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COMMUNICATION

First total syntheses of chrestifoline-B and (\pm)-chrestifoline-C, and improved routes to bismurrayafoline-A, bismurrayafolinol and chrestifoline-D†‡

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We describe an efficient synthesis of the methylene-bridged biscarbazole alkaloids bismurrayafoline-A, bismurrayafolinol and chrestifoline B–D using an Ullmann-type coupling at the benzylic position.

A wide range of carbazole alkaloids has been isolated and investigated towards their biological activity.^{1–3} Much less is known about the pharmaceutical potential of biscarbazoles and only few synthetic approaches have been described.^{1,4} We have developed several methods for the synthesis of carbazoles.^{1,2} Using our palladium-catalysed construction of the carbazole framework,⁵ we recently described efficient routes to biscarbazole alkaloids,^{6–8} for example the oxygen-bridged biscarbazole oxydimurrayafoline and the N-aryl linked murrayafoline-A.^{7,8} The biscarbazole linkage was constructed by etherification,⁷ Buchwald–Hartwig amination,⁹ or Ullmann coupling.¹⁰ Herein, we report the synthesis of methylene-bridged biscarbazole alkaloids by palladium(0)- and copper(I)-catalysed coupling reactions at the benzylic position at C-3 of the carbazole framework.

The first methylene-bridged biscarbazole alkaloid obtained from natural sources was bismurrayafoline-A (**1**), isolated in 1983 by Furukawa *et al.* from the root bark of *Murraya euchrestifolia* Hayata (Fig. 1).¹¹ Bismurrayafoline-A (**1**) showed a weak activity against some cancer cell lines.¹² In 2001, Bringmann *et al.* reported the formation of bismurrayafoline-A (**1**) in up to 19% yield as by-product of the reduction of mukonine (**6d**) (7 steps, 9% overall yield of **1**).¹³ We have described a total synthesis of bismurrayafoline-A (**1**) *via* an unprecedented rearrangement during an Ullmann coupling (6 steps, 28% overall yield of **1**).⁸ In 1987, Furukawa *et al.* isolated bismurrayafolinol (**2**), from the root bark of *Murraya euchrestifolia* Hayata.¹⁴ Bringmann *et al.* reported the formation of bismurrayafolinol (**2**) as by-product in up to 6% yield (7 steps, 3% overall yield of **2**) during their synthesis of murrayafoline-A (**6a**).¹³ Chrestifoline-D (**3**) was isolated in 1992 by Furukawa and Wu *et al.* from the root bark of *M. euchrestifolia*.¹⁵ The first synthetic approach by partial synthesis

starting from bismurrayafolinol (**2**) was reported along with the isolation. Chrestifoline-B (**4**) and chrestifoline-C (**5**) were isolated in 1990 by Furukawa *et al.* from the same natural source.¹⁶ Chrestifoline-C (**5**) has been obtained in optically active form ($[\alpha]_D = -5.6$, CHCl₃),¹⁶ but its absolute configuration is not known.

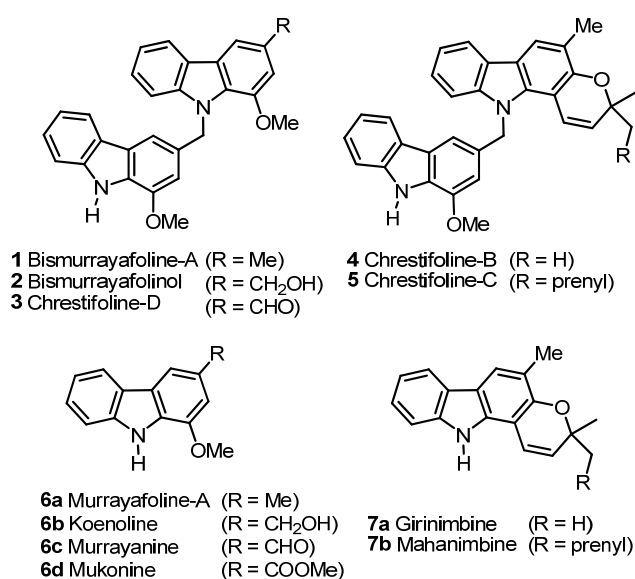
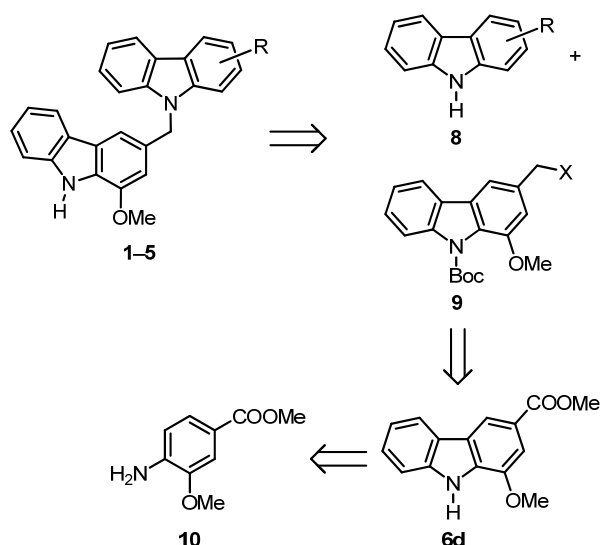


