Total Synthesis of Dictyodendrins A–F by the Gold-Catalyzed Cascade Cyclization of Conjugated Diyne with Pyrrole

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Abstract: The total synthesis of dictyodendrins A–F was achieved using the gold(I)-catalyzed annulation of a conjugated diyne with *N*-Boc-pyrrole for direct construction of the pyrrolo[2,3-*c*]carbazole scaffold. Late-stage functionalization of the resulting pyrrolo[2,3-*c*]carbazole to introduce various substituents provided divergent access to dictyodendrins. Some dictyodendrin analogues exhibited inhibitory activities toward CDK2/CycA2 and GSK3.

Introduction

Dictyodendrins (Figure 1), a family of marine indole alkaloids with important bioactivities, were first isolated by Fusetani and co-workers from Japanese marine sponge *Dictyodendrilla verongiformis* in 2003.[1] Capon and co-workers isolated new dictyodendrins (F–I) in 2012 from the southern Australian marine sponge *Ianthella* sp.[2] The Fusetani group reported that dictyodendrins A–E have inhibitory activity against telomerase, making them potential lead compounds as anticancer agents. In a recent report, Ready showed that dictyodendrins F, H, and I display cytotoxicity against several human cancer cell lines.[3] Interestingly, the DNA cleavage activity of dictyodendrin derivatives is highly dependent on the methylation level of the phenol moieties, as reported by Fürstner and co-workers.[4] As dictyodendrins F, H, and I exhibit inhibitory activity towards β-site amyloid-cleaving enzyme 1 (BACE1), they are also recognized as potential lead compounds for the treatment of Alzheimer's disease.[2]

The highly substituted pyrrolo[2,3-*c*]carbazole core of dictyodendrins has attracted much interest from the synthetic community.[5] In 2005, the Fürstner group disclosed the first total syntheses of dictyodendrins B, C, E, and F through a carefully designed stepwise construction of the fused carbazole core (Scheme 1).[6,7] Subsequently, several total syntheses of dictyodendrins have been established by the research groups of Ishibashi (dictyodendrin B),[8,9] Tokuyama (A–E),[10,11] Jia (B, C, and E),[12,13] Gaunt (B),[14] Yamaguchi/Itami/Davies (A and F),[15] Ready (F, H, and I),[3] and He (F, G, H, and I).[16] Most reported syntheses used strategies based on introducing the requisite substituents prior to construction of the pyrrolo[2,3-*c*]carbazole core. The important exception is Fürstner's synthesis of dictyodendrins B and E, in which pyrrolo[2,3-*c*]carbazole **14** was converted to **15** via bromination, lithiation, and acylation at the C2 position (Scheme 2).[7] We envisaged that early-stage construction of the core structure followed by regioselective introduction of the substituents could facilitate a diversity-oriented synthetic route of a series of dictyodendrins. This would further expand the medicinal applications of dictyodendrin derivatives.

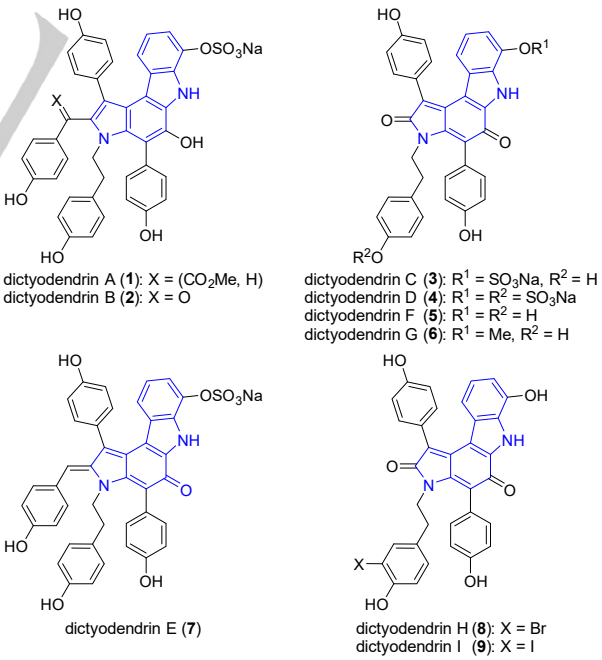

Figure 1. Structures of dictyodendrins A–I.

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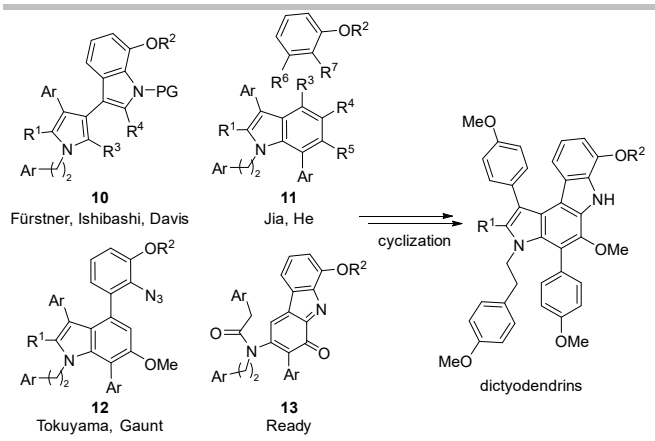
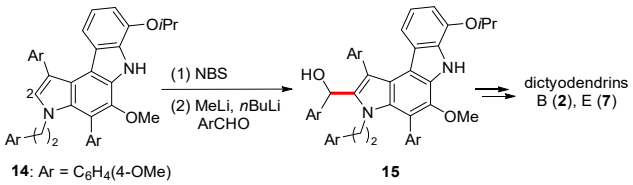
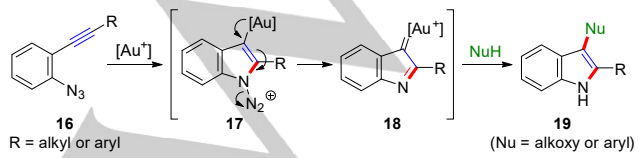


Scheme 1. Reported total syntheses of dictyodendrins.

