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Total Synthesis of the Natural Carbazoles *O*-Demethylmurrayanine and Murrastanine A, and of a C4,C4′ Symmetric Murrastanine A Dimer from *N*-Phenyl-4,5-dimethylene-1,3-oxazolidin-2-one

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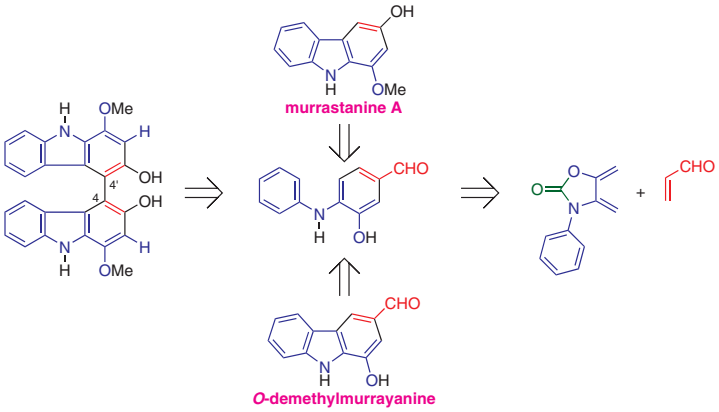

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Abstract The synthesis of natural carbazoles *O*-demethylmurrayanine and murrastanine A starting from the title *exo*-heterocyclic diene is described. In the synthesis of murrastanine A, its symmetric C4,C4′ dimer can be obtained as the sole product under rather mild conditions. In all cases, the key intermediate is the same diarylamine. The carbazole nucleus is obtained through a Pd-promoted cyclization of the appropriate diarylamine. For the synthesis of *O*-demethylmurrayanine, the cyclization takes place on a silylated derivative. The crystal structures of murrayanine, two diarylamines, and two non-natural carbazole intermediates are also presented.

Key words *O*-demethylmurrayanine, murrastanine A, natural carbazole synthesis, biscarbazoles, Pd(II)-promoted diarylamine coupling, *exo*-heterocyclic dienes, Diels–Alder cycloaddition

The first carbazole found in a living organism, murrayanine [1-methoxy-9*H*-carbazole-3-carbaldehyde (**1**)], was isolated from *Murraya koenigii* in 1965.[1–3] However, the isolation of its demethylated analogue, *O*-demethylmurrayanine [1-hydroxy-9*H*-carbazole-3-carbaldehyde (**2**)], from *Clausena anisata*, was not reported until 1989.[4] Since then, **2** has been obtained a number of times from plants of the Rutaceae family: *C. anisata*,[5] *C. excavata*,[6,7] *C. harmandiana*,[8,9] *C. lansium*,[10–14] *C. emarginata*,[15] and *M. koenigii*.[16,17] On the other hand, murrastanine A [3-hydroxy-1-methoxy-9*H*-carbazole (**3**)] is a carbazole only recently isolated from *M. koenigii*[18] and also from *C. emarginata*[19] (Figure 1).

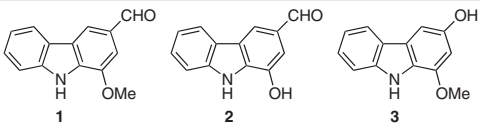

Figure 1 Murrayanine (**1**), *O*-demethylmurrayanine (**2**), and murrastanine A (**3**)

Carbazole **2** has been tested for biological activity, exhibiting weak antitumor activity[5] and a cytotoxic effect against human small cell lung cancer, human epidermoid carcinoma,[8] and other cancer cells,[7] as well as a strong activity against the MCF-7 and SMMC7721 cancer cell lines.[12] It has also been found to be weakly active against *Staphylococcus aureus* and *Salmonella typhimurium*,[9] to have moderate hepatoprotective activity against D-galactosamine-induced cell damage[16] and DL-galactosamine-induced toxicity in WB-F344 cells,[15] and potent anti-inflammatory activity.[13] It has even been proposed for the treatment of bronchial asthma and chronic obstructive pulmonary disease.[20] In contrast, murrastanine A (**3**) has only been found to be moderately active against the HL-60 and HeLa cancer cell lines, at least until now.[18]

The synthesis of **2** has been reported only once by Bringmann et al., who synthesized mukonine (**4**) from 3-formylindole (**5**) (Scheme 1a).[21] Mukonine was then converted in two steps into murrayanine (**1**), which was demethylated by treatment with BBr_3 in CH_2Cl_2 to afford **2**.

Murrastanine A (**3**) was synthesized by Knölker et al. through their iron-mediated synthetic methodology (Scheme 1b), much before it was found in nature.[22] In this case, **3** was obtained through cyclization of the iron complex **6**, which in turn was prepared through the electrophilic

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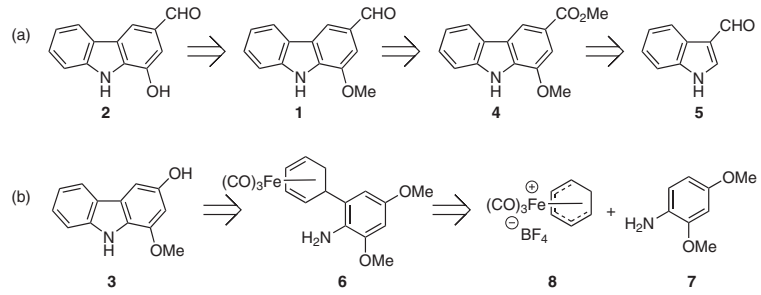
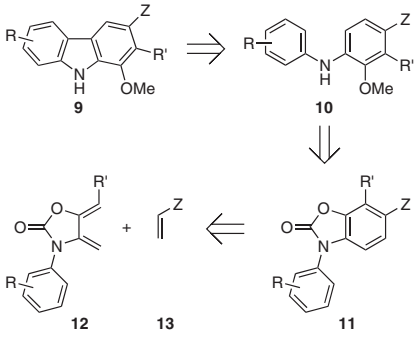


Scheme 1 (a) Bringmann's strategy for the synthesis of *O*-demethylmurrayanine (**2**); (b) Knölker's strategy for the synthesis of murrastanine A (**3**).

substitution reaction on arylamine **7** by the cationic iron complex **8**. So far, no other synthesis of **3** has been reported.

