Synthesis of *β*,*β*-Dimethylated Amino Acid Building Blocks Utilizing the 9-Phenylfluorenyl Protecting Group

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Optically pure *β*,*β*-dimethylated amino acid building blocks with functionalized side chains have been prepared from D-aspartic acid. The dimethylation was accomplished by regioselective dialkylation of 9-phenylfluorenyl (PhFl)-protected aspartate diesters. The bulk of the PhFl protecting group also allowed for a variety of functional group manipulations to be carried out on the side chain without affecting the C^{α} ester of the aspartate. As a result, the derivatives of the following novel amino acids were synthesized in this study: *β*,*β*-dimethyl-D-aspartic acid, *β*,*β*-dimethyl-D-homoserine, 3,3-dimethyl-D-2,4-diaminobutyric acid, *β*,*β*-dimethyl-D-lysine, *β*,*β*-dimethyl-D-homoglutamate, *β*,*β*-dimethyl-D-ornithine, and 3,3-dimethylazetidine-2-carboxylic acid. The *β*,*β*-dimethylated amino acids were synthesized in high enantiomeric excess as determined by coupling the novel building blocks to chiral reagents.

Introduction

Biologically active peptides elicit their effects by binding to a receptor or enzyme active site. This recognition process requires the peptides to possess the necessary constitution or pharmacophoric groups and to present them in an appropriate three-dimensional array. Although endogenous and naturally occurring peptides are highly potent, they tend to display a large degree of conformational mobility. The flexibility of these naturally occurring ligands may decrease the receptor selectivity and complicate efforts directed toward the elucidation of the three-dimensional structures necessary for biological activity. In addition, the clinical application of peptides is limited because of unfavorable pharmacological properties such as poor metabolic stability and low bioavailability. Thus, much work has focused on the development of analogues of bioactive peptides through the incorporation of novel amino acid analogues or isosteres designed to counteract these undesirable pharmacological properties.[1−4] These modified peptides are often subjected to a series of experimental measurements and calculations. The results are correlated with biological activity and receptor selectivity. From these studies, valuable insights are obtained regarding the conformations required for activity and selectivity. In this report, we describe the syntheses of a series of novel building blocks (i.e., highly functionalized amino acids), *β*,*β*-side chain dimethylated amino acids. Specifically, we developed the synthesis of optically pure *β*,*β*-dimethylated amino acids including N^{α}-PhFl-*β*,*β*-dimethyl-α-*tert*-butyl-D-aspartate [PhFl-*β*,*β*-diMe-D-Asp-O*t*Bu] (**1**), N^{α}-Boc-*β*,*β*-dimethyl-D-homoserine-*tert*-butyl ester [Boc-*β*,*β*-diMe-D-Hser-O*t*Bu] (**2**), (2*R*)-N^{α}-Boc-N^{γ}-Cbz-2,4-diamino-3,3-dimethylbutyric acid [Boc-*β*,*β*-diMe-D-Dab(Cbz)-OH] (**3**), N^{α}-Cbz-N^{ϵ}-Boc-*β*,*β*-dimethyl-D-lysine [Cbz-*β*,*β*-diMe-D-Lys(Boc)-OH] (**4**), N^{α}-Boc-*β*,*β*-dimethyl-D-homoglutamic acid α-methyl ester [Boc-*β*,*β*-diMe-D-Hglu-OMe] (**5**), N^{α}-Boc-N^{Δ}-Cbz-*β*,*β*-dimethyl D-ornithine methyl ester [Boc-*β*,*β*-diMe-D-Orn(Cbz)-OMe] (**6**), and (2*R*)-N^{α}-PhFl-3,3-dimethyl-azetidine-2-carboxylic acid α-methyl ester [PhFl-*β*,*β*-diMe-D-Azt-OMe] (**7**) (Figure 1).

Numerous methods have been developed for the asymmetric synthesis of unusual α-amino acids including stereoselective α-carbon enolate alkylation and hydrogenation of α,*β*-conjugated esters.[5] However, these methods cannot be adapted to the synthesis of *β*,*β*-dimethylated amino acids. We have chosen to utilize the unique properties of the 9-phenylfluorenyl (PhFl) protecting group originally developed by Rapoport and co-workers.[6−10] The steric bulk of the PhFl group attached to the amine of an aspartate diester prevents abstraction of the C^{α} proton by strong bases, resulting in enolization exclusively of the side chain ester. Additionally, the PhFl group shields the α-carbonyl of the aspartate, allowing for chemistry to be selectively performed on the side chain ester. These properties allow for the syntheses of a wide variety of peptidomimetic structures with the chirality of the α-carbon determined by that of the initial aspartate. Lubell[11−16] and Chamberlin, using *N*-benzyl-*N*-

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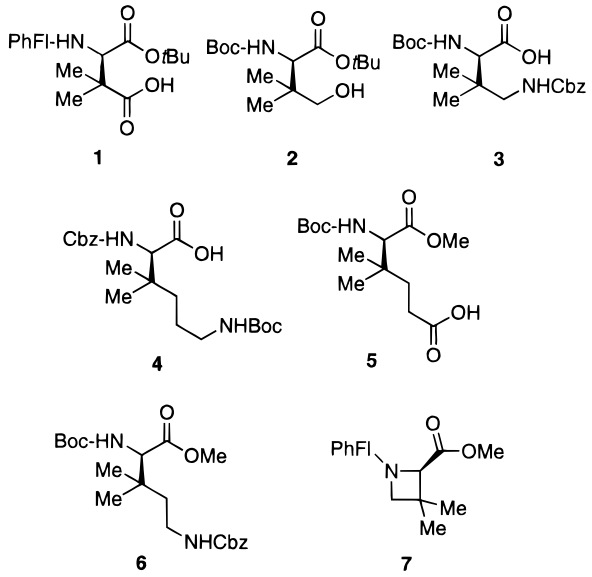


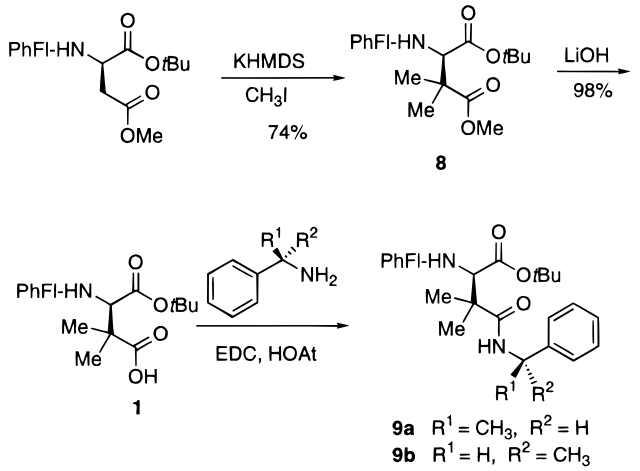
Figure 1. The target β,β-dimethylated amino acid analogues PhFl-β,β-diMe-D-Asp-O*t*Bu (**1**), Boc-β,β-diMe-D-Hser-O*t*Bu (**2**), Boc-β,β-diMe-D-Dab(Cbz)-OH (**3**), Cbz-β,β-diMe-D-Lys(Boc)-OH (**4**), Boc-β,β-diMe-D-Hglu-OMe (**5**), Boc-β,β-diMe-D-Orn(Cbz)-OMe (**6**), and PhFl-β,β-diMe-D-Azt-OMe (**7**).

phenylfluorenyl,[17−19] have recently exploited these properties in synthesizing constrained β-turn mimetics and unusual amino acids. Adding to the utility of the PhFl group are the relatively mild conditions required for its removal either by treatment with TFA or by catalytic hydrogenation.

