Synthesis of Anisolylated Aspartyl and Glutamyl Tripeptides

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A process has been developed for transforming the β-carboxyl of aspartate and the γ-carboxyl of glutamate into anisolyl ketones. These ketones are occasional byproducts in peptide synthesis, resulting from deprotection or resin-removal processes in the presence of anisole as a scavenger. The ketone amino acids have been incorporated in a tripeptide by coupling with CBMIT. During peptide bond formation the keto group of the glutamyl residue required protection, which was provided as the ethylene dithioketal.

Introduction

The potential importance of artifacts produced during peptide synthesis as a result of deprotection and resin-removal protocols has been dramatically demonstrated in a recent example involving anti-inflammatory undecapeptides.[1] In that case, a byproduct formed by acylation of the anisole scavenger by the γ-glutamyl carboxyl led to a component more biologically active than the parent peptide.

The structure of this component with enhanced potency was established by comparison of NMR spectra with those of authentic samples of 2-amino-5-(methoxyphenyl)-5-oxopentanoates (γ-anisolylated glutamates, AnGlu[2]). This comparison also established that the anisolylated component was approximately 94% para and 6% ortho isomer.

To pursue these findings further, we have developed methods for synthesizing tripeptides containing either ortho or para 2-amino-4-(methoxyphenyl)-4-oxobutanoates (β-anisolylated aspartates, AnAsp) or AnGlu residues. Our examples have central AnAsp or AnGlu residues flanked by isoleucine at the carboxy terminus and methionine at the amino terminus. They were chosen for subsequent elaboration into anti-inflammatory peptides[3] and to provide a modest degree of generality for the synthesis of such ketone-containing peptides.

Results and Discussion

Preparation of β-Anisolylated Aspartates. There has been a recent flurry of interest in the synthesis of oxo-α-amino acids.[4] We now present another method which is quite efficient and may have broad generality. The differentially protected aspartate **2** (Scheme 1), readily prepared from aspartic acid,[5] was converted to the corresponding aryl ketone via the isoxazolidide **3**.[6] Trial experiments showed the anisolyllithium to be far superior to the Grignard reagent.

With *o*-anisolyllithium, prepared from *o*-bromoanisole, the reaction was straightforward. The case of the para isomer, however, was more complex. The complication arose from ortho metalation of *p*-bromoanisole by the initially formed *p*-anisolyllithium when the reaction was carried out in ether or pentane. Thus the solution contained two aryllithium reagents: *p*-anisolyllithium and (5-bromo-2-methoxyphenyl)lithium. The major product, *p*-anisolyllithium, then could be purified by precipitation with hexane and re-solution for ketone formation.[7] These side products were minimized when halogen−metal exchange was performed in THF. For both isomers of ketones **4** the yields were good: 73% para, 76% ortho. In preparation for peptide formation, both *tert*-butyl groups were removed and the amino reprotected as the *N*-BOC acid **5**.

Preparation of Anisolylated Aspartyl Tripeptides. The preparation of the tripeptides Met-AnAsp-Ile is shown in Scheme 2. Coupling proceeded from the amino terminus using the carbonylbis(3-methylimidazolium triflate) (CBMIT) reagent.[8] For coupling to Ile-OCH_3, the yields of dipeptides **6** were 72% and 80% for the ortho and para isomers, respectively, and 86% (ortho) and 92% (para) in the coupling of Met to **6** to form tripeptides **8**.

Peptide formation was uneventful, and no changes in the normal procedures were required to accommodate the keto function. For flexibility in continuing peptide synthesis, the tripeptide was made available as the *N*-BOC carboxylic acid **9** and the amine hydrochloride methyl ester **10**.

Preparation and Protection of γ-Anisolylated Glutamate. Both the ortho and para isomers of the γ-anisolylated glutamates **11** were prepared in good yield (65%) from the γ-carboxylic acid following the sequence described for the aspartate analogue.[1]

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) Thomas, H. A.; Ling, N; Wei, E. T.; Berrée, F.; Cobas, A.; Rapoport, H. *J. Pharmacol. Expt. Ther.* **1993**, *267*, 1321. Other examples of anisolyl ketone formation are cited in this reference.

(2) The prefix An will be used to designate the anisolyl ketone formed from anisole and the γ-carboxyl of glutamic acid and the β-carboxyl of aspartic acid, thus AnGlu and AnAsp. A superscript will be used to designate ortho or para regiochemistry, e.g., An^{p}Asp, An^o-Glu.

(3) Work in progress by H. A. Thomas and E. T. Wei. Direct synthesis of pure para and ortho isomers of the anisolylated derivatives may provide information on the relative contribution of these two isomers to activity.

(4) Some selected references: (a) Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438. (b) Ko, K.-Y.; Lee, K.-I.; Kim, W.-J. *Tetrahedron Lett.* **1992**, *33*, 6651. (c) Ho, T. L.; Gopalan, B.; Nestor, J. J., Jr. *J. Org. Chem.* **1986**, *51*, 2405. (d) Ezquerra, J.; de Mendoza, J.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *33*, 5589. (e) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397. (f) Burger, K.; Rudolph, M.; Neuhauser, H. *Liebigs Ann. Chem.* **1991**, 1365. (g) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Smith, M. L.; Russel, A. T. *Synlett* **1993**, 51.

(5) Bergmeier, S. C.; Cobás, A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.

(6) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.

(7) (a) Fraenkel, G.; Dayagi, S.; Kobayashi, S. *J. Phys. Chem.* **1968**, *72*, 953. (b) Glaze, W. H.; Ranade, A. C. *J. Org. Chem.* **1971**, *36*, 3331. (c) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106. (d) Gilman, H.; Jacoby, A. L. *J. Org. Chem.* **1938**, *3*, 108.

(8) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4859.

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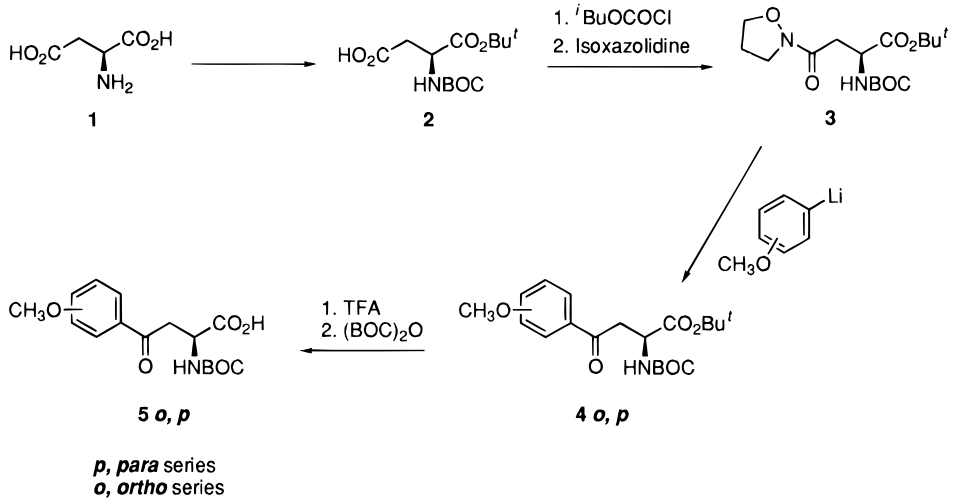
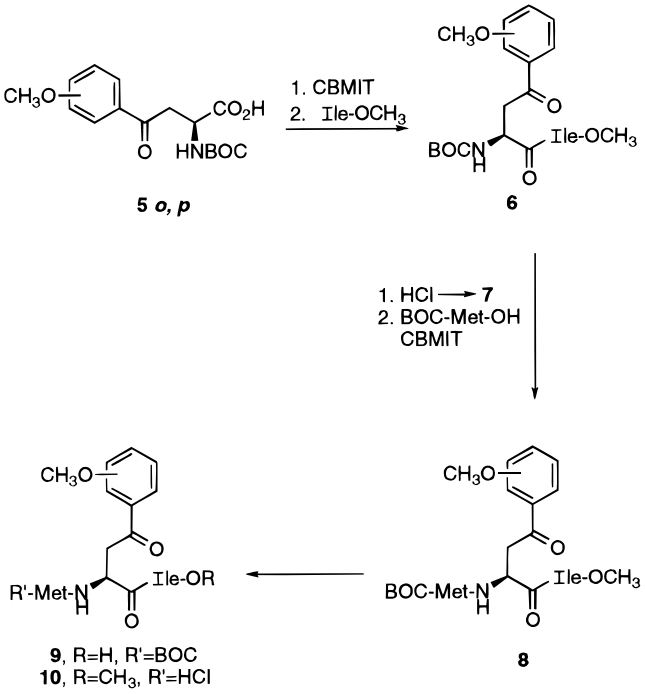
Scheme 1. Anisolylated Aspartate



Scheme 2. Preparation of Anisolylated Aspartyl Tripeptides



A complication in the glutamate series, however, immediately appeared because of the juxtaposition of the ketone and amine, resulting in intramolecular pyrroline formation. Protection of the keto group was required, and various possibilities were considered under the constraints of subsequent utilization in peptide formation. Alcohol formation would adequately avoid pyrroline production but was not pursued because of diastereomers and the necessity to protect and reoxidize, which would be incompatible with many amino acid residues in a peptide.

