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Total Synthesis of Aspercyclides A and B via Intramolecular Oxidative Diaryl Ether Formation

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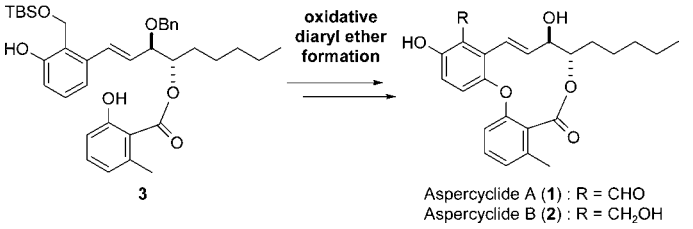
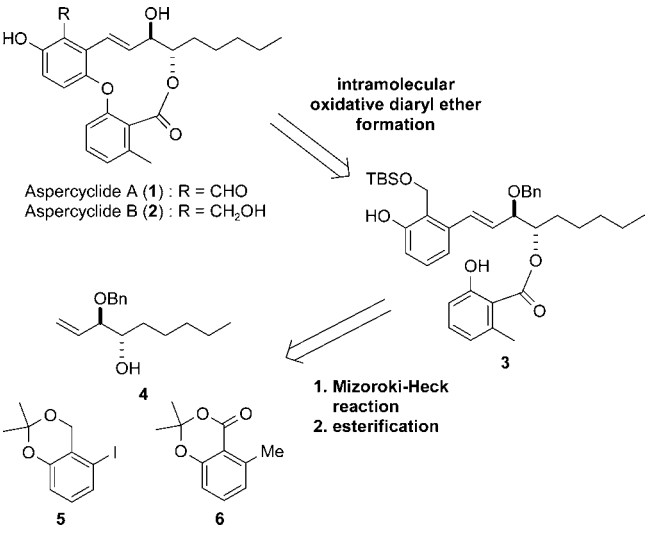
ABSTRACT



A highly efficient total synthesis of the 11-membered cyclic aspercyclides A (1) and B (2) has been achieved by chemo- and regioselective intramolecular oxidative C−O bond formation from differently substituted diphenols.

In 2004, Singh and co-workers isolated and characterized aspercyclides A (**1**), B (**2**), and C from the fermentation broth of *Aspergillus* sp.[1] Aspercyclide A (**1**) inhibited the binding of immunoglobulin E antibodies (IgE) to the human IgE receptor. Therefore, compound **1** and its analogues are expected to act on allergic disorders.[1] These noble compounds consist of an 11-membered unsaturated lactone flanked by differently substituted diaryl ether backbones. The first synthesis of (+)-aspercyclide C was reported by Fürstner et al. in 2005.[2,3] They constructed the 11-membered ring via ring-closing metathesis (RCM). In 2009, they synthesized (+)-aspercyclides A (**1**) and B (**2**) more effectively using an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction.[3] Spivey et al. reported a synthesis of (±)-aspercyclide A (**1**) via an intramolecular Mizoroki–Heck reaction in 2010.[4] We describe herein a total synthesis of pure (+)-aspercyclides A (**1**) and B (**2**) via chemo- and regioselective intramolecular oxidative diaryl ether formation.

Scheme 1. Retrosynthesis of Aspercyclides A (**1**) and B (**2**)



Aspercyclides A (**1**) and B (**2**) were envisioned to be constructed via an intramolecular oxidation of diphenol **3** as the most challenging key step of this synthesis (Scheme 1).

