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Total Synthesis of (±)-Taiwaniaquinol F and Related Taiwaniaquinoids

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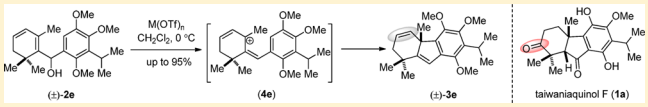
Supporting Information

ABSTRACT: Total synthesis of (±)-taiwaniaquinol F (**1a**) has been accomplished via an efficient Lewis acid-catalyzed Nazarov-type cyclization of aryldiallylcarbinols (±)-**2e** derived from safranal **7**. The methodology works under mild conditions using only 2 mol % of metal triflate as catalyst to afford a previously unknown carbotricyclic core sharing an olefin functionality in excellent yield. The aforementioned methodology also offers enough flexibility to complete the total syntheses of various taiwaniaquinoids, including (±)-taiwaniaquinone H (**1d**), (±)-dichroanone (**1e**), (±)-5-*epi*-taiwaniaquinone G (*ent*-**1h**), and (±)-taiwaniaquinol B (**1b**).



INTRODUCTION

Taiwaniaquinoids (**1a**–**k**, Figure 1)[1] are a family of unusual diterpenoids possessing a [6,5,6]-*abeo*-abietane skeleton sharing an all-carbon quaternary stereocenter at the pseudobenzylic position. Most of these diterpenoids have been isolated since 1995 from *Taiwania cryptomerioides* Hayata (Taxodiaceae) of the central mountains of Taiwan independently by Cheng[2] and Kuo,[3] from *Salvia dichroantha* Stapf (Lamiaceae), a Turkish flowering sage by Kawazoe,[4] and from *Thuja standishii* (Cupressaceae), a Japanese conifer by Tanaka.[5] Reportedly, a few members of taiwaniaquinoids are found to exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells,[3b] and one of the members, standishinal (**1i**), has shown aromatase inhibitory activity.[6] Because of their diverse biological profiles and uncommon structural features, taiwaniaquinoids have gained extensive attention from the synthetic community leading to numerous efficient approaches.

The approaches to taiwaniaquinoids include Pd(0)-catalyzed intramolecular reductive cyclization by Banerjee,[7] a domino intramolecular acylation carbonyl α-*tert*-alkylation reaction by Fillion,[8] intramolecular Heck cyclization by Node,[9] Nazarov cyclization by Trauner,[10] tandem acylation–Nazarov cyclization reaction by Chiu,[11] acid promoted Friedel–Crafts acylation/alkylation approach independently by She[12] and Cheng,[13] intramolecular cyclization of aryldienes independently by Balme,[14] Alvarez-Manzaneda,[15] and Majetich (Scheme 1),[16] ring contraction from abietane diterpenoids by Li,[17] our Friedel–Crafts alkylations to set all-carbon quaternary center (Scheme 1),[18] thermal ring expansion/4π-electrocyclization by Hu,[19] and other approaches.[20] Asymmetric syntheses include enantioselective decarboxylative allylation by Stoltz,[21] enantiospecific thermal 6π-electrocyclization by Alvarez-Manzaneda,[22] enantioselective Heck reaction by Node,[23] ring contraction of abietane diterpenoids by Gademann,[24] semisynthesis involving cleavage of the C7–C8 double bond of abietane diterpenes by Alvarez-Manzaneda,[25] iridium-catalyzed borylation and palladium-catalyzed asymmetric α-arylation by Hartwig,[26] and recent Pd(0)-catalyzed enantioselective conjugate addition of arylboronic acid by Stoltz.[27,28] All of these syntheses mainly concentrate on taiwaniaquinoids comprising a saturated *gem*-dimethyl cyclohexane ring system (A ring of **1a**–**k**). However, there is no report on taiwaniaquinoids with various oxidation patterns of the A-ring, such as (±)-taiwaniaquinol F (**1a**) until today, mainly due to difficulty functionalizing the A-ring.

We envisioned that the carbotricyclic core of type (±)-**3** (Scheme 1), having an olefin functionality at the A-ring, could be an advanced intermediate to access various oxidized variants of taiwaniaquinoids (**1a**). Herein, we report the synthesis of carbotricycle (±)-**3** by Lewis acid-catalyzed Nazarov-type cyclization and its application to a protecting-group-free first total synthesis of (±)-taiwaniaquinol F (**1a**).

RESULTS AND DISCUSSION

For our study, arylvinylcarbinol (±)-**2a**/**b** was synthesized by 1,2-addition of the aryllithium corresponding to aryl bromides **6a** or **6b** to safranal **7** (Scheme 2). Having the key intermediate aryldivinylcarbinol (±)-**2a** in hand, the stage was set for cyclization to **3a**. At the outset, we examined Nazarov-type cyclization of (±)-**2a** using various Lewis acids in different solvents to affect the synthesis of carbotricyclic structure (±)-**3a** (Table 1).

Initially, the Nazarov-type cyclization of (±)-**2a** was carried out using 5 mol % of $Bi(OTf)_3$ using different solvents (entries 1–6, Table 1), and it was found that dichloromethane was preferred and afforded (±)-**3a** in 99% isolated yield at 0 °C in just 5 min (entry 5). It is important to note that inert atmosphere is not required for efficient reaction. The use of 5 mol % of metal triflates such as $Cu(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$, $Nd(OTf)_3$, or

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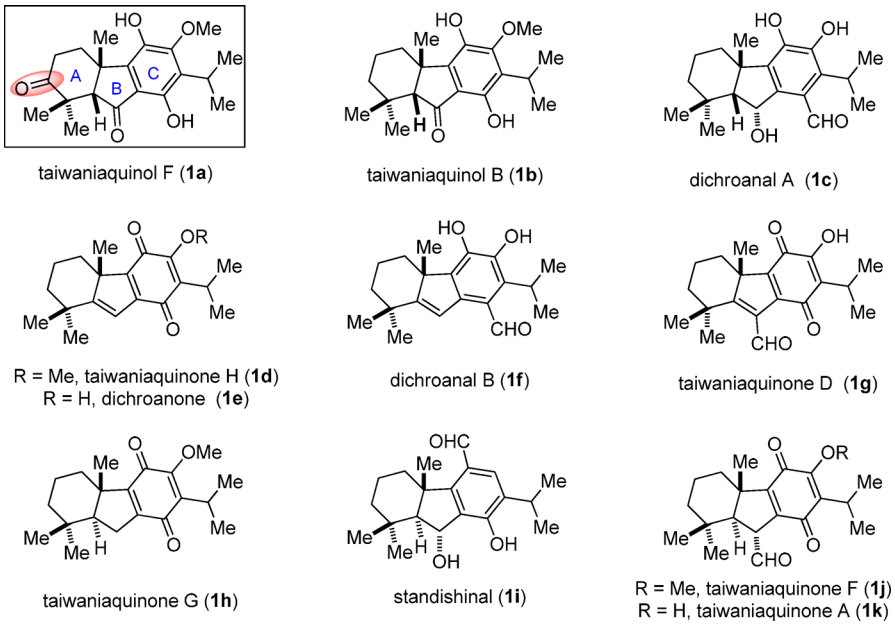
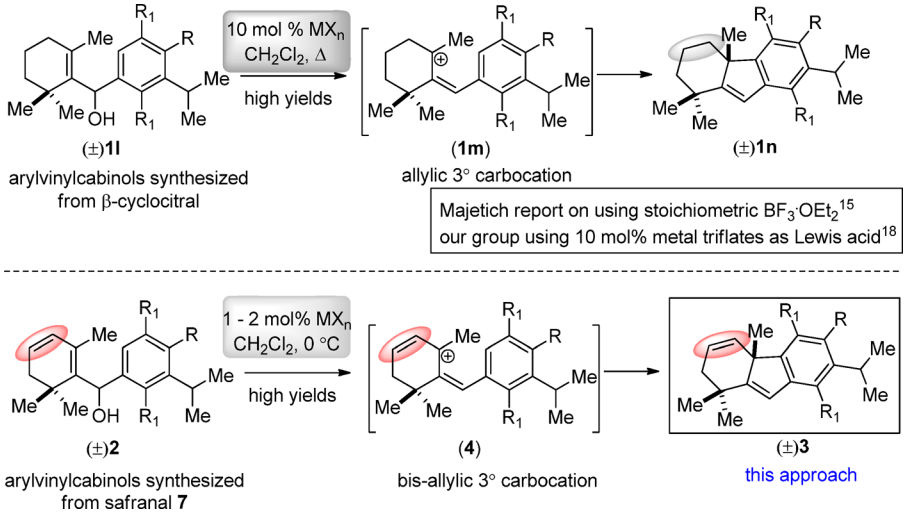
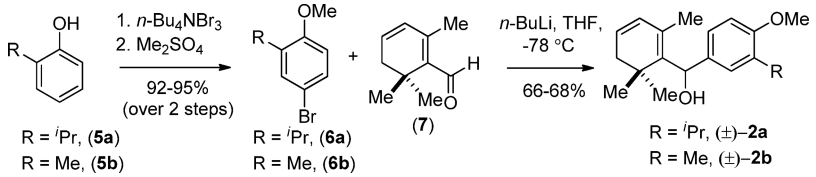


Figure 1. Selected taiwaniaquinoids (**1a**–**k**).

