Total Syntheses of (±)-Taiwaniaquinol D and (±)-Taiwaniaquinone D *via* a Key Lewis Acid-Catalyzed Nazarov Type Cyclization

Badrinath N. Kakde, Amarchand Parida, Pooja Kumari, Alakesh Bisai

PII: S0040-4039(16)30699-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.06.030
Reference: TETL 47757

To appear in: *Tetrahedron Letters*

Received Date: 31 March 2016
Revised Date: 7 June 2016
Accepted Date: 8 June 2016

Please cite this article as: Kakde, B.N., Parida, A., Kumari, P., Bisai, A., Total Syntheses of (±)-Taiwaniaquinol D and (±)-Taiwaniaquinone D *via* a Key Lewis Acid-Catalyzed Nazarov Type Cyclization, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.06.030

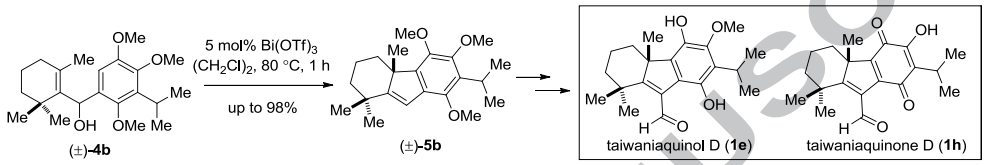
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Total Syntheses of (±)-Taiwaniaquinol D and (±)-Taiwaniaquinone D via a key Lewis Acid-Catalyzed Nazarov Type Cyclization

Leave this area blank for abstract info.

Badrinath N. Kakde, Amarchand Parida, Pooja Kumari,[§] and Alakesh Bisai*



Tetrahedron Letters
journal homepage: www.elsevier.com

Total Syntheses of (±)-Taiwaniaquinol D and (±)-Taiwaniaquinone D *via* a Key Lewis Acid-Catalyzed Nazarov Type Cyclization

Badrinath N. Kakde, Amarchand Parida, Pooja Kumari, [§] and Alakesh Bisai*

Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal - 462 066, Madhya Pradesh, India
Contact: +91-755-6692374, Fax: +91-755-6692392. Address for correspondence: alakesh@iiserb.ac.in

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
abeo-Abietane
Total Synthesis
Nazarov Cyclization
Quaternary Stereocenter
Taiwaniaquinoids

ABSTRACT

Total syntheses of structurally intriguing taiwaniaquinoids *viz* (±)-taiwaniaquinol D (**1e**) and (±)-taiwaniaquinone D (**1h**) has been disclosed *via* a key Lewis acid catalyzed Nazarov type cyclization of arylvinylcarbinols.

The 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 are isolated since 1995 from *Taiwania cryptomerioides* Hayata (Taxodiaceae) of central mountains of Taiwan independently by Cheng[2] and Kuo,[3] *Salvia dichroantha* Stapf (Lamiaceae) of a Turkish flowering sage by Kawazoe,[4a] *Thuja standishii* (Cupressaceae) of a Japanese conifer by Tanaka.[4b] Preliminary studies revealed that few members of taiwaniaquinoids are found to exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells.[3b] Taiwaniaquinone D (**1h**) possesses antitumoral cytotoxic activity and one of the members such as standishinal (**1c**) has shown aromatase inhibitory activity and, therefore, this class of compounds may be promising candidates for the treatment of breast cancer.[5] On the other hand, few congeners of this family are also found to be the core structure of complex taiwaniadducts (Figure 1)[6a,b] such as taiwaniadduct B (**2a**)[6c] having vicinal all-carbon quaternary sterecenters and taiwaniadduct F (**2b**) sharing complex 1,3-bis all-carbon quaternary stereocenters, when coupled with naturally occurring *trans*-ozic acid (**3**).