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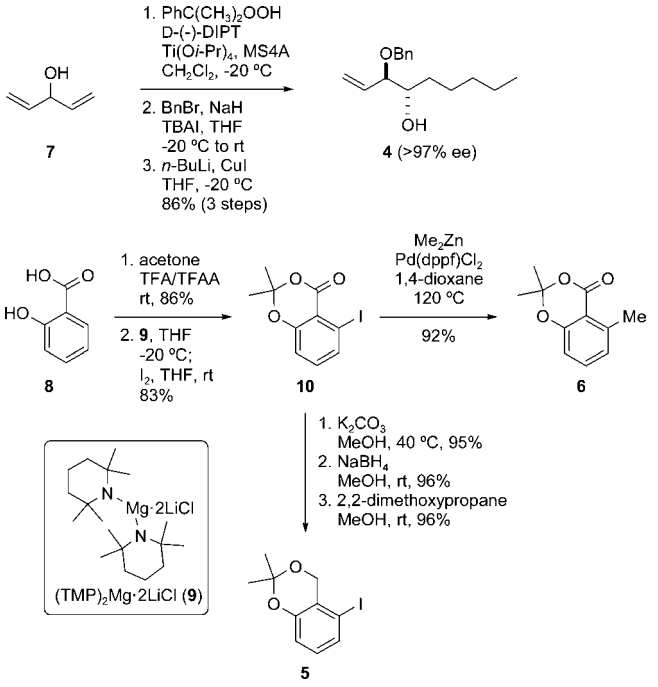
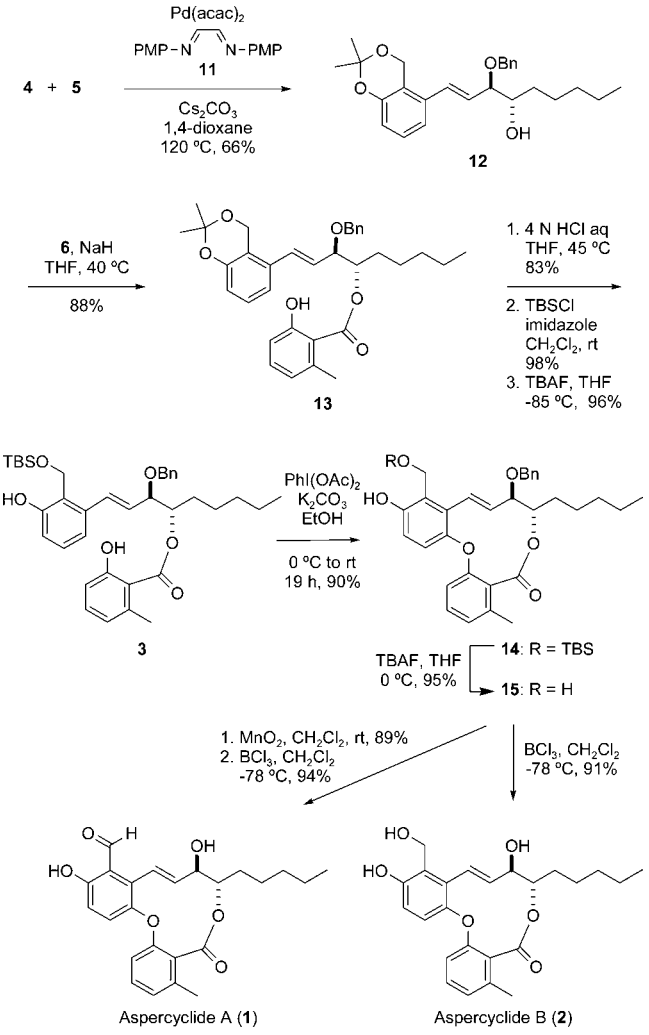
Scheme 2. Synthesis of the Fragments **4**–**6**



The diphenol **3** would be assembled from **4**–**6**. The enantiomerically pure diol derivative **4** was prepared from **7** via Sharpless epoxidation with D-(−)-diisopropyl tartrate (DIPT)[5] and protection as the benzyl ether,[5f,g] followed by treatment with *n*-BuLi and CuI (I)[6] (1:1.2) in 86% yield (three steps, Scheme 2). Salicylic acid **8** was converted to **10** (71%, two steps),[7] which was then transformed to both of the key phenol fragments **5** (88%, three steps) and **6** (92%).[8]

With the key fragments in hand, we then turned to their assembly. Mizoroki–Heck reaction of **4** with aryl iodide **5** in the presence of diazabutadiene ligand **11** gave **12** (Scheme 3).[4a,9] Esterifying the alcohol **12** with salicylic acid derivative **6** furnished ester **13**.[10] The acetonide group of **13** was hydrolyzed and TBS-protected, followed by selective deprotection of two of the three TBS groups to produce the diphenol **3**.

Scheme 3. Total Synthesis of Aspercyclides A (**1**) and B (**2**)



Next was the phenolic oxidation of **3**, which is the most critical and dangerous step, to realize the aryl C–O bond. In fact, oxidizing reagents such as $K_3Fe(CN)_6$,[11] CAN,[12] and [bis(trifluoroacetoxy)iodo]benzene (PIFA)[13] did not afford the desired product **14**. However, we were very pleased to find that 3 mM of **3** with 1.0 molar equiv of (diacetoxyiodo)benzene [$PhI(OAc)_2$] and 3.0 molar equiv of K_2CO_3 in EtOH at room temperature gave rise to the desired diaryl ether **14** as the sole product in high yield (90%). Selection of the reaction solvent turned out to be critical; when either CH_3CN, CF_3CH_2OH, or THF was used, diphenol **3** quickly decomposed. MeOH gave only a small amount of **14**. The exclusive formation of **14** can be

