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A Concise Total Synthesis of Dictyodendrins F, H, and I Using Aryl Ynol Ethers as Key Building Blocks

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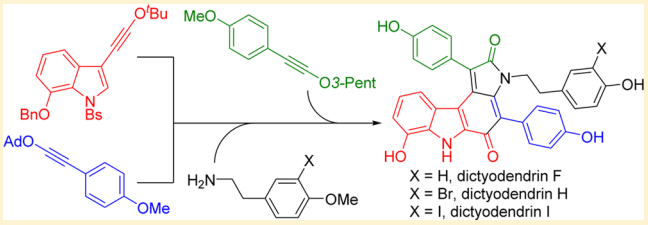
Supporting Information

ABSTRACT: We report a concise total synthesis of dictyodendrin F and the first total syntheses of dictyodendrins H and I in six steps. In these syntheses, aryl ynol ethers were employed as the key building blocks to introduce aryl and heteroaryl rings in the dictyodendrins. This rapid synthesis utilized a novel hetero-[2 + 2]-cycloaddition reaction between two aryl ynol ethers to yield a cyclobutenone ring. The cyclobutenone was sequentially converted into a highly substituted carbazole via a retro-4π/6π-electrocyclization−*N*-acylation cascade reaction to provide the dictyodendrin core. Consecutive intramolecular oxidative coupling and deprotection gave dictyodendrins F, H, and I.



INTRODUCTION

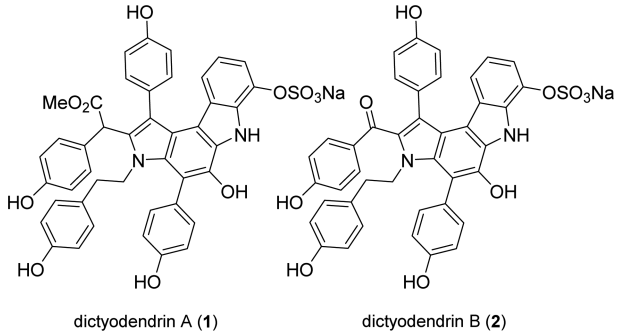
Fusetani and co-workers isolated dictyodendrins A−E from the marine sponge *dictyodendrilla verongiformis* in 2003 in a search for inhibitors of telomerase.[1,2] In 2012, Capon and co-workers discovered dictyodendrins F−J from the *Ianthella sponge* and showed that they were moderately potent inhibitors of β-site amyloid-cleaving enzyme 1 (BACE1),[3] a potential target for treating Alzheimer's disease.[4] Because of their unique structure and intriguing biological activities, the dictyodendrins are popular targets for synthetic chemists. Structurally, dictyodendrins contain a highly substituted pyrrolo[2,3-*c*]carbazole core[5] at the phenol or quinone oxidation state. The Fürstner group reported the first syntheses of dictyodendrins B, C, E, and F (Figure 1, **2**−**5**) in 2005 and 2006. Additionally, they demonstrated the DNA-cleaving activity of dictyodendrins and their analogs.[6] Subsequently, five other groups have disclosed their synthetic strategies toward this natural product family.[5,7] Tokuyama and co-workers developed a general and flexible synthetic approach targeting dictyodendrins A−E, but their synthesis involved 21−22 linear steps.[8] Recently, the development of C−H activation methods has enabled the efficient syntheses of these natural products. Gaunt,[9] Davies,[10] and Jia[11] groups disclosed elegant syntheses of several dictyodendrins using C−H functionalization strategies in 9−13 synthetic steps.[12] Currently, dictyodendrins H and I (Figure 1, **6**, **7**) have not been synthesized. These two dictyodendrins contain a halide on the tyramine side chain, making the use of transition-metal-catalyzed reactions challenging. Additionally, a short, flexible synthesis is still needed to provide access to the dictyodendrins and to allow for further SAR studies. Herein, we present a concise synthetic strategy to access previously inaccessible dictyodendrins.

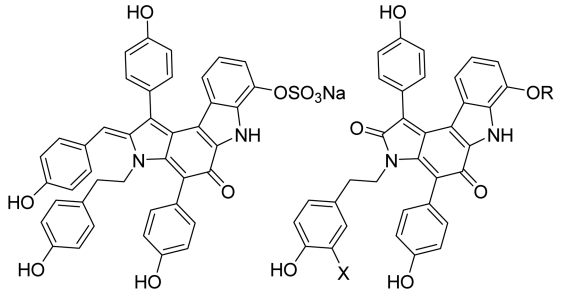
In 2014, we demonstrated that the *tert*-butyl ynol ether **8** could be prepared using a Sonogashira coupling. Upon heating, the ynol ether converted to aryl ketene **9**, which could react with diverse nucleophiles to form the corresponding aryl acetic acid derivatives **10** (Figure 2A).[13] This method allowed for the rapid introduction of a two-carbon motif on the aromatic ring. However, we also noticed the propensity of aryl ketene **9** to undergo a [2 + 2]-cycloaddition reaction with the aryl ynol ether starting material when nucleophilic trapping was slow. This homo-[2 + 2]-cycloaddition gave diarylated cyclobutenone **11**.[14] Upon further heating, cyclobutenone **11** underwent a tandem retro-4π/6π electrocyclization to generate 1,3-dihydroxyl naphthalene **13** in high yield. This transformation is reminiscent of the Danheiser benzannulation, in which vinylated cyclobutenones undergo a retro-4π and subsequent 6π electrocyclization to generate highly substituted aromatic rings.[15] More broadly, 6π electrocyclization has emerged as an efficient method for forming multisubstituted carbazoles.[16] The Li group in particular has constructed the central benzene ring of several natural products using 6π electrocyclization.[17,18] Inspired by this cycloaddition/rearrangement sequence, we hypothesized that a hetero-[2 + 2]-cycloaddition between indole ynol ether **14** and 4-anisolyl ynol ether **15** would allow for a rapid synthesis of the dictyodendrin carbazole core **16** (Figure 2B).

To advance carbazole **16** toward the dictyodendrin F we envisioned replacing the *tert*-butyl ether with the tyramine side chain to give aminocarbazole **17**. A late stage construction of the oxypyrrole ring could involve *N*-acylation followed by an intramolecular oxidative coupling to obtain the desired natural

Received: June 22, 2016
Published: July 29, 2016

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692





Synthetic Steps (L.L.S)

Dictyodendrins	A	B	C	D	E	F	H	I
Furstner		13	10		13	9		
Ishibashi		18						
Tokuyama	21	21	21	21	22			
Jia		9			11			
Davies	12					10		
Guant		13						
this work						6	6	6

Biological activity

dictyodendrin A-E: telomerase inhibitor

dictyodendrin F-J: BACE1 inhibitor

Figure 1. Dictyodendrin family of marine alkaloids and previous synthetic reports of dictyodendrins.

