

SYNTHESIS OF 2-(INDOL-3-YL)METHYL-5-METHYLPYRAZINES,  
THE SKELETON OF ASTECHROME

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**Abstract** --- By the coupling reaction between indolyl-  
magnesium bromide and 2-tosyloxymethyl-5-methylpyrazines,  
three 2-(indol-3-yl)-5-methylpyrazines were synthesized.  
These compounds constitute the skeleton of astechrome, an  
iron-containing metabolite of Aspergillus terreus IFO 6123  
and 8835.

Some natural products, such as Cypridina luciferin,<sup>1</sup> OPC-15161<sup>2</sup> and  
astechrome,<sup>3</sup> contain indole and pyrazine rings. Among these, astechrome  
(1),<sup>3</sup> an iron containing metabolite, was isolated from Aspergillus terreus  
IFO 6123 and 8835, and possesses a hydroxamic acid structure. We were  
interested in the synthesis of 1 and now report the synthesis of three  
2-(indol-3-yl)methyl-5-methylpyrazines (2-4) (Figure 1). The coupling  
between pyrazine and indole rings through a methylene linkage was carried  
out by the reaction of indolylmagnesium bromide with tosyloxymethyl-  
pyrazines (6, 10 and 14).<sup>4</sup> Among the intermediates for the synthesis  
of compounds (2-4), 2-hydroxymethyl-5-methylpyrazine (5) was prepared  
in the reported manner.<sup>5</sup>

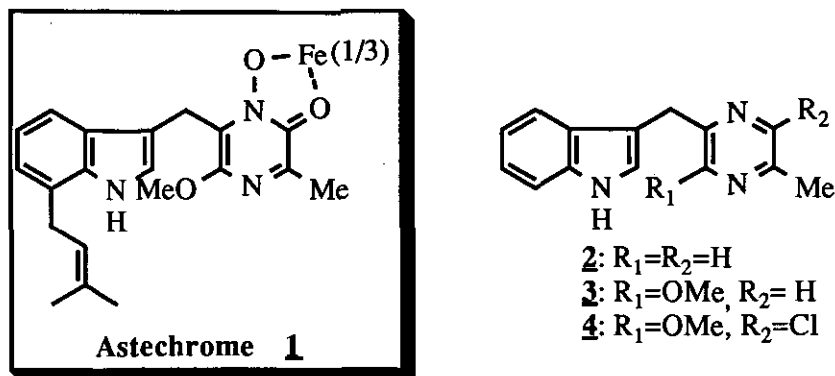
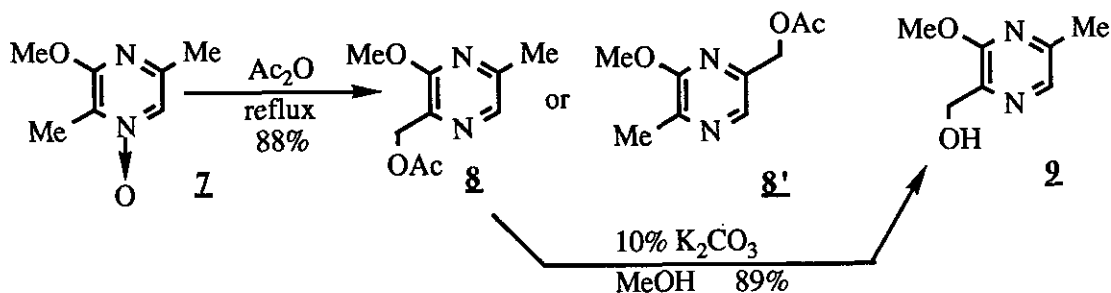


Figure 1

The synthesis of 2-hydroxymethyl-3-methoxy-5-methylpyrazine (9) was conducted as shown in Scheme 1.