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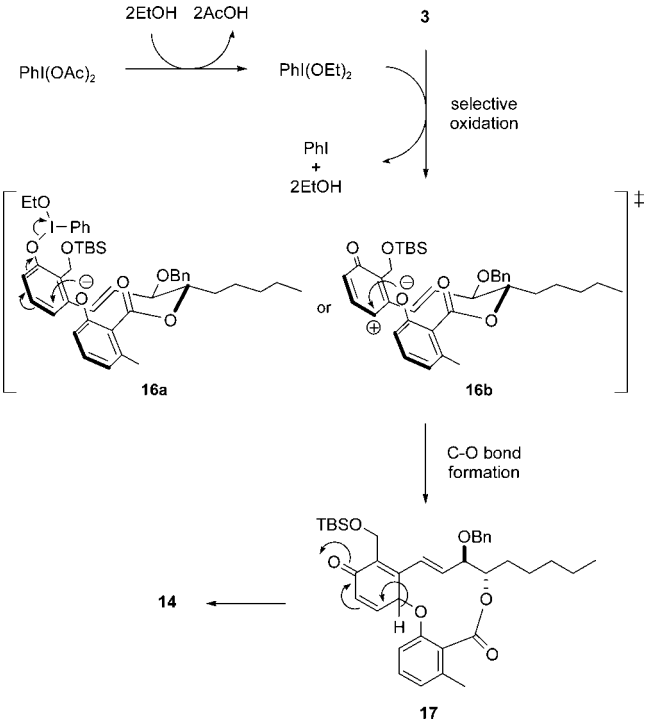
Scheme 4. Proposed Mechanism



explained as shown in Scheme 4. In EtOH, $PhI(OAc)_2$ should form $PhI(OEt)_2$,[14a] which may act as an appropriately mild two-electron oxidizing reagent to selectively oxidize the more electron-rich phenol unit of **3**.[14b,15,16] The carbon chains of the reaction intermediate **16a** (aryloxyiodonium (III) species) or **16b** (aryloxenium ion)[15] may adopt a zig-zag conformation in the most favorable transition state, in which the phenoxide oxygen of the untouched phenol would attack the nearby oxidized phenol, leading to the intermediate **17** followed by aromatization to **14**.

Completion of the total synthesis of (+)-aspercyclide B (**2**) required only cleavage of the protecting groups of **14** with TBAF at 0 °C followed by treatment with BCl_3 at −78 °C (86%, two steps). Our total synthesis of (+)-**2** was accomplished in 13 steps in the longest linear sequence (22% overall yield from **8**). The total synthesis of pure (+)-aspercyclide A (**1**) required the oxidation of benzyl alcohol **15** with MnO_2, followed by treatment with BCl_3 at −78 °C in 83% yield (two steps). For the first time, pure synthetic (+)-**1** was isolated. We found that compound **1** is stable enough for flash chromatography.[3] Spectroscopic data of the synthetic (+)-**1** and (+)-**2** are completely identical to those of natural aspercyclide A[1] and Fürstner's synthetic aspercyclide B,[3,17] respectively.

In summary, we accomplished the total synthesis of pure (+)-aspercyclides A (**1**) and B (**2**) with complete control of chemo-, stereo-, and regioselectivities. In particular, we would like to emphasize the efficient chemo- and regioselective assembly of the diaryl ether linkage in the 11-membered ring skeleton through the intramolecular oxidation of the diphenol segments. This synthetic strategy will be readily applicable to the syntheses of other diaryl ether natural[18] and designed bioactive molecules. Related synthetic studies are currently under investigation in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic data for synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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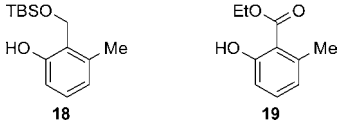
(16) When a 1:1 mixture of **18** and **19** was treated with $PhI(OAc)_2$ (1.0 molar equiv for the mixture) in ethanol for 2 h as the control experiments, **18** was completely consumed, while **19** was untouched. Furthermore, CAN (1.0 molar equiv, 30 min) oxidation of the mixture showed a complete decomposition of both **18** and **19**. These results clearly indicated that $PhI(OAc)_2$ can differentiate the two distinct phenol units.



(17) The ^1H NMR spectrum of **2** was highly concentration dependent as indicated by Fürstner et al. See ref 3.

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The authors declare no competing financial interest.