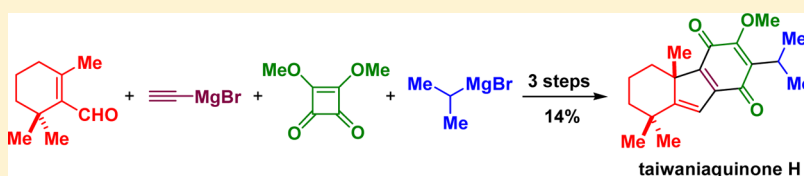


Protecting-Group-Free Synthesis of Taiwaniquinone H Using a One-Pot Thermal Ring Expansion/ 4π -Electrocyclization Strategy

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Supporting Information



ABSTRACT: A strategy to the 6-5-6 tricyclic scaffold of taiwaniquinoids was established on the basis of a one-pot thermal ring expansion/ 4π -electrocyclization process. The efficiency of this methodology has been demonstrated through its application in the total synthesis of taiwaniquinone H, which has been accomplished in three steps and 14% overall yield in a protecting-group-free manner starting from commercially available materials.

INTRODUCTION

Extensive research on taiwania cryptomerioides Hayata (*Taxodiaceae*) has uncovered a large number of natural products, including sesquiterpenes, diterpenes, lignans, and biflavones.¹ Among them, taiwaniquinoids (Figure 1) are an attractive family of terpenoids bearing an uncommon 6-5-6 tricyclic scaffold.

Various synthetic approaches have been developed for the total synthesis of taiwaniquinoids in the past few decades

because of the unusual molecular skeleton and promising biological activities, such as the antitumor activity of standishinal (**6**)² and cytotoxicity of taiwaniquinol D (**8**).³ Basically, there were five models applied to the construction of the 6-5-6 ABC tricyclic core of taiwaniquinoids in literatures. The A-AB-ABC model was utilized in the synthesis of (+)-dichroanone (**5**) by Stoltz involving an asymmetric palladium-catalyzed allylation⁴ and in the synthesis of A/B trans-fused taiwaniquinone G (**3**) by Alvarez-Manzaneda involving a thermal 6π -electrocyclization process,⁵ respectively. The C-ABC model was applied to the synthesis of taiwaniquinol B (**7**) by Fillion⁶ and Chiu⁷ through an intramolecular Friedel–Crafts acylation/carbonyl α -tert-alkylation cascade or intramolecular successive cationic cyclization, respectively. The AC-ABC model has been repetitively proven to be a divergent strategy to multiple taiwaniquinoids by groups of Node,⁸ Banerjee,⁹ Trauner,¹⁰ Alvarez-Manzaneda,¹¹ Majetich,¹² Hartwig,¹³ and Ozeki.¹⁴ A highly efficient one-step approach to the ABC tricyclic scaffold was developed by She in the synthesis of **5** and **7** through a Friedel–Crafts acylation/alkylation process.¹⁵ The B ring contraction of the 6-6-6 ABC tricyclic core has been achieved through three strategies: (1) the benzylic acid rearrangement/decarboxylation cascade in the synthesis of (–)-taiwaniquinone H (**4**) by Gademann,¹⁶ (2) the B ring-opening–ring-closure pathway to multiple A/B trans-fused taiwaniquinoids through an ozonolysis–aldol reaction process in the synthesis of standishinal (**6**) by Node¹⁷ and in the synthesis of (–)-taiwaniquinone A (**1**), (–)-taiwaniquinone F (**2**), (–)-**3**, (–)-**4**, (–)-**5**, and (–)-**7** by Alvarez-Manzaneda,^{18,19} and (3) the Wolff-rearrangement-promoted ring contraction, a divergent approach to multiple A/B trans-fused taiwaniqui-

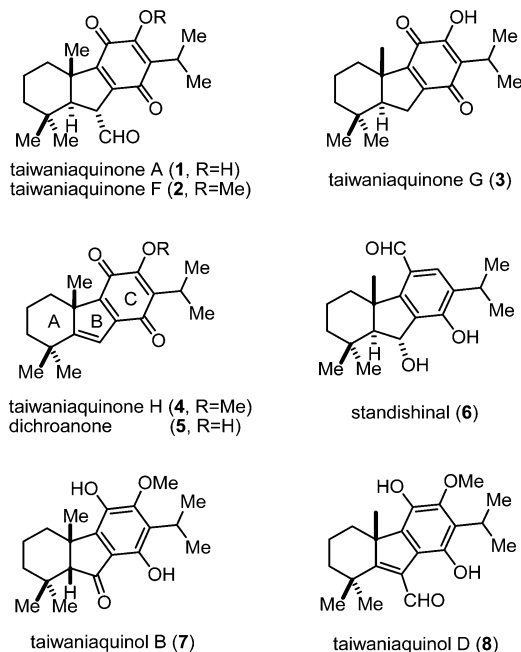


Figure 1. Representative taiwaniquinoids.

