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Synthesis of methylene-bridged binary carbazole alkaloids and a related tricarbazole

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Abstract—The first synthesis of the methylene-bridged binary carbazole alkaloids bismurrayafoline-A and chrestifoline-A is described. As an interesting side product, a likewise benzylically connected trimer was identified, a potential natural product.

1. Introduction

Among the few binary carbazole alkaloids connected through a methylene unit,[1] three are formally derived from the 1-methoxy-3-methyl- and 1-methoxy-3-hydroxymethyl-carbazoles murrayafoline-A (**1**) and koenoline (**2**) (Fig. 1): bismurrayafoline-A (**3**),[2] bismurrayafolinol (**4**)[3] and chrestifoline-A (**6**).[4] All of them have been isolated from *Murraya euchrestifolia* and the latter also from *M. koenigii* (Rutaceae). For bismurrayafoline-A (**3**) and chrestifoline-A (**6**), a moderate anti-tumor activity has been found recently.[5]

None of these methylene-bridged biscarbazole alkaloids, however, have as yet been synthesized.[6] Furukawa et al. only mentioned the synthesis of the related (but unnatural) benzylic acetate **5** by $NaBH_4$ reduction of murrayanine (1-methoxycarbazole-3-carbaldehyde), acidification with HCl, and subsequent treatment with Ac_2O, without isolating the intermediate bismurrayafolinol (**4**) and without giving yields or any further details.[3] In this paper, the first synthesis of bismurrayafoline-A (**3**) and chrestifoline-A (**6**) is described.

2. Results and discussion

A more recent detailed investigation of the side products in the course of an upscaling of our total synthesis of

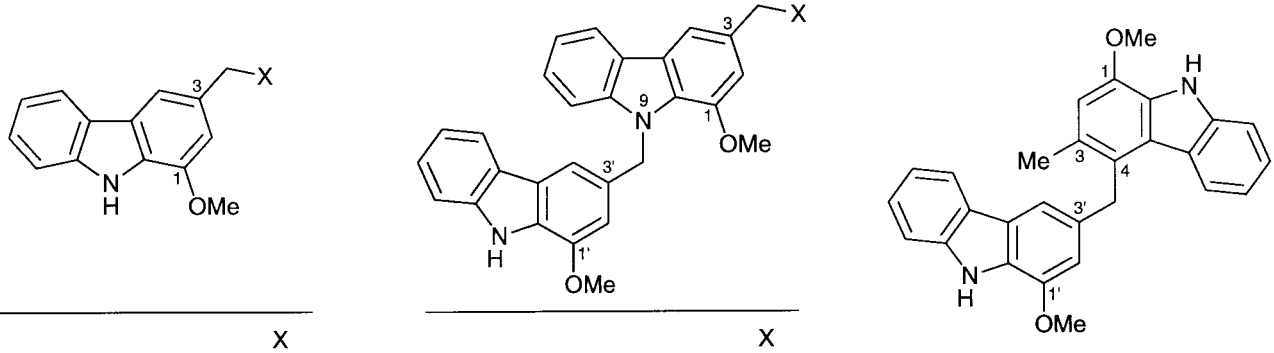

Figure 1. Mono- and dimeric carbazoles.