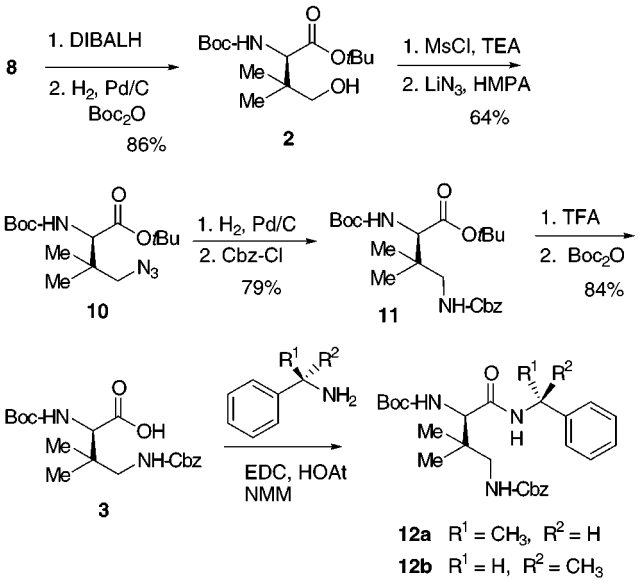
Synthesis

The synthesis of PhFl-β,β-diMe-D-Asp-O*t*Bu (**1**) was initiated with the synthesis of the protected aspartic acid derivative PhFl-D-Asp(OMe)-O*t*Bu as described by Rapoport and co-workers.[9] Treatment of PhFl-D-Asp(OMe)-O*t*Bu with two successive additions of potassium bis(trimethylsilyl)amide (KHMDS) (2 equiv each addition) and methyl iodide (3 equiv each addition) gave the dimethylated PhFl-β,β-diMe-D-Asp(OMe)-O*t*Bu (**8**) in good yield (Scheme 1). Rapoport and co-workers have previously observed β,β-dimethyl aspartate as a minor side product during attempts to obtain monoalkylated PhFl-protected aspartates.[8,9] In the current study, the application of excess base and electrophile provided the β,β-dimethylated species as the major product. These findings are in agreement with those of Sharma and Lubell in their studies of the dimethylation of proline derivatives.[15] Treatment of PhFl-β,β-diMe-D-Asp(OMe)-O*t*Bu (**8**) with LiOH gave the desired building block **1**. The sterically congested environment surrounding the methyl ester necessitated longer reaction times and higher reaction temperatures (80 °C) than normally required for saponification of a methyl ester. To assess the retention of optical purity during the alkylation and saponification steps, the carboxylic acid of PhFl-β,β-diMe-D-Asp-O*t*Bu

Scheme 1



Scheme 2



(**1**) was coupled with (*R*)- and (*S*)-α-methylbenzylamine (separate reactions) to give the diastereomeric adducts **9a** and **9b**. In each case, only one diastereomer was obtained as the major product. The comparison of the ^{1}H NMR spectra of the crude diastereomers indicated that PhFl-β,β-diMe-D-Asp-O*t*Bu (**1**) was obtained with a high degree of optical purity (>95% ee).

With PhFl-β,β-diMe-D-Asp(OMe)-O*t*Bu (**8**) in hand, the targeted Boc-β,β-diMe-D-Hser-O*t*Bu derivative (**2**) was obtained by treatment of the side chain ester **8** with DIBAL-H (Scheme 2), followed by the interchanging of the PhFl for a Boc group. The alteration in protecting groups decreases the nucleophilicity of the nitrogen, thus diminishing the possibility of cyclization in the subsequent steps. The alcohol **2** was converted to the mesylate and then to the azide **10**. Reduction of the azide by catalytic hydrogenation followed by treatment with benzyl chloroformate gave the fully protected Boc-β,β-diMe-Dab(Cbz)-O*t*Bu (**11**). The Boc and *t*-Bu groups were removed by treatment with TFA, and Boc_2O was used to reprotect the amine to yield the desired building block Boc-β,β-diMe-D-Dab(Cbz)-OH (**3**). The carboxylic acid of Boc-β,β-diMe-D-Dab(Cbz)-OH (**3**) was coupled to (*R*)- and (*S*)-α-methylbenzylamine (in separate reactions) to give the amides **12a** and **12b**. In each case, only one diaste-

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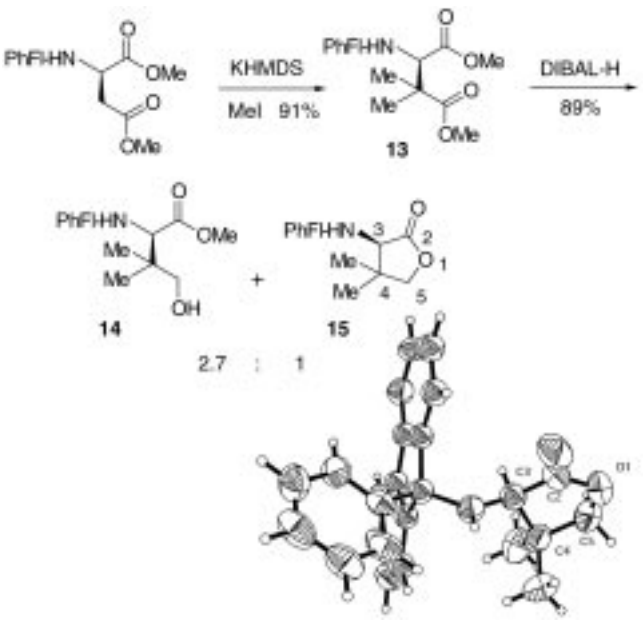
Scheme 3



reomer was obtained as the major product. Comparison of the ^{1}H NMR spectra of the diastereomers indicated that Boc-*β*,*β*-diMe-D-Dab(Cbz)-OH (**3**) is obtained with minimal epimerization of the Dab α-carbon (>95%ee).

The synthesis of the *β*,*β*-dimethyl-D-lysine building block was initiated by dimethylation of PhFl-D-Asp(OMe)-OMe using conditions similar to those used for the synthesis of PhFl-*β*,*β*-diMe-D-Asp(OMe)-O*t*Bu (**8**). PhFl-*β*,*β*-diMe-D-Asp(OMe)-OMe (**13**) (Scheme 3) was obtained in higher yields than PhFl-*β*,*β*-diMe-D-Asp(OMe)-O*t*Bu (**8**). This is likely because of the decreased steric crowding of the α-methyl ester versus the α-*tert*-butyl ester. Initial attempts to obtain the PhFl-*β*,*β*-diMe-D-Hser-OMe (**14**) regioselectively using DIBAL-H resulted in a large amount of the lactone **15**. Thus, the bulk of the PhFl protecting group is sufficient to protect the α-ester from reduction, but the α-carbonyl is still prone to intramolecular attack as previously observed by Rapoport and co-workers.[7] The X-ray crystallographic analysis of lactone **15** (P. Gantzel, UC San Diego X-ray Crystallography Facility) confirms that the two methyl groups are placed at the *β*-position of the side chain with no alkylation of the nitrogen. The structure also points to the fact that the methyl ester reduction occurs regioselectively on the side chain.

Previous reports indicated that formation of lactone (**15**) could be avoided by carrying out the reduction in THF.[7] In our hands, we found that after treatment of PhFl-*β*,*β*-diMe-D-Asp(OMe)-OMe (**13**) with DIBAL-H in DCM, the acylic hydroxyester remained intact. Apparently, the formation of lactone **15** occurred during purification by silica gel column chromatography. Thus, crude PhFl-*β*,*β*-diMe-D-Hser-OMe (**14**) was oxidized to the aldehyde **16** using the Dess Martin periodinane[20] (Scheme 4) and was purified in good yield. The additional carbons necessary for the lysine side chain were provided via a Horner−Wadsworth−Emmons reaction using diethylphosphononacetate to give the α,*β*-unsaturated ester **17**. The *E*-olefin was obtained as the major product.

The α,*β*-unsaturated ester **17** was reduced to the allylic alcohol **18** using DIBAL-H. As with the reduction of the side chain ester **13**, the reaction was fully regioselective. In this case, the presence of the *trans* double bond precluded any concerns regarding lactone formation. A one-pot process[21] was used to convert the allylic alcohol to the allylic azide **19** (Scheme 4). Reduction of the azide to the amine using triphenylphosphine (Ph_3P) followed by treatment with di-*tert*-butyl dicarbonate (Boc_2O) gave the side chain Boc-protected allylic amine **20**. The Ph_3P-mediated reduction of the azide was chosen over catalytic hydrogenation because of the fear that concurrent reduction of the olefin and the azide would result in lactamization. Catalytic hydrogenation of the allylic amine **20** resulted in the simultaneous removal of the PhFl group and reduction of the olefin. The crude amine was allowed to react with benzyl chloroformate to give the orthogonally protected lysine derivative Cbz-*β*,*β*-diMe-D-Lys-(Boc)-OMe (**21**).

