Efficient Method for the Total Asymmetric Synthesis of the Isomers of β-Methyltyrosine

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Received May 21, 1993[•]

α-Amino acids modified at the β-carbon atom can provide topographical constraints when incorporated into a peptide. Such modifications can modulate the physical, chemical, and biological properties of the compound. In order to properly evaluate the effect of such modifications, large-scale asymmetric syntheses of the isomers are needed. A method for the stereoselective large-scale synthesis of all four stereoisomers of β-methyltyrosine is described in this paper. The stereochemistry of both the α- and β-stereocenters was set using 4-phenyl-2-oxazolidinone as a chiral auxiliary. The key reactions were an asymmetric Michael-like addition of an organocuprate to a chiral α,β-unsaturated acyloxazolidinone (β center) and subsequent stereoselective electrophilic bromination of the resulting product (α center). Conversion of the bromide to the azide, catalyzed hydrolysis to the azido acid with simultaneous recovery of the chiral auxiliary, reduction of the azide, and final deprotection of the phenol group afforded the desired amino acids. In general, the reactions were performed in yields over 80%, and the isomers were obtained in enantiomeric purities of 98:2 to 99:1.

Introduction

The introduction of non-natural amino acids into biologically active peptides has become one of the most powerful approaches for examining the properties of such peptides. Specific structural, stereoelectronic, steric, and conformational properties can be examined by proper design of such structures. For some years, we have been focusing our attention to those amino acids that introduce specific minor conformational and topographical modifications to their side chains because of the significant changes in potency, receptor selectivity, and biostability that can result when they are incorporated into bioactive peptides.[1-5] Since many biologically active peptides possess critical aromatic amino acid residues we have focused our attention on non-natural β-substituted aromatic amino acids. The potential of such an approach has been demonstrated in studies carried out in our laboratory with biological active phenylalanine and/or tyrosine containing peptides.[1-4,6,7] These studies have shown, for example, that topographical constraints introduced by a β-methyl substituent in a critical aromatic amino acid residue could lead to dramatic changes in the potency and receptor selectivity of the peptide. These investigations also revealed a strong dependence of these properties on the stereoisomer used.

In early studies, preparation of these amino acids was achieved following conventional, nonstereoselective, procedures.[8] *Erythro* and *threo* mixtures were obtained and used directly for the synthesis of the peptide analogues. The resulting diastereoisomeric peptide mixtures were then separated by reversed phase high-performance liquid chromatography. The encouraging results obtained from these studies have prompted us to develop asymmetric synthetic methods for the preparation of quantities of each of the possible stereoisomers.

Recently, the asymmetric synthesis of α-amino acids has become an area of substantial activity.[9] Many of the procedures described in the literature make use of a suitable chiral auxiliary to generate stereoselectivity at the α position of the amino acid. Some methodologies have the advantage of recovering the chiral auxiliary at the end of the synthesis, resulting in a reduction of the cost of the process. We decided to explore this strategy in order to design a method which allowed the preparation of reasonable quantities of the four stereoisomers of β-methylphenylalanine and β-methyltyrosine. Our first studies were directed toward the asymmetric preparation of the α-stereocenter with the β-stereocenter being established by resolution of racemic 3-arylbutanoic acids by fractional recrystallization.[10,11] In this initial work, our strategy incorporated, with some modifications, a methodology described by Evans et al.,[12] making use of 4-benzyl-2-oxazolidinone as the chiral auxiliary for the asymmetric induction at the α position (Figure 1; method a, R_1 = Bn). The benzyl-containing chiral auxiliary was chosen because

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• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

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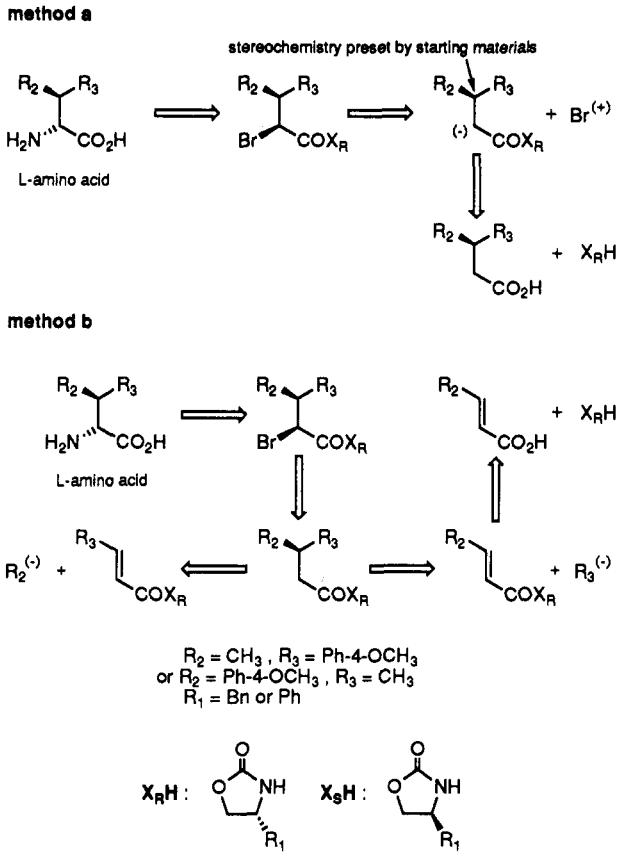

Figure 1.

it could be prepared in large amounts in a relatively simple way from commercially available starting materials and could be recovered in high yields after the stereoselective process. We have described recently the large-scale synthesis of the four stereoisomers of β-methylphenylalanine following this procedure.[13] In this paper, we report our results on the large-scale asymmetric synthesis of the isomers of β-methyltyrosine using a procedure in which both the α- and β-stereocenters are produced by the same chiral auxiliary.

Results and Discussion

Our first studies were directed to the extension of the methodology applied to the preparation of β-methylphenylalanines to the synthesis of the isomers of β-methyltyrosine.[11] The main difference was the need to protect the phenol in this particular case. Methyl ether protection proved to be stable to all reaction conditions used, and it was removed with refluxing HBr/AcOH at the end of the synthesis. Thus, the synthesis of the β-methyltyrosines started from optically pure (*R*)- and (*S*)-(4-methoxyphenyl)butanoic acids (Figure 2; **1a,b**, respectively).

