A Practical Synthesis of L-Azatyrosine†

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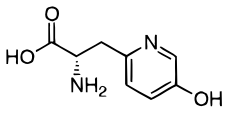
Oncogenic Ras genes and the G-proteins which they encode are important targets for anticancer research.[1] Ras proteins have been implicated to function as components of the cellular signal transduction pathways related to cell proliferation and differentiation.[2] In their oncogenic form, the natural GTP-ase activity of Ras proteins is inhibited, leading to overstimulation of the signaling pathway for cell growth. The potential importance of oncogenic Ras genes and gene products as targets for cancer chemotherapy is underscored by the observation that up to 40% of human colon tumors and 95% of human pancreatic tumors have been found to contain oncogenic Ras genes.[3]

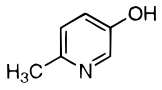
L-Azatyrosine (L-*β*-(5-hydroxy-2-pyridyl)alanine) (**1**) is an antibiotic isolated from *Steptomyces chibaensis*[4] that has recently been shown to restore normal phenotypic behavior to transformed cells bearing oncogenic Ras genes.[5] Importantly, L-azatyrosine (**1**) does not appear to affect cells possessing normal Ras genes.[5a,d] In addition, **1** has been found to inhibit chemical carcinogen-induced tumor growth in mice harboring normal human c-Ha Ras genes.[6]



L-Azatyrosine (**1**)

The limited availability of natural **1** for chemotherapeutic studies has stimulated the development of two recent syntheses of optically active **1**.[7] The first of these[7a] employed Williams' method for the asymmetric synthesis of amino acids,[8] while the second[7b] made use of an organometallic coupling protocol using an organozinc reagent derived from iodoalanine.[9] In addition, several syntheses of racemic **1** have been published, including a synthesis by Norton et al. that predated the isolation of natural **1** by 14 years.[4,10] We have recently described a new method for the synthesis of highly enantiomerically enriched α-amino acids that is based on the diastereoselective alkylation of pseudoephedrine glycinamide (**2**).[11] The method is well suited to the large-scale preparation of α-amino acids. Both enantiomers of pseudoephedrine glycinamide (**2**) are readily prepared on large scale in a single step from inexpensive reagents.[12] Enolates derived from **2** are powerful nucleophiles and undergo highly diastereoselective alkylation reactions with a wide range of electrophiles. Importantly, the pseudoephedrine auxiliary is readily removed under mild conditions without significant epimerization of the α-stereocenter.[10] In this note, we describe a highly practical preparation of multigram quantities of L-azatyrosine of ≥99% ee using this methodology.

The key feature in the planning of our synthetic route was the selection of an appropriate 2-(halomethyl)-5-hydroxypyridine derivative as the electrophilic component in the alkylation reaction. The benzenesulfonyl group proved to be ideal for protection of the phenol group by virtue of its stability to the conditions of free-radical bromination and the conditions of enolate alkylation. In addition, the benzenesulfonyl group conferred greatly enhanced stability to pyridyl benzyl halides such as **5** and **6** (versus, e.g., the corresponding silyl ethers[7a]) and was readily cleaved under the conditions of auxiliary removal (vide infra). The (iodomethyl)pyridine derivative **6** was chosen over the bromide **5** because we have generally found alkylations with iodides to be more diastereoselective than the corresponding bromides.



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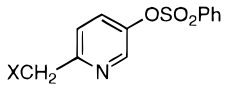

4 X = H
5 X = Br
6 X = I

The (iodomethyl)pyridine derivative **6** was prepared in three steps from commercially available 5-hydroxy-2-methylpyridine (**3**). Treatment of **3** (1 equiv) with benzenesulfonyl chloride (1.1 equiv) and triethylamine (1.2 equiv) in dichloromethane at 0 °C for 2 h provided the benzenesulfonate derivative **4** in 95% yield. Bromination of the methyl group of **4** was achieved using *N*-bromosuccinimide (1.4 equiv) with 2,2′-azobis(2-methylpropiononitrile) as initiator in carbon tetrachloride at reflux. The principal byproduct of the reaction was the corresponding dibromide, which was readily removed by flash-column chromatography. The desired monobro-

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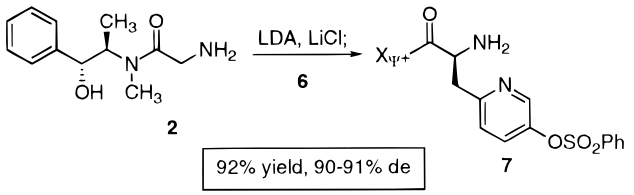
mide **5** was isolated as a white solid (mp 103−108 °C) in 52% yield. In marked contrast to silyl ether derivatives, benzenesulfonate **5** proved to be stable to storage in the solid state. Finkelstein exchange of the bromide with sodium iodide in acetone produced the crystalline iodide **6** (mp 111−113 °C) in 93% yield. Like the bromide, iodide **6** proved to be a storable, stable synthetic intermediate.

