NEW SYNTHESES OF MURRAYAFOLINE-A AND MURRAYAQUINONE-A *VIA* FISCHER INDOLIZATION OF 2-SULFONYLOXYPHENYLHYDRAZONE (FISCHER INDOLIZATION AND ITS RELATED COMPOUNDS. PART 29[1])

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Abstract - Two carbazole alkaloids, murrayafoline-A (**4a**) and murrayaquinone-A (**4b**), were synthesized from 1, 2, 3, 4-tetrahydro-8-methanesulfonyloxy-6-methylcarbazole (**8**) prepared in the application of Fischer indolization of 2-sulfonyloxyphenylhydrazone.

Previously,[1] we reported a new method for the synthesis of 7-oxygenated indoles *via* Fischer indolization of 2-sulfonyloxyphenylhydrazones. The Fischer indolization of 2-sulfonyloxyindoles (**1a, b**) gave the corresponding normal products, 7-sulfonyloxyindoles (**2a, b**), in high ratio along with the abnormal products, 5-sulfonyloxyindoles (**3a**). Use of the phenylhydrazone with cyclohexanone (**1b**) gave better results than the one with ethyl pyruvate.

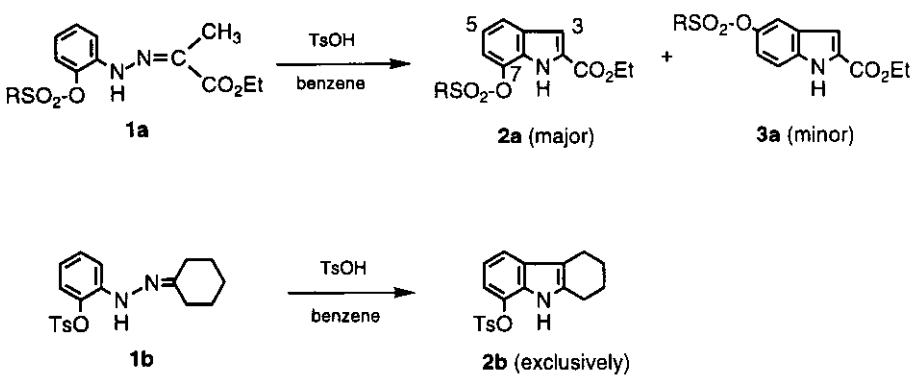

Figure 1

This method was applied[1] to the synthesis of eudistomidin-A starting with ethyl 5-bromo-7-(*p*-toluenesulfonyloxy)indole-2-carboxylate prepared by the Fischer indolization of a 2-sulfonyloxyphenylhydrazone. Here, we report the synthesis of murrayafoline-A (**4a**) and murrayaquinone-A (**4b**) starting with a 1, 2, 3, 4-tetrahydrocarbazole derivative as another application of this Fischer indolization reaction.

Murrayafoline-A[2] (**4a**) and murrayaquinone-A[2] (**4b**) are alkaloids isolated from an Rutaceous plant, *Murraya euchrestifolia*, and the latter (**4b**) is known to induce myocardial contraction.[3] There have been a few reports[4] of their total synthesis, all of which involved the use of unsubstituted aniline or indole derivative as starting materials.

2-Hydrazino-5-methylphenol *p*-toluenesulfonate (**6**) prepared from the corresponding aminophenol (**5**) was allowed to react with cyclohexanone to yield the corresponding hydrazone, which was then converted to *O*-methanesulfonyl (mesyl) derivative (**7**). The *O*-mesylphenylhydrazone (**7**) without purification was allowed to react with TsOH/benzene under Fischer indolization conditions.

