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General Route to 4a-Methylhydrofluorene Diterpenoids: Total Syntheses of (±)-Taiwaniaquinones D and H, (±)-Taiwaniaquinol B, (±)-Dichroanal B, and (±)-Dichroanone

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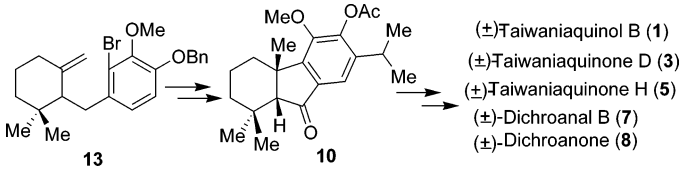

A general and convergent route for the synthesis of the 4a-methylhydrofluorene diterpenoids has been established through a common hexahydrofluorenone intermediate (**10**) obtained via Pd(0)-catalyzed reductive cyclization of a substituted 2-(2-bromobenzyl) methylene cyclohexane (**13**). The strategy has been successfully utilized for the synthesis of (±)-taiwaniaquinones D (**3**) and H (**5**), (±)-taiwaniaquinol B (**1**), (±)-dichroanal B (**7**), and (±)-dichroanone (**8**).

Introduction

Recently a large number of highly rearranged abietane-type diterpenoids possessing the uncommon 4a-methyl tetra- (or hexa-) hydrofluorene skeleton were isolated mainly from a common Taiwanese pine tree, *Taiwania cryptomerioides*.[1] These include taiwaniaquinols B (**1**)[1a] and D (**2**),[1c] and taiwaniaquinones D (**3**),[1b] F (**4**),[1c] and H (**5**)[1d] (Figure 1). A few more structurally related diterpenoids such as dichroanals A (**6**) and B (**7**), and dichroanone (**8**) were isolated from *Salvia dichroantha*.[2] Another novel diterpenoid, standishinal (**9**), was obtained from *Thuja standishii*.[3] Though the bioactivities of this family of compounds are yet to be examined comprehensively, preliminary studies[1d] revealed that taiwaniaquinone D (**3**) possesses antitumoral cytotoxic activity, and standishinal (**9**) has promising antitumor[4] and aromatase inhibitory[5] potential. The published results on their bioactivities and the unique structural pattern make them attractive synthetic targets. Reports on the syntheses of the basic 4a-methyl hydrofluorene skeleton are relatively few,[6−10] though a large volume of literature exists on the synthesis of the gibberellin group of diterpenoids possessing a bridged hydrofluorene nucleus.[11] In the course of our studies on the synthesis of rearranged polycyclic diterpenoids[12] we have recently disclosed[12a] in a preliminary account the first total syntheses of dichroanal B (**7**) and dichroanone

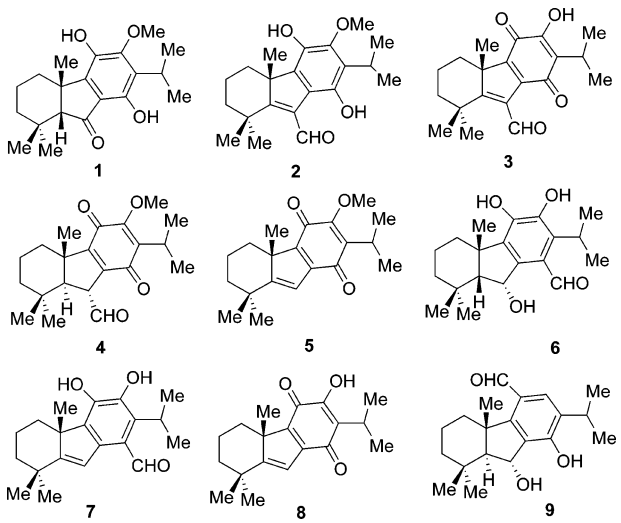

FIGURE 1. 4a-Methylhydrofluorene diterpenoids.

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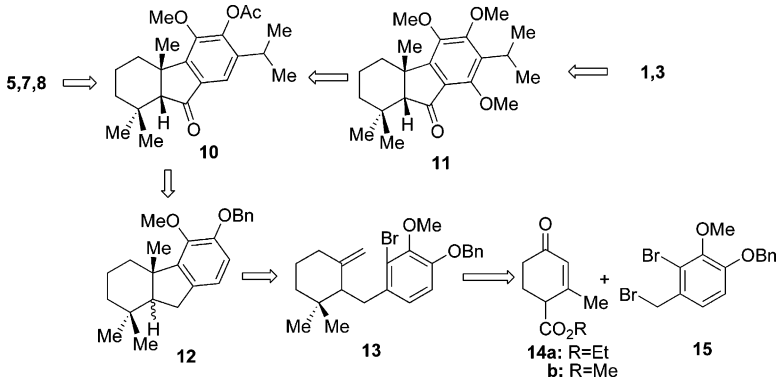
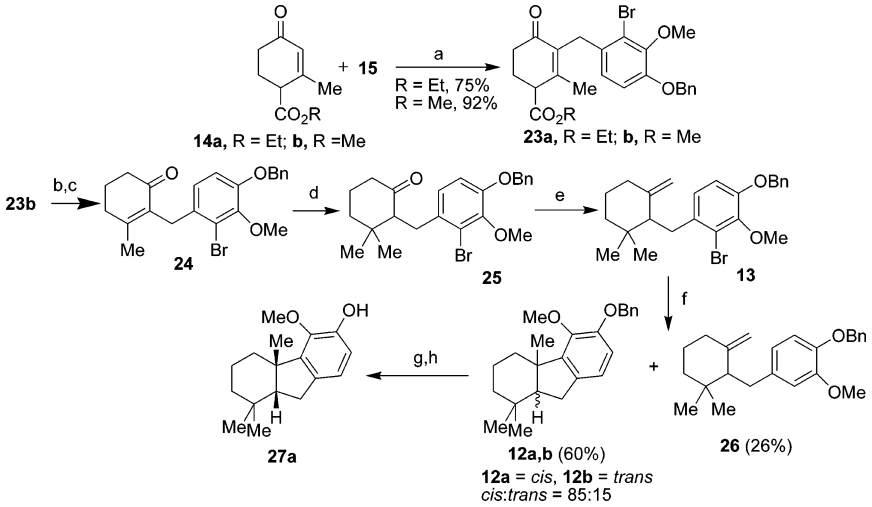
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of the Basic Hexahydrofluorene Skeleton 27a[a]



[a] Reagents and conditions: (a) KO^{t}Bu, ^{t}BuOH, NaI, reflux, 6 h. (b) LiOH, MeOH, H_2O, rt, 12 h. (c) SiO_2, 80 °C, 4 h, 64% over two steps. (d) Me_2CuLi, $BF_3{\cdot}Et_2O$, Et_2O, −30 to 0 °C, 1 h, 94%. (e) NaH, DMSO, $MePPh_3I$, THF, −10 to 10 °C, 1.5 h, 92%. (f) $Pd(PPh_3)_4$, HCOONa, DMF, 95−100 °C, 30 h, 60%. (g) Pd/C (10%), H_2, EtOH, 12 h. (h) Recrystallization, 72% over two steps.

(**8**) using Pd(0)-catalyzed reductive intramolecular cyclization[6a] as the key step to construct the basic hydrofluorenone intermediate (**10**). This crucial intermediate has the potential for being equally effective for the synthesis of other rearranged abietane-type diterpenoids such as taiwaniaquinol B (**1**)[13] and taiwaniaquinones D (**3**) and H (**5**). We describe herein our efforts directed toward this goal as well as the details of our earlier work on the synthesis of **7** and **8**.

Results and Discussion

In a short retrosynthetic plan (Scheme 1), the hydrofluorene diterpenoids **1** and **3** could be obtained from the common hexahydrofluorenone intermediate **10** through trimethoxyhydrofluorenone **11**. As described already, **7** and **8** (and hence **5**) are also derivable from **10**, prepared in turn from the basic 4a-methyl hydrofluorene **12**. The latter is conveniently obtainable through Pd(0)-catalyzed reductive Heck reaction[6a] of the exo-olefin **13**, which could be generated from Hagemann's ester (**14a**) and an appropriately substituted benzyl bromide **15**.

Synthesis of Common Intermediate 10. The required benzyl bromide (**15**) was obtained from commercially available vanillin using a sequence of standard reactions,[12a,14] with 27% yield over seven steps (see Supporting Information). For the construction of the 4a-methyl hydrofluorene **12**, we adopted an established route[15] involving alkylation of Hagemann's ester **14a** to give the alkylated product **23a** (Scheme 2) in good yield. Attempted

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(13) The total synthesis of taiwaniaquinol B (**1**) via a domino intramolecular Friedel−Crafts acylation reaction has recently been reported (see: Fillion, E.; Fishlock, D. *J. Am. Chem. Soc*. **2005**, *127*, 13144−13145).

