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Baeyer–Villiger oxidation: a promising tool for the synthesis of natural products: a review

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Baeyer–Villiger oxidation is a well-known reaction utilized for the synthesis of lactones and ester functionalities from ketones. Chiral lactones can be synthesized from chiral or racemic ketones by employing asymmetric Baeyer–Villiger oxidation. These lactones act as key intermediates in the synthesis of most of the biologically active natural products, their analogues, and derivatives. Various monooxygenases and oxidizing agents facilitate BV oxidation, providing a broad range of synthetic applications in organic chemistry. The variety of enzymatic and chemoselective Baeyer–Villiger oxidations and their substantial role in the synthesis of natural products *i.e.*, alkaloids, polyketides, fatty acids, terpenoids, *etc.* (reported since 2018) have been summarized in this review article.

1. Introduction

The Baeyer–Villiger oxidation reaction is a primitive conversion of aliphatic or cyclic ketones to their corresponding esters and lactones.[1] The conversion is carried out in the presence of peracids *i.e.*, per sulfuric acid, perchloric acid, *meta*-chloroperoxybenzoic acid (*m*-CPBA), and hydrogen peroxide under acidic conditions.[2] In 1899, Adolf Von Baeyer[3] with his student, Victor Villiger accomplished the renowned BVO reaction for the first time by using Caro's acid (potassium mono persulfate: $KHSO_5$) as a novel oxidant to convert cyclic ketones into respective lactones with 50% yield.[4] Its conversion into a catalytic process was achieved in 1993 by the use of Pt(II) complexes.[5]

In 1950, three different possible intermediates related to Baeyer–Villiger oxidation reaction were distinguished by Speers and Doering.[6] The first intermediate (dioxirane) was proposed by Baeyer and Villiger while the second was carbonyl oxide[7] and the third one was "Criegee intermediate".[8,9] Doering and Dorfman[10] in 1953, elucidated the mechanism of Baeyer–Villiger oxidation. They illustrated that the reaction occurs by the insertion of an oxygen atom between a carbonyl carbon and an adjacent carbon atom in ketone. As a result, an ester or lactone is generated through the formation of a "Criegee intermediate" as shown in Scheme 1.

In 1994, Bolm[11] and Strukul[12] individually demonstrated that there is a probability to obtain specific stereoselectivity of Criegee intermediate by applying the combination of two different solvents and catalysts (giving 92% and 58% ee values).[1]

Reagents used for the Baeyer–Villiger oxidation are *m*-CPBA, peracetic acid, perfluoro acetic acids, H_2O_2/protic acid, H_2O_2/Lewis acid, and H_2O_2/base systems.[7] It has also been reported by Murahashi in 1992 that when an aldehyde and molecular oxygen are added, peroxides are produced *in situ*. This drawback was eliminated by Kaneda in 1994 by utilizing Fe-based catalysts.[13] Fe catalysts are favorable because they are less harmful and easily available. Nowadays, efficient transformations can be carried out with high enantioselectivities by using chiral metal complexes[14–16] (transition metals[17] *i.e.*, Co,[18] Zr,[19–21] Pt,[12,22] Hf[23] or Cu[24] and non-transition metals *i.e.*, Mg,[25] Al,[26–29] *etc.*) and optically active enantiopure organo-catalysts.[15] Besides this, Baeyer–Villiger oxidation, carried out in the presence of hydrogen peroxide is more convenient due to low cost of H_2O_2, high content of oxygen, easy handling and production of water as a byproduct.[30] Enzymatic BVOs are also environmentally safe in which molecular oxygen is used as an atom-efficient oxidant and water as a solvent for biosynthesis.[1] Many BVMOs are also used as biocatalysts, thus contributing to green chemistry approaches.[31]

Baeyer–Villiger oxidation reaction offers powerful methodologies and synthetic tools for industrial and natural product syntheses. In recent years, an enormous number of natural products have been isolated from insects, plants, and marine

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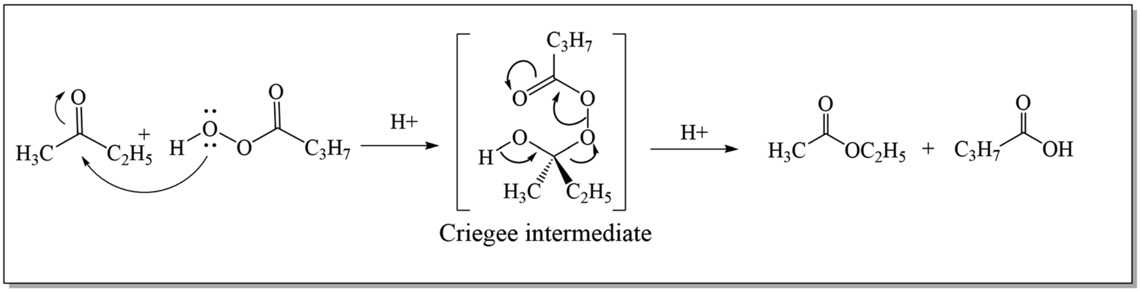

Scheme 1 General mechanism of Baeyer–Villiger oxidation.

sources (invertebrates and sponges) with a wide range of pharmaceutical activities.[32–34] BVO reaction is of great interest in organic chemistry due to its diverse implementations in the synthesis of antibiotics, monomers for polymerization,[35] pheromones, and steroids[3] *etc.* In the biosynthetic pathway, MtmOIV [a Baeyer Villiger monooxygenase (BVMO)] is also responsible for the synthesis of mithramycin[36] (anticancer antibiotic). Potential BVMOs have also a major role in the biosynthesis of aurafurones[37] and aflatoxins[38] which belong to the class of polyketides.

