ORGANIC LETTERS

2013
Vol. 15, No. 8
2022–2025

Divergent Total Synthesis of Taiwaniaquinones A and F and Taiwaniaquinols B and D

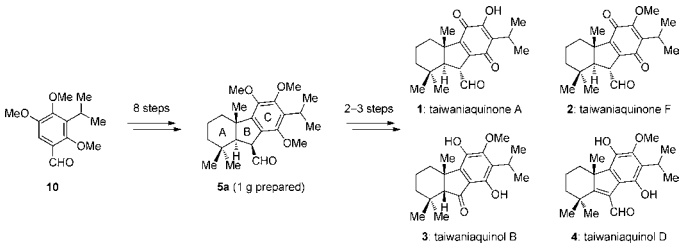
Jun Deng,[†] Ruofan Li,[†] Yijie Luo, Jian Li, Shupeng Zhou, Yongjian Li, Jingyu Hu, and Ang Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ali@sioc.ac.cn

Received March 18, 2013

ABSTRACT



A divergent approach was developed toward the total synthesis of taiwaniaquinoids. An advanced intermediate 5a with *trans* A/B ring junction was concisely assembled by employing a $Bi(OTf)_3$-catalyzed cationic cyclization and a Wolff-type ring contraction as key steps. This common intermediate was readily converted to racemic taiwaniaquinones A and F and taiwaniaquinols B and D, respectively.

Taiwaniaquinoids are a class of natural products possessing an unusual 6,5,6-abeoabietane scaffold first isolated from *Taiwania cryptomerioides* by Cheng and co-workers.[1] To date, more than 20 members (e.g., **1**–**4**, Figure 1) from this diterpenoid family have been identified, some of which display antitumor activities.[1f,2] In the past decade, taiwaniaquinoids attracted remarkable attention from the synthetic community: a stream of total and formal syntheses of these fascinating molecules have been accomplished,[2c,3] during which a number of synthetically useful reactions were developed.[3b,e,f,o]

Notably, intense efforts were focused on the synthesis of taiwaniaquinoids with a *cis* A/B ring junction such as

[†] These authors contributed equally to this work.

(1) (a) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871. (b) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657. (c) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493. (d) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419. (e) Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420. (f) Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72. A comprehensive review: (g) Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284.

(2) (a) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911. (b) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742. (c) Katoh, T.; Akagi, T.; Noguchi, C.; Kajimoto, T.; Node, M.; Tanaka, R.; Nishizawa, M.; Ohtsu, H.; Suzuki, N.; Saito, K. *Bioorg. Med. Chem.* **2007**, *15*, 2736.

(3) (a) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Org. Lett.* **2003**, *5*, 3931. (b) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144. (c) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2006**, *71*, 2787. (d) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896. (e) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738. (f) Liang, G. X.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022. (g) Li, S. L.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741. (h) Tang, S. C.; Xu, Y. F.; He, J. M.; He, Y. P.; Zheng, J. Y.; Pan, X. F.; She, X. G. *Org. Lett.* **2008**, *10*, 1855. (i) Majetich, G.; Shimkus, J. M. *Tetrahedron Lett.* **2009**, *50*, 3311. (j) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernandez, A. *J. Org. Chem.* **2009**, *74*, 3384. (k) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Charrah, Y.; Es-Samti, H. *Org. Biomol. Chem.* **2009**, *7*, 5146. (l) Node, M.; Ozeki, M.; Planas, L.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimoto, T. *J. Org. Chem.* **2010**, *75*, 190. (m) Jana, C. K.; Scopelliti, R.; Gademann, K. *Synthesis* **2010**, 2223. (n) Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem.—Eur. J.* **2010**, *16*, 7692. (o) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088. (p) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592. (q) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. *Chem. Commun.* **2010**, 9244. (r) Tapia, R.; Guardia, J. J.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2012**, *77*, 573.