Scheme 1. Our Approach to Taiwaniaquinoids



Scheme 2. Synthesis of Arylvinylcarbinol (±)-2a



$Sn(OTf)_2$ afforded (±)-**3a** in 87, 71, 62, 64, 74, 55, 67, and 98% isolated yields, respectively (entries 7–14). Interestingly, we found that 2 mol % of $Bi(OTf)_3$ and $Sn(OTf)_2$ (entries 16 and 17) are equally efficient at furnishing carbotricycle (±)-**3a** in 98 and 93% isolated yields, respectively. The high reactivity of (±)-**2a** is presumably due the formation of the tertiary bis-allyic carbocation **4a** during the course of the reaction. Gratifyingly, 1 mol % of $Bi(OTf)_3$ and $Sn(OTf)_2$ also afforded cyclization products in 94 and 62% isolated yields, respectively (entries 18 and 19). Significantly, the reaction is highly regioselective, involving only the aryl carbon para to the *i*-Pr group and affording only (±)-**3a**; presumably, involvement of the aryl carbon ortho to *i*-Pr group is disfavored due to severe steric crowding. On the basis of our optimization studies, we further choose 2 mol % of each $Bi(OTf)_3$ (condition **A**) and $Sn(OTf)_2$ (condition **B**) for further substrate scope.

Aryldivinyl carbinols (±)-**2b**–**d** were then subjected to our optimized conditions to access carbotricyclic cores (±)-**3b**–**d**, and the results are shown in Scheme 3. We found that the arylvinyl carbinols (±)-**2a**–**c**, containing electron-donating

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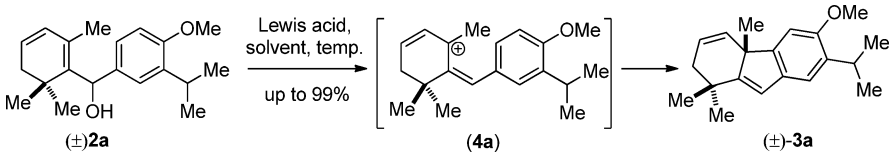
Table 1. Selected Optimization of the Nazarov-Type Reaction of 2a

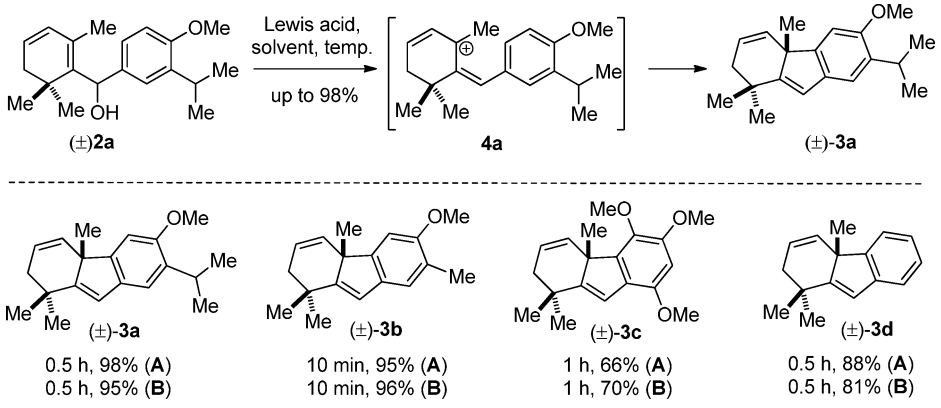


(±)**2a** (**4a**) (±)-**3a**

no.	Lewis acid (mol %)	solvent	temp	time	% yield (**3**)[a]
1	5 mol % $Bi(OTf)_3$	Et_2O	25 °C	3 h	51%[b]
2	5 mol % $Bi(OTf)_3$	$CHCl_3$	25 °C	2.5 h	80%[b]
3	5 mol % $Bi(OTf)_3$	$(CH_2Cl)_2$	25 °C	20 min	85%
4	5 mol % $Bi(OTf)_3$	CH_2Cl_2	25 °C	5 min	82%[b]
5	5 mol % $Bi(OTf)_3$	CH_2Cl_2	0 °C	5 min	99%
6	5 mol % $Bi(OTf)_3$	CH_3CN	0 °C	10 min	86%
7	5 mol % $Cu(OTf)_2$	CH_2Cl_2	25 °C	30 min	87%
8	5 mol % $In(OTf)_3$	CH_2Cl_2	0 °C	20 min	71%[b]
9	5 mol % $Yb(OTf)_3$	CH_2Cl_2	25 °C	12 h	62%[b]
10	5 mol % $Zn(OTf)_2$	CH_2Cl_2	25 °C	2 h	64%[b]
11	5 mol % $Sc(OTf)_3$	CH_2Cl_2	0 °C	20 min	74%[b]
12	5 mol % $La(OTf)_3$	CH_2Cl_2	25 °C	12 h	55%[b]
13	5 mol % $Nd(OTf)_3$	CH_2Cl_2	0 °C	12 h	67%[b]
14	5 mol % $Sn(OTf)_2$	CH_2Cl_2	0 °C	5 min	98%
15	2 mol % $Cu(OTf)_2$	CH_2Cl_2	25 °C	1 h	79%
16	2 mol % $Bi(OTf)_3$	CH_2Cl_2	0 °C	10 min	98%[c]
17	2 mol % $Sn(OTf)_2$	CH_2Cl_2	0 °C	10 min	93%[d]
18	1 mol % $Bi(OTf)_3$	CH_2Cl_2	0 °C	10 min	94%
19	1 mol % $Sn(OTf)_2$	CH_2Cl_2	0 °C	10 min	62%

[a]All of the reactions were performed using 0.3 mmol of (±)-**2a**. Isolated yields after column chromatography. [b]Decomposition of the rest of the mass balance. [c]Condition **A**: 2 mol % of $Bi(OTf)_3$. [d]Condition **B**: 2 mol % of $Sn(OTf)_2$.

Scheme 3. Substrate Scope of Nazarov-Type Cyclization of (±)-2a−d[a]



(±)**2a** **4a** (±)-**3a**

(±)-**3a** (±)-**3b** (±)-**3c** (±)-**3d**

0.5 h, 98% (**A**)
0.5 h, 95% (**B**)

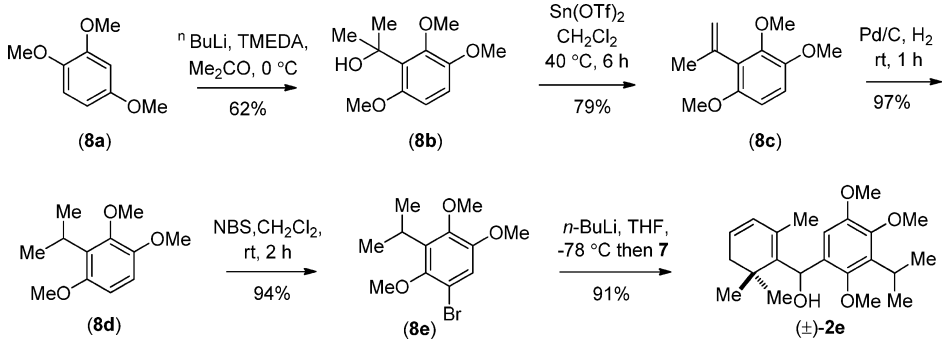
10 min, 95% (**A**)
10 min, 96% (**B**)

1 h, 66% (**A**)
1 h, 70% (**B**)

0.5 h, 88% (**A**)
0.5 h, 81% (**B**)

[a]**A**: 2 mol % of $Bi(OTf)_3$; **B**: 2 mol % of $Sn(OTf)_2$.

Scheme 4. Synthesis of Arylvinylcarbinol (±)-2e



(**8a**) (**8b**) (**8c**)

