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Synthesis of 5-*epi*-Taiwaniaquinone G

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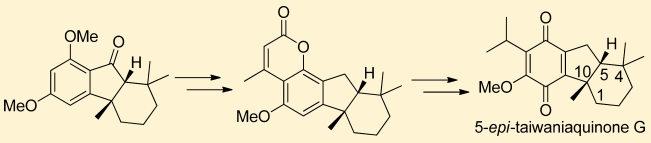
Supporting Information

ABSTRACT: A concise synthetic approach to the unnatural 5-*epi*-taiwaniaquinone G has been developed via a Lewis acid catalyzed tandem acylation−Nazarov cyclization reaction to construct the tricyclic skeleton, followed by installation of the isopropyl group through a strategy involving coumarin formation and its subsequent hydrolysis.



The taiwaniaquinoids **1**−**18**[1] (Figure 1) refer to a family of tricyclic diterpenoids possessing a [6,5,6]-*abeo*-abietane skeleton[2] that have been reported in the literature. Among these, the norditerpenoids taiwaniaquinol B (**2**), E (**5**), and F (**6**); taiwaniaquinone G (**13**) and H (**14**); dichroanone (**15**); dichroanal A (**16**) and B (**17**); and standishinal (**18**) have lost one carbon in the course of the biosynthesis. Although relatively little is known about the biological activities of this family of natural products, preliminary studies have revealed that the taiwaniaquinones A, D, and F and taiwaniaquinols A and C exhibit cytotoxic activity,[2f] and standishinal has shown aromatase inhibitory activity.[3]

Banerjee et al.[4] reported the first total synthesis of (±)-dichroanone and (±)-dichroanal B using a Pd(0)-catalyzed intramolecular reductive cyclization as the key step. Since then, many synthetic approaches have been developed for the total or formal synthesis of the taiwaniaquinoids.[5] The strategies for the construction of the tricyclic skeleton include domino acylation/alkylation reaction,[5a,f] intramolecular aldol condensation,[5d,k] sequential cationic cyclization,[5e,o] thermal 6π electrocyclization,[5g,h] intramolecular Friedel−Crafts alkylation,[5j] Lewis acid promoted cascade reaction,[5l] and intramolecular Heck cyclization.[5b,c,n] Trauner et al.[6] described a concise and convergent synthetic approach toward taiwaniaquinoids using a Nazarov cyclization reaction of the aryl vinyl ketone **20** to afford the *cis*-indane product **21** (Scheme 1). Starting from the known resorcinol derivative **19**,[5l,7] the Nazarov cyclization precursor **20** was synthesized following a sequence of reactions, viz., including regioselective bromination, halo-metal exchange, nucleophilic addition of the resulting organolithium to β-cyclocitral to provide the sensitive aryl vinyl carbinol intermediate, and the oxidation.

Recently, we have developed a tandem acylation−Nazarov cyclization approach for the synthesis of fused cyclopentenones by treatment of heteroaromatics (pyrrole, indole) with α,β-unsaturated carboxylic acids in the presence of TFAA and a suitable Lewis acid catalyst and successfully applied this highly efficient methodology to the syntheses of bioactive natural products.[8] Although Trauner[6] indicated that their attempts to produce compound **20** from **19** more directly via Friedel−Crafts acylation failed, we wondered whether our tandem reaction strategy could be adopted to generate **21** directly. However, when resorcinol derivative **19** was subjected to the β-cyclogeranic acid **22** under our optimized reaction conditions,[8] the desired cyclization product **21** was not obtained. Instead, the diketone **23** resulting from allylic oxidation of the acylation product **20** by the Lewis acid catalyst ($FeCl_3$, $ZnCl_2$) was isolated in 30% yield (Scheme 2). Attempt to cyclize **23** under Trauner's conditions[6] failed, probably because of the presence of the extra keto function, which destabilized the intermediate carbenium ion inhibiting Nazarov cyclization. We then treated the resorcinol dimethyl ether **24** with β-cyclogeranic acid **22** in the presence of TFAA and $ZnCl_2$. Delightfully, the reaction proceeded as expected and gave the thermodynamically more stable *cis*-tricyclic product **25** in 57% isolated yield. The relative stereochemistry of **25** was assigned by NOE correlations.

