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COMMUNICATION

Novel approach to biscarbazole alkaloids *via* Ullmann coupling – synthesis of murrastifoline-A and bismurrayafoline-A†‡

Carsten Börger, Olga Kataeva and Hans-Joachim Knölker*

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Unprecedented Ullmann couplings of murrayafoline-A with either 6-bromo- or 4-bromocarbazole derivatives provide highly efficient synthetic routes to the biscarbazole alkaloids murrastifoline-A (6 steps, 66% overall yield) and bismurrayafoline-A (6 steps, 28% overall yield).

Carbazole alkaloids exhibit a broad variety of useful biological activities (*e.g.* anti-tumour, antibiotic, anti-viral, anti-inflammatory and anti-malarial) which has led to the development of many synthetic routes to carbazoles.[1,2] We have described efficient iron-mediated and palladium-catalysed syntheses of carbazoles.[3,4] Biscarbazole alkaloids are interesting because of their structural characteristics. However, due to the low natural abundance of biscarbazole alkaloids and the still limited synthetic access, there is only scant knowledge of their bioactivity.[1,5,6] Therefore, we are seeking to develop new synthetic routes to biscarbazoles. Herein, we describe a novel synthetic approach to murrastifoline-A and bismurrayafoline-A using an Ullmann coupling for the construction of the biscarbazole linkage.

In 1990, Furukawa *et al.* reported the isolation of the N-aryl linked biscarbazole alkaloid murrastifoline-A (**1**) from the root bark of *Murraya euchrestifolia* Hayata (Fig. 1).[7] A synthesis of murrastifoline-A (**1**) has been described by Chida *et al.* in 2005 *via* a twofold Buchwald–Hartwig amination as the key step (9 steps and 23% overall yield).[8] Three years after the isolation of murrastifoline-A (**1**), Furukawa *et al.* isolated murrastifoline-F (**2**) from the root and stem bark of *Murraya koenigii* (L.) Spreng.[9] In 2001, Bringmann *et al.* described the first total synthesis of murrastifoline-F (**2**) by oxidation of murrayafoline-A (**4a**) with lead(IV) acetate and the separation and assignment of the absolute configuration of the atropisomers.[10] In 1983, Furukawa *et al.* isolated bismurrayafoline-A (**3**) from *Murraya euchrestifolia* Hayata.[11] In 2001, Bringmann and co-workers reported the formation of bismurrayafoline-A (**3**) in up to 19% yield as a by-product of the reduction of mukonine (**4e**) with lithium aluminium hydride (9% yield of **3** over seven steps from commercially available compounds).[12]

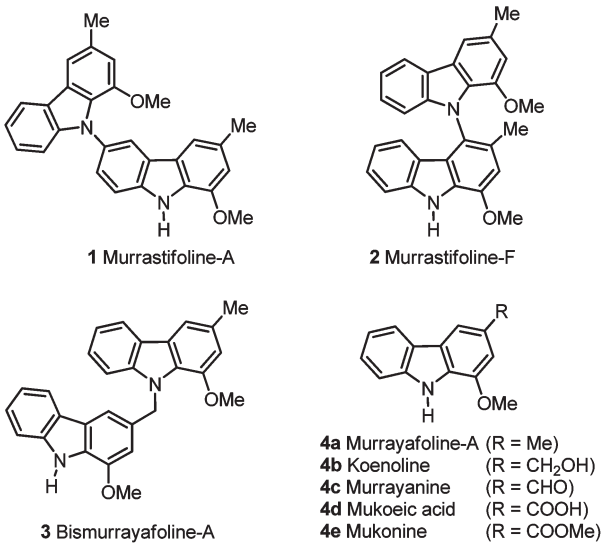

Fig. 1 Murrastifoline-A (**1**), murrastifoline-F (**2**), bismurrayafoline-A (**3**) and the 1-methoxycarbazole alkaloids **4a–e**.