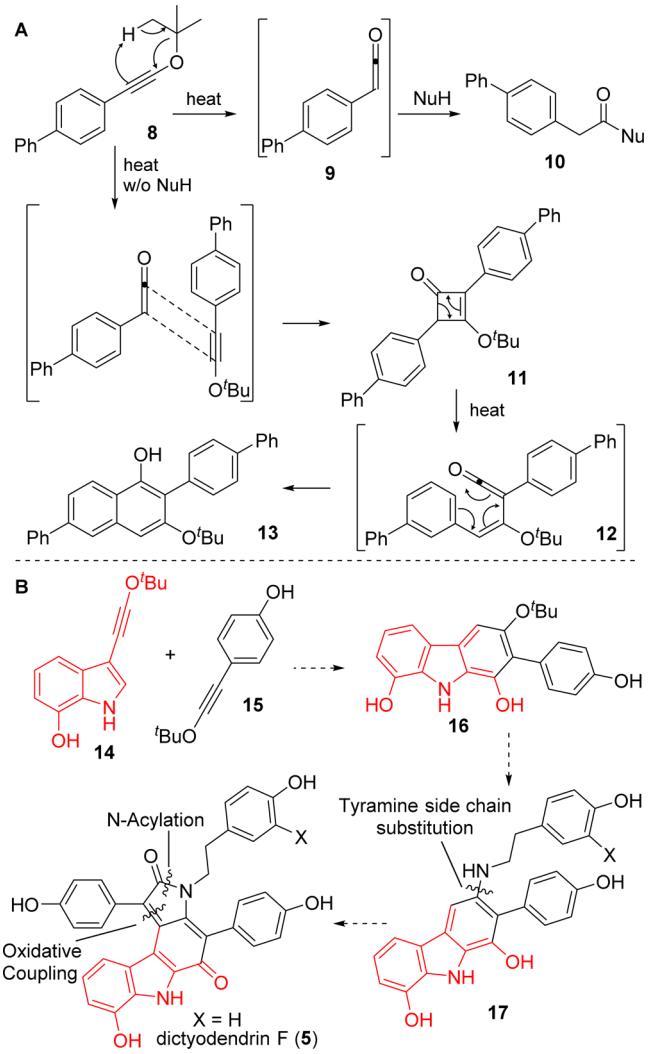


Figure 2. (A) The discovery of homo-[2 + 2] cycloaddition of aryl ynol ethers, followed by a rearrangement to naphthol **13**. (B) The hetero-[2 + 2]-cycloaddition of aryl ynol ethers in the synthesis of dictyodendrins.

product. This new synthetic route is short but flexible, as it also provides access to dictyodendrins H and I with an installation of a halogenated tyramine side chain.

Two challenges needed to be addressed to implement this straightforward synthetic route. First, we needed to develop a hetero-[2 + 2]-cycloaddition reaction between two different aryl ynol ethers with good selectivity. The second challenge would be developing a practical oxidative coupling reaction to afford an oxypyrrole ring. While an oxidative coupling of this type is unprecedented, we reasoned that the electron-rich carbazole **17** could be coaxed to undergo the desired transformation.

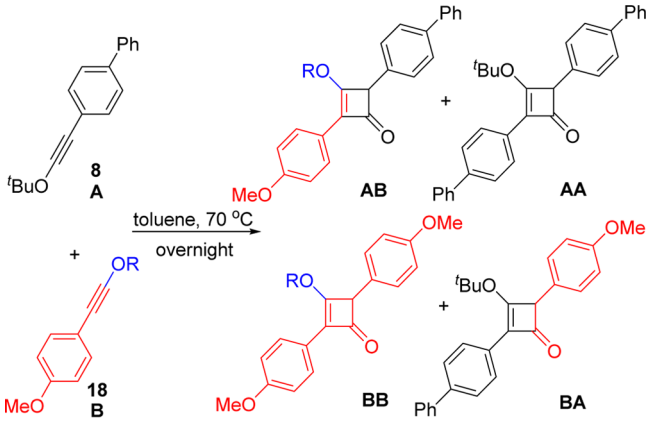
RESULTS AND DISCUSSION

To initiate the synthesis, we first explored the hetero-[2 + 2]-cycloaddition reaction via a model study between two *tert*-butyl ynol ethers (**8** and **18a**) (Table 1). Unfortunately, we observed all four possible cycloaddition products. Changing the equivalents of ynol ether **18a** induced a slight improvement of the selectivity toward the desired heterodimer **AB** (entries 1−3). However, increasing **18a** also introduced more undesired heterodimer **BA** and homodimer **BB**. Since the selectivity was not improved by changing the ratio of the starting materials, we next explored the use of different ynol ethers. In particular, we reasoned that the use of a thermally stable aryl ynol ether would suppress its ketene formation, which should eliminate two undesired products, **BA** and **BB**. With this in mind, we synthesized adamantyl ynol ether **18b** (see below). Its cage structure forbids the 1,5-hydride shift to prevent the generation of a bridge-head double bond. As expected, no aryl ketene was generated when adamantyl ynol ether **18b** was heated at reflux in toluene for several days, and a quantitative recovery of **18b** was possible.

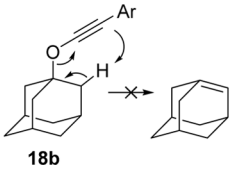
We tested adamantyl ynol ether **18b** in the [2 + 2]-cycloaddition reaction with *tert*-butyl ynol ether **8**. To our delight, a vast improvement for the desired homodimer **AB** was observed with no appreciable amount of products **BB** and **BA**. Further improvement in this reaction was achieved by increasing the amount of ynol ether **18b** (entries 3−6). A 19:1 selectivity of the hetero- versus homocyclization product was obtained when 2.5 equiv of **18b** were used. In this context, the methyl ynol ether would also not undergo the retro-ene reaction to form ketene. However, methyl ynol ethers are much more hydrolytically labile than their bulkier counterparts. Thus, the adamantyl ynol ether appeared to combine stability with the reactivity profile we needed.

