First Total Synthesis of Murrastifoline B and an Improved Route to Murrastifoline F

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Abstract: We report the first total synthesis of murrastifoline B and an improved route to murrastifoline F using a twofold palladium-catalyzed Buchwald–Hartwig amination as key step. The monomeric carbazole and the biaryl precursor are also prepared via palladium-catalyzed coupling reactions.

Key words: alkaloids, catalysis, cyclization, natural products, palladium

The broad range of biological activities observed for carbazole alkaloids induced a strong interest in this class of compounds and the development of diverse synthetic methods.[1–4] However, only a few synthetic approaches have been reported for biscarbazole alkaloids.[3,5] We have developed an efficient palladium-catalyzed route to carbazole alkaloids which is also applicable to the synthesis of biscarbazoles.[6] Recently, we have completed the total synthesis of murrastifoline A (**1**) using an Ullmann coupling to form the C–N linkage (Figure 1).[6h] Herein, we describe the synthesis of the biscarbazole alkaloids murrastifoline B (**2**) and murrastifoline F (**3**) using a twofold Buchwald–Hartwig coupling of an appropriately functionalized aminocarbazole and a bistriflate as key step.

In 1990, Furukawa and co-workers isolated murrastifoline B (**2**) from the stem bark of *Murraya euchrestifolia* Hayata.[7] Three years later, the same group isolated murrastifoline F (**3**) from the root and stem bark of the same plant.[8] In 2001, Bringmann et al. described the first synthesis of murrastifoline F (**3**) by oxidizing murrayafoline A (**4a**) using lead(IV) acetate in 60% yield (22% over eight steps).[9]

The simple 1-oxygenated carbazole alkaloids murrayafoline A (**4a**)[10] and mukonine (**4b**)[11] are precursors for these biscarbazole alkaloids, not only for the proposed biosynthesis but also for the chemical synthesis (vide infra).

For the synthesis of murrastifoline B (**2**) and murrastifoline F (**3**), we envisaged a twofold Buchwald–Hartwig coupling of the bistriflate **5** with the appropriately substituted arylamines **6** and **7** to construct the second carbazole framework (Scheme 1). In 2003, Nozaki et al. applied the twofold Buchwald–Hartwig amination for the first time to generate a carbazole framework.[12] Using this method, Chida et al. synthesized the biscarbazole alkaloid murrastifoline A (**1**) in 2005.[13]

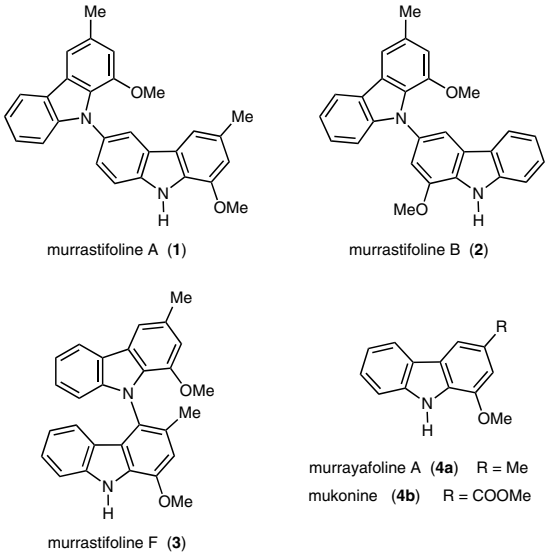
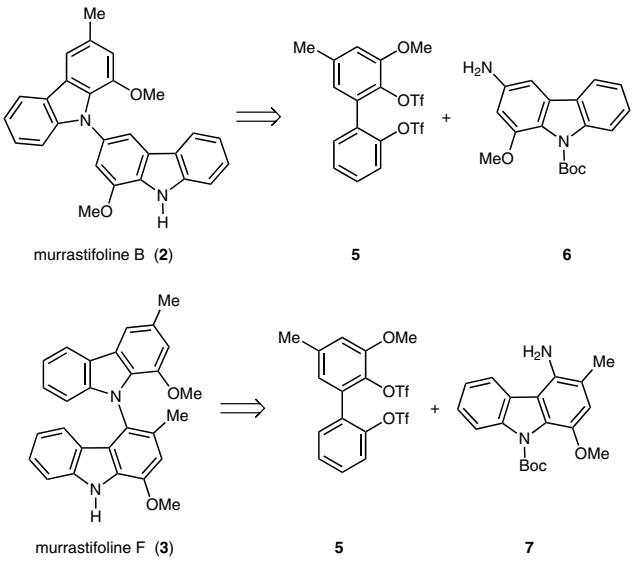


