

Enantioselective Total Syntheses of (–)-Taiwaniaquinone H and (–)-Taiwaniaquinol B by Iridium-Catalyzed Borylation and Palladium-Catalyzed Asymmetric α -Arylation

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Supporting Information

ABSTRACT: We report a concise, enantioselective total synthesis of (–)-taiwaniaquinone H and the first enantioselective total synthesis of (–)-taiwaniaquinol B by a route that includes asymmetric palladium-catalyzed α -arylation of a ketone with an aryl bromide that was generated by sterically controlled halogenation via iridium-catalyzed C–H borylation. This asymmetric α -arylation creates the benzylic quaternary stereogenic center present in the taiwaniaquinoids. The synthesis was completed efficiently by developing a Lewis acid-promoted cascade to construct the [6,5,6] tricyclic core of an intermediate common to the synthesis of a number of taiwaniaquinoids. Through the preparation of these compounds, we demonstrate the utility of constructing benzylic quaternary stereogenic centers, even those lacking a carbonyl group in the α -position, by asymmetric α -arylation.

The taiwaniaquinoids are a family of unusual diterpenoids possessing a [6,5,6]-*abeo*-abietane skeleton that was unknown in nature prior to 1995.^{1–7} Each member of this family contains a benzylic quaternary stereogenic center (Figure 1). Studies of the biological activities of taiwaniaquinoids are ongoing, but preliminary data have indicated that some members of this family exhibit antitumor activities.^{8–11} The structural features and the biological activities of these compounds have led many groups to report total and formal syntheses of the taiwaniaquinoids.^{11–25} However, the majority of these syntheses have targeted racemic versions of this class of natural products.

Asymmetric syntheses of the taiwaniaquinoids are challenging because of the limited number of enantioselective reactions that establish quaternary stereogenic centers.^{26–29} One approach

that eliminates this challenge is to prepare the material by a ring-contractive derivatization of enantioenriched terpenes. Alvarez-Manzaneda and co-workers prepared (–)-taiwaniaquinone G (**1**),²² (–)-taiwaniaquinone H (**2**), and (–)-dichroanone (**3**) in 15 or 16 steps from (+)-sclareolide,²³ and Gademann and co-workers prepared **2** in 13 steps from methyl dehydroabiatic.²⁵ Recently, Alvarez-Manzaneda and co-workers reported the syntheses of (–)-taiwaniaquinone A (**4**) in 15 steps and (–)-taiwaniaquinone F (**5**) in 16 steps from (+)-podocarpa-8(14)-en-13-one.³⁰ To date, only two enantioselective total syntheses of taiwaniaquinoids from achiral or racemic starting materials have been reported. McFadden and Stoltz reported an 11-step synthesis of (+)-dichroanone (*ent*-**3**) in which the quaternary stereogenic center was set by an asymmetric Tsuji allylation.¹⁷ Recently, Node and co-workers employed an enantioselective intramolecular Heck reaction to complete the total syntheses of (–)-dichroanal B (**6**) in 12 steps, **3** in 14 steps, and **2** in 15 steps beginning with a tetrasubstituted arene.²⁴

Recently, our group reported asymmetric α -arylations of ketones to form products containing quaternary benzylic stereogenic centers with high enantioselectivities.³¹ Although the taiwaniaquinoids do not contain a carbonyl group α to the benzylic stereogenic center, we envisioned that asymmetric α -arylation could be used to construct this center and that the ketone function could be integral to creation of the [6,5,6] tricyclic core. Further, we envisioned that the aryl electrophile for the proposed α -arylation process could be generated from a simple arene by a sterically controlled iridium-catalyzed borylation and halogenation sequence developed by our group.^{32,33}

Herein, we report concise enantioselective total syntheses of (–)-taiwaniaquinone H (**2**) and (–)-taiwaniaquinol B (**7**) from simple achiral and racemic reactants through this halogenation process and an asymmetric α -arylation for the first time in the synthesis of a natural product. A Lewis acid-promoted cascade then establishes the unusual [6,5,6] tricyclic core.

Scheme 1 illustrates the strategy we envisioned to achieve the enantioselective total syntheses of **2** and **7**. Both molecules would be accessible from the same intermediate, tetrahydrofluorene **8**, by demethylation and oxidation procedures. We considered that the tricyclic core of tetrahydrofluorene **8** could be formed from epoxide **9** by a formal intramolecular addition of the electron-rich arene ring to the epoxide unit. Epoxide **9** would be derived from α -aryl ketone **10**, which would be generated by our palladium-catalyzed asymmetric α -arylation of ketones.

