Building Functionalized Peptidomimetics: The Use of Electroauxiliaries for Introducing N-Acyliminium Ions Into Peptides

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SUPPLEMENTARY MATERIAL

General Information

All proton magnetic resonance spectra were recorded using a Varian Mercury 300, Varian Unity 300, or a Varian Inova 500 spectrometer with $CDCl_3$ as solvent. Chemical shifts for proton spectra are reported as parts per million (ppm) downfield from tetramethysilane (TMS) in δ units, and coupling constants have been reported in cycles per second (hertz, Hz). The splitting patterns are designated as follows: s for singlet or br s for a broad singlet, d for doublet or br d for a broad doublet, t for triplet, q for quartet, and m for multiplet. ^{13}C NMR spectra are fully decoupled and were obtained using a Varian Mercury 300 at 75 MHz or a Varian Inova 500 at 125 MHz. Chemical shifts are reported in ppm with the central line of the chloroform-d triplet referenced by 77.23 ppm. Infrared spectra (IR) were obtained from neat samples on NaCl plates using a Perkin Elmer Spectrum BS FT-IR System spectrophotometer. Nominal mass (referred to below as LR) spectral data were obtained using the first two sectors of a Micromass ZAB-T spectrometer with an 8 keV acceleration voltage and resolving power of 1000. Accurate mass (referred to below as HR) electron ionization (EI) mass spectral data were obtained using a Micromass ZAB-T spectrometer with an 8 keV acceleration voltage, resolving power of at least 7000, an internal mass standard of polyfluorinated kerosene (PFK), and were acquired by magnet scan. Accurate mass (HR) fast atom bombardment (FAB) mass spectral data were obtained using a Kratos MS-50 spectrometer operated at a resolving power of at least 7000 with an external calibration compound of glycerol/lithium, a 3-nitrobenzylalcohol/lithium matrix, and were acquired by peak match.

HPLC data were obtained using a Helwett-Packard 1100 Series HPLC system equipped with a quaternary pump, variable wavelength detector, HP Chemstation software, and a Discovery HS C18 HPLC column (25cm x 4.6mm x 5μm) with a 2 μm precolumn filter. The HPLC solvents used were isopropanol (IPA), acetonitrile, and water. All solvents were HPLC grade and purchased from either Sigma-Aldrich or EDM. Before use, solvents were sonicated and sparged with Argon. Sample injection volumes were 20μL, and analytes were either dissolved or co-dissolved in IPA. All elutions were isocratic and run at ambient temperatures with a flow rate of 1 mL/minute. Analytes were detected at 254 nm. Solvent systems are indicated on HPLC chromatograms.

Reactions were monitored by TLC with general-purpose silica gel coated glass plates purchased from Sigma-Aldrich Chemical Co. All preparative chromatography was flash chromatography and was carried out using ICN SiliTech 32-63D/60A silica gel. The solvents used for chromatography were mixed by volume and are reported for each experiment.

All electrolyses were accomplished using either a model 630 coulometer, a model 420A power supply, and a model 410 potentiostat available from Electrolytica or an Arbin Power supply equipped with MITS'97 software. Reactions were carried out at ambient temperature under untreated air unless otherwise indicated. Two carbon electrodes with Reticulated Vitreous Carbon (RVC) on the anode were used for all electrolyses. Carbon electrodes and RVC were purchased from Electrolytica, Inc. Tetrabutylammonium tetrafluoroborate was used as the electrolyte for all electrolyses and was purchased from Aldrich Chemical Co.

Chemical reagents and solvents were purchased from Aldrich Chemical Co., Sigma Chemical Co., Fluka, and Acros Organics and used without further purification unless otherwise noted.

Dichloromethane was distilled over calcium hydride. Chloroform-d was purchased from Cambridge Isotope Laboratories or Aldrich Chemical Co. and used without further purification.
The purity of all compounds was determined by proton NMR and/or reverse phase HPLC data.

General procedure for preparative electrochemical amide oxidations with silylated peptide derivatives in methanol:

An oven-dried three-neck 100 mL round bottom flask was fitted with a Pt wire cathode, a RVC anode, and a rubber septum. A syringe needle was pushed through the septum and used as a nitrogen inlet. The flask was charged with the silylated dipeptide substrate (0.5 mmol), anhydrous MeOH (16.7 mL), and tetrabutylammonium tetrafluroborate (0.5 mmol). The reaction mixture was degassed by sonication while a slow stream of nitrogen was passed through the solution for 10 min. The mixture was then electrolyzed at a constant current of 21.0 mA until 2.1-2.3 F/mol had been passed. When complete, the MeOH was removed under reduced pressure and the crude product chromatographed through silica gel.

General procedure for deprotection of Boc protecting groups:

The Boc protected amino acid substrate (2 mmol) was dissolved in ethyl acetate (15 mL) in a 50 mL round bottom flask and treated with a saturated aqueous HCl solution (5 mL). The reaction mixture was allowed to stir at room temperature for 30 min, and then the solvent removed under reduced pressure. After most of the solvent was removed benzene was added to the mixture and then the pressure reduced again in order to remove any remaining water. The crude amine was left on the vacuum line for at least 8 h and then used without purification for the following step.

General procedure for deprotection of Cbz protecting group:

A 250 mL round bottom flask was charged with the Cbz protected amino acid substrate (2.0 mmol), palladium hydroxide (10% w/w), and methanol (15 mL). A balloon full of hydrogen gas was attached to the flask using a needle through a rubber septum. The mixture was vigorously stirred at room temperature for 12 h and then filtered through a short plug of celite. The filtrate was concentrated *in vacuo* and used without purification for the next reaction.

General procedure for the hydrolysis of amino acid methyl esters:

A 250 mL round bottom flask was charged with the amino acid methyl ester (2.0 mmol), MeOH (22.5 mL), and water (7.5 mL). Lithium hydroxide (168 mg, 4.0 mmol) was added at 0 ^{o}C, and the reaction was allowed to stir for 3 h at 0 ^{o}C followed by an additional 12 h at room temperature. The mixture was concentrated under reduced pressure and the remaining aqueous solution was acidified until the pH reached ~2.0. The aqueous solution was then extracted three times with ethyl acetate. The combined EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product could be further purified using a silica gel column or used directly for the following step.

General procedure for preparation of phenyldimethylsilyl lithium:

Lithium wire (1% sodium) (0.5 g, 72 mmol) was washed two times with dry hexane, cut into small slices in the hexane, and then quickly transferred under argon atmosphere (using an inverted argon funnel) to a flame-dried 100 mL round bottom flask containing dry THF (20 mL). Chlorodimethylphenylsilane (5 mL, 29.8 mmol) was added slowly to this mixture at room temperature. The reaction was then sonicated in order to activate the lithium and initiate the reaction which led to a dark red solution. The reaction mixture was allowed to stir at room temperature for 12 h. The resulting silyl lithium solution can be used immediately or stored under argon at 0 ^{o}C for one to two weeks.

2-Methoxymethylpyrrolidine-1-carboxylic acid tert-butyl ester:

In an oven-dried 250 mL round bottom flask was added L-prolinol (3.51 g, 34.7 mmol) and dry ethyl acetate (25 mL) under nitrogen. The solution was cooled to 0 ^{o}C using an ice bath. While stirring,

$(Boc)_2O$ (6.48 g, 29.6 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 90 min. The reaction was quenched with 25 mL of 1 N HCl solution and transferred to a separatory funnel. The reaction mixture was washed with 1 N HCl solution (2 X 25 mL), brine (2 X 25 mL) and the combined organic layers then dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and used without further purification for the following step.

To a solution of the crude N-(tert-butoxycarbonyl)-L-prolinol (7.28 g, ~34 mmol) in DMF (60 mL) at room temperature were added methyl iodide (4.42 mL, 70 mmol) and potassium hydroxide (8 g, 137 mmol). The obtained suspension was allowed to stir for 12 h and methyl iodide (2.2 mL, 35 mmol) and potassium hydroxide (4 g, 68 mmol) were added. The reaction was stirred for an additional 8 h and then the reaction mixture quenched with 125 mL of H_2O. The mixture was washed with ethyl acetate (3 X 40 mL) and the combined organic layers dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed through silica gel (slurry packed with hexane and eluted with 1:4 EtOAc/hexane) and the desired product (5.51 g) was obtained as colorless oil in a 74% yield over two steps. The spectroscopic data for the product were consistent with those previously reported in the literature (Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221).

2-Methoxy-5-methoxymethylpyrrolidine-1-carboxylic acid tert-butyl ester:

An oven-dried three-neck 100 mL round bottom flask was charged with the protected L-prolinol methyl ether (1.52g, 7.0 mmol), MeOH (14.1 mL), and tetraethylammonium tosylate (127 mg, 0.42 mmol). The flask was equipped with a carbon rod anode, a platinum wire cathode, and a nitrogen inlet. The reaction mixture was degassed by sonication while a slow stream of nitrogen that was passed through the solution for 5 min. The mixture was then electrolyzed at a constant current of 26.8 mA until 2.1 F/mol had been passed. When complete, the MeOH was removed under reduced pressure and the crude oil chromatographed through silica gel using a gradient elution from 1:5 EtOAc/hexane to 1:3 EtOAc/hexane. The column afforded 1.25 g (72%) desired methoxylated amide as a mixture of two diastereomers. The yield of this reaction was determined using GC-MS because the product isolated from the column was always a mixture of the desired methoxylated prolinol derivative and the starting material. The GC-MS was used to determine the ratio of product to starting material which usually ranged from 6:1 to 3:1. The yield reported represents the best yield obtained for the reaction.

2-(Dimethylphenylsilyl)-5-methoxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (12b):

A THF solution of lithium dimethylphenylsilane (<29.8 mmol, ~20 mL) was prepared according to the general procedure outlined above. The volume of THF was then reduced *in vacuo* (about 75% of the THF was removed), and dry ether (20 mL) was added. The silyl lithium solution in ether/THF was transferred into a flame-dried 100 mL round bottom flask charged with copper cyanide (900 mg, 10 mmol) and dry ether (10 mL). The mixture was dark black in color. After stirring at room temperature for 10 min, the reaction mixture was cooled to -40 ^oC and stirred for another 25 min. At the same time, the methoxylate prolinol substrate (1.54 g, 6.3 mmol) was added to a flame-dried 250 mL round bottom flask and dissolved in 5 mL of ether. The prepared silyl cuprate solution was then transferred into the flask containing the substrate by cannulation under argon. To this mixture was added $BF_3{\cdot}Et_2O$ (0.5 mL, 3.9 mmol) at -40 ^oC. The reaction was stirred for 3 h at -40 ^oC and then allowed to warm to room temperature and quenched with a 1:1 $NH_3{\cdot}H_2O/NH_4Cl$ buffer solution. The resulting mixture was stirring for 30 min until a bright blue color appeared and then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was chromatographed through silica gel using a gradient elution from 1:20 EtOAc/hexane to 1:6 EtOAc/hexane as eluant to afford 1.34 g (61%) of the product. ^1H NMR ($CDCl_3$/300 MHz) (mixture of two diastereomers with approximately 2:1 ratio and their rotamers observed) δ 7.61-7.50 (m, 2H), 7.34-7.24 (m, 3H), 3.84 (br s, 0.33H), 3.72 (br s, 0.67H), 3.64 (d, J=6.6Hz, 0.33H), 3.56 (d, J=9.9Hz, 0.33H), 3.49 (dd, J=9.0, 3.0Hz, 0.67H), 3.42 (dd, J=9.4, 3.4Hz,

0.67H), 3.31 (s, 3H), 3.18 (t, J=8.8Hz, 1H), 2.17-1.61 (m, 4H), 1.44 and 1.38 (s and s, 9H), 0.40 and 0.38 (s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 154.3, 139.0, 134.4, 134.2, 134.0, 132.9, 129.0, 128.5, 128.0, 127.8, 79.1, 78.8, 73.6, 72.1, 59.2, 59.0, 56.9, 56.7, 49.0, 29.3, 28.8, 28.,4, 27.1, 26.2, -1.7, -2.4, -2.8, -3.2, -3.7; IR (neat/NaCl) 3069, 2974, 1693, 1392, 1247, 1175, 1112, 821, 736, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 356 (2) MLi^+, 313 (23) MLi^+-C_2H_4O+H^+, 160 (100) ; HRFAB MS m/z calculated for $[M+Li]^+$ 356.2233, found 356.2224.

{1-Benzyl-2-[2-(dimethylphenylsilyl)-5-methoxymethylpyrrolidin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester (13):

The t-Boc protected silylated prolinol substrate (0.94 g, 2.2 mmol) was deprotected using the general procedure described above and then the amine carried into the coupling reaction. A 250 mL oven-dried round bottom flask was charged with the amine substrate obtained in the above step and 15 mL of dry dichloromethane. The mixture was treated with 0.61 mL of triethylamine. The solution was stirred at room temperature for 15 min and then DCC (1.14 g, 5.5 mmol), HOBT (0.6 g, 4.4 mmol), and phenylalanine methyl ester (1.17 g, 4.4 mmol) were added in sequence. The reaction mixture was allowed to stir for 16 h at room temperature. The reaction was then quenched with water and the layers were separated in a separatory funnel. The aqueous layer was washed with dichloromethane three times and the combined organic layers were washed with brine twice before being dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The crude product was chromatographed through silica gel using a gradient elution from 1:7 EtOAc/hexane to 1:2 EtOAc/hexane as eluant to afford 1.26 g (61%) of the product. ^{1}H NMR ($CDCl_3$/300 MHz) (mixture of two diastereomers with approximately 1:1 ratio and their rotamers were observed) δ 7.57-7.41 (m, 2H), 7.40-7.09 (m, 7H), 7.05-7.02 (m, 1H), 5.50 (d, J=7.8Hz, 0.03H), 5.27 (dd, J=8.7, 6.0Hz, 0.97H), 4.82-4.45 (m, 1.5H, peaks in 4.69 (dd, J=16.4, 7.6Hz) and 4.59 (td, J=9.3, 5.4Hz) represent two main isomers), 3.60-3.45 (m, 0.4H), 3.48-3.46 (m, 0.1H), 3.34-3.00 (m, 2H), 3.28, 3.22, 3.12 and 3.07 (s, s, s and s, 3H), 2.97-2.74 (m, 2H), 2.67-2.52 (m, 1H), 1.81-1.16 (m, 3.5H), 1.41, 1.38, 1.36, 1.30 and 1.29 (s, s, s, s and s, 9H), 0.88-0.76 (m, 0.5H), 0.42, 0.36, 0.35 0.32, 0.28, 0.27 (s, s, s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.3, 170.0, 155.0, 154.8, 139.2, 137.3, 137.1, 136.3, 134.5, 134.2, 134.0, 130.0, 129.9, 129.6, 129.2, 128.6, 128.6, 128.3, 127.9, 127.1, 126.9, 79.4, 79.4, 74.0, 71.2, 59.3, 59.0, 57.8, 57.2, 55.2, 53.5, 50.7, 49.0, 41.7, 40.8, 28.9, 28.7, 28.6, 27.5, 26.6, 26.2, -0.7, -1.0, -2.4, -3.3, -3.6; IR (neat/NaCl) 3428, 3286, 2972, 1704, 1624, 1495, 1448, 1248, 1169, 1111, 828, 735, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 503 (75) MLi^+, 403 (90) MLi^+-Boc+H^+, 294 (30), 160 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 503.2917, found 503.2898.

[1-Benzyl-2-(2-methoxy-5-methoxymethylpyrrolidin-1-yl)-2-oxoethyl]-carbamic acid tert-butyl ester (14):

The silylated dipeptide substrate (189 mg, 0.38 mmol) was oxidized using the general procedure outlined above. For this experiment 2.3 F/mol of current was passed. The crude product was chromatographed through silica gel using a gradient elution from 1:5 EtOAc/hexane to 1:3 EtOAc/hexane. The column afforded 116 mg (78%) of the desired product along with 26 mg (14%) of recovered starting material. ^{1}H NMR ($CDCl_3$/300 MHz) (mixture of two diastereomers with approximately 2:1 ratio and their rotamers observed) δ 7.28-7.10 (m, 5H), 5.39-5.34 (m, 0.5H), 5.35 (d, J=5.1Hz, 0.67H), 5.12 (d, J=9.3Hz, 0.33H), 4.94-4.86 (m, 0.5H), 4.68-4.53 (m, 0.67H), 4.27-4.14 (m, 0.67H), 3.80-3.75 (m, 0.33H), 3.65 (dd, J=8.8, 4.0Hz, 0.33H), 3.42-3.04 (m, 3H), 3.34, 3.34, 3.31, 3.29, 3.28, 3.18 and 3.17 (s, s, s, s, s, s and s, 6H), 2.97-2.79 (m, 1H), 2.09-1.62 (m, 4H), 1.48, 1.44, 1.41 and 1.34 (s, s, s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.8, 172.6, 172.1, 155.4, 155.0, 137.1, 137.0, 136.7, 129.9, 129.8, 129.8, 129.7, 128.7, 128.6, 127.2, 1127.1, 126.9, 90.0, 89.4, 88.1, 79.9, 79.7, 77.8, 73.7, 71.5, 59.2, 59.1, 56.9, 56.8, 56.4, 56.0, 54.8, 54.1, 53.5, 53.2, 41.4, 39.6, 30.6, 30.2, 29.9, 28.9, 28.6, 28.5, 26.0, 24.3; IR (neat/NaCl) 2972, 1706, 1391, 1366, 1169, 1130 cm^{-1}; LRFAB MS (relative

intensity) m/z 399 (100) MLi^+, 299 (94) MLi^+-Boc+H^+, 120 (47); HRFAB MS m/z calculated for $[M+Li]^+$ 399.2471, found 399.2475.

2-Benzyl-5-methoxymethyl-hexahydro-pyrrolo[1,2-a]imidazol-3-one (15):

To an oven-dried 50 mL round bottom flask was added the methoxylated dipeptide substrate (165 mg, 0.42 mmol) and anhydrous ether (15 mL) at -78 ^oC. $BF_3{\cdot}Et_2O$ (50 μl, 0.42 mmol) was added and the reaction mixture was allowed to stir at -78 ^oC for 1 hour before it was allowed to warm up to room temperature over a 30 min period. The reaction was stopped and the solvent was removed *in vacuo.* The crude product was chromatographed through silica gel using a gradient elution from 1:4 EtOAc/hexane to 1:2 EtOAc/hexane. The column afforded 108 mg (71%) of the desired cyclized product. ^1H NMR ($CDCl_3$/300 MHz) δ 7.31-7.17 (m, 5H), 4.81 (dd, J=7.8, 5.1Hz, 1H), 4.12 (dd, J=8.4, 3.9Hz, 1H), 4.01-3.95 (m, 1H), 3.43 (d, J=4.6Hz, 2H), 3.36 (s, 3H), 3.16 (dd, J=13.5, 3.9, 1H), 2.78 (dd, J=13.8, 8.7Hz, 1H), 2.18 (br s, 1H), 2.11-1.82 (m, 3H), 1.12-1.02 (m,1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 174.8, 138.4, 129.5, 128.3, 126.4, 76.1, 74.1, 64.4, 59.1, 53.5, 38.8, 33.8, 28.0; IR (neat/NaCl) 3350, 2923, 1698, 1402, 1121, 750, 701 cm^{-1}; LRFAB MS (relative intensity) m/z 267 (5) MLi^+, 219 (7), 160 (100), 89 (28); HRFAB MS m/z calculated for $[M+Li]^+$ 267.1685, found 267.1682.

{2-[2-(Dimethylphenylsilyl)-5-methoxymethylpyrrolidin-1-yl]-1-hydroxymethyl-2-oxoethyl}-carbamic acid tert-butyl ester (two main rotamers with approximately 3:1 ratio) (16):

Before the coupling reaction, the BOC protected silylated prolinol substrate (0.768 g, 2.2 mmol) was deprotected using the general procedure outlined above.

A 250 mL round bottom flask was charged with N-(tert-butoxycarbonyl)-serine (452 mg, 2.2 mmol), N-methylmorpholine (0.308 mL, 2.9 mmol), isobutylchloroformate (0.285 mL, 2.2 mmol), and CH_2Cl_2 (36 mL). The reaction mixture was stirred at –15 ^oC for 25 min. The silylated prolinol amine substrate (crude) dissolved in CH_2Cl_2 (6 mL) was canulated into the above solution. Two additional washings with dichloromethane ensured complete transfer of the substrate. The reaction mixture was warmed up to room temperature and stirred for 12 h. After the reaction was quenched with water and the layers were separated, the organic layer was washed with water (3 x 20 mL) and dried over the $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo*. The residue was chromatographed through a silica gel column using an eluant of 1:1 Hexane/EtOAc to afford 668 mg (70%) of the silated dipeptide product. ^1H NMR ($CDCl_3$/300 MHz) δ 7.52-7.48 (m, 2H), 7.38-7.30 (m, 3H), 5.48 (d, J=8.4Hz, 1H), 4.64-4.60 (m, 1H), 4.20-4.15 (m, 1H), 3.70-3.66 (m, 2H), 3.48-3.41 (m, 2H), 3.20 and 3.18 (s and s, 3H), 3.13-3.08 (m, 1H), 2.99-2.78 (m, 1H), 1.87-1.66 (m, 4H), 1.46 (s, 9H), 0.40 and 0.39 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 169.4, 155.6, 147.2, 137.4, 134.2, 129.0, 127.5, 79.7, 72.8, 64.1, 58.8, 58.7, 57.6, 53.3, 49.2, 29.1, 28.3, 28.3, 26.0, -2.8, -3.6 ; IR (neat/NaCl) 3435, 2953, 1747, 1713, 1634, 1496, 1456, 1247, 1170, 855, 735, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 443 (97) MLi^+, 343 (100) MLi^+-Boc+H, 256 (30), 135 (50); HRFAB MS m/z calculated for $[M+Li]^+$ 443.2554, found 443.2548.

(6-Methoxymethyl-4-oxo-hexahydropyrrolo[2,1-b][1,3]oxazin-3-yl)-carbamic acid tert-butyl ester (17):

An oven-dried 50 mL three-neck round bottom flask was fitted with a Pt wire cathode, a RVC anode, and a septum. A syringe needle was pushed through the septum and used as a nitrogen inlet. The flask was charged with the silylated dipeptide substrate (90 mg, 0.21 mmol), anhydrous acetonitrile (6.1 mL), isopropyl alcohol (0.7 mL), and tetrabutylammonium tetrafluroborate (68 mg, 0.21 mmol). The resulting mixture was degassed by sonication while a slow stream of nitrogen was passed through the solution for 10 min. The mixture was then electrolyzed at a constant current of 21.0 mA until 2.2 F/mol had been passed. When complete, the MeOH was removed under reduced pressure and the crude oil chromatographed through silica gel using a gradient elution from 1:3 EtOAc/hexane to 1:1 EtOAc/hexane. The column afforded 49 mg (80%) of the desired product. ^1H NMR ($CDCl_3$/300 MHz) δ 5.45 (br s, 1H), 5.14 (t, J=6.0Hz, 1H), 4.44-4.36 (m, 1H), 4.11 (td, J=4.5, 3.3Hz, 1H), 3.69 (dd, J=9.2,

3.2Hz, 1H), 3.57 (dd, J=8.4, 7.2Hz, 1H), 3.49 (dd, J=9.3, 7.5Hz, 1H), 3.35(s, 3H), 2.23-2.17(m, 1H), 2.10-1.88(m, 3H), 1.44(s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 166.4, 155.8, 86.9, 80.1, 70.7, 68.2, 59.1, 56.3, 49.2, 30.3, 28.2, 25.1; IR (neat/NaCl) 3326, 2979, 1717, 1680, 1440, 1169, 870, 771 cm^{-1}; LRFAB MS (relative intensity) m/z 307 (21) MLi^+, 160 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 307.1845, found 307.1834.

5-Benzenesulfonylpyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (18):

To a 250 mL oven-dried round bottom flask was added the methoxylated substrate (1.94g, 6.6 mmol) synthesized above, the sodium salt of phenylsulfinic acid (2.95 g, 18 mmol), magnesium sulfate (2.17 g, 18 mmol), and dichloromethane (24 mL). Trifluroacetic acid (1.39 mL/ 18 mmol) was added while the white suspension was stirring. The reaction was allowed to stir at room temperature for 2 h and then quenched with water. The mixture was transferred to a separatory funnel and extracted three times with dichloromethane. The combined organic layers were then washed with sat. sodium bicarbonate solution and brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was run through a short column using an eluant of 4:2:1 hexane:EtOAc:CH_2Cl_2. The yellow product obtained was then recrystallized using hexane/ether. The product (2.27 g/ 85%) was obtained as a white solid. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio observed) δ 7.90 (d, J=7.5Hz, 1H), 7.80 (d, J=7.5, 1H), 7.66-7.37 (m, 3H), 7.36-7.27 (m, 3H), 7.21-7.11 (m, 2H), 5.32 (d, J=7.8Hz, 0.5H), 5.22 (d, J=7.8Hz, 0.5H), 5.02 (A of AB, $J_{A'B'}$=12.6Hz, 0.5H), 4.96 (A of AB, J_{AB}=12.0Hz, 0.5H), 4.81 (B of AB, J_{AB}=12.0Hz, 0.5H), 4.58 (d, J=8.7Hz, 0.5H), 4.52 (d, J=9.3Hz, 0.5H), 4.17 (B of AB, $J_{A'B'}$=12.3Hz, 0.5H), 3.72 and 3.47 (s and s, 3H), 2.84-2.63 (m, 2H), 2.43-2.26 (m, 1H), 2.05-1.98 (m, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 172.4, 154.1, 153.9, 137.7, 137.6, 135.6, 135.3, 134.2, 134.1, 129.4, 129.3, 129.2, 129.2, 128.6, 128.6, 128.5, 128.4, 128.0, 78.9, 78.6, 68.0, 68.0, 60.7, 60.5, 52.7, 52.4, 29.6, 28.3, 26.3, 25.2; IR (neat/NaCl) 3065, 2955, 1755, 1732, 1721, 1447, 1398, 1346, 1322, 1291, 1147, 732, 690 cm^{-1}; LRFAB MS (relative intensity) m/z 410 (38) MLi^+, 313 (67), 218 (42), 160 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 410.1250, found 410.1254.