Figure 1 Murrastifoline A (**1**), murrastifoline B (**2**), murrastifoline F (**3**), and the 1-methoxycarbazole alkaloids **4a**,**b**



Scheme 1 Retrosynthetic analysis of murrastifoline B (**2**) and murrastifoline F (**3**)

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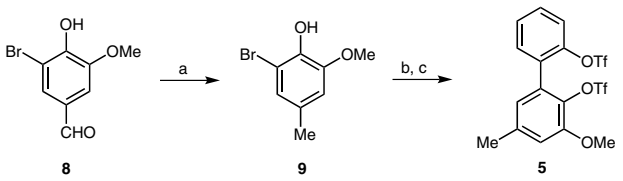
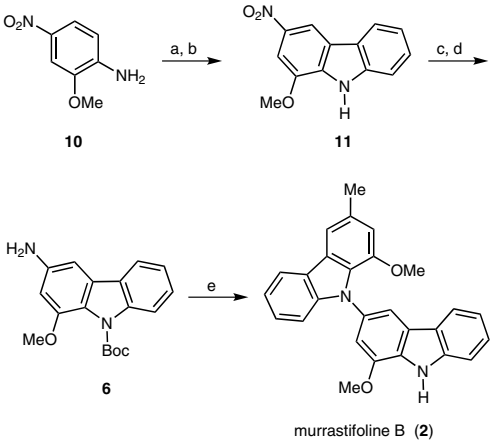
The required aminocarbazoles **6** and **7** are available using our palladium-catalyzed approach to carbazoles. For the synthesis of 1-oxygenated carbazoles via double Buchwald–Hartwig coupling, two different biaryl precursors have been described in the literature.[13,14] In their approach to murrastifoline A (**1**), Chida et al. described the dibromo analogue of **5** which requires a six-step synthesis.[13] The biaryl compound developed by Nozaki and co-workers is accessible in only three steps but has an ester group instead of the methyl substituent.[14] However, we require a methyl group at this position. Direct reduction of a methyl carboxylate at C-3 of the carbazole to a methyl group is feasible,[15,16] but only if the nitrogen atom is unsubstituted.[6f] Based on these considerations, we have prepared the bistriflate **5** which is the methyl analogue of the biaryl compound used by Nozaki.

2-Bromo-6-methoxy-4-methylphenol (**9**) was prepared from commercially available 5-bromovanillin (**8**) using the procedure of Nazih and co-workers (Scheme 2).[18] Suzuki–Miyaura coupling of compound **9** with 2-hydroxyphenylboronic acid under the conditions used by Nozaki and co-workers for the ester analogue resulted in decomposition.[14] However using the conditions of Ganesh et al., the corresponding biphenyl is available in 95% yield.[19] Subsequent reaction with triflic anhydride afforded the biaryl bistriflate **5**.



Scheme 2 Synthesis of the biaryl **5**. *Reagents and conditions*: (a) N_2H_4 (2 equiv), diethylene glycol, 110 °C, 15 min, then KOH (6 equiv), 150 °C, 2 h, 94%; (b) 2-hydroxyphenylboronic acid (1.5 equiv), $Pd(PPh_3)_4$ (7.5 mol%), K_2CO_3 (3 equiv), DME, EtOH, H_2O, 130 °C, sealed tube, 16 h, 95%; (c) Tf_2O (3 equiv), pyridine (3 equiv), CH_2Cl_2, 0 °C to r.t., 3 h, 84%.

