Transition Metals in Organic Synthesis, Part 85.[1] A General Approach to 1,6-Dioxygenated Carbazole Alkaloids – First Total Synthesis of Clausine G, Clausine I, and Clausine Z

Carsten Börger, Hans-Joachim Knölker*

Department Chemie, Technische Universität Dresden, Bergstraße 66, 01069 Dresden, Germany
Fax +49(351)46337030; E-mail: hans-joachim.knoelker@tu-dresden.de

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Abstract: Using the palladium-catalyzed construction of the carbazole framework, a highly efficient route to 1,6-dioxygenated carbazole alkaloids has been developed and applied to the total synthesis of clausenine, 6-methoxymurrayanine, clausenol, clausine G, clausine I, and clausine Z. The three latter natural products have been synthesized for the first time.

Key words: alkaloids, antibiotics, catalysis, cyclizations, palladium

Carbazole alkaloids continue to attract a great interest and induce an intense research activity because of their promising pharmacological potential.[1–4] The key precursor for carbazole alkaloids isolated from terrestrial plants is 3-methylcarbazole.[2] Further biogenetic transformations of this crucial intermediate include oxidation of the methyl group and oxygenation at different positions. Thus, a systematic classification of tricyclic carbazole alkaloids has been suggested based on their oxygenation pattern.[2a] We have developed transition metal catalyzed procedures for the construction of the carbazole framework.[3h] Herein, we report a concise palladium-catalyzed route to the 1,6-dioxygenated carbazole alkaloids clausenine (**1**), 6-methoxymurrayanine (**2**), clausenol (**3**), clausine I (**4**), clausine G (**5**), and clausine Z (**6**, Figure 1). The total synthesis of the alkaloids **4**–**6** is described for the first time.

The first isolation of a 1,6-dioxygenated carbazole alkaloid has been reported in 1991 by El-Feraly et al., who obtained 6-methoxymurrayanine (**2**) from the roots of *Clausena lansium*.[5] Four years later, Chakraborty and co-workers described the isolation of clausenine (**1**) and clausenol (**3**) from the dried stem bark of *Clausena anisata*.[6] Both alkaloids were reported to exhibit antibiotic activity. Clausenol (**3**) was more active and its inhibition against some bacteria can be compared to streptomycin. In 1996, Wu et al. isolated clausine I (**4**) and clausine G (**5**) from *Clausena excavata*.[7] Clausine I (**4**) showed inhibition of blood platelet aggregation. Only very recently, Potterat and co-workers from the Boehringer Ingelheim Pharma GmbH isolated clausine Z (**6**), another novel 1,6-dioxygenated carbazole alkaloid, from the stems and leaves of *Clausena excavata*.[8] Clausine Z (**6**) exhibited an inhibitory activity against cyclin-dependent kinase 5 (CDK5). Moreover, clausine Z (**6**) showed a protective effect on cerebral granule neurons against cell death induced by free radicals.