Fig. 1 Bismurrayafoline-A (**1**), bismurrayafolinol (**2**), chrestifoline-B (**4**), chrestifoline-C (**5**), chrestifoline-D (**3**), the 1-methoxycarbazole alkaloids **6a–6d**, girinimbine (**7a**) and mahanimbine (**7b**).

The biscarbazoles **1–5** have an identical benzylic subunit which corresponds to murrayafoline-A (**6a**), but they differ in the benzylic substituent (Fig. 1). For the biscarbazoles **1–3**, the benzylic linkage leads to the nitrogen atom of a 1-oxygenated tricyclic carbazole corresponding to either murrayafoline-A (**6a**), koenoline (**6b**) or murrayanine (**6c**), respectively. For chrestifoline-B (**4**) and chrestifoline-C (**5**), the pyrano[3,2-*a*]carbazole alkaloids girinimbine

(7a) and mahanimbine (7b) serve as benzylic substituents. The monocarbazole building blocks of the biscarbazoles 1–5 are found in nature as well. The 1-methoxycarbazole alkaloids, murrayafoline-A (6a), koenoline (6b), murrayanine (6c) and mukonine (6d), have been obtained from diverse plants of the Rutaceae family.¹ The pyrano[3,2-*a*]carbazole alkaloids girinimbine (7a) and mahanimbine (7b) were isolated first by Chakraborty *et al.* from *Murraya koenigii* Spreng.^{17,18} Our group previously described synthetic routes to all individual carbazole fragments present in the biscarbazoles 1–5. An efficient iron-mediated synthesis of the 1-methoxycarbazole alkaloids 6a–d was reported early on.^{7,19} More recently, an optimised palladium-catalysed synthesis of mukonine (6d) was described.⁷ Several synthetic routes to girinimbine (7a) and an efficient access to mahanimbine (7b) were also developed by our group.²⁰

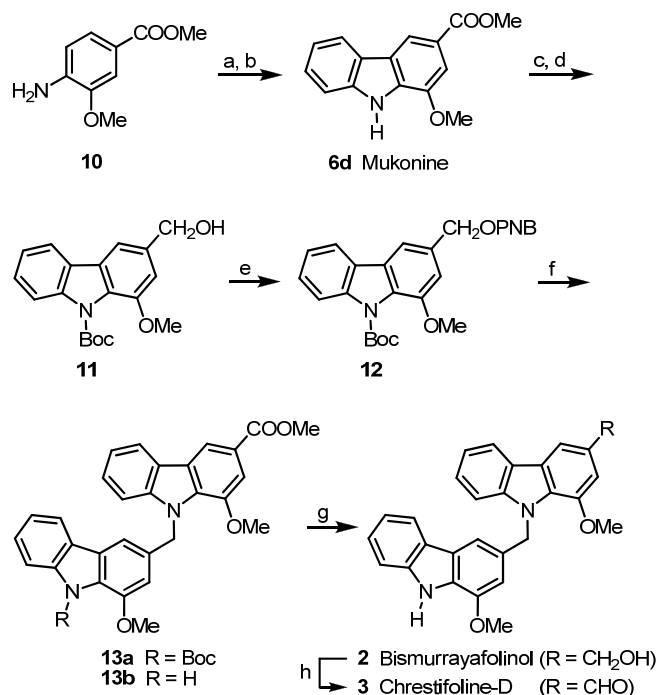


Scheme 1 Retrosynthetic analysis of the methylene-bridged biscarbazoles 1–5.

