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First total synthesis of the biologically active 2,7-dioxygenated tricyclic carbazole alkaloids 7-methoxy-*O*-methylmukonal, clausine H (clauszoline-C), clausine K (clauszoline-J) and clausine O

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Using the iron-mediated arylamine cyclization as the key step we have achieved a short and highly efficient access to the biologically active 2,7-dioxygenated tricyclic carbazole alkaloids 7-methoxy-*O*-methylmukonal, clausine H (clauszoline-C), clausine K (clauszoline-J) and clausine O.

Carbazole alkaloids are continuing to attract strong interest due to their promising biological activities.[1–3] The tricyclic carbazole alkaloids exhibit a broad range of different structures with diverse functional groups. They have been classified according to their oxygenation pattern.[3] Several methods have been applied to the synthesis of these natural products.[3,4] We reported a highly convergent route to carbazoles by an iron-mediated oxidative coupling of arylamines and cyclohexadienes.[3,5] Our approach proved to be very efficient for the synthesis of 1-, 3-, 3,4-di- and 3,4,7-tri-oxygenated tricyclic carbazole alkaloids, but was limited in the case of 2-oxygenated carbazoles.[6] In the present paper we describe the application of our methodology to the synthesis of a series of biologically active 2,7-dioxygenated tricyclic carbazole alkaloids (Fig. 1).

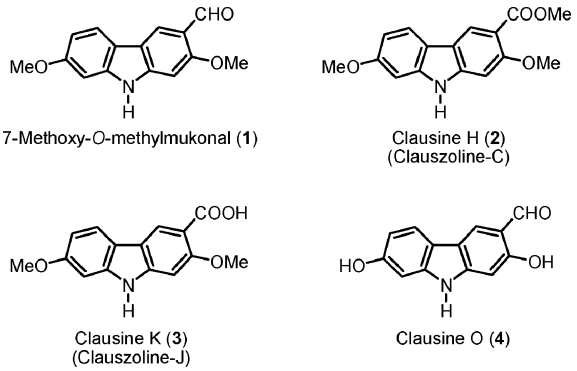
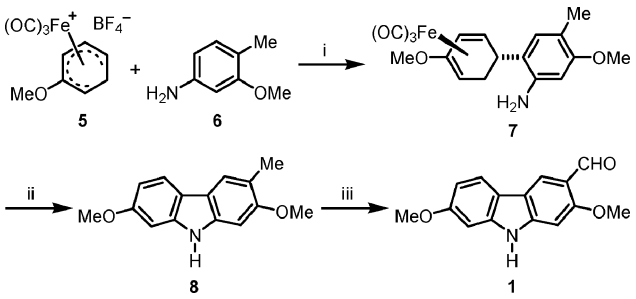


Fig. 1 Naturally-occurring 2,7-dioxygenated tricyclic carbazole alkaloids.

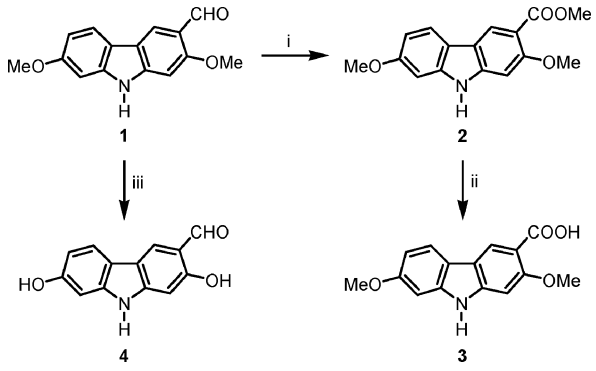
7-Methoxy-*O*-methylmukonal (**1**) was isolated by Lange and co-workers from the roots of *Murraya siamensis*.[7] Wu *et al.* obtained clausine H (**2**) and clausine K (**3**) from the stem bark of *Clausena excavata* collected in Taiwan.[8] The same alkaloids were isolated by Ito *et al.* from *Clausena excavata* Burm. f. and were named clauszoline-C (**2**)[9] and clauszoline-J (**3**).[10] Moreover, Wu *et al.* isolated clausine O (**4**) from the root bark of *Clausena excavata*.[11] Extracts of the leaves and bark of *Clausena excavata* have been used as a folk medicine for the treatment of infections and various diseases. Clausine K (clauszoline-J) (**3**) was also obtained from the roots of the plant *Clausena harmandiana*.[12] Clausine H (clauszoline-C) (**2**) exhibits antiplasmodial activity against *Plasmodium falciparum*.[12] Recently, clausine K (clauszoline-J) (**3**) was found to show antimycobacterial activity against *Mycobacterium tuberculosis*.[13]