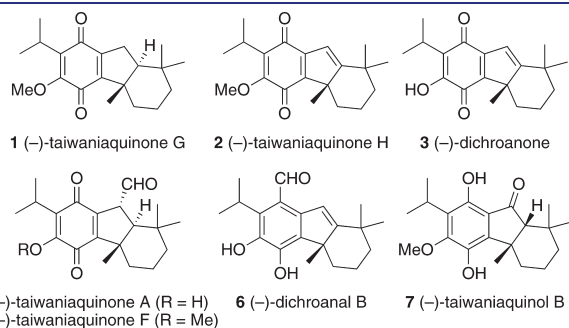
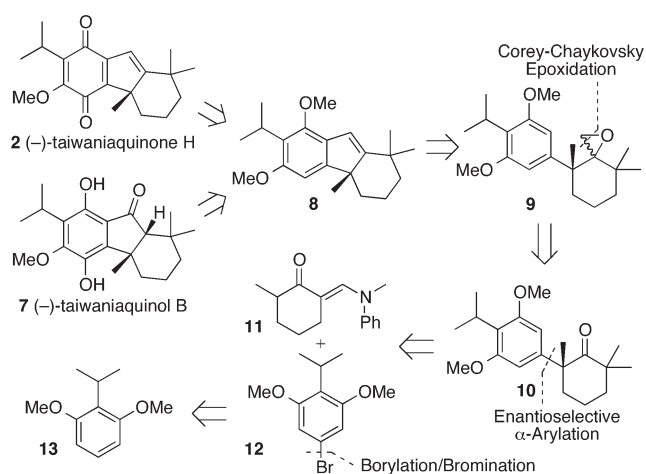
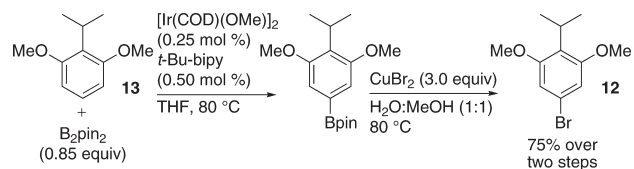


Figure 1. Representative taiwaniaquinoids.

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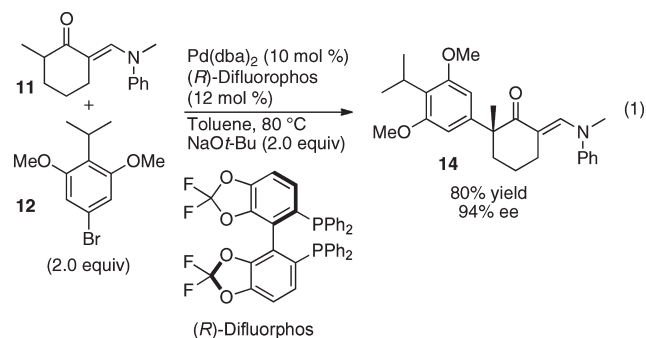
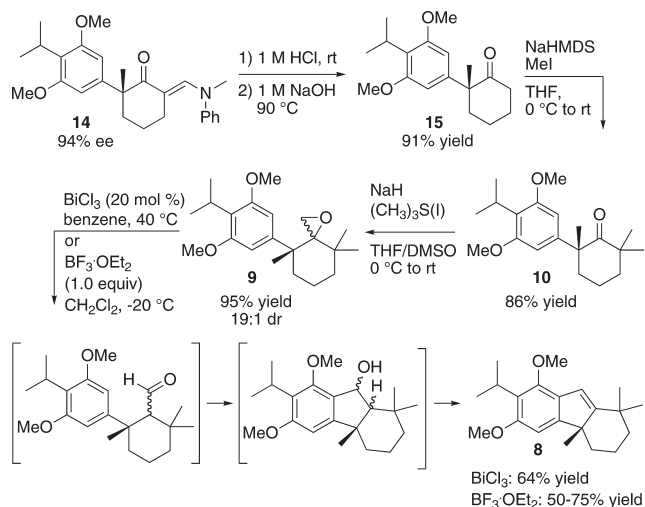
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Scheme 1. Retrosynthetic Analysis for the Syntheses of (–)-Taiwaniaquinone H (2) and (–)-Taiwaniaquinol B (7)**Scheme 2. One-Pot Synthesis of Aryl Bromide 12^a**

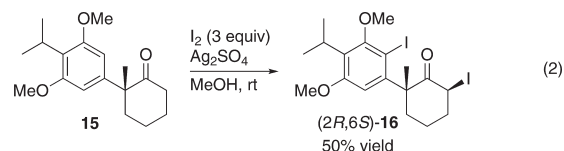
^a B_2pin_2 = bis(pinacolato)diboron; dtbpy = 4,4'-di-*tert*-butylbipyridine.