For the synthesis of the biscarbazoles 1–5 we envisaged a retrosynthetic cleavage of the C–N linkage between both carbazole units which leads to the carbazoles 8 and 9 as precursors (Scheme 1). In our approach the nitrogen atom of carbazole 8 serves as nucleophile. Thus, carbazole 8 is represented by the unprotected naturally occurring carbazoles 6a–c, 7a and 7b. Fragment 9 should have a leaving group at the benzylic position and would be represented by an appropriate koenoline derivative. Compound 9 can be prepared from mukonine (6d) which is readily available using the arylamine 10 as starting material.⁷

Buchwald–Hartwig coupling of bromobenzene and arylamine 10 in the presence of SPhos followed by palladium(II)-catalysed oxidative cyclisation afforded mukonine (6d) in 91% yield over both steps (Scheme 2).⁷ Boc-protection of 6d and subsequent reduction of the ester group led to the protected koenoline 11. Next, the hydroxy group had to be transformed into a leaving group. However, in light of the high reactivity of the benzylic position of the koenoline derivative 11,⁷ the resulting compound should have sufficient stability in order to serve as the central intermediate *en route* to the methylene-bridged biscarbazole alkaloids. Treatment of 11 with *p*-nitrobenzoyl chloride in the presence of stoichiometric amounts of DMAP afforded quantitatively the *p*-nitrobenzoate 12. In contrast to the corresponding mesylate,⁷ the *p*-nitrobenzoate 12 is much more stable towards benzyl cation formation.

Thus, the koenoline derivative 12 with an activated benzylic position is available in five steps and 88% overall yield and was subsequently used as relay compound for the synthesis of the methylene-bridged biscarbazole alkaloids 1–5.



Scheme 2 Synthesis of bismurrayafolinol (2) and chrestifoline-D (3). Reagents and conditions: a) 1.2 equiv. PhBr, 6 mol% Pd(OAc)₂, 12 mol% SPhos, 1.4 equiv. Cs₂CO₃, toluene, reflux, 40 h, 100%; b) 10 mol% Pd(OAc)₂, 10 mol% K₂CO₃, PivOH, 115 °C, air, 14 h, 91%; c) 2 equiv. Boc₂O, 1 equiv. DMAP, MeCN, rt, 17 h, 97%; d) 3.2 equiv. DIBAL-H, Et₂O, –78 °C, 3.5 h, 100%; e) 1.5 equiv. *p*-(NO₂)C₆H₄COCl, 1.5 equiv. DMAP, CH₂Cl₂, rt, 1.5 h, 100%; f) 1.3 equiv. mukonine (6d), 0.2 equiv. CuBr, 0.4 equiv. pyrrole-2-carboxylic acid, 4 equiv. K₃PO₄, DMSO, 110 °C, 40 h, 63%; g) 3.2 equiv. DIBAL-H, Et₂O, –78 °C, 4 h, 96%; h) 5 equiv. MnO₂, CH₂Cl₂, rt, 24 h, 78%.

Table 1 Coupling of the *p*-nitrobenzoate 12 with mukonine (6d)

Reaction Conditions	Products, yield (%)
1.3 equiv. 6d, 10 mol% Pd(OAc) ₂ , 10 mol% <i>rac</i> -BINAP, 1.4 equiv. Cs ₂ CO ₃ , toluene, reflux, 4 d	13a, 27%; 13b, 35%
1.3 equiv. 6d, 0.2 equiv. CuBr, 0.4 equiv. pyrrole-2-carboxylic acid, 4 equiv. K ₃ PO ₄ , DMSO, 110 °C, 40 h	13b, 63%

First, we envisaged a Buchwald–Hartwig coupling reaction of the *p*-nitrobenzoate 12 with mukonine (6d). Only a few methods have been described so far using transition metal-catalysed coupling reactions at the benzylic position.²¹ Reaction of 12 and 6d in the presence of catalytic amounts of palladium(II) acetate, *rac*-BINAP and stoichiometric amounts of caesium carbonate in toluene at reflux provided the desired biscarbazole 13a in 27% yield along with the deprotected biscarbazole 13b in 35% yield (Scheme 2, Table 1). The concomitant partial removal of the Boc group could result either from a pericyclic reaction under thermal conditions²² or from a base-promoted saponification. Coupling of 12 and 6d under Ullmann conditions, using

substoichiometric amounts of copper(I) bromide in the presence of pyrrole-2-carboxylic acid,²³ led only to the deprotected biscarbazole **13b** in 63% yield (see experimental procedure).[§] Therefore, the Ullmann coupling reaction is superior for the present synthesis as it provides directly the biscarbazole **13b** and thus avoids an additional deprotection step. Reduction of biscarbazole **13b** with diisobutylaluminium hydride provided bismurrayafolinol (**2**) in 96% yield. The spectroscopic data of **2** are in full agreement with those reported for the natural product.[¶] Reduction of **13b** using lithium aluminium hydride afforded bismurrayafolinol (**2**) in 90% yield but did not lead to bismurrayafoline-A (**1**). Apparently, *N*-substituted carbazoles do not form the quinone imine methide intermediate required for the complete reduction to a 3-methylcarbazole,^{51,13,24} and thus, further reduction of the 3-(hydroxymethyl)carbazole does not occur. Oxidation of bismurrayafolinol (**2**) with manganese(IV) oxide^{25,26} led to chrestifoline-D (**3**).[¶]

