

Concise Syntheses of Dictyodendrins A and F by a Sequential C–H Functionalization Strategy

Atsushi D. Yamaguchi,^{†,⊥} Kathryn M. Chepiga,^{‡,⊥} Junichiro Yamaguchi,^{*,†} Kenichiro Itami,^{*,†,§,||} and Huw M. L. Davies^{*,‡}

[†]Department of Chemistry, Graduate School of Science, [§]Institute of Transformative Bio-Molecules (WPI-ITbM), and ^{||}JST, ERATO, Itami Molecular Nanocarbon Project, Nagoya University, Chikusa, Nagoya 464-8602, Japan

[‡]Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States

Supporting Information

ABSTRACT: Syntheses of dictyodendrins A and F have been achieved using a sequential C–H functionalization strategy. The *N*-alkylpyrrole core is fully functionalized by means of a rhodium(I)-catalyzed C–H arylation at the C3-position, a rhodium(II)-catalyzed double C–H insertion at the C2- and C5-positions, and a Suzuki–Miyaura cross-coupling reaction at the C4-position. The syntheses of dictyodendrins A and F were completed by formal 6 π -electrocyclization to generate the pyrrolo[2,3-*c*]carbazole core of the natural products.

Since their isolation in 2003 by Fusetani and Matsunaga,¹ dictyodendrins A–E have drawn the interest of the scientific community due to their unique potential for cancer chemotherapy by telomerase inhibition.² Recently, dictyodendrins F–J have also been isolated, which show a potent inhibitory activity for β -site amyloid-cleaving enzyme 1 (BACE) (Figure 1A).³ In addition to these significant biological activities, their common structural feature, consisting of a highly substituted pyrrolo[2,3-*c*]carbazole core,⁴ has attracted the attention of synthetic organic chemists. In 2005 and 2006, the first total syntheses of dictyodendrins B, C, and E were achieved by Fürstner,⁵ followed by the syntheses of Iwao and Ishibashi,⁶ Tokuyama⁷ and more recently, Jia.⁸ To date, however, there has only been one report of the synthesis of dictyodendrin A (1)⁷ and dictyodendrin F (5).⁵ Although Tokuyama's synthetic route was flexible enabling the synthesis of dictyodendrins A–E, the synthesis of 1 took 21 linear steps in total.

We planned a streamlined synthetic route to the dictyodendrins by sequential C–H functionalizations (Figure 1B). Thus, it was envisioned that the dictyodendrins would be derived from the fully functionalized pyrrole, which in turn would be derived from an *N*-alkylpyrrole. The conversion of the simple *N*-alkylpyrrole to the fully functionalized pyrrole would use C3-selective C–H arylation with iodoanisole, double C–H insertion with an α -aryldiazoester, and Suzuki–Miyaura coupling with an indole-3-boronate. The general strategy would be to generate complexity by means of a logical series of C–H functionalization methods.^{9–11} Herein, we report concise syntheses of dictyodendrins A and F through a sequential C–H functionalization strategy.