Keywords: binary carbazole alkaloids; biscarbazole; tricarbazole; *Murraya*.
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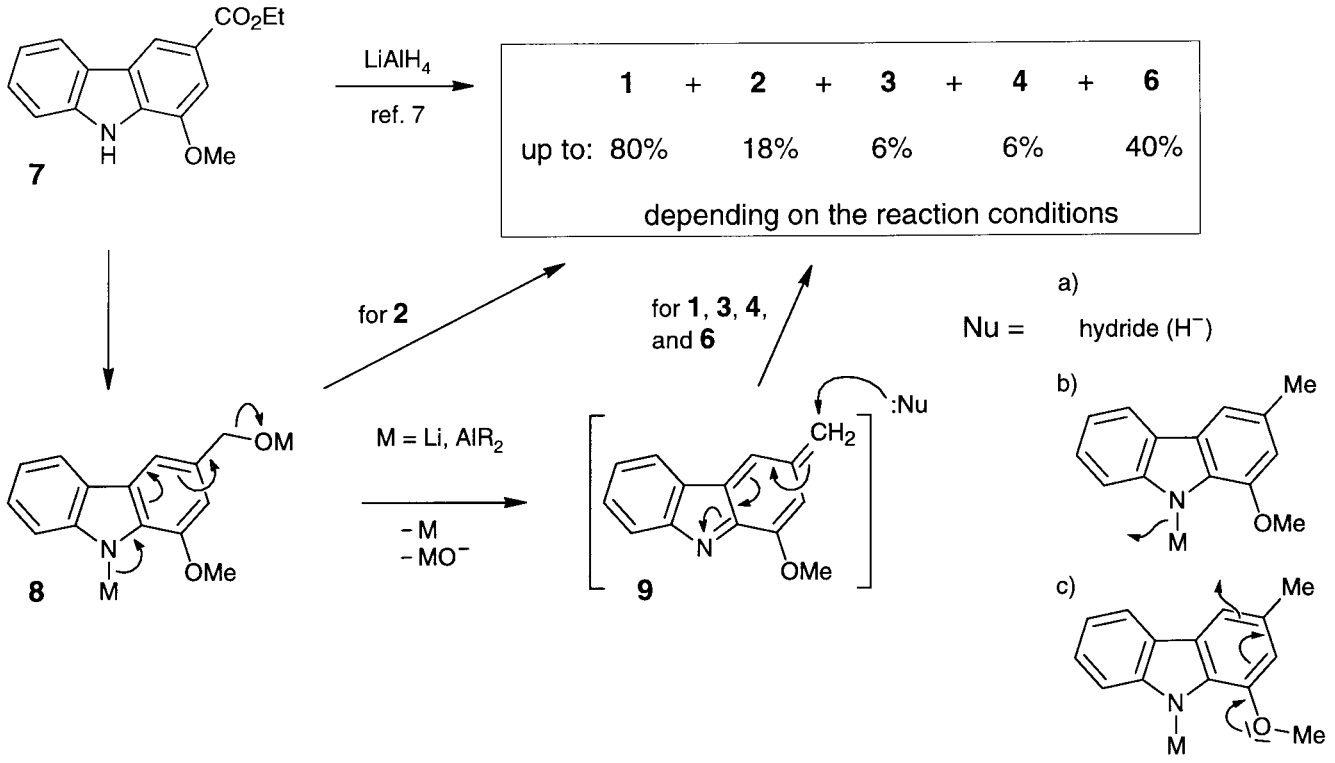
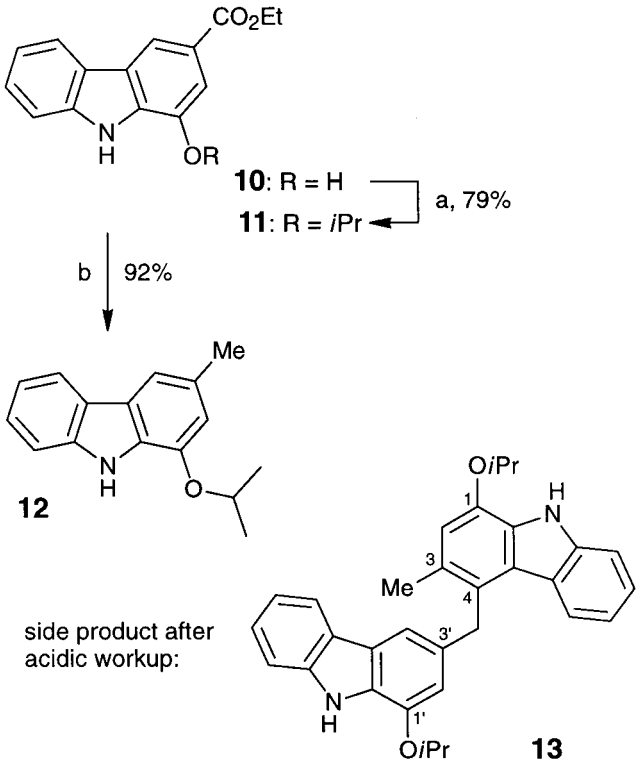


Scheme 1. $LiAlH_4$ reduction of **7** to give i.a. the binary alkaloids **3**, **4** and **6**.

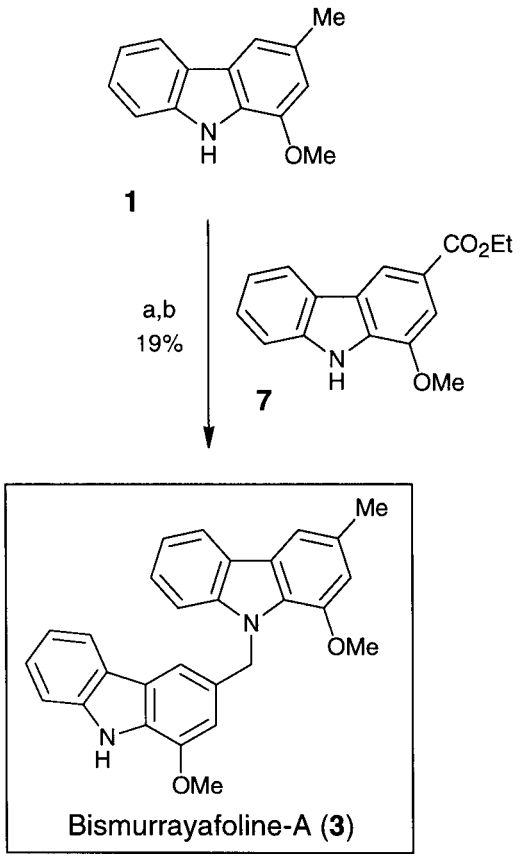
murrayafoline-A (**1**),[7] viz the final reduction of the ester function of **7** with $LiAlH_4$ to give the methyl group directly, has now revealed this reaction to yield the binary carbazole alkaloids **3** and **4** as minor products (up to 6% each) and **6** in even up to 40% after acidic workup in a few cases. The product quantities obtained seemed to be dependent on factors like the concentration of the reaction solution and the pH value during workup.[8] The standard outcome of this reaction was the formation of murrayafoline-A (**1**) in 80% yield besides 10–18% of koenoline (**2**) (Scheme 1). In the case of the isolation of 40% of chrestifoline-A (**6**), no koenoline (**2**) was found any more and the yield in murrayafoline-A (**1**) decreased to 56%, indicating that almost equimolar quantities of these two compounds had reacted to give **6**, most probably during acidic workup. These results made it rewarding to look for more efficient synthetic pathways to give the bicarbazoles in better yields.

