The Free Internet Journal for Organic Chemistry

Review

Archive for Organic Chemistry

Arkivoc **2018**, part vi, 0-0

Naturally occurring taiwaniaquinoids: biosynthetic relationships and synthetic approaches

Vishnumaya Bisai,*[a] Aditi Gupta,[b] and Alakesh Bisai*[c]

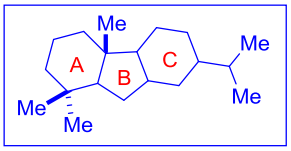
[a]Department of Chemistry, Indian Institute of Science Education and Research Berhampur, Government ITI, Engineering School Junction, Berhampur, Odisha 760 010, India; [b]*Department of Chemistry, St. Stephen's College, Delhi University, India;* [c]*Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal – 462066, Madhya Pradesh, India*

Email: vishnumayabisai@gmail.com; alakesh@iiserb.ac.in

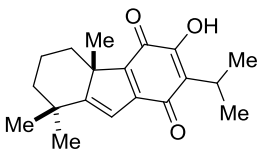
Received 05-20-2018 **Accepted** 07-11-2018 **Published on line** 09-01-2018

Abstract

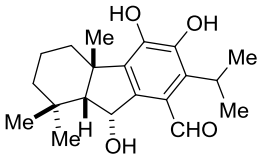
The diterpenoids possessing a fused 6,5,6-*abeo*-abietane skeleton (**1**, Figure 1) have gained interest from synthetic community owing to their significant biological properties in addition to interesting complex architecture. These are a family of carbotricyclic diterpenoids bearing an unusual 4a-methyltetra- (and hexa-) hydrofluorene skeleton with an all-carbon quaternary stereocenter. A number of *abeo*-abietanes isolated from different East Asian conifers viz. Taiwanese pine tree *Taiwania cryptomerioides* and hence they are popularly named as the taiwaniaquinoids. In this review article, we discuss on the biosynthetic proposal as well as recent efforts on the total syntheses of naturally occurring complex taiwaniaquinoids.



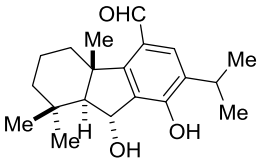
abeo-abietane skeleton (**1**)



dichroanone (**1a**)



dichroanal A (**1b**)



standishinal (**1c**)

Keywords: Taiwaniaquinoids, *abeo*-abietane diterpenoids, natural products, total synthesis, biological activities

Table of Contents

1. Introduction
2. Biological Profiles of Taiwaniaquinoids (*abeo*-Abietane Diterpenoids)
3. Proposed Biosynthesis of Taiwaniaquinoids
4. Representatives of Taiwaniaquinoids
5. Synthetic Approaches to the Taiwaniaquinoids
    5.1 Total syntheses of (±)-taiwaniaquinoids
    5.2 Stereocontrolled total syntheses of taiwaniaquinoids
6. Conclusions
Acknowledgements
References and notes
Authors biographies

1. Introduction

Naturally occurring terpenoids and their derivatives have greatly impacted the human experience. Nearly every human on earth has experienced their effects as flavors, fragrances, poisons, and medicines. In this context, taiwaniaquinoid based natural products are a subset of *abeo*-abietane,[1] which constitute an important class of diterpenoids (Figure 1). The taiwaniaquinoids share 6,5,6-carbotricyclic core [*abeo*-abietane diterpenoids **1**] and are biosyntically proposed to be arisen from a 6,6,6-abietane skeleton[2] (**2**, Figure 1) via degradation of one carbon unit from 'B'-ring.

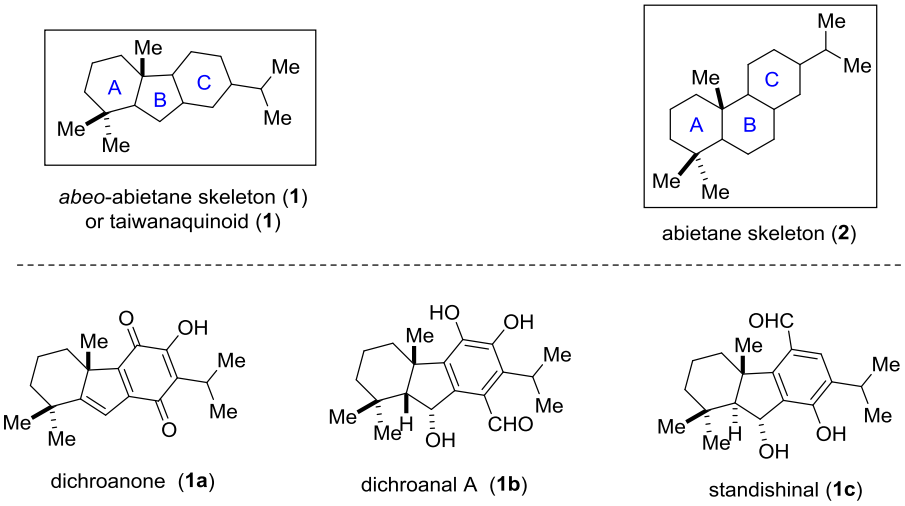


Figure 1. Representative skeleton of *abeo*-abietane and abietane diterpenoids.

Diterpenoids possessing a fused 6,5,6-*abeo*-abietane skeleton (**1**, Figure 1) have gained substantial interest owing to their significant biological properties and interesting architecture.[3] These are a family of carbotricyclic diterpenoids bearing an unusual 4a-methyltetra- (and hexa-) hydrofluorene structures. *Taiwania cryptomerioides* Hayata (*Taxodiaceae*) is an economically important, decay-resistant evergreen tree indigenous to the central mountains of Taiwan. Since 1995, a number of *abeo*-abietanes isolated from different East Asian conifers viz. Taiwanese pine tree *Taiwania cryptomerioides* and hence they are named as

taiwaniaquinoids.[4, 5, 6, 7] In 2010, Majetich and Shimkus reported comprehensive overview of the taiwaniaquinoid family of natural products summarizing the isolation, biosynthesis, and biological activities followed by a discussion of various synthetic strategies to the skeletal framework during 1995-2010.[3] Very recently, in 2016, Shi and Guo have reported an excellent review on fluorenone and fluorenone containing natural products highlighting case studies of syntheses representing members of different subgroups.[8]

2. Biological Profiles of Taiwaniaquinoids (*abeo*-Abietane Diterpenoids)

Total synthesis of natural products is important area of research, as many of the current available drugs are natural products or their derivatives. The advantage of drugs derived from natural products with respect to fully synthesized compounds is their greater structural complexity. Also, the derivatives of natural product tend to be more selective toward a wide range of targets. As per literature report, few members of taiwaniaquinoids are found to exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells[9] and one of the members standishinal (**1c**), could be a promising candidate in breast cancer therapy, due to its aromatase inhibitory potential.[10, 11, 12] These biological activities together with their intriguing carbotricyclic structure make taiwaniaquinoids an attractive synthetic target leading to elegant approaches to this class of diterpenoids.

The promising biological activity and the unusual structure of these terpenoids have stimulated research into the synthesis of this type of compound,[13, 14, 15] including total and stereoselective syntheses. The synthesis starting with natural terpenoids facilitates the formation of enantiopure taiwaniaquinoids. Recently, Chahboun and Alvarez-Manzaneda and co-workers[16] have synthesized new taiwaniaquinoids starting from natural terpenoids and the evaluation of their in vitro antiproliferative activities, as well as that of other synthesized taiwaniaquinoids, against human breast, colon, and lung tumor cells. This group has shown that, the in vitro antiproliferative activities of some taiwaniaquinoids and related compounds with functionalized A, B, or C rings against human breast (MCF-7), colon (T-84), and lung (A-549) tumor cell lines were assayed (Figure 2). [16] It is discovered that the most potent compounds **3a-c** were more effective than the naturally occurring taiwaniaquinones A (**1d**) and F (**1e**) in all above three cell lines. The structure–activity relationship study of these new taiwaniaquinoids highlighted the correlation between the bromo substituent and the antiproliferative activity, especially in MCF-7 (human breast) cells. These findings indicate that some of the taiwaniaquinoids might be useful as cytostatic agents against breast, colon, and lung cancer cell lines. Therefore, further studies are welcome towards this direction.

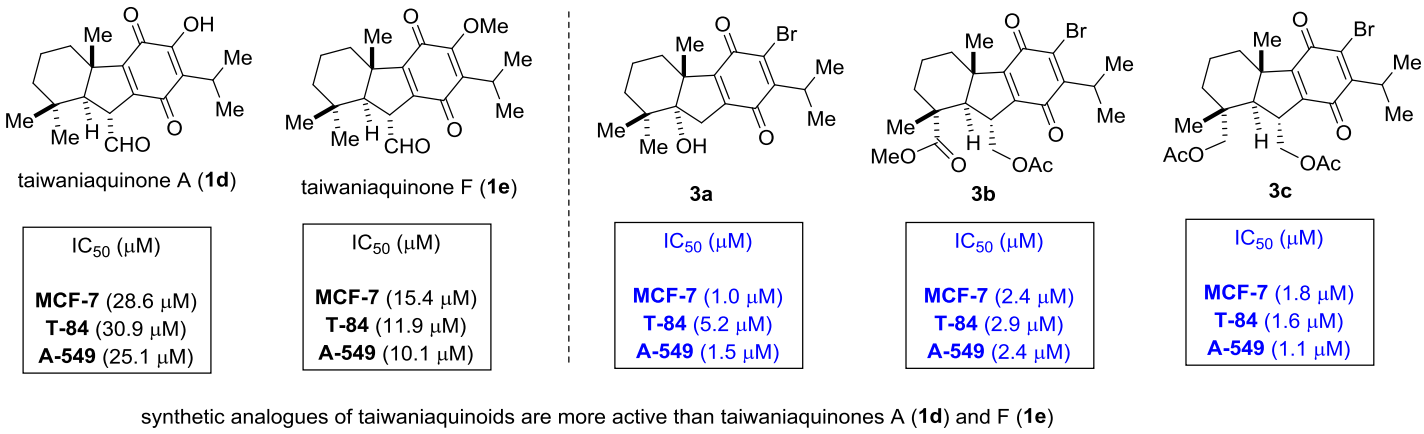
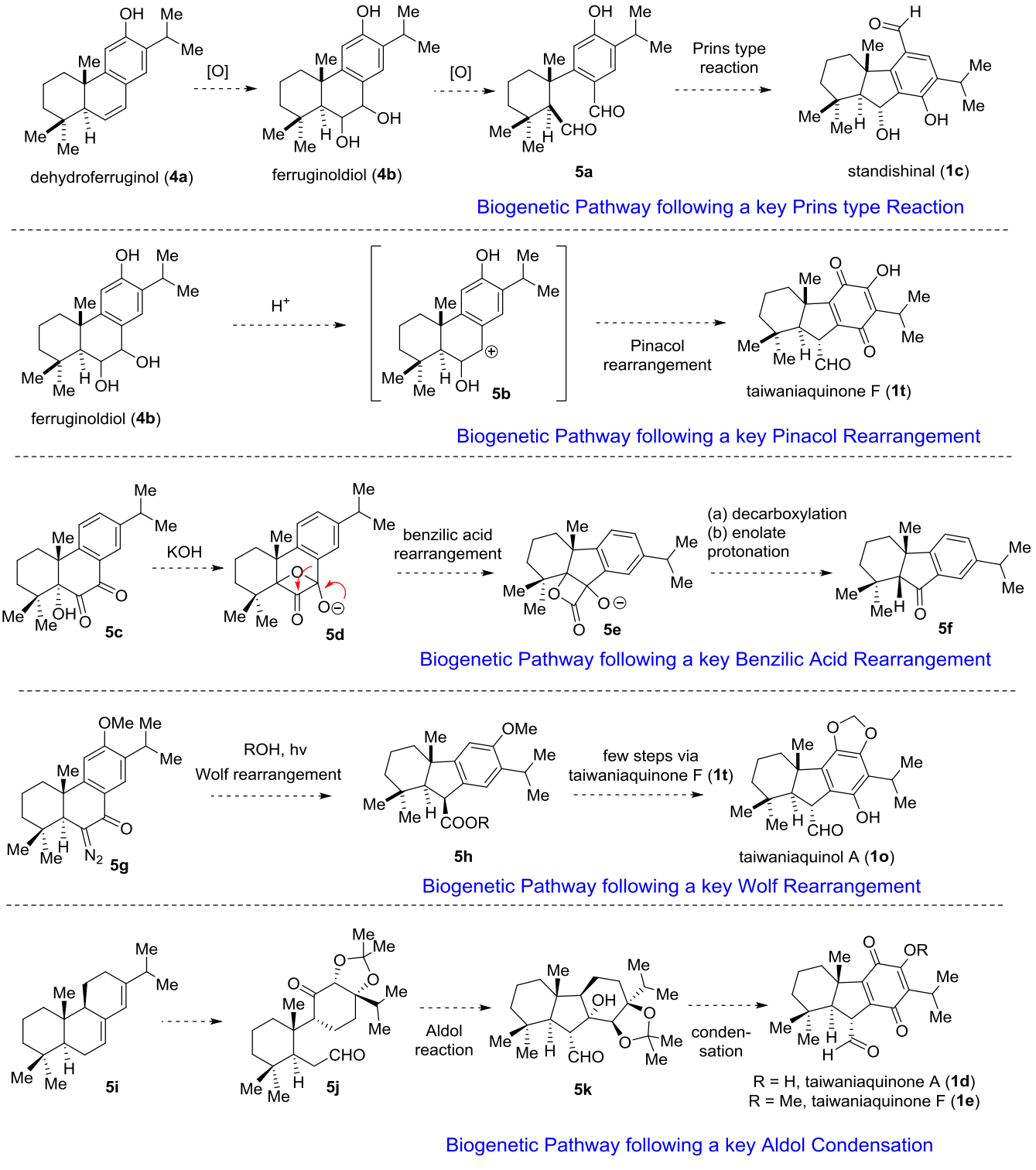


Figure 2. *abeo*-Abietane diterpenoids, taiwaniaquinones A (**1d**), F (**1e**) and analogues **3a-c**.

3. Proposed Biosynthesis of Taiwaniaquinoids (*abeo*-Abietane Diterpenoids)

A plausible biogenetic pathway of taiwaniaquinoids (*abeo*-abietane diterpenoids) from abietane diterpenoids is shown in Scheme 1.[3] As per Node et. al.,[17] biosynthetically, the *abeo*-abietane diterpenoid skeleton is believed to be arisen from a Prins-type alkylations of dialdehyde **5** (alkylation at *ortho*-position of phenol),[17] which in turn can be synthesized biogenetically from a more common abietane skeleton ferruginoldiol (**4b**) via



Scheme 1. Biosynthetic relationship of *abeo*-abietane and abietane diterpenoids.

an oxidative cleavage of vicinal diol (Scheme 1). Hypothetical precursor ferruginoldiol (**4b**) can be obtained from an oxidation event of dehydroferruginol (**4a**) or from other congeners of abietane diterpenoids (Scheme 1). A biogenetic proposal for the synthesis of taiwaniaquinoids is reported to go through a key Pinacol rearrangement (Scheme 1) of **5b** generated from ferruginoldiol (**4b**).[18]

In 2010, Gademann's biogenetic proposal for the synthesis of taiwaniaquinoid skeleton **5f** relies on a key benzilic acid rearrangement of **5c** through the intermediates **5d** and **5e** (Scheme 1).[19] Later, the same group, in 2013, had reported a biogenetic proposal for the synthesis of taiwaniaquinol A (**1o**) via Wolf rearrangement of **5g** through the intermediacy of ester **5h** (Scheme 1).[20] In 2010, Alvarez-Manzaneda and co-workers have shown a proposal for the synthesis of taiwaniaquinone A (**1d**) and taiwaniaquinone F (**1E**) via a key Aldol condensation aldehyde **5j** (which was synthesized from **5i**) through the intermediacy of carbotricyclic core **5k** (Scheme 1).[21]

4. Representatives of Taiwaniaquinoids (*abeo*-Abietane Diterpenoids)

Since 1995, a number of *abeo*-abietane diterpenoids have been isolated from various sources. The representatives of these diterpenoids are shown in Figures 4-6. In 1995, while continuing their investigation of the leaf extracts, Cheng et al. discovered[22, 23] a new family of diterpenoids (four diterpenes and one norditerpene) possessing a [6,5,6]-*abeo*-abietane skeleton[24] previously unknown in nature.[25] They named these compounds as taiwaniaquinones A (**1d**), B (**1n**), and C (**1l**) and taiwaniaquinols A (**1o**) and B (**1f**) (Figures 3 and 4) according to their botanical origin, C-ring functionality, and order of isolation, respectively.

