Synthesis of Murrayaquinone-A

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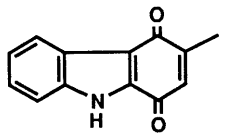
Murrayaquinone-A, one of the carbazolequinone alkaloids isolated from *Murraya euchrestifolia* HAYATA (Rutaceae), was prepared starting from 1,2,3,4-tetrahydrocarbazol-4(9*H*)-one in good overall yield.

Keywords carbazolequinone alkaloid; murrayaquinone-A; cardiotonic activity; synthesis; debenzylation; Fremy's salt

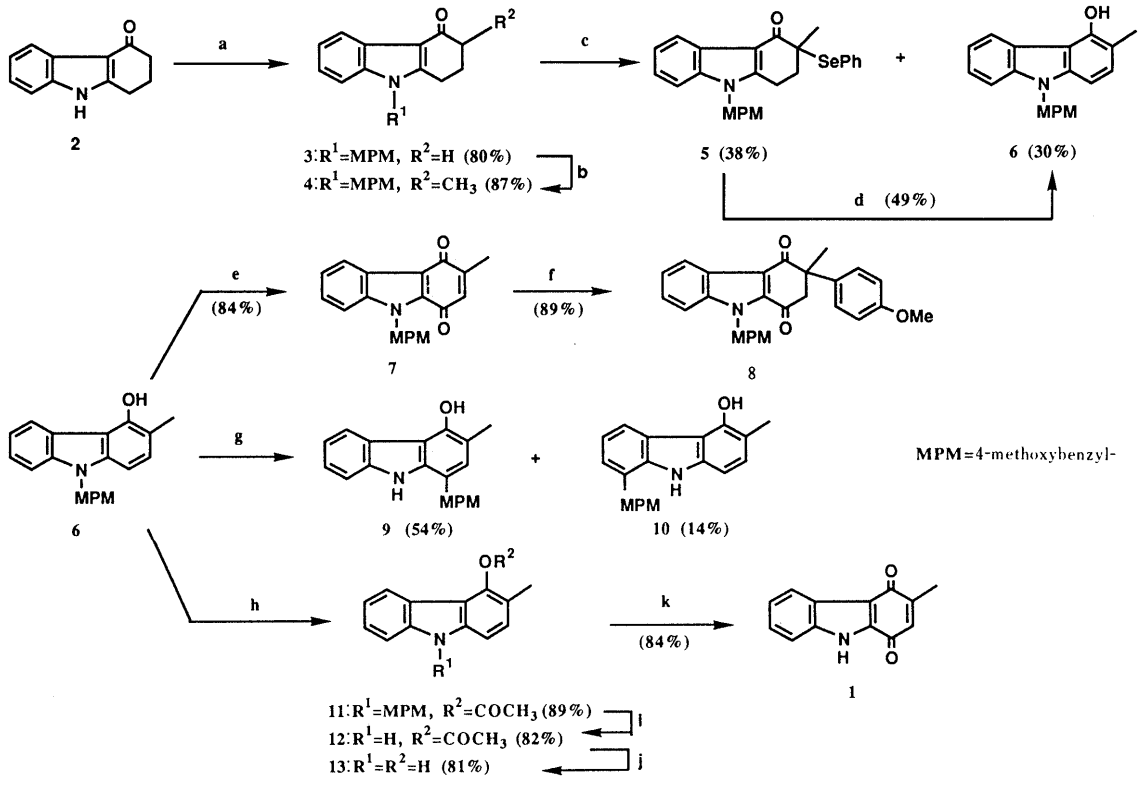
In the course of our synthetic studies on biologically active natural products,[1] we planned to synthesize murrayaquinone-A (**1**), which is one of the carbazolequinone alkaloids isolated from the root bark of *Murraya euchrestifolia* HAYATA (Rutaceae).[2] Murrayaquinone-A has a cardiotonic activity on guinea-pig papillary muscle.[3] Some synthetic studies of this alkaloid have already been reported.[4]



1
murrayaquinone-A

Our synthetic approach to the title compound started with 1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (**2**), which had been prepared in several ways, *i.e.*, by the Fischer indole synthesis of 1,3-cyclohexanedione monophenylhydrazone,[5a] by treatment of 3-(2-iodophenyl)amino-2-cyclohexen-1-one with sodium hydride–copper(I) iodide in hexamethylphosphoramide (HMPA),[5b] and also by photocyclization[5c] or palladium-catalyzed cyclization[5d] of 3-(2-bromophenyl)amino-2-cyclohexen-1-one.

