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Iron-Mediated Total Synthesis of 2,7-Dioxygenated Carbazole Alkaloids[‡]

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We describe the efficient iron-mediated total synthesis of clausine O, clausine H (clauszoline-C) and anti-HIV active 7-methoxy-*O*-methylmukonal and clausine K (clauszoline-J). Consecutive C–C and C–N bond formations between 3-methoxy-4-methylaniline and a cyclohexadienyliumiron complex salt afforded 2,7-dimethoxy-3-methylcarbazole, which served as common intermediate en route to the four alkaloids.

Introduction

The promising biological activities of carbazole alkaloids have prompted strong interest in these natural products and have led to the development of numerous methods for their synthesis.[1] Carbazoles have been isolated from various natural sources, including fungi, bacteria, algae, molds, and higher plants of the genera *Murraya*, *Clausena*, and *Glycosmis* (family Rutaceae). Although plants of the genera *Murraya*, *Clausena*, and *Glycosmis* are often used in folk medicine for the treatment of various ailments, the bioactive components are often unknown. Nevertheless, in a number of studies, the 2,7-dioxygenated carbazole alkaloids 7-methoxy-*O*-methylmukonal (**1**), clausine O (**2**), clausine H (clauszoline-C, **3**), and clausine K (clauszoline-J, **4**) have shown biological activity (see Figure 1). In 1996, Wu et al. reported the potent inhibitory activity of 7-methoxy-*O*-methylmukonal (**1**), clausine H (clauszoline-C, **3**), and clausine K (clauszoline-J, **4**) on platelet aggregation.[2] The antiplasmodial activity of clausine H (**3**, IC_{50} = 5.5–10.7 μg/mL) was reported by Yenjai and co-workers in 2000.[3] Kongkathip et al. described the anti-HIV-1 activity of 7-methoxy-*O*-methylmukonal (**1**) and clausine K (clauszoline-J, **4**).[4] Interestingly, these compounds showed only weak activity in a reverse transcriptase assay. Thus, the HIV replication was influenced by a different mode of action. Kongkathip and co-workers also reported the activity of clausine K (**4**) against *Mycobacterium tuberculosis* $H_{37}Ra$ strain [MIC (minimum inhibitory concentration) = 100 μg/mL].[5] However, Franzblau and Knölker et al. showed that the carbazoles **1** and **4** were essentially inactive against the *M. tuberculosis* $H_{37}Rv$ strain, but clausine O (**2**) exhibited some activity (MIC = 89 μg/mL).[6] At the same time, these compounds were shown to be cytotoxic against African green monkey kidney epithelial (Vero) cells. Recently, Ye and Shen et al. tested compounds **1**–**4** for the inhibition in the growth of HepG2 liver carcinoma cells and reported an IC_{50} of approximately 30 μg/mL for compounds **2** and **4**.[7]

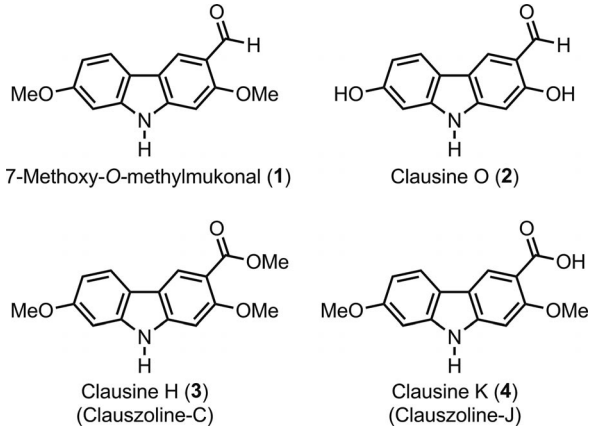

Figure 1. Naturally occurring 2,7-dioxygenated carbazole alkaloids.

