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Enantiospecific Synthesis of 5-Methoxy-D(+)- OR L(-) Tryptophan

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SYNTHETIC COMMUNICATIONS, 25(23), 3883-3900 (1995)

ENANTIOSPECIFIC SYNTHESIS OF 5-METHOXY-D(+)- OR L(-) TRYPTOPHAN

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ABSTRACT: A method for the enantiospecific synthesis of 5-methoxy-D(+)-tryptophan 8 or the L(-)-optical antipode is described. This procedure can be scaled up and performed without the need for extensive chromatographic separations. It provides for the first time the synthesis of the optically pure 5-methoxy-D(+) or L(-)-tryptophans required for alkaloid total synthesis.

Over the past several years the isolation of a number of C-10 ring-A oxygenated indole alkaloids in the macroline/sarpagine series have been reported (Scheme I)[1,2] including 10-methoxyvellosimine, 19, 20-dehydro-10-methoxytalcarpine, sarpagine, lochnerine, N_a-methylsarpagine, 18-hydroxylochnerine, neo-sarpagine, spegatrine, lochneram, 21-hydroxy-

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cyclolochnerine and verticillatine. Recently, the enantiospecific synthesis of a number of *Alstonia* macroline/sarpagine alkaloids has been demonstrated[3] employing the *trans* 1,3-transfer of asymmetry during the Pictet-Spengler reaction; use of D(+)-tryptophan provided the natural indole alkaloids *via* this approach. Interest in the synthesis of N_a-methylsarpagine as well as 19,20-dehydro-10-methoxytalcarpine has prompted the need for a preparative synthesis of 5-alkoxy-D(+)-tryptophans *via* a route which would also provide the L(-) enantiomers, if desired. D(+)-Tryptophans *via* this chemistry (*trans* transfer of asymmetry) would provide the natural alkaloids while the L(-)-isomers would furnish the unnatural antipodes for biological screening.[1-3]

Although a number of elegant syntheses of amino acids have been reported,[4] the Schöllkopf chiral auxiliary[5] was chosen here for the desired D(+)-tryptophan would be available from L-valine while the L(-)-isomer would originate from D-valine. This alkylation sequence has been employed in our laboratory for the preparation of 1-benzenesulfonyl-6-methoxy-D(-)-tryptophan ethyl ester.[6] The success of this sequence rests on the ability to scale up the first few steps to multihundred-gram scale. For this reason, the well known Fischer indole cyclization,[7] *via* the thermally mediated [3,3]sigmatropic rearrangement, was chosen as the means by which to generate (from *p*-anisidine **1**) large quantities of 5-methoxy-3-methylindole **3**. The synthesis of 5-methoxy-D(+)-tryptophan *via* a route that can also be employed for the L(-)-isomer forms the subject of this report.

Ethyl 5-methoxy-3-methylindole-2-carboxylate **2** was prepared on a large scale from *p*-anisidine and ethyl α-ethylacetoacetate by the Fischer indole cyclization *via* a Japp-Klingmann azo-ester intermediate (Scheme

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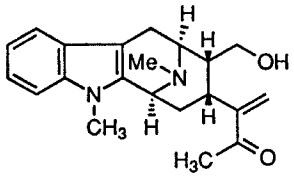
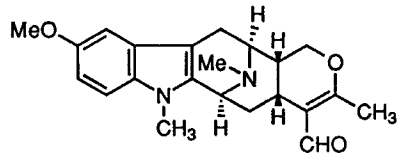
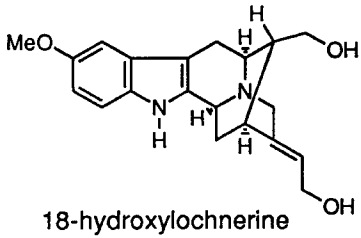
Scheme I