The protecting regimen of choice appeared to be ketal protection, which is presented in Scheme 3. Normal, acid-catalyzed dimethyl or ethylene ketal formation was poor, but 2-methoxy-1,3-dioxolane with catalytic triflic acid[9] gave 75−79% yields of the ethylene ketals **12**. Problems then arose in utilizing **12** in peptide synthesize. Clean *N*-BOC or *tert*-butyl ester cleavage,[10] leaving the ketal intact, could not be achieved. Any acid treatment sufficient to remove the *N*-BOC immediately led to *in situ* formation of pyrroline **17**.

An obvious solution was to protect the ketone as the much more acid stable dithioketal, provided that compatible conditions could be found for subsequent regeneration of the ketone. Dithioketal was readily formed by exchange with 1,2-ethanedithiol, catalyzed by $BF_3 \cdot Et_2O$. Thus the thioketal was available as the *N*-BOC derivative **13** or the NH_2 compound **14**.[10b] For application in peptide synthesis, both the *N*-BOC and *tert*-butyl ester were acid-cleaved, giving **15** from which the *N*-BOC acid **16** was prepared.

To develop conditions for cleavage of the dithioketal, applicable after incorporation into our tripeptide, we used **13** as the substrate. When applied to **13**, a series of recently reported promising methods all failed: photochemical,[11] reflux in DMSO,[12] exchange catalyzed by TMSOTf,[13] 1-fluoro-2,4,6-trimethylpyridinium triflate.[14] From all reactions, **13** was recovered in high yield unchanged. A method that was quite effective was $AgNO_2/I_2$,[15] but this reagent cannot be used in the presence of methionine residues, which are oxidized to sulfoxides.

A variation[16] on an older method was finally found to satisfy all the requirements. Thus treatment of **13** at room temperature with $Hg(ClO_4)_2/CHCl_3/CH_3OH/H_2O$ gave an almost quantitative yield of **11**. Furthermore, methionine and its *N*-BOC *tert*-butyl ester were recovered unchanged from a similar treatment.

Preparation of Anisolylated Glutamyl Tripeptides. With the ethylene dithioketal *N*-BOC anisolylated glutamic acids **16** at hand, we proceeded to prepare the target tripeptide as shown in Scheme 4. Coupling with

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(11) Epling, G. A.; Wang, Q. *Tetrahedron Lett.* **1992**, *33*, 5909; *Synlett* **1992**, 335.

(12) Rao, C. S.; Chandrasekharam, M.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1992**, *33*, 8163.

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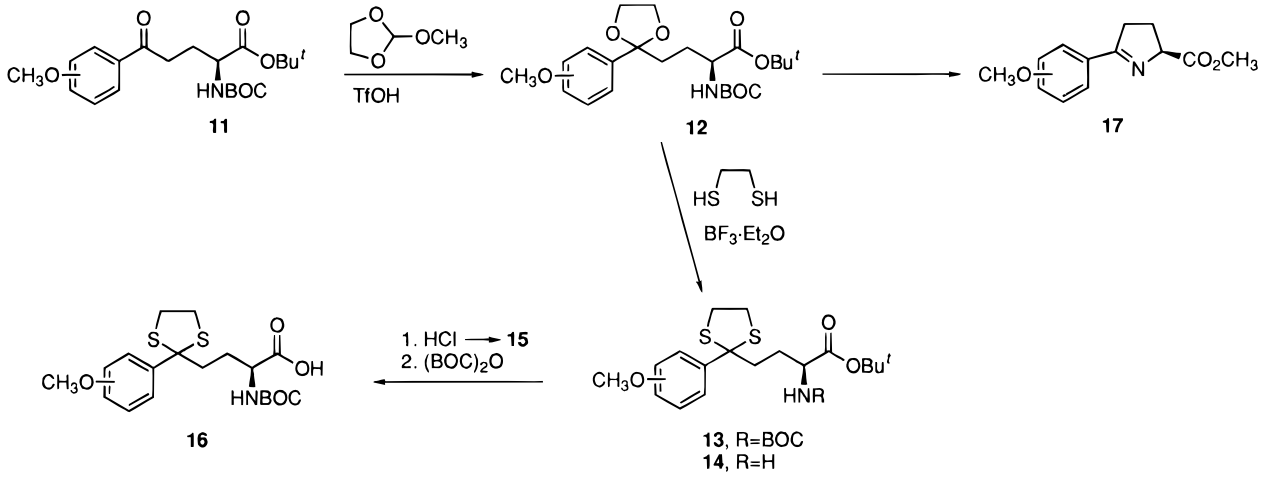
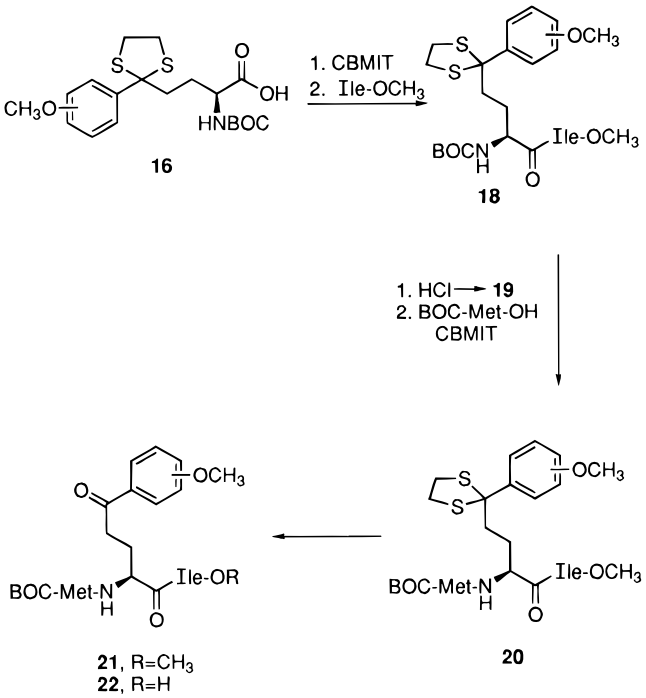
(16) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393.

Scheme 3. Ketals of Anisolylated Glutamate



Scheme 4. Preparation of Anisolylated Glutamyl Tripeptides



isoleucine methyl ester mediated by CBMIT gave the peptides **18**. Following removal of the BOC group from **18**, the amine **19** formed was coupled with *N*-BOC methionine resulting in ethylene dithioketal tripeptides **20**. In all the couplings the yields were about 70%.

Dethioketalization then was readily effected in 85−88% yield using the $Hg(ClO_4)_2$ reagent. For possible use in extended peptide synthesis, the keto tripeptide *N*-BOC methyl ester **21** also was converted to the carboxylic acid **22**.

The protocols thus developed should be applicable to a wide variety of keto peptides.

Experimental Section

General. NMR spectra were obtained in $CDCl_3$ unless otherwise noted and are referenced to internal tetramethylsilane; coupling constants are reported in hertz. Chromatography was carried out using silica gel 230−400 mesh. TLC analysis were performed on aluminum-backed silica gel F_{250}, 0.2 mm plates. All reactions were conducted under a nitrogen or argon atmosphere. THF and ether were distilled from sodium−benzophenone; pentane was distilled from lithium aluminum hydride; nitromethane, DMF, *N*-methylmorpholine, and triethylamine were distilled from calcium hydride and stored over 4A molecular sieves; and methanol was distilled from Mg. Final solutions before rotary evaporation were dried over Na_2SO_4. The isoleucine methyl ester was freed immediately before use from its hydrochloride.[17]

α-*tert*-Butyl *N*-(*tert*-Butoxycarbonyl)-L-aspartate *β*-Isoxazolidide (3). *N*-Methylmorpholine (4.0 mL, 36.2 mmol) was added to a solution of α-*tert*-butyl *N*-(*tert*-butoxycarbonyl)-L-aspartate (**2**, 10.5 g, 36.1 mmol)[4] in THF (200 mL) at −20 °C, and after 1 min isobutyl chloroformate (4.7 mL, 36.2 mmol) was added. The mixture was stirred for 5 min and then a suspension of isoxazolidine hydrochoride (4.36 g, 39.4 mmol) and triethylamine (5.5 mL, 39.8 mmol) in DMF (100 mL) was added. The reaction mixture was stirred for 15 min at −15 °C and 2.5 h at rt and then was partitioned between ethyl acetate (400 mL) and 1 M H_3PO_4 (300 mL). The aqueous layer was extrated with ethyl acetate (200 mL), and the combined organic layer was washed with saturated $NaHCO_3$ (2 × 300 mL), dried, and evaporated to give an oil which was chromatographed (ethyl acetate/hexane 1/1) to give **3** (11.8 g, 95%) as an oil: ^{1}H NMR δ 5.61 (d, J = 8.7, 1H), 4.42 (m, 1H), 3.94 (t, J = 6.8, 2H), 3.66 (t, J = 6.5, 2H), 3.08 (dd, J = 4.2, 6.9, 1H), 2.83 (dd, J = 4.2, 6.9, 1H), 2.29 (m, 2H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR δ 170.4, 170.1, 155.5, 81.6, 79.3, 69.1, 50.2, 42.9, 35.0, 28.2, 27.7, 27.3; $[\alpha]^{20}_D$ +15.7° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}N_2O_6$: C, 55.8; H, 8.2; N, 8.1. Found: C, 55.4; H, 7.9; N, 8.0.

