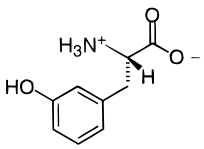
An Efficient Synthesis of (*S*)-*m*-Tyrosine

David M. Bender and Robert M. Williams*

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Received April 14, 1997

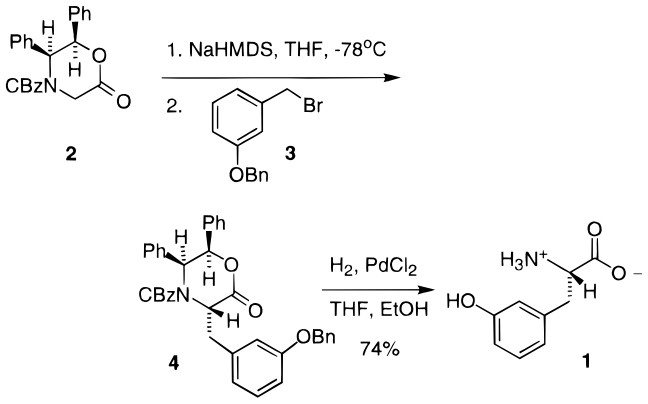
The amino acid (*S*)-*m*-tyrosine[1] (**1**) has found wide use in the area of medicinal chemistry since its discovery. This amino acid has been utilized extensively in the study of the metabolic pathways of the central nervous system.[2] The biological effects of this molecule have been shown to be identical to that of L-Dopa (3,4-dihydroxyphenylalanine), which has been used in the treatment of Parkinson's disease.[3] More recently, this unnatural amino acid has been found in a new class of peptidylnucleoside antibiotics, the mureidomycins[4] and the pacidamycins.[5] In addition, (*S*)-*m*-tyrosine has been used in the synthesis of several aminodiol HIV protease inhibitors.[6] Despite the simplicity of this amino acid, there exist very few methods reported in the literature[7,8] for its synthesis in optically pure form. The method most frequently used to obtain this amino acid appears to be resolution of *d,l*-*m*-tyrosine.[1a,c] We report here a very simple and convenient procedure that can be utilized to unambiguously prepare either (*S*)- or (*R*)-*m*-tyrosine in high optical purity.



1, *meta*-Tyrosine

Optically active (>98% ee) oxazinone **2**[9,10] was condensed with *m*-(benzyloxy)benzyl bromide (**3**) via formation of the sodium enolate (NaHMDS, THF, HMPA, −78 °C). The alkylation product (**4**) was obtained in 87% yield with a diastereomeric excess of >95%. This substance was conveniently converted into *m*-tyrosine (**1**) by catalytic hydrogenation (74% overall from **4**) (Scheme 1). Mosher amide analysis[11] of this material by NMR and GC revealed that the product was obtained in an enantiomeric excess of >96%.

Scheme 1



The current methodology provides a mild and efficient means to prepare *m*-tyrosine in optically active form of high enantiomeric purity. Since both antipodes of **2** are commercially available,[9] this procedure permits the stereochemically unambiguous synthesis of either (*R*)- or (*S*)-*m*-tyrosine in a rapid and convenient manner.

Experimental Section[12]

Preparation of *m*-(Benzyloxy)benzyl Bromide. Commercially available 3-benzyloxy benzyl alcohol (Aldrich) (5.0 g, 23.4 mmol) was converted to the benzyl bromide derivative **3** by reaction with Ph_3P (6.74 g, 25.7 mmol) and CBr_4 (8.50 g, 25.7 mmol) in THF (100 mL) at 25 °C for 1 h. Solid material was removed by filtration, and the crude product was purified by flash chromatography (hexanes) to yield **3** (5.89 g, 91%) as a white solid (recryst hexanes), mp 37−39 °C (dec) ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.39 (2H, s), 4.98 (2H, s), 6.83−6.95 (3H, m), 7.17−7.39 (6H, m). ^{13}C NMR (300 MHz, $CDCl_3$): δ 33.6, 70.2, 115.1, 115.6, 121.7, 127.7, 128.2, 128.8, 130.0, 136.9, 139.4, 159.1. IR ($NaCl/CH_2Cl_2$): 3013, 2985 cm^{-1} HRMS (ES^+) calcd for $C_{13}H_{13}OBr$ 276.0150, found 276.0145.