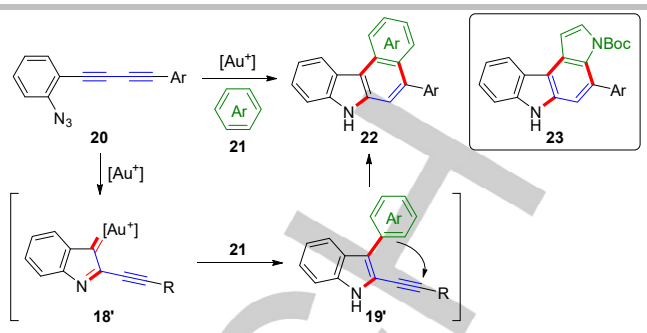


Scheme 2. Acyl group installation at the C2 position by Fürstner.

Currently, gold carbenoids[17,18] have emerged as versatile intermediates for the construction of heterocyclic compounds.[19–21] Gagosz[22] and Zhang[23] reported pioneering works on gold-catalyzed indole synthesis based on intramolecular acetylenic Schmidt reactions using ethynylbenzene **16** (Scheme 3). This reaction proceeds through the formation of gold carbenoid species **18** by gold-catalyzed nucleophilic attack of the azide moiety on the activated alkyne followed by nitrogen elimination. Subsequent nucleophilic trapping of gold carbenoid species **18** produces indole **19** bearing an electron-donating substituent at the C3 position. Recently, we disclosed that the gold-catalyzed annulation of azido-diynes **20** with arene **21** leads to the formation of various aryl-annulated [*c*]carbazoles **22** (Scheme 4).[24] This reaction constructs three bonds and two rings through the initial formation of alkyne-substituted gold carbenoid **18'**, intermolecular arylation with arene **21**, and 6-*endo-dig* hydroarylation.[25] Notably, the reaction using *N*-Boc-pyrrole as arene component **21** afforded pyrrolo[2,3-*c*]carbazole derivative **23** regioselectively, reflecting the dictyodendrin core structure. Therefore, if the late-stage introduction of substituents was successful, we expected that this annulation could be applied to the diversity-oriented total synthesis of dictyodendrins.[26]



Scheme 3. Gold-catalyzed intramolecular acetylenic Schmidt reaction reported by Gagosz and Zhang.

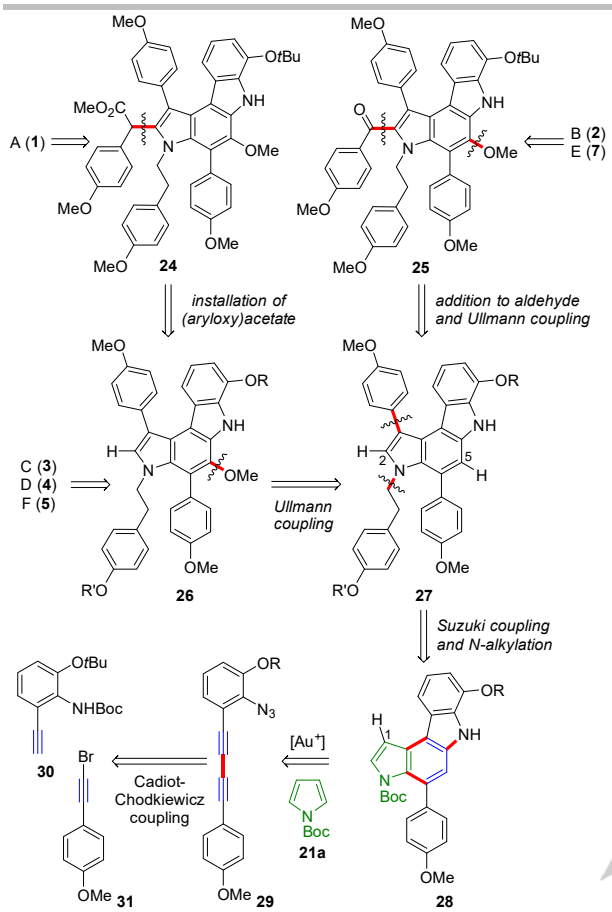


Scheme 4. Our previous work on construction of the pyrrolo[2,3-*c*]carbazole core structure.

Herein, we describe total/formal syntheses of dictyodendrins A–F based on the gold-catalyzed annulation of azido-diynes and *N*-Boc-pyrrole for construction of the pyrrolo[2,3-*c*]carbazole core.[27] Biological evaluation of the dictyodendrin derivatives is also presented.

