Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 19, pp. 3213–3221, 1997

Printed in Great Britain
PII: S0957-4166(97)00381-9 0957-4166/97 $17.00 + 0.00

Asymmetric synthesis of all four isomers of topographically constrained novel amino acids: β-isopropyltyrosines

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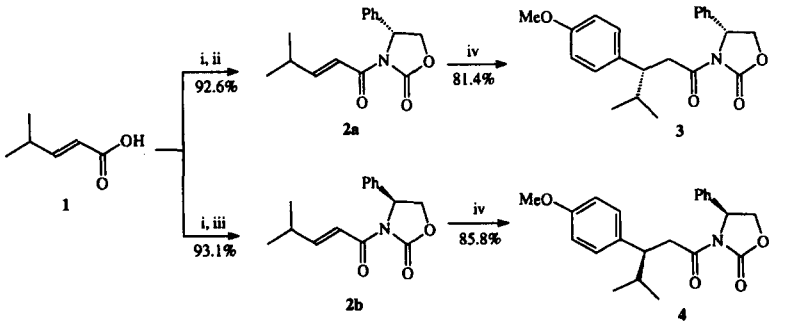
Abstract: All four stereoisomers of the highly constrained novel amino acid, β-isopropyltyrosine, have been synthesized with high stereoselectivities (>90% de) and in 40–50% overall yields by using the optically pure 4-phenyloxazolidinone as a chiral auxiliary via asymmetric Michael addition, direct or indirect azidation, hydrogenolysis and demethylation reactions. © 1997 Elsevier Science Ltd

Stereostructural properties of the side chain groups of amino acid residues in bioactive peptides are extremely important in peptide-receptor/acceptor recognition and subsequent bioactivity.[1] Design and synthesis of novel amino acids with specific, conformationally constrained side chain groups have been crucial for the design of highly selective and potent peptide analogues using topographical considerations.[1b,2] We have designed and synthesized a series of β-branched amino acids[3] and incorporated them into several biologically active peptides in the past decade. These studies have shown that developing novel topographically constrained amino acids with substantial restrictions of side chain torsional mobility can be directly related to successful peptide design.[4] In this paper, we report the total asymmetric synthesis of all four isomers of a new member of the β-branched amino acid family, β-isopropyltyrosine.

The synthesis started from isohexenoic acid **1** (Scheme 1), which was coupled with the optically pure (4R)- or (4S)-4-phenyloxazolidinone to yield the (4R)- or (4S)-4-phenyl-3-isohexenyl-2-oxazolidinone **2a** and **2b** via the mixed anhydride method.[5] An asymmetric Michael addition to the chiral Michael acceptor **2a** or **2b** produced β-isohexenoic acid derivatives **3** or **4**.[6]



i. Et_3N, Me_3CCOCl, -78°C ii. Lithium (R)-(-)-4-phenyloxazolidinone, -78°C-r.t.
iii. Lithium (S)-(+)-4-phenyloxazolidinone, -78°C-r.t. iv. ArMgBr, CuBr·Me_2S(0.5eq), -78°C-10°C

Scheme 1.

Introduction of the azido group to **3** and **4** was accomplished (Scheme 2) either directly by stereoselective electrophilic azidation with trisyl azide,[7] or indirectly by stereoselective bromination

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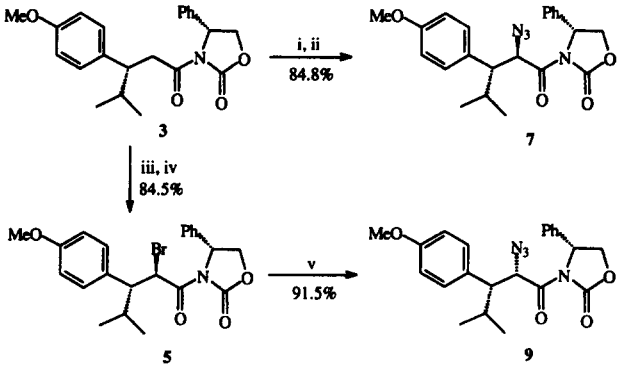
with NBS followed by S_N2 displacement of the bromo group with tetramethylguanidium azide[3,8] to give α-azido products with different α configuration. As illustrated in Scheme 2, the intermediate **3** was converted into the azido compounds **7** and **9** (Scheme 2) by these methods. In both cases the chiral selectivity was excellent (>90% de) in 75–85% yields. The other two isomers **8** and **10** were obtained by the same method.

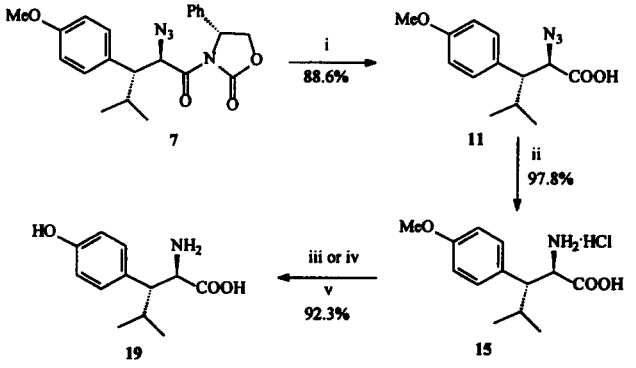


i. KHMDS, Trisyl azide, -78°C-r.t. ii. HOAc

iii. DIEA, $(n\text{-}Bu)_2BOTf$, 0°C iv. NBS, -78°C-0°C v. TMGA, r.t.

Scheme 2.

