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ENTRY INTO 6-METHOXY-D(+)-TRYPTOPHANS. STEREOSPECIFIC SYNTHESIS OF 1-BENZENESULFONYL-6-METHOXY-D(+)-TRYPTOPHAN ETHYL ESTER

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ABSTRACT: A strategy for the synthesis of optically active ring-A methoxylated indole alkaloids which employs the Moody azide/Schollkopf chiral auxiliary protocol has resulted in the successful preparation of 1-benzenesulfonyl-6-methoxy-D(+)-tryptophan ethyl ester **16**. This amino ester is required for the synthesis of *Alstonia* bisindole alkaloids including macralstonine **2** *via* an enantiospecific Pictet-Spengler reaction.

The recent isolation of a number of important biologically active ring-A oxygenated indole alkaloids[1-4] has stimulated a renewed interest in the preparation of ring-A methoxylated D(+)-tryptophans with respect to the total synthesis of natural products. In particular, the development of a synthesis of optically pure 6-methoxy-D(+)-tryptophan when coupled with

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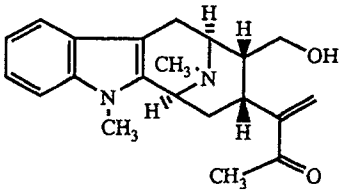
the stereospecific Pictet-Spengler reaction[1] would permit entry into the fumitremorgin class of tremorgenic mycotoxins[2,3] and the macroline family of indole alkaloids.[4] With respect to the latter class of compounds, the stereospecific total synthesis of the indole alkaloid (-)-alstonerine **1** was recently reported from D(+)-tryptophan.[5] The preparation of (-)-alstonerine **1** represented the first stereocontrolled synthesis of a member of the macroline related indole alkaloids. In addition, over 55 macroline/sarpagine alkaloids have been isolated[4] and many of these contain ring-A methoxylated indole units.

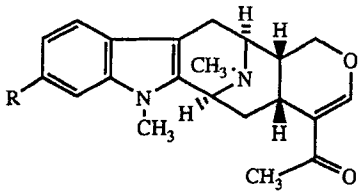
Currently, work is in progress to extend this approach to the synthesis of various bisindole alkaloids including macralstonine **2** which has been shown to exhibit potent hypotensive properties.[6] The total synthesis of macralstonine **2** (**Scheme 1**) rests on the coupling reaction of macroline **3** and alstophylline **4** in optically active form. Macroline has recently been prepared[5] and the successful preparation of macralstonine **2** now requires the synthesis of (-)-alstophylline **4**. The synthesis of (-)-alstonerine **1** began with D(+)-tryptophan, consequently the preparation of (-)-alstophylline **4** depends on the preparation of 6-methoxy-D(+)-tryptophan in hundred-gram quantities. A key to success in this approach rests on the synthesis of 6-methoxyindole on large scale for this indole analog is extremely expensive due to its limited commercial availability.

One of the best ways to prepare large quantities of 6-methoxyindole utilizes the Moody azide pyrolysis protocol[7,8]

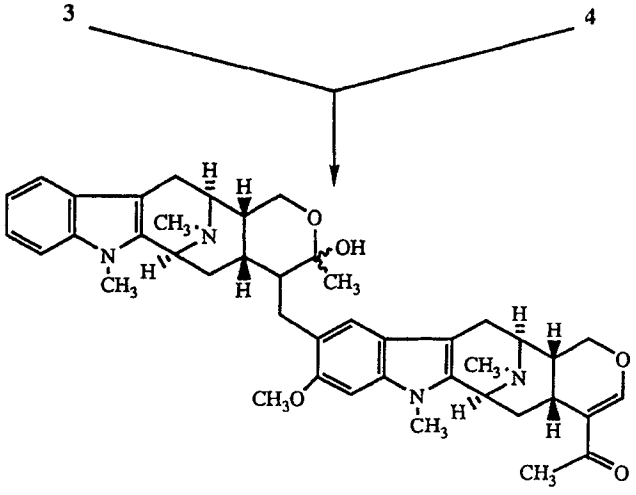
Scheme 1



3; macroline



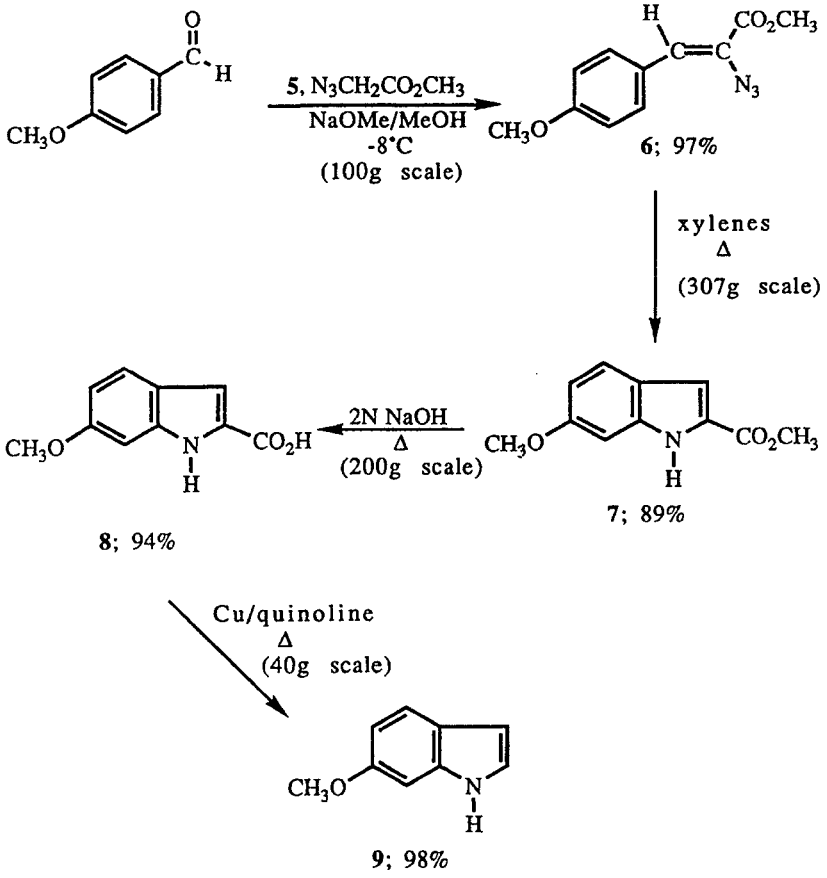
1; R = H, alstonerine
4; R = OCH_3, alstophylline



