DOI: 10.1002/adsc.200600587

Synthesis of Biaryls *via* Palladium-Catalyzed [2+2+2] Cocyclization of Arynes and Diynes: Application to the Synthesis of Arylnaphthalene Lignans

Yoshihiro Sato,[a,*] Takayuki Tamura,[a] Atsushi Kinbara,[a] and Miwako Mori[b]

[a] Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan
Fax: (+81)-11-706-4982; e-mail: biyo@pharm.hokudai.ac.jp
[b] Health Sciences University of Hokkaido, Ishikari-tobetsu, Hokkaido 061-0293, Japan

Received: November 12, 2006

This paper is dedicated to Professor Masakatsu Shibasaki on his 60th birthday.

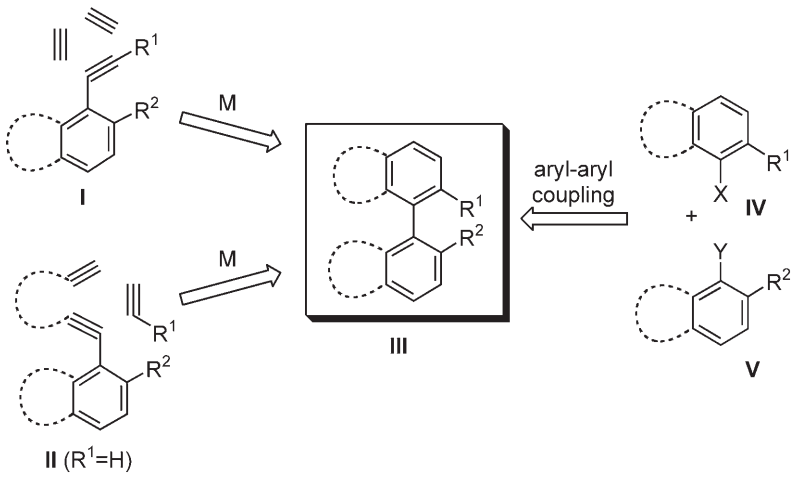
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A novel method for construction of biaryls *via* palladium(0)-catalyzed [2+2+2] cocyclization of diynes and arynes was developed. By this [2+2+2] cocyclization, various arylnaphthalene derivatives, including a sterically hindered 2,2′-disubstituted-1,1′-binaphthyl, can be constructed by virtue of a variety of combinations of diynes and aryne precursors. Using this [2+2+2] cocyclization as a key step, the total syntheses of natural arylnaphthalene lignans, taiwanin C, taiwanin E, and dehydrodesoxypodophyllotoxin were achieved.

Keywords: arynes; biaryls; cycloaddition; dehydrodesoxypodophyllotoxin; palladium; taiwanin

Introduction

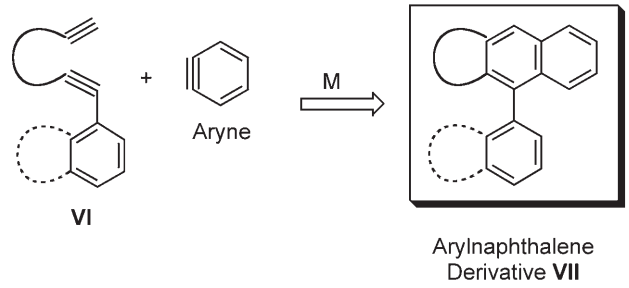
Biaryls are an important class of compounds, not only as structures found in a variety of natural products, including molecules of medicinal interest, but also as a chiral source for asymmetric synthesis. A biaryl skeleton such as **III**, which consists of two aromatic rings attached to each other, is usually constructed through an aryl-aryl coupling reaction between two aromatic compounds such as **IV** and **V** (Scheme 1).[1] On the other hand, a transition metal-catalyzed [2+2+2] cocyclization of alkynes is a useful and highly atom-economic way for the construction of various aromatic rings,[2] and this advantage compared to the above-mentioned usual aryl-aryl coupling methodology prompted us to utilize the [2+2+2] cocyclization for the synthesis of biaryl derivatives. In this context, we have recently established a conceptually new method-



Scheme 1. Synthesis of biaryls *via* [2+2+2] cocyclization.

ology for the synthesis of biaryls *via* Ni(0)-catalyzed [2+2+2] cocyclization, by which various biaryls **III** were obtained in excellent yields by the [2+2+2] cocyclization of alkyne **I** and two molecules of acetylene or by that of diyne **II** and one molecule of acetylene.[3]

We speculated that this methodology could be further expanded to the construction of various arylnaphthalene skeletons **VII** if the [2+2+2] cocyclization of diyne **VI** and an aryne, in which C–C bond formation occurs three times, would proceed (Scheme 2).[4–7]



Scheme 2. Plan for [2+2+2] cocyclization of diynes and arynes.

Thus, the [2+2+2] cocyclization between **VI** and an aryne is expected to provide us with novel methodology for the synthesis of various arylnaphthalenes **1** in short-step reactions, and these arylnaphthalene derivatives should be key intermediates for the syntheses of chinensin, justicidin B, diphyllin, and taiwanins C and E (Figure 1). Herein we describe the construction of an arylnaphthalene skeleton by the palladium-catalyzed [2+2+2] cocyclization of diyne **3** and aryne **2** derived from precursor **2′**.[8] We also report the application of this reaction to the total syntheses of taiwanin C, taiwanin E, and dehydrodesoxypodophyllotoxin.

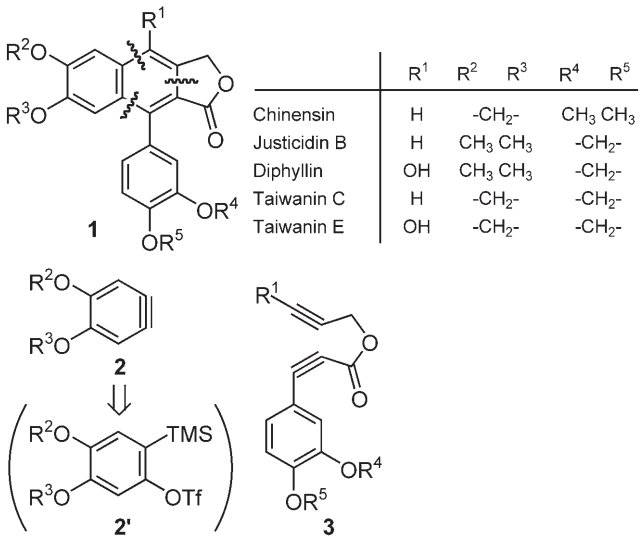


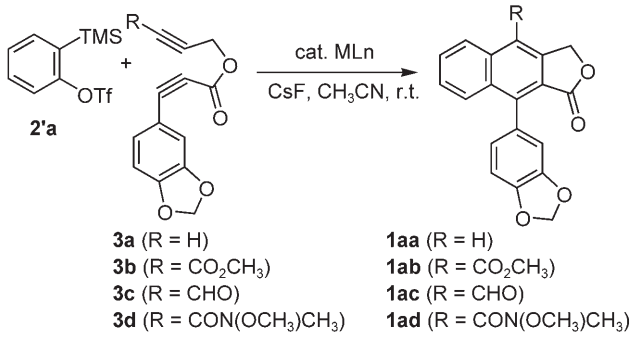
Figure 1. Plan for syntheses of arylnaphthalene lignans.

Results and Discussion

Synthesis of Arylnaphthalene Derivatives by Pd(0)-Catalyzed [2+2+2] Cocyclization of Diynes and Benzyne Derived from an Aryne Precursor with CsF

To examine the feasibility of the above-mentioned plan shown in Scheme 2, we initially investigated the [2+2+2] cocyclization of diynes **3a–d** and benzyne generated from precursor **2′a**[9] (Table 1). When the reaction of **3a** or **3b** and aryne precursor **2′a** in the presence of CsF was carried out in CH_3CN at room temperature using a Ni(0) catalyst prepared from Ni-

Table 1. [2+2+2] Cocyclization of diynes **3** and benzyne derived from the precursor **2′a** in the presence of CsF.[a]



Run	Substrate	Catalyst[b]	Ligand	Time [h]	Product	Yield [%]
1	**3a**	$Ni(acac)_2$/DIBAL-H	PPh_3	16	**1aa**	-
2	**3b**	$Ni(acac)_2$/DIBAL-H	PPh_3	2	**1ab**	-
3	**3a**	Pd_2dba_3	-	4	**1aa**	18
4	**3b**	Pd_2dba_3	-	18	**1ab**	43
5	**3b**	Pd_2dba_3	PPh_3	18	**1ab**	5
6	**3b**	Pd_2dba_3	dppb	6	**1ab**	6
7	**3b**	Pd_2dba_3	$P(o\text{-tol})_3$	2	**1ab**	73
8	**3c**	Pd_2dba_3	$P(o\text{-tol})_3$	2	**1ac**	2
9	**3d**	Pd_2dba_3	$P(o\text{-tol})_3$	2	**1ad**	78

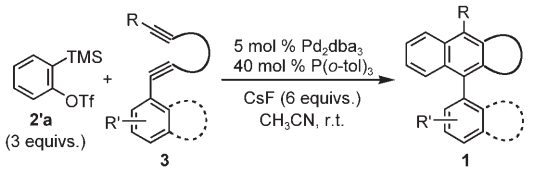
[a] All reactions were carried out in CH_3CN at room temperature in the presence of **2′a** (3 equivs.) and CsF (6 equivs.).

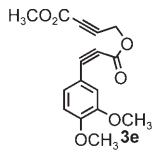
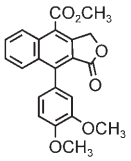
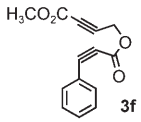
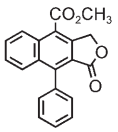
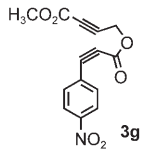
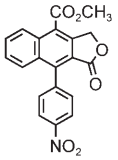
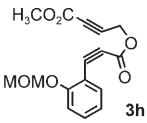
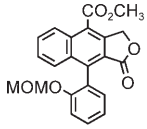
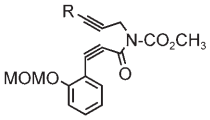
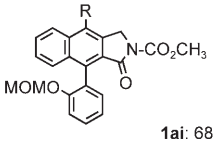
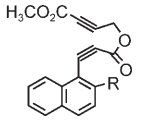
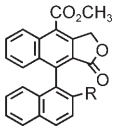
[b] For runs 1 and 2, the Ni(0) catalyst was prepared by reduction of $Ni(acac)_2$ (20 mol%) with DIBAL-H (40 mol%) in the presence of PPh_3 (80 mol%). For runs 3–9, 5 mol% of Pd_2dba_3 was used. For runs 5, 7, 8 and 9, 40 mol% of a ligand was used. For run 6, 20 mol% of dppb was used.

$(acac)_2$, PPh_3, and DIBAL-H,[3] the desired product **1aa** or **1ab** was not produced, and a complex mixture containing some polymerization products was obtained (runs 1 and 2). Thus, the catalyst was changed from nickel(0) to palladium(0)[5–7] (runs 3–9). The reaction of **3a** and aryne precursor **2′a** in the presence of CsF in CH_3CN at room temperature was again investigated using Pd_2dba_3 as a catalyst, and the desired product **1aa** was obtained in 18% yield (run 3). The reaction of **3b** under similar conditions afforded the desired product **1ab** in 43% yield (run 4). It is known that an alkyne having an electron-withdrawing substituent is more reactive than that having no or an electron-donating substituent for Ni(0)- or Pd(0)-catalyzed [2+2+2] cocyclization, which is consistent with the results of runs 3 and 4.[3,10] Next, ligand effects in the reaction of **3b** and **2′a** under similar conditions were investigated (runs 5–7), and it was found that P(*o*-tol)$_3$ is suitable for this reaction and that the yield of **1ab** was greatly improved to 73% (run 7). The reaction of **3c**, having an aldehyde on the alkyne, with **2′a** gave the desired product **1ac** in only 2% yield along with a complex mixture of polymerization products as a major product (run 8). On the other hand, the reaction of **3d**, which has an *N*-methoxy-*N*-methylcarboxamide moiety and was synthesized with the aim of application to the synthesis of natural arylnaphthalene lignans, under similar conditions gave the desired product in 78% yield (run 9).