Tamariz and co-workers reported a synthesis of 1-oxygenated carbazoles **9**, in which one of the key steps was the palladium-promoted cyclization of diarylamines **10** (Scheme 2). The latter were generated by the hydrolysis of benzoxazolones **11**, which in turn were obtained from the oxidation of the adducts of the Diels–Alder reaction between the *N*-aryl-4,5-dialkylidene-2-oxazolidinones **12** and dienophiles **13**.[23] By careful selection of the reactants and slight modifications to the general methodology, a number of natural and non-natural carbazoles have been synthesized.[24] Other approaches to the synthesis of 1- and 2-oxygenated carbazoles have been developed by the same research group.[25]

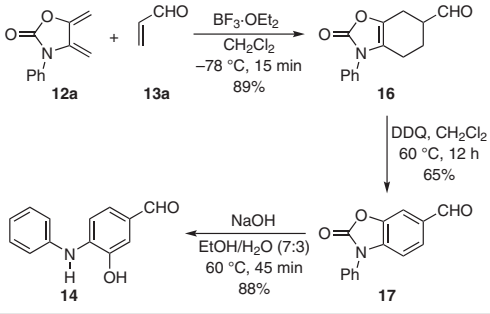


Scheme 2 Tamariz's general strategy for the synthesis of carbazoles **9**

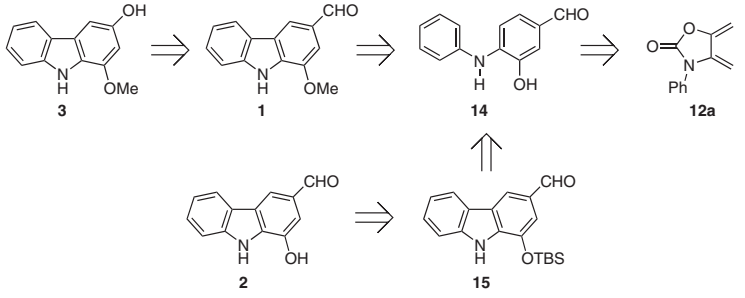
Herein we report the use of the methodology depicted in Scheme 2 for the synthesis of compounds **2** and **3**, as well as the unexpected formation of dimer **20**. In addition, two more non-natural carbazoles were obtained along the way.

Carbazole **3** was obtained from murrayanine (**1**) which, in turn, was synthesized from diarylamine **14** (Scheme 3). The latter was not only obtained from the exocyclic diene **12a** but was also the key precursor in the synthesis of **2**, through the silyl-protected carbazole **15**.

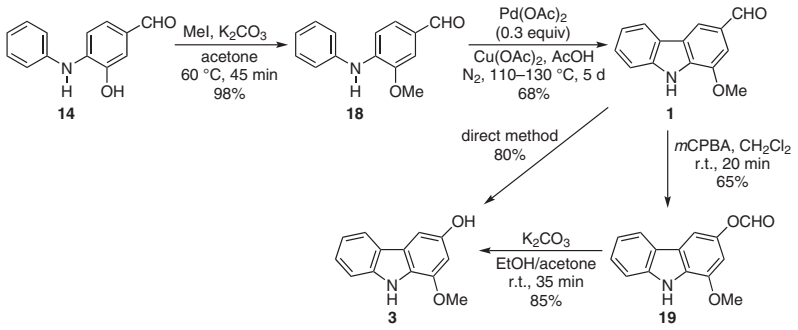
Starting from diene **12a**, the key diarylamine **14** was prepared in 51% overall yield through the series of reactions reported previously in the synthesis of murrayanine (**1**, Scheme 4).[26,27] The regioselective Lewis acid catalyzed Diels–Alder reaction of **12a** with acrolein (**13a**) was carried out within a short reaction time at low temperature, to furnish **16** in good yield. Upon aromatization with DDQ,



Scheme 4 Synthesis of diarylamine **14** starting from diene **12a**



Scheme 3 General strategy for the synthesis of naturally occurring carbazoles **1–3**



Scheme 5 Synthesis of murrastanine A (**3**) from diarylamine **14**

followed by basic hydrolysis of the resulting benzoxazol-2-one **17**, the desired diarylamine was obtained as a yellow solid.

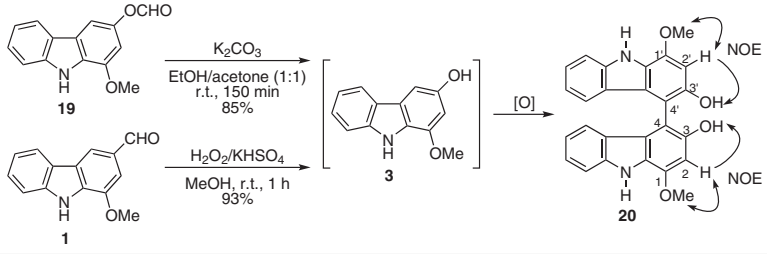
Murrastanine A (**3**) was synthesized from **14** through the reaction sequences shown in Scheme 5. The phenolic hydroxyl group of the latter compound was methylated with MeI under basic conditions to provide diarylamine **18** in almost quantitative yield. Further cyclization by a Pd(II)-catalyzed double C–H activation process with $Cu(OAc)_2$ as the oxidant,[28] led to murrayanine (**1**) in 68% yield.

The cyclization of **18** was also carried out under stoichiometric conditions [$Pd(OAc)_2$, 1.5 mol equiv], furnishing **1** in lower yield (62%) although in a much shorter reaction time (6 h) (see experimental section). It should be noted that the formyl group in **18** (and **1**) is very sensitive to the conditions of the cyclization. In the presence of air, the formyl group tends to oxidize to the corresponding carboxyl, leading to the formation of mukoeic acid and other oxidation by-products, and to lower yields of **1**, particularly when catalytic amounts of Pd(II) are used.

Baeyer–Villiger reaction of **1** afforded the formyl ester **19** in 65% yield, which was hydrolyzed under basic conditions to give **3** in 85% yield. The yield of the Baeyer–Villiger step was not very good because the ester hydrolyzed slowly under the reaction conditions. A further improvement to the overall yield was made by carrying out the transformation of **1** into **3** in 80% yield, by employing the same reagents and similar reaction conditions in each step, without purification of the carbazole intermediate **19**. The isolation of the final product had to be carried out very carefully (controlling pH and time) due to the presence of *m*-chlorobenzoic acid in the reaction mixture (see experimental section).

Carbazole **19** was found to be stable when left in solution under acidic or neutral conditions after extraction. However, **3** is not stable in solution under basic or slightly basic conditions (vide infra), although it can stand longer under neutral or slightly acidic conditions. The ^1H and ^{13}C NMR spectral data of **3** obtained in acetone-d_6 corresponded with those reported by Knölker in the first synthesis of this carbazole.[22]

The hydrolysis of carbazole **19** to yield **3** also disclosed an interesting fact. It was observed that murrastanine A (**3**), readily observed by TLC, changed into something else in the reaction mixture, which would become the major product after longer reaction times (Scheme 6). The ^1H and ^{13}C NMR spectra of this product were consistent with the structure of a carbazole. A more detailed analysis of the ^1H NMR spectrum showed that the four signals of ring C were present, while only a singlet was observed for ring A, suggesting that the latter had three substituents. As the signals for the O–H, OMe, and N–H protons were present in the spectrum, the nature of the third substituent in ring A was not readily apparent. The mass of the molecular ion of this molecule suggested a dimer, a symmetric dimer if both MS and NMR data were considered.



