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Total Asymmetric Synthesis of Highly Constrained Amino Acids β-Isopropyl-2′,6′-Dimethyl-Tyrosines

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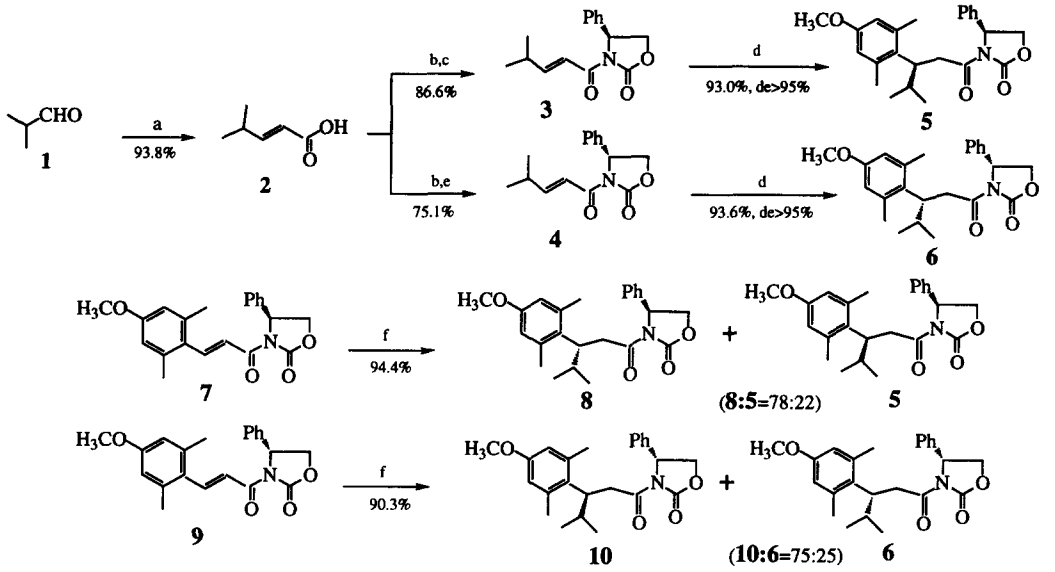
Abstracts: All four stereoisomers of the highly constrained aromatic α-amino acid β-isopropyl-2′,6′-dimethyltyrosine have been asymmetrically synthesized on a large scale. A catalytic asymmetric Michael addition of an organocuprate to a chiral α,β-unsaturated acyloxazolidinone and subsequent direct or indirect stereoselective electrophilic azidation of the α-position of the resulting product was followed by hydrolysis, hydrogenation and finally deprotection of the phenol group to afford the desired amino acids. The reactions generally proceeded in good stereoselectivitities (75-95% ee/de) and yields (70-90%), making these optically pure amino acids available in large scale practical for the synthesis of peptides and other studies. © 1997 Elsevier Science Ltd.

The introduction of topographically constrained unusual amino acids into biologically active peptides is one of the most powerful approaches for examining the topographical requirements of peptide bioactivities.[1] In our laboratory we have designed and synthesized several β-branched amino acids of phenylalanine, tyrosine and other aromatic amino acids[2] and utilized them in the design of several biologically active peptides.[1g, 3] These studies have shown that utilizing topographically constrained analogues can lead to dramatic changes in potency and receptor selectivity of the peptide, and have provided valuable insights about how these amino acid residues in the peptide interact with their receptors.[4] As part of our continuing studies of peptide molecular design, we report here the total asymmetric synthesis of all four isomers of β-isopropyl-2′,6′-dimethyltyrosines on a large scale.

The synthesis began with the synthesis of the unsaturated acid 2*(E)*-5-methyl-2-hexanoic acid (**2**, **Scheme I**) which was prepared by a literature method with some modifications.[5] The coupling of the optically pure chiral auxiliary (4R)-4-phenyloxazolidinone or (4S)-4-phenyloxazolidinone to the acid **2** was accomplished via the mixed anhydride method.[6] We recently reported the synthesis of highly constrained β-aryl isohexanoic acid derivatives starting from the unsaturated acid derivatives **7** and **9** via asymmetric Michael addition.[7] When we used isopropylmagnesium chloride as Grignard reagent to react with an α,β-unsaturated N-acyloxazolidinone, the ratios of the major products **8** and **10** over the minor products **5** and **6** respectively were 4:1~5:1 as determined by quantitative ^{1}H-NMR. Various modifications of the reaction conditions to improve the stereoselectivities failed. Nonetheless, the predominant isomer could be easily obtained in diastereomerically pure form by fractional crystallization from ethyl acetate-hexane. On the other hand, when 2,6-dimethyl-4-methoxyphenylmagnesium bromide was used as the Grignard reagent, only **5** and **6** were obtained, and none of the adducts **8** and **10** were observed in the crude product.[7]

