Synthesis of Novel Annulated Hymenialdisine Analogues via Palladium-Catalyzed Cross-Coupling Reactions with Aryl Boronic Acids

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Abstract: Palladium-catalyzed Suzuki cross-coupling reactions of an indole vinyl triflate provides an efficient pathway for the synthesis of a diverse class of novel hymenialdisine analogues.

Key words: hymenialdisine analogues, cross-coupling, silica gel, palladium, heterocycles

Protein kinases have emerged as one of the major drug target classes that are amenable to the development of small-molecule inhibitors.[1] Because protein kinases play critical roles in cellular signaling networks, the development and application of small-molecule kinase inhibitors as potential therapeutic agents and experimental tools to help understand the physiological role of these enzymes, has generated much interest.[2,3] Towards this end, intense efforts have been devoted to the identification and development of such small-molecule inhibitors to fight diseases; such drug discovery projects currently account for 20–30% of research and development work at many pharmaceutical companies.[3] Currently, several small-molecule kinase inhibitors are either approved or being developed for use in the treatment of various human diseases including cancer, cardiovascular disorders, and inflammation.[3–5] Among them, the natural product hymenialdisine (HMD; **1**), and its annulated analogues (**2**), exhibited promising results in inhibiting various kinases selectively (Figure 1).[6] For example, Meijer et al. reported the crystal structure of hymenialdisine (**1**) as a complex in the ATP (adenosine triphosphate) binding pocket of the protein kinase CDK2. Hymenialdisine (**1**) binds to the CDK2 pocket in a competitive manner. The crucial structural elements of the molecule were identified as the NH–CO–C–NH sequence on the lower part of the molecule, and the heterocycle connected at the α-position of the upper part of the molecule (for its effective hydrogen bonding).[7] In agreement with this analysis, it was also reported that the kinase-inhibiting activity of HMDs varies significantly depending on the heterocycle that is attached to its core structure.[6] It should be also noted that stevensine (or odiline; **3**), a marine alkaloid with a similar structural scaffold, showed antitumor and weak antimicrobial activity.[7,8] Hence, the synthesis of HMD analogues is of significant interest for researchers in a number of areas of medicinal chemistry.

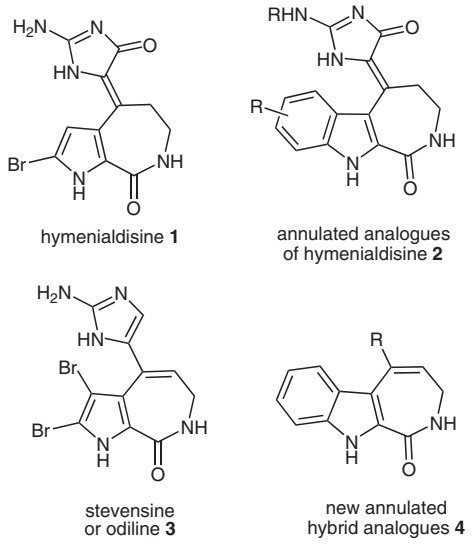

Figure 1

As part of our program devoted to the application of catalytic methods to the synthesis of potential bio-active compounds,[9] and because of our background in catalytic oxidation methodologies,[10] we became interested in preparing a novel compound library of small-molecule kinase inhibitors using the hymenialdisine (**1**) scaffold as backbone. Our initial efforts in this field recently culminated in the synthesis of novel annulated HMD-type bisindoles employing ring-opening reactions of aziridines and epoxides.[11] In order to investigate structure–activity relationships of these novel analogues,[11d] we set out to prepare a set of novel hybrid annulated analogues (**4**) of hymenialdisine (**1**) and stevensine (**3**) by introducing arenes and heteroarenes instead of the imidazole ring on its core scaffold (Figure 1). Here, we report a convenient, diversified synthetic strategy using palladium-catalyzed Suzuki coupling reactions of indole triflate derivatives.[12]

Initially, we prepared ketone **6** from commercially available indole-2-carboxylic acid (**5**) following a protocol reported previously by us (Scheme 1).[11] In order to increase the solubility and purity, the crude ketone **6** was treated with excess $(Boc)_2O$, DMAP, and triethylamine in dichloromethane at room temperature to obtain the pure, stable di-Boc-protected ketone **7** in 25–28% yield from **5**.