The monomeric carbazole units of the biscarbazole alkaloids have also been found as natural products. In 1978, Chakraborty and co-workers described the isolation of mukonine (**4e**) from *Murraya koenigii*.[13] In the late nineties, Wu *et al.* isolated mukonine (**4e**) from the stem bark and the root bark of *Clausena excavata*.[14] In 1983, the parent compound of the 1-methoxycarbazole alkaloids, murrayafoline-A (**4a**), was obtained for the first time from the root bark of *Murraya euchrestifolia* Hayata by Furukawa *et al.*[15,16] Further isolations of murrayafoline-A (**4a**) have been reported in the following years from the roots of *Murraya crenulata* (Turz.) Oliver,[17] the root and stem bark of *Murraya koenigii* (L.) Spreng[9,18] and the root and stem bark of *Clausena excavata*.[14b] In 1990, we described an iron-mediated total synthesis of mukonine (**4e**),[19] which has been significantly improved later on.[20,21] Several alternative methods for the synthesis of mukonine (**4e**) have been reported.[13,22] Very

Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany. E-mail: hans-joachim.knoelker@tu-dresden.de; Fax: +49 351-463-37030

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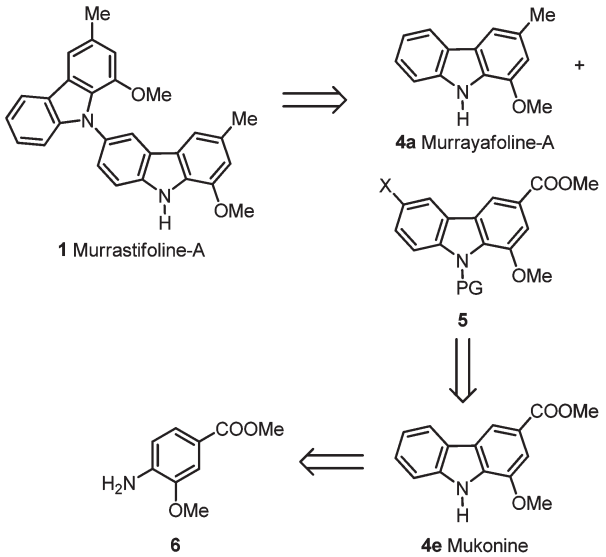
‡ Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR data of compounds **1**, **3**, **4a**, **9** and **12**. CCDC 883858. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26229k



Scheme 1 Retrosynthetic analysis of murrastifoline-A (**1**).

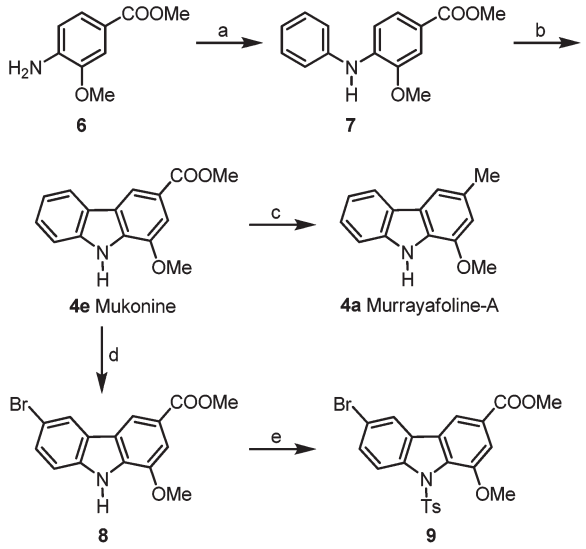
recently, we have described the best current approach to mukonine (**4e**) (2 steps, 91% overall yield).[21] A range of different approaches to murrayafoline-A (**4a**) has been reported.[12,20*a*,22*b*,*g*,23]

We decided to use murrayafoline-A (**4a**) and the 6-functionalised N-protected mukonine derivative **5** as key intermediates for our projected synthesis of murrastifoline-A (**1**) (Scheme 1). Both murrayafoline-A (**4a**)[22*b*] and carbazole **5** should be available from mukonine (**4e**) which can be prepared from methyl 4-amino-3-methoxybenzoate (**6**).[21]

