First total synthesis of clausine L and pityriazole, a metabolite of the human pathogenic yeast *Malassezia furfur*†‡

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The first total synthesis of the alkaloid pityriazole is described using three consecutive palladium-catalyzed coupling reactions.

The lipophilic yeast *Malassezia furfur* is believed to represent one of the pathogenic agents responsible for pityriasis versicolor, a *Malassezia*-associated common skin disease characterized by flaky lesions.[2] Recently, Steglich and co-workers have isolated eleven novel tryptophan metabolites from the cultures of *M. furfur*, among them the hitherto unprecedented 1-(indol-3-yl)carbazole alkaloid pityriazole **1** (Fig. 1).[3] Carbazole alkaloids are of general interest due to their broad range of biological activities.[4,5] Thus, the report from Steglich *et al.* prompted us to develop an efficient synthetic approach to pityriazole (**1**) using our palladium-catalyzed route.

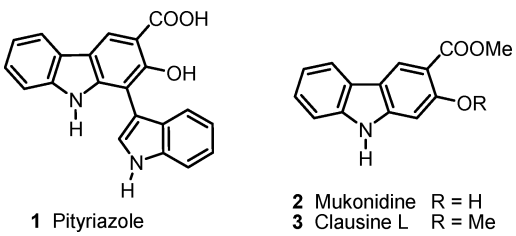
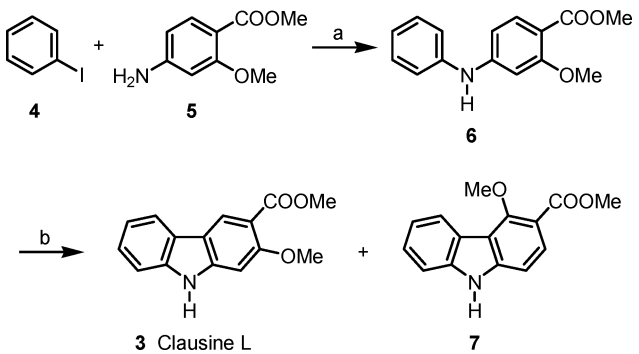


Fig. 1 Pityriazole (**1**) and structurally related 2-oxygenated carbazoles.

Generally carbazole alkaloids having a carbon substituent at the 3-position biogenetically derive from the anthranilic acid pathway and have been isolated from terrestrial plants of the Rutaceae family. While carbazole alkaloids from other sources are biosynthesized from tryptophan and have the carbon substituent at C2.[4a] Steglich *et al.* could demonstrate that pityriazole with a carbon substituent at C3 biogenetically derives from tryptophan.[3] We realized the structural similarity of pityriazole (**1**) to mukonidine (**2**) and clausine L (*O*-methylmukonidine) (**3**), both isolated by Wu and co-workers from the Chinese medicinal plant *Clausena excavata*.[6] Therefore, we envisaged a synthetic approach to pityriazole (**1**) using mukonidine (**2**) and clausine L (**3**) as intermediates.

Our previous synthesis of mukonidine using an iron-mediated approach was limited (4 steps, 17% overall yield).[7] In the present approach, we applied our palladium-catalyzed construction of the carbazole framework (Scheme 1). The coupling of iodobenzene (**4**) with the commercial arylamine **5** *via* a palladium(0)-catalyzed Buchwald–Hartwig amination[8] led quantitatively to the diarylamine **6**. The subsequent palladium(II)-catalyzed oxidative cyclization *via* a double C–H bond activation provides clausine L (**3**) as the major product. Clausine L (**3**), obtained by total synthesis for the first time, has been characterized by comparison of its spectroscopic data with those reported for the natural product[6] and an X-ray analysis (Fig. 2).§ For steric reasons, the regioselective cyclization to clausine L (**3**) predominates. Only on a large scale could the minor regioisomer **7** be isolated (2% yield) and fully characterized.§



Scheme 1 Palladium-catalyzed synthesis of clausine L (**3**). *Reagents and conditions*: (a) 5 mol% $Pd(OAc)_2$, 6 mol% BINAP, 1.5 equiv. Cs_2CO_3, toluene, Ar, reflux, 2 d, 100%; (b) 12 mol% $Pd(OAc)_2$, 10 mol% $Mn(OAc)_3 \cdot 2\,H_2O$, pivalic acid, air, 100 °C, 3 d, 62% of **3**, 2% of **7**.

