

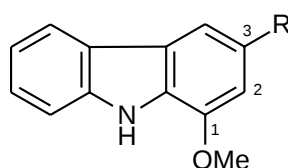
A CONCISE SYNTHESIS OF THE NATURAL CARBAZOLE MUKONINE

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Abstract - A short and total synthesis of the natural carbazole mukonine (**1**) is described, based on a regioselective Diels-Alder reaction of *N*-phenyl 4,5-dimethylidene-2-oxazolidinone (**9**) with methyl propiolate (**10**). Successive transformation of the cycloadduct in one step to the corresponding phenylarylamine (**16**), and palladium promoted cyclization of the latter provided carbazole (**1**).

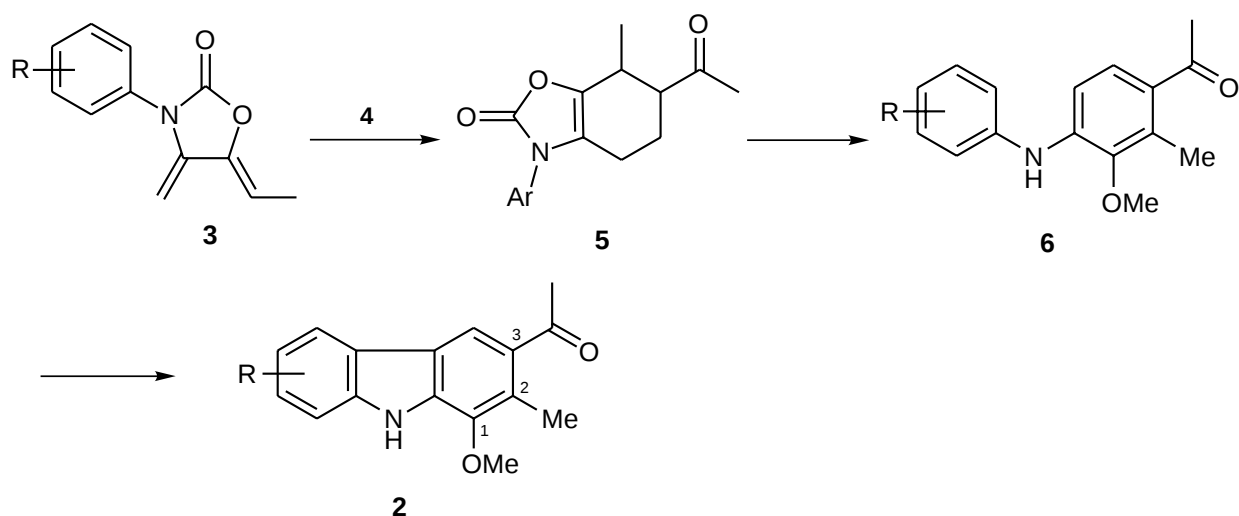
Given the biological importance of natural carbazole alkaloids,¹ an intensive effort has been directed toward their isolation,² and total synthesis.^{1c,3} Among them, mukonine (**1**) has been isolated from *Murraya koenigii*⁴ and *Clausena excavata*.^{2c,2f} From a biogenetical viewpoint, carbazole (**1**) probably arises from *in vivo* oxidation of the 3-methyl precursor called murrayafoline A.^{1j,4,5} Several synthetic routes have been reported for its preparation.^{4,6}



R = CO₂Me, mukonine (**1**)

