APPROACH TO THE SYNTHESIS OF ASTECHROME

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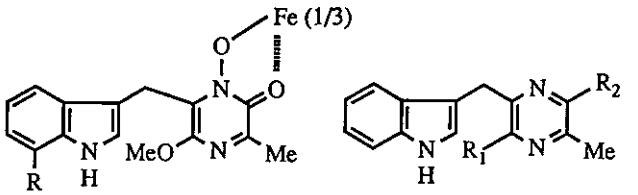
Abstract ---The coupling reaction between 2-chloro-6-chloromethyl-5-methoxy-3-methylpyrazine 1-oxide and indolylmagnesium bromide gave 2-chloro-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-oxide, which was converted to a hydroxamic acid derivative *via* an indoline. The synthesis of 2-hydroxy-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-oxide, constituting the skeleton of astechrome, was accomplished from the Fe salt of the corresponding indolinehydroxamic acid derivative by oxidation with bis(salicylidene)ethylenediaminato cobalt(II) [Co(Salen)].

Astechrome (1),[1] an iron-containing metabolite, was isolated from *Aspergillus terreus* IFO 6123 and 8835, and possesses a hydroxamic acid structure. It is of chemical interest that compound (1) embodies a functionalized pyrazine ring and an indolyl group (Figure 1). Herein, we report the synthesis of 2-hydroxy-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-oxide (2), which constitutes the skeleton of 1.

First, to obtain the functionalized pyrazine moiety, the peracid and persulfate oxidation of compounds (3-5)[2] was studied. However, the oxidation resulted in giving complex products, which could not be separated from each other.

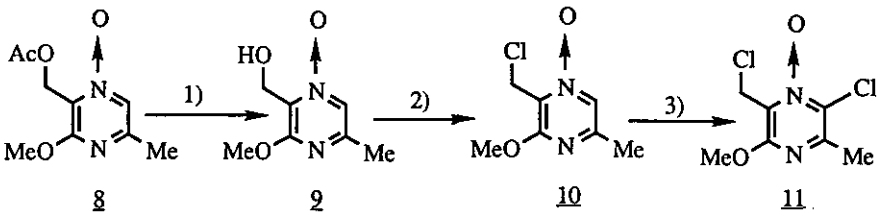


1 R=dimethylallyl
2-Fe R=H

3 R_1=R_2=H
4 R_1=OMe, R_2= H
5 R_1=OMe, R_2=Cl

Figure 1

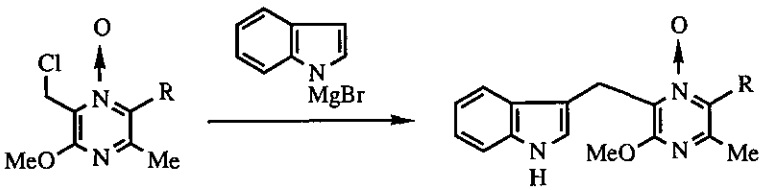
Then the alternative synthesis of 2-(indol-3-yl)methyl-3-methoxy-5-methyl-pyrazine 1-oxide (6) and 2-chloro-6-(indol-3-yl)methyl-5-methoxy-3-methyl-pyrazine 1-oxide (7) was attempted. 2-Acetoxymethyl-3-methoxy-5-methyl-pyrazine 1-oxide (8)[2] was hydrolyzed in an alkaline medium to give 2-hydroxymethyl-3-methoxy-5-methylpyrazine 1-oxide (9). Although 9 was treated with tosyl chloride after addition of n-butyllithium in expectation of giving the tosylated compound, the chlorinated substance (10) was obtained in 85% yield. Direct halogenation on the pyrazine N-oxide (10) was accomplished by combination of N-chlorosuccinimide (NCS) and N,N-dimethylformamide (DMF)[3] to give 2-chloro-6-chloromethyl-5-methoxy-3-methylpyrazine 1-oxide (11) (Scheme 1).



1) 10% K_2CO_3/MeOH 2) i) BuLi ii) TsCl 3) NCS

Scheme 1

The coupling reaction of indole with 10 and 11 was conducted as follows. The solution of 10 or 11 in toluene was added dropwise to the ethereal solution of indolylmagnesium bromide, prepared from indole and ethylmagnesium bromide, under stirring at 0°C. The reaction mixture was stirred overnight at room temperature to give 2-(indol-3-yl)methyl-3-methoxy-5-methylpyrazine 1-oxide (6) and 2-chloro-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-oxide (7) in 77% and 66% yields, respectively (Scheme 2).



