HETEROCYCLES, Vol. 61, 2003, pp. 563 - 567
Received, 27th June, 2003, Accepted, 8th September, 2003, Published online, 2nd October, 2003

A STEREOCONTROLLED SYNTHESIS OF (*R*)- AND (*S*)-AZATYROSINE‡

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Abstract – An asymmetric synthesis of (*R*)- or (*S*)- azatyrosine, starting from (2*S*)- or (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **(5)** (Schöllkopf reagent) and 5-benzenesulfonyloxy-2-hydroxymethylpyridine **(3)**, is reported. The diastereocontrolled addition gives mainly one of two possible adducts with the (2*S*, 5*R*) or (2*R*, 5*S*) configuration respectively. After the removal of the chiral auxiliary and benzenesulfonyloxy group, azatyrosine is obtained in good yields and high ee.

In continuation of our studies in the field of heterocyclic substituted α-aminoacids[1,2] we have investigated the preparation of azatyrosine. This antibiotic, first isolated in homochiral form from *Streptomyces chibanesis*,[3] has recently been found to possess important antitumoral properties.[4] In view of its biological activity and potential lead compound in anticancer research the requirement for different synthetic methods is so far apparent.

Many syntheses of (*R*)- or (*S*)- azatyrosine have been described[5] prompting us to report our own method based on the use of Schöllkopf reagent as a chiral auxiliary.

As outlined in the **Scheme**, commercially available 5-hydroxy-2-methylpyridine **(1)** was transformed in conventional way to **3**. Owing the known instability of 2-halomethylpyridines,[4,5b] **3** was treated with diphenylphosphoryl chloride to give **4**. This derivative proved to be useful for the activation of the 2-pyridylmethyl residue, resulting the most efficient leaving group in the enolate alkylation conditions.

‡ On the occasion of the 30th Anniversary of Heterocycles
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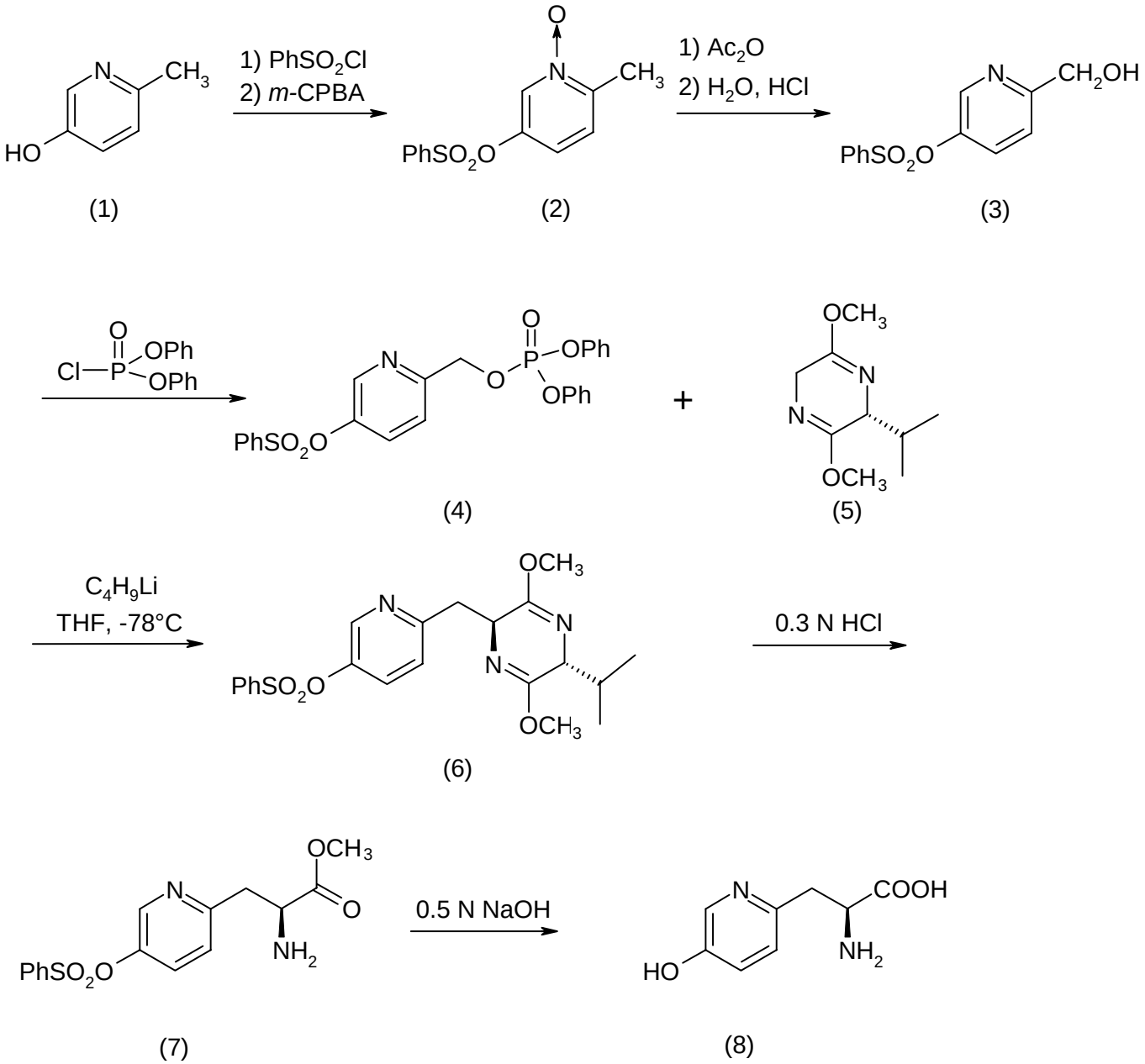
The diastereoisomeric ratio of the reaction product mixture, determinated by ^{1}H-NMR spectroscopy, ranges from 85:15 to 93:7 according to the leaving group on 2-pyridylmethyl residue; chloride, bromide or diphenylphosphate, respectively.



