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First Total Synthesis of Astechrome: Novel Hydroxamic Acid with an Indole–Pyrazine Skeleton

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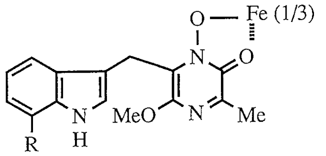
Astechrome (1), isolated from *Aspergillus terreus* IFO 6123 and 8835, was synthesized. Indolylmagnesium bromide (4) was coupled with a chloromethylpyrazine (5) to give 2-chloro-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)indol-3-yl]methylpyrazine 1-oxide (6), which was converted to the Fe salt (9) of a hydroxamic acid derivative (8). Oxidation of 9 with Co(salen) afforded 1.

Keywords astechrome; *Aspergillus terreus*; synthesis; pyrazine; indole

Astechrome (**1**), a novel hydroxamic acid containing iron, was isolated from *Aspergillus terreus* IFO 6123 and 8835.[1] It is of considerable chemical interest, since it embodies a functionalized pyrazine ring and an indole group. In previous papers,[2,3] we reported the synthesis of the skeleton of **1** by coupling of a chloromethylpyrazine or tosyloxymethylpyrazine with indolylmagnesium bromide. Having completed the synthesis of 2-hydroxy-5-methoxy-3-methyl-6-(3-indolyl)methylpyrazine 1-oxide iron complex (**2**),[3] we tried to convert **2** to **1** directly by various methods. The coupling reaction of 7-bromoindole with a chloromethylpyrazine was also carried out. However, these trials were unsuccessful. In this paper, we will describe the synthesis of **1**, starting from 7-(3-methyl-2-butenyl)indole (**3**), using essentially the same method as reported for the synthesis of **2**.[3] The synthetic procedures are shown in Chart 1.

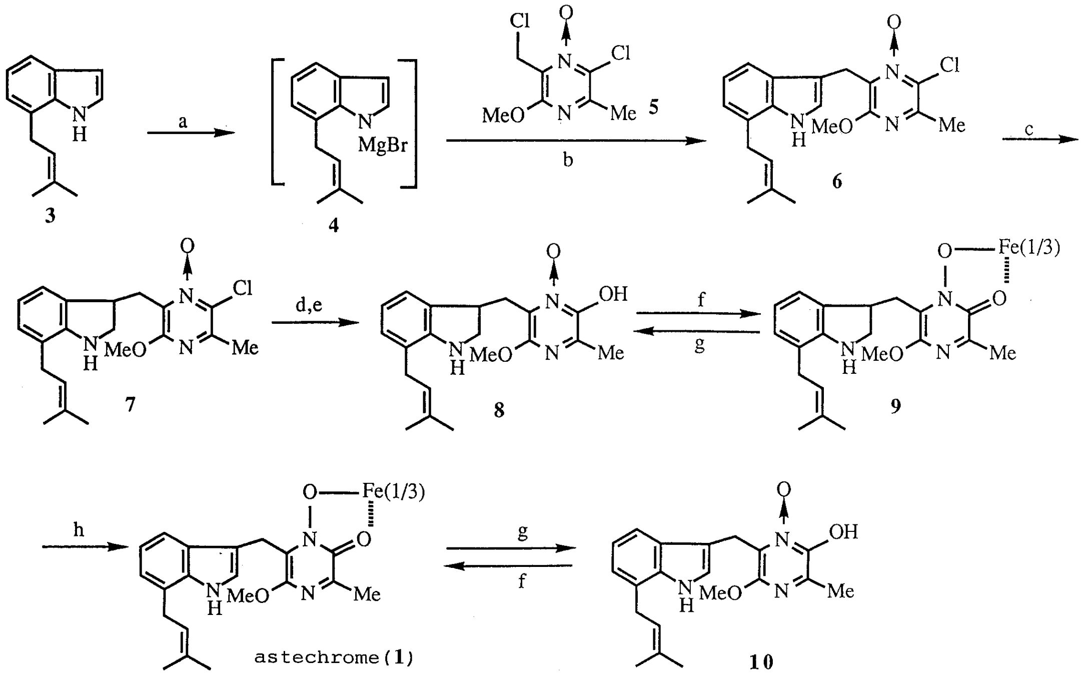
Results and Discussion

A dry toluene solution of 2-chloro-6-chloromethyl-5-methoxy-3-methylpyrazine 1-oxide (**5**)[2] was added dropwise to an ethereal solution of 7-(3-methyl-2-butenyl) indolylmagnesium bromide (**4**), prepared from 7-(3-



