anal. Calcd for $C_{26}H_{31}N_3O_6 \cdot 0.5H_2O$: C, 63.6; H, 6.4; N, 8.6. Found: C, 63.8; H, 6.5; N, 8.6.

Trans isomer 7b: mp 68–70 °C; $[\alpha]^{22}_D$ −117° (*c* = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 2.86 (dd, 1 H, *J* = 15.4, 11.5 Hz), 3.37–3.51 (m, 2 H), 3.58–3.72 (m, 2 H), 3.93 (dd, 1 H, *J* = 7.4, 7.4 Hz), 5.09–5.18 (m, 2 H), 5.34–5.38 (m, 2 H), 7.15–7.41 (m, 12 H); MS (CI) $(M + H)^+$ 482. Anal. Calcd for $C_{26}H_{31}N_3O_6 \cdot 1.0H_2O$: C, 62.5; H, 6.7; N, 8.4. Found: C, 62.3; H, 6.3; N, 8.7.

***N*-(*tert*-Butyloxycarbonyl)-L-aspartic Acid α-(Trimethylsilyl)ethyl Ester (9).** To a solution of **5** (225 mg, 0.53 mmol) in EtOAc (5 mL) was added 5% $Pd/BaSO_4$ (10 mg), and the reaction mixture was vigorously stirred under 1 atm of H_2 for 4.5 h. The reaction mixture was passed through filter paper and then concentrated in vacuo to afford 176 mg (100%) of pure **9** as a colorless oil, which solidified on standing: mp 78–79 °C; $[\alpha]^{24}_D$ +7.4° (*c* = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H), 0.98 (m, 2 H), 1.45 (s, 9 H), 2.89 (dd, 1 H, *J* = 17.3, 4.4 Hz), 3.06 (dd, 1 H, *J* = 17.3, 4.4 Hz), 4.24 (m, 2 H), 4.54 (m, 1 H), 5.48 (d, 1 H, *J* = 7.2 Hz); MS (CI) $(M + H)^+$ 334. Anal. Calcd for $C_{14}H_{27}NO_6Si$: C, 50.4; H, 8.2; N, 4.2. Found: C, 50.1; H, 8.0; N, 4.1.

2(*S*)-((*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoic Acid (Trimethylsilyl)ethyl Ester (10) [from **9**]. To a solution of acid **9** (121 mg, 0.29 mmol) in dry THF (5 mL) at 0 °C was added a 1 M THF solution of BH_3·THF (1.43 mL, 1.43 mmol), and the reaction mixture was maintained at 0 °C for 3.5 h. Excess borane was quenched by the dropwise addition of H_2O, the solution was warmed to room temperature and diluted with brine (5 mL), and the organics were extracted with EtOAc (2 × 10 mL). The organic phase was dried (Na_2SO_4) and then concentrated in vacuo to afford a colorless oil, which was purified by column chromatography (EtOAc/hexane 1:1) to yield 60 mg (66%) of **10** as a colorless oil: $[\alpha]^{23}_D$ −1.5 ° (*c* = 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H), 1.02 (m, 2 H), 1.45 (s, 9 H), 1.57 (masked m, 1 H), 3.26 (dd, 1 H, *J* = 8.5, 4.8 Hz), 3.71 (m, 2 H), 4.24 (m, 2 H), 4.46 (m, 1 H), 5.37 (d, 1 H, *J* = 8.1 Hz); MS (CI) $(M + H)^+$ 320, $(M + NH_4)^+$ 337. [From **13**]: A solution of **13** (42 mg, 0.13 mmol) in THF (2 mL) at 0 °C was treated with a 1 M THF solution of BH_3·THF (0.144 mL, 0.144 mmol) and left at 0 °C for 1 h. The reduction was worked up in a similar fashion as that described above to afford 27 mg (65%) of **10**.

