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An Expedient Protecting-Group-Free Total Synthesis of (±)-Dievodiamine

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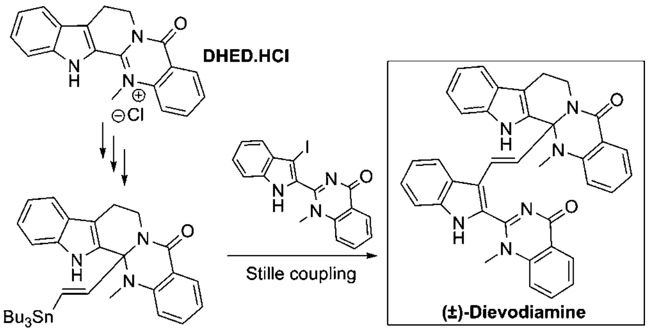
ABSTRACT



The first total synthesis of the *Evodia rutaecarpa* derived natural product dievodiamine is described. The convergent synthesis was performed without protecting groups, delivering a route that is short and high yielding and uses limited chromatography. Key steps include organometallic addition into a DHED adduct and the Stille coupling of two advanced intermediates to complete the synthesis.

In recent years, protecting-group-free methods have received widespread attention as ways to improve the efficiency of synthesis. Furthermore, such an approach provides an ‘opportunity for invention’, as the development of novel synthetic methodology becomes necessary.[1] Herein we report the successful application of these principles in the first total synthesis of (±)-dievodiamine **1**.

Dievodiamine was recently isolated from *Evodia rutaecarpa*.[2] None of its biological properties have been reported, although the *Evodia* fruits are used in numerous traditional Chinese remedies to treat a wide range of conditions including headaches, abdominal pain, migraine, chill limbs, postpartum hemorrhage, nausea, inflammation, and cancer.[2] Its structure is closely related to evodiamine **2**, another *Evodia rutaecarpa* derived natural product, which was recently synthesized by our group using direct imine acylation methodology.[3] Evodiamine is a known thermogenic and stimulant and is included in a number of dietary supplements, principally used to promote weight loss. In addition, more recent studies have shown that it binds to a diverse range of proteins; its therapeutic potential against a number of diseases, including cancer, Alzheimer’s disease, and cardiovascular disease, and its ability to inhibit human DNA topoisomerase I have been reported and reviewed.[4] Furthermore, a recent SAR study has shown evodiamine analogues to be highly promising antitumor candidates.[5] Dievodiamine **1** is not a simple dimer of evodiamine, as its name may suggest, but it does contain the basic framework of two evodiamine subunits (following oxidation and ring opening) suggesting that evodiamine **2** is a likely biosynthetic precursor.[6] Bisindole alkaloids constitute a major class of natural products, and their interesting biology has been well documented.[7] The isolation, synthesis, and biological evaluation of bisindole alkaloids remains a highly

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(6) For the biosynthesis of related *Evodia* alkaloids, see: (a) Yamazaki, M.; Ikuta, A. *Tetrahedron Lett.* **1966**, *7*, 3221. (b) Yamazaki, M.; Ikuta, A.; Mori, T.; Kawana, T. *Tetrahedron Lett.* **1967**, *8*, 3317.

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active area of research[8] with their potential antimalarial properties in particular receiving prominent attention recently.[8c−e] An unusual, although not unique,[8b] structural feature of dievodiamine is the ethylene bridge linking the two indole-containing portions. This is convenient from a synthetic viewpoint, as it provides a handle for a convergent synthesis, via the cross-coupling of two evodiamine-like fragments (Figure 1). With this in mind, and in view of the diverse biological profile of evodiamine and related compounds, we decided to embark on the total synthesis of (±)-dievodiamine, to confirm the reported structure and to enable its therapeutic potential to be better examined.