The optimum conditions for the alkylation reaction involved the addition of a solution of iodide **6** (1 equiv) to a solution of the enolate derived from (*R*,*R*)-(−)-pseudoephedrine glycinamide [1.5 equiv, generated at 0 °C using 2.93 equiv (relative to **6**) LDA] in the presence of lithium chloride (9 equiv) in tetrahydrofuran at −78 °C. After 3 h at −78 °C, the reaction mixture was warmed to −45 °C and was held at that temperature for 3 h. These conditions typically provided the alkylation



product **7** in 90−95% yield after flash column chromatography. A direct method for the analysis of the diastereoselectivity of the alkylation reaction was not found.[13] Therefore, an indirect procedure was adopted involving complete hydrolysis of **7** to the amino acid **1** (vide infra) followed by analysis of the enantiomeric excess of **1** using a chiral HPLC column.[14,15] In this manner and using the crude alkylation reaction mixture, it was established that the alkylation reaction had proceeded with a minimum diastereoselectivity of 90−91%. When the alkylation reaction was conducted at 0 °C, the diastereoselectivity was slightly diminished (89% de), as was the product yield (80%). The maximum reaction diastereoselectivity (94−95% de) was achieved by conducting the alkylation at −78 °C; however, considerable crystallization of the iodide **6** occurs at this temperature, particularly on larger scales, resulting in diminished yields of product (50−75%). For this reason, the "optimized" protocol, outlined above, entails incubation at −45 °C for 3 h, to allow the reaction to proceed to completion. In this context, it is important to note that if complete consumption of the iodide is not achieved, significant *N*-alkylation of both the starting material **2** and the product **7** will occur upon concentration after workup.[16] The diastereomeric ratio of the alkylation product mixture can be enriched upon flash column chromatography (4:4:92 methanol:triethylamine:dichloromethane), where the undesired minor diastereomer is found to elute first. In a larger-scale preparation, conducted using the "optimum" procedure described above and involving purification by flash column chromatography, **7** was obtained in 97% de and 70% yield (25 g). As expected, use of the bromide **5** in the alkylation reaction led to reduced diastereoselectivity (85% de at 0 °C) relative to the iodide.

As in our previous studies, the pseudoephedrine auxiliary was readily cleaved from the alkylation product **7** by basic hydrolysis (4 equiv of NaOH, H_2O, reflux), conditions which also rapidly hydrolyzed the benzenesulfonate protecting group. Extraction of the crude hydrolysis reaction mixture with dichloromethane led to 90% recovery of the pseudoephedrine auxiliary. The free amino acid **1** was then isolated by ion exchange chromatography (to remove benzenesulfonic acid), followed by recrystallization (H_2O). When this procedure was conducted on **7** of 97% de, a 73% yield (7.7 g) of optically pure (≥99% ee) L-azatyrosine was obtained. Synthetic **1** provided spectroscopic data and physical constants that were identical with those reported for the natural product.[4] Hydrolysis of **7** of lower de (90%) also gave reasonable yields of enantiomerically enriched product (47% yield, 99% ee) after a single recrystallization from water. The chemistry described should be readily adaptable to provide enantiomerically pure L-azatyrosine (**1**) in whatever quantity might be needed.

Experimental Section

General Experimental. All reagents were commercial materials and were used without further purification with the following exceptions. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Toluene was distilled from calcium hydride. Lithium chloride was dried in vacuo (150 °C, 0.5 mmHg) for 12 h and was briefly flame-dried in vacuo after transfer to reaction flasks. Glycinamide **2** was prepared as described.[12] All reactions were carried out under an argon atmosphere. Chromatography was conducted according to the method of Still[17] with 230−400 mesh silica gel. NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. High resolution mass spectra were obtained from the Biomedical Mass Spectrometry Facility, University of California, Los Angeles. HPLC analysis was conducted on a Chiralpak WH column (25 cm × 10 mm, available from J. T. Baker Inc.) using a 0.5 mM $CuSO_4$ mobile phase (5 mL/min) at 50 °C. Retention times for D- and L-azatyrosine are 15.8 min and 22.9 min, respectively (255 nm detection).[15]

