A thermal 6π electrocyclization strategy towards taiwaniaquinoids. First enantiospecific synthesis of (−)-taiwaniaquinone G†

Enrique Alvarez-Manzaneda,*[a] Rachid Chahboun,[a] Eduardo Cabrera,[a] Esteban Alvarez,[a] Ali Haidour,[a] Jose Miguel Ramos,[a] Ramón Alvarez-Manzaneda,[b] Mohammed Hmamouchi[c] and Hakima Es-Samti[c]

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The first route towards taiwaniaquinoid terpenes bearing an A/B *trans*-configuration has been developed through a sequence which includes a thermal 6π electrocyclization.

During the last few years a large number of rearranged abietane-type diterpenes bearing the rare 4a-methyltetra- (or hexa-) hydrofluorene skeleton have been isolated from some species of East Asian conifers. This group of compounds, named taiwaniaquinoids because most of them were found in the common Taiwanese pine tree *Taiwania cryptomerioides*,[1] includes taiwaniaquinones A (**1**),[1a] D (**2**),[1b] G (**3**)[1d] and H (**4**),[1d] taiwaniaquinols A (**5**),[1a] B (**6**)[1a] and C (**7**),[1c] standishinal (**8**) isolated from *Thuja standishii*,[2] and dichroanone (**9**)[3] obtained from *Salvia dichroantha*, among others (Fig. 1). In some cases, one carbon is lost in the course of the biosynthesis to afford norditerpenoids, such as compounds **4**, **6** and **9**.

Though the bioactivities of this family of compounds are yet to be examined comprehensively, recent studies have revealed that taiwaniaquinone D (**2**) possesses antitumour activity,[1d] and standishinal (**8**) shows aromatase inhibitory potential, making it a promising candidate as an anti-breast cancer agent.[4]

These biologically significant activities and the intriguing structure of these terpenoids have attracted considerable attention among organic chemists, and several total syntheses have been developed for some of these compounds. Four main strategies have been utilized for the construction of the core 6,5,6-ABC tricyclic skeleton of taiwaniaquinoids. Stoltz used an A–AB–ABC approach for synthesizing (+)-dichroanone (**9**), the enantiomer of the natural product; the 5-membered B ring was formed after a novel asymmetric palladium-catalyzed allylation.[5] Other authors used a C–ABC strategy, involving a bis cyclization process; thus, Fillion synthesized (±)-taiwaniaquinol B (**6**), through a domino intramolecular acylation carbonyl α-*tert*-alkylation reaction,[6] while Chiu synthesized the same compound **6** *via* an intramolecular acid-promoted sequential cationic cyclization.[7] The AC–ABC approach has been the most widely-utilized strategy to synthesize this type of metabolites. Trauner described a concise synthetic approach toward taiwaniaquinoids utilizing a Nazarov cyclization.[8] Node[9] and Banerjee[10] reported approaches toward other members of the family utilizing intramolecular Heck reactions. Very recently, She described the synthesis of (±)-taiwaniaquinol B (**6**) and dichroanone (**9**) using an acid-promoted Friedel–Crafts acylation/alkylation process.[11]