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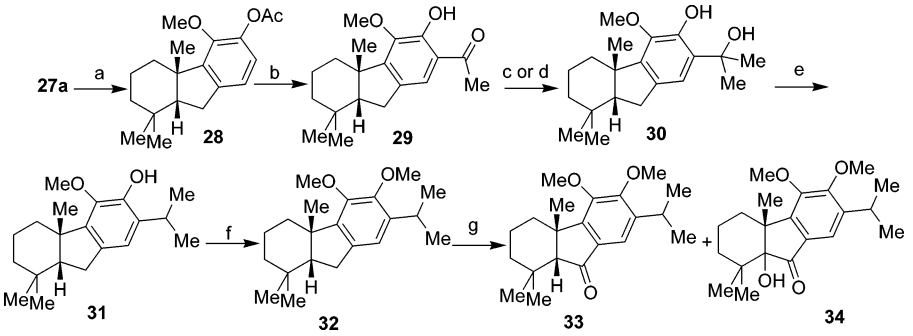
TABLE 1. Results of Heck Cyclization Reaction on Olefin 13[a]

entry	catalyst (mol %)	reducing agent (equiv)	temp (°C)	time (h)	yield (%) **12** (*cis*:*trans*)	yield (%) **26**
1	$Pd(OAc)_2$ (5) PPh_3 (20)	HCOONa (1)	80−85	24	56[b] (85:15)	32[b]
2	$Pd(PPh_3)_4$ (5)	HCOONa (1)	95−100	30	60 (85:15)	26
3	$Pd(PPh_3)_4$ (10)	HCOONa (1.5)	130	24	42 (80:20)	31
4	$Pd(PPh_3)_4$ (5)	$HCOONH_4$ (1.1)	95−100	30	36 (85:15)	28
5[c]	$Pd(OAc)_2$ (120)		reflux	24	no reaction	
6[c]	$Pd(OAc)_2$ (10) PPh_3 (10) Bu_4NBr (4 equiv)	HCOONa (1)	80	24	32[b] (85:15)	24[b]

[a] DMF used as solvent except for entry 5 where THF was used. [b] Based on recovered starting material. [c] Et_3N (5 equiv) used as base.

SCHEME 3. Synthesis of Hexahydrofluorenone 33[a]



[a] Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h, 92%. (b) $AlCl_3$, $PhNO_2$, 58−60 °C, 4 h, 64−67%. (c) MeMgI, THF, reflux, 2 h, 64%. (d) MeLi, Et_2O, −78 °C, 1 h, 99%. (e) H_2, Pd/C, $HClO_4$ (cat.), EtOH, 30 min, 61%. (f) MeI, K_2CO_3, acetone−MeOH (2:1), rt, 12 h, 97%. (g) PCC, Celite, benzene, reflux, 4 h, 40% (of **33**) based on recovery of **32**.

hydrolytic decarboxylation of **23a** to synthesize cyclohexenone **24** proved unsatisfactory using usual conditions[6c,15] (refluxing with aqueous ethanolic KOH), producing a complex mixture of products presumably due to oxidative side reactions involving the heavily oxygenated aromatic ring. However, the alkylated methyl ester **23b**, obtained in 92% yield from the methyl ester analogue **14b**[16] of Hagemann's ester, underwent smooth hydrolysis with aqueous methanolic LiOH. The resulting crude acid produced the desired cyclohexenone **24** when heated as a slurry with silica gel. Treatment of **24** with Me_2CuLi furnished the cyclohexanone **25**, which on Wittig olefination afforded the olefin **13** in excellent yield. Conversion of the bicyclic intermediate to a tricyclic product was next accomplished via Pd(0)-catalyzed cyclization in the presence of a hydride donor.[6a,17] Initially, the reaction was attempted in dry DMF in the presence of 5 mol % $Pd(OAc)_2$ and 20 mol % PPh_3, but this surprisingly afforded an inseparable mixture of epimeric hydrofluorenes **12a** and **12b** in a ratio of ca. 85:15 (as determined by ^1H NMR) along with a substantial amount of the debrominated product **26**, in contrast to that reported for the sterically uncongested analogues.[6a] The ring fusion in the major isomer (**12a**) was assigned as *cis* by analogy with reports on similar systems.[6a] Attempts to achieve better yields of **12a** by changing the reaction condition[6a,17,18] or the hydride donor proved unfruitful (Table 1). The buttressing effect[19] of the benzyloxy and the *o*-methoxy substituents in addition to the cyclohexylmethyl residue appeared to be responsible for the relatively low yield and stereochemical nonselectivity in the cyclization of **13**. However cleavage of the *O*-benzyl ether in **12a**,**b** and careful recrystallization of the resulting isomeric mixture from methanol afforded the desired epimer **27a**, also the major isomer, in pure form. NMR spectral analysis of the product supported the *cis* ring fusion originally assumed on the basis of analogy with similar ring systems. The methyl singlet at δ 1.62, showing a prominent HMBC correlation peak with an aromatic carbon signal (δ 145.2), was easily assigned to the ring juncture substituent (Figure 2). The δ 1.12 methyl signal showed ROESY cross-peaks with this as well as the other methyl signal (at δ 0.88). The signal for the ring juncture methine proton (δ 1.84) showed cross-peaks with both the δ 1.12 and 1.62 methyl signals in the ROESY spectrum. The benzylic proton signal, on the other hand, showed distinct ROESY correlation peak only with the δ 0.88 methyl singlet. The results suggest a *cis* ring fusion with the two β-methyl groups axially oriented on the cyclohexane ring. This also

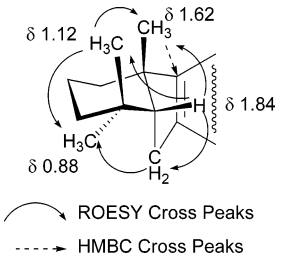


FIGURE 2. Selected ROESY and HMBC correlations in **27a**.

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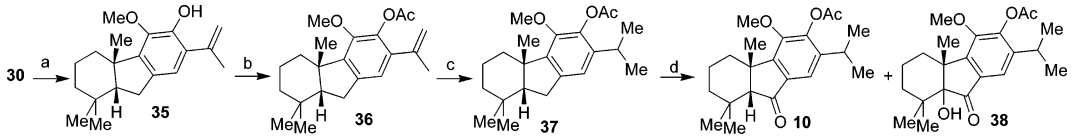
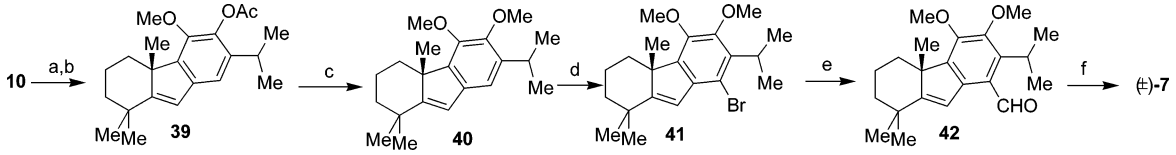
SCHEME 4. Synthesis of Common Hexahydrofluorenone 10[a]



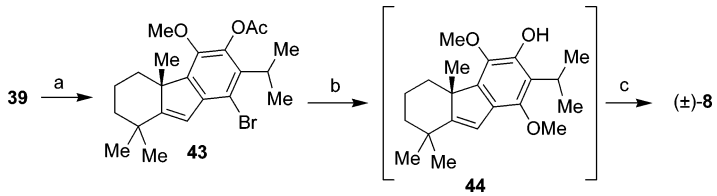
[a] Reagents and conditions: (a) SiO_2, 80 °C, 4 h, 96% based on recovery of **30**. (b) Ac_2O, Et_3N, DMAP, 0 °C, 1 h, 93%. (c) H_2, Pd/C (10 mol %), EtOH, 6 h, 95%. (d) PCC, Celite, benzene, reflux, 10 h, 86% (of **10**) based on recovery of **37**.

SCHEME 5. Synthesis of Dichroanal B (7)[a]



[a] Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, −40 to 0 °C, 1 h. (b) $SOCl_2$/pyridine, −10 °C, 2 h, 96% over two steps. (c) K_2CO_3, MeI, acetone−MeOH (2:1), rt, 12 h, 94%. (d) NBS, CH_3CN, rt, 16 h, 92%. (e) *n*-BuLi, DMF, THF, −78 °C, 4 h, 60%. (f) PhSH, NMP, K_2CO_3, 160 °C, 20 min, 91%.

SCHEME 6. Synthesis of (±)-Dichroanone (8)[a]



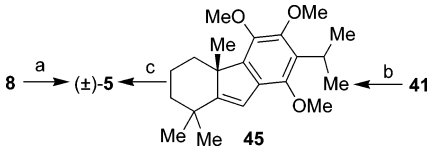
[a] Reagents and conditions: (a) NBS, CH_3CN, rt, 24 h, 82%. (b) NaOMe, CuI, MeOH, DMF, 110 °C, 20 min. (c) CAN, CH_3CN-H_2O (2:1), 10 min, 62% in two steps.

explains the J_{vic} values observed (8.4,10.2 Hz) for the methine proton as the dihedral angles determined from a model study for the proposed structure are 36° and 162°.