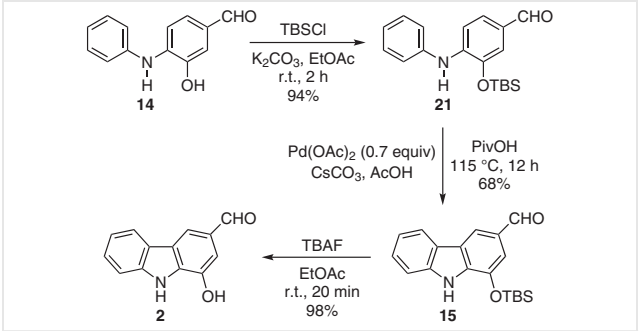
Scheme 6 Formation of **20** by dimerization of carbazole **3** in the basic hydrolysis of **19** (above); in the oxidation/hydrolysis of **1** through the Dakin reaction (below).

Due to the structure of **3**, a symmetric dimer in ring A could be formed only at C2 or C4. The chemical shifts of H2 and H4 in **3** (acetone-d_6) are 6.59 and 7.11 ppm, respectively. The chemical shift of the ring-A singlet in the dimer is 6.83 ppm, slightly closer to the chemical shift of H2 in **3**, suggesting the formation of the C4,C4′ dimer **20**. Further confirmation of this assignment came from NOE experiments. Irradiation of the signal attributed to H2 caused an increase in the intensity of the O–H and OMe signals. Similarly, irradiation of the OMe signal increased the intensity of the H2 singlet (Scheme 6).

Additional experiments showed that the dimerization of murrastanine A (**3**) is spontaneous in solution under basic conditions and that it is promoted by atmospheric oxygen. A small amount of purified **3** stirred in aqueous ethanol under aerobic atmosphere dimerizes, although rather reluctantly, after a long time. When the hydrolysis of **19** was carried out under nitrogen atmosphere, or when **3** was left standing in a slightly basic aqueous solution under nitrogen, the dimerization took place although slowly. The dimerization was also slowed if hydroquinone was added to a slightly basic aqueous solution of **3** under air. An attempt to obtain murrastanine A (**3**) by the direct oxidation of **1** through the Dakin reaction,[29,30] led to the exclusive formation of **20** in excellent yield, with no free murrastanine A (**3**) being detected (Scheme 6). The above experiments suggest that the stronger oxidizing conditions (H_2O_2/H^+) in the Dakin reaction promote dimerization through oxidation of **3**, while the dimerization observed in the basic hydrolysis of **19** takes place through oxidation of the phenolate of **3**, with O_2 as the oxidant.

It is of interest to note that, to date, only one symmetric C4,C4′ natural carbazole dimer has been reported,[31] although a number of symmetric C1,C1′ and a few C2,C2′ bis-carbazoles have been isolated.[32–44] However, we found three examples of symmetric C4,C4′ bis-carbazoles obtained through oxidative coupling of the corresponding natural carbazoles.[45–47] It is also remarkable that the oxidative dimerization of **3** took place under such mild conditions. The reported synthesis of symmetric carbazole dimers through oxidative coupling usually occurs under more stringent reaction conditions.[2,48] Typical reagents include manganese(IV) oxide,[45] benzoyl peroxide,[45] di-*tert*-butyl peroxide,[49,50] chloranil,[51] iron(III) chloride,[40] and iron hexadecafluorophthalocyanine.[52] There is one case of formation of small amounts of a symmetric dimer under Pd-promoted diarylamine coupling.[53] Traces of symmetric dimers have also been obtained in the reduction of monomers with $LiAlH_4$[45] and in oxidations with lead(IV) acetate.[46] We found a single case of efficient formation of a C4,C4′ natural symmetric carbazole dimer under mild conditions by oxidative coupling of the monomer with a vanadium complex.[47] The high reactivity of murrastanine A (**3**) in the oxidation/dimerization reaction can be attributed to the high electron density furnished by the substituents of ring A; the electron density becomes even higher in the phenolate.

The synthesis of *O*-demethylmurrayanine (**2**) started from diarylamine **14**, which was converted into the silylated derivative **21** in excellent yield by treatment with TBDMSCl under basic conditions (Scheme 7). The cyclization to carbazole **15** was carried out in fair yield with 0.7 equivalent of Pd(II). A problem with the latter reaction is the partial deprotection of the phenol, which yielded a mixture of the expected product **15** and small amounts of **2** and **14**. The cyclization was also carried out with an excess of Pd(II), with similar results (64% yield, see experimental section). Thus, this represents an additional example of the use of silylated diarylamines in the synthesis of natural carbazoles through Pd(II) coupling.[54] Desilylation of **15** with TBAF led to **2** in quantitative yield. The ^1H and ^{13}C NMR data (acetone-d_6) matched those reported in the literature.[21] The direct transformation of **14** into **2** was also attempted, but only mixtures of products were obtained, with no formation of the expected carbazole.



Scheme 7 Conversion of **14** into the natural carbazole *O*-demethylmurrayanine (**2**)

On a slightly different matter, it was possible to grow single crystals of diarylamine **14**, which led to the determination of the corresponding X-ray crystal structure (Figure 2a). The two aromatic rings are out of the plane, as evidenced by the C4–N1–C7–C8 and C5–C4–N1–C7 dihedral angles (30.9° and 20.3°, respectively). The nitrogen atom is planar (the sum of the three associated bond angles is 360°) with dihedral angles of 30.0° and 15.9° for the H1–N1–C7–C8 and H1–N1–C4–C5 torsions (H1 on nitrogen), respectively. The plane of the nitrogen is thus more coplanar with the trisubstituted aromatic ring, as expected from the effect of the substituents, particularly resonance with the formyl group; the OH and CHO groups are essentially coplanar with this ring. The hydroxyl proton is oriented away from the NH bond to favor the NH···OH hydrogen bond interaction. In addition, the carbonyl oxygen is oriented toward C2.

Likewise, a single crystal of diarylamine **18** was grown from a mixture of EtOAc, leading to the corresponding X-ray crystal structure (Figure 2b), which is fairly similar to that

of **14** despite the fact that the corresponding space groups are different (see experimental section). In this case the C4–N1–C7–C8 and C5–C4–N1–C7 dihedral angles have values of 25.2° and 20.3°, respectively. The orientation of the OMe and CHO groups is the same as in **14**.

It was also possible to crystallize murrayanine (**1**). The X-ray crystal structure is shown in Figure 2c. The asymmetric unit contains two molecules; only one of them is presented in Figure 2. All the substituent atoms are coplanar with the heterocycle, with the CHO and OMe groups having the same orientation as in the corresponding diarylamine.

For carbazole **19**, single crystals were grown from mixture of CH_2Cl_2/hexane (1:1). The corresponding X-ray crystal structure is shown in Figure 2d. In this case the formyloxy group at C3 is essentially perpendicular to the plane of the heterocycle, with a C2–C3–O10–C11 dihedral angle of 96.7° and the carbonyl oxygen oriented toward the ring system.