2; macralstonine

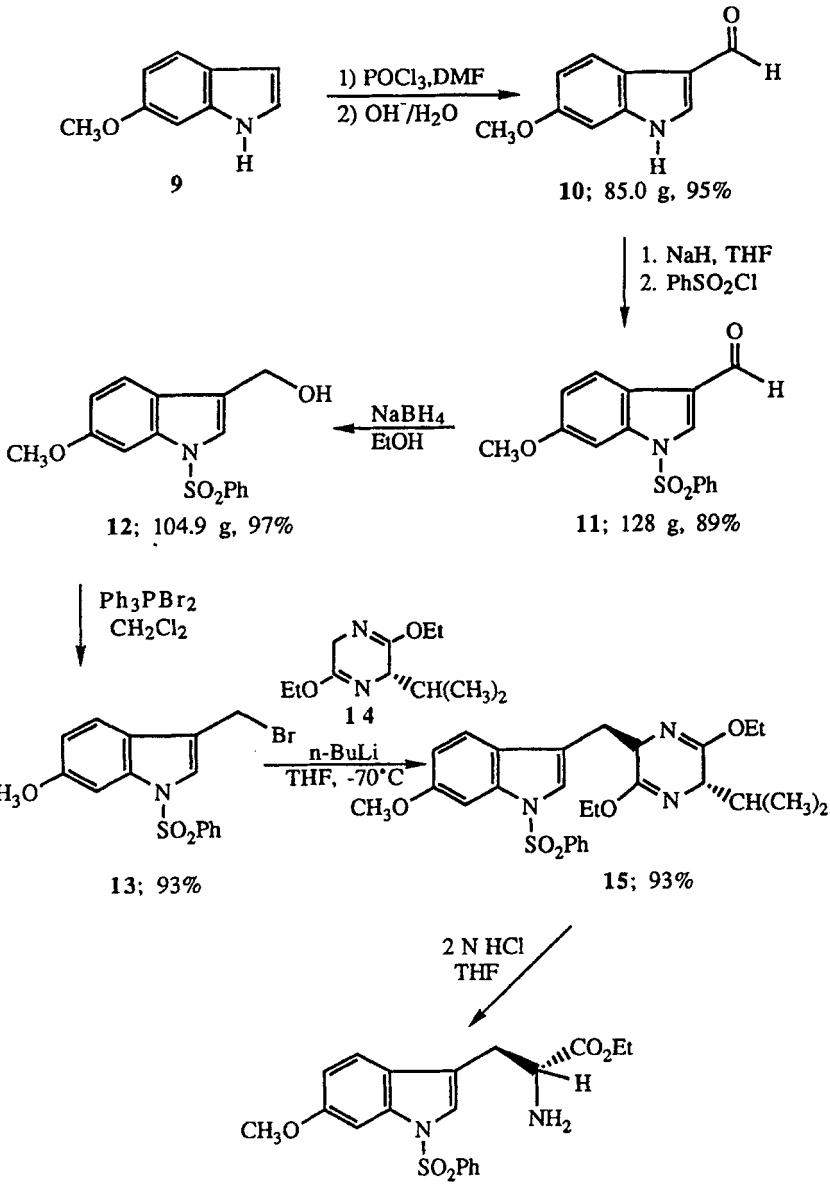
(**Scheme 2**). In this method, 4-methoxybenzaldehyde was condensed with methyl azidoacetate **5** in the presence of sodium methoxide at low temperature. The azidocinnamate **6** which resulted was then heated ($-N_2$) in a mixture of refluxing xylenes to provide the methyl-6-methoxyindole-2-carboxylate **7**. Subsequent ester hydrolysis and Cu/quinoline mediated decarboxylation of the acid **8** which resulted, afforded the 6-

Scheme 2



methoxyindole **9**. The attractive feature of this sequence was the ability to prepare over one hundred grams of 6-methoxyindole in a very short time (several days). Moreover, no chromatographic separations were needed which enhanced the feasibility of this route. With multi-hundred gram quantities of 6-methoxyindole **9** in hand, it was necessary to

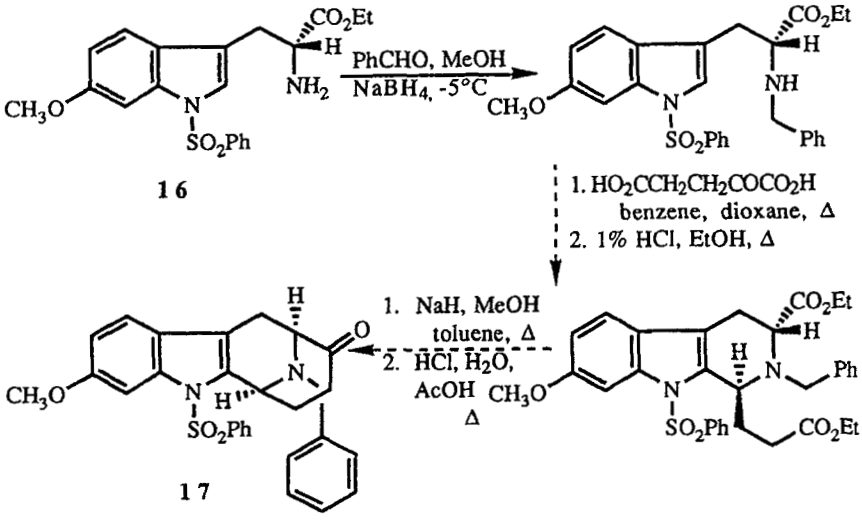
Scheme 3



build on the structural components of the D(+)-tryptophan to complete the formation of the desired D(+)-amino acid (**Scheme 3**).