2,5-Dimethyl-3-methoxy-1-oxypyrazine (7)<sup>6</sup> was heated with acetic anhydride to give 2-acetoxymethyl-3-methoxy-5-methylpyrazine (8). The position of the acetoxyl group was determined by the long-range selective proton decoupling (LSPD) method of nmr spectra. On irradiating the 5-methyl proton at 2.42 ppm, a doublet-quartet due to C-5 was changed into a doublet. Thus, the structure of 8 was assigned as 2-acetoxymethyl-3-methoxy-5-methylpyrazine as shown in Figure 2. Compound (8) was converted to 9 by an alkaline hydrolysis.

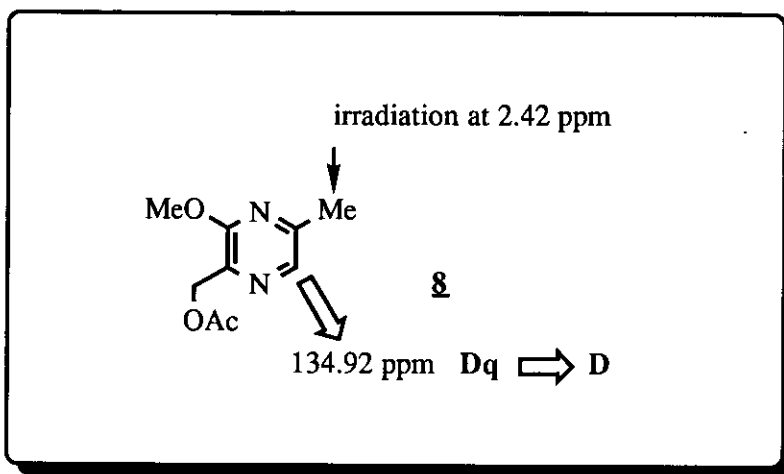
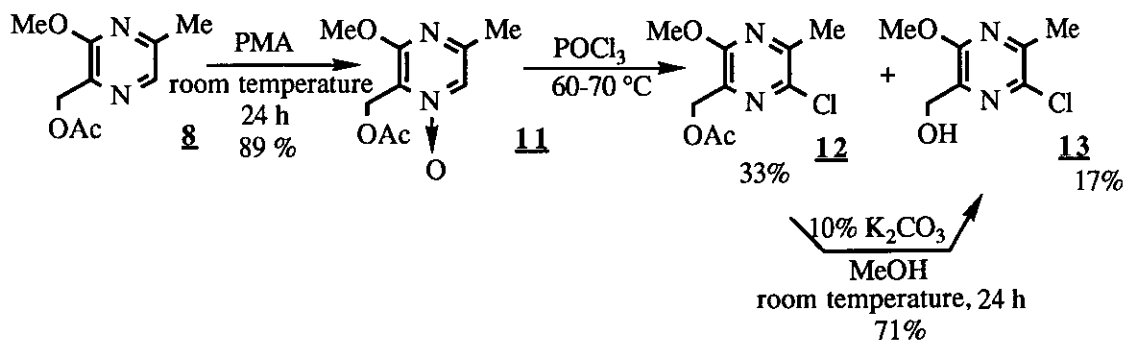