10.1021/ol400717h
Published on Web 04/11/2013

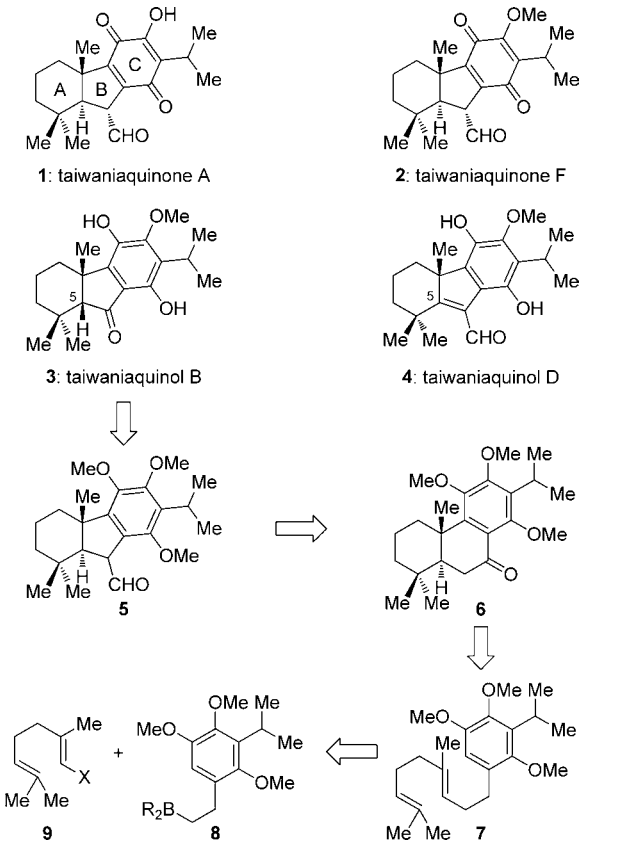


Figure 1. Structures of selected taiwaniaquinoids (**1**–**4**) and retrosynthetic analysis.

taiwaniaquinol B (**3**, Figure 1), as well as those containing a C5 sp^2 center such as taiwaniaquinol D (**4**, Figure 1).[3a–o] However, only two total syntheses of taiwaniaquinone A (**1**) or F (**2**) possessing a *trans* A/B ring junction have been disclosed; both started with stereochemically advanced precursors (e.g., naturally occurring abietic acid and manool).[3q,r,4] Herein, we report a concise and scalable route leading to the total synthesis of racemic taiwaniaquinones A and F and taiwaniaquinols B and D (**1**–**4**, Figure 1).

In their original isolation report, Cheng et al. proposed a biosynthetic hypothesis of the 6,5,6-tricyclic core of taiwaniaquinoids involving a pinacol type rearrangement of a 6,6,6-tricyclic diol precursor. Inspired by this speculation, we devised a ring contraction strategy for the divergent synthesis of taiwaniaquinoids **1**–**4**, as shown in Figure 1; 6,5,6-tricyclic aldehyde **5** with a *trans* A/B ring junction was considered as a common intermediate. Taiwaniaquinol D (**4**) bearing a C5 sp^2 center should be readily accessible by dehydrogenation, while *cis*-fused taiwaniaquinol B (**3**) could be reached through oxidative cleavage of the carbonyl functionality of **5** followed by C5 epimerization under thermodynamic conditions.[5] For the construction of **5**, a Wolff rearrangement[6] reaction was considered as a manner of ring contraction. Thus, ketone **6** would serve as the suitable precursor for preparing the corresponding α-diazoketone. Assembly of **6** may require a cationic cyclization of diene **7**,[7] which was further traced back to readily available alkylborane **8** and alkenyl halide **9**.[8]

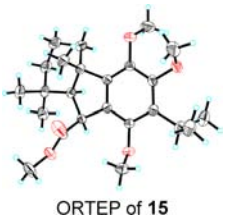


Figure 2. X-ray derived ORTEP of compound **15**.

Based on the above analysis, we first focused our attention to the assembly of the common intermediate **5**, as shown in Scheme 1. Aldehyde **10** was readily prepared from commercially available 1,2,4-trimethoxybenzene in four steps.[9] Treatment of **10** with methylenetriphenylphosphorane furnished styrene **11** in 92% yield, which was hydroborated with 9-BBN to afford the corresponding alkylborane.[10,11] This in situ generated borane was subjected to Suzuki–Miyaura coupling conditions [$Pd(dppf)Cl_2$ (5%), aq NaOH, THF, 40 °C][11] in the presence of alkenyl iodide **12**[8] to give homogeranyl arene **7** in 83% overall yield from **11**. A variety of Brønsted and Lewis acids were examined to effect a cationic cyclization of **7**, and $Bi(OTf)_3$ was the most efficient promoter. Thus, treatment of $Bi(OTf)_3$ (10%) in $MeNO_2$ at 80 °C provided tricyclic compound **13** in 71% yield as a single diastereomer. The *trans* A/B ring junction was secured by the Friedel–Crafts process. Introduction of the benzylic carbonyl functionality to **13** was achieved by oxidation with freshly prepared CrO_3/3,5-dimethylpyrazole[12] at −10 °C (89% yield), while other chromic oxidants such as PCC,[3c] CrO_3/AcOH,[2c] and Jones reagent resulted in modest to poor

(4) Gademann et al. pubished the synthesis of taiwaniaquinone F and taiwaniaquinol A using a similar ring contraction strategy when this manuscript was being written: Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390.

(5) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, 2911.

