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Exploring the synthetic potential of epoxide ring opening reactions toward the synthesis of alkaloids and terpenoids: a review

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Epoxides are oxygen containing heterocycles which are significantly employed as crucial intermediates in various organic transformations. They are considered highly reactive three-membered heterocycles due to ring strain and they undergo epoxide ring opening reactions with diverse range of nucleophiles. Epoxide ring-opening reactions have gained prominence as flexible and effective means to obtain various functionalized molecules. These reactions have garnered substantial attention in organic synthesis, driven by the need to comprehend the synthesis of biologically and structurally important organic compounds. They have also found applications in the synthesis of complex natural products. In this review article, we have summarized the implementation of epoxide ring opening reactions in the synthesis of alkaloids and terpenoids based natural products reported within the last decade (2014–2023).

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Introduction

Epoxides are 3-membered oxygen containing heterocycles that play an important role in the synthesis of natural products. Epoxides are considered highly reactive molecules due to ring strain[1] and they undergo enantioselective ring opening reaction with a diverse range of reagents (Gilman reagent[2]) and nucleophiles[3] such as carbon[4] and oxygen nucleophiles *i.e.*, trimethylsilyl cyanides,[5] aryllithiums,[6] trialkylsilyl halides,[7] alkylamines,[8] carboxylic acids[9] and phenols[10] in the presence of numerous catalysts. The general reaction of epoxide ring opening reaction in the presence of nucleophile is shown in the Fig. 1.

Similarly, π-nucleophiles *i.e.*, allylsilanes, olefins,[12] and arenes[13] have also been used for the ring opening reactions of epoxides. Sulfur nucleophiles[14] also play an important role towards the epoxide ring opening reactions *i.e.*, alkanes and arene-thiols can also be used for the ring opening reaction of epoxides to synthesize β-hydroxy mercaptans or regioselective products *i.e.*, β-hydroxysulfides.[15] Similarly, α-azido ketone is prepared by the reaction of chloroepoxide with sodium azide.[16]

The epoxide ring opening reactions are highly employed in the synthesis of various natural products such as alkaloids, steroids, terpenoids, biopolymers, carotenoids, polyketides and flavonoids *etc.* which exhibit medicinal value. In 1963, an epoxide was first time reacted with heteroaromatic π-nucleophile to synthesize a natural product named as Indolmycin (an antibiotic).[17] Vinyl epoxides are important synthetic precursors in organic synthesis[18] as they lead towards the synthesis of (−)-(4*R*,5*R*)-Muricatacin (a natural acetogenin) *via* regio or stereoselective ring opening reaction of epoxide.[19] Syntheses of numerous biological active compounds such as Sphingofungin,[20] Zoanthenol,[21] marine ladder polyethers,[22] Zampanolide,[23] *epi*-Muscarine,[24] Molestin E,[25] (−)-Epicoccin G and (−)-Rostratin A,[26] homoisoflavonoids,[27] Chlorotonils,[28] Lingzhiol,[29] Phomarol,[30] Isoandrographolide,[31] Citrinadins,[32] Isosilybin,[33] polyester,[34] Mupirocin[35] and Bisfuranoxide[36] *etc.* have been accomplished by involving epoxide chemistry.

Predominantly, biologically active natural products *i.e.*, Epothilone A[37] **3** (antitumor activity), methyl-L-Callipeltose[38] **6** (cytotoxic activity against NSCLCN6 and P388 cell lines),

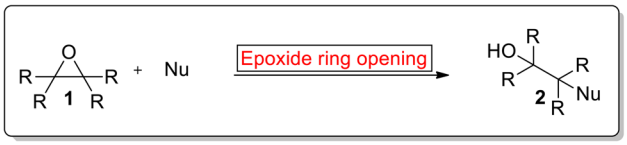

Fig. 1 General reaction of epoxide ring opening reaction.[11]

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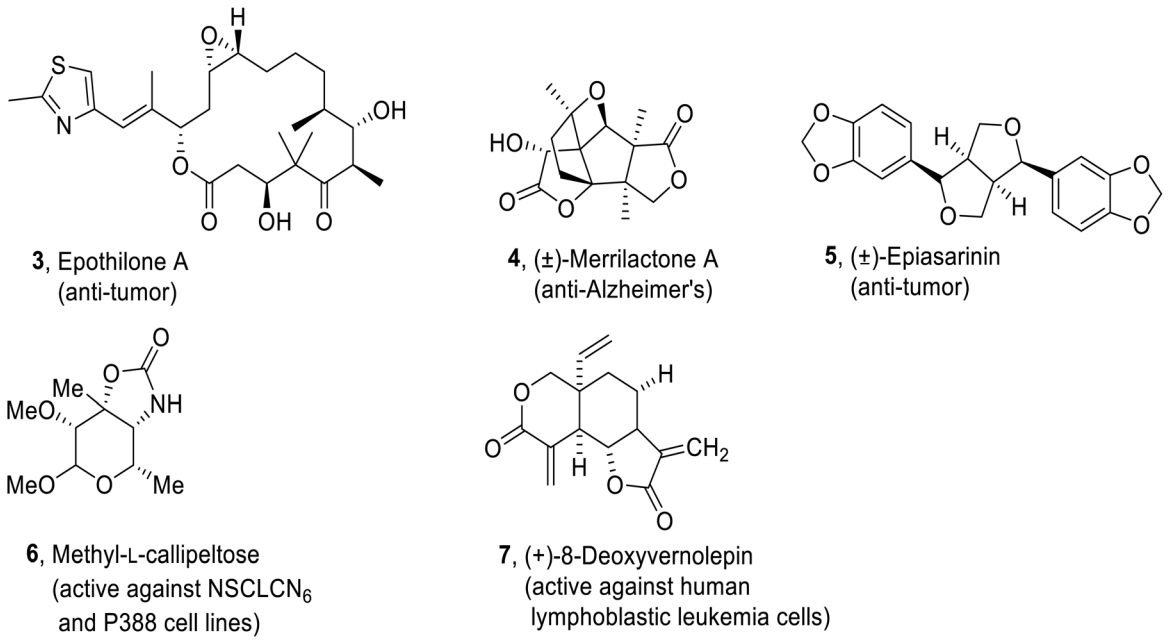


Fig. 2 Structures of some biologically active natural products (Epothilone A **3**, (±)-Merrilactone A **4**, (±)-Epiasarinin **5**, Methyl-L-callipeltose **6**, (+)-8-Deoxyvernolepin **7**).

(−)-Dactylolide,[39] Petuniasterone D[40] (insecticidal), (±)-Merrilactone A[41] **4** (active against Alzheimer's disease), (−)-Preussomerin,[42], (+)-8-Deoxyvernolepin[43] **7** (active against human lymphoblastic leukemia cells), (±)-Epiasarinin[44] **5** (antitumour activity), Laulimalide,[45], (−)-Nakamurol A,[46] Prenylbisabolane,[47], (−)- Delobanone and (−)-*epi*-Delobanone[47] are generated by employing epoxide ring opening reactions (Fig. 2).

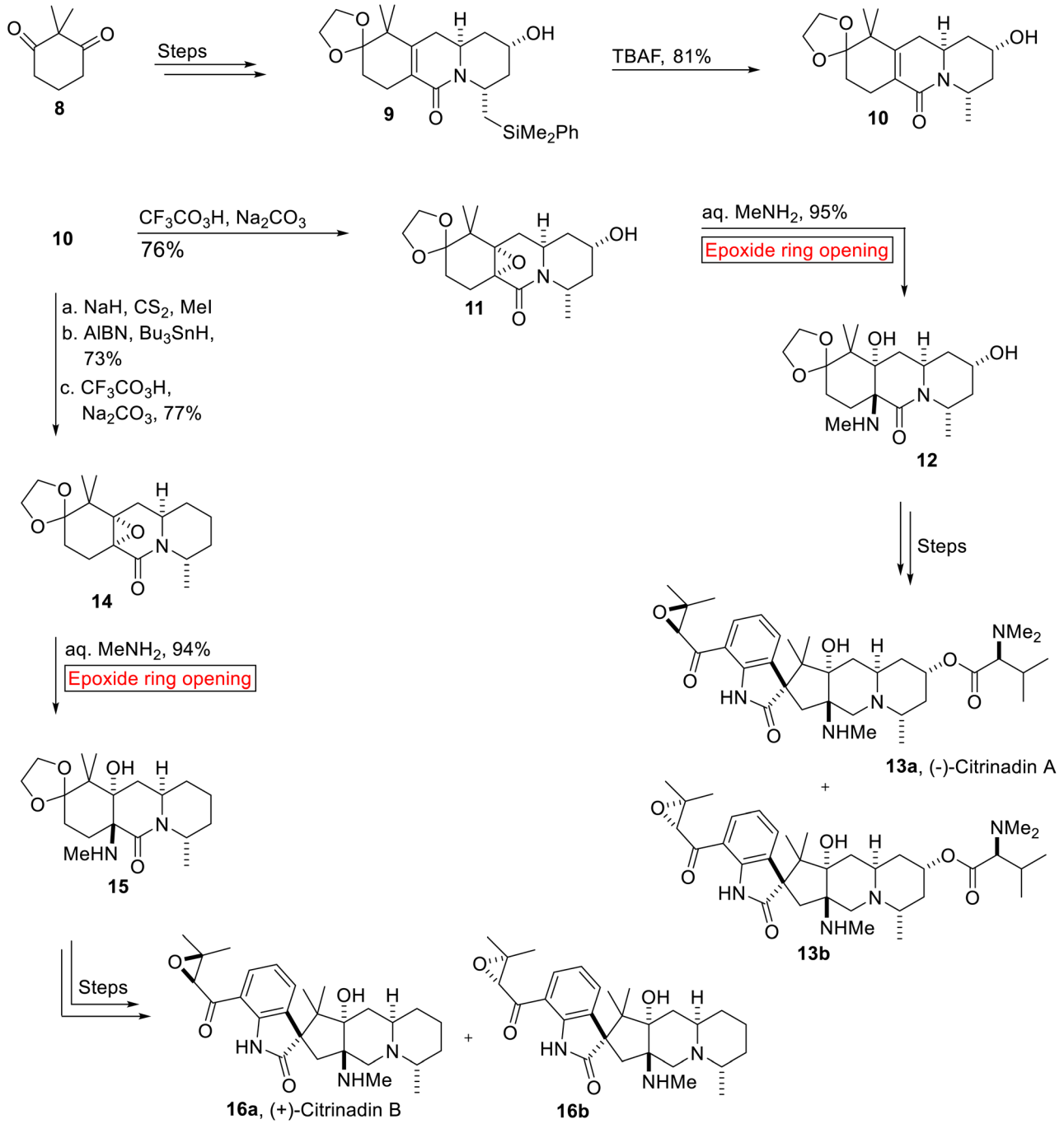
In 2006, research group of Oltra[48] reviewed the synthesis of natural products by involving epoxide opening reaction in the presence of titanocene (III). Vilotijevic and Jamison overviewed the syntheses of polycyclic polyether natural products and marine polycyclic polyethers by employing epoxide-opening reactions and endo-selective epoxide-opening pathways in 2009 (ref. 49) and 2010 (ref. 50) respectively. Similarly, Bugarin and allies, provided a review on the syntheses of polypropionates and other bioactive natural products by using epoxide chemistry in 2023.[51] Our review focuses on the formation of alkaloids and terpenoids due to the comprehensive work reported on the syntheses of these natural products by involving epoxide ring opening reaction as one of the key steps, reported within the past decade (2014–2023).

Review of literature

Syntheses of alkaloid-based natural products

Spirooxindole alkaloid. (−)-Citrinadin A **13a** and (+)-Citrinadin B **16a** are spirooxindole alkaloids which were isolated and reported by research group of Kobayashi in 2004 and 2005. They were found to demonstrate significant efficacy against human epidermoid carcinoma KB (**13a**, $IC_{50} = 10\ \mu g\ mL^{-1}$) and murine leukemia L1210 (**13a**, $IC_{50} = 6.2\ \mu g\ mL^{-1}$; **16a**, $IC_{50} = 10\ \mu g\ mL^{-1}$)[52] cells. In 2014, Martin and co-workers disclosed the concise, enantioselective syntheses of Citrinadins A **13a** and B **16a** that resulted in the revision of their stereochemical structures. Their strategy minimized protection/deprotection processes, refunctionalization and showed high diastereoselectivity. The stereochemistry of Citrinadins was based on the substrate-controlled reactions involving stereoselective epoxidation and epoxide ring opening reaction as key steps.[53] Total synthesis of (−)-Citrinadin A **13a** and (+)-Citrinadin B **16b** was accomplished from common intermediate lactam **10**. The synthetic scheme initiated with the preparation of **9** from 2,2-dimethylcyclohexane-1,3-dione **8** over few steps. Then, **9** experienced tetra-*n*-butylammonium fluoride (TBAF)-mediated desilylation to produce unsaturated lactam **10** (81%) which was further subjected to peroxytrifluoroacetic acid-mediated diastereoselective epoxidation in order to furnish epoxide **11** (76%). In the next step, **11** underwent base-catalyzed diastereoselective epoxide ring opening reaction to generate amino alcohol **12** (95%) which forged (−)-Citrinadins A **13a** over few steps. Similarly, synthesis of (+)-Citrinadin B **16a** commenced with the formation of epoxide **14** (77%) from lactam **10** upon Barton deoxygenation followed by CF_3CO_3H-mediated epoxidation. Then, epoxide **14** was exposed to similar base (Me_2NH_2)-catalyzed epoxide ring opening reaction to generate another amino alcohol **15** (94%) which was further converted into a mixture of (+)-Citrinadin B (dr = 2.5 : 1) **16a** and **16b** over few steps (Scheme 1).

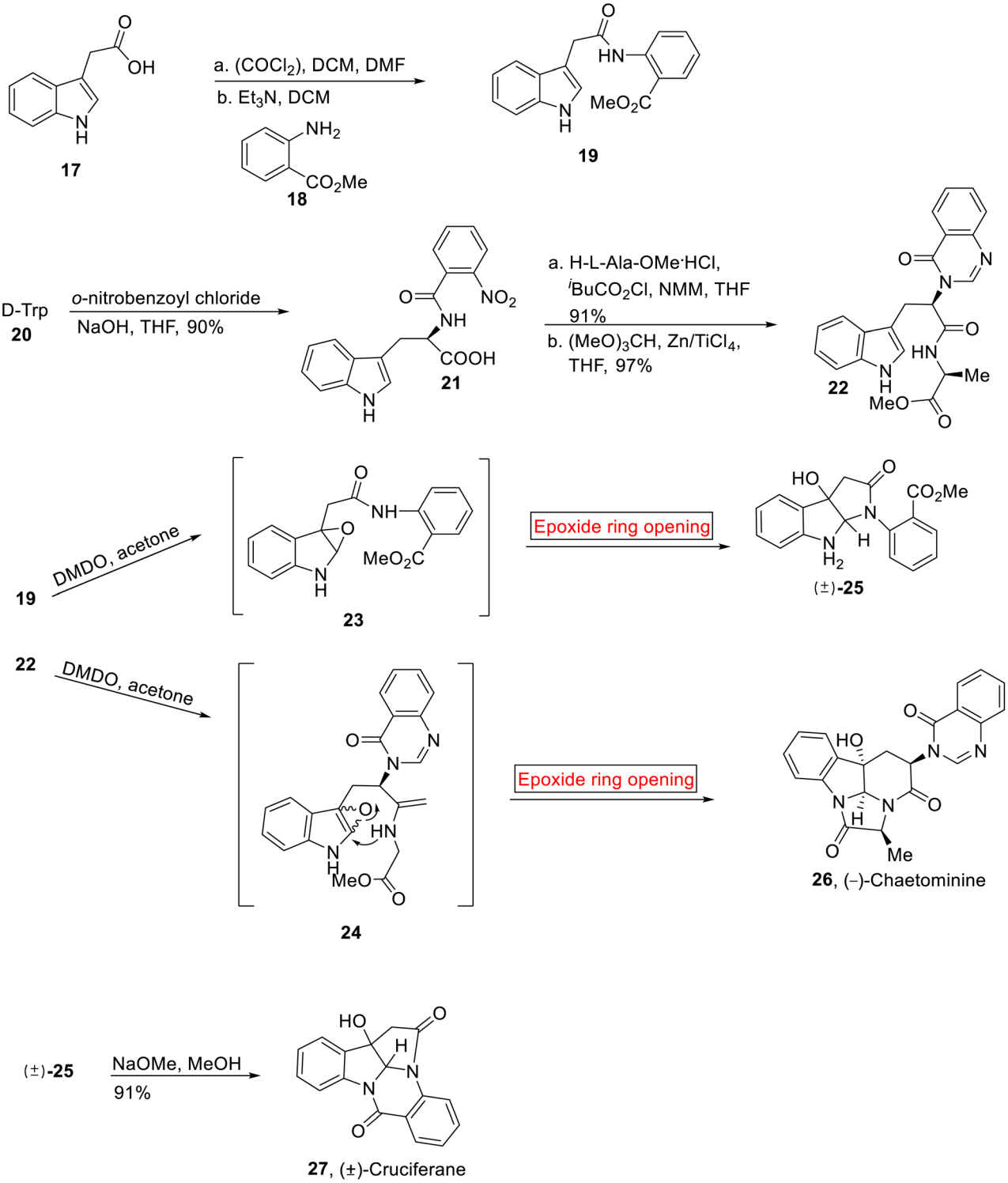
Cruciferane **27** (alkaloid) was extracted from the roots of plant (*Isatis indigotica*[54]) by the research group of Shi in 2012. It is used in traditional medicines to treat encephalitis B, carbuncles, erysipelas, influenza, and epidermic hepatitis. It has antipyretic properties as well. Total synthesis of Cruciferane was first reported in 2013 by research groups of Nair[55] and then



Scheme 1 Synthesis of (−)-Citrinadin A **13a** and (+)-Citrinadin B **16b**.

by Argade.[56] Further, Ji[57] has developed the synthesis of Cruciferane from complex and expensive starting materials and reagents. In the present work, Ghosh and Nagarajan in 2014 have reported the synthesis of (±)-Cruciferane **31** from simple route and economical starting materials by employing epoxide ring opening reaction as a key step (60.3%, overall yield).[58] Similarly, (−)-Chaetominine **36** is an alkaloid which was isolated by research group of Tan from *Chaetomium* sp. IFB-E015 (fungus present on the leaves of *Adenophora axilliflora*) in 2006.[59] It exhibits strong activity opposite to human colon cancer SW1116 (28 nM)[59] and human leukemia K562 (21 nM) cell lines. The first total synthesis of (−)-Chaetominine **26** has been previously reported by research group of Snider,[60] second by Evano,[61] third by Papeo.[62] Then, the fourth approach was reported by Evano and colleagues in nine steps (14% overall yield).[63] In 2014, Huang *et al.*, reported the asymmetric, protecting group free total synthesis of (−)-Chaetominine **26** that features excellent overall yield (33.4%) as compared to other approaches, in one-pot sequence reactions. They devised the facile and shorter synthetic route by employing epoxide ring

opening reaction as one of the key steps.[64] Total synthesis of Cruciferane **27** was initiated by the reaction between indole 3-acetic acid **17** and oxalyl chloride, followed by base (Et_3N)-catalyzed amidation in the presence of methyl anthranilate **18** to afford amidation product **19** (78%). The synthesis towards (−)-Chaetominine **36** began with the preparation of aroylated product **21.** The aroylated product **21** (90%) was obtained by the treatment of D-tryptophan **20** with *o*-nitrobenzoyl chloride which was further treated with L-alanine methyl ester hydrochloride and $^{i}BuCO_2Cl$/NMM (*N*-methylmorpholine) followed by reaction with $HC(OMe)_3$ and *in situ* generated $TiCl_4$ to provide quinazolinone **22** (97%). Then, compound **19** and **22**



Scheme 2 Synthesis of (−)-Chaetominine **26** and (±)-Cruciferane **27**.