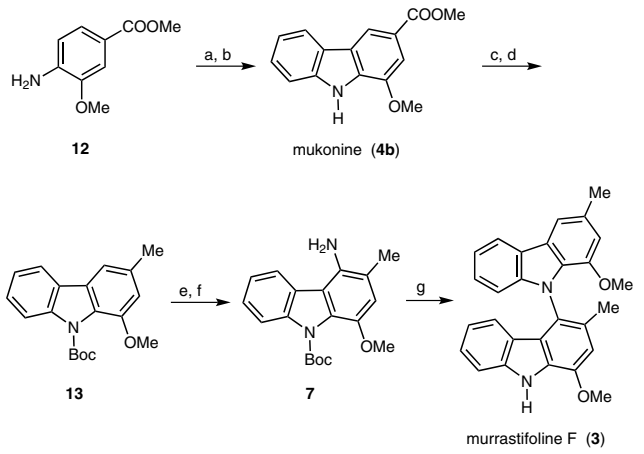
Our approach to murrastifoline B (**2**) requires the 3-aminocarbazole **6** as precursor for the twofold Buchwald–Hartwig amination (Scheme 1). Buchwald–Hartwig coupling[17] of 2-methoxy-4-nitroaniline (**10**) with bromobenzene to the corresponding diarylamine and subsequent oxidative cyclization led to the carbazole **11** (Scheme 3). Using Fagnou's protocol,[20] we observed only decomposition of the diarylamine. Our original conditions for the palladium(II)-catalyzed oxidative cyclization,[21,22] provided carbazole **11** in only 20% yield. Using two equivalents of palladium(II) acetate in acetic acid at reflux, the conditions reported by Åkermark et al. for the cyclization of electron-deficient diarylamines,[23] carbazole **11** was formed in 58% yield. The best result (78% yield of carbazole **11**) was obtained using only a slight excess of palladium(II) acetate in the presence of copper(II) acetate, conditions recently reported by us for the synthesis of 1,6-dioxygenated carbazoles bearing an ester group.[6f] Protection of the carbazole nitrogen atom and subsequent catalytic hydrogenation provided the 3-aminocarbazole **6**. Twofold Buchwald–Hartwig coupling of **6** with the bistriflate **5** in the presence of XantPhos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] following Nozaki's protocol[14] with concomitant cleavage of the Boc group provided directly murrastifoline B (**2**). The spectroscopic data of our synthetic murrastifoline B (**2**)[24] are in full agreement with those reported for the natural product.[7] An assignment of the ^1H and ^{13}C NMR data for **2** has been achieved by the following set of 2D NMR spectra: COSY, HSQC, HMBC, and NOESY (see Supporting Information).



Scheme 3 Synthesis of murrastifoline B (**2**). *Reagents and conditions*: (a) PhBr (1.2 equiv), $Pd(OAc)_2$ (6 mol%), SPhos (12 mol%), Cs_2CO_3 (1.4 equiv), toluene, reflux, 40 h, 100%; (b) $Pd(OAc)_2$ (1.3 equiv), $Cu(OAc)_2$ (2.5 equiv), AcOH, 117 °C, 40 h, 78%; (c) Boc_2O (2 equiv), DMAP (1 equiv), MeCN, r.t., 20 h, 91%; (d) 10% Pd/C, H_2, EtOAc, r.t., 5 d, 100%; (e) **5** (1 equiv), **6** (1 equiv), $Pd_2(dba)_3$ (20 mol%), XantPhos (40 mol%), K_3PO_4 (4.8 equiv), *o*-xylene, 130 °C, 64 h, 66%.

The synthesis of murrastifoline F (**3**) requires the Boc-protected 4-amino-1-methoxy-3-methyl-9*H*-carbazole **7** for the twofold Buchwald–Hartwig amination with **5** (Scheme 4). Thus, murrayafoline A (**4a**) appeared to represent a suitable intermediate. Murrayafoline A (**4a**) is available in three steps and 79% overall yield via mukonine (**4b**) starting from the commercially available arylamine **12**.[6g,h] Subsequent *N*-Boc protection of murrayafoline A (**4a**) afforded carbazole **13**. Nitration using clay-supported copper(II) nitrate (claycop)[25] takes place at C-4, as observed previously in analogous cases.[26] Catalytic hydrogenation of the 4-nitrocarbazole afforded the 4-aminocarbazole **7**. Using Nozaki's protocol,[14] the twofold Buchwald–Hartwig coupling of **7** and the bistriflate **5** with concomitant deprotection afforded directly murrastifoline F (**3**). The spectroscopic data of murrastifoline F (**3**)[27] are in agreement with those reported in the literature.[8,9]

In conclusion, our present approach, based on a twofold Buchwald–Hartwig coupling of an appropriately substituted arylamine with the bistriflate **5**, provides murrastifo-