(3S,5S,6R)-4-[(Benzyloxy)carbonyl)]-5,6-diphenyl-3-{[3′-(benzyloxy)phenyl]methyl}-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4). NaHMDS (12.3 mL, 12.3 mmol, 1 M solution in THF) was added dropwise to a solution of oxazinone **2**[9] (3.17 g, 8.20 mmol) (Aldrich) and *m*-(benzyloxy)benzyl bromide (**3**) (2.50 g, 9.02 mmol) in THF (160 mL) and HMPA (16 mL) at −78 °C. After 3 h, the reaction mixture was poured into ethyl acetate and extracted with brine and H_2O. The organic extracts were dried ($MgSO_4$) and concentrated to a yellow oil which was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1) to give **4** (4.15 g, 87%) as a white solid (recryst CH_2Cl_2/hexanes), mp 146−148 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6, 393 K): δ 3.37 (1H, dd, J = 13.8, 3.9 Hz), 3.49 (1H, dd, J = 13.5, 8.1 Hz), 5.04 (2H, s), 5.09 (2H, s), 5.14 (2H, s), 5.47 (1H, s (br)), 6.59 (2H, d, J = 7.5 Hz), 6.83−7.42 (22H, m). ^{13}C NMR (300 MHz, DMSO-d_6): δ 39.3, 59.9, 67.7, 69.9, 78.4, 114.8, 122.7−138.6 (unresolved), 154.6, 159.6, 168.6. IR (KBr): 1698, 1750, 2950, 3030 cm^{-1} $[a]^{25}_D$ = +52.45° (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{38}H_{33}NO_5$: C, 78.19; H, 5.69; N, 2.39. Found: C, 78.18; H, 5.52; N, 2.19.

Synthesis of (*S*)-*m*-Tyrosine Hydrochloride. To a solution of compound **4** (0.5 g, 0.857 mmol) in ethanol (5 mL) and

(1) (a) Sealock, R. R.; Speeter, M. E.; Schweet, S. *J. Am. Chem. Soc.* **1951**, *73*, 5386; (b) Tong, J. H.; Petitclerc, C.; D'Iorio, A.; Benoiton, N. L. *Can. J. Biochem.* **1971**, *49*, 877. (c) Smith, I. K.; Fowden, L. *Phytochemistry* **1968**, *7*, 1065. (d) Byrkjedal, A.; Mostad, A.; Romming, C. *Acta Chem. Scand.* **1974**, *B28*, 750.

(2) (a) Hollunger, G.; Persson, S.-A. *Acta. Pharmacol Toxicol.* **1974**, *34*, 391. (b) Fell, V.; Greenway, A. M.; Hoskins, J. A. *Biochem. Med.* **1979**, *22*, 246.

(3) Ungerstedt, U.; Fuxe, K.; Goldstein, M.; Battista, A.; Ogawa, M.; Anagnoste, B. *Eur. J. Pharmacol.* **1973**, *21*, 230.

(4) (a) Inukai, M.; Isono, F.; Takahashi, S.; Enokita, R.; Sakaida, Y.; Haneishi, T. *J. Antibiot.* **1989**, *42*, 662. (b) Isono, F.; Inukai, M.; Takahashi, S.; Haneishi, T. *J. Antibiot.* **1989**, *42*, 667. (c) Isono, F.; Katayama, T.; Inukai, M.; Haneishi, T. *J. Antibiot.* **1989**, *42*, 674.