Next, we used **25** as precursor for further elaboration toward the synthesis of taiwaniaquinoids. The most proven literature method for the installation of the isopropyl group onto an aromatic ring involves nucleophilic addition of acetone on **26** with the aryllithium (Scheme 3), followed by reductive removal of the hydroxyl group of the resulting 2-arylisopropanol (e.g., **28** → **29**).[5h,j,l,7] To explore such a transformation, we prepared the tetrahydrofluorene derivative **26** from the tetrahydrofluorenone **25** via ketone reduction and acidic workup (Scheme 3). While the resorcinol dimethyl ether **24** could be successfully converted into **19** in 77% isolated yield,[5l,7] it was found that the reaction between the lithium salt of **26** (generated in situ by treatment with *n*-BuLi) and acetone failed and a large amount (>80%) of the unreacted **26** was recovered after stirring the reaction mixture at ambient temperature for 12 h. No improvement was observed by replacing TMEDA with HMPA or varying the reaction temperature, although a minor product 7-tetrahydrofluorenol derivative **27** (12%) was isolated

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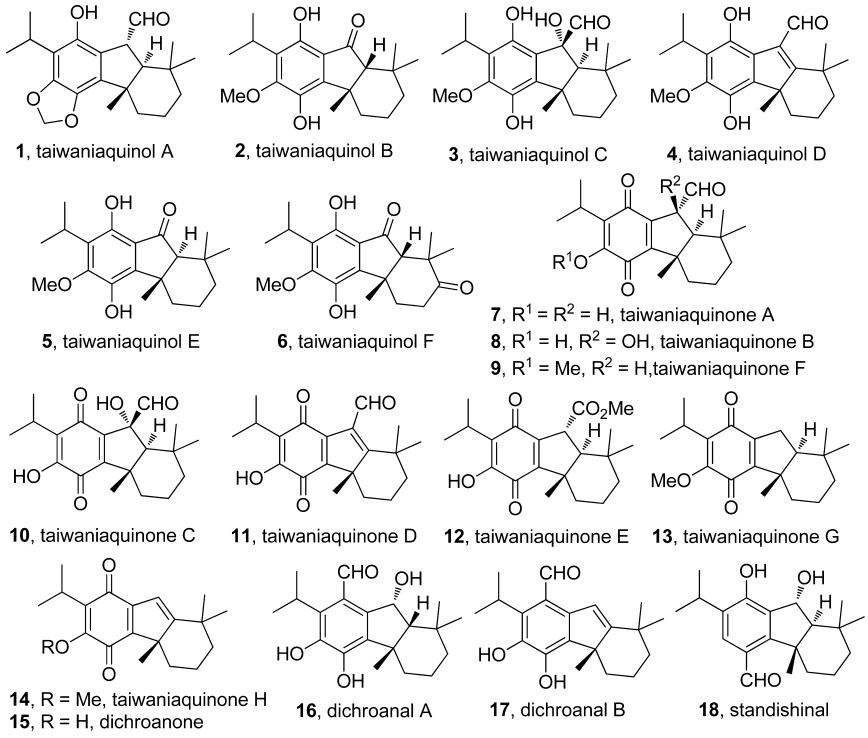
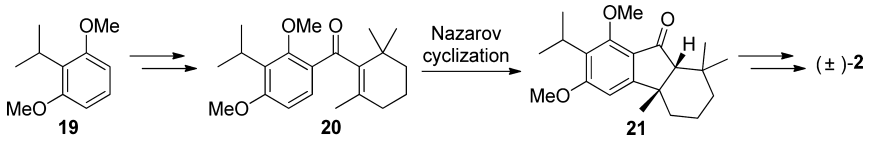
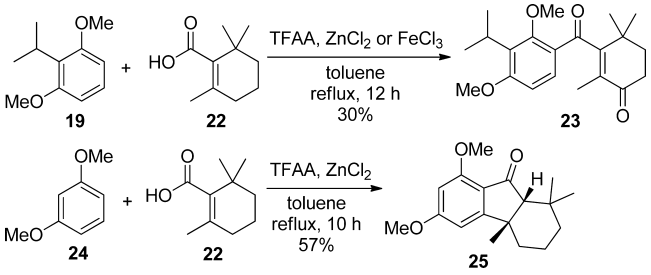


Figure 1. Taiwaniaquinoids.

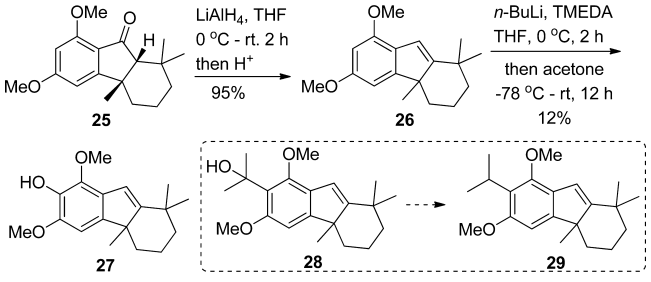
Scheme 1. Trauner's Nazarov Cyclization Approach to (±)-Taiwaniaquinol B 2



Scheme 2. Synthesis of the Diketone 23 and the Tricyclic Product 25



Scheme 3. Synthesis of the 7-Fluorenol Derivative 27



from the reaction, instead of the benzylic alcohol **28**. Attempts to react the lithium salt of **26** directly with 2-halopropane also failed.