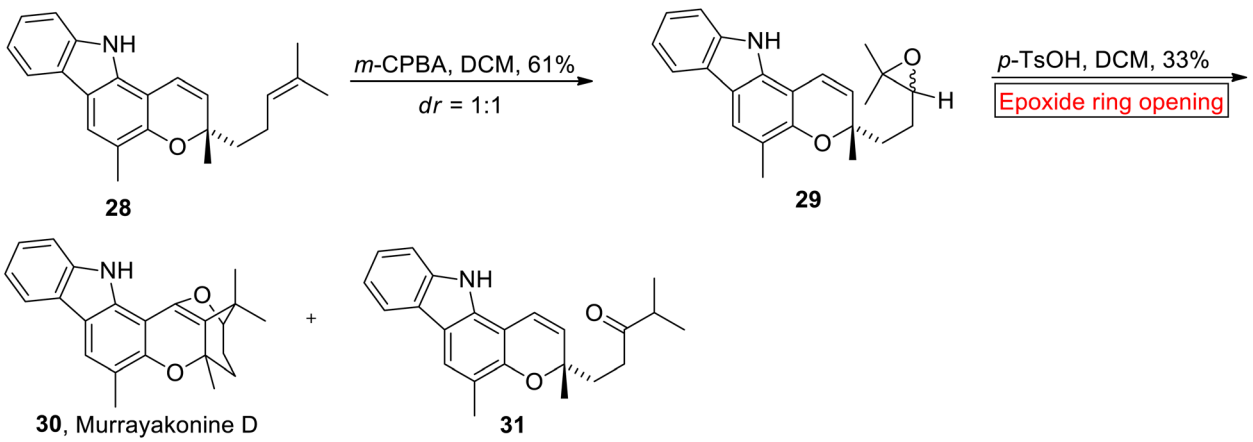
were individually subjected to DMDO-mediated epoxidation to provide epoxides **23** and **24** (96%) respectively which further experienced intramolecular epoxide ring opening reaction to furnish (±)-**25** (85%) and (−)-Chaetominine **26** (42%) respectively. Then, the compound (±)-**25** was reacted with NaOMe (MeOH) to render racemic (±)-Cruciferane **27** in 91% yield (Scheme 2).

Carbazole alkaloids. Carbazole alkaloids (with a pyrrole moiety) are prevalent natural substances derived from multiple plant species as well as bacteria and fungi.[65] Murrayakonine D **30** (carbazole alkaloid) has 6/6/6/5 ring system which was extracted from *Murraya koenigi* (medicinal plant).[66] Research group of George has reported the synthesis of Murrayakonine D **30** (33% overall yield) in 2017 *via* epoxide ring opening reaction.[67] In the first step, Mahanimbine **28** (which was prepared according to research group of Knölker[68]) went through meta-chloroperoxybenzoic acid (*m*-CPBA)-mediated epoxidation to generate **29** (61%). The compound **29** was further subjected to acid (*p*-TsOH)-catalyzed epoxide ring opening reaction in DCM to provide inseparable mixture of **30** and undesired ketone **31**. The mixture was washed with cold MeOH to separate Murrayakonine D **30** (Scheme 3).

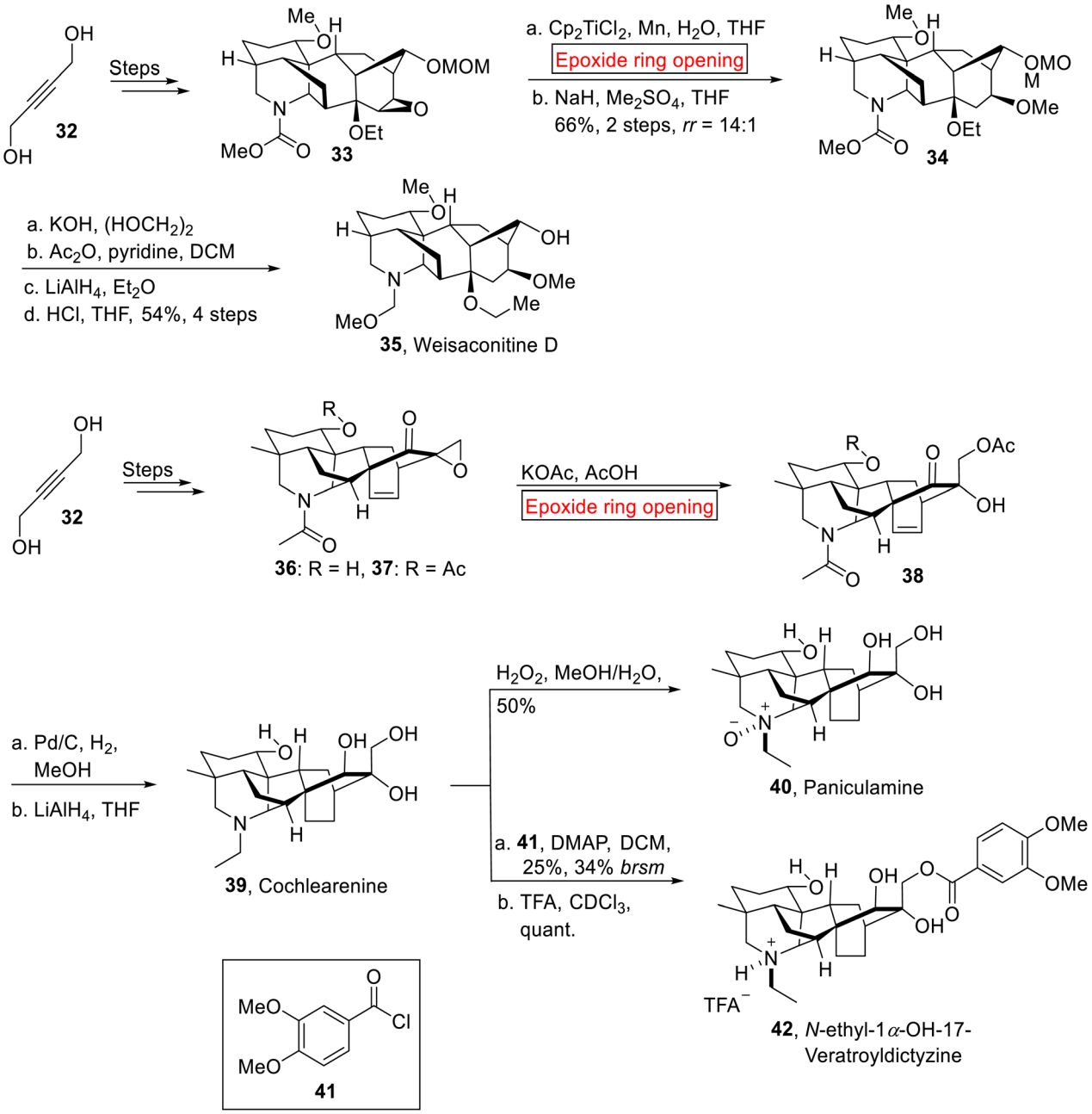
Diterpenoid alkaloids. Weisaconitine D **35**, Cochlearenine **39**, Paniculamine **40** and *N*-ethyl-1α-hydroxy-17-Veratroyldictyzine **42** are polycyclic diterpenoid alkaloids which are extracted from *Aconitum*, *Delphinium*, and *Consolidum* plants. These diterpenoid alkaloids exhibit anti-arrhythmic, anti-inflammatory, analgesic, and other medicinal properties.[69–71] Owing to the structural complexity and pharmacological activities of diterpenoid alkaloids with varying oxygenation and substitution patterns, research group of Sarpong in 2017 reported the first syntheses of C-18, C-19 and C-20 diterpenoid alkaloids by involving ring opening reaction of epoxide.[72] The synthetic route towards C-18 diterpenoid alkaloid (Weisaconitine D) **35** initiated with the formation of epoxy ether **33** from allylic alcohol **32** over few steps. The epoxy ether **33** underwent titanium-mediated epoxide ring opening reaction regioselectivity, followed by methylation, which rendered **34** (66%, 2 steps, rr = 14 : 1). The compound **34** was subjected to KOH-catalyzed hydrolysis, acetylation, $LiAlH_4$-mediated reduction and subsequent deprotection using aq. HCl to furnish Weisaconitine D **35** (54%, 4 steps). Similarly, the synthetic endeavor towards C-20 diterpenoid alkaloids (Cochlearenine **39**, Paniculamine **40**, Veratroyldictyzine **42**) was commenced with the preparation of demethylated products **36** and **37** (51%) from allylic alcohol **32** over few steps. Then, compound **36** and **37** were subjected to KOAc-catalyzed epoxide ring opening reaction to render α-hydroxyketone **38** which was further exposed to Pd/C hydrogenation accompanied by reduction ($LiAlH_4$) to forge Cochlearenine **39** (63–77%, 3 steps). Then, further treatment of **39** with H_2O_2 furnished Paniculamine **40**. Finally, *N*-ethyl-1α-OH-17-Veratroyldictyzine **42** (quant.) was attained by veratroylation of **39** with **41** in DMAP followed by titration with trifluoroacetic acid (TFA) (Scheme 4).

Guaipyridine alkaloid. Cananodine **49a** is a rare[73] guaipyridine alkaloid which was isolated from *Cananga odorata*[74] (ylang–ylang). In South Asia, *C. odorata* has been used in folk medicines. Recently, Cananodine **49a** was isolated from *Cyperus scariosus*.[75] It is biologically potent opposite to Hep 2,2,15 hepatocarcinoma (IC_{50} = 3.8 μg mL^{-1}) and Hep G2 (IC_{50} = 0.22 μg mL^{-1}) cell lines.[76] Various transition metals-mediated cross-coupling reactions have been employed to carry out the synthesis of several intricate organic compounds.[77,78] In 2017, Shelton *et al.* reported the synthesis of optically active Cananodine **49a** by utilizing palladium-mediated cross coupling and epoxide ring opening reaction as significant steps.[79] In the first step, pyridyl iodide **43** and dienylboronate **44** were reacted under Pd-catalyzed cross coupling reaction in the presence of Ag_2O to afford **45** in excellent yield (81%). Next, **45** underwent asymmetric dihydroxylation to furnish diol **46** (52%). In the next step, diol **46** was converted into epoxide **47** (57%) which was further subjected to *n*-butyllithium-mediated intramolecular epoxide ring opening reaction as a key step to provide **48** (33%). Lastly, compound **48** underwent hydrogenation of methylene group in the presence of Wilkinson's catalyst to synthesize Cananodine **49a** and its epimer **49b** as a 1 : 1 inseparable mixture of diastereomers in 49% yield (Scheme 5).

Akuammiline alkaloid. Alstolactine A **54** belongs to a family of akuammiline alkaloids which is genetically related to indole monoterpenoids. It was isolated by Liu and research group of



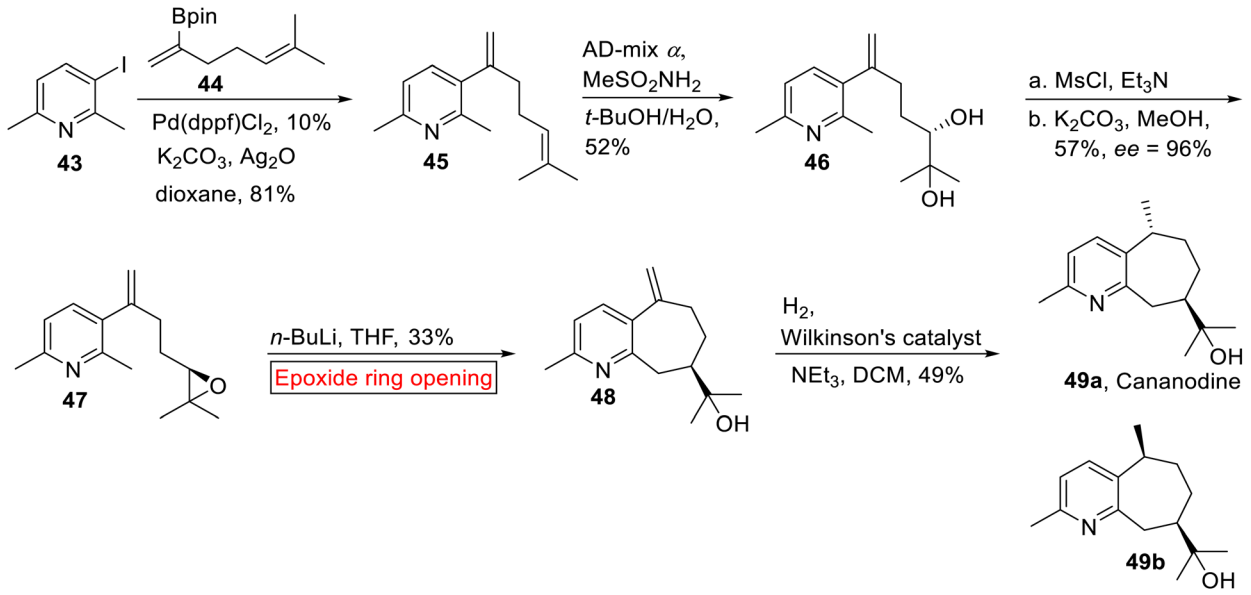
Scheme 3 Synthesis of Murrayakonine D **30**.



Scheme 4 Synthesis of Weisaconitine D **35**, Cochlearenine **39**, Paniculamine **40**, Veratroyldictyzine **42**.

Luo, from leaves of *Alstonia scholaris*.[80,81] In the present research, Gao and co-workers have used an epoxide ring opening reaction for the first total synthesis of Alstolactine A **54** in 2017.[82] The strategies described by research group of Gao may offer a unique perspective in the synthesis of akuammilines and their derivatives for future medicinal studies. The synthetic endeavor commenced with the synthesis of **51** from L-2-allylglycine **50** over several steps, which further experienced base-mediated epoxidation in MeOH to forge epoxide **52** (80%). In the next step, epoxide **52** underwent acid-catalyzed epoxide ring opening reaction to afford compounds **53a** (31%) and **53b** (42%). Finally, compound **53a** was subjected to Pd/C-mediated hydrogenation followed by methylation to furnish asymmetric Alstolactine **54** in 79% yield (Scheme 6).

