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Total synthesis of natural products facilitated by prins reaction: a review

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Natural products have been identified as bioactive compounds, featuring anticancer, antibacterial, antiviral and anti-inflammatory properties. Synthesis of natural products is the field of high interest with an ongoing need for efficient synthetic methodologies leading to these intricate compounds. Prins reaction is one of the valuable strategies for the construction of sophisticated natural products and their derivatives. In this account, we have reviewed recent research accomplishments in synthesizing several natural products such as alkaloids, terpenoids, polyketides, steroids, spiroketals and polyphenolic compounds utilizing Prins protocol.

1. Introduction

Establishing unprecedented synthetic pathways is always a lasting motivation for the preparation of bioactive pharmaceuticals and intricate natural products.[1] In organic synthesis, C–C bond construction reactions stand as cornerstone synthetic transformations. For instance, the Friedel–Crafts reaction is an effective bond-forming process, which originally leverages stoichiometric Lewis acids, has evolved to encompass greener and milder conditions.[2] In addition, aldol reaction requires stoichiometric enolate preparation, affecting its efficiency.[3] However, the Prins reaction offers more ecofriendly alternatives by using catalytic asymmetric approach.[4] Moreover, Prins reaction is acknowledged as a leading approach towards tetrahydropyran (THP) construction owing to its robust stereoselective synthesis aspects, rendering it crucial for natural product preparation.[5] The promising bioactivities of THP motifs have stimulated significant interest in their asymmetric synthesis, notably *via* Prins cyclization.[6] Furthermore, segment-coupling Prins cyclization circumvents key obstacles of prior methods.[7] In addition, Prins reaction paves the way for building complex carbohydrate ring structures.[8] The value of Prins reaction in synthetic chemistry has been amplified by recent catalytic methods, component diversification, enantioselective versions and cascade processes.[9] Further, Prins-Pinacol sequence involves migration reaction for quenching cation, rendering it highly atom economical.[10] Initially, Kriewitz performed the condensation reaction between olefins and aldehydes; in 1899, he observed the formation of unsaturated alcohols by heating dipentene or pinene with paraformaldehyde.[11] Hendrik Jacobus Prins, the inventor of Prins reaction, in 1917, pioneered the first study of chemical reaction between formaldehyde and ethylenic hydrocarbons. Additionally, Prins explored the reaction pathways of styrene, camphene, anethole and pinene with formaldehyde facilitated by sulfuric acid catalyst, leveraging glacial acetic acid or water as solvent. In aqueous solution, formals of unsaturated alcohols or of 1,3-butanediols were achieved, whereas acetic acid typically gave its esters.[12] Owing to this seminal work, the Prins reaction is the widely recognized term for these transformations. Moreover, in 1919, the Prins reaction was first appeared in English language.[12] In 1955, Hanschke achieved the key milestone in this reaction by constructing THP ring selectively through the acid-mediated reaction of 3-butene-1-ol with diverse ketones or aldehydes.[13]

The original Prins reaction documented in 1919 was the acid-facilitated addition reaction between an aldehyde **1a** and an alkene **1b** (Scheme 1).[10] The obtained carbocation **1c** may give a substitution product with a nucleophile or undergo deprotonation to produce homoallylic alcohol **1d**.

Further, oxocarbenium ions are regarded as electrophiles and π-nucleophiles as nucleophilic reactants, broadening the synthetic utility of Prins reaction. The similar additions to thiocarbenium and iminium ions have been termed as thia-Prins and aza-Prins reactions, respectively. The array of products resulting from Prins reaction included unsaturated alcohols, 1,3-diols or 1,3-dioxanes, depending on substrate and the reaction conditions.[14] Additionally, the Prins-type cyclization, involving

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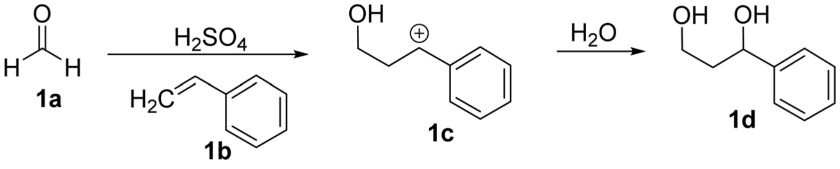


Scheme 1 Acid catalyzed Prins reaction.

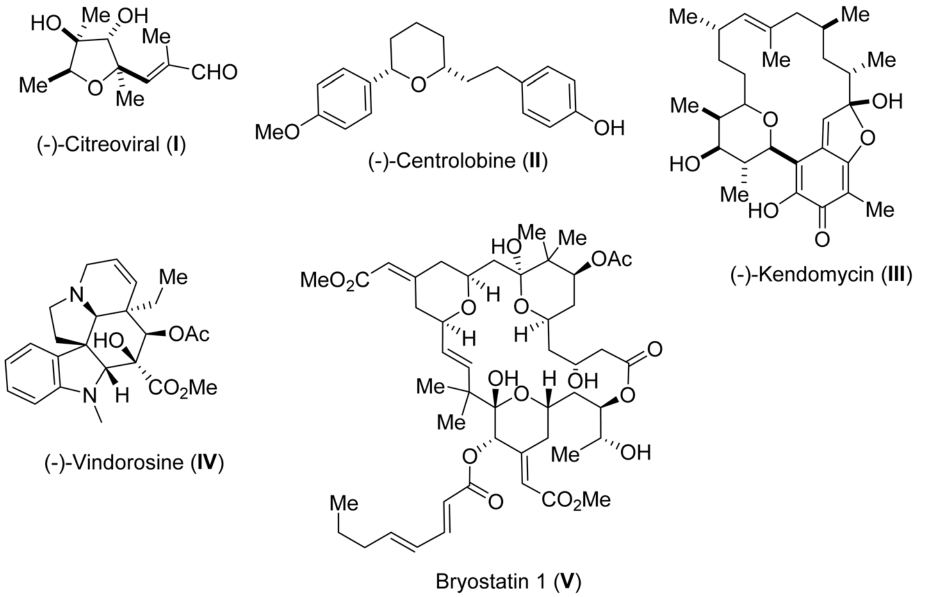


Fig. 1 Structures of some natural products synthesized *via* Prins reaction.

the reaction of unsaturated alcohol with aldehyde to render heterocyclic compound, is a groundbreaking synthetic strategy widely employed in the preparation of important targets. Significantly, Prins reaction is a valuable and crucial tool in synthesis, enabling direct formation of products with molecular frameworks, commonly present in bioactive compounds and fragrances.[4] The key breakthrough is attained by cascade/tandem reactions owing to their expedient access, high atom economy and remarkable bond-forming features.[15] Among these, new approaches such as, Prins/Friedel–Crafts reaction,[16] Prins/Peterson reaction,[15] and Prins/Conia-ene cascade cyclization[17] have been developed from Prins cyclization. For example, naturally occurring phomactin A was synthesized employing Prins/Conia-ene cascade reaction.[18] Thus, Prins reaction and its ensuing tandem reaction have been emerged as pivotal processes in the preparation of carbocyclic and heterocyclic natural products.[14] Various catalysts such as Lewis acids, Brønsted acids, heterogeneous catalysts (solid-anchored acids or zeolites), ionic liquids, iodine and heteropolyacids have been leveraged in prior methodologies regarding catalytic Prins reaction.[4]

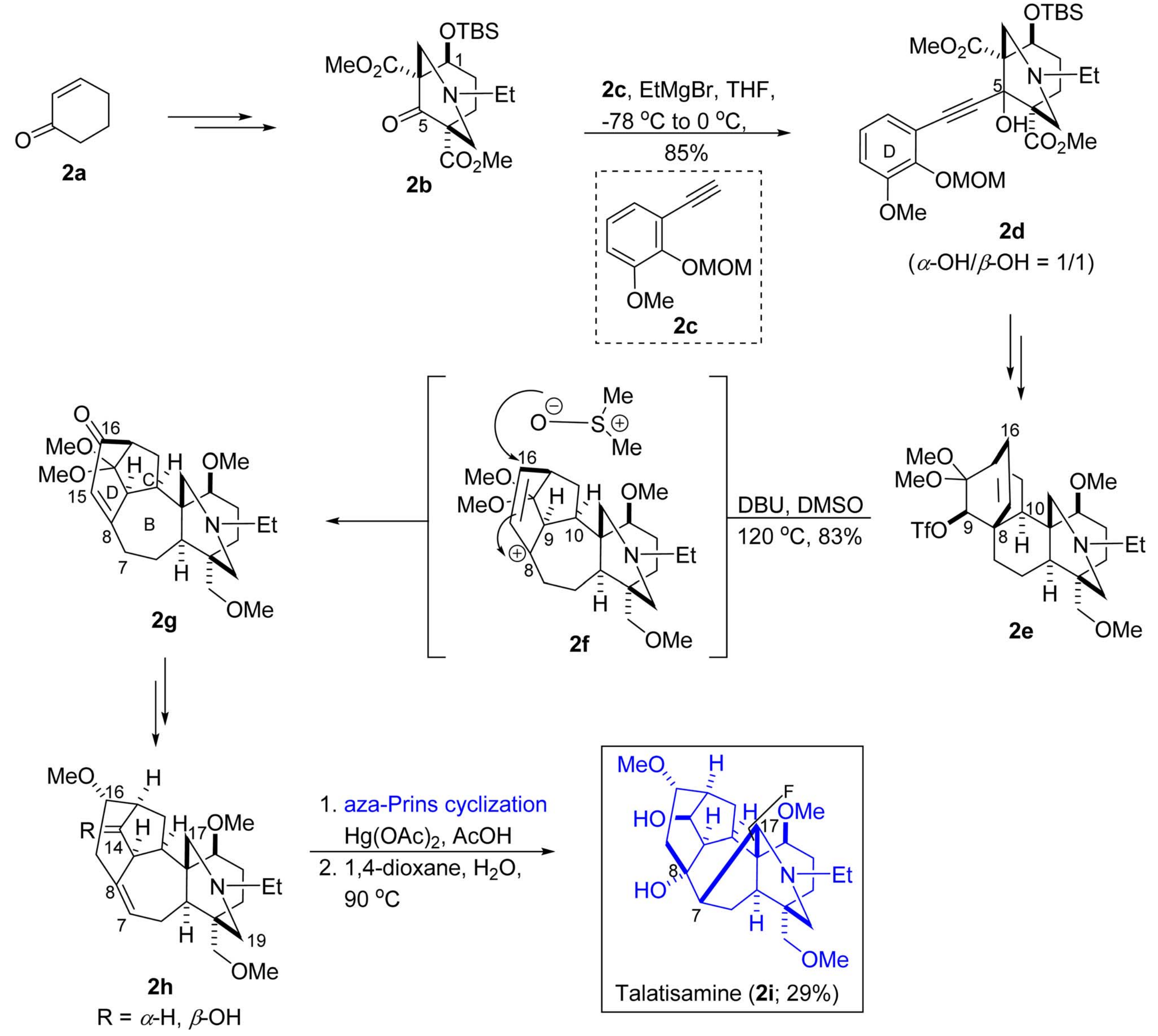
Natural products research has provided numerous bioactive compounds and potent leads, accelerating remarkable advancements in their total synthesis in recent times. Excess literature exists on the preparation of intricate natural products and structurally sophisticated organic compounds featuring the Prins reaction.[8,9] Various natural products, including alkaloids,[19] terpenoids,[20] lactones,[21] macrolides,[22] steroids,[23] spiroketals,[24] and polyketides,[25] have been constructed employing the Prins reaction. In this context, Marumoto and coworkers in 2002, attempted the total synthesis of (−)-centrolobine (**II**) utilizing Prins cyclization.[26] Further, Bahnck and Rychnovsky (2008) accomplished the synthesis of a macrocycle (−)-kendomycin (**III**) (osteoprotective agent) employing this protocol.[25] Similarly, other bioactive compounds such as, (−)-citreoviral (**I**),[27] vindorosine (**IV**)[28] and bryostatin 1 (**V**)[29] were also synthesized utilizing Prins reaction (Fig. 1).

The Prins reaction has shown exponential growth in recent times and its importance necessitates a thorough assessment. In 2022, Tadiparthi *et al.* reported a review which delves into Prins cyclization, showcasing the significance of various aspects of the Prins reaction in the total synthesis of natural products.[1] Since then, there has been significant advancement towards the applications of Prins reaction. Thus, this review article aims to discuss the recent progress (reported within 2020–2025), describing the recent applications of broadened Prins reaction towards the synthesis of natural products belonging to different classes.

2. Review of literature

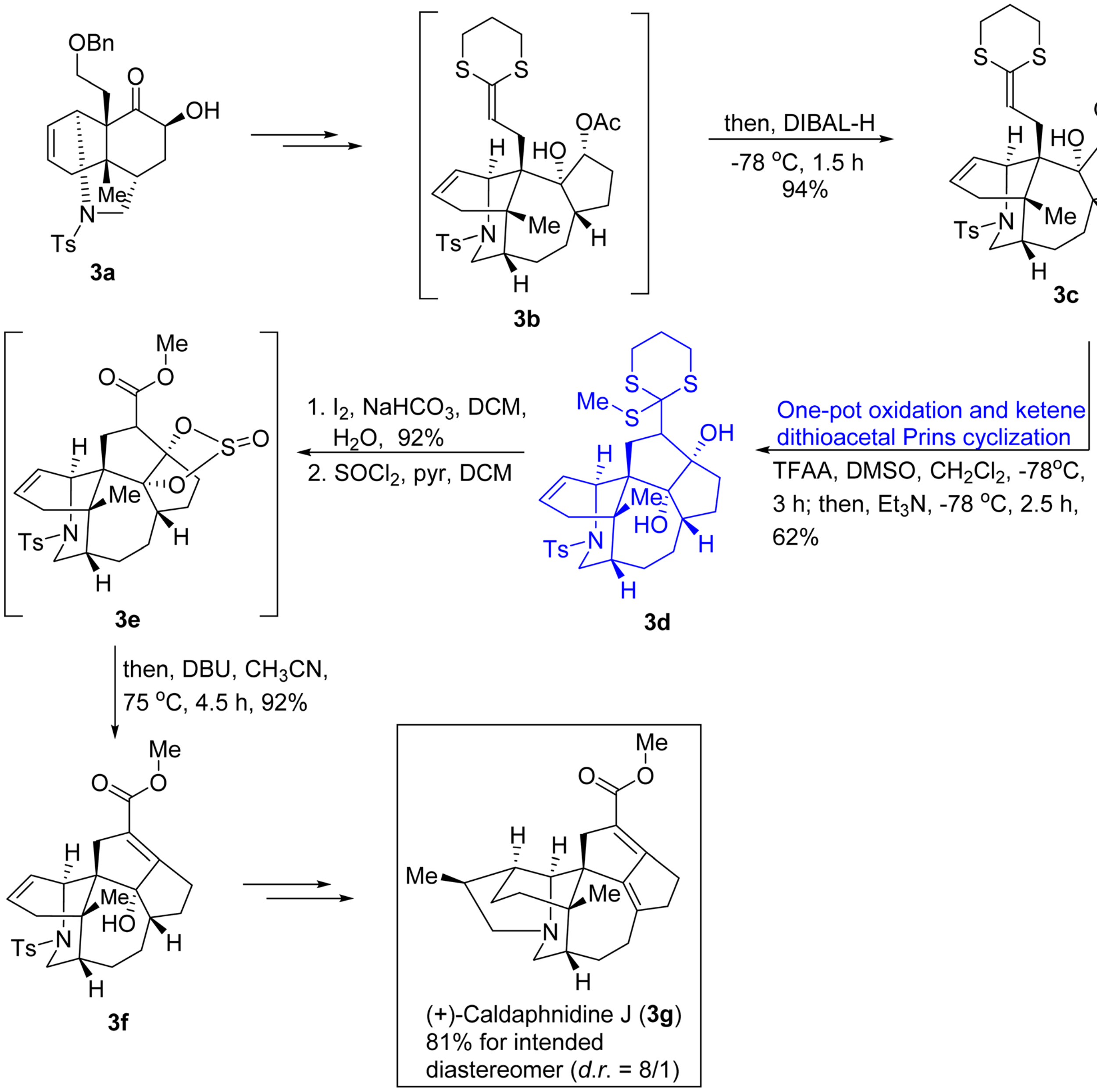
2.1. Synthesis of alkaloid-derived natural products

2.1.1. Talatisamine synthesis. The densely oxygenated C_{19}-diterpenoid alkaloid, talatisamine (**2i**) isolated from *Aconitum*



Scheme 2 Total synthesis of talatisamine (2i) according to Kamakura and co-workers.[31]

species, exhibited antiarrhythmic and potassium ion channel inhibitory activities.[27] This natural product is characterized by complex 6/7/5/6/6/5-membered rings (ABCDEF) having 12 contiguous stereogenic centers. In 1970s, Wiesner group[30] attempted the first total synthesis of talatisamine with 5 oxygen substituents in a 43-step sequence. Later, in 2020, Kamakura and co-workers[31] accomplished its second synthesis in a 33-step sequence from 2-cyclohexenone. The total synthesis of **2i** commenced with the construction of AE-ring system **2b** from 2-cyclohexenone **2a** with appropriate stereochemical configuration at C1, C4 and C11 after several transformations. The obtained fragment **2b** was coupled to D-ring fragment **2c** introducing the C5 stereochemistry at neopentyl position and leaving the methoxy carbonyl moieties intact. As such, the compound **2c** was derivatized to Grignard compound, followed by chemoselective addition at C5-carbonyl moiety, providing compound **2d** (85% yield) (*a*-OH/*b*-OH = 1/1). Next, compound **2d** gave β-oriented triflate **2e** over a few steps, completing the carboskeleton of (**2i**) with 19 carbon atoms. The compound **2e** then underwent heating in DMSO (dimethyl sulfoxide) with DBU (1,8-diazabicycloundec-7-ene); the antiperiplanar conformation of bonds C8–C10 and C9–O caused the incorporation of C9-stereocenter through 1,2-shift. The resulting allylic cation **2f** was trapped by DMSO at sterically favored C-16 position, affording ABCDE-pentacycle **2g**. Next, the building block *i.e.*, ABCDE-ring **2h** was assembled from **2g** over a few steps. Lastly, the optimized conditions for achieving aza-Prins cyclization to forge the remaining F-ring in compound **2h** included $Hg(OAc)_2$ and acetic acid which was then followed by deacetylation in 1,4-dioxane to afford the desired compound **2i** (29% yield). The synthetic strategy reported herein should offer valuable insights for the construction of other bioactive C_{18}- and C_{19}-diterpenoid alkaloids (Scheme 2).

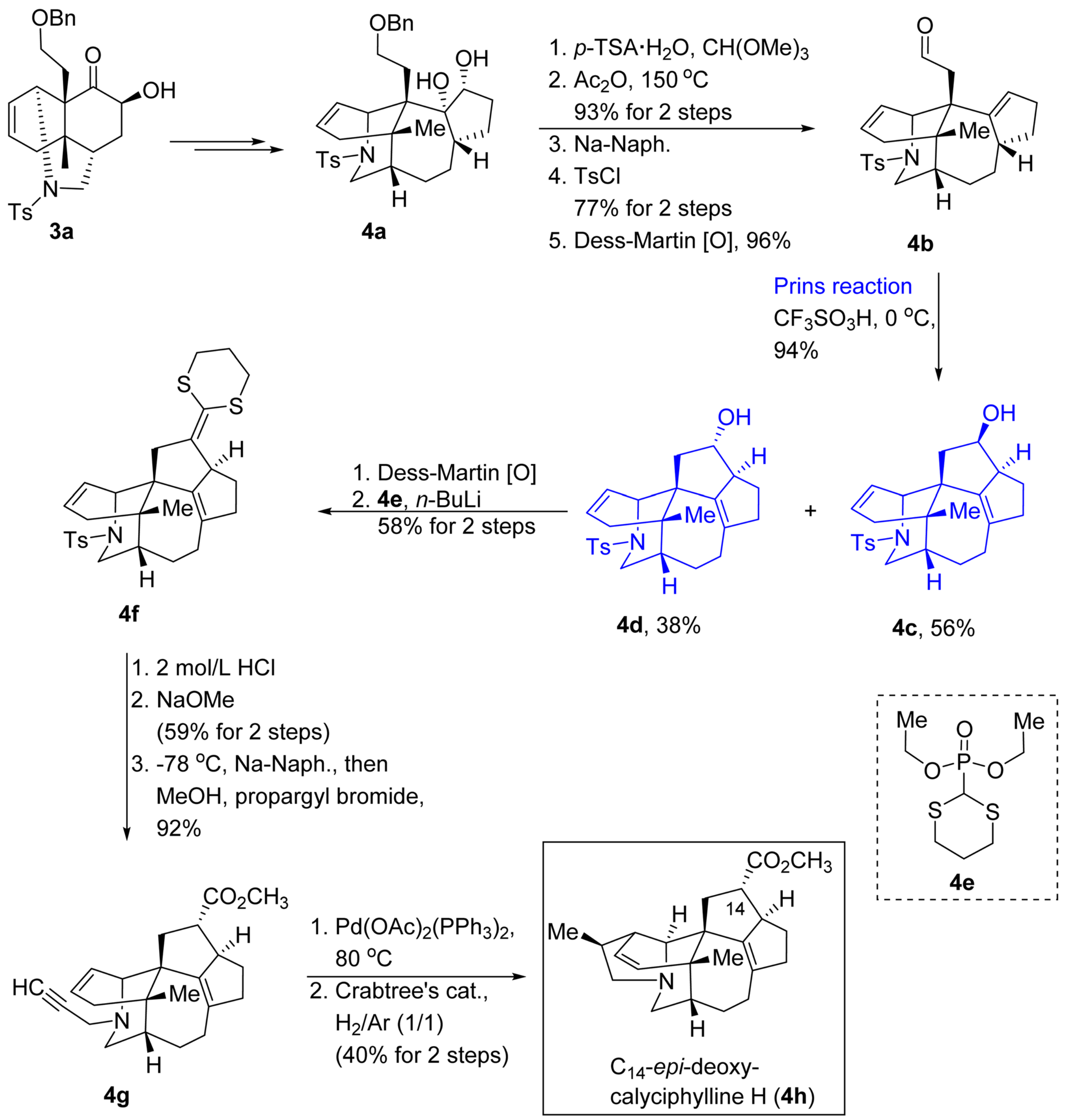


Scheme 3 Total synthesis of (+)-caldaphnidine J (**3g**) according to Guo and co-workers.[33]

2.1.2. Yuzurimine-based *daphniphyllum* alkaloids synthesis

2.1.2.1. (+)-Caldaphnidine J synthesis. The yuzurimine-related *daphniphyllum* alkaloid (+)-caldaphnidine J (**3g**) was isolated in 2008 by Yue group,[32] characterized by hexacyclic framework possessing six consecutive stereocenters, two quaternary carbon centers, and an α, β, γ, δ-unsaturated ester moiety. Owing to promising bioactivities, including neurotrophic, *anti*-HIV and anticarcinogenic properties, *daphniphyllum* alkaloids have attracted interest from research community. Regarding this, Guo and co-workers[33] in 2020, accomplished the enantioselective synthesis of (+)-caldaphnidine J **3g**. The synthetic route for (+)-caldaphnidine J began with ketone **3a** which gave intermediate acetate **3b** over a few-step sequence followed by DIBAL-H mediated reduction to furnish ketene dithioacetal **3c** (94%). Intriguingly, one-pot Swern oxidation and ketene dithioacetal-based Prins reaction (to forge C_{14}–C_{15} bond) occurred with trifluoroacetic anhydride (TFAA) and DMSO to transform compound **3c** into product **3d** (62% yield). While the reported methods required strong Lewis acids ($TiCl_4$, $BF_3 \cdot Et_2O$ and trimethylsilyl trifluoromethanesulfonate (TMSOTf)) for intermolecular ketene dithioacetal Prins-type reaction, the ketone intermediate obtained from **3c** reacted effectively without using strong Lewis acid. The resulted compound **3d** was exposed to methanolic iodine, followed by the treatment with $SOCl_2$ in the presence of base and then subjected to E2cB elimination to afford allylic alcohol **3f** in 92% yield *via* an intermediate **3e**. Next, compound **3f** afforded intended diastereomer of **3g** (81% yield, *d. r.* = 8/1) over a few steps (Scheme 3).

2.1.2.2. C$_{14}$–epi-deoxycalyciphylline H synthesis. C$_{14}$–*epi*-Deoxycalyciphylline H (**4h**), another reported yuzurimine-type alkaloid compound belonging to *Daphniphyllum*[34] family, possesses caged aza-polycyclic skeleton, stereogenic centers and quaternary all-carbon centers in vicinal relationship. Xu's group[35] attempted the total synthesis of natural product **4h**, closely related to calyciphylline H in 2024. Their synthetic strategy commenced with the preparation of vicinal diol **4a** from tricyclic compound **3a** through a number of steps. Sequentially, compound **4a** underwent Ando's olefination (*p*-toluenesulfonic acid, CH(OMe)$_3$, Ac$_2$O), benzyl group elimination, *N*-detosylation (sodium naphthalene), re-tosylation (tosyl chloride) and oxidation to afford aldehyde **4b** in 96% yield. Next, compound **4b** was subjected to key Prins reaction in the presence of TfOH at 0 °C, resulting in alcohols **4c** (56% yield, unambiguously assigned) and **4d** (38% yield). The obtained mixture of alcohols was then oxidized utilizing Dess–Martin reagent, followed by the deployment of Horner–Wadsworth–Emmons reaction



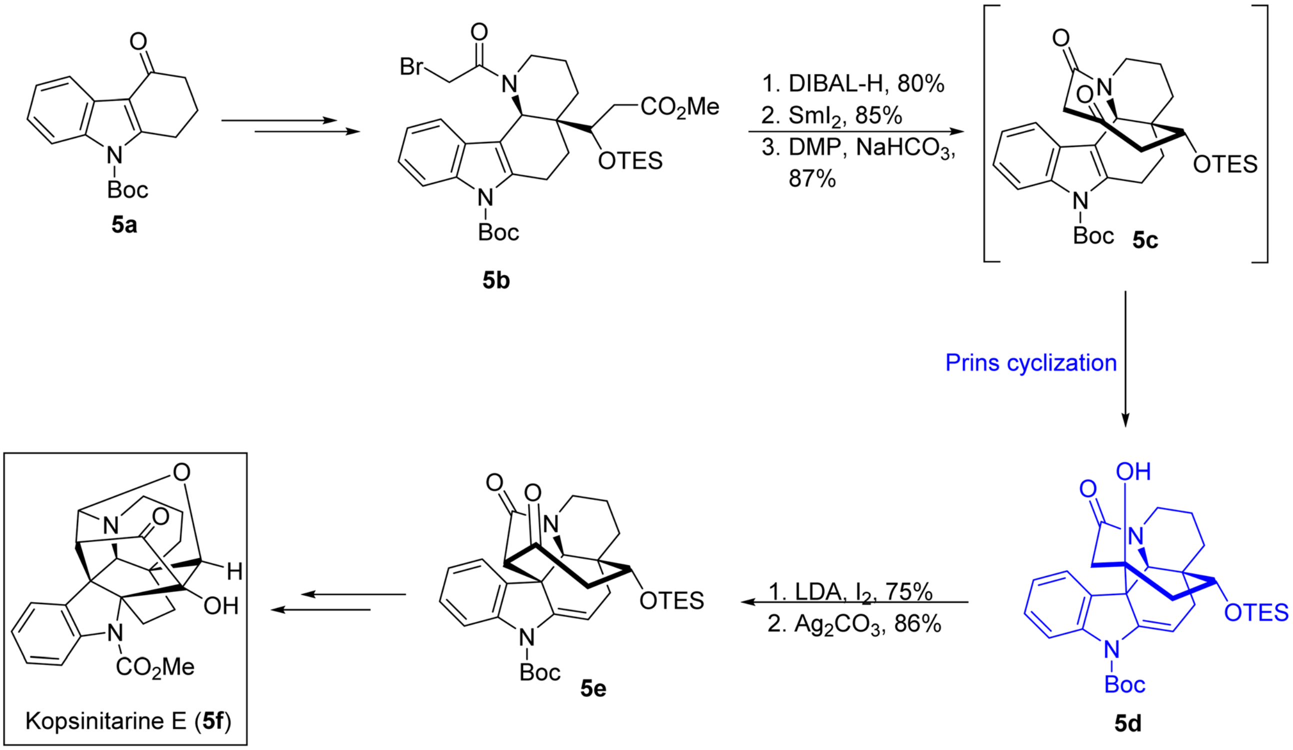
Scheme 4 Total synthesis of C$_{14}$–*epi*-deoxycalyciphylline H (**4h**) according to Hu & Xu.[35]

conditions (**4e**, *n*-BuLi), leading to the synthesis of homologated product **4f**. Further, compound **4f** was subjected to hydrolysis to install α-face selective carboxylic acid ester group at C-14, followed by *N*-tosyl group replacement with propargyl moiety, affording enyne **4g** (92% yield). Furthermore, compound **4g** underwent enyne cycloisomerization ($Pd(OAc)_2(PPh_3)_2$) to generate key tetrahydropyrrole and C3–C4 alkene motifs and subsequent selective hydrogenation (H_2, Crabtree's catalyst) afforded **4h** (Scheme 4).

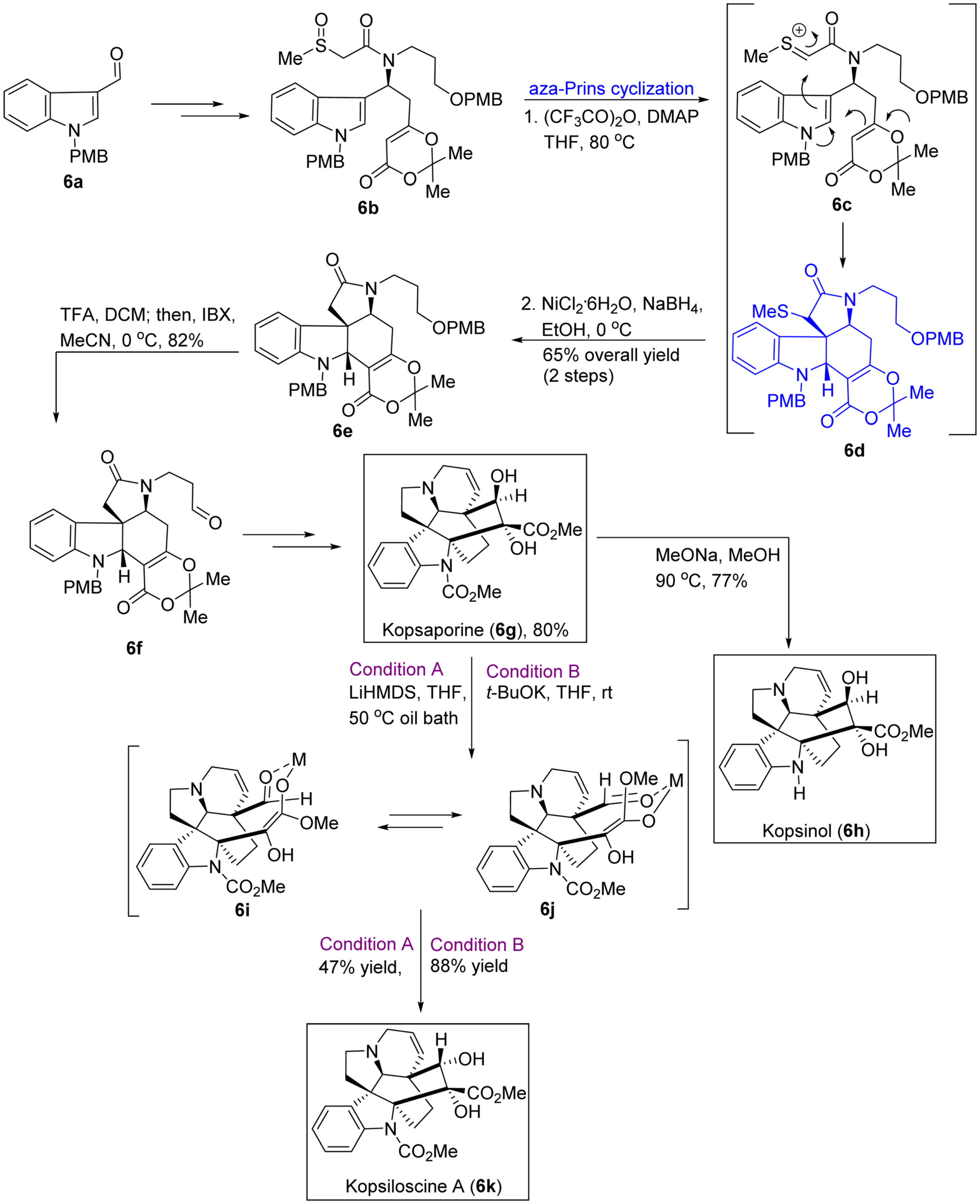
2.1.3. *Kopsia* alkaloids synthesis

2.1.3.1. Kopsinitarine E synthesis. Kopsinitarine E (**5f**), a structurally complex octacyclic *Kopsia* alkaloid, isolated by Lim and colleagues,[36] possesses a strained cage-like architecture with distinct cyclic features. The structural nuances of kopsinitarine E render its total synthesis formidable. In 2020, Nagaraju and co-workers[37] disclosed the first-time total synthesis of kopsinitarine E. Their synthetic sequence for kopsinitarine E commenced with reported Boc-masked carbazolone **5a**. First, compound **5a** provided bromide **5b** over a few steps. Next, tetracyclic intermediate **5b** gave β-keto lactam **5c** (87%) *via* subsequent reduction, SmI_2 treatment, and oxidation. The oxidation product **5c** was then subjected to cyclization through Prins reaction as the position of ketone and indole was suitable to promote such cyclization to afford alcohol **5d**. Importantly, Prins cyclization strategy facilitated the construction of characteristic 5,7-fused ring structure in the natural product (**5f**). Next, compound **5d** was sequentially made to react with LDA, iodine (for anion trapping) and silver carbonate under refluxing toluene conditions through semi-pinacol rearrangement approach to produce rearranged product **5e** (86% yield). Further, compound **5e** was transformed into desired **5f** (64% yield) over a few steps. The total synthesis of kopsinitarine E was reported to be attempted in total of 20 steps, starting from readily accessible carbazolone. This developed strategy is expected to be highly versatile for the construction of other related *Kopsia* alkaloids featuring the fundamental architecture and the synthetic success fully showcases the power of the demonstrated strategy (Scheme 5).

