Prayogik Rasayan

$FeCl_3$-Catalyzed Highly Efficient Nazarov Type Cyclization of Arylvinyl Carbinols: Total Syntheses of Naturally Occurring Taiwaniaquinoids

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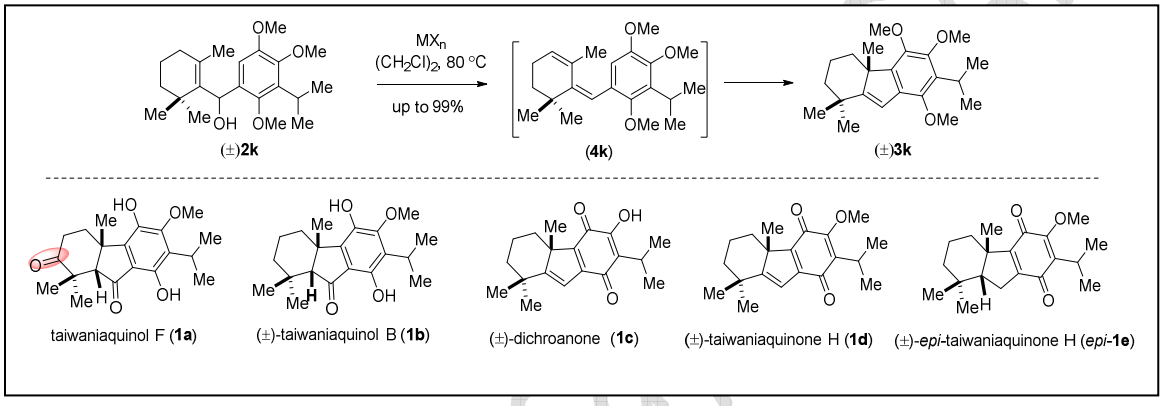


Abstract

$FeCl_3$-catalyzed cyclization of arylvinylcarbinols for the synthesis of [6,5,6]-carbotricyclic core sharing an all-carbon quaternary center has been described in this full article. A careful mechanistic details suggest that the reaction follows a stepwise mechanism *via* the intermediacy of arylallyl carbocationic species. The carbocation subsequently reacts with an adjacent aromatic ring to form [6,5,6]-carbotricyclic scaffold of *abeo*-abietane diterpenoids. The methodology works under mild conditions to afford a variety of carbotricyclic core in good to excellent yields (up to 99% yield). Our strategy has been applied to a concise synthesis of a number of structurally intriguing naturally occurring taiwaniaquinoids, (±)-taiwaniaquinol F (**1a**), (±)-taiwaniaquinol B (**1b**), (±)-dichronanone (**1c**), (±)-taiwaniaquinone H (**1d**) and unnatural (±)-5-*epi*-taiwaniaquinone G (*epi*-**1e**).

Keywords: *abeo*-abietane diterpenoids, natural products, taiwaniaquinoids, arylvinylcarbinols, Nazarov-type Cyclization, all-carbon quaternary center, toatal synthesis

1. Introduction

The taiwaniaquinoids (**1a-j**, Figure 1)[1] are a family of naturally occurring diterpenoids having a [6,5,6]-carbotricyclic core. These secondary metabolites share an all-carbon quaternary stereocenter at the ring junction of hydrindane skeleton. Most of these diterpenoids are isolated since 1995 from *Taiwania cryptomerioides* Hayata (Taxodiaceae) of central mountains of Taiwan independently by Cheng[2-4] and Kuo.[5-6] Further, in 1999, Kawazoe *et. al.* isolated a number of congeners of taiwaniaquinoids from *Salvia dichroantha* Stapf (Lamiaceae) of a Turkish flowering sage.[7] Independently, Tanaka *et. al.* have isolated [6,5,6]-*abeo*-abietane from *Thuja standishii* (Cupressaceae) of a Japanese conifer.[8] Reportedly, few members of taiwaniaquinoids are found to exhibit interesting biological activities. Congeners of this family of diterpenoids show cytotoxic activity against KB epidermoid carcinoma cancer cells.[6] Standishinal (**1j**) is reported to show aromatase inhibitory activity.[9-11] Therefore, the taiwaniaquinoids have gained considerable attention from the synthetic community and a number of efficient approaches are reported.

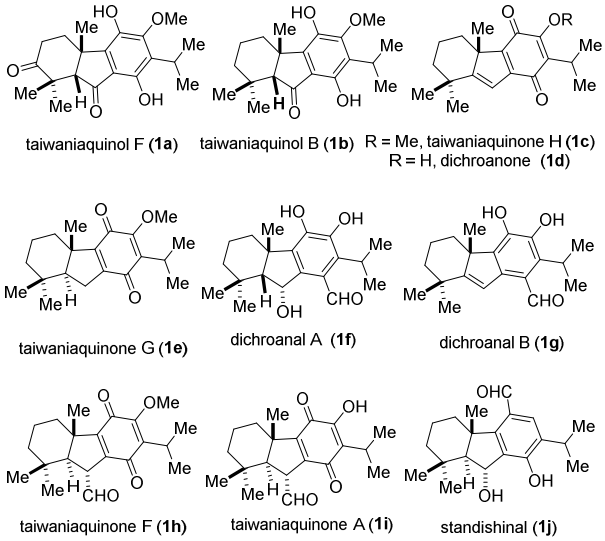
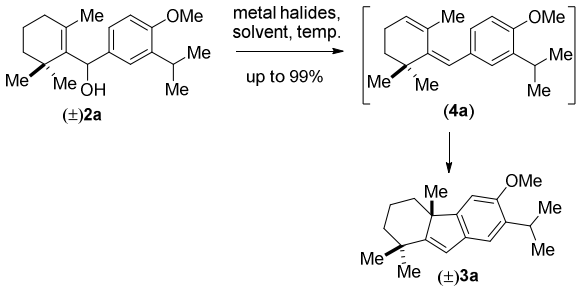


Figure 1: Selected taiwaniaquinoids sharing an all-carbon quaternary stereocenters.