(6) A comprehensive review: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

(7) (a) Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (c) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (d) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (e) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (f) Godeau, J.; Olivero, S.; Antoniotti, S.; Duñach, E. *Org. Lett.* **2011**, *13*, 3320. (g) Godeau, J.; Fontaine-Vive, F.; Antoniotti, S.; Duñach, E. *Chem.—Eur. J.* **2012**, *18*, 16815. (h) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992.

(8) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

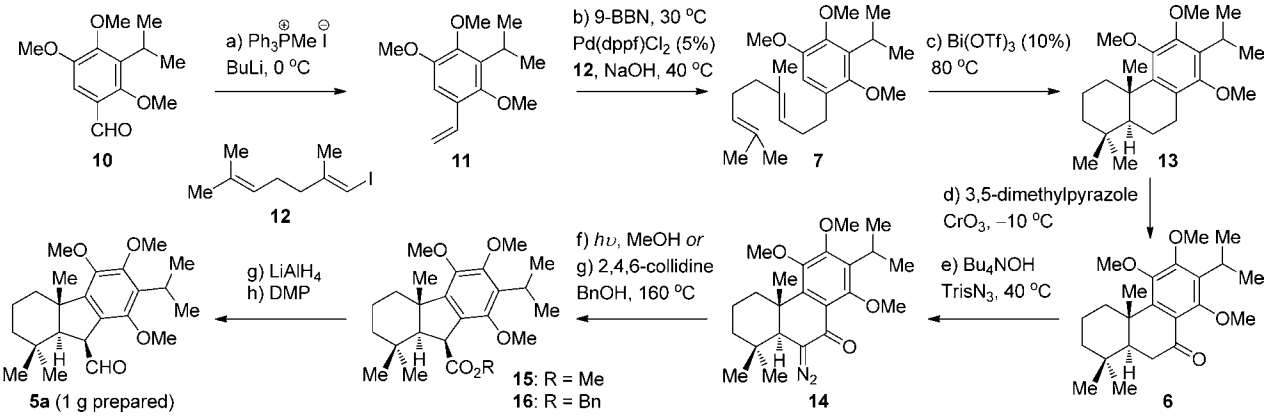
(9) Padwa, A.; Chughtai, M. J.; Boonsombat, J.; Rashatasakhon, P. *Tetrahedron* **2008**, *64*, 4758.

(10) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Org. Synth.* **1993**, *71*, 89.

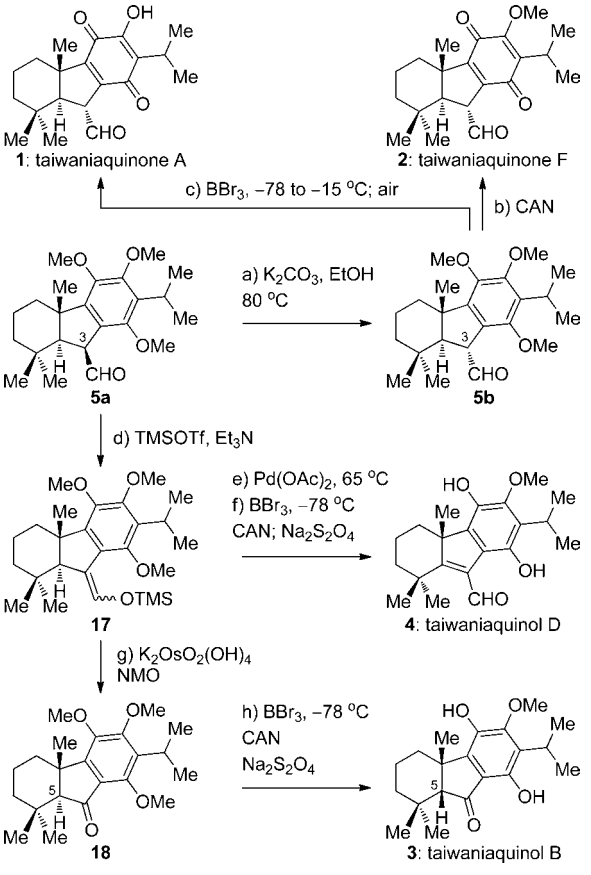
(11) Winne, J. M.; Guang, B.; D'herde, J.; De Clercq, P. J. *Org. Lett.* **2006**, *8*, 4815.