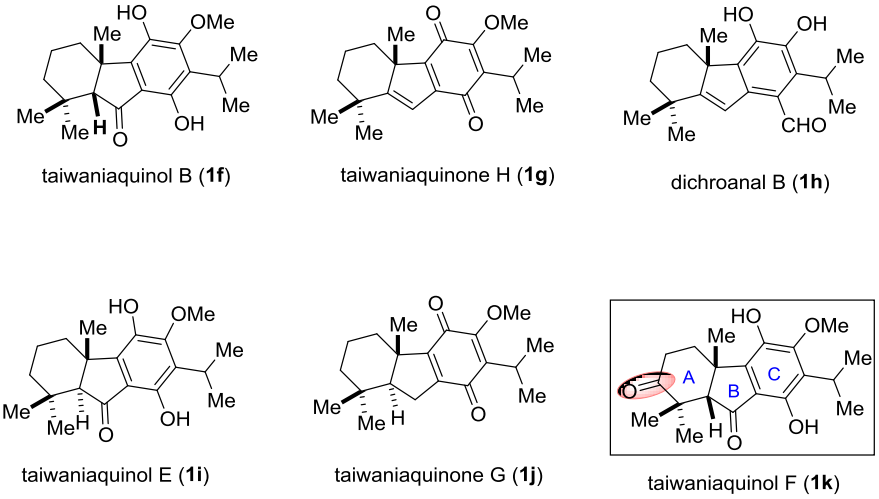


Figure 3. *abeo*-Abietane diterpenoids sharing all-carbon quaternary stereocenters.

Cheng's continued work expanded this family in 1996, when the leaf extracts yielded taiwaniaquinones D (**1s**) and E (**1q**) (Figure 7).[23] A similar skeleton was soon discovered in other families of abietane-rich plants. In 1999, Kawazoe et al. reported the isolation of three structurally similar compounds (Figures 1 and 3) from the roots of *Salvia dichroantha* Stapf (Lamiaceae), a Turkish flowering sage. These new compounds were named dichroanals A (**1b**) and B (**1h**) and dichroanone (**1a**).[26]

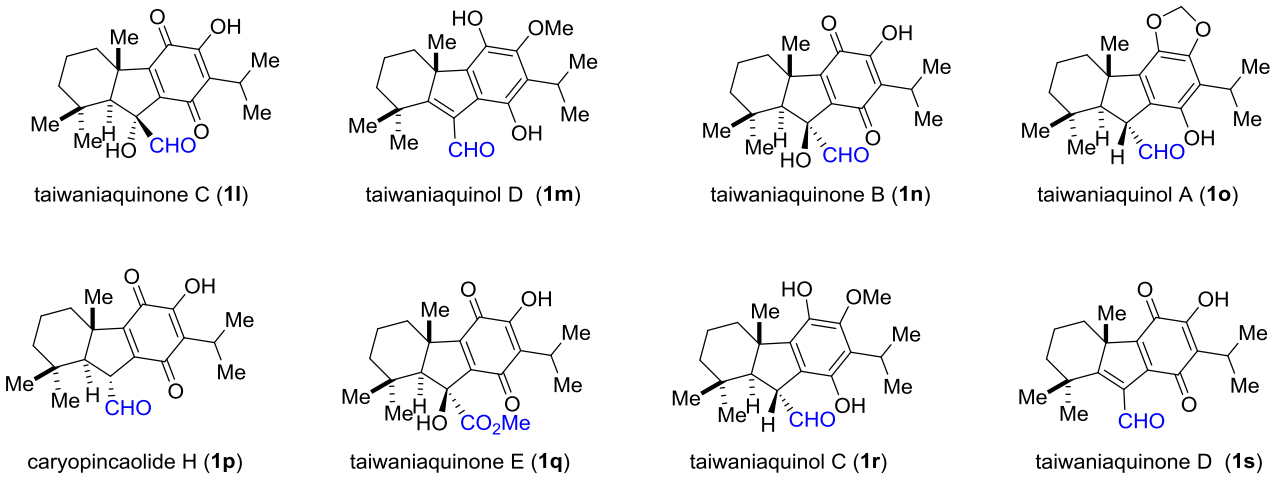


Figure 4. *abeo*-Abietane diterpenoids sharing an additional carbon.

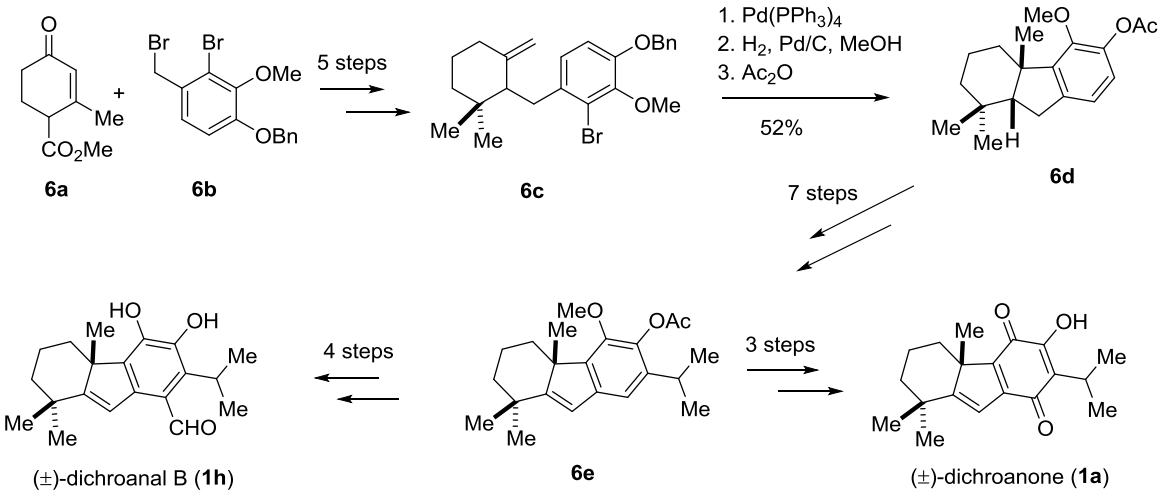
Tanaka and co-workers have isolated the compound designated standishinal (**1c**) from the bark of *Thuja standishii* (Cupressaceae), a Japanese conifer, in the same year.[27] Meanwhile, Kuo et al. reinvestigated the bark extracts from *T. cryptomerioides*, and the structures of taiwaniaquinone F (**1k**) and taiwaniaquinols C (**1r**) and D (**1m**) were reported in 2003.[28] Further study of the bark extract resulted in the 2005 report of taiwaniaquinones G (**1j**) and H (**1g**) and taiwaniaquinols E (**1i**) and F (**1k**).[29] Figure 7 shows a number of *abeo*-abietane diterpenoids having an additional carbon as compared to taiwaniaquinoids shown in figure 6.[30] It is also interestingly to note that there could be oxidized A-ring present in taiwanaquinoids, such as taiwaniaquinol F (**1k**) (Figure 6).

5. Synthetic Approaches to the Taiwaniaquinoids (*abeo*-Abietane Diterpenoids)

The synthetic approaches to this class of diterpenoids are shown in sections 5.1 and 5.2.

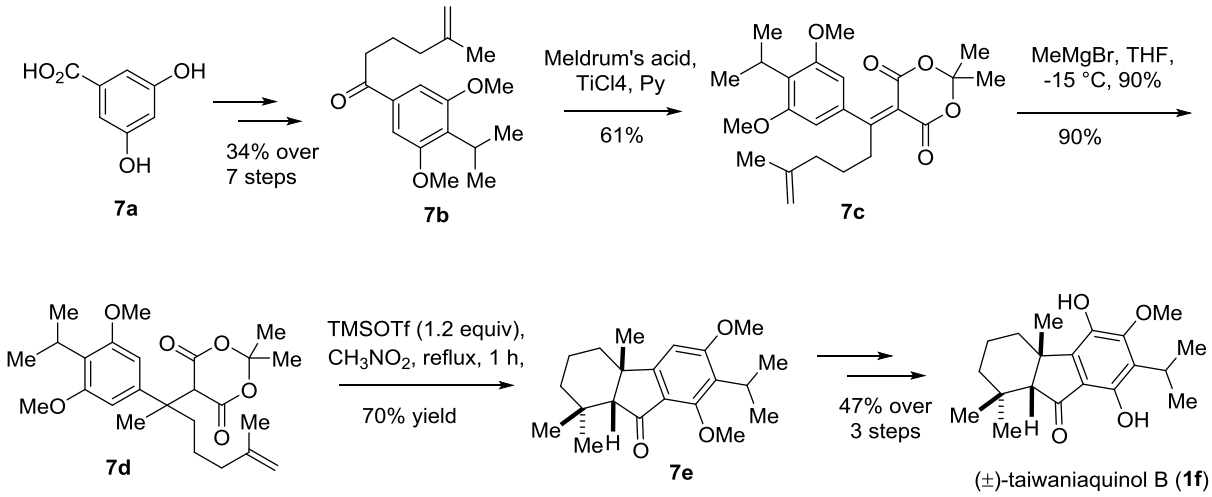
5.1 Total syntheses of (±)-taiwaniaquinoids

In 2003, Banerjee *et. al.*[31, 32] reported first general and convergent route for the synthesis of taiwaniaquinoids by utilizing a common *cis*-fused hexahydrofluorenone intermediate **6d** (Scheme 2). Compound **6d** was obtained via Pd(0)-catalyzed reductive cyclization of **6c**,[31] which in turn was synthesized from Hagemann's ester (**6a**) and benzyl bromide (**6b**) in 5 steps. Carbotricylcic core **6d** was elaborated to intermediate **6e** in seven overall steps. Utilizing above strategy, the first total syntheses of (±)-dichroanone (**1a**) and (±)-dichronal B (**1h**) has been realized through a simple and convergent route (Scheme 2).[31] In this strategy, required benzyl bromide (**6b**) was obtained from commercially available vanillin using a sequence of standard reactions, with 27% yield over seven steps. Later, same strategy has been successfully utilized for total syntheses of (±)-taiwaniaquinones D (**1s**) and H (**1g**), (±)-taiwaniaquinol B (**1f**) by the Banerjee group (Scheme 2).[32]



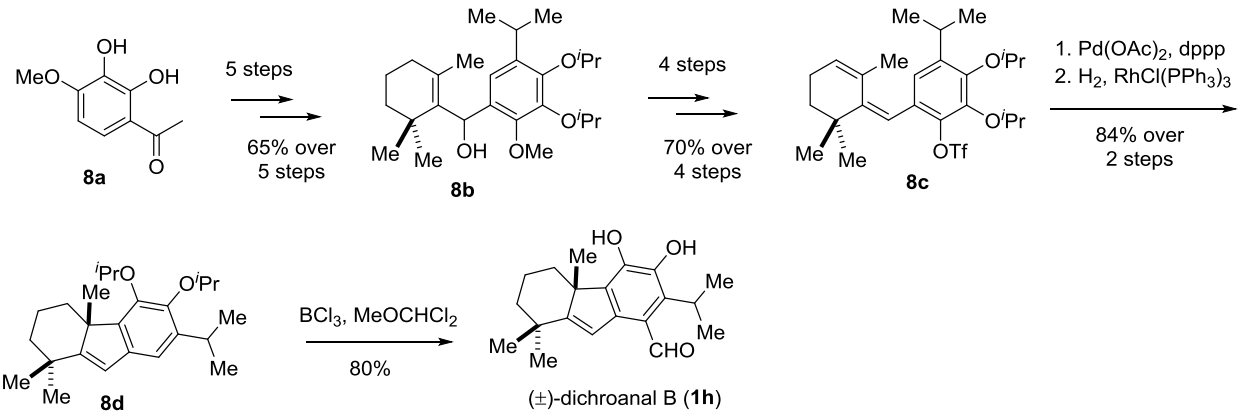
Scheme 2. Intramolecular Heck strategy by Banerjee (2003).

In 2005, Fillon and Fishlock reported the first total synthesis of taiwaniaquinol B (**1a**) in 15 steps and 6% overall yield (Scheme 3). The key feature of this approach is a TMSOTf-mediated intramolecular Friedel-Crafts acylation/carbonyl α-*tert*-alkylation domino reaction[33] of compound **7d** to furnish carbotricyclic ketone **7e** (70% yield). Intermediate **7e** was further elaborated towards total synthesis of taiwaniaquinol B (**1f**) over 3 steps. Compound **7d** was synthesized from **7c** *via* a 1,4-addition, which in turn was synthesized from arylketone **7b** in 61% yield by reacting with Meldrum's ester (Scheme 3). The arylketone **7b** was synthesized from a commercially available 3,5-dihydroxybenzoic acid in 34% overall yields over 7 steps.



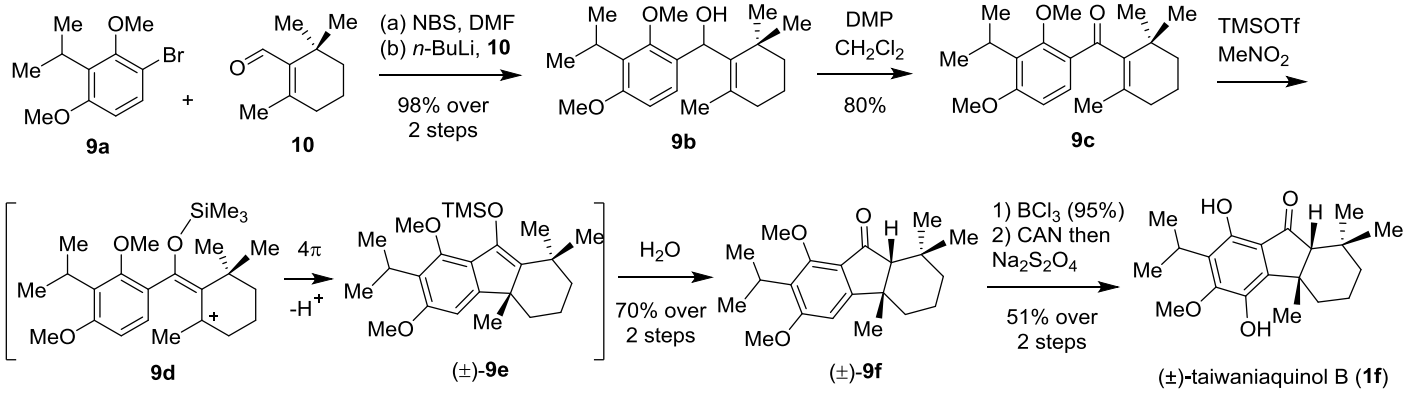
Scheme 3. Intramolecular domino Friedel-Crafts acylation/carbonyl α-*tert*-alkylation by Fillon (2005).