(**8d**) (**8e**) (±)-**2e**

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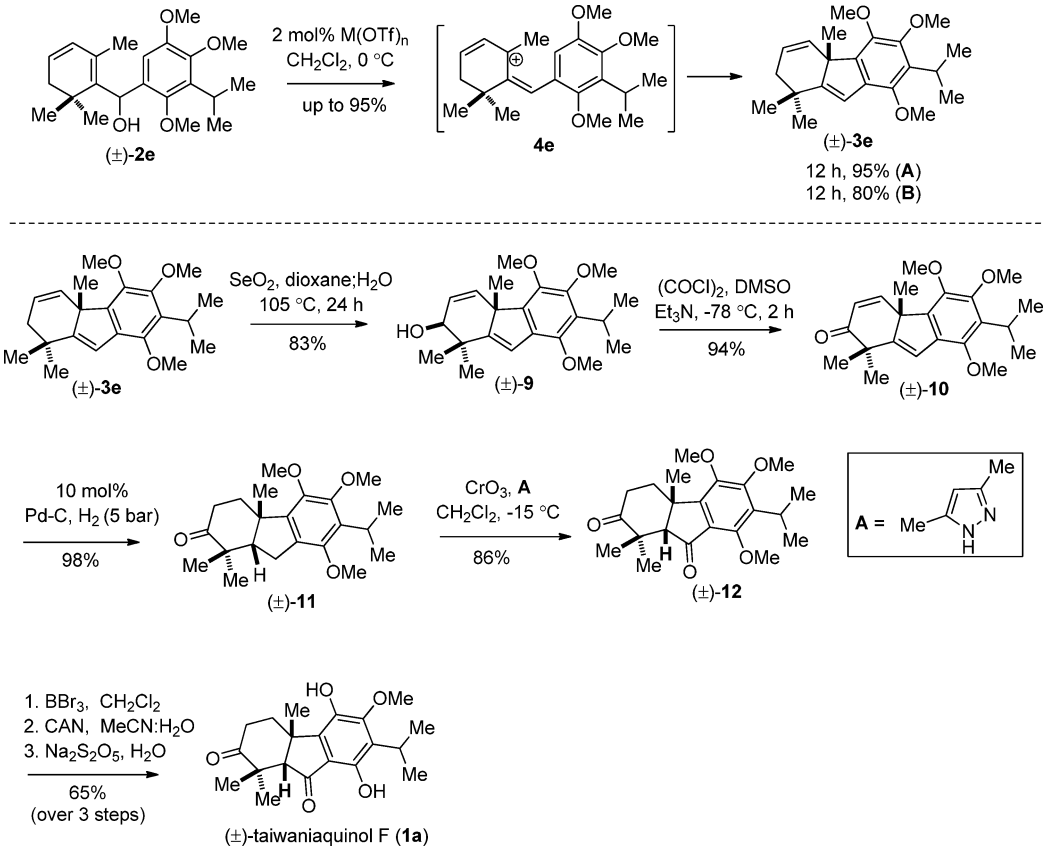
Scheme 5. Total Synthesis of (±)-Taiwaniaquinol F (1a)



groups, were good starting materials for this process, which afforded products **3b** and **3c** in good to excellent yields (Scheme 3). Interestingly, we also observed that arylvinylcarbinols (±)-**2d** with no aromatic ring substituent also afforded (±)-**3d** in high yields (Scheme 3).

Targeting carbotricyclic core (±)-**3e** having additional olefin functionality (Scheme 5), we synthesized aryldivinyl carbinol (±)-**2e** (Scheme 4). 1,2,4-Trimethoxybenzene (**8a**) was reacted with acetone in the presence of *n*-BuLi and TMEDA at 0 °C to afford benzylalcohol **8b** in 62% yield, which was then reacted in the presence of $Sn(OTf)_2$ to furnish α-methylstyrene **8c** in 79% yield. The later was hydrogenated in the presence of Pd−C at 1 atm pressure to afford cumene derivative **8d** in 97% yield, which was then reacted with *N*-bromo succinimide (NBS) to afford bromoarene **8e** in 94% yield. From bromoarene **8e**, aryldivinylcarbinol (±)-**2e** was synthesized in 91% yield (Scheme 4). We found that when (±)-**2e** was reacted under our optimized **A** and **B** conditions, it afforded product (±)-**3e** in 80−95% yield (Scheme 5).

With carbotricyclic core (±)-**3e** in hand, we were positioned to complete the total synthesis of (±)-taiwaniaquinol F (**1a**). Thus, allylic oxidation of (±)-**3e** with SeO_2 in dioxane:water afforded allylalcohol (±)-**9** as a single diastereomer in 83% yield (Scheme 5). The excellent diastereoselectivity observed in this allylic oxidation was attributed to the approach of the oxidant SeO_2 from the less hindered convex face of substrate (±)-**3e**.[29] In fact, the energy minimization (MM2) calculation of diene **3e** (Figure 2) also supports our observed selectivity.

Neopentyl alcohol (±)-**9** was oxidized to obtain α,β-unsaturated ketone (±)-**10** in 94% yield under Swern oxidation conditions. Enone (±)-**10** was then hydrogenated in the

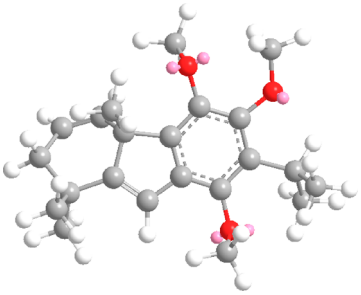


Figure 2. Energy-minimized representation of **3e**.[29]

presence of 10% Pd−C at 5 bar pressure of H_2 in MeOH to afford tricyclic ketone (±)-**11** in 98% yield. Later, (±)-**11** was reacted with CrO_3 in the presence of 3,5-dimethylpyrazole to effect benzylic oxidation[30] to furnish diketone (±)-**12** in 86% yield, the structure of which was confirmed from X-ray crystallography (CCDC: 1405987). From intermediate (±)-**12**, total synthesis of (±)-taiwaniaquinol F **1a** was completed in 3 steps in 65% overall yield by treatment with BBr_3, followed by oxidation using ceric(IV) ammonium nitrate (CAN), and finally reduction with $Na_2S_2O_5$. The X-ray structure of (±)-**1a** (CCDC: 1405985) unambiguously proved the structure of (±)-taiwaniaquinol F **1a**.

Furthermore, we turned our attention to pursue total syntheses of (±)-taiwaniaquinone H (**1d**) and (±)-dichrononone (**1e**) from a common precursor (±)-**3e**. For this purpose, we synthesized carbotricyclic core (±)-**13** from (±)-**3e** via selective hydrogenation of the more exposed disubstituted olefin (A-ring) over trisubstituted styrene olefin (B-ring) in the presence of 10% Pd−C under 1 atm pressure of H_2 in MeOH

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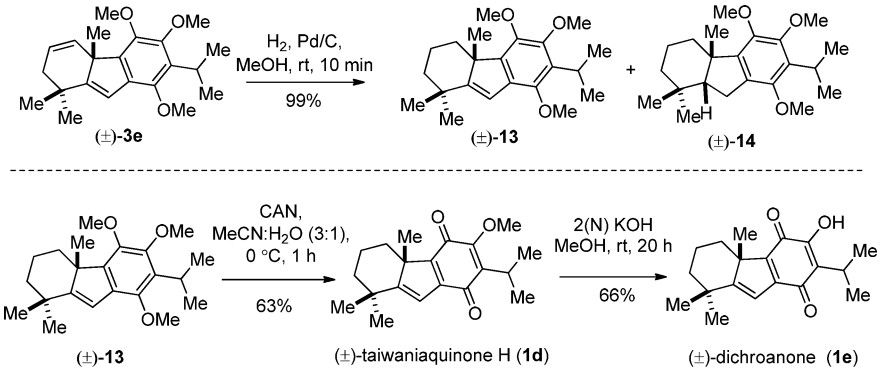
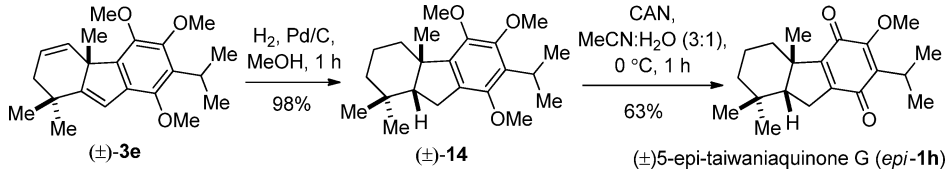
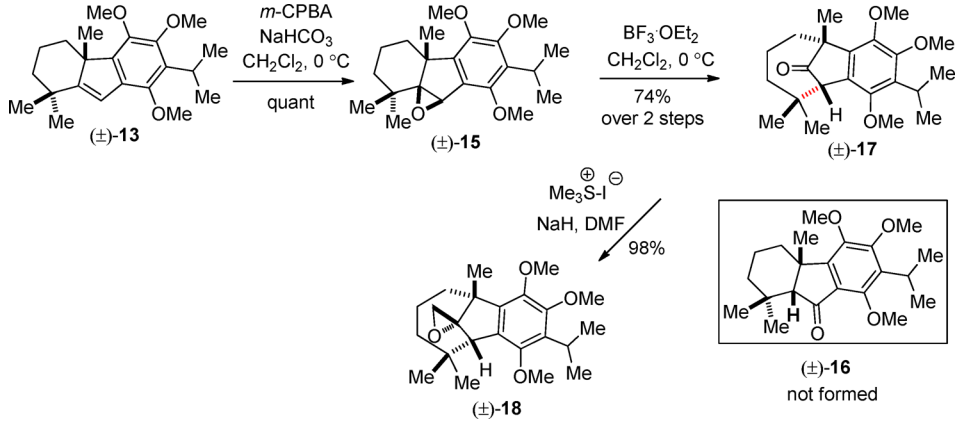
Scheme 6. Total Syntheses of (±)-Taiwaniaquinone H (1d) and (±)-Dichroanone (1e)



Scheme 7. Total Synthesis of (±)-5-*epi*-Taiwaniaquinone G (*ent*-1h)



Scheme 8. Unexpected Formation of (±)-17



(Scheme 6). This reaction led to the formation of required carbotricycle (±)-**13** in 50% isolated yield and consistently produced over-reduced *cis*-fused (±)-**14** in 48% yield. This is probably due to the preferential hydrogenation from the less hindered convex face (Figure 2), leading to the formation of highly stereoselective *cis*-fused (±)-**14**.

