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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.<sup>1</sup> Development of efficient methods for the construction of a carbazole ring is still an important issue.<sup>2</sup> While many monomeric carbazoles have been isolated from higher plants,<sup>1</sup> recently, much attention has been focused on biaryllic biscarbazole alkaloids<sup>3,4</sup> due to their interesting structures and expected biological activities.

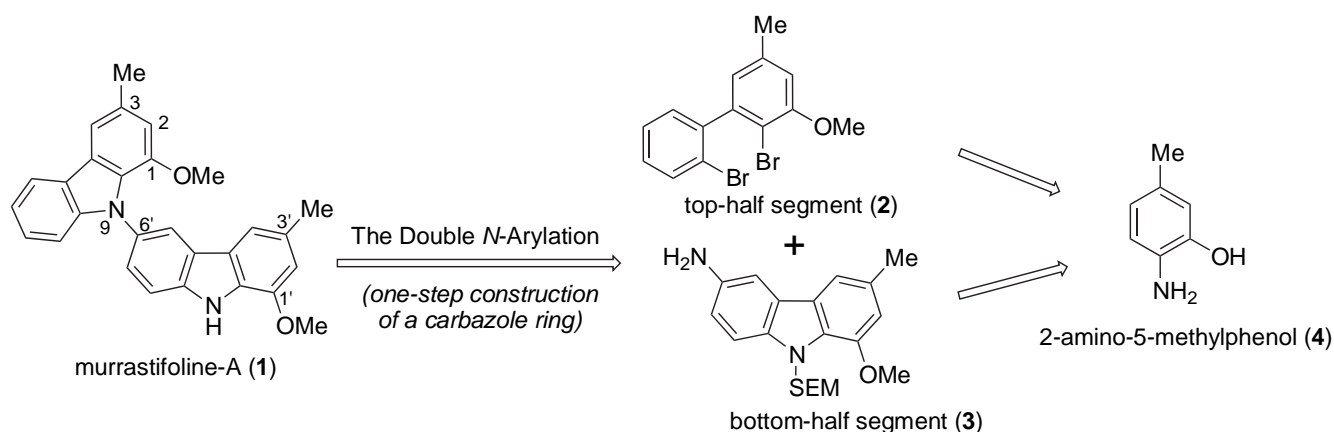
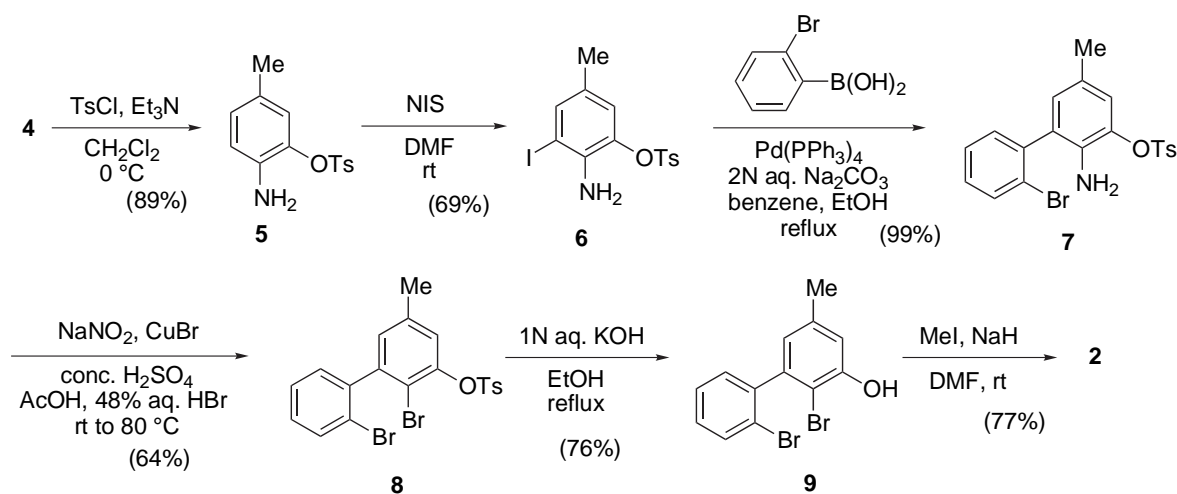


Figure. Structure of murrastifoline-A (**1**) and retrosynthetic way to **1**.