Bis-indole alkaloid. (−)-Melodinine K **60** is a bis-indole alkaloid which belongs to the class of *Aspidosperma–Aspidosperma* which was isolated from *Melodinus tenuicaudatus* (plant) by Luo and colleagues in 2010.[83] It displays strong cytocidal activity opposite to cell line of breast cancer (IC_{50} = 2.7 μM) as compared to cisplatin (IC_{50} = 18.7 μM) and vinorelbine (IC_{50} = 17.2 μM). In 2020, Andrade and allies disclosed the first synthesis of (−)-Melodinine K **60** by employing epoxide ring opening reaction as one of the key steps.[84] Due to structural complexity and low isolation yield from natural source, they



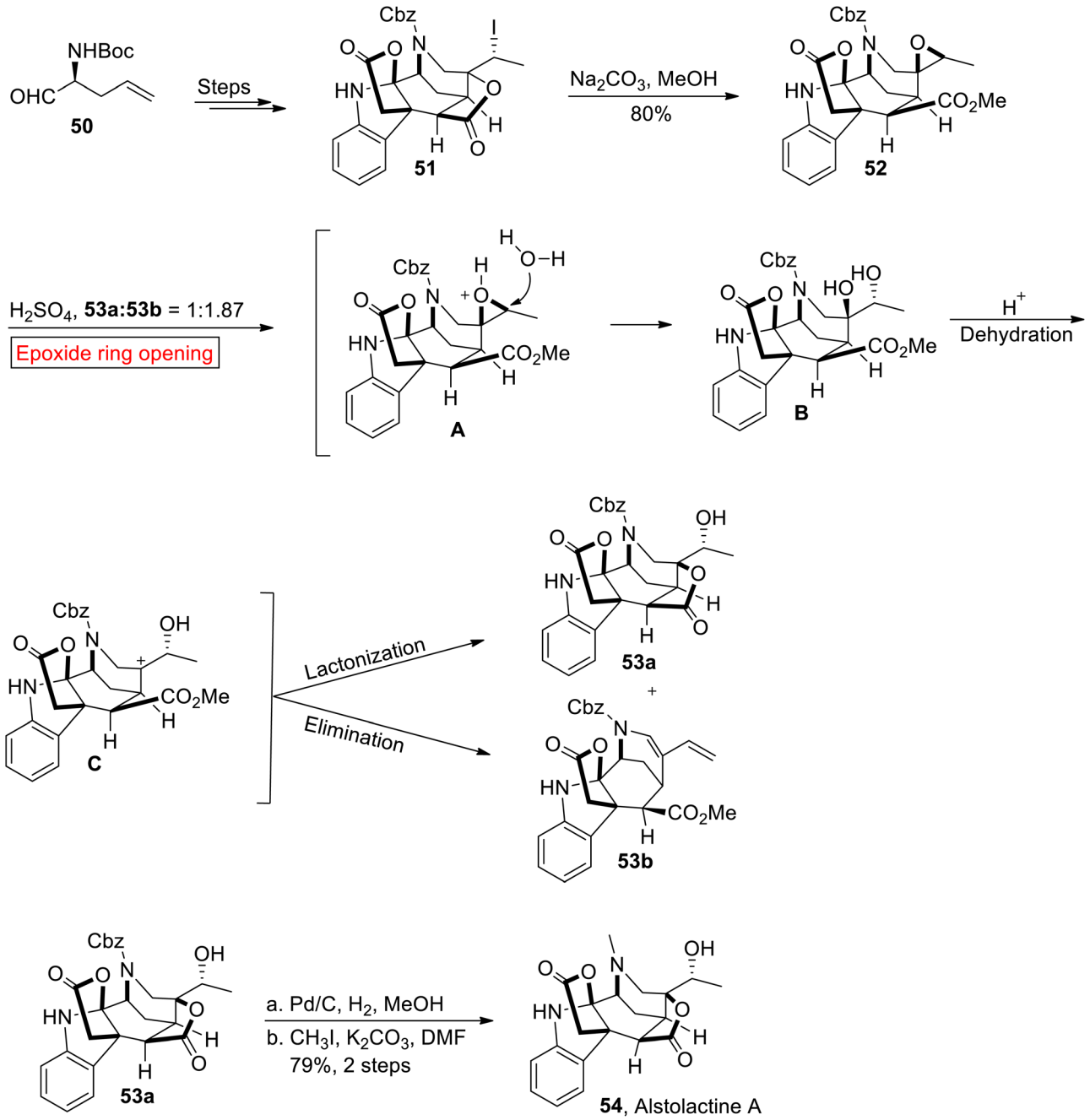
Scheme 5 Synthesis of optically active Cananodine **49a**.

developed an efficient method for the synthesis of (−)-Melodinine K **60** for future research on its biological functions. In the first step, (−)-tabersonine **55** was treated with NaH and TrocCl (2,2,2-trichloroethoxycarbonyl chloride) followed by stereo divergent oxidation in the presence of TFA and *m*-CPBA to afford *N*-Troc pachysiphine **56** (38%). In the next step, compound **56** was treated with *m*-CPBA and then with trifluoroacetic anhydride (TFAA) to afford iminium ion **57**. Then, the stereo divergent attack of iminium ion **57** at the C-15 of (−)-16-allyloxytabersonine **58** followed by Pd $(PPh_3)_4$-catalyzed deprotection afforded alcohol **59**. Finally, alcohol **59** went through epoxide ring opening reaction with subsequent deprotection reaction to forge (−)-Melodinine K **60** in 40% yield (Scheme 7).

Quinolone alkaloid. Virdicatin **65** is a quinolone alkaloid (secondary metabolites) which exhibits antiviral, antibacterial, antiallergic, and antitumor activities.[85,86] Quinolone core containing Virdicatin **65** acts as a scaffold for synthesis of natural and synthetic compounds.[87] In 2021, Chang *et al.* reported the synthesis of Viridicatin **97** by involving epoxide ring opening reaction as one of the key steps.[88] Their research work demonstrates the utilization of natural and synthetic processes for the efficient synthesis of quinolone alkaloids that would suggest promising directions for exploring their biological activities in future studies. In the first step, cyclopeptin **63** was obtained by Asqk (methyl transferase)-mediated cyclization with subsequent treatment (methylation) of **61** with **62.** Then, cyclopeptin **63** was subjected to desaturation accompanied by asymmetric epoxidation in the presence of 2-oxoglutarate (Fe/2OG) dependent oxygenase and AsqJ to synthesize cyclopenin **64**. In the next step, cyclopenin **64** experienced AsqI-catalyzed epoxide ring opening reaction to render Virdicatin **65** (Scheme 8).

Isoquinolones such as Siamine **69**, Cassiarin A **71** and Rupreschstyril **75** are biological active compounds. Research groups of Glorius[89] (2014), Huang[90] (2017) and Kou[91] described the synthesis of isoquinolones in different ways but their synthetic route faced several drawbacks due to coupling partners. In 2021, Wang and coworkers reported the syntheses of isoquinolones by employing epoxide ring opening reaction as one of the key steps for the first time in efficient yield within fewer steps.[92] In the first step, Pd-catalyzed ring opening of epoxide **67** occurred with *N*-methoxybenzamide **98** to render *N*-methoxyisoquinolone **68** in the presence of hexafluoroisopropanol (HFIP) and appropriate base *i.e.*, triethylamine (TEA). In the next step, isoquinolone **68** was converted into Siamine **69** (76%, 2 steps) *via* sequential reduction and demethylation. Similarly, isoquinolone **68** underwent reduction (NaH) followed by coupling with *in situ* prepared propyne to afford alkyne **70** (87%). Finally, Cassiarin A **71** (37%, overall yield) was obtained from alkyne **70** *via* demethylation (BBr_3) with subsequent 6-*endo*-dig cyclization. The synthetic endeavor towards Rupreschstyril **75** was initiated with the formation of isoquinolin-1-one **74** from **72** and epoxide **73** through epoxide ring opening reaction under optimized conditions. Lastly, compound isoquinolin-1-one **74** experienced reduction followed by deprotection (MOM) reaction to afford Rupreschstyril **75** in 83% yield over 2 steps (Scheme 9).

Broussonetine alkaloid. The Glyphaeaside C **84** (iminosugars) having polyhydroxylated phenylalkyl chain belongs to broussonetine alkaloid family which was extracted from *Glyphaea brevis*.[93] Because of side-chain character of Glyphaeaside C **84**, it inhibits almond β-glucosidase, rice α-glucosidase and snail β-mannosidase. In 2021, Pyne *et al.* reported the synthesis of Glyphaeaside C **84** by utilizing epoxide ring opening reaction.[94] For stereochemical reasons, they synthesized **79** by utilizing epoxide ring opening reaction instead of carbonyl addition. Firstly, β-D-arabinofuranose **76** rendered vinylpyrrolidine **77** (28%) *via* treatment over few steps which

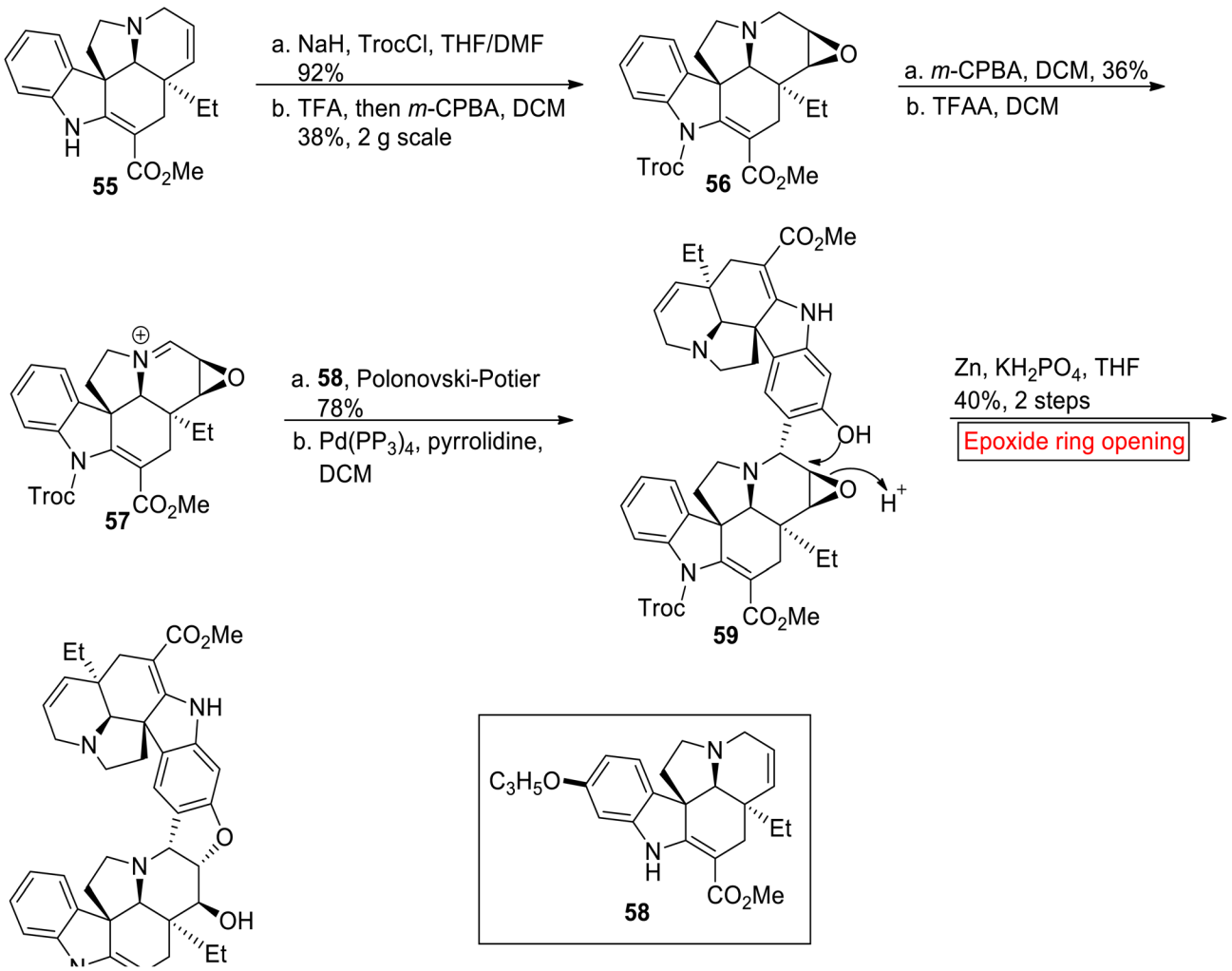


Scheme 6 Total synthesis of Alstolactine A **54**.

upon epoxidation (*m*-CPBA) furnished epoxides **78a** (57%) and **78b** (29%). In the next step, **78a** underwent epoxide ring opening reaction in the presence of Gilman reagent in THF to synthesize alcohol **79** in a good yield (84%). Secondly, 4-allylanisole **80** was subjected to *O*-demethylation with BBr_3 (in DCM) accompanied by benzylation (acetone) to yield **81** (44%). In the next step, alkene **82** was prepared by the Grrubs' I-catalyzed reaction of **79** with **81**. Finally, alkene **82** was reacted with AD-mix-α/AD-mix-β (Sharpless asymmetric dihydroxylation) with subsequent deprotection reaction to furnish four enantiomers **83a**/**83a**′, and **83b**/**83b**′ respectively. According to the specific rotation data, it was suggested that **83a** was the enantiomer of Glyphaeaside C **84** (Scheme 10).

Syntheses of terpenoid-based natural products

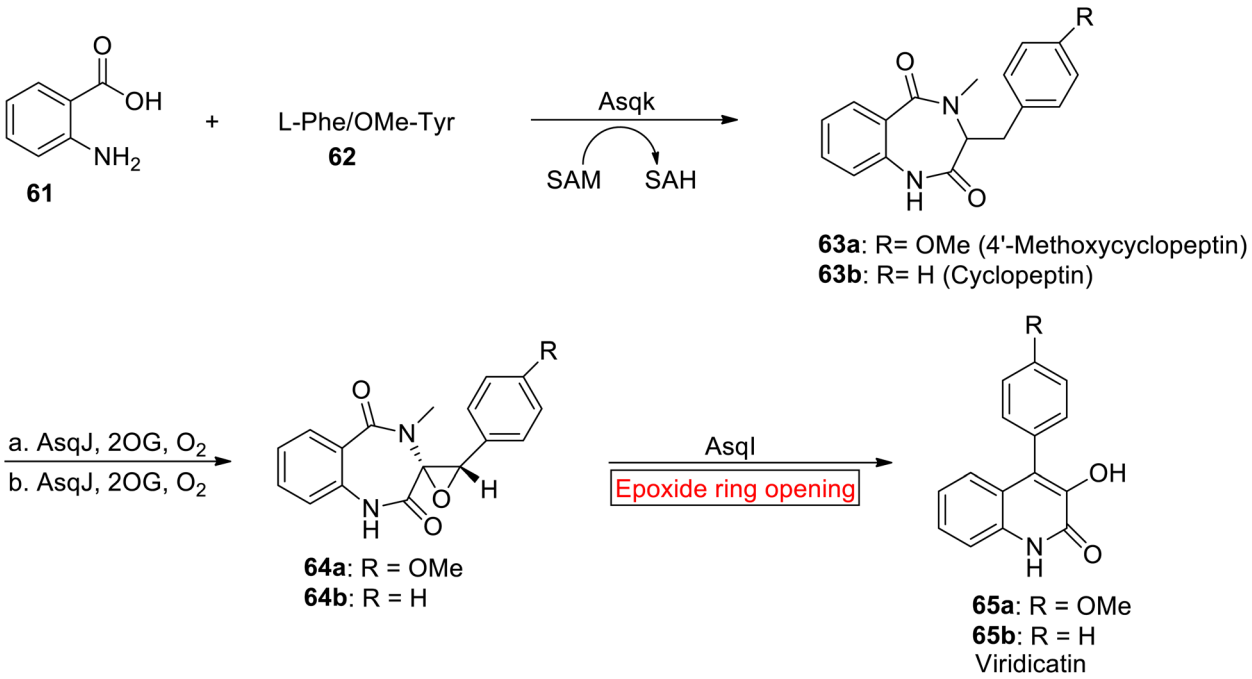
Diterpenoid. Eurifoloid A **94** is a diterpenoid, belongs to a phorboid family of natural product which was extracted from *Euphorbia neriifolia*.[95] It exhibits biological activities[96] such as antitumor and anti-HIV. Synthesis of Eurifoloid A **94** has remained a challenging task[97] for chemists due to the presence of congested stereogenic centers such as quaternary stereocenter, angeloyloxy and tigloyloxy groups in its structure. Liu[98]



Scheme 7 Synthesis of (−)-Melodinine K **60**.

and colleagues, first time reported the synthesis of tricyclic core **93** of Eurifoloid A **94** by employing ring opening reaction of epoxide as one of the key steps in 2017. The synthetic route initiated by the reaction of compound **85** with alkyl bromide **86** using Mg, THF (*in situ* Grignard reagent) followed by Wittig reaction to generate *Z*-vinyl iodide **87** (70%). In the next step, bromofuran carbaldeyde **88** underwent reduction (DIBAL-H), followed by protection and then Br–Sn exchange yielded tin reagent **89** (90%). Further, *Z*-vinyl iodide **87** and tin reagent **89** were reacted under Stille coupling conditions. Later, TBS group deprotection rendered coupled product **90** (70%). The coupled product **90** further experienced oxidative rearrangement and then type II intramolecular [5 + 2] cycloaddition reaction in the presence of tetramethylpiperidine (TMP) to provide the compound **91** (30%) having [5-7-7] tricyclic core. Compound **91** was then subjected to sequential diastereoselective reduction and *m*-CPBA-mediated oxidation (DCM) to furnish the epoxide **92** (79%). Finally, the ring opening reaction of epoxide **92** in the presence of $BF_3 \cdot Et_2O$ using DCM as solvent, resulted in the core structure **93** (that contains reduced strain bicyclo[4.4.1] undecane ring system featuring *cis*-bridgehead) of Eurifoloid A **94** but with opposite stereochemistry at C8 (Scheme 11).