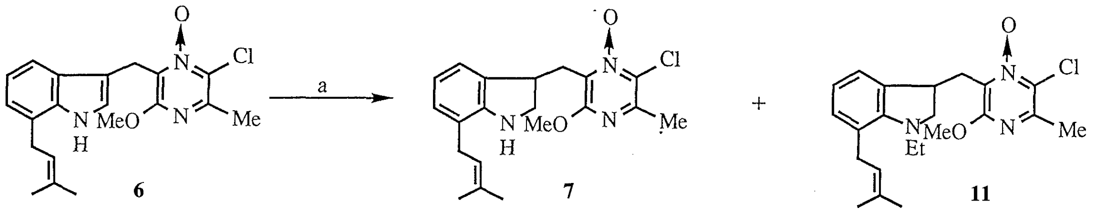
1:R=3-methyl-2-butenyl
2:R=H

Fig. 1



a: EtMgBr, Et_2O; b: toluene; c: $NaBH_3CN$, AcOH; d: NaOMe, MeOH; e: H^+; f: 5%$FeCl_3$ in H_2O;
g: 0.2 N NaOH, Me_2CO; h: Co(salen), MeOH, O_2

Chart 1



a : $NaBH_3CN$, AcOH

Chart 2

methyl-2-butenyl)indole[4,5] and ethylmagnesium bromide, under stirring at 10 °C. The reaction mixture was further stirred overnight at room temperature to give the coupling product (**6**) in 53% yield. Compound **6** was treated under acidic or alkaline conditions in order to obtain a hydrolyzed product (**10**), but the attempt was unsuccessful. Therefore **6** was reduced with sodium cyanoborohydride in acetic acid[6] at room temperature for 6 h to afford the corresponding indoline (**7**) in 75% yield, along with traces of a reduction–ethylation product (**11**). Further investigations have revealed that a higher reaction temperature (> 60 °C) and a longer reaction time (> 12 h) increased the yield of **11** (Chart 2).

Replacement of the chlorine atom in **7** with a hydroxy group was performed by treatment with an excess of sodium methoxide in methanol and then with 5% hydrochloric acid. The product (**8**) was dehydrogenated with bis(salicylidene)ethylenediaminato cobalt(II) [Co(salen)][7] to prepare the desired product (**10**). However, this dehydrogenation resulted in many products which could not be separated from each other.

Then **8** was converted to the iron complex (**9**). In this context, it was found that excess ferric ions decreased the yield of **9**.

Dehydrogenation of **9** was accomplished with Co(salen)[7] in methanol under bubbling dioxygen at room temperature for 4 h. Thus, the desired title compound, astechrome (**1**), was obtained in 50% yield, mp 176—185 °C (dec.). This melting point was considerably different from the reported one [mp 188—189 °C (dec.)].[1] However, a sample provided by Dr. Shimizu, showed the same melting point as the synthetic product and the mixed melting point of both samples was also the same. Further, the IR and UV spectra of the synthetic compound were identical with those of the authentic sample. The ^{1}H-NMR spectrum could not be measured.

When **1** was treated with aqueous sodium hydroxide in acetone, an iron-free colorless powder, mp 45—50 °C (lit.,[1] mp 45—55 °C), was obtained. The ^{1}H-NMR and IR spectra of this compound (**10**) were identical with the reported ones.

In conclusion, we have accomplished the synthesis of astechrome (**1**), by exploiting the coupling reaction of a functionalized pyrazine with indole. This method should be a useful synthetic pathway for other compounds of this class.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian GEMINI 300 in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Low-(MS) and high-resolution mass spectra (HR-MS) were measured on a Hitachi M-80 spectrometer. IR and UV spectra (in MeOH) were taken with an A-100 spectrometer and an UVIDEC-610 spectrometer (Japan Spectroscopic Co., Ltd.), respectively.