Scheme

The optimum conditions for the alkylation reaction involved the addition of a solution of **4** in THF to a solution of the enolate of **(**2*R*)-**5** in THF at –78°C. After 1h at this temperature, the mixture was held to –20 °C and a phosphate buffer solution was added. These experimental conditions in connection with the use of diphenyl phosphate group, gave a maximum of diastereoselectivity of 93% and a yield of 85% for **6**, after flash column chromatography. The (2*R*, 5*S*) configuration was assigned to the more abundant **6** on the basis of spectroscopic data and on accepted model[6] for the enolate alkylation reactions of **5**. As in our previous studies,[1] the chiral auxiliary was removed with a controlled acid hydrolysis giving **7**, which was

led to final **8** by treatment with 0.5 N sodium hydroxide. Synthetic **8** provided physical and spectroscopic data that were identical with those reported for the natural compound.[3]

This protocol allows the preparation of both enantiomers of azatyrosine using the (*R*) or (*S*) chiral auxiliary respectively, and shows the usefulness of Schöllkopf reagent in the stereocontrolled synthesis.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Elemental analysis was performed by the Microanalytical Laboratory of the Department. ^{1}H-NMR spectra were recorded by means of a Brüker AC 300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS; all coupling constants (J) are in Hertz.

5-Benzenesulfonyloxy-2-methylpyridine *N*-oxide (2). According to the reported method,[5b] 5-hydroxy-2-methylpyridine (**1**) was converted with benzenesulfonyl chloride and triethylamine to the corresponding *O*-protected benzenesulfonyloxy derivative.