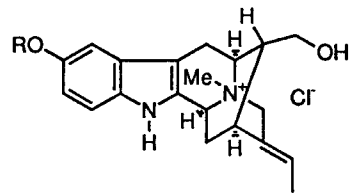
macroline



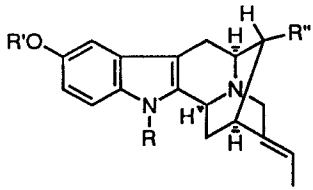
19,20-dehydro-10-methoxytalcarpine



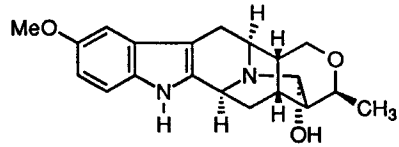
18-hydroxylochnerine



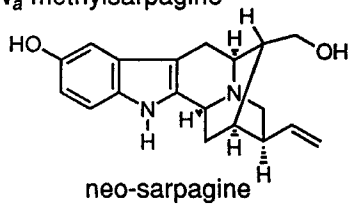
R = H, spegatrine
R = Me, lochneram



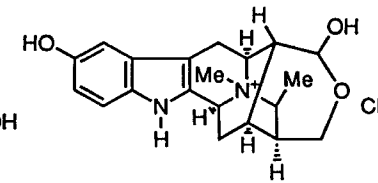
R = H, R' = Me, R" = CHO,
10-methoxyvellosimine
R = H, R' = H, R" = CH_2OH sarpagine
R = H, R' = Me, R" = CH_2OH
lochnerine
R = Me, R' = H, R" = CH_2OH
N_a-methylsarpagine



21-hydroxycyclolochnerine



neo-sarpagine



verticillatine

II).[8] This process has been fully explored by Abromovitch and Shapiro as well as reviewed.[9,10] Alkaline hydrolysis of ester **2** and subsequent copper/quinoline mediated decarboxylation of the carboxylic acid which resulted, furnished the 5-methoxy-3-methylindole in excellent yield. Care must be exercised on decarboxylation of the corresponding acid on a large scale. The best yields were obtained when the carboxylic acid was fully dried and the decarboxylation was executed at reflux in a well-stirred minimum amount of distilled quinoline (1.5-2 equivalents of quinoline with respect to the carboxylic acid). Only a catalytic amount of copper powder is required to ensure yields of **3** in excess of 90%.

In order to employ the Schöllkopf chiral auxillary in the indole series, protection/deactivation of the indole N(H) group was required and was accomplished as shown with benzenesulfonyl chloride (94% yield).[5,11] As illustrated in Scheme II, the protected indole was then reacted with NBS[12] under free radical conditions (AIBN) to afford the protected 3-bromomethylindole **5a** in excellent yield. On occasion, it was found that electrophilic bromination at C(2) of the indole **4** competed with the desired radical bromination of the C(3) alkyl moiety (Scheme III). Judicious use of AIBN (see Experimental Section) during the radical bromination suppressed the formation of **5b** (Scheme III) and provided a high yield of the desired **5a**. A detailed study of the electrophilic *vs* free radical bromination of various 3-methylindoles has been reported.[13]

The alkylation of the anion of the Schöllkopf chiral auxiliary derived from L-valine was performed under conditions analogous to those described in the literature[6,11] and afforded the protected tryptophan derivative **6**. This pyrazine was hydrolyzed under acidic conditions (aq. 2N HCl, THF) to provide the desired 1-benzenesulfonyl-5-methoxy-

