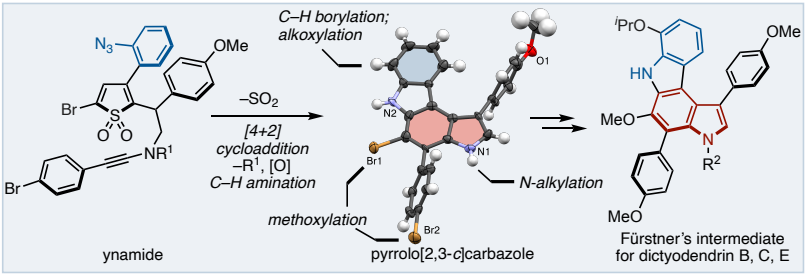
Formal Syntheses of Dictyodendrins B, C, and E by a Multi-substituted Indole Synthesis

Akira Kabuki and Junichiro Yamaguchi*

Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan

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.[1a] 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.[1b] These natural products have β-selectase (β-site APP-cleaving enzyme: BACE) inhibitory activity, which is expected to be applied to the research of Alzheimer's disease.[3] 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.[4] 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.[4e,f] 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.[4h] 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.[4j] 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).[5] In this method, an ynamide intermediate containing thiophene-*S,S*-dioxide was synthesized by a simple four-unit coupling reaction. Then, the ynamide was reacted with the thiophene-*S,S*-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.[6] 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, ynamide [4+2] cycloaddition would afford a multi-substituted indoline, 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

