exo-2-Oxazolidinone Dienes in the Total Synthesis of the Natural Carbazoles, 6-Methoxymurrayanine and Clausenine

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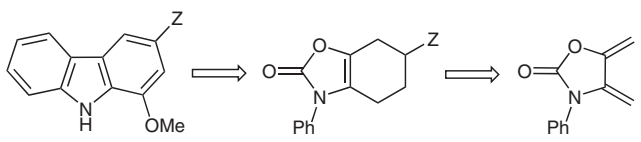
Received 21 February 2007

Abstract: A new application of *exo*-2-oxazolidinone dienes in the regioselective synthesis of natural carbazoles, 6-methoxymurrayanine (**6**) and clausenine (**7**), is described. The regioselective cycloaddition of novel diene **10** to acrolein by Lewis acid catalysis provided adduct **12**, which after aromatization gave benzoxazolone **14** as the key intermediate for the preparation of both carbazoles. A straightforward and efficient synthesis of **7** was carried out by a procedure with no isolation of intermediates, starting from **14** and went through a sequence of hydrogenation–hydrolysis–methylation and Pd-cyclization to give the desired carbazole **7** in high overall yield.

Key words: carbazoles, 4,5-dimethylene-2-oxazolidinone dienes, 6-methoxymurrayanine, clausenine, Diels–Alder reaction, decarbonylation

Naturally occurring 1-oxygenated carbazoles have attracted great interest due to their diverse and significant biological activity.[1] These alkaloids are mainly extracted from species of the genera *Murraya* and *Clausena*, and in the case of 2- and 3-substituted families, their biogenesis has been established.[1c,d,2] For instance, murrayanine (**1**)[1c,3] and mukonine (**2**)[1g,2a] arise from the in vivo oxidation of murrayafoline A (**3**).[1c,2b,4] Moreover, from the synthetic viewpoint, the carbazole framework has been an attractive target in the development of novel and efficient strategies for the total synthesis of natural and unnatural carbazoles.[1a,3a,5,6] We have described a general synthetic approach for the preparation of the carbazole scaffold,[7] and it has been applied in the total synthesis of carbazoles **1**–**3**.[8] This strategy was based on the regioselective Diels–Alder cycloaddition of the *exo*-2-oxazolidinone dienes **4**,[9] whose adducts **5** were transformed into the natural carbazoles in a short and efficient methodology (Scheme 1).

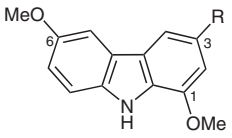


1, Z = CHO
2, Z = CO_2Me
3, Z = Me

5 **4**

Scheme 1

Another example of the biogenetic relationship between carbazoles could be found in the case of 6-methoxymurrayanine (**6**)[10] and clausenine (**7**),[1h] in which the latter is probably the natural precursor of **6**. Interestingly, these carbazoles and the extracts from their natural sources display antifungal and antibacterial activities,[1h,11] and, to the best of our knowledge, the synthesis of **6** has not been previously reported. With the aim of evaluating the versatility of our methodology in the synthesis of C-ring substituted carbazoles, we herein disclose the synthetic study for the preparation of natural carbazoles **6** and **7**[12] (Figure 1).

