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A formal total synthesis of the telomerase inhibitor dictyodendrin B

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ABSTRACT

A formal synthesis of the telomerase inhibitory marine pyrrolocarbazole alkaloid dictyodendrin B is described. The key features are consecutive palladium-catalyzed cross-coupling reactions and intramolecular reductive coupling reaction to construct the pyrrolo[2,3-*c*]carbazole framework.

Dictyodendrins A–E (**1**–**5**) are tyramine-based pyrrolocarbazole alkaloids isolated from the marine sponge *Dictyodendrilla verongiformis* collected in southern Japan by Fusetani et al. in 2003 (Fig. 1).[1] These alkaloids completely inhibit telomerase at a concentration of 50 μg/ml and are reported to be the first telomerase-inhibitory marine natural products. They also demonstrated that the sulfate functions of the molecules are essential for the bioactivity as the desulfated compound was completely inactive. Recently, Fürstner et al. reported that dictyodendrins B (**2**), E (**5**) and its desulfated derivative have the ability to cleave double strand DNA under oxidative conditions.[2] The first total synthesis of dictyodendrin B (**2**) was achieved by Fürstner's group in 2005.[3] They utilized a low-valent titanium-mediated reductive cyclization and subsequent photochemical dehydrogenative cyclization for the formation of the core pyrrolo[2,3-*c*]carbazole ring. Thereafter, they extended this strategy to the total syntheses of dictyodendrins C (**3**) and E (**5**).[4] Two groups including us recently reported the synthesis of core structures of dictyodendrin. Álvarez and co-workers reported a synthesis of the pyrrolo[2,3-*c*]carbazole core of dictyodendrin based on a Suzuki–Miyaura cross-coupling reaction of a 3-arylpyrrole-4-boronate with a 3-bromoindole derivative and tandem photochemical 6π–electrocyclization/aromatization.[5] We also synthesized the putative precursor to dictyodendrins having the core pyrrolo[2,3-*c*]carbazole system by using Hinsberg-type pyrrole synthesis and consecutive palladium-catalyzed cross-coupling reactions.[6] Here, we describe a formal total synthesis of **2** based on the strategy with modification in the B-ring construction.

Our retrosynthetic analysis of **2** is depicted in Scheme 1. The target compound has been previously synthesized by Fürstner's group from the intermediate **6** through three steps involving sulfation of the 20-hydroxyl group and demethylation.[3] We envisioned that the pyrrolo[2,3-*c*]carbazole system would be constructed by intramolecular pinacol coupling and subsequent dehydration of the keto-aldehyde **7**. In our preliminary approach, we found that installation of the aldehyde function at the later stage of the synthesis was quite challenging due to low reactivity of the indole 2-position of **8** in electrophilic substitution reactions.[6] Thus, in the present synthesis, we planned to synthesize the pinacol coupling precursor **7** via a palladium-catalyzed cross-coupling reaction of triflate **10** with indole-3-boronate **11** having an aldehyde equivalent substituent at the 2-position. The intermediate triflate **10** has been prepared as an intermediate in our previous synthesis

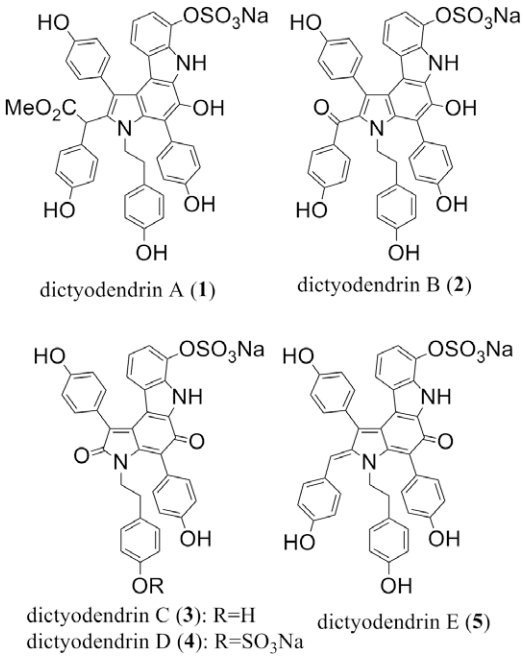

Figure 1. Structure of dictyodendrins A–E.