Preparation of *p*-Anisolyllithium. *n*-Butyllithium (31.9 mL, 2.35 M in hexane, 75 mmol) was added dropwise over a period of 40 min to a solution of *p*-bromoanisole (9.5 mL, 75 mmol) in THF (60 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C, and then stirring was continued as pentane (250 mL) was added dropwise. The precipitate was allowed to settle, and the solvent was cannulated off. Pentane (150 mL) was again added dropwise and then cannulated off as a wash. After being washed one more time with pentane, the precipitate was allowed to reach rt, ether (90 mL) was added, and the resulting solution was found to be 0.54 M by titration with diphenylacetic acid. The yield of *p*-anisolyllithium was about 70%. An aliquot of this solution was quenched with H_2O, extracted with ether, dried, and evaporated to give anisole, containing <2% (limit of detection) of 4-bromoanisole as determined by ^{1}H NMR (doping assay).

***tert*-Butyl (*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-(4-methoxyphenyl)-4-oxobutanoate (4*p*).** To a solution of the isoxazolidide **3** (6.16 g, 17.9 mmol) in ether (100 mL) at −20 °C was added dropwise a solution of *p*-anisolyllithium in ether (75 mL, 0.54 M, 40.5 mmol, 225 mol %) over a period of 20 min, and the reaction mixture was stirred for 45 min. After the addition of NaH_2PO_4 (1 M, 100 mL) and vigorous stirring for 2 min, the mixture was extracted with EtOAc (2 × 100

(17) Toniolo, C. *Biopolymers* **1971**, *10*, 1707.

mL), dried, evaporated, and chromatograped (hexane/EtOAc, 4/1), to give **4*p*** (4.92 g, 73%) as an oil which solidified by standing: mp 92 °C; ^{1}H NMR δ 7.91 (m, 2H), 6.92 (m, 2H), 5.59 (d, J = 8.4, 1H), 4.52 (m, 1H), 3.85 (s, 3H), 3.61 (dd, J = 4.25, 17.6, 1H), 3.37 (dd, J = 4.2, 17.6, 1H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C NMR δ 196.3, 170.5, 163.8, 155.7, 130.4, 129.5, 113.8, 81.9, 79.6, 55.5, 50.4, 40.6, 28.3, 27.8; $[\alpha]^{20}_D$ +24.3° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.3; H, 7.7; N, 3.7. Found: C, 62.9; H, 7.6; N, 4.0.

tert*-Butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(2-methoxyphenyl)-4-oxobutanoate (4*o*)** was prepared as described for the corresponding para isomer, using *o*-anisolyllithium.[7b] From 12g of **3**, after chromatography (hexane/EtOAc, 4/1), was isolated 10.0 g, 76% yield, of **4*o as an oil: ^{1}H NMR δ 7.77 (d, J = 7.7, 1H), 7.48 (m, 1H), 6.99 (m, 2H), 5.57 (d, J = 8.6, 1H), 4.50 (m, 1H), 3.92 (s, 3H), 3.67 (dd, J = 4.5, 18.5, 1H), 3.47 (dd, J = 3.9, 18.5, 1H), 1.44 (s, 9H), 1.43 (s, 9H); ^{13}C NMR δ 199.0, 170.8, 159.1, 155.7, 134.2, 130.5, 126.7, 120.6, 111.5, 81.6, 79.4, 55.5, 50.5, 46.5, 28.3, 27.9; $[\alpha]^{20}_D$ +25.5° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.3; H, 7.7; N, 3.7. Found: C, 63.1; H, 7.8; N, 3.7.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-(4-methoxyphenyl)-4-oxobutanoic Acid (BOC-An^{p}Asp, 5*p*). A solution of ketone **4*p*** (4.92 g, 13.0 mmol) in TFA (100 mL) was stirred for 2.5 h. The solvent was evaporated at rt, methanol (2 × 150 mL) was added and evaporated twice, and then ether (100 mL) was added and evaporated to give the intermediate **(*S*)-2-amino-4-(4-methoxyphenyl)-4-oxobutanoic acid trifluoroacetate** as a yellow solid: ^{1}H NMR δ (CD_3OD) δ 8.02 (m, 2H), 7.04 (m, 2H), 4.40 (t, J = 5.3, 1H), 3.88 (s, 3H), 3.70 (d, J = 5.3, 2H); ^{13}C NMR (CD_3OD) δ 196.3, 171.6, 165.8, 131.7, 129.6, 115.0, 56.1, 50.1, 38.9.

This salt was dissolved in THF/H_2O (1/1, 250 mL), and BOC_2O (5.66 g, 25.9 mmol) was added followed by triethylamine (5.42 mL, 38.91 mmol). The reaction was stirred for 2 h at rt and then was partitioned between H_2O (150 mL) and ethyl acetate (150 mL). The aqueous layer was acidified with 1 M H_3PO_4 to pH 2 and extracted with ethyl acetate (2 × 100mL). The residue left after drying and evaporating the ethyl acetate was chromatograped (hexane/ethyl acetate/acetic acid, 20/79/1) to give an oil. Removal of the remaining HOAc by azeotropic distillation with benzene gave a foam which was triturated with hexane to give 3.36 g (80%) of **5*p*** as a white solid: mp 114−117 °C; ^{1}H NMR δ 7.91 (m, 2H), 6.92 (m, 2H), 5,67 (d, J = 8.4, 1H), 4.70 (m, 1H), 3.85 (s, 3H), 3.71 (dd, J = 4.4, 18.0, 1H), 3.45 (dd, J = 4.4, 18.0, 1H), 1.41 (s, 9H); ^{13}C NMR δ 197.5, 175.8, 164.1, 155.7, 130.6, 129.1, 113.9, 80.2, 55.5, 49.5, 40.5, 28.28; $[\alpha]^{20}_D$ +83.3° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.4; H, 6.5; N, 4.3. Found: C, 59.1; H, 6.5; N, 4.3.

(*S*)-2-((*tert*-Butoxcarbonyl)amino)-4-(2-(methoxyphenyl)-4-oxobutanoic acid (BOC-An^{o}Asp (5*o*) was prepared as described for the para isomer. The intermediate **(*S*)-2-amino-4-(2-methoxyphenyl)-4-oxobutanoic acid trifluoroacetate** displayed the following spectroscopic data: ^{1}H NMR (CD_3OD) δ 7.81 (m, 1H), 7.54 (m, 1H), 7.09 (d, J = 8.4, 1H), 6.99 (m, 1H), 4.39 (t, J = 5.1, 1H), 3.91 (s, 3H), 3.75 (d, J = 5.1, 2H); ^{13}C NMR (CD_3OD) δ 198.2, 171.5, 161.2, 136.5, 131.6, 126.5, 121.7, 113,3, 56.2, 50.2, 44.7.

The *N*-BOC amino acid **5*o*** was isolated in 92% yield: mp 113−117 °C; ^{1}H NMR δ 7.82 (d, J = 7.7, 1H), 7.49 (m, 1H), 6.97 (m, 2H), 5.61 (m, 1H), 4.66 (m, 1H), 3.92 (s, 3H), 3.72−3.49 (m, 2H), 1.42 (s, 9H); ^{13}C NMR δ 198.8, 176.8, 159.5, 155.7, 134.7, 130.9, 126.1, 120.7, 111.7, 80.0, 55.5, 49.8, 46.3, 28.3; $[\alpha]^{20}_D$ +59.7° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.4; H, 6.5; N, 4.3. Found: C, 59.1; H, 6.5; N, 4.3.

BOC-An^{p}Asp-Ile-OCH$_3$ (6*p*). Methyl triflate (0.87 mL, 7.65 mmol) was added dropwise (1 min) to a solution of CDI (0.62 g, 3.82 mmol) in nitromethane (17 mL) at 0 °C. The solution was stirred for 5 min, and a solution of BOC-An^{p}Asp (**5*p*** 1.23 g, 3.82 mmol) and *N*-methylimidazole (30.5 μL, 0.38 mmol) in THF/$MeNO_2$ (12 mL, 1:1) was added (via cannula, 3 min). The mixture was stirred for 5 min, and a solution of isoleucine methyl ester (1.28 g, 8.8 mmol) and *N*-methylmorpholine (0.84 mL, 7.64 mmol) in THF (4 mL) was added (via cannula). The reaction mixture was stirred for 2 h at rt, H_2O (3 mL) was added, and the mixture was stirred for 1 min and partitioned between saturated $NaHCO_3$ (30 mL) and ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (30 mL), the combined organic layers were dried and evaporated, and the residue was chromatographed (EtOAc/Hexane, 1/1) to give 1.37 g (80%) of dipeptide **6*p*** as an oil, which was crystallized from $CHCl_3$/hexane: mp 114−117 °C; ^{1}H NMR δ 7.93 (d, J = 8.9, 2H), 7.19 (br d, J = 8.2, 1H), 6.93 (d, J = 8.9, 2H), 5.89−5.86 (m, 1H), 4.71 (m, 1H), 4.52 (dd, J = 8.7, 4.9, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 3.25 (dd, J = 17.9, 6.4, 1H), 1.95−1.89 (m, 1H), 1.46 (s, 9H), 1.46−1.40 (m, 1H), 1.25−1.19 (m, 1H), 0.94−0.90 (m, 6H); ^{13}C NMR δ 197.5, 171.8, 171.0, 163.8, 155.5, 130.5, 129.3, 113.7, 80.3, 56.7, 55.5, 52.0, 50.5, 39.9, 37.7, 28.3, 25.0, 15.5, 12.0; $[\alpha]^{25}_D$ +80.9° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}N_2O_7$: C, 61.3; H, 7.6; N, 6.2. Found: C, 61.4; H, 7.7; N, 6.2.