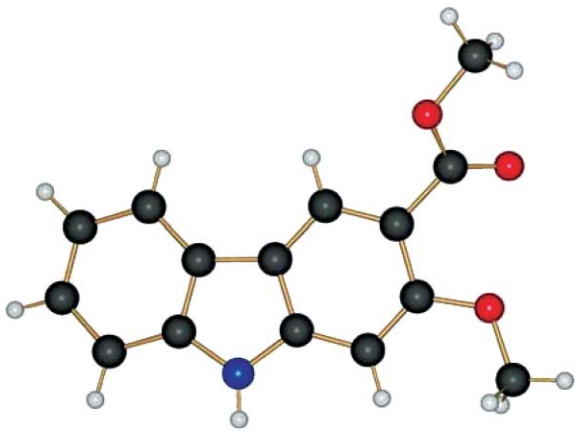


Fig. 2 Molecular structure of clausine L (**3**) in the crystal.

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‡ Electronic supplementary information (ESI) available: Additional details of the crystal structure determinations. CCDC reference numbers 683126 and 683127. For crystallographic data in CIF or other electronic format and ESI see DOI: 10.1039/b805451g

Table 1 Palladium(II)-catalyzed cyclization of **6** to clausine L (**3**)[a]

$Pd(OAc)_2$	Reoxidant	Time	**3**, Yield (%)	**6**, Yield (%)
10 mol%	2.5 equiv. Cu(II)	1 d	44	55
10 mol%	10 mol% Cu(II)	17 h	55	38
5 mol%	10 mol% Cu(II)	3.5 d	61	24
12 mol%	10 mol% Mn(III)	3 d	62	15

[a] All reactions have been carried out in pivalic acid as solvent at 100 °C in the presence of air. Reoxidants: $Cu(OAc)_2$ and $Mn(OAc)_3 \cdot 2\,H_2O$.

In an extension to our previous investigations on the catalytic version of this reaction,[9,10] we optimized the reaction conditions for the palladium(II)-catalyzed cyclization (Table 1). Initiated by a recent report of Fagnou *et al.*,[11] we demonstrated in an independent investigation that pivalic acid is superior to acetic acid as solvent for this reaction.[12] In the present study we could make this reaction become catalytic not only in palladium(II) but also in copper(II). The catalysis in palladium(II) as well as in copper(II) is well-known for the Wacker oxidation,[13] but for the C–C bond formation by double aryl C–H bond activation it is reported for the first time. Moreover, we have tested other agents for the oxidation of palladium(0) to palladium(II). While iron(III) appears to be inefficient, manganese(III) is almost as efficient as copper(II) for the regeneration of palladium(II).

For the projected introduction of the indolyl substituent by a Suzuki–Miyaura coupling,[14] a halogenation at C1 of the carbazole framework was required. Electrophilic bromination of clausine L (**3**) under the usual conditions afforded 6-bromoclausine L (**8**) (Scheme 2). This result corresponds to the general regioselectivity of electrophilic substitutions at carbazoles. However, chlorination under the same reaction conditions takes place exclusively at C1 providing 1-chloroclausine L (**9**). This outcome is explained by the steric requirement of the bromo substituent. In the course of our total synthesis of 6-chlorohyellazole, we observed a related regioselectivity reversal from halogenation at C6 *versus* halogenation at C4 by switching from bromination to chlorination.[15] We expected that cleavage of the methyl ether for steric and electronic reasons should favor even more the halogenation at C1. Cleavage of the methyl ether of clausine L (**3**) afforded mukonidine (**2**), providing a considerably improved route (*cf.* ref. 7) to this natural product (3 steps, 59% overall yield).¶ All electrophilic halogenations of mukonidine including the iodination[16] take place exclusively at C1 (85–99% yield).