5-(Dimethylphenyl-silyl)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (19):

A THF solution of lithium dimethylphenylsilane (<29.8 mmol) was prepared according to the general procedure described above and then transferred into a flame-dried 100 mL round bottom flask charged with copper cyanide (900 mg, 10 mmol) and dry THF (10 mL) under argon. The mixture was dark black in color. After stirring at room temperature for 10 min, the reaction mixture was cooled to -78 ^{o}C and stirred for another 30 min. At the same time, the sulphonyl proline substrate (3.15 g, 7.81 mmol) was added to a flame-dried 250 mL round bottom flask and dissolved in 20 mL ether. The substrate was then transferred to the prepared silyl cuprate solution by cannulation under argon and allowed to stir for 1.5 h at -78 ^{o}C. The reaction was allowed to warm to room temperature and quenched with a 1:1 $NH_3{\cdot}H_2O/NH_4Cl$ buffer solution. The mixture was stirred for 30 min until a bright blue color showed up. The reaction was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was chromatographed through silica gel using a gradient elution from 1:10 EtOAc/hexane to 1:5 EtOAc/hexane to afford 2.18 g (71%) of the product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.61-7.26 (m, 10H), 5.20 (A of AB, J_{AB}=12.3Hz, 0.33H), 5.16 (A of AB, $J_{A'B'}$=12.6Hz, 0.67H), 5.01 (B of AB, $J_{A'B'}$=12.3Hz, 0.67H), 4.90 (B of AB, J_{AB}=12.0Hz, 0.33H), 4.38 (br, 0.33H), 4.24 (dd, J=6.6, 4.2Hz, 0.33H), 4.17 (dd, J=8.2, 3.8Hz, 0.34H), 3.78-3.55 (m, 1H), 3.70 and 3.47 (s and s, 3H), 2.19-1.67 (m, 4H), 0.44, 0.40 0.24 and 0.23 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.5, 136.6, 134.1, 133.9, 133.7, 133.0, 129.1, 128.5, 128.3, 128.0, 127.9, 127.9, 127.8, 67.0, 60.1, 59.9, 52.1, 51.9, 49.7, 48.9, 31.2, 31.0, 29.8, 27.8, 27.1, 26.8, -2.8, -3.6, -3.8, -4.0; IR (neat/NaCl) 2952, 1747, 1699, 1413, 1351, 1110, 834, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 404 (21) MLi^+, 313 (58) MLi^+-$PhCH_2$, 154 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 404.1869, found 404.1852.

1-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-5-(dimethylphenylsilyl)-pyrrolidine-2-carboxylic acid methyl ester (20):

Prior to the coupling reaction, the Cbz protected silylated proline substrate (451 mg, 1.71 mmol) was deprotected using the general procedure described above. To an oven dried 250 mL round bottom flask was added Boc protected phenylalanine (531 mg, 2 mmol), pyridine (162 μL, 2 mmol) and dry dicholomethane (25 mL) at -15°C. Cyanuric floride (900 μL, 10 mmol) was then added slowly and the mixture was stirred at -15°C for 1 hour. The reaction was quenched with ice and the layers were separated. The organic layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The colorless crude was carried on to the next step without further purification.

A 250 mL round-bottom flask was charged with the acid fluoride prepared above and then charged with N-methylmorpholine (770 μL, 7 mmol) and dichloromethane (30 mL). A solution of the deprotected silylated proline in 10 mL dichlomethane was then added by cannulation to the flask under an argon atmosphere. The mixture was allowed to stir at room temperature for 12 h and then quenched with water. The layers were separated and the organic layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was chromatographed through silica gel using an eluant of 1:4 EtOAc/hexane to afford 470 mg (54%) of the product. ^{1}H NMR ($CDCl_3$/300 MHz) (mixture of two diastereomers with approximately 2:1 ratio and their rotamers observed) δ 7.52-7.15 (m, 10H), 5.46 (d, J=8.1Hz, 0.33H), 5.31 (d, J=9.3Hz, 0.67H), 4.53 (dd, J=13.5, 7.4Hz, 0.33H), 4.36 (dd, J=16.4, 7.4Hz, 0.67H), 4.14 (d, J=9.3Hz, 0.33H), 3.95 (d, J=6.0Hz, 0.67H), 3.73 and 3.70 (s and s, 3H), 3.07-2.70 (m, 3H), 1.92-1.44 (m, 4H), 1.40, 1.34 and 1.31 (s, s and s, 9H), 0.40, 0.36, 0.34, 0.33, 0.26 (s,s,s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 171.1, 170.3, 154.8, 138.0, 137.4, 137.0, 135.9, 134.2, 133.9, 133.7, 130.0, 129.5, 129.4, 128.7, 128.5, 128.4, 128.0, 127.0, 126.9, 79.4, 60.4, 59.1, 54.8, 53.8, 53.1, 52.3, 50.3, 50.2, 41.0, 31.4, 28.7, 28.5, 28.5, 27.2, 25.8, -1.9, -3.2, -3.8, -3.9; IR (neat/NaCl) 3434, 1742, 1713, 1645, 1634, 1495, 1428, 1170 cm^{-1}; LRFAB MS (relative intensity) m/z 517 (74) MLi^+, 495 (8) M^+-CH_3, 466 (4), 433 (14) MLi^+-C_4H_8-CO, 417 (25) MLi^+-Boc+H, 377 (94), 313 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 517.2710, found 517.2700.

1-(2-tert-Butoxycarbonylamino-3-hydroxypropionyl)-5-(dimethylphenylsilyl)-pyrrolidine-2-carboxylic acid methyl ester (21):

Prior to the coupling reaction, the Cbz protected silylated prolinol substrate (1.05 g, 2.6 mmol) synthesized in the previous experimental was deprotected using the general procedure described earlier. A 250 mL round bottom flask was charged with N-(tert-butoxycarbonyl)-serine (616 mg, 3.0 mmol), N-methylmorpholine (0.99 mL, 9.0 mmol), isobutylchloroformate (0.428 mL, 3.3 mmol) and CH_2Cl_2 (60 mL). The reaction mixture was stirred at –15 °C for 25min. A solution of the crude silylated proline amine substrate in CH_2Cl_2 (6 mL) was canulated into the reaction. An additional 2 mL of dichloromethane was used in order to ensure complete transfer of the substrate. The mixture was then warmed to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. Then the organic layer was washed with water and then dried over the $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed through a silica gel column using an eluant of 1:1 hexane/EtOAc to afford 690 mg (58%) of the silated dipeptide product. Two isomers of the product were obtained in a 2:1 ratio. **Isomer 1:** ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 9:1 ratio) δ 7.54-7.51 (m, 2H), 7.39-7.32 (m, 3H), 5.65 (d, J=8.4Hz, 0.9H), 5.54 (d, J=6.9Hz, 0.1H), 5.13 (dd, J=7.5, 2.3Hz, 1H), 4.43-4.35 (m, 0.1H), 4.25-4.21 (m, 0.9H), 3.67 (s, 3H), 3.77-3.57 (m, 2H), 3.44-3.41 (broad d, 1H), 2.15-2.00 (m, 2H), 1.87-1.71 (m, 2H), 1.43 and 1.41 (s and s, 9H), 0.47, 0.44, 0.42, 0.41 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.4, 171.9, 155.9, 138.0, 134.3, 129.2, 128.2, 127.7, 80.1, 63.7, 60.5, 52.7, 51.6, 50.2, 31.1, 28.4, 27.2, -2.5, -4.1; IR (neat/NaCl) 3427, 1744, 1714, 1633, 1503, 1447, 1171 cm^{-1}; LRFAB MS (relative intensity) m/z 451 (10) MLi^+, 435 (2), 373 (4) MLi^+-PhH, 334 (2) MLi^+-Boc-NH_2, 317 (26),

299(18), 154 (100), 136 (88), 107 (42), 89 (66), ; HRFAB MS m/z calculated for $[M+H]^+$ 451.2200, found 451.2214. **Isomer 2:** ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.76-7.73 (m, 0.33H), 7.60-7.51 (m, 1.33H), 7.42-7.33 (m, 3.33H), 5.37 (d, 9.9Hz, 0.33H), 5.23 (d, 8.7Hz, 0.67H), 4.66-4.63 (m, 0.33H), 4.46-4.38 (m, 0.67H), 4.01-3.98 (m, 0.33H), 3.87-3.80 (m, 0.67H), 3.79 and 3.72 (s and s, 3H), 3.70-3.52 (m, 2H), 3.19-3.09 (m, 1H), 2.33-1.98 (m, 2H), 1.89-1.66 (m, 2H), 1.46, 1.45 and 1.42 (s, s and s, 9H), 0.48, 0.46, 0.45 and 0.40 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 172.3, 169.8, 155.6, 138.7, 135.0, 134.3, 134.1, 130.0, 129.1, 128.3, 128.0, 127.7, 80.4, 64.2, 62.9, 60.4, 59.9, 53.7, 52.7, 52.4, 50.6, 50.3, 32.1, 28.9, 28.5, 28.4, 28.0, 26.9, -2.2, -3.4, -4.2; IR (neat/NaCl) 3427, 1744, 1714, 1633, 1503, 1447, 1171 cm^{-1}; LRFAB MS (relative intensity) m/z 451 (10) MLi^+, 435 (2), 373 (4) MLi^+-PhH, 334 (2) MLi^+-Boc-NH_2, 317 (26), 299(18), 154 (100), 136 (88), 107 (42), 89 (66), ; HRFAB MS m/z calculated for $[M+H]^+$ 451.2200, found 451.2214.

5-(Dimethylphenylsilyl)-1-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-pent-4-enoyl]-pyrrolidine-2-carboxylic acid methyl ester (22):

Prior to the coupling reaction, the Cbz protected silylated proline substrate (1.5 g, 3.78 mmol) was deprotected using the general procedure described above. Phthalimide protected-homoallylglycine was prepared by treating 2-aminopent-4-enoic acid (240 mg, 2.08 mmol) with 1,3-dioxo-1,3-dihydro-isoindole-2-carboxylic acid ethyl ester (470 mg, 2.29 mmol) and sodium carbonate (242 mg, 2.29 mmol) in 3 mL of water. The mixture was stirred at room temperature for 1 hour and then neutralized with 1 M $NaHSO_4$ solution to pH=2. The layers are separated and aqueous layer washed three times with EtOAc. The combined organic layers were concentrated *in vacuo* and the crude product used directly for the next step without purification.

A 100 mL round bottom flask was charged with Phth-homoallylglycine (crude, 400 mg, ~1.64 mmol) and ether (2.76 mL). PCl_5 (0.99 mL, 9.0 mmol) was added and the mixture stirred at room temperature for 1 hour until all the PCl_5 was dissolved. The solution was decanted and washed with ether. The combined ether solution was concentrated under reduced pressure leading to the crude product of the acid chloride as a yellow solid.

A 250 mL round bottom flask was charged with the deprotected proline derivative (crude, ≤3.78 mmol), triethylamine (0.71 mL, 4.6 mmol), and ether (10.5 mL). The crude phthalimide protected-homoallylglycine acid chloride in ether (5 mL) was then canulated into the above solution. Ether (2 mL) was used to ensure a complete transfer of the substrate. The reaction mixture was stirred at room temperature for 12 h and quenched with water. The layers were separated and the organic layer was washed with water before being dried over the $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed through a silica gel column using an eluant of 1:3.5 hexane/EtOAc to afford 381 mg (47%) of the silated dipeptide product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.83-7.79 (m, 2H), 7.74-7.68 (m, 2H), 7.58-7.49 (m, 2H), 7.35-7.33 (m, 3H), 5.76-5.65 (m, 1H), 5.12 (d, J=20.1Hz, 1H), 5.01 (d, J=10.2Hz, 1H), 4.93-4.85 (m, 2H), 3.74 (s, 3H), 3.68 (t, J=8.7Hz, 1H), 3.56-3.45 (m, 1H), 2.63-2.54 (m, 1H), 2.09-2.01 (m, 2H), 1.79-1.68 (m, 2H), 0.48 (s, 3H), 0.44 (s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 168.4, 168.3, 138.2, 134.4, 134.3, 134.1, 131.9, 129.2, 127.8, 123.6, 118.5, 60.3, 53.7, 52.7, 50.6, 32.8, 31.8, 27.0, -2.2, -4.5; IR (neat/NaCl) 1745, 1714, 1650, 1382, 718 cm^{-1}; LRFAB MS (relative intensity) m/z 491 (4) MLi^+, 431 (2) MLi^+-COO=CH_2, 413 (27) MLi^+-PhH, 289 (11), 252 (8), 200 (24), 136 (100), 89 (84); HRFAB MS m/z calculated for $[M+H]^+$ 491.1935, found 491.1940.

1-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-5-methoxy-pyrrolidine-2-carboxylic acid methyl ester:

The silylated dipeptide substrate (385 mg, 0.76 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.1 F/mol of current was passed through the cell. The crude product was chromatographed through silica gel using a gradient elution from 1:3 EtOAc/hexane to 1:2 EtOAc/hexane. The column afforded 250 mg (82%) of the desired product along with 17 mg (4.4%) of

recovered starting material. Two isomers of the product were obtained in a 2:1 ratio. **Isomer 1:** ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 9:1 ratio observed) δ 7.33-7.24 (m, 5H), 5.46 (d, J=3.9Hz, 0.1H), 5.33 (d, J=8.7Hz, 0.9H), 4.77-4.70 (m, 1H), 4.53 (d, J=9.3Hz, 1H), 4.43 (d, J=3.9Hz, 1H), 3.75 and 3.72 (s and s, 3H), 3.39 and 3.23 (s and s, 3H), 3.10-2.94 (m, 2H), 2.32-2.20 (m 1H), 1.92-1.86 (m, 2H), 1.79-1.60 (m, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.1, 172.0, 154.9, 136.9, 129.9, 129.7, 128.6, 127.0, 88.8, 79.6, 58.7, 55.1, 53.9, 52.4, 40.8, 29.7, 29.5, 28.5, 25.9; IR (neat/NaCl) 3314, 1742, 1651, 1520, 1249, 1169, 853 cm^{-1}; LRFAB MS (relative intensity) m/z 413 (100) MLi^+, 397 (6), 395 (57) MLi^+-H_2O, 313 (61) MLi^+-Boc+H, 289 (20); HRFAB MS m/z calculated for $[M+Li]^+$ 413.2264, found 413.2246. **Isomer 2:** ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.32-7.20 (m, 5H), 5.48 (d, J=4.8Hz, 0.67H), 5.39 (d, J=5.1Hz, 0.33H), 5.01 (d, J=9.3Hz, 1H), 4.73 (td, J=9.0, 3.9Hz, 1H), 4.46-4.40 (m, 1H), 3.75and 3.71 (s and s, 3H), 3.36 and 3.33 (s and s, 3H), 3.49-3.26 (m, 1H), 2.86-2.79 (m, 1H), 2.32-1.90 (m, 4H), 1.45, 1.42 and 1.34 (s, s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.9, 172.1, 172.0, 137.1, 129.6, 128.8, 128.5, 128.4, 127.3, 89.2, 87.7, 79.9, 59.4, 58.2, 56.2, 54.1, 53.6, 53.3, 52.9, 52.4, 41.4, 39.0, 31.1, 30.6, 28.5, 28.4, 27.2, 26.5, 26.1; IR (neat/NaCl) 3314, 1742, 1651, 1520, 1249, 1169, 853 cm^{-1}; LRFAB MS (relative intensity) m/z 413 (100) MLi^+, 397 (6), 395 (57) MLi^+-H_2O, 313 (61) MLi^+-Boc+H, 289 (20); HRFAB MS m/z calculated for $[M+Li]^+$ 413.2264, found 413.2246.

2-Benzyl-3-oxo-hexahydropyrrolo[1,2-a]imidazole-5-carboxylic acid methyl ester (23):

To an oven-dried 50 mL round bottom flask was added the methoxylated dipeptide substrate (175 mg, 0.43 mmol) and anhydrous ether (15 mL) at -78 ^{o}C. $BF_3{\cdot}Et_2O$ (54.5 µl, 0.43 mmol) was added and the reaction mixture was allowed to stir at -78 ^{o}C for 1 hour. The solution was then allowed to warm to room temperature over a period of 30 min. The reaction was quenched with sat. sodium bicarbonate solution and transferred to a separatory funnel. The layers were separated and the aqueous layer extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through silica gel using a gradient elution from 1:1 EtOAc/hexane to 5% methanol/EtOAc. The column afforded 88 mg (75%) of the desired cyclized product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.30-7.16 (m, 5H), 4.94 (dd, J=7.4, 5.0Hz, 1H), 4.42 (dd, J=9.2, 6.2Hz, 1H), 4.16 (dd, J=8.3, 3.8Hz, 1H), 3.72 (s, 3H), 3.14 (dd, J=13.8, 3.6Hz, 1H), 2.76 (dd, J=13.8, 8.7Hz, 1H), 2.34-2.23 (m, 2H), 2.03-1.90 (m, 2H), 1.14-1.05 (m, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 174.9, 172.2, 138.3, 129.7, 128.5, 126.6, 76.0, 63.9, 55.1, 52.6, 39.0, 33.3, 29.8; IR (neat/NaCl) 3353, 2951, 1744, 1707, 1401, 1200, 1178 cm^{-1}; LRFAB MS (relative intensity) m/z 275 (14) MH^+, 154 (100); HRFAB MS m/z calculated for $[M+H]^+$ 275.1396, found 275.1392. The stereochemistry was assigned using an NOE crosspeak between the proton on the bridge-head carbon and the proton on the carbon next to the benzyl.

1-(2-tert-Butoxycarbonylamino-3-hydroxypropionyl)-5-methoxypyrrolidine-2-carboxylic acid methyl ester:

The silylated dipeptide substrate (202 mg, 0.45 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.2 F/mol of current was passed through the electrolysis cell. The crude product was chromatographed through silica gel using a gradient elution from 1:1.5 EtOAc/hexane to 10% mehthanol/EtOAc. The column afforded 118 mg (76%) of the desired product as a mixture of two isomers (1:1 ratio). **Isomer 1:** ^{1}H NMR ($CDCl_3$/300 MHz) δ 5.51 (br s, 1H), 5.26 (dd, J=5.0, 4.0Hz, 1H), 4.76 (dd, J=7.4, 5.2Hz, 1H), 4.48-4.37 (m, 2H), 3.75 (s, 3H), 3.69 (dd, J=10.0, 6.4Hz, 1H), 3.48 (s, 3H), 2.35-2.29 (m, 2H), 2.02-1.95 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.9, 171.6, 171.3, 166.8, 155.9, 89.1, 88.0, 87.5, 80.3, 69.3, 68.8, 64.0, 59.2, 59.0, 58.8, 58.2, 57.9, 54.7, 52.9, 52.7, 52.5, 49.2, 31.9, 31.6, 31.2, 30.9, 30.2, 28.9, 28.4, 27.8, 26.5, 26.3, 26.2, 26.0; IR (neat/NaCl) 3432, 2978, 1747, 1714, 1667, 1435, 1170, 1086, 859 cm^{-1}; LRFAB MS (relative intensity) m/z 353 (100) MLi^+, 253 (20) MLi^+-Boc+H, 134 (53); HRFAB MS m/z calculated for $[M+Li]^+$ 353.1919, found 353.1923. **Isomer 2:** ^{1}H NMR ($CDCl_3$/300 MHz) δ 5.49 (d, J=4.2Hz, 1H), 5.38 (d, J=7.5Hz, 1H), 4.83 (br d, J=6.6Hz, 1H), 4.69 (d, J=9.3Hz, 1H), 3.89 (dd, J=11.1, 5.4Hz, 1H), 3.76 (s, 3H), 3.63 (dd, J=11.1, 8.1Hz, 1H), 3.38 (s,

3H), 2.49-2.35 (m, 1H), 2.12-1.88 (m, 3H), 1.44 and 1.43 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.9, 171.6, 171.3, 166.8, 155.9, 89.1, 88.0, 87.5, 80.3, 69.3, 68.8, 64.0, 59.2, 59.0, 58.8, 58.2, 57.9, 54.7, 52.9, 52.7, 52.5, 49.2, 31.9, 31.6, 31.2, 30.9, 30.2, 28.9, 28.4, 27.8, 26.5, 26.3, 26.2, 26.0; IR (neat/NaCl) 3432, 2978, 1747, 1714, 1667, 1435, 1170, 1086, 859 cm^{-1}; LRFAB MS (relative intensity) m/z 353 (100) MLi^+, 253 (20) MLi^+-Boc+H, 134 (53); HRFAB MS m/z calculated for $[M+Li]^+$ 353.1919, found 353.1923.

3-tert-Butoxycarbonylamino-4-oxo-hexahydropyrrolo[2,1-b][1,3]oxazine-6-carboxylic acid methyl ester (24):

To an oven-dried 50 mL round bottom flask was added the methoxylated dipeptide substrate (83 mg, 0.24 mmol) synthesized above and anhydrous dichloromethane (10 mL). The solution was cooled to -20 ^{o}C and trifluoroacetic acid (5.0 μl, 0.065 mmol) added. The mixture was then stirred at -20 ^{o}C for 1 hour before being allowed to warm to room temperature over a period of 30 min. The reaction was quenched with triethylamine (15 μL) and concentrated directly under reduced pressure. The crude product was chromatographed through silica gel using a gradient elution from 1:1 EtOAc/hexane to 2:1 EtOAc/hexane. The column afforded 61 mg (81%) of the desired cyclized product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 5.48 (br s, 1H), 5.26 (dd, J=5.4, 4.0Hz, 1H), 4.76 (dd, J=7.5, 5.1Hz, 1H), 4.50-4.46 (broad, 1H), 4.41 (t, J=9.0Hz, 1H), 3.75 (s, 3H), 3.68 (dd, J=10.2, 6.5Hz, 1H), 2.38-2.27 (m, 2H), 2.05-1.93 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.6, 166.8, 155.9, 87.6, 80.4, 68.9, 58.2, 52.8, 49.3, 31.7, 28.5, 26.3; IR (neat/NaCl) 3351, 1745, 1682, 1436, 1167 cm^{-1}; LRFAB MS (relative intensity) m/z 315 (9) MH^+, 289 (4), 259 (50) MH^+-C_4H_8, 215 (16) MH^+-Boc+H, 154 (51), 128 (100), 107 (47); HRFAB MS m/z calculated for $[M+H]^+$ 315.1558, found 315.1559. The stereochemistry was assigned using the NOE crosspeak between the proton on the bridgehead carbon and the proton on the carbon next to the BocNH- group and the NOE crosspeak between the proton on the bridgehead carbon and the proton on the carbon next to the -COOMe group.

1-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-pent-4-enoyl]-5-methoxypyrrolidine-2-carboxylic acid methyl ester:

The silylated dipeptide substrate (280 mg, 0.57 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.1 F/mol of current was passed through the cell. In addition, six equivalents of 2, 6-lutidine was added as a proton scavenger. The crude product from the electrolysis was chromatographed through silica gel using a gradient elution from 1:2 EtOAc/hexane to 1:1 EtOAc/hexane. The column afforded 162 mg (73%) of the desired product as a 2:1 ratio of isomers. ^{1}H NMR ($CDCl_3$/300 MHz) (mixture of two diastereomers with approximately 2:1 ratio and their rotamers) δ 7.87-7.82 (m, 2H), 7.74-7.71 (m, 2H), 5.83-5.7 (m, 1H), 5.30 (dd, J=22.9, 4.4Hz, 0.5H), 5.19-4.95 (m, 3.5H), 4.63 (d, J=9.3Hz, 0.33H), 4.52 (d, J=9.0Hz, 0.33H), 4.39 (t, J=8.4Hz, 0.34H), 3.75, 3.74 and 3.64 (s, s and s, 3H), 3.46, 3.40 and 2.77 (s, s and s, 3H), 3.08-2.83 (m, 2H), 2.33-1.81 (m, 4H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 179.4, 176.3, 172.6, 171.9, 169.1, 168.2, 167.8, 148.1, 134.4, 134.3, 134.2, 133.9, 133.7, 132.1, 131.8, 131.8, 123.7, 123.6, 123.5, 119.4, 118.9, 118.7, 118.6, 89.0, 88.8, 88.3, 75.2, 59.7, 59.4, 54.5, 54.3, 53.6, 53.0, 52.5, 52.5, 52.3, 51.3, 37.5, 34.0, 33.1, 30.8, 29.2, 28.4, 26.3, 25.8, 25.5, 20.9; IR (neat/NaCl) 3478, 2953, 1748, 1715, 1673, 1384, 1201, 1086, 783, 721 cm^{-1}; LRFAB MS (relative intensity) m/z 387 (1) MLi^+, 355 (15) MLi^+-CH_3OH, 228 (8), 200 (100), 136 (24), 89 (31); HRFAB MS m/z calculated for $[M+H]^+$ 387.1557, found 387.1558.

