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A Synthetic Entry into the Taiwaniaquinoids Based on a Biogenetic Hypothesis: Total Synthesis of (−)-Taiwaniaquinone H

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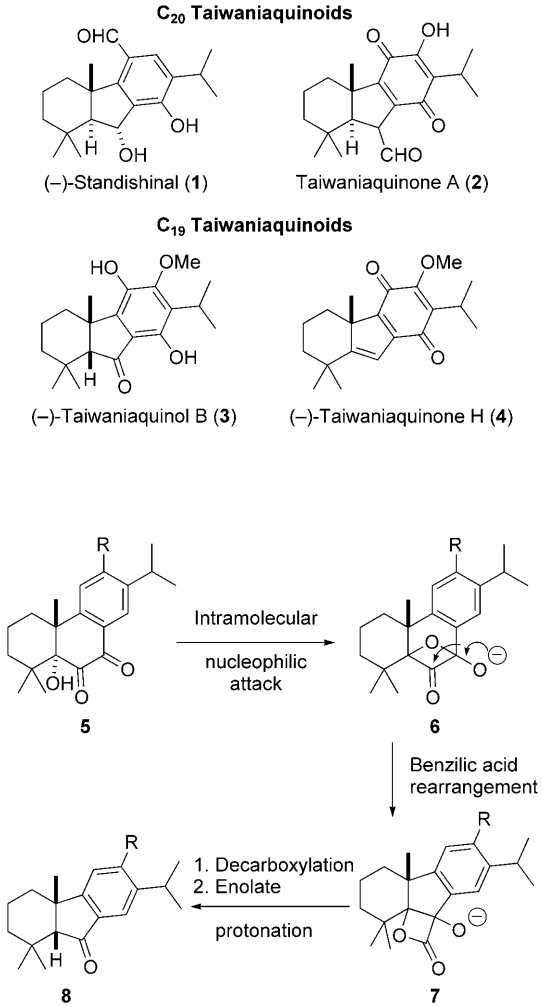
The complex structures of terpenes have been stimulating the creativity of chemists for decades[1] and many powerful synthetic approaches addressing these challenges have been developed. Taiwaniaquinoids are rearranged diterpenoids either featuring a CHO group at unusual positions, such as in **1** or **2**, or have undergone loss of one carbon to represent C_{19} nor-diterpenoids (e.g., **3** and **4**).[2] Their interesting structure combined with significant bioactivity (such as aromatase inhibition or cytotoxicity to human oral epidermoid carcinoma KB cells) prompted the syntheses of several members of this family.[3] All synthetic strategies reported so far rely on ring-formation approaches for the buildup of the unusual 6-5-6 ring system. As the biogenesis of these compounds has not yet been investigated, we became interested in their possible biosynthesis. Herein, we present a hypothesis for the biosynthesis of the C_{19} tawaniaquinoids and evaluate this proposal in the chemical laboratory by a protecting-group-free total synthesis[4] of (−)-taiwaniaquinone H (**4**) from abietane.

Two biosynthetic proposals have been set forth in the context of the formation of the rearranged C_{20} diterpenes **1**[2c] and **2**.[2a] However, both hypotheses did not account for the loss of a carbon atom as required for the formation of the C_{19} nor-diterpenes, such as dichronanone, **3**, **4**, and taiwaniaquinone G.

Therefore, the formation of these C_{19} compounds can be rationalized by the sequence shown in Scheme 1. The starting point would be a suitably oxidized precursor (such as **5**) of ferruginol or abietane, of which similar compounds have been isolated from natural sources.[5] Then, a benzilic acid rearrangement involving an internal nucleophile mediated by base could result in the 3-oxetanone **6**. This postulated structure of **6** is supported by over 20 steroid derivatives



Scheme 1. Formation of the 6-5-6 taiwaniaquinoid skeleton by benzilic acid rearrangement and decarboxylation.