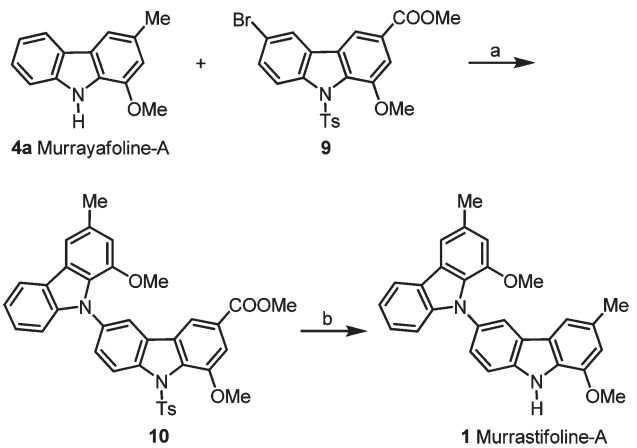
Buchwald–Hartwig coupling of the commercially available arylamine **6** and bromobenzene followed by palladium(II)-catalysed oxidative cyclisation of the diarylamine **7** afforded mukonine (**4e**) (Scheme 2).[21,22*g*] Reduction of **4e** with lithium aluminium hydride provided murrayafoline-A (**4a**) which was structurally confirmed by its spectroscopic data.§ Using the present route, murrayafoline-A (**4a**) is available in three steps and 79% overall yield.

Bromination of mukonine (**4e**) by slow addition of *N*-bromosuccinimide in acetonitrile at room temperature provided methyl 6-bromo-1-methoxy-9*H*-carbazole-3-carboxylate (**8**) (Scheme 2). Subsequent protection of the nitrogen atom by reaction with *para*-toluenesulfonyl chloride led to the 6-bromo-9-tosylcarbazole **9**.

With the readily available carbazoles **9** and **4a** in hand, we envisaged direct access to murrastifoline-A (**1**). In a model study, an attempted Buchwald–Hartwig coupling of mukonine (**4e**) and a 6-bromocarbazole [cat. $Pd(OAc)_2$, cat. BINAP, Cs_2CO_3 or K_2CO_3, toluene, reflux][24] failed. Using Ullmann conditions as reported for the synthesis of oligomer- and polymer-bound carbazoles,[25] coupling of murrayafoline-A (**4a**) with the 6-bromocarbazole **9** provided the biscarbazole **10** in 76% yield (Scheme 3).§ Reduction of compound **10** using an excess of lithium aluminium hydride with concomitant removal of the tosyl protecting group afforded directly murrastifoline-A (**1**) (6 steps and 66% overall yield based on **6**). The spectroscopic data of murrastifoline-A (**1**) are in good agreement with those reported in the literature.§[7]

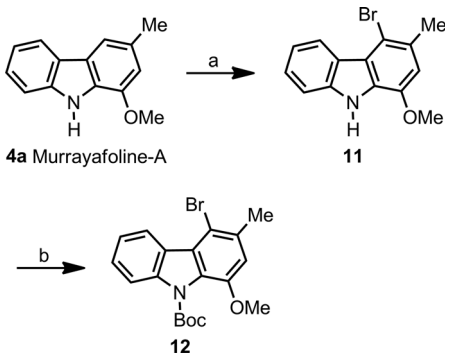


Scheme 2 Synthesis of murrayafoline-A (**4a**) and the 6-bromocarbazole **9**. *Reagents and conditions*: (a) 6 mol% $Pd(OAc)_2$, 12 mol% SPhos, 1.1 equiv. PhBr, 1.4 equiv. Cs_2CO_3, toluene, reflux, 40 h, 100%; (b) 0.1 equiv. $Pd(OAc)_2$, 0.1 equiv. K_2CO_3, PivOH, 115 °C, 14 h, 91%; (c) 3 equiv. $LiAlH_4$, Et_2O, CH_2Cl_2, rt, 4.5 h, 87%; (d) 1.04 equiv. NBS, MeCN, rt, 3 h; (e) 6.8 equiv. NaH, 3.4 equiv. TsCl, THF, 0 °C to rt, 16 h, 95% (two steps).