5-(Benzenesulfonyloxy)-2-methylpyridine (4). Benzenesulfonyl chloride (12.9 mL, 101 mmol, 1.10 equiv) was added to a stirred solution of 5-hydroxy-2-methylpyridine (10.0 g, 91.6 mmol, 1 equiv) and triethylamine (15.3 mL, 110 mmol, 1.20 equiv) in dichloromethane (100 mL) at 0 °C. After stirring for 2 h at 0 °C, water (20 mL) was added and the resulting two-phase mixture was stirred vigorously for 1 h at 23 °C to quench any remaining sulfonyl chloride. Saturated aqueous potassium carbonate solution (100 mL) was added, and the layers were separated. The aqueous layer was extracted with a second portion of dichloromethane (150 mL). The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of 4:1 to 1:1 of hexane and ethyl acetate to provide **4** (21.8 g, 95%) as an oil. Chromatography may be avoided by using exactly 1 equiv of benzenesulfonyl chloride to afford a product of sufficient purity for direct submission to benzylic bromination conditions (see below): IR (neat) 3066, 1594, 1480, 1450, 1384, 1286, 1204, 1177, 1093, 1024, 865, 837, 804, 757, 741, 724, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1H, J = 2.7 Hz), 7.84 (d, 2H, J = 7.9 Hz), 7.70 (t, 1H, J = 7.2 Hz), 7.55 (t, 2H, J = 7.8 Hz), 7.33 (dd, 1H, J = 8.5, 2.7 Hz), 7.13 (d, 1H, J = 8.5 Hz), 2.53 (s, 3H). Anal. Calcd

(13) ^{1}H NMR analysis is complicated by the presence of amide rotamers. The involatility of **1** made capillary GC analysis impractical, and conditions for the separation of the diastereomeric alkylation products by HPLC have not been found.

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(15) In order to properly identify the minor enantiomer for HPLC analysis, D-azatyrosine was prepared by alkylation of the enantiomeric pseudoephedrine glycinamide ((*S*,*S*)-(+)-**2**) with iodide **6** followed by alkaline hydrolysis. D-Azatyrosine showed equivalent spectroscopic properties as L-azatyrosine, but opposite optical rotation.

(16) In contrast to other alkyl halides we have studied, small amounts of *N*-alkylation products are observed (<5%) during the alkylation with the highly reactive electrophile **6** whenever the reactions are conducted above −78 °C. These *N*-alkylation products are readily separated from the desired product by chromatography.

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for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.66; H, 4.33; N, 5.47.

5-(Benzenesulfonyloxy)-2-(bromomethyl)pyridine (5). A mixture of **4** (33.48 g, 134.3 mmol, 1 equiv) and *N*-bromosuccinimide (33.47 g, 188.0 mmol, 1.40 equiv) in deoxygenated carbon tetrachloride (300 mL) was heated to reflux. 2,2′-Azobis-(2-methylpropiononitrile) (2.00 g, 11.6 mmol, 0.09 equiv) was added to the refluxing mixture and heating was continued. Additional 2.00-g portions of 2,2′-Azobis(2-methylpropiononitrile) were added to the refluxing reaction mixture at 30 min intervals over a a total reaction period of 2 h. Heating was discontinued after 2 h, and the reaction mixture was allowed to cool. The crude reaction mixture was concentrated in vacuo to remove the bulk of the carbon tetrachloride, and the resulting slurry was diluted with ethyl acetate (500 mL) and washed with water (400 mL). The organic layer was washed with a mixture of saturated aqueous sodium bicarbonate solution (250 mL) and saturated aqueous sodium thiosulfate solution (100 mL). The aqueous layers were extracted with a second portion of ethyl acetate (250 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with a gradient of 4:1 dichloromethane:hexanes to dichloromethane to 10:1 dichloromethane:ethyl acetate to provide **5** (23.08 g, 52%) as a white solid: mp 103−108 °C; IR (KBr) 3022, 1584, 1480, 1376, 1368, 1023, 1180, 1087, 1022, 854, 812, 766, 734, 689, 620, 603, 579, 548 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (s, 1H), 7.86 (d, 2H, J = 7.4 Hz), 7.72 (t, 1H, J = 7.5 Hz), 7.57 (t, 2H, J = 7.9 Hz), 7.45 (d(obs), 2H, J = 1.5 Hz), 4.51 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 155.6, 145.5, 143.4, 134.8, 134.6, 131.0, 129.4, 128.4, 124.2, 32.5. Anal. Calcd for $C_{12}H_{10}BrNO_3S$: C, 43.92; H, 3.07; N, 4.27. Found: C, 43.72; H, 3.01; N, 4.16.

