Natural Products Synthesis

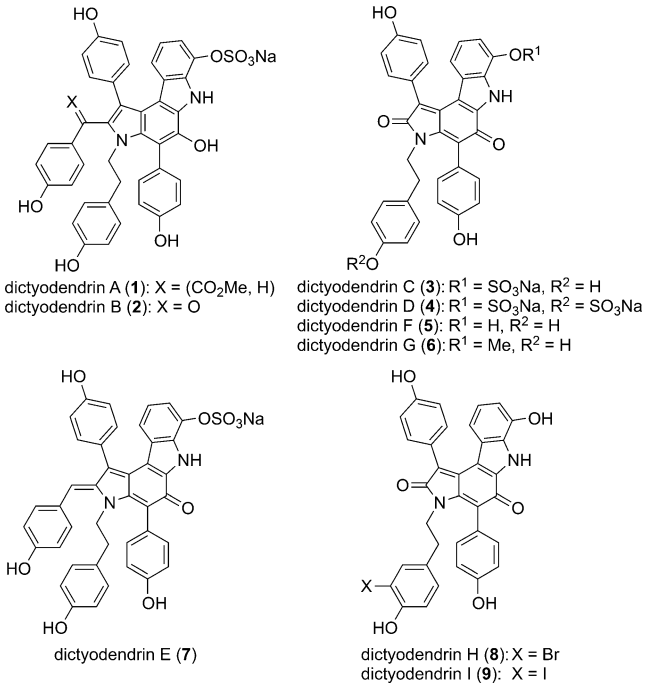
International Edition: DOI: 10.1002/anie.201703279
German Edition: DOI: 10.1002/ange.201703279

Total Synthesis of Dictyodendrins by the Gold-Catalyzed Cascade Cyclization of Conjugated Diynes with Pyrroles

*Junpei Matsuoka, Yuka Matsuda, Yuiki Kawada, Shinya Oishi, and Hiroaki Ohno**

Abstract: *In total and formal syntheses of dictyodendrins B, C, E, and F, the key step involved the direct construction of the pyrrolo[2,3-c]carbazole core by the gold-catalyzed annulation of a conjugated diyne with a pyrrole to form three bonds and two aromatic rings. The subsequent introduction of substituents at the C1 (Suzuki–Miyaura coupling), C2 (addition to an aldehyde), N3 (alkylation), and C5 positions (Ullman coupling) provided divergent access to dictyodendrins.*

Dictyodendrins A–E (Scheme 1) were initially isolated by Fusetani and co-workers from the Japanese marine sponge *Dictyodendrilla verongiformis* in 2003.[1] These compounds belong to a family of marine indole alkaloids and have been reported to inhibit the activity of telomerase, thus making them potential anticancer agents. Dictyodendrins F–J were first isolated by Capon and co-workers in 2012 from the southern Australian marine sponge *Ianthella* sp. These compounds exhibited inhibitory activity towards β-site amyloid-cleaving enzyme 1 (BACE1), and are therefore recognized as potential targets for the treatment of Alzheimer's disease.[2]



Scheme 1. Structures of dictyodendrins A–I.

In terms of their structural characteristics, dictyodendrins consist of a highly substituted pyrrolo[2,3-*c*]carbazole core, the complexity of which has attracted the interest of synthetic chemists. In 2005, the Fürstner group reported the first total synthesis of dictyodendrins B, C, E, and F through a carefully devised process involving the stepwise construction of the complex ring systems of these compounds.[3] Subsequently, the research groups of Ishibashi,[4] Tokuyama,[5] Jia,[6] Gaunt,[7] Yamaguchi/Itami/Davies,[8] and Ready[9] disclosed total syntheses of these interesting natural products. A common feature of these strategies was the introduction of several optimally placed substituents prior to the construction of the pyrrolo[2,3-*c*]carbazole core. We envisaged that the development of a diversity-oriented synthesis for the construction of these natural products on the basis of the early-stage construction of the core structure, followed by the introduction of the different substituents, would be more amenable to medicinal applications.