10 R=H
11 R=Cl

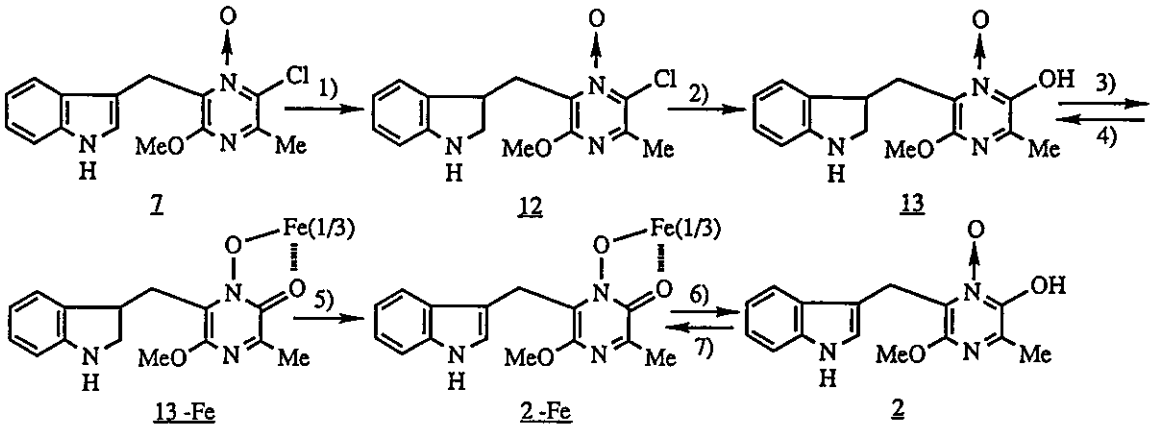
6 R=H
7 R=Cl

Scheme 2

Although 7 was treated under various conditions (treated with NaOMe in MeOH, NaOMe in dioxane, aq. NaOH, TDA-1,[4] HCl and AgOAc etc.), the direct conversion of 7 to the corresponding hydroxamic acid (2) was unsuccessful. Therefore, 7 was reduced to the corresponding indoline derivative (12) with $NaBH_3CN$ in acetic acid.[5] After treating 12 with sodium methoxide in methanol and then with hydrochloric acid, the product (13) was oxidized with bis(salicylidene)ethylenediaminato cobalt(II) [Co(salen)].[6] However, this oxidation resulted in the formation of many products which could not be separated from each other.

Consequently, 13 was treated with ferric (III) chloride to produce the iron complex (13-Fe), which was oxidized with Co(salen) to give the corresponding indole iron complex (2-Fe). Removal of iron from 2-Fe by treatment with sodium hydroxide in acetone afforded 2-hydroxy-6-(indol-

3-yl)methyl-5-methoxy-3-methylpyrazine 1-oxide (2), whose ms and ^{1}H-nmr spectra agreed with the proposed structure (Scheme 3).



1) $NaBH_3CN$/AcOH 2) i) NaOMe/MeOH ii) H^+ 3) $FeCl_3$ 4) NaOH
5) Co(Salen)/MeOH 6) NaOH 7) $FeCl_3$

Scheme 3

EXPERIMENTAL

The melting points are uncorrected. ^{1}H-Nmr spectral data were obtained with a Varian Gemini-300 in $CDCl_3$ using TMS as the internal standard. Other spectral data were obtained using the following instruments; Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80 Mass Spectrometer.

Hydrolysis of 2-Acetoxymethyl-3-methoxy-5-methylpyrazine 1-Oxide (8):

A solution of 8 (9.80 g, 46.2 mmol) in a mixture of 10% aq. K_2CO_3 (90 ml, 65.1 mmol) and MeOH (90 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 9 was obtained by recrystallization of the crude product. Colorless needles (from cyclohexane); mp 95-96°C; Yield: 7.58 g (97%); ms: m/z 153 (M^+-17); ir (KBr): 3400 (OH) cm^{-1}; ^{1}H-nmr: 2.40 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 4.43 (br s, 1H, OH), 4.84 (s, 2H, CH_2OH), 7.67 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.52; H, 5.93; N, 16.28.

