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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 strain¹ and they undergo enantioselective ring opening reaction with a diverse range of reagents (Gilman reagent²) and nucleophiles³ such as carbon⁴ and oxygen nucleophiles i.e., trimecyanides,⁵ aryllithiums,6 trialkylsilyl halides,7 alkylamines,8 carboxylic acids9 and phenols10 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 arenes¹³ have also been used for the ring opening reactions of epoxides. Sulfur nucleophiles14 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

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 synthesis18 as they lead towards the synthesis of (-)-(4R,5R)-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 Mupirocin35 and Bisfuranoxide36 etc. have been accomplished by involving epoxide chemistry.

Predominantly, biologically active natural products i.e., Epothilone A³⁷ 3 (antitumor activity), methyl-L-Callipeltose³⁸ 6 (cytotoxic activity against NSCLCN6 and P388 cell lines),

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

products i.e., β-hydroxysulfides.¹⁵ Similarly, α-azido ketone is prepared by the reaction of chloroepoxide with sodium azide. 16

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3, Epothilone A (anti-tumor)

6, Methyl-L-callipeltose (active against NSCLCN₆ and P388 cell lines)

4, (±)-Merrilactone A (anti-Alzheimer's)

5, (±)-Epiasarinin (anti-tumor)

7, (+)-8-Deoxyvernolepin (active against human lymphoblastic leukemia cells)

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 D40 (insecticidal), (±)-Merrilactone A41 4 (active against Alzheimer's disease), (-)-Preussomerin,42, (+)-8-Deoxyvernolepin43 7 (active against human lymphoblastic leukemia cells), (±)-Epiasarinin⁴⁴ 5 (antitumour Laulimalide,45, (–)-Nakamurol Prenylbisabolane, 47, (-)- Delobanone and (-)-epi-Delobanone are generated by employing epoxide ring opening reactions (Fig. 2).

In 2006, research group of Oltra48 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, $IC_{50} = 6.2 \mu g \text{ mL}^{-1}$; 16a, $IC_{50} = 10$ μg 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 2,2dimethylcyclohexane-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 CF₃CO₃H-mediated epoxidation. Then, epoxide 14 was exposed to similar base (Me₂NH₂)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 indigotica54) 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 Nair⁵⁵ and then

16b

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

16a, (+)-Citrinadin B

by Argade.⁵⁶ Further, Ji⁵⁷ 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 (\pm) -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

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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 ⁱBuCO₂Cl/NMM (N-methylmorpholine) followed by reaction with HC(OMe)3 and in situ generated TiCl4 to provide quinazolinone 22 (97%). Then, compound 19 and 22

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

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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 (\pm)-**25** (85%) and (-)-Chaetominine **26** (42%) respectively. Then, the compound (\pm)-**25** was reacted with NaOMe (MeOH) to render racemic (\pm)-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. Murrayakonine D 30 (carbazole alkaloid) has 6/6/6/5 ring system which was extracted from *Murraya koenigi* (medicinal plant). Research group of George has reported the synthesis of Murrayakonine D 30 (33% overall yield) in 2017 *via* epoxide ring opening reaction. In the first step, Mahanimbine 28 (which was prepared according to research group of Knölker went through metachloroperoxybenzoic 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 40 and N-ethyl-1α-hydroxy-17-39. Paniculamine 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, LiAlH₄-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 (LiAlH₄) to forge Cochlearenine 39 (63–77%, 3 steps). Then, further treatment of 39 with H₂O₂ furnished Paniculamine 40. Finally, *N*-ethyl-1 α -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 rare⁷³ guaipyridine alkaloid which was isolated from Cananga odorata74 (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 (${
m IC}_{50}=3.8~\mu{
m g~mL}^{-1}$) and Hep G2 (${
m IC}_{50}=0.22$ μg mL⁻¹) cell lines.⁷⁶ Various transition metals-mediated crosscoupling 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 Ag₂O 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

$$m$$
-CPBA, DCM, 61% $dr = 1:1$ p -TsOH, DCM, 33% Epoxide ring opening m -NH m -CPBA, DCM, 61% m -CPBA, DCM, 61% m -TsOH, DCM, 33% m -TsOH, DCM, 34% m -TsOH, D

Scheme 3 Synthesis of Murravakonine D 30.