Taking into consideration the deadly aspects of cancer, several research groups are striving to synthesize and develop effective anti-cancer agents.[39,40] Prostaglandins **4** are biologically active hormones (chemical messengers) that have a role in pharmaceuticals synthesis,[41] such as latanoprost is a valuable prostaglandin-related drug. Similarly, steroidal lactones are valuable compounds due to their antiandrogenic and anticancerous action.[42] These suppress the 5α-reductase[43] enzyme and therefore are used to treat androgen-dependent ailments *i.e.*, steroidal testololactone is used to treat breast cancer.[44] BVO reaction can also be employed within the synthetic approach leading to steroidal lactones. For example, dehydroepiandrosterone (DHEA) is converted to testololactone by using BVMO.[45] Similarly, zoapatanol (diterpenoid) **5** is a biologically active molecule obtained by BVO. It naturally occurs in the zoapatle plant (Montanoa tomentosa)[46] and is used to treat labor pain.[47] Fig. 1 elaborates the structures of some biologically active compounds synthesized *via* involving BVO reaction.

Brink *et al.* in 2004, provided an overview of reaction features, mechanisms and catalysts of BVO reaction by utilizing green reaction conditions.[48] Gonzalo *et al.* in 2021, presented a review on BVMOs-assisted biosynthesis of a variety of compounds.[49] In 2016, Bucko *et al.* also reported different biotechnological approaches towards novel monooxygenase-promoted Baeyer–Villiger oxidation.[50] In 2018, Perkel *et al.* published a review to provide organized information on configuration of esters and lactones synthesized by the Baeyer–Villiger oxidation reaction.[51] The current review provides

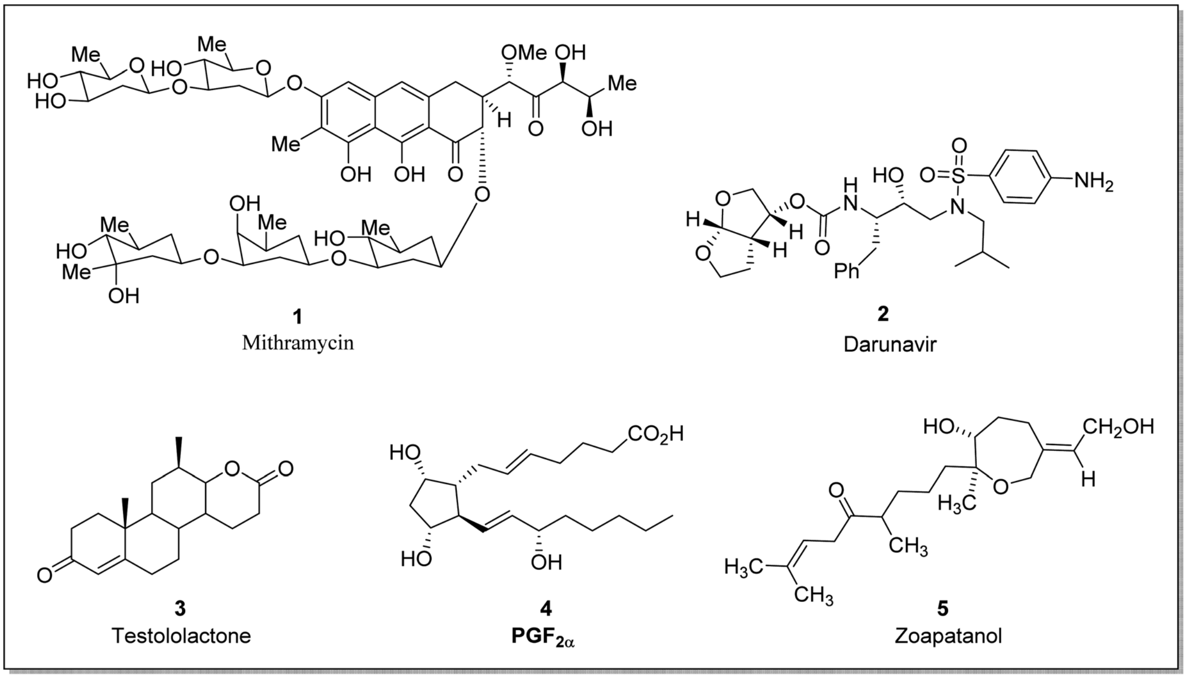

Fig. 1 Structures of a few biologically active natural products synthesized by BVO.

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a critical update on the role of Baeyer–Villiger oxidation reaction towards the synthesis of natural products (alkaloids, terpenoids, polyketides, and fatty acids) with high enantio- and stereoselectivity, and efficient yields, reported since 2018.