2-Chloro-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)-1*H*-indol-3-yl]methylpyrazine 1-Oxide (6) A solution of EtMgBr (1.01 M in THF, 15 ml, 15 mmol) was diluted with dry Et_2O (12 ml). To this solution, an Et_2O (24 ml) solution of **3**[6] (1.66 g, 9 mmol) was added at 10 °C under stirring. The reaction mixture was further stirred for 0.5 h at room temperature, and a dry toluene (12 ml) solution of **5**[2] (1.99 g, 9 mmol) was added dropwise at 0 °C. After stirring of the mixture overnight at room temperature, the reaction was quenched by successive addition of 10% aqueous NH_4Cl (15 ml) and water (50 ml). The organic layer was separated and the water layer was extracted with CH_2Cl_2 (25 ml × 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–EtOAc (5 : 1) to give **6** (1.77 g, 53%) as colorless crystals, mp 173—175 °C (from cyclohexane). *Anal.* Calcd for $C_{20}H_{22}ClN_3O_2$: C, 64.60; H, 5.96; N, 11.30. Found: C, 64.50; H, 5.96; N, 11.41. MS *m/z*: 354 (M^+ − OH). IR (KBr): 3450, 2920 cm^{-1}. ^{1}H-NMR δ: 1.75 and 1.80 (each 3H, 2s, $CH_2CH=C(C\underline{H}_3)_2$), 2.49 (3H, s, 3-$CH_3$), 3.53 (2H, d, J = 7 Hz, $C\underline{H}_2CH=C(CH_3)_2$), 4.08 (3H, s, OCH_3), 4.37 (2H, s, indole-$C\underline{H}_2$-pyrazine), 5.37 (1H, m, $CH_2C\underline{H}=C(CH_3)_2$), 6.97 (1H, d, J = 7 Hz, indole 6-H), 7.04 (1H, m, indole 5-H), 7.41 (1H, d, J = 2 Hz, indole 2-H), 7.70 (1H, d, J = 8 Hz, indole 4-H), 8.04 (1H, br s, NH).

2-Chloro-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)indolin-3-yl]-methylpyrazine 1-Oxide (7) A solution of **6** (202 mg, 0.55 mmol) and 95% $NaBH_3CN$ (220 mg, 3.23 mmol) in AcOH (6 ml) was stirred for 5 h at room temperature, then poured into ice-water (10 ml). The resulting solution was made alkaline with powdered K_2CO_3, followed by extraction with AcOEt (10 ml × 2). Removal of the solvent left the crude product, which was purified by silica gel chromatography with hexane–AcOEt (3 : 1) to afford **7** (150 mg, 75%) as a pale yellow viscous oil. HR-MS: Calcd for $C_{20}H_{24}ClN_3O_2$: 373.1557. Obsd: 373.1561. IR (KBr): 3350, 2950 cm^{-1}. ^{1}H-NMR δ: 1.74 (3H, s, $CH_2CH=C(C\underline{H}_3)_2$), 1.76 (3H, d, J = 1 Hz, $CH_2CH=C(C\underline{H}_3)_2$), 2.58 (3H, s, 3-$CH_3$), 3.22 (2H, dd, J = 16, 8 Hz, indoline-$C\underline{H}_2$-pyrazine), 3.26 (2H, d, J = 6 Hz, $C\underline{H}_2CH=C(CH_3)_2$), 3.37 and 3.56 (each 1H, 2dd, J = 9, 6 Hz, indoline 2-H), 3.84 (1H, m, indoline 3-H), 3.88 (3H, s, OCH_3), 5.26 (1H, m, $CH_2C\underline{H}=C(CH_3)_2$), 6.67 (1H, dd, J = 7 Hz, indoline 5-H), 6.88 (1H, d, J = 7 Hz, indoline 6-H), 6.90 (1H, d, J = 7 Hz, indoline 4-H).