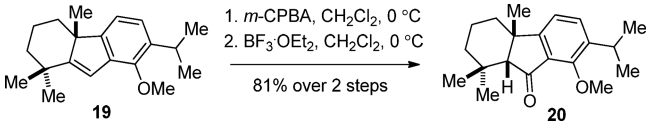
With (±)-**13** in hand, we then performed ceric(IV) ammonium nitrate (CAN)-mediated oxidative transformation of (±)-**13** to *p*-quinone, thus completing total synthesis of (±)-taiwaniaquinone H (**1d**) in 63% yield. The later was then demethylated using 2N KOH in MeOH to complete the total synthesis of (±)-dichroanone (**1e**) (Scheme 6).

For further synthetic elaboration, carbotricyclic core (±)-**3e** was completely hydrogenated in the presence of 10% Pd−C under 1 atm pressure of H_2 in MeOH for 1 h to furnish (±)-**14** in 98% yield, which was then followed by an oxidative quinone formation in the presence of CAN to accomplish total synthesis of (±)-5-*epi*-taiwaniaquinone G (*epi*-**1h**) in 63% overall yield from (±)-**3e** (Scheme 7). To our delight, it was found that oxidative quinone formation of carbotricyclic cores (±)-**13** and (±)-**14** having electron-rich systems work fine only in the presence of CAN (Schemes 6 and 7).

Next, we were interested in completing the total synthesis of (±)-taiwaniaquinol B (**1b**) from dimethyl ether of (±)-**16**. We thought that tricyclic ketone (±)-**16** could be synthesized from a $BF_3{\cdot}OEt_2$-mediated rearrangement of epoxide (±)-**15** (Scheme 8),[22b] which in turn could be accessed from olefin (±)-**13** via a reaction with *m*-chloroperbenzoic acid (*m*-CPBA). In the forward direction, we oxidized olefin (±)-**13** in the presence of *m*-CPBA to furnish epoxide (±)-**15** in quantitative yield. However, as per literature shown in Scheme 9, $BF_3{\cdot}OEt_2$ treatment of (±)-**15** did not afford even a trace amount of the expected tricyclic ketone (±)-**16**.[22b]

In fact, from this reaction, we could only isolate unexpected ring expansion ketone (±)-**17** as the sole product in 74% yield. Reaction of ketone (±)-**17** with trimethylsulfonium iodide in

Scheme 9. Synthesis of Tricyclic Ketone 20 by Alvarez-Manzaneda.[22b]



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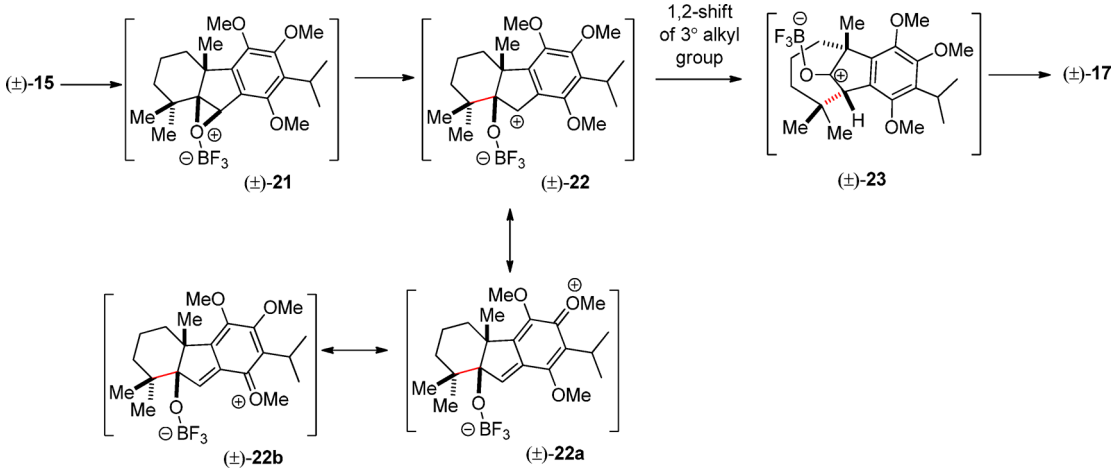
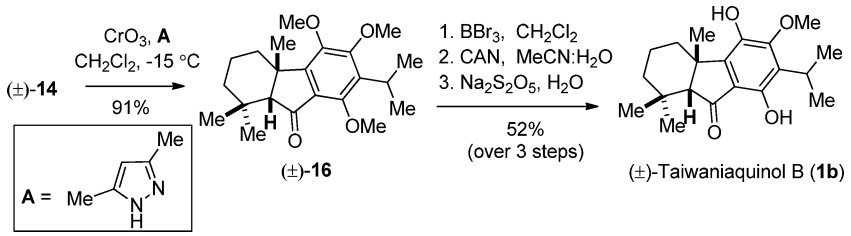
Scheme 10. Unexpected Formation of 7-Membered (±)-17



Scheme 11. Total Synthesis of (±)-Taiwaniaquinol B (1b)



the presence of sodium hydride afforded product (±)-**18**, which was unambiguously confirmed by the X-ray structure (CCDC: 1405989).

A plausible mechanism for the formation of the cycloheptane ring of (±)-**17** is shown in Scheme 10. In the presence of BF_3·OEt_2, (±)-**15** forms intermediate **21**, which forms benzylic carbocation **22** from which a 1,2-migration of the 3° alkyl group leads to the formation of ketone (±)-**17** via carbocation **23**. The stability of carbocation **22** is attributed to the highly electron-rich aromatic ring, which stabilizes **22** via intermediates **22a**/**b** (Scheme 10).

Thus, we adopted an alternate route in which carbotricyclic core (±)-**14** was reacted with CrO_3 in the presence of 3,5-dimethylpyrazole to effect benzylic oxidation to furnish ketone (±)-**16** in 91% yield. From this intermediate, total synthesis of (±)-taiwaniaquinol B was accomplished in a three step sequence in 52% overall yield via demethylation using BBr_3, oxidation in the presence of CAN followed by reduction with $Na_2S_2O_5$ (Scheme 11). It was observed that oxidative quinone formation of carbotricyclic cores (±)-**12** and (±)-**16** with electron-deficient systems with CAN was unsuccessful, and thus, a three-step sequence was used (Scheme 11).

CONCLUSIONS

In summary, we have demonstrated an operationally simple, inexpensive, yet efficient process for the synthesis of a variety of taiwaniaquinoids via a Nazarov-type cyclization of aryldivinylcarbinols in the presence of a catalytic amount of a metal triflate as a Lewis acid. The methodology affords a variety of carbotricyclic structures in excellent yields. This methodology has been applied to the total synthesis of (±)-taiwaniaquinol F (**1a**) by using minimum protecting groups in 36.4% overall yield starting from safranal (**7**) over 8 steps. In addition, we have also accomplished concise and straightforward total syntheses of (±)-taiwaniaquinone H (**1d**), (±)-dichronanone (**1e**), (±)-5-*epi*-taiwaniaquinone G (*epi*-**1h**), and (±)-taiwaniaquinol B (**1b**). Further exploration of this strategy toward the synthesis of *trans*-fused taiwaniaquinoids is currently under active investigation in our laboratory.

EXPERIMENTAL SECTION

Materials. Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled over calcium hydride. All other solvents, such as acetonitrile, chloroform, methanol, 1,2-dichloroethane, and reagents were used as received. Thin layer chromatography was performed using silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain, and other stains. Silicagel of particle size 100−200 mesh was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded on 400 and 500 MHz spectrometers with ^{13}C operating frequencies of 100 and 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$ and DMSO-d_6) signal (δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). IR spectra were recorded on an FTIR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorption bands are reported. High-resolution mass spectrometry (HRMS) data were recorded on MicrOTOF-Q-II mass spectrometer using methanol as the solvent.

General Procedure for the Synthesis of Arylvinylcarbinols ±(2a−c and 2e). A flame-dried round-bottom flask was charged with substituted bromoarene (13.56 mmol; 1.1 equiv) under nitrogen

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atmosphere in dry THF (30 mL). To this solution was added 7.5 mL of a 2.0 M solution of *n*-BuLi in cyclohexane (14.92 mmol; 1.2 equiv) dropwise via a syringe over a period of 5 min at −78 °C. After 5 min of stirring at this temperature, safranal **7** (1.8 mL, 11.30 mmol; 1.0 equiv) (dissolved in 10 mL THF) was added dropwise via a syringe over a period of 5 min. The mixture was treated with a saturated aq solution of NH_4Cl over a period of 5 min. Then, it was transferred to the separatory funnel and shaken vigorously. An aqueous layer was extracted with EtOAc (50 mL × 2). The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude product was finally purified by column chromatography with EtOAc/hexane (1:9) to afford pure compound (±)-**2.**

*(3-Isopropyl-4-methoxyphenyl)(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methanol ((±)-**2a**).* The product was obtained as a colorless viscous oil (2.3 g, 68%); R_f = 0.5 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 1.6 Hz, 1H), 7.22 (dd, J = 8.4, 1.6 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 5.78−5.77 (m, 2H), 5.69 (d, J = 4.6 Hz, 1H, CH−OH), 3.81 (s, 3H), 3.30 (septet, J = 6.9 Hz, 1H), 2.08−2.07 (m, 2H), 1.88−1.87 (m, 1H), 1.74 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.04 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 140.9, 136.6, 135.2, 130.1, 128.8, 125.5, 124.23, 124.2, 109.9, 71.5, 55.4, 40.7, 34.2, 27.0, 26.8, 26.5, 22.8, 22.7, 19.6; IR (film) υ_{max} 3460, 3033, 2959, 1498, 1465, 1245, 1089, 1035, 734 cm^{-1}; HRMS (ESI) m/z 323.1998 $[M + Na]^+$, calcd for $[C_{20}H_{28}O_2 + Na]^+$ 323.1982.