Towards this, the first approach was reported by Banerjee et. al.,[12-13] via an efficient Pd(0)-catalyzed intramolecular reductive cyclization. Later, a domino intramolecular acylation carbonyl α-*tert*-alkylation reaction was explored by Fillion.[14] An intramolecular Heck cyclization was developed by Node and co-workers.[15-16] Further, a Nazarov cyclization was reported by Trauner et. al.,[17] and a tandem acylation-Nazarov cyclization reaction by Chiu and co-workers.[18] Later, an acid promoted Friedel–Crafts acylation/alkylation approach was developed independently by She[19] and Cheng co-workers.[20] A number of expeditious intramolecular cyclization of aryldienes were reported independently by Balme,[21] Alvarez-Manzaneda[22] and Majetich.[23] A ring contraction from abietane diterpenoids was reported by Li and co-workers in 2013.[24] Later, a thermal ring expansion/4π-electrocyclization was reported by Hu et. al.[25] and other approaches.[26-28]

The asymmetric syntheses include, enantioselective decarboxylative allylation for the total synthesis of dichroanone (**1d**) by Stoltz in 2006,[29] enantiospecific approach via a thermal 6π-electrocyclization by Alvarez-Manzaneda and co-workers,[30-31] Pd(0)-catalyzed enantioselective Heck reaction by Node,[32-33] ring contraction of a [6,6,6]-abietane diterpenoids to obtain a [6,5,5]-carbotricyclic scaffold by Gademann,[34-35] a semisynthetic approach involving cleavage of the C7–C8 double bond of abietane diterpenes by Alvarez-Manzaneda.[36-37] Further, in 2011, Hartwig et. al. had reported palladium-catalyzed asymmetric α-arylation.[38] Later, in 2014, Stoltz et. al. had reported an impressive Pd(0)-catalyzed enantioselective conjugate addition of arylboronic acid.[39-41]

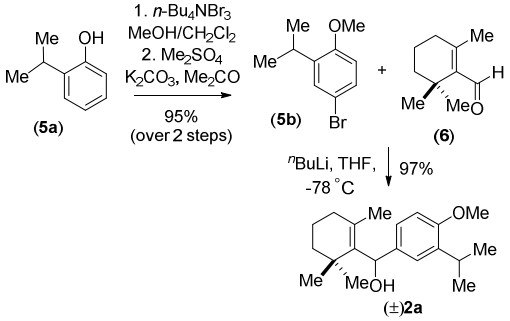


Scheme 1: Our approach to the diterpenoids sharing *abeo*-Abietane skeleton.

Recently, our group reported an efficient entry to *abeo*-abietane diterpenoids[42] via an efficient cyclization of arylvinyl carbinols **2**.[43-44] Using aforementioned methodology, we have synthesized a variety of carbotricycles in good to excellent yields. Herein, we report a $FeCl_3$-catalyzed cyclization of arylvinyl carbinols **2** (Scheme 1) for a general approach to [6,5,6]-tricyclic based structures. This process was utilized for protecting-group-free formal total syntheses of naturally occurring taiwaniaquinoids (Figure 1), (±)-taiwaniaquinol F (**1a**), (±)-taiwaniaquinol B (**1b**), (±)-dichronanone (**1c**), (±)-taiwaniaquinone H (**1d**) and unnatural (±)-5-*epi*-taiwaniaquinone G (*epi*-**1e**).

2. Results and Discussions

For our study, arylvinyl carbinol (±)-**2a** was synthesized by 1,2-addition of aryllithium (*in-situ* generated from bromoarene **5b**) onto β-cyclocitral **6** (Scheme 2). The arylvinyl carbinol (±)-**2a** is an excellent substrate for Lewis-acid catalyzed activation to generate an electron-deficient center. Thus, it was thought of exploring (±)-**2a** for a C-C bond-forming to obtain [6,5,6]-carbotricyclic core of *abeo*-abietane structure.

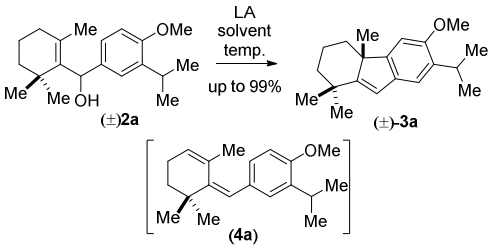


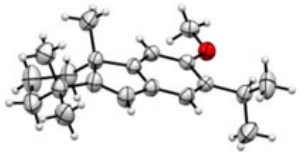
Scheme 2: Synthesis of arylvinylcarbinol (±)-**2a**.

In case of solvents such as tetrahydrofuran, and chloroform under different temperature, we could isolate (±)-**3a** in 20-50% isolated yields along with 40-65% yields of diene **4a** (entries 1-3, Table 1). Among various solvents used, it was found that Et_2O, hexane, acetonitrile, toluene, and dichloroethane are better choice of solvents which afforded product (±)-**3a** in 82%, 89%, 88%, 95%, and 99%

yields, respectively (entries 4-8). We could isolate 11% of diene **4a** when Et_2O was used as solvent. We could isolate (±)-**3a** in almost quantitative yield, where aromatic ring approach to vinylic position from *p*-position of *i*-Pr group.

Table 1: Optimization of cyclization of arylvinylcarbinol (±)-**2a**.



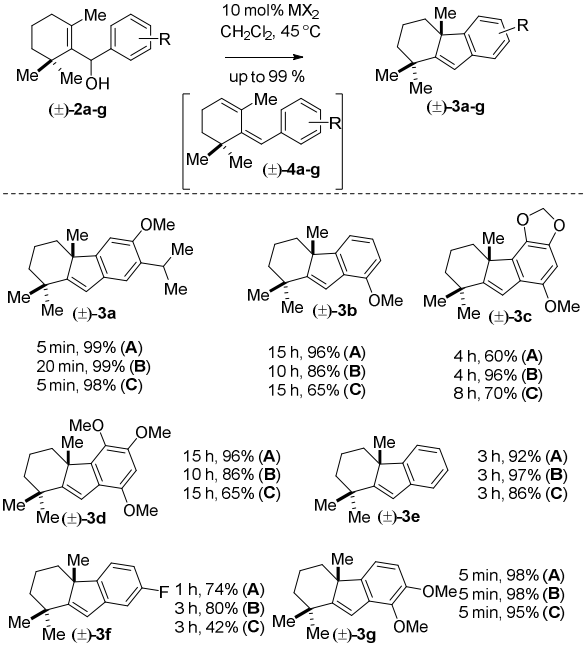


X-ray structure of ±(**3a**) [CCDC 926020]