Obviously, an alternative strategy for the introduction of the isopropyl group was necessary. Inspired by our recent findings that thymol analogues could be obtained by reductive hydrolysis of 4-methylcoumarins,[9] we decided to install the isopropyl group through coumarin formation. As shown in Scheme 4, selective deprotection of the methoxy group adjacent to the carbonyl group[5a,l,6] in **25** gave the tetrahydrofluorenone **30**, which was converted into tetrahydrofluorene **31** following the same procedure as that described for the synthesis of **26**. Attempted coumarin formation via a solvent-free Pechmann condensation[10] upon treatment of **31** with ethyl acetoacetate (EAA) catalyzed by methanesulfonic acid afforded a colorless solid, which was highly unstable, and a clean ^{1}H NMR spectrum could not be obtained. Therefore, the crude product was subjected to reductive hydrolysis without further purification. On treatment with KOH in ethylene glycol,[9] the diene **32** (with methyl group migration) was obtained in 18% isolated yield over the two steps. The yield could be improved to 40% by changing the solvent to a mixture of DMSO and water (5:1). We believed that migration of the methyl group occurred during the coumarin formation (either before or after coumarin formation) rather than the hydrolysis step, and a mechanism was proposed in Scheme 5. Protonation of the double bond in I provided the carbenium ion II. Methyl group migration generated the more stable benzylic cation III, which lost a proton to give IV. Although the desired reduction of the isopropenyl double bond did not occur, hydrogenation of both double bonds in **32** gave **33** in almost quantitative yield.

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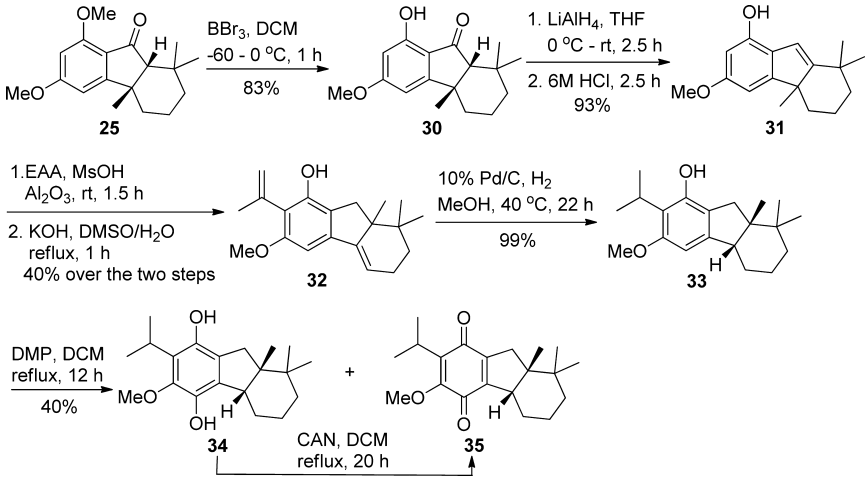
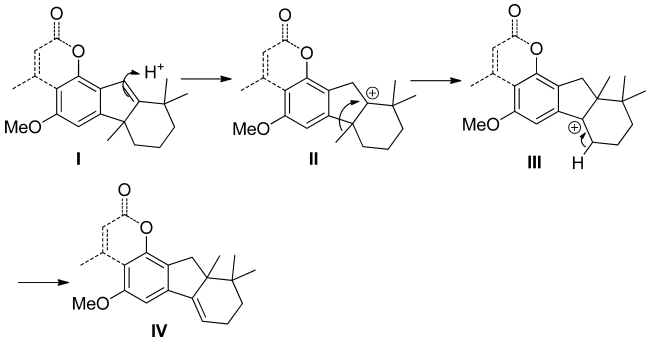
Scheme 4. Synthesis of an Isomer 35 of Taiwaniaquinone G



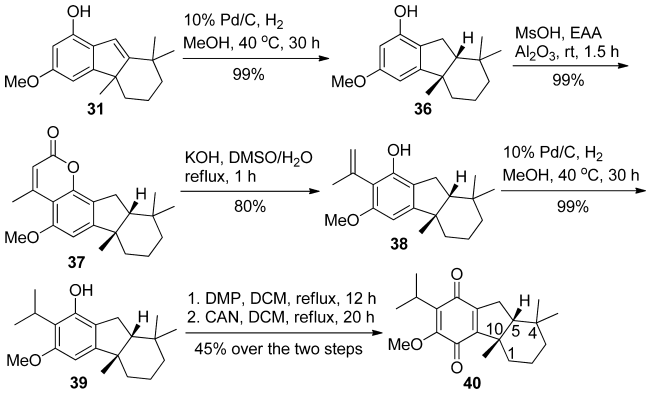
Scheme 5. Proposed Mechanism for Methyl Group Migration



Oxidation of **33** with Dess–Martin periodinane (DMP) yielded an inseparable mixture of the hydroquinone **34** and quinone **35** (an isomer of taiwaniaquinone G) in a ratio of 1:10. Treatment of this crude mixture with CAN afforded **35** in 35% isolated yield. It should be indicated that direct oxidation of **33** with CAN[4,5a,f,l,o,6] or HNO_3[5b,n] mainly resulted in nitration of the aromatic ring.