Scheme 4 Synthesis of murrastifoline F (**3**). *Reagents and conditions*: (a) PhBr (1.2 equiv), $Pd(OAc)_2$ (6 mol%), SPhos (12 mol%), Cs_2CO_3 (1.4 equiv), toluene, reflux, 40 h, 100%; (b) $Pd(OAc)_2$ (10 mol%), K_2CO_3 (10 mol%), PivOH, 115 °C, 14 h, 91%; (c) $LiAlH_4$ (3 equiv), Et_2O, CH_2Cl_2, r.t., 4.5 h, 87%; (d) Boc_2O (4 equiv), DMAP (1 equiv), MeCN, r.t., 40 h, 91%; (e) claycop (250 mg/mmol), Ac_2O (5 equiv), Et_2O, r.t., 40 h, 96%; (f) 10% Pd/C, H_2, EtOAc, r.t., 7 d, 100%; (g) **5** (1 equiv), **7** (1.2 equiv), $Pd_2(dba)_3$ (20 mol%), XantPhos (40 mol%), K_3PO_4 (6 equiv), *o*-xylene, 120 °C, 4 d, 64%.

line B (**2**) in five steps (47% overall yield) and murrastifoline F (**3**) in seven steps (44% overall yield).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References and Notes

(1) Part 116 of Transition Metals in Organic Synthesis; for Part 115, see: Hesse, R.; Krahl, M. P.; Jäger, A.; Kataeva, O.; Schmidt, A. W.; Knölker, H.-J. *Eur. J. Org. Chem.* **2014**, submitted.

(2) (a) 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. (b) Chakraborty, D. P. In *The Alkaloids*; Vol. 44; Cordell, G. A., Ed.; Academic Press: New York, **1993**, 257.

(3) (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115. (c) Knölker, H.-J.; Reddy, K. R. In *The Alkaloids*; Vol. 65; Cordell, G. A., Ed.; Academic Press: Amsterdam, **2008**, 1. (d) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, *309*, 203. (e) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.

(4) (a) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967. (b) Pindur, U. *Chimia* **1990**, *44*, 406. (c) Kawasaki, T.; Sakamoto, M. *J. Indian Chem. Soc.* **1994**, *71*, 443. (d) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243. (e) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099.

(5) (a) Furukawa, H. *Trends Heterocycl. Chem.* **1993**, *3*, 185. (b) Tasler, S.; Bringmann, G. *Chem. Rec.* **2002**, *2*, 113.

(6) Reviews: (a) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309. (b) Knölker, H.-J. *Chem. Lett.* **2009**, *38*, 8. Recent applications: (c) Fuchsenberger, M.; Forke, R.; Knölker, H.-J. *Synlett* **2011**, 2056. (d) Gensch, T.; Rönnefahrt, M.; Czerwonka, R.; Jäger, A.; Kataeva, O.; Bauer, I.; Knölker, H.-J. *Chem. Eur. J.* **2012**, *18*, 770. (e) Huet, L.; Forke, R.; Jäger, A.; Knölker, H.-J. *Synlett* **2012**, *23*, 1230. (f) Börger, C.; Knölker, H.-J. *Tetrahedron* **2012**, *68*, 6727. (g) Börger, C.; Krahl, M. P.; Gruner, M.; Kataeva, O.; Knölker, H.-J. *Org. Biomol. Chem.* **2012**, *10*, 5189. (h) Börger, C.; Kataeva, O.; Knölker, H.-J. *Org. Biomol. Chem.* **2012**, *10*, 7269. (i) Kumar, V. P.; Gruner, K. K.; Kataeva, O.; Knölker, H.-J. *Angew. Chem. Int. Ed.* **2013**, *52*, 11073.

(7) Ito, C.; Wu, T.-S.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, *38*, 1143.

(8) Ito, C.; Thoyama, Y.; Omura, M.; Ichiro, K.; Furukawa, H. *Chem. Pharm. Bull.* **1993**, *41*, 2096.

(9) Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703.

(10) Furukawa, H.; Wu, T.-S.; Ohta, T. *Chem. Pharm. Bull.* **1983**, *31*, 4202.

(11) Chakraborty, D. P.; Bhattacharyya, P.; Roy, S.; Bhattacharyya, S. P.; Biswas, A. K. *Phytochemistry* **1978**, *17*, 834.

(12) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 2051.

(13) (a) Kitawaki, T.; Hayashi, Y.; Chida, N. *Heterocycles* **2005**, *65*, 1561. (b) Kitawaki, T.; Hayashi, Y.; Ueno, A.; Chida, N. *Tetrahedron* **2006**, *62*, 6792.

(14) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413.

(15) Chakraborty, D. P.; Roy, S.; Dutta, A. K. *J. Indian Chem. Soc.* **1987**, *64*, 215.

(16) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 2337.

(17) (a) Charles, M. D.; Schulz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.