R = Me, murrayafoline A

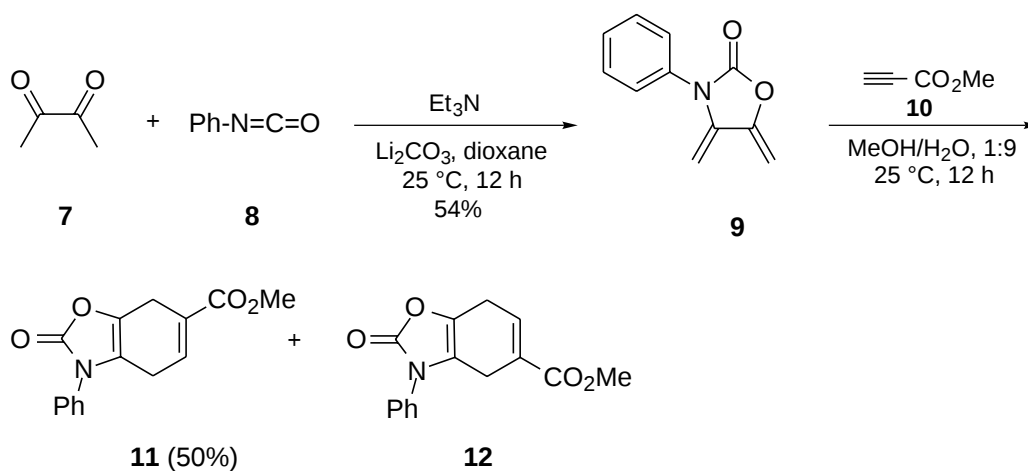
Recently, we described a straightforward synthesis of substituted carbazoles (**2**), taking advantage of the regioselective Diels-Alder addition of a series of novel *N*-substituted 5-ethylidene-4-methylidene-2-oxazolidinones (**3**) toward methyl vinyl ketone (**4**).⁷ Dienes (**3**) were readily prepared from an α -diketone and the corresponding isocyanates.⁸ Thus, the obtained adducts (**5**) were transformed to diarylamine intermediates (**6**) by a one-pot procedure, and they were converted to the desired carbazoles (**2**) via palladium-promoted cyclization (Scheme 1). As an extension of this synthetic strategy, and with the aim of testing it as an efficient methodology for the synthesis of natural carbazoles, hereby we describe a short synthesis of mukonine (**1**).



Scheme 1

RESULTS AND DISCUSSION

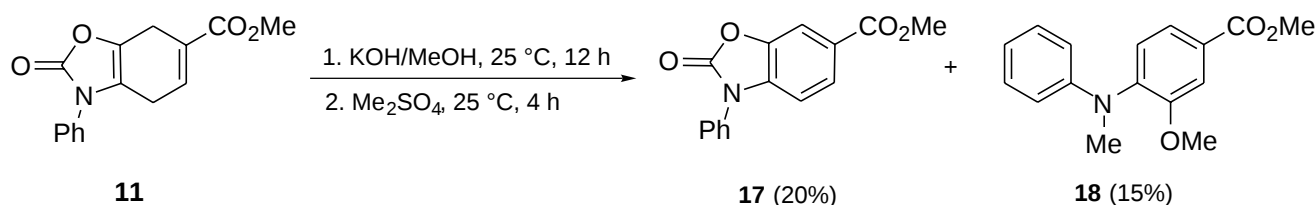
Following the synthetic pathway of Scheme 1, the preparation of **1** should include as a key step the regioselective Diels-Alder addition of diene (**9**) toward methyl propiolate (**10**) as the dienophile (Scheme 2). Diene (**9**) has been previously prepared in 54% yield from the condensation reaction of 2,3-butanedione (**7**) with phenyl isocyanate (**8**).^{8a} Even though the cycloaddition between **9** and **10** has proven to be highly regioselective in the presence of Lewis acid catalysts to give preferentially adduct (**11**),^{8a} the reaction was not suitable on a larger scale, since the formation of a byproduct was preferred. The latter corresponded to the byproduct isolated during the preliminary investigation on Diels-Alder additions of these dienes, and tentatively attributed to a bicycle structure.^{8b}