We recently reported a gold-catalyzed annulation of conjugated diynes and pyrroles for the synthesis of 4,7-disubstituted indoles (Scheme 2 A).[10] This reaction proceeds through a double hydroarylation cascade involving two alkynes to form a disubstituted benzene ring. We envisaged that this reaction could be combined with gold carbenoid chemistry[11] to provide a useful method for the direct construction of the core structure of dictyodendrins. Our original hypothesis is shown in Scheme 2 B: The conjugated diyne **10** bearing an azido group would generate a gold carbenoid species **A** through the gold-mediated nucleophilic attack of the azide moiety on the activated alkyne, followed by the elimination of nitrogen.[12] Subsequent arylation of the carbenoid at the 3- or 2-position of pyrrole **11** would lead to the formation of pyrrole-substituted 2-alkynylindole intermediates **B** and **C**, respectively. A subsequent 6-*endo-dig* intramolecular hydroarylation would produce the pyrrolo-[2,3-*c*]carbazole and pyrrolo[3,2-*c*]carbazole derivatives **12** and **13**, respectively. However, the efficient construction of the dictyodendrin core structure would be dependent on controlling the regioselectivity (i.e., C2 vs. C3) of the arylation step. We anticipated that the desired C3-selective arylation could be promoted by tuning the nature of the protecting groups on the substrates.

Our retrosynthetic analysis of the dictyodendrins on the basis of the proposed novel gold-catalyzed annulation is

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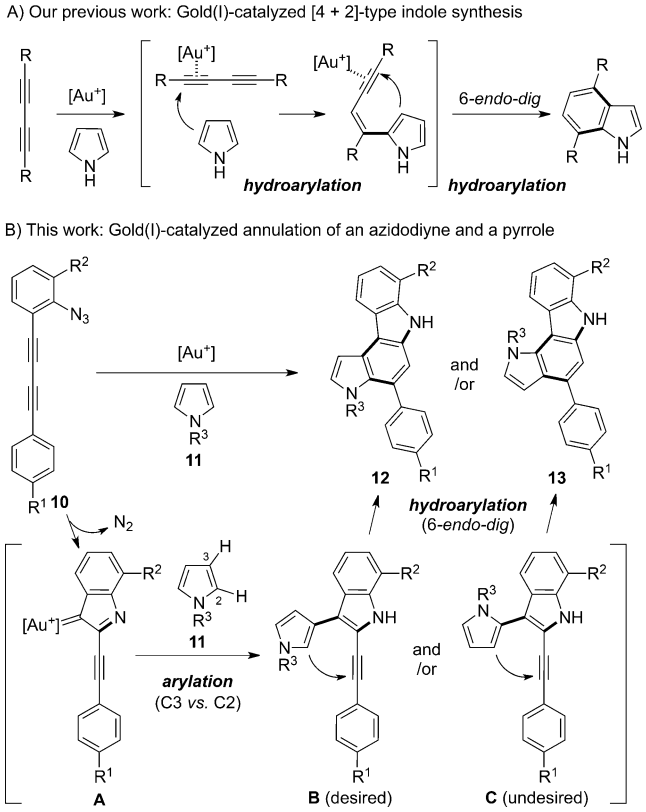
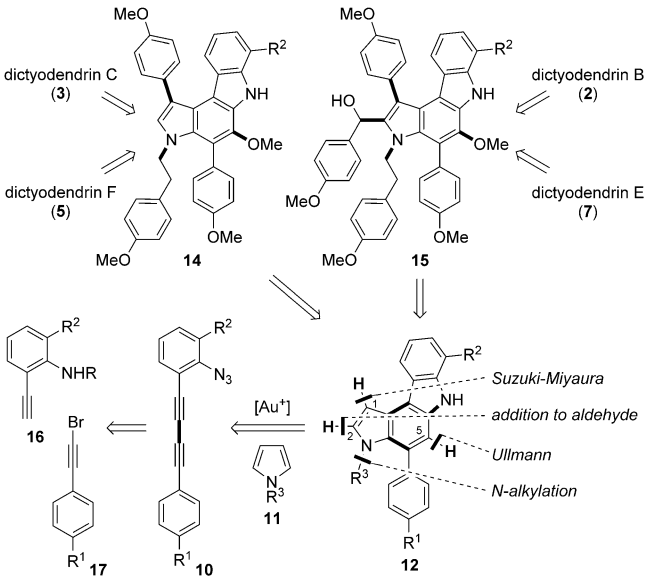
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201703279.



