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Cationic Polyene Cyclizations

Cationic Polyene Cyclization for Taiwaniaquinoid Construction

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Abstract: An acid-catalyzed polyene cyclization has been used to rapidly generate the 6/5/6-fused ring system of the taiwaniaquinoid natural products. The *cis*-fused diastereomer was formed selectively, which enabled a step-efficient synthesis of (±)-5-*epi*-taiwaniaquinone G.

Introduction

The taiwaniaquinoids are a family of 18 rearranged abietane-type diterpenes possessing a 4a-methyltetrahydrofluorene skeleton, i.e., a 6/5/6-ring system (Figure 1).[1] This ring system occurs in nature much less frequently than the corresponding 6/6/6-fused system,[2] and this has led to speculation that taiwaniaquinoid biosynthesis involves a ring contraction.[3] Several elegant biomimetic syntheses that exploit such a ring contraction have been reported.[4] Most members of the family contain a *trans*-fused 5/6-ring system (e.g., **1** and **2**), but there are several taiwaniaquinones that have a *cis*-fused 5/6-ring junction (e.g., **4** and **5**). Our particular attention was taken by the norditerpene taiwaniaquinone G (**6**).[5] This molecule has not only undergone biosynthetic excision of a carbon atom, but it also lacks the unsaturation and/or oxygen functionality that would be immediately amenable to biomimetic chemistry.

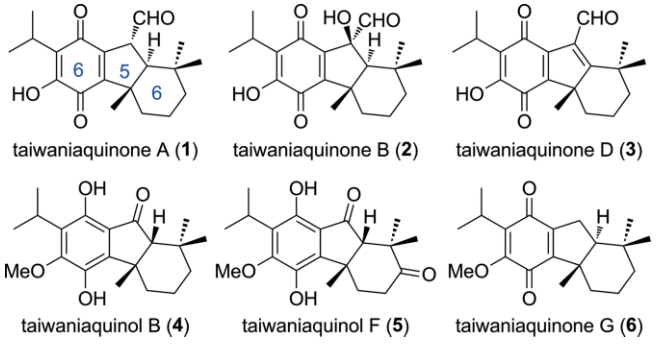
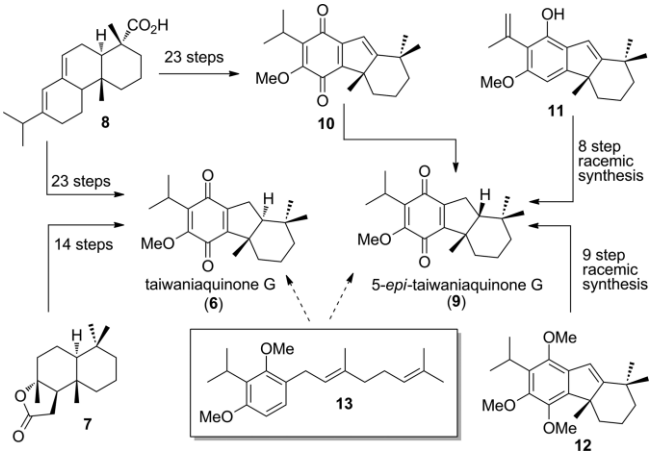


Figure 1. Taiwaniaquinones A–F (**1**–**5**) and G (**6**).

Taiwaniaquinone G (**6**) has been the target of two previous syntheses (Scheme 1). The first approach by Alvarez-Manzaneda and coworkers in 2009 used (+)-sclareolide (**7**) as a chiral-pool source with the necessary *trans* configuration.[6] Installation of the quinone ring by using an electrocyclization delivered (–)-taiwaniaquinone G (**6**) in just 14 steps. Demonstrating the difficulty of applying biomimetic strategies, Alvarez-Manzaneda subsequently reported a biomimetically inspired synthesis from (+)-abietic acid (**8**) that gave (–)-taiwaniaquinone G (**6**) in 23 steps overall.[3c] The *cis*-fused isomer, (±)-5-*epi*-taiwaniaquinone G (**9**), has also been synthesized on three occasions (Scheme 1).[7] In each case, hydrogenation of an alkene precursor installed the *cis*-5/6-ring junction: Alvarez-Manzaneda and coworkers hydrogenated compound **10**;[3c] Chang, Song, and coworkers hydrogenated compound **11**;[7b] and Bisai and coworkers reported the hydrogenation of compound **12**.[7a]



Scheme 1. Previous syntheses of taiwaniaquinone G (**6**) and 5-*epi*-taiwaniaquinone G (**9**).

We wondered whether the *trans*-fused 5/6-ring system could be installed directly from an appropriate geranylbenzene derivative such as **13** (Scheme 1) by using a cationic polyene cyclization.[8] Surprisingly, this particular polyene cyclization has not been reported. Longer polyene systems have been cyclized to give 6/5/6/6-ring systems[9] and steroidal frameworks with excellent *trans* selectivity.[10] Our strategy was to initiate a polyene cyclization by using simple Brønsted- or Lewis-acid catalysis.