In the forward direction, the first step of the synthesis required aryl bromide 12. Under traditional conditions for electrophilic aromatic substitution, the known resorcinol derivative 13³⁴ undergoes bromination at the position located ortho to the two methoxy groups.¹⁶ To overcome this electronic bias, we used a one-pot, two-step sequence to prepare aryl bromide 12 from 13 by the combination of a sterically controlled iridium-catalyzed borylation and a subsequent bromination of the aryl boronate ester with copper(II) bromide (Scheme 2).³² This method provided aryl bromide 12 in 75% yield on a multigram scale.

Access to aryl bromide 12 enabled us to explore the key enantioselective α -arylation. The reaction of aryl bromide 12 with 2,2,6-trimethylcyclohexanone did not generate the α -arylation product in the presence of a catalyst generated from $\text{Pd}(\text{dba})_2$ and (*R*)-Segphos or (*R*)-Difluorophos. However, the reaction of aryl bromide 12 with the 2-methylcyclohexanone derivative 11^{35,36} in the presence of the combination of $\text{Pd}(\text{dba})_2$ and (*R*)-Difluorophos as catalyst (10 mol %) formed α -aryl ketone 14 in 80% yield with 94% ee (eq 1).³⁷

**Scheme 3. Synthesis of Tetrahydrofluorene 8**

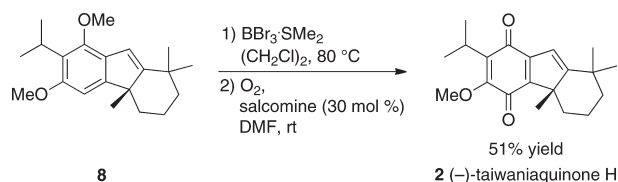
The synthesis of the key tetrahydrofluorene intermediate 8 was accomplished in five steps from enantioenriched ketone 14 (Scheme 3). Acid-promoted hydrolysis of ketone 14 followed by deformylation of the resulting β -ketoaldehyde in the presence of aqueous sodium hydroxide provided deprotected ketone 15 in 91% yield over two steps. Dimethylation of 15 with methyl iodide using sodium bis(trimethylsilyl)amide (NaHMDS) as the base formed tetrasubstituted cyclohexanone 10 in 86% yield.



The absolute configuration of the stereogenic center in these products was established by iodination of 15. The reaction of 15 with iodine and silver sulfate formed diiodide 16 (eq 2). Single-crystal X-ray diffraction of the major diastereomer of 16 enabled the assignment of the absolute configuration as (2*R*,6*S*)-16 (see Figure S1 in the Supporting Information). Thus, the enantioselective α -arylation of ketone 11 conducted with (*R*)-Difluorophos and $\text{Pd}(\text{dba})_2$ generated (*R*)-14 and created the appropriate enantiomer for preparation of (–)-taiwaniaquinone H (2) and (–)-taiwaniaquinol B (7).

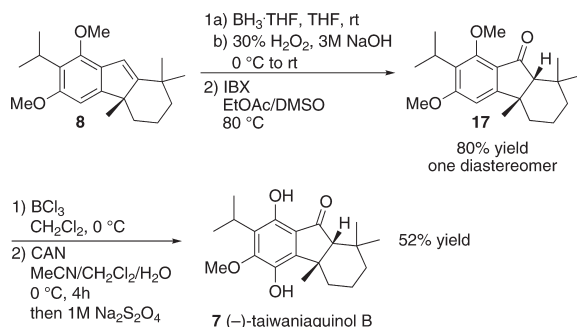
Attempts to convert ketone 10 to epoxide 9 by Corey–Chaykovsky epoxidation using the common sulfur ylide dimethylsulfoxonium methylide^{38,39} led to recovery of 10, even under forcing conditions (80 °C). We presumed that this lack of reactivity resulted from the steric hindrance surrounding the ketone functionality in 10. Thus, we attempted a Corey–Chaykovsky epoxidation of ketone 10 using the smaller and more reactive sulfur ylide dimethylsulfonium methylide.^{39,40} This reaction formed epoxide 9 in 95% yield with >15:1 diastereoselectivity.