The key reaction of this strategy is the stereoselective electrophilic bromination of the di(*n*-butyl)boron enolate of a 4-substituted N-acyloxazolidinone with NBS (Figure 1, method a). The bromides needed for the synthesis of the isomers of β-methyltyrosine were obtained in good yields and excellent diastereomeric excesses. Subsequent treatment of the *N*-(α-bromoacyl)oxazolidinones with

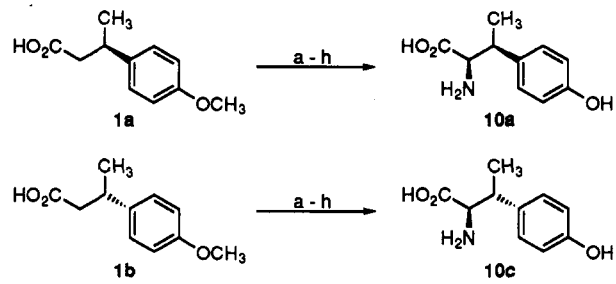

Figure 2. Key: (a) (1) pivaloyl chloride, Et_3N, −78 °C; (2) lithium salt of (*S*)-4-benzyl-2-oxazolidinone; (b) (1) $(n\text{-Bu})_2BOTf$, $(i\text{-Pr})_2NEt$, 0 °C; (c) NBS, CH_2Cl_2, −78 °C; (d) tetramethylguanidium azide, CH_3CN, 40 °C; (e) 30% H_2O_2, LiOH, THF/H_2O, 0 °C, recovery of chiral auxiliary; (f) NH_4HCOO, 5% Pd/C, MeOH; (g) HBr/AcOH, 140 °C; (h) 10% aqueous NH_4OH to pH 6.

tetramethylguanidinium azide afforded the azido derivatives which were hydrolyzed to the azido acids with excellent recovery of the chiral auxiliary (>90%). The final amino acids were synthesized from the azido acids by reduction with H_2 using 10% Pd/C catalyst and deprotection of the phenol as previously discussed. The *threo*-D and *erythro*-D isomers (Figure 2; **10a,c**) were obtained with 84% and 98% de, respectively. The stereochemistry of the bromination reaction was confirmed after the final amino acids were obtained by comparison to *threo* and *erythro* isomers isolated by fractional recrystallization from a racemic synthesis.

As mentioned above, our earlier syntheses of the four stereoisomers of β-methyltyrosine started from optically pure (*R*)- and (*S*)-3-(4-methoxyphenyl)butanoic acid (**1a,b**; Figure 2).[11] The preparation of these acids was accomplished by conventional methods, resulting in an enantiomeric mixture of the products, and the products were then separated by fractional crystallization of diastereoisomeric mixtures of their (*R*)- or (*S*)-α-methylbenzylamine salts. Despite the fact that the racemic acid could be prepared in good yields and on a large scale, the optically pure acids were obtained in low yields (<20%). Moreover, these acids were prepared following a three-step synthesis, and their optical resolution was an extremely tedious process because of the number of crystallizations needed. To circumvent these problems, increase the final yields, and shorten the synthesis, we decided that a preparation of the β-stereocenter by asymmetric synthesis would be advantageous. For introduction of a substituent in a position β to a carbonyl group, a Michael-like 1,4-conjugate addition of a suitable reagent to an *N*-substituted α,β-unsaturated acyloxazolidinone seemed an excellent method to build the side chain of the non-natural amino acid (Figure 1, method b). The fact that 4-benzyl-2-oxazolidinone nicely fulfilled our purposes for establishing the α-stereocenter[11,13] prompted us to study the potential of this chiral auxiliary to perform asymmetric 1,4-conjugate additions to set the stereochemistry of the β center. Tomioka *et al.*[15] have described a 5-substituted 2-pyrrolidinone as a suitable chiral auxiliary for asymmetric 1,4-conjugate additions of Grignard reagents to α,β-unsaturated carbonyl compounds in the presence of $CuBr/Me_2S$. We applied similar conditions to perform the stereoselective conjugate addition of (4-methoxyphenyl)magnesium bromide to (4*S*)-3-[2(2*E*)-butenoyl]-4-benzyl-2-oxazolidinone (Figure 1; method b, R_1 = Bn, R_2 = CH_3,

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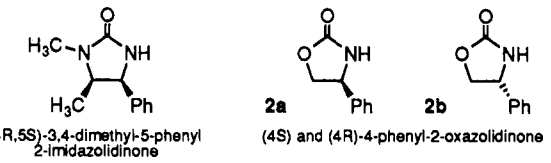


Figure 3.

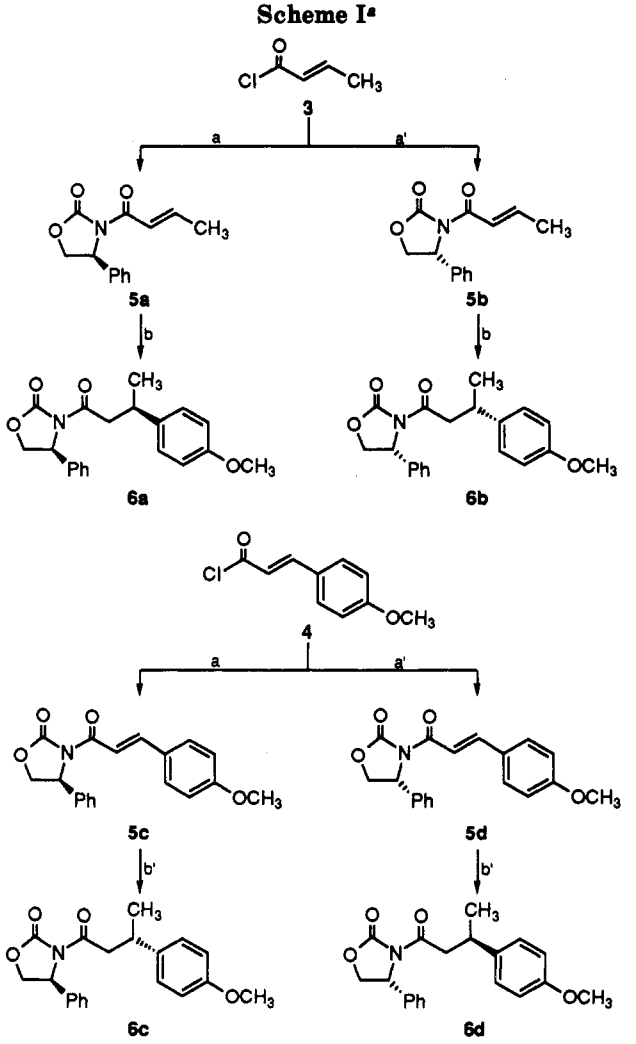
R_3 = Ph-4-OCH_3) because of the structural similarity between the two chiral auxiliaries.[16] Unfortunately, we achieved practically no stereoselectivity (only a 5% diastereoisomeric excess). However, the starting material was quantitatively transformed into a mixture of the expected addition products.

Melnyk et al.[17] introduced 3,4-dimethyl-5-phenyl-2-imidazolidinone (Figure 3; prepared from natural ephedrine and urea) as a chiral auxiliary to perform stereoselective conjugate additions under similar conditions to those mentioned above. The excellent results achieved by using 4-benzyl-2-oxazolidinone as chiral auxiliary in the bromination step and the fact that similar stereochemical considerations can be applied to N-substituted 2-imidazolidinone and 2-oxazolidinone rings prompted us to study 4-phenyl-2-oxazolidinone (Figure 1, method b, R_1 = Ph; Figure 3, **2a,b**) as a chiral auxiliary for these purposes.[16]

Scheme I shows the preparation of *N*-acyloxazolidinones **6a–d**. The preparation of optically pure 4-phenyl-2-oxazolidinone (**2a,b**) was carried out from (*S*)- or (*R*)-phenylglycine as previously described.[16] The substrates for conjugate additions (**5a–d**) were prepared from the lithium salt of the chiral auxiliary and α,β-unsaturated acylchlorides **3** and **4**.[18] Acyloxazolidinones **5a–d** smoothly underwent conjugate addition to afford adducts **6a,b** (>98% de) and **6c,d** (84% de) in nearly quantitative yields. The de values were determined by hydrolysis of the *N*-acyl-2-oxazolidinones, preparation of the 4-benzyl-2-oxazolidinone derivatives of the resulting acids, and reversed phase HPLC analysis.[19] Similar values were obtained by high-field proton NMR spectra by integration of the signals resulting from the proton at position 4 of the heterocyclic ring. The stereochemistry of the process was established by hydrolysis of **6a** and **6c** and determination of the optical rotation of the resulting acids (**1a,b**) whose configuration was already known.[20]

