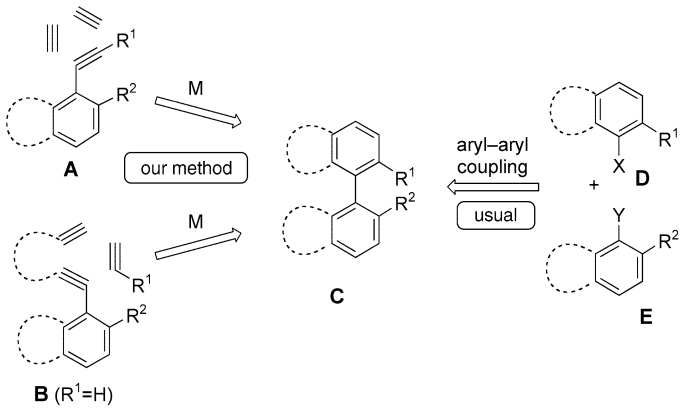
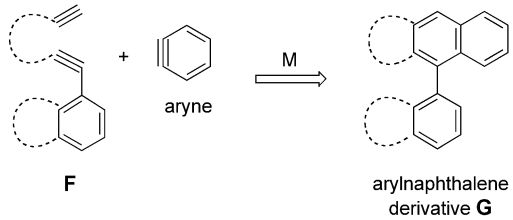


Scheme 1. Synthesis of biaryl compounds by [2+2+2] cocyclization.

zation of alkyne **A** and two molecules of acetylene or by that of diyne **B** and one molecule of acetylene.[3] In this context, we planned the synthesis of arylnaphthalene derivatives **G** through the [2+2+2] cocyclization of diyne **F** and an aryne (Scheme 2).



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

Biaryl Compounds

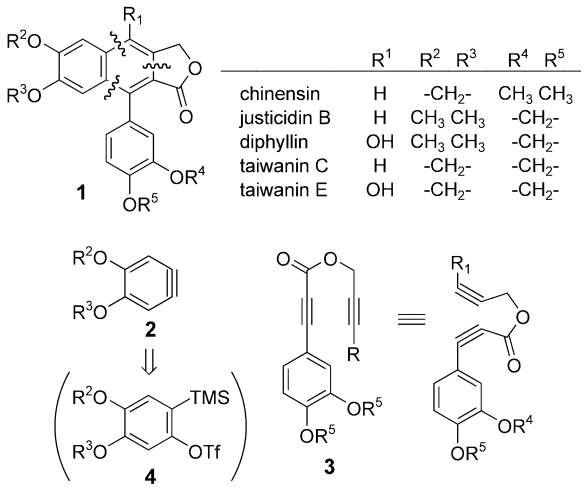
Arylnaphthalene Lignans through Pd-Catalyzed [2+2+2] Cocyclization of Arynes and Diynes: Total Synthesis of Taiwanins C and E

Yoshihiro Sato, Takayuki Tamura, and Miwako Mori**

Biaryl compounds are an important class of substances, not only as structures found in a variety of natural products, but also as a chiral source for asymmetric synthesis. A biaryl skeleton such as **C** is usually constructed through an aryl–aryl coupling reaction between two aromatic compounds such as **D** and **E** (Scheme 1).[1]

On the other hand, a transition-metal-catalyzed [2+2+2] cocyclization of alkynes is useful for the construction of an aromatic ring.[2] Recently, we reported a conceptually new methodology for the synthesis of biaryl molecules through Ni^0-catalyzed [2+2+2] cocyclization, by which various biaryls **C** were obtained in excellent yields by the [2+2+2] cocycli-

Arylnaphthalene lignans occur widely in nature and exhibit various biological activities.[4] If this [2+2+2] cocyclization were to proceed between diyne **3** and aryne **2**[5–8] (derived from precursor **4**[9]), various arylnaphthalene derivatives **1** would be synthesized in a few steps involving three C–C bond-forming reactions (Scheme 3). Those arylnaph-



Scheme 3. Retrosynthetic analysis for the synthesis of arylnaphthalene lignans. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

