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A concise total synthesis of the natural carbazole clauraila A

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A short and efficient total synthesis of naturally occurring carbazole clauraila A (**1**) is described. The approach is designed on the basis of the key regioselective Diels-Alder reaction of the properly substituted *exo*-2-oxazolidinone diene **3** with acrolein (**4**) to give the corresponding adduct **2**. The latter is converted to functionalised diarylamine **8**, which is cyclised to the desired carbazole **1** through a Pd-promoted or -catalysed double C—H bond activation process in a fairly good overall yield.

Keywords: 1-methoxycarbazoles; 4,5-dimethylene-2-oxazolidinone dienes; clauraila A; Pd(II) cyclisation; C—H bond activation

1. Introduction

Among the new naturally occurring clauraila carbazoles recently extracted from the roots of *Clausena harmandiana* (Rutaceae), clauraila A (**1**) exhibits a significant selective cytotoxicity against human lung cancer cells (NCI-H187), but not against normal cells (Songsiang, Thongthoom, Boonyarat, & Yenjai, 2011). Interestingly, this plant is currently used in Thai traditional folk medicine for treating headaches, stomach aches and stomach sickness (Yenjai et al., 2000).

Clauraila A (**1**) is a 1-oxygenated carbazole, as are many biologically active carbazoles isolated from the *Clausena* genus (Knölker & Reddy, 2002, 2008). Both the 1-methoxy and 3-formyl groups seem to be the responsible pharmacophores for its anticancer activity (Songsiang et al., 2011). Owing to the broad and important pharmacological activity and applications in materials science (Sridharan, Martín, & Menéndez, 2009) of carbazoles, an intense effort has been generated for accomplishing the synthesis of natural carbazoles (Knölker & Reddy, 2002, 2008; Schmidt, Reddy, & Knölker, 2012), including clauraila A (**1**) (Yang, Zhou, Wang, & Ren, 2011) and clausine Q (Fuchsenberger, Forke, & Knölker, 2011), among other 1,7-dioxygenated carbazole alkaloids.

Previously we described a novel methodology for the preparation of the carbazole scaffold (Mandal, Delgado, & Tamariz, 1998), which was applied to the total synthesis of 1-methoxycarbazoles such as mukonine (Zempoalteca & Tamariz, 2002), murrayanine, murrayafoline A (Benavides, Peralta, Delgado, & Tamariz, 2004; Bernal & Tamariz, 2007), 6-methoxymurrayanine, clausenine (Bernal, Benavides, Bautista, & Tamariz 2007) and glycozolicine, mukolidine and mukoline (Bautista, Bernal, Montiel, Delgado, & Tamariz, 2011). Considering the relevant anticancer activity of carbazole **1** and the interest in testing the

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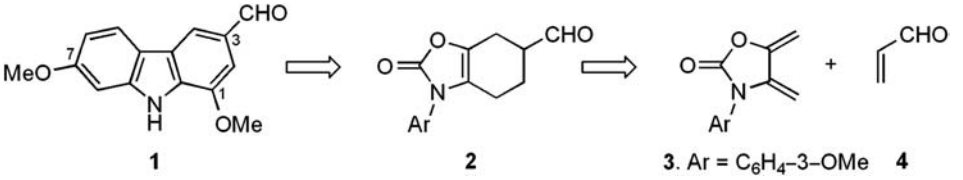


Scheme 1. Retrosynthetic analysis of naturally occurring carbazole **1**.

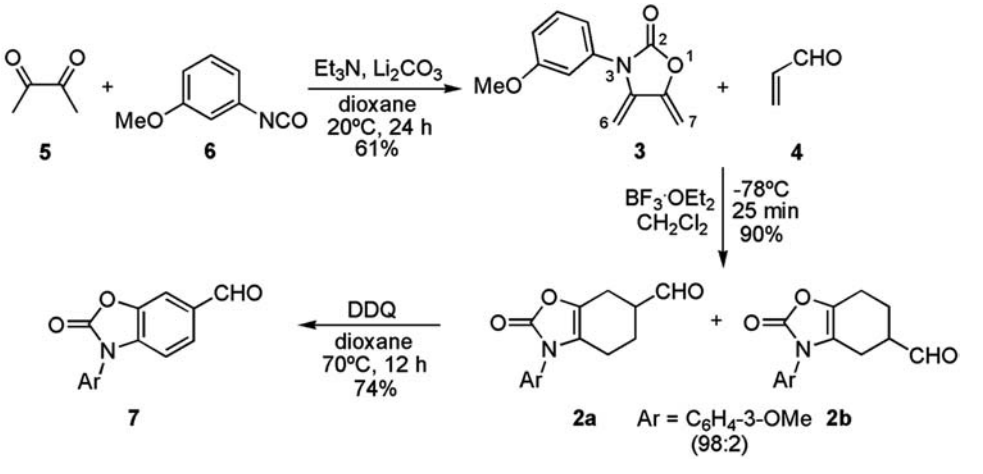
versatility and effectiveness of our methodology, we herein report a new total synthesis of **1**, involving the *exo*-2-oxazolidinone diene **3** in a Diels-Alder cycloaddition, which provides the corresponding adduct **2**, followed by an efficient transformation to the carbazole alkaloid natural product (Scheme 1).