2.1.3.2. Synthesis of kopsaporine, kopsinol and kopsiloscine A. The monoterpene-based indole alkaloids contained six rings with a pair of them constructing a bicyclo [2.2.2] octane ring structure, included kopsaporine, kopsinol, kopsiloscines A and H which were biosynthetically related. These alkaloids exhibited robust bioactivities such as antihypertensive activity and overcoming drug resistance in KB cells.[38] These alkaloids were mainly obtained from *Kopsia* genera (family Apocynaceae).[39] Since 15 aspidofractine-related alkaloids have been synthesized yet the total syntheses of biologically active kopsaporine (**6g**), kopsinol (**6h**) and kopsiloscine A (**6k**) remain challenging. In 2023, Tian and co-workers[40] described the preliminary chiral synthesis of kopsaporine alkaloids which involved aza-Prins cyclization as one of the key strategies. The synthesis began with aldehyde **6a** which gave amide **6b** over a series of steps. Next, TFAA and DMAP combination in THF gave cyclization product **6d** (81% yield) through intermediate **6c**. Noteworthily, the hexahydro-1*H*-pyrrolo[2,3-d]carbazol-2(3*H*)-one framework was constructed through pioneering cascade Pummerer rearrangement-initiated nucleophilic addition and aza-Prins



Scheme 5 Total synthesis of kopsinitarine E (5f) according to Nagaraju and co-workers.[37]

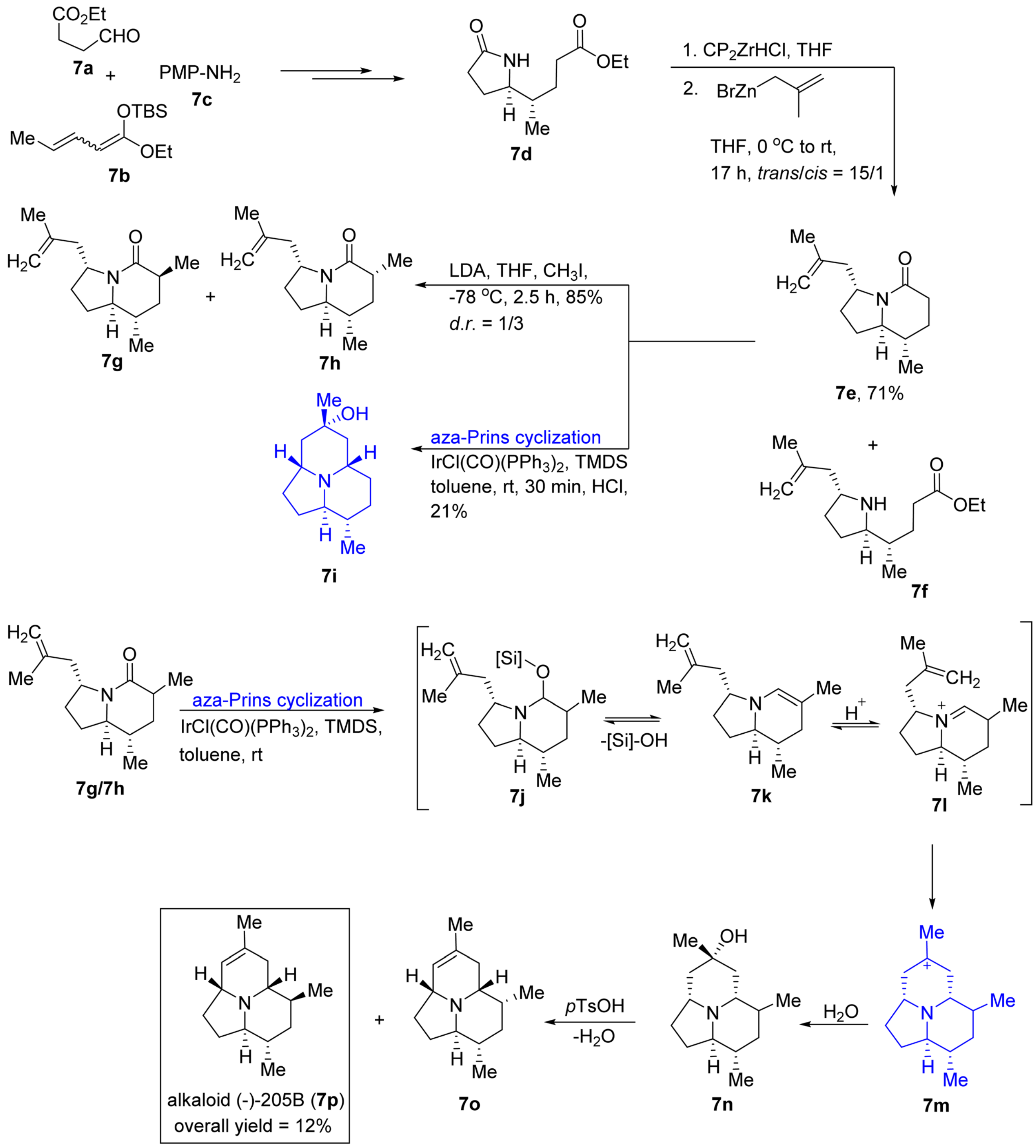


Scheme 6 Total synthesis of kopsaporine (**6g**), kopsinol (**6h**) and kopsiloscine A (**6k**) according to Tian and co-workers.[40]

cyclization. Next, compound **6e** was formed through reductive desulfurization, in an overall yield of 65% (2 steps). Further, compound **6e** was subjected to sequential PMB group cleavage and oxidation to generate intermediate **6f** (82% yield) which finally gave **6g** over a few steps. The natural product **6g** was then treated with methanolic sodium methoxide to deliver kopsinol

6h (77% yield). The product **6g** was also treated with LiHMDS in the presence of THF to afford kopsiloscine A **6k** (47% yield) (Condition A) through the conformers **6i** and **6j**. Alternatively, *t*-BuOK was used in THF to give **6k** in an isolated yield of 88% (Condition B) (Scheme 6).

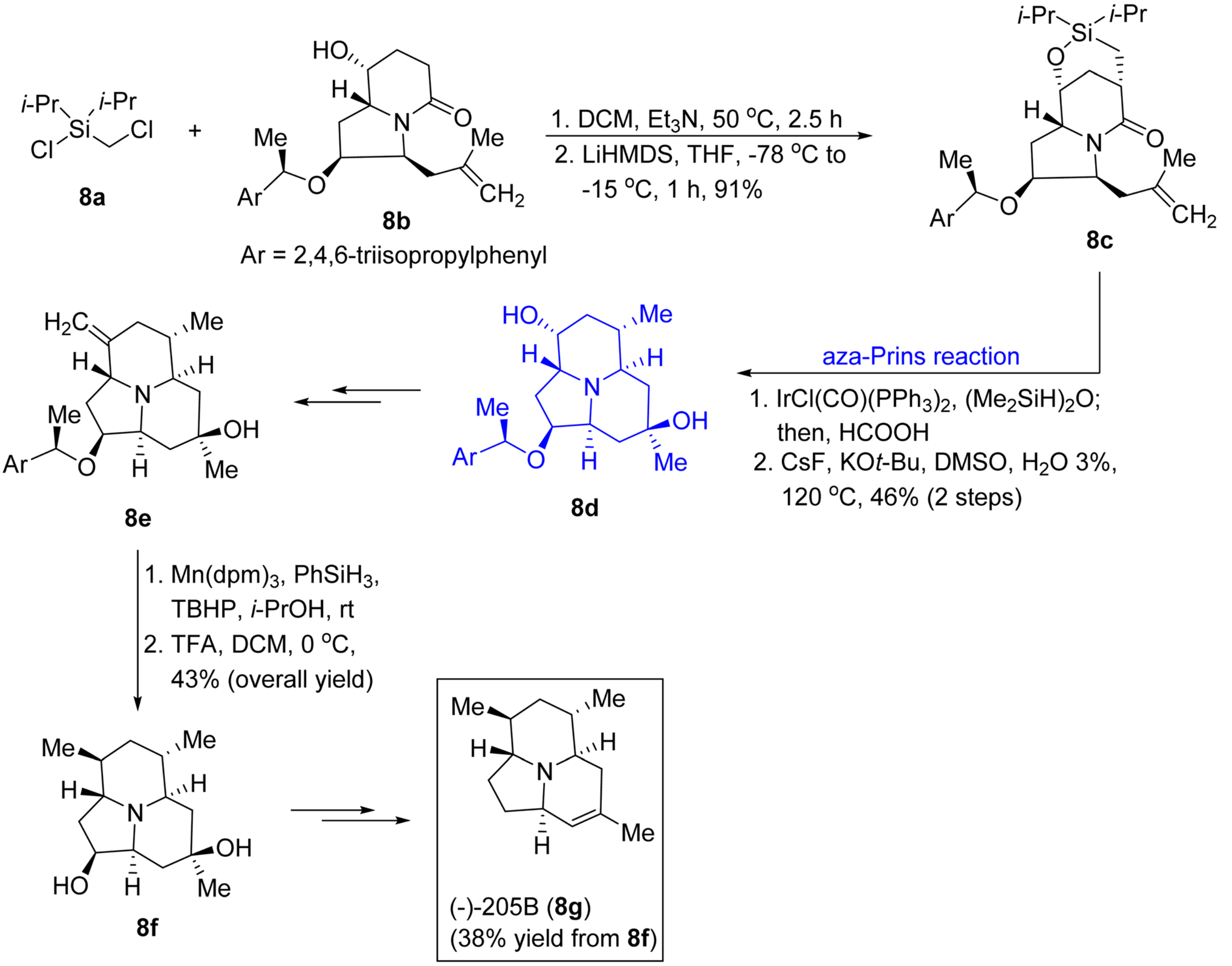
2.1.4. Alkaloid (−)-205B synthesis. The lipid-soluble bioactive (−)-205B alkaloid (**7p**) was first introduced by Daly and colleagues.[41] The (−)-205B (**7p**) alkaloid is featured by 8b-azaacenonaphthylene architecture having five stereocenters. In 2003, Toyooka and colleagues[42] attempted the first 29-step synthesis of enantiomer of this natural product and hence determined its absolute stereochemistry. Tripathy and Schneider[43] in 2020, proposed the shortest straightforward 6-step synthetic sequence to achieve the natural product in 12% overall yield. Their synthetic sequence began with the construction of lactam **7d** using aldehyde **7a** with compound **7b**



Scheme 7 Total synthesis of alkaloid (−)-205B (**7p**) according to Tripathy and Schneider.[43]

and **7c** in a few steps. The synthesized lactam **7d** was then treated with Cp_2ZrHCl to circumvent side reactions, followed by the treatment with zinc and methallylbromide under Barbier conditions (zinc, 2-methallyl bromide), affording compound **7e** in 71% yield with the maintenance of stereoselectivity (*trans*/*cis* = 15/1). No isolation and purification of the uncyclized pyrrolidine **7f** was observed and the intended *trans*-diastereomer **7e** was produced as the major product. Next, in compound **7e**, the methyl group was introduced at 6-position in the presence of base LDA/THF and then treated with methyl iodide which provided good yield but generated the unintended stereoisomer predominantly (**7g**/**7h** = 1/3). Next, the formation of third ring between lactam and methallyl group was formed *via* employing Vaska's complex ($IrCl(CO)(PPh_3)_2$) with 1,1,3,3-tetramethyldisiloxane (TMDS) to convert amides into enamines. By employing established conditions, the model substrate **7e** was elaborated into amino alcohol **7i** (21% yield, as major product) through aza-Prins cyclization. The polar nature of amino alcohol likely resulted in reduced yield owing to the significant loss during chromatography and workup. In order to get good yield and to avoid workup problems, the lactam **7g**/**7h** underwent one-pot aza-Prins cyclization and dehydration in the presence of Vaska's complex and TMDS to furnish compound **7j** which further gave rise to enamine **7k** and iminium ion **7l** in the form of equilibrating mixture. Compound **7l** was then subjected to aza-Prins reaction with methallyl moiety to form tertiary carbocation **7m** which upon exposure to water afforded alcohol **7n**. The final step consisted of acid-assisted dehydration, delivering natural product **7p** and its C6-epimer **7o** (in 70% combined yield) (Scheme 7).

The rare tricyclic lipophilic (−)-205B alkaloid (**8g**) was obtained from *Dendrobate pumilio* (an amphibian) skin.[44] Selectively, unnatural enantiomer was reported to suppress α7 nicotinic receptors. However (−)-205B (**8g**) alkaloid in its natural form demonstrated the modest allosteric behavior against α7 nAChRs at low concentrations of 1 μM, with antagonist effects at higher concentrations of 100 μM. While Tripathy & Schneider (2020, aforementioned strategy) prepared this natural product's stereoisomer *via* a short-step sequence, Mazeh and co-workers[45] in 2023, achieved the total synthesis of (−)-205B alkaloid (**8g**), starting from chiral hydroxyindolizidinone **8b** (obtained from (*R*)-Stericol®). First, the

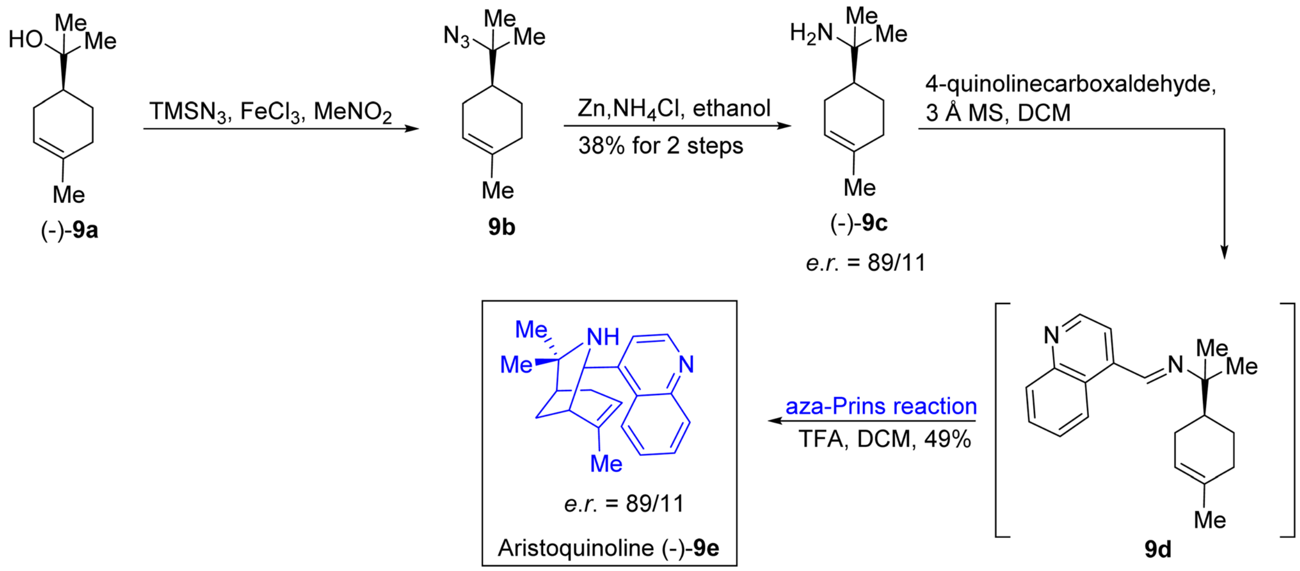


Scheme 8 Total synthesis of (−)-205B alkaloid (**8g**) according to Mazeh and co-workers.[45]

hydroxy group in intermediate **8b** was silylated by readily available dimethylbromosilane **8a** and then treated with a strong base *i.e.*, LiHMDS, resulting in the formation of alkylation product **8c** (91% yield). Next, lactam **8c** was subjected to aza-Prins cyclization with lactam partial reduction under iridium catalysis ($IrCl(CO)(PPh_3)_2$) followed by the utilization of CsF (fluoride source) and dry dimethyl sulfoxide for the unmasking of C6 methyl group to give tricyclic structure **8d** (46% two-step yield). Further, compound **8d** was converted to **8e** (exocyclic) over a few steps. Next, the compound **8e** was transformed into amino alcohol **8f** (43% overall yield) *via* chiral auxiliary cleavage, methylenation, and HAT reaction. The obtained compound **8f** then gave the desired natural alkaloid **8g** (38% yield from **8f**) over a few steps (Scheme 8).

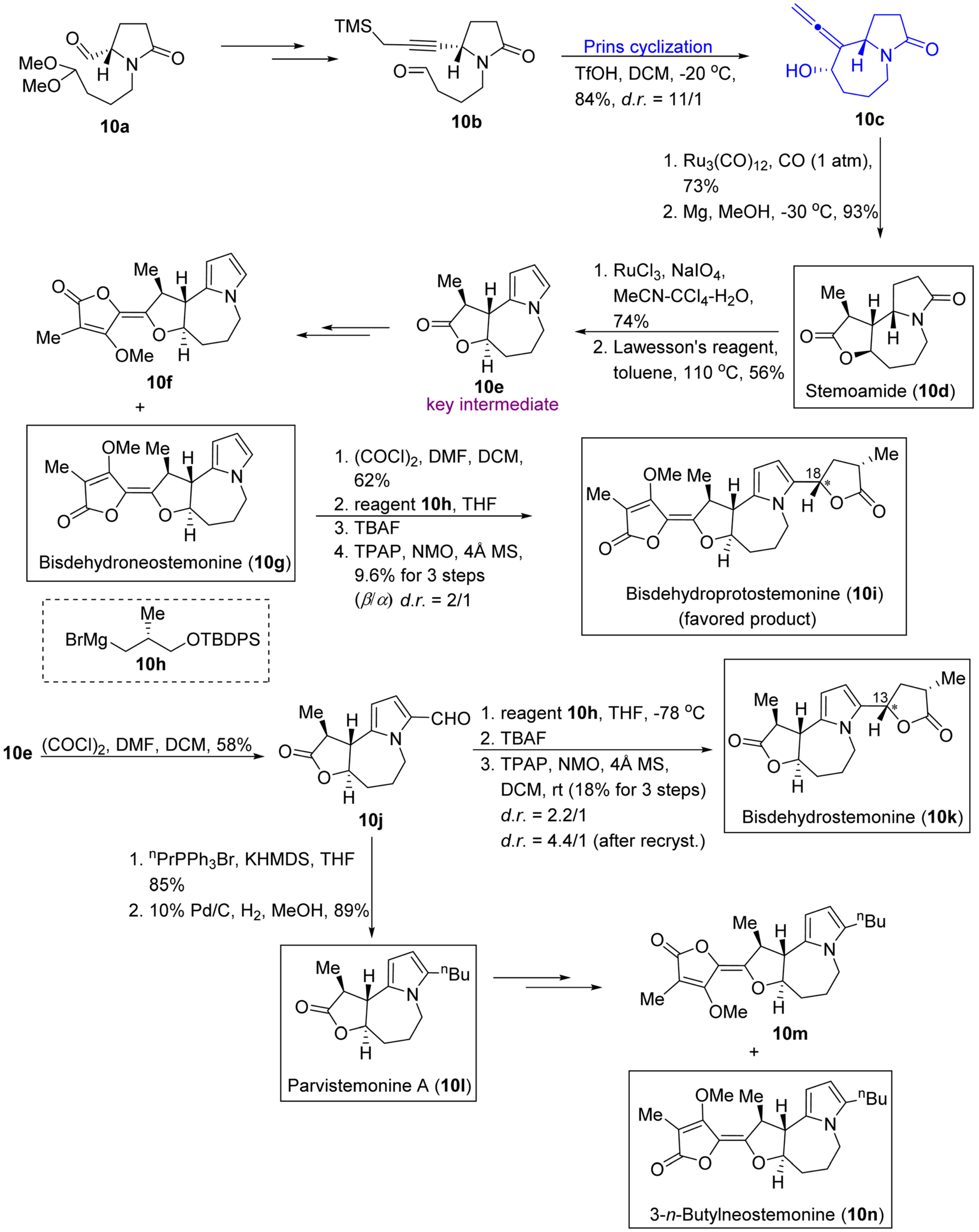
2.1.5. Aristoquinoline synthesis. The natural nicotinic receptor antagonist aristoquinoline (**9e**) was obtained from *Aristotelia chilensis* leaves in 1993.[46] The *Aristotelia* alkaloids are mainly characterized by 3-azabicyclo[3.3.1]nonane structure. Preferably, **9e** exhibited rare α3, β4 subtype (nAChRs) selectivity, addressing polysubstance usage issues.[47] In 2021, this motivated Argade and co-workers[48] to accomplish the first-time synthesis of **9e**. The total synthesis involved key aza-Prins reaction for improving the enantiopurity of the product. Towards this, tertiary alcoholic functionality in (−)-α-terpineol (−)-**9a** was first transformed into azide **9b**, which was then subjected to reduction with zinc to give rise to primary amine (−)-**9c**. The obtained compound (−)-**9c** was condensed with 4-quinolinecarboxaldehyde by means of molecular sieves (3 Å) to form imine **9d**. Next, the solution of compound **9d** was added to TFA to provide the desired aristoquinoline (−)-**9e**, with improved enantiopurity (*e.r.* = 89(−)/11(+)). Further, detailed analysis of (−)-**9c** through (*R*)-Mosher amide production and (−)-**9a** through optical rotation revealed comparable enantiopurity. Thus, aza-Prins reaction was proceeded with perfect stereospecificity. Additionally, the aforementioned technique was also applicable for the synthesis of aristoquinoline (+)-**9e** (*e.r.* ≤ 1(−)/99(+), overall yield = 13%) (Scheme 9).

2.1.6. *Stemona* alkaloids synthesis. Up to now, over 250 distinct *Stemona* alkaloids have been identified with various bioactivities, possessing diverse structures owing to various oxidation states in nitrogen-containing five-membered ring.[49] Thus, *Stemona* alkaloids can be categorized as pyrrolidone type, pyrrole type and pyrrolidine type compounds. In 2022, Wang and co-workers[50] attempted the divergent syntheses of five pyrrole-based *Stemona* alkaloids namely, bisdehydroneostemonine (**10g**), bisdehydroprotostemonine (**10i**), parvistemonine A (**10l**), 3-*n*-butylneostemonine (**10n**) and bisdehydrostemonine (**10k**), which were extracted from *Stemona japonica* or *Stemona parviflora*[47] with a common pyrrole-based 5/7/5 tricyclic system. Moreover, **10l** and **10n** possess *n*-butyl group substituted on pyrrole ring while **10i** and **10k** contain lactone functionality on pyrrole ring. The natural products **10g**, **10i** and **10n** contain γ-butyrolactone moiety substituted on lactone ring of 5/7/5 structure *via* C=C bond. The synthesis started with the preparation of stemoamide (**10d**) from known compound **10a** which first gave alkyne **10b** over a few-step sequence. The obtained compound **10b** was then subjected to Prins cyclization in the presence of both Brønsted acid and Lewis acid to form 7-membered ring. In this regard, the optimum reaction conditions involved trifluoromethanesulfonic acid (TfOH) and dichloromethane (DCM), producing cyclized allenol **10c** (84% yield, *d. r.* = 11/1). Next, the compound **10c** underwent reaction with $Ru_3(CO)_{12}$, followed by reduction (Mg/methanol), providing the intended **10d** in 93% yield. The synthesized **10d** underwent reaction with $RuCl_3$ and $NaIO_4$, followed by the treatment with Lawesson's reagent, affording key intermediate **10e** in 56% yield. The compound **10e** then provided **10g** along with its *E*-isomer **10f** (28% yield, *Z*/*E* = 1/2) *via* several steps. The synthesized **10g** underwent Vilsmeier–Haack reaction to form γ-butyrolactone

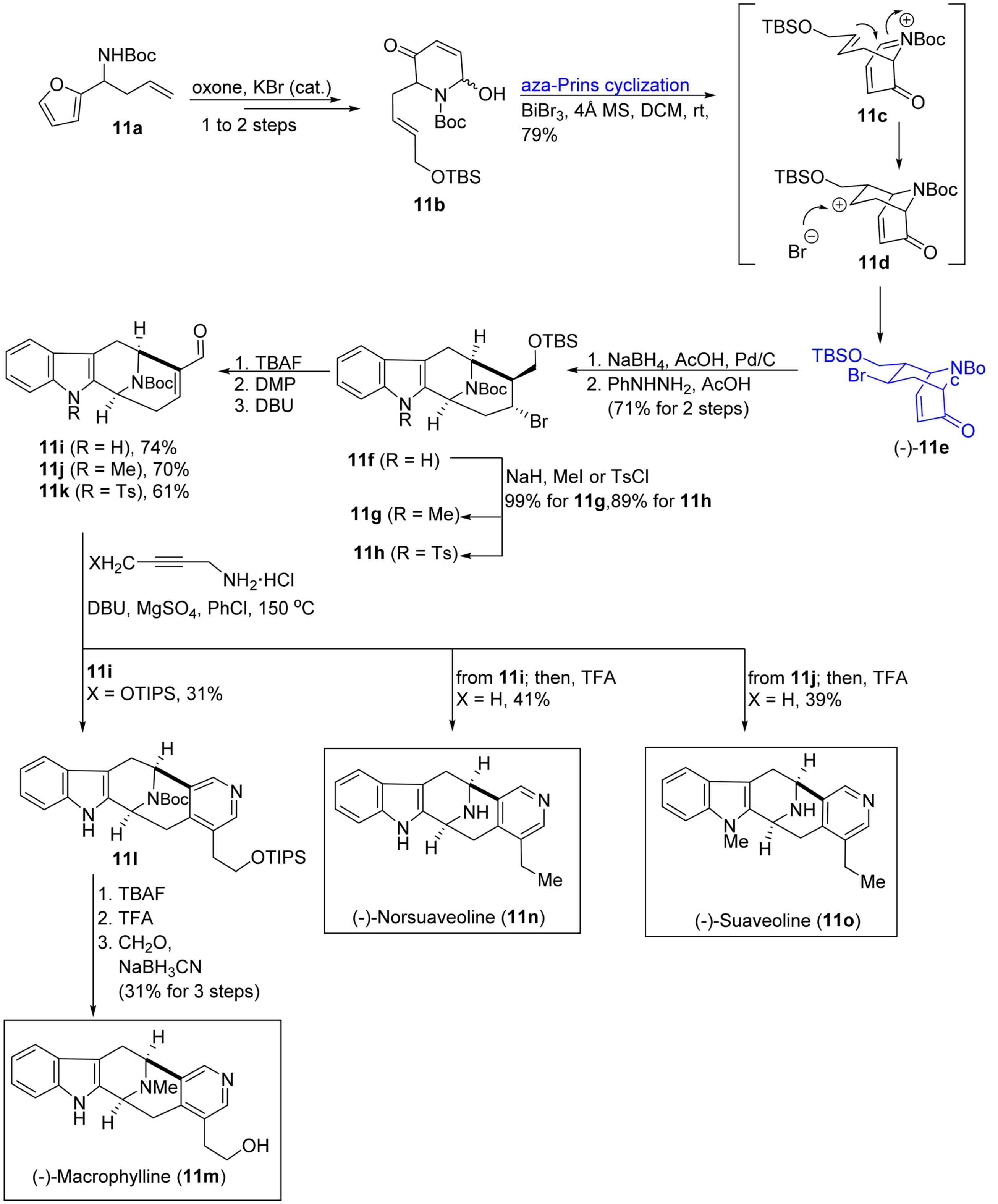


Scheme 9 Total synthesis of aristoquinoline (−)-**9e** according to Argade and co-workers.[48]

ring, followed by the sequential treatment with Grignard reagent **10h** (for nucleophilic addition), tetrabutylammonium fluoride (TBAF), tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide, to provide **10i** and its 18α-H epimer (9.6% 3-step yield, *d. r.* = 2/1). Similarly, **10k** was prepared by first subjecting the synthesized intermediate **10e** to sequential

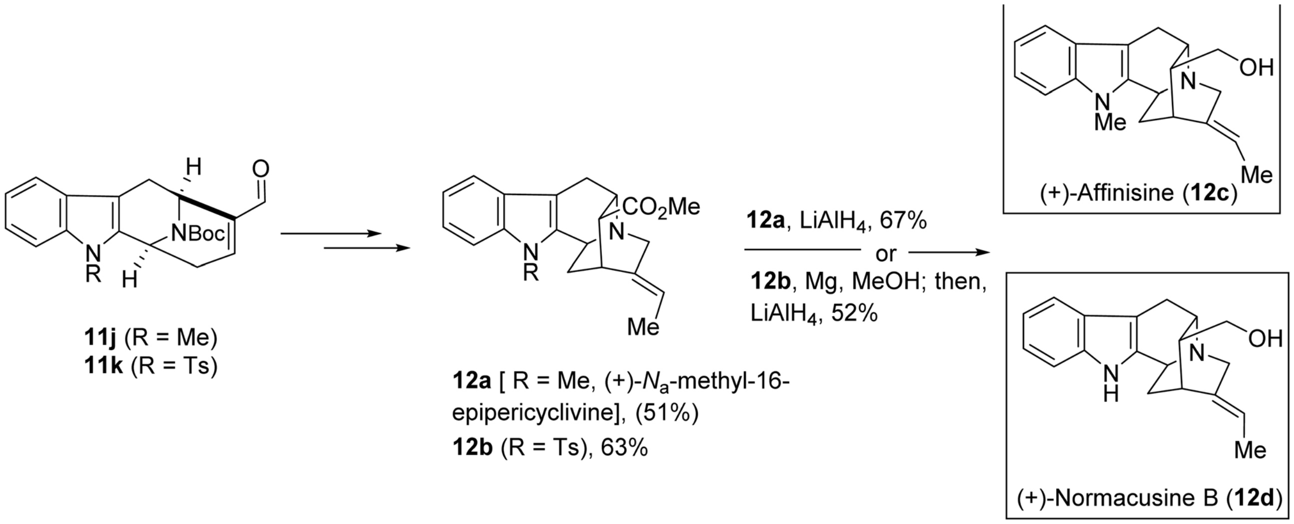


Scheme 10 Total synthesis of *Stemona* alkaloids **10g**, **10i**, **10k**, **10l** and **10n** according to Wang and co-workers.[50]



Scheme 11 Total syntheses of (−)-suaveoline (**11o**), norsuaveoline (**11n**) and (−)-Macrophylline (**11m**) according to Cheng and co-workers.[51]

Vilsmeier–Haack reaction to afford aldehyde **10j** (58%) and then, nucleophilic addition, cleavage of protecting group and oxidation were carried out, giving 18% yield over a three-step sequence with improved diastereomeric ratio of 4.4/1. Further, the compound **10j** underwent Wittig reaction, followed by hydrogenation, resulting in **10l** with 89% yield. The obtained natural



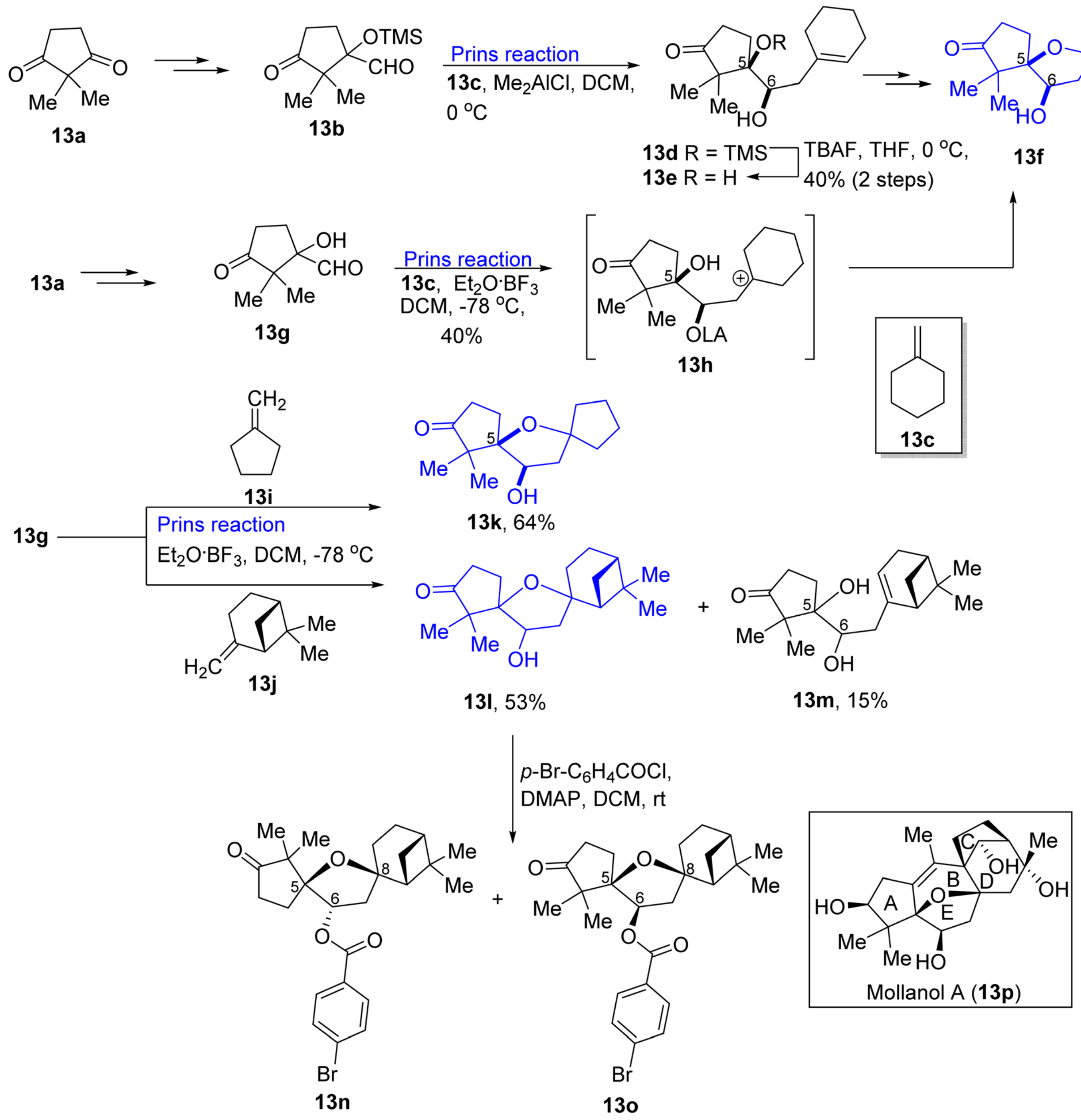
Scheme 12 Syntheses of (+)-N_a-methyl-16-epipericyclivine (**12a**), (+)-normacusine B (**12d**) and (+)-affinisine (**12s**) according to Cheng and co-workers.[51]

product **10l** gave rise to another natural product **10n** and its *E*-isomer **10m** ($E/Z = 2/1$ ratio) over a few-step sequence (Scheme 10).