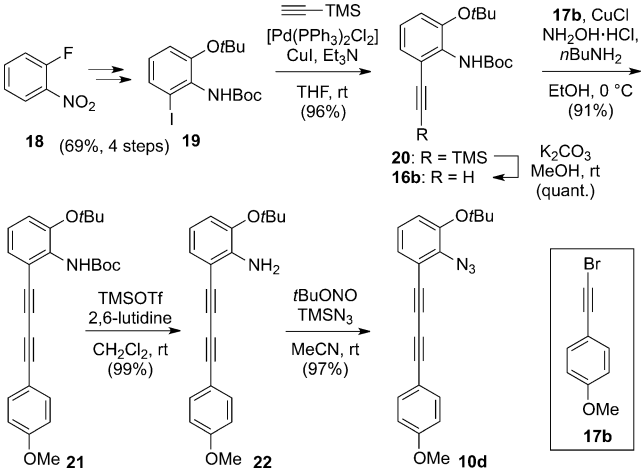
Scheme 2. Our strategy for the construction of the pyrrolo[2,3-*c*]carbazole core structure.

shown in Scheme 3. The known precursor **14** of dictyodendrins C (**3**) and F (**5**) could be prepared by the sequential functionalization of pyrrolo[2,3-*c*]carbazole **12** at the C1, N3, and C5 positions through Suzuki–Miyaura coupling, N-alkylation, and Ullmann coupling reactions,[7] respectively, after bromination when necessary. The synthesis of intermediate **15** for dictyodendrins B (**2**) and E (**7**) would require the introduction of the C2 substituent, which would be possible by a bromination–metalation sequence, followed by addition to *p*-anisaldehyde.[3] The conjugated diyne **10** required for the gold-catalyzed [4+2] annulation could be readily prepared by the Cadiot–Chodkiewicz coupling reaction[13] of alkynes **16** and **17**. The success of this strategy would depend on the selective functionalization of the pyrrolo[2,3-*c*]carbazole **12**, as well as regiocontrol of the gold-catalyzed annulation. Herein, we disclose a new method for the total/formal synthesis of dictyodendrins B, C, E, and F on the basis of the regioselective gold-catalyzed direct construction of their pyrrolo[2,3-*c*]carbazole core structure.



Scheme 3. Retrosynthetic analysis of dictyodendrins.

The route used for the preparation of the azido-substituted conjugated diyne **10d** is shown in Scheme 4. The

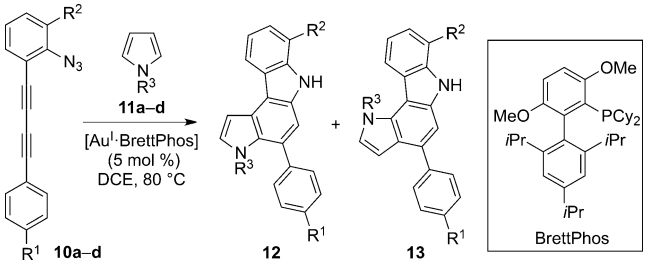


Scheme 4. Synthesis of azidodiyne **10d**. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

protected 2-amino-3-iodophenol **19** was prepared from 1-fluoro-2-nitrobenzene (**18**) in four steps (i.e., *tert*-butoxylation, reduction, N-protection, and iodination) according to a reported procedure.[5] The subsequent Sonogashira coupling of **19** with trimethylsilylacetylene, followed by desilylation of the coupling product with K_2CO_3 and methanol, afforded the corresponding terminal alkyne **16b** in quantitative yield.[14] Cadiot–Chodkiewicz coupling[13a] between **16b** and bromoalkyne **17b**[15] afforded the corresponding conjugated diyne **21**. Treatment with TMSOTf and 2,6-lutidine[16] led to selective removal of the Boc protecting group, and the resulting aniline **22** was then treated with *t*BuONO and $TMSN_3$ to give the corresponding azido alkyne **10d** in 87% yield over three steps from **16b**.[17] Several other conjugated diynes were prepared either in a similar manner (for **10a**) or by the derivatization of the conjugated diyne **21** (for **10b**,**c**; see the Supporting information).