Node and co-worker, in 2006, have developed a new efficient method to prepare a 4a-methyltetrahydrofluorene system. The key reaction of this approach is an intramolecular Heck cyclization of the novel diene compound with a triflate functionality **8c** to furnish carbotricyclic core **8d** (Scheme 4).[34] The methodology was applied to the synthesis of (±)-dichroanal B (**1h**) with an improved yield, compared to the previously reported total synthesis. The required arene triflate **8c** was synthesized from arylvinylcarbinol **8b** in 4 steps, which in turn was synthesized from acetophenone **8a** in 5 steps (Scheme 4). This methodology also provides the opportunity for a convenient construction of chiral 4a-methyltetrahydrofluorene.



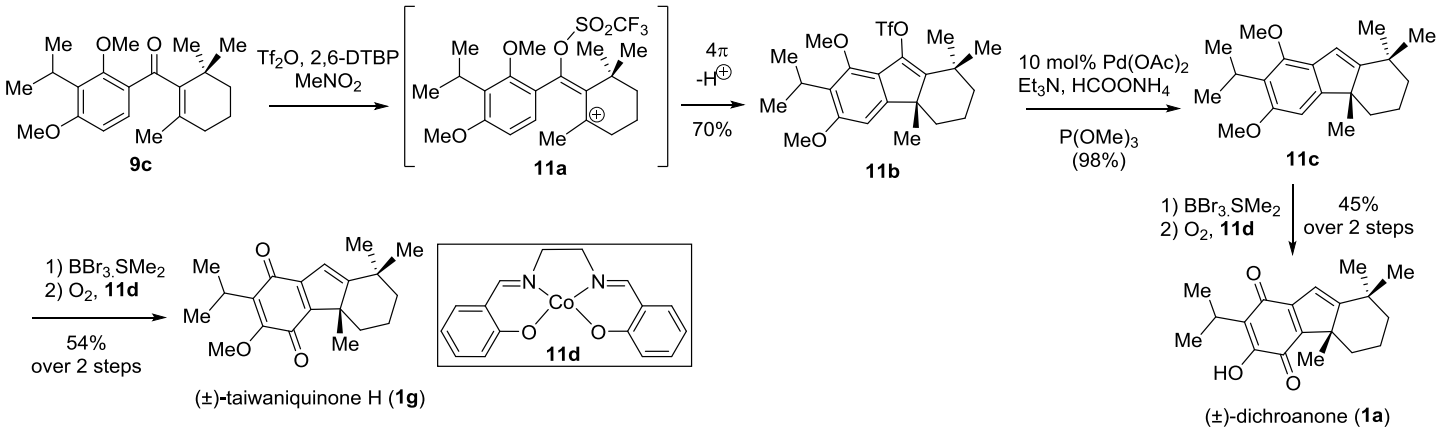
Scheme 4. Intramolecular Heck strategy by Node (2006).

In 2006, Trauner *et. al.* reported total synthesis of (±)-taiwaniaquinol B (**1f**), (±)-taiwaniaquinone H (**1g**) and (±)-dichroanone (**1a**) via a key Nazarov cyclization.[35] Lithiation of bromoarene **9a** followed by reaction with commercially available *β*-cyclocitral **10** afforded aryl vinyl carbinol **9b**, which was oxidized immediately to yield aryl vinyl ketone **9c** (Scheme 5). It is reported that **9c** could be cyclized in the presence of trimethylsilyl triflate (TMSOTf) in nitromethane to afford the highly unstable silyl enol ether **9e**, presumably through the intermediacy of cation **9d**. Upon aqueous workup, this procedure afforded the thermodynamically more favorable *cis*-indane product **9f** as the only stereoisomer observed, from where (±)-taiwaniaquinol B (**1f**) was synthesized in 3 steps, viz. selective demethylation by BCl_3, oxidation in the presence of CAN [ceric(IV) ammonium nitrate], and reduction of *p*-bezoquinone with $Na_2S_2O_4$ to quinol.



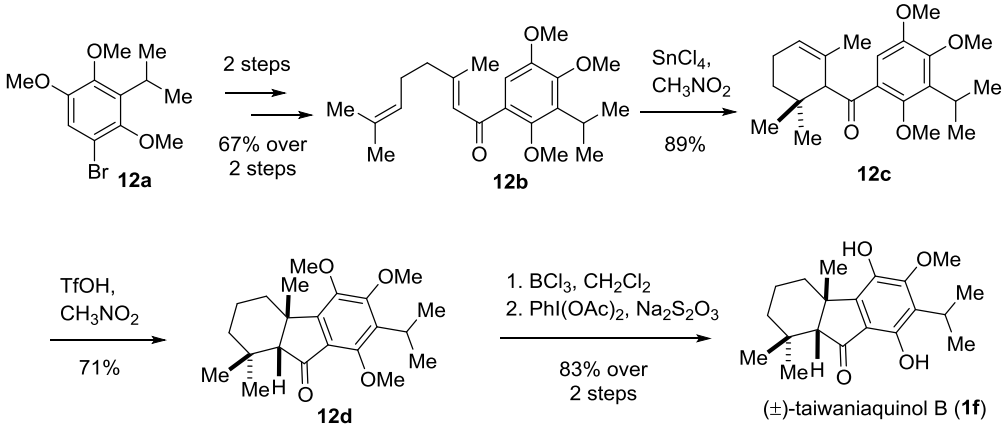
Scheme 5. Collective total syntheses of taiwaniaquinoids by Taruner.

Interestingly, heating of aryl vinyl ketone **9c** with triflic anhydride in the presence of a hindered base (2,6-di-*tert*-butylpyridine; 2,6-DTBP) cleanly afforded trifloxy indene **11b** through the intermediacy of cation **11a** (Scheme 6). This reaction is proposed to proceed through 4π electrocyclization of intermediate cation **11a** followed by deprotonation to yield **11b**. Later, Pd(0)-catalyzed reduction of **11b** gave indene **11c** in excellent yield. Complete demethylation followed by oxidation catalyzed by salcomine (**11d**) gave (±)-dichroanone (**1a**). Alternatively, following a more selective demethylation and oxidation they completed total synthesis of (±)-taiwaniaquinol H (**1g**).[35]



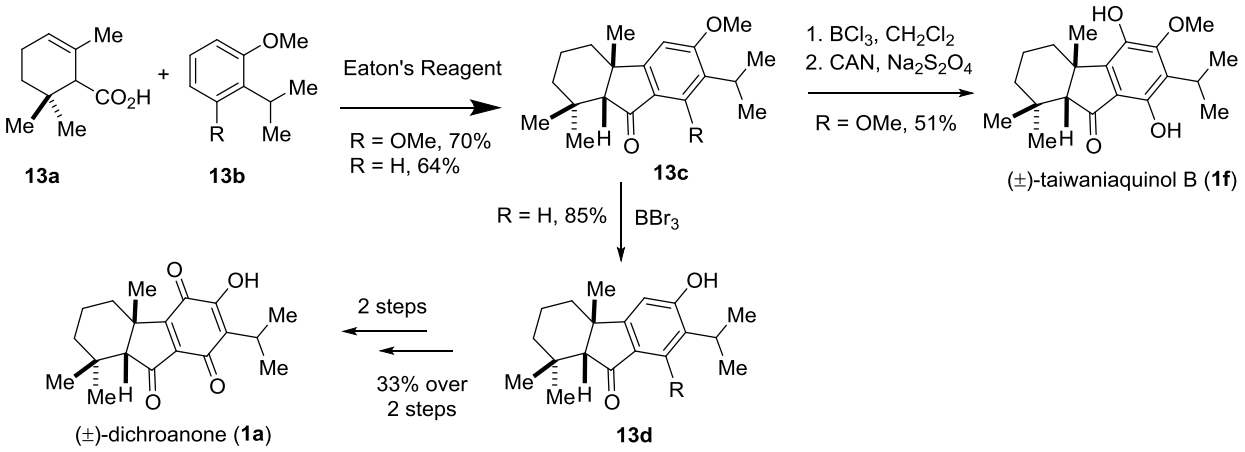
Scheme 6. Collective total syntheses of taiwaniaquinoids by Taruner (2006).

In 2008, Chiu and co-worker,[36] have reported an efficient route for the synthesis of the hydrofluorenone skeleton by sequential cationic cyclizations promoted by acid (Scheme 7). From enone **12b** (prepared from bromoarene **12a** and geranyl aldehyde over 2 steps), the cyclization using $SnCl_4$ afforded arylketone **12c** in 89% yield. Later, cyclization of **12c** was induced by Brønsted acid to afford carbotricyclic core **12d** in 2 steps in 54% overall yield (Scheme 7). This route is applicable to the synthesis of other taiwaniaquinoid natural products and analogues with similar skeletons, e.g. total synthesis of (±)-taiwaniaquinol B (**1f**) was achieved from 12d over 2 steps viz. selective demethylation, oxidation, and reduction protocol.



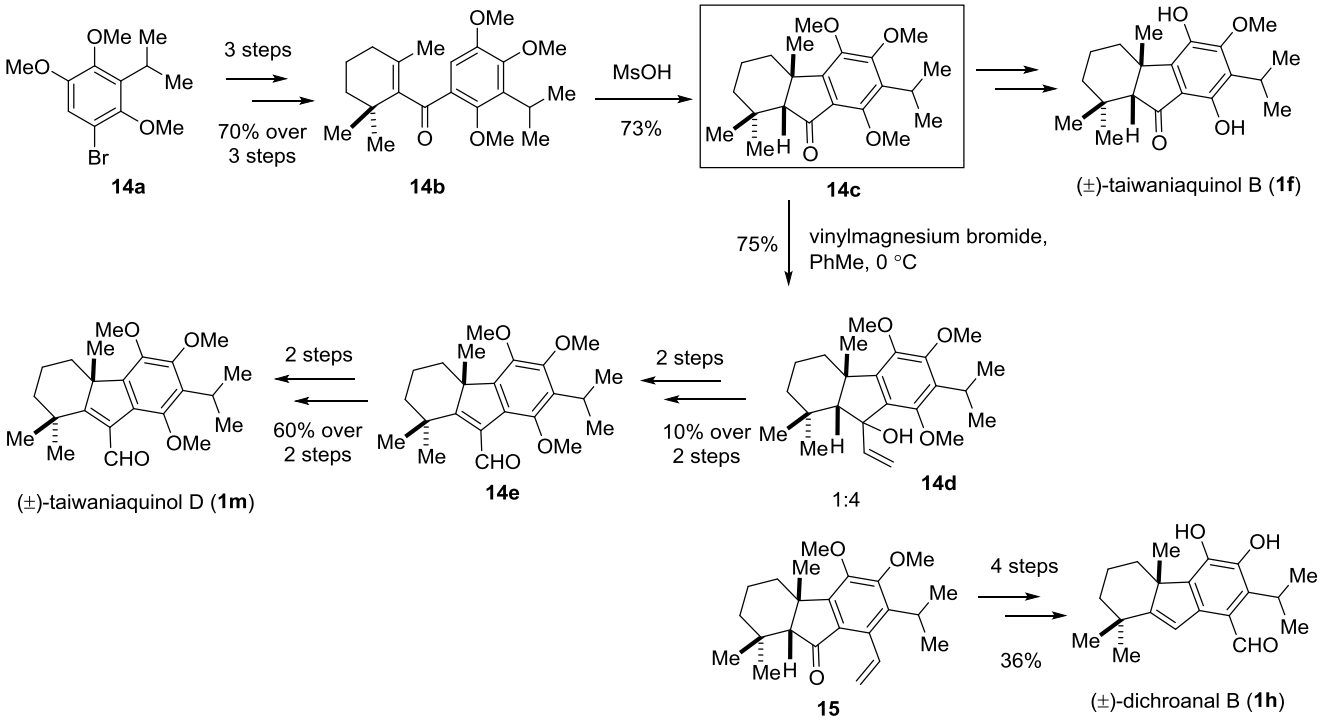
Scheme 7. Total synthesis of (±)-Taiwaniaquinol B (**1f**) by Chiu (2008).

She and co-workers,[37] in 2008, have reported efficient synthesis of carbotricyclic core **13c** related to the taiwaniaquinoids starting from aldehyde **13a** and arene **13b** in the presence of Eaton's reagent (Scheme 8). The process essentially follows a domino Friedel-Craft Acylation/Alkylation reactions to yield **13c** in 64-70% overall yield. Total syntheses of (±)-taiwaniaquinol B (**1f**) and (±)-dichroanone (**1a**) were accomplished from intermediate **13c** as shown in Scheme 8.



Scheme 8. Domino Friedel-Craft acylation/alkylation by She (2008).

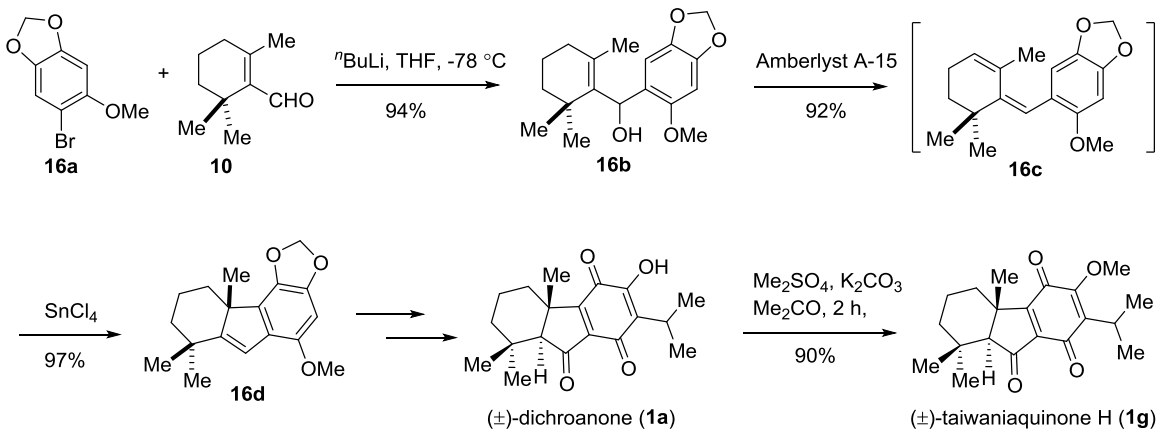
In 2009, Majetich and co-worker,[38] have reported efficient Nazarov cyclization of arylvinyl ketone **14b** strategy for efficient synthesis of carbotricyclic ketone **14c** (Scheme 9). The required arylvinyl ketone **14b** was synthesized from bromoarene **14a** in 2 steps by reacting with β-cyclocitral in 80% overall yields. Carbotricyclic ketone **14c** was converted to (±)-taiwaniaquinol B (**1f**) in few steps (Scheme 9). Later, ketone **14c** was reacted with vinylmagnesium bromide to afford mixture of products, allylcarbinol **14d** and styrerne **15** in 75% overall yield (Scheme 9). Allylcarbinol **14d** was elaborated to the total synthesis of (±)-taiwaniaquinol D (**1m**) via the intermediacy of **14e**. On the otherhand, styrerne **15** was the advanced intermediate for the total synthesis of (±)-dichroanal B (**1h**).