BOC-An^{o}Asp-Ile-OCH$_3$ (6*o*) was prepared as described for the para isomer. From 3.00 g (9.3 mmol) of **5*o*** was obtained 3.00 g (72%) of **6*o*** as an oil: ^{1}H NMR δ 7.80−7.77 (m, 1H), 7.51−7.45 (m, 1H), 7.16−7.13 (m, 1H), 7.02−6.94 (m, 2H), 5.80−5.78 (m, 1H), 4.68−4.64 (m, 1H), 4.53 (dd, J = 8.7, 4.9, 1H), 3.90 (s, 3H), 3.77−3.70 (m, 1H), 3.67 (s, 3H), 3.37 (dd, J = 18.7, 6.3, 1H), 1.50−1.39 (m, 1H), 1.46 (s, 9H), 1.28−1.20 (m, 1H), 0.95−0.87 (m, 6H); ^{13}C NMR δ 200.2, 171.9, 171.2, 159.1, 155.5, 134.4, 130.6, 126.7, 120.6, 111.5, 80.1, 56.7, 55.5, 52.0, 50.8, 45.8, 37.7, 28.3, 24.9, 15.5, 11.6; $[\alpha]^{25}_D$ +75.5° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}N_2O_7$: C, 61.3; H, 7.6; N, 6.2. Found: C, 61.0; H, 7.6; N, 6.1.

HCl·An^{p}Asp-Ile-OCH$_3$ (7*p*). Acetyl chloride (3.2 mL, 45 mmol) was added dropwise to a solution of methanol (1.8 mL, 45 mmol) in ethyl acetate (10 mL) at 0 °C, and the solution was stirred for 15 min at 0 °C and 1 h at rt. This solution was added dropwise to a solution of BOC-An^{p}Asp-Ile-OCH$_3$ (**6*p***, 1.01 g, 2.24 mmol) in ethyl acetate (10 mL) at rt, and the reaction mixture was stirred for 2 h and then evaporated at rt. The residue was dissolved in a small amount of methanol, and ether was added to afford 800 mg (92%) of **7*p*** as a white solid: mp 155−157 °C; ^{1}H NMR (CD_3OD) δ 8.04−8.01 (m, 2H), 7.05 (dd, J = 7.1, 1.8, 2H), 4.47 (m, 2H), 3.89 (s, 3H), 3.74 (m, 1H), 3.70 (s, 3H), 3.69−3.52 (m, 1H), 1.93 (m, 1H), 1.47 (m, 1H), 1.26 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (CD_3OD) δ 195.8, 173.2, 170.3, 116.0, 131.7, 129.8, 115.1, 58.6, 56.2, 52.6, 50.3, 40.4, 38.2, 26.3, 16.1, 11.9; $[\alpha]^{25}_D$ −11.2° (*c* 1, MeOH). Anal. Calcd for $C_{18}H_{27}N_2O_5Cl$: C, 55.9; H, 7.0; N, 7.2. Found: C, 56.1; H, 7.2; N, 7.2.

HCl·An^{o}Asp-Ile-OCH$_3$(7*o*) was prepared as described for the para isomer. From 1.81 g, 4.02 mmol of **6*o*** was obtained 1.33 g (86%) of **7*o***: mp 180−182 °C; ^{1}H NMR (CD_3OD) δ 7.89 (dd, J = 7.8, 1.8, 1H), 7.64−7.58 (m, 1H), 7.19 (d, J = 8.3, 1H), 7.09−7.03 (m, 1H), 4.47 (m, 2H), 3.99 (s, 3H), 3.83 (dd, J = 19.5, 3.2, 1H), 3.71 (s, 3H), 3.54 (dd, J = 19.5, 9.6, 1H), 1.93 (m, 1H), 1.44 (m, 1H), 1.27 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (CD_3OD) δ 198.6, 173.7, 171.2, 161.9, 137.2, 132.3, 127.3, 122.5, 114.1, 59.2, 57.0, 53.3, 51.2, 47.1, 38.8, 27.0, 16.8, 12.6; $[\alpha]^{25}_D$ +16.9° (*c* 1, MeOH). Anal. Calcd for $C_{18}H_{27}N_2O_5Cl$: C, 55.9; H, 7.0; N, 7.2. Found: C, 55.5; H, 7.0; N, 6.8.

BOC-Met-An^{p}Asp-Ile-OCH$_3$ (8*p*). Methyl triflate (0.95 mL, 8.37 mmol) was added dropwise (1 min) to a solution of CDI (0.68 g, 4.19 mmol) in nitromethane (10 mL) at 0 °C. The solution was stirred for 5 min, and a solution of BOC-Met (99 mg, 3.96 mmol) and *N*-methylimidazole (33 μL, 0.41 mmol) in THF/$MeNO_2$ (10 mL, 1/1) was added (via cannula, 3 min). The mixture was stirred for 8 min, and a solution HCl·An^{p}Asp-Ile-OCH$_3$ (**7*p***, 800 mg, 2.06 mmol) and *N*-methylmorpholine (0.92 mL, 8.36 mmol) in THF/DMF (1/1, 5 mL) was added. The reaction mixture was stirred for 1.5 h at rt, H_2O (3 mL) was added, and the mixture was stirred for 2 min and then was partitioned between saturated $NaHCO_3$ (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL), and the combined organic layer was dried and evaporated. The residue was chromatographed (EtOAc/hexane, 3/2) to give 1.17 g (98%) of tripeptide **8*p***: mp (CH_2Cl_2/hexane) 109−114 °C; ^{1}H NMR δ 7.92 (d, J = 8.8, 2H), 7.49 (br d, J = 7.2, 1H), 7.27 (br d, J = 8.0, 1H), 6.92 (d, J = 8.8, 2H), 5.27−5.24 (m, 1H), 5.02−5.01 (m, 1H), 4.48 (dd, J = 8.4, 4.8, 1H), 4.30−4.28 (m, 1H), 3.87 (s, 3H), 3.77−3.71 (m, 1H),

3.71 (s, 3H), 3.22 (dd, J = 17.9, 7.1, 1H), 2.58 (t, J = 7.2, 2H), 2.15−1.90 (m, 3H), 2.11 (s, 3H), 1.43−1.22 (m, 2H), 1.43 (s, 9H), 0.93−0.88 (m, 6H); ^{13}C NMR δ 197.3, 171.6, 171.3, 170.4, 163.9, 155.4, 130.5, 129.1, 113.7, 80.2, 56.9, 55.5, 53.7, 52.0, 49.1, 39.9, 37.3, 31.5, 30.2, 28.2, 25.0, 15.5, 15.3, 11.6; $[\alpha]^{25}_D$ +59.1° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{43}N_3O_8S$: C, 57.8; H, 7.5; N, 7.2. Found: C, 57.5; H, 7.5; N, 7.4.

BOC-Met-An^{o}Asp-Ile-OCH$_3$ (8*o*) was prepared as described for the para isomer. From 800 mg of **7*o*** was obtained 970 mg (81%) of tripeptide **8*o***: mp (CH_2Cl_2/hexane) 90−95 °C; ^{1}H NMR δ 7.77 (dd, J = 7.8, 1.6, 1H), 7.48−7.42 (m, 1H), 7.34−7.31 (m, 1H) 7.24−7.15 (m, 1H), 6.99−6.91 (m, 2H), 5.20−5.18 (m, 1H), 4.98−4.94 (m, 1H), 4.46 (dd, J = 8.4, 4.9, 1H), 4.26 (m, 1H), 3.87 (s, 3H), 3.68 (dd, J = 18.9, 3.4, 1H), 3.61 (s, 3H), 3.33 (dd, J = 18.7, 7.1, 1H), 2.54 (t, J = 7.2, 2H), 2.11−2.05 (m, 1H), 2.07 (s, 3H), 1.94−1.86 (m, 2H), 1.44−1.18 (m, 2H), 1.40 (s, 9H), 0.91−0.86 (m, 6H); ^{13}C NMR δ 199.9, 171.6, 171.2, 170.6, 159.2, 155.4, 134.5, 130.7, 126.5, 120.6, 111.5, 80.2, 56.9, 55.5, 53.7, 51.9, 49.3, 45.9, 37.4, 31.7, 30.1, 28.2, 25.0, 15.5, 15.3, 11.6; $[\alpha]^{25}_D$ +54.0° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{28}H_{43}N_3O_8S$: C, 57.8; H, 7.5; N, 7.2. Found: C, 58.0; H, 7.6; N, 7.0.