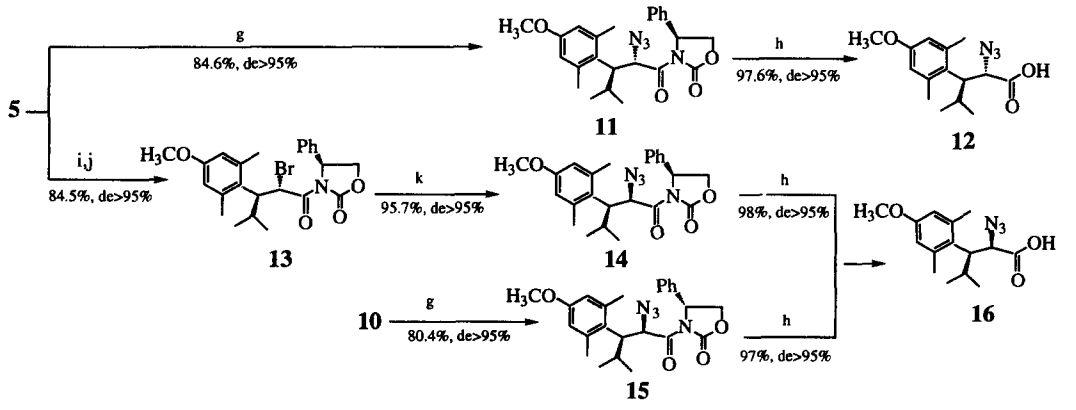
Scheme I



Keys: (a) malonic acid, pyridine, piperidine, r.t.→reflux; (b) triethylamine, trimethylacetyl chloride, -78°C 10min, 0°C 1 hr, -78°C 10min; (c) lithium (S)-(+)-4-phenyloxazolidinone, -78 °C 1 hr, r.t. 3 hrs; (d) 4-methoxy-2,6-dimethylphenyl magnesium bromide, $CuBr{\bullet}Me_2S$, -10~-4 °C 2 hrs, r.t. 2 hrs; (e) lithium (R)-(-)-4-phenyloxazolidinone, -78 °C 1 hr, r.t. 3 hrs; (f) isopropylmagnesium bromide, $CuBr{\bullet}Me_2S$, -10~-4 °C 2 hrs, r.t. 2 hrs

Introduction of the azido group to **5** (or **6**) was achieved either directly by stereoselective electrophilic azidation[8] or indirectly by stereoselective bromination[8] and subsequent replacement of the bromide with nucleophilic tetramethylguanidium azide[9] (**Scheme II**). In both cases the selectivities were excellent (>90% ee/de) with 75-85% yields. The X-ray crystallographic structure of 3(2R,3S),4(S)-3-[2-azido-3-(4′-methoxy-2′,6′-dimethylphenyl)-5-methyl-1-oxohexanyl]-4-phenyl-2-oxazolidinone **15** was obtained to confirm the suggested absolute stereochemistry.[10] The azido acids were obtained by catalyzed hydrolysis of the azido acids

Scheme II



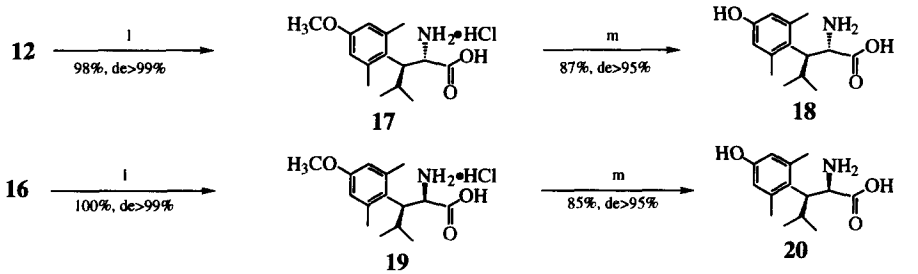
Keys: (g) KHMDS, trisyl azide, -78°C→r.t.; (h) LiOH, H_2O_2, -10~-4 °C, 2 hrs; (i) DIPEA, Bu_2BOTf, -0°C; (j) NBS, -78 °C, 4 hrs, 0 °C, 2 hrs; (k) TMGA, acetonitrile, r.t., 4 days.

with simultaneous recovery of the chiral auxiliary according to the published procedures.[2e] In all cases, no epimerization at the α-carbon was detected.