Briefly, 6-methoxyindole **9** was formylated using standard Vilsmeier-Haack reaction conditions[9] to provide the 6-methoxyindole-3-carboxaldehyde **10** in 95% yield. Protection of the indole NH functionality as the sulfonamide was achieved by reaction of 6-methoxyindole-3-carboxaldehyde **10** with sodium hydride and benzenesulfonyl chloride to provide 1-benzenesulfonyl-6-methoxyindole-3-carboxaldehyde **11**. The sulfonamide function will be carried through in the total synthesis of **4**, removed and the product methylated in the last step to provide (-)-alstophylline **4**. This is important, for the same N_a-(H) intermediate will serve as one half of a second *Alstonia* bisindole, alkaloid H,[10] whose structure is closely related to N_a'-desmethylmacralstonine.[10] This would permit the synthesis of two natural products from a common intermediate. Sodium borohydride reduction of 1-benzenesulfonyl-6-methoxyindole-3-carboxaldehyde **11** to the hydroxymethyl analog **12** was achieved in excellent yield. Conversion of the hydroxymethyl indole **12** to the bromomethyl derivative **13** was effected with dibromotriphenylphosphorane in methylene chloride. The bromomethyl indole was then reacted with the anion derived from Schollkopf's chiral auxiliary[11] (3S-isopropyl-2,5-diethoxypyrazine **14**) to provide the (3R,6S)-3-[1-

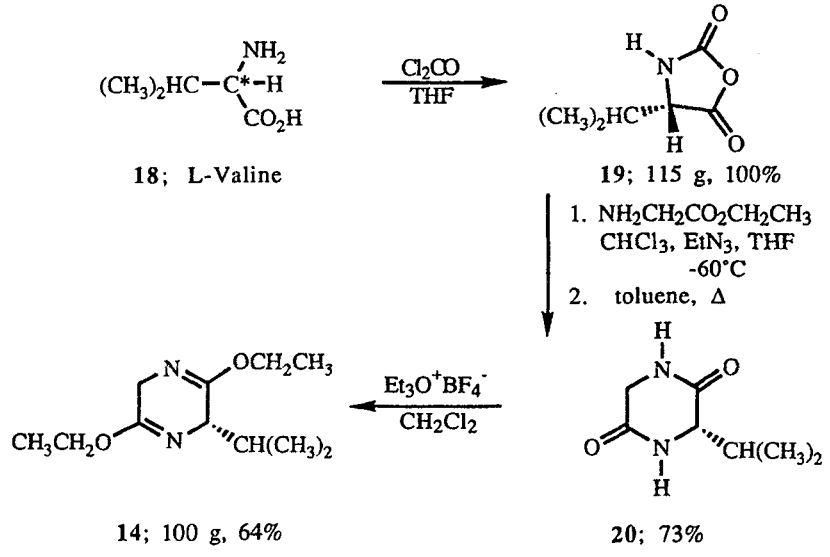
Scheme 4



(benzenesulfonyl-6-methoxy)-3-indoyl]methyl-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine **15**. Subsequent acidic hydrolysis of this material provided the 1-benzenesulfonyl-6-methoxy-D(+)-tryptophan **16**. With multigram quantities of this amino ester in hand, the synthesis of optically active (-)-alstophylline **4**, macralstonine **2**[12,13] and alkaloid H[10,14] *via* the tetracyclic ketone **17** (**Scheme 4**) are underway. In addition, the synthesis of other sarpagine-macroline alkaloids including 11-methoxy-N_a-methyl-dihydro-pericyclivine[15] and N_b-desmethylalstophylline oxindole[16] are possible *via* this route.

The preparation of the chiral auxiliary (3S)-isopropyl-2,5-diethoxypyrazine **14** (**Scheme 5**) reported by Schollkopf[17] was derived from the inexpensive L-valine **18**, which was

Scheme 5



18; L-Valine

19; 115 g, 100%

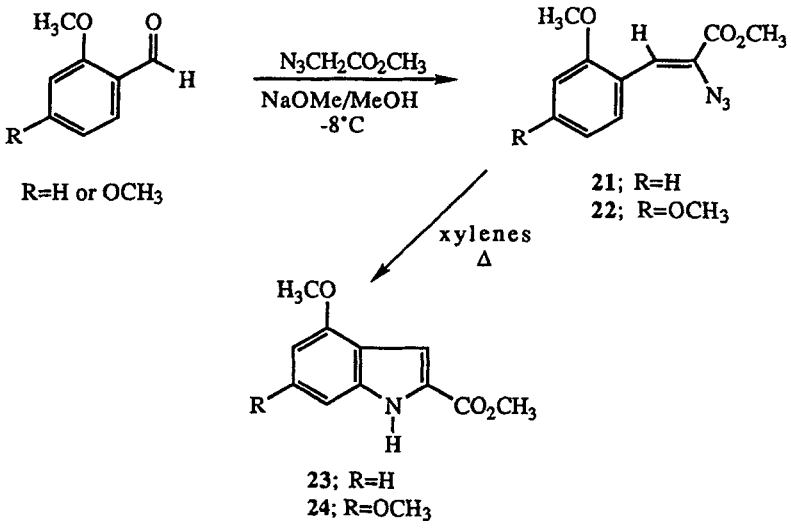
14; 100 g, 64%

20; 73%

initially allowed to react with phosgene in tetrahydrofuran. The N-carboxyanhydride **19** which resulted was stirred with glycine ethyl ester hydrochloride and triethylamine in chloroform at -60 °C. The intermediate generated *in situ* was cyclized in refluxing toluene to provide diketopiperazine **20**. This analog was then *O*-alkylated with triethyloxonium tetrafluoroborate in methylene chloride to generate (3S)-isopropyl-2,5-diethoxypiperazine **14** on a 115 gram scale, as shown in Scheme 5.