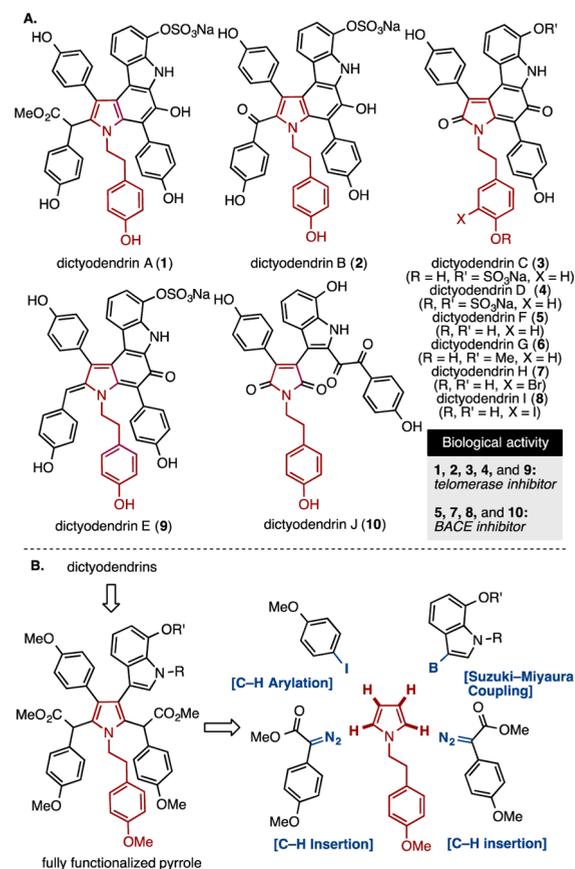


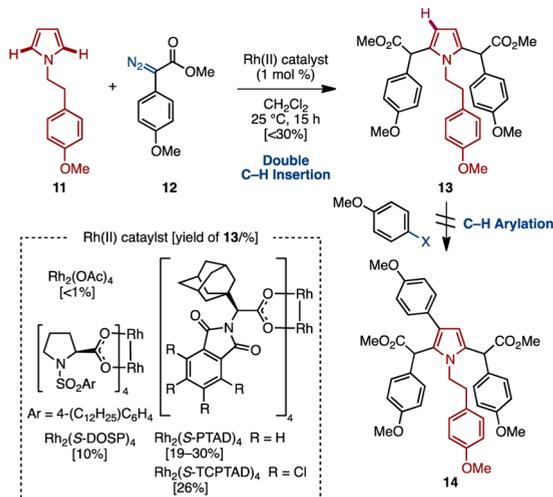
Figure 1. (A) The dictyodendrin family of marine alkaloids. (B) Retrosynthetic analysis of the dictyodendrins.

To achieve a rapid synthesis of the dictyodendrins, enhancing reactivity and controlling regioselectivity in each coupling reaction are the most critical issues. At the outset of this project, the optimal sequence of the C–H functionalization events needed to be determined. Initially, we explored the option of conducting the double carbenoid C–H insertion of *N*-alkylpyrrole 11 with aryldiazoacetate 12, followed by the C–H arylation at the C3 position of thus-generated 13 (Scheme

Received: November 25, 2014

1). While $\text{Rh}_2(\text{OAc})_4$ showed no catalytic activity in the reaction of **11** and **12**, $\text{Rh}_2(\text{S-DOSP})_4$ provided the desired 2,5-