Further transformations are exemplified with intermediate **7**. The azido acid **11** was obtained (Scheme 3) by hydrolysis of azido compound **7** with simultaneous recovery of the chiral auxiliary.[3k] No epimerization at the α-carbon was detected in any case. The hydrogenolysis of the azido acid **11** at 40–50 psi H_2 in the presence of 10% palladium/carbon catalyst in mixed solvents of acetic acid and water (2:1, v/v) or ethanol containing a little 2 N HCl yielded the amino acid hydrochloride **15**. Finally, the methoxy group of the amino acid was removed either by trifluoromethane sulfonic acid and thioanisole in TFA, or by sodium iodide in 47% hydrobromic acid[9] to yield the free β-isopropyltyrosine **19** (Scheme 3). Using the same methodology the other three stereoisomers **20–22** were synthesized.



i. LiOH, H_2O_2, 0°C ii. 40-50 psi H_2, Pd/C iii. F_3CSO_3H, Thioanisole, TFA

iv. NaI, 47% HBr v. Ion exchange

Scheme 3.

Experimental

All reagents, unless otherwise noted, were purchased from Aldrich and were used without further purification. THF and CH_2Cl_2 were freshly distilled from Na and CaH_2 before use. Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AM 250 spectrometer in $CDCl_3$ or D_2O solvent. Optical rotations were taken on an Autopol III polarimeter. Infrared spectra were taken on an Perkin Elmer FT-IR spectrometer. Elemental analysis was done by Desert Analysis Co., Tucson, Arizona. High resolution mass spectra were determined on JEOL JMS-HX110 Mass Spectrometer, Mass Spectroscopy Facility, Department of Chemistry, The University of Arizona.

General procedure to synthesize 3-(2′-isohexenyl)-4-phenyl-2-oxazolidinone

A solution of (2E)-isohexenoic acid (6.85 g, 60 mmol) in THF (250 mL) was stirred under Ar at −78°C for 15 min, and then triethylamine (6.07 g, 60 mmol) was added via a syringe followed by trimethylacetyl chloride (7.24 g, 60 mmol). The resulting suspension was stirred at −78°C for 15 min, 0°C for 1 h, and then −78°C for 15 min before being transferred via cannula into a slurry of lithium 4-phenyl-2-oxazolidinone at 0°C, which was prepared 10 min in advance at −78°C by addition of n-butyllithium (37.5 mL, 60 mmol) into a solution of 4-phenyl-2-oxazolidinone (9.79 g, 50 mmol) in THF (150 mL) at −78°C. The resulting slurry was stirred at −78°C for 1 h and room temperature for 2 h. The reaction was quenched with saturated ammonium chloride (200 mL). The organic phase was separated. A little water was added to the aqueous phase to dissolve solid, and the solution was extracted with ethyl acetate (2×75 mL). The combined organic phase was washed with saturated bicarbonate (2×100 mL), brine (100 mL) and water (100 mL), dried over anhydrous magnesium sulfate, rotary evaporated, and the crude product was purified by recrystallization from ethyl acetate and hexanes to give the pure product.

*3(2′E),4(R)-3-(4′-Methyl-1′-oxo-2′-pentenyl)-2-oxazolidinone (**2a**)*

Yield 92.6%, white solid, m.p. 103–104°C, $[\alpha]_D^{22}=-103.4$ (c 1.07, $CHCl_3$). IR (KBr, cm^{-1}): 3036, 2962, 1775, 1682, 1630, 1391, 1352, 1213, 713. ^1H NMR (δ, ppm): 7.42–7.01 (m, 7H, aromatic protons and –CH=CH–), 5.50 (dd, J=13.9Hz, 6.1 Hz, 1H, oxazolidinone PhCH–), 4.68 (t, 1H, J=10.6, Hz, oxazolidinone, –HC*H*–), 4.28 (dd, J=14.2 Hz, 6.2 Hz, 1H, oxazolidinone, –*H*CH–), 2.51 (m, 1H, –C*H*$(CH_3)_2$), 1.07 (d, J=11.1 Hz, 6H, –CH(C*H*$_3)_2$). ^{13}C NMR (δ, ppm): 164.9, 158.1, 153.7, 139.1, 129.3, 128.5, 125.7, 117.6, 70.4, 57.2, 31.7, 21.4, 21.3. Anal. for $C_{15}H_{18}O_3N$: Calcd C, 69.48; H, 6.61; N, 5.40. Found C, 69.64; H, 6.57; N, 5.36.

*3(2′E),4(S)-3-(4′-Methyl-1′-oxo-2′-pentenyl)-2-oxazolidinone (**2b**)*

Yield 93.1%, white solid, m.p. 103.5–104°C, $[\alpha]_D^{22}=+103.8$ (c 1.07, $CHCl_3$). IR (KBr, cm^{-1}): 3017, 2964, 1774, 1683, 1636, 1394, 1361, 1212, 712. ^1H NMR (δ, ppm): 7.39–7.01 (m, 7H, aromatic protons and –CH=CH–), 5.49 (dd, J=13.9 Hz, 6.2 Hz, 1H, oxazolidinone PhCH–), 4.70 (t, 1H, J=14.0 Hz, oxazolidinone, –*H*CH–), 4.29 (dd, J=14.1 Hz, 6.0 Hz, 1H, oxazolidinone, –HC*H*–), 2.51(m, 1H, –C*H*$(CH_3)_2$), 1.07 (d, J=11.0 Hz, 6H, –CH(C*H*$_3)_2$). ^{13}C NMR (δ, ppm): 164.9, 158.0, 153.7, 139.1, 129.1, 128.0, 125.9, 117.6, 69.8, 57.7, 31.4, 21.2, 21.1. Anal. for $C_{15}H_{18}O_3N$: Calcd C, 69.48; H, 6.61; N, 5.40. Found C, 69.46; H, 6.57; N, 5.53.