Saponification of the methyl ester of the protected building block **21** using LiOH gave the targeted Cbz-*β*,*β*-diMe-D-Lys(Boc)-OH (**4**) (Scheme 4). To determine the retention of enantiomeric integrity, the carboxylic acid of Cbz-*β*,*β*-diMe-D-Lys(Boc)-OH (**4**) was coupled (in separate reactions) to (*R*)- and (*S*)-α-methylbenzylamine to give the amides **22a** and **22b**, respectively. In each case, only one diastereomer was obtained as the major product. The comparison of the ^{1}H NMR spectra of the crude diastereomers indicated that the reactions were carried out with a high retention of chiral integrity (95% ee). It is believed that the saponification step could cause a small amount of epimerization because the steric constraints of the *β*-dimethyl groups required that the saponification reaction be carried out over longer times than are routinely used for less sterically encumbered α-amino acids.

In the effort to synthesize the *β*,*β*-dimethylated ornithine building block, we were concerned with the possibility of lactam formation during the functional group manipulations. Specifically, if the side chain amine was generated in the presence of the methyl ester, there could be a distinct possibility of the formation of a six-membered lactam. Treatment of the α,*β*-unsaturated ester **17** with magnesium in methanol (Scheme 5) gave PhFl-*β*,*β*-diMe-D-Hglu(OMe)-OMe (**23**) without the removal of the PhFl protecting group. Saponification of the side chain methyl ester was carried out with high regioselectivity because of the presence of the PhFl protecting group. Previous studies directed toward the synthesis of 3-alkyl-2,3-diaminopropionic acid revealed that a cyclic urea resulted when a PhFl-protected amine reacted with an isocyanate intermediate of a Curtius reaction.[8] Thus, in our synthesis, the PhFl group was interchanged with a Boc protecting group to give the building block Boc-*β*,*β*-diMe-D-Hglu-OMe (**5**) because the regio-directing properties of the PhFl group were no longer needed. A Curtius reaction using diphenylphosphoryl azide (DPPA) in the presence of benzyl alcohol provided Boc-*β*,*β*-diMe-D-Orn(Cbz)-OMe (**6**). We believe that the cyclic urea formation was avoided by use of a urethane-protected amine.

To confirm that the transformations were carried out without loss of chiral integrity, the Boc group of the Boc-*β*,*β*-diMe-D-Orn(Cbz)-OMe (**6**) was removed and the amine was coupled to Boc-Tyr(*t*Bu)-OH to give the dipeptide **24**

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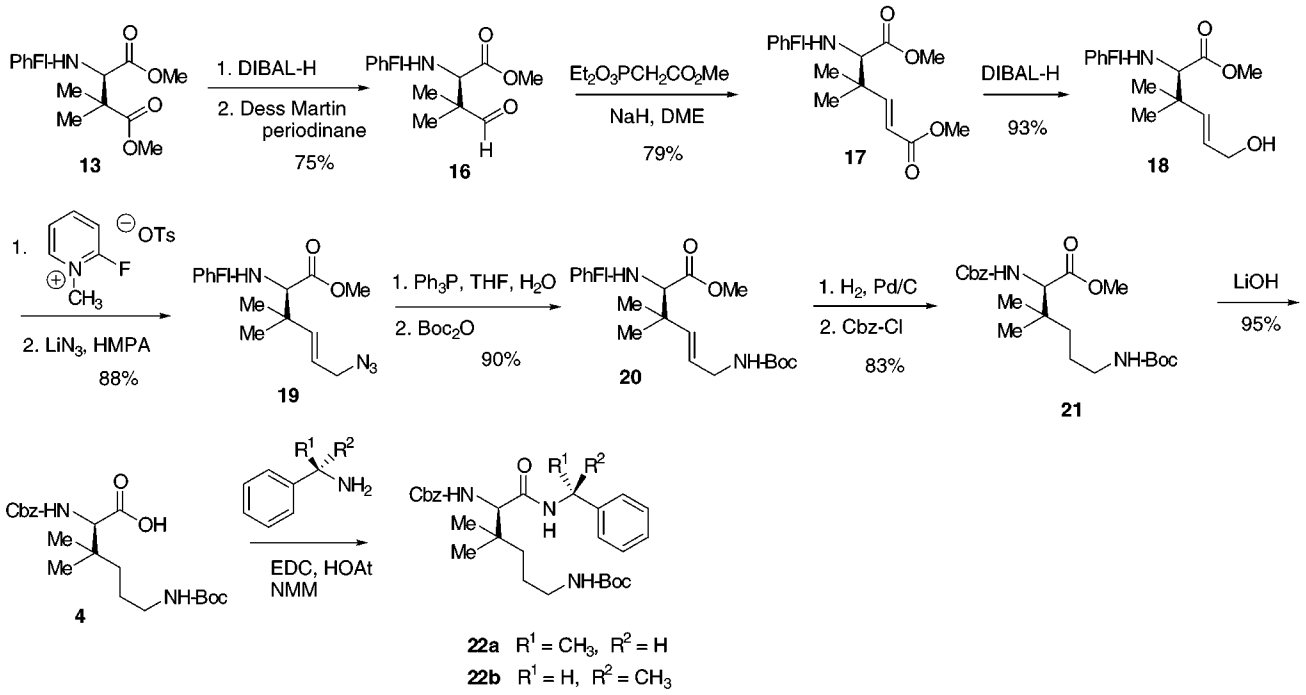
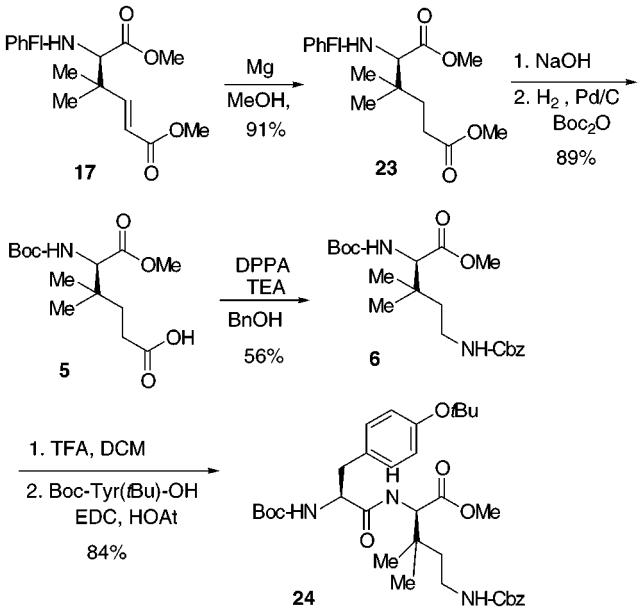
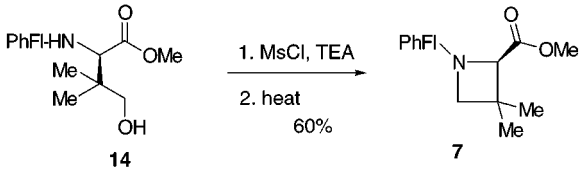
Scheme 4



Scheme 5



Scheme 6



as the major product. This dipeptide was identified as a single diastereomer by ^{1}H NMR, thus indicating that the reactions were carried out without effect on the chirality of the α-carbon of the ornithine derivative.

Reports of intramolecular cyclization[8] prompted us to examine the synthesis of the proline derivative azetidine-2-carboxylate. PhFl-β,β-diMe-D-Hser-OMe (**14**) (Scheme 6) was converted to the mesylate and then heated to give the novel β,β-dimethyl azetidine-2-carboxylic acid building block PhFl-β,β-diMe-D-Azt-OMe (**7**).