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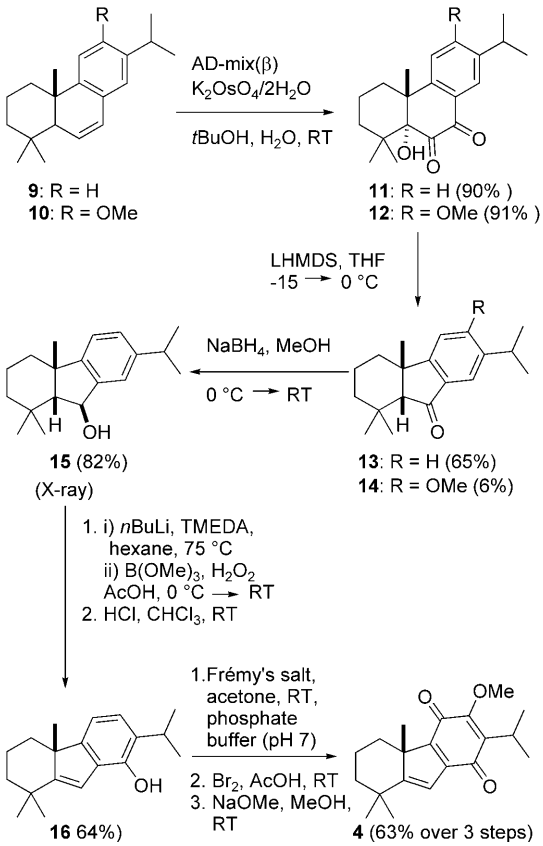
featuring a 3-oxetanone in the B ring.[6] Alternatively, internal attack of the nucleophile on the other keto group or external, intermolecular processes are also feasible. The 3-oxetanone **6** could then undergo a benzilic acid rearrangement with migration of the aryl group resulting in the lactone **7**. This compound would then decarboxylate and the resulting enolate, after protonation, would give rise to the hydrofluorenone **8** featuring the desired 6-5-6 ring system of the taiwaniaquinoids.

Further support for this hypothesis stems from decades of research on the biosynthesis of gibberellins,[7] in which ring contractions of suitably oxidized precursors enable the transformation of the kaurene into the gibberellane skeleton. To evaluate the feasibility of this biogenetic proposal outlined above in the chemical laboratory, we embarked on the total synthesis of **4** through the sequence outlined in Scheme 2.



Scheme 2. Total synthesis of **4**. LHMDS = lithium hexamethyldisilazide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

The starting material **9** can be obtained from commercially available methyl dehydroabiate in five steps according to literature procedures.[8b] The hydroxydiketone functionality of the key intermediates **11** and **12** was installed in a single step from the known[8] 6,7-dehydroabietatrienes **9** and **10**, respectively, through a Sharpless asymmetric dihydroxylation reaction[9] (Scheme 2). The hydroxydiketones **11** (90%) and **12** (91%) were thus obtained in very good yields and with excellent diastereoselectivities. The relative configuration of **11** was confirmed by X-ray crystallography (see Figure 1).[10] The ring contraction of the hydroxydiketone as

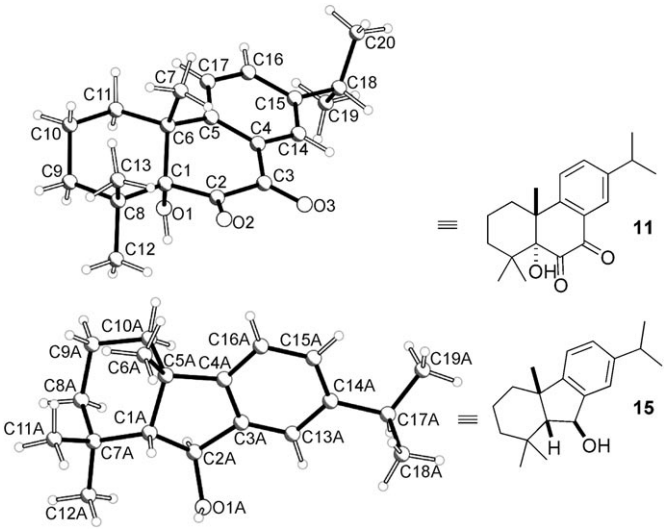


Figure 1. X-ray crystal structures of **11** and **15**.

