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Concise syntheses of (±)-dichroanone, (±)-dichroanal B, (±)-taiwaniaquinol B, and (±)-taiwaniaquinone D

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ABSTRACT

The total syntheses of dichroanone and dichroanal B, as well as the formal syntheses of taiwaniaquinol B and taiwaniaquinone D, are reported.

In 1995, Cheng and co-workers isolated a new class of diterpenoids having a fused [6,5,6]-tricyclic skeleton from the Taiwanese evergreen *Taiwania cryptomerioides*.[1] Over the next decade, this species, along with *Salvia dichroantha* and *Thuja standishii,* provided numerous examples of this class of rearranged abietanes, which have been named according to their source of origin and order of isolation (Figure 1).[2–4] These natural products have been collectively called taiwaniaquinoids which, although convenient, may be incorrect from the standpoint of their phytochemical origin.[5]

In 2003, Banerjee and co-workers reported the total syntheses of dichroanone (**1**) and dichroanal B (**2**) using a Pd(0)-catalyzed reductive cyclization to create the [6,5,6]-skeleton.[6a] Since then taiwaniaquinoids **3**, **4**, **5**, **6**, and **7** have been synthesized through various ring forming strategies as summarized in Scheme 1. For example, Fillion and Fishlock appended Meldrum's acid to an appropriately substituted C-ring precursor to effect a novel domino bis-cyclization route to taiwaniaquinol B.[6b] Node and co-workers featured a Heck reaction in their streamlined synthesis of dichroanal B.[6c] In 2005, Banerjee and co-workers utilized their reductive cyclization approach to synthesize taiwaniaquinol B and taiwaniaquinones D and H.[6d] Stoltz and McFadden used an enantioselective Tsuji allylation in their A → AB → ABC construction of *ent*-dichroanone.[6e] In 2006, Trauner et al. showcased a triflic anhydride-promoted Nazarov cyclization in their syntheses of dichroanone, taiwaniaquinols B and D, and taiwaniaquinone H.[6f] Chiu and Li attempted a domino bis-cyclization route to taiwaniaquinol B through the geranoyl system, but were forced into two sequential cyclizations to build the tricyclic ring system.[6g] She's synthesis of dichroanone[6h] and taiwaniaquinol B exploited a domino Friedel–Crafts acylation/alkylation strategy, which was first reported by Bhar and Ramana,[6i,j] to achieve tricycle formation. Recently, Alvarez-Mansaneda and co-workers featured a thermal 6π cyclization to introduce the six-membered C-ring onto a chiral [6,5]-system in their synthesis of taiwaniaquinone G.[6k] We synthesized racemic dichroanone in 2006,[7] but deemed it necessary to prepare other taiwaniaquinoids before reporting this work. Herein, we detail the total syntheses of dichroanone, dichroanal B, and the formal syntheses of taiwaniaquinol B and taiwaniaquinone D.

We decided to prepare the carbocyclic skeleton of dichroanone using an A + C → ABC strategy (Scheme 2). Vinyl iodide **8**[8,9] was smoothly lithiated in THF and coupled with aldehyde **9**[10] to form allylic alcohol **10** in 80% yield. The anticipated intramolecular Friedel–Crafts alkylation was effected by treating **10** with BF_3–Et_2O in DCM at 0 °C to yield tricyclic alkene **11** in quantitative yield. Heating **11** in DCM with excess BBr_3 gave (±)-dichroanone in 81% yield, with spectral data identical to those reported.[3]

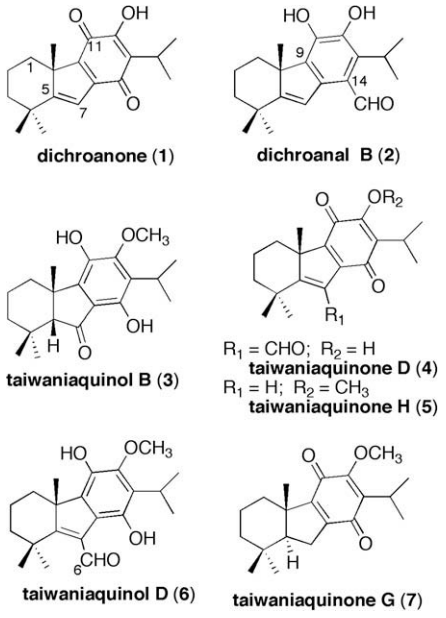

Figure 1.