Protection of the NH group of **2** with 4-methoxybenzyl chloride (MPMCl) in *N*,*N*-dimethylformamide (DMF) at room temperature in the presence of sodium hydride followed by methylation of the 3-position of **3** with methyl iodide in tetrahydrofuran (THF) in the presence of lithium cyclohexylisopropylamide (LCIA) gave **4** in 70% overall yield. In order to introduce a double bond into the



a) NaH (1.1 eq), MPMCl (1.1 eq) in DMF, r.t., 2 h; b) LCIA (2 eq), CH_3I (13.8 eq) in THF, −23——20°C, then r.t.; c) LCIA (2 eq), HMPA (2.8 eq), PhSeCl (1.3 eq) in THF, −23——14°C, then r.t., 2 N HCl; d) 30% H_2O_2, AcOH, −2—0°C, 1 h; e) Fremy's salt, KH_2PO_4; f) $AlCl_3$ in anisole; g) $AlCl_3$ in benzene; h) AcCl (1.2 eq), Et_3N (2.1 eq) in CH_2Cl_2; i) $AlCl_3$ (5 eq) in anisole, 0—3°C, 10 min; j) aq. HCl in MeOH, reflux 4 h; k) Fremy's salt (1.7 eq), KH_2PO_4 (20 mol%) in acetone–water, r.t., 30 min.

Chart 1

2—3-position of **4**, the enone (**4**) was successively treated with LCIA and phenylselenenyl chloride in THF in the presence of HMPA. After work-up with 2 N HCl, a phenylselenenylated compound (**5**) and an aromatized compound (**6**) were obtained in 38 and 30% yields, respectively. Oxidative work-up ($NaIO_4$) of the above selenenylated reaction mixture resulted in the isolation of **5** and **6** in 21 and 23% yields, respectively. The selenenylated compound (**5**) was converted into the aromatized compound (**6**) in 49% yield by means of peracetic acid oxidation and concomitant elimination reaction.

Oxidation of the phenol ring of **6** to the quinone ring was then examined. Treatment of **6** with Fremy's salt in the presence of potassium dihydrogen phosphate (KH_2PO_4) in acetone–water (1 : 1) at room temperature gave the quinone (**7**) in 84% yield. An attempt to remove the protecting group in **7** with trifluoroacetic acid in methylene chloride at room temperature[6] resulted only in the recovery of the starting material (80%). Therefore, we tried to apply the method developed recently by Murakami *et al.* for debenzylation of indole derivatives.[7] Thus, when **7** was treated with anhydrous aluminum chloride in anisole at 0 °C for 10 min, a conjugate addition product of anisole to **7**, in which the protecting group still remained, was isolated in 89% yield. These observations led us to change the reaction sequence, and removal of the protecting group in **6** was examined. Treatment in **6** with anhydrous aluminum chloride (8 eq) in benzene at 7—10 °C for 1.5 h resulted only in the isolation of the rearranged compounds **9** and **10** in 54 and 14% yields, respectively. These results probably reflect the fact that the benzene rings of **6** were more nucleophilic than benzene used as the solvent. Therefore, benzene was replaced by anisole and the hydroxyl group of **6** was converted into an acetyl group to reduce the nucleophilicity of the phenol ring. The acetate (**11**) was prepared by the usual method (acetyl chloride and triethylamine in methylene chloride). Treatment of **11** with anhydrous aluminum chloride (5 eq) in anisole at 0—3 °C for 10 min afforded the desired deprotected compound **12** in 82% yield. Hydrolysis of the ester group of **12** was performed with aqueous HCl in methanol to give **13** in 81% yield. Finally, oxidation of **13** with Fremy's salt in acetone–water (1 : 1) at room temperature in the presence of KH_2PO_4 (20 mol%) cleanly gave the title compound (**1**) in 84% yield. Ammonium cerium(IV) nitrate oxidation of **13** gave **1** in 34% yield.[8] IR, ^{1}H-NMR and MS spectra of the synthesized **1** were identical with those reported for natural **1**.[2b] In summary, murrayaquinone-A (**1**) was synthesized starting from 1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (**2**) through 8 steps in good overall yield.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 IR spectrometer, and ^{1}H-NMR spectra were recorded on a JEOL JNM-FX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. MS were taken with a JEOL LMS-HX100 instrument.

