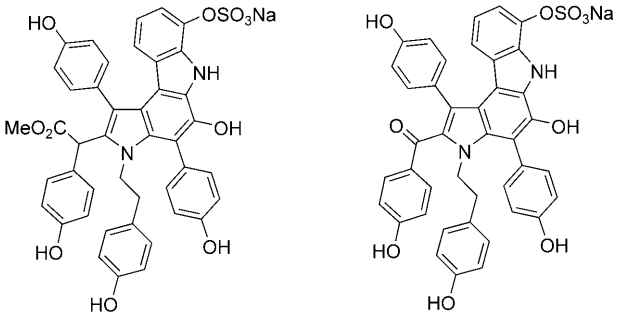
Natural Product Synthesis

DOI: 10.1002/ange.201001966

Total Synthesis of Dictyodendrin A and B**

*Kentaro Okano, Hideto Fujiwara, Toshiharu Noji, Tohru Fukuyama, and Hidetoshi Tokuyama**

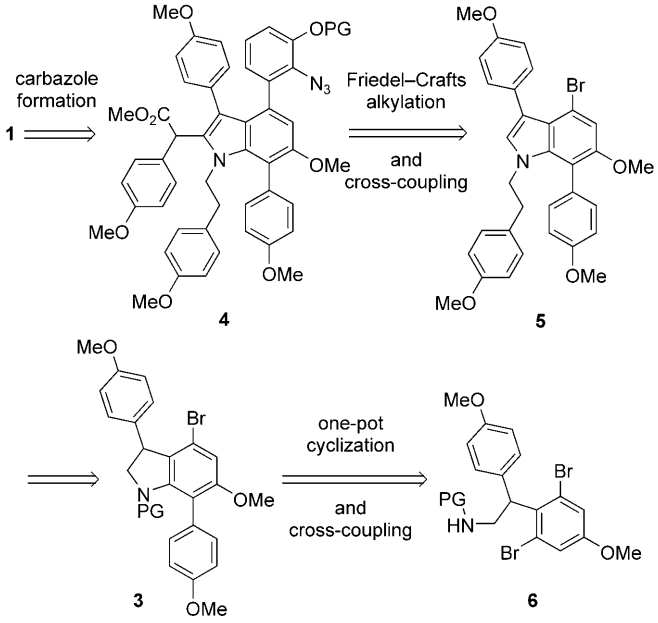
Dictyodendrins were isolated by Fusetani and Matsunaga from the marine sponge *Dictyodendrilla verongiformis* collected off Nagashima Island in Southern Japan in 2003 (Scheme 1).[1] These compounds have been the first marine



Scheme 1. Structures of dictyodendrin A (**1**) and B (**2**).

alkaloids known to possess inhibitory activity against telomerase. As telomerase is expressed in most tumor cell lines and its activity is associated with cell proliferation, telomerase inhibition represents a potential target for cancer chemotherapy. These compounds have received considerable attention as synthetic targets, not only owing to their intriguing biological activity but also to their characteristic structure, having the highly substituted pyrrolo[2,3-*c*]carbazole core. Among numerous studies toward dictyodendrin synthesis,[2] only Fürstner and co-workers[3] succeeded in the total synthesis of dictyodendrins B, C, and E, which was followed by the recent total synthesis of dictyodendrin B by Iwao and coworkers.[4] Herein, we report the first total synthesis of dictyodendrin A (**1**) and a total synthesis of B (**2**) which features a hitherto unprecedented benzyne-mediated one-pot cyclization/cross-coupling sequence.

In planning the synthesis of dictyodendrins, we designed a flexible route involving introduction of peripheral segments on the pivotal indoline intermediate **3** (Scheme 2). Thus, the



Scheme 2. Retrosynthetic analysis of dictyodendrin A (**1**). PG = protecting group.