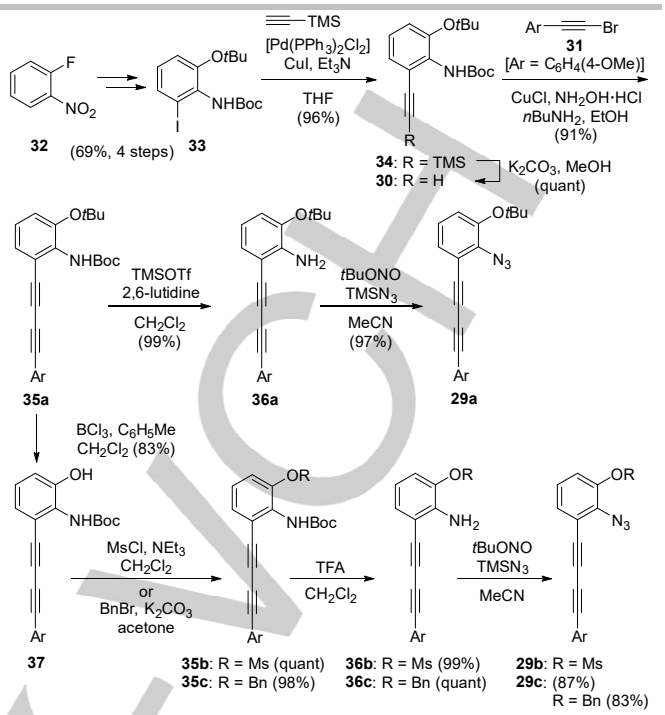
Results and Discussion

Retrosynthesis: Our retrosynthetic analysis of dictyodendrins based on the gold-catalyzed annulation is shown in Scheme 5. Dictyodendrin A (**1**) could be synthesized from **24** by installation of a sulfate group and removal of the methyl groups, according to Tokuyama's protocol.[11] Ester **24** could be prepared from pyrrolocarbazole **26** through, for example, a Friedel–Crafts reaction. Pyrrolocarbazole **26**, known as the precursor of dictyodendrins C (**3**), D (**4**), and F (**5**), could be obtained by bromination of **27** followed by an Ullmann coupling with NaOMe.[14] Compound **27** would be prepared by consecutive functionalization of **28** at the C1 and N3 positions[28] after bromination, when necessary. We also envisaged that ketone **25**, a known synthetic intermediate of dictyodendrins B (**2**) and E (**7**), would be constructed from **27** via a sequence of bromination, metalation, and addition to *p*-anisaldehyde at the C2 position.[7] As described above, the gold-catalyzed annulation of conjugated diyne **29** with pyrrole **21a** would produce pyrrolo[2,3-*c*]carbazole **28** bearing an oxygen functional group (OR group). Cyclization precursor **29** could be readily prepared by the Cadiot–Chodkiewicz coupling reaction between terminal and brominated alkynes **30** and **31**, respectively.[29,30]



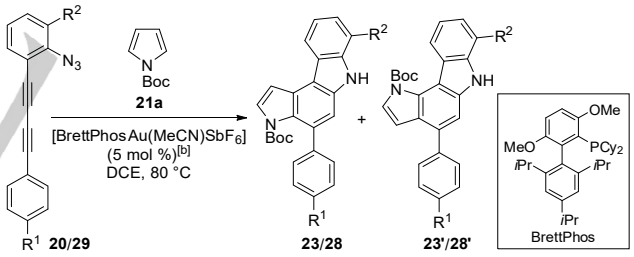
Scheme 5. Retrosynthetic analysis of dictyodendrins.

Preparation and gold-catalyzed annulation of conjugated diynes. We prepared conjugated diynes **29a**–**c** bearing an oxygen functional group as shown in Scheme 6. According to the reported protocol,[11] 1-fluoro-2-nitrobenzene (**32**) was converted to the protected 2-amino-3-iodophenol **33** in four steps. The subsequent Sonogashira coupling of **33** with trimethylsilylacetylene, followed by desilylation of the coupling product with K_2CO_3 and methanol, afforded corresponding terminal alkyne **30** in quantitative yield.[31,32] Cadiot–Chodkiewicz coupling[29] of **30** with bromoalkyne **31**[33] and deprotection of resulting conjugated diyne **35a** with TMSOTf and 2,6-lutidine gave the corresponding diyne (**36a**) bearing a free amino group.[34] Finally, azidation of **36a** using *t*BuONO and $TMSN_3$ afforded substrate **29a** with a *t*Bu protecting group.[35] Other conjugated diynes **29b** (R = OMs) and **29c** (R = OBn) were prepared from **35a** in a similar manner through protecting group modifications and azidation, as shown in Scheme 6.



Scheme 6. Synthesis of azido-diynes **29a**–**c**.