9-(4-Methoxybenzyl)-1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (3) NaH (0.77 g, 60% in oil, 19.3 mmol) was added to a solution of **2**[5] (3.24 g, 17.5 mmol) in dry DMF (25 ml) and the resulting solution was stirred at room temperature under N_2 for 1 h. A solution of MPMCl (2.6 ml, 19.2 mmol) in dry DMF (5 ml) was added to the above solution, and the whole was stirred at room temperature for 2 h. After the addition of water under ice-cooling, the mixture was extracted with AcOEt and the extract was washed successively with water and brine. Drying over anhydrous Na_2SO_4 and concentration of the organic layer under reduced pressure gave a brown oil, which was purified by SiO_2 column chromatography ($CHCl_3$) to furnish **3** (4.29 g, 80%) as brown plates after crystallization from MeOH; mp 115—116 °C. IR (Nujol) cm^{-1}: 1640, 1610, 1515. ^{1}H-NMR ($CDCl_3$) δ: 2.16—2.30 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.58 (2H, dd, J=7, 6 Hz, $COC\underline{H}_2CH_2$), 2.88 (2H, t, J=6 Hz, $CC\underline{H}_2CH_2$), 3.77 (3H, s, OCH_3), 5.27 (2H, s, NCH_2), 6.82 (2H, dt, J=9, 2 Hz, ArH), 6.97 (2H, dt, J=9, 2 Hz, ArH), 7.18—7.32 (3H, m, ArH), 8.26—8.32 (1H, m, ArH). MS *m/z*: Calcd for $C_{20}H_{19}NO_2$: 305.1416. Found: 305.1416.

9-(4-Methoxybenzyl)-3-methyl-1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (4) A solution of **3** (2.59 g, 8.5 mmol) in dry THF (50 ml) was added dropwise under N_2 to a THF solution of LCIA [prepared from cyclohexylisopropylamine (2.8 ml, 17.0 mmol) and 1.6 M solution of *n*-BuLi in hexane (15 ml, 24.0 mmol) in dry THF (20 ml) at −23 °C] and the resulting reaction mixture was stirred at −23—−20 °C for 5 h. To this reaction mixture was added a solution of CH_3I (5.3 ml, 85 mmol) in dry THF (5 ml) at −23—−10 °C and the whole was stirred at −23—−19 °C for 2 h. After further addition of a solution of CH_3I (2 ml, 32 mmol) in dry THF (2 ml), the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched by the addition of 2 N HCl (40 ml) and extracted with AcOEt. The combined organic layers were washed with water and brine successively and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to leave 3.16 g of a brown oil, which was crystallized from MeOH to give **5** (1.614 g) as colorless plates. The mother liquor was concentrated and purified by SiO_2 column chromatography ($CHCl_3$: MeOH = 100 : 1) to furnish more **4** (0.748 g, total yield 87%); mp 118—120 °C. IR (Nujol) cm^{-1}: 1645, 1620, 1515. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 1.90—2.08 (1H, m, $C\underline{H}CH_3$), 2.23—2.36 (1H, m, $CHC\underline{H}_2CH_2$), 2.52—2.68 (1H, m, $CHC\underline{H}_2CH_2$), 2.80—3.03 (2H, m, $CH_2C\underline{H}_2C$), 3.77 (3H, s, OCH_3), 5.26 (2H, s, NCH_2), 6.82 (2H, dt, J=9, 2 Hz, ArH), 6.98 (2H, dt, J=9, 2 Hz), 7.17—7.34 (3H, m, ArH), 8.25—8.33 (1H, m, ArH). MS *m/z*: Calcd for $C_{21}H_{21}NO_2$: 319.1573. Found: 319.1598.

