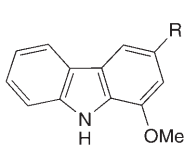
Total Synthesis of Murrayanine Involving 4,5-Dimethyleneoxazolidin-2-ones and a Palladium(0)-Catalyzed Diaryl Insertion

by **Pablo Bernal** and **Joaquín Tamariz***

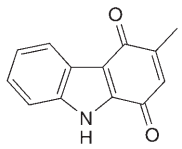
Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala, 11340 México, D.F. Mexico (phone: (+5255)5729-6300/62411; fax: (+5255)5729-6300/46211; e-mail: jtamariz@woodward.encb.ipn.mx)

A new total synthesis of the natural carbazole murrayanine (**1**) was developed by using the 4,5-dimethyleneoxazolidin-2-one **12** as starting material. The latter underwent a highly regioselective *Diels–Alder* cycloaddition with acrylaldehyde (= prop-2-enal; **13**) to give adduct **14** (*Scheme 3*). Conversion of this adduct into diarylamine derivative **9** was carried out *via* hydrolysis and methylation (*Scheme 4*). Differing from our previous synthesis, in which such a diarylamine derivative was transformed into **1** by a Pd^{II}-stoichiometric cyclization, this new approach comprised an improved cyclization through a more efficient Pd^{0}-catalyzed intramolecular diaryl coupling which was applied to **9**, thus obtaining the natural carbazole **1** in a higher overall yield.

1. Introduction. – Murrayanine (**1**) was the first naturally occurring carbazole alkaloid to be isolated [1]. It was extracted from *Murraya koenigii* SPRENG (Rutaceae) [2] but later also from other species of the genus *Murraya* and *Clausena* [3][1]), and shows significant biological activity [4]. For instance, it has proved to potently inhibit platelet aggregation [3b], act as an antibacterial and antifungal agent [2b][2c], and have cytotoxic activity [3f]. As a result, several total [5] and partial [6] syntheses have been carried out. Interestingly, owing to the fact that carbazole **1** bears a formyl group at C(3), it can be converted into a series of other analogous carbazoles such as koenoline (**2**) [1][2a][5c][5d], mukoeic acid (**3**) [2a], murrayafoline A (**4**) [2a], and murrayaquinone A (**5**) [4][5d], through common functional-group manipulations.



1 R = CHO
2 R = CH_2OH
3 R = COOH
4 R = Me



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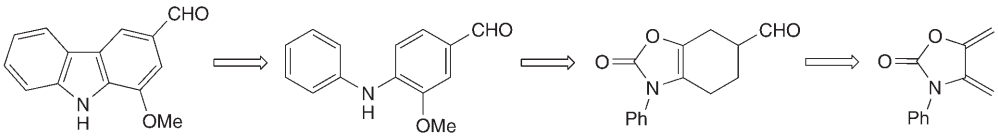
[1]) From *C. lansium*, see [3a]; from *M. euchrestifolia*, see [3b]; from *C. heptaphylla*, see [3c]; from *C. excavata*, see [3d,e]; From *C. dunniana*, see [3f]; from *M. kwangsiensis*, see [3g].

Recently, we have described a total synthesis of carbazole **1** [7] following our general synthetic approach for the preparation of the carbazole scaffold [8]. This approach was based on the regioselective *Diels–Alder* cycloaddition of the 4,5-dimethyleneoxazolidin-2-one **6** [9], whose adduct **7** was transformed into diarylamine derivative **8** through a two-step methodology (*Scheme 1*). The latter was converted into the natural carbazole by a stoichiometric palladium(II) insertion in a 36% overall yield. In fact, the closure of substituted diarylamines to yield the natural carbazole framework by a Pd^{II}-mediated oxidative cyclization has been widely applied in the past [10]. In contrast, the Pd^0-catalyzed insertion process [11] has been useful for the construction of both unsubstituted [12] and substituted carbazoles [13] although it is limited for the total synthesis of natural carbazoles [10][11]. This is probably due to the difficulty in preparing the diarylamine derivative with both the appropriate functionalization and the presence of a halogen atom at a proper position of the arene rings for a feasible intramolecular *Heck* coupling [11].