To explore the influence of a sterically more demanding substituent at C-1, the reduction of the 3-ester functionality was likewise performed on the *O*-isopropyl substrate **11** (Scheme 2). The O*i*-Pr group was found to prevent side reactions at the endocyclic nitrogen, giving rise to 92% of the 3-methyl compound **12** without yielding any *C*–*N*-bonded biscarbazoles. If, however, 2N HCl was used for acidification of the reaction mixture, instead of saturated aqueous NH_4Cl, the di-*O*-isopropyl analog **13** of chrestifoline-A (**6**) could be isolated in up to 14% yield, decreasing the amount of **12** to 83%.

For an enhanced formation of *C*–*N*-bonded carbazoles, the standard reduction of **7** was carried out in a highly concentrated solution with only 1.0 equiv. (instead of 3.0) of $LiAlH_4$ in the presence of $AlCl_3$ as a Lewis acid, in order to keep the actual amount of metalated koenoline **8** (Scheme 1) constant while decreasing the concentration of *H*-nucleophiles in the reaction mixture. This should permit other nucleophiles (like *N*-deprotonated carbazole molecules;



Scheme 2. Ester reduction of the *O*-isopropyl compound **11**: (a) 2-iodopropane, Cs_2CO_3, acetone, Δ, 9 h; (b) $LiAlH_4$, Et_2O/CH_2Cl_2, rt, 2 h.

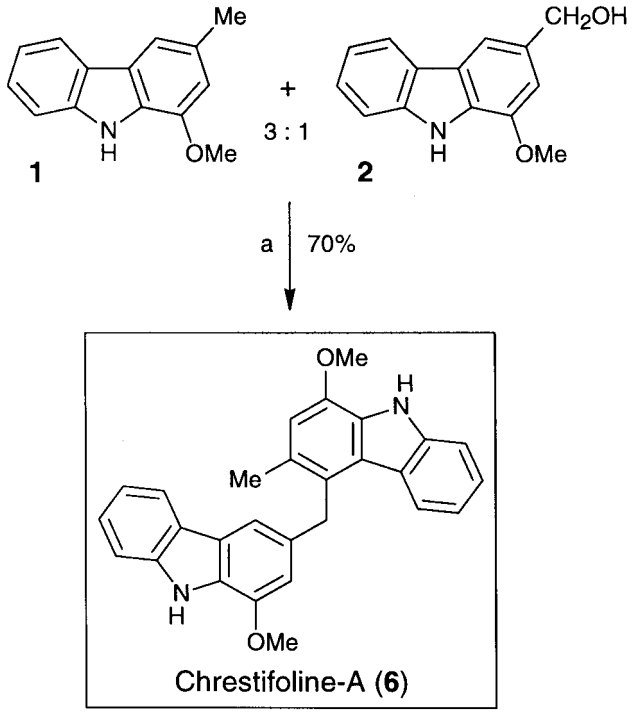


Scheme 3. Synthesis of bismurrayafoline-A (**3**): (a) $LiAlH_4$, Et_2O/CH_2Cl_2, rt, 30 min; (b) addition of **7** in Et_2O/CH_2Cl_2 over 30 min, rt, further 60 min.

see Scheme 1, nucleophile b) to compete in the final trapping of the reactive intermediate **9**. This procedure, however, led to an isolation of 53% koenoline (**2**) besides 33% murrayafoline-A (**1**), while the benzylic bicarbazoles were again formed only as minor products.

In another approach, 2.0 equiv. of murrayafoline-A (**1**) were stirred in a small volume of Et_2O/CH_2Cl_2 together with 3.0 equiv. of $LiAlH_4$ for 30 min at rt prior to the slow addition of 1.0 equiv. of ester **7** dissolved in the same solvent (Scheme 3). The first step was expected to provide an excess of carbazolic nucleophiles—the *N*-deprotonated murrayafoline-A—which should thus more easily 'win' against the *H*-nucleophiles in the competition to react with **9** formed by the reduction of **7**. After 1 h stirring at rt, as much as 19% of **7** (i.e. three times more than above) had been converted to bismurrayafoline-A (**3**).[9]

For an improved synthesis of chrestifoline-A (**6**), acidic conditions seemed to be appropriate according to the observations mentioned above for the coincidental formation of **6** and **13**. A concentrated solution of 1.0 equiv. of koenoline (**2**) and 3.0 equiv. of murrayafoline-A (**1**) in Et_2O/CH_2Cl_2 was treated with some drops of concentrated HCl and stirred for 30 min. In this case, up to 70% of koenoline (**2**) and the same absolute amount of murrayafoline-A (**1**) reacted to give the desired binary carbazole **6** (Scheme 4). The reaction was, however, not easy to control, so that the product quantities could vary.



Scheme 4. Preparation of chrestifoline-A (**6**): (a) Et_2O/CH_2Cl_2, concd HCl, rt, 30 min.

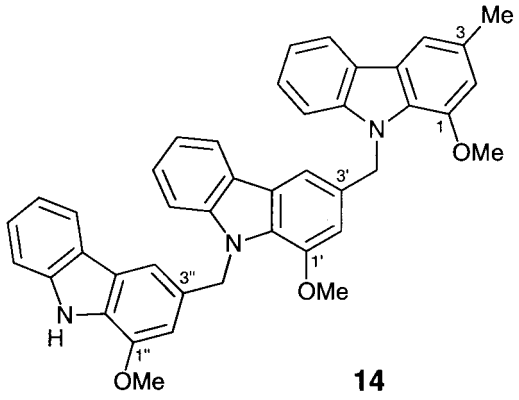


Figure 2. Structure of the novel tricarbazole **14**.