Results and Discussion

We planned to install the required polyene unit by using a Suzuki coupling, so geraniol (**14**) was converted into the corre-

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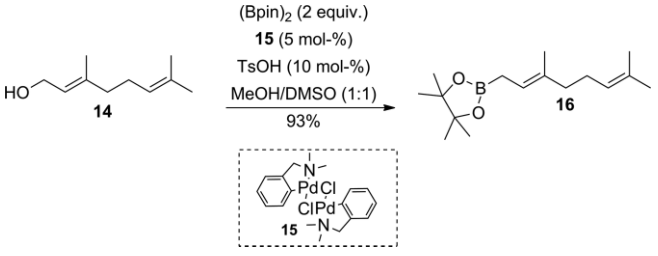
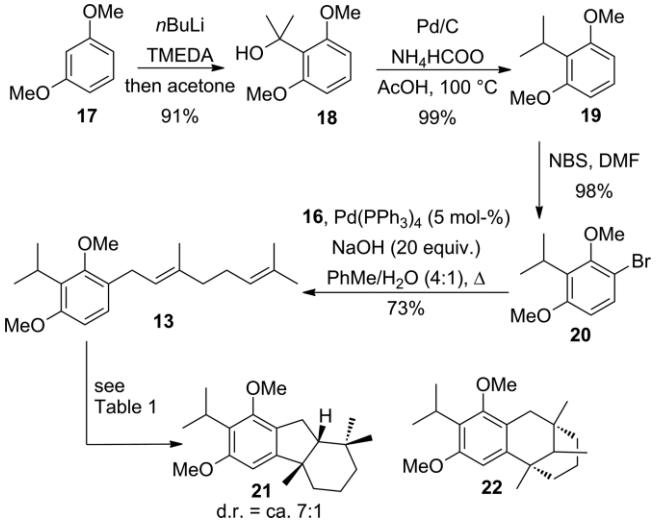
sponding boronate ester **16** (Scheme 2).[11] The synthesis of the second coupling partner is shown in Scheme 3.



Scheme 2. Synthesis of cyclization polyene chain **16**. pin = pinacolato.



Scheme 3. Synthesis of cyclization substrate **13**. TMEDA = tetramethylethylenediamine.

3-Methoxyanisole (**17**) underwent *ortho*-lithiation and reaction with acetone to give **18**. Elimination and in-situ transfer hydrogenation gave compound **19**, which was smoothly converted into aryl bromide **20**. An sp^2–sp^3 Suzuki coupling with **16** gave the desired cyclization precursor **13** in good yield.

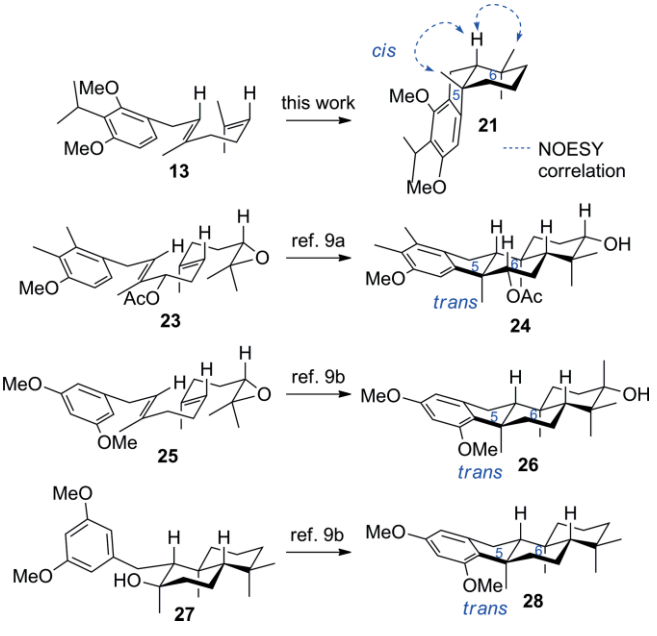
Our attempts to effect the polyene cyclization are detailed in Table 1. Cyclization with tosic acid was ineffective, regardless of the solvent used (Table 1, entries 1 and 2). In contrast, bismuth triflate initiated the desired polyene cyclization to give tricyclic products **21** and **22** in modest yield when a polar solvent was used (contrast Table 1, entries 3 and 8). Lowering the reaction temperature proved detrimental, and below 40 °C cyclization was not observed (Table 1, entries 4–7). Aluminium trichloride was ineffective (Table 1, entries 9 and 10), but we were delighted to observe a 50 % combined yield of tricyclic products **21** and **22** when boron trifluoride diethyl etherate was used (Table 1, entry 11). Again, this reaction proved to be solvent specific, with no cyclization occurring in the less polar THF (Table 1, entry 12). HSQC and HMBC 2D NMR spectroscopic analysis of the tricyclic products revealed that the polyene cyclization had indeed delivered the desired 6/5/6-ring system as a 2:1 mixture of **21** and the rearranged product **22** (Scheme 3),[12] which were separated by laborious HPLC. The mass balance of the reaction consisted of a mixture of monocyclized products, alkene-rearranged products, and the cleaved aromatic unit **19**.