To estimate the scope and limitations of the reaction, various diynes were subjected to the above optimal reaction conditions. The results are summarized in Table 2. The reaction of **3e** under similar conditions gave the corresponding arylnaphthalene **1ae** in good yield (77%) (run 1). The reaction of **3f**, having a phenyl group on the alkyne, gave the product **1af** in a slightly lower yield (54%) (run 2). An electron-withdrawing group on the benzene ring is tolerated in this reaction, and the reaction of **3g**, having a nitro group on the alkyne, gave the product **1ag** in good yield (66%) (run 3). A substituent (MOM group) at the *ortho*-position on the benzene ring is also tolerated, and the cyclized product **1ah** was obtained in 53% yield from **3h** (run 4). The cyclized product **1ai**, having a lactam structure in the arylnaphthalene skeleton, was also obtained from the nitrogen-containing diyne **3i** in good yield (run 5). On the other hand, the reaction of **3j**, having no electron-withdrawing substituent on the terminus of alkyne, gave the cyclized product in a low yield (27%, run 6) compared to that in the case of the reaction of **3i** (run 5), which is consistent with the above-described results in the cases of **3a** and **3b** (Table 1, runs 3 and 4). Binaphthyl skeletons can be also constructed by this reaction. Thus, the reaction of **3k** and benzyne derived from **2′a** under the similar conditions gave binaphthyl derivative **1ak** in 46% yield (run 7). It is noteworthy that the sterically hindered 2,2′-disubstituted-1,1′-binaphthyl derivative **1al** was also obtained by [2+2+2] cocyclization of diyne **3l** and benzyne derived from **2′a**, although the yield was fairly low (run 8).

Table 2. Pd(0)-catalyzed [2+2+2] cocyclization of various diynes **3** and benzyne derived from the precursor **2′a** and CsF.

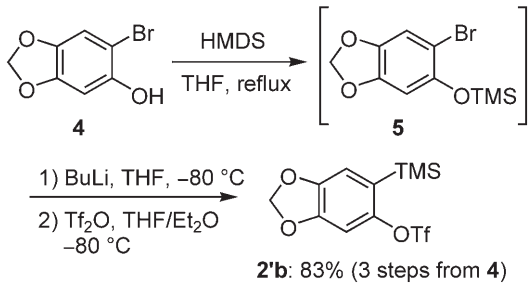


Run	Substrate	Time [h]	Product: Yield [%]
1	 **3e**	14	 **1ae**: 77
2	 **3f**	3.5	 **1af**: 54
3	 **3g**	14	 **1ag**: 66
4	 **3h**	7.5	 **1ah**: 53
5	 **3i** (R = CO_2CH_3)	12	 **1ai**: 68
6	**3j** (R = H)	12	**1aj**: 27
7	 **3k** (R = H)	2.5	 **1ak**: 46
8	**3l** (R = MOM)	22	**1al**: 18

Application of Pd(0)-Catalyzed [2+2+2] Cocyclization of Diyne and Aryne to the Syntheses of Natural Arylnaphthalene Lignans: Total Syntheses of Taiwanins C and E

Having established the Pd(0)-catalyzed [2+2+2] cocyclization of diynes and benzyne derived from **2′a**

producing various arylnaphthalene derivatives, we next turned our attention to applications of this methodology to the synthesis of natural arylnaphthalene lignans. Arylnaphthalene lignans, some of which are shown in Figure 1, occur widely in nature and possess various biological activities.[11] We planned to synthesize the natural arylnaphthalene lignans, taiwanins C and E,[12] through [2+2+2] cocyclization of diyne **3d** and aryne precursor **2′b**. The synthesis of aryne precursor **2′b** was achieved by a procedure similar to that reported by Pérez and Guitián,[6d] as shown in Scheme 3. TMS ether **5**, which was prepared from **4** and HMDS, was reacted with BuLi followed by treatment of the resulting silyl-migration product with Tf_2O, giving **2′b** in 83% yield (3 steps).

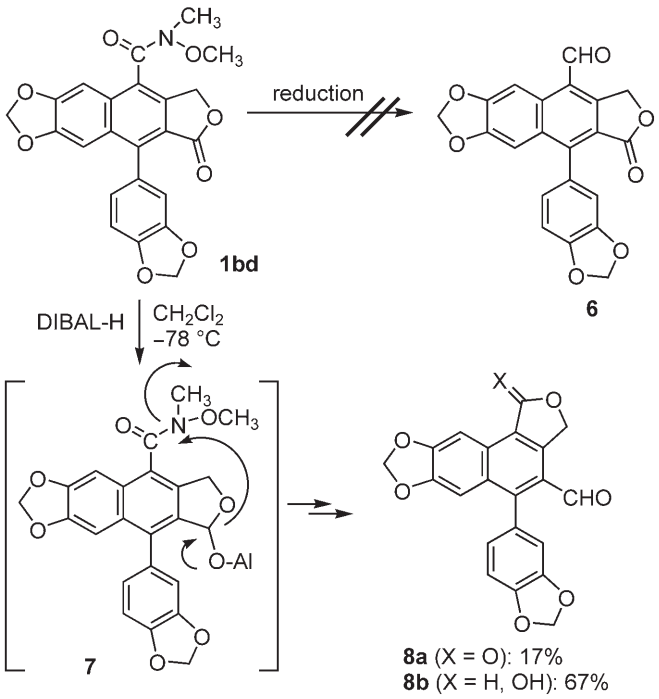


Scheme 3. Synthesis of aryne precursor **2′b**.

The reaction of diyne **3d** and aryne precursor **2′b** under the above-stated optimized conditions successfully proceeded and gave the arylnaphthalene derivative **1bd** in 61% yield (Scheme 4).

Next, we attempted transformation of arylnaphthalene product **1bd** into taiwanins. In order to convert **1bd** into aldehyde-lactone **6**, chemoselective reduction[13] of the amide moiety in **1bd** was initially tried using DIBAL-H at −78 °C (Scheme 5).

However, the desired product **6** was not obtained under the conditions used, although lactone-aldehyde **8a** and lactol-aldehyde **8b** were obtained in 17% and 67% yields, respectively. These products would have been produced through reduction of the lactone moiety in **1bd**, indicating that chemoselective reduction of the lactone moiety in **1bd** is relatively difficult at this stage.[14] On the other hand, when **1bd** was treated with NaOMe in CH_2Cl_2 at room temperature, ring-opening followed by rearrangement of the lactone ring occurred to produce lactone-ester **9** in 78% yield (Scheme 6).

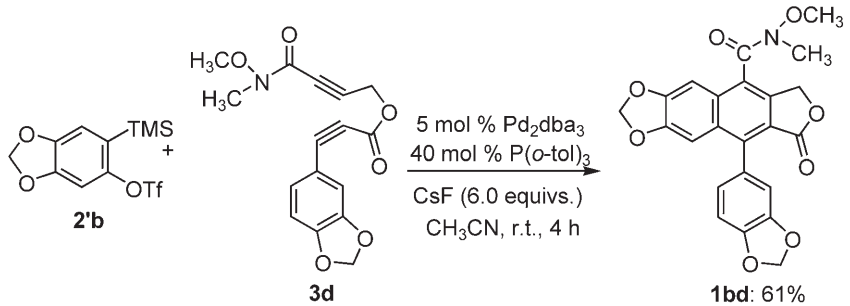


Scheme 5. Attempts at conversion of **1bd** into aldehyde **6**.

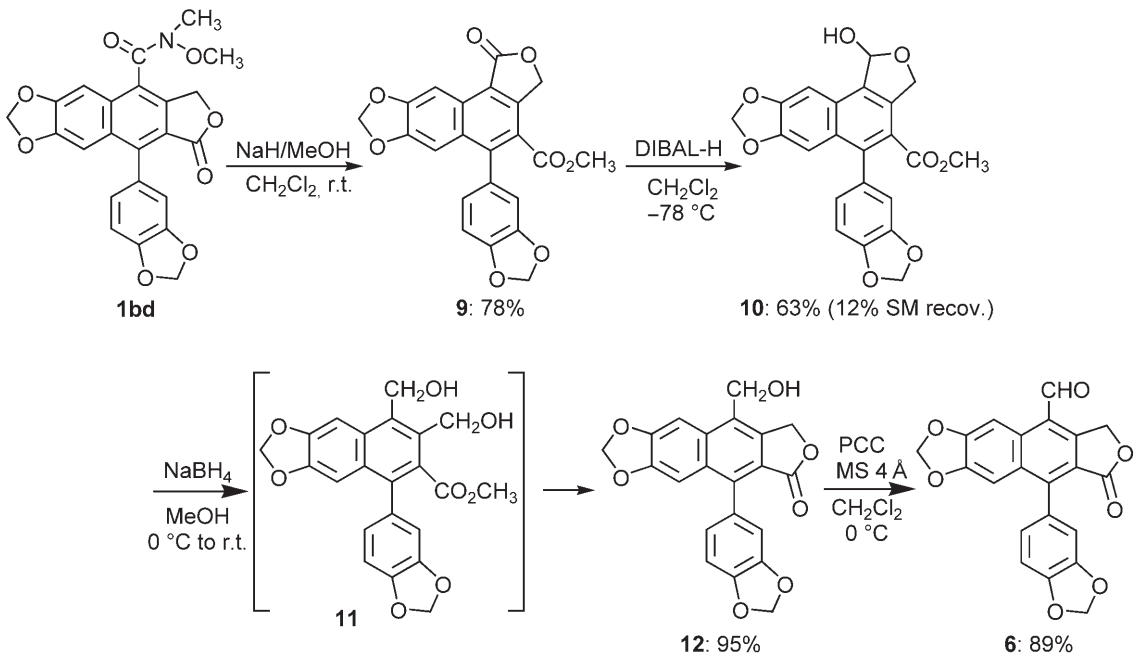
Chemoselective reduction of the lactone moiety in **9** proceeded successfully, giving lactol **10** in good yield. Treatment of **10** with $NaBH_4$ followed by acidic work-up gave the desired alcohol-lactone **12** in excellent yield in a one-pot operation *via* diol **11**. PCC oxidation of **12** afforded the desired aldehyde-lactone **6** in 89% yield.

Finally, transformations of aldehyde-lactone **6** into taiwanins C and E were investigated (Scheme 7).

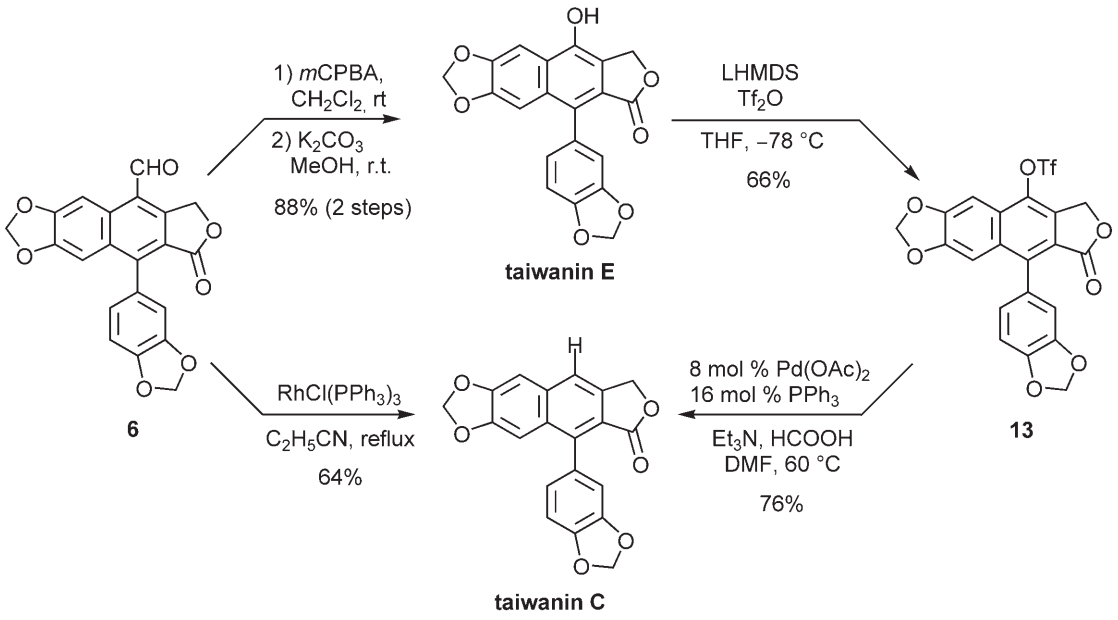
Baeyer–Villiger oxidation of **6** with *m*CPBA followed by hydrolysis of the corresponding formate gave taiwanin E in 88% yield (2 steps). The spectral



Scheme 4. [2+2+2] Cocyclization of diyne **3d** and aryne precursor **2′b**.



Scheme 6. Conversion of **1bd** into aldehyde **6**.