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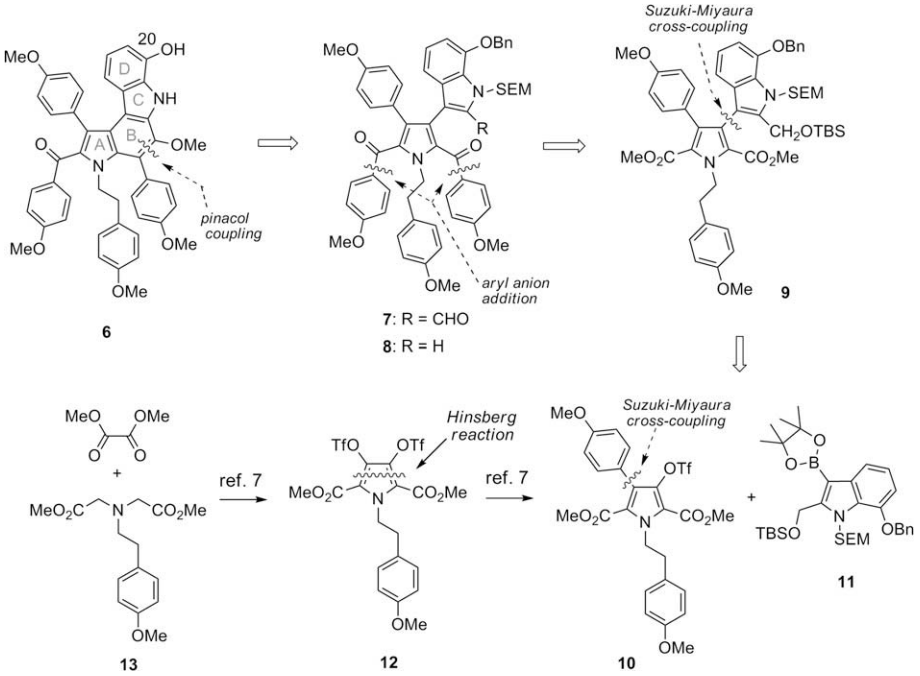
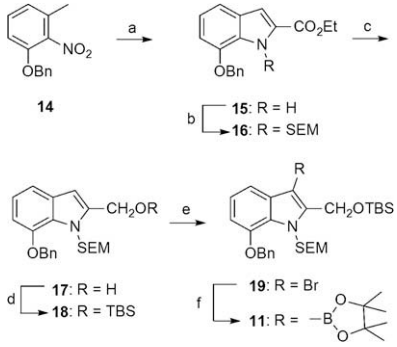


Scheme 1. Retrosynthetic analysis of dictyodendrin B.