Acetylation of **27a** (to **28**) was thereafter carried out and followed with Fries rearrangement[20] to obtain the desired 2-acetyl phenol **29** (Scheme 3). After some experimentation based on the choice of Lewis acid, solvent, or reaction temperature, use of 1.2 equiv $AlCl_3$ in dry nitrobenzene at 58−60 °C proved to be the most effective, affording **29** in good yield (minor amount of the deacetylated product **27a** was also encountered, which could be recycled). Treatment of **29** with excess of MeMgI in dry THF under reflux afforded the unstable benzylic alcohol **30** in moderate yield; however, the yields were almost quantitative when MeLi was used as the alkylating agent. The product was immediately subjected to acid-catalyzed hydrogenolysis[21] (to **31**) followed by methylation to afford **32**. Benzylic oxidation of **32** however proved difficult using a variety of reagents (PCC/Celite,[22] CrO_3 in $Ac_2O-AcOH$,[23] CrO_3/1,3-dimethyl pyrazole,[24] or PDC with TBHP[25]), which produced either a complex mixture of products or higher yields of the over oxidation[6c] product **34**.

An alternative approach was therefore adopted to convert **30** to the common intermediate **11** (Scheme 4). Thus, heating **30** as a slurry with silica gel produced the styrene **35**. Acetylation of **35** and thereafter hydrogenation of the resulting acetate **36** furnished **37**. Benzylic oxidation of the hydrofluorene **37** delivered the desired intermediate **10**. PCC proved to be the best oxidizing agent, producing 86% of the desired ketone based on recovery of the starting material (conversion 52%) with a minor amount of the over oxidation product **38**.

SCHEME 7. Synthesis of (±)-Taiwaniaquinone H (5)[a]



[a] Reagents and conditions: (a) K_2CO_3, MeI, acetone−MeOH (2:1), reflux, 10 h, 58%. (b) NaOMe, CuI, MeOH, DMF, 110 °C, 20 min, 89%. (c) AgO, HNO_3, dioxane, rt, 30 min, 67%.

Following the same sequence of reactions, the epimeric mixture of the cyclized products **12a** and **12b** (ca. 85:15) was directly converted to the more stable *cis*-ketone **10**, eliminating the necessity for separation of the epimeric intermediates. The *cis* ring fusion for **10**, assumed on the basis of analogy,[6c,26] received support from the NOESY spectrum also. Thus the singlet for the ring juncture methine proton showed cross-peaks with two methyl singlets, including that for the angular methyl.

Synthesis of (±)-Dichroanal B (7). With a convenient synthesis of the ketone **10** accomplished, our next task was to

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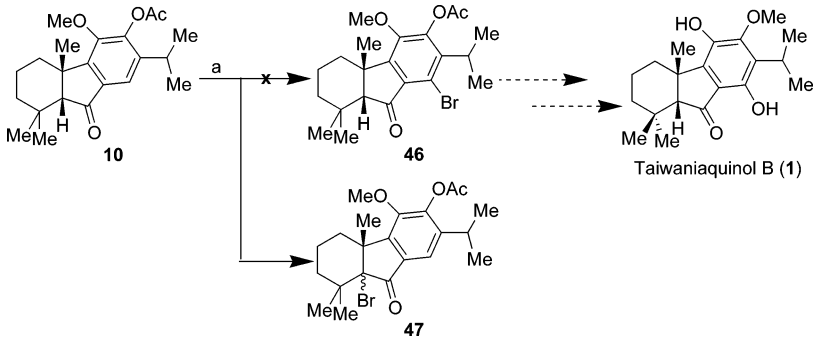
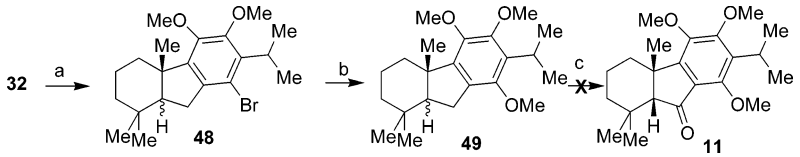
SCHEME 8. Attempted Ring Bromination of 10[a]



[a] Reagents and conditions: (a) NBS, CH_3CN, rt, 3 days, 98%.

SCHEME 9. Attempted Synthesis of 11 from 32[a]



[a] Reagents and conditions: (a) NBS, CH_3CN, rt, 12 h, 92%. (b) NaOMe, CuI, DMF−MeOH, 110 °C, 2 h, 80%. (c) PCC, Celite, benzene, reflux, 10 h.

convert it to different hydrofluorene natural products. For the synthesis of dichroanal B (**7**), reduction of **10** was carried out under controlled condition,[27] followed by dehydration with $SOCl_2$/pyridine[28] to afford the acetate **39** (Scheme 5). Subsequent hydrolysis of **39** and methylation of the resulting phenol yielded the tetrahydrofluorene **40**. Introduction of the aldehyde group in **40** was realized by bromination with NBS[29] to **41** followed by formylation,[30] and the resulting product **42** was smoothly converted[31] to (±)-dichroanal B (**7**) through deprotection of the catechol dimethyl ether residue by heating with thiophenol. The synthetic product exhibited spectral data identical to those reported[2] for the natural material.

Synthesis of (±)-Dichroanone (8). Only three reactions were required to complete the synthesis of the norditerpenoid (±)-dichroanone (**8**) from **39** (Scheme 6). The acetate **39** was smoothly transformed to the bromo derivative **43**, which on treatment with NaOMe in MeOH and DMF in the presence of CuI[32] produced the unstable dimethoxy phenol intermediate **44**. This was immediately subjected to oxidation with CAN[33] in the presence of acetonitrile−water to afford (±)-dichroanone (**8**) in good yield, identified by comparison of the spectral data with those for the natural product.[2]

Synthesis of (±)-Taiwaniquinone H (5). The synthesis of the diterpenoid taiwaniaquinone H (**5**) was achieved (Scheme 7) either by simple methylation of dichroanone (**8**) or, more conveniently, by conversion of **41** to the corresponding trimethoxy derivative **45** with NaOMe in the presence of CuI followed by oxidation with an acidic solution of freshly prepared AgO[34] in dioxane. The spectral data of the synthetic compound were in good agreement with those reported for the natural product.[1d]

Synthesis of Taiwaniaquinol B (1). With the aim of converting **10** to the trimethoxy ketone **11** as the stepping stone to **1** and **3**, we subjected **10** to ring bromination with NBS (Scheme 8). To our dismay this delivered, instead of the desired **46**, the α-bromo ketone **47** exclusively. Similar result was also obtained with the dimethoxy ketone **33**. In an alternative way, bromination could be carried out on the electron rich hexahydrofluorene derivative **32** to get the desired bromo compound **48** in excellent yield (Scheme 9). However, the introduction of the 9-oxo group, attempted using a variety of oxidizing agents[22−25] and under different reaction conditions, could not be effected satisfactorily. Conversion of the bromo derivative **48** to the trimethoxy derivative **49** followed by attempted oxidation to the desired ketone **11** also led to a mixture of intractable products.

A promising route for the total synthesis of taiwaniaquinol B (**1**) was thereafter developed (Scheme 10) by employing the dimethoxy benzyl alcohol **50** as the substrate for bromination. The common intermediate **10** was hydrolyzed and methylated in situ to form the ketone **33**. This on controlled reduction[27] afforded the alcohol **50**, a single isomer of unknown stereochemistry. Unlike the ketone **10**, it could be brominated at low temperature to produce **51** in good yield. This was then oxidized using Jones reagent to the ketone **52**, which was successfully converted to the trimethoxy derivative **11**. Silver(II) oxide oxidation of **11** smoothly afforded the quinone **53**, which was easily reduced[35] to (±)-taiwaniaquinol B (**1**). The spectral data of the synthetic product matched closely with those of the natural product.[1a]

