JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Total Synthesis of Dictyodendrins B and E

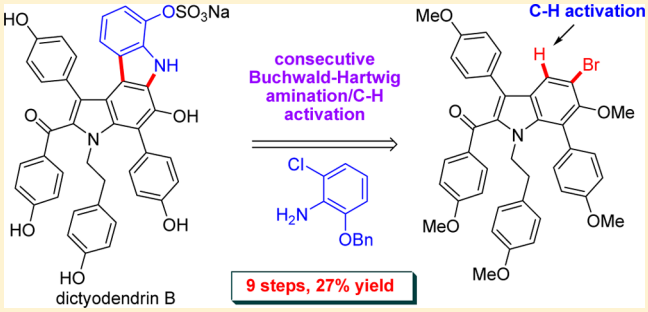
Jingjing Liang,[§,†] Weimin Hu,[§,†] Pengyu Tao,[†] and Yanxing Jia*[,†,‡]

[†]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: The concise synthesis of the novel telomerase inhibitors dictyodendrins B and E was completed in only 9 and 11 steps (longest linear sequence). The highly convergent strategy employed a palladium-catalyzed Larock indole synthesis and a palladium-mediated one-pot consecutive Buchwald–Hartwig amination/C–H activation reaction as key steps. The present synthesis exhibits respectable levels of atom-, redox-, and step-economy.



The development of shorter synthetic sequences for the synthesis of complex natural products is currently pursued actively by organic chemists.[1−4] Cascade reactions offer an attractive strategy for the ideal synthesis of complex natural products.[5] Meanwhile, transition-metal-mediated direct C–H activation has garnered increasing attention in the synthetic community as the "ideal" method for carbon–carbon bond formation, and some successful applications of C–H activation for the total synthesis of complex natural products are emerging.[6] With our ongoing study on the efficient synthesis of indole and pyrrole alkaloids, we report herein a concise and efficient total synthesis of dictyodendrins B and E using a palladium-mediated C–H activation strategy.

Dictyodendrins A–E (**1**–**5**) were isolated by Fusetani and Matsunaga from the sponge of *Dictyodendrilla verongiformis* that was collected off the south Japanese coast (Figure 1).[7] These compounds belong to a new family of alkaloids that feature a characteristic and unique pyrrolo[2,3-*c*]carbazole moiety and carry at least one sulfate group in the periphery. These scarce alkaloids were claimed to be the first marine natural products with telomerase inhibitory properties (100% inhibition at 50 μg/mL concentration). Since the telomerase enzyme is overexpressed in >85% tumor cells but not in normal cells,[8] telomerase inhibition represents a promising target for cancer chemotherapy.[9]

Because of their unique chemical structures and promising biological activity, the total synthesis of dectyodendrins has been investigated by many chemists.[10−13] Fürstner and co-workers reported the first total synthesis of dictyodendrins B, C, and E using their original titanium-induced reductive coupling reaction.[10] Tokuyama et al. reported the total synthesis of dectyodendrins A–E (**1**–**5**) by using an elegant cascade of indoline formation/cross-coupling sequence.[11] In addition, Iwao, Ishibashi, and co-workers disclosed the formal

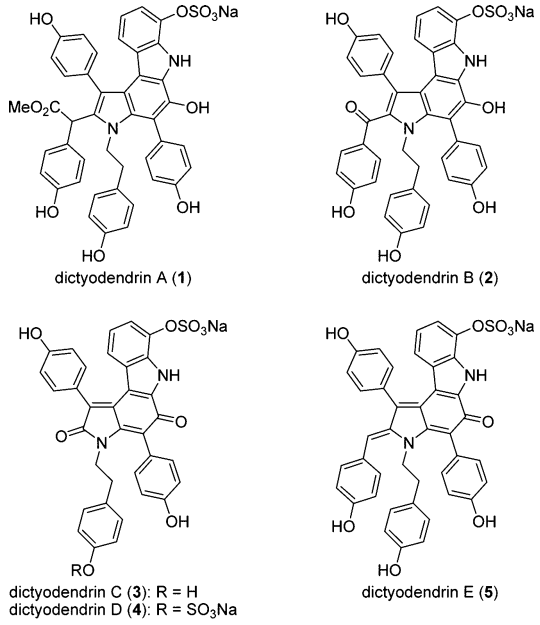


Figure 1. Structures of dictyodendrins A–E.