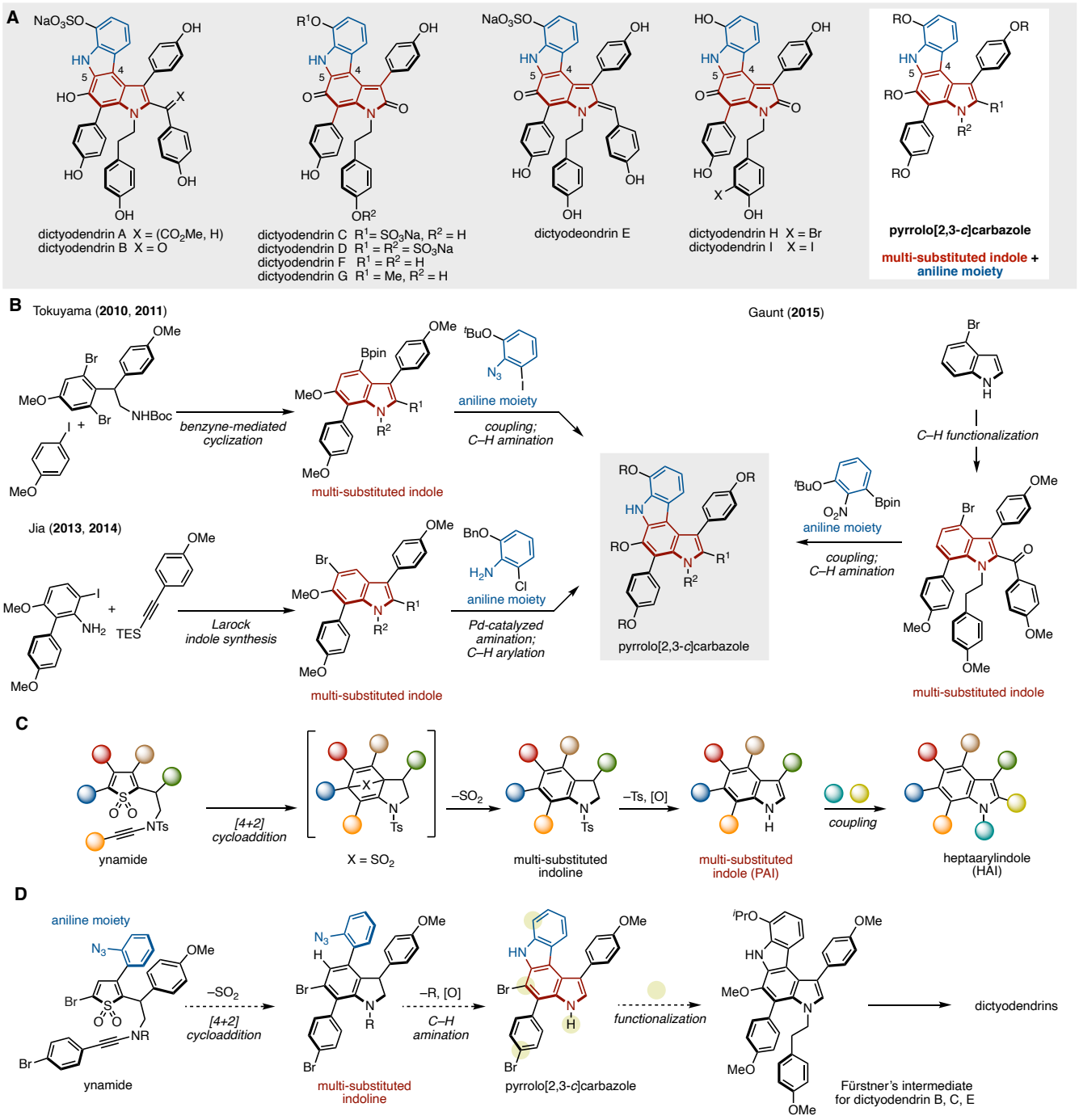


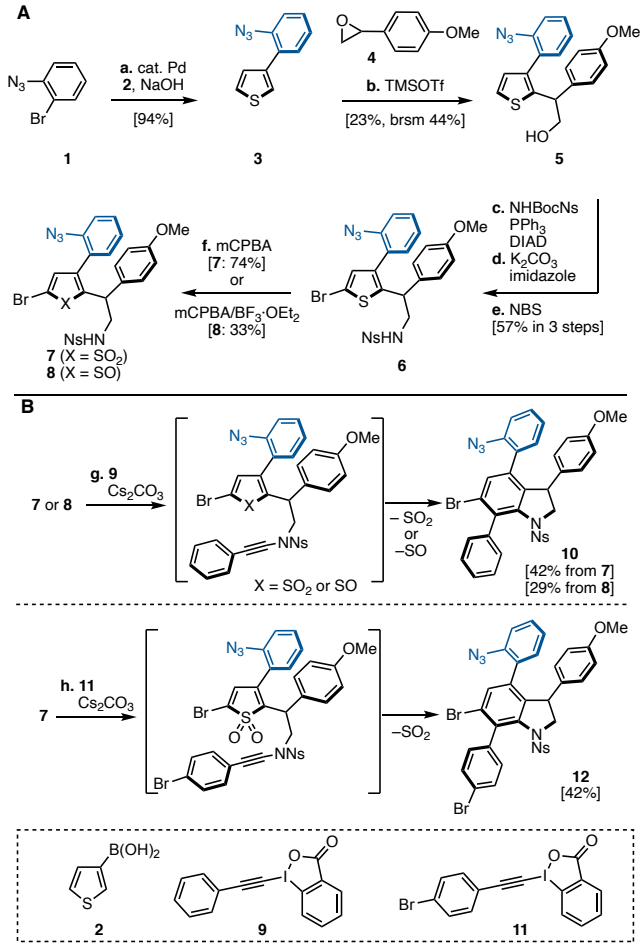
Figure 1. (A) Structures of dictyodendrin A–I. (B) Syntheses of dictyodendrins using the construction of the main skeleton by connecting an indole with an aniline moiety. (C) Our multi-substituted(arylated) indole synthesis. (D) Our synthetic strategy toward dictyodendrins B, C, and E.

of dictyodendrins B, C, and E that was generated by Fürstner and coworkers.[4a,b]

First, the synthesis of the key multi-substituted indoline 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-arylthiophenes 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).[7] Alcohol **5** was subsequently converted to amide **6** by Mitsunobu reaction with NHBocNs and removal of the Boc group, followed by bromination at the C5-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 *S,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

amount of $BF_3{\cdot}OEt_2$ to suppress over-oxidation.[6a] Then, ynamide formation from **7** and **8** with alkynylating 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 alkynylating agent **9** and Cs_2CO_3 were used,[8] 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 dictyodendrins, we also reacted **7** with a bromo-bearing alkynylating 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[a]



