A General Access to Taiwaniaquinoids Based on a Hypothetical Abietane C7-C8 Cleavage Biogenetic Pathway

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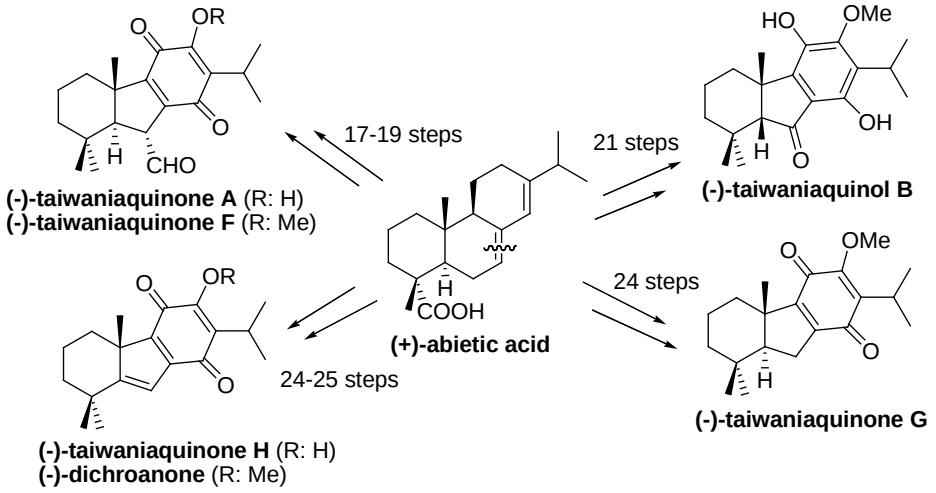


A new strategy for synthesizing taiwaniaquinoids, a group of terpenoids with an unusual rearranged 5(6→7) or 6-nor-5(6→7)abeo-abietane skeleton, which exhibit promising biological activities, is reported. The procedure, based on the cleavage of the C7-C8 double bond of abietane diterpenes, is the only one yet reported for synthesizing C_{20} taiwaniaquinoids bearing a carbon function on the cyclopentane B ring; it is also applicable to the synthesis of the wide variety of existing taiwaniaquinoids. Utilizing this, (-)-taiwaniaquinone A, F, G and H, (-)-taiwaniaquinol B and (-)-dichroanone have been synthesized from (+)-abietic acid. The versatility of this strategy allows us to propose the abietane C7-C8 cleavage as a possible biosynthetic pathway to this type of rearranged diterpenes; this proposal seems to be supported by phytochemical evidences.

Introduction

Taiwaniaquinoids are a group of terpenoids, bearing the unusual rearranged 5(6→7) or 6-nor-5(6→7)abeo-abietane skeleton, which have been isolated from some species of East Asian conifers, such as the common Taiwanese pine tree *Taiwania cryptomerioides*, during the last fifteen years.[1] These compounds, which possess a phenolic or a 1,4-benzoquinone ring, can be classified according to three main structural types: (a) those bearing a 4a-methyltetrahydrofluorene skeleton, such as taiwaniaquinone D (**1**),[2] H (**2**),[3] dichroanone (**3**) or dichroanal B (**4**), isolated from *Salvia dichroantha*;[4] (b) compounds bearing a 4a-methylhexahydrofluorene skeleton with a *cis* A/B union, such as taiwaniaquinol B (**5**)[5] or dichroanal A (**6**);[4] and (c) terpenoids having a 4a-methylhexahydrofluorene skeleton with a *trans* A/B union, such as taiwaniaquinone A (**7**),[5] F (**8**)[6] and G (**9**),[3] taiwaniaquinol A (**10**)[5] and E (**11**)[3] and standishinal (**12**), found in *Thuja standishii*.[7] *Nor*-diterpenoids **2**, **3**, **5**, **9** and **11** have lost one carbon in the course of the biosynthesis.

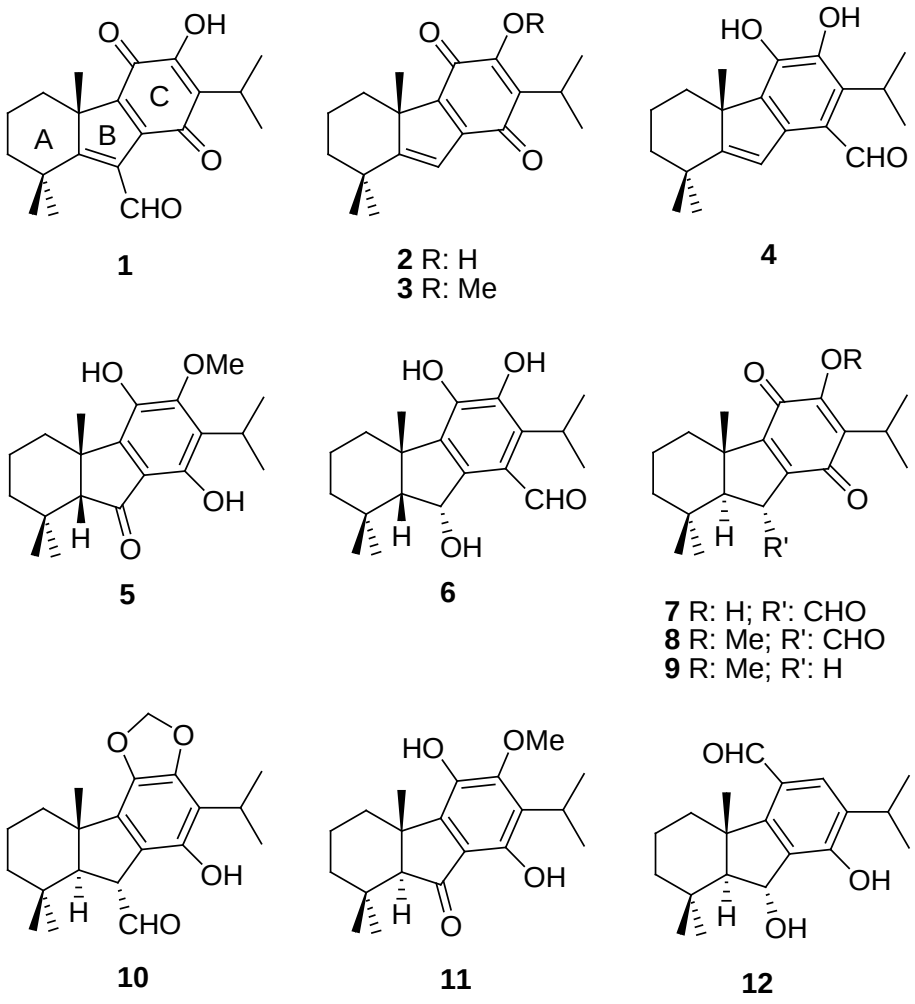


FIGURE 1. Representative taiwaniaquinoids

Although not much is known about their bioactivities, preliminary studies have revealed that taiwaniaquinones A (**7**), D (**1**) and F (**8**) and taiwaniaquinol A (**10**) exhibit cytotoxic activity,[3] while standishinal (**12**) is a potential antitumour agent for treating breast cancer, due to its aromatase inhibitory activity.[8]

These promising biological activities and the unusual carbotricyclic structure of these compounds have motivated the development of varied synthetic approaches during the last few years. Four main strategies have been utilized for the construction of the core 6,5,6-

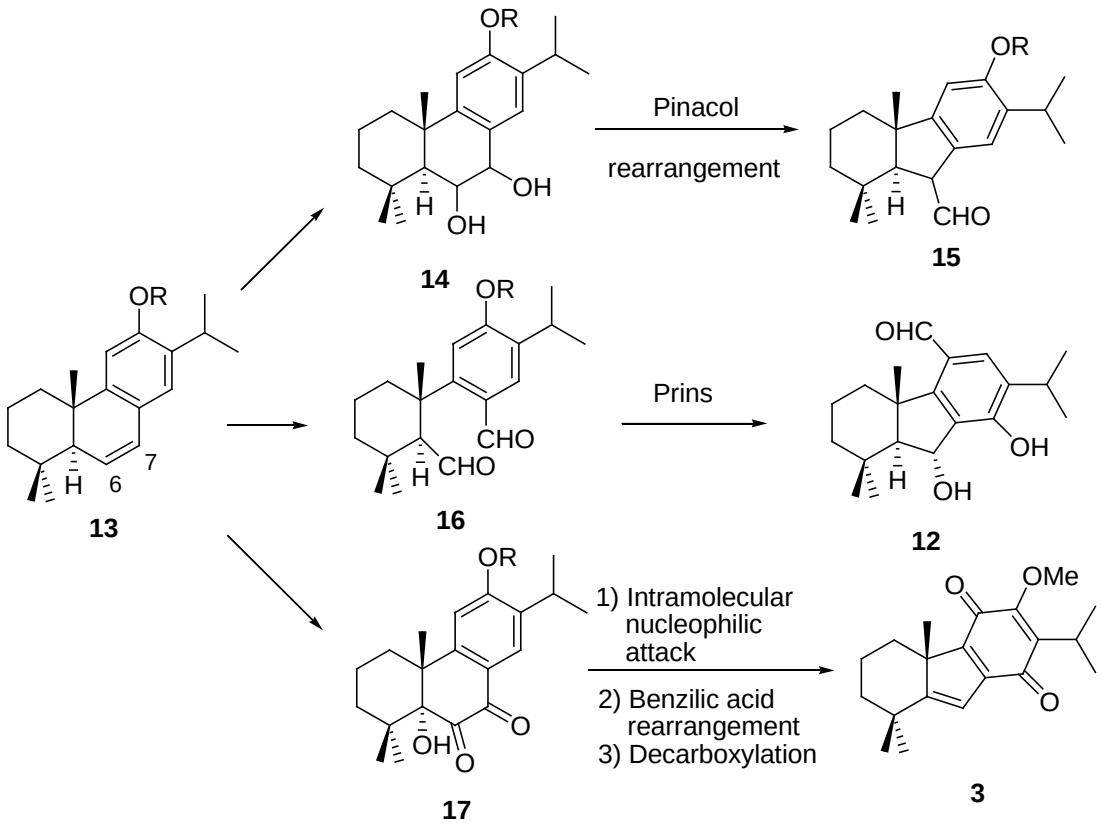
ABC tricyclic skeleton of taiwaniaquinoids. An A-AB-ABC approach[9] was used by McFadden and Stoltz for synthesizing (+)-dichroanone (**3**), the antipode of the natural product; the 5-membered B ring was formed *via* a novel asymmetric palladium-catalyzed allylation.[10] Fillion's group reported the synthesis of (+/-)-taiwaniaquinol B (**5**), utilizing a C-ABC strategy, involving a bis-cyclization process, through a domino intramolecular acylation carbonyl α-*tert*-alkylation reaction.[11] The same strategy was utilized by Li and Chiu for synthesizing compound **5** *via* an intramolecular acid-promoted sequential cationic cyclization.[12] The AC-ABC approach is currently the most widely utilized strategy for synthesizing this type of terpenoid. The construction of the 4a-methyltetra- (or hexa-) hydrofluorene skeleton usually involves the utilization of a monoterpene synthon, such as β-cyclocitral or cyclogeranic acid, together with a phenol derivative. Node et al.[13] and Banerjee et al.[14] utilized the intramolecular Heck reaction to prepare some compounds of this family. Trauner et al. described an interesting synthetic approach toward taiwaniaquinoids utilizing Nazarov cyclization.[15] She et al. described the synthesis of compounds **2** and **5**, through an acid-promoted Friedel-Crafts acylation/alkylation process, which allows the construction of the ABC tricyclic skeleton in one step.[16] Our group has reported a very short synthesis of taiwaniaquinone H (**2**) and (+/-)-dichroanone (**3**) *via* an intramolecular Friedel-Crafts alkylation.[17] Very recently, Hartwig et al. described the enantioselective total synthesis of (-)-taiwaniaquinone H (**2**) and (-)-taiwaniaquinol B (**5**), utilizing as key steps an iridium-catalyzed borylation and a palladium-catalyzed asymmetric α-arylation.[18] Gademann et al. recently reported a formal synthesis of (-)-taiwaniaquinone H (**2**) from commercial methyl dehydroabietate; the cyclopentane B ring is

formed *via* an internal-nucleophile-induced intramolecular benzilic acid type rearrangement of a hydroxydione, followed by decarboxylation. [19]