2.1.7. Suaveoline & sarpagine alkaloids synthesis. In 2023, Cheng and co-workers[51] synthesized the six indole-based sarpagine and suaveoline alkaloids namely (−)-suaveoline (**11o**), (−)-norsuaveoline (**11n**), (−)-macrophylline (**11m**), (+)-N_a-methyl-16-epipericyclivine (**12a**), (+)-normacusine B (**12d**) and (+)-affinisine (**12c**). These alkaloids were particularly found in genera *Alstronia* or *Rauwolfia* (Apocynaceae family) which showed potential cytotoxicity towards various cancerous cells and circumvented multidrug resistance mechanisms.[52,53] The total synthesis commenced from compound **11a** which was subjected to aza-Achmatowicz rearrangement under oxone-KBr to synthesize **11b**. The obtained compound **11b** then underwent intramolecular aza-Prins reaction in the presence of bismuth tribromide catalyst to afford 9-ABN (−)-**11e** *via* intermediates **11c** and **11d**, in 79% yield. Notably, the efficient production of 9-ABN was due to the electron-donating masking groups (OTBS & OBn) on allylic alcohol. Next, the unified protocol began with enantiopure 9-ABN (−)-**11e** which underwent conjugate reduction, followed by Fischer indolization, giving tetracyclic indole-based 9-ABN **11f** as a common intermediate. Next, the *N*-methylation or protection was attempted with the assistance of methyl iodide and tosyl chloride to achieve derivatives **11g** and **11h** respectively. The three intermediates **11f–11h** then gave their enals **11i–11k** upon sequential *tert*-butyldimethylsilyl group elimination, oxidation and HBr elimination, in 74%, 70% and 61% yields, respectively. Further, enals **11i** and **11j** were reacted with propargylic amine in the presence of base to promote alkyne isomerization which was followed by 6π 3-azatriene electrocyclization and Boc-deprotection in sequence, resulting in desired (−)-suaveoline (**11o**; 39% yield from **11j**) and norsuaveoline (**11n**; 41% yield from **11i**). Furthermore, enal **11j** was also condensed with 4-((triisopropylsilyl)oxy)but-2-yn-1-amine to afford pentacyclic pyridine **11l** (31% yield) which underwent sequential protodesilylation, Boc-cleavage and reductive amination to form (−)-macrophylline (**11m**, 31% yield over a three-step sequence) (Scheme 11). Next, tetracyclic indole-based 9-ABN intermediates **11j** and **11k** were utilized to accomplish sarpagine alkaloids through a unified strategy. Regarding this, compounds **11j** and **11k** gave rise to corresponding (+)-N_a-methyl-16-epipericyclivine (**12a**, 51% yield) and compound **12b** (63%) over few steps. Further, the synthesized (**12a**) was subjected to reduction to afford (+)-affinisine (**12c**, 67% yield). In the same manner, the compound **12b** underwent sequential *N*-Ts deprotection and ester reduction to produce (+)-normacusine B (**12d,** 52% yield) (Scheme 12).

2.2. Terpene-derived natural products synthesis

2.2.1. Synthetic approach towards mollanol A. In 2014, an unprecedented grayanoid, mollanol A (**13p**) was obtained from *Rhododendron mole* fruits.[54] Biosynthetically, it was characterized by grayanane-based skeleton with tandem ring-rearrangement and ring-cyclization. Further, it exhibits the therapeutic activity against ulcerative colitis and showed transcriptional activation of xbp1 promoters in various cell types.[54] In 2020, Miao and co-workers[55] accomplished the stereoselective synthesis of A-ring section and designed an efficacious Prins reaction to establish E-ring of **13p**. The synthesis began with the construction of ring aldehydes **13g** and **13b** separately over a few steps from symmetric dione **13a,** which was obtained from readily accessible 2-methylcyclopentane-1,3-dione. Next, synthesized ring segments **13b** underwent Prins reaction with methylenecyclohexane **13c** in the presence of Me_2AlCl to afford a mixture of **13d** and TMS-unmasked product. The mixture was subjected to react with TBAF to obtain diol **13e** (40% yield) as single diastereomer. Further, the cyclization product **13f** was

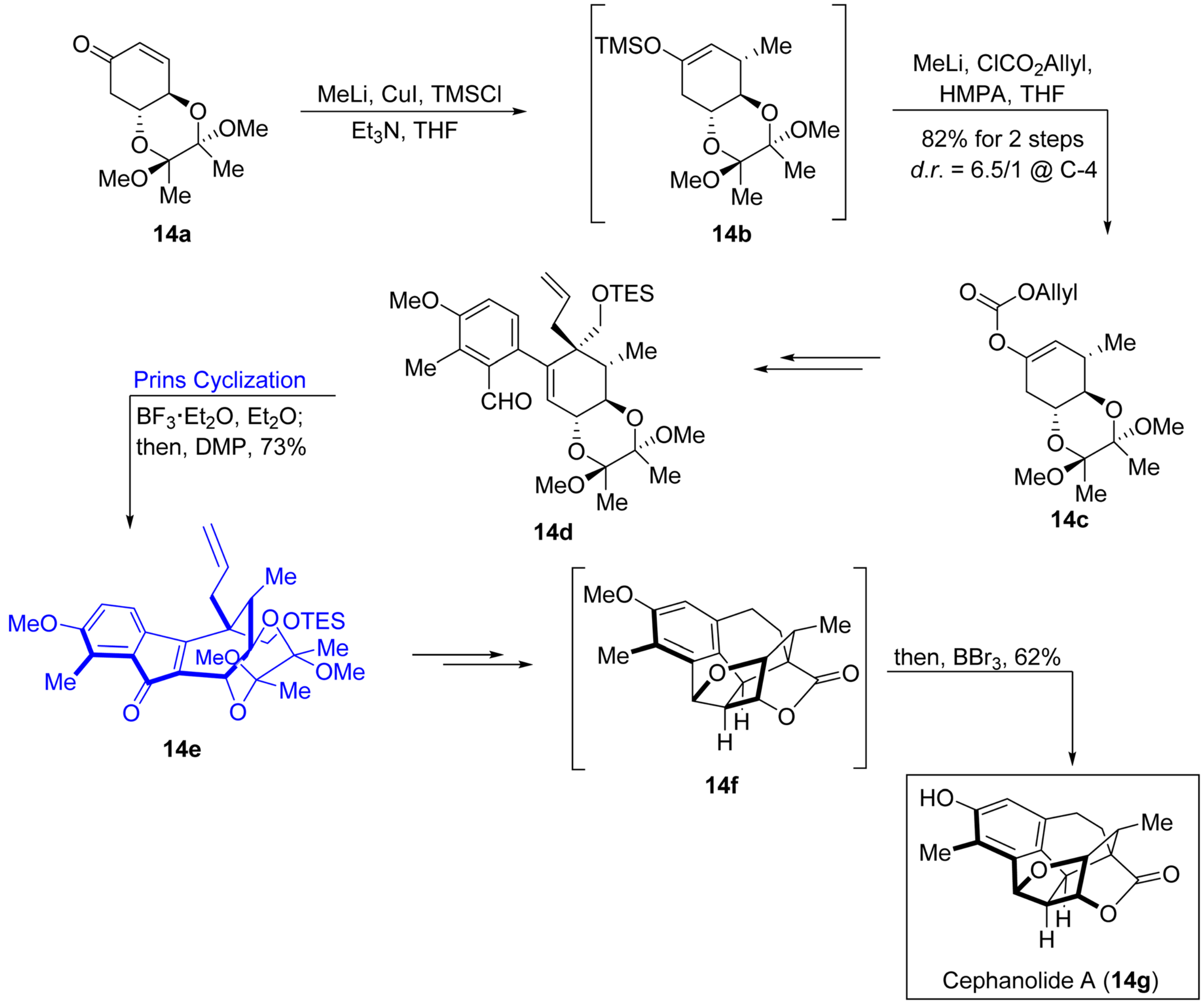


Scheme 13 Synthetic approach toward mollanol A (**13p**) by Miao and co-workers.[55]

prepared from compound **13e** over a few steps. Afterwards, the unmasked hydroxyaldehyde **13g** was also treated with compound **13c** in the presence of $Et_2O \cdot BF_3$ (Prins reaction) to produce [3 + 2] product **13f** as single diastereomeric compound directly through the cyclization of cationic intermediate **13h** (40% yield). Remarkably, this single step strategy is more efficient than aforementioned 4-step protocol. Additionally, the Prins reaction was also proceeded with other olefins **13i** and **13j**, giving cyclized products **13k** and **13l** with good diastereoselectivity and yields. Afterwards, the synthesis of ester **13o** implied the notable strength of Prins [3 + 2] cyclization strategy for accomplishing the synthesis of **13p.** Hence, this key strategy provided two new asymmetric carbons and one tetrahydrofuran (THF) ring which had not been previously synthesized *via* Prins reaction of unmasked hydroxyaldehydes (Scheme 13).

2.2.2. Cephanolide A synthesis.

Cephanolide A (**14g**), a highly complex C_{18} dinorditerpenoid, was isolated from *Cephalotaxus sinensis*, characterized by the cage-like hexacyclic framework with a tetracyclic core, a fused lactone and a THF ring.[56] In 2020, Zhang and co-workers[57] accomplished the first enantioselective synthesis of **14g** employing a unified strategy. Aside from the intricate skeleton, the biological activities of cephanolide A attracted the research community. The optimized total synthesis of **14g** commenced with the treatment of the enone **14a** (acquired from (−)-quinic acid in a three-step

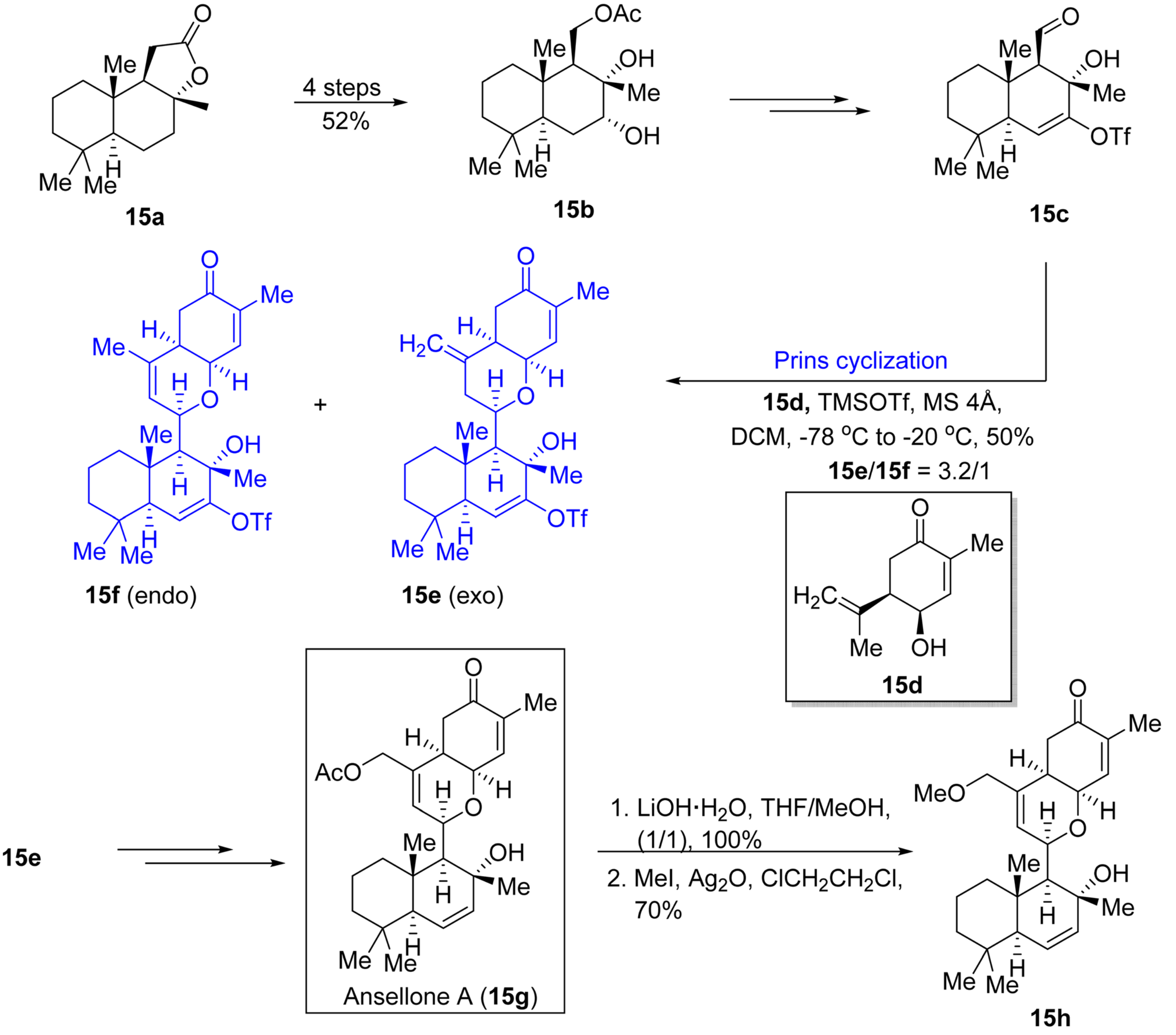


Scheme 14 Synthesis of cephanolide A (**14g**) by Zhang and co-workers.[57]

sequence) with lithium dimethylcuprate and TMSCl to afford silyl enolate **14b.** Next, allyl chloroformate captured the lithium enolate produced by Si–Li exchange protocol, affording the diastereomeric mixture of allyl carbamate **14c** (82% two-step yield, *d. r.* = 6.5/1 at C-4). The obtained compound **14c** was transformed into intended coupling product **14d** over a few-step sequence. After successful screening of Prins cyclization conditions, the compound **14d** was subjected to one-pot Prins cyclization ($BF_3 \cdot Et_2O$, Et_2O) and oxidation to give enone **14e** (73%). The compound **14e** then provided precursor **14f** over a few steps. Afterwards, methyl group cleavage generated the compound **14g** in 62% yield. Hence, the total synthesis of *cephalotaxus* dinorditerpenoid cephanolide A was reported to be accomplished in a 15-step sequence (Scheme 14).

2.2.3. Synthesis of ansellone derivatives

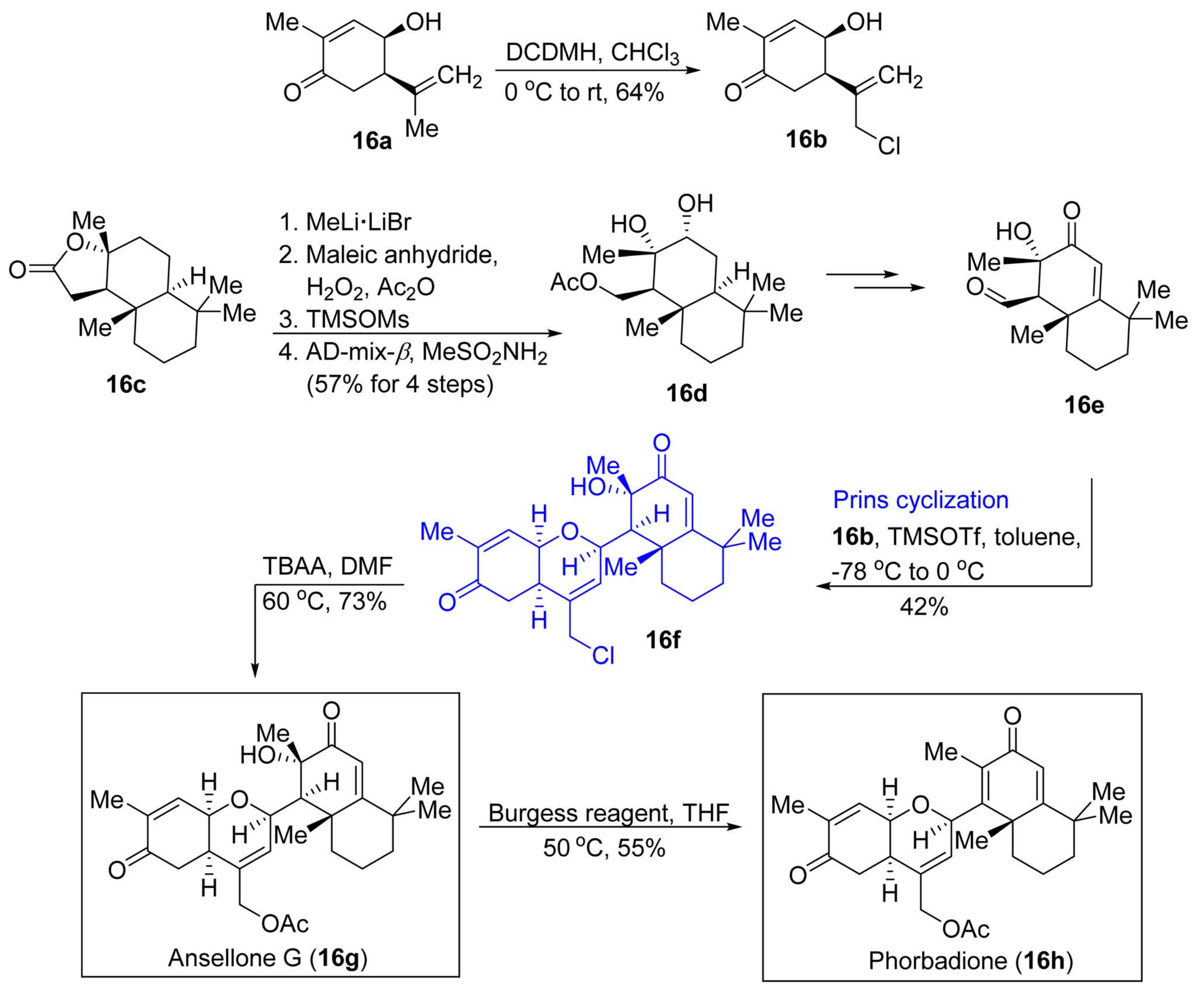
2.2.3.1. Ansellone A synthesis. Ansellone A (**15g**), a marine sesterterpenoid, isolated from *Cadlina luteomarginata* (dorid nudibranch) and *Phorbas* sp., exhibits LRA (latency-reversing agent) properties and contains unprecedented "ansellane" carbon skeleton.[58] This remarkable bioactivity and novel structural framework renders ansellone A an attractive prospect to enable the design of LRA tools and pharmaceutical leads. Tong's group in 2017, described the total synthesis of **15g** from (+)-sclareolide in 24 steps, featuring a 16-step linear sequence.[59] In 2021, Yanagihara and co-workers[60] achieved the concise total synthesis of this compound **15g** along with its analogues from (+)-sclareolide in 17 steps with a 13-step linear sequence. Their synthetic sequence for attaining the natural product commenced with the preparation of key aldehyde **15c**. First, the diol **15b** (52% yield) was prepared in a four-step sequence from (+)-sclareolide **15a**. The obtained compound **15b** gave key aldehyde **15c** in a series of steps. Importantly, the incorporation of TfO group enabled the Prins cyclization by stabilizing acid-sensitive *tert*-allylic alcohol. Finally, aldehyde **15c** was subjected to Prins cyclization with *cis*-γ-hydroxycarvone **15d** facilitated by TMSOTf, to give 2,6-*cis*-THP moiety stereoselectively. The resulting isomers exo-olefin **15e** and endo-olefin **15f** were produced in 3.2/1 ratio. Further, the compound **15e** provided



Scheme 15 Synthesis of ansellone A (**15g**) by Yanagihara and co-workers.[60]

the natural product **15g** over a few steps. The compound **15g** was then subjected to hydrolysis with lithium hydroxide, followed by methylation with methyl iodide in the presence of Ag_2O to afford methyl ether **15h** in 70% yield (Scheme 15). The compound **15g** was reported to exhibit the EC_{50} value of 1.14 μM.

2.2.3.2. Ansellone G & phorbadione syntheses. Ansellone G (**16g**) and phorbadione (**16h**) are the ansellane-type marine sesterterpenoids, sourced from Pacific Rim.[61] Both natural products feature novel architectures, where hydrobenzopyran is linked to decalin scaffolds with different oxidation levels. These natural compounds showcased LRA activity against HIV and activating ability for cAMP.[58,62] Yanagihara and co-workers[63] in 2022, also attempted the inaugural synthesis of ansellone G along with the synthesis of phorbadione. The salient aspect of this synthetic strategy is the exploitation of the homoallyl alcohol **16b** in the key Prins cyclization reaction, streamlining the acetoxy group incorporation, while circumventing strategic late-stage modifications. First, the required homoallyl alcohol **16b** was constructed by treating *cis*-hydroxycarvone **16a** with chlorinating agent 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), in 64% yield. In the context of ansellone G (**16g**), first, the coupling partner aldehyde **16e** was prepared. In this regard (+)-sclareolide **16c** was transformed into diol **16d** (57% overall yield) in a four-step sequence. The compound **16d** then afforded required aldehyde **16e** over a few steps. Next, to construct hydrobenzopyran structure, Prins cyclization conditions were examined. To this end, Prins cyclization was realized between the synthesized homoallyl alcohol **16b** and aldehyde **16e** in the presence of TMSOTf to get the cyclized product **16f** in 42% yield. Notably, this synthetic strategy is the inaugural case in Prins cyclization that utilizes chloro-substituted homoallyl

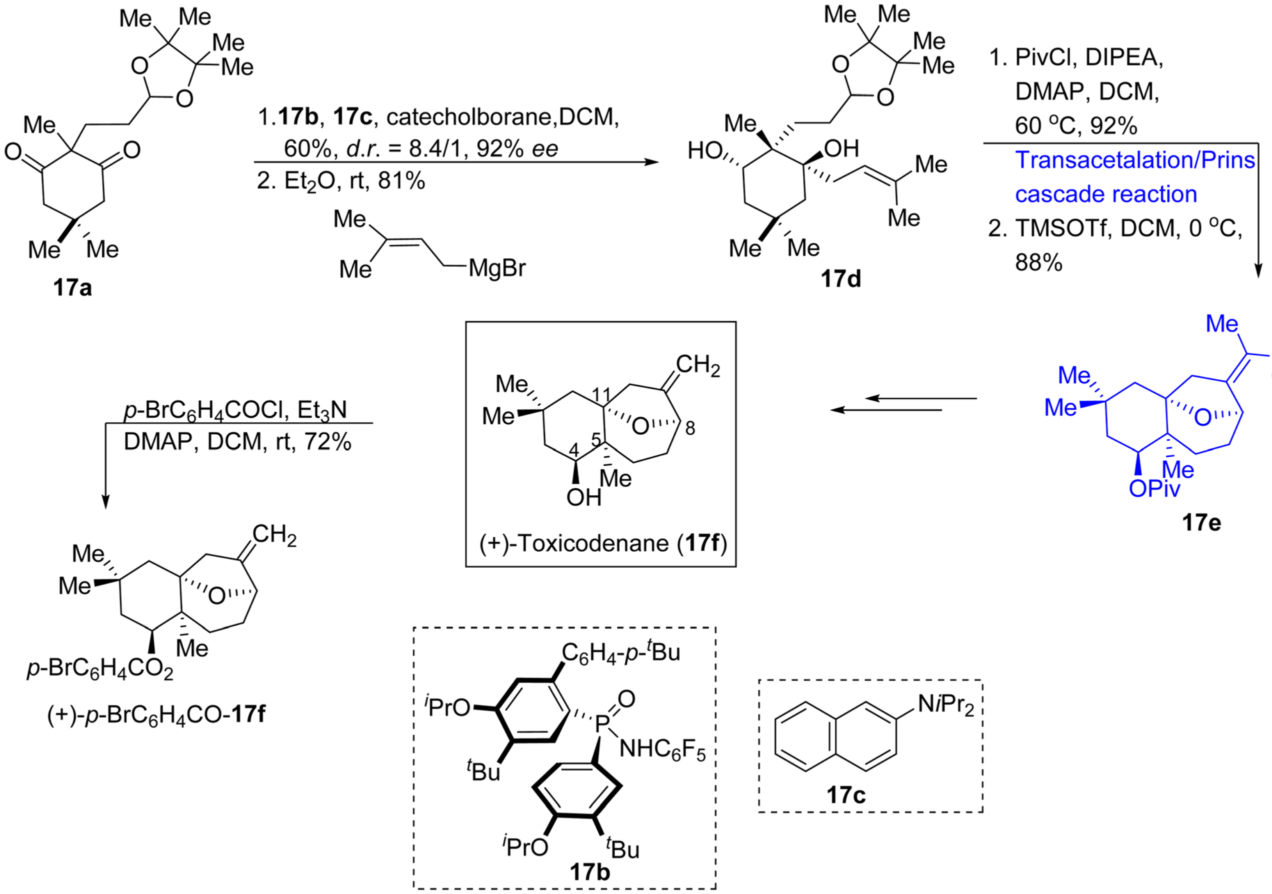


Scheme 16 Total syntheses of ansellone G (**16g**) and phorbadione (**16h**) according to Yanagihara and co-workers.[63]

alcohol **16b** to construct natural product. Further, compound **16f** was subjected to substitution reaction in the presence of tetrabutylammonium acetate (TBAA) to produce the natural compound **16g** in 73% yield. The obtained ansellone G then underwent dehydrative transformation with Burgess reagent ((methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt) in the presence of THF solvent to deliver another natural product **16h** (55% yield). Leveraging this expedient method, compound **16g** was synthesized in a 10-step linear synthetic sequence with an overall yield of 13% and compound **16h** was synthesized in an 11-step sequence with an overall yield of 7.2% (Scheme 16).

2.2.4. (+)-Toxicodenane A synthesis. Toxicodenane A (**17f**), a sesquiterpenoid was isolated from *Toxicodendron vernicifluum*,[64] which had been utilized in Chinese traditional medicine for treating atherosclerosis, stomach cancer and gastritis. Structurally, this natural product contains oxa-bridged [6.6.5]-tricyclic skeleton with all-carbon stereocenter at ring junction. In 2021, Qin and co-workers[65] attempted the first chiral synthesis of (**17f**) in nine steps. In this context, the compound **17a** underwent enantioselective desymmetric reduction with organocatalyst *P*-stereogenic phosphinamide **17b** and *N*,*N* diisopropylnaphthalen-2-amine **17c** (as additive), followed by the addition of prenylmagnesium bromide with Et_2O, resulting in the formation of *trans*-product **17d** (81% yield). A negligible amount of stereoisomer was isolated and there was no realization of unintended *cis*-product. Next, the synthesized compound **17d** was subjected to secondary alcohol protection, followed by crystallization (CH_2Cl_2/*n*-hexane) and transacetalation/Prins cyclization in cascade sequence with TMSOTf, providing an oxa-bridged tricyclic structure **17e** (88% yield). Further, the compound **17e** gave the desired compound **17f** (61% two-step yield) over a few steps. Finally, the *p*-bromobenzoic ester of (+)-toxicodenane A [*i.e.* (+)-*p*-BrC_6H_4CO-**17f**], was synthesized from (+)-toxicodenane A under the presence of 4-bromobenzoyl chloride, Et_3N and DMAP in DCM (Scheme 17).

