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TOTAL SYNTHESIS OF MURRASTIFOLINE-A BY WAY OF THE Pd-CATALYZED DOUBLE *N*-ARYLATION OF A CARBAZOLAMINE WITH A 2,2'-DIBROMOBIPHENYL DERIVATIVE

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Abstract – The first total synthesis of murrastifoline-A (**1**), a biscarbazole alkaloid is described. The biscarbazole skeleton of **1** was effectively constructed by the Pd-catalyzed double *N*-arylation of carbazolamine (bottom-half segment, **3**) with dibromobiphenyl derivative (top-half segment, **2**) in one-step reaction. Both segments were synthesized starting from 2-amino-5-methylphenol (**4**).

Carbazole alkaloids are known to show wide range of biological activities such as antitumor, antibiotic, psychotropic, antiinflammatory, and antihistaminic activities.[1] Development of efficient methods for the construction of a carbazole ring is still an important issue.[2] While many monomeric carbazoles have been isolated from higher plants,[1] recently, much attention has been focused on biarylic biscarbazole alkaloids[3,4] due to their interesting structures and expected biological activities.

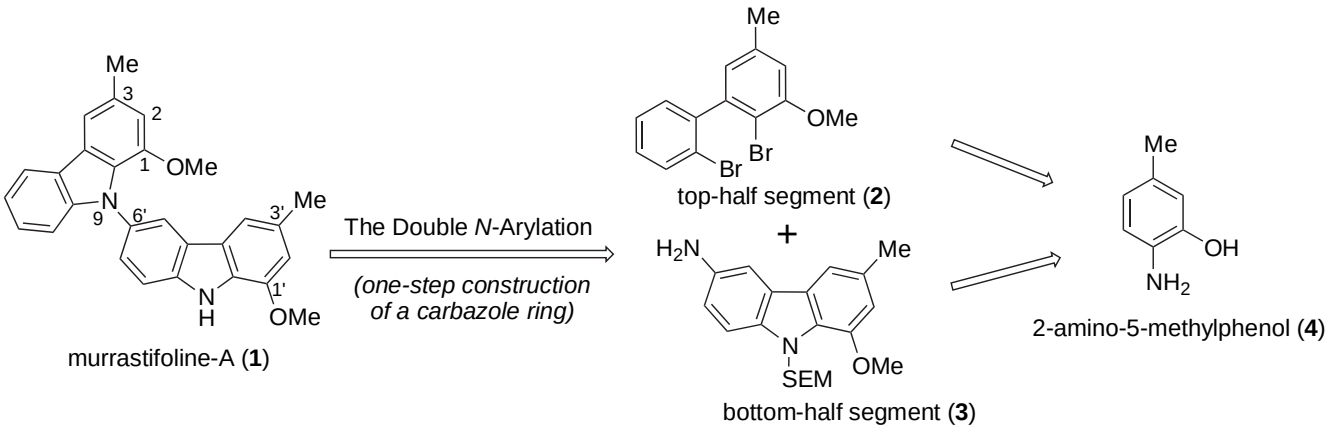
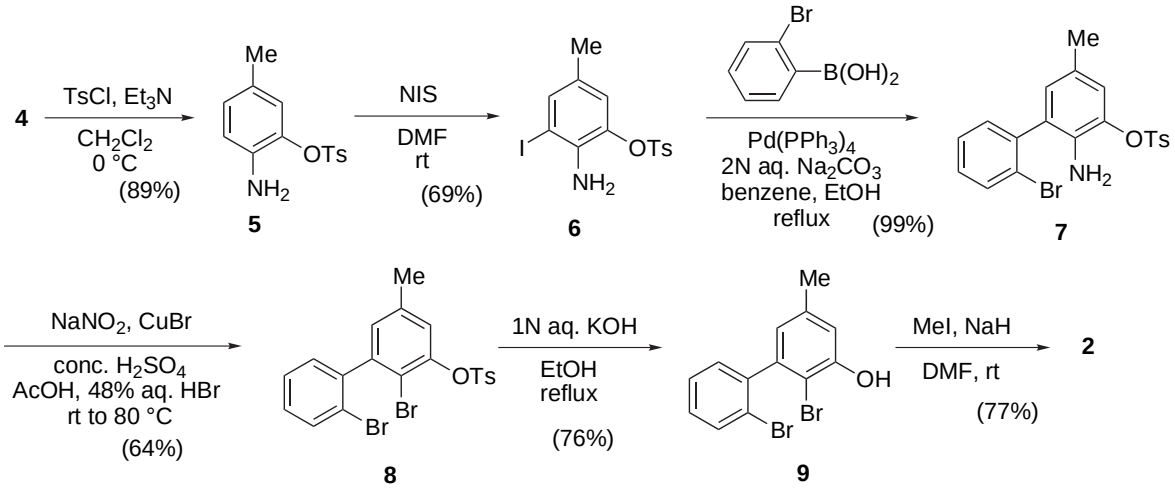


Figure. Structure of murrastifoline-A (**1**) and retrosynthetic way to **1**.