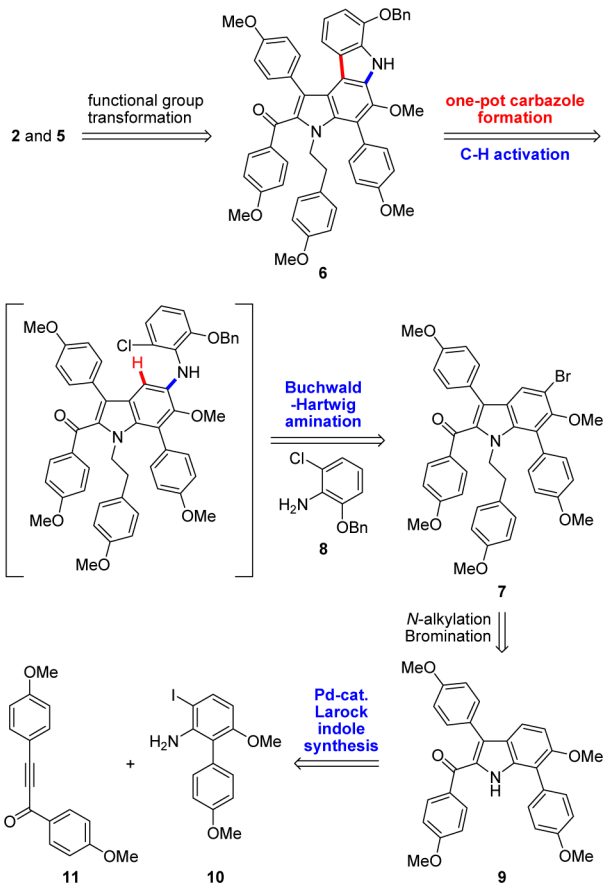
total synthesis of dictyodendrin B by mainly using palladium-catalyzed cross-coupling reactions.[12]

From our point of view, dictyodendrins have a common fully substituted indole moiety but differ in their respective substituents at the 2-position. We performed retrosynthetic analysis of **2** and **5** as shown in Scheme 1. We envisioned that both **2** and **5** could be prepared from the same advanced

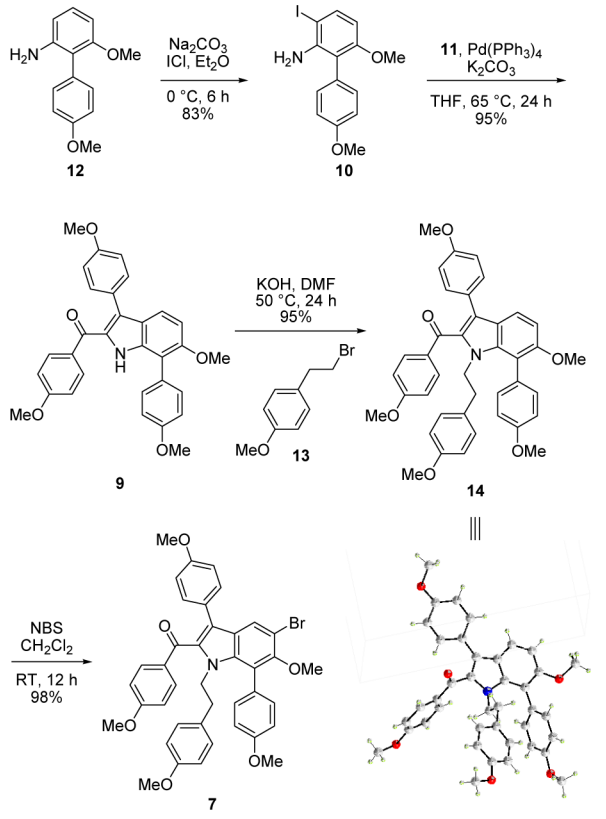
Received: April 18, 2013
Published: May 13, 2013