2. Review of literature

2.1. Synthesis of alkaloid-based natural products *via* Baeyer–Villiger oxidation

Several natural alkaloids are isolated from herbs and these exhibit antiproliferative, antiviral, antibacterial, insecticidal, and antimetastatic properties against cancer cells. Baeyer–Villiger oxidation reaction plays a key role in the synthesis of alkaloid-based natural compounds *i.e.*, synthesis of homoproaporphine alkaloids, indole-based alkaloids, and other marine alkaloids *etc.* (Fig. 2.)

Five-membered heterocyclic compounds are fundamental in medicinal chemistry due to their antifungal, antibacterial, and antiviral properties.[52] Homoproaporphine alkaloids (*i.e.*, (+)-regeline, (+)-jolantidine, and (+)-regilinine, *etc.*) are naturally occurring five-membered heterocyclic compounds that belong to biologically active tetrahydroisoquinones.[53] This class consists of over 10 members, some of them exhibit anticholinesterase activity[54] and are also used as drugs to prevent the demolition of the neurotransmitter acetylcholine in the nervous system. The synthesis of stereogenic carbons of these alkaloids has always been a challenging task for chemists.[55–57] In 1975, the only diastereoselective synthesis ($d:r = 1:1$) of regeline was presented by Kametani group in which they employed the oxidative coupling of the phenethylisoquinoline to obtain ring system.[58] However, to achieve the first enantioselective total synthesis of homoproaporphine alkaloids in 5.3 to 9.6% overall yield (13 to 16 steps), Pu *et al.* in 2020, presented the total synthesis by utilizing many fundamental pathways including Baeyer–Villiger oxidation.[59] In the first step of synthesis, the chiral intermediate **6** was treated with *N*-bromo succinimide (NBS) in an acidic medium to afford aryl bromide **7** in 94% yield. In the next step, compound **7** was converted to enol ether **8** over a few steps. Then, compound **8** upon treatment with trifluoroacetic acid (TFA) followed by acylation, generated a chiral ketone **9** in 90% yield. Consequently, ketone **9** underwent *m*-CPBA-mediated Baeyer–Villiger oxidation in the presence of lithium carbonate in dichloromethane (DCM) to give compound **10** in 92% yield ($d:r \sim 5.7:1$), which upon further reduction with diisobutylaluminium hydride (DIBAL-H) in DCM and consecutive oxidation with pyridinium chlorochromate

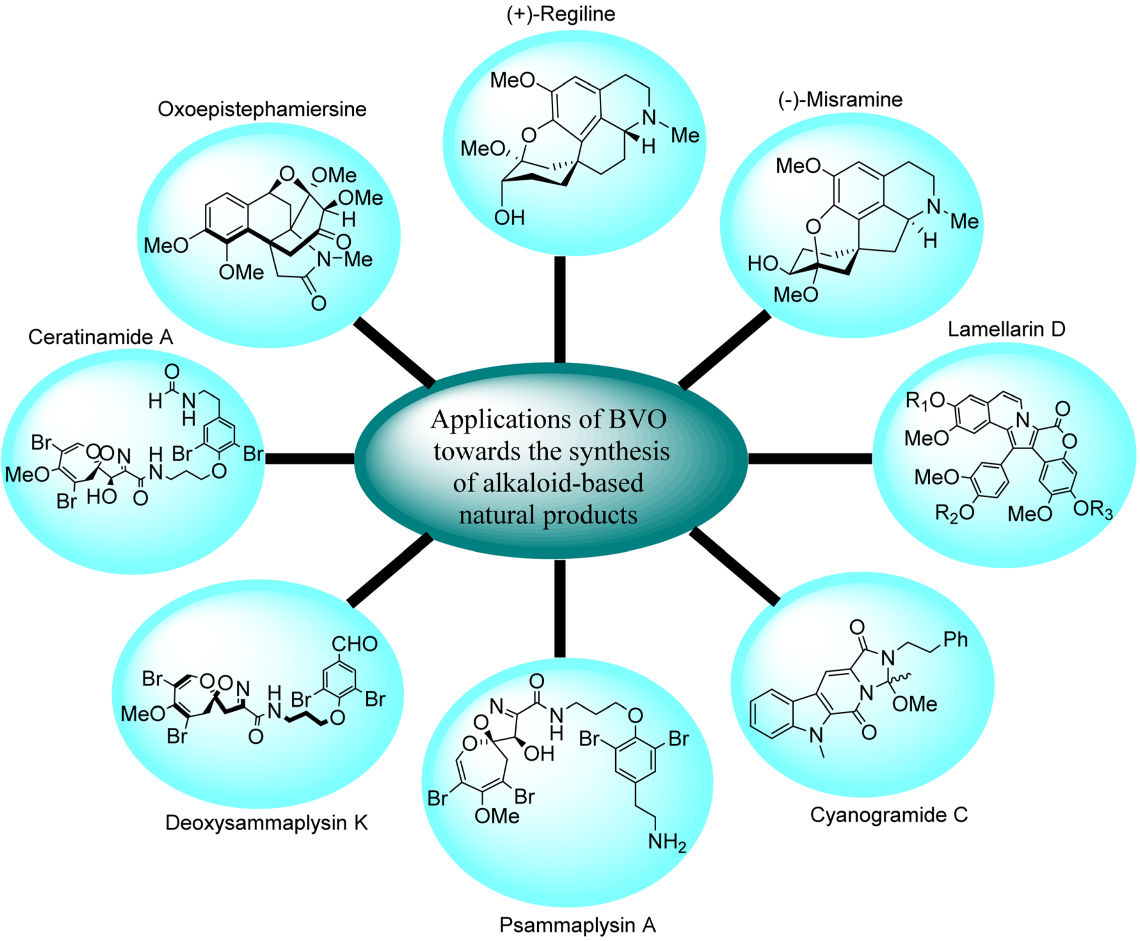

Fig. 2 Pictorial representation of alkaloid-based natural products synthesized by Baeyer–Villiger oxidation reaction.