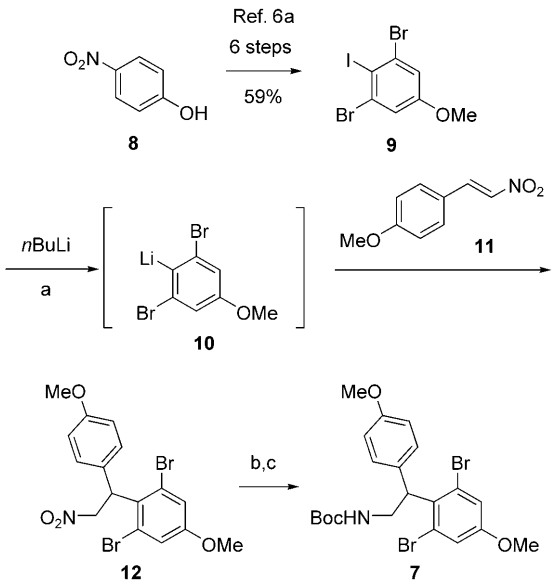
carbazole skeleton would be formed by installation of an aryl azide segment and intramolecular C–H insertion via a nitrene intermediate generated by thermolysis. The *para*-anisylacetate moiety in **4** could be introduced on bromoindole **5** by regioselective Friedel–Crafts alkylation. Since the *para*-anisylethyl group in **5** should be easily attached to the nitrogen atom by conventional alkylation, the key issue in the synthesis should be the construction of the highly substituted indoline intermediate **3**. The relatively high electrophilic nature of the aromatic rings and the sterically congested environment on the benzene ring may hamper the utilization of a classical heterocyclic synthesis and transition-metal-catalyzed cross-coupling reactions or amination reactions. We successfully circumvented these problems by developing a one-pot benzyne-mediated indoline formation/cross-coupling sequence using 2,6-dibromo-β-phenylethylamine derivative **6**.

The synthesis commenced with the preparation of **7**, employing the protocol developed in our total syntheses of duocarmycins (Scheme 3). After conversion of *para*-nitrophenol (**8**) into 2,6-dibromo-iodobenzene derivative **9**[5] in six steps,[6a] halogen–lithium exchange on treatment with BuLi in toluene at −78 °C,[6] followed by addition to nitroolefin **11** gave Michael adduct **12** in excellent yield.[6a,d] Then, the nitro

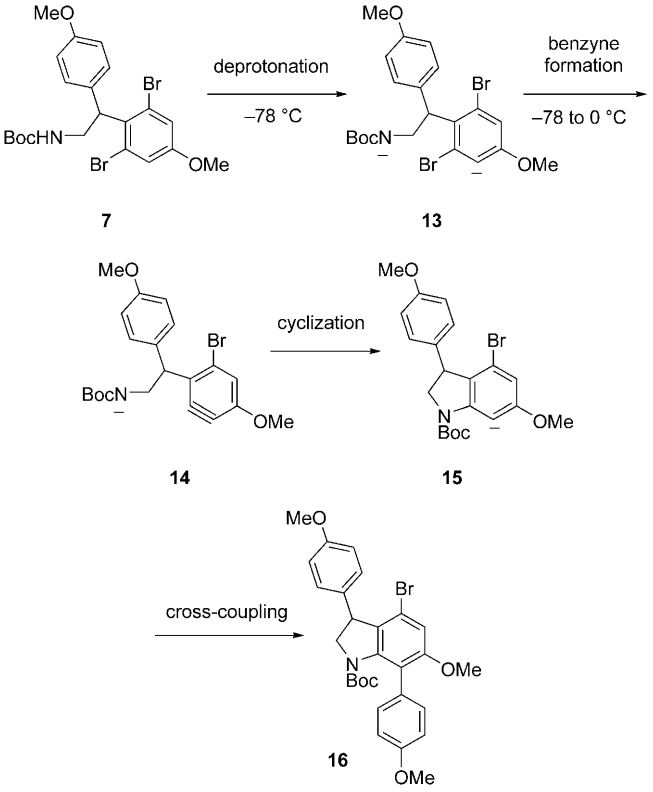
[*] Dr. K. Okano, H. Fujiwara, T. Noji, Prof. Dr. H. Tokuyama
Graduate School of Pharmaceutical Sciences, Tohoku University
Aoba, Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
Fax: (+81) 22-795-6877
E-mail: tokuyama@mail.pharm.tohoku.ac.jp
Dr. K. Okano, Prof. Dr. T. Fukuyama, Prof. Dr. H. Tokuyama
Graduate School of Pharmaceutical Sciences, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

[**] This work was financially supported by the KAKENHI, Grant-in-Aid for Scientific Research (B; 20390003), Young Scientists (Start-up; 19890014), Young Scientists (B; 21790006), and Suntory (Sunbor Grant). The authors thank Profs. S. Matsunaga and N. Fusetani (University of Tokyo) for providing valuable information and their spectral data.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001966.