Murrastifoline-A (**1**) was isolated by the Furukawa group from the root bark of *Murraya euchrestifolia* (Rutaceae) collected in Taiwan.[3] The structure elucidation study by spectral analyses revealed that murrastifoline-A is a new biscarbazole possessing a dimeric structure of 1-methoxy-3-methylcarbazole (murrayafoline-A), where the nitrogen in one carbazole unit is connected to the carbon atom at 6'-position of another carbazole unit.[3] Such a *C,N*-bonded biaryl biscarbazole structure is very unique among the biscarbazole alkaloids,[4] however, reports on the synthetic approach to *C,N*-bonded biaryl biscarbazoles are limited,[4d,5] and synthesis of **1** has not been achieved to date. In 2001, Bringmann disclosed the total synthesis of murrastifoline-F, an isomer of **1** in which the nitrogen in a carbazole unit is bonded to another carbazole at C-4', by a lead tetraacetate-mediated oxidative coupling of 1-methoxy-3-methylcarbazole.[5b] In this communication, we report the first total synthesis of murrastifoline-A, which fully confirmed the proposed unique structure.

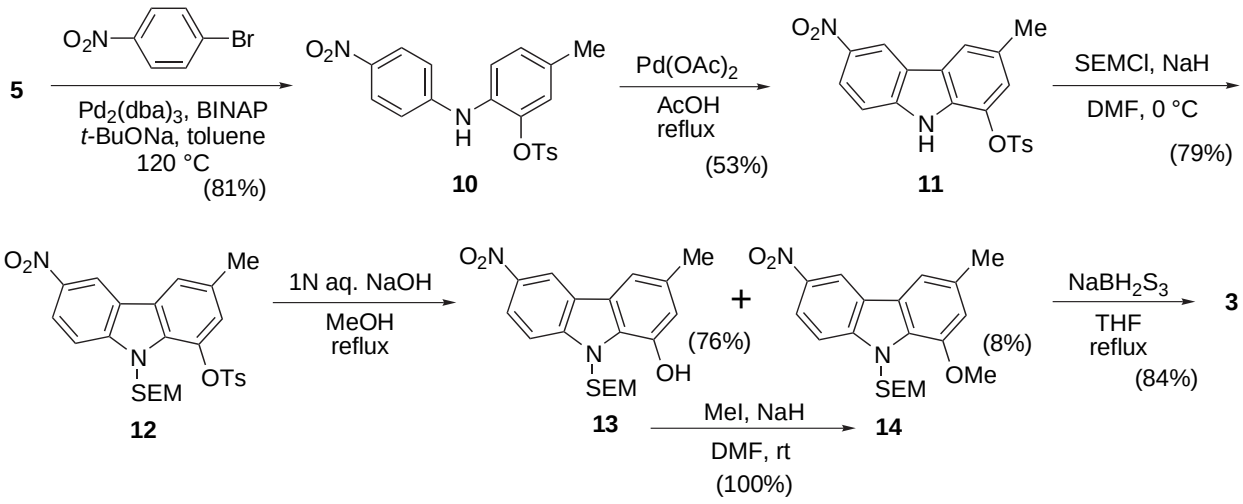
Our retrosynthetic analysis suggested that the Pd-catalyzed double *N*-arylation of carbazolamine (bottom-half segment, **3**) with 2,2'-dibromobiphenyl derivative (top-half segment, **2**) would construct the biscarbazole skeleton of **1** in one-step reaction (Figure). The double *N*-arylation of primary amines with biphenyls possessing leaving groups at C-2 and 2', recently developed by Nozaki and co-workers,[6] is an important extension of the Buchwald-Hartwig Pd-catalyzed *N*-arylation reaction,[7a] and proved to be an excellent protocol for the regioselective construction of multi-substituted carbazoles in one-step. The Nozaki group also reported successful synthesis of various substituted carbazoles including a monocarbazole alkaloid, mukonine by this novel methodology.[6b] For preparation of both top- and bottom segments (**2** and **3**), we chose 2-amino-5-methylphenol (**4**) as the common starting material.