General procedure for Michael addition reaction

To a mixture of ArMgBr and copper(I) bromidedimethyl sulfide complex (5.15 g, 25 mmol) in THF (80 mL) at −78°C was added dropwise a solution of 3(2′E)-3-(4′-methyl-1′-oxo-2′-pentenyl)-4-phenyl-2-oxazolidinone (12.97 g, 50 mmol) in THF (100 mL) under Ar. The resulting mixture was stirred vigorously at −78°C for 15 min and 0°C for 2 h, then slowly warmed to room temperature during 1 h. The reaction was quenched by addition of saturated ammonium chloride (120 mL). The organic phase was separated and the aqueous phase was extracted with ether (2×40 mL). The combined

organic phase was washed with brine (2×50 mL) and water (50 mL), dried over anhydrous magnesium sulfate, and rotary evaporated to give crude product which was purified by column chromatography.

3(3'R),4(R)-3-[3'-(4''-Methoxyphenyl)-4'-methyl-1'-oxo-2'-pentanyl]-4-phenyl-2-oxazolidinone (3)

Yield 81.4%, colorless needles, m.p. 82–84°C. $[\alpha]_D^{22}$=−55.5 (c 1.06, $CHCl_3$). IR (KBr, cm^{-1}): 3027, 2950, 1788, 1702, 1392, 1364, 1327, 1187, 709. ^1H NMR (δ, ppm): 7.21–6.74 (m, 9H, aromatic protons), 5.32 (dd, J=14.0 Hz, 6.5 Hz, 1H, oxazolidinone, PhCH–), 4.56 (t, 1H, J=14.1 Hz, 1H, oxazolidinone, –HCH–), 4.09 (dd, J=14.0 Hz, 6.5 Hz, 1H, oxazolidinone, –*H*CH–), 3.79, (s, 3H, OCH_3), 3.76 (dd, J=16.6 Hz, 5.9 Hz, 1H, $-C_\alpha H-$), 3.06 (dd, J=24.8 Hz, 8.2 Hz, 1H, $-C_\alpha H-$), 2.86 (m, 1H, $-C_\beta H-$), 1.83 (m, 1H, $-CH(CH_3)_2$), 0.95 (d, J=10.7 Hz, 3H, $-CH_3$), 0.73 (d, J=10.7 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 172.1, 157.9, 153.6, 138.5, 134.4, 129.3, 128.8, 128.0, 125.1, 113.3, 69.6, 57.4, 55.0, 48.1, 38.2, 33.3, 20.7, 20.1. Anal. for $C_{22}H_{25}O_4N$: Calcd C, 71.91; H, 6.86; N, 3.81. Found C, 71.92; H, 6.92; N, 3.82.

3(3'S),4(S)-3-[3'-(4''-Methoxyphenyl)-4'-methyl-1'-oxo-2'-pentanyl]-4-phenyl-2-oxazolidinone (4)

Yield 85.8%, colorless needles, m.p. 85–86°C. $[\alpha]_D^{22}$=+54.7 (c 1.02, $CHCl_3$). IR (KBr, cm^{-1}): 3030, 2950, 1777, 1709, 1392, 1510, 1387, 1357, 1240, 1177, 701. ^1H NMR (δ, ppm): 7.24–6.74 (m, 9H, aromatic protons), 5.32 (dd, J=13.9 Hz, 6.5 Hz, 1H, oxazolidinone, PhCH–), 4.60 (t, 1H, J=14.0 Hz, 1H, oxazolidinone, –*H*CH–), 4.12 (dd, J=14.1 Hz, 6.5 Hz, 1H, oxazolidinone, –HC*H*–), 3.82 (s, 3H, $-OCH_3$), 3.74 (dd, J=16.5 Hz, 5.9 Hz, 1H, $-C_\alpha H-$), 3.09 (dd, J=24.9 Hz, 8.2 Hz, 1H, $-C_\beta H-$), 2.88 (m, 1H, $-C_\beta H-$), 1.85 (m, 1H, $-CH(CH_3)_2$), 0.96 (d, J=10.6 Hz, 3H, $-CH_3$), 0.74 (d, J=10.6 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 172.1, 157.9, 153.6, 138.5, 134.4, 129.3, 128.8, 128.0, 125.1, 113.3, 69.6, 57.4, 55.0, 48.1, 38.2, 33.3, 20.7, 20.2. High resolution MS for $C_{22}H_{26}O_4N$: $[M+H]^+$ (Calcd 368.1862. Found 368.1857).

General procedure for direct azidation of N-acyloxazolidinones

A solution of N-acyloxazolidinone **3** (7.35 g, 20 mmol) in THF (50 mL) was stirred at −78°C under Ar. A precooled solution of KHMDS (60 mL, 1 M, 30 mmol) in THF (30 mL) was added via a cannula. The resulting mixture was stirred at −78°C for 30 min. A precooled solution of trisyl azide (9.28 g, 30 mmol) in THF (30 mL) was added via a cannula. The reaction was stirred at −78°C for 15 min and then quenched by addition of acetic acid (5.5 mL, 4.6 eq.). The reaction flask was immersed into a water bath (30–40°C) for 35 min. Then brine (100 mL) was added and the organic phase was separated. The aqueous phase was extracted with ether (2×30 mL). The combined organic phase was washed with brine (2×80 mL) and water (2×80 mL), and dried over anhydrous magnesium sulfate. Removal of the solvents gave the crude product as a light yellow oil, which was purified by column chromatography.