Table 1. Optimization of gold-catalyzed annulation of 1,3-diyne and pyrrole.[a]



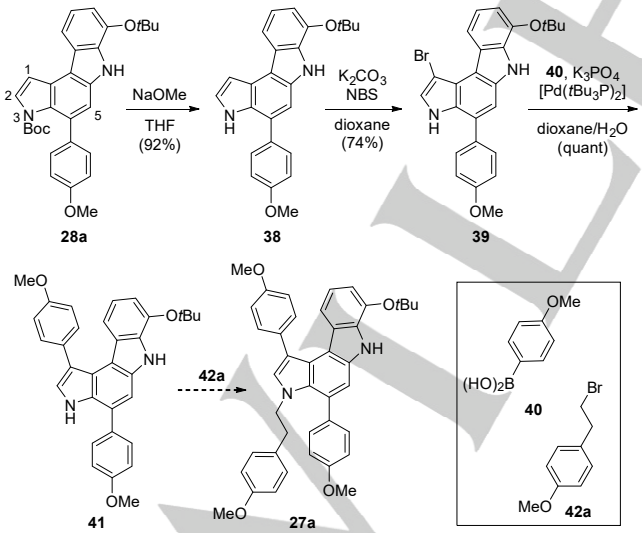
entry	**20/29**	R^1	R^2	Yield[b]	ratio[c]
1[24]	**20a**	H	H	58%	95 : 5 (**23a**/**23'a**)
2	**29a**	OMe	O*t*Bu	79%	84 : 16 (**28a**/**28'a**)
3	**29b**	OMe	OMs	83%	75 : 25 (**28b**/**28'b**)
4	**29c**	OMe	OBn	68%	81 : 19 (**28c**/**28'c**)

[a] Reaction conditions: **20**/**29** (1 equiv.), **21a** (5 equiv.), [BrettPhosAu(MeCN)SbF_6] (5 mol%), 1,2-dichloroethane (DCE), 80 °C. [b] Combined isolated yields. [c] Determined by ^{1}H NMR.

We then explored appropriate oxygen functional groups for the gold-catalyzed annulation (Table 1). We recently showed that treatment of diyne **20a** and *N*-Boc-pyrrole **21a** with [BrettPhosAuSbF_6][36] (5 mol%) in dichloroethane (DCE) at 80 °C proceeded with high regioselectivity to afford the desired

pyrrolo[2,3-*c*]carbazole (58% yield, **23a**/**23'a** = 95:5).[24] Therefore, these optimized conditions for **20a** were applied to conjugated diynes **29a**–**c** bearing an oxygen functional group. The reaction of **29a** bearing methoxy (R^1 = OMe) and *tert*-butoxy groups (R^2 = O*t*Bu) showed slightly decreased regioselectivity (**28a**/**28'a** = 84:16) with an improved combined yield (79%). In contrast, **29b** (R^2 = OMs) and **29c** (R^2 = OBn) gave the annulation products with relatively low regioselectivities (**28**/**28'** = 75:25–81:19). Unfortunately, the reaction with 3-bromo-*N*-Boc-pyrrole was unsuccessful, leading to the formation of a complex mixture of unidentified products. Considering the facile deprotection of *tert*-butyl group and slightly better regioselectivity in the annulation reaction, we selected **29a** as the suitable building block for the total synthesis of dictyodendrins. Notably, the gram-scale reaction of **29a** (2.76 g) with **21a** (6.69 g) in the presence of a decreased amount of [BrettPhosAu(MeCN)SbF_6] (162 mg, 2 mol%) afforded **28a** (2.27 g) in 58% isolated yield.

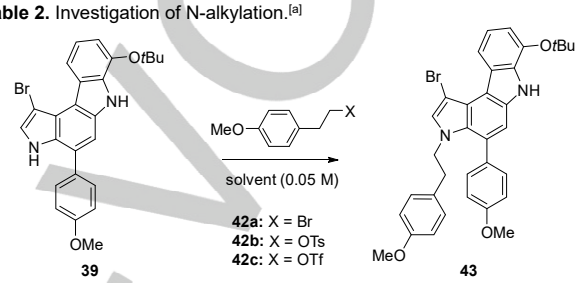
Total syntheses of dictyodendrins C, D, and F. With pyrrolo[2,3-*c*]carbazole **28a** in hand, the total syntheses of dictyodendrins C and F bearing a 2,5-dioxo moiety on the core structure were investigated. Our first attempt at direct C–H arylation of **28a** at the C1 position[28] failed, resulting in starting material recovery. Therefore, the Boc group was removed to increase the reactivity of the pyrrole ring in **28a** (Scheme 7). Although the C–H arylation of resulting unprotected pyrrolo[2,3-*c*]carbazole **38** using a palladium catalyst was also unsuccessful, C1 bromination with *N*-bromosuccinimide (NBS; 1.05 equiv.) proceeded smoothly to give desired product **39**. The Suzuki–Miyaura coupling of **39** with anisylboronic acid (**40**) afforded C1-arylated product **41**. Unfortunately, N-alkylation with **42a** led only to the formation of a complex mixture without producing desired product **27a**.



Scheme 7. Attempted synthesis of **27a**.

As the strategy to introduce the C1-aryl group at the first stage had failed, we optimized the order of substituent introduction. As the first N-alkylation was found to significantly decrease the reactivity for C1 bromination, we focused on the N-alkylation of brominated product **39** (Table 2). The screening of reaction conditions, including different electrophiles, bases, solvents, and reaction temperatures (entries 1–5) showed that treating **39** with bromide **42a** in the presence of NaOH in THF afforded the desired N3-alkylated product **43** in 26% yield (entry 5). Addition of 18-crown-6 (3 equiv.) using THF/H_2O (10:1) significantly improved the yield of **43** to 82%. Notably, the gram-scale bromination to prepare **39** was unsuccessful, presumably owing to a rapid 'bromine dance'[7] during evaporation of the reaction solvent. Therefore, a one-pot C1-bromination/N3-alkylation protocol was employed for the total synthesis.