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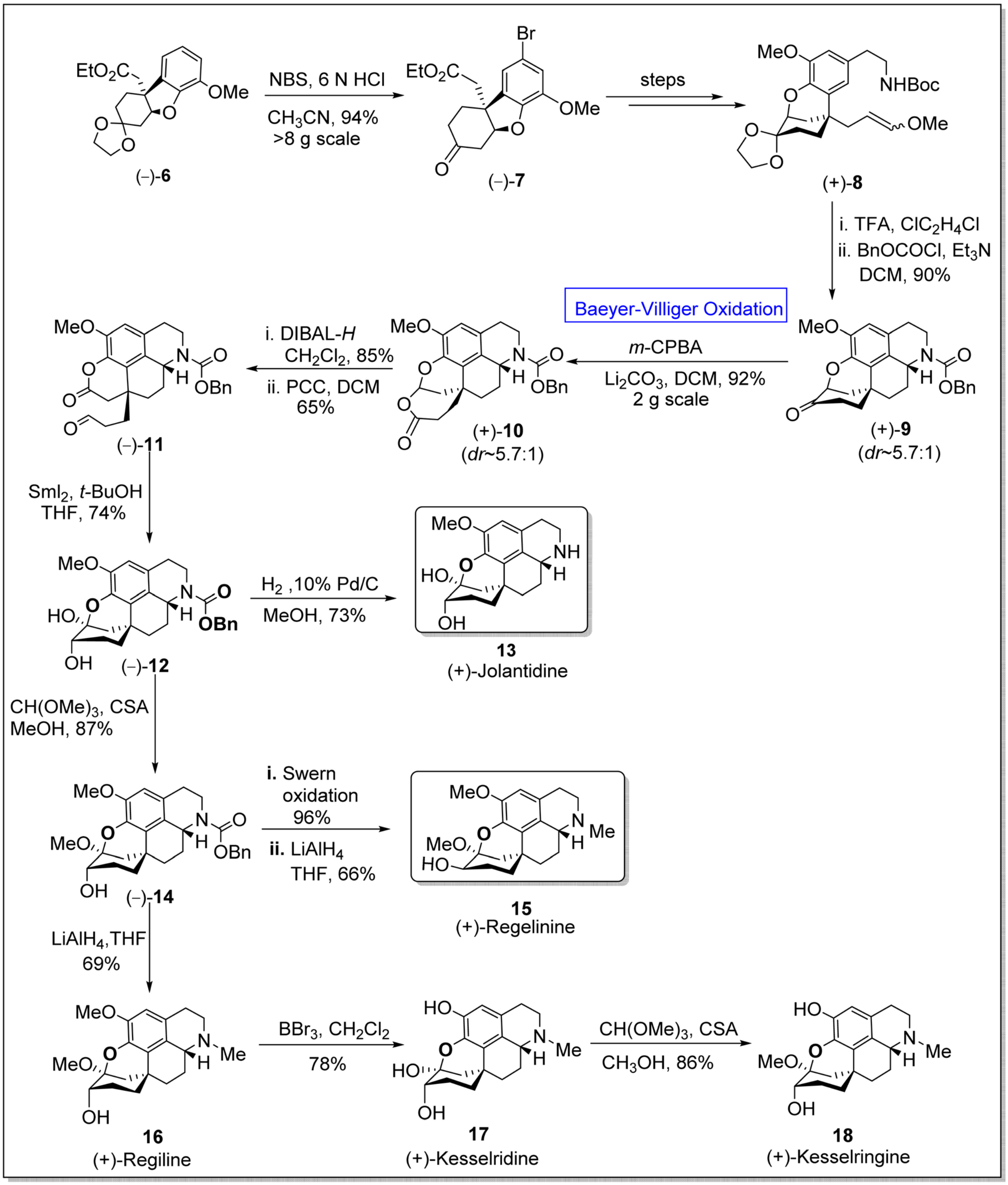

Scheme 2 Synthesis of homoproaporphine alkaloids; jolantidine **13**, regelinine **15**, and kesselringine **18** *via* Baeyer–Villiger oxidation.

