Total Synthesis of the Natural Carbazoles Murrayanine and Murrayafoline A, Based on the Regioselective Diels–Alder Addition of *exo*-2-Oxazolidinone Dienes

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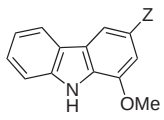
Dedicated to Professor Pierre Vogel on the occasion of his 60th birthday

Abstract: A new synthesis of the natural carbazoles Murrayanine (**1**) and Murrayafoline A (**3**) is described. The key step in the synthetic route involved the regioselective cycloaddition of the diene 4,5-dimethylene-3-phenyl-1,3-oxazolidin-2-one (**4**) to acrolein (**6**) catalyzed by Lewis acids at low temperature. Direct aromatization of the substituted cyclohexene moiety of adduct **7**, and further hydrolysis of the 2-oxazolidinone ring, proved to be a more efficient strategy than the opposite synthetic sequence for the preparation of the corresponding arylphenylamines **14** and **18**. Palladium-promoted cyclization of the latter furnished the desired carbazoles **1** and **3** in high overall yields.

Key words: 4,5-dimethylene-2-oxazolidinone dienes, murrayanine, murrayafoline A, Diels–Alder, palladium acetate

Murrayanine (**1**)[1] belongs to an extensive family of natural carbazoles mainly isolated from species of the genera *Murraya* and *Clausena*, which are characterized by a methoxy group at C-1 and a substituent at C-3.[2] These alkaloids have attracted especial attention as a result of their wide and significant biological activity.[2a,3] Accordingly, novel and efficient synthetic methodologies have been reported in order to assemble the carbazole scaffold,[4] leading to the total synthesis of natural carbazoles,[5] among them **1**.[6] It has been established that murrayanine (**1**) and mukonine (**2**)[7] biogenetically arise from the in vivo oxidation of murrayafoline A (**3**) (Figure 1).[2a,8] The latter has been prepared by reduction of **1**,[1a,6c] or **2**,[6a] and by total synthesis.[6b,9]

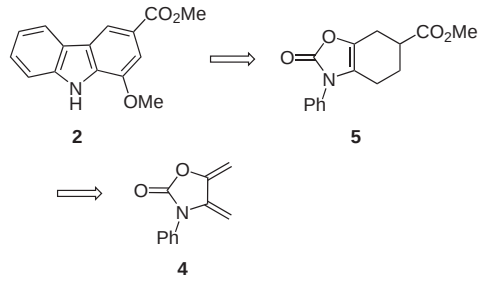
We have recently described a total synthesis of **2**,[10] through a short strategy based on the use of the *exo*-2-oxazolidinone diene **4**[11,12] in a regioselective Diels–Alder cycloaddition.[13] The adduct thus obtained (**5**) was hydrolyzed and aromatized in a single step to give the corresponding arylphenylamine, which provided carbazole **2** by palladium-promoted cyclization (Scheme 1).



1, Z = CHO
2, Z = CO_2Me
3, Z = CH_3

Figure 1

Following a methodology modified with respect to that designed for mukonine (**2**), we herein describe a total synthesis of carbazoles **1** and **3**, via a highly regioselective cycloaddition of diene **4** to acrolein (**6**), which is a dienophile not previously studied in Diels–Alder additions to *exo*-2-oxazolidinone dienes.[12]



Scheme 1

Considering that the thermal Diels–Alder addition of diene **4** to activated alkenes with electron-withdrawing groups, such as methyl vinyl ketone[12] and alkyl acrylates,[10] yields a relatively low regioselectivity (*para*/*meta*, ca. 74:26), we attempted to improve it by means of Lewis acid catalysis at low temperature.[12] Thus, the catalyzed addition ($BF_3{\cdot}OEt_2$, –78 °C) of diene **4** to acrolein (**6**) led to a mixture of the *para*/*meta* regioisomers **7**/**8** in a high ratio (98:2), and the desired adduct **7** was separated by column chromatography (Scheme 2). When the cycloaddition was carried out under thermal conditions (160 °C, 2.5 h) the ratio of **7** to **8** was lower (70:30).