2(*S*)-((*tert*-Butyloxycarbonyl)amino)-4-(2(*R*)-methoxy-2-(trifluoromethyl)phenacetoxy)butanoic Acid (Trimethylsilyl)ethyl Ester (11). To a solution of **10** (29.3 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added pyridine (28 mg, 0.36 mmol) and (*R*)-MTPA-Cl[12] (57 mg, 0.23 mmol), and the reaction mixture was maintained at 0 °C for 2 h. After being warmed to room temperature the reaction mixture was diluted with additional CH_2Cl_2 (10 mL) and then washed with 1 N HCl (5 mL) followed by saturated aqueous $NaHCO_3$ (5 mL). The organic phase was dried ($NaSO_4$) and concentrated in vacuo to give an oil, which was purified by column chromatography (EtOAc/hexane, 1:2). This afforded 46 mg (95%) of pure **11** as a colorless oil: ^1H NMR (C_6D_6) δ 0.15 (s, 9 H), 0.89 (m, 2 H), 1.55 (s, 9 H), 1.65 (m, 1 H), 2.12 (m, 1 H), 3.64 (br s, 3 H), 4.14–4.35 (m, 4 H), 4.65 (m, 1 H), 5.10 (d, 1 H, *J* = 8.8 Hz), 7.17–7.37 (m, 3 H), 7.87 (d, 2 H, *J* = 7.4 Hz); MS (CI) $(M + H)^+$ 536, $(M + NH_4)^+$ 553.

2(*S*)-((*tert*-Butyloxycarbonyl)amino)-4-(2(*S*)-methoxy-2-(trifluoromethyl)phenacetoxy)butanoic Acid (Trimethylsilyl)ethyl Ester (12). **12** was prepared from **10** as described above, utilizing (*S*)-MTPA-Cl: ^1H NMR (C_6D_6) δ 0.14 (s, 9 H), 0.88 (apparent t, 2 H, *J* = 8.4 Hz), 1.55 (s, 9 H), 1.75 (m, 1 H), 2.15 (m, 1 H), 3.59 (d, 3 H), 4.12–4.27 (m, 4 H), 4.62 (ddd, 1 H, *J* = 8.0, 8.0, 5.4 Hz), 5.09 (d, 1 H, *J* = 8.0 Hz), 7.15–7.27 (m, 3 H), 7.83 (d, 2 H, *J* = 7.7 Hz); MS (CI) $(M + H)^+$ 536, $(M + NH_4)^+$ 553.

2(*S*)-((*tert*-Butyloxycarbonyl)amino)-4-oxobutanoic Acid (Trimethylsilyl)ethyl Ester (13). To a solution of **6** (77.5 mg, 0.17 mmol) in EtOAc (5 mL) was added 5% $Pd/BaSO_4$ (5 mg), and the reaction mixture was stirred vigorously under 1 atm of H_2 for 3 h. The catalyst was removed by filtration, and then the supernatent was heated to 60 °C for 2 h. Concentration in vacuo gave an oil, which was passed through a plug of silica gel (EtOAc) to afford 49 mg (89%) of the aldehyde **13** as a colorless oil: $[\alpha]^{23}_D$ +13.2° (*c* = 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.04 (s, 9 H), 1.00 (m, 2 H), 1.44 (s, 9 H), 3.00 (dd, 1 H, *J* = 11.0, 4.5 Hz), 3.07 (dd, 1 H, *J* = 11.0, 5.5 Hz), 4.23 (m, 2 H), 4.55 (m, 1 H), 5.38 (d, 1 H, *J* = 7.4 Hz), 9.74 (s, 1 H); MS (FAB) $(M + H)^+$ 318; exact mass calcd for $C_{14}H_{28}NO_5Si$ $(M + H)^+$ 318.1737, found 318.1737.

Alkylation To Produce O- and C-Allylated Derivatives 14 and 15a,b. To a solution of **6** (531 mg, 1.18 mmol) in acetone (10 mL) was added diisopropylethylamine (198 mg, 1.53 mmol) and allyl iodide (237 mg, 1.41 mmol). The reaction mixture was allowed to stand at room temperature in the dark for 16 h after which time it was concentrated in vacuo. The residue was taken up in EtOAc (25 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a light yellow oil. Column chromatography (EtOAc/hexane, 2:3) of the crude products gave 57 mg (10%) of the more mobile C-allylated adducts **15a,b** (1:1 diastereomeric mixture) and 447 mg (77%) of the less mobile allyl enol ether **14** as colorless oils. **14**: ^1H NMR ($CDCl_3$) δ 0.01 (s,

9 H), 0.90 (apparent t, 2 H, J = 8.5 Hz), 1.44 (s, 9 H), 4.13 (m, 2 H), 4.56 (br d, 2 H, J = 5.2 Hz), 5.15 (d, 1 H, J = 12.5 Hz), 5.19 (d, 1 H, J = 12.5 Hz), 5.29 (dd, 1 H, J = 10.7, 1.1 Hz), 5.37 (dd, 1 H, J = 17.3, 1.1 Hz), 5.57–5.62 (m, 2 H), 5.91 (ddd, 1 H, J = 17.3, 10.7, 5.2 Hz), 7.31–7.37 (m, 5 H), 7.47 (s, 1 H); MS (FAB) $(M + H)^+$ 492; exact mass calcd for $C_{25}H_{38}NO_7Si$ $(M + H)^+$ 492.2417, found 492.2413.