7-Methoxy-*O*-methylmukonal (**1**) was first isolated in 1990 by Lange et al. from the ethanol extract of the roots of *Murraya siamensis* collected in Sukhothai Province, Thailand.[8] Locally, these small trees are known as "Prong faa", and the powdered roots are used for the treatment of snakebites, eye sores, and tuberculosis. The corresponding free diol, clausine O (**2**), was first described by Wu et al. in 1999.[9] This compound was obtained from the root bark of *Clausena excavata* collected in Taiwan. Clausine H (**3**) and clausine K (**4**) were first isolated in 1996 from the methanol extract of the stem bark of the same plant, which was also collected in Taiwan.[2] In Taiwanese folk medicine, *C. excavata* is used for the treatment of abdominal pain, snakebites,

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and as a detoxification agent. In the same year, Ito and coworkers isolated the same carboxylic ester **3** from the root bark of *C. excavata* Burm. f., which was collected in Singapore, and named it clauszoline-C (**3**).[10] In 1997, the corresponding carboxylic acid **4** was also obtained by Ito et al. from the acetone extract of the roots of *C. excavata* Burm. f., which were collected in a green house in Shizuoka, Japan, and named clauszoline-J (**4**).[11] Subsequently, carbazole alkaloids **1**–**4** have also been isolated from other Southeast Asian *Clausena* species (see Table 1).

Table 1. Occurrence of the carbazole alkaloids **1**–**4**.

	Plant name	Part	Collected in	Ref.
1	*M. siamensis*	roots	Thailand	[8]
1, **3**, **4**	*C. excavata*	stem bark	Taiwan	[2]
3	*C. excavata*	stem bark	Singapore	[10]
4	*C. excavata*	roots	Japan[a]	[11]
2, **4**	*C. excavata*	root bark	Taiwan	[9]
4	*Clausena harmandiana*	roots	Thailand	[3]
4	*C. excavata*	roots	Thailand	[5]
1, **4**	*C. excavata*	roots and rhizomes	Thailand	[4a]
4	*C. excavata*	stem bark	Malaysia	[12]
4	*C. excavata*	stem and leaves	China	[13]
1–**4**	*Clausena vestita*	whole plant	China	[14]
1	*C. excavata*	leaves	Malaysia	[12b]
1, **2**, **4**	*C. harmandiana*	roots	Thailand	[15]
1, **3**	*Clausena wallichii*	roots	Thailand	[16]

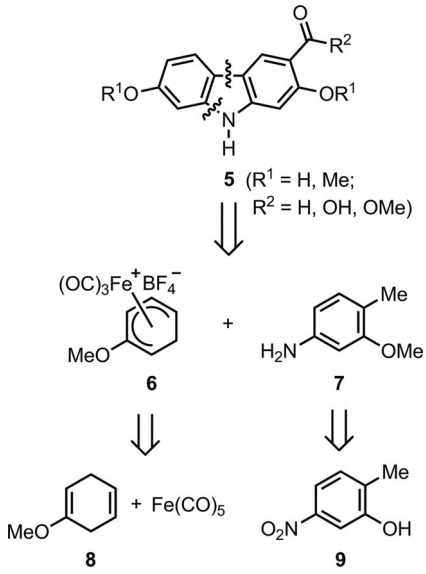
[a] Plant material was collected in a green house.

Results and Discussion

We have developed an iron-mediated[17] and a palladium(II)-catalyzed[18] approach for the synthesis of carbazole alkaloids. Herein, we describe the iron-mediated total synthesis of the 2,7-dioxygenated carbazole alkaloids 7-methoxy-*O*-methylmukonal (**1**), clausine O (**2**), clausine H (clauszoline-C, **3**), and clausine K (clauszoline-J, **4**) using 2,7-dimethoxy-3-methylcarbazole as a relay compound.[17h]

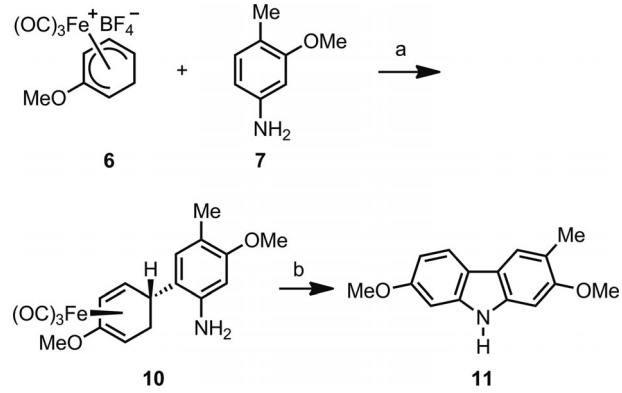
Key step of the iron-mediated carbazole synthesis is the coupling of a substituted aniline with a cyclohexadienyliumiron complex salt. Retrosynthetic analysis of the 2,7-dioxygenated carbazole alkaloids **5** led to iron complex salt **6**[19] and 3-methoxy-4-methylaniline (*ortho*-cresidine, **7**) as the starting materials for our approach (see Scheme 1). Iron complex salt **6** is easily available on a large scale by the 1-azadiene-catalyzed complexation of 1-methoxycyclohexa-1,4-diene (**8**) with pentacarbonyliron.[20] Aniline **7** is commercially available, but, alternatively, can also be prepared in two steps by *O*-alkylation and hydrogenation from the much cheaper nitrophenol **9**.[21]