Scheme 3 Synthesis of murrastifoline-A (**1**). *Reagents and conditions*: (a) 1 equiv. **9**, 3 equiv. **4a**, 1 equiv. Cu, 2.5 equiv. K_2CO_3, nitrobenzene, 170 °C, 112 h, 76%; (b) 20 equiv. $LiAlH_4$, Et_2O, CH_2Cl_2, rt, 17 h, 100%.

Reaction of murrastifoline-A (**1**) with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride led to the corresponding (*S*)-amide.[26] We performed several NMR experiments with the murrastifoline-A-(*S*)-Mosher amide to gather information on the conformational stability of the atropisomers. At room temperature, we observed only one set of signals, whereas at −10 °C, signals corresponding to four diastereoisomers could be detected. Thus, we concluded that racemisation of murrastifoline-A (**1**) occurs very rapidly at room temperature. Unfortunately, the activation energy for the rotation about the C–N bond of **1** could not be determined due to the additional presence of isomers resulting from hindered rotation of the amide bond.[27]



Scheme 4 Synthesis of *tert*-butyl 4-bromo-1-methoxy-3-methyl-9*H*-carbazole-9-carboxylate (**12**). *Reagents and conditions*: (a) 1.03 equiv. NBS, MeCN, rt, 4 h; (b) 2 equiv. Boc_2O, 1 equiv. DMAP, MeCN, rt, 20 h, 99% (two steps).

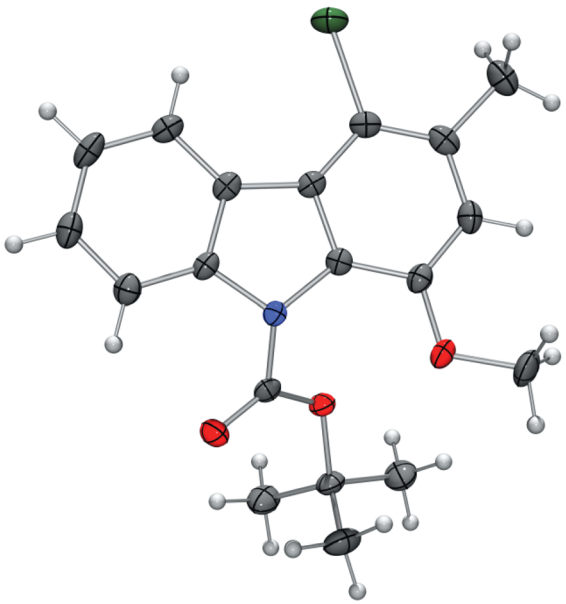
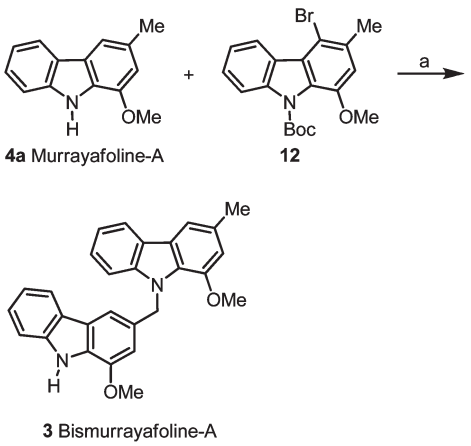


Fig. 2 Molecular structure of *tert*-butyl 4-bromo-1-methoxy-3-methyl-9*H*-carbazole-9-carboxylate (**12**) in the crystal.

We envisaged a similar strategy for the synthesis of murrastifoline-F (**2**). Bromination of the electron-rich A-ring of murrayafoline-A (**4a**) was expected to take place at C-4.[28] In fact, reaction of murrayafoline-A (**4a**) with *N*-bromosuccinimide in acetonitrile provided exclusively the 4-bromo derivative **11** (Scheme 4). Protection of the nitrogen atom using di-*tert*-butyl dicarbonate led to *tert*-butyl 4-bromo-1-methoxy-3-methyl-9*H*-carbazole-9-carboxylate (**12**). The structure of compound **12** has been unequivocally confirmed by an X-ray crystal structure determination (Fig. 2).¶