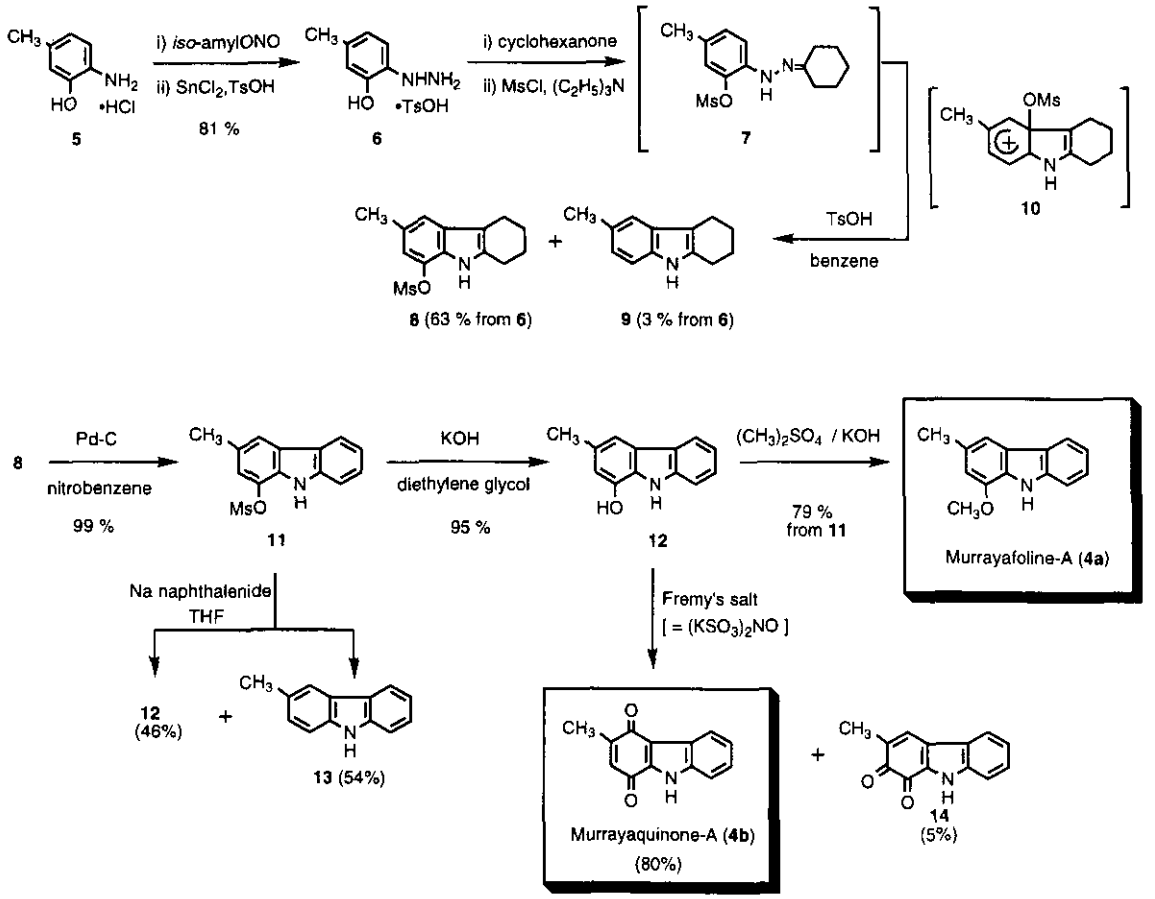

Figure 2 Total Synthesis of Murrayafoline-A and Murrayaquinone-A

The reaction gave two indolic products, 1, 2, 3, 4-tetrahydro-8-mesyloxy-6-methylcarbazole (**8**) in 63% yield and 1, 2, 3, 4-tetrahydro-6-methylcarbazole (**9**) in 3% yield. The former (**8**) was the normal and desired product, while the latter was the abnormal and undesired product. This latter compound was formed by cyclization toward the mesyloxy group (the intermediate:**10**) with an unknown reduction step. The 8-mesyloxy compound (**8**) was dehydrogenated with 10% Pd-C in nitrobenzene in excellent yield to afford 8-mesyloxy-6-methylcarbazole (**11**). Dehydrogenation with DDQ or chloranil gave **11** in low yields. Hydrolysis of the mesyl group in **11** with KOH/EtOH or NaOMe/MeOH was unsuccessful, but was successful with potassium hydroxide in diethylene glycol to afford 8-hydroxy-6-methylcarbazole (**12**). Reductive cleavage with sodium naphthalenide gave **12** in 46% yield along with undesirable 3-methylcarbazole (**13**) (54%). *O*-Methylation of **12** gave murrayafoline-A (**4a**) in 40% total yield from the aniline (**5**). The synthetic compound was identical with the natural murrayafolin-A (**4a**) in all respects. On the other hand, the oxidation of **12** with Fremy's salt gave two products, murrayaquinone-A (**4b**) which was identical with the natural compound, and isomer (**14**) of **4b**. The latter (**14**) showed isomeric characteristics of **4b** in spectral data. Thus, the latter (**14**) was 1, 2-dihydro-3-methylcarbazole-1, 2-dione. The two examples described above indicate that the Fischer indolization of 2-sulfonyloxyphenylhydrazone is a useful method for preparing 7-oxygenated indoles.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrophotometer (in Nujol, unless otherwise stated). ^{1}H-NMR spectra were measured on a Hitachi R-24B (60 MHz), unless otherwise stated. Deuteriochloroform was used as the solvent with tetramethylsilane as an internal reference, unless otherwise stated. The assignments of NH signals were confirmed by disappearance of the signals after addition of deuterium oxide. MS spectra were measured on JEOL JMS-01-SG-2,JEOL JMS-D300, and JEOL JMS-DX303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70-230 mesh ASTM, Merck, unless otherwise stated), and for TLC, Silica gel $60F_{254}$(Merck) were used. All identifications of products were done by analysis of MS, IR, and especially NMR spectra. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; Ar, aromatic; B.P., base peak.