In light of these results, we decided to carry out the large-scale asymmetric synthesis of the four stereoisomers of β-methyltyrosine. However, in order to scale up the process, we slightly modified our strategy. As mentioned above, **6c** was obtained from **5c** together with 8% of the undesired isomer **6a**. In order to avoid the separation of **6c** from **6a**, and overcome the poor solubility **5c**, we decided to explore the strategy shown in Scheme II. Adducts **6a** and **6b** (precursors for the *threo* isomers) were prepared, and part of the material was set aside. The chiral auxiliary of **6a** and **6b** was hydrolyzed from the remainder of the material to afford acids **1a** and **1b**. The acids were then

Scheme I[a]



[a] Key: (a) *n*-BuLi, **2a**, THF, −25 °C; (a') *n*-BuLi, **2b**, THF, −25 °C; (b) (4-methoxyphenyl)magnesium bromide, CuBr/Me_2S, THF, −15 °C; >98% de; (b') methylmagnesium bromide, CuBr/Me_2S, THF, −10 °C to rt; 84% de.

recoupled to the enantiomeric chiral auxiliary to yield **6d** and **6c** (precursors for the erythro isomers) in good yields. We have been able to carry out this transformation on scales up to 40 g without a noticeable loss in yield. The four *N*-acyloxazolidinones thus obtained were used for the stereoselective bromination.

The excellent results achieved with 4-phenyl-2-oxazolidinone and 4-benzyl-2-oxazolidinone in the conjugate addition and electrophilic bromination steps, respectively, prompted us to study the stereoselectivity induced by 4-phenyl-2-oxazolidinone during bromination. On the basis of the results of the conjugate additions with the 4-phenyl- and 4-benzyloxazolidinones (>90% de *vs* 5% de, respectively), it appears that a phenyl group is more capable of shielding the *si* face of the α,β-unsaturated acyloxazolidinones than is a benzyl group. Thus, the attack of incoming nucleophiles is primarily from the opposite (*re*) face. We extended this analogy to the enolate generated during the bromination reaction and hypothesized that bromination at the α-carbon would occur with greater stereoselectivity than was observed with 4-benzyloxazolidinone as the chiral auxiliary. This assumes absence of any appreciable influence from the β-stereocenter during the reaction. The brominations were performed under similar conditions to those used when 4-benzyl-2-oxazolidinone was the chiral auxiliary, and the starting materials

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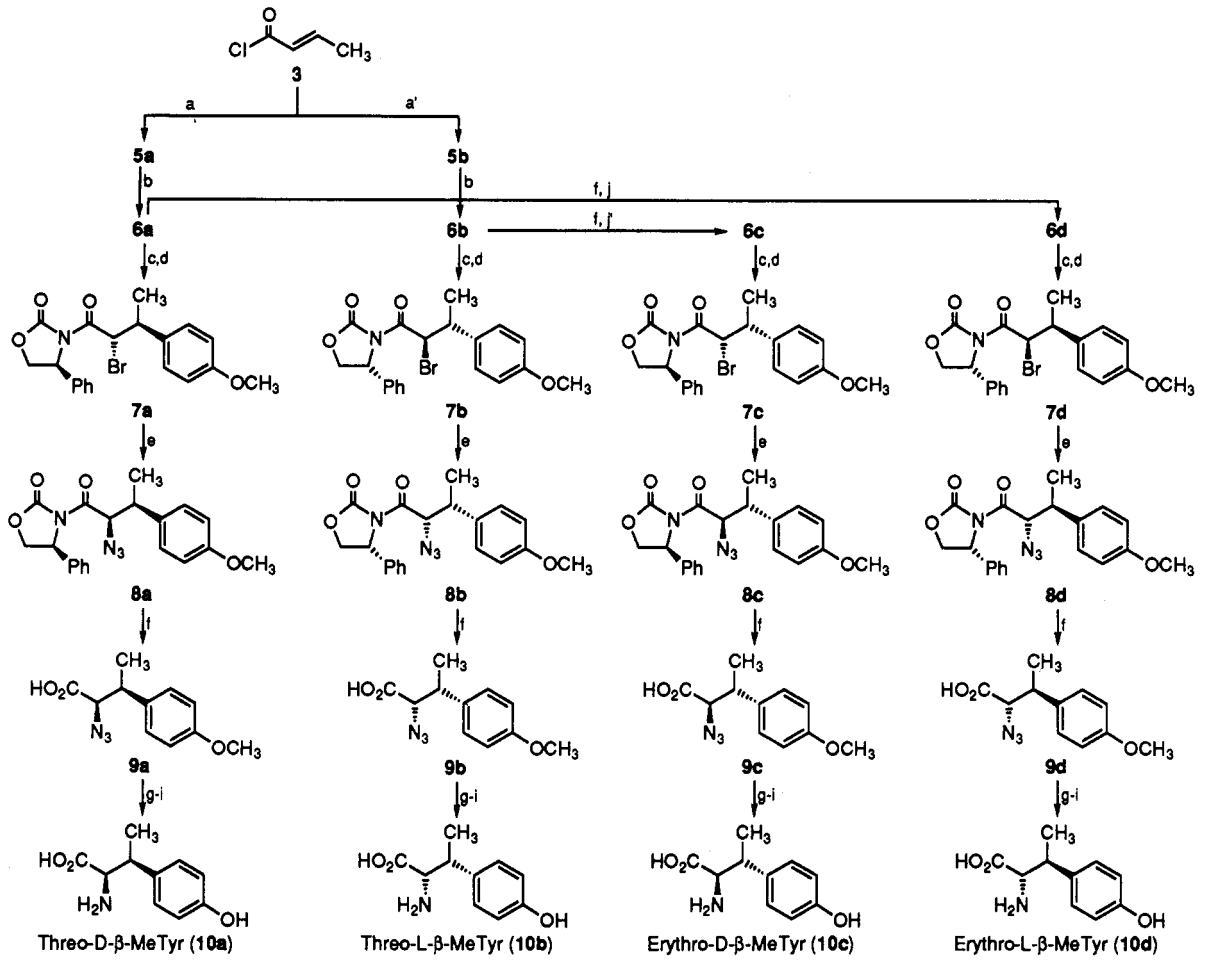
(19) Analytical conditions: VYDAC C_{18} (5-mm particle size), 5 × 250 mm; A, water; B, acetonitrile; gradient, from 40% to 70% in 30 min; 1.5 mL/min; 280 nm; t_R, **6c**, 16.6 min; **6a**, 15.3 min.
(20) Viswanatha, V.; Hruby, V. J. *J. Org. Chem.* **1980**, *45*, 2011.