a key step of the postulated biogenesis was evaluated next and several conditions for this ring contraction have been evaluated (Table 1). While organic bases such as DBU resulted in no conversion, CaO affected product formation in trace amounts. Significantly, NaH at room temperature resulted in 20% yield of ketone **13**, which could be improved by lowering the temperature to 0°C (Table 1, entry 4). Increased yields were obtained by using LHMDS (Table 1, entries 5 and 6), and treatment of the hydroxydione **11** with LHMDS gave the hydrofluorene derivative **13** in good yield which could be improved to 65% by lowering the temperature (Table 1, entry 6). Other bases such as NaOMe or Lewis acids did not initiate this process.

Table 1. Bases evaluated in the ring contraction of compound **11**.[a]

Entry	Base	Temperature [°C]	Yield [%][b]
1	DBU[c]	RT	no reaction
2	CaO[d]	RT	trace
3	NaH	RT	20
4	NaH	0	30
5	LHMDS	RT	42
6	LHMDS	−15 to 0	65
7	NaOMe[e]	RT	complex mixture
8	$Ti(OiPr)_4$	RT	no reaction

[a] Reaction conditions: 1.2 equiv base in THF at 0.01 M concentration. [b] Yield of isolated product. [c] DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene. [d] Reaction was carried out in MeOH. [e] A solution of 0.5 M NaOMe in MeOH was used and the reaction was carried out in THF.

We rationalize the formation of this compound through an internal-nucleophile-induced intramolecular benzilic acid type rearrangement followed by decarboxylation in analogy to the biosynthetic proposal outlined in Scheme 1. As expected, conversion of the electron-rich hydroxydione **12**, when treated under the same conditions, resulted in much lower yield, which is in line with the decreased electrophilicity of the benzylic keto group. This difference, based on electronic structure, offers further support to our mechanistic proposal for the ring contraction through an 3-oxetanone intermediate (see Scheme 1).

By securing the required carbon skeleton for the C_{19} taiwaniaquinoids, the stage was ready for the oxidation of the aromatic ring of ketone **13**. To that end, various methods have been attempted in vain. Finally, to facilitate the aromatic oxidation, we decided to use the hydroxy group of benzylic alcohol **15**, which was obtained from the ketone **13** through a $NaBH_4$-mediated diastereoselective reduction (82%). The relative configuration of **15** was confirmed by single-crystal X-ray diffraction analysis (Figure 1).[10] Accordingly, a one-pot sequence of hydroxy-group-directed *ortho* lithiation of the benzylic alcohol **15** following a method developed by Seebach and Meyer,[11a] subsequent borylation of the aryl lithium compound and oxidation of the corresponding aryl boronate gave the hydroxylated phenol derivative. A straightforward dehydration under acidic conditions then readily resulted in the dehydrated phenol **16** in 64% yield over two steps (Scheme 2). This phenol **16** was then cleanly oxidized using Frémy's salt to the corresponding *p*-quinone. Electrophilic bromination of the quinone followed by substitution with a methoxy group gave **4** in 63% yield over three steps (from **16**). The analytical data obtained for **4** are in agreement with the literature.[2f,3d,4k,n] However, the value of the optical rotation measured ($[\alpha]_D^{23} = -95.7$ (*c* 0.21, $CHCl_3$)) was higher than that of reported values.[12]