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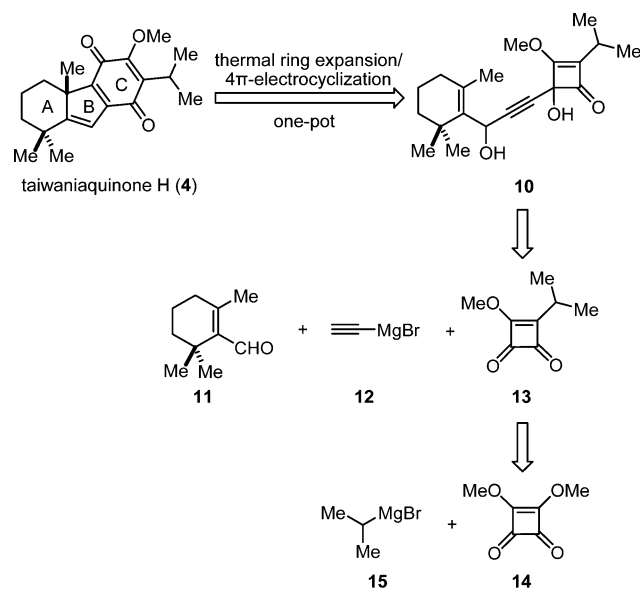
noids, applied to the synthesis of (–)-2 and (–)-taiwaniaquinol A by Gademann²⁰ and the synthesis of 1, 2, 7, and 8 by Li.²¹ As mentioned above, there have already been a number of reports on the total synthesis of taiwaniaquinoids employing different models to construct the 6-5-6 tricyclic scaffold efficiently. However, the development of a new synthetic strategy with higher efficiency is still required but is challenging.

The thermal ring expansion of cyclobutenones has initially been proven by the seminal explorations of Moore to be a powerful class of transformations and an efficient synthetic strategy to the total synthesis of various natural products.^{22–32} Notably, the thermal ring expansion of alkynyl cyclobutenones has been established as an efficient access to quinones by Moore,^{24,28,29,31} which has been utilized in our study to construct ring C of 4. Investigations from other groups, including Lieberskind,^{33–35} Paquette,^{36–40} and Martin,^{41,42} also made important contributions to the continuing development of this field. Following our interest in the development of new transformations of cyclobutenones and their applications in the synthesis of natural products,^{43,44} we developed a one-pot thermal ring expansion/ 4π -electrocyclization strategy of cyclobutenones as a concise approach to the 6-5-6 tricyclic scaffold of taiwaniaquinoids. The application of this methodology facilitated the total synthesis of 4 in only three steps starting from commercially available materials, providing, so far, the shortest synthetic route to 4. In addition, the approach features an A-AC-ABC construction pattern to the tricyclic scaffold, and no protecting groups were required.

RESULTS AND DISCUSSION

Our retrosynthetic analysis is shown in Scheme 1. Cyclobutenone 10 is furnished from the stepwise nucleophilic attack

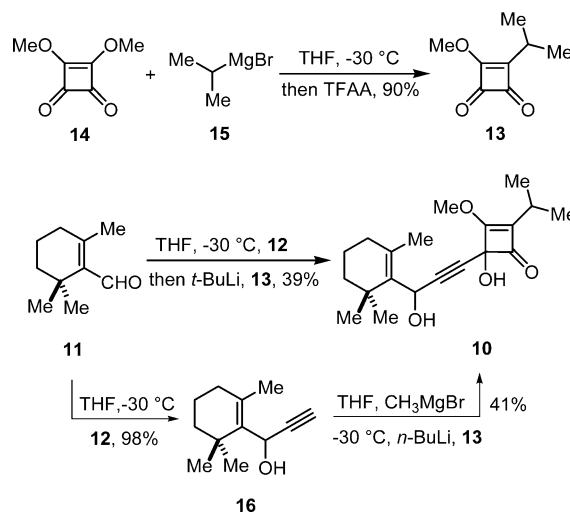
Scheme 1. Retrosynthetic Pathway to 4



of ethynylmagnesium bromide 12 to β -cyclocitral 11 and cyclobutenedione 13, which is obtained from 14 and 15 according to a known procedure.⁴⁵ As the crucial part, the one-pot thermal ring expansion/ 4π -electrocyclization process of cyclobutenone 10 accomplishes not only the construction of the B and C rings but also the total synthesis of 4.