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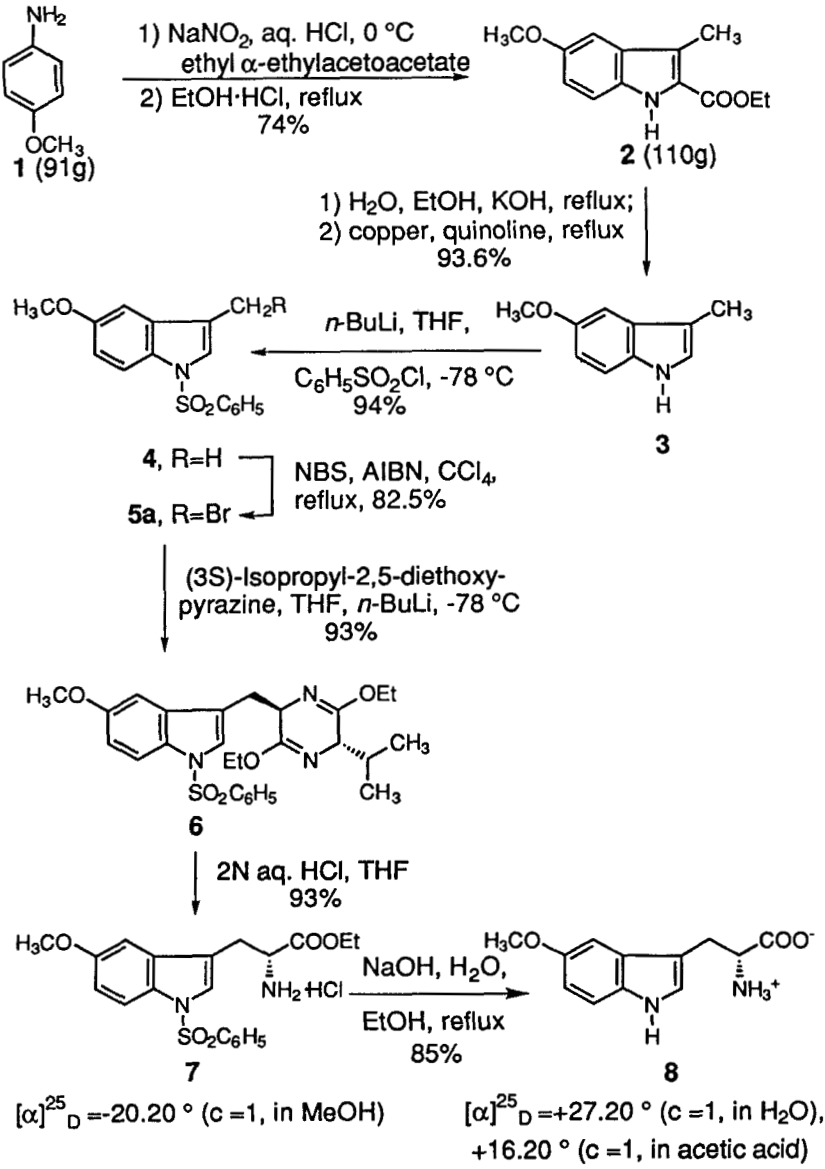
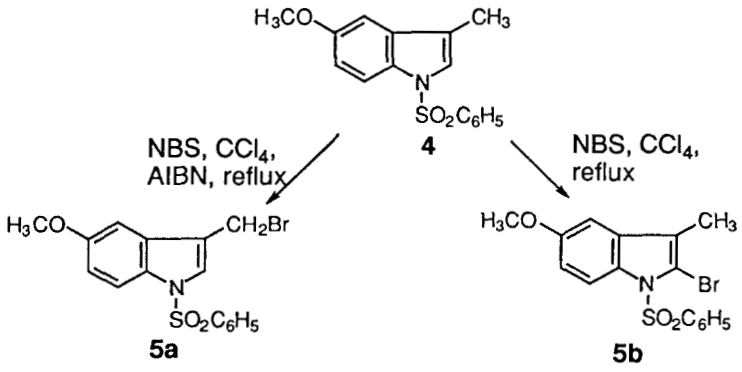
Scheme II



$[\alpha]^{25}_D$ =-20.20 ° (c =1, in MeOH)

$[\alpha]^{25}_D$ =+27.20 ° (c =1, in H_2O), +16.20 ° (c =1, in acetic acid)

Scheme III



tryptophan ethyl ester **7** as its hydrochloride salt. With easy access to **7** in hand, 5-methoxy-D(+)-tryptophan **8** was obtained in a single step on alkaline hydrolysis of both the 1-benzenesulfonyl protecting group and the ethyl ester moiety (Scheme II). The racemization of the chiral center of the amino acid **8** was not observed under the conditions of hydrolysis (8 h) for treatment of **8** under the same conditions for an additional 72 h returned the same amino acid **8** with the same optical rotation observed on hydrolysis of **7** for only 8 h.