Because of their diverse biological profiles and uncommon structural features, taiwaniaquinoids (**1a-k**) have gained extensive attention from the synthetic community all over world leading to numerous efficient synthetic approaches. This includes, 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,[9a] Nazarov cyclization by Trauner,[9b] a tandem acylation-Nazarov cyclization reaction by Chiu,[9c] acid promoted Friedel−Crafts acylation/alkylation approach independently by She[10a] and Cheng,[10b] intramolecular cyclization of aryldienes independently by Balme,[10c] Alvarez-Manzaneda[10d] and Majetich,[10e] ring contraction reactions from abietane diterpenoids by Li,[10f] including our Nazarov type cyclization to set all-carbon quaternary center (Scheme 1).[11]

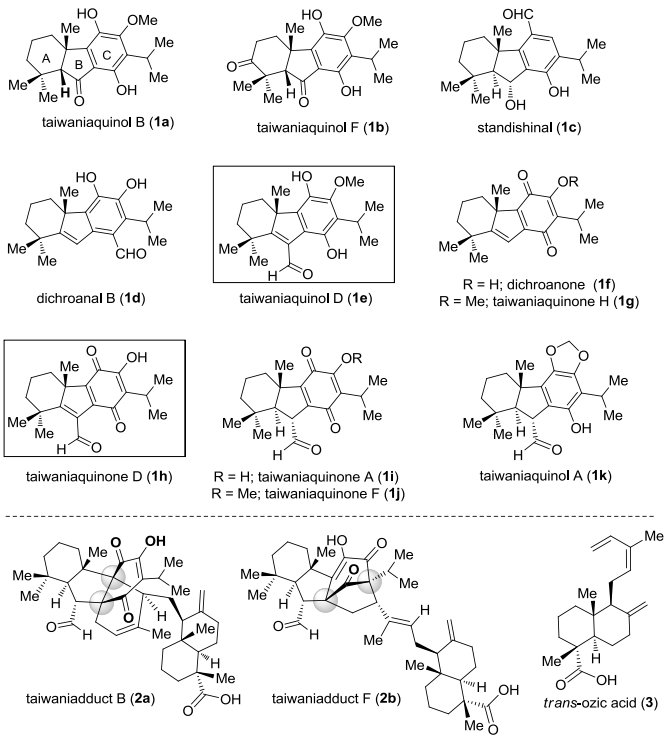
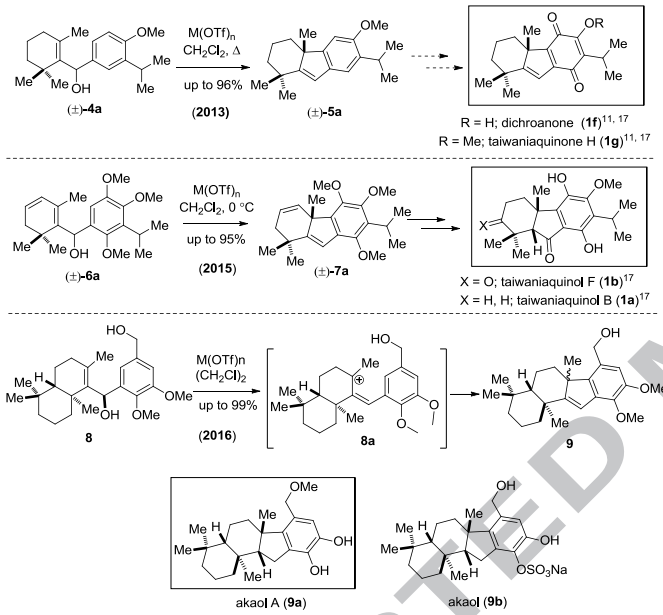


Figure 1: *abeo*-Abietane diterpenoids (**1a-k**) and related terpenoids sharing all-carbon quaternary stereocenters.