BOC-Met-An^{p}Asp-Ile-OH (9*p*). To a solution of BOC-Met-An^{p}Asp-Ile-OCH$_3$ (**8*p***, 620 mg, 1.07 mmol) in dioxane (8mL) at rt was added a solution of lithium hydroxide monohydrate (720 mg, 17 mmol) in H_2O (8 mL). This mixture was stirred for 30 min as a white precipitate was formed. The suspension was diluted with H_2O (20 mL), 1 M H_3PO_4 was added to pH 4, and the mixture was extrated with CH_2Cl_2 (3 × 20 mL), dried, and evaporated. Remaining dioxane was removed by azeotropic distillation with toluene (100 mL), giving 569 mg (94%) of **9*p*** as an oil which solidified on standing: mp 86−90 °C; ^{1}H NMR δ 7.89 (d, J = 8.8, 2H), 7.78 (m, 1H), 7.48 (m, 1H), 6.68 (d, J = 8.8, 1H), 5.58 (m, 1H), 5.03 (m, 1H), 4.46 (m, 1H), 3.41 (m, 1H), 3.84 (s, 3H), 3.62−3.34 (m, 2H), 2.51 (t, J = 7.2, 2H), 2.07−1.85 (m, 3H), 2.05 (s, 3H), 1.5−1.45 (m, 2H), 1.41 (s, 9H), 0.92 (m, 6H); ^{13}C NMR δ 197.0, 174.0, 171.9, 170.9, 163.7, 155.6, 130.5, 129.0, 113.6, 80.12, 57.0, 55.4, 53.6, 49.3, 39.7, 37.0, 31.7, 30.0, 28.1, 24.8, 15.4, 15.1, 11.5; $[\alpha]^{22}_D$ +31.7° (*c* 1, $CHCl_3$); HRMS Calcd for $C_{27}H_{42}N_3O_8S$ (MH^+) 568.2692, found 568.2707. Anal. Calcd for $C_{27}H_{41}N_3O_8S$: C, 57.1; H, 7.3; N, 7.4. Found: C, 57.5; H, 7.0; N, 7.2.

BOC-Met-An^{o}Asp-Ile-OH (9*o*) was prepared as described for the para isomer. From 850 mg, 1.46 mmol, of **8*o*** was obtained 775 mg (93%) of **9*o***: mp 68−72 °C; ^{1}H NMR δ 7.73 (d, J = 7.6, 1H), 7.56 (m, 1H), 7.44 (m, 1H), 7.30 (m, 1H), 6.96−6.89 (m, 2H), 5.46 (m, 1H), 4.99 (m, 1H), 4.47−4.43 (m, 1H), 3.85 (s, 3H), 3.62−3.41 (m, 2H), 2.51 (t, J = 7.0, 2H), 2.04 (s, 3H), 2.04−1.89 (m, 3H), 1.48−1.17 (m, 2H), 1.39 (s, 9H), 0.91 (m, 6H); ^{13}C NMR δ 199.6, 174.3, 171.8, 170.9, 159.0, 155.6, 134.4, 130.6, 126.4, 120.5, 111.5, 80.1, 56.9, 55.4, 53.6, 49.4, 45.6, 37.1, 31.7, 30.0, 28.2, 24.8, 15.4, 15.1, 11.6; $[\alpha]^{22}_D$ +26.5° (*c* 1, $CHCl_3$); HRMS calcd for $C_{27}H_{42}N_3O_8S$ (MH^+) 568.2692, found 568.2699. Anal. Calcd for $C_{27}H_{41}N_3O_8S$: C, 57.1; H, 7.3; N, 7.4. Found: C, 57.1; H, 7.0; N, 6.9.

HCl·Met-An^{p}Asp-Ile-OCH$_3$ (10*p*). A 1 M solution of HCl in ethyl acetate (30 mmol) was added dropwise to a solution of BOC-Met-An^{p}Asp-Ile-OCH$_3$ (**8*p***, 790 mg, 1.36 mmol) in ethyl acetate (7 mL). The solution was stirred for 2 h and then evaporated, and the residue, after trituration with ether, was crystallized from methanol/ether to give 597 mg (85%) of **10*p***: mp 161−164 °C; ^{1}H NMR (CD_3OD) δ 7.96 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 5.01−4.97 (m 1H), 4.35 (d, J = 5.7 Hz, 1H), 3.93 (t, J = 6.5 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 3H), 3.49−3.45 (m, 2H), 2.58 (t, J = 7.8 Hz, 2H), 2.15−2.06 (m, 2H), 2.09 (s, 3H), 1.89−1.85 (m, 1H), 1.48−1.41 (m, 1H), 1.28−1.21 (m, 1H), 0.91−0.88 (m, 6H); ^{13}C NMR (CD_3OD) δ 196.5, 173.3, 173.2, 169.6, 165.6, 131.5, 130.5, 114.9, 58.4, 56.1, 53.5, 52.5, 50.9, 40.6, 38.4, 32.3, 29.6, 26.3, 16.0, 15.1, 11.8; $[\alpha]^{25}_D$ +11.6° (*c* 1, CH_3OH). Anal. Calcd for $C_{23}H_{36}N_3O_6SCl$: C, 53.3; H, 7.0; N, 8.1. Found: C, 53.6; H, 6.9; N, 7.9.

HCl·Met-An^{o}Asp-Ile-OCH$_3$ (10*o*) was prepared as described for the para isomer. From 315 mg, 0.54 mmol, of **8*o*** was obtained 262 mg (93%) of **10*o***: mp 167−169 °C; ^{1}H NMR (CD_3OD) δ 7.77−7.34 (m, 1H), 7.58−7.53 (m, 1H), 7.17−7.14 (m, 1H), 7.05−7.00 (m, 1H), 5.01−4.95 (m, 1H), 4.41−4.36 (m, 1H), 3.98−3.94 (m, 1H), 3.96 (s, 3H), 3.69 (s, 3H), 3.57−3.50 (m, 2H), 2.60 (t, J = 7.8 Hz, 2H), 2.17−2.09 (m, 1H), 2.11 (s, 3H), 1.92−1.85 (m, 1H), 1.51−1.44 (m, 1H), 1.27−1.20 (m, 1H), 0.94−0.89 (m, 6H); ^{13}C NMR (CD_3OD) δ 199.0, 173.4, 173.3, 169.6, 160.8, 135.8, 131.4, 127.8, 121.6, 113.3, 58.4, 56.2, 53.5, 52.5, 51.0, 46.5, 38.4, 32.3, 29.6, 26.3, 16.0, 15.1, 11.8; $[\alpha]^{25}_D$ +13.2° (*c* 1, CH_3OH). Anal. Calcd for $C_{23}H_{36}N_3O_6SCl$: C, 53.3; H, 7.0; N, 8.1. Found: C, 52.9; H, 7.1; N, 7.8.

tert*-Butyl (*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-[2,2-(1,3-dioxolanyl)]-5-(4-methoxyphenyl)pentanoate (12*p*).** Triflic acid (5 μL, 0.06 mmol) was slowly added at 0 °C to a solution of ketone **11*p (0.45 g, 1.14 mmol) and 2-methoxy-1,3-dioxolane (0.24 g, 2.35 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 1 h, Et_2O was added, and the organic layer was washed with saturated $NaHCO_3$ (1×) and H_2O (2×), dried, filtered, and evaporated. The residue was purified by chromatography (EtOAc/hexanes, 4/1) to give 0.39 g (79%) of **12*p*** as a white solid: mp 106−107 °C; ^{1}H NMR δ 1.42 (s, 18H), 1.66−1.94 (m, 2H), 1.86 (m, 2H), 3.76 (s, 2H), 3.80 (s, 3H), 3.98 (s, 2H), 4.14 (1H), 5.01 (1H), 6.85 (d, J = 7.5, 2H), 7.33 (d, J = 7.5, 2H); ^{13}C NMR δ 26.8, 27.9, 28.3, 36.0, 53.2, 55.2, 64.4, 64.5, 79.4, 81.5, 109.8, 113.4, 126.8, 134.4, 155.3, 159.3, 171.8; $[\alpha]^{22}_D$ −8.9° (*c* 1, EtOH). Anal. Calcd for $C_{23}H_{35}NO_7$: C, 63.1; H, 8.1; N, 3.2. Found: C, 62.8; H, 8.1; N, 3.6.

tert*-Butyl (*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-[2,2-(1,3-dioxolanyl)]-5-(2-methoxyphenyl)pentanoate (12*o*)** was prepared as described for the para isomer. From 1.1 g (2.8 mmol) of ketone **11*o was obtained 735 mg, 75% yield, of ketal **12*o*** as an oil: ^{1}H NMR δ 7.42 (dd, J = 7.8, 1.7, 1H), 7.25 (dd, J = 15.6, 1.7, 1H), 6.90−6.86 (m, 2H), 5.01 (d, J = 8.2, 1H), 4.09 (m, 1H), 4.00−3.95 (m, 2H), 3.86−3.80 (m, 5H), 2.19−2.10 (m, 1H), 1.91−1.77 (m, 1H), 1.63−1.57 (m, 1H), 1.41 (s, 18H); ^{13}C NMR δ 171.9, 157.1, 155.2, 129.5, 129.1, 127.2, 120.0, 111.8, 109.7, 81.3, 79.2, 64.7, 55.7, 53.7, 33.1, 28.2, 27.9, 26.8; $[\alpha]^{22}_D$ −5.1° (*c* 1, EtOH). Anal. Calcd for $C_{23}H_{35}NO_7$: C, 63.1; H, 8.1; N, 3.2. Found: C, 62.9; H, 7.9; N, 3.1.