Using the present route, the biscarbazole alkaloids **1–5** become available *via* short and efficient routes, bismurrayafoline-A (**1**): 6 steps, 41% overall yield; bismurrayafolinol (**2**): 7 steps, 53% overall yield; chrestifoline-D (**3**): 8 steps, 42% overall yield; chrestifoline-B (**4**): 6 steps, 36% overall yield; (±)-chrestifoline-C (**5**): 6 steps, 28% overall yield based on the arylamine **10**. Chrestifoline-B (**4**) and (±)-chrestifoline-C (**5**) have been obtained by total synthesis for the first time. Studies concerning the bioactivity of the biscarbazole alkaloids **1–5** are in progress.

Notes and references

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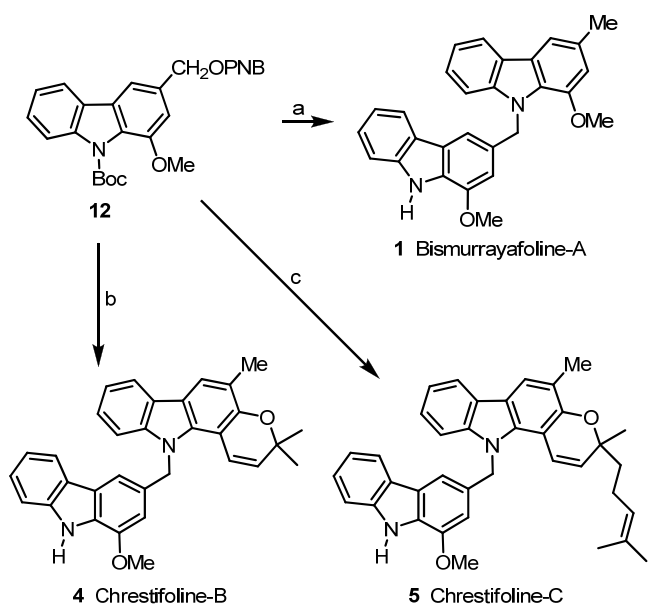
[†] Part 117 of Transition Metals in Organic Synthesis; for Part 116, see: ref. 6b.

[‡] Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of the biscarbazole alkaloids **1–5**. For ESI see DOI: 10.1039/c000000x/

[§] Experimental procedure for the Ullmann-type coupling to biscarbazole **13b**:

A solution of the *p*-nitrobenzoate **12** (66.6 mg, 0.140 mmol), freshly dried potassium phosphate (120 mg, 0.566 mmol), mukonine (**6d**) (46.4 mg, 0.182 mmol), copper(I) bromide (4.0 mg, 28 μmol), and pyrrole-2-carboxylic acid (6.2 mg, 56 μmol) in DMSO (1 mL) was heated at 110 °C for 40 h. Water (1.5 mL) and a saturated aqueous solution of ammonium chloride (3 mL) were added, the layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (gradient elution with petroleum ether/ethyl acetate, 19:1 to 7:3) afforded the biscarbazole **13b** (40.9 mg, 63%) as a colourless solid; mp 152.5–153 °C. UV (MeOH): λ = 240 (sh), 252 (sh), 270, 292 (sh), 325 nm; IR (ATR): ν = 3360, 3055, 2992, 2949, 2933, 2836, 1771, 1734, 1716, 1692, 1653, 1625, 1582, 1542, 1503, 1489, 1448, 1401, 1358, 1338, 1306, 1266, 1251, 1200, 1167, 1134, 1103, 1037, 1011, 991, 947, 906, 861, 837, 764, 729, 694, 665, 613 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 3.81 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 6.05 (s, 2 H), 6.76 (d, *J* = 0.8 Hz, 1 H), 7.17 (ddd, *J* = 7.9 Hz, 6.9 Hz, 1.1 Hz, 1 H), 7.27 (ddd, *J* = 7.8 Hz, 7.0 Hz, 0.8 Hz, 1 H), 7.37 (ddd, *J* = 8.1 Hz, 7.0 Hz, 1.1 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.497 (d, *J* = 8.1 Hz, 1 H), 7.500 (s, 1 H), 7.66 (d, *J* = 1.3 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 8.14 (d, *J* = 7.8 Hz, 1 H), 8.20 (br s, 1 H), 8.54 (d, *J* = 1.3 Hz, 1 H); ¹³C NMR and DEPT (125 MHz, CDCl₃): δ = 49.76 (CH₂), 52.18 (CH₃), 55.51 (CH₃), 56.08 (CH₃), 104.89 (CH), 108.20 (CH), 110.38 (CH), 110.99 (CH), 111.09 (CH), 116.38 (CH), 119.46 (CH), 120.23 (CH), 120.56 (CH), 120.66 (CH), 121.50 (C), 123.51 (C), 123.65 (C), 124.17 (C), 124.55 (C), 125.88 (CH), 126.48 (CH), 129.13 (C), 130.65 (C), 133.19 (C), 139.49 (C), 141.76 (C), 145.87 (C), 146.57 (C), 168.03 (C); ESI-MS (+50 V): *m/z* = 487 [M+Na]⁺, (–100 V): *m/z* = 463 [M–H][–]; MS (EI): *m/z* (%) = 464 (26, M⁺), 255 (32), 240 (8), 224 (8), 210 (100), 167 (11); HRMS: *m/z* calcd. for C₂₉H₂₄N₂O₄ (M⁺): 464.1736; found: 464.1741.

