Transition Metals in Organic Synthesis, Part 91:[1] Palladium-Catalyzed Approach to 2,6-Dioxygenated Carbazole Alkaloids – First Total Synthesis of the Phytoalexin Carbalexin C

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Abstract: The palladium(0)-catalyzed C–N bond formation and palladium(II)-catalyzed oxidative cyclization provide an efficient route to a series of 2,6-dioxygenated carbazole alkaloids including the first total synthesis of the phytoalexin carbalexin C.

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

Carbazole alkaloids, especially those which are highly substituted, are attracting a lot of interest because of their broad range of useful biological activities.[1–5] Their biogenesis in terrestrial plants starts from 3-methylcarbazole as parent compound.[2,3] Further biogenetic transformations are oxygenation at different positions, oxidation of the methyl group, prenylation, and annelation of additional rings. The in vivo conversion leads to the large structural variety found for naturally occurring carbazoles. Based on the oxygenation pattern of tricyclic carbazole alkaloids, we have introduced a novel classification system for these natural products.[3]

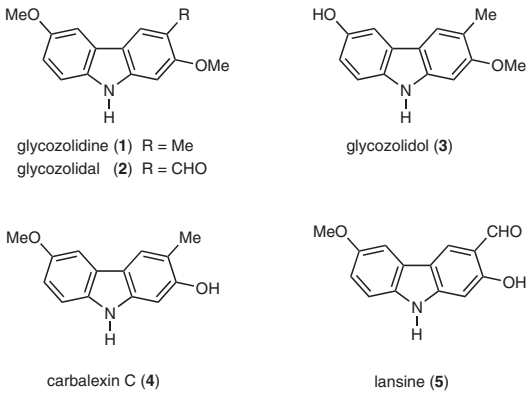

Figure 1 Naturally occurring 2,6-dioxygenated carbazole alkaloids

We have developed efficient routes to highly oxygenated carbazoles which are sensitive to oxidation. Recently, we have reported a short iron-mediated synthesis for 2,7-dioxygenated carbazole alkaloids.[6] Our palladium-catalyzed approach has been applied to the synthesis of 7-oxygenated,[7] 6-oxygenated,[8] 1,6-dioxygenated,[9] 2-oxygenated, and 2,7-dioxygenated carbazole alkaloids.[10] Herein, we describe an efficient palladium-catalyzed route to 2,6-dioxygenated carbazole alkaloids including the first total synthesis of the phytoalexin carbalexin C (**4**).

Glycozolidine (**1**, Figure 1), the first 2,6-dioxygenated carbazole from natural sources, was isolated by Chakraborty et al. from the root bark of *Glycosmis pentaphylla* (Rutaceae) in 1966.[11] In traditional folk medicine, extracts of this plant are used for the treatment of fever. Glycozolidal (**2**) and glycozolidol (**3**) have been obtained much later from the same natural source by Bhattacharyya et al.[12,13] Glycozolidine (**1**) was also isolated from the roots of *Glycosmis arborea* by Chakravarty et al.[14] In 2001, Greger et al. observed that wounding, UV irradiation, or treatment with the fungus *Botrytis cinerea* induced the generation of a series of carbazole alkaloids in the leaves of *Glycosmis pentaphylla* and *Glycosmis parviflora*.[15] Among these stress-induced carbazole phytoalexins were the novel carbalexins, for example, carbalexin C (**4**). Lansine (**5**) was isolated by Kapil et al. from the leaves of *Clausena lansium*.[16] Moreover, glycozolidal (**2**) and lansine (**5**) were obtained by Wu et al. from the stem bark of the Chinese medicinal plant *Clausena excavata*.[17]

Our interest in the natural products described above was induced by the carbalexins, described as the first carbazole-containing phytoalexins,[15] as well as the pharmacological potential of these compounds. In 2005, Franzblau et al. isolated lansine (**5**) from *Micromelum hirsutum* and found that it inhibits the growth of *Mycobacterium tuberculosis* (strain $H_{37}Rv$).[18] In a cooperation with the Franzblau group, we could identify several carbazoles with promising anti-TB activity.[19] Thus, we had a strong interest to develop a general access to 2,6-dioxygenated carbazoles. A few individual syntheses of the natural products **1**–**3** and also one synthesis of lansine (**5**) have been reported.[20] However, no synthesis has been reported so far for carbalexin C (**4**). In the present paper, we describe a flexible modular approach to the 2,6-dioxygenated carbazole alkaloids **1**–**5** using the palladium-catalyzed route developed by our group.