(±)-Brussonol **104** and (±)-Komaroviquinone **106** belong to a family of ictexane diterpenes, isolated from terrestrial plants containing fused tricyclic skeleton (6-7-6). (±)-Brussonol **104** and (±)-Komaroviquinone **106** display antiprotozoal, anticancer and cytotoxic activities. These natural products were synthesized by a number of reactions such as Ga(III)-catalyzed cycloisomerization,[99] tandem C–H oxidation/cyclization/rearrangement,[100] intramolecular Marson-type cyclization,[101] Pd-catalyzed intramolecular Heck reaction,[102] intramolecular nucleophilic cyclization,[103] cationic ring expansion,[104] $TiCl_4$-catalyzed Friedel–Crafts cyclialkylation[105,106] and Pt-mediated hydrative cyclization.[107] In 2019, Burtoloso and Ahmad[108] disclosed the syntheses of (±)-Brussonol **104** (18.4%, overall yield) and (±)-Komaroviquinone **106** (7% overall yield) by utilizing regioselective epoxide ring-opening reaction. The method developed by Burtoloso and Ahmad facilitated the efficient synthesis of these compounds till date, in order to achieve high yields in less steps as compared to previous approaches by employing similar starting materials. The synthetic approach

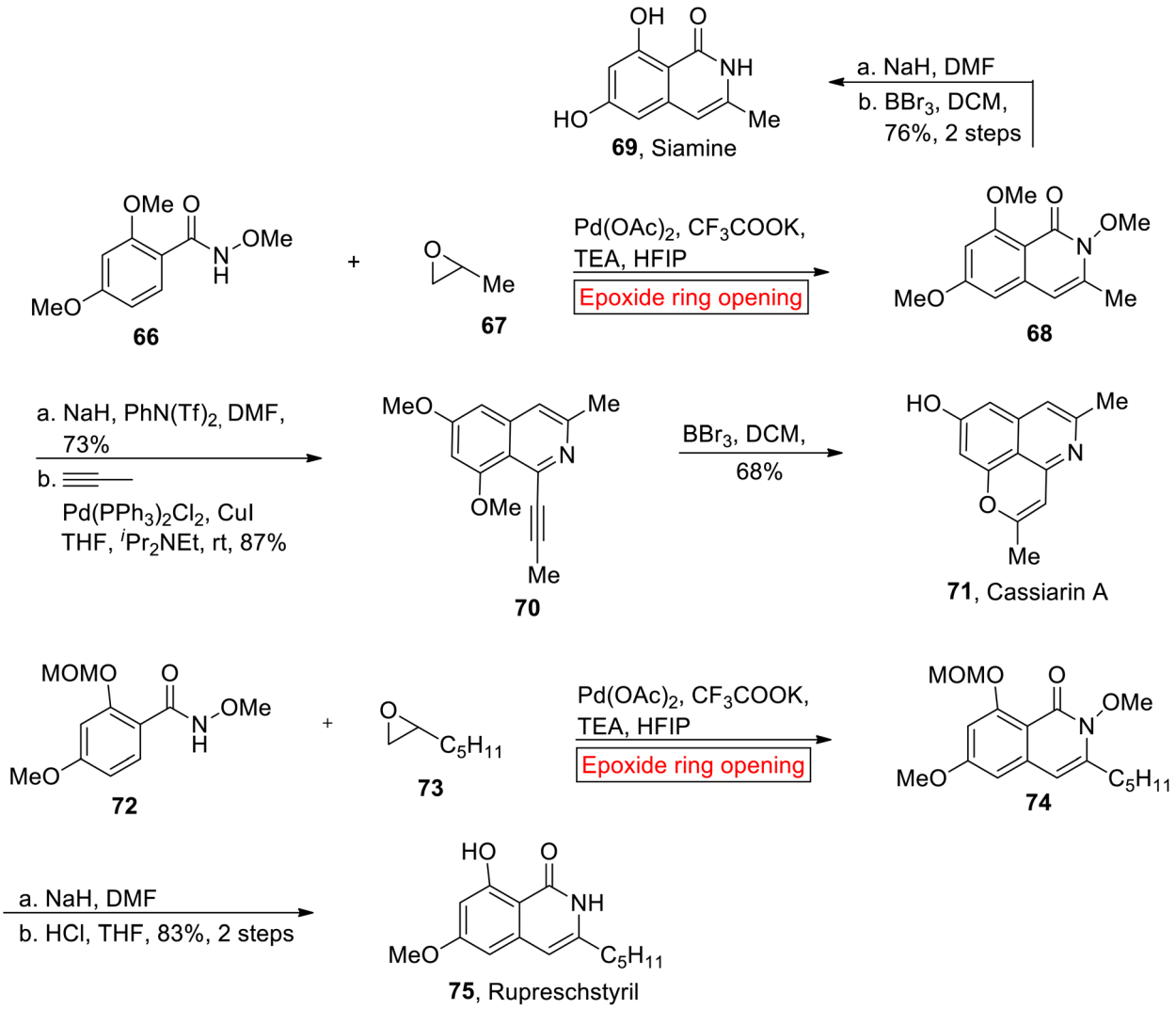


Scheme 8 Synthesis of Viridicatin **65**.

towards (±)-Brussonol **104** and Komaroviquinone **106** was initiated with the formation of coupling fragment **98.** In the first step, α, β-unsaturated ketone **95** experienced Michael addition reaction with MeMgBr in the presence of DPMU and $CuBr \cdot SMe_2$, followed by enolate quenching with allyl bromide **96** and Corey–Chaykovsky epoxidation to forge single diastereomer of epoxide **97** (88%). In the next step, epoxy-aldehyde **98** (89%) was obtained by Lemieux–Johnson oxidation of epoxide **97**. Then, aryl ester **99** underwent nucleophilic addition reaction (MeMgBr) followed by dehydration/hydrogenation reaction and selective bromination in the presence of tetramethylethylenediamine (TMEDA) and Et_2O to afford aryl bromide **100** (65–81%). Similarly, the coupling partner 1-bromo-4-isopropyl-2,3,5-trimethoxybenzene **102** was synthesized from 1,2,4-trimethoxybenzene **101** over few steps. Then, the epoxide **98** was coupled with aryl bromide **100** and trimethoxybenzene **102** individually *via* Zn-catalyzed epoxide ring opening reaction in the presence of NaI, $Et_3N \cdot HCl$ and 4,4′-dimethoxy-2,2′-bipyridine (DMBP) to yield acetals **103** (40%) and **105** (25%) respectively. Acetal **103** was then subjected to Friedel–Crafts cyclization followed by sodium thiolate-mediated demethylation to furnish (±)-Brussonol **104** (89%). Similarly, diastereoselective (±)-Komaroviquinone **106** was obtained from acetal **105** over few steps (Scheme 12).

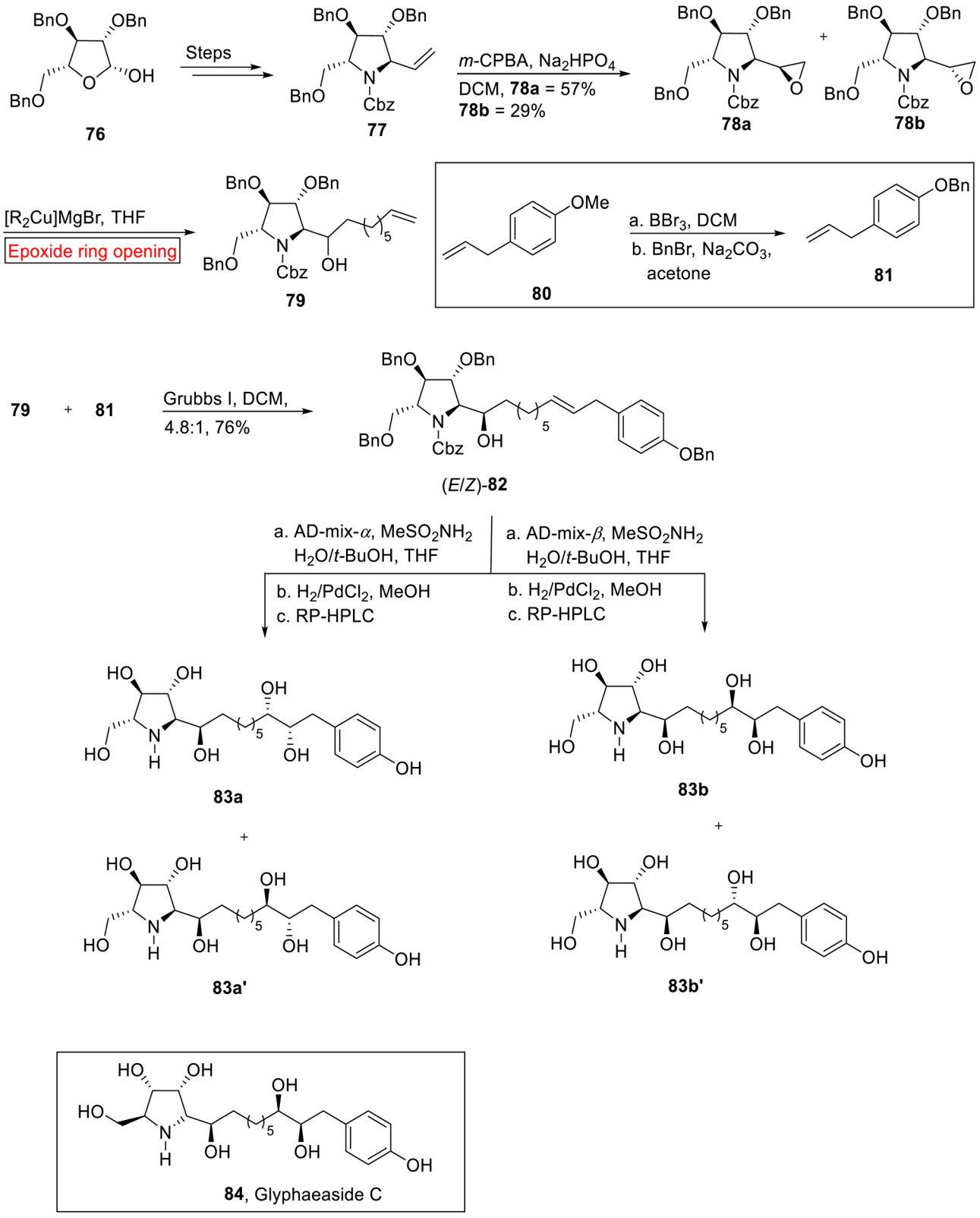
(−)-Scabrolide A **116** is a norcembranoid diterpenoid which belongs to the family of marine natural products.[109] In 2002, it was isolated for the first time from *Sinularia scabra* (soft coral) by the research group of Sheu.[110] (−)-Scabrolide A **116** acts as an anti-inflammatory agent[111] as it inhibits the production of IL-6 and IL-12. In 2020, Stoltz[112] reported the first total synthesis of (−)-Scabrolide A **116** by employing epoxide ring opening reaction as one of the key steps. This research report represented the first synthesis of any member of polycyclic furanobutenolide-derived norcembranoid diterpenoid family that have remained elusive to synthetic efforts for over two decades since their original discovery. The synthetic route began with the preparation of dihydroxyvinyl cyclopentene **108** and ynoic acid **110** which were utilized as the starting materials for the synthesis of (−)-Scabrolide A **116.** In the first step, cyclopentene **108** and ynoic acid **110** were synthesized individually from enone **107** and monoprotected dialdehyde **109** respectively over few steps. Compounds **108** and **110** were reacted under Steglich conditions followed by Diels's reaction to yield Diels's alder adduct with subsequent epoxidation to furnish intermediate **111** (94%). In the next step, intermediated **111** was exposed to Cp_2TiCl_2-mediated epoxide ring opening reaction in the presence of collidine·HCl, 1,4-cyclohexadiene (1,4-CHD), THF and Mn^0 to render diol **112** (86%, dr = >20 : 1). The diol **112** was further treated with 2-iodoxybenzoic acid (IBX) accompanied by selective epoxidation to afford mixture of epimers in good yield **113** (87%, 1.7 : 1). Then, the mixture **113** experienced Ru-mediated hydrosilylation to generate diastereomeric mixture of **114** (85%). In the next step, compound **114** was subjected to irradiation in the presence of PhH followed by Cp_2TiCl_2-mediated reductive epoxide ring opening reaction by utilizing earlier mentioned conditions (1,4-CHD, collidine·HCl, THF) to produce diol **115** (dr = 1.7 : 1, 70%). The resulting diol **115** was converted to (−)-Scabrolide A **116** over few steps (Scheme 13).

Flowering plants that belong to genus *Marrubium* are found in temperate and Mediterranean region.[113] These plants are used as a local medicine in Eurasion zone due to the presence of Marrubiin **122** (furanoid) compound as it acts as analgesic, vasorelaxant, antispasmodic, anti-diabetic, hypoglycemic and anti-inflammatory agent.[114] Marrubiin **122** is a labdane



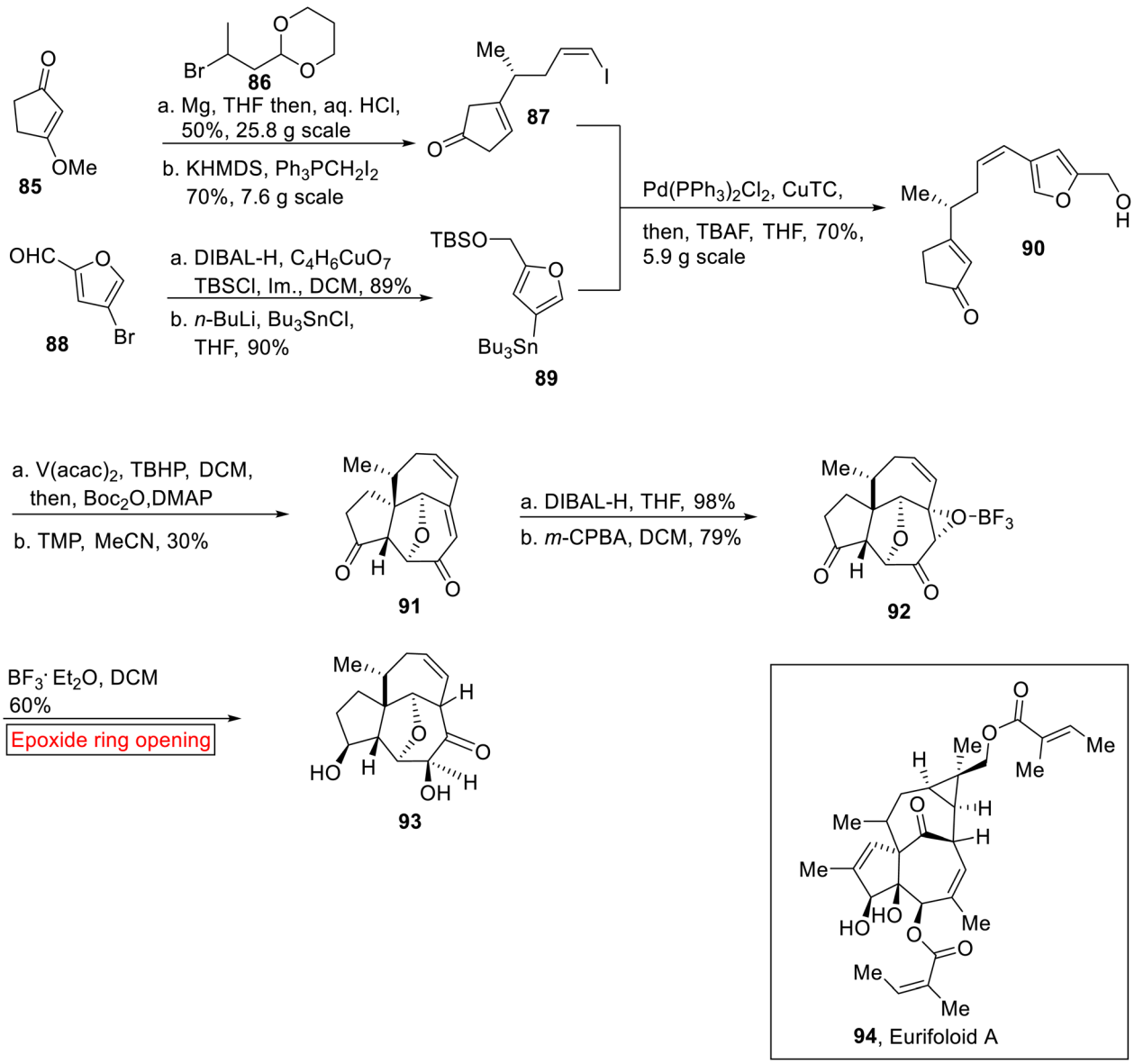
Scheme 9 Synthesis of Siamine **69**, Cassiarin A **71**, and Rupreschstyril **75**.

diterpene lactone which was extracted from *Marrubium vulgare* in 1842 for the first time and later its effect on rat aorta[115] was also explored. The phytochemical analysis of this family (mints) also led to the isolation of various labdane diterpene lactones.[116] Previously, research group of Mangoni[117] described the total synthesis of Marrubasch F, Marrulibanoside, Premarrubiin (semi-syntheses) and Marrubiin (racemic form). Nakamura *et al.* disclosed the stereoselective total syntheses of Marrubasch F **121**, Marrubiin **122**, Desertine **124b**, Marrulibacetal **159a**, Marrulibacetal A **125b**, Marrulactone **129**, Marrulanic acid **130** and Cyllenine C **132** in 2020.[118] Their synthetic approach features the extention of C-9 side chain of **118** *via* nucleophilic epoxide ring opening reaction with high level of malleability and convergency. The synthetic route initiated with the preparation of epoxide intermediate **118** from the enyne **117** over few steps. In the next step, intermediate **118** underwent epoxide ring opening reaction with Grignard reagent **119** in the presence of $CuBr{\cdot}SMe_2$ (Et_2O) to afford **120** (76%) which was then exposed to oxidation (*m*-CPBA, DCM) to furnish Marrubasch F **121** (57%). In the same way, Marrubiin **122** (70%) was obtained by the deprotection (BuNF, THF) of TMS group of **120**. Marrubiin **122** went through oxidative acetalization (pyridine·HBr) followed by reaction with NMO (4-methylmorpholine *N*-oxide) in aq. THF to provide Desertine **124b** along other isomers. Mixture of diols **123a** and **124a** were treated with TsOH and PhH to generate Marrulibacetal **125a** and Marrulibacetal A **125b** respectively. Some other isomers and diastereomers were also formed with them. In accordance, intermediate **118** experienced Cu-catalyzed epoxide ring opening reaction with Grignard reagent **127** to render alcohol **128** (48%), which was further exposed to desilylation with subsequent oxidation to forge Marrulactone **129** (91%). Then, the Marrulactone **129** was converted to Marrulanic acid **130** (84%) *via* LiOH-mediated regioselective saponification. Synthesis of Cyllenine C **132** (96%) was achieved by nucleophilic epoxide ring opening reaction of intermediate **118** in the presence of lithium acetylide ethylenediamine in dimethyl sulfoxide (DMSO) to afford alcohol **131** (95%) followed by gold(I)-mediated cycloisomerization/oxidation sequence (Scheme 14).



Scheme 10 Synthesis of Glyphaeaside C **84**.