Scheme II[a]



[a] Key: (a) and (b) see Scheme I; (c) (1) Bu_2BOTf, $(i\text{-}Pr)_2NEt$, 0 °C, (2) CH_2Cl_2, rt; (d) NBS, CH_2Cl_2, −40 °C, (**7a,b** 92% de; **7c,d** >98% de); (e) $(n\text{-}Bu)_4NN_3$, CH_3CN; (f) 30% H_2O_2, LiOH, THF/H_2O, 0 °C, recovery of **2a** or **2b**; (g) H_2, 10% Pd/C, 0.1 M aqueous HCl, rt; (h) HBr/AcOH, 140 °C; (i) 10% aqueous NH_4OH to pH 6; (j) (1) pivaloyl chloride/Et_3N, −78 °C, (2) *n*-BuLi, **2a**, −78 to 0 °C; (j') (1) pivaloyl chloride/Et_3N, −78 °C, (2) *n*-BuLi **2b**, −78 to 0 °C.

were converted stereoselectively to the desired bromides **7a–d** in high yields.[21] High-field proton NMR spectra of the bromination products of **6a,b** showed only one stereoisomer, while a 96:4 mixture of bromides was determined for **6c,d** (92:8 when 4-benzyl-2-oxazolidinone was used as the chiral auxiliary[11]). The bromides thus obtained could be used for the preparation of the four isomers of β-methyltyrosine, as when 4-benzyl-2-oxazolidinone was the chiral auxiliary.

Treatment of bromides **7a–d** with tetra-*n*-butylammonium azide in acetonitrile at room temperature lead to azides **8a–d** without any detectable racemization.[22] Hydrolysis of the chiral auxiliary with LiOH in the presence of hydrogen peroxide produced azido acids **9a–d** and allowed >90% recovery of the corresponding optically pure 4-phenyl-2-oxazolidinone. Special attention has to be paid to the addition of base during this reaction. The 4-phenyl-2-oxazolidinone ring has proven to be more sensitive to internal nucleophilic attack than 4-benzyl-2-oxazolidinone. It is not clear whether this is the result of electronic or steric factors. The dropwise addition of the base solution and strict control of the temperature (slightly below 0 °C) is required to avoid ring opening. The reduction of the azido acids was accomplished with 10% Pd/C catalyst, using 1 N aqueous hydrochloric acid as the solvent. The insoluble powdered azido acids went into solution as they were converted to the *O*,β-dimethyltyrosines, their total disappearance indicating the end of the reaction. The desired amino acids **10a–d** were obtained in high yields after deprotection of phenol group in refluxing 30% HBr in $AcOH/H_2O$.

The optical purity of the amino acids was checked as follows: crude sample of the products were converted to the *N*-(trifluoroacetyl) isopentyl ester derivatives and analyzed by reversed phase HPLC.[25] The analyses of the *erythro* and *threo* amino acid derivatives showed a 98:2 diastereoisomeric mixture and one single peak, respectively. Mosher's reagent was used to evaluate their enantiomeric purity. The four stereoisomers were converted to the corresponding *N*,*O*-Bis[(2'*S*)-2-(trifluoro-

(21) To obtain optimum yields from the bromination reactions, the enolates had to be warmed to 0 °C, the methyl group at the β-carbon being the most likely cause.

(22) In our previous work[11] we used tetramethylguanidinium azide which was prepared from hydrazoic acid and tetramethylguanidine. Tetra-(*n*-butyl)ammonium azide can be obtained safely from sodium azide and tetra(*n*-butyl)ammonium hydroxide in chloroform/water in large quantities.[23]

(23) Brändström, A.; Lamm, B.; Palmertz, I. *Acta Chem. Scand.* **1974**, *28B*, 699.

(24) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

(25) Analytical conditions: VYDAC C_{18} (5-mm particle size), 5 × 250 mm; A, water; B, acetonitrile; isocratic, 40%; 1.0 mL/min; 280 nm; t_R, **10a**, 11.8 min; **10d**, 14.5 min.

methyl)-2-methoxyphenylacetyl]-β-methyltyrosine isobutyl esters.[26] High-field ^{19}F NMR of *erythro*-D and *erythro*-L derivatives showed signals at −70.61 ppm and −70.50 ppm, respectively, corresponding to one of the trifluoromethyl groups. In the case of *threo*-D and *threo*-L derivatives, the signals appears at −70.36 and −70.29 ppm, respectively. Only one stereoisomer could be detected in each case.

In summary, we have demonstrated a facile asymmetric synthesis of the four stereoisomers of the nonproteinogenic amino acid β-methyltyrosine. The synthesis has been devised in such a way that four isomers can be prepared in gram quantities. The methodology should be extendable to a variety of β-substituted α-amino acids and applicable to their preparation on a multigram scale. We are currently working on the synthesis of ring-alkylated β-methyltyrosine and β-methyltryptophan derivatives. The results of these works will be reported elsewhere.

Experimental Section

All reactions were performed under a dry argon atmosphere except for the azide reductions which were carried out under H_2. Unless otherwise noted all reagents were purchased from Aldrich Chemical Co. Tetrahydrofuran was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane, diisopropylethylamine, and triethylamine were distilled from CaH_2. Pivaloyl chloride and crotonyl chloride were distilled under argon atmosphere. *N*-Bromosuccinimide was recrystallized from water and dried *in vacuo* for 24 h prior to use. Tetra-*n*-butylammonium azide was prepared as described in the literature.[23] Elemental analysis was performed by Desert Analytics, Tucson, AZ. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin-Elmer polarimeter using a 1.0-dm cell. Column chromatography was performed using Aldrich silica gel (230–400 mesh, 60 Å). Analytical thin-layer chromatography was performed on E. Merck precoated silica gel 60 F_{254} plates. Detection was done using either I_2, ninhydrin, or UV light. Solvents for chromatography were used without further purification. The (*S*)- and (*R*)-4-phenyl-2-oxazolidinones were prepared according to previously reported methods.[16]

(3(2*E*),4*S*)-3-(2-Butenoyl)-4-phenyl-2-oxazolidinone (5a). To a 1-L round-bottomed flask was added optically pure (4*S*)-4-phenyl-2-oxazolidinone (15 g, 92 mmol, 1 equiv) and dry tetrahydrofuran (450 mL). The solution was cooled to −78 °C, and *n*-butyllithium (58 mL, 92 mmol, 1 equiv; 1.6 M in hexanes) was added. The slurry formed was stirred for 15 min before freshly distilled (2*E*)-butenoyl chloride (9.7 mL, 101 mmol, 1.1 equiv) was added. The resulting clear solution was stirred for 30 min at −78 °C and 1.5 h at 0 °C. The reaction was quenched with a saturated ammonium chloride solution (50 mL), and the volatiles were evaporated. To the resulting suspension was added ether (270 mL) and water (100 mL). The aqueous layer was separated, and the organic layer was washed with saturated sodium bicarbonate solution (2 × 100 mL) and brine (100 mL). The organic solution was dried over anhyd magnesium sulfate. After filtration, the solvent was taken off under vacuum. The solid obtained was chromatographed on a silica gel column (hexanes–ethyl acetate (7:3)) to yield 19.3 g of the title compound as a white solid (91%): R_f = 0.26 (7:3 hexane–ethyl acetate); $[\alpha]^{25}_D$ = +111.8° (*c* = 1.08, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ TMS 7.40–7.25 (m, 6 H), 7.15–6.90 (m, 1 H), 5.47 (dd, *J* = 3.9, 8.8 Hz, 1 H), 4.67 (dd, *J* = 8.8, 8.8 Hz, 1 H), 4.24 (dd, *J* = 3.9, 8.8 Hz, 1 H), 1.92 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.3, 153.6, 147.1, 139.0, 129.0, 128.5, 125.8, 121.6, 69.80, 57.57, 18.39; IR (KBr) 2990, 1785, 1690, 1640, 1340, 1190, 715 cm^{-1}; MS *m/e* (rel intensity) 231 (M, 5), 69 (100); mp 77–79 °C. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.50; H, 5.68; N, 6.05.