However, coupling of murrayafoline-A (**4a**) and the N-Boc protected 4-bromocarbazole **12** using the same reaction conditions as described above afforded bismurrayafoline-A (**3**), instead of the expected murrastifoline-F (**2**) (Scheme 5). At temperatures of 200 °C, the Boc protecting group is removed.[3d] Optimisation of this novel rearrangement led to bismurrayafoline-A (**3**) in up to 36% yield (Table 1, entry 1). The structural



Scheme 5 Synthesis of bismurrayafoline-A (**3**). *Reagents and conditions*: (a) 1 equiv. **12**, 3 equiv. **4a**, 1 equiv. Cu, 2.5 equiv. K_2CO_3, nitrobenzene, 200 °C, 7 d, 36%.

Table 1 Synthesis of bismurrayafoline-A (**3**)[a]

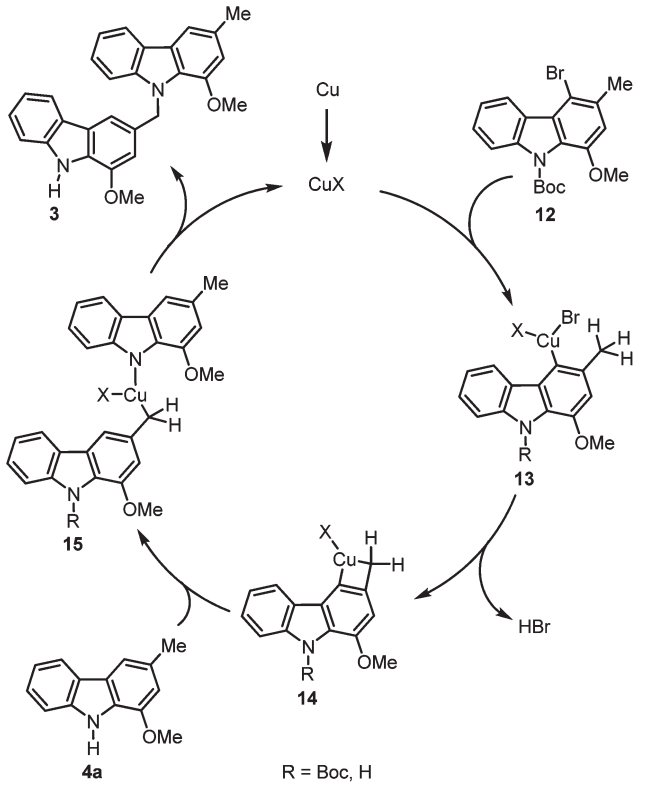
Entry	**4a**	**12**	Cu	**3**, Yield	**4a**, Yield[b]
1	3 equiv.	1 equiv.	1 equiv.	36	61
2	3 equiv.	1 equiv.	—	—	87[c]
3	1 equiv.	—	1 equiv.	2	80
4	—	1 equiv.	1 equiv.	Decomp.	—

[a] All reactions in nitrobenzene with 2.5 equiv. K_2CO_3 at 200 °C for 7 d. [b] Re-isolated starting material. [c] Additionally 62% of **12** were re-isolated.

assignment for bismurrayafoline-A (**3**) is based on the spectroscopic data,‖ which are in full agreement with those reported in the literature,[11] and has been additionally supported by 2D-NMR experiments (ESI‡).

The mechanism of this unprecedented rearrangement leading to functionalisation of a carbazole 3-methyl group is intriguing. In the absence of copper, no product was obtained and the starting material could be re-isolated almost quantitatively even after seven days at 200 °C (Table 1, entry 2). Reaction of murrayafoline-A (**4a**) using the optimised conditions but without the 4-bromocarbazole **12** led to bismurrayafoline-A (**3**) in only 2% yield along with large amounts of starting material (entry 3). This result indicated that a copper-mediated oxidative dimerisation of murrayafoline-A (**4a**) contributes only insignificantly to the formation of bismurrayafoline-A (**3**). Heating of the 4-bromocarbazole **12** under Ullmann coupling conditions in the absence of murrayafoline-A (**4a**) resulted in complete decomposition of the starting material (entry 4).