Entry	Lewis acid	solvent	temp	time	% of (±)-**3a**[a,b]	% of (±)-**4a**[a,b]
1.	10 mol% $FeCl_3$	THF	25 ºC	24 h	20%	65%
2.	10 mol% $FeCl_3$	THF	65 ºC	15 h	48%	46%
3.	10 mol% $FeCl_3$	$CHCl_3$	25 ºC	15 h	49%	41%
4.	10 mol% $FeCl_3$	Et_2O	25 ºC	12 h	82%	11%
5.	10 mol% $FeCl_3$	hexane	35 ºC	14 h	87%	05%
6.	10 mol% $FeCl_3$	MeCN	70 ºC	1 h	89%	00%
7.	10 mol% $FeCl_3$	PhMe	100 ºC	2 h	95%	00%
8.	10 mol% $FeCl_3$	$(CH_2Cl)_2$	80 ºC	1.5 h	99%	00%
9.	10 mol% $AlCl_3$	$(CH_2Cl)_2$	80 ºC	24 h	28%[c]	12%[c]
10.	10 mol% $CuBr_2$	$(CH_2Cl)_2$	80 ºC	24 h	45%[c]	19%[c]
11.	10 mol% CuI	$(CH_2Cl)_2$	80 ºC	17 h	34%[c]	15%[c]
12.	10 mol% $NiCl_2$	$(CH_2Cl)_2$	80 ºC	15 h	00%	60%[c]
13.	10 mol% $SnCl_4$	$(CH_2Cl)_2$	80 ºC	1 h	98%	00%
14.	10 mol% $InCl_3$	$(CH_2Cl)_2$	25 ºC	1 h	99%	00%
15.	10 mol% $FeCl_3$	$(CH_2Cl)_2$	25 ºC	2.5 h	90%	06%
16.	10 mol% $FeCl_3$	CH_2Cl_2	25 ºC	5 min	99%	00%
17.	5 mol% $FeCl_3$	CH_2Cl_2	25 ºC	5 min	98%	00%
18.	2 mol% $FeCl_3$	CH_2Cl_2	25 ºC	5 min	99%	00%
19.	2 mol% $InCl_3$	CH_2Cl_2	25 ºC	20 min	98%	00%
20.	2 mol% $SnCl_4$	CH_2Cl_2	25 ºC	5 min	97%	00%
21.	1 mol% $FeCl_3$	CH_2Cl_2	25 ºC	5 min	94%	05%
22.	1 mol% $InCl_3$	CH_2Cl_2	25 ºC	20 min	89%	08%
23.	1 mol% $SnCl_4$	CH_2Cl_2	25 ºC	5 min	90%	07%

(a) unless noted otherwise, all the reactions were performed using 0.3 mmol of 2a in open reaction vessel. (b) isolated yields after column chromatography. (c) decomposition of the rest of the mass balances. (d) determined from 1H-NMR of unpurified reaction mixtures. Optimized conditions: 2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**).

On further optimization using different metal halides in dichloroethane (entries 9-14), we found that, 10 mol% $InCl_3$ and $SnCl_4$ under refluxing dichloromethane could also solely give rise to cyclization product in 98% and 99% yields, respectively (entries 13-14). Interestingly, 5 mol% $FeCl_3$ also affords (±)-**3a** in 98% isolated yield at ambient temperature in dichloromethane (entries 15 - 17). We found that 2 mol% $FeCl_3$ (condition **A**), 2 mol% $InCl_3$ (condition **B**), and 2 mol% $SnCl_4$ (condition **C**) afforded (±)-**3a** in almost quantitative yields in just 5 - 20 mins (entries (18-20). However, on further decreasing metal halides to 1 mol% of catalyst, we observed the formation of diene **4a** in 2-6% yields (entries 21-23).



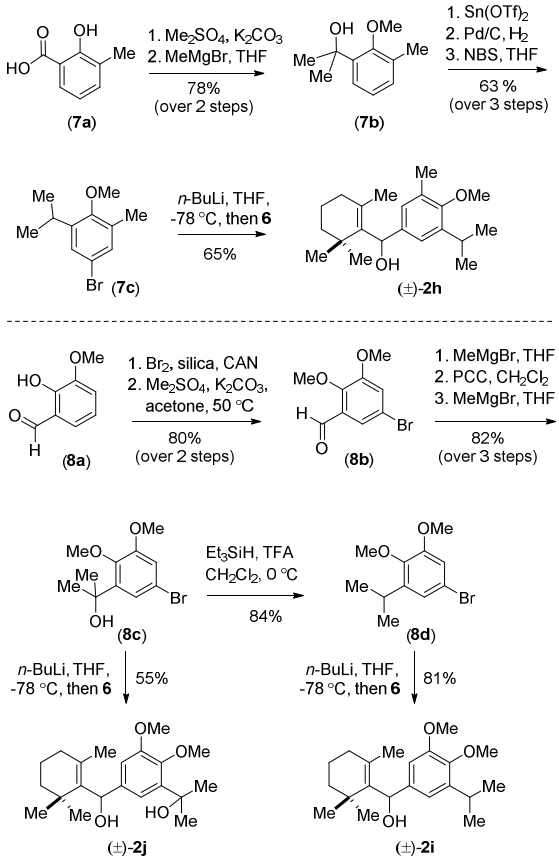
2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**)

Scheme 3: Substrates scope of metal halide catalyzed cyclization of arylvinylcarbinols.

We then extended our methodology to furnish carbotricyclic cores (±)-**3b-g** of taiwaniaquinoids and the results are shown in Scheme 3. The arylvinyl carbinols (±)-**2a-d** containing electron-donating group/s were excellent substrates that afforded products in good to excellent yields (up to 99% yield). Impressively, we also observed that arylvinyl carbinols (±)-**2e-f** with no substituent on aromatic ring, and having electron-withdrawing group afforded (±)-**3e-f** in 42-97% yields (Scheme 3).