Scheme 1

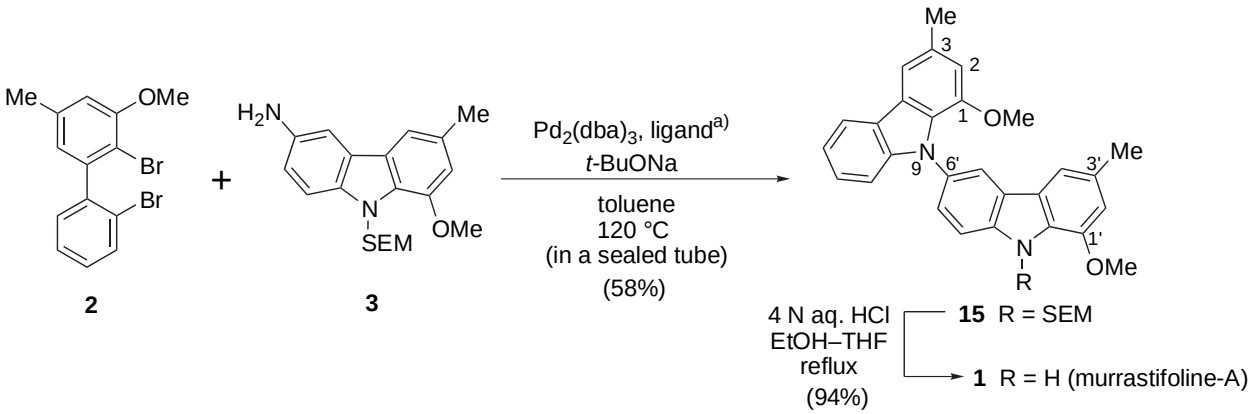
The synthesis of the top-half segment (**2**) commenced from the known *O*-tosylate (**5**),[8] prepared from commercially available **4** in 89% yield (Scheme 1). Conventional iodination with *N*-iodosuccinimide

(NIS) of **5** afforded **6**[9] (69%), whose Suzuki-Miyaura cross-coupling reaction[10] with 2-bromophenylboronic acid in the presence of $Pd(PPh_3)_4$ in EtOH–benzene–2N aqueous Na_2CO_3 cleanly afforded **7** in 99% yield. Sandmeyer reaction of **7** with $NaNO_2$ and CuBr in acetic acid, conc. H_2SO_4 and 48% aqueous HBr gave dibromobiphenyl (**8**) in 64% yield. The *O*-Ts protecting group in **8** was removed by basic hydrolysis to give **9**, whose *O*-methylation furnished the top-half segment (**2**)[11] in 59% yield from **8**. The bottom-half segment (**3**) was synthesized as shown in Scheme 2. Thus, the Buchwald-Hartwitg Pd-catalyzed amination[7b] of *p*-bromonitrobenzene with **5** afforded diarylamine (**10**) in 81% yield. Treatment of **10** with excess $Pd(OAc)_2$ in AcOH induced the cyclization[12] to provide carbazole (**11**)[11] in 53% yield. After protection of the nitrogen function in **11** with 2-trimethylsilylethoxymethyl (SEM) group (79% yield), the product (**12**) was treated with NaOH in MeOH–H_2O to provide de-*O*-tosyl derivative (**13**) along with its methyl ether (**14**)[13] in 76 and 8% isolated yields, respectively. *O*-Methylation of **13** afforded **14**, quantitatively. Reduction of the nitro function in **14** with $NaBH_2S_3$[14] cleanly provided the bottom-half segment (**3**)[11] in 84% yield.



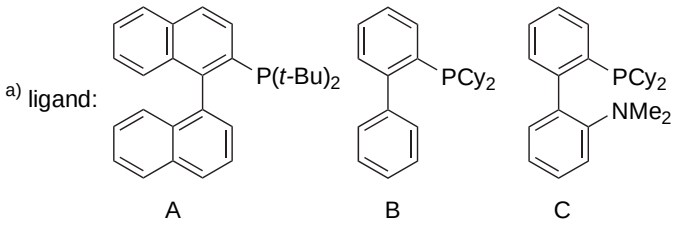
Scheme 2

With both top- and bottom-half segments in hand, the crucial double *N*-arylation reaction was explored (Scheme 3). When a mixture of segments (**2**) and (**3**) was heated in toluene at 120 °C in the presence of $Pd_2(dba)_3$, *t*-BuONa, and ligands, the double *N*-arylation successfully took place to provide the desired *N*-protected biscarbazole (**15**)[11] in one-step reaction. Use of 2-dicyclohexylphosphinobiphenyl[15] as the ligand was found to give good results, and **15** was obtained in 58% yield.[16] Finally, the *N*-SEM group was removed under acidic conditions to furnish murrastifoline-A (**1**)[11] in 94% yield. The spectral data of synthetic **1** were fully identical with those of the natural product.[1a]