Next, in order to prevent the methyl group migration, the tetrahydrofluorene derivative **31** was hydrogenated to the hexahydrofluorene **36** prior to coumarin formation (Scheme 6). It was possible to convert tetrahydrofluorenone derivative **30** directly into **36** via Wolff–Kishner or Clemmensen reduction, but neither of the reactions proceeded cleanly to afford **36** in any respectable yield. The relative stereochemistry of **36** was assigned as cis on the basis of NOE correlations. Pechmann condensation with EAA provided coumarin derivative **37** as a stable product that could be isolated, fully characterized, and stored at ambient temperature for more than 1 month. Hydrolysis of the coumarin moiety, followed by hydrogenation of the double bond in **38**, provided **39** in good yield. Finally, two-step oxidation of **39** as described for the synthesis of **35** furnished 5-*epi*-taiwaniaquinone G (**40**), the spectroscopic data of which were identical to those previously reported in the literature.[5m]

Scheme 6. Total Synthesis of the 5-*epi*-Taiwaniaquinone G (40)



In summary, we have developed a facile synthetic route to 5-*epi*-taiwaniaquinone G. The key steps involve a tandem acylation–Nazarov cyclization reaction to construct the tricyclic skeleton and a subsequent coumarin formation–hydrolysis strategy for the introduction of the isopropyl group onto the aromatic ring.

■ EXPERIMENTAL SECTION

Solvents were dried according to standard procedures[11] where needed. Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using an FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. Mass spectra were recorded on a Q-TOF micro spectrometer. Flash column chromatography was performed over silica gel 200–300 mesh. *β*-Cyclogeranic acid **22** was synthesized following known literature procedures[12] by oxidation of the commercially available *β*-cyclocitral.

3-(3′-Isopropyl-2′,4′-dimethoxybenzoyl)-2,4,4-trimethylcyclohex-2-enone (23). To a solution of 2-isopropyl-1,3-dimethoxybenzene **19** (180 mg, 1.0 mmol), *β*-cyclogeranic acid **22** (201 mg, 1.2 mmol), and TFAA (340 mg, 1.6 mmol) in dry toluene (14 mL) was added $ZnCl_2$ (231 mg, 1.1 mmol). The resulting mixture was heated at reflux for 12 h, and then cooled. Saturated aqueous $NaHCO_3$ was added until a pH of 8–9 was reached. The separated organic layer was washed with brine (3 × 5 mL) and then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (14% ethyl acetate in petroleum ether) to give **23** (99 mg, 30%) as an orange oil; IR (neat): ν_{max} = 1730, 1672, 1584, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, 1H, J = 8.9 Hz), 6.67 (d, 1H, J = 8.9 Hz), 3.89 (s, 3H), 3.80 (s, 3H), 3.60 (hept, 1H, J = 7.0 Hz), 2.63 (t, 2H, J = 6.8 Hz), 2.00 (t, 2H, J = 6.8 Hz), 1.63 (s, 3H), 1.32 (d, 6H, J = 7.0 Hz), 1.22 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 195.6, 164.4, 162.7, 159.9, 133.1,

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131.3, 129.1, 122.9, 106.7, 62.4, 55.6, 38.3, 35.4, 34.5, 27.6, 25.0, 20.9, 13.5 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{29}O_4$: 345.2066 $[M + H]^+$; found 345.2063.

2,3,4,4*a*-Tetrahydro-6,8-dimethoxy-1,1,4*a*-trimethyl-1*H*-fluoren-9(9*aH*)-one (25). To a solution of resorcinol dimethyl ether **24** (0.75 g, 5.41 mmol), β-cyclogeranic acid **22** (1.0 g, 5.95 mmol), and TFAA (2.83 g, 13.47 mmol) in dry toluene (25 mL) was added $ZnCl_2$ (810 mg, 5.95 mmol). The resulting mixture was heated at reflux for 10 h, and then cooled. Saturated aqueous $NaHCO_3$ was added until a pH of 8−9 was reached. The separated aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (2 × 20 mL) and then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (17% ethyl acetate in petroleum ether) to give **25** (0.89 g, 57%) as a colorless solid; mp 107−108 °C; IR (KBr): ν_{max} = 1679, 1641, 1593, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.44 (d, 1H, J = 1.9 Hz), 6.29 (d, 1H, J = 1.9 Hz), 3.90 (s, 3H), 3.89 (s, 3H), 2.12 (s, 1H), 2.09 (m, 1 H), 1.63−1.55 (m, 2H), 1.48−1.30 (m, 3H), 1.24 (s, 3H), 1.21 (s, 3H), 0.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6, 166.99, 166.7, 159.2, 118.2, 98.4, 96.9, 66.0, 55.9, 55.7, 41.6, 38.8, 34.8, 33.9, 33.3, 32.3, 24.5, 18.5 ppm; HRMS (ESI): m/z calcd for $C_{18}H_{25}O_3$: 289.1804 $[M + H]^+$; found 289.1805.

