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Synthesis of Hindered 1-Arylnaphthalene Derivatives via Ring Expansion of Benzocyclobutenones

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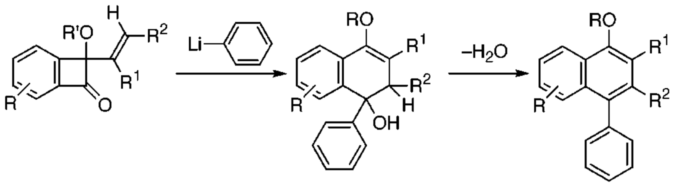
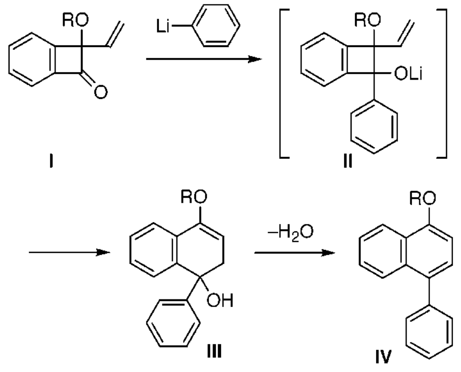
ABSTRACT



Various 1-arylnaphthalenes, including highly substituted derivatives, are accessible via a simple two-step process. Treatment of alkenylbenzocyclobutenones with aryllithium provides two-carbon expanded dihydronaphthalenes, which are readily dehydrated by MsCl–Et$_3$N or PPTS in MeOH.

Biaryl linkages are embedded as a key structural motif in various compounds ranging from biologically active natural products such as vancomycin to structually defined ligands and materials such as BINAP.[1] Herein, we report a new synthetic method of hindered 1-arylnaphthalenes starting from benzocyclobutene derivatives[2] that is comprised of two processes as shown in eq 1: (1) the reaction of vinylbenzocyclobutenone **I** with an aryllithium to generate an alkoxide intermediate **II**, which undergoes a ring enlargement in situ to give dihydronaphthalene **III**[3,4] and (2) the dehydration of **III** effected by either of the two protocols (vide infra) to give 1-arylnaphthalene **IV**.



(1)

Two isomeric benzocyclobutenones, **1** and **2**, were prepared by the [2 + 2] cycloaddition of benzyne and ketene silyl acetal as reported before,[5] which in turn were converted to the model substrates **3**−**6**. For example, treatment of **1**

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(1) For recent reviews, see: (a) Bringman, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525−558. Bringman, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−991. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303.

(2) Matsumoto, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 8985−8988. Matsumoto, T.; Hamura, T.; Miyamoto, M.; Suzuki, K. *Tetrahedron Lett.* **1998**, *39*, 4853−4856.

(3) For selected examples, see: (a) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800−1806. Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825−4836. (b) Hickman, D. N.; Hodgetts, K. J.; Mackman, P. S.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron* **1996**, *52*, 2235−2260. Hickman, D. N.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron Lett.* **1991**, *32*, 819−822. (c) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572−7574.

(4) For reviews on the charge-accelerated rearrangements, see: Wilson, S. R. *Org. React.* (*N. Y.*) **1993**, *43*, 93−250. Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 999−1035.

(5) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177−179. Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377−3380. Hosoya, T.; Hamura, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **2000**, 520−522.

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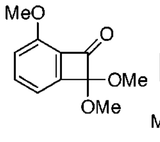
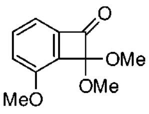
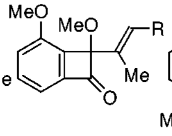
with 2-propenyllithium followed by trapping of the resulting alkoxide in situ with methyl triflate (Et_2O, −78 → 25 °C) and acid hydrolysis (2 M H_2SO_4, 25 °C) gave **3** in 84% yield. A similar sequence of reactions starting from **1** and 2-*cis*-butenyllithium afforded **4**. In a similar manner, the benzocyclobutenones **5** and **6**, the regio isomers of **3** and **4**, respectively (see the position of MeO− group), were obtained by adding the corresponding alkenyllithium to the isomeric ketone **2** followed by the methylation−hydrolysis sequence.