Conclusions

We have synthesized a unique set of modified enantiopure amino acid building blocks. The regioselective dimethylation of the C$^\beta$ of PhFl-protected aspartates was successfully accomplished without methylation of the nitrogen or the C$^\alpha$. The PhFl protecting group was also effective at preventing C$^\alpha$ epimerization under the highly basic conditions necessary for dimethylation. In addition, we have demonstrated that the Horner−Wadsworth−Emmons and Mg-mediated olefin reduction reactions are tolerated by the PhFl protecting group and do not epimerize the C$^\alpha$ of PhFl-protected aspartates or react with the α-ester. Additionally, we have shown that these building blocks can be coupled with chiral amines or amino acid derivatives.

The flexibility of the methods outlined above leads to the synthesis of a variety of side chain functionalized β,β-dialkylated amino acids. Similar strategies utilizing glutamic acid can result in a family of γ,γ-dialkylated amino acids by starting with PhFl-protected glutamic acid. We will continue to take advantage of the unique properties of this valuable protecting group in order to develop other novel peptidomimetic building blocks. The incorporation of these peptidomimetics into families of bioactive peptides is currently underway in our laboratories. These modified molecules are key to the elucidation of bioactive conformations of peptide-based hormones, opioids, and other bioactive molecules. We will report these results in future publications.

Experimental Section

General. Proton nuclear magnetic resonance spectra were recorded at either 360 or 500 MHz. Chemical shifts are given in ppm (δ scale) downfield from internal TMS, and coupling

constants (*J*) are given in Hz. Fast atom bombardment and electrospray mass spectrometry were obtained from the University of California, Riverside (Dr. Richard Kondrat) and The Scripps Research Institute (Dr. Gary Siuzdak). Infrared spectroscopy was carried out using either CaF_2 plates or KBr pellets. Optical rotation was measured using a 1.00 dm path length cell.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica gel plates from E. Merck, Darmstadt (60F-254) were used for thin-layer chromatography. Visualization of the compounds was carried out by UV light, ninhydrin, vanillin, *o*-tolidine, $KMnO_4$, bromocresol, or phosphomolibdic acid. Column chromatography was performed using the indicated solvent mixture on Kieselgel 60 (60−200 mesh) from E. Merck.

***N*$^{\alpha}$-(9-Phenylfluoren-9-yl)-3,3-dimethyl-*C*$^{\beta}$-methyl ester-D-aspartic acid-*C*$^{\alpha}$-*tert*-butyl ester [PhF-*β*,*β*-diMe-D-Asp-(OMe)-O*t*Bu] (8).** A solution of PhFl-D-Asp(OMe)-O*t*Bu[9] (600 mg, 1.35 mmol) in dry THF (15 mL) was cooled (−78 °C) under N_2, and a solution of KHMDS (3.3 mL, 0.91 M in THF) was added over 5 min. After 15 min, the reaction was allowed to warm to −40 °C, and MeI (0.25 mL, 4.02 mmol) was added. After 1.5 h, the reaction mixture was cooled to −78 °C, and a second addition of KHMDS and MeI was carried out in the same manner as the first. After the MeI addition, the reaction was placed in a freezer (−20 °C). After 16 h, saturated NH_4Cl (5 mL) was added followed by H_2O (5 mL). The mixture was extracted three times with EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/hex (3%) as eluent. The desired product **8** was obtained as a colorless oil (0.473 g, 74%): R_f EtOAc/hex (20%) 0.46; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.67 (dd, J = 3.2, 7.6 Hz, 2H); 7.40−7.19 (m, 11H); 3.53 (s, 3H); 2.82 (s, 3H); 1.17 (s, 3H); 1.12 (s, 9H); 1.05 (s, 3H); IR (neat/CaF_2) 2979, 1731 cm^{-1}; HRMS calcd for $C_{30}H_{34}NO_4$ 472.2488, found *m*/*z* 472.2478.

***N*$^{\alpha}$-(9-Phenylfluoren-9-yl)-*β*,*β*-dimethyl-D-aspartic acid-*C*$^{\alpha}$-butyl ester [PhF-*β*,*β*-diMe-D-Asp-O*t*Bu] (1).** Lithium hydroxide (1.1 mL, 1 N) was added to a solution of **8** (200 mg, 0.424 mmol) in dioxane (5 mL). The reaction was allowed to warm to 50 °C and was stirred for 3.5 h. The reaction was heated to 90 °C. After 16 h, another 1.1 mL of LiOH (1 N) was added to drive the reaction to completion. The reaction was concentrated to one-third the original volume, and EtOAc (30 mL) was added. The solution was acidified with 1 N HCl, and the aqueous layer was extracted twice with EtOAc. The pooled organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and chromatographed through silica gel using EtOAc/petroleum ether (pet ether) (25%) as eluent. The desired product **1** was obtained as a colorless foam (170 mg, 98%): R_f EtOAc/pet ether (20%) 0.27; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.70 (d, J = 7.2 Hz, 2H); 7.68−7.19 (m, 11H); 2.83 (s, 1H); 1.20 (s, 3H); 1.11 (s, 9H); 1.05 (s, 3H); IR (neat/CaF_2) 2979, 1724, 1702 cm^{-1}; $[\alpha]^{27}_D$ 30.2 (c = 0.87, $CHCl_3$); HRMS calcd for $C_{29}H_{32}NO_4$ 458.2331, found *m*/*z* 458.2346.

***N*$^{\alpha}$-(9-Phenylfluoren-9-yl)-*β*,*β*-dimethyl-D-aspartic acid-*C*$^{\beta}$-(*R*)- or (*S*)-α-methylbenzylamide *C*$^{\alpha}$-*tert*-butyl ester (9a and 9b).** A solution of the *β*,*β*-dimethylated aspartate (**1**) (9 mg, 20 μmol) was dissolved in DMF (0.5 mL), and 1-hydroxy-7-azabenzotriazole (HOAt) (4 mg, 30 μmol) was added. A dilute solution of (*R*)-α-methylbenzylamine in DMF was added until the pH of the solution was neutral. The solution was cooled (−20 °C), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (6 mg, 30 μmol) was added. After 16 h, 1 N HCl (2 mL) was added, and the mixture was extracted twice with EtOAc. The organic extracts were pooled and washed with 1 N HCl, brine, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **9a** as a colorless oil.

The diastereomer **9b** was synthesized using (*S*)-α-methylbenzylamine and the method described above for **9a**. The 500 MHz ^{1}H NMR spectra of the crude diastereomers were obtained, and the chemical shifts of the of the amide protons were used for comparison.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*β*,*β*-dimethyl-D-homoserine-*C*$^{\alpha}$-*tert*-butyl ester [Boc-*β*,*β*-diMe-D-Hser-O*t*Bu] (2).** A solution of **8** (400 mg, 0.848 mmol) in dry dichloromethane (DCM) (10 mL) was cooled (−78 °C) under N_2, and a solution of DIBAL-H (2.7 mL, 1 N in hexane) was added over 4 min. After 10 min, MeOH (0.5 mL) was added, and the reaction was allowed to warm to ambient temperature. Ethyl acetate (50 mL) and saturated aqueous Rochelle's salt (10 mL) were added, and the reaction was allowed to stir for 15 min. The organic layer was collected, and the aqueous layer was extracted with EtOAc. The organic extracts were pooled, washed with brine, and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give the crude alcohol as an oil.