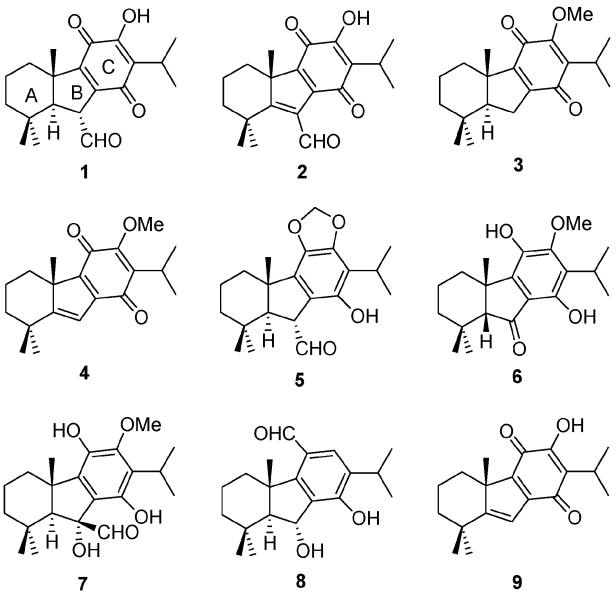


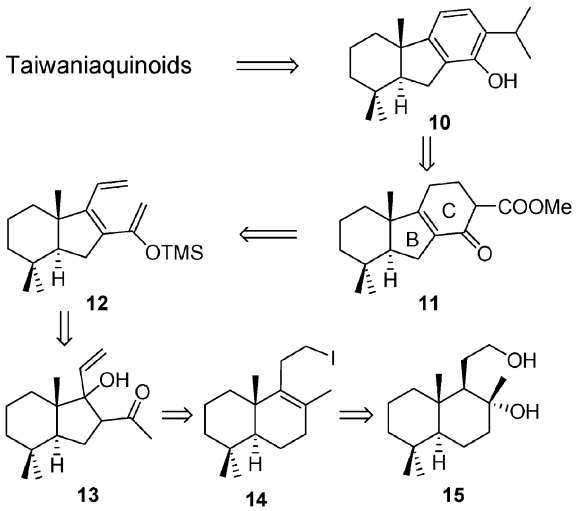
Fig. 1 Some representative taiwaniaquinoids.

However, all these previously reported methods are restricted to synthesizing compounds with an A/B *cis*-configuration or a cyclopentane double bond, such as compounds **6** and **9**, respectively.

Continuing our research into the synthesis of bioactive compounds from natural enantiopure precursors, we are interested in developing a route which makes it feasible to prepare a wider range of taiwaniaquinoids, including those possessing an A/B *trans*-configuration, which are widespread. Scheme 1 shows the synthetic strategy we planned to achieve this goal. The BC system of the core 6,5,6-ABC tricyclic skeleton of target compounds will be elaborated after an intramolecular aldol condensation–6π electrocyclization sequence. The isopropyl group of precursor **10** was planned to be introduced utilizing the ester group of methyl salicylate derived from ketoester **11**, obtained from the enone resulting from the electrocyclization of

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain. E-mail: eamt@ugr.es; Fax: +34 958 24 80 89; Tel: +34 958 24 80 89*
[b] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Almería, 04120 Almería, Spain*
[c] *Departement de Biologie, Unité des Substances Naturelles, Faculté de Medecine et Pharmacie, Universite Mohammed V-Suissi, Rabat, Morocco*

† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}C NMR. See DOI: 10.1039/b816812a



Scheme 1 Retrosynthetic analysis.

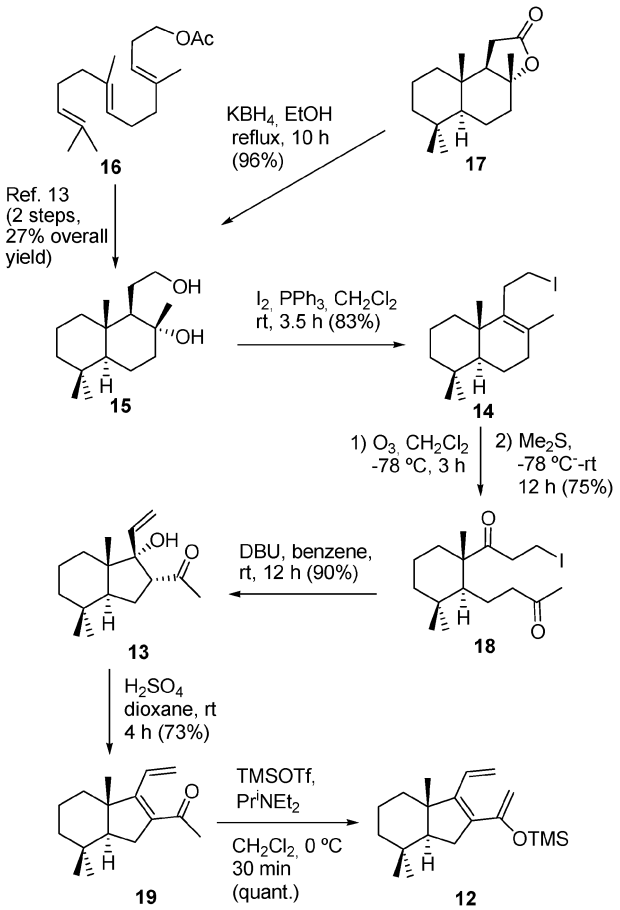
silyl enol ether **12**. This was expected to be obtained from the conjugate dienone formed after dehydration of ketol **13**. This compound would result from the intramolecular aldol condensation of diketone derived from the oxidative rupture of the homoallylic iodide **14**, easily prepared from diol **15**.

