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# An expedient synthesis of ellipticine via Suzuki–Miyaura coupling

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ABSTRACT

A simple and efficient total synthesis of ellipticine was developed via the Suzuki–Miyaura coupling of sterically sensitive 2-hydroxybenzeneboronic acid with a multifunctional aryl halide using $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an additive in $DMSO/H_2O$ as a key step followed by double N-arylation and cyclization.

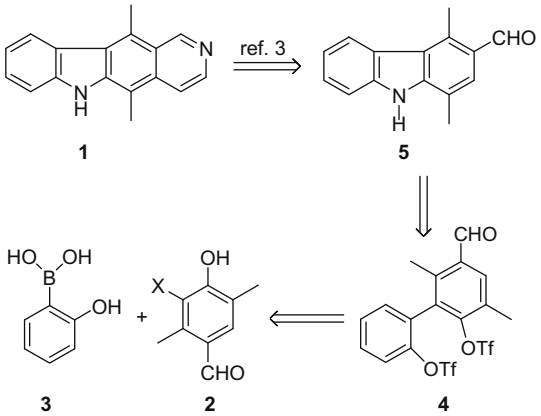


Ellipticine (**1**), first isolated from the leaves of *Ochrosia elliptica* Labill in 1959, is a member of the pyrido[4,3-*b*]carbazole family. Ellipticine and its derivatives display potent antitumor and anticancer properties. These compounds are good DNA intercalating molecules, and their high DNA binding affinity is thought to be responsible in part for these pharmacological properties.[1] More recent studies have also indicated that ellipticine and its derivatives are active against HIV.[2] The unique structural features, limited toxic side effects, and complete lack of hematological toxicity of these compounds has prompted chemists to develop synthetic strategies for the preparation of ellipticine and several of its analogues for pharmacological evaluation.[1,3]

A wide variety of synthetic studies and total syntheses of ellipticine have been reported by many groups,[4] which includes our own work in this area.[5] The most convenient synthesis starts with indole.[4a–f] Gribble and Moody have reported useful procedures for the synthesis of ellipticine using the Diels–Alder approach.[4g–i] All these procedures, however, involve protection/deprotection problems[4b–h] and a large number of steps,[4j] and some require triazene, which is a potential carcinogen.[4i,k] While recognizing these limitations, it must be noted that the Gribble and Moody procedures have improved the yields and regioselectivity.[4l] Recently, a radical cascade protocol was applied to the synthesis of ellipticine, but the reaction intermediates need a toxic phosgene solution for their preparation.[4m] In light of all the afore-mentioned problems, and considering the interesting biological activities of **1**, a general and efficient approach for the synthesis of this compound is desirable.

A retro synthetic strategy for the synthesis of **1** is outlined in Scheme 1. The compound **1** could be readily prepared by a selective coupling of multifunctional aryl halide **2** with 2-hydroxybenzeneboronic acid (**3**) using Suzuki–Miyaura coupling followed by double N-arylation of biphenyl triflate **4** and cyclization of the formylated carbazole derivative **5**.[3]

The complete synthetic sequence of **1** via Suzuki–Miyaura coupling is shown in Scheme 2. Initially, the formylation of 2,5-dimethylphenol (**6**) was examined. Using the Reimer–Tiemann




**Scheme 1.** Retro synthesis of ellipticine.

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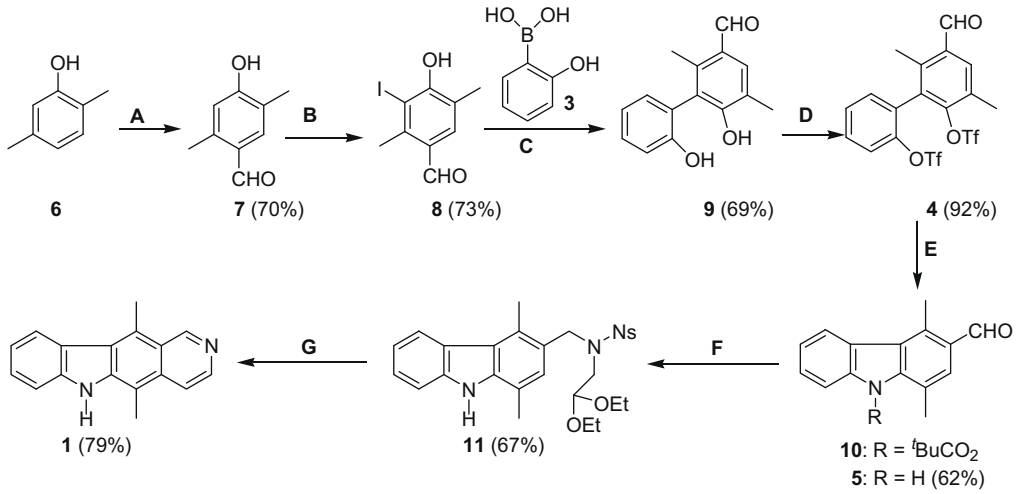