Palladium(0)-catalyzed Buchwald–Hartwig coupling of 4-bromoanisole (**6**) and 3-methoxy-4-methylaniline (**7**) afforded the diarylamine **8** (Scheme 1).[21] The palladium(II)-catalyzed oxidative cyclization to the carbazole framework was achieved by reoxidation of palladium(0) to palladium(II) with cupric acetate, using the reaction conditions developed previously by our group.[4d,7–10,22]

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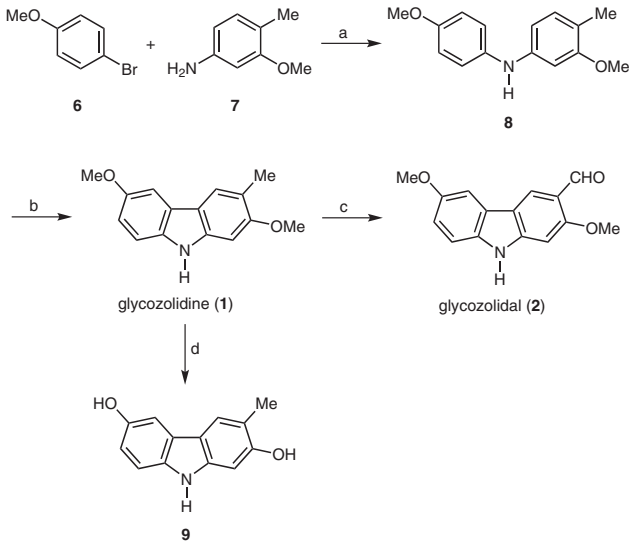
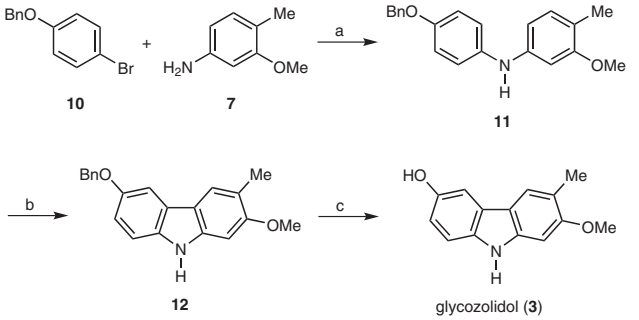
Thus, reaction of the diarylamine **8** in the presence of 10 mol% of palladium(II) acetate and 2.5 equivalents of cupric acetate with microwave heating at 130 °C[23] provided glycozolidine (**1**).[24] Oxidation of **1** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to glycozolidal (**2**). Cleavage of both methyl ether groups of glycozolidine (**1**) afforded 2,3-dihydroxy-3-methylcarbazole (**9**), which was known by degradation of the natural product.[11b,20a] The spectroscopic data for the carbazole alkaloids were in good agreement with those reported in the literature.[24]



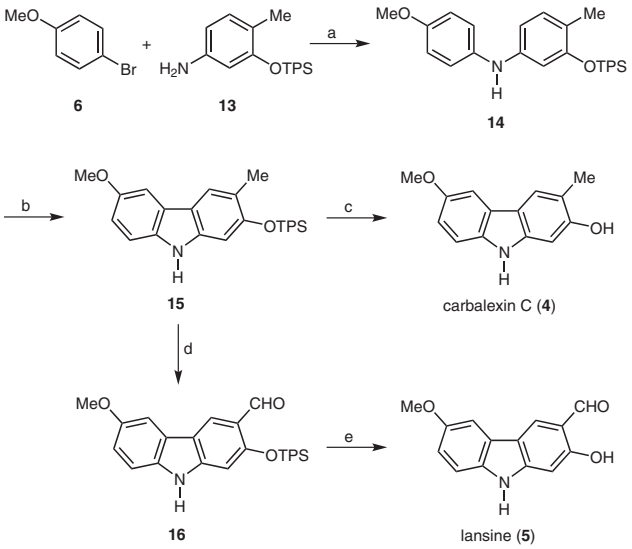
Scheme 1 Palladium-catalyzed synthesis of glycozolidine (**1**) and glycozolidal (**2**). *Reagents and conditions*: a) **7** (1.1 equiv), $Pd(OAc)_2$ (6 mol%), BINAP (6 mol%), Cs_2CO_3 (1.2 equiv), toluene, 111 °C, 1 d, Ar (75%); b) $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.5 equiv), AcOH, air, MW, 130 °C, 2 h (68%); c) DDQ (2.2 equiv), MeOH–THF–H_2O (10:3:1), r.t., 1.5 h (75%); d) BBr_3 (2 equiv), CH_2Cl_2, –78 °C (30 min) to 0 °C (1 h) to r.t. (20 h), Ar (99%).