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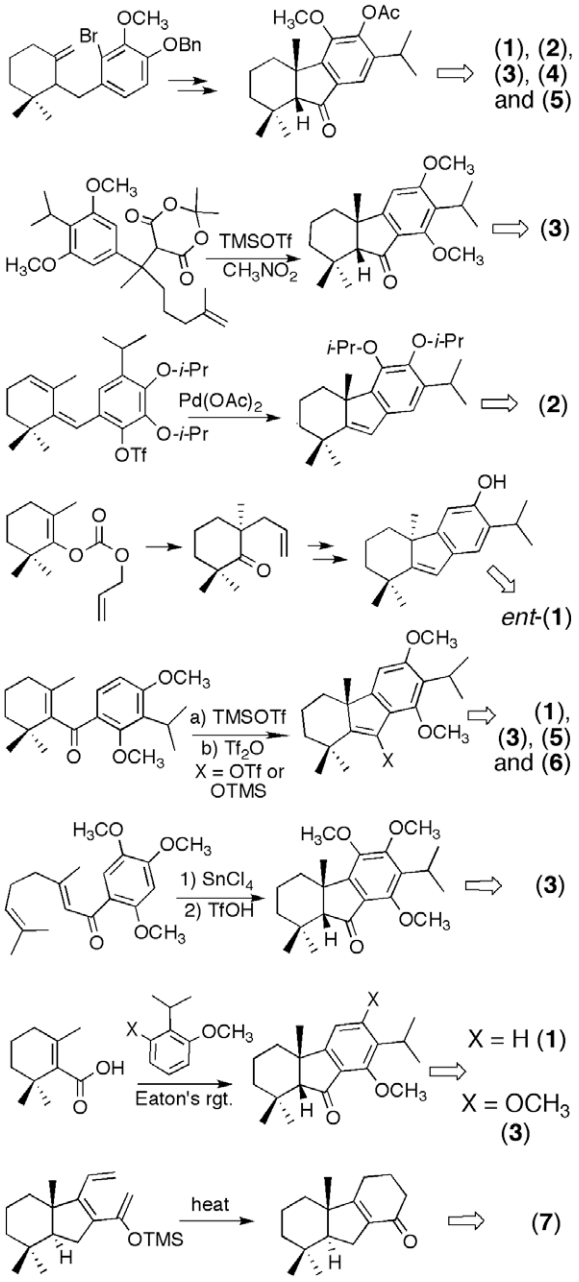
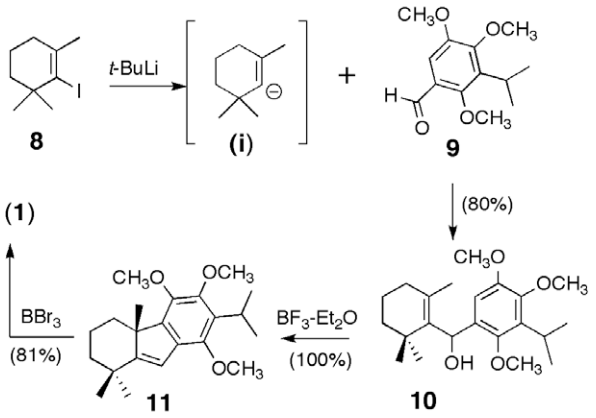


Scheme 1.

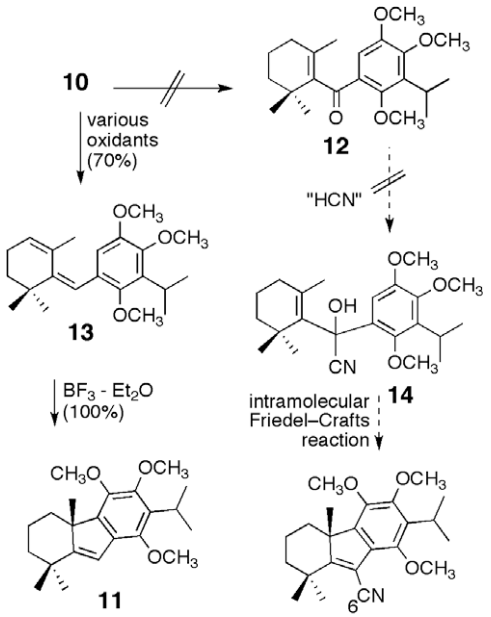
We were confident that oxidation of alcohol **10**, followed by cyanohydrin formation, would yield Friedel–Crafts precursor **14**, in which the C(7) nitrile serves as a latent formyl group (Scheme 3). Unfortunately, all attempts to oxidize alcohol **10** using standard methods instead resulted in the formation of diene **13**; exposure of this diene to BF_3–Et_2O in DCM produced alkene **11** in quantitative yield.

Enone **12** was prepared in 70% yield by adding a solution of the vinyl anion (**i**) to acid chloride **15** (Scheme 4). Unfortunately, all efforts to form cyanohydrin **14**, including using TMSCN,[11] failed. Moreover, all attempts to first assemble the taiwaniaquinoid nucleus via a Nazarov cyclization of enone **12** failed under standard conditions despite the examination of several Lewis acids and commonly used mineral acid catalysts. We found that gently warming **12** in neat methanesulfonic acid produced ketone **16** in 73% yield. We were gratified to learn that Trauner and co-workers

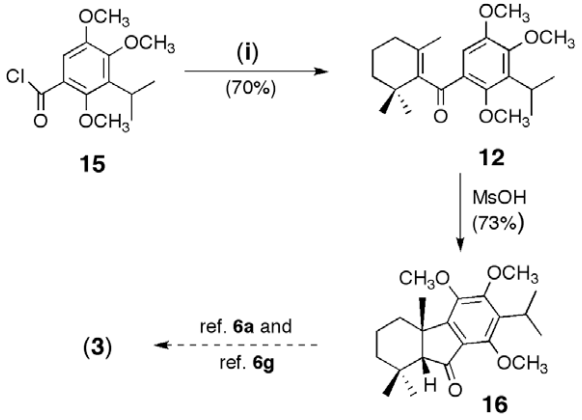


Scheme 2.