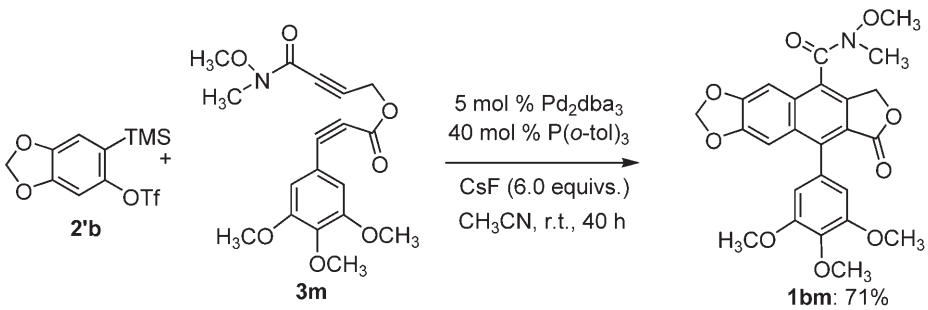


Scheme 7. Total syntheses of taiwanins C and E.

data were identical to those previously reported.[12i] On the other hand, taiwanin C was obtained in 64% yield directly from the same intermediate **6** in one step through a decarbonylation reaction by treatment of **6** with a stoichiometric amount of Wilkinson's catalyst.[15] In addition, conversion of aldehyde-lactone **6** into taiwanin C was also achieved without the use of a stoichiometric amount of expensive rhodium catalyst *via* Pd(0)-catalyzed hydrogenolysis[16] of triflate **13** derived from taiwanin E (Scheme 7).

Total Synthesis of Dehydrodesoxypodophyllotoxin

Encouraged by the successful syntheses of taiwanins C and E, we applied the present method to the total synthesis of dehydrodesoxypodophyllotoxin.[17] The [2+2+2] cocyclization of diyne **3m** and aryne precursor **2′b** under the optimized conditions again successfully proceeded and gave the corresponding product **1bm** in 71% yield (Scheme 8).



Scheme 8. [2+2+2] Cocyclization of diyne **3m** and aryne precursor **2′b**.

Conversion of **1bm** into dehydrodesoxypodophyllotoxin was succesfully achieved in a similar manner to the synthesis of taiwanin C *via* Pd(0)-catalyzed hydrogenolysis of the corresponding triflate **16** (Scheme 9). The spectral data of the synthetic dehydrodesoxypodophyllotoxin were identical to those previously reported.

Conclusions

We succeeded in developing the novel method for the synthesis of biaryls *via* Pd(0)-catalyzed [2+2+2] cocyclization of diynes and arynes, that could apply to the construction of various arylnaphthalene skeletons including the sterically hindered 2,2′-disubstituted-1,1′-binaphthyl. Furthermore, using this cocyclization as a key step, the total syntheses of taiwanin C, taiwanin E, and dehydrodesoxypodophyllotoxin were achieved. The present convergent strategy paves the way for the synthesis of various arylnaphthalene lignans by virtue of a variety of combinations of diynes and aryne precursors.

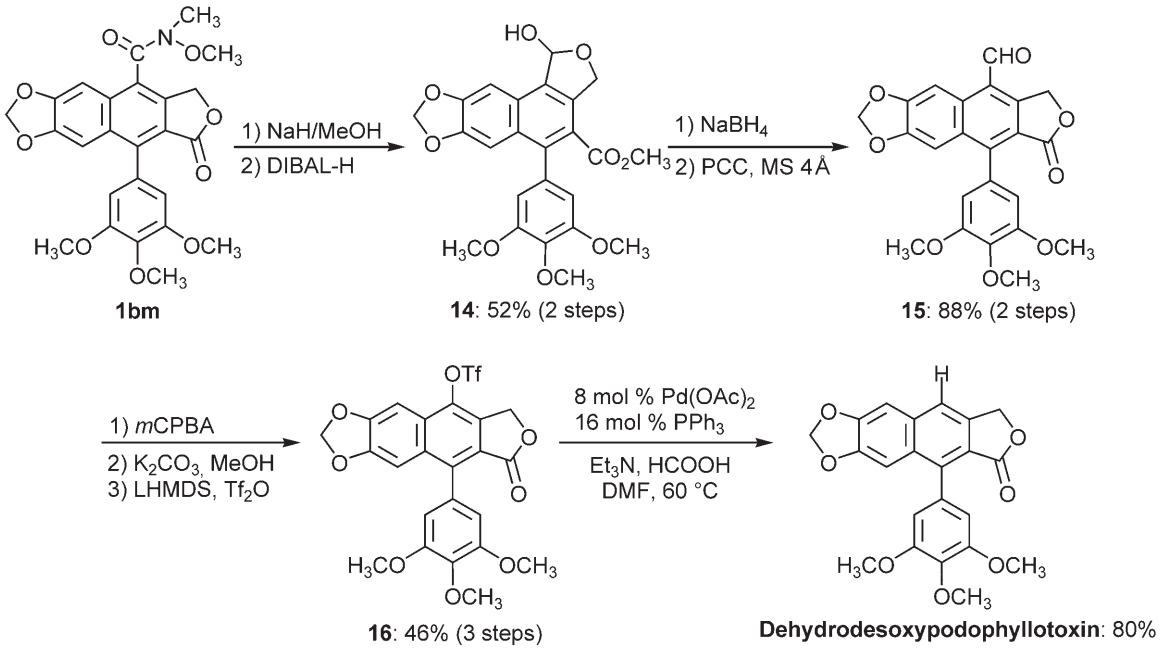
Experimental Section

General Information

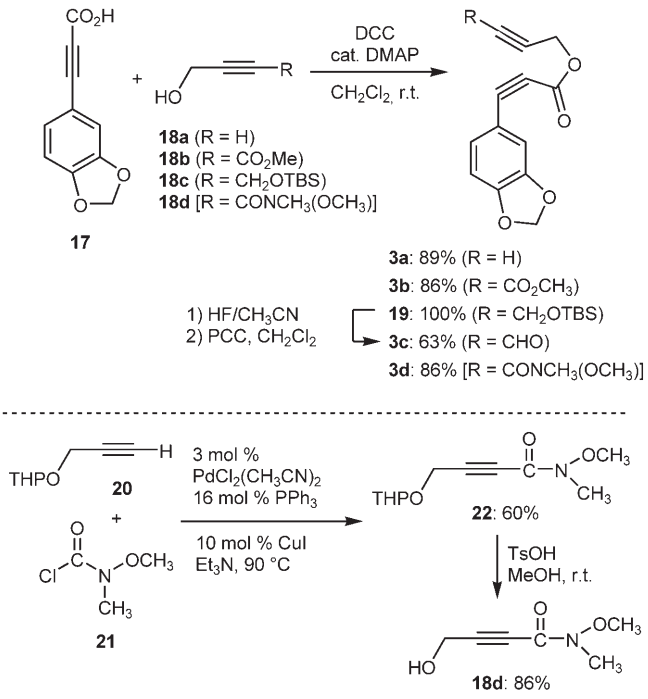
All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh), and flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh).

Preparation of Substrates 3a–j (See Scheme 10). Prop-2-ynyl 3-(Benzo[*d*][1,3]dioxol-5-yl)propiolate (3a)

To a solution of 3-(benzo[*d*][1,3]dioxol-5-yl)propiolic acid (**17**)[18] (2.21 g, 12 mmol), propargyl alcohol (**18a**) (1.4 mL,



Scheme 9. Total synthesis of dehydrodesoxypodophyllotoxin.



Scheme 10. Synthesis of substrates **3a–d**.

24 mmol), and DMAP (0.43 g, 3.4 mmol) in CH_2Cl_2 (55 mL) was added DCC (3.65 g, 18 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and dried. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 12/1) to give **3a** as an off-white solid; yield: 2.36 g (89%); mp 62–63 °C; IR (neat): ν = 3268, 2214, 2133, 1716 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.17 (dd, J = 1.6, 7.9 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.03 (s, 2H), 4.81 (d, J = 2.6 Hz, 2H), 2.54 (t, J = 2.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 53.1, 75.7, 76.8, 78.8, 88.2, 101.7, 108.7, 112.1, 112.5, 129.0, 47.5, 150.1, 153.0; EI-LR-MS: m/z = 228 (M^+), 173, 146; EI-HR-MS: m/z = 228.0418, calcd. for $C_{13}H_8O_4$: 228.0422.

Methyl 4-[3-(Benzo[*d*][1,3]dioxol-5-yl)propioloyloxy]-but-2-ynoate (3b)

Following the similar procedure for **3a**, the crude product, which was prepared from the carboxylic acid **17** (200 mg, 1.1 mmol), the propargylic alcohol **18b**[19] (181 mg, 1.6 mmol), DMAP (39 mg, 0.32 mmol), and DCC (326 mg, 1.6 mmol) in CH_2Cl_2 (5 mL) at room temperature for 20 min, was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **3b** as an off-white solid; yield: 258 mg (86%); mp 102–103 °C; IR (neat): ν = 2210, 1717, 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.18 (dd, J = 1.6, 8.1 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.03 (s, 2H), 4.92 (s, 2H), 3.80 (s, 3H); EI-LR-MS: m/z = 286 (M^+), 271, 173; EI-HR-MS: m/z = 286.0476, calcd. for $C_{15}H_{10}O_6$: 286.0477.

4-*tert*-Butyldimethylsilyloxybut-2-ynyl 3-(Benzo[*d*][1,3]-dioxol-5-yl)propiolate (19)

Following the similar procedure for **3a**, the crude product, which was prepared from **17** (82 mg, 0.42 mmol), the propargylic alcohol **18c**[20] (132 mg, 0.66 mmol), DMAP (15 mg, 0.12 mmol), and DCC (133 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) at room temperature for 1.5 h, was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give **19** as a colorless oil; yield: 195 mg (100%); IR (nujol): ν = 2212, 1715, 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.16 (dd, J = 1.6, 7.9 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.02 (s, 2H), 4.85 (t, J = 2.0 Hz, 2H), 4.37 (t, J = 2.0 Hz, 2H), 0.91 (s, 9H), 0.12 (s, 6H); EI-LR-MS: m/z = 372 (M^+), 329, 315, 241, 173; EI-HR-MS: m/z = 372.1380, calcd. for $C_{20}H_{24}O_5Si$ (M^+): 372.1393.

4-Hydroxybut-2-ynyl 3-(Benzo[*d*][1,3]dioxol-5-yl)propiolate

To a solution of **19** (273 mg, 0.73 mmol) in CH_3CN (3.4 mL) was added HF-CH_3CN solution (prepared by mixing concentrated aqueous HF with CH_3CN (ratio of 1:9), 0.9 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the solution was added saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with Et_2O. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/2) to give the corresponding alcohol as a colorless solid: yield: 179 mg 9(4%); mp 95–96 °C; IR (nujol): ν = 3517, 2211, 1681 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.17 (dd, J = 1.6, 8.3 Hz, 1H), 7.01 (d, J = 1.6 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.03 (s, 2H), 4.86 (t, J = 1.6 Hz, 2H), 4.33 (dt, J = 1.6, 6.3 Hz, 2H), 1.58 (t, J = 6.3 Hz, 1H); EI-LR-MS: m/z = 258 (M^+), 241, 173; EI-HR-MS: m/z = 258.0534, calcd. for $C_{14}H_{10}O_5$ (M^+): 258.0528.

3-Formylprop-2-ynyl 3-(Benzo[*d*][1,3]dioxol-5-yl)propiolate (3c)

To a solution of the above alcohol (86 mg, 0.33 mmol) in CH_2Cl_2 (1.6 mL) were added MS 4 Å (643 mg) and PCC (214 mg, 0.99 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. The mixture was diluted with Et_2O, and filtered through a pad of Florisil. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **3c** as a yellowish oil; yield: 57 mg (67%); IR (nujol): ν = 2907, 2209, 1714, 1673, 1602 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 9.25 (s, 1H), 7.21 (dd, J = 1.6, 7.9 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.03 (s, 2H), 4.99 (s, 2H); EI-LR-MS: m/z = 256 (M^+), 227, 199; EI-HR-MS: m/z = 256.0363, calcd. for $C_{14}H_8O_5$ (M^+): 256.0371.