ACS Publications © 2013 American Chemical Society

Scheme 1. Retrosynthetic Analysis of Dictyodendrins B and E



Scheme 2. Synthesis of 2-Acylindole Derivative 7



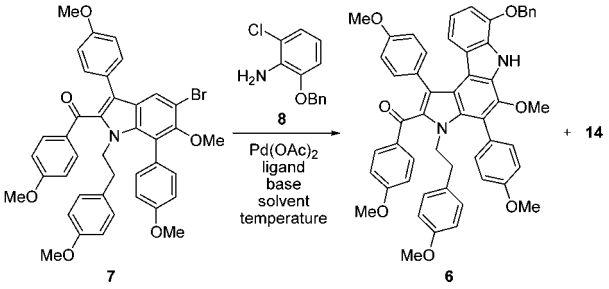
intermediate **6**. The carbazole skeleton of **6** could be produced from bromide **7** and 2-chloroaniline **8** via a palladium-catalyzed one-pot consecutive Buchwald–Hartwig amination/C–H activation reaction.[14,15] The brominated indole **7** should be easily obtained by a sequence of N-alkylation followed by bromination from indole **9**. In turn, the indole **9** could be prepared by the palladium-catalyzed Larock indole synthesis[16] from *o*-iodoaniline **10** and the known alkyne ketone **11**.[17]

The synthesis of indole **14** commenced with the known compound **12** (Scheme 2).[18] Iodination of aniline **12** using ICl gave *o*-iodoaniline **10** in 83% yield. Surprisingly, an extensive literature search did not show any report on the use of such alkynyl ketone compounds for the Larock indole annulation. Although an alkynyl ester compound for the Larock indole annulation has been reported in the literature,[19] the regioselectivity of this annulation reaction was not clear. The reaction of *o*-iodoaniline **10** with alkynyl ketone **11** under the standard Larock reaction conditions ($Pd(OAc)_2$, PPh_3, Na_2CO_3, LiCl, DMF, 100 °C) was carried out.[16] Gratifyingly, the reaction was highly regioselective and yielded the desired indole **9** as the only regioisomer, albeit in lower yield (44%). Subsequently, a variety of conditions (palladium source, base, solvent, and concentration) were further optimized to increase the yield. We eventually found that the optimal condition was 10% $Pd(PPh_3)_4$ in the presence of 2.0 equiv of K_2CO_3 in THF (c = 0.50 M), which provided the desired indole **9** in 95% yield. N-Alkylation of **9** with **13** afforded the desired indole **14** in 95% yield. The structure of **14** was unequivocally confirmed by X-ray crystallographic analysis. Chemoselective bromination of 5-position of indole **14** with NBS provided **7** in 98% yield. The short synthesis of this key intermediate **7** could be carried out on a multigram scale.

After the synthesis of the key intermediate **7**, we investigated the synthesis of the key carbazole by palladium-catalyzed one-pot consecutive Buchwald–Hartwig amination/C–H activation reaction (Table 1). Once again, an extensive literature search did not show any use of this one-pot methodology for the synthesis of complex carbazole natural products. To our disappointment, treatment of **7** and **8** under Bedford's reaction conditions did not afford the desired product **6**.[15] Instead, only the debrominated product **14**, resulting from a reductive process, was obtained in 50% yield (Table 1, entry 1). Of the other catalyzed conditions examined, carbazole **6** was not obtained. Subsequently, a variety of conditions (base, solvent, and temperature) were examined in the presence of $Pd(OAc)_2$ and (t-Bu_3P)HBF_4, and some of the representative results are shown in Table 1. After the amount of $Pd(OAc)_2$ and ligand was increased, the desired **6** was obtained, albeit in very low yield (Table 1, entries 2 and 3). When the reaction was conducted with 1.0 equiv of $Pd(OAc)_2$, the desired **6** was obtained in 30% yield. Therefore, further optimization of reaction conditions was carried out in the presence of 1.0 equiv of $Pd(OAc)_2$. Among the bases tested, t-BuONa was the best one (entries 4 and 5). Of the solvents examined, although toluene was the best one (entries 4 and 6–8), the polar solvent DMSO also produced good result (entry 8). Since it was reported that the higher temperature facilitates the one-pot reaction, we then performed the reaction at 160 °C in DMSO and found that the desired product carbazole **6** was obtained in 71% yield (entry 9). Surprisingly, when the nonpolar solvent mesitylene was used as the solvent at 160 °C, only a trace amount of **6** was obtained (entry 10). In all cases, the major

dx.doi.org/10.1021/jo400841d | J. Org. Chem. 2013, 78, 5810–5815

Table 1. Optimization of the Reaction Conditions[a]