Scheme 1. Initial Approach to Synthesize the Dictyodendrins

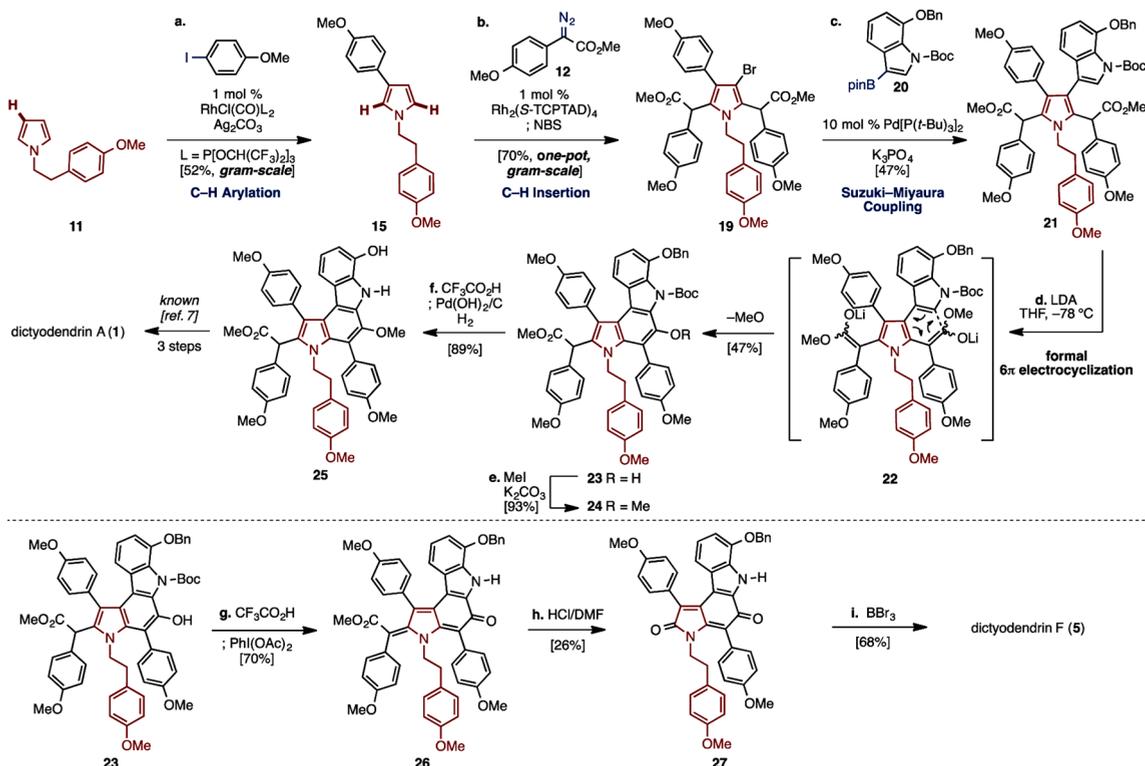


difunctionalized product **13** in 10% yield together with inseparable 3,4-difunctionalized isomer. $\text{Rh}_2(\text{S-TCPTAD})_4$ gave the highest, yet still low yield of **13** (<30% yield).¹² In addition to the low reaction efficiency of the double C-H

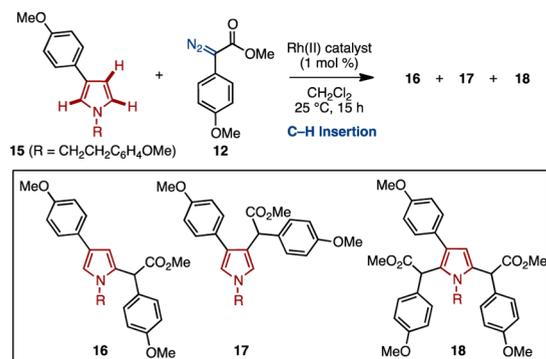
insertion, unfortunately, the subsequent C-H arylation of **13** to furnish the corresponding coupling product **14** did not proceed in this relatively crowded system. Therefore, we next chose to focus on a synthetic sequence that began with the C3 arylation of pyrrole **11**.

We have already reported the β -arylation of pyrroles using $\text{RhCl}(\text{CO})\{\text{P}[\text{OCH}(\text{CF}_3)_2]_3\}_2$, a strongly electrophilic rhodium(I) catalyst.^{11,13} Using this catalytic system, 3-arylpyrrole **15** was obtained from **11** in a regioselective manner (see details in Scheme 2). The next proposed step was the C-H insertion (alkylation) of pyrrole **15** with aryldiazoacetate **12**. The metal-catalyzed alkylation of pyrroles with diazoacetate derivatives is a well-established process¹⁴ and the 2-alkylation of a 3,4-diarylated *N*-alkylpyrrole with an aryldiazoacetate has been used as a key step in the synthesis of ningalin C.¹⁵ In our case, however, the pyrrole alkylation was expected to be challenging in terms of site selectivity because the substrate **15** contains two electron-rich aromatic rings and activated methylene sites that could be susceptible to C-H insertion. The reaction was examined with a range of dirhodium catalysts, as summarized in Table 1. Neither $\text{Rh}_2(\text{OAc})_4$ nor the most commonly used chiral catalyst for the reaction of aryldiazoacetates, $\text{Rh}_2(\text{S-DOSP})_4$, gave any of the desired alkylation product (entries 1 and 2). Only an inseparable mixture of the C5- and C4-monoalkylated products (**16** and **17**) was obtained when $\text{Rh}_2(\text{esp})_2$, $\text{Rh}_2(\text{S-PTAD})_4$, and $\text{Rh}_2(\text{S-PPTL})_4$ were used