5-(Benzenesulfonyloxy)-2-(iodomethyl)pyridine (6). Sodium iodide (5.48 g, 36.6 mmol, 2.00 eqiuv) was added to a solution of **5** (6.00 g, 18.3 mmol, 1 equiv) in acetone (75 mL), and the resulting heterogeneous mixture was stirred for 2.5 h at 23 °C. Acetone was removed by concentration in vacuo. The residue was diluted with ethyl acetate (100 mL), and the resulting mixture was washed with water (100 mL). The organic layer was extracted with a mixture of saturated aqueous sodium bicarbonate solution (30 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The aqueous layers were extracted with a second portion of ethyl acetate (75 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to produce a yellow-brown solid. The product was recrystallized from a mixture of ethyl acetate (15 mL) and ether (30 mL) to provide 5.18 g of **6** as a stable, light brown crystalline solid. Concentration of the mother liquors and recrystallization provided an additional 1.19 g of **6** (total 6.37 g, 93%). Larger scale preparations of this compound (20 g of **6**) provided yields of 75−82%: mp 111−113 °C; IR (KBr) 3032, 1584, 1475, 1450, 1375, 1299, 1203, 1179, 1087, 1020, 946, 853, 808, 763, 733, 689, 611, 583, 568, 545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (dd, 1H, J = 1.0, 2.2 Hz), 7.85 (dd, 2H, J = 1.0, 8.2 Hz), 7.72 (t, 1H, J = 6.3 Hz) 7.57 (t, 2H, J = 7.4 Hz), 7.39 (m, 2H), 4.47 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 157.1, 144.9, 143.3, 134.7, 134.4, 130.8, 129.4, 128.3, 123.5, 4.5. Anal. Calcd for $C_{12}H_{10}INO_3S$: C, 38.42; H, 2.69; N, 3.73. Found: C, 38.51; H, 2.85; N, 3.47.

[[*R*,*R*]-2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl 2-amino-3-(2-(5-benzenesulfonyloxy)pyridyl)propionamide (7). A solution of *n*-butyllithium in hexanes (2.64 M, 29.5 mL, 78.0 mmol, 2.93 equiv) was added to a solution of diisopropylamine (11.2 mL, 80.0 mmol, 3.00 equiv) in deoxygenated tetrahydrofuran (50 mL) at 0 °C. After 15 min, the resulting solution of lithium diisopropylamide was transferred via cannula over 5 min to a stirred slurry of anhydrous **2** (8.89 g, 40.0 mmol, 1.50 equiv) and flame-dried lithium chloride (10.2 g, 240 mmol, 9.00 equiv) in deoxygenated tetrahydrofuran (100 mL) at 0 °C. After 20 min, the bright yellow suspension was cooled to −78 °C and a solution of **6** (10.0 g, 26.7 mmol, 1 equiv) in tetrahydrofuran (40 mL with a 10-mL wash) was added slowly to the reaction mixture. The reaction mixture was stirred for 3 h at −78 °C and was then warmed to −45 °C and stirred for an additional 3 h. Water (400 mL) was added, and the resulting two-phase mixture was warmed to 23 °C and extracted with one 400-mL and two 200-mL portions of dichloromethane. The combined organic layers were dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with 4:4:92 methanol:triethylamine:dichloromethane. Although the diasteromers were largely separable, they were collected together in order to establish the true overall reaction yield. After concentration of appropriate fractions, the product residue was concentrated from toluene (2 × 150 mL) and then chloroform (2 × 150 mL) to remove residual triethylamine. The product **7** was isolated as a very thick oil (11.6 g, 92%). The diastereoselectivity of the reaction was determined by removing a small sample of the crude reaction product (prior to chromatography) and subjecting it to aqueous alkaline hydrolysis conditions (see below), followed by acidification of the aqueous hydrolysis mixture to pH 6 with concd H_3PO_4 and analysis on a chiral HPLC column (see General Experimental). TLC R_f major diasteromer = 0.52, minor diasteromer = 0.65 (5:5:90 MeOH:NEt_3:CH_2Cl_2); IR (neat) 3352, 3062, 2980, 1634, 1480, 1454, 1379, 1205, 1177, 1093, 1024, 868, 755, 738, 702 cm^{-1}; ^1H NMR (approximately 1:1 rotamer ratio, $CDCl_3$) δ 8.10 (d, 0.5H, J = 4.2 Hz), 8.09 (d, 0.5H, J = 2.7 Hz), 7.83 (d, 2H, J = 7.2 Hz), 7.69 (t, 1H, J = 7.4 Hz), 7.55 (t, 2H, J = 7.9 Hz), 7.16−7.41 (m, 7H), 4.71 (d, 0.5H, J = 8.4 Hz), 4.60 (d, 0.5H, J = 9.3 Hz), 4.33 (dd, 0.5H, J = 6.8, 4.8 Hz), 4.16−4.26 (m, 1H), 4.12 (dd, 0.5H, J = 7.0, 5.7 Hz), 3.44 (dd, 0.5H, J = 14.5, 4.7 Hz), 3.12 (dd, 0.5H, J = 14.5, 7.0 Hz), 2.94 (s, 1.5H), 2.90 (s, 1.5H), 2.83−2.99 (m, 1H), 1.5−3.0 (s(br), 3H), 1.01 (d, 1.5H, J = 6.9 Hz), 0.97 (d, 1.5H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 175.3, 174.6, 157.6, 156.9, 144.9, 143.0, 142.8, 142.1, 141.5, 134.9, 134.5, 130.2, 130.1, 129.8, 128.5, 128.3, 128.2, 128.1, 127.6, 127.1, 126.6, 124.8, 124.7, 75.4, 75.3, 59.0, 58.0, 51.6, 51.2, 42.9, 42.7, 32.5, 26.9, 15.7, 14.1. HRMS for $C_{24}H_{28}N_3O_5S$ (MH+) requires 470.1750, found 470.1737. Anal. Calcd for $C_{24}H_{27}N_3O_5S$: C, 61.39; H, 5.80; N, 8.95. Found: C, 59.96; H, 5.81; N, 8.64.