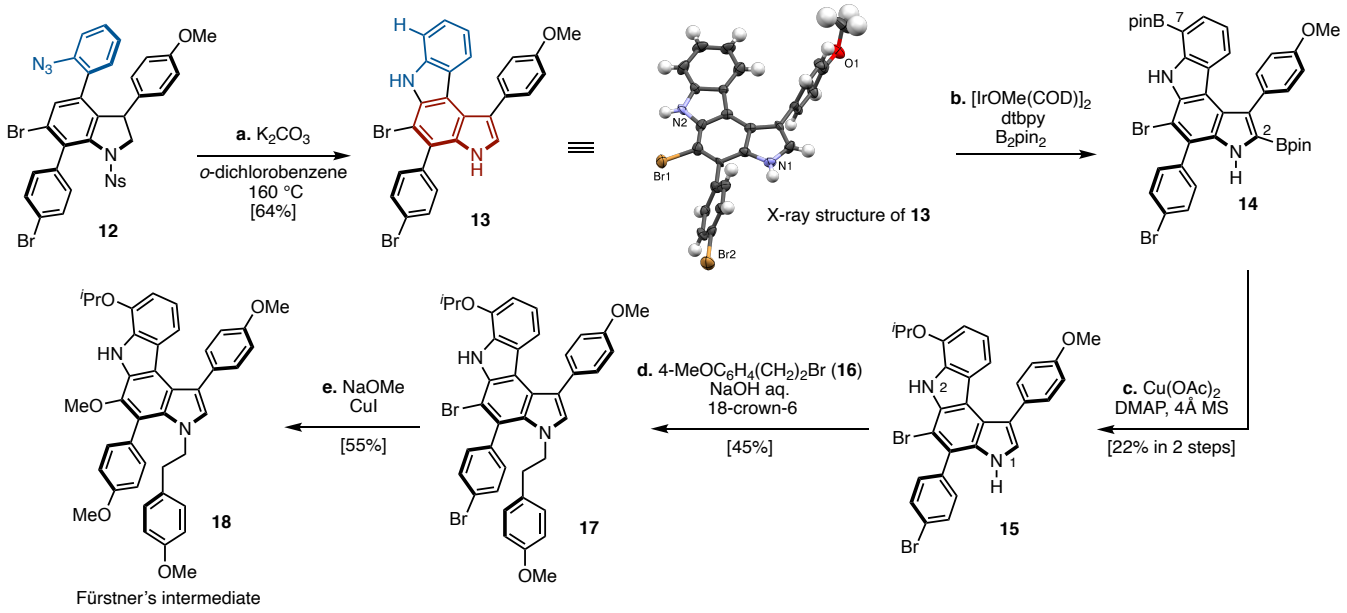
[a]Conditions. (a) 3-Thiopheneboronic acid (**2**: 1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.70 mol%), $P(^tBu)_3{\cdot}HBPh_4$ (1.4 mol%), NaOH aq. (3.0 equiv), THF, 65 °C, 4 h (94%); (b) **4** (1.0 equiv), TMSOTf (2.0 equiv), CH_2Cl_2, –78 °C , 2 h (23% + 48% recovered **3**); (c) NHBocNs (1.7 equiv), DIAD (1.7 equiv), THF, 0 °C, 12 h; (d) K_2CO_3 (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**: *m*CPBA (2.5 equiv), 1,2-dichloroethane, 65 °C, 6 h (74%); for **8**: $BF_3{\cdot}OEt_2$ (10 equiv), *m*CPBA (1.0 equiv), CH_2Cl_2, –20 °C, 1 h (33%); (g) Cs_2CO_3 (1.5 equiv), **9** (1.5 equiv), 1,4-dioxane, 80 °C, 12 h (42% from **7**, 29% from **8**); (h) Cs_2CO_3 (2.8 equiv), **11** (1.5 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,[4e,f,j] 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 *o*-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 undetermined 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, K_2CO_3 was added to neutralize the acid, and the yield of **13** significantly improved to 64%.

We then attempted a formal syntheses of dictyodendrins B, C, and E by elaborating the resulting pyrrolocarbazoles to known synthetic intermediates. From **13**, an isopropoxy 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 isopropoxylation of the C7 position, we selected C–H borylation. When pyrrolocarbazole **13** was subjected to iridium-catalyzed C–H borylation conditions,[9] only the compound with borylation at the C2 position, not the C7 position, was obtained in 62% yield when 1.4 equiv of B_2pin_2 was used. When the amount of B_2pin_2 was increased to 2.6 equiv, compound **14** with borylated C2 and C7 positions was obtained in 66% yield as judged by ^1H 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 isopropoxylation or C2-selective protodeborylation of **14** were possible, we would be able to generate the desired product **15**. To this end, a chemoselective isopropoxylation 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 CH_2Cl_2 and ^iPrOH.[9] As a result, not only the isopropoxylation 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.[10] Next, for the alkylation of **15** at the N1 position, treatment of **15** with alkyl tosylate and potassium hydroxide 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.[4l] Finally, methoxylation 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 dictyodendrins B, C, and E.