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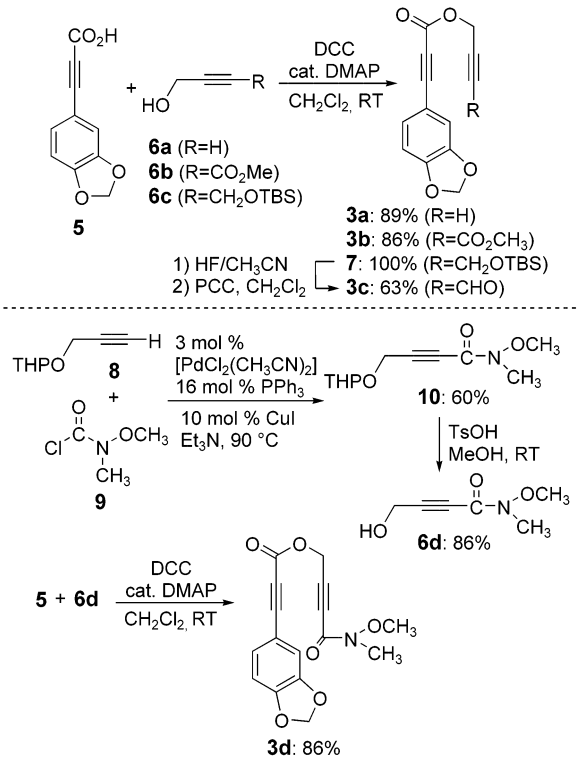
thalene derivatives should be key intermediates for the syntheses of chinensin, justicidin B, diphyllin, and taiwanins C and E. Herein we report the total synthesis of taiwanins C and E[10] by using [2+2+2] cocyclization as a key step.

With the aim of synthesizing the taiwanins, substrates **3a**–**3d** were synthesized as shown in Scheme 4. Diynes **3a** and **3b**

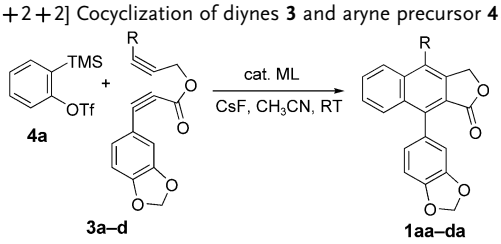


Scheme 4. Synthesis of substrates **3a**–**d**. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, PCC = pyridinium chlorochromate, Ts = *p*-toluenesulfonyl.

were prepared by DCC-mediated esterification of carboxylic acid **5**[11] with the corresponding propargylic alcohols **6a** and **6b**,[12] respectively. Diyne **3c** was synthesized by similar esterification of **5** with **6c**[13] followed by cleavage of the TBS protecting group of **7** and oxidation of the corresponding alcohol to the aldehyde. Diyne **3d**, which bears an *N*-methoxy-*N*-methylcarboxamide moiety (Weinreb amide),[14,15] was also synthesized by similar esterification of **5** with **6d**, which in turn was prepared by the Pd-catalyzed coupling reaction of **8** and **9**[16] followed by cleavage of the THP protecting group of **10**.

To examine the feasibility of the above-mentioned plan, we initially investigated the [2+2+2] cocyclization of diynes **3a**–**d** and a simple aryne precursor **4a** (Table 1). When the reaction of **3a** or **3b** and aryne precursor **4a** in the presence of CsF was carried out in CH_3CN at room temperature with a Ni^0 catalyst prepared from $[Ni(acac)_2]$, PPh_3, and DIBAL-H,[3] the desired product **1aa** or **1ba** was not produced, and a complex mixture containing some polymerization products was obtained (Table 1, entries 1 and 2). Thus, the catalyst was changed from nickel(0) to palladium(0)[6–8] (Table 1, entries 3–9). The reaction of **3a** and aryne precursor **4a** in the presence

Table 1: [2+2+2] Cocyclization of diynes **3** and aryne precursor **4a**[a]

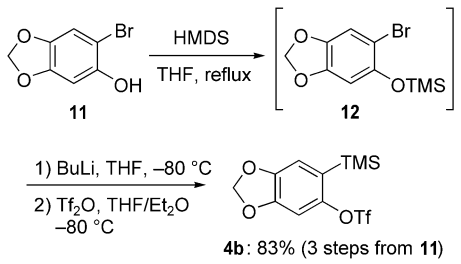


Run	3	R	Catalyst[b]	Ligand	*t* [h]	1	Yield [%]
1	**3a**	H	$[Ni(acac)_2]$/DIBAL-H	PPh_3	16	**1aa**	–
2	**3b**	CO_2CH_3	$[Ni(acac)_2]$/DIBAL-H	PPh_3	2	**1ba**	–
3	**3a**		$[Pd_2(dba_3)]$	–	4	**1aa**	18
4	**3b**		$[Pd_2(dba_3)]$	–	18	**1ba**	43
5	**3b**		$[Pd_2(dba_3)]$	PPh_3	18	**1ba**	5
6	**3b**		$[Pd_2(dba_3)]$	dppb	6	**1ba**	6
7	**3b**		$[Pd_2(dba_3)]$	P(*o*-tol)$_3$	2	**1ba**	57
8	**3c**	CHO	$[Pd_2(dba_3)]$	P(*o*-tol)$_3$	2	**1ca**	2
9	**3d**	$CON(OCH_3)CH_3$	$[Pd_2(dba_3)]$	P(*o*-tol)$_3$	2	**1da**	78