2.2.5. Synthesis of western sections of janthitrem B, JBIR-137, and shearinine G. The indole diterpenoids namely

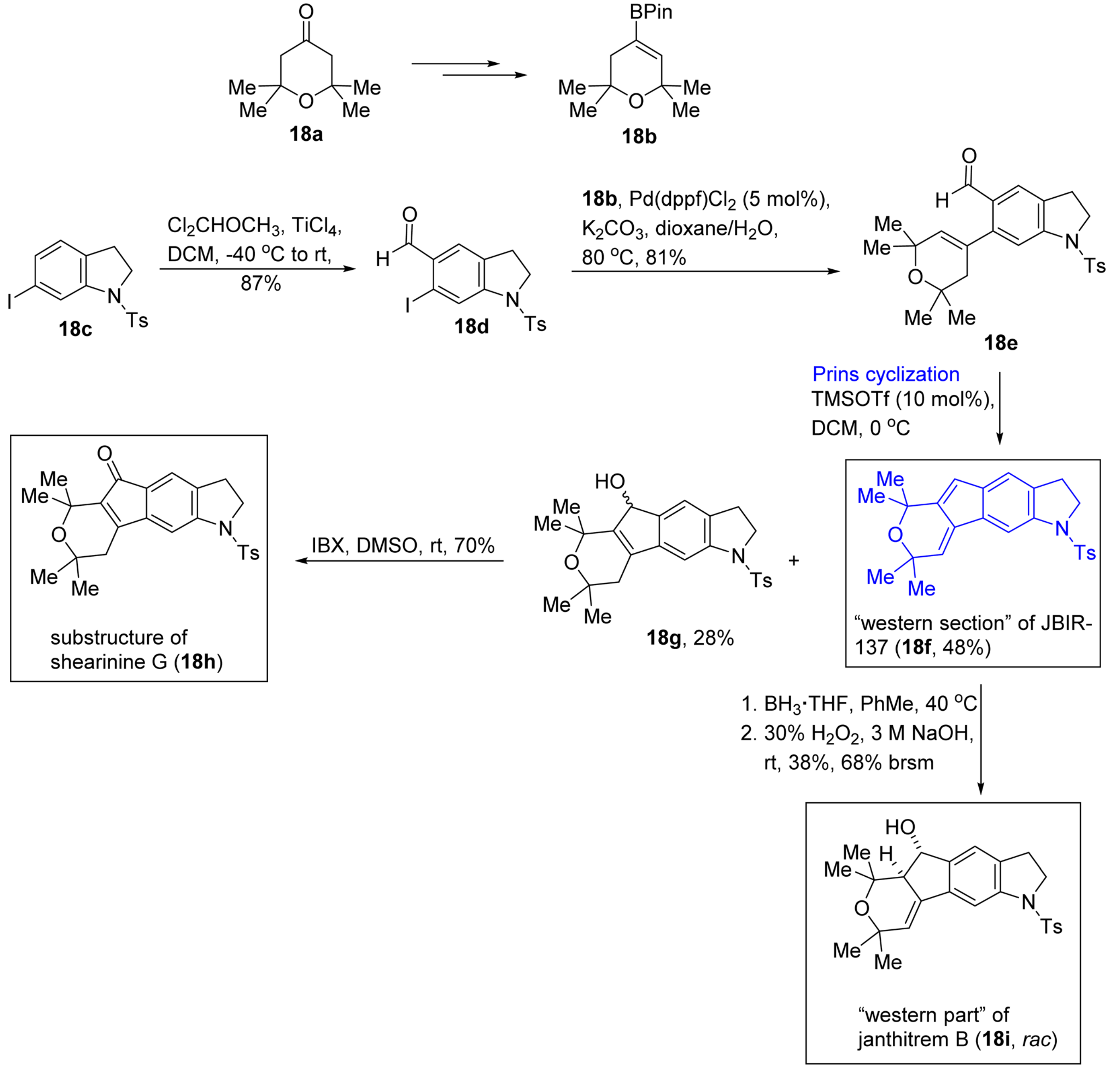


Scheme 17 Total synthesis of (+)-toxicodenane A (**17f**) by Qin and co-workers.[65]

janthitrem B, JBIR-137, and shearinine G were isolated from *Penicillium janthinellum*, *Epichloë* sp. and *Penicillium* sp., respectively.[66] The pyrano[4′,3′ : 3,4]cyclopenta[1,2-*f*]indole is the common structural motif present in these natural products. Intriguingly, many shearinines and janthitrems demonstrated tremorgenic effect by targeting calcium-activated potassium channels.[67] Additionally, they also exhibited insect-repelling activities.[68] In 2022, Fresia & Lindel[69] reported the synthesis of tetracyclic structures as western sections of JBIR-137 **18f**, shearinine G **18h** and janthitrem B (**18i**, *rac*) employing Prins cyclization approach. The total synthesis commenced from *N*-tosyl-6-iodoindoline **18c** which underwent formylation, leveraging Rieche conditions, to attain compound **18d** (87%). Next, Suzuki–Miyaura coupling was performed between aldehyde **18d** and dihydropyranylboronic ester **18b** (obtained from tetramethyltetrahydropyranone **18a** over few steps), leading to the generation of formylated dihydropyranylindoline **18e** in 81% yield. The prepared compound **18e** was treated with TMSOTf *via* Prins cyclization to give tetracyclic diene **18f** in 48% yield and allylic alcohol **18g** with tetracyclic structure as byproduct in 28% yield. Importantly, compound **18f** was represented as "western half" of JBIR-137. The obtained compound **18g** was oxidized to form tetracycle **18h**, which was the substructure of shearinine G. Next, the western section of janthitrem B (**18i**, *rac*), which was isomeric with compound **18g**, was constructed from compound **18f** through oxygenation. In this regard, compound **18f** was subjected to direct reduction with borane and subsequent oxidative workup to provide western fragment of janthitrem B (**18i**, 38% yield, 68% brsm). This western section was obtained in eight-step sequence and in an overall yield of 10% (Scheme 18).

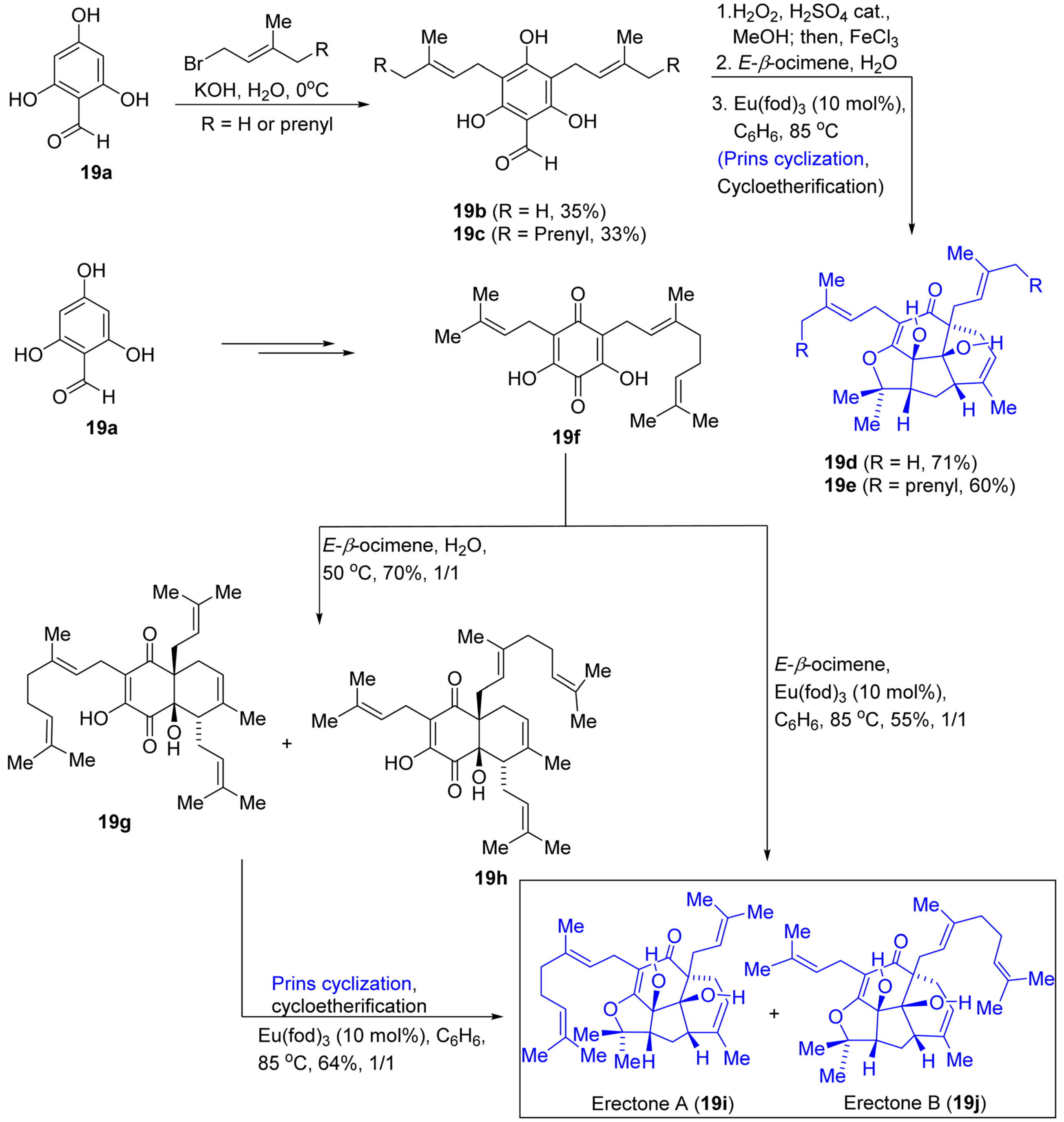
2.2.6. Synthesis of erectones A and B, and revised structure of hyperelodione D.

Erectone A (**19i**), erectone B (**19j**) and hyperelodione D (**20d**) are the biogenetically related meroterpenoids which were isolated from *Hypericum* plant.[70] In 2022, Franov and co-workers[71] demonstrated the biomimetic total syntheses of erectones A and B and the structural revision of hyperelodione D employing Prins cyclization as one of the significant steps. To achieve the target, they initially attempted the concise total synthesis of the proposed structure of hyperelodione D **19e**. For this purpose, the synthetic sequence commenced with prenylation and geranylation of readily available 2,4,6-trihydroxybenzaldehyde **19a** to afford aldehydes **19b** and **19c**. The compounds **19b** and **19c** were then subjected to sequential Dakin oxidation, intermolecular Diels–Alder reaction, Prins cyclization and cycloetherification, providing diprenylated analogue **19d** (71% yield) and proposed framework of hyperelodione D **19e** (60% yield). It was realized that the NMR



Scheme 18 Preparation of western part of JBIR-137 **18f**, janthitrem B (**18i**, *rac*) and substructure of shearinine G **18h** by Fresia & Lindel.[69]

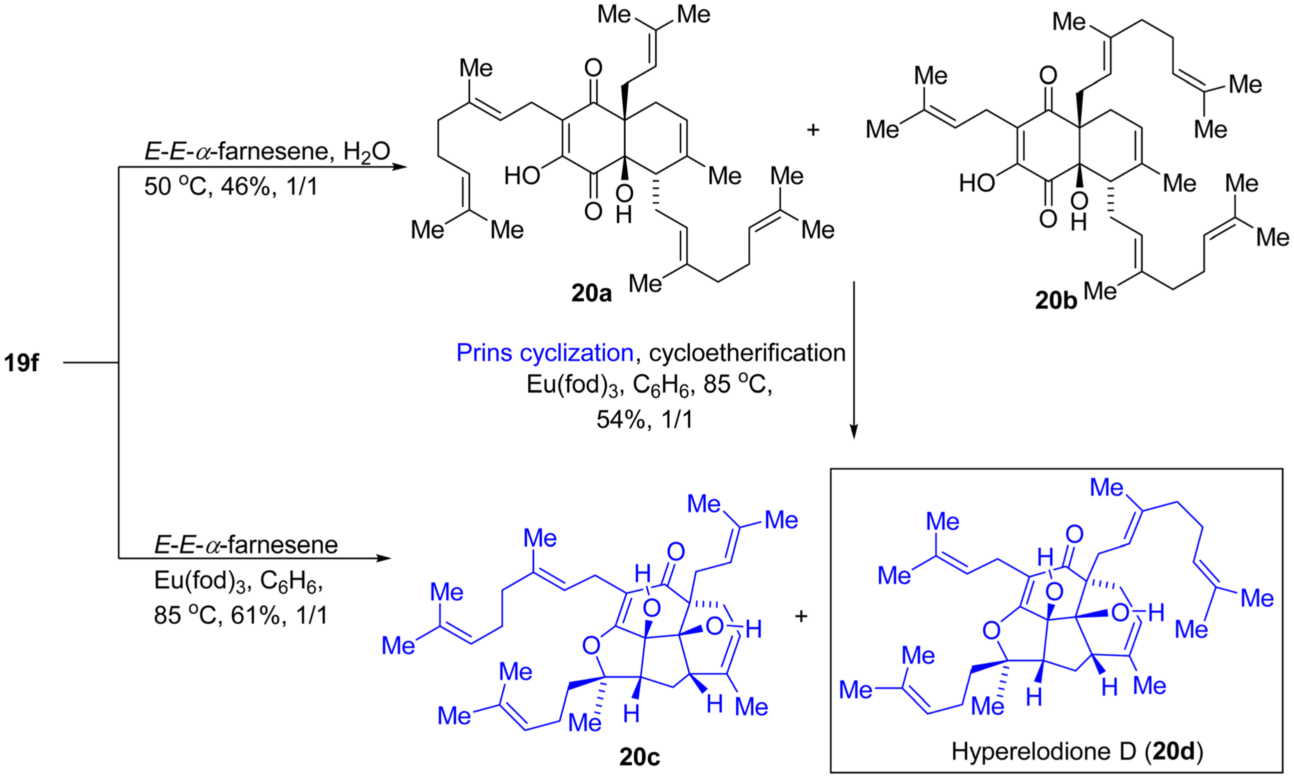
results for the synthesized compound **19e** were not in correspondence with the reported data for naturally occurring hyperelodione D. Thus, the structural revision of hyperelodione D was confirmed by devising the synthetic route that involved the construction of erectquione A **19f** (quinone dienophile). In this context, the compound **19f** was attained from 2,4,6-trihydroxybenzaldehyde **19a** over a few steps which underwent water-catalyzed Diels–Alder reaction with *E*-β-ocimene to afford the regioisomeric mixture of Diels–Alder adducts **19g** and **19h** (70%, 1/1 ratio). Next, the compounds **19g** and **19h** upon treatment with Eu(fod)$_3$ in the presence of C_6H_6 afforded the mixture of natural compounds *i.e.*, **19i** and **19j** (64%, 1/1 ratio) through Prins cyclization and cycloetherification. In an alternative approach, the direct construction of compounds **19i** and **19j** was made possible through a one-pot Diels–Alder cascade, in combined yield of 55% (ratio = 1/1) (Scheme 19). Further, treatment of erectquione A **19f** with *E*,*E*-α-farnesene (found in *Hypericum* species) in the presence of water provided natural regioisomers **20a** and **20b** (46%, 1/1 ratio). Next, Prins reaction and cycloetherification were performed on compounds **20a** and **20b**, yielding the tetracyclic compounds **20c** and **20d** in the form of mixture (54%, 1/1 ratio). This tetracyclic mixture could also be obtained directly from the combination of compound **19f** and *E*,*E*-α-farnesene utilizing the aforementioned Diels–Alder cascade protocol, in 61% yield and 1/1 ratio (Scheme 20). Fortunately, the authors realized that the NMR



Scheme 19 Syntheses of Erectones A (**19i**) and B (**19j**) according to Franov and co-workers.[71]

results for the revised structure of **20d** were identical to those of natural hyperelodione D, thus confirming the structural revision of this intricate meroterpenoid.

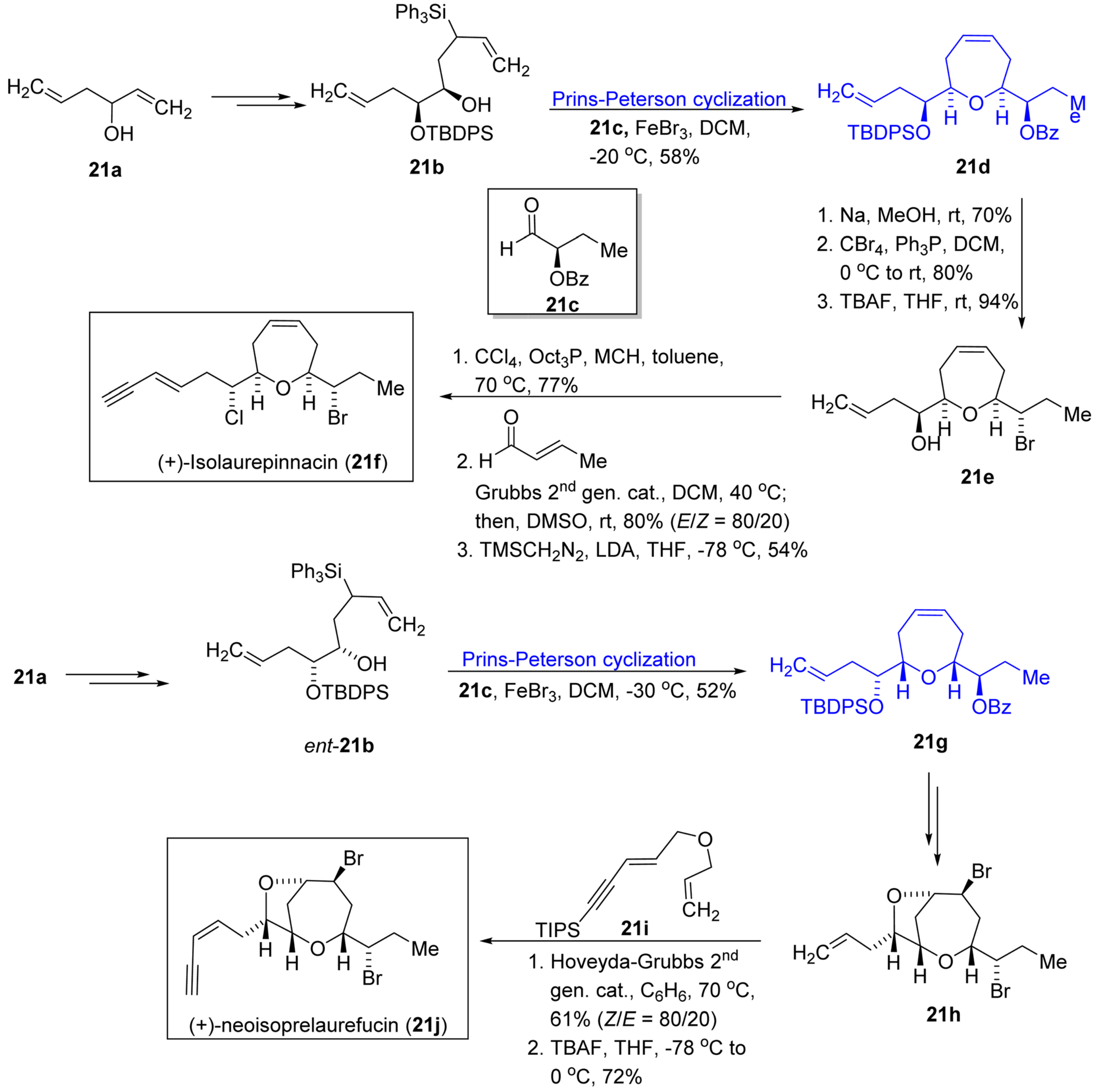
2.2.7. (+)-Isolaurepinnacin & (+)-Neoisoprelaurefucin syntheses. The marine naturally-occurring compounds (+)-isolaurepinnacin (**21f**) and (+)-neoisoprelaurefucin (**21j**) were isolated from *Laurencia pinnata* Yamada and *Laurencia nipponica* Yamada, respectively.[72,73] These compounds contained 7-membered cyclic ether moiety with α,α'-*cis*-disubstitution, functionalized with terminal enyne fragment and halogen atoms. The enyne was configured as *E* in (+)-isolaurepinnacin and *Z* in (+)-neoisoprelaurefucin. In 1993, Overman and co-workers[74] achieved the total synthesis and in 2001, Suzuki[75] *et al.* attempted the formal synthesis of **21f**. Whereas, in 2003, Kim and co-workers accomplished the only total synthesis of **21j**.[76] In 2022, Sinka and co-workers[77] synthesized **21f** and **21j** *via* a shortest convergent synthetic route, utilizing a common strategy with the Prins–Peterson



Scheme 20 Synthesis of hyperelodione D (**20d**).

cyclization (PPC) as a significant step. The total synthesis of **21f** began with 1,5-hexadien-3-ol **21a** which afforded silyl alcohol **21b** over a few steps. The obtained compound **21b** underwent Prins–Peterson cyclization with freshly synthesized aldehyde **21c** in the presence of stoichiometric quantity of $FeBr_3$. The resulting product Δ4-2,7-disubstituted 7-membered oxygen-containing ring **21d** was obtained in 58% yield. The bulky *tert*-butyldiphenylsilyl (TBDPS) group promoted Prins–Peterson cyclization, leading to the formation of *cis*-oxepene as a major product. Next, the benzoate group in oxepene **21d** was replaced with bromine atom, with suitable configuration of **21f.** To this end, the compound **21d** underwent sequential basic hydrolysis, Appel reaction and silyl group cleavage, giving alcohol **21e** in 94% yield. Further, the compound **21e** was subjected to sequential Appel reaction, Grubbs catalyst-mediated olefin metathesis and Colvin rearrangement, providing **21f** in 54% yield. Next, the total synthesis of **21j** commenced with the utilization of common protocol of **21f**. First, the alcohol **21a** generated silyl alcohol *ent*-**21b** over a few steps. Then, the Prins–Peterson cyclization of *ent*-**21b** and aldehyde **21c** was performed to produce oxepene **21g** (52% yield) which then gave alcohol **21h** over a few step-sequence. Further, the alkyne group was introduced in the side chain utilizing allyl enyne ether **21i**, followed by TIPS-cleavage, resulting in the preparation of **21j** (72% yield). The enantioselective syntheses described herein were completed through the shortest synthetic route in a ten-step sequence for (+)-isolaurepinnacin (5% overall yield) and in a twelve-step sequence for (+)-neoisoprelaurefucin (1.3% overall yield) (Scheme 21).

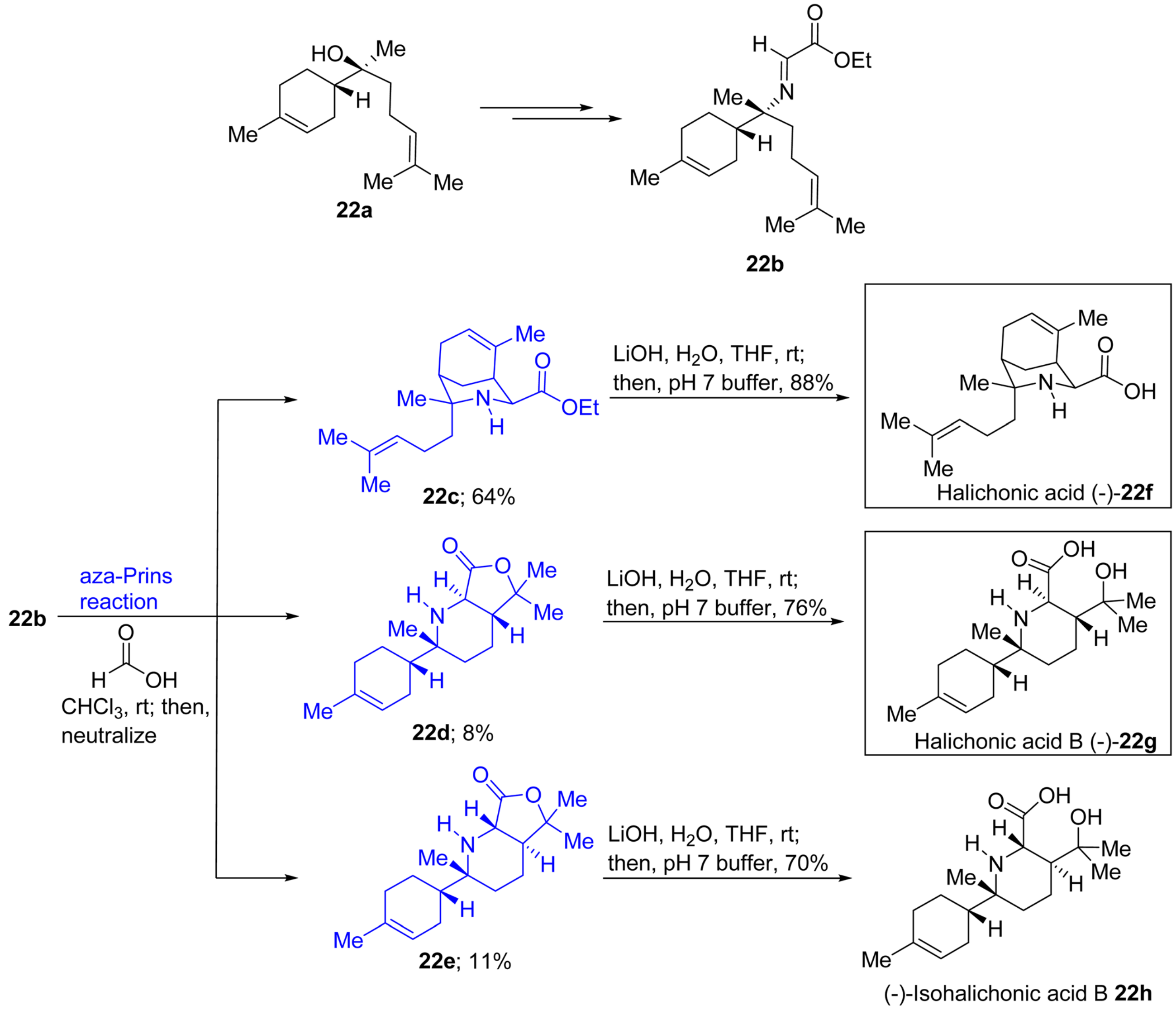
2.2.8. (−)-Halichonic acid & (−)-halichonic acid B syntheses. Halichonic acid, an aminobisabolene sesquiterpenoid isolated from *Halichondra* sp., by Tsukamoto[78] *et al.*, (2019) possess 3-azabicyclo[3.3.1]nonane ring structure with four stereocenters in piperidine ring. Architecturally, halichonic acid B is the derivative of pipecolic acid bearing a cyclohexenyl ring with four stereocenters (three of these stereocenters are found in piperidine ring) and contains tertiary alcohol. In 2022, Reber & Niner[79] accomplished the first total synthesis of the enantiomers of halichonic acids. The syntheses began with (−)-α-bisabolol **22a** which was reported to be a commercially accessible sesquiterpenoid. In this context, **22a** was converted into imine intermediate **22b** over a number of synthetic steps. The ^1H NMR spectroscopy revealed that the imine **22b** was produced as single stereoisomer and its configuration was assigned as (*E*)-isomer. Next, intramolecular aza-Prins cyclization was realized to build bicyclic halichonic acid frameworks. For this purpose, the solution of imine **22b** in chloroform was reacted with formic acid (in excess), affording major bicyclic compound **22c** (64% yield). The compound **22c** is (−)-halichonic acid ester which contains 3-azabicyclo[3.3.1]nonane ring structure of this natural compound. The isomeric lactones **22d** (8%) and **22e** (11%) were also formed after the cyclization process. In order to achieve the enantiomers of natural product, the obtained bicyclic product **22c** was hydrolyzed with aqueous lithium



Scheme 21 Total syntheses of (+)-isolaurepinnacin (**21f**) and (+)-neoisoprelaurefucin (**21j**) according to Sinka and co-workers.[77]

hydroxide, followed by the neutralization with phosphate buffer, producing halichonic acid ((−)-**22f**, 88% yield). Likewise, the lactone **22d** and **22e** upon hydrolysis under the similar conditions produced halichonic acid B ((−)-**22g**, 76% yield) and "unnatural" compound **22h** (70% yield) which was identified as (−)-isohalichonic acid B, respectively. The syntheses of stereoisomers of halichonic acid B and halichonic acid, described herein, were completed in a ten-step sequence (Scheme 22).

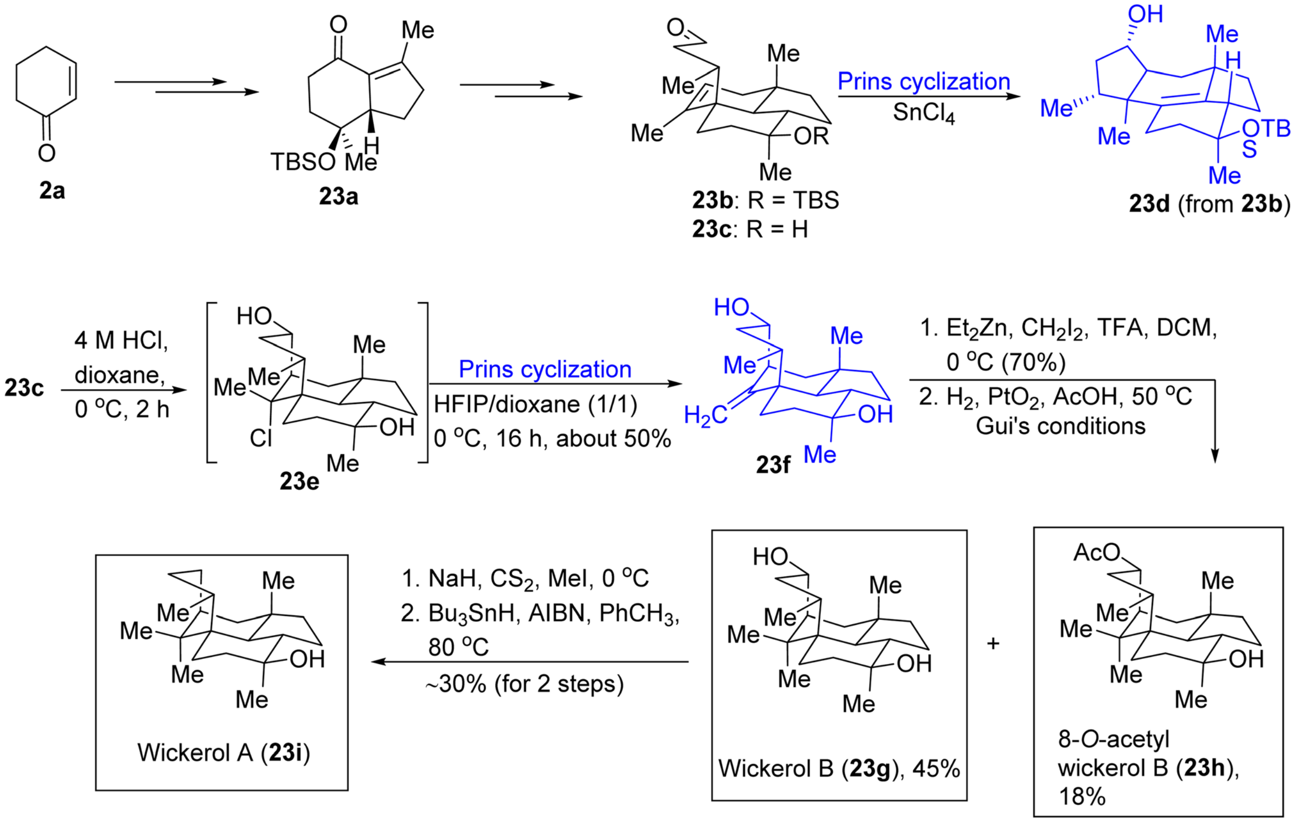
2.2.9. Wickerols A & B syntheses. The cage-like tetracyclic diterpenoid, wickerol A (**23i**) was isolated from *Trichoderma atroviride* (filamentous fungus) which showed potential antiviral activity towards influenza A H1N1 strains (A/PR/8/34 & A/WSN/33) with IC_{50} of 0.07 μg mL^{-1}. Another cage-like tetracyclic diterpenoid, wickerol B (**23g**), demonstrated reduced antiviral activity towards A/PR/8/34 strain, having IC_{50} of 5 μg mL^{-1}.[80] In 2023, Chung and co-workers[81] achieved the total synthesis of **23i** and **23g** by employing Prins cyclization. The total synthesis commenced with enantioselective preparation of key intermediate **23a** from cyclohexanone **2a** over few steps. The obtained compound **23a** then afforded Prins cyclization precursors **23b** and **23c** over a series of synthetic steps. Next, investigations for ring closure in wickerol B were initiated and for this purpose, aldehyde **23b** was treated with $SnCl_4$ (Prins



Scheme 22 Syntheses of (−)-halichonic acid (−)-22f & (−)-halichonic acid B (−)-22g.

condition) to give fused cyclopentane **23d** through π-cyclization resulting in undesired alkyl shift. Further, aldehyde **23c** was reacted with aqueous HCl in the presence of dioxane and the concentration was increased under vacuum to synthesize chlorinated Prins product *i.e.*, chloro-norwickerol B **23e**. Next, bridged tetracycle **23f** was obtained under the influence of optimal Prins reaction conditions including hexafluoroisopropanol/dioxane, in an isolated yield of ~50%. Notably, the Prins reaction played its role in the formation of sterically strained and congested bridging ring, leading to the desired framework of natural product. The compound **23f** was then subjected to altered Simmons–Smith cyclopropanation, followed by hydrogenolysis (Adam's catalyst), providing product (**23g**, 45%). Additionally, in accord with Gui's conditions,[79] 8-*O*-acetyl wickerol B (**23h**, 18%) was also produced through hydrogenolysis reaction. Afterwards, Barton–McCombie protocol was utilized smoothly to give **23i** without optimization, in ~30% yield (Scheme 23).