Scheme 2

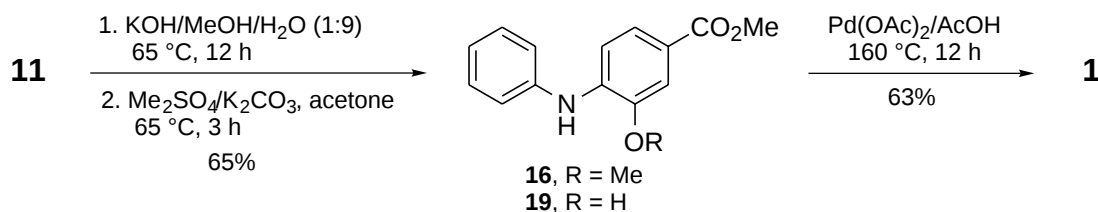
Accordingly, we carried out the reaction under a series of new conditions in order to improve the low selectivity provided by the thermal reaction conditions (Table 1, Entry 1). Thus, methyl and ethyl

solvent to furnish the desired adduct (**11**) in moderate yield after separation and recrystallization (Table 1, Entries 4 and 5). It is noteworthy that diene (**9**) was stable under aqueous conditions, and the cycloaddition was sensitive to the catalytic effect of the polarity of the solvent. These conditions were also applied for olefin (**13a**), and the proportion of the major adduct (**14a**) was improved (Table 1, Entry 6). Basic hydrolysis (NaOH/MeOH) of adduct (**11**), followed by methylation with dimethyl sulfate in the same flask, in accord with the previous report,⁷ failed to provide the expected phenylarylamine (**16**), and only side products (**17**) and (**18**) were isolated in low yields (Scheme 4). Besides, the ratio of these compounds depended on the temperature and reaction time, along with the presence of additional polar byproducts. In particular, the structure of **17** indicates that the aromatization of the cyclohexadiene ring is a favorable and, probably, faster process than the hydrolysis of the 2-oxazolidinone ring.



Scheme 4

Optimized conditions were found when the hydrolysis of **11** was carried out under more drastic reaction conditions (65 °C, 12 h), including up to 30% of water in the solvent, and by isolating the phenol precursor (**19**) before methylation. Moreover, the latter reaction was carried out by treatment with dimethyl sulfate and potassium carbonate in acetone at 65 °C for 3 h,¹¹ to give the desired product (**16**) in 65% yield (Scheme 5). Unfortunately, these and further investigated conditions were not efficient in transforming isomer (**14a**) into the amine (**16**), since only decomposition of starting material was observed. This was probably due to the unfavorable oxidation state of the cyclohexene ring, since **14a**, in contrast to **11**, possesses only one unsaturation.



Scheme 5

Mukonine (**1**) was then prepared by oxidative coupling cyclization of the phenyl and aryl rings of **16** promoted by stoichiometric Pd(OAc)₂ in acetic acid.⁷ Although the reported reaction conditions (110 °C, 3 h) were unable to consume the starting material, even at longer reaction time, by increasing both temperature and time, the target product (**1**) was isolated in fair yield (Scheme 5).

In conclusion, we have described a new and concise synthesis of mukonine (**1**), by using the novel approach that involves a regioselective Diels-Alder addition of the exo-heterocyclic diene (**9**), as a building block of the functionalized A-ring of the carbazole. With the preparation of **1**, a formal synthesis of other related carbazoles may be considered, such as koenoline,^{1j,5a} murrayanine,^{5,6a,12} murrayafoline A,^{6a,12} and mukoeic acid.^{5b,6a}

EXPERIMENTAL

General. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. NMR spectra were recorded at 300 MHz for ¹H, and at 75.4 MHz for ¹³C, on a Varian Gemini-300, using TMS as internal standard. MS and HRMS spectra were obtained, in electron impact (EI) (70 eV) and fast atom bombardment (FAB) modes, on a Hewlett-Packard 5971A, and on a Jeol JMS-AX 505 HA spectrometers. X-Ray analyses were collected on a P-4 Siemens diffractometer, using Mo K α radiation (graphite crystal monochromator, λ = 0.71073 Å). Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ). Analytical TLC was carried out using E. Merck silica gel 60 F₂₅₄, 0.25 mm coated plates, visualizing by long- and short-wavelength UV lamp. All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dioxane and xylene were freshly distilled from sodium, and methylene chloride from calcium hydride, prior to use. Li₂CO₃ was dried overnight at 120 °C before using. Triethylamine was freshly distilled from NaOH. All other reagents were used without further purification. Preparation of diene (**9**) was reported elsewhere.^{8a}