Table 1. Polyene cyclization conditions.

Entry	Catalyst[a]	Solvent	Temp. [°C]	Yield of **21** + **22** [%][b]
1	TsOH	toluene	110	decomp.
2	TsOH	$EtNO_2$	112	decomp.
3	$Bi(OTf)_3$	$EtNO_2$	100	33
4	$Bi(OTf)_3$	$EtNO_2$	80	33
5	$Bi(OTf)_3$	$EtNO_2$	60	27
6	$Bi(OTf)_3$	$EtNO_2$	40	4
7	$Bi(OTf)_3$	$EtNO_2$	room temp.	0
8	$Bi(OTf)_3$	THF	66	n.r.
9	$AlCl_3$	$EtNO_2$	r.t.	0
10	$AlCl_3$	THF	r.t.	n.r.
11	$BF_3{\cdot}OEt_2$	$EtNO_2$	r.t	50
12	$BF_3{\cdot}OEt_2$	THF	r.t.	n.r.

[a] 10 mol-% catalyst loading, reaction time 18 h. [b] Yield of isolated products. n.r. = no reaction.

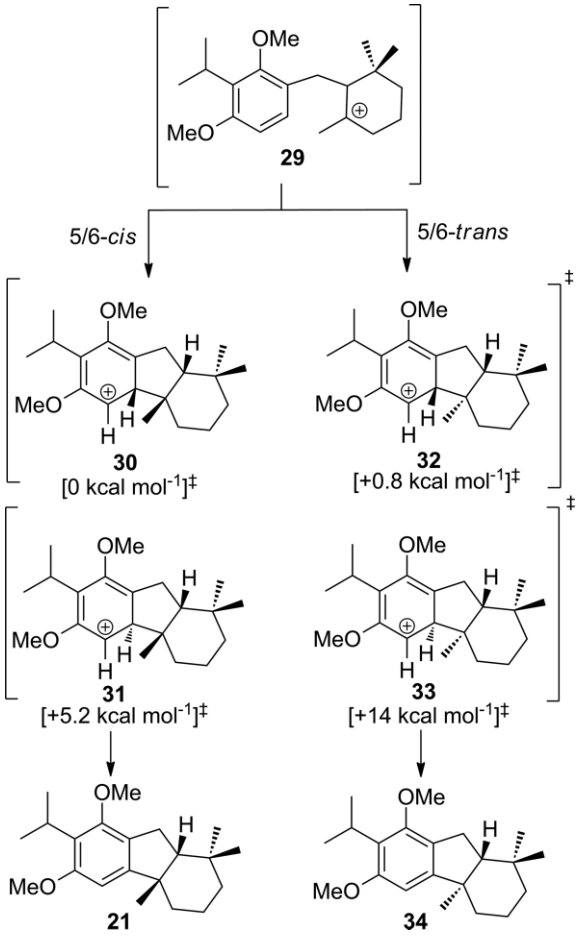
NMR spectroscopic analysis of the 6/5/6-containing compound **21** demonstrated that the cyclization had produced a 6.7:1 mixture of diastereomers at the ring junction. Surprisingly, NOESY experiments unambiguously demonstrated that the predominant product **21** had a *cis*-fused 5/6-ring junction (Scheme 4). This result contrasts with the work of Xie, She, and coworkers, who reported the cyclization of the extended polyene **23** during their synthesis of (–)-walsucochin B.[9a] In that instance, compound **24**, with a *trans*-fused 5/6-ring junction, was the exclusive product; the authors rationalized this result on the basis of a chair-like transition state. Similarly Anderson and coworkers reported the cationic polyene cyclization of **25**; they obtained the *trans*-fused compound **26**.[9b] Friedel–Crafts alkylation of the cation generated from compound **27** also gave a *trans*-fused 5/6-ring junction. The fact that **19**, **22**, and monocyclized compounds were isolated from the reaction of **13** to



Scheme 4. Cyclizations to give 6/5/6- and 6/5/6/6-fused systems.

give **21** suggests that the reaction is not a concerted process, but that it occurs in a stepwise manner. To further understand the stereochemical outcome of the cyclization we turned to computational methods.