2-Hydrazino-5-methylphenol *p*-Toluenesulfonate (6)--A solution of isoamyl nitrite (3.11 mL, 23.2 mmol) in EtOH (10 mL) was added dropwisely to a solution of 2-amino-5-methylphenol hydrochloride (**5**)(3.198 g, 20.0 mmol) in EtOH (10 mL) at 0°C. The resulting diazonium salt solution was then added dropwisely to a solution of $SnCl_2$ (7.56 g, 40.8 mmol) and $TsOH•H_2O$ (4.08 g, 21.4 mmol) in EtOH (4 mL) under ice-cooling and the reaction mixture was stirred for 1 h at the same temperature. After the reaction was over, Et_2O (60 mL) was added to the reaction mixture and the resulting precipitates were collected with suction. The collected precipitates were washed with Et_2O to give the title compound (**6**) (5.03 g, 81%), mp 207-220°C (decomp). The product was used for next reaction without further purification. FAB MS *m/z*: 311(M^++1). IR $\nu_{max}cm^{-1}$:3290 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.13 (3H, s, Ar-CH_3), 2.25

(3H, s, Ar-CH_3), 6.42-7.48 (8H, m, Ar-H, NH or OH), 9.60 (4H, br s, NH and OH). This compound was too unstable to purify by recrystallization.

Fischer Indolization of Cyclohexanone 2-Methanesulfonyloxy-4-methylphenylhydrazone (7)--A solution of cyclohexanone (1.87 mL, 18 mmol) in CH_2Cl_2 (15 mL) was added to 2-hydrazino-5-methylphenol *p*-toluenesulfonate (**6**) (3.72 g, 12.0 mmol) in a flask under argon atmosphere and ice-cooling. Et_3N (1.74 mL, 12.5 mmol) was added to this suspension under ice-cooling until the mixture became clear solution. After the mixture was stirred for 15 min, methanesulfonyl chloride (2.79 mL, 36.0 mmol) and Et_3N (5.01 mL, 35.9 mmol) were added to this mixture and the whole was stirred for 50 min under ice-cooling. To the reaction mixture was added CH_2Cl_2 (50 mL) and the organic layer was washed with 5%HCl, sat. $NaHCO_3$, and sat. NaCl, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave cyclohexanone 2-methanesulfonyloxy-4-methylphenylhydrazone (**7**) as a brown oil (4.85 g).
This oil (**7**) was transferred to a solution of TsOH in benzene (60 mL), which was prepared from TsOH•H_2O (4.57 g, 24.0 mmol) by refluxing in Dean-Stark water separator, and the whole was heated with stirring at 50°C for 1 h. AcOEt (50 mL) was then added to the reaction mixture. The organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give dark brown solid. Column chromatography over silica gel using hexane-AcOEt (5:1) gave 1,2,3,4-tetrahydro-6-methylcarbazole (**9**) (63 mg, 3%) and 1, 2, 3, 4-tetrahydro-8-methanesulfonyloxy-6-methylcarbazole (**8**) (2.12 g, 63%).

1, 2, 3, 4-Tetrahydro-8-methanesulfonyloxy-6-methylcarbazole (8)--Colorless needles from AcOEt-hexane, mp 161-162°C. *Anal.* Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13;N, 5.01. Found: C, 60.13; H, 6.18; N, 5.05. MS *m/z*: 279(M^+, 41%), 200 (B.P.). IR $\nu_{max}cm^{-1}$: 3400 (NH). ^{1}H-NMR δ: 1.50-2.10 (4H, m, C_2-H_2 and C_3-H_2), 2.40 (3H, s, C_6-CH_3), 2.40-3.35 (4H, m, C_1-H_2 and C_4-H_2), 3.12 (3H, s, SO_2CH_3), 6.72, (1H, s, C_5-H or C_7-H), 7.08 (1H, s, C_7-H or C_5-H), 8.15 (1H, br s, NH).