9-(4-Methoxybenzyl)-3-methyl-3-phenylselenenyl-1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (5) and 4-Hydroxy-9-(4-methoxybenzyl)-3-methyl-9*H*-carbazole (6) A solution of **4** (2.36 g, 7.4 mmol) in dry THF (50 ml) was added dropwise to a solution of LCIA [prepared from cyclohexylisopropylamine (2.5 ml, 15.2 mmol) and a 1.6 M solution of *n*-BuLi in hexane (13 ml, 20.8 mmol) in dry THF (20 ml)] at −23 °C, and the whole was stirred for 10 min. After the addition of dry HMPA (3.6 ml, 20.7 mmol), the reaction mixture was stirred at −23—−19 °C for 5 h. A solution of phenylselenenyl chloride (1.90 g, 9.6 mmol) in dry THF (30 ml) was added to the above solution, and the whole was stirred at −23—−14 °C for 2 h. The reaction mixture was warmed to room temperature and stirred overnight. After the addition of 2 N HCl (80 ml) under ice-cooling, the reaction mixture was extracted with AcOEt, and then the combined organic layers were washed with water and brine successively, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a brown oil (4.15 g), which was purified by SiO_2 column chromatography ($CHCl_3$) to give **5** (1.318 g, 38%) and **6** (0.697 g, 30%), after crystallization from MeOH. **5**: mp 167—169 °C (colorless crystalline powder). IR (Nujol) cm^{-1}: 1645, 1615, 1585, 1540, 1515. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (3H, s, CCH_3), 2.23—2.44 (2H, m, $CH_2C\underline{H}_2C$), 2.78—2.92 (1H, m, $=CC\underline{H}_2CH_2$), 3.12—3.28 (1H, m, $=CC\underline{H}_2CH_2$), 3.77 (3H, s, OCH_3), 5.25 (2H, d, J=4 Hz, NCH_2), 6.84 (2H, dt, J=9, 2 Hz, ArH), 6.97 (2H, dt, J=9, 2 Hz, ArH), 7.17—7.38 (6H, m, ArH), 7.51—7.59 (2H, m, ArH), 8.26—8.32 (1H, m, ArH). MS *m/z*: 473 (M^+), 317, 121. **6**: mp 137—138 °C (reddish brown crystalline powder). IR (Nujol) cm^{-1}: 1605, 1580, 1515. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 5.25 (1H, s, OH), 5.41 (2H, s, NCH_2), 6.78 (2H, dt, J=9, 2 Hz, ArH), 6.88 (2H, dt, J=9, 2 Hz, ArH), 7.07 (1H, d, J=8 Hz, ArH), 7.17 (1H, d, J=8 Hz, ArH), 7.20—7.44 (3H, m, ArH), 8.28—8.35 (1H, m, ArH). MS *m/z*: Calcd for $C_{21}H_{19}NO_2$: 317.1416. Found: 317.1401.

6 from 5 Acetic acid (0.31 ml) and 30% H_2O_2 (1.5 ml) were added successively to a solution of **5** (0.976 g, 2.06 mmol) in dry THF (40 ml) at −2—0 °C, and the whole was stirred at the same temperature for 1 h.

After the addition of a saturated $NaHCO_3$ solution (20 ml), the reaction mixture was warmed to room temperature and extracted with AcOEt. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil (0.786 g), which was purified by SiO_2 column chromatography ($CHCl_3$) to furnish **6** (0.317 g, 49%), after crystallization from MeOH; mp 137—138 °C. The IR, ^{1}H-NMR, and mass spectral data were identical with those of the compound obtained above.

9-(4-Methoxybenzyl)-3-methyl-1,4-dihydrocarbazole-1,4(9*H*)-dione (7) A solution of Fremy's salt (0.60 g, 1.34 mmol) and KH_2PO_4 (36 mg, 0.26 mmol) in water (36 ml) was added to a solution of **6** (0.250 g, 0.79 mmol) in acetone (36 ml) and the whole was stirred at room temperature for 30 min. After removal of acetone under reduced pressure, the crystals formed were collected by filtration and washed with water. Recrystallization of the crude product from acetone gave **7** (0.218 g, 84%) as reddish needles; mp 164—165 °C. IR (Nujol) cm^{-1}: 1640, 1615, 1510. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, d, J=2 Hz, CH_3), 3.74 (3H, s, OCH_3), 5.77 (2H, s, NCH_2), 6.45 (1H, q, J=2 Hz, quinone-H), 6.80 (2H, dt, J=9, 2 Hz, ArH), 7.14 (2H, dt, J=9, 2 Hz, ArH), 7.31—7.50 (3H, m, ArH), 8.27—8.35 (1H, m, ArH). MS *m/z*: Calcd for $C_{21}H_{17}NO_3$: 331.1208. Found: 331.1194.