(18) Nazih, A.; Benezra, C.; Lepoittevin, J. P. *Chem. Res. Toxicol.* **1993**, *6*, 215.

(19) Ganesh, T.; Thepchatri, P.; Li, L.; Du, Y.; Fu, H.; Snyder, J. P.; Sun, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4982.

(20) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.

(21) Knölker, H.-J.; O'Sullivan, N. *Tetrahedron* **1994**, *50*, 10893.

(22) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Synthesis* **2002**, 557.

(23) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365.

(24) **Experimental Procedure for the Twofold Buchwald–Hartwig Coupling to Murrastifoline B (2)**
A solution of the aminocarbazole **6** (19.1 mg, 0.061 mmol), the bistriflate **5** (30.2 mg, 0.061 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), XantPhos (14.1 mg, 0.024 mmol), and K_3PO_4 (61.9 mg, 0.292 mmol) in *o*-xylene (3 mL) was heated at 130 °C for 64 h. The reaction mixture was diluted with EtOAc and a sat. aq. solution of NH_4Cl was added. The aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and purification of the residue by flash chromatography on silica gel (isohexane–EtOAc, 6:1) afforded murrastifoline B (**2**); yield 16.4 mg (66%); colorless crystals; mp 58.5–59 °C (lit.[7] oil). UV (MeOH): λ = 229 (sh), 242, 291, 335 nm. IR (ATR): ν = 3407, 3055, 2923, 2852, 1692, 1624, 1582, 1542, 1502, 1453, 1419, 1395, 1323, 1277, 1222, 1134, 1104, 1037, 1014, 991, 952, 909, 827, 765, 746, 698, 659, 638, 619 cm^{-1}. ^1H NMR (600 MHz, acetone-d_6): δ = 2.55 (s, 3 H), 3.63 (s, 3 H), 4.06 (s, 3 H), 6.89 (s, 1 H), 7.07 (d, *J* = 1.6 Hz, 1 H), 7.21–7.25 (m, 3 H), 7.35–7.37 (m, 1 H), 7.46 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1 H), 7.66 (dd, *J* = 1.3, 0.8 Hz, 1 H), 7.68 (dt, *J* = 8.2, 0.8 Hz, 1 H), 7.84 (m, 1 H), 8.15–8.17 (m,

2 H), 10.61 (br s, 1 H). ^{13}C NMR and DEPT (150 MHz, acetone-d_6): δ = 21.68 (CH_3), 56.10 (CH_3), 56.24 (CH_3), 108.13 (CH), 110.82 (CH), 111.20 (CH), 112.30 (CH), 113.11 (CH), 113.36 (CH), 119.88 (CH), 120.16 (CH), 120.69 (CH), 121.29 (CH), 123.8 (C), 124.4 (C), 126.45 (CH), 126.56 (CH), 129.97 (C), 130.06 (C), 132.77 (C), 141.2 (C), 144.0 (C), 146.39 (C), 147.82 (C); 3 C signals are missing. ESI-MS (10 V): *m/z* = 407 $[M + H]^+$.

(25) (a) Cornélis, A.; Lazlo, P. *Synthesis* **1985**, 909. (b) Laszlo, P.; Pennetreau, P. *J. Org. Chem.* **1987**, *52*, 2407. (c) Gigante, B.; Prazeres, A. O.; Marcelo-Curto, M. J.; Cornélis, A.; Laszlo, P. *J. Org. Chem.* **1995**, *60*, 3445.

(26) Knott, K. E.; Auschill, S.; Jäger, A.; Knölker, H.-J. *Chem. Commun.* **2009**, 1467.

(27) **Murrastifoline F (3)**
Colorless crystals; 288–289 °C (lit.[9] 289 °C). UV (MeOH): λ = 227, 242 (sh), 260 (sh), 287 (sh), 351 nm. IR (ATR): ν = 3055, 2923, 2852, 1653, 1592, 1500, 1460, 1444, 1395, 1318, 1281, 1227, 1192, 1170, 1104, 1072, 1041, 938, 822, 745, 695, 637, 606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.40 (s, 3 H), 3.80 (s, 3 H), 3.91 (s, 3 H), 6.50–6.56 (m, 3 H), 6.69–6.82 (m, 4 H), 6.83 (s, 1 H), 6.94 (s, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.73 (d, *J* = 7.0 Hz, 1 H). ESI-MS (25 V): *m/z* = 438 $[M + NH_4]^+$.