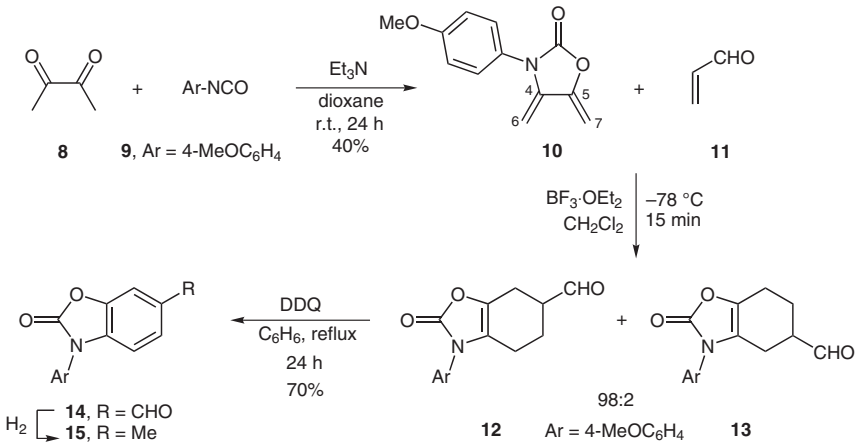


6, R = CHO
7, R = Me

Figure 1

Taking into account that carbazoles **6** and **7** have a methoxy group at the C-6 position of their frame, the design of the synthetic route included the preparation of diene **10**, which bears the desired substituent. The latter was obtained as a white solid in moderate yield by reacting butane-2,3-dione (**8**) and 4-methoxyphenyl isocyanate (**9**), according to the procedure previously described (Scheme 2).[9] In a similar strategy to that used for the preparation of compounds **1** and **3** (Scheme 1),[8b] the A-ring of carbazoles **6** and **7** was built through a regioselective Diels–Alder addition of diene **10** to acrolein (**11**) under Lewis acid catalysis ($BF_3{\cdot}OEt_2$, –78 °C) at low temperature, which, after only 15 minutes of stirring, proceeded until the complete disappearance of starting materials, to give a mixture of isomeric adducts *para/meta* derivatives **12/13** in a high ratio (98:2). The desired product **12** was obtained in high yield (93%) after purification by column chromatography (Scheme 2). Highly regioselective Diels–Alder cycloadditions of analogous *exo*-2-oxazolidinone dienes with electron-deficient dienophiles have also been carried out under hydrophobic conditions.[13] Therefore, this reaction was conducted under a similar methodology (MeOH–H_2O, 9:1) at room temperature for 18 hours. However, the regioselectivity was lower, since the mixture **12/13** was obtained as an 85:15 ratio.

SYNTHESIS 2007, No. 13, pp 1943–1948
Advanced online publication: 18.06.2007
DOI: 10.1055/s-2007-983741; Art ID: M01007SS



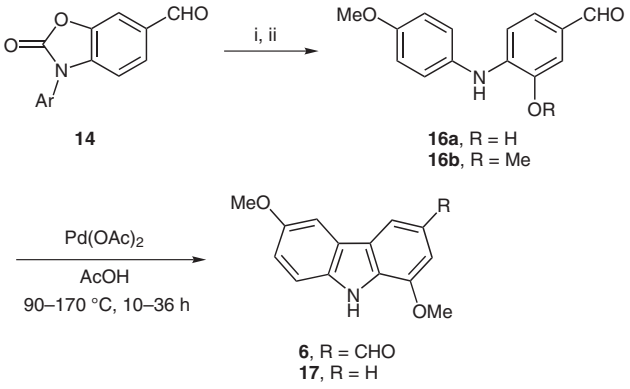
Scheme 2

The cyclohexene ring was aromatized by treating **12** with DDQ in benzene at reflux to furnish 2-(3*H*)-benzoxazolone **14** in good yield. The latter might be the key intermediate for the preparation of both carbazoles **6** and **7**, since the C-3 methyl group required in the structure of **7** could be obtained by reduction of the formyl group of **14**. Therefore, 2-(3*H*)-benzoxazolone **15** was prepared in an almost quantitative yield by the hydrogenation of **14** (Scheme 2).

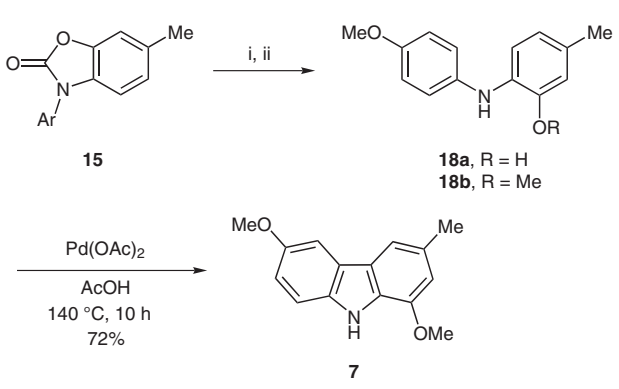
Upon saponification of **14** under mild basic conditions (NaOH, EtOH–H_2O, 25 °C, 1 h) diarylamine **16a** was obtained in 85% yield (Scheme 3). The phenol group was methylated by using methyl iodide in acetone and potassium carbonate as the base to give **16b** in high yield. Finally, efficient conversion of the latter into the desired carbazole **6** was carried out by a Pd(II)-mediated cyclization in good yield.[6f,14] Spectroscopic data and melting point of **6** were in agreement with those reported for the natural product.[10] It is worth noting that the efficacy of the last step depended on the reaction temperature. The transformation did not proceed at <80 °C, and was very slow at 80 °C (4 days). However, it turned out well (80%) when the temperature is ranged between 90–110 °C. Unexpectedly, when the temperature rises to 140–170 °C, not only does the cyclization take place but also the decarbonylation, to give carbazole **17** in 74% overall yield. Although Pd-promoted decarbonylation of aromatic aldehydes has already been described,[3a,15] under our conditions this process is hitherto unknown.