(PCC) in the presence of DCM yielded aldehyde-lactone **11** in 65% yield. Subsequently, Pinacol-type cyclization of compound **11** with samarium(II)iodide and removal of the *N*-benzyloxycarbonyl group from compound **12** resulted in the synthesis of (+)-jolantidine **13** in 73% yield. Afterwards, the insertion of a methyl group to hemiketal **12** with CH(OMe)$_3$ and camphorsulfonic acid (CSA) in methanol furnished compound **14** in 85% yield. Compound **14** underwent Swern oxidation followed by LiAlH$_4$-mediated reduction in THF to afford the desired natural compound, regilinine **15** in 66% yield. In another approach, compound (+)-**15** on reduction with LiAlH$_4$ in THF furnished (+)-regiline **16** in 69% yield which upon further treatment with boron tribromide (BBr$_3$) in dichloromethane synthesized (+)-kesselridine **17** in 78% yield. To achieve the synthesis of natural product **18** in 86% yield, compound **17** was treated with CH(OMe)$_3$ and CSA in methanol (Scheme 2).

(−)-Misramine **26** is a pentacyclic proaporphine alkaloid,[52] a member of isoquinoline alkaloids.[60] The former is a biologically active compound and was found in *Roemeria hybrida* and *R. dodecandra*.[61] In 2018, Yoshida and Takao *et al.* synthesized

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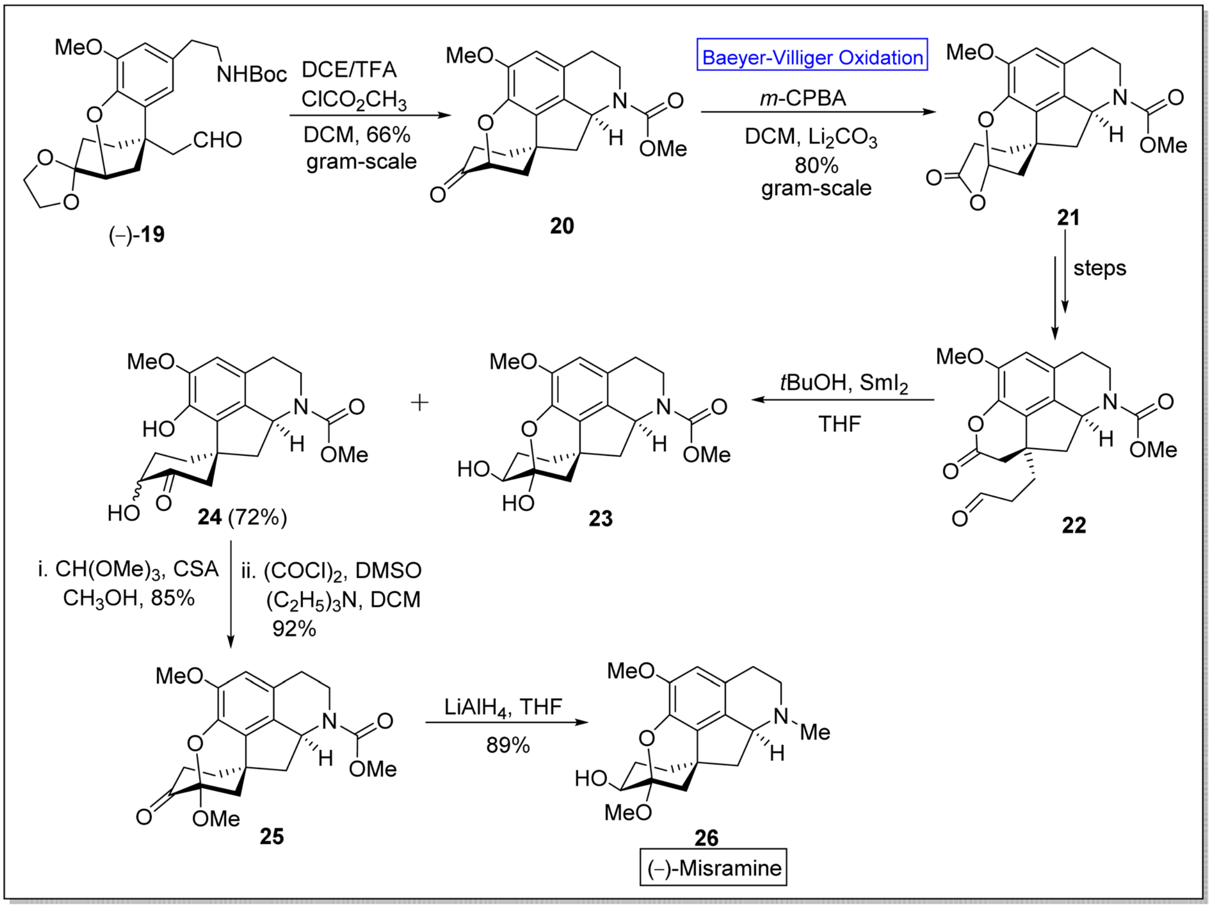
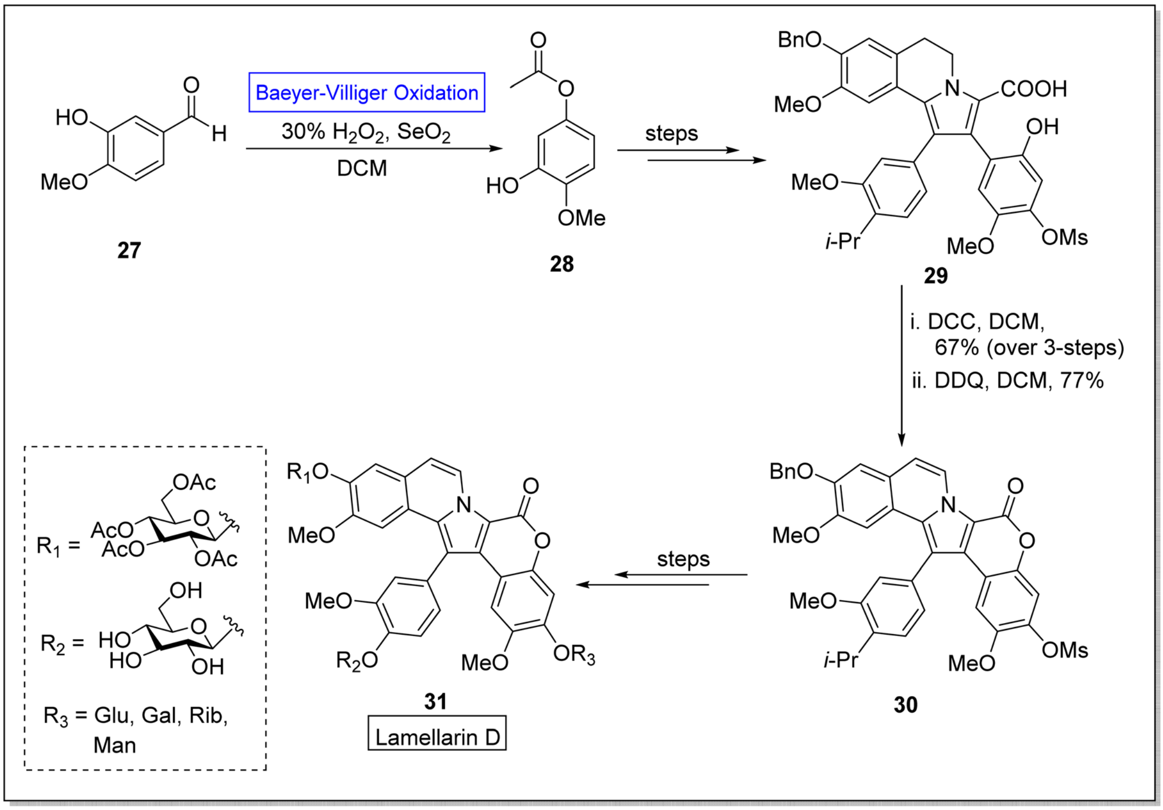