**Scheme 2.** Reagents and conditions: (A) dichloromethyl methyl ether (1.1 equiv), $AlCl_3$ (1.5 equiv), 0 °C, 5 min; (B) NaOAc (1 equiv), $I_2$ (1 equiv), 1:1 MeOH/$H_2O$, rt, 12 h; (C) $Pd(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$, $Na_2CO_3$, DMSO/$H_2O$, 130 °C, 3 h; (D) $Tf_2O$, $Et_3N$, $CH_2Cl_2$, rt, 20 min; (E) $^tBuCO_2NH_2$, $Pd(OAc)_2$, Xantphos, $K_3PO_4$, xylene, 130 °C, 18 h [compound **10** (not detected); compound **5**]; (F) (i) aminoacetal, benzene, reflux; (ii) MeOH, $NaBH_4$, rt, 1 h; (iii) Ns–Cl, pyridine, MeCN, rt, 6 h; (G) 6 M HCl–dioxane, reflux, 3 h.

reaction, 4-hydroxy-2,5-dimethylbenzaldehyde (**7**) was obtained from **6** in only 16% yield. Due to this low yield, formylation of **6** under Vilsmeier–Haack conditions was attempted, resulting in the formation of 2,5-dimethylphenyl formate (**12**) in moderate yield.[6,7] We overcame the problem of low yield with the synthesis of **7** by changing the reagent combination and reducing the quantity, as reported by Gross et al.[8] We observed the formation of **7** (70%), 2-hydroxy-3,6-dimethylbenzaldehyde (**7a**, 22%), and 4-hydroxy-2,5-dimethylisophthaldehyde (**7b**, 3%) from **6** using our modified conditions.[7,9] From **7**, we prepared 4-hydroxy-3-iodo-2,5-dimethylbenzaldehyde (**8**) using iodinating reagent $I_2$/NaOAc (1:1 equiv) in aq MeOH.[7,10] From 2-bromophenol (**13**), we prepared 2-hydroxybenzeneboronic acid (**3**) in high yields by modifying the Gilman et al. procedure.[7,11,12]

In the synthesis of **1** via Suzuki–Miyaura coupling, it is necessary to prepare the unsymmetrical biphenyl compound **9** (Scheme 1). Suzuki–Miyaura coupling is one of the most general and powerful methods for the synthesis of unsymmetrical biphenyl derivatives by the coupling of aryl halide derivatives with arylboronic acid.[13] Morris and Nguyen[14] reported the expected coupling of arylboronic acid with halosalicylaldehyde derivatives in the presence of $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$, both of which are expensive compounds. However, Lee et al.[15] unsuccessfully attempted a similar type of coupling using the conditions reported by Morris and Nguyen.[14] In addition, the nature of both the solvent and the catalytic system greatly impact the arylboronic acid coupling reactions;[16] for example, the addition of chloroform turns a conventional palladium compound into a catalyst for the 1,2 addition of arylboronic acids to aldehydes in the presence of a base[16a] and further phosphine-free Suzuki–Miyaura coupling conditions are favorable.[13d,e] Therefore, we re-examined the reaction conditions for the selective preparation of **9** by the reaction of **3** with **8** in polar and non-polar solvents using various Pd-catalysts under phosphine-free conditions (Table 1; entries 1–15).[7] The Suzuki–Miyaura coupling of compounds **3** with **8** was not successful even after 24 h in a DME/$H_2O$ system containing 3 mol % of $Pd(PPh_3)_4$ or $PdCl_2$ (entries 1 and 2). In a toluene/$H_2O$ system, the deiodination of **8** was observed, which led to the formation of **7** from **8** in the presence of 3 mol % of palladium catalysts (entries 3–5). On the other hand, the reaction in the MeOH/$H_2O$ system resulted in the formation of the expected product **9** in low yield along with **7** and unidentified byproducts (entries 6 and 7), but no reaction using Pd/C (entry 8). The yield of **9** improved when DMSO was employed, but the formation of some byproducts was observed (entries 9 and 10). In addition, we improved the reaction conditions for the preparation of **9** by reducing both the amount of Pd-catalyst (2 mol %) and the duration of exposure to 5 mol % of $Cu(OAc)_2{\cdot}H_2O$ (entries 11 and 12). Reportedly, a formyl group will not react with arylboronic acid **3** under our developed conditions.[15,16] The use of DMF/$H_2O$ with 3 mol % of palladium catalysts resulted in the formation of unidentified products (entries 13–15).