As shown in Scheme 5, an initial alkene cyclization would give cyclohexyl cation **29**, which can then be transformed into each of the observed reaction products. Friedel–Crafts alkylation *meta* to both methoxy groups can lead to the *cis*-configured Wheland intermediates **30** and **31**, or to the *trans*-configured intermediates **32** and **33**. Gas-phase DFT calculations using the ωB97X-D/6-31G* functional/basis set combination indicated that the *endo* transition states **30** and **32** were substantially lower in energy than the corresponding *exo* transition states **31** and **33**.[13] Calculations carried out with the inclusion of solvation effects by using the CPCM (conductor-like polarizable continuum model) method, indicated two steric interactions that destabilized the transition state leading to the *trans* configured diastereomer **32** relative to that leading to its *cis* counterpart **30**. In the transition state leading to **32**, the hydrogen atom on the aromatic ring comes within the Van der Waals radius of the hydrogen atom at the ring junction (Figure 2). Additionally, the 1,3-diaxial interaction between the angular methyl groups at the 5/6-ring junction and one of the *gem*-dimethyl groups is slightly more pronounced in the transition state leading to **32**. These results indicate that the reaction proceeds through intermediate **30**.



Scheme 5. Calculated gas-phase energies for transition states leading to predicted reaction intermediates **30**–**33**.

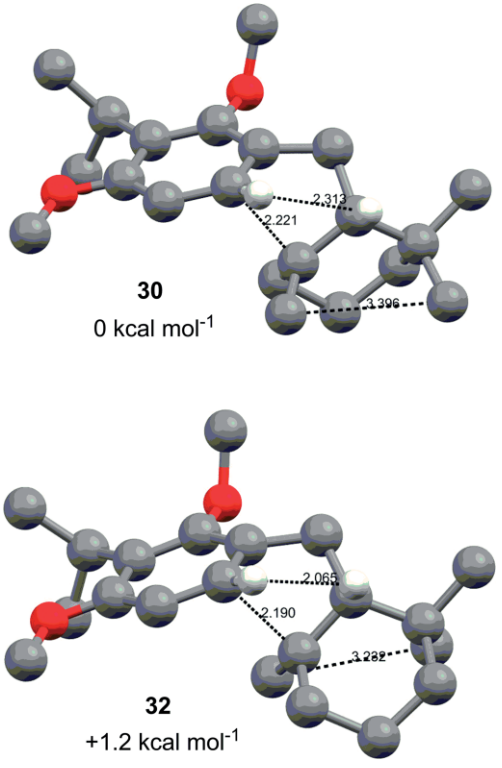
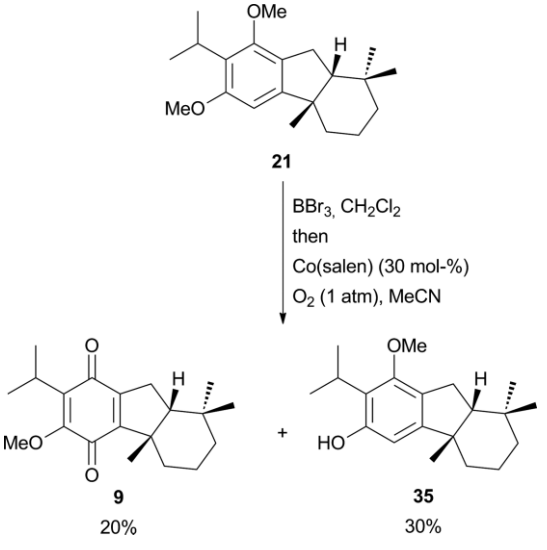


Figure 2. Calculated energies for solvated transition states leading to intermediates **30** and **32**.

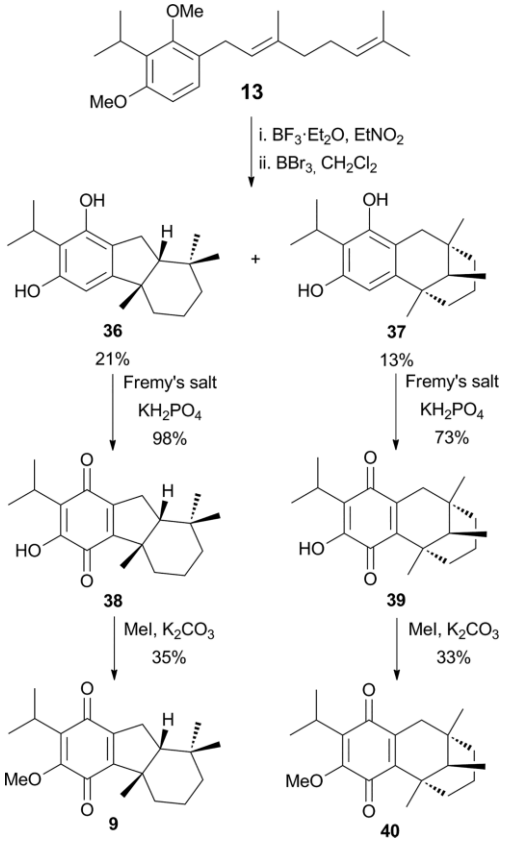
Compound **21** has the same relative stereochemistry at the 5/6-ring junction as (±)-5-*epi*-taiwaniaquinone G (**9**), and the synthesis of that compound is shown in Scheme 6. Treatment of compound **21** with BBr_3 resulted in an unselective demethylation, and the crude reaction mixture was exposed to the action of salcomine under an atmosphere of oxygen to give (±)-5-*epi*-taiwaniaquinone G (**9**) in just seven steps from methoxyanisole (**14**). Although this approach was concise, it suffered



Scheme 6. Initial synthesis of 5-*epi*-taiwaniaquinone G (**9**).

from two limitations: the nontrivial separation of **21** and **22**, and the unselective demethylation of **21**, which resulted in significant material loss.