The synthesis began with the preparation of 10 (Scheme 2). Cyclobutenedione 13 was first prepared in 90% yield from

Scheme 2. Synthesis of Cyclobutenone 10

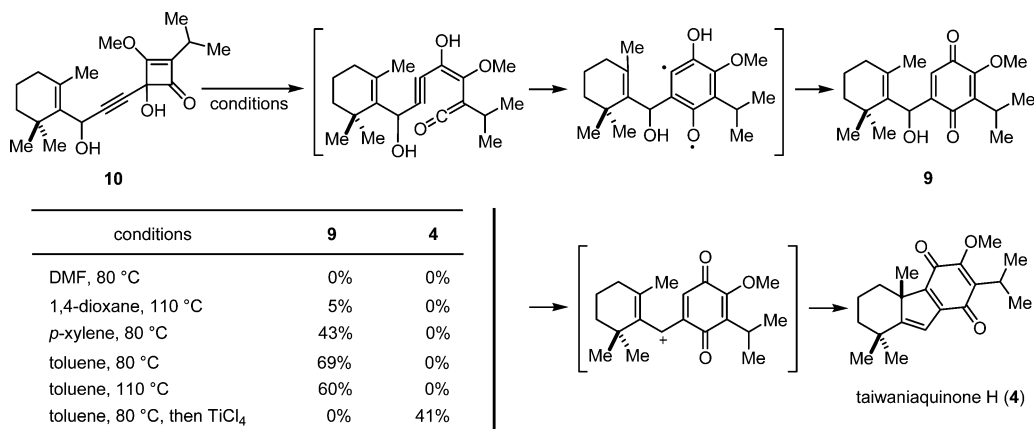


dimethyl squarate 14 and isopropylmagnesium bromide 15 through Moore's method,⁴⁵ completing the introduction of the methoxy group and the isopropyl group of the final target at the early synthetic stage. The commercially available 11 was treated with 12, t -BuLi, and 13 sequentially at -30 °C, affording 10 in one pot and 39% yield. The employment of n -BuLi led to a poorer yield. The synthesis of 10 was also executed stepwise in an attempt to optimize the synthesis of 10. The treatment of 11 with 12 formed intermediate 16 in excellent yield. The following process of the connection of 16 and 13 using the procedure of Liu⁴⁶ gave 10 in 41% yield, affording an overall yield similar to that of the one-pot procedure.

With 10 in hand, the accomplishment of the expected thermal ring expansion/ 4π -electrocyclization process is the challenge that we faced. We first checked the thermal conditions with different solvents (Scheme 3). The best result came from the treatment in toluene at 80 °C. The electrocyclic ring-opening/ring-closure cascade³¹ of 10 occurred smoothly and gave the desired ring expansion product 9 in 69% yield. Higher temperature led to the decomposition of 9, giving a decrease in the yield in the end. However, no formation of 4 was observed under these conditions. We then turned our attention to the employment of acids. Various acids have been tested in this regard. Only the reaction with TiCl_4 was confirmed as the effective access to the expected thermal ring expansion/ 4π -electrocyclization process, generating 4 in 41% yield from 10. The spectroscopic properties of 4 were identical with those of taiwaniaquinone H reported in the literature.^{9–11,13,16} Notably, worse yields were obtained when TiCl_4 was added before the thermal ring expansion was complete. The application of other reagents, including SnCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, TMSOTf , AgSbF_6 , and $\text{Pd}(\text{OAc})_2$, all led to a complex reaction system without the generation of 9 or 4 in the end.⁴⁷ To this point, the total synthesis of 4 has been achieved in only three steps.

CONCLUSIONS

In summary, a one-pot thermal ring expansion/ 4π -electrocyclization approach has been developed as a progress in our endeavors to the development of new transformations of

Scheme 3. Study of the One-Pot Thermal Ring Expansion/ 4π -Electrocyclization and Synthesis of **4**

cyclobutenones and their practical applications. It serves as a concise strategy to construct the 6-5-6 tricyclic scaffold of taiwaniaquinoids in an A-AC-ABC pattern. The accomplishment of protecting-group-free synthesis of taiwaniaquinone H in three steps and 14% total yield clearly demonstrated the efficiency of this strategy.