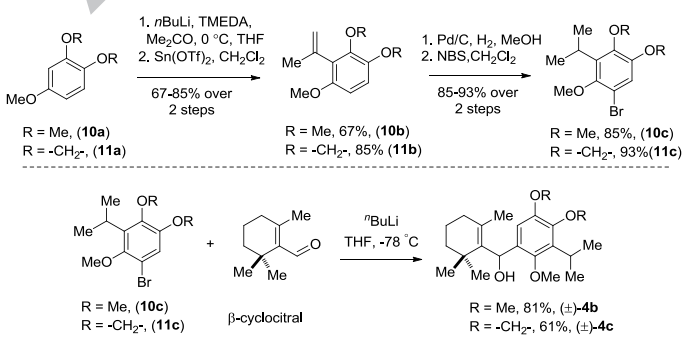
The asymmetric syntheses include, enantioselective decarboxylative allylation by Stoltz,[12] enantiospecific approach *via* a

thermal 6π-electrocyclization by Alvarez-Manzaneda,[13] enantioselective Heck reaction by Node,[14a-b] ring contraction of abietane diterpenoids by Gademann,[14c] a semisynthetic approach involving cleavage of the C7−C8 double bond of abietane diterpenes by Alvarez-Manzaneda,[14d-e] an iridium catalyzed borylation and a palladium-catalyzed asymmetric α-arylation by Hartwig,[15] a recent Pd(0)-catalyzed enantioselective conjugate addition of arylboronic acid by Stoltz.[16] Recently our group has also reported total synthesis of taiwaniaquinoids with various oxidation pattern of A-ring, such as (±)-taiwaniaquinol F (**1b**), using Nazarov type cyclization of arylvinylcarbinol (±)-**6a** (Scheme 1).[17] Utilizing aforementioned strategy, we have also accomplished total syntheses of (±)-taiwaniaquinol B (**1a**), (±)-dichroanone (**1f**) and (±)-taiwaniaquinone H (**1g**).[17] Later, we have synthesized a variety of enantioenriched carbotetracycle of type **9** (Scheme 1) from arylvinylcarbinol **8** via efficient metal triflate catalyzed Nazarov-type cyclization. This methodology provides a concise route to the marine sesquiterpene quinol akaol A (**9a**).[18]



Scheme 1: Our Approches towards taiwaniaquinoids.

We envisioned that, highly oxygenated carbotricyclic core (±)-**5b-c** could be potential advanced intermediates for unified total synthesis of various taiwaniaquinoids *viz* (±)-taiwaniaquinol D (**1e**), (±)-taiwaniaquinones D (**1h**), A (**1i**), and F (**1j**) having an additional formyl group following synthetic elaborations (Figure 1). These carbotricyclic cores (±)-**5b-c** could be obtained from a key Lewis acid-catalyzed Nazarov type cyclization of arylvinylcarbinol (±)-**4b** (Scheme 2). With above hypothesis, we have synthesized arylvinyl carbinol (±)-**4b-c** from a reaction of aryllithium (prepared *in situ* from bromoarene **10c**) with β-cyclocitral (Scheme 2).

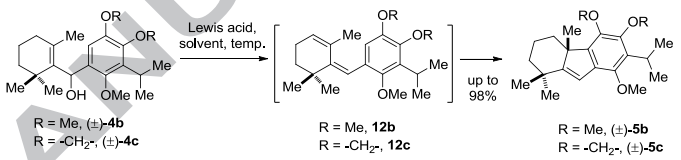


Scheme 2: Synthesis of arylvinylcarbinol (±)-**4b-c**.

For this purpose, 1,2,4-trimethoxybenzene (**10a**) and methylether of sesamol (**11a**) was reacted with acetone in presence of *n*-BuLi and TMEDA at 0 °C to afford corresponding benzyl alcohol which on further elimination in presence of $Sn(OTf)_2$ to furnish α−methylstyrene **10b** and **11b** in 2 steps. The later was hydrogenated in presence of Pd-C at 1 atm pressure followed by reaction with *N*-bromosuccinimide (NBS) to afford bromoarenes **10c** and **11c** over 2 steps (Scheme 2). Arylvinyl carbinols (±)-**4b-c** were synthesized from bromoarenes **10c** and **11c** in 81% and 61% yields, respectively.