The crude alcohol was dissolved in EtOAc (10 mL) and MeOH (5 mL), and 10% Pd/C (5 mg) and Boc_2O (278 mg, 1.27 mmol) were added. The solution was degassed under reduced pressure and placed under H_2 (2 atm). After 18 h, the mixture was filtered through Celite, and the filtrate was concentrated. The crude mixture was chromatographed through silica gel using EtOAc/hex (10%) as eluent to give the product **2** as a colorless solid (222 mg, 86%): R_f EtOAc/hex (20%) 0.33; mp 100−101 °C; ^{1}H NMR (360 MHz/$CDCl_3$) δ 5.38 (d, J = 7.9 Hz, 1H); 4.18 (d, J = 8.3 Hz, 1H); 3.31 (A of AB, J = 12 Hz, 1H); 3.05 (B of AB, J = 12 Hz, 1H); 1.50 (s, 9H); 1.45 (s, 9H); 1.11 (s, 3H); 0.74 (s, 3H); IR (neat/CaF_2) 3436, 2978, 1725 cm^{-1}; $[\alpha]^{27}_D$ −27.2 (c = 1.8, $CHCl_3$); HRMS calcd for $C_{15}H_{30}NO_5$ 304.2124, found *m*/*z* 304.2120.

(2*R*)-4-Azido-2-*tert*-butyloxycarbonylamino-3,3-dimethyl-butyric acid *tert*-butyl ester (10). A solution of **2** (400 mg, 1.32 mmol) and triethylamine (TEA) (368 μL, 2.64 mmol) in DCM (4 mL) was cooled (0 °C), and MsCl (153 μL, 1.98 mmol) was added. After 5 min, the reaction was diluted with Et_2O (30 mL) and washed with H_2O (6 mL). The aqueous layer was extracted twice with Et_2O, and the pooled organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the crude mesylate as an oil.

The crude mesylate was dissolved in HMPA (3.5 mL), and LiN_3 (650 mg, 13.2 mmol) was added. The reaction was heated to 90 °C and allowed to stir for 16 h. The reaction was cooled, and H_2O (10 mL) was added. The aqueous layer was extracted three times with EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and chromatographed through silica gel using EtOAc/pet ether (10%) as eluent. The desired product **10** was obtained as a colorless oil (0.278 g, 64%): R_f EtOAc/pet ether (20%) 0.48; ^{1}H NMR (360 MHz/$CDCl_3$) δ 5.19 (d, J = 8.3 Hz, 1H); 4.16 (d, J = 9.4 Hz, 1H); 3.23 (dd, J = 8.5, 15 Hz, 2H); 1.49 (s, 9H); 1.45 (s, 9H); 0.99 (s, 3H); 0.98 (s, 3H); IR (neat/CaF_2) 2978, 2104, 1717 cm^{-1}; $[\alpha]^{27}_D$ −10.0 (c = 1.8, $CHCl_3$); HRMS calcd for $C_{15}H_{29}N_4O_4$ 329.2189, found *m*/*z* 329.2197.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-benzyloxycarbonyl-*β*,*β*-dimethyl-D-diaminobutyric acid-*tert*-butyl ester [Boc-*β*,*β*-diMe-D-Dab(Cbz)-O*t*Bu] (11).** To a solution of **10** (220 mg, 0.670 mmol) in MeOH (5 mL) was added 10% Pd/C (5 mg). The mixture was degassed under reduced pressure and placed under H_2 (2 atm). After 20 h, the catalyst was removed by filtration through Celite, and the filtrate was concentrated and dried under reduced pressure to give the crude amine as a colorless oil.

The crude amine and 4-methylmorpholine (NMM) (0.15 mL, 1.4 mmol) were dissolved in DCM (4 mL), and benzyl chloroformate (Cbz-Cl) (125 μL, 0.876 mmol) was added dropwise by syringe. After 18 h, the reaction was diluted with Et_2O (40 mL) and H_2O (10 mL). The aqueous layer was extracted twice with Et_2O, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/pet ether (8%) as eluent. The desired product **11** was obtained as a colorless oil (0.232 g, 79%): R_f EtOAc/pet ether (20%) 0.46; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.36 (m, 5H); 6.00 (m, 1H); 5.22 (d, J = 7.9 Hz, 1H); 5.11 (s, 2H); 4.08 (d, J = 8.6 Hz, 1H); 3.19 (dd, J = 8.5, 14 Hz, 1H); 2.87 (dd, J

= 4.5, 14 Hz, 1H); 1.48 (s, 9H); 1.44 (s, 9H); 1.01 (s, 3H); 0.86 (s, 3H); IR (neat/CaF_2) 3360, 2977, 1723 cm^{-1}; $[\alpha]^{27}_D$ 14.8 (c = 10.8, $CHCl_3$); HRMS calcd for $C_{23}H_{37}N_2O_6$ 437.2652, found m/z 437.2672.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-benzyloxycarbonyl-β,β-dimethyl-D-diaminobutyric acid [Boc-β,β-diMe-D-Dab(Cbz)-OH] (3).** A solution of **11** (195 mg, 0.447 mmol) in DCM (1 mL) was cooled (0 °C), and TFA (1 mL) was added. After 20 min, the reaction was allowed to warm to ambient temperature, and after 3 h, the solvent was removed under reduced pressure. Residual TFA was removed by codistillation with toluene. The crude amino acid was dissolved in dioxane (4 mL), and saturated $NaHCO_3$ (1 mL) and Boc_2O (195 mg, 0.894 mmol) were added. The reaction was allowed to stir at ambient temperature. After 20 h, the reaction was concentrated, and the residue was dissolved in Et_2O (30 mL) and 0.5 N HCl (8 mL). The aqueous layer was extracted twice with Et_2O, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated, and chromatographed through silica gel using $CHCl_3$/MeOH/AcOH (98:1:1) as eluent. The purified fractions were concentrated and codistilled with toluene to remove residual AcOH to yield the desired product **3** as a colorless oil (138 mg, 84%): R_f $CHCl_3$/MeOH/AcOH (95:5:3) 0.48; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.35 (m, 5H); 5.71 (m, 1H); 5.33 (d, J = 9.0 Hz, 1H); 5.18 (A of AB, J = 12 Hz, 1H); 5.00 (B of AB, J = 12 Hz, 1H); 4.28 (d, J = 9.4 Hz, 1H); 3.39 (dd, J = 8.1, 14 Hz, 1H); 2.86 (dd, J = 4.7, 15 Hz, 1H); 1.44, 0.97 (bd, 6H); IR (neat/CaF_2) 3338, 2976, 1705 cm^{-1}; $[\alpha]^{27}_D$ 4.9 (c = 6.1, $CHCl_3$); HRMS calcd for $C_{19}H_{29}N_2O_6$ 381.2026, found m/z 381.2019.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-benzyloxycarbonyl-β,β-dimethyl-D-diaminobutyric acid (*R*)- or (*S*)-α-methylbenzylamide (12a and 12b).** The title diastereomers were obtained by coupling **3** to optically active α-methylbenzylamine as described for **9a**. The 360 MHz ^{1}H NMR spectra of the crude diastereomers were obtained, and the chemical shifts of the β-methyl groups of the β,β-dimethylated Dab were used for comparison.

Dimethyl-*N*$^{\alpha}$-(9-phenylfluoren-9-yl)-3,3-dimethyl-D-aspartate [PhF-β,β-diMe-D-Asp(OMe)-OMe] (13). A solution of PhF-D-Asp(OMe)-OMe[9] (5.96 g, 14.9 mmol) in dry THF (170 mL) was cooled (−70 °C) under N_2, and a solution of KHMDS in THF (32 mL, 0.91 M) was added over 5 min. After 20 min, MeI (1.7 mL, 27.3 mmol) was added. The reaction mixture was allowed to stir for 20 min at −70 °C and then allowed to warm to 0 °C. After 3.5 h following the MeI addition, the reaction mixture was cooled (−70 °C), and the addition of KHMDS and MeI was repeated as before. After 15 h following the second MeI addition, saturated NH_4Cl (50 mL) was added along with H_2O (20 mL). The aqueous layer was extracted twice with EtOAc, and the pooled organic extracts were washed with 5% citric acid and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was chromatographed through silica gel using EtOAc/hex (4−10% gradient) to give the desired product **13** as a colorless oil (5.79 g, 91%): R_f EtOAc/hex (20%) 0.33; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.68 (dd, J = 7.6, 13 Hz, 2H); 7.42−7.11 (m, 11H); 3.55 (s, 3H); 3.15 (s, 3H); 2.84 (s, 1H); 1.19 (s, 3H); 1.04 (s, 3H); IR (neat/CaF_2) 2993, 1736 cm^{-1}; $[\alpha]^{27}_D$ 34.3 (c = 0.46, $CHCl_3$); HRMS calcd for $C_{27}H_{28}NO_4$ 430.2018, found m/z 430.2028.