2.2.10. (−)-Retigeranic acid A synthesis. A sesterterpene, retigeranic acid A (**24i**) first extracted from *Lobaria retigera* as the mixture containing retigeranic acid B.[82] Structurally, **24i** contains angular triquinane core and pentacyclic framework with fused *trans*-hydrindane structure having eight stereocenters with three quaternary centers and two vicinal quaternary carbons at bridgehead sites. In 2023, Chen and co-workers[83] attempted the convergent and concise total synthesis of (−)-retigeranic acid A (**24i**) by applying the key diastereoselective intramolecular Prins cyclization. This strategy began with ester **24a**, which gave aldehyde **24b** over a few steps. Next, the complex *trans*-hydrindane structure **24g** was constructed utilizing another aldehyde **24c**. The compound **24c** (obtained from geraniol) was subjected to Horner–Wadsworth–Emmons reaction with **24d** to provide ketone **25e** (90% yield). Next, one C–C bond and two continuous stereocenters were expected to be established by Prins cyclization. After the successful screening of reaction conditions, the Prins product

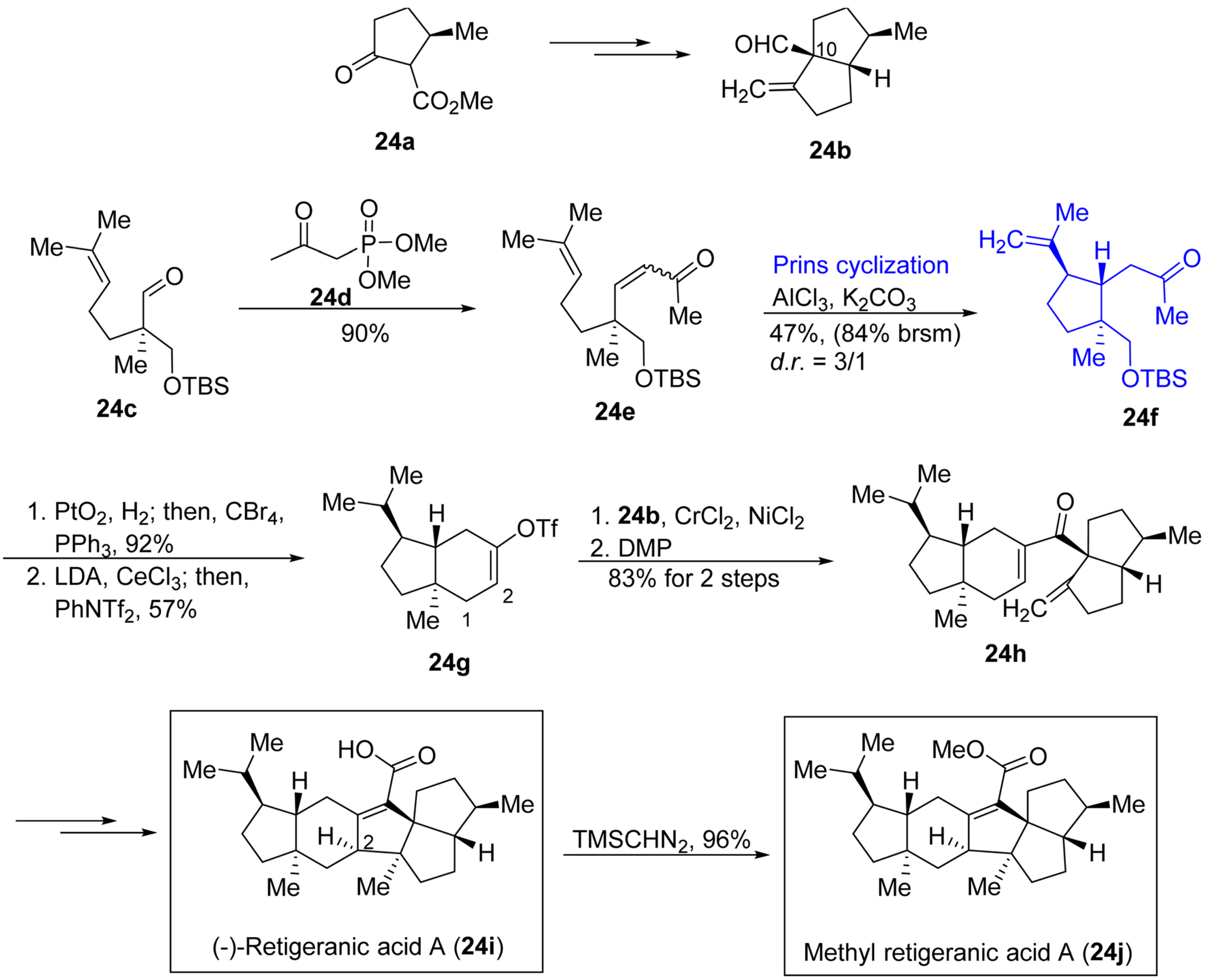


Scheme 23 Total syntheses of wickerol A (23i) and wickerol B (23g) according to Chung and co-workers.[81]

24f (47% yield, 84% brsm, *d. r.* = 3/1) was formed in the presence of $AlCl_3$ catalyst and K_2CO_3 as base additive. The compound **24f** then underwent sequential reaction with PtO_2/H_2 and CBr_4/PPh_3 in one-pot fashion. In next step, optimized conditions were examined for the formation of bond between carbon 1 and 2. Thus, deprotonation and subsequent phenyl triflimide treatment afforded vinyl triflate **24g** (57% yield) with forged bond. Further, Nozaki–Hiyama–Kishi reaction was performed between compound **24b** and compound **24g** in the presence of $NiCl_2$/$CrCl_2$ which was followed by Dess–Martin oxidation to give ketone **24h** (83%). Next, the compound **24h** led to the formation of desired (−)-retigeranic acid A (**24i**, 30% yield) over a few modifications. Further, **24i** provided (−)-methyl retigeranic acid A (**24j**, 96% yield) in the presence of TMS diazomethane. (−)-Retigeranic acid A was synthesized in a linear sequence of 18 steps. The strategy described herein would facilitate the preparation of the related cyclopentanes having quaternary stereocenters, incorporated in several natural products (Scheme 24).

2.2.11. Truncated rhopaloic acid & natural doremox derivative. Rhopaloic acid C was extracted from *Rhopaloeides* sp. (marine sponge) which displays potential inhibitory effect on *Asterina pectinifera* (starfish) embryo gastrulation and triggered autophagy and apoptosis in cancerous cells of human bladder.[84] In 2024, Peña and co-workers[85] achieved the selective short-time synthesis of *cis*-2,6-dihydropyrans through silyl-Prins cyclization (Scheme 26), leading toward the syntheses of natural doremox derivative (**25f**) and rhopaloic acid analogue (**25l**). In their synthetic approach, racemic *Z*-vinylsilyl alcohol **25a** was reacted with aldehyde **25b** under optimal silyl-Prins reaction conditions (TMSOTf, DCM, −78 °C, 20 min), to give dihydropyran **25c** (74% yield, *d. r.* > 95/5). In this context, the generation of *E*-oxocarbenium ion **25d** at initial stage contributed to the formation of 2,6-*cis*-dihydropyrans with high stereoselectivity. The obtained *E*-oxocarbenium ion **25e** underwent 6-endo cyclization *via* transition state having stable chair-like conformation with equatorially oriented C2- and C6-substituents. The obtained β-silyl carbocation **25e** was subjected to silyl group cleavage to generate dihydropyran **25c**. The synthesized compound **25c** gave doremox derivative (**25f**), a fragrance equivalent to rose oxide, through standard hydrogenation, in 80% yield. Moreover, the silyl-Prins methodology was also applied for the preparation of rhopaloic acid C analogue. In this regard, vinyl silyl alcohol **25g** underwent silyl-Prins cyclization with methyl 3,3-dimethoxypropionate **25h** and 2-(isobutyryloxy)acetaldehyde **25i**, to provide dihydropyrans **25j** and **25k**, respectively, having ester functionality attached to C2. In the next step, compound **25j** led to the formation of truncated product (**25l**) through saponification, in 82% yield (Scheme 25).

2.2.12. Bipolarolides A and B. The novel ophiobolin-based sesterterpenoids bipolarolides A (**26j**) and B (**26i**) were isolated

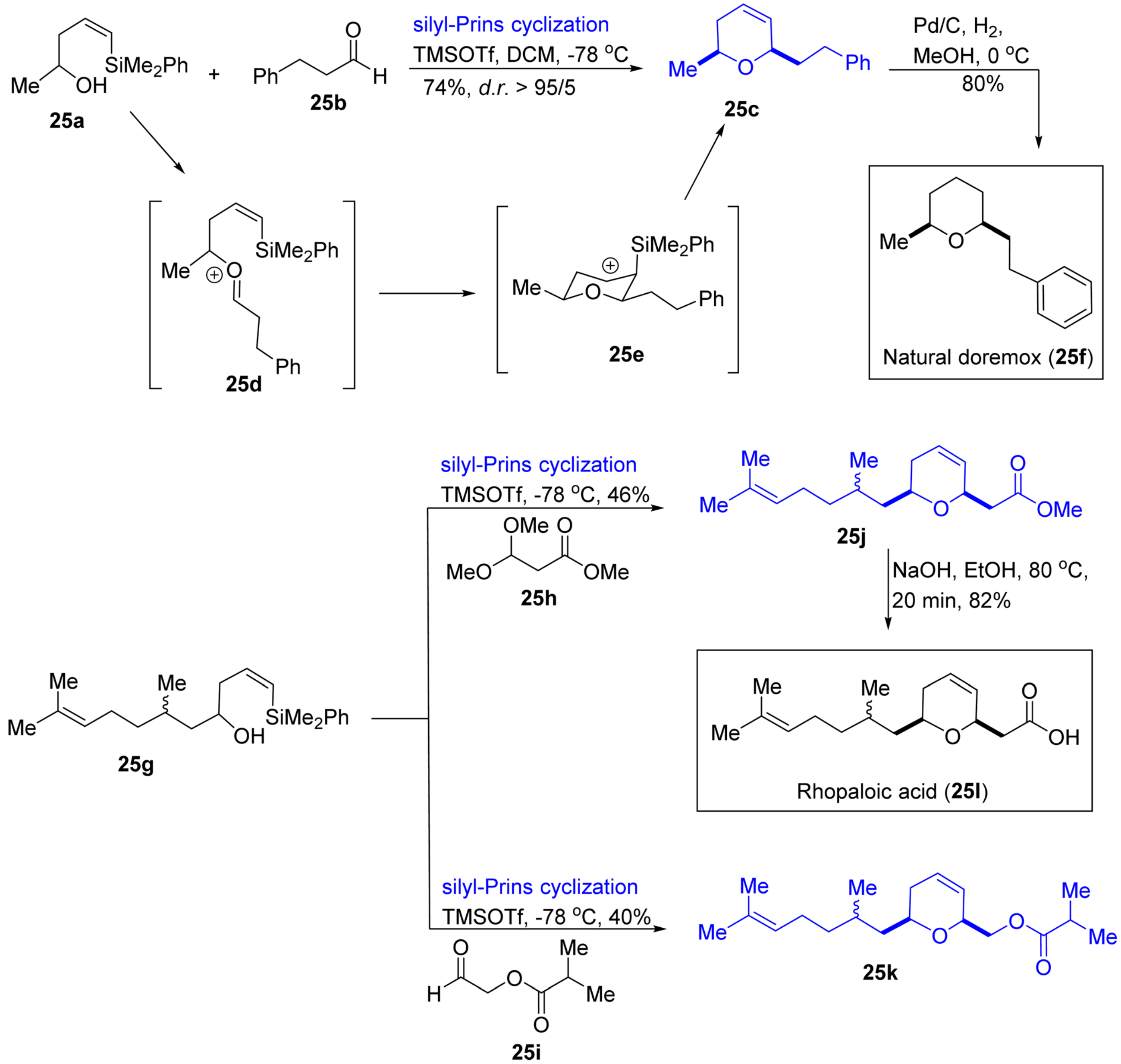


Scheme 24 Total synthesis of (−)-retigeranic acid A (**24i**) according to Chen and co-workers.[83]

from *Bipolaris* sp. TJ403-B1 by Zhang *et al.*, in 2019.[86] The natural product (**26j**) was reported to exhibit potential 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) inhibitory properties with the IC_{50} of 2.46 ± 0.07 μM, leading to the decrease in intracellular lipid concentration within HepG2 cells. Commonly, bipolarolides A and B contain caged 5/6/6/6/5 framework with seven continuous stereogenic centers. Apart from isolation, the biosynthetic pathway was also proposed by Zhang[86] *et al.* for achieving **26j** and **26i** from ophiobolin F *via* Prins cyclization. However, the first total synthesis of these natural products was accomplished through biologically inspired cascade cyclization by Li and co-workers,[87] in 2024. The synthetic sequence began with the formation of alkenyl bromide **26b** from established (4*S*)-hydroxycyclopent-2-enone **26a** over few steps. Next, bromide **26b** was reacted with *t*-BuLi to produce alkenyllithium species which were then treated with aldehyde **26c** (prepared from readily available (−)-citronellal) to give rise to vinyl alcohol **26d** which led to the construction of 5/8/5 tricycle **26e**, over a few steps. The compound **26e** then underwent sequential hydrogenation and mesylation, followed by *tert*-butyldimethylsilyl (TBS) group cleavage and subsequent oxidation to give cyclopentadiene **26f** which was isomerized to **26g.** At this stage of synthesis, not only the *cis*-fused 5/8 ring was forged but also the stereocenter was correctly established at carbon 3. The synthesized compound **26f** (during its purification) provided an unexpected compound **26h** (5% yield) which was the product of Prins-facilitated ether cyclization. Thus, the conditions were optimized for the better conversion to compound **26h**, which was then achieved in an overall yield of 92% by employing 4-methylbenzenesulfonic acid pyridinium salt (PPTS). In the next step, the natural products **26i** and **26j** were obtained from Prins product **26h** over a number of steps in 91% and 95% yield, respectively (Scheme 26).

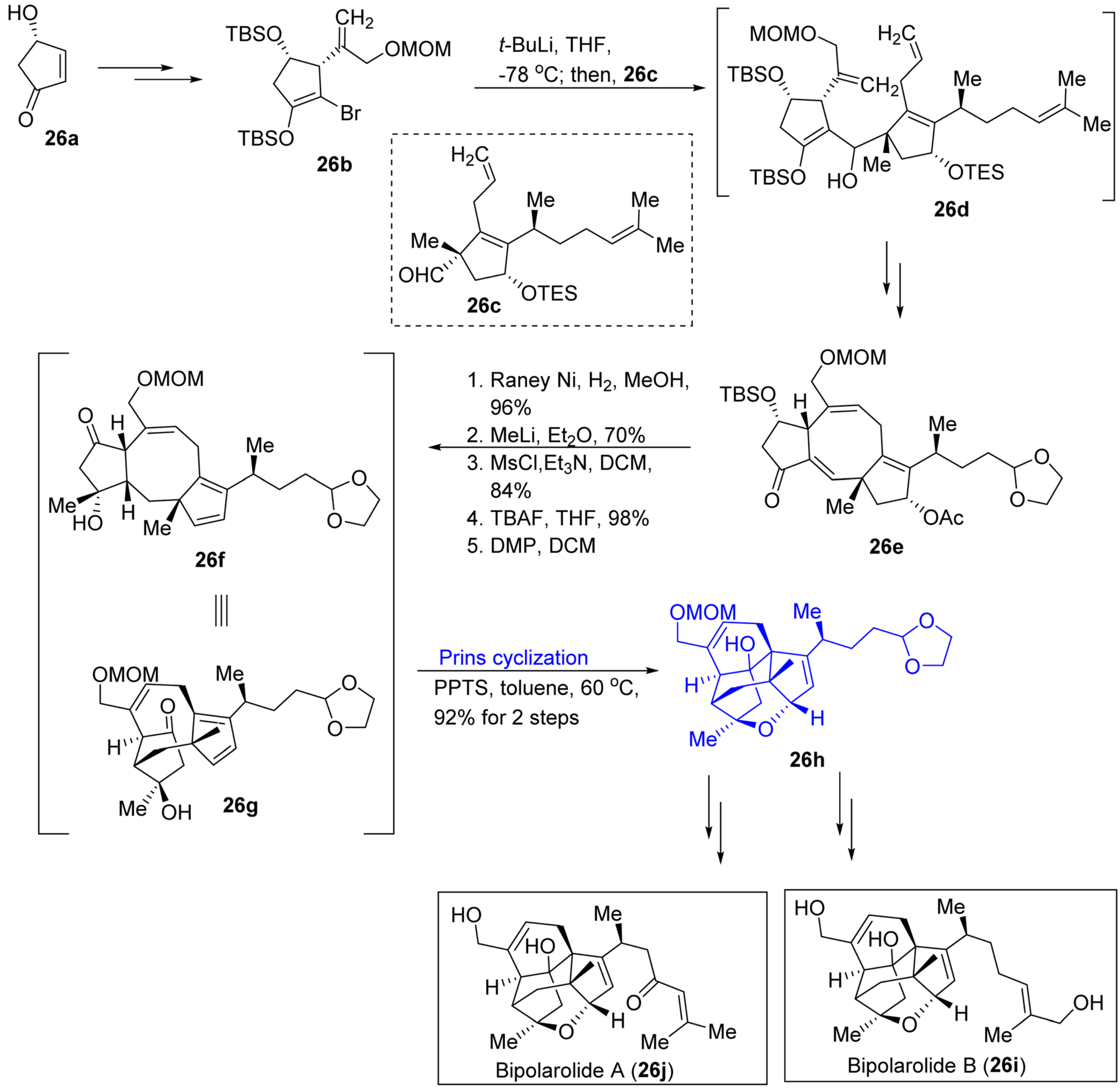
2.2.13. (−)-Lucidumone synthesis.

Lucidumone, a novel cage-like Ganoderma meroterpenoids isolated from *Ganoderma lucidum* by Cheng and colleagues, contains polycyclic 6/5/6/6/5 ring structure with unmasked secondary alcohol, indanone scaffold and bicyclo[2.2.2]octane framework having six



Scheme 25 Synthesis of natural doremox derivative (**25f**) and rhopaloic acid (**25l**) according to Peña and co-workers.[85]

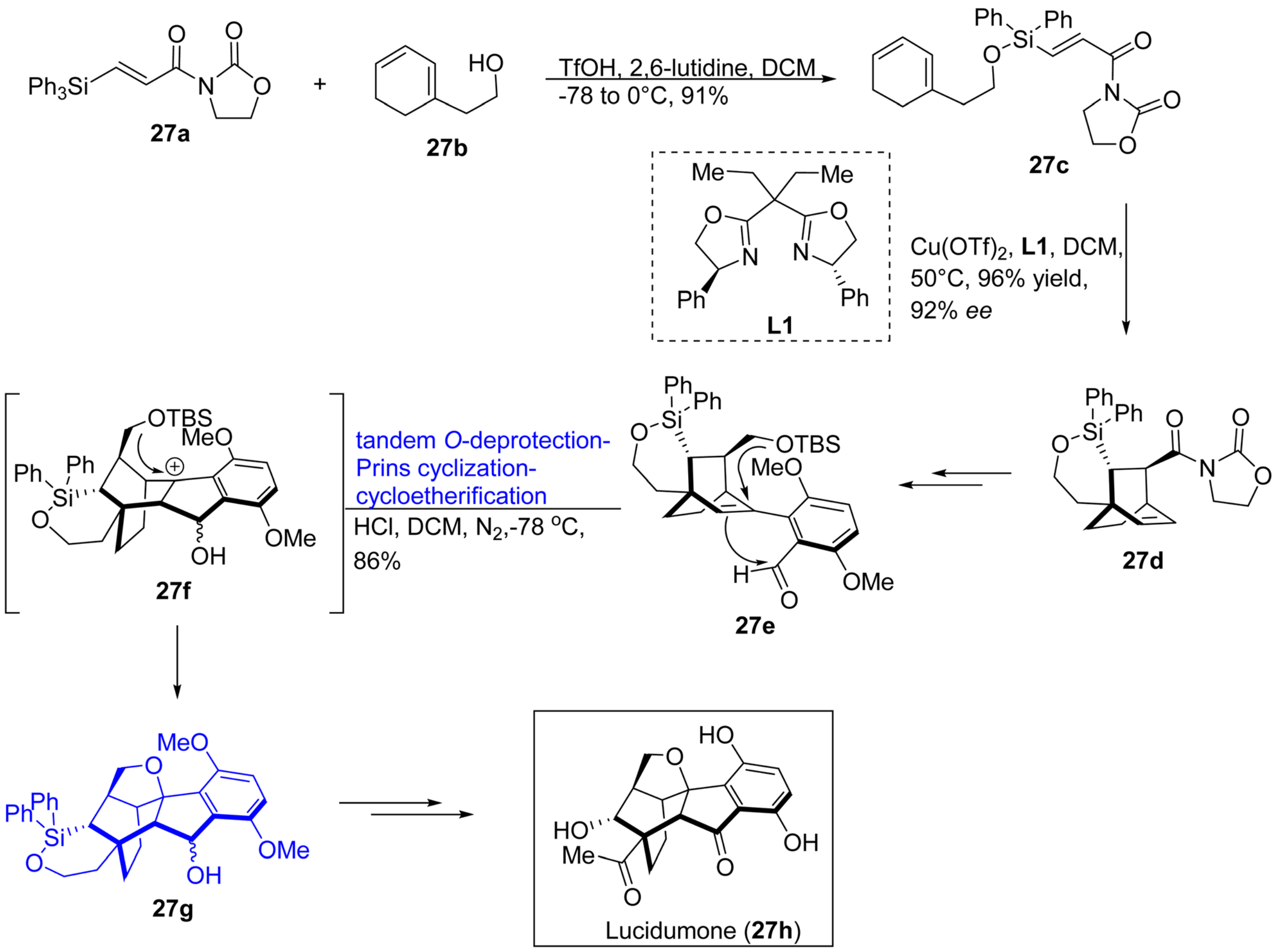
stereogenic centers.[88] The enantiomers of lucidumone display robust inhibition of COX-1 and COX-2. Selectively, (−)-lucidumone (**27h**) shows inhibition against COX-2 by binding to Ser530 and Tyr385 residues, proving as a therapeutic lead for the treatment of inflammatory diseases. The biological relevance and structural complexity renders **27h** a promising candidate for synthetic chemists. In 2024, Liao and co-workers[89] accomplished the enantioselective synthesis of natural (−)-lucidumone, involving Cu-assisted asymmetric silicon-based intramolecular Diels–Alder reaction to construct the bicyclo[2.2.2]octane architecture and sequential *O*-deprotection, Prins reaction, cycloetherification, and oxidation reactions for the concurrent formation of THF and indanone motif. The total synthesis of **27h** began with the construction of silyl ether **27c**. For this, commercially available silyl-substituted acrylate imide **27a** was treated with triflic acid, followed by the treatment with primary alcohol **27b**, resulted in the preparation of silyl ether **27c** (91% yield). Next, the Diels–Alder reaction of obtained compound **27c** was realized employing the optimized conditions ($Cu(OTf)_2$, ligand (*S*,*S*)-**L1**) to afford cycloadduct **27d** (96% yield, 92% *ee*). The obtained asymmetric bicyclo[2.2.2]octane intermediate **27d** then gave substituted tetracycle **27e** (69% yield) in a series of steps. Afterwards, tetracycle **27e** was transformed into the diastereomeric hexacyclic intermediate **27g** (86% yield) through intermediate **27f** by acid-mediated tandem *O*-deprotection-Prins cyclization-cycloetherification under optimal conditions (DCM, HCl, −78 °C, 24 h). Next, hexacyclic intermediate **27g** gave rise to desired **27h**, in 70% yield, over



Scheme 26 Total syntheses of bipolarolides A (**26j**) and B (**26i**) according to Li and co-workers.[87]

a few steps (Scheme 28). This study demonstrates the feasibility of Prins cyclization towards the synthesis of biologically active (−)-lucidumone (Scheme 27).

2.2.14. 11-*Epi*-badkhysin synthesis. Badkhysin, an intricate 6,12-guaianolide-type sesquiterpene lactone, extracted from *Ferula oopoda* roots, contains 5-7-5 tricyclic ring structure characterized by sequence of five stereocenters with *cis*-fused γ-butyrolactone functionality.[90] In 2024, Xu and co-workers[91] accomplished the asymmetric synthesis of 11-*epi*-badkhysin (**28m**) employing Prins cyclization as one of the significant steps. The flexible total synthesis commenced with the coupling of dioxinone-based lithium dienolate (obtained from **28b**) and chiral aldehyde **28a** through vinylogous addition, to give alcohol **28c** (77% yield). Next, isopropenyl alkene functionality in **28c** was subjected to the oxidative cleavage to give hemiketal **28d** (87% yield). Further, various Prins cyclization conditions were investigated to get the desired product but the steric strain due to protons on carbon 4 and 7 in structure **28e** inhibited product formation. Thus, the authors inferred that the stereochemistry inversion at C-6 might circumvent this unfavorable interaction to enable efficient cyclization through framework **28f**. Based on this observation, alcohol **28c** was subjected to oxidation, reduction, and oxidative cleavage (osmium tetroxide/sodium periodate), leading to the formation of another hemiketal **28g** (92% yield) with stereochemistry inversion at C-6. Compound **28g** was then treated with Prins cyclization conditions

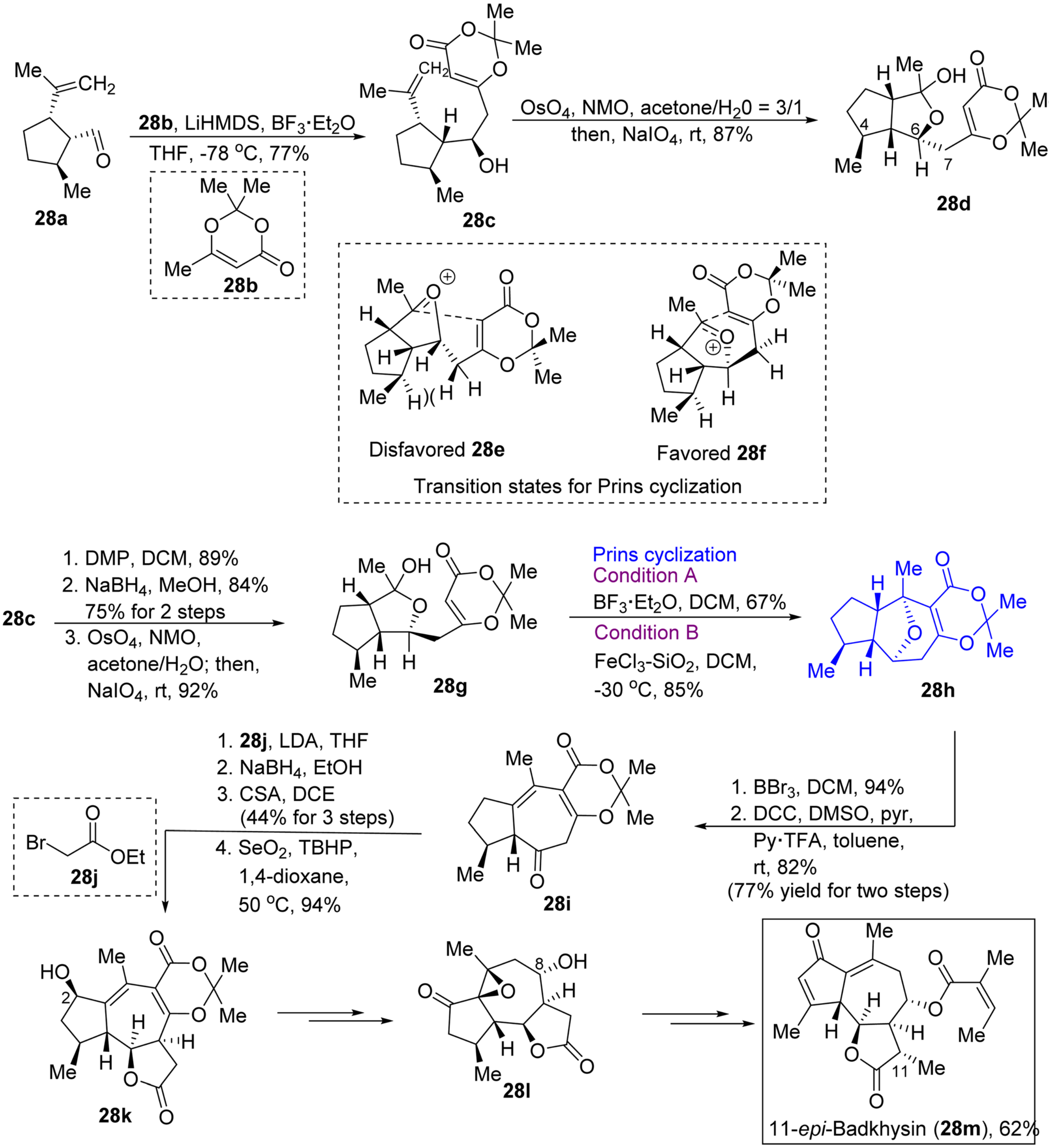


Scheme 27 Total synthesis of (−)-lucidumone (**27h**) according to Liao and co-workers.[89]

($BF_3 \cdot Et_2O$, DCM) to generate the intended adduct **28h** (67% yield). In order to enhance the product yield, the conditions for Prins cyclization were optimized (silica-based $FeCl_3$ and DCM), which then gave desired oxa-bridged adduct **28h** in 85% yield. After obtaining the intermediate **28h**, next, the focus was on installing *cis*-fused γ-butyrolactone functionality. To this end, intermediate **28h** was reacted with BBr_3, followed by the treatment under Pfitzner–Moffatt reaction conditions, to furnish ketone **28i** (77% yield for two steps). Next, ketone **28i** sequentially underwent alkylation with ethyl 2-bromoacetate **28j**, reduction and lactonization, in conjugation with installation of hydroxyl functionality on carbon 2 with selenium dioxide and *tert*-butyl hydroperoxide, affording γ-butyrolactone intermediate **28k** in excellent yield. Next, compound **28k** afforded the desired alcohol intermediate **28l** in a series of steps. Finally intermediate **28l** was transformed into **28m** (62% yield) over a few steps, which was then identified as 11-*epi*-badkhysin employing NMR spectroscopy (Scheme 28).

2.2.15. (±)-Rubriflordilactone A synthesis.