2,3,4,4*a*-Tetrahydro-6,8-dimethoxy-1,1,4*a*-trimethyl-1*H*-fluorene (26). To an ice-cooled solution of **25** (307 mg, 1.06 mmol) in dry THF (20 mL) under N_2 was added $LiAlH_4$ (121 mg, 3.18 mmol). The resulting mixture was stirred at 0 °C for 0.5 h before being allowed to warm to ambient temperature and stirred for a further 1.5 h and was then cooled to 0 °C again. The reaction was quenched with 6 M aqueous HCl until a pH of 1−2 was reached. The bulk of THF was evaporated in vacuo. The residue was partitioned between ethyl acetate (20 mL) and brine (50 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered. and evaporated in vacuo. The residue was purified by column chromatography on silica gel (3% ethyl acetate in petroleum ether) to give **26** (275 mg, 95%) as a colorless oil; IR (neat): ν_{max} = 1600, 1576, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.46 (d, 1H, J = 1.7 Hz), 6.44 (s, 1H), 6.34 (d, 1H, J = 1.7 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 2.07 (m, 1H), 1.94 (qt, 1H, J = 13.8, 3.5 Hz), 1.64−1.56 (m, 2H), 1.34 (s, 3H), 1.29 (s, 3H), 1.22 (s, 3H), 1.09 (td, 1H, J = 13.2, 4.2 Hz), 0.99 (td, 1H, J = 13.2, 3.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5, 159.1, 158.3, 153.1, 123.4, 116.2, 99.4, 96.5, 55.8, 55.5, 51.7, 43.0, 38.3, 35.6, 31.4, 25.7, 23.8, 20.0 ppm; HRMS (ESI): m/z calcd for $C_{18}H_{25}O_2$: 273.1855 $[M + H]^+$; found 273.1851.

2,3,4,4*a*-Tetrahydro-6,8-dimethoxy-1,1,4*a*-trimethyl-1*H*-fluoren-7-ol (27). To an ice-cooled solution of **26** (1.0 g, 3.7 mmol) and TMEDA (0.76 mL, 5.1 mmol) in dry THF (30 mL) under N_2 was added *n*-BuLi (1.6 M solution in hexane, 3.2 mL, 5.1 mmol). The resulting mixture was stirred at 0 °C for 2 h before being cooled to −78 °C. Acetone (0.43 g, 7.4 mmol) was added dropwise. After addition, the mixture was stirred for 12 h without further cooling. The reaction was quenched with iced-cooled water (20 mL). The bulk of THF was evaporated in vacuo. The residue was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (17% ethyl acetate in petroleum ether) to give **27** (128 mg, 12%) as a colorless solid, mp 119−120 °C; IR (KBr): ν_{max} = 3508, 1607, 1576, 1489, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1H), 6.44 (s, 1H), 5.49 (*br.* s, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 2.06 (m, 1H), 1.93 (qt, 1H, J = 13.7, 3.5 Hz), 1.66−1.59 (m, 2H), 1.33 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H), 1.10 (td, 1H, J = 13.2, 4.2 Hz), 0.97 (td, 1H, J = 13.2, 3.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 147.3, 145.4, 140.2, 136.5, 126.6, 116.6, 100.9, 61.2, 56.8, 51.2, 42.9, 38.7, 35.7, 31.4, 25.5, 24.1, 20.0 ppm; HRMS (ESI): m/z calcd for $C_{18}H_{25}O_3$: 289.1804 $[M + H]^+$; found 289.1800.

2,3,4,4*a*-Tetrahydro-8-hydroxy-6-methoxy-1,1,4*a*-trimethyl-1*H*-fluoren-9(9*aH*)-one (30). To a solution of **25** (1.27 g, 4.4 mmol) in dry DCM (35 mL) at −60 °C under N_2 was added BBr_3 (1.0 M solution in DCM, 4.8 mL, 4.8 mmol). After addition, the mixture was stirred at −60 °C for 0.5 h before being allowed to warm to 0 °C and stirred for a further 0.5 h. The reaction was quenched with ice-cooled water (20 mL). The separated organic layer was washed with brine (50 mL) and then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (11% ethyl acetate in petroleum ether) to give **30** (1.0 g, 83%) as a colorless solid; mp 83−84 °C; IR (KBr): ν_{max} = 3365, 1668, 1621, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 6.37 (d, 1H, J = 1.9 Hz), 6.25 (d, 1H, J = 1.9 Hz), 3.84 (s, 3H), 2.17 (s, 1H), 1.96 (m, 1H), 1.68−1.61 (m, 2H), 1.51 (m, 1H), 1.39−1.35 (m, 2H), 1.29 (s, 3H), 1.23 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 167.8, 164.8, 159.2, 115.6, 100.8, 98.7, 65.3, 55.9, 43.0, 37.9, 34.2, 33.2, 33.0, 32.6, 24.5, 18.2 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{23}O_3$: 275.1647 $[M + H]^+$; found 275.1644.