N-Methoxy-*N*-methyl-4-(tetrahydro-2*H*-pyran-2-yloxy)-but-2-ynamide (22)

A solution of **20** (100 mg, 0.71 mmol), **21**[21] (137 mg, 1.1 mmol), $PdCl_2(CH_3CN)_2$ (5.8 mg, 0.02 mmol), PPh_3 (30 mg, 0.11 mmol), and CuI (15 mg, 0.077 mmol) in Et_3N (3.6 mL) was stirred at 90 °C for 2 h. The mixture was con-

centrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt = 8/1 to 2/1) to give **22** as a colorless oil; yield: 98 mg (61%); IR (neat): ν = 2240, 1644 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.84$ (s, 1H), 4.44 (s, 2H), 3.88–3.80 (m, 1H), 3.78 (s, 3H), 3.58–3.50 (m, 1H), 3.24 (s, 3H), 1.90–1.55 (m, 6H); EI-LR-MS: *m/z* = 227 (M^+), 167, 127; EI-HR-MS: *m/z* = 227.1156, calcd. for $C_{11}H_{17}NO_4$: 227.1157.

4-Hydroxy-*N*-methoxy-*N*-methylbut-2-ynamide (18d)

To a solution of **22** (949 mg, 4.2 mmol) in MeOH (11 mL) was added *p*-TsOH (80 mg, 0.42 mmol), and the mixture was stirred at room temperature for 2 h. To the mixture was added saturated aqueous $NaHCO_3$ solution, and the solution was concentrated. The solution was extracted with CH_2Cl_2 and the organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1/2) to give **18d** as a colorless oil; yield: 429 mg (81%); IR (neat): ν = 3395, 2239, 1639 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.45$ (s, 2H), 3.79 (s, 3H), 3.24 (s, 3H), 2.78 (br. s, 1H); EI-LR-MS: *m/z* = 143 (M^+), 83; EI-HR-MS: *m/z* = 143.0576, calcd. for $C_6H_9NO_3$: 143.0582.

3-(*N*-Methoxy-*N*-methylcarbamoyl)prop-2-ynyl 3-(Benzo[*d*][1,3]dioxol-5-yl)propiolate (3d)

Following the similar procedure for **3a**, the crude product, which was prepared from **17** (405 mg, 2.1 mmol), the propargylic alcohol **18d** (358 mg, 2.5 mmol), DMAP (77 mg, 0.63 mmol), and DCC (676 mg, 3.3 mmol) in CH_2Cl_2 (15 mL) at room temperature for 20 min, was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **3d** as a yellowish solid; yield: 576 mg (86%); mp 103–105 °C; IR (film): ν = 2210, 1714, 1644 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.17$ (dd, $J = 1.6$, 8.1 Hz, 1H), 7.01 (d, $J = 1.6$ Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 6.03 (s, 2H), 4.96 (s, 2H), 3.79 (s, 3H), 3.24 (s, 3H); EI-LR-MS: *m/z* = 315 (M^+), 284, 255, 183; EI-HR-MS: *m/z* = 315.0731, calcd. for $C_{16}H_{13}NO_6$: 315.0743.

Methyl 4-[3-(3,4-Dimethoxyphenyl)propioloyloxy]but-2-ynoate (3e)

To a solution of methyl methyl 3-(3,4-dimethoxyphenyl)propiolate[22] (1.00 g, 4.5 mmol) in MeOH (90 mL) was added 10% aqueous NaOH solution (45 mL), and the mixture was stirred at room temperature for 13.5 h. The mixture was acidified by the addition of 1 M aqueous HCl solution, and extracted with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the crude material of 3-(3,4-dimethoxyphenyl)propiolic acid was obtained, which was used in the next step without further purification; yield: 902 mg.

To a solution of the crude carboxylic acid (200 mg, 0.97 mmol) and **18b** (132 mg, 1.2 mmol) in THF (6.7 mL) were successively added PPh_3 (304 mg, 1.2 mmol) and a solution of DIAD (diisopropyl azodicarboxylate) (0.23 mL, 1.2 mmol) in THF (3.0 mL) at 0 °C, and the mixture was stirred at 70 °C for 4 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **3e** as a colorless solid; yield: 203 mg (69% for 2 steps); mp 125–126 °C; IR (film): ν = 2207, 1711, 1595, 1514, 1443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.80$ (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.93 (s, 2H), 6.85–6.87 (m, 1H), 7.08–7.08 (m, 1H), 7.24–7.26 (m, 1H); EI-LR-MS: *m/z* = 302 (M^+), 301, 287, 273, 189, 75; EI-HR-MS: *m/z* = 302.0789, calcd. for $C_{16}H_{14}O_6$: 302.0732.

Methyl 4-(3-Phenylpropioloyloxy)but-2-ynoate (3f)

To a solution of 3-phenylpropiolic acid (commercially available from Aldrich®, 200 mg, 0.97 mmol) and **18b** (133 mg, 1.2 mmol) in THF (6.3 mL) were successively added PPh_3 (306 mg, 1.2 mmol) and a solution of DIAD (0.23 mL, 1.2 mmol) in THF (3.2 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **3f** as a colorless solid; yield: 171 mg (72%); mp 50–52 °C; IR (film): ν = 2958, 2223, 1719, 1490, 1435, 1262, 1184, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$–7.61 (m, 2H), 7.45–7.50 (m, 1H), 7.39 (br. t, $J = 7.6$ Hz, 2H), 4.94 (s, 2H), 3.80 (s, 3H); EI-LR-MS: *m/z* = 241 (M^+–H), 227, 184, 129, 101; EI-HR-MS: *m/z* = 241.0498, calcd. for $C_{14}H_9O_4$: 241.0501.

Methyl 4-[3-(4-Nitrophenyl)propioloyloxy]but-2-ynoate (3g)

To a solution of 3-(4-nitrophenyl)propiolic acid (CAS Registry No. 2216–24–2, 88 mg, 0.458 mmol) and **18b** (63 mg, 0.55 mmol) in THF (3.5 mL) were successively added PPh_3 (306 mg, 1.2 mmol) and a solution of DIAD (0.10 mL, 0.55 mmol) in THF (1.5 mL) at 0 °C, and the mixture was stirred at 70 °C for 12 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **3g** as a colorless solid; yield: 61 mg (47%); mp 115–116 °C; IR (film): ν = 2231, 1716, 1597, 1524, 1436, 1349, 1263, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.27$ (d, $J = 8.8$ Hz, 2H), 7.77 (d, $J = 8.8$ Hz, 2H), 4.97 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 153.0$, 152.0, 148.7, 133.8, 125.6, 123.8, 84.8, 82.8, 79.6, 78.6, 53.0, 52.7; EI-MS: *m/z* = 286 (M^+–1), 272, 258, 240, 229, 213, 184, 174, 128; EI-HR-MS: *m/z* = 286.0366, calcd. for $C_{14}H_8NO_6$: 286.0351.

Methyl 3-[2-(Methoxymethoxy)phenyl]propiolate

To a solution of 1-(2,2-dibromovinyl)-2-(methoxymethoxy)-benzene[23] (4.29 g, 13.3 mmol) in THF (44 mL) was added BuLi (1.47 M hexane solution, 27.2 mL, 40 mmol) at −78 °C, and the mixture was stirred at the same temperature for 10 min. To the solution was added methyl chloroformate (3.1 mL, 40 mmol) at −78 °C, and the mixture was stirred at 0 °C for 1.5 h. To the mixture was added saturated aqueous NH_4Cl solution, and the mixture was extracted with AcOEt. The organic layer was washed with brine, and dried over

Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 50/1) to give the ester as a yellowish oil; yield: 1.51 (52%); IR (neat): ν = 3021, 2955, 2829, 2224, 1711, 1598, 1577, 1491, 1452, 1435, 1404, 1274, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.55 (m, 1H), 7.35–7.31 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.97–7.02 (m, 1H),), 5.26 (s, 2H), 3.84 (s, 3H), 3.52 (s, 3H); EI-MS: m/z = 220 (M^+), 205, 189, 175, 161, 144, 77; EI-HR-MS: m/z = 220.0722, calcd. for $C_{24}H_{16}O_4$: 220.0735.

Methyl 4-{3-[2-(Methoxymethoxy)phenyl]propioloyloxy}but-2-ynoate (3h)

To a solution of methyl 3-[2-(methoxymethoxy)phenyl]propiolate (1.21 g, 5.5 mmol) in MeOH (70 mL) was added 10% aqueous NaOH solution (55 mL), and the mixture was stirred at room temperature for 1 h. The mixture was acidified by the addition of 1M aqueous HCl solution, and the mixture was extracted with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the crude material of 3-[2-(Methoxymethoxy)-phenyl]propiolic acid was obtained, which was used in the next step without further purification; yield: 1.04 g.

To a solution of the crude carboxylic acid (247 mg, 1.2 mmol) and **18b** (164 mg, 1.4 mmol) in THF (7.5 mL) were successively added PPh_3 (378 mg, 1.4 mmol) and a solution of DEAD (0.23 mL, 1.4 mL) in THF (4.5 mL) at 0°C, and the mixture was stirred at room temperature for 2.5 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **3h** as a yellowish oil; yield: 292 mg (80%); IR (neat): ν = 2956, 2219, 1721, 1597, 1576, 1490, 1452, 1437, 1298, 1265, 1199, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (dd, J = 7.7, 1.7 Hz, 1H), 7.41 (ddd, J = 8.6, 7.5, 1.7 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.01 (br. t, J = 7.6 Hz, 1H), 5.28 (s, 2H), 4.94 (s, 2H), 3.80 (s, 3H), 3.53 (s, 3H); EI-MS: m/z = 301 (M^+−H), 287, 271, 241, 189, 159, 144, 116, 77; EI-HR-MS: m/z = 301.0707, calcd. for $C_{16}H_{13}O_6$: 301.0712.

3-[2-(Methoxymethoxy)phenyl]-*N*-(prop-2-ynyl)propiolamide

To a solution of the above-mentioned crude 3-[2-(methoxymethoxy)phenyl]propiolic acid (100 mg, 0.49 mmol) in CH_3CN (0.6 mL) were added PPh_3 (127 mg, 0.49 mmol), Et_3N (0.07 mL, 0.49 mmol), propargylamine (0.03 mL, 0.39 mmol), and CCl_4[24] (0.05 mL, 0.49 mmol) at room temperature, and the mixture was stirred for 10 h. After removal of the solvent, the residue was dissolved in Et_2O, and the Et_2O solution was filtered through a pad of Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give the amide as a colorless oil; yield: 52 mg (44%); IR (neat): ν = 3438, 3307, 3019, 2220, 1653, 1598, 1508, 1452, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J = 7.5, 1.7 Hz, 1H), 7.33–7.39 (m, 1H), 7.15 (br, d, J = 8.5 Hz, 1H), 6.95–7.02 (m, 1H), 6.12 (br. S, 1H), 5.26 (s, 2H), 4.15–4.18 (m, 2H), 3.52 (s, 3H), 2.27–2.32 (m, 1H); EI-MS: m/z = 243 (M^+), 212, 198, 130, 77; EI-HR-MS: m/z = 243.0892, calcd. for $C_{14}H_{13}NO_3$: 243.0895.

Methyl 4-{3-[2-(Methoxymethoxy)phenyl]-*N*-(methoxycarbonyl)propiolamido}but-2-ynoate (3i) and Methyl 3-[2-(Methoxymethoxy)phenyl]propioloyl(prop-2-ynyl)-carbamate (3j)

To a THF solution of LDA, which was prepared *in situ* by mixing *i*-Pr_2NH (0.09 mL, 0.65 mmol) and BuLi (1.56M hexane solution, 0.41 mL, 0.65 mmol) in THF (1.1 mL) at 0°C for 15 min, was added a solution of the above-mentioned 3-[2-(methoxymethoxy)phenyl]-*N*-(prop-2-ynyl)propiolamide (52 mg, 0.22 mmol) in THF (1.1 mL) at −78°C, and the mixture was stirred at the same temperature for 1 h. To the solution was added methyl chloroformate (0.04 mL, 0.45 mmol) at −78°C, and the mixture was stirred at the same temperature for 2 h. To the mixture was added saturated aqueous NH_4Cl solution, and the solution was extracted with Et_2O. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 6/1) to give **3i** (yield: 28 mg, 36%) and **3j** (yield: 38 mg, 59%) as a yellowish oil, respectively.

Spectral data of 3i: IR (neat): ν = 3021, 2957, 2208, 1718, 1659, 1597, 1575, 1490, 1441, 1411, 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J = 7.7, 1.7 Hz, 1H), 7.40 (ddd, J = 8.5, 7.4, 1.7 Hz, 1H), 7.16 (br. d, J = 8.5 Hz, 1H), 7.02 (m, 1H), 5.28 (s, 2H), 4.75 (s, 2H), 3.96 (s, 2H), 3.77 (s, 2H), 3.53 (s, 2H); EI-MS: m/z = 359 (M^+), 343, 329, 314, 283, 254; EI-HR-MS: m/z = 359.1011, calcd. for $C_{18}H_{17}NO_7$: 359.1005.

