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Solvent-mediated Tuning of the Regioselectivity of Intramolecular Diaryl Ether Formation: Total Synthesis of (+)-Aspercyclide C

Tatsuya Yoshino,[1] Shuji Yamashita,[1] Itaru Sato,[1,2] Yujiro Hayashi,[1] and Masahiro Hirama*[1,2]
[1]*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai, Miyagi 980-8578*
[2]*Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai, Miyagi 980-8578*

(E-mail: hirama@m.tohoku.ac.jp)

A concise total synthesis of the 11-membered cyclic (+)-aspercyclide C is reported. Key to success was the fine-tuning of the reaction media to realize an oxidative, macrocyclic diaryl C–O bond formation in a regioselective and direct fashion.

In 2004, Singh and co-workers isolated three novel natural products from the fermentation broth of *Aspergillus* sp., named aspercyclides A (**1**), B (**2**), and C (**3**) (Figure 1).[1] Each structure features an 11-membered unsaturated macrolactone flanked by differently substituted diaryl ether backbones. Due to their intriguing frameworks and potential use against allergy disorders,[2,3] the aspercyclides have attracted keen interest from synthetic organic chemists.[4–8] The total synthesis of (+)-aspercyclide C (**3**) was first achieved by Fürstner et al. in 2005 using ring-closing metathesis (RCM) to construct the 11-membered macrolactone ring.[4,5] In 2007, Ramana et al. reported a formal total synthesis of **3**, also via RCM.[6] In 2009, Fürstner et al. disclosed the first synthesis of (+)-aspercyclides A (**1**) and B (**2**) using an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction.[5] In 2010, Spivey et al. synthesized (±)- and (+)-aspercyclide A (**1**) via an intramolecular Mizoroki–Heck reaction.[7] Recently, we reported the total synthesis of (+)-aspercyclides A (**1**) and B (**2**) via a unique oxidative macrocyclization strategy by adopting a chemo- and regioselective intramolecular diaryl etherification step.[8] The present report demonstrates that this new strategy is not only versatile but also applicable to the efficient construction of aspercyclide C (**3**).

The most challenging step in the synthesis of **3** was assumed to be the intramolecular oxidative cyclization of the substituted diphenol **4** (Scheme 1). In particular, the regiochemical control of C–O bond formation in **4** was anticipated to be more difficult than that encountered in the synthesis of **1** and **2**, because the C2 position of the electron-rich phenol unit of **4** would be more sterically hindered than C4.

Our synthesis began by reacting the MOM ether **5** of *m*-bromophenol (**8**) with the chiral alcohol **6**[8] under Mizoroki–Heck conditions to afford **9** in 72% yield (Scheme 2).[7a,9,10] Esterification of alcohol **9** with the salicylate **7**,[11] followed by hydrolysis of the MOM group, furnished the diphenolic cy-

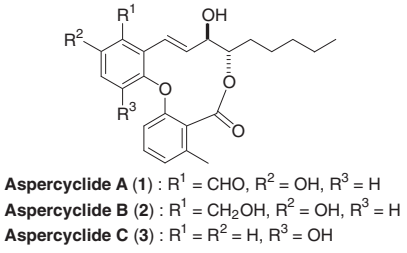
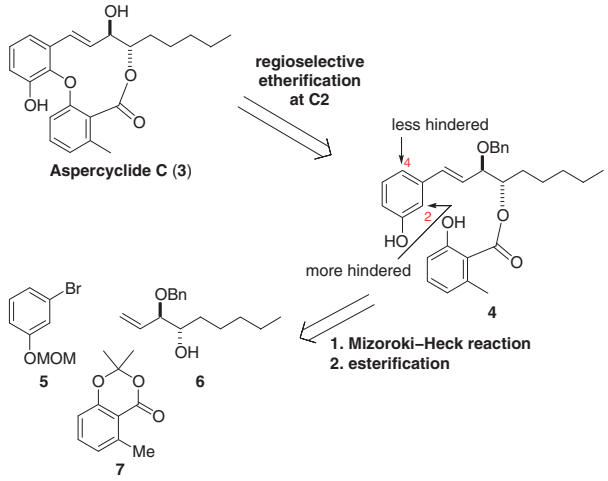
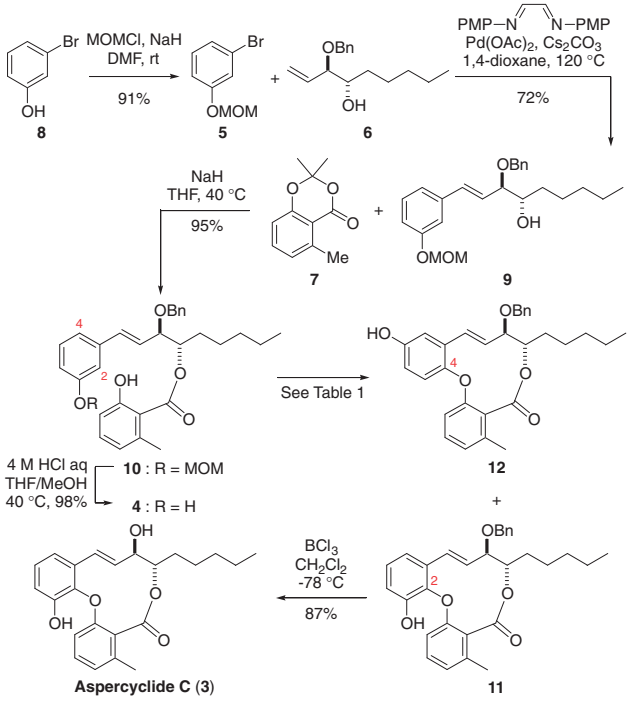


Figure 1. Structures of aspercyclides A–C (**1**–**3**).