4-(Benzyloxybromo)benzene (**10**)[25] was chosen as precursor for glycozolidol (**3**). Buchwald–Hartwig amination of **10** with the arylamine **7** afforded the diarylamine **11** (Scheme 2). Palladium(II)-catalyzed oxidative cyclization of **11** to the carbazole **12** followed by cleavage of the benzyl ether provided glycozolidol (**3**).[24]



Scheme 2 Palladium-catalyzed synthesis of glycozolidol (**3**). *Reagents and conditions*: a) **7** (1.1 equiv), $Pd(OAc)_2$ (6 mol%), BINAP (6 mol%), Cs_2CO_3 (1.2 equiv), toluene, 111 °C, 2 d, Ar (83%); b) $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.5 equiv), AcOH, air, MW, 130 °C, 3 h (60%); c) 10% Pd/C, H_2, CH_2Cl_2–THF (1:2), r.t., 4 d (91%).

For the synthesis of the phytoalexin carbalexin C (**4**) and lansine (**5**), we prepared the silyl-protected arylamine **13** quantitatively in two steps from 2-methyl-5-nitrophenol.[26] Buchwald–Hartwig coupling of 4-bromoanisole (**6**) and arylamine **13** led to the diarylamine **14** (Scheme 3). Palladium(II)-catalyzed cyclization of **14** provided the carbazole **15**, a crucial precursor for both natural products.[27] Desilylation of **15** using tetrabutylammonium fluoride (TBAF) afforded carbalexin C (**4**). Although, carbalexin C (**4**) has been described as an oil,[15] we obtained this compound in solid form (mp 187–191 °C).[24] Oxidation of **15** with DDQ to the 3-formyl derivative **16** and subsequent removal of the silyl group with TBAF provided lansine (**5**).



Scheme 3 Palladium-catalyzed synthesis of carbalexin C (**4**) and lansine (**5**); TPS = *tert*-$BuPh_2Si$. *Reagents and conditions*: a) **13** (1.1 equiv), $Pd(OAc)_2$ (6 mol%), BINAP (6 mol%), Cs_2CO_3 (1.2 equiv), toluene, 111 °C, 1 d, Ar (86%); b) $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.5 equiv), AcOH, air, MW, 130 °C, 2 h (76%); c) TBAF (1.6 equiv), DMF, 0 °C to r.t., 1 h, Ar (90%); d) DDQ (2.2 equiv), MeOH–THF–H_2O (10:3:1), r.t., 80 min (77%); e) TBAF (1.6 equiv), DMF, 0 °C to r.t., 1 h, Ar (65%).

In conclusion, we have developed an efficient access to 2,6-dioxygenated carbazole alkaloids using a sequence of palladium(0)-catalyzed amination and palladium(II)-catalyzed cyclization via double C–H bond activation. The present work reports the first total synthesis of the novel phytoalexin carbalexin C (**4**) in 5 steps and 59% overall yield based on 2-methyl-5-nitrophenol.

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(24) **Characteristic Spectroscopic Data of the 2,6-Dioxygenated Carbazole Alkaloids 1–5 and 9**

Glycozolidine (**1**): light yellow solid; mp 158–161 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 6.78 (s, 1 H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.23 (d, *J* = 8.7 Hz, 1 H), 7.44 (d, *J* = 2.5 Hz, 1 H), 7.70 (br s, 1 H), 7.74 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 16.70 (CH_3), 55.47 (CH_3), 56.03 (CH_3), 92.42 (CH), 102.51 (CH), 110.88 (CH), 112.95 (CH), 116.20 (C), 118.94 (C), 121.37 (CH), 123.98 (C), 134.13 (C), 140.00 (C), 153.84 (C), 157.42 (C). Anal. Calcd (%) for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.81; H, 6.33; N, 5.71.

Glycozolidal (**2**): yellow solid; mp 188–193 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 3.98 (s, 3 H), 6.83 (s, 1 H), 7.00 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.49 (d, *J* = 2.5 Hz, 1 H), 8.12 (br s, 1 H), 8.52 (s, 1 H), 10.47 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 55.83 (CH_3), 55.92 (CH_3), 92.35 (CH), 103.14 (CH), 111.34 (CH), 114.64 (CH), 117.47 (C), 118.76 (C), 121.85 (CH), 124.34 (C), 134.42 (C), 145.51 (C), 154.84 (C), 161.51 (C), 189.44 (CHO). Anal. Calcd (%) for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.71; H, 5.29; N, 5.39.