Table 2. Investigation of N-alkylation.[a]



entry	**42** [equiv.]	base [equiv.]	solvent	temp [°C]	additive [equiv]	yield [%]
1	**42a** [3]	K_2CO_3 [10]	DMF	80	-	trace
2	**42b** [3]	Cs_2CO_3 [10]	DMF	rt	-	0
3	**42c** [3]	K_2CO_3 [10]	DMF	80	-	0
4	**42a** [1.2]	NaH [2.5]	DMF	80	-	0
5	**42a** [2]	NaOH [10]	THF	50	-	26
6	**42a** [10]	NaOH [15]	THF/H_2O (1 : 1)	rt	18-C-6 [3]	0
7	**42a** [10]	NaOH [15]	THF/H_2O (10 : 1)	rt	18-C-6 [3]	82

[a] Reaction conditions: Substrate **39** (1 equiv.), **42**, base (X equiv.), solvent (0.05 M), additive (3 equiv. where applicable). 18-C-6 = 18-crown 6-ether.

We next proceeded to synthesize dictyodendrins C and F (Scheme 8). One-pot bromination of **38** with NBS (1.05 equiv.) and N-alkylation with **42a** under the optimized conditions (Table 2, entry 7), followed by Suzuki–Miyaura coupling with anisylboronic acid (**40**), afforded **27a** bearing newly-introduced substituents at the C1 and N3 positions. Introducing an oxygen functional group at the C5 position proved to be difficult. After several unsuccessful attempts, such as direct C–H borylation[37] or lithiation,[38] we finally succeeded in forming mono-bromide **45** through dibromination of **27a** with NBS (2.05 equiv.) at the C2 and C5 positions, followed by C2-selective mono-debromination of **44** with $NaBH_4$ in the presence of [$PdCl_2$(dppf)].[39] The Ullmann coupling of **45** with NaOMe in the presence of CuI gave **26a** quantitatively, which has been reported as a precursor of dictyodendrin C by Tokuyama.[11] We completed the total synthesis of dictyodendrin F through deprotection of **26a** with BBr_3 and aerobic oxidation.[7]

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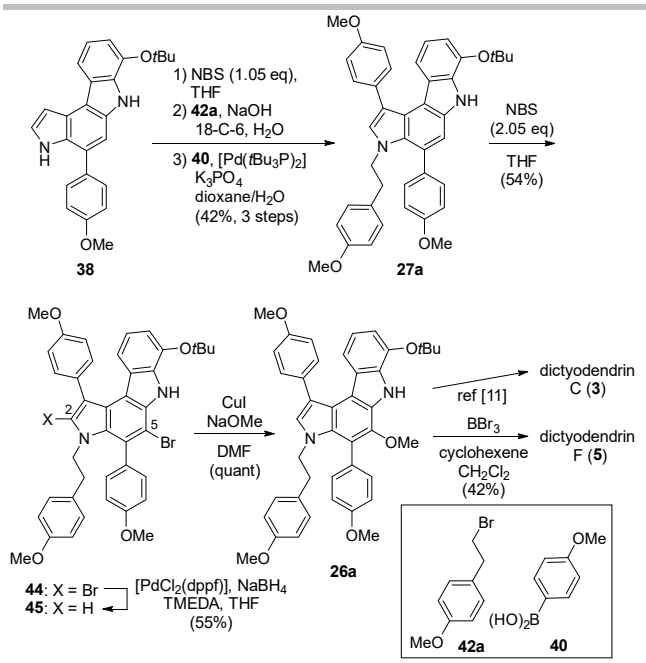
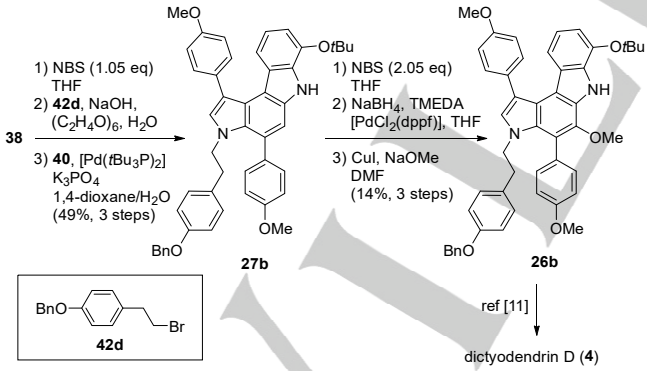