To circumvent those issues, a second approach was pursued. As shown in Scheme 7, the 2:1 mixture of **21** and **22** that resulted from the polyene cyclization of **13** was globally demethylated, and the diols **36** and **37** were separated. Oxidation of **36** with Fremy's salt gave quinone **38**. Methylation of **38** gave (±)-5-*epi*-taiwaniaquinone G (**9**) in a total of eight steps from methoxyanisole (**17**). A chemical-shift comparison between compound **9** synthesized by a cationic polyene cyclization and the literature data reported for 5-epi-taiwaniaquinone G[7a] reveals only minor differences as shown in Figures 3 and 4 and thus confirms the structure. In an analogous manner, diol **37** was transformed into the new quinone **40**.



Scheme 7. Synthesis of 5-*epi*-taiwaniaquinone G (**9**) and quinone **40**.

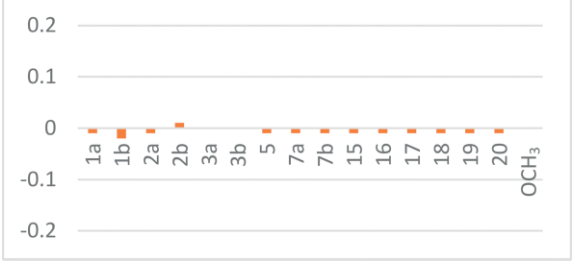


Figure 3. ^{1}H NMR chemical-shift differences between **9** and literature data reported for 5-*epi*-taiwaniaquinone G.[7a]

Figure 4. ^{13}C NMR chemical-shift differences between **9** and literature data reported for 5-*epi*-taiwaniaquinone G.[7a]

Conclusions

In contrast to published results involving longer polyene systems, the cationic cyclization of geranylbenzene derivative **13** preferentially gave the *cis*-fused 5/6-ring-containing compound **21**. We used this polyene cyclization to complete a concise synthesis of (±)-5-*epi*-taiwaniaquinone G (**9**). Our approach is the first to install the *cis* ring junction of this compound by means other than hydrogenation. While this approach is relevant for the synthesis of several taiwaniaquinoid natural products, the exclusive production of a *trans*-fused ring junction would require an additional stereocontrolling group (mimicking a fused ring) that would alter the conformation of the six-membered ring to avoid undesired H–H interactions, and favour the *trans*-selective Friedel–Crafts alkylation. Efforts to achieve this goal are currently underway.

Experimental Section

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16):[11] Compound **15** (79 mg, 0.14 mmol), geraniol (**14**; 0.46 g, 3.0 mmol), and bis(pinacolato)diborane (1.46 g, 5.75 mmol) were dissolved in methanol (6.0 mL) and DMSO (6.0 mL). *p*-Toluenesulfonic acid (29 mg, 0.17 mmol) was added, and the solution was heated to 50 °C for 20 h. The reaction mixture was cooled to room temperature, and water (10 mL) was added. The mixture was extracted with diethyl ether (3 × 15 mL), and the combined organic extracts were washed with water (15 mL) and saturated brine (15 mL), and dried with Na_2SO_4. The solvent was removed in vacuo to give a crude yellow oil. Flash chromatography (eluting with 2 % diethyl ether in hexanes) gave **16** (0.75 g, 95 %) as a pale yellow oil. IR (film): $\tilde{\nu}$ = 2956, 2928, 2872, 2835, 1595, 1484, 1452, 1415, 1377, 1358, 1346, 1250, 1105, 1053 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (m, 1 H), 5.10 (m, 1 H), 2.06–1.99 (m, 4 H), 1.68–1.58 (m, 2 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3 H), 1.25 (s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 131.1, 124.5, 118.5, 83.0, 39.8, 26.8, 25.7, 24.7, 24.6, 17.7, 15.9 ppm.