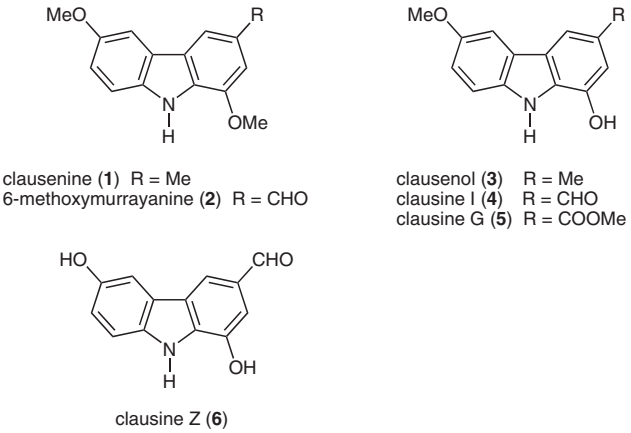

Figure 1 Naturally occurring 1,6-dioxygenated carbazole alkaloids

Due to their useful biological activities, the 1,6-dioxygenated carbazole alkaloids are attractive synthetic targets. Using a Fischer–Borsche cyclization, Chakraborty et al. achieved in 1995 the first total synthesis of clausenine (**1**) (4 steps, 6% overall yield) and clausenol (**3**) (3 steps, 6% overall yield).[6] In 1999, Lin and Zhang described an improved route to clausenol via the same approach (3 steps, 17% overall yield).[9] In 2007, Tamariz et al. reported a synthesis of clausenine (**1**) (6 steps, 20% overall yield) and the first total synthesis of 6-methoxymurrayanine (**2**) (6 steps, 16% overall yield).[10]

We envisaged a broad and general access to the whole family of 1,6-dioxygenated carbazole alkaloids using a convergent approach. Starting from the appropriate precursors, the carbazole framework should be assembled via a sequence of palladium(0)-catalyzed Buchwald–Hartwig amination[11] followed by a palladium(II)-catalyzed oxidative cyclization.[12]

The palladium(0)-catalyzed amination of 4-bromoanisole with methyl 4-amino-3-methoxybenzoate (**7b**) (prepared in 99% yield by esterification of the corresponding acid **7a**)[13,14] using 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) as ligand led quantitatively to the diarylamine **8** (Scheme 1). The palladium(II)-catalyzed oxidative cyclization of **8** using 10 mol% of palladium(II)

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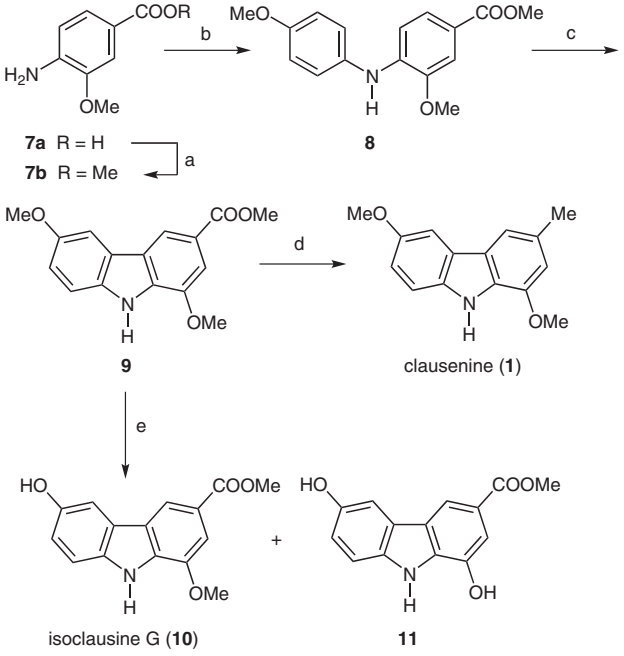
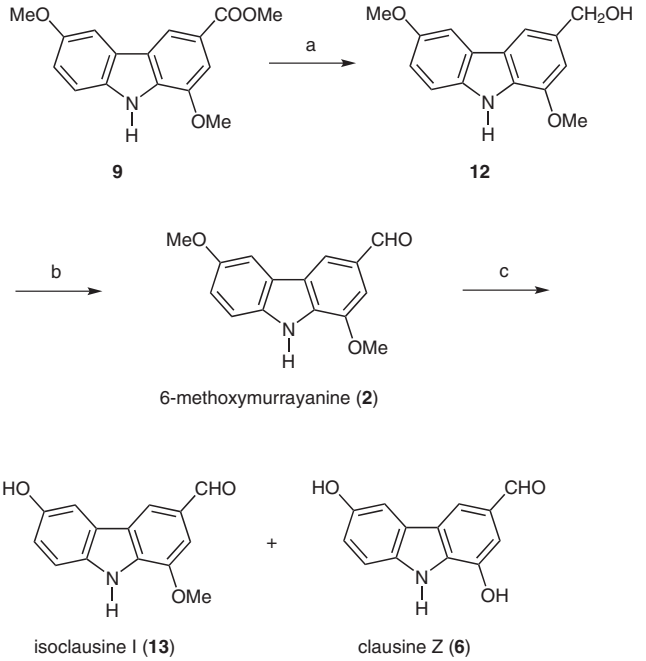