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692

Table 1. Model Study of the Hetero-[2 + 2]-Cycloaddition Reaction of Aryl Ynol Ethers

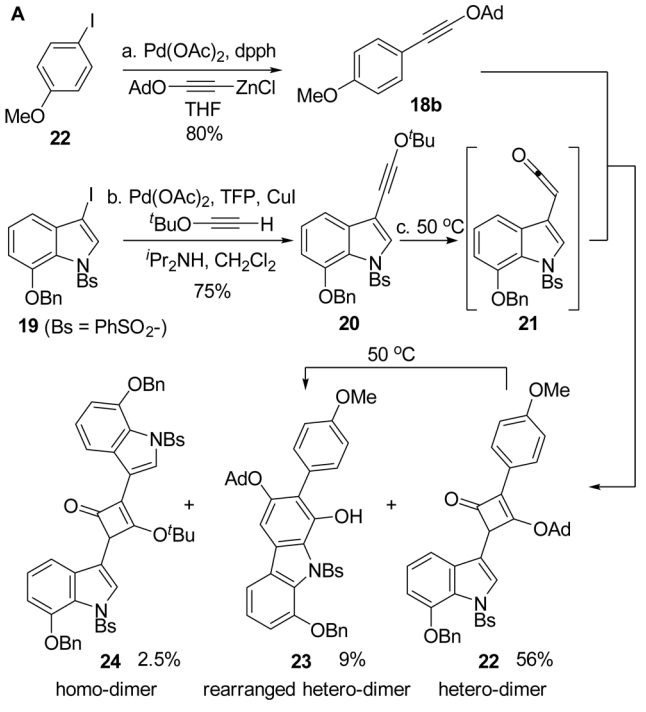


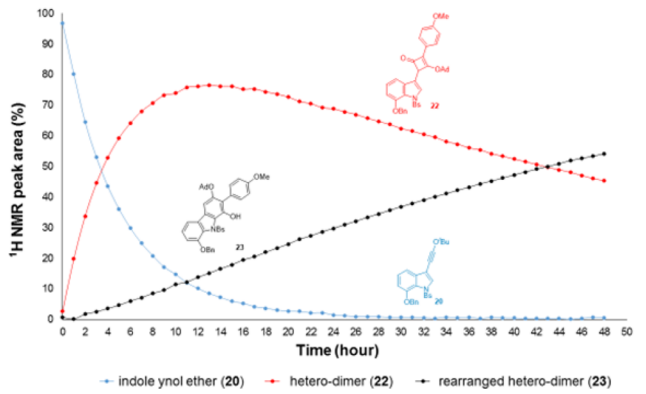
entry	R	equiv B	AB : AA : BB : BA[a]
1	^{t}Bu (**18a**)	0.5	1 : 1 : 0.25 : 0.25
2	^{t}Bu	1.0	4 : 1 : 2.5 : 1
3	^{t}Bu	2.5	5 : 1 : 10 : 1.5
4	Ad (**18b**)	0.5	3 : 1 : NA : NA
5	Ad	1.0	8 : 1 : NA : NA
6[b]	Ad	2.5	19 : 1 : NA : NA



[a]Crude ratio by ^{1}H NMR. [b]69% isolated yield of **AB**.

Scheme 1. Synthesis of the Hetero-[2 + 2]-cycloaddition Product[a]





[a]Reagents and conditions: (a) 1,6-bis(diphenylphosphine)hexane (10 mol %), Pd(OAc)2 (5 mol %), adamantoxylethynyl zinc chloride (1.5 equiv), THF, 23 °C, 4 h, 80%; (b) $Pd(OAc)_2$ (10 mol %), tri(2-furyl)phosphine (20 mol %), CuI (15 mol %), *tert*-butoxylacetylene (10 equiv), diiospropylamine/DCM (1:1), 23 °C, 12 h, 75%; (c) toluene, 50 °C, 9 h, 56% **22** (68% b.r.s.m.).

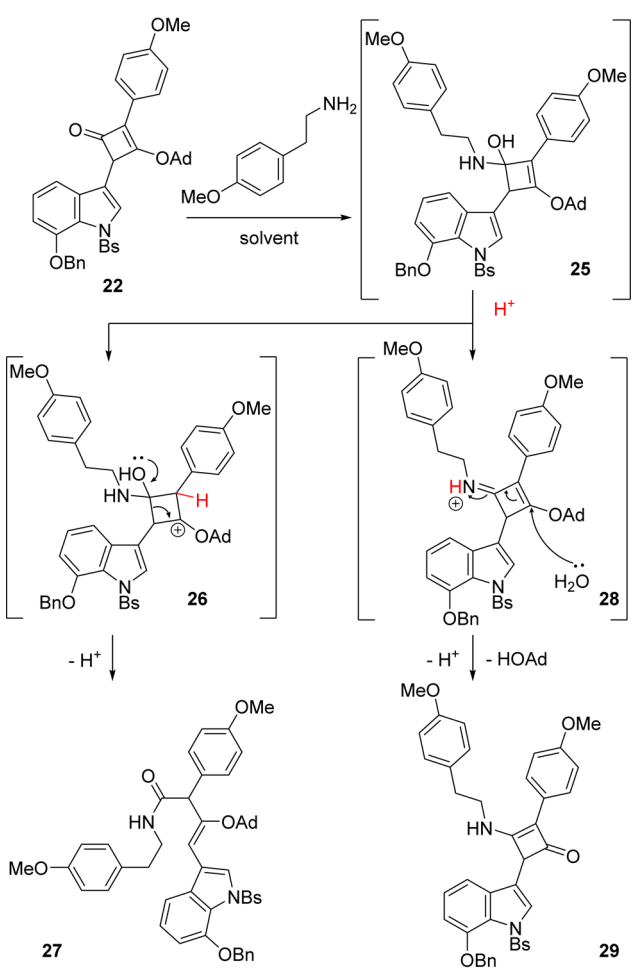
Following the preliminary optimization of the hetero-[2 + 2]-cycloaddition reaction, we next attempted to use this reaction with *tert*-butyl indolyl ynol **20** ether and **18b** to synthesize dictyodendrins. The adamantyl anisolyl ynol ether **18b** was synthesized via a Negishi coupling of adamantoxyethynyl zinc chloride and 4-iodoanisole **22** (Scheme 1). Himbert and Löffler's original protocol for related couplings used PPh_3 as the ligand.[19] In our hands, these conditions resulted in polymerization of the ynol ether. Similarly, in 2014 the Stoltz group disclosed a Negishi coupling between methoxyethynyl zinc chloride and a vinyl iodide; they noted that a xantphos ligand minimized polymerization of the alkyne due to its large bite angle.[20,21] Following their lead, we evaluated chelating diphosphines in the series $Ph_2P-(CH_2)_n-PPh_2$ and found that the yield in the Negishi coupling correlated with the bite angle. Under optimized conditions, 1,6-bis(diphenylphosphine)hexane (dpph) ligand afforded adamantyl anisolyl ynol ether **18b** in 80% yield (Scheme 1A).[22] In parallel, *tert*-butyl indolyl ynol ether **20** was synthesized according to the Sonogashira coupling condition that we reported previously.[13] Dichloromethane was added as cosolvent to improve the solubility of the starting material **19**,[23] and a 75% yield of the benzenesulfonamide (Bs) protected indole **20** was obtained.