[a] All reactions were carried out in CH_3CN at room temperature in the presence of **4a** (3 equiv) and CsF (6 equiv). [b] For entries 1 and 2, 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 entries 3–9, $[Pd_2(dba)_3]$ (5 mol%) was used. For entries 5, 7, 8, and 9, 40 mol% of the ligand was used. For entry 6, dppb (20 mol%) was used. dba = dibenzylideneacetone, acac = acetylacetonate, DIBAL-H = diisobutylaluminum hydride, dppb = 1,1′-bis(diphenylphosphanyl)butane.

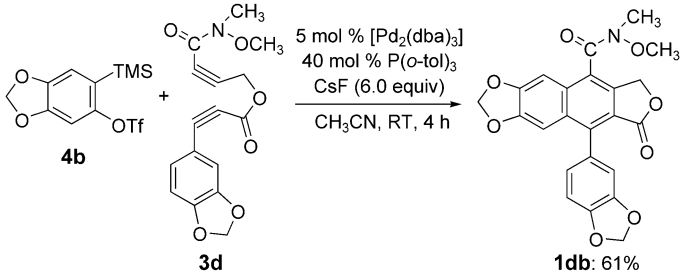
of CsF in CH_3CN at room temperature was again investigated with $[Pd_2(dba_3)]$ as catalyst, and the desired product **1aa** was obtained in 18% yield (Table 1, entry 3). The reaction of **3b** under similar conditions afforded the desired product **1ba** in 43% yield (Table 1, entry 4). It is known that an alkyne with an electron-withdrawing substituent is more reactive than an one without an electron-withdrawing group or even one with an electron-donating substituent in Ni^0- or Pd^0-catalyzed [2+2+2] cocyclization, which is consistent with the results of entries 3 and 4.[3,17] Next, ligand effects in the reaction of **3b** and **4a** under similar conditions were investigated (Table 1, entries 5–7), and it was found that P(*o*-tol)$_3$ is suitable for this reaction and that the yield of **1ba** was improved to 57% yield (Table 1, entry 7). The reaction of aldehyde-terminated **3c** with **4a** gave the desired product **1ca** in only 2% yield along with a complex mixture of polymerization products as the major product (Table 1, entry 8). On the other hand, the yield of the desired product was greatly improved to 78% in the reaction of **3d**, which has an *N*-methoxy-*N*-methylcarboxamide moiety, with **4a** under similar conditions (Table 1, entry 9).

Encouraged by these results, we turned our attention to the synthesis of taiwanins C and E through the Pd^0-catalyzed [2+2+2] cocyclization of diyne **3d** (Scheme 4) and aryne precursor **4b** (Scheme 5). Aryne precursor **4b** was synthesized by a procedure similar to that reported by Peña et al.:[7d] TMS ether **12**, which was prepared by the reaction of **11** with HMDS, was treated with BuLi. The resulting silyl-migration product was subsequently treated with Tf_2O to give **4b** in 83% yield (3 steps) (Scheme 5).



Scheme 5. Synthesis of benzyne precursor **4b**. HMDS = hexamethyldisilazane.

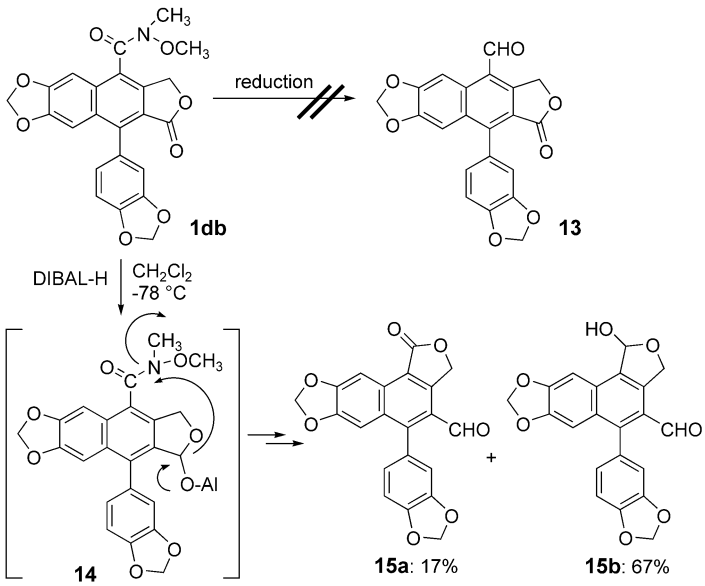
The reaction of **3d** and aryne precursor **4b** under the above-mentioned optimized conditions proceeded successfully and gave the desired product **1db** in 61% yield (Scheme 6).