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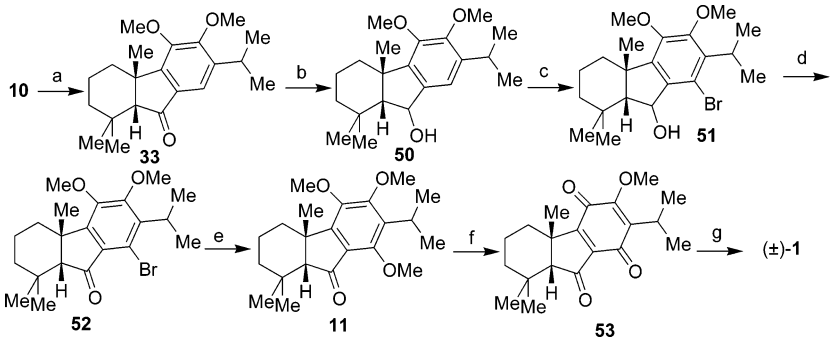
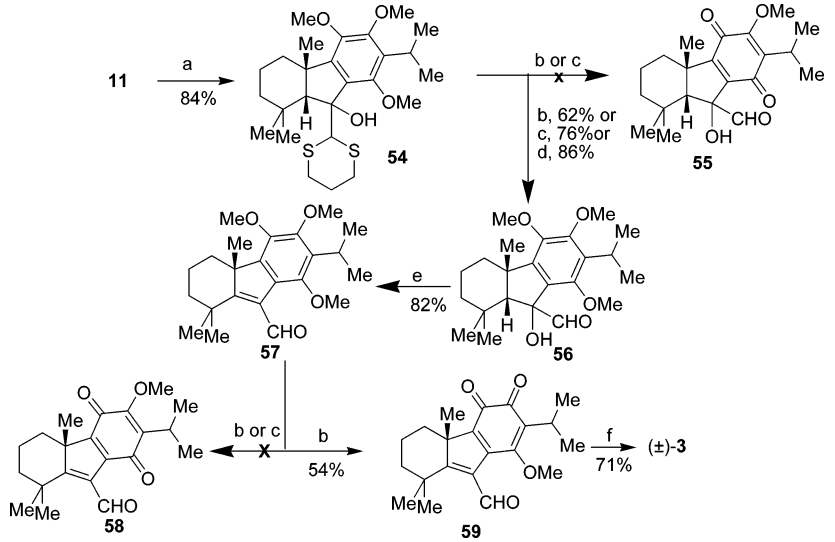
SCHEME 10. Synthesis of Taiwaniaquinol B (1)[a]



[a] Reagents and conditions: (a) K_2CO_3, MeI, acetone−MeOH (2:1), 96%. (b) $NaBH_4/CeCl_3$, EtOH, −40 to 0 °C, 1 h, 98%. (c) NBS/CH_3CN, 0 °C, 16 h, 78%. (d) Jones reagent, acetone, 0 °C, 1 h, 98%. (e) NaOMe/CuI, MeOH−DMF, 110 °C, 1 h, 78%. (f) AgO/HNO_3, dioxane, rt, 30 min, 82%. (g) $Na_2S_2O_4$, ether−H_2O, 2 h, 67%.

SCHEME 11. Synthesis of Taiwaniaquinone D (3)[a]



[a] Reagents and conditions: (a) 1,3-Dithiane (3 equiv), *n*-BuLi (2.5 equiv), −78 °C to rt, 16 h. (b) CAN (2.4 equiv), CH_3CN-H_2O (2:1), 30 min. (c) AgO (4 equiv), dioxane−H_2O, HNO_3 6 N, 30 min. (d) MeI, CH_3CN-H_2O (5:1), 12 h. (e) $KHSO_4$, 205 °C, 30 min, 82%. (f) TMSCl, NaI, CH_2Cl_2, 0 °C to rt, 2 h.

Synthesis of Taiwaniaquinone D (3). Conceptually, taiwaniaquinol B (**1**) appeared to be the most promising intermediate to **3**, requiring only the addition of a formyl group to carbonyl with minor alterations in the aromatic substituents. However, initial attempts to introduce a formyl group at the 9-oxo functionality of **1** by umpolung reaction with 1,3-dithiane and *n*-BuLi[36] resulted only in the recovery of the starting material. Attributing this to the reduced electrophilicity of the carbonyl center due to conjugation with the initially generated quinol dianion, we chose **11** as the substrate for the reaction, which indeed afforded (Scheme 11) the desired dithiane alcohol **54**, a single isomer of undetermined stereochemistry, in very good yield. Attempted transformation of **54** to the α-hydroxy formyl quinone **55** with CAN or AgO resulted only in desulfurization, furnishing the hydroxy aldehyde **56**. The deprotection of **54** was in fact best achieved[37] by stirring with MeI in acetonitrile−water. Unfortunately, oxidation of **56** with CAN or AgO gave back the ketone **11**. Literature survey reveals that tertiary alcohols are prone to undergo fragmentation with the reagent.[38] We therefore decided to test the α,β-unsaturated aldehyde (**57**) as the substrate for oxidation. Dehydration of **56** was smoothly achieved by heating the compound with fused $KHSO_4$,[39] furnishing **57** in 82% yield (18−20% when $SOCl_2$−pyridine was used). Though the projected transformation of the sterically congested trimethoxy aldehyde **57** to the corresponding *p*-benzoquinone derivative **58** proved elusive, oxidation with CAN produced a dark red product in moderate yield (54% based on recovery of **57**), identified as the *o*-quinone derivative **59** from the presence of a long-range UV absorption peak. Demethylation of **59** with TMSCl[40] and NaI at room temperature then smoothly delivered the (±)-taiwaniaquinone D (**3**), identified by spectral comparison with the natural product.[1b]

Conclusion

In conclusion, we have developed a convenient route for the total synthesis of a number of hydrofluorene natural products

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and their analogues. The protocol was followed to realize the total synthesis of (±)-dichroanal B (**7**), (±)-dichroanone (**8**), (±)-taiwaniaquinol B (**1**), and (±)-taiwaniaquinones D (**3**) and H (**5**). The methodology is general and applicable to the other natural products of similar skeleton.

Experimental Section

6-Benzyloxy-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (12a,b). To a solution of **13** (7.6 g, 0.018 mol) in 130 mL of dry DMF were added palladium(0) tetrakistriphenylphosphine (1 g, 0.88 mmol) and sodium formate (1.2 g, 0.018 mol), and the suspension was heated at 95−100 °C for 30 h. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine, dried, and concentrated. The crude product was carefully column chromatographed over silica gel (petroleum ether) to give **12a**,**b** (*cis*:*trans* = 85:15) (3.8 g, 60%) as a white solid: mp 55−56 °C; IR (KBr) ν 2925, 1483, 1257, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (3H, s), 1.13 (3H, s), 1.24−1.45 (4H, m), 1.54−1.68 (1H, m), 1.63 (3H, s), 1.71−1.89 (2H, m), 2.66−2.78 (2H, m), 3.87 (3H, s), 5.06 (2H, s), 6.75 (1H, d, J = 8 Hz), 6.81 (1H, d, J = 8 Hz), 7.30−7.40 (3H, m), 7.46 (2H, d like, J = 7.1 Hz) [additional small peaks at 0.95 (3H, s) and 1.02 (3H, s) are attributed to the *trans*-isomer]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.7, 25.8, 30.4, 31.0, 32.2, 33.8, 34.8, 35.4, 47.2, 57.1, 60.8, 71.2, 112.7, 119.3, 127.3 (2C), 127.7, 128.5 (2C), 135.7, 137.6, 145.9, 146.4, 150.8 (one carbon signal undetermined due to overlap); [additional small peaks at 20.0, 20.2, 21.1, 29.8, 33.1, 33.4, 36.8, 41.5, 47.1, 61.0, 71.1, 112.1, and 120.0 are attributed to the *trans*-isomer]. Mass (EI) *m*/*z* 351 (M^+ + 1), 350 (M^+), 260, 228. Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 81.98; H, 8.60.

The debrominated product **26** (1.55 g, 25%) was also eluted out with petroleum ether as a colorless viscous liquid.

6-Hydroxy-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene (27a). A well-stirred suspension of **12a,b** (3.5 g, 0.01 mol) and Pd/C (10% w/w, 600 mg) in dry ethanol (30 mL) was fitted to a source of hydrogen (1 atm) and stirred vigorously for 12 h. The mixture was filtered through a pad of Celite and washed with ethanol. The combined filtrates were concentrated and the residue was column chromatographed over silica gel (2% EtOAc in petroleum ether) to give a *cis*−*trans* mixture (85:15) of **27a,b**. Recrystallization of the diastereomeric mixture from methanol in cold condition afforded the pure *cis*-phenol **27a** (1.82 g, 72%) as a white solid: mp 94−95 °C; IR (KBr) ν 3283, 2929, 1358, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (3H, s), 1.12 (3H, s), 1.27 (1H, bd, J = 13.0 Hz), 1.38 (1H, dt, J = 3.0, 13.0 Hz), 1.42−1.47 (2H, m), 1.58−1.68 (1H, m, overlapped), 1.62 (3H, s), 1.72−1.78 (1H, m), 1.84 (1H, dd, J = 8.4, 10.5 Hz), 2.67 (1H, dd, J = 10.5, 15.0 Hz), 2.72 (1H, dd, J = 8.4, 15.0 Hz), 3.80 (3H, s), 5.29 (1H, s, exchangeable), 6.73 (1H, d, J = 7.8 Hz), 6.82 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 25.5, 29.8, 30.8, 32.2, 33.7, 35.1, 35.3, 47.2, 57.6, 61.8, 113.8, 120.7, 134.9, 143.9, 145.2, 147.8; Mass (EI) *m*/*z* 261 (M^+ + 1), 260 (M^+), 245. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.62; H, 9.36.