The previously reported cascade method of hydrolysis of the heterocyclic ring and aromatization of the cyclohexene ring under basic conditions (NaOH–EtOH–H_2O)[13] failed to give the desired phenolic aniline **9** in good yield. In addition, a complex mixture of products was obtained, alcohol **10** among them, which has the phenyl arylamine scaffold but the aldehyde group reduced.

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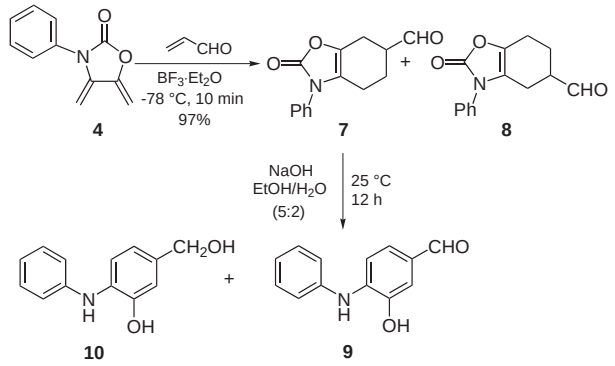
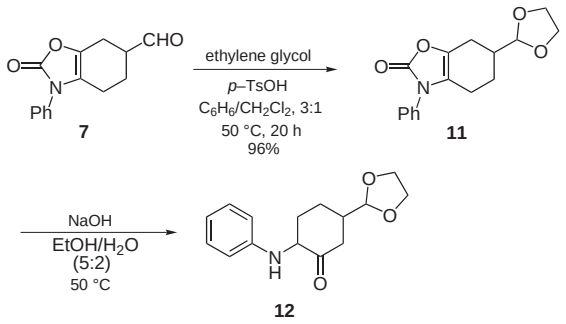


Scheme 2

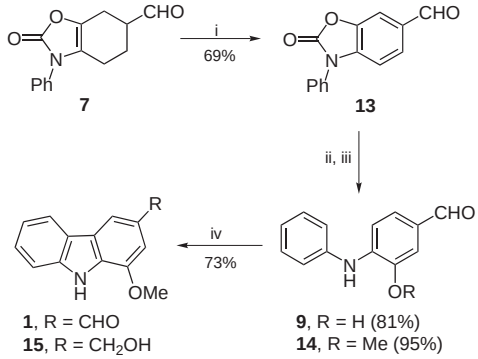
In order to prevent the reduction of the carbonyl group, compound **7** was protected with ethylene glycol to give **11** in high yield (Scheme 3). However, the basic hydrolysis of **11** led to a complex mixture of products. From this mixture compound **12**, which decomposes rapidly, was isolated in low yield. It is noteworthy that the six-membered ring did not undergo aromatization, suggesting that the unusual aerial oxidation of the ring, likely promoted by superoxide species,[13] requires a highly enolizable substrate to take place, as it is the case with those compounds having carbonylic substituents at C-3 position of the carbazole skeleton.[10,13] Further attempts to promote aromatization by oxidation of **12** with chloramine-T[14] or DDQ[15] were unsuccessful.



Scheme 3

A one-step longer but more efficient methodology consisted in the treatment of isomer **7** with DDQ in refluxing benzene to aromatize the six-membered ring, furnishing compound **13** in 69% yield (Scheme 4). Hydrolysis of **13** under mild basic conditions (NaOH, EtOH–H_2O, 25 °C, 1 h) gave the arylphenylamine **9** in high yield. Then, methylation using MeI in acetone and K_2CO_3 (reflux, 3 h) yielded **14** almost quantitatively.[5c] Finally, the coupling of the aromatic rings of **14**, promoted by palladium in acetic acid,[13,16] provided carbazole **1** in 38% overall yield (Scheme 4), whose spectroscopic data matched those reported for the natural product.[1b]