2-(2,6-Dimethoxyphenyl)propan-2-ol (18):[14] 1,3-Dimethoxybenzene (9.4 mL, 72 mmol) was dissolved in THF (200 mL). Tetramethylethylenediamine (12.0 mL, 80 mmol) was added, and the solution was cooled to −78 °C. *n*-Butyllithium (1.90 M in hexanes; 40 mL, 76 mmol) was added over 40 min, then the mixture was stirred at −78 °C for 2.5 h. Acetone (6.4 mL, 87 mmol) was added over 20 min, and the mixture was stirred at −78 °C for 30 min. Saturated aqueous ammonium chloride (40 mL) was added slowly, then the solution was warmed to room temperature and stirred overnight. The layers were separated, and the aqueous phase was

extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (2 × 100 mL), dried with Na_2SO_4, and concentrated in vacuo to give **18** (8.76 g, 62 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (t, J = 8.4 Hz, 1 H), 6.60 (d, J = 8.4 Hz, 2 H), 5.74 (br. s, 1 H), 3.82 (s, 6 H), 1.65 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 127.6, 124.4, 106.0, 74.1, 56.1, 31.1 ppm. MS (ESI): m/z (%) = 179 (100) $[M - OH]^+$.

2-Isopropyl-1,3-dimethoxybenzene (19):[14] Compound **18** (7.76 g, 39.5 mmol) was dissolved in glacial acetic acid (85 mL). Palladium on carbon (10 wt.-%; 0.59 g, 0.55 mmol) was added, and then ammonium formate (12.5 g, 199 mmol) was added portionwise. The suspension was slowly heated to 100 °C (gas evolution was observed). The mixture was kept at 100 °C for 1.5 h, then it was cooled to room temperature. The suspension was filtered through Celite, eluting with ethyl acetate (3 × 50 mL). The filtrate was washed with water (3 × 200 mL) and saturated brine (200 mL), and was then dried with Na_2SO_4. The solvent was removed in vacuo to give **19** (7.12 g, 99 %) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (t, J = 8.4 Hz, 1 H), 6.61 (d, J = 8.4 Hz, 2 H), 3.86 (s, 6 H), 3.71 (septet, J = 7.2 Hz, 1 H), 1.38 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 126.6, 124.6, 104.7, 55.8, 24.2, 20.8 ppm. MS (ESI): m/z (%) = 203 (10) $[M + Na]^+$, 219 (55) $[M + K]^+$.

1-Bromo-3-isopropyl-2,4-dimethoxybenzene (20):[14] Compound **19** (4.53 g, 25.1 mmol) was disolved in DMF (55 mL), and *N*-bromosuccinimide (4.54 g, 25.5 mmol) was added. The resulting solution was stirred in the dark for 42 h. The mixture was then poured into water (200 mL), and extracted with a hexanes/diethyl ether mixture (2:3; 3 × 100 mL). The organic extracts were washed with water (100 mL) and saturated brine (100 mL), and dried with Na_2SO_4. The solvent was removed in vacuo to give **20** (6.37 g, 98 %) as an orange-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.7 Hz, 1 H), 6.55 (d, J = 8.7 Hz, 1 H), 3.79 (app. s, 6 H), 3.52 (septet, J = 7.2 Hz, 1 H), 1.32 (d, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 155.2, 131.9, 130.4, 108.9, 108.8, 61.6, 55.7, 26.3, 21.0 ppm. MS (ESI): m/z (%) = 259/261 (10) $[M + H]^+$, 281/283 (30) $[M + Na]^+$.

(*E*)-1-(3,7-Dimethylocta-2,6-dien-1-yl)-3-isopropyl-2,4-dimethoxybenzene (13): A mixture of **16** (0.37 g, 1.4 mmol), **20** (0.75 g, 2.8 mmol), powdered sodium hydroxide (1.12 g, 28 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.086 g. 0.074 mmol) was placed under an argon atmosphere. Toluene (30 mL) and water (7.5 mL) were added, and the mixture was stirred at 90 °C for 20 h. The mixture was cooled to room temperature, and diluted with hexane (30 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (20 mL). The combined organic extracts were filtered through Celite, and the solvent was removed in vacuo. The residue was diluted with diethyl ether (10 mL) and passed through a short plug of silica gel, before being subjected to preparative reverse-phase HPLC [water/acetonitrile/0.1 % TFA (trifluoroacetic acid), gradient elution over 55 min] to give **13** (0.33 g, 73 %) as a pale yellow oil. IR (film): $\tilde{\nu}$ = 2956, 2928, 2872, 2835, 1596, 1483, 1453, 1414, 1377, 1345, 1250, 1215, 1195, 1149, 1105, 1053, 899, 801 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.4 Hz, 1 H), 5.32 (td, J = 7.2, 1.2 Hz, 1 H), 5.13 (m, 1 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.50 (septet, J = 7.1 Hz, 1 H), 3.34 (d, J = 7.2 Hz, 2 H), 2.05–2.15 (m, 4 H), 1.73 (s, 3 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.36 (d, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 156.4, 135.9, 131.5, 129.5, 127.2, 127.0, 124.5, 123.6, 107.6, 61.7, 55.5, 39.9, 27.9, 26.8, 25.8, 25.7, 21.2, 17.8, 16.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}O_2Na$ $[M + Na]^+$ 339.2295; found 339.2292.