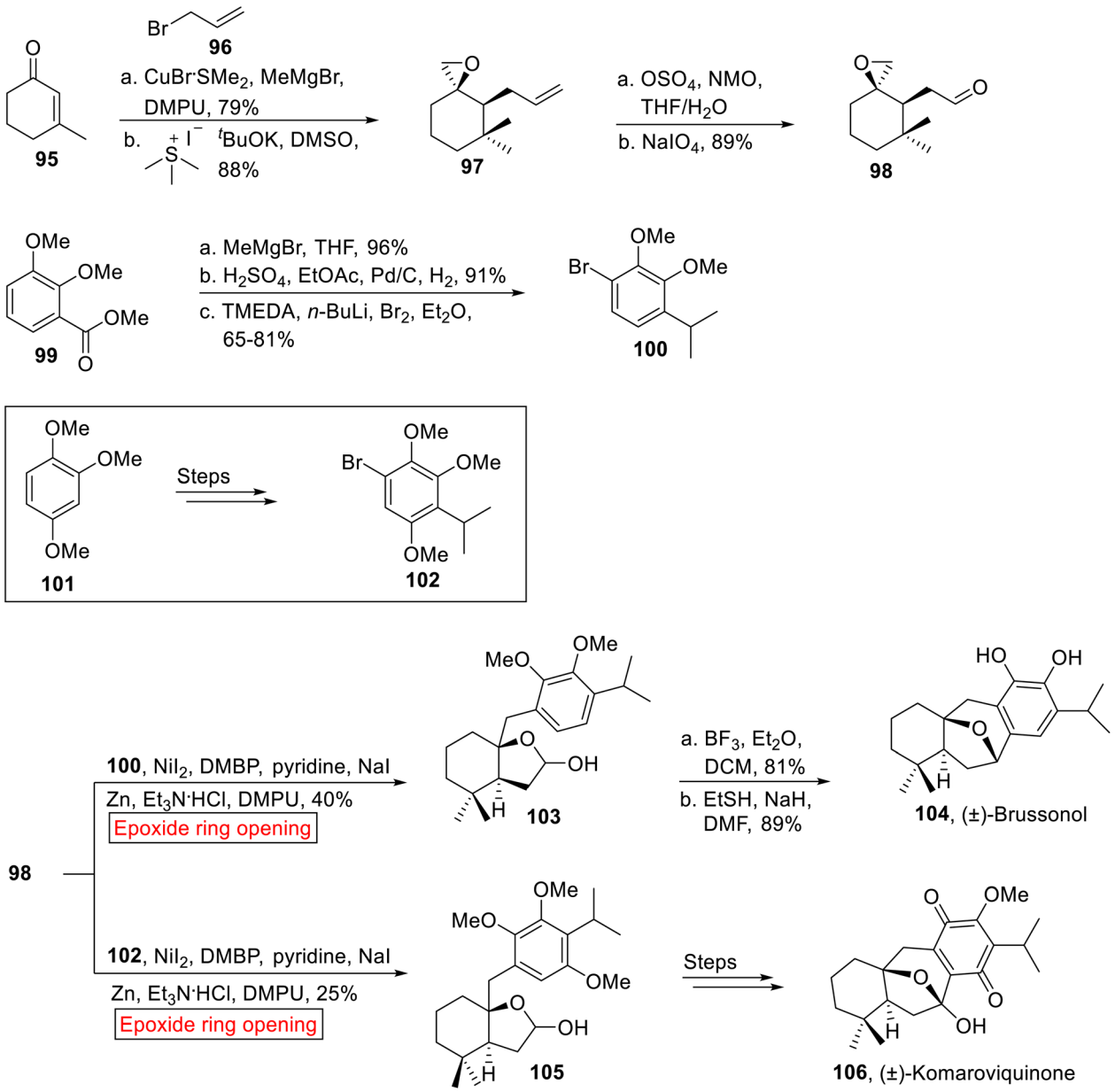
(±)-Rameswaralide **140** is a diterpene related to the class of secondary metabolites[119] (a marine cembranoid), which was extracted in 1998 (ref. 120) from *Sinularia dissecta* (soft coral) featuring a tricyclic skeleton. It exhibits anti-inflammatory and anti-cancer activity.[121] In this regard, development of various anticancer agents has been the focus of researchers.[122] In 2022,



Scheme 11 Synthesis of tricyclic core **93** of Eurifoloid A **94**.

research group of Romo developed an elegant approach toward the first total synthesis of (±)-Rameswaralide **140** by employing ring opening reaction of epoxide as one of the key steps.[123] The synthetic route initiated with the syntheses of epoxy α-bromo enone **134** from **133** over few steps. The stannane **136** was obtained from vinyl iodide **135** *via* sequential alkylation, treatment with *n*-BuLi and tributyl tin chloride. In the next step, epoxy α-bromo enone **134** and stannane **136** upon Stille coupling followed by base-catalyzed oxidation with subsequent ring opening reaction of epoxide under desilylation conditions afforded α-methelyene butyrolactone **137** (44%, 2 steps). The compound **137** was further subjected to $Pd(OAc)_2$-catalyzed oxidation followed by Stork enamine cyclization to render **138a** (26%) and **138b** (4%) diastereomers. In the next step, major diastereomeric ketone **138a** was treated with **139** under Julia–Kocienski olefination by utilizing optimized conditions to forge (±)-Rameswawalide **140** in 32% yield (Scheme 15).

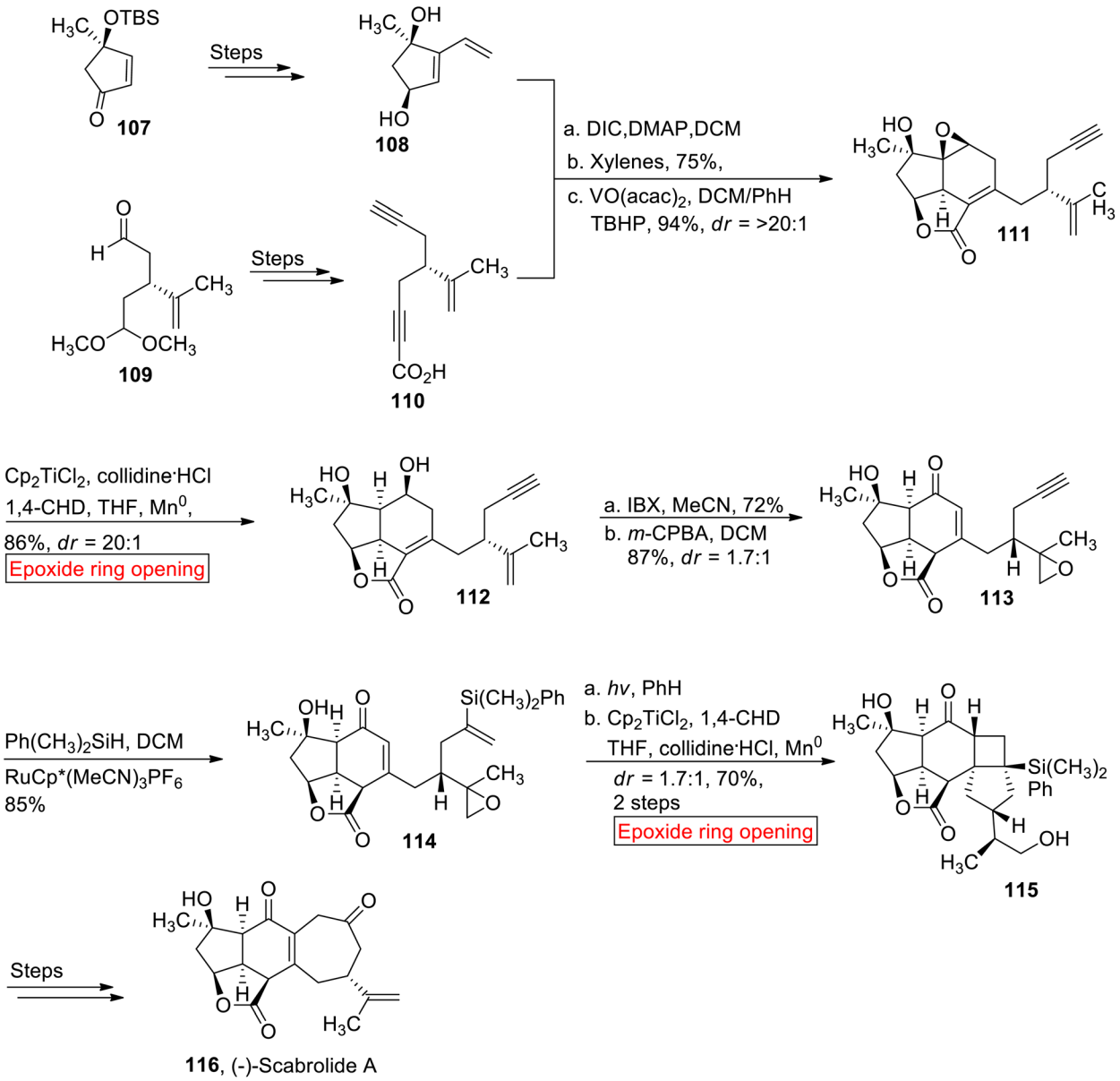
(+)-Ryanodine was extracted from *Ryana speciosa* Vahl (plant) found in South America.[124] In 1967, ryanodine's structure was disclosed by Wiesner[125] and afterward reported by Deslongchamps.[126] The *de novo* synthesis of Ryanodine and Ryanodol (hydrolysis product of Ryanodine) was very difficult because they are composed of eleven stereogenic centers. Previously different efforts have been reported on the preparation of these targets, Ryanodol by Deslongchamps,[126] Ryanoid by Inoue[127] and recently Ryanodol by Reisman.[128] In 2020, Micalizio *et al.* reported the synthetic approach towards the novel synthesis of Ryanodol **146** that was achieved by the synthesis of its degradation product (+/−)-Anhydroryanodol **145**.[129] They utilized carbocyclic approach for the synthesis of (+/−)-Anhydroryanodol **145** by employing epoxide ring opening reaction as of the key steps. Initially, divinyl epoxide **142** was obtained from alkyne **141** over few steps. In the next step, divinyl epoxide **142** went through sequential deprotection (TASF = trissulfonium



Scheme 12 Synthesis of (±)-Brussonol **104** (±)-Komaroviquinone **106**.

difluorotrimethylsilicate), oxidation (TPAP = tetrapropylammonium perruthenate, NMO), base (NaOH)-catalyzed epoxide ring opening reaction in DCM. Then, subsequent ring-closing metathesis afforded a mixture of lactones **143a** and **143b** in equal amount. Compound **143a** was also converted into **143b** (65%) in the presence of base (NaOH). Then, **143b** was silylated selectively by treating it with neat TMS-Im (imidazole) to forge **144.** In the next step, (+/−)-Anhydroryanodol **145** (38%, 2 steps) was obtained by *m*-CPBA-mediated epoxidation, Cp_2TiCl_2-catalyzed epoxide ring opening reaction in the presence of Et_3SiH followed by TASF-mediated deprotection. Finally, (+/−)-Anhydroryanodol **145** was converted into (+/−)-Ryanodol **146** (38%) *via* site-specific epoxidation (CF_3CO_3H) followed by Li/NH_3-catalyzed epoxide ring opening reaction reported by Deslongchamps[126] and Reisman[128] (Scheme 16).

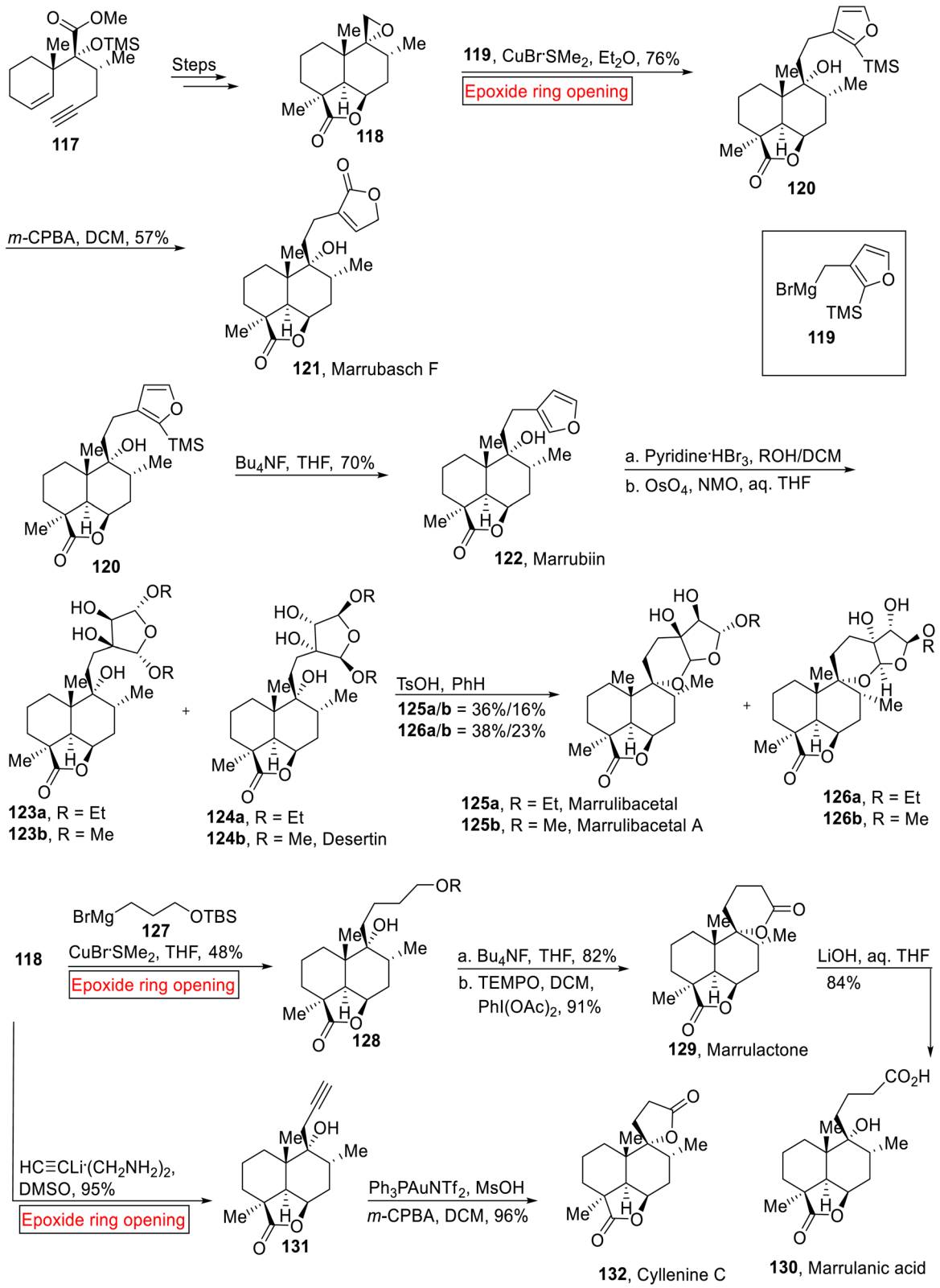
Triterpenoid. Isodehydrothyrsiferol **154** belongs to the family of triterpenoid[130] which was drawn from *Laurencia viridis* (red alga) by Munro and colleagues in 1978.[131] It depicts potent cytocidal activity opposite to P388 cell lines (IC_{50} = 17 nm).[130] It has unique structural features because it displays partial enantiodivergent as a novel phenomenon in the biosynthesis of natural products. In 2017, research group of Morimoto disclosed the synthesis of Isodehydrothyrsiferol **154** by employing epoxide ring opening reaction as a key step.[132] In the first step, 2,3-epoxy alcohol **147** experienced $Ti(O^iPr)_4$-mediated epoxide ring opening reaction in the presence of PivOH and toulene to generate pivalate **148** (99%). The resulting pivalate **148** was further converted into another epoxide **149** (87%, 2 steps) by sequential protection and



Scheme 13 Synthesis of (−)-Scabrolide A **116**.