With the desired ynol ethers **20** and **18b** in hand, we turned our attention to the key [2 + 2]-cycloaddition reaction. As we established in the model study, heating indolyl *tert*-butyl ynol ether **20** to 50 °C afforded indolyl ketene **21**, which reacted with adamantyl ynol **18b**. The cycloaddition formed the desired product **22** as an 11:1 mixture with homodimer **24**. As expected there was no ketene generated from adamantyl ynol ether **18b**. Interestingly, the protecting group of the indole nitrogen affected the hetero/homo dimer selectivity (**22**:**24**; N-Bs: 11:1; N-Cbz: 7:1; N-Ns: unstable; N-Ts: poor solubility). Moreover, the Bs-protected indole could be synthesized most efficiently among the substrates that we examined.[24]

To our surprise, the desired cyclobutenone **22** spontaneously underwent the retro-4π/6π electrocyclization to yield the *O*-adamantyl carbazole **23** in 50−60% yield after 48 h at 50 °C. In the model study (Table 1), the electrocyclization product was not formed until the reaction was heated over 90 °C for extended times. To take advantage of the unexpected formation of carbazole **23**, we next attempted to introduce the tyramine side chain. Unfortunately, we were unable to displace or remove the adamantyl group successfully. We therefore decided to introduce the tyramine moiety onto the cyclobutenone **22** instead of at the carbazole stage. This idea was inspired by literature precedent from Turnbull and Moore, wherein they replaced a methoxyl group on a cyclobutenone with an aliphatic amine.[15d]

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692

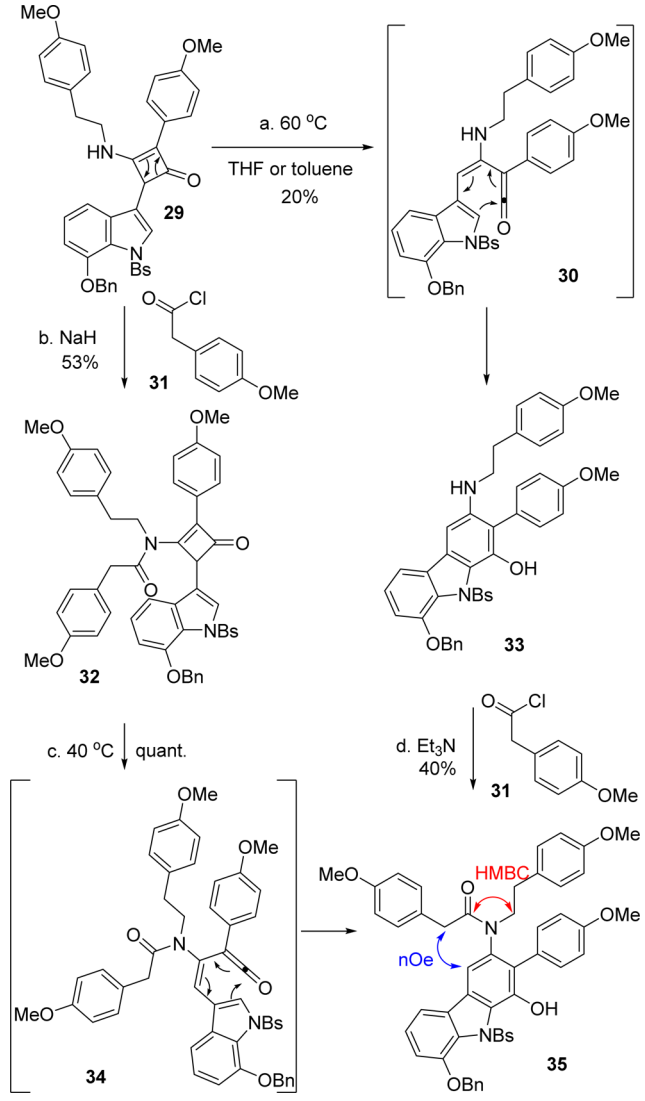
Scheme 2. Synthesis of the Tyramine-Substituted Cyclobutenone[a]



entry[a]	solvent	**29** : **27** : **22** (%)
1[b]	Et_3N	1 : 3 : 94
2[b]	toluene	7 : 26 : 65
3[c]	MeCN	43 : 25 : 18
4[c]	neat	11 : 50 : -
5[c]	DMF	71 : 26 : -
6[c]	DMSO	79 : 14 : -

[a]Reagents and conditions: *O*-methyltyramine (5 equiv), solvent, 36 h, 23 °C. [b]NMR integration ratio. [c]Isolated yields.

Scheme 3. Synthesis of Acylated Carbazole[a]



[a]Reagents and conditions: (a) THF or toluene, 60 °C, overnight, 20%; (b) NaH (1.1 equiv), 4-anisolyl acetic acid chloride (**31**, 1.1 equiv), THF, −78 °C to rt, 3−4 h, 53%; (c) toluene, 40 °C, overnight, quantitative yield; (d) Et_3N (2.0 equiv), 4-anisolyl acetic acid chloride (2.0 equiv), THF, −78 °C to rt, overnight, 40%.

For cyclobutanone **22** to serve as a viable synthetic intermediate, we needed to stop the reaction of ynol ethers **18b** and **20** after [2 + 2]-cycloaddition, but before rearrangement to carbazole **23**. *In situ* ^{1}H NMR was utilized to study the product distribution from this reaction as a function of time (Scheme 1B).[25] Analysis of this experiment showed a quick consumption of *tert*-butyl ynol ether **20** as well as accumulation of the desired cyclobutenone **22** within the first 12 h. Meanwhile, the formation of the undesired carbazole **23** was comparatively slow. Therefore, terminating the cycloaddition after 9 h at 50 °C allowed us to isolate 56% cyclobutenone **22**, 9% carbazole **23**, 2.5% homodimer **24**, and 20% unreacted indolyl ynol ether **20** (Scheme 1B). Resubjection of the unreacted indolyl ynol ether **20** to the reaction conditions afforded a 68% total yield of the desired cyclobutenone **20** and 14% of undesired carbazole **23**.[26]

With access to gram quantities of cyclobutenone **22**, the substitution reaction was then studied. Besides Turnbull and Moore's work,[15d] similar substitution reactions have been extensively studied, wherein different nucleophiles were investigated to replace alkoxyl moieties on cyclobutenediones.[27] Inspired by previous studies, we assumed that *O*-methyltyramine would react with the carbonyl on cyclobutenone **22** to form hemiaminal **25** (Scheme 2). Loss of water would yield the iminium **28**. Substitution with water (shown) or loss of the adamantyl cation (not shown) should furnish the desired cyclobutenone **29**. Performing the reaction in acetonitrile unfortunately led to a substantial amount of undesired ring-open product **27** (Scheme 2, entry 3). The ring-open product **27** presumably arose from hemiaminal intermediate **26** via protonation and fragmentation (Scheme 2). The product distribution was inert to changes in temperature, pH, or

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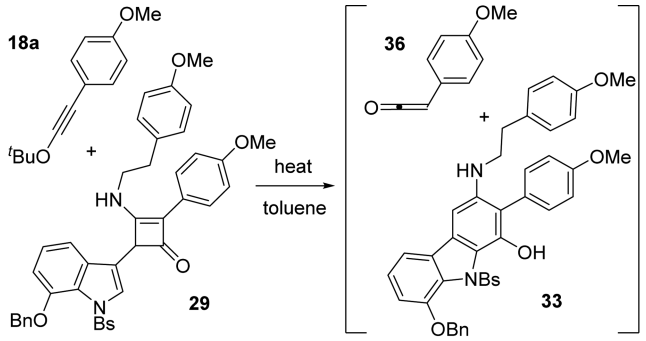


Conditions[a]

Entry	Temp.	Product	Conv.
1	50 °C	27%	40%
2	60 °C	38%	60%
3	70 °C	47%	100%

[a]Reaction conditions: **18a** (5.0 equiv), 12 h, toluene.