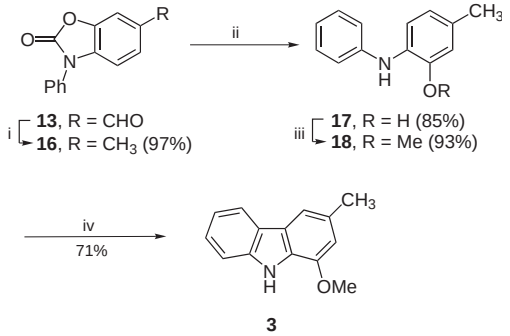
Murrayafoline A (**3**) has been prepared by partial synthesis from **1a** by reduction of the aldehyde group.[6c] When we investigated the reduction of **1** with zinc amalgam in refluxing EtOH, natural carbazole **3** was obtained along



Scheme 4 *Conditions*: i) DDQ, C_6H_6, reflux, 24 h. ii) NaOH, EtOH–H_2O (2.5:1), 25 °C, 1 h. iii) MeI, K_2CO_3, Me_2CO, reflux, 3 h. iv) $Pd(OAc)_2$, AcOH, 160 °C, 12 h.

with the product of partial reduction, koenoline (**15**),[6a,b] in a ca. 1:1 ratio. Furthermore, we were able to prepare **3** following a pathway analogous to that developed for **1** (Scheme 5). Thus, palladium-catalyzed hydrogenation of **13** yielded the methylated derivative **16** in high yield. By successive hydrolysis of the latter, methylation of the phenol intermediate **17**, and intramolecular cyclization of the arylphenylamine **18**, carbazole **3** was obtained in 36% overall yield.

In conclusion, we have demonstrated that the natural carbazole murrayanine (**1**) can be prepared in five steps by a highly regioselective Diels–Alder addition reaction between the 2-oxazolidinone diene **4** and acrolein (**6**). Aromatization of the six-membered ring of adduct **7** allowed us to carry out the hydrolysis of the oxazolidinone moiety successfully leading to the arylphenylamine intermediate **9**, under soft and efficient conditions. Natural carbazole **3**, which is the biogenetical precursor of **1**, was also prepared starting from **7** through a similar synthetic route, and in a good overall yield.



Scheme 5 *Conditions*: i) H_2/Pd/C (30 psi), EtOAc, 25 °C, 6 h. ii) NaOH, EtOH–H_2O (5:2), 60 °C, 2 h. iii) MeI, K_2CO_3, Me_2CO, reflux, 3 h. iv) $Pd(OAc)_2$, HOAc, 140 °C, 10 h.

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Jeol GSX-270 (270 MHz), Varian Mercury (300 MHz), and Jeol-400 (400 MHz) instruments, in $CDCl_3$ or acetone-d_6 as solvents and TMS as internal standard. MS and HRMS were obtained, in electron impact (EI) (70 eV) and FAB (*m*NBA) modes,

on a Hewlett-Packard 5971A and on a Jeol JMS-AX 505 HA spectrometers, respectively. Analytical TLC was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualizing by long- and short-wavelength UV lamps. Flash column chromatography was performed on silica gel (230–400 mesh, Natland Int.). All air moisture sensitive reactions were carried out under N_2 using oven-dried glassware. Benzene and xylene were freshly distilled over sodium, and CH_2Cl_2 and EtOAc over CaH_2, prior to use. Acetone was dried by distillation after treatment with 4 Å molecular sieves. K_2CO_3 was dried overnight at 120 °C prior to use. All other reagents were used without further purification. Diene **4** was prepared as reported.[12]

6-Formyl-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (7); Typical Procedure

Method A: To a stirred solution of **4** (0.20 g, 1.07 mmol) in anhyd CH_2Cl_2 (6 mL), at –78 °C under N_2 atmosphere, **6** (0.072 g, 1.28 mmol) and $BF_3{\cdot}Et_2O$ (0.003 g, 0.021 mmol) were added dropwise, and the mixture was stirred for 10 min at the same temperature. The mixture was washed with a 5% aq solution of $NaHCO_3$ (2 × 15 mL), 5% aq solution of NH_4NO_3 (2 × 15 mL), and water (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under vacuum, giving a mixture of **7**/**8** (98:2). The residue was purified by column chromatography over silica gel (8 g, hexane–EtOAc, 3:2), to give **7** (0.24 g, 91%) as a white solid.