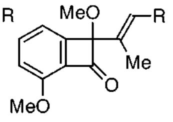
1



2



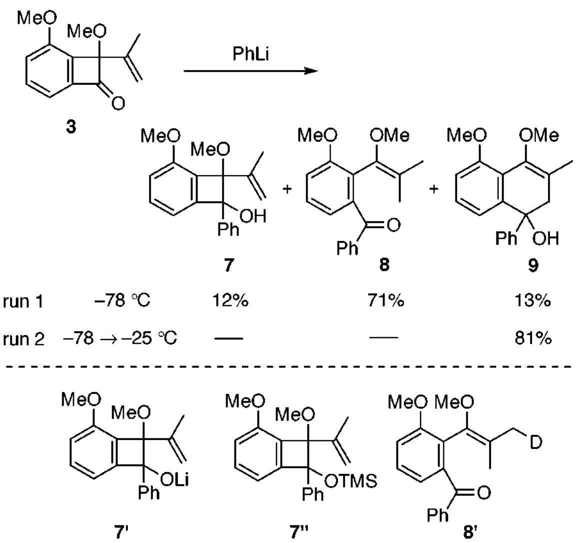
3: R = H; 84%
4: R = Me; 85%



5: R = H; 76%
6: R = Me; 82%

Scheme 1 shows the preliminary experiments on the benzocyclobutenone **3**. Upon treatment of **3** with phenyllithium[6] (1.3 equiv) in THF at −78 °C, the starting material **3** was quickly consumed, and immediate quenching with H_2O gave a mixture of three products, **7**−**9** (run 1). Though the ring-opened compound **8** was the major product, the dominant species in the reaction seemed to be the lithium alkoxide **7′** judging from the following additional facts. (1) When the reaction was quenched with TMSCl, the silyl ether **7″** was obtained in 78% yield along with small amounts of **8** (8%) and **9** (10%). (2) D_2O-quenching gave the deuterated ketone **8′** (85% D) with the *Z* geometry, whose structure was determined by NOE experiment. Thus, the ring-opened ketone **8** is most probably an artifact produced from **7′** after the quenching.

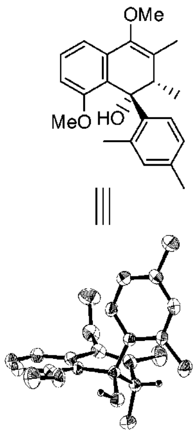
Scheme 1



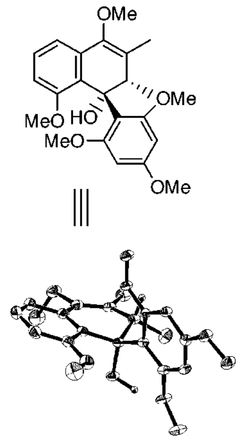
After a series of optimization experiments, we were pleased to find suitable conditions to obtain the ring-enlarged product **9** in high yield. When the above-mentioned reaction was warmed to −25 °C, monitoring by TLC showed that the initially observed products at −78 °C converged to a single compound, and the workup gave the alcohol **9** in 81% yield (see run 2, Scheme 1).[6] Interestingly, the product **9** was far more stable than expected and was readily isolated with silica gel preparative thin-layer chromatography without dehydration. On the other hand, the dehydration could be achieved by either of two straightforward protocols as described below.

This reaction pattern was amenable to various substrate combinations, and some representative results are summarized in Table 1. Upon treatment of **3** with 1-naphthyllithium, the reaction sequence occurred at −78 °C, thereby giving the alcohol **10** in 70% yield (run 2).[7] Likewise, the reaction proved to be applicable to substrate **4** with an additional methyl group on the olefin. Upon treatment of **4** with phenyllithium (−78 °C → room temperature), the alcohol **11** was obtained as a single isomer (stereochemistry unassigned) in 85% yield (run 3).[7] Similarly, treatment of the benzocyclobutenone **5**, isomeric to **3**, with 2-methoxyphenyllithium (−78 °C → room temperature) gave the alcohol **12** in 77% yield (run 4).[7]

Furthermore, we became able to synthesize such sterically congested compounds as **13** and **14** by the reaction of **6** with the corresponding aryllithiums (runs 5 and 6).[8] It is notable that these compounds were mainly composed of the cis isomers with respect to the relation of the hydroxy and the methyl groups as evidenced by the X-ray analysis (see below).[9] The molecular motion in these compounds appeared to be restricted, not surprisingly, in the vicinity of the bond between the aryl group and the dihydronaphthalene moiety.



13



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These ring-enlarged products **9**−**14** are intriguing in their own right, but they could also be dehydrated to give the corresponding biaryls by either of the following two manners: methanesulfonyl chloride and Et_3N at room temperature (method A) or PPTS (pyridinium *p*-toluenesulfonate) in MeOH at 60 °C (method B). For example, the alcohol **9** was subjected to the conditions of method A, where a smooth