6-Acetoxy-7-isopropyl-5-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-fluoren-9-one (10). Celite (4.36 g) was heated to 140 °C under vacuum for 2 h and cooled. To it dry benzene (40 mL) was added followed by PCC (1.98 g, 9.2 mmol), and the slurry was stirred for 15 min to make a homogeneous mixture. Then a solution of hydrofluorene **37** (792 mg, 2.3 mmol) in dry benzene (40 mL) was added, and the reaction mixture was refluxed for 10 h. After cooling, the reaction mixture was filtered through a pad of Celite, and the bed was washed with benzene. The combined organic extracts were washed with water and brine, then dried and concentrated. Column chromatography of the crude product over silica gel (4% EtOAc in petroleum ether) afforded **10** (428 mg, 52%) as a white solid: mp 78 °C; IR (KBr) ν 2964, 1776, 1710, 1188 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (3H, s), 1.21 (6H, d, J = 6.8 Hz), 1.25 (3H, s), 1.42 (3H, s), 1.47−1.75 (4H, m), 1.80−1.97 (1H, m), 2.10 (1H, s), 2.16−2.25 (1H, m), 2.39 (3H, s), 2.96 (1H, sept, J = 6.8 Hz), 3.85 (3H, s), 7.45 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 20.7, 23.0 (2C), 24.5, 27.7, 31.2, 31.8, 32.6, 34.2, 37.3, 42.4, 61.1, 65.4, 116.6, 135.8, 142.6, 147.4, 149.1, 151.4, 168.1, 207.0; Mass (EI) *m*/*z* 358 (M^+), 316, 301, 247, 234. Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 74.00; H, 8.56.

Further elution with 10% EtOAc in petroleum ether afforded the α-hydroxy ketone **38** (52 mg, 6%) as a white solid, and 315 mg (40%) of starting material (**37**) was also recovered.

6-Acetoxy-7-isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (39). To a stirred solution of **10** (430 mg, 1.2 mmol) in ethanol (30 mL) was added $CeCl_3 \cdot 7H_2O$ (447 mg, 1.2 mmol), and the temperature was brought down to −40 °C. $NaBH_4$ (45.6 mg, 1.2 mmol) was added portionwise to the stirred solution, the temperature was allowed to come to 0 °C, and the stirring was continued for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were washed with brine and dried. The solvent was evaporated to afford the crude alcohol (420 mg, 1.17 mmol). The alcohol was taken in dry CH_2Cl_2 (20 mL) and cooled to −10 °C. Pyridine (0.56 mL, 7 mmol) was added followed by $SOCl_2$ (0.19 mL, 2.6 mmol) dropwise. The reaction mixture was stirred at the same temperature for 2 h and then quenched by adding excess saturated NH_4Cl solution. The organic part was separated out and the aqueous part was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with 2 N HCl, water, and brine and dried. The solvent was evaporated and the crude product was purified by column chromatography over silica gel (1% ethyl acetate in petroleum ether) to furnish **39** (394 mg, 96%) as a white solid: mp 80−82 °C; IR (KBr) ν 2961, 2936, 1769, 1211, 1194 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02−1.26 (2H, m, overlapped), 1.21 (6H, d, J = 6.9 Hz), 1.23 (3H, s), 1.27 (3H, s), 1.46 (3H, s), 1.57−1.64 (2H, m), 1.88−1.98 (1H, m), 2.35 (3H, s), 2.35−2.44 (1H, m, overlapped), 2.95 (1H, sept, J = 6.9 Hz), 3.82 (3H, s), 6.26 (1H, s), 6.96 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 20.7, 21.4, 23.3 (2C), 25.4, 27.5, 31.4, 35.4, 36.8, 42.4, 52.2, 61.3, 113.2, 120.4, 138.8, 140.3, 141.5, 143.7, 147.3, 165.0, 169.2; Mass (EI) *m*/*z* 342 (M^+), 301, 300, 285, 231. Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 76.97; H, 8.88.

7-Isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (40). The acetyl tetrahydrofluorene **39** (171 mg, 0.5 mmol) and K_2CO_3 (276 mg, 2 mmol) were taken in 2:1 mixture of acetone and methanol (6 mL) and the mixture was stirred for 1 h. Then CH_3I (0.31 mL, 5 mmol) was added and the reaction mixture was stirred for 16 h more. The solvent was evaporated, and the residue was dissolved in a mixture of water (10 mL) and ethyl acetate (10 mL). The aqueous part was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine, dried and concentrated. Column chromatography of the residue over silica gel (1% EtOAc in petroleum ether) afforded **40** (144 mg, 92%) as a white solid: mp 68−70 °C; IR (KBr) ν 2963, 2933, 1448, 1408, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02−1.26 (2H, m, overlapped), 1.22−1.26 (12H, four overlapped methyl signals), 1.46 (3H, s), 1.56−1.63 (2H, m), 1.91−1.97 (1H, m), 2.44 (1H, bd, J = 12.9 Hz), 3.31 (1H, sept, J = 6.9 Hz), 3.82 (3H, s), 3.90 (3H, s), 6.23 (1H, s), 6.88 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 21.5, 23.9 (2C), 25.5, 26.8, 31.5, 35.4, 36.8, 42.5, 52.2, 60.3, 60.7, 112.8, 120.4, 138.8, 141.2, 143.7, 147.7, 148.8, 164.0; Mass (EI) *m*/*z* 315 (M^+ + 1), 314 (M^+), 299, 271, 245. Anal. Calcd for $C_{21}H_{30}O_2$ C, 80.21; H, 9.62. Found: C, 79.93; H, 9.58.

8-Bromo-7-isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (41). NBS (76.9 mg, 0.432 mmol) was added portion wise to a stirred solution of **40** (123 mg, 0.36 mmol) in dry acetonitrile (6 mL) at −5 °C and the mixture was stirred for 16 h at room temperature. The acetonitrile was removed in a

vacuum and the residue was chromatographed over silica gel (petroleum ether) to afford **41** (143 mg, 92%) as a white solid: mp 104−105 °C; IR (KBr) ν 2959, 2934, 1448, 1338, 1021 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02−1.19 (2H, m), 1.23 (3H, s), 1.29 (3H, s), 1.35 (3H, d, J = 6.8 Hz), 1.37 (3H, d, J = 6.8 Hz), 1.44 (3H, s), 1.58−1.64 (2H, m), 1.87−1.97 (1H, m), 2.40−2.45 (1H, m), 3.61−3.65 (1H, m), 3.83 (3H, s), 3.85 (3H, s), 6.37 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 21.2, 21.28, 21.35, 25.4, 31.4, 35.6, 36.7, 42.5, 53.7, 60.0, 60.5, 121.1, 138.6, 139.1, 144.7, 148.7, 150.5, 164.9 (two carbon signals remained undistinguished due to overlap); Mass (EI) m/z 394/392 (M^+, Br = 81/79), 379, 377, 325, 323, 277. Anal. Calcd for $C_{21}H_{29}BrO_2$: C, 64.12; H, 7.43. Found: C, 64.33; H, 7.59.

2-Isopropyl-3,4-dimethoxy-4b,8,8-trimethyl-5,6,7,8-tetrahydro-4b*H*-fluorene-1-carbaldehyde (42). To a stirred solution of **41** (110 mg, 0.28 mmol) in dry THF (6 mL) was added *n*-BuLi (0.21 mL, 1.6 M in hexane) slowly during 5 min at −78 °C and the mixture was stirred for 2 h. Then a cold solution of DMF (0.11 mL, 1.4 mmol) in dry THF (2 mL) was added dropwise through a cannulae and the mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched with an excess of saturated NH_4Cl solution and allowed to come to room temperature, the THF layer was separated and concentrated, and the residue was taken in ether (25 mL). The aqueous part was extracted with ether (2 × 20 mL). The combined ether extracts were washed with brine and dried. The solvent was evaporated to dryness and the residue was chromatographed (silica gel, petrol/EtOAc, 98:2) to afford **42** (56 mg, 60%) as a white solid: mp 82−83 °C; IR (KBr) ν 2936, 1681, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04−1.18 (2H, m), 1.25 (3H, s), 1.31 (3H, s), 1.42−1.44 (9H, overlapped signals of two methyl doublets and a methyl singlet), 1.56−1.74 (2H, m), 1.88−1.97 (1H, m), 2.46 (1H, bd, J = 12.8 Hz), 3.81 (3H, s), 3.86−3.95 (1H, m, overlapped), 3.94 (3H, s), 7.09 (1H, s), 10.62 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 21.0, 23.3, 23.4, 25.3, 26.3, 31.4, 35.8, 36.4, 42.5, 51.2, 60.0, 60.5, 120.1, 123.2, 141.7, 143.4, 145.4, 148.8, 152.9, 168.8, 192.2; Mass (EI) m/z 343 (M^+ + 1), 342(M^+), 327, 273. Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 76.90; H, 8.66.

The debrominated product **40** (28 mg, 32%) was also recovered (eluted with 1% EtOAc in petroleum ether).