The utility of this approach was extended to permit the preparation of methyl-4-methoxyindole-2-carboxylate **21** and methyl-4,6-dimethoxyindole-2-carboxylate **22** (**Scheme 6**) and other ring-A oxygenated indole-2-carboxylates.[18] These

Scheme 6



indoles serve as key intermediates for the synthesis of many natural canthine-6-one alkaloids and related congeners which exhibit cytotoxic activity.[19-21] Briefly, methyl azidoacetate **5** was condensed with 2-methoxybenzaldehyde and 2,4-dimethoxybenzaldehyde, individually, in the same manner employed for the preparation of **6**. The azidocinnamates which resulted (**21** and **22**) were then pyrolyzed to give methyl-4-methoxy and methyl-4,6-dimethoxyindole-2-carboxylates **23** and **24**, respectively.

Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus or an Electrothermal model IA8100 digital

melting point apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker 250 MHz NMR spectrometer or on a GE 500 MHz instrument. Infrared spectra were recorded with a Beckman Acculab-1 or a Mattson Polaris IR-10400 spectrometer. Mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985B GC-mass spectrometer, while high resolution mass spectral data were obtained from a Finnigan HR mass spectrometer. Microanalyses were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen and nitrogen analyzer. Analytical TLC plates employed were E. Merck Brinkmann UV active silica gel (Kieselgel 60 F254) on plastic.

Methyl azidoacetate (5).[22] Methyl bromoacetate (623.2 g, 4.07 mol, 377 mL) was dissolved in methanol (625 mL). Sodium azide (317.8 g, 4.89 mol, 1.20 eq.) in H_2O (275 mL) was added to the above solution with stirring. The mixture which resulted was brought to reflux for 4 h. After cooling, the methanol was removed under reduced pressure after which H_2O (550 mL) was added and the solution extracted with ether (4 X 425 mL). The combined ether layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to provide **5** as a clear liquid (400.5 g, 86.2 %): ^1H NMR ($CDCl_3$, 250 MHz) δ 3.77 (s, 3H), 3.86 (s, 2H). The NMR spectrum of **5** was identical to that reported earlier.[22]

Methyl-2-azido-3-(4-methoxyphenyl)propenoate (6). Analogous to the modified procedure of Moody,[7] methanol (750 mL) and sodium methoxide (25 % ^{w}/w, 448 mL, 1.96 mol) were added to a three neck flask (3 L) equipped with an overhead stirrer and pressure equilibrating dropping funnel (under N_2). The funnel was charged with a solution of p-methoxybenzaldehyde (68.0 g, 0.49 mol) in methanol (125 mL) and methyl azidoacetate **5** (225.2 g, 1.96 mol). The mixture was then added dropwise (3.5 h) to the methoxide solution at -8 °C. The mixture was allowed to stir for an additional 2 h while the temperature was maintained below 5 °C. The heterogeneous mixture was poured over ice (1.5 kg) and stirred manually. The suspension which resulted was filtered and washed with water (4 X 100 mL). The light yellow solid which had formed was dried in the vacuum oven (rt) for 6 h and collected to provide the azidocinnimate **6** (110.6 g, 97 %). This material was used without further purification in the next step. It is imperative to use this compound within the next 24 h and it should be kept in the dark until used to minimize decomposition.

Methyl-6-methoxyindole-2-carboxylate (7). A three neck flask (22 L) of boiling xylenes (5.5 L) was equipped with an overhead stirrer, reflux condenser and pressure equilibrating dropping funnel. The funnel was charged with a solution of methyl-2-azido-3-(4-methoxyphenyl)-propenoate **6** (306.9 g,

1.32 mol) in xylenes (4.25 L). This solution was slowly added dropwise to the boiling xylenes over 8 h. The evolution of nitrogen gas was observed *via* a gas bubbler. The reaction mixture was allowed to reflux for an additional hour after nitrogen evolution had ceased. **CAUTION: the azido analog 6 was slowly dripped into refluxing xylenes and the gas evolution carefully monitored to prohibit a buildup of excess azidocinnamate 6 in solution.** The xylenes were cooled and then removed under reduced pressure and the residue which remained was crystallized from benzene to provide the methyl-6-methoxyindole-2-carboxylate **7** (240.1 g, 89.0 %): mp 118-120 °C; IR (KBr) 3320, 3026, 2950, 1695, 1624, 1524, 1253, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.84 (s, 3H), 3.91 (s, 3H), 6.80 (m, 2H), 7.14 (d, 1H, J = 2 Hz), 7.54 (d, 1H, J = 7 Hz), 8.81 (s, indole, 1H); MS (CI, CH_4), 206 (M + 1); Anal. Calcd. for $C_{11}H_{11}NO_3$ (7): C, 64.36%; H, 5.40%; N, 6.83%. Found: C, 64.29%; H, 5.40%; N, 6.64%.