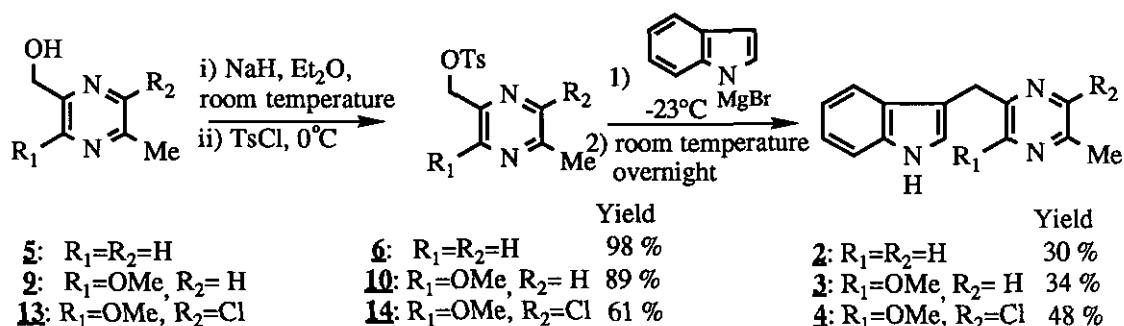
Figure 2

The synthesis of the intermediate (**13**) started from **8**. Compound (**8**) was oxidized with permaleic acid (PMA) to give 2-acetoxymethyl-3-methoxy-5-methylpyrazine 1-oxide (**11**). The  $^1\text{H}$ -nmr spectrum of **11** was consistent with the proposed structure. Namely, the ring proton signal of **11** appeared in a higher field than that of **8** and the signal of the methylene protons of **11** in a lower field.<sup>7</sup> The reaction of **11** with phosphoryl chloride gave a mixture of 2-acetoxymethyl-6-chloro-3-methoxy-5-methylpyrazine (**12**) and 6-chloro-2-hydroxymethyl-3-methoxy-5-methylpyrazine (**13**). Compound (**12**) and (**13**) could be separated from each other by column chromatography on silica gel. The alkaline hydrolysis of **12** led to give **13** (Scheme 2).

Scheme 2 Synthesis of Compound **13**

The hydroxymethylpyrazines (5, 9 and 13) were respectively treated with sodium hydride and the addition of tosyl chloride to the reaction mixture gave the corresponding tosylates (6, 10 and 14) in 98, 89 and 61% yields, respectively.

The coupling reaction of indole with 6, 10 and 14 was conducted as follows. The solution of tosyloxymethylpyrazines in methylene chloride was added dropwise to the ethereal solution of indolylmagnesium bromide, prepared from indole and ethylmagnesium bromide, under stirring at  $-23^{\circ}\text{C}$ . The reaction mixture was then stirred overnight at room temperature to give the corresponding 2-(indol-3-yl)methyl-5-methylpyrazines (2, 3 and 4) in 30, 34 and 48% yields, respectively. The analytical and spectral data were consistent with the proposed structures (Scheme 3).



### Scheme 3 Synthesis of Compound **2**, **3**, and **4**

#### EXPERIMENTAL

The melting and boiling points are uncorrected. The distillation of the liquid products was carried out using a micro boiling apparatus (Sibata, Model G70-250RS).  $^1\text{H-Nmr}$  spectral data were obtained with a Varian Gemini-300 or Bruker AM-400 instrument in  $\text{CDCl}_3$  using TMS as the internal standard.  $^{13}\text{C-Nmr}$  spectra were measured by a Bruker AM-400 instrument. Other spectral data were obtained using the following instruments. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80 spectrometer.

Synthesis of 2-Acetoxymethyl-3-methoxy-5-methylpyrazine (8): A solution of 7 (2.43 g) in  $\text{Ac}_2\text{O}$  (100 ml) was refluxed for 1 h and poured into ice-water. The solution was made alkaline with powdered  $\text{K}_2\text{CO}_3$  and extracted with  $\text{Et}_2\text{O}$ . A usual work-up of the extract gave a red-brownish oil, which was purified by column chromatography on silica gel with hexane containing an increasing amount of  $\text{AcOEt}$  to give 8 as a colorless oil; bp  $70\text{--}80^\circ\text{C}/3$  torr; yield: 2.72 g (88%); ms:  $m/z$  196 ( $\text{M}^+$ ); ir (neat):  $1750$  ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr: 2.11 (s, 3H,  $\text{CH}_2\text{OCOCH}_3$ ), 2.42 (s, 3H, pyrazine  $\text{CH}_3$ ), 3.95 (s, 3H,  $\text{OCH}_3$ ), 5.16 (s, 2H,  $\text{CH}_2\text{OCOCH}_3$ ), 7.95 (s, 1H, pyrazine H) ppm; Anal. Calcd for  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ : C, 55.09; H, 6.14; N, 14.28. Found: C, 54.94; H, 6.12; N, 14.38.