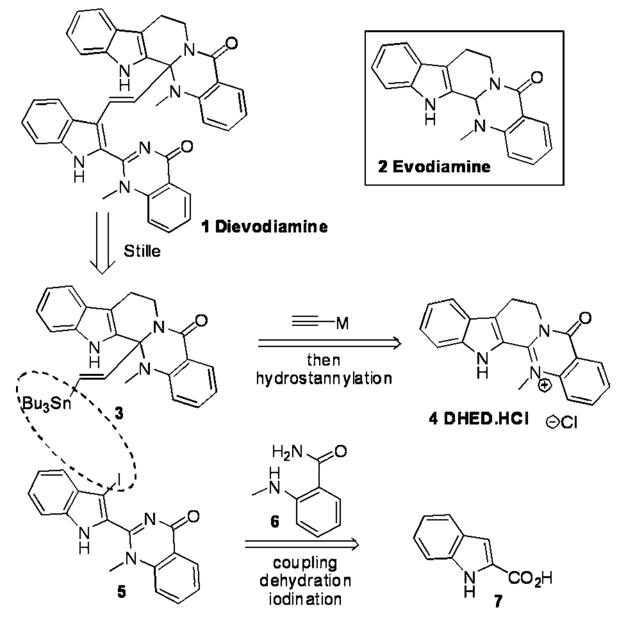

Figure 1. Retrosynthetic strategy.

Our convergent retrosynthetic strategy hinged upon the Stille reaction of two indole-containing fragments **3** and **5**. It was thought that the requisite stannane **3** could be obtained via the novel addition of a metalated alkyne into dehydroevodiamine hydrochloride (DHED·HCl, **4**), itself an alkaloid derived from *Evodia rutaecarpa*, followed by hydrostannylation. It was hoped that the 3-iodo-indole fragment **5** could be synthesized from 2-(methylamino)-benzamide **6** and commercially available indole-2-carboxylic acid **7** (Figure 1).

The synthesis began with the conversion of indole **8** into known lactam **9**[9] via a Curtius rearrangement and subsequent electrophilic aromatic substitution (Scheme 1). This was then converted to DHED·HCl **4** by heating with dimethyl anthranilate **10** and $POCl_3$, using a procedure modified from that of Decker.[10] In our hands, a particularly convenient purification was developed; the crude reaction mixture was poured into water, and the resulting precipitate was removed by filtration, rinsed with water, and dried, affording the desired quinazolinium salt **4** as a yellow solid in high yield. It was then planned to trap this adduct with an organometallic species. However, surprisingly little is known about the reactivity of DHED systems[11] and, to the best of our knowledge, there are no reports of C−C bond formation at the electrophilic carbon of any DHED. To test this idea, a small excess of ((trimethylsilyl)ethynyl)lithium was added to a suspension of DHED·HCl **4** in THF at −78 °C and allowed to warm to RT before quenching with water. As expected, only a trace amount of alkyne **11** was isolated, with the bulk of the starting material **4** recovered by filtration of the crude reaction mixture. In contrast, when 3 equiv of ((trimethylsilyl)ethynyl)lithium were used all of the starting material **4** was consumed and **11** was isolated cleanly, suggesting that 1 equiv of the organolithium species must deprotonate the indole, before the requisite nucleophilic addition takes place. Conveniently, the progress of the reaction could be monitored visually, as the mixture became homogeneous upon completion of the reaction. Following aqueous workup and treatment of the intermediate alkyne **11** with TBAF, alkynyl dihydroquinazolinone **12** was isolated in 90% yield over the two-step sequence. Of course, the TMS group present during this sequence necessitates a separate cleavage step and therefore does not satisfy the ideals of a protecting group-free synthesis. Thus, the same transformation was attempted using an excess of a lithium acetylide ethylenediamine complex. This was unsucessful, but the use of an excess of commercially available ethynylmagnesium chloride did give product **12**. Initial results were disappointing, however, as under the conditions described above the desired alkyne **12** was only isolated in trace amounts, with the bulk of the material remaining insoluble as the reaction progressed and was lost during aqueous workup. The poor solubility of DHED·HCl **4** was thought to be a limiting factor in this reaction, and pleasingly, when the solvent was switched to toluene, and lithium chloride[12] was included as an additive, alkyne **12** was isolated in a much improved yield following a single, truly protecting-group-free transformation. Finally, hydrostannylation with tributyltin hydride and AIBN in refluxing benzene completed the synthesis of stannane coupling partner **3**, which was isolated as a single regio- and stereoisomer in reasonable yield. It should be noted that column chromatography was only used in the final step of either of these three- or four-step sequences from lactam **9**.

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(11) Limited examples of reduction or hydrolysis reactions of DHED adducts can be found in refs 5 and 10.