6-Methoxyindole-2-carboxylic acid (8). Methyl-6-methoxyindole-2-carboxylate **7** (200.0 g, 0.976 mol) was added to a solution of aqueous sodium hydroxide (2N, 5500 mL). The suspension which resulted was stirred and heated until the reaction mixture became homogeneous, after which the solution was heated at reflux for 30 m. The clear mixture was cooled, washed with ethyl acetate (1000 mL) and acidified with 2N HCl. The precipitate which formed was filtered, washed

with water (3 X 500 mL) and dried under vacuum to provide the carboxylic acid **8** as a clean white solid (175.0 g, 93.9%): mp 204-206 °C; IR (KBr) 3392, 3300-2400 (broad), 1670, 1626, 1532, 1262, 828 cm^{-1}; ^1H NMR (Me_2SO-d_6, 250 MHz) δ 3.76 (s, 3H), 6.70 (dd, 1H, J = 8.8 Hz, J = 2.2 Hz), 6.85 (d, 1H, J = 2.2 Hz), 7.00 (s, 1H), 7.50 (d, 1H, J = 8.8 Hz), 11.54 (s, indole, 1H), 12.70 (s, 1H, broad); MS (CI, CH_4), 192 (M + 1); Anal. Calcd. for $C_{10}H_9NO_3$ (**8**): C, 62.80%; H, 4.74%; N, 7.33%. Found: C, 62.13%; H, 4.66%; N, 7.18%.

6-Methoxyindole (9). The 6-Methoxyindole-2-carboxylic acid **8** (40.0 g, 0.21 mol), copper powder (9.4 g) and freshly distilled quinoline (650 mL) were combined in a 2 L flask under argon. The mixture which resulted was brought to reflux with heat and magnetic stirring. After 2 h, the reaction solution was cooled to room temperature and the copper was filtered from the medium. The filtrate was poured over ice (2 kg). The aqueous solution was brought to pH 4 with aqueous concentrated hydrochloric acid and extracted with ethyl acetate (6 X 650 mL). The combined ethyl acetate extracts were washed with 1 N HCl (8 X 500 mL), saturated aqueous $NaHCO_3$ (6 X 500 mL) and brine (2 X 500 mL). The organic solution was dried (K_2CO_3) and concentrated under reduced pressure to provide **9** (30.0 g, 97.6 %): mp 92-94 °C; IR (KBr) 3395, 3009, 2959, 1631, 1509, 1249, 815 cm^{-1}; ^1H NMR (Me_2SO-d_6, 250 MHz), δ, 3.73 (s, 3H), 6.30 (m, 1H), 6.61 (dd, 1H, J = 8.5 Hz, 2.2

Hz), 6.86 (d, 1H, J = 2.0 Hz), 7.15 (t, 1H, J = 2.5 Hz), 7.37 (d, 1H, J = 8.5 Hz), 10.83 (s, 1H, indole); MS (CI, CH_4), m/e 148 (M + 1); Anal. Calcd. for C_9H_9NO (**9**): C, 73.44%; H, 6.16%; N, 9.52%. Found: C, 73.27%; H, 5.92%; N, 9.46%.

6-Methoxyindole-3-carboxaldehyde (10). A three neck flask (1000 mL) was charged with N,N-dimethylformamide (DMF) (164 g, 2.24 mol) at -5 °C and stirred for 30 m. Phosphorous oxychloride (86.8 g, 0.57 mol) was added dropwise to the above solution and the mixture was stirred for 1 h. A solution of 6-methoxyindole **9** (75.0 g, 0.51 mol) in DMF (75 mL) was then added to the solution over 75 m., after which the mixture was stirred for an additional 2 h at 35 °C. Ice (250 g) was added to the warm solution and then transferred to a three neck flask (3000 mL) to which a solution of sodium hydroxide (225.6 g, 5.64 mol) in water (1000 mL) was added dropwise employing overhead stirring. The mixture was then heated rapidly to reflux with evolution of dimethylamine. The mixture was cooled and placed in the refrigerator overnight. The precipitate which formed was collected *via* vacuum filtration and washed with water (3 X 500 mL). The solid filter cake was then resuspended in water (2000 mL) and filtered. The wet golden-brown crude product was dissolved in ethanol (2000 mL) and brought to reflux on a steam bath. Activated charcoal was added and boiling continued for 5 m. The hot solution was filtered and concentrated to furnish the

carboxaldehyde **10** as a golden colored powder (84.8 g, 95.0%): mp 195-196 °C; IR (KBr) 3187, 2824, 1638, 1630, 1532, 1423, 1228 cm^{-1}; ^1H NMR (Me_2SO-d_6, 250 MHz) δ 3.78 (s, 3H), 6.84 (dd, 1H, J = 8.6, 2.3 Hz), 6.97 (d, 1H, J = 2.3 Hz), 7.92 (d, 1H, J = 8.6 Hz), 8.14 (s, 1H), 9.85 (s, 1H, aldehyde), 10.90 (s, 1H, indole); MS (CI, CH4) m/e 176 (M + 1); Anal. Calcd. for $C_{10}H_9NO_2$ (**10**): C, 68.55%; H, 5.18%;, N, 8.00%. Found: C, 68.32%; H, 5.18%; N, 7.69%.