(±)-Rubriflordilactone A (367), a nortriterpenoid lactone isolated from *Schisandra rubriflora* (herbal medicine) in 2006 by Sun and colleagues[92] which contains unique polyfunctionalized aromatic moiety and displays *anti*-HIV properties. In 2024, Zheng and co-workers[93] reported the total synthesis of **367**. The synthesis commenced with the preparation of intermediate **29d** which was the required substrate for key Prins cyclization reaction. To this end, phenol **29a** was subjected to Fries–Finck rearrangement and Nazarov cyclization, followed by sequential Rosenmund–von Braun cyanation, masking of phenol hydroxyl moiety, ketone-carbonyl's reduction and cyano group's partial reduction, to generate aldehyde **29b** (60%). Next, aldehyde **29b** was treated with *N*,*N*,*N*′-trimethylethylenediamine in the presence of *n*-butyllithium, followed by the treatment with isopentenyl chloride and sodium borohydride to afford olefin **29c** (71% yield). Further, compound **29c** was sequentially transformed into **29d** over few steps. After achieving the required substrate **29d**, key Prins cyclization reaction was investigated. In this regard, intermediate **29d** was treated with $BF_3 \cdot OEt_2$ to afford tetracyclic compounds **29e** and **29f** (yield = 58%, *d. r.* = 2.3/1) in the form of mixture. Next, tetracycle **29e** was treated with MOMCl and then subjected to Mukaiyama hydration to generate pentacyclic indanone **29g** (53% yield for two steps). Next, compound **29g** was converted to compounds **29h** and **29i** over a few steps. Finally, rubriflordilactone A (**29j**, 75% yield)

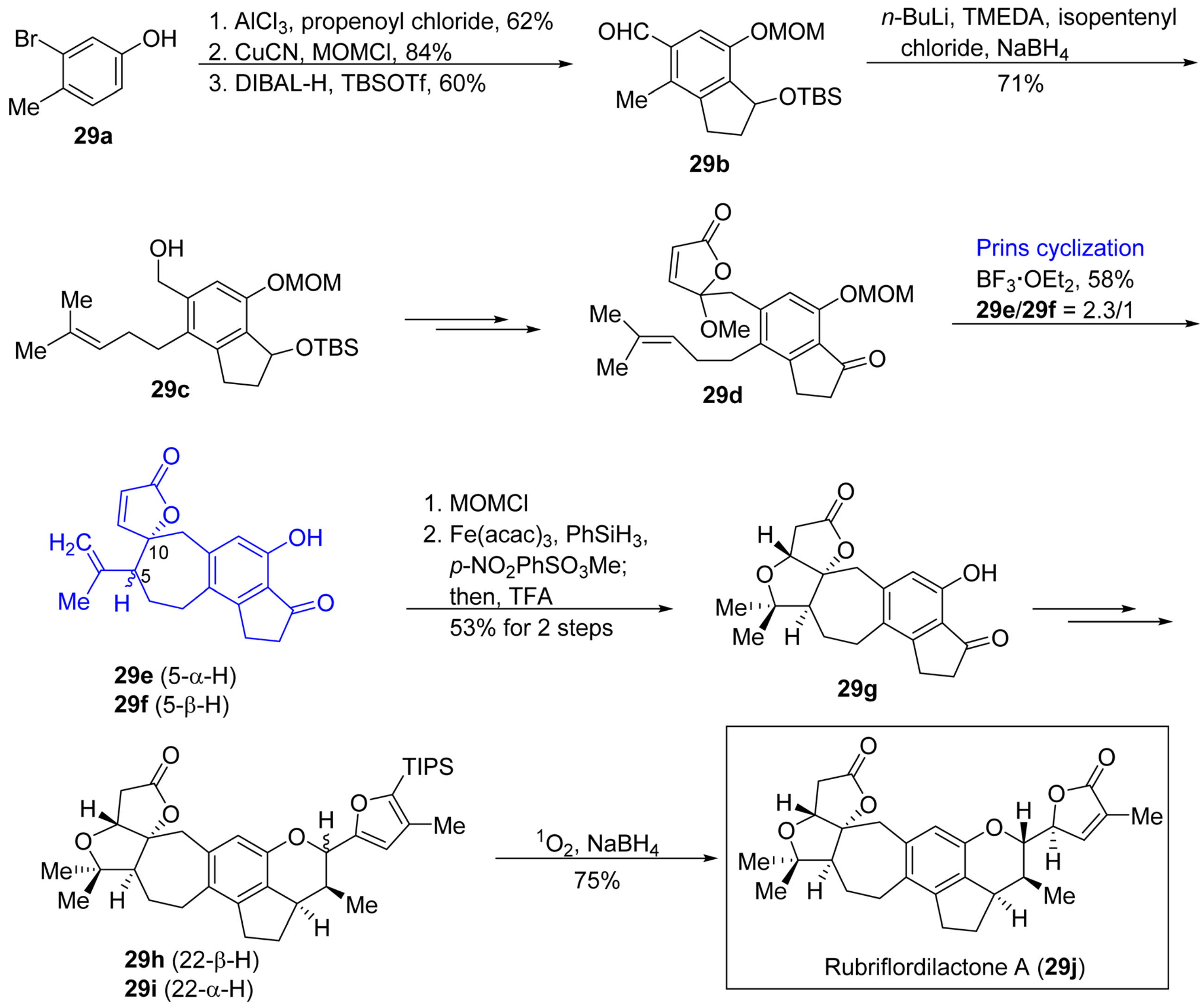


Scheme 28 Synthesis of 11-*epi*-badkhysin (28m) according to Xu and co-workers.[91]

was accomplished *via* a two-step protocol encompassing photocatalytic oxidation and NaBH$_4$-mediated reduction (Scheme 29).

2.3. Syntheses of amino acid and lipid-derived natural products

2.3.1. (−)-Galantinic acid & 1-deoxy-5-hydroxysphingolipids syntheses. Galantinic acid is a 1,3-diol-containing 7C non-proteinogenic amino acid that provides core framework for antibiotic galantin.[94] The first-time total synthesis of galantinic acid was attempted by Sakai & Ohfune.[95] Another natural product 1-deoxy-5-hydroxysphingolipid (**30g**) is found in cell membrane with notable efficacy towards prostate cancer cells.[96] In 2020, Rahman and co-workers[97] described the total syntheses of **30f** and **30g** by employing Prins cyclization reaction as a key step. The synthesis began with the preparation of homoallylic alcohol **30b**. For this purpose, benzyl ether **30a** was treated with (*S*,*S*)-Jacobsen catalyst for



Scheme 29 Total synthesis of (±)-rubriflordilactone A (**29j**) by Zheng and co-workers.[93]

hydrokinetic resolution and then subjected to reaction with vinyl Grignard reagent for regioselective ring opening, followed by debenzylation, resulting into the formation of intended homoallylic alcohol **30b** (75% yield). The obtained compound **30b** was coupled with acrolein **30c** under Prins cyclization conditions (TFA, DCM, 0 °C to 25 °C, 5 h), followed by the reaction with methanolic potassium carbonate, generating 2,4,6-*cis*-trisubstituted tetrahydropyranol **30d** (65% yield in a two-step sequence) with strong diastereoselectivity. Next, Prins product **30d** was transformed into epoxide **30e** over a few steps. The obtained common intermediate **30e** provided **30f** (89% yield) and **30g** (91% yield) in sequential steps. The syntheses of other bioactive leads including enigmol **VI**, *N*-methyl enigmol **VII**, SSR-enigmol **VIII**, SRR-enigmol **IX**, were also reported to be achieved from common epoxide intermediates (Fig. 2). Altogether (−)-galantinic acid and 1-deoxy-5-

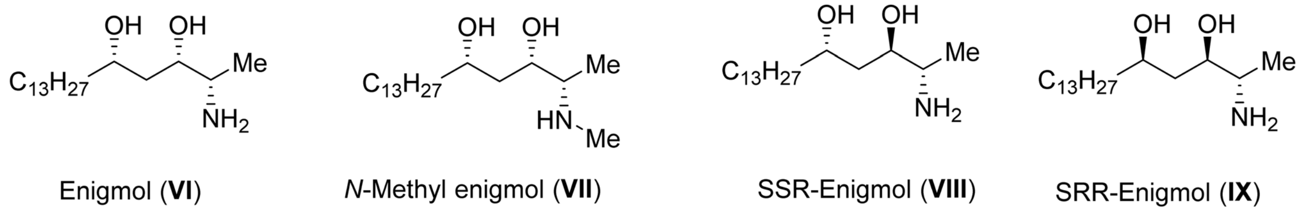
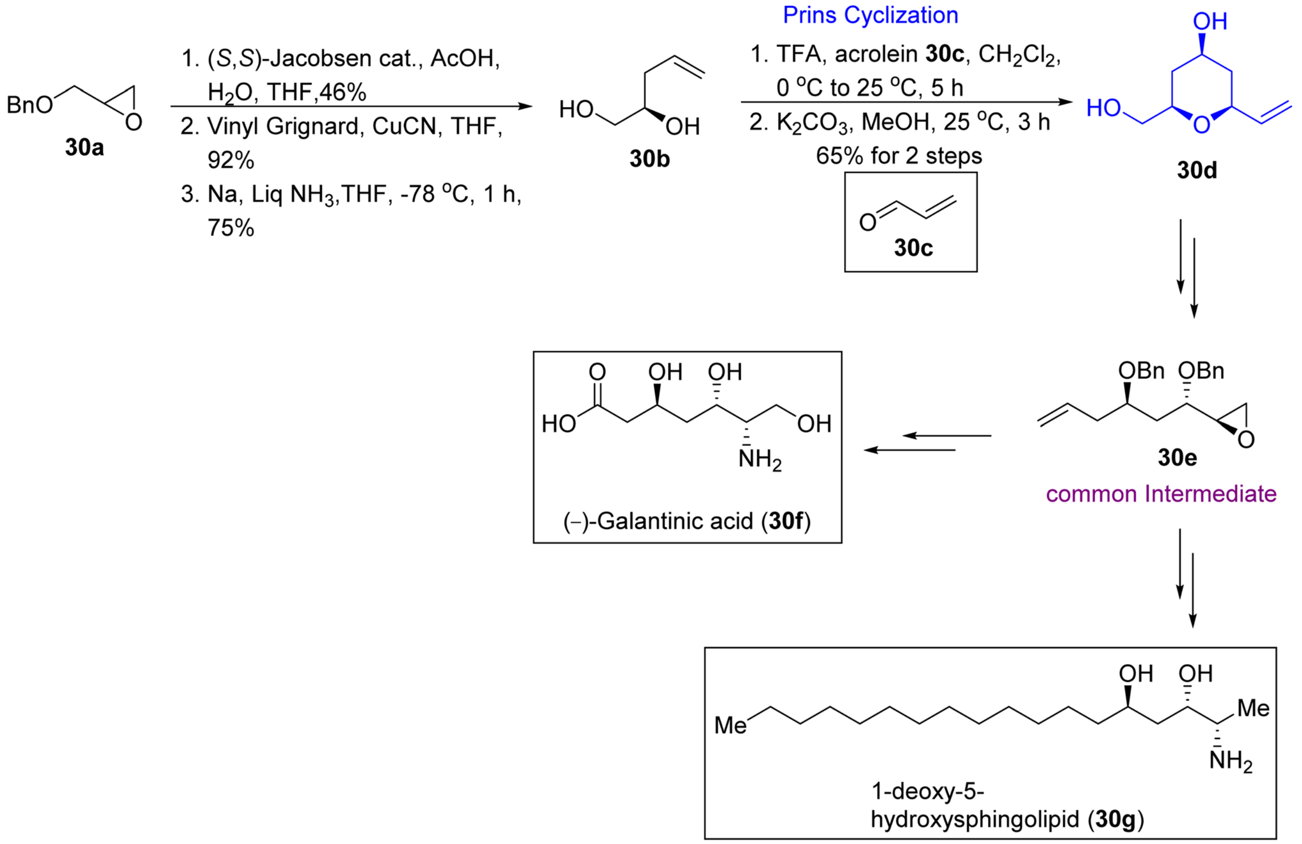


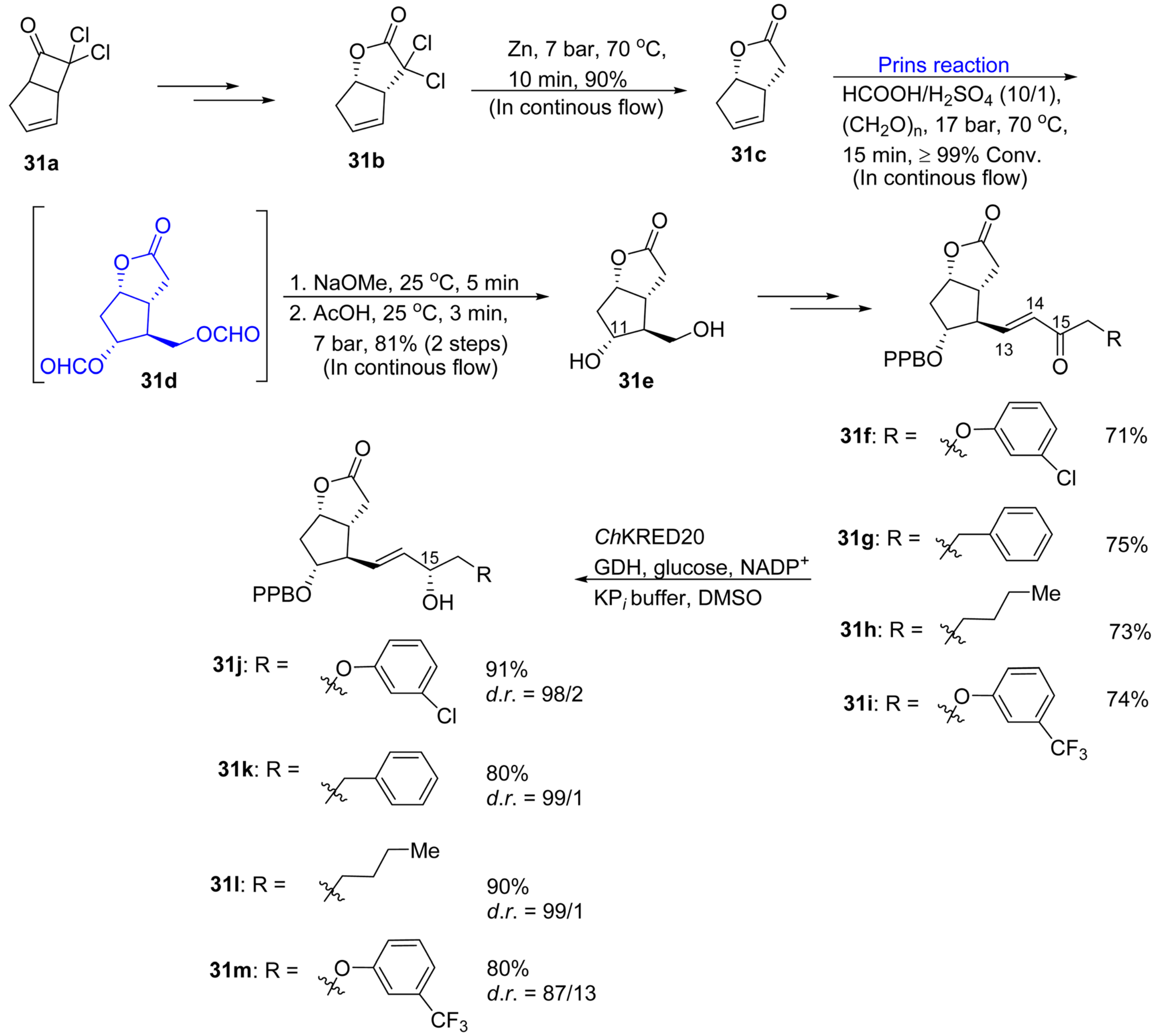
Fig. 2 Bioactive leads *via* common intermediates by Rahman and co-workers.



Scheme 30 Total syntheses of (–)-galantinic acid (30f) and 1-deoxy-5-hydroxysphingolipid (30g) according to Rahman and co-workers.[97]

hydroxysphingolipid were synthesized in seven linear steps each, with overall yields of 16.79% and 15.59%, respectively. The protocol described herein successfully utilizes Prins cyclization to afford natural products along with their congeners through the utilization of common epoxide intermediate (Scheme 30).

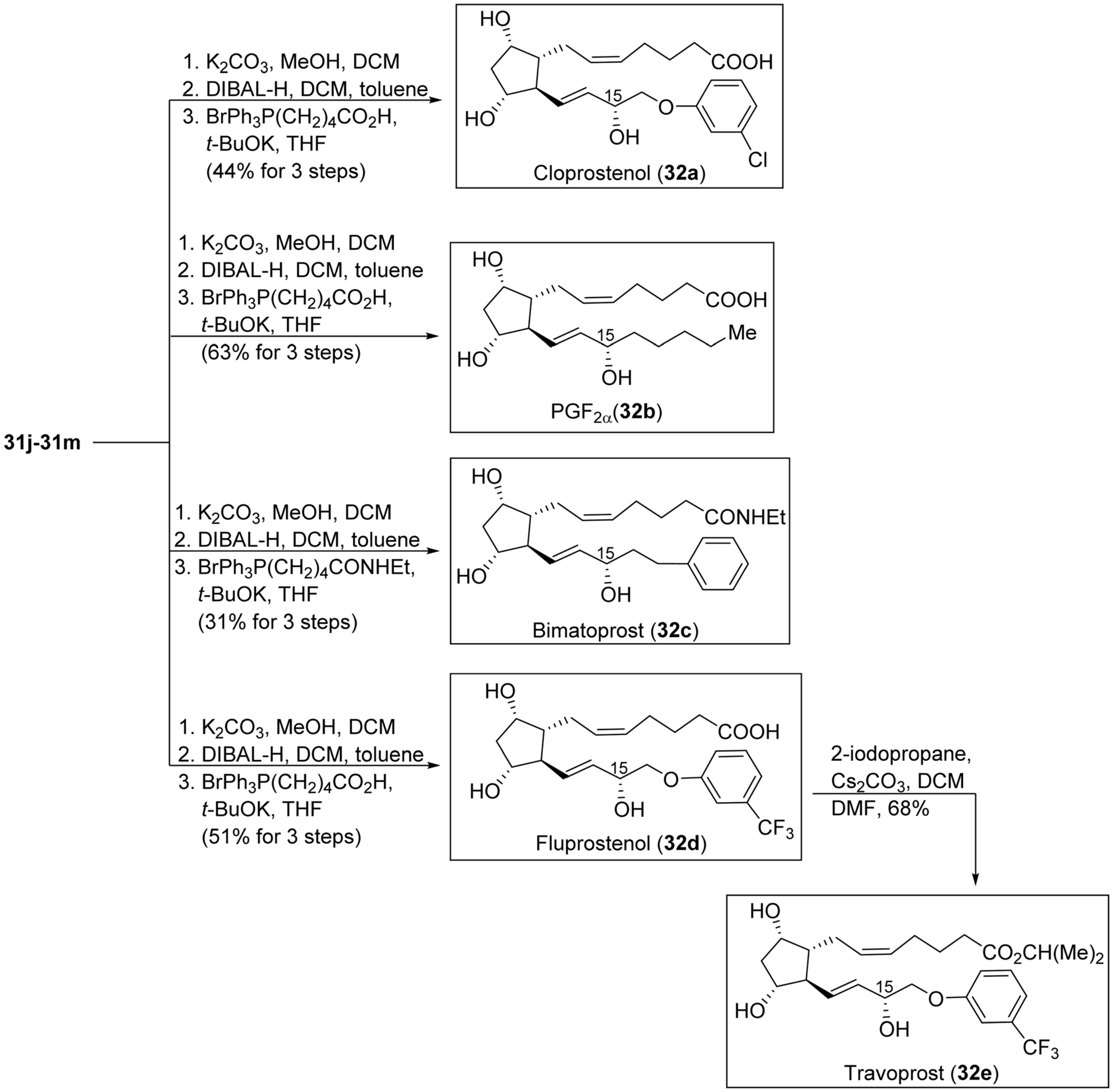
2.3.2. Synthesis of prostaglandins. Up to now, more than twenty prostaglandins have been established as therapeutic compounds including cloprostenol, fluprostenol, bimatoprost, and travoprost.[98] In 2021, Zhu and co-workers[99] adopted a common, modular and efficient route to prostaglandins. The synthetic route involved the stereocontrolled preparation of versatile lactone intermediate **31b** from bicyclic ketone **31a** over a number of synthetic steps. Next, dechlorination of compound **31b** was achieved in a packed reactor *via* continuous flow approach containing zinc particles, providing normal lactone **31c** (90% yield). Next, compound **31c** was added in formic acid/sulfuric acid (10/1) solution with already dissolved paraformaldehyde and then this mixture was added into polytetrafluoroethylene reactor coil, affording crude **31d** predominantly, through Prins reaction with full conversion of substrate (Scheme 30). Following the neutralization and elimination of inorganic salt, the methanolic crude **31d** was reacted with NaOMe and added in reactor coil for deformylation through T-junction. This reaction step was then followed by termination with AcOH to generate diol **31e** smoothly (81% 2-step yield). Thus, this three-step transformation was remarkably more expeditious than batch reactions. The compound **31e** then gave enones **31f–31i** through several transformations in isolated yields (71% to 75%) as single *E*-isomer, with newly incorporated C_{13}–C_{14} bond. Further, compound **31f** was subjected to *Ch*KRED20-mediated reduction under optimized reaction conditions to impart intended allylic alcohol **31j** in isolated yield of 91% with 97.9/2.1 *d. r.* Interestingly, α-configuration was assigned to the newly formed C-15 stereocenter in prostaglandin. Next, the prepared PPB ester **31j** was hydrolyzed into alcohol, followed by lactone reduction to hemiacetal with DIBAL-H and Wittig reaction to provide cloprostenol (**32a**) in 44% yield over a 3-step sequence. Similarly, allylic alcohols **31k–31m** were also prepared by ChKRED20-facilitated reduction from enones **31g–31i** in 80 to 90% yields with 87/13 to 99/1 *d. r.* (Scheme 31). According to the aforementioned protocol to synthesize cloprostenol (**32a**), $PGF_{2\alpha}$ (**32b**), bimatoprost (**32c**) and fluprostenol (**32d**) were also generated from **31k**, **31l** and **31m** in three steps with yields of 31%, 63%, and 51%, respectively. For the synthesis of travoprost (**32e**, 68% yield), fluprostenol (**32d**) was reacted with 2-iodopropane employing cesium carbonate in a mixture of DCM/DMF. Hence, the syntheses of cloprostenol (**32a**), $PGF_{2\alpha}$ (**32b**), bimatoprost (**32c**), fluprostenol (**32d**) and travoprost (**32e**) were accomplished in eleven to twelve steps, in 3.8 to 8.4% overall yields (Scheme 32).



Scheme 31 Utilization of Prins reaction in common synthetic route towards the synthesis of prostaglandins **32a–32e**.

2.4. Synthesis of polyketide-derived natural products

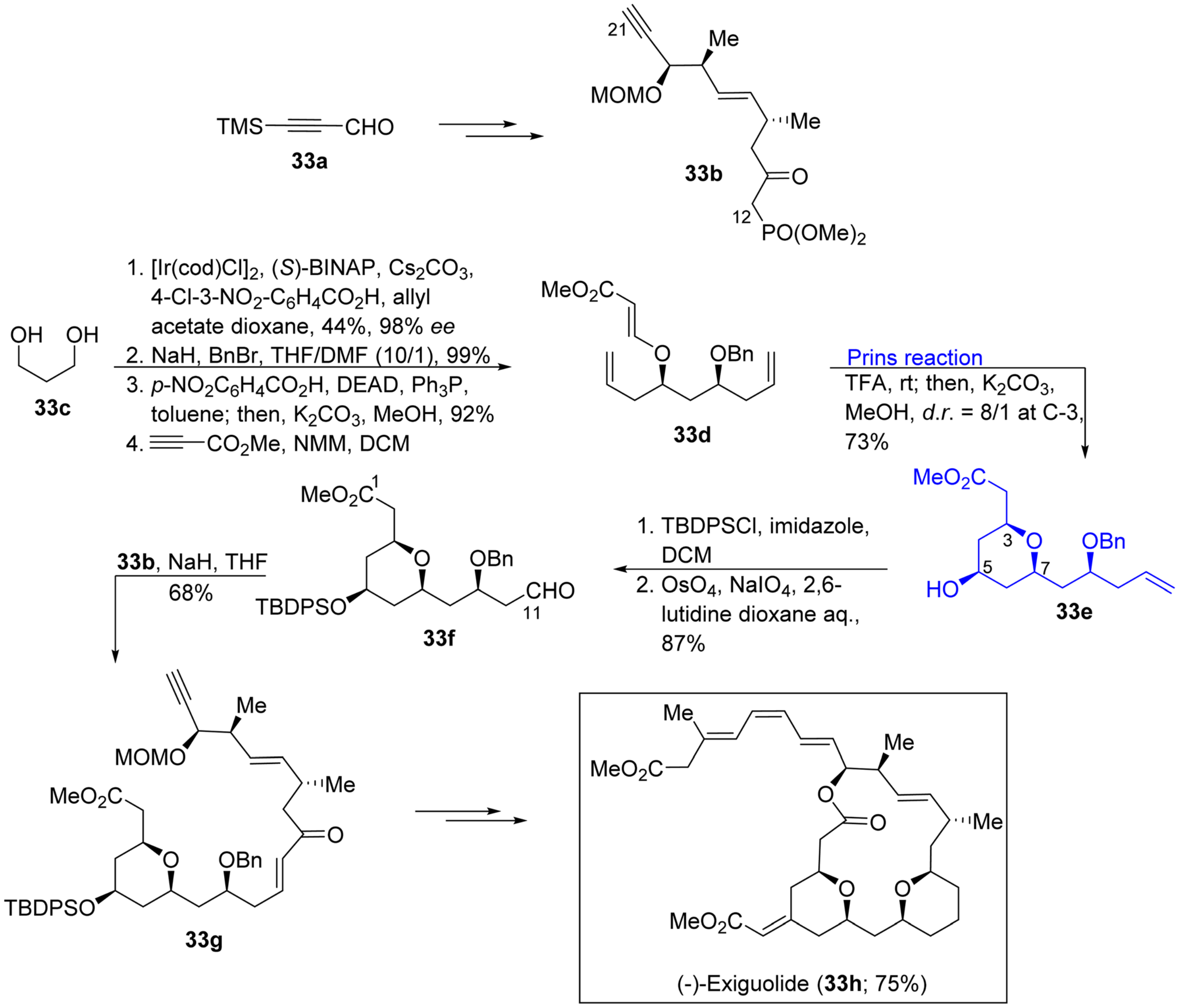
2.4.1. Exiguolide synthesis. Exiguolide, a twenty-membered macrolide with a novel bis-THP structural motif, isolated in 2006 by Ohta and co-workers from *Geodia exigua Thiele*.[100] Cossy demonstrated that this natural product may be bryostatin-like which are effective protein kinase C activators and exhibit activities against cancer, HIV and Alzheimer's disease.[101] Moreover, Fuwa and Scheidt[102] proposed that exiguolide displays inhibitory activities against various cancerous cells such as human lung cell carcinoma (NCI–H460, IC_{50} = 0.60 μM), lung adenocarcinoma cells (A549, IC_{50} = 1.66 μM), pancreatic cancer (BxPC3) and breast cancer (MB-231) cells. In 2020, Oka and co-workers[103] accomplished a novel stereocontrolled 21-step synthesis of **33h** and pioneered preparation of its diastereomer *i.e.*, 15-*epi*-exiguolide **34e.** First, the C12–C21 segment *i.e.*, phosphonate **33b** was constructed from readily accessible aldehyde **33a** over a few steps. Next, C1–C11 chiral THP segment **33f** was prepared in a short-step sequence utilizing Prins reaction. In this context, 1,3-propanediol **33c** underwent sequential Ir-mediated double allylation, monobenzylation, Mitsunobu inversion and oxy-Michael addition to afford enol ester **33d**. The compound **33d** was then subjected to intramolecular Prins cyclization with TFA to give rise to THP **33e** (73% yield, *d. r.* = 8/1) and its C3-epimer. The obtained compound **33e** then underwent silylation, followed by Lemieux–Johnson oxidation to afford the intended aldehyde **33f** (87% yield). Next, the synthesized phosphonate **33b** was coupled with aldehyde **33f** through Horner–Wadsworth–Emmons (HWE) protocol in the presence of NaH, giving ester **33g** (68% yield). The compound **33g** gave the intended **33h** (75%) over a few steps (Scheme 33). Notably, the promising stereochemistry at C15 arising from stereochemical transfer *via* Johnson–Claisen



Scheme 32 Syntheses of cloprostenol (32a), $PGF_{2\alpha}$ (32b), bimatoprost (32c), fluprostenol (32d) and travoprost (32e) according to Zhu and co-workers.[99]

rearrangement led to investigating secondary alcohol inversion in compound **34a**. For this purpose, the compound **34a** was then converted into phosphonate **34b** over a few steps. The resulting compound **34b** underwent HWE reaction with the already synthesized aldehyde **33f** to form compound **34c** (83% yield). Next, reaction of compound **34c** with Stryker's reagent ($Cu(OAc)_2 \cdot H_2O$, BDPB (1,2-bis(diphenylphosphino)benzene), PMHS (polymethylhydroxysilane, a hydride source) and TMSI, followed by silane reduction, provided THP ring-containing compound **34d**, in 71% yield (*d.r.* > 20/1). Noteworthily, *cis* stereochemistry was detected in prepared compound **34d**. The obtained compound **34d** was converted into desired 15-*epi*-exiguolide (**34e**; 100% yield, Scheme 36) over a few steps (Scheme 34).

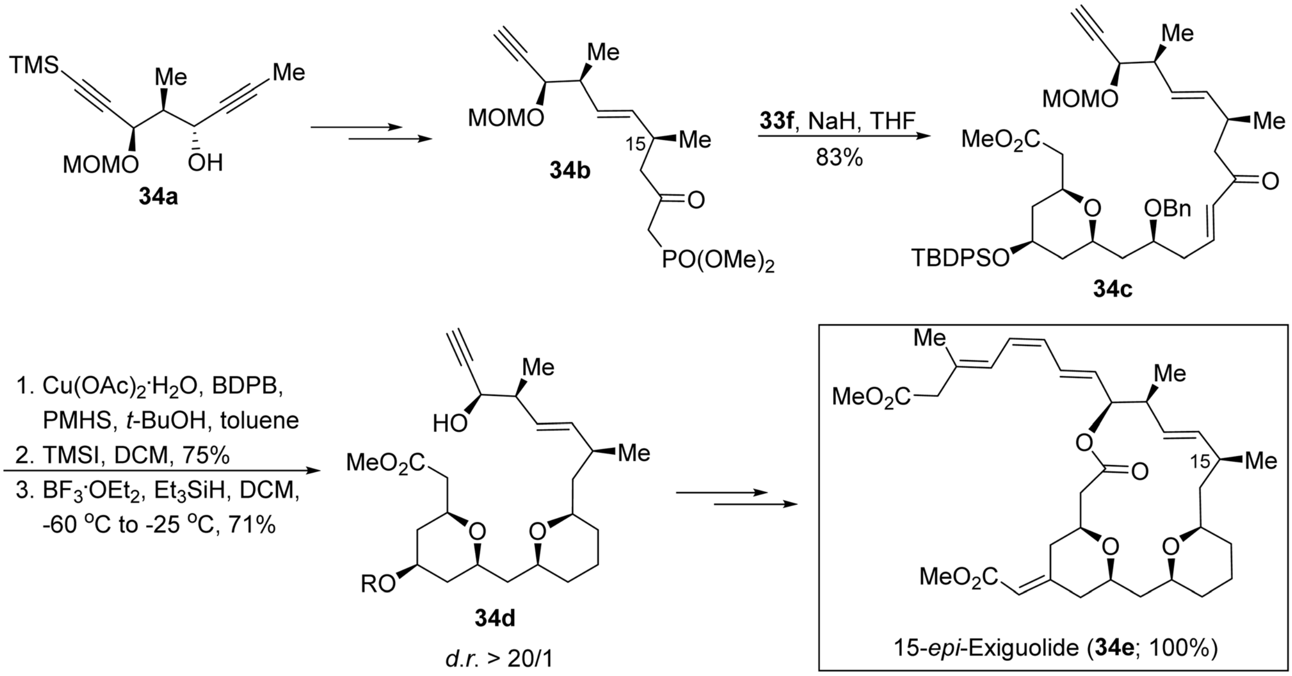
2.4.2. **Tetraketide & euscapholide syntheses.** Tetraketide (**35e**) and euscapholide (**35f**), the natural products isolated from *Euscaphis japonica* leaves, feature dioxabicyclo[3.3.1]nonan-3-one and α,β-unsaturated ᴅ-lactone moieties.[104] Owing to the novel structural motif, electrophilic nature, and diverse bioactivities such as, antifungal, antibacterial, analgesic, antidiabetic, antiparasitic, and cytotoxic properties, these natural products have garnered significant interest by research communiuty. The scarce availability of tetraketide and euscapholide prompted Biradar and co-workers[105] in 2022, to achieve their



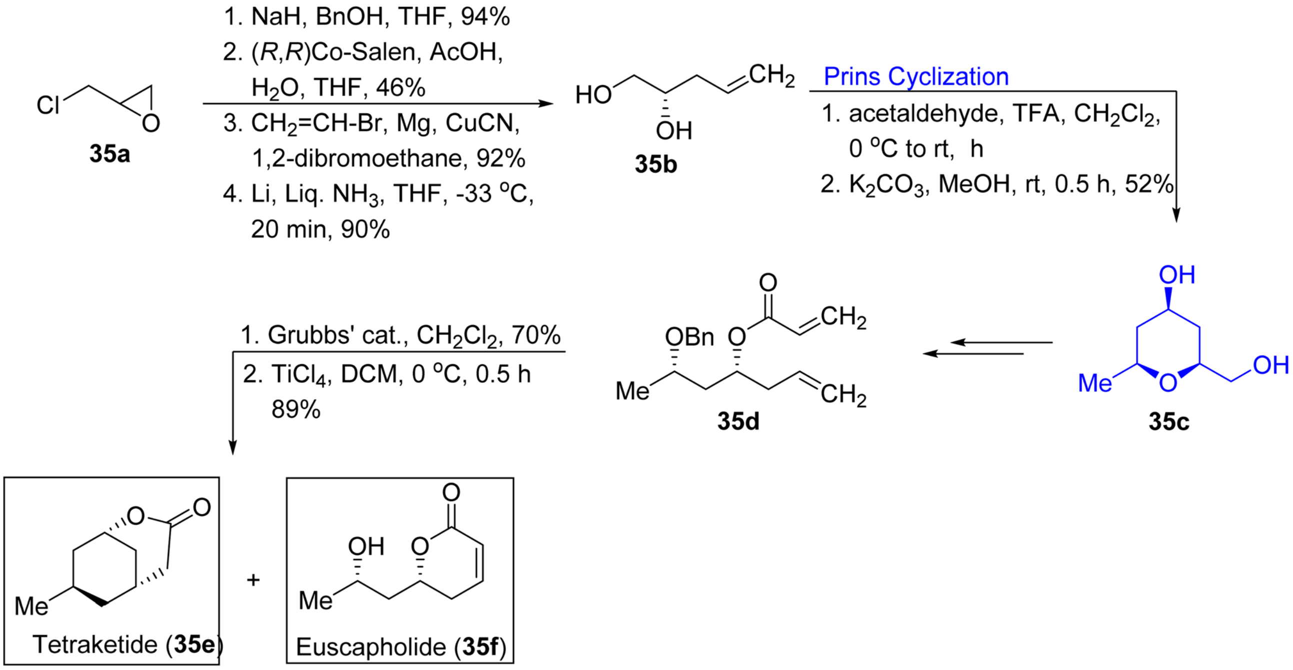
Scheme 33 Synthesis of exiguolide (**33h**) according to Oka and co-workers.[103]

total syntheses *via* unified approach. The total syntheses began with the preparation of (*S*)-pent-4-ene-1,2-diol which served as the precursor for achieving Prins cyclization reaction. Notably, epichlorohydrin **35a** can serve as a valuable precursor to both homoallylic alcohol enantiomers (*R*) and (*S*). To this end, racemic epichlorohydrin **35a** underwent reaction with sodium hydride, followed by Jacobsen's kinetic resolution with (*R*,*R*)–(salen)Co(II) complex, and subsequent regioselective epoxide ring opening and debenzylation generated homoallylic alcohol **35b** (90% yield). Next, the compound **35b** was subjected to key Prins cyclization reaction with acetaldehyde in the presence of TFA and DCM, followed by hydrolysis, affording 2,6-*cis*-THP **35c** exclusively (52% yield). Further, a sequence of synthetic steps transformed compound **35c** into ester **35d**. The obtained key intermediate **35d** underwent ring-closing metathesis (RCM) reaction with Grubbs' catalyst, followed by $TiCl_4$-mediated debenzylation to afford **35e** and **35f** *via* oxa-Michael reaction, in combined yield of 89%. Both natural products **35e** and **35f** were synthesized in a ten-step sequence with 10% overall yield. Thus, this synthetic strategy facilitates the synthesis of α-pyrones and α,β-unsaturated *d*-lactones derivatives (Scheme 35).