Spectral data of 3j: IR (neat): ν = 3020, 2958, 2208, 1752, 1656, 1597, 1491, 1442, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J = 7.7, 1.7 Hz, 1H), 7.39 (ddd, J = 8.5, 7.5, 1.7 Hz, 1H), 7.16 (br. d, J = 8.5 Hz, 1H), 7.01 (ddd, J = 7.7, 7.5, 0.9 Hz, 1H), 5.28 (s, 2H), 4.61 (d, J = 2.5 Hz, 2H), 3.96 (s, 3H), 3.53 (s, 3H), 2.22 (t, J = 2.5 Hz, 1H); EI-MS: m/z = 301 (M^+), 271, 241, 189, 77; EI-HR-MS: m/z = 300.0874 (M^+−H), calcd. for $C_{16}H_{14}NO_5$: 300.0872.

Methyl 4-[3-(Naphthalen-1-yl)propioloyloxy]but-2-ynoate (3k)

Following the similar procedure for **3a**, the crude product, which was prepared from 3-(naphthalen-1-yl)propiolic acid[25] (1.63 g, 8.3 mmol), the propargylic alcohol **18b**[19] (1.09 g, 9.5 mmol), DMAP (310 mg, 2.5 mmol), and DCC (2.79 g, 13.5 mmol) in CH_2Cl_2 (47 mL) at room temperature for 1.5 h, was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **3k** as a yellowish solid; yield: 1.29 g (53%); mp 92–94°C; IR (film): ν = 3021, 2954, 2250, 2217, 1714, 1586, 1509, 1436, 1273, 1196, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br. d, J = 8.3 Hz, 1H), 7.98 (br. d, J = 8.3 Hz, 1H), 7.86–7.91 (m, 2H), 7.62–7.68 (m, 1H), 7.55–7.60 (m, 1H), 7.48 (dd, J = 8.3, 7.5 Hz, 1H), 5.00 (s, 2H), 3.82 (s, 3H); EI-MS: m/z = 291 (M^+−H), 277, 233, 179, 163, 151; EI-HR-MS: m/z = 291.0658(M^+−H), calcd. for $C_{18}H_{11}O_4$: 291.0657.

Methyl 4-{3-[2-(Methoxymethoxy)naphthalen-1-yl]propioloyloxy}but-2-ynoate (3l)

To a solution of methyl 3-[2-(methoxymethoxy)naphthalen-1-yl]propiolate[3c] (571 mg, 2.1 mmol) on MeOH (26 mL) was added 10% aqueous NaOH solution (21 mL), and the mixture was stirred at room temperature for 1 h. The mixture was acidified by the addition of 1 M HCl aqueous solution, and the mixture was extracted with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the crude carboxylic acid was obtained, which was used in the next step without further purification; yield: 563 mg.

Following the similar procedure for **3a**, the crude product, which was prepared from the carboxylic acid (410 mg, 1.6 mmol), the propargylic alcohol **18b**[19] (236 mg, 2.1 mmol), DMAP (58.6 mg, 0.48 mmol), and DCC (528 mg, 2.6 mmol) in CH_2Cl_2 (8.0 mL) at room temperature for 1.5 h, was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **3l** as a yellowish oil; yield: 283 mg (50%); IR (neat): $\nu = 3021$, 2210, 1719, 1260 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$): $\delta = 8.23$ (br. d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.9$ Hz, 1H), 7.81 (br. d, $J = 8.1$ Hz, 1H), 7.61 (ddd, $J = 8.4$, 7.0, 1.3 Hz, 1H), 7.45 (ddd, $J = 8.1$, 7.0, 1.1 Hz, 1H), 7.43 (d, $J = 8.9$ Hz, 1H), 5.40 (s, 2H), 4.99 (s, 2H), 3.81 (s, 3H), 3.58 (s, 3H); EI-MS: $m/z = 352$ (M^+), 321, 239, 194; EI-HR-MS: $m/z = 352.0942$, calcd. for $C_{20}H_{16}O_6$: 352.0947.

[2+2+2] Cocyclization of Diynes 3a–l and Benzyne; General Procedure

A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol% to substrate diyne), P(*o*-tol)$_3$ (40 mol% to substrate diyne), and CsF (dried under vacuum at 100 °C for 2 h just before its use, 6.0 equivs. to substrate diyne) in degassed CH_3CN (0.04 M to Pd catalyst) was stirred at room temperature for 20 min. To the catalyst solution was added a solution of substrate diyne and benzyne precursor (3.0 equivs. to diyne) in CH_3CN (0.16 M to diyne) *via* a cannula at 0 °C, and the mixture was stirred at room temperature until the diyne disappeared on TLC. To the mixture was added saturated aqueous NH_4Cl solution, and the solution was stirred for 1 h with exposure to air. Then the mixture was extracted with AcOEt, the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel to give the cyclized product.

9-(Benzo[*d*][1,3]dioxol-5-yl)naphtho[2,3-*c*]furan-1(3*H*)-one (1aa): Mp 229–231 °C; IR (nujol): $\nu = 1760$, 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.96$ (d, $J = 8.3$ Hz, 1H), 7.89 (s, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.64 (dd, $J = 7.1$, 8.3 Hz, 1H), 7.50 (dd, $J = 7.1$, 8.3 Hz, 1H), 6.98 (d, $J = 7.9$ Hz, 1H), 6.86–6.82 (m, 2H), 6.08 (d, $J = 6.7$ Hz, 1H), 6.08 (d, $J = 6.7$ Hz, 1H), 5.45 (s, 2H); EI-LR-MS: $m/z = 304$ (M^+), 275; EI-HR-MS: $m/z = 304.0737$, calcd. for $C_{19}H_{12}O_4$: 304.0735.

Methyl 9-(Benzo[*d*][1,3]dioxol-5-yl)-1,3-dihydro-1-oxonaphtho[2,3-*c*]furan-4-carboxylate (1ab): Mp. 218–219 °C; IR (nujol): $\nu = 1770$, 1717 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 9.10$ (d, $J = 8.7$ Hz, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.81–7.75 (m, 1H), 7.59–7.53 (m, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 6.84–6.83 (m, 2H), 6.09 (d, $J = 6.3$ Hz, 2H), 5.64 (s, 2H), 4.10 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 52.5$, 70.1, 101.4, 108.3, 110.5, 115.3, 120.2, 123.6, 126.1, 127.0, 127.4, 128.8, 130.5, 133.9, 134.3, 144.6, 146.7, 147.6, 148.1, 166.3, 168.9; EI-LR-MS: $m/z = 362$ (M^+), 348, 331; EI-HR-MS: $m/z = 362.0779$, calcd. for $C_{21}H_{12}O_4$: 362.0790.

9-(Benzo[*d*][1,3]dioxol-5-yl)-1-oxo-1,3-dihydronaphtho-[2,3-*c*]furan-4-carbaldehyde (1ac): Mp. 209–211 °C (sublim.); IR (neat): $\nu = 2926$, 1679, 1672 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 11.16$ (s, 1H), 8.84 (d, $J = 8.6$ Hz, 1H), 8.03 (d, $J = 8.6$ Hz, 1H), 7.90 (t, $J = 7.9$, 8.6 Hz, 1H), 7.62 (dd, $J = 7.9$, 8.6 Hz, 1H), 7.00 (d, $J = 7.9$ Hz, 1H), 6.85–6.82 (m, 2H), 6.11 (s, 1H), 6.09 (s, 1H), 5.77 (s, 2H); EI-LR-MS: $m/z = 332$ (M^+), 303; EI-HR-MS: $m/z = 332.0691$, calcd. for $C_{20}H_{12}O_5$: 332.0684.

9-(Benzo[*d*][1,3]dioxol-5-yl)-1,3-dihydro-*N*-methoxy-*N*-methyl-1-oxonaphtho[2,3-*c*]furan-4-carboxamide (1ad): IR (neat): $\nu = 1768$, 1646 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J = 8.7$ Hz, 1H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 6.89–6.79 (m, 2H), 6.08 (s, 1H), 6.05 (s, 1H), 5.43 (s, 2H), 3.55 (s, 3H), 3.39 (s, 3H); EI-LR-MS: $m/z = 391$ (M^+), 331; EI-HR-MS; $m/z = 391.1065$, calcd. for $C_{22}H_{17}NO_6$: 391.1056.

Methyl 9-(3,4-Dimethoxyphenyl)-1,3-dihydro-1-oxonaphtho[2,3-*c*]furan-4-carboxylate (1ae): Mp 67–69 °C; IR (film): $\nu = 2953$, 1768, 1719, 1592, 1511, 1453 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.87$ (s, 3H), 4.00 (s, 3H), 4.11 (s, 3H), 5.64 (s, 2H), 6.88–6.95 (m, 2H), 7.04–7.07 (m, 1H), 7.75–7.81 (m, 1H), 7.93–7.96 (m, 1H), 9.11 (m, 1H); EI-LR-MS: $m/z = 378$ (M^+), 363, 347, 331, 75; EI-HR-MS: $m/z = 378.1103$, calcd. for $C_{22}H_{18}O_6$: 378.1106.

Methyl 1-Oxo-9-phenyl-1,3-dihydronaphtho[2,3-*c*]furan-4-carboxylate (1af): Mp 225–230 °C; IR (film): $\nu = 3020$, 2952, 1769, 1719, 1261, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.14$ (d, $J = 8.7$ Hz, 1H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.78 (ddd, $J = 8.8$, 6.8, 1.3 Hz, 1H), 7.50–7.58 (m, 4H), 7.33–7.38 (m, 2H), 5.65 (s, 2H), 4.11 (s, 3H); EI-MS: $m/z = 318$ (M^+), 243, 215, 129, 101, 77; EI-HR-MS: $m/z = 318.0891$, calcd. for $C_{20}H_{14}O_4$: 318.0892.

Methyl 9-(4-Nitrophenyl)-1,3-dihydro-1-oxonaphtho[2,3-*c*]furan-4-carboxylate (1ag): Mp 263–265 °C; IR (film): $\nu = 1766$, 1718, 1514, 1347, 1027 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 9.16$ (d, $J = 8.6$ Hz, 1H), 8.43 (d, $J = 8.6$ Hz, 2H), 7.83 (ddd, $J = 8.6$, 6.6, 1.3 Hz, 1H), 7.69 (d, $J = 7.9$ Hz, 1H), 7.50–7.70 (m, 3H), 5.69 (s, 2H), 4.13 (s, 3H); EI-MS: $m/z = 363$ (M^+), 348,334, 319, 303, 288, 276, 257, 230, 201, 189; EI-HR-MS: $m/z = 363.0747$, calcd. for $C_{20}H_{13}NO_6$: 363.0743.

Methyl 9-[2-(Methoxymethoxy)phenyl]-1-oxo-1,3-dihydronaphtho[2,3-*c*]furan-4-carboxylate (1ah): Mp 184–186 °C; IR (film): $\nu = 3019$, 2956, 2852, 1764, 1712, 1600, 1490, 1438, 1404, 1283, 1258, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.12$ (d, $J = 8.7$ Hz, 1H), 7.84 (d, $J = 8.7$ Hz, 1H), 7.77 (ddd, $J = 8.8$, 6.8, 1.2 Hz, 1H), 7.45–7.55 (m, 2H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.15–7.22 (m, 2H), 5.67 (d, $J = 16.0$ Hz, 1H), 5.62 (d, $J = 16.0$ Hz), 5.09 (d, $J = 7.0$ Hz, 1H), 4.90 (d, $J = 7.0$ Hz, 1H), 4.10 (s, 3H), 3.18 (s, 3H); EI-MS: $m/z = 378$ (M^+), 346, 316, 274; EI-HR-MS: $m/z = 378.1102$, calcd. for $C_{22}H_{18}O_6$ ($M^+ - H$): 378.1103.