As an entirely unprecedented minor side product (up to 4%), the twofold methylene-bridged tricarbazole **14** (Fig. 2) was identified in a few cases. The possibility of oligomer formation had already been mentioned by Furukawa et al., who, however, did not provide any concrete structures or spectral evidence.[3]

3. Conclusion

In summary, the binary carbazoles bismurrayafoline-A (**3**) and chrestifoline-A (**6**) were prepared for the first time, giving up to 19 and 70% yields, respectively. Bismurrayafolinol (**4**) was likewise attained synthetically even though only as a minor product during the standard reduction of ester **7**. With these alkaloids now preparatively available, further investigations on biological activities have become

possible. The tricarbazole **14** with its unprecedented structure represents a potential novel type of natural products.

4. Experimental

4.1. General

Melting points (Reichert-Jung Thermovar microscope) are uncorrected. IR spectra were measured using Perkin–Elmer 1420 and FTIR 1600 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded at rt on a Bruker AM 250. Chemical shifts δ are reported in ppm and coupling constants J in Hz. The solvent signal was used as the internal standard [^{1}H: δ ($CDCl_3$)=7.26, δ (d_6-acetone)=2.05; ^{13}C: δ ($CDCl_3$)=77.01, δ (d_6-acetone)=29.82]. The mass (MS) and high resolution mass (HRMS) spectra were measured on a Finnigan MAT 90 and MAT 8200 mass spectrometer by using electron impact ionization (EI). The spectra are reported in wave numbers (cm^{-1}), the relative intensities are given in brackets. Microanalyses were performed by the microanalytical laboratory of the Institute of Inorganic Chemistry of the University of Würzburg. All reactions, except those involving H_2O, were done under nitrogen and with dried solvents and glassware.

4.1.1. Ethyl 1-hydroxy-9*H*-carbazole-3-carboxylate (10). Compound **10** was prepared in analogy to the final step in the synthesis of clausine E,[7] but here using ethanol as the solvent. A mixture of the cyclization products ethyl 1-acetoxy-9-acetyl-9*H*-carbazole-3-carboxylate and ethyl 1-acetoxy-9*H*-carbazole-3-carboxylate (together 37.8 mmol) were dissolved in 150 ml EtOH and treated with 15.7 g (113 mmol) of K_2CO_3 for 4.5 h under reflux. The reaction was quenched by acidification to pH 4–5 using 2N HCl. The solvents were removed in vacuo and by lyophilization and the residue was separated between H_2O and diethyl ether. After drying of the combined organic layers over $MgSO_4$, and removal of the solvent gave **10** in 95% yield (9.19 g, 36.0 mmol) as crude, orange colored product, which was directly used for the following *O*-alkylation reaction. For a complete characterization, a sample was recrystallized from EtOH/pentane to provide beige crystals: mp 184°C; IR (KBr): ν=3310 (N–H, O–H), 3020 (Ar–H), 2950, 2900, 2820 (C–H), 1630 (C=O), 1610, 1580 (Ar), 1470 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=1.39 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.37 (q, J=7.0 Hz, 2H, $CO_2CH_2CH_3$), 7.25 (ddd, J=7.9, 7.0, 0.9 Hz, 1H, 6-H), 7.45 (ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7-H), 7.64 (d, J=1.2 Hz, 1H, 2-H), 7.65 (dt, J=8.2, 0.9 Hz, 1H, 8-H), 8.19 (d, J=7.9 Hz, 1H, 5-H), 8.44 (d, J=1.2 Hz, 1H, 4-H), 9.09 (s, 1H, OH), 10.66 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=14.74 ($CO_2CH_2CH_3$), 60.97 ($CO_2CH_2CH_3$), 111.5 (C-2), 112.5 (C-8), 115.4 (C-4), 120.4 (C-6), 121.2 (C-5), 122.8, 124.4, 124.9 (each C_q), 127.0 (C-7), 133.6, 141.3, 143.4 (each C_q), 167.6 (CO_2Et); MS: *m*/*z* (%)=255 (100) [M^+], 240 (11) [M^+-Me], 227 (45) [$M^+-C_2H_4$], 210 (89) [M^+-OEt], 182 (37) [210−CO]; Anal. calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.31; H, 5.21; N, 5.43.