a. Cp2TiCl2, Mn, H2O, THF OH Epoxide ring opening ОМО Steps **OMOM** b. NaH, Me₂SO₄, THF OMe 66%, 2 steps, rr = 14:1 ŌEt 32 ŌEt 33 ÓН Me. a. KOH, (HOCH₂)₂ b. Ac₂O, pyridine, DCM OMe c. LiAlH₄, Et₂O .Me d. HCI, THF, 54%, 4 steps MeC 35, Weisaconitine D ОН OAc Steps KOAc, AcOH Epoxide ring opening 32 ÓН **36**: R = H, **37**: R = Ac 38 .OH H₂O₂, MeOH/H₂O 50% Ο, a. Pd/C, H₂, MeOH 40, Paniculamine b. LiAIH₄, THF OMe a. 41, DMAP, DCM, 25%, 34% brsm 39, Cochlearenine OMe b. TFA, CDCI₃, quant.

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

MeO

MeO

41

hydrogenation followed by methylation to furnish asymmetric Alstolactine 54 in 79% yield (Scheme 6).

42, *N*-ethyl-1 α -OH-17-Veratroyldictyzine

TFA

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 (IC₅₀ = 2.7 μM) as compared to cisplatin (IC₅₀ = 18.7 μM) and vinorelbine (IC₅₀ = 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

AD-mix
$$\alpha$$
,

MeSO₂NH₂

t-BuOH/H₂O,
52%

AD-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
52%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,

MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

t-BuOH/H₂O,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

AB-mix α ,
MeSO₂NH₂

b. K₂CO₃, MeOH,
57%, ee = 96%

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 (PPh₃)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 Glorius89 (2014), Huang90 (2017) and Kou91 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 Nmethoxyisoquinolone 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 (BBr₃) 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-p-arabinofuranose **76** rendered vinylpyrrolidine **77** (28%) *via* treatment over few steps which

Cbz

QΗ

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 BBr₃ (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 ADmix- 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

CO₂Me

58

Scheme 7 Synthesis of (-)-Melodinine K 60

Et

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 BF₃·Et₂O 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).

(\pm)-Brussonol **104** and (\pm)-Komaroviquinone **106** belong to a family of ictexane diterpenes, isolated from terrestrial plants containing fused tricyclic skeleton (6-7-6). (\pm)-Brussonol 104 and (\pm) -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-Hoxidation/cyclization/ rearrangement,100 intramolecular Marson-type cyclization,101 Pd-catalyzed intramolecular Heck reaction,102 intramolecular nucleophilic cyclization, 103 cationic ring expansion, 104 TiCl₄catalyzed Friedel-Crafts cyclialkylation105,106 and Pt-mediated hydrative cyclization.107 In 2019, Burtoloso and Ahmad108 disclosed the syntheses of (\pm) -Brussonol **104** (18.4%, overall yield) and (\pm) -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

63a: R= OMe (4'-Methoxycyclopeptin)

63b: R= H (Cyclopeptin)

Scheme 8 Synthesis of Virdicatin 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·SMe₂, 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 Et₂O 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, Et₃N·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 (\pm)-Brussonol **104** (89%). Similarly, diastereoselective (\pm)-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 furanobutenolidenorcembranoid 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 Cp₂TiCl₂-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 Rumediated 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 Cp2TiCl2-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 aorta115 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 Mangoni¹¹⁷ 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·SMe₂ (Et₂O) 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 gold(1)-mediated by cycloisomerization/oxidation sequence (Scheme 14).

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Scheme 10 Synthesis of Glyphaeaside C 84.

(±)-Rameswaralide **140** is a diterpene related to the class of secondary metabolites¹¹⁹ (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 (\pm) -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 (\pm)-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 Wiesner¹²⁵ 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 Inoue127 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

94, Eurifoloid A

٦_,H

105

Scheme 12 Synthesis of (\pm) -Brussonol 104 (\pm) -Komaroviquinone 106

Epoxide ring opening

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, Cp₂-TiCl₂-catalyzed epoxide ring opening reaction in the presence of Et₃SiH followed by TASF-mediated deprotection. Finally, (+/-)-Anhydroryanodol **145** was converted into (+/-)-Ryanodol **146** (38%) *via* site-specific epoxidation (CF₃CO₃H) followed by Li/NH₃-catalyzed epoxide ring opening reaction reported by Deslongchamps¹²⁶ and Reisman¹²⁸ (Scheme 16).