Synthesis of 2-Hydroxymethyl-3-methoxy-5-methylpyrazine (9): A solution of 8 (18.0 g) in a mixture of 10% aq.  $\text{K}_2\text{CO}_3$  (150 ml) and  $\text{MeOH}$  (150 ml) was stirred for 24 h at room temperature, followed by removal of the solvent by distillation in vacuo. Water was added to the residue and the solution was extracted with  $\text{Et}_2\text{O}$ . After drying of the extract with  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated and the crude products were purified by recrystallization. Colorless needles; mp  $50\text{--}51^\circ\text{C}$  (from cyclohexane); yield: 12.6 g (89%); ms:  $m/z$  154 ( $\text{M}^+$ ); ir (KBr):  $3230$  ( $\text{OH}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr: 2.43 (s, 3H,  $\text{CH}_3$ ), 3.75 (s, 1H,  $\text{CH}_2\text{OH}$ ), 3.96 (s, 3H,  $\text{OCH}_3$ ), 4.67 (s, 2H,  $\text{CH}_2\text{OH}$ ), 7.91 (s, 1H, pyrazine H) ppm; Anal. Calcd for  $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$ : C, 54.53; H, 6.54; N, 18.17. Found: C, 54.31; H, 6.47; N, 18.05.

Oxidation of 2-Acetoxymethyl-3-methoxy-5-methylpyrazine (11): A solution of 8 (4.90 g, 25.0 mmol), 60%  $\text{H}_2\text{O}_2$  (2.34 g, 41.3 mmol) and maleic anhydride (4.15 g, 42.3 mmol) in  $\text{CHCl}_3$  (200 ml) was stirred for 24 h at room temperature. Then the reaction mixture was washed successively with  $\text{H}_2\text{O}$ , 10%  $\text{KHCO}_3$  and  $\text{H}_2\text{O}$ . The  $\text{CHCl}_3$  layer was worked up as usual to give a crystalline mass, which was recrystallized from cyclohexane to afford 4.96 g (89%) of 11 as colorless needles; mp  $92\text{--}94^\circ\text{C}$ ; ms:  $m/z$  212

(M<sup>+</sup>); ir (KBr): 1720 (C=O) cm<sup>-1</sup>; <sup>1</sup>H-nmr: 2.09 (s, 3H, CH<sub>2</sub>OCOCH<sub>3</sub>), 2.39 (s, 3H, pyrazine CH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 5.32 (s, 2H, CH<sub>2</sub>OCOCH<sub>3</sub>), 7.71 (s, 1H, pyrazine H) ppm; Anal. Calcd for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.95; H, 5.68; N, 13.13.

Reaction of 2-Acetoxymethyl-3-methoxy-5-methylpyrazine 1-Oxide (11) with POCl<sub>3</sub>: A mixture of 11 (160 mg) and POCl<sub>3</sub> (0.8 ml) was heated at 60-70°C for 1 h in an oil bath and then poured into ice-water. The solution was made alkaline with powdered K<sub>2</sub>CO<sub>3</sub> and extracted with Et<sub>2</sub>O. A usual work-up of the Et<sub>2</sub>O layer gave a brownish oil, which was applied to a silica gel column and eluted with hexane containing an increasing amount of AcOEt. Compounds 12 (56 mg, 33%) and 13 (23.5 mg, 17%) were eluted successively. 2-Acetoxymethyl-6-chloro-3-methoxy-5-methylpyrazine (12): colorless prisms; bp 100-110°C/1 torr; mp 47-48°C; ms: m/z 230 (M<sup>+</sup>); ir (KBr) 1740 (C=O) cm<sup>-1</sup>; <sup>1</sup>H-nmr: 2.14 (s, 3H, CH<sub>2</sub>OCOCH<sub>3</sub>), 2.55 (s, 3H, pyrazine CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 5.16 (s, 2H, CH<sub>2</sub>OCOCH<sub>3</sub>) ppm; Anal. Calcd for C<sub>9</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>Cl: C, 46.86; H, 4.81; N, 12.15. Found: C, 46.69; H, 4.80; N, 12.23. 6-Chloro-2-hydroxymethyl-3-methoxy-5-methylpyrazine (13): colorless needles; mp 97-99°C (from hexane); ms: m/z 188 (M<sup>+</sup>); <sup>1</sup>H-nmr: 2.55 (s, 3H, CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.70 (s, 2H, CH<sub>2</sub>OH) ppm; Anal. Calcd for C<sub>7</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>Cl: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.70; H, 4.84; N, 14.74.