Scheme 3. Preparation of dibromide **7** for key reaction. Reagents and conditions: a) *n*BuLi (1.0 equiv), toluene, −78 °C, 20 min; **11** (1.0 equiv), −78 °C, 25 min, 90%; b) Fe (10 equiv), $FeCl_2$ (1.0 equiv), EtOH/1 M HCl (10:1), reflux, 3.5 h; c) Boc_2O (1.0 equiv), Et_3N (1.1 equiv), $MeCN/H_2O$ (10:1), RT, 20 min, 85% (2 steps). Boc = *tert*-butoxycarbonyl.



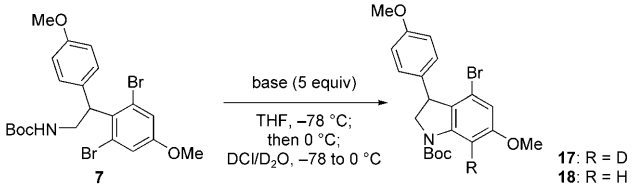
Scheme 4. Working hypothesis of the benzyne-mediated one-pot indoline formation/cross-coupling reaction.

group was chemoselectively reduced and the resultant primary amine was protected as Boc-carbamate to give the desired substrate **7**.

With substrate **7** in hand, we then investigated the key benzyne-mediated cyclization/arylation sequence. Our working hypothesis is shown in Scheme 4. After generation of dianion species **13** at low temperature, benzyne formation and cyclization should proceeded by elevating the reaction temperature to provide 7-metalated indoline **15**. We considered the possibility that the metalated species **15** should serve as a suitable substrate for the subsequent cross-coupling to furnish the desired 7-anisyl derivative **16**. However, an extensive literature search revealed that no example of this type of sequential reaction has been reported so far. Whilst several examples of benzyne-mediated cyclization/functionalization[7] with simple electrophiles have been described, their scope is limited owing to the use of strong bases, such as *t*BuLi or *s*BuLi.[8]

To establish the benzyne formation/cyclization process, substrate **7** was treated with several bases and the reaction was quenched with DCl/D_2O. We observed that the yield of the cyclized product and the D/H ratio depended dramatically on the choice of base (Table 1). Thus, after treatment of **7** with LiTMP[9] at −78 °C for 1 hour, the reaction mixture was allowed to warm to 0 °C.[10] Next, the reaction was quenched with CD_3OD at −78 °C. Unfortunately, the desired deuterated indoline **17** was obtained in low yield with substantial amount of byproducts[11] (Table 1, entry 1). When the reaction was affected by $[Me_2Zn(TMP)]Li$,[12] the yield improved dramatically. However, the level of deuteration was not satisfactory (Table 1, entry 2). To our delight, we found that $Mg(TMP)_2{\cdot}2\,LiBr$[13] quite effectively promoted the benzyne

Table 1: Optimization of trapping of the generated anion species using metalated TMP as a base.[a] TMP = 2,2,6,6-tetramethylpiperidine.



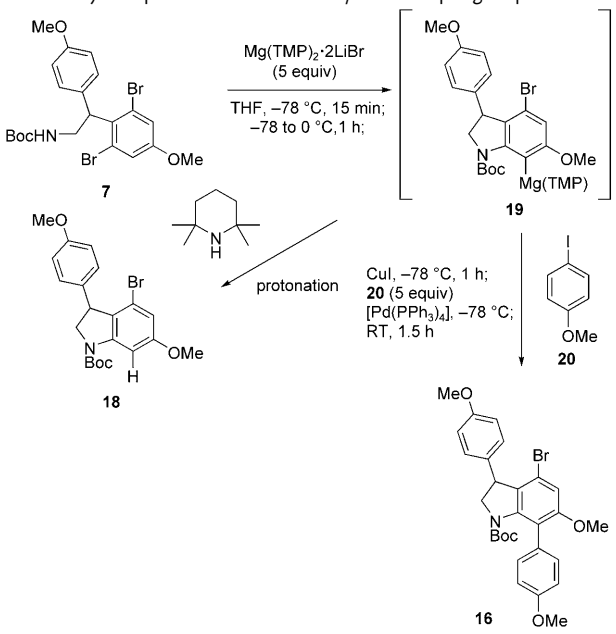
Entry	Base	Yield [%][b]	R = D/H[c]
1[d]	LiTMP	30	30:–[e]
2	$[Me_2Zn(TMP)]Li$	80	66:14
3	$Mg(TMP)_2{\cdot}2\,LiBr$	quant.	87:13
4[f]	$Mg(TMP)_2{\cdot}2\,LiBr$	95	65:30