2.4.3. Cryptoconcatone H synthesis. The styryl-bearing tetrahydropyranol-dihydropyranone, cryptoconcatone H (**36h**), extracted from the branches and leaves of *Cryptocarya concinna* (monsoon evergreen) by Luo, and coworkers.[106] In 2023, Ford and co-workers[107] achieved the facile and concise syntheses of **36h** and its C6 diastereomer **36i** using Prins cyclization as a key contributor. Their synthetic approach for the natural product cryptoconcatone H (**36h**) began with the preparation of diols *syn*-**36b** and *anti*-**36c** from 1,1,3,3-tetramethoxypropane **36a** through the procedure reported by Samoshin[108] *et al.* Next, the Mitsunobu esterification of *anti*-**36c** with crotonic acid **36d** gave homoallylic alcohol **36e** (67% yield). The obtained compound **36e** underwent Prins cyclization reaction with cinnamaldehyde **36f** to acquire 2,4,6-*cis*-tetrahydropyranol ring structure found

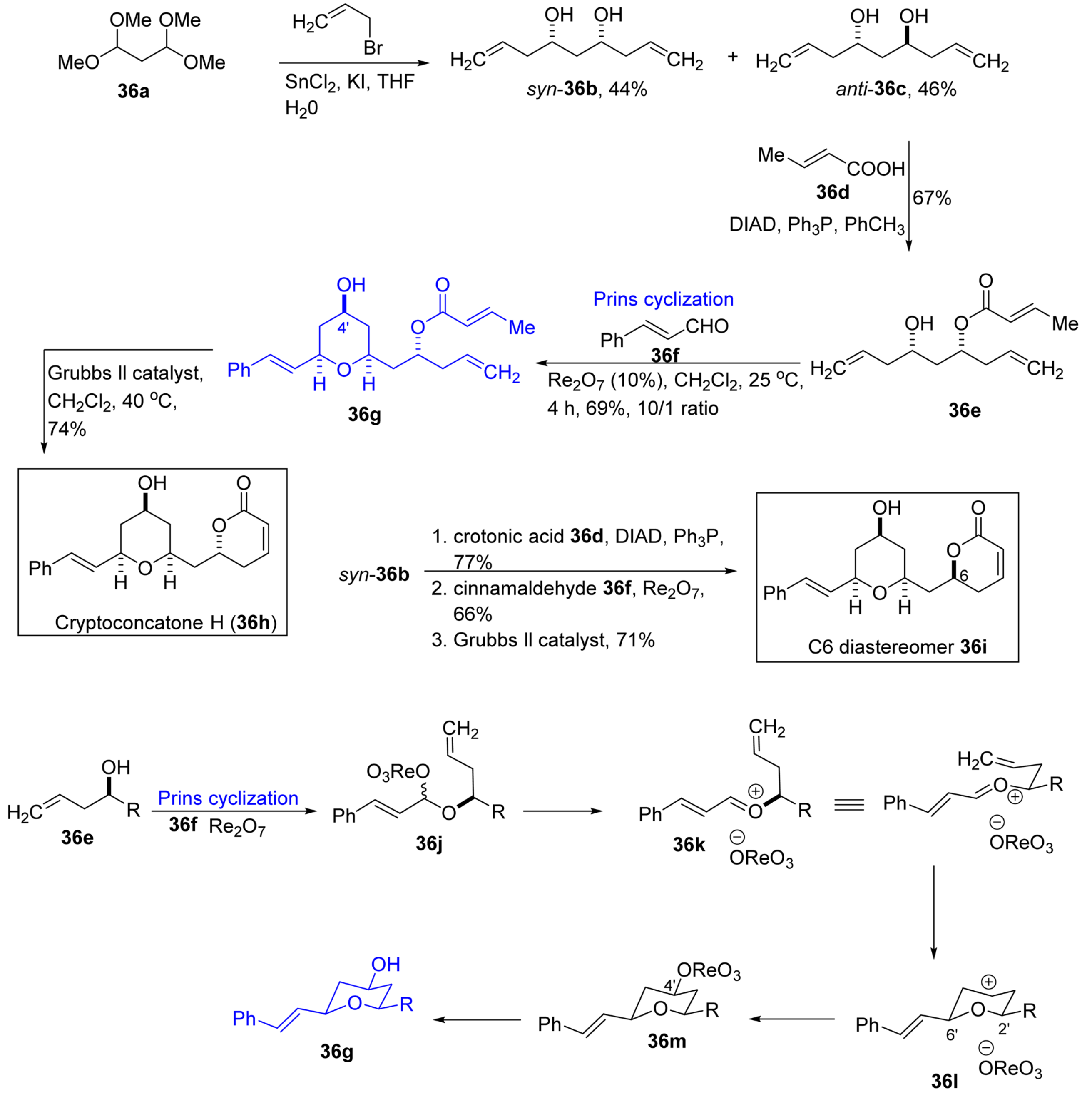


Scheme 34 Synthesis of 15-*epi*-exiguolide (**34e**) according to Oka and co-workers.[103]



Scheme 35 Total syntheses of tetraketide (**35e**) and euscapholide (**35f**) according to Biradar and co-workers.[105]

in natural product (**36h**). The optimal Prins reaction conditions for attaining 2,4,6 *cis*-tetrahydropyranol **36g** entailed Re_2O_7 (as catalyst), DCM (as solvent), and 4 hour duration. As a result, the mixture of compound **36g** and its epimer was obtained in 10/1 ratio in 69% yield. Next, dihydropyranone ring was constructed through ring-closing metathesis of utilizing Grubbs second-generation catalyst to obtain the intended **36h** (74% yield) from compound **36g**. C6 Diastereomer **36i** (71% yield) was also synthesized from diol *syn*-**36b** *via* aforementioned protocol. The stereochemistry of Prins cyclization reaction can be understood

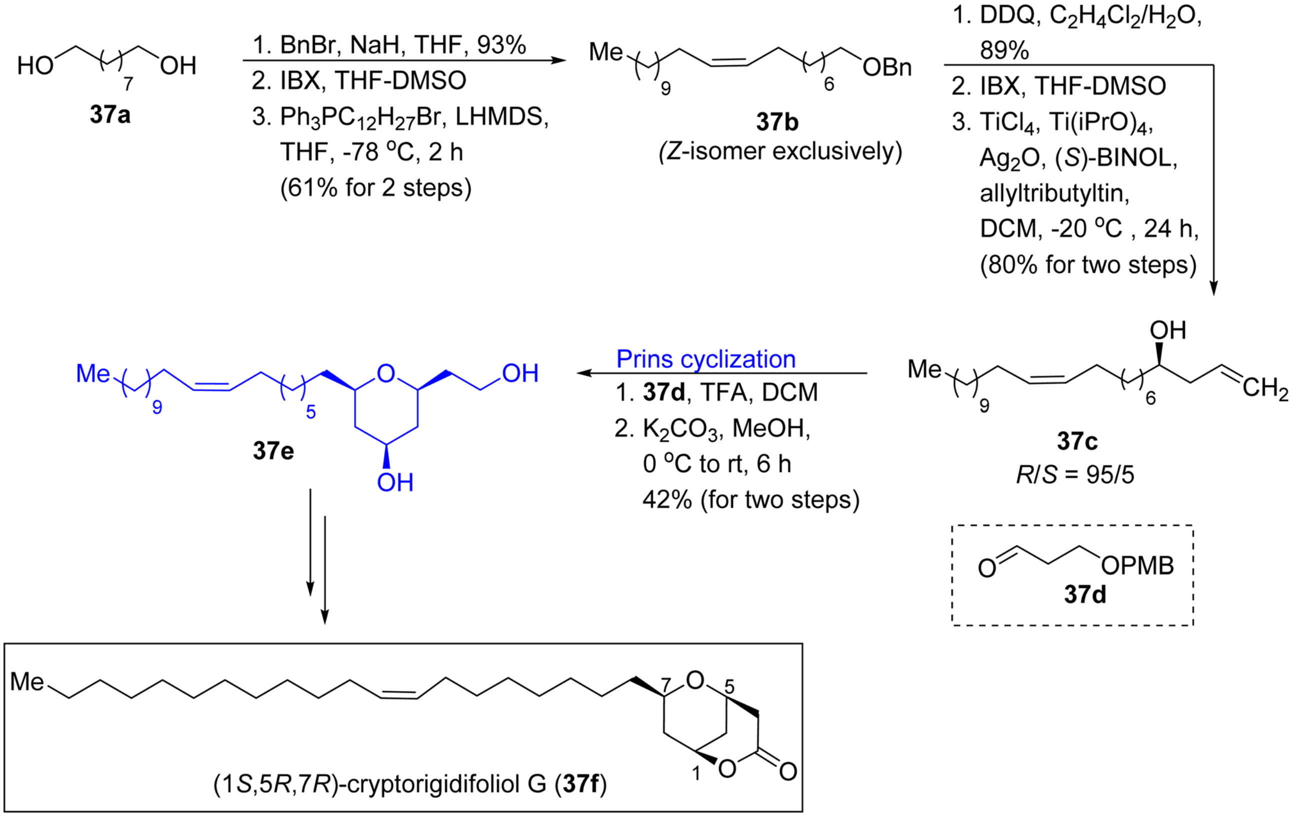


Scheme 36 Total synthesis of cryptoconcatone H (**36h**) by Ford and co-workers.[107]

by its mechanistic pathway which first involved the Re_2O_7-mediated condensation of compounds **36e** and **36f.** The resulting perrhenate ester **36j** was ionized to generate oxonium ion **36k** which was then cyclized in a chair-like geometry, resulting in *cis*-positioning substituents on carbons 2′ and 6′ through pseudoequatorial orientations, commonly found in Prins reactions. The obtained carbocation **36l** was then transformed into perrhenate ester **36m** as a consequence of the equatorial attack, which was favored by steric factors in Prins reactions featuring oxygen nucleophiles. Next, compound **36m** was made to react with perrhenic acid to produce the intended 2,4,6 *cis*-tetrahydropyranol **36g,** leading to the regeneration of Re_2O_7 catalyst. Altogether, cryptoconcatone H along with its C6 diastereomer were obtained utilizing (±)- and meso-1,8-nonadiene-4,6-diol with 32% and 36% yields, sequentially in three steps. This synthetic strategy is free from any type of protecting group and redox transformation and demonstrates the unique applicability of Re_2O_7 as the catalyst for achieving Prins cyclization (Scheme 36).

2.4.4. Cryptorigidifoliol G synthesis.

Cryptorigidifoliol G is a polyketide-derived aliphatic lactone, isolated in 2015 from *Cryptocarya rigidifolia* (family Lauraceae) root wood by Kingston

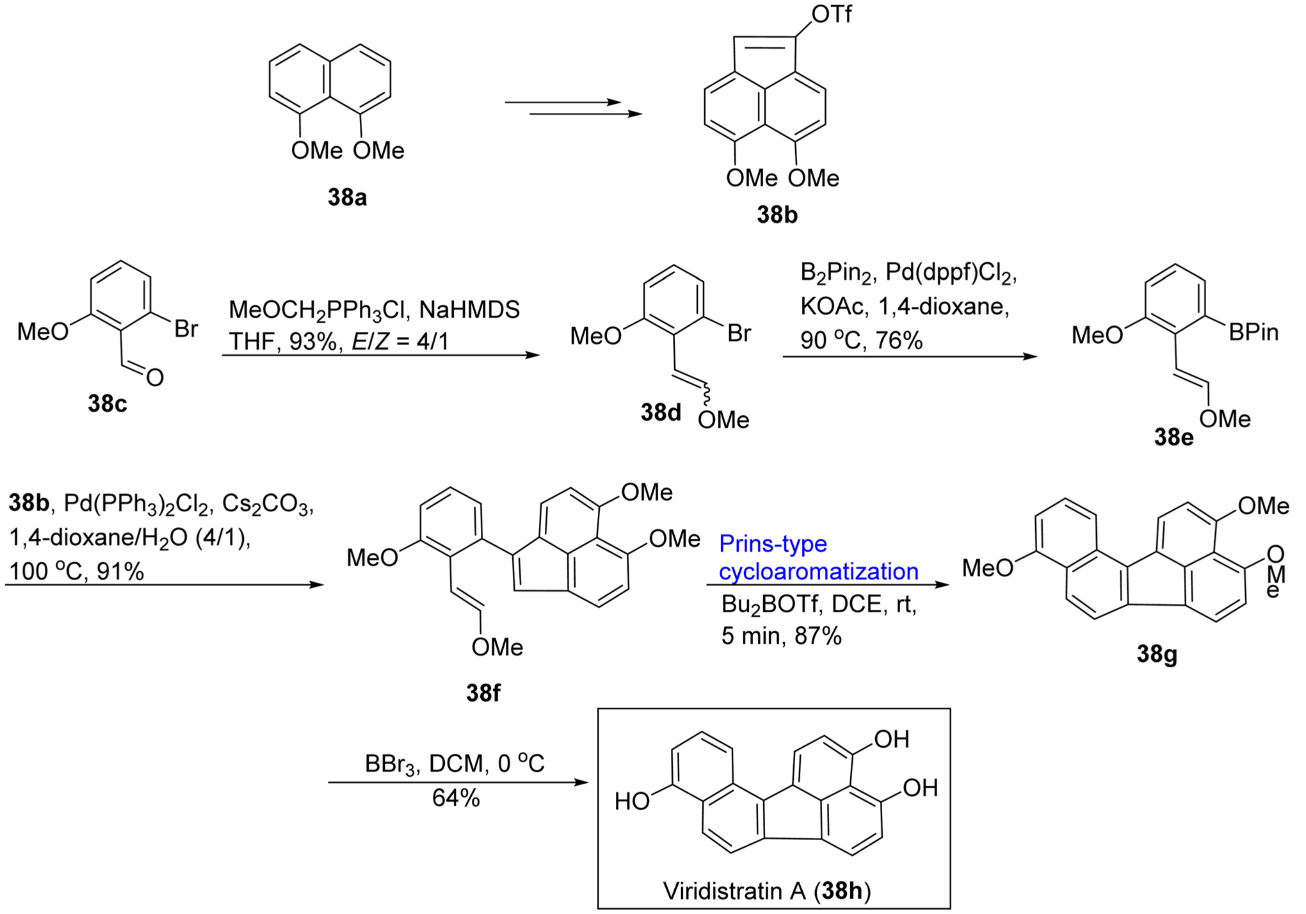


Scheme 37 Total synthesis of (1*S*,5*R*,7*R*)-cryptorigidifoliol G (**37f**) according to Choudhury and co-workers.[110]

and co-workers,[109] possesses bicyclic tetrahydropyrone scaffold with three stereocenters on carbons 1, 5 and 7 and connected to aliphatic lateral chain on carbon 7, having *Z*-olefinic bond between carbons 8′ and 9′. Moreover, cryptorigidifoliol G exhibits antiproliferative and antimalarial activity towards human ovarian cancerous cell line (A2780, $IC_{50} > 10$ μM) and *Plasmodium falciparum*'s Dd2 ($IC_{50} > 10$ μM), respectively. In 2022, Choudhury and co-workers[110] attempted the pioneering syntheses of (1*S*,5*R*,7*S*)-cryptorigidifoliol G and (1*S*,5*R*,7*R*)-cryptorigidifoliol G (**37f**). Their total synthesis of **37f** began with the protection of 1,9-nonanediol **37a** with benzyl bromide in the presence of NaH, followed by oxidation and *cis*-Wittig olefination, that resulted in the formation of single *Z*-isomer **37b** (61% yield for two steps). Next, compound **37b** was subjected to oxidative cleavage, oxidation, silica gel purification and Keck allylation to afford homoallyl alcohol **37c** (80% yield in a two-step sequence, 95/5 enantiomeric ratio). Next, alcohol **37c** was subjected to Prins cyclization (TFA, DCM, 6 h) with aldehyde **37d** in conjugation with hydrolysis to generate diol **37e** (42% yield in a two-step sequence). Further, diol **37e** provided desired **37f**, in 82% yield, over a few step involving sequence (Scheme 37).

2.4.5. Viridistratin A synthesis. In 2020, the secondary metabolite viridistratin A (**38h**) isolated from *Annulohypoxylon viridistratum* stomata, contained highly oxidized benzo[*j*]fluoranthene architecture and showed wide range of cytotoxic and antimicrobial activities.[111] Concerning this, Jeong and co-workers[112] in 2024, optimized a Lewis acid-mediated Prins-like cyclization approach for the synthesis of benzfluorenes and benzo[*j*]fluoranthene core structures and utilized this strategy for the total synthesis of **38h**. The total synthesis began with 1,8-dimethoxynaphthalene **38a** (obtained from naphthalene-1,8-diol), which afforded key acenaphthenone **38b** over few steps. Afterwards, commercially available 2-bromo-6-methoxybenzaldehyde **38c** was subjected to react with Wittig reagent to afford enol ether **38d** (pro-electrophilic) ($E/Z = 4/1$, 93% yield). Next, boration of compound **38d** with B_2Pin_2 in the presence of Pd catalyst ($Pd(dppf)Cl_2$) gave boronate **38e** in 76% yield. The obtained compound **38e** was cross-coupled with acenaphthylene triflate **38b** to get tetracyclic precursor **38f** in 91% yield. Further, compound **38f** was exposed to Bu_2BOTf to afford benzo[*j*]fluoranthene architecture **38g** (87% yield) through Prins-type cycloaromatization. In final step, global demethylation with BBr_3 smoothly gave **38h** in 64% yield and 22% overall from ten-step sequence (Scheme 38).

2.4.6. Polyrhacitide A synthesis. The polyketide-based natural products such as polyrhacitides are ant-sourced secondary metabolites. Jiang and co-workers[113] (in 2008), obtained bicyclic lactones *i.e.*, polyrhacitide A (**39i**) and its homologue polyrhacitide B from medicinal *Polyrhacis Lamellidens* (ant species). This specie exhibits anti-inflammatory and analgesic properties. The polyrhacitide A and polyrhacitide B structurally possess bicyclic lactone and *syn*-1,3-polyhydroxy segment. Menz and co-workers[114] in 2009,



Scheme 38 Total synthesis of viridistratin A (**38h**) according to Jeong and co-workers.[112]

reported the pioneering synthesis of these natural products employing chiral Overmann's esterification. Further, in 2025, Biradar and co-workers[115] accomplished the total synthesis of **39i** using Prins cyclization as main step, for the first time. The synthetic route commenced with the construction of **35b** from racemic epichlorohydrin **35a** over a number of steps. Next, Prins cyclization was performed between compound **35b** and *n*-octanal **39a** mediated by TFA in conjugation with hydrolysis with methanolic potassium carbonate to afford trisubstituted THP **39b** (70% yield, *d. e.* = >96). Intriguingly, the feasible

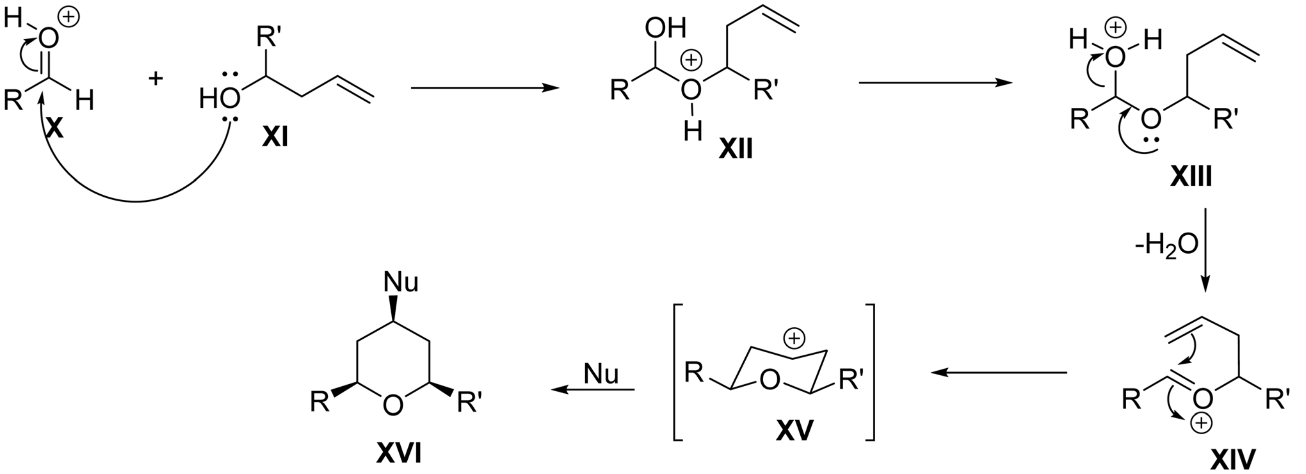
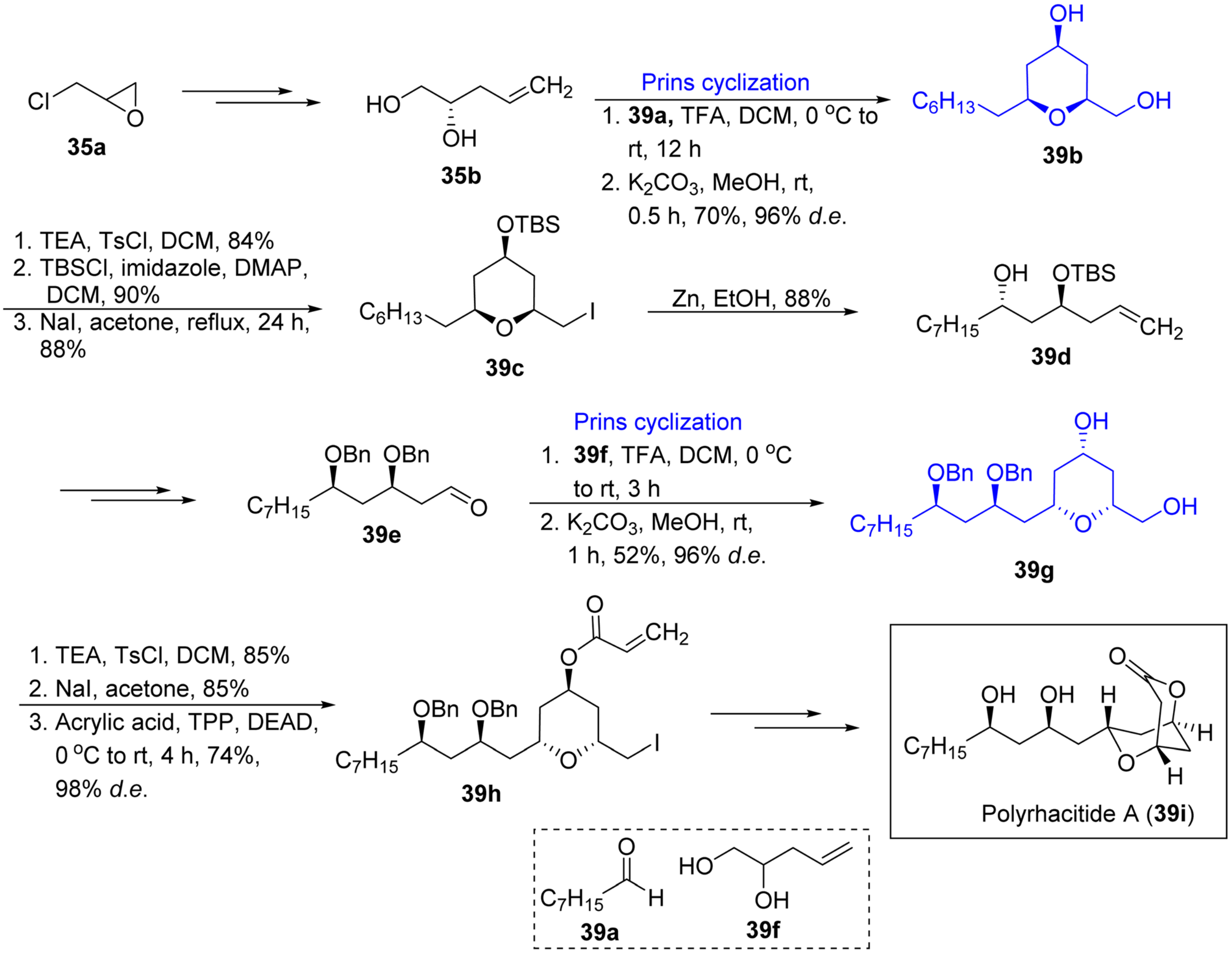


Fig. 3 Feasible mechanism and stereochemical consequences of Prins cyclization.

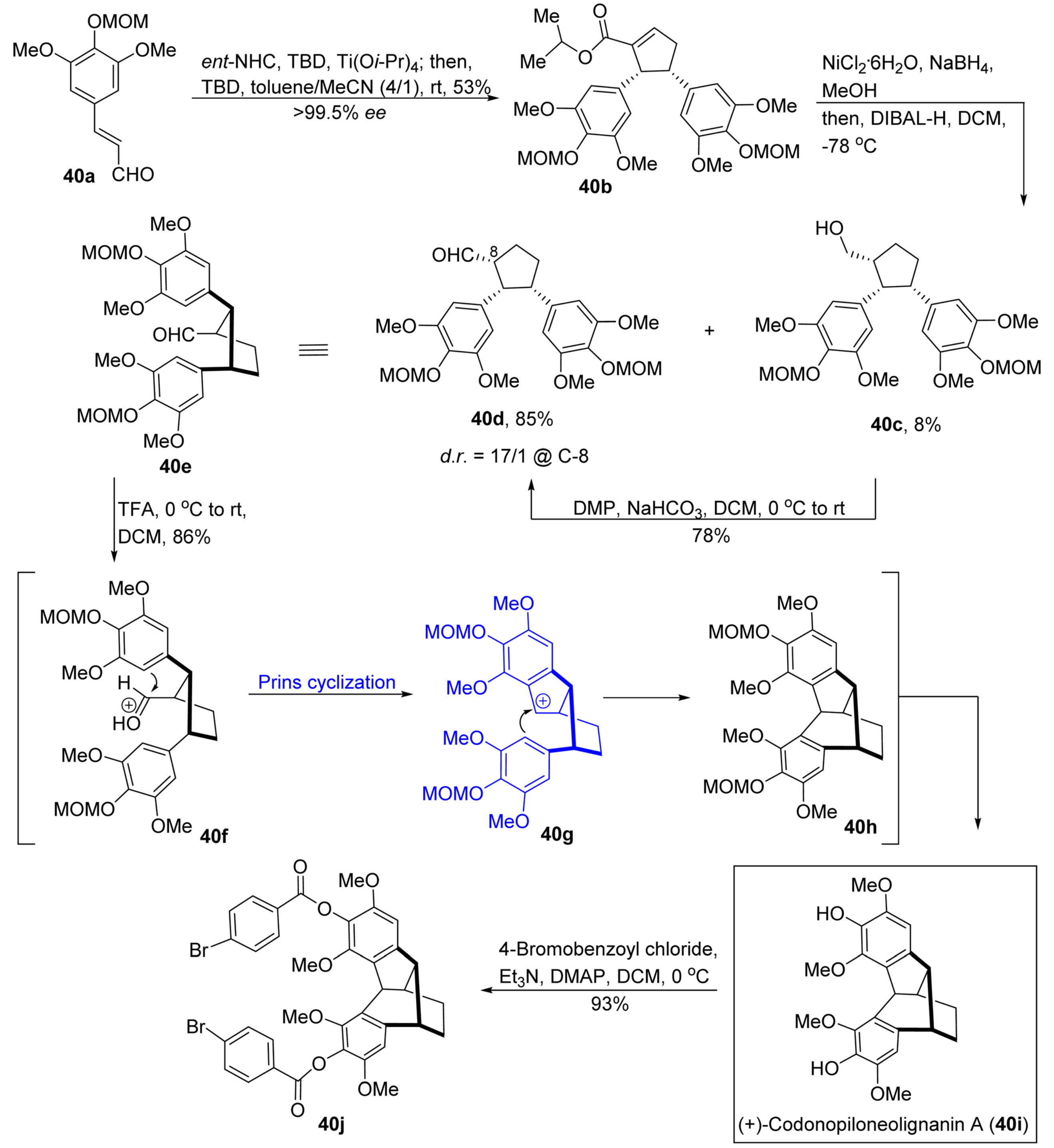


Scheme 39 Synthetic approach towards polyrhacitide A (**39i**) according to Biradar and co-workers.[115]

mechanism and stereochemical consequences of Prins cyclization are depicted (Fig. 3). Furthermore, compound **39b** underwent tosylation, *tert*-butyldimethylsilyl chloride (TBSCl) protection and NaI treatment in sequence to give iodide **39c** (88% yield) which was then subjected to reductive cleavage to provide key intermediate **39d** with desired *anti*-1,3-diol (88% yield). The compound **39d** gave aldehyde **39e** through several transformations. The obtained compound **39e** then underwent TFA-facilitated key Prins cyclization with pent-4-ene-1,2-diol **39f** in DCM, followed by hydrolysis with methanolic K_2CO_3, generating trisubstituted THP **39g** (52% yield, >96% *cis*-selectivity). Next, compound **39g** underwent regioselective tosylation and then reacted with NaI in refluxing acetone, followed by esterification, affording ester **39h** (74% yield, 98% *d.e.*) with configurational inversion. In the final stage, the synthesized compound **39h** provided intended **39i** as diastereopure compound, over few steps. Stereoselectively, Prins cyclization was employed to achieve the preparation of polyrhacitide A in total of 16 steps, in 1.1% overall yield (Scheme 39).