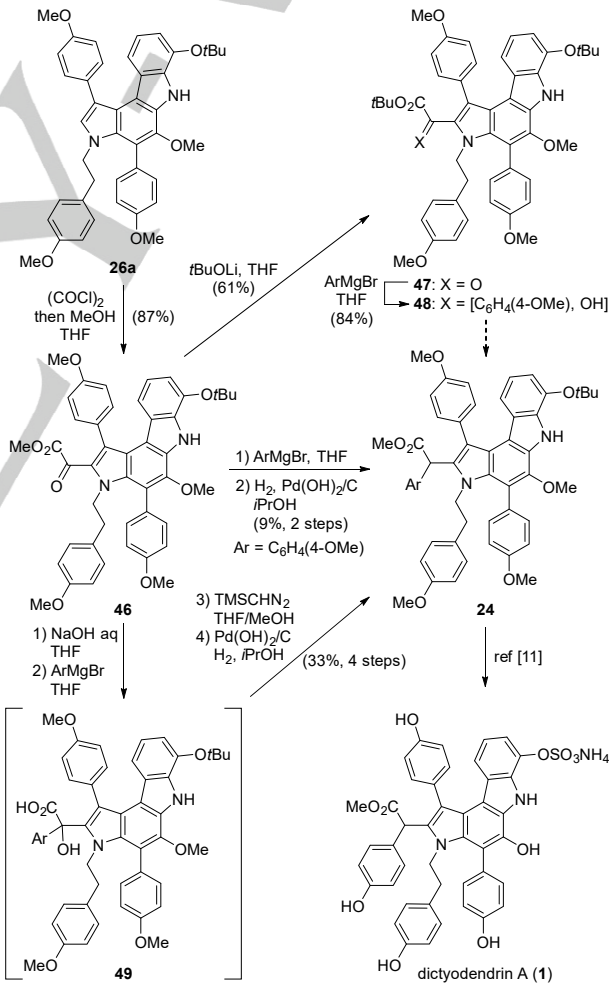
Scheme 8. Formal and total syntheses of dictyodendrins C and F.

Formal synthesis of dictyodendrin D (**4**) was achieved in a similar manner (Scheme 9). As dictyodendrin D has a sulfate moiety on the N-alkyl group, benzyl-protected bromide **42d** was employed for the N-alkylation according to Tokuyama's synthesis.[11] Therefore, key intermediate **27b** was obtained from **38** through a sequence of reactions, including C1-bromination, N3-alkylation with **42d**, and a Suzuki–Miyaura coupling reaction. The formal total synthesis of dictyodendrin D was accomplished by introducing a methoxy group into **27b**, affording known precursor **26b**.[11]



Scheme 9. Formal total synthesis of dictyodendrin D.

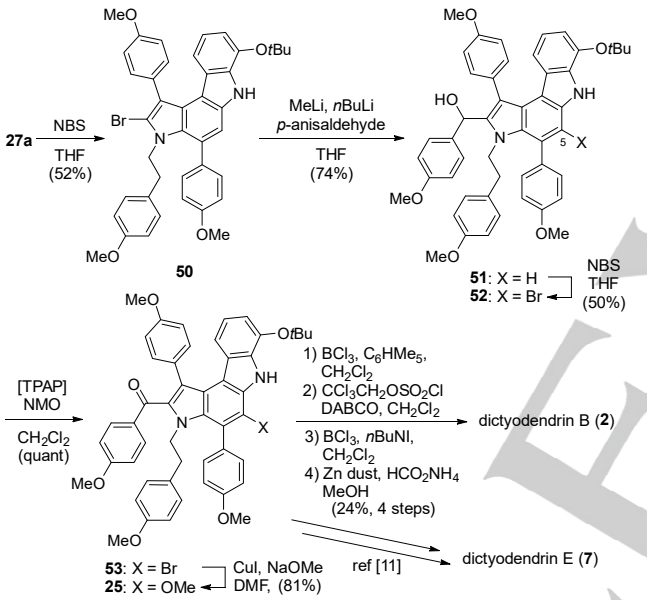
Total synthesis of dictyodendrin A. We next focused on the total synthesis of dictyodendrins A (Scheme 10), which required introduction of a (4-hydroxyphenyl)acetate moiety at the C2 position. Our initial attempts at introducing the C2 substituent on **26a**, including C–H insertion and Friedel–Crafts reactions under various reaction conditions, resulted in decomposition of the starting material. In contrast, acylation of **26a** with oxalyl chloride followed by methyl esterification led to the formation of keto-ester **46** in 87% yield. Unfortunately, subsequent addition of a Grignard reagent to introduce an anisyl group into **46** resulted in the formation of a complex mixture, affording only 9% of the desired ester **24** after $Pd(OH)_2$/C-mediated hydrogenation to remove the hydroxy group. To prevent side reactions derived from the methyl ester moiety of **46**, we prepared *tert*-butyl ester **47** by reacting **46** with *t*BuOLi. The Grignard reaction of **47** showed clean conversion to α-hydroxyester **48**, as expected. However, the subsequent conversion to methyl ester **24** was unsuccessful. Therefore, we conducted the Grignard reaction after hydrolysis of **46**. Pleasingly, the carboxylic acid derived from **46** reacted with anisylmagnesium bromide more efficiently, affording ester **24** after esterification with TMS diazomethane and hydrogenation (33% yield, four steps). In this conversion, rapid esterification of **49** without purification was essential to prevent conversion to aryl ketone **25** (*vide infra*, Scheme 12). Removal of the methyl and *tert*-butyl groups in **24** would complete the total synthesis of dictyodendrin A.[11]



Scheme 10. Formal total synthesis of dictyodendrin A.