Further regioselective issues were checked using arylvinyl carbinols (±)-**2h-j**, which were synthesized according to Scheme 4. In one case, 6-methylsalicylic acid (**7a**) was converted into benzylalcohol **7b** in 2 steps viz. bis-methylation using Me_2SO_4 followed by MeMgBr addition, from where bromoarene **7c** was synthesized in 3 steps viz. $Sn(OTf)_2$-catalyzed elimination, hydrogenation followed by reaction with *N*-bromosuccinimide (NBS). The later was then reacted with β-cyclocitral **6** at -78 ºC to furnish arylvinyl carbinols (±)-**2h**. Along same line, *ortho*-vanillin **8a** afforded

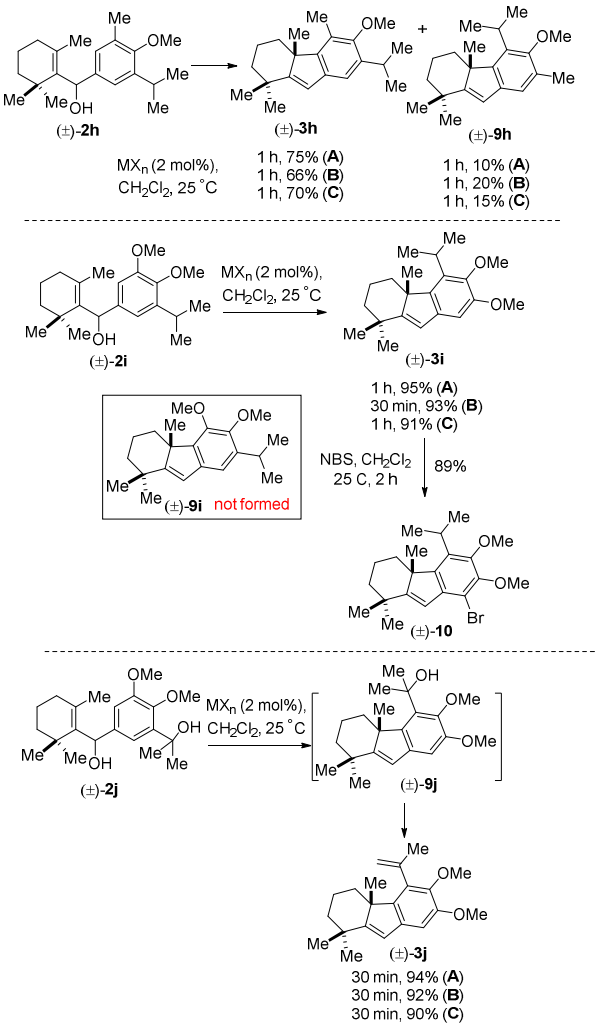
8b when reacted with bromine followed by O-methylation using dimethylsulfate. Next, reaction with MeMgBr, oxidation using pyridinium chlorochromate (PCC) followed by again MeMgBr addition afforded bromoarene **8c**. The later was then reacted with triethylsilane (Et_3SiH) in the presence of trifluoroacetic acid (TFA) to furnish bromoarene **8d**. Next, the arylvinyl carbinols (±)-**2i-j** were synthesized from β-cyclocitral **6** by reacting with bromoarenes **8c** and **8d** (Scheme 4).



Scheme 4: Synthesis of arylvinylcarbinols (±)-**2h-j** of β-cyclocitral.

3. Total Synthesis of (±)-Taiwaniaquinone H (1c) and (±)-Dichroanone (1d)

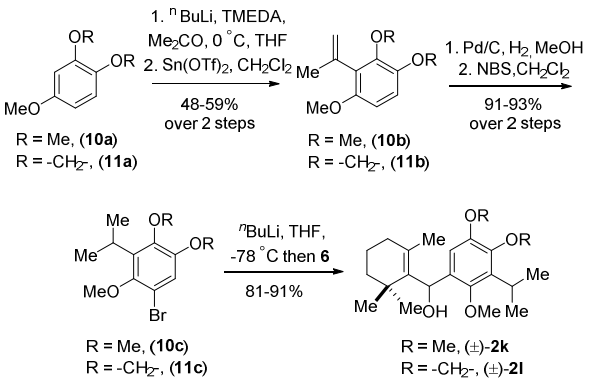
Under the optimized conditions **A**-**C**, arylvinylcarbinol (±)-**2h** afforded two regioisomers, where attack from the *p*-position of *i*-Pr group led to major regioisomer (±)-**3h** in 66-75% yields and *o*-position of *i*-Pr group led to the formation of minor regioisomer (±)-**9h** in 10-20% yields (Scheme 5). Interestingly, when **2i** was reacted under our optimized conditions, it afforded only (±)-**3i** in 91-95% and no traces of (±)-**91** was observed. A similar scenario was observed in case of arylvinylcarbinol (±)-**2j**, where a highly regioselective reaction led to the formation of (±)-**3j** in 90-94% yields. We assume that the reaction goes through an intermediate carbotricycle (±)-**9j**, which then furnished (±)-**3j** after a β-elimination process (Scheme 5).



2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**)

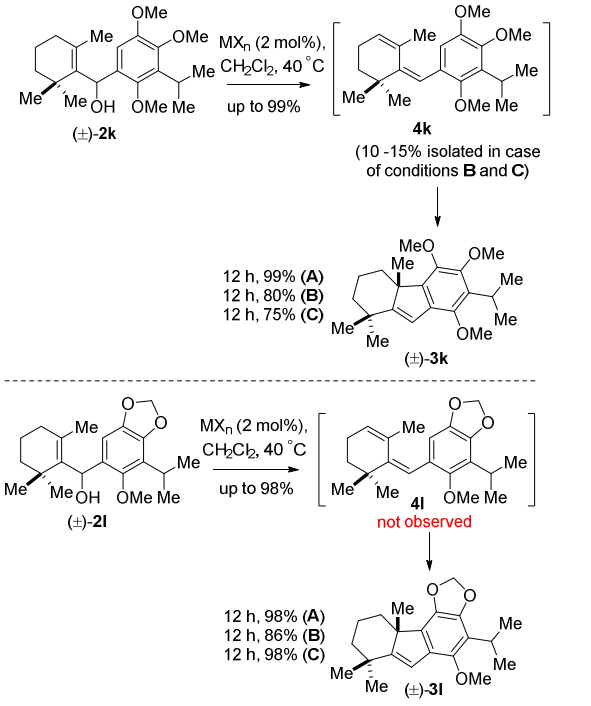
Scheme 5: Substrates scope using arylvinylcarbinols (±)-**2h-j**.

Further, we have shown the total syntheses of (±)-taiwaniaquinone H (**1c**), (±)-dichronanone (**1d**) and related taiwaniaquinoids utilizing our methodology. Towards this end, we synthesized arylvinyl carbinols **2k-l** following Scheme 6. Next, reactions of 1,2,4-Trimethoxybenzene and sesamol methylether (**10a** and **11a**) with *n*-BuLi in the presence of TMEDA at -78 ˚C afforded benzylalcohols followed by elimination in presence of $Sn(OTf)_2$ to furnish α-methylstyrenes **10b** and **11b** in 79-81% overall yields over 2 steps. Later, hydrogenation of **10b** and **11b** followed by reaction with *N*-bromosuccinimide (NBS) afforded bromoarenes **10c** and **11c** in 91-93% yields. From bromoarenes, arylvinyl carbinols (±)-**2j-k** were synthesized in 81-91% yields overall yields over 2 steps (Scheme 5).