Methyl 9-[(2-Methoxymethoxy)phenyl]-2-methoxycarbonyl-1-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-4-carboxylate (1ai): Mp 70–74 °C; IR (film): $\nu = 3020$, 2955, 1785, 1722, 1607, 1492, 1440, 1282, 1255, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.86$ (d, $J = 8.8$ Hz, 1H), 7.78 (br. d, $J = 8.5$ Hz,

1H), 7.72 (ddd, $J=8.7$, 6.6, 1.3 Hz, 1H), 7.46–7.7.53 (m, 1H), 7.46 (ddd, $J=8.5$, 6.6, 2.6 Hz, 1H), 7.25–7.35 (m, 1H), 7.10–7.18 (m, 2H), 5.17 (s, 2H), 5.11 (d, $J=6.8$ Hz, 1H), 4.83 (d, $J=6.8$ Hz, 1H), 4.13 (s, 3H), 3.92 (s, 3H), 3.12 (s, 3H); EI-MS: $m/z=435$ (M^+), 420, 390, 374, 358, 344, 302; EI-HR-MS: $m/z=435.1320$, calcd. for $C_{24}H_{21}NO_7$: 435.1318.

9-[(2-Methoxymethoxy)phenyl]-2-methoxycarbonyl-1-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole (1aj): Mp 201–203 °C; IR (film): $\nu=3060$, 3006, 2955, 1771, 1629, 1581, 1489, 1438, 1400, 1271, 1236, 1194 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): $\delta=7.94$ (br. d, $J=8.5$ Hz, 1H), 7.93 (br. s, 1H), 7.73 (d, $J=8.7$ Hz, 1H), 7.58–7.63 (m, 1H), 7.41–7.47 (m, 2H), 7.29 (br. d, $J=8.3$ Hz, 1H), 7.10–7.19 (m, 1H), 5.10 (d, $J=6.8$ Hz, 1H), 4.97 (s, 2H), 4.84 (d, $J=6.8$ Hz, 1H), 3.91 (s, 3H), 3.13 (s, 3H); EI-MS: $m/z=377$ (M^+), 332, 316; EI-HR-MS: $m/z=377.1259$, calcd. for $C_{22}H_{19}NO_5$: 377.1263.

Methyl 9-(Naphthalen-1-yl)-1-oxo-1,3-dihydronaphtho-[2,3-*c*]furan-4-carboxylate (1ak): Mp 215–222 °C; IR (film): $\nu=3019$, 2952, 1771, 1694, 1605, 1508, 1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.16$ (br. d, $J=8.7$ Hz, 1H), 8.04 (d, $J=8.3$ Hz, 1H), 7.97 (d, $J=8.3$ Hz, 1H), 7.77 (ddd, $J=8.7$, 6.6, 1.3 Hz, 1H), 7.65 (dd, $J=8.3$, 7.0 Hz, 1H), 7.58 (br. d, $J=7.5$ Hz, 1H), 7.39–7.50 (m, 3H), 7.22–7.28 (m, 1H), 7.04 (br. d, $J=8.3$ Hz, 1H),), 5.69 (s, 2H), 4.14 (s, 3H); EI-MS: $m/z=368$ (M^+-H), 353, 293; EI-HR-MS: $m/z=368.1053$, calcd. for $C_{24}H_{16}O_4$: 368.1048.

Methyl 9-[2-(Methoxymethoxy)naphthalen-1-yl]-1-oxo-1,3-dihydronaphtho[2,3-*c*]furan-4-carboxylate (1al): Mp 180–184 °C; IR (nujol): $\nu=1771$, 1725, 1593, 1508, 1239, 802, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.17$ (br. d, $J=8.8$ Hz, 1H), 8.04 (d, $J=9.0$ Hz, 1H), 7.90 (d, $J=8.3$ Hz, 1H), 7.77 (ddd, $J=8.8$, 6.8, 1.3 Hz, 1H), 7.63 (d, $J=9.0$ Hz, 1H), 7.60 (br. d, $J=7.9$ Hz, 1H), 7.39–7.45 (m, 1H), 7.31–7.37 (m, 1H), 7.15–7.21 (m, 1H), 6.79 (br. d, $J=8.5$ Hz, 1H), 5.69 (s, 2H), 5.16 (d, $J=7.0$ Hz, 1H), 4.96 (d, $J=7.0$ Hz, 1H), 4.14 (s, 3H), 3.15 (s, 3H); EI-MS: $m/z=428$ (M^+), 398, 383, 366, 351, 339, 324, 308; EI-HR-MS: $m/z=428.1263$, calcd. for $C_{26}H_{20}O_6$: 428.1260.

Total Synthesis of Taiwanins; 5-Bromobenzo[*d*][1,3]-dioxol-6-yl Trifluoromethanesulfonate (Aryne Precursor, 2′b)

To a solution of 6-bromobenzo[*d*][1,3]dioxol-5-ol (**4**) (876 mg, 4.0 mmol) in THF (17 mL) was added hexamethyldisilazane (1.3 mL, 6.2 mmol), and the mixture was refluxed with stirring for 3 h. The mixture was concentrated under vacuum, and the residual crude **5** was dissolved in THF (17 mL). To the mixture was added BuLi (1.65 M hexane solution, 2.6 mL, 4.3 mmol) at −100 °C, and the temperature of the mixture was raised to −80 °C for 20 min. The mixture was again cooled to −100 °C, and Et_2O (17 mL) and trifluoromethanesulfonic anhydride (0.88 mL, 5.2 mmol) were added to the mixture. The temperature of the mixture was again raised to −80 °C for 20 min, and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at the same temperature, and the mixture was slowly warmed to room temperature. The solution was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 30/1) to give **2′b** as a purplish oil; yield: 1.15 g (83% from **4**); IR (neat): $\nu=1330$, 1142 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=6.88$ (s, 1H), 6.84 (s, 1H), 6.03 (s, 2H), 0.33 (s, 9H); EI-LR-MS: $m/z=342$ (M^+), 327, 194; EI-HR-MS: $m/z=342.0197$, calcd. for $C_{11}H_{13}O_5F_3SSi$: 342.0205; anal. calcd. for $C_{11}H_{13}O_5F_3SSi$: C 38.59, H 3.83; found: C 38.58, H 3.83.

[2+2+2] Cocyclization of 3d and 2′b Producing 1bd

$Pd_2(dba)_3{\cdot}CHCl_3$ (26 mg, 0.025 mmol) and P(*o*-tol)$_3$ (61 mg, 0.20 mmol) were dissolved in CH_3CN (1.2 mL), and the mixture was stirred at room temperature for 15 min. The catalyst solution was added *via* a cannula using CH_3CN (1.0 mL) for washing to a solution of **3d** (160 mg, 0.51 mmol), **2′b** (530 mg, 1.6 mmol) and CsF (472 mg, 3.1 mmol) in CH_3CN (1.8 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. To the mixture was added saturataed aqueous NH_4Cl solution, and the solution was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3/2) to give **1bd** (yield: 134 mg, 61%) as a yellowish solid along with the recovery of unchanged **2′b** (257 mg, 48% recovery). **1bd:** Mp 239–241 °C (decomp.); IR (neat): $\nu=1762$, 1653 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=7.26$ (s, 1H), 7.25 (s, 1H), 6.97 (d, $J=7.9$ Hz, 1H), 6.83–6.74 (m, 2H), 6,10–6.06 (m, 4H), 5.35 (s, 2H), 3.51 (s, 3H), 3.43 (s, 3H); EI-LR-MS $m/z=435$ (M^+), 375; EI-HR-MS: $m/z=435.0942$, calcd. for $C_{23}H_{17}NO_8$: 435.0954.

Transformation of 1bd into Taiwanins C and E; Reduction of 1bd with DIBAL-H Producing 8a and 8b (Scheme 5)

To a solution of **1bd** (40 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was DIBAL-H (1.0 M toluene solution, 0.1 mL, 0.01 mmol) at −78 °C, and the mixture was stirred at the same temperature for 4 h. To the solution was added an additional DIBAL-H (0.1 mL, 0.01 mmol) at the same temperature, and the mixture was stirred for 1.5 h. To the mixture were successively added MeOH (0.03 mL) and saturated potassium sodium tartrate aqueous solution at −78 °C, and the solution was warmed to room temperature. The solution was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O = 30/1 \sim 8/1$) to give **8a** (yield: 6 mg, 17%) and **8b** (yield: 23 mg, 67%).

8a: IR (nujol): $\nu=2901$, 1753, 1673 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=9.89$ (s, 1H), 8.52 (s, 1H), 7.08 (s, 1H), 7.00 (d, $J=7.9$ Hz, 1H), 6.87 (d, $J=2.0$ Hz, 1H), 6.84 (dd, $J=7.9$, 2.0 Hz, 1H), 6.15 (s, 2H), 6.13 (d, $J=5.3$ Hz, 1H), 6.13 (d, $J=5.3$ Hz, 1H), 5.67 (s, 2H); EI-LR-MS: $m/z=376$ (M^+), 347, 319; EI-HR-MS: m/z = 376.0591, calcd. for $C_{21}H_{12}O_7$: 376.0583.

8b: IR (neat): $\nu=3382$, 2922, 1673 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=9.84$ (s, 1H), 7.42 (s, 1H), 7.01 (s, 1H), 6.96 (d, $J=7.3$ Hz, 1H), 6.84 (d, $J=1.3$ Hz, 1H), 6.82 (s, 1H), 6.79 (d, $J=1.3$, 7.3 Hz, 1H), 6.11–6.08 (m, 4H), 5.70–5.61 (m, 1H), 5.44 (dd, $J=4.6$, 15.2 Hz, 1H), 3.31 (s, 1H); EI-LR-MS: $m/z=360$ (M^+-OH-1), 332

($M^+-OH-CHO$); EI-HR-MS: $m/z=360.0626$, calcd. for $C_{21}H_{12}O_6$ (M^+-OH-1): 360.0634.

1,3,7,9-Tetrahydro-5-(benzo[*d*][1,3]dioxol-5-yl)-4-carbomethoxy-1-oxo-2,7,9-trioxaindeno[5,6-*e*]indene (9)

To a solution of **1bd** (320 mg, 0.74 mmol) in CH_2Cl_2 (7 mL) were successively added MeOH (7 mL) and NaH (88 mg, 60% dispersion in mineral oil, 2.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 h. To the mixture was added saturated aqueous NH_4Cl at 0 °C, and the solution was evaporated in order to remove MeOH. The resultant aqueous layer was extracted with AcOEt, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=45/1$) to give **9** as a colorless solid; yield: 236 mg (78%); mp 218–220 °C; IR (neat): $\nu=1732$, 1703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=8.51$ (s, 1H), 6.98 (s, 1H), 6.94 (d, $J=7.9$ Hz, 1H), 6.74 (d, $J=1.6$ Hz, 1H), 6.71 (dd, $J=1.6$, 7.9 Hz, 1H), 6.12 (s, 2H), 6.08 (d, $J=2.8$ Hz, 1H), 6.08 (d, $J=2.8$ Hz, 1H), 5.54 (d, $J=3.2$ Hz, 2H), 3.69 (s, 3H); EI-LR-MS: $m/z=406$ (M^+), 374, 346; EI-HR-MS: $m/z=406.0692$, calcd. for $C_{22}H_{14}O_8$ (M^+) 406.0688.

1,3,7,9-Tetrahydro-5-(benzo[*d*][1,3]dioxol-5-yl)-4-carbomethoxy-1-hydroxy-2,7,9-trioxaindeno[5,6-*e*]indene (10)

To a solution of **9** (26 mg, 0.064 mmol) in CH_2Cl_2 (1.6 mL) was added DIBAL-H (1.0 M toluene solution, 0.076 mL, 0.076 mmol) at −78 °C, and the mixture was stirred at the same temperature for 2 h. To the mixture were successively added MeOH (0.03 mL) and saturated aqueous potassium sodium tartrate solution at −78 °C, and the solution was warmed to room temperature. The solution was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=50/1$ to 6/1) to give **10** (yield: 16 mg, 63%) as a colorless solid along with the starting material **9** (3 mg, 12%). **10:** Mp 182–183 °C; IR (neat): $\nu=3381$, 1706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=7.39$ (s, 1H), 6.95 (s, 1H), 6.90 (d, $J=7.9$ Hz, 1H), 6.87–6.84 (m, 1H), 6.73 (d, $J=7.9$ Hz, 1H), 6.69–6.63 (m, 1H), 6.06 (s, 1H), 5.60–5.50 (m, 1H), 5.30 (m, 1H), 3.63 (s, 3H), 3.09 (d, $J=7.9$ Hz, 1H); EI-LR-MS: $m/z=408$ (M^+), 390, 376; EI-HR-MS: $m/z=408.0850$, calcd for $C_{22}H_{16}O_8$ (M^+): 408.0845.