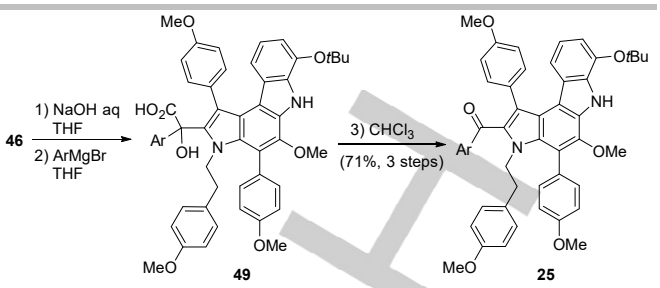
Total syntheses of dictyodendrins B and E. Dictyodendrins B and E possess acyl and benzylidene groups at the C2 position, respectively (Figure 1). We selected the C2 acylation strategy

reported by Fürstner (Scheme 2),[7] in which a sequence of reactions involving bromine–lithium exchange and addition to *p*-anisaldehyde afforded C2-substituted pyrrolo[2,3-*c*]carbazole **15**. Accordingly, regioselective mono-bromination of **27a** with NBS (1.05 equiv.) gave **50** in moderate yield (52%) (Scheme 11). Subsequent bromine–lithium exchange with MeLi (1.1 equiv.) and *n*BuLi (1.1 equiv.), followed by addition to *p*-anisaldehyde, afforded corresponding C2-substituted product **51** in 74% yield. Methyl ether **25** was obtained through selective mono-bromination of **51** at the C5 position, Ley–Griffith oxidation of the resulting bromide **52**, and Ullmann coupling with NaOMe. We accomplished the total synthesis of dictyodendrin B (**2**) through selective removal of the *tert*-butyl group using BCl_3 at –78 °C, sulfate formation, and deprotection using BCl_3 (0 °C→rt) and Zn dust as reported.[11] Tokuyama and co-workers reported that **25** can be transformed to dictyodendrin E by reduction of the carbonyl group, demethylation, sulfate moiety construction, and oxidation with DDQ.[11]



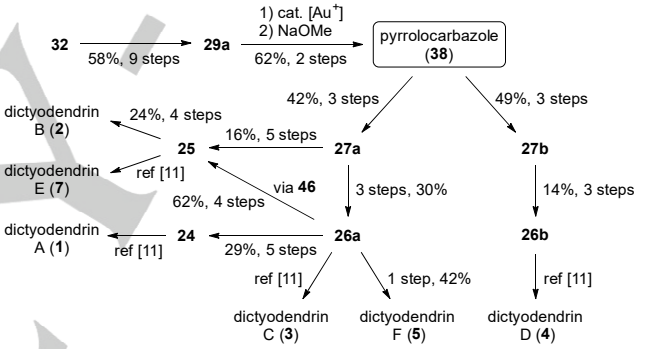
Scheme 11. Formal and total syntheses of dictyodendrins B and E.

As an alternative route, dictyodendrins B and E can be accessed from advanced intermediate **46** from the synthesis of dictyodendrin A. As described in the Grignard reaction of acid **49** (Scheme 10), we unexpectedly found that **49** was gradually converted into ketone **25** when standing in $CDCl_3$ (Scheme 12). This oxidative decarboxylation reaction would proceed through anionic[40] or radical pathways.[41] After complete consumption of **49** in $CHCl_3$, ketone **25** was obtained in 71% yield in three steps from **46**. Therefore, **46** (obtained from **26a**) can be considered as a common intermediate for dictyodendrins A, B, and E. Spectral data of all the synthetic natural products and the known intermediates were in good accordance with those of reported in the literature.[11]



Scheme 12. Alternative route to **25**.

As summarized in Scheme 13, our dictyodendrin synthesis was highly diversity-oriented. Pyrrolocarbazole **38**, obtained by the gold-catalyzed annulation of diyne **29a** with *N*-Boc-pyrrole followed by removal of the Boc group, was the common intermediate for all dictyodendrins synthesized in this study. Therefore, this strategy has potential applications in the synthesis of various dictyodendrin analogues for medicinal applications.



Scheme 13. Summary of our dictyodendrin synthesis.

Biological evaluation. The biological activities of the synthesized dictyodendrin analogues were evaluated. As dictyodendrin F has previously been reported to show cytotoxicity against human colon cancer HCT116 cells (IC_{50} = 27.0 μM),[3] we assessed the cytotoxicity of newly synthesized dictyodendrin analogues toward HCT116 cells at 30 μM using the colorimetric MTS assay (Figure 2). Among the pyrrolo[2,3-*c*]carbazole derivatives investigated, **28a** and **38** with no substituents at the C1 and C2 positions exhibited relatively high cytotoxicity against HCT116 cells (44%–64% cell viability), comparable to that of dictyodendrin F (55%). Interestingly, pyrrolo[3,2-*c*]carbazole derivative **28'b**, the unnatural regioisomer with no substituents at C2 and C3, showed the highest activity (19%). In contrast, no cytotoxicity against HCT116 cells was observed for C1- and C2-substituted pyrrolocarbazoles **25**, **26a**, **27a**, and **50**–**52**, even at 30 μM.