All these approaches are total syntheses and the methods are restricted to synthesizing 4a-methyltetrahydrofluorene derivatives, such as compounds **2-4**, or compounds with an A/B *cis*-configuration, such as compound **5**. Node et al. reported the synthesis of (+/-)-standishinal (**12**) starting from 2,2,6-trimethylcyclohexanone and p-formylanisol; the A/B *trans*-configuration of the target compound was achieved after cyclization of an α-(arylethyl)cyclohexanol.[20] Very recently, our group reported an enantiospecific route towards taiwaniaquinoids bearing an A/B *trans*-configuration, such as (+)-taiwaniaquinone G (**9**), *via* a thermal 6π-electrocyclization; this new methodology, which is also applicable to the synthesis of 4a-methyltetrahydrofluorene derivatives, was utilized for synthesizing (-)-taiwaniaquinone H (**2**) and (-)-dichroanone (**3**).[21]

Although the biogenesis of these interesting terpenes has not yet been investigated, three biosynthetic proposals have been made, which postulate a 6,7-dehydroferruginol derivative **13** as the precursor (Scheme 1). The pinacol rearrangement of abietane 6,7-diol **14** could afford aldehyde **15**, a possible precursor of the C_{20} taiwaniaquinoids, such as compounds **1**, **7**, **8** and **10**; however, no work has been done to verify this conjecture, postulated by Cheng.[5] The seco-abietane dialdehyde **16** could be transformed into standishinal (**12**), through a Prins type reaction; Node et al. gave credence to this idea by smoothly converting dialdehyde **16** into compound **12**.[20] The third proposal, involving the benzilic acid rearrangement of hydroxydione **17** induced by an intramolecular nucleophilic attack, has also been supported experimentally.[19]

SCHEME 1. Biosynthetic proposals for taiwaniaquinoids



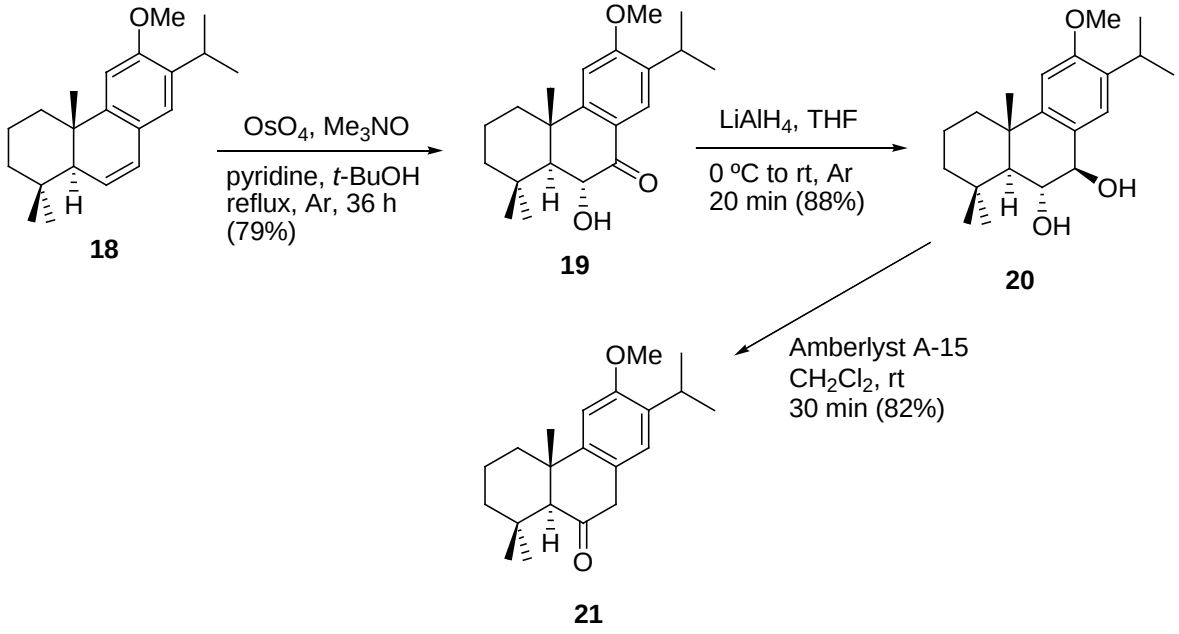
Results and Discussion

As mentioned above, the synthesis of taiwaniaquinoids with an A/B *trans*-configuration encounters serious difficulties, due to the considerable stability of the A/B *cis*-fused system.[20,21] The synthesis of taiwaniaquinoids with an A/B *trans*-configuration and an additional carbon functionality on the cyclopentane B ring, such as compounds **7**, **8** and **10**, appears to be an even more difficult task; in this case, the pinacol rearrangement of an abietane 6,7-diol derivative, such as compound **14**, postulated by Cheng as a possible biosynthetic pathway, would be the most direct way to access these types of compounds.

After our investigation of the synthesis of C_{19} taiwaniaquinoids with an A/B *trans*-configuration, such as taiwaniaquinone G (**9**),[21] we focused on the preparation of related

C_{20} taiwaniaquinoids bearing an additional carbon functionality on the cyclopentane B ring. Although, at first sight, an abietane 6,7-diol, such as **14**, does not appear suitable to undergo a pinacol rearrangement to give a cyclopentane aldehyde like **15**, we investigated this possibility. Under the dihydroxylation conditions, *O*-methyl 6,7-dehydroferruginol (**18**) was converted into α-hydroxyketone **19**,[22] which was then reduced to afford the *trans*-6,7-diol **20**;[23] treatment of compound **20** with different acids led in all cases to ketone **21** (Scheme 2). Reasonably, the dehydration of benzyl alcohol, which leads to the enol of ketone **21**, is a more favoured process than the pinacol rearrangement to a cyclopentane carbaldehyde type **15**.

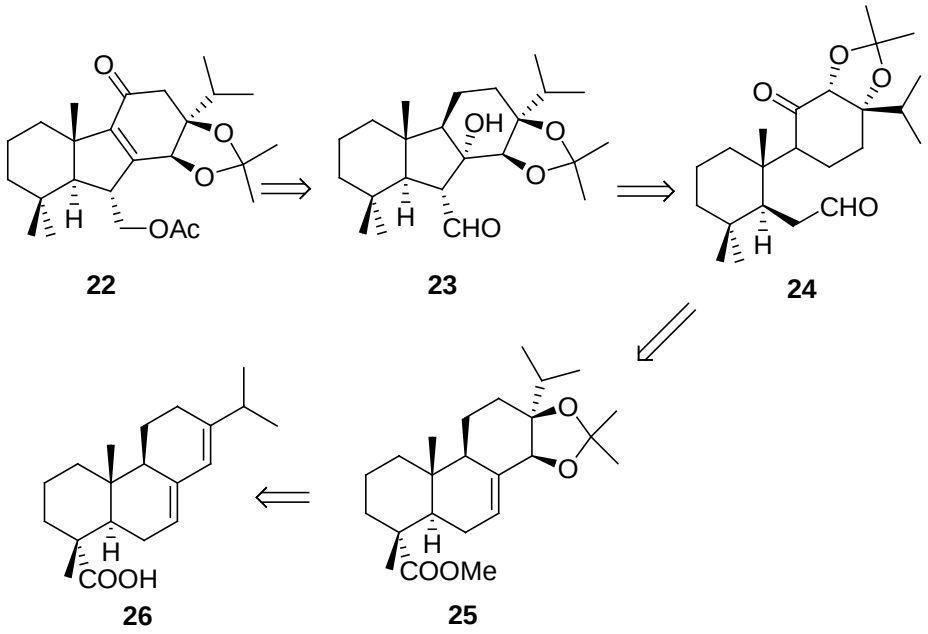
SCHEME 2. Preparation of the 6,7-Dihydroxyabietane Derivative **20** and its acid treatment



These results led us to plan an alternative strategy to access the C_{20} taiwaniaquinoids, related to compound **15**, starting from abietic acid (**26**) (Scheme 3). The functionalized B

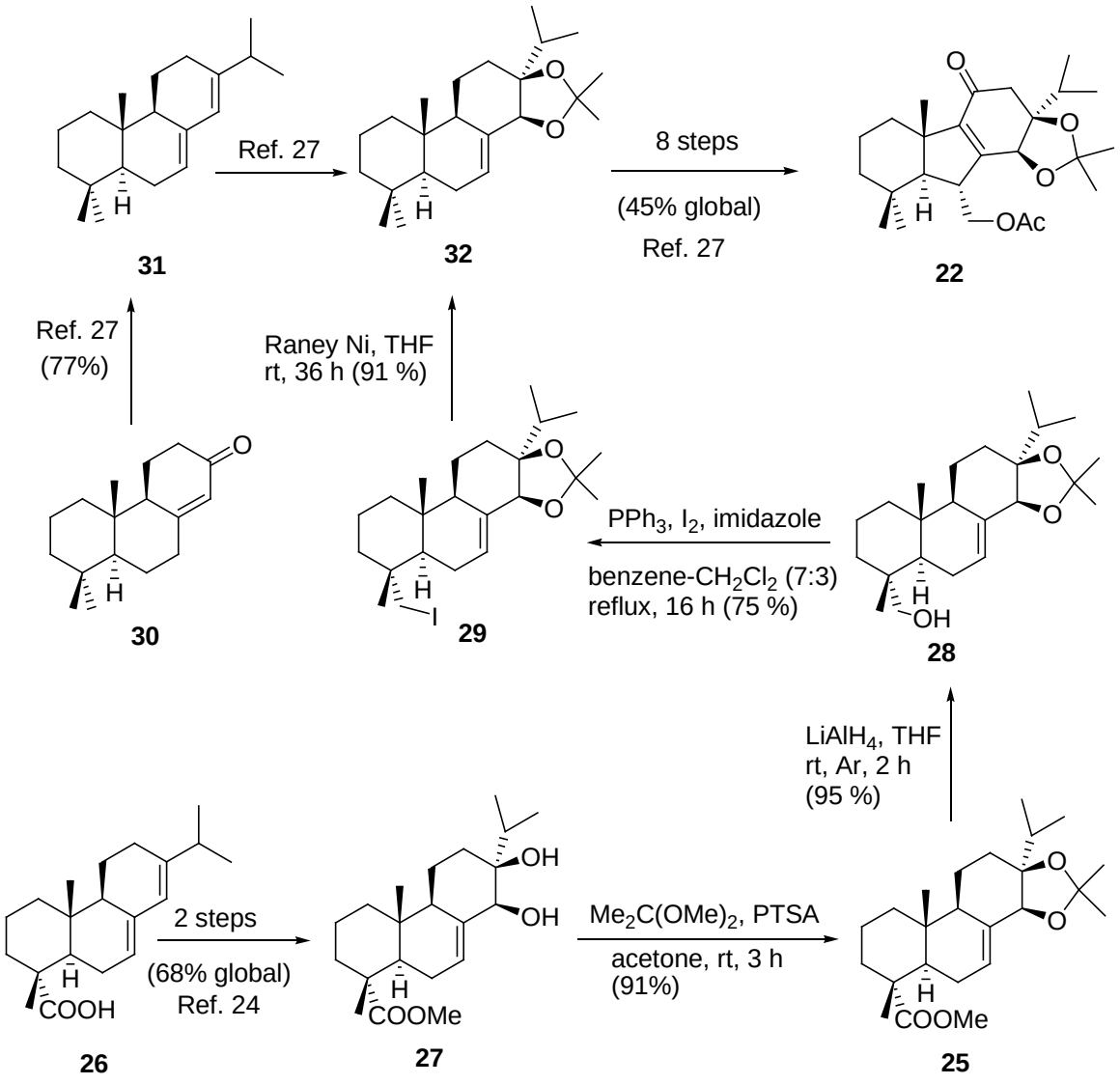
ring of taiwaniaquinoids is elaborated after the intramolecular aldol condensation of a ketoaldehyde resulting from the oxidative cleavage of the C7-C8 double bond of abietic acid (**26**). The α,β-enone **22**, which has a taiwaniaquinoid carbon skeleton and a suitably oxygenated C ring, is obtained after the allyl oxidation of the cyclohexene derivative formed from hydroxy aldehyde **23**, which results from the aldol condensation of ketoaldehyde **24**. The isopropylidene ketal **25** would be obtained after the chemoselective dihydroxylation of acid **26**.[24]

SCHEME 3. Retrosynthetic Analysis



The α,β-enone **22** has been synthesized in our laboratory from tricyclic α,β-enone **30**,[25,26] via the isopropylidene ketal **32**,[27] derived from abietane **31**.[28] Compound **32** has also been easily prepared from abietic acid (**26**) (Scheme 4).