[a] Reaction conditions: base (5 equiv), THF, −78 °C; then 0 °C; DCl/D_2O, −78 to 0 °C. [b] Yield of isolated product. [c] The ratio was determined by ^1H NMR spectroscopy. [d] The reaction was quenched with CD_3OD. [e] Not observed. [f] $Mg(TMP)_2{\cdot}2\,LiBr$: three equivalents.

formation/cyclization/deuteration sequence and a mixture of the 7-deuterated indoline **17** (87%) and 7-protonated compound **18** (13%) was obtained (Table 1, entry 3). Diminished amounts of $Mg(TMP)_2{\cdot}2\,LiBr$ resulted in lower yields and a lower D/H ratio (Table 1, entry 4). We reasoned that the success of $Mg(TMP)_2{\cdot}2\,LiBr$ was due to the relative stability of 7-magnesiospecies **15**.

We next investigated an expansion of the benzyne-mediated indoline formation protocol into a one-pot indoline formation/cross-coupling sequence (Scheme 4). First, direct coupling of 7-magnesiospecies **19** was examined under

Table 2: Key one-pot indoline formation/cross-coupling sequence.[a]

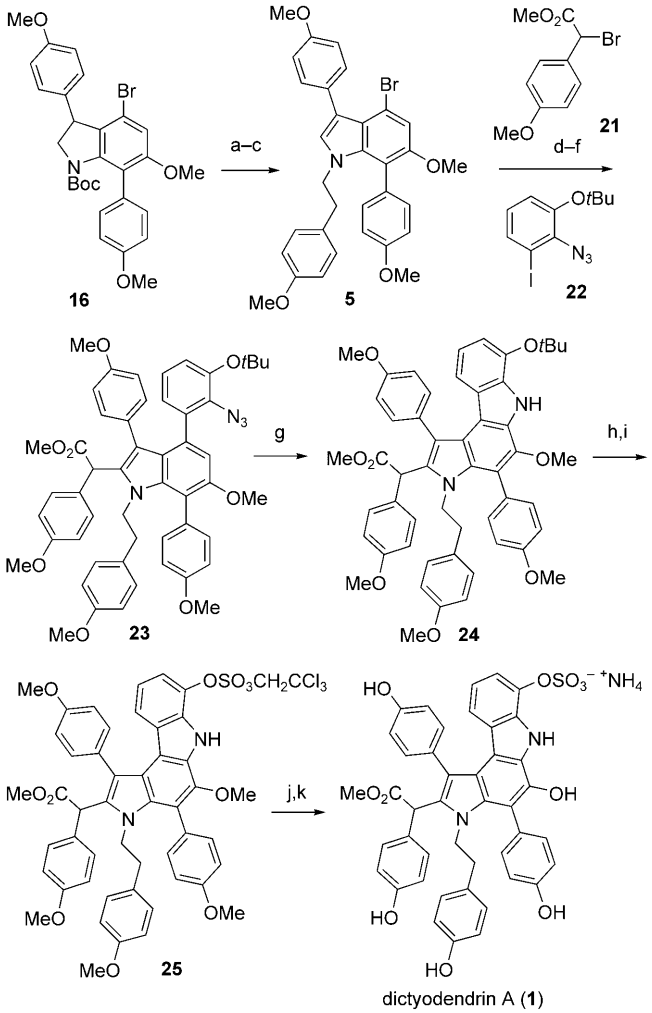


Entry	CuI [equiv]	[Pd(PPh$_3$)$_4$] [mol%]	**16** [%][b]	**18** [%][b]
1	none	10	trace	77
2	10	10	76	13
3	10	20	93 (89[c])	5 (–[c,d])

[a] Reaction conditions: Mg(TMP)$_2$·2 LiBr (5 equiv), THF, −78 °C, 15 min; −78 to 0 °C, 1 h; CuI, −78 °C, 1 h; **20** (5 equiv), [Pd(PPh$_3$)$_4$], −78 °C; RT, 1.5 h. [b] Yield of isolated product. [c] Performed on a gram scale. [d] Not isolated.