8-Chloro-6-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-5-oxooctahydropyrrolo[1,2-a]azepine-3-carboxylic acid methyl ester (25):

A 100 mL round-bottom flask was charged with the methoxylated dipeptide substrate (97 mg, 0.25 mmol) generated above and dichloromethane (25 mL). The solution was cooled to -78 ^{o}C and a titanium (IV) chloride (0.50 mL, 1.0 M) in dichloromethane solution added slowly. After 30 min, the reaction was warmed to room temperature and stirred for 40 h. The reaction was quenched with a

dropwise addition of a 30% (w/w) sodium potassium tartrate solution (3 mL) and transferred to a 125 mL Erlenmeyer flask. An additional 5 mL sodium potassium tartrate solution added. The resulting emulsion was stirred for 3 h until two clear layers were formed. The mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was extracted five times with dichloromethane and then the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was chromatographed through a silica gel column using an eluant of 1:1 EtOAc/hexane. The column afforded 33 mg (64%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.84-7.83 (m, 2H), 7.74-7.69 (m, 2H), 4.84 (d, J=8.7Hz, 1H), 4.70 (t, J=5.4Hz, 1H), 4.17 (tt, J=12.0, 3.6Hz, 1H), 3.92 (app q, J=8.7Hz, 1H), 3.74 (s, 3H), 3.16 (app q, J=12.9Hz, 1H), 2.60 (d, J=2.7Hz, 1H), 2.56-2.22 (m, 3H), 2.12-2.05 (m, 2H), 1.96-1.85 (m, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.3, 168.1, 167.3, 134.3, 123.8, 60.8, 57.9, 56.6, 52.8, 51.9, 44.7, 38.8, 33.1, 27.8, 20.3; IR (neat/NaCl) 2926, 1717, 1662, 1390, 1356, 721 cm^{-1}; LRFAB MS (relative intensity) m/z 391 (1) MH^+, 289 (11) M^+-PhCO-H, 252 (10), 154 (100), 136 (89), 89 (78); HRFAB MS m/z calculated for $[M+H]^+$ 391.1062, found 391.1056. The stereochemistry was assigned using an NOE crosspeak between the proton on the bridgehead carbon and the proton on the carbon next to the phthalimide protected amine.

3-Phenyl-2-(trimethylsilylmethylamino)propionic acid methyl ester (27):

A 250 mL oven-dried round bottom flask was charged with the hydrochloride salt of L-phenylalanine methyl ester (3.2g, 15 mmol), (chloromethyl)trimethylsilane (3.14 mL, 22 mmol), KI (3.7g, 22 mmol), K_2CO_3 (3.1g, 22 mmol) and DMF (65mL). The suspension was stirred at 90 ^{o}C for 12 h. The mixture was then poured into water (60 mL) and extracted with ether (4 x 30 mL). The extracts were combined and washed with water (2 x 30 mL) and brine (2 x 30 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was chromatographed through a silica gel column (Hexane/EtOAc, 1:7) to give the silylated amino acid 2.8 g (69%) as colorless oil. The spectroscopic data was consistent with that previously reported in the literature (Zhang, C.; Ito, H.; Maeda, Y.; Shiral, N.; Ikeda, S.; Sato, Y. *J. Org. Chem.* **1999**, *64*, 581.

2-[(3-Benzyloxy-2-tert-butoxycarbonylaminopropionyl)trimethylsilylmethylamino]-3-phenyl-propionic acid methyl ester (51a – see below):

A 250 mL round bottom flask was charged with tert-butoxycarbonyl-(O-benzyl)-serine (1.02 g, 3.45 mmol), N-methylmorpholine (0.48 mL, 4.4 mmol), isobutylchloroformate (0.45 mL, 3.5 mmol), and CH_2Cl_2 (65 mL). The reaction mixture was stirred at –15 ^{o}C for 25 min. The silylated phenyl alanine was dissolved in CH_2Cl_2 (10 mL) and cannulated into the reaction mixture above. An additional 2 mL of CH_2Cl_2 was used to ensure complete transfer. The mixture was then warmed to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. Then the organic layer was washed with water and dried over the $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the crude product chromatographed through a silica gel column using an eluant of 1:6 hexane/EtOAc to afford 863 mg (51%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio were observed)δ 7.32-7.12 (m, 10H), 5.36 (d, J=8.1Hz, 0.5H), 5.15 (d, J=9.3Hz, 0.5H), 5.08 (t, J=7.4Hz, 1H), 4.75-4.71 (m, 1H), 4.58 (br s, 1H), 4.42 (d, J=11.7Hz, 0.5H), 4.31 (d, J=11.7Hz, 0.5H), 3.73 and 3.66 (s and s, 3H), 3.60 (d, J=6.0Hz, 1H), 3.49-3.16 (m, 2H), 3.08 (A of AB, J_{AB}=16.2Hz, 0.5H), 3.08-3.03 (m, 0.5H), 2.90 (dd, J=13.6, 7.6Hz, 0.5H), 2.70 (A of AB, J_{AB}=14.1Hz, 0.5H), 2.64 (B of AB, J_{AB}=14.4Hz, 0.5H), 1.91 (B of AB, J_{AB}=16.5Hz, 0.5H), 1.42 and 1.40 (s and s, 9H), 0.07 and 0.06 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.7, 170.2, 170.1, 169.3, 155.0, 138.2, 137.7, 137.5, 136.5, 129.3, 129.2, 128.6, 128.4, 128.3, 128.3, 127.9, 127.6, 127.5, 126.8, 79.6, 79.4, 73.2, 70.9, 70.6, 65.1, 61.7, 52.2, 52.0, 50.1, 49.2, 42.3, 36.1, 35.9, 34.6, 28.2, 28.2, -0.8, -2.4; IR (neat/NaCl) 3431, 2952, 1744, 1711, 1637, 1497, 1455, 1248, 1170, 854, 736, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 549 (41) MLi^+, 449 (100) MLi^+-Boc+H, 91 (12); HRFAB MS m/z calculated for $[M+Li]^+$ 549.2972, found 549.2982.

2-[(2-tert-Butoxycarbonylamino-3-hydroxypropionyl)trimethylsilylmethylamino]-3-phenyl-propionic acid methyl ester (28):

A 250 mL round bottom flask was charged with the benzyl protected serine substrate (1.245 g, 2.3 mmol), palladium hydroxide (250 mg, 20% w/w), and methanol (150 mL). A hydrogen balloon was attached to the flask through a needle that was pushed through a rubber septum. The reaction was vigorously stirred at room temperature for 12 h and then filtered through a short column of celite. The filtrate was concentrated *in vacuo* to afford 680 mg (66%) of a crude product that was carried on without further purification. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio were observed) δ 7.30-7.14 (m, 5H), 5.58 (d, J=7.8Hz, 0.33H), 5.47 (d, J=9.6Hz, 0.67H), 5.24 (dd, J=11.1, 3.9Hz, 0.67H), 4.48-4.45 (br, 0.33H), 3.91-3.80 (m, 1H), 3.72 and 3.71 (s and s, 3H), 3.74-3.63 (m, 1H), 3.37-3.31 (m, 1.66H), 3.28-2.88 (m, 2H), 2.90 (A of AB, J_{AB}=16.5Hz, 0.33H), 2.74 (A of AB, J_{AB}=14.1Hz, 0.67H), 2.38 (B of AB, J_{AB} =14.1Hz, 0.67H), 1.88 (B of AB, J_{AB} =16.2Hz, 0.33H), 0.40 and 1.37 (s and s, 9H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.5, 170.2, 170.0, 169.2, 155.7, 155.2, 137.6, 136.5, 129.1, 129.1, 128.8, 128.6, 127.1, 126.8, 80.0, 71.6, 71.0, 64.5, 64.4, 63.1, 62.3, 61.7, 52.6, 52.3, 52.1, 48.8, 42.0, 36.4, 35.5, 34.3, 31.6, 28.2, 28.1, 19.2, 13.8, -0.8, -1.1, -2.3; IR (neat/NaCl) 3434, 1745, 1707, 1628, 1497, 1248, 1170 cm^{-1}; LRFAB MS (relative intensity) m/z 459 (90) MLi^+, 359 (100) MLi^+-Boc+H^+, 303 (13), 160 (40); HRFAB MS m/z calculated for $[M+Li]^+$ 459.2503, found 459.2495.

2-(5-tert-Butoxycarbonylamino-4-oxo[1,3]oxazinan-3-yl)-3-phenylpropionic acid methyl ester (29):

An oven-dried 50 mL three-neck round bottom flask was fitted with a Pt wire cathode, a RVC anode, and a septum. A syringe needle was pushed through the septum and used as a nitrogen inlet. The flask was charged with the silylated dipeptide substrate made above (260 mg, 0.58 mmol), anhydrous acetonitrile (17.2 mL), trifluroethanol (1.9 mL), and tetrabutylammonium tetrafluroborate (189 mg, 0.58 mmol). The reaction mixture was degassed by sonication while a slow stream of nitrogen was passed through the solution for 10 min. The mixture was then electrolyzed at a constant current of 21.0 mA until 1.9 F/mol had been passed. When complete, the solvent was removed under reduced pressure and the crude oil chromatographed through silica gel using a gradient elution from 1:2.5 EtOAc/hexane to 1:1 EtOAc/hexane. The column afforded 98 mg (45%) of the desired product along with 99 mg (38%) of recovered starting material. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.33-7.22 (m, 3H), 7.18-7.15 (m, 2H), 5.23 (br s, 1H), 4.87 (dd, J=11.0, 5.3Hz, 1H), 4.70 (d, J=7.8Hz, 1H), 4.53 (d, J=8.1Hz, 1H), 4.34-4.29 (m, 1H), 4.11 (br s, 1H), 3.75 (s, 3H), 3.47 (t, J=10.1Hz, 1H), 3.34 (dd, J=14.4, 5.4Hz, 1H), 3.10 (dd, J=14.6, 11.0Hz, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.2, 167.4, 155.7, 136.3, 128.8, 127.2, 80.1, 68.3, 57.2, 52.6, 52.5, 49.9, 34.4, 28.2, 28.2; IR (neat/NaCl) 3360, 1744, 1715, 1667, 1497, 1249, 1166 cm^{-1}; LRFAB MS (relative intensity) m/z 385 (19) MLi^+, 313 (25), 160 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 385.1951, found 385.1943.

2-[(2-tert-Butoxycarbonylaminoacetyl)trimethylsilanylmethylamino]-3-phenyl-propionic acid methyl ester (30a):

A 250 mL round bottom flask was charged with N-(tert-butoxycarbonyl)glycine (1.9 g, 11 mmol), NMM (2.4 mL, 22 mmol), isobutylchloroformate (1.51 mL, 12.1 mmol) and CH_2Cl_2 (180 mL). The resulting solution was allowed to stir at –15 ^{o}C for 25min. The N-α-silylated phenyl alanine methyl ester (10 mmol) was dissolved in CH_2Cl_2 (10 mL) and cannulated into the reaction mixture above. An additional 2 mL of CH_2Cl_2 was used to ensure the complete transfer. The mixture was then warmed to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. Then the organic layer was washed with water and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the crude product chromatographed through a silica gel column using an eluant of 1:1:4 EtOAc/CH_2Cl_2/hexane to afford 3.2 g (76%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio observed) δ 7.35-7.20(m, 3H), 7.16-7.11(m, 2H), 5.54 and 5.34(br s and br s, 1H), 4.42(dd, J=9.3, 5.7Hz, 0.5H), 3.93 (dd, J=11.2, 4.6Hz, 0.5H), 3.87 (dd, J=11.8, 5.0Hz, 0.5H), 3.80-3.71(m, 1H), 3.73 and 3.72(s, and s, 3H),

3.35-3.22(m, 2H), 3.00(dd, J=14.2, 9.1Hz, 0.5H), 2.72(A of AB, J_{AB}= 14.4Hz, 0.5H), 2.58(A of AB, $J_{A'B'}$=16.2Hz, 0.5H), 2.53(B of AB, J_{AB}=13.5Hz, 0.5H), 1.76(B of AB, J_{AB}=16.5Hz, 0.5H), 1.44 and 1.40(s and s, 9H), 0.03(s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.1, 169.9, 168.1, 167.3, 155.6, 137.8, 136.0, 129.1, 128.9, 128.6, 127.2, 126.7, 79.4, 64.5, 61.1, 52.4, 52.1, 42.6, 41.8, 40.7, 35.8, 35.4, 34.3, 28.8, 28.2, -0.7, -2.1; IR (neat/NaCl) 3411, 2956, 1742, 1714, 1633, 1470, 1453, 1246, 1161, 1053, 854, 754, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 429 (59) MLi^+, 351 (8) MLi^+-PhH, 329 (100) MLi^+-Boc+H, 160 (8); HRMS m/z calculated for $[M+Li]^+$ 429.2397, found 429.2370 and 429.2380.

2-[(2-tert-Butoxycarbonylaminoacetyl)methoxymethylamino]-3-phenylpropionic acid methyl ester (31a):

The silylated dipeptide substrate (432 mg, 1.02 mmol) was oxidized using the general procedure described above. In this experiment, 2.1 F/mol of charge was passed through the cell. The crude product was chromatographed through silica gel using a gradient elution from 1:4 EtOAc/hexane to 1:1 EtOAc/hexane to afford 360 mg (92%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.28-7.12 (m, 5H), 5.42 (br s, 1H), 4.50 (dd, J=9.6, 5.4Hz, 1H), 4.43 (d, J =11.1Hz, 1H), 3.99-3.95 (m, 3H), 3.70 and 3.69 (s and s, 3H), 3.34 (dd, J=14.1, 5.4Hz, 1H), 3.25-3.15 (m, 1H), 3.19 (s, 3H), 1.42 and 1.40 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.9, 169.9, 156.0, 137.7, 129.3, 128.9, 127.0, 79.9, 79.3, 61.0, 55.9, 52.6, 42.5, 35.3, 28.5; IR (neat/NaCl) 3423, 2978, 2928, 1739, 1711, 1498, 1451, 1435, 1364, 1273, 1169, 1023, 913, 752, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 387 (100) MLi^+, 331 (24) MLi^+-$O(CH_3)_2$, 313 (7) , 287 (72) MLi^+-Boc+H, 243 (6), 198 (13), 160 (33); HRFAB MS m/z calculated for $[M+Li]^+$ 387.2107, found 387.2094.

3-Phenyl-2-{[2-(2,2,2-trifluoro-acetylamino)acetyl]trimethylsilylmethylamino}-propionic acid methyl ester (30b):

A 100 mL round bottom flask was charged with Tfa protected glycine (170 mg, 1 mmol) and ether (3.0 mL). To this mixture was added PCl_5 (369 mg, 1.25 mmol) and the resulting solution allowed to stir at room temperature for about 1 hour until all the PCl_5 was dissolved. The solution was then decanted and washed with ether. The combined ether solution was concentrated under reduced pressure and the crude acid chloride obtained as a yellow solid.

A 250 mL round bottom flask was charged with the silylated phenyl alanine (292 mg, 1.1 mmol), triethyl amine (0.35 mL, 2.5 mmol), and ether (8.0 mL). The Tfa-glycine acid chloride (crude) was dissolved in ether (5 mL) and cannulated into the reaction. An additional 1 mL of ether was used to ensure complete transfer of the acid chloride. The reaction mixture was stirred at room temperature for 12 h and then quenched with water. The layers were separated and the organic layer was washed with water and then dried over the $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was chromatographed through a silica gel column using an eluant of 1:3.5 hexane/EtOAc to afford 243 mg (58%) of the silylated dipeptide product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio were observed) δ 7.59 (br s, 1H), 7.35-7.25 (m, 3H), 7.17-7.12 (m, 2H), 4.35 (dd, J=9.9, 4.8Hz, 0.5H), 4.06-3.97 (m, 0.33H), 3.96 (dd, J=19.4, 4.1Hz, 1H), 3.84 (dd, J=9.9, 5.4Hz, 0.67H), 3.78 and 3.78 (s and s, 3H), 3.37-3.25 (m, 2H), 3.07 (dd, J=14.1, 9.9Hz, 0.5H), 2.84 (A of AB, J_{AB}=14.4Hz, 0.5H), 2.58 (B of AB, J_{AB}=14.4Hz, 0.5H), 2.57 (A of AB, J_{AB}=16.5Hz, 0.5H), 1.81 (B of AB, J_{AB}=16.5Hz, 0.5H), 0.07 and 0.06 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.0, 169.7, 166.1, 165.4, 137.7, 136.1, 129.4, 129.2, 129.0, 127.8, 127.2, 65.1, 61.8, 53.0, 52.6, 41.9, 41.3, 41.0, 36.5, 35.4, 34.5, -0.5, -1.8; IR (neat/NaCl) 3270, 1728, 1642, 1249, 1160, 849 cm^{-1}; LRFAB MS (relative intensity) m/z 425 (100) MLi^+, 406 (11) MLi^+-F, 206 (6); HRFAB MS m/z calculated for $[M+H]^+$ 419.1615, found 419.1626.

(2S)-2-{Methoxymethyl-[2-(2,2,2-trifluoroacetylamino)acetyl]-amino}-3-phenyl-propionic acid methyl ester (31b):

The silylated dipeptide substrate (251 mg, 0.60 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.1 F/mol of charge was passed through the cell. The crude was chromatographed through silica gel using a gradient elution from 1:3 EtOAc/hexane to 1:1 EtOAc/hexane. The column afforded 157 mg (70%) of the desired product along with 42 mg (10%) of recovered starting material. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.41 (br s, 1H), 7.33-7.15 (m, 5H), 4.62 (dd, J=10.2, 5.4Hz, 1H), 4.46 (dd, J=11.2, 3.1Hz, 1H), 4.19 (d, J=4.2Hz, 2H), 4.06 (d, J=11.7Hz, 1H), 3.76 and 3.75 (s and s, 3H), 3.40 (dd, J=14.0, 5.3Hz, 1H), 3.32-3.16 (m, 1H), 3.26 and 3.11 (s and s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.4, 167.8, 163.1, 137.3, 129.1, 129.0, 128.8, 127.3, 127.0, 80.3, 79.3, 61.4, 57.2, 56.1, 55.3, 52.8, 52.7, 41.6, 35.3, 34.7; IR (neat/NaCl) 3326, 1736, 1672, 1218, 1162 cm^{-1}; LRFAB MS (relative intensity) m/z 383 (100) MLi^+, 339 (3) MLi^+-CO_2, 258 (12), 198 (2); HRFAB MS m/z calculated for $[M+H]^+$ 377.1325, found 377.1314.

2-{But-3-enyl-[2-(2,2,2-trifluoroacetylamino)acetyl]-amino}-3-phenylpropionic acid methyl ester (32):

A 100 mL oven-dried round bottom flask was charged with the methoxylated substrate (120 mg, 0.32 mmol), allylsilane (0.51 μL, 3.2 mmol), and ether (9 mL). The reaction mixture was cooled to -40°C and $BF_3{\cdot}Et_2O$ (44.6 μL, 0.33 mmol) was added. The solution was allowed to stir at -40°C for 1 hour, and then warmed to room temperature and stirred for another 16 h. After this period, the mixture was concentrated under reduced pressure and the crude product chromatographed through a silica gel column using an eluant of 1:2 hexane/EtOAc to afford 87 mg (71%) of the desired product along with 17 mg (14%) of recovered starting material. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.55 (br s, 1H), 7.34-7.25 (m, 3H), 7.16-7.13 (m, 2H), 5.64 (ddt, J=16.8, 11.8, 6.0Hz, 1H), 5.08-5.01 (m, 2H), 4.11-4.06 (m, 3H), 3.77 and 3.77 (s and s, 3H), 3.46 (A of ABX, J_{AB}=14.0Hz, J_{AX}=5.1Hz, 1H), 3.28 (B of ABX, J_{AB}=14.0Hz, J_{BX}=10.4Hz, 1H), 3.10 (dt, J=15.3, 7.8Hz, 1H), 2.55 (dt, J=14.4, 7.5Hz, 1H), 2.12 (app q, J=7.5Hz, 2H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.2, 169.9, 166.4, 157.4, 157.3, 137.6, 135.9, 134.7, 133.6, 129.3, 129.2, 129.1, 129.0, 127.8, 127.2, 118.5, 117.3, 63.4, 60.8, 53.1, 52.8, 48.9, 44.1, 41.7, 41.4, 35.6, 34.7, 32.6, 32.3; IR (neat/NaCl) 3306, 1728, 1652, 1211, 1160 cm^{-1}; LRFAB MS (relative intensity) m/z 393 (100) MLi^+, 313 (6), 219 (3), 160 (22), 91 (4); HRFAB MS m/z calculated for $[M+H]^+$ 387.1532, found 387.1522.

General procedure for the preparation of nitrophenylsulfonyl N-β-silylated peptide substrate (35 & 36):

To a 250 mL oven-dried round-bottom flask was added an amino acid methyl ester (15 mmol), triethylamine (4.18 mL, 30 mmol), and dichloromethane (100 mL). The mixture was cooled to 0 °C with an ice bath and 2-nitrobenzenesulfonic chloride (3.3g, 15 mmol) was added slowly. The reaction solution was allowed to stir at room temperature for 12 h and then quenched with water. The reaction was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was carried forward without further purification. A 250 mL oven-dried round bottom flask was charged with the sulfonyl amino acid substrate (~15 mmol), (chloromethyl)trimethylsilane (2.62 mL, 18.8 mmol), KI (3.1 g, 18.8 mmol), K_2CO_3 (2.07 g, 15 mmol) and DMF (100 mL). The suspension was stirred at 60 °C for 12 h. The mixture was poured into water (150 mL) and extracted with ether (4 x 40 mL). The extracts were combined, washed with water (2 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed through a silica gel column to give the product.

4-Methyl-2-[(4-nitrobenzenesulfonyl)trimethylsilanylmethylamino]-pentanoic acid methyl ester (35):

Compound **35** was prepared using the general procedure from L-leucine methyl ester (3.32 g, 15 mmol). The crude product was chromatographed through a silica gel column using an eluant of 1:3

EtOAc/hexane. The column afforded 4.6 g (74% for 2 steps) of the desired product along with 703 mg (14%) of recovered nitrophenylsulfonyl leucine methyl ester. ^{1}H NMR ($CDCl_3$/300 MHz) δ 8.35 (d, J=6.8Hz, 2H), 7.97 (d, J=7.0Hz, 2H), 4.56 (dd, J=8.2, 5.6Hz, 1H), 3.44 (s, 3H), 2.63 (d, J=16.5Hz, 1H), 2.44 (d, J=16.5Hz, 1H), 1.77-1.67 (m, 2H), 1.46 (t, J=8.4Hz, 1H), 0.98 (d, J=4.8Hz, 3H), 0.96 (d, J=5.1Hz, 3H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.4, 151.5, 145.8, 130.5, 125.4, 61.1, 53.5, 40.7, 38.1, 26.0, 24.3, 23.2, 0.5; IR (neat/NaCl) 2956, 1743, 1532, 1350, 1168, 852, 742 cm^{-1}; LRFAB MS (relative intensity) m/z 417 (4) MH^+, 401 (4) MH^+-16, 154 (100); HRFAB MS m/z calculated for $[M+H]^+$ 417.1516, found 417.1501.

2-[(4-Nitro-benzenesulfonyl)trimethylsilanylmethylamino]propionic acid methyl ester (36):

Compound **36** was prepared using the general procedure from L-alanine methyl ester (2.09 g, 15 mmol). The crude was chromatographed through silica gel column using an eluant of 1:4 EtOAc/hexane. The column afforded 3.36 g (60% for 2 steps) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 8.29 (d, J=9.0Hz, 2H), 7.93 (d, J=9.1Hz, 2H), 4.58(dd, J=14.4, 7.2Hz, 1H), 3.46 (s, 3H), 2.60 (d, J=16.2Hz, 1H), 2.37 (d, J=16.2Hz, 1H), 1.33 (d, J=7.5Hz, 3H), 0.10 and 0.09 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.1, 150.0, 144.7, 129.0, 124.1, 57.0, 52.3, 36.8, 16.4, -1.2; IR (neat/NaCl) 3106, 2953, 1742, 1733, 1538, 1532, 1350, 1172, 1151, 1004, 855, 752, 742, 609 cm^{-1}; LRFAB MS (relative intensity) m/z 375 (61) MH^+, 359 (65) MH^+-16, 188 (68) M^+-NO_2-Ph-SO_2-, 89 (100); HRFAB MS m/z calculated for $[M+H]^+$ 375.1064, found 375.1030 and 376.1068 (^{13}C).