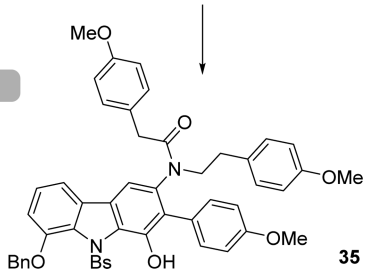


Figure 3. Retro-4π/6π-electrocyclization–acylation cascade reaction.

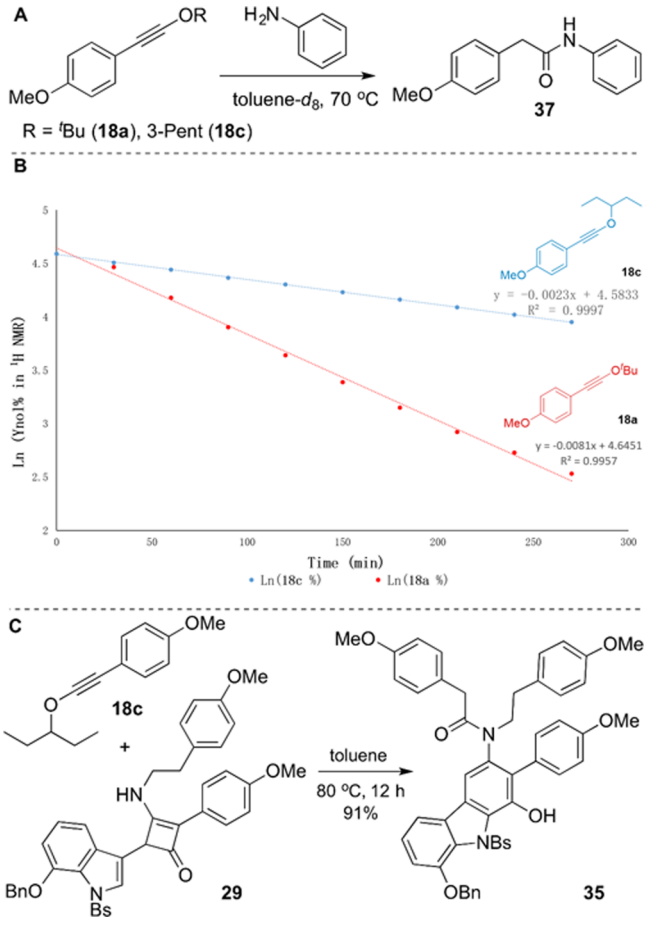


Figure 4. (A) Acylation of aniline using different anisolyl ynol ethers. (B) Reaction rate comparison between **18a** and **18c** based on *in situ* ^{1}H NMR analysis. The slopes of the best-fit lines indicate k_{18a}/k_{18c} = 3.5. (C) The 3-pentyl ynol ether afforded an excellent yield of the retro-4π/6π-electrocyclization–acylation cascade reaction.

concentration, but it displayed a noticeable solvent effect. In nonpolar solvents (such as toluene, entry 2) or amine solvent (such as Et_3N, entry 1), the reaction was slow and favored the ring-open product **27**. Even if cyclobutenone **22** was treated with neat tyramine **25**, we failed to obtain a reasonable yield of the desired product **29**, although starting material was consumed (entry 4). In contrast, highly polar solvents accelerated the reaction and preferentially led to the formation of vinylogous amide **29**. For example, when DMF was the reaction solvent, full conversion of starting material **22** indicated a faster reaction rate, and the desired tyramine-substituted product **29** was isolated in 71% yield (entry 5). Finally, DMSO gave the desired product in the highest yield, 79% (entry 6). Cyclobutenone **29** proved to be light-sensitive, but it could be handled in amber vials and dark fume hoods.

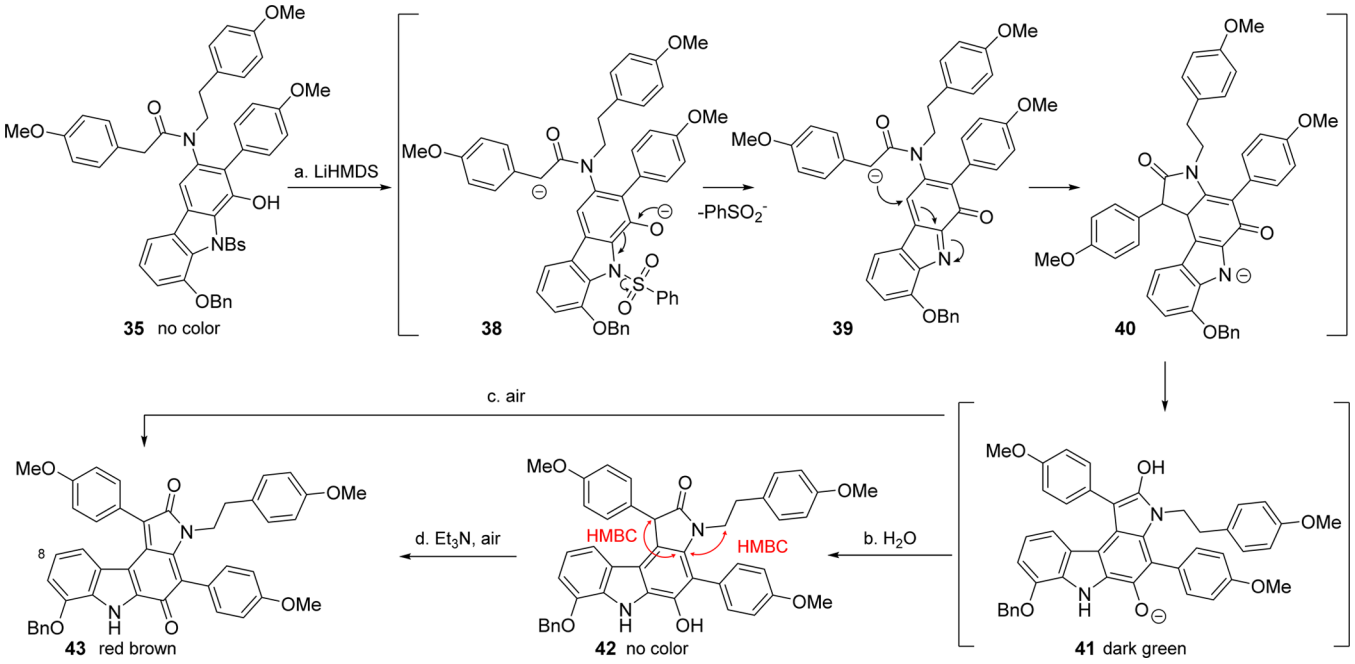
The next step in the synthesis was the retro-4π/6π rearrangement. We first tested this rearrangement by heating cyclobutenone **29** at 60 °C (Scheme 3). A 4π electrocyclic ring opening could generate the conjugated ketene intermediate **30**; subsequent 6π electrocyclization and tautomerization would afford carbazole **33**. However, this substrate generated only a 20% yield of desired product **33** along with numerous unidentified decomposition products. Further study revealed carbazole **33** was prone to aerobic oxidation and was thermally unstable. We hypothesized that the instability of carbazole **33** arose from the electron-rich heteroaromatic ring system. We therefore reasoned that N-acylation might reduce the electron density of carbazole **33**, thereby generating a more stable intermediate. To test this hypothesis, we acylated carbazole **33** using the acid chloride **31** to generate carbazole **35** in 40% yield. The regioselectivity of this acylation was confirmed using HMBC and NOE experiments. As expected, the N-acylated carbazole **35** was much more stable under aerobic and thermal conditions than its N–H counterpart **33**. Given the increased stability of the acylated product, we attempted to avoid isolating the unstable intermediate **33** in order to improve the total yield of the sequence. Thus, cyclobutenone **29** was N-acylated to provide vinylogous imide **32**. Unlike the N-acylation of carbazole **33**, the acylation of cyclobutenone **29** required a strong base, NaH. Moreover, this acylation was messy, only yielding 53% of the desired intermediate **32**. Even though the subsequent electrocyclization gave the carbazole **35** in quantitative yield, the total mass balance for these two steps was disappointing due to the difficult N-acylation.