Kumada–Tamao coupling conditions[14] (Table 2). After formation of the indoline by elevating the reaction temperature to 0 °C, the reaction mixture was re-cooled to −78 °C. *para*-Iodoanisole (**20**) and [Pd(PPh$_3$)$_4$] were then added to the mixture. Only a low yield of the desired cross-coupling product **16** was isolated, associated with protonated indoline **18** as the major byproduct, thus suggesting that the rate of protonation should be faster than that of the cross-coupling reaction (Table 2, entry 1). Screening of a variety of phosphorus ligands did not improve the yield of **16**. Eventually, we found that transmetalation to the copper species was crucial for a high yielding cross-coupling process.[15] Thus, after the formation of indoline, the reaction mixture was recooled at −78 °C, and CuI, **20**, and [Pd(PPh$_3$)$_4$] were added. The desired product **16** was obtained in 76% yield after stirring the mixture for two hours at room temperature (Table 2, entry 2). In addition, the yield of **16** was improved up to 93% when 20 mol% of [Pd(PPh$_3$)$_4$] was used (Table 2, entry 3). The reaction was also conducted on a gram scale to give **16** in 89% yield.

Having developed a facile preparation for the pivotal core structure **16** using a one-pot indoline formation/cross-coupling sequence, we turned our attention to the introduction of peripheral substructures (Scheme 5). Removal of the Boc group followed by DDQ oxidation gave the corresponding indole, which was subjected to S_N2 reaction with *para*-methoxyphenylethyl bromide to give **5**. Friedel–Crafts alkylation with **21**[16] proceeded under mild conditions using



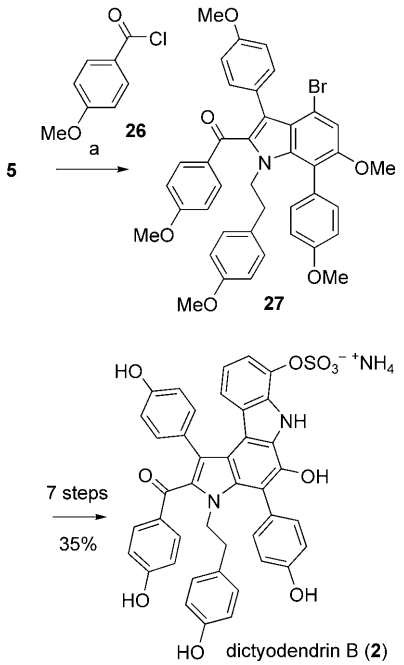
Scheme 5. Total synthesis of dictyodendrin A (**1**). Reagents and conditions: a) TMSOTf (2 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, 0 °C, 2 h, 95%; b) DDQ (1.0 equiv), toluene, RT, 1 h, 98%; c) *para*-methoxyphenylethyl bromide (5 equiv), KOH (20 equiv), DMF, RT, 2 h, 97%; d) **21** (3 equiv), AgOTf (4 equiv), THF, −78 °C, 2 h, 81%; e) pinB–Bpin (3 equiv), [PdCl$_2$(dppf)]·CH_2Cl_2 (5 mol%), KOAc (9 equiv), 1,4-dioxane, reflux, 3 h; f) **22** (3 equiv), [PdCl$_2$(dppf)]·CH_2Cl_2 (5 mol%), 3 M NaOH (5 equiv), 1,4-dioxane, reflux, 20 min, 63% (2 steps); g) *o*-$C_6H_4Cl_2$, reflux, 20 min, 79%; h) BCl_3 (2.5 equiv), C_6HMe_5 (3 equiv), CH_2Cl_2, −78 °C, 25 min, 92%; i) $Cl_3CCH_2OSO_2Cl$ (2 equiv), DABCO (3 equiv), CH_2Cl_2, RT, 2 h, 93%; j) BCl_3 (24 equiv), nBu$_4$NI (24 equiv), CH_2Cl_2, 0 °C to RT, 1.5 h, 67%; k) Zn dust (4 equiv), HCO_2NH_4 (6 equiv), MeOH, RT, 2 h, 98%. TMS = trimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, pin = pinacol, Ac = acetyl, DABCO = 1,4-diazabicyclo[2.2.2]octane.