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

Scheme 2. Formal Syntheses of Dictyodendrins B, C and E.[a]



[a]Conditions: (a) K_2CO_3 (1.0 equiv), *o*-dichlorobenzene, 160 °C, 2 h, air (64%), ORTEP drawing of **13** with 50% thermal ellipsoid; (b) B_2pin_2 (2.0 equiv), 30 mol% dtbpy, 15 mol% $[IrOMe(COD)]_2$, THF, 70 °C, 12 h; (c) $Cu(OAc)_2$ (1.0 equiv), DMAP (2.0 equiv), ^{i}PrOH, 4Å MS, CH_2Cl_2, 40 °C, 12 h (22% in 2 steps); (d) **16** (3.0 equiv), NaOH aq. (3.0 equiv), 18-crown-6 (6.0 equiv), THF (45%); (e) CuI (6.0 equiv), NaOMe (60 equiv), DMF/MeOH , 100 °C, 12 h (55%).

From here, a four-step functionalization including C–H borylation led to a known intermediate, and the formal syntheses of dictyodendrins B, C, and E were achieved. Furthermore, pyrrolocarbazole **15** with unsubstituted C2 and N1 positions could be a common intermediate toward the synthesis of other dictyodendrin analogues, which are currently ongoing projects in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.
Spectroscopic data for all compounds including ^{1}H, ^{13}C NMR spectra, and crystallographic data (PDF). CCDC 2070911 contains the supplementary crystallographic data for this paper.

AUTHOR INFORMATION

Corresponding Author

*junyamaguchi@waseda.jp

Author Contributions

Junichiro Yamaguchi: 0000-0002-3896-5882

Notes

No competing financial interests have been declared.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP19H02726 (to J.Y.). This work was partly supported by JST ERATO Grant Number JPMJER1901. We thank Dr. Kenta Kato (Waseda University) for assistance with X-ray crystallography. The Materials Characterization Central Laboratory in Waseda University is acknowledged for the support of HRMS measurements.

REFERENCES

(1) (a) Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. Dictyodendrins A–E, the First Telomerase-Inhibitory Marine Natural Products from the Sponge *Dictyodendrilla verongiformis*. *J. Org. Chem.* **2003**, *68*, 2765–2770. (b) Zhang, H.; Conte, M. M.; Khalil, Z.; Huang, X.-C.; Capon, R. J. New Dictyodendrins as BACE Inhibitors from a Southern Australian Marine Sponge, *Ianthella* sp.. *RSC Adv.* **2012**, *2*, 4209–4214.

(2) Seimiya, H. *Drug Deliv. Syst.* **2006**, *21*, 24–31.

(3) Baxter, E. W.; Conway, K. A.; Kennis, L.; Bischoff, F.; Mercken, M. H.; De Winter, H. L.; Reynolds, C. H.; Tounge, B. A.; Luo, C.; Scott, M. K.; Huang, Y.; Braeken, M.; Pieters, S. M. A.; Berthelot, D. J. C.; Masure, S.; Bruinzeel, W. D.; Jordan, A. D.; Parker, M. H.; Boyd, R. E.; Qu, J.; Alexander, R. S.; Brenneman, D. E.; Reitz, A. B. 2-Amino-3,4-dihydroquinazolines as Inhibitors of BACE-1 (*β*-Site APP Cleaving Enzyme): Use of Structure Based Design to Convert a Micromolar Hit into a Nanomolar Lead. *J. Med. Chem.* **2007**, *50*, 4261–4264.

(4) (a) Fürstner, A.; Domostoj, M. M.; Scheiper, B. Total Synthesis of Dictyodendrin B. *J. Am. Chem. Soc.* **2005**, *127*, 11620–11621. (b) Fürstner, A.; Domostoj, M. M.; Scheiper, B. Total Synthesis of the Telomerase Inhibitors Dictyodendrin B, C, and E. *J. Am. Chem. Soc.* **2006**, *128*, 8087–8094. (c) Hirao, S.; Sugiyama, Y.; Iwao, M.; Ishibashi, F. Synthetic Approach to Telomerase Inhibitor Dictyodendrin B: Synthesis of the Pyrrolo[2,3-*c*]carbazole Core. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1764–1772. (d) Hirao, S.; Yoshinaga, Y.; Iwao, M.; Ishibashi, F. A Formal Total Synthesis of the Telomerase Inhibitor Dictyodendrin B. *Tetrahedron Lett.* **2010**, *51*, 533–536. (e) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. Total Synthesis of Dictyodendrin A and B. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925–5929. (f) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. Total Synthesis of Dictyodendrins A–E. *Chem. Asian J.* **2011**, *6*, 560–572. (g) Liang, J.; Hu, W.; Tao, P.; Jia, Y. Total Synthesis of Dictyodendrins B and E. *J. Org.*