(3(3*R*),4*S*)-3-[3(4′-Methoxyphenyl)butanoyl]-4-phenyl-2-oxazolidinone (6a). In a 50-mL round-bottomed flask equipped with a reflux condenser were added magnesium turnings (3.60 g, 0.15 mol, 1.7 equiv) and dry tetrahydrofuran (120 mL). The suspension was cooled to 0 °C, and 4-methoxybromobenzene (16.2 mL, 0.13 mol, 1.5 equiv) was added by syringe. The mixture was allowed to warm to room temperature and stirred for 1 h. Separately, to a 2-L three-necked round-bottomed flask equipped with an addition funnel was added copper(I) bromide–dimethyl sulfide complex (26.6 g, 0.13 mol, 1.5 equiv), dry tetrahydrofuran (300 mL), and anhyd dimethyl sulfide (144 mL). The resulting solution was cooled to −50 °C, and the dark Grignard solution was transferred to it via cannula. The resulting yellow-green mixture was stirred for 10 min and allowed to warm to −10 to −15 °C when a solution of **5a** (20 g, 43.3 mmol, 1 equiv) in dry tetrahydrofuran (160 mL) was added dropwise over 3.5 h. The final solution was stirred for 15 min at room temperature, and the reaction quenched with a saturated aqueous ammonium chloride solution (300 mL). The solids formed were filtered over glass wool. The organic layer was separated and the aqueous solution extracted with dichloromethane (70 mL). The volatiles were evaporated, and dichloromethane (250 mL) was added. The suspension formed was filtered again and the resulting solution washed with 10% aqueous ammonia, water, and brine (200 mL each). The organic solution was dried over anhyd magnesium sulfate. After filtration, the solvent was rotary evaporated under reduced pressure and the crude solid chromatographed on a silica gel column (hexanes–ethyl acetate (7:3)) to yield 26.6 g of the title compound as a white solid (90%): R_f = 0.23 (7:3 hexane–ethyl acetate); $[\alpha]^{25}_D$ = +18.2° (*c* = 0.99, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ TMS 7.28–7.24 (m, 3 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 7.09–7.02 (m, 2 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 5. 36 (dd, *J* = 3.9, 8.8 Hz; 1 H), 4.59 (dd, *J* = 8.8, 8.8 Hz, 1 H), 4.14 (dd, *J* = 3.9, 8.8 Hz, 1 H), 3.77 (s, 3 H), 3.47 (dd, *J* = 6.9, 15.5 Hz, 1 H), 3.27 (m, 1 H), 2.97 (dd, *J* = 7.6, 15.5 Hz, 1 H), 1.22 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 157.8, 153.4, 138.7, 137.3, 128.8, 128.2, 127.7, 125.4, 113.6, 69.60, 57.25, 54.99, 43.08, 35.08, 21.76; IR (KBr) 2960, 1785, 1700, 1515, 1380, 1245, 1205 cm^{-1}; MS *m/e* (relative intensity) 339 (M, 13), 148 (50), 135 (100); mp 85.5–86.5 °C. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.85; H, 6.24; N, 4.10.

(*R*)-3-(4-Methoxyphenyl)butanoic Acid (1a). To a 1-L three-necked round-bottomed flask equipped with an addition funnel, thermometer for measuring internal temperature, and overhead stirrer was added optically pure **6a** (20 g, 59.0 mmol, 1 equiv), tetrahydrofuran (300 mL), and water (100 mL). The mixture was cooled to between −5 and 0 °C when a 30% aqueous solution of hydrogen peroxide (26 mL, 236 mmol, 4 equiv) was added dropwise over 15 min, maintaining the internal temperature below 0 °C. To the slurry formed was added a solution of lithium hydroxide (4 g, 94.4 mmol, 1.6 equiv; in 120 mL water) dropwise over 45 min, again keeping the internal temperature below 0 °C. The mixture was stirred for 2 h when the reaction was quenched with 1.5 N sodium sulfite (180 mL). The volatiles were removed by rotary evaporation under reduced pressure (25–30 °C water bath). The aqueous solution was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and dried over anhyd magnesium sulfate. After removal of the solvents, the oxazolidinone was obtained as a white solid (9.2 g, 95.1% yield). The aqueous phase was acidified with 6 N hydrochloric acid and the precipitated product extracted with dichloromethane (2 × 200 mL). The organics were dried over anhyd magnesium sulfate, filtered, and rotary evaporated under reduced pressure to yield 10.8 g of acid as a colorless oil (94.2%): R_f = 0.26 (7:2.9:0.1 hexane–ethyl acetate–acetic acid); $[\alpha]^{25}_D$ = −55.4° (*c* 1.08, benzene); ^1H NMR (250 MHz, $CDCl_3$) δ TMS 7.15 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 3.79 (s, 3 H), 3.31–3.16 (m, 1 H), 2.69–2.50 (m, 2 H), 1.30 (d, 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 178.9, 158.1, 137.5, 127.6, 113.9, 55.18, 42.89, 42.83, 35.31, 21.98. IR (KBr): 3000, 1700, 1510, 1200, 710, 660 cm^{-1}; MS *m/e* (relative intensity) 195 (M − 1, 14), 135 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.30.

(3(3*R*),4*R*)-3-[3-(4-Methoxyphenyl)butyroyl]-4-phenyl-2-oxazolidinone (6d). To a 1-L round-bottomed flask was added optically pure (*R*)-4-phenyl-2-oxazolidinone (10.0 g, 61.5 mmol, 0.95 equiv) and dry tetrahydrofuran (250 mL). The solution was cooled to −78 °C when *n*-butyllithium (38.5 mL, 61.5 mmol, 0.95 equiv; 1.6 M in hexanes) was added. The slurry formed was