2,3,4,4*a*-Tetrahydro-6-methoxy-1,1,4*a*-trimethyl-1*H*-fluoren-8-ol (31). To an ice-cooled solution of **30** (1.0 g, 3.64 mmol) in dry THF (25 mL) under N_2 was added $LiAlH_4$ (415 mg, 10.93 mmol). The resulting mixture was stirred at 0 °C for 0.5 h before being allowed to warm to ambient temperature and stirred for a further 2 h. 6 M aqueous HCl was added until a pH of 1−2 was reached. The mixture was stirred vigorously for 2.5 h. The bulk of THF was evaporated in vacuo. The residue was extracted with ethyl acetate (5 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (17% ethyl acetate in petroleum ether) to give **31** (875 mg, 93%) as a colorless solid; mp 137−139 °C; IR (KBr): ν_{max} = 3303, 1631, 1597, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.46 (d, 1H, J = 2.0 Hz), 6.38 (s, 1H), 6.27 (d, 1H, J = 2.0 Hz), 5.09 (*br.* s, 1H), 3.77 (s, 3H), 2.07 (m, 1 H), 1.94 (qt, 1H, J = 13.7, 3.4 Hz), 1.66−1.58 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 1.10 (td, 1H, J = 13.4, 4.3 Hz), 1.00 (td, 1H, J = 13.2, 3.7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 158.9, 158.8, 148.8, 121.7, 115.1, 101.1, 99.6, 55.8, 51.7, 42.9, 38.3, 35.6, 31.4, 25.7, 23.9, 19.9 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{23}O_2$: 259.1698 $[M + H]^+$; found 259.1687.

2,3,9,9*a*-Tetrahydro-6-methoxy-1,1,9*a*-trimethyl-7-(prop-1′-en-2′-yl)-1*H*-fluoren-8-ol (32). A mixture of **31** (271 mg, 1.05 mmol), Al_2O_3 (214 mg, 2.10 mmol), ethyl acetoacetate (0.27 mL, 2.10 mmol), and methanesulfonic acid (1.5 mL) was stirred at ambient temperature for 1.5 h. Saturated aqueous $NaHCO_3$ was added until no bubbling. The mixture was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was dissolved in DMSO (10 mL). Aqueous KOH (1.5 M, 2 mL) was added. The resulting mixture was heated at reflux for 1 h and cooled. Then, 6 M aqueous HCl was added until a pH of 4−5 was reached. The mixture was extracted with diethyl ether (5 × 15 mL). The combined organic extracts were washed with brine (3 × 5 mL) and then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (2% ethyl acetate in petroleum ether) to give **32** (140 mg, 40%) as an orange oil; IR (KBr): ν_{max} = 3500, 1611, 1563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.68 (s, 1 H), 6.01 (m, 1 H), 5.81 (s, 1 H), 5.49 (s, 1 H), 5.09 (s, 1 H), 3.81 (s, 3 H), 2.63−2.44 (m, 4 H), 2.07 (s, 3 H), 2.05−1.99 (m, 1 H), 1.59 (m, 1 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.81 (s, 3 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 150.3, 146.8, 141.4, 131.6, 121.3, 117.6, 116.8, 115.3, 98.4, 55.6, 51.8, 36.7, 34.6, 32.4, 30.6, 24.9, 24.7, 23.5, 20.5 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{27}O_2$: 299.2011 $[M + H]^+$; found 299.2007.

2,3,4,4*a*,9,9*a*-Hexahydro-7-isopropyl-6-methoxy-1,1,9*a*-trimethyl-1*H*-fluoren-8-ol (33). A mixture of **32** (140 mg, 0.47 mmol), 10% Pd/C (56 mg), and methanol (4 mL) was hydrogenated (6 atm) at 45 °C for 22 h. The catalyst was filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (1% ethyl acetate in petroleum ether) to give **33** (140 mg, 99%) as a colorless solid; mp 65−66 °C; IR (KBr): ν_{max}= 3459, 1611, 1582, 1489, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.25 (s, 1H), 4.65 (s, 1H), 3.75 (s, 3H), 3.47 (hept, 1H, J = 7.2 Hz); 2.75 (dd, 1H, J = 7.8, 2.8 Hz), 2.47 (d, 1H, J = 15.6 Hz), 2.30 (m, 1H), 2.19 (d, 1H, J = 15.6 Hz), 1.77−

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1.42 (m, 5H), 1.32 (d, 6H, J = 7.2 Hz), 1.04 (s, 3H), 1.02 (s, 3H), 0.86 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 151.4, 140.3, 118.4, 114.5, 103.5, 55.6, 48.8, 47.4, 34.9, 34.5, 33.9, 26.3, 24.9, 24.5, 22.8, 22.7, 21.2, 21.1 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{31}O_2$: 303.2324 $[M + H]^+$; found: 303.2322.

