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

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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 6π-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] Tokuyama[7] 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.

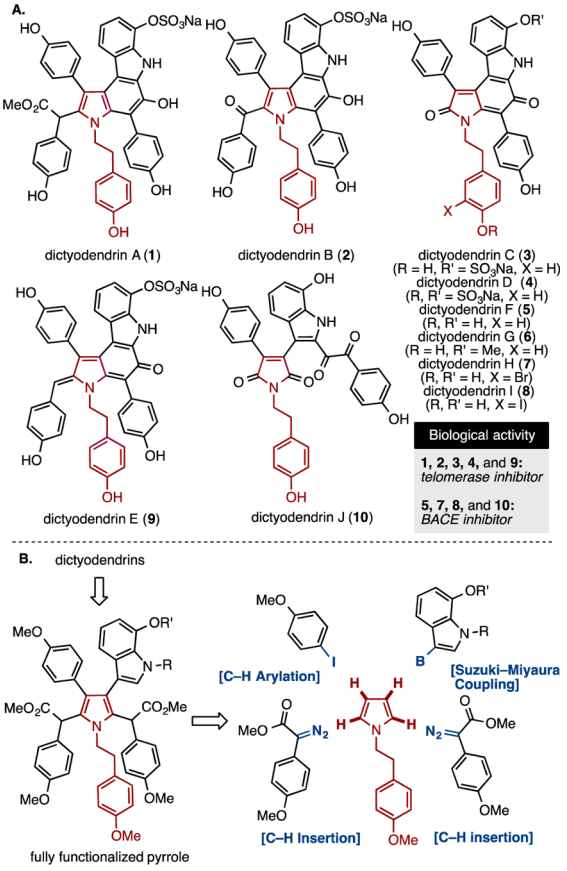

Figure 1. (A) The dictyodendrin family of marine alkaloids. (B) Retrosynthetic analysis of the dictyodendrins.

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

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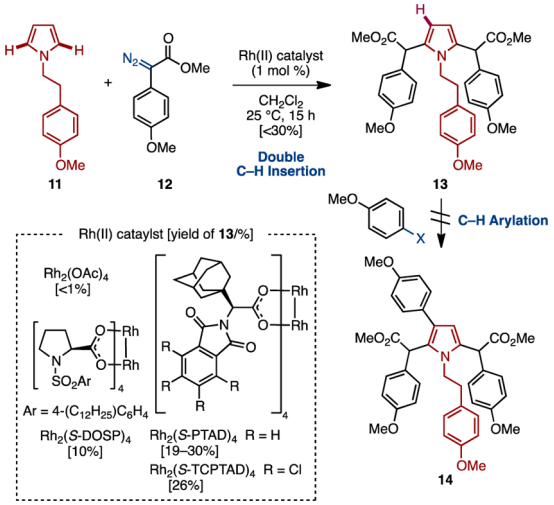
1). While $Rh_2(OAc)_4$ showed no catalytic activity in the reaction of **11** and **12**, $Rh_2(S\text{-DOSP})_4$ provided the desired 2,5-

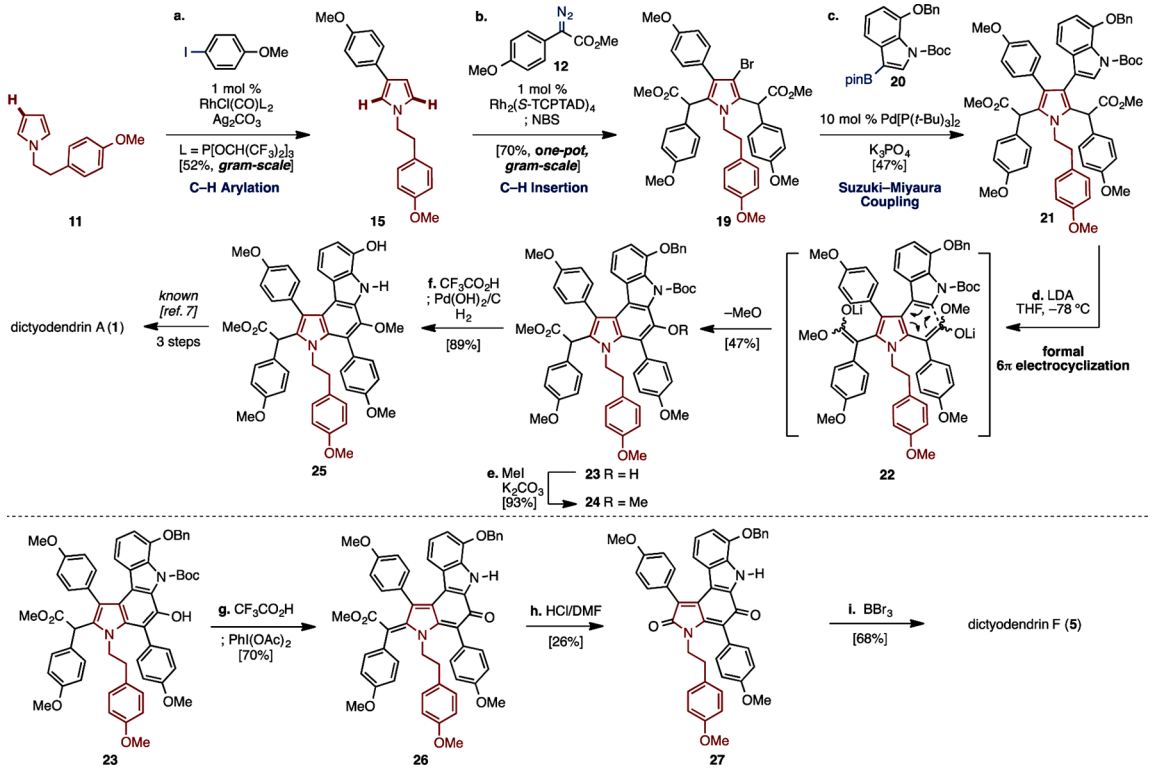
Scheme 1. Initial Approach to Synthesize the Dictyodendrins