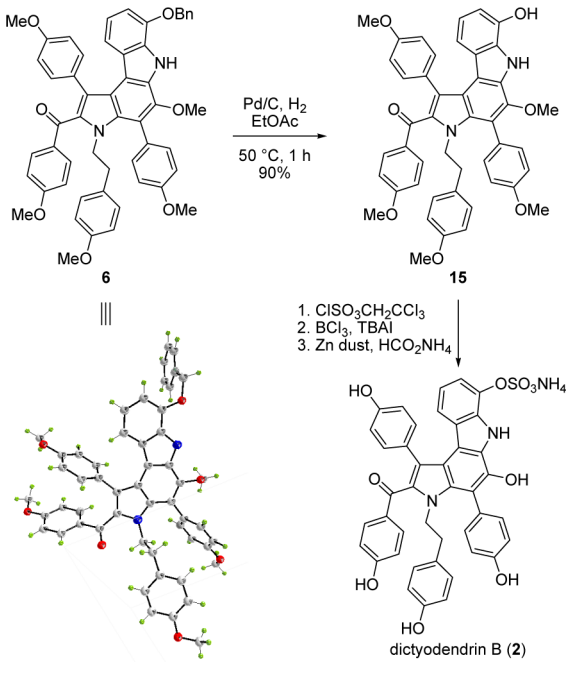
				yield[b] (%)	
entry	$Pd(OAc)_2$ (equiv)	solvent	temp (°C)	**6**	**14**
1	0.1	toluene	110	0	50
2	0.2	toluene	110	5	91
3	0.5	toluene	110	6	86
4	1.0	toluene	110	30	61
5[c]	1.0	toluene	110	0	95
6	1.0	1,4-dioxane	110	0	83
7	1.0	DMF	110	0	86
8	1.0	DMSO	110	23	58
9	**1.0**	**DMSO**	**160**	**71**	**19**
10	1.0	mesitylene	160	5	88

[a]Reaction conditions: **7** (0.1 mmol), **8** (0.3 mmol), $Pd(OAc)_2$, (t-Bu_3P)HBF_4 (2 equiv of $Pd(OAc)_2$), t-BuONa (0.5 mmol) in solvent (4.0 mL). [b]Isolated yields. [c]Cs_2CO_3 was used as the base.

side product frequently observed was the debrominated starting material **14**. Moreover, the structure of **6** was unequivocally confirmed by X-ray crystallographic analysis.

With the advanced intermediate **6** in hand, we proceeded with the total synthesis of dictyodendrin B (**2**) (Scheme 3). Removal of the benzyl ether by hydrogenolysis afforded **15** in 90% yield, and its characterization data were in agreement with those reported in the literatures.[10,11] Finally, according to the protocol reported by Fürstner and Tokuyama, compound **15**

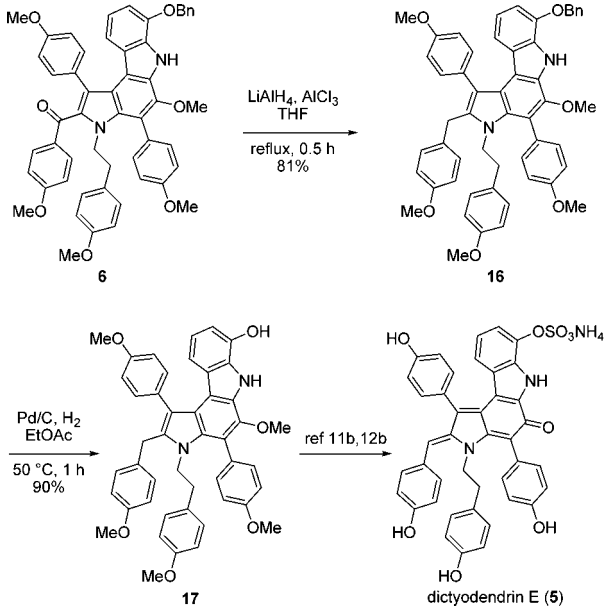
Scheme 3. Total Synthesis of Dictyodendrin B (2)



was readily converted to dictyodendrin B in a three-step sequence. Thus, our total synthesis of dictyodendrin B was achieved in only nine steps and 27% overall yield from the known compound **12**.

After completion of the synthesis of dictyodendrin B, we turned our attention to the synthesis of dictyodendrin E from the advanced intermediate **6** (Scheme 4). Gratefully, reduction

Scheme 4. Total Synthesis of Dictyodendrin E (5)



of the carbonyl group in **6** using $LiAlH_4$ in the presence of $AlCl_3$ provided the desired product **16** in 81% yield. Removal of the benzyl ether by hydrogenolysis afforded the known compound **17**, which was then transformed to dictyodendrin E in four steps.[10,11] Our total synthesis of dictyodendrin E was achieved in only 11 steps and 29% overall yield from the known compound **12**.