1, 2, 3, 4-Tetrahydro-6-methylcarbazole (9)--Colorless needles from benzene-hexane, mp 143-146°C (unstable). MS *m/z*: 185 (M^+, 89%), 157 (B.P.). ^{1}H-NMR (400 MHz) δ: 1.81-1.95 (4H, m, C_2-H_2 and C_3-H_2), 2.43 (3H, s, C_6-H), 2.63-2.74 (4H, m, C_1-H_2 and C_4-H_2), 6.93 (1H, d, *J*=8.2 Hz, C_7-H), 7.15 (1H, d, *J*=8.2 Hz, C_8-H), 7.24 (1H, br d, C_5-H), 7.56 (1H, br s, NH).

This sample was identical with the reported compound (lit.,[5] mp 141-142 °C).

1-Methanesulfonyloxy-3-methylcarbazole (11)--A mixture of 1, 2, 3, 4-tetrahydro-8-methanesulfonyloxy-6-methylcarbazole (**8**) (140 mg, 0.50 mmol) and 10%Pd-C (40 mg) in nitrobenzene (1.0 mL) was heated with stirring under argon atmosphere at 200 °C for 45 min. After the reaction was over, the reaction mixture was diluted with AcOEt (50 mL) and the catalyst was filtered off. The filtrate was evaporated *in vacuo* to give an yellow oil, which was chromatographed over silica gel using hexane-AcOEt (10:1) to give the title compound (136 mg, 99%). Recrystallization from benzene gave colorless needles, mp 169-171°C. *Anal.* Calcd for $C_{14}H_{13}NO_3S$: C, 61.08; H, 4.76; N, 5.09: Found: C, 60.90; H, 4.79; N, 5.15. MS *m/z*: 275 (M^+, 45%), 196 (B.P.). IR $\nu_{max}cm^{-1}$: 3380, 3440 (NH). ^{1}H-NMR δ: 2.58 (3H, s, C_3-CH_3), 3.20 (3H, s, SO_2CH_3), 7.00-7.53 (3H, m, Ar-H), 7.60-8.10 (2H, m, Ar-H), 8.55 (1H, br s, NH).

1-Hydroxy-3-methylcarbazole (12)--A solution of 1-methanesulfonyloxy-3-methylcarbazole (**11**) (140 mg, 0.51 mmol) and KOH (112 mg, 1.70 mmol) in diethylene glycol (12 mL) was heated with stirring at 90 °C for 1 h. The reaction mixture was diluted with water (50 mL) and acidified with dil. HCl. This mixture was extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave brown oil (118 mg), which was column chromatographed over silica gel using hexane-AcOEt (5:1) to give the title compound (96 mg, 95%). Recrystallization from benzene-hexane gave colorless needles, mp 162-164°C (lit.,[4b] mp 153-156 °C). *Anal.* Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.86; H, 5.60; N, 7.04. MS *m/z*: 197 (M^+, B.P.). IR $\nu_{max}cm^{-1}$: 3370 (NH), 3280 (br, OH). ^{1}H-NMR δ: 2.41 (3H, s, CH_3), 5.15 (1H, br s, OH), 6.52 (1H, s, C_2-H), 6.85-7.60 (4H, m, Ar-H), 7.60-8.25 (2H, m, Ar-H and NH).

Reductive Cleavage of 11 with Sodium Naphthalenide in THF--A solution of naphthalene (262 mg, 2.0 mmol) in THF (4.7 mL) was added to the mixture of Na (50 mg, 2.2 matom) and THF (2 mL), and the whole was stirred at rt for 1 h under argon atmosphere. After the color of solution was changed to green, a solution of the methanesulfonyloxycarbazole (**11**) (140 mg, 0.51 mmol) in THF (1 mL) was added and the whole was stirred at -30 °C for 1 h. The reaction mixture was poured into ice-water containg NH_4Cl and extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to leave yellow solid (374 mg). The column chromatography over silica gel using hexane-AcOEt (3:1) gave the 1-hydroxy compound (**12**) (46 mg, 46%) and 3-methylcarbazole (**13**) (50 mg, 54%).