3(2'R,3'R),4(R)-3-[2'-Azido-3'-(4''-methoxyphenyl)-4'-methyl-1'-oxo-2'-pentanyl]-4-phenyl-2-oxazolidinone (7)

Yield 84.8%, colorless oil. $[\alpha]_D^{22}$=−56.4 (c 0.11, $CHCl_3$). IR (film, cm^{-1}): 3031, 2958, 2109, 1777, 1708, 1392, 1510, 1383, 1247, 1037, 698. ^1H NMR (δ, ppm): 7.37–6.77 (m, 9H, aromatic protons), 5.65 (d, J=11.3 Hz, 1H, $-C_\alpha H-$), 5.22 (dd, J=13.4 Hz, 5.0 Hz, 1H, oxazolidinone, PhCH–), 4.73 (t, J=4.8 Hz, 1H, oxazolidinone, –HC*H*–), 4.34 (dd, J=14.1 Hz, 4.8 Hz, 1H, oxazolidinone, –*H*CH–), 3.80 (s, 3H, OCH_3). 2.96 (t, J=11.9 Hz, 1H, $-C_\beta H-$), 2.05 (m, 1H, $-CH(CH_3)_2$), 1.04 (d, J=10.6 Hz, 3H, $-CH_3$), 0.75 (d, J=10.7 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 168.7, 158.7, 153.3, 138.2, 130.1, 130.0, 129.2, 128.9, 125.7, 113.6, 70.5, 62.7, 58.1, 55.1, 52.2, 30.0, 20.9, 20.0. High resolution MS for $C_{22}H_{25}O_4N_4$: $[M+H]^+$ (Calcd 409.1876. Found 409.1867).

3(2'S,3'S),4(S)-3-[2'-Azido-3'-(4''-methoxyphenyl)-4'-methyl-1'-oxo-2'-pentanyl]-4-phenyl-2oxazolidinone (8)

Yield 86.5%, colorless oil. $[\alpha]_D^{22}$=+63.3 (c 0.12, $CHCl_3$). IR (film, cm^{-1}): 3031, 2958, 2109, 1778, 1708, 1392, 1510, 1381, 1247, 1037, 698. ^1H NMR (δ, ppm): 7.36–6.75 (m, 9H, aromatic protons),

5.67 (d, J=11.3 Hz, 1H, $-C_{\alpha}H-$), 5.21 (dd, J=13.4 Hz, 5.0 Hz, 1H, oxazolidinone, PhCH–), 4.71 (t, J=13.9 Hz, oxazolidinone, –*H*CH–), 4.31 (dd, J=10.1 Hz, 5.0 Hz, 1H, oxazolidinone, –HC*H*–), 3.81 (s, 3H, OCH_3), 2.97 (t, J=11.9 Hz, 1H, $-C_{\beta}H-$), 2.05 (m, 1H, $-CH(CH_3)_2$), 1.05 (d, J=10.6 Hz, 3H, $-CH_3$), 0.75 (d, J=10.6 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 168.7, 158.7, 153.3, 138.2, 130.1, 130.0, 129.1, 128.8, 125.6, 113.5, 70.5, 62.6, 57.4, 58.1, 52.2, 29.9, 20.9, 20.0. High resolution MS for $C_{22}H_{25}O_4N_4$: $[M+H]^+$ (Calcd 409.1876. Found 409.1883).

General procedure for asymmetric bromination of N-acyloxazolidinone

A solution of N-acyloxazolidinone (7.35 g, 20 mmol) in DCM (60 mL) was cooled to −78°C with stirring under Ar, and then diisopropylethylamine (3.10 g, 24 mmol) and dibutylborontriflate (7.4 mL, 1 M, 22 mmol) were added via syringe. The light yellow solution was stirred at −78°C for 15 min, 0°C for 1 h and recooled to −78°C for 15 min. The above solution was transferred to a precooled suspension of NBS (7.12 g, 40 mmol) in DCM (50 mL) via cannula. The resulting mixture was stirred at −78°C for 1 h and 0°C for 3 h. The reaction was quenched by addition of 0.5 N sodium bisulfite (100 mL). The organic phase was separated and the aqueous phase was extracted with DCM (2×50 mL). The combined organic phase was washed with brine (2×100 mL) and water (2×100 mL), dried over anhydrous magnesium sulfate, and rotary evaporated to give crude product which was purified by column chromatography.

3(2′R,3′R),4(R)-3-[2′-Bromo-3′-(4′-methoxyphenyl)-4′-methyl-1′-oxo-2′-pentanyl]-4-phenyl-2-oxazolidinone (5)

Yield 84.5%, white solid, m.p. 171–173°C. $[\alpha]_D^{22}$=+15.5 (c 0.86, $CHCl_3$). IR (KBr, cm^{-1}): 3029, 2963, 1781, 1722, 1384, 1345, 1229, 698. ^1H NMR (δ, ppm): 7.40–6.75 (m, 9H, aromatic protons), 6.28 (d, J=17.7 Hz, 1H, $-C_{\alpha}H-$), 5.48 (dd, J=14.3 Hz, 7.5 Hz, 1H, oxazolidinone, PhCH–), 4.78 (t, J=14.2 Hz, 1H, oxazolidinone, –HC*H*–), 4.32 (dd, J=14.4 Hz, 7.4 Hz, 1H, oxazolidinone, –HC*H*–), 3.80 (s, 3H, $-OCH_3$), 3.32 (dd, J=17.8 Hz, 7.1 Hz, 1H, $-C_{\beta}H-$), 1.99 (m, 1H, $-CH(CH_3)_2$), 0.83 (d, J=10.8 Hz, 3H, $-CH_3$), 0.75 (d, J=10.9 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 168.5, 157.9, 153.0, 138.5, 134.5, 129.3, 128.8, 128.0, 125.9, 125.1, 113.3, 69.6, 57.4, 55.1, 48.2, 33.3, 20.7, 17.4. High resolution MS for $C_{22}H_{25}O_4NBr$: $[M+H]^+$ (Calcd 446.0967. Found 446.0973).