In summary, we have accomplished the robust, scalable, and highly efficient total synthesis of dictyodendrins B and E from the known compound **12**. Our route delivered dictyodendrin B in only nine steps with 27% overall yield and dictyodendrin E in 11 steps with 29% overall yield. The highly convergent strategy employed was made possible by a palladium-mediated one-pot consecutive Buchwald−Hartwig amination/C−H activation reaction and a palladium-catalyzed Larock indole synthesis. The present syntheses represent the shortest pathway for the total synthesis of dictyodendrins B and E to date. The synthesis represented another example of C−H activation strategy for the rapid synthesis of biologically active natural products. The synthesis and biological studies of the other members of the dictyodendrin family and analogues are currently under investigation.

EXPERIMENTAL SECTION

General Remarks. All reagents were obtained from commercial suppliers unless otherwise stated. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from potassium sodium alloys; dichloromethane was distilled from calcium hydride; *N*,*N*-dimethylformamide (DMF) was distilled from magnesium sulfate under vacuum. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under vacuum. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. ^{1}H NMR were recorded on a 400 MHz NMR

dx.doi.org/10.1021/jo400841d | J. Org. Chem. 2013, 78, 5810−5815

spectrometer and ^{13}C NMR on a 100 MHz NMR spectrometer unless otherwise stated. The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, m: multiplet, br s: broad singlet for proton spectra and carbon spectra. Coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were acquired on an FT-MS (7.0 T) equipped with an ESI source in positive mode. Infrared spectra were recorded with a thin layer of the product on a KBr disk. Flash column chromatography was performed using silica gel (200−300 mesh) with solvents distilled prior to use.

Compound 10. To a stirred solution of **12** (2.29 g, 10 mmol) in Et_2O (50 mL) were added saturated aqueous Na_2CO_3 solution (11 mL) and iodine monochloride (1.78 g, 11 mmol) dissolved in Et_2O (45 mL) in the dark. The reaction mixture was stirred for 6 h. After completion of the reaction, the mixture was diluted with Et_2O and quenched with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 12:1) afforded compound **10** as a white solid (2.95 g, 83%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.20 (d, J = 8.8 Hz, 1H), 3.96 (br s, 2H), 3.81 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.8, 145.3, 137.6, 131.3, 127.0, 115.8, 114.3, 103.2, 74.5, 55.7, 55.1; IR (KBr) 3447, 3359, 2965, 2932, 2836, 1608, 1576, 1510, 1294, 1239, 1033, 830, 777, 579 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{15}INO_2$ $(M + H)^+$ 356.0142, found 356.0136.

Compound 9. To a stirred solution of **10** (356 mg, 1 mmol) in anhydrous THF (2 mL) was added K_2CO_3 (276 mg, 2 mmol) under argon atmosphere. After oxygen was discharged with argon for 0.5 h, compound **11** (798 mg, 3 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) were added under argon, and then the solution was heated at 65 °C for 24 h. The mixture was cooled to room temperature, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 5:1) to afford **9** (467 mg, 95%) as a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.54−7.50 (m, 4H), 7.15 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 9.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 162.3, 159.0, 158.5, 155.1, 136.6, 131.8, 131.8, 131.0, 130.9, 130.2, 126.4, 126.0, 124.7, 122.9, 121.5, 114.5, 113.6, 113.0, 112.8, 108.5, 56.9, 55.3, 55.3, 55.2; HRMS (ESI) m/z calcd for $C_{31}H_{28}NO_5$ $(M + H)^+$ 494.1962, found 494.1973.

Compound 14. To a stirred solution of **9** (316 mg, 0.64 mmol) in dry DMF (22 mL) was added KOH (714 mg, 12.8 mmol). The resulting suspension was stirred at room temperature for 30 min. To the solution was added **13** (860 mg, 2.56 mmol). The reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with water. The resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 3:1) to afford **14** (385 mg, 95%) as a yellow amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.05−7.00 (m, 3H), 6.73 (d, J = 8.8 Hz, 2H), 6.62−6.53 (m, 6H), 4.00−3.96 (m, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 2.50−2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 163.1, 159.1, 158.2, 157.9, 155.7, 136.8, 134.2, 132.4, 132.1, 131.2, 131.1, 130.3, 129.6, 127.6, 126.5, 122.8, 121.0, 114.8, 113.7, 113.6, 113.5, 113.1, 107.7, 57.3, 55.3, 55.3, 55.2, 55.1, 46.6, 36.6; IR (KBr) 3433, 2936, 2837, 1594, 1511, 1462, 1248, 1175, 1083, 1033, 833, 732, 607, 533 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{38}NO_6$ $(M + H)^+$ 628.2694, found 628.2702.