2. Results and discussion

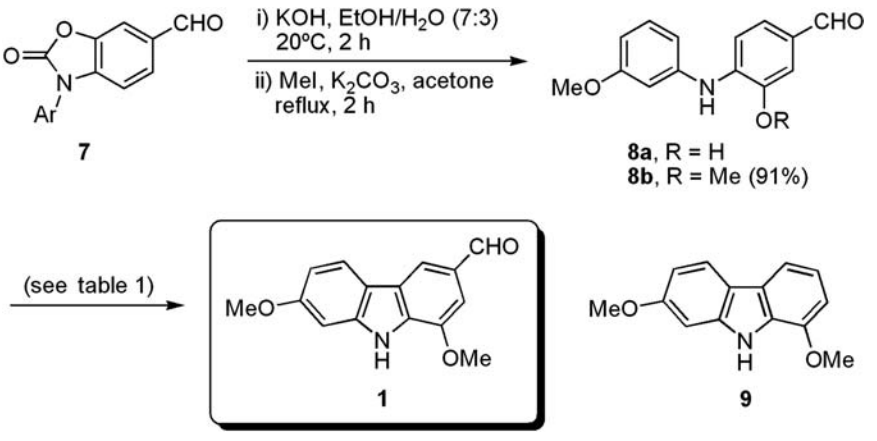
Preparation of diene **3** involved the condensation of diacetyl (**5**) with 3-methoxyphenylisocyanate (**6**) under the reported reaction conditions (Bernal et al., 2007) to afford the desired product in 61% yield (Scheme 2). The modest yield was due to the instability of this new diene, which contrasts with all the similar dienes nowadays described (Fuentes et al., 2005; Mandal et al., 1997). Consequently, once the workup is finished, the crude mixture must be immediately purified and the product kept refrigerated to avoid its decomposition.

The Diels-Alder cycloaddition of diene **3** to acrolein (**4**) under Lewis acid catalysis ($BF_3{\cdot}OEt_2$), at low temperature (− 78°C) for 25 min, yielded a mixture of the *para/meta* (relative position of the formyl group with respect to the nitrogen atom in the cyclohexene ring) adducts **2a/2b** (98:2) in high regioselectivity (Scheme 2), as determined in the crude mixture by ^{1}H NMR. This mixture was separated by column chromatography to obtain the desired adduct **2a** in high yield (90%) as a stable colourless oil. Aromatisation of the cyclohexene ring moiety of adduct **2a** was carried out with 4,5-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in dry dioxane at 70°C for 12 h to furnish benzoxazol-2-one **7** in 74% yield (Scheme 2).

With the aim of isolating diarylamine **8a**, saponification of **7** was carried out under mild conditions (KOH, EtOH/H_2O, 20°C, 2 h) (Scheme 3). Although **8a** was identified by ^{1}H NMR of



Scheme 2. Synthesis of benzoxazol-2-one **7** from 2-oxazolidinone diene **3**.



Scheme 3. Transformation of benzoxazol-2-one **7** to natural carbazole **1**.

the crude mixture, its instability under the purification conditions over silica gel or neutral alumina did not allow us to obtain a sample pure enough to be characterised. This is probably due to its propensity to be oxidised to polar quinoid side-products (Mandal et al., 1998). Therefore, following the previous methodology (Bautista et al., 2011), **7** was hydrolysed under the same mild conditions and, without purification, the resulting crude mixture was treated with methyl iodide along with K_2CO_3, affording diarylamine **8b** in high yield (91%).