In conclusion, we have presented a biogenetic hypothesis for the transformation of an abietane-type diterpene into the 6-5-6 skeleton of the taiwaniaquinoids by a ring contraction of an oxidized precursor. This blueprint has been successfully utilized for the total synthesis of **4** in 12 steps from a commercially available starting material. Salient features of this synthesis based on a biogenetic proposal include 1) a benzilic acid rearrangement featuring an intramolecular nucleophilic attack and subsequent decarboxylation, 2) a protecting-group-free reaction sequence, and 3) functionalization of the aryl group by directed metalation. The biogenetic proposal outlined herein could help to elucidate the actual biosynthesis, to identify currently unknown intermediates in the producing organism, and to facilitate additional stereoselective syntheses of these unusual taiwaniaquinoids.

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Keywords: natural products · protecting-group-free synthesis · rearrangement · terpenes · total synthesis

[1] a) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890–1904; b) W. C. Still, *J. Am. Chem. Soc.* **1979**, *101*, 2493–2495; c) D. P. Curran, D. M. Rakiewicz, *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449; d) P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977; e) M. E. Layton, C. A. Morales, M. D. Shair, *J. Am. Chem. Soc.* **2002**, *124*, 773–775.

[2] a) W. H. Lin, J. M. Fang, Y. S. Cheng, *Phytochemistry* **1995**, *40*, 871–873; b) K. Kawazoe, M. Yamamoto, Y. Takaishi, G. Honda, T. Fujita, E. Sezik, E. Yesilada, *Phytochemistry* **1999**, *50*, 493–497; c) H. Ohtsu, M. Iwamoto, H. Ohishi, S. Matsunaga, R. Tanaka, *Tetrahedron Lett.* **1999**, *40*, 6419–6422; d) C. I. Chang, S. C. Chien, S. M. Lee, Y. H. Kuo, *Chem. Pharm. Bull.* **2003**, *51*, 1420–1422; e) C. I. Chang, J. Y. Chang, C. C. Kuo, W. Y. Pan, Y. H. Kuo, *Planta Med.* **2005**, *71*, 72–76; f) For a recent review, see: G. Majetich, J. M. Shimkus, *J. Nat. Prod.* **2010**, *73*, 284–298.

[3] a) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *Org. Lett.* **2003**, *5*, 3931–3933; b) E. Fillion, D. Fishlock, *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145; c) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *J. Org. Chem.* **2006**, *71*, 2787–2796; d) G. X. Liang, Y. Xu, I. B. Seiple, D. Trauner, *J. Am. Chem. Soc.* **2006**, *128*, 11022–11023; e) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739; f) L. Planas, M. Mogi, H. Takita, T. Kajimoto, M. Node, *J. Org. Chem.* **2006**, *71*, 2896–2898; g) T. Katoh, T. Akagi, C. Noguchi, T. Kajimoto, M. Node, R. Tanaka, M. Nishizawa, H. Ohtsu, N. Suzuki, K. Saito, *Bioorg. Med. Chem.* **2007**, *15*, 2736–2748; h) S. L. Li, P. Chiu, *Tetrahedron Lett.* **2008**, *49*, 1741–1744; i) S. Tang, Y. Xu, J. He, J. Zheng, X. Pan, X. She, *Org. Lett.* **2008**, *10*, 1855–1858; j) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, R. Alvarez-Manzaneda, R. Meneses, H. Es-Samti, A. Fernandez, *J. Org. Chem.* **2009**, *74*, 3384–3388; k) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, Y. Charrah, H. Es-Samti, *Org. Biomol. Chem.* **2009**, *7*, 5146–5155; l) E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, M. Hmamouchi, H. Es-Samti, *Chem. Commun.* **2009**, 592–594; m) G. Majetich, J. M. Shimkus, *Tetrahedron Lett.* **2009**, *50*, 3311–3313; n) M. Node, M. Ozeki, L. Planas, M. Nakano, H. Takita, D. Mori, S. Tamatani, T. Kajimoto, *J. Org. Chem.* **2010**, *75*, 190–196.