(2*R*)-3,3-Dimethyl-4-hydroxy-2-[(9-phenylfluoren-9-yl)-amino]-butyric acid methyl ester [Boc-β,β-diMe-D-Hser-OMe] (14); (2*R*)-3,3-Dimethyl-4-hydroxy-2-[(9-phenylfluoren-9-yl)amino]-butyric acid-β-lactone (15). A solution of **1** (1.04 g, 2.41 mmol) in DCM (20 mL) was cooled (−40 °C) under N_2, and a solution of DIBAL-H in hexanes (7.5 mL, 1 M) was added over 3 min. After 3 h, the reaction was quenched with acetone (1 mL), and 10 min later, MeOH (3 mL) and H_3PO_4 (10 mL, 1 N) were added. The emulsion was extracted three times with EtOAc, and the pooled organic extracts were washed with brine, evaporated onto Florisil, and chromatographed through silica gel using EtOAc/pet ether (15%) as eluent. The alcohol **14** was obtained as a yellow oil (630 mg, 65%), and the lactone **15** was obtained as a colorless solid (217 mg, 24%). Recrystallization of **15** using EtOAc/hex gave crystals suitable for X-ray analysis. (**14**): R_f EtOAc/hex (40%) 0.27; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.71 (dd, J = 3.8, 7.4 Hz, 2H); 7.45 (d, J = 7.6 Hz, 1H); 7.39−7.12 (m, 9H); 7.11 (d, J = 7.9 Hz, 1H); 3.35 (A of AB, J = 11 Hz, 1H); 3.23 (B of AB, J = 11 Hz, 1H); 3.17 (s, 3H); 2.53 (s, 1H); 1.01 (s, 3H); 0.58 (s, 3H); IR (neat/CaF_2) 3342, 1728, cm^{-1}; MS (FAB) 402 $(M + H)^+$. (**15**): R_f EtOAc/hex (40%) 0.66; mp 175−176 °C; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1H); 7.63 (d, J = 7.6 Hz, 1H); 7.53 (d, J = 7.6 Hz, 1H); 7.46−7.17 (m, 8H); 3.70 (A of AB, J = 11 Hz, 1H); 3.44 (B of AB, J = 11 Hz, 1H); 2.90 (bs, 1H); 2.60 (s, 1H); 1.04 (s, 3H); 0.22 (s, 3H); IR (neat/CaF_2) 2958, 1766 cm^{-1}; $[\alpha]^{27}_D$ 34.1 (c = 1.1, $CHCl_3$); HRMS calcd for $C_{25}H_{24}NO_2$ 370.1807, found m/z 370.1797.

(2*R*)-3,3-Dimethyl-4-oxo-2-([(9-phenylfluoren-9-yl)-amino]-butyric acid methyl ester (16). A solution of **13** (5.47 g, 12.7 mmol) in dry DCM (100 mL) was cooled (−70 °C) under N_2, and a solution of DIBAL-H in hexanes (28 mL, 1 N) was added over 5 min. After 20 min, saturated Rochelle's salt (50 mL) was added followed by Et_2O (200 mL). The mixture was allowed to warm to ambient temperature and stirred for 15 min. The aqueous layer was extracted twice with Et_2O, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give the crude alcohol as (**14**) as an oil.

The crude alcohol **14** was dissolved in DCM (75 mL) and cooled (0 °C) under N_2. Dess Martin periodinane[20] (7.08 g, 16.2 mmol) was added, and the reaction was allowed to warm to ambient temperature. After 2 h, the reaction was diluted with EtOAc (100 mL) and an aqueous solution of saturated $Na_2S_2O_3$/saturated $NaHCO_3$ (1:3, 30 mL). The mixture was allowed to stir for 5 min. The aqueous layer was extracted twice with EtOAc, and the pooled organic extracts were washed with saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/hex (5−10% gradient) as eluent. The desired product **16** was obtained as a colorless solid (3.79 g, 75%): R_f EtOAc/hex (25%) 0.48; mp 149−150 °C; ^{1}H NMR (360 MHz/$CDCl_3$) δ 9.19 (s, 1H); 7.70 (dd, J = 7.2, 14 Hz, 2H); 7.40−7.21 (m, 10H); 7.14 (d, J = 7.2 Hz, 1H); 3.22 (s, 3H); 2.77 (s, 1H); 1.07 (s, 3H); 0.80 (s, 3H); IR (neat/CaF_2) 2975, 1731 cm^{-1}; $[\alpha]^{27}_D$ 43.6 (c = 0.29, $CHCl_3$); HRMS calcd for $C_{26}H_{26}NO_3$ 400.1913, found m/z 400.1926.

Dimethyl-*N*$^{\alpha}$-(9-phenylfluoren-9-yl)-3,3-dimethyl-γ,δ-dehydro-D-homoglutamate (17). Methyl diethylphosphonoacetate (2.59 g, 12.3 mmol) in dry DME (15 mL) was added over 5 min to a cooled (0 °C) mixture of NaH (483 mg, 60% oil dispersion, 12.1 mmol) in dry DME (15 mL) under N_2. After 15 min, a solution of **16** (3.71 g, 9.29 mmol) in DME (40 mL) was added over 5 min. After 0.5 h, the reaction was allowed to warm to ambient temperature. After 3 h following addition of **16**, the reaction was concentrated under reduced pressure, and H_2O (20 mL) was added. The aqueous mixture was extracted three times with EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/hex (5%) as eluent. The product **17** was obtained as a colorless foam (3.36 g, 79%): R_f EtOAc/hex (20%) 0.29; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.67 (dd, J = 7.8, 15 Hz, 2H); 7.42 (dd, J = 1.8, 7.2 Hz, 2H); 7.37−7.10 (m, 9H); 6.91 (d, J = 16 Hz, 1H); 5.72 (d, J = 16 Hz, 1H); 3.75 (s, 3H); 3.13 (s, 3H); 2.37 (s, 1H); 1.00 (s, 3H); 0.97 (s, 3H); IR (neat/CaF_2) 2949, 1727 cm^{-1}; $[\alpha]^{27}_D$ 152 (c = 0.79, $CHCl_3$); HRMS calcd for $C_{29}H_{30}NO_4$ 456.2175, found m/z 456.2191.

Methyl-(2*R*)-3,3-dimethyl-6-hydroxy-2-[(9-phenylfluoren-9-yl)amino]-4-hexenoate (18). A solution of (**17**) (770 mg, 1.69 mmol) in DCM (15 mL) was cooled (−45 °C) under N_2, and a solution of DIBAL-H in hexanes (3.4 mL, 1 M) was added over 3 min. After 15 min, MeOH (2 mL) was added followed by saturated Rochelle's salt (20 mL) and EtOAc (100 mL). The mixture was allowed to warm to ambient temperature. After 10 min of stirring, the organic layer was collected, and the aqueous layer was extracted twice with EtOAc. The pooled organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was evaporated onto Florisil

and chromatographed using EtOAc/hex (25%) as eluent to give the desired product **18** as a colorless oil (668 mg, 93%): R_f EtOAc/hex (25%) 0.37; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.68 (dd, J = 7.8, 12 Hz, 2H); 7.43 (m, 2H); 7.36−7.18 (m, 8H); 7.11 (d, J = 7.9 Hz, 1H); 5.58 (m, 2H); 4.08 (d, J = 4.7 Hz, 2H); 3.12 (s, 3H); 2.31 (s, 1H); 0.98 (s, 3H); 0.94 (s, 3H); IR (neat/CaF_2) 3400, 2961, 1728 cm^{-1}; $[\alpha]^{27}_D$ 32.4 (c = 1.6, $CHCl_3$); HRMS calcd for $C_{28}H_{30}NO_3$ 428.2226, found m/z 428.2228.