Scheme 3 Synthesis of (–)-misramine **26** *via* Baeyer–Villiger oxidation.



Scheme 4 Synthesis of glycosylated derivatives of Lamellarin D **31** *via* Baeyer–Villiger oxidation.

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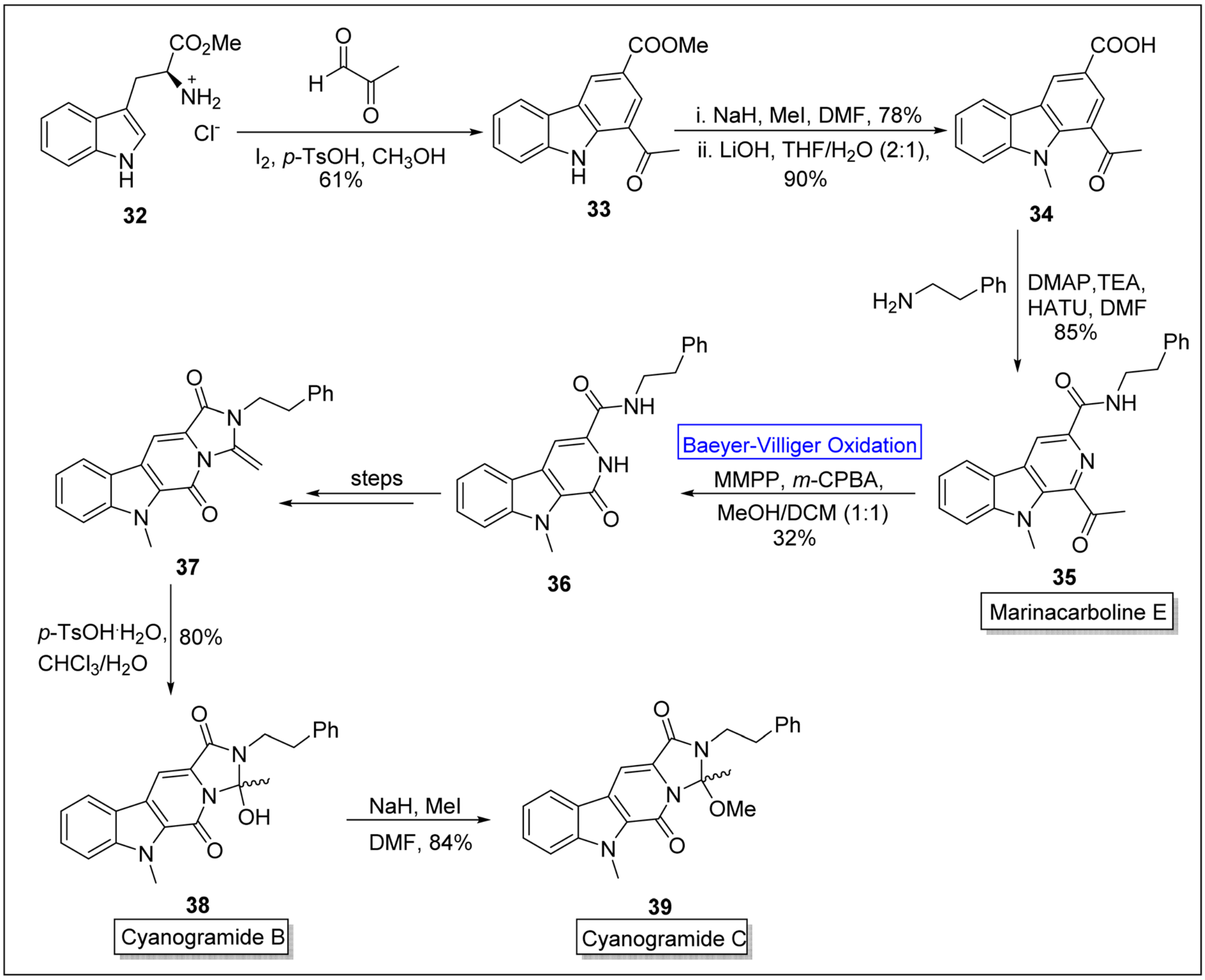