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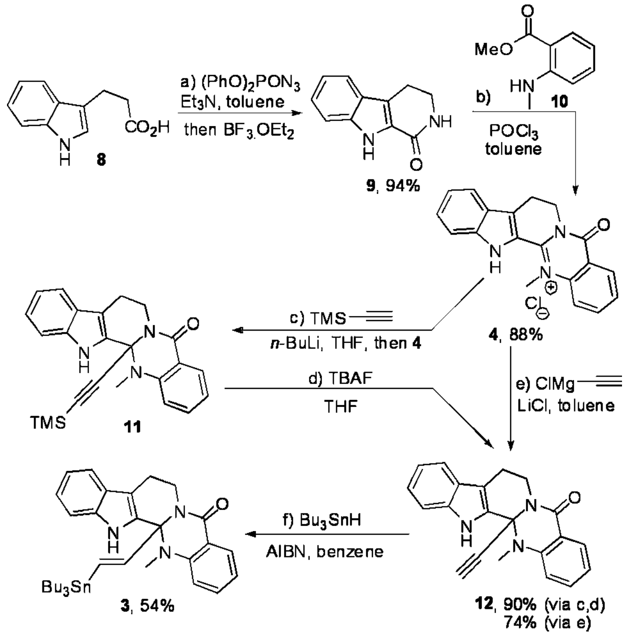
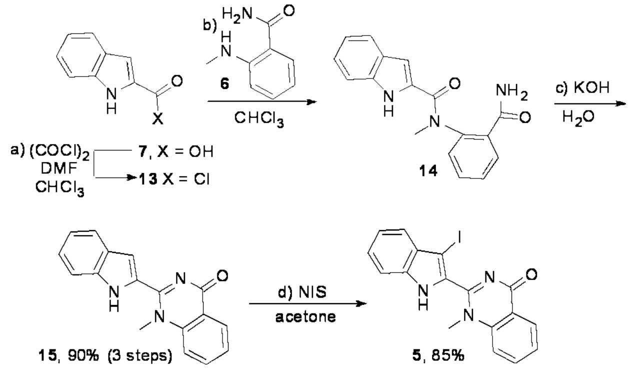
Scheme 1. Synthesis of Stannane **3**



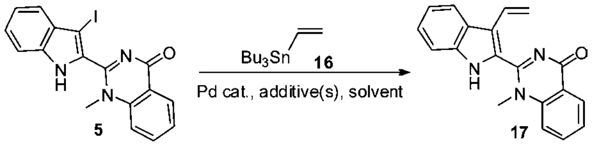
Scheme 2. Synthesis of Indole **5**



The synthesis of iodide coupling partner **5** was achieved extremely efficiently from commercially available indole-2-carboxylic acid **7**. Acid chloride formation was followed by reaction with aniline **6**[13] to form amide **14**, which was then heated at reflux in aqueous KOH.[14] The insoluble material was then collected by filtration, affording quinazolinone **15** in excellent yield over the three-step sequence. The synthesis of indole **5** was completed by reaction with *N*-iodosuccinimide in acetone, affording the desired product **5** in 77% overall yield from **7** (Scheme 2) following column chromatography. Note that this was the only chromatography required throughout the four-step synthesis, which could be performed on a multigram scale. The limited use of chromatography is an important feature in the syntheses of both coupling partners **3** and **5**, especially during scale-up. Unprotected indoles are often difficult to handle due to their relatively low solubility in many organic solvents, but pleasingly, we were instead able to exploit this property to our advantage by developing efficient workup conditions that may not have been possible had protecting groups been employed on the indole nitrogen atoms.

Conditions for the final Stille coupling were established using vinyl tributylstannane **16** with iodide **5** (Table 1). First, no reaction was observed following their treatment with $Pd(PPh_3)_4$ in refluxing THF (entry i). Baldwin's conditions,[15] which exploit the synergistic effect of CuI and CsF along with $Pd(PPh_3)_4$ in DMF, were also ineffective on this system, affording no product at 45 °C (entry ii) and led only to the partial reduction of iodide **5** (entry iii) and its eventual decomposition (entry iv) at elevated temperatures. The additive Et_4NCl, which is more commonly used as an additive in Heck reactions,[16] has found limited use in related Stille reactions,[17] but under the conditions trialled (Et_4NCl, $PdCl_2(PPh_3)_2$ at 80 °C in DMF, entry v) no reaction was observed. It was considered that the reason for the poor reactivity of **5** may be due to its steric bulk inhibiting the transmetalation step. Copper salts are known to accelerate sluggish Stille couplings by promoting an initial transmetalation of the organostannane to generate a more reactive organocopper intermediate.[18] Pleasingly when the additives CuI and Et_4NCl were