Scheme 1 Synthesis of clausenine (**1**) and isoclausine G (**10**). *Reagents and conditions*: a) MeOH, cat. H_2SO_4, 65 °C, 17 h (99%); b) $Pd(OAc)_2$ (6 mol%), S-Phos (12 mol%), Cs_2CO_3 (1.4 equiv), 4-bromoanisole (1.1 equiv), toluene, 110 °C, 5 d (100%); c) $Pd(OAc)_2$ (2 equiv), AcOH, 117 °C, 4 h, Ar (96%); d) $LiAlH_4$ (4 equiv), THF, 67 °C, 4 h (74%); e) BBr_3 (4 equiv), CH_2Cl_2, –78 °C to –10 °C, 24 h (33% of **10** and 67% of **11**).



Scheme 2 Synthesis of 6-methoxymurrayanine (**2**), isoclausine I (**13**), and clausine Z (**6**). *Reagents and conditions*: a) DIBAL-H (2.6 equiv), Et_2O, –78 °C, 3.5 h (87%); b) MnO_2 (5 equiv), CH_2Cl_2, r.t., 24 h (100%); c) BBr_3 (3 equiv), CH_2Cl_2, –78 °C to r.t., 24 h (73% of **13** and 24% of **6**).

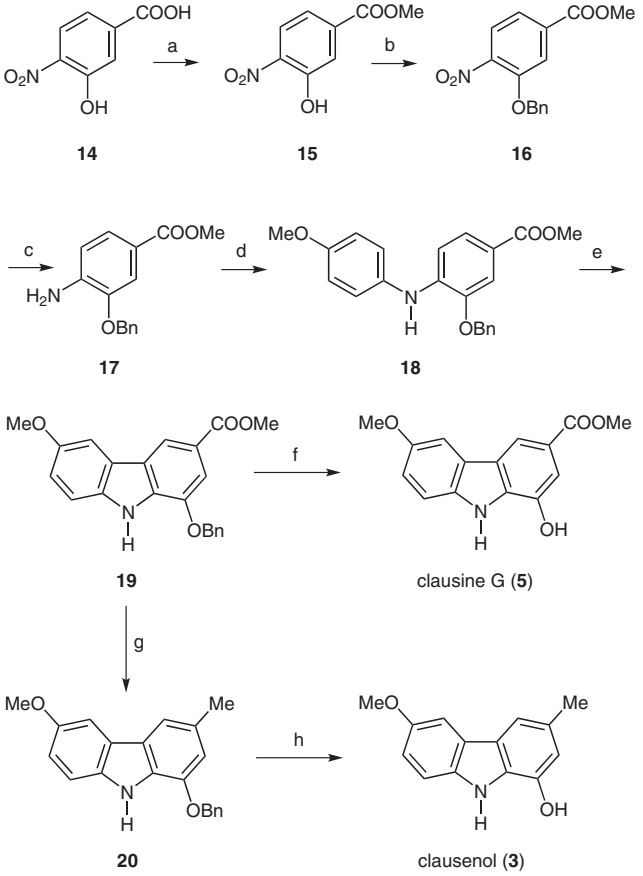
acetate and 2.5 equivalents of cupric acetate afforded the carbazole **9** in only 40% yield along with 35% of starting material. By application of stoichiometric amounts of palladium(II) acetate the desired product was obtained in up to 73% yield. Finally, oxidative cyclization using two equivalents of palladium(II) actetate provided the carbazole **9** in 96% yield. Åkermark has already noted that two equivalents of palladium(II) acetate are required for high yields in the cyclization of acceptor-substituted precursors.[12a] Reduction of the carbazole **9** with lithium aluminum hydride led directly to clausenine (**1**).[15] A selective cleavage of the methyl ether at C-1 would lead to clausine G (**5**). However, we found that under mild reaction conditions the methyl ether at C-6 is cleaved first. Thus, treatment with four equivalents of boron tribromide at low temperature provided isoclausine G (**10**) in 33% yield along with the 1,6-dihydroxycarbazole **11** (67% yield).