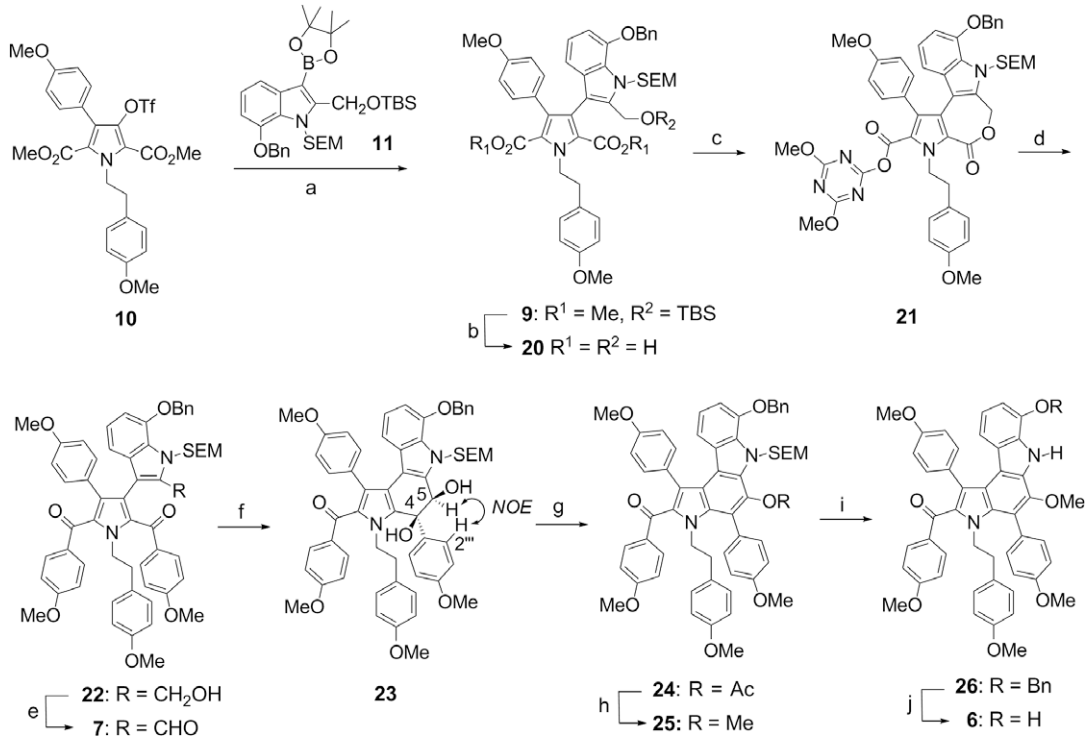


Scheme 2. Reagents and conditions: (a) $(CO_2Et)_2$, *t*-BuOK, ether, reflux, 22 h, then Fe, AcOH, 80 °C, 17 h, 76%; (b) SEM-Cl, NaH, DMF, rt, 1 h, 93%; (c) $LiAlH_4$, THF, rt, 50 min, 90%; (d) TBS-Cl, imidazole, DMF, rt, 12 h, 98%; (e) NBS, THF, −78 °C to rt, then rt, 1 h, 100%; (f) bis(pinacolato)diboron, KOAc, 7 mol %, $PdCl_2$(dppf), DMSO, 80 °C, 19 h, 76%.

of 3,4-diarylpyrrole marine alkaloids[7] by a Suzuki–Miyaura cross-coupling reaction of 3,4-dihydroxy-pyrrole bistriflate **12** obtained via a Hinsberg-type reaction of iminodiacetate **13**.

The indole boronate **11**, a requisite for the cross-coupling reaction with **10**, was prepared via a Reissert indole synthesis as shown in Scheme 2. Condensation of 3-benzyloxy-2-nitrotoluene (**14**) with diethyl oxalate followed by a reduction with iron in AcOH gave 7-benzyloxyindole-2-carboxylate **15**[8] in 76% yield. After protection of the indole nitrogen atom with SEM ether, the ester was reduced with LAH and the primary hydroxyl group was protected as TBS ether to give **18** in high yield. Bromination of **18** with NBS in THF at a low temperature (−78 °C) exclusively occurred at 3-position, affording **19** as the sole product in quantitative yield. Finally, the boronate **11** was obtained by a palladium-catalyzed cross-coupling reaction[9] of **19** with bis(pinacolato)diboron in 76% yield.

A palladium-catalyzed cross-coupling reaction of the triflate **10** with the indole-3-boronate **11** using 10 mol % of $Pd(PPh_3)_4$ and K_2CO_3 as the base in refluxing DME furnished **9** in 72% yield (Scheme 3). Alkaline hydrolysis of the diester **9** proceeded with concomitant removal of the TBS protecting group to give hydroxy-diacid **20** in quantitative yield. In order to activate the carboxylic acid functions for the next aryl anion addition reaction, the diacid **20** was esterified with 2-chloro-4,6-dimethoxy-1,3,5-triazine[10] in the presence of *N*-methylmorpholine, whereupon one of the carboxyl group located near the 2-hydroxymethylindole moiety was lactonized to give **21** in 83% yield. Treatment of **21** with 3.86 equiv of 4-methoxyphenylmagnesium bromide in ether gave **22** in 71% yield, which on Dess–Martin oxidation afforded the keto-aldehyde **7** in 99% yield. The B-ring of the tetracyclic system was constructed by SmI_2-promoted intramolecular pinacol coupling[11] of **7**, in which diol **23** was obtained in 78% yield. Analysis of the ^{1}H NMR spectrum of the cyclized product confirmed that the reaction afforded only a single diastereomer, whose relative stereochemistry was identified as 4*S**,5*R** on the basis of strong NOE correlation between 5-H and 2′-H. A similar ring construction by a low-valent titanium-mediated oxo-ester coupling reaction has been reported for the synthesis of benzo[*c*]carbazole analogs of dictyodendrin.[2] However, the low-valent titanium ($TiCl_4$/Zn)[12] and the magnesium (Mg, TMSCl)[13] reagents were not effective for the pinacol coupling of **7**. An acid-catalyzed dehydration of **23** using CSA in CH_2Cl_2, which was accompanied by deprotection of the SEM ether, methylation of the resulting hydroxyl group, and debenzylation afforded a single product, however, its ^{1}H NMR spectrum data did not match with those of **6** reported by Fürstner et al.[3] The compound thus obtained was identified to be the rearranged compound **27** on the basis of ^{1}H NMR spectrum (Fig. 2), in which both methylenes of the phenethyl moiety of **27** (δ_H 3.09 and 4.67 ppm), which are out of the shielding cone of the adjacent aromatic ring, resonate 0.57–0.71 ppm downfield to those of **6** (δ_H 2.52 and 3.96 ppm). The assignment was further supported by NOE correlations observed between 2′-H/6-NH and 1′-H/4-OCH_3 in its NOESY spectrum.[14] The unexpected product might be formed through a pinacol rearrangement during the dehydration process as illustrated in Figure 2. The aryl migration appears to be driven by the release of strain energy caused by the steric interaction between the migrating aryl group and the phenethyl substituent at the pyrrole nitrogen atom. The undesirable rearrangement