Scheme 6: Synthesis of arylvinylcarbinol (±)-**2k-l**.

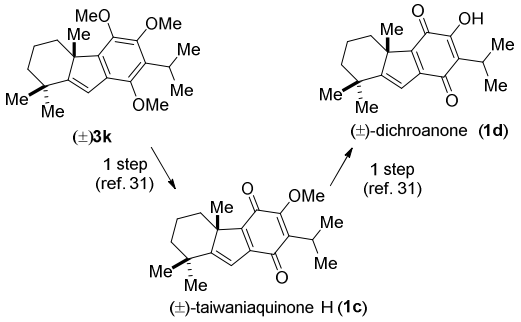
Arylvinyl carbinol **2k** afforded product (±)-**3k** in 75-99% along with 10-15% of **4k** under conditions **B** and **C** (Scheme 7). We also found that, diene intermediate **4k** can be converted into (±)-**3k** in 75-99%, when treated under optimized conditions. Thus, this indicating that diene of the type **4** is the intermediate for synthesis of carbotricyclic core. To our delight, arylvinylcarbinol (±)-**2l** afforded only tricarbocyclic core (±)-**3l** in 86-98% as sole products.



2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**)

Scheme 7: Substrate scope using arylvinylcarbinols (±)-**2k-l**.

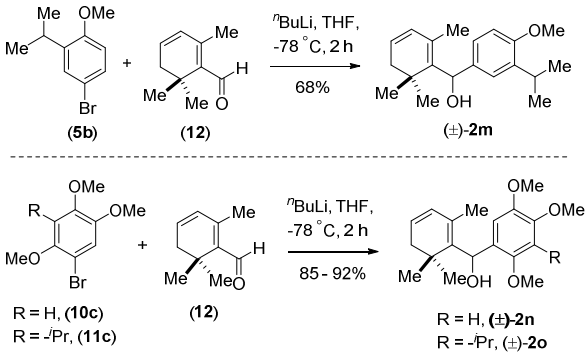
Gratifyingly, these two intermediates (±)-**3k-l** are crucial for the total synthesis a variety of taiwaniaquinoids after synthetic manipulations. For the application of our strategy, we have carried out oxidative transformation of carbotricycle (±)-**3k**, to complete the total synthesis of (±)-taiwaniaquinone H (**1c**) in 63% yield. Next, a reaction of **1c** with 2(*N*) KOH completed total synthesis of (±)-dichroanone (**1d**) (Scheme 8).



Scheme 8: Total syntheses of (±)-taiwaniaquinone H (**1c**) and (±)-dichroanone (**1d**).

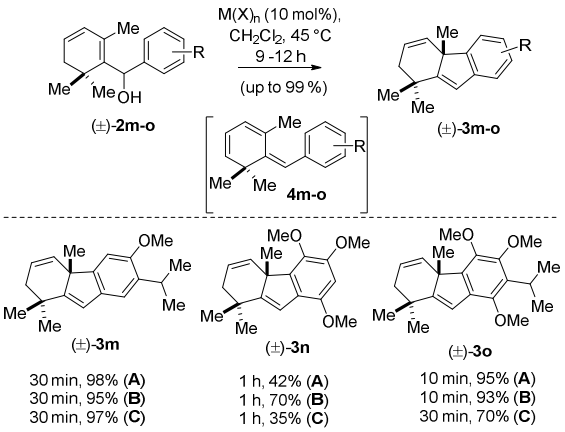
4. Total Synthesis of (±)-Taiwaniaquinol F

Further in search for few carbotricyclic core (±)-**3m-o** having additional olefin functionality, bromoarenes **5b**, **10c**, and **11c** were reacted independently with α,β,γ,δ-unsaturated aldehyde, safranal **12** to synthesize arylvinyl carbinols (±)-**2m-o** (Scheme 9). We hypothesized that (±)-**3o** could be advanced intermediate for the total syntheses of taiwaniaquinol F **1a** and related structures having a ketone functionality in A-ring (Figure 1).[45-46]



Scheme 9: Synthesis of arylvinylcarbinols (±)-**2m-o**.

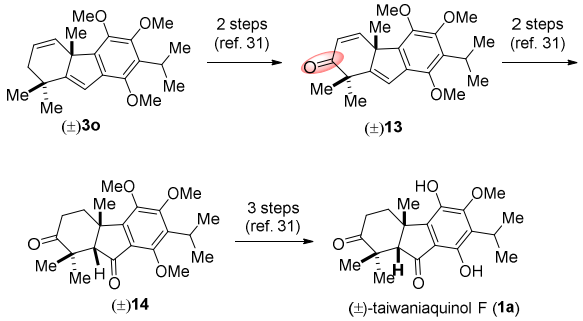
Gratifyingly, under our optimized conditions **A**-**C**, we found that (±)-**2m-o** were good substrates which afforded carbotricyclic core (±)-**3m-o** (up to 98% yield) sharing dienes in good to excellent yields. We have seen that, Nazarov type cyclization of (±)-**2m-o** were can be done at room temperature. The high reactivities of (±)-**2m-o** are probably due to the intermediate carbocation which is a 3º carbocation having bis-allylic structure.



2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**)

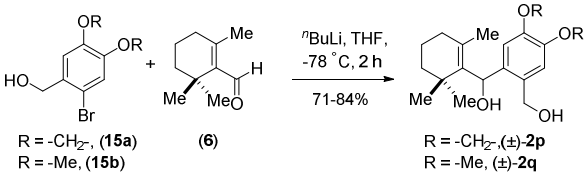
Scheme 10: Substrates scope of metal triflate catalyzed cyclization of arylvinylcarbinols.

Recently, we completed total synthesis of taiwaniaquinol F (±)-**1a** starting from (±)-**3o**.[47] We have synthesized carbotricycle (±)-**13** in 2 steps, which was then converted to diketone intermediate (±)-**14** in 2 steps. The later then afforded total synthesis of taiwaniaquinol F (±)-**1a** in 3 steps (Scheme 11).