The insertion of the benzene rings of diarylamine **8b** to give the natural product **1** was attempted by the Pd(II)-catalysed oxidative cyclisation, via a double C—H activation process (Bauer & Knölker, 2012; Bedford & Betham, 2006; Campeau & Fagnou, 2006; Knölker, 2005, 2009; Knölker & Fröhner, 1998; Knölker, Fröhner, & Reddy, 2002; Knölker & Knöll, 2003; Knölker, & Reddy, 2003; Krahl, Jäger, Krause, & Knölker, 2006) in accordance with a known protocol (Forke, Krahl, Krause, Schlechtingen, & Knölker, 2007; Schmidt & Knölker, 2009; Sridharan et al., 2009). However, instead of the desired product, the decarbonylated compound **9** was obtained in good yield (70%) (Table 1, entry 1), in agreement with our previous results (Bautista et al., 2011). In order to avoid the loss of the formyl group, the reaction was carried out under similar conditions but with a decreased reaction temperature (Table 1, entry 2). Indeed, the change of temperature furnished the desired product **1**, albeit in a modest yield (60%). An improvement of the yield was accomplished when **8b** was subjected to Pd(II)-promoted insertion conditions (Table 1, entry 3), by using stoichiometric amounts of $Pd(OAc)_2$ (Knölker & O'Sullivan, 1994), to give carbazole **1** in 75% yield. Spectroscopic data and mp of **1** were in agreement with those reported for the natural (Songsiang et al., 2011) and synthetic product (Yang et al., 2011).

Table 1. Yields of carbazoles **1** and **9** obtained by Pd(II) insertion of diarylamine **8b**.[a]

Entry	$Pd(OAc)_2$ (mol equiv.)	$Cu(OAc)_2$ (mol equiv.)	Solvent	MW (watts)	T (°C)	t	Product (%)[b]
1	0.1	2.5	DMF	100	130	70 min	**9** (70)
2	0.1	2.5	DMF	100	90	3 h	**1** (60)
3	1.1	–	AcOH	–	140	24 h	**1** (75)

[a] Reaction conditions: **8b** (1.0 mol equiv.).
[b] After column chromatography.

3. Experimental

3.1. General

Melting points (uncorrected) were determined with an electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian VNMR System instruments, with TMS as internal standard. Mass spectra (MS) and high-resolution mass spectra (HR-MS) were obtained, in electron impact (EI) (70 eV) mode on Thermo-Finnigan Polaris Q and on Jeol JSM-GcMateII spectrometers, respectively. Microwave (MW) irradiation was carried out on a CEM MW reactor. Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualised by a long- and short-wavelength UV lamp. Flash column chromatography was carried out over Natland International Co. silica gel, N.C. 27709, USA (230–400 mesh). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Dioxane was freshly distilled over sodium, and DMF and methylene chloride over calcium hydride, prior to use. Acetone was dried by distillation after treatment with potassium permanganate, followed by a second distillation over anhydrous sodium sulphate. K_2CO_3 and Li_2CO_3 were dried overnight at 200°C prior to use. Triethylamine was freshly distilled from KOH. All other reagents were used without further purification.

3.2. Procedures

*3.2.1. 3-(3-Methoxyphenyl)-4,5-dimethylene-1,3-oxazolidin-2-one (**3**)*

A mixture of **5** (0.49 g, 5.7 mmol) in anhydrous dioxane (15 mL), triethylamine (1.15 g, 11.4 mmol) and Li_2CO_3 (4.22 g, 57.0 mmol) was kept in the dark and stirred at 20°C under N_2 atmosphere for 1 h. Then, a solution of **6** (1.270 g, 8.55 mmol) in anhydrous dioxane (10 mL) was added over a period of 1 h and stirred for 24 h at 20°C. The mixture was filtered over Celite, the residue washed with CH_2Cl_2 (3 × 15 mL) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel impregnated with triethylamine (10%) (10 g/g of crude, hexane–EtOAc, 95:5), to give 0.75 g (61%) of **3** as a colourless oil. R_f 0.37 (hexane–EtOAc, 4:1); IR (KBr): ν_{max} 1777, 1664, 1634, 1517, 1405, 1292, 1255, 1058, 988, 881, 832 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 4.39 (d, $J = 3.0$ Hz, 1H, H-6), 4.76 (d, $J = 3.0$ Hz, 1H, H-6), 4.92 (d, $J = 3.5$ Hz, 1H, H-7), 4.97 (d, $J = 3.5$ Hz, 1H, H-7), 6.88 (t, $J = 2.5$ Hz, 1H, H-2′), 6.91–6.98 (m, 2H, H-4′, H-6′), 7.40 (t, $J = 8.5$ Hz, 1H, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5 (OCH_3), 84.7 (C-6), 86.9 (C-7), 112.6 (C-2′), 114.6 (C-4′), 119.0 (C-6′), 130.4 (C-5′), 134.0 (C-1′), 138.8 (C-4), 148.8 (C-5), 152.2 (C-2), 160.6 (C-3′); MS (70 eV): *m/z* (%) 217 (M^+, 100), 186 (27), 158 (33), 133 (34), 121 (69), 103 (54), 77 (20); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{12}H_{11}NO_3$: 217.0739; found: 217.0739.