In the case of 2-(3*H*)-benzoxazolone **15**, the hydrolysis step was slower than that for **14**, reacting only after five hours with heating to 60 °C under the basic treatment to give anilinophenol **18a** (Scheme 4). It is likely that the electron-withdrawing effect of the formyl group enhances the delocalization of the lone-pair of the nitrogen atom towards the aromatic ring, increasing the reactivity of the nucleophilic addition onto the carbonyl group of the carbamate. Owing to the decomposition of compound **18a** at room temperature, it was not possible for it to be fully characterized. Thereby, once it was purified, compound **18a** was O-methylated with MeI and K_2CO_3 to furnish derivative **18b** in high yield (94%, Scheme 4). Clausenine (**7**) was prepared in 72% yield via the usual treatment with palladium acetate in acetic acid.

With the aim of improving the synthesis of clausenine (**7**), we investigated a straightforward and shorter methodology, through a four-step procedure with no purification of intermediates, starting from the key compound **14**. Thus, palladium-catalyzed hydrogenation of a mixture of **14** in

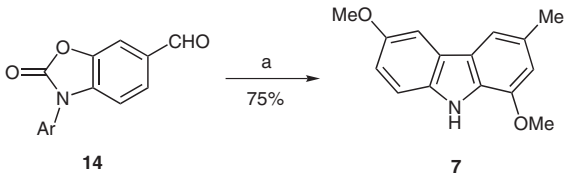


Scheme 3 *Reagents and conditions*: i) NaOH, EtOH–H_2O (2:1), r.t., 6 h, 85%; ii) MeI, K_2CO_3, acetone, reflux, 3 h, 91%.



Scheme 4 *Reagents and conditions*: i) NaOH, EtOH–H_2O (5:2), 60 °C, 5 h, 83%; ii) MeI, K_2CO_3, acetone, reflux, 3 h, 94%.

the presence of KOH at room temperature for 12 hours, followed by heating to reflux for 12 hours, yielded the crude reaction mixture of phenol **18a**. Then, successive treatment of the latter with MeI and palladium acetate provided **7** in 75% overall yield (Scheme 5).



14 7

Scheme 5 *Reagents and conditions*: (a) (i) H_2/Pd/C (30 psi), KOH, EtOH& ndash;H_2O (7:3), r.t., 12 h; then reflux, 12 h; (ii) MeI, K_2CO_3, acetone, reflux, 12 h; (iii) $Pd(OAc)_2$, AcOH, 120 °C, 18 h.

A partial synthesis of **7** from **6** by reduction of the aldehyde group was also attempted. When the process was carried out by palladium-catalyzed hydrogenation of the latter, **7** was obtained in 93% yield.

In summary, *exo*-2-oxazolidinone dienes have proved to be efficient synthons in the total synthesis of natural carbazoles substituted in both A and C rings. Thus, naturally occurring 6-methoxymurrayanine (**6**) and clausenine (**7**) were prepared starting from a highly regioselective Diels–Alder addition of diene **10** onto acrolein (**11**) in 40% and 36% overall yield, respectively. The 2-(3*H*)-benzoxazolone **14** was used as the key intermediate not only for the preparation of **6** via a three-step methodology, but also for obtaining benzoxazolone **15**, which was transformed into **7** following a similar procedure. Moreover, the latter was obtained in 75% overall yield from **14** in a four-step reaction sequence with no isolation of intermediates. Therefore, these results represent a new approach for the synthesis of clausenine (**7**), and the first total synthesis of natural carbazole 6-methoxymurrayanine (**6**).

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a PerkinElmer 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury (300 MHz) instrument, with $CDCl_3$ as the solvent and TMS as internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained, in electron impact (EI) (70 eV) mode on Hewlett-Packard 5971A and on Jeol JMS-AX 505 HA spectrometers, respectively. Analytical TLC was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by a long- and short-wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230–400 mesh). All air moisture sensitive reactions were carried out under N_2 using oven-dried glassware. Dioxane, benzene, and toluene 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 4Å molecular sieves. K_2CO_3 and Li_2CO_3 were dried overnight at 120 °C prior to use. Et_3N was freshly distilled from NaOH. All other reagents were used without further purification.