The applicability of this approach rests on the ease of execution of each step (see Experimental Section), moreover the optically active 5-methoxytryptophan was obtained in only five steps from 5-methoxy-3-methylindole. As noted above, this sequence of reactions can also be carried out with the Schöllkopf chiral auxillary from D-valine to provide L(-)-**8**. Furthermore, the Schöllkopf chiral auxiliary can tolerate strongly alkaline conditions and serves as a protecting group for the amino acid functionality. In this regard, the benzenesulfonyl group of a pyrazine

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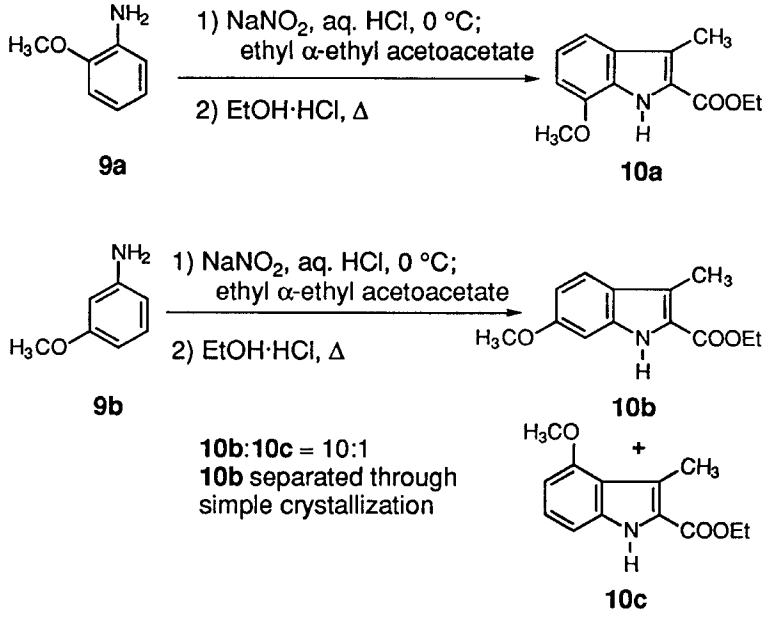
Scheme IV



related to **6** has been removed with Na/NH_3 followed by methylation with methyl iodide in a one-pot process. This took place without destroying the chiral auxiliary or racemization and provided a crucial intermediate required for the total synthesis of the indole alkaloid alstophylline.[14]

When the Fischer indole approach was applied to *o*-anisidine **9a**, the preparation of 7-methoxyindole **10a** was realized. Moreover, when the sequence was executed with *m*-anisidine **9b**, the 6-methoxyindole isomer **10b** was realized in about 70% yield (Scheme IV). The desired 6-methoxyindole regioisomer **10b** was separated from the undesired 4-methoxyindole isomer **10c** (about 7%) by simple crystallization of the crude reaction mixture from the Fischer indole cyclization. At present,

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attempts to convert **10a** and **10b** into the corresponding optically pure 7-methoxy- and 6-methoxytryptophans, respectively, are underway. This sequence provides the first synthetic entry into either 5-methoxy-D-(+)- or L(-)-tryptophan[15,16] and makes these materials available on multigram scale for total synthesis.

EXPERIMENTAL

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Melting points were taken on a Thomas-Hoover melting point apparatus or an Electrothermal model IA8100 digital melting point apparatus and are reported uncorrected. The ^{1}H NMR spectra were recorded on a Bruker 250-MHz multiple-probe instrument or a GE 500-MHz spectrometer. Infrared spectra were recorded on a Nicolet Dx FTIR DX V5.07 spectrometer or a Mattson Polaris IR-10400 instrument. Low resolution mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985 B GC-mass spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. Microanalyses were performed on a Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer. Analytical TLC plates employed were E. Merck Brinkman UV active silica gel (Kieselgel 60 F254) on plastic while silica gel 60b for flash chromatography was purchased from E. M. Laboratories. All chemicals were purchased from Aldrich Chemical Co. unless otherwise indicated.