*3.2.2. 6-Formyl-3-(3-methoxyphenyl)-2,3,4,5,6,7-hexahydrobenzoxazol-2-one (**2a**)*

To a stirred solution of **3** (0.200 g, 0.92 mmol) in anhydrous CH_2Cl_2 (20 mL), at − 78°C under N_2 atmosphere, **4** (0.155 g, 2.76 mmol) and $BF_3{\cdot}Et_2O$ (0.026 g, 0.18 mmol) were added dropwise, and the mixture was stirred for 25 min at the same temperature. The mixture was diluted with CH_2Cl_2 (15 mL) and poured into H_2O (10 mL). The organic layer was washed with a 5% aqueous solution of $NaHCO_3$ (2 × 5 mL) and with a 5% aqueous solution of NH_4Cl (2 × 5 mL), dried (Na_2SO_4) and the solvent was removed under vacuum, giving a mixture of **2a/2b** (98:2). The residue was purified by column chromatography over silica gel (20 g, hexane–EtOAc, 8:2), to give 0.23 g (90%) of **2a** as a colourless oil. R_f 0.14 (hexane–EtOAc, 7:3); IR (film): ν_{max} 1760, 1713, 1604, 1495, 1396, 1266, 1252, 1041, 997, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87-1.98 (m, 1H, H-5), 2.12–2.22 (m, 1H, H-5), 2.35–2.43 (m, 2H, H-4), 2.68–2.87 (m, 2H,

H-6, H-7), 3.81 (s, 3H, OCH_3), 6.82–6.94 (m, 3H, H-2′, H-4′, H-6′), 7.29–7.36 (m, 1H, H-5′), 9.73 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2 (C-4), 20.7 (C-7), 21.7 (C-5), 45.4 (C-6), 55.4 (CH_3O), 111.1 (C-2′), 113.4 (C-4′), 117.2 (C-6′), 120.9 (C-3a), 130.1 (C-5′), 133.3 (C-7a), 134.8 (C-1′), 154.3 (C-2), 160.3 (C-3′), 201.6 (CHO); MS (70 eV): *m/z* (%) 273 (M^+, 71), 245 (44), 200 (31), 173 (42), 160 (44), 147 (100), 107 (13), 77 (22); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.1005.

*3.2.3. 6-Formyl-3-(3-methoxyphenyl)-2,3-dihydrobenzoxazol-2-one (**7**)*

A mixture of **2a** (0.150 g, 0.55 mmol) in anhydrous dioxane (15 mL) and DDQ (0.25 g, 1.1 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, and heated at 70°C for 12 h. The mixture was filtered on a Büchner funnel packed with Celite (lower layer) and silica gel (upper layer) (2:3), and washed with CH_2Cl_2 (4 × 15 mL). The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel (20 g/g of crude, hexane–EtOAc, 95:5) to give 0.11 g (74%) of **7** as a white solid. R_f 0.41 (hexane–EtOAc, 7:3); mp 134–135°C; IR (KBr): ν_{max} 1788, 1684, 1606, 1498, 1451, 1282, 1248, 1165, 997, 820, 784 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3), 7.03 (ddd, J = 8.5, 2.5, 1.0 Hz, H-4′), 7.08 (dd, J = 2.5, 2.0 Hz, 1H, H-2′), 7.12 (ddd, J = 8.5, 2.0, 1.0 Hz, H-6′), 7.22 (d, J = 8.0 Hz, H-4), 7.49 (t, J = 8.5 Hz, 1H, H-5′), 7.75 (dd, J = 8.0, 1.5 Hz, 1H, H-5), 7.80 (d, J = 1.5 Hz, 1H, H-7), 9.97 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5 (OCH_3), 109.6 (C-4), 109.8 (C-7), 111.0 (C-2′), 114.6 (C-4′), 117.1 (C-6′), 128.2 (C-5), 130.7 (C-5′), 132.2 (C-6), 133.5 (C-1′), 136.3 (C-3a), 142.8 (C-7a), 152.7 (C-2), 160.6 (C-3′), 190.3 (CHO); MS (70 eV): *m/z* (%) 269 (M^+, 100), 268 (58), 240 (6), 224 (13), 182 (14), 154 (26), 127 (7), 77 (8); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{15}H_{11}NO_4$: 269.0688; found: 269.0683.