1-Benzenesulfonyl-6-methoxyindole-3-carboxaldehyde (11). To an oven dried three neck flask (3 L) flushed with argon containing freshly distilled anhydrous tetrahydrofuran (THF, 2000 mL) was added 6-methoxyindole-3-carboxaldehyde **10** (80.0 g, 0.46 mol). The solution which resulted was cooled to 0 °C, after which NaH (60% w/w, 28.0 g, 0.685 mol, 1.5 eq.) was added in small portions. The reaction solution was then warmed to 40 °C and stirred for 90 m before cooling to 0 °C. Benzenesulfonyl chloride (82.5 g, 0.467 mol, 1.02 eq) was then added dropwise over 20 m and the solution which resulted was stirred at room temperature for 18 h. The reaction mixture was poured into water (2000 mL) and extracted with methylene chloride (2 X 2000 mL). The organic layer was washed with water (2000 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to provide an oil which crystallized upon the addition of hexane (128.0 g, 89.0%): mp 163-164 °C; IR (KBr) 3461, 3135, 2966, 2804, 1680, 1618,

1372, 1182 cm^{-1}; ^1H NMR (Me_2SO-d_6, 250 MHz) δ 3.84 (s, 3H), 7.03 (dd, 1H, J = 8.8, 2.2 Hz), 7.39 (d, 1H, J = 2.2 Hz), 7.66 (t, 2H, J = 7.8 Hz), 7.77 (t, 1H, J = 7.3 Hz), 7.97 (d, 1H, J = 8.7 Hz), 8.12 (d, 2H, J = 8.2 Hz), 8.76 (s, 1H), 10.01 (s, 1H, aldehyde); MS (CI, CH_4) m/e 316 (M + 1); Anal. Calcd. for $C_{16}H_{13}NO_4S$ (**11**): C, 60.94%; H, 4.16%; N, 4.44%. Found: C, 60.78%; H, 4.14%; N, 4.33%.

1-Benzenesulfonyl-3-hydroxymethyl-6-methoxyindole (12). The 1-benzenesulfonyl-6-methoxyindole-3-carboxaldehyde **11** (107.2 g, 0.34 mol) was suspended in anhydrous ethanol (3750 mL) to which $NaBH_4$ (37.0 g, 0.98 mol, 2.87 eq) was added. The solution which resulted was stirred for 4 h at room temperature after which the ethanol was removed under reduced pressure. The residue which resulted was dissolved in 1 N NaOH (3000 mL) and extracted with ether (5 X 1000 mL). The ethereal fractions were dried (K_2CO_3) and the solvent removed *in vacuo* to provide the hydroxymethyl indole **12** (104.9 g, 97.2%): mp 106.5-108 °C; IR (KBr) 3304, 3114, 2997, 1622, 1369, 1209, 1181 cm^{-1}; ^1H NMR (Me_2SO-d_6, 250 MHz) δ 3.82 (s, 3H), 4.55 (d, 2H, J = 6.3 Hz), 5.12 (t, 1H, J = 5.5 Hz), 6.89 (dd, 1H, J = 8.7, 2.2 Hz), 7.41 (d, 1H, J = 2.2 Hz), 7.48-7.69 (m, 5H), 7.95 (d, 2H, J = 7.2 Hz); MS (CI, CH_4) m/e 318 (M + 1), 300 (M - H_2O); Anal. Calcd. for $C_{16}H_{15}NO_4S$ (**12**): C, 60.53%; H, 4.77%; N, 4.42%. Found: C, 60.74%; H, 4.71%; N, 4.40%.

1-Benzenesulfonyl-3-bromomethyl-6-methoxyindole (13). To a stirred solution of 1-benzenesulfonyl-3-hydroxymethyl-6-methoxyindole **12** (9.03 g, 28.5 mmol) in anhydrous methylene chloride (220 mL) under argon was added a solution of dibromotriphenylphosphorane (12.02 g, 28.5 mmol) in anhydrous methylene chloride (100 mL). The purple solution which resulted was stirred for 15 h after which the solvent was removed under reduced pressure. The oily residue was taken up in ether (3 X 300 mL). The residue solidified and the ether was removed by decantation. Upon standing, triphenylphosphine oxide began to crystallize from the combined ethereal layers. The solution was filtered to remove the triphenylphosphine oxide by-product. This process was carried out twice. The ethereal solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide **13** as a clear oil which slowly crystallized upon standing (10.1 g, 93.4 %): mp 103-104 °C; IR (KBr) 3100, 2959, 1616, 1491, 1366, 1219, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.86 (s, 3H), 4.56 (s, 2H), 6.91 (dd, 1H, J = 8.8, 2.2 Hz), 7.41-7.55 (m, 6H), 7.85 (d, 2H, J = 7.3 Hz), MS (CI, CH_4) m/e 380 (M + 1), 382 (M + 3); Anal. Calcd. for $C_{16}H_{14}NSO_3Br$ (**13**): C, 50.50%; H, 3.71%; N, 3.69%. Found: C, 51.01%; H, 3.72%; N, 3.84%.

L-Valine-N-carboxyanhydride (19).[17] To a stirred suspension of L-valine **18** (94.0 g, 0.80 mol) in tetrahydrofuran (1200 mL) was passed a vigorous stream of phosgene. The temperature

was maintained at 40 °C with a heating mantle. After 90 m, the reaction mixture became homogeneous and phosgene addition was terminated. The solution which resulted was purged with N_2 for 2 h. The solvent was removed *in vacuo* and the residue was flashed with tetrahydrofuran (3 X 500 mL). The N-carboxyanhydride which formed was dried in the vacuum oven at 40 °C for 2 h to provide a quantitative yield of **19** (114.7 g, 100%). Due to the unstable nature of this anhydride it was used immediately in the next step without further purification. ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 0.84 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.9 Hz), 2.04 (m, 1H), 4.34 (dd, 1H, J = 4.1, 0.93 Hz)), 9.11 (s, 1H, NH). MS (CI, CH_4) 144 (M + 1).