The single-crystal X-ray structure of carbazole **15** is shown in Figure 2e. The OTBS group is out of the plane of the fused heterocycle, with a C2–C1–O12–Si13 torsion angle of 37.0°. It is worth noting that even if the orientation of

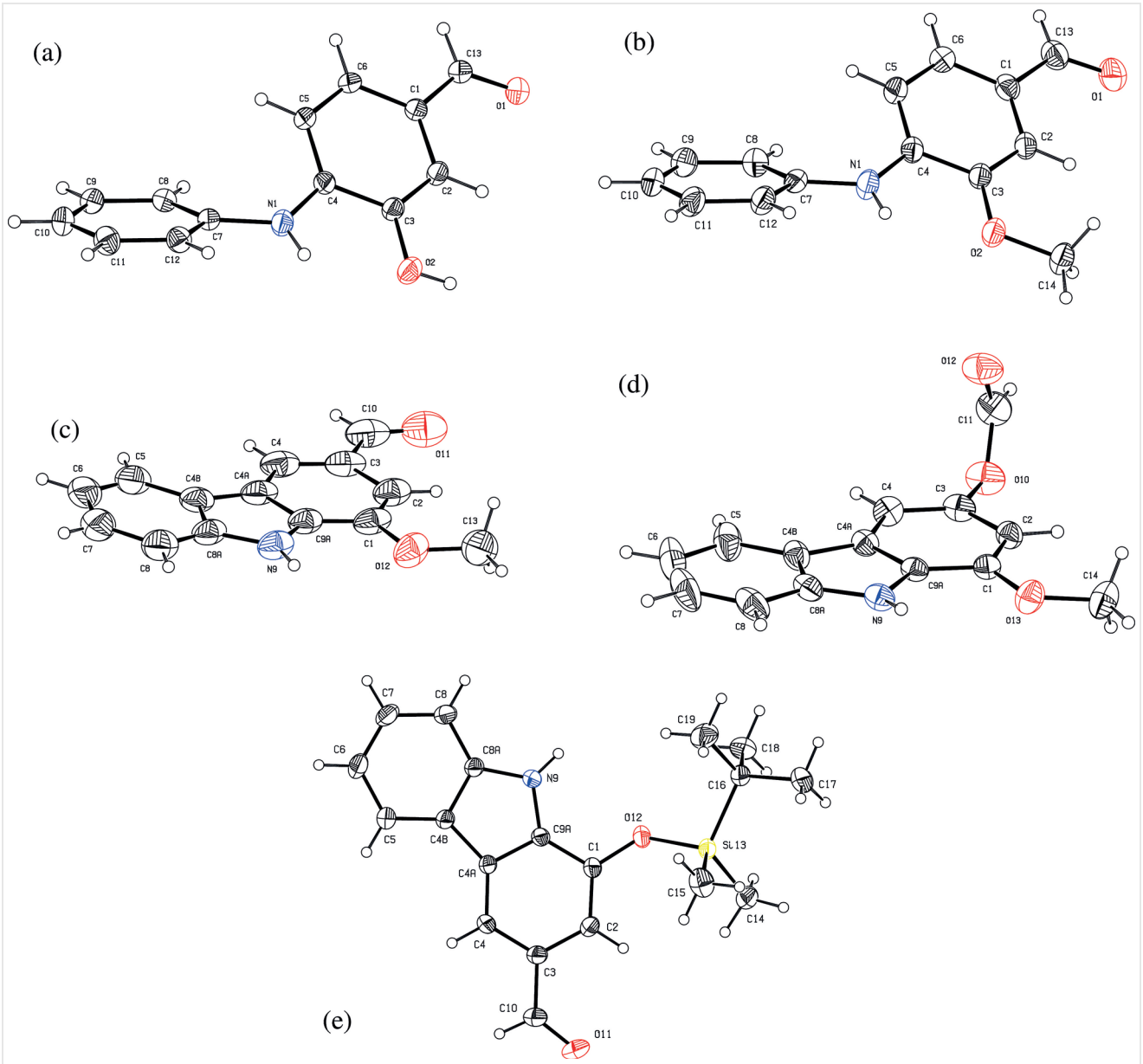


Figure 2 ORTEP plot of the X-ray crystal structures of (a) **14**, (b) **18**, (c) **1**, (d) **19**, and (e) **15**. Thermal ellipsoids drawn at 30% probability. For **1**, only one of the two molecules in the asymmetric unit is displayed.

the OTBS group is not quite coplanar with the plane of the heterocycle, its orientation and that of the CHO group in the carbazole is the same as those in diarylamines **14** and **18**, *syn* with respect to C2.

In order to investigate the conformational preference in the solid state of the formyl group in compounds **1**, **14**, **15**, and **18**, geometry optimizations of both possible orientations of the formyl group in these molecules (*syn* and *anti* with respect to C2) were carried out with the ωB97X-D functional[55] combined with the *aug*-cc-pVDZ basis set[56] (see Supporting Information for more details; the ωB97X-D functional has demonstrated to be quite good for the calculation of the relative stability of organic molecules[57,58]). The largest difference between the solid-state and the calculated geometries was observed for the silylated carbazole. The O–Si bond in the calculated structure was almost perpendicular to the plane of the heterocycle. The Si13–O12–C1–C2 dihedral angle in the X-ray structure (Figure 2e) was 37.0°, while for the geometry calculated in the gas phase was 80.6°. The calculations also showed that the *syn*-conformer was indeed the most stable in the gas phase for the four molecules, although only by approximately 1.0 kcal/mol (Table 1). In addition, the dipole moment was smaller for the *syn*-conformer by about 1.2 D. Thus, it is likely that the main reasons for the predominance of the *syn* geometry in the solid state are the lower dipole moment of this conformation and the generation of continuous and compact arrays of chains kept together through hydrogen bonding within the crystal structure (Figure 3).

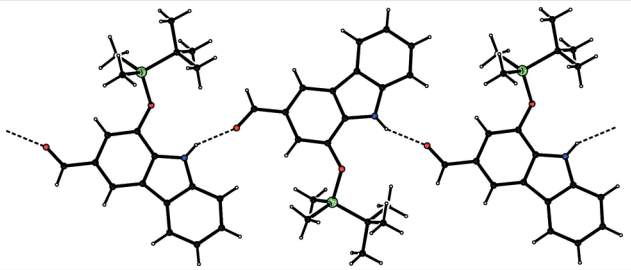


Figure 3 Small fragment of the X-ray crystal structure of **15**. Hydrogen bonding between the carbazole N–H bonds and the formyl groups forms zigzag chains of molecules that extend along one direction within the crystal lattice. The crystal structures of **1**, **14**, and **18** bear similar motifs.