Methyl-(2*R*)-6-azido-3,3-dimethyl-2-[(9-phenylfluoren-9-yl)amino]-4-hexenoate (19). To a solution of **18** (658 mg, 1.54 mmol) and TEA (430 μL, 3.08 mmol) in dry $CHCl_3$ (10 mL) was added 2-fluoro-*N*-methylpyridinuim tosylate (872 mg, 3.08 mmol). The solution was neutralized with TEA, and after 15 min, the solvent was removed under reduced pressure. The residue was dissolved in dry HMPA (10 mL), and LiN_3 (151 mg, 3.08 mmol) was added. The reaction was heated to 90 °C under N_2. After 15 h following LiN_3 addition, the reaction was allowed to cool to ambient temperature, diluted with H_2O (20 mL), and extracted three times with EtOAc. The pooled organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure, and the residue was chromatographed through silica gel using EtOAc/hex (7%) as eluent. The azide **19** was obtained as a colorless oil (616 mg, 88%): R_f EtOAc/hex (25%) 0.59; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.68 (dd, J = 7.9, 11 Hz, 2H); 7.42 (m, 2H); 7.36−7.16 (m, 8H); 7.11 (d, J = 7.6 Hz, 1H); 5.68 (d, J = 16 Hz, 2H); 5.44 (dt, J = 6.5, 15 Hz, 1H); 3.71 (d, J = 6.5 Hz, 2H); 3.11 (s, 3H); 2.93 (bs, 1H); 2.31 (s, 1H); 1.01 (s, 3H); 0.94 (s, 3H); IR (neat/CaF_2) 2964, 2100, 1731 cm^{-1}; $[\alpha]^{27}_D$ −76.3 (c = 76.3, $CHCl_3$); HRMS calcd for $C_{28}H_{28}N_4O_2Na$ 475.2110, found m/z 475.2089.

***N*$^\alpha$-(9-Phenylfluoren-9-yl)-*N*$^\epsilon$-*tert*-butyloxycarbonyl-3,3-dimethyl-γ,δ-dehydro-D-lysine methyl ester (20).** Triphenylphosphine (163 mg, 0.621 mmol) was added to a solution of **19** (200 mg, 0.442 mmol) in dry THF (6 mL), and the reaction was allowed to warm to 65 °C. After 22 h, H_2O (0.13 mL) was added, and the reaction was allowed to stir for another 22 h, at which point the reaction was concentrated under reduced pressure. The residue was dissolved in dioxane (5 mL), and saturated $NaHCO_3$ (1 mL) and Boc_2O (157 mg, 0.720 mmol) were added. After 6 h, the reaction was concentrated, and the residue was taken up in H_2O (10 mL). The aqueous mixture was extracted three times with Et_2O and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed through silica gel using EtOAc/pet ether (15%) as eluent. The desired product **20** was obtained as a colorless oil (210 mg, 90%): R_f EtOAc/pet ether (20%) 0.28; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.68 (dd, J = 7.9, 11 Hz, 2H); 7.42 (m, 2H); 7.36−7.16 (m, 8H); 7.11 (d, J = 7.6 Hz, 1H); 5.68 (d, J = 16 Hz, 1H); 5.44 (dt, J = 6.5, 15 Hz, 1H); 3.71 (d, J = 6.5 Hz, 2H); 3.11 (s, 3H); 2.93 (bs, 1H); 2.31 (s, 1H); 1.01 (s, 3H); 0.94 (s, 3H); IR (neat/CaF_2) 3371, 2973, 1716 cm^{-1}; $[\alpha]^{27}_D$ 29.0 (c = 0.40, $CHCl_3$); HRMS calcd for $C_{33}H_{39}N_2O_4$ 527.2910, found m/z 527.2929.

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\epsilon$-*tert*-butyloxycarbonyl-3,3-dimethyl-D-lysine methyl ester [Cbz-β,β-diMe-D-Lys(Boc)-OMe] (21).** A mixture of **20** (172 mg, 0.327 mmol) and 10% Pd/C (7 mg) in MeOH/EtOAc (10 mL, 2:1) was degassed under reduced pressure and placed under H_2 (2 atm). After 16 h, the catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dry DCM (5 mL) and NMM (71 μL, 0.65 mmol) was added. The solution was cooled (0 °C) under N_2, and Cbz-Cl (70 μL, 0.49 mmol) was added over 3 min. After 18 h, H_2O (8 mL) was added, and the mixture was extracted twice with Et_2O. The pooled organic extracts were washed with 0.5 N HCl and brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/pet ether (15−25% gradient) as eluent. The desired product **21** was obtained as a colorless oil (115 mg, 83%): R_f EtOAc/pet ether (30%) 0.24; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.36 (m, 5H); 5.37 (d, J = 9.7 Hz, 1H); 5.11 (s, 2H); 4.69 (bs, 1H); 4.28 (d, J = 10 Hz, 1H); 3.73 (s, 3H); 3.08 (m, 2H); 1.52 (m, 2H); 1.33 (s, 9H); 1.28 (m, 2H); 0.92 (s, 6H); IR (neat/CaF_2) 2971, 1713 cm^{-1}; $[\alpha]^{27}_D$ −8.0 (c = 3.5, $CHCl_3$); HRMS calcd for $C_{22}H_{35}N_2O_6$ 423.2495, found m/z 423.2508.

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\epsilon$-*tert*-butyloxycarbonyl-3,3-dimethyl-D-lysine [Cbz-β,β-diMe-D-Lys(Boc)-OH] (4).** A solution of LiOH (1.2 mL, 1 N) was added to a cooled (0 °C) solution of **21** (101 mg, 0.239 mmol) in dioxane (4.8 mL). After 1.5 h, the reaction was allowed to warm to ambient temperature, and after 9 h, the reaction was concentrated to approximately one-third the original volume. The residue was diluted with EtOAc (10 mL) and washed with 1 N HCl (4 mL). The aqueous layer was extracted with fresh EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and chromatographed through silica gel using $CHCl_3$/MeOH/AcOH (98:1:1) as eluent. The desired product **4** was obtained as a colorless oil (93 mg, 95%): R_f $CHCl_3$/MeOH/AcOH (95:5:3) 0.46; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.35 (m, 5H); 6.29 (bs, 1H); 5.46 (d, J = 9.7 Hz, 1H); 5.11 (s, 2H); 4.74 (bs, 1H); 4.28 (d, J = 8.6 Hz, 1H); 3.05 (bm, 2H); 1.44 (m, 13H); IR (neat/CaF_2) 3338, 2973, 1709 cm^{-1}; $[\alpha]^{27}_D$ −9.4 (c = 1.7, $CHCl_3$); HRMS calcd for $C_{21}H_{33}N_2O_6$ 409.2339, found m/z 409.2354.

***N*$^\alpha$-Benzyloxycarbonyl-*N*$^\epsilon$-*tert*-butyloxycarbonyl-3,3-dimethyl-D-lysine (*R*)- and (*S*)-α-methylbenzylamide (22a and 22b).** The title diastereomers were obtained by coupling **4** to optically active α-methylbenzylamine as described for **9a**. The 360 MHz ^{1}H NMR spectra of the crude diastereomers **22a** and **22b** were obtained, and the chemical shifts of the β-methyl groups were used for comparison.

Dimethyl-(2*R*)-3,3-dimethyl-2-(9-phenylfluoren-9-yl)-homoglutamate [Boc-β,β-diMe-D-Hglu(OMe)-OMe] (23). Magnesium powder (139 mg, 5.70 mmol) was added to a solution of **17** (0.650 g, 1.43 mmol) in MeOH (15 mL). The mixture was sonicated for 3 h, and the reaction was monitored by TLC with $KMnO_4$ stain to monitor the disappearance of starting material. The reaction was diluted with EtOAc (100 mL), and 1 N HCl (15 mL) was added. The aqueous layer was extracted twice with EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/hex (15%) as eluent. The desired product **23** was obtained as a colorless oil (0.594 g, 91%): R_f EtOAc/hex (20%) 0.42; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.68 (dd, J = 7.6, 15 Hz, 2H); 7.45 (d, J = 6.5 Hz, 2H); 7.37 (m, 7H); 7.13 (dd, J = 7.4 Hz, 13 Hz, 2H); 3.64 (s, 3H); 3.14 (s, 3H); 2.77 (s, 1H); 2.26 (s, 1H); 2.05 (m, 1H); 1.73 (m, 2H); 1.51 (m, 1H); 0.91 (s, 3H); 0.71 (s, 3H); IR (neat/CaF_2) 2950, 1732 cm^{-1}; $[\alpha]^{27}_D$ 28.3 (c = 0.15, $CHCl_3$); HRMS calcd for $C_{29}H_{32}NO_4$ 458.2331, found m/z 458.2329.