3-(4-Anisyl)-4,5-dimethylene-1,3-oxazolidin-2-one (10)

A mixture of **8** (2.04 g, 23.69 mmol) in anhyd dioxane (6 mL), Et_3N (4.79 g, 47.34 mmol) and Li_2CO_3 (2.5 g, 0.034 mol) was stirred at r.t. under N_2 for 30 min. Then, a solution of 4-methoxyphenyl isocyanate (**9**; 5.30 g, 35.53 mmol) in dioxane (10 mL) was added over a period of 30 min and stirring was continued for 24 h at r.t. The mixture was filtered on Celite, the residue washed with CH_2Cl_2 (3 × 15 mL), and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel conditioned with Et_3N (10%) in hexane (30 g/g of crude) (hexane–EtOAc, 95:5), to give 2.06 g (40%) of **10** as a white solid; R_f = 0.60 (hexane–EtOAc, 4:1); mp 97–98 °C (hexane–EtOAc, 9:1).

IR (CH_2Cl_2): 1777, 1634, 1518, 1405, 1292, 1256, 1214, 1160, 1109, 988, 881, 832 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, CH_3O), 4.20 (d, *J* = 3.0 Hz, 1 H, H-6), 4.65 (d, *J* = 3.0 Hz, 1 H, H-6), 4.83 (d, *J* = 3.4 Hz, 1 H, H-7), 4.88 (d, *J* = 3.4 Hz, 1 H, H-7), 6.88–6.95 (m, 2 H, ArH), 7.13–7.20 (m, 2 H, ArH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.4 (CH_3O), 84.4 (C-6), 86.8 (C-7), 114.9 (ArH), 125.3 (Ar), 128.2 (ArH), 139.2 (C-4), 148.8 (C-5), 152.6 (C-2), 159.6 (Ar).

MS (70 eV): *m*/*z* (%) = 217 (M^+, 20), 186 (22), 158 (10), 146 (18), 142 (10), 130 (11), 121 (100), 103 (30), 91 (6), 77 (8).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{12}H_{11}NO_3$: 217.0739; found: 217.0742.

6-Formyl-3-(4-methoxyphenyl)-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (12)

To a stirred solution of **10** (1.57 g, 7.23 mmol) in anhyd CH_2Cl_2 (40 mL) at –78 °C under N_2, were added dropwise **11** (0.49 g, 8.74 mmol) and $BF_3{\cdot}OEt_2$ (0.021 g, 0.15 mmol), and the mixture was stirred for 15 min at the same temperature. The mixture was washed with a 5% aq solution of $NaHCO_3$ (3 × 15 mL), 5% aq solution of NH_4NO_3 (2 × 15 mL), and H_2O (15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under vacuum, giving a mixture of **12/13** (98:2). The residue was purified by column chromatography over silica gel (60 g, hexane–EtOAc, 3:2) to give 1.84 g (93%) of **12** as a colorless oil; R_f = 0.34 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 1753, 1709, 1611, 1513, 1445, 1400, 1300, 1248, 1166, 1114, 1028, 980, 833 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86–2.02 (m, 1 H, H-5), 2.10–2.22 (m, 1 H, H-5), 2.29–2.37 (m, 2 H, H-4), 2.68–2.81 (m, 2 H, H-7), 2.81–2.88 (m, 1 H, H-6), 3.82 (s, 3 H, CH_3O), 6.91–6.99 (m, 2 H, ArH), 7.19–7.23 (m, 2 H, ArH), 9.74 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.7 (C-4), 20.7 (C-7), 21.6 (C-5), 45.5 (C-6), 55.5 (CH_3O), 114.6 (ArH), 121.1 (C-3a), 126.3 (Ar), 126.7 (ArH), 132.8 (C-7a), 154.7 (C-2), 158.9 (Ar), 201.6 (CHO).

MS (70 eV): *m*/*z* (%) = 273 (M^+, 100), 245 (30), 217 (38), 188 (22), 173 (6), 160 (34), 147 (92), 133 (26), 121 (12), 92 (28), 77 (32).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.1000.

6-Formyl-3-(4-methoxyphenyl)-2,3-dihydrobenzoxazol-2-one (14)

To a stirred solution of **12** (0.58 g, 2.12 mmol) in anhyd benzene (50 mL), at reflux under N_2, was added dropwise a solution of DDQ (1.06 g, 4.67 mmol) in anhyd benzene (40 mL) through a cannula, and the mixture was stirred for 24 h at the same temperature. The mixture was filtered on Celite, the solvent removed under vacuum, and the residue purified by column chromatography over silica gel (12 g, hexane–EtOAc, 9:1) to give 0.40 g (70%) of **14** as a white solid; R_f = 0.31 (hexane–EtOAc, 7:3); mp 186–187 °C.