In summary, the synthetic methodology of Tamariz et al., which starts from the *exo*-heterocyclic diene **12a**, has been extended to the total synthesis of the natural carbazoles *O*-demethylmurrayanine (**2**) and murrastanine A (**3**) in fair overall yields. A key intermediate in this work was diarylamine **14** from which both carbazoles were obtained. In the synthesis of **2**, silylation of the OH group of **14** allowed for the Pd-promoted coupling and subsequent deprotection in good overall yield for the last three steps. In the synthesis of **3**, diarylamine **14** was used to obtain murrayanine (**1**),

Table 1 Relative ZPE-Corrected Electronic Energies (ΔE_0) and Dipole Moments (μ) for the *syn*- and *anti*-Conformers of Diarylamines **14** and **18**, and Carbazoles **1** and **15**, Obtained at the ωB97X-D/*aug*-cc-pVDZ Level of Theory

Molecule[a]	ΔE_0 (kcal/mol)	μ (D)
14-*syn*	0.00	3.86
14-*anti*	0.96	4.69
18-*syn*	0.00	4.08
18-*anti*	1.23	5.28
1-*syn*	0.00	4.07
1-*anti*	1.23	5.48
15-*syn*	0.00	4.96
15-*anti*	0.56	6.16

[a] The *syn*- and *anti*-conformations correspond to the oxygen atom of the C3 formyl group with respect to C2.

which was then transformed into the desired carbazole through a Baeyer–Villiger/basic hydrolysis reaction sequence. In the latter process, the unexpected high-yield oxidative dimerization of **3** was observed under rather mild conditions leading to the symmetric dimer **20**. No other examples of such facile coupling are found in the literature. Careful manipulation of the dimerization conditions led to the exclusive formation of either carbazole **3** or dimer **20**. The dimerization took place more efficiently by submitting **1** to the Dakin reaction. Non-natural carbazoles **15** and **19** were also synthesized as intermediates in this work. The X-ray structures of diarylamines **14** and **18**, and of carbazoles **1** and **15** showed that the formyl group adopts the same conformation (*syn* with respect to C2) in the four molecules. Additional theoretical calculations indicated that the *syn*-conformer is more stable than the *anti*, probably as a result of the smaller dipole moment of the former. In the solid state the *syn* conformation of the CHO group is further stabilized by intermolecular hydrogen bonding. Furthermore, to the best of our knowledge, the crystal structure of **1** has been determined for the first time. The crystal structure of carbazole **19** was also obtained.

Melting points were determined in a Fisher–Johns apparatus and are reported uncorrected. TLC was carried out on E. Merck 60F-254 aluminum sheets covered with silica gel and visualized with short-wave UV light or with I_2. Column chromatography purification was done using Natland International Co. silica gel (230–400 or 200–300 mesh). IR spectra were recorded on a PerkinElmer 200 spectrophotometer. ^{1}H NMR spectra were obtained in 5 mm NMR tubes on 300 (Varian Mercury), 500 (Varian NMR System), or 600 MHz (Bruker Avance) spectrometers, using TMS as internal reference in $CDCl_3$, acetone-d_6 or CD_3OD. ^{13}C NMR spectra were obtained in the same spectrometers at 75.5, 125.8, or 150.9 MHz, respectively. ^{1}H and ^{13}C NMR spectra were assigned with the help of additional 2D experiments. High-resolution mass spectra were obtained by electronic impact at 70 eV on a

JEOL JSM-GCmate II spectrometer. Single crystal X-ray diffraction data were obtained on an Oxford Diffraction Xcalibur S diffractometer. Flasks, stirring bars, syringes, and needles employed in anhydrous reactions were dried for at least 4 h at 120 °C before use. Solvents were distilled before use: 1,4-dioxane and THF from Na and benzophenone ketyl, acetone from $KMnO_4$, CH_2Cl_2 from NaH, and Et_3N from NaOH. The synthesis of compounds **16**, **17**, **14**, **18**, and **1** has been described previously.[26]

2,3,4,5,6,7-Hexahydro-2-oxo-3-phenylbenzo[*d*]oxazole-6-carbaldehyde (16)

Starting from **12a** (493 mg, 2.63 mmol), and following the methodology already described, afforded **16**; yield: 570.4 mg (2.34 mmol, 89%). Melting point and spectroscopic data matched those reported in the literature.[26]

2,3-Dihydro-2-oxo-3-phenylbenzo[*d*]oxazole-6-carbaldehyde (17)

Starting from **16** (106.0 mg, 0.44 mmol), and following the methodology already described afforded **17**; yield: 68.0 mg (0.284 mol, 65%). Melting point and spectroscopic data matched those reported in the literature.[26]

3-Hydroxy-4-(phenylamino)benzaldehyde (14)

Starting from **17** (152 mg, 0.64 mmol), and following the methodology already described afforded **14**; yield: 120 mg (0.56 mmol, 88%). Melting point and spectroscopic data matched those reported in the literature.[26]

3-Methoxy-4-(phenylamino)benzaldehyde (18)

Starting from **14** (120 mg, 0.56 mmol), and following the methodology already described afforded **18**; yield: 125.8 mg (0.55 mmol, 98%). Melting point and spectroscopic data matched those reported in the literature.[26]

1-Methoxy-9*H*-carbazole-3-carbaldehyde [Murrayanine (1)]

Method A: In a pressure tube provided with a magnetic stir bar, **18** (62.1 mg, 0.22 mmol) and $Pd(OAc)_2$ (75 mg, 0.33 mmol, 1.5 equiv) were mixed with AcOH (1.0 mL) under N_2 atmosphere. The solution was stirred at 140 °C for 6 h, filtered through a bed of diatomite using CH_2Cl_2 to rinse the filter, and washed with sat. aq $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phases were washed with H_2O (2 × 15 mL) and dried (anhyd Na_2SO_4). The solvent was evaporated under vacuum and the residue purified by column chromatography on silica gel (hexane/EtOAc 8:2) to give **1** as a yellowish solid; yield: 38.6 mg (0.17 mmol, 63%).

Method B: In a pressure tube provided with a magnetic stir bar, **18** (9 mg, 0.04 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 0.3 equiv), and $Cu(OAc)_2$ (18.3 mg, 0.1 mmol, 2.5 equiv) were mixed with AcOH (1.0 mL) under N_2 atmosphere. The solution was stirred at 110 °C for 3 days, 120 °C for 2 days, and 130 °C for 24 h, concentrated under vacuum and filtered through a bed of diatomite using CH_2Cl_2 to rinse the filter. The solvent was evaporated under vacuum and the residue purified by column chromatography on silica gel (hexane/EtOAc 8:2) to give **1** as a yellowish solid; yield: 6.1 mg (0.027 mmol, 68%); R_f = 0.41 (hexane/EtOAc 7:3); mp 167–168 °C.