Reaction of iron complex salt **6** and aniline **7** in acetonitrile at room temperature provided iron–diene complex **10** in good yield on a multigram scale (9.49 g of **10**, see Scheme 2). Treatment of complex **10** with iodine in pyridine at 90 °C induced an oxidative cyclization with concomitant aromatization and demetalation to provide 2,7-dimethoxy-3-methylcarbazole (**11**) in 68% yield (64% yield on a gram scale). The same procedure for the oxidative



Scheme 1. Retrosynthetic analysis of 2,7-dioxygenated carbazole alkaloids.

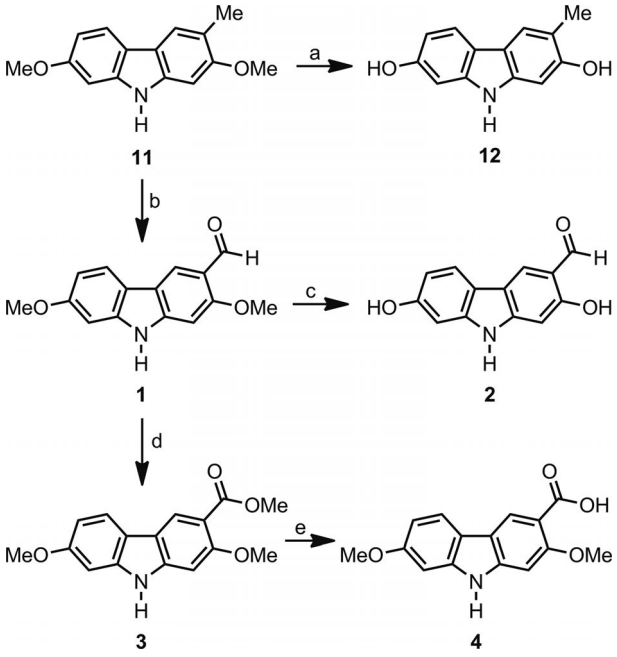
cyclization of an analogous 2,7-dioxygenated carbazole has also been applied in our total synthesis of the furo[3,2-*a*]-carbazole alkaloid furoclausine A.[20g,22]



Scheme 2. Iron-mediated synthesis of carbazole **11**. Reagents and conditions: (a) **7** (2.2 equiv.), **6** (1.0 equiv.), MeCN, room temp., 4.5 h, 76%; (b) I_2 (2.6 equiv.), pyridine, 90 °C, 5.5 h, 68%.

Carbazole **11** then served as relay compound for the total synthesis of natural products **1**–**4** and dihydroxycarbazole **12**, which has been reported in the literature (see Scheme 3). Cleavage of the methyl ether groups in **11** by using boron tribromide at low temperatures provided 2,7-dihydroxy-3-methylcarbazole (**12**), which was an intermediate in Kapil's synthesis of the pyrano[3,2-*a*]carbazole alkaloid *O*-methylmahanine.[23] Unfortunately, Kapil et al. did not provide any spectroscopic data for **12**. For the synthesis of the natural products **1**–**4**, the methyl group at C-3 was first oxidized to a formyl group, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of methanol and water, to provide 7-methoxy-*O*-methylmukonal (**1**) in 73% yield. Cleavage of the methyl ether groups in **1** by using boron tribromide under carefully controlled conditions led to the

oxygen-sensitive clausine O (**2**). Clausine H (clauszoline-C, **3**) was obtained by oxidation of 7-methoxy-*O*-methylmukonal (**1**) using Corey's cyanohydrin method.[24] The treatment of **1** with an excess amount of manganese dioxide in the presence of potassium cyanide in methanol provided **3**, quantitatively. The structure of clausine H (**3**) was confirmed by an X-ray crystal structure analysis (see Figure 2). Finally, the cleavage of the methyl ester in clausine H (**3**) under basic conditions provided clausine K (**4**). The spectroscopic data of our synthetic products are in full agreement with those reported for the natural compounds **1**–**4**.[2,8–11]