Owing to the promising pharmacological potential of these carbazole alkaloids, we have developed a straightforward three-step approach to 7-methoxy-*O*-methylmukonal (**1**), which was then transformed into the other natural products. Electrophilic substitution by reaction of the 2-methoxy-substituted iron complex salt **5**[14] with 3-methoxy-4-methylaniline (**6**) afforded the iron complex **7** (Scheme 1). Treatment of complex **7** with iodine in pyridine at 90 °C provided 2,7-dimethoxy-3-methylcarbazole (**8**) by iron-mediated arylamine cyclization with concomitant aromatization and demetalation, thus furnishing the framework with the desired substitution pattern. Oxidation of the carbazole **8** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to 7-methoxy-*O*-methylmukonal (**1**).



Scheme 1 Iron-mediated synthesis of 7-methoxy-*O*-methylmukonal (**1**). *Reagents and conditions*: (i) MeCN, rt, 4.5 h, 76%; (ii) iodine, pyridine, 90 °C, 5.5 h, 68%; (iii) 4.2 equiv. DDQ, MeOH/H_2O, rt, 70 min, 67%.

We considered alkaloid **1** as a crucial precursor for the synthesis of the other 2,7-dioxygenated carbazoles (Scheme 2). Thus, oxidation of **1** with manganese dioxide in methanol in the presence of potassium cyanide[15] provided quantitatively clausine H (clauszoline-C) (**2**). The structure of compound **2** was additionally confirmed by an X-ray crystal structure (Fig. 2).† Subsequent ester cleavage led to clausine K (clauszoline-J) (**3**), which was obtained in five steps and 18% overall yield based on the iron complex salt **5**. The cleavage of both methyl ethers



Scheme 2 Transformation of carbazole **1** into the clausines H, K and O. *Reagents and conditions*: (i) MnO_2, KCN, MeOH, rt, 24 h, 100%; (ii) KOH, EtOH, reflux, 3 h, 53%; (iii) BBr_3, CH_2Cl_2, −78 to −25 °C, 3 d, 68%.

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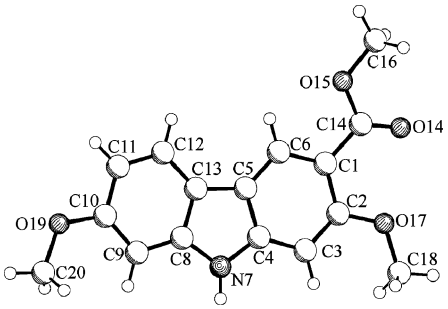

Fig. 2 Molecular structure of clausine H (clauszoline-C) (**2**) in the crystal. Selected bond lengths (Å): C1–C2 1.423(3), C2–C3 1.385(3), C3–C4 1.394(3), C4–C5 1.402(3), C5–C6 1.386(3), C1–C6 1.395(3), C4–N7 1.376(2), N7–C8 1.389(2), C8–C13 1.404(3), C5–C13 1.452(3), C8–C9 1.394(3), C9–C10 1.387(2), C10–C11 1.397(3), C11–C12 1.377(3), C12–C13 1.396(3).

of **1** on treatment with boron tribromide led to clausine O (**4**). The spectral data of our synthetic compounds (see Experimental section) are in full agreement with those reported for the natural products.[7–11]

In conclusion, using the iron-mediated arylamine cyclization to 2,7-dimethoxy-3-methylcarbazole as a platform, we have developed the first synthesis of the biologically active 2,7-dioxygenated tricyclic carbazole alkaloids. Further synthetic transformations and structure–activity studies are in progress.