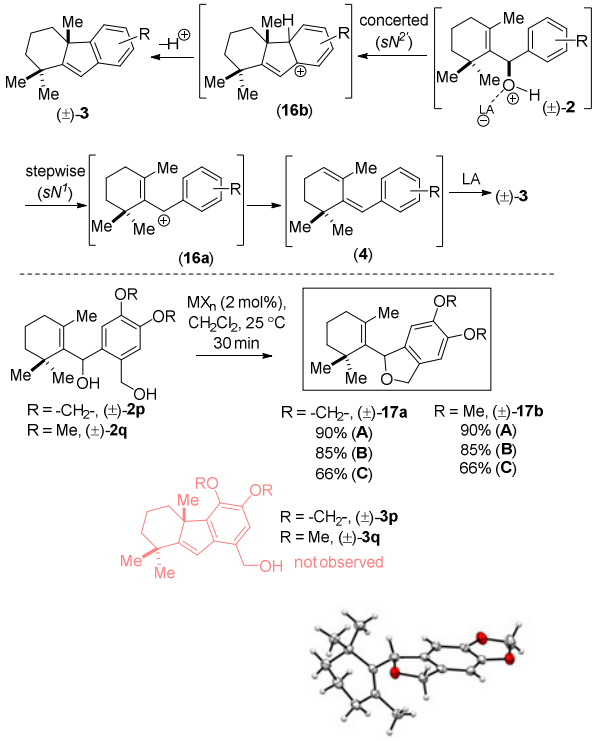
Scheme 11: Formal total synthesis of taiwaniaquinol F (±)-**1a**.

Further to illustrate the plausible mechanism of our approach we synthesized arylvinyl carbinols (±)-**2p-q** (Scheme 12) from a reaction of 2-bromo substituted benzyl alcohol with β-cyclocitral **6**.



Scheme 12: Synthesis of arylvinylcarbinol (±)-**2p-q**.

A plausible pathway for the formation of [6,5,6]-carbotricycle has been shown in scheme 13. We imagined that, there could be easy formation of aryl dienes **4** through the intermediacy of arylallyl cation **16a**, which in turn could undergo a Nazarov type process in presence of Metal halide. However, at the same time one can't rule out the possibility of cyclization through carbocationic intermediate **16b** following a concerted mechanism via 5-*endo* cyclization. Thus, we used arylvinylcarbinols (±)-**2p-q** (Scheme 12) under optimized conditions **A**-**C**. To our pleasure, (±)-**2p-q** afforded only furan derivative (±)-**17a-b**, under the influence of 2 mol% of $FeCl_3$ (**condition A**), $InCl_3$ (**condition B**), $SnCl_4$ (**condition C**), respectively, as sole products without the formation of trace amount of (±)-**3p-q**. This probably indicates a stepwise process might be operating through a stable arylallyl cation **16a** for the cyclization step (Scheme 13).



X-ray structure of ±(**17a**) [CCDC 926021]

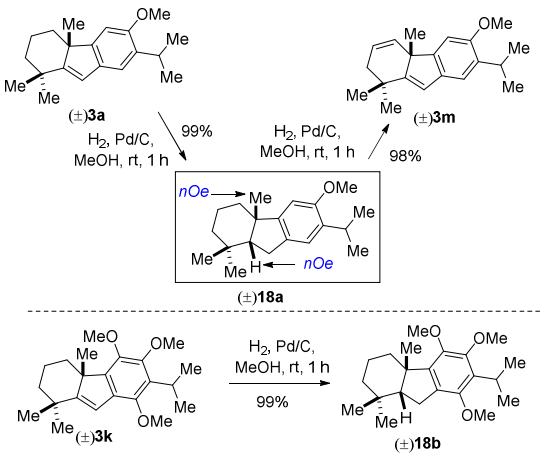
2 mol% of $FeCl_3$ (**condition A**); 2 mol% of $InCl_3$ (**condition B**); 2 mol% of $SnCl_4$ (**condition C**)

Scheme 13: Plausible mechanism of Nazarov type cyclization and substrate scope using (±)-**2p-q**.

5. Formal Total Synthesis of (±)-*epi*-Taiwaniaquinone G

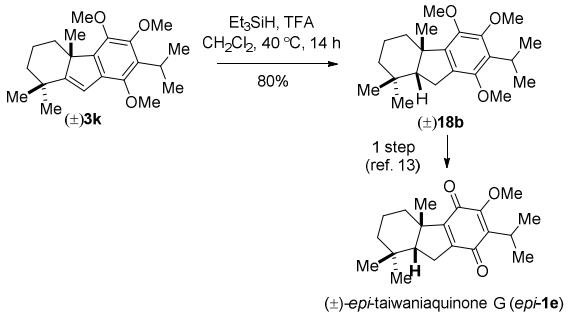
Next, the hydrogenation of **3a** in presence of H_2 (1 atm.) and Pd/C afforded *cis*-fused **18a** as sole product, which was confirmed by nOe experiment and by X-ray studies (Scheme 14). X-ray structure of **(**±)-**3a** (Table 1) clearly depicts a high degree of concavity in carbotricyclic core due to the *gem*-dimethyl groups and a double bond. Therefore, the hydrogenation process from the α-face of the carbotricycle

(±)-3a to afford *cis*-fused **18a**. Along similar line, tricyclic diene **3m** also afforded **(±)-15a** in 98% isolated yield. We next hydrogenated carbotricycle **(±)-3k** to afford *cis*-fused **18b** as sole product.



Scheme 14: Formal total synthesis of taiwaniaquinol B (±)-**1b**.

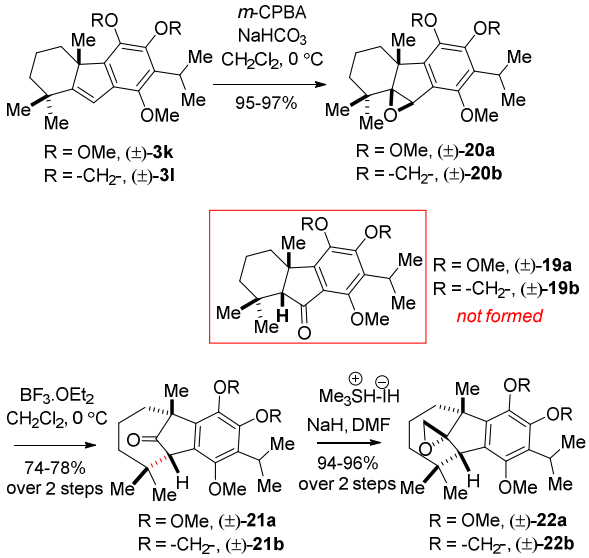
Later, we found that *cis*-fused carbotricycle **18b** can be obtained from (±)-**3k** when treated with triethylsilane in presence of trifluroacetic acid (Scheme 15). As we have shown total synthesis of *epi*-taiwaniaquinone G (±)-*epi*-**1e** from **18b** in 1 step, this approach culminated as a formal total synthesis of unnatural (±)-*epi*-**1e** (Scheme 15).