*(4-Methoxy-3-methylphenyl)(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methanol ((±)-**2b**).* The product was obtained as a colorless viscous oil (2.0 g, 66%); R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2H), 6.77 (d, J = 8.1 Hz, 1H), 5.81−5.73 (m, 2H),5.66 (d, J = 2.6 Hz, 1H), 3.82 (s, 3H), 2.22 (s, 3H), 2.10−2.07 (m, 1H), 1.83−1.82 (m, 1H), 1.74 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 139.9, 135.1, 130.1, 128.8, 128.7, 126.2, 125.5, 124.5, 73.3, 55.3, 40.6, 34.2, 27.1, 26.5, 19.6, 16.4; IR (film) υ_{max} 3500, 3433, 2956, 2918, 1503, 1463, 1250, 1127, 1110, 1036, 814, 700 cm^{-1}; HRMS (ESI) m/z 295.1673 $[M + Na]^+$, calcd for $[C_{18}H_{24}O_2 + Na]^+$ 295.1669.

*(2,4,5-Trimethoxyphenyl)(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methanol ((±)-**2c**).* The product was obtained as a colorless viscous oil (2.76 g, 77%); R_f = 0.45 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.0 (s, 1H), 6.46 (s, 1H), 5.70−5.56 (m, 3H), 3.91 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 1.98 (d, J = 17.0 Hz, 1H), 1.86 (dd, J = 17.0, 4.5 Hz, 1H), 1.76 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 151.7, 148.8, 142.3, 138.4, 130.6, 128.3, 124.6, 123.3, 113.5, 97.6, 67.1, 56.7, 56.2, 56.1, 40.6, 34.4, 26.7, 25.7, 20.0; IR (film) υ_{max} 3500, 2934, 2360, 1609, 1506, 1466, 1309, 1206, 1105, 1035, 861, 768 cm^{-1}; HRMS (ESI) m/z 317.1739 $[M - H]^+$, calcd for $[C_{19}H_{26}O_4 - H]^+$ 317.1747.

*(3-Isopropyl-2,4,5-trimethoxyphenyl)(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methanol ((±)-**2e**).* The product was obtained as a colorless solid (3.7 g, 91%); R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 5.81−5.82 (m, 2H), 5.77−5.73 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.36 (septet, J = 7.0 Hz, 1H), 3.32 (d, J = 1.6 Hz, 1H), 2.13−2.00 (m, 2H), 1.83 (s, 3H), 1.36 (d, J = 7.1 Hz, 3H), 1.32 (d, J = 7.0 Hz, 3H), 1.10 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 149.1, 148.6, 137.3, 135.0, 130.3, 130.26, 129.8, 125.0, 110.5, 69.0, 62.0, 60.6, 55.9, 40.3, 34.3, 26.8, 26.0, 25.6, 21.9, 20.3; IR (film) υ_{max} 3472, 2957, 1589, 1455, 1235, 1105, 1041, 855 cm^{-1}; mp 105−108 °C.

Procedure for the Synthesis of (±)-2d. A flame-dried round-bottom flask was charged with safranal **7** (3.21 mmol; 1.0 equiv) under a nitrogen atmosphere in dry THF (10 mL). The reaction mixture was cooled to 0 °C. To this solution was added 1.0 M solution of phenylmagnesium bromide in THF (3.86 mmol; 1.2 equiv) dropwise via a syringe over a period of 5 min, and stirring was continued for additional 1 h. The mixture was treated with a saturated aq solution of NH_4Cl for 5 min. It was transferred to the separatory funnel and shaken vigorously. An aqueous layer was extracted with EtOAc. The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and concentrated using a rotator evaporator under vacuum. The crude product was finally purified by column chromatography with EtOAc/hexane to afford pure compound (±)-**2d**.

*Phenyl(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)methanol ((±)-**2d**).* The product was obtained as a colorless viscous oil (734 mg, 94%); R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.38−7.35 (m, 2H), 5.29−7.25 (m, 1H), 5.84 (s, 1H), 5.83−5.80 (m, 2H), 2.13 (m, 1H), 2.04 (d, J = 4.8 Hz, 1H), 1.75 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.9, 129.9, 128.1, 126.5, 125.9, 125.8, 71.45, 40.8, 34.3, 27.1, 26.7, 19.5; IR (film) υ_{max} 3438, 2955, 2914, 1445, 1359, 1168, 1004, 984, 837, 721, 703 cm^{-1}; HRMS (ESI) m/z 251.1384 $[M + Na]^+$, calcd for $[C_{16}H_{20}O + Na]^+$ 251.1406.

General Procedure for Metal Triflate-Catalyzed Cyclization of Arylvinylcarbinols. In an oven-dried round-bottom flask, aryldivinylcarbinols (0.3 mmol; 1.0 equiv) were dissolved in dichloromethane (3 mL) and cooled to 0 °C. To this solution was added solid $Bi(OTf)_3$ (2 mol %) [condition **A**] or $Sn(OTf)_2$ (2 mol %) [condition **B**]. The reaction mixture was stirred at 0 °C for the indicated time (5−10 min). Upon complete consumption of starting material (TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution. The whole reaction mixture was transferred to a separatory funnel and extracted with 5 mL of EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude products were purified by flash chromatography (10:1 hexanes/EtOAc) to afford cyclization products.

*7-Isopropyl-6-methoxy-1,1,4a-trimethyl-2,4a-dihydro-1H-fluorene ((±)-**3a**).* The product was obtained as a colorless viscous oil (83 mg, 98%); R_f = 0.5 (2% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.86 (s, 1H), 6.36 (s, 1H), 6.0 (d, J = 9.4 Hz, 1H), 5.58−5.54 (m, 1H), 3.85 (s, 3H), 3.34−3.28 (m, 1H), 2.18 (dd, J = 17.2, 5.0 Hz, 1H), 1.96 (bd, J = 17.2 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 6H), 1.23 (d, J = 6.7 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.8, 150.1, 135.3, 134.7, 131.8, 125.1, 120.8, 118.1, 104.9, 56.0, 53.3, 45.4, 34.9, 29.3, 27.1, 27.0, 26.7, 23.2, 22.9; IR (film) υ_{max} 2960, 2931, 1464, 1419, 1256, 1044, 888 cm^{-1}; HRMS (ESI) m/z 283.2076 $[M + H]^+$, calcd for $[C_{20}H_{26}O + H]^+$ 283.2056.

*6-Methoxy-1,1,4a,7-tetramethyl-2,4a-dihydro-1H-fluorene ((±)-**3b**).* The product was obtained as a colorless viscous oil (73 mg, 96%); R_f = 0.5 (2.5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.85 (s, 1H), 6.32 (s, 1H), 6.02−6.00 (m, 1H), 5.59−5.54 (m, 1H), 3.86 (s, 3H), 2.21 (s, 3H), 2.17−2.15 (m, 1H), 1.98−1.94 (m, 1H), 1.44 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 155.7, 151.6, 134.5, 131.7, 125.1, 124.7, 122.7, 120.5, 104.5, 55.8, 53.3, 45.4, 35.0, 29.2, 27.0, 26.97, 16.4; IR (film) υ_{max} 3024, 2915, 1482, 1463, 1292, 1195, 1042, 880, 701 cm^{-1}; HRMS (ESI) m/z 255.1730 $[M + H]^+$, calcd for $[C_{18}H_{22}O + H]^+$ 255.1743.

*5,6,8-Trimethoxy-1,1,4a-trimethyl-2,4a-dihydro-1H-fluorene ((±)-**3c**).* The product was obtained as a colorless viscous oil (63 mg, 70%); R_f = 0.55 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 6.40 (s, 1H), 6.28 (dd, J = 9.7, 2.2 Hz, 1H), 5.58−5.54 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 2.17−2.11 (dd, J = 17.1, 5.1 Hz, 1H), 2.0−1.92 (d, J = 17.1 Hz, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 151.2, 148.3, 145.3, 139.7, 131.1, 125.1, 123.8, 116.3, 97.0, 61.0, 56.5, 56.2, 45.1, 35.0, 29.3, 27.0, 24.6; IR (film) υ_{max} 2958, 2835, 1614, 1468, 1314, 1269, 1125, 1045, 987, 735 cm^{-1}; HRMS (ESI) m/z 301.1798 $[M + H]^+$, calcd for $[C_{19}H_{24}O_3 + H]^+$ 301.1798.

