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

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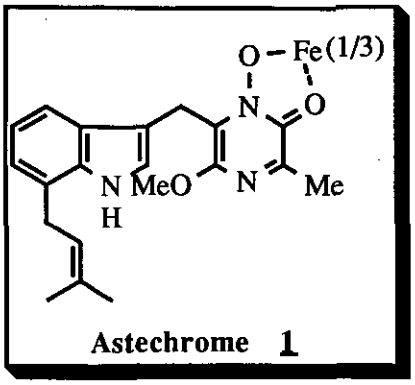
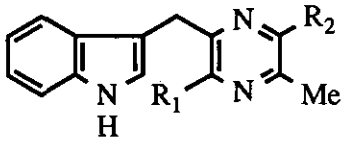
Abstract --- By the coupling reaction between indolylmagnesium bromide and 2-tosyloxymethyl-5-methylpyrazines, three 2-(indol-3-yl)-5-methylpyrazines were synthesized. These compounds constitute the skeleton of astechrome, an iron-containing metabolite of Aspergillus terreus IFO 6123 and 8835.

Some natural products, such as Cypridina luciferin,[1] OPC-15161[2] and astechrome,[3] contain indole and pyrazine rings. Among these, astechrome (1),[3] 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 tosyloxymethylpyrazines (6, 10 and 14).[4] Among the intermediates for the synthesis of compounds (2-4), 2-hydroxymethyl-5-methylpyrazine (5) was prepared in the reported manner.[5]

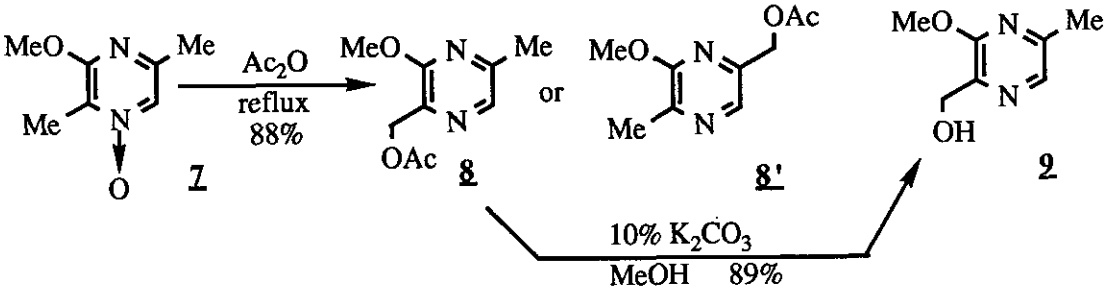




2: R_1=R_2=H
3: R_1=OMe, R_2= H
4: R_1=OMe, R_2=Cl

Figure 1

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



Scheme 1 Synthesis of Compound 9

2,5-Dimethyl-3-methoxypyrazine 1-oxide (7)[6] 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.

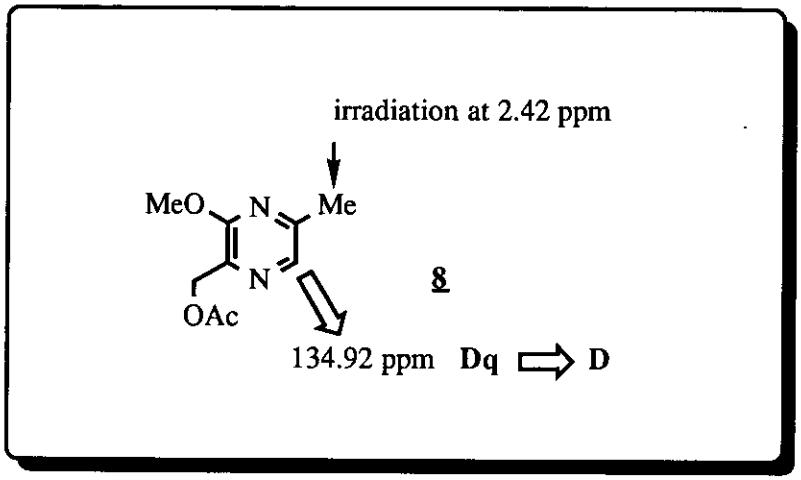
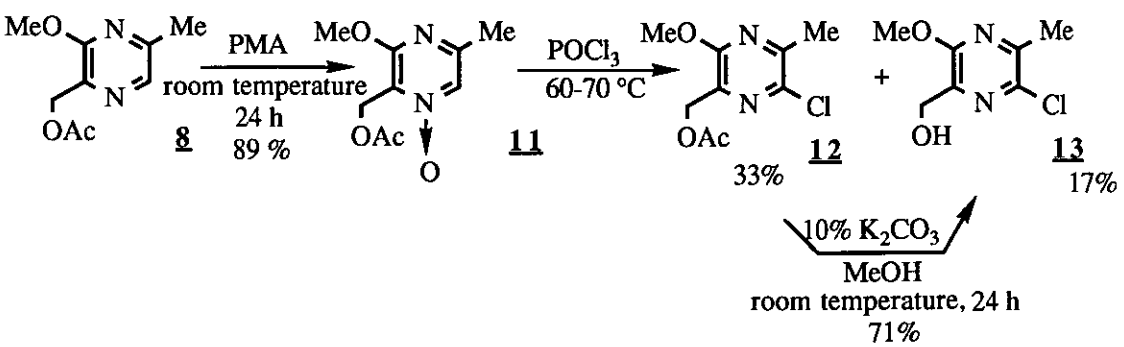