3(2′S,3′S),4(S)-3-[2′-Bromo-3′-(4″-methoxyphenyl)-4′-methyl-1′-oxo-2′-pentanyl]-4-phenyl-2-oxazolidinone (6)

Yield 78.8%, white solid, m.p. 173–174°C. $[\alpha]_D^{22}$=−14.5 (c 0.88, $CHCl_3$). IR (KBr, cm^{-1}): 3031, 2954, 1769, 1705, 1388, 1349, 1210, 699. ^1H NMR (δ, ppm): 7.40–6.83 (m, 9H, aromatic protons), 6.27 (d, J=17.7 Hz, 1H, $-C_{\alpha}H-$), 5.48 (dd, J=14.3 Hz, 7.4 Hz, 1H, oxazolidinone, PhCH–), 4.77 (t, J=14.2 Hz, 1H, oxazolidinone, –*H*CH–), 4.32 (dd, J=14.2 Hz, 7.4 Hz, 1H, oxazolidinone, –HC*H*–), 3.80 (s, 3H, $-OCH_3$), 3.30 (dd, J=17.7 Hz, 7.1 Hz, 1H, $-C_{\beta}H-$), 1.99 (m, 1H, $-CH(CH_3)_2$), 0.83 (d, J=10.8 Hz, 3H, $-CH_3$), 0.76 (d, J=11.0 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 172.1, 168.5, 157.9, 138.5, 134.5, 129.3, 128.8, 128.0, 125.1, 113.3, 69.6, 57.4, 55.1, 48.2, 38.2, 33.3, 20.7, 20.2. High resolution MS for $C_{22}H_{25}O_4NBr$: $[M+H]^+$ (Calcd 446.0967. Found 446.0951).

General procedure for azide displacement

3(2′R,3′R),4(R)-3-[2′-Bromo-3′-(4″-methoxyphenyl)-4′-methyl-1′-oxo-2′-pentanyl]-4-phenyl-2-oxazolidinone **5** (6.25 g, 15 mmol) and tetramethylguanidine azide (3.56 g, 22.5 mmol) were dissolved in acetonitrile (100 mL). The solution was stirred under Ar at room temperature for 12 h. The solids were filtered off, and the filtrate was evaporated by rotary evaporation. The crude product was purified by silica gel chromatography.

3(2′S,3′R),4(R)-3-[2′-Azido-3′-(4″-methoxyphenyl)-4′-methyl-1′-oxo-2′-pentanyl]-4-phenyl-2-oxazolidinone (9)

Yield 91.5%, white solid, m.p. 173–174°C. $[\alpha]_D^{22}$=−3.4 (c 0.54, $CHCl_3$). IR (KBr, cm^{-1}): 3030, 2957, 2099, 1767, 1698, 1510, 1393, 1225, 1039, 701. ^1H NMR (δ, ppm): 7.17–6.48 (m, 9H, aromatic

protons), 5.69 (d, J=18.5 Hz, 1H, $-C_{\alpha}H-$), 5.34 (dd, J=14.1 Hz, 7.1 Hz, 1H, oxazolidinone, PhCH–), 4.63 (t, J=14.1 Hz, 1H, oxazolidinone, –HC*H*–), 4.07 (dd, J=12.9 Hz, 7.1 Hz, 1H, oxazolidinone, –*H*CH–), 3.83 (s, 3H, $-OCH_3$). 3.08 (dd, J=18.4 Hz, 11.9 Hz, 1H, $-C_{\beta}H-$), 2.26 (m, 1H, $-CH(CH_3)_2$), 0.91 (d, J=11.0 Hz, 3H, $-CH_3$), 0.79 (d, J=10.9 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 168.7, 158.7, 153.2, 138.1, 131.3, 129.4, 128.6, 128.5, 125.5, 114.0, 70.3, 59.2, 58.1, 55.6, 51.9, 29.0, 21.6, 17.6. High resolution MS for $C_{21}H_{25}O_4N_4$: $[M+H]^+$ (Calcd 409.1876. Found 409.1867).

3(2′R,3′S),4(S)-3-[2′-Azido-3′-(4″-methoxyphenyl)-4′-methyl-1′-oxo-2′-pentanyl]-4-phenyl-2oxazolidinone (10)

Yield 87.3%, white solid, m.p. 167–169°C. IR (KBr, cm^{-1}): 3030, 2956, 2098, 1767, 1697, 1510, 1392, 1225, 1039, 701. ^1H NMR (δ, ppm): 7.20–6.48 (m, 9H, aromatic protons), 5.69 (d, J=18.4 Hz, 1H, $-C_{\alpha}H-$), 5.34 (dd, J=14.2 Hz, 7.1 Hz, 1H, oxazolidinone, PhCH–), 4.63 (t, J=14.1 Hz, 1H, oxazolidinone, *H*CH–), 4.07 (dd, J=14.1 Hz, 7.0 Hz, 1H, oxazolidinone, –HC*H*–), 3.83 (s, 3H, $-OCH_3$), 3.08 (dd, J=18.4 Hz, 6.7 Hz, 1H, $-C_{\beta}H-$), 2.26 (m, 1H, $-CH(CH_3)_2$), 0.91 (d, J=11.0 Hz, 3H, $-CH_3$), 0.79 (d, J=10.9 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 168.7, 158.7, 153.2, 138.1, 131.3, 129.1, 129.4, 128.6, 128.5, 125.5, 114.0, 70.3, 59.2, 58.1, 55.6, 51.9, 29.0, 21.6, 17.6. High resolution MS for $C_{22}H_{25}O_4N_4$: $[M+H]^+$ (Calcd 409.1876. Found 409.1878).