Scheme 3. Reagents and conditions: (a) 10 mol % $Pd(PPH_3)_4$, K_2CO_3, DME 95 °C 26 h, 72%; (b) 3 M, NaOH, EtOH, dioxane, 90 °C, 15 h; (c) 2-chloro-4,6-dimethoxy-1,3,5-triazine, *N*-methylmorpholine, THF, rt, 22 h, 83% (2 steps); (d)4-$MeOC_6H_4MgBr$, ether, rt, 40 min, 71%; (e) DMP, CH_2Cl_2, rt, 20 min, 99%; (f) SmI_2, THF, 0 °C, 1 h, 78%; (g) Ac_2O, pyridine, cat. DMAP, 65 °C, 1 h; (h) NaOMe, DMF, rt, 1 h, then MeI, rt, 1.5 h, 91%, (2 steps); (i) CSA, THF, rt, 5 h; (j) H_2, $Pd(OH)_2$/C, EtOAc, 50 °C, 1 h, 97% (2 steps).

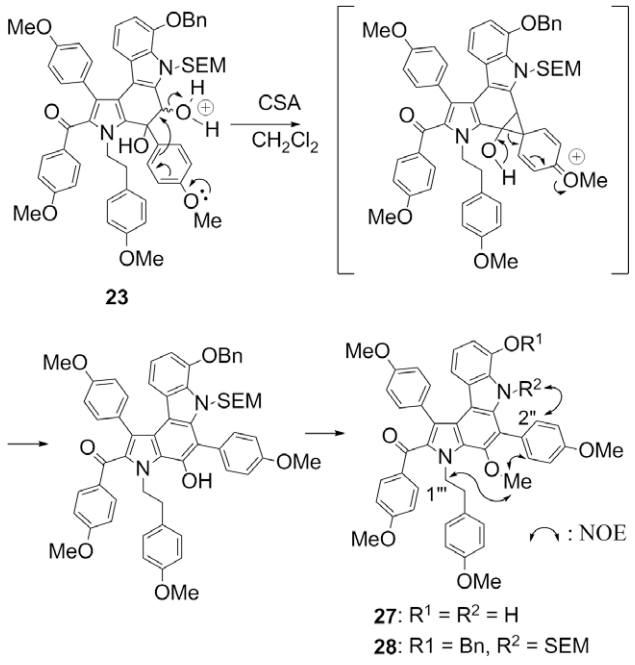


Figure 2. Proposed mechanism of formation of **27**.

could be reduced by simply conducting the dehydration under nonacidic condition. Heating of **23** in a mixture of Ac_2O and pyridine containing a catalytic amount of DMAP followed by deacetylation and methylation predominantly gave **25** in 91% yield with a small amount of the rearranged product **28** (6%). Finally, deprotections of the SEM and the benzyl ethers afforded **6** in 97% yield, whose ^1H and ^{13}C NMR data were identical to those reported in the literature.[3]

In conclusion, we have accomplished a formal total synthesis of dictyodendrin B by using consecutive palladium-catalyzed cross-coupling reactions of 3,4-dihydroxypyrrole bistriflate and intramolecular pinacol coupling as the key reactions. Further studies directed toward the total synthesis of other dictyodendrins from the intermediate **9** are currently underway in our laboratory.

Acknowledgment

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Supplementary data

Experimental procedures and ^1H NMR spectrum chart of the new compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.083.

References and notes

1. Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765–2770.
2. Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519–6534.
3. Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620–11621.
4. Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc* **2006**, *128*, 8087–8094.
5. Ayats, C.; Soley, R.; Albericio, F.; Álvarez, M. *Org. Biomol. Chem.* **2009**, *7*, 860–862.

6. Hirao, S.; Sugiyama, Y.; Iwao, M.; Ishibashi, F. *Biosci., Biotechnol., Biochem.* **2009**, *73*, 1764–1772.
7. Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett.* **2003**, *44*, 4443–4446.
8. Albrecht, R.; Heindl, J.; Loge, O. *Eur. J. Med. Chem.* **1985**, *20*, 57–60.
9. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
10. Blotny, G. *Tetrahedron* **2006**, *62*, 9507–9522.
11. Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765–766.
12. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041–1044.
13. Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, *45*, 3869–3872.
14. See Supplementary data.