For characterization purposes a small quantity of **15a,b** was further separated into its constituent diastereoisomers by PTLC ($CHCl_3/Et_2O$, 50:1, 3 developments). **15a**: ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.89 (m, 2 H), 1.45 (s, 9 H), 2.60 (d, 2 H, J = 7.4 Hz), 4.10 (m, 2 H), 5.04–5.12 (m, 3 H), 5.19 (d, 1 H, J = 12.3 Hz), 5.24 (d, 1 H, J = 12.3 Hz), 5.37 (d, 1 H, J = 11.0 Hz), 5.73 (m, 1 H), 7.35 (br s, 5 H), 9.96 (d, 1 H, J = 1.1 Hz); MS (CI) $(M + H)^+$ 492. **15b**: ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.90 (m, 2 H), 1.46 (s, 9 H), 2.62 (d, 2 H, J = 7.4 Hz), 4.08 (m, 2 H), 5.04–5.12 (m, 3 H), 5.21 (d, 1 H, J = 12.3 Hz), 5.27 (d, 1 H, J = 12.3 Hz), 5.45 (d, 1 H, J = 10.7 Hz), 5.68 (m, 1 H), 7.33–7.41 (m, 5 H), 9.97 (s, 1 H); MS (CI) $(M + H)^+$ 492.

C-Allylated Derivatives 15a,b via Claisen Rearrangement. A solution of **14** (323 mg, 0.66 mmol) in decalin was heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was applied to the top of a silica gel column. Gradient elution of the column (hexane → EtOAc/hexane, 1:2) afforded 215 mg (66%) of **15** which by ^1H NMR was a 1:7 mixture of diastereomeric aldehydes **15a** and **15b**.

3(*R*,*S*)-Formyl-2(*S*)-((*tert*-butyloxycarbonyl)amino)-hexanoic Acid (Trimethylsilyl)ethyl Ester (16). To a solution of a 1:7 mixture of **15a** and **15b** (174 mg, 0.35 mmol) in EtOAc (4.5 mL) was added 5% $Pd/BaSO_4$ (10 mg), and the reaction mixture was stirred vigorously under 1 atm of H_2 for 7 h. The catalyst was removed by filtration, and then the supernatent was concentrated in vacuo. Purification of the residual oil by column chromatography (Et_2O/hexane, 1:2) afforded a 1:1 diastereomeric mixture of aldehydes **16** (95 mg) in 75% yield: ^1H NMR ($CDCl_3$) δ 0.04 (s, 4.5 H), 0.05 (s, 4.5 H), 0.90–1.05 (m, 5 H), 1.30–1.63 (m, 3 H), 1.43 (s, 4.5 H), 1.45 (s, 4.5 H), 1.65–1.75 (m, 1 H), 2.76 (m, 0.5 H), 3.09 (m, 0.5 H), 4.56 (dd, 0.5 H, J = 8.8, 3.8 Hz), 4.68 (dd, 0.5 H, J = 7.7, 3.5 Hz), 5.20 (d, 0.5 H, J = 7.7 Hz) 5.26 (d, 0.5 H, J = 8.8 Hz), 9.61 (s, 0.5 H), 9.68 (d, 0.5 H, J = 1.1 Hz); MS (FAB) $(M + K)^+$ 398; exact mass calcd for $C_{17}H_{33}NO_5SiK$ $(M + K)^+$ 398.1781, found 398.1765. Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.8; H, 9.3; N, 3.9. Found: C, 56.8; N, 9.1; N, 3.8.