Compound 7. To a stirred solution of **14** (3.14 g, 5 mmol) in dry CH_2Cl_2 (500 mL) was added NBS (0.98 g, 5.5 mmol) in the dark at 0 °C. The resulting mixture was warmed to room temperature and stirred for 12 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to afford **7** (3.46 g, 98%) as a yellow amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 6.52 (d, J = 8.6 Hz, 2H), 4.02−3.98 (m, 2H), 3.90 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.53 (s, 3H), 2.49−2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 163.3, 159.5, 158.4, 158.0, 152.1, 135.2, 135.2, 132.4, 131.8, 131.0, 130.5, 129.8, 129.5, 126.6, 125.6, 125.4, 124.0, 121.7, 121.2, 113.8, 113.7, 113.5, 113.2, 110.9, 61.2, 55.3, 55.1, 55.0, 46.6, 36.6; IR (KBr) 3705, 3680, 2969, 2931, 1598, 1540, 1511, 1457, 1247, 1174, 1055, 1033, 836 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{37}NO_6Br$ $(M + H)^+$ 706.1799, found 706.1787.

Compound 6. To a stirred solution of compound **7** (159.3 mg, 0.2 mmol) in dry DMSO (9 mL) were added **8** (158.1 mg, 0.6 mmol) and t-BuONa (108.4 mg, 1.0 mmol) successively under argon atmosphere, After oxygen was discharged with argon for 0.5 h, $Pd(OAc)_2$ (50.5 mg, 0.2 mmol) and $(t\text{-}Bu_3P)HBF_4$ (116.0 mg, 0.4 mmol) were added under argon, and then the solution was heated at 160 °C for 6 h. The mixture was then filtered through a pad of Celite, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 3:1) to afford **6** (130.5 mg, 71%) as a yellow amorphous solid: ^1H NMR (400 MHz, CD_2Cl_2) δ 8.74 (s, 1H), 7.59−7.55 (m, 6H),7.44−7.35 (m, 3H), 7.26 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.66 (t, J = 8.4 Hz, 1H), 6.61 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 5.83 (d, J = 8.4 Hz, 1H), 5.26 (s, 2H), 3.95 (t, J = 8.0 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 2.55−2.51 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 189.9, 163.5, 159.9, 159.4, 158.5, 145.0, 143.2, 137.6, 136.5, 133.4, 132.6, 132.5, 132.0, 131.5, 130.7, 130.1, 130.0, 129.8, 128.9, 128.5, 128.3, 127.6, 124.9, 122.1, 119.7, 119.1, 118.6, 117.7, 115.8, 114.1, 113.8, 113.5, 113.5, 106,1, 70.8, 61.6, 55.8, 55.7, 55.7, 55.4, 54.3, 54.1, 53.5, 53.3, 47.9, 36.9; IR (KBr) 3357, 1632, 1595, 1573, 1536, 1513, 1461, 1441, 1423, 1286, 1246, 1174, 1157, 1030 cm^{-1}; HRMS (ESI) m/z calcd for $C_{53}H_{47}N_2O_7$ $(M + H)^+$ 823.3378, found 823.3369.

Compound 15. Compound **6** (50.3 mg, 0.06 mmol) was hydrogenated over 10% Pd/C (64.0 mg, 0.06 mmol) in EtOAc (6 mL) at 50 °C for 1 h. The mixture was then filtered through a pad of Celite, and the insoluble material was washed well with hot EtOAc. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 3:1) to afford **15** (40.3 mg, 90%) as a yellow amorphous solid: ^1H NMR (400 MHz, CD_2Cl_2) δ 8.91 (s, 1H), 7.56−7.54 (m, 4H), 7.24 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.69 (m, 3H), 6.59 (m, 3H), 6.51 (d, J = 8.8 Hz, 2H), 6.07 (br s, 1H), 5.78 (d, J = 8.4 Hz, 1H), 3.94 (t, J = 8.0 Hz, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 2.53−2.50 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 190.2, 163.6, 159.8, 159.4, 158.5, 143.3, 141.6, 136.5, 133.4, 132.7, 132.6, 131.8, 131.6, 130.7, 130.3, 129.9, 129.2, 128.9, 127.5, 125.5, 122.4, 119.8, 119.2, 118.7, 117.5, 115.9, 114.1, 113.8, 113.5, 109.3, 61.5, 55.8, 55.7, 55.7, 55.4, 47.9, 36.9; IR (KBr) 3399, 2933, 1606, 1513, 1460, 1295, 1245, 1172, 1107, 1067, 1032, 966, 838, 772 cm^{-1}; HRMS (ESI) m/z calcd for $C_{46}H_{41}N_2O_7$ $(M + H)^+$ 733.2908, found 733.2879.