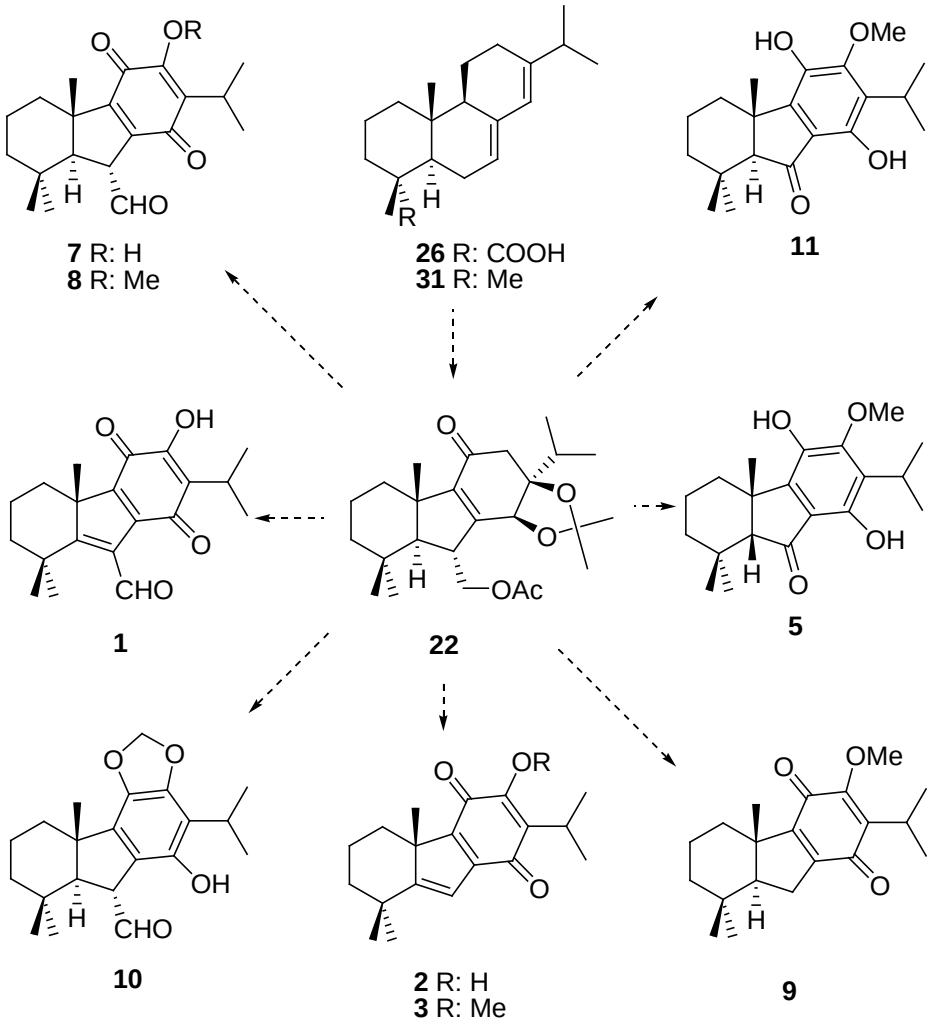
SCHEME 4. Synthesis of α,β-enone **22**



α,β-Enone **22** seems to be a suitable intermediate in the synthesis of the different types of taiwaniaquinoids (Scheme 5). The most immediate derivatives are the A/B *trans*-fused taiwaniaquinoids **7**, **8** and **10**, which result from the oxidation of the alcohol derived from **22**, or the corresponding α,β-unsaturated aldehyde **1**. Moreover, C_{19} taiwaniaquinoids could also be obtained from ketone **22**. Elimination of acetic acid from **22**, or dehydration of the

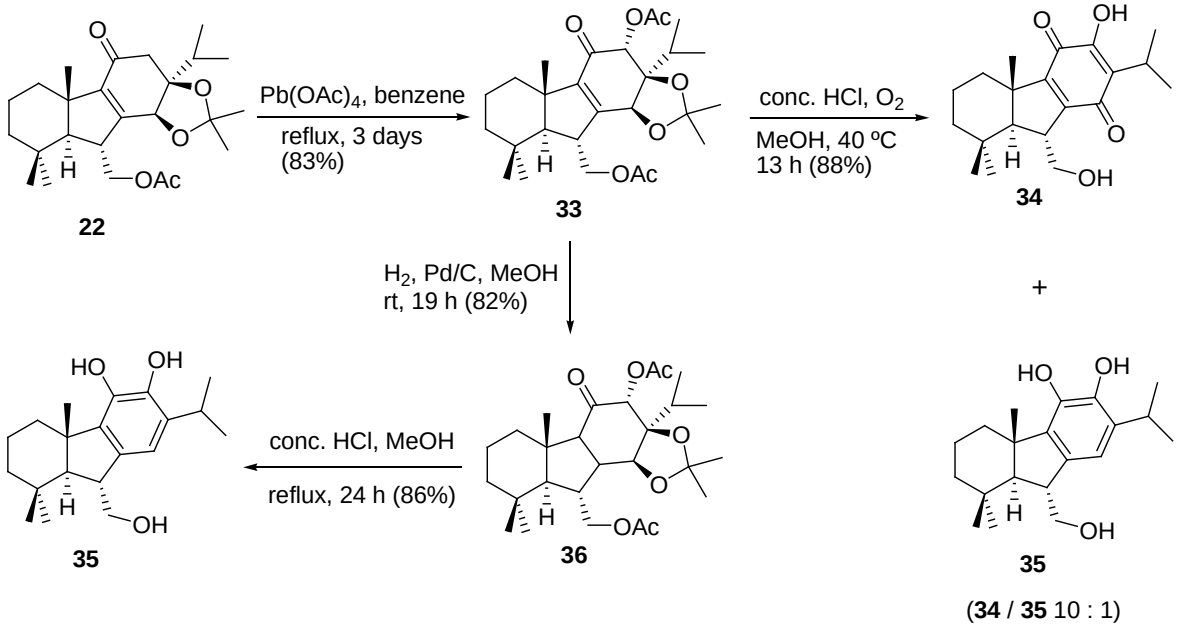
corresponding alcohol, and the further oxidative cleavage of the resulting carbon-carbon double bond, will afford taiwaniaquinol E (**11**) or its A/B *cis*-fused epimer **5**. A/B *trans*-fused taiwaniaquinoids, such as **9**, will be obtained after deoxygenation of the 7-oxo group of compound **11**. 4a-Methyltetrahydrofluorene derivatives **2** and **3** will also be formed after the reduction of 7-oxo compounds such as **5** and **11**.

SCHEME 5. The Abietane C7-C8 Cleavage Pathway to the Diverse Types of Taiwaniaquinoids



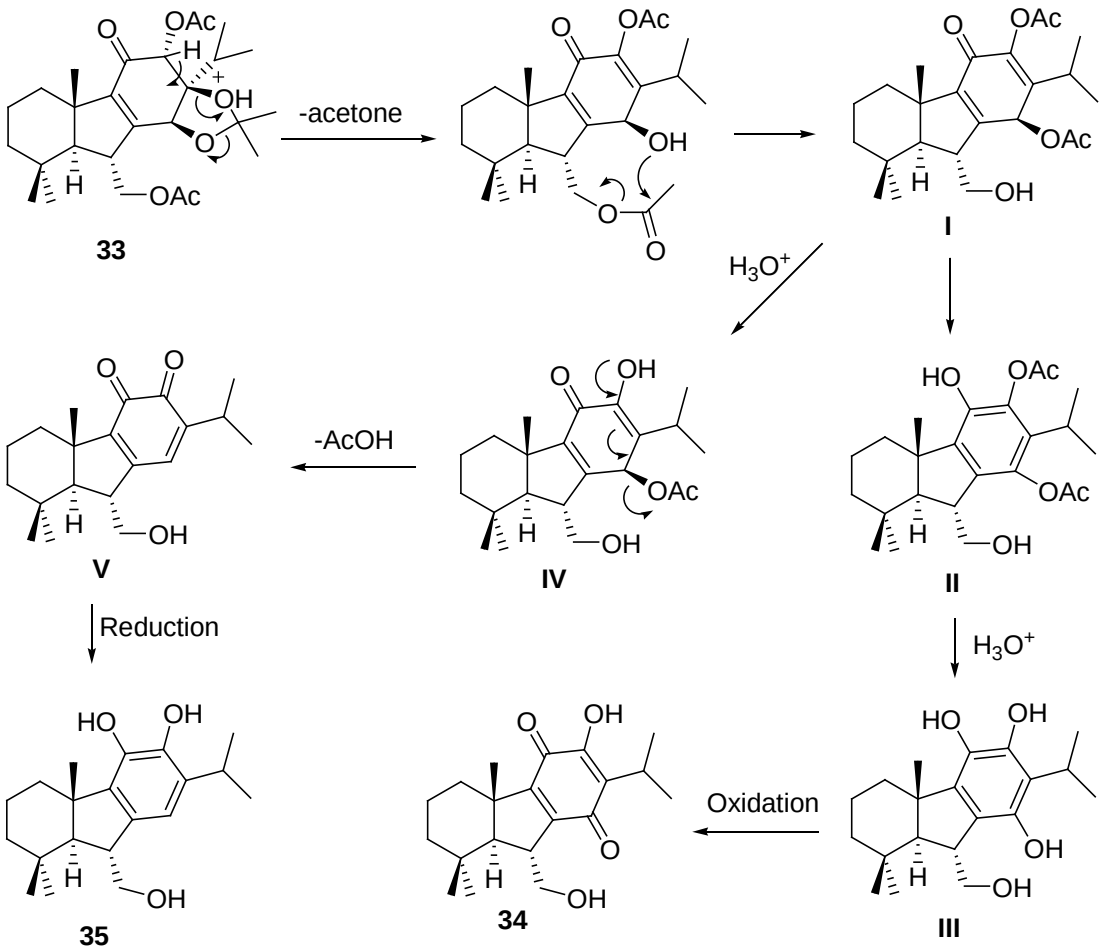
Some of the above transformations have been carried out in our laboratory. Scheme 6 shows the construction of the substitution pattern of the C ring of taiwaniaquinoids. The treatment of ketone **22** with $Pb(OAc)_4$ in benzene under reflux gave α-acetoxy ketone **33**, which by heating with conc. HCl in MeOH at 40 ºC under an oxygen atmosphere gave directly in high yield hydroxyl quinone **34**, together with a small proportion of catechol **35** (10:1 ratio).[27] Compound **35**, which could be a suitable intermediate for synthesizing taiwaniaquinol A (**10**), was obtained as the only product after treating the saturated acetoxy ketone **36** with conc. HCl in MeOH.