(±)-Dichroanal B (7). A mixture of **42** (26 mg, 0.076 mmol), K_2CO_3 (4.2 mg, 0.03 mmol), thiophenol (15.6 μL, 0.152 mmol), and dry NMP (0.3 mL) was heated in a tightly capped vessel at 160 °C for 30 min and then cooled. The reaction mixture was poured into 2 N HCl solution (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with water and brine, dried, and concentrated. The crude product was purified by preparative TLC to furnish **7** (20.7 mg, 87%) as a yellow solid: mp 148−150 °C; IR (KBr) ν 3444, 3284, 2921, 1641, 1551, 1274 cm^{-1}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 1.08−1.17 (2H, m,), 1.20 (3H, s), 1.26 (3H, s), 1.41−1.57 (2H, m), 1.62 (6H, d, J = 7.0 Hz), 1.68 (3H, s), 1.84−1.89 (1H, m), 2.88 (1H, bd, J = 12.5 Hz), 4.43 (1H, sept, J = 7.0 Hz), 5.27 (2H, bs, exchangeable), 7.54 (1H, s), 10.91 (1H, s); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 19.6, 20.2, 22.6, 22.7, 25.5, 27.0, 31.5, 35.8, 36.2, 43.0, 51.0, 120.5, 120.9, 139.0, 139.2, 140.8, 142.6, 167.0, 191.7 (the 142.6 ppm signal may represent two carbon peaks as suggested for the natural product);[2] Mass (EI) m/z 315 (M^+ + 1), 314 (M^+), 299, 245, 91. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.59; H, 8.26.

6-Acetoxy-8-bromo-7-isopropyl-5-methoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (43). The same procedure as described for **41** was followed to synthesize **43** from **39** (171 mg, 0.5 mmol). The reaction mixture was stirred for 24 h. The acetonitrile was evaporated and the residue chromatographed (silica gel, petrol/EtOAc, 99:1) to afford **43** (172 mg, 92%) as a white solid: mp 128−130 °C; IR (KBr) ν 2962, 1776,1193 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09−1.24 (2H, m, overlapped), 1.24 (3H, s), 1.30 (9H, bs, overlapped three methyl signals), 1.46 (3H, s), 1.57−1.65 (2H, m), 1.87−1.96 (1H, m), 2.35 (3H, s), 2.35−2.42 (1H, m, overlapped), 3.56−3.60 (1H, m), 3.78 (3H, s), 6.40 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 20.76, 20.83, 21.2, 25.2, 31.3, 35.7, 36.8, 42.3, 53.7, 61.3, 121.1, 137.7, 141.0, 142.0, 144.5, 147.2, 166.1, 168.8 (two carbon signals remained undistinguished); Mass (EI) m/z 422/420 (M^+, Br = 81/79), 380, 378, 365, 363, 311, 309. Anal. Calcd for $C_{22}H_{29}BrO_3$: C, 62.71; H, 6.94. Found: C, 62.53; H, 7.08.

(±)-Dichroanone (8). To a well-stirred suspension of CuI (19 mg, 0.01 mmol) in dry DMF (0.2 mL) was added a freshly prepared solution of NaOMe in dry methanol (8.5 mg of Na in 0.3 mL of methanol) and the mixture was heated to 90 °C. Then a solution of **43** (35 mg, 0.083 mmol) in dry DMF (0.2 mL) was added to the hot suspension dropwise; the mixture was heated at 110 °C for 30 min and then cooled. The reaction mixture was diluted with water and extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with brine and dried. The solvent was evaporated to give the unstable phenol **44** (28 mg) as a sticky liquid (immediately produces a red color when exposed to air), which was dissolved in acetonitrile−water (2 mL, 2:1) and kept at −5 °C. Then a solution of CAN (125 mg, 0.25 mmol) in acetonitrile−water (1 mL, 2:1) was added and the mixture was allowed to stir for 30 min. The solvent was evaporated, and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried, and concentrated. The crude product was purified by preparative TLC to afford **8** (16 mg, 65%) as an amorphous red solid: mp 102−104 °C; IR (KBr) ν 3271, 2934, 1639, 1318, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04−1.16 (2H, m), 1.23−1.25 (9H, three overlapped methyl signals), 1.29 (3H, s), 1.45 (3H, s), 1.58−1.73 (2H, m), 1.85−2.00 (1H, m), 2.38 (1H, dd, J = 2.0, 13.0 Hz), 3.22 (1H, sept, J = 7.0 Hz), 6.45 (1H, s), 7.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 20.0 (2C), 20.1, 23.9, 24.7, 30.9, 37.0, 37.3, 43.4, 55.3, 118.0, 122.7, 147.8, 148.9, 152.4, 177.1, 178.2, 185.7; Mass (EI) m/z 300 (M^+), 285 (M^+ − Me), 231, 173. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.08; H, 8.13.

7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (45). The same procedure as described for the conversion of **43** to **44** (during the synthesis of **8**) was followed to synthesize **45** from **41** (30 mg, 0.076 mmol). After usual workup, column chromatography of the residue over silica gel (1% EtOAc in petroleum ether) afforded **45** (23.4 mg, 89%) as a white solid: mp 82−84 °C; IR (KBr) ν 2938, 1453, 1409, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.09−1.16 (2H, m), 1.23 (3H, s), 1.26 (3H, s), 1.33 (3H, d, J = 6.9 Hz), 1.34 (3H, d, J = 6.9 Hz), 1.46 (3H, s), 1.59−1.63 (2H, m), 1.91−1.96 (1H, m), 2.42−2.45 (1H, m), 3.45 (1H, sept, J = 6.9 Hz), 3.82 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 6.35 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.5, 21.6, 22.25, 22.28, 25.5, 25.6, 31.5, 35.5, 36.8, 42.5, 52.3, 60.2, 60.5, 62.0, 116.8, 130.3, 132.7, 145.0, 145.7, 147.2, 149.3, 162.9; Mass (ESI) m/z 367 (M^+ + Na), 345 (M^+ + 1). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.52.

(±)-Taiwaniaquinone H (5). A mixture of **45** (16 mg, 0.046 mmol) and freshly prepared silver(II) oxide (35 mg, 0.275 mmol) taken in dry dioxane (1 mL, freshly distilled over Na) was sonicated for 5 min. Then 6 N HNO_3 (0.1 mL) was added slowly (the solid AgO dissolved during the addition of acid to from a clear yellow solution) to the reaction mixture. The mixture was stirred for 30 min, then diluted with water and extracted with ether (2 × 10 mL). The combined ethereal extracts were washed several times with brine, dried and concentrated. Column chromatography over silica gel (petroleum ether/EtOAc, 97:3) of the crude product gave **5** (9.8 mg, 67%) as a red amorphous solid: mp 75−76 °C; IR (KBr) ν 2934, 1645, 1536, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.06−1.12 (2H, m), 1.22−1.25 (9H, three overlapped methyl signals), 1.28 (3H, s), 1.45 (3H, s), 1.56−1.67 (2H, m), 1.91−1.93 (1H, m), 3.25 (1H, sept, J = 7.0 Hz), 3.99 (3H, s), 6.38 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.1, 20.1, 20.68, 20.70, 24.5, 24.8, 31.0, 36.7, 37.2, 43.4, 55.6, 61.4, 116.7, 136.0, 145.8, 150.6, 157.3,

175.7, 178.8, 186.3; Mass (ESI) *m*/*z* 315 ($M^+ + 1$). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8. 33. Found: C, 76.56; H, 8.38.

7-Isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-fluoren-9-one (33). The same procedure as described for the conversion of **39** to **40** was followed to synthesize **33** from **10** (300 mg, 0.84 mmol). Column chromatography of the residue over silica gel afforded **33** (265 mg, 96%) as a white solid: mp 76−77 °C; IR (KBr) 3473, 2972, 1708, 1461, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (3H, s), 1.22 (6H, d, $J = 6.9$ Hz), 1.26 (3H, s), 1.41 (3H, s), 1.38−1.43 (1H, m, overlapped), 1.48−1.78 (3H, m), 1.88−1.96 (1H, m), 2.06 (1H, s), 2.12−2.22 (1H, m), 3.28 (1H, sept, $J = 6.9$ Hz), 3.89 (3H, s), 3.90 (3H, s), 7.36 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.8, 23.2, 23.3, 24.3, 27.0, 30.7, 31.3, 32.7, 34.0, 37.0, 42.1, 59.8, 60.2, 65.0, 116.0, 133.0, 143.2, 149.8, 152.0, 156.5, 206.8; Mass (EI) *m*/*z* 331 ($M^+ + 1$), 330 (M^+), 315, 261, 248, 247. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.19; H, 9.03.