Method B: A mixture of diene **4** (0.10 g, 0.53 mmol), dienophile **6** (0.06 g, 1.07 mmol), and hydroquinone (0.003 g) in anhyd xylene (4 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N_2 atmosphere, and in the dark. The mixture was stirred and heated to 160 °C for 2.5 h. The solvent was removed under vacuum and the residue (**7**/**8**, 70:30) purified by column chromatography on silica gel (30 g/g of crude) (hexane–EtOAc, 4:1), to give **7** (0.086 g, 66%) as a white solid; R_f 0.56 (hexane–EtOAc, 1:1); mp 109–110 °C.

IR (CH_2Cl_2): 1757, 1711, 1597, 1503, 1395, 1360, 1273, 1166, 980 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.79–1.94 (m, 1 H, H-5β), 2.04–2.17 (m, 1 H, H-5α), 2.24–2.41 (m, 2 H, H-4), 2.59–2.75 (m, 2 H, H-7), 2.75–2.86 (m, 1 H, H-6), 7.17–7.50 (m, 5 H, PhH), 9.68 (s, 1 H, CHO).

^{13}C NMR (67.94 MHz, $CDCl_3$): δ = 18.9 (C-4), 20.5 (C-7), 21.5 (C-5), 45.3 (C-6), 120.7 (C-3a), 124.9 (PhH), 127.5 (PhH), 129.2 (PhH), 133.1 (C-7a or Ph), 133.6 (Ph or C-7a), 154.2 (C-2), 201.5 (CHO).

MS (70 eV): *m*/*z* = 243 (94) [M^+], 215 (51), 187 (20), 174 (19), 158 (26), 143 (28), 130 (37), 117 (100), 104 (22), 77 (97).

HRMS (FAB): *m*/*z* [MH^+] calcd for $C_{14}H_{14}NO_3$: 244.0974; found: 244.0973.

6-(1,3-Dioxolan-2-yl)-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (11); Typical Procedure

A solution of **7** (0.50 g, 2.06 mmol), ethylene glycol (0.2 g, 3.2 mmol), and *p*-toluenesulfonic acid (few crystals), in an anhyd mixture of benzene–CH_2Cl_2 (3:1) (10 mL), was stirred at 50 °C under N_2 atmosphere for 20 h. The mixture was treated with a 5% aq solution of $NaHCO_3$ until neutral, and was then extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane), to give **11** (0.57 g, 96%) as a white solid; R_f 0.26 (hexane–EtOAc, 7:3); mp 145–146 °C.

IR (KBr): 1757, 1713, 1497, 1400, 1148, 977 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.48–1.68 (m, 1 H, H-5β), 1.96–2.08 (m, 1 H, H-5α), 2.08–2.21 (m, 1 H, H-6), 2.24–2.48 (m, 3 H, H-4, H-7), 2.52–2.65 (m, 1 H, H-7), 3.84–4.02 [m, 4 H, $O(CH_2)_2$], 4.81 (d, *J* = 4.7 Hz, 1 H, OCHO), 7.25–7.46 (m, 5 H, PhH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 20.0 (C-4), 21.7 (C-7), 23.2 (C-5), 38.1 (C-6), 65.1 [$O(CH_2)_2$], 105.6 (OCHO), 120.6 (C-3a), 124.9 (PhH), 127.4 (PhH), 129.3 (PhH), 134.0 (Ph), 134.5 (C-7a), 154.4 (C-2).

MS (70 eV): *m*/*z* = 287 (100) [M^+], 259 (3), 226 (54), 215 (36), 171 (22), 158 (17), 130 (23), 117 (28), 77 (49), 73 (65).

HRMS (FAB): *m*/*z* [MH^+] calcd for $C_{14}H_{18}NO_4$: 288.1236; found: 288.1238.