Iodide **14** is fundamental in our planned synthesis; our previously reported methodology, which enables the simultaneous dehydration of tertiary alcohols and the transformation of primary alcohols into the corresponding iodides utilizing the I_2–PPh_3 system,[12] allows us to prepare this iodide from diol **15** in 83% yield. This compound has been obtained by lipase catalyzed kinetic resolution after the acid cyclization of homofarnesyl acetate (**16**) (2 steps, 27% overall yield);[13] alternatively, we have prepared diol **15** in almost quantitative yield from commercial (+)-sclareolide (**17**). The phenol derivative **10**, bearing the characteristic tricyclic [6-5-6] ring system with the A/B *trans*-configuration, would be a suitable intermediate to achieve the different types of taiwaniaquinoid metabolites.

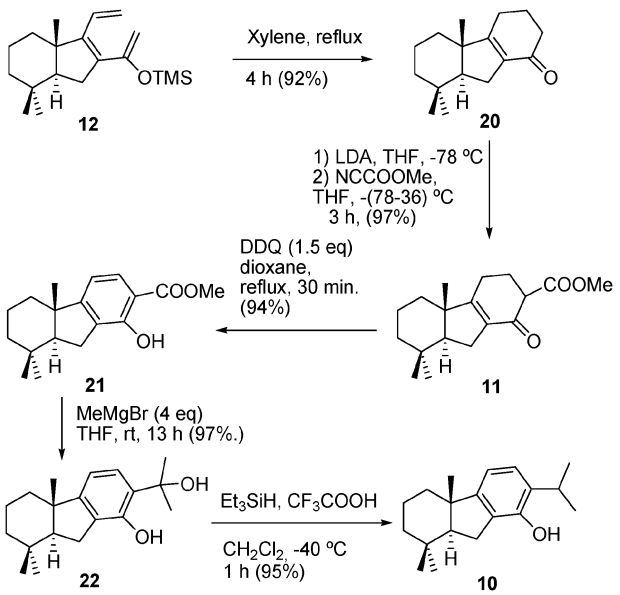
Scheme 2 shows the synthesis of silyl enol ether **12**. The sequence starts from homoallylic iodide **14**,[14] whose ozonolysis afforded in good yield the 1,6-diketone **18**.[15] β-Hydroxy ketone **13** ($[\alpha]_D^{25}$: −43.0°; c 1.0, $CHCl_3$) was obtained in high yield when compound **18** was treated with DBU in benzene at room temperature. Dehydration of hydroxy ketone **13** presented some difficulties, probably due to the tough hydrogen bond in the molecule. After assaying different reaction conditions, we concluded that the best results were achieved utilizing conc. H_2SO_4 in dioxane at room temperature, which afforded dienone **19** ($[\alpha]_D^{25}$: −59.5°; c 0.9, $CHCl_3$) in 73% yield. Finally, triene **12** was obtained in quantitative yield after treatment with TMSOTf and Pr^iNEt_2 in dichloromethane at 0 °C.

Next, the construction of the aromatic C ring of the target compounds was undertaken. The transformation of silyl enol ether **12** into the tricyclic precursor **10** of the taiwaniaquinoids is depicted in Scheme 3.