IR (CH_2Cl_2): 1762, 1709, 1696, 1612, 1518, 1455, 1382, 1360, 1305, 1284, 1259, 1160, 1034, 818 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, CH_3O), 7.05–7.10 (m, 2 H, ArH), 7.12 (d, *J* = 8.1 Hz, 1 H, H-4), 7.40–7.48 (m, 2 H,

ArH), 7.74 (dd, *J* = 8.1, 1.2 Hz, 1 H, H-5), 7.80 (d, *J* = 1.2 Hz, 1 H, H-7), 9.97 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (CH_3O), 109.0 (C-4), 109.9 (C-7), 115.2 (ArH), 125.0 (Ar), 126.8 (ArH), 128.2 (C-5), 132.2 (C-6), 136.9 (C-3a), 142.9 (C-7a), 153.3 (C-2), 159.9 (Ar), 190.3 (CHO).

MS (70 eV): *m*/*z* (%) = 269 (M^+, 100), 254 (5), 224 (5), 210 (16), 182 (20), 154 (14), 92 (8), 77 (9).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{15}H_{11}NO_4$: 269.0688; found: 269.0691.

3-Hydroxy-4-(4-methoxyphenylamino)benzaldehyde (16a)

A mixture of **14** (0.23 g, 0.86 mmol) and 0.17 g (4.3 mmol) of NaOH in EtOH (12.5 mL) and H_2O (6 mL) at 20 °C was stirred for 6 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 0.18 g (85%) of **16a** as a yellow solid; R_f = 0.44 (hexane–EtOAc, 7:3); mp 184–185 °C.

IR (CH_2Cl_2): 3353, 1662, 1596, 1515, 1454, 1348, 1242, 1167 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, CH_3O), 6.56 (br s, 1 H, NH), 6.90–6.97 (m, 2 H, ArH), 6.98 (d, *J* = 8.1 Hz, 1 H, H-5), 7.15–7.23 (m, 2 H, ArH), 7.28 (dd, *J* = 8.1, 2.1 Hz, 1 H, H-6), 7.42 (d, *J* = 2.1 Hz, 1 H, H-2), 7.50 (br s, 1 H, OH), 9.68 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.5 (s, CH_3O), 110.1 (C-2), 112.0 (C-5), 114.7 (ArH), 124.7 (ArH), 127.0 (C-1), 128.1 (C-6), 132.6 (Ar), 141.5 (Ar), 143.4 (C-3), 156.7 (Ar), 190.7 (CHO).

MS (70 eV): *m*/*z* (%) = 243 (M^+, 13), 242 (100), 227 (5), 211 (44), 198 (20), 182 (4), 170 (9), 128 (11), 121 (5), 77 (8).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_{13}NO_3$: 243.0895; found: 243.0885.

3-Methoxy-4-(4-methoxyphenylamino)benzaldehyde (16b)

A mixture of **16a** (0.08 g, 0.33 mmol), MeI (0.14 g, 0.99 mmol), and K_2CO_3 (0.68 g, 4.93 mmol) in anhyd acetone (25 mL) was heated to 60 °C for 3 h. The solvent was removed under vacuum, the residue dissolved in EtOAc (15 mL), and 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 (30 g/g of crude, hexane–EtOAc, 9:1) to give 0.077 g (91%) of **16b** as a pale yellow oil; R_f = 0.83 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3391, 1669, 1591, 1513, 1461, 1358, 1294, 1256, 1126, 1032, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, CH_3O), 3.96 (s, 3 H, CH_3O), 6.57 (br s, 1 H, NH), 6.90–6.99 (m, 3 H, H-5, ArH), 7.15–7.22 (m, 2 H, ArH), 7.29 (dd, *J* = 8.1, 1.8 Hz, 1 H, H-6), 7.37 (d, *J* = 1.8 Hz, 1 H, H-2), 9.73 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.5 (CH_3O), 55.7 (CH_3O), 107.4 (C-2), 109.2 (C-5), 114.7 (ArH), 125.0 (ArH), 127.0 (C-1), 128.2 (C-6), 132.4 (Ar), 141.9 (Ar), 146.6 (C-3), 156.8 (C-10), 190.3 (CHO).