Free amino acids were obtained by hydrogenolysis of the resulting azido acids in mixed solvents of acetic acid and water (50/50, w/w) or better, in ethanol containing 2 equivalents of hydrochloric acid to yield the hydrochloride salts of the phenol-protected tyrosine derivatives. A high hydrogen pressure (50-70 psi) and long reaction time were employed. The methoxy protecting group of the amino acids was removed either by trifluoromethane sulfonic acid and thioanisole in trifluoroacetic acid at low temperature or by sodium iodide in 47% hydrobromic acid at 90~95°C (**Scheme III**). No racemizations were found in either case. A small scale preparation of the free amino acids were obtained by using ion-exchange resin chromatography for analysis.[11]

Using the same methodology the other two stereoisomers were obtained.[11]

Scheme III



Keys: (l) H_2, 10% Pd/C, 50 psi, EtOH with 2 eq. HCl, 6 hrs,; (m) TFA, trifluoromethanesulfonic acid, thioanisole, 0 °C, 2 hrs.

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References and Notes

1. (a) Hruby, V.J. *Life Sciences*, **1982**, *31*, 189-199. (b) Veber, D.F.; Freidinger, R.M. *Trends Neurosci.* **1985**, *8*, 392-396. (c) Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 512-513. (d) Mosberg, H.I.; Hurst, R.; Hruby, V.J.; Gee, K.; Yamamura, H.I.; Galligan, J.J.; Burks, T.F. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5871-5874. (e) Milner-White, E.J. *Trends Pharm. Sci.* **1989**, *10*, 70-74. (f) Kazmierski, W.; Wire, S.W.; Liu, G.K.; Knapp, R.J.; Shook, J.E.; Burks, T.F.; Yamamura, H.I.; Hruby, V.J. *J. Med. Chem.* **1988**, *31*, 2170-2177. (g) Hruby, V.J.; Tóth, G.; Gehrig, C.A.; Kao, L.-F.; Knapp, R.; Liu, G.K.; Yamamura, H.K.; Kramer, T.H.; Davis, P.; Burks, T.F. *J. Med. Chem.* **1991**, *34*, 1823-1830.

2. (a) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733-4748; (b) Nicolas, E.; Russell, K.C.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 766-770; (c) Nicolas, E.; Russell, K.C.; Knollenberg, J.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 7565 -7571; (d) Jiao, D.; Russell, K.C.; Hruby, V.J. *Tetrahedron* **1993**, *49*, 3511- 3520; (e) Li, G.; Patel, D.; Hruby, V.J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3057-3059; (f) Qian, X.; Russell, K. C.; Boteju, L.W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033-1054. (g) Liao, S.; Hruby, V.J. *Tetrahedron.*

Lett. **1996**, *37*, 1563-1566; (h) Li, G.; Jarosinski, M.A.; Hruby, V.J. *Tetrahedron Lett*, **1993**, *34*, 2561-2564; (I) Li, G.; Patel D.; Hruby, V.J. *Tetrahedron Lett.* **1994**, *35*, 2301-2304; (j) Kazmierski, W.M.; Hruby, V.J. *Tetrahedron Lett.* **1991**, *32*, 5769-5772; (k) Boteju, L.W.; Wegner, K.; Hruby, V.J. *Tetrahedron Lett.* **1992**, *33*, 7491-7494.