SCHEME 6. Functionalization of the Taiwaniaquinoid C Ring



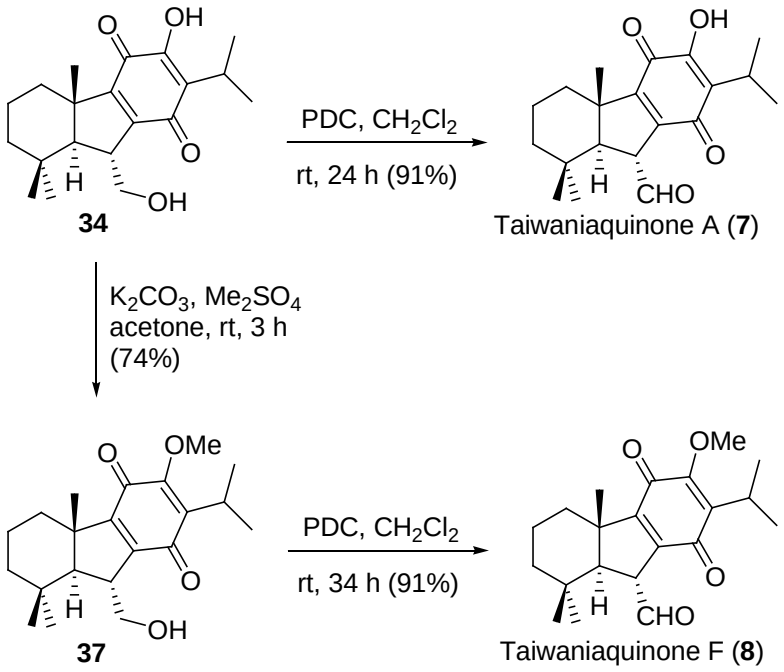
A possible mechanism for the formation of compounds **34** and **35** from α-acetoxy ketone **33** is shown in scheme 7. Compound **34** results from the oxidation of 2-hydroxyhydroquinone **III** by atmospheric oxygen. The *o*-quinone **V**, precursor of the minor catechol **35**, would be formed after the elimination of acetic acid from intermediate **IV**, resulting from the partial hydrolysis of diacetate **I**; intermediate **III** could reduce *o*-quinone **V**.

SCHEME 7. Mechanism for the Formation of Compounds **34** and **35** from α-Acetoxy Ketone **33**



Hydroxymethyl hydroxyquinone **34** was finally converted into taiwaniaquinone A (**7**) and F (**8**)(Scheme 8). The oxidation of alcohol **34** with PDC in dichloromethane led to taiwaniaquinone A (**7**). The treatment of compound **34** with Me_2SO_4 and K_2CO_3 in acetone led to methoxy derivative **37**, which was then easily converted into taiwaniaquinone F (**8**).[27]

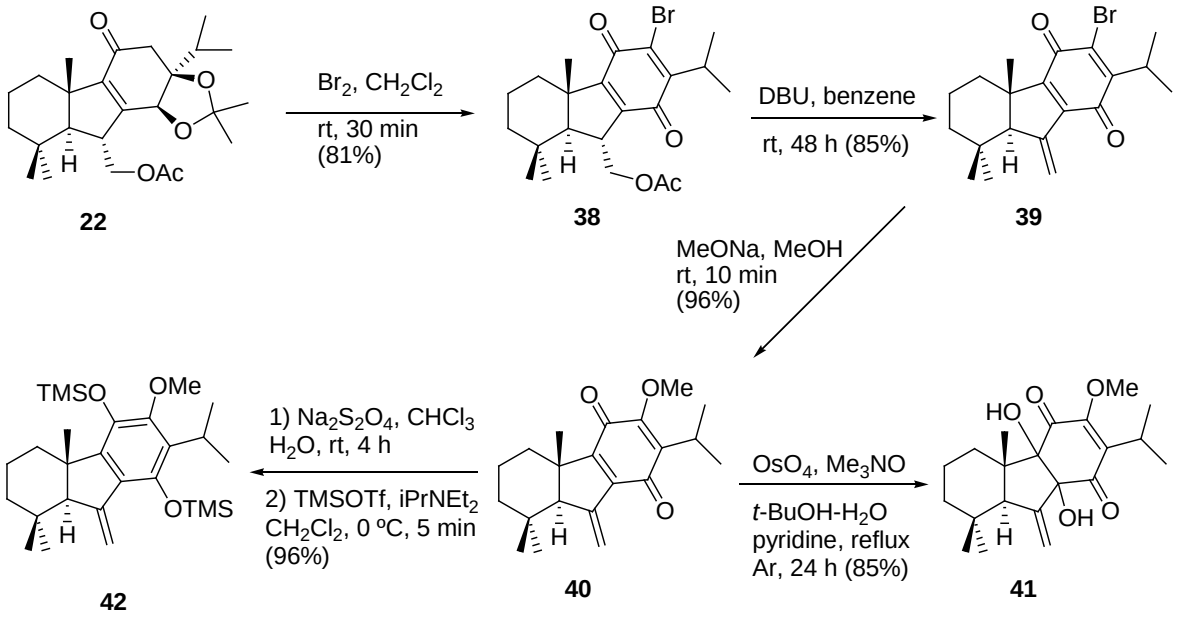
SCHEME 8. Synthesis of Taiwaniaquinone A (**7**) and F (**8**)



Next, the preparation of 7-oxo taiwaniaquinoids, such as compounds **5** and **11**, was undertaken. The treatment of ketone **22** with Br_2 in CH_2Cl_2 gave directly the bromoquinone **38**,[27] which was reacted with DBU in benzene at room temperature to afford the methylene derivative **39**, which was further converted into methoxy quinone **40** by treatment with MeONa in MeOH (Scheme 9). The oxidative degradation of the exocyclic carbon-carbon double bond of this compound under different reaction conditions was then investigated. The ozonolysis of quinone **40** gave a complex mixture of compounds. The treatment of this

with osmium tetroxide afforded the dihydroxy derivative **41**, with the exocyclic double bond remaining unaltered. On the other hand, the treatment of the hydroquinone disilyl derivative **42** with potassium osmate afforded the same quinone **40** as before.

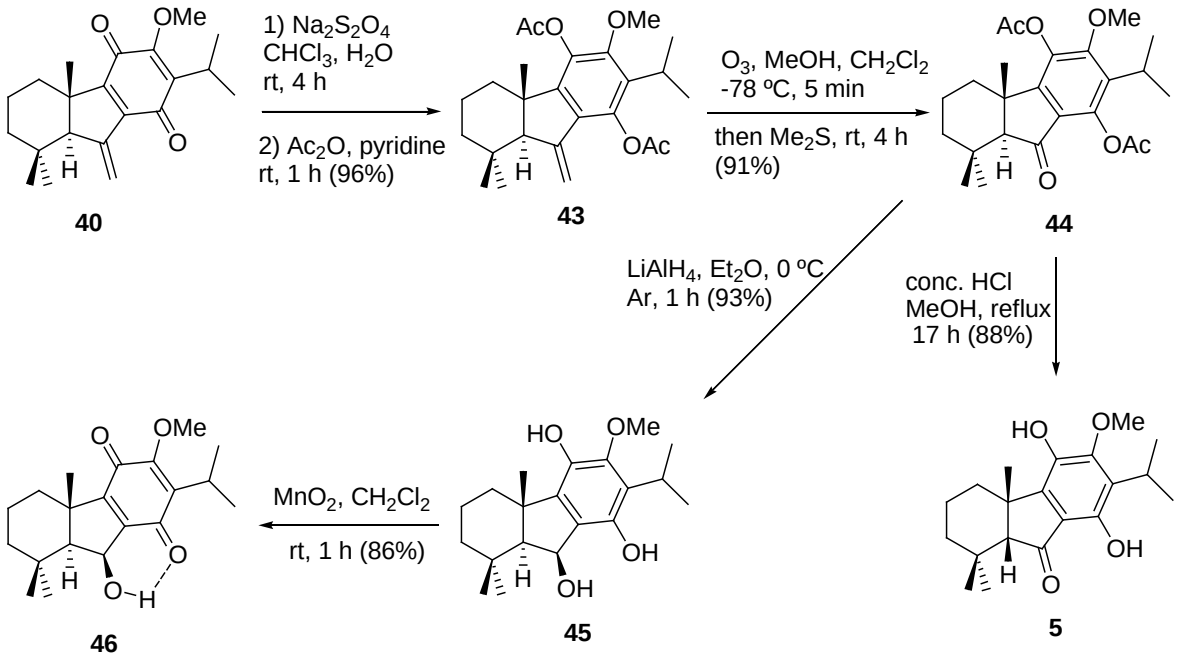
SCHEME 9. Attempts at Preparing 7-Oxo Taiwaniaquinoids



Alternatively, diacetate **43** was successfully oxidized to ketone **44** after ozonolysis. The transformation of the latter into taiwaniaquinol E (**11**) was next attempted; however, deprotection of diacetyl compound **44** took place with simultaneous epimerization, affording the A/B *cis*-fused taiwaniaquinol B (**5**), under acid or basic conditions. The treatment of ketone **44** with HCl in MeOH under reflux gave compound **5** in 88% yield. When diacetate **44** was treated with KOH in MeOH, compound **5** was obtained in 83% yield. These results confirm that the A/B *cis*-fused system is considerably more stable than the A/B *trans*-fused system, as stated in our previous publications.[21b] This led us to hypothesize that the A/B *cis*-fused 7-oxo taiwaniaquinoids, such as taiwaniaquinol B (**5**),

could be artifacts, resulting from the epimerization of the natural related A/B *trans*-fused taiwaniaquinol E (**11**) during the isolation process. Other attempts at transforming ketone **44** into the A/B *trans*-fused taiwaniaquinol E (**11**) involved the reduction of compound **44** with $LiAlH_4$ to give the 7-hydroxy hydroquinone **45**; the β disposition of 7-hydroxy group was established on the basis of the comparison of the observed *J* values for H-7 in the ^1H NMR spectrum of compound **45** with those previously reported for related 7-hydroxy taiwaniaquinoids. [19, 21b] The treatment of hydroxyl hydroquinone **45** with MnO_2 gave the hydroxy quinone **46** as the only product; the unreactivity of the 7-hydroxy group of the latter could be attributed to the very stable hydrogen bond.

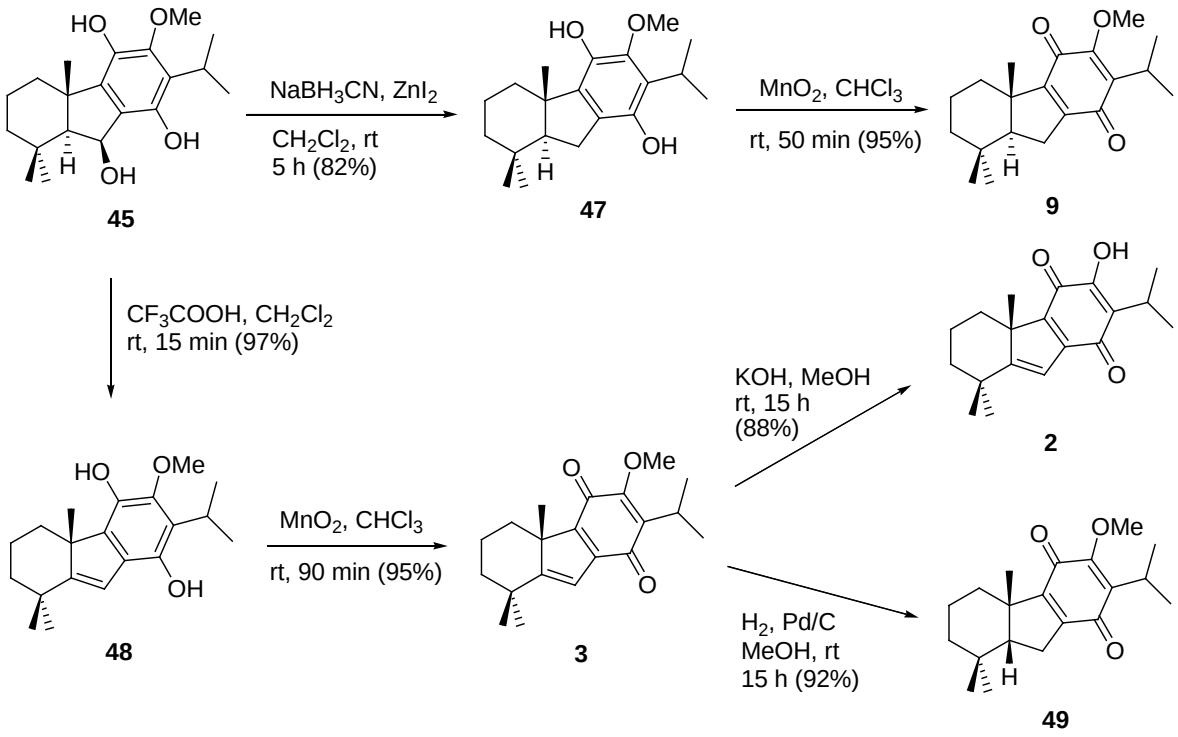
SCHEME 10. Synthesis of Taiwaniaquinol B (**5**)



The 7-hydroxy hydroquinone **45** was found to be a suitable precursor of taiwaniaquinoids with a 4a-methylhexahydrofluorene skeleton, such as taiwaniaquinone G (**9**)(Scheme 11).