General Procedures for the Diels-Alder Reaction of Dienophiles Methyl Propiolate (10**), Methyl Acrylate (**13a**), and Ethyl Acrylate (**13b**), with Diene (**9**). Method A.** A mixture of **9** (0.500, 2.67 mmol), dienophile (5.35 mmol), and hydroquinone (0.003 g) in dry xylene (3 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N₂ atmosphere, and in the dark. The mixture was stirred and heated to 160 °C for 6 h. The solvent was removed under vacuum and the residue purified by column chromatography (hexane/EtOAc, 8:2) on silica gel (30 g/g of crude) to give the corresponding adducts. **Method B.** To a solution of diene (**9**) (0.500 g, 2.67 mmol) in a mixture of MeOH/H₂O (1:9, 20 mL) the olefin (5.35 mmol) was added at rt, under N₂ atmosphere, and in the dark. The mixture was stirred at the same temperature for 12 h, and the solvent was removed under vacuum. The crude was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic phase was dried (Na₂SO₄), and the solvent was removed under vacuum. The crude was purified by column chromatography (hexane/EtOAc, 8:2) on silica gel (30 g/g of crude) to give the corresponding adducts.

6-Methoxycarbonyl-3-phenyl-2,3,4,7-tetrahydrobenzoxazol-2-one (11**). 5-Methoxycarbonyl-3-phenyl-2,3,4,7-tetrahydrobenzoxazol-2-one (**12**). Method A.** With 0.45 g of methyl propiolate (**10**), gave a mixture of **11/12** (60:40) as a pale yellow powder, which was recrystallized (hexane/CH₂Cl₂, 8:2) to yield 0.235 g (32%) of **11** as a white powder. **Method B.** With 0.45 g of **10**, gave a mixture of **11/12**

(78:22) as a pale yellow powder, which was recrystallized (hexane/CH₂Cl₂, 8:2) to yield 0.36 g (50%) of **11** as a white powder: mp 175-176 °C [lit.,^{8a} 175-176 °C].

6-Methoxycarbonyl-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (14a). **5-Methoxycarbonyl-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (15a).** **Method A.** With 0.46 g of methyl acrylate (**13a**), gave a mixture of **14a/15a** (72:28), which was purified by column chromatography to yield 0.46 g (63%) of **14a** as a white powder. **Method B.** With 0.46 g of **13a**, gave a mixture of **14a/15a** (81:19), which was purified by column chromatography to yield 0.42 g (57%) of **14a** as a white powder: mp 111-112 °C (hexane/CH₂Cl₂, 8:2). *R_f* 0.53 (hexane/EtOAc, 1:1). IR (KBr) 1757, 1730, 1598, 1500, 1407, 1331, 1171 cm⁻¹; ¹H NMR (CDCl₃) δ 1.85-1.95 (m, 1H, H-5), 2.14-2.24 (m, 1H, H-5), 2.32-2.50 (m, 2H, H-4), 2.74-2.82 (m, 2H, H-7), 2.82-2.95 (m, 1H, H-6), 3.74 (s, 3H, CO₂CH₃), 7.28-7.38 (m, 3H, PhH), 7.40-7.49 (m, 2H, PhH); signals attributed to minor isomer (**15a**): 3.70 (s, CO₂CH₃); ¹³C NMR (CDCl₃) δ 19.6 (C-4), 23.6 (C-7), 24.7 (C-5), 38.9 (C-6), 52.1 (CO₂CH₃), 120.4 (C-3a), 125.0 (C-11), 127.6 (C-13), 129.3 (C-12), 133.6 (C-7a), 133.9 (C-10), 154.3 (C-2), 173.9 (CO₂CH₃); MS (70 eV) 273 (M⁺, 98), 258 (1), 242 (3), 228 (4), 213 (60), 187 (25), 171 (34), 158 (100), 143 (61), 130 (66), 117 (42), 77 (74). Anal. Calcd for C₁₅H₁₅NO₄: C, 65.95; H, 5.49; N, 5.13. Found: C, 66.05; H, 5.56; N, 5.27.