General procedure for the deprotection of nitrophenylsulfonyl protecting group for compound 35 & 36:

A 250 mL round bottom flask was charged with nitrophenylsulfonyl protected substrate (5 mmol), potassium carbonate (2.07 g, 15 mmol), benzene thiol (565 μL, 5.5 mmol), and aectonitrile (100 mL). The mixture was stirred at room temperature for 12 h. The resulting solution was concentrated under reduced pressure and redissolved in ether (35 mL). A 1 M aqueous HCl solution was added dropwise to the solution until it reached a pH=2.0. The mixture was then stirred for 10 min and the layers were separated. The organic layer was washed two times with water and the aqueous layers were combined. Potassium carbonate was added to neutralize the aqueous solution until the pH reached about 7.0. The aqueous phase was then extracted three times with ether and then the combined ether extracts dried over $MgSO_4$ and concentrated *in vacuo*. The obtained crude product was very pure and could be used for the following steps without further purification.

2-[(2-Benzyloxycarbonylamino-3-phenylpropionyl)trimethylsilylmethylamino]-propionic acid methyl ester (37):

Silylated leucine methyl ester (~4.2 mmol) was obtained using the general procedure described above for deprotection of nitrophenylsulfonyl leucine substrate (2.3 g, 5.3 mmol).

A 250 mL round bottom flask was charged with N-(benzyloxycarbonyl)-phenylalanine (1.5 g, 5.0 mmol), N-methylmorpholine (1.1 mL, 10 mmol), isobutylchloroformate (0.713 mL, 5.5 mmol), and CH_2Cl_2 (90 mL). The reaction mixture was stirred at –15 ^{o}C for 25 min. The silylated leucine substrate (crude) was dissolved in CH_2Cl_2 (10 mL) and cannulated into the above solution. An additional 2 mL of CH_2Cl_2 was used to ensure complete transfer of the substrate. The mixture was then warmed up to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. The organic layer was then washed with water before being dried over the $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the residue chromatographed through a silica gel column using an eluant of 1:4 EtOAc/ hexane to afford 1.7 g (67% for 2 steps) of the silylated dipeptide product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio observed) δ 7.43-7.09 (m, 10H), 5.73 (br dd, J=8.6, 5.0Hz, 1H), 5.14 and 5.11 (s and s, 2H), 4.99 (dd, J=15.9, 7.2Hz, 0.5H), 4.78 (dd, J=14.8, 7.6Hz, 0.5H), 4.47 (dd, J=13.8, 6.9Hz, 0.5H), 3.86 (dd, J=14.1, 6.9Hz, 0.5H), 3.73 and 3.66 (s and s, 3H), 3.06-3.03 (m, 2H), 2.70 (A of AB, J_{AB}=16.8Hz, 0.5H), 2.64 (A of AB, J_{AB}=15.0Hz, 0.5H), 2.40 (B of AB,

J_{AB}=14.7Hz, 0.5H), 2.30 (B of AB, J_{AB}=16.5Hz, 0.5H), 1.41 (d, J=6.9Hz, 1.5H), 1.01 (d, J=7.2Hz, 1.5H), 0.13 and 0.07 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.3, 171.2, 170.1, 155.6, 155.4, 136.6, 136.5, 136.2, 129.8, 129.6, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 128.0, 127.2, 127.1, 66.8, 66.8, 57.7, 55.9, 52.6, 52.4, 52.2, 52.1, 40.5, 40.3, 39.5, 35.9, 15.4, 13.8, -0.6, -2.1; IR (neat/NaCl) 3294, 2952, 1743, 1717, 1636, 1454, 1245, 1052, 848, 747, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 471 (40) MH^+, 455 (48) M^+-CH_3, 347 (12) M^+-CH_3-$PhCH_2O$, 190 (100); HRFAB MS m/z calculated for $[M]^+$ 470.2237, found $[M+H]^+$ 471.2315, and 472.2339 (^{13}C).

2-[(3-Benzyloxycarbonylaminopropionyl)trimethylsilylmethylamino]-4-methylpentanoic acid methyl ester (38):

Silylated leucine methyl ester (~5.2 mmol) was obtained using the general procedure described above for deprotection of the nitrophenylsulfonyl leucine substrate (3.0 g, 7.2 mmol).

A 250 mL round bottom flask was charged with N-(benzyloxycarbonyl)-β-alanine (1.16 g, 5.2 mmol), N-methylmorpholine (1.1 mL, 10 mmol), isobutylchloroformate (0.742 mL, 5.72 mmol), and CH_2Cl_2 (100 mL). The reaction mixture was stirred at –15 °C for 25 min. The silylated leucine substrate was dissolved in CH_2Cl_2 (10 mL) and then added to the solution above with the use of a cannulation. An additional 2 mL of CH_2Cl_2 was used to ensure complete transfer of the silylated leucine. Following the cannulation, the reaction was warmed to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. The organic layer was then washed with water before being dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the resulting residue chromatographed through a silica gel column using an eluant of 1:2.5 EtOAc/ hexane to afford 1.82 g (58% for 2 steps) of the silylated dipeptide product. ^{1}H NMR ($CDCl_3$/ 300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.35-7.29 (m, 5H), 5.57 (br s, 1H), 5.08 (s, 2H), 4.36 (dd, J=8.2, 6.4Hz, 0.67H), 4.15 (t, J=6.8Hz, 0.33H), 3.69 and 3.67 (s and s, 3H), 3.50 (app. sextet, J=5.7Hz, 2H), 0.98 (d, J=16.5Hz, 0.33H), 2.66-2.44 (m, 3.67H), 1.97-1.75 (m, 1H), 1.66-1.52 (m, 2H), 0.93 (app. t, J=6.8Hz, 6H), 0.13 and 0.04 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.8, 171.4, 171.3, 156.6, 136.9, 128.6, 128.1, 128.1, 66.6, 58.7, 58.5, 52.5, 52.1, 39.5, 38.7, 38.2, 37.1, 36.9, 35.4, 33.9, 33.2, 25.2, 24.7, 23.0, 23.0, 22.5, 22.3, -0.4, -1.4; IR (neat/NaCl) 3338, 2955, 1732, 1634, 1504, 1455, 1248, 1002, 850, 697 cm^{-1}; LRFAB MS (relative intensity) m/z 443 (100) MLi^+, 91 (12); HRFAB MS m/z calculated for $[M+Li]^+$ 443.2554, found 443.2548.

2-[(2-Benzyloxycarbonylamino-3-phenylpropionyl)methoxymethylamino]-propionic acid methyl ester:

The silylated dipeptide substrate (1.15 g, 2.55 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.1 F/mol of charge was passed through the cell. The crude product was chromatographed through silica gel using a gradient elution from 1:3 EtOAc/hexane to 1:1.5 EtOAc/hexane. The column afforded 919 mg (88%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.38-7.18(m, 10H), 5.54(d, J=5.7Hz, 1H), 5.10(A of AB, J_{AB}=12.0Hz, 1H), 5.04(B of AB, J_{AB}=12.3Hz, 1H), 4.93(q, J=7.4Hz, 1H), 4.50(A' of AB, J_{AB}=11.4Hz, 1H), 4.50-4.43(m, 1H), 4.40(B of AB, J_{AB}=10.8Hz, 1H), 3.68(s, 3H), 3.24(s, 3H), 3.08(dd, J=13.2, 7.5Hz, 1H), 2.97(dd, J=13.2, 6.3Hz, 1H), 1.41(d, J=6.6Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.4, 171.9, 155.7, 136.1, 129.8, 129.7, 128.7, 128.3, 128.2, 127.2, 78.1, 67.0, 55.5, 54.0, 52.7, 52.4, 40.2, 14.9; IR (neat/NaCl) 3311, 2947, 1740, 1720, 1656, 1496, 1452, 1239, 1080, 744, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 435 (100) MLi^+, 313 (20), 160 (76); HRMS m/z calculated for $[M+Li]^+$ 435.2107, found 435.2092.

2-[(2-Benzyloxycarbonylamino-3-phenylpropionyl)phenylsulfanylmethylamino]-propionic acid methyl ester (39):

To a 50 mL oven-dried round bottom flask was added the methoxylated substrate (135 mg, 0.32 mmol), benzene thiol (97 μL, 0.96 mmol), and ether (2 mL). $BF_3{\cdot}Et_2O$ (8 μL, 0.06 mmol) was added to this mixture and the reaction was allowed to stir at room temperature for 24 h. The solution was

concentrated *in vacuo* and the crude product was chromatographed through silica gel using 1:2 EtOAc/hexane as eluant. The column afforded 102 mg (64%) of the desired product along with 38 mg (28%) of recovered startimg material. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 4:1 ratio were observed) δ 7.49-7.42(m, 1H), 7.41-7.22(m, 13H), 7.14-7.11(m, 1H), 5.67(d, J=8.7Hz, 0.2H), 5.43(d, J=8.1Hz, 0.8H), 5.07-5.00(m, 2H), 4.89-4.83(m, 0.2H), 4.78-4.68(m, 0.8H), 4.56(A of AB, J_{AB}=14.1Hz, 1H), 4.40(B of AB, J_{AB}=14.1Hz, 1H), 4.39-4.34(m, 1H), 3.68 and 3.53(s and s, 3H), 3.02-2.88(m, 2H), 1.43 and 1.40(s and s, 2.4H), 0.95 and 0.93(s and s, 0.6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.7, 171.4, 155.4, 136.5, 136.1, 135.8, 133.6, 132.7, 131.8, 129.8, 129.7, 129.6, 129.1, 128.9, 128.7, 128.3, 128.1, 127.5, 127.4, 127.2, 66.9, 55.1, 54.5, 53.6, 52.7, 52.6, 52.4, 48.9, 39.9, 14.7; IR (neat/NaCl) 3305, 3025, 1740, 1656, 1438, 1220, 1049, 744, 696 cm^{-1}; LRFAB MS (relative intensity) m/z 513 (100) MLi^+, 313 (11), 160 (51); HRMS m/z calculated for $[M+Li]^+$ 513.2036, found 513.2040.

2-[(3-Benzyloxycarbonylaminopropionyl)methoxymethylamino]-4-methylpentanoic acid methyl ester:

The silylated dipeptide substrate (1.46 g, 3.34 mmol) was oxidized using the general procedure outlined above. In this experiment, 2.3 F/mol of charge was passed through the electrolysis cell. The crude product was chromatographed through silica gel using 1:3 EtOAc/hexane as eluant. The column afforded 1.14 g (87%) of the desired product. ^{1}H NMR ($CDCl_3$/ 300 MHz) δ 7.35-7.28 (m, 5H), 5.54 (br s, 1H), 5.08 (s, 2H), 5.02 (dd, J=9.2, 5.2Hz, 1H), 4.68 (d, J=10.8Hz, 1H), 4.52 (d, J=10.5Hz, 1H), 3.68 (s, 3H), 3.54-3.48 (m, 2H), 3.28 (s, 3H), 2.70 (t, J=5.6Hz, 2H), 1.83-1.73 (m, 1H), 1.68-1.57 (m, 2H), 0.93, 0.92, 0.91 and 0.90 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.4, 172.6, 156.5, 136.8, 128.6, 128.1, 128.1, 77.8, 66.6, 55.4, 54.8, 52.3, 38.8, 38.5, 36.9, 36.8, 33.2, 24.8, 24.6, 23.0, 22.9, 22.1, 21.9; IR (neat/NaCl) 3347, 2955, 1722, 1661, 1514, 1435, 1391, 1242, 1076, 754, 698 cm^{-1}; LRFAB MS (relative intensity) m/z 401 (100) MLi^+, 91 (20); HRFAB MS m/z calculated for $[M+Li]^+$ 401.2264, found 401.2255.

2-[(3-Benzyloxycarbonylaminopropionyl)phenylsulfanylmethylamino]-4-methylpentanoic acid methyl ester (40):

To a 50 mL oven-dried round bottom flask was added the methoxylated substrate (189 mg, 0.48 mmol), benzene thiol (197 μL, 1.9 mmol), and ether (5 mL). $BF_3{\cdot}Et_2O$ (20 μL, 0.16 mmol) was added to this mixture and the reaction was allowed to stir at room temperature for 16 h. The solution was concentrated *in vacuo* and the crude product was chromatographed through silica gel using 1:1 EtOAc/hexane as eluant. The column afforded 170 mg (75%) of the desired product along with 34 mg of an unknown byproduct. ^{1}H NMR ($CDCl_3$/ 300 MHz) (two main rotamers with approximately 9:1 ratio were observed) δ 7.47-7.42 (m, 2H), 7.34-7.24 (m, 8H), 5.49 (br t, J=6.0Hz, 1H), 5.08 (br s, 2H), 4.93 (td, J=8.7, 3.0H, 1H), 4.73 (A of AB, J_{AB}=14.1Hz, 0.9H), 4.66 (B of AB, J_{AB}=14.1Hz, 0.9H), 4.35 (br t, J=6.9Hz, 0.2H), 3.69 and 3.62 (s and s, 3H), 3.49 (dd, J=11.4, 6.0Hz, 0.2H), 3.40 (dd, J=11.6, 6.2Hz, 1.8H), 2.62-2.41 (m, 2H), 1.90-1.80 (m, 1H), 1.78-1.54 (m, 2H), 0.94 and 0.92 (s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.7, 171.9, 171.3, 156.4, 136.7, 133.4, 133.2, 131.5, 129.5, 129.0, 128.5, 128.4, 128.1, 128.0, 127.3, 66.5, 57.0, 55.6, 53.0, 52.6, 52.3, 48.6, 38.4, 38.1, 36.7, 33.8, 33.5, 25.1, 24.6, 22.8, 22.7, 22.1, 14.3; IR (neat/NaCl) 3350, 2955, 1738, 1716, 1661, 1511, 1439, 1413, 1256, 1002, 748, 695 cm^{-1}; LRFAB MS (relative intensity) m/z 473 (1) MH^+, 363 (8) MH^+-PhS, 91 (100); HRFAB MS m/z calculated for $[M+H]^+$ 473.2110, found 473.2093 and 474.2159.

2-({2-[2-(2-tert-Butoxycarbonylaminoacetylamino)acetylamino]acetyl}-trimethylsilylmethyl-amino)-3-phenylpropionic acid methyl ester (41):

A 250 mL oven-dried round bottom flask was charged with Boc-Gly-Gly-OH (162 mg, 0.7 mmol), silylated H-Gly-Phe-OMe (155 mg, 0.48 mmol), HATU (280 mg, 0.74 mmol), 2,4,6-collidine (154 μL, 1.16 mmol) and DMF (8.5 mL). The reaction mixture was allowed to stir at room temperature

for 16 h and then quenched with water. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through silica gel using a gradient elution from 1:2 EtOAc/hexane to 10% MeOH/EtOAc. The column afforded 137 mg (53%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers were observed in an approximately 1:1 ratio) δ 7.31-7.10 (m, 5H), 5.47 (br s, 1H), 4.50 (dd, J=9.6, 5.1Hz, 0.5H), 4.03-3.91 (m, 3.5H), 3.84-3.74 (m, 3H), 3.72 and 3.71 (s and s, 3H), 3.38-3.20 (m, 1.5H), 3.06-2.98 (m, 0.5H), 2.75 (A of AB, J_{AB}=14.1Hz, 0.5H), 2.61 (A of AB, J_{AB}=16.5HZ, 0.5H), 2.52 (B of AB, J_{AB}=14.7Hz, 0.5H), 1.76 (B of AB, J_{AB}=16.5Hz, 0.5H), 1.42 and 1.41 (s and s, 9H), 0.02 and 0.01 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.3, 170.1, 168.8, 168.4, 167.7, 167.0, 159.3, 137.8, 136.2, 129.3, 129.1, 128.9, 127.5, 127.0, 80.3, 64.8, 61.5, 52.8, 52.4, 44.2, 42.8, 42.6, 41.7, 41.1, 40.9, 36.2, 35.4, 34.4, 28.5, -0.5, -1.8; IR (neat/NaCl) 3323, 1746, 1703, 1699, 1694, 1661, 1652, 1435, 1172 cm^{-1}; LRFAB MS (relative intensity) m/z 543 (27) MLi^+, 518 (2), 474 (4), 443 (15) MLi^+-Boc+H, 412 (4), 260 (83), 160 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 543.2826, found 543.2836.

2-({2-[2-(2-tert-Butoxycarbonylaminoacetylamino)acetylamino]-acetyl}-methoxymethylamino)-3-phenylpropionic acid methyl ester (42):

The silylated tetrapeptide substrate (128 mg, 0.24 mmol) was oxidized using the general procedure described above. In this experimtent, 2.1 F/mol of charge was passed through the cell. The crude product was chromatographed through silica gel using a gradient elution from EtOAc to 5% MeOH/EtOAc to afford 92 mg (78%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.28-7.13 (m, 5H), 5.51 (br s, 1H), 4.52-4.46 (m, 2H), 4.10 (dd, J=12.0, 4.5Hz, 1H), 4.03-3.98 (m, 4H), 3.93-3.69 (m, 2H), 3.69 (s, 3H), 3.33 (dd, J=14.1, 5.4Hz, 1H), 3.28-3.11 (m, 1H), 3.21 and 3.21 (s and s, 3H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.5, 170.2, 169.2, 168.9, 156.1 137.3, 129.5, 129.0, 128.6, 126.8, 80.1, 79.0, 60.9, 55.6, 52.4, 44.1, 42.6, 41.1, 35.0, 28.2; IR (neat/NaCl) 3331, 1741, 1652, 1660, 1531, 1280, 1248, 1170 cm^{-1}; LRFAB MS (relative intensity) m/z 501 (100) MLi^+, 445 (10) MLi^+-C_4H_8, 401 (48) MLi^+-Boc+H, 192 (32), 91 (24); HRFAB MS m/z calculated for $[M+Li]^+$ 501.2537, found 501.2546.

General procedure for coupling protected, N-terminus amino acids to N-trimethylsilylmethyl-L-phenylalanine methyl ester (27). A variation of the procedure used to synthesize 30a:

A 250 mL round bottom flask was flame-dried and filled with argon. It was then charged with dichloromethane, N-methylmorpholine (NMM), and isobutylchloroformate. The resulting solution was cooled to -20°C. Next, the protected, N-terminus amino acid was added to 20 mL of dichloromethane and dripped into the aforementioned solution over a period of approximately one hour via an addition funnel and with stirring. After complete addition of N-terminus amino acid, the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) was dissolved in 20 mL of dichloromethane and added to the reaction solution. The solution was allowed to warm to room temperature as it stirred for 18 h. The reaction was then quenched with brine and extracted with diethyl ether four times. The ethereal extracts were combined and concentrated *in vacuo*. The crude product was then chromatographed (unless otherwise noted below) through a silica gel column with a stepwise elution. The elution started with 25% diethyl ether in hexanes and increased to 60% diethyl ether in steps of 5% ether per each additional column volume of eluent passed through the column. Amounts of reagents and yields for each coupling reaction are specified below.

2-[N-(2-tert-Butoxycarbonylaminoacetyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (44a):

Compound **44a** was prepared using the general procedure outlined above. Dichloromethane (50 mL), NMM (0.99 mL, 9.0 mmol), and isobutylchloroformate (0.58 mL, 4.5 mmol) were initially combined. N-(tert-butoxycarbonyl)-glycine (0.786 g, 4.49 mmol) and the N-trimethylsilylmethyl-L-

phenylalanine methyl ester derivative (**27**) (0.829 g, 3.11 mmol) were then added. The crude product was purified by recrystallization from hexanes to afford 1.01 g (77.1%) of pure product from two crops of white, needle-like crystals. ^{1}H NMR ($CDCl_3$/300 MHz) (Two main rotamers with approximately 1:1 ratio were observed.) δ 7.35-7.20 (m, 3H), 7.16-7.11 (m, 2H), 5.54 and 5.34 (br s and br s, 1H), 4.42 (dd, J=9.3, 5.7 Hz, 0.5H), 3.93 (dd, J=11.2, 4.6 Hz, 0.5H), 3.87 (dd, J=11.8, 5.0 Hz, 0.5H), 3.80-3.71 (m, 1H), 3.73 and 3.72 (s, and s, 3H), 3.35-3.22 (m, 2H), 3.00 (dd, J=14.2, 9.1 Hz, 0.5H), 2.72 (A of AB, J_{AB}= 14.4 Hz, 0.5H), 2.58 (A of AB, J_{AB}=16.2 Hz, 0.5H), 2.53 (B of AB, J_{AB}=13.5 Hz, 0.5H), 1.76 (B of AB, J_{AB}=16.5 Hz, 0.5H), 1.44 and 1.40 (s and s, 9H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.1, 169.9, 168.1, 167.3, 155.6, 137.8, 136.0, 129.1, 128.9, 128.6, 127.2, 126.7, 79.4, 64.5, 61.1, 52.4, 52.1, 42.6, 41.8, 40.7, 35.8, 35.4, 34.3, 28.8, 28.2, -0.7, -2.1; IR (neat/NaCl) 3411, 2956, 1742, 1714, 1633, 1470, 1453, 1246, 1161, 1053, 854, 754, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 429 (59) MLi^+, 351 (8) MLi^+-PhH, 329 (100) MLi^+-Boc+H, 160 (8); HRFAB MS m/z calculated for $[M+Li]^+$ 429.2397, found 429.2370 and 429.2380.

2-[N-(2-tert-Butoxycarbonylaminopropionyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (44b):

Compound **44b** was prepared using the general procedure outlined above. Dichloromethane (35 mL), NMM (0.62 mL, 5.6 mmol), and isobutylchloroformate (0.36 mL, 2.8 mmol) were initially combined. N-(tert-butoxycarbonyl)-L-alanine (0.719 g, 3.80 mmol) and the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) (0.503 g, 1.89 mmol) were then added. The crude product was chromatographed as described above to afford 0.440 g (53%) of pure product, which was a very viscous, colorless liquid. ^{1}H NMR ($CDCl_3$/500 MHz) (Two rotamers with an approximate ratio of 1:1 were observed). δ 7.32-7.16 (m, 5H), 5.49 (br d, J=8.0 Hz, 1H of one rotamer), 5.02 (m, 2H of one rotamer or 1H of each), 4.40 (quartet of doublets, app quintet, J≈7 Hz, 1H of one rotamer), 4.33 (quartet of doublets, app quintet, J≈7 Hz, 1H of one rotamer), 3.77 (s, 3H of one rotamer), ca 3.77 (1H of one rotamer buried under s), 3.74 (s, 3H of one rotamer), 3.37 (A of ABX, J_{AB}=14.0 Hz, J_{AX}=4.5 Hz, 1H of one rotamer), 3.35 (dd, J=4.5, 14.5, 1H of one rotamer), 3.29 (B of ABX, J_{AB}=14.0Hz, J_{BX}=11.0 Hz, 1H of one rotamer), 3.01 (dd, J=9.5, 14.0 Hz, 1H of one rotamer), 2.73 (A of AB, J_{AB}=16.5 Hz, 1H of one rotamer), 2.70 (A of AB, J_{AB}=14.0 Hz, 1H of one rotamer), 2.53 (B of AB, J_{AB}=14.0 Hz, 1H of one rotamer), 1.87 (B of AB, J_{AB}=17.0 Hz, 1H of one rotamer), 1.43 (s, 9H of one rotamer), 1.41 (s, 9H of one rotamer), 1.26 (d, J=6.5 H, 3H of one rotamer), 0.74 (d, J=7.0 Hz, 3H of one rotamer), 0.07 (s, 9H of one rotamer), 0.06 (s, 9H of one rotamer); ^{13}C NMR ($CDCl_3$/125 MHz)δ 173.0, 171.7, 170.5, 170.3, 155.0, 154.9, 138.0, 136.8, 129.5, 129.4, 129.0, 128.7, 127.3, 126.9, 79.6, 79.3, 64.9, 62.5, 52.5, 52.2, 46.8, 45.1, 42.4, 36.5, 35.9, 34.7, 28.5, 28.4, 19.3, 18.4, -0.5, -2.2; IR (neat/NaCl) 3428, 3334, 3108, 3087, 3064, 3028, 2977, 2951, 2899, 1949, 1747-1694, 1656-1634, 1605, 1586, 1495, 1454, 1366, 1166, 1050, 1028, 968, 922, 858, 752, 702 cm^{-1}; LREI MS (relative intensity) m/z 436 (10) M^+, 421 (42), 365 (100), 363 (10), 347 (27), 130 (67); HREI MS m/z calculated for M^+ 436.2394, found 436.2384 and 437.2408 (^{13}C).