Reduction of carbazole **9** with diisobutylaluminum hydride[16] to the corresponding carbinol **12** and subsequent oxidation with activated manganese dioxide[17] afforded 6-methoxymurrayanine (**2**)[15] (Scheme 2). Also in this case, treatment of 6-methoxymurrayanine (**2**) with boron tribromide at low temperature resulted in selective cleavage of the methyl ether at C-6 and provided isoclausine I (**13**) in 73% yield along with clausine Z (**6**) in 24% yield.[15] Extended treatment of the carbazoles **2** or **13** using additional boron tribromide leads to decomposition and does not represent a viable route to clausine Z (**6**).

The results described above show that ether cleavage of 1,6-dimethoxycarbazoles takes place at C-6 first. Therefore, a differentiation of the protecting groups was required for the projected synthesis of the 1-hydroxy-6-methoxycarbazoles clausenol (**3**), clausine I (**4**), and clausine G (**5**). For this purpose, the commercial 3-hydroxy-4-nitrobenzoic acid (**14**) was converted via the methyl ester **15** and the benzyl ether **16** into the benzyl-protected arylamine **17**,[18] which corresponds to the *O*-benzyl analogue of the arylamine **7b** (Scheme 3). Buchwald–Hartwig coupling of **17** with 4-bromoanisole to the diarylamine **18** followed by oxidative cyclization led to the carbazole **19**. Removal of the benzyl ether afforded clausine G (**5**).[15] Reduction of **19** to the carbazole **20** using lithium aluminum hydride and subsequent debenzylation provided clausenol (**3**).[15]

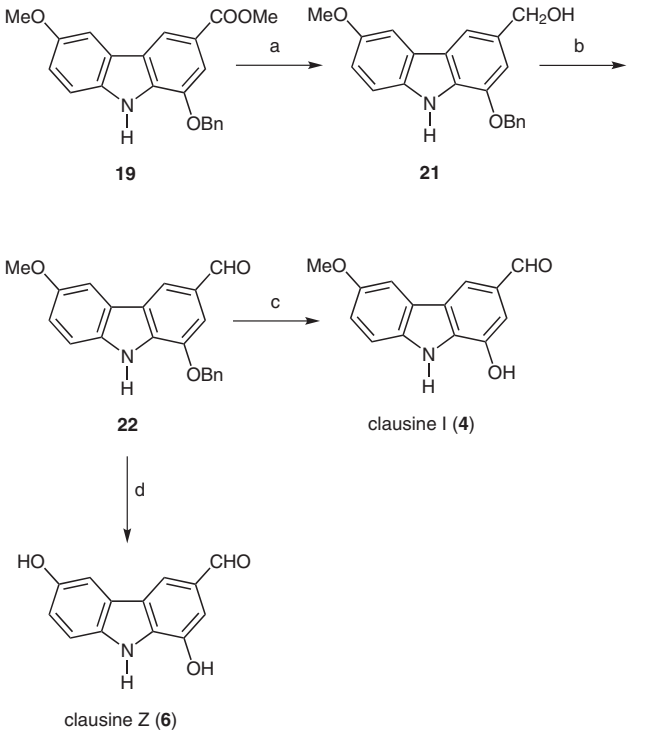
Reduction of carbazole **19** to the carbinol **21** using diisobutylaluminum hydride[16] followed by oxidation with activated manganese dioxide[17] led to the 3-formylcarbazole **22** (Scheme 4). A selective cleavage of the benzyl ether was achieved with a large excess of aluminum trichloride in refluxing dioxane and provided quantitatively clausine I (**4**).[15] Finally, treatment with boron tribromide led to the cleavage of both ethers of the carbazole **22** and afforded clausine Z (**6**),[15] which is sensitive towards oxidation in air.