Figure 2

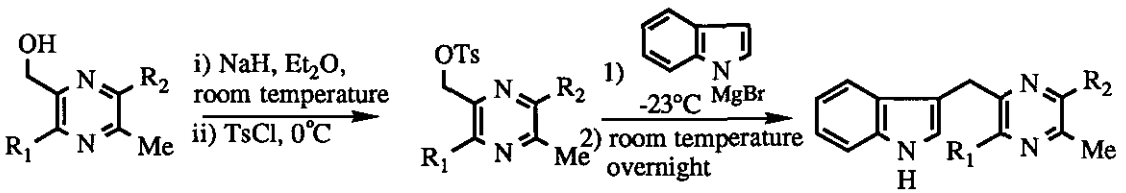
The synthesis of the intermediate (13) started from 8. Compound (8) was oxidized with permaleic acid (PMA) to give 2-acetoxymethyl-3-methoxy-5-methylpyrazine 1-oxide (11). The ^{1}H-nmr spectrum of 11 was consistent with the proposed structure. Namely, the ring proton signal of 11 appeared in a higher field than that of 8 and the signal of the methylene protons of 11 in a lower field.[7] 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°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).



		Yield		Yield
5: R_1=R_2=H	6: R_1=R_2=H	98 %	2: R_1=R_2=H	30 %
9: R_1=OMe, R_2= H	10: R_1=OMe, R_2= H	89 %	3: R_1=OMe, R_2= H	34 %
13: R_1=OMe, R_2=Cl	14: R_1=OMe, R_2=Cl	61 %	4: R_1=OMe, R_2=Cl	48 %

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}H-Nmr spectral data were obtained with a Varian Gemini-300 or Brucker AM-400 instrument in $CDCl_3$ using TMS as the internal standard. ^{13}C-Nmr spectra were measured by a Brucker 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 Ac_2O (100 ml) was refluxed for 1 h and poured into ice-water. The solution was made alkaline with powdered K_2CO_3 and extracted with Et_2O. 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 AcOEt to give 8 as a colorless oil; bp 70-80°C/3 torr; yield: 2.72 g (88%); ms: m/z 196 (M^+); ir (neat): 1750 (C=O) cm^{-1}; ^{1}H-nmr: 2.11 (s, 3H, $CH_2OCOC\underline{H}_3$), 2.42 (s, 3H, pyrazine CH_3), 3.95 (s, 3H, OCH_3), 5.16 (s, 2H, $C\underline{H}_2OCOCH_3$), 7.95 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{12}N_2O_3$: 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. K_2CO_3 (150 ml) and 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 Et_2O. After drying of the extract with Na_2SO_4, the solvent was evaporated and the crude products were purified by recrystallization. Colorless needles; mp 50-51°C (from cyclohexane); yield: 12.6 g (89%); ms: m/z 154 (M^+); ir (KBr): 3230 (OH) cm^{-1}; ^{1}H-nmr: 2.43 (s, 3H, CH_3), 3.75 (s, 1H, $CH_2O\underline{H}$), 3.96 (s, 3H, OCH_3), 4.67 (s, 2H, $C\underline{H}_2OH$), 7.91 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_7H_{10}N_2O_2$: 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% H_2O_2 (2.34 g, 41.3 mmol) and maleic anhydride (4.15 g, 42.3 mmol) in $CHCl_3$ (200 ml) was stirred for 24 h at room temperature. Then the reaction mixture was washed successively with H_2O, 10% $KHCO_3$ and H_2O. The $CHCl_3$ 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 92-94°C; ms: m/z 212