With (±)-**4b** in hand, we then optimized Lewis acid catalyzed Nazarov type cyclization of arylvinylcarbinol (±)-**4b** for efficient synthesis of carbotricyclic core (±)-**5b.** Our optimization studies are shown in Table 1. It was observed that, 10 mol % of $Bi(OTf)_3$ afforded desired product (±)-**5b** only in 22% yield along with 73% yield of diene **12b** (Table 1). We have also found that, diene intermediate **12b** can be converted into (±)-**5b** under elevated temperature.[19] This clearly indicates that the reaction goes through intermediate diene of type **12**. Based on this result, we decided to carry out cyclization of (±)-**4b** at elevated temperature and the results are shown in Table 1 (entries 2-8).

Table 1: Optimization of cyclization of arylvinylcarbinol (±) **4b-c**.

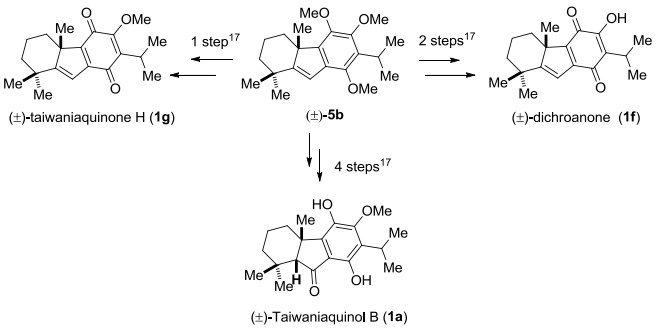


S. No.	catalyst	solvent	temp	time	%yield[a,b]	%yield of diene
1.	10 mol% $Bi(OTf)_3$	CH_2Cl_2	25 °C	12 h	22% (**5b**)	73% (**12b**)
2.	10 mol% $Bi(OTf)_3$	CH_2Cl_2	35 °C	5 h	97% (**5b**)	00% (**12b**)
3.	10 mol% $Sn(OTf)_2$	CH_2Cl_2	35 °C	7 h	95% (**5b**)	00% (**12b**)
4.	10mol% $Cu(OTf)_2$	CH_2Cl_2	35 °C	12 h	62% (**5b**)	31% (**12b**)
5.	10 mol% $Zn(OTf)_2$	CH_2Cl_2	35 °C	12 h	43% (**5b**)	52% (**12b**)
6.	10 mol% $In(OTf)_3$	CH_2Cl_2	35 °C	12 h	49% (**5b**)	33% (**12b**)
7.	5 mol% $Bi(OTf)_3$	CH_2Cl_2	35 °C	7 h	95% (**5b**)	00% (**12b**)
8.	5 mol% $Sn(OTf)_2$	CH_2Cl_2	35 °C	10 h	91% (**5b**)	05% (**12b**)
9.	5 mol% $Bi(OTf)_3$	$(CH_2Cl)_2$	80 °C	1 h	98% (**5b**)	00% (**12b**)
10.	2 mol% $Bi(OTf)_3$	$(CH_2Cl)_2$	80 °C	2 h	96% (**5b**)	00% (**12b**)
11.	10 mol% $Bi(OTf)_3$	CH_2Cl_2	25 °C	12 h	12% (**5c**)	86% (**12c**)
12.	5 mol% $Bi(OTf)_3$	$(CH_2Cl)_2$	80 °C	1 h	97% (**5c**)	00% (**12c**)

[a]all the reactions were performed with 0.3 mmol of (±)-**4b-c**. [b]isolated yields after column chromatography.