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

allowed to warm to between −20 and −25 °C and was stirred for 10 min. Separately, to a 500-mL round-bottomed flask, was added **1a** (12.5 g, 64.5 mmol, 1.00 equiv) and dry tetrahydrofuran (300 mL). The solution was cooled to −78 °C, and triethylamine (10.8 mL, 77.3 mmol, 1.20 equiv) and pivaloyl chloride (7.8 mL, 67.8 mmol, 1.05 equiv) were added. The mixture was stirred for 10 min at −78 °C and 45 min at 0 °C. The suspension was cooled back to −78 °C, and the lithium salt was transferred via cannula to the mixed anhydride. The mixture was stirred for 4 h at 0 °C and 2 h at room temperature when the reaction was quenched with a saturated aqueous ammonium chloride solution (50 mL). The volatiles were removed by rotary evaporation and the aqueous suspension extracted with dichloromethane (3 × 120 mL). The organic layers were combined and washed with 1 M sodium hydroxide, 1 M sodium bisulfate, and brine (250 mL each). The organics were dried over anhyd magnesium sulfated and filtered, and the solvent was taken off under vacuum to yield 18.0 g of the title compound as a white solid (82.2%). The product can be chromatographed in a short column if there is any unreacted oxazolidinone by TLC: R_f = 0.28 (7:3 hexane–ethyl acetate); $[\alpha]^{25}_D$ = −97.4° (*c* 1.04 $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ TMS 7.37–7.21 (m, 5 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 5.27 (dd, *J* = 3.5, 8.7 Hz, 1 H), 4.51 (dd, *J* = 8.7, 8.7 Hz, 1 H), 4.18 (dd, *J* = 3.5, 8.7 Hz, 1 H), 3.75 (s, 3 H), 3.39–3.22 (m, 2 H), 3.10 (dd, *J* = 4.8, 14.6 Hz, 1 H), 1.22 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 158.0, 139.0, 137.6, 129.0, 128.5, 127.8, 125.8, 113.7, 69.77, 57.41, 55.09, 43.39, 35.01, 22.30; IR (KBr) 2980, 1790, 1520, 1330, 1250, 1235 cm^{-1}; MS *m/e* (relative intensity) 339 (M, 25), 148 (92), 135 (100), 91 (59), 77 (64); mp 87.0–88.0 °C. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.67; H, 6.29; N, 4.11.

General Procedure for the Preparation of Chiral 3-[2-Azido-3-(4-methoxyphenyl)butyroyl]-4-phenyl-2-oxazolidinones, Illustrated by the Preparation of (3(2*S*,3*S*),4*R*)-3-[2-Azido-3-(4-methoxyphenyl)butyroyl]-4-phenyl-2-oxazolidinone (8d). To a 400-mL round-bottomed flask was added (28 g, 82.8 mmol, 1.00 equiv) and dry dichloromethane (72 mL). The solution was cooled to 0 °C when dibutylboron triflate (90.8 mL, 90.8 mmol, 1.10 equiv; 1 M in dichloromethane) and diisopropylethylamine (17.2 mL, 99.2 mmol, 1.20 equiv) were added. The orange solution was allowed to warm to room temperature and stir for 1.5 h. The mixture was cooled to −78 °C and transferred via cannula to a suspension of *N*-bromosuccinimide (19.2 g, 107.6 mmol, 1.30 equiv) in dry dichloromethane (32.0 mL) at −78 °C. The dark violet mixture was stirred for 4 h when the reaction was quenched with pH 7 phosphate buffer (100 mL). Methanol (264 mL) and a 2:1 methanol/30% hydrogen peroxide solution (264 mL) were added dropwise over 1 h, keeping the temperature below 5 °C. The final mixture was stirred for 1 h at 5–10 °C. The volatiles were evapoated, and the residue was partitioned between chloroform and water (360 mL each). The aqueous solution was separated and the organic layer washed with 1 M aqueous sodium bicarbonate (2 × 200 mL), water (400 mL), and brine (200 mL). The organic solution was dried over anhyd magnesium sulfate and filtered, and the solvent was taken off *in vacuo*. The product was prepurified by column chromatography (3:7 ethyl acetate–hexane), and the crude product obtained after removing the volatiles under vacuum was added to a 250-mL round-bottomed flask together with 180 mL of acetonitrile and 148 g of tetra-*n*-butylammonium azide (0.50 mol, 6 equiv). The mixture was stirred for 6 h when the solvent was evaporated and dichloromethane and water (250 mL each) were added. The aqueous layer was separated, and the organic solution was washed with water (4 × 250 mL) and brine (250 mL). The solution was dried over anhyd magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure. The resulting material was purified on a silica gel column (ethyl acetate–hexanes (3:7)) to yield 26.4 g of the title compound as a colorless oil (84%): R_f = 0.29 (4:1 hexane–ethyl acetate); $[\alpha]^{25}_D$ = −99.9° (*c* = 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ TMS 7.41 (m, 5 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 5.36 (dd, *J* = 8.7, 3.6 Hz, 1 H), 5.23 (d, *J* = 8.4 Hz, 1 H), 4.78 (dd, *J* = 9.0, 8.9 Hz, 1 H), 4.44 (d, *J* = 9.0, 3.6 Hz, 1 H), 3.77 (s, 3 H), 3.27–3.10 (m, 1 H), and 1.15 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.3, 156.8, 138.8, 133.6, 129.9, 129.5, 129.3, 127.3, 114.6, 70.77, 64.52, 58.42, 55.78, 42.14, 19.03; IR (KBr) 2980, 2105, 1780, 1740, 1710, 1515, 1250 cm^{-1}; MS *m/e* (relative intensity) 352 (M, 0.1), 135 (100), 91 (20.6), 77 (31.3), 65 (8.6); oil. Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.25; H, 5.33; N, 14.75.

(3(2*R*,3*S*),4*S*)-3-[2-Azido-3-(4-methoxyphenyl)butyroyl]-4-phenyl-2-oxazolidinone (8a). 28.3 g of white solid (90%); R_f = 0.32 (4:1 hexane–ethyl acetate); $[\alpha]^{25}_D$ = +4.8° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ TMS 7.32–7.16 (m, 3 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 6.88–6.77 (m, 2 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 5.39 (dd, *J* = 8.7, 4.2 Hz, 1 H), 5.36 (d, *J* = 8.5 Hz, 1 H), 4.66 (dd, *J* = 8.9, 8.9 Hz, 1 H), 4.16 (dd, *J* = 8.7, 4.2 Hz, 1 H), 3.81, (s, 3 H), 3.35–3.20 (m, 1 H) and 1.26 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.7, 157.9, 152.3, 137.0, 132.8, 128.4, 128.3, 127.7, 124.9, 113.3, 69.38, 63.24, 56.85, 54.50, 40.01, 16.83; IR (KBr) 2980, 2100, 2080, 1780, 1770, 1705, 1220 cm^{-1}; MS *m/e* (relative intensity) 352 (M, 0.02), 135 (100), 91 (17.6), 77 (30.1), 65 (9.0); mp 155.5–6.5 °C. Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.15; H, 5.27; N, 14.72.