Scheme 9. Synthetic strategy by Majetich (2009) following a Nazarov cyclization.

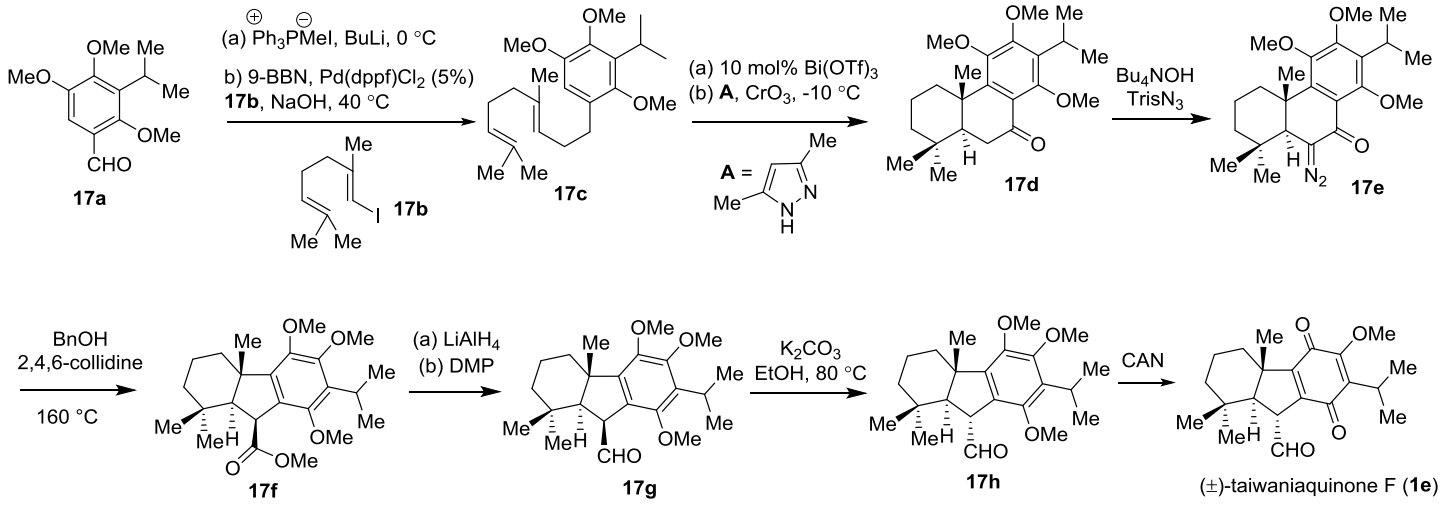
In the same year, Alvarez-Manzaneda and co-worker,[39] have reported effcient Lewis acid-catalyzed cyclization of diene **16c** for synthesis of carbotricyclic structure **16d** in high yield (Scheme 10). The diene

precursor **16c** was synthesized from arylvinyl carbinol **16b**, which was synthesized from bromoarene **16a** and β-cyclocitral (**10**) via a 1,2-addition reaction (Scheme 10). Total syntheses of (±)-dichroanone (**1a**) and (±)-taiwaniaquinone H (**1g**) were synthesized following a strategy shown as per Scheme 10.



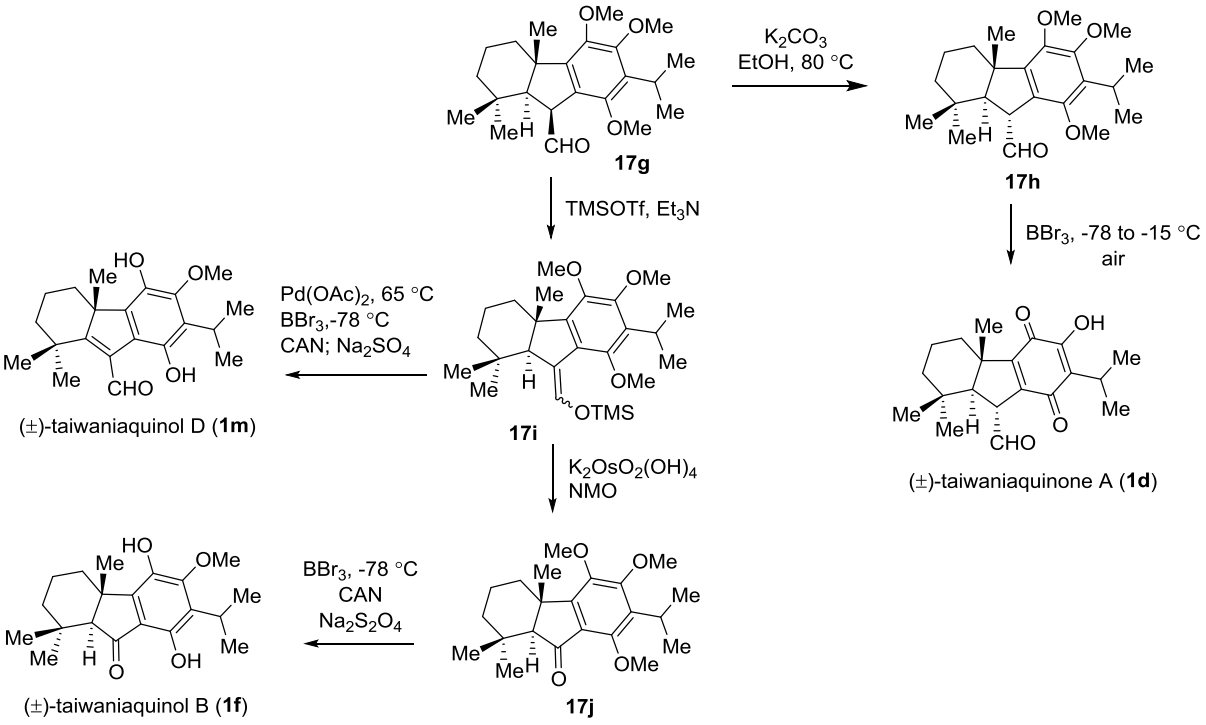
Scheme 10. Lewis acid-catalyzed cyclization of diene by Alvarez-Manzaneda (2009).

In 2013, Li *et. al.* have developed an efficient route for the divergent total syntheses of (±)-taiwaniaquinone A (**1d**), (±)-taiwaniaquinone F (**1e**), (±)-taiwaniaquinol B (**1f**) and (±)-taiwaniaquinol D (**1m**) via a key Wolff type ring contraction reaction of a *trans*-fused [6,5,6]-ring system (Scheme 11).[40] The reaction of adehyde **17a** (prepared from commercially available 1,2,4-trimethoxybenzene in 4 steps[41]) with methylenetriphenylphosphorane furnished styrene, which was hydroborated with 9-BBN to afford the corresponding alkylborane.[41, 42, 43] This in situ generated borane was subjected to Suzuki-Miyaura coupling[43] in the presence of alkenyl iodide **17b** to afford **17c** in 83% yield from aldehyde **17a** (Scheme 11). Treatment of **17c** with 10 mol% $Bi(OTf)_3$ provided tricyclic compound in 71% yield with a *trans*-A/B ring junction, which was oxidized at benzylic position to provide **17d** in 89% yield. Ketone **17d** was then converted to α-diazoketone **17e** in 78% yield by treatment of $TrisN_3$ and Bu_4NOH. Wolff rearrangement of **17e**[44, 45] afforded benzyl ester **17f** as a single detectable diastereomer in 56% yield (Scheme 11).



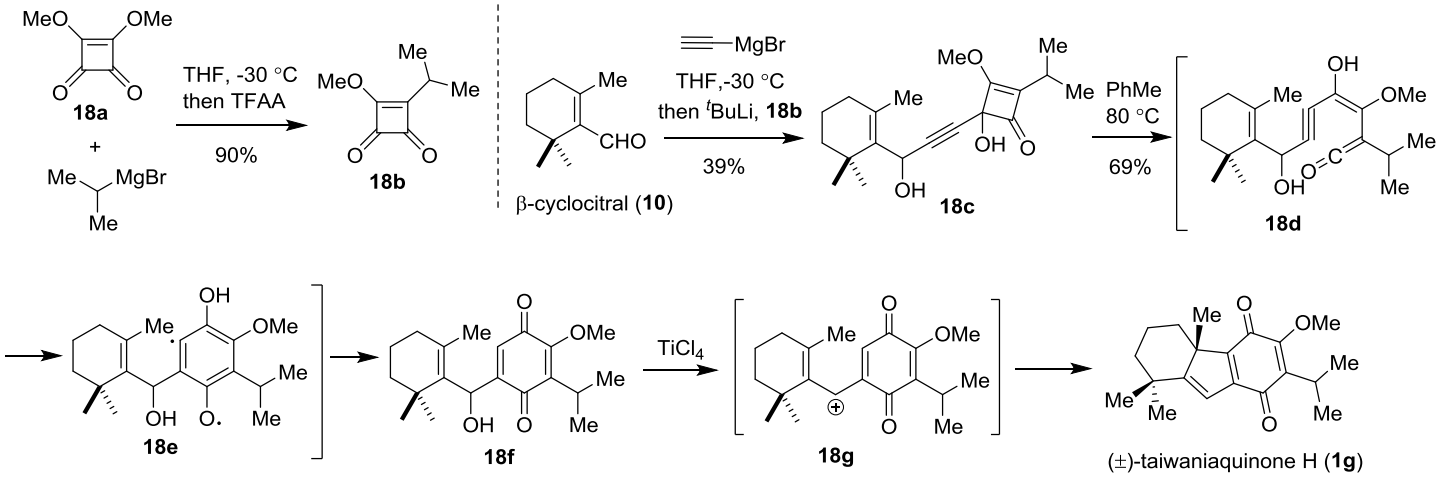
Scheme 11. Total syntheses of taiwaniaquinoids by Li (2013).

Reduction of ester **17f** followed by oxidation with Dess-Martin periodione furnished aldehyde **17g** in 75% yield over 2 steps, which was epimerize to furnish **17h** (Scheme 11). Compound **17h** was reacted with excess of BBr_3 followed by aerobic oxidation completed total synthesis of (±)-taiwaniaquinone A (**1d**) in 76% yield. Intermediate **17h** was oxidized with CAN to afford (±)-taiwaniaquinone F (**1e**) in 76% yield. In another direction, treatment of **17g** with TMSOTf and Et_3N gave silyl enol ether **17i** (ca. 1.2:1 *cis*/*trans* isomers), which underwent a sequence of Saegusa-Ito oxidation,[46] monodemethylation, and one-pot oxidation/reduction to afford (±)-taiwaniaquinol D (**1m**). Further, dihydroxylation of **17i** using $K_2OsO_2(OH)_4$ and NMO afforded ketone **17j**, from which total synthesis of (±)-taiwaniaquinol B (**1f**) was obtained in 81% overall yield (Scheme 12).



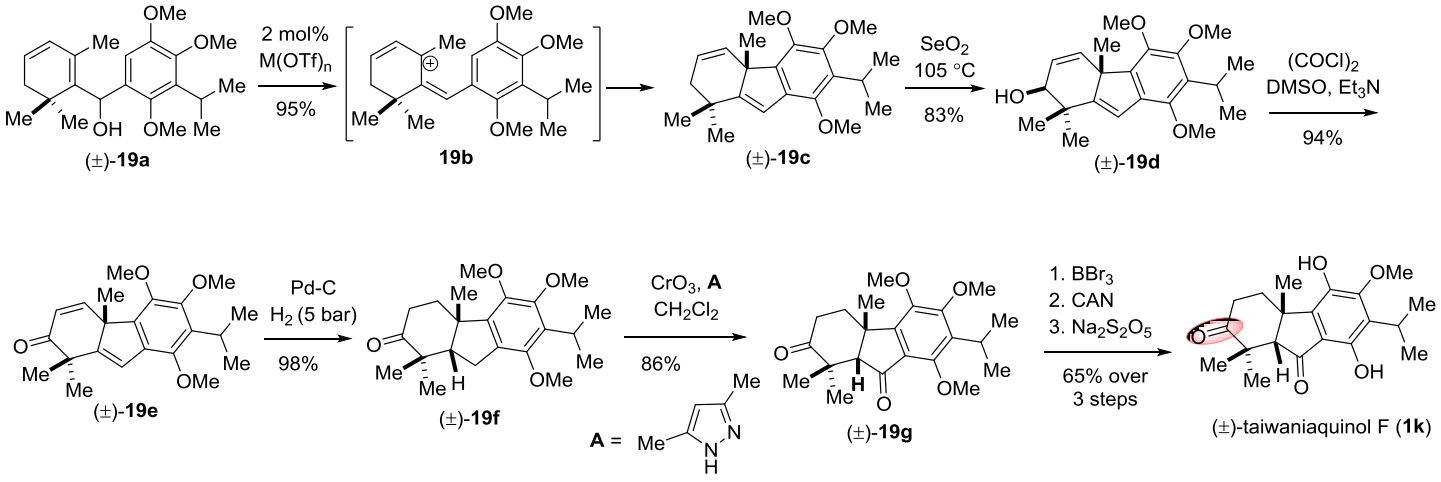
Scheme 12. Collective Total syntheses by Li and co-workers (2013).

In 2014, Hu and Yan reported protecting group-free total synthesis of (±)-taiwaniaquinone H (**1g**) via a key thermal ring expansion/4π-electrocyclization of 2-hydroxy-cyclobutenone derivative **18c** (Scheme 13).[47] In a synthetic sequence, cyclobutenedione **18b** was prepared in 90% yield from dimethyl squarate **18a** and isopropylmagnesium bromide following Moore's established protocol.[48] Ethynylmagnesium bromide was added to commercially available β-cyclocitral **10** at −30 °C, which was subsequently treated with ^{t}BuLi and cyclobutenedione **18b** sequentially to afford **18c** in 39% yield in a one-pot fashion.[49] Thermal ring expansion/4π-electrocyclization of **18c** afforded the desired ring expansion product **18f** in 69% yield. However, when the reaction was carried out in the presence of $TiCl_4$, the expected thermal ring expansion/4π-electrocyclization process afforded (±)-taiwaniaquinone H (**1g**) in 41% yield from **18c**.



Scheme 13. Total synthesis of (±)-taiwaniaquinone H (**1g**) by Hu and Yan.