Table 1. Optimization of Stille Conditions[a]



entry	cat.	additives (equiv)	temp (°C)/ time (h)	outcome (yield)[c]
i[b]	A	none	70/20	no reaction
ii	A	CsF (2), CuI (0.1)	45/1	no reaction
iii	A	CsF (2), CuI (0.1)	80/1	3:2 **15:5**
iv	A	CsF (2), CuI (0.1)	100/1	decomp.
v	B	Et_4NCl (1.0)	80/20	no reaction
vi	B	Et_4NCl (1.0), CuI (0.1)	80/20	**17** (10%)
vii	B	Et_4NCl (1.0), CuI (1.5)	80/2	**17** (81%)

[a] Reactions were performed on a 0.2–0.5 mmol scale using iodide **5** (1.0 equiv), stannane **16** (1.5 equiv), and a Pd catalyst [A = $Pd(PPh_3)_4$ or B = $PdCl_2(PPh_3)_2$, 0.05 equiv], with the additives and conditions shown, in DMF unless stated. [b] Reaction performed in THF. [c] Isolated yield following column chromatography.

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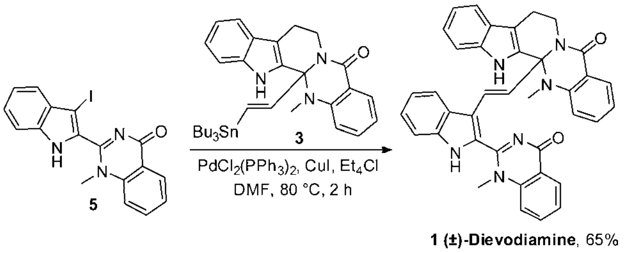
combined with $PdCl_2(PPh_3)_2$ and heated at 80 °C in DMF (entry vi), this led to the isolation of a small quantity of coupled product **17**. Furthermore, the yield was increased dramatically by using an excess of CuI (81%, entry vii).

Focus then switched to completing the synthesis of (±)-dievodiamine **1** (Scheme 3). The coupling of iodide **5** with stannane **3** was slower than with test substrate **17**, but nonetheless, the desired coupled product **1** was obtained in 35% yield using the conditions developed above with a 20 h reaction time. Furthermore, increasing the amounts of $PdCl_2(PPh_3)_2$ and Et_4NCl (0.2 and 2.0 equiv respectively) led to a reduced reaction time (2 h) and a cleaner reaction mixture, allowing the target compound to be isolated in a much improved 65% yield following column chromatography and recrystallization.[19] The spectral properties of the synthetic material (^1H and ^{13}C NMR data, IR, mass spectrum)[20] closely matched those reported for the natural product, with the ^{13}C NMR data being particularly conclusive (see Supporting Information), thus confirming its assigned structure.[2]

The first total synthesis of (±)-dievodiamine **1** has therefore been completed. The two key coupling partners **3** and **5** were each synthesized in just four steps, in 33% and 77% yield respectively, and the final Stille coupling completed the synthesis of this potentially valuable natural product in 65% yield. The brevity and efficiency of the synthesis was undoubtedly aided by the absence of protecting groups.

Scheme 3. Total Synthesis of (±)-Dievodiamine



Not only did this help to reduce the total number of steps, but also imparted suitable solubility properties that enabled us to minimize chromatography, thus facilitating scale-up. Key steps include the first example of an organometallic addition into a DHED adduct and a Stille reaction in which two sterically hindered components coupled using $PdCl_2(PPh_3)_2$ and the unusual combination of Et_4NCl and CuI as additives. Future work will focus on testing the biological properties of dievodiamine and, if these results show promise, performing SAR studies on related analogues.

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Supporting Information Available. Synthetic procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(19) A lower yield (22%) was obtained when Et_4NCl was omitted under otherwise identical conditions, and no product was isolated in the absence of CuI, thus confirming the importance of both additives.

(20) We also obtained a melting point for **1**, but no literature melting point has been reported for comparison.