[¶] Bismurrayafoline-A (**1**): Light brownish solid, mp 209–210 °C; UV (MeOH): λ = 224, 243, 251, 262 (sh), 282, 292, 323 (sh), 338, 352 (sh) nm; MS (EI): *m/z* (%) = 420 (M⁺, 40), 210 (100).



Scheme 3 Synthesis of bismurrayafoline-A (**1**), chrestifoline-B (**4**), and chrestifoline-C (**5**). *Reagents and conditions*: a) 1.5 equiv. **6a**, 0.4 equiv. CuBr, 0.8 equiv. pyrrole-2-carboxylic acid, 4 equiv. K₃PO₄, DMSO, 110 °C, 2 d, 46%; b) 1.5 equiv. **7a**, 0.2 equiv. CuBr, 0.4 equiv. pyrrole-2-carboxylic acid, 4 equiv. K₃PO₄, DMSO, 125 °C, 40 h, 41%; c) 1.5 equiv. **7b**, 0.2 equiv. CuBr, 0.4 equiv. pyrrole-2-carboxylic acid, 4 equiv. K₃PO₄, DMSO, 120 °C, 40 h, 32%.

Using the Ullmann-type coupling of the *p*-nitrobenzoate **12** with the appropriate carbazole building blocks **6a**, **7a** and **7b**, the methylene-bridged biscarbazoles **1**, **4** and **5** became directly available (Scheme 3). Thus, reaction of murrayafoline-A (**6a**)⁸ with the *p*-nitrobenzoate **12** provided bismurrayafoline-A (**1**) in 46% yield.[¶] Ullmann-type coupling of the nitrobenzoate **12** with girinimbine (**7a**)^{20c} afforded chrestifoline-B (**4**) and reaction of **12** with mahanimbine (**7b**)^{20c} provided (±)-chrestifoline-C (**5**).[¶] Comparison of the four Ullmann-type couplings described herein reveals that mukonine (**6d**), which obviously is more stable under the reaction conditions, provided the best yield (63%) for the copper-induced C–N bond formation with compound **12**.

In conclusion, five naturally occurring methylene-bridged biscarbazole alkaloids were synthesised using the Ullmann-type coupling at the benzylic carbon atom of the relay compound **12** as key

Bismurrayafolinol (**2**): Colourless solid, mp 120–121.5 °C; UV (MeOH): λ = 225, 243, 252, 261 (sh), 281, 292, 331, 343 (sh) nm; MS (EI): m/z (%) = 436 (M^+ , 12), 210 (100).

Chrestifoline-D (**3**): Colourless solid, mp 163.5–164 °C; UV (MeOH): λ = 222, 242, 251, 275, 291, 338, 346 (sh) nm; MS (EI): m/z (%) = 434 (M^+ , 22), 210 (100).

Chrestifoline-B (**4**): Light brownish solid, mp 106–107 °C; UV (MeOH): λ = 227 (sh), 239, 251 (sh), 258 (sh), 290, 325, 338, 358 (sh) nm; ESI-MS (–10 V): m/z = 471 [$M-H$][–].

(±)-Chrestifoline-C (**5**): Light brownish solid, mp 90 °C; UV (MeOH): λ = 228 (sh), 242, 251 (sh), 282 (sh), 290, 327, 340, 360 nm; ESI-MS (+10 V): m/z = 541 [$M+H$]⁺.

For the ¹H and ¹³C NMR spectra of the biscarbazoles **1–5**, see: ESI.

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