Scheme 5 Synthesis of cyanogramides B **38** and C **39** *via* Baeyer–Villiger oxidation.

the (−)-misramine with overall 2.0% yield (in twenty four steps) from 2,4,6-tribromoanisole by employing asymmetric Friedel–Crafts 1,4-addition. However, Pu *et al.* in 2021 presented the enantioselective total synthesis of the natural product, (−)-misramine **26** in 11.4% overall yield (in nine steps) by utilizing Baeyer–Villiger oxidation as a significant step.[60] The synthesis was commenced with the reaction of chiral intermediate (−)-**19** with TFA and methyl chloroformate in DCM to afford a pentacyclic intermediate **20** in 66% yield. Compound **20** underwent Baeyer–Villiger oxidation with *m*-CPBA in DCM to generate a lactone **21** in 80% yield. An aldehyde-lactone **22** was synthesized from lactone **21** in a sequence of a few steps. Then, the aldehyde-lactone **22** experienced pinacol-type cyclization in the presence of THF to furnish hydroxy ketone **24** in 72% yield instead of compound **23**. Methylation of compound **24** with $CH(OMe)_3$ in methanol followed by Swern oxidation with $(COCl)_2$, DMSO, and triethyl amine (NEt_3) in DCM produced a ketone **25** in 92% yield. Reduction of compound **25** with $LiAlH_4$ in THF furnished the desired product (−)-**26** in 89% yield (Scheme 3).

Lamellarins are marine alkaloids isolated from mollusk *Lamellaria* species.[62] Lamellarins show broad range anticancer,[63,64] antibacterial,[65] antioxidant, and multidrug resistant activities.[66,67] The typical derivatives of lamellarin D **31** show different IC_{50} values *i.e.*, some exhibit 3 nM, 10 nM and 15 nM against fine lines of human lung, colon, and hepatocellular cancer cells respectively. Lamellarin D is the most notable compound owing to its biological potential. Despite the potential activities of lamellarin D **31**, its further advancement was restricted due to its poor solubility,[68] which is due to the pentacyclic framework of Lamellarin. To improve the solubility of target compound **31**, Zheng and colleagues in 2021, reported the synthesis of glycosidic lamellarin derivatives in multiple steps with overall 0.6–2.8% yield by utilizing the Baeyer–Villiger oxidation reaction as a key step.[69] The synthesis was accomplished with Baeyer–Villiger oxidation of commercialized isovaniline **27** with H_2O_2 in the presence of selenium dioxide and DCM to afford an ester **28**. In the next step, ester **28** was converted into compound **29** over a few steps. Subsequently, compound **29** was reacted with di-cyclohexyl carbodiimide (DCC) in DCM and then with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in DCM to synthesize the compound **30** which further furnished the derivatives of lamellarin D **31** over a few steps (Scheme 4).