Compounds 36 and 37: Compound **16** (790 mg, 2.5 mmol) was dissolved in nitroethane (20 mL). The solution was cooled to 0 °C, and boron trifluoride diethyl etherate (0.70 mL, 0.57 mmol) was added. The mixture was stirred for 18 h, then it was warmed to room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL). The mixture was diluted with water (40 mL) and ethyl acetate (40 mL), then extracted with ethyl acetate (2 × 30 mL). The organic layer was dried with sodium sulfate, and concentrated in vacuo to yield a crude yellow oil.

This crude oil was dissolved in dichloromethane (70 mL). The resulting solution was cooled to 0 °C, and boron tribromide (1.0 M solution in CH_2Cl_2; 7.5 mL, 7.5 mmol) was added dropwise. The solution was warmed to room temperature, and stirred for 4 h. It was then cooled to 0 °C, and ice-cold water (10 mL) was added. The mixture was diluted with ethyl acetate (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude red residue was passed through a short silica plug (eluting with ethyl acetate/pentane, 3:7). Product-containing fractions were concentrated in vacuo to give a dark yellow oil (330 mg). This was further purified by HPLC (water/acetonitrile, 35:65, isocratic, Sunfire C_{18}) to give *cis*-diol **36** (149 mg, 21 %) as a yellow oil. IR (film): $\tilde{\nu}$ = 3425, 2953, 2926, 2866, 1710, 1623, 1596, 1437, 1376, 1362, 1328, 1301, 1274, 1253, 1220, 1146, 1120, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (s, 1 H), 5.10–3.00 (br., 2 H, OH), 3.42 (septet, J = 7.2 Hz, 1 H), 2.63 (dd, J = 14.3, 7.9 Hz, 1 H), 2.51 (dd, J = 14.3, 10.8 Hz, 1 H), 1.86 (dd, J = 10.6, 8.2 Hz, 1 H), 1.62–1.53 (m, 1 H), 1.45–1.14 (m, 5 H), 1.37 (s, 3 H), 1.35 (d, J = 7.2 Hz, 6 H), 1.10 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.83, 153.81, 150.8, 118.2, 117.8, 102.1, 57.5, 45.7, 36.4, 35.2, 32.2, 31.2, 29.5, 29.2, 25.4, 24.7, 21.12, 21.10, 19.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}NaO_2$ $[M + Na]^+$ 311.19815; found 311.19829.

And rearranged diol **37** (91 mg, 13 %) as a yellow oil. IR (film): $\tilde{\nu}$ = 3425, 2929, 2868, 1710, 1617, 1587, 1459, 1421, 1376, 1314, 1256, 1213, 1196, 1145, 1097 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (s, 1 H), 4.90–4.20 (br., 2 H, OH), 3.43 (septet, J = 6.9 Hz, 1 H), 2.42 (d, J = 16.1 Hz, 1 H), 2.36 (d, J = 16.0 Hz, 1 H), 1.61–1.45 (m, 3 H), 1.36 (d, J = 7.1 Hz, 6 H), 1.32–1.27 (m, 1 H), 1.24 (s, 3 H), 1.23–1.06 (m, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 151.0, 144.5, 117.3, 116.1, 104.7, 42.8, 39.4, 38.4, 34.6, 34.0, 32.8, 31.2, 25.5, 24.8, 21.2, 21.1, 20.5, 9.3 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}O_2$ $[M - H]^-$ 287.20165; found 287.20203.

Compound 38: A solution of Fremy's salt (265 mg, 988 µmol) and potassium dihydrogenphosphate (78.0 mg, 573 µmol) in water (26 mL) was added to a solution of *cis*-diol **36** (126 mg, 437 µmol) in acetone (63.0 mL) at 0 °C. The solution was stirred overnight in the dark. The mixture was diluted with ethyl acetate (100 mL) and water (100 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried with sodium sulfate and concentrated in vacuo to give a crude orange oil. The crude mixture was passed through a silica plug (eluting with 3 % ethyl acetate/pentane) to give **38** (130 mg, 98 %) as an orange oil. UV/Vis (MeCN): λ_{max} (ε, L mol^{-1} cm^{-1}) = 286 (8780) nm. IR (film): $\tilde{\nu}$ = 3377, 2958, 2929, 2871, 1637, 1610, 1459, 1372, 1317, 1284, 1201, 1173, 1121, 1099, 1081 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (s, 1 H), 3.17 (septet, J = 7.1 Hz, 1 H), 2.71 (dd, J = 18.5, 8.1 Hz, 1 H), 2.39 (dd, J = 18.5, 11.4 Hz, 1 H), 1.85 (dt, J = 13.4, 3.6 Hz, 1 H), 1.77 (dd, J = 11.4, 8.1 Hz, 1 H), 1.69–1.55 (m, 1 H), 1.53 (s, 3 H), 1.48–1.35 (m, 1 H), 1.30 (dd, J = 8.3, 3.7 Hz, 2 H), 1.26–1.17 (m, 1 H), 1.22 (d, J = 7.0 Hz,

3 H), 1.21 (d, J = 7.1 Hz, 3 H), 1.08 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 182.1, 151.4, 149.8, 149.6, 124.2, 55.2, 47.7, 35.0, 34.3, 31.9, 31.8, 31.2, 29.6, 24.5, 24.1, 20.1, 20.0, 18.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{26}NaO_3$ $[M + Na]^+$ 325.17742; found 325.17770.