The double *N*-arylation of **3** with **2**.

run	ligand[a)]	time (h)	yield of **15** (%)
1	A	6	23
2	B	6	56
3	B	24	58
4	C	24	31



Scheme 3

In summary, the first total synthesis of murrastifoline-A (**1**) has been accomplished. This work fully confirmed the proposed structure of the natural product and revealed that the double *N*-arylation methodology is highly effective for the one-step construction of the *C,N*-bonded biaryl biscarbazole structures. Further application of the double *N*-arylation strategy to the preparation of structurally more complex natural products is under investigation in our laboratory.

ACKNOWLEDGEMENTS

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11. Selected data for **2**: IR (neat) 2940 and 1580 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.48 (dd, 1 H, *J* = 7.5 and 1.2 Hz), 7.10 (dd, 1 H, *J* = 7.3 and 1.8 Hz), 6.96 (ddd, 1 H, *J* = 7.4, 7.3 and 1.2 Hz), 6.78 (ddd, 1 H, *J* = 7.5, 7.4 and 1.8 Hz), 6.54 (d, 1 H, *J* = 1.6 Hz), 6.32 (d, 1 H, *J* = 1.6 Hz), 3.27 (s, 3 H) and 2.01 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 156.6, 144.0, 143.1, 138.0, 132.9, 131.3, 129.3, 127.2, 124.1, 123.9, 112.3, 110.7, 55.7 and 21.3; MS (EI) *m*/*z* 358 (M^+ +4, 49.0), 356 (M^+ +2, 100), 354 (M^+, 51.4), 277 (77.3), 275 (79.4), 196 (43.0), 181 (41.4), 165 (21.5); high resolution MS (EI) calcd for $C_{14}H_{12}OBr_2$ (M^+), 353.9255; Found 353.9254. For **11**: IR (neat) 3370, 1520 and 1320 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, 1 H, *J* = 2.0 Hz), 8.94 (s, 1 H), 8.37 (dd, 1 H, *J* = 9.0 and 2.0 Hz), 7.80 (s, 1 H), 7.78 (d, 2 H, *J* = 8.3 Hz), 7.47 (d, 1 H, *J* = 9.0 Hz), 7.35 (d, 2 H, *J* = 8.3 Hz), 6.71 (s, 1 H), 2.47 (s, 3 H) and 2.41 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 146.3, 143.2, 141.6, 134.3, 131.9, 131.6, 131.5, 130.1, 128.8, 126.4, 122.8, 122.5, 122.0, 119.9, 117.6, 111.1, 21.9 and 21.4; MS (EI) *m*/*z* 396 (M^+, 9.6), 348 (11.0), 330 (30.9), 241 (33.5), 197 (100); high resolution MS (EI) calcd for $C_{20}H_{16}N_2O_5S$ (M^+), 396.0780; Found 396.0780. For **3**: IR (neat) 3350, 2950 and 2860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 7.36 (d, 1 H, *J* = 8.4 Hz), 7.31 (d, 1 H, *J* = 2.1 Hz), 6.87 (dd, 1 H, *J* = 8.4 and 2.1 Hz), 6.72 (s, 1 H), 5.95 (s, 2 H), 3.97 (s, 3 H), 3.60 (brs, 1 H), 3.53 (t, 2 H, *J* = 8.1 Hz), 2.49 (s, 3 H), 0.85 (t, 2 H, *J* = 8.1 Hz) and -0.12 (s, 9 H); ^{13}C (75 MHz, $CDCl_3$) δ 146.7, 139.7, 136.0, 129.2, 128.6, 125.0, 124.5, 115.8, 112.8, 110.9, 109.1, 105.8, 74.3, 65.1, 55.5, 21.8, 18.0 and -1.3; MS (EI)