Dictyodendrin B (2). Dictyodendrin B (**2**) was prepared from compound **15** followed the procedure as described in refs 11 and 12: ^1H NMR (400 MHz, CD_3OD) δ 7.45 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.06−7.02 (m, 4H), 6.65 (d, J = 8.4 Hz, 2H), 6.59−6.55 (m, 3H), 6.48 (d, J = 8.8 Hz, 2H), 6.41 (d, J = 8.4 Hz, 2H), 6.01 (d, J = 8.0 Hz, 1H), 3.98−3.94 (m, 2H), 2.49−2.45 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 191.9, 163.1, 158.7, 157.7, 156.8, 141.7, 138.7, 136.1, 134.2, 134.0, 134.0, 133.8, 131.9, 130.6, 130.6, 129.3, 129.2, 127.0, 126.8, 125.7, 122.7, 118.8, 118.2, 117.2,

dx.doi.org/10.1021/jo400841d | J. Org. Chem. 2013, 78, 5810−5815

116.8, 116.0, 116.0, 115.5, 115.5, 112.6, 40.4, 37.7; HRMS (ESI) m/z calcd for $C_{41}H_{29}N_2O_{10}S$ $(M - NH_4)^-$ 741.1548, found 741.1540.

Compound 16. To a stirred solution of compound **6** (41.4 mg, 0.05 mmol) in dry THF were added $AlCl_3$ (100.0 mg, 0.75 mmol) and $LiAlH_4$ (60 mg, 1.5 mmol) successively under argon atmosphere. The solution was refluxed for 0.5 h. The mixture was quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 4:1) to afford **16** (33.0 mg, 81%) as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.45−7.41 (m, 2H), 7.39−7.36 (m, 1H), 7.07−7.02 (m, 6H), 6.84 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.72 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 8.4 Hz, 2H), 5.95 (d, J = 8.0 Hz, 1H), 5.27 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.85 (s, 2H), 3.81−3.77 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.59 (s, 3H), 2.37 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.9, 158.0, 158.0, 144.5, 140.0, 137.2, 136.4, 133.0, 132.5, 131.7, 130.5, 130.5, 129.7, 129.6, 128.9, 128.6, 128.2, 128.1, 127.9, 127.8, 125.0, 119.9, 118.5, 117.7, 117.2, 116.5, 115.0, 113.9, 113.7, 113.5, 113.4, 105.6, 70.5, 61.1, 55.4, 55.4, 55.2, 55.2, 46.6, 36.2, 30.4; HRMS (ESI) m/z calcd for $C_{53}H_{49}N_2O_6$ $(M + H)^+$ 809.3585, found 809.3565.

Compound 17. Compound **16** (46.3 mg, 0.06 mmol) was hydrogenated over 10% Pd/C (60.9 mg, 0.06 mmol) in EtOAc (6 mL) at 50 °C for 1 h. The mixture was then filtered through a pad of Celite, and the insoluble material was washed well with hot EtOAc. The filtrate was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/EtOAc = 3:1) to afford **17**[11,12] (37.0 mg, 90%) as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.06−7.00 (m, 6H), 6.78 (d, J = 8.6 Hz, 2H), 6.68−6.61 (m, 4H), 6.35 (d, J = 8.6 Hz, 2H), 5.91 (d, J = 7.6 Hz, 1H), 5.53 (br s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.83 (s, 2H), 3.80−3.75 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.60 (s, 3H), 2.38−2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.9, 158.0, 158.0, 140.7, 140.0, 136.5, 133.0, 132.4, 131.7, 130.5, 130.4, 129.6, 129.2, 129.0, 128.9, 128.2, 127.8, 125.7, 119.9, 118.6, 117.9, 117.2, 116.5, 115.0, 113.9, 113.7, 113.5, 113.4, 108.8, 61.1, 55.5, 55.4, 55.4, 55.3, 55.2, 46.5, 36.2; HRMS (ESI) m/z calcd for $C_{46}H_{43}N_2O_6$ $(M + H)^+$ 719.3116, found 719.3116.