Obviously, bismurrayafoline-A (**3**) is generated *via* two independent mechanistic pathways. It is assumed that the oxidative coupling of two molecules of murrayafoline-A (**4a**) to bismurrayafoline-A (**3**) may be induced by the solvent nitrobenzene[29] or by traces of air. The major mechanistic pathway is proposed to proceed *via* initial oxidative addition of bromocarbazole **12** to a copper(I) salt generating the aryl copper(III) species **13** as suggested for the classical Ullmann coupling (Scheme 6).[30] Subsequent elimination of hydrobromic acid activates a C–H bond of the methyl group and generates the metallacycle **14**. Copper-



Scheme 6 Proposed mechanism for the formation of bismurrayafoline-A (**3**).

mediated C–H bond activations have been described previously.[31] Addition of murrayafoline-A (**4a**) to intermediate **14** *via* ring opening leads to the copper(III) complex **15**. Finally, reductive elimination provides bismurrayafoline-A (**3**) and regenerates the copper catalyst.

Conclusions

Following our optimised route, murrayafoline-A (**4a**) has been prepared in three steps and 79% overall yield which currently represents the best route to this alkaloid. Using mukonine (**4e**) and murrayafoline-A (**4a**) as building blocks, we have achieved a highly efficient total synthesis of murrastifoline-A (**1**) (six steps and 66% overall yield starting from commercially available compounds). The key-step of our approach is an Ullmann coupling of murrayafoline A (**4a**) with a 6-bromocarbazole derivative. Moreover, an unprecedented rearrangement in the course of a copper-mediated coupling of murrayafoline-A (**4a**) and a 4-bromo-3-methylcarbazole derivative opened up a novel route to bismurrayafoline-A (**3**) (six steps and 28% overall yield). Both of our synthetic approaches are much superior to those previously reported for biscarbazole alkaloids.

Acknowledgements

We thank Dr. M. Gruner (TU Dresden) for 2D-NMR experiments and the Deutsche Forschungsgemeinschaft for financial support (grant KN 240/16-1).

Notes and references

§ Spectroscopic data for murrayafoline-A (**4a**): Colourless crystals, mp 54–54.5 °C (ref. 16*a*: 52–53 °C); UV (MeOH): λ = 221, 226, 240, 243, 251 (sh), 259 (sh), 281 (sh), 291, 316 (sh), 328, 341 nm; IR (ATR): ν = 3414, 3054, 2917, 2848, 1616, 1587, 1543, 1502, 1450, 1391, 1333, 1303, 1278, 1261, 1228, 1186, 1133, 1104, 1036, 1011, 942, 826, 766, 746, 730, 671, 640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 4.00 (s, 3 H), 6.74 (s, 1 H), 7.20 (ddd, J = 8.0 Hz, 6.9 Hz, 1.3 Hz, 1 H), 7.39 (ddd, J = 8.2 Hz, 6.9 Hz, 1.2 Hz, 1 H), 7.44 (dt, J = 8.1 Hz, 0.9 Hz, 1 H), 7.48 (s, 1 H), 8.02 (d, J = 7.8 Hz, 1 H), 8.16 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 22.08 (CH_3), 55.61 (CH_3), 107.77 (CH), 111.03 (CH), 112.63 (CH), 119.27 (CH), 120.59 (CH), 123.64 (C), 124.42 (C), 125.63 (CH), 128.08 (C), 129.58 (C), 139.56 (C), 145.44 (C); MS (EI): m/z (%) = 211 (M^+, 100), 196 (83), 180 (9), 168 (62), 167 (60), 166 (13), 152 (6), 140 (7), 139 (10), 106 (6), 84 (7); anal. calc. for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63; found: C 79.73, H 6.48, N 6.75.