Attempted coupling reactions of the 1-chloro derivatives **9** and **10a** with 1-(phenylsulfonyl)indol-3-yl-boronic acid (**11**) using tetrakis(triphenylphosphane)palladium as catalyst under the usual conditions gave no product. But Suzuki–Miyaura coupling of **11** with the more reactive 1-bromomukonidine **10b** afforded the desired product **12** in up to 50% yield. Compound **12** has been confirmed by an X-ray crystal structure determination (Fig. 3).‖ Finally, Suzuki–Miyaura coupling of 1-iodomukonidine (**10c**) with **11** using S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) as ligand under optimized conditions (microwave heating and moist potassium phosphate as base)[17] led to the 1-(indol-3-yl)carbazole **12** in 82% yield (Scheme 3). Cleavage of the ester and the phenylsulfonyl group under basic conditions provided, after purification by HPLC, pure pityriazole (**1**).** The spectroscopic data of our synthetic pityriazole (**1**) were in full agreement with those reported for the natural product. The

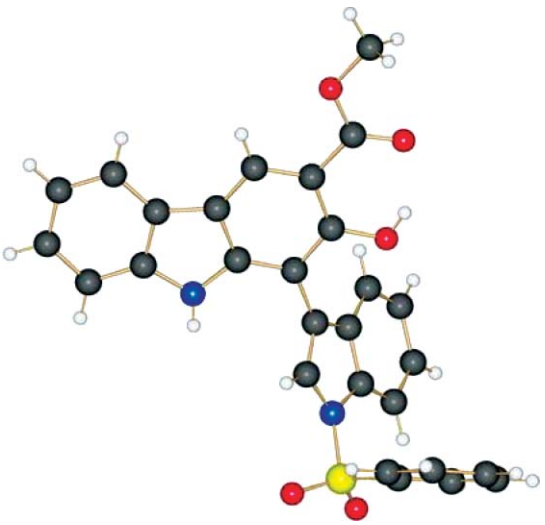
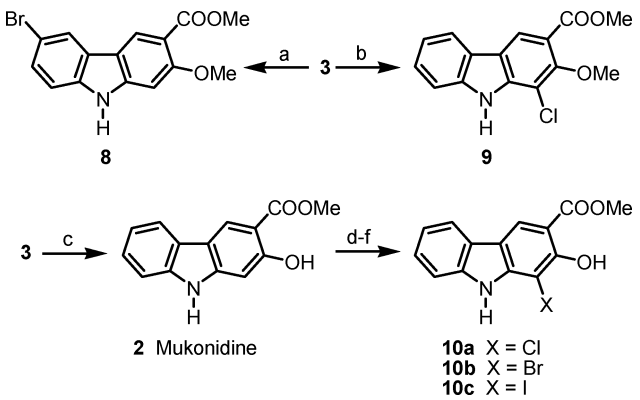
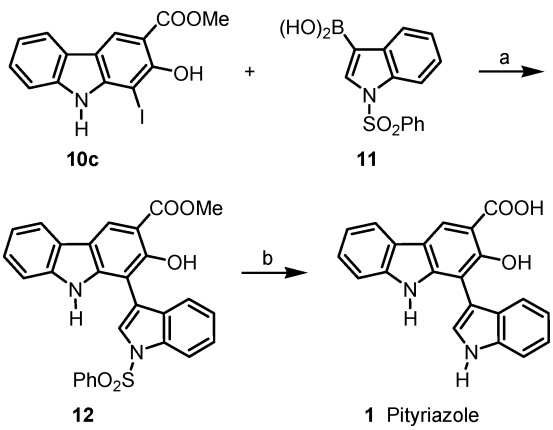


Fig. 3 Molecular structure of compound **12** in the crystal.



Scheme 2 Halogenations of clausine L (**3**) and mukonidine (**2**). *Reagents and conditions*: (a) 1.05 equiv. NBS, cat. HBr, CH_2Cl_2, 25 °C, 6 h, 84%; (b) 1.05 equiv. NCS, cat. HCl, CH_2Cl_2, 25 °C, 22 h, 85%; (c) 2.2 equiv. BBr_3, CH_2Cl_2, −78 to −4 °C, 1 h, 95%; (d) 1.01 equiv. NCS, CH_2Cl_2, 25 °C, 7 h, 85% **10a**; (e) 1.05 equiv. NBS, CH_2Cl_2, 25 °C, 4 h, 99% **10b**; (f) 1.05 equiv. I_2, 1.05 equiv. $Cu(OAc)_2$, 80 °C (microwave), 2 h, 85% **10c**.