An alternative solution to address the instability of unacylated carbazole **33** would be to trap it *in situ* in a one-pot electrocyclization/acylation sequence. All efforts to effect this one-pot procedure were in vain using traditional acid chloride/base conditions. The starting material **29** quickly decomposed under thermal conditions in the presence of any base. We therefore turned to chemistry previously developed in our lab using *tert*-butyl ynol ethers as acylating reagents. Heating ynol ethers generates aryl ketenes under neutral conditions. Hence, we carried out a one-pot electrocyclization–acylation reaction with cyclobutenone **29** and 4-anisolyl *tert*-butyl ynol ether **18a** as the acylating reagent (Figure 3). We were pleased to see a 27% yield of the acylated carbazole **35** was obtained with 60% starting material **29** was recovered at 50 °C (40% conversion, entry 1). The mass recovery of this reaction was encouraging, but the low conversion indicated room for improvement.

Initial efforts to optimize this retro-4π/6π-cyclization–acylation cascade reaction focused on increasing the reaction

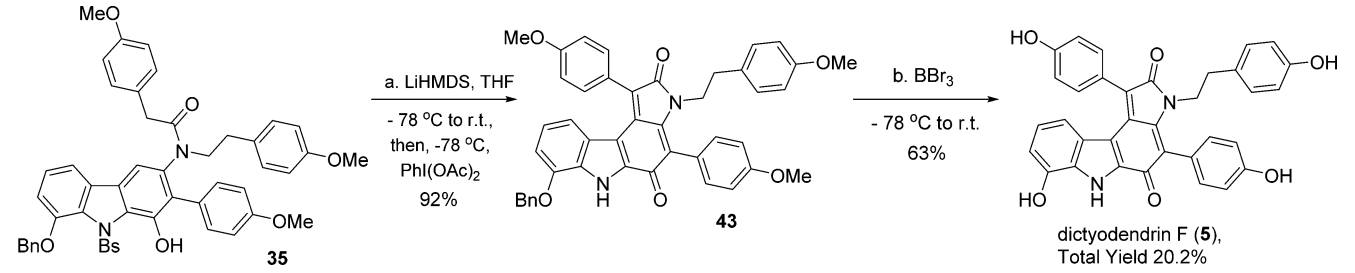
DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684–10692

Scheme 4. Oxidative Cyclization of Anilide 35[a]



[a]Reagents and conditions: (a) LiHMDS (2.1 equiv), THF, −78 °C to rt, 15 min; (b) H_20 (degas), rt, 3 min, 62%; (c) air, rt, 10 min, 67%; (d) Et_3N (5.0 equiv), CH_2CI_2, rt, 1.5 h, quantitative yield.

Scheme 5. Synthesis of Dictyodendrin F[a]



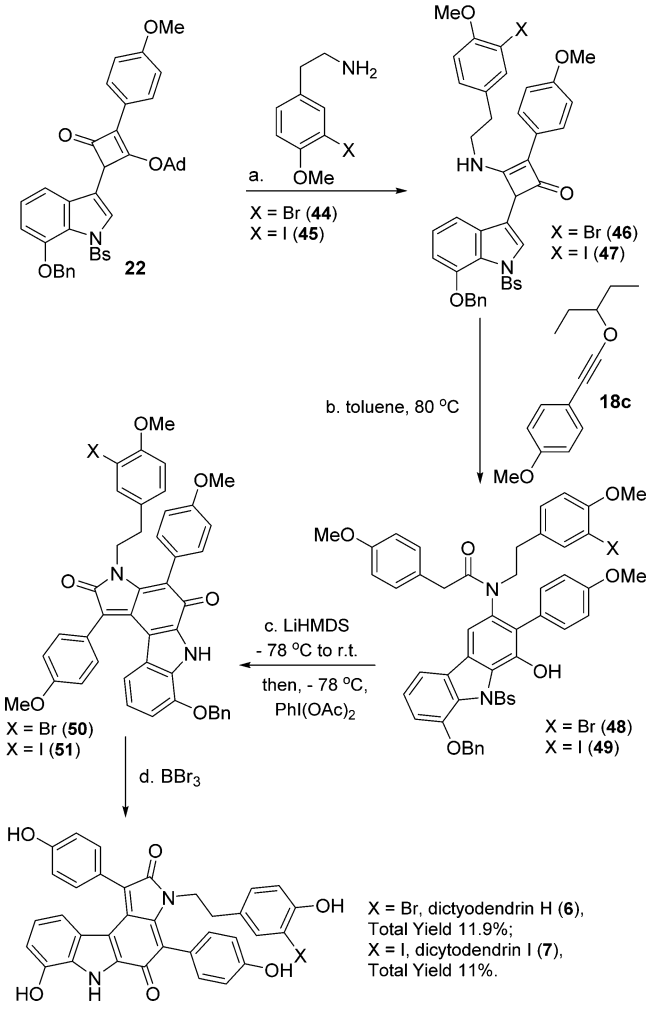
[a]Reagents and conditions: (a) LiHMDS (2.1 equiv), THF, −78 °C to rt, 15 min, then, −78 °C, $PhI(OAc)_2$ (1.0 equiv), 20 min, THF 92%; (b) BBr_3 (100 equiv) CH_2CI_2, −78 °C to rt, overnight, 63%.