*1,1,4a-Trimethyl-2,4a-dihydro-1H-fluorene ((±)-**3d**).* The product was obtained as a colorless viscous oil (55 mg, 88%); R_f = 0.5 (in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.2 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.28 (td, J = 7.4, 1.1 Hz, 1H), 7.13 (td, J = 7.4, 1.2 Hz, 1H), 6.43 (s, 1H), 6.06−6.04 (m, 1H), 5.59−5.56 (m, 1H), 2.23−2.18 (m, 1H), 2.00−1.96 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 152.6, 142.2, 131.5, 126.5, 125.0, 124.3, 121.1, 121.06, 120.6, 53.2, 45.2, 35.0, 29.3, 26.9, 26.7; IR (film) υ_{max} 3017, 2960, 2916, 1465, 1363, 1256, 1048, 987, 872, 848, 792, 746, 712 cm^{-1}; HRMS (ESI) m/z 211.1482 $[M + H]^+$, calcd for $[C_{16}H_{18} + H]^+$ 211.1481.

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*7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,4a-dihydro-1H-fluorene ((±)-**3e**).* The product was obtained as a colorless solid (992 mg, 95%, in 3.05 mmol); R_f = 0.6 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.4 (s, 1H), 6.28 (dd, J = 9.7, 2.1 Hz, 1H), 5.59−5.54 (m, 1H), 3.90 (s, 3H), 3.81 (s,3H), 3.80 (s, 3H), 3.47−3.39 (m, 1H), 2.17 (dd, J = 17.0, 4.7 Hz, 1H), 1.99−1.95 (m, 1H), 1.52 (s, 3H), 1.34−1.33 (m, 9H), 1.31 (d, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.5, 147.5, 145.5, 142.4, 132.2, 131.3, 130.2, 124.9, 117.2, 62.0, 60.5, 60.2, 54.5, 45.2, 35.1, 29.3, 27.0, 24.8, 22.22, 22.21; IR (film) υ_{max} 2960, 1455, 1415, 1120, 1051 cm^{-1}; HRMS (ESI) m/z 343.2296 $[M + H]^+$, calcd for $[C_{22}H_{30}O_3 + H]^+$ 343.2268; mp 71−74 °C.

*Synthesis of (2,4a)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,4a-dihydro-1H-fluoren-2-ol ((±)-**9**).* In a sealed tube, compound **3e** (910 mg, 2.66 mmol; 1.0 equiv) was taken in mixture of dioxane (12 mL) and water (3 mL) (4:1 ratio). To this solution was added SeO_2 (354 mg, 3.19 mmol; 1.2 equiv) at room temperature. Then, the reaction mixture was heated to reflux at 105 °C, and stirring was continued for 22 h. After full consumption of starting material (evaluated by TLC), the reaction mixture was extracted with ethyl acetate and purified by column chromatography (9:1 hexanes/EtOAc) to furnish 790 mg (83% yield) of (±)-**9** as a white solid; R_f = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.44 (d, J = 9.6 Hz, 1H), 5.81 (dd, J = 9.6, 5.1 Hz, 1H), 3.91 (s, 3H), 3.83 (s,3H), 3.82 (s, 3H), 3.73 (dd, J = 10.9, 5.1 Hz, 1H), 3.44 (septet, J = 7.1 Hz, 1H), 1.51 (s, 3H), 1.36 (s, 3H), 1.338 (d, J = 7.0 Hz, 3H), 1.332 (s, 3H), 1.331 (d, J = 7.1 Hz, 3H), 0.86 (d, J = 11.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 149.9, 147.4, 145.5, 141.5, 134.8, 133.6, 129.6, 127.1, 121.1, 76.6, 62.1, 60.5, 60.2, 54.7, 40.9, 25.7, 25.4, 23.6, 23.5, 22.18, 22.16; IR (film) υ_{max} 3472, 3019, 2918, 1445, 1414, 1333, 1272, 1121, 1050, 989, 701 cm^{-1}; HRMS (ESI) m/z 359.2232 $[M + H]^+$, calcd for $[C_{22}H_{30}O_4 + H]^+$ 359.2217; mp 69−71 °C.

*Synthesis of 7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-1H-fluoren-2(4aH)-one ((±)-**10**).* To a stirred solution of dry DMSO (0.53 mL, 7.97 mmol; 4.5 equiv) in CH_2Cl_2 (20 mL) at −78 °C was carefully added oxalyl chloride (0.3 mL, 3.55 mmol; 2.0 equiv). Then, the mixture was stirred for 20 min at −78 °C followed by dropwise addition of compound (±)-**9** (635 mg, 1.77 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1 h at −78 °C followed by the addition of Et_3N (1.23 mL, 8.88 mmol; 5.0 equiv) at the same temperature. Later, the reaction was slowly brought to room temperature. Upon completion of starting material (evaluated by TLC), the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (20 × 2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (15:1 hexanes/EtOAc) to give 593 mg (94% yield) of (±)-**10** as a white solid; R_f = 0.6 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 9.7 Hz, 1H), 6.57 (s, 1H), 5.97 (d, J = 9.8 Hz, 1H), 3.96 (s, 3H), 3.82 (s, 3H), 3.45 (septet, J = 7.0 Hz, 1H), 1.69 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.33 (d, J = 7.1 Hz, 3H), 1.33 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 155.9, 150.6, 150.1, 147.8, 145.7, 139.0, 134.5, 129.8, 127.3, 121.0, 62.2, 60.5, 60.2, 54.3, 47.8, 26.5, 25.7, 24.8, 23.7, 20.1; IR (film) υ_{max} 2982, 2923, 1681, 1462, 1450, 1415, 1338, 1272, 1122, 1048, 1019, 826 cm^{-1}; HRMS (ESI) m/z 357.2067 $[M + H]^+$, calcd for $[C_{22}H_{28}O_4 + H]^+$ 357.2060; mp 104−106 °C.

*Synthesis of (4a)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-4,4a,9,9a-tetrahydro-1H-fluoren-2(3H)-one ((±)-**11**).* In an oven-dried pear-shaped round-bottom flask, compound (±)-**10** (500 mg, 1.40 mmol) was dissolved in HPLC-grade methanol (70 mL). This solution was passed through H-Cube hydrogenator with a 10% Pd/C cartridge at 34 °C and 5 bar pressure at 0.3 mL/min flow of solution. Then, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexanes/EtOAc) to afford 495 mg (98% yield) of (±)-**11** as a white solid; R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.39 (septet, J = 7.1 Hz, 1H), 3.10 (dd, J = 16.5, 9.1 Hz, 1H), 2.53 (dd, J = 16.5, 7.7 Hz, 1H), 2.49−2.43 (m, 1H), 2.27 (dd, J = 9.0, 7.7 Hz, 1H), 2.24−2.21 (m, 2H), 2.17−2.11 (m, 1H), 1.60 (s, 3H), 1.316 (d, J = 7.1 Hz, 3H), 1.314 (d, J = 7.1 Hz, 3H), 1.29 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 151.5, 149.7, 146.2, 141.6, 133.6, 128.9, 60.4, 60.2, 60.0, 55.8, 47.3, 47.28, 36.4, 33.5, 33.4, 28.9, 26.7, 25.7, 23.7, 22.1; IR (film) υ_{max} 2969, 2909, 1712, 1463, 1449, 1412, 1337, 1268, 1118, 1047, 976, 741 cm^{-1}; HRMS (ESI) m/z 361.2348 $[M + H]^+$, calcd for $[C_{22}H_{32}O_4 + H]^+$ 361.2373; mp 79−81 °C.

*Synthesis of (4a)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-4,4a-dihydro-1H-fluorene-2,9(3H,9aH)-dione ((±)-**12**).* To a stirred solution of 3,5-dimethylpyrazole (4.16 g, 43.31 mmol; 17.93 equiv) in CH_2Cl_2 (10 mL) was added CrO_3 (4.3 g, 43.31 mmol; 17.93 equiv) at −15 °C. Then, the reaction mixture was stirred for 15 min at the same temperature before a solution of tricyclic compound (±)-**11** (870 mg, 2.41 mmol; 1.0 equiv) in CH_2Cl_2 (5 mL) was added dropwise. This dark mixture was stirred for 1 h at −10 °C, and it was directly purified by flash chromatography (10:1 hexanes/EtOAc) to furnish 777 mg (86% yield) of (±)-**12** as a white solid; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.46 (septet, J = 7.1 Hz, 1H), 2.52−2.43 (m, 3H), 2.33−2.26 (m, 1H), 2.26 (s, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 201.8, 159.1, 152.8, 152.4, 146.0, 135.7, 124.1, 63.2, 62.2, 60.2, 60.0, 46.7, 41.1, 34.8, 30.3, 28.3, 25.3, 25.2, 22.3, 21.7; IR (film) υ_{max} 2962, 2925, 1704, 1579, 1469, 1449, 1415, 1316, 1272, 1129, 1045, 958, 701 cm^{-1}; HRMS (ESI) m/z 375.2192 $[M + H]^+$, calcd for $[C_{22}H_{30}O_5 + H]^+$ 375.2166; mp 112−114 °C.

*Synthesis of (±)-Taiwaniaquinol F (**1a**).* To a stirred solution of compound (±)-**12** (166 mg, 0.444 mmol; 1.0 equiv) in dry CH_2Cl_2 (6 mL) was added BBr_3 (147 μL, 1.55 mmol; 3.5 equiv) at −78 °C. Then, the reaction mixture was stirred for 1.5 h. After complete consumption of starting material (evaluated by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (10 × 2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo.