5,6,7,8,8*a*,9-Hexahydro-2-isopropyl-3-methoxy-8,8,8*a*-trimethyl-1*H*-fluorene-1,4(4*bH*)-dione (35). To a solution of **33** (73 mg, 0.24 mmol) in dry DCM (5 mL), was added Dess−Martin periodinane (213 mg, 0.48 mmol). The resulting mixture was heated at reflux for 12 h. CAN (266 mg, 0.48 mmol) was added, and the mixture was refluxed for a further 20 h and cooled. The bulk of solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (1% ethyl acetate in petroleum ether) to give **35** (27 mg, 35%) as a yellow oil; IR (KBr): ν_{max} = 1737, 1651, 1609, 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3H), 3.23 (hept, 1H, J = 7.1 Hz); 2.70 (dt, 1H, J = 9.1, 4.5 Hz), 2.38 (dd, 1H, J = 19.0, 1.4 Hz), 2.33 (m, 1H), 2.22 (dd, 1H, J = 19.0, 3.0 Hz); 1.71−1.28 (m, 5H), 1.21 (d, 3H, J = 7.1 Hz), 1.20 (d, 3H, J = 7.1 Hz), 1.01 (s, 3H), 1.00 (s, 3H); 0.81(s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.1, 184.4, 156.1, 144.4, 139.7, 137.3, 61.1, 47.5, 43.7, 34.6, 34.5, 34.4, 31.9, 25.4, 24.8, 24.4, 23.0, 22.2, 20.8, 20.7 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{29}O_3$: 317.2117 $[M + H]^+$; found: 317.2118.

2,3,4,4*a*,9,9*a*-Hexahydro-6-methoxy-1,1,4*a*-trimethyl-1*H*-fluoren-8-ol (36). A mixture of **31** (258 mg, 1.0 mmol), 10% Pd/C (104 mg), and methanol (4 mL) was hydrogenated (4 atm) at 40 °C for 30 h. The catalyst was filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (11% ethyl acetate in petroleum ether) to give **36** (259 mg, 99%) as a colorless solid; mp 112−113 °C; IR (KBr): ν_{max} = 3395, 1607, 1506, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (d, 1H, J = 2.1 Hz), 6.21 (d, 1H, J = 2.1 Hz), 4.70 (*br.* s, 1H), 3.76 (s, 3H), 2.71 (dd, 1H, J = 14.7, 7.8 Hz), 2.54 (dd, 1H, J = 14.7, 10.8 Hz), 1.87 (dd, J = 10.8, 7.8 Hz, 1H), 1.58 (m, 1H), 1.46−1.34 (m, 6H), 1.29 (m, 1H), 1.21 (m, 1H), 1.11 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 157.8, 152.3, 118.2, 100.4, 98.9, 57.6, 55.6, 46.0, 36.2, 35.3, 32.2, 31.0, 29.6, 28.9, 25.7, 19.0 ppm; HRMS (ESI): m/z calcd for $C_{17}H_{25}O_2$: 261.1855 $[M + H]^+$; found 261.1851.

7,8,9,10,10*a*,11-Hexahydro-5-methoxy-4,6*b*,10,10-tetramethylindeno[1,2-*h*]chromen-2(6*bH*)-one (37). A mixture of **36** (50 mg, 0.19 mmol), Al_2O_3 (39 mg, 0.38 mmol), ethyl acetoacetate (76 mg, 0.58 mmol), and methanesulfonic acid (2 mL) was stirred at ambient temperature for 1.5 h. Saturated aqueous $NaHCO_3$ was added until no bubbling. The mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (11% ethyl acetate in petroleum ether) to give **37** (64 mg, 99%) as a colorless solid; mp 103−105 °C; IR (KBr): ν_{max} = 1727, 1621, 1602, 1473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (s, 1H), 6.02 (s, 1H), 3.89 (s, 3H), 3.04 (dd, 1H, J = 15.8, 8.0 Hz), 2.71 (dd, 1H, J = 15.8, 10.8 Hz), 2.55 (s, 3H), 1.89 (dd, 1H, J = 10.8, 8.0 Hz), 1.62−1.20 (m, 9H), 1.12 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 159.8, 157.9, 155.0, 151.3, 120.5, 113.1, 108.9, 100.0, 57.3, 56.0, 46.7, 36.1, 35.2, 32.2, 30.8, 29.7, 29.5, 25.6, 24.7, 18.9 ppm; HRMS (ESI): m/z calcd for $C_{21}H_{27}O_3$: 327.1960 $[M + H]^+$; found 327.1957.