Murrastifoline-A (**1**) was isolated by the Furukawa group from the root bark of *Murraya euchrestifolia* (Rutaceae) collected in Taiwan.<sup>3</sup> The structure elucidation study by spectral analyses revealed that murrastifoline-A is a new bis-carbazole 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.<sup>3</sup> Such a *C,N*-bonded biaryl bis-carbazole structure is very unique among the bis-carbazole alkaloids,<sup>4</sup> however, reports on the synthetic approach to *C,N*-bonded biaryl bis-carbazoles are limited,<sup>4d,5</sup> 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.<sup>5b</sup> In this communication, we report the first total synthesis of murrastifoline-A, which fully confirmed the proposed unique structure.

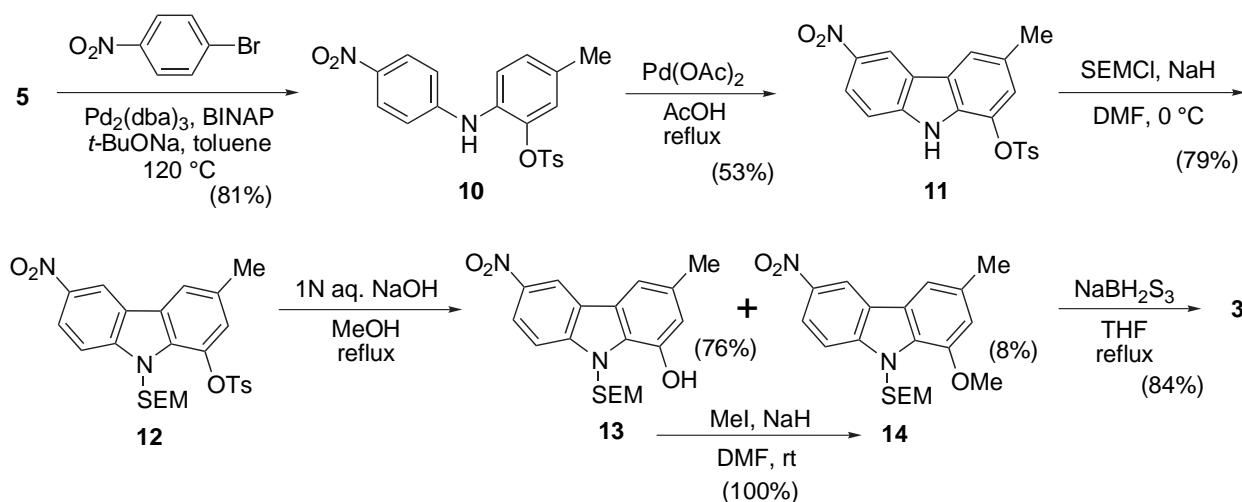
Our retrosynthetic analysis suggested that the Pd-catalyzed double *N*-arylation of carbazamine (bottom-half segment, **3**) with 2,2'-dibromobiphenyl derivative (top-half segment, **2**) would construct the bis-carbazole skeleton of **1** in one-step reaction (Figure). The double *N*-arylation of primary amines with biphenyls possessing leaving groups at C-2 and 2', recently developed by Nozaki and co-workers,<sup>6</sup> is an important extension of the Buchwald-Hartwig Pd-catalyzed *N*-arylation reaction,<sup>7a</sup> 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.<sup>6b</sup> 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