A solution of this compound (5 g, 20 mmol) in $CHCl_3$ (50 mL) was treated with *m*-CPBA (3.8 g, 22 mmol) and stirred at rt for 4 h. The solution was washed with 20% Na_2CO_3 and dried on Na_2SO_4. The solvent was evaporated off and the solid residue was stirred with diisopropyl ether and filtered to give **2** (4.26 g, 80.4%), mp 88.5-90.1°C. ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.97 (dd, *J*=2.20 Hz, *J*=8.69 Hz, 1H, H-4 pyridine), 7.14 (d, *J*=8.69 Hz, 1H, H-3 pyridine), 7.48-7.80 (m, 5H, Ph), 7.87 (d, *J*=2.2 Hz, 1H, H-6 pyridine). *Anal.* Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.28; H, 4.18; N, 5.25.

5-Benzenesulfonyloxy-2-hydroxymethylpyridine (3). A mixture of **2** (3.2 g, 12 mmol) and acetic anhydride (5.7 mL) was heated at 100°C for 3 h. The excess of acetic anhydride and acetic acid were evaporated off *in vacuo* and the crude residue was treated with 36% HCl (2.5 mL) in THF (25 mL) at 25°C for 48 h. The solvent was evaporated off and the residue was treated with 10% K_2CO_3 until pH 10. The product was extracted with AcOEt, the solution dried on Na_2SO_4 and the solvent eliminated. The residue was purified by flash column chromatography on silica gel (toluene/ethyl acetate 90/10). Oil. (2.67 g, 84%). ^{1}H-NMR ($CDCl_3$): δ 4.70 (s, 2H, CH_2OH), 7.18 (d, *J*=8.68 Hz, 1H, H-3 pyridine), 7.36 (dd, *J*=2.65 Hz, *J*=8.65 Hz, 1H, H-4 pyridine), 7.49-7.78 (m, 5H, Ph), 8.05 (d, *J*=2.55 Hz, 1H, H-6 pyridine).

5-Benzenesulfonyloxy-2-hydroxymethylpyridyldiphenylphosphate (4). This compound was prepared following the method described by Yus[7] for trisubstituted phosphates. To a solution of **3** (10.6 g, 40

mmol) and Et_3N (5.15 g, 50 mmol) in THF (60 mL), cooled to 0°C, was added dropwise diphenyl-phosphoryl chloride (10.75 g, 40.0 mmol) and the mixture was stirred for 8 h allowing the temperature to rise to 20°C. Conventional work-up gave **4** (15.9 g, 80%), mp 50-52°C (diisopropyl ether). ^{1}H-NMR ($CDCl_3$): δ 5.25 (d, *J*=8.54 Hz, 2H, CH_2), 7.15-7.40 (m, 12H, 2PhO, H-3 pyridine, H-4 pyridine), 7.50-7.80 (m, 5H, $PhSO_2$), 8.05 (d, *J*=2.79 Hz, 1H, H-6 pyridine). *Anal.* Calcd for $C_{24}H_{20}NO_7PS$: C, 57.94; H, 4.05; N, 2.82. Found: C, 57.76; H, 4.05; N, 2.74.

(2*R*, 5*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-[(5-benzenesulfonyloxypyridin-2-yl)methyl]pyrazine (6). To a solution of (*R*)-**5** (1.02 g, 5.52 mmol) in anhydrous THF (50 mL) at –78°C under N_2, butyllithium (67.0 mmol, 3.9 mL of a 1.6 N solution in hexane) was added and the mixture stirred for 1 h. A solution of **4** (2.74 g, 5.52 mmol) in THF (25 mL) was added and the mixture was stirred at –78°C for 4 h. The reaction mixture was allowed to warm to –20°C and phosphate buffer solution (30 mL) was added. The solvent was evaporated off and the residue taken up with ether. The organic phase was separated and dried with Na_2SO_4, the solvent evaporated *in vacuo* and the residue was purified by flash column chromatography on silica gel (toluene/ethyl acetate 75/25). Oil (2.0 g, 85%). Diastereoisomeric ratio = 93:7. $[\alpha]^{20}_D$ ─ 105° (c 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 0.60 (d, *J*=6.80 Hz, 3H, CH_3CH), 0.93 (d, *J*=6.80 Hz, 3H, CH_3CH), 2.10 (m, 1H, $CH(CH_3)_2$), 3.00 (dd, *J*=7.26 Hz, *J*=12.60 Hz, 1H, CH_2), 3.25 (dd, *J*=4.67 Hz, *J*=12.60 Hz, 1H, CH_2), 3.50 (s, 3H, CH_3O), 3.57 (t, *J*=3.49 Hz, 1H, H-2 pyrazine), 3.62 (s, 3H, CH_3O), 4.31 (m, 1H, H-5 pyrazine), 7.02 (d, *J*=8.50 Hz, 1H, H-3 pyridine), 7.26 (dd, *J*=2.80 Hz, *J*=8.50 Hz, 1H, H-4 pyridine), 7.45-7.80 (m, 5H, $PhSO_2$), 7.96 (d, *J*=2.80 Hz, 1H, H-6 pyridine). *Anal.* Calcd for $C_{21}H_{25}N_3O_5S$: C, 58.45; H, 5.84; N, 9.74. Found: C, 58.65; H, 5.42; N, 9.81.