Ethyl 5-methoxy-3-methylindole-2-carboxylate (2). To a mixture of *p*-anisidine (91g, 0.74 mol), conc. aq. HCl (185 mL), and water (350 mL) was added a solution of $NaNO_2$ [(54g, 0.77 mol) in 100 mL of water] in a dropwise manner at -5 °C. After addition, the mixture was stirred at 0 °C

for 15 min and brought to pH 3~4 by addition of sodium acetate (60g, 0.74 mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (100g, 0.64 mol) in ethanol (500 mL) at 0 °C was treated with an aq. solution of KOH (0.64 mol in 50 mL of H_2O), followed by addition of ice (1000g). The diazonium salt prepared above was immediately added to this alkaline solution. The mixture was then adjusted to pH 5~6 and stirred at 0 °C for 3 h. After the solution was kept for a further 12 h at 4 °C, the mixture was extracted with ethyl acetate (4x200 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Most of the solvent was removed under reduced pressure and the liquid residue was added dropwise to a solution of 14.5% ethanolic HCl at 70 °C. After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (100 mL) and CH_2Cl_2 (300 mL). The aq. layer was extracted with CH_2Cl_2 (3x100 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave **2** as a white solid (110g, 74%): mp 151-152 °C (lit.[17] mp 151-152 °C); ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H, J = 7.2 Hz), 2.61 (s, 3H), 3.90 (s, 3H), 4.42 (q, 2H, J = 7.3 Hz), 7.01 (m, 2H), 7.30 (d, 1H, J = 7.6 Hz). MS (EI) *m/e* 233 (M^+, 38), 187 (100), 172 (21), 140 (10).

5-Methoxy-3-methylindole (3). A mixture of **2** (72g, 0.3 mol), EtOH (150 mL), KOH pellets (85%, 60g, 0.9 mol), and water (100 mL) was heated to reflux for 1 h. The volume was reduced to 100 mL under reduced pressure and acidified with an aq. solution of 3N HCl. The precipitate which resulted was collected on a filter, washed with distilled water, and dried in a vacuum oven at 80 °C to afford 5-methoxy-3-methylindole-2-carboxylic acid as a white solid (61.5g, 100%): mp 202-203 °C (lit.[17] mp 200-

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201 °C). This acid (60g, 0.29 mol) was then heated to reflux in a well-stirred (mechanical stirrer) mixture of quinoline (125 mL) and copper powder (2.5g) under nitrogen for 2.5 h. The copper powder was removed by filtration, after which the filtrate was brought to pH 2~3 with an aq. solution of 6N HCl and the solution which resulted was extracted with diethyl ether (4x100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **3** as a brown solid (44g, 94%): mp 68-69 °C (lit.[17] mp 66 °C); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H), 3.91 (s, 3H), 6.85 (dd, 1H, J = 8.8, 2.5 Hz), 6.95 (s, 1H), 7.01 (d, 1H, J = 2.3 Hz), 7.25 (d, 1H, J = 8.8 Hz), 7.80 (br, 1H, D_2O exchangeable).

1-Benzenesulfonyl-5-methoxy-3-methylindole (4). A solution of **3** (39g, 0.24 mol) in THF (800 mL) was treated at -78 °C with *n*-butyllithium (2.5 M in hexane, 107 mL, 0.266 mol) under nitrogen. The mixture was stirred at -78 °C for 20 min and then allowed to slowly warm to rt. After 2 h, a clear solution was obtained which was cooled to -78 °C and treated with benzenesulfonyl chloride (36 mL, 0.28 mol). The reaction mixture was stirred at -78 °C for 30 min and then at rt for 4 h. The solvent was removed under reduced pressure to give a yellow solid which was recrystallized from a mixture of ethyl acetate and hexane to afford **4** as a yellow-colored solid (68g, 94%): mp 137-138 °C; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.80 (s, 3H), 6.88 (d, 1H, J = 2.3 Hz), 6.92 (dd, 1H, J = 9.0, 2.4 Hz), 7.27 (s, 1H), 7.4 (t, 2H, J = 7.2 Hz), 7.50 (d, 1H, J = 7.2 Hz), 7.85 (m, 3H); IR (KBr) 3100, 2924, 1609 cm^{-1}; Anal. Calcd. for $C_{16}H_{15}NSO_3$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.54; H, 4.98; N, 4.32.