m/*z* 356 (M^+, 13.5), 239 (10.7), 226 (15.2), 211 (10.7), 149 (17.2), 75 (100); high resolution MS (EI) calcd for $C_{20}H_{28}N_2O_2Si$ (M^+), 356.1920; Found 356.1922. For **15**: IR (neat) 2950 and 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1 H, *J* = 7.8 Hz), 8.04 (d, 1 H, *J* = 1.8 Hz), 7.62 (d, 1 H, *J* = 8.7 Hz), 7.60 (s, 1 H), 7.47 (dd, 1 H, *J* = 8.7 and 1.8 Hz), 7.42 (s, 1H), 7.32 (ddd, 1 H, *J* = 7.9, 7.9 and 1.2 Hz), 7.22 (ddd, 1 H, *J* = 7.9, 7.9 and 1.2 Hz), 7.18 (d, 1 H, *J* = 7.9 Hz), 6.81 (d, 1 H, *J* = 0.6 Hz), 6.74 (d, 1 H, *J* = 0.6 Hz), 6.09 (d, 2 H, *J* = 3.9 Hz), 4.03 (s, 3 H), 3.65 (t, 2 H, *J* = 7.5 Hz), 3.55 (s, 3 H), 2.55 (s, 3 H), 2.50 (s, 3 H), 0.93 (t, 2 H, *J* = 7.5 Hz) and -0.07 (s, 9 H); ^{13}C (75 MHz, $CDCl_3$) δ 146.9, 146,8, 143.2, 140.4, 132.2, 130.2, 129.7, 129.4, 128.6, 126.4, 125.7, 125.4, 123.6, 123.2, 123.1, 120.1, 119.9, 119.4, 112.9, 112.9, 110.5, 110.1, 109.8, 109.5, 74.5, 65.5, 56.1, 55.7, 21.9, 21.8, 18.1 and -1.3; MS (EI) *m*/*z* 550 (M^+, 0.5), 433 (0.9), 405 (0.6), 359 (0.5), 167 (12.1), 59 (100); high resolution MS (EI) calcd for $C_{34}H_{38}N_2O_3Si$ (M^+), 550.2652; Found 550.2657. For **1**: IR (neat) 3420 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.45 (s, 1 H), 8.13 (d, 1 H, *J* = 8.1 Hz), 8.09 (d, 1 H, *J* = 2.1 Hz), 7.66 (d, 1 H, *J* = 8.4 Hz), 7.62 (s, 1 H), 7.54 (s, 1 H), 7.40 (dd, 1 H, *J* = 8.4 and 2.1 Hz), 7.32 (ddd, 1 H, *J* = 8.4, 7.8 and 1.2 Hz), 7.20 (ddd, 1 H, *J* = 7.8, 7.8 and 1.2 Hz), 7.15 (d, 1 H, *J* = 8.4 Hz), 6.88 (s, 1 H), 6.84 (s, 1 H), 4.02 (s, 3 H), 3.56 (s, 3 H), 2.51 (s, 3 H) and 2.48 (s, 3 H); ^{13}C (75 MHz, acetone-d_6) δ 147.8, 146.7, 144.0, 140.0, 132.0, 130.4, 130.1, 130.0, 129.9, 126.6, 126.4, 126.0, 125.1, 124.0, 123.9, 120.8, 120.5, 120.2, 113.4, 113.4, 117.2, 111.1, 110.7, 108.9, 56.1, 55.9, 21.9 and 21.7; MS (EI) *m*/*z* 420 (M^+, 5.7), 270 (14.4), 252 (11.8), 58 (100); high resolution MS (EI) calcd for $C_{28}H_{24}N_2O_2$ (M^+), 420.1838; Found 420.1838.

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13. Methyl ether (**14**) would be formed by nucleophilic aromatic substitution reaction of compound (**12**) with methoxide ion. The similar substitution reactions, in which the bromo substituents in 1-bromo-3-methylcarbazole, 8-bromo-1,2,3,4-tetrahydrocarbazole, and 7-bromo-1,2,3,4-tetrahydrocarbazole were displaced with methoxy groups by treatment with sodium methoxide in the presence or absence of CuI, have been reported. See, Y. Kikugawa, Y. Miyake, and M. Kawase, *Chem Pharm. Bull.*, 1981, **29**, 1231; Y. Kikugawa, Y. Aoki, and T. Sakamoto, *J. Org. Chem.*, 2001, **66**, 8612.
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16. Experimental procedure for the preparation of **15**: Ar was bubbled into a mixture of compound (**2**) (17.2 mg, 48.3 μmol), compound (**3**) (15.2 mg, 42.6 μmol), $Pd_2(dba)_3$ (7.8 mg, 8.5 μmol), 2-dicyclohexylphosphinobiphenyl (9.2 mg, 26 μmol) and *t*-BuONa (8.2 mg, 85 μmol) in toluene (0.6 mL) for 10 min. The reaction mixture was then heated at 120 °C in a sealed tube for 24 h. After cooling, the mixture was purified by column chromatography (silica gel: 2 g, EtOAc / *n*-hexane = 1/30) to afford **15** (13.6 mg, 58%) as a syrup.