Chem. **2013**, *78*, 5810–5815. (h) Tao, P.; Liang, J.; Jia, Y. Total Synthesis of Dictyodendrins B and E, and Formal Synthesis of Dictyodendrin C. *Eur. J. Org. Chem.* **2014**, 5735–5748. (i) Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. Concise Syntheses of Dictyodendrins A and F by a Sequential C–H Functionalization Strategy. *J. Am. Chem. Soc.* **2015**, *137*, 644–647. (j) Pitts, A. K.; O'Hara, F.; Snell, R. H.; Gaunt, M. J. A Concise and Scalable Strategy for the Total Synthesis of Dictyodendrin B Based on Sequential C–H Functionalization. *Angew. Chem., Int. Ed.* **2015**, *54*, 5451–5455. (k) Zhang, W.; Ready, J. M. A Concise Total Synthesis of Dictyodendrins F, H, and I Using Aryl Ynol Ethers as Key Building Blocks. *J. Am. Chem. Soc.* **2016**, *138*, 10684–10692. (l) Matsuoka, J.; Matsuda, Y.; Kawada, Y.; Oishi, S.; Ohno, H. Total Synthesis of Dictyodendrins by the Gold-Catalyzed Cascade Cyclization of Conjugated Diynes with Pyrroles. *Angew. Chem., Int. Ed.* **2017**, *56*, 7444–7448. (m) Matsuoka, J.; Inuki, S.; Matsuda, Y.; Miyamoto, Y.; Otani, M.; Oka, M.; Oishi, S.; Ohno, H. Total Synthesis of Dictyodendrins A–F by the Gold-Catalyzed Cascade Cyclization of Conjugated Diyne with Pyrrole. *Chem. Eur. J.* **2020**, *26*, 11150–11157. (n) Banne, S.; Reddy, D. P.; Li, W.; Wang, C.; Guo, J.; He, Y. A Unified Modular Synthetic Strategy for Dictyodendrins F, H, I, and G. *Org. Lett.* **2017**, *19*, 4996–4999.

(5) Suzuki, S.; Asako, T.; Itami, K.; Yamaguchi, J Modular Synthesis of Heptaarylindole. *Org. Biomol. Chem.* **2018**, *16*, 3771–3776.

(6) (a) Suzuki, S.; Segawa, Y.; Itami, K.; Yamaguchi, J. Synthesis and Characterization of Hexaarylbenzenes with Five or Six Different Substituents Enabled by Programmed Synthesis. *Nat. Chem.* **2015**, *7*, 227–233. (b) Suzuki, S.; Itami, K.; Yamaguchi, J. Synthesis of Octaaryl Naphthalenes and Anthracenes with Different Substituents. *Angew. Chem., Int. Ed.* **2017**, *56*, 15010–15013. (c) Asako, T.; Suzuki, S.; Itami, K.; Muto, K.; Yamaguchi, J. Synthesis of A Heptaarylisoquinoline: Unusual Disconnection for Constructing Isoquinoline Frameworks. *Chem. Lett.* **2018**, *47*, 968–970. (d) Tanaka, S.; Asako, T.; Ota, E.; Yamaguchi, J. Synthesis of a Pentaarylcarbazole: Installation of Different Aryl Groups on a Benzenoid Moiety. *Chem. Lett.* **2020**, *49*, 918–920. (e) Asako, T.; Suzuki, S.; Tanaka, S.; Ota, E.; Yamaguchi, J. Synthesis of Decaarylanthracene with Nine Different Substituents. *J. Org. Chem.* **2020**, *85*, 15437–15448.

(7) Taylor, S. K.; Clark, D. L.; Heinz, K. J.; Schramm, S. B.; Westermann, C. D.; Barnell, K. K. Friedel–Crafts Reactions of Some Conjugated Epoxides. *J. Org. Chem.* **1983**, *48*, 592–596.

(8) Vaillant, F. L.; Courant, T.; Waser, J. Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 11200–11204.

(9) Liyu, J.; Sperry, J. Synthesis of Putative Clausenal from Carbazole Using Sequential C–H Borylations. *Tetrahedron Lett.* **2017**, *58*, 1699–1701.

(10) Loach, R. P.; Fenton, O. S.; Amaike, K.; Siegel, D. S.; Ozkal, E.; Movassaghi, M. C7-Derivatization of C3-Alkylindoles Including Tryptophans and Tryptamines. *J. Org. Chem.* **2014**, *79*, 11254–11263.