Scheme 3 Transformation of 1-iodomukonidine (**10c**) into pityriazole (**1**). *Reagents and conditions*: (a) 1.6 equiv. **11**, 0.2 equiv. $Pd(OAc)_2$, 0.4 equiv. S-Phos, 2 equiv. moist K_3PO_4, dioxane, Ar, 90 °C (microwave), 3 h, 82%; (b) 15 equiv. KOH, EtOH, Ar, 40 °C, 2 d, 86%.

identity has been additionally confirmed by comparison of the UV, IR, ^{1}H NMR and ^{13}C NMR spectra of our synthetic compound with the corresponding original spectra of the natural product, kindly provided by Professor W. Steglich.

In conclusion, we have developed a highly efficient route which provides pityriazole (**1**) in six steps and 35% overall yield *via* three palladium-catalyzed coupling reactions. In the course of our work, we have also achieved the first synthesis of clausine L (**3**) (2 steps, 62% overall yield) and an improved access to mukonidine (**2**) (3 steps, 59% overall yield). As only 1.0 mg of pityriazole (**1**) has been obtained by Steglich *et al.* from natural sources, an investigation of the bioactivity of this natural product as well as its structural analogues can be initiated based on our synthetic approach.

We are grateful to Professor Wolfgang Steglich, Universität München, for providing us the files of the original spectra for natural pityriazole.

Notes and references

§ Spectroscopic data for clausine L (**3**): Colorless crystals, mp 172–173 °C; UV (MeOH): λ = 235, 241, 269, 282 (sh), 319, 333 nm; IR (ATR): ν = 3264, 2951, 2922, 2852, 1690, 1632, 1608, 1574, 1486, 1462, 1427, 1392, 1348, 1313, 1278, 1239, 1201, 1163, 1115, 1082, 1035, 979, 950, 909, 875, 825, 789, 775, 766, 750, 727 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d$_6$): δ = 3.85 (s, 3 H), 3.92 (s, 3 H), 7.15 (s, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 7.35 (t, J = 7.8 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 8.54 (s, 1 H), 10.53 (br s, 1 H); ^{13}C NMR and DEPT (75 MHz, acetone-d$_6$): δ = 51.77 (CH$_3$), 56.44 (CH$_3$), 94.85 (CH), 111.83 (CH), 113.76 (C), 116.97 (C), 120.47 (CH), 120.63 (CH), 124.19 (C), 124.99 (CH), 126.00 (CH), 141.53 (C), 144.70 (C), 159.83 (C), 167.45 (C=O); MS (EI): m/z (%) = 255 (M$^+$, 100), 240 (5), 224 (89), 209 (18), 194 (9), 181 (7), 166 (14), 153 (15), 139 (11); HRMS: m/z calc. for $C_{15}H_{13}NO_3$ (M$^+$): 255.0895, found: 255.0889. Crystal data for clausine L (**3**): $C_{15}H_{13}NO_3$, crystal size: 0.32 × 0.11 × 0.10 mm^3, M_r = 255.26 g mol^{-1}, orthorhombic, space group $Pna2_1$, λ = 0.71073 Å, a = 14.127(1), b = 11.910(2), c = 7.618(2) Å, V = 1281.7(4) Å^3, Z = 4, ρ_{calcd} = 1.323 g cm^{-3}, μ = 0.093 mm^{-1}, T = 198(2) K, θ range = 3.35–25.40°; reflections collected: 7318, independent: 2201 (R_{int} = 0.0868). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0464, wR_2 = 0.0940 [$I > 2\sigma(I)$]; maximal residual electron density: 0.163 e Å^{-3}. CCDC 683126. Spectroscopic data for methyl 4-methoxycarbazole-3-carboxylate (**7**): Colorless crystals, mp 175–178 °C; UV (MeOH): λ = 234, 244, 266, 307, 318, 331 nm; IR (ATR): ν = 3319, 2928, 2855, 1701, 1623, 1599, 1584, 1485, 1454, 1431, 1395, 1339, 1310, 1284, 1250, 1224, 1211, 1138, 1078, 1056, 1010, 970, 874, 833, 803, 748, 731 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d$_6$): δ = 3.90 (s, 3 H), 4.10 (s, 3 H), 7.27 (t, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 7.45 (t, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 8.5 Hz, 1 H), 8.29 (d, J = 8.0 Hz 1 H), 10.78 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d$_6$): δ = 51.86 (CH$_3$), 61.77 (CH$_3$), 107.40 (CH), 111.88 (CH), 114.74 (C), 117.57 (C), 120.87 (CH), 122.62 (C), 123.50 (CH), 126.76 (CH), 130.06 (CH), 140.85 (C), 145.11 (C), 158.52 (C), 166.99 (C=O); MS (EI): m/z (%) = 255 (M$^+$, 97), 224 (100), 222 (25), 212 (17), 209 (29), 194 (14), 181 (15), 169 (16), 166 (16), 153 (33), 139 (15), 126 (11).