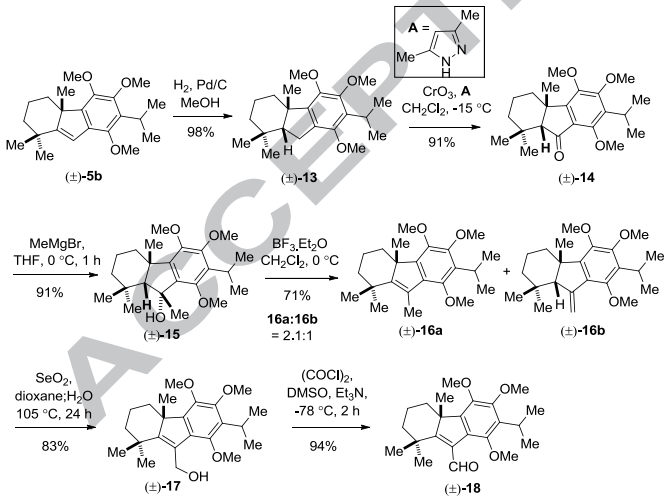
It was observed that, among various metal tiflates $Bi(OTf)_3$, and $Sn(OTf)_2$ afforded (±)-**5b** in 95-97% yields (entries 2-3), whereas $Cu(OTf)_2$, $Zn(OTf)_2$, and $In(OTf)_3$ furnished (±)-**5b** in 43-62% yields along with 31-52% yield of **12b** as by product. Interestingly, 5 mol% of $Bi(OTf)_3$ and $Sn(OTf)_2$ afforded (±)-**5b** in 95% and 91% yields (entries 7-8). To our delight, 5 mol% and 2 mol% of $Bi(OTf)_3$ furnished (±)-**5b** in 98% and 96% yields, respectively, in refluxing dichloroethane (entries 9-10). Since total syntheses of (±)-taiwaniaquinol B (**1a**), (±)-dichroanone (**1f**) and (±)-taiwaniaquinone H (**1g**) have already reported from our group from (±)-**5b**, this efforts also culminated formal total syntheses of these taiwaniaquinoids (Scheme 3). In case of arylvinyl carbinol (±)-**4c**, we have isolated aryldiene **12c** in 86% yield when the reaction was carried out at room temperature (entry 11). Interestingly, we could synthesize carbotricyclic core (±)-**5c** in 97% yield under our optimized condition (entry 12).

For further synthetic elaboration, carbotricyclic core (±)-**5b** was completely hydrogenated in presence of 10% Pd-C under 1 atm pressure of H_2 in MeOH to furnish (±)-**13** in 98% yield (Scheme 4). Later, (±)-**13** was reacted with CrO_3 in presence of 3,5-dimethylpyrazole to affect benzylic oxidation to furnish ketone (±)-**14** in 91% yield (Scheme 4), which on subsequent reaction with methylmagnesium bromide afforded (±)-**15** as single diastereomer in 91% yield. The excellent diastereoselectivity observed in methylmagnesium bromide addition was attributed to the approach of the nucleophile from the less hindered convex face of substrate (±)-**14** (Scheme 4).[20] In fact, the energy minimization (MM2) calculation of diene (±)-**14** (Figure 2) also supports our observed selectivity.



Scheme 3: Formal total syntheses of taiwanaquinoids.

Next, benzyl alcohol (±)-**15** was further treated with $BF_3{\cdot}Et_2O$ leading to the formation of two different regioisomers (±)-**16a** and (±)-**16b** in 2.1:1 ratio in 71% yield (Scheme 4), which on subsequent allylic oxidation using SeO_2 in dioxane and H_2O mixture exclusively afforded (±)-**17** in 83% yield.[21] The later was oxidized under Swern oxidation to furnish α,β-unsaturated aldehyde (±)-**18** in 94% yield (Scheme 4). Next, compound (±)-**18**[22-23] was treated with BBr_3 followed by oxidation using ceric (IV) ammonium nitrate simply afforded potential *p*-quinone intermediate (±)-**19** required for taiwaniaquinoids (±)-**1h** and (±)-**1e**.



Scheme 4: Synthesis of common precursor to (±)-taiwaniaquinone D (**1h**) and (±)-taiwaniaquinol D (**1e**).