2,6-Dihydroxy-3-methylcarbazole (**9**): colorless solid; mp >250 °C (decomp.). ^{1}H NMR (500 MHz, acetone-d_6): δ = 2.35 (s, 3 H), 6.84 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.93 (s, 1 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 7.40 (d, *J* = 2.4 Hz, 1 H), 7.70 (s, 1 H), 7.80 (br s, 1 H), 8.21 (br s, 1 H), 9.65 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 16.65 (CH_3), 96.84 (C), 96.89 (CH), 105.02 (CH), 111.40 (CH), 113.44 (CH), 116.90 (C), 122.08 (CH), 125.15 (C), 135.08 (C), 141.76 (C), 151.47 (C), 155.48 (C).

Glycozolidol (**3**): yellow solid; mp 245–250 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.22 (s, 3 H), 3.82 (s, 3 H), 6.72 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.84 (s, 1 H), 7.16 (d, *J* = 8.5 Hz, 1 H), 7.23 (d, *J* = 2.4 Hz, 1 H), 7.65 (s, 1 H), 8.75 (br s, 1 H), 10.60 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 16.62 (CH_3), 55.24 (CH_3), 92.51 (CH), 104.11 (CH), 110.83 (CH), 112.93 (CH), 115.18 (C), 116.56 (C), 121.08 (CH), 123.28 (C), 133.52 (C), 140.26 (C), 150.30 (C), 156.60 (C). Anal. Calcd (%) for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.74; H, 5.89; N, 6.17.

Carbalexin C (**4**): light yellow solid; mp 187–191 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 3.90 (s, 3 H), 6.81 (s, 1 H), 6.94 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.24 (d, *J* = 8.7 Hz, 1 H), 7.43 (d, *J* = 2.5 Hz, 1 H), 7.70 (br s, 1 H), 7.73 (s, 1 H), 7.89 (br s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 16.14 (CH_3), 56.07 (CH_3), 96.52 (CH), 102.71 (CH), 110.88 (CH), 113.20 (CH), 116.03 (C), 117.40 (C), 121.70 (CH), 123.97 (C), 134.36 (C), 140.15 (C), 153.16 (C), 153.89 (C). Anal. Calcd (%) for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.32; H, 5.97; N, 6.26.

Lansine (**5**): yellow solid; mp 202–204 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 6.82 (s, 1 H), 7.02 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.47 (d, *J* = 2.4 Hz, 1 H), 8.11 (br s, 1 H), 8.12 (s, 1 H), 9.91 (s, 1 H),

11.43 (s, 1 H). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 56.01 (CH_3), 96.79 (CH), 103.36 (CH), 111.41 (CH), 114.48 (CH), 115.30 (C), 117.81 (C), 123.96 (C), 127.49 (CH), 134.68 (C), 146.11 (C), 154.96 (C), 161.10 (C), 195.12 (CHO). Anal. Calcd (%) for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.75; H, 4.70; N, 5.69.

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(26) Synthesis of 3-(*tert*-butyldiphenylsilyloxy)-4-methylaniline (**13**): 1. commercial 2-methyl-5-nitrophenol (1.0 equiv), *t*-BuPh_2SiCl (1.5 equiv), imidazole (2 equiv), DMF, r.t., 4 h; 2. 10% Pd/C, H_2 (5 bar), CH_2Cl_2, r.t., 24 h (100% overall yield).

(27) **Experimental Procedure for the Palladium(II)-Catalyzed Oxidative Cyclization**
The diarylamine **14** (132 mg, 283 μmol), $Pd(OAc)_2$ (6.3 mg, 28 μmol), $Cu(OAc)_2$ (128 mg, 705 μmol), and AcOH (1.5 mL) were heated in a 10 mL microwave vessel for 2 h at 130 °C. Removal of the solvent in vacuum and flash chromatography (PE–EtOAc, 15:1) of the crude product on Celite/silica gel provided *O*-*tert*-butyldiphenylsilylcarbalexin C (**15**; 100 mg, 76%) as a yellow oil. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 17.70 (CH_3), 19.61 (C), 26.50 (3 CH_3), 56.02 (CH_3), 100.55 (CH), 102.55 (CH), 110.71 (CH), 113.03 (CH), 117.07 (C), 120.70 (C), 121.30 (CH), 123.73 (C), 127.84 (4 CH), 129.86 (2 CH), 132.91 (2 C), 134.23 (C), 135.45 (4 CH), 139.39 (C), 152.96 (C), 153.69 (C).