The crude product was taken in 20 mL of MeCN:H_2O (3:1) at 0 °C. To this reaction mixture was added a solution of ammonium ceric nitrate (CAN) (1217 mg, 2.22 mmol; 5.0 equiv) in water (7 mL), and it was stirred for 20 min at 0 °C. After complete consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_5$ and kept stirring for 20 min. Upon completion of the reaction (evaluated by TLC), it was diluted with water (10 mL) and extracted with EtOAc (25 mL) using a separatory funnel. The organic filtrate was dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude was purified by flash chromatography (4:1 hexanes/EtOAc) to afford 99 mg (overall 65% yield in two steps) of (±)-taiwaniaquinol F (**1a**) as a crystalline solid; R_f = 0.45 (20% EtOAc/hexanes); ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.41 (s, 1H), 5.48 (s, 1H), 3.81 (s, 3H), 3.28 (septet, J = 7.1 Hz, 1H), 2.50−2.39 (m, 4H), 2.38 (s, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H), 1.37 (d, J = 7.1 Hz, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 208.3, 152.9, 151.0, 141.4, 138.5, 127.0, 118.0, 63.2, 62.1, 46.8, 42.0, 34.6, 29.4, 26.7, 26.0, 25.8, 22.2, 20.53, 20.52; IR (film) υ_{max} 3418 (br), 2997, 2967, 2915, 1708, 1660, 1425, 1328, 1112, 1021, 932, 891, 739, 701 cm^{-1}; HRMS (ESI) m/z 347.1832 $[M + H]^+$, calcd for $[C_{20}H_{26}O_5 + H]^+$ 347.1853; mp 119−121 °C.[3b]

*Synthesis of (±)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1H-fluorene ((±)-**13**).* A flame-dried round-bottom flask was charged with compound (±)-**3e** (85 mg, 0.30 mmol; 1.0 equiv) under nitrogen atmosphere in MeOH (5 mL). The solution was purged under nitrogen atmosphere for 20 min. To this solution was added Pd on activated charcoal (1.6 mg) and purged with a hydrogen balloon for a period of 10 min. The reaction mixture was filtered through Celite and concentrated using a rotary evaporator under vacuum. The crude productc was finally purified by flash chromatography (10:1 hexanes/EtOAc) to furnish 52 mg in 50% yield of (±)-**13** as a colorless solid; R_f = 0.6 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.47−3.40 (m,1H), 2.44−2.40 (m, 1H), 2.0−1.87 (m, 1H), 1.62−1.58 (m, 2H), 1.43 (s, 3H), 1.33 (d, J = 1.7 Hz, 3H), 1.31 (d, J =

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1.3 Hz, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.15−1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 149.3, 147.2, 145.7, 145.0, 132.7, 130.3, 116.8, 61.9, 60.5, 60.2, 52.3, 36.8, 35.5, 31.4, 29.7, 25.7, 25.5, 22.3, 22.2, 21.6, 19.5; IR (film) υ_{max} 2935, 1455, 1414, 1119, 1053 cm^{-1}; HRMS (ESI) m/z 367.2236 $[M + Na]^+$, calcd for $[C_{22}H_{32}O_3 + Na]^+$ 367.2244; mp 79−83 °C.

*Synthesis of (±)-Taiwaniaquinone H ((±)-**1d**).* An oven-dried round-bottom flask was charged with compound (±)-(**13**) (270 mg, 0.783 mmol; 1 equiv) in MeCN:H_2O (3:1) (30 mL). To this solution was added a solution of ceric ammonium nitrate (CAN) (1288 mg, 2.35 mmol; 3.0 equiv) in water (12 mL) at 0 °C. The reaction mixture was stirred at that temperature for 10 min and then diluted with water (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated using a rotator evaporator under vacuum. The crude product was finally purified by flash chromatography (20:1 hexanes/EtOAc) to afford 167 mg (63% yield) of (±)-taiwaniaquinone H (**1d**) as a red syrup; R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (s, 1H), 4.0 (s, 3H), 3.24 (septet, J = 7.1 Hz, 1H), 2.40−2.35 (m, 1H), 1.89 (qt, J = 13.8, 3.5 Hz, 1H), 1.68−1.64 (m, 1H), 1.61−1.60 (m, 1H), 1.42 (s, 3H), 1.24 (s, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.21 (s, 3H), 1.09−1.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 178.8, 175.5, 157.3, 150.6, 145.8, 136.0, 116.7, 61.4, 55.6, 43.4, 37.2, 36.7, 31.0, 24.8, 24.5, 20.7, 20.67, 20.1, 19.1; IR (film) υ_{max} 2922, 1646, 1560, 1536, 1354, 1290, 1265, 1152, 1025, 930 cm^{-1}; HRMS (ESI) m/z 315.1941 $[M + H]^+$, calcd for $[C_{20}H_{26}O_3 + H]^+$ 315.1955.[10]

*Synthesis of (±)-Dichroanone ((±)-**1e**).* An oven-dried round-bottom flask was charged with (±)-taiwaniaquinone H (60 mg, 0.19 mmol; 1.0 equiv) in MeOH (5 mL). To this solution was added a solution of 2 M KOH solution in MeOH (3 mL) at room temprature. The reaction mixture was stirred at room temperature for 24 h. Then, 2N HCL (1.5 mL) was added slowly, and the mixture was diluted with dichloromethane (15 mL). The combined organic phase washed with brine, dried over Na_2SO_4, and concentrated using a rotator evaporator under vacuum. The crude product was purified by flash chromatography (20:1 hexanes/EtOAc) to give 35 mg (66% yield) of (±)-dichroanone (**1e**) as a red syrup; R_f = 0.4 (2.5% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (brs, 1H), 6.45 (s, 1H), 3.21 (septet, J = 7.0 Hz, 1H), 2.39−2.35 (m, 1H), 1.93 (qt, J = 14.1, 3.4 Hz, 1H), 1.73−1.69 (m, 1H), 1.65−1.60 (m, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.24 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.234 (s, 3H), 1.14−1.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.3, 178.8, 175.5, 157.3, 150.6, 145.8, 136.0, 116.7, 61.4, 55.6, 43.4, 37.2, 36.7, 31.0, 24.8, 24.5, 20.7, 20.67, 20.1, 19.1; IR (film) υ_{max} 3354, 2912, 1643, 1633, 1527, 1372, 1360, 1319, 1170, 965, 919, 871 cm^{-1}; HRMS (ESI) m/z 301.1776 $[M + H]^+$, calcd for $[C_{19}H_{24}O_3 + H]^+$ 301.1798.[2c]

*Synthesis of (4a,9a)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-fluorene ((±)-**14**).* A flame-dried round-bottom flask was charged with compound (±)-**3e** (630 mg, 1.83 mmol; 1.0 equiv) under a nitrogen atmosphere in MeOH (5 mL) and purged with nitrogen gas. To this reaction mixture was added Pd on activated charcoal (19 mg, 0.18 mmol; 0.1 equiv), and the mixture was then placed with a hydrogen balloon for a period of 1 h. The reaction mixture was filtered through Celite and concentrated using a rotary evaporator under vacuum. The crude products were purified by flash chromatography (9:1 hexanes/EtOAc) to afford 618 mg of compound (±)-**14** in 98% yield as a colorless viscous oil; R_f = 0.55 (5% EtOAc and hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.40−3.31 (m, 1H), 2.85−2.79 (m, 1H), 2.63−2.56 (m, 1H), 1.82−1.73 (m, 2H), 1.59 (s, 3H), 1.43−1.40 (m, 1H), 1.39−1.35 (m, 2H), 1.32 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 150.3, 146.3, 144.3, 132.3, 128.9, 60.5, 60.3, 60.2, 56.6, 47.1, 35.2, 35.0, 32.2, 31.2, 31.1, 29.9, 25.6, 25.5, 22.24, 22.23, 18.7; IR (film) υ_{max} 2919, 1452, 1413, 1338, 1255, 1154, 1042 cm^{-1}; HRMS (ESI) m/z 369.2425 $[M + Na]^+$, calcd for $[C_{22}H_{34}O_3 + Na]^+$ 369.2400.