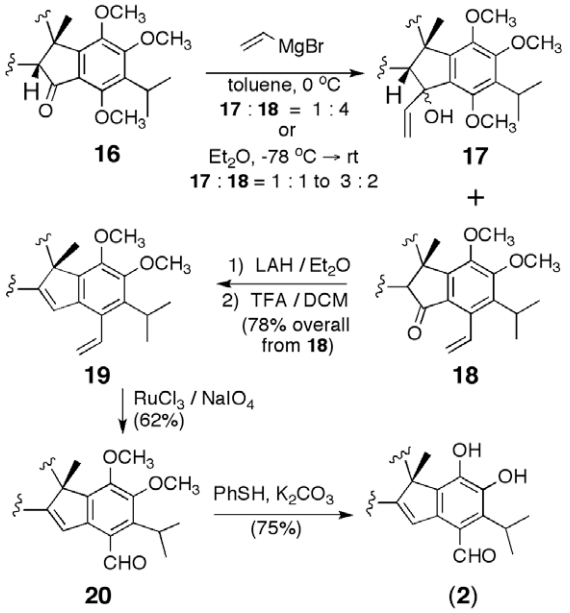
also found that the Nazarov reaction failed on a similar system, but effected ring closure when nitromethane was used as the reaction solvent.[6f] Ketone **16** can be converted into taiwaniaquinol B, using known transformations.[6f]



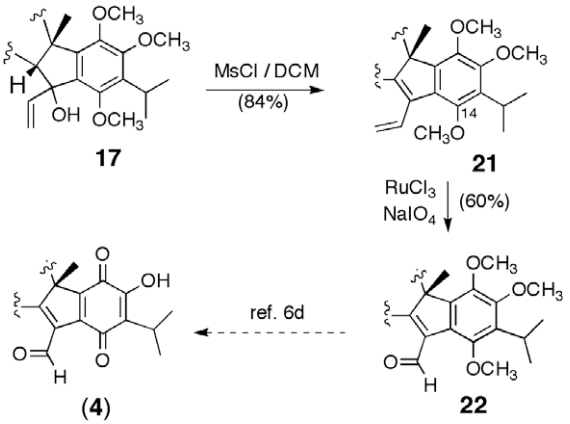
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

We believed that more nucleophilic reagents, such as vinylmagnesium bromide, would add to the C(7) carbonyl (Scheme 5). If so, dehydration of the resulting tertiary alcohol, followed by oxidative cleavage of the vinyl group, would introduce a formyl group at C(7). To our satisfaction, treatment of ketone **16** with vinylmagnesium bromide in ether produced a mixture of the expected tertiary alcohol **17** and ketone **18**, clearly the result of a nucleophilic aromatic substitution reaction. We recognized that ketone **18** represented an avenue to dichroanal B, whereas alcohol **17** would serve as an attractive precursor for taiwaniaquinol D and taiwaniaquinone D. The subtle control of the reaction temperature and the choice of solvent allowed us to influence whether the vinyl moiety was introduced at C(7) or at C(14). Adding the Grignard reagent to ketone **16** at −78 °C and slowly warming the reaction mixture over several hours produced a 1:1 ratio of adducts **17**:**18** in 77% yield. In contrast, adding the Grignard reagent to ketone **16** in toluene at 0 °C gave a 1:4 ratio of adducts **17**:**18**, respectively, in 75% yield. The reduction of ketone **18** with LAH, followed by dehydration using trifluoroacetic acid, produced diene **19** in 78% yield over two steps. The selective cleavage of the vinyl moiety in the presence of the C(5),C(7)-double bond was achieved in 62% yield using ruthenium chloride and $NaIO_4$.[12] Treatment of **20** with a catalytic amount of thiophenolate anion[13] yielded dichroanal B in 75% yield.[3]

Scheme 6 details our formal synthesis of taiwaniaquinone D. Treatment of tertiary alcohol **17** with 6 equiv of methanesulfonyl chloride in refluxing DCM furnished diene **21** in 84% yield. The oxidative cleavage of the vinyl moiety was accomplished using ruthenium chloride and $NaIO_4$ to furnish aldehyde **22**, an intermediate in Banerjee's synthesis[6d] of taiwaniaquinone D.

Acknowledgment

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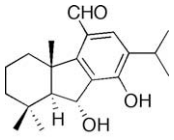

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9. The preparation of iodide **7** requires the oxidation of the hydrazone generated from 2,2,6-trimethylcyclohexanone with iodine;[9] however, in our hands, the yield of this two-step procedure varied, presumably due to the stability of the intermediate hydrazone.
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