9-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydrocarbazole-1,4(9*H*)-dione (8) A solution of **7** (50 mg, 0.15 mmol) in dry anisole (2 ml) was added dropwise under N_2 to a stirred solution of $AlCl_3$ (101 mg, 0.76 mmol) in dry anisole (0.6 ml) at 0 °C and the reaction mixture was stirred at the same temperature for 10 min. After the addition of water, the mixture was extracted with AcOEt. The combined organic layers were washed with 5% $NaHCO_3$ and brine successively, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crystals (97 mg), which were recrystallized from acetone–hexane to yield **8** (59 mg, 89%) as pinkish prisms; mp 197—199 °C. IR (Nujol) cm^{-1}: 1730, 1670, 1610, 1515. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, s, CH_3), 3.31 (1H, d, J=16 Hz, CCH_2CO), 3.52 (1H, d, J=16 Hz, CCH_2CO), 3.72 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 5.70 (1H, d, J=16 Hz, NCH_2), 5.81 (1H, d, J=16 Hz, NCH_2), 6.71—6.82 (4H, m, ArH), 6.99 (2H, dt, J=9, 2 Hz, ArH), 7.28—7.43 (5H, m, ArH), 8.34—8.42 (1H, m, ArH). MS *m/z*: Calcd for $C_{28}H_{25}NO_4$: 439.1784. Found: 439.1798.

4-Hydroxy-1-(4-methoxybenzyl)-3-methyl-9*H*-carbazole (9) and 4-Hydroxy-8-(4-methoxybenzyl)-3-methyl-9*H*-carbazole (10) A solution of **6** (100 mg, 0.31 mmol) in dry benzene (4.4 ml) was added dropwise under N_2 to a stirred suspension of $AlCl_3$ (336 mg, 2.52 mmol) in dry benzene (1.4 ml) at 8 °C and the resulting reaction mixture was stirred at 7—10 °C for 1.5 h. After the addition of water under ice-cooling, the mixture was extracted with AcOEt and the combined organic layers were washed with 5% $NaHCO_3$ and brine successively. After drying over anhydrous Na_2SO_4, the organic layer was concentrated under reduced pressure to give a yellow oil (153 mg), which was purified by SiO_2 column chromatography (hexane : AcOEt = 5 : 1) to yield **9** (54 mg, 54%), and **10** (14 mg, 14%) as oils. Because of the instability of **9** and **10**, they were converted into the acetates by the method described for the preparation of **11** from **6**, in 43 and 35% yields, respectively. The acetate of **9**: mp 189—192 °C (MeOH) (pinkish prisms). IR (Nujol) cm^{-1}: 3450, 1750, 1610, 1510. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, $COCH_3$), 2.58 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 4.16 (2H, s, CH_2), 6.84 (2H, dt, J=9, 2 Hz, ArH), 7.08 (1H, d, J=1 Hz, ArH), 7.15—7.20 (3H, m, ArH), 7.28—7.37 (2H, m, ArH), 7.71 (1H, br s, NH), 7.88—7.91 (1H, m, ArH). MS *m/z*: Calcd for $C_{23}H_{21}NO_3$: 359.1521. Found: 359.1521. The acetate of **10**: pale yellow oil. IR ($CHCl_3$) cm^{-1}: 3400, 1745, 1610, 1515. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s, $COCH_3$), 2.34 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.09 (2H, s, CH_2), 6.86 (2H, dt, J=9, 2 Hz, ArH), 7.12—7.34 (6H, m, ArH), 7.56—7.60 (1H, m, ArH), 7.97 (1H, br s, NH). MS *m/z*: Calcd for $C_{23}H_{21}NO_3$: 359.1521. Found: 359.1495.