6-Ethoxycarbonyl-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (14b). **5-Ethoxycarbonyl-3-phenyl-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (15b).** **Method A.** With 0.535 g of ethyl acrylate (**13b**), gave a mixture of **14b/15b** (69:31), which was purified by column chromatography to yield 0.415 g (54%) of **14b** as a white powder: mp 103-104 °C (hexane/CH₂Cl₂, 7:3). *R_f* 0.70 (hexane/EtOAc, 1:1). IR (KBr) 1757, 1730, 1709, 1597, 1502, 1397, 1326, 1187, 1162, 1022 cm⁻¹; ¹H NMR (CDCl₃) δ 1.29 (t, *J* = 7.1 Hz, 3H, CO₂CH₂CH₃), 1.86-2.00 (m, 1H, H-5), 2.14-2.24 (m, 1H, H-5), 2.32-2.45 (m, 2H, H-4), 2.73-2.81 (m, 2H, H-7), 2.81-2.92 (m, 1H, H-6), 4.20 (q, *J* = 7.1 Hz, 2H, CO₂CH₂CH₃), 7.27-7.41 (m, 3H, PhH), 7.42-7.54 (m, 2H, PhH); signals attributed to minor isomer (**15b**): 1.29 (t, *J* = 7.1 Hz, CO₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 14.2 (CO₂CH₂CH₃), 19.7 (C-4), 23.6 (C-7), 24.7 (C-5), 39.0 (C-6), 61.0 (CO₂CH₂CH₃), 120.4 (C-3a), 125.0 (C-12), 127.6 (C-14), 129.4 (C-13), 133.7 (C-7a), 133.9 (C-11), 154.4 (C-2), 173.5 (CO₂CH₂CH₃); MS (70 eV) 287 (M⁺, 100), 272 (73), 256 (12), 241 (63), 198 (13), 170 (16), 154 (13), 115 (15), 77 (14). Anal. Calcd for C₁₆H₁₇NO₄: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.79; H, 5.79; N, 4.89.

6-Methoxycarbonyl-3-phenyl-2,3-dihydrobenzoxazol-2-one (17). **Methyl 3-Methoxy-4-(*N*-methyl-*N*-phenylamino)benzoate (18).** A mixture of compound (**11**) (0.50 g, 1.84 mmol) in methanol (95%) (10 mL) and NaOH (0.29 g, 7.3 mmol) was stirred at rt for 12 h. The solution was concentrated under vacuum, water (2 mL) added, cooled to 0 °C, and methyl sulfate (1.16 g, 9.19 mmol) was added dropwise. The mixture was stirred at 5 °C for 4 h, and then at rt for 4 h. The mixture was extracted with CH₂Cl₂ (2 x 20 mL), washed with a saturated solution of NH₄Cl (2 x 20 mL) and dried (Na₂SO₄). The solvent was removed under vacuum, and the crude purified by column chromatography on silica gel (hexane/EtOAc, 9:1) to give 0.1 g (20%) of **17**, and 0.09 g (15%) of **18** as white powders. Data of **17**: mp 128-129 °C