We then examined the gold-catalyzed annulation of different substrates (Table 1). The treatment of conjugated diyne **10a** and unprotected pyrrole (**11a**) as model substrates with [BrettPhosAu(MeCN)SbF_6] resulted in complete consumption of the starting materials and the formation of an isomeric mixture of the two possible annulation products

Table 1: Optimization of the gold-catalyzed annulation of 1,3-diynes and pyrroles.[a]



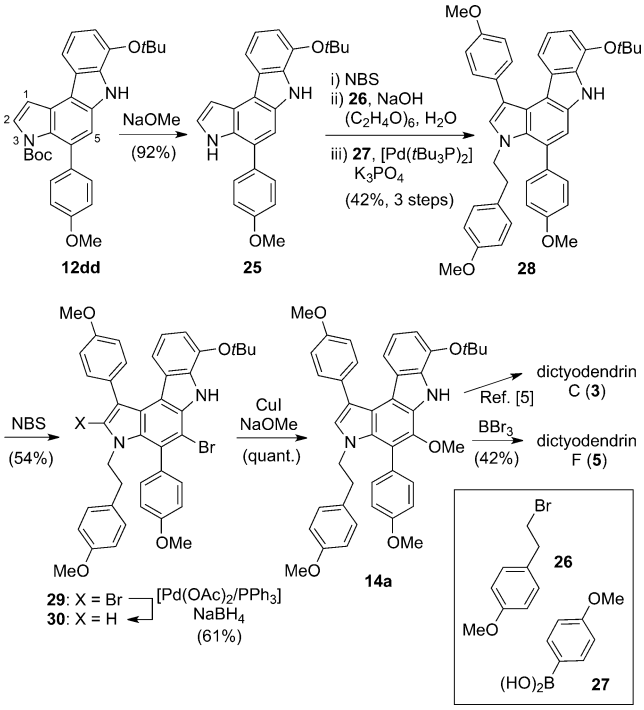
Entry	10	R^1	R^2	11	R^3	Yield[b] [%]	12/13[c]
1	**10a**	H	H	**11a**	H	< 62	25:75 (**aa**)
2	**10a**	H	H	**11b**	Bn	62	18:82 (**ab**)
3[d]	**10a**	H	H	**11c**	Ts	34	58:42 (**ac**)
4	**10a**	H	H	**11d**	Boc	60	92:8 (**ad**)
5	**10b**	OMe	OMs	**11d**	Boc	83	75:25 (**bd**)
6[e]	**10c**	OMe	OBn	**11d**	Boc	68	81:19 (**cd**)
7[e]	**10d**	OMe	O*t*Bu	**11d**	Boc	79	84:16 (**dd**)

[a] Reaction conditions: **10** (1 equiv), **11** (5 equiv), [BrettPhosAu(MeCN)SbF_6] (5 mol%), 1,2-dichloroethane (DCE), 80°C. [b] Combined yield of the isolated products. [c] Ratio was determined by ^{1}H NMR spectroscopy. [d] The reaction was carried out with [BrettPhosAu(MeCN)SbF_6] (10 mol%) in 1,1,2,2-tetrachloroethane (TCE) at 140°C. [e] When the catalyst loading was decreased to 2 mol%, slightly lower yields were observed (47% yield for **12cd**; 58% yield for **12dd**). Bn = benzyl, Cy = cyclohexyl, Ms = methanesulfonyl (mesyl), Ts = toluenesulfonyl (tosyl).