Triterpenoid. Isodehydrothyrsiferol **154** belongs to the family of triterpenoid¹³⁰ 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

ΉO

106, (±)-Komaroviquinone

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

epoxidation. Next, geranyl phenyl sulfide **150** was added to **149** followed by reaction with Na, ⁱPrOH 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 (^tBuOK) to attain **153** (75%). The synthesized compound **153** was finally converted to Isodehydrothyrsiferol **154** over few steps (Scheme 17).

116, (-)-Scabrolide A

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 Baran¹⁴⁰ 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 Cp₂TiCl₂-catalyzed epoxide ring opening reaction in the presence of $^{\rm i}$ Pr₂Net, 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)

.OMe OTMS 119, CuBrSMe2, Et2O, 76% Steps TMS HO, Epoxide ring opening Me' 117 120

m-CPBA, DCM, 57% BrMg TMS 119 121, Marrubasch F

HO, TMS a. Pyridine HBr $_3$, ROH/DCM ,√Me Bu₄NF, THF, 70% b. OsO₄, NMO, aq. THF ó 122, Marrubiin 120

OR ΩR HO HO, HO HO, ŐR OH ЮH OR Me ó.Me TsOH, PhH Me Me 125a/b = 36%/16% 126a/b = 38%/23% Me' Me' 126a, R = Et 125a, R = Et, Marrulibacetal 123a, R = Et 124a, R = Et 126b, R = Me 125b, R = Me, Marrulibacetal A 123b, R = Me 124b, R = Me, Desertin

OTBS ÓΗ 127 O_{Me} CuBr SMe2, THF, 48% 118 a. Bu₄NF, THF, 82% LiOH, aq. THF b. TEMPO, DCM, 84% **Epoxide ring opening** Me' PhI(OAc)₂, 91% Me^{\'} 129, Marrulactone .CO₂H .OH Me Me HCECLi'(CH2NH2)2, **DMSO, 95%** Ph₃PAuNTf₂, MsOH m-CPBA, DCM, 96% Epoxide ring opening 0 131 130, Marrulanic acid

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/Pr₂Net 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

132, Cyllenine C

reacted with compound **166** in the presence of CuI followed by deprotection with TSAF to render Dixiamycin C **167** (96%, over 2

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

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 Faulkner¹⁴³ and Köck.¹⁴⁴ Its structure was first reported in 1981 by Faulkner and colleagues and then was revised by Clardy and coworkers¹⁴⁵ (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 POCl₃-mediated dehydration followed by *ortho*-lithiation, then quenching by utilizing DMF with subsequent deprotection (BCl₃) 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 NaHCO₃ and CCl₄ 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 Day⁶⁷ 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

146, (+/-)-Ryanodol

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). 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 (TESCI) of tertiary alcohol moiety followed by copper(1) chloride-catalyzed epoxide ring opening reaction with allyl magnesium bromide in Et₂O 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 ketonemediated asymmetric epoxidation to give epoxides 185a (81%) and 185b (82%). Finally, 185b was converted into (+)-Heronapyrrole C 186 via TBAF-mediated deprotection accompanied

OTBS OTBS Ti(OⁱPr)₄, PivOH, PhMe a. MsCl, pyr, DCM 99% HO b. K₂CO₃, MeOH, Epoxide rina openina 87%, 2 steps 148 147 OTBS **OTBS** a. 150, BuLi, TMEDA, THF, then, 149 a. TESCI, ImH, DCM b. Na, PrOH, THF, 90%, b. TBHP, VO(acac)₂, HO 2 steps PhH, 58% 149 151 OH OMOM a. MOMCI, Pr2NEt, DCM, 99% Steps OTBS b. TBAF, THF, quant. Epoxide ring opening 153 c. ^tBuOK, DMSO, 75% PivO 152 ŚΡh 150

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

Synthesis of Isodehydrothyrsiferol 154.

154, Isodehydrothyrsiferol

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, 1epi-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 Taylor¹⁵⁷ 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 LiAlH₄-catalyzed epoxide ring opening reaction in the presence of AlCl₃ 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·H₂O (MeCN) followed by reduction (LiAlH₄) yielded Guaia-4(5)-en-11ol 191 with 26% overall yield (91%). In the next step, alcohol moiety of 191 experienced dehydration (SOCl2) 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 CrO₃-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 (SOCl₂) of **190** accompanied by treatment with Li wire and naphthalene in THF. Similarly, compound **196** went through *m*-CPBA-mediated epoxidation accompanied by LiAlH₄-mediated epoxide ring opening reaction in the presence of AlCl₃ 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 LiAlH₄-catalyzed epoxide ring opening reaction reductively by using AlCl₃ 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)

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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 $_3$ ·Et $_2$ O)-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 Dev¹⁶³ 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, Benesova¹⁶⁴ and coworkers 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.