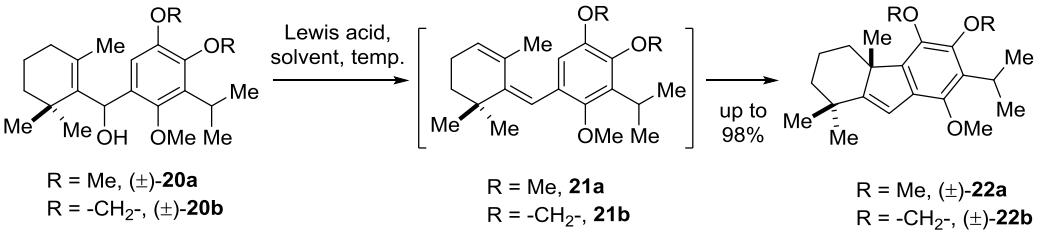
In 2015, Bisai et. al. have reported first total synthesis of (±)-taiwaniaquinol F (**1k**), sharing an oxidized A-ring (Scheme 14).[50, 51] This synthesis began with Lewis acid-catalyzed cyclization of aryl divinylcarbinol **19a** to afford carbotricyclic core **19c** with two olefin functionality via the intermediacy of diallylcarbocation **19b** (Scheme 14). Compound **19a** was prepared in one step via 1,2-addition of known bromoarene onto commercially available safranal.[50] Allylic oxidation of **19c** with SeO_2 afforded allylalcohol **19d** as single diastereomer in 83% yield. Excellent diastereoselectivity of allylic oxidation of **19c** was attributed because of oxidation taken place from less hindered convex face. Next, **19d** was oxidized to obtain α,β-unsaturated ketone **19e**, which was further hydrogenated to afford tricyclic ketone **19f** in 98% yield. The later was reacted with CrO_3 to affect benzylic oxidation to give **19g**, from where total synthesis of (±)-taiwaniaquinol F **1k** was completed in 3 steps viz reaction with BBr_3 followed by oxidation using CAN and reduction with $Na_2S_2O_5$. This strategy was successfully utilized for concise total syntheses of other congeners such as (±)-dichronanone (**1a**), (±)-taiwaniaquinone H (**1g**), and (±)-taiwaniaquinol B (**1k**) (Scheme 14).[50]



Scheme 14. Total synthesis of (±)-taiwaniaquinol F (**1k**) by Bisai.

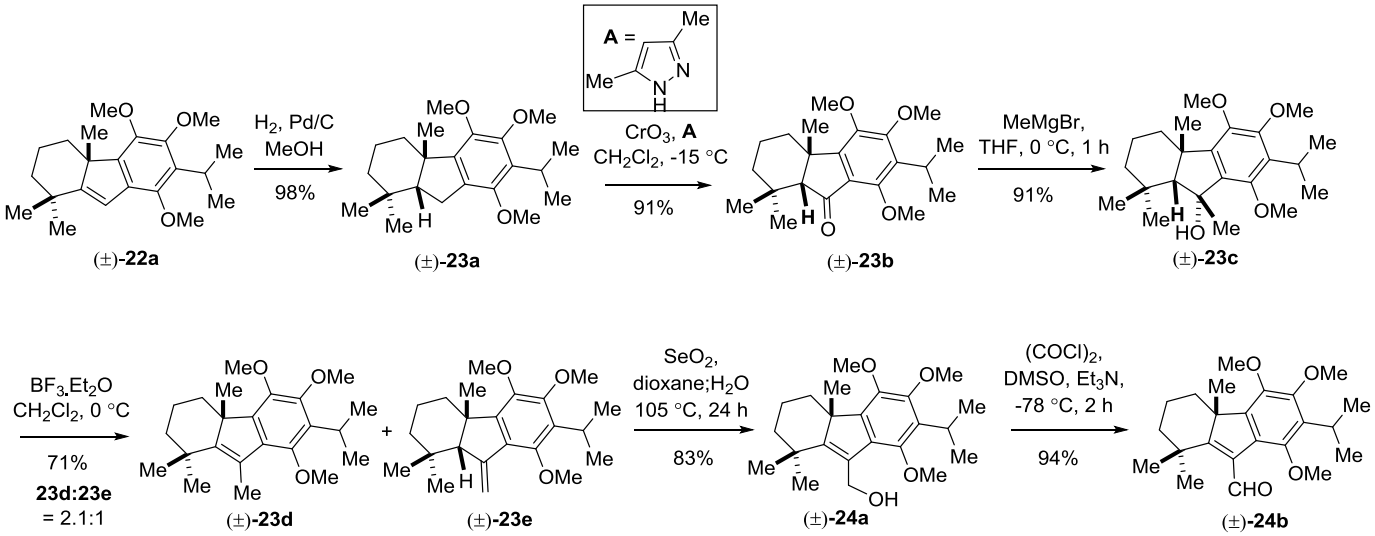
In 2016, Bisai et. al. have reported total syntheses of naturally ocurrring abeo-abietane diterpenoids, (±)-taiwaniaquinone D (**1s**) and (±)-taiwaniaquinol D (**1m**).[52] In a synthetic sequence, carbotricyclic core **22a** (which was prepared from a Nazarov type cyclization of **20** via the intermediacy of diene **21**) was completely

hydrogenated in presence of 10% Pd-C under 1 atm pressure of H_2 in MeOH to furnish **23a** in 98% yield (Scheme 16). Later, **23a** was reacted with CrO_3 in presence of 3,5-dimethylpyrazole to affect benzylic oxidation to furnish ketone **23b** in 91% yield, which on subsequent reaction with methylmagnesium bromide afforded **23c** as single diastereomer in 91% yield.[53]



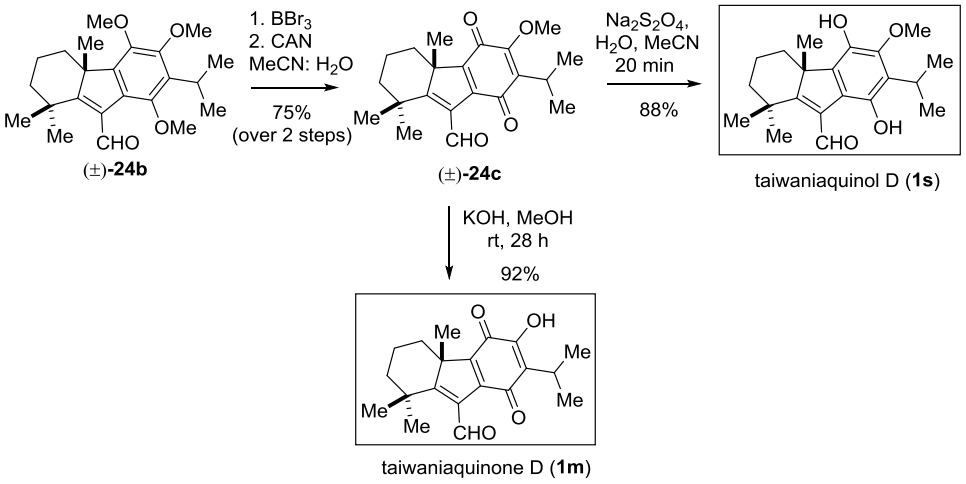
Scheme 15. Optimization of cyclization of arylvinylcarbinol **20a-b**.

Later, benzyl alcohol **23d** was treated with $BF_3{\cdot}Et_2O$ leading to the formation of **23e** and **23f** in 2.1:1 ratio (Scheme 16), which on subsequent allylic oxidation using SeO_2 afforded **24a** as an exclusive product.[53] The later was oxidized under Swern oxidation to furnish α,β-unsaturated aldehyde **24b** in 94% yield (Scheme 16). Next, compound **24b** was treated with BBr_3 followed by oxidation using ceric (IV) ammonium nitrate simply afforded potential *p*-quinone intermediate **24c**.



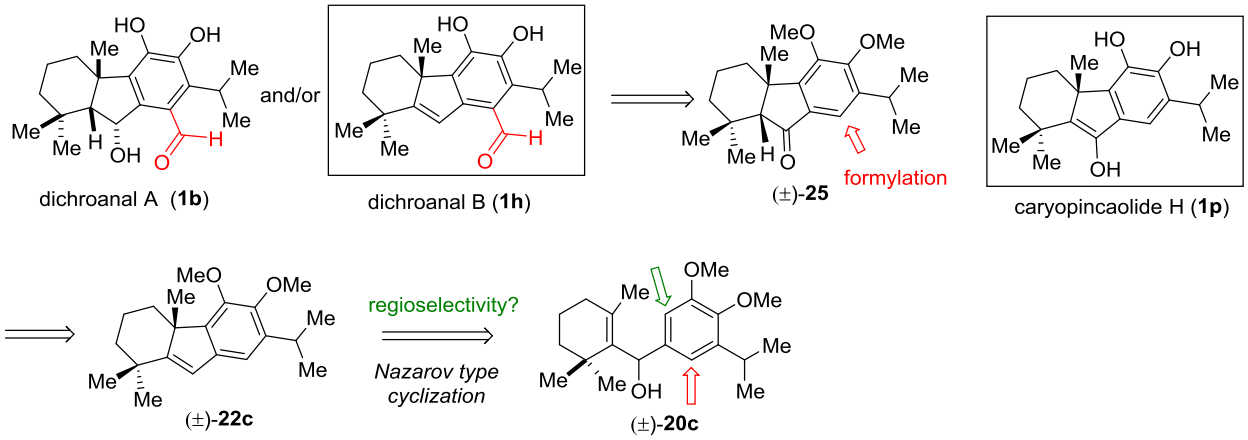
Scheme 16. Synthesis of common precursor **24b**.

Further, hydrolysis of intermediate **24c** in KOH in MeOH at room remperature completed total synthesis of (±)-taiwaniaquinone D (**1s**). On the other hand, reduction of *p*-quinone functionality was performed with $Na_2S_2O_4$ to complete total synthesis of (±)-taiwaniaquinol D (**1m**) in 88% yields (Scheme 17).[53]



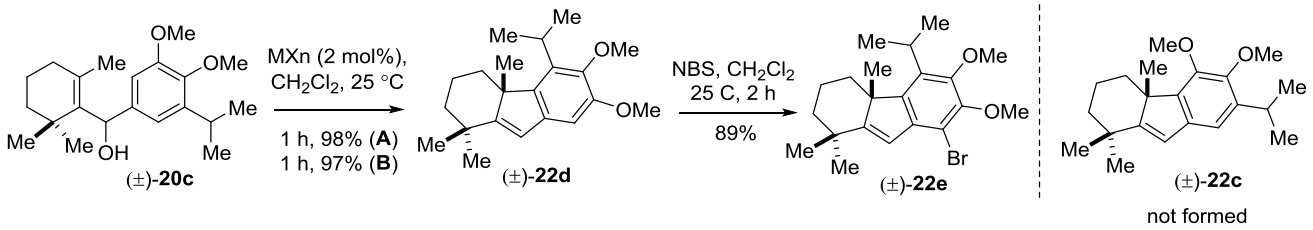
Scheme 17. Total synthesis of (±)-taiwaniaquinone D (**1h**) and (±)-taiwaniaquinol D (**1e**).

Further, the same group have reported total syntheses of taiwaniaquinoids, dichroanal A (**1b**), dichroanal B (**1h**) and keto form of caryopincaolide H (**1p**) following a key Nazarov type cyclization.[53] Initially, it was thought to access from a Nazarov type cyclization of arylvinyl carbinol **20c** (Scheme 18). However, under the optimized conditions A and B, **20c** went through a highly regioselective manner to afford only **22d** in 97-98% and no traces of **22c** was observed.



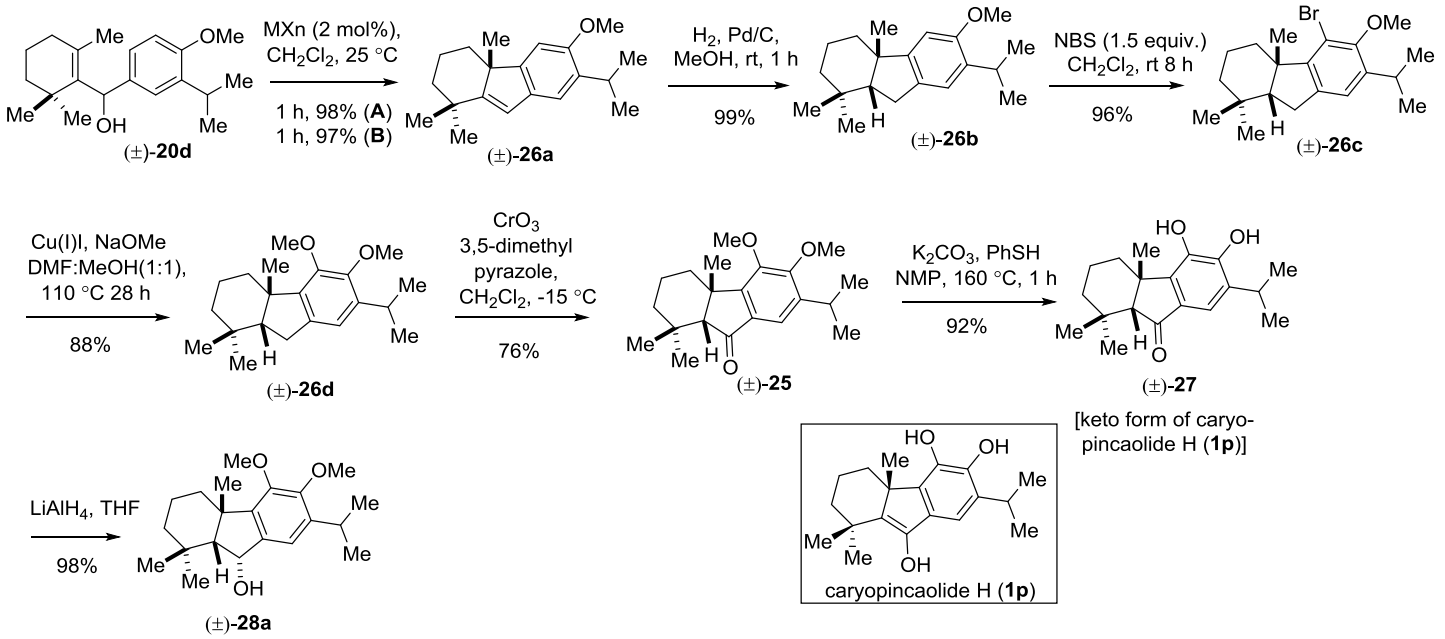
Scheme 18. Retrosynthetic analysis of (±)-dichroanals A (**1b**) and B (**1h**).

Compound **22d** was converted into bromoarene **22e**, which afforded suitable single crystal for X-ray analysis (Scheme 19). Therefore, regioisomer **22d** was unequivocally proved by X-ray crystal analysis of **22e**. This reaction clearly indicate that the regioselectivity of Nazarov type reaction is completely governed by electronic nature of aromatic ring, but not the sterics imposed by the bulky *i*-pr group of arylvinyl carbinol **20c** (Scheme 19).



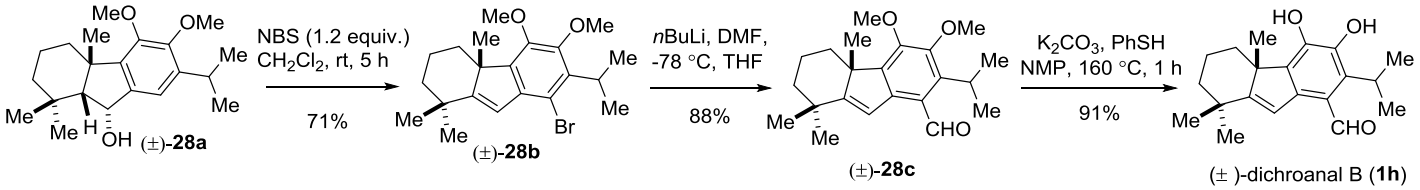
Scheme 19. Complete regioselectivity using arylvinylcarbinol **20c**. [2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $SnCl_4$ (**condition B**)]

Based on the result of Scheme 19, carbotricylic core **26a** (prepared from a Nazarov type cyclization of **20d**) was envisioned for total synthesis of dichroanal B (**1g**) (Scheme 20). Towards this, hydrogenation of **26a** to afford **26b** in 99% yield as sole diastereomer. Next, bromination of **26b** in presence of *N*-bromosuccinamide in dichloromethane afforded **26c** in 93% yield (Scheme 20). The later was reacted with sodium methoxide to obtain catechol dimethylether derivative **26d**. CrO_3-Oxidation of **26d** afforded tricyclic ketone **25** (Scheme 20). A simple demethylation using PhSH in the presence of K_2CO_3 led to the synthesis of keto form of caryopincaolide H (**1p**) in 92% yield.