4.1.2. Ethyl 1-methoxy-9*H*-carbazole-3-carboxylate (7). Following a literature procedure for the synthesis of mukonine,[7] 542 mg (3.92 mmol) of K_2CO_3 and 298 μl (396 mg, 3.14 mmol) of dimethyl sulfate were added to a solution of 1.00 g (3.92 mmol) crude ester **10** in 40 ml dry acetone. After 7 h under reflux, excessive dimethyl sulfate was scavenged by treatment of the mixture with 5 ml concd aqueous NH_3 and renewed heating under reflux for 30 min. Removal of the solvents, purification of the remaining residue by column chromatography on silica gel (petroleum ether/diethyl ether 5:1), and recrystallization from EtOH/pentane afforded 899 mg (3.34 mmol, 85%) of **7**: mp 209°C (pale yellow crystals); IR (KBr): ν=3320 (N–H), 3040 (Ar–H), 2980, 2960, 2910 (C–H), 1675 (C=O), 1615, 1595, 1570 (Ar), 1485 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=1.41 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.07 (s, 3H, OMe), 4.39 (q, J=7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.20 (s, 3H, NMe), 7.26 (ddd, J=7.9, 7.0, 1.2 Hz, 1H, 6-H), 7.46 (ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7H), 7.60 (d, J=1.2 Hz, 1H, 2-H), 7.63 (d, J=8.2 Hz, 1H, 8-H), 8.20 (d, J=7.9 Hz, 1H, 5-H), 8.49 (d, J=1.2 Hz, 1H, 4-H), 10.78 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=14.79 ($CO_2CH_2CH_3$), 56.03 (OMe), 61.07 ($CO_2CH_2CH_3$), 107.1 (C-2), 112.6 (C-8), 116.5 (C-4), 120.6 (C-6), 121.3 (C-5), 122.8, 124.3 (each C_q), 127.0 (C-7), 134.0, 141.3, 146.3 (each C_q), 167.5 (CO_2Et); one C_q signal overlayed; MS: *m*/*z* (%)=269 (100) [M^+], 254 (24) [M^+-Me], 241 (31) [$M^+-C_2H_4$], 226 (28) [241−Me], 224 (50) [M^+-OEt], 196 (20) [M^+-CO_2Et], 182 (28) [196−CH_2], 181 (21) [182−H]; Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.51; H, 5.32; N, 5.08. Likewise obtained were 6% (62.2 mg, 220 μmol) of the corresponding *N*-methyl derivative, ethyl 1-methoxy-9-methyl-9*H*-carbazole-3-carboxylate:[10] mp 108°C (EtOH/pentane, colorless needles); IR (KBr): ν=3030 (Ar–H), 2985, 2950, 2935, 2910, 2875, 2810 (C–H), 1675 (C=O), 1605, 1575, 1560 (Ar); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=1.41 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.07 (s, 3H, OMe), 4.21 (s, 3H, NMe), 4.39 (q, J=7.0 Hz, 2H, $CO_2CH_2CH_3$), 7.28 (ddd, J=7.6, 6.7, 1.2 Hz, 1H, 6-H), 7.52 (ddd, J=8.2, 6.7, 1.2 Hz, 1H, 7-H), 7.57 (dd, J=8.2, 1.2 Hz, 1H, 8-H), 7.61 (d, J=1.2 Hz, 1H, 2-H), 8.20 (dt, J=7.6, 1.2 Hz, 1H, 5-H), 8.46 (d, J=1.2 Hz, 1H, 4-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.48 ($CO_2CH_2CH_3$), 31.96 (NMe), 55.62 (OMe), 60.64 ($CO_2CH_2CH_3$), 107.5 (C-2), 108.9 (C-8), 115.9 (C-4), 119.6 (C-6), 120.2 (C-5), 121.3, 123.0, 123.8 (each C_q), 126.0 (C-7), 132.9, 141.7, 146.3 (each C_q), 167.3 (CO_2Et); MS: *m*/*z* (%)=283 (100) [M^+], 268 (42) [M^+-Me], 255 (19) [$M^+-C_2H_4$], 240 (61) [255−Me], 210 (10) [M^+-CO_2Et], 195 (10) [210−Me], 180 (4) [195−Me]; Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.74; H, 6.03; N, 4.91.

4.2. Spectral data for binary carbazole alkaloids

A detailed analysis of the product mixture obtained from $LiAlH_4$ reductions of up to 500 mg (up to 1.86 mmol) of ester **7** to give murrayafoline-A (**1**) as the main product following a literature procedure[7] revealed varying quantities of bismurrayafoline-A (**3**), bismurrayafolinol (**4**) and chrestifoline-A (**6**) as side products.

4.2.1. Bismurrayafoline-A (3). Mp 174°C (EtOH/pentane, colorless powder) {Ref.[2] 176–177°C (diethyl ether)}; IR (film): ν=3380 (N–H), 3020 (Ar–H), 2940, 2920, 2840

(C–H), 1710 (C–N), 1570 (Ar), 1445 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=2.49 (s, 3H, Me), 3.84 (s, 3H, 1-OMe), 4.04 (s, 3H, 1′-OMe), 6.03 (s, 2H, NCH_2), 6.92 (s, 1H, 2-H), 7.00 (s, 1H, 2′-H), 7.09, 7.14 (each ddd, J=7.9, 7.0, 0.9 Hz, 1H, 6-H, 6′-H), 7.32, 7.36 (each ddd, J=7.9, 7.0, 0.9 Hz, 1H, 7-H, 7′-H), 7.51 (d, J=7.9 Hz, 1H, 8′-H), 7.56 (s, 1H, 4′-H), 7.61 (s, 1H, 4-H), 7.64 (d, J=7.9 Hz, 1H, 8-H), 7.90 (d, J=7.9 Hz, 1H, 5′-H), 8.05 (d, J=7.9 Hz, 1H, 5-H), 10.29 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=21.67 (Me), 49.77 (NCH_2), 55.70, 56.09 (1-OMe, 1′-OMe), 106.3, 110.0, 110.9, 111.8, 112.1, 113.5 (C-2, C-2′, C-4, C-4′, C-8, C-8′), 119.6 (C-6, C-6′), 120.8 (C-5, C-5′), 124.1, 124.7, 125.8 (each C_q), 126.2 (C-7, C-7′, C_q), 129.6, 129.9, 131.9, 132.0, 141.0, 142.2, 146.7, 147.7 (each C_q); MS: m/z (%)=420 (16) [M^+], 210 (100) [$C_{14}H_{12}NO$], 195 (10) [210−Me], 180 (6) [195−Me], 167 (36) [$C_{12}H_9N$].