171, (+)-Liphagal

first step, 4-methylbenzyl cyanide **204** went through aldol reaction (Me-CHO) followed by DIBAL-H-mediated reduction, acid-catalyzed hydrolysis with subsequent reduction (NaBH₄) to furnish *E*-allylic alcohol **205** (85%, 3 steps). Then, *E*-allylic alcohol **205** was subjected to asymmetric epoxidation followed by *tert*-butyldiphenyl chlorosilane (TBDPSCI)-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).

 (\pm) -Isoclavukerin A **216** belongs to sesquiterpene (tri-*nor*-guaiane) family of natural products. It was isolated by research

groups of Kitagawa^{167,168} and Bowden¹⁶⁹ from Clavularia koellikeri (Okinawan soft coral) and Cespitularia sp. (Australian soft coral) respectively. In 2023, Chakraborty¹⁷⁰ et al. reported the synthesis of (\pm) -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 PBu₃ followed by treatment with AcCl with subsequent epoxidation (m-CPBA). In the next step, compound 213a and 213b were subjected to Cp2TiCl-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

OHC Steps OoN

Review

177 R 178a, R = BOM 178b, R = Boz

OH Me Me a. Ti(OⁱPr)₄, TBHP, (-)-DIPT,

Me DCM, 90%
b. MsCl, Et₃N, DCM, 85%

MsO Me Me Me

a. K_2CO_3 , $K_3Fe(CN)_6$, OsO_4 , $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, H_2O/t -BuOH, 65%

b. CSA, PhMe

Epoxide ring opening

MsO OH 181 Me Me Me OH H OH 182

a. TESCI, imid., DMF, 80%
b. MgBr, Et₂O, CuCI,
80%

Epoxide ring opening
c. TESCI, imid. DMF, 85%

Me" OTES

a. Hg(OAc)₂, THF/H₂O, then NaBH₄, 75% b. *p*-TsOH, Ph₃P, DIED, THF, 85% c. *m*-CPBA, DCM, 75%

Me, OTES

N Ph ÖTES

N 184

a. NaHMDS, THF, then 178b

b. Shi catalyst, KHSO $_5$, K $_2$ CO $_3$, MeCN/DME/buffer, **185a** = 81%, **185b** = 82%

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 (\pm)-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

186, (+)-Heronapyrrole C

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)

199

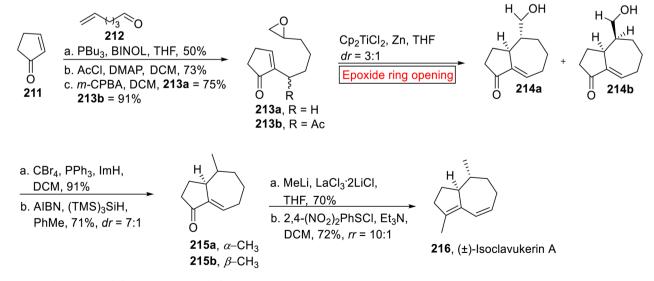
ring opening reaction as one of the significant steps. The enantioselective synthesis of (-)-Artatrovirenol A 226 initiated with the formation of TBS silyl ketene acetal 221. In the first step, iso-prene 217 was reacted with enolate 218 using oxazaborolidine 219 and bistriflimide (Tf2NH) followed by chemoselective reduction (NaBH₄), acid-mediated lactonization

(TsOH) and deprotection (TBAF) of silvl ether to provide γ lactone 220 (93%, 3 steps). In the next step, -OH group of lactone 220 was protected with MsCl accompanied by TBAImediated Finkelstein iodination and elimination with subsequent deprotection reaction (by using KHMDS = potassium bis(trimethylsilyl)amide). The deprotection strategy was then

200, 1-epi-Guaia-4(5)-en-11-ol

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 (\pm) -Isoclavukerin A 216.

 $Ar = 3,5-CF_3-C_6H_3$

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 BF₃·OEt₂-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 ^tBuNH₂·BH₃ 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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