Melting point and spectroscopic data agreed with those reported in the literature.[1,26]

1-Methoxy-9*H*-carbazol-3-yl Formate (19)

In a round-bottomed flask provided with a magnetic stir bar, **1** (15.5 mg, 0.07 mmol) and *m*CPBA (24.15 mg, 0.14 mmol, 2 equiv) were mixed with CH_2Cl_2 (2 mL) under N_2 atmosphere. The suspension was stirred at r.t. for 20 min and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica gel (hexane/CH_2Cl_2/EtOAc 50:45:5) to give **19** as a brown oil; yield: 11 mg (0.045 mmol, 65%); R_f = 0.54 (hexane/EtOAc 7:3); mp 99–100 °C.

IR (CH_2Cl_2): 3413, 2936, 1738, 1633, 1586, 1505, 1307, 1164 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, OCHO), 8.28 (br, 1 H, NH), 7.98 (d, *J* = 7.8 Hz, 1 H, H-5), 7.45 (t, *J* = 7.5 Hz, 1 H, H-7), 7.41–7.44 (m, 2 H, H-4, H-8), 7.23 (t, *J* = 7.30 Hz, 1 H, H-6), 6.70 (d, *J* = 1.6 Hz, 1 H, H-2), 3.98 (s, 3 H, OCH_3).

^{13}C NMR (150.9 MHZ, $CDCl_3$): δ = 160.6 (OCHO), 145.9 (C-1), 143.8 (C-3), 139.7 (C-8a), 127.9 (C-9a), 126.4 (C-7), 123.7 (C-4b), 123.4 (C-4a), 120.8 (C-5), 119.8 (C-6), 111.4 (C-8), 104.9 (C-4), 100.7 (C-2), 55.6 (OCH_3).

HRMS (EI) *m*/*z* [M^+] calcd for $C_{14}H_{11}NO_3$: 241.0739; found: 241.0749.

3-Hydroxy-1-methoxy-9*H*-carbazole [murrastanine A (3)]

Method A: In a 5 mL pear-shaped flask provided with a magnetic stir bar, **1** (27.9 mg, 0.124 mmol) and *m*CPBA (33.0 mg, 0.191 mmol, 1.54 equiv) were mixed with CH_2Cl_2 (1.0 mL) under N_2 atmosphere, and the mixture was stirred at r.t. for 20 min. Then 5% aq $NaHCO_3$ (1 mL) and H_2O (10 mL) were added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were washed with H_2O (2 × 10 mL), dried (anhyd Na_2SO_4), and the solvent evaporated under vacuum. The residue was dissolved in a mixture of EtOH/acetone (1:1, 4 mL) in a 5 mL pear-shaped flask and K_2CO_3 (36 mg, 0.260 mmol, 2.1 equiv) was added. The suspension was stirred at r.t. for 10 min, treated with 5% aq HCl (2 mL) down to pH 5. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic phases dried (anhyd Na_2SO_4), and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 85:25, then 70:30) to give **3** as a colorless oil; yield: 21 mg (0.099 mmol, 80%).

Method B: In a 5 mL pear-shaped flask provided with a magnetic stir bar, **19** (12 mg, 0.05 mmol) and K_2CO_3 (6.95 mg, 0.05 mmol, 1 equiv) were mixed with a mixture of EtOH/acetone (1:1, 2 mL) under N_2 atmosphere. The mixture was stirred at r.t. for 35 min, the solvent was evaporated under vacuum, and the residue treated with 5% aq HCl (1 mL) and H_2O (5 mL). The product was extracted with CH_2Cl_2 (3 × 5 mL), the combined extracts were washed with H_2O (2 × 5 mL), dried (anhyd Na_2SO_4), and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 7:3) to give **3** as a colorless oil; yield: 9 mg (0.0425 mmol, 85%); R_f = 0.42 (hexane/EtOAc 6:4).

IR (CH_2Cl_2): 3412, 2927, 2852, 1634, 1591, 1506, 1452, 1317 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (br, 1 H, NH), 7.94 (d, *J* = 7.8 Hz, 1 H, H-5), 7.41 (dd, *J* = 7.7, 0.4 Hz, 1 H, H-8), 7.39 (td, *J* = 6.9, 1.1 Hz, 1 H, H-7), 7.17 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 1 H, H-6), 7.07 (d, *J* = 2.0 Hz, 1 H, H-4), 6.54 (d, *J* = 2.0 Hz, 1 H, H-2), 4.75 (s, 1 H, OH), 3.97 (s, 3 H, OCH_3).

^1H NMR (500 MHz, acetone-d_6): δ = 10.06 (br, 1 H, NH), 7.96 (br, 1 H, OH), 7.94 (d, *J* = 7.7 Hz, 1 H, H-5), 7.50 (d, *J* = 8.1 Hz, 1 H, H-8), 7.32 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1 H, H-7), 7.11 (d, *J* = 2.1 Hz, 1 H, H-4), 7.06–7.10 (m, 1 H, H-6), 6.59 (d, *J* = 2.0 Hz, 1 H, H-2), 3.95 (s, 3 H, OCH_3).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 149.9 (C-3), 146.1 (C1), 139.8 (C-8a), 125.7 (C-7), 124.8 (C-4b), 124.0 (C-9a), 123.6 (C-4a), 120.5 (C-5), 119.0 (C-6), 111.0 (C-8), 97.33 (C-4), 97.1 (C-2), 55.6 (OCH_3).

^{13}C NMR (125.8 MHz, acetone-d_6): δ = 152.3 (C-3), 147.1 (C1), 141.3 (C-8a), 126.0 (C-7), 125.2 (C-9a), 124.8 (C-4b), 124.1 (C-4a), 120.9 (C-5), 118.4 (C-6), 112.1 (C-8), 98.1 (C-4), 97.4 (C-2), 55.8 (OCH_3).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0794.

The NMR data determined in acetone-d_6 matches that reported by Knölker.[22] The NMR spectra in $CDCl_3$ had not been reported previously.

3,3′-Dihydroxy-1,1′-dimethoxy-4,4′-bis-(9,9′*H*-carbazole) (20)

Method A: In a 10 mL round-bottomed flask provided with a magnetic stir bar and under N_2 atmosphere, **19** (8 mg, 0.033 mmol) and K_2CO_3 (4.56 mg, 0.033 mmol) were suspended in a mixture of EtOH/acetone (1:1, 2 mL). The mixture was stirred at r.t. for 2.5 h, and treated with 5% aq HCl (1 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were washed with H_2O (2 × 5 mL), and dried (anhyd Na_2SO_4). The solvent was removed under vacuum and the residue purified by column chromatography on silica gel (hexane/EtOAc 7:3) to give **20** as an orange oil; yield: 6 mg (0.014 mmol, 85%); R_f = 0.44 (hexane/EtOAc 1:1).

Method B: In a 50 mL round-bottomed flask provided with a magnetic stir bar and under N_2 atmosphere, **1** (18 mg (0.080 mmol) and $KHSO_4$ (3 mg, 0.020 mmol) were suspended in MeOH (3 mL). To this mixture was added 30% H_2O_2 (5 mg, 0.16 mmol). The mixture was stirred for 1 h at r.t.; EtOAc (5 mL) was added and then 5% HCl was added until pH 4 (about 3 mL). The product was extracted with EtOAc (3 × 5 mL), the combined organic phases were dried (anhyd Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 7:3) to yield **20** as a dark green oil;[59] yield: 16 mg (0.037 mmol, 93%); R_f = 0.40 (hexane/EtOAc 6:4).