(M^+); ir (KBr): 1720 (C=O) cm^{-1}; ^{1}H-nmr: 2.09 (s, 3H, CH_2OCOCH_3), 2.39 (s, 3H, pyrazine CH_3), 4.00 (s, 3H, OCH_3), 5.32 (s, 2H, CH_2OCOCH_3), 7.71 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{12}N_2O_4$: 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 $POCl_3$: A mixture of 11 (160 mg) and $POCl_3$ (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_2CO_3 and extracted with Et_2O. A usual work-up of the Et_2O 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^+); ir (KBr) 1740 (C=O) cm^{-1}; ^{1}H-nmr: 2.14 (s, 3H, CH_2OCOCH_3), 2.55 (s, 3H, pyrazine CH_3), 3.98 (s, 3H, OCH_3), 5.16 (s, 2H, CH_2OCOCH_3) ppm; Anal. Calcd for $C_9H_{11}N_2O_3Cl$: 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^+); ^{1}H-nmr: 2.55 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2OH) ppm; Anal. Calcd for $C_7H_9N_2O_2Cl$: 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 soltuiton of 2-hydroxymethylpyrazine (0.65 mmol) in dry Et_2O (2 ml) was added to a suspension of NaH (28.8 mg, 0.72 mmol) in dry Et_2O (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_2O and dried over Na_2SO_4. 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^++1); ^{1}H-nmr: 2.44 (s, 3H, pyrazine CH_3 or $C_6H_4C\underline{H}_3$), 2.55 (s, 3H, pyrazine CH_3 or $C_6H_4C\underline{H}_3$), 5.15 (s, 2H, $CH_3C_6H_4SO_2OC\underline{H}_2$), 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 $C_{13}H_{14}N_2O_3S$: 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^++1); ^{1}H-nmr: 2.43 (s, 3H, pyrazine CH_3 or $C_6H_4C\underline{H}_3$), 2.45 (s, 3H, pyrazine H or $C_6H_4C\underline{H}_3$), 3.88 (s, 3H, OCH_3), 5.14 (s, 2H, $CH_3C_6H_4SO_2OC\underline{H}_2$), 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 $C_{14}H_{16}N_2O_4S$: 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): colorles oil; yield: 61%; ms: m/z 342 (M^+); ^{1}H-nmr: 2.44 (s, 3H, pyrazine CH_3 or $C_6H_4C\underline{H}_3$), 2.51 (s, 3H, pyrazine CH_3 or $C_6H_4C\underline{H}_3$), 3.90 (s, 3H, OCH_3), 5.10 (s, 2H, $CH_3C_6H_4SO_2OC\underline{H}_2$), 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 $C_{14}H_{15}N_2O_4ClS$: 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_2O (1.4 ml). To this solution an Et_2O (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_2Cl_2 (1.4 ml)

was added to this mixture. The whole mixture was cooled to -23°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% NH_4Cl was added to the reaction mixture. The organic layer was separated and the water layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried over Na_2SO_4 and the evaporation of the CH_2Cl_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 128-129°C (from iso-Pr_2O); yield: 30%; ms: m/z 223 (M^+); ^{1}H-nmr: 2.51 (s, 3H, CH_3), 4.28 (s, 2H, 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 $C_{14}H_{13}N_3$: 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 136-138°C (from cyclohexane); yield: 34%; ms: m/z 253 (M^+); ^{1}H-nmr: 2.38 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.24 (s, 2H, 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 $C_{15}H_{15}N_3O$: 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 104-106°C (from hexane); yield: 48%; ms: m/z 287 (M^+); ^{1}H-nmr: 2.47 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.20 (s, 2H, 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 $C_{15}H_{14}N_3OCl$: C, 62.61; H, 4.90; N, 14.60. Found: C, 62.53; H, 4.87; N, 14.83.

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Received, 7th October, 1991