(3S)-Isopropyl-2,5-diketopiperazine (20).[17] A solution of the N-carboxyanhydride **19** (50.6 g, 0.354 mol) in tetrahydrofuran (400 mL) was added dropwise to a vigorously stirred mixture of glycine ethyl ester hydrochloride (49.4 g, 0.354 mol), triethylamine (80.6 g, 0.80 mol) and chloroform (500 mL) at -70 °C in a three neck flask (3000 mL). After 3 h of stirring at -70 °C and 2 h at room temperature, the reaction solution was filtered to remove the triethylamine hydrochloride. The filtrate was concentrated *in vacuo* (<40 °C). To the residue which resulted was added toluene (1700 mL). The suspension which resulted was heated at reflux for 12 h and then cooled to 0 °C. The bis-lactim which resulted was recovered by vacuum filtration, washed with ether (4 X 200 mL) and dried under

vacuum at 100 °C to provide pure **20** (40.0 g, 73%): mp 235-238 °C (lit. mp 240-241 °C[17]); ^{1}H NMR (Me_2SO-d_6, 250 MHz) δ 0.84 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 7.0 Hz), 2.09 (m, 1H), 3.51 (m, 1H), 3.60 (dd, 1H, J = 17.7, 3.0 Hz), 3.81 (d, 1H, J = 17.7 Hz), 8.01 (s, 1H, NH), 8.18 (s, 1H, NH); MS (CI, CH_4) m/e 157 (M + 1).

(3S)-Isopropyl-2,5-diethoxypyrazine (14).[17] To a stirred solution of triethyloxonium tetrafluoroborate (384 g, 2.02 mol, 2.75 eq) in methylene chloride (3000 mL) was added the bis-lactim **20** (114.6 g, 0.735 mol) in portions. After 2 h the reaction mixture became homogeneous. The reaction was stirred at room temperature under argon for 72 h, after which a solution of NaH_2PO_4.•$7H_2O$ (201.6 g, 1.47 mol) and Na_2HPO_4•7 H_2O (2357 g, 8.8 mol) in water (7.5 L) was added to the solution with stirring. The organic phase was separated and the aqueous phase was re-extracted with methylene chloride (3 X 1000 mL). The combined organic layers were dried ($MgSO_4$), after which the solvent was removed under reduced pressure. The residue which resulted was vacuum distilled at 6 torr (90 °C) to provide the pure bis-ethoxy lactim ether **14** as a colorless liquid (100.1 g, 64%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.67 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.9 Hz), 1.19 (dt, 6H, J = 5.9 Hz), 2.14 (m, 1H), 3.77 (m, 3H), 4.06 (dq, 4H, J = 7.2 Hz); MS (CI, CH_4) m/e 213 (M + 1). The spectral data for **14** were identical to those of the published values.[17]

(3R,6S)-3-[1-(Benzenesulfonyl-6-methoxy)-3-indoyl]methyl-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (15).[11] *n*-Butyllithium (1.4 M, 8.50 mL, 11.9 mmol, 1.20 eq) was added to a solution of the bis-ethoxy lactim ether **14** (2.10 g, 9.89 mmol) in anhydrous tetrahydrofuran (40 mL) at -70 °C. The solution which resulted was stirred for 15 m after which a solution of the 1-benzenesulfonyl-3-bromomethyl-6-methoxyindole **13** (3.76 g, 9.89 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise. The reaction mixture was stirred for 48 h at -70 °C before warming to 0 °C, after which the THF was removed under reduced pressure. The oily residue which resulted was dissolved in ether (100 mL) and washed with water (2 X 50 mL). The ethereal layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude alkylated pyrazine **15**. The oil was chromatographed (SiO_2; ethyl acetate 20%, hexanes 80%) to provide pure **15** as an oil (4.7 g, 93%): ^1H NMR ($CDCl_3$, 250 MHz) δ 0.59 (d, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.9 Hz), 1.25 (dt, 6H, J = 7.1 Hz), 2.09 (m, 1H), 3.14 (t, 2H, J = 3.4 Hz), 3.83 (s, 3H), 3.89 (m, 1H), 4.10 (dq, 4H, J = 7.2 Hz), 4.27 (d, 1H, J = 3.7 Hz), 6.79 (dd, 1H, J = 8.7, 2.4 Hz), 7.15 (s, 1H), 7.36-7.53 (m, 5H), 7.76 (d, 2H, J = 7.3 Hz); MS (CI, CH_4) 512 (M + 1). This material was employed directly in the next step without further purification.

1-Benzenesulfonyl-6-methoxy-D(+)-tryptophan ethyl ester (16). The indoyl methyl pyrazine **15** (4.8 g, 9.39 mmol) was suspended in 2 N HCl (120 mL) to which tetrahydrofuran (150

mL) was added. The homogeneous solution which resulted was stirred at room temperature for 1 h, after which the reaction solution was concentrated *in vacuo*. The aqueous acidic residue was washed with ether (2 X 150 mL) and the ether was discarded. Ether (400 mL) and ice (100 g) were added to the aqueous acidic layer and the solution was brought to pH 8.5 with aqueous concentrated NH_4OH. The ether layer was removed and the aqueous basic solution was extracted with ether (3 X 125 mL). The combined ethereal fractions were dried ($MgSO_4$) and concentrated *in vacuo* to provide crude **16** and the L-valine ethyl ester by-product as a yellow oil. Kugelrohr distillation of the crude residue (0.3 torr, 75-80 °C) permitted separation of the tryptophan and valine ethyl esters. At a distillation temperature of 73 °C, the L-valine ethyl ester was removed as the forerun providing pure 1-benzenesulfonyl-6-methoxy-D(+)-tryptophan ethyl ester **16** (3.70 g, 98 %)which remained: ^1H NMR (Me_2SO-d_6, 250 MHz) δ 0.98 (t, 3H, J = 7.1 Hz), 1.74 (s, 2H, br, NH_2), 2.86 (t, 2H, J = 5.8 Hz), 3.61 (t, 1H, J = 6.6 Hz), 3.81 (s, 3H), 3.90 (q, 2H, J = 7.0 Hz), 6.89 (dd, 1H, J = 8.6, 2.2 Hz), 7.35-7.45 (m, 4H), 7.56 (t, 2H, J = 7.0 Hz), 7.65 (d, 1H, J = 7.1 Hz), 7.91 (d, 2H, J = 7.1 Hz); MS (CI, CH_4) 403 (M+1); Anal. Calcd. for $C_{20}H_{22}N_2O_5S$ (**16**): C, 59.70%, H, 5.47%; N, 6.96%. Found: C, 59.80%; H, 5.36%; N, 6.87%. $[\alpha]^{27}_D$= -21.4° (c=5, EtOH).