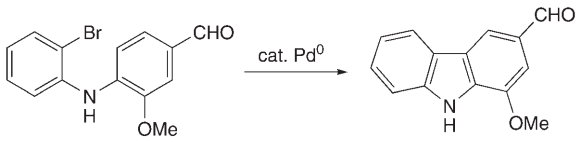
Scheme 1



1 **8** **7** **6**

With the aim of improving our general synthetic approach to carbazoles and, in particular, our synthesis of murrayanine (**1**), we herein present the preparation of **1** by a Pd^0-catalyzed insertion of the properly substituted diarylamine derivative **9** (*Scheme 2*).

Scheme 2

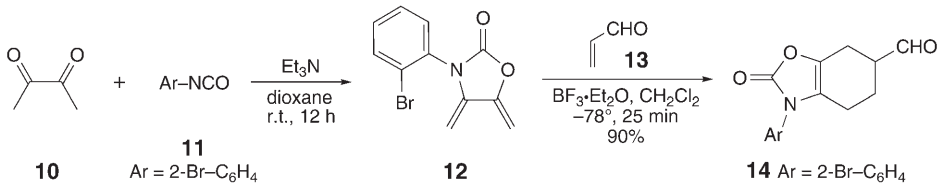


9 **1**

2. Results and Discussion. – 2.1. *Preparation of Dimethyleneoxazolidinone* **12** *and its Regioselective* Diels–Alder *Addition to Acrylaldehyde* (**13**). To achieve the appropriate functionalization of diarylamine derivative **9**, we prepared the (2-bromophenyl)-substituted dimethyleneoxazolidinone **12** and evaluated its regioselectivity in the *Diels–Alder* reaction with acrylaldehyde (= prop-2-enal; **13**) to give the key adduct **14** (*Scheme 3*). Compound **12** has been previously prepared by condensing butane-2,3-dione (**10**) with isocyanate **11** in the presence of Et_3N, lithium carbonate, and dioxane as the solvent [9]. Similarly to the preparation of adduct **7**, the *Diels–Alder* reaction of **12** with **13** occurred satisfactorily by carrying out the process under *Lewis*-acid catalysis.

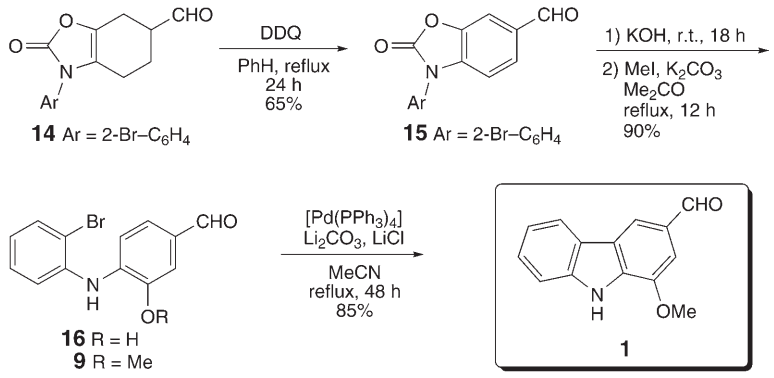
Thus, upon addition of $BF_3 \cdot Et_2O$ to the reaction mixture at $-78°$, the starting materials were completely consumed after 25 min, to provide the desired adduct **14** in high yield (90%), as a single regioisomer. Notably, this cycloaddition was slightly more selective than that between dimethyleneoxazolidinone **6** and **13** [7], but was still much more regioselective than the cycloadditions between **6** and methyl vinyl ketone (= but-3-en-2-one) or methyl propiolate (= methyl prop-2-ynoate) [9] under the same conditions of *Lewis*-acid catalysis and temperature.

