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Syntheses of Taiwaniaquinone F and Taiwaniaquinol A via an Unusual Remote C−H Functionalization

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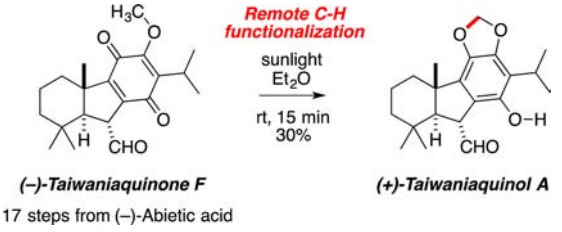
ABSTRACT



A protecting-group-free route to (−)-taiwaniaquinone F based on a ring contraction and subsequent aromatic oxidation of a sugiol derivative is reported. In addition, the first synthesis of (+)-taiwaniaquinol A is reported via short time exposure of (−)-taiwaniaquinone F to sunlight triggering a remote C−H functionalization. The hypothesis that the biogenesis of some methylenedioxy bridged natural products could proceed via similar nonenzymatic mechanisms is presented.

Natural products remain a strong inspiration for chemistry due to their structural diversity combined with intriguing transformations in their biosynthesis.[1] In particular, terpenes display a vast array of different structural types resulting from simple isoprenoid precursors. This is due to the plasticity of their enzyme-mediated biosynthesis[2] combined with subsequent chemical transformations. In particular, terpenoid rearrangements have long puzzled chemists due to the often unexpected structural outcomes of such transformations, either in their biogenesis or during isolation and degradation studies.[3] Taiwaniaquinoids are interesting diterpenoids that feature an unusual 6−5−6 ring system.[4] They have attracted considerable interest from both isolation chemists and synthesis groups alike, and several syntheses of members of this family have been reported.[5] As the biogenesis of taiwaniaquinoids has not been investigated in detail, general hypotheses for the

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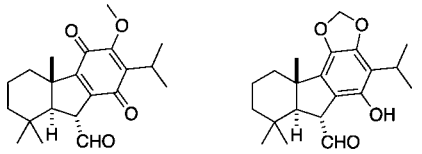
biogenesis of the unusual 6−5−6 ring system have been proposed by us[5o,p] and others[5h,s,6] based on the structural features of isolated C_{20} diterpenoids.

Taiwaniaquinone F (**1**)[7a] and taiwaniaquinol A (**2**)[6] are two prominent members of this family, characterized by the presence of a 1,4-quinone and a methylene-bridged catechol, respectively (Figure 1).[7] Preliminary studies showed that many taiwaniaquinoids possess intriguing biological activities, and **1** and **2** showed potent cytotoxicity against the epidermoid carcinoma (KB) cancer cell line.[7b]

In this communication, we report on the preparation of taiwaniaquinone F (**1**) from abietic acid via a carbene mediated ring contraction followed by aromatic oxidation reactions. In addition, taiwaniaquinol A (**2**) was obtained for the first time in synthetic form via an unusual rearrangement.



(−)-taiwaniaquinone F (1) (+)-taiwaniaquinol A (2)

Figure 1. Structures of (−)-taiwaniaquinone F and (+)-taiwaniaquinol A.

The synthesis of taiwaniaquinone F (**1**) started from the natural product sugiol methyl ether (**4**), which was prepared from commercially available abietic acid (**3**) in 36% yield over nine steps interconnecting eight natural intermediates in multigram scale following known synthetic procedures with some experimental modifications[8] (Scheme 1).

The establishment of the characteristic 6−5−6 ring system through ring contraction of the B ring of sugiol methyl ether (**4**) was addressed next. Diazotization of ketone **4** using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU afforded diazoketone **5** in 65% yield together with a smaller amount of remaining starting material **4** (30%). When diazoketone **5** was subjected to irradiation of a medium pressure Hg lamp in a dilute solution of dry MeOH, it underwent a smooth Wolff rearrangement yielding the ring contracted product **6** with excellent diastereoselectivity (20:1). Interestingly, this rearrangement could also be performed under bright sunlight giving identical results. The relative configuration of the major diastereoisomer **6** was established as (6*S*) by NMR analysis (8.3 Hz coupling constant between H5 and H6) and was confirmed by subsequent X-ray crystal structure analysis (see Scheme 1). A possible explanation for the formation of the kinetic *cis* product would be a protonation from the sterically less hindered face of the enolate double bond (denoted HA in red, Scheme 1, **9**).[9] A subsequent epimerization of the C6 stereogenic center was achieved using NaOMe in MeOH giving the (6*R*)-ester **7** in a quantitative yield and a dr of 33:1 (as determined by NMR analysis).