7-Isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-9-ol (50). To a stirred solution of **33** (240 mg, 0.73 mmol) in ethanol (20 mL) was added $CeCl_3 \cdot 7H_2O$ (272 mg, 0.73 mmol) and temperature was brought down to −40 °C. Then $NaBH_4$ (27.6 mg, 0.73 mmol) was added portionwise, the temperature of the mixture was allowed to come to 0 °C. The mixture was stirred for 1 h and then quenched by adding excess saturated NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried and concentrated to furnish the crude alcohol. Column chromatography over silica gel (petroleum ether/EtOAc, 99:1) gave **50** (235 mg, 98%) as a white solid: mp 96−98 °C; IR (KBr) ν 3520, 2961, 2932, 2865, 1450, 1409, 1313, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (3H, s), 1.20 (3H, d, $J = 7.0$ Hz), 1.21 (3H, d, $J = 7.0$ Hz), 1.28 (3H, s), 1.41−1.67 (4H, m, overlapped), 1.61 (3H, s), 1.72−1.80 (2H, m), 2.05 (1H, bd, $J = 11.8$ Hz), 3.29 (1H, sept, $J = 7.0$ Hz), 3.82 (3H, s), 3.86 (3H, s), 4.99 (1H, d, $J = 5.1$ Hz), 6.98 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 23.5, 23.7, 25.3, 26.9, 29.8, 31.4, 32.8, 36.9, 37.8, 46.5, 59.7, 60.1, 60.2, 77.7, 116.7, 139.7, 141.9, 144.4, 149.9, 150.9; Mass (EI) *m*/*z* 332 (M^+), 317, 314, 299. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.68; H, 10.03.

8-Bromo-7-isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-9-ol (51). The same procedure as described for **41** was followed to synthesize **51** from **50** (200 mg, 0.6 mmol) except that the mixture was stirred at 0−5 °C for 16 h. Acetonitrile was removed in a vacuum and the residue was column chromatographed over silica gel (petroleum ether) to afford **51** (190 mg, 78%) as a white solid: mp 111−112 °C; IR (KBr) ν 3547, 2939, 2869, 1449, 1336, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, s), 1.29 (3H, s), 1.34 (6H, d, $J = 6.9$ Hz), 1.56−1.67 (4H, m, overlapped), 1.59 (3H, s), 1.72−1.88 (2H, m), 1.95−1.98 (1H, m), 3.57 (1H, sept, $J = 6.9$ Hz), 3.81 (3H, s), 3.83 (3H, s), 5.15 (1H, d, $J = 5.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.5, 21.0, 21.2, 25.1, 29.8, 31.4, 32.8, 36.7, 37.0, 48.4, 58.5, 60.0, 60.2, 78.9, 115.2, 139.2, 139.5, 145.8, 150.0, 153.7 (one carbon signal could not be distinguished); Mass (EI) *m*/*z* 412/410 (M^+, Br isotopes), 397, 395, 379, 361, 330, 315, 248, 199. Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60. Found: C, 61.42; H, 7.87.

8-Bromo-7-isopropyl-5,6-dimethoxy-1,1,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-fluoren-9-one (52). To a stirred solution of **51** (150 mg, 0.365 mmol) in acetone (3 mL) at 0 °C was added freshly prepared Jones reagent (0.44 mL, 0.438 mmol) dropwise and the mixture was stirred for 2 h. Then few drops of 2-propanol were added and the mixture was allowed to stir for few minutes until the color of the Jones reagent disappeared. The reaction mixture was diluted with ether (10 mL) and water (5 mL). The ethereal part was separated out and the aqueous part was extracted with ether (2 × 5 mL). The combined ether extracts were washed with brine, dried and concentrated. The residue was column chromatographed over silica gel (3% EtOAc in petroleum ether) to give **52** (146 mg, 98%) as a white solid: mp 67−68 °C; IR (KBr) ν 2951, 1708, 1303, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.73 (3H, s), 1.23 (3H, s), 1.33−1.37 (9H, s, overlapped three methyl signals), 1.44−1.73 (4H, m), 1.76−1.85 (1H, m), 2.10 (1H, s), 2.28−2.37 (1H, m), 3.76−3.85 (1H, m, overlapped), 3.85 (3H, s), 3.92 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.2, 20.8, 20.9, 24.6, 31.5, 31.7, 32.5, 34.2, 37.7, 41.0, 59.7, 60.3, 65.9, 115.0, 130.5, 141.6, 149.6, 153.6, 158.8, 204.5 (one carbon peak was not distinguished); Mass (EI) *m*/*z* 410/408 (M^+, Br isotopes), 395, 393, 328, 326. Anal. Calcd for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14. Found: C, 61.83; H, 7.27.

7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-1,2,3,4,4a,9a-hexahydro-fluoren-9-one (11). To a well-stirred suspension of CuI (84 mg, 0. 44 mmol) in dry DMF (1 mL) was added a freshly prepared 1.2 M solution of sodium methoxide in dry methanol (34 mg of Na in 2 mL of methanol) and the mixture was heated to 90 °C. Then a solution of **52** (120 mg, 0.293 mmol) in dry DMF (2 mL) was added to the hot suspension dropwise and the mixture was heated to 110 °C. The heating was continued for 30 min. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried and concentrated. Column chromatography of the residue over silica gel (petroleum ether/EtOAc, 98:2) afforded **11** (54 mg, 78%) as a white solid: mp 93−95 °C; IR (KBr) ν 2931, 1697, 1465, 1270, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (3H, s), 1.24 (3H, s), 1.31 (6H, d, $J = 7.0$ Hz), 1.38 (3H, s), 1.45−1.75 (4H, m), 1.80−1.89 (1H, m), 2.03 (1H, s), 2.22−2.32 (1H, m), 3.49 (1H, sept, $J = 7.0$ Hz), 3.84 (3H, s), 3.88 (3H, s), 3.89 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.1, 21.9 (2C), 24.6, 25.3, 31.5 (2C), 32.7, 34.2, 37.5, 41.9, 59.9, 60.3, 62.1, 65.6, 124.8, 134.8, 146.2, 152.7, 152.9, 158.6, 204.7; Mass (EI) *m*/*z* 361 ($M^+ + 1$), 345, 278, 277, 247. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 72.99; H, 8.81.

2-Isopropyl-3-methoxy-4b,8,8-trimethyl-4b,5,6,7,8,8a-hexahydro-fluorene-1,4,9-trione (53). The same procedure as described for **5** (from **45**) was followed to synthesize **53** from **11** (28 mg, 0.078 mmol). Column chromatography of the residue over silica gel (petroleum ether/EtOAc, 97:3) of the crude product gave **53** (21 mg, 82%) as a yellow liquid: IR (neat) ν 2948, 2872, 1726, 1656, 1586, 1462, 1143 cm^{-1}; ^1H NMR (MeOH-d_4, 300 MHz) δ 0.96 (3H, s), 1.23−1.25 (9H, three overlapped methyl signals), 1.35−1.54 (2H, m, overlapped), 1.48 (3H, s), 1.58−1.72 (1H, m), 1.74−1.83 (1H, m), 1.99 (2H, t like, $J = 7.0$ Hz), 2.12 (1H, s), 3.26 (1H, sept, $J = 7.0$ Hz), 4.01(3H, s); ^{13}C NMR (MeOH-d_4, 75 MHz) δ 18.3, 20.7, 20.8, 24.9, 25.6, 27.9, 31.3, 33.1, 35.7, 36.9, 44.2, 61.6, 66.2, 135.5, 138.4, 158.9, 171.9, 184.5, 185.7, 206.7; Mass (EI) *m*/*z* 332 ($M^+ + 2$), 330 (M^+), 315, 249, 247. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.49; H, 8.07.

(±)-Taiwaniaquinol B (1). The quinone **53** (18 mg, 0.054 mmol) was dissolved in the minimum volume of ether (0.1 mL) and a solution of sodium dithionite (94 mg, 0.54 mmol) in water (0.1 mL) was added. The biphasic solution was stirred vigorously for 2 h, diluted with water and extracted with ether (2 × 5 mL). The combined ether extracts were washed with brine, dried and concentrated. The crude compound was immediately purified by preparative TLC to afford (±)-taiwaniaquinol B (**1**) (11.6 mg, 67%) as a white solid: mp 140−141 °C (lit.[21] 142−144 °C); IR (KBr) ν 3442, 3276, 2950, 1650, 1627, 1426, 1328, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, s), 1.26 (3H, s), 1.38 (6H, d, $J = 7.0$ Hz), 1.45 (3H, s), 1.51−1.76 (4H, m), 1.99−2.06 (2H, m), 2.12 (1H, s), 3.27 (1H, sept, $J = 7.0$ Hz), 3.80 (3H, s), 5.28 (1H, s), 9.54 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.5, 20.6 (2C), 24.4, 25.9, 28.8, 30.3, 33.0, 34.3, 36.5, 42.7, 62.1, 65.1, 118.3, 126.1, 138.4, 142.7, 151.1, 152.2, 211.1; Mass (EI) *m*/*z* 332 (M^+), 317, 249, 149. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.33.