Scheme 15: Formal total synthesis of *epi*-taiwaniaquinone G (±)-*epi*-**1e**.

6. Unexpected Ring Expansion under the Standard Condition

Later, we were interested for total synthesis of (±)-taiwaniaquinol B (**1b**) from dimethylether of (±)-**19a-b**, which can be synthesized from epoxide (±)-**20a-b** (Scheme 16). Towards this, we treated (±)-**3k-l** with *m*-chloroperbenzoic acid (*m*-CPBA) to access (±)-**20a-b** in excellent yields (Scheme 16). However, to our disappointment, $BF_3.OEt_2$ treatment of (±)-**20a-b**, as per literature report by Alvarez-Manzaneda,[33, 48] afforded ring expansion ketone (±)-**21a-b** as sole product in 74-78% yields, without the formation of even trace amount of (±)-**19a-b**. The expoxidation of ketone (±)-**21a-b** using trimethylsulfonium iodide afforded product (±)-**22a-b**, which was unambiguously confirmed from X-ray structure (Scheme 16).



Scheme 16: Unexpected formation of (±)-**21**.

Mechanistically, (±)-**20a-b** form benzylic carbocations (±)-**24a-b** by the influence of $BF_3.OEt_2$, from where a 1,2-migration of 3º alkyl group afforded ketone (±)-**21a-b** via a carbocation intermediate (±)-**25a-b**. Thus, our assumption of getting *cis*-fused ketones (±)-**19a-b** from *trans*-fused ketones (±)-**28a-b** through the intermediacy of (±)-**27a-b** (arising from 3º catbocations (±)-**26a-b**) did not work the way we thought. The reactions go through intermediates (±)-**24a-b** rather than 3º catbocations (±)-**26a-b**. The stability of benzylic carbocations (±)-**24a-b** are attributed because of highly electron-rich aromatic ring (Scheme 17).

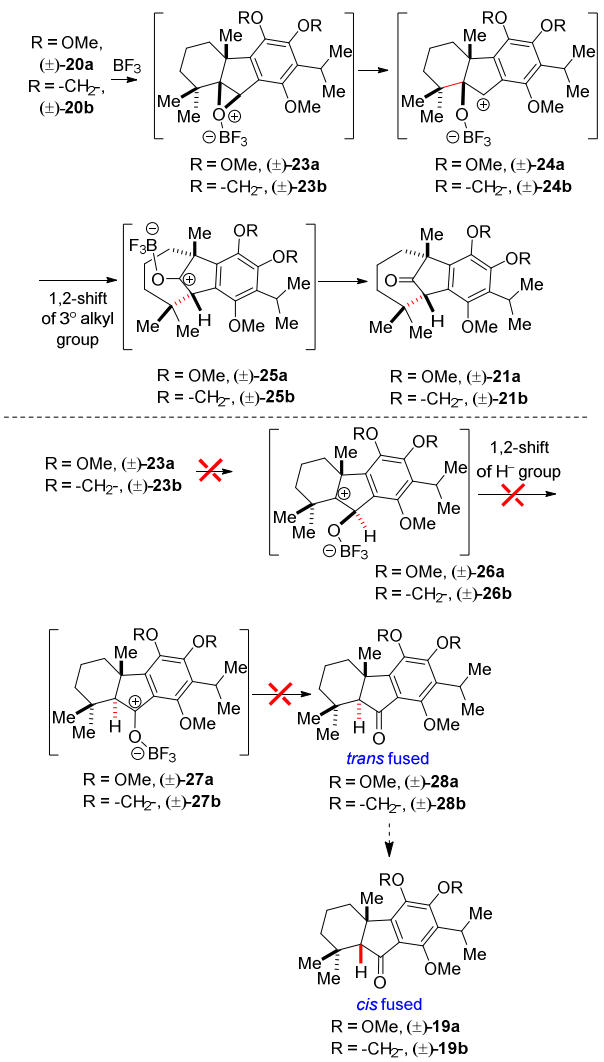
7. Total Synthesis of (±)-Taiwaniaquinol B

For the total synthesis of (±)-taiwaniaquinol B (**1b**), carbotricyclic core (±)-**18b** was reacted with CrO_3 in presence of 3,5-dimethylpyrazole to affect benzylic oxidation to furnish ketone (±)-**29** in 91% yield. As the total synthesis of taiwaniaquinol B **(±)-1b** is known from **(±)-29** in 3 steps, this approach is culminated as a formal total synthesis of **(±)-1b** (Scheme 18).

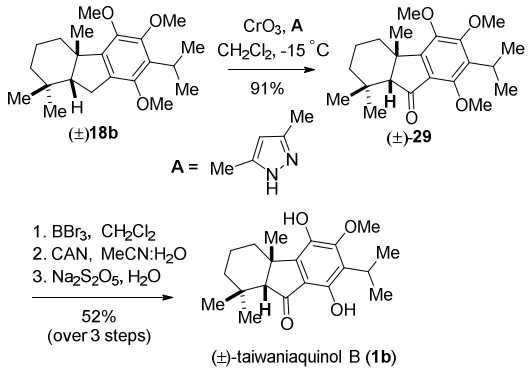
8. Conclusions

In conclusion, we have demonstrated metal halide catalyzed Nazarov type cyclization of suitably substituted arylvinyl carbinol. The methodology affords a variety of carbotricyclic structures in excellent yields under operationally simple condition. A tentative mechanism via a carbocationic intermediate has been proposed for Narazov type cyclization. Our methodology provides expeditious synthesis of naturally occurring taiwaniaquinoids, (±)-taiwaniaquinol F (**1a**), (±)-taiwaniaquinol B (**1b**), (±)-dichronanone (**1c**), (±)-taiwaniaquinone H (**1d**) and unnatural

(±)-5-*epi*-taiwaniaquinone G (*epi*-**1e**). Further explorations to access *trans*-fused taiwaniaquinoids is under active investigations in our laboratory.