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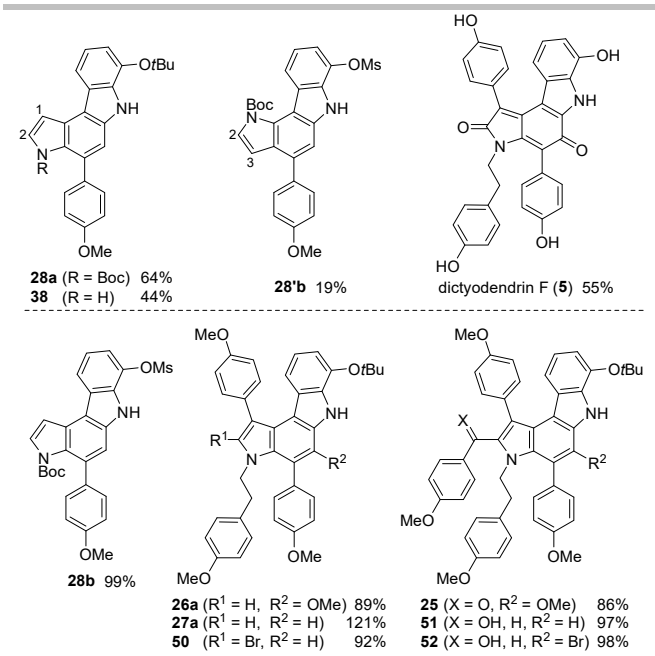

Figure 2. Cytotoxicity of dictyodendrin derivatives (% values of cell viability at 30 μM are shown).

Several fused carbazoles are known to exhibit inhibitory activities against protein kinases. For example, PD407824 (Figure 3), containing a pyrrolo[3,4-*c*]carbazole scaffold, has been reported to inhibit protein kinases (Wee1, Chk1, PKC, and CDK4) at nM levels. To examine the potential of pyrrolo[2,3-*c*]- and pyrrolo[3,2-*c*]carbazoles as templates for kinase inhibitors, we next screened unsubstituted derivatives **54** and **55**[42] at 10 μM against 32 protein kinases. As shown in Figure 3, these carbazoles showed inhibitory activity against CDK2/CycA2[43,44] [IC_{50}: 0.78 μM (**54**) and 2.6 μM (**55**)] and GSK3β[45] [IC_{50}: 3.1 μM (**54**) and 1.8 μM (**55**)]. Furthermore, as some CDK2 inhibitors have been found to inhibit nucleolar formation, we evaluated the inhibitory activity of the dictyodendrin analogues against nucleolar localization of the flavivirus core protein.[46] However, these carbazoles did not exhibit antiviral activity like that of the known CDK2/9 inhibitor (see Supporting information).

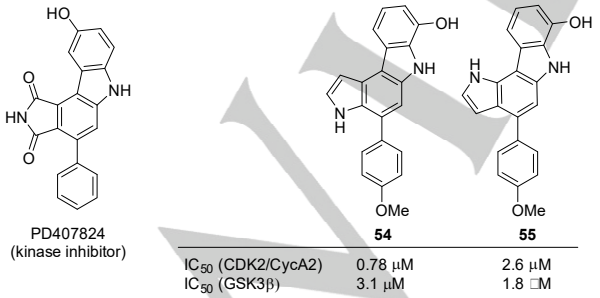

Figure 3. Inhibition of CDK2/CycA2 and GSK3β.

Overall, we found that pyrrolo[3,2-*c*]carbazole derivative **28'b** showed the highest cytotoxicity against HCT116 cells among the dictyodendrin analogues examined, and that pyrrolo[2,3-*c*]carbazole derivative **54** and its [3,2-*c*] congener **55** are promising templates for kinase inhibitors.

Conclusions

We have accomplished total and formal syntheses of dictyodendrins A–F. The gold-catalyzed annulation of diynes bearing a *tert*-butoxy group proceeded efficiently to provide the pyrrolo[2,3-*c*]carbazole required for dictyodendrin synthesis. The late-stage functionalization of pyrrolo[2,3-*c*]carbazole **38**, including C1 arylation, C2 acylation, N3 alkylation, and C5 oxidation, served as a diversity-oriented synthesis of dictyodendrins. Resulting dictyodendrin analogues **54** and **55** exhibited inhibitory activity against CDK2/CycA2 and GSK3β. This strategy enables the comprehensive synthesis of dictyodendrin derivatives and facilitates a new approach toward biologically active pyrrolocarbazole-type compounds.

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Keywords: cascade reaction • conjugated diyne • dictyodendrin • gold catalyst • pyrrolocarbazole

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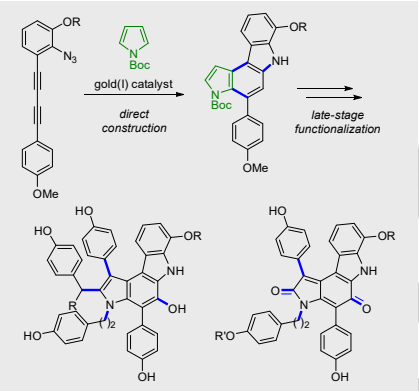
FULL PAPER

Total syntheses of dictyodendrins A–F were achieved based on a gold-catalyzed cascade reaction for construction of the pyrrolo[2,3-*c*]carbazole scaffold. This synthetic strategy features functionalization of the pyrrolo[2,3-*c*]carbazole scaffold at C1 (arylation), C2 (acylation), N3 (alkylation), and C5 (oxidation) positions. This synthetic method could be used for the diversity-oriented synthesis of dictyodendrin derivatives for medicinal applications.



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Total Synthesis of Dictyodendrins A–F by the Gold-Catalyzed Cascade Cyclization of Conjugated Diyne with Pyrrole

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