Scheme 6. [2+2+2] Cocyclization of diyne **3d** and benzyne precursor **4b**.

We next attempted the transformation of arylnaphthalene product **1db** into the taiwanins. To convert **1db** into aldehyde lactone **13**, chemoselective reduction[14] of the amide moiety in **1db** was initially tried with DIBAL-H at −78 °C (Scheme 7). The desired product **13** was not obtained under these conditions, but lactone aldehyde **15a** and lactol aldehyde **15b** were obtained in 17 and 67% yield, respectively. These products would have been produced through reduction of the lactone moiety in **1db**, indicating that chemoselective reduction of the lactone moiety in **1db** is relatively difficult at this stage.[18] On the other hand, when **1db** 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 **16** in 78% yield (Scheme 8).

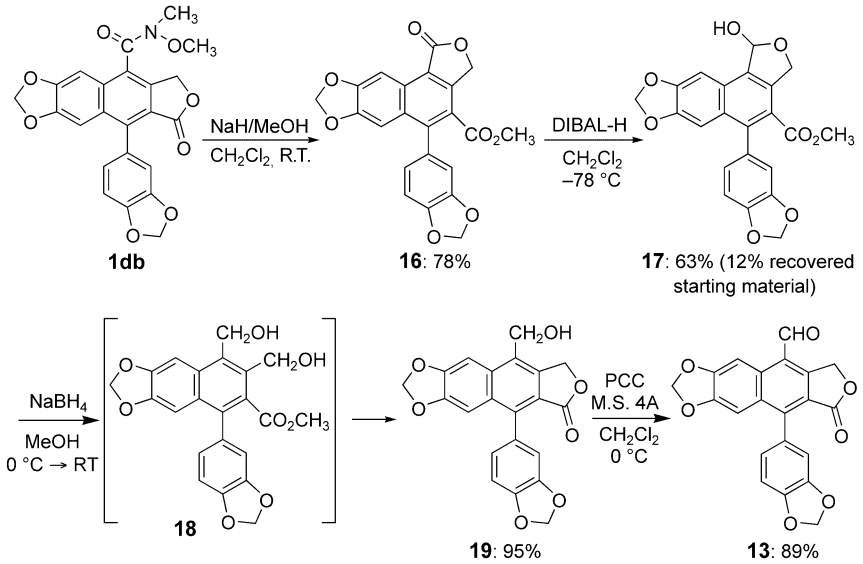
Chemoselective reduction of the lactone moiety in **16** successfully gave lactol **17** in good yield. Treatment of **17** with $NaBH_4$ followed by acidic workup gave the desired alcohol lactone **19** in excellent yield in a one-pot operation via diol **18**. Oxidation of **19** with PCC afforded the desired aldehyde lactone **13** in 89% yield.



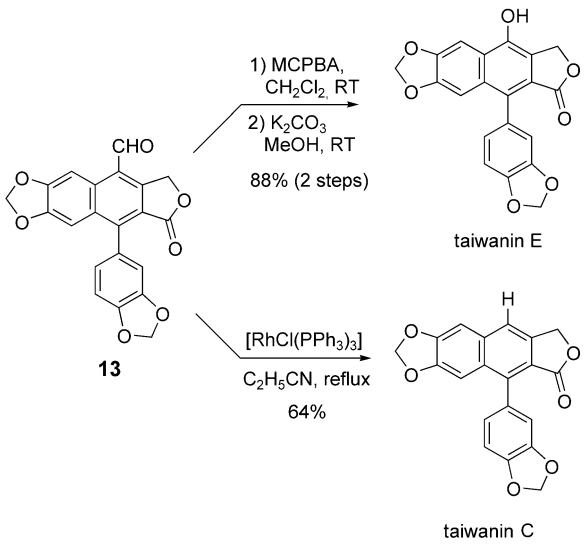
Scheme 7. Attempted chemoselective reduction of **1db**.