2,3,4,4*a*,9,9*a*-Hexahydro-6-methoxy-1,1,4*a*-trimethyl-7-(prop-1′-en-2′-yl)-1*H*-fluoren-8-ol (38). A mixture of **37** (225 mg, 0.69 mmol), KOH (194 mg, 3.45 mmol), DMSO (10 mL), and H_2O (2 mL) was heated at reflux for 1 h and cooled. Then, 6 M aqueous HCl was added until a pH of 2−3 was reached. The mixture was extracted with ethyl acetate (5 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL) and then dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (2% ethyl acetate in petroleum ether) to give **38** (167 mg, 80%) as a colorless solid; mp 52−54 °C; IR (KBr): ν_{max} = 3499, 3477, 1622, 1581 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (s, 1H), 5.71 (s, 1H), 5.46 (s, 1H), 5.05 (s, 1H), 3.80 (s, 3H), 2.81 (dd, 1H, J = 15.2, 8.0 Hz), 2.59 (dd, 1H, J = 15.2, 11.0 Hz), 2.06 (s, 3H), 1.86 (dd, 1H, J = 11.0, 8.0 Hz), 1.61 (m, 1H), 1.47−1.37 (m, 6H), 1.30−1.19 (m, 2H), 1.12 (s, 3H), 0.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 155.8, 148.1, 141.4, 118.6, 117.4, 115.9, 96.6, 57.6, 56.0, 46.0, 36.4, 35.2, 32.3, 31.2, 29.9, 29.6, 25.5, 23.5, 19.1 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{29}O_2$: 301.2168 $[M + H]^+$; found 301.2164.

2,3,4,4*a*,9,9*a*-Hexahydro-7-isopropyl-6-methoxy-1,1,4*a*-trimethyl-1*H*-fluoren-8-ol (39). A mixture of **38** (300 mg, 1.0 mmol), 10% Pd/C (120 mg), and methanol (4 mL) was hydrogenated (6 atm) at 40 °C for 30 h. The catalyst was filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (3% ethyl acetate in petroleum ether) to give **39** (300 mg, 99%) as a colorless solid; mp 79−80 °C; IR (KBr): ν_{max} = 3424, 1619, 1587, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (s, 1H), 4.48 (s, 1H), 3.78 (s, 3H), 3.49 (hept, 1H, J = 7.1 Hz), 2.65 (dd, 1H, J = 14.3, 8.0 Hz), 2.52 (dd, 1H, J = 14.3, 10.8 Hz), 1.87 (dd, 1H, J = 10.8, 8.0 Hz), 1.60 (m, 1H), 1.46−1.30 (m, 13H), 1.19 (m, 1H), 1.11 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.4, 150.5, 119.8, 118.4, 97.9, 57.6, 56.1, 46.0, 36.5, 35.2, 32.3, 31.3, 29.5, 29.2, 25.5, 24.5, 21.1, 21.1, 19.0 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{31}O_2$: 303.2324 $[M + H]^+$; found 303.2320.

5,6,7,8,8*a*,9-Hexahydro-2-isopropyl-3-methoxy-4*b*,8,8-trimethyl-1*H*-fluorene-1,4(4*bH*)-dione (40). To a solution of **39** (40 mg, 0.13 mmol) in dry DCM (8 mL) was added Dess−Martin periodinane (120 mg, 0.26 mmol). The resulting mixture was heated at reflux for 12 h. CAN (142 mg, 0.26 mmol) was added, and the mixture was refluxed for a further 20 h and cooled. The bulk of solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (3% ethyl acetate in petroleum ether) to give 5-*epi*-taiwaniaquinone G **40** (19 mg, 45%) as a yellow oil; IR (neat): ν_{max} = 1648, 1592, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 3.20 (hept, 1H, J = 7.0 Hz), 2.65 (dd, 1H, J = 18.0, 8.2 Hz), 2.36 (dd, 1H, J = 18.0, 11.4 Hz), 1.89 (m, 1H), 1.74 (dd, 1H, J = 11.4, 8.2 Hz), 1.52 (s, 3H), 1.46−1.40 (m, 2H), 1.30−1.28 (m, 3H), 1.21 (d, 3H, J = 7.0 Hz), 1.19 (d, 3H, J = 7.0 Hz), 1.08 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 182.8, 156.7, 152.6, 146.3, 136.9, 61.2, 55.1, 48.1, 35.1, 34.4, 31.9, 31.2, 31.1, 29.6, 24.6, 24.4, 20.8, 20.7, 18.1 ppm; HRMS (ESI): m/z calcd for $C_{20}H_{29}O_3$: 317.2117 $[M + H]^+$; found 317.2113.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **23**, **25**−**27**, **30**−**33**, and **35**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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