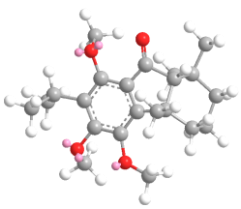
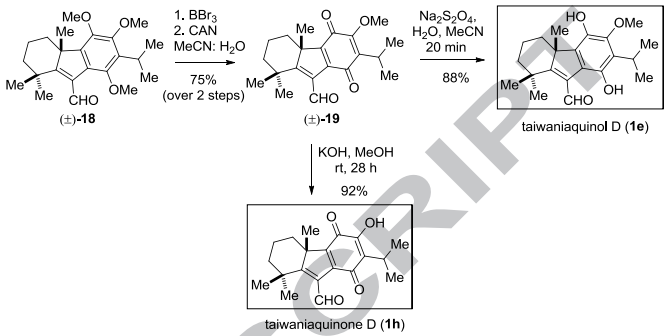


Figure 2: Energy minimized representation of (±)-**14**.

We then carried out the hydrolysis of intermediate (±)-**19** in KOH in MeOH at room remperature, which simply completed total synthesis of (±)-taiwaniaquinone D (**1h**). On the other hand, reduction of *p*-quinone functionality was performed with $Na_2S_2O_4$ to complete total synthesis of (±)-taiwaniaquinol D (**1e**) in 88% yields.[24]



Scheme 5: Total synthesis of (±)-taiwaniaquinone D (**1h**) and (±)-taiwaniaquinol D (**1e**).

In conclusion, we have demonstrated Nazarov type cyclization of arylvinyl carbinols, is a strategic platform for concise total synthesis of various taiwaniaquinoids. We have completed total syntheses of (±)-taiwaniaquinol D (**1e**) and (±)-taiwaniaquinone D (**1h**) in 15 steps from commercially available 1,2,4-trimethoxybenzene in overall yield of 13.4% and 14.0%, respectively.[25-26] We believe that (±)-**1h** could be further elaborated to the expeditious approach to taiwaniaquinones A (**1i**) and F (**1j**), which in turn could give us the opportunity for synthetic approaches to complex taiwaniadducts B (**2a**) and taiwaniadduct F (**2b**) sharing all-carbon quaternary centers. Importantly, enantioselective strategy of our Nazarov type cyclization in the presence of chiral Lewis acid complex could be an excellent platform for asymmetric total syntheses of naturally occurring taiwaniaquinoids. Further studies towards these directions are currently under active investigation in our laboratory.

Acknowledgments

A.B. thanks the Board of Research in Nuclear Sciences (BRNS), Department of Atomic Energy (DAE) and Science and Engineering Research Board (SERB), Department of Science and Technology (DST) for research grants. B.N.K., A.P., P.K. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for Research Fellowship (SRF and JRF, respectively). Facilities from Department of Chemistry, IISER Bhopal is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http:.....

§Current Address:
Department of Chemistry, Indian Institute of Science Education and Research Pune, Pashan Road, MH - 462 066, India.

References and notes:

1. For review on taiwaniaquinoids, see; Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284.

2. (a) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871. (b) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493.

3. (a) Chang, C. I.; Chien, S. C; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420. (b) Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72.

4. (a) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sesik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493–497. (b) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419.

5. (a) 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. (b) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742. (c) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911.

6. (a) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657. (b) Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1997**, *46*, 169. (c) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185.

7. (a) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Org. Lett.* **2003**, *5*, 3931. (b) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2006**, *71*, 2787.

8. Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144.

9. (a) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896. (b) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022. (c) Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741.

10. (a) Tang, S.; Xu, Y.; He, J.; He, Y.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855. (b) Wang, J.; Wang, J.; Li, C.; Meng, Y.; Wu, J.; Song, C.; Chang, J. *J. Org. Chem.* **2014**, *79*, 6354. (c) Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055. (d) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernández, A. *J. Org. Chem.* **2009**, *74*, 3384. (e) Majetich, G.; Shimkus, J. H. *Tetrahedron Lett.* **2009**, *50*, 3311. (f) Deng, J.; Li, R.; Luo, Y.; Li, J.; Zhou, S.; Li, Y.; Hu, J.; Li, A. *Org. Lett.* **2013**, *15*, 2022.