General procedure for the hydrolysis of azido compounds

Into a solution of azido compound **9** (4.08 g, 10 mmol) in THF (120 mL) was added water (40 mL). The solution was stirred at 0°C for 15 min, and then 30% H_2O_2 (6.8 mL, 6 equiv.) was added dropwise followed by dropwise addition of lithium hydroxide (0.92 g, 22 mmol) in water (15 mL). The resulting mixture was stirred at 0°C for 4 h. The reaction was quenched by addition of saturated sodium sulfite (60 mL) and stirred at room temperature for 30 min. The aqueous phase was seperated and extracted with DCM (3×40 mL) for recovery of auxiliary, then acidified with 6 N HCl to pH=1, extracted with DCM (3×40 mL). The combined organic phase was dried over anhydrous magnesium sulfate, rotary evaporated to give crude product, which was used in the next step directly.

(2R,3R)-2-Azido-3-(4′-methoxyphenyl)-4-methylpentanoic acid (11)

Light yellow oil. IR (film, cm^{-1}): 3500–2500, 2109, 1709, 1608, 1510, 1385, 1367, 1249, 1034, 830. ^1H NMR (δ, ppm): 10.6 (s, br, 1H, COOH), 7. 12 (d, J=10.8 Hz, 2H, aromatic protons), 6.82 (d, J=10.8, Hz, 2H, aromatic protons), 4.49 (d, J=8.3 Hz, 1H, $-C_{\alpha}H-$), 3.79 (s, 3H, $-OCH_3$), 2.76 (dd, J=15.1 Hz, 8.3 Hz, 1H, $-C_{\beta}H-$), 2.09 (m, 1H, $-CH(CH_3)_2$), 1.07 (d, J=10.5 Hz, 3H, $-CH_3$), 0.72 (d, J=10.9 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 175.6, 158.6, 130.2, 129.8, 129.0, 113.4, 64.0, 55.1, 53.2, 29.4, 20.9, 20.4.

(2S,3S)-2-Azido-3-(4′-methoxyphenyl)-4-methylpentanoic acid (12)

Light yellow oil. IR (film, cm^{-1}): 3500–2500, 2110, 1712, 1608, 1510, 1385, 1307, 1249, 1035, 830. ^1H NMR (δ, ppm): 10.9 (s, br, 1H, COOH), 7.13 (d, J=13.9 Hz, 2H, aromatic protons), 6.81 (d, J=14.0 Hz, 2H, aromatic protons), 4.49 (d, J=8.3 Hz, 1H, $-C_{\alpha}H-$), 3.79 (s, 3H, $-OCH_3$), 2.76 (dd, J=15.0 Hz, 8.3 Hz, 1H, $-C_{\beta}H-$), 210 (m, 1H, $-CH(CH_3)_2$), 1.06 (d, J=10.5 Hz, 3H, $-CH_3$), 0.72 (d, J=10.6 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 175.6, 158.6, 130.2, 129.8, 129.0, 113.4, 64.0, 55.1, 53.2, 29.4, 20.9, 20.4.

(2S,3R)-2-Azido-3-(4′-methoxyphenyl)-4-methylpentanoic acid (13)

Light yellow oil. IR (film, cm^{-1}): 3500–2500, 2109, 1709, 1608, 1510, 1385, 1367, 1249, 1034, 830. ^1H NMR (δ, ppm): 10.3 (s, br, 1H, COOH), 7.08 (d, J=13.8 Hz, 2H, aromatic protons), 6.82 (d, J=13.9, Hz, 2H, aromatic protons), 4.14 (d, J=11.7 Hz, 1H, $-C_{\alpha}H-$), 3.79 (s, 3H, $-OCH_3$), 2.87 (t, J=11.7 Hz, 1H, $-C_{\beta}H-$), 2.25 (m, 1H, $-CH(CH_3)_2$), 0.94 (d, J=10.7 Hz, 3H, $-CH_3$), 0.77 (d, J=10.9 Hz, 3H, $-CH_3$).

*(2R,3S)-2-Azido-3-(4′-methoxyphenyl)-4-methylpentanoic acid (**14**)*

Light yellow oil. IR (film, cm^{-1}): 3500–2500, 2109, 1709, 1608, 1510 1385, 1367, 1249, 1034, 830. ^1H NMR (δ, ppm): 10.3 (s, br, 1H, COOH), 7.08 (d, J=15.3 Hz, 2H, aromatic protons), 6.82 (d, J=13.9, Hz, 2H, aromatic protons), 4.14 (d, J=11.7 Hz, 1H, $-C_\alpha H-$), 3.79 (s, 3H, $-OCH_3$), 2.87 (t, J=11.7 Hz, 1H, $-C_\beta H-$), 2.27 (m, 1H, $-CH(CH_3)_2$), 0.93 (d, J=10.7 Hz, 3H, $-CH_3$), 0.77 (d, J=10.8 Hz, 3H, $-CH_3$).