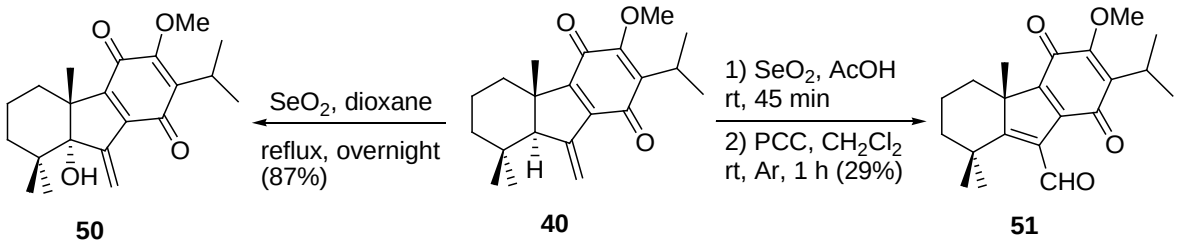
The cationic reduction of compound **45**, induced by $NaBH_3CN$ and ZnI_2, gave hydroquinone **47**, which after treatment with MnO_2 was converted into quinone **9**. Alcohol **45** was also an appropriate precursor of terpenes bearing a 4a-methyltetrahydrofluorene skeleton, such as dichroanone (**3**) and taiwaniaquinone H (**2**). Compound **45** was dehydrated to **48** by treatment with CF_3COOH. Further oxidation of hydroquinone **48** gave dichroanone (**3**), whose transformation into taiwaniaquinone H (**2**) has been previously reported by our group.[21] Compound **3** was also obtained after the dehydration of alcohol **46** by treating with conc. HCl in MeOH under reflux. It is important to point out that the hydrogenation of 4a-methyltetrahydrofluorene derivatives led to the corresponding 4a-methylhexahydrofluorene derivatives with an A/B *cis*-fused system; thus, dichroanone (**3**) was converted into the unnatural 5-epi-taiwaniaquinone G (**49**) after treatment with hydrogen in the presence of Pd/C.

SCHEME 11. Synthesis of Dichroanone (**3**) and Taiwaniaquinone G (**9**) and H (**2**)



The transformation of quinone **40** into taiwaniaquinoids bearing a α,β-unsaturated aldehyde function, such a taiwaniaquinone D (**1**), was also investigated. The oxidation of compound **40** with SeO_2 in dioxane under reflux led to allyl alcohol **50**, which remained unaltered when was treated with different oxidizing reagents, such as PCC or PDC. The treatment of compound **40** with SeO_2 in AcOH at room temperature and the further treatment with PCC gave aldehyde **51**, the *O*-methyl derivative of taiwaniaquinone D (**1**); unfortunately, all attempts at transforming compound **51** into the natural quinone **1**, under different reaction conditions, were unsuccessful (Scheme 12).

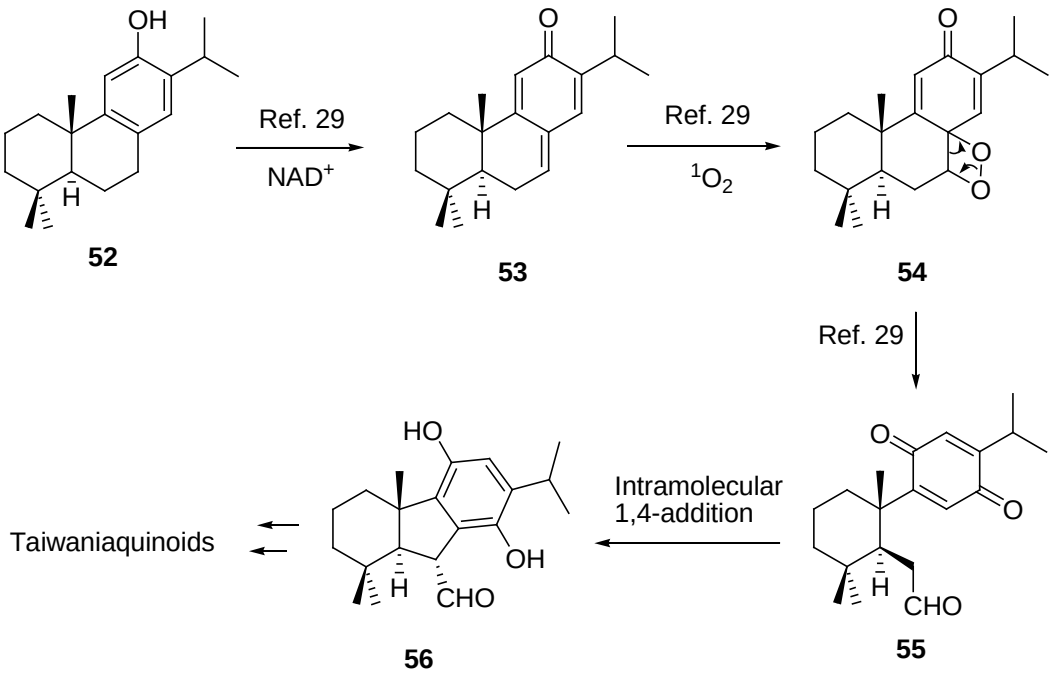
SCHEME 12. Synthesis of *O*-Methyl Taiwaniaquinone D (**51**)



50 **40** **51**

Considering the results reported here, a possible biogenetic route towards C_{20} taiwaniaquinoids can be proposed, starting from ferruginol (**52**), an abietane phenol found in *Taiwania cryptomerioides* along with this type of taiwaniaquinoids[5] (Scheme 13). The cyclopentane carbaldehyde B ring of C_{20} taiwaniaquinoids could be formed after the intramolecular 1,4-addition of an enol aldehyde type intermediate derived from the quinone aldehyde **55**. In fact, compound **55**, a natural seco-abietane diterpenoid, has been synthesized in high yield after the oxidation of ferruginol (**52**), and its biogenesis in the plant *via* the radical oxidation of phenol **52** has been previously postulated.[29] Even though the transformation of compound **55** into the taiwaniaquinoid precursor **56** is a 5-*endo-trig* cyclization, not favoured by the geometrical demands,[30] this biosynthetic process can not be ruled out. It should be noted that C_{20} taiwaniaquinoids with an ester function in the cyclopentane B ring have also been found in plant species,[3] having likewise recently isolated the corresponding seco-abietane diterpenoid related with compound **55**, with a quinone acid structure.[31]

SCHEME 13. Biosynthetic Proposal Based on the Abietane C7-C8 Cleavage



In summary, a new strategy for synthesizing taiwaniaquinoids, based on the cleavage of the C7-C8 double bond of abietane diterpenes, is described. To date, this procedure is the only one reported for synthesizing C_{20} taiwaniaquinoids bearing a carbon function on the cyclopentane B ring, such as taiwaniaquinone A (**7**) and F (**8**), and it is also applicable to the synthesis of 4a-methyltetrahydrofluorene derivatives, such as taiwaniaquinone H (**2**) and dichroanone (**3**), and 4a-methylhexahydrofluorene derivatives, having an A/B *trans*-fused system, such as taiwaniaquinone G (**9**), or an A/B *cis*-fused union, such as taiwaniaquinol B (**5**). In this paper, the synthesis of compounds **2**, **3**, **5**, **7**, **8** and **9** starting from abietic acid is reported.

The versatility of this strategy, which makes it feasible to synthesize the wide variety of existing taiwaniaquinoids, allows us to propose the abietane C7-C8 cleavage as a possible biosynthetic pathway to this type of rearranged diterpenes. This proposal seems to be supported by phytochemical evidences.

On the other hand, the great stability of the A/B *cis*-fused system that the above results reveal allows to propose as a possible hypothesis that taiwaniaquinoids having such A/B junction could be artifacts resulting from the epimerization of the related naturally occurring A/B *trans*-fused compounds (e.g. transformation of compound **11** into the *cis* ketone **5**).

Experimental Section

4aS,10R)-10-hydroxy-7-isopropyl-6-methoxy-1,1,4a-trimethyl-2,3,4,4a,10,10a-hexahydrophenanthren-9(1H)-one (19).

To a solution of **18** (100 mg, 0.335 mmol) in strictly deoxygenated *t*-BuOH – H_2O (10 : 2 mL) were added trimethylamine *N*-oxide dihydrate (200 mg, 2.66 mmol) and pyridine (0.2 mL) under argon atmosphere. The solution was stirred for 10 min at room temperature, and 2 % aq. OsO_4 (1 mL, 0.2%, 0.075 mmol) was added and the reaction mixture was further stirred under argon atmosphere at reflux for 36 h, at which time TLC indicated no remaining starting material. Then the solvent was removed under vacuum to afford a crude product that was dissolved in ether (20 mL) and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product which was directly purified by flash chromatography on silica gel (20 % ether/hexanes) to yield 87 mg of pure **19** (79%) as a yellow syrup; the spectroscopic properties were identical to those previously reported.[22]

(4aS,9R,10R,10aS)-7-isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-9,10-diol (20).

$LiAlH_4$ (37 mg, 39.7 mmol) was added to a stirred solution of **19** (342 mg, 0.92 mmol) in dry diethyl ether (15 mL) cooled at 0 °C and the mixture was stirred at room temperature under an argon atmosphere for 20 min, at which time TLC showed no compound **19**. Then, acetone (1 mL) was slowly added at 0 °C and Et_2O –water (50 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (25% ether/hexanes) to give pure **20** (259 mg, 88%) as a colorless oil.

$[\alpha]_D^{25}$ = + 40.3 (c = 3.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.23 (s, 3H), 1.31 (s, 3H), 1.32 - 1.46 (m, 1H), 1.55 - 1.62 (m, 2H), 1.72 (m, 1H), 1.75 (dt, *J* = 13.5, 3.4 Hz, 1H), 2.12 (br s, 1H), 2.21 (br d, *J* = 13.5 Hz, 1H), 3.24 (h, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 4.11 (dd, *J* = 11.3, 7.8 Hz, 1H), 4.56 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1 (CH_2), 22.2 (CH_3), 22.6 (CH_3), 22.7 (CH_3), 26.5 (CH_3), 26.8 (CH), 33.6 (C), 36.2 (CH_3), 39.3 (CH_2), 40.5 (C), 43.4 (CH_2), 53.3 (CH), 55.5 (CH_3), 75.2 (CH), 78.7 (CH), 105.8 (CH), 124.8 (CH), 127.4 (C), 135.4 (C), 147.3 (C), 156.7 (C). IR (film): 1655, 1500, 1460, 1216, 1167, 1083, 1052, 904, 845, 772 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{32}O_3Na$ ($M+Na^+$) 355.2249, found: 355.2239.

(4bS,8aS)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-4b,5,6,7,8,8a-hexahydrophenanthren-9(10H)-one (21).

To a solution of **20** (89 mg, 0.27 mmol) in dry CH_2Cl_2 (10 mL) was added Amberlyst A-15 ion-exchange (0.3 g), and the reaction mixture was stirred for 30 min, at which time TLC showed no starting material. Then the mixture was filtered, and the solvent was removed to give a crude product which was purified by flash chromatography on silica gel (5% ether/hexanes) affording **21** (69 mg, 82 %) as a colourless oil.

$[\alpha]_D^{25}$ = + 77.7 (c = 13.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.09 (s, 3H), 1.17 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.32 (s, 3H), 1.43 (br d, *J* = 15.4 Hz, 1H), 1.64 - 1.80 (m, 4H), 2.32 (m, 1H), 2.43 (s, 1H), 3.27 (h, *J* = 6.9 Hz, 1H), 3.53 (d, *J* = 21.5 Hz, 1H), 3.59 (d, *J* = 21.5 Hz, 1H), 3.84 (s, 3H), 6.80 (s, 1H), 6.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.2 (CH_2), 21.6 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 24.5 (CH_3), 26.5 (CH), 32.6 (C), 32.9 (CH_3), 38.6 (CH_2), 40.6 (C), 42.8 (CH_2), 44.6 (CH_2), 55.6 (CH_3), 62.6 (CH), 105.9 (CH), 123.9 (C), 125.9 (CH), 135.4 (C), 147.0 (C), 155.7 (C), 210.0 (C). IR (film): 1711, 1502, 1464, 1290, 1237, 1204, 1052, 990, 887, 848, 770 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{30}O_2Na$ ($M+Na^+$) 337.2143, found: 337.2152.