In conclusion, we have achieved a broad and general access to the tricyclic 1,6-dioxygenated carbazole alkaloids by using our two-step, palladium-catalyzed construction



Scheme 3 Synthesis of clausine G (**5**) and clausenol (**3**). *Reagents and conditions*: a) MeOH, cat. H_2SO_4, 65 °C, 17 h (100%); b) BnBr (1.3 equiv), K_2CO_3 (1.3 equiv), acetone, 56 °C, 17 h (100%); c) Fe (10 equiv), AcOH, r.t. to 40 °C, 4 h (100%); d) $Pd(OAc)_2$ (6 mol%), S-Phos (12 mol%), Cs_2CO_3 (1.4 equiv), 4-bromoanisole (1.1 equiv), toluene, 80 °C, 64 h (90%); e) $Pd(OAc)_2$ (2 equiv), AcOH, 100 °C, 14 h, Ar (62%); f) 10% Pd/C, H_2, CH_2Cl_2–MeOH (1:1), r.t., 18 h (89%); g) $LiAlH_4$ (4 equiv), THF, 67 °C, 7 h (94%); h) 10% Pd/C, H_2, CH_2Cl_2–MeOH (1:1), r.t., 40 h (100%).

of the carbazole framework. Clausenine (**1**) was obtained in four steps and 70% overall yield, 6-methoxymurrayanine (**2**) in five steps and 83% overall yield, and clausenol (**3**) in seven steps and 52% overall yield. A comparison of these results with those of the previous syntheses described above demonstrates the high efficiency of our method. Moreover, we have achieved the first total syntheses for clausine I (**4**) in eight steps and 53% overall yield, clausine G (**5**) in six steps and 50% overall yield, and clausine Z (**6**) in eight steps and 29% overall yield. The spectroscopic data of our synthetic carbazoles **1**–**6** (UV, IR, ^{1}H NMR, and ^{13}C NMR)[15] are in good agreement with those reported for the natural products. Based on our previous findings on the antibiotic properties of some other carbazole alkaloids,[19,20] an investigation of the pharmacological potential of the present compounds is in progress.



Scheme 4 Synthesis of clausine I (**4**) and clausine Z (**6**). *Reagents and conditions*: a) DIBAL-H (2.6 equiv), Et_2O, –78 °C, 3.5 h (95%); b) MnO_2 (5 equiv), CH_2Cl_2, r.t., 24 h (100%); c) $AlCl_3$ (10 equiv), dioxane, 101 °C, 3 h (100%); d) BBr_3 (4 equiv), CH_2Cl_2, –78 °C to r.t., 24 h (55%).

References and Notes

(1) Part 84: Fröhner, W.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2007**, *74*, 895.
(2) For some comprehensive reviews, see: (a) Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*, Vol. 65; Cordell, G. A., Ed.; Academic Press: Amsterdam, **2008**, 1. (b) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115. (c) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (d) Chakraborty, D. P. In *The Alkaloids*, Vol. 44; Cordell, G. A., Ed.; Academic Press: New York, **1993**, 257. (e) Chakraborty, D. P.; Roy, S. In *Progress in the Chemistry of Organic Natural Products*, Vol. 57; Herz, W.; Grisebach, H.; Kirby, G. W.; Steglich, W.; Tamm, C., Eds.; Springer: Wien, **1991**, 71.
(3) For accounts, see: (a) Pindur, U. *Chimia* **1990**, *44*, 406. (b) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967. (c) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443. (d) Moody, C. J. *Synlett* **1994**, 681. (e) Hibino, S.; Sugino, E. In *Advances in Nitrogen Heterocycles*, Vol. 1; Moody, C. J., Ed.; JAI Press: Greenwich, CT, **1995**, 205. (f) Kirsch, G. H. *Curr. Org. Chem.* **2001**, *5*, 507. (g) Lemster, T.; Pindur, U. *Recent Res. Dev. Org. Bioorg. Chem.* **2002**, *5*, 99. (h) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309. (i) Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Heterocycles* **2004**, *63*, 2393.
(4) Recent contributions: (a) Krahl, M. P.; Jäger, A.; Krause, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2006**, *4*, 3215. (b) Yamabuki, A.; Fujinawa, H.; Choshi, T.; Tohyama, S.; Matsumoto, K.; Ohmura, K.; Nobuhiro, J.; Hibino, S.