(hexane/EtOAc/CH₂Cl₂, 8:1:1). *R_f* 0.60 (hexane/EtOAc, 1:1). IR (KBr) 1722, 1607, 1482, 1242 cm⁻¹; ¹H NMR (CDCl₃) δ 3.95 (s, 3H, CO₂CH₃), 7.11 (d, *J* = 8.8 Hz, 1H, H-4), 7.45-7.63 (m, 5H, PhH), 7.93-7.98 (m, 2H, H-5, H-7); ¹³C NMR (CDCl₃) δ 52.4 (CO₂CH₃), 108.7 (C-4), 111.4 (C-7), 125.1 (C-11), 125.4 (C-6), 126.5 (C-5), 128.8 (C-13), 130.0 (C-12), 132.9 (C-3a or C-10), 135.0 (C-10 or C-3a), 142.2 (C-7a), 153.0 (C-2), 166.1 (CO₂CH₃); MS (70 eV) 269 (M⁺, 99), 238 (100), 194 (28), 166 (24), 154 (39), 127 (8), 77 (34). HRMS (FAB⁺, *m*NBA) Calcd for C₁₅H₁₁NO₄: 269.0689. Found: 269.0688. Data of **18**: mp 194-195 °C (hexane/CH₂Cl₂, 7:3). *R_f* 0.67 (hexane/EtOAc, 1:1). IR (KBr) 1713, 1597, 1500, 1438, 1337, 1270, 1233, 1122, 1024 cm⁻¹. ¹H NMR (CDCl₃) δ 3.23 (s, 3H, NCH₃), 3.83 (s, 3H, CO₂CH₃ or OCH₃), 3.86 (s, 3H, OMe or CO₂CH₃), 6.63 (d, *J* = 7.8 Hz, 2H, H-8), 6.75 (t, *J* = 7.3 Hz, 1H, H-10), 7.00 (d, *J* = 8.4 Hz, 1H, H-5), 7.15-7.20 (m, 2H, H-9), 7.90 (d, *J* = 2.4 Hz, 1H, H-2), 7.95 (dd, *J* = 8.4, 2.4 Hz, 1H, H-6); ¹³C NMR (CDCl₃) δ 39.1 (NCH₃), 51.9 (CO₂CH₃), 55.8 (OCH₃), 111.7 (C-2), 113.6 (C-8), 117.6 (C-5), 123.2 (C-1), 128.8 (C-9), 129.0, 130.5, 136.5, 149.0, 159.8, 166.5 (CO₂CH₃); MS (70 eV) 271 (M⁺, 100), 256 (19), 240 (13), 208 (14), 196 (38), 181 (27), 168 (29), 104 (16), 91 (37). Anal. Calcd for C₁₆H₁₇NO₃: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.57; H, 6.46; N, 4.97.

Methyl 3-Methoxy-4-phenylaminobenzoate (16). A mixture of compound (**11**) (0.50 g, 1.85 mmol) in a mixture of methanol/H₂O (5:2) (10 mL) and KOH (0.31 g, 5.55 mmol) was stirred and heated to 65 °C for 12 h. The solution was concentrated under vacuum, CH₂Cl₂ (20 mL) was added, and washed with a 10% aqueous solution of HCl until pH = 5. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL), and the combined organic layers were dried (Na₂SO₄). The solvent was removed under vacuum, and the brown solid crude was dissolved in acetone (5 mL). To this solution, dimethyl sulfate (0.35 g, 2.77 mmol) and potassium carbonate (0.38 g, 2.77 mmol) were added at rt, and the mixture was heated to 65 °C for 3 h. The mixture was filtered, the solvent was removed under vacuum, and the crude purified by column chromatography on silica gel treated with 10% of triethylamine in hexane (hexane/EtOAc, 8:2) to give 0.31 g (65%) of **16** as a white powder: mp 179-180 °C (hexane/CH₂Cl₂, 6:4). *R_f* 0.63 (hexane/EtOAc, 1:1). IR (KBr) 3344, 1696, 1592, 1523, 1297, 1231 cm⁻¹; ¹H NMR (CDCl₃) δ 3.88 (s, 3H, OCH₃), 3.95 (s, 3H, CO₂CH₃), 6.55 (br s, 1H, NH), 7.02-7.09 (m, 1H, H-10), 7.19-7.40 (m, 2H, H-5, H-8), 7.34 (dd, *J* = 8.2, 7.6 Hz, 2H, H-9), 7.51 (d, *J* = 1.8 Hz, 1H, H-2), 7.59 (dd, *J* = 8.2, 1.8 Hz, 1H, H-6); ¹³C NMR (CDCl₃) δ 51.8 (CO₂CH₃), 56.7 (OCH₃), 110.7 (C-5), 110.8 (C-2), 119.9 (C-1), 120.7 (C-8), 122.9 (C-10), 123.8 (C-6), 129.4 (C-9), 138.1 (C-4 or C-7), 140.6 (C-7 or C-4), 146.4 (C-3), 167.1 (CO₂CH₃); MS (70 eV) 257 (M⁺, 100), 242 (5), 226 (25), 208 (7), 181 (17), 154 (30), 128 (9), 107 (14), 91 (26), 77 (41). HRMS (FAB⁺, *m*NBA) Calcd for C₁₅H₁₅NO₃: 257.1052. Found: 257.1052.