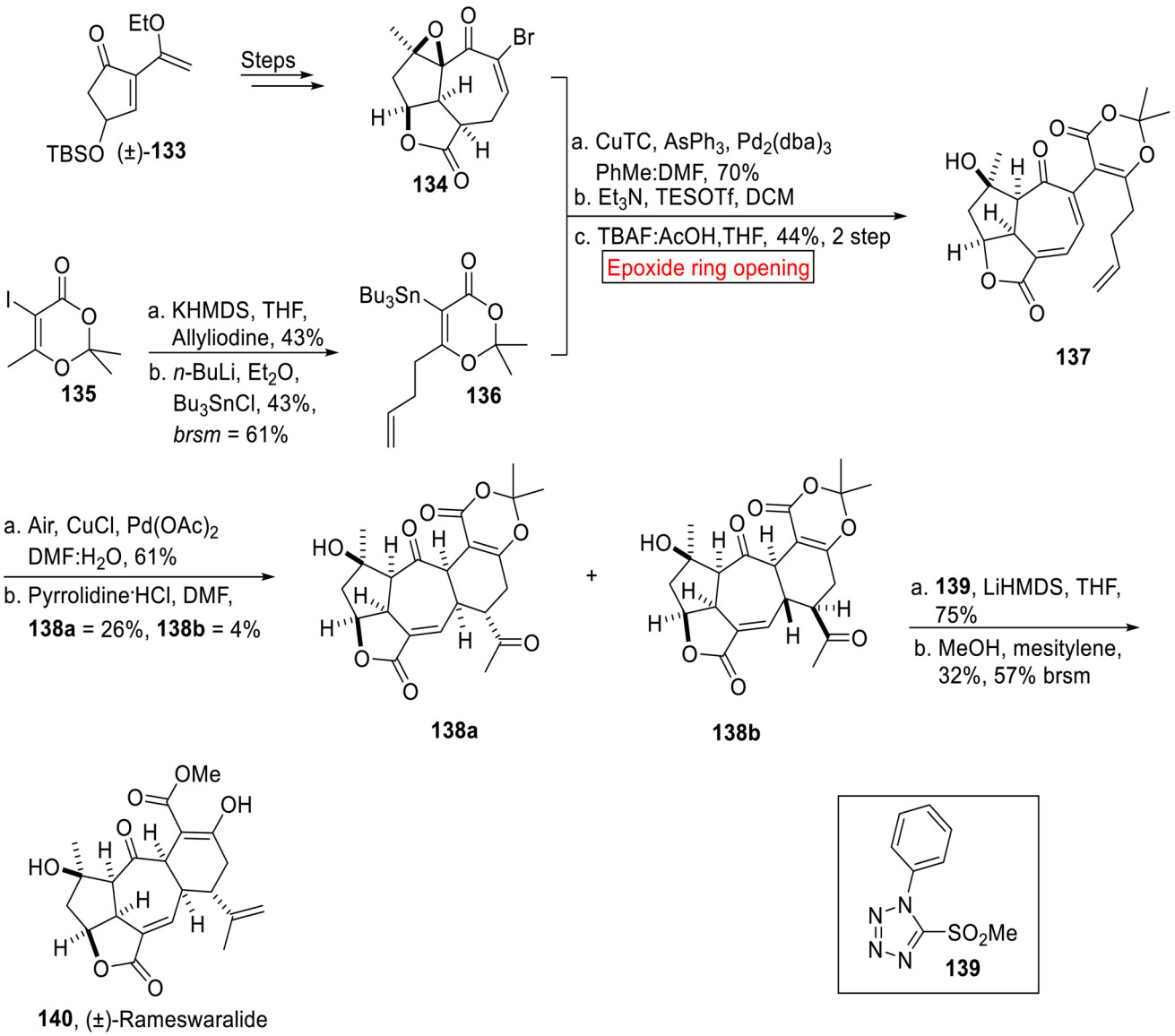
epoxidation. Next, geranyl phenyl sulfide **150** was added to **149** followed by reaction with Na, ^{i}PrOH to furnish compound **151** (90%, over 2 steps). The tertiary alcohol moiety of compound **151** was exposed to protection with TESCl (Triethylchlorosilane) and then diastereoselective epoxidation provided epoxide **152** (58%). In the next step, the –OH group of compound **152** underwent protection followed by TBAF-mediated epoxide ring opening reaction in THF with subsequent deprotection (^{t}BuOK) to attain **153** (75%). The synthesized compound **153** was finally converted to Isodehydrothyrsiferol **154** over few steps (Scheme 17).

Indole sequequiterpenenoids. Xiamycin A **163** and Dixiamycin C **167** are indole sequequiterpenenoids which were extracted by Hertweck[133–136] and Zhang[137–139] from *Streptomyces* species. Xiamycin **163** and Dixiamycin C **167** demonstrate substantial inhibitory activity opposite to herpes simplex virus-1 (HSV-1). Recently, work on Xiamycin A **163** and Dixiamycin B was reported by research group of Baran[140] for the first. In 2015, Meng *et al.* described the total synthesis of Xiamycin **163** and Dixiamycin C **167** (for the first time) by employing epoxide ring opening reaction as one of the key steps.[141] The synthetic route started with the preparation of α, β-epoxy ester **156** (76%, 2 steps) from optically active epoxide **155** through AZADO (2-azaadamantane *N*-oxyl)-mediated oxidation and esterification. Next, the compound **156** underwent Cp_2TiCl_2-catalyzed epoxide ring opening reaction in the presence of $^{i}Pr_2Net$, TMSCl, Mn and THF to furnish *trans*-decalin **157**. In the next step, compound **158** (44%, 3 steps) was obtained from decalin **157** *via* TBS protection accompanied by acetyl deprotection. Then, compound **158** was subjected to oxidation (using DMP)



Scheme 14 Total syntheses of Marrubasch F **121**, Marrubiin **121**, Desertine **124b**, Marrulibacetal **125a**, Marrulibacetal A **125b**, Marrulactone **129**, Marrulanic acid **130** and Cyllenine C **132**.

followed by Grignard addition (**159** or **160**) with subsequent dehydration in the presence of MsCl/^{i}Pr$_2$Net to afford triene **161** or **162**. Next, triene **161** or **162** experienced thermal 6π-electrocyclization accompanied by aromatization, desulfonation and TMSE deprotection to achieve Xiamycin A **163** in excellent yield (95%). Similarly, compounds **164** and **165** were

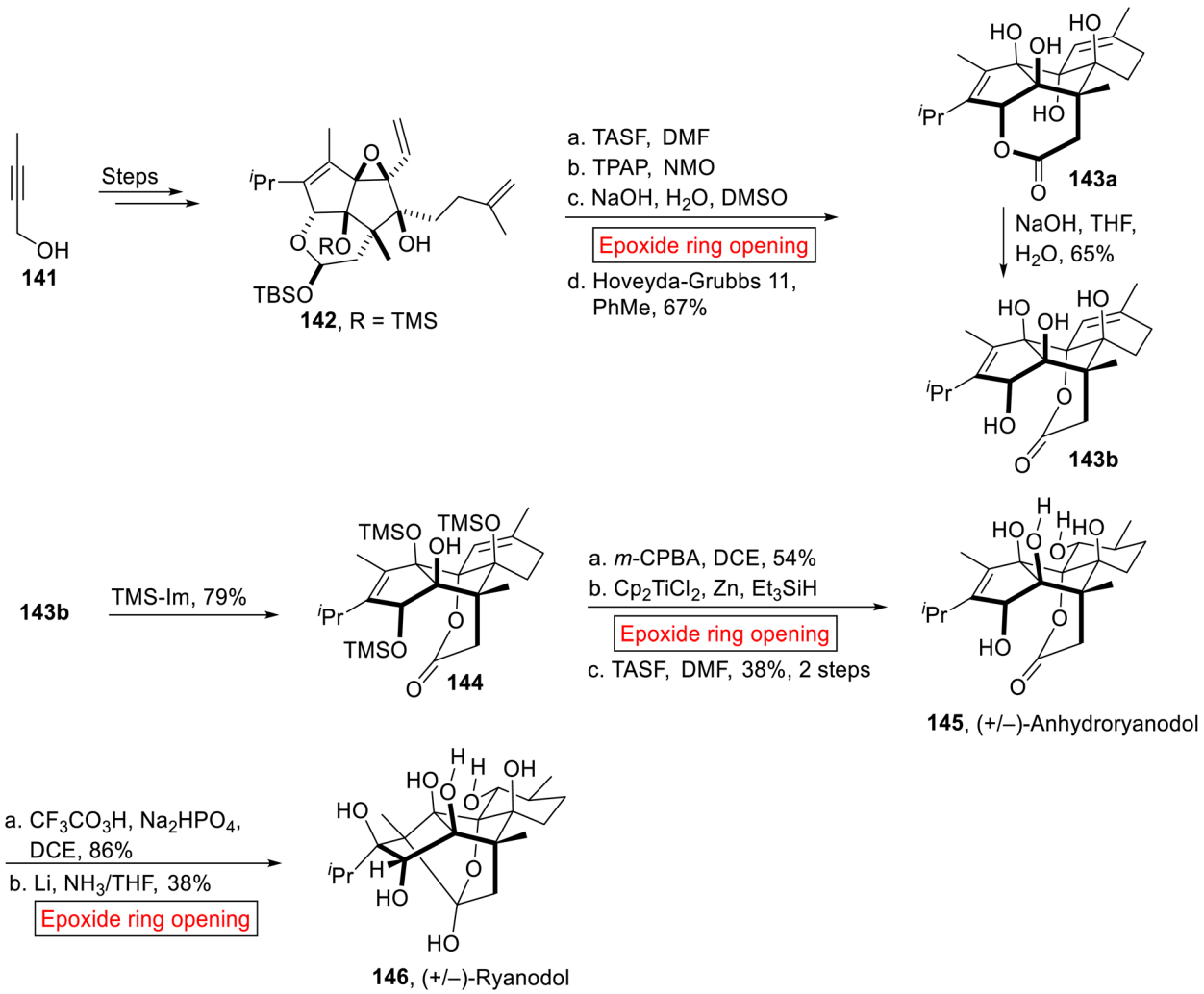


Scheme 15 First total synthesis of (±)-Rameswaralide **140**.

reacted with compound **166** in the presence of CuI followed by deprotection with TSAF to render Dixiamycin C **167** (96%, over 2 steps) in a good yield (Scheme 18).

Meroterpenoid. (−)-Siphonodictyal B **170** (marine sponge) and (+)-Liphagal **171** belong to the meroterpenoid family of natural products. (+)-Liphagal **171** was extracted by Andersen and colleagues from *Aka coralliphaga*[142] while Siphonodictyal B was also isolated from *Aka coralliphaga* by the research groups of Faulkner[143] and Köck.[144] Its structure was first reported in 1981 by Faulkner and colleagues and then was revised by Clardy and coworkers[145] (1986). In 2015, George *et al.* reported the correct revised structure of (−)-Siphonodictyal B **170** which was then converted into (+)-Liphagal **171** by employing epoxide ring opening reaction as one of the key steps.[146] Their research work highlights the significance of biosynthetic suppositions which help in the development of innovative sequential reactions and structural reassignment of natural products. The synthetic route commenced with the preparation of benzylic alcohol **169** from (+)-sclareolide **168** over few steps. In the next step, alcohol **169** underwent $POCl_3$-mediated dehydration followed by *ortho*-lithiation, then quenching by utilizing DMF with subsequent deprotection (BCl_3) of isopropyl ether to afford (−)-Siphonodictyal B **170** (77%). Finally, synthesis of (+)-Liphagal **171** (42%) was achieved by *m*-CPBA-mediated epoxidation in the presence of $NaHCO_3$ and CCl_4 accompanied by TFA-catalyzed epoxide ring opening reaction (Scheme 19).

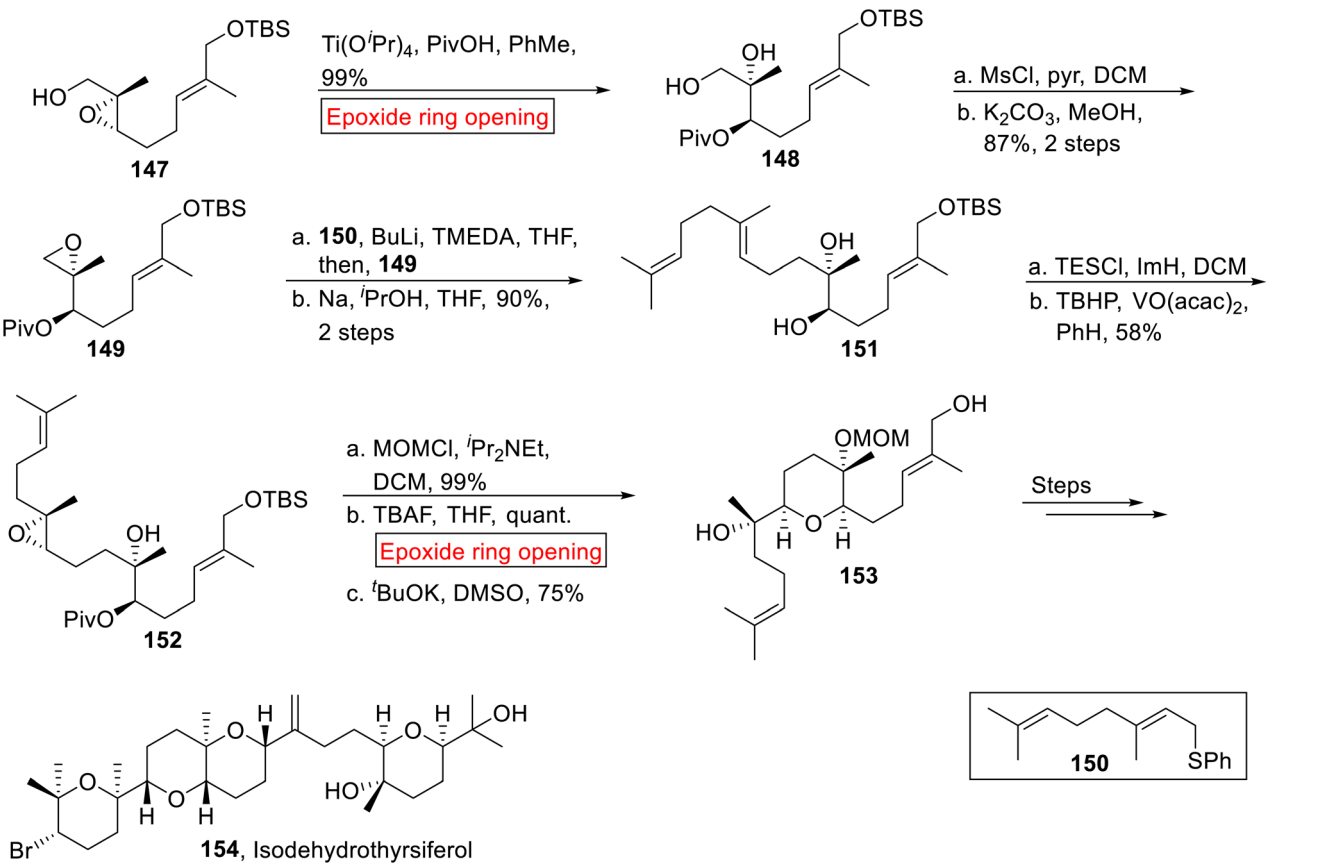
Rhodonoids C **174** and D **175** belong to the class of meroterpenoids extracted from *Rhododendron capitatum*.[147] Rhodonoids C **174** and D **175** have 6/6/6/5 and 6/6/5/5 ring systems respectively. In 2017, research group of Day[67] synthesized Rhodonoids C **174** and D **175** by using Chromene **172** (meroterpenoid) which was prepared according to Hsung and colleagues[148] from orcinol and citral. In the first step, prenyl side chain of Chromene **172** underwent *m*-CPBA-mediated



Scheme 16 Synthesis of (+/–)-Anhydroryanodol **145**.

epoxidation to furnish diastereomer **173** (51%, dr = 1 : 1). Then, **173** experienced $SnCl_4$-catalyzed epoxide ring opening reaction with subsequent cyclization in the presence of $CHCl_3$ to synthesize Rhodonoids C **174** (32%), D **175** (5%) and **176** (Scheme 20).

Sesquiterpenoids. Heronapyrrole C **186** belongs to a sesquiterpene (rare nitropyrrole) family of natural product which was isolated from the culture of *Streptomyces* sp. (CMB-M0423) in 2010 (Australia).[149] Considering the widespread microbial diseases, researchers are continuously making efforts to develop efficient anti-microbial agents.[150] Nitropyrrole natural products exhibit activity opposite to Gram-positive bacteria without exhibiting cytocidal activity towards mammalian cell lines. In 2012, Stark disclosed the synthesis of Heronapyrrole C with less yield.[151] In 2014, Brimble *et al.* reported the regioselective synthesis of (+)-Heronapyrrole C **186** by employing epoxide ring opening reaction as one of the key steps.[152] Their strategy was based on the synthesis of regiocontrolled 2-nitropyrrole building blocks that have received limited attention until now. The synthetic scheme towards (+)-Heronapyrrole C **186** began with the syntheses of aldehyde fragments **178a** and **178b** from 2-nitropyrrole **177** over few steps. The synthesis of second fragment **184** was initiated with the preparation of epoxy mesylate **180** from geraniol **179** by Sharpless asymmetric epoxidation followed by mesylation. Then, epoxy mesylate **180** went through Sharpless asymmetric dihydroxylation accompanied by acid-catalyzed (CSA = Camphorsulfonic acid) epoxide ring opening reaction to afford **181**. In the next step, **181** went through epoxidation to render terminal epoxide **182** (85%). Then, compound **182** was subjected to protection (TESCl) of tertiary alcohol moiety followed by copper(I) chloride-catalyzed epoxide ring opening reaction with allyl magnesium bromide in Et_2O and again protection with TESCl to furnish alkene **183** (85%). Next, alkene **183** upon Markovnikov oxymercuration reduction followed by Mitsunobu inversion (*p*-TsOH) with *m*-CPBA-mediated oxidation rendered olefination partner **184** (75%). Then, the coupling partner **178b** and **184** were coupled through Julia-Kocienski olefination followed by (−)-Shi ketone-mediated asymmetric epoxidation to give epoxides **185a** (81%) and **185b** (82%). Finally, **185b** was converted into (+)-Heronapyrrole C **186** *via* TBAF-mediated deprotection accompanied



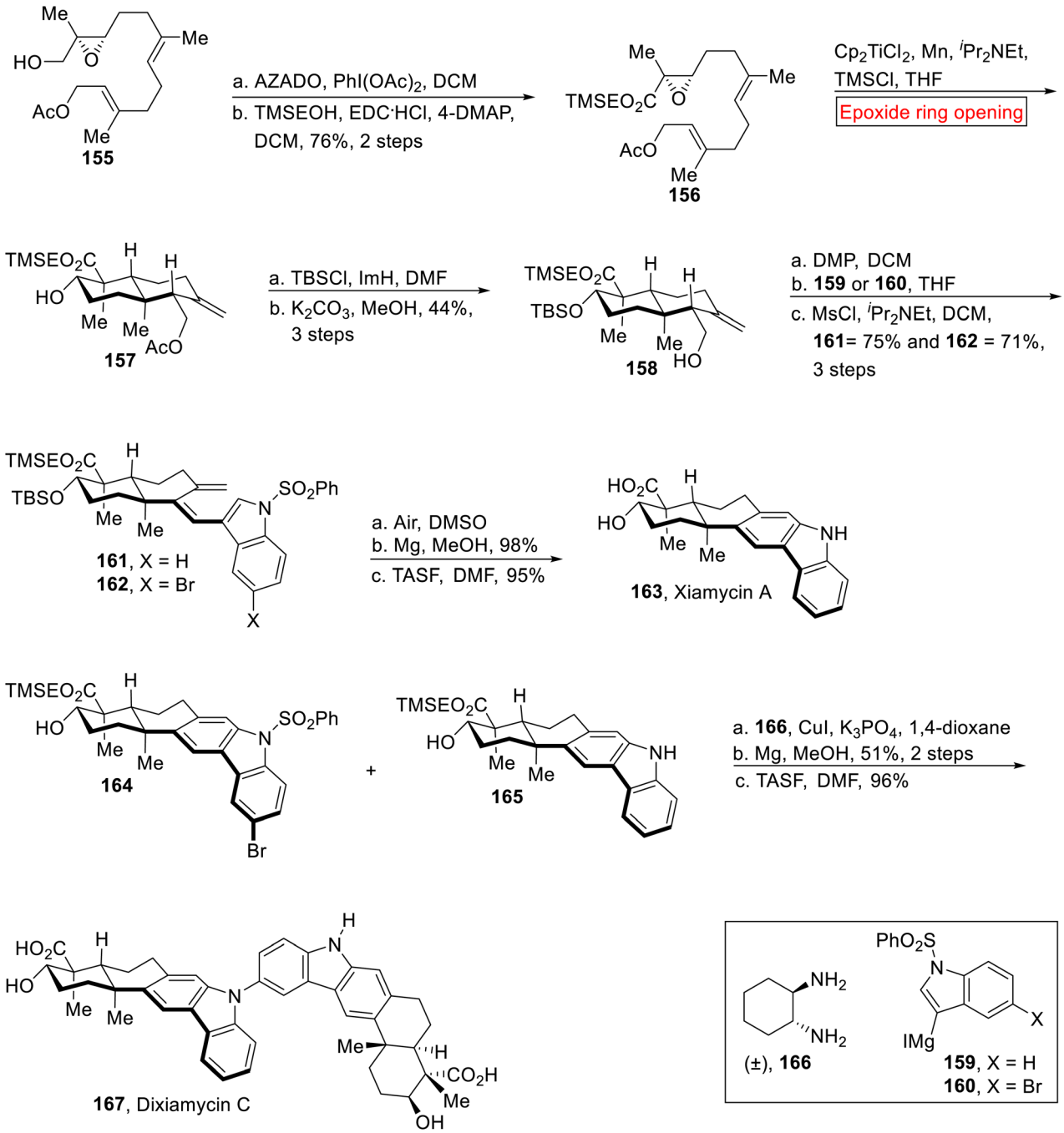
Scheme 17 Synthesis of Isodehydrothyrsiferol **154**.

by acid (CSA)-catalyzed epoxide ring opening reaction in toluene with subsequent heating at 50 °C (Scheme 21).