3-Methylcarbazole (13)--Colorless plates from AcOEt-hexane, mp 205-207 °C. MS *m/z*: 181 (M^+, B.P.). IR ν_{max} cm^{-1}: 3380 (NH). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.47 (3H, s, CH_3), 6.65-7.60 (5H, m, Ar-H), 7.80-8.20 (2H, m, Ar-H), 11.0 (1H, br s, NH). This sample was identical with the reported compound (lit., [6] mp 206-207 °C).

Murrayafoline-A (4a) (One-pot Process from 11) --To a solution of 1-methanesulfonyloxy-3-methylcarbazole (**11**) (140 mg, 0.51 mmol) in diethylene glycol (12 mL) was added KOH (112 mg, 1.70 mmol) and the whole was heated with stirring at 90°C for 1 h. To the cooled reaction mixture were added KOH (84 mg, 1.27 mmol) and $(CH_3)_2SO_4$ (0.194 mL, 1.15 mmol), and the whole was heated with stirring at 50°C for 1 h. The reaction mixture was diluted with water (30 mL), neutralized by adding dil. HCl and extracted with AcOEt. The organic layer was washed with sat. $NaHCO_3$ and sat. NaCl, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a brown oil (132 mg). Column chromatography of this oil over silica gel using hexane-benzene (1:2) gave murrayafoline-A (**4a**) (85 mg, 79%). Recrystallization from hexane gave colorless plates, mp 62-64°C.(lit.,[2] mp52-54°C). Picrate ($C_{20}H_{16}N_4O_8$): mp 188-190°C from benzene. (lit.,[2] mp 188-190°C from benzene)

1, 4-Dihydro-3-methylcarbazole-1, 4-dione (Murrayaquinone-A) (4b)--Commercially available Fremy's salt (potassium nitrosodisulfonate, 60% purity) (178 mg, 0.40 mmol) was dissolved in a solution of KH_2PO_4 (7.1 mg, 0.052 mmol) in water (7.0 mL). A solution of 1-hydroxy-3-methylcarbazole (**12**) (31 mg, 0.159 mmol) in acetone (7 mL) was added to the above Fremy's salt solution and the whole was

stirred under ice-cooling for 25 min. The reaction mixture was then poured into ice water (50 mL). The whole was condensed *in vacuo* to about 1/3 volume, and extracted with AcOEt. The organic layer was washed with sat. NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to leave brown solid (47 mg). The column chromatography over silica gel using hexane-AcOEt (5:1) gave the title compound, 1, 4-dihydro-3-methylcarbazole-1,4-dione (murrayaquinone-A) (**4b**) (27 mg, 80%) as a red solid and the by-product, 1, 2-dihydro-3-methylcarbazole-1, 2-dione (**14**) (1.7 mg, 5%) as a dark brown solid.

1, 4-Dihydro-3-methylcarbazole-1, 4-dione (**4b**): Dark red needles from acetone, mp 238-240°C (lit.,[2] mp 246-247 °C). *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.92; H, 4.29; N, 6.63. MS *m/z*:211 (M^+, B.P.). IR $\nu_{max}cm^{-1}$ (KBr): 3200 (NH), 1660, 1635 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.06 (3H, d, *J*=2 Hz, CH_3), 6.56 (1H, m, C_2-H), 7.15-7.80 (3H, m, Ar-H), 7.90-8.20 (2H, m, Ar-H and NH). UV λ_{max}(EtOH) nm (log ε): 223 (4.58), 245sh (4.27), 255 (4.39), 265sh (4.30), 2.90sh (3.47), 390 (3.65). This sample was identified with the natural product.[2]

1, 2-Dihydro-3-methylcarbazole-1, 2-dione (**14**): Dark brown plates from acetone, mp around 220°C (decomp). HR-MS Calcd for $C_{13}H_9NO_2$: 211.0634. Found: 211.0623. MS *m/z*: 211(M^+, 74%), 183 (B.P.). IR $\nu_{max}cm^{-1}$ (KBr): 3270 (NH), 1645, 1620 (CO). ^{1}H-NMR (400 MHz, acetone-d_6) δ: 1.94 (3H, d, *J*=2 Hz, CH_3), 7.21 (1H, t, *J*=7 Hz, C_6 or C_7-H), 7.40 (1H, t, *J*=7 Hz, C_7 or C_6-H), 7.50 (1H, d, *J*=7 Hz, C_5 or C_8-H), 7.59 (1H, br q, *J*=2 Hz, C_4-H), 7.83 (1H, d, *J*=7 Hz, C_8 or C_5-H), 11.34 (1H, br s, NH).

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