Experimental procedure for the Ullmann coupling of murrayafoline-A (**4a**) with the 6-bromocarbazole **9** to the biscarbazole **10**: A mixture of murrayafoline-A (**4a**) (57.2 mg, 0.271 mmol), 6-bromocarbazole **9** (44.1 mg, 0.090 mmol), copper bronze (6.2 mg, 0.098 mmol) and potassium carbonate (31.2 mg, 0.226 mmol) in nitrobenzene (5 mL) was heated at 170 °C for 112 h. After cooling to room temperature, the reaction mixture was filtered over magnesium sulfate (ethyl acetate). Removal of the solvent and flash chromatography (gradient elution with petroleum ether–ethyl acetate, 49 : 1 to 1 : 1) on silica gel provided the biscarbazole **10** (42.2 mg, 76%) as colourless crystals; mp 120.5–121 °C. UV (MeOH): λ = 225 (sh), 243, 268 (sh), 290, 330, 344 (sh) nm; IR (ATR): ν = 3341, 3058, 2998, 2934, 2840, 1711, 1653, 1633, 1581, 1499, 1451, 1403, 1325, 1285, 1242, 1221, 1175, 1156, 1122, 1095, 1035, 981, 953, 912, 875, 812, 767, 745, 703, 682, 661, 632 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.57 (s, 3 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 3 H), 6.77 (d, J = 0.8 Hz, 1 H), 7.23–7.25 (m, 1 H), 7.25–7.28 (m, 1 H), 7.32 (d, J = 7.9 Hz, 2 H), 7.36 (ddd, J = 8.4 Hz, 7.3 Hz, 1.0 Hz, 1 H), 7.59–7.60 (m, 2 H), 7.63 (d, J = 1.1 Hz, 1 H), 7.86 (d, J = 8.3 Hz, 2 H), 8.05 (d, J = 2.3 Hz, 1 H), 8.09 (dd, J = 7.9 Hz, 1.1 Hz, 1 H), 8.21 (d, J = 1.1 Hz, 1 H), 8.50 (d, J = 9.0 Hz, 1 H); ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 21.82 (CH_3), 21.90 (CH_3), 52.46 (CH_3), 55.90 (CH_3), 56.03 (CH_3), 109.93 (CH), 110.20 (CH), 111.67 (CH), 112.92 (CH), 114.78 (CH), 116.44 (CH), 116.76 (CH), 119.95 (CH), 120.35 (CH), 120.53 (C), 123.51 (C), 125.69 (C), 125.94 (CH), 126.18 (C), 126.81 (2 CH), 127.18 (CH), 128.32 (C), 129.54 (2 CH), 130.33 (C), 131.94 (C), 136.18 (C), 138.51 (C), 140.05 (C), 142.63 (C), 143.06 (C), 144.43 (C), 146.74 (C), 148.27 (C), 166.81 (C=O); ESI-MS: 619 $[M + H]^+$.

Spectroscopic data for murrastifoline-A (**1**): Colourless crystals, mp 174 °C (ref. 7: oil); UV (MeOH): λ = 226, 243, 253 (sh), 262 (sh), 292, 334, 346 nm; IR (ATR): ν = 3419, 3317, 2921, 2852, 1582, 1502, 1484, 1453, 1375, 1329, 1311, 1285, 1223, 1141, 1115, 1094, 1033, 1015, 977, 944, 910, 827, 801, 764, 746, 667, 633 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6): δ = 2.48 (s, 3 H), 2.51 (s, 3 H), 3.56 (s, 3 H), 4.02 (s, 3 H), 6.84 (s, 1 H), 6.87 (s, 1 H), 7.15 (dt, J = 8.5 Hz, 0.9 Hz, 1 H), 7.20 (ddd, J = 7.9 Hz, 6.9 Hz, 0.9 Hz, 1 H), 7.32 (ddd, J = 8.2 Hz, 7.3 Hz, 1.3 Hz, 1 H), 7.40 (dd, J = 8.5 Hz, 1.9 Hz, 1 H), 7.54 (s, 1 H), 7.62 (dd, J = 1.4 Hz, 0.8 Hz, 1 H), 7.66 (d, J = 8.5 Hz, 1 H), 8.09 (dd, J = 2.2 Hz, 0.6 Hz, 1 H), 8.12 (dt, J = 7.9 Hz, 0.9 Hz, 1 H), 10.45 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 21.72 (CH_3), 21.93 (CH_3), 55.87 (CH_3), 56.09 (CH_3), 108.77 (CH), 110.75 (CH), 111.06 (CH), 111.71 (CH), 113.36 (CH), 113.41 (CH), 120.16 (CH), 120.53 (CH), 120.75 (CH), 123.86 (C), 123.98 (C), 125.07 (C), 126.00 (C), 126.43 (CH), 126.58 (CH), 129.90 (C), 129.97 (C), 130.10 (C), 130.40 (C), 132.00 (C), 139.99 (C), 144.01 (C), 146.70 (C), 147.77 (C); MS (EI): m/z (%) = 420.3 (M^+, 100), 406.2 (11), 405.2 (7), 391.1 (6), 390.2 (16), 375.2 (5), 374.2 (8); HRMS: m/z calc. for $C_{28}H_{24}N_2O_2$ (M^+): 420.1838; found: 420.1823.