When the same substrate **6** was subjected to aqueous KOH, the (6*R*)-carboxylic acid **8** was obtained in 88% yield and a dr of 8.3:1. The configuration at C6 was established by NMR analysis (11.6 Hz coupling constant between H5 and H6) and confirmed by subsequent X-ray crystal structure analysis. The same (6*R*)-ester **7** required for the next steps was obtained quantitatively by methylation of **8** using $TMSCHN_2$. Subsequently, $LiAlH_4$ reduction of the (6*R*)-ester **7** afforded the corresponding alcohol **10** in quantitative yield.

With the alcohol **10** in hand, the oxidation of the aromatic ring system was addressed next (Scheme 2). The crude alcohol **10** was brominated (Br_2 in CH_2Cl_2) to give **11** in good yields. Initially, a one pot lithiation−boronation−oxidation reaction using *n*-BuLi, TMEDA, $B(OMe)_3$, and H_2O_2 was attempted to convert **11** to phenol **12**. However, traces of product could already be detected by TLC after the lithiation step, which led us to the conclusion that O_2 (dissolved in the solvent) could operate as the oxidant in this reaction. To our great satisfaction, a simplified procedure using a one pot lithiation/oxygenation protocol with *n*-BuLi, TMEDA, and dioxygen[10] afforded the phenol **12** in 58% yield from **11**. Oxidation of phenol **12** to the corresponding *p*-quinone **13** was accomplished using Co(salen)[11] with dioxygen in CH_3CN in quantitative yield. It is noteworthy that this reaction and the purification of the product were carried out under exclusion from light to avoid decomposition of this sensitive compound. Final oxidation of alcohol **13** was accomplished by treatment with Dess−Martin periodinane (DMP) in CH_2Cl_2 in the dark, to produce (−)-taiwaniaquinone F (**1**) in quantitative yield. All spectroscopic data of this synthetic compound were in agreement with those reported for the authentic natural product.[6]

To avoid decomposition of the natural product (−)-taiwaniaquinone F (**1**), it was also essential in this step to perform the workup and purification under strict exclusion from light. To our great surprise, if such precautions were not taken, minor amounts of impurities

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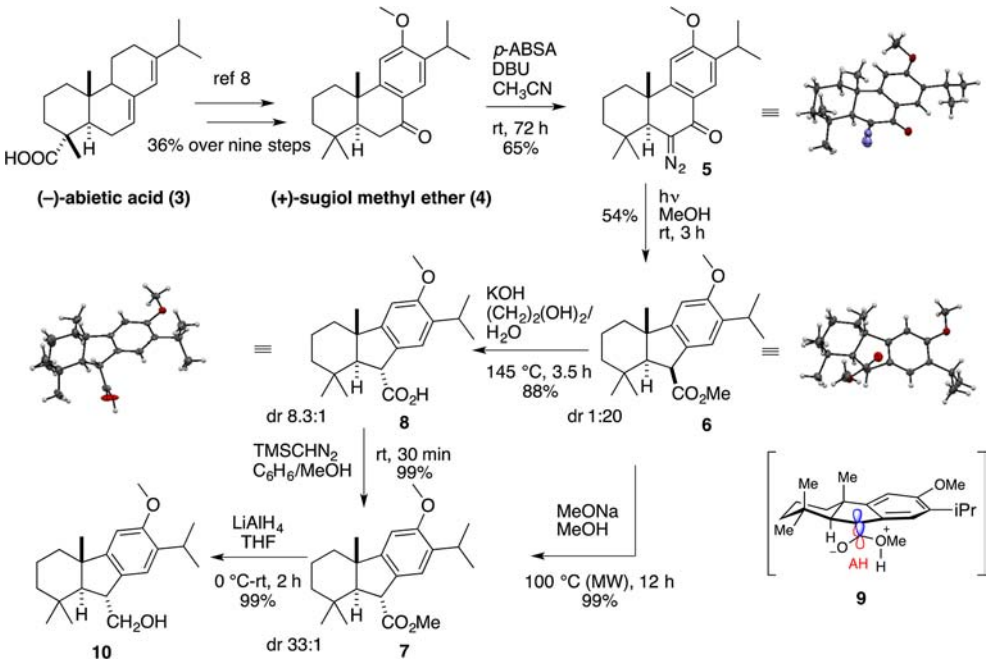
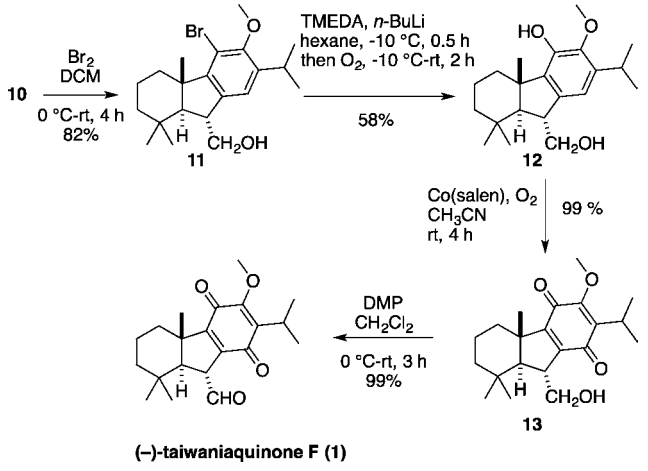
Scheme 1. Preparation of Ring Contracted Intermediate **10**