General procedure for the reduction of azido acid

Into a solution of the azido compound (2.07 g, 8 mmol) in 50 mL of methanol (50 mL) and 6 N HCl (2 mL) in a hydrogenation vessel was added 10% Pd/C (0.3 g). The reaction vessel was emptied and refilled with hydrogen for three times, and then shaken under 40–50 psi H_2 for 24 hours. The catalyst was filtered off and washed with methanol. The solvent was removed by rotary evaporation. The residue was dissolved in 6 N HCl (6 mL), and rotary evaporated to give the crude product which was used in the next step directly.

*(2R,3R)-2-Amino-3-(4′-methoxyphenyl)-4-methylpentanoic acid (**15**)*

Yield 97.8%, white solid. $[\alpha]_D^{22}=-11.7$ (c 1.04, $CHCl_3$). IR(KBr, cm^{-1}): 3500–2500, 1736, 1608, 1512, 1388, 1368, 1251, 1034, 835. ^1H NMR(δ, ppm): 6.98 (d, J=10.7 Hz, 2H, aromatic protons), 6.78 (d, J=10.7, Hz, 2H, azomatic protons), 4.19 (d, J=8.9 Hz, 1H, $-C_\alpha H-$), 3.60 (s, 3H, $-OCH_3$), 2.84 (dd, J=14.6 Hz, 8.9 Hz, 1H, $-C_\beta H-$), 1.96 (m, 1H, $CH(CH_3)_2$), 0.79 (d, J=10.5 Hz, 3H, $-CH_3$), 0.58 (d, J=11.2, Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 171.9, 158.4, 130.4, 127.8, 114.4, 55.5, 55.3, 51.8, 27.6, 20.1, 19.3. High resolution MS for $C_{13}H_{20}O_3N$: $[M+H]^+$ (Calcd 238.1443. Found 238.1445).

*(2S,3S)-2-Amino-3-(4′-methoxyphenyl)-4-methylpentanoic acid (**16**)*

Yield 91.7%, white solid. $[\alpha]_D^{22}=+12.0$ (c 1.04, $CHCl_3$). IR(KBr, cm^{-1}): 3500–2500, 1729, 1608, 1511, 1386, 1249, 1033, 834. ^1H NMR(δ, ppm): 6.98 (d, J=14.0 Hz, 2H, aromatic protons), 6.79 (d, J=13.9, Hz, 2H, azomatic protons), 4.18 (d, J=9.0 Hz, 1H, $-C_\alpha H-$), 3.60 (s, 3H, $-OCH_3$), 2.84 (dd, J=14.6 Hz, 8.7 Hz, 1H, $-C_\beta H-$), 1.97 (m, 1H, $CH(CH_3)_2$), 0.79 (d, J=10.5 Hz, 3H, $-CH_3$), 0.59 (d, J=10.5, Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 171.9, 158.4, 130.4, 127.8, 114.4, 55.5, 55.3, 51.8, 27.6, 20.1, 19.3. High resolution MS for $C_{13}H_{20}O_3N$: $[M+H]^+$ (Calcd 238.1443. Found 238.1442).

*(2S,3R)-2-Amino-3-(4′-methoxyphenyl)-4-methylpentanoic acid (**17**)*

Yield 96.3%, white solid. IR (KBr, cm^{-1}): 3500–2500, 1729, 1608, 1511, 1386, 1249, 1033 834. ^1H NMR (δ, ppm): 6.96(d, J=14.1 Hz, 2H, aromatic protons), 6.76 (d, J=14.1, Hz, 2H, azomatic protons), 4.22 (d, J=8.9 Hz, 1H, $-C_\alpha H-$), 3.60 (s, 3H, $-OCH_3$), 2.43 (dd, J=16.2 Hz, 7.6 Hz, 1H, $-C_\beta H-$), 2.14 (m, 1H, $-CH(CH_3)_2$), 0.94 (d, J=10.2 Hz, 3H, $-CH_3$), 0.47 (d, J=10.6, Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 171.9, 158.5, 130.4, 129.2, 114.2, 55.3, 55.1, 53.9, 28.9, 20.6, 20.4. High resolution MS for $C_{13}H_{20}O_3N$: $[M+H]^+$ (Calcd 238.1443. Found 238.1438).

*(2R,3S)-2-Amino-3-(4′-methoxyphenyl)-4-methylpentanoic acid (**18**)*

Yield 95.9%, white solid. IR (KBr, cm^{-1}): 3500–2500, 1730, 1609, 1511, 1387, 1368, 1249, 1034, 833. ^1H NMR (δ, ppm): 6.96 (d, J=12.4 Hz, 2H, aromatic protons), 6.77 (d, J=12.3, Hz, 2H, azomatic protons), 4.25 (d, J=5.7 Hz, 1H, $-C_\alpha H-$), 3.60 (s, 3H, $-OCH_3$), 2.46 (dd, J=16.1 Hz, 7.5 Hz, 1H, $-C_\beta H-$), 2.16 (m, 1H, $-CH(CH_3)_2$), 0.95 (d, J=10.3 Hz, 3H, $-CH_3$), 0.47 (d, J=10.4, Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 171.9, 158.5, 130.4, 129.2, 114.2, 55.3, 55.1, 53.9, 28.9, 20.6, 20.4. High resolution MS for $C_{13}H_{20}O_3N$: $[M+H]^+$ (Calcd 238.1443. Found 238.1449).