*3.2.4. 3-Methoxy-4-(3-methoxyphenylamino)benzaldehyde (**8b**)*

A mixture of **7** (0.121 g, 0.45 mmol) and KOH (0.10 g, 1.8 mmol) in a mixture of EtOH–H_2O (7:3) (10 mL) was stirred at 20°C for 2 h. The mixture was neutralised with 10% aqueous solution of HCl, and was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was mixed with MeI (0.097 g, 0.68 mmol) and K_2CO_3 (0.094 g, 0.68 mmol) in anhydrous acetone (20 mL), and was heated to reflux for 2 h. The solvent was removed under vacuum, the residue was purified by column chromatography over silica gel (20 g/g of crude, hexane–EtOAc, 9:1) to give 0.105 g (91%) of **8b** as a pale yellow oil. R_f 0.48 (hexane–EtOAc, 7:3); IR (film): ν_{max} 3302, 1668, 1596, 1510, 1461, 1302, 1251, 1157, 1126, 1031, 813, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3-3′), 3.96 (s, 3H, OCH_3-3), 6.66 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H, H-4′), 6.72 (br s, 1H, NH), 6.80 (dd, J = 2.5, 2.0 Hz, 1H, H-2′), 6.83 (br dd, J = 8.0, 2.0 Hz, 1H, H-6′), 7.26 (t, J = 8.0 Hz, 1H, H-5′), 7.28 (d, J = 8.0 Hz, 1H, H-5), 7.35 (dd, J = 8.0, 1.5 Hz, 1H, H-6), 7.38 (d, J = 1.5 Hz, 1H, H-2), 9.76 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.3 (OCH_3-C3′), 55.8 (OCH_3-C3), 107.2 (C-2′), 107.7 (C-2), 109.0 (C-4′), 110.6 (C-5), 113.7 (C-6′), 127.8 (C-6), 127.9 (C-1), 130.2 (C-5′), 140.0 (C-4), 141.2 (C-1′), 147.1 (C-3), 160.6 (C-3′), 190.4 (CHO); MS (70 eV): *m/z* (%) 257 (M^+, 100), 242 (29), 211 (73), 198 (31), 183 (16), 154 (14), 121 (20); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{15}H_{15}NO_3$: 257.1052; found: 257.1057.

*3.2.5. 3-Formyl-1,7-dimethoxy-9H-carbazole (Clauraila A) (**1**)*

3.2.5.1. Method A. A mixture of **8b** (0.100 g, 0.39 mmol) and $Pd(OAc)_2$ (0.105 g, 0.47 mmol) in glacial acetic acid (6.5 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap, under N_2 atmosphere. The mixture was stirred and heated to 140°C for 24 h in

the dark, then filtered over Celite. The mixture was diluted in 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 (10 g/g of crude, hexane–EtOAc, 95:5), to give 0.074 g (75%) of **1** as a pale yellow solid.