Scheme 3



2.2. *Aromatization of Adduct* **14** *and its Transformation into the Natural Carbazole Murrayanine* (**1**). The cyclohexene moiety of adduct **14** was aromatized by using DDQ (= 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) in refluxing benzene, to give 2-oxo-1,3-benzoxazol-6-carboxaldehyde **15** in 65% yield (*Scheme 4*). Differing from the previous synthetic route, where diarylamine derivative **8** was prepared from **7** by a two-step procedure through isolation of its hydrolysis precursor, hydroxydiarylamine derivative **16** was not isolated after hydrolysis of **15** but converted directly into the methoxydiarylamine derivative **9** (*Scheme 4*); otherwise, the yield was largely decreased. Thus, after hydrolysis of **15** under smooth basic conditions (KOH, EtOH/H_2O, 25°, 18 h), the crude mixture was treated with MeI in acetone and the base K_2CO_3 to give **9** in 90% yield.

Scheme 4



Finally, murrayanine (**1**) was efficiently prepared by a Pd^0-catalyzed insertion of the bromodiarylamine derivative **9**. The best conditions furnishing **1** in 85% yield from **9** (1 mol-equiv.) were achieved with 0.02 mol-equiv. of $[Pd(PPh_3)_4]$ catalyst [14] in the presence of Na_2CO_3 (2.0 mol-equiv.) and LiCl (1.0 mol-equiv.) [15] in MeCN under

reflux for 48 h. Spectral and physical data of the product **1** were in agreement with those reported for the natural product [2a][3a]. 2D NMR Experiments (HMQC and HMBC) were performed to assign the signals of the ^{13}C-NMR spectrum of **1** (see *Exper. Part*).

3. Conclusions. – A new total synthesis of the naturally occurring carbazole alkaloid murrayanine (**1**) through a four-step route was described, starting from the (2-bromophenyl)-substituted 4,5-dimethyleneoxazolidin-2-one **12** and achieving a 45% overall yield. The highly regioselective *Diels–Alder* reaction of **12** with acrylaldehyde (**13**) provided the key adduct **14**, which was efficiently converted into diarylamine derivative **9**. In contrast to our previous procedure, the ring-closure process to give the carbazole framework of **1** was accomplished by a Pd^0-catalyzed reaction of the precursor **9**, demonstrating the utility of this methodology for the preparation of natural carbazoles. The application of this approach for the synthesis of other natural carbazoles is currently under investigation, and the results will be described in due course.

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Experimental Part

General. All air-moisture-sensitive reactions were carried out under N_2 in oven-dried glassware. Benzene was freshly distilled from Na, and CH_2Cl_2 and MeCN from CaH_2. Li_2CO_3 and Na_2CO_3 were dried overnight at 120° prior to use. Et_3N was distilled from NaOH. All other reagents were used without further purification. Compound **12** was prepared as reported [9]. Anal. TLC: *E. Merck* silica gel *60 F_{254}*-coated plates; visualization by a long- and short-wavelength UV lamp. CC = Column chromatography.

M.p.: uncorrected; *Electrothermal* capillary melting-point apparatus. IR Spectra: *Perkin-Elmer 1600* spectrophotometer; in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75.4 MHz) Spectra: *Varian Mercury-300* instrument; in $CDCl_3$ with Me_4Si as internal standard; δ in ppm, J in Hz. MS: EI mode (70 eV); *Thermo-Finnigan Polaris Q* spectrometer. HR-MS: FAB mode (*m*NBA); *Jeol JMS-AX-505-HA* spectrometer.