Tetrahedron Lett. **2006**, *47*, 5859. (c) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403. (d) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (e) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (f) Ackermann, L.; Althammer, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1627. (g) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2007**, *9*, 1883. (h) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516. (i) St. Jean Jr., D. J.; Poon, S. F.; Schwarzbach, J. L. *Org. Lett.* **2007**, *9*, 4893. (j) Liu, C.-Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106. (k) Naffziger, M. R.; Ashburn, B. O.; Perkins, J. R.; Carter, R. G. *J. Org. Chem.* **2007**, *72*, 9857.

(5) Li, W.-S.; McChesney, J. D.; El-Feraly, F. S. *Phytochemistry* **1991**, *30*, 343.

(6) Chakraborty, A.; Chowdhury, B. K.; Bhattacharyya, P. *Phytochemistry* **1995**, *40*, 295.

(7) (a) Wu, T.-S.; Huang, S.-C.; Wu, P.-L.; Teng, C.-M. *Phytochemistry* **1996**, *43*, 133. (b) Wu, T.-S.; Huang, S.-C.; Wu, P.-L. *Phytochemistry* **1996**, *43*, 1427.

(8) Potterat, O.; Puder, C.; Bolek, W.; Wagner, K.; Ke, C.; Ye, Y.; Gillardon, F. *Pharmazie* **2005**, *60*, 637.

(9) (a) Lin, G.; Zhang, A. *Tetrahedron Lett.* **1999**, *40*, 341. (b) Lin, G.; Zhang, A. *Tetrahedron* **2000**, *56*, 7163.

(10) (a) Bernal, P.; Benavides, A.; Bautista, R.; Tamariz, J. *Synthesis* **2007**, 1943. (b) González-Romero, C.; Bernal, P.; Jiménez, F.; del Carmen Cruz, M.; Fuentes-Benites, A.; Benavides, A.; Bautista, R.; Tamariz, J. *Pure Appl. Chem.* **2007**, *79*, 181.

(11) (a) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.

(12) (a) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365. (b) Miller, R. B.; Moock, T. *Tetrahedron Lett.* **1980**, *21*, 3319. (c) Furukawa, H.; Ito, C.; Yogo, M.; Wu, T.-S. *Chem. Pharm. Bull.* **1986**, *34*, 2672. (d) Knölker, H.-J.; O'Sullivan, N. *Tetrahedron* **1994**, *50*, 10893. (e) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Synthesis* **2002**, 557. (f) Knölker, H.-J.; Reddy, K. R. *Heterocycles* **2003**, *60*, 1049. (g) Knölker, H.-J.; Knöll, J. *Chem. Commun.* **2003**, 1170.

(13) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1988**, *41*, 1087.

(14) Knölker, H.-J.; Wolpert, M. *Tetrahedron* **2003**, *59*, 5317.

(15) Characteristic Spectroscopic Data of the 1,6-Dioxygenated Carbazole Alkaloids **1**–**6**.