tert*-Butyl (*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-[2,2-(1,3-dithiolanyl)]-5-(4-methoxyphenyl)pentanoate (13*p*).** To a stirred solution of ketal **12*p (1.53 g, 2.8 mmol) and 1,2-ethanedithiol (1.64 g, 17.5 mmol) at 0 °C was added BF_3·Et_2O (400 mg, 2.8 mmol) over a 5 min period. The reaction mixture was stirred for 15 min at 0 °C and then warmed to rt and stirred for 2 h, diluted with CH_2Cl_2 (20 mL), and washed with saturated $NaHCO_3$ (25 mL) and H_2O (2 × 25 mL). The organic layer was dried, filtered, and evaporated. Chromatography of the residue (EtOAc/hexanes, 1/6) gave thioketal **13*p*** (800 mg, 49%) as a colorless oil. Continued elution with MeOH/CH_2Cl_2, 1/20, gave the free amine **14*p*** from which the *tert*-butoxycarbonyl group had been cleaved. Reprotection by the standard procedure gave additional **13*p*** (704 mg, 43%), for a total yield of 92%: ^{1}H NMR δ 7.56 (d, J = 8.8, 2H), 6.82 (d, J = 8.8, 2H), 4.97 (br d, 1H), 4.18−4.12 (m, 1H), 3.79 (s, 3H), 3.40−3.23 (m, 4H), 2.39 (td, J = 8.3, 4.1, 1H), 2.25 (td, J = 8.3, 4.6, 1H), 1.82−1.78 (m, 1H), 1.66−1.56 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H); ^{13}C NMR δ 171.3, 158.5, 155.1, 136.3, 129.3, 128.1, 111.3, 81.8, 79.6, 73.0, 55.2, 53.6, 41.2, 39.3, 30.6, 28.1, 28.0; $[\alpha]^{22}_D$ +6.7° (*c* 1, EtOH). Anal. Calcd for $C_{23}H_{35}NO_5S_2$: C, 58.8; H, 7.5; N, 3.0. Found: C, 59.0; H, 7.5; N, 3.0.

The intermediate *N*-deprotected amine isolated in the above ketal to thioketal transformation, ***tert*-butyl (*S*)-2-amino-5-[2,2-(1,3-dithiolanyl)]-5-(4-methoxyphenyl)pentanoate (14*p*)** was further characterized: ^{1}H NMR δ 7.58 (d, J = 8.8, 2H), 6.82 (d, J = 8.8, 2H), 3.79 (s, 3H), 3.41−3.22 (m, 5H), 2.47−2.39 (m, 4H), 1.74−1.65 (m, 1H), 1.63−1.56 (m, 1H), 1.43 (s, 9H); ^{13}C NMR δ 174.6, 158.3, 136.3, 128.1, 113.1, 80.9, 73.1, 55.1, 54.5, 41.6, 39.2, 32.7, 27.9; $[\alpha]^{22}_D$ +7.4° (*c* 1, EtOH). Anal. Calcd for $C_{18}H_{27}NO_3S_2$: C, 58.5; H, 7.4; N, 3.6. Found: C, 58.5; H, 7.4; N, 3.6.

tert*-Butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-[2,2-(1,3-dithiolanyl)]-5-(2-methoxyphenyl)pentanoate (13*o*)** was prepared as described for the para isomer. The product, **13*o, was obtained as an oil in 90% yield: ^{1}H NMR δ 7.79 (dd, J = 8.0, 1H), 7.26−7.21 (m, 1H), 6.91−6.86 (m, 2H), 4.93 (br d, 1H), 3.88 (s, 3H), 3.33−3.15 (m, 4H), 2.53−2.37 (m, 2H), 1.76−1.53 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C NMR δ 171.5, 156.7, 155.0, 132.3, 128.7, 127.8, 120.2, 111.9, 81.5, 79.2, 72.3,

55.5, 53.6, 38.8, 38.8, 30.9, 28.3, 27.9; $[\alpha]^{22}_D$ +6.0° (*c* 1, EtOH). Anal. Calcd for $C_{23}H_{35}NO_5S_2$: C, 58.8; H, 7.5; N, 3.0. Found: C, 58.6; H, 7.7; N, 3.0.

The intermediate *N*-deprotected amine isolated in the above ketal to thioketal transformation, ***tert*-butyl (*S*)-2-amino-5-[2,2-(1,3-dithiolanyl)]-5-(2-methoxyphenyl)pentanoate-(14*o*)**, was further characterized: ^{1}H NMR δ 7.79 (dd, J = 8.0, 1.6, 1H), 7.26−7.21 (m, 1H), 6.91−6.86 (m, 2H), 3.88 (s, 3H), 3.31−3.41 (m, 4H), 2.52 (t, J = 7.9, 3H), 1.76 (br s, 2H), 1.59−1.45 (m, 2H), 1.42 (s, 9H); ^{13}C NMR δ 174.8, 156.6, 132.3, 128.6, 127.7, 120.1, 111.8, 80.7, 72.5, 55.5, 54.6, 39.3, 38.7, 33.4, 27.9; $[\alpha]^{22}_D$ +10.7° (*c* 1, EtOH). Anal. Calcd for $C_{18}H_{27}NO_3S_2$: C, 58.5; H, 7.4; N, 3.8. Found: C, 58.5; H, 7.1; N, 3.8.

(*S*)-2-Amino-5-[2,2-(1,3-dithiolanyl)]-5-(4-methoxyphenyl)pentanoic Acid Hydrochloride (15*p*). To a stirred solution of *N*-BOC *tert*-butyl ester **13*p*** (2.10 g, 4.80 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added dry HCl dissolved in EtOAc (5.2 M, 27.7 mL, 144 mmol) over a 10 min period. The reaction mixture was warmed to rt, stirred for 16 h, filtered, and washed with EtOAc to give **15*p*** (1.51 g, 90%): mp 175−178 °C; ^{1}H NMR δ (CD_3OD) δ 7.58 (d, J = 8.9, 2H), 6.86 (d, J = 8.9, 2H), 3.93 (t, J = 6.2, 1H), 3.78 (s, 3H), 3.45−3.28 (m, 4H), 2.61−2.51 (m, 1H), 2.47−2.37 (m, 1H), 2.00−1.80 (m, 2H); ^{13}C NMR (CD_3OD) δ 171.6, 160.4, 137.3, 129.6, 114.5, 73.8, 56.0, 55.9, 42.4, 40.6, 29.8; $[\alpha]^{22}_D$ +26.1° (*c* 1, EtOH). Anal. Calcd for $C_{14}H_{20}NO_3S_2Cl$: C, 48.1; H, 5.7; N, 4.0. Found: C, 48.3; H, 6.0; N, 3.9.

(*S*)-2-Amino-5-[2,2-(1,3dithiolanyl)]-5-(2-methoxyphenyl)pentanoic acid hydrochloride (15*o*) was prepared as described for the para isomer in 86% yield: mp 217−218 °C dec; ^{1}H NMR (CD_3OD) δ 7.78 (dd, J = 7.8, 1.6, 1H), 7.26 (ddd, J = 8.1, 7.5, 1.6, 1H), 6.99 (dd, J = 8.1, 1.0, 1H), 6.88 (td, J = 7.5, 1.0, 1H), 3.86 (s, 3H), 3.35−3.28 (m, 2H), 3.26−3.16 (m, 2H), 2.64−2.56 (m, 2H), 1.87−1.77 (m, 2H); ^{13}C NMR (CD_3OD) δ 171.5, 158.3, 133.1, 130.1, 128.7, 121.1, 113.1, 72.9, 56.1, 53.7, 39.8, 30.1; $[\alpha]^{22}_D$ +45.5° (*c* 1.3, EtOH). Anal. Calcd for $C_{14}H_{20}NO_3S_2Cl$: C, 48.1; H, 5.8; N, 4.0. Found: C, 47.8; H, 5.7; N, 3.9.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-[2,2-(1,3-dithiolanyl)]-5-(4-methoxyphenyl)pentanoic Acid (BOC-An^{p}Glu Ethylene Dithioketal, 16*p*). To a stirred solution of the salt **15*p*** (1.12 g, 3.2 mmol) in THF (10 mL) and H_2O (10 mL) were added $(BOC)_2O$ (1.39 g, 6.4 mmol) and Et_3N (0.97 g, 9.6 mmol) at rt. The reaction mixture was stirred for 17 h at rt, EtOAc (30 mL) was added, and then the aqueous layer was acidified to pH 2 with 1 M H_3PO_4. It was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried, filtered, and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH, 12/1) to give the acid **16*p*** (1.22 g, 92%): mp 127−130 °C; ^{1}H NMR δ 7.56 (d, 2H), 6.82 (d, 2H), 5.01 (br d, 1H), 4.24 (s, 1H), 3.79 (s, 3H), 3.39−3.25 (m, 4H), 2.43−2.35 (m, 2H), 1.93−1.67 (m, 2H), 1.43 (s, 9H); ^{13}C NMR δ 176.5, 158.4, 155.4, 136.1, 128.1, 113.3, 80.0, 72.9, 55.1, 53.1, 41.4, 39.3, 30.3, 28.2. Anal. Calcd for $C_{19}H_{27}NO_5S_2$: C, 55.2; H, 6.6; N, 3.4. Found: C, 55.0; H, 6.4; N, 3.2.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-5-[2,2-(1,3-dithiolanyl)]-5-(2-methoxyphenyl)pentanoic acid (BOC-An^{o}Glu ethylene dithioketal, 16*o*) was prepared as described for the para isomer in 95% yield: mp 144−145.5 °C; ^{1}H NMR δ 9.8 (br s, 1H), 7.78 (d, J = 6.6, 1H), 7.23 (d, J = 7.8, 1H), 6.88 (t, J = 6.9, 2H), 4.86 (d, J = 7.7, 1H), 4.18−4.12 (m, 1H), 3.86 (s, 3H), 3.30−3.15 (m, 4H), 2.58−2.49 (m, 2H), 1.83−1.72 (m, 1H), 1.58−1.49 (m, 1H), 1.41 (s, 9H); ^{13}C NMR δ 177.5, 156.7, 155.5, 132.1, 128.9, 128.4, 127.8, 120.3, 112.0, 80.1, 72.3, 55.5, 54.3, 53.2, 38.9, 30.5, 28.3; $[\alpha]^{22}_D$ +25.0° (*c* 1.26, EtOH). Anal. Calcd for $C_{19}H_{27}NO_5S_2$: C, 55.2; H, 6.6; N, 3.4. Found: C, 55.0; H, 6.7; N, 3.2.