Dictyodendrin E (5). Dictyodendrin E (**5**) was prepared from compound **17** following the same procedure as described in refs 10b and 11b: ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (d, J = 8.4 Hz, 2H), 7.23−7.14 (m, 5H), 6.98−6.96 (m, 4H), 6.82 (d, J = 8.4 Hz, 2H), 6.64 (m, 1H), 6.00 (s, 1H), 6.43 (br s, 4H), 5.77 (d, J = 8.4 Hz, 1H), 3.50−3.47 (m, 2H), 2.31−2.28 (m, 2H); HRMS (ESI) m/z calcd for $C_{41}H_{31}N_2O_9S$ $(M - NH_3 + H)^+$ 727.1745, found 727.1758.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectra for compounds **10**, **9**, **14**, **7**, **6**, **15**, dictyodendrin B (**2**), **16**, **17**, and dictyodendrin E (**5**). X-ray crystal structures of **14** and **6** and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yxjia@bjmu.edu.cn.

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the National Natural Science Foundation of China (Nos. 21290180, 20972007), the National Basic Research Program of China (973 Program, NO. 2010CB833200), and the Ph.D. Programs Foundation of Ministry of Education of China (No. 20120001110100).

■ REFERENCES

(1) For the ideal synthesis, see: (a) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657−4673. (b) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784−5800.

(2) For atom economy, see: (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259−281. (b) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(3) For step economy, see: (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40−49. (b) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2.

(4) For redox economy, see: (a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854−2867. (b) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938−17954.

(5) For recent reviews on cascade reactions in total synthesis, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167−178. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

(6) (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (b) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452−9474.

(7) Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765−2770.

(8) (a) Lavelle, F.; Riou, J.-F.; Laoui, A.; Mailliet, P. *Crit. Rev. Oncol. Hematol.* **2000**, *34*, 111−126. (b) Neidle, S.; Parkinson, G. *Nature Reviews, Drug Discovery* **2002**, *1*, 383.

(9) Gowan, S. M.; Harrison, J. R.; Patterson, L.; Valenti, M.; Read, M. A.; Neidle, S.; Kelland, L. R. *Mol. Pharmacol.* **2002**, *61*, 1154−1162.

(10) (a) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620−11621. (b) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087−8094. For derivatization of dictyodendrins (c) Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519−6534.

(11) (a) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925−5929. (b) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560−572.

(12) Hirao, S.; Yoshinaga, Y.; Iwao, M.; Ishibashi, F. *Tetrahedron Lett.* **2010**, *51*, 533−536.

(13) (a) Ayats, C.; Soley, R.; Albericio, F.; Álvarez, M. *Org. Biomol. Chem.* **2009**, *7*, 860−862. (b) Hirao, S.; Sugiyama, Y.; Iwao, M.; Ishibashi, F. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1764−1772.

(14) For a recent review on carbazole synthesis, see: Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193−3328.

(15) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403−9410.

(16) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652−7662.

(17) Compound **11** was prepared by one-step Pd-catalyzed coupling of commercially available benzoyl chloride and terminal alkyne; see: Roy, S.; Davydova, M. P.; Pal, R.; Gilmore, K.; Tolstikov, G. A.; Vasilevsky, S. F.; Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 7482−7490.

(18) Cornforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299−2315.

(19) (a) Gavara, L.; Anizon, F.; Moreau, P. *Tetrahedron* **2011**, *67*, 7330−7335. (b) Hwu, J. R.; Hsu, Y. C.; Josephrajan, T.; Tsay, S.-C. *J. Mater. Chem.* **2009**, *19*, 3084−3090. (c) Watterson, S. H.; Dhar, T. G. M.; Ballentine, S. K.; Shen, Z.; Barrish, J. C.; Cheney, D.; Fleener, C. A.; Rouleau, K. A.; Townsend, R.; Hollenbaugh, D. L.; Iwanowicz, E. J.

Bioorg. Med. Chem. Lett. **2003**, *13*, 1273−1276. (d) Zhang, H.-C.; Brumfield, K. K.; Maryanoff, B. E. *Tetrahedron Lett.* **1997**, *38*, 2439−2442.