1-Benzenesulfonyl-3-bromomethyl-5-methoxyindole (5a). A solution of **4** (36g, 0.118 mol) in CCl_4 (500 mL) was heated to reflux after

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which *N*-bromosuccinimide (22g, 0.123 mol) and AIBN (500 mg) were carefully added in a portionwise manner over 5 min. After completion of the addition, three portions of AIBN (3x200mg) were added every 30 min. After 3 h the mixture was cooled to rt and the succinimide which resulted was filtered off and washed with CCl_4 (3x50 mL). The solvent was removed under reduced pressure to yield a brown solid. A further purification by recrystallization from diethyl ether afforded **5a** as off-white colored crystals (37g, 82%): mp 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 4.60 (s, 2H), 6.95 (dd, 1H, J = 8.7, 2.4 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.65 (s, 1H), 7.85 (m, 3H); IR (KBr) 3103, 2856, 1607 cm^{-1}; MS (EI) *m/e* 381 (M^+, 21), 379 (18), 240 (51), 238 (53), 160 (39), 159 (100), 116 (77). Anal. Calcd. for $C_{16}H_{14}BrNSO_3$: C, 50.54; H, 3.71; N, 3.68. Found: C, 50.36; H, 3.47; N, 4.01.

1-Benzenesulfonyl-2-bromo-5-methoxy-3-methylindole (5b) was isolated as a by-product with **5a** when a mixture of **4**, *N*-bromosuccinimide, AIBN and CCl_4 was heated to reflux without continuous addition of AIBN. In the absence of AIBN, a mixture of **4**, *N*-bromosuccinimide, and CCl_4 was heated to reflux for 3 h and afforded exclusively **5b**: mp 148-150 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.85 (s, 3H), 6.80 (d, 1H, J = 2.1 Hz), 6.95 (dd, 1H, J = 8.6, 2.2 Hz), 7.40 (t, 2H, J = 8.2 Hz), 7.50 (t, 1H, J = 8.6 Hz), 7.81 (d, 2H, J = 8.5 Hz), 8.17 (d, 1H, J = 8.5 Hz). IR (KBr) 3064, 2839, 1609 cm^{-1}; Anal. Calcd. for $C_{16}H_{14}BrNSO_3 \cdot 1/2H_2O$: C, 49.37; H, 3.88; N, 3.60. Found: C, 49.20; H, 3.52; N, 3.34.

(3R, 6S)-3-(1-Benzenesulfonyl-5-methoxy-3-indoyl)methyl-3, 6-dihydro-6-isopropyl-2,5-diethoxypyrazine (6). To a solution of (3S)-isopropyl-2,5-diethoxypyrazine (12g, 0.056 mol) in THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 24 mL, 0.06 mol) at -78 °C under

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nitrogen. The solution which resulted was stirred at -78 °C for 30 min after which a solution of **5a** (20g, 0.053 mol) in THF (100 mL) under nitrogen was added dropwise. After the mixture was allowed to stir at -78 °C for 20 h, the reaction solution was slowly warmed to rt and treated with a saturated aq. solution of $(NH_4)_2CO_3$ (50 mL). Most of the solvent was removed under reduced pressure and the residue which resulted was treated with diethyl ether to give two layers. The organic layer was separated and the aq. layer was extracted with diethyl ether (3x100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford **6** as a brown oil (25g, 93%): ^{1}H NMR ($CDCl_3$) δ 0.60 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.7 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.10 (m, 1H), 3.1 (m, 2H), 3.20 (t, 1H, J = 3.4 Hz), 3.80 (s, 3H), 3.95 (m, 1H), 4.10 (m, 3H), 4.25 (q, 1H, J = 4.1 Hz), 6.85 (dd, 1H, J = 9.0, 2.4 Hz), 6.96 (d, 1H, J = 2.0 Hz), 7.38 (t, 2H, J = 8.0 Hz), 7.46 (t, 1H, J = 7.7 Hz), 7.75 (d, 2H, J = 8.6 Hz), 7.80 (d, 2H, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ 14.28, 14.33, 16.56, 18.95, 29.20, 31.55, 55.67, 60.53, 103.09, 113.16, 114.28, 119.08, 125.41, 126.51, 129.05, 129.70, 132.86, 133.34, 138.57, 156.34, 161.79, 163.59. MS (EI) *m/e* 511 (M^+, 5), 301 (19), 300 (71), 211 (9), 160 (26), 159 (100), 144 (30). The pyrazine **6** was employed in the next step without further purification.