Scheme 20. Synthesis of keto form of (±)-caryopincaolide H (**1p**) and advanced intermediate (±)-**28a**.

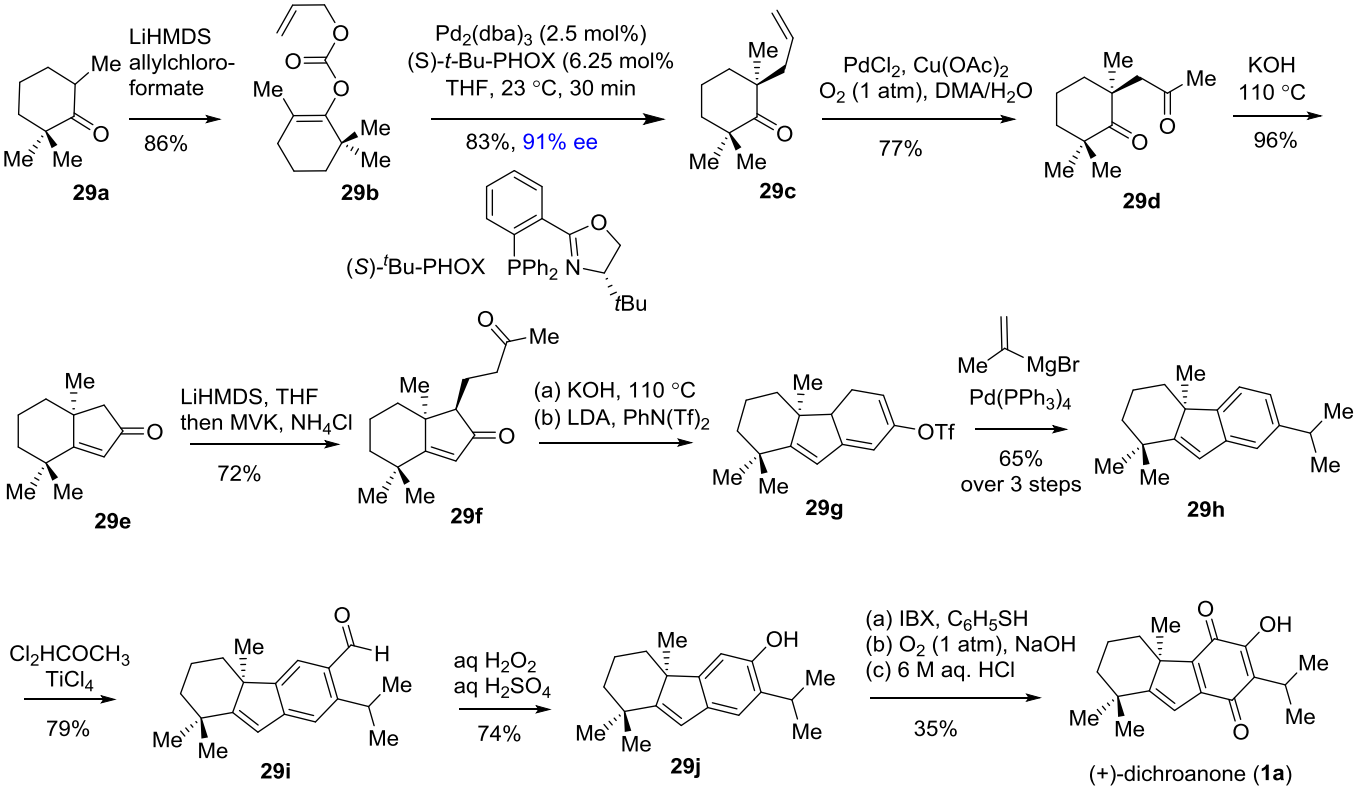
Later, ketone **27** was reduced to benzyl alcohol **28a** in presence of $LiAlH_4$ (Scheme 20). The excellent diastereoselectivity observed in $LiAlH_4$-meidated reaction was attributed to the approach of the hydride from the less hindered convex face of substrate **27**. Benzyl alcohol **28a** was treated with *N*-bromosuccinamide, where a one-pot bromination and dehydration led to the formation of **28b** in 71% yield. Finally, total synthesis of (±)-dichroanal B (**1h**) was completed in 2 steps in 87% overall yield *viz.* treatment with *n*-BuLi and DMF to form aldehyde **28c** followed by demethylation using thiophenol in the presence of K_2CO_3 (Scheme 21).[53]



Scheme 21. Total synthesis of (±)-dichroanal B (**1h**).

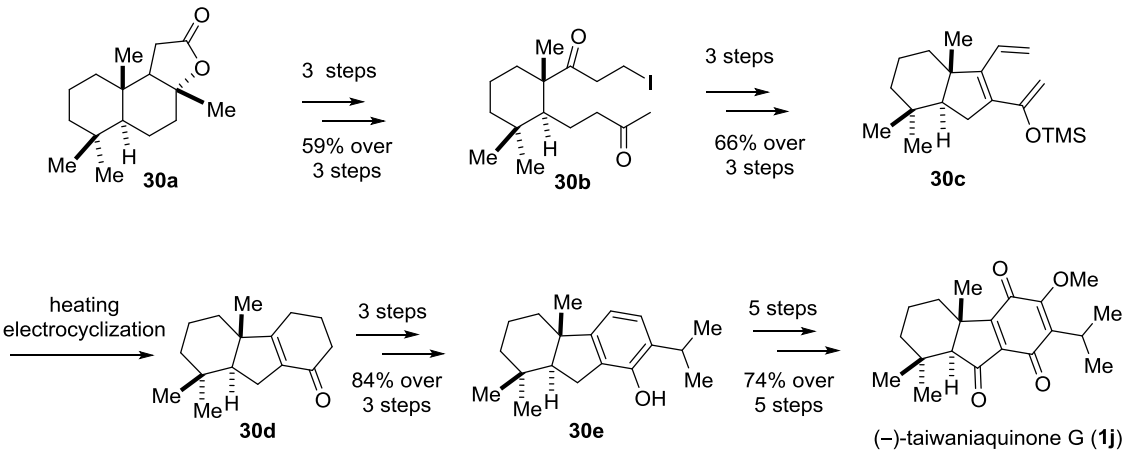
5.2 Stereocontrolled total syntheses of taiwaniaquinoids

In the year 2006, Stoltz and co-worker, have reported first enantioselective synthesis of (-)-dichroanone (**1a**) featuring an enantioselective Pd(0)-catalyzed decarboxylative allylation strategy.[54] This synthesis takes advantage of a Pd(0)-catalyzed asymmetric allylation methodology to generate all-carbon quaternary centres adjacent to carbonyls. Catalytic enantioselective decarboxylative allylation (DcA) of compound **29b** (prepared from **29a** by reacting with allylchloroformate) installed the quaternary center in **29c** with 91% ee (Scheme 22). Wacker oxidation[55] of **29c** followed by condensation provided bicyclic enone **29e** in excellent yield.[56] Michael addition of the lithium enolate of **29e** to methyl vinyl ketone (MVK) formed the keto-enone **29f** with high diastereoselectivity. The later was reacted under Robinson annulation strategy followed by reaction with *N*-phenyltriflimide afforded enoltriflate **29g** (Scheme 22). The later was immediately subjected to Kumada coupling with isopropenylmagnesium bromide led to a mixture of isomeric products, which converted irreversibly to compound **29h** upon exposure to acid. Later, a formylation of **29h** afforded aldehyde **29i** in 79% yield, which was under Baeyer–Villiger sequence installed the first oxygen in **29j** (74% yield). Finally, a one-pot oxidative reaction sequence was followed to complete the synthesis of (+)-dichroanone (**1a**) under protecting group-free manner.



Scheme 22. Total syntheses of (+)-dichroanone (**1a**) by Stoltz.

In the year 2009, Alvarez-Manzaneda and co-worker,[57, 58] have reported first enantiospecific synthesis of (-)-taiwaniaquinone G (**1j**) from **30c** following a key thermal 6π-electrocyclization (Scheme 23). From **30c**, carbotricyclic enone **30d** was synthesized just by heating, which was then elaborated to carbotricyclic structure **30e** over 3 steps in 84% overall yield. Finally, first total synthesis of (-)-taiwaniaquinone G (**1j**) has been achieved from **30e** in total 5 steps in an overall yield of 74% (Scheme 23).



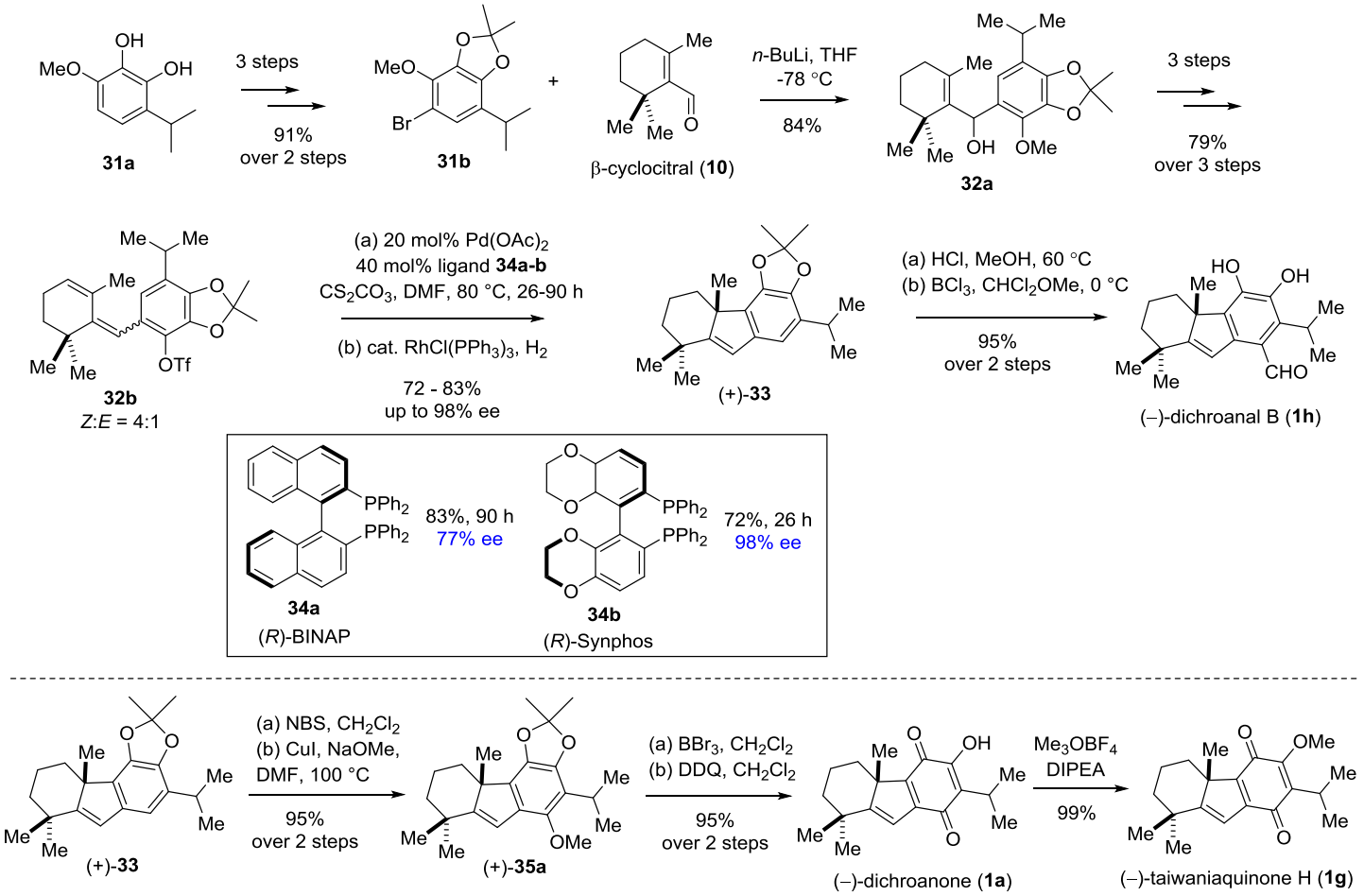
Scheme 23. Thermal 6π-electrocyclization by Alvarez-Manzaneda (2009).

In 2010, Node and co-worker have reported asymmetric total syntheses of (-)-dichroanal B (**1h**), (-)-dichroanone (**1a**), and taiwaniaquinone H (**1g**), by using a catalytic intramolecular asymmetric Heck reaction.[59, 60] They have designed substrate **32b** bearing a rigid acetonide group in the catechol moiety, which was prepared by modifying a previously reported method. Commercially available **31a** was treated with acetone in the presence of $BF_3.Et_2O$ to give the acetonide which was under bromination with NBS afforded **31b** in excellent yield. After lithiation of the bromide **31b** with *n*-butyllithium, the aryllithium generated was reacted with β-cyclocitral (**10**) to afford the benzylic alcohol **32a**. Dehydration of **32a** by treatment with methanolic hydrochloric acid gave the diene as a mixture of E and Z isomers (ca. 1:4), which after demethylation and subsequent triflation afforded required diene **32b**.

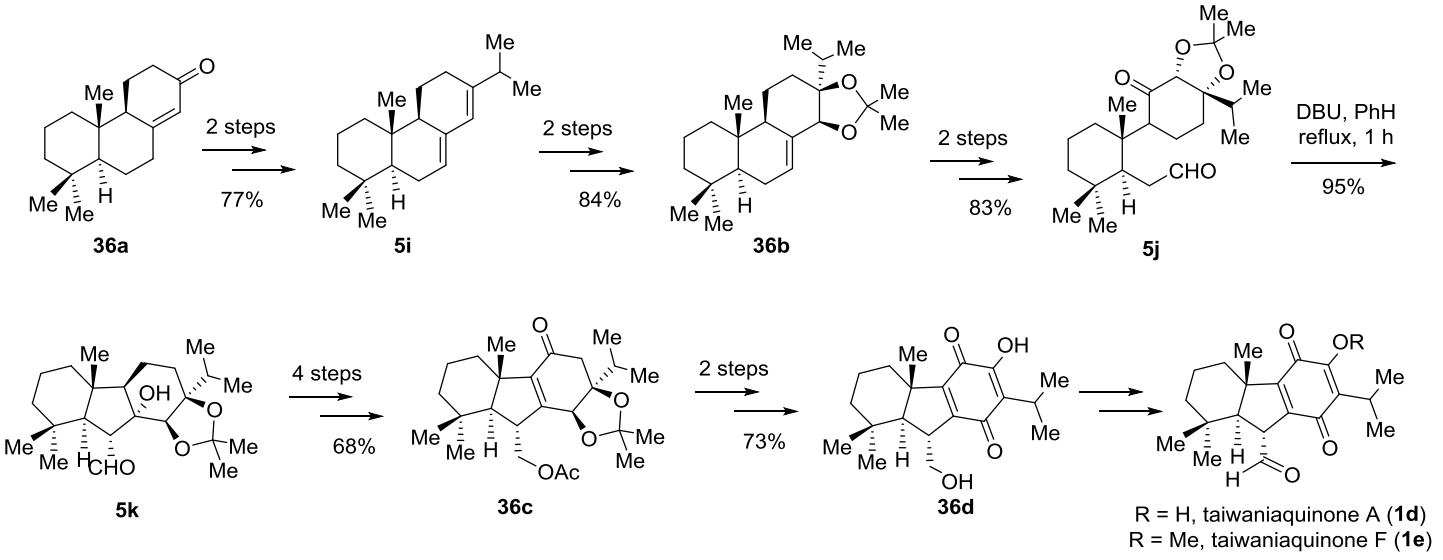
The intramolecular asymmetric Heck reaction of triflate **32b** (a mixture of E/Z isomers) in the presence of palladium(II) acetate, (*R*)-BINAP (**34a**) afforded **33** in 77% ee (Scheme 24). Following exhaustive optimization, it was found that the Heck reaction of triflate **32b** and successive hydrogenation gave **33** in good yield (<86% in 2 steps) with excellent ee (94-98%ee) when (*R*)-Synphos (**34b**) was used. Later, the acetonide of **33** was subjected to deprotection with HCl-MeOH followed by a reaction with dichloromethoxymethane in the presence of BCl_3 completed total synthesis of (-)-dichroanal B **1h**. Further treatment of **33** with *N*-bromosuccinimide followed by reaction with sodium methoxide in the presence of CuI followed by removal of the acetonide and oxidation with DDQ afforded total synthesis of (-)-dichroanone A (**1a**). Finally, the later was reacted with the Meerwein reagent to complete total synthesis of (-)-taiwaniaquinone H (**1g**) (Scheme 24).