AgOTf at −78 °C. After pinacolborylation at the bromo group of **5**, the azidephenyl group[17] was introduced by Suzuki–Miyaura coupling to give **23**.[18,19a] The azide group remained untouched under these conditions. The carbazole skeleton was formed at this stage by thermolysis of azide **23** at 180 °C and subsequent insertion of the resultant nitrene into the adjacent C_{sp^2}–H bond to give tetracyclic compound **24**.[19] The endgame strategy leading to dictyodendrin A (**1**) was established by modification of protocol reported by Fürstner et al.[3a,b] The *tert*-butyl group was removed using boron

trichloride in the presence of pentamethylbenzene as a non-Lewis-basic cation scavenger.[20] The resultant phenol was converted into trichloroethylsulfamate **25**. Finally, five methyl groups[21] and a trichloroethyl group were removed to provide dictyodendrin A (**1**) in 8.2% overall yield over 21 steps from *para*-nitrophenol (**8**).

A notable feature of this synthetic strategy is a high flexibility for the synthesis of a broad range of dictyodendrins and derivatives based on the facile and efficient assembly of the molecule in a modular fashion using key intermediate **5** as a core structure.

We demonstrated the advantage of this synthetic strategy by application to the synthesis of dictyodendrin B (**2**); 12% overall yield from *para*-nitrophenol (**8**) over 21 steps (Scheme 6). By starting from the common bromoindole **5**,



Scheme 6. Total synthesis of dictyodendrin B (**2**). Reagents and conditions: a) **26** (3 equiv), $ZnCl_2$ (10 equiv), Et_2O, 0°C, 1 h, 99%.

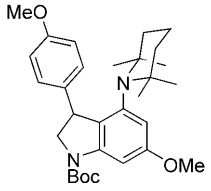
regioselective Friedel–Crafts acylation using $ZnCl_2$[22] gave **27**, which was then transformed into dictyodendrin B (**2**) in seven steps following the established synthetic route to dictyodendrin A (**1**).[23]

In conclusion, we have accomplished a highly efficient total synthesis of dictyodendrin A and B by development of an unprecedented one-pot benzyne-mediated indoline formation/cross-coupling sequence using transmetalation to copper species. This methodology provides direct access to the highly substituted indoline, which would be applicable to various nitrogen-containing heterocyclic compounds. In addition, the highly flexible modular approach should be a powerful tool for the synthesis of not only natural dictyodendrins but also a range of artificial derivatives.

Received: April 2, 2010
Published online: July 19, 2010

Keywords: arynes · cross-coupling · cyclization · natural products · total synthesis