***C*$^\alpha$-Methyl-3,3-dimethyl-2-(*tert*-butyloxycarbonylamino)-D-homoglutamate [Boc-β,β-diMe-D-Hglu-OMe] (5).** Sodium hydroxide (1.0 mL, 1 N) was added to a solution of **23** (153 mg, 0.334 mmol) in MeOH (10 mL). The solution was heated to reflux, and after 6 h, the reaction was cooled to 0 °C. The solution was carefully acidified to pH 2−3 by the addition of 1 N HCl. The mixture was extracted three times with EtOAc, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the carboxylic acid as an oil.

The crude carboxylic acid was dissolved in MeOH (2 mL) and EtOAc (2 mL), and 10% Pd/C (3 mg) and Boc_2O (110 mg, 0.505 mmol) were added. The solution was degassed under reduced pressure and placed under H_2 (2 atm). After 40 h, the mixture was filtered through Celite, and the filter was washed with EtOAc. The filtrate was concentrated and chromatographed through silica gel using $CHCl_3$/MeOH/AcOH (98:1:1) as eluent. The purified fractions were concentrated, and residual AcOH was removed by codistillation with toluene. The product **5** was obtained as a colorless oil (91.0 mg, 89%): R_f $CHCl_3$/MeOH/AcOH (98:1:1) 0.30; ^{1}H NMR (360 MHz/$CDCl_3$) δ 5.18 (d, J = 9.7 Hz, 1H); 4.21(d, J = 9.7 Hz, 1H); 3.74 (s, 3H); 2.42 (m, 1H); 1.65 (m, 2H); 1.44 (s, 9H); 0.95 (s, 3H); 0.94

(s, 3H); IR (neat/CaF_2) 3284, 2975, 1713 cm^{-1}; $[\alpha]^{27}_D$ −23.5 (*c* = 1.7, $CHCl_3$); HRMS calcd for $C_{14}H_{26}NO_6$ 304.1760, found *m/z* 304.1760.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*N*$^{\delta}$-benzyloxycarbonyl-3,3-dimethyl-D-ornithine-methyl ester [Boc-β,β-diMe-D-Orn(Cbz)-OMe] (6).** Benzyl alcohol (34 μL, 0.33 mmol), DPPA (71 μL, 0.33 mmol), and TEA (69 μL, 0.50 mmol) were added to a solution of **5** (50 mg, 0.165 mmol) in toluene (3 mL). The solution was heated to reflux under N_2. After 22 h, the reaction was diluted with saturated $NaHCO_3$ (5 mL) and extracted twice with Et_2O. The pooled organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated and chromatographed through silica gel using EtOAc/pet ether (25%) as eluent to give **6** as a colorless oil (38 mg, 56%): R_f EtOAc/pet ether (25%) 0.28; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.35 (m, 5H); 5.13 (d, *J* = 10 Hz, 1H); 5.09 (s, 2H); 4.86 (m, 1H); 4.20 (d, *J* = 9.4 Hz, 1H); 3.73 (s, 3H); 3.27 (m, 2H); 1.51 (t, *J* = 8.4 Hz, 2H); 1.43 (s, 9H); IR (neat/CaF_2) 2974, 1712 cm^{-1}; $[\alpha]^{27}_D$ −15.7 (*c* = 8.7, $CHCl_3$); HRMS calcd for $C_{21}H_{33}N_2O_6$ 409.2339, found *m/z* 409.2318.

***N*$^{\alpha}$-*tert*-Butyloxycarbonyl-*O*-*tert*-butyl-tyrosinyl-*N*$^{\delta}$-benzyloxycarbonyl-3,3-dimethyl-D-ornithine-methyl ester [Boc-Tyr(*t*Bu)-β,β-diMe-D-Orn(Cbz)-OMe] (24).** A solution of **6** (24 mg, 59 μmol) in DCM (0.5 mL) was cooled (0 °C), and TFA (0.5 mL) was added. After 5 min, the reaction was allowed to warm to ambient temperature, and after 1 h, the solvent was removed under reduced pressure. Residual TFA was removed by codistillation with toluene. The crude amine was dissolved in DMF (1 mL), and HOAt (12 mg, 88 μmol) and Boc-Tyr(*t*Bu)-OH (30 mg, 89 μmol) were added. The reaction was cooled (−20 °C) under N_2 and neutralized with NMM, and EDC (17 mg, 89 μmol) was added. The reaction was allowed to warm to ambient temperature, and after 18 h, the reaction was concentrated under reduced pressure. The residue was dissolved in 0.5 N HCl (3 mL), and the solution was extracted three times with EtOAc. The pooled organic extracts were washed with 0.5 N HCl, brine, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated onto Florisil, and chromatographed through silica gel using EtOAc/hex (30%) as eluent. The desired product **24** was obtained as a colorless foam (31 mg, 84%): R_f EtOAc/hex (50%) 0.48; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.36 (m, 5H); 7.11 (d, *J* = 7.9 Hz, 2H); 6.92 (d, *J* = 7.9 Hz, 2H); 6.35 (bd, *J* = 6.5 Hz, 1H); 5.21 (m, 1H); 5.10 (s, 2H); 5.00 (m, 1H); 4.41 (d, *J* = 9.0 Hz, 1H); 4.33 (m, 1H); 3.69 (s, 3H); 3.22 (m, 1H); 3.01 (m, 3H); 1.41 (s, 9H); 1.31 (s, 9H); 1.26 (m, 1H); 1.12 (m, 1H); 0.86 (s, 3H); 0.82 (s, 3H); HRMS calcd for $C_{34}H_{50}N_3O_8$ 628.3598, found *m/z* 628.3607.

(*R*)-*N*-(9-Phenylfluoren-9-yl)-3,3-dimethyl-azetidine-2-carboxylic acid methyl ester [PhFl-β,β-diMe-D-Azt-OMe] (7). Mesyl chloride (58 μL, 0.75 mmol) was added to a solution of **14** (100 mg, 0.250 mmol) and TEA (105 μL, 0.750 mmol) in DCM (4 mL), and the mixture was allowed to stir at ambient temperature. After 0.5 h, the reaction was diluted with DCM (10 mL) and H_2O (4 mL). The aqueous layer was extracted with DCM, and the pooled organic extracts were washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a yellow oil. The crude material was dissolved in HMPA (2 mL), and TEA (0.10 mL, 0.75 mmol) was added. The reaction was heated (85 °C) and allowed to stir under N_2. After 16 h, the reaction was diluted with H_2O (5 mL) and extracted twice with EtOAc. The pooled organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude material was chromatographed through silica gel using EtOAc/pet ether (8%) as eluent to give the azetidine **7** as a colorless oil (60 mg, 60%): R_f EtOAc/pet ether (10%) 0.50; ^{1}H NMR (360 MHz/$CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1H); 7.59−7.11 (m, 12H); 3.35 (s, 3H); 3.20 (m, 2H); 3.05 (s, 1H); 1.16 (s, 3H); 0.83 (s, 3H); IR (neat/CaF_2) 2952, 1752 cm^{-1}; $[\alpha]^{27}_D$ −20.1 (*c* = 0.34, $CHCl_3$); HRMS calcd for $C_{26}H_{26}NO_2$ 384.1966, found *m/z* 384.1972.

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Supporting Information Available: ^{1}H NMR spectra of compounds **1**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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