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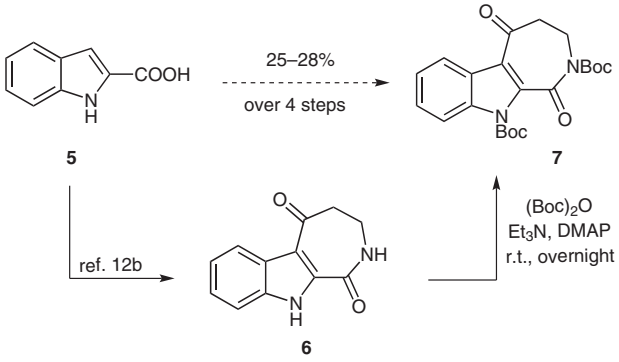
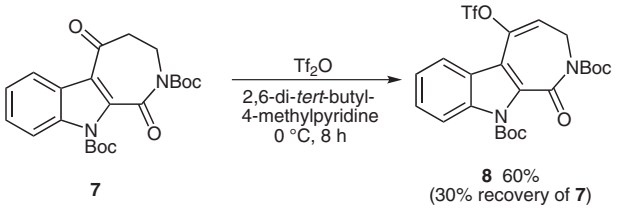


Scheme 1 Synthesis of di-Boc-protected ketone 7

Initial attempts to transform compound **7** into triflate **8** using methods such as LDA/triflimide at –78 °C or Hünig's base/triflimide, were unsuccessful.[13] However, to our delight, the reaction proceeded smoothly in good yield (60% with 30% recovery of **7**) to give triflate **8** using trifluoromethanesulfonic anhydride in dichloromethane in the presence of 2,6-di-*tert*-butyl-4-methylpyridine at 0 °C for eight hours (Scheme 2).[14] Our repeated attempts to encourage the reaction to proceed further towards completion by varying the reaction conditions, such as increasing the amount of base/triflic anhydride and prolonged reaction time, were not successful but showed a tendency to decrease the yield (14 h, 35%; 20 h, 27%). This is explained by slow decomposition of **8** in the reaction mixture.[15]

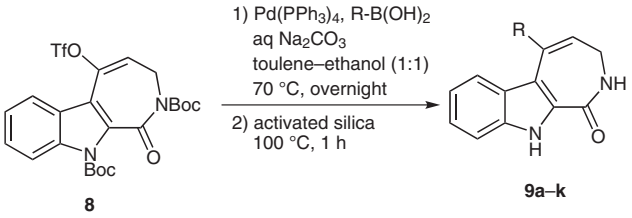


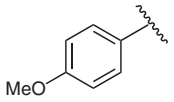
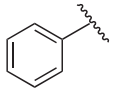
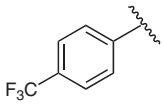
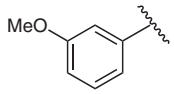
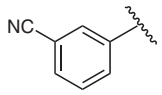
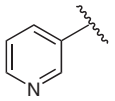
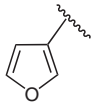
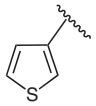
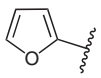
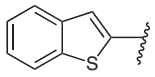
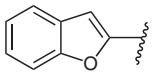
Scheme 2 Synthesis of indole triflate **8**

Nevertheless, with the key building block **8** in hand, we envisioned the synthesis of novel hymenialdisine analogues following standard Suzuki coupling protocols.[16] Treatment of **8** with 4-methoxyphenyl boronic acid (1.1 equiv) in the presence of $Pd(PPh_3)_4$ (1 mol%) and aqueous sodium carbonate (2 M) as base in a mixture of toluene and ethanol (1:1) at 70 °C for 12–16 h, gave the desired product along with minor amounts of the deprotected compound **9a** (R = 4-methoxyphenyl). Because the next step involves removal of the protecting groups, to simplify the synthetic procedure we used the crude mixture directly. Thus, the reaction mixture was adsorbed onto activated silica gel using dichloromethane and the mixture was heated at 100 °C for one hour following our previous deprotection protocol,[12] which yielded **9a** in 75% yield over two steps (Table 1, entry 1).

Consequently, we applied this protocol to the preparation of a number of novel hybrid analogues of hymenialdisine

Table 1 Suzuki Coupling Reactions of Indole Triflate **8**[a]



Entry	R	Product	Yield (%)[b]
1		**9a**	75
2		**9b**	74
3		**9c**	52
4		**9d**	63
5		**9e**	40
6		**9f**	60
7		**9g**	50
8		**9h**	78
9		**9i**	0[c]
10		**9j**	59
11		**9k**	52

[a] Reaction conditions: (1) triflate **8** (600 mg, 1.10 mmol), boronic acid (1.2 mmol), 2 M Na_2CO_3 (0.55 mL), $Pd(PPh_3)_4$ (0.011 mmol), toluene–EtOH (1:1, 6 mL), Argon, 70 °C, overnight; (2) activated silica (0.040–0.063 mm, 2.46 g), argon, 100 °C, 1 h.
[b] Isolated yield.
[c] Compound **6** was formed as the major product (75%).