[1] K. Warabi, S. Matsunaga, R. W. M. van Soest, N. Fusetani, *J. Org. Chem.* **2003**, *68*, 2765–2770.
[2] a) C. Ayats, R. Soley, F. Albericio, M. Álvarez, *Org. Biomol. Chem.* **2009**, *7*, 860–862; b) S. Hirao, Y. Sugiyama, M. Iwao, F. Ishibashi, *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1764–1772.
[3] a) A. Fürstner, M. M. Domostoj, B. Scheiper, *J. Am. Chem. Soc.* **2005**, *127*, 11620–11621; b) A. Fürstner, M. M. Domostoj, B. Scheiper, *J. Am. Chem. Soc.* **2006**, *128*, 8087–8094; For derivatization of dictyodendrins: c) P. Buchgraber, M. M. Domostoj, B. Scheiper, C. Wirtz, R. Mynott, J. Rust, A. Fürstner, *Tetrahedron* **2009**, *65*, 6519–6534.
[4] S. Hirao, Y. Yoshinaga, M. Iwao, F. Ishibashi, *Tetrahedron Lett.* **2010**, *51*, 533–536.
[5] M. Dąbrowski, J. Kubicka, S. Luliński, J. Serwatowski, *Tetrahedron Lett.* **2005**, *46*, 4175–4178. Trihalobenzene **9** was known in the literature; however, preparation of this compound could be carried out according to our previous report (Ref. [6a]).
[6] We have previously reported several total syntheses of natural products starting from 2,6-dibromolithiobenzene species, see: a) K. Yamada, T. Kurokawa, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2003**, *125*, 6630–6631; b) K. Okano, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2006**, *128*, 7136–7317; c) K. Okano, H. Tokuyama, T. Fukuyama, *Chem. Asian J.* **2008**, *3*, 296–309; d) T. Kurokawa, M. Isomura, H. Tokuyama, T. Fukuyama, *Synlett* **2009**, 775–778.
[7] A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem.* **2009**, *121*, 5301–5304; *Angew. Chem. Int. Ed.* **2009**, *48*, 5199–5202.
[8] a) T. M. Sielecki, A. I. Meyers, *J. Org. Chem.* **1992**, *57*, 3673–3676; b) J. Barluenga, F. J. Fañanás, R. Sanz, Y. Fernández, *Tetrahedron Lett.* **1999**, *40*, 1049–1052; c) R. Sanz, Y. Fernández, M. P. Castroviejo, A. Pérez, F. J. Fañanás, *J. Org. Chem.* **2006**, *71*, 6291–6294.
[9] R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.* **1973**, *95*, 582–584.
[10] In this case, a benzyne species would be generated between −20 and 0°C since most of the starting material was recovered when the reaction was run below −20°C.
[11] We did not isolate the protonated indoline **18** at all, presumably because of side-reaction via in situ protonation of the unstable 7-lithioindoline **15** with TMP. Once protonation of 7-lithioindoline took place, the second deprotonation occurred at the other site. Then, benzyne formation and subsequent nucleophilic addition of LiTMP proceeded to give the major byproduct.



[12] a) D. V. Graham, E. Hevia, A. R. Kennedy, R. E. Mulvey, *Organometallics* **2006**, *25*, 3297–3300; b) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* **2008**, *130*, 472–480.
[13] $Mg(TMP)_2 \cdot 2LiBr$ has been used as a selective deprotonating reagent; however, it has not been used for benzyne generation: a) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.* **1989**, *111*, 8016–8018; b) P. E. Eaton, Y. Xiong, R. Gilardi, *J. Am. Chem. Soc.* **1993**, *115*, 10195–10202; c) T. Ooi, Y. Uematsu, K. Maruoka, *J. Org. Chem.* **2003**, *68*, 4576–4578; For a review, see: d) K. W. Henderson, W. J. Kerr, *Chem. Eur. J.* **2001**, *7*, 3430–3437.
[14] A. Sekiya, N. Ishikawa, *J. Organomet. Chem.* **1977**, *125*, 281–290.

[15] The coupling reaction required both CuI and [Pd(PPh_3)$_4$].
[16] Preparation of **21** is described in the Supporting Information.
[17] Synthesis of the azidephenyl iodide **22** was carried out from commercially available *ortho*-fluoronitrobenzene in six steps.
[18] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508 – 7510.
[19] a) M. Pudlo, D. Csányi, F. Moreau, G. Hajós, Z. Riedl, J. Sapi, *Tetrahedron* **2007**, *63*, 10320 – 10329; b) G. D. Mendenhall, P. A. S. Smith, *Org. Synth.,* Coll. Vol. V **1973**, 829 – 833.
[20] In the absence of C_6HMe_5, the yield of the desired phenol dropped significantly to 60%. K. Okano, K. Okuyama, T. Fukuyama, H. Tokuyama, *Synlett* **2008**, 1977 – 1980.
[21] P. R. Brooks, M. C. Wirtz, M. G. Vetelino, D. M. Rescek, G. F. Woodworth, B. P. Morgan, J. W. Coe, *J. Org. Chem.* **1999**, *64*, 9719 – 9721.
[22] E. Duval, G. D. Cuny, *Tetrahedron Lett.* **2004**, *45*, 5411 – 5413.
[23] For the detail, see the Supporting Information.