(3aS,5aR,6R,9aR,9bR,11aS)-methyl 11a-isopropyl-2,2,6,9a-tetramethyl-3a,5,5a,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxole-6-carboxylate (25).

To a solution of **27** (15 g, 42.86 mmol) in dry acetone (100 mL) were added 2,2-dimethoxypropane (8.3 mL, 67.8 mmol) and *p*-toluenesulfonic acid monohydrate (2 g, 1.05

mmol) and the reaction mixture was stirred at room temperature for 3 h, at which time TLC showed no starting material. Then, the solvent was removed under vacuum and ether – water (150 - 40 mL) was added and the phases were shaken and separated. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10% ether/hexanes) to yield 14.6 g of **25** (91%) as a yellow syrup.

$[\alpha]_D^{25}$= - 0.37 (c = 21.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.82 (d, *J* = 6.9 Hz, 3H), 0.82 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.09 (ddd, *J* = 12.9, 12.9, 5.3 Hz, 1H), 1.21 (s, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.39 - 1.90 (m, 11H), 1.98 - 2.10 (m, 2H), 3.65 (s, 3H), 4.21 (s, 1H), 5.75 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 16.3 (CH_3), 16.5 (CH_2), 16.9 (CH_3), 17.8 (CH_3), 18.2 (CH_2), 26.2 (CH_2), 26.8 (CH_3), 27.1 (CH), 28.3 (CH_3), 30.3 (CH_2), 34.5 (C), 37.1 (CH_2), 37.7 (CH_2), 37.8 (CH), 45.7 (CH), 46.6 (C), 51.9 (CH_3), 52.9 (CH), 81.8 (CH), 84.2 (C), 106.4 (C), 127.8 (CH), 133.8 (C), 178.9 (C). IR (film): 1727, 1462, 1367, 1244, 1210, 1189, 1151, 111, 1028, 916, 889, 756, 889 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{24}H_{38}O_4Na$ ($M+Na^+$) 413.2668, found: 413.2659.

3aS,5aR,6R,9aS,9bR,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-3a,5,5a,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxol-6-yl)methanol (28).

$LiAlH_4$ (1.5 g, 39.47 mmol) was added at 0 °C to a stirred solution of **25** (9.047 g, 24.12 mmol) in dry THF (150 mL) and the mixture was stirred at room temperature under an

argon atmosphere for 2 h. Then, the mixture was quenched with acetone (1 mL) and following the same work-up used for **20**, 8.29 g of **28** (95%) was obtained as a colorless syrup.

$[\alpha]_D^{25}$= + 7.4 (c = 12.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.82 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 3H), 0.84 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.98 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H), 1.30 - 1.73 (m, 10H), 1.37 (s, 3H), 1.41 (s, 3H), 1.77 (br d, *J* = 12.9, 1H), 1.85 (h, *J* = 6.8 Hz, 1H), 1.97 (m, 1H), 2.11 (br d, *J* = 18.4 Hz, 1H), 3.12 (d, *J* = 10.8 Hz, 1H), 3.37 (d, *J* = 10.8 Hz, 1H), 4.22 (s, 1H), 5.80 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.2 (CH_3), 16.7 (CH_2), 16.94 (CH_3), 17.04 (CH_3), 17.8 (CH_3), 18.3 (CH_2), 24.4 (CH_2), 26.7 (CH_3), 27.0 (CH), 28.2 (CH_3), 30.3 (CH_2), 34.6 (C), 35.6 (CH_2), 37.7 (C), 37.8 (CH), 38.2 (CH_2), 44.0 (CH), 52.8 (CH), 71.7 (CH_2), 81.9 (CH), 84.2 (C), 106.4 (C), 128.0 (CH), 133.7 (C). IR (film): 1468, 1380 1251, 1211, 1164, 1070, 1027, 888, 756, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2711.

3aS,5aR,6R,9aR,9bR,11aS)-6-(iodomethyl)-11a-isopropyl-2,2,6,9a-tetramethyl-3a,5,5a,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxole (29).

To a solution of triphenylphosphine (8.52 g, 32.48 mmol) in dry CH_2Cl_2 (40 mL) was added successively iodine (9.15 g, 36.05 mmol) and imidazole (4.58 g, 67.23 mmol). The mixture was stirred at room temperature for 5 min and a solution of alcohol **28** (4 g, 11.05 mmol) in dry benzene (100 mL) was added. The resulting mixture was stirred at reflux for 16 h, at this time TLC showed no **28**. Then, aq. 5% $NaHSO_3$ (10 mL) was added and the mixture was stirred for 5 min. The solvent was removed under vacuum and the crude

product was diluted with Et_2O – water (100 – 30 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give **29** (3.92 g, 75 %) as a colourless oil.

$[\alpha]_D^{25}$= - 14.3 (c = 9.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.81 (s, 3H), 0.84 (s, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.20 - 1.48 (m, 5H), 1.37 (s, 3H), 1.41 (s, 3H), 1.52 - 1.64 (m, 4H), 1.66 - 1.77 (m, 2H), 1.85 (h, *J* = 6.8 Hz, 1H), 1.92 (m, 1H), 2.08 (m, 1H), 3.18 (s, 2H), 4.23 (s, 1H), 5.78 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.7 (CH_3), 16.8 (CH_2), 17.0 (CH_3), 17.8 (CH_3), 18.0 (CH_3), 18.6 (CH_2), 24.1 (CH_2), 26.7 (CH_3), 28.0 (CH_2), 28.2 (CH_3), 30.2 (CH_2), 34.9 (C), 35.5 (C), 37.8 (CH), 38.0 (CH_2), 39.7 (CH_2), 47.5 (CH), 52.7 (CH), 81.8 (CH), 84.2 (C), 106.4 (C), 127.6 (CH), 133.8 (C). IR (film): 1457, 1378, 1366, 1252, 1211, 1025, 772 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{37}O_2INa$ ($M+Na^+$) 495.1736, found: 495.1745.

(3aS,5aS,9aS,9bR,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3a,5,5a,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxole (32). [27]

To a solution of **29** (3.0 g, 6.35 mmol) in THF (40 mL) was added 50% aqueous solution of Raney Nickel (12 mL) and the mixture was stirred at room temperature for 36 h, at this time TLC showed no **29**. Then, the reaction mixture was filtered through a silica gel – Na_2SO_4 pad (40 : 10 g), washed with acetone (20 mL) and concentrated to give pure **32** (2.0 g, 91 %).

(3aS,4R,5bS,10R,10bS)-10-(acetoxymethyl)-3a-isopropyl-2,2,5b,9,9-pentamethyl-5-oxo-dodecahydro-3aH-fluoreno[1,2-d][1,3]dioxol-4-yl acetate (36).

To a solution of **33** (200 mg, 0.42 mmol) in dry MeOH (30 mL) was added 10% Pd/C (70 mg) and the mixture was stirred at room temperature under hydrogen atmosphere for 19 h. Filtration of the mixture through a silica gel pad (10 g) and concentration gave **36** (165 mg, 82%) as a colourless syrup.

$[\alpha]_D^{25}$ = -35.9 (c = 14.0 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.81 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 3H), 0.97 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 3H), 1.10 - 1.70 (m, 7H), 1.40 (s, 3H), 1.49 (s, 3H), 1.83 (br d, *J* = 12.7 Hz, 1H), 2.08 (s, 3H), 2.20 (s, 3H), 2.25 - 2.47 (m, 2H), 2.85 (m, 1H), 3.96 (dd, *J* = 11.2, 8.0 Hz, 1H), 4.44 (d, *J* = 6.4 Hz, 1H), 4.56 (dd, *J* = 11.2, 3.8 Hz, 1H), 5.50 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.3 (CH_3), 17.4 (CH_3), 17.6 (CH_3), 19.3 (CH_2), 20.6 (CH_3), 21.0 (CH_3), 21.8 (CH_3), 26.3 (CH_3), 27.7 (CH_3), 29.0 (CH), 33.6 (C), 34.5 (CH_3), 39.1 (CH_2), 40.0 (CH), 41.0 (CH), 42.5 (CH_2), 46.8 (C), 58.5 (CH), 60.5 (CH), 67.4 (CH_2), 73.6 (CH), 80.1 (CH), 88.3 (C), 107.2 (C), 170.2 (C), 170.8 (C), 204.6 (C). IR (film): 1743, 1587, 1479, 1464, 1449, 1381, 1234, 1174, 1092, 1045, 883, 803, 769, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{27}H_{42}O_7Na$ ($M+Na^+$) 501.2828, found: 501.2819.

(4bS,8aS,9R)-9-(hydroxymethyl)-2-isopropyl-4b,8,8-trimethyl-5,6,7,8,8a,9-hexahydro-4bH-fluorene-3,4-diol (35). [27]

Conc. hydrochloric acid (1 mL) was added to a stirred solution of **36** (178 mg, 0.37 mmol) in MeOH (5 mL) and the reaction mixture was refluxed for 24 h, at which time TLC showed no starting material remaining. Then, the solvent was removed in vacuum and ether - water (30 : 10 mL) was added. The phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography (45 % ether/hexanes) to yield 101 mg of **35** (86 %) as a white solid.

(4bS,8aR)-3-bromo-2-isopropyl-4b,8,8-trimethyl-9-methylene-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-dione (39).

1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) (97 mg, 0.64 mmol) was added to a stirred solution of bromoquinone **38** (140 mg, 0.32 mmol) in benzene (10 mL) and the mixture was stirred at room temperature for 48 h, at which time TLC showed no **38**. Then, the reaction mixture was diluted with ether – water (30 – 10 mL) and the phases were shaken and separated. The organic phase was washed with 1M HCl (2 x 10 mL), water, brine and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (7% ether/hexanes) to give pure **39** (102 mg, 85%) as a yellow syrup.

$[\alpha]_D^{25}$ = - 44.7 (c 3.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.10 (s, 3H), 1.15 (s, 3H), 1.16 (s, 3H), 1.20 (ddd, *J* = 13.3, 13.3, 4.3 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.45 – 1.53 (m, 2H), 1.61 (m, 1H), 1.75 (m, 1H), 2.26 (t, *J* = 2.7 Hz, 1H), 2.37 (dt, *J* = 12.9, 3.6 Hz, 1H), 3.43 (h, *J* = 7.0 Hz, 1H), 5.52 (d, *J* = 2.5 Hz, 1H), 6.20 (d, *J* = 2.9

Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.0 (CH_2), 19.93 (CH_3), 19.95 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 32.8 (CH_3), 33.1 (C), 33.7 (CH_2), 34.0 (CH), 42.8 (CH_2), 47.8 (C), 63.1 (CH), 116.6 (CH_2), 135.7 (C), 141.9 (C), 144.4 (C), 152.3 (C), 153.9 (C), 178.0 (C), 182.9 (C). IR (film): 1664, 1560, 1462, 1292, 1244, 1054, 909, 752 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{25}O_2BrNa$ ($M+Na^+$) 399.0936, found: 399.0927.

(4bS,8aR)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-methylene-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-dione (40). [27]

To a solution of **39** (203 mg, 0.54 mmol) in dried methanol (10 mL) was added sodium methoxide (130 mg, 2.41 mmol) and the solution was stirred at room temperature for 10 min, at which time TLC showed no **39**. Then, the solvent was removed under vacuum and ether – water (40 : 10 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded, after flash chromatography on silica gel (5% ether/hexanes), 169 mg of **40** (96%) as a yellow syrup.

(4bS,8aR)-4a,9a-dihydroxy-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-methylene-4b,5,6,7,8,8a,9,9a-octahydro-4aH-fluorene-1,4-dione (41).

To a solution of **40** (82 mg, 0.25 mmol) in strictly deoxygenated *t*-BuOH – H_2O (35 : 5 mL) were added trimethylamine *N*-oxide dihydrate (36 mg, 0.32 mmol) and pyridine (0.05 mL) under argon atmosphere. The solution was stirred for 10 min at room temperature, and 0.2

% aq. OsO_4 (0.5 mL) was added and the reaction mixture was further stirred under argon atmosphere at reflux for 24 h, at which time TLC indicated no starting material. Following the same work-up used for **19** (15 % ether/hexanes), 72 mg of pure **41** (85%) was obtained as colourless syrup.