6-Formyl-3-phenyl-2,3-dihydrobenzoxazol-2-one (13); Typical Procedure

To a stirred solution of **7** (0.22 g, 0.90 mmol) in anhyd benzene (25 mL), at reflux under N_2 atmosphere, a solution of DDQ (0.45 g, 1.98 mmol) in anhyd benzene (20 mL) was added dropwise through a cannula, and the mixture was stirred for 24 h at the same temperature. The mixture was filtered on celite, the solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (7 g, hexane–EtOAc, 9:1), to give **13** (0.15 g, 69%) as a white solid; R_f 0.46 (hexane–EtOAc, 7:3); mp 161–162 °C.

IR (CH_2Cl_2): 1759, 1704, 1598, 1448, 1379, 1354, 1279, 1163 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.0 Hz, 1 H, H-4), 7.47–7.63 (m, 5 H, PhH), 7.74 (dd, *J* = 8.0, 1.3 Hz, 1 H, H-5), 7.80 (d, *J* = 1.3 Hz, 1 H, H-7), 9.96 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3 (C-4), 110.0 (C-7), 125.2 (PhH), 128.2 (PhH), 129.1 (C-5), 130.1 (PhH), 132.3 (Ar or Ph), 132.7 (Ph or Ar), 136.4 (Ph or Ar), 143.0 (C-7a), 152.9 (C-2), 190.3 (CHO).

MS (70 eV): *m*/*z* = 239 (82) [M^+], 238 (49), 211 (16), 207 (37), 186 (36), 166 (25), 149 (16), 135 (86), 105 (45), 91 (24), 77 (100), 73 (30).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_9NO_3$: 239.0582; found: 239.0578.

3-Hydroxy-4-phenylaminobenzaldehyde (9); Typical Procedure

A mixture of **13** (0.19 g, 0.79 mmol) and NaOH (0.16 g, 4.0 mmol) in EtOH (9.4 mL) and H_2O (3.8 mL) at 20 °C was stirred for 1 h. The mixture was neutralized with 5% aq solution of HCl, and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane–EtOAc, 9:1), to give **9** (0.137 g, 81%) as a yellow solid; R_f 0.31 (hexane–EtOAc, 7:3); mp 116–117 °C.

IR (CH_2Cl_2): 3456, 3375, 1665, 1597, 1529, 1451, 1317, 1247, 1175 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.82 (br s, 1 H, NH), 7.08–7.14 (m, 1 H, PhH), 7.21–7.27 (m, 3 H, H-5, PhH), 7.29–7.40 (m, 3 H, H-6, PhH), 7.63 (d, *J* = 1.8 Hz, 1 H, H-2), 8.25 (br s, 1 H, OH), 9.66 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 110.1 (C-2), 113.0 (C-5), 121.5 (PhH), 123.6 (PhH), 127.2 (C-6), 128.3 (C-1), 129.5 (PhH), 139.6 (C-4), 140.1 (Ph), 144.1 (C-3), 191.9 (CHO).

MS (70 eV): *m*/*z* = 213 (100) [M^+], 212 (65), 211 (40), 182 (21), 156 (12), 128 (19), 91 (14), 77 (25).

3-Methoxy-4-phenylaminobenzaldehyde (14); Typical Procedure

A mixture of **9** (0.134 g, 0.63 mmol), MeI (0.27 g, 1.9 mmol) and K_2CO_3 (1.3 g, 9.4 mmol) in anhyd acetone (10 mL) was heated to 60 °C for 3 h. The solvent was removed under vacuum, the residue was dissolved in EtOAc (15 mL), and was washed with brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chro-

matography over silica gel (30 g/g of crude, hexane–EtOAc, 9:1), to give **14** (0.136 g, 95%) as yellow crystals; R_f 0.47 (hexane–EtOAc, 7:3); mp 114–115 °C.

IR (CH_2Cl_2): 3396, 3301, 1669, 1571, 1521, 1496, 1361, 1305, 1250, 1130, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OMe), 6.74 (br s, 1 H, NH), 7.09–7.15 (m, 1 H, PhH), 7.23–7.26 (m, 3 H, H-5, PhH), 7.32–7.41 (m, 4 H, H-2, H-6, PhH), 9.76 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7 (OMe), 107.7 (C-2), 110.1 (C-5), 121.5 (PhH), 123.7 (PhH), 127.8 (2C), 129.4 (PhH), 139.9, 140.3, 147.1 (C-3), 190.3 (CHO).