EXPERIMENTAL SECTION

General Experimental Methods. All of the reactions were performed under an argon atmosphere. Commercial grade solvents were distilled prior to use. Column chromatography was performed using 200–300 mesh silica gel. Thin-layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plates was accomplished with UV light (254 nm) and staining over a phosphomolybdic acid alcohol solution or a solution of 2,4-dinitrophenylhydrazine followed by heating. High-resolution mass spectra (HRMS) were recorded in ESI mode using a Q-TOF analyzer. Proton and carbon nuclear magnetic resonance spectra (¹H NMR, ¹³C NMR) were recorded on the basis of the resonating frequencies as follows: ¹H NMR at 400 MHz and ¹³C NMR at 100 MHz having the solvent resonance as internal standard (¹H NMR, CDCl₃ at 7.26 ppm and DMSO-*d*₆ at 2.50 ppm; ¹³C NMR, CDCl₃ at 77.0 ppm). Chemical shifts are reported in ppm with tetramethylsilane (TMS) at 0.00 ppm used as an internal standard and the residual solvent peak as an internal indicator.

3-Isopropyl-4-methoxycyclobut-3-ene-1,2-dione (13). Compound **13** was prepared in 90% yield according to a known procedure.⁴⁵ *R*_f = 0.7 (PE/EtOAc = 2/1). IR (neat): $\nu_{\max}$ 2972, 2876, 1792, 1762, 1599, 1469, 1368, 1318, 1029 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 4.38 (s, 3H), 2.93–3.00 (m, 1H), 1.24 (s, 3H), 1.23 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 197.7, 194.7, 194.4, 188.5, 60.9, 26.8, 19.0. HRMS (ESI⁺): *m/z* [M + Na]⁺ calcd for C₈H₁₀NaO₃, 177.0522; found, 177.0525.

1-(2,6,6-Trimethylcyclohex-1-enyl)prop-2-yn-1-ol (16). A solution of ethynylmagnesium bromide (**12**; 0.5 M in THF, 2.4 mL, 1.2 mmol) was added to a solution of β -cyclocitral (**11**; 152 mg, 1.0 mmol) in THF (10 mL) at –30 °C under argon. The system was stirred for 15 min and warmed to room temperature. The resulting reaction mixture was stirred at room temperature for another 1 h and quenched with saturated ammonium chloride solution. The aqueous phase was extracted with diethyl ether three times. The combined organic layers were washed with saturated ammonium chloride solution and saturated brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (PE/EtOAc, 20/1) to give **16** (174 mg, 98%) as a colorless oil. *R*_f = 0.4 (PE/EtOAc = 10/1). IR (neat): $\nu_{\max}$ 3392, 3306, 2930, 2867, 1459, 1370, 1023, 719, 654, 617 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.02 (s, 1H), 2.49 (s, 1H), 1.98 (t, 2H), 1.94 (s, 3H), 1.55–1.56 (m, 2H), 1.43–1.44 (m, 2H), 1.08 (s, 3H), 1.02 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 137.7, 134.5, 85.0, 72.3,

59.4, 39.3, 34.6, 33.5, 28.3, 27.5, 20.9, 19.0. HRMS (ESI⁺): *m/z* [M + Na]⁺ calcd for C₁₂H₁₈NaO, 201.1250; found, 201.1259.

4-Hydroxy-4-(3-hydroxy-3-(2,6,6-trimethylcyclohex-1-enyl)prop-1-ynyl)-2-isopropyl-3-methoxycyclobut-2-enone (10). A solution of methylmagnesium bromide (1.0 M in THF, 2.9 mL, 2.9 mmol) was added to a solution of compound **16** (428 mg, 2.4 mmol) in THF (20 mL) at –30 °C under argon. The system was stirred for 15 min and warmed to 0 °C. The system was treated with *n*-BuLi (2.4 M in hexanes, 1.2 mL, 2.9 mmol) at –30 °C and warmed to 0 °C. After 30 min of stirring, the system was added to a solution of **13** (740 mg, 4.8 mmol) in THF (5 mL). The resulting reaction mixture was stirred at –30 °C for another 5 min and quenched with saturated ammonium chloride solution. The aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with saturated ammonium chloride solution and saturated brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (PE/EtOAc, 5/1) to give **10** (326 mg, 41%) as a yellow oil. *R*_f = 0.2 (PE/EtOAc = 2/1). IR (neat): $\nu_{\max}$ 3364, 2930, 2871, 2225, 1752, 1675, 1622, 1465, 1361, 1308, 1134 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.12 (s, 1H), 4.20 (s, 3H), 2.45–2.52 (m, 1H), 2.05 (s, 1H), 1.96 (t, *J* = 8 Hz, 2H), 1.90 (s, 3H), 1.55–1.57 (m, 2H), 1.45 (t, *J* = 4 Hz, 2H), 1.15 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 187.1, 179.4, 137.1, 134.7, 134.4, 91.9, 82.4, 78.5, 59.6, 59.4, 39.4, 34.6, 33.5, 28.5, 27.5, 23.8, 21.0, 19.99, 19.95, 19.1. HRMS (ESI⁺): *m/z* [M + Na]⁺ calcd for C₂₀H₂₈NaO₄, 355.1880; found, 355.1898.

