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Synthesis of Taiwaniaquinoids via Nazarov Triflation

Guangxin Liang, Yue Xu, Ian B. Seiple, and Dirk Trauner*

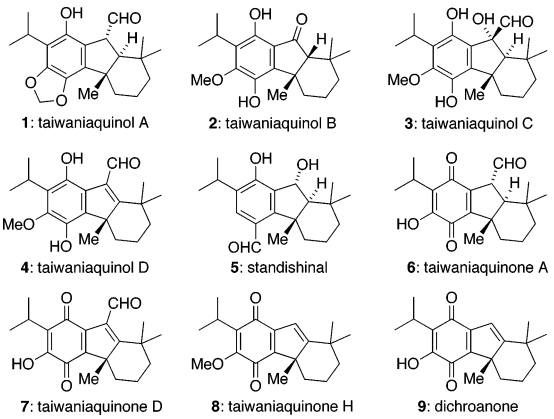
Department of Chemistry, University of California, Berkeley, Berkeley, California 94720-1460

Received April 11, 2006; E-mail: trauner@cchem.berkeley.edu

The taiwaniaquinoids are a family of unusual tricyclic diterpenoids isolated from East Asian conifers with interesting biological activities (Chart 1).[1] Structurally, their members are marked by a rare tricyclic [6-5-6] ring system, which is presumably formed by an oxidative ring contraction of a more regular hydrophenanthrene precursor.[1a] In some cases, one carbon has been lost in the course of the biosynthesis to afford norditerpenoids such as taiwaniaquinol B (**2**), taiwaniaquinone H (**8**) and dichroanone (**9**).

Several members of the taiwaniaquinoids have shown activity as aromatase inhibitors and are currently under evaluation for their potential as drug leads.[1e−h] Thus, it comes as no surprise that the taiwaniaquinoids have attracted the interest of several synthetic groups.[2] Fillion reported a total synthesis of (±)-taiwaniaquinol B featuring an interesting domino acylation/alkylation step.[2a] Very recently, Stoltz published a synthesis of (+)-dichroanone based on a novel asymmetric palladium-catalyzed alkylation.[2b] Approaches toward other members of the family based on intramolecular Heck reactions have also been reported.[2c−e]

Chart 1. The Taiwaniaquinoids

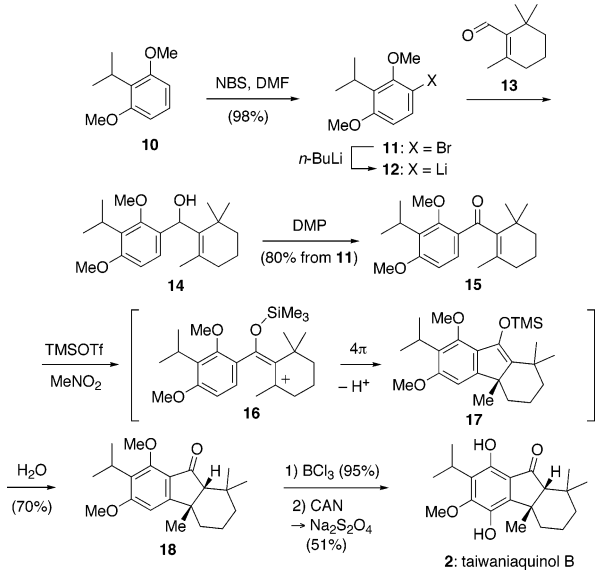


We now report a concise and convergent synthetic approach toward the taiwaniaquinoid family that hinges on Nazarov chemistry.[3] Indeed, aromatic Nazarov reactions are well suited for the construction of the central indanone or indene moieties of these natural products. In the course of our studies we have developed a new aromatic Nazarov cyclization that directly produces indenyl triflates and could be of general use for the synthesis of substituted indenes.

Our total synthesis of taiwaniaquinol B is outlined in Scheme 1. Bromination of the known resorcinol derivative **10** gave aryl bromide **11**. Lithiation of this material (**11** → **12**), followed by addition of the commercially available β-cyclocitral **13** afforded aryl vinyl carbinol **14**. This sensitive alcohol was oxidized immediately to yield aryl vinyl ketone **15**. Attempts to produce **15** more directly via Friedel−Crafts acylation, possibly with concomitant Nazarov cyclization, failed.

After an extensive survey of conditions, we found that **15** could be cyclized in the presence of trimethylsilyl triflate in nitromethane

Scheme 1. Total Synthesis of Taiwaniaquinol B



to afford the highly unstable silyl enol ether **17**, presumably through the intermediacy of cation **16**. Upon aqueous workup, this procedure afforded the thermodynamically more favorable *cis*-indane product **18** as the only stereoisomer observed. It is important to note that the use of solvents less polar than nitromethane gave little or no cyclization.