2-[N-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (44c):

Compound **44c** was prepared using the general procedure outlined above. Dichloromethane (50 mL), NMM (0.99 mL, 9.0 mmol), and isobutylchloroformate (0.59 mL, 4.5 mmol) were initially combined. N-(tert-nutoxycarbonyl)-L-phenylalanine (1.199 g, 4.519 mmol) and the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) (0.809 g, 3.04 mmol) were then added. The crude product was chromatographed as described above to afford 0.855 g (55%) of pure product, which was a very viscous, colorless liquid. ^{1}H NMR ($CDCl_3$/300 MHz) (Two main rotamers with approximately 1:1 ratio were observed.) δ 7.33-6.95 (m, 8H), 7.04-6.95 (m, 2H), 5.21 (br d, J=9.0 Hz, 0.5H), 5.10 (dd, J=4.5, 9.9 Hz, 0.5H), 4.81 (br d, J=9.9 Hz, 0.5H), 4.67 (ddd, app quartet, J≈7 Hz, 0.5H), 4.48 (dt, J=4.5, 9.9 Hz, 0.5H), 3.79 (dd, J=5.4, 9.0 Hz, 0.5H), 3.74 (s, 1.5H), 3.71 (s, 1.5H), 3.40 (dd, J=5.4, 14.1 Hz, 0.5H), 3.29 (dd, J=5.1, 14.1 Hz, 0.5H), 3.08-2.70 (m, 3H), 2.63 (dd, J=9.9, 14.4 Hz,

0.5H), 2.52 (d, J=14.4 Hz, 0.5H), 2.16 (dd, J=4.8, 14.1 Hz, 0.5H), 1.89 (d, J=16.2 Hz, 0.5H), 1.34 (s, 4.5H), 1.27 (s, 4.5H), 0.06 (s, 4.5H), 0.03 (s, 4.5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.7, 170.3, 170.2, 169.9, 154.7, 154.5, 137.9, 136.8, 136.7, 136.6, 129.5, 129.1, 128.7, 128.4, 128.2, 128.0, 126.9, 126.5, 126.5, 126.2, 79.1, 79.1, 64.2, 62.0, 52.0, 51.8, 51.7, 49.9, 41.3, 39.9, 37.9, 36.3, 35.5, 34.6, 28.1, 28.0, -0.7, -2.4; IR (neat/NaCl) 3300, 2975, 2947, 1743, 1706, 1642, 1634, 1494, 1454, 1245, 1169, 850, 760, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 519 (53) MLi^+, 419 (100) MLi^+-Boc+H, 206 (18), 91 (40); HRFAB MS m/z calculated for $[M+Li]^+$ 519.2867, found 519.2880 and 520.2915 (^{13}C).

General procedure for preparative electrolyses of silylated dipeptides 30a, 44b, and 44c for comparison with the parallel electrolyses:

A three-neck round bottom flask was flame-dried and fitted with two carbon electrodes, one of which (the anode) bore a piece of RVC (approximately 1cm x 1cm x 1cm) on its tip. The flask was charged with a solution of anhydrous alcohol containing Bu_4NBF_4 (100 mM) and dipeptide substrate (10 mM). The electrodes of the reaction cell were connected to an Arbin power supply, and a constant current electrolysis (8 mA) was carried out with stirring until 2.2 Faradays/mole of electrons had been passed through the cell. After the reaction was complete, the alcoholic reaction solvent was removed *in vacuo* and the electrolyte was removed by precipitation with diethyl ether and filtration. The crude material recovered after removal of the ethereal filtrate was chromatographed through a silica gel column with a stepwise elution. The elution started with 25% diethyl ether in hexanes and increased to 60% ether in steps of 5% ether per each additional column volume of eluent passed through the column. Amounts of reagents and yields for all preparative electrolyses are specified below. Purity percentages are calculated from the molar ratios of products to starting materials observed in the proton NMR spectra.

Note: The purpose of doing these preparative electrolyses was to obtain pure products for full characterization. Therefore, difficult chromatographic separations on silica gel necessitated the sacrifice of yield for purity in some cases. More accurate yield data are reported in the parallel synthesis experiment described below.

2-[N-(2-tert-Butoxycarbonylaminoacetyl)-N-*methoxy*methylamino]-3-phenylpropionic acid methyl ester (31a):

The methoxy ether from **30a** was prepared using the general procedure described above. The substrate (**30a**) (0.080 g, 0.19 mmol), tetrabutylammonium tetrafluoroborate (0.615 g, 1.89 mmol), and anhydrous methanol (19 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.061 g (82%) of pure product (the lower yield than that reported above was most likely due to the change in scale). The spectral data matched that reported above.

2-[N-(2-tert-Butoxycarbonylaminoacetyl)-N-*ethoxy*methylamino]-3-phenylpropionic acid methyl ester (made from 30a):

The ethoxy ether from **30a** was prepared using the general procedure described above. The substrate (**30a**) (0.080 g, 0.19 mmol), tetrabutylammonium tetrafluoroborate (0.621 g, 1.89 mmol), and anhydrous ethanol (19 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.068 g (91%) of pure product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.31-7.15 (m, 5H), 5.42 (br s, 1H), 4.58 (dd, J=9.8, 5.8Hz, 1H), 4.50 (d, J=11.4Hz, 1H), 4.08 (d, J=11.7Hz, 1H), 4.02 (d, J=4.5Hz, 2H), 3.72 (s, 3H), 3.48-3.33 (m, 3H), 3.21 (dd, J=14.1, 9.9 Hz, 1H), 1.45 (s, 9H), 1.13 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.9, 169.7, 156.6, 156.4, 155.9, 151.5, 137.7, 129.3, 128.8, 127.0, 126.7, 77.6, 63.9, 63.8, 60.6, 52.6, 42.5, 35.3, 28.6, 20.0, 15.0; IR (neat/NaCl) 3423, 2969, 1740, 1715, 1667, 1494, 1454, 1365, 1242, 1166, 1091, 750, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 401 (50) MLi^+, 345 (20) MLi^+-C_4H_8, 301 (49) MLi^+-Boc+H , 160 (66), 89 (100); HRMS m/z calculated for $[M+Li]^+$ 401.2264, found 401.2248 and 402.2279 (^{13}C).

2-[N-(2-tert-Butoxycarbonylaminoacetyl)-N-(n-*propoxy*)methylamino]-3-phenylpropionic acid methyl ester (made from 30a):

The propoxy ether from **30a** was prepared using the general procedure described above. The substrate (**30a**) (0.083 g, 0.20 mmol), tetrabutylammonium tetrafluoroborate (0.624 g, 1.89 mmol), and anhydrous n-propanol (19 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.059 g (74%) of >98% pure product. ^{1}H NMR ($CDCl_3$/300 MHz). δ 7.31-7.16 (m, 5H), 5.42 (br s, 1H), 4.59 (dd, J=5.7, 9.6 Hz, 1H), 4.51 (A of AB, J_{AB}=11.4 Hz, 1H), 4.09 (B of AB, J_{AB}=11.4 Hz, 1H), 4.02 (d, J=3.9 Hz, 2H), 3.72 (s, 3H), 3.40-3.17 (m, 4H), 1.52 (sextet, J=7.5 Hz, 2H), 1.45 (s, 9H), 0.87 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 170.9, 169.8, 155.9, 137.7, 129.3, 128.8, 127.0, 79.8, 77.8, 70.2, 60.6, 52.5, 42.5, 35.3, 28.5, 22.8, 10.7; IR (neat/NaCl) 3424, 3086, 3062, 3028, 2973, 2935, 2877, 1954, 1744-1667, 1604, 1584, 1496, 1455, 1366, 1247, 1169, 1087, 1048, 1026, 982, 949, 909, 865, 822, 754, 702, 650 cm^{-1}; LRFAB MS (relative intensity) m/z 415 (71) MLi^+, 359 (31), 329 (10), 315 (100), 243 (15), 198 (18), 91 (68), 89 (51); HRFAB MS m/z calculated for $[M+Li]^+$ 415.2420, found 415.2423 and 416.2460 (^{13}C).

2-[N-(2-tert-Butoxycarbonylaminoacetyl)-N-(n-*butoxy*)methylamino]-3-phenylpropionic acid methyl ester (made from 30a):

The butoxy ether from **30a** was prepared using the general procedure described above. The substrate (**30a**) (0.082 g, 0.19 mmol), tetrabutylammonium tetrafluoroborate (0.623 g, 1.89 mmol), and anhydrous n-butanol (19 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed twice as described above to afford 0.019 g of ~85% pure product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.31-7.16 (m, 5H), 5.43 (br s, 1H), 4.58 (dd, J=9.4, 5.6 Hz, 1H), 4.50 (d, J=11.4 Hz, 1H), 4.08 (d, J=11.4 Hz, 1H), 4.02 (d, J=4.2 Hz, 2H), 3.71 (s, 3H), 3.44-3.53 (m, 3H), 3.21 (dd, J=14.1, 9.6 Hz, 1H), 1.53-1.39 (m, 2H), 1.46 (s, 9H), 1.44-1.24 (m, 2H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.9, 169.7, 155.9, 137.7, 129.3, 128.8, 127.0, 79.9, 77.8, 68.3, 66.9, 60.7, 52.6, 42.5, 35.3, 31.6, 28.5, 19.4, 14.0; IR (neat/NaCl) 3423, 2930, 1743, 1715, 1667, 1454, 1365, 1244, 1169, 1088, 752, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 429 (15) MLi^+, 329 (13) MLi^+-Boc+H, 202 (13), 160 (68), 89 (100); HRMS m/z calculated for $[M+Li]^+$ 429.2577, found 429.2568 and 430.2605(^{13}C).

2-[N-(2-tert-Butoxycarbonylaminopropionyl)-N-*methoxy*methylamino]-3-phenylpropionic acid methyl ester (made from 44b):

The methoxy ether from **44b** was prepared using the general procedure described above. The substrate (**44b**) (0.100 g, 0.229 mmol), tetrabutylammonium tetrafluoroborate (0.755 g, 2.30 mmol), and anhydrous methanol (23 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.073 g (81%) of pure product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.30-7.15 (m, 5H), 5.31 (br d, J=6.6 Hz, 1H), 4.60 (quartet of doublets, app quintet, J≈7 Hz, 1H), 4.43 (A of AB, J_{AB}=11.4 Hz, 1H), ca 4.43 (methine buried under A of AB), 4.15 (B of AB, J_{AB}=11.1 Hz, 1H), 3.73 (s, 3H), 3.39 (A of ABX, J_{AB}=14.1 Hz, J_{AX}=5.4 Hz, 1H), 3.24 (B of ABX, J_{AB}=14.1 Hz, J_{BX}=10.2 Hz, 1H), 3.24 (s, 3H), 1.43 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 173.8, 170.9, 155.2, 137.8, 129.5, 128.7, 127.0, 79.8, 79.6, 60.3, 55.8, 52.5, 46.8, 35.1, 28.5, 19.8; IR (neat/NaCl) 3425, 3335, 3086, 3062, 3027, 2978, 2932, 2845, 1957, 1744-1652, 1604, 1584, 1495, 1455, 1391, 1366, 1165, 1056, 1022, 981, 913, 875, 855, 753, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 401 (100) MLi^+, 345 (29), 301 (42), 198 (20), 89 (80); HRFAB MS m/z calculated for $[M+Li]^+$ 401.2264, found 401.2252 and 402.2281 (^{13}C).

2-[N-(2-tert-Butoxycarbonylaminopropionyl)-N-*ethoxy*methylamino]-3-phenylpropionic acid methyl ester (made from 44b):

The ethoxy ether from **44b** was prepared using the general procedure described above. The substrate (**44b**) (0.099 g, 0.23 mmol), tetrabutylammonium tetrafluoroborate (0.748 g, 2.27 mmol), and

anhydrous ethanol (23 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.063 g (67%) of pure product. ^{1}H NMR ($CDCl_3$/500 MHz). δ 7.28-7.16 (m, 5H), 5.34 (d, J=7.5 Hz, 1H), 4.60 (quartet of doublets, app. quintet, J≈7 Hz, 1H), 4.49 (A of AB, J_{AB}=11.5 Hz, 1H), 4.46 (dd, J=5.0, 9.5 Hz, 1H), 4.23 (B of AB, J_{AB}=11.0 Hz, 1H), 3.71 (s, 3H), 3.52 (quartet of doublets, app quintet, J≈7 Hz, 1H), 3.39 (A of ABX, J_{AB}= 14.0 Hz, J_{AX}=5.5 Hz, 1H), 3.32 (quartet of doublets, J=6.5, 8.5 Hz, 1H), 3.24 (B of ABX, J_{AB}= 14 Hz, J_{BX}= 9.5 Hz, 1H), 1.43 (s, 9H), 1.26 (d, J=7.0 Hz, 3H), 1.12 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 173.7, 170.9, 155.1, 137.8, 129.5, 128.7, 126.9, 79.7, 78.1, 63.7, 60.2, 52.4, 46.8, 35.0, 28.5, 19.9, 15.0; IR (neat/NaCl) 3428, 3343, 3108, 3087, 3063, 3029, 2979, 2873, 1952, 1755-1644, 1605, 1585, 1538-1434, 1392, 1361, 1277, 1092, 1025, 982, 925, 907, 875, 856, 753, 701 cm^{-1}; LRFAB MS (relative intensity) m/z 415 (55) MLi^+, 313 (18), 160 (100), 136 (11), 89 (16); HRFAB MS m/z calculated for $[M+Li]^+$ 415.2420, found 415.2411 and 416.2453 (^{13}C).

2-[N-(2-tert-Butoxycarbonylaminopropionyl)-N-(n-*propoxy*)methylamino]-3-phenylpropionic acid methyl ester (44b):

The propoxy ether from **44b** was prepared using the general procedure described above. The substrate (**44b**) (0.099 g, 0.23 mmol), tetrabutylammonium tetrafluoroborate (0.748 g, 2.27 mmol), and anhydrous n-propanol (23 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.058 g (61%) of >97% pure product. ^{1}H NMR ($CDCl_3$/500 MHz). δ 7.28-7.16 (m, 5H), 5.34 (br d, J=7.5 Hz, 1H), 4.61 (quartet of doublets, app quintet, J≈7 Hz, 1H), 4.49 (A of AB, J_{AB}=10.5 Hz, 1H), ca 4.48 (dd, J=5.5, 9.5 Hz, 1H), 4.27 (B of AB, J_{AB}=11.0 Hz, 1H), 3.71 (s, 3H), 3.43 (triplet of doublets, app quartet, J≈7 Hz, 1H), ca 3.39 (A of ABX, J_{AB}=14.0 Hz, J_{AX}=5.5 Hz, 1H), 3.25-3.19 (m, 2H), 1.50 (sextet, J=7.5 Hz, 2H), 1.43 (s, 9H), 1.26 (d, J=7.0 Hz, 3H), 0.87 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 173.9, 171.0, 155.2, 137.8, 129.5, 128.7, 127.0, 79.7, 78.3, 69.9, 60.2, 52.4, 46.9, 35.1, 28.5, 22.8, 19.9, 10.6; IR (neat/NaCl) 3429, 3347, 3108, 3087, 3063, 3029, 2977, 2877, 1954, 1755-1644, 1605, 1585, 1538-1434, 1367, 1247, 1162, 1089, 1024, 982, 908, 872, 855, 752, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 429 (18) MLi^+, 373 (12), 329 (14), 136 (16), 89 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 429.2577, found 429.2561 and 430.2594 (^{13}C).

2-[N-(2-tert-Butoxycarbonylaminopropionyl)-N-(n-*butoxy*)methylamino]-3-phenylpropionic acid methyl ester (made from 44b):

The butoxy ether from **44b** was prepared using the general procedure described above. The substrate (**44b**) (0.094 g, 0.21 mmol), tetrabutylammonium tetrafluoroborate (0.710 g, 2.14 mmol), and anhydrous n-butanol (21 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.060g (64%) of >98% pure product. ^{1}H NMR ($CDCl_3$/500 MHz). δ 7.28-7.16 (m, 5H), 5.33 (br d, J=7.5 Hz, 1H), 4.61 (quartet of doublets, app quintet, J≈7 Hz, 1H), 4.49 (A of AB, J_{AB}=11.0 Hz, 1H), ca 4.47 (dd, J=6.0, 10.0 Hz, 1H), 4.26 (B of AB, J_{AB}=11.5 Hz, 1H), 3.71 (s, 3H), 3.47 (triplet of doublets, app quartet, J≈7 Hz, 1H), 3.38 (A of ABX, J_{AB}=14.0 Hz, J_{AX}=5.5 Hz, 1H), ca 3.26 (app quartet buried under B of ABX, 1H), 3.22 (B of ABX, J_{AB}=14.0 Hz, J_{BX}=10.5 Hz, 1H), ca 1.45 (methylene buried under s), 1.43 (s, 9H), 1.31 (app sextet, J=7.5 Hz, 2H), 1.26 (d, J=7.0 Hz, 3H), 0.89 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz). 173.9, 171.0, 155.2, 137.9, 129.5, 128.7, 127.0, 79.7, 78.3, 68.2, 60.3, 52.4, 46.9, 35.1, 31.7, 28.5, 20.0, 19.4, 14.0; IR (neat/NaCl) 3427, 3345, 3086, 3063, 3028, 2959, 2933, 2872, 1953, 1745-1660, 1605, 1585, 1496, 1454, 1391, 1366, 1247, 1166, 1092, 1025, 983, 935, 908, 856, 753, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 443 (3) MLi^+, 313 (17), 160 (100), 136 (13), 89 (14); HRFAB MS m/z calculated for $[M+Li]^+$ 443.2733, found 443.2720 and 444.2753 (^{13}C).

2-[(N-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-N-*methoxy*methylamino]-3-phenylpropionic acid methyl ester (made from 44c):

The methoxy ether from **44c** was prepared using the general procedure described above. The substrate (**44c**) (0.096 g, 0.19 mmol), tetrabutylammonium tetrafluoroborate (0.617 g, 1.87 mmol), and anhydrous methanol (18 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.067 g (76%) of pure product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.32-7.15 (m, 8H), 7.05-7.03 (m, 2H), 5.10 (d, J=9.3 Hz, 1H), 4.81 (ddd, app quartet, J≈7 Hz, 1H), 4.52 (dd, J=8.7, 6.0 Hz, 1H), 4.42 (d, J=10.8 Hz, 1H), 4.30 (d, J=11.4 Hz 1H), 3.70 (s, 3H), 3.38 (dd, J=14.2, 6.2 Hz, 1H), 3.13 (s, 3H), 3.16-3.01 (m, 2H), 2.86 (dd, J=13.5, 7.2 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.7, 170.9, 155.1, 137.8, 136.7, 129.7, 129.4, 128.7, 127.0, 126.8, 80.0, 79.2, 60.2, 55.6, 52.5, 52.2, 39.9, 35.4, 28.4; IR (neat/NaCl) 3327, 2975, 2924, 1743, 1698, 1659, 1454, 1250, 1169, 1082, 912, 752, 733, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 477 (100) MLi^+, 377 (34) MLi^+-Boc+H, 198 (22), 89 (72); HRMS m/z calculated for $[M+Li]^+$ 477.2577, found 477.2588 and 478.2613 (^{13}C).

2-[N-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-N-*ethoxy*methylamino]-3-phenylpropionic acid methyl ester (made from 44c):

The ethoxy ether from **44c** was prepared using the general procedure described above. The substrate (**44c**) (0.094 g, 0.18 mmol), tetrabutylammonium tetrafluoroborate (0.601 g, 1.83 mmol), and anhydrous ethanol (18 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.052 g (59%) of pure product. ^{1}H NMR ($CDCl_3$/500 MHz). δ 7.29-7.05 (m, 10H), 5.11 (br d, J=9.5 Hz, 1H), 4.83 (ddd, app quartet, J≈7 Hz, 1H), 4.56 (dd, J=6.0, 8.5 Hz, 1H), 4.46 (A of AB, J_{AB}=11.5 Hz, 1H), 4.40 (B of AB, J_{AB}=11.5 Hz, 1H), 3.68 (s, 3H), 3.41-3.35 (m, 2H), 3.23 (quartet of doublets, app quintet, J≈7 Hz, 1H), 3.07-3.02 (m, 2H), 2.87 (dd, J=7.0, 14.0 Hz, 1H), 1.37 (s, 9H), 1.07 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.7, 170.9, 155.1, 137.9, 136.8, 129.7, 129.4, 128.6, 127.0, 126.8, 79.9, 77.7, 63.6, 60.1, 52.4, 52.1, 40.0, 35.4, 28.4, 15.0; IR (neat/NaCl) 3426, 3331, 3167, 3108, 3087, 3063, 3029, 2978, 2872, 1951, 1887, 1807, 1754-1634, 1605, 1585, 1538-1361, 1167, 1097, 1018, 982, 924, 906, 856, 823, 801, 751, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 491 (100) MLi^+, 435 (35), 391 (30), 299 (12), 242 (15), 198 (58), 160 (49), 120 (53), 91 (30); HRFAB MS m/z calculated for $[M+Li]^+$ 491.2733, found 491.2720 and 492.2756 (^{13}C).

2-[N-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-N-(n-*propoxy*)methylamino]-3-phenylpropionic acid methyl ester (made from 44c):

The propoxy ether from **44c** was prepared using the general procedure described above. The substrate (**44c**) (0.093 g, 0.18 mmol), tetrabutylammonium tetrafluoroborate (0.605 g, 1.84 mmol), and anhydrous n-propanol (18 mL) were combined to make the electrolysis reaction solution. The crude product was chromatographed as described above to afford 0.050 g (55%) of ~98% pure product. ^{1}H NMR ($CDCl_3$/500 MHz). δ 7.29-7.06 (m, 10H), 5.11 (br d, J=9.5 Hz, 1H), 4.84 (ddd, app quartet, J≈8, 1H), 4.57 (dd, J=6.0, 8.0 Hz, 1H), 4.46 (A of AB, J_{AB}=11.5 Hz, 1H), 4.41 (B of AB, J_{AB}=11.5 Hz, 1H), 3.68 (s, 3H), 3.38 (dd, J=6.0, 14.0 Hz, 1H), 3.30 (triplet of doublets, app quartet, J≈7, 1H), 3.14 (triplet of doublets, app quartet, J≈7, 1H), 3.07-3.02 (m, 2H), 2.87 (dd, J=6.5, 13.0 Hz, 1H), 1.46 (sextet, J=7.0 Hz, 2H), 1.37 (s, 9H), 0.84 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.8, 170.9, 155.1, 137.9, 136.8, 129.7, 129.4, 128.6, 127.0, 126.8, 79.9, 77.9, 69.9, 60.1, 52.3, 52.1, 40.0, 35.5, 28.5, 22.8, 10.6; IR (neat/NaCl) 3426, 3333, 3168, 3108, 3087, 3063, 3029, 3003, 2978, 2920, 2877, 2857, 2252, 1952, 1880, 1766-1633, 1605, 1585, 1556-1454, 925, 908, 858, 697 cm^{-1}; HRFAB MS m/z calculated for $[M+Li]^+$ 505.2890, found 505.2890 and 506.2917 (^{13}C).

2-[N-(2-tert-Butoxycarbonylamino-3-phenylpropionyl)-N-(n-*butoxy*)methylamino]-3-phenylpropionic acid methyl ester (made from 44c):

The butoxy product from **44c** was prepared using the general procedure described above. The substrate (**44c**) (0.098 g, 0.19 mmol), tetrabutylammonium tetrafluoroborate (0.626 g, 1.90 mmol), and anhydrous n-butanol (18 mL) were combined to make the electrolysis reaction solution. The crude

product was chromatographed as described above to afford 0.030 g (31%) of ~94% pure product. ^{1}H NMR ($CDCl_3$/500 MHz) δ 7.29-7.06 (m, 10H), 5.11 (br d, J=9.0 Hz, 1H), 4.84 (ddd, app quartet, J≈8 Hz, 1H), 4.56 (dd, J=6.5, 8.5 Hz, 1H), 4.45 (A of AB, J_{AB}=11.0 Hz, 1H), 4.40 (B of AB, J_{AB}=11.0 Hz, 1H), 3.68 (s, 3H), 3.40-3.33 (m, 2H), 3.18 (triplet of doublets, app quartet, J≈7 Hz, 1H), 3.06-3.01 (m, 2H), 2.87 (dd, J=7.0, 13.5 Hz, 1H), 1.45-1.33 (methylene buried under s), 1.37 (s, 9H), 1.30-1.24 (m, 2H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.8, 170.9, 155.1, 137.9, 136.8, 129.7, 129.4, 128.6, 127.0, 126.8, 79.9, 78.0, 68.1, 60.1, 52.3, 52.1, 40.0, 35.5, 31.7, 28.4, 19.4, 14.0; IR (neat/NaCl) 3430, 3332, 3107, 3087, 3063, 3029, 3003, 2958, 2932, 2872, 1950, 1888, 1807, 1746-1644, 1605, 1585, 1515, 1495, 1454, 1392, 1366, 1282, 1247, 1168, 1087, 1048, 1020, 983, 930, 908, 857, 824, 751, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 519 (100) MLi^+, 464 (8), 420 (8), 314 (5), 160 (28); HRFAB MS m/z calculated for $[M+Li]^+$ 519.3046, found 519.3043 and 520.3070 (^{13}C).

HPLC Characterization of electrolysis products:

Compounds 8-19 were characterized by reverse phase HPLC with toluene and/or benzene internal standards. Response factors (RF) were calculated from peak areas (Absorption Units x Time) and are indicated on the chromatograms shown below. The response factors indicated are the average value of at least three response factors calculated from chromatograms generated using different relative concentrations of substrates and internal standard. In addition, response factors have been corrected for starting material impurities in the analytes.