General procedure for demethylation

Method I. Amino acid chloride **15** (1.45 g, 5.3 mmol) was dissolved in trifluoroacetic acid (60 mL). The solution was cooled to −4°C, thioanisole (4.61 g, 7 eq.) was added and stirred for 10 min, and then trifluoromethensulforic acid (11.9 g, 15 eq.) was added via a syringe. The light yellow cloudy solution

was stirred at 0°C for 4 h. Volatiles were removed by rotary evaporation. The residue was dissolved in water (150 mL) and extracted with DCM (2×30 mL). The aqueous phase was loaded on an ion-exchange column (2.5×46 cm) with Amberlite IR-120 (H^+) resin. The column was washed with 2:3 ($NH_3 \cdot H_2O$:H_2O) ammonium solution. Fractions containing the product were combined, evaporated to remove excess ammonium and water, frozen and lyophilized to give final amino acid **19**. **Method II.** To an amino acid chloride **16** (1.37 g, 5.0 mmol) in hydrobromic acid (48%, 70 mL) was added sodium iodide. The solution was stirred at 90°C for 3 h. Volatiles were removed by rotary evaporation. The residue was dissolved in water (50 mL), and extracted with ethyl acetate (2×30 mL). The aqueous phase was loaded on an ion-exchange column (2.5×46 cm) with Amberlite IR-120 (H^+) resin. The column was washed with 2:3 ($NH_3 \cdot H_2O$:H_2O) ammonium solution. Fractions containing the product were combined, evaporated to remove excess ammonium and water, frozen and lyophilized to give amino acid **20**.

*(2R,3R)-2-Amino-3-(4'-hydroxyphenyl)-4-methylpentanoic acid (**19**)*

Yield 92.3%, white solid, m.p. 235°C decomposed. $[\alpha]_D^{22}=-16.4$ (c=0.56, 1 N HCl). IR (KBr, cm^{-1}): 3500–2500, 1650, 1611, 1581, 1512, 1400, 1345, 1248, 832. ^1H NMR (D_2O, δppm): 6.88(d, J=5.64 Hz, 2H, aromatic protons), 6.67 (d, J=8.45 Hz, 2H, aromatic protons), 3.87 (d, 1H, J=5.57 Hz, 1H, $-C_\alpha H$), 2.69 (m, 1H, $-C_\beta H$), 1.94 (m, 1H, $CH(CH_3)_2$), 0.79 (d, J=6.55 Hz, 3H, CH_3), 0.59 (d, J=6.47, 3H, CH_3). High resolution MS for $C_{12}H_{18}O_3N$: $[M+H]^+$ (Calcd 224.1287. Found 224.1288).

*(2S,3S)-2-Amino-3-(4'-hydroxyphenyl)-4-methylpentanoic acid (**20**)*

Yield 76.2%, white solid, m.p. 230°C decomposed. $[\alpha]_D^{22}=+15.2$ (c=0.57, 1 N HCl).). IR (KBr, cm^{-1}): 3500–2500, 1649, 1612, 1581, 1511, 1401, 1345, 1248, 832. ^1H NMR (D_20, δppm): 6.89 (d, J=10.51 Hz, 2H, aromatic protons), 6.70 (d, J=10.31 Hz, 2H, aromatic protons), 3.86 (d, 1H, J=5.53 Hz, 1H, $-C_\alpha H$), 2.69 (m, 1H, $-C_\beta H$), 1.94 (m, 1H, $CH(CH_3)_2$), 0.78 (d, J=6.53 Hz, 3H, CH_3), 0.58 (d, J=6.61, 3H, CH_3). High resolution MS for $C_{12}H_{18}O_3N$: $[M+H]^+$ (Calcd 224.1287. Found 224.1292).

*(2S,3R)-2-Amino-3-(4'-hydroxyphenyl)-4-methylpentanoic acid (**21**)*

Yield 89.8%, white solid, m.p. 235°C decomposed. $[\alpha]_D^{22}=+5.3$ (c=0.55, 1 N HCl).). IR (KBr, cm^{-1}): 3500–2500, 1610, 1585, 1511, 1409, 1387, 1248, 840. ^1H NMR (D_2O, δppm) 6.88 (d, J=8.57 Hz, 2H, aromatic protons), 6.63 (d, J=8.52 Hz, 2H, aromatic protons), 3.94 (d, 1H, J=4.67Hz, $-C_\alpha H$), 2.37 (dd, J=16.0 Hz, 7.3 Hz, 1H, $-C_\alpha H$), 2.15 (m, 1H. $CH(CH_3)_2$), 0.92 (d, J=6.35 Hz, 3H, CH_3), 0.45 (d, J=6.65, 3H, CH_3). High resolution MS for $C_{12}H_{18}O_3N$: $M+H]^+$ (Calcd 224.1287. Found 224.1284).

*(2R,3S)-2-Amino-3-(4'-hydroxyphenyl)-4-methylpentanoic acid (**22**)*

Yield 92.3%, white solid, m.p. 230°C decomposed. $[\alpha]_D^{22}=-5.1$ (c=0.74, 1 N HCl). IR (KBr, cm^{-1}): 3500–2500, 1610, 1585, 1511, 1409, 1387, 1247, 840. ^1H NMR (D_2O, δppm): 6.88 (d, J=6.62 Hz, 2H. aromatic protons), 6.63 (d, J=7.30 Hz, 2H, aromatic protons), 3.93 (d, J=4.47, 1H, $-C_\alpha H$), 2.35 (m, 1H, $-C_\beta H$), 2.15 (m, 1H, $CH(CH_3)_2$), 0.92 (d, J=6.20 Hz, 3H, CH_3), 0.45 (d, J=6.44, 3H, CH_3). High resolution MS for $C_{12}H_{18}O_3N$: $[M+H]^+$ (Calcd 224.1287. Found 224.1283).

Acknowledgements

This work has been supported by NIDA Grants DA 06284 and DA 04248, and U.S. Public Health Service Grant DK 17420. The contents are the responsibility of the authors and do not necessarily reflect the official views of the US PHS.

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(Received in USA 27 May 1997; accepted 6 August 1997)