IR (CH_2Cl_2): 3398, 2925, 2853, 1706, 1625, 1589, 1454, 1313 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (br, 1 H, NH), 7.38 (d, *J* = 8.0 Hz, 1 H, H-5), 7.22 (t, *J* = 7.6 Hz, 1 H, H-7), 6.93 (d, *J* = 8.0 Hz, 1 H, H-8), 6.87 (s, 1 H, H-2), 6.78 (t, *J* = 7.4 Hz, 1 H, H-6), 5.07 (s, 1 H, OH), 4.11 (s, 3 H, OCH_3).

^{1}H NMR (500 MHz, acetone-d_6): δ = 10.18 (br, 1 H, NH), 7.43 (dt, *J* = 8.1, 0.8 Hz, 1 H, H-5), 7.11 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1 H, H-7), 6.98 (s, 1 H, OH), 6.83 (s, 1 H, H-2), 6.75–6.78 (m, 1 H, H-8), 6.58 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H, H-6), 4.09 (s, 3 H, OCH_3).

^{13}C NMR (125.8 MHz, acetone-d_6): δ = 150.4 (C-3), 147.1 (C-9a), 141.3 (C-8a), 125.6 (C-1), 125.5 (C-7), 124.6 (C-4a), 124.3 (C-4b), 122.4 (C-8), 118.6 (C-6), 111.6 (C-5), 106.6 (C-4), 98.1 (C-2), 56.0 (OCH_3).

HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{26}H_{20}N_2O_4$: 424.1423; found: 424.1419.

3-(*tert*-Butyldimethylsilyloxy)-4-phenylaminobenzaldehyde (21)

In a 10 mL round-bottom flask, diarylamine **14** (35.8 mg, 0.17 mmol), TBDMSCl (30.4 mg, 0.20 mmol, 1.18 equiv), and K_2CO_3 (27.8 mg, 0.20 mmol, 1.18 equiv) were mixed with anhyd EtOAc (2 mL). The mixture was stirred at r.t. for 2 h, treated with 2% aq HCl (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with H_2O (2 × 5 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 9:1) to give **21** as a colorless oil; yield: 52 mg (0.16 mmol, 94%); R_f = 0.48 (hexane/EtOAc 9:1).

IR (CH_2Cl_2): 3414, 2953, 2930, 2858, 2812, 2723, 1682, 1586, 1525, 1280 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.73 (s, 1 H, CHO), 7.32–7.41 (m, 4 H, H-2, H-6, H-3′), 7.26 (d, *J* = 8.2 Hz, 1 H, H-5), 7.22 (d, *J* = 8.4 Hz, 2 H, H-2′), 7.10 (t, *J* = 7.4 Hz, 1 H, H-4′), 6.63 (br, 1 H, NH), 1.05 [s, 9 H, $SiC(CH_3)_3$], 0.32 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 190.4 (CHO), 143.2 (C-3), 142.2 (C-4), 140.2 (C-1′), 129.7 (C-3′), 128.2 (C-1), 127.5 (C-6), 123.8 (C-4′), 121.2 (C-2′), 116.5 (C-2), 111.3 (C-5), 26.0 [$C(CH_3)_3$], 18.4 [$SiC(CH_3)_3$], –4.2 [$Si(CH_3)_2$].

HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{19}H_{25}NO_2Si$: 327.1655; found: 327.1653.

1-(*tert*-Butyldimethylsilyloxy)-9*H*-carbazole-3-carbaldehyde (15)

Method A: In a high-pressure tube provided with a magnetic stir bar, **21** (25 mg, 0.076 mmol) and $Pd(OAc)_2$ (23.9 mg, 0.106 mmol, 1.4 equiv) were mixed with AcOH (1 mL) under N_2 atmosphere. The mixture was stirred at 115 °C for 12 h, filtered through a sintered-glass Büchner funnel covered with a bed of diatomite, treated with concd aq $NaHCO_3$ (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were was washed with H_2O (2 × 5 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 95:5) to give **15** as colorless crystals; yield: 16 mg (0.049 mmol, 64%).

Method B: In a high-pressure tube provided with a magnetic stir bar, **21** (10 mg, 0.0305 mmol), $Pd(OAc)_2$ (4.8 mg, 0.021 mmol, 0.7 equiv), Cs_2CO_3 (3 mg, 0.009 mmol, 0.3 equiv), and PivOH (300 mg, 2.94 mmol, 96.2 equiv) were mixed with AcOH (1 mL). The mixture was stirred and heated at 120 °C for 36 h. The mixture was filtered through a sintered-glass Büchner funnel covered with a bed of diatomite and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 95:5) to give **15** as colorless crystals; yield: 6.8 mg (0.021 mmol, 68%); R_f = 0.83 (hexane/EtOAc 7:3); mp 144 °C.

IR (CH_2Cl_2): 3328, 3928, 2856, 1669, 1600, 1578, 1497, 1342, 1252 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.03 (s, 1 H, CHO), 8.39 (br, 1 H, NH), 8.22 (d, *J* = 0.6 Hz, 1 H, H-4), 8.11 (d, *J* = 8.4 Hz, 1 H, H-5), 7.57–7.52 (m, 1 H, H-8), 7.49 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1 H, H-7), 7.42 (d, *J* = 1.3 Hz, 1 H, H-2), 7.29–7.34 (m, 1 H, H-6), 1.09 [s, 9 H, $SiC(CH_3)_3$], 0.35 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 191.8 (CHO), 141.6 (C-1), 139.4 (C-8a), 136.5 (C-9a), 130.2 (C-3), 126.7 (C-7), 124.5 (C-4a), 123.9 (C-4b), 120.8 (C-5), 120.7 (C-6), 119.7 (C-4), 112.35 (C-2), 111.5 (C-8), 25.9 [$C(CH_3)_3$], 18.4 [$SiC(CH_3)_3$], –4.1 [$Si(CH_3)_2$].

HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{19}H_{23}NO_2Si$: 325.1498; found: 325.1500.

1-Hydroxy-9*H*-carbazole-3-carbaldehyde [*O*-Demethylmurrayanine (2)]

In a round-bottomed flask provided with a magnetic stir bar, **15** (12 mg, 0.037 mmol) and TBAF (290.2 mg, 1.11 mmol, 30 equiv) were mixed with EtOAc (1.5 mL) under N_2 atmosphere. The mixture was stirred at r.t. for 20 min, treated with 2% aq HCl (3 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), dried (anhyd Na_2SO_4), and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc 7:3), to give **2** as an amorphous white solid; yield: 7.7 mg (0.036 mmol, 98%); R_f = 0.60 (hexane/EtOAc 6:4); mp 240–241 °C (Lit.[4] mp 237–239 °C).