L-Aspartic Acid β-Benzyl-α-(trimethylsilyl)ethyl Diester Hydrochloride (17). Compound **5** (983 mg, 2.3 mmol) was dissolved in 4.5 N HCl–dioxane (10 mL) and allowed to stand at room temperature for 2 h. Concentration in vacuo gave a colorless oil, which was recrystallized from ether–hexane (–20 °C) to yield 553 mg (67%) of **17** as a white solid: mp 95–97 °C; $[\alpha]^{24}_D$ +17.9° (c = 1.3, EtOH); ^1H NMR (D_2O, $Me_3Si(CH_2)_2CO_2Na$) δ –0.12 (s, 9 H), 0.75 (m, 2 H), 3.00 (dd, 1 H, J = 18.0, 5.1 Hz), 3.14 (dd, 1 H, J = 18.0, 5.1 Hz), 4.09 (m, 2 H), 4.32 (t, 1 H, J = 5.2 Hz), 4.69 (HOD), 5.09 (d, 1 H, J = 11.4 Hz), 5.13 (d, 1 H, J = 11.4 Hz), 7.42–7.45 (m, 5 H); MS (CI) $(M + H)^+$ 324. Anal. Calcd for $C_{16}H_{26}ClNO_4Si$: C, 53.5; H, 7.3; N, 3.9. Found: C, 53.6; H, 7.2; N, 4.0.

3-(Carbobenzyloxy)-2(*S*)-(3(*S*)-((*tert*-butyloxycarbonyl)amino)-4(*R* and *S*)-*n*-propyl-2-oxo-1-pyrrolidinyl)propanoic Acid (Trimethylsilyl)ethyl Ester (18a,b). To a solution of **16** (79 mg, 0.22 mmol), **17** (72 mg, 0.24 mmol), and sodium acetate (20 mg, 0.24 mmol) in absolute ethanol (2.5 mL) was added $NaBH_3CN$ (33 mg, 0.53 mmol). The reaction mixture was stirred at room temperature for 24 h and then at 50 °C for 24 h. The reaction mixture was concentrated in vacuo, and the residue was taken up in EtOAc (20 ml) and washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4) and then concentrated in vacuo to give a yellow oil. Purification of the crude products by column chromatography (Et_2O/hexane, 3:2) afforded 37 mg (31%) of the more mobile diastereoisomer **18a** and 35 mg (29%) of the less mobile diastereoisomer **18b** both as a colorless oils.

Cis isomer 18a: $[\alpha]^{23}_D$ +6.2° (c 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.90 (masked t, 3 H, J = 7.0 Hz), 0.95 (m, 2 H), 1.00–1.40 (m, 4 H), 1.46 (s, 9 H), 2.56 (m, 1 H), 2.87 (dd, 1 H, J = 16.5, 8.8 Hz), 3.01 (dd, 1 H, J = 16.5, 5.5 Hz), 3.18 (d, 1 H, J = 9.6 Hz), 3.34 (dd, 1 H, J = 9.6, 5.9 Hz), 4.16–4.22 (m, 3 H), 4.97 (br s, 1 H), 5.00 (dd, 1 H, J = 8.8, 5.5 Hz), 5.12 (s, 2 H), 7.31–7.40 (m, 5 H); MS (FAB) $(M + H)^+$ 549; exact mass calcd for $C_{28}H_{45}N_2O_7Si$ $(M + H)^+$ 549.2996, found 549.2998. Anal. Calcd for $C_{28}H_{44}N_2O_7$: C, 61.3; H, 8.1; N, 5.1. Found: C, 61.5; H, 8.0; N, 4.8.

Trans isomer 18: $[\alpha]^{23}_D$ –43.2° (c 0.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H), 0.91 (masked t, 3 H, J = 7.4 Hz), 0.96 (m, 2 H), 1.19–1.42 (m, 4 H), 1.45 (s, 9 H), 2.13 (m, 1 H), 2.89 (dd, 1 H, J = 8.5, 8.5 Hz), 2.92 (dd, 1 H, J = 18.0 8.6 Hz), 3.01 (dd, 1 H, J = 18.0, 5.4 Hz), 3.44 (dd, 1 H, J = 8.5, 8.5 Hz), 3.98 (m, 1 H), 4.19 (m, 2 H), 4.78 (br s, 1 H), 4.95 (dd, 1 H, J = 8.6, 5.4 Hz), 5.13 (s, 2 H), 7.33–7.38 (m, 5 H); MS (FAB) $(M + H)^+$ 549; exact mass calcd for $C_{28}H_{45}N_2O_7Si$ $(M + H)^+$ 549.2996, found 549.3000. Anal. Calcd for $C_{28}H_{44}N_2O_7$: C, 61.3; H, 8.1; N, 5.1. Found: C, 61.7; H, 8.2; N, 5.0.

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