Since **18** was featured as an intermediate in Fillion's first total synthesis of (±)-taiwaniaquinol B,[2a] the overall sequence constitutes a short formal total synthesis of the natural product. In a slightly modified endgame, we found that selective deprotection, followed by CAN-oxidation and sodium dithionite reduction upon workup[4] afforded (±)-taiwaniaquinol B (**2**) in comparable overall yield from **18**.

Contemplating the mechanism of the key aromatic Nazarov cyclization, we came to the conclusion that treatment of **15** with triflic anhydride (instead of TMS triflate) should afford the corresponding enol triflate.[5] Indeed, heating of aryl vinyl ketone **15** with triflic anhydride in the presence of a hindered base (2,6-di-*tert*-butylpyridine; 2,6-DTBP) cleanly gave trifloxy indene **20** (Scheme 2). This reaction is proposed to proceed through trifloxy cation **19**, which undergoes 4π electrocyclization followed by deprotonation to yield **20**. A systematic survey of substrates showed that the reaction works reasonably well with electron-rich aryl vinyl ketones but fails with most substrates bearing electron-withdrawing substituents on the aryl ring (see Supporting Information). This reflects general reactivity trends among aromatic Nazarov reactions.

Enol triflate **20** can serve as a key intermediate to access several taiwaniaquinoids. Its use in a total synthesis of taiwaniaquinone H (**8**) and dichroanone (**9**) is shown in Scheme 3. Palladium-catalyzed reduction gave indene **21** in excellent yield. Because of steric hindrance, the comparatively small ligand trimethyl phosphite was

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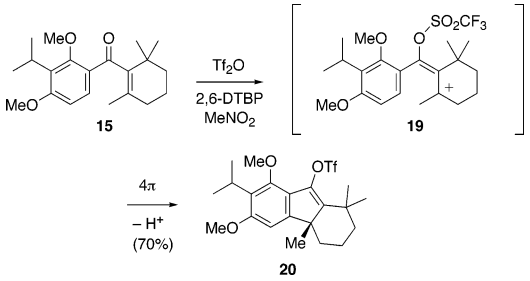
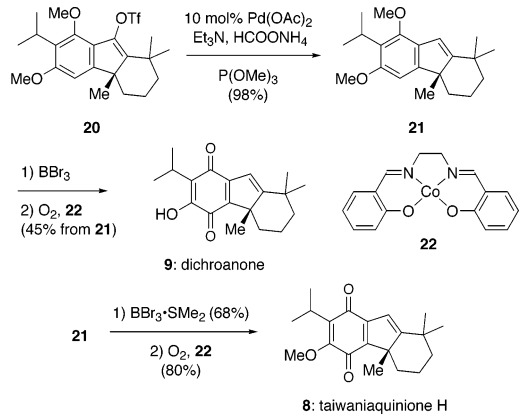
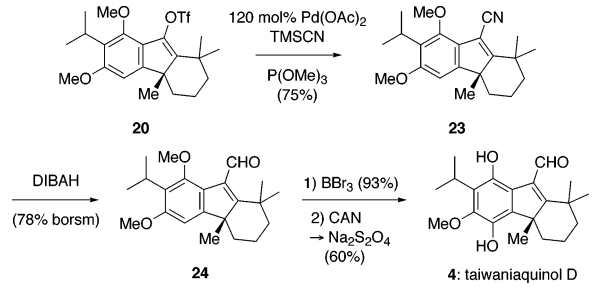
Scheme 2. Nazarov Cyclization/Triflation



Scheme 3. Total Syntheses of Taiwaniaquinone H and Dichroanone



Scheme 4. Total Synthesis of Taiwaniaquinol D



required to effectively carry out this reaction.[6] Yields decreased markedly if bulkier phosphine ligands were used. Global demethylation, followed by oxidation catalyzed by salcomine (**22**) gave (±)-dichroanone (**9**). Alternatively, a more selective demethylation and oxidation led to (±)-taiwaniaquinol H (**8**).

The further extension of this strategy toward the total synthesis of taiwaniaquinol D (**4**) is shown in Scheme 4. A challenging palladium-mediated cyanation of enol triflate **20** afforded nitrile **23**.[7] Reduction with diisobutylaluminum hydride, followed by regioselective demethylation of the resultant aldehyde **24** and oxidation/reduction gave (±)-taiwaniaquinol D (**4**). In accordance with the literature,[8] the DIBAH reduction of unsaturated cyanide **23** proceeded cleanly but was difficult to drive to completion. Attempts to perform the overall transformation **20** → **24** more directly through palladium-catalyzed carbonylation failed.

In summary, we have described a concise, unified approach to the taiwaniaquinoids that hinges on new variants of the aromatic Nazarov reaction. Asymmetric versions of this reaction are currently under investigation.

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Supporting Information Available: Synthetic procedures and spectroscopic data for compounds **11**, **15**, **18**, **20**, **21**, **23**, and **24**, as well as the natural products **2**, **4**, **8**, and **9**. Further investigations on the Nazarov triflation are also described. This material is available free of charge via the Internet at http://pubs.acs.org.

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