temperature to achieve a high conversion. A slight increase in temperature to 60 °C led to a small improvement in yield (38%, Figure 3, entry 2). Unfortunately, the unacylated carbazole **33** was also observed, as well as its decomposition products at this temperature. Increasing the reaction temperature further to 70 °C only gave a 47% yield at 100% conversion (entry 3). Again, we used *in situ* ^{1}H NMR to study this reaction. Unacylated carbazole **33** was present throughout the reaction time course, indicating that the acylation actually occurred on carbazole **33**, not on the cyclobutenone **29**. Moreover we found that the *tert*-butyl ynol ether **18a** was consumed in the first 4 h at 60 °C. These observations indicated that there was insufficient ketene **36** being formed in the later stages of the reaction to trap newly formed carbazole **33**. Accordingly, we next tried a batchwise addition of ynol ether **18a** to introduce aryl ketene **36** slowly, but this attempt to increase the yield had limited success.[28] Batchwise addition of ynol **18a** likely sustained low levels of ketene **36** for a longer time relative to our original reaction conditions, as intended. However, this protocol also increased the chance of introducing oxygen and diluted the reaction medium, both of which were detrimental. We therefore considered alternative approaches to generate aryl ketene **36** more slowly.

We reasoned that the kinetics of ketene generation could be modulated by changing the *tert*-butyl group of the ynol ether, which could allow for extending the release time of aryl ketene **36** during the reaction. Thus, with slower generation, aryl ketene **36** could be available to acylate carbazole **33** throughout the entire 12 h reaction without the need for a slow addition protocol. To identify an appropriate ketene precursor and to quantify the rate of ketene generation, we studied the acylation of aniline (Figure 4A). Tracking these reactions by *in situ* ^{1}H NMR, we could obtain the rate of ketene generation from various anisolyl ynol ethers at 70 °C.[25] The kinetic traces shown in Figure 4B indicated that ketene generation was first order in ynol ether **18**, as expected. The 3-pentyl anisolyl ynol ether **18c** emerged as an ideal aryl ketene precursor. Specifically, 3-pentyl ynol ether **18c** generated ketene **36** approximately one-third as quickly as *tert*-butyl ynol ether **18a**, leading to ketene generation over a longer time period. Ultimately, utilizing 3-pentyl anisolyl ynol ether **18c** as the acylating reagent in the retro-4π/6π-cyclization−acylation

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692

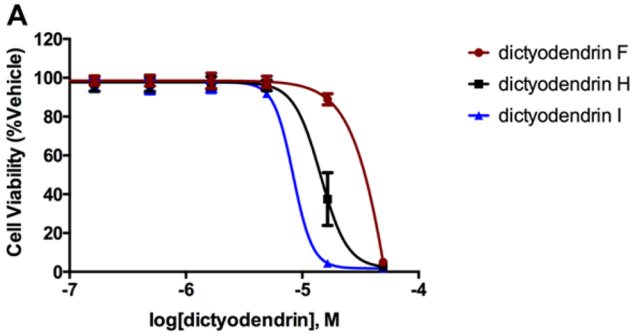
Scheme 6. First Total Synthesis of Dictyodendrins H and I[a]



[a]Reagents and conditions: (a) **44** or **45** (5.0 equiv), DMSO, rt, 24−36 h, 73% for **46** or 66% for **47**; (b) **18c** (5−10 equiv), toluene, 80 °C, 12 h, 75% for **48** or 88% for **49**; (c) LiHMDS (2.1 equiv), THF, −78 °C to rt, 15 min, then, −78 °C, $PhI(OAc)_2$ (1.0 equiv), 20 min, 79% for **50** or 62% for **51**; (d) BBr_3 (100 equiv), CH_2CI_2, −78 °C to rt, overnight, 54% for dictyodendrin H (**6**) or 60% for dictyodendrin I (**7**).

cascade sequence, we obtained the desired N-acylated carbazole product **35** in 91% isolated yield (Figure 4C).

With the acylated carbazole intermediate **35** in hand, we turned our attention to the oxidative coupling reaction to form the desired oxypyrrole ring. Although not totally unprecedented, there are limited reports of analogous intramolecular oxidative couplings between benzyl and aryl carbons. The Baran group demonstrated a series of iron- and copper-mediated intermolecular oxidative couplings between enolates and indoles or pyrroles,[29] but this was limited to electron-rich heterocycles as the oxidative coupling partner. More recently, the Ma group used a diradical intermediate to couple the C3 of an indole and the α-position of an aryl acetamide in their synthesis of communisin F.[30] However, an electron-withdrawing group on the aryl acetamide was required to achieve a good yield for this reaction. Subjecting substrate **35** to Ma's conditions, I_2 and LiHMDS, only resulted in *para*-iodination of the phenol.[31]



B

	HCT116	H157	H2073	H2122
dictyodendrin F	26.98	14.76	>50	>50
dictyodendrin H	13.00	9.57	38.54	28.14
dictyodendrin I	8.78	6.39	35.39	20.22

Figure 5. (A) Cytotoxicity of dictyodendrins against colon cancer cell line HCT116. (B) The IC_{50} values of dictyodendrins (μM) against cancer cell lines.

Fortuitously, we found that the benzenesulfonate protecting group could act as the oxidant in the oxidative cyclization of amide **35** (Scheme 4). In detail, when LiHMDS was added to substrate **35** at −78 °C and warmed to room temperature, the reaction solution changed from colorless to dark green. The reaction mixture subsequently evolved to a red-brown solution from which we isolated the desired oxidative coupling product **43**. To our surprise, the benzenesulfonate group was lost during the reaction. We first excluded air as the oxidant in the reaction by executing a strict degassing protocol. The dramatic color change still occurred, indicating the formation of the large conjugated system in the dictyodendrins' scaffold. Quenching the dark green intermediate **41** with a degassed aqueous solution of $NaHCO_3$ afforded a colorless cyclized product **42** at a phenolic oxidation state in 62% yield.[32] The structure of cyclized product **42** was confirmed through one- and two-dimensional NMR.[33] Intermediate **42** slowly converted into the red-brown quinone **43** in the presence of Et_3N under aerobic conditions. However, injecting a trace amount of air to the dark green anionic intermediate **41** immediately gave the red-brown quinone product **43** in 67% yield.