The non-reactivity of compound **3** with **8**, as shown in Table 1 (entries 1, 2, and 8), was due, in many cases, only to the poor reactivity of *ortho*-substituted arylboronic acid **3**, presumably because of steric sensitivity.[13b,c] We overcame this problem when using a Pd-catalyst by using MeOH/$H_2O$ and DMSO/$H_2O$ as a solvent (entries 6, 7, and 9–12). This reveals that the aryl–aryl exchange between the palladium(II) complex may be enhanced in high polar solvents. In general, the synthesis of a biphenyl substance with electron-donating groups results in contamination of the coupling product (entries 3–5, 13–15), which may be due to competitive hydrolytic deiodination in aqueous conditions.[17] This problem was overcome by our newly developed conditions (entries 9–12). The use of a base as a suspension in DMF or dioxane produced no significant results.

Copper and its salts have been used in Suzuki–Miyaura coupling by some groups.[13e,18] Li et al. reported the use of $Cu(OAc)_2{\cdot}H_2O$/1,4-diaza-bicyclo[2.2.2]octane for the Suzuki–Miyaura coupling of benzeneboronic acid with 1-iodo-4-methoxybenzene using $Cs_2CO_3$ as a base and DMF as a solvent.[18d] Mao et al., obtained the Suzuki–Miyaura coupling product 4-methyl-benzeneboronic acid with iodobenzene in low yields in the presence of $Cu(OAc)_2{\cdot}H_2O$ as a catalyst, $K_2CO_3$ as a base, and DMF as a solvent.[18f] Gros et al. reported Cu salts as an additive along with Pd-catalyst to minimize the formation of byproducts in a Suzuki reaction.[18c] Thus, we selected $Cu(OAc)_2{\cdot}H_2O$ as an additive to reduce the formation of byproducts in our Suzuki–Miyaura coupling of **3** with **8** for the preparation of **9**, and we succeeded (entries 11 and 12).

The obtained biphenyl derivative **9** was converted into the corresponding ditriflate **4**,[7] which was then subjected to double N-arylation[19] with *O-tert*-butyl carbamate[19c] to get *tert*-butyl-3-formyl-1,4-dimethyl-9*H*-9-carbazolecarboxylate (**10**). Under our reaction conditions, 1,4-dimethyl-9*H*-carbazole-3-carbaldehyde (**5**) was formed instead of the expected **10**.[7] It is possible that **5** is formed from **10** by in situ thermolysis.[20] Furthermore, the elec-