Parallel electrolysis of silylated dipeptides 44a, 44b, and 44c:

Substrates in amounts indicated in Table 1A (below) were added to twelve 20 mL vials (reaction cells). Next, 10 mL of 100 mM Bu_4NBF_4/alcohol solution (anhydrous) was added to each vial as indicated in Table 1A. Onto each vial was placed a plastic cap, into which two carbon electrodes had been inserted (the anodes bearing 1cm x 1cm x 1cm pieces of RVC on their tips). Each cell was connected to an independent potentiostat of the Arbin power supply, and electrolyses were performed simultaneously in each cell with stirring. All electrolyses were run with a constant current of 8 mA, supplying 2.2 Faradays/mole of electrons with the exception of cell 8. The resistance across cell 8 was great enough to exceed the voltage limit of the Arbin potentiostat. As result, approximately 6 mA was passed during the run time, supplying approximately 1.6 Faradays/mole of electrons to that cell. After the electrolyses were complete, all vials were capped until analysis was performed the following day (~15 h later).

Table 1A

Cell	Starting Material	Mass Used	mMoles	Alcohol Solvent	Run Time (Min:Sec)	F/mole Passed
1	**30a**	42mg	0.099	Methanol	45:00	2.2
2	**30a**	42mg	0.099	Ethanol	45:00	2.2
3	**30a**	43mg	0.10	n-Propanol	45:00	2.2
4	**30a**	43mg	0.10	n-Butanol	45:00	2.2
5	**44b**	44mg	0.10	Methanol	44:52	2.2
6	**44b**	44mg	0.10	Ethanol	44:52	2.2
7	**44b**	44mg	0.10	n-Propanol	44:52	2.2
8	**44b**	44mg	0.10	n-Butanol	44:52	~1.6
9	**44c**	51mg	0.099	Methanol	43:44	2.2
10	**44c**	51mg	0.099	Ethanol	43:44	2.2
11	**44c**	50mg	0.098	n-Propanol	43:44	2.2
12	**44c**	50mg	0.098	n-Butanol	43:44	2.2

HPLC analysis was performed by co-dissolving measured amounts crude electrolysis solutions with internal standard solutions (made in IPA) and injecting those mixtures directly into the HPLC

column. Elution conditions and response factors used for each assay were those established by earlier HPLC characterizations. Yields of the parallel syntheses are listed in Table 1 of the text. Adequate resolution between the butoxy ether products and their unreacted silylated starting materials was not achieved by HPLC. Therefore, those products were isolated by silica gel chromatography. Percent yields listed for the butoxy ether products have been corrected for any residual starting material observed in their NMR spectra. In addition, the product from experiment 5 was isolated by silica gel chromatography so that its percent yield of isolated product could be compared to its percent yield by HPLC analysis.

2-[N-(2-Benzyloxycarbonylaminoacetyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (45a):

Compound **45a** was prepared using the general procedure outlined above. Dichloromethane (60 mL), NMM (1.0 mL, 9.1 mmol), and isobutylchloroformate (0.58 mL, 4.5 mmol) were initially combined. N-(Carbobenzyloxy)-glycine (0.948 g, 4.53 mmol) and the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) (0.822 g, 3.08 mmol) were then added. The crude product was chromatographed as described above to afford 1.176 g (84%) of pure product, which was a very viscous, colorless liquid. ^{1}H NMR ($CDCl_3$/300 MHz) (Two main rotamers with approximately 1:1 ratio were observed.) δ 7.34-7.09 (m, 10H), 5.81 and 5.62 (br s and br s, 1H), 5.10 and 5.03 (s and s, 2H), 4.40 (dd, J=9.4, 5.2 Hz, 0.5H), 3.99-3.76 (m, 2H), 3.70 and 3.69 (s and s, 3H), 3.34-3.20 (m, 2H), 2.99 (dd, J=14.2, 9.4 Hz, 0.5H), 2.72 (A of AB, J_{AB}=14.7 Hz, 0.5H), 2.57 (A of AB, J_{AB}=16.5 Hz, 0.5H), 2.50 (B of AB, J_{AB}=14.4 Hz, 0.5H), 1.77 (B of AB, J_{AB}=16.5 Hz, 0.5H), 0.02 and 0.01 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.2, 170.0, 167.8, 167.1, 156.2, 155.9, 137.8, 136.6, 136.5, 136.2, 129.2, 129.0, 129.0, 128.8, 128.5, 128.5, 128.1, 128.0, 127.4, 126.9, 66.8, 66.7, 64.6, 61.3, 52.6, 52.3, 43.1, 42.2, 40.8, 36.0, 35.4, 34.4; IR (neat/NaCl) 3410, 3064, 3030, 2952, 1738, 1699, 1660, 1505, 1435, 1351, 1248, 1049, 851, 753, 699 cm^{-1}; LR MS (relative intensity) m/z 457 (100) MH^+, 441 (72), 266 (84), 206 (79), 121 (56); HR MS m/z calculated for $[M+H]^+$ 457.2159, found 457.2138, and 458.2176 (^{13}C).

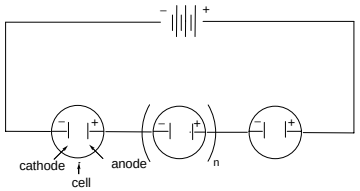
2-[N-(2-Benzyloxycarbonylaminopropionyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (45b):

Compound **45b** was prepared using the general procedure outlined above. Dichloromethane (60 mL), NMM (0.99 mL, 9.0 mmol), and isobutylchloroformate (0.59 mL, 4.5 mmol) were initially combined. N-(Carbobenzyloxy)-L-alanine (1.001 g, 4.480 mmol) and the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) (0.800 g, 3.00 mmol) were then added. The crude product was chromatographed as described above to afford 0.738 g (52%) of pure product, which was a very viscous, colorless liquid. ^{1}H NMR ($CDCl_3$/500 MHz) (Two rotamers with an approximate ratio of 4:3 were observed) δ 7.37-7.16 (m, 10H), 5.78 (br d, J=7.5 Hz, 1H of major rotamer), 5.41 (d, J=8.0 Hz, 1H of minor rotamer), 5.10 (s, 2H of major rotamer), 5.08 (s, 2H of minor rotamer), 4.85 (dd, J=6.0, 9.0 Hz, 1H of one rotamer), 4.45 (quartet of doublets, app quintet, J≈7 Hz, 1H of both rotamers), 3.75 (s, 3H of major rotamer), ca 3.75 (1H of one rotamer buried under s), 3.68 (s, 3H of minor rotamer), 3.37 (A of ABX, J_{AB}=14.0 Hz, J_{AX}=4.5 Hz, 1H of one rotamer), 3.35 (dd buried under A of ABX, 1H of one rotamer), 2.28 (B of ABX, J_{AB}=13.5 Hz, J_{BX}= 11.0 Hz, 1H of one rotamer), 3.01 (dd, J=8.5 Hz, 14.0 Hz, 1H of one rotomer), 2.71 (A of AB, J_{AB}=16.5 Hz, 1H of major rotamer), 2.70 (A of AB, J_{AB}=14.0 Hz, 1H of minor rotamer) 2.59 (B of AB, J_{AB}=14.5 Hz, 1H of minor rotamer), 1.87 (B of AB, J_{AB}=17.0 Hz, 1H of major rotamer), 1.30 (d, J=6.5 Hz, 3H of major rotamer), 0.84 (d, J=7.0 Hz, 3H of minor rotamer); 0.07 (s, 9H of major rotamer), 0.06 (s, 9H of minor rotamer); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.6, 171.3, 170.3, 170.2, 155.5, 155.3, 138.0, 136.7, 136.6, 129.5, 129.3, 129.0, 128.7, 128.6, 128.1, 128.0, 127.4, 127.0, 66.8, 66.7, 64.9, 62.3, 52.5, 52.2, 47.3, 46.1, 42.4, 36.4, 35.9, 34.7, 19.2, 18.6, -0.5, -2.1; IR (neat/NaCl) 3417, 3306, 3108, 3088, 3064, 3031, 2952, 2898, 2846, 2251, 1951, 1874, 1807, 1754-1695, 1658-1606, 1586, 1537-1434, 1375, 1346, 1065, 970, 911, 849, 771, 749, 699, 645, 622 cm^{-1}; LREI MS (relative intensity) m/z 470 (9) M^+, 455 (53), 379 (5), 347 (7), 292 (9), 206 (10), 160 (19), 130 (27), 91 (100); HREI MS m/z calculated for M^+ 470.2237, found 470.2248 and 271.2243 (^{13}C).

2-[N-(2-Benzyloxycarbonylamino-3-phenylpropionyl)-N-trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (45c):

Compound **45c** was prepared using the general procedure outlined above. Dichloromethane (50 mL), NMM (1.11 mL, 10.1 mmol), and isobutylchloroformate (0.66 mL, 5.1 mmol) were initially combined. N-(Carbobenzyloxy)-L-phenylalanine (1.520 g, 5.08 mmol) and the N-trimethylsilylmethyl-L-phenylalanine methyl ester derivative (**27**) (0.900 g, 3.37 mmol) were then added. The crude product was chromatographed as described above to afford 0.876 g (48%) of pure product, which was a very viscous, colorless liquid. ^{1}H NMR ($CDCl_3$/300 MHz) (Two main rotamers with approximately 1:1 ratio were observed.) δ 7.60-7.00 (m, 15H), 5.63 (d, J=9.0 Hz, 0.5H), 5.37 (d, J=7.8 Hz, 0.5H), 5.16-4.95 (m, 2.5H), 4.83 (ddd, app quartet, J≈7 Hz, 0.5H), 4.66 (td, J=9.6, 5.1 Hz, 0.5H), 3.93 (dd, J=8.7, 5.4 Hz, 0.5H), 3.79 and 3.70 (s and s, 3H), 3.52 (dd, J=14.2, 5.6 Hz, 0.5H), 3.39 (dd, J=14.0, 5.2 Hz, 0.5H), 3.14 (dd, J=13.8, 9.3 Hz, 0.5H), 3.09 (t, J=6.8 Hz, 0.5H), 3.01-2.93 (m, 1H), 2.85 (A of AB, J_{AB}=16.2 Hz, 0.5H), 2.84 (A of AB, J_{AB}=14.4 Hz, 0.5H), 2.75 (dd, J=14.4, 9.6 Hz, 0.5H), 2.64 (B of AB, J_{AB}=14.1 Hz, 0.5H), 2.33 (dd, J=14.2, 5.0 Hz, 0.5H), 2.03 (B of AB, J_{AB}=16.5 Hz, 0.5H), 0.15 and 0.13 (s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.7, 170.4, 170.3, 170.3, 155.6, 155.4, 138.2, 136.7, 136.6, 136.6, 136.3, 135.0, 130.3, 129.7, 129.4, 129.4, 129.1, 129.0, 128.7, 128.6, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.1, 126.9, 126.7, 126.5, 69.0, 67.1, 66.9, 64.5, 62.4, 52.5, 52.2, 51.0, 41.6, 40.1, 38.4, 36.6, 35.8, 34.9, -0.4, -2.0; IR (neat/NaCl) 3302, 3030, 2951, 1732, 1634, 1455, 1248, 1029, 851, 736, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 553 (100) MLi^+, 91 (100); HR MS m/z calculated for $[M+Li]^+$ 553.2710, found 553.2713.

Electrolysis of silylated dipeptides 45a, 45b, and 45c using reaction cells connected in series:



Substrates in amounts indicated in Table 2A were added to six 20 mL vials. Next, 15 mL of 100 mM Bu_4NBF_4/methanol solution (anhydrous) was added to each vial. Onto each vial was placed a plastic cap, into which two carbon electrodes had been inserted (the anodes bearing 1cm x 1cm x 1cm pieces of RVC on their tips). A serial circuit was established by connecting the cells in a cathode-to-anode and anode-to-cathode fashion (see figure), with the cells at the ends connected to a single potentiostat of the Arbin power supply. The electrolysis was run with a constant current of 8 mA for 1 h and 19 min, supplying 2.6 Faradays/mole of electrons to each reaction cell. At 8 mA, the potential drop across the circuit was approximately 20 V. After the electrolysis was complete, the vials were sealed until analysis was performed the next day (~15 h).

Table 2A

Cell	Starting Material	Mass Used	mMoles	Product	Mass of Crude Material Recovered	% Conversion of Starting Material	% Yield of Product
1	**45a**	69mg	0.15	**46a**	60mg	84	79
2	**45a**	69mg	0.15	**46a**	55mg	85	74
3	**45b**	71mg	0.15	**46b**	58mg	>99	90
4	**45b**	71mg	0.15	**46b**	60mg	83	77
5	**45c**	82mg	0.15	**46c**	70mg	>99	91
6	**45c**	82mg	0.15	**46c**	68mg	92	82

Samples were prepared for analysis by first removing methanol *in vacuo*. Then electrolyte was removed by filtration through silica gel with thorough washing of the gel with diethyl ether in order to capture the reaction products. Next, the ethereal filtrates were concentrated, the residues were weighed (see Table 2A), and proton NMR spectra of those samples were obtained. NMR spectra indicated the presence of only desired products and starting materials in the crude reaction mixtures. Percent conversions of starting materials to products were calculated from the molar ratios of starting materials to products observed in the proton NMR spectra of the crude reaction mixtures. Percent yields were calculated from the masses of crude materials recovered and the ratios of starting materials to products in those crude materials (see Table 2A). The crude mixtures from cells containing the same products were combined and chromarographed using the same stepwise elution described above for preparative electrolysis products. These materials were then fully characterized (see below) and used for the subsequent experiments described below.

2-[N-(2-Benzyloxycarbonylaminoacetyl)-N-methoxymethylamino]-3-phenylpropionic acid methyl ester (46a):

^{1}H NMR ($CDCl_3$/300 MHz) δ 7.37-7.14 (m, 10H), 5.68 (br s, 1H), 5.12 (s, 2H), 4.54 (dd, J=9.9, 5.4 Hz, 1H), 4.45 (d, J=11.1 Hz, 1H), 4.68 (d, J=4.8 Hz, 2H), 4.01 (d, J=11.1 Hz, 1H), 3.72 (s, 3H), 3.36 (dd, J=14.2, 5.6 Hz, 1H), 3.28-3.17 (m, 1H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.7, 169.4, 156.3, 137.6, 136.6, 129.2, 128.8, 128.7, 128.3, 128.2, 127.0, 79.2, 67.1, 61.0, 55.9, 52.6, 42.8, 35.2; IR (neat/NaCl) 3345, 2951, 1738, 1673, 1454, 1235, 1046, 754, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 421 (100) MLi^+, 91 (100); HR MS m/z calculated for $[M+Li]^+$421.1951, found 421.1958.

2-[N-(2-Benzyloxycarbonylaminopropionyl)-N-methoxymethylamino]-3-phenylpropionic acid methyl ester (46b):

^{1}H NMR ($CDCl_3$/300 MHz) δ 7.36-7.14 (m, 10H), 5.63 (br d, J=7.8 Hz, 1H), 5.09 (s, 2H), 4.68 (quartet of doublets, app quintet, J≈7 Hz, 1H), 4.44 (A of AB, J_{AB}=11.1 Hz, 1H), 4.42 (methine buried under A of AB), 4.12 (B of AB, J_{AB}=11.1 Hz, 1H), 3.71 (s, 3H), 3.39 (A of ABX, J_{AB}=14.1 Hz, J_{AX}=5.6 Hz, 1H), 3.25 (s, 3H), 3.23 (B of ABX, J_{AB}=14.1 Hz, J_{BX}=10.2 Hz, 1H), 1.29 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.3, 170.8, 155.6, 137.7, 136.5, 129.4, 128.7, 128.7, 128.3, 128.1, 127.0, 79.6, 66.9, 60.4, 55.8, 52.5, 47.3, 35.0, 19.9; IR (neat/NaCl) 3316, 3108, 3087, 3063, 3030, 2983, 2950, 2841, 1958, 1887, 1743-1694, 1682-1651, 1605, 1586, 1538-1496, 1462-1434, 1393, 1354, 1239, 1096, 1057, 1028, 980, 913, 750, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 435 (100) MLi^+, 91 (20); HRFAB MS m/z calculated for $[M+Li]^+$ 435.2107, found 435.2116 and 436.2113 (^{13}C).

2-[N-(2-Benzyloxycarbonylamino-3-phenylpropionyl)-N-methoxymethylamino]-3-phenylpropionic acid methyl ester (46c):

^{1}H NMR ($CDCl_3$/300 MHz) δ 7.37-7.05 (m, 15H), 5.38 (d, J=9.0 Hz, 1H), 5.04 (app. d, J=3.6 Hz, 2H), 4.89 (dd, J=16.2, 7.2 Hz, 1H), 4.58 (dd, J=8.8, 6.2 Hz, 1H), 4.40 (d, J=11.4 Hz, 1H), 4.32 (d, J=11.1 Hz, 1H), 3.66(s, 3H), 3.37 (dd, J=14.2, 6.2 Hz, 1H), 3.12 (s, 3H), 3.08-2.98 (m, 2H), 2.89 (dd, J=13.4, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 172.6, 170.8, 155.7, 137.7, 136.4, 129.7, 129.4, 129.0, 128.8, 128.7, 128.3, 128.1, 127.2, 126.9, 100.0, 79.1, 67.0, 60.1, 55.6, 52.7, 39.9, 35.5; IR (neat/NaCl) 3309, 3029, 1741, 1656, 1529, 1454, 1244, 1085, 1044, 750, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 511 (100) MLi^+, 313 (14), 160 (69); HRMS m/z calculated for $[M+Li]^+$ 511.2420, found 511.2413.

General procedure for the preparation of N-phenylsulfanylmethyl substituted dipeptides (48a, 48b, and 48c) and N-ethylsulfanylmethyl substituted dipeptides (47a, 47b, and 47c) from N-methoxymethyl substituted dipeptides (46a, 46b, and 46c):

A flame-dried, 2 mL, screw-cap vial was charged with dipeptide starting material (1 equiv). Benzene was then added and removed *in vacuo* in order to remove residual water via a benzene/water azeotrope. Next, the vial was purged with argon and an injection port adaptor was screwed on in order to

seal the vial. After that, dry dichloromethane, thiol (2 equiv), and $BF_3{\cdot}OEt_2$ (0.25 or 0.5 equiv as indicated) were added in that order, and the reaction solution was stirred for *ca.* 18 h. After completion, the reaction solution was concentrated and chromatographed through silica gel using the same stepwise elution described above for preparative electrolysis products. Amounts of reagents used and yields of products are indicated below. The purity of the products was determined by HPLC.

2-[N-(2-Benzyloxycarbonylaminoacetyl)-N-ethylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (47a):

Compound **47a** was prepared using the general procedure described above. Dry dichloromethane (0.66 mL), ethanethiol (9.9 μL, 0.13 mmol), and $BF_3{\cdot}EtO_2$ (2.1 μL, 0.017 mmol) were added to 28 mg (0.067 mmol) of N-methoxylmethylated dipeptide (**46a**). The crude product was chromatographed as described above to afford 24 mg (79%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/300 MHz) (Two rotamers with an approximate ratio of 5:1 were observed. Only the major rotamer is reported.) δ 7.37-7.14 (m, 10H), 5.71 (br s, 1H), 5.14 (s, 2H), 4.44 (dd, J=5.1, 10.5 Hz, 1H), 4.22 (A of AB, J_{AB}=14.4 Hz, 1H), 4.05 (d, J=4.5 Hz, 2H), 3.74 (s, 3H), ca 3.42 (A of ABX, J_{AB}=13.8 Hz, J_{AX}=5.1 Hz, 1H), 3.38 (B of AB, J_{AB}=14.4, 1H), 3.30 (B of ABX, J_{AB}=14.1 Hz, J_{BX}=10.5 Hz, 1H), 2.54-2.44 (m, 2H), 1.19 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 170.4, 168.2, 156.3, 137.7, 136.6, 129.3, 129.0, 128.7, 128.3, 128.2, 127.1, 67.1, 61.1, 52.7, 50.3, 43.1, 34.6, 24.7, 14.4; IR (neat/NaCl) 3407, 3340, 3087, 3063, 3030, 3003, 2951, 2930, 2871, 1957, 1882, 1738-1716, 1666-1652, 1604, 1585, 1537-1497, 1454, 1355, 1211, 1082, 1048, 1028, 987, 931, 910, 770, 752, 699 cm^{-1}; LREI MS (relative intensity) m/z 444 (<0.01) M^+, 383 (4) $[M\text{-}SEt]^+$, 339 (6), 217 (8), 192 (75), 132 (53), 107 (19), 91 (100); LRFAB MS (relative intensity) m/z 451 (70) MLi^+, 91 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 451.1879, found 451.1861 and 452.1903 (^{13}C).

2-[N-(2-Benzyloxycarbonylaminopropionyl)-N-ethylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (47b):

Compound **47b** was prepared using the general procedure described above. Dry dichloromethane (0.39 mL), ethanethiol (5.8 μL, 0.078 mmol), and $BF_3{\cdot}EtO_2$ (1.8 μL, 0.014 mmol) were added to 17 mg (0.039 mmol) of N-methoxylmethylated dipeptide (**46b**). The crude product was chromatographed as described above to afford 14 mg (76%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/300 MHz) (Two rotamers with an approximate ratio of 5:1 were observed. Only the major rotamer is reported.) δ 7.37-7.14 (m, 10H), 5.66 (br d, J=7.8 Hz, 1H), 5.09 (s, 2H), 4.60 (m, 1H), ca 4.41 (dd, J=4.8, 10.8 Hz, 1H), ca 4.36 (A of AB, J_{AB}=14.7 Hz, 1H), 3.72 (s, 3H), 3.43 (A of ABX, J_{AB}=13.8 Hz, J_{AX}=4.5 Hz, 1H), 3.32 (B of AB, J_{AB}=14.7, 1H), 3.29 (B of ABX, J_{AB}=14.1 Hz, J_{BX}=10.8 Hz, 1H), 2.53 (q, J=7.5 Hz, 2H), 1.29 (d, J=6.6 Hz, 3H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.3, 170.5, 155.6, 137.8, 136.6, 129.5, 128.9, 128.7, 128.3, 128.2, 127.2, 67.0, 60.5, 52.6, 51.2, 47.3, 34.7, 24.3, 19.8, 14.4; IR (neat/NaCl) 3318, 3106, 3087, 3063, 3030, 2952, 2928, 2872, 2852, 1955, 1879, 1801, 1748-1634, 1605, 1586, 1538-1418, 1375, 1353, 1255, 1061, 990, 936, 906, 847, 824, 738, 697 cm^{-1}; LREI MS (relative intensity) m/z 397 (6) $[M\text{-}SEt]^+$, 353 (6), 282 (8), 192 (22), 132 (13), 91 (100); LRFAB MS (relative intensity) m/z 465 (58) MLi^+, 313 (22), 160 (100), 91 (84); HRFAB MS m/z calculated for $[M+Li]^+$ 465.2036, found 465.2021 and 466.2060 (^{13}C).

2-[N-(2-Benzyloxycarbonylamino-3-phenylpropionyl)-N-ethylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (47c):

Compound **47c** was prepared using the general procedure described above. Dry dichloromethane (0.64 mL), ethanethiol (9.5 μL, 0.13 mmol), and $BF_3{\cdot}EtO_2$ (2.0 μL, 0.016 mmol) were added to 32 mg (0.064 mmol) of N-methoxylmethylated dipeptide (**46c**). The crude product was chromatographed as described above to afford 27 mg (78%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/300 MHz) (Three rotamers with approximate ratios of 5:1:1 were observed. Only the major rotamer is reported.) δ 7.33-7.02 (m, 15H), 5.35 (d, J=9.0 Hz, 1H), 5.04 (s,

2H), 4.86 (ddd, app quartet, J≈7 Hz, 1H), 4.51 (dd, J=5.4, 9.3 Hz, 1H), ca 4.32 (A of AB, J_{AB}=14.4 Hz, 1H), 3.68 (s, 3H), ca 3.66 (B of AB buried under s, 1H), 3.44 (A of ABX, J_{AB}=14.4 Hz, J_{AX}=5.7 Hz, 1H), 3.12-3.02 (m, 2H), 2.89 (B of ABX, J_{AB}=13.5, J_{BX}=7.2 Hz, 1H), 2.39 (doublet of quartets, J=2.1, 7.2 Hz, 2H), 1.14 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 171.5, 170.6, 155.7, 137.9, 136.5, 129.7, 129.4, 128.8, 128.8, 128.7, 128.3, 128.0, 127.2, 126.9, 67.0, 60.4, 52.6, 52.5, 50.7, 39.9, 35.1, 24.5, 14.5; IR (neat/NaCl) 3304, 3108, 3086, 3062, 3029, 2951, 2927, 2870, 2854, 1953, 1880, 1806, 1739-1715, 1658-1635, 1604, 1585, 1530, 1496, 1454, 1231, 1151, 1083, 1028, 988, 909, 845, 824, 749, 699 cm^{-1}; LREI MS (relative intensity) m/z 534 (<0.01) M^+, 473 (5) $[M\text{-}SEt]^+$, 365 (5), 282 (9), 210 (6), 192 (17), 132 (15), 91 (100); LRFAB MS (relative intensity) m/z 540 (78) MLi^+, 313 (14), 91 (74), 89 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 541.2349, found 541.2336 and 542.2374 (^{13}C).