3.2.5.2. Method B. A mixture of **8b** (0.100 g, 0.39 mmol) and $Pd(OAc)_2$ (0.008 g, 0.039 mmol) and $Cu(OAc)_2$ (0.177 g, 0.98 mmol) in dry DMF (0.5 mL) was stirred and heated to 90°C for 3 h under MW irradiation (100 W). The mixture was filtered over Celite, diluted in toluene (10 mL) and the solvent was removed under vacuum. This evaporation procedure was repeated twice. The residue was purified by column chromatography over silica gel (10 g/g of crude, hexane–EtOAc, 95:5), to give 0.06 g (60%) of **1** as a pale yellow solid. R_f 0.45 (hexane–EtOAc, 7:3); mp 183–184°C [175–177°C (Songsiang et al., 2011); 183–185°C (Yang et al., 2011)]; IR (film): ν_{max} 3380, 3157, 1656, 1608, 1498, 1329, 1263, 1220, 1142, 1032, 845, 750 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$–$CDCl_3$, 1:1):δ 3.80 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.74 (dd, $J = 9.0$, 2.0 Hz, 1H, H-6), 6.96 (d, $J = 2.0$ Hz, 1H, H-8), 7.44 (s, 1H, H-2), 7.81 (d, $J = 9.0$ Hz, 1H, H-5), 8.24 (s, 1H, H-4), 10.01 (s, 1H, CHO), 10.90 (br s, 1H, NH); ^{13}C NMR (125 MHz, $(CD_3)_2SO$–$CDCl_3$, 1:1): 54.27 δ (OCH_3), 54.31 (OCH_3), 94.1 (C-8), 104.6 (C-2), 107.7 (C-6), 114.1 (C-4), 115.8 (C-4a), 119.7 (C-5), 120.7 (C-4), 122.3 (C-9a), 131.6 (C-3), 140.6 (C-8a), 143.7 (C-1), 157.9 (C-7), 191.0 (CHO); MS (70 eV): *m/z* (%) 255 (M^+, 91), 240 (100), 212 (29), 184 (22), 169 (13), 140 (9), 127 (7), 113 (4); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{15}H_{13}NO_3$: 255.0895; found: 255.0899.

*3.2.6. 1,7-Dimethoxy-9H-carbazole (**9**)*

A mixture of **8b** (0.100 g, 0.39 mmol) and $Pd(OAc)_2$ (0.0087 g, 0.039 mmol) and $Cu(OAc)_2$ (0.177 g, 0.98 mmol) in dry DMF (0.5 mL) was stirred and heated to 130°C for 70 min under MW irradiation (100 W). The mixture was filtered over Celite, diluted in toluene (10 mL) and the solvent was removed under vacuum. This evaporation procedure was repeated twice. The residue was purified by column chromatography over silica gel (10 g/g of crude, hexane–EtOAc, 95:5), to give 0.062 g (70%) of **9** as a white solid. R_f 0.62 (hexane–EtOAc, 7:3); mp 164–165°C [164–166°C (Bedford & Betham, 2006)]; IR (film): ν_{max} 3412, 1632, 1619, 1579, 1504, 1450, 1320, 1280, 1263, 1244, 1157, 1097, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.83 (d, $J = 8.0$ Hz, 1H, H-2), 6.84 (dd, $J = 8.5$, 2.0 Hz, 1H, H-6), 6.90 (d, $J = 2.0$ Hz, 1H, H-8), 7.12 (t, $J = 8.0$ Hz, 1H, H-3), 7.57 (d, $J = 8.0$, 1H, H-4), 7.89 (d, $J = 8.5$ Hz, 1H, H-5), 8.17 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5 (OCH_3), 55.6 (OCH_3), 94.8 (C-8), 105.0 (C-2), 108.3 (C-6), 112.2 (C-4), 117.6 (C-4a), 119.9 (C-3), 121.2 (C-5), 124.5 (C-4b), 129.6 (C-9a), 140.5 (C-8a), 145.5 (C-1), 159.0 (C-7); MS (70 eV): *m/z* (%) 227 (M^+, 100), 212 (30), 184 (70), 169 (13), 141 (18); HR-MS (EI): *m/z* [M^+] Anal. Calcd for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0945.

4. Conclusions

The total synthesis of the naturally occurring and anticancer alkaloid clauraila A (**1**) is described. The synthetic pathway starts from the *exo*-2-oxazolidinone diene **3**, through a regioselective Diels-Alder reaction, followed by transformation of adduct **2a** to the diarylamine precursor **8b**. The B-ring of the desired natural product **1** was generated via the C—H bond activation reaction of **8b**, catalysed or assisted by $Pd(OAc)_2$ to give **1** in fairly good overall yields (22–28%). More severe conditions of the Pd(II)-catalysed reaction resulted in the deformylated carbazole **9**. Therefore, modulating the reaction temperature can selectively lead to the diaryl insertion with or without decarbonylation of the carbazole framework.

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