3-(2-Bromophenyl)-2,3,4,5,6,7-hexahydro-2-oxobenzoxazol-6-carboxaldehyde (**14**). To a stirred soln. of **12** (0.5 g, 1.9 mmol) and prop-2-enal (**13**; 0.32 g, 5.7 mmol) in anh. CH_2Cl_2 (50 ml) at −78° under N_2, $BF_3 \cdot Et_2O$ (0.081 g, 0.57 mmol) was added dropwise, and the mixture was stirred for 25 min at −78°. The mixture was diluted with CH_2Cl_2 (15 ml) and added to H_2O (10 ml). The aq. layer was washed with CH_2Cl_2 (3 × 15 ml), the combined org. phase washed with 5% aq. $NaHCO_3$ soln. (3 × 15 ml) and 5% aq. NH_4Cl soln. (2 × 15 ml) and dried (Na_2SO_4), the solvent evaporated, and the residue purified by CC (silica gel (20 g), hexane/AcOEt 8:2): 0.54 g (90%) of **14**. Pale redish oil. TLC (hexane/AcOEt, 7:3): R_f 0.27. IR (film): 1767, 1716, 1485, 1399, 1176, 1054, 981, 765, 727. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.88–2.02 (*m*, 1 H−C(5), 1 H−C(7)); 2.04–2.34 (*m*, 2 H−C(4), 1 H−C(5)); 2.71–2.92 (*m*, H−C(6), 1 H−C(7)); 7.22–7.48 (*m*, H−C(4′), H−C(5′), H−C(6′)); 7.67–7.74 (*m*, H−C(3′)), 9.74 (*d*, J = 0.8, CHO). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 18.2 (C(4)); 20.7 (C(7)); 21.4 (C(5)); 45.6 (C(6)); 121.7 (C(3a)); 123.1 (C(2′)); 128.6 (C(5′)); 130.3 (C(6′)); 130.9 (C(4′)); 132.6 (C(7a) or C(1′)); 133.2 (C(1′) or C(7a)); 133.7 (C(3′)); 154.5 (C(2)); 201.5 (CHO). EI-MS (70 eV): 323 (4, M^+ (^{81}Br)), 321 (4, M^+ (^{79}Br)), 295 (18), 293 (20), 251 (26), 249 (25), 214 (20), 197 (20), 186 (80), 170 (100), 156 (30), 142 (22), 130 (18), 115 (12). HR-FAB-MS: 320.9998 (M^+, $C_{14}H_{12}BrNO_3^+$; calc. 321.0001).

3-(2-Bromophenyl)-2,3-dihydro-2-oxobenzoxazol-6-carboxaldehyde (**15**). To a stirred soln. of **14** (0.50 g, 1.55 mmol) in anh. benzene (15 ml) under reflux and N_2, DDQ (0.44 g, 1.94 mmol) was added,

and the suspension was stirred for 12 h under reflux. Then, more DDQ (0.44 g, 1.94 mmol) was added, and the reflux was maintained for 12 h. The mixture was filtered over *Celite*, the solvent evaporated, and the residue purified by CC (silica gel (20 g), hexane/CH_2Cl_2 1:1): 0.32 g (65%) of **15**. White solid. TLC (hexane/AcOEt 7:3): R_f 0.42. M.p. 150–151° (hexane/CH_2Cl_2 7:3). IR (KBr): 1791, 1691, 1606, 1500, 1478, 1450, 1380, 1354, 1287, 1252, 1156, 983, 765, 715. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.86 (*d*, *J* = 7.8, H–C(4)); 7.43–7.60 (*m*, H–C(4′), H–C(5′), H–C(6′)); 7.74 (*dd*, *J* = 7.8, 1.2, H–C(5)); 7.82 (*dd*, *J* = 8.2, 1.2, H–C(3′)); 7.83 (*d*, *J* = 1.2, H–C(7)); 9.98 (*s*, CHO). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 109.5 (C(4)); 110.1 (C(7)); 122.5 (C(2′)); 128.2 (C(5)); 129.2 (C(5′)); 130.0 (C(6′)); 131.5 (C(1′)); 131.8 (C(4′)); 132.4 (C(6)); 134.4 (C(3′)); 136.4 (C(3a)); 143.0 (C(7a)); 156.7 (C(2)); 190.3 (CHO). EI-MS (70 eV): 238 (100, $[M-HBr]^+$), 209 (8), 181 (6), 166 (20), 140 (6), 126 (2). HR-FAB-MS: 317.9772 ($[M+1]^+$, $C_{14}H_9{}^{79}BrNO_3^+$; calc. 317.9766).