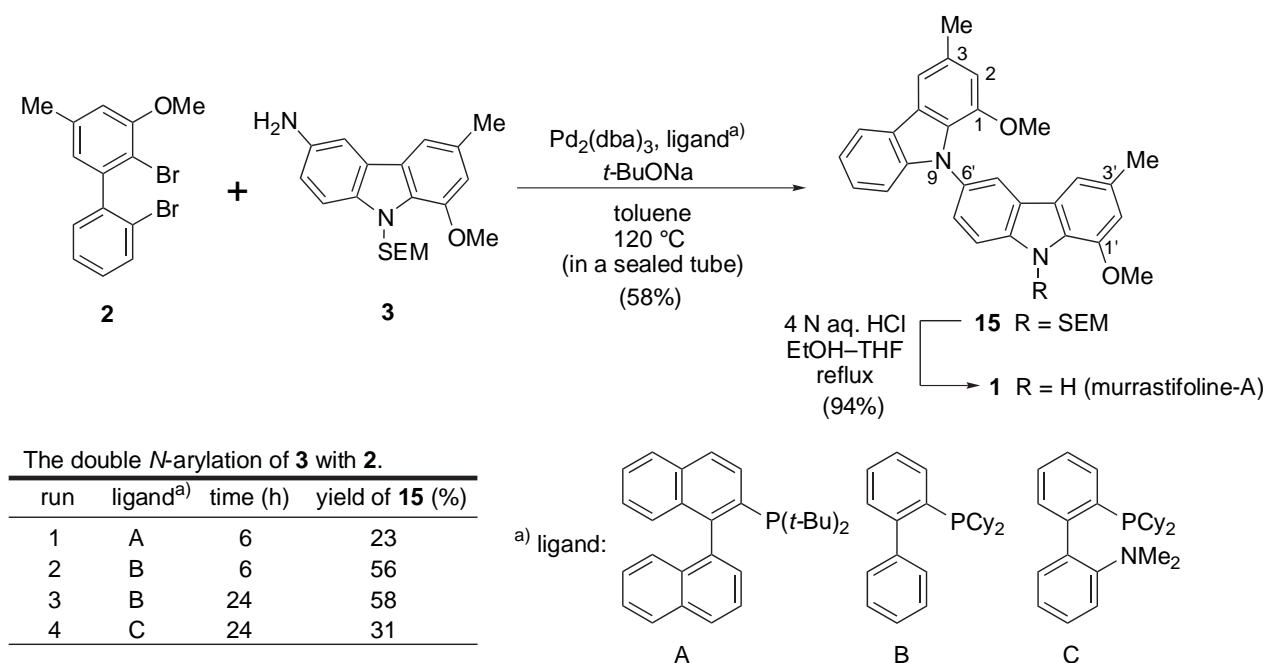
The synthesis of the top-half segment (**2**) commenced from the known *O*-tosylate (**5**),<sup>8</sup> prepared from commercially available **4** in 89% yield (Scheme 1). Conventional iodination with *N*-iodosuccinimide

(NIS) of **5** afforded **6**<sup>9</sup> (69%), whose Suzuki-Miyaura cross-coupling reaction<sup>10</sup> with 2-bromophenylboronic acid in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> in EtOH–benzene–2N aqueous Na<sub>2</sub>CO<sub>3</sub> cleanly afforded **7** in 99% yield. Sandmeyer reaction of **7** with NaNO<sub>2</sub> and CuBr in acetic acid, conc. H<sub>2</sub>SO<sub>4</sub> 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**)<sup>11</sup> in 59% yield from **8**. The bottom-half segment (**3**) was synthesized as shown in Scheme 2. Thus, the Buchwald-Hartwig Pd-catalyzed amination<sup>7b</sup> of *p*-bromonitrobenzene with **5** afforded diarylamine (**10**) in 81% yield. Treatment of **10** with excess Pd(OAc)<sub>2</sub> in AcOH induced the cyclization<sup>12</sup> to provide carbazole (**11**)<sup>11</sup> 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<sub>2</sub>O to provide de-*O*-tosyl derivative (**13**) along with its methyl ether (**14**)<sup>13</sup> in 76 and 8% isolated yields, respectively. *O*-Methylation of **13** afforded **14**, quantitatively. Reduction of the nitro function in **14** with NaBH<sub>2</sub>S<sub>3</sub><sup>14</sup> cleanly provided the bottom-half segment (**3**)<sup>11</sup> 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<sub>2</sub>(dba)<sub>3</sub>, *t*-BuONa, and ligands, the double *N*-arylation successfully took place to provide the desired *N*-protected biscarbazole (**15**)<sup>11</sup> in one-step reaction. Use of 2-dicyclohexylphosphinobiphenyl<sup>15</sup> as the ligand was found to give good results, and **15** was obtained in 58% yield.<sup>16</sup> Finally, the *N*-SEM group was removed under acidic conditions to furnish murrastifoline-A (**1**)<sup>11</sup> in 94% yield. The spectral data of synthetic **1** were fully identical with those of the natural product.<sup>1a</sup>



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.

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$m/z$  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,  $CDCl_3$ )  $\delta$  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,  $CDCl_3$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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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16. Experimental procedure for the preparation of **15**: Ar was bubbled into a mixture of compound (**2**) (17.2 mg, 48.3  $\mu\text{mol}$ ), compound (**3**) (15.2 mg, 42.6  $\mu\text{mol}$ ),  $\text{Pd}_2(\text{dba})_3$  (7.8 mg, 8.5  $\mu\text{mol}$ ), 2-dicyclohexylphosphinobiphenyl (9.2 mg, 26  $\mu\text{mol}$ ) and *t*-BuONa (8.2 mg, 85  $\mu\text{mol}$ ) 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.