Scheme 3. Synthesis of **12** and the carbazole alkaloids **1**–**4**. Reagents and conditions: (a) BBr_3 (7.2 equiv.), CH_2Cl_2, from –78 °C to –30 °C to room temp., 3.5 d, 99%; (b) DDQ (4.3 equiv.), MeOH/H_2O (10:1), room temp., 80 min, 73%; (c) BBr_3 (4.2 equiv.), CH_2Cl_2, –30 °C, 3 d, 68%; (d) KCN (4.5 equiv.), MnO_2 (30 equiv.), MeOH, room temp., 16 h, 100%; (e) KOH (160 equiv.), EtOH/H_2O (2:1), reflux, 3 h, 53%.

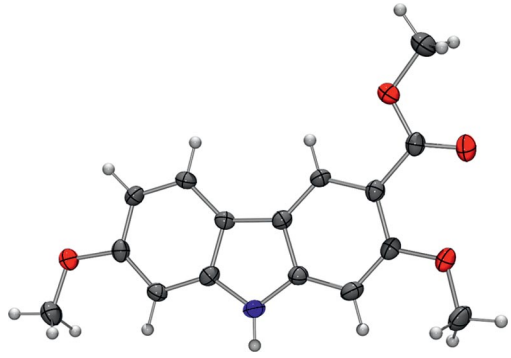


Figure 2. Molecular structure of clausine H (**3**) in the crystal. ORTEP plot showing thermal ellipsoids at the 50% probability level.

Conclusions

Four naturally occurring 2,7-dioxygenated carbazole alkaloids have been synthesized using our iron-mediated approach. The key steps were carried out on a large scale, and intermediate **11** was delivered in gram quantities. 7-Methoxy-*O*-methylmukonal (**1**) was obtained in three steps and 38% overall yield based on iron complex salt **6**. Clausine O (**2**, four steps, 26% overall yield), clausine H (**3**, four steps, 38% overall yield), and clausine K (**4**, five steps, 20% overall yield) were synthesized from **1** by one or two simple transformations. Thus, the iron-mediated carbazole synthesis provides convenient access to 2,7-dioxygenated carbazole alkaloids.

Experimental Section

General Methods: All reactions were carried out in oven-dried glassware using dry solvents under argon, unless stated otherwise. Dichloromethane was dried using a solvent purification system (MBraun-SPS). Chemicals were used as received from the commercial sources. Flash chromatography was performed using silica gel from Merck (0.040–0.063 mm). Thin layer chromatography was performed with TLC plates from Merck (60 F_{254}) using UV light for visualization. Melting points were measured with an Electrothermal IA9100 melting point apparatus. Ultraviolet spectra were recorded with a Perkin–Elmer 25 UV/Vis spectrometer (sh, shoulder). Infrared spectra were recorded with a Thermo Nicolet Avatar 360 FTIR spectrometer using the ATR method (Attenuated Total Reflectance). The NMR spectroscopic data were recorded with a Bruker DRX 500 spectrometer. Chemical shifts δ are reported in ppm with the nondeuterated solvent as the internal standard. The abbreviations used are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of dd), dt (doublet of triplet), m (multiplet), and br. (broad). Mass spectra were recorded with a Finnigan MAT-95 spectrometer (electron impact, 70 eV) or by GC–MS coupling with an Agilent Technologies 6890 N GC System, equipped with a 5973 Mass Selective Detector (electron impact, 70 eV). Elemental analyses were measured with a EuroVector EuroEA3000 elemental analyzer.

3-Methoxy-4-methylaniline (7): A solution of 2-methyl-5-nitroanisole (20.2 g, 121 mmol) in methanol (200 mL) was added to a suspension of palladium on activated carbon (10 wt.-% Pd, 2.15 g) in a minimum amount of methanol, and the mixture was hydrogenated in a Parr shaker hydrogenation apparatus (model 3911 EF) under hydrogen (5 bar) for 10 h. The mixture was filtered through a short pad of Celite® 557 (diethyl ether), and the solvent was removed to provide 3-methoxy-4-methylaniline (**7**, 16.5 g, 120 mmol, 99%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 3.55 (br. s, 2 H), 3.77 (s, 3 H), 6.21 (m, 2 H), 6.89 (m, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 15.31 (CH_3), 55.14 (CH_3), 98.49 (CH), 106.75 (CH), 116.51 (C), 130.95 (CH), 145.49 (C), 158.40 (C) ppm.