3. (a) Hruby, V.J.; Fang, S.N.; Tóth, G.; Jiao, D.; Matsunaga T.O.; Collins, N.; Knapp, R.; Yamamura, H.I. *Peptide 1990, Proceedings of the 21st European Peptide Symposium*, E. Giralt and D. Andreu, eds., ESCOM Publishers, Leiden, The Netherlands; (b) Lebl, M.; Tóth, G.; Slaninová, J.; Hruby, V.J. *Int. J. Peptide Protein Res.* **1992**, *39*, 401-414; (c) Tóth, G.; Russell, K.C.; Landis, G.; Kramer, T.H.; Fang, L.; Knapp, R.; Davis, P.; Burks, T.F.; Yamamura, H.I.; Hruby, V.J. *J. Med. Chem.* **1992**, *35*, 2384-2391; (d) Nikiforovich, G.V.; Prakash, O.; Gehrig, C.A.; Hruby, V.J. *Int. J. Peptide Res.* **1993**, *41*, 347-361; (e) Qian, X.; Kövér, K.E.; Shenderovich, M.D.; Misicka, A.; Zalewska, T.; Horvath, R.; Davis, P.; Porreca, F.; Yamamura, H.I.; Hruby, V.J. *J. Med. Chem.*. **1994**, *37*, 1746-1757; (f) Shenderovich, M.D.; Kövér, K.E.; Nikiforovich, G.V., Jiao, D.; Hruby, V.J. *Biopolymers* **1996**, *38*, 141-156; (g) Haskell-Luevano, C.; Boteju, L.W.; Miwa, H.; Dickinson, C.; Gantz, I.; Yamada, T.; Hadley, M.E.; Hruby, V.J. *J. Med. Chem.* **1995**, *38*, 4720-4729; (h) Azizeh, B.Y.; Shenderovich, M.D.; Trivedi, D.; Li, G.; Sturm, N.S.; Hruby, V.J. *J. Med. Chem.*. **1996**, *39*, 2449-2455.
4. (a) Hruby, V. J. *Biopolymers* **1993**, 33, 1073-1082 (b) Toniolo, C. *Int. J. Pep.Protein Res.* **1990**, *35*, 287-300. (c) Hruby, V.J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249-262.
5. Pirrung, M.C.; Han, H.; Ludwig, R.T. *J. Org. Chem.* **1994**, *59*, 2430-2436.
6. Evans, D.A.; Weber, A.E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.
7. Liao, S.; Han, Y.; Qiu, W.; Bruck, M.; Hruby, V.J. *Tetrahedron Lett.* **1996**, *37*, 7917-7920.
8. Evans, D.A.; Britton, T.C.; Ellman, J.A.; Dorow, R.L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030.
9. Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426-1430.
10. Will be deposited with the Cambridge Crystallographic Data Centre.
11. ***(2S,3S)* 2-Amino-3-(4′-hydroxy-2′,6′-dimethylphenyl)-4-methylpentanoic acid 18**. δppm: 6.41 (s, 2H, aromatic protons), 4.60 (H_2O), 3.82 (d, J=7.2Hz, 1H, -C_αH), 2.92 (2d, J=10.2, 7.2Hz, 1H, -C_βH), 2.15 (m, 1H, C**H**$(CH_3)_2$), 2.12 (s, 3H, Ar-CH_3), 2.09 (s, 3H, Ar-CH_3), 0.85 (d, J=6.2Hz, 3H, CHC**H**$_3$), 0.35(d, J=6.7Hz, 3H, CHC**H**$_3$). High Resolution-CIMS calcd for $C_{14}H_{21}NO_3$: 252.1600 (M^++1). FOUND: 252.1586. $[\alpha]^{22}_D$=+39.95 (c 0.103, MeOH). ***(2S, 3R)* 2-Amino-3-(4′-hydroxy-2′,6′-dimethylphenyl)-4-methylpentanoic acid**. δppm: 6.36 (s, 1H, aromatic protons), 6.34 (s, 1H, aromatic protons), 4.60 (H_2O), 3.89 (d, J=7.2Hz, 1H, -C_αH), 3.02 (2d, J=Hz, 1H, -C_βH), 2.30 (m, 1H, C**H**$(CH_3)_2$), 2.09 (s, 3H, Ar-CH_3), 2.05 (s, 3H, Ar-CH_3), 0.97 (d, J=6.3Hz, 3H, CHC**H**$_3$), 0.40(d, J=6.6Hz, 3H, CHC**H**$_3$). High Resolution-CIMS calcd for $C_{14}H_{21}NO_3$: 252.1600 (M^++1). FOUND: 252.1593. $[\alpha]^{22}_D$=-22.33 (c 0.093, MeOH). ***(2R, 3S)* 2-Amino-3-(4′-hydroxy-2′,6′-dimethylphenyl)-4-methylpentanoic acid 20**. δppm: 6.37 (s, 1H, aromatic protons), 6.35 (s, 1H, aromatic protons), 4.60 (H_2O), 3.88 (d, J=7.2Hz, 1H, -C_αH), 3.02 (2d, J=10.3, 7.2Hz, 1H, -C_βH), 2.30 (m, 1H, C**H**$(CH_3)_2$), 2.09 (s, 3H, Ar-CH_3), 2.06 (s, 3H, Ar-CH_3), 0.97 (d, J=6.3Hz, 3H, CHC**H**$_3$), 0.35(d, J=6.7Hz, 3H, CHC**H**$_3$). High Resolution-CIMS calcd for $C_{14}H_{21}NO_3$: 252.1600 (M^++1). FOUND: 252.1603. $[\alpha]^{22}_D$=+23.29 (c 0.125, MeOH). ***(2R, 3R)* 2-Amino-3-(4′-hydroxy-2′,6′-dimethylphenyl)-4-methylpentanoic acid.** δppm: 6.41 (s, 2H, aromatic protons), 4.60 (H_2O), 3.83 (d, J=7.2Hz, 1H, -C_αH), 2.93 (2d, J=10.4, 7.2Hz, 1H, -C_βH), 2.05 (m, 1H, C**H**$(CH_3)_2$), 2.13 (s, 3H, Ar-CH_3), 2.09 (s, 3H, Ar-CH_3), 0.86 (d, J=6.2Hz, 3H, CHC**H**$_3$), 0.35(d, J=6.7Hz, 3H, CHC**H**$_3$). High Resolution-CIMS calcd for $C_{14}H_{21}NO_3$: 252.1600 (M^++1). FOUND: 252.1597. $[\alpha]^{22}_D$=-38.77 (c 0.127, MeOH).

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