4-[(2-Bromophenyl)amino]-3-methoxybenzaldehyde (**9**). A mixture of **15** (0.28 g, 0.88 mmol) and KOH (0.197 g, 3.52 mmol) in EtOH/H_2O 7:3 (5 ml) at 20° was stirred for 18 h. The mixture was neutralized with 5% aq. HCl soln., the solvent evaporated, the residue dissolved in CH_2Cl_2 (10 ml), and H_2O (5 ml) added. The aq. layer was washed with CH_2Cl_2 (3 × 10 ml), the combined org. phase dried (Na_2SO_4) and the solvent evaporated. The residue was dissolved in acetone (10 ml), and K_2CO_3 (0.304 g, 2.20 mmol) and MeI (0.374 g, 2.63 mmol) were added. The mixture was heated under reflux for 12 h and then filtered over *Celite* washing with acetone (3 × 10 ml), and the solvent was evaporated. The residue was purified by CC (silica gel (28 g), hexane/AcOEt 9:1): 0.24 g (90%) of **9**. White solid. TLC (hexane/AcOEt 4:1): R_f 0.40. M.p. 95–96° (hexane/AcOEt/CH_2Cl_2 8:1:1). IR (KBr): 3391, 1678, 1579, 1527, 1488, 1462, 1354, 1294, 1261, 1157, 1129, 1032, 749. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.00 (*s*, MeO); 6.92 (br. *s*, NH); 6.95 (*td*, *J* = 7.8, 1.6, H–C(4′)); 7.23 (*d*, *J* = 8.2, H–C(5)); 7.30 (*td*, *J* = 7.8, 1.6, H–C(5′)); 7.37 (*dd*, *J* = 8.2, 1.6, H–C(6)); 7.42 (*d*, *J* = 1.6, H–C(2)); 7.51 (*dd*, *J* = 7.8, 1.6, H–C(6′)); 7.62 (*dd*, *J* = 7.8, 1.6, H–C(3′)); 9.79 (*s*, CHO). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 55.9 (MeO); 108.0 (C(2)); 111.1 (C(5)); 116.3 (C(2′)); 120.8 (C(6′)); 124.2 (C(4′)); 127.3 (C(6)); 128.1 (C(5′)); 128.7 (C(1)); 133.4 (C(3′)); 138.1 (C(1′)); 138.7 (C(4)); 147.7 (C(3)); 190.3 (CHO). EI-MS (70 eV): 307 (10, M^+ (^{81}Br)), 305 (10, M^+ (^{79}Br)), 211 (100), 182 (10), 154 (6). HR-FAB-MS: 305.0051 (M^+, $C_{14}H_{12}{}^{79}BrNO_2^+$; calc. 305.0051).

Murrayanine (=*1-Methoxy-9*H*-carbazole-3-carboxaldehyde*; **1**). A mixture of **9** (0.07 g, 0.23 mmol), [$Pd(PPh_3)_4$] (0.0053 g, 0.0046 mmol), Na_2CO_3 (0.048 g, 0.45 mmol), and LiCl (0.00978 g, 0.23 mmol), in dry MeCN (1 ml) was stirred and heated under reflux and N_2 for 48 h. The mixture was diluted with MeCN (10 ml) and filtered, and the residue on the filter was washed with MeCN (10 ml). The solvent was evaporated and the residue purified by CC (silica gel (10 g), hexane/AcOEt, 9:1): 0.044 g (85%) of **1**. White solid. TLC (hexane/AcOEt 7:3): R_f 0.42. M.p. 167–168° ([3a][7]: 167–168°; [2a]: 168°; [5a]: 166.5°). IR (KBr): 3165, 1659, 1608, 1579, 1500, 1451, 1342, 1239, 1140, 846, 726. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.05 (*s*, MeO); 7.32 (*ddd*, *J* = 7.8, 7.2, 1.6, H–C(6)); 7.45 (br. *s*, H–C(2)); 7.46–7.55 (*m*, H–C(7), H–C(8)); 8.10 (br. *d*, *J* = 7.8, H–C(5)); 8.18 (br. *s*, H–C(4)); 8.72 (br. *s*, NH); 10.04 (*s*, CHO). ^{13}C-NMR (75.4 MHz, $CDCl_3$): 55.7 (MeO); 103.4 (C(2)); 111.5 (C(8)); 120.5 (C(4)); 120.6 (C(5), C(6)); 123.5 (C(4a) or C(4b)); 123.6 (C(4b) or C(4a)); 126.6 (C(7)); 130.0 (C(3)); 134.0 (C(9a)); 139.4 (C(8a)); 146.0 (C(1)); 192.0 (CHO). EI-MS (70 eV): 225 (3, M^+), 210 (5), 182 (4), 154 (100), 139 (9), 128 (26), 127 (18), 73 (26).

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