[4] For reviews, see: a) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193–205; b) K. Gademann, S. Bonazzi *Angew. Chem.* **2007**, *119, 5754–5756; Angew. Chem. Int. Ed.* **2007**, 46, 5656–5658; *Angew. Chem. Int. Ed.* **2007**, *46*, 5656–5658; c) R. W. Hoffmann, *Synthesis* **2006**, 3531–3541.

[5] a) J. B. Bredenberg, *Acta Chem. Scand.* **1960**, *14*, 385–390; b) T. Miyase, P. Rüedi, C. H. Eugster, *Helv. Chim. Acta* **1977**, *60*, 2770–2779; c) N. Kusumoto, T. Ashitani, Y. Hayasaka, T. Murayama, K. Ogiyama, K. Takahashi, *J. Chem. Ecol.* **2009**, *35*, 635–642.

[6] a) A. T. Rowland, P. J. Bennett, T. S. Shoupe, *J. Org. Chem.* **1968**, *33*, 2426–2436; b) R. Hanna, G. Maalouf, B. Muckensturm, A. Cherry, *Tetrahedron* **1973**, *29*, 2297–2303; c) A. T. Rowland, R. S. Drawbaugh, J. R. Dalton, *J. Org. Chem.* **1977**, *42*, 487–490; d) H. Duddeck, J. Frelek, D. Horvatic, B. Kojicprodic, G. Snatzke, W. J. Szczepek, P. Wagner, *J. Phys. Org. Chem.* **1990**, *3*, 404–413.

[7] a) A. Tahara, *Chem. Pharm. Bull.* **1961**, *9*, 252–253; b) J. F. Grove, B. J. Riley, *J. Chem. Soc.* **1961**, 1105–1112; c) B. Brückner, D. Blechschmidt, *Appl. Microbiol. Biotechnol.* **1991**, *35*, 646–650; d) B. Brückner, D. Blechschmidt, *Crit. Rev. Biotechnol.* **1991**, *11*, 163–192; e) B. Brückner, D. Blechschmidt, R. D. Recknagel, *J. Basic Microbiol.* **1991**, *31*, 243–250; f) J. MacMillan, D. A. Ward, A. L. Phil-

lips, M. J. Sanchez Beltran, P. Gaskin, T. Lange, P. Hedden, *Plant Physiol.* **1997**, *113*, 1369–1377; g) B. Tudzynski, K. Holter, *Fungal Genet. Biol.* **1998**, *25*, 157–170; h) B. Tudzynski, *Appl. Microbiol. Biotechnol.* **1999**, *52*, 298–310; i) J. Anaya, J. J. Fernandez, M. Grande, J. Martianez, P. Torres, *Nat. Prod. Commun.* **2008**, *3*, 483–494; j) L. N. Mander, *Nat. Prod. Rep.* **2003**, *20*, 49–69.

[8] a) 6,7-Dehydroferruginol is also found in nature, see reference [2a]; b) J. Geiwiz, E. Haslinger, *Helv. Chim. Acta* **1995**, *78*, 818–832.

[9] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X-L Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771.

[10] CCDC-770124 (**11**), 770125 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The crystallographic abstracts for these compounds are given in the Supporting Information.

[11] a) N. Meyer, D. Seebach, *Angew. Chem.* **1978**, *90*, 553–554; *Angew. Chem. Int. Ed. Eng.* **1978**, *17*, 521–522; b) T. P. Loh, Q. Y. Hu, *Org. Lett.* **2001**, *3*, 279–281.

[12] Literature values for (−)-taiwaniaquinone (**4**): $[\alpha]_D^{21} = -36.9$ ($c = 0.30$ in $CHCl_3$)[3n], $[\alpha]_D^{25} = -11.9$ ($c = 0.56$ in $CHCl_3$)[3k]; $[\alpha]_D^{25} = -9.0$ ($c = 0.29$ in $CHCl_3$)[2f]).

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