$[\alpha]_D^{25}$ = - 42.6 (c = 5.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.08 (s, 3H), 1.18 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H). 1.25 (d, *J* = 6.9 Hz, 3H), 1.29 (s, 3H), 1.42 (br d, *J* = 12.7 Hz, 1H), 1.53 - 1.88 (m, 6H), 2.34 (s, 1H), 2.96 (h, *J* = 6.9 Hz, 1H), 3.32 (br s, 1H), 3.88 (s, 3H), 4.81 (s, 1H), 5.59 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.4 (CH_3), 17.5 (CH_2), 19.1 (CH_3), 20.8 (CH_3), 23.4 (CH_3), 24.3 (CH), 32.3 (CH_3), 33.4 (CH_2), 34.3 (C), 45.0 (CH_2), 48.9 (C), 53.5 (CH), 59.3 (CH_3), 80.9 (C), 84.7 (C), 119.3 (C), 124.8 (C), 141.3 (C), 173.5 (C), 202.7 (C), 211.5 (C). IR (film): 3463, 1732, 1669, 1458, 1390, 1370,1035, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{30}O_5Na$ ($M+Na^+$) 385.1991, found: 385.1983.

((4bS,8aR)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-methylene-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-diyl)bis(oxy)bis(tert-butyldimethylsilane) (42).

$Na_2S_2O_4$ (727 mg, 4.18 mmol) was added to a suspension of quinone **40** (274 mg, 0.83 mmol) in 20 mL of H_2O - $CHCl_3$ (1:1) and the mixture was stirred for 4 h, at which time TLC showed no starting material. Then, $CHCl_3$ was removed under vacuum, and the mixture was diluted with ether (30 mL) and the phases were shaken and separated. The organic layer was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product (253 mg), which was used in the next step without purification.

To a stirred solution of this crude (80 mg) in dry CH_2Cl_2 (10 ml) were added at 0ºC, N,N-diisopropylethylamine (85 µL, 0.49 mmol) and trimethylsilyl trifluoromethanesulfonate (0.13 mL, 0.72 mmol). The reaction mixture was stirred at 0ºC for 5 min, at which time TLC showed no starting material remaining. Then, the solvent was evaporated and the crude product was diluted with ether - water (20 : 5 mL) and the phases were shaken and separated. The organic phase was washed with water (5 x 8 mL), brine, dried over anhydrous Na_2SO_4. Removal of the solvent under vaccum afforded a crude product which after flash chromatography (3% ether/hexanes) gave 111 mg (96 %) of **42** as a colourless syrup.

$[\alpha]_D^{25}$ = + 12.7 (c = 16.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.19 (s, 9H), 0.21 (s, 9H), 1.05 (s, 3H), 1.16 (s, 3H), 1.17 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.40 - 1.64 (m, 4H), 1.76 (m, 1H), 2.15 (s, 1H), 2.41 (d, *J* = 13.0 Hz, 1H), 3.36 (h, *J* = 7.0 Hz, 1H), 3.63 (s, 3H), 5.22 (s, 1H), 5.71 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 0.6 (CH_3), 0.9 (CH_3), 19.4 (CH_2), 20.5 (CH_3), 20.9 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 25.3 (CH), 32.9 (CH_3), 33.0 (C), 35.7 (CH_2), 43.5 (CH_2), 45.7 (C), 60.7 (CH_3), 65.0 (CH), 108.0 (CH_2), 127.8 (C), 131.0 (C), 139.8 (C), 142.1 (C), 142.8 (C), 147.1 (C), 151.5 (C). IR (film): 1646, 1448, 1429, 1341, 1251, 1119, 1095, 1017, 982, 965, 845, 759, 669 cm^{-1}.

(4bS,8aR)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-methylene-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-diyl diacetate (43).

To a solution of the crude product (130 mg) resulting of the reduction of quinone **40** in pyridine (2 ml) was added at 0 ºC acetic anhydride (1 mL) and the reaction mixture was

stirred at room temperature for 1 h, at which time TLC showed no starting material. Then, water (2 mL) was added at 0 ºC to quench the reaction and the reaction mixture was stirred for an additional 10 min. Then, ether (50 mL) was added and the phases were shaken and separated. The organic phase was washed with 2N HCl solution (5 x 10 mL), water (20 mL), sat. aq $NaHCO_3$ (5 x 10 mL), brine, and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (5 % ether/hexanes) to yield 156 mg of **43** (96 %) as a colourless syrup.

$[\alpha]_D^{25}$ = 22.2 (c 4.7, $CHCl_3$). ^{13}H NMR ($CDCl_3$, 600 MHz) δ: 1.04 (s, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.20 – 1.34 (m, 3H), 1.21 (*J* = 6.9 Hz, 3H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.43 (br d, *J* = 13.4 Hz, 1H), 1.54 - 1.82 (m, 5H), 2.05 (m, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 3.24 (h, *J* = 6.9 Hz, 1H), 3.73 (s, 3H), 5.20 (s, 1H), 5.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 19.1 (CH_2), 20.2 (CH_3), 20.8 (CH_3), 21.4 (CH_3), 21.5 (CH_3), 21.7 (CH_3), 25.8 (CH_3), 26.9 (CH), 29.7 (CH_2), 32.7 (CH_3), 33.0 (C), 42.8 (CH_2), 46.2 (C), 61.6 (CH_3), 64.1 (CH) 107.4 (CH_2), 124.9 (C), 129.8 (C), 132.6 (C), 137.5 (C), 142.8 (C), 144.3 (C), 145.8 (C), 150.1 (C), 168.9 (C). IR (film): 1771, 1456, 1368, 1320, 1187, 1019, 888, 760 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{25}H_{34}O_5Na$ ($M+Na^+$) 437.2304, found: 437.2293.

(4bS,8aS)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-oxo-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-diyl diacetate (44).

A stirred solution of **43** (160 mg, 0.38 mmol) in CH_2Cl_2 – MeOH (45 : 15 mL) was slowly bubbled with an O_3/O_2 mixture at -78 ºC, and the course of the reaction was monitored by TLC. When the starting material was consumed (5 min), the solution was flushed with

argon, and dimethyl sulfide (0.5 mL) was added. The mixture was further stirred at room temperature under argon atmosphere for 4 h and the solvent was removed under vaccum. Flash chromatography on silica gel (15 % ether/hexanes) gave ketone **44** (146 mg, 91 %) as a colourless syrup.

$[\alpha]_D^{25}$ = - 24.1 (c 17.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (s, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.26 (d, *J* = 7.1 Hz, 3H), 1.15 - 1.27 (m, 2H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.48 (br d, *J* = 13.9 Hz, 1H), 1.65 (m, 1H), 1.70 – 1.85 (m, 2H), 2.12 (m, 1H), 2.35 (s, 3H), 2.35 (s, 1H), 2.39 (s, 3H), 3.34 (h, *J* = 7.1 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.5 (CH_2), 20.7 (CH_3), 20.9 (CH_3), 21.40 (CH_3), 21.41 (CH_3), 21.44 (CH_3), 25.7 (CH_3), 26.6 (CH), 32.1 (CH_3), 32.5 (C), 34.6 (CH_2), 41.6 (CH_2), 43.3 (C), 61.8 (CH_3), 68.6 (CH), 124.1 (C), 134.0 (C), 137.2 (C), 144.1 (C), 150.2 (C), 155.6 (C), 168.6 (C), 169.0 (C), 199.4 (C). IR (film): 1774, 1720, 1612, 1456, 1367, 1313, 1183, 1117, 1021, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{24}H_{32}O_6Na$ ($M+Na^+$) 439.2097, found: 439.2088.

(-)-Taiwaniaquinol B (5).

Conc. hydrochloric acid (1 mL) was added to a stirred solution of **44** (118 mg, 0.28 mmol) in MeOH (5 mL) the reaction mixture was refluxed for 17 h, at which time TLC showed no starting material remaining. Then, the solvent was removed in vaccum and ether - water (30 : 10 mL) was added. The phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography (15 % ether/hexanes) to yield 82 mg of (-)-taiwaniaquinol B (**5**) (88 %) as a white solid.

Mp 140-142 ºC, from EtOAc-hexane (1:9). $[\alpha]_D^{25}$ = - 40.6 (c 7.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (s, 3H), 1.26 (s, 3H), 1.385 (d, *J* = 7.1 Hz, 3H), 1.387 (d, *J* = 7.1 Hz, 3H), 1.33 – 1.44 (m, 2H), 1.45 (s, 3H), 1.59 (m, 1H), 1.72 (m, 1H), 1.95 - 2.11 (m, 2H), 2.13 (s, 1H), 3.28 (h, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 5.25 (s, 1H), 9.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.5 (CH_2), 20.6 (CH_3), 20.6 (CH_3), 24.4 (CH_3), 26.0 (CH), 28.8 (CH_3), 30.4 (CH_2), 33.0 (CH_3), 34.3 (C), 36.5 (CH_2), 42.7 (C), 62.1 (CH_3), 65.1 (CH), 118.3 (C), 126.1 (C), 138.4 (C), 142.7 (C), 151.1 (C). 152.3 (C), 211.0 (C). IR (film): 3287, 1647, 1621, 1449, 1423, 1326, 1114, 1020, 953, 669 cm^{-1}.

(4bS,8aS,9S)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4,9-triol (45).

$LiAlH_4$ (66 mg, 1.74 mmol) was added at 0 °C to a stirred solution of **44** (146 mg, 0.35 mmol) in anhydrous Et_2O (15 mL) and the mixture was stirred at 0 °C under an argon atmosphere for 1 h. Then, 2N KH_2PO_4 solution (2 mL) was slowly added at 0 °C and the resulting mixture was diluted with Et_2O – water (30 -10 mL) and the layers were shaken and separated. The organic phase was washed with brine, dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded pure **45** (109 mg, 93%) as a colourless syrup.

$[\alpha]_D^{25}$ = - 21.5 (c 12.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (s, 3H), 1.20 (m, 1H), 1.26 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.45 (s, 3H), 1.45 - 1.57 (m, 2H), 1.55 (d, *J* = 4.8 Hz, 1H), 1.63 (m, 1H), 1.72 (br s, 1H), 1.86 (m, 1H), 2.32 (m, 1H), 2.37 (br d, *J* = 12.6 Hz, 1H), 3.33 (h, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 5.24 (s, 2H). ^{13}C NMR

($CDCl_3$, 125 MHz) δ: 19.9 (CH_2), 21.15 (2 CH_3), 22.6 (CH_3), 25.0 (CH_3), 25.9 (CH), 32.5 (CH_3), 33.5 (C), 37.0 (CH_2), 43.4 (CH_2), 46.9 (C), 61.7 (CH_3), 62.0 (CH), 72.7 (CH), 125.9 (C), 126.0 (C), 137.6 (C), 138.2 (C), 145.1 (C), 145.9 (C). IR (film): 3408, 1450, 1423, 1336, 1218, 1123, 1016, 971, 899, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{30}O_4Na$ ($M+Na^+$) 357.2042, found: 357.2053.

(4bS,8aS)-9-hydroxy-2-isopropyl-3-methoxy-4b,8,8-trimethyl-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-dione (46).

To a solution of **45** (90 mg, 0.27 mmol) in chloroform (10 mL) was added manganese (IV) oxide (146 mg, 1.68 mmoles) and the reaction mixture was stirred at room temperature for 1h. The inorganic solid was removed by filtration of the mixture through silica gel pad (10 g) and washed with ether (10 mL). The combined filtrates were evaporated to yield 77 mg (86 %) of compound **46** as a yellow syrup.