[*S*]-2-Amino-3-(5-hydroxypyridyl)propanoic Acid (L-Azatyrosine, 1). A suspension of **7** (27.22 g, 57.97 mmol, 1 equiv, 97% de) in aqueous sodium hydroxide solution (0.500 M, 464 mL, 232 mmol, 4.00 equiv) was heated at reflux for 6 h. The resulting homogeneous solution was then cooled to 23 °C and extracted with two portions of dichloromethane (500 mL, 250 mL). The organic layers were combined and extracted with water (200 mL) and then dried over anhydrous potassium carbonate. Concentration of the organic layers provided 8.61 g (90%) of recovered pseudoephedrine. The combined aqueous layers were acidified with aqueous hydrochloric acid solution (1.00 M, 232 mL, 232 mmol, 4.00 equiv) producing a slightly acidic solution (pH = 3). The volume of the aqueous solution was reduced to approximately 100 mL in vacuo, and the concentrate was applied to an ion exchange resin (100 g, Dowex 50WX4, 50−100 mesh). The resin was flushed with water until the eluent was neutral (pH = 6). The product was then eluted with 0.25 M aqueous ammonium hydroxide solution (Note: on occasion the product will begin to precipate on the column. In this case, the column contents are transferred to a large sintered-glass funnel and the product is eluted with 0.25 M aqueous ammonium hydroxide solution). The ninhydrin-positive fractions were combined and concentrated to provide 9.73 g of a pale yellow solid. The solid was recrystallized from water (400 mL) to afford 4.358 g (41%) of L-azatyrosine as a pale solid. Concentration and crystallization of the mother liquors provided two additional crops of product (3.399 g, 32%). If desired, the mother liquors may be decolorized by the addition of activated charcol and filtration through Celite prior to recrystallization. All three crops of amino acid were ≥99% ee and all passed CHN analysis: mp 253−256 °C dec, lit.[4] 262−263 °C dec; $[\alpha]^{20}_D$ = +59.3 (c = 1.08, 1 N HCl), lit.[4] +55 (c = 1.1, 1 N HCl); IR (KBr) 3084, 2988, 1625, 1597, 1571, 1489, 1410, 1347, 1294, 1255, 1150, 850, 692, 525 cm^{-1}; ^1H NMR (D_2O) δ 8.05 (d, 1H, J = 2.5 Hz), 7.28 (dd, 1H, J = 8.5, 2.8 Hz), 7.21, (d, 1H, J = 8.4 Hz), 4.03 (dd, 1H, J = 7.9, 5.1 Hz), 3.29 (dd, 1H, J = 15.1, 5.1 Hz), 3.15 (dd, 1H, J = 15.1, 7.9 Hz). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.57; H, 5.65; N, 15.00.

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