Experimental

Iron-mediated oxidative cyclization to 2,7-dimethoxy-3-methylcarbazole (8)

Iodine (309 mg, 1.22 mmol) was added to a solution of the iron complex **7** (180 mg, 0.47 mmol) in pyridine (5.5 mL) at 90 °C. After stirring for 5.5 h at 90 °C in air, the reaction mixture was cooled to room temperature. A solution of $Na_2S_2O_3$ (670 mg) and citric acid (350 mg) in H_2O (5 mL) was added and the mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (hexane–EtOAc, 3 : 1) of the residue on silica gel provided 2,7-dimethoxy-3-methylcarbazole (**8**), yield: 76.4 mg (68%). Colorless crystals; mp: 243–244 °C. UV (MeOH): $\lambda = 236$, 263, 312, 320 nm. IR (ATR): $\nu = 3377$, 3003, 2947, 2839, 1612, 1578, 1498, 1452, 1342, 1327, 1308, 1267, 1231, 1192, 1161, 1141, 1020, 946, 881, 822, 811, 792, 726, 673 cm^{-1}. ^1H NMR (500 MHz, pyridine-d_5): $\delta = 2.48$ (s, 3 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 7.06 (dd, $J = 8.5$, 2.2 Hz, 1 H), 7.14 (s, 1 H), 7.21 (d, $J = 2.2$ Hz, 1 H), 7.93 (s, 1 H), 8.12 (d, $J = 8.5$ Hz, 1 H), 11.83 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, pyridine-d_5): $\delta =$ 17.09 (CH_3), 55.38 (CH_3), 55.50 (CH_3), 93.47 (CH), 95.73 (CH), 107.93 (CH), 117.05 (C), 118.15 (C), 118.48 (C), 120.41 (CH), 121.35 (CH), 140.88 (C), 142.25 (C), 156.95 (C), 158.59 (C). MS (EI): $m/z = 241$ (100) [M^+], 226 (85), 211 (8), 198 (5), 183 (8), 167 (6). HRMS: m/z calc. for $C_{15}H_{15}NO_2$ [M^+]: 241.1103; found: 241.1121. Anal. calc. for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81; found: C 74.73, H 6.30, N 5.88%.

7-Methoxy-*O*-methylmukonal (1)

Light yellow solid; mp: 225 °C. UV (EtOH): $\lambda = 240$, 300, 347 nm. IR (ATR): $\nu = 3234$, 3009, 2856, 1665, 1595, 1509, 1469, 1427, 1354, 1323, 1272, 1249, 1205, 1152, 1033, 899, 860, 818, 812, 784, 730, 614 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): $\delta = 3.90$ (s, 3 H), 4.04 (s, 3 H), 6.89 (dd, $J = 8.5$, 2.2 Hz, 1 H), 7.07 (d, $J = 2.2$ Hz, 1 H), 7.16 (s, 1 H), 8.04 (d, $J = 8.5$ Hz, 1 H), 8.42 (s, 1 H), 10.49 (s, 1 H), 10.55 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): $\delta = 55.76$ (CH_3), 56.30 (CH_3), 93.77 (CH), 96.18 (CH), 109.47 (CH), 117.87 (C), 118.24 (C), 119.46 (C), 120.12 (CH), 121.48 (CH), 143.01 (C), 146.58 (C), 160.00 (C), 161.71 (C), 188.55 (CHO). MS (EI): $m/z = 255$ (100) [M^+], 254 (10), 240 (45), 226 (6), 212 (14), 209 (13), 198 (8), 184 (11), 169 (21), 141 (11). HRMS: m/z calc. for $C_{15}H_{13}NO_3$ [M^+]: 255.0895; found: 255.0903. Anal. calc. for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49; found: C 70.64, H 5.32, N 5.38%.

Clausine H (clauszoline-C) (2)

Colorless crystals; mp: 191–192 °C. UV (MeOH): $\lambda = 223$, 245, 279, 282, 309, 320, 332 (sh) nm. IR (ATR): $\nu = 3286$, 2943, 2837, 1696, 1615, 1575, 1435, 1226, 1185, 1152, 1086, 1039, 1025, 797, 780, 727, 618 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): $\delta = 3.88$ (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 6.86 (dd, $J = 8.5$, 2.2 Hz, 1 H), 7.07 (d, $J = 2.2$ Hz, 1 H), 7.15 (s, 1 H), 7.99 (d, $J = 8.5$ Hz, 1 H), 8.46 (s, 1 H), 10.46 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): $\delta = 51.62$ (CH_3), 55.72 (CH_3), 56.37 (CH_3), 94.91 (CH), 95.94 (CH), 109.18 (CH), 113.44 (C), 117.17 (C), 117.71 (C), 121.08 (CH), 123.85 (CH), 142.80 (C), 144.66 (C), 158.92 (C), 159.68 (C), 167.41 (C=O). MS (EI): $m/z = 285$ (100) [M^+], 270 (32), 254 (17), 240 (7). HRMS: m/z calc. for $C_{16}H_{15}NO_4$ [M^+]: 285.1001; found: 285.1020. Anal. calc. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found: C 66.82, H 5.31, N 4.94%.