difunctionalized product **13** in 10% yield together with inseparable 3,4-difunctionalized isomer. $Rh_2(S\text{-TCPTAD})_4$ 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 $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, 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 process[14] 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 $Rh_2(OAc)_4$ nor the most commonly used chiral catalyst for the reaction of aryldiazoacetates, $Rh_2(S\text{-DOSP})_4$, 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 $Rh_2(esp)_2$, $Rh_2(S\text{-PTAD})_4$, and $Rh_2(S\text{-PPTL})_4$ were used

Scheme 2. Formal Synthesis of 1 and Synthesis of 5



[a]Reagents and conditions: (a) *p*-methoxyiodobenzene (1.0 equiv), **11** (1.5 equiv), $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (1 mol %), Ag_2CO_3 (1.0 equiv), DME (1.0 equiv), *m*-xylene, 150 °C, 66 h, 52%; (b) **12** (2.5 equiv), $Rh_2(S\text{-TCPTAD})_4$ (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), $Pd[P(t\text{-}Bu)_3]_2$ (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*-Pr_2NH (6.0 equiv), THF, −78 °C, 47%; (e) MeI (6.0 equiv), K_2CO_3 (6.0 equiv), DMF, rt, 2 h, 93%; (f) CF_3CO_2H/CH_2Cl_2 (1:6), rt, 30 min; $Pd(OH)_2/C$ (40 wt %) under H_2 (1 atm), EtOAc, 50 °C, 5 h, 89%; (g) CF_3CO_2H/CH_2Cl_2 (1:6), rt, 30 min; $PhI(OAc)_2$ (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.

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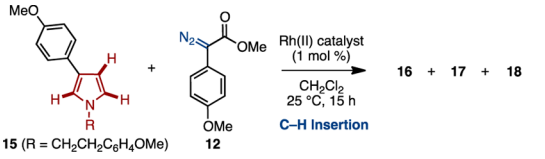
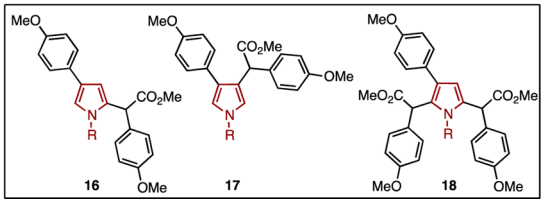
Table 1. Rh-Catalyzed Regioselective C−H Insertion of 3-Arylpyrrole 15[a]

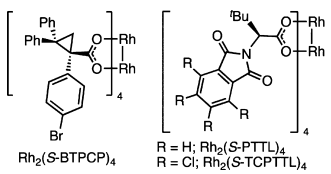




entry	Rh(II) catalyst	ratio[b] (16:17:18)	yield of 16 and 17 (%)[c]	yield of 18 (%)[d]
1	$Rh_2(OAc)_4$	–	<1	–
2	Rh_2(*S*-DOSP)$_4$	–	<1	–
3	$Rh_2(esp)_2$	76/24/<1	53	–
4	Rh_2(*S*-PTAD)$_4$	55/45/<1	33	–
5	Rh_2(*S*-PPTL)$_4$	61/39/<1	54	–
6	Rh_2(*S*-BTPCP)$_4$	53/47/<1	12	–
7	Rh_2(*S*-TCPPTL)$_4$	54/46/<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

[a]Reaction conditions: **15** (0.1 mmol), **12** (2.0 equiv), and Rh(II) catalyst (1 mol %) in CH_2Cl_2 (0.05 M), 25 °C, 15 h. [b]Determined by ^{1}H NMR. [c]Combined yield of the mixture of **16** and **17**. [d]Isolated yields. [e]Rh(II) cat. (0.1 mol %), **15** (3.0 mmol), and **12** (1.3 equiv) were used. [f]Rh(II) cat. (2 mol %), **15** (0.1 mmol), **12** (6.0 equiv) were used. [g]Rh(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 Rh_2(*S*-BTPCP)$_4$, Rh_2(*S*-TCPPTL)$_4$, and Rh_2(*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 Rh_2(*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 K_3PO_4 in 1,4-dioxane/H_2O 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 debenzylation 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 CF_3CO_2H (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.

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Notes

The authors declare no competing financial interest.

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(17) Concurrently with this work, a similar concept was used to achieve a similar target by Gaunt et al.: Pitts, A. K.; Snell, R. H.; O'Hara, F.; Gaunt, M. J. *Abstracts of Papers of the American Chemical Society* **2014**, *248*, 429−ORGN.

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