MS (70 eV): *m*/*z* (%) = 257 (M^+, 70), 242 (100), 211 (80), 198 (40), 171 (36), 148 (30), 79 (10).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{15}H_{15}NO_3$: 257.1052; found: 257.1049.

6-Methoxymurrayanine (6)

A mixture of **16b** (0.04 g, 0.16 mmol) and $Pd(AcO)_2$ (0.043 g, 0.19 mmol) in glacial AcOH (2.5 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2. The mixture was stirred and heated to 90 °C for 36 h in the dark. The mixture was diluted with toluene (10 mL) and the solvent was removed under vacuum. This procedure was repeated twice. The residue was purified by column chromatography over silica gel (30 g/g of crude, hexane–EtOAc, 9:1), to give 0.033 g (80%) of **6** as a white solid; R_f = 0.69 (hexane–EtOAc, 7:3); mp 230–232 °C [Lit.[10] mp 231–233 °C].

IR (CH_2Cl_2): 3150, 1657, 1609, 1582, 1496, 1442, 1328, 1260, 1221, 1142, 1031, 847, 709 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3O), 4.07 (s, 3 H, CH_3O), 7.12 (dd, *J* = 8.7, 2.4 Hz, 1 H, H-7), 7.43 (d, *J* = 8.7 Hz, 1 H, H-8), 7.44 (br s, 1 H, H-2), 7.57 (d, *J* = 2.4 Hz, 1 H, H-5), 8.17 (s, 1 H, H-4), 8.51 (br s, 1 H, NH), 10.04 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.8 (CH_3O), 56.0 (CH_3O), 103.1 (C-5), 103.2 (C-2), 112.2 (C-8), 116.1 (C-7), 120.6 (C-4), 123.5 (C-4a), 124.2 (C-5a), 129.8 (C-3), 134.1 (C-8a), 134.7 (C-1a), 146.1 (C-1), 154.7 (C-6), 191.8 (CHO).

MS (70 eV): *m*/*z* (%) = 255 (M^+, 57), 240 (100), 212 (52), 184 (61), 169 (17), 154 (4), 141 (9).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{15}H_{13}NO_3$: 255.0895; found: 255.0892.

1,6-Dimethoxy-9*H*-carbazole (17)

Following the method of preparation of **6**, a mixture of **16b** (0.04 g, 0.16 mmol) and $Pd(AcO)_2$ (0.043 g, 0.19 mmol) in glacial AcOH (2.5 mL) was stirred and heated to 140 °C for 24 h or to 170 °C for 10 h to give 0.026 g (74%) of **17** as a white solid; R_f = 0.61 (hexane–EtOAc, 7:3); mp 118–120 °C.

IR (CH_2Cl_2): 3406, 1616, 1579, 1481, 1463, 1394, 1294, 1256, 1213, 1175, 1025, 800, 738 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, CH_3), 3.97 (s, 3 H, CH_3O), 6.85 (dd, *J* = 8.0, 0.8 Hz, 1 H, H-2), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1 H, H-7), 7.12 (t, *J* = 8.0 Hz, 1 H, H-3), 7.31 (d, *J* = 8.8 Hz, 1 H, H-8), 7.52 (d, *J* = 2.4 Hz, 1 H, H-5), 7.62 (dd, *J* = 8.0, 0.8 Hz, 1 H, H-4), 8.14 (br s, 1 H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.4 (CH_3O), 56.0 (CH_3O), 103.1 (ArH), 105.7 (ArH), 111.6 (ArH), 112.7 (ArH), 115.0 (ArH), 119.3 (ArH), 124.0 (C-4a or C-5a), 124.3 (C-5a or C-4a), 130.6 (C-1a), 134.1 (C-8a), 145.7 (C-1), 153.8 (C-6).

MS (70 eV): *m*/*z* (%) = 227 (M^+, 84), 212 (100), 197 (16), 184 (22), 169 (7), 153 (7), 141 (26), 113 (11).

HRMS (FAB): *m*/*z* [M^+] calcd for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0941.

3-(4-Methoxyphenyl)-6-methyl-2,3-dihydrobenzoxazol-2-one (15)

A mixture of **14** (0.20 g, 0.74 mmol) and 10% Pd/C (0.14 g, 0.13 mmol) in EtOAc (20 mL) at 20 °C and under H_2 (30 psi) was stirred for 6 h. The mixture was filtered on Celite, the solvent removed under vacuum, and the residue purified by column chromatography over silica gel (6.0 g, hexane–EtOAc, 9:1) under N_2 pressure, to give 0.186 g (98%) of **15** as a white solid; R_f = 0.76 (hexane–EtOAc, 7:3); mp 173–175 °C.