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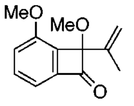
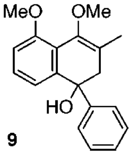
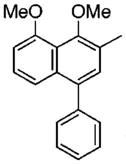
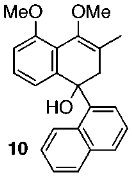
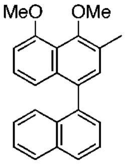
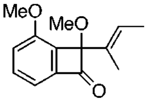
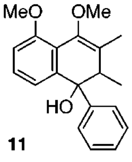
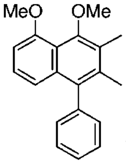
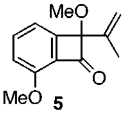
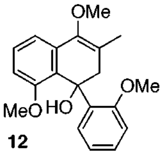
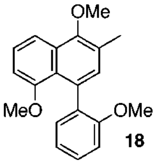
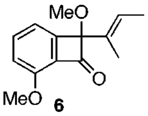
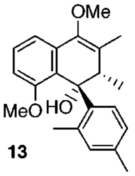
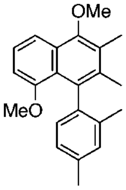
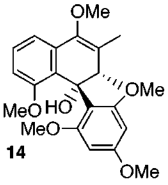
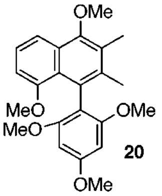
(6) Generated from the aryl bromide (1.3 equiv) and *t*-BuLi (2.5 equiv) in THF at −78 °C. *n*-BuLi was not effective.

(7) All new compounds were fully characterized by spectroscopic means and combustion analysis. See Supporting Information.

Table 1

Run	Benzocyclobutenone	Reaction Temp.	Alcohol	Yield/%	Aryl Naphthalene	Yield/%[b]
1	 **3**	−78 → −25 °C	 **9**	81	 **15**	quant.[c]
2		−78 °C	 **10**	70	 **16**	quant.[c]
3	 **4**	−78 °C → r.t.	 **11**	85	 **17**	99[c]
4	 **5**	−78 °C → r.t.	 **12**	77	 **18**	92[d]
5	 **6**	−78 °C → r.t.	 **13**	91 (16:1)[a]	 **19**	92[d]
6		−78 °C → r.t.	 **14**	85 (11:1)[a]	 **20**	94[d]

[a] Major isomer was cis with respect to the hydroxy and the methyl groups, as determined by X-ray analysis. The ratio of the stereoisomers is shown in parenthesis. [b] Yields from the dihydronaphthalene. [c] Method A: MsCl, Et_3N. [d] Method B: PPTS in MeOH at 60 °C.

elimination occurred to give 1-arylnaphthalene **15** in quantitative yield (run 1, Table 1). Similarly, the alcohols **10** and **11** were converted to the arylnaphthalenes **16** and **17**. However, method A proved to be ineffective for the dehydration of the alcohols **12**−**14** due to the high steric hindrance around the hydroxy group. However, method B nicely provided the arylnaphthalenes in excellent yields (runs 4−6).[9] Runs 5 and 6 illustrate that the reaction sequence is applicable to the synthesis of such sterically congested tri- and tetrasubstituted biaryls as **19** and **20**, which are difficult to obtain via conventional methods.[10]

In summary, vinylbenzocyclobutenone undergoes two-carbon expansion of the cyclobutenes and provides a facile

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(8) Representative experimental procedures: Synthesis of alcohol **13**. To a solution of 4-bromo-*m*-xylene (34 mg, 0.18 mmol) in THF (1.0 mL) was slowly added *t*-BuLi (1.64 M in pentane, 0.22 mL, 0.36 mmol) at −78 °C, and the reaction mixture was further stirred for 40 min; to the stirred solution was added benzocyclobutene **5** (32.7 mg, 0.141 mmol) in THF (1.2 mL). After the mixture was warmed to 25 °C in 1 h and stirred for an additional 1 h, the reaction was quenched with water. The products were extracted with Et_2O (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified with PTLC (hexane/EtOAc = 8/2) to give alcohol **13** (43.5 mg, 91%, d.s. 16:1). Recrystallization from hexane/Et_2O gave colorless prisms: mp 144.5−147.0 °C.

(9) The minor isomers of the alcohols **13** and **14**, in which the hydroxyl and the methyl moieties are trans, were converted to the corresponding arylnaphthalenes by treatment with PPTS in MeOH at 40 °C. Representative experimental procedures: Synthesis of arylnaphthalene **19**. A solution of alcohol **13** (34.5 mg, 0.102 mmol) and PPTS (13 mg, 0.053 mmol) in MeOH (1.5 mL) was stirred at 60 °C for 10 min. After the mixture was cooled and saturated aqueous $NaHCO_3$ was added, the products were extracted with EtOAc (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified with PTLC (hexane/CH_2Cl_2/Et_2O = 8/1/1) to give **19** (30.2 mg, 92%). Colorless prisms: mp 70.8−72.0 °C (hexane).

synthesis of arylnaphthalene derivatives. Further studies are currently underway in our laboratories.

Supporting Information Available: General procedures and spectral data for compounds **7**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) If the metal-catalyzed cross-coupling reaction is taken as an example, the presence of even a single ortho substituent on each aromatic moiety substantially retards the reaction. For cross-coupling of aryl halides or triflates with hindered arylmetals, see: Saá, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963−1966 and references therein.