MS (70 eV): *m*/*z* = 227 (100) [M^+], 212 (60), 183 (22), 154 (27), 129 (24), 77 (20).

HRMS (FAB): *m*/*z* [MH^+] calcd for $C_{14}H_{14}NO_2$: 228.1025; found: 228.1028.

Murrayanine (1); Typical Procedure

A mixture of **14** (0.05 g, 0.22 mmol) and $Pd(AcO)_2$ (0.074 g, 0.33 mmol) in glacial HOAc acid (3 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N_2 atmosphere, and in the dark. The mixture was stirred and heated to 160 °C for 12 h. The mixture was filtered, neutralized with aq sat. solution of $NaHCO_3$, and extracted with EtOAc (2 × 15 mL). The organic layer was washed with brine (2 × 15 mL), dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane/EtOAc, 9:1), to give **1** (0.036 g, 73%) as a white solid; R_f 0.41 (hexane–EtOAc, 7:3); mp 167–168 °C [Lit.[1b] 167–168 °C; 168 °C[1a]].

IR (CH_2Cl_2): 3152, 1657, 1607, 1577, 1499, 1342, 1238, 1136 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.05 (s, 3 H, OMe), 7.32 (ddd, *J* = 7.7, 7.0, 1.3 Hz, 1 H, H-6), 7.46 (br s, 1 H, H-2), 7.48–7.51 (m, 2 H, H-7, H-8), 8.10 (d, *J* = 7.7 Hz, 1 H, H-5), 8.18 (br s, 1 H, H-4), 8.70 (br s, 1 H, NH), 10.05 (s, 1 H, CHO).

^1H NMR (300 MHz, Me_2CO-d_6): δ = 3.07 (br s, 1 H, NH), 4.09 (s, 3 H, OMe), 7.29 (ddd, *J* = 7.8, 7.2, 0.7 Hz, 1 H, H-6), 7.47 (d, *J* = 1.2 Hz, 1 H, H-2), 7.49 (ddd, *J* = 8.4, 7.0, 0.9 Hz, 1 H, H-7), 7.67 (br d, *J* = 8.4 Hz, 1 H, H-8), 8.22 (br d, *J* = 7.8 Hz, 1 H, H-5), 8.36 (d, *J* = 1.2 Hz, 1 H, H-4), 10.06 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.7 (OMe), 103.4 (C-2), 111.5 (C-8), 120.4 (C-4), 120.6 (C-5, C-6), 123.5 (C-4a or C-5a), 123.6 (C-5a or C-4a), 126.6 (C-7), 130.0 (C-1a or C-3), 134.0 (C-3 or C-1a), 139.4 (C-8a), 146.0 (C-1), 191.9 (CHO).

^{13}C NMR (75.4 MHz, Me_2CO-d_6): δ = 55.5 (OMe), 103.5 (C-2), 112.1 (C-8), 119.9 (C-4), 120.4 (C-6), 120.7 (C-5), 123.6 (C-5a), 123.8 (C-4a), 126.6 (C-7), 130.4 (C-3), 140.5 (C-1a or C-8a), 140.6 (C-8a or C-1a), 146.6 (C-1), 191.4 (CHO).

MS (70 eV): *m*/*z* = 225 (100) [M^+], 210 (62), 182 (11), 154 (51), 139 (11), 126 (18).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_{11}NO_2$: 225.0790; found: 225.0789.

6-Methyl-3-phenyl-2,3-dihydrobenzoxazol-2-one (16); Typical Procedure

A mixture of **13** (0.23 g, 0.96 mmol) and 10% Pd/C (0.23 g, 0.22 mmol) in EtOAc (25 mL) at 20 °C and under an H_2 atmosphere (30 psi) was stirred for 6 h. The mixture was filtered on celite, the solvent was removed under vacuum, and the residue was purified by flash column chromatography over silica gel (6.3 g, hexane–EtOAc, 9:1), under N_2 pressure, to give **16** (0.21 g, 97%) as a white solid; R_f 0.68 (hexane–EtOAc, 7:3); mp 90–91 °C.