Mukonine (1).^{6a} A mixture of **16** (0.30 g, 1.17 mmol) and palladium acetate (0.39 g, 1.75 mmol) in glacial acetic acid (5 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N₂ atmosphere. The mixture was stirred and heated to 160 °C for 12 h. The mixture was filtered, diluted with water (20 mL), neutralized with an aqueous saturated solution of NaHCO₃, and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phase was dried (Na₂SO₄), and the solvent was removed under vacuum. The crude was purified by column chromatography on silica gel treated with

10% of triethylamine in hexane (100 g, hexane/EtOAc, 8:2) to give 0.19 g (63%) of **1** as a white solid: mp 197-198 °C [lit.,⁴ 195 °C]. *R_f* 0.78 (hexane/EtOAc, 1:1). IR (KBr) 3339, 1676, 1610, 1591, 1496, 1448, 1356, 1265, 1032, 747 cm⁻¹. ¹H NMR (acetone-*d*₆) δ 3.92 (s, 3H, CO₂CH₃), 4.07 (s, 3H, OCH₃), 7.26 (dd, *J* = 7.6, 7.0 Hz, 1H, H-6), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1H, H-7), 7.59 (s, 1H, H-2), 7.65 (d, *J* = 8.2 Hz, 1H, H-8), 8.21 (d, *J* = 7.6 Hz, 1H, H-5), 8.48 (s, 1H, H-4), 10.84 (br s, 1H, NH); ¹³C NMR (acetone-*d*₆) δ 52.2 (CO₂CH₃), 56.3 (OCH₃), 107.3 (C-2), 112.8 (C-8), 116.8 (C-4), 120.9 (C-6), 121.5 (C-5), 122.6 (C-3), 124.5 (Cq), 124.55 (Cq), 127.3 (C-7), 134.2 (Cq), 141.5 (Cq), 146.5 (C-1), 168.2 (CO₂CH₃); MS (70 eV) 255 (M⁺, 100), 240 (48), 224 (46), 212 (13), 196 (19), 181 (31), 153 (43), 139 (10), 126 (33), 87 (7), 63 (14).

X-Ray Structure Determination of 14b. Crystal data: C₁₆H₁₇NO₄; *M* = 287.31; triclinic; space group P-1; *a* = 7.2018 (9), *b* = 8.487 (2), *c* = 12.202 (2) Å; α = 105.56 (2)°, β = 90.064 (12)°, γ = 91.001 (14)°; *V* = 718.3 (2) Å³, *Z* = 2; *D* = 1.328 mg/m³; absorption coefficient: 0.096 mm⁻¹; No. of reflections collected: 3865; No. of independent reflections: 3107; No. of observed reflections: 3089; *R* = 0.0545, *R_w* = 0.0839; goodness of fit on *F*² = 1.033.⁹

ACKNOWLEDGEMENTS

We are grateful to Dr. Hugo A. Jiménez-Vázquez for reviewing the manuscript. We thank Fernando Labarrios for his help in spectrometric measurements. J.T. acknowledges CGPI/IPN (Grants 200410 and 32.14) and CONACYT (Grant 32273-E) for financial support. A.Z. thanks CONACYT for a graduate scholarship awarded, and the Ludwig K. Hellweg Foundation for a scholarship complement.

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