Formal Syntheses of Dictyodendrins B, C, and E by a Multi-substituted Indole Synthesis

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Supporting Information Placeholder

ABSTRACT: The dictyodendrins are a family of marine alkaloids, which possess a highly substituted pyrrolo[2,3-c]carbazole core. This core structure can be regarded as a multi-substituted indole and aniline moiety. To achieve a concise synthesis of dictyodendrins, we planned to capitalize on our previously developed multi-substituted indole synthesis. By using this method along with two C–H functionalizations, formal syntheses of dictyodendrin B, C, and E were achieved.

Dictyodendrins A–J are alkaloids from marine sponges (Figure 1A). Of these compounds, dictyodendrins A–E were isolated from the Japanese sponge Dictyodendrilla verongiformis, and structurally assigned by Fusetani and Matsunaga in 2003.1 These are the first natural marine products to show telomerase inhibitory activity, and therefore could potentially be lead compounds for anticancer drugs.2 Dictyodendrins F–J were isolated from an Australian sponge of the genus Ianthella by Capon and coworkers in 2012.3 These natural products have β-secretase (β-site APP-cleaving enzyme: BACE) inhibitory activity, which is expected to be applied to the research of Alzheimer’s disease.4 As a structural feature, all analogues except dictyodendrin J possess a highly substituted pyrrolo[2,3-c]carbazole core.

Dictyodendrins have attracted attention as synthetic targets due to their important biological activities and unique structures, and to date, nine research groups have reported total syntheses including our group.5 Pyrrolo[2,3-c]carbazole, the main skeleton of dictyodendrins, is a ring-fused structure of pyrrole and carbazole, but it can also be regarded as a structure in which an aniline is attached to the C4 and C5 positions of an indole. There have been three reports on the synthesis of dictyodendrins using the construction of the main skeleton by connecting the indole with the aniline moiety (Figure 1B). Tokuyama and co-workers reported the synthesis of dictyodendrins by benzyne-mediated cyclization and cross-coupling/C–H amination of multi-substituted indoles with aryl azides.6,7 Jia and coworkers constructed the main skeleton by Buchwald–Hartwig amination of the multi-substituted indole obtained from the Larock indole synthesis with an aniline moiety, followed by intramolecular C–H arylation.8 Gaunt and coworkers reported an elegant synthesis using C–H functionalization leading to multi-substituted indoles, and then conducted a Suzuki–Miyaura coupling with aryl azides (aniline moiety), followed by intramolecular C–H amination to form the main skeleton.9 In all of these synthetic examples, the unique indole synthetic method was key. Hence, we proposed that an efficient synthesis of the dictyodendrin family could be achieved through the synthesis of a multi-substituted indole by a coupling/ring transformation strategy developed in our laboratory (Figure 1C).10 In this method, an anamide intermediate containing thiophene-5,5-dioxide was synthesized by a simple four-unit coupling reaction. Then, the anamide was reacted with the thiophene-5,5-dioxide via an inverse-electron-demand [4+2] cycloaddition and oxidation/deprotection to give pentaarylindole (PAI). Subsequent two-fold arylation of PAI led to heptaarylindole (HAI), in which all C–H/N–H bonds of the indole are substituted with aryl groups.11 A variety of multi-substituted indoles can be synthesized by simply changing the substituents at each site. Based on this multi-substituted indole synthesis, we set out to synthesize the dictyodendrin family (Figure 1D). As a forward synthetic plan, an anamide [4+2] cycloaddition would afford a multi-substituted indole, followed by oxidation/C–H amination to a pyrrolo[2,3-c]carbazole. After several functionalizations including a C–H functionalization to the pyrrolocarbazole, the compound would lead to a synthetic intermediate.
of dictyodendrins B, C, and E that was generated by Fürstner and coworkers.\(^{(4a)}\)

First, the synthesis of the key multi-substituted indole was conducted (Scheme 1A). The synthesis was commenced with a Suzuki–Miyaura coupling of 1-azido-2-bromobenzene (1) with 3-thiopheneboronic acid (2) in the presence of a palladium catalyst and base to afford 3-arylthiophene 3 in 94% yield. Alcohol 5 was synthesized by epoxide opening of 2-(4-methoxyphenyl)oxirane (4) with 3-ar@lythiophenes under Lewis acid conditions. Although we extensively investigated this epoxide-opening reaction using various Lewis acids and conditions, TMSOTf gave the best results to give alcohol 5 in a low 23% yield, along with 48% recovered starting material 3 (see the supporting information for details).\(^{(4b)}\) Alcohol 5 was subsequently converted to amide 6 by Mitsunobu reaction with NHBOC and removal of the Boc group, followed by bromination at the CS-position of the thiophene to afford Ns-amide 6 in 57% yield over 3 steps. In order to examine the \([4+2]\) cycloaddition with ynamides, the synthesis of two thiophene oxides 7 and 8 was carried out. Thiophene 7, S-dioxide 7 can be readily prepared by oxidation with \(m\)-CPBA. S-Oxide 8 was also prepared using \(m\)-CPBA in the presence of an excess

Figure 1. (A) Structures of dictyodendrin A–E. (B) Syntheses of dictyodendrins using the construction of the main skeleton by connecting an indole with an aniline moiety. (C) Our multi-substituted(arylated) indole synthesis. (D) Our synthetic strategy toward dictyodendrins B, C, and E.
amount of BF₃·OEt₂ to suppress over-oxidation. Then, ynamide formation from 7 and 8 with alkylnating agents, followed by [4+2] cycloaddition, was investigated (Scheme 1B). After screening of several alkylation conditions (see the supporting information for details), when hypervalent iodine alkylnating agent 9 and Cs₂CO₃ were used, we successfully obtained desired indoline 10 in 42% yield from S,S-dioxide 7 and in 29% yield from S-oxide 8. Since the yield of 10 from S,S-dioxide 7 was higher than that of S-oxide 8, we selected 7 as the more appropriate precursor. To make dictyoylendrins, we also reacted 7 with a bromo-bearing alkylnating agent 11 and succeeded in producing the desired indoline 12 in 42% yield.