11. Kakde, B. N.; De, S.; Dey, D.; Bisai, A. *RSC Adv.* **2013**, *3*, 8176.

12. McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738.

13. (a) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidöur, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592. (b) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidöur, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Charrah, Y.; Es-Samti, H. *Org. Biomol. Chem.* **2009**, *7*, 5146.

14. (a) Node, M.; Ozeki, M.; Planas, L.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimoto, T. *J. Org. Chem.* **2010**, *75*, 190. (b) Ozeki, M.; Satake, M.; Toizume, T.; Fukutome, S.; Arimitsu, K.; Hosoi, S.; Kajimoto, T.; Iwasaki, H.; Kojima, N.; Node, M.; Yamashita, M. *Tetrahedron* **2013**, *69*, 3841. (c) Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. Eur. J.* **2010**, *16*, 7692. (b) Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390. (d) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. *Chem. Commun.* **2010**, *46*, 9244. (e) Tapia, R.; Guardia, J. J.; Alvarez, E.; Haidöur, A.; Ramos, J. A.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2012**, *77*, 573.

15. Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088.

16. (a) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (b) Shockley, S. E.; Holder, J. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 6362.

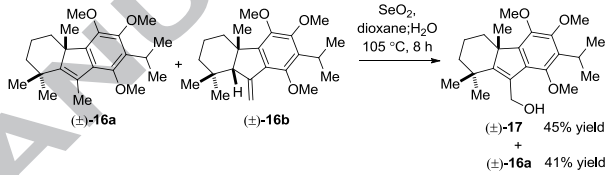
17. Kakde, B. N.; Kumari, P.; Bisai, A. *J. Org. Chem.* **2015**, *80*, 9889.

18. Our approach to the merosesquiterpenoids, see: Kakde, B. N.; Kumar, N.; Mondal, P. K.; Bisai, A. *Org. Lett.* **2016**, *18*, 1752.

19. We have carried out cyclization of aryldiene **12b** (0.3 mmol) in the presence of 10 mol% $Bi(OTf)_3$ in refluxing dichloromethane (6 mL) to afford carbotricycle (±)-**5b** in 85% isolated yield (10 h).

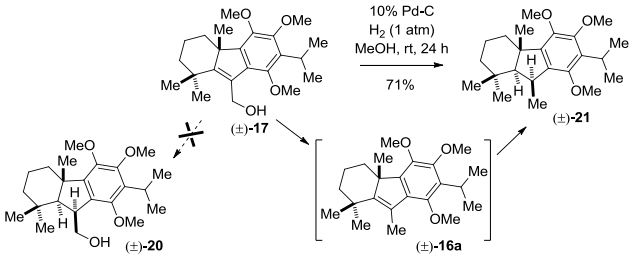
20. Energy minimization (MM2) of carbotricyclic ketone (±)-**14** was performed using ChemBio 3D Ultra Version 12.0.

21. 2.1:1 Mixture of (±)-**16a** and (±)-**16b** afforded 45% of isolated allylic oxidation product (±)-**17** along with 41% of (±)-**16a**, when the reaction was carried out for 8 h in dioxane:H_2O (4:1) at 105 °C. However, there were no traces of terminal olefin (±)-**16b** isolated from this reaction. This probably indicates that the allylic oxidation of (±)-**16b** goes through the isomerization to more substituted olefin (±)-**16a** in the presence of *insitu* generated H_2SeO_3.



22. Hydrogenation of tetrasubstituted olefinic functionality of α,β-unsaturated aldehyde (±)-**18** afforded mixture of spots on thin layer chromatography (TLC).