¶ Crystal data for *tert*-butyl 4-bromo-1-methoxy-3-methyl-9*H*-carbazole-9-carboxylate (**12**): $C_{19}H_{20}BrNO_3$, crystal size: 0.26 × 0.11 × 0.03 mm^3, M = 390.27 g mol^{-1}, monoclinic, space group $P2_1/n$, λ = 0.71073 Å, a = 8.8228(3), b = 20.4039(7), c = 9.9068(4) Å, β = 106.586(2)°, V = 1709.21(11) Å^3, Z = 4, ρ_c = 1.517 g cm^{-3}, μ = 2.422 mm^{-1}, T = 150(2) K, θ range = 2.00° to 28.48°, reflections collected: 20 882, independent: 4197 (R_{int} = 0.0803). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0335; wR_2 = 0.0693

[$I > 2\sigma(I)$]; maximal residual electron density: 0.971 e Å^{-3}. CCDC 883858.

‖ Spectroscopic data for bismurrayafoline-A (**3**): colourless crystals, mp 209.5–210 °C from petroleum ether–EtOAc (ref. 11: 176–177 °C from Et_2O); UV (MeOH): λ = 224, 243, 251, 262 (sh), 282, 292, 323 (sh), 338, 352 (sh) nm; IR (ATR): ν = 3434, 3051, 3015, 2965, 2927, 2843, 1727, 1626, 1582, 1542, 1502, 1451, 1393, 1341, 1299, 1258, 1227, 1211, 1146, 1119, 1104, 1037, 1012, 942, 827, 764, 746, 730, 657, 640, 618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 3.80 (s, 3 H), 3.91 (s, 3 H), 5.97 (s, 2 H), 6.77 (d, J = 0.6 Hz, 1 H), 6.77 (d, J = 0.9 Hz, 1 H), 7.11–7.18 (m, 2 H), 7.31–7.36 (m, 2 H), 7.36–7.43 (m, 2 H), 7.48 (s, 1 H), 7.53 (s, 1 H), 7.91 (d, J = 7.9 Hz, 1 H), 8.03 (d, J = 7.9 Hz, 1 H), 8.14 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.85 (CH_3), 49.59 (CH_2), 55.53 (CH_3), 55.89 (CH_3), 105.10 (CH), 109.28 (CH), 109.84 (CH), 110.93 (CH), 111.03 (CH), 112.92 (CH), 118.93 (CH), 119.36 (CH), 120.27 (CH), 120.70 (CH), 123.29 (C), 123.62 (C), 124.15 (C), 125.11 (C), 125.65 (CH), 125.74 (CH), 128.55 (C), 129.02 (C), 129.21 (C), 131.48 (C), 139.48 (C), 141.53 (C), 145.76 (C), 146.80 (C); MS (EI): m/z (%) = 420.2 (M^+, 40), 211.1 (39), 210.2 (100), 196.1 (6), 180.1 (5), 167.1 (14); HRMS: m/z calc. for $C_{28}H_{24}N_2O_2$ (M^+): 420.1838; found: 420.1824.

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