4.2.2. Bismurrayafolinol (4). Mp 117°C (EtOH/pentane, colorless powder) (Ref.[3] colorless oil); IR (KBr): ν=3380 (N–H), 3280 (O–H), 3040 (Ar–H), 2970, 2920, 2820 (C–H), 1575 (Ar), 1445 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=3.84 (s, 3H, 1-OMe), 4.06 (s, 3H, 1′-OMe), 4.16 (t, J=5.8 Hz, 1H, CH_2OH), 4.78 (d, J=5.8 Hz, 2H, CH_2OH), 6.06 (s, 2H, NCH_2), 7.01 (d, J=1.2 Hz, 1H, 2-H), 7.12 (d, J=1.2 Hz, 1H, 2′-H), 7.09, 7.16 (each ddd, J=7.9, 7.3, 0.9 Hz, 1H, 6-H, 6′-H), 7.33, 7.38 (each ddd, J=8.2, 7.3, 1.2 Hz, 1H, 7-H, 7′-H), 7.51 (d, J=8.2 Hz, 1H, 8′-H), 7.61 (s, 1H, 4′-H), 7.67 (d, J=8.2 Hz, 1H, 8-H), 7.74 (d, J=1.2 Hz, 1H, 4-H), 7.90 (d, J=7.9 Hz, 1H, 5′-H), 8.09 (d, J=7.9 Hz, 1H, 5-H), 10.30 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=49.80 (NCH_2), 55.71, 56.12 (1-OMe, 1′-OMe), 65.43 (CH_2OH), 106.3, 107.9 (C-2, C-2′), 111.0, 111.8, 112.2 (C-4, C-4′, C-8, C-8′), 119.6, 119.8 (C-6, C-6′), 120.8 (C-5, C-5′), 124.0, 124.2, 124.7, 125.4 (each C_q), 126.2, 126.3 (C-7, C-7′), 130.0, 130.1, 131.8, 135.3, 141.0, 142.2, 146.7, 147.8 (each C_q); MS: m/z (%)=436 (7) [M^+], 227 (6) [$C_{14}H_{13}NO_2$], 210 (100) [$C_{14}H_{12}NO$], 195 (11) [210−Me], 180 (4) [195−Me], 167 (32) [$C_{12}H_9N$].

4.2.3. Chrestifoline-A (6). Mp 150°C (EtOH/pentane, pale beige powder) (Ref.[4] colorless oil); IR (film): ν=3380 (N–H), 3020 (Ar–H), 2960, 2920, 2900, 2820 (C–H), 1565 (Ar), 1480, 1435 (alkyl); the ^{1}H NMR spectrum is identical with that reported in Ref. 4; ^{13}C NMR (62.9 MHz, d_6-acetone): δ=19.64 (3-Me), 36.15 (3′-CH_2), 55.70 (1′-OMe), 55.83 (1-OMe), 107.8 (C-2′), 109.7 (C-2), 112.0 (C-8), 112.1 (C-4′, C-8′), 119.4 (C-6, C6′), 120.8 (C-5′), 123.3 (C-5), 124.1 (C-4b′), 124.2 (C-4b), 124.5 (4a′), 125.0 (C-3′), 125.5 (C-7), 125.9 (C-7′), 126.1 (C-4a), 128.3 (C-4), 129.5 (C-9a′), 129.9 (C-9a), 132.4 (C-3), 141.0 (C-8a′), 141.2 (C-8a), 144.9 (C-1), 146.8 (C-1′); MS: m/z (%)=420 (100) [M^+], 405 (24) [M^+−Me], 390 (9) [405−Me], 375 (9) [390−Me], 224 (19) [$C_{15}H_{14}NO$], 223 (59) [224−H], 210 (100) [$C_{14}H_{12}NO$].

4.3. *O*-Isopropyl compounds

4.3.1. Ethyl 1-isopropoxy-9*H*-carbazole-3-carboxylate (11). To a solution of 1.00 g (3.92 mmol) of crude **10** in 100 ml dry acetone, 2.55 g (7.84 mmol) of Cs_2CO_3 and 510 μl (867 mg, 5.10 mmol) of 2-iodopropane were added and the mixture was stirred for 9 h under reflux. The reaction was quenched by addition of 10 ml concd aqueous NH_3 solution and stirring for another 30 min under reflux. The product **11** was attained as colorless needles after removal of the solvents in vacuo, subsequent purification by column chromatography on silica gel (petroleum ether/diethyl ether 4:1), and recrystallization from EtOH/pentane in 79% yield (877 mg, 3.10 mmol): mp 120°C; IR (KBr): ν=3350 (N–H), 3090, 3030 (Ar–H), 2970, 2930, 2890, 2850 (C–H), 1670 (C=O), 1615, 1595, 1570 (Ar), 1485 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=1.39 (d, J=6.1 Hz, 6H, $OCH(CH_3)_2$), 1.45 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.46 (q, J=7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.85 (sept, J=6.1 Hz, 1H, $OCH(CH_3)_2$), 7.27 (ddd, J=7.9, 7.0, 1.2 Hz, 1H, 6-H), 7.47 (ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7-H), 7.67 (d, J=8.2 Hz, 1H, 8-H), 7.72 (d, J=0.9 Hz, 1H, 2-H), 8.21 (d, J=7.9 Hz, 1H, 5-H), 8.59 (d, J=0.9 Hz, 1H, 4-H), 10.73 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=14.77 ($CO_2CH_2CH_3$), 22.34 ($OCH(CH_3)_2$), 61.04 ($CO_2CH_2CH_3$), 71.60 ($OCH(CH_3)_2$), 109.8 (C-2), 112.5 (C-8), 116.3 (C-4), 120.6 (C-6), 121.2 (C-5), 122.8, 124.4, 124.5 (each C_q), 127.0 (C-7), 135.2, 141.2, 144.3 (each C_q), 167.5 (CO_2Et); MS: m/z (%)=297 (44) [M^+], 255 (100) [$M^+-C_3H_6$], 240 (12) [255−Me], 227 (40) [255−C_2H_4], 210 (54) [255−OEt], 182 (34) [210−CO]; Anal. calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.89; H, 6.25; N, 4.64.