Clausenine (**1**): colorless crystals; mp 149–150 °C (lit.[6] 151 °C). UV (MeOH): λ_{max} = 226, 241, 258 (sh), 287 (sh), 299, 340, 354 nm. IR (ATR): ν = 3385, 2955, 2918, 2852, 1619, 1581, 1505, 1486, 1459, 1451, 1437, 1394, 1304, 1268, 1207, 1145, 1129, 1035, 1025, 940, 838, 821, 800, 769 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 2.45 (s, 3 H), 3.82 (s, 3 H), 3.95 (s, 3 H), 6.78 (s, 1 H), 6.97 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.46 (s, 1 H), 7.55 (d, *J* = 2.4 Hz, 1 H), 10.92 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 21.57 (CH_3), 55.23 (CH_3), 55.51 (CH_3), 102.64 (CH), 107.53 (CH), 111.97 (CH), 112.31 (CH), 114.56 (CH), 122.75 (C), 123.48 (C), 127.45 (C), 128.56 (C), 134.68 (C), 145.33 (C), 152.80 (C). MS (EI): *m/z* (%) = 241 (91) [M^+], 226 (100), 211 (11), 198 (20), 183 (7), 167 (9), 155 (17), 154 (14). Anal. Calcd (%) for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.88; H, 6.36; N, 5.50.

6-Methoxymurrayanine (**2**): colorless crystals; mp 230–231 °C (lit.[5] 231–233 °C). UV (MeOH): λ_{max} = 240, 253, 277, 296, 337, 350 nm. IR (ATR): ν = 3138, 3010, 2921, 2852, 1655, 1628, 1608, 1578, 1496, 1466, 1437, 1360, 1327, 1305, 1262, 1239, 1217, 1185, 1139, 1105, 1031, 1023, 944, 844, 805, 782, 749, 705, 668 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 3.92 (s, 3 H), 4.08 (s, 3 H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.43 (d, *J* = 1.0 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.79 (d, *J* = 2.4 Hz, 1 H), 8.34 (d, *J* = 1.0 Hz, 1 H), 10.03 (s, 1 H), 10.83 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 56.06 (CH_3), 56.08 (CH_3), 103.64 (CH), 103.78 (CH), 113.50 (CH), 116.86 (CH), 120.81 (CH), 124.44 (C), 124.87 (C), 130.71 (C), 135.45 (C), 135.80 (C), 147.27 (C), 155.60 (C), 191.72 (CHO). MS (EI): *m/z* (%) = 255 (100) [M^+], 240 (96), 225 (10), 224 (11), 212 (13), 184 (8), 169 (8).

Clausine Z (**6**): colorless crystals; mp 151 °C (dec.). UV (MeOH): λ_{max} = 226, 246, 279, 298, 342, 355 nm. IR (ATR): ν = 3219, 2922, 2853, 1657, 1579, 1457, 1327, 1196, 1136, 958, 851, 800, 711 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 6.93 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.24 (d, *J* = 1.0 Hz, 1 H), 7.34 (d, *J* = 8.6 Hz, 1 H), 7.44 (d, *J* = 2.4 Hz, 1 H), 8.13 (d, *J* = 1.0 Hz, 1 H), 9.12 (br s, 1 H), 9.90 (s, 1 H), 10.29 (br s, 1 H), 11.41 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 104.93 (CH), 106.44 (CH), 112.42 (CH), 115.73 (CH), 118.88 (CH), 123.15 (C), 123.84 (C), 128.71 (C), 134.04 (C), 134.48 (C), 143.65 (C), 151.30 (C), 191.72 (CHO). MS (EI): *m/z* (%) = 227 (100) [M^+], 226 (60), 198 (27), 197 (24), 170 (13), 169 (10). HRMS: *m/z* calcd for $C_{13}H_9NO_3$ [M^+]: 227.0582; found: 227.0573.