The rapid aerobic oxidation of intermediate **41** excludes trace oxygen as the oxidant for the first C−C bond-forming step in this sequence (**35** → **41**). In particular, oxidation of **41** is faster than the oxidative cyclization of **35**. For this reason, had trace levels of oxygen been present in the reaction mixture, four-electron oxidation to **35** to quinone **43** would have been observed. In practice, we were able to isolate phenol **42**, the product of a two-electron oxidative cyclization. The oxidative cyclization could use the S−O bond of the benezulfonate as the oxidizing equivalent as illustrated in Scheme 4. Following deprotonation, loss of sulfinate ion $PhSO_2^-$ from carbazole **35** could generate an azaquinone-type intermediate **39**. 5-Exo cyclization of the enolate could form the final C−C bond of the natural product, and tautomerization and protonation could yield the lactam **42**.[34,35] Our final optimized conditions for the oxidative coupling reaction used $PhI(OAc)_2$ as a co-oxidant instead of air to oxidize diphenolic intermediate **41** into the desired quinone **43**, and it gave a 92% yield of the desired product **43** (Scheme 5). This protected form of dictyodendrin

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692

F was previously prepared by the Davies group.[10] Following their prescription, global deprotection gave dictyodendrin F in 63% yield. In summary, we synthesized dictyodendrin F with the longest linear sequence of six operations from indole **19** and a 20.2% total yield.

With this efficient synthetic strategy developed, we were also able to synthesize dictyodendrins H and I using the same synthetic sequence and only changing tyramine to a halogenated tyramine (Scheme 6). Unlike dictyodendrin F, dictyodendrins H and I contain a halogen atom on the tyramine side chain, making transition metal catalyzed cross-couplings or C−H activation strategies challenging. In addition, a late stage halogenation could also be difficult given the large number of electron-rich aromatic rings. By contrast, our approach avoids these problems by using the desired halogenated tyramines to replace the adamantoxyl group on the cyclobutenone. In detail, halogenated *O*-methyl tyramines **44** (X = Br) and **45** (X = I)[36] were used to replace the adamantoxyl group on cyclobutenone **22** to obtain the tyramine substituted cyclobutenones **46** and **47**. The subsequent retro-4π/6π-cyclization−acylation cascade reaction afforded the carbazole intermediates **48** and **49** using 3-pentyl anisolyl ynol ether **18c** as the acylating reagent. Finally, oxidative coupling and global deprotection gave dictyodendrins H and I. The ^{1}H NMR spectra for the synthetic materials matched the reported data for the natural products. The isolation group was unable to obtain complete ^{13}C NMR data sets, but our synthetic material generated spectra that were consistent with the limited data that are available.[37] During the synthesis, we found that the halide on the side chain caused some instability during the cascade reaction (more light-sensitive) as well as during the oxidative coupling reaction. In conclusion, we report the first total synthesis of dictyodendrins H (**6**) and I (**7**) in six steps with an 11.9% and 11% total yield, respectively.

The cytotoxicity of dictyodendrins F, H, and I was evaluated against three nonsmall cell lung cancer cell lines (H157, H2073, H2122) and a colorectal cancer cell line (HCT116).[33] Interestingly, with the increasing size of the tyramine side chain from dictyodendrin F to I, we observed increasing, albeit modest cytotoxicity of the natural products against cancer cells. For example, the IC_{50} values against HCT116 decreased from dictyodendrin F (26.9 μM) to dictyodendrin H (13 μM) and dictyodendrin I (8 μM) (Figure 5). The concise syntheses described here should provide a route to access multiple derivatives of the dicyodendrins to optimize their activity and identify relevant biological targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06460.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We appreciate helpful suggestions from Prof. George O'Doherty (Northeastern University) regarding the mechanism of oxidative cyclization. We thank Dr. Lin Feng (UT Southwestern) for help with *in situ* NMR experiments and Dr. Shi Heping (UT Southwestern) for help with mass spectrometry. We thank Dr. Bruce Posner (UT Southwestern) and Chensu Wang (UT Southwestern) for help measuring cytotoxicity. We thank Prof. Robert Capon (The University of Queensland) providing NMR spectra of isolated dictyodendrins F and I for comparison. Sarah Winterton and Aaron Coffin helped edit the manuscript. Funding was provided by the Sarah and Frank McKnight Fellowship for Biochemical Research, NIGMS (R01 GM102403), and the Welch Foundation (I-1612).

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(22) (a) dpp-Hexane is a poor ligand for palladium-catalyzed CO/C_2H_4 copolymerization. See: Leeuwen, P. W. N. M. v.; Freixa, Z. *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH & Co. KGaA: 2008; p 10. (b) For the bite angle of Pd[PH_2(CH2)$_6$$PH_2$], see: van Zeist, W.-J.; Visser, R.; Bickelhaupt, F. M. *Chem. - Eur. J.* **2009**, *15*, 6112−6115.

(23) Commercially available from Chendu Aofan Pharm-tech Co., Ltd. (TEL 86-28-85655382) or available from a 1-pot iodination−sulfonylation of the corresponding indole. See Supporting Information for details.

(24) N-Cbz gave an 84% yield of impure material in the coupling reaction; N-Ns decomposed during the coupling reaction; N-Ts had poor solubility for the coupling reaction and gave 21% yield.

(25) ^{1}H NMR key parameters: nt = 32, d1 = 4. The graph in Scheme 1B was generating by assuming [**20**]% + [**22**]% + [**23**]% = 100%. No other products were observed in the ^{1}H NMR spectra. The hetero-/homodimer selectivity did not change over the course of the reaction.

(26) The starting material was reused once.

(27) (a) Schmidt, A. H.; Debo, M.; Wehner, B. *Synthesis* **1990**, *1990*, 237−242. (b) Sejwal, P.; Han, Y.; Shah, A.; Luk, Y.-Y. *Org. Lett.* **2007**, *9*, 4897−4900. (c) Li, J.; Han, Y.; Freedman, T. B.; Zhu, S.; Kerwood, D. J.; Luk, Y.-Y. *Tetrahedron Lett.* **2008**, *49*, 2128−2131.

(28) We added 2.5 equiv of the ynol ether every 4 h. Batchwise addition gave 42% of **37** at 60 °C compared to 38% yield when all reagents were combined at the beginning of the reaction.

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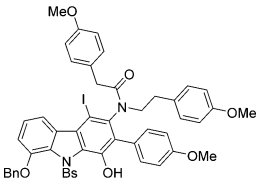
(31) The iodinated product was the only product we isolated after the reaction.



(32) **41** could exist as a dianion or one of several monoanions.

(33) See Supporting Information for details.

(34) For benzenesulfonate acting as an oxidant in the Shapiro reaction, see: Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55−59.

(35) An alternative mechanism involves migration of the benzenesulfonate from the indole nitrogen to the phenolate anion to form an ArOSO_2Ph intermediate. Enolate addition to the aromatic ring with loss of $PhSO_2^-$ and tautomerization would form carbazole **41**.

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(37) HSQC and HMBC were employed to assign carbons of dictyodendrins H and I by the isolation group. The quantity of natural products was not enough for direct a ^{13}C NMR experiment. See ref 3.

DOI: 10.1021/jacs.6b06460
J. Am. Chem. Soc. 2016, 138, 10684−10692