(*S*)-2-(Methoxycarbonyl)-5-(4-methoxyphenyl)-5-pyrroline (17*p*). A solution of ketal **12*p*** (360 mg, 1.1mmol) in 3 mL of 3 M HCl in methanol was stirred for 5 h at rt. The reaction mixture was then evaporated, the residue was dissolved in CH_2Cl_2 (5mL), triethylamine (0.18 mL, 1.3 mmol) was added, and the mixture was stirred for 15h at rt. It was then washed with H_2O (2 × 2 mL), dried, and evaporated. Recrystallization of the residue from EtOAc/hexanes gave pyrroline **17*p***, 150 mg, 61% yield: mp 72−73 °C; ^{1}H NMR δ 2.20−2.33 (m, 2H), 2.93−3.12 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 4.88 (t, 1H), 6.90 (d, 2H), 7.82 (d, 2H); ^{13}C NMR δ 26.3, 35.2, 52.1, 55.2, 74.2, 113.5, 126.4, 129.6, 161.6, 173.4, 175.1. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.9; H, 6.4; N, 5.7.

BOC-An^{p}Glu Ethylene Dithioketal Ile-OCH$_3$ (18*p*). Coupling between glutamic acid analogue **16*p*** and isoleucine methyl ester was carried out as described for the synthesis of dipeptide **6**. From 430 mg, 1.04 mmol, of **16*p*** was obtained 382 mg, 72% yield, of dipeptide **18*p***: ^{1}H NMR δ 7.51 (d, J = 8.8, 2H), 6.75 (d, J = 8.8, 2H), 6.48 (br d, 1H), 4.86 (br d, 1H), 4.46 (dd, J = 4.9, 3.7 1H), 3.96−3.88 (m, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.32−3.20 (m, 4H), 2.33−2.30 (m, 2H), 1.88−1.75 (m, 2H), 1.58−1.46 (m, 1H), 1.37 (s, 9H), 1.19−1.12 (m, 2H), 0.85−0.79 (m, 5H); ^{13}C NMR δ 171.9, 171.3, 158.5, 155.6, 136.2, 128.2, 113.3, 80.1, 73.1, 56.4, 55.2, 54.2, 52.0, 41.7, 39.4, 37.7, 29.8, 28.2, 24.9, 15.3, 11.4; $[\alpha]^{20}_D$ −3.0° (*c* 1, EtOH). Anal. Calcd for $C_{26}H_{40}N_2O_6S_2$: C, 57.7; H, 7.5; N, 5.2. Found: C, 57.7; H, 7.5; N, 5.1.

BOC-An^{o}Glu ethylene dithioketal Ile-OCH$_3$ (18*o*) was prepared as described for the para isomer. From 213 mg, 0.52 mmol, of **16*o*** was obtained 170 mg, 61% yield, of **18*o***: mp 94−95 °C; ^{1}H NMR δ 7.74 (dd, J = 7.6, 1.4, 1H), 7.18 (t, J = 6.7, 1H), 6.84−6.80 (br d, 1H), 4.87 (br d, 1H), 4.46 (dd, J = 8.8, 5.0, 1H), 3.90−3.83 (m, 1H), 3.83 (s, 3H), 3.24−3.21 (m, 2H), 3.13−3.10 (m, 2H), 1.85−1.66 (m, 2H), 1.51−1.28 (m, 3H), 1.37 (s, 9H), 1.14−1.03 (m, 1H), 0.84−0.79 (m, 6H); ^{13}C NMR δ 172.1, 171.5, 156.7, 155.6, 132.2, 128.8, 127.8, 120.2, 111.9, 79.9, 72.4, 56.3, 55.5, 54.3, 52.0, 39.3, 38.9, 37.8, 30.9, 29.9, 28.3, 25.0, 15.3, 11.5; $[\alpha]^{20}_D$ −5.9° (*c* 1, EtOH). Anal. Calcd for $C_{26}H_{40}N_2O_6S_2$: C, 57.7; H, 7.5; N, 5.2. Found: C, 57.7; H, 7.8; N, 5.3.

HCl·An^{p}Glu Ethylene Dithioketal Ile-OCH$_3$ (19*p*). To a stirred solution of dipeptide **18*o*** (297 mg, 0.57 mmol) in 2 mL of EtOAc at 0 °C was added dry HCl in EtOAc (2.7 M solution, 3.3 mL, 11.3 mmol) over 5 min. The reaction mixture was stirred for 3h at rt, methanol (10 mL) was added, and the solution was evaporated to give the salt **19*p*** (251 mg, 93%) as an oil: ^{1}H NMR (CD_3OD) δ 8.6 (d, 1H), 7.58 (d, 2H), 6.83 (d, 2H), 4.38 (br s, 1H), 3.96 (br s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.45−3.19 (m, 4H), 2.49−2.43 (m, 1H), 1.89 (br s, 2H), 1.51−1.21 (m, 2H), 0.98−0.93 (m, 6H); ^{13}C NMR (CD_3OD) δ 171.5, 171.3, 158.6, 135.5, 128.3, 113.3, 72.3, 57.2, 56.2, 55.7, 53.0, 40.2, 36.9, 36.8, 29.5, 25.3, 15.3, 11.2. Anal. Calcd for $C_{21}H_{33}N_2O_4S_2Cl$: C, 52.9; H, 7.0; N, 5.9. Found: C, 52.5; H, 7.2; N, 5.7.

HCl·An^{p}Glu ethylene dithioketal Ile-OCH$_3$ (19*o*) was prepared as described for the para isomer **19*p***, except that the reaction product was purified by chromatography (CH_2Cl_2/MeOH, 12/1). From 130 mg, 0.24 mmol, of BOC-dipeptide **18*o*** was obtained 94 mg, 82% yield, of **19*o*** as an oil: ^{1}H NMR (CD_3OD) δ 7.74 (d, J = 7.8, 1H), 7.26−7.17 (m, 1H), 6.94 (d, J = 8.1, 1H), 6.83 (td, J = 7.5, 1.0, 1H), 4.33 (d, J = 6.5, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.32−3.11 (m, 4H), 2.59−2.41 (m, 2H), 1.91−1.78 (m, 1H), 1.58−1.37 (m, 3H), 1.29−1.12 (m, 1H), 0.91−0.88 (m, 6H); ^{13}C NMR (CD_3OD) δ 177.2, 173.2, 158.4, 133.9, 129.8, 128.8, 121.0, 113.2, 73.7, 58.0, 52.5, 40.9, 39.7, 39.6, 38.4, 35.3, 26.3, 16.0, 11.7.

BOC-Met-An^{p}Glu Ethylene Dithioketal Ile-OCH$_3$ (20*p*). The dipeptide salt **19*p*** (267 mg, 0.55 mmol) and *N*-methylmorpholine (107 mg, 1.06 mmol) in 2 mL of DMF/THF, 1/1, was coupled with BOC-Met (263 mg, 1.06 mmol) using CBMIT activation as previously described. The resulting reaction mixture was stirred for 3h at rt and then diluted with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were dried, filtered, and evaporated. The residue was purified by chromatography (EtOAc/hexanes, 1/1) to give **20*p*** (253 mg, 70%): mp 151−152 °C; ^{1}H NMR δ 7.57 (d, 2H), 6.82 (d, 2H), 6.61 (d, 1H), 5.26 (1H), 4.51 (s, 1H), 4.39 (1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.33 (m, 4H), 2.54 (2H), 2.09 (s, 3H), 2.06 (2H), 1.91 (2H), 1.63−1.46 (2H), 1.44 (s, 9H), 1.34 (1H), 1.28 (1H), 1.26 (d, 1H), 0.87 (m, 6H); ^{13}C NMR δ 173.9, 171.9, 170.7, 158.3, 155.3, 135.9, 128.0, 113.1, 79.6, 72.7, 56.3, 54.9, 53.2, 52.6, 51.8, 40.9, 39.2, 37.3, 31.9, 29.8, 28.6, 28.1, 24.8, 15.2,

15.0, 11.2; $[\alpha]^{20}_D$ −9.7° (*c* 1.3, EtOH). Anal. Calcd for $C_{31}H_{49}N_3O_7S_3$: C, 55.4; H, 7.3; N, 6.2. Found: C, 55.2; H, 7.3; N, 6.1.

