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Catalytic asymmetric formal total synthesis of (+)-dichroanone and (+)-taiwaniaquinone H

Liang-Qun Li [a,b,c], Ming-Ming Li [b], Dong Chen [b,c], Hao-Miao Liu [b,c], Hui-chun Geng [b,c], Jun Lin [a,*], Hong-Bo Qin [b,*]

[a] Key Laboratory of Medicinal Chemistry for Natural Resources (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, China
[b] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China
[c] University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

Catalytic asymmetric formal total synthesis of (+)-dichroanone and (+)-taiwaniaquinone H has been achieved. Key step involved construction of all-carbon quaternary carbon by palladium-catalyzed conjugate addition of arylboronic acid to 3-methyl cyclohexenone. Furthermore, a new approach to build [6-5-6] tricyclic backbone via formyl introduction and subsequent aldol-type condensation was also explored.

Taiwaniaquinoids represent a family of over 20 diterpenes with unusual *abeo*-abietane skeleton and have been mainly isolated from *Taiwania cryptomerioides*, *Salvia dichroantha* and *Thuja standishii*, during the past decade (Fig. 1).[1] Standishinal (**3**) is a potential antitumor agent for treating estrogen-dependent cancer due to its aromatase inhibitory activity. Thus, diterpenoids possessing the same skeleton of this family, such as (−)-dichroanone (**1**) and (−)-taiwaniaquinone H (**2**), are expected to be antitumor active.[2] The promising biological properties and distinctive [6-5-6] fused ring system of these compounds have been attracting considerable attention of several synthetic groups. Among many total syntheses of these diterpenes,[3] only few enantioselective syntheses of taiwaniaquinoids have been reported. In Stoltz's total synthesis of (+)-dichroanone, a quaternary stereogenic center was formed by an asymmetric Tsuji allylation.[3e] Node's group utilized the enantioselective intramolecular Heck reaction to complete total synthesis of (−)-dichroanal B, (−)-dichroanone, and taiwaniaquinone H.[3m] Hartwig reported an enantioselective total synthesis of (−)-taiwaniaquinol B and (−)-taiwaniaquinone H by asymmetric palladium-catalyzed α-arylation of a ketone with an aryl bromide.[3q] Apparently, to achieve catalytic asymmetric syntheses of the taiwaniaquinoids, enantioselective construction of quaternary carbon has to be addressed.[3]

To develop general synthetical strategy of abietane diterpenes, we focused on Palladium catalyzed enantioselective conjugate addition of arylboronic acid to cyclic enone, a methodology pioneered by Lu[4a] and developed by Stoltz,[4b–d] to construct quaternary carbon. Since no such application in total synthesis of abietane diterpenes has been reported, a new strategy to build [6-5-6] tricycle skeleton remains to be explored. Herein, we report our preliminary results on the aspects.

Our retrosynthetic analysis is depicted in Scheme 1. According to related literature's report,[3h,m] we found that enantioselective formal syntheses of (+)-dichroanone (**1**) and (+)-taiwaniaquinone H (**2**) could be accomplished through same intermediate tetrahydrofluorene **7**. Geminal dimethyl unit was supposed to be accessible from ketone **9** via methylation of tertiary alcohol **8** using Reetz reagent.[5–7] Tricyclic enone **9**, would be easily obtained by a consecutive operation of formyl introduction into the aromatic ring and a subsequent aldol condensation with ketone **10**. Compound **10** would be obtained by Palladium-catalyzed enantioselective conjugate addition of known aryl boronic acid **12**[8] to 3-methyl-2-cyclohexenone **11** as mentioned before.[4]

Our synthesis commenced with the enantioselective conjugate addition between 3-methyl-2-cyclohexenone **11** and 3-methoxy-4-isopropyl benzeneboronic acid **12** in the presence of Pd $(OCOCF_3)_2$

* Corresponding authors. Tel./fax: +86 871 6503 3215 (J.L.), +86 871 6523 8010 (H.-B.Q.).
E-mail addresses: linjun@ynu.edu.cn (J. Lin), qinhongbo@mail.kib.ac.cn (H.-B. Qin).