General Procedure for the Preparation of the Azido Acids, Illustrated by the Preparation of (2*S*,3*S*)-2-Azido-3-(4-methoxyphenyl)butyric Acid (9d). To a 1-L three-necked round-bottomed flask equipped with an addition funnel, thermometer for measuring internal temperature, and overhead stirrer was added optically pure **8d** (15 g, 44.3 mmol, 1 equiv), tetrahydrofuran (650 mL), and water (230 mL). The mixture was cooled to between −5 and 0 °C when a 30% aqueous solution of hydrogen peroxide (19.5 mL, 177 mmol, 4 equiv) was added dropwise over 15 min, maintaining the internal temperature below 0 °C. To the slurry formed was added a solution of lithium hydroxide (3 g, 70.9 mmol, 1.6 equiv; in 25 mL of water) dropwise over 45 min, again keeping the internal temperature near 0 °C. The mixture was stirred for 45 min (or after complete disappearance of the starting material by TLC, 7.9:2.0:0.1 hexane–ethyl acetate: acetic acid) when the reaction was quenched with 1.5 N sodium sulfite (140 mL). The volatiles were removed by rotary evaporation under reduced pressure (25–30 °C water bath). The aqueous solution was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and dried over anhyd magnesium sulfate. After removal of the solvents, the oxazolidinone was obtained as a white solid (over 95% yield). The aqueous phase was acidified with 6 N hydrochloric acid and the precipitated product extracted with dichloromethane (4 × 200 mL). The organics were dried over anhyd magnesium sulfate, filtered, and rotary evaporated under reduced pressure to yield 12.1 g of the title compound as a white solid (87%): R_f = 0.12 (7.9:2.0:0.1 hexane–ethyl acetate–acetic acid); $[\alpha]^{25}_D$ = −84.5° (*c* 1.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ TMS 7.20 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.00 (d, *J* = 7.4 Hz, 1 H), 3.80 (s, 3 H), 3.39–3.22 (m, 1 H), 1.39 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.1, 158.3, 132.5, 128.8, 114.0, 67.68, 55.21, 40.84, 18.79; IR (KBr) 2960, 2105, 1715, 1515, 1250, 830 cm^{-1}; MS *m/e* (relative intensity 235 (M, 1), 135 (100), 105 (13), 91 (16), 77 (12); mp 71–2 °C. Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.00; H, 5.53; N, 17.83.

(2*R*,3*S*)-2-Azido-3-(4-methoxyphenyl)butyric acid (9d): 9.7 g (93%); R_f = 0.08 (7.9:2.0:0.1 hexane–ethyl acetate–acetic acid); $[\alpha]^{25}_D$ = −37.0° (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ TMS 7.20 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.01 (d, *J* = 6.2 Hz, 1 H), 3.80 (s, 3 H), 3.40–3.27 (m, 1 H), 1.36 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 158.7, 133.1, 128.6, 113.9, 67.99, 55.20, 40.66, 16.13; IR (KBr) 3080, 2100, 1730, 1500, 1180, 820 cm^{-1}; MS *m/e* (relative intensity) 235 (M, 1), 163 (7), 135 (100), 136 (12), 105 (12), 91 (15), 77 (10); mp 108–10 °C. Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.00; H, 5.65; N, 17.98.

General Procedure for the Preparation of the Amino Acids, Illustrated by the Preparation of erythro-L-(2*S*,3*S*)-β-Methyltyrosine (10d). In a 250-mL hydrogenation vessel was suspended 2 g of powdered **9d** (8.5 mmol) in 80 mL of 0.2 N hydrochloric acid. Argon was bubbled through the suspension, and 0.4 g of 10% Pd/C catalyst was added. The final mixture was shaken in a hydrogen atmosphere (1 atm) until the solid disappeared (10–15 h). The catalyst was filtered over Celite and the aqueous solution washed with 2 × 50 mL of chloroform and evaporated to dryness under vacuum. The solid obtained was dissolved in a mixture of 52 mL of 48% aqueous hydrobromic

acid and glacial acetic acid (12 mL). The solution was refluxed (135 °C) for 6 h and decolorized with active charcoal. The suspension was filtered over Celite, and the solvent was evaporated (hydrogen bromide was trapped in a potassium hydroxide tower). The light orange crystalline solid was dissolved in water (20 mL) and the solution neutralized to pH 6 with 10% aqueous ammonium hydroxide. The suspension was cooled to 4 °C and the solid filtered. The solution was concentrated under vacuum, and more product was recovered. A total of 6.6 g of the title compound was obtained as a white solid (two crops, 80%): $[\alpha]^{25}_D$ = −17.2° (c 1.02, aqueous 0.1 N HCl); ^{1}H NMR (chlorohydrate, D_2O) δ TMS 7.22 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.5 Hz, 2 H), 3.93 (d, J = 7.5 Hz, 1 H), 3.38–3.23 (m, 1 H), 1.39 (d, 7.1 Hz, 3 H); ^{13}C NMR (chlorohyrate, D_2O) δ 171.8, 155.4, 131.1, 129.4, 116.1, 59.14, 39.68, 17.26; IR (KBr) 3470, 3310, 1710, 1520, 1220, 1180, 1160 cm^{-1}; FABMS (glycerol) m/e (relative intensity) 196.1 (M + H$^+$, 100); mp 223–4 °C. HPLC analysis[24] of the *N*-(trifluoroacetyl) isobutyl ester derivative of this compound (CIMS-NH_3, m/z M$^+$ + 1 = 348 (<1), M$^+$ + 1 + NH_3 = 365 (100)) showed a 98:2 ratio of **10d** to **10a**. High-field ^{1}H NMR of (2*S*,3*S*,2′*S*)-*N*,*O*-bis[2′-methoxy-2′-(trifluoromethyl)phenylacetyl]-β-methyltyrosine isobutyl ester showed only one enantiomer.

threo-D-(2*R*,3*S*)-β-Methyltyrosine (10a): 1.4 g of white solid (81.7%); $[\alpha]^{25}_D$ = −13.8° (c 0.99, aqueous 0.1 N HCl); ^{1}H NMR (chlorohyrate, D_2O) δ TMS 7.24 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 4.03 (d, J = 5.2 Hz, 1 H), 3.55–3.41 (m, 1 H), 1.38 (d, J = 7.3 Hz, 3 H); ^{13}C (D_2O) δ 171.5, 155.3, 131.1, 129.4, 116.0, 59.00, 39.10, 15.02; IR (KBr) 3320, 2970, 1710, 1670, 1520, 1210, 1180 cm^{-1}; FABMS (glycerol) m/e (relative intensity) 196.1 (M + H$^+$, 100); mp 230–2 °C; HPLC analysis[24] of the *N*-(trifluoroacetyl) isobutyl ester derivative of this compound (CIMS-NH_3, m/z M$^+$ + 1 = 348 (<1), M$^+$ + 1 + NH_3 = 365 (100)) showed a >99:1 ratio of **10a** to **10d**. High-field ^{1}H NMR of (2*R*3*S*,2′*S*)-*N*,*O*-bis[2′-methoxy-2′-(trifluoromethyl)phenyl acetyl]-β-methyltyrosine isobutyl ester showed only one enantiomer.

The enantiomers of the products above described were prepared in an identical fashion. **(3(2*E*),4*R*)-3-(2-Butenoyl)-4-phenyl-2-oxazolidinone (5b)**: $[\alpha]^{25}_D$ = −113.7° (c 1.16, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.14; H, 5.70; N, 5.98. **(3(3*S*),4*R*)3-[3-(4′-Methoxyphenyl)-butanoyl]-4-phenyl-2-oxazolidinone (6b)**: $[\alpha]^{25}_D$ = −20.3° (c 1.07, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.84; H, 6.26; N, 4.15. **(*S*)-3-(4-Methoxyphenyl)butanoic acid (1b)**: $[\alpha]^{25}_D$ = +53.9° (c 1.04, benzene). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.30. **(3(3*S*),4*S*)-3-[3-(4′-methoxyphenyl)butanoyl]-4-phenyl-2-oxazolidinone (6c)**: $[\alpha]^{25}_D$ = +94.3° (c 1.02 $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.78; H, 6.30; N, 4.15. **(3(2*R*,3*R*),4*S*)-3-[2-Azido-3-(4-methoxyphenyl)-butyroyl]-4-phenyl-2-oxazolidinone (8c)**: $[\alpha]^{25}_D$ = +106.4° (c 1.13, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.41; H, 5.31; N, 14.69.