Ethyl 1-benzenesulfonyl-5-methoxy-D(-)-tryptophan hydrochloride (7). A mixture of **6** (8g, 0.015 mol), THF (40 mL), and 2N aq. HCl (60 mL) was stirred at rt for 2 h. The precipitate which resulted was collected by filtration to furnish the first crop of **7** as its hydrochloride salt. The filtrate was concentrated *in vacuo* and the precipitate which formed was collected to afford the second crop of **7** (combined yield 6g, 93%): mp 244-245 °C; $[\alpha]^{26}_D$ = -20.20 ° (c =1, in methanol). ^{1}H NMR ($CDCl_3$) δ 1.15 (t,

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3H, J = 7.1 Hz), 1.65 (br, 3H), 2.90 (dd, 1H, J = 14.5, 7.3 Hz), 3.10 (dd, 1H, J = 14.5, 5.3 Hz), 3.70 (m, 1H), 3.75 (s, 3H), 4.10 (dq, 2H, J = 7.1, 1.8 Hz), 6.90 (dd, 1H, J = 8.1, 2.5 Hz), 6.95 (s, 1H), 7.35-7.60 (m, 4H), 7.85 (m, 3H). IR (KBr) 3465, 3423, 2832, 2400-3500, 1735, 1602 cm^{-1}; Anal. Calcd. for $C_{20}H_{22}N_2SO_5 \cdot HCl$: C, 54.79; H, 5.25; N, 6.39. Found: C, 55.16; H, 5.41; N, 6.12.

5-Methoxy-D(+)-tryptophan (8). A mixture of 7 (2g, 0.005 mol), H_2O (20 mL), EtOH (30 mL), and NaOH (1.8 g) was heated at reflux for 8 h. The ethanol was removed under reduced pressure. After the aq. solution of residue which remained was brought to pH 2~3 with aq. 6N HCl and extracted with CH_2Cl_2 (3x50 mL) to remove by-products, the water layer was then brought to a final pH of 6-7 with aq. 3N NaOH. The water was then removed under reduced pressure. The white solid residue which resulted was ground, placed on a pad of silica gel and washed through with a mixture of CH_3OH, $CHCl_3$ and conc. aq. NH_4OH (18.5:28.5:3 by volume). The filtrate was concentrated to afford 8 as a white solid. Further recrystallization of 8 in a mixture of ethanol and water afforded 5-methoxy-D(+)-tryptophan 8 as white crystals (0.91g, 85%): mp 238-240 °C; $[\alpha]^{25}_D$ =+27.20 ° (c =1, in H_2O) and +16.20 ° (c = 1, in acetic acid); lit.[15] $[\alpha]^{22}_D$ =+15.50 ° (c= 1, in acetic acid). ^1H NMR (D_2O) δ 3.15-3.35 (m, 2H), 3.70 (s, 3H), 4.10 (t, 1H, J = 5.8 Hz), 6.78 (dd, 1H, J = 8.9, 2.3 Hz), 7.05 (d, 1H, J = 2.3 Hz), 7.15 (s, 1H), 7.27 (d, 1H, J = 8.9 Hz). MS (EI) *m/e* 234 (M^+, 7), 161 (14), 160 (100), 145 (17), 117 (19). IR (KBr) 3575, 3462, 3382, 3043, 2950, 2831, 1629, 1602 cm^{-1}; Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.15; H, 5.91; N, 11.89.

Ethyl 7-methoxy-3-methylindole-2-carboxylate (10a). To a mixture of *o*-anisidine (12g, 0.1 mol), conc. aq. HCl (25 mL), and water (40 mL) was