Guaiane-type sesquiterpenoids (Guaia-4(5)-en-11-ol **191**, Aciphyllene **192**, 1-*epi*-Melicodenones C **193**, 1-*epi*-Melicodenones E **194**, Guaia-5(6)-en-11-ol **195**, 1-*epi*-Aciphyllene **198**, 1-*epi*-Guaia-4(5)-en-11-ol **200**) were isolated from fungi plants and marine life.[153,154] Previously synthesized Guaiane-type sesquiterpenoids have low overall yield[155,156] and experienced difficulties in installing the required stereochemistry while synthesizing the [5.3.0]-bicyclic ring cores. The problem was then solved by Taylor and coworkers by using inexpensive naturally occurring Guaiol **187** as a starting material for the synthesis of Guaiane-type sesquiterpenoids. In 2014, research group of Taylor[157] reported the synthesis of these sesquiterpenoids *via* epoxide ring opening reaction as one of the key steps. The synthetic route initiated with the formation of β-epoxyguaiol **188** from **187** over few steps. Then, **188** was subjected to $LiAlH_4$-catalyzed epoxide ring opening reaction in the presence of $AlCl_3$ in THF to render **189** (79%). Then, compound **189** was exposed to selective benzylation under Ogawa's method in the presence of *in situ* generated benzyl iodide to afford compound **190** (73%). Treatment of compound **190** with $TsOH{\cdot}H_2O$ (MeCN) followed by reduction ($LiAlH_4$) yielded Guaia-4(5)-en-11-ol **191** with 26% overall yield (91%). In the next step, alcohol moiety of **191** experienced dehydration ($SOCl_2$) followed by SNIS (silver nitrate impregnated upon silica gel) chromatography purification to synthesize Aciphyllene **192** in 18% overall yield (72%). Then, Aciphyllene **192** upon sequential allylic and Dess-Martin periodinane oxidation provided 1-*epi*-Melicodenones C **193** (72%) which was further treated with base (NaOMe) followed by CrO_3-mediated oxidation to generate the 1-*epi*-Melicodenones E **194** (32%).

Guaia-5(6)-en-11-ol **195** (31%, overall yield) was obtained by the dehydration ($SOCl_2$) of **190** accompanied by treatment with Li wire and naphthalene in THF. Similarly, compound **196** went through *m*-CPBA-mediated epoxidation accompanied by $LiAlH_4$-mediated epoxide ring opening reaction in the presence of $AlCl_3$ in THF to afford alcohol **197** (43%) which was subjected to dehydration to afford 1-*epi*-Aciphyllene **198** (87%). Then, alcohol **197** was subjected to sequential epoxidation and dehydration to generate epoxide **199**. In the next step, compound **199** went through $LiAlH_4$-catalyzed epoxide ring opening reaction reductively by using $AlCl_3$ and THF to accomplish 1-*epi*-Guaia-4(5)-en-11-ol **200** in 73% yield over 3 steps (Scheme 22).

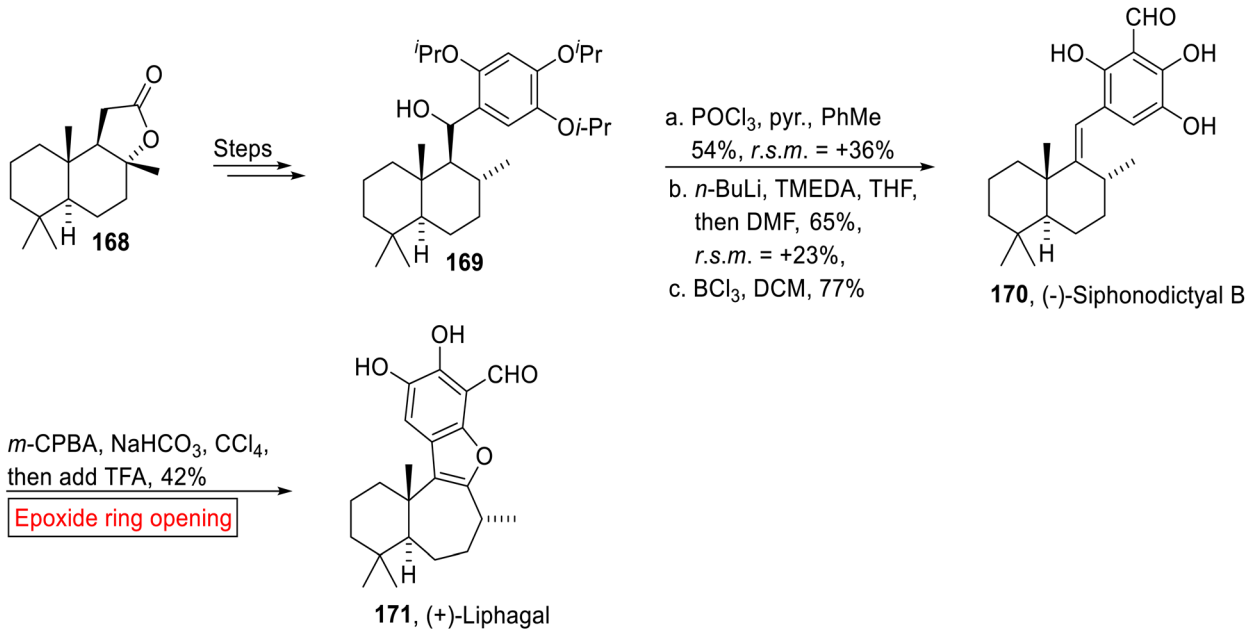
Arglabin **203** (guaianolide) belongs to the family of sesquiterpene lactones which was isolated from *Artemisia glabella*[158] specie. The dimethyl amino adduct of Arglabin exhibits antitumor activity against lung, breast, colon and ovarian cancer.[159] Total synthesis and hemisynthesis of Arglabin **203** from parthenolide have been reported by the research groups of Reiser[160] and Chen[161] respectively. In 2015, Lone and Bhat have accomplished the hemisynthesis of Arglabin **203** (51%, overall yield)



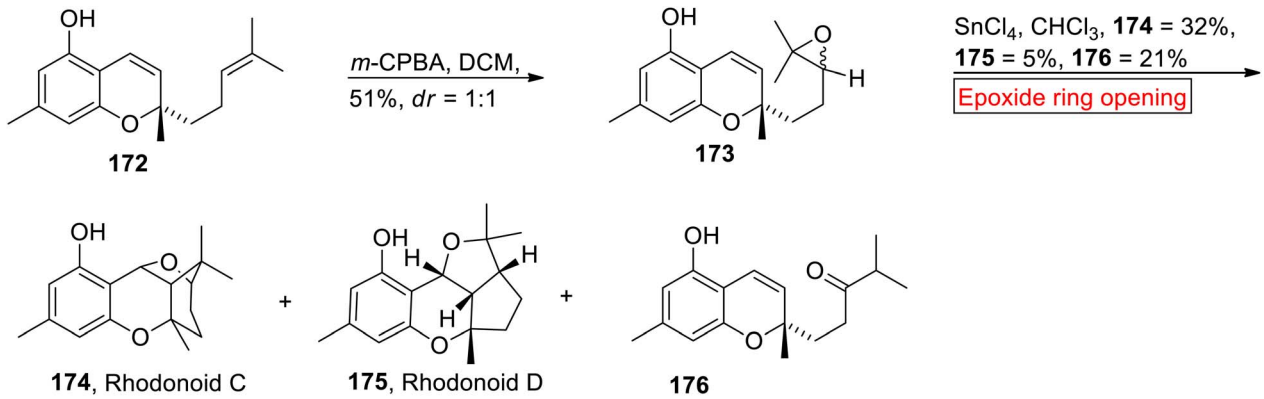
Scheme 18 Total synthesis of Xiamycin **163** and Dixiamycin C **167**.

from ludartin **201** (ref. 162) *via* short and efficient reaction process, by taking into account the less side effects of Arglabin as compared to other chemotherapeutics. They utilized epoxide ring opening reaction as one of the key steps in their strategy for the synthesis of Arglabin. In the first step, ludartin **201** underwent Lewis acid ($BF_3 \cdot Et_2O$)-catalyzed regioselective ring opening of epoxide using $NaBH_4$, which resulted in compound **202** (90%). Stereoselective epoxidation of compound **202** in DCM followed by selective reduction synthesized Arglabin **203** in excellent yield (Scheme 23).

In 1964, Chetty and Dev[163] extracted α-Cuparenones **208** and β-Cuparenones **210**, sesquiterpenes from the oil of *Thuja orientallis* leaves (Family – Cupressaceae) which display a number of biological activities. Then in 1976, Benesova[164] and co-workers isolated α and β-Cuparenones from Mania fragrans (liverworts). Similarly, (*S*)-Cuparene **209**, a sesquiterpene was isolated in 1958 by Erdtman and colleagues.[165] Nanda and allies reported the optically pure synthesis of (*R*)-α-Cuparenone **208**, (*R*)-β-Cuparenone **210** and (*S*)-Cuparene **209** by employing epoxide ring opening reaction as one of the key steps.[166] In the



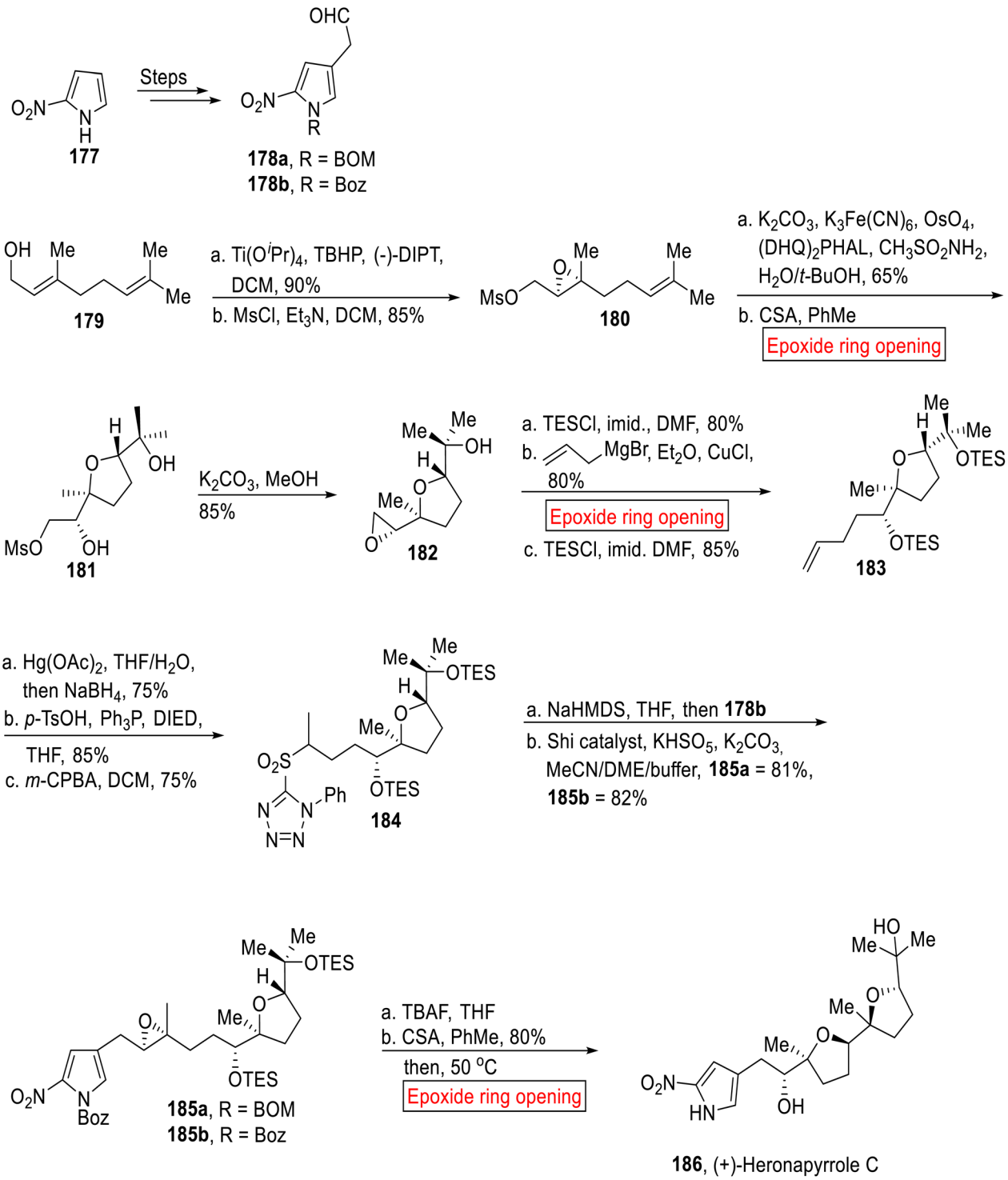
Scheme 19 Synthesis of (−)-Siphonodictyal B **170** and (+)-Liphagal **171**.



Scheme 20 Synthesis of Rhodonoids C **174**, D **175** and **176**.

first step, 4-methylbenzyl cyanide **204** went through aldol reaction (Me-CHO) followed by DIBAL-H-mediated reduction, acid-catalyzed hydrolysis with subsequent reduction ($NaBH_4$) to furnish *E*-allylic alcohol **205** (85%, 3 steps). Then, *E*-allylic alcohol **205** was subjected to asymmetric epoxidation followed by *tert*-butyldiphenyl chlorosilane (TBDPSCl)-mediated protection to provide protected epoxide **206** (90%). In the next step, compound **206** experienced Lewis acid-mediated epoxide ring opening reaction which caused Meinwald rearrangement to forge aldehyde intermediate **207** (95%). The compound **207** was converted to (*R*)-α-Cuparenone **208** and (*R*)-β-Cuparenone **210** *via* several steps. In the next step, (*S*)-cuparene **209** was obtained (7.5%, overall yield) from (*R*)-α-Cuparenone **208** (9.4%, overall yield) *via* reductive deoxygenation under Huang-Minlon conditions (Scheme 24).