Clausine G (**5**): light yellow crystals; mp 145–147 °C (lit.[7b] >280 °C). UV (MeOH): λ_{max} = 224, 241, 250, 268, 284, 325 (sh), 334, 349 nm. IR (ATR): ν = 3355, 2952, 2922, 2833, 1667, 1630, 1612, 1582, 1500, 1471, 1431, 1355, 1322, 1297, 1251, 1202, 1172, 1125, 1087, 1026, 1001, 916, 871, 828, 793, 765, 751, 723 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 3.88 (s, 3 H), 3.92 (s, 3 H), 7.08 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 7.55 (d, *J* = 1.1 Hz, 1 H), 7.77 (d, *J* = 2.5 Hz, 1 H), 8.37 (d, *J* = 1.1 Hz, 1 H), 9.04 (br s, 1 H), 10.45 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 51.91 (CH_3), 56.07 (CH_3), 103.59 (CH), 111.10 (CH), 113.23 (CH), 115.71 (CH), 116.67 (CH), 121.96 (C), 124.94 (C), 124.98 (C), 134.35 (C), 136.09 (C), 143.46 (C), 155.26 (C), 168.01 (C=O). Anal. Calcd (%) for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.43; H, 4.95; N, 4.76.

Clausenol (**3**): light yellow crystals; mp 191–192 °C (lit.[6] 139 °C). UV (MeOH): λ_{max} = 227, 242, 292 (sh), 299, 343, 357 nm. IR (ATR): ν = 3367, 3228, 2921, 2851, 1652, 1621, 1590, 1578, 1520, 1481, 1457, 1434, 1388, 1318, 1298, 1269, 1210, 1178, 1142, 1095, 1024, 1005, 988, 943, 871, 833, 796, 748 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 2.37 (s, 3 H), 3.81 (s, 3 H), 6.61 (s, 1 H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.31 (s, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 7.51 (d, *J* = 2.5 Hz, 1 H), 9.59 (s, 1 H), 10.64 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 21.38 (CH_3), 55.55 (CH_3), 102.67 (CH), 110.92 (CH), 111.38 (CH), 111.91 (CH), 114.39 (CH), 123.00 (C), 124.00 (C), 127.45 (C), 128.47 (C), 134.74 (C), 142.88 (C), 152.68 (C).

Clausine I (**4**): colorless crystals; mp 222–223 °C (lit.[7a] 222–224 °C). UV (MeOH): λ_{max} = 225 (sh), 242, 255, 278, 296, 340 (sh), 354 nm. IR (ATR): ν = 3385, 2955, 2919, 2852, 1619, 1581, 1486, 1460, 1437, 1393, 1304, 1268, 1207, 1184, 1145, 1130, 1111, 1035, 1025, 940, 838, 821, 800, 769, 733, 712 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 3.92 (s, 3 H), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.40 (d, *J* = 0.6 Hz, 1 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.77 (d, *J* = 2.4 Hz, 1 H), 8.25 (d, *J* = 0.6 Hz, 1 H), 9.27 (s, 1 H), 9.98 (s, 1 H), 10.64 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 56.05 (CH_3), 103.66 (CH), 107.95 (CH), 113.46 (CH), 116.76 (CH), 119.60 (CH), 125.04 (C), 125.08 (C), 130.79 (C), 135.43 (C), 136.03 (C), 144.40 (C), 155.47 (C), 191.76 (CHO). MS (EI): *m/z* (%) = 241 (100) [M^+], 240

(10), 226 (78), 198 (15). HRMS: *m/z* calcd for $C_{14}H_{11}NO_3$ [M^+]: 241.0739; found: 241.0735.
(16) Winterfeldt, E. *Synthesis* **1975**, 617.
(17) (a) Manganese dioxide (precipitated, active) from Merck (art. 805958). (b) Knölker, H.-J. *J. Prakt. Chem.* **1995**, *337*, 75.
(18) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synthesis* **2006**, 3467.
(19) Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *ChemMedChem* **2006**, *1*, 812.
(20) Choi, T. A.; Czerwonka, R.; Knöll, J.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *Med. Chem. Res.* **2006**, *15*, 28.