4.3.2. 1-Isopropoxy-3-methyl-9*H*-carbazole (12). According to the procedure presented in Ref. 7 for the synthesis of murrayafoline-A (**1**), 200 mg (673 μmol) of ester **11** were dissolved in 40 ml of CH_2Cl_2/diethyl ether (1:1) and reduced with 76.6 mg (2.02 mmol) $LiAlH_4$ for 3 h at rt. The reaction mixture was neutralized with saturated aqueous NH_4Cl solution and the pH value was adjusted to 5–6 using 0.5N HCl. After extraction with diethyl ether, drying of the combined organic layers over $MgSO_4$, and removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether 3:1) to yield 148 mg (618 μmol, 92%) of **12** as a pale yellow oil, which failed to crystallize from a solvent, but solidified upon standing: mp 72°C; IR (KBr): ν=3320 (N–H), 3030 (Ar–H), 2955, 2930, 2890 (C–H), 1570 (Ar), 1440 (alkyl); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ=1.48 (d, J=6.1 Hz, 6H, $OCH(CH_3)_2$), 2.57 (s, 3H, 3-Me), 4.79 (sept, J=6.1 Hz, 1H, $OCH(CH_3)_2$), 6.79 (s, 1H, 2-H), 7.23 (ddd, J=7.9, 6.1, 2.0 Hz, 1H, 6-H), 7.38–7.47 (m, 2H, 7-H, 8-H), 7.51 (s, 1H, 4-H), 8.05 (d, J=7.9 Hz, 1H, 5-H), 8.21 (s, 1H, NH); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=21.93 (3-Me), 22.38 ($OCH(CH_3)_2$), 70.60 ($OCH(CH_3)_2$), 110.2 (C-2), 110.8 (C-8), 112.4 (C-4), 119.0 (C-6), 120.4 (C-5), 123.6, 124.5 (each C_q), 125.4 (C-7), 129.1, 129.3, 139.4, 143.4 (each C_q); MS: m/z (%)=239 (34) [M^+], 197 (100) [$M^+-C_3H_6$], 196 (46) [$M^+-C_3H_7$], 167 (25) [$C_{12}H_9N$]; Anal. calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.82. Found: C, 80.23; H, 7.14; N, 5.82.

4.3.3. 1-Isopropoxy-4-[1′-isopropoxy-3′-methylene-9′*H*-carbazole]-3-methyl-9*H*-carbazole (13). If 2N HCl was used for quenching the reduction described above, up to 22.8 mg (47.9 μmol, 14%) of dimer **13** could be isolated

along with 134 mg (560 μmol, 83%) **12**. Product **13** crystallized as a yellow solid from EtOH/pentane: mp 127°C; IR (film): ν=3400 (N–H), 3020 (Ar–H), 2995, 2920, 2880, 2820 (C–H), 1555 (Ar), 1470, 1425 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=1.26 (d, J=6.1 Hz, 6H, 1′-OCH(CH_3)$_2$), 1.42 (d, J=6.1 Hz, 6H, 1-OCH(CH_3)$_2$), 2.47 (s, 3H, 3-Me), 4.55 (sept, J=6.1 Hz, 3H, 1′-OCH(CH$_3$)$_2$), 4.78 (s, 2H, NCH$_2$), 4.83 (sept, J=6.1 Hz, 3H, 1-OCH(CH$_3$)$_2$), 6.96–7.02 (m, 3H, 2-H, 2′-H, 6-H), 7.04 (ddd, J=7.9, 7.0, 1.2 Hz, 1H, 6′-H), 7.28 (ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7-H), 7.29 (ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7′-H), 7.46 (s, 1H, 4′-H), 7.49 (d, J=8.2 Hz, 1H, 8′-H), 7.55 (d, J=8.2 Hz, 1H, 8-H), 7.83 (d, J=7.9 Hz, 1H, 5′-H), 8.11 (d, J=7.9 Hz, 1H, 5-H), 10.13 (s, 1H, 9′-H), 10.25 (s, 1H, 9-H); ^{13}C NMR (62.9 MHz, d_6-acetone): δ=19.64 (3-Me), 22.34 (1′-OCH(CH_3)$_2$), 22.60 (1-OCH(CH_3)$_2$), 36.09 (3′-CH$_2$), 71.01 (1′-OCH(CH$_3$)$_2$), 71.32 (1-OCH(CH$_3$)$_2$), 110.8 (C-2′), 111.9 (C-2), 112.0 (C-8), 112.2 (C-4′), 112.8 (C-8′), 119.3 (C-6, C-6′), 120.7 (C-5′), 123.2 (C-5), 124.1 (C-4b′), 124.3 (C-4b), 124.6 (4a′), 125.2 (C-3′), 125.5 (C-7), 125.9 (C-7′), 126.4 (C-4a), 128.1 (C-4), 130.6 (C-9a′), 131.3 (C-9a), 132.3 (C-3), 140.9 (C-8a′), 141.2 (C-8a), 142.8 (C-1), 144.6 (C-1′); MS: m/z (%)=476 (100) [M$^+$], 434 (33) [M$^+$−C$_3$H$_7$], 392 (71) [M$^+$−2C$_3$H$_6$], 377 (11) [392−Me], 210 (22) [C$_{14}$H$_{12}$NO], 209 (49) [C$_{14}$H$_{11}$NO], 196 (67) [392, z=2], 188.5 (19) [377, z=2]; HRMS calcd for C$_{32}$H$_{32}$N$_2$O$_2$ 476.246, found 476.246.