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added a solution of $NaNO_2$ [(7.6 g, 0.11 mol) in 10 mL of water] in a dropwise manner at -5 °C. After addition, the mixture was stirred at 0 °C for 15 min and brought to pH 3~4 by addition of sodium acetate (8g, 0.1 mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (16g, 0.1 mol) in ethanol (80 mL) at 0 °C was treated with an aq. solution of KOH (0.1 mol in 10 mL of H_2O), followed by addition of ice (200g). The diazonium salt prepared above was immediately added to the alkaline solution of ethyl α-ethylacetoacetate. The mixture was then adjusted to pH 5~6 and stirred at 0 °C for 3 h. After the mixture was kept a further 12 h at 4 °C, it was extracted with ethyl acetate (4x200 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Most of the solvent was removed under reduced pressure and the liquid residue was added dropwise to a solution of 14.5% ethanolic HCl at 70 °C. After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (20 mL) and CH_2Cl_2 (100 mL). The aq. layer was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave **10a** as a yellow-colored solid (17g, 72%): mp 118-120 °C (lit.[18] mp 116-117 °C); ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H, J = 7.1 Hz), 2.60 (s, 3H), 3.90 (s, 3H), 4.41 (q, 2H, J = 7.1 Hz), 6.72 (d, 1H, J = 7.6 Hz), 7.05 (t, 1H, J = 8.1 Hz), 7.25 (d, 1H, J = 7.9 Hz), 8.81 (br, 1H, D_2O exchangeable).

Ethyl 6-methoxy-3-methylindole-2-carboxylate (10b). To a mixture of *m*-anisidine (12g, 0.1 mol), conc. aq. HCl (25 mL), and water (40 mL) was added a solution of $NaNO_2$ (7.6 g, 0.11 mol in 10 mL of water) in a dropwise manner at -5 °C. After addition, the mixture was stirred at 0 °C for 15 min and brought to pH 3~4 by addition of sodium acetate (8.3g, 0.1

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mol). In a separate flask, a solution of ethyl α-ethylacetoacetate (15.8g, 0.1 mol) in ethanol (80 mL) at 0 °C was treated with an aq. solution of KOH (0.1 mol in 10 mL of H_2O), followed by addition of ice (200g). The diazonium salt prepared above was immediately added to the alkaline solution of ethyl α-ethylacetoacetate. The mixture was then adjusted to pH 5~6 and stirred at 0 °C for 4 h. After the mixture was kept a further 12 h at 4 °C, it was extracted with ethyl acetate (4x200 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Most of the solvent was removed under reduced pressure and the liquid residue was added dropwise to a solution of 3 N ethanolic HCl at 70 °C. After addition, the mixture was held at 78 °C for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (20 mL) and CH_2Cl_2 (100 mL). The aq. layer was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Purification on a short wash column (silica gel, ethyl acetate/hexane, 1:3) gave a mixture of **10b** and **10c** (10:1 ratio as determined by ^1H NMR) as a dark brown solid (17.1g, 73.5%). Recrystallization of this mixture from ethyl acetate furnished **10b** as brown crystals: mp 122-123 °C (lit.[19] 122 °C); ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 2.60 (s, 3H), 3.81 (s, 3H), 4.40 (q, 2H, J = 7.1 Hz), 6.78 (d, 1H, J = 1.8 Hz), 6.81 (dd, 1H, J = 8.8, 1.9 Hz), 7.50 (d, 1H, J = 8.4 Hz), 8.55 (br, 1H, D_2O exchangeable).

(3S)-Isopropyl-2,5-diethoxypyrazine.[5,6] A detailed procedure for the preparation of (3S)-isopropyl-2,5-diethoxypyrazine was reported from this laboratory.[6] It was noticed that the bisalkylation of the diketopiperazine in this sequence was troublesome when using commercially available triethyloxonium tetrafluoroborate and required a tedious work-up. Described below is a modified procedure which

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resulted in a large scale synthesis of this chiral auxiliary and is easier to execute. Triethyloxonium tetrafluoroborate was prepared from boron trifluoride etherate (454g, 3.6 mol) and epichlorohydrin (244g, 2.6 mol) as described by Meerwein.[20] The crystalline triethyloxonium tetrafluoroborate obtained was washed with anhydrous diethyl ether several times under an atmosphere of nitrogen and then dissolved in dry CH_2Cl_2 (3L). To this solution was added (3S)-isopropyl-2,5-diketopiperazine (100g, 0.64 mol) in portions with stirring. The mixture which resulted was allowed to stir at rt for 72 h and then added to a mixture of conc. aq. NH_4OH (1 L) and ice (1000g). The organic layer was separated and the aq. layer was extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was vacuum distilled at 6 torr (90 °C) to provide pure (3S)-isopropyl-2,5-diethoxypyrazine (125g, 92%). The spectral data for this agent were identical to those previously reported.[5,6]

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