Scheme 2. Formal Synthesis of **1** and Synthesis of **5**



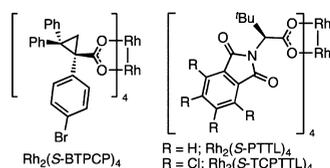
^aReagents and conditions: (a) *p*-methoxyiodobenzene (1.0 equiv), **11** (1.5 equiv), $\text{RhCl}(\text{CO})\{\text{P}[\text{OCH}(\text{CF}_3)_2]_3\}_2$ (1 mol %), Ag_2CO_3 (1.0 equiv), DME (1.0 equiv), *m*-xylene, 150°C , 66 h, 52%; (b) **12** (2.5 equiv), $\text{Rh}_2(\text{S-TCPTAD})_4$ (1 mol %), CH_2Cl_2 , 25°C , 13 h; NBS (1.0 equiv), CH_3CN , -10°C , 5 min, 70%; (c) **20** (4.0 equiv), $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ (10 mol %), K_3PO_4 (4.0 equiv), 1,4-dioxane/ H_2O , 80°C , 15 h, 47%; (d) *n*-BuLi (6.0 equiv), *i*-Pr₂NH (6.0 equiv), THF, -78°C , 47%; (e) MeI (6.0 equiv), K_2CO_3 (6.0 equiv), DMF, rt, 2 h, 93%; (f) $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2$ (1:6), rt, 30 min; $\text{Pd}(\text{OH})_2/\text{C}$ (40 wt %) under H_2 (1 atm), EtOAc, 50°C , 5 h, 89%; (g) $\text{CF}_3\text{CO}_2\text{H}/\text{CH}_2\text{Cl}_2$ (1:6), rt, 30 min; $\text{PhI}(\text{OAc})_2$ (1.5 equiv), CH_2Cl_2 , rt, 20 min, 70%; (h) 4 M HCl/DMF (1:1), 100°C , 2.5 h, 26%; (i) BBr_3 (20 equiv), CH_2Cl_2 , -78°C to rt, 1.5 h, 68%. DME = 1,2-dimethoxyethane, NBS = *N*-bromosuccinimide.

Table 1. Rh-Catalyzed Regioselective C–H Insertion of 3-Arylpyrrole 15^a

entry	Rh(II) catalyst	ratio ^b (16:17:18)	yield of 16 and 17 (%) ^c	yield of 18 (%) ^d
1	Rh ₂ (OAc) ₄	—	<1	—
2	Rh ₂ (S-DOSP) ₄	—	<1	—
3	Rh ₂ (esp) ₂	76/24/<1	53	—
4	Rh ₂ (S-PTAD) ₄	55/45/<1	33	—
5	Rh ₂ (S-PPTL) ₄	61/39/<1	54	—
6	Rh ₂ (S-BTPCP) ₄	53/47/<1	12	—
7	Rh ₂ (S-TCPPTL) ₄	54/46/<1	23	—
8	Rh ₂ (S-TCPTAD) ₄	90/10/<1	36	—
9 ^e	Rh ₂ (S-TCPTAD) ₄	92/8/<1	78	—
10 ^f	Rh ₂ (S-TCPTAD) ₄	<1/7/93	2	30
11 ^g	Rh ₂ (S-TCPTAD) ₄	<1/7/93	2	82

^aReaction conditions: **15** (0.1 mmol), **12** (2.0 equiv), and Rh(II) catalyst (1 mol %) in CH₂Cl₂ (0.05 M), 25 °C, 15 h. ^bDetermined by ¹H NMR. ^cCombined yield of the mixture of **16** and **17**. ^dIsolated yields. ^eRh(II) cat. (0.1 mol %), **15** (3.0 mmol), and **12** (1.3 equiv) were used. ^fRh(II) cat. (2 mol %), **15** (0.1 mmol), **12** (6.0 equiv) were used. ^gRh(II) cat. (1 mol %) and **12** (1.25 equiv) were added initially, but a second portion of Rh(II) cat. (1 mol %) and **12** (1.25 equiv) were added after 8 h.

as the catalyst (entries 3–5). In order to further enhance the regioselectivity between the C5- and C4-positions, sterically more demanding and rigid catalysts including Rh₂(S-BTPCP)₄, Rh₂(S-TCPPTL)₄, and Rh₂(S-TCPTAD)₄ were explored, and we were gratified to observe that the ratio of C5 (**16**) to C4 (**17**) products was improved to 90:10 with the use of Rh₂(S-TCPTAD)₄ (entries 6–8).