1,3,6,8-Tetrahydro-4-(benzo[*d*][1,3]dioxol-5-yl)-10-hydroxymethyl-3-oxo-2,6,8-trioxaindeno[5,6-*f*]indene (12)

To a solution of **10** (124 mg, 0.30 mmol) in MeOH/THF (8 mL/8 mL) was added $NaBH_4$ (59 mg, 1.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. To the mixture was added again $NaBH_4$ (59 mg, 1.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 15 h. Then, to the mixture was added again $NaBH_4$ (22 mg, 0.60 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture was added 5% aqueous HCl at 0 °C, then the mixture was evaporated in order to remove MeOH and THF. The resultant aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=9/2$) to give **12** as a colorless solid; yield: 109 mg (95%); mp 240–241 °C; IR (neat): $\nu=3438$, 1751 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=7.47$ (s, 1H), 7.13 (s, 1H), 6.95 (d, $J=7.5$ Hz, 1H), 6.77–6.73 (m, 2H), 6.10 (s, 2H), 6.07 (d, $J=6.9$ Hz, 1H), 6.07 (d, $J=6.9$ Hz, 1H), 5.53 (s, 2H), 5.16 (s, 2H); EI-LR-MS: $m/z=378$ (M^+), 349; EI-HR-MS: $m/z=378.0741$, calcd. for $C_{21}H_{14}O_7$ (M^+): 378.0740.

1,3,6,8-Tetrahydro-4-(benzo[*d*][1,3]dioxol-5-yl)-10-formyl-3-oxo-2,6,8-trioxaindeno[5,6-*f*]indene (6)

To a solution of **12** (109 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) were added MS 4 Å (545 mg) and PCC (186 mg, 0.86 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. The mixture was dilute with Et_2O, and filtered through a pad of Florisil. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=50/1$) to give **6** as a yellowish solid; yield: 96 mg (89%); mp 269–270 °C (sublim.); IR (neat): $\nu=$ 2907, 1757, 1682 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=10.9$ (s, 1H), 8.16 (s, 1H), 7.22 (s, 1H), 6.99 (d, $J=7.3$ Hz, 1H), 6.80 (s, 1H), 6.79 (d, $J=7.3$ Hz, 1H), 6.17 (s, 2H), 6.09 (d, $J=6.6$ Hz, 2H), 5.70 (s, 1H); EI-LR-MS: $m/z=376$ (M^+), 358, 347; EI-HR-MS: $m/z=376.0584$, calcd. for $C_{21}H_{12}O_7$ (M^+): 376.0583.

Synthesis of Taiwanin C from 6 Using $RhCl(PPh_3)_3$

To a solution of **6** (14 mg, 0.037 mmol) in C_2H_5CN (2 mL) was added $RhCl(PPh_3)_3$ (48 mg, 0.052 mmol), and the mixture was refluxed for 2 h. The reaction mixture was cooled to 0 °C, and EtOH was added to the solution. The mixture was concentrated, and the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=60/1$) to taiwanin C (yield: 8 mg, 64%) as a colorless solid, whose spectral data were identical with those previously reported by Padwa et al.[12n]

Synthesis of Taiwanin E from 6

To a solution of **6** (64 mg, 0.17 mmol) in CH_2Cl_2 (4.2 mL) was added *m*CPBA (8234 mg, 1.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O. The solution was successively washed with 10% saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and brine, and dried over Na_2SO_4. After removal of the solvent, the crude formate was dissolved in MeOH (7 mL), and K_2CO_3 (35 mg, 0.25 mmol) was added to the solution. The mixture was stirred at room temperature for 30 min, and the mixture was diluted with Et_2O, and filtered. The filtrate was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O=30/1$) to give taiwanin E (yield: 54 mg, 88% from **6**) as a colorless solid, whose spectral data were identical with those previously reported by Iwasaki et al.[12i]

Conversion of Taiwanin E into Taiwanin C *via* Triflate 13

To a solution of taiwani E (30 mg, 0.084 mmol) in THF (4.2 mL) was added LHMDS (1.0 M THF solution, 0.13 mL, 0.13 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added Tf_2O (0.028 mL, 0.17 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at −78 °C, and the mixture was slowly warmed to room temperature. The solution was extracted with Et_2O, and the organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **13** as a colorless solid; yield: 27 mg (66 %); mp 165–166 °C; IR (film): $\nu = 1778$, 1468, 1215, 1037 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.44$ (s, 1H), 7.16 (s, 1H), 6.97 (s, 1H), 6.79–6.75 (m, 2H), 6.16 (s, 2H), 6.09 (d, $J = 6.5$ Hz, 1H), 6.08 (d, $J = 6.5$ Hz, 1H), 5.47 (s, 2H); EI-LR-MS: $m/z = 496$ (M^+), 363, 335; EI-HR-MS: $m/z = 496.0086$, calcd. for $C_{21}H_{11}SO_9F_3$: 496.0075.

To a solution of **13** (27 mg, 0.054 mmol), $Pd(OAc)_2$ (1.0 mg, 4.5 μmol), PPh_3 (2.3 mg, 8.7 μmol) in DMF (1.2 mL) were added triethylamine (0.023 mL, 0.165 mmol) and formic acid (0.004 mL, 0.106 mmol), and the mixture was stirred at 60 °C for 1.5 h. To the mixture was added brine, and the solution was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CH_2Cl_2/Et_2O = 40/1$) to give taiwanin C; yield: 14 mg (76 %).

Total Synthesis of Dehydroxydesoxypodophyllotoxin; Synthesis of 3-(*N*-Methoxy-*N*-methylcarbamoyl)prop-2-ynyl 3-(3,4,5-Trimethoxyphenyl)propiolate (3m)

Following the similar procedure for **3e**, the crude product, which was prepared from 3-(3,4,5-trimethoxyphenyl)propiolic acid (CAS Registry No. 4698–21–9, 980 mg, 4.1 mmol), propargylic alcohol **18d** (710 mg, 5.0 mmol), PPh_3 (1.3 g, 5.0 mmol) and DIAD (1.0 mL, 5.0 mmol) in THF (14 mL) at 0 °C for 2 h, was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give **3m** as a yellowish oil; yield: 1.2 g (88 %); IR (neat): $\nu = 2940$, 2213, 1717, 1649, 1577, 1454, 1414 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.24$ (br, 3H), 3.79–3.90 (m, 12H), 4.98 (s, 2H), 6.85 (s, 2H); EI-LR-MS: $m/z = 361$ (M^+), 330, 315, 290, 275, 257; EI-HR-MS: $m/z = 361.1154$, calcd. for $C_{18}H_{19}NO_7$: 361.1161.

[2+2+2] Cocyclization of 3m and 2′b Producing 1bm

$Pd_2(dba)_3{\cdot}CHCl_3$ (41 mg, 0.040 mmol), P(*o*-tol)$_3$ (97 mg, 0.32 mmol), and CsF (727 mg, 4.79 mmol) were dissolved in CH_3CN (1.0 mL), and the mixture was stirred at room temperature for 20 min. To the catalyst solution was added a solution of **3m** (288 mg, 0.80 mmol) and **2b** (821 mg, 2.4 mmol) in CH_3CN (1.8 mL) at 0 °C, and the mixture was stirred at room temperature for 40 h. To the mixture was added saturated aqueous NH_4Cl solution, and the solution was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 30/1) to give **1bm** as a yellowish solid; yield: 272 mg (71 %); mp 266–268 °C; IR (film): $\nu = 2937$, 1767, 1644, 1580, 1504, 1465, 1413 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (s, 1H), 7.14 (s, 1H), 6.51–6.58 (m, 2H), 6.11 (s, 2H), 5.37 (br, 2H), 3.97 (s, 3H), 3.84–3.86 (m, 6H), 3.44–3.52 (m, 6H); EI-LR-MS: $m/z = 481$ (M^+), 451, 421, 406, 393; EI-HR-MS: $m/z = 481.1368$, calcd. for $C_{25}H_{23}NO_9$ (M^+): 481.1372.

Methyl 1-Oxo-5-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2,7,9-trioxadicyclopenta[*a*,*g*]naphthalene-4-carboxylate

Following the similar procedure for **9**, the crude product, which was prepared from **1bm** (263 mg, 0.55 mmol), MeOH (2.8 mL), and NaH (66 mg, 60 % dispersion in mineral oil, 1.6 mmol) in CH_2Cl_2 (2.8 mL) at room temperature for 24 h, was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give the corresponding lactone as a colorless solid; yield: 210 mg (85 %); mp 287–289 °C; IR (film): $\nu = 2912$, 1730, 1580, 1498, 1464, 1410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.64$ (s, 3H), 3.85–3.97 (m, 9H), 3.53 (s, 2H), 6.13 (s, 2H), 6.48 (s, 2H), 6.99 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 52.1$, 56.2, 61.1, 70.2, 100.2, 102.1, 105.1, 106.5, 119.3, 120.5, 129.0, 130.7, 134.0, 137.6, 145.9, 147.4, 149.0, 151.4, 153.1, 166.4, 171.1; EI-LR-MS: $m/z = 452$ (M^+-H), 437, 423, 405, 389, 377; EI-HR-MS $m/z = 452.11059$ (M^+-H), calcd. for $C_{24}H_{20}O_9$: 452.11070.

1-Hydroxy-5-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-2,7,9-trioxa-dicyclopenta[*a*,*g*]naphthalene-4-carboxylic acid methyl ester (14)

Following the similar procedure for **10**, the crude product, which was prepared from the above lactone (110 mg, 0.24 mmol) and DIBAL-H (1.0 M toluene solution, 0.29 mL, 0.29 mmol) in CH_2Cl_2 (6.0 mL) at −78 °C for 2 h, was purified by column chromatography on silica gel (hexane/AcOEt = 2/1) to give **14** (yield: 67 mg, 61 %) as a colorless solid along with the recovered lactone (8 mg, 7 %). **14:** Mp 208–210 °C; IR (film): n = 3441, 2940, 1701, 1582, 1508, 1465 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.93$ (m, 1H), 3.60 (s, 3H), 3.83 (m, 6H), 3.95 (s, 3H), 5.35 (s, 1H), 5.53–5.60 (m, 1H), 6.07 (s, 2H), 6.47–6.48 (m, 2H), 6.85–6.89 (m, 1H), 6.98 (s, 1H), 7.40 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 51.9$, 56.2 (2H), 61.0, 73.7, 100.3, 101.7, 101.8, 104.8, 106.8, 106.9, 121.3, 127.2, 130.1, 133.6, 134.6, 135.1, 137.3, 142.3, 148.2, 149.6, 152.9, 167.6; EI-LR-MS: $m/z = 452$ (M^+-2H), 436, 421, 405; FAB-HR-MS: $m/z = 452.1117$ (M^+-2H), calcd. for $C_{24}H_{20}O_9$: 452.1139.

9-Hydroxymethyl-5-(3,4,5-trimethoxyphenyl)-8*H*-furo[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-6-one

Following the similar procedure for **12**, the crude diol, which was prepared from **14** (61 mg, 0.13 mmol) and $NaBH_4$ (36 mg, 1.1 mmol) in THF (3.4 mL) and MeOH (3.4 mL) at 0 °C for 16 h, was treated with 5 % HCl at 0 °C. After the usual work-up, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1/1) to give the corresponding alcohol as a colorless solid; yield: 52 mg (92 %); mp 276–279 °C; IR (film): $\nu = 3489$, 2920, 1747, 1734, 1614, 1582, 1507, 1468, 1410 cm^{-1}; ^1H NMR (270 MHz, DMSO-

d_6): $\delta = 3.77$–3.82 (m, 9H), 5.01 (d, $J = 5.5$ Hz, 2H), 5.51 (d, $J = 5.5$ Hz, 1H), 6.23 (s, 2H), 6.61 (s, 2H), 6.95 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (68 MHz, DMSO-d_6): $\delta = 56.9$, 59.5, 61.0, 69.1, 101.3, 103.1, 103.8, 108.3, 119.0, 130.7, 131.0, 131.6, 132.6, 137.9, 139.0, 139.4, 148.8, 150.7, 153.4, 170.1; EI-LR-MS: $m/z = 424$ (M^+), 409, 393, 381; EI-HR-MS: $m/z = 424.1155$ (M^+), calcd. for $C_{23}H_{20}O_8$: 424.1158.