Scheme 1. Retrosynthesis of aspercyclide C (**3**).



Scheme 2. Total synthesis of aspercyclide C (**3**).

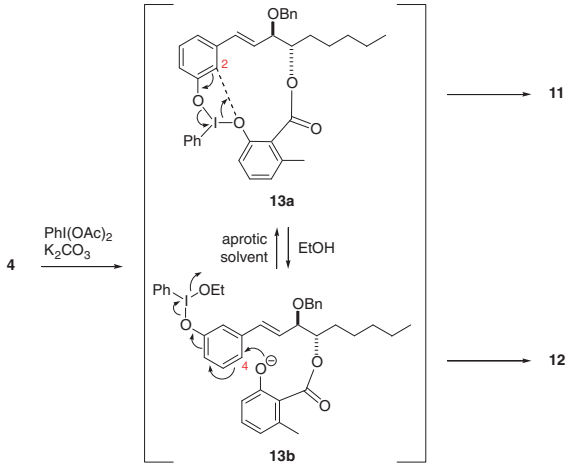
Table 1. Examination of regioselective diaryl ether formation

Entry	Reagents	Solvents	Results[a]
1	$PhI(OAc)_2$ (1.0 equiv) K_2CO_3 (3.0 equiv)	EtOH	**11**:**12** = 0:1
2	$PhI(OAc)_2$ (2.0 equiv) K_2CO_3 (5.0 equiv)	CH_2Cl_2/EtOH (= 5/1)	**11**:**12** = 1:4
3	$PhI(OAc)_2$ (2.0 equiv) K_2CO_3 (5.0 equiv)	CH_3CN/EtOH (= 5/1)	**11**:**12** = 1:2
4	$PhI(OAc)_2$ (2.0 equiv) K_2CO_3 (5.0 equiv)	$ClCH_2CH_2Cl$/EtOH (= 5/1)	**11**:**12** = 3:2
5	$PhI(OAc)_2$ (2.0 equiv) K_2CO_3 (5.0 equiv)	PhCl/EtOH (= 5/1)	**11**:**12** = 3:1 (**11**: 52%, **12**: 18%)[b]
6	$PhI(OAc)_2$ (2.0 equiv) K_2CO_3 (5.0 equiv)	PhCl	decomposed

[a]Determined by ^{1}H NMR analysis. [b]Isolated yield.

clization precursor **4** in 93% yield over two steps. The key intramolecular, oxidative aryl C–O bond formation was then examined using $PhI(OAc)_2$ and K_2CO_3 in ethanol at room temperature.[8] In practice, this step proceeded with high chemoselectivity but resulted in exclusive formation of the undesired C4-bonded diaryl ether **12** (Table 1, Entry 1). We thus decided to investigate solvent effects to alter the regioselectivity by careful consideration of the potential mechanistic modes of cyclization (Scheme 3). Thus, the putative aryloxy iodonium(III) intermediate **13b**, which would afford undesired **12**, was speculated to equilibrate with a cyclic intermediate (e.g., **13a**) in less polar aprotic media, which would lead to the desired cyclic diaryl ether **11**.[12] Under this speculation, various aprotic cosolvents were added to the ethanolic reaction mixture (Table 1). Indeed, mixed solvent systems such as CH_2Cl_2/EtOH and CH_3CN/EtOH started to produce the desired regioisomer **11**, although undesired **12** still predominated (Entries 2 and 3). While the solvent mixture $ClCH_2CH_2Cl$/EtOH favorably gave **11** in an improved ratio (**11**:**12** = 3:2, Entry 4), a 5:1 ratio of PhCl/EtOH was eventually found to yield **11** as the major regioisomer (**11**:**12** = 3:1, Entry 5). By careful thin layer chromatography (TLC) examination of the reaction, an unstable intermediate was transiently detected. High-resolution mass spectrometry (ESI) of the intermediate (m/z found 677.1761) indicated that the species corresponded to the putative iodonium species **13a** (calcd for $C_{36}H_{38}IO_5$ $[M + H]^+$ 677.1764), which disappeared as the reaction proceeded to give **11**. In the absence of ethanol, aryl ether products were not produced and decomposition was observed (Entry 6). Thus the presence of ethanol was found to be indispensable for the reaction to proceed via the desired oxidative pathway.

Lastly, cleavage of the benzyl ether of **11** with BCl_3 at −78 °C gave (+)-aspercyclide C (**3**) in 87% yield. The



Scheme 3. Alternative mechanistic modes of regioselective etherification.

spectroscopic data of synthetic (+)-**3** matched exactly those of authentic natural aspercyclide C,[1] thereby confirming its identity. The optical rotation of our synthetic material was found to be identical to Fürstner's report.[4]

In summary, an efficient regioselective total synthesis of (+)-aspercyclide C (**3**) was accomplished by virtue of a versatile, intramolecular, oxidative diaryl etherification tactic. It should be noted that the direct chemo- and regioselective aryl C–O bond formation was realized without the need to resort to aryl C–halogens or aryl C–O–triflates. More interestingly, the regiocontrol in the macrocyclization step was manifested by appropriately tuning the polarity and nucleophilicity of the reaction media. Collectively, our synthetic strategy described herein represents a new and concise entry to the syntheses of various bioactive natural and unnatural diaryl ethers.[13,14]

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