Further optimization studies determined that the reaction could be conducted with 0.1 mol % of catalyst to generate the monoalkylated product **16** in 78% yield after scale up (from 0.1 to 3.0 mmol), with reduction of the amount of **12** (from 2.0 to 1.3 equiv; entry 9). Having established the site-selectivity of the monoalkylation, we then explored the possibility of conducting the double C–H alkylation of the pyrrole using excess amounts of **12** (6.0 equiv; entry 10). Although the bis-2,5-alkylation of

pyrroles has not been reported previously, the desired bis-adduct **18** was successfully obtained, albeit in lower yield (36% yield). To our delight, when the two C–H alkylations were carried out sequentially in one pot (addition of 1 mol % of Rh catalyst and 1.25 equiv of diazoester initially, followed by a second addition of 1 mol % of Rh catalyst and 1.25 equiv of diazoester after 8 h), less diazoester was necessary (2.5 equiv in total), and a good isolated yield of **18** was obtained (82% yield, entry 11).¹⁶

Having established the viability of the two C–H functionalization steps, the synthesis of dictyodendrin A was first conducted (Scheme 2). *N*-Alkylpyrrole **11** used in the exploratory studies was readily obtained in 70% yield from dimethoxytetrahydrofuran and the *N*-alkyl amine via a Paal–Knorr synthesis.¹¹ The C3-selective arylation of **11** with 4-iodoanisole successfully afforded the coupling product **15** in greater than 1 g scale. The developed double C–H insertion method was then applied to generate the tetrasubstituted pyrrole, followed by bromination of the remaining C–H bond of the pyrrole in one-pot and gram-scale to generate **19**. Next, Suzuki–Miyaura cross-coupling of **19** with indole-3-boronic acid pinacol ester **20** was carried out. After extensive screening of catalysts and reaction conditions,¹² Pd[P(*t*-Bu)₃]₂ (10 mol %), and K₃PO₄ in 1,4-dioxane/H₂O successfully afforded the corresponding coupling product **21**, albeit in moderate yield (47% isolated yield). Although the desired pentasubstituted pyrrole **21** could seemingly be transformed into the pyrrolo-[2,3-*c*]carbazole core by several methods, e.g., the intramolecular Friedel–Crafts type cyclization was unsuccessful. Surprisingly, treatment of **21** with LDA at –78 °C smoothly generated the pyrrolo[2,3-*c*]carbazole structure **23**, likely through a formal 6π-electrocyclization of dianion intermediate **22** (47% yield), followed by methylation of the resulting phenol (93% yield of **24**). Removal of the Boc group of **24** followed by debenzoylation in one-pot furnished **25**, which is an intermediate from a previous synthesis of dictyodendrin A (**1**).⁷ Therefore, **25** can be converted to **1** by Tokuyama's protocol over three steps.⁷

Treatment of **23**, an intermediate of dictyodendrin A, with CF₃CO₂H (removal of Boc group) and then with PhI(OAc)₂ led to **26**. The oxidized product **26** was easily transformed to dictyodendrin F (**5**) by hydrolysis and deprotection (two steps). This represents an efficient formal synthesis of dictyodendrin A (12 longest linear steps and 15 steps in total including the preparation of **12** and **20**) and the synthesis of dictyodendrin F in a longest linear sequence of 10 steps.

In conclusion, these studies demonstrate opportunities for streamlining total synthesis by using a sequential C–H functionalization strategy. In our studies, we demonstrate the possibility of building a complex structure through sequential C–H functionalization of a pyrrole system. A complementary study by the group of Gaunt illustrates an alternative C–H functionalization strategy to a related alkaloid beginning with an indole framework.¹⁷ The two studies demonstrate the possibilities of developing novel disconnection strategies relying on the logic of C–H functionalization.

■ ASSOCIATED CONTENT

📄 Supporting Information

General experimental procedures, characterization of new compounds, and spectral data is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Authors

junichiro@chem.nagoya-u.ac.jp

itami@chem.nagoya-u.ac.jp

hmdavie@emory.edu

Author Contributions

[†]These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the Funding Program for Next Generation World-Leading Researchers from JSPS (K.I.), a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (25105720 to J.Y.), KAKENHI (25708005 to J.Y.) from MEXT, and NSF under the Science Across Virtual Institutes program as part of the CCI Center for Selective C–H Functionalization, CHE-1205646 (to H.M.L.D. and K.M.C.). ITbM is supported by the World Premier International Research Center (WPI) Initiative, Japan.

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