$[\alpha]_D^{25}$ = - 26.8 (c 10.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.09 (s, 3H), 1.15 (ddd, *J* = 13.2, 13.2, 4.1 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.21 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.36 (d, *J* = 5.0 Hz, 1H), 1.33 – 1.43 (m, 2H), 1.45 (s, 3H), 1.62 (m ,1H), 1.77 – 1.92 (m, 2H), 2.24 (br d, *J* = 12.7 Hz, 1H), 3.22 (h, *J* = 7.0 Hz, 1H), 3.95 (s, 3H), 5.12 (br d, *J* = 3.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.5 (CH_2), 20.5 (CH_3), 20.6 (CH_3), 22.4 (CH_3), 23.5 (CH_3), 24.5 (CH), 32.2 (CH_3), 33.3 (C), 35.2 (CH_2), 43.0 (CH_2), 48.8 (C), 60.3 (CH_3), 61.1 (CH), 71.9 (CH), 137.1 (C), 146.0 (C), 155.1 (C), 156.6 (C), 182.9 (C), 187.5 (C). IR (film): 3498, 1661, 1644, 1587, 1458, 1261, 1140, 926, 771 cm^{-1}.

(-)-Dichroanone (3) from 46.

Conc. hydrochloric acid (0.5 mL) was added to a stirred solution of **46** (120 mg, 0.36 mmol) in MeOH (4 mL) and the reaction mixture was stirred at reflux for 2 h, at which time TLC showed no starting material remaining. Then, the solvent was removed in vaccum and ether -water (30 : 10 mL) was added. The phases were shaken, separated and the organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography (5 % ether/hexanes) to yield 100 mg of **3** (87%) as red syrup.

(4bS,8aS)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-diol (47).

To a stirred solution of **45** (117 mg, 0.35 mmol) in dichloromethane (10 mL) were added at room temperature solid zinc iodide (166 mg, 0.52 mmol) and sodium cyanoborohydride (164 mg, 2.62 mmol). The reaction mixture was stirred at room temperature for 5 h, at which time TLC showed no starting material. Then, the mixture was filtered through silica gel pad (16 g) and washed with ether (50 mL). The combined filtrate was evaporated to yield pure **47** (91 mg, 82%) as a colourless syrup.

$[\alpha]_D^{25}$ = - 38.4 (c 6.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.96 (s, 3H), 1.03 (s, 3H), 1.10 (s, 3H), 1.20 (ddd, *J* = 13.6, 4.1, 4.1 Hz, 1H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.51 (m, 1H), 1.59 - 1.60 (m, 2H), 1.73 - 1.85 (m, 2H), 2.40 (br d, *J*= 12.4 Hz, 1H), 2.42 (d, *J* = 13.6 Hz, 1H), 2.56 (dd, *J* = 13.6, 6.3 Hz, 1H), 3.33 (h, *J* = 7.1 Hz, 1H), 3.73 (s, 3H), 4.08 (s, 1H), 5.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.3 (CH_3), 20.0

(CH_2), 21.10 (CH_3), 21.14 (CH_3), 21.3 (CH_3), 25.5 (CH_2), 25.8 (CH), 33.1 (C), 33.3 (CH_3), 36.4 (CH_2), 41.5 (CH_2), 46.9 (C), 60.0 (CH_3), 62.0 (CH), 123.9 (C), 124.6 (C), 137.4 (C), 138.0 (C), 143.9 (C), 144.1 (C). IR (film): 3462, 1450, 1425, 1336, 1243, 1078, 1022, 897, 754 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{30}O_3Na$ ($M+Na^+$) 341.2093, found: 341.2085.

(-)-Taiwaniaquinone G (9).

To a solution of **47** (77 mg, 0.24 mmol) in chloroform (8 mL) was added manganese (IV) oxide (142 mg, 1.63 mmol) and the reaction mixture was stirred at room temperature for 50 min. following the same work-up used for **46**, 72 mg of (-)-taiwaniaquinone G (9) (95%) was obtained as a red syrup.

$[\alpha]_D^{25}$ = - 40.6 (c 7.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.88 (s, 3H), 1.26 (s, 3H), 1.385 (d, *J* = 7.1 Hz, 3H), 1.387 (d, *J* = 7.1 Hz, 3H), 1.37 – 1.40 (m, 2H), 1.45 (s, 3H), 1.59 (m, 1H), 1.72 (m, 1H), 1.97 - 2.05 (m, 2H), 2.13 (s, 1H), 3.28 (h, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 5.25 (s, 1H), 9.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.5 (CH_2), 20.6 (CH_3), 20.6 (CH_3), 24.4 (CH_3), 26.0 (CH), 28.8 (CH_3), 30.4 (CH_2), 33.0 (CH_3), 34.3 (C), 36.5 (CH_2), 42.7 (C), 62.1 (CH_3), 65.1 (CH), 118.3 (C), 126.1 (C), 138.4 (C), 142.7 (C), 151.1 (C). 152.3 (C), 211.0 (C). IR (film): 3287, 1647, 1621, 1449, 1423, 1326, 1114, 1020, 953, 669 cm^{-1}.

(S)-2-isopropyl-3-methoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4bH-fluorene-1,4-diol (48).

To a solution of **45** (132 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (200 μL) and the solution was stirred at room temperature for 15 min, at which time TLC showed no **45**. Then, ether – water (20 : 5 mL) were added and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded **48** (119 mg, 97%) which was used in the next step without purification.

$[\alpha]_D^{25}$ = +1.5 (c 8.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.23 (s, 3H), 1.28 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.48 (s, 3H), 1.55-1.68 (m, 4H), 1.93 (m, 1H), 2.51 (br d, *J* = 12.9 Hz, 1H), 3.37 (h, *J* = 7.1 Hz, 1H), 4.31 (br s, 1H), 5.22 (s, 1H), 6.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.4 (CH_2), 20.3 (CH_3), 21.30 (CH_3), 21.30 (CH_3), 25.5 (CH_3), 25.9 (CH), 31.4 (CH_3), 35.6 (C), 36.0 (CH_2), 42.7 (CH_2), 52.3 (C), 62.2 (CH_3), 114.6 (CH), 125.6 (C), 126.2 (C), 136.9 (C), 138.8 (C), 140.4 (C), 142.7 (C), 163.4 (C). IR (film): 3422, 1638, 1437, 1423, 1114, 1081, 1022, 758 cm^{-1}.

(-)-Dichroanone (3) from 48.

To a solution of **48** (102 mg, 0.32 mmol) in chloroform (8 mL) was added manganese (IV) oxide (150 mg, 1.72 mmol) and the reaction mixture was stirred at room temperature for 90 min. following the same work-up used for **46**, 93 mg of (-)-dichroanone (**3**) (95%) was obtained as a red syrup.

5-*epi*-Taiwaniaquinone G (49).

To a solution of **3** (64 mg, 0.20 mmol) in dry MeOH (20 mL) was added 10% Pd/C (60 mg) and the mixture was stirred at room temperature under hydrogen atmosphere for 15 h. Filtration of the mixture through a silica gel pad (10 g) and concentration gave **49** (59 mg, 92 %) as yellow syrup.

$[\alpha]_D^{25}$ = + 60 (c 6.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.92 (s, 3H), 1.08 (s, 3H), 1.19 (d, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.1 Hz, 3H), 1.29 (m, 2H), 1.43 (m, 1H), 1.51 (s, 3H), 1.57 (m, 1H), 1.74 (dd, *J* = 11.6, 8.6 Hz, 1H), 1.89 (br d, *J* = 13.5, 1H), 2.36 (dd, *J* = 18.1, 11.5 Hz, 1H), 2.65 (dd, *J* = 18.1, 8.0 Hz, 1H), 3.20 (h, *J* = 7.1 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.9 (CH_2), 20.5 (CH_3), 20.6 (CH_3), 24.3 (CH), 24.5 (CH_3), 29.4 (CH_3), 31.0 (CH_2), 31.1 (CH_3), 31.7 (C), 34.2 (CH_2), 34.9 (CH_2), 48.0 (C), 55.0 (CH), 61.0 (CH_3), 136.7 (C), 146.2 (C), 152.4 (C), 156.5 (C), 182.6 (C), 187.3 (C). IR (film): 1648, 1591, 1458, 1287, 1261, 1013, 746 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{28}O_3Na$ ($M+Na^+$) 339.1936, found: 339.1947.

(4bR,8aS)-8a-hydroxy-2-isopropyl-3-methoxy-4b,8,8-trimethyl-9-methylene-5,6,7,8,8a,9-hexahydro-4bH-fluorene-1,4-dione (50).

To a solution of **40** (227 mg, 0.69 mmol) in 1,4-dioxane was added selenium dioxide (95 mg, 0.85 mmol) and the solution was stirred at reflux overnight, at which time TLC showed no starting material. Then the solvent was removed under vaccum and the residue was diluted with ether – water (35 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water (20 mL), brine, and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash

chromatography on silica gel (10 % ether/hexanes) to yield 206 mg of **50** (87 %) as a yellow syrup.

$[\alpha]_D^{25}$ = - 107.1 (c 2.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.75 (s, 3H), 1.00 (s, 3H), 1.12 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.20-1.70 (m, 6H), 2.63 (dt, *J* = 13.5, 4.7 Hz, 1H), 3.23 (h, *J* = 7.1 Hz, 1H), 3.96 (s, 3H), 5.47 (s, 1H), 6.26 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1 (CH_2), 20.59 (CH_3), 20.59 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 25.8 (CH_3), 28.0 (CH), 29.8 (CH_2), 35.2 (CH_2), 37.9 (C), 49.8 (C), 61.2 (CH_3), 86.0 (C), 117.0 (CH_2), 137.6 (C), 140.7 (C), 149.1 (C), 149.8 (C), 156.5 (C), 182.5 (C), 185.8 (C). IR (film): 3552, 1656, 1461, 1290, 1264, 1148, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{28}O_4Na$ ($M+Na^+$) 367.1885, found: 367.1874.

_O_-Methyl taiwaniaquinone D (51).

To a solution of **40** (168 mg, 0.51 mmol) in glacial acetic acid (15 mL) was added selenium dioxide (47 mg, 0.42 mmol) and the solution was stirred at room temperature for 45 min, at which time TLC showed no **40**. Then, 2 N HCl (2 mL) was added and the mixture was stirred at room temperature for 1 h and the mixture was diluted with ether (40 mL), washed with water (10 x 15 mL),brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent in vacuum afforded a crude product (154 mg) which was used in the next step without purification.

To a stirred solution of this crude (154 mg) in dry CH_2Cl_2 (10 mL) was added pyridinium chlorochromate (232 mg, 1.08 mmol), and the mixture was stirred at room temperature under argon atmosphere for 1 h. Then, the reaction was worked up by the addition of ether

(10 mL), and the resulting mixture was filtered through a silica gel pad and washed with ether (2 x 10 mL). The filtrate was evaporated to give a crude product which was purified by flash chromatography on silica gel (10 % ether/hexanes) giving 50 mg of *o*-methyl taiwaniaquinone D (**51**) (29 %) as a yellow syrup.

$[\alpha]_D^{25}$ = - 54.5 (c 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.18 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.25 (m, 1H), 1.32 (s, 3H), 1.47 (s, 3H), 1.53 (m, 1H), 1.65 (m, 1H), 1.72 (m, 1H), 1.90 (m, 1H), 2.47 (m, 1H), 3.23 (h, *J* = 7.0 Hz, 1H), 4.00 (s, 3H), 10.43 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.3 (CH_2), 20.57 (CH_3), 20.62 (CH_3), 21.6 (CH_3), 24.7 (CH_3), 25.9 (CH_3), 33.6 (CH_3), 35.0 (CH_2), 37.9 (C), 43.2 (CH_2), 56.4 (C), 61.4 (CH_3), 133.5 (C), 136.3 (C), 144.4 (C), 150.4 (C), 157.0 (C), 175.1 (C), 178.7 (C), 185.7 (C), 193.9 (CH). IR (film): 1699, 1648, 1541, 1458, 1287, 1267, 1032, 756, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{26}O_4Na$ ($M+Na^+$) 365.1729, found: 365.1738.

Acknowledgement. The authors thank the Spanish Ministry of Science and Innovation (Project CTQ2009-09932) and the Regional Government of Andalucia (Project P07-FQM-03101 and assistance to the FQM-348 group) for financial support. R. T. thanks the Spanish Ministry of Science and Innovation for the predoctoral grant provided.

Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for compounds **3, 5, 9, 20, 21, 25, 28, 29, 36, 39** and **41-51**. This material is available free of charge via the internet at http://pubs.acs.org.http://pubs.acs.org.

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