[(1–4-η)-5-(2-Amino-4-methoxy-5-methylphenyl)-2-methoxycyclohexa-1,3-diene]tricarbonyliron (10): A solution of 3-methoxy-4-methylaniline (**7**, 9.86 g, 71.9 mmol) and iron complex salt **6** (10.9 g, 32.4 mmol) in acetonitrile (380 mL) was stirred at room temperature for 4.5 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1) to afford iron complex **10** (9.49 g, 24.6 mmol, 76%) as light yellow crystals; m.p. 115–117 °C. UV (MeOH): λ = 213,

298 nm. IR (ATR): $\tilde{\nu}$ = 3420, 3343, 2969, 2930, 2841, 2041, 1963, 1950, 1613, 1583, 1507, 1483, 1461, 1443, 1422, 1409, 1317, 1297, 1266, 1247, 1229, 1201, 1170, 1149, 1118, 1092, 1021, 1000, 928, 897, 881, 824, 756, 735, 686, 648 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (ddd, J = 14.8, 3.4, 2.3 Hz, 1 H), 2.10 (s, 3 H), 2.37 (ddd, J = 14.8, 11.0, 3.8 Hz, 1 H), 2.74 (dd, J = 6.5, 3.4 Hz, 1 H), 3.14 (dt, J = 11.0, 3.4 Hz, 1 H), 3.43 (dt, J = 3.8, 2.3 Hz, 1 H), 3.46 (br. s, 2 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 5.25 (dd, J = 6.5, 2.3 Hz, 1 H), 6.14 (s, 1 H); 6.79 (s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 15.55 (CH_3), 32.66 (CH_2), 37.55 (CH), 53.13 (CH), 54.09 (CH), 54.39 (CH_3), 55.29 (CH_3), 66.99 (CH), 98.99 (CH), 116.65 (C), 122.25 (C), 128.48 (CH), 139.95 (C), 142.15 (C), 156.55 (C), 211.27 (3 CO) ppm. MS (EI): m/z (%) = 385 (5) $[M]^+$, 357 (5), 329 (68), 301 (40), 299 (100), 269 (11), 245 (6), 243 (15), 193 (40), 137 (16). HRMS: calcd. for $C_{18}H_{19}FeNO_5$ $[M]^+$ 385.0613; found 385.0626. $C_{18}H_{19}FeNO_5$ (385.19): calcd. C 56.13, H 4.97, N 3.64; found C 56.11, H 5.01, N 3.66.

2,7-Dimethoxy-3-methylcarbazole (11): (A) Milligram scale: Iodine (309 mg, 1.22 mmol) was added to a solution of iron complex **10** (180 mg, 0.468 mmol) in pyridine (5.5 mL) at 90 °C. After stirring at 90 °C under air for 5.5 h, the reaction mixture was cooled to room temperature. A solution of sodium thiosulfate (670 mg) and citric acid (350 mg) in H_2O (5 mL) was added, and the mixture was extracted with diethyl ether. The combined organic layers were dried with $MgSO_4$. Evaporation of the solvent and purification of the residue by flash chromatography on silica gel (hexane/ethyl acetate, 3:1) provided 2,7-dimethoxy-3-methylcarbazole (**11**, 76.4 mg, 0.317 mmol, 68%). (B) Gram scale: Iodine (5.68 g, 22.4 mmol) was added to a solution of iron complex **10** (3.18 g, 8.26 mmol) in pyridine (100 mL) at 90 °C. After stirring at 90 °C under air for 6.5 h, the reaction mixture was cooled to room temperature. A solution of sodium thiosulfate (10.6 g) and citric acid (4.26 g) in H_2O (20 mL) was added, and the mixture was extracted with diethyl ether. The combined organic layers were dried with magnesium sulfate. Evaporation of the solvent and purification of the residue by flash chromatography on silica gel (hexane/ethyl acetate, 3:1) provided 2,7-dimethoxy-3-methylcarbazole (**11**, 1.28 g, 5.30 mmol, 64%) as colorless crystals; m.p. 243–244 °C. UV (MeOH): λ = 236, 263, 312, 320 nm. IR (ATR): $\tilde{\nu}$ = 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, [D_5]pyridine): δ = 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) ppm. ^{13}C NMR and DEPT (125 MHz, [D_5]pyridine): δ = 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) ppm. MS (EI): m/z (%) = 241 (100) $[M]^+$, 226 (85), 211 (8), 198 (5), 183 (8), 167 (6). HRMS: calcd. for $C_{15}H_{15}NO_2$ $[M]^+$ 241.1103; found 241.1121. $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.73, H 6.30, N 5.88.