IR (CH_2Cl_2): 1768, 1612, 1517, 1446, 1383, 1303, 1254, 1162, 1028, 983 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3O), 6.88 (d, *J* = 8.1 Hz, 1 H, H-4), 6.97 (br d, *J* = 8.1 Hz, 1 H, H-5), 7.01–7.08 (m, 2 H, ArH), 7.10 (br s, 1 H, H-7), 7.41–7.49 (m, 2 H, ArH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.4 (CH_3), 55.5 (CH_3O), 108.7 (C-4), 110.7 (C-7), 114.9 (ArH), 124.2 (C-5), 126.1 (Ar), 126.5

(ArH), 129.2 (C-3a), 133.1 (C-6), 142.7 (C-7a), 153.6 (C-2), 159.2 (Ar).

MS (70 eV): *m/z* (%) = 255 (M^+, 100), 240 (7), 210 (8), 196 (27), 168 (22), 154 (4), 77 (8).

HRMS (FAB): *m/z* [M^+] calcd for $C_{15}H_{13}NO_3$: 255.0895; found: 255.0894.

2-(4-Methoxyphenylamino)-5-methylphenol (18a)

A mixture of **15** (0.08 g, 0.31 mmol) and 0.125 g (3.13 mmol) of NaOH in a solution of EtOH–H_2O (5:2, 8 mL), previously deoxygenated by bubbling N_2, was heated to 60 °C under N_2 for 5 h. The solvent was evaporated under vacuum, the residue dissolved in EtOAc (25 mL) and washed with 5% aq solution of NH_4Cl (2 × 15 mL), 5% aq solution of $NaHCO_3$ (2 × 15 mL), and H_2O (2 × 15 mL). The organic layer was dried (Na_2SO_4) and the solvent 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 0.06 g (83%) of **18a** as an orange oil; R_f = 0.42 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3365, 1511, 1458, 1292, 1235, 1178, 1112, 1034, 806 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3O), 4.93 (br s, 1 H, OH), 5.88 (br s, 1 H, NH), 6.60–6.88 (m, 6 H, H-4, H-6, ArH), 6.99 (d, *J* = 8.1 Hz, 1 H, H-3).

***N*-(4-Methoxyphenyl)-*N*-(2-methoxy-4-methylphenyl)amine (18b)**

A mixture of **18a** (0.045 g, 0.20 mmol), MeI (0.084 g, 0.59 mmol), and K_2CO_3 (0.407 g, 2.95 mmol) in anhyd acetone (10 mL) was heated to reflux for 3 h. The solvent was removed under vacuum, the residue 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 30 g/g of crude, hexane–EtOAc, 9:1) under N_2 pressure to give 0.045 g (94%) of **18b** as a pale yellow oil; R_f = 0.57 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3349, 2934, 1614, 1513, 1461, 1400, 1339, 1243, 1156, 1131, 1035, 809, 773, 647 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (br s, 3 H, CH_3), 3.79 (s, 3 H, CH_3O), 3.87 (s, 3 H, CH_3O), 5.83 (br s, 1 H, NH), 6.64 (ddd, *J* = 8.0, 1.7, 0.8 Hz, 1 H, H-5), 6.69 (br d, *J* = 1.7 Hz, 1 H, H-3), 6.81–6.89 (m, 2 H, ArH), 6.96 (d, *J* = 8.0 Hz, 1 H, H-6), 7.04–7.12 (m, 2 H, ArH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.0 (CH_3), 55.50 (CH_3O), 55.55 (CH_3O), 111.3 (C-3), 113.4 (C-6), 114.5 (ArH), 120.9 (C-5), 121.8 (ArH), 128.6 (C-1 or C-4), 132.1 (C-4 or C-1), 136.1 (Ar), 147.7 (C-2 or Ar), 154.8 (Ar or C-2).

MS (70 eV): *m/z* (%) = 243 (M^+, 100), 228 (74), 213 (12), 197 (65), 184 (19), 168 (6), 156 (5), 121 (9), 92 (4), 77 (9).

HRMS (FAB): *m/z* [M^+] calcd for $C_{15}H_{17}NO_2$: 243.1259; found: 243.1264.