IR (CH_2Cl_2): 3290, 3923, 2852, 1666, 1577, 1454, 1347, 1248, 724 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 10.80 (br, 1 H, NH), 10.02 (s, 1 H, CHO), 9.32 (br, 1 H, OH), 8.28 (d, *J* = 1.1 Hz, 1 H, H-4), 8.21 (d, *J* = 7.9 Hz, 1 H, H-5), 7.65 (d, *J* = 8.2 Hz, 1 H, H-8), 7.47 (t, *J* = 8.2 Hz, 1 H, H-7), 7.44 (d, *J* = 1.2 Hz, 1 H, H-2), 7.28 (t, *J* = 7.9 Hz, 1 H , H-6).

^{1}H NMR (500 MHz, CD_3OD): δ = 9.91 (s, 1 H, CHO), 8.17 (d, *J* = 1.3 Hz, 1 H, H-4), 8.10 (d, *J* = 7.8 Hz, 1 H, H-5), 7.54 (d, *J* = 8.2 Hz, 1 H, H-8), 7.42 (t, *J* = 8.2 Hz, 1 H, H-7), 7.34 (d, *J* = 1.3 Hz, H-2), 7.23 (t, *J* = 7.5 Hz, 1 H, H-6).

^{13}C NMR (125.8 MHz, acetone-d_6): δ = 191.9 (CHO), 144.5 (C-1), 141.4 (C-8a), 134.9 (C-9a), 131.3 (C-3), 127.2 (C-7), 125.1 (C-4a), 124.5 (C-4b), 121.3 (C-5), 120.8 (C-6), 119.2 (C-4), 112.7 (C-8), 108.4 (C-2).

^{13}C NMR (125.8 MHz, CD_3OD): δ = 194.1 (CHO), 145.2 (C-1), 141.8 (C-8a), 136.0 (C-9a), 131.0 (C-3), 127.3 (C-7), 125.4 (C-4a), 124.9 (C-4b), 121.3 (C-5), 121.0 (C-6), 120.2 (C-4), 112.7 (C-8), 108.1 (C-2).

HRMS (EI) *m*/*z* [M$^+$] calcd for $C_{13}H_9NO_2$: 211.0633; found: 211.0626.

The ^{13}C NMR data in acetone-d_6 agrees with that reported in the literature.[21] The ^{1}H NMR data in acetone-d_6 and the ^{1}H and ^{13}C NMR data in CD_3OD had not been reported previously.

Single-Crystal X-ray Crystallography

Colorless crystals of **1** and **15** were grown from CH_2Cl_2, colorless crystals of **19** from CH_2Cl_2/hexane (1:1). Light yellow crystals of diarylamine **14** were grown from CH_2Cl_2/hexane (1:1); light ochre crystals of **18** from EtOAc. Crystallographic measurements were carried out using an area detector and MoKα radiation (λ = 0.71073 Å, graphite monochromator) at r.t. Crystals were mounted in glass fibers. Unit cell parameters were obtained from least-squares refinement. Data collection was carried out at 21 °C using ω scans. Intensities were corrected for Lorentz and polarization effects. Empirical (multi-scan) absorption corrections were applied. Structures were solved with SHELXT[60] and refined with SHELXL,[61] both within the WinGX[62] environment. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined using unit weights, except for hydrogens on oxygen or nitrogen. For the latter, hydrogen atoms were located from the difference density map and their positions and isotropic temperature factors were refined accordingly. ORTEP plots were drawn with PLATON.[63] A summary of the crystallographic information of these structures is shown in Table 2, including the CCDC deposition numbers.[64]

Theoretical Calculations

Geometries of the *syn*- and *anti*-conformers of **1**, **14**, **15**, and **18** were constructed and visualized with Molden[65] and optimized with Gaussian 09[66] at the HF/6-31G* level of theory. All optimizations were carried out using the OPT=TIGHT option. The resulting structures were used as starting points for optimization using the ωB97X-D functional[55] combined with the *aug*-cc-pVDZ basis set.[56] Vibrational frequencies of the optimized geometries were calculated at the same level of theory to verify that they corresponded to minima and to obtain Gibbs free-energy corrections. All DFT calculations were carried out with the INT(GRID=ULTRAFINE) option of Gaussian 09.

Table 2 Crystal and Structure Refinement Data for Carbazoles **1**, **15**, **19**, and Diarylamines **14** and **18**

Structure	**1**	**15**	**19**	**14**	**18**
Empirical formula	$C_{14}H_{11}NO_2$	$C_{19}H_{23}NO_2Si$	$C_{14}H_{11}NO_3$	$C_{13}H_{11}NO_2$	$C_{14}H_{13}NO_2$
Molecular weight	225.24	325.47	241.24	213.23	227.25
Crystal size (mm)	0.11 × 0.19 × 0.52	0.16 × 0.27 × 0.46	0.11 × 0.12 × 0.32	0.15 × 0.19 × 0.64	0.47 × 0.49 × 0.75
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P\,2_12_12_1$	$P\,2_1/c$	$P\,2_1/c$	$P\,2_1/c$	$P\,ca2_1$
Unit cell parameters (Å, °)	a = 6.9111(3), α = 90 b = 8.4474(3), β = 90 c = 39.9853(15), γ = 90	a = 8.5223(2), α = 90 b = 17.5156(3), β = 100.889(2) c = 12.5874(3), γ = 90	a = 10.8851(6), α = 90 b = 14.6132(4), β = 110.459(7) c = 7.9560(5), γ = 90	a = 11.9372(6), α = 90 b = 7.1152(3), β = 97.568(4) c = 12.5195(5), γ = 90	a = 20.9024(11), α = 90 b = 7.1900(4), β = 90 c = 7.7353(4), γ = 90
Volume (Å^3)	2334.38(16)	1845.13(7)	1185.70(12)	1054.09(8)	1162.52(11)
Z	8	4	4	4	4
Density (calcd, Mg/m^3)	1.282	1.172	1.351	1.344	1.298
Absorption coefficient (mm^{-1})	0.087	0.136	0.096	0.091	0.087
Theta range (°)	3.157–32.623	2.912–29.523	3.068–32.575	3.283–32.537	3.277–32.540
Reflections collected	24835	26941	7043	11505	6828
Independent reflections	7817	4620	3482	3537	3523
Observed reflections	3622	3648	2095	2840	2823
Final R indices	$R1$ = 0.0563, $wR2$ = 0.1159	$R1$ = 0.0472, $wR2$ = 0.1123	$R1$ = 0.0508, $wR2$ = 0.1200	$R1$ = 0.0551, $wR2$ = 0.1303	$R1$ = 0.0493, $wR2$ = 0.1033
Goodnes-of-fit on F^2	1.007	1.025	1.027	1.062	1.065
CCDC deposition number	1998392	1998394	1998396	1998393	1998395

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1385-9052.

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