4-Acetoxy-9-(4-methoxybenzyl)-3-methyl-9*H*-carbazole (11) Acetyl chloride (0.05 ml, 0.76 mmol) was added to a stirred solution of **6** (200 mg, 0.63 mmol) and triethylamine (0.18 ml, 1.3 mmol) in dry CH_2Cl_2 (8 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h. After the addition of 1 N HCl, the mixture was extracted with CH_2Cl_2, washed with saturated $NaHCO_3$, water and brine, successively, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left colorless crystals (260 mg), which were crystallized from MeOH to yield **11** (200 mg, 89%) as a colorless crystalline powder; mp 116—118 °C. IR (Nujol) cm^{-1}: 1750, 1610, 1515. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $COCH_3$), 2.56 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 5.42 (2H, s, CH_2), 6.78 (2H, dt, J=9, 2 Hz, ArH), 7.08 (2H, dt, J=9, 2 Hz, ArH), 7.14—7.46 (5H, m, ArH), 7.93—8.02 (1H, m, ArH). MS *m/z*: Calcd for $C_{23}H_{21}NO_3$: 359.1521. Found: 359.1521.

4-Acetoxy-3-methyl-9*H*-carbazole (12) A solution of **11** (220 mg, 0.61 mmol) in dry anisole (5 ml) was added dropwise to a stirred suspension of $AlCl_3$ (408 mg, 3.06 mmol) in dry anisole (3 ml) at 0 °C and the resulting reaction mixture was stirred at 0 °C for 10 min. After the addition of water, the mixture was extracted with AcOEt and the combined organic layers were washed with 5% $NaHCO_3$ and brine successively, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give an oil (284 mg), which was purified by SiO_2 column chromatography (hexane : AcOEt = 4 : 1) to yield **12** (120 mg, 82%) and the acetate of **10** (10 mg, 5%). **12**: mp 151—152 °C (MeOH, colorless crystalline powder). IR (Nujol) cm^{-1}: 3430, 1740, 1610. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $COCH_3$), 2.55 (3H, s, CH_3), 7.17—7.28 (3H, m, ArH), 7.38—7.42 (2H, m, ArH), 7.90—7.95 (1H, m, ArH), 8.05 (1H, br s, NH). MS *m/z*: Calcd for $C_{15}H_{13}NO_2$: 239.0946. Found: 239.0961.

4-Hydroxy-3-methyl-9*H*-carbazole (13) A reaction mixture obtained by the addition of dilute HCl (12 ml) to a solution of **12** (90 mg, 0.38 mmol) in MeOH (15 ml) was refluxed for 4 h. Removal of MeOH gave crystals, which were collected by filtration and washed with water. Recrystallization of the crude product from hexane–acetone yielded **13** (60 mg, 81%) as a colorless crystalline powder; mp 161—163 °C. IR (Nujol) cm^{-1}: 3380, 1590. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 5.20 (1H, br s, OH), 6.94 (1H, d, J=8 Hz, ArH), 7.16 (1H, d, J=8 Hz, ArH), 7.20—7.30 (1H, m, ArH), 7.33—7.42 (2H, m, ArH), 7.95 (1H, br s, NH), 8.24—8.30 (1H, m, ArH). MS *m/z*: Calcd for $C_{13}H_{11}NO$: 197.0841. Found: 197.0855.

Murrayaquinone-A (1) A solution of **13** (30 mg, 0.15 mmol) in acetone (7 ml) was added dropwise to a stirred solution of Fremy's salt (117 mg, 0.26 mmol) and KH_2PO_4 (7 mg, 0.05 mmol) in water (7 ml) and the whole was stirred at room temperature for 10 min. Removal of acetone under reduced pressure yielded crystals, which were collected by filtration and washed with water. Recrystallization of the crude product from acetone gave **1** (27 mg, 84%) as reddish brown needles; mp 230—234 °C (lit. mp 240—241 °C[4a]; mp 237—239 °C[4c]). IR (Nujol) cm^{-1}: 3200, 1740, 1730, 1665, 1635, 1605, 1535. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, d, J=2 Hz, CH_3), 6.52 (1H, q, J=2 Hz, quinone-H), 7.32—7.52 (3H, m, ArH), 8.22—8.30 (1H, m, ArH), 9.11 (1H, br s, NH). *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.62; H, 4.40; N, 6.64. MS *m/z*: Calcd for $C_{13}H_9NO_2$: 211.0633. Found: 211.0608.

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