2,7-Dihydroxy-3-methylcarbazole (12): Boron tribromide (1 M solution in dichloromethane, 500 µL, 500 µmol) was added at –78 °C to a solution of 2,7-dimethoxy-3-methylcarbazole (**11**, 50.3 mg, 208 µmol) in dichloromethane (10 mL), and the mixture was stirred at that temperature for 2 h. The mixture was warmed to –30 °C and stirred for 19 h at that temperature. Boron tribromide (1 M solution in dichloromethane, 500 µL, 500 µmol) was added, and the mixture was stirred at –30 °C for 24 h. Then, an additional portion of boron tribromide (1 M solution in dichloromethane, 500 µL, 500 µmol) was added. The solution was stirred at –30 °C for 25 h and then at room temperature for 17 h. Methanol (3 mL) was added, and the mixture was poured into water. The resulting solution was extracted with dichloromethane. The organic layers were dried with magnesium sulfate, and the solvent was evaporated to provide 2,7-dihydroxy-3-methylcarbazole (**12**, 43.7 mg, 205 µmol, 99%) as a colorless solid; m.p. 225 °C. UV (MeOH): λ = 238, 265, 315, 322 nm. IR (ATR): $\tilde{\nu}$ = 3395, 3207, 2919, 1615, 1499, 1452, 1345, 1316, 1257, 1218, 1186, 1129, 1011, 952, 879, 827, 802, 746, 725, 626 cm^{-1}. ^1H NMR (500 MHz, [D_6]acetone): δ = 2.36 (s, 3 H), 6.70 (dd, J = 8.3, 2.1 Hz, 1 H), 6.88 (d, J = 2.1 Hz, 1 H), 6.93 (s, 1 H), 7.67 (s, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 8.07 (s, 1 H), 8.14 (s, 1 H), 9.73 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]acetone): δ = 16.65 (CH_3), 97.11 (CH), 97.35 (CH), 108.55 (CH), 117.03 (C), 117.40 (C), 117.60 (C), 120.18 (CH), 121.14 (CH), 140.68 (C), 142.32 (C), 154.23 (C), 156.05 (C) ppm. MS (EI): m/z (%) = 213 (100) $[M]^+$, 212 (36), 196 (5), 184 (10). HRMS: calcd. for $C_{13}H_{11}NO_2$ $[M]^+$ 213.0790; found 213.0796. $C_{13}H_{11}NO_2$ (213.23): calcd. C 73.23, H 5.20, N 6.57; found C 72.52, H 5.50, N 6.55.

7-Methoxy-*O*-methylmukonal (1): DDQ (5.65 g, 18.8 mmol) was added to a solution of 2,7-dimethoxy-3-methylcarbazole (**11**, 1.05 g, 4.35 mmol) in a mixture of methanol (300 mL) and water (30 mL), and the solution was stirred at room temperature for 80 min. Diethyl ether (150 mL) was added, and the mixture was washed with sodium hydroxide (2 N aqueous solution). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried with magnesium sulfate. The solvent was evaporated, and purification of the residue by flash chromatography on silica gel (petroleum ether/acetone, 2:1) provided 7-methoxy-*O*-methylmukonal (**1**, 815 mg, 3.19 mmol, 73%) as a light yellow solid; m.p. 225 °C. UV (EtOH): λ = 240, 300, 347 nm. IR (ATR): $\tilde{\nu}$ = 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, [D_6]acetone): δ = 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) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]-acetone): δ = 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) ppm. 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: calcd. for $C_{15}H_{13}NO_3$ $[M]^+$ 255.0895; found 255.0903. $C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.64, H 5.32, N 5.38.