12aa and **13aa** in around 62% yield, along with several minor impurities. Unfortunately, however, detailed spectroscopic analysis of the separated isomers, including NOE, HMBC, and HMQC experiments, revealed that the undesired isomer **13aa** was obtained as the major product (**12**/**13** 25:75; Table 1, entry 1). This result was attributed to the higher reactivity of the C2 position of pyrrole (**11a**) towards arylation relative to the C3 position.[11c]

Considering that the regioselectivity of gold-carbenoid-mediated reactions can be influenced by steric and electronic factors,[12b] we subsequently evaluated the impact of adding different substituents to the pyrrole nitrogen atom. Among pyrroles **11b–d** bearing a benzyl, tosyl, or Boc protecting group (Table 1, entries 2–4), Boc derivative **11d** showed the highest regioselectivity for the desired isomer **12ad** (**12**/**13** 92:8; entry 4). This result could be attributed in part to the steric bulk of the Boc group, thus leading to a decrease in the reactivity of the neighboring 2-position. The introduction of the oxygen functional groups required for the synthesis of dictyodendrin had a noticeable impact on the outcome of the annulation reaction. For example, the reaction of **10b** bearing methoxy and mesyloxy groups (as R^1 and R^2, respectively) with **11d** delivered the annulation products with relatively low regioselectivity (**12**/**13** 75:25; entry 5), although we did observe an increase in the combined yield to 83%. Fortunately, the reactions of alkyl ether derivatives **10c** (R^2 = OBn) and **10d** (R^2 = O*t*Bu) showed better regioselectivity (**12**/**13** 81:19 and 84:19) and good yields (68 and 79%). We subsequently decided to use the annulation product **12dd** (entry 7) for the total synthesis of dictyodendrins, on the basis of the efficacy of the annulation reaction as well as the facile removal of the *tert*-butyl group. Thus, the reaction was conducted on a gram scale (**10d**: 2.76 g; **11d**: 6.69 g) with a decreased amount of the catalyst (162 mg, 2 mol%), and product **12dd** (2.27 g) was isolated in 58% yield.[19]

Having successfully constructed the pyrrolo[2,3-*c*]carbazole core, we proceeded to investigate the total synthesis of dictyodendrins C and F (Scheme 5), which are 2,5-dioxo



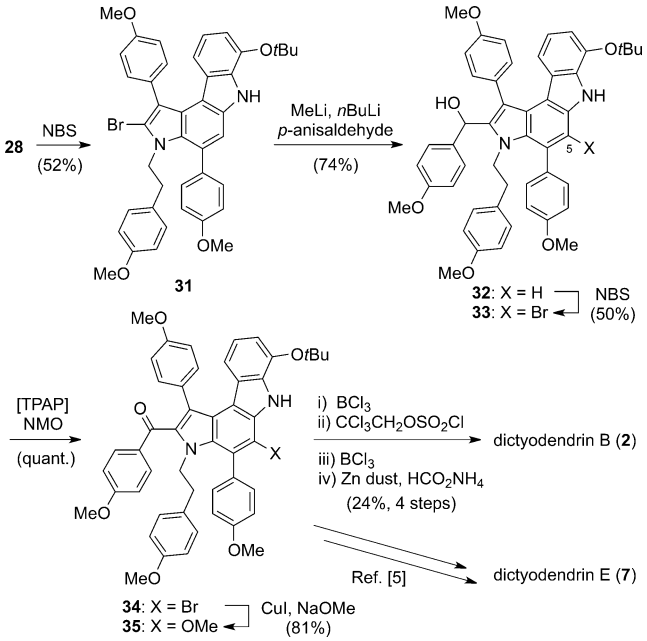
Scheme 5. Total synthesis of dictyodendrins C and F.

congeners with an oxidized core structure (Scheme 1). Our first attempt at the direct introduction of the C1 aryl group into **12dd** by C–H arylation[18] led only to the recovery of the staring material or the formation of a complex mixture. To increase the reactivity of the pyrrole ring, we removed the Boc group with NaOMe to give **25**. Although the C–H arylation of **25** was also unsuccessful, bromination proceeded smoothly with *N*-bromosuccinimide (NBS; 1.05 equiv) to give the desired C1-brominated product. However, this material decomposed during the evaporation of the reaction solvent, and was therefore subjected to a one-pot C1-bromination/N-alkylation sequence, followed by a Suzuki–Miyaura coupling reaction. We screened various conditions for the N-alkylation reaction (i.e., the electrophile, the base, the temperature, the solvent, and the use of additives) and found that the treatment of the C1-brominated material with alkyl bromide **26** and NaOH in the presence of H_2O and 18-crown-6 in THF[20] afforded the desired 1,3-disubstituted product **28** after a Suzuki–Miyaura coupling reaction.[8]