In 2010, Alvarez-Manzaneda and co-worker,[21, 61] have reported semisynthesis of taiwaniaquinone A (**1d**) and F (**1e**) from abieatic acid (Scheme 25). A new strategy for synthesizing taiwaniaquinoids, based on the cleavage of the C7−C8 double bond of abietane diterpenes is described in this strategy. This procedure is the only one reported for synthesizing C_{20} taiwaniaquinoids bearing a carbon function on the cyclopentane B ring, such as taiwaniaquinone A (**1d**) and F (**1e**), and it is also applicable to the synthesis of 4a-methyltetrahydrofluorene derivatives, such as taiwaniaquinone H (**1g**) and dichroanone (**1a**), and

4amethylhexahydrofluorene derivatives, having an A/B trans-fused system, such as taiwaniaquinone G (**1j**), or an A/B cis-fused union, such as taiwaniaquinol B (**1f**).

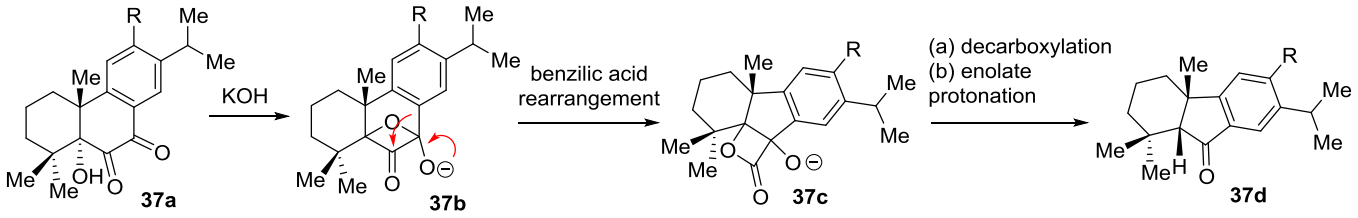


Scheme 24. Asymmetric total syntheses by Node via an intramolecular Heck strategy (2010).



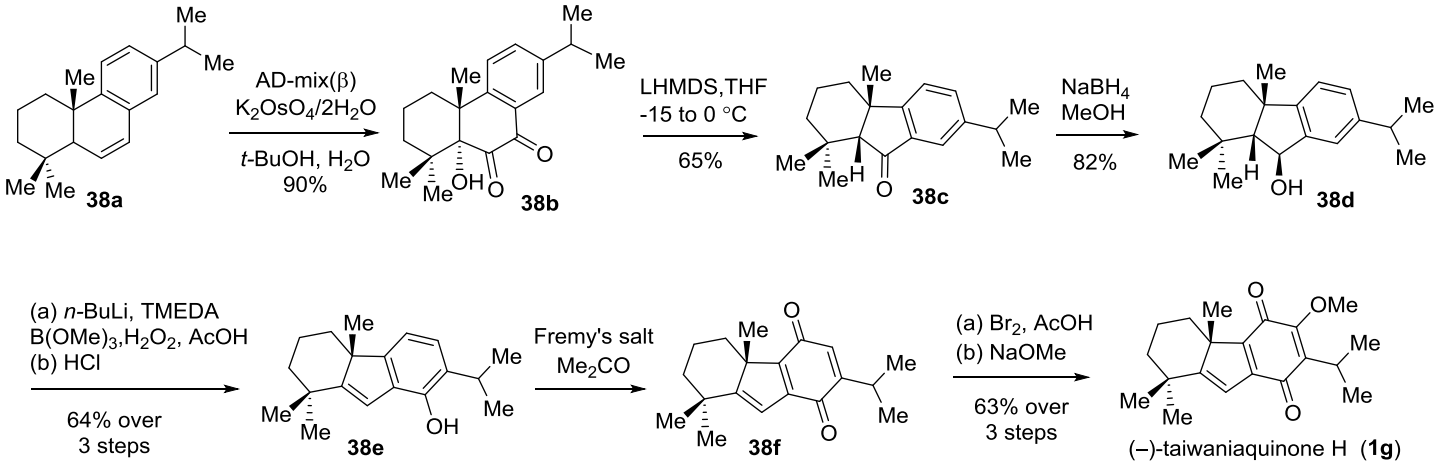
Scheme 25. Semisynthesis of taiwaniaquinoids by Alvarez-Manzaneda (2010).

In 2010, Gademann reported 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 (Scheme 26).[19, 20] The overall hypothesis of this strategy is summarized in Scheme 26, which was utilized for the total synthesis of (+)-taiwaniaquinone H (**1g**) under protecting group-free condition.



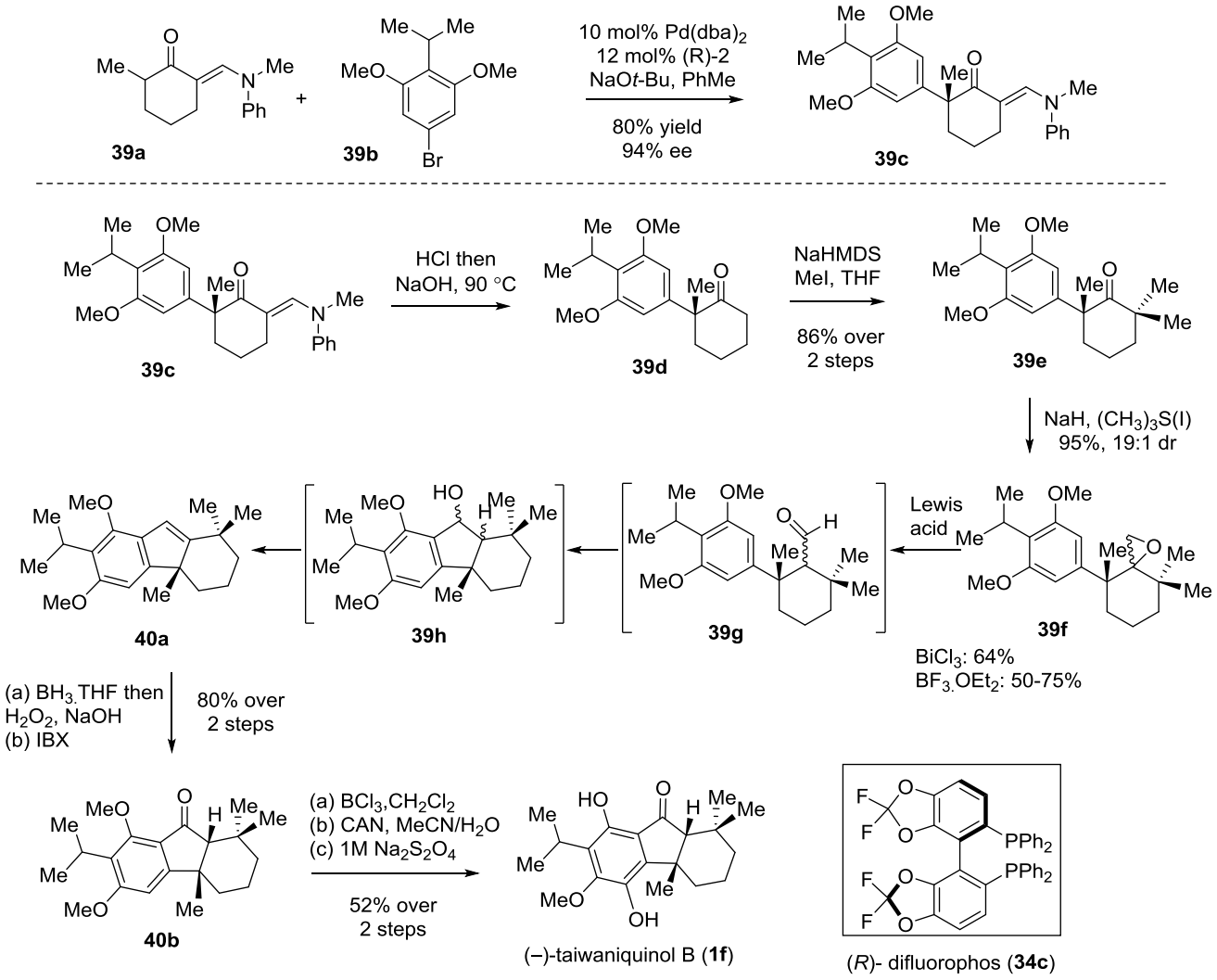
Scheme 26. Hypothesis of conversion of abietane (**37a**) to *abeo*-abietane (**37d**) by Gademann.

The starting material **38a** was obtained from commercially available methyl dehydroabiate in 5 steps.[62, 63] The hydroxydiketone functionality of the key intermediate **38b** was installed through a Sharpless asymmetric dihydroxylation reaction[64] (Scheme 27). Treatment of the hydroxydione **38b** with LHMDS gave the hydrofluorene derivative **38c**, as per proposal shown in Scheme 26, which was reduced with $NaBH_4$ to afford **38d**. Later, a one-pot sequence of hydroxy-group-directed *ortho* lithiation of the benzylic alcohol **38d**,[65, 66] and subsequent borylation of the aryl lithium compound and oxidation of the corresponding aryl boronate gave the hydroxylated phenol derivative, which was dehydrated under under acidic conditions to furnish dehydrated phenol **38e** in 64% yield over 2 steps (Scheme 27). The later was then cleanly oxidized using Fremy's salt to the corresponding *p*-quinone **38f**. Electrophilic bromination of the quinone **38f** followed by substitution with a methoxy group completed total synthesis of (+)-taiwaniaquinone H (**1g**) in 63% yield over 3 steps (Scheme 27).



Scheme 27. Total syntheses of (+)-taiwaniaquinone H (**1g**) by Gademann.

First enantioselective total synthesis of (-)-taiwaniaquinol B (**1f**) was reported by Hartwig *et. al.*[67] The reaction of **39b** with **39a**[68, 69] in the presence of $Pd(dba)_2$ and (*R*)-Difluorophos (10 mol %) afforded **39c** in 80% yield with 94% ee (Scheme 28).[67]

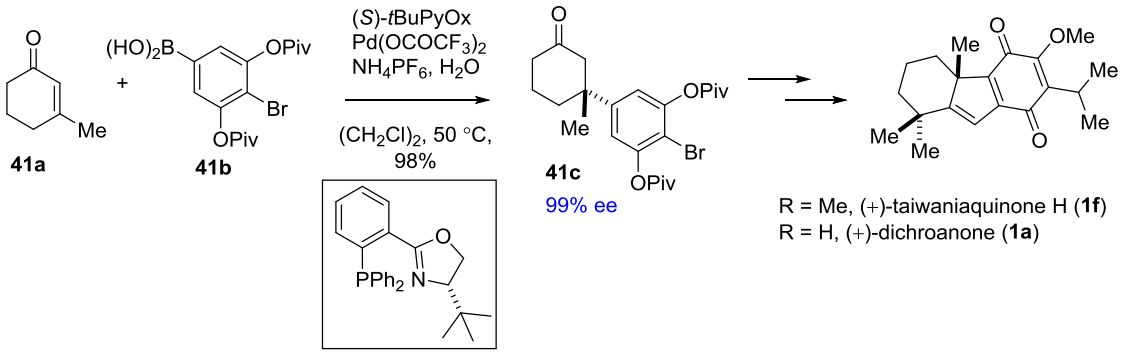


Scheme 28. Total syntheses of (–)-taiwaniaquinol B (**1f**) by Hartwig.

Acid-promoted reaction of ketone **39c** provided ketone **39d** in 91% yield over 2 steps. Dimethylation of **39d** with methyl iodide using NaHMDS afforded cyclohexanone **39e** in 86% yield. Corey-Chaykovsky epoxidation of ketone **39e** using sulfur ylide dimethylsulfonium methylide,[70, 71, 72] furnished epoxide **39f** in 95% yield with excellent diastereoselectivity. Later, Lewis acid catalyzed rearrangement of the epoxide **39f** to the aldehyde **39g** followed by Friedel-Crafts alkylation reaction with **39g** afforded corresponding alcohol, which underwent elimination to form the target tetrahydrofluorene **40a**. The later under selective monodemethylation followed by oxidation provided (–)-taiwaniaquinone H (**1g**) in 51% yield over 2 steps (Scheme 6).[35] Further, hydroboration-oxidation of **40b** and further oxidation with 2-iodoxybenzoic acid (IBX) gave **40a** as a single diastereomer. Finally, selective monodemethylation of **40b** with BCl_3, oxidation with CAN and reductive workup with sodium dithionite gave (–)-taiwaniaquinol B (**1f**) in 52% yield over 2 steps, as per report by Fillon[33] and Trauner.[35]

Recently, in 2014, Stoltz and co-workers,[73, 74] have reported a catalytic, enantioselective formal total synthesis of (+)-dichroanone (**1a**) and (+)-taiwaniaquinone H (**1g**) starting from commercially available 2-bromoresorcinol (Scheme 29). The required aromatic boronic acid **41b** was synthesized from 2-bromoresorcinol in few steps. In this strategy, a key all-carbon quaternary stereocenter was constructed in **41c** by asymmetric conjugate addition catalyzed by a palladium(II)-(*S*)-*tert*-butyl PHOX complex (Scheme 29). This

cyclohexanone intermediate was further utilized for formal total syntheses of a variety of naturally occurring taiwaniaquinoids.



Scheme 29. Pd(II)-Catalyzed enantioselective strategy by Stoltz (2014).

6. Conclusions

This review is intended to provide an overview of the complex taiwaniaquinoids where biosynthetic relationship of diterpenoids and synthetic approaches to this family of diterpenoids have been discussed elaborately. The literature on the synthesis of taiwaniaquinoids summarized in this review very well suggest that they have been proposed in the literature to be arisen from abietane diterpenoids. It has been over 23 years since the first member of the *abeo*-abietane family was isolated in 1995 from the roots of *Salvia dichroantha* Stapf (Lamiaceae), a Turkish flowering sage. Since that time, an additional twenty abeo-abietanes have been isolated from a variety of plant species from variety of species. The fascinating molecular architecture of the members of this natural product family has stimulated the interest of numerous synthetic chemists which has led to a number of creative synthetic approaches and beautiful total syntheses. Although, the biological activities of only a few numbers of taiwaniaquinoids are reported, the exhaustive biological potential of the majotiry of taiwaniaquinoids has yet to be evaluated. The knowledge from biological stidues would be useful in screening these products for therapeutic applications.