Scheme 1. (A) Preparation of S-Oxide and S,S-Dioxide. (B) Ynamide Formation and [4+2] Cycloaddition

![Diagram]

**Conditions.** (a) 3-Thiopheneboronic acid (2: 1.5 equiv), Pd₃(dba)₃·CHCl₃ (0.70 mol%), P(Bu)₃·HBF₄ (1.4 mol%), NaOH aq. (3.0 equiv), THF, 65 °C, 4 h (94%); (b) TMSOTf (2.0 equiv), CH₂Cl₂, −78 °C, 1 h (97%); (c) NHBocNs (1.7 equiv), DIAD (1.7 equiv), THF, 0 °C, 12 h; (d) K₂CO₃ (5.0 equiv), imidazole (5.0 equiv), MeCN, 60 °C, 12 h; (e) NBS (1.0 equiv), THF RT, 9 h (57% in 3 steps); (f) for 7: mCPBA (2.5 equiv), 1,2-dichloroethane, 65 °C, 6 h (74%); for 8: BF₃·OEt₂ (10 equiv), mCPBA (1.0 equiv), CH₂Cl₂, −20 °C, 1 h (33%); (g) Cs₂CO₃ (1.5 equiv), 1,4-dioxane, 80 °C, 12 h (42% from 7, 29% from 8); (h) Cs₂CO₃ (2.8 equiv), 1,4-dioxane, 50 °C, 12 h (42%).

Next, we attempted to access Fürstner’s intermediate from the obtained indoline 12 (Scheme 2). From 12, pyrrolocarbazole 13 could be synthesized with intramolecular C–H amination, removal of the nosyl group, then oxidation of the indoline to the corresponding indole. First, the C–H amination of 12 was investigated by heating at 160 °C in 0-dichlorobenzene. The expected indoline was not obtained, but surprisingly, the desired pyrrolocarbazole 13 was directly obtained in 16% yield, indicating spontaneous denosylation and oxidation. Pyrrolocarbazole 13 was crystallized from toluene/hexane and its structure was confirmed by X-ray crystallographic analysis. Although the three reactions proceeded efficiently in a single step, several undesired byproducts were formed, resulting in low yields. We hypothesized that the cause of the complexity of the reaction was due to the acid generated during the removal of the nosyl group. Therefore, K₂CO₃ was added to neutralize the acid, and the yield of 13 significantly improved to 64%.

We then attempted a formal syntheses of dictyoylendrins B, C, and E by elaborating the resulting pyrrolocarbazoles to known synthetic intermediates. From 13, an isoproxy group needed to be introduced at the C7 position, an alkyl chain needed to be installed at the N3 position, and the C–Br bond needed to be methoxylated to reach the synthetic intermediate of Fürstner and coworkers. First, for the isoproxylation of the C7 position, we selected C–H borylation. When pyrrolocarbazole 13 was subjected to iridium-catalyzed C–H borylation conditions, only the compound with borylation at the C2 position, not the C7 position, was obtained in 62% yield when 1.4 equiv of Bpin₂ was used. When the amount of Bpin₂ was increased to 2.6 equiv, compound 14 with borylated C2 and C7 positions was obtained in 66% yield, as judged by ‘H NMR. It should be noted that 14 and other borylated products were unstable to purification by silica gel column chromatography, and these compounds could not be isolated. Although C7-selective borylation was not achieved, introducing a boryl group at the C7 position was successful. Then, we considered that if C7-selective isoproxylation or C2-selective protodeborylation of 14 were possible, we would be able to generate the desired product 15. To this end, a chemoisomopropoxylation at the C7 position was conducted by using Cu(OAc)₂ as an oxidant and DMAP/4Å MS as additives onto 14 in a mixture of CH₂Cl₂ and PrOH. As a result, not only the isoproxylation of the C7 position, but also the protodeborylation of the C2 position proceeded under these conditions, and desired 15 was successfully obtained in a single step (33% yield, 22% in two steps from 13), along with recovered 13 in 21% yield. We believe that the regioselective protodeborylation is possible because the electron-rich C2 position is easily protonated. Next, for the alkylation of 15 at the N1 position, treatment of 15 with Allyl tosylate and potassium hydride gave the desired N2-alkylated product 17, but the yield was only 5%. Contrary to our expectations, the N-Alkylation product was preferentially obtained. After extensive investigation, the desired product 17 was obtained with complete N1 selectivity and moderate yield when the leaving group was changed to bromide (16), the base was modified to NaOH, and 18-crown-6 was employed as an additive. Finally, methoxylolation of the two bromo atoms of 17 with copper iodide and sodium methoxide led to the synthetic intermediate of Fürstner and coworkers, thus completing the formal synthesis of dictyoylendrins B, C, and E.

In summary, we have accomplished the formal syntheses of dictyoylendrins by a multi-substituted indole synthesis. We constructed a highly substituted pyrrolocarbazole skeleton by alkylnylation and intramolecular C–H amination of thiophene-S,S-dioxide, which is different from the conventional method.
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