2-[N-(2-Benzyloxycarbonylaminoacetyl)-N-phenylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (48a):

Compound **48a** was prepared using the general procedure described above. Four vials were charged with 16 mg (0.038 mmol) each of N-methoxylmethylated dipeptide (**46a**). To each vial, dichloromethane (0.28 mL) and benzenethiol (8.0 μL, 0.078 mmol) were added. Next, different volumes of $BF_3{\cdot}OEt_2$ were added to each vial as indicated: To vial 1, 1.2 μL (0.0094 mmol) was added; to vial 2, 2.4 μL (0.019 mmol) was added; to vial 3, 3.5 μL (0.028 mmol) was added, to vial 4, 4.7 μL (0.038 mmol) was added. The reactions were monitored by TLC, and after 20 h the starting material had been consumed in vials 2-4. Reaction solutions from vials 2-4 were combined and chromatographed as described above to afford 49 mg (88%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/ 300 MHz) (Two rotamers with an approximate ratio of 5:1 were observed. Only the major rotamer is reported.) δ 7.47-7.45 (m, 2H), 7.38-7.20 (m, 11H), 7.12 (d, J=6.9 Hz, 2H), 5.48 (br s, 1H), 5.09 (s and s, 2H), 4.48 (d, J=14.4 Hz, 1H), 4.37 (dd, J=10.0, 5.2 Hz, 1H), 3.86 (dd, J=11.7, 5.1 Hz, 1H), 3.78 (d, J=14.4 Hz, 1H), 3.74 (s, 3H), 3.52 (dd, J=17.1, 3.9 Hz, 1H), 3.39 (dd, J=14.1, 5.4 Hz, 1H), 3.21 (dd, J=14.0, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.1, 168.4, 156.1, 137.5, 136.5, 134.0, 132.7, 129.6, 129.3, 129.0, 129.0, 128.6, 128.2, 128.1, 127.1, 67.0, 61.7, 55.1, 52.6, 42.6, 34.9; IR (neat/NaCl) 3406, 3339, 3059, 3020, 2947, 1734, 1664, 1451, 1245, 1208, 1046, 747, 696 cm^{-1}; LRFAB MS (relative intensity) m/z 499 (73) MLi^+, 313 (17), 160 (100); HR MS m/z calculated for $[M+Li]^+$ 499.1879, found 499.1864.

2-[N-(2-Benzyloxycarbonylaminopropionyl)-N-phenylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (48b):

Compound **48b** was prepared using the general procedure described above. Dry dichloromethane (0.72 mL), Benzenethiol (15 μL, 0.15 mmol), and $BF_3{\cdot}EtO_2$ (4.6 μL, 0.036 mmol) were added to 31 mg (0.073 mmol) of N-methoxylmethylated dipeptide (**46b**). The crude product was chromatographed as described above to afford 33 mg (89%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/300 MHz) (Three rotamers with approximate ratios of 5:2:1 were observed. Only the major rotamer is reported.) δ 7.52-7.12 (m, 15H), 5.46 (d, J=7.5 Hz, 1H), 5.12-5.05 (m, 2H), 4.54 (A of AB, J_{AB}=14.4 Hz, 1H), 4.41 (dd, J=5.1, 10.2, 1H), 4.22 (quartet of doublets, app quintet, J≈7 Hz, 1H), 4.04 (B of AB, J_{AB}=14.4, 1H), 3.74 (s, 3H), 3.42 (A of ABX, J_{AB}=14.4 Hz, J_{AX}=5.1 Hz, 1H), 3.20 (B of ABX, J_{AB}=14.1 Hz, J_{BX}=10.2, 1H), 1.17 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$/125 MHz) δ 172.6, 170.3, 155.2, 137.6, 136.7, 133.7, 132.7, 129.5, 129.5, 128.8, 128.8, 128.7, 128.3, 128.2, 127.2, 66.8, 61.3, 55.4, 52.5, 47.2, 35.0, 19.5; IR (neat/NaCl) 3322, 3106, 3086, 3062, 3030, 2981, 2950, 2872, 2852, 1955, 1883, 1746-1635, 1604, 1584, 1574, 1538-1418, 1353-1167, 1113, 1088, 1065, 1026, 938, 908, 847, 824, 746, 697 cm^{-1}; LREI MS (relative intensity) m/z 397 (32) $[M\text{-}SPh]^+$, 353 (40), 282 (48), 231 (28), 229 (31), 192 (100), 132 (82), 91 (100); LRFAB MS (relative intensity) m/z 512 (40) MLi^+, 91 (63), 89 (100); HRFAB MS m/z calculated for $[M+Li]^+$ 513.2036, found 513.2030 and 514.2068 (^{13}C).

2-[N-(2-Benzyloxycarbonylamino-3-phenylpropionyl)-N-phenylsulfanylmethylamino]-3-phenylpropionic acid methyl ester (48c):

Compound **48c** was prepared using the general procedure described above. Dry dichloromethane (0.57 mL), benzenethiol (12 μL, 0.11 mmol), and $BF_3 \cdot EtO_2$ (3.6 μL, 0.029 mmol) were added to 29 mg (0.057 mmol) of N-methoxylmethylated dipeptide (**46c**). The crude product was chromatographed as described above to afford 31 mg (91%) of product. The HPLC chromatogram of the purified material showed one major peak. ^{1}H NMR ($CDCl_3$/ 300 MHz) δ 7.50-7.02 (m, 20H), 5.26 (br d, J=9.0 Hz, 1H), 5.07-4.98 (m, 2H), 4.75 (ddd, app. quartet, J≈7 Hz, 1H), 4.58 (dd, J=8.7, 6.6 Hz, 1H), 4.49 (d, J=14.1 Hz, 1H), 4.36 (d, J=13.8 Hz, 1H), 3.67 and 3.53 (s and s, 3H), 3.40 (dd, J=14.2, 6.4 Hz, 1H), 3.05-3.85 (m, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.9, 170.4, 155.5, 137.5, 136.3, 133.2, 129.7, 129.5, 129.4, 129.2, 129.0, 128.7, 128.7, 128.5, 128.3, 128.1, 127.2, 127.0, 67.0, 60.8, 54.2, 52.6, 52.5, 39.6, 35.3; IR (neat/NaCl) 3311, 3064, 1740, 1720, 1709, 1642, 1438, 1231, 747, 696 cm^{-1}; LRFAB MS (relative intensity) m/z 589 (46) MLi^+, 313 (16), 160 (100); HR MS m/z calculated for $[M+Li]^+$ 589.2349, found 589.2332.

General procedure for the preparation of (chloromethyl)dimethyl(2-methoxyphenyl)silane and (chloromethyl)dimethyl(2,4-methoxyphenyl)silane:

To a 250 mL flame-dried round bottom flask was added (mono or di-) bromoanisole (20 mmol) and dry THF (30 mL). The solution was cooled to -78 ^{o}C and n-butyllithium (9.6 mL, 1.6 M in hexane) was added. The mixture was then stirred at -78 ^{o}C for 30 min before being treated with chloro(chloromethyl)silane (2.90 mL, 22 mmol). The resulting white suspension was stirred at room temperature for 2 h and then quenched with a saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column using pure hexane as eluant to afford the desired monomethoxyphenyl product (3.74 g, 87%) or the desired dimethoxyphenyl product (4.5 g, 92%). The spectroscopic data for both chlorosilanes were consistent with those previously reported in the literature (Gotteland, J.; Guilhem, M.; Halazy, S. *Syn. Commun.* **1996**, *26*, 2928.

2-{[(Dimethylphenylsilanyl)methyl]amino}-3-phenylpropionic acid methyl ester (50b):

Compound **50b** was prepared using the general procedure described above for the synthesis of **27**. In this experiment, the crude product was chromatographed through a silica gel column using 1:4 EtOAc/hexane as eluant. The column afforded 3.3 g (68%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.49-7.46 (m, 2H), 7.38-7.31 (m, 3H), 7.22-7.19 (m, 3H), 7.09-7.08 (m, 2H), 3.57 (s, 3H), 3.40 (t, J=7.0Hz, 1H), 2.86 (d, J=7.0Hz, 2H), 2.26 (d, J=13.5Hz, 1H), 2.10 (d, J=13.5Hz, 1H), 0.28 (s, 3H), 0.26 (s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 175.2, 139.4, 137.6, 133.9, 133.2, 129.7, 129.4, 129.3, 128.4, 128.0, 126.7, 66.8, 51.6, 39.3, 37.3, -3.7, -4.0; IR (neat/NaCl) 3472, 3048, 3024, 2954, 1737, 1529, 1428, 1358, 1251, 1118, 872, 830, 778, 730, 699 cm^{-1}; LRFAB MS (relative intensity) m/z 334 (68) MLi^+, 328 (96) M^+, 268 (30) M^+-$HCOOCH_3$, 236 (100); HRMS m/z calculated for $[M+H]^+$ 328.1733, found 328.1733.

2-{[(Methyldiphenylsilanyl)methyl]amino}-3-phenylpropionic acid methyl ester (50c):

Compound **50c** was prepared using the procedure described above for the synthesis of **27**. In this experiment, the crude product was chromatographed through a slica gel column using 1:5 EtOAc/hexane as eluant. The column afforded 4.4 g (75%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.61-7.46 (m, 5H), 7.40-7.27 (m, 6H), 7.25-7.17 (m, 2H), 7.16-7.09 (m, 2H), 3.61 (d, J=0.6Hz, 1.5H), 3.61 (s, 1.5H), 3.46 (t, J=6.3Hz, 1H), 2.90-2.81 (m, 2H), 2.61 (dd, J=13.5, 1.5Hz, 1H), 2.38 (dd, J=13.5, 1.5Hz, 1H), 0.55, 0.55 and 0.55 (s, s and s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 175.2, 137.9, 135.9, 135.6, 134.8, 134.8, 129.6, 129.6, 129.3, 128.4, 128.1, 128.0, 126.6, 66.9, 51.6, 39.4, 36.2, -5.0; IR (neat/NaCl) 3068, 2951, 2788, 1737, 1589, 1428, 1253, 1170, 1114, 789, 698cm^{-1}; LRFAB MS (relative intensity) m/z 390

(41) MLi^+, 298 (57) MLi^+-$PhCH_2$-H, 197 (100), 135 (68); HRMS m/z calculated for $[M+H]^+$ 390.1889, found 390.1876 and 390.1881.

2-({[(2-Methoxyphenyl)dimethylsilanyl]methyl}amino)-3-phenylpropionic acid methyl ester (50d):

Compound **50d** was prepared using the procedure described above for the synthesis of **27**. In this experiment, the crude product was chromatographed through a slica gel column using 1:4 EtOAc/hexane as eluant. The column afforded 4.4 g (82%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.41-7.32 (m, 2H), 7.28-7.20 (m, 3H), 7.16-7.11 (m, 2H), 6.94 (t, J=7.8Hz, 1H), 6.79 (d, J=8.2Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.45 (t, J=6.9Hz, 1H), 2.90 (d, J=6.6Hz, 2H), 2.31 (d, J=12.9Hz, 1H), 2.19 (d, J=12.9Hz, 1H), 0.28 (s, 1.5H), 0.27 (s, 4.5H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 175.2, 164.4, 137.9, 135.7, 131.5, 131.3, 129.4, 128.5, 126.7, 125.5, 120.8, 109.6, 67.0, 55.1, 51.6, 39.3, 37.5, -3.4, -3.5; IR (neat/NaCl) 2952, 1736, 1589, 1460, 1430, 1237, 1166, 1024, 840, 758, 699cm^{-1}; LRFAB MS (relative intensity) m/z 358 (70) MH^+, 313 (32), 250 (4) M^+-$PhOCH_3$, 160 (100); HRMS m/z calculated for $[M+H]^+$ 357.1760, found 358.1838 and 359.1859 (^{13}C).

2-({[(2,4-Dimethoxyphenyl)dimethylsilanyl]methyl}amino)-3-phenyl-propionic acid methyl ester (50e):

Compound **50e** was prepared using the procedure described above for the synthesis of **27**. In this experiment, the crude product was chromatographed through a slica gel column using 1:3 EtOAc/hexane as eluant. The column afforded 5.3 g (91%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.28-7.19 (m, 5H), 7.14-7.11 (m, 1H), 6.49-6.46 (m, 1.5H), 6.37-6.36 (m, 0.5H), 3.82 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 3.44 (t, J=7.0Hz, 1H), 2.89 (dd, J=7.0, 2.0Hz, 2H), 2.27 (d, J=13.0Hz, 1H), 2.15 (d, J=13.0Hz, 1H), 0.24 (s, 3H), 0.24 (s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 175.3, 165.8, 162.8, 137.9, 136.6, 129.4, 128.5, 126.6, 1004.8, 97.8, 67.0, 55.4, 55.1, 51.6, 39.3, 37.6, -3.3, -3.4; IR (neat/NaCl) 2953, 2834, 1736, 1597, 1462, 1405, 1301, 1246, 1208, 1157, 1089, 1033, 839, 700cm^{-1}; LRFAB MS (relative intensity) m/z 394 (63) MLi^+, 313 (11), 250 (100) M^+-2Li-$(MeO)_2Ph$, 165 (67); HRMS m/z calculated for $[M+Li]^+$ 394.2026, found 394.2037 and 395.2063 (^{13}C).

2-{(2-tert-Butoxycarbonylaminoacetyl)-[(dimethylphenylsilanyl)methyl]amino}-3-phenyl-propionic acid methyl ester (49b):

Compound **49b** was prepared using the procedure described above for the synthesis of **30a**. In this experiment, the crude product was chromatographed through a silica gel column using 1:3 EtOAc/hexane as eluant. The column afforded 3.4 g (71%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio were observed) δ 7.60-7.50 (m, 1H), 7.42-7.18 (m, 7H), 7.12-7.10 (m, 1H), 7.07-7.00 (m, 1H), 5.52 and 5.35 (br s and br s, 1H), 4.44 (dd, J=9.0, 5.4Hz, 0.5H), 3.96-3.85 (m, 1H), 3.70 and 3.65 (s and s, 3H), 3.54 (t, J=7.6Hz, 0.5H), 3.31 (dd, J=16.4, 3.4Hz, 0.5H), 3.37-3.20 (m, 2H), 2.95 (dd, J=14.2, 9.15Hz, 0.5H), 2.90 (A of AB, J_{AB}=14.7Hz, 0.5H), 2.77 (B of AB, J_{AB}=14.7Hz, 0.5H), 2.74 (A' of A'B', $J_{A'B'}$=16.5Hz, 0.5H), 1.92 (B' of A'B', $J_{A'B'}$=16.5Hz, 0.5H), 1.45 and 1.42 (s and s, 9H), 0.40, 0.38 (s and s, 3H), 0.30 and 0.24 (s, and s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.0, 170.0, 168.5, 167.6, 155.9, 137.9, 136.2, 136.1, 133.8, 133.7, 130.0, 129.2, 129.0, 128.7, 128.2, 127.8, 127.3, 126.8, 79.5, 64.3, 61.3, 52.6, 52.1, 42.7, 41.9, 40.4, 35.5, 34.3, 28.4, 28.4, -2.0, -2.3, -3.5, -4.4; IR (neat/NaCl) 3421, 2976, 1743, 1718, 1654, 1496, 1465, 1366, 1249, 1169, 1113, 840, 700cm^{-1}; LRFAB MS (relative intensity) m/z 485 (14) MLi^+, 429 (9) MLi^+-C_4H_8, 407 (17) MLi^+-PhH, 351 (100) MLi^+-$PhMeSi{=}CH_2$, 307 (26), 154 (27), 135 (98); HRMS m/z calculated for $[M+H]^+$ 485.2472, found 485.2452 and 485.2452.

2-{(2-tert-Butoxycarbonylaminoacetyl)-[(methyldiphenylsilanyl)methyl]amino}-3-phenyl-propionic acid methyl ester (49c):

Compound **49c** was prepared using the procedure described above for the synthesis of **30a**. In this experiment, the crude product was chromatographed through a silica gel column using a gradient

elution from 1:3 EtOAc/hexane to 1:1.5 EtOAc/hexane. The column afforded 3.3 g (60%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 1:1 ratio were observed) δ 7.58-7.19 (m, 13H), 7.10-7.08 (d, J=1.5Hz, 1H), 7.08-6.98 (m, 1H), 5.50 and 5.28 (br s, and br s, 1H), 4.43 (dd, J=9.0, 5.7Hz, 0.5H), 3.92 (td, J=17.9, 4.0Hz, 1H), 3.72-3.59 (m, 1H), 3.63 and 3.49 (s and s, 3H), 3.52-3.38 (m, 1H), 3.33-3.15 (m, 2H), 3.05 (d, J=16.5Hz, 0.5H), 2.96 (dd, J=14.2, 9.2Hz, 0.5H), 2.23 (d, J=16.5Hz, 0.5H), 1.45 and 1.41 (s and s, 9H), 0.69 and 0.59 (s and s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 169.9, 168.7, 167.8, 138.0, 137.6, 136.2, 134.8, 134.8, 134.5, 133.9, 130.4, 130.1, 129.3, 129.3, 129.2, 129.1, 129.0, 128.8, 128.3, 128.3, 27.9, 127.4, 127.0, 79.6, 64.2, 61.4, 52.7, 52.1, 42.8, 42.1, 39.2, 35.6, 34.5, 34.0, 28.5, 28.5, -3.5, -5.6; IR (neat/NaCl) 3421, 2977, 1743, 1713, 1650, 1496, 1428, 1456, 1250, 1168, 793, 734, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 553 (50) MLi^+, 453 (100) MLi^+-Boc+H, 197 (60) , 105 (26); HRMS m/z calculated for $[M+H]^+$ 553.2710, found 553.2696 and 553.2697.

2-((2-tert-Butoxycarbonylaminoacetyl)-{[(2-methoxyphenyl)dimethylsilanyl]methyl}amino)-3-phenylpropionic acid methyl ester (49d):

Compound **49d** was prepared using the procedure described above for the synthesis of **30a**. In this experiment, the crude product was chromatographed through a silica gel column using 1:3.5 EtOAc/hexane as eluant. The column afforded 4.1 g (80%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 3:1 ratio were observed) δ 7.39-7.29 (m, 1H), 7.28-7.11 (m, 4H), 7.09-7.04 (m, 2H), 6.96-6.90 (m, 1H), 6.88-6.75 (m, 1H), 5.56 and 5.38 (br s and br s, 1H), 4.38-4.35 (m, 0.1H), 3.95-3.52 (m, 2.9H), 3.81 and 3.76 (s and s, 3H), 3.64 and 3.56 (s and s, 3H), 3.39-3.18 (m, 2H), 2.84 (d, J=16.2Hz, 1H), 2.12 (d, J=16.2Hz, 1H), 1.44 and 1.40 (s and s, 9H), 0.35, 0.27 and 0.25 (s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.1, 169.9, 168.4, 167.5, 163.8, 155.6, 138.1, 136.4, 135.6, 135.0, 131.8, 130.8, 129.2, 129.0, 128.9, 128.6, 127.4, 127.2, 126.6, 123.4, 120.6, 120.5, 109.6, 109.4, 79.3, 64.5, 61.4, 55.0, 52.4, 52.0, 42.7, 42.0, 39.9, 35.4, 34.3, 28.4, 28.3, -2.2, -2.7, -3.5, -3.7; IR (neat/NaCl) 3421, 2953, 1742, 1713, 1651, 1597, 1464, 1247, 1208, 1157, 1088, 1031, 840, 703 cm^{-1}; LRFAB MS (relative intensity) m/z 515 (8) MLi^+, 499 (19), 473 (5), 443 (19), 407 (29) MLi^+-$PhOCH_3$, 351 (100), 307 (36), 165 (34), 135 (71); HRMS m/z calculated for $[M+H]^+$ 515.2577, found 515.2563 and 515.2575.

2-((2-tert-Butoxycarbonylaminoacetyl)-{[(2,4-dimethoxyphenyl)dimethylsilanyl]methyl}amino)-3-phenylpropionic acid methyl ester (49e):

Compound **49** was prepared using the procedure described above for the synthesis of **30a**. In this experiment, the crude product was chromatographed through a silica gel column using 1:3 EtOAc/hexane as eluant. The column afforded 4.4 g (81%) of the desired product. ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.32-7.11 (m, 5H), 7.08-7.05 (m, 1H), 6.53-6.37 (m, 2H), 5.58 and 5.42 (br s and br s, 1H), 4.46-4.38 (m, 0.2H), 3.96-3.81 (m, 2.8H), 3.80, 3.79, 3.75, 3.66 (s, s, s and s, 9H), 3.78-3.55 (m, 2H), 3.36-3.20 (m, 2H), 2.82 (d, J=16.3Hz, 1H), 2.11 (d, J=16.3Hz, 1H), 1.46, 1.45, 1.42 amd1.41 (s, s, s and s, 9H), 0.34, 0.30, 0.27, 0.23 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.4, 167.6, 165.4, 163.4, 161.0, 155.8, 138.3, 136.8, 130.1, 129.4, 129.2, 129.1, 129.1, 128.7, 126.8, 114.8, 106.3, 104.9, 100.6, 97.9, 97.8, 79.5, 64.7, 55.4, 55.2, 52.2, 42.9, 40.1, 34.5, 28.6, 28.5, -3.3, -3.4; IR (neat/NaCl) 2975, 1744, 1711, 1648, 1465, 1235, 1165, 841, 758, 702 cm^{-1}; LRFAB MS (relative intensity) m/z 551 (31) MLi^+, 529 (8), 501 (6), 473 (16) MLi^+-PhH, 451 (70) MLi^+-Boc-H, 351 (85), 165 (100), 133 (87); HRMS m/z calculated for $[M+Li]^+$ 551.2765, found 551.2776, and 551.2751.

General procedure for the chemical oxidation of silylated peptide derivatives 30a and 49b-e with ceric ammonium nitrate (formation of 31a):

A 100 mL oven-dried round bottom flask was charged with the silylated dipeptide (0.5 mmol) and a mixture of anhydrous methanol and CH_2Cl_2 (25 mL) (the best ratio of MeOH to CH_2Cl_2 for substrates **49d** and **49e** is 15% and 20% respectively). The resulting solution was stirred and ceric

ammonium nitrate (1.1 g, 2 mmol) added under argon. The reaction mixture was then allowed to stir at room temperature (or –40 °C, 0 °C) for 30 min to 12 h (see Table 3 in the text for reaction times and temperatures) and quenched with 1 mL 30% Na_2SO_3 solution. The resulting mixture was stirred for 15 min until two clear layers were formed. The layers were then separated. The organic layer was washed with water (2 x 20 mL) and the combined aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column using 1:1 hexane/EtOAc as eluant to obtain the oxidation product **62**. The yields for different substrates are listed in Table 3. In all cases, the spectral data for the product were consistent with that reported above for compound **31a**.

2-[(3-Benzyloxy-2-tert-butoxycarbonylaminopropionyl)trimethylsilanylmethylamino]-3-phenyl-propionic acid methyl ester (51a):

Compound **51a** was synthesized above in connection with Scheme 12 (the converstion of amino acid **27** to the dipeptide equivalent **28**).

2-((3-Benzyloxy-2-tert-butoxycarbonylaminopropionyl)-{[(2-methoxyphenyl)dimethylsilanyl]-methyl}amino)-3-phenyl-propionic acid methyl ester (51b):

Compound **51b** was prepared using the procedure described above for the synthesis of **30a**. The crude product was chromatographed through a silica gel column using 1:4 EtOAc/hexane as eluant. The column afforded 0.91 g (36%) of the desired product (the yield was not optimized). ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.38-7.04 (m, 12H), 6.98-6.89 (m, 1H), 6.81 (dd, J=17.7, 8.1Hz, 1H), 5.45 (d, J=8.1Hz, 0.67H), 5.25 (d, J=7.8Hz, 0.33H), 5.00-4.89 (m, 0.33H), 4.87-4.79 (m, 0.67H), 4.58 (br s, 2H), 4.46-4.30 (m, 1H), 3.80, 3.72, 3.65 and 3.52 (s, s, s and s, 6H), 3.79-3.50 (m, 2H), 3.36-2.87 (m, 3.5H), 2.30 (d, J=16.2Hz, 0.5H), 1.44 and 1.41 (s and s, 9H), 0.40, 0.35, 0.32 and 0.29 (s, s, s, and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.6, 170.3, 170.3, 169.5, 164.0, 163.9, 155.0, 155.0, 138.6, 138.0, 137.7, 137.0, 135.8, 135.1, 131.8, 131.0, 129.5, 129.4, 129.2, 129.0, 128.7, 128.5, 128.5, 128.2, 127.9, 127.7, 127.6, 126.9, 126.6, 123.9, 120.7, 109.7, 109.5, 79.5, 73.5, 73.4, 71.1, 65.2, 62.1, 55.1, 55.1, 52.4, 52.0, 50.5, 49.6, 41.5, 36.1, 34.7, 28.5, 28.4, -2.3, -2.5, -3.9, -4.1; IR (neat/NaCl) 3432, 3064, 3030, 2977, 1745,1714, 1634, 1588, 1496, 1455, 1431, 1236, 1173, 1064, 1025, 844, 735, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 641 (68) MLi^+, 541 (50) M^+-Boc+H, 471 (12), 363 (7), 278 (4), 135 (100); HRMS m/z calculated for $[M+Li]^+$ 641.3234, found 641.3216 and 642.3246 (^{13}C).