**Table 1**
Examination of the Suzuki–Miyaura coupling of **3** with **8** to afford **9**

| Entry | Pd-catalyst (3 mol %) | Additive (5 mol %) | Solvent | Temp (°C) | Time (h) | **9**[b] (%) |
|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | —[a] | $DME/H_2O$ | 80 | 24 | —[b] |
| 2 | $PdCl_2$ | —[a] | $DME/H_2O$ | 80 | 24 | —[b] |
| 3 | $Pd(PPh_3)_4$ | —[a] | $Toluene/H_2O$ | 100 | 12 | —[c] |
| 4 | $PdCl_2$ | —[a] | $Toluene/H_2O$ | 100 | 12 | —[c] |
| 5 | $Pd(OAc)_2$ | —[a] | $Toluene/H_2O$ | 100 | 12 | —[c] |
| 6 | $Pd(PPh_3)_4$ | —[a] | $MeOH/H_2O$ | 100 | 12 | 12 |
| 7 | $PdCl_2$ | —[a] | $MeOH/H_2O$ | 100 | 12 | 14 |
| 8 | Pd/C | —[a] | $MeOH/H_2O$ | 50 | 12 | —[b] |
| 9 | $Pd(OAc)_2$ | —[a] | $DMSO/H_2O$ | 130 | 12 | 57 |
| 10 | $PdCl_2$ | —[a] | $DMSO/H_2O$ | 130 | 12 | 50 |
| **11**[e] | **$Pd(OAc)_2$**[f] | **$Cu(OAc)_2 \cdot H_2O$** | **$DMSO/H_2O$** | **130** | **3** | **69** |
| 12 | $PdCl_2$[e] | $Cu(OAc)_2 \cdot H_2O$ | $DMSO/H_2O$ | 130 | 3 | 63 |
| 13 | $Pd(PPh_3)_4$ | —[a] | $DMF/H_2O$ | 100 | 12 | —[d] |
| 14 | $PdCl_2$ | —[a] | $DMF/H_2O$ | 100 | 12 | —[d] |
| 15 | $Pd(OAc)_2$ | —[a] | $DMF/H_2O$ | 100 | 12 | —[d] |

[a] With no additive.
[b] No reaction; starting materials were recovered quantitatively.
[c] Formation of **7** by deiodination of **8** was observed.
[d] Unidentified byproducts were observed.
[e] Conditions to get the highest yield of **9**.
[f] 2 mol % of Pd catalyst used.

tron-withdrawing group (–CHO) on the heteroarenes activates deprotonation of the *tert*-butyl group in mildly basic conditions.[21]

Finally, the synthesis of ellipticine (**1**) was accomplished simply from compound **5**, in contrast to previous reports.[22] Compound **5** was condensed with aminoacetaldehyde diethyl acetal to provide the imine quantitatively.[22] Next, we reduced the imine to its amine with $NaBH_4$ in MeOH; then we converted the formed amine into the corresponding *N*-nocyl (Ns) derivative with 2-nitrobenzenesulfonyl chloride in the presence of pyridine in rt of 6 h. These three steps can be performed on a large scale without purification to provide **11** in 67% overall yield.[7] The compound **11** was then refluxed for 3 h in 6 M HCl–dioxane and was purified by column chromatography to give ellipticine (**1**) as the sole product in 79% yield. The mechanism of the reaction probably involves ring closure and then solvolysis of sulfonamide. The electronic effects of the substituent at the *ortho* position of the sulfonamides probably dramatically influence their stability against solvolysis. In a previous report,[22] hydrogenation of the imine at a pressure of 5 atm provided an amine that was then tosylated (three days reaction at 20 °C) with toluene-*p*-sulfonyl chloride in pyridine; this was then subjected to cyclization with aq HCl–dioxane to obtain ellipticine (**1**) along with *N*-tosyl-3,4-dihydroellipticine, which also afforded ellipticine (**1**) following further alkaline hydrolysis. Our new protocol was an improvement over that found in previous reports because of its simplicity[4c–g] and ease of handling.[4f,j]

In conclusion, we developed a simple protocol for the total synthesis of ellipticine starting from substituted phenol. The merit of this procedure is that it provides for the introduction of active functionality into the ellipticine skeleton by starting with substituted halophenols or boronic acids. Further, under the conditions of our protocol, the steric sensitivity of 2-hydroxybenzeneboronic acid is not a significant factor in Suzuki–Miyaura coupling. Currently, we are working to develop new bioactive molecules.

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## Supplementary data

Supplementary data (experimental procedures and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.125.

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6. 2,5-Dimethylphenol formate (**12**).


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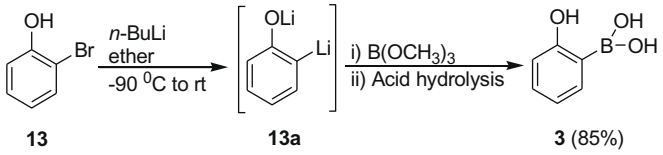
12. We noticed that rapid addition of trimethyl borate to the pre-cooled ether solution of lithium *o*-lithiophenoxide (**13a**) is an exothermic and gives the better results than, slow addition of **13a** to the pre-cooled ether solution of trimethyl borate as reported.[11] Further our simple workup improves the yield (85%; lit.[11] 47%) and purity of **3**.[7]

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