starting from triflate **8** (Table 1). Most of the boronic acids reacted smoothly to give **9a–k** in moderate to good yields (40–78%).[17] Functional groups on the boronic acids such as electron-rich (methoxy) and electron-withdrawing (trifluoromethyl and cyano) were tolerated (Table 1, en-

tries 3–5). The structure of **9d** was confirmed by X-ray crystal structure analysis (Figure 2).[18] Notably, heteroaromatic boronic acids were also effective under these conditions, giving the expected products in good yields (Table 1, entries 7–11).

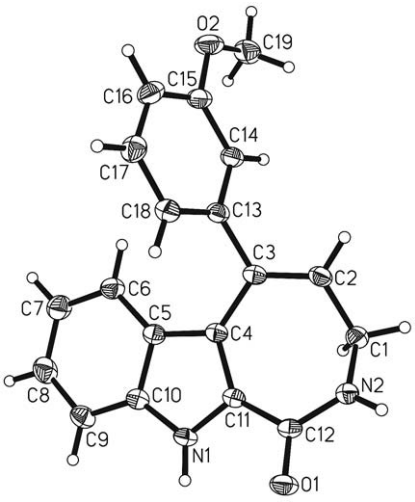


Figure 2 Molecular structure of **9d**; thermal ellipsoids correspond to 30% probability[18,19]

The one exception was 2-furylboronic acid (Table 1, entry 9), which gave **6** in 75% yield. Efforts to elucidate the biological activity of these novel analogues are currently underway.

In conclusion, we have developed a convenient method for the synthesis of novel hybrid annulated analogues of hymenialdsine (**1**) and stevansine (**3**) using a Suzuki-coupling protocol.[17]

The strategy described is of particular significance for providing a synthetic pathway for a diverse class of new HMD kinase inhibitors and can be applied to other biologically interesting compounds.

Acknowledgment

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(15) Decomposition of compound **8** was observed on storage (~5 d).
(16) (a) Chacun-Lefèvre, L.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2000**, *56*, 4491. (b) Perron, J.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2003**, *59*, 6659. (c) Chacun-Lefèvre, L.; Joseph, B.; Mérour, J.-Y. *Synlett* **2001**, 848; Note: Although this reference reports a similar kind of approach, it suffers with the unprotected NH–CO–C–NH backbone, which is critical for kinase inhibition.
(17) **General procedure for the Suzuki coupling of 8 with aryl boronic acids 9a–k**: To a stirring mixture of **8** (600 mg, 1.1 mmol) in toluene (3 mL) and absolute EtOH (3 mL) under an argon atmosphere, $Pd(PPh_3)_4$ (12.6 mg, 0.011 mmol), boronic acid (1.2 mmol) and 2 M aq Na_2CO_3 solution (0.55

mL) were added. The mixture was heated at 70 °C overnight (~12–16 h), then the solvent was removed under reduced pressure and the mixture was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was used for the deprotection step without further purification. The above crude product was dissolved in anhydrous CH_2Cl_2 (50 mL) and activated silica (2.46 g, 0.040–0.063 mm) was added. The solvent was removed under reduced pressure and the solid mixture was heated under argon at 100 °C for 1 h. Purification by column chromatography (silica gel 70–230 mesh, hexane–EtOAc, 6:4) yielded pure compounds **9a**–**k**.

(18) **X-ray crystal data for 9d**: Empirical formula: $C_{19}H_{16}N_2O_2$; M_r = 304.34; monoclinic; space group: $P2_1/c$; cell dimensions: a = 9.3756 (3), b = 6.5948 (2), c = 25.3990 (8) Å, β = 100.003 (2)°; V = 1546.55 (8) Å^3; Z = 4; ρ_{calcd} = 1.307 g·cm^{-3}; 22763 reflections measured, 3292 independent reflections, of which 2312 were observed [$I > 2\sigma(I)$], final R indices [$I > 2\sigma(I)$]: R_1 = 0.0306, wR_2 = 0.0686, R indices (all data): R_1 = 0.0486, wR_2 = 0.0715, 217 refined parameters. Data were collected on a STOE IPDS II diffractometer using graphite-monochromated MoKα radiation. The structure was solved by direct methods (SHELXS-97)[19] and refined by full-matrix least-squares techniques on F^2 (SHELXL-97).[19] XP (Bruker AXS) was used for graphical representation. CCDC 748111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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