Finally, transformations of aldehyde–lactone **13** into taiwanins C and E were investigated (Scheme 9). Baeyer–Villiger oxidation of **13** with MCPBA followed by hydrolysis of the corresponding formate gave taiwanin E in 88% yield (2 steps). The spectral data of the product were completely identical with those previously reported.[10i] Taiwanin C was also obtained in 64% yield from the same intermediate **13** in one step through a decarbonylation reaction by treatment of **13** with the Wilkinson catalyst (Scheme 9).[19]

In conclusion, we succeeded in developing a novel method for the construction of arylnaphthalene skeletons through a Pd^0-catalyzed [2+2+2] cocyclization of diynes and arynes. This cocyclization was the key step in the total synthesis of taiwanins C and E, which required 9 and 10 steps, respec-



Scheme 8. Conversion of **1db** into the key intermediate **13**. M.S. = molecular sieves.



Scheme 9. Synthesis of taiwanins C and E from **13**.

tively, from reported or commercially available compounds. The present convergent strategy paves the way for the synthesis of various arylnaphthalene lignans from the combination of various diynes **3** and aryne precursors **4**. Further studies along this line are in progress in our laboratories.

Experimental Section

1db: $[Pd_2(dba)_3]\cdot CHCl_3$ (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 through a cannula to a solution of **3d** (160 mg, 0.51 mmol), **4b** (530 mg, 1.6 mmol), and CsF (472 mg, 3.1 mmol) in CH_3CN (1.8 mL) at 0 °C. (More CH_3CN (1.0 mL) was used to wash the catalyst through.) The mixture was stirred at room temperature for 4 h and then quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc, 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/EtOAc 3:2) to give **1db** (134 mg, 61 %) as a yellowish solid. Unconverted **4b** (257 mg, 48 %) was recovered. IR (neat): $\tilde{\nu}$ = 1762, 1653 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 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 LRMS: *m/z* (%): 435 [M$^+$] (375); EI HRMS: calcd for $C_{23}H_{17}NO_8$: 435.0954; found: 435.0942.

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Keywords: arynes · cycloaddition · lignans · palladium · synthetic methods · total synthesis

[1] For reviews, see: a) M. Sainsbury, *Tetrahedron* **1980**, *36*, 3327; b) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102*, 1006; *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, Oxford, **1991**, p. 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.* **1984**, *96*, 525; *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, Oxford, **1995**, p. 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 recent leading reviews on 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.

[5] For the [2+2+2] cycloaddition of an 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.

[6] For the Pd^0-catalyzed [2+2+2] homocyclotrimerization of three aryne molecules, see: a) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem.* **1998**, *110*, 2804; *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.

[7] For the Pd^0-catalyzed [2+2+2] cocyclotrimerization of an aryne–aryne–alkyne or and aryne–alkyne–alkyne system to produce 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.

[8] For the Pd^0-catalyzed [2+2+2] cocyclotrimerization of an aryne–aryne–alkene or an aryne–alkyne–alkene system, see: a) E. Yoshikawa, Y. Yamamoto, *Angew. Chem.* **2000**, *112*, 185; *Angew. Chem. Int. Ed.* **2000**, *39*, 173; b) E. Yoshikawa, K. V. Radhakrishnan, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7280.

[9] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

[10] For references on the previous synthesis of taiwanins C and/or 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 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 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.
[11] Carboxylic acid **5** [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 (two steps) by dibromoolefination with CBr_4–PPh_3 followed by treatment with BuLi–methyl chloroformate.
[12] R. C. Larock, C.-L. Liu, *J. Org. Chem.* **1983**, *48*, 2151.
[13] R. Livingston, L. R. Cox, S. Odermatt, F. Diederich, *Helv. Chim. Acta* **2002**, *85*, 3052.
[14] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
[15] For reviews, see: a) M. P. Sibi, *Org. Prep. Proced. Org. Prep. Proced. Int.* **1993**, *25*, 15; b) M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 517; c) J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340.
[16] M. Murakami, Y. Hoshino, H. Ito, Y. Ito, *Chem. Lett.* **1998**, 163.
[17] 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 references [3] and [7a].
[18] Attempts at the chemoselective reduction of **1db** with other reducing reagents such as $LiAl(OtBu)_3H$[18a] and L-Selectride with MeOTf[18b] were unsuccessful: 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.
[19] All spectral data of synthetic taiwanin C are completely identical to those previously reported.[10n]