Methyl (2*S*)-2-Amino-3-(5-benzenesulfonyloxypyridin-2-yl)propanoate (7). A solution of **6** (0.84 g, 19.5 mmol) in acetonitrile (6 mL) was treated with HCl (36 mmol, 12 mL of a 0.3 N solution) and stirred at rt for 36 h. The solution was treated with 26% ammonia until pH 9 and the solvent evaporated off. The residue was extracted with AcOEt (3x20 mL), the solution dried with Na_2SO_4 and the solvent was removed *in vacuo*. The residue was distilled bulb-to-bulb to eliminate methyl valinate as forerun. The residue was dissolved in AcOEt, filtered on a celite pad and the solvent evaporated *in vacuo*. Oil (0.59 g, 90%). $[\alpha]^{20}_D$ + 2.3° (c 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 3.00 (dd, *J*=7.78 Hz, *J*=14.56 Hz, 1H, CH_2), 3.20 (dd, *J*=4.65 Hz, *J*=14.55 Hz, 1H, CH_2), 3.64 (s, 3H, CH_3O), 3.98 (m, 1H, *CH*-NH_2), 7.15 (d, *J*=8.51 Hz, 1H, H-3 pyridine), 7.30 (dd, *J*=2.73 Hz, *J*=8.48 Hz, 1H, H-4 pyridine), 7.50-7.80 (m, 5H, Ph), 8.00 (d, *J*=2.71 Hz, 1H, H-6 pyridine).

(2*S*)-2-Amino-3-(5-hydroxypyridin-2-yl)propanoic acid (8). A suspension of **7** (0.5 g, 1.47 mmol) in aqueous NaOH (25 mL of a 0.5 N solution) was heated at reflux for 6 h. The solution was cooled to rt and acidified with 5% HCl to pH 3. The volume of the solution was reduced to 10 mL and the concentrate was applied to an ion exchange resin (10 g, Dowex 50 X 8). The resin was eluted with water until the eluent was neutral. The product was then recovered with 0.25 M ammonium hydroxide solution. The fractions containing the product were concentrated to give **8** (0.170 g, 65%), mp 255-257° (water). (lit.,[3] mp 262-263°C). $[\alpha]^{20}_{D}$ + 58.3° (c 1, 1N HCl). (lit.,[3] $[\alpha]^{20}_{D}$ + 55° (c 1, 1N HCl)). ^{1}H-NMR ($CDCl_3$): δ 3.10 (dd, *J*=14.9 Hz, *J*=8.54 Hz, 1H, CH_2), 3.29 (dd, *J*=14.9 Hz, *J*=4.91 Hz, 1H, CH_2), 3.9 (dd, *J*=8.49 Hz, *J*=4.85 Hz, 1H, CH), 7.21 (m, 2H, H-3 pyridine, H-4 pyridine), 7.96 (d, *J*=2.48 Hz, 1H, H-6 pyridine). *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.62; H, 5.49; N, 15.28.

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