Compound 39: This compound was prepared in the same manner described above for the synthesis of **38**, but starting from **37** (68 mg, 240 µmol), to give **39** (52 mg, 73 %) as an orange oil. UV/Vis (MeCN): λ_{max} (ε, L mol^{-1} cm^{-1}) = 280 (8820) nm. IR (film): $\tilde{\nu}$ = 3365, 2929, 2870, 1635, 1609, 1456, 1395, 1380, 1362, 1328, 1271, 1258, 1242, 1210, 1157, 1105 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (s, 1 H), 3.16 (septet, J = 7.1 Hz, 1 H), 2.39 (d, J = 20.4 Hz, 1 H), 2.35 (d, J = 20.4 Hz, 1 H), 1.56–1.44 (m, 2 H), 1.50–1.37 (m, 2 H), 1.47–1.38 (m, 1 H), 1.40–1.33 (m, 1 H), 1.38 (s, 3 H), 1.22 (d, J = 7.1 Hz, 3 H), 1.21 (d, J = 7.1 Hz, 3 H), 1.21–1.15 (m, 1 H), 0.97 (d, J = 7.0 Hz, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.0, 183.3, 150.8, 148.4, 143.2, 123.9, 44.0, 40.7, 38.9, 33.8, 32.3, 30.2, 28.6, 24.2, 23.1, 20.8, 20.1, 20.0, 8.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_3$ $[M - H]^-$ 301.18092; found 301.18125.

(±)-5-*epi*-Taiwaniaquinone G (9):[7a] Compound **38** (110 mg, 360 µmol) was dissolved in acetonitrile (8.0 mL). Potassium carbonate (270 mg, 1.90 mmol) and methyl iodide (300 µL, 4.80 mmol) were added. The mixture was stirred in the dark for 18 h, then saturated aqueous sodium hydrogen carbonate (15 mL) and ethyl acetate (15 mL) were added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers dried with sodium sulfate, and concentrated in vacuo to give a crude orange oil. The crude material was purified by chromatography on neutral alumina (pentane/ethyl acetate, 99:1) to give **9** (40 mg, 130 µmol, 35 %) as an orange oil. UV/Vis (MeCN): λ_{max} (ε, L mol^{-1} cm^{-1}) = 280 (6780) nm. IR (film): $\tilde{\nu}$ = 2930, 2869, 1730, 1647, 1592, 1459, 1377, 1319, 1287, 1260, 1199, 1160, 1147 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 3.19 (septet, J = 7.1 Hz, 1 H), 2.64 (dd, J = 18.0, 8.1 Hz, 1 H), 2.35 (dd, J = 18.0, 11.5 Hz, 1 H), 1.88 (td, J = 13.5, 3.5 Hz, 1 H), 1.73 (dd, J = 11.3, 8.1 Hz, 1 H), 1.62–1.53 (m, 1 H), 1.51 (s, 3 H), 1.45–1.39 (m, 1 H), 1.30–1.15 (m, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.07 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 182.7, 156.7, 152.5, 146.3, 136.8, 61.1, 55.1, 48.1, 35.0, 34.3, 31.8, 31.2, 31.1, 29.5, 24.6, 24.4, 20.7, 20.6, 18.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}NaO_3$ $[M + Na]^+$ 339.19307; found 339.19331.

Compound 40: This compound was prepared in the same manner described above for the synthesis of **9**, but starting from **38** (52 mg, 170 µmol), to give **40** (18 mg, 57 µmol, 33 %) as an orange oil. UV/Vis (MeCN): λ_{max} (ε, L mol^{-1} cm^{-1}) = 276 (4690) nm. IR (film): $\tilde{\nu}$ = 2929, 2870, 1729, 1704, 1644, 1603, 1457, 1376, 1294, 1268, 1252, 1142 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.17 (septet, J = 6.9 Hz, 1 H), 2.37 (d, J = 20.8 Hz, 1 H), 2.24 (d, J = 20.8 Hz, 1 H), 1.75–1.69 (m, 1 H), 1.51–1.13 (m, 6 H), 1.30 (s, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.7, 184.3, 156.9, 146.7, 144.6, 135.2, 60.6, 44.1, 39.8, 39.2, 33.9, 32.2, 30.2, 28.9, 24.5, 23.0, 20.8, 20.7, 20.5, 8.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}NaO_3$ $[M + Na]^+$ 339.19307; found 339.19330.

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