IR (CH_2Cl_2): 1773, 1597, 1503, 1455, 1374, 1347, 1273, 1202, 1162, 986 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, Me), 6.96–7.00 (m, 2 H, H-4, H-5), 7.11 (br s, 1 H, H-7), 7.39–7.47 (m, 1 H, PhH), 7.53–7.59 (m, 4 H, PhH).

^1H NMR (300 MHz, Me_2CO-d_6): δ = 2.40 (s, 3 H, Me), 6.99–7.07 (m, 2 H, H-4, H-5), 7.18 (br s, 1 H, H-7), 7.45–7.51 (m, 1 H, PhH), 7.57–7.67 (m, 4 H, PhH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.4 (Me), 108.9 (C-4), 110.8 (C-7), 124.3 (C-5), 124.8 (PhH), 128.1 (PhH), 128.7 (C-6), 129.7 (PhH), 133.4 (Ar or Ph), 133.7 (Ph or Ar), 142.8 (C-7a), 153.3 (C-2).

^{13}C NMR (75.4 MHz, Me_2CO-d_6): δ = 20.7 (Me), 109.1 (C-4), 110.6 (C-7), 124.5 (C-5), 125.4 (PhH), 128.2 (PhH), 129.2 (C-6), 129.8 (PhH), 133.3 (Ar or Ph), 134.3 (Ph or Ar), 143.0 (C-7a), 152.9 (C-2).

MS (70 eV): *m*/*z* = 225 (100) [M^+], 180 (70), 168 (16), 90 (5), 77 (34).

HRMS (FAB): *m*/*z* [MH^+] calcd for $C_{14}H_{12}NO_2$: 226.0868; found: 226.0871.

3-Methyl-2-phenylaminophenol (17); Typical Procedure

A mixture of **16** (0.07 g, 0.31 mmol) and NaOH (0.06 g, 1.5 mmol) in a mixture of EtOH–H_2O (5:2, 7 mL), previously deoxygenated by N_2 bubbling, was heated to 60 °C under stirring for 2 h. The solvent was evaporated under vacuum, and the residue was dissolved in EtOAc (20 mL) and washed with 5% aq solution of NH_4Cl (2 × 15 mL), 5% aq solution of $NaHCO_3$ (2 × 15 mL), and water (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane–EtOAc, 9:1), under N_2 pressure, to give **17** (0.053 g, 85%) as an orange oil; R_f 0.62 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3372, 1598, 1502, 1457, 1411, 1308, 1238, 1177, 1154, 799, 749, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, Me), 5.05 (br s, 1 H, OH), 5.93 (br s, 1 H, NH), 6.64–6.74 (m, 3 H, H-4, PhH), 6.79–6.87 (m, 2 H, H-6, PhH), 7.02 (d, *J* = 8.1 Hz, 1 H, H-3), 7.14–7.22 (m, 2 H, PhH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.2 (Me), 115.2 (PhH), 115.8 (C-6), 119.8 (C-3 or PhH), 121.5 (PhH or C-3), 125.8 (C-4), 129.3 (PhH), 137.1 (C-2, C-5), 146.2 (Ph), 151.7 (C-1).

MS (70 eV): *m*/*z* = 199 (100) [M^+], 184 (10), 170 (11), 154 (16), 128 (10), 122 (8), 107 (4), 93 (25), 77 (28).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.0994.