8-Oxo-9-(3,4,5-trimethoxy-phenyl)-6,8-dihydrofuro-[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxole-5-carbaldehyde (15)

Following the similar procedure for **6**, the crude product, which was prepared from the above alcohol (33 mg, 0.24 mmol), PCC (50 mg, 0.23 mmol), and MS 4 Å (150 mg) in CH_2Cl_2 (3.8 mL) at 0 °C for 2 h, was purified by column chromatography on silica gel (hexane/AcOEt = 1/2) to give **15** as a colorless solid; yield: 32 mg (98%); mp 285–286 °C; IR (film): $\nu = 3389$, 2914, 1761, 1676, 1620, 1586, 1498, 1475, 1417 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.85$ (s, 6H), 3.98 (s, 3H), 5.71 (s, 2H), 6.18 (s, 2H), 6.52 (s, 1 2), 7.21 (s, 1H), 8.16 (s, 1H), 10.94 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 56.2$, 61.0, 69.9, 98.5, 102.5, 104.9, 106.9, 119.2, 122.8, 129.5, 131.6, 134.0, 138.3, 144.7, 146.4, 148.7, 152.3, 153.1, 168.5, 189.1; EI-LR-MS: $m/z = 422$ (M^+), 422, 407, 391, 347; EI-HR-MS: $m/z = 422.1008$, calcd. for $C_{23}H_{18}O_8$: 422.1001.

8-Oxo-9-(3,4,5-trimethoxyphenyl)-6,8-dihydrofuro-[3′,4′:6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl Trifluoromethanesulfonate (16)

Following the similar procedure for conversion of **6** to **13**, the crude alcohol was obtained through Bayer–Villiger oxidation of **15** (16 mg, 0.037 mmol) using *m*CPBA (51 mg, 0.29 mmol) in CH_2Cl_2 (0.9 mL) at 0 °C for 2 h followed by hydrolysis using K_2CO_3 (7.6 mg, 0.55 mmol) in MeOH (1.2 mL) at room temperature for 4 h. Then the crude alcohol was treated with LHMDS (1.0 M THF solution, 0.05 mL, 0.05 mmol) and Tf_2O (8.4 μL, 0.05 mmol) in THF (1.8 mL) at −78 °C. After the usual work-up, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1/1) to give **16** as a colorless solid; yield: 9 mg (46%, 3 steps); mp 221–224 °C; IR (film): $\nu = 2924$,1766 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 3.85$ (s, 6H), 3.97 (s, 3H), 5.48 (s, 2H), 6.16 (s, 2H), 6.53 (s, 2H), 7.16 (s, 1H), 7.45 (s, 1H); EI-LR-MS: $m/z = 542$ (M^+), 409, 350; EI-HR-MS: $m/z = 542.0489$, calcd. for $C_{23}H_{17}F_3O_{10}S$: 542.0494.

Dehydrodesoxypodophyllotoxin

To a solution of **16** (7 mg, 0.013 mmol), $Pd(OAc)_2$ (0.2 mg, 0.001 mmol), PPh_3 (0.6 mg, 0.002 mmol) in DMF (0.3 mL) were added triethylamine (0.006 mL, 0.043 mmol) and formic acid (0.001 mL, 0.03 mmol), and the mixture was stirred at 60 °C for 1.5 h. To the mixture was added brine, and the solution was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give dehydrodesoxypodophyllotoxin (yield: 4 mg, 80%) as a colorless solid, whose spectral data were identical with those previously reported by Nishii et al.[17c]

Acknowledgements

This work was financially supported by Grant-in-Aid for Scientific Research (C) (No. 17590001) from the Japan Society for the Promotion of Sciences (JSPS), and by the Naito Foundation, which are gratefully acknowledged.

References

[1] For reviews, see: a) M. Sainsbury, *Tetrahedron* **1980**, *36*, 3327; b) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977; c) D. W. Knight, in: *Comprehensive Organic Synthesis*, Vol. 3, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, pp 481–520; d) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263; e) J. Hassan, M. Sévignon, C. Gozzi, E. Schultz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.

[2] For reviews, see: a) K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539; b) N. E. Shore, *Chem. Rev.* **1988**, *88*, 1081; c) D. B. Grotjahn, in: *Comprehensive Organometallic Chemistry II*, Vol. 12, (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon Press, Oxford, **1995**, pp 741–770; d) M. Lautens, W. Klute, W. Tam. *Chem. Rev.* **1996**, *96*, 49; e) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901.

[3] For our recent papers on Ni-catalyzed [2+2+2] cocyclization, see: a) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133; b) Y. Sato, T. Nishimata, M. Mori, *Heterocycles* **1997**, *44*, 443; c) Y. Sato, K. Ohashi, M. Mori, *Tetrahedron Lett.* **1999**, *40*, 5231.

[4] For [2+2+2] cycloaddition of Ni(0)-aryne complex and alkynes, see: a) M. A. Bennett, E. Wenger, *Organometallics* **1995**, *14*, 1267; b) M. A. Bennett, E. Wenger, *Organometallics* **1996**, *15*, 5536; c) M. A. Bennett, E. Wenger, *Chem. Ber.* **1997**, *130*, 1029.

[5] For Pd(0)-catalyzed [2+2+2] homocyclotrimerization of three molecules of arynes, see: a) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem. Int. Ed.* **1998**, *37*, 2659; b) D. Peña, D. Pérez, E. Guitián, L. Castedo, *Org. Lett.* **1999**, *1*, 1555; c) D. Peña, A. Cobas, D. Pérez, E. Guitián, L. Castedo, *Org. Lett.* **2000**, *2*, 1629; d) D. Peña, A. Cobas, D. Pérez, E. Guitián, L. Castedo, *Org. Lett.* **2003**, *5*, 1863.

[6] For Pd(0)-catalyzed [2+2+2] cocyclotrimerization of aryne-aryne-alkyne or aryne-alkyne-alkyne producing phenanthrene or naphthalene derivatives, see: a) D. Peña, D. Pérez, E. Guitián, L. Castedo, *J. Am. Chem. Soc.* **1999**, *121*, 5827; b) K. V. Radhakrishnan, E. Yoshikawa, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 7533; c) D. Peña, D. Pérez, E. Guitián, L. Castedo, *Synlett* **2000**, 1061; d) D. Peña, D. Pérez, E. Guitián, L. Castedo, *J. Org. Chem.* **2000**, *65*, 6944.

[7] For Pd(0)-catalyzed [2+2+2] cocyclotrimerization of aryne-aryne-alkene or aryne-alkyne-alkene, see: a) E. Yoshikawa, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2000**, *39*, 173; b) E. Yoshikawa, K. V. Radhakrishnan, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7280.

[8] A part of this work has recently been communicated; see: Y. Sato, T. Tamura, M. Mori, *Angew. Chem. Int. Ed.* **2004**, *43*, 2346.

[9] The *in situ* formation of benzyne from **2′a** with fluoride ion was reported, see: Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.
[10] a) L. D. Brown, K. Itoh, H. Suzuki, K. Hirai, J. A. Ibers, *J. Am. Chem. Soc.* **1978**, *100*, 8232; b) C. Stephan, C. Munz, H. Dieck, *J. Organomet. Chem.* **1993**, *452*, 223; see also see ref.[6a]
[11] For recent leading reviews of arylnaphthalene lignans, see: a) R. S. Ward, *Nat. Prod. Rep.* **1995**, *12*, 183; b) R. S. Ward, *Nat. Prod. Rep.* **1997**, *14*, 43; c) R. S. Ward, *Nat. Prod. Rep.* **1999**, *16*, 75.
[12] For references on the previous syntheses of taiwanin C and/or taiwanin E, see: a) T. L. Holmes, R. Stevenson, *J. Org. Chem.* **1971**, *36*, 3450; b) B. J. Arnold, S. M. Mellows, P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1* **1973**, 1266; c) Z. Horii, M. Tsujiuchi, K. Kanai, T. Momose, *Chem. Pharm. Bull.* **1977**, 25, 1803; T. Momose, K. Kanai, K. Hayashi, *Chem. Pharm. Bull.* **1978**, *26*, 3195; d) H. P. Plaumann, J. G. Smith, R. Rodrigo, *J. Chem. Soc., Chem. Commun.* **1980**, 354; S. O. De Silva, C. St. Denis, R. Rodrigo, *J. Chem. Soc., Chem. Commun.* **1980**, 995; e) J. Mann, S. E. Piper, L. K. P. Yeung, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2081; f) S. Takano, S. Otaki, K. Ogasawara, *Tetrahedron Lett.* **1985**, *26*, 1659; g) Y. Ishii, T. Ikariya, M. Saburi, S. Yoshikawa, *Tetrahedron Lett.* **1986**, *27*, 365; h) R. Stevenson, J. V. Weber, *J. Nat. Prod.* **1989**, *52*, 367; i) T. Ogiku, M. Seki, M. Takahashi, H. Ohmizu, T. Iwasaki, *Tetrahedron Lett.* **1990**, *31*, 5487; T. Ogiku, S. Yoshida, H. Ohmizu, T. Iwasaki, *J. Org. Chem.* **1995**, *60*, 4585, and references cited therein; j) S. Seko, Y. Tanabe, G. Suzukamo, *Tetrahedron Lett.* **1990**, *31*, 6883; Y. Tanabe, S. Seko, Y. Nishii, T. Yoshida, N. Utsumi, G. Suzukamo, *J. Chem. Soc., Perkin Trans. 1* **1996**, 2157; k) D. C. Harrowven, *Tetrahedron Lett.* **1991**, *32*, 3735; S. R. Flanagan, D. C. Harrowven, M. Bradley, *Tetrahedron* **2002**, *58*, 5989, and references cited therein; l) K. Kobayashi, Y. Kanno, S. Seko, H. Suginome, *J. Chem. Soc., Perkin Trans. 1* **1992**, 3111; m) T. Hattori, H. Tanaka, Y. Okaishi, S. Miyano, *J. Chem. Soc., Perkin Trans. 1* **1995**, 235; n) J. E. Cochran, A. Padwa, *J. Org. Chem.* **1995**, *60*, 3938; A. Padwa, J. E. Cochran, C. O. Kappe, *J. Org. Chem.* **1996**, *61*, 3706; o) C. Cow, C. Leung, J. L. Charlton, *Can. J. Chem.* **2000**, *78*, 553.
[13] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815; for reviews, see: b) M. P. Sibi, *Org. Prep. Proc. Int.* **1993**, *25*, 15; c) M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517; d) J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340.
[14] Attempts at chemoselective reduction of **1bd** using other reducing reagents such as $LiAl(OtBu)_3H$[14a] and L-Selectride with MeOTf[14b] were unfruitful: a) M. Paris, C. Pothion, A. Heitz, J. Martinez, J.-A. Fehrentz, *Tetrahedron Lett.* **1998**, *39*, 1341; b) S.-C. Tsay, J. A. Robl, J. R. Hwu, *J. Chem. Soc., Perkin Trans. 1* **1990**, 757.
[15] All spectral data of synthetic taiwanin C are completely identical with those previously reported.[12n]
[16] S. Cacchi, P. G. Ciattini, E. Morea, G. Ortar, *Tetrahedron Lett.* **1986**, *27*, 5541.
[17] For the isolation of dehydrodesoxypodophillotoxin, see: a) H. Yamaguchi, M. Arimoro, M. Tanoguchi, T. Ishida, M. Inoue, *Chem. Pharm. Bull.* **1982**, *30*, 3212; for references on the synthesis of dehydrodesoxypodophyllotoxin, see: b) C. Cow, C. Leung, J. L. Charlton, *Can. J. Chem.* **2000**, *78*, 553; c) Y. Nishii, T. Yoshida, H. Asano, K. Wakasugi, J.-i. Morita, Y. Aso, E. Yoshida, J. Motoyoshiya, H. Aoyama, Y. Tanabe, *J. Org. Chem.* **2005**, *70*, 2667.
[18] Carboxylic acid **17** [CAS Registry No. 10231–46–6] was prepared in 91% yield by hydrolysis of the corresponding methyl ester, which was obtained from piperonal in 90% yield (2 steps) *via* dibromo-olefination with CBr_4-PPh_3 followed by treatment with BuLi-methyl chloroformate.
[19] R. C. Larock, C.-L. Liu, *J. Org. Chem.* **1983**, *48*, 2151.
[20] R. Livingston, L. R. Cox, S. Odermatt, F. Diederich, *Helv. Chim. Acta* **2002**, *85*, 3052.
[21] M. Murakami, Y. Hoshino, H. Ito, Y. Ito, *Chem. Lett.* **1998**, 163.
[22] D. H. Wadsworth, S. M. Geer, M. R. Detty, *J. Org. Chem.* **1987**, *52*, 3662.
[23] S. Thielges, E. Meddah, P. Bisseret, J. Eustache, *Tetrahedron Lett.* **2004**, *45*, 907.
[24] L. E. Barstow, V. J. Hruby, *J. Org. Chem.* **1971**, *36*, 1305.
[25] K. Okuhara, *J. Org. Chem.* **1976**, *41*, 1487.