Hydrolysis of 2-Acetoxymethyl-6-chloro-3-methoxy-5-methylpyrazine (12): Compound 12 was treated the same as the case of hydrolysis of 8. Compound 13 was obtained in 71% yields.

General Procedure for Tosylation of 2-Hydroxymethylpyrazines (5, 9 and 13): A solution of 2-hydroxymethylpyrazine (0.65 mmol) in dry Et<sub>2</sub>O (2 ml) was added to a suspension of NaH (28.8 mg, 0.72 mmol) in dry Et<sub>2</sub>O (2 ml). After stirring at room temperature for 1 h, a solution of TsCl (163.4 mg, 0.86 mmol) in dry THF (2 ml) was added to the above solution

at 0°C. The reaction mixture was then stirred for 1.5 h at 0°C, washed with H<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. After a usual work-up of the organic layer, the product was applied to a silica gel column and eluted with hexane containing an increasing amount of AcOEt. 5-Methyl-2-tosyloxymethylpyrazine (6): colorless prisms; mp 62-64°C (from hexane); yield: 98%; ms: m/z 279 (M<sup>+</sup>+1); <sup>1</sup>H-nmr: 2.44 (s, 3H, pyrazine CH<sub>3</sub> or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 2.55 (s, 3H, pyrazine CH<sub>3</sub> or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 5.15 (s, 2H, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>OCH<sub>2</sub>), 7.35 (d, J = 8.5 Hz, 2H, benzene H), 7.82 (d, J = 8.5 Hz, 2H, benzene H), 8.36 (s, 1H, pyrazine H), 8.50 (s, 1H, pyrazine H) ppm; Anal. Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.06; H, 5.11; N, 10.14. 3-Methoxy-5-methyl-2-tosyloxymethylpyrazine (10): colorless needles; mp 98-100°C (decomp.) (from EtOH); yield: 89%; ms: m/z 309 (M<sup>+</sup>+1); <sup>1</sup>H-nmr: 2.43 (s, 3H, pyrazine CH<sub>3</sub> or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 2.45 (s, 3H, pyrazine H or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 5.14 (s, 2H, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>OCH<sub>2</sub>), 7.32 (d, J = 8.3 Hz, 2H, benzene H), 7.81 (d, J = 8.3 Hz, 2H, benzene H), 7.92 (s, 1H, pyrazine H) ppm; Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: C, 54.53; H, 5.23; N, 9.09. Found: C, 54.74; H, 5.24; N, 9.09. 6-Chloro-3-methoxy-5-methyl-2-tosyloxymethylpyrazine (14): colorless oil; yield: 61%; ms: m/z 342 (M<sup>+</sup>); <sup>1</sup>H-nmr: 2.44 (s, 3H, pyrazine CH<sub>3</sub> or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 2.51 (s, 3H, pyrazine CH<sub>3</sub> or C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 5.10 (s, 2H, CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>OCH<sub>2</sub>), 7.33 (d, J = 8.4 Hz, 2H, benzene H), 7.77 (d, J = 8.4 Hz, 2H, indole H) ppm; High resolution mass. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>ClS: 342.0439. Found: 342.0425.