BOC-Met-An^{o}Glu ethylene dithioketal Ile-OCH$_3$ (20*o*) was prepared by coupling dipeptide **19*o*** with BOC-Met (89 mg, 0.36 mmol) as described for the para isomer. The yield of tripeptide **20*o*** was 70 mg, 71%: mp 159−161 °C; ^{1}H NMR (CD_3OD) δ 7.78 (dd, J = 7.7, 1.4, 1H), 7.23 (t, J = 7.6, 1H), 6.90−6.86 (m, 2H), 6.58 (br d, 1H), 6.47 (br d, 1H), 5.8 (br, 1H), 4.49 (dd, J = 8.6, 5.0, 1H), 4.28−4.22 (m, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 3.31−3.16 (m, 4H), 2.52−2.46 (m, 4H), 2.07 (s, 3H), 2.06−1.82 (m, 5H), 1.73−1.31 (m, 2H), 1.43 (s, 9H), 1.18−1.05 (m, 1H), 0.88 (t, J = 3H), 0.84 (d, J = 7.8); ^{13}C NMR (CD_3OD) δ 219.3, 171.8, 171.5, 170.6, 156.8, 155.4, 132.3, 128.9, 127.8, 120.3, 112.1, 85.3, 80.2, 72.4, 56.5, 55.7, 53.2, 52.1, 39.1, 38.9, 38.8, 37.8, 31.9, 30.2, 28.3, 25.1, 15.4, 15.3, 11.5; $[\alpha]^{20}_D$ −18.6° (*c* 1, EtOH). Anal. Calcd for $C_{31}H_{49}N_3O_7S_3$: C, 55.4; H, 7.3; N, 6.2. Found: C, 55.2; H, 7.6; N, 6.1.

BOC-Met-An^{p}Glu-Ile-OCH$_3$ (21*p*). To a stirred solution of **20*p*** (145 mg, 0.22 mmol) in 8.5 mL of $CHCl_3$ at rt was added a solution of $Hg(C1O_4)_2 \cdot 3H_2O$ (200 mg, 0.44 mmol) in 5 mL of MeOH over 3 min. The reaction mixture was stirred for 1.5h at rt and then filtered and basified with 10% K_2CO_3. The concentrated filtrate was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic layer was washed with brine (10 mL), dried, filtered, and evaporated. Chromatography of the residue (EtOAc/hexane, 1/2) gave **21*p*** (112 mg, 85%): mp 86−88 °C; ^{1}H NMR δ 7.88 (d, J = 8.8, 2H), 7.19 (d, J = 11.4, 2H), 6.85 (d, J = 8.8, 2H), 5.19 (d, J = 8.0, 1H), 4.49−4.42 (m, 2H), 4.24−4.17 (1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.28−3.17 (m, 1H), 2.06−1.97 (m, 1H), 2.00 (s, 3H), 1.92−1.79 (m, 2H), 1.35 (s, 9H), 1.19−1.11 (m, 1H), 0.86−0.82 (m, 6H); ^{13}C NMR δ 198.8, 172.0, 171.6, 171.1, 163.7, 130.5, 129.6, 113.7, 80.1, 56.8, 55.4, 53.7, 52.8, 37.4, 34.5, 31.8, 30.1, 28.2, 25.1, 15.5, 15.2, 11.5; $[\alpha]^{20}_D$ −11.8° (*c* 0.9, EtOH). Anal. Calcd for $C_{29}H_{45}N_3O_8S$: C, 58.5; H, 7.6; N, 7.1. Found: C, 58.3; H, 7.5; N, 6.9.

BOC-Met-An^{o}Glu-Ile-OCH$_3$ (21*o*) was prepared as described for the para isomer. From 840 mg, 1.25 mmol, of **20*o*** was obtained 658 mg, 88% yield, of **21*o***: mp 124−125 °C; ^{1}H NMR δ 7.67 (dd, J = 7.7, 1.8, 1H), 7.09 (d, J = 6.8, 1H), 7.02 (d, J = 8.4, 1H), 6.92 (q, J = 8.3, 2H), 5.15 (br d, 1H), 4.49−4.40 (m, 2H), 4.13−4.25 (m, 1H), 3.83 (s, 3H), 3.64 (s, 3H), 3.31−2.98 (m, 2H), 2.48 (t, J = 7.3, 2H), 2.27−1.70 (m, 6H), 2.02 (s, 3H), 1.41−1.30 (m, 2H), 1.35 (s, 9H), 1.22−1.05 (m, 2H), 0.87−0.82 (m, 6H); ^{13}C NMR δ 202.4, 172.0, 171.6, 171.2, 158.9, 155.5, 133.9, 130.5, 127.6, 120.6, 111.6, 80.1, 56.8, 55.5, 53.7, 53.1, 52.1, 40.2, 37.6, 31.9, 30.2, 28.3, 27.2, 25.1, 15.6, 15.3, 11.6; $[\alpha]^{20}_D$ −21.6° (*c* 1.2, EtOH). Anal. Calcd for $C_{29}H_{45}N_3O_8S$: C, 58.5; H, 7.6; N, 7.1. Found: C, 58.1; H, 7.5; N, 6.8.

BOC-Met-An^{p}Glu-Ile-OH (22*p*). To a stirred solution of **21*p*** (270 mg, 0.45 mmol) in 3 mL of 1,4-dioxane at rt was added a solution of $LiOH \cdot H_2O$ (74.4 mg, 1.81 mmol) in 3 mL of H_2O, and the reaction mixture was stirred for 35 min at rt. Water (15 mL) was added, and the aqueous phase was washed with Et_2O (10 mL) and then acidified to pH 3 (0.5M H_3PO_4) and extracted with EtOAc (3 × 15 mL). Drying, filtering, and evaporating the organic phase gave a residue which was chromatographed (CH_2Cl_2/MeOH, 12/1) to give **22*p*** (240 mg, 93%) as a foam: ^{1}H NMR δ 7.89 (d, J = 8.7, 1H), 7.66 (dt, J = 6.1, 1.7, 2H), 7.44−7.39 (m, 1H), 3.82 (s, 3H), 3.22−3.03 (m, 2H), 2.49 (t, J = 7.2, 2H), 2.92−2.12 (m, 1H), 2.02 (s, 3H), 2.08−2.82 (m, 4H), 1.61−1.32 (m, 1H), 1.39 (s, 9H), 1.26−1.24 (m, 1H), 0.789 (d, J = 7.4, 3H), 0.74 (t, J = 7.1, 3H); ^{13}C NMR δ 198.9, 174.1, 172.3, 171.7, 163.6, 130.6, 129.5, 113.7, 80.1, 57.1, 55.4, 53.8, 52.8, 37.2, 34.2, 32.1, 30.0, 28.3, 27.5, 25.1, 15.5, 15.3, 11.6; $[\alpha]^{20}_D$ −10.8° (*c* 0.8, EtOH). HRMS calcd for $C_{28}H_{44}N_3O_8S$ (MH^+) 582.2849, found 582.2847. Anal. Calcd for $C_{28}H_{43}N_3O_8S$: C, 57.8; H, 7.4; N, 7.2. Found: C, 57.4; H, 7.6; N, 7.0.

BOC-Met-An^{o}Glu-Ile-OH (22*o*) was prepared as described for the para isomer. From 240 mg, 0.4 mmol, of methyl ester **21*o*** was obtained 218 mg, 93% yield, of acid **22*o*** as an amorphous solid: ^{1}H NMR δ 7.71 (dd, J = 7.7, 1H), 7.61 (br d, 1H), 7.47−7.42 (m, 2H), 7.42 (br d, 1H), 6.96 (q, J = 7.4, 2H), 5.50 (d, J = 7.2, H), 4.60−4.52 (m, 2H), 4.30 (br, 1H), 3.87 (s, 3H), 3.26−3.06 (m, 2H), 2.52 (t, J = 7.3, 2H), 2.24−2.19 (m, 1H), 2.05 (s, 3H), 1.93−1.86 (m, 4H), 1.51−1.47 (m, 1H), 1.40 (s, 9H), 1.30−1.18 (m, 1H), 0.96−0.89 (m, 6H); ^{13}C NMR δ 202.5, 174.0, 172.2, 171.7, 158.9, 155.7, 133.9, 130.5, 127.5, 120.6, 111.7, 80.2, 57.1, 55.5, 53.9, 53.2, 40.0, 37.2, 32.0, 30.1, 28.3, 27.1, 25.1, 15.5, 15.3, 11.6; $[\alpha]^{20}_D$ −16.9° (*c* 1.9, EtOH); HRMS calcd for $C_{28}H_{44}N_3O_8S$ (MH^+) 582.2849, found 582.2843. Anal. Calcd for $C_{28}H_{43}N_3O_8S$: C, 57.8; H, 7.4; N, 7.2. Found: C, 58.0; H, 7.7; N, 6.9.

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