Our final challenge for the total synthesis of dictyodendrins C and F was the introduction of a methoxy group at the less reactive C5 position. After several failed attempts at the borylation[21] or lithiation[22] of the C5 position, we successfully introduced a methoxy group through a dibromination–

debromination sequence. This process involved the reaction of **28** with NBS (2.05 equiv) to afford the dibromination product **29** in 54% yield. The subsequent regioselective debromination of **29** with $NaBH_4$ in the presence of a catalytic amount of $Pd(OAc)_2$ afforded the desired monobromide **30**.[23] Finally, the Ullmann coupling of **30** with NaOMe in the presence of CuI afforded the known precursor **14a**,[5] which can be converted into dictyodendrin C in a three-step sequence as reported by Tokuyama and co-workers. We also completed the total synthesis of dictyodendrin F by the deprotection of **14a** with BBr_3 and cyclohexene, followed by aerobic oxidation.[3]

We then focused on the total synthesis of dictyodendrins B and E (Scheme 6), which required the introduction of a C2 acyl group. Compound **28** was subjected to a regioselective monobromination with NBS (1.05 equiv) to give **31**, which underwent bromine–lithium exchange followed by addition to *p*-anisaldehyde to give the corresponding C2-substituted product **32** in 74% yield.[3] Selective monobromination of the C5 position proceeded smoothly in this case to furnish **33** in 50% yield. The Ley–Griffith oxidation of **33** with TPAP and NMO, followed by the introduction of a methoxy group at the C5 position under the Ullmann coupling conditions described above, led to the known precursor **35**. This material could be converted into dictyodendrin E by deprotection and construction of the sulfate moiety.[5] We also completed the total synthesis of dictyodendrin B (**2**) by selective removal of the *tert*-butyl group with BCl_3 (−78 °C), formation of a sulfate, and deprotection with BCl_3 (0 °C→rt) and Zn dust, according to the protocol of Tokuyama and co-workers.[5]



Scheme 6. Total synthesis of dictyodendrins B and E. NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

In conclusion, we have completed total syntheses of dictyodendrins B, C (formal), E (formal), and F on the basis of a novel gold-catalyzed method for the direct construction of the pyrrolo[2,3-*c*]carbazole core structure of these compounds. This new strategy involves the early-stage construction of the pyrrolo[2,3-*c*]carbazole under gold catalysis prior to the introduction of the substituents at the C1, C2, N3, and C5 positions. This synthetic route could be used for the diversity-oriented synthesis of dictyodendrin derivatives for medicinal applications.

Acknowledgements

This research was supported by the JSPS KAKENHI (grant numbers JP15KT0061 and JP24689001), the Platform Project for Supporting Drug Discovery and Life Science Research from the Japan Agency for Medical Research and Development (AMED), and the Astellas Foundation for Research on Metabolic Disorders. J.M. is grateful for a Nagai Memorial Research Scholarship from the Pharmaceutical Society of Japan.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cascade reactions · diynes · gold · pyrrolocarbazoles · total synthesis

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Manuscript received: March 29, 2017
Version of record online: ■■ ■■, ■■■■

Communications

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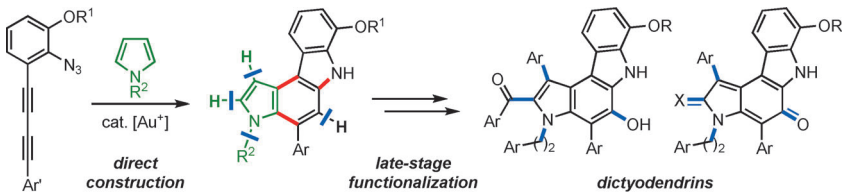

Why settle for one? In total and formal syntheses of dictyodendrins B, C, E, and F, the key step was the direct construction of the tetracyclic pyrrolo[2,3-*c*]carbazole core by the gold-catalyzed annulation of a conjugated diyne with a pyrrole (see scheme). This synthetic route could be used for the diversity-oriented synthesis of dictyodendrin derivatives for medicinal applications.