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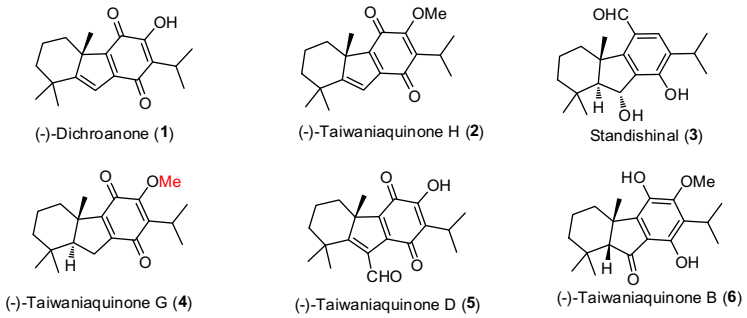
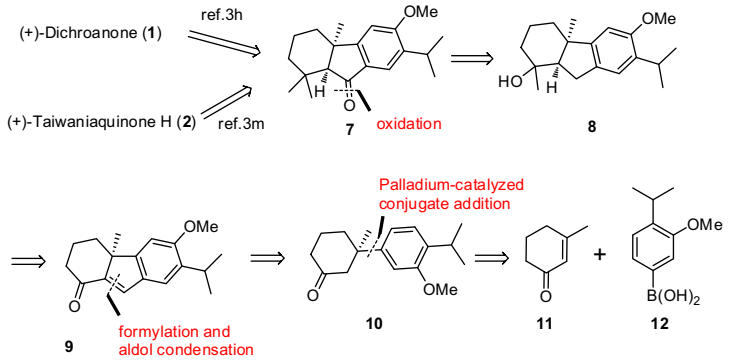
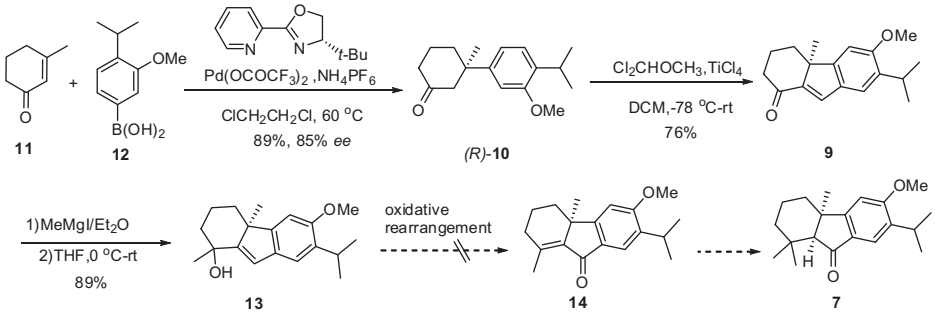


Figure 1. Representative taiwaniaquiniods.



Scheme 1. Retrosynthetic analysis.

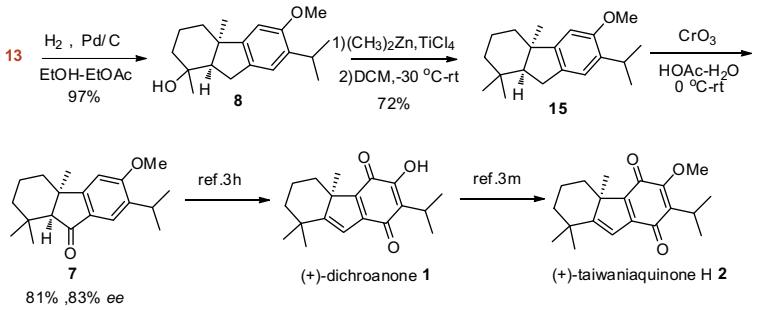


Scheme 2. Construction of [6-5-6] tricyclic backbone.