Some Lewis acids are known to promote the rearrangement of epoxides to carbonyl compounds.^{41–45} We tested the ability of such Lewis acids to initiate the cascade shown in Scheme 3, in which epoxide 9 would form tetrahydrofluorene 8 via rearrangement of the epoxide to the aldehyde. This aldehyde would then be attacked by the electron-rich arene in the presence of a Lewis acid to form the corresponding alcohol, which could undergo

Scheme 4. Synthesis of (–)-Taiwaniaquinone H (2)^a

^a Salcomine = *N,N'*-bis(salicylidene)ethylenediaminocobalt(II).

Scheme 5. Synthesis of (–)-Taiwaniaquinol B (7)



elimination to form the target tetrahydrofluorene **8**. After testing a series of Lewis acid catalysts for this sequence (see Table S1 in the Supporting Information), we found that treatment of epoxide **9** with $\text{BF}_3 \cdot \text{OEt}_2$ or a Bi(III) salt generated tetrahydrofluorene **8** in good yield. The cascade promoted by $\text{BF}_3 \cdot \text{OEt}_2$ formed tetrahydrofluorene **8** in up to 75% yield; however, the yields of this reaction varied from 50 to 75%. Slightly lower yields were observed for the formation of tetrahydrofluorene **8** from epoxide **9** in the presence of a Bi(III) salt as the Lewis acid, but this reaction was less sensitive to variations in temperature. Ultimately, we conducted this cascade promoted by 20 mol % BiCl_3 to generate tetrahydrofluorene **8** in 64% yield.

The synthesis of (–)-taiwaniaquinone H (**2**) was completed according to methods developed by Trauner and co-workers for the synthesis of (±)-taiwaniaquinone H.¹⁶ Selective monodemethylation of tetrahydrofluorene **8** with $\text{BBr}_3 \cdot \text{SMe}_2$ followed by oxidation of the resulting tetrahydrofluoren-1-ol in the presence of salcomine formed (–)-taiwaniaquinone H (**2**) in 51% yield over two steps (Scheme 4).

Tetrahydrofluorene **8** is also a suitable intermediate for the synthesis of (–)-taiwaniaquinol B (**7**). The enantioselective total synthesis of **7** was completed in four steps from tetrahydrofluorene **8** (Scheme 5). Hydroboration of **8** followed by oxidation of the resulting alkylborane in the presence of basic hydrogen peroxide formed a diastereomeric mixture of hexahydrofluoren-9-ols. Oxidation of these alcohols with 2-iodoxybenzoic acid (IBX) gave tetrahydrofluoren-9-one **17** as a single diastereomer in 80% yield. Tetrahydrofluoren-9-one **17** was converted to (–)-taiwaniaquinol B according to procedures reported by Fillion¹³ and Trauner¹⁶ for the synthesis of racemic taiwaniaquinol B. Selective monodemethylation of **17** with BCl_3 , oxidation of the resulting 8-hydroxyfluoren-9-one intermediate with ceric ammonium nitrate (CAN), and reductive workup with sodium dithionite gave **7** in 52% yield over two steps.

In summary, an enantioselective total synthesis of (–)-taiwaniaquinone H was accomplished in 14.6% overall yield in just

10 steps, and the first enantioselective total synthesis of (–)-taiwaniaquinol B was completed in 11.9% overall yield in just 12 steps. Two catalytic protocols reported by our group, a one-pot meta bromination of 2-isopropyl-1,3-dimethoxybenzene by iridium-catalyzed borylation followed by reaction of the resulting arylboronate with copper(II) bromide and a palladium-catalyzed enantioselective α -arylation, were used in early steps on multi-millimolar scales. The syntheses were completed efficiently by developing a Lewis acid-promoted cascade to construct the [6,5,6] tricyclic core of an intermediate common to the synthesis of a number of taiwaniaquinoids. Finally, we emphasize that the quaternary stereogenic center in the taiwaniaquinoids bears no carbonyl group in the α -position but is readily set by the asymmetric α -arylation and that the ketone functionality serves as a key point of reaction to complete the syntheses. Thus, the enantioselective α -arylation of ketones should be considered as a strategic method for establishing quaternary benzylic stereogenic centers for complex-molecule synthesis. Further studies to increase the scope of this enantioselective process are ongoing.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details, characterization data, ¹H and ¹³C NMR spectra, and crystallographic data for **16** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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