(12) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

Scheme 1. Construction of a Common Intermediate **5a** Employing a Ring-Contraction Strategy



Scheme 2. Conversion of **5a** to Taiwaniaquinones A and F, and Taiwaniaquinols B and D



efficiency. Ketone **6** was then converted to α-diazoketone **14** in 78% yield by treatment of 2,4,6-triisopropylbenzenesulfonyl azide and Bu_4NOH,[13] which set the stage for the devised Wolff rearrangement. Attempts to initiate such rearrangement using silver salts[6,14] were fruitless, while irritation of a solution of **14** in MeOH with a medium-pressure Hg lamp[6,15] rendered methyl ester **15** as a single diastereomer in 30% yield, the structure of which was unambiguously verified by X-ray crystallographic analysis (Figure 2, mp 139–141 °C, EtOAc/petroleum ether 1:1). However, the efficiency of this reaction decreased drastically on a more practical scale (> 50 mg), which hampered the subsequent progress toward the collective synthesis of taiwaniaquinoids. To our delight, thermal conditions (BnOH, 2,4,6-collidine, 160 °C)[6,16] were found to be superior to the above photochemical conditions on a large scale, affording the corresponding benzyl ester **16** as a single detectable diastereomer in 56% yield. Reduction of **16** with $LiAH_4$ followed by oxidation with Dess–Martin periodione furnished aldehyde **5a** in 75% yield over the two steps. The above sequence scaled reliably, and 1 g of **5a** was readily prepared.

With the advanced intermediate **5a** in hand, we moved forward to investigate its conversion to taiwaniaquinones A and F and taiwaniaquinols B and D in a divergent manner, as shown in Scheme 2. Epimerization of aldehyde **5a** promoted by K_2CO_3/EtOH at 80 °C afforded **5b** in 93% yield, which established the desired C3 stereochemistry for taiwaniaquinones A and F. Global demethylation of **5a** with excess of BBr_3 followed by spontaneous aerobic oxidation furnished the former natural product in 76% yield, while oxidation with CAN rendered the latter natural product in 76% yield. The spectral data of the synthetic taiwaniaquinones A and F are identical to those reported for the natural products, respectively.[1a,e] In another direction, treatment of **5a** with TMSOTf and Et_3N gave silyl enol ether **17** (an inconsequential mixture of ca. 1.2:1 *cis*/*trans* isomers) in 92% yield, which underwent a sequence of Saegusa–Ito oxidation,[17] monodemethylation,

(13) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

(14) (a) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (b) Nicolaou, K. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2678.

(15) Ihara, M.; Katogi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 721.

(16) (a) Wilds, A. L.; Meader, A. L., Jr. *J. Org. Chem.* **1948**, *13*, 763. (b) Sudrik, S. G.; Chavan, S. P.; Chandrakumar, K. R. S.; Pal, S.; Date, S. K.; Chavan, S. P.; Sonawane, H. R. *J. Org. Chem.* **2002**, *67*, 1574.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

and one-pot oxidation/reduction[3f] to afford taiwaniaquinol D in 80% yield over the three steps. When **17** was subjected to dihydroxylation conditions [$K_2OsO_2(OH)_4$, NMO], a cleavage product **18** (79% yield) was obtained directly, together with a small amount of the expected α-hydroxy aldehyde.[18] Notably, compound **18** could be epimerized at the C5 position under basic conditions (DBU, toluene, 80 °C)[5] to generate the corresponding *cis*-fused isomer that was widely used as a late intermediate in the previous syntheses of taiwaniaquinol B.[3c,i,g] To our delight, the *trans*-fused intermediate **18** underwent the same sequence used for taiwaniaquinol D synthesis to render taiwaniaquinol B in 81% overall yield.[3g] It was detected by TLC analysis that the epimerization at C5 occurred rapidly under the BBr_3 conditions even before monodemethylation took place.[19] The spectral data of the synthetic taiwaniaquinols B and D are consistent with those of the naturally occurring compounds, respectively.[1a,b]

(18) A mechanistically inspiring oxidative cleavage: Burden, P. M.; Cheung, A. H. T.; Watson, T. R.; Ferguson, G.; Seymour, P. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 169.

(19) An $AlCl_3$-promoted epimerization of a similar tricyclic system: House, H. O.; Paragamian, V.; Ro, R. S.; Wluka, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1457.

In conclusion, we developed an efficient route for the divergent total synthesis of taiwaniaquinones A and F and taiwaniaquinols B and D in racemic forms. The common intermediate **5a** possessing a *trans*-fused 6,5,6-ring system was synthesized on a large scale by using a Wolff type ring contraction reaction as a key step. This intermediate was further converted to the above natural products in 2−3 steps. This work may facilitate the biological studies on taiwaniaquinoids and analogues thereof. The asymmetric version of the synthesis is currently underway in our laboratories.

Acknowledgment. We thank Prof. Guangxin Liang (Nankai University) for helpful discussions. Financial support was provided by the Ministry of Science & Technology (2013CB836900), National Natural Science Foundation of China (21290180, 21172235, and 21222202), and Chinese Academy of Sciences.

Supporting Information Available. Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.