(3(2*S*,3*R*),4*R*)-3-[2-Azido-3-(4-methoxyphenyl)butyroyl]-4-phenyl-2-oxazolidinone (8b): $[\alpha]^{25}_D$ = −4.5° (c 1.11, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.2; H, 5.30; N, 14.65. **(2*R*,3*R*)-2-Azido-3-(4-methoxyphenyl)butyric acid (9c)**: $[\alpha]^{25}_D$ = +84.1° (c 1.09, $CHCl_3$). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.43; H, 5.49; N, 17.87. **(2*S*,3*R*)-2-Azido-3-(4-methoxyphenyl)butyric acid (9b)**: $[\alpha]^{25}_D$ = +33.9° (c 1.12, $CHCl_3$). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.24; H, 5.54; N, 17.86. *erythro*-D-(**2*R*,3*R*)-β-Methyltyrosine (10c)**: $[\alpha]^{25}_D$ = +17.0° (c 0.99, aqueous 0.1 N HCl). *threo*-L-**(2*S*,3*R*)-β-Methyltyrosine (10b)**: $[\alpha]^{25}_D$ = +12.5° (c 1.02, aqueous 0.1 N HCl).

Derivatization of the Four Diastereomers of β-Methyltyrosine. Five mg of the amino acid was dissolved in HCl/2-butanol (1 mL) and heated at 100 °C for 1 h in a stopped tube. The alcohol and the acid were removed at 100 °C under a flow of nitrogen, affording a crystalline product. Dichloromethane (2 mL), (*S*)-2-(trifluoromethyl)-2-methoxyphenylacetyl chloride (10.6 μL, 2.2 equiv), and triethylamine (7.85 μL, 2 equiv) were then added and the solution stirred for a few min. After the reaction was completed (only one spot by TLC, AcOEt–hexanes (1:4)), the organic solution was washed in the same tube with water, a 0.1 M aqueous solution of HCl, water, saturated aqueous $NaHCO_3$, water, and brine (2 mL each). The final solution was dried over anhyd $MgSO_4$, filtered, concentrated, and eluted on a short silica gel column (CH_2Cl_2). The solvent was evaporated under flow of nitrogen and then under vacuum, affording an oil which was used for characterization.

(2*S*,3*S*,2′*S*)-*N*,*O*-Bis[2-(trifluoromethyl)-2-methoxyphenylacetyl]-β-methyltyrosine isobutyl ester: 11.7 mg of colorless oil (67%), R_f = 0.40 (AcOEt–hexanes (1:4)); $[\alpha]^{22}_D$ = −8.5 (c = 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ TMS 7.63–7.24 (m, 10 H), 6.93 (d, J = 9 Hz, 2 H), 6.89 (d, J = 9 Hz, 2 H), 4.90 (dd, J = 6, 10 Hz, 1 H), 3.87 (m, 2 H), 3.65 (s, 3 H), 3.41 (s, 3 H), 3.34 (m, 1 H), 1.90 (m, 1 H), 1.23 (d, J = 7 Hz, 3 H), 0.90 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −70.50 (s, 3 F), −73.08 (s, 3 F); IR (KBr) 3420, 2960, 2925, 1770, 1740, 1705, 1510, 1270, 1225, 1165 cm^{-1}; CIMS (CH_4) m/e (relative intensity) 684 (M + 1, 100), 664 (5), 468 (7), 281 (6), 189 (18).

(2*R*,3*R*,2′*S*)-*N*,*O*-Bis[2-(trifluoromethyl)-2-methoxyphenylacetyl]-β-methyltyrosine isobutyl ester: 12.5 mg of colorless oil (71.5%); R_f = 0.41 (AcOEt–hexanes (1:4); $[\alpha]^{22}_D$ = −11.5 (c = 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ TMS 7.63–7.24 (m, 10 H), 7.23 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8 Hz, 1 H), 7.09 (d, J = 8.5 Hz, 2 H), 4.89 (dd, J = 4.5, 9 Hz, 1 H), 3.84 (m, 2 H), 3.67 (s, 3 H), 3.49 (m, 1 H), 3.19 (s, 3 H), 1.87 (m, 1 H), 1.36 (d, J = 7.5 Hz, 3 H), 0.87 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −70.61 (s, 3 F), −73.11 (s, 3 F); IR (KBr) 3420, 2930, 1770, 1740, 1705, 1505, 1270, 1225, 1165 cm^{-1}; CIMS (CH_4) m/e (relative intensity) 684 (M + 1, 100), 664 (7), 450 (11), 337 (6), 189 9 (19).

(2*S*,3*R*,2′*S*)-*N*,*O*-Bis[2-(trifluoromethyl)-2-methoxyphenylacetyl]-β-methyltyrosine isobutyl ester: 13 mg of colorless oil (74%); R_f = 0.40 (AcOEt–hexanes (1:4); $[\alpha]^{22}_D$ = −34.3 (c = 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ TMS 7.63–7.24 (m, 10 H), 7.06 (d, J = 9.5 Hz, 1 H), 7.03 (d, J = 9 Hz, 2 H), 6.96 (d, J = 9 Hz, 2 H), 4.89 (dd, J = 6, 9.3 Hz, 1 H), 3.80 (m, 2 H), 3.66 (s, 3 H), 3.48 (s, 3 H), 3.27 (m, 1 H), 1.82 (m, 1 H), 1.26 (d, J = 7.5 Hz, 3 H), 0.85 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −70.29 (s, 3 F), −73.11 (s, 3 F); IR (KBr) 3420, 2965, 1770, 1740, 1700, 1510, 1230, 1165, 1115 cm^{-1}; CIMS (CH_4) m/e (relative intensity) 684 (M + 1, 46), 664 (4), 468 (7), 231 (100), 189 (97).

(2*R*,3*S*,2′*S*)-*N*,*O*-Bis[2-(trifluoromethyl)-2-methoxyphenylacetyl]-β-methyltyrosine isobutyl ester: 12.9 mg of colorless oil (74%); R_f = 0.43 (AcOEt/hexanes (1:4); $[\alpha]^{22}_D$ = −30.8 (c = 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ TMS 7.63–7.24 (m, 11 H), 7.24 (d, J = 9 Hz, 2 H), 7.07 (d, J = 9 Hz, 2 H), 4.80 (dd, J = 6.5, 9 Hz, 1 H), 3.74 (m, 2 H), 3.67 (s, 3 H), 3.30 (s, 3 H), 3.29 (m, 1 H), 1.75 (m, 1 H), 1.39 (d, J = 7.5 Hz, 3 H), 0.80 (m, 6 H); ^{19}F NMR ($CDCl_3$) δ −70.36 (s, 3 F), −73.16 (s, 3 F); IR (KBr) 3415, 2925, 1770, 1740, 1700, 1505, 1270, 1225, 1165, 1105 cm^{-1}; CIMS (CH_4) m/e (relative intensity) 684 (M + 1, 100), 664 (6), 450 (9), 337 (5), 189 (11).

Acknowledgment. This research was supported by grants from the U.S. Public Health Service (DK-17420 and DA-06284) and by a grant from the National Science Foundation. E.N. is a recipient of CIRIT Grant No. 88.44/89.49.