2-((3-Benzyloxy-2-tert-butoxycarbonylaminopropionyl)-{[(2,4-dimethoxyphenyl)dimethylsilanyl]-methyl}-amino)-3-phenyl-propionic acid methyl ester (51c):

Compound **51c** was prepared using the procedure described above for the synthesis of **30a**. The crude product was chromatographed through a silica gel column using an eluant of 1:4 EtOAc/hexane as eluant. The column afforded 1.04 g (39%) of the desired product (yield was not optimized). ^{1}H NMR ($CDCl_3$/300 MHz) (two main rotamers with approximately 3:1 ratio were observed) δ 7.34-7.07 (m, 11H), 6.53-6.50 (m, 2H), 5.45 (d, J=8.4Hz, 0.75H), 5.26 (d, J=8.7Hz, 0.25H), 4.98 (br t, J=5.0Hz, 0.25H), 4.88-4.80 (m, 0.75H), 4.58 (s, 1.5H), 4.45 (d, J=11.7Hz, 0.25H), 4.32 (d, J=11.7Hz, 0.25H), 3.82, 3.81, 3.80 and 3.79 (s, s, s and s, 6H), 3.80-3.74 (m, 1H), 3.70, 3.66, 3.62 and 3.60 (s, s, s and s, 6H), 3.54-3.46 (m, 2H), 3.32-3.14 (m, 1.75H), 3.28 (A of AB, J_{AB}=16.5Hz, 0.75H), 2.93-2.80 (m, 0.75H), 2.26 (B of AB, J_{AB}=16.2Hz, 0.75H), 1.44 and 1.40 (s and s, 9H), 0.37, 0.36, 0.32, 0.29 and 0.24 (s, s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 169.8, 168.9, 164.9, 162.6, 154.5, 138.0, 137.5, 136.4, 136.2, 135.4, 135.0, 129.0, 128.8, 128.2, 128.0, 127.9, 127.7, 127.4, 127.2, 127.1, 126.3, 126.0, 114.6, 104.2, 97.3, 97.1, 78.9, 72.8, 70.5, 64.6, 54.8, 54.6, 54.5, 51.9, 51.5, 49.9, 41.0, 34.2, 27.9, 27.9, -2.8, -3.0, -4.5, -4.5; IR (neat/NaCl) 3334, 2978, 1744, 1712, 1659, 1497, 1454, 1240, 1168, 1089, 913, 738, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 671 (79) MLi^+, 571 (37) MLi^+-Boc+H, 471 (17), 165 (100); HRMS m/z calculated for $[M+Li]^+$ 671.3340, found 671.3329 and 672.3364 (^{13}C).

Procedure for the chemical amide oxidation with N-α-silylated peptide derivatives 51a-c using ceric ammonium nitrate):

In each case, a 100 mL oven-dried round bottom flask was charged with silylated dipeptide (0.5 mmol) and a mixture of anhydrous methanol and CH_2Cl_2 (25 mL). The best ratio of MeOH/CH_2Cl_2 for substrate **51b** and **51c** is 15% and 20% respectively. For the trimethylsilyl electroauxiliary case (**51a**) the overall yield of oxidation product **52** was never higher that 15% regardless of the conditions. In each case, the resulting solution was stirred at room temperature and ceric ammonium nitrate (1.1 g, 2 mmol) added under argon. The reaction mixture was then allowed to stir at room temperature (or 0 ^oC). In the case of **51b** the reaction was allowed to stand for roughly 90 min at room temp in order to afford a 72% yield of the methoxylated product **52**. In the case of **51c**, a room temperature reaction that stood for approximately 15 min led to a 70% yield of product while a 0 ^oC reaction allowed to stand for 35 min led to an 80% isolated yield of product. After each reaction was complete, it was quenched with 1 mL 30% Na_2SO_3 solution. The resulting mixture was stirred for 15 min until two clear layers were formed. The layers were then separated. The organic layer was washed with water (2 x 20 mL) and the combined aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column using 1:1 hexane/EtOAc as eluant to obtain the oxidation product **52**.

2-[(3-Benzyloxy-2-tert-butoxycarbonylamino-propionyl)-methoxymethyl-amino]-3-phenyl-propionic acid methyl ester (52):

^1H NMR ($CDCl_3$/300 MHz) δ 7.36-7.19 (m, 10H), 5.32 (d, J=8.7Hz, 1H), 4.87 (dd, J=14.7, 6.3Hz, 1H), 4.67 (d, J=11.4Hz, 1H), 4.53 (br s, 2H), 4.39 (dd, J=9.6, 5.4Hz, 1H), 4.13 (d, J=11.4Hz, 1H), 3.69 (s, 3H), 3.67-3.53 (m, 2H), 3.41 (dd, J=14.2, 5.2Hz, 1H), 3.23 (s, 3H), 3.17 (dd, J=9.4, 4.7Hz, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 171.5, 170.8, 155.2, 138.0, 137.7, 129.4, 128.7, 128.6, 128.5, 127.9, 127.7, 126.8, 80.0, 79.7, 73.4, 71.0, 60.8, 55.7, 52.4, 50.6, 35.2, 28.4; IR (neat/NaCl) 3432, 2954, 1744, 1712, 1639, 1597, 1495, 1455, 1248, 1209, 1157, 1088, 839, 749, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 507 (100) MLi^+, 451 (16) M^+-C_4H_8, 407 (26) MLi^+-Boc+H, 285 (5), 160 (63); HRMS m/z calculated for $[M+Li]^+$ 507.2683, found 507.2687 and 508.2728 (^{13}C).

2-({2-[2-((2-Benzyloxycarbonylaminoacetyl)-{[(2,4-dimethoxyphenyl)dimethylsilanyl]methyl}-amino)-3-phenylpropionylamino]acetyl}trimethylsilanylmethylamino)-3-phenylpropionic acid methyl ester (53):

The tetrapeptide substrate **53** was made from two of the dipeptide substrates made earlier using the coupling procedure described below. The carboxylic acid needed for the reaction was obtained by hydrolyzing Cbz-Gly-[N-CH_2-(2,4-dimethoxyphenyldimethylsilyl)]-Phe-OMe (made in a fashion identical to **49e** except for the use of Cbz protected glycine instead of the t-Boc protected glycine) using 2 equiv of LiOH in a 2:1 mixture of methanol to water. The reaction was stirred at 0 ^oC for 3 h and then room temperature for 12 h. The spectral data for Cbz-Gly-[N-CH_2-(2,4-dimethoxyphenyldimethylsilyl)]-Phe-OH were as follows: ^1H NMR ($CDCl_3$/ 300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.36-7.06 (m, 11H), 6.54-6.37 (m, 2H), 5.96-5.94 (m, 1H), 5.15-5.06 (m, 2H), 4.68 (s, 1.5H), 3.99-3.78 (m, 1H), 3.81, 3.80, 3.78, 3.77, 3.76 and 3.75 (s, s, s, s, s and s, 4H), 3.86-3.65 (m, 2H), 3.55 (s, 0.5H), 3.31-3.23 (m, 2H), 2.88 (d, J=17.0Hz, 1H), 2.09 (d, J=17.0Hz, 1H), 0.37, 0.34, 0.29 and 0.27 (s, s, s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 168.5, 165.4, 163.4, 161.0, 156.5, 141.0, 137.9, 136.8, 136.7, 136.6, 130.0, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.2, 128.1, 127.8, 126.9, 114.5, 106.3, 105.1, 100.6, 66.9, 65.8, 65.4, 56.1, 55.5, 55.4, 55.2, 43.3, 40.9, 34.4, -3.1, -3.4, -4.2; IR (neat/NaCl) 3416, 3031, 2956, 1727, 1648, 1604, 1494, 1455, 1288, 1256, 1210, 1152, 1051, 840, 752, 700cm^{-1}; LRFAB MS (relative intensity) m/z 577 (14) MLi^+, 539 (4) M^+-CH_3O, 427 (17) MLi^+-CbzNH, 390 (4), 334 (26), 194 (35), 165 (100), 121 (29); HRMS m/z calculated for $[M+Li]^+$ 571.2452, found 571.2455, and 572.2487(^{13}C).

The amine needed for the coupling reaction was obtained by deprotecting the t-Boc group from t-Boc-Gly-(N-CH2-TMS)-Phe-OMe **30a** by treatment with 5 mL (for 2 mmol of substrate) of a saturated aqueous HCl solution in 15 mL of ehtyl acetate. The reaction was allowed to stir at room temperature for 30 min. The amine was carried forward into the coupling reaction.

Once these two transformations were complete, a 250 mL oven-dried round bottom flask was charged with Cbz-Gly-[N-CH_2-(2,4-dimethoxyphenyl-dimethylsilyl)]-Phe-OH (310 mg, 0.55 mmol), H-Gly-(N-CH2-TMS)-Phe-OMe (480 mg, 1.5 mmol), HBTU (237 mg, 0.6 mmol), HOAT (10.4 mg, 0.075 mmol), 2,4,6-collidine (264 μL, 2.0 mmol) and DMF (20 mL). The resulting solution was allowed to stir at room temperature for 16 h and then quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column using a gradient elution from 1:3 EtOAc/hexane to 1:1.5 EtOAc/hexane. The column afforded 237 mg (49% for 2 steps of the deesterification and coupling reactions) of the desired product. ^{1}H NMR ($CDCl_3$/ 300 MHz) δ 7.38-7.00 (m, 16H), 6.47-6.39 (m, 2H), 5.85 (d, J=16.2Hz, 0.75H), 5.60 (s, 0.25H), 5.13 (s, 2H), 4.44-4.40 (m, 0.5H), 4.23-3.86 (m, 3.5H), 3.81, 3.79, 3.73 and 3.72 (s, s, s and s, 9H), 3.34-3.21 (m, 4H), 3.09-2.86 (m, 2H), 2.74 (dd, J=14.2, 6.4Hz, 0.5H), 2.70-2.51 (m, 1.5H), 2.41-2.27 (m, 1H), 1.82-1.72 (m, 1H), 0.37, 0.35, 0.32, 0.30, 0.29 and 0.28 (s, s, s, s, s and s, 6H), 0.04, 0.03 and 0.02 (s, s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.4, 170.2, 169.9, 169.6, 168.9, 167.0, 165.6, 163.4, 156.3, 138.1, 137.8, 137.6, 137.2, 136.7, 136.4, 136.2, 129.4, 129.3, 129.2, 128.9, 128.8, 128.7, 128.2, 128.1, 127.5, 127.9, 126.9, 105,1, 104.8, 97.9, 67.1, 66.9, 65.9, 65.7, 64.6, 61.3, 55.4, 55.2, 52.8, 52.4, 43.7, 42.1, 41.3, 40.9, 39.6, 36.0, 35.7, 34.6, 34.4, 30.5, -0.4, -1.8, -3.0; IR (neat/NaCl) 3423, 2952, 1743, 1648, 1495, 1250, 1152, 1052, 846, 700 cm^{-1}; LRFAB MS (relative intensity) m/z 875 (6) MLi^+, 313 (31), 160 (100); HRMS m/z calculated for $[M+Li]^+$ 875.4059, found 875.4053 and 876.4090 (^{13}C).

2-[(2-{2-[(2-Benzyloxycarbonylaminoacetyl)methoxymethylamino]-3-phenylpropionylamino}-acetyl)trimethylsilanylmethylamino]-3-phenylpropionic acid methyl ester (54):

A 100 mL oven-dried round bottom flask was charged with compound **53** (170 mg, 0.20 mmol) and a mixture of anhydrous methanol and CH_2Cl_2 (9.8 mL, 1:7 v/v). The resulting solution was stirred at room temperature (or -40 ^{o}C) and ceric ammonium nitrate (429 mg, 0.78 mmol) was added under argon. The reaction mixture was allowed to stir at room temperature for 25 min (or -40 ^{o}C for 95 min) and then quenched with 1 mL 30% Na_2SO_3 solution. The mixture was stirred for 5 min until two clear layers were formed. The layers were then separated. The organic layer was washed with water (2 x 10 mL) and the combined aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed through a silica gel column using a gradient elution from 1:2 EtOAc/hexane to 1:1 EtOAc/hexane to afford 93 mg (68%) of the desired product for the room temperature condition or 101 mg (74%) of the desired product for the -40 ^{o}C condition. ^{1}H NMR ($CDCl_3$/ 300 MHz) δ 7.70 (br s, 1H), 7.38-7.11 (m, 15H), 5.74-5.49 (m, 1H), 5.14 (d, J=3.3Hz, 2H), 4.87-4.78 (m, 0.67H), 4.72-4.62 (m, 0.33H), 4.58-4.43 (m, 1 H), 4.36-4.28 (m, 0.5H), 4.22-4.02 (m, 2H), 4.00-3.80 (m, 1.5H), 3.48-3.36 (m, 2H), 3.77, 3.75 and 3.73 (s, s and s, 3H), 3.48-2.98 (m, 3H), 3.33, 3.32, 3.30 and 3.29 (s, s, s and s, 3H), 2.76-2.53 (m, 1.67H), 2.51-2.28 (m, 0.33H), 1.82 (dd, J=16.5, 4.8Hz, 1H), 0.14, 0.06, 0.03 and 0.02 (s, s, s and s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 170.4, 170.2, 169.9, 169.6, 169.4, 167.7, 167.0, 156.4, 143.3, 138.0, 137.7, 137.6, 136.6, 136.2, 129.3, 129.2, 129.2, 128.9, 128.8, 128.7, 128.2, 128.2, 127.5, 127.0, 126.9, 116.6, 116.2, 78.4, 67.1, 64.6, 62.0, 61.4, 55.9, 52.8, 52.4, 42.9, 42.0, 41.3, 40.9, 36.0, 35.7, 35.2, 25.0, 34.8, 34.6, 30.5, 27.4, 20.2, -0.5, -1.2, -1.8; IR (neat/NaCl) 3423, 2952, 2280, 2119, 1742, 1649, 1526, 1454, 1248, 857, 701 cm^{-1}; LRFAB MS (relative intensity) m/z 711 (3) MLi^+, 313 (20), 160 (100); HRMS m/z calculated for $[M+Li]^+$ 711.3401, found 711.3385 and 712.3413 (^{13}C).

2-({[(4-Dimethylaminophenyl)dimethylsilanyl]methyl}amino)-3-phenylpropionic acid methyl ester (57):

A 250 mL round bottom flask containing (chloromethyl)[4-(dimethylamino)-phenyl]dimethylsilane[26] (1.89 g 8.29 mmol) was charged with KI (1.38 g, 8.29 mmol), diisopropylamine (4.7 mL, 33 mmol), and the hydrochloride salt of L-Phenylalanine methyl ester (3.58 g, 16.6 mmol) and subsequently filled with argon. Anhydrous DMF (50 mL) was then added and the resulting suspension was heated to 85 °C for 42 h. The reaction solution was next quenched with brine and extracted four times with diethyl ether. The ethereal extracts were combined and washed once with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was then chromatographed through a silica gel column using an eluant of 15%-20% EtOAc in hexane to afford 1.43 g (47%) of the desired product as an pale yellow oil. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.36 (ddd, J=9Hz, 2.2Hz, 2.2Hz, 2H), 7.28-7.10(m, 5H), 6.71 (ddd, J=8.7Hz, 2.0Hz, 2.0Hz, 2H), 3.60 (s, 3H), 3.428 (t, J=7.2Hz, 1H), 2.95 (s, 6H), 2.88 (dd, J=7.1Hz, 3.1Hz, 2H), 2.16 (dd, J=51Hz, 13Hz, 2H), 1.28 (broad s, 1H), 0.248 and 0.227 (s and s, 6H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 175.5, 151.5, 138.0, 135.1, 129.4, 128.6, 126.7, 122.7, 112.2, 67.0, 51.5, 40.6, 39.6, 37.9, -3.4; IR (NMR sample/NaCl) 3325, 3083, 3026, 2950, 2893, 2850, 2794, 1736, 1598, 1543, 1514, 1495, 1454, 1444, 1355, 1275, 1246, 1222, 1206, 1169, 1112, 1061, 1006, 983, 946, 913, 839, 805, 747, 700, 526 cm^{-1}; LRFAB MS (relative intensity) m/z M^+, 370 (2), M^+-benzyl, 279 (8), SilylAryl$^+$, 178 (100); HRMS m/z calculated for M^+ 370.2077, found 370.2090, m/z calculated for M^++1 372.2110, found 371.2091

2-((2-tert-Butoxycarbonylaminoacetyl)-{[(4-dimethylaminophenyl)dimethylsilanyl]methyl}-amino)-3-phenylpropionic acid methyl ester (58):

A 250 mL round bottom flask was charged with N-(tert-butoxycarbonyl)glycine (0.085 g, 0.49 mmol), NMM (55 uL, 0.49 mmol), isobutylchloroformate (85 uL, 0.65 mmol) and CH_2Cl_2 (30 mL). The resulting solution was allowed to stir at 0 °C for 120 min. The N-α-silylated phenylalanine methyl ester (0.32 mmol) was dissolved in CH_2Cl_2 (10 mL) and cannulated into the reaction mixture above. An additional 20 mL of CH_2Cl_2 was used to ensure the complete transfer. The mixture was then warmed to room temperature and stirred for 12 h. The reaction was quenched with water and the layers were separated. Then the organic layer was washed with water and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and the crude product chromatographed through a silica gel column using an eluant of 10% EtOAc in hexane to afford 125 mg (73%) of the desired product as an oil. ^{1}H NMR (CD_3CN/300 MHz) (two main rotamers with approximately 2:1 ratio observed) δ 7.41 (d, J=8.7Hz, 1H), 7.34-7.19 (m, 5H), 7.11 (d, J=8.1Hz, 1H), 6.75 (d, J=8.4Hz, 1H), 6.74 (d, J=8.7Hz, 1H), 5.42 and 5.32 (br s and br s, 1H), 4.68-4.60 (m, 0.3H), 3.95-3.52 (m, 3H), 3.69 and 3.63 (s and s, 3H), 3.29-3.00 (m, 2H), 3.36-3.20 (m, 2H), 2.93 (s, 6H), 2.80 (d, J=14.7Hz, 1H), 2.66 (d, J=14.4Hz, 1H), 1.44, and 1.40 (s and s, 9H), 0.34, 0.27, 0.24, 0.20 (s, s, s and s, 6H); ^{13}C NMR (CD_3CN/ 75 MHz) δ 171.6, 170.3, 169.3, 153.0, 152.6, 139.8, 138.5, 136.2, 130.8, 129.8, 128.3, 127.8, 122.1, 113.3, 80.1, 72.1, 65.1, 62.5, 53.5, 52.7, 43.7, 43.0, 42.1, 41.7, 40.8, 36.8, 36.1, 35.4, 29.0, 19.6, -1.0, -1.3, -2.6, -3.6, IR (NMR sample/NaCl) 3418, 3084, 3063, 2953, 2809, 1743, 1715, 1648, 1597, 1514, 1496, 1465, 1392, 1365, 1276, 1248, 1228, 1170, 1111, 1082, 1052, 1029, 1005, 946, 868, 840, 808, 754, 703, 636 cm^{-1}.

Solid Phase Peptide Synthesis of Compounds 59 and 60:

A 100 mL oven-dried round bottom flask was charged with Merrifield resin (2.0 g, 9.4 mmol), 2-mercaptoethanol (5.27 mL, 75.2 mmol), potassium carbonate (2.6 g, 19 mmol) and dry DMF (44 mL). The resulting suspension was stirred at 60 °C for 4 h and then at room temperature for 20 h. The reaction mixture was then filtered through a glass filter. The resin was washed with H_2O (5x), DMF (2x), H_2O (2x), MeOH (2x), DCM (2x), MeOH- H_2O (1:1) (2x) and DCM (5x) and dried *in vacuo* to afford ~2 g of white resin **A**.

To the suspension of the resin **A** (~2 g) in dichloromethane (110 mL) was added MCPBA (13.1 g, 77%, 58.4 mmol) in portions at 0 °C. When the addition was complete, the resulting solution was allowed to stir for 20 h at room temperature and then filtered through a glass filter. The resin was washed with DCM (2x), MeOH (5x) and DCM (5x) and dried *in vacuo* to afford ~2.5 g of white resin **B**.

To a 100 mL oven-dried round bottom flask was added the Cbz-Gly-[N-CH_2-(2,4-dimethoxyphenyldimethylsilyl)]-Phe-OH dipeptide acid (1.4 mmol) made above for the synthesis of **53**, HBTU (586 mg, 1.5 mmol), HOAT (25.5 mg, 0.18 mmol), 2,4,6-collidine (330 μL, 2.5 mmol) and DMF (24 mL). The resulting solution was stirred for 15 min and the resin **B** (186 mg, ~0.7 mmol) added. The reaction mixture was allowed to stir at room temperature for 18 h and then filtered through a glass filter. The resin was washed with DCM (2x), DMF (5x) and DCM (5x) and dried *in vacuo* to afford yellow white resin **C**.

The resin **C** was suspended in 20 mL of benzene in a 100 mL round bottom flask. A mixture of Ac_2O and HCOOH (654 μL/1.29 mL, 9:20, w/w) was then added to the above suspension. The reaction mixture was allowed to stir at room temperature for 16 h and then filtered through a glass filter. The resin was washed with MeOH (3x), DMF (3x) and DCM (5x) and dried *in vacuo* to afford 260 mg yellow white resin **D** (**59**).

The resin **D** (107 mg, ~0.045 mmol) was suspended in a mixture of CH_2Cl_2 and MeOH (1.9 mL/0.34 mL, 7:1). The resulting suspension was stirred and CAN (107 mg, 0.20 mmol) added under argon. The reaction mixture was allowed to stir at room temperature for 40 min and then filtered through a glass filter. The resin was washed with MeOH (3x), DMF (3x) and DCM (5x) and dried *in vacuo* to afford 94 mg yellow white resin **E**.

To a 100 mL oven-dried round bottom flask was added resin **E** (94 mg), allylsilane (144 μL, 0.90 mmol) and ether (2 mL). The resulting suspension was stirred and $BF_3{\cdot}Et_2O$ (2 μL, 0.016 mmol) added under argon. The reaction mixture was allowed to stir at room temperature for 6 h and then filtered through a glass filter. The resin was washed with MeOH (3x), CH_2Cl_2 (5x) and dried *in vacuo* to afford a yellow white resin. This procedure was repeated for one more time and 96 mg yellow white resin **F** was obtained (**60**).

The resin **F** was treated with a mixture of NaOH solution (4N, 1 mL), dioxane (30 mL) and water (9 mL) in a 100 mL round bottom flask. The resulting suspension was allowed to stir at room temperature for 1 min and quickly filtered through a glass filter into a HCl solution (1N, 4 mL). The resin was washed with ether (2x), EtOAc (2x) and DCM (5x). The filtrate was concentrated under reduced pressure. The obtained crude product was dissolved in EtOAc and washed with sat. sodium carbonate solution twice. The aqueous solution was combined and acidified with HCl solution (1N) until the pH=3.0. The acidic solution was then extracted with ether three times and the combined ether solution was dried and concentrated *in vacuo.* The obtained crude product (12.7 mg) was clean by ^{1}H NMR. The crude product can also be chromatographed through a silica gel column. The spectral data are given below.

For comparison, a portion of resin **D** is used for the cleavage directly. Similar procedure for the cleavage of resin **F** was used. 57 mg resin **D** afforded 14 mg the cleaved silylated dipeptide acid indicating that the oxidation, allylsilane additions steps went in a combined 66% yield.

2-[(2-Benzyloxycarbonylaminoacetyl)but-3-enylamino]-3-phenylpropionic acid:
^{1}H NMR ($CDCl_3$/ 300 MHz) δ 7.41-7.12 (m, 10H), 6.16 and 6.00 (br s and br s, 1H), 5.84-5.54 (m, 1H), 5.09-4.96 (m, 3.5H), 4.70 (br s, 0.5H), 4.22-4.03 (m, 1H), 3.96-3.78 (m, 2H), 3.56-3.34 (m, 2H), 3.28-3.05 (m, 1H), 2.84-2.75 (m, 0.25H), 2.79-2.33 (m, 1.75H), 2.19-2.04 (m, 1H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 173.6, 169.2, 164.7, 156.6, 137.9, 136.6, 134.4, 134.2, 133.9, 130.1, 129.3, 129.0, 128.9, 128.6, 128.2, 128.1, 127.8, 127.2, 127.0, 118.0, 118.0, 67.1, 63.8, 49.3, 44.2, 44.1, 42.9, 37.3, 34.5, 32.5, 32.3, 31.8; IR (neat/NaCl) 3416, 3064, 3030, 2939, 1724, 1658, 1497, 1454, 1252, 1215, 1051, 1000, 920, 736, 701 cm^{-1}; LRFAB MS (relative intensity) m/z 423 (36) MLi^+, 315 (22) M^+-$PhCH_2O$, 91 (100); HRMS m/z calculated for $[M+2Li-H]^+$ 423.2084, found 423.2067, and 424.2100(^{13}C).