2-Hydroxy-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)indolin-3-yl]methylpyrazine 1-Oxide (8) Compound **7** (100 mg, 0.27 mmol) was added to an NaOMe–MeOH solution, prepared from dry MeOH (6 ml) and Na (190 mg, 8.3 mg atom), and the mixture was heated under reflux for 2 h. The solvent was removed by distillation *in vacuo*, and the residue was dissolved in H_2O (10 ml). The solution was acidified to pH 5—6 with 5% HCl and extracted with AcOEt (10 ml × 2). After evaporation of the solvent, the product was recrystallized from cyclohexane to give **8** (87.2 mg, 91%) as colorless plates, mp 140—142 °C. *Anal.* Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.28; H, 6.99; N, 11.74. MS *m/z*: 355 (M^+). IR ($CHCl_3$): 3400, 2950, 1480 cm^{-1}. ^{1}H-NMR δ: 1.74 and 1.76 (each 3H, 2 s, $CH_2CH=C(C\underline{H}_3)_2$), 2.50 (3H, s, 3-$CH_3$), 3.21 (2H, d, J = 9 Hz, indoline-$C\underline{H}_2$-pyrazine), 3.25 (2H, d, J = 6 Hz, $C\underline{H}_2CH=C(CH_3)_2$), 3.39 (1H, dd, J = 7 Hz, indoline 2-H), 3.55 (1H, dd, J = 9 Hz, indoline 2-H), 3.82 (1H, m, indoline 3-H), 3.84 (3H, s, OCH_3), 5.25 (1H, m, $CH_2C\underline{H}=C(CH_3)_2$), 6.69 (1H, dd, J = 7 Hz, indoline 5-H), 6.88 (1H, d, J = 6 Hz, indoline 6-H), 6.90 (1H, d, J = 6 Hz, indoline 4-H).

2-Hydroxy-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)indolin-3-yl]methylpyrazine 1-Oxide Iron Complex (9) Compound **8** (32 mg, 0.09 mmol) in MeOH (4 ml) was added to a solution of 5% $FeCl_3$ in H_2O (4 ml, 0.03 mmol). The solvent was removed by distillation *in vacuo* and the residue was purified by silica gel chromatography with CH_2Cl_2–AcOEt (1 : 1) to give a red solid (**9**) (28.5 mg, 85%), mp 95—100 °C (dec.). IR (KBr): 3400, 2940, 1480 cm^{-1}. The ^1H-NMR spectrum could not be measured.

2-Hydroxy-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)-1*H*-indol-3-yl]methylpyrazine 1-Oxide Iron Complex (Astechrome, 1) A suspension of **9** (33 mg, 0.03 mmol) and 97% Co (salen) (2.47 mg, 0.07 mmol) in MeOH (10 ml) was bubbled with a fine stream of O_2 for 4 h at room temperature. The solvent was then evaporated *in vacuo* and the product was purified by silica gel chromatography, eluting with CH_2Cl_2–AcOEt (20 : 1) to give a dark red solid (**1**) (16.7 mg, 50%), mp and mixed mp with an authentic sample 176—185 °C (dec.) [lit.,[1] mp 188—189 °C (dec.)]. The IR and UV spectra were identical with those of the authentic sample. The ^1H-NMR spectrum could not be measured.

2-Hydroxy-5-methoxy-3-methyl-6-[7-(3-methyl-2-butenyl)-1*H*-indol-3-yl]methylpyrazine 1-Oxide (10) Aqueous 0.2 N NaOH (1 ml, 0.2 mmol) was added dropwise to a solution of **1** (27.2 mg, 0.024 mmol) in Me_2CO (5 ml) under stirring, and the resulting precipitates were removed by suction. After removal of Me_2CO by distillation *in vacuo*, the residue was acidified with 5% HCl to pH 5—6. The precipitates were collected by filtration, washed with H_2O, and dried to give **10** (14 mg, 54%), mp 45—50 °C (lit.,[1] mp 45—55 °C). The ^1H-NMR and IR spectra were identical with those reported.[1]

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