4-Hydroxy-4-(3-hydroxy-3-(2,6,6-trimethylcyclohex-1-enyl)prop-1-ynyl)-2-isopropyl-3-methoxycyclobut-2-enone (10). A solution of ethynylmagnesium bromide (**12**; 0.5 M in THF, 2.4 mL, 1.2 mmol) was added to a solution of β -cyclocitral (**11**; 152 mg, 1.0 mmol) in THF (10 mL) at –30 °C under argon. The system was stirred for 5 min and warmed to room temperature. The system was treated with *t*-BuLi (1.3 M in pentane, 1.2 mL, 1.6 mmol) at –30 °C and warmed to room temperature. After 10 min of stirring, the system was added to a solution of **13** (305 mg, 2.0 mmol) in THF (5 mL). The resulting reaction mixture was stirred at –30 °C for another 5 min and quenched with saturated ammonium chloride solution. The aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with saturated ammonium chloride solution and saturated brine and dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (PE/EtOAc, 5/1) to give **10** (130 mg, 39%), whose NMR spectra are consistent with those of compound **10** obtained from the connection of **16** and **13**.

5-(Hydroxy(2,6,6-trimethylcyclohex-1-enyl)ethyl)-3-isopropyl-2-methoxycyclohexa-2,5-diene-1,4-dione (9). Compound **10** (102 mg, 0.306 mmol) was dissolved in toluene (8 mL) and purged with argon for 15 min. The mixture was stirred at 80 °C for 6 h under argon. The reaction was then cooled to room temperature, and the solvent was removed under reduced pressure. The crude residue was

purified by silica gel chromatography (PE/EtOAc, 20/1) to give **9** (70 mg, 69%) as a yellow oil. $R_f = 0.5$ (PE/EtOAc = 10/1). IR (neat): $\nu_{\max}$ 3523, 2933, 2871, 1649, 1598, 1460, 1365, 1215 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 6.36 (s, 1H), 5.34 (s, 1H), 4.01 (s, 3H), 3.42 (s, 1H), 3.25–3.28 (m, 1H), 2.03 (t, 2H), 1.67 (s, 3H), 1.63 (m, 2H), 1.41–1.48 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 190.1, 184.6, 155.9, 147.5, 137.9, 136.0, 133.9, 131.0, 67.4, 61.0, 39.4, 34.6, 33.4, 28.4, 27.8, 24.6, 22.4, 20.4, 20.3, 19.0. HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{28}\text{NaO}_4$, 355.1880; found, 355.1871.

Taiwaniaquinone H (4). Compound **10** (31 mg, 0.095 mmol) was dissolved in toluene (4 mL), and the solution was purged with argon for 15 min. The mixture was stirred at 80 °C for 6 h under argon. The reaction mixture was cooled to room temperature and treated with titanium tetrachloride (1.0 M in methylene chloride, 0.095 mL, 0.095 mmol). After it was stirred for 30 min, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with EtOAc three times. The combined organic layers were washed with saturated sodium bicarbonate solution and saturated brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography (PE/EtOAc, 20/1) to give taiwaniaquinone H (**4**; 12 mg, 41%) as a red-orange solid. The analytical data for **4** agreed with those reported previously.^{9–11,13,16} $R_f = 0.6$ (PE/EtOAc = 10/1). Mp: 81–83 °C. IR (neat): $\nu_{\max}$ 2930, 2870, 1643, 1615, 1457, 1353, 1120 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 6.38 (s, 1H), 3.99 (s, 3H), 3.26 (septet, 1H), 2.36–2.42 (m, 1H), 1.87–1.97 (m, 1H), 1.67–1.71 (m, 1H), 1.60–1.64 (m, 1H), 1.44 (s, 3H), 1.27 (s, 3H), 1.246 (d, 3H), 1.243 (d, 3H), 1.22 (s, 3H), 1.03–1.13 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 186.3, 178.7, 175.7, 157.3, 150.5, 145.8, 135.9, 116.7, 61.3, 55.6, 43.3, 37.2, 36.7, 30.9, 24.8, 24.4, 20.7, 20.6, 20.1, 19.1. HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_3$, 337.1774; found, 337.1781.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra of related compounds. 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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