Scheme 17: Plausible mechanism of formation of unexpected 7-membered (±)-**17a-b**.



Scheme 18: Total synthesis of (±)-taiwaniaquinol B (**1b**).

9. Experimental Section

Material. Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et_2O) was distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. All other solvents such as DMF, mesitylene, 1,2-dimethoxyethane, acetonitrile, chloroform, methanol, ethanol, and reagents were used as received. Thin layer chromatography was performed using silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain and other stains. Silicagel of particle size 100-200 mesh was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded 400, 500 MHz spectrometers with ^{13}C operating frequencies of 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$) signal (δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants and number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a FT-IR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-Resolution Mass Spectrometry (HRMS) and Low-Resolution Mass Spectrometry (LRMS) data were recorded on MicrOTOF-Q-II mass spectrometer using methanol as solvent.

Representative experimental procedure for metal-chloride catalyzed cyclization of aryl-vinyl carbinols: In an oven-dried round-bottom flask, arylvinylcarbinols of β-cyclocitral (0.25 mmol; 1.0 equiv.) and $FeCl_3$ (2 mol%) [**Condition A**] or $InCl_3$ (2 mol%) [**Condition B**] or $SnCl_4$ (2 mol%) [**Condition C**] were taken in dichloromethane (3 mL). The round-bottom flask was stirred at 40 ºC for indicated time (9-12 h). Upon completion, as judged by running TLC, the reaction mixture was quenched with $NaHCO_3$ solution and extracted with dichloromethane. The crude products were purified by flash chromatography (10:1 hexanes/EtOAc) to afford Friedel-crafts alkylation products.

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Notes
The authors declare no competing financial interest.

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REFERENCES AND NOTES

1. For review on taiwaniaquinoids, see; Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284.
2. Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1995**, *40*, 871.
3. Lin, W. H.; Fang, J. M.; Cheng, Y. S. *Phytochemistry* **1996**, *42*, 1657.
4. Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493.
5. Chang, C. I.; Chien, S. C.; Lee, S. M.; Kuo, Y. H. *Chem. Pharm. Bull.* **2003**, *51*, 1420.
6. Chang, C. I.; Chang, J. Y.; Kuo, C. C.; Pan, W. Y.; Kuo, Y. H. *Planta Med.* **2005**, *71*, 72.
7. Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sesik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493–497.
8. Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419.
9. 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.
10. Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742.
11. Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911.
12. Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Org. Lett.* **2003**, *5*, 3931.
13. Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *J. Org. Chem.* **2006**, *71*, 2787.
14. Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144.
15. Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896.
16. 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.
17. Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022.
18. Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741.
19. Tang, S.; Xu, Y.; He, J.; He, Y.; Zheng, J.; Pan, X.; She, X. *Org. Lett.* **2008**, *10*, 1855.
20. Wang, J.; Wang, J.; Li, C.; Meng, Y.; Wu, J.; Song, C.; Chang, J. *J. Org. Chem.* **2014**, *79*, 6354.
21. Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055.
22. 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.
23. Majetich, G.; Shimkus, J. H. *Tetrahedron Lett.* **2009**, *50*, 3311.
24. Deng, J.; Li, R.; Luo, Y.; Li, J.; Zhou, S.; Li, Y.; Hu, J.; Li, A. *Org. Lett.* **2013**, *15*, 2022.
25. Yan, X.; Hu, X. *J. Org. Chem.* **2014**, *79*, 5282.
26. Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899.
27. Kakde, B. N.; Bhunia, S.; Bisai, A. *Tetrahedron Lett.* **2013**, *54*, 1436.
28. Wu, X.; Li, M.-L.; Chen, D.-F.; Chen, S.-S. *J. Org. Chem.* **2014**, *79*, 4743.
29. McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738.
30. 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.
31. 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.
32. Node, M.; Ozeki, M.; Planas, L.; Nakano, M.; Takita, H.; Mori, D.; Tamatani, S.; Kajimoto, T. *J. Org. Chem.* **2010**, *75*, 190.
33. 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.
34. Jana, C. K.; Scopelliti, R.; Gademann, K. *Chem. Eur. J.* **2010**, *16*, 7692.
35. Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390.
36. Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Tapia, R.; Alvarez-Manzaneda, R. *Chem. Commun.* **2010**, *46*, 9244.
37. 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.
38. Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088.
39. Shockley, S. E.; Holder, J. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 6362.

40. Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902.

41. For a similar approach, see: Li, L.-Q.; Li, M.-M.; Chen, D.; Liu, H.-M.; Geng, H.; Lin, J.; Qin, H.-B. *Tetrahedron Lett.* **2014**, *55*, 5960.

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

43. Kakde, B. N.; Bhunia, S.; Bisai, A. *Tetrahedron Lett.* **2013**, *54*, 1436.

44. Kakde, B. N.; Parida, A.; Kumar, N.; Bisai, A. *ChemistrySelect* **2016**, *1*, 3357.

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

46. Hayashi, K.; Tanimoto, H.; Zhang, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K.*Org. Lett.* **2012**, *14*, 5728.

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

48. Alvarez-Manzaneda reported synthesis of **31** from **30** (see: ref. 22b). However, a similar strategy using (±)-**3k-l** afforded (±)-**21a-b**, respectively, as sole products.

10. About the author(s)

After receiving B.Sc. degree from Midnapore College, Vidyasagar University and a M.Sc. degree in Organic Chemistry from BHU, Varanasi, Alakesh obtained his Ph.D. under the supervision of Professor Vinod K. Singh from IIT Kanpur in Sept. 2006. Immediately afterward, he moved to University of California at Berkeley, CA, USA, where he held postdoctoral position with 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. In Dec. 2009, he left Berkeley and joined IISER Bhopal as an Assistant Professor, where he served as a Professor of Chemistry till May, 2020. During his stay at IISER Bhopal he served as Dean of the Faculty Affairs (DoFA) and Chief Vigilance Officer (CVO). In May, 2019, he moved to the Department of Chemical Sciences, IISER Kolkata and set a research lab. on Natural Product synthesis and Drug Discovery.

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 interesting biological relevant secondary metabolites sharing all-carbon quaternary stereocenters have been synthesized by his research group. Recently, his total synthesis of pyrroloindoline alkaloids had been highlighted in '*Organic Chemistry Portal*' as '*The Bisai Synthesis of (-)-Physovenine*'.