Synthesis of 2-Chloromethyl-3-methoxy-5-methylpyrazine 1-Oxide (10): A solution of 1.6 M n-BuLi (6.29 ml, 10 mmol) in hexane was added to a solution of 9 (1.70 g, 10 mmol) in dry THF (20 ml) at -78°C. After stirring at -78°C for 20 min, a solution of TsCl (4.28 g, 22 mmol) in dry THF (20 ml) was added to the above solution. The whole mixture was stirred overnight at room temperature. Water was added to the reaction mixture, the organic layer was separated and dried over Na_2SO_4. After evaporation of the solvent, a red-brownish oil was obtained, which was purified by applying to a silica gel column and eluted with hexane containing an increasing amount of AcOEt to give 10. Colorless prisms (from cyclohexane); mp 112-113°C; Yield: 1.60 g (85%); ms: m/z 188 (M^+); ^{1}H-nmr: 2.39 (s, 3H, CH_3), 4.04 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2Cl), 7.72 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_7H_9N_2O_2Cl$: C, 44.47; H, 4.81; N, 14.85. Found: C, 44.75; H, 4.84; N, 14.96.

Synthesis of 2-Chloro-6-chloromethyl-5-methoxy-3-methylpyrazine 1-Oxide (11): A solution of 10 (1.42 g, 7.5 mmol) and NCS (1.12 g, 8.34 mmol) in dry DMF (8 ml) was stirred overnight at room temperature and then poured into ice-water. The resulting colorless solid was collected by filtration and purified by recrystallization to give 1.52 g (90%) of 11. Colorless neeldes (from hexane); mp 109-110°C; ms: m/z 222 (M^+); ^{1}H-nmr: 2.56 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2Cl) ppm;

Anal. Calcd for $C_7H_8N_2O_2Cl_2$: C, 37.69; H, 3.61; N, 12.56. Found: C, 37.79; H, 3.66; N, 12.78.

General Procedure for the Synthesis of 2-(Indol-3-yl)methyl-3-methoxy-5-methylpyrazine 1-Oxide (6) and 2-Chloro-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide (7): An Et_2O solution of 1.01 M EtMgBr (0.68 ml, 0.68 mmol), purchased from Kanto Chemical Co., Inc., was diluted with Et_2O (0.5 ml). To this solution, an Et_2O (1 ml) solution of indole (46.8 mg, 0.4 mmol) was added at 0°C under stirring. The reaction mixture was then stirred for 0.5 h at room temperature and a dry toluene (0.5 ml) solution of 10 or 11 (0.2 mmol) was added dropwise at 0°C. After stirring overnight at room temperature, 10% aq. 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 organic extract was dried over Na_2SO_4 and evaporation of the solvent gave a 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-3-methoxy-5-methylpyrazine 1-Oxide (6): Colorless prisms (from cyclohexane); mp 112-114°C; Yield: 77%; ms: m/z 269 (M^+); ^{1}H-nmr: 2.32 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.36 (s, 2H, CH_2), 7.13-7.16 (m, 2H, indole 5- and 6-H), 7.32 (m, 2H, indole 2- and 7-H), 7.66 (s, 1H, pyrazine H), 7.84 (d, J = 8 Hz, 1H, indole 4-H), 8.08 (br s, 1H, indole 1-H) ppm; Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.62; H, 5.66; N, 15.55.

2-Chloro-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide (7): Colorless prisms (from cyclohexane); mp 159-161°C ; Yield: 66%; ms: m/z 303 (M^+); ^{1}H-nmr: 2.49 (s, 3H, CH_3), 4.07 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2), 7.11-7.25 (m, 2H, indole 5-, and 6-H), 7.31 (d, J = 8 Hz, 1H, indole 7-H), 7.40 (d, J = 2 Hz, 1H, indole 2-H), 7.83 (d, J = 8 Hz, 1H, indole

4-H), 8.15 (br s, 1H, indole 1-H) ppm; Anal. Calcd for $C_{15}H_{14}N_3O_2Cl$: C, 59.13; H, 4.64; N, 13.83. Found: C, 59.22; H, 4.62; N, 14.08.

Reduction of 2-Chloro-6-(indol-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide (7) with $NaBH_3CN$-AcOH: A solution of 7 (540 mg, 1.76 mmol) and $NaBH_3CN$ (550 mg, 8.75 mmol) in AcOH (18 ml) was stirred for 5 h at room temperature. The reaction mixture was poured into ice-water and the resulting solution was made alkaline with powdered K_2CO_3, followed by extraction with AcOEt. An usual work-up of the extract gave a yellow oil, which was purified by column chromatography on a silica gel with hexane containing an increasing amount of AcOEt to give 12. Colorless prisms (from cyclohexane); mp 123-124°C; Yield: 380 mg (70%); CIms: m/z 306 (M^++1); ^{1}H-nmr: 2.58 (s, 3H, CH_3), 3.25 (dd, J = 8 and 6 Hz, 2H, CH_2), 3.38 (dd, J = 9 and 5 Hz, 1H, indoline 2-H), 3.58 (t, J = 9 Hz, 1H, indoline 2-H), 3.87 (s, 3H, OCH_3), 3.89 (m, 1H, indoline 3-H), 6.70 (m, 2H, indoline 5- and 6-H), 6.98 (d, J = 7 Hz, 1H, indoline 4-H), 7.04 (m, 1H, indoline 7-H) ppm; Anal. Calcd for $C_{15}H_{16}N_3O_2Cl$: C, 58.92; H, 5.27; N, 13.74. Found: C, 59.10; H, 5.27; N, 13.96.