9-{[1,3]Dithian-2-yl}-7-isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluoren-9-ol (54). To a stirred solution of 1,3-dithiane (200 mg, 1.67 mmol) in dry THF (4 mL)

was added *n*-BuLi (0.87 mL, 1.6 M in hexane) dropwise at −25 °C and the stirring was continued at the same temperature for 90 min. Then the mixture was cooled to −78 °C and a solution of **11** (200 mg, 0.56 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was stirred at that temperature for 4 h. Then it was allowed to reach room temperature slowly and left overnight. After quenching the reaction mixture with ice water, the product was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed successively with water and brine and then dried. Evaporation of the solvent and purification of the crude product over neutral alumina (2% EtOAc in petroleum ether) afforded **54** (224 mg, 84%) as white fluffy solid: mp 52−54 °C; IR (KBr) ν 3531, 2936, 1458, 1412, 1340, 1119, 1030 cm^{-1}; ^{1}H NMR (pyridine-d_5, 300 MHz) δ 1.38−1.41 (9H, three overlapped methyl signals), 1.41 (3H, d, J = 6.8 Hz), 1.20−1.50 (2H, m, overlapped), 1.73 (3H, s), 1.86 (3H, s), 1.58−1.86 (4H, m, overlapped), 1.93−1.99 (1H, m), 2.08−2.12 (1H, m), 2.55 (1H, s), 2.67−2.87 (4H, m), 3.53 (1H, sept, J = 7.0 Hz), 3.78 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 5.42 (1H, s), 5.74 (1H, s, exchangeable); ^{13}C NMR (pyridine-d_5, 75 MHz) δ 18.9, 22.2, 22.3, 26.2, 26.8, 27.7, 29.8, 32.5, 32.8, 34.08, 34.13, 35.2, 37.9, 47.0, 59.7 (2C), 61.6, 62.7, 63.6, 87.7, 132.6, 134.1, 144.7, 146.5, 151.3, 154.6; Mass (ESI) *m*/*z* 503 (M$^+$ + Na), 463. Anal. Calcd for $C_{26}H_{40}O_4S_2$: C, 64.96; H, 8.39. Found: C, 65.21; H, 8.31.

9-Hydroxy-7-isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-fluorene-9-carbaldehyde (56). To a well-stirred solution of **54** (160 mg, 0.33 mmol) in CH_3CN-H_2O (1.2 mL, 5:1 v/v) was added CH_3I (0.2 mL, 3.3 mmol) and the mixture allowed to stir for another 10 h. After removal of solvent, the residue was taken in ether (25 mL), and the ether layer was washed successively with $Na_2S_2O_3$ (5%) and brine and dried. The ethereal part was concentrated and the crude product was purified by neutral alumina column chromatography (1% EtOAc in petroleum ether) to afford **56** (112 mg, 86%) as a white solid: mp 135−136 °C; IR (KBr) ν 3436, 2939, 1724, 1459, 1337, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (3H, s), 1.15 (3H, s), 1.19 (1H, bs), 1.27 (3H, d, J = 7.0 Hz), 1.33 (3H, d, J = 7.0 Hz), 1.69 (3H, s), 1.65−1.77 (2H, m, overlapped), 1.73−1.86 (2H, m), 2.01−2.06 (2H, m), 3.24 (1H, sept, J = 7.0 Hz), 3.55 (3H, s), 3.72 (1H, bs, exchangeable), 3.81 (3H, s), 3.86 (3H, s), 9.63 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 21.9 (2C), 25.0, 25.8, 31.3, 31.7, 34.0, 36.3, 36.7, 48.4, 59.0, 59.9, 60.0, 62.5, 89.2, 129.4, 133.9, 146.0, 147.0, 149.4, 155.1, 201.6; Mass (EI) *m*/*z* 390 (M$^+$), 374, 362, 361, 345, 331, 277, 263, 247, 237. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.01; H, 8.89.

7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene-9-carbaldehyde (57). The hydroxy aldehyde **56** (80 mg, 0.205 mmol) was fused with $KHSO_4$ (1 g) at 200−205 °C during 30 min. After cooling to room temperature, the solid residue was dissolved in water (2 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine, dried and concentrated. Column chromatography of the residue over silica gel (1% EtOAc in petroleum ether) afforded **57** (62.5 mg, 82%) as a white solid: mp 162−165 °C; IR (KBr) ν 2940, 1698, 1455, 1034 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, s), 1.21−1.31 (1H, m, overlapped), 1.31−1.38 (9H, three overlapped methyl signals), 1.46 (3H, s), 1.51−1.65 (3H, m), 1.85−1.89 (1H, m), 2.50 (1H, bd, J = 12.7 Hz), 3.36 (1H, sept, J = 7.0 Hz), 3.53 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 10.50 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 22.1 (2C), 22.9, 25.9, 26.6, 34.2, 35.1, 36.6, 42.7, 53.7, 60.0, 60.1, 62.5, 129.0, 133.6, 133.7, 143.8, 146.1, 146.7, 151.6, 162.1, 197.3; Mass (EI) *m*/*z* 373 (M$^+$ + 1), 372 (M$^+$), 343, 303, 275. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.08; H, 8.72.

7-Isopropyl-8-methoxy-1,1,4a-trimethyl-5,6-dioxo-2,3,4,4a,5,6-hexahydro-1*H*-fluorene-9-carbaldehyde (59). To a stirred solution of **57** (15 mg, 0.040 mmol) in THF−acetonitrile (0.45 mL, 2:1) at 0 °C was added a solution of CAN (55 mg, 0.10 mmol) in acetonitrile−water (0.45 mL, 1:2) dropwise and the mixture was stirred for 10 min. The solvent was removed and the residue was diluted with ethyl acetate (5 mL) and water (2 mL). The organic part was separated, and the aqueous part was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with brine, dried and concentrated. The crude product was purified by preparative TLC to give quinone **59** (3.6 mg, 26%, 54% based on recovery of **57**), as dark red colored sticky liquid along with the starting material **57** (7.6 mg, 51%). **Data for 59:** IR (CCl_4) ν 2928, 1699, 1645, 1459, 1385 cm^{-1}; UV (in EtOH) λ_{max} (ϵ) 474 (348), 342 (5345), 273 (5766), 211 (20622); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (3H, s), 1.26−1.31 (9H, three overlapped methyl signals), 1.47 (3H, s), 1.05−1.73 (4H, m, overlapped), 1.82−1.91 (1H, m), 2.42 (1H, bd, J = 12.9 Hz), 3.05 (1H, sept, J = 7.0 Hz), 3. 72 (3H, s), 10.31 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.4, 20.7, 20.9, 21.6, 25.9, 26.4, 34.2, 36.0, 38.1, 43.9, 56.5, 61.7, 134.0, 134.4, 145.8, 150.4, 160.7, 172.0, 176.9, 182.7, 194.7; Mass (ESI) *m*/*z* 365 (M$^+$ + Na), 343 (M$^+$ + 1). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.91; H, 7.79.

(±)-Taiwaniaquinone D (3). To a stirred mixture of **59** (3.4 mg, 0.01 mmol) and NaI (3 mg, 0.02 mmol) in dry CH_2Cl_2 (0.1 mL) at 0 °C was added a solution of TMSCl (15 μL, 0.12 mmol) in CH_2Cl_2 (0.1 mL) dropwise and the mixture was stirred for 1 h. One drop of methanol was added to the reaction mixture and allowed to stir for 30 min. The mixture was diluted with CH_2Cl_2 (1 mL) and water (1 mL). The organic part was separated out and the aqueous part was extracted twice with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were washed with 5% $NaHCO_3$, water and brine, dried, and concentrated. The product was purified by preparative TLC to give quinone **3** (2.3 mg, 71%) as a red gum: IR (CCl_4) ν 3363, 2921, 2852, 1700, 1639, 1315 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (3H, s), 1.21−1.24 (6H, two overlapped methyl signals), 1.32 (3H, s), 1.48 (3H, s), 1.67−1.75 (2H, m), 1.86−1.97 (1H, m), 2.44 (1H, br d, J = 13.0 Hz), 3.19 (1H, sept, J = 7.0 Hz), 7.21 (1H, s, exchangeable), 10.42 (1H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 18.3, 19.9, 21.4, 24.0, 25.7, 33.7, 35.3, 38.1, 43.4, 55.9, 123.2, 134.4, 147.2, 147.8, 152.2, 176.6, 177.3, 185.1, 194.1 (the 19.9 ppm signal may represent two carbon peaks as suggested for the natural product);[1b] Mass (ESI) *m*/*z* 351 (M$^+$ + Na). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.49; H, 7.48.

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Supporting Information Available: Scheme S1 (containing compounds **15**−**22**); experimental procedures for **13**, **15**, **17**−**25**, **28**−**37**, and **47**−**49**; alternative procedures for **5** and **56**; spectral data of **26** and **38**; ^{1}H and ^{13}C NMR spectra of compounds **12ab**, **27a**, **10**, **7**, **8**, **45**, **5**, **50**−**52**, **11**, **53**, **1**, **54**, **56**, **59**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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