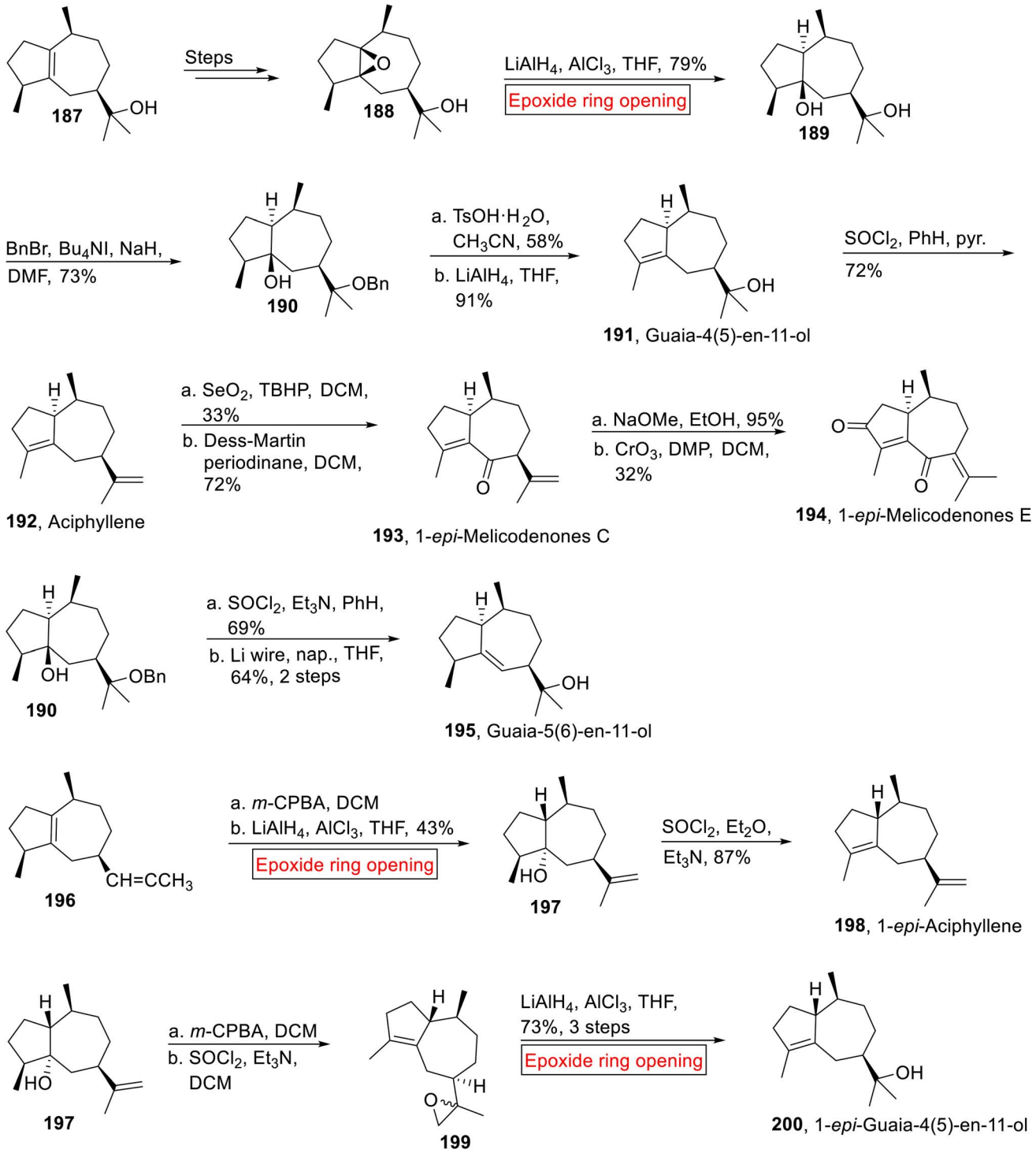
(±)-Isoclavukerin A **216** belongs to sesquiterpene (tri-*nor*-guaiane) family of natural products. It was isolated by research groups of Kitagawa[167,168] and Bowden[169] from *Clavularia koelli-keri* (Okinawan soft coral) and *Cespitularia* sp. (Australian soft coral) respectively. In 2023, Chakraborty[170] *et al.* reported the synthesis of (±)-Isoclavukerin A **216** by employing epoxide ring opening reaction as one of the key steps. The method used by research group of Chakraborty is an attractive approach for the synthesis of sesquiterpenoids owing to high diastereoselective route, simple pathway focusing on step economy and mild reaction conditions. The synthetic endeavor started with the preparation of epoxides **213a** (75%) and **213b** (91%) from cyclopentenone **211** and hex-6-enal **212** in the presence of PBu_3 followed by treatment with AcCl with subsequent epoxidation (*m*-CPBA). In the next step, compound **213a** and **213b** were subjected to Cp_2TiCl-catalyzed epoxide ring opening reaction in THF to afford corresponding cyclized products **214a** and **214b**. Then, the mixture of **214a** and **214b** experienced sequential bromination and debromination to afford enones **215a** and



Scheme 21 Regioselective synthesis of (+)-Heronapyrrole C **186**.

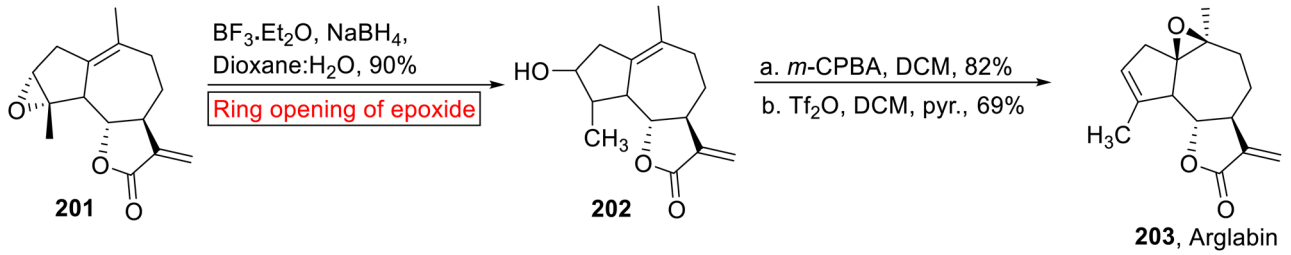
215b (dr = 7 : 1). In the last step, mixture of enones **215a** and **215b** upon treatment with MeLi and additive $LaCl_3 \cdot 2LiCl$ accompanied by 1,4-conjugate elimination in the presence of 2,4-dinitrobenzenesulfinylchloride and Et_3N forged (±)-Isoclavukerin A **216** in 72% yield (Scheme 25).

Taking into account the deadly aspects of cancer, several research groups have focused their attention towards the synthesis of efficacious anti-proliferative agents.[171–173] (−)-Artatrovirenol A **226** was isolated from *Artemisia atrovirens* in 2020 (ref. 174) which exhibits cytocidal activity opposite to hepatocellular carcinoma (SMMC-7721, HepG2, and Huh7). Bridged, fused, and spirocyclic ring systems make a cage-like structure of (−)-Artatrovirenol A **226**. In 2023,[175] Zhu *et al.* disclosed the first total synthesis of (−)-Artatrovirenol A **226** by employing epoxide

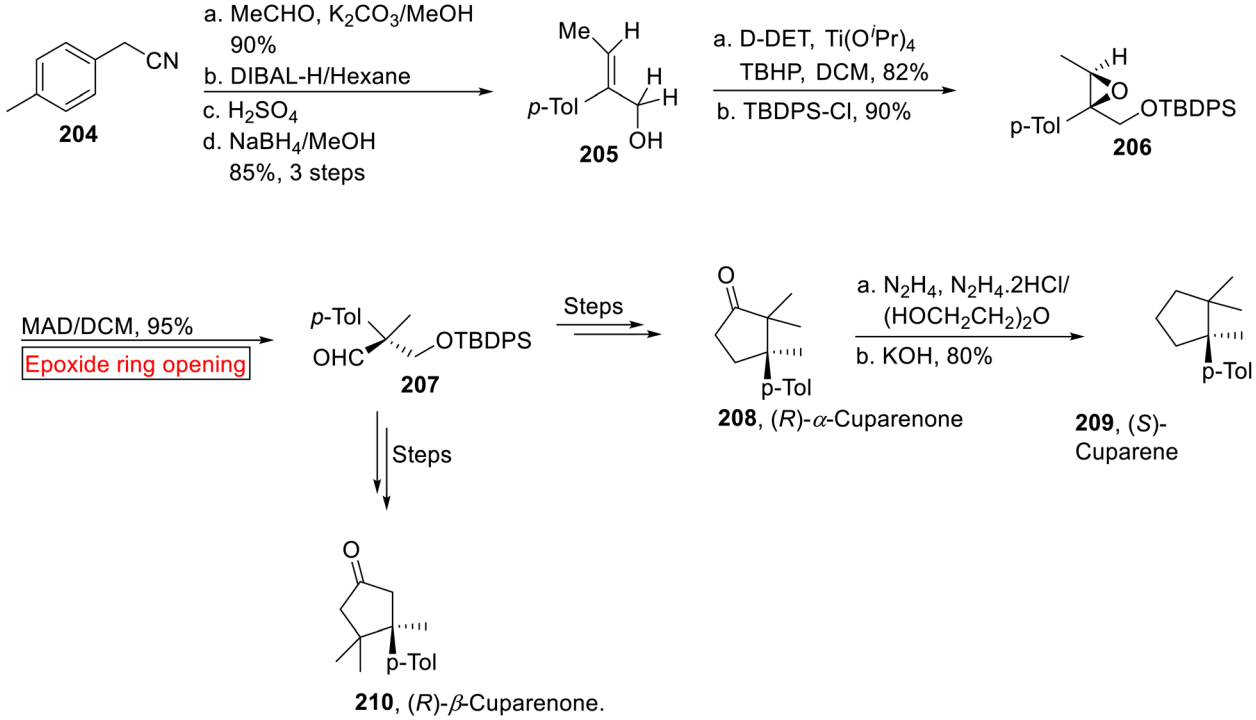


Scheme 22 Syntheses of Guaiane-type sesquiterpenoids (Guaia-4(5)-en-11-ol **191**, Aciphyllene **192**, 1-*epi*-Melicodenones C **193**, 1-*epi*-Melicodenones E **194**, Guaia-5(6)-en-11-ol **195**, 1-*epi*- Aciphyllene **198**, 1-*epi*-Guaia-4(5)-en-11-ol **200**).

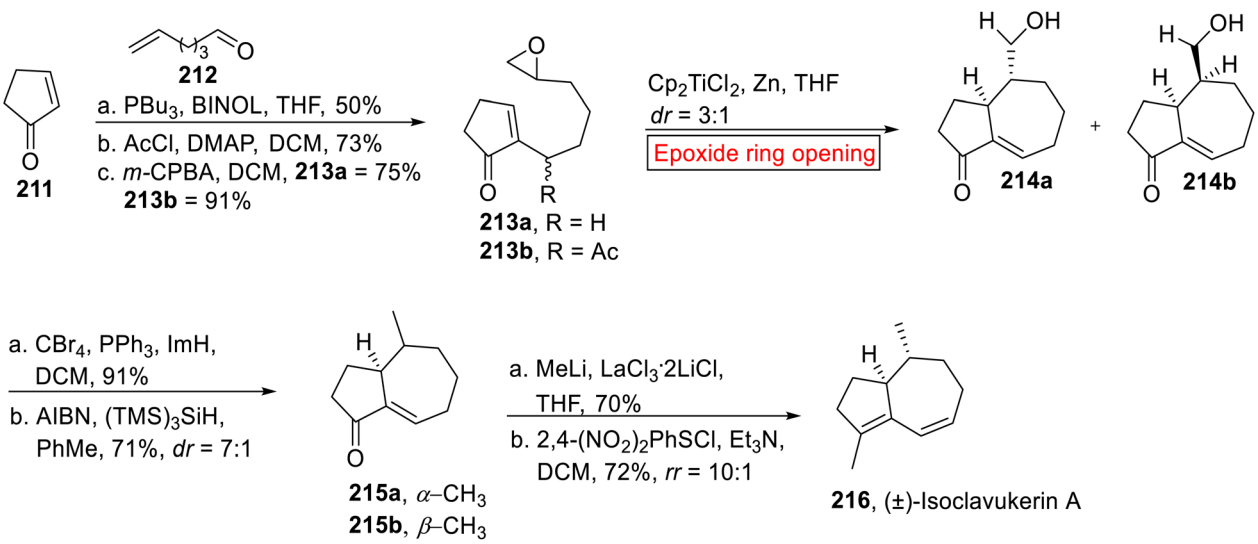
ring opening reaction as one of the significant steps. The enantioselective synthesis of (−)-Artatrovirenol A **226** initiated with the formation of TBS silyl ketene acetal **221**. In the first step, iso-prene **217** was reacted with enolate **218** using oxazaborolidine **219** and bistriflimide (Tf_2NH) followed by chemoselective reduction ($NaBH_4$), acid-mediated lactonization (TsOH) and deprotection (TBAF) of silyl ether to provide γ-lactone **220** (93%, 3 steps). In the next step, –OH group of lactone **220** was protected with MsCl accompanied by TBAI-mediated Finkelstein iodination and elimination with subsequent deprotection reaction (by using KHMDS = potassium bis(trimethylsilyl)amide). The deprotection strategy was then



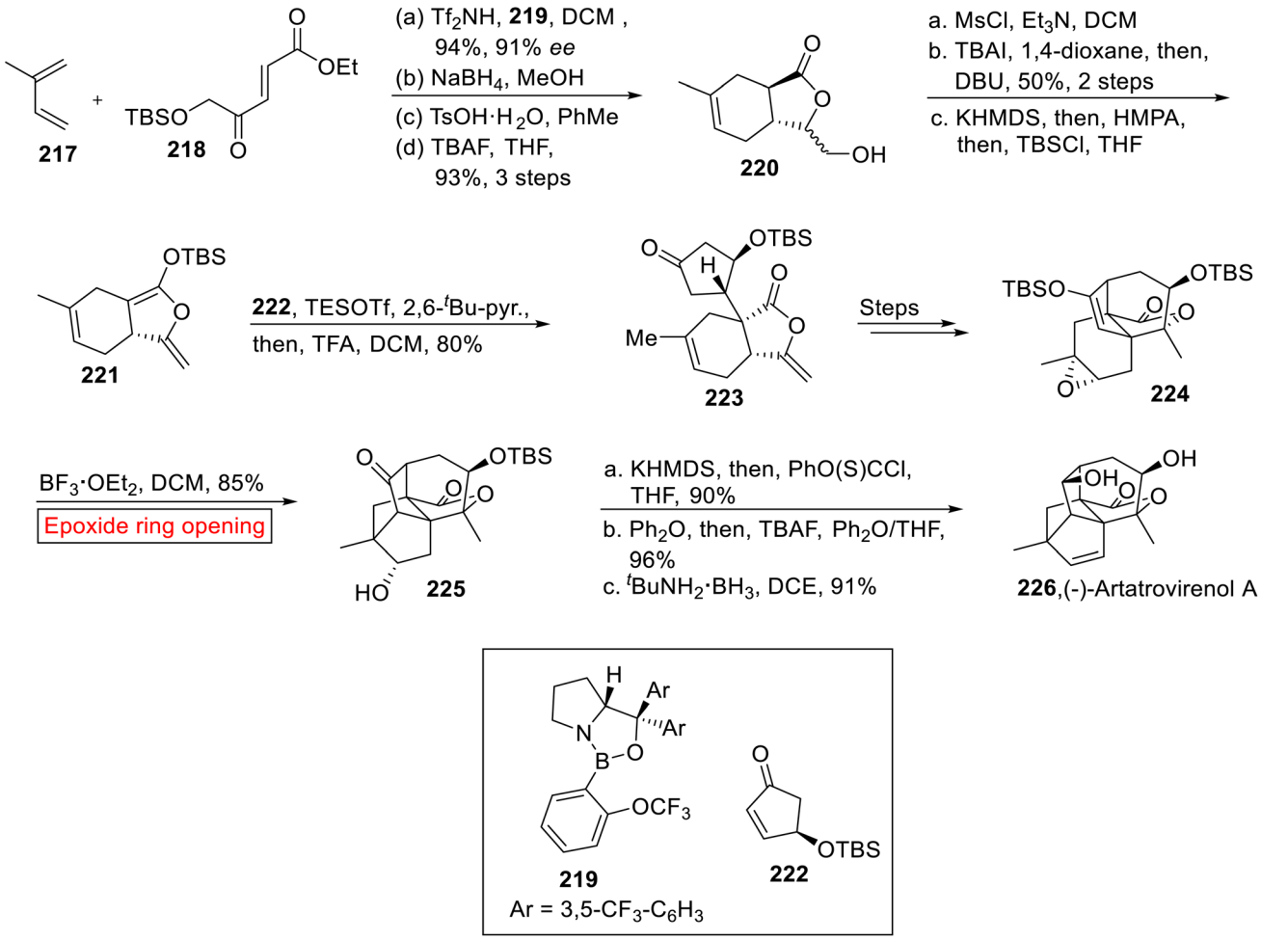
Scheme 23 Hemisynthesis of Arglabin **203**.



Scheme 24 Synthesis of (*R*)-α-Cuparenone **208**, (*R*)-β-Cuparenone **210** and (*S*)-Cuparene **209**.



Scheme 25 Synthesis of (±)-Isoclavukerin A **216**.



Scheme 26 Total synthesis of (−)-Artatrovirenol A **226**.

followed by HMPA (hexamethylphosphoramide) and TBSCl (*tert*-butyldimethylsilyl chloride) addition to furnish silyl ketene acetal **221**. Then, acetal **221** and enone **222** were reacted in the presence of TESOTf (trimethylsilyl trifluoromethanesulfonate) followed by TFA-mediated hydrolysis to render 5,6-*cis*-fused bicyclic lactone **223** (80%) which was further converted into **224** over several steps. In the next step, compound **224** experienced $BF_3 \cdot OEt_2$-catalyzed epoxide ring opening reaction in DCM to afford the product **225** (85%). In the next step, the compound **225** went through sequential thioacylation of alcohol, TBS deprotection (TBAF) and treatment with $^tBuNH_2 \cdot BH_3$ to furnish (−)-Artatrovirenol **226** in 91% yield (Scheme 26).

Conclusion

This article provides an overview of the previous ten years of research on the epoxide ring opening reactions that have been employed towards the synthesis of natural products. Epoxides are frequently used as building blocks in synthetic organic chemistry by undergoing epoxide ring opening reaction. A number of reagents, catalysts, and solvents are used in an epoxide ring opening process which determine its outcome. Moreover, the total synthesis of various natural products also utilizes epoxide ring opening reaction as one of the key steps. An updated summation of synthetic methods involving the utilization of epoxide ring opening for the production of interesting natural products with important biological activities is presented in this review article. These natural products include alkaloids and terpenoids. This review will motivate organic chemists to focus their efforts on epoxide ring opening reactions and their chemistry to devise more effective pathways for further advancements towards the synthesis of natural products in the future.

Conflicts of interest

There are no conflicts to declare.

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