(5) (a) Karwowski, J. P.; Jackson, M.; Theriault, R. J.; Chen, R. H.; Barlow, G. J.; Maus, M. L. *J. Antibiot.* **1989**, *42*, 506. (b) Chen, R. H.; Buko, A. M.; Whittern, D. N.; McAlpine, J. B. *J. Antibiot.* **1989**, *42*, 512. (c) Fernandes, R. B.; Swanson, R. N.; Hardy, D. J.; Hanson, C. W.; Coen, L.; Rasmussen, R. R. *J. Antibiot.* **1989**, *42*, 521.

(6) Chen, P.; Cheng, P. T. W.; Alam, M.; Beyer, B. D.; Bisacchi, G. S.; Dejneka, T.; Evans, A. J.; Greytok, J. A.; Hermsmeier, M. A.; Humphreys, W. G.; Jacobs, G. A.; Kocy, O.; Lin, P.-F.; Lis, K. A.; Marella, M. A.; Ryono, D. E.; Sheaffer, A. K.; Spergel, S. H.; Sun, C.-q.; Tino, J. A.; Vite, G.; Colonno, R. J.; Zahler, R.; Barrish, J. C. *J. Med. Chem.* **1996**, *39*, 1991.

(7) Dugave, C., *J. Org. Chem.* **1995**, *60*, 601.

(8) For reviews on methods to prepare α-amino acids, see: (a) Williams, R. M. *Organic Chemistry Series, Vol. 7: Synthesis of Optically Active a-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press, Oxford, 1989. (b) Duthaler, R. O., *Tetrahedron* **1994**, *50*, 1539.

(9) Both antipodes of **3** are commercially available from Aldrich Chemical Co.: **3**, catalog #33,187-2; antipode of **3**, catalog #33-185-6.

(10) (a) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075. (b) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (c) Williams, R. M. *Aldrichimica Acta* 1992, 25, 11.

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

(12) For general experimental conditions, see ref 10b.

S0022-3263(97)00658-0 CCC: $14.00

THF (5 mL) was added $PdCl_2$ (0.045 g, 0.254 mmol). The reaction mixture was hydrogenated at 50 psi for 18 h. The mixture was purged with nitrogen and filtered through Celite to remove the catalyst. Removal of the solvents *in vacuo*, followed by trituration with Et_2O, produced 0.154 g (99%) of *m*-tyrosine (**1**). This compound was dissolved in 1 N HCl and concentrated, followed by trituration with Et_2O, to give (*S*)-*m*-tyrosine hydrochloride. $[a]^{25}_D$ −7.4° (*c* 2.0, 1 N HCl) (lit.[1b] $[a]^{25}_D$ (*S*)-*m*-tyrosine hydrochloride −7.9° (*c* 2.0, 1 N HCl)) . ^{1}H NMR (300 MHz, D_2O vs HOD): δ 3.11 (1H, dd, J = 14.7, 7.5 Hz), 3.24 (1H, dd, J = 14.4, 5.4 Hz), 4.29 (1H, dd, J = 7.5, 5.7 Hz), 6.71−6.85 (3H, m), 7.26 (1H, t).

Determination of Optical Purity. Oxalyl chloride (48.0 mL, 0.550 mmol) was added dropwise to a solution of the amino acid **1** in ethanol (1 mL) at 0 °C, followed by refluxing for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude amino ester hydrochloride salt was combined with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (24.6 mL, 0.132 mmol) and propylene oxide (40 mL, 0.571 mmol) in THF (1 mL) and heated at 50 °C for 2 h. Optical purity was measured by examination of the ^{1}H NMR spectrum of the resulting Mosher amide and glc analysis (Alltech AT-1, nonpolar polymethylsiloxane) (>96% ee).

Acknowledgment. We are indebted to the National Science Foundation (CHE 8717017) and Microcide Pharmaceutical Co. (in part) for providing financial support. Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumental Grant GM49631.

JO9706584