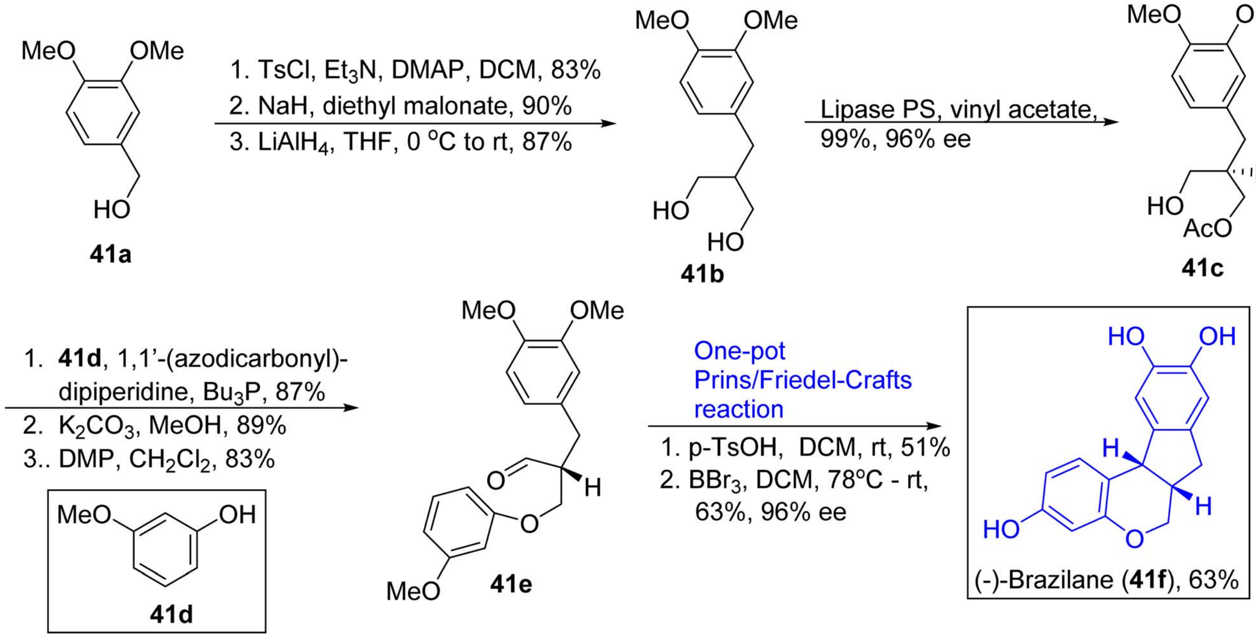
2.5. Synthesis of polyphenol derived-natural products

2.5.1. Synthesis of (+)- & (−)-Codonopiloneolignanin A. The unprecedented polycyclic neolignane, codonopiloneolignanin A (**40i**), isolated by Shi[116] *et al.*, in 2016 from *Codonopsis pilosula* roots, contained 2,9 : 2,9 : 7,7 tricyclo-8,9′-neolignane structure with two benzocycloheptane units. Additionally, it was reported to be first naturally occurring lignin with a tricyclic [5, 3, 0, 0 (ref. 3 and 8)] decane structure and four contiguous stereocenters. The compounds **40i** and *ent*-**40i** are reported to exhibit induced apoptosis, cell cycle arresting and anti-proliferative effects against HT-29 and SW-480 cancer cells. In 2021, Li and co-workers[117] attempted the inaugural gram-scale chiral total synthesis of both (+)- and (−)-codonopiloneolignanin A. The synthesis began with the construction of key *cis*-cyclopentene **40b** (53% yield, >99.5% *ee*) from multi-substituted cinnamaldehyde **40a** (obtained from readily available sinapic acid) through enantio- and diastereoselective dimerization. The obtained *cis*-cyclopentene **40b** underwent stereoselective reduction at double bond in the presence of nickel(II) chloride hexahydrate and $NaBH_4$ followed by further reduction with



Scheme 40 Total syntheses of (+)-codonopiloneolignanin A (**40i**) by Li and co-workers.[117]

diisobutylaluminum hydride (DIBAL-H), that resulted in epimeric mixture of targeted compound *cis*-1,2,3-trisubstituted cyclopentane **40d** (*d.r.* = 17/1, 85% yield) and undesired **40c** (obtained due to over-reduction), which was then converted to **40d** (78% yield) through Dess–Martin oxidation. Next, the Lewis acids such as, aluminum trichloride and zinc chloride were tried to facilitate cascade cyclization. As such, no reaction occurred with $ZnCl_4$, however, the use of $AlCl_3$ resulted in **40i** formation, in 53% yield, whereas, the use of TFA enhanced the yield of **40i** upto 86%. Thus, the authors speculated that aldehyde functionality in compound **40d** was activated using TFA to give the intermediate **40f.** This intermediate **40f** then underwent Prins cyclization with β-aryl to forge a ring, giving rise to a benzyl carbocation **40g.** The formed compound **40g** could be subjected to electrophilic substitution in the presence of γ-aryl to give tricyclic [5, 3, 0, 0 (ref. 3 and 8)] decane structure **40h.**

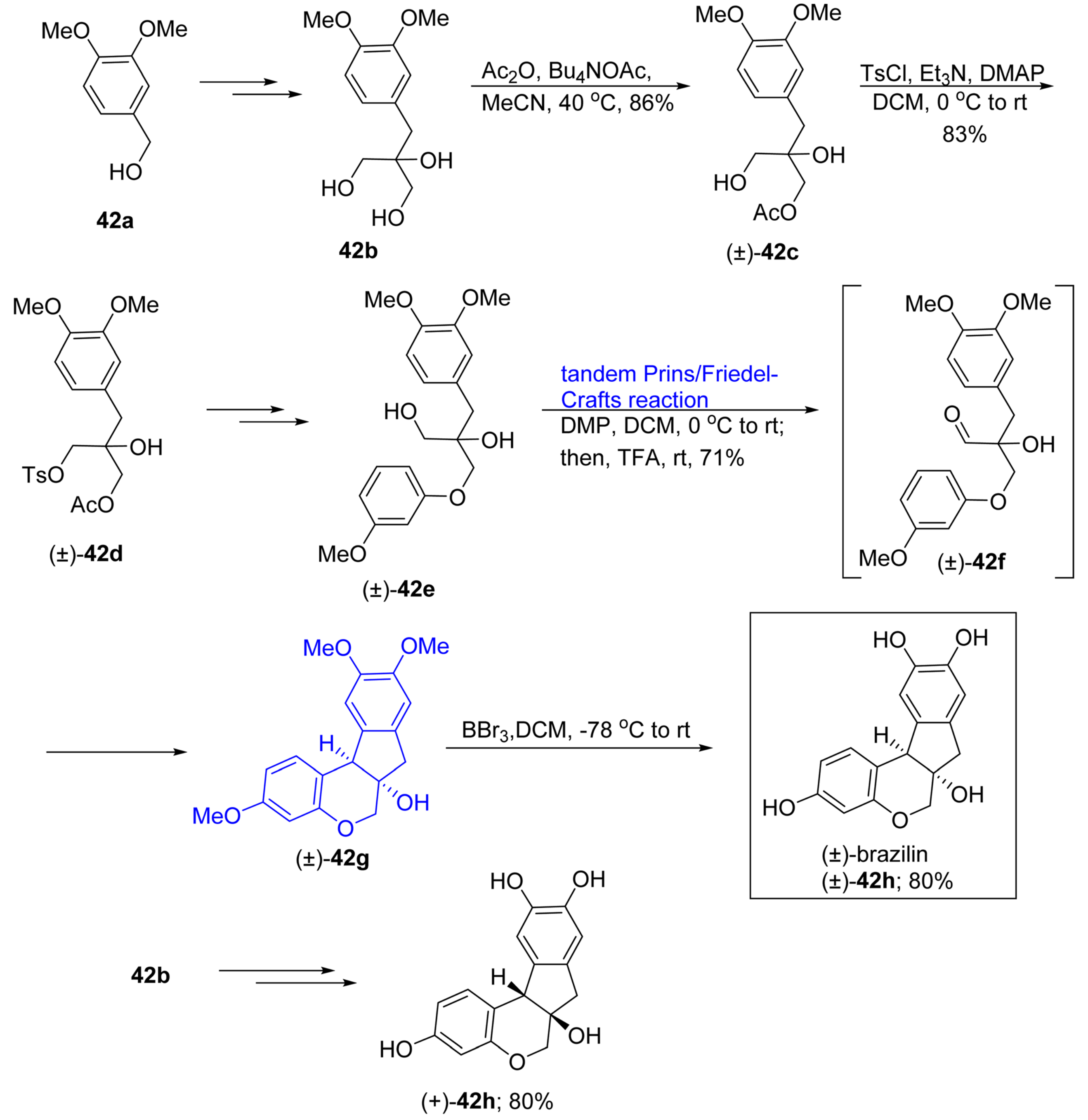


Scheme 41 Total synthesis of (−)-brazilane (**41f**) by Guo and co-workers.[119]

Next, the protecting group MOM was cleaved utilizing TFA in one-pot manner, resulting in the preparation of **40i**. The natural product **40i** was further derivatized to afford the compound **40j**, leading to the confirmation of stereochemistry. Hence, the total syntheses of (+)- and (−)-codonopiloneolignanin A were achieved in a four-step sequence with an overall yield of 37% (Scheme 40).

2.5.2. (−)-Brazilane synthesis. Brazilane is a tetracyclic natural product with homoisoflavonoid structure, isolated from *Caesalpinia sappan* L. (family Leguminosae) heartwood which have been traditionally utilized in Chinese medicine for treating convulsions, menstrual disorders, straumatic disease, and emmeniopathy.[118] In 2022, Guo and co-workers[119] accomplished an expedient asymmetric synthesis of (−)-brazilane (**41f**). Their synthetic route for attaining **41f** began with the transformation of readily accessible 3,4-dimethoxybenzyl alcohol **41a** into diol **41b** (87% yield) under the presence of tosyl chloride and triethylamine which was followed by subsequent S_N2 reaction (diethyl malonate, sodium hydride) and reduction. The diol **41b** then underwent reaction with lipase (in the presence of vinyl acetate) to provide mono-protected alcohol **41c** (99% yield, 96% *ee*) with supposed stereochemistry as *R*, consistent with the configuration of end product. The compound **41c** was then made to react with 3-methoxyphenol **41d** in the presence of 1,1′-(azodicarbonyl)-dipiperidine/Bu_3P, followed by acetyl group cleavage and subsequent Dess–Martin oxidation to yield aldehyde **41e** (83%). Finally, aldehyde **41e** was subjected to one-pot Prins/Friedel–Crafts reaction under the presence of *p*-TsOH in DCM followed by its deprotection under the presence of BBr_3 in DCM to afford **41f** in about 63% yield with 96% *ee*. The synthetic route described herein shows an alternative approach towards brazilane and related compounds with indane and chromane scaffold, focusing on the potential applications of the outlined approach to access pharmaceuticals and natural products (Scheme 41).

2.5.3. (+)-Brazilin synthesis. The naturally occurring homoisoflavonoid, brazilin is the representative of *Caesalpinia sappan* L. (Chinese traditional medicine) and is characterized by chromane framework with *cis*-fused 2,3-dihydro-1*H*-indene component. The bioactivities exhibited by this natural product include antitumor, anti-inflammatory, antibacterial, hypoglycemic, hepatoprotective activities.[120] In 2022, Xu and co-workers[121] designed a concise nine-step route to construct the *cis*-annulated chromane core and indane skeleton of (+)-brazilin (+)-**42h** *via* tandem Prins/Friedel–Crafts protocol. Their synthetic sequence commenced with the synthesis of (±)-**42h** which initially involved the preparation of intermediate **42b** from readily available 3,4-dimethoxy benzyl alcohol **42a** through several modifications. The compound **42b** upon treatment with Ac_2O and tetrabutylammonium acetate afforded diol (±)-**42c** (86% yield). Next, the compound (±)-**42c** was converted to its *p*-toluenesulfonate (±)-**42d** (83% yield) in the presence of *p*-toluenesulfonyl chloride, Et_3N and DMAP. The obtained compound (±)-**42d** underwent several steps transformation to afford the intended ether (±)-**42e**. Next, the compound (±)-**42e** underwent oxidation to give aldehyde (±)-**42f** which was further subjected to Prins/Friedel–Crafts reaction with TFA to afford the intended cyclized product (±)-**42g** in one-pot manner (71% yield). Successfully, **42h** (80% yield) was attained by deprotection in the presence of boron tribromide. The chiral total synthesis of (+)-brazilin **42h** was attempted utilizing enzyme-mediated desymmetrization protocol. For this purpose, the intermediate **42b** was subjected to lipase-mediated enantioselective esterification followed by aforementioned protocol to provide (+)-**42h** in 80% yield. Hence (+)-brazilin was achieved



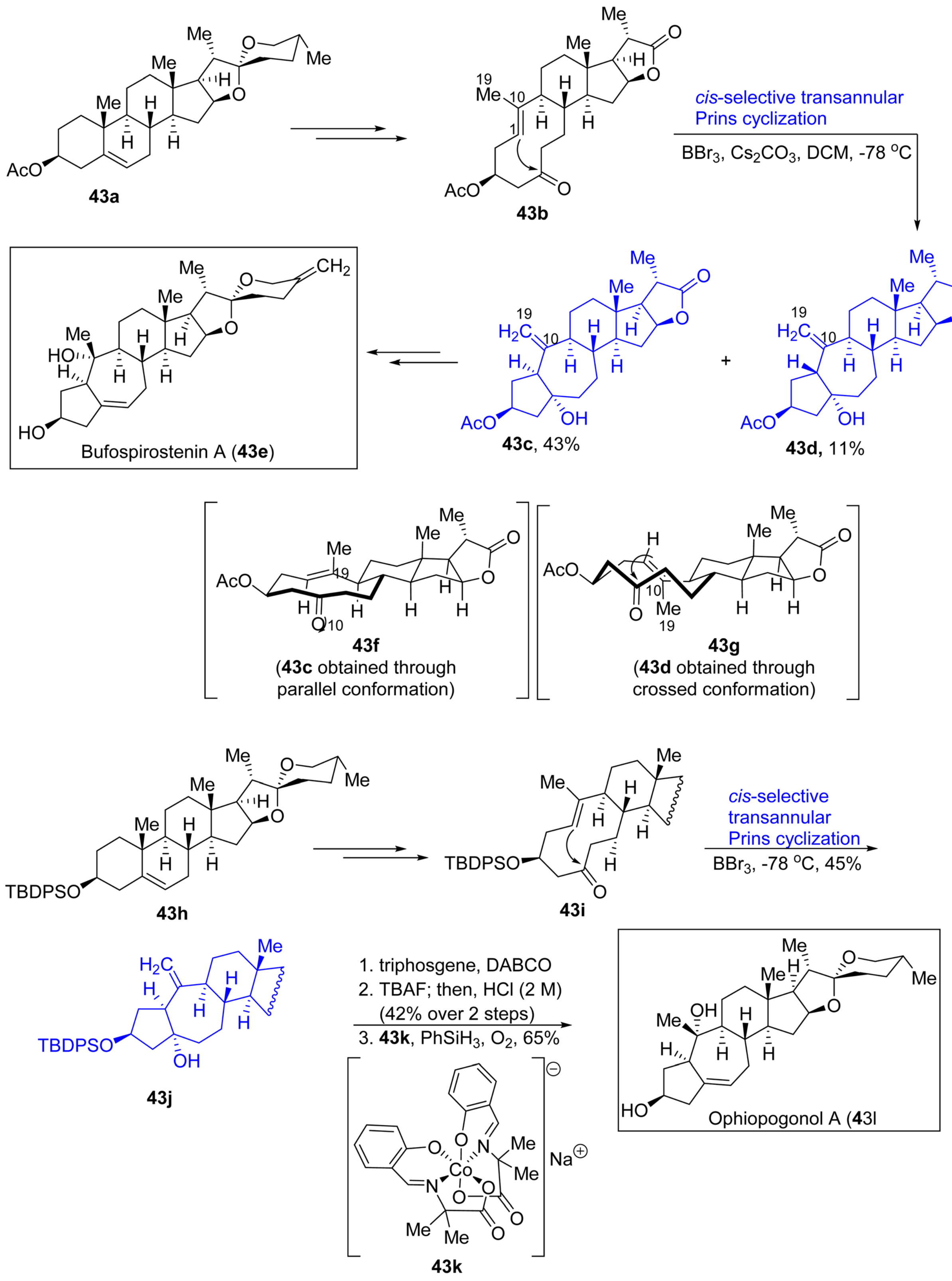
Scheme 42 Total synthesis of (+)-brazilin (+)-**42h** by Xu and co-workers.[121]

from compound **42a** utilizing the concise synthetic strategy consisting of overall nine steps (Scheme 42).

2.6. Miscellaneous

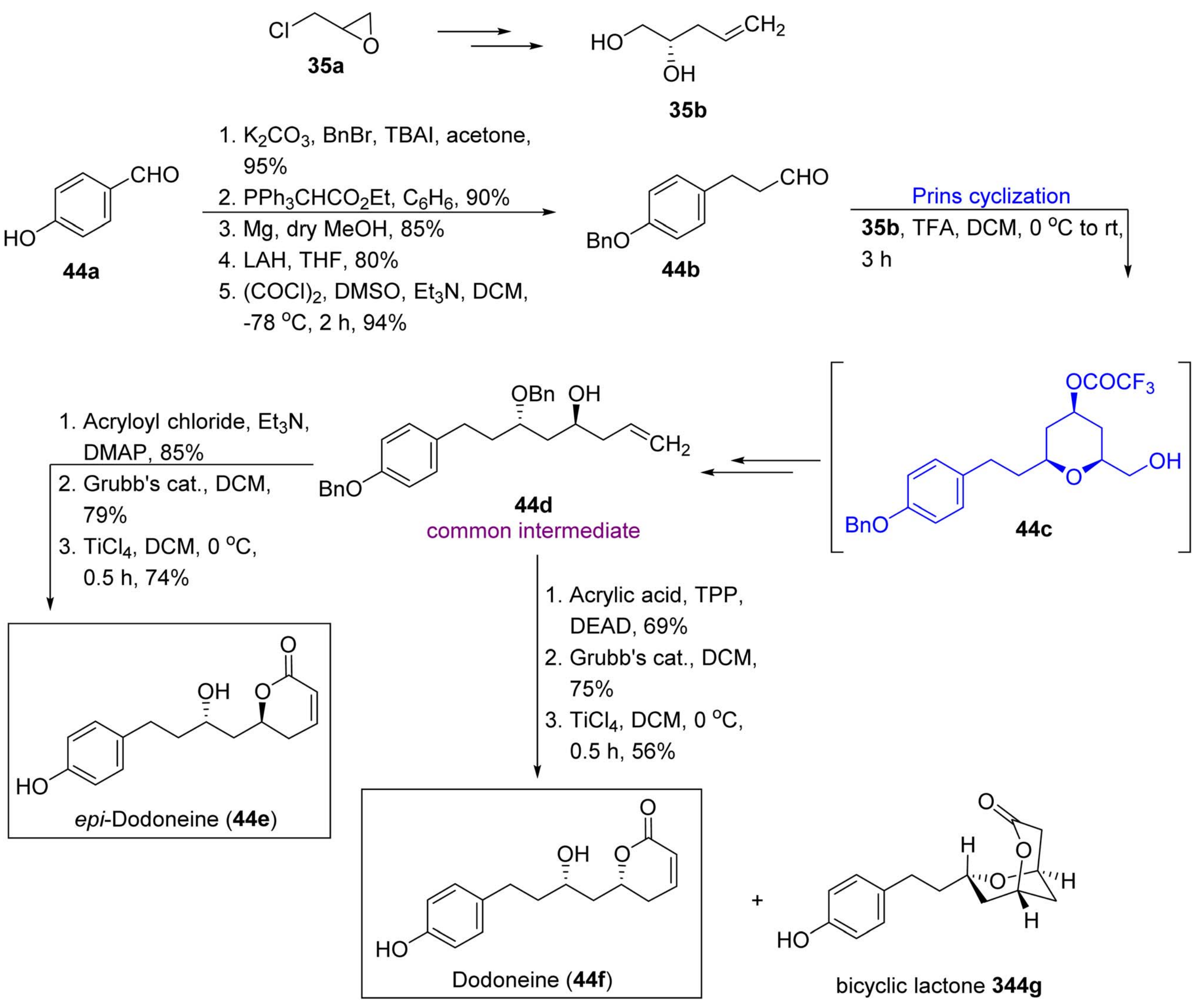
2.6.1. Bufospirostenin A & ophiopogonol A synthesis.

Bufospirostenin A (**43e**) and ophiopogonol A (**43l**) are intricate naturally occurring *abeo*-steroids isolated from bile of *Bufo bufo gargarizans* and *Ophiopogon japonicus* rhizomes.[122,123] Both compounds contain 5/7/6/5/5/6 hexacyclic structure with ten stereogenic centers and exhibit potential sodium/potassium ATPase inhibitory activities. In 2022, Yang[124] *et al.* attempted the syntheses of **43e** and **43l** through the selective generation of *cis*- and *trans*-fused hydroazulenols *via* stereoselective trans-annular Prins cyclization. The total synthesis of **43e** commenced with the preparation of olefin **43b** for transannular Prins reaction. In this regard, diosgenin acetate **43a** afforded compound **43b** over few-steps. Next, the synthesis of N5/7-fused bicyclic alcohol **43c** was achieved in the presence of increased quantity of Lewis acid BBr_3 and Cs_2CO_3, in 43% yield. In addition, undesired compound **43d** was also formed along with



Scheme 43 Total syntheses of bufospirostenin A (**43e**) and ophiopogonol A (**43k**) by Yang and co-workers.[124]

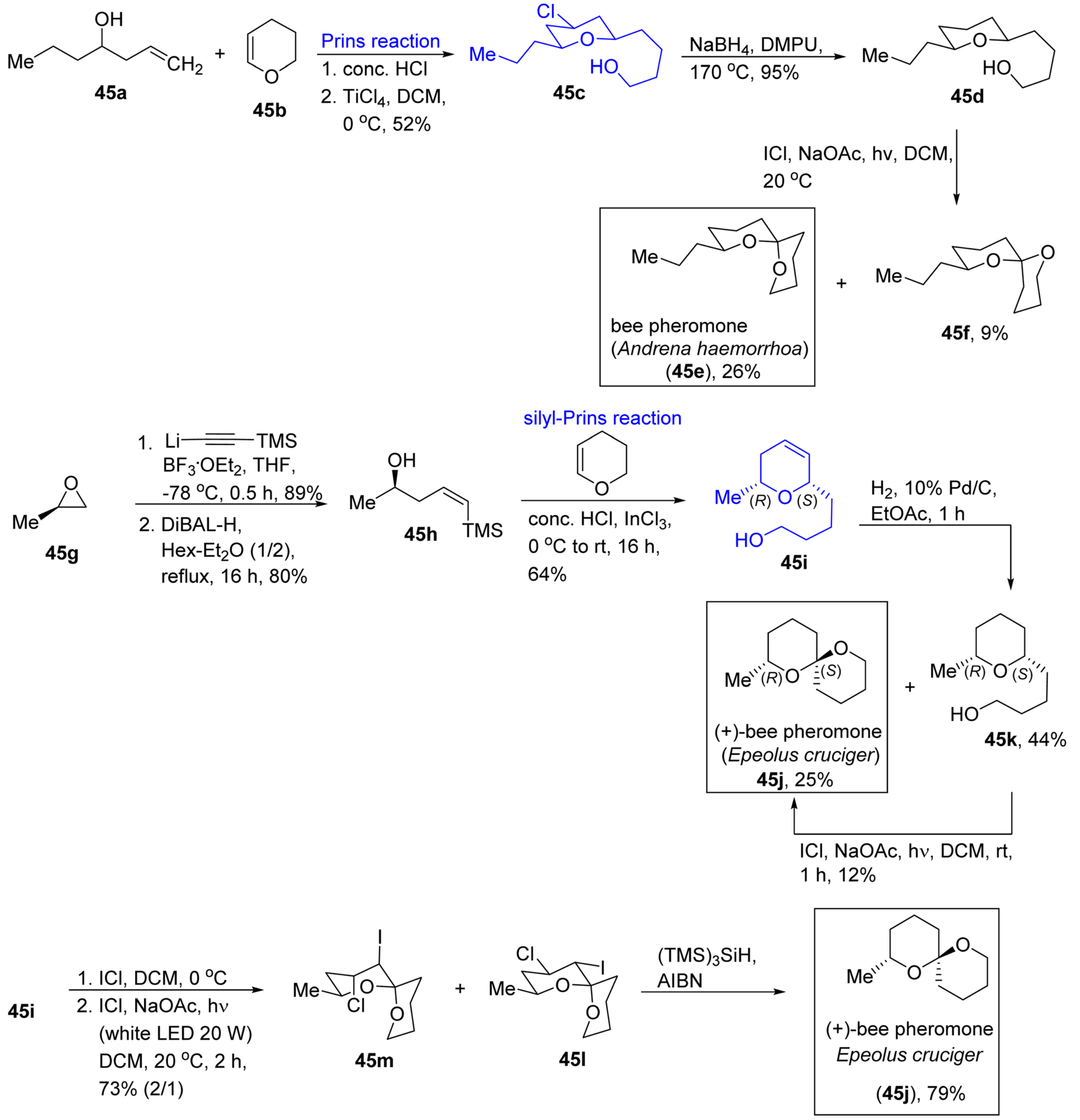
recovered compound **43b**, in 11% and 30% yields, respectively. The compound **43c** was reported to be obtained *via* parallel conformation **43f** while compound **43d** was produced *via* crossed conformation **43g**. Finally, compound **43c** gave rise to **43e** over a few steps. Next, **43l** was also synthesized employing the transannular Prins reaction. The synthesis of **43l** began with



Scheme 44 Total synthesis of dodoneine (**44f**) and *epi*-dodoneine (**44e**) by Biradar and co-workers.[127]

tert-butyldiphenylsilyl-masked diosgenin **43h** which afforded (*E*)-olefin **43i** over a few-step sequence. The compound **43i** was then subjected to *cis*-selective Prins reaction in the presence of BBr_3 and DCM, generating *cis* alcohol **43j** (45% yield), together with recovered **43i** (25% yield). Further, the compound **43j** was subjected to sequential dehydration, *tert*-butyldiphenylsilyl group cleavage, acidic workup, and selective Mukaiyama hydration (with Carreira's cobalt catalyst **43k**) to attain **43l** in 65% yield. Hence, the syntheses of both *abeo*-steroids were completed independently in total of seven steps, by utilizing the affordable starting materials (Scheme 43).

2.6.2. Dodoneine & *epi*-dodoneine syntheses. The unsaturated γ-lactone, dodoneine (**44f**) was extracted from *Tapinunthus dodoneifolius* and *Agelanthus dodoneifolius* which contain ((*R*)-6-[(*S*)-2-hydroxy-4 (4-hydroxyphenyl) butyl]-5,6-dihydropyran-2-one) structure.[125] *T. dodoneifolius* is the therapeutic plant used for treating respiratory diseases, abdominal pain, diarrhea, cholera and wounds. Dodoneine demonstrates diverse bioactivities including HIV protease suppression, anti-leukemic response, potent vasorelaxant response and apoptosis induction ($IC_{50} = 81.4 \pm 0.9$ μM).[126] In 2023, Biradar and co-workers[127] attempted the diastereoselective syntheses of **44f** and its stereoisomer *epi*-dodoneine **44e** leveraging Prins cyclization as a key strategy. The synthesis began from readily accessible racemic epichlorohydrin **35a** that yielded the precursor (*S*)-pent-4-ene-1,2-diol **35b** for Prins cyclization over few steps. Next, another substrate *i.e.*, aldehyde **44b** (94% yield was formed from *p*-hydroxybenzaldehyde **44a** *via* subsequent benzylation, C2-Wittig reaction, reduction and Swern oxidation. The obtained aldehyde **44b** underwent Prins cyclization with synthesized compound **35b** mediated by TFA in DCM at 0 °C to room temperature to deliver trifluoroacetate **44c**. The synthesized cyclized product **44c** gave key intermediate **44d** with desired *anti*-1,3-diol, over few steps. In sequence, the compound **44d** was then subjected to acryloyl chloride-facilitated esterification, RCM reaction, and debenzylation to produce *epi*-dodoneine (**44e**, 74% yield). Likewise, dodoneine **44f** along with bicyclic lactone **44g**, were prepared by subjecting the compound



Scheme 45 Total syntheses of insect pheromones (**45e**) and (**45j**) according to Trevorrow and co-workers.[129]

44d to acrylic acid-mediated esterification, RCM reaction and debenzylation, in 56% and 31% yields, respectively. Overall, both natural products **44f** and **44e** were generated in 11.2% yield (Scheme 44).

2.6.3. Insect pheromones synthesis.

The spiroketal unit is a spirocyclic acetal structure with two carbocycles connected at central carbon with two oxygen atoms on separate rings. Many natural products contain this spiroketal unit such as insect pheromones.[128] In 2024, Trevorrow and co-workers[129] attempted the syntheses of two insect pheromones **45f** and **45j** employing Prins reaction. The synthetic strategy involved the racemic preparation of **45f** found in mining bee's (*Andrena haemorrhoa*) mandibular secretions. This synthesis began with the utilization of sequential Prins reaction and treatment of hept-1-en-4-ol **45a** with 3,4-dihydro-2*H*-pyran **45b** by means of concentrated HCl, followed by the addition of $TiCl_4$ to afford hydroxy THP (**45c**, 52% yield). Next, dehalogenation gave cyclization precursor **45d** (95%) which upon oxidation rendered natural compound **45e** (26%) along with its stereoisomer **45f** (9%). Another pheromone was enantiopure (2*R*,6*S*)-2-methyl-1,7-dioxaspiro[5.5]undecane **45j** found in cuckoo bee's (*Epeolus cruciger*) mandibular secretions. The synthetic sequence for this natural product commenced with the reaction of epoxide **45g** with TMS-acetylene followed by treatment with *n*-BuLi, $BF_3{\cdot}OEt_2$, and (*R*)-propylene oxide, that afforded *Z*-vinylsilane **45h** (80% yield) as single enantiomer *via* reduction. Next, silyl-Prins reaction occurred in the presence of 3,4-dihydro-2*H*-pyran and Lewis acid ($InCl_3$) to give single enantiomer of dihydropyran **45i** (64% yield). Further, catalytic hydrogenation resulted in cyclized product **44j** (25% yield) and reduced compound **44k** (44%) in the form of mixture, which was further subjected to oxidative photocyclization to furnish the compound **45j** in an isolated yield of 12%. To circumvent rearrangement in hydrogenation step, addition of iodine monochloride and spiroketalisation took place in two-step sequence and one-pot manner, converting cyclized product **45i** into inseparable mixture of compound **45l** and **45m** (2/1, 73% yield). Next, dehalogenation was performed using tris(trimethylsilyl)silane with AIBN, leading to the complete reduction and formation of stereopure **45j** (79% isolated yield) with an overall yield of 26% within five-step sequence (Scheme 45).

3. Conclusion and outlook

In this review article, the importance of Prins reaction in the total synthesis of bioactive natural products has been highlighted. This protocol enables the C–C bond formation, leading towards the construction of significant scaffolds in many natural products, such as complex THP motifs. Moreover, the Prins reaction exhibits stereoselectivity and enhanced enantioselectivity, facilitating the generation of specific stereocenters within the target compound. Research advancements render the Prins reaction effective in streamlining complex compounds synthesis. This manuscript summarizes the total synthesis of diverse natural products, including alkaloids, terpenoids, lactones, flavonoids and polyketides *via* Prins reaction, showcasing its applications in natural product chemistry, reported since 2020. Though the employed Prins reactions resulted in efficient yields of corresponding products, however, its applications in asymmetric synthesis are yet to be explored broadly. With ongoing developments, innovations in designing of the green catalyst, mild reaction conditions and environmentally benign solvents may potentially enhance its utility in natural product and complex organic synthesis. Additionally, the scalability and sustainability of Prins reaction would be reinforced by implementing flow chemistry techniques.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review

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