Refluxing triene **12** in xylene for 4 h gave directly tricyclic β-enone **20** ($[\alpha]_D^{25}$: −66.1°; c 0.7, $CHCl_3$). Treatment of this compound with LDA and NCCOOMe in THF led to

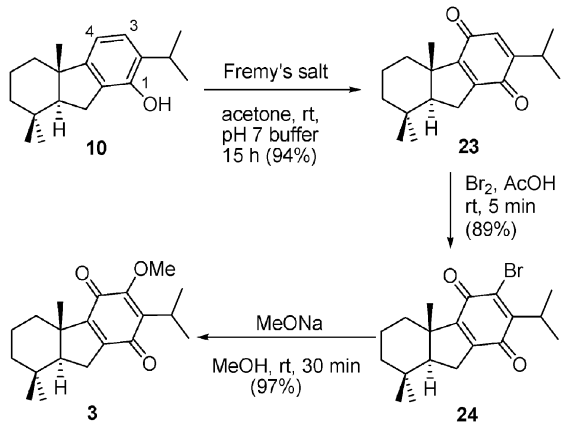


Scheme 2 Synthesis of triene **12**.



Scheme 3 Synthesis of intermediate **10** from triene **12**.

β-ketoester **11**, obtained as a 1 : 1 mixture of epimers, which was transformed into the methyl salicylate **21** ($[\alpha]_D^{25}$: −14.7°; c 1.0, $CHCl_3$) by reaction with DDQ (1.5 equiv.) in dioxane under reflux. Ester **21** was then transformed into



Scheme 4 Synthesis of (−)-taiwaniaquinone G (**3**) from phenol **10**.

hydroxyphenol **22** ($[\alpha]_D^{25}$: −17.4°; c 0.8, $CHCl_3$) by treatment with MeMgBr (4 equiv.). Treatment of this compound with Et_3SiH and CF_3COOH gave the desired phenol **10** ($[\alpha]_D^{25}$: −19.4°; c 1.1, $CHCl_3$).

Finally, the functionalization of the aromatic C ring was addressed. After considering the previously reported taiwaniaquinoids, we focused on taiwaniaquinone G (**3**), the most immediate terpenoid possessing an A/B *trans*-configuration which has not yet been synthesized. At this point, it should be emphasized that intermediate **10** possesses a different substitution pattern from that of the phenolic precursors utilized in previously reported syntheses, which forced us to investigate new strategies to achieve the target quinone. Most preceding authors utilized 1,3-[6,8] or 3,4-dihydroxy[10] derivatives, instead of the 1-hydroxy substituted compound **10** reported here; those were transformed into the final compound after a 2- or 3-step sequence in 45–52% yield. Stoltz[5] and She[11] used a 3-hydroxy precursor, which afforded quinone **9** in a 3-step sequence (35% overall yield). Starting from phenol **10**, we have developed a very efficient synthesis of taiwaniaquinone G (**3**) (Scheme 4).

Quinone **23** ($[\alpha]_D^{25}$: −26.3°; c 0.9, $CHCl_3$) was smoothly obtained by treating phenol **10** with Fremy's salt. All our attempts to directly transform compound **23** into methoxy derivative **3**, utilizing diverse previously reported conditions, *e.g.* $HgCl_2$, I_2, MeOH[16] or $Fe_2(SO_4)_3$, MeOH,[17] were unsuccessful. This goal was finally achieved after treatment of bromoquinone **24** ($[\alpha]_D^{25}$: −23.6°; c 1.1, $CHCl_3$) with MeONa in MeOH.

In this way, phenol **10** was transformed into taiwaniaquinone G (**3**) in a 3-step sequence in 81% overall yield. The optical rotation of synthetic taiwaniaquinone G (**3**) ($[\alpha]_D^{25}$: −91.4°; c 1.1, $CHCl_3$) was similar to that reported for the natural product ($[\alpha]_D^{22}$: −120.8°; c 0.29, $CHCl_3$); the spectroscopic properties were identical to those previously described.[1d]

In summary, a new synthetic strategy towards taiwaniaquinoids, based on a thermal 6π electrocyclization, is described. In contrast with previously reported approaches, the present methodology reported also allows us to synthesize taiwaniaquinoids which present an A/B *trans*-configuration. Thus, phenol **10** is a suitable intermediate for synthesizing a wide range of taiwaniaquinoids. Utilizing this, the first synthesis of (−)-taiwaniaquinone G (**3**) starting from commercial (+)-sclareolide (**17**) (14 steps, 25% overall yield) has been achieved.

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