Clausenine (7)

Method A: A mixture of **6** (0.025 g, 0.098 mmol) and 10% Pd/C (0.018 g, 0.017 mmol) in EtOAc (10 mL) at 20 °C (30 psi) was stirred under H_2 for 6 h. The mixture was filtered on Celite, the solvent removed under vacuum, and the residue was purified by flash column chromatography over silica gel (3.0 g, hexane–EtOAc, 9:1) under N_2 pressure to give 0.022 g (93%) of **7** as a pale yellow solid.

Method B: A mixture of **18b** (0.035 g, 0.14 mmol) and $Pd(AcO)_2$ (0.039 g, 0.17 mmol) in glacial AcOH (2.0 mL), was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N_2. The mixture was stirred and heated to 140 °C for 10 h in the dark. The mixture was filtered, neutralized with 5% aq solution of NaOH, and extracted with EtOAc (20 mL). The organic layer was washed with 5% aq solution of NH_4Cl (2 × 15 mL) and H_2O (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) under N_2 pressure to give 0.025 g (72%) of **7** as a pale yellow powder.

Method C: A mixture of **14** (0.1 g, 0.37 mmol), a solution of KOH (0.083 g, 1.48 mmol) in EtOH–H_2O (7:3, 10 mL), and 10% Pd/C (0.1 g, 0.093 mmol) at 20 °C and under H_2 (30 psi) was stirred for 12 h, and then heated to reflux for 12 h. The mixture was filtered on Celite, and the residue was washed with EtOH (3 × 15 mL). The solution was neutralized with aq HCl (39%). The solvent was removed under vacuum, the residue dissolved in CH_2Cl_2 (10 mL), and H_2O (5 mL) was added. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was dissolved in acetone (15 mL), then K_2CO_3 (0.13 g, 0.93 mmol) and MeI (0.26 g, 1.85 mmol) were added, and the mixture was heated to reflux for 12 h. The mixture was filtered on Celite, the solvent removed under vacuum, and the residue mixed in a threaded ACE glass pressure tube with a sealed Teflon screw cap with $Pd(AcO)_2$ (0.17 g, 0.76 mmol) in glacial AcOH (2 mL) under N_2. The mixture was stirred and heated to 120 °C for 18 h in the dark. The mixture was diluted with toluene (15 mL) and the solvent was removed under vacuum. This procedure was repeated twice. The residue was purified by column chromatography over silica gel (20 g/g of crude, hexane–EtOAc, 9:1) to give 0.067 g (75%) of **7** as a pale yellow solid; R_f = 0.47 (hexane–EtOAc, 7:3); mp 149–150 °C (acetone–hexane, 9:1) (Lit.[1h] mp 150 °C).

IR (CH_2Cl_2): 3416, 2930, 1583, 1462, 1393, 1304, 1266, 1214, 1146, 1037, 944, 828 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3O), 3.98 (s, 3 H, CH_3O), 6.71 (br s, 1 H, H-2), 7.03 (dd, *J* = 8.7, 2.3 Hz, 1 H, H-7), 7.32 (d, *J* = 8.7 Hz, 1 H, H-8), 7.43 (br s, 1 H, H-4), 7.49 (d, *J* = 2.3 Hz, 1 H, H-5), 8.01 (br s, 1 H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.9 (CH_3), 55.4 (CH_3O), 56.0 (CH_3O), 103.0 (C-5), 107.5 (C-2), 111.6 (C-8), 112.3 (C-4), 114.8 (C-7), 123.9 (C-4a), 124.2 (C-5a), 128.8 (C-1a), 129.0 (C-3), 134.4 (C-8a), 145.4 (C-1), 153.6 (C-6).

MS (70 eV): *m/z* (%) = 241 (M^+, 94), 226 (100), 211 (9), 198 (20), 183 (7), 168 (8), 155 (18), 120 (16), 77 (4).

HRMS (FAB): *m/z* [M^+] calcd for $C_{15}H_{15}NO_2$: 241.1103; found: 241.1099.

Acknowledgment

We thank Fernando Labarrios and Fabiola Jiménez for his help in spectrometric measurements. J.T. acknowledges DEPI/IPN (Grants 20030147, 20040123, 20050151, 20060583) and CONACYT (Grants 32273E and 43508Q) for financial support. A.B. and P.B. thank CONACYT for the award of a graduate scholarship. R.B. thanks SNI/CONACYT for a scholarship. A.B. and P.B. also thank CGPI/IPN (PIFI) and Ludwig K. Hellweg Foundation for scholarship awards. J.T. is a fellow of the EDI-IPN and COFAA-IPN programs.

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