23. Alcohol (±)-**20** could be the advanced intermediate for the synthesis of (±)-taiwaniaquinone A (**1i**), (±)-taiwaniaquinone F (**1j**), and (±)-taiwaniaquinol A (**1k**) (Figure 1). We envisioned that, hydrogenation of (±)-**17** could efficiently afford (±)-**20**. However, in an attempt to hydrogenate tetrasubstituted allylic alcohol (±)-**17** using catalytic amount of 10 % Pd-C (W/W) in methanol a room temperature for 24 h afforded carbotricyclic compound (±)-**21** in 71% yield, probably via the intermediacy of α-methylstyrene (±)-**16a**.



24. A one-pot direct conversion of (±)-**18** to (±)-taiwaniaquinol D (**1e**) using excess amount of BBr_3 solutuon (12.66 equiv), as per Ozeki's procedure, yielded (±)-**1e** in only 27% yield along with mixture of compounds.

25. **(±)-taiwaniaquinol D (±)-1e**: To a stirred solution of compound (±)-**19** (60 mg, 0.175 mmol; 1.0 equiv) in acetonitrile and water (7 mL) was added saturated aqueous solution of $Na_2S_2O_4$ (2 mL) kept on stirring for 20 min. Upon completion of the reaction (monitoring by TLC), it was diluted by water (10 mL) and extracted with EtOAc (25 mL) by 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 give 53 mg (88% yield) of (±)-taiwaniaquinol D **(1e)** as red color oil. $\mathbf{R_f}$ = 0.4 (5% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.42 (s, 1H),

10.41 (s, 1H), 5.26 (s, 1H), 3.78 (s, 3H), 3.40 (septet, *J* = 7.1 Hz, 1H), 2.73-2.68 (m, 1H), 2.01-1.93 (m, 1H), 1.90-1.86 (m, 1H), 1.69-1.63 (m, 1H), 1.60 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.53-1.48 (m, 2H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.44 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 192.4, 185.8, 145.2, 144.6, 136.9, 135.9, 135.0, 126.3, 119.3, 62.1, 53.8, 42.5, 38.5, 35.6, 32.3, 29.1, 26.4, 23.4, 20.7, 18.1; **IR** (film) υ_{max} 3387, 3175, 2951, 2869, 1633, 1454, 1426, 1369, 1335, 1211, 1115, 1059, 1015, 977,945, 899, 736^{-1}; **HRMS** (ESI) m/z 345.2063 $[(M + H)]^+$; calculated for $[C_{21}H_{28}O_4 + H]^+$: 345.2060.

26. **(±)-taiwaniaquinone D (±)-1h**: Oven dried round-bottom flask was charged with (±)-**19** (45 mg, 0.13 mmol, 1.0 equiv) in MeOH (3 mL). To this solution was added a solution of 2M KOH solution in MeOH (3 mL) at room temprature. 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 and dried over Na_2SO_4 and concentrated using rotator evaporator under vaccum. The crude products were purified by flash chromatography (20:1 hexanes/EtOAc) to give 39 mg (92% yield) of (±)-taiwaniaquinone D **(±)-1h** as a red syrup. R_f = 0.4 (5% EtOAc in hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.44(s, 1H), 3.20 (septet, *J* = 7.1 Hz, 1H), 2.47-2.43 (m, 1H), 1.93 (qt, *J* = 13.7, 3.7 Hz, 1H), 1.71-1.65 (m, 1H), 1.49 (s, 3H), 1.34 (s, 3H), 1.27 (m, 2H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.19 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 194.1, 185.2, 177.3, 176.7, 152.2, 147.7, 147.2, 134.5, 123.3, 55.9, 43.4, 38.1, 35.2, 33.7, 25.7, 24.0, 21.3, 19.94, 19.91, 18.3; **IR** (film) υ_{max} 3359, 2930, 2872, 1698, 1633, 1593, 1531, 1463, 1366, 1316, 1224, 1165, 1104, 969, 924, 790, 737 cm^{-1}; **HRMS** (ESI) m/z 329.1761 $[(M + H)]^+$; calculated for $[C_{20}H_{24}O_4 + H]^+$: 329.1747.