Hydrolysis of 2-Chloro-6-(indolin-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide (12): In a $NaOCH_3$-MeOH solution, prepared from abs. MeOH (20 ml) and Na (410 mg, 17.6 mg atom), 12 (250 mg, 0.82 mmol) was heated under reflux for 2 h. After the solvent was removed by distillation in vacuo, the residue was dissolved in water. The solution was acidified with 5% HCl and extracted with AcOEt. The extract was then worked up as usual to give a yellow oil, which was purified by silica gel column chromatography with hexane containing an increasing amount of AcOEt to give 13 as a yellow viscous oil, which could not be purified by distillation. Yield: 160 mg (69%); ms: m/z 287 (M^+); ^{1}H-nmr: 2.50 (s, 3H, CH_3), 3.24 (dd, J = 14 and 9 HZ, 2H, CH_2), 3.37 (dd, J = 9 and 6

Hz, 1H, indoline 2-H), 3,54 (t, J = 9 Hz, 1H, indoline 2-H), 3.80 (m, 1H, indoline 3-H), 3.86 (s, 3H, OCH_3), 6.70 (m, 2H, indoline 5- and 6-H), 6.78 (d, J = 7 Hz, 1H, indoline 4-H), 7.06 (m, 1H, indoline 7-H) ppm; High resolution ms Calcd for $C_{15}H_{17}N_3O_3$: 287.1271. Found: 287.1270.

Synthesis of 2-Hydroxy-6-(indolin-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide Iron Complex (13-Fe): Compound 13 (160 mg, 0.56 mmol) in MeOH (2 ml) was added to a solution of 5% $FeCl_3$ in MeOH (5 ml). The solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with CH_2Cl_2 containing an increasing amount of MeOH to give a red solid (136 mg, 80%), mp 76-88°C (decomposition); ir (KBr): 3400(NH), 1620(C=O) cm^{-1}. The ms and ^{1}H-nmr spectra could not be measured.

Oxidation of 2-Hydroxy-6-(indolin-3-yl)methyl-5-methoxy-3-methylpyrazine 1-Oxide Iron Complex (13-Fe): To a solution of 13-Fe (100 mg, 0.11 mmol) in MeOH (50 ml) was added to Co(Salen) (4.2 mg, 0.01 mmol) and the resulting suspension was bubbled with a fine stream of O_2 for 4 h at room temperature. The solvent was then evaporated in vacuo and the products were purified by silica gel chromatography eluting with CH_2Cl_2 containing an increasing amount of MeOH to give a dark-red solid (2-Fe) (64 mg, 64%), mp 134-140°C (decomposition); ir (KBr): 3450 (NH), 1500 (C=O) cm^{-1}. The ms and ^{1}H-nmr spectra could not be measured.

Removal of Iron from 2-Hydroxy-6-(indol-3-yl)methyl-5-methoxy-3-methyl pyrazine 1-Oxide Iron Complex (2-Fe); To a solution of 2-Fe (64 mg, 0.07 mmol) in acetone (14 ml), 0.2N NaOH (2 ml) was added dropwise under stirring, and the resulting precipitates were removed by filtration. After removal of acetone by distillation in vacuo, the reaction mixture was acidified with 5% HCl and extracted with CH_2Cl_2. An usual work-up of the extract gave 2 as a viscous oil; Yield: 37 mg (62%); ms: m/z 285

(M^+); ^{1}H-nmr: 2.43 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.37 (s, 2H, CH_2), 7.16 (m, 2H, indole 5- and 6-H), 7.27 (s, 1H, indole 2-H), 7.32 (d, J = 8 Hz, 1H, indole 7-H), 7.83 (d, J = 8 Hz, indole 4-H), 8.30 (br s, 1H, indole 1-H) ppm; High resolution ms Calcd for $C_{15}H_{15}N_3O_3$: 285.1114. Found: 285.1116.

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