Clausine K (clauszoline-J) (3)

Light yellow solid; mp: 239–240 °C. UV (MeOH): $\lambda = 225$, 238 (sh), 244, 279, 284, 309, 319, 337 (sh) nm. IR (ATR): $\nu =$ 3308, 2925, 1660, 1615, 1575, 1442, 1409, 1286, 1232, 1199, 1161, 1114, 1082, 1037, 1022, 902, 817, 802 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.83$ (s, 3 H), 3.89 (s, 3 H), 6.77 (dd, $J = 8.5$, 2.2 Hz, 1 H), 6.97 (d, $J = 2.2$ Hz, 1 H), 7.03 (s, 1 H), 7.94 (d, $J =$ 8.5 Hz, 1 H), 8.40 (s, 1 H), 11.28 (s, 1 H), 12.15 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): $\delta = 55.28$ (CH_3), 55.91 (CH_3), 93.88 (CH), 95.01 (CH), 108.13 (CH), 112.24 (C), 115.74 (C), 116.29 (C), 120.50 (CH), 123.19 (CH), 141.60 (C), 143.41 (C), 157.37 (C), 158.09 (C), 167.47 (C=O). MS (EI): $m/z = 271$ (100) [M^+], 256 (28), 212 (14), 184 (7), 169 (7). HRMS: m/z calc. for $C_{15}H_{13}NO_4$ [M^+]: 271.0845; found: 271.0863. Anal. calc. for $C_{15}H_{13}NO_4$: C 66.41, H 4.83, N 5.16; found: C 66.53, H 4.93, N 4.82%.

Clausine O (4)

Light yellow solid; mp: >300 °C (decomp.). UV (MeOH): $\lambda =$ 222, 238, 253 (sh), 290 (sh), 301, 322 (sh), 340 nm. IR (ATR): $\nu = 3363$, 3216, 2923, 1608, 1576, 1463, 1441, 1372, 1325, 1252, 1216, 1171, 1146, 815, 691 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): $\delta = 6.83$ (dd, $J = 8.4$, 2.1 Hz, 1 H), 6.87 (s, 1 H), 6.98 (d, $J = 2.1$ Hz, 1 H), 7.92 (d, $J = 8.4$ Hz, 1 H), 8.31 (s, 1 H), 8.54 (s, 1 H), 10.00 (s, 1 H), 10.55 (br s, 1 H), 11.48 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): $\delta = 97.16$ (CH), 98.21 (CH), 110.30 (CH), 115.91 (C), 116.82 (C), 118.99 (C), 121.35 (CH), 126.68 (CH), 143.53 (C), 147.20 (C), 157.68 (C), 161.14 (C), 196.53 (CHO). MS (EI): $m/z = 227$ (100) [M^+], 226 (39), 198 (9), 170 (12). HRMS: m/z calc. for $C_{13}H_9NO_3$ [M^+]: 227.0582; found: 227.0576.

Acknowledgements

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Notes and references

† Crystal data for **2**: $C_{16}H_{15}NO_4$, $M = 285.29$, orthorhombic, space group $Pca2_1$, $a = 23.051(1)$, $b = 7.509(1)$, $c = 7.739(1)$ Å, $V = 1339.5(3)$ Å^3, $Z = 4$, $D_c = 1.415$ g cm^{-3}, $\mu = 0.102$ mm^{-1}, $T = 198(2)$ K, $\lambda = 0.71073$ Å, θ range: 3.17–25.40°, 15467 reflections measured, 2198 independent ($R_{int} = 0.0463$), 193 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices for 1835 observed reflections [$I > 2\sigma(I)$]: $R_1 = 0.0324$, $wR_2 = 0.0693$; maximal residual electron density: 0.137 e Å^{-3}. CCDC reference number 273763. See http://dx.doi.org/10.1039/b507660a for crystallographic data in CIF or other electronic format.

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