Clausine O (2): Boron tribromide (1 M solution in dichloromethane, 9.20 mL, 9.20 mmol) was added at –78 °C to a solution of 7-methoxy-*O*-methylmukonal (**1**, 559 mg, 2.19 mmol) in dichloromethane (300 mL), and the mixture was stirred at –30 °C for 3 d. Methanol (40 mL) and water (80 mL) were added, and the mixture was extracted several times with diethyl ether. The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by flash chromatography on degassed silica gel (hexane/acetone, 10:7) provided clausine O (**2**, 337 mg, 1.48 mmol, 68%) as a light yellow solid; m.p. > 300 °C (decomp). UV (MeOH): λ = 222, 238, 253 (sh), 290 (sh), 301, 322 (sh), 340 nm. IR (ATR): $\tilde{\nu}$ = 3363, 3216, 2923, 1608, 1576, 1463, 1441, 1372, 1325, 1252, 1216, 1171, 1146, 815, 691 cm^{-1}. ^1H NMR (500 MHz, [D_6]acetone): δ = 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) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]acetone): δ = 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) ppm. MS (EI): *m/z* (%) = 227 (100) $[M]^+$, 226 (39), 198 (9), 170 (12). HRMS: calcd. for $C_{13}H_9NO_3$ $[M]^+$ 227.0582; found 227.0576.

Clausine H (Clauszoline-C, 3): Potassium cyanide (124 mg, 1.90 mmol) and manganese(IV) oxide (Merck Schuchardt, precipitated active, 1.10 g, 12.7 mmol) were sequentially added at room temperature to a solution of 7-methoxy-*O*-methylmukonal (**1**,107 mg, 0.419 mmol) in methanol (30 mL), and the mixture was stirred at room temperature for 16 h under argon. The mixture was filtered through Celite® 557 (ethyl acetate), and the solvent was evaporated to give clausine H (clauszoline-C, **3**, 119 mg, 0.417 mmol, 100%) as colorless crystals; m.p. 191–192 °C. UV (MeOH): λ = 223, 245, 279, 282, 309, 320, 332 (sh) nm. IR (ATR): $\tilde{\nu}$ = 3286, 2943, 2837, 1696, 1615, 1575, 1435, 1226, 1185, 1152, 1086, 1039, 1025, 797, 780, 727, 618 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]acetone): δ = 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) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]acetone): δ = 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) ppm. MS (EI): *m/z* (%) = 285 (100) $[M]^+$, 270 (32), 254 (17), 240 (7). HRMS: calcd. for $C_{16}H_{15}NO_4$ $[M]^+$ 285.1001; found 285.1020. $C_{16}H_{15}NO_4$ (285.29): calcd. C 67.36, H 5.30, N 4.91; found C 66.82, H 5.31, N 4.94. Crystal data for **3**: $C_{16}H_{15}NO_4$, M = 285.29, orthorhombic, space group $Pca2_1$, a = 23.051(1) Å, b = 7.509(1) Å, c = 7.739(1) Å, V = 1339.5(3) $Å^3$, Z = 4, ρ calcd. = 1.415 $g\,cm^{-3}$, μ = 0.102 mm^{-1}, T = 198(2) K, λ = 0.71073 Å, θ range was 3.17–25.40°, 15467 reflections measured, 2198 independent reflections (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-273763 (for **3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Clausine K (Clauszoline-J, 4): Clausine H (clauszoline-C, **3**, 95.3 mg, 0.334 mmol) was added at room temperature to a solution of potassium hydroxide (3.00 g, 53.5 mmol) in ethanol (8 mL) and water (4 mL), and the mixture was heated at reflux for 3 h. The mixture was cooled to room temperature, and the major part of the solvent was evaporated. The residue was acidified with hydrochloric acid (2 N solution), and the mixture was extracted several times with diethyl ether. The combined organic extracts were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by flash chromatography on silica gel (hexane/ethyl acetate, 2:1) provided clausine K (clauszoline-J, **4**, 47.8 mg, 0.176 mmol, 53%) as a light yellow solid; m.p. 239–240 °C. UV (MeOH): λ = 225, 238 (sh), 244, 279, 284, 309, 319, 337 (sh) nm. IR (ATR): $\tilde{\nu}$ = 3308, 2925, 1660, 1615, 1575, 1442, 1409, 1286, 1232, 1199, 1161, 1114, 1082, 1037, 1022, 902, 817, 802 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 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) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]DMSO): δ = 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) ppm. MS (EI): *m/z* (%) = 271 (100) $[M]^+$, 256 (28), 212 (14), 184 (7), 169 (7). HRMS: calcd. for $C_{15}H_{13}NO_4$ $[M]^+$ 271.0845; found 271.0863. $C_{15}H_{13}NO_4$ (271.27): calcd. C 66.41, H 4.83, N 5.16; found C 66.53, H 4.93, N 4.82.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for all key intermediates and final products.

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