Acknowledgements

VB sincerely thanks the Science Engineering Research Board (SERB), Department of Science and Technology (DST) [CS-021/2014] for financial support and Department of Chemistry, IISER Berhampur. AB sincerely thanks the SERB, DST, Govt. of INDIA [EMR/2016/000214], the Council of Scientific and Industrial Research (CSIR), Govt. of India [02(0295)/17/EMR-II], and Ministry of Earth Science (MoES), Govt. of India [MoES-2/DS/6/2007 PC-IV] for generous support. Facilities from the Department of Chemistry, IISER Bhopal is gratefully acknowledged.

References and Notes

1. Terpenes are a diverse class of organic compounds, produced by a variety of plants, particularly conifers, for a review, see; Hanson, J. R. *Nat. Prod. Rep.* **2013**, *30*, 1346. https://doi.org/10.1039/c3np70046a
2. For a recent review on abietane terpenoids, see, Gonzalez, M. A. *Nat. Prod. Rep.* **2015**, *32*, 684. https://doi.org/10.1039/C4NP00110A

3. For an excellent review on taiwaniaquinoids, see; Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284. https://doi.org/10.1021/np9004695
4. Lin, W. ; Fang, J. ; Cheng, Y. *Phytochemistry* **1996**, *42*, 1657. https://doi.org/10.1016/0031-9422(96)00198-7
5. Kawazoe, K.; Yamamoto, M. ; Takaishi, Y.; Honda, G. ; Fujita, T.; Sezik, E. ; Yesilada, E. *Phytochemistry* **1999**, *50*, 493. https://doi.org/10.1016/S0031-9422(98)00471-3
6. Lin, W. ; Fang, J.; Cheng, Y. *Phytochemistry* **1995**, *40*, 871. https://doi.org/10.1016/0031-9422(95)00358-E
7. 7. Chang, C.; Chien, S.; Lee, S.; Kuo, Y. *Chem. Pharm. Bull.* **2003**, *51*, 1420. https://doi.org/10.1248/cpb.51.1420
8. For an excellent review on fluorenone and fluorene containing natural products, see; Shi, Y.; Gao, S. *Tetrahedron* **2016**, *72*, 1717. https://doi.org/10.1016/j.tet.2016.02.022
9. Chang, C. -I.; Chang, J. -Y.; Kuo, C. -C.; Pan, W. -Y.; Kuo, Y. -H. *Planta Med.* **2005**, *71*, 72. https://doi.org/10.1055/s-2005-837754
10. Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911. https://doi.org/10.1016/S0968-0896(01)00099-2
11. Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742. https://doi.org/10.1055/s-2002-33787
12. Hanson, J. *Nat. Prod. Rep.* **2004**, *21*, 312.
13. For syntheses of [6-5-6] and [6-5-5]tricyclic core embedded heterocycles, see; Singh, R.; Parai, M. K.; Panda, G. *Org. Biomol. Chem.* **2009**, *7*, 1858. https://doi.org/10.1039/b901632e
14. For syntheses of tricyclic core embedded polycycles, see; Singh, R.; Panda, G. *Org. Biomol. Chem.* **2011**, *9*, 4782. https://doi.org/10.1039/c0ob00892c
15. For syntheses of [6-5-6]-carbotricyclic core via organocatalysis, see; Wu, X.; Li, M.-L.; Chen, D.-F.; Chen, S.-S. *J. Org. Chem.* **2014**, *79*, 4743. https://doi.org/10.1021/jo5006729
16. Guardia, J. J.; Tapia, R.; Mahdjour, S.; Rodriguez-Serrano, F.; Mut-Salud, N.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Nat. Prod.* **2017**, *80*, 308. https://doi.org/10.1021/acs.jnatprod.6b00700
17. 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. https://doi.org/10.1016/j.bmc.2007.01.031
18. For a summary of biogenetic proposal, see; Katakawa, K. *J. Syn. Org. Chem.* (Japan) **2014**, *72*, 305. https://doi.org/10.5059/yukigoseikyokaishi.72.305
19. Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. –Eur. J.* **2010**, *16*, 7692. https://doi.org/10.1002/chem.201001085
20. Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390. https://doi.org/10.1021/ol4003652
21. Alvarez-Manzaneda E.; Chahboun R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda R. *Chem. Commun.,* **2010**, *46*, 9244. https://doi.org/10.1039/c0cc03763j
22. Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871. https://doi.org/10.1016/0031-9422(95)00358-E

23. Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657. https://doi.org/10.1016/0031-9422(96)00198-7
24. Cheng recognized the rearranged abietane core, but only referred to it as "the uncommon skeleton of fused 6-5-6 rings" probably arising from abietane diterpenoids.
25. For a review on this historically important class having a fused [6,5,6]-system, see: Mander, L. N. *Nat. Prod. Rep.* **2003**, *20*, 49 and references therein. https://doi.org/10.1039/b007744p
26. Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sesik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493. https://doi.org/10.1016/S0031-9422(98)00471-3
27. Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419. https://doi.org/10.1016/S0040-4039(99)01191-0
28. Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420. https://doi.org/10.1248/cpb.51.1420
29. Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72. https://doi.org/10.1055/s-2005-837754
30. Lin, W. -H.; Fang, J. -M.; Cheng, Y. -S. *Phytochemistry.* **1997**, *46*, 169. https://doi.org/10.1016/S0031-9422(97)00267-7
31. 31Banerjee M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. *Org. Lett.* **2003**, *5*, 3931. https://doi.org/10.1021/ol035506b
32. Banerjee M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. *J. Org. Chem.* **2006**, *71*, 2787. https://doi.org/10.1021/jo052589w
33. Fillion E.; Fishlock D. *J.Am. Chem. Soc.* **2005**, *127*, 13144. https://doi.org/10.1021/ja054447p
34. Planas, L.; Mogi, M.; Hirofumi, T.; Kajimato, T.; Node, M. O. *J. Org. Chem.* **2006,** *71*, 2896. https://doi.org/10.1021/jo052454q
35. G. Liang, Y. Xu, I. B. Seiple, D. Trauner *J. Am. Chem. Soc.* **2006**, *128*, 11022. https://doi.org/10.1021/ja062505g
36. Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741. https://doi.org/10.1016/j.tetlet.2008.01.084
37. Tang, S.; Xu, Y.; He, J.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855. https://doi.org/10.1021/ol800513v
38. Majetich, G.; Shimkus, J. M. *Tetrahedron Lett.* **2009**, *50*, 3311. https://doi.org/10.1016/j.tetlet.2009.02.074
39. Alvarez-Manzaneda E.; Chahboun R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzeneda, R.; Meness, R.; Es-Samti, H.; Ferna'ndez, A. *J. Org. Chem.,* **2009**, *74*, 3384. https://doi.org/10.1021/jo900153y
40. Deng, J.; Li, R.; Luo, Y.; Li, J.; Zhou, S.; Li, Y.; Hu, J.; Li, A. *Org Lett*. **2013**, *15*, 2022. https://doi.org/10.1021/ol400717h
41. Padwa, A.; Chughtai, M. J.; Boonsombat, J.; Rashatasakhon, P. *Tetrahedron* **2008**, *64*, 4758. https://doi.org/10.1016/j.tet.2008.01.129
42. Ishiyama, T.; Miyaura, N.; Suzuki, A. *Org. Synth.* **1993**, *71*, 89. https://doi.org/10.15227/orgsyn.071.0089
43. Winne, J. M.; Guang, B.; Dherde, J.; De Clercq, P. J. *Org. Lett.* **2006**, *8*, 4815. https://doi.org/10.1021/ol061962z
44. Wilds, A. L.; Meader, Jr. A. L. *J. Org. Chem.* **1948**, *13*, 763. https://doi.org/10.1021/jo01163a024

45. 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. https://doi.org/10.1021/jo010951a
46. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. https://doi.org/10.1021/jo00399a052
47. Yan, X.; Hu, X. *J. Org. Chem.* **2014**, *79*, 5282. https://doi.org/10.1021/jo5008652
48. Tomooka, C. S.; Liu, H.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 6009. https://doi.org/10.1021/jo960421s
49. Huang, X.; Song, L.; Xu, J.; Zhu, G.; Liu, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 952. https://doi.org/10.1002/anie.201208687
50. Kakde, B. N.; Kumari, P.; Bisai, A. *J. Org. Chem.* **2015**, *80*, 9889. https://doi.org/10.1021/acs.joc.5b01345
51. Kakde, B. N.; De, S.; Dey, D.; Bisai, A. *RSC Adv.* **2013**, *3*, 8176. https://doi.org/10.1039/c3ra41497c
52. Kakde, B. N.; Parida, A.; Kumari, P.; Bisai, A. *Tetrahedron Lett.* **2016**, *57*, 3179. https://doi.org/10.1016/j.tetlet.2016.06.030
53. Kakde, B. N.; Parida, A.; Kumar, N.; Mourya, A.; Bisai, A. *ChemistrySelect* **2016**, *1*, 3357. https://doi.org/10.1002/slct.201600890
54. McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738. https://doi.org/10.1021/ja061853f
55. Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765. https://doi.org/10.1016/S0040-4039(98)01992-3
56. Thomas, A. F.; Ozainne, M.; Guntz-Dubini, R. *Can. J. Chem.* **1980**, *58*, 1810. https://doi.org/10.1139/v80-286
57. Alvarez-Manzaneda E.; Chahboun R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzeneda, R.; Hmamouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592. https://doi.org/10.1039/B816812A
58. Alvarez-Manzaneda E.; Chahboun R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzeneda, R.; Charrah, Y.; Es-Samti, H. *Org. Biomol. Chem.* **2009**, *7*, 5146. https://doi.org/10.1039/b916209g
59. Node, M.; Ozeki, M.; Planas, l.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimato, T. O. *J. Org. Chem.* **2010,** *75*, 190. https://doi.org/10.1021/jo901972b
60. Ozeki, M.; Satake, M.; Toizume, T.; Fukutome, S.; Arimitsu, K.; Hosai, S.; Kajimato, T.; Iwasaki, N.; Kajima, N.; Node, M.; Yamashita, M. O. *Tetrahedron,* **2013,** *69*, 3841. https://doi.org/10.1016/j.tet.2013.03.051
61. 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. https://doi.org/10.1021/jo202163y
62. Lin, W. H. ; Fang, J. M. ; Cheng, Y. S. *Phytochemistry* **1995**, 40, 871. https://doi.org/10.1021/jo202163y
63. Geiwiz, J.; Haslinger, E. *Helv. Chim. Acta* **1995**, *78*, 818. https://doi.org/10.1002/hlca.19950780404
64. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. https://doi.org/10.1021/jo00036a003
65. Meyer, N.; Seebach, D. *Angew. Chem. Int. Ed.* **1978**, *17*, 521.

https://doi.org/10.1002/anie.197805211
66. Loh, T. P.; Hu, Q. Y. *Org. Lett.* **2001**, *3*, 279. https://doi.org/10.1021/ol006918c
67. Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088. https://doi.org/10.1021/ja110215b
68. Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. https://doi.org/10.1021/ol0159470
69. Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223. https://doi.org/10.1021/ja01137a001
70. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. https://doi.org/10.1021/ja00864a040
71. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. https://doi.org/10.1021/ja00878a046
72. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. https://doi.org/10.1021/ja01084a034
73. Shockley, S. E.; Holder, J. C.; Stoltz, B. M. *Org. Lett.* **2014,** *16,* 6362. https://doi.org/10.1021/ol5031537
74. Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011,** *133,* 6902. https://doi.org/10.1021/ja200664x

Authors' Biographies

Vishnumaya Bisai was born in Gorakhpur, India on August 30, 1979. She completed M.Sc. in Chemistry from DDU Gorakhpur University, India in July 2002 and Ph.D. in the area of organocatalytic Carbon-Carbon bond-forming reactions with Prof. Vinod K. Singh from the Indian Institute of Technology (IIT) Kanpur, India in January, 2009. Immediately afterward, she started post-doctoral research in the area of total synthesis of lycopodium alkaloids with Prof. Richmond Sarpong from the University of California (UC), Berkeley, USA and continued till November, 2010. She joined the Department of Applied Sciences, National Institute of Technical Teachers' Training and Research *(*NITTTR*)*, Bhopal, India as an Assistant Professor of Chemistry *(*Apr., 2011 – Apr. 2012*).* After spending 3 years at IISER Bhopal (Sr. Research Scientist during May, 2012 – July, 2014 and Visiting Faculty during Aug. 2014 – Aug. 2015), she joinded as an Assistant Professor in the Department of Chemistry, IISER Tirupati *(*Aug. 2015 – July. 2016*).* Later, she moved to the Department of Chemistry, IISER Berhampur as an Assistant Professor of Chemistry in Aug. 2016. Her research interest involves the design and development of enantioenriched ligands and their applications in the area of asymmetric catalysis and stereoselective synthesis of natural/hybrid molecules.

Aditi Gupta completed her Bachelors in Chemistry (Hons.) from St. Stephen's College, Delhi University in 2007 and Masters in Chemistry from IIT Delhi in 2009. She has received prestigious CSIR-JRF and CSIR-SRF fellowships from the Govt. of India and completed her Ph.D. in Applied Chemistry with Prof. Satyawati Sharma from Indian Institute of Technology Delhi, India in 2013. Thereafter, she has been working as an Assistant Professor in the Department of Chemistry, St. Stephen's College, Delhi University. She has over 18 international publications (h-index = 7) in peer reviewed journals and conferences to her credit. Her major research interests include plant metabolites, waste management, biomass to bioenergy conversion, development of biopesticides, nutraceuticals, etc.

Alakesh Bisai received his M.Sc. degree in Organic Chemistry from Banaras Hindu University and obtained Ph.D. in synthetic Organic Chemistry under the supervision of Professor Vinod K. Singh from the Department of Chemistry, Indian Institute of Technology Kanpur in Sept. 2006. Immediately afterward, he moved to the College of Chemistry, University of California at Berkeley, where he held postdoctoral position in the research group of Professor Richmond Sarpong. During his stay at Berkeley, he completed concise total synthesis of '*lycopodium alkaloids*' lyconadin A, which received considerable attention from the synthetic community. During his Postdoctoral research, he received the GRC (*Gordon Research Conference*) award to Post-docs by Chair, 17th GRC on Stereochemistry (2008), RI. In Dec. 2009, he left Berkeley and joined the Department of Chemistry, IISER Bhopal as an Assistant Professor. In Nov. 2013, he was appointed as an Associate Professor in the Department Chemistry. The research focus of the AB research group includes the total synthesis of architecturally interesting biologically active natural products that provide an ideal platform for the invention of new strategies and highly selective organic transformations. A number of naturally occurring architecturally intriguing biological relevant secondary metabolites sharing all-carbon quaternary stereocenters have been synthesized by his research group at IISER Bhopal. He is the recipient of *Young Scientist Research Grant* by the DST (in form of FAST-TRACK grant) (2011) and by the BRNS, DAE (2011). Recently, his total synthesis of pyrroloindoline alkaloids had been highlighted in '*Organic Chemistry Portal*' as '*The Bisai Synthesis of (-)-*

Physovenine' (http://www.organic-chemistry.org/Highlights/2016/18July.shtm). Since January, 2018, he has been working as a Professor of Chemistry at IISER Bhopal.