Methyl-2-azido-3-(2-methoxyphenyl) propenoate (21). Analogous to the modified procedure of Moody,[7] methanol (650

mL) and sodium methoxide (25% w/w, 379.5 mL, 1.66 mol) were added to a three neck flask (3 L) equipped with an overhead stirrer and pressure equilibrating dropping funnel (under nitrogen). The funnel was charged with a solution of 2-methoxybenzaldehyde (56.5 g, 0.41 mol) in methanol (2000 mL) and methyl azidoacetate **5** (190.9 g, 1.66 mol). The mixture was added dropwise (4 h) to the methoxide solution at -8 °C. The mixture was allowed to stir for an additional 1.5 h while the temperature was maintained below 5 °C. The heterogeneous mixture was poured over ice (1.25 kg) and stirred manually. The suspension which resulted was filtered and washed with water (4 X 100 mL). The light yellow solid which resulted was dried (6 h) in a vacuum oven at room temperature to provide the azidocinnimate **21** (47.1 g, 49%): This material was used within 24 h and without further purification in the next step for the preparation of **23**. The yield of this preparation on smaller scale was much improved.

Methyl-4-methoxyindole-2-carboxylate (23). A three neck flask (5 L) charged with boiling xylenes (2000 mL) was equipped with an overhead stirrer, reflux condenser and pressure equilibrating dropping funnel. The funnel was charged with a solution of methyl-2-azido-3-(2-methoxyphenyl)-propenoate **21** (102.5 g, 0.44 mol) in xylenes (1000 mL), after which it was **slowly** dripped into the boiling xylenes over 2.5 h. **CAUTION: the azido analog 21 was slowly dripped into refluxing xylenes and the gas evolution carefully**

monitored to prohibit a buildup of excess azidocinnamate 21 in solution. The reaction mixture was allowed to stir at reflux for an additional hour after the evolution of nitrogen gas had ceased. The reaction mixture was cooled and the solvent was removed under reduced pressure. The residue which remained was crystallized from benzene to provide pure methyl-4-methoxyindole-2-carboxylate **23** (65.0 g, 72.1%): mp 147-148 °C; IR (KBr) 3320, 3026, 1695, 1624, 1524, 1253, 829 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.85 (s, 3H), 3.87 (s, 3H), 6.52 (d, 1H, J = 7.4 Hz), 7.01 (d, 1H, J = 7.5 Hz), 7.08 (s, 1H), 7.17 (t, 1H, J = 7.9 Hz), 10.95 (s, indole, 1H); MS (CI, CH_4) 206 (M + 1); Anal. Calcd. for $C_{11}H_{11}NO_3$ (**23**): C, 64.36%; H, 5.40%; N, 6.83%. Found: C, 64.27%; H, 5.39%; N, 6.60%.

Methyl-2-azido-3-(2,4-dimethoxyphenyl) propenoate (22). Analogous to the previously cited protocol,[7] methanol (850 mL) and sodium methoxide (25% w/w, 536 g, 2.48 mol) were added to a three neck flask (5 L) equipped with an overhead stirrer and pressure equilibrating dropping funnel under nitrogen. The funnel was charged with a solution of 2,4-dimethoxybenzaldehyde (100.0 g, 0.62 mol) in methanol (1500 mL) and methyl azidoacetate **5** (285.4 g, 2.48 mol). The solution was added dropwise (4 h) to the methoxide mixture at -8 °C. The mixture was allowed to stir for an additional 1.5 h while the temperature was maintained below 5 °C. The heterogeneous mixture was poured over ice (2 kg) and stirred

manually. The suspension which resulted was filtered and washed with water (4 X 200 mL). The light yellow solid which formed was dried (6 h) in a vacuum oven at room temperature to yield the azidocinnimate **22** (82.0 g, 50.3%). This material was used within 24 h and without further purification for the synthesis of **24** in the next step.

Methyl-4,6-dimethoxyindole-2-carboxylate (24). A three neck flask (5 L) which contained boiling xylenes (1500 mL) was equipped with an overhead stirrer, reflux condenser and pressure equilibrating dropping funnel. The funnel was charged with a solution of methyl-2-azido-3-(2,4-dimethoxyphenyl)-propenoate **22** (79.5 g, 0.30 mol) in xylenes (1500 mL), after which this solution was slowly dripped into the boiling xylenes over 2 h. **CAUTION: the azido analog 22 was slowly dripped into refluxing xylenes and the gas evolution carefully monitored to prohibit a buildup of excess azidocinnamate 22 in solution.** The reaction mixture was allowed to stir at reflux for an additional one half hour after the evolution of nitrogen gas had ceased. The reaction solution was cooled and the solvent was removed under reduced pressure. The residue which remained was crystallized from benzene to provide pure methyl-4,6-dimethoxyindole-2-carboxylate **24** (65.6 g, 92.4%): mp 186-187 °C; IR (KBr) 3320, 3026, 1695, 1624, 1524, 1253, 829 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.76 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 6.18 (d, 1H, J = 1.9 Hz), 6.45 (d, 1H, J = 1.0 Hz), 6.99 (s, 1H), 11.10 (s, indole, 1H); MS (CI, CH_4) 236 (M + 1); Anal. Calcd.

for $C_{12}H_{13}NO_4$ (24): C, 61.25%; H, 5.57%; N, 5.96%. Found: C, 61.08%; H, 5.57%; N, 5.61%.

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