¶ Spectroscopic data for mukonidine (**2**): Colorless crystals, mp 189 °C; UV (MeOH): λ = 235, 243, 270 (sh), 276 (sh), 284, 325, 338 nm; IR (ATR): ν = 3347, 2952, 2922, 2852, 1644, 1627, 1582, 1481, 1464, 1432, 1373, 1363, 1329, 1258, 1236, 1189, 1165, 1118, 1093, 1014, 991, 949, 898, 871, 821, 784, 762, 740, 719 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d$_6$): δ = 4.00 (s, 3 H), 6.93 (s, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 7.36 (t, J = 7.8 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 8.62 (s, 1 H), 10.52 (br s, 1 H), 11.07 (s, 1 H); ^{13}C NMR and DEPT (75 MHz, acetone-d$_6$): δ = 52.60 (CH$_3$), 97.70 (CH), 105.95 (C), 111.79 (CH), 117.85 (C), 120.58 (CH), 120.89 (CH), 123.41 (CH), 124.30 (C), 126.51 (CH), 141.96 (C), 146.62 (C), 161.62 (C), 172.22 (C=O); MS (EI): m/z (%) = 241 (M$^+$, 46), 209 (100), 181 (20), 153 (33), 126 (10), 104 (10).

‖ Crystal data for compound **12**: $C_{28}H_{20}N_2O_5S$, crystal size: 0.25 × 0.09 × 0.08 mm^3, M_r = 496.52 g mol^{-1}, monoclinic, space group $P2_1/c$ λ = 0.71073 Å, a = 12.061(1), b = 22.545(1), c = 9.161(1) Å, β = 107.45(1)°, V = 2376.4(3) Å^3, Z = 4, ρ_{calcd} = 1.388 g cm^{-3}, μ = 0.180 mm^{-1}, T = 293(2) K, θ range = 3.06–27.00°; reflections collected: 36307, independent: 5184 (R_{int} = 0.0590). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0524, wR_2 = 0.1031 [$I > 2\sigma(I)$]; maximal residual electron density: 0.226 e Å^{-3}. CCDC 683127.

** Spectroscopic data for pityriazole (**1**): Colorless crystals, mp 236 °C (decomp.); UV (MeOH): λ = 223, 282, 327, 338 nm; IR (ATR): ν = 3398, 3037, 1628, 1609, 1542, 1477, 1456, 1410, 1375, 1328, 1310, 1253, 1219, 1135, 1098, 1056, 1015, 993, 889, 793, 736, 716 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 6.99 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 2 H), 7.28–7.31 (m, 2 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.59 (s, 1 H), 8.11 (d, J = 7.7 Hz, 1 H), 8.62 (s, 1 H), 10.83 (s, 1 H), 11.44 (s, 1 H), 11.91 (br s, 1 H), 13.63 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, DMSO-d$_6$): δ = 104.62 (C), 105.14 (C), 106.81 (C), 111.45 (CH), 111.59 (CH), 115.64 (C), 118.79 (CH), 119.56 (CH), 119.73 (CH), 120.31 (CH), 121.12 (CH), 121.42 (CH), 123.28 (C), 125.16 (CH), 125.50 (CH), 126.91 (C), 136.36 (C), 140.89 (C), 144.60 (C), 157.84 (C), 173.55 (C=O); MS (EI): m/z (%) = 342 (M$^+$, 48), 324 (100), 298 (93), 297 (22), 296 (24), 269 (21), 268 (16), 267 (22), 241 (12), 240 (11), 162 (16); HRMS: m/z calc. for $C_{21}H_{14}N_2O_3$ (M$^+$): 342.1004, found: 342.0989.

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