(2-Methoxy-4-methylphenyl)phenylamine (18); Typical Procedure

A mixture of **17** (0.07 g, 0.35 mmol), MeI (0.15 g,1.06 mmol), and K_2CO_3 (0.73 g, 5.29 mmol) in anhyd acetone (10 mL) was heated to reflux for 3 h. The solvent was removed under vacuum, the residue was dissolved in EtOAc (15 mL), and was washed with brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (2.1 g, hexane–EtOAc, 9:1), under N_2 pressure, to give **18** (0.07 g, 93%) as an orange oil; R_f 0.77 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3411, 2927, 1596, 1521, 1498, 1462, 1409, 1315, 1259, 1156, 1129, 1036, 804, 747, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, Me), 3.86 (s, 3 H, MeO), 5.99 (br s, 1 H, NH), 6.66–6.75 (m, 2 H, H-3, H-5), 6.89 (t, *J* = 7.2 Hz, 1 H, PhH), 7.05–7.14 (m, 2 H, PhH), 7.20 (d, *J* = 7.7 Hz, 1 H, H-6), 7.22–7.30 (m, 2 H, PhH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.1 (Me), 55.5 (OMe), 111.6 (C-3), 115.8 (C-6), 117.6 (PhH), 120.4 (PhH), 120.8 (C-5), 129.2 (PhH), 129.9 (C-1 or C-4), 130.1 (C-4 or C-1), 143.4 (Ph), 148.6 (C-2).

MS (70 eV): *m*/*z* = 213 (100) [M^+], 198 (78), 183 (36), 170 (28), 154 (16), 128 (11), 77 (20).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_{15}NO$: 213.1143; found: 213.1154.

Murrayafoline A (3);[6a,b] Typical Procedure

A mixture of **18** (0.04 g, 0.19 mmol) and $Pd(AcO)_2$ (0.05 g, 0.22 mmol) in glacial HOAc acid (2.5 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N_2 atmosphere, and in the dark. The mixture was stirred and heated to 140 °C for 10 h. The mixture was filtered, neutralized with aq sat. solution of $NaHCO_3$, and extracted with EtOAc (2 × 20 mL). The organic layer was washed with a 5% aq solution of NH_4Cl (2 × 15 mL), and water (2 × 15 mL), then dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (1.2 g, hexane–EtOAc, 9:1), under N_2 pressure, to give **3** (0.028 g, 71%) as a pale pink oil; R_f 0.67 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3418, 2923, 1588, 1503, 1452, 1393, 1335, 1305, 1263, 1231, 1135, 1038, 828, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, Me), 3.98 (s, 3 H, OMe), 6.73 (br s, 1 H, H-2), 7.19 (ddd, *J* = 7.8, 6.6, 1.5 Hz, 1 H, H-7), 7.33–7.45 (m, 2 H, H-6, H-8), 7.47 (s, 1 H, H-4), 8.01 (d, *J* = 8.1 Hz, 1 H, H-5), 8.16 (br s, 1 H, NH).

^{1}H NMR (300 MHz, Me_2CO-d_6): δ = 2.48 (s, 3 H, Me), 3.97 (s, 3 H, OMe), 6.82 (d, *J* = 0.9 Hz, 1 H, H-2), 7.14 (ddd, *J* = 7.8, 7.1, 1.1 Hz, 1 H, H-6), 7.35 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1 H, H-7), 7.49 (s, 1 H, H-4), 7.54 (ddd, *J* = 8.1, 1.1, 0.6 Hz, 1 H, H-8), 8.03 (dd, *J* = 7.8, 0.6 Hz, 1 H, H-5), 10.29 (br s, 1 H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.9 (Me), 55.4 (OMe), 107.6 (C-2), 110.9 (C-8), 112.5 (C-4), 117.3 (C-1a), 119.1 (C-6), 120.4 (C-5), 123.5 (C-4a or C-5a), 124.2 (C-5a or C-4a), 125.4 (C-7), 129.4 (C-3), 139.4 (C-8a), 145.3 (C-1).

^{13}C NMR (75.4 MHz, Me_2CO-d_6): δ = 21.3 (Me), 55.1 (OMe), 107.8 (C-2), 111.5 (C-8), 112.4 (C-4), 116.9 (C-1a), 118.8 (C-6), 120.2 (C-5), 123.4 (C-4a or C-5a), 124.3 (C-5a or C-4a), 125.4 (C-7), 128.9 (C-3), 140.4 (C-8a), 145.9 (C-1).

MS (70 eV): *m*/*z* = 211 (100) [M^+], 196 (84), 180 (10), 168 (77), 167 (72), 139 (13), 115 (6), 84 (5).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_{13}NO$: 211.0997; found: 211.0991.

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