*Synthesis of (±)-5-epi-Taiwaniaquinone G (epi-**1h**).* An oven-dried round-bottom flask was charged with compound **14** (187 mg, 0.30 mmol; 1.0 equiv) in MeCN:H_2O (3:1) (25 mL). To this solution was added a solution of ceric ammonium nitrate (CAN) (1480 mg, 2.69 mmol; 5.0 equiv) in water (8 mL) at 0 °C. The reaction mixture was stirred at that temperature for 1 h and then diluted with water (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated using a rotary evaporator under vacuum. The crude products were purified by flash chromatography (20:1 hexanes/EtOAc) to furnish 116 mg (68% yield) of (±)-5-*epi*-taiwaniaquinone G as a red viscous oil; R_f = 0.5 (5% EtOAc and hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.18 (septet, J = 7.1 Hz, 1H), 2.65 (dd, J = 18.0, 8.1 Hz, 1H), 2.34 (dd, J = 18.0, 11.5 Hz, 1H), 1.90 (dt, J = 13.5, 3.4 Hz, 1H), 1.73 (dd, J = 11.5, 8.1 Hz, 1H), 1.61−1.52 (m, 1H), 1.50 (s, 3H), 1.41 (dt, J = 13.9, 3.9 Hz, 1H), 1.29−1.26 (m, 2H), 1.22−1.20 (m, 1H), 1.19 (d, J = 7.2 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 182.6, 156.5, 152.4, 146.2, 136.7, 61.1, 54.9, 47.9, 34.9, 34.2, 31.7, 31.1, 31.0, 29.4, 24.5, 24.2, 20.6, 20.5, 17.9; IR (film) υ_{max} 2984, 2964, 2919, 2845, 1658, 1651, 1596, 1449, 1262, 1162 cm^{-1}; HRMS (ESI) m/z 339.1935 $[M + Na]^+$, calcd for $[C_{20}H_{28}O_3 + Na]^+$ 339.1931.[25b]

*Synthesis of (4a,9a)-7-Isopropyl-5,6,8-trimethoxy-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (±)-**16**.* To a stirred solution of 3,5-dimethylpyrazole (1.5 g, 15.55 mmol; 17.93 equiv) in CH_2Cl_2 (5 mL) was added CrO_3 (1555 mg, 15.55 mmol; 17.93 equiv) at −15 °C. Then, the reaction mixture was stirred for 15 min at the same temperature before adding a solution of tricyclic compound ((±)-**14**) (300 mg, 0.867 mmol; 1.0 equiv) in CH_2Cl_2 (3 mL). This dark mixture was stirred at −10 °C until TLC showed complete consumption of starting material (1 h). Then, it was directly purified by flash chromatography (15:1 hexanes/EtOAc) to afford 284 mg (91% yield) of (±)-**16** as a colorless solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.47 (septet, J = 7.0 Hz, 1H), 2.28−2.23 (m, 1H), 2.01 (s, 1H), 1.86−1.81 (m, 1H), 1.70−1.63 (m, 1H), 1.59−1.50 (m, 1H), 1.36 (s, 3H), 1.29 (d, J = 7.0 Hz, 6H), 1.23 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 158.6, 152.9, 152.7, 146.2, 134.8, 124.8, 65.6, 62.1, 60.3, 59.9, 41.9, 124.8, 65.6, 62.1, 60.3, 59.9, 41.9, 37.5, 34.2, 32.7, 31.5, 25.3, 24.6, 21.9, 18.1; IR (film) υ_{max} 2934, 1743, 1454, 1413, 1340, 1294, 1259, 1187, 1116 cm^{-1}; HRMS (ESI) m/z 383.2204 $[M + Na]^+$, calcd for $[C_{22}H_{32}O_4 + Na]^+$ 383.2193; mp 87−89 °C.

*Synthesis of (±)-Taiwaniaquinol B (**1b**).* To a stirred solution of compound (±)-**16** (270 mg, 0.75 mmol; 1.0 equiv) in dry CH_2Cl_2 (3 mL) was added BBr_3 (180 μL, 1.87 mmol; 2.5 equiv) at −78 °C. Then, the reaction mixture was stirred for 1.5 h at −78 °C. After complete consumption of starting material (evaluated by TLC), the reaction mixture was quenched with water and extracted with ethyl acetate (10 × 2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo.

The crude product was taken in 20 mL of MeCN:H_2O (3:1) at 0 °C. To this reaction mixture was added a solution of ammonium ceric nitrate (CAN) (2.1 g, 3.75 mmol; 5.0 equiv) in water (8 mL), and it was stirred for 20 min at 0 °C. After complete consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_5$ and kept stirring for an additional 20 min. Upon completion of the reaction (evaluated by TLC), it was diluted with water (5 mL) and extracted with EtOAc (10 × 2 mL) using a separatory funnel. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude product was purified by flash chromatography (10:1 hexanes/EtOAc) to afford 130 mg (overall 52% yield in two steps) of (±)-taiwaniaquinol B as a crystalline solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 5.31 (brs, 1H), 3.80 (s, 3H), 3.27 (septet, J = 7.1 Hz, 1H), 2.12 (s, 1H), 2.08−1.96 (m, 2H), 1.75−1.67 (m, 1H), 1.63−1.55 (m, 1H), 1.44 (s, 3H), 1.42−1.40 (m, 2H), 1.38 (d, J = 7.1 Hz, 3H), 1.38 (d, J = 7.1 Hz, 3H), 1.25 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 152.3, 151.1, 142.7, 138.4, 126.1, 118.3, 65.1, 62.1, 42.7, 36.5, 34.3, 33.0, 30.3, 28.8, 25.9, 24.3, 20.6, 17.5; IR (film) υ_{max} 2945, 2927, 2850, 1720, 1450, 1426, 1286, 1256, 1187, 1125 cm^{-1}; HRMS (ESI) m/z 333.2040

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$[M + H]^+$, calcd for $[C_{22}H_{28}O_4 + H]^+$ 333.2060; mp 143−145 °C (lit.[2a] mp 142−144 °C).

*3-Isopropyl-1,2,4-trimethoxy-5,6,6-trimethyl-6,7,8,9-tetrahydro-5H-5,9-methanobenzo[7]-annulen-10-one ((±)-**17**).* An oven-dried round-bottom flask was charged with compound **13** (104 mg, 0.302 mmol; 1.0 equiv) in CH_2Cl_2 (15 mL), and *m*-CPBA (115 mg, 0.453 mmol; 1.5 equiv) was added at 0 °C. Then, solid $NaHCO_3$ (76 mg, 0.908 mmol; 3.0 equiv) was added to the reaction mixture at the same tempature, and it was allowed to stir for 1 h. The reaction mixture was treated with an aq saturated solution of Na_2SO_3 (2 mL) and stirred for an additional 10 min. It was poured into a mixture of CH_2Cl_2 (15 mL) and ice water (3 mL), and the mixture was shaken and separated. The organic phase was washed with saturated aq $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated using a rotary evaporator under vacuum.

Crude product (95 mg) was taken in CH_2Cl_2 (8 mL), and $BF_3{\cdot}Et_2O$ (0.205 mL, 0.65 mmol; 2.1 equiv) was added at 0 °C. After 30 min of stirring, water (1 mL) was added to this mixture, and stirring continued for an additional 15 min. Then, a saturated aq solution of $NaHCO_3$ (8 mL) was added to the reaction mixture, and it was extracted with CH_2Cl_2 (8 mL). The organic layer was dried over Na_2SO_4 and concentrated using a rotary evaporator under vacuum. The crude compound was finally purified by column chromatography (9:1 hexanes/EtOAc) to afford compound **17** in 74% overall yield as a colorless viscous oil; R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 3.42−3.37 (m, 1H), 3.25 (s, 1H), 1.97 (dt, *J* = 13.4, 4.4 Hz, 1H), 1.59−1.48 (m, 1H), 1.46 (s, 3H), 1.40−1.36 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.26−1.23 (m, 1H), 1.17 (s, 3H), 1.15−1.05 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.6, 152.1, 151.3, 140.2, 136.4, 134.1, 127.6, 60.5, 60.1, 59.8, 54.5, 42.1, 41.6, 35.7, 30.8, 26.9, 25.8, 22.3, 21.9, 20.4, 20.3; IR (film) υ_{max} 2934, 1743, 1454, 1413, 1340, 1294, 1259, 1187, 1116 cm^{-1}.[22b]

*Synthesis of 3-Isopropyl-1,2,4-trimethoxy-5,6,6-trimethyl-6,7,8,9-tetrahydro-5H-spiro[5,9-methanobenzo[7]annulene-10,2′-oxirane] ((±)-**18**).* NaH (60% in mineral oil) (28 mg, 0.706 mmol; 1.2 equiv) was added to dimethyl sulfoxide (2 mL) at room temperature. To this solution was added trimethylsulfonium iodide (144 mg, 0.706 mmol; 1.2 equiv), which was then stirred for 30 min. A solution of compound **17** (212 mg, 0.588 mmol; 1.0 equiv) in THF (1 mL) was added to this reaction mixture and stirring continued overnight. The reaction mixture was diluted with EtOAc (10 mL) and water (10 mL) at room temperature, and the layers were separated. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated in a rotatory evaporator under reduced pressure to furnish compound **18** in 98% yield as a colorless solid; R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 3.46−3.37 (m, 1H), 2.91 (d, *J* = 5.3 Hz, 1H), 2.83 (s, 1H), 2.54 (d, *J* = 5.3 Hz, 1H), 1.87−1.80 (m, 2H), 1.71−1.64 (m, 1H), 1.43−1.37 (m, 1H), 1.34 (d, J = 7.1 Hz, 3H), 1.31 (d, J = 7.1 Hz, 3H), 1.28−1.23 (m, 1H), 1.20 (s, 3H), 1.10 (s, 3H), 1.06−0.96 (m, 1H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.1, 146.2, 137.9, 133.4, 130.4, 70.0, 60.4, 60.2, 60.0, 53.0, 52.9, 47.1, 42.4, 40.9, 37.7, 33.0, 27.2, 25.8, 22.4, 22.0, 21.8, 20.7; IR (film) υ_{max} 2928, 2916, 2837, 1448, 1450, 1408, 1338, 1257, 1114 cm^{-1}; HRMS (ESI) *m*/*z* 397.2360 $[M + Na]^+$, calcd for $[C_{23}H_{34}O_4 + Na]^+$ 397.2349.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01345.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

CIF file for (±)-**12** (CIF)

CIF file for (±)-**1a** (CIF)

CIF file for (±)-**18** (CIF)

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Notes

The authors declare no competing financial interest.

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