4.4. Attempts for a directed synthesis of bismurrayafoline-A (3)

Method A. The reduction of 60.0 mg (223 μmol) of ethyl 1-methoxy-9*H*-carbazole-3-carboxylate (**7**) was performed in 1 ml CH$_2$Cl$_2$/diethyl ether (1:1) using 8.46 mg (223 μmol) LiAlH$_4$ in the presence of 29.7 mg (223 μmol) of AlCl$_3$, first for 4 h at 0°C, then for further 20 h at rt. The reaction mixture was neutralized with saturated aqueous NH$_4$Cl solution and the pH value was adjusted to 5–6 using 0.5N HCl. After extraction with diethyl ether, drying of the combined organic layers over MgSO$_4$, and removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether 5:1) to yield 15.5 mg (73.6 μmol, 33%) murrayafoline-A (**1**), 26.8 mg (118 μmol, 53%) koenoline (**2**) and 23.5 mg (5.60 μmol, 5%) bismurrayafoline-A (**3**), along with 4.74 mg (17.6 μmol, 8%) of starting material **7**. Spectral data of **1** and **2** were identical to those given in Ref. 7.

Method B. A solution of 47.0 mg (222 μmol) of murrayafoline-A (**1**) in 3 ml CH$_2$Cl$_2$/diethyl ether (1:1) was treated with 12.7 mg (334 μmol) of LiAlH$_4$ and stirred for 30 min at rt. Over a period of 30 min, 30.0 mg (111 μmol) of ester **7** dissolved in 2 ml of the same solvent mixture were added and the suspension was stirred for another 60 min before it was treated with further 4.22 mg (111 μmol) of LiAlH$_4$. After additional 60 min of stirring, workup was done according to method A. Besides the 47.0 mg (222 μmol) murrayafoline-A (**1**) used as starting material, further 16.4 mg (77.6 μmol, 70% referring to the reduction of **7**) **1** and 4.46 mg (10.6 μmol, 19%)[9] bismurrayafoline-A (**3**) were isolated.

4.5. Synthesis of chrestifoline-A (6)

To a solution of 11.0 mg (48.4 μmol) of koenoline (**2**) and 30.7 mg (145 μmol) of murrayafoline-A (**1**) in 3 ml CH$_2$Cl$_2$/diethyl ether (1:1), 5 drops of concd aqueous HCl were added at rt and the solution was stirred for 30 min. The mixture was diluted with 5 ml of H$_2$O and extracted with diethyl ether. Further workup in accordance to the one described for the synthesis of **3**, gave, besides 22.8 mg (108 μmol) murrayafoline-A (**1**), 14.2 mg (33.8 μmol, 70% referring to the incorporation of one molecule of **2** into one molecule of **6**) of chrestifoline-A (**6**).

4.5.1. 1-Methoxy-9-[1′-methoxy-9′-(1″-methoxy-3″-methylene-9″*H*-carbazole)-3′-methylene-9′*H*-carbazole]-3-methyl-9*H*-carbazole (14). In a few cases, compound **14** could be isolated as a minor product (up to 4%, yellow oil) from the reaction mixture of the chrestifoline-A synthesis. IR (KBr): ν=3370 (N–H), 3020 (Ar–H), 2930, 2900, 2830 (C–H), 1570, 1490 (Ar), 1440 (alkyl); ^{1}H NMR (250.1 MHz, d_6-acetone): δ=2.49 (s, 3H, 3-Me), 3.78, 3.89, 4.04 (each s, 3H, 1OMe, 1′-OMe, 1″-OMe), 5.99, 6.04 (each s, 2H, 3′-CH$_2$, 3″-CH$_2$), 6.92, 6.94 (each d, J=1.2 Hz, 1H, 2-H, 2″-H), 7.10 (d, J=1.2 Hz, 1H, 2′-H), 7.08, 7.11, 7.14 (each ddd, J=7.9, 7.0, 0.9 Hz, 1H, 6-H, 6′-H, 6″-H), 7.31, 7.34, 7.37 (each ddd, J=8.2, 7.0, 1.2 Hz, 1H, 7-H, 7′-H, 7″-H), 7.49 (d, J=8.2 Hz, 1H, 8″-H), 7.55, 7.56 (each s, 1H, 4′-H, 4″-H), 7.65 (s, 1H, 4-H), 7.62, 7.67 (each d, J=8.2 Hz, 1H, 8-H, 8′-H), 7.86, 7.91 (each d, J=7.9 Hz, 1H, 5′-H, 5″-H), 8.05 (d, J=7.9 Hz, 1H, 5-H), 10.26 (s, 1H, NH); MS: m/z (%)=629 (6) [M$^+$], 419 (11) [M$^+$−C$_{14}$H$_{12}$NO], 405 (1) [419−CH$_2$], 224 (2) [C$_{15}$H$_{14}$NO], 210 (100) [C$_{14}$H$_{12}$NO], 196 (8) [C$_{13}$H$_{10}$NO], 195 (7) [C$_{13}$H$_9$NO], 180 (7) [195−Me], 167 (23) [C$_{12}$H$_9$N]; HRMS calcd for C$_{42}$H$_{35}$N$_3$O$_3$ 629.268, found 629.269.

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8. The reaction mixture should be quenched using saturated aqueous NH_4Cl solution and the pH value should be adjusted to 5–6 with 0.5N HCl rather than only using 2N HCl as stated in Ref. 7.
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