(6 mol %) catalyst and (*s*)-*t*-BuPyOX ligand (5 mol %) (Scheme 2). β-Aryl ketone **10** was isolated in 89% yield and 85% ee determined by chiral HPLC analysis. The absolute configuration of compound (−)-**10** was confirmed to be *R* according to Stoltz's report.[4] Due to no further improvement in ee after optimization process (ligand, solvent etc.) or chiral resolution, it was used in following synthesis. Cyclization could be realized by introducing a formyl group and subsequent aldol condensation. In fact, on treatment with 1, 1-dichlorodimethyl ether and $TiCl_4$, a formyl group was introduced into the *para*-position of the methoxyl aromatic ring and to our delight, tricyclic enone **9** was isolated directly from β-aryl ketone **10** in 76% yield in one-pot, which means a spontaneous aldol-type condensation occurred in situ. Thus the basic [6-5-6]-tricyclic skeleton containing an all-carbon quaternary benzylic stereogenic center was furnished smoothly.

Next, germinal dimethyl group is to be installed and conjugate addition of Methyl to β-Me enone **14** seemed to be effective. Addition of methyl magnesium iodide to ketone **9** proceeded smoothly to give allyl alcohol **13** in 89% yield which could be oxidized into an Michael acceptor **14**. However, attempts to convert allyl alcohol **13** into β-Me enone **14** via oxidative rearrangement using TEMPO/$NaIO_4$–SiO_2 only led to the recovery of **13** even under refluxing condition.[9] We were forced to try another way to install the geminal dimethyl group.

Direct conversion of ketone **9** into germinal dimethyl was attempted with Reetz reagent, but no desired product was isolated. Therefore, an alternative way is illustrated in Scheme 3. Hydrogenation of allyl alcohol **13** catalyzed by 5% Pd–C afforded saturated tertiary alcohol **8** in 97% yield. Satisfactorily, geminal dimethyl was installed in 72% yield through methylation of compound **8** using the excessive Reetz reagent in CH_2Cl_2 from −40 °C to room temperature. Oxidation of compound **15** with CrO_3 in aqueous acetic acid (90% v/v) gave key intermediate tetrahydrofluorene **7** as a single diastereomer in 81% yield. Its enantiomeric excess was determined to be 82.6% by chiral HPLC analysis. The relative stereochemistry of **7** was assigned as *cis* by the ROESY (see Supporting information). The ^1H and ^{13}C spectrum data of (+)-**7** are in agreement with the literatures.[3o,3h] The tetrahydrofluorene 7 can serve as a common



Scheme 3. Synthesis of key intermediate **7**.

intermediate in She's syntheses of (+)-dichroanone,[3h] and be further converted into (+)-taiwaniaquinone H, following transformations reported by Node.[3m]

In conclusion, a catalytic asymmetric formal total synthesis of (+)-dichroanone (**1**) and (+)-taiwaniaquinone H (**2**) has been accomplished. Key tricyclic intermediate 7 was synthesized in 6 steps and 34% yield. Key reaction involves palladium-catalyzed conjugate addition of arylboronic acids to 3-methyl-2-cyclohexenone to construct all-carbon quaternary stereocenter. Cyclization was realized by a one-pot operation of formyl group introduction and in situ aldol-type condensation. Furthermore, installing geminal dimethyl unit through methylation of tertiary alcohol using Reetz reagent constitutes an efficient strategy to access abietane diterpene skeleton. Further applications of this new strategy in diterpenes total synthesis are currently underway in our lab.

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Liang-Qun Li and Ming-Ming Li contributed equally.

Supplementary data

Supplementary data (experiment details and NMR spectra for compounds **15**, **13**, **12**, **10**, **9**, **8** and **7**, chiral HLPC chromatograms chart of compounds **10** and **7**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.110.

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