General Procedure for the Synthesis of 2-(Indol-3-yl)methyl-5-methylpyrazines (2, 3 and 4): A THF solution of 0.93M EtMgBr (0.31 ml, 0.29 mmol), purchased from Kanto Chemical Co. Inc., was diluted with Et<sub>2</sub>O (1.4 ml). To this solution an Et<sub>2</sub>O (1.4 ml) solution of indole (31.1 mg, 0.27 mmol) was added at -23°C under stirring. The reaction mixture was then stirred for 0.5 h at room temperature and dry CH<sub>2</sub>Cl<sub>2</sub> (1.4 ml)

was added to this mixture. The whole mixture was cooled to  $-23^{\circ}\text{C}$  and a solution of a tosyloxymethylpyrazine (0.18 mmol) in THF (1.4 ml) was added to the above mixture. After stirring overnight at room temperature, 10%  $\text{NH}_4\text{Cl}$  was added to the reaction mixture. The organic layer was separated and the water layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined  $\text{CH}_2\text{Cl}_2$  extract was dried over  $\text{Na}_2\text{SO}_4$  and the evaporation of the  $\text{CH}_2\text{Cl}_2$  gave a red-brownish oil, which was applied to a silica gel column and eluted with hexane containing an increasing amount of AcOEt.

2-(Indol-3-yl)methyl-5-methylpyrazine (2): colorless prisms; mp  $128\text{--}129^{\circ}\text{C}$  (from iso- $\text{Pr}_2\text{O}$ ); yield: 30%; ms:  $m/z$  223 ( $\text{M}^+$ );  $^1\text{H}$ -nmr: 2.51 (s, 3H,  $\text{CH}_3$ ), 4.28 (s, 2H,  $\text{CH}_2$ ), 7.08-7.21 (m, 3H, indole 2-, 5-, and 6-H), 7.34 (d,  $J = 9.0$  Hz, 1H, indole 4- or 7-H), 7.55 (d,  $J = 9.0$  Hz, 1H, indole 4- or 7-H), 8.22 (br s, 1H, indole 1-H), 8.38 (s, 1H, pyrazine H), 8.40 (s, 1H, pyrazine H) ppm; Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3$ : C, 75.31; H, 5.87; N, 18.82. Found: C, 75.04; H, 5.90; N, 18.75. 2-(Indol-3-yl)methyl-3-methoxy-5-methylpyrazine (3): colorless needles; mp  $136\text{--}138^{\circ}\text{C}$  (from cyclohexane); yield: 34%; ms:  $m/z$  253 ( $\text{M}^+$ );  $^1\text{H}$ -nmr: 2.38 (s, 3H,  $\text{CH}_3$ ), 3.97 (s, 3H,  $\text{OCH}_3$ ), 4.24 (s, 2H,  $\text{CH}_2$ ), 7.07-7.18 (m, 3H, indole 2, 5- and 6-H), 7.31 (d,  $J = 8.0$  Hz, 1H, indole 4- or 7-H), 7.70 (d,  $J = 8.0$  Hz, 1H, indole 4- or 7-H), 7.89 (s, 1H, pyrazine H), 7.98 (br s, 1H, indole 1-H) ppm; Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$ : C, 71.12; H, 5.97; N, 16.59. Found: 70.91; H, 6.02; N, 16.59. 6-Chloro-2-(indol-3-yl)methyl-3-methoxy-5-methylpyrazine (4): colorless prisms; mp  $104\text{--}106^{\circ}\text{C}$  (from hexane); yield: 48%; ms:  $m/z$  287 ( $\text{M}^+$ );  $^1\text{H}$ -nmr: 2.47 (s, 3H,  $\text{CH}_3$ ), 3.94 (s, 3H,  $\text{OCH}_3$ ), 4.20 (s, 2H,  $\text{CH}_2$ ), 7.10-7.17 (m, 3H, indole 2, 5- and 6-H), 7.31 (d,  $J = 9.0$  Hz, 1H, indole 4- or 7-H), 7.74 (d,  $J = 9.0$  Hz, 1H, indole 4- or 7H), 7.92 (br s, 1H, indole 1-H) ppm; Anal. Calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_3\text{OCl}$ : C, 62.61; H, 4.90; N, 14.60. Found: C, 62.53; H, 4.87; N, 14.83.



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