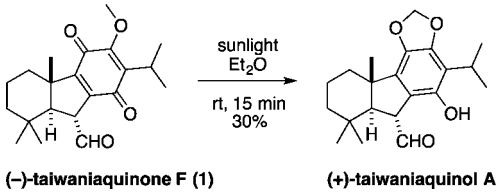


Scheme 2. Completion of the Synthesis of (−)-Taiwaniaquinone F



corresponding to (+)-taiwaniaquinol A were detected by ^{1}H NMR analysis. Consequently, a diluted solution of (−)-taiwaniaquinone F (**1**) was exposed to sunlight to produce (+)-taiwaniaquinol A (**2**) in 30% yield with all spectroscopic data of synthetic **2** in agreement with those of the authentic natural product (Scheme 3).[7a] Mechanistic studies to rationalize this transformation are currently ongoing in our group; however, several possible hypotheses have been postulated for related quinone photolysis reactions that account for a 1,5-hydrogen abstraction.[12] In our case the alkoxy radical would abstract a proton of the OMe group which is sterically forced to occupy a favorable position for 1,5-H abstraction.[13] Such photolysis of a similar quinone moiety was achieved in 1978 by Edwards et al. but has received only little attention afterward.[14] With the recent emergence of remote C−H functionalization methods on complex unprotected substrates,[15] this interesting transformation might add novel aspects of strategic disconnections in natural product synthesis.

Scheme 3. Synthesis of (+)-Taiwaniaquinol A



The ease of this transformation by simply exposing the quinone to sunlight leading to product conversion

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suggests that this transformation could be part of the biosynthetic pathway in *Taiwania cryptomoides*. Interestingly, taiwaniaquinone F (**1**) was isolated from the bark of *T. cryptomerioides*, whereas taiwaniaquinol A (**2**) was isolated from the leaves of the same tree[7] lending further support to this biosynthetic hypothesis. It might be possible that the transformation observed in our synthetic studies is also occurring in the leaves of *T. cryptomerioides* that are exposed to sunlight.

While the previously proposed mechanisms for the biogenesis of methylenedioxy bridged natural products invoked the participation of enzymes,[16] the absence of any enzymes in our synthetic route suggests that this nonenzymatic pathway could present a viable biogenetic option to other methylenedioxy bridged catechols. For example, cyclocoulterone[17] could be generated (either synthetically or in the biosynthesis) from coulterone through a very similar mechanism. Given the prevalence of these compounds in nature,[18] we propose that other members of this class could be formed formed by similar nonenzymatic mechanisms.

In summary, a new protecting-group-free route to (−)-taiwaniaquinone F (**1**) and the first synthesis of (+)-taiwaniaquinol A (**2**) was developed starting from commercially available abietic acid. Salient features of this synthesis include (1) the Wolff ring contraction of the diazo derivative of sugiol methyl ether **4**; (2) the aromatic oxidations of the ring contracted product **10** by molecular oxygen; and (3) an unanticipated formation of a methylenecatechol moiety via the photolysis of (−)-taiwaniaquinone F (**1**) to (+)-taiwaniaquinol A (**2**) via a remote C−H functionalization. A hypothesis for the biogenesis of the frequently encountered methylenedioxy motif in natural products was proposed, and bioactive compounds such as ecteinascidin 743 will be studied in more detail in our laboratory and may provide further insight to the biogenesis of this interesting class of natural products.

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Supporting Information Available. Detailed experimental procedures, full characterization, and copies of all NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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