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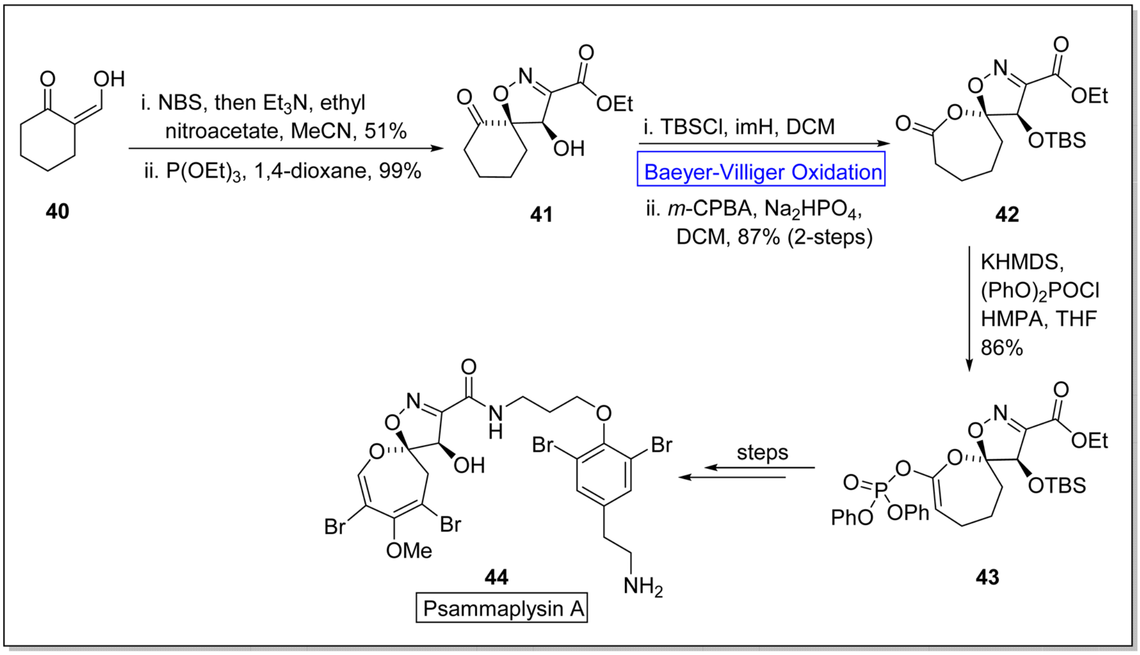
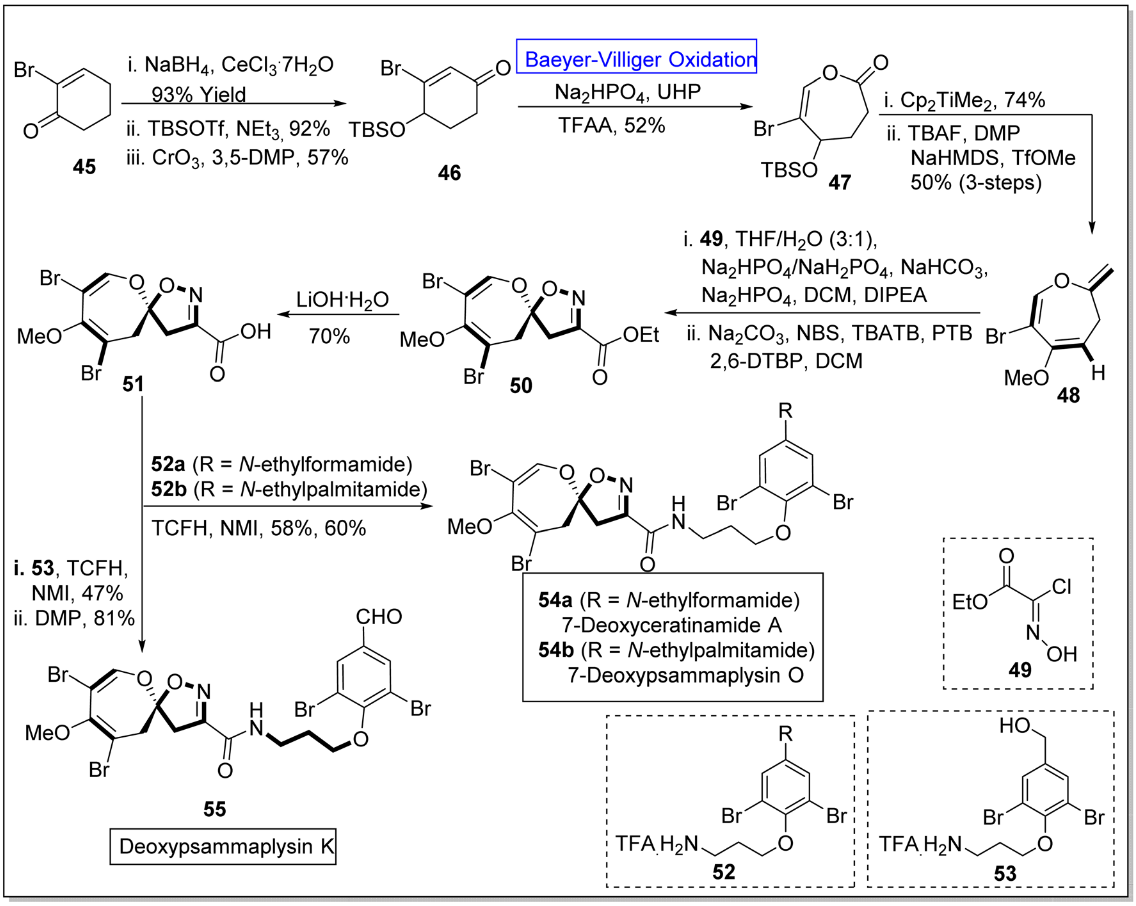


Scheme 6 Synthesis of psammaplysin A **44** *via* Baeyer–Villiger oxidation.



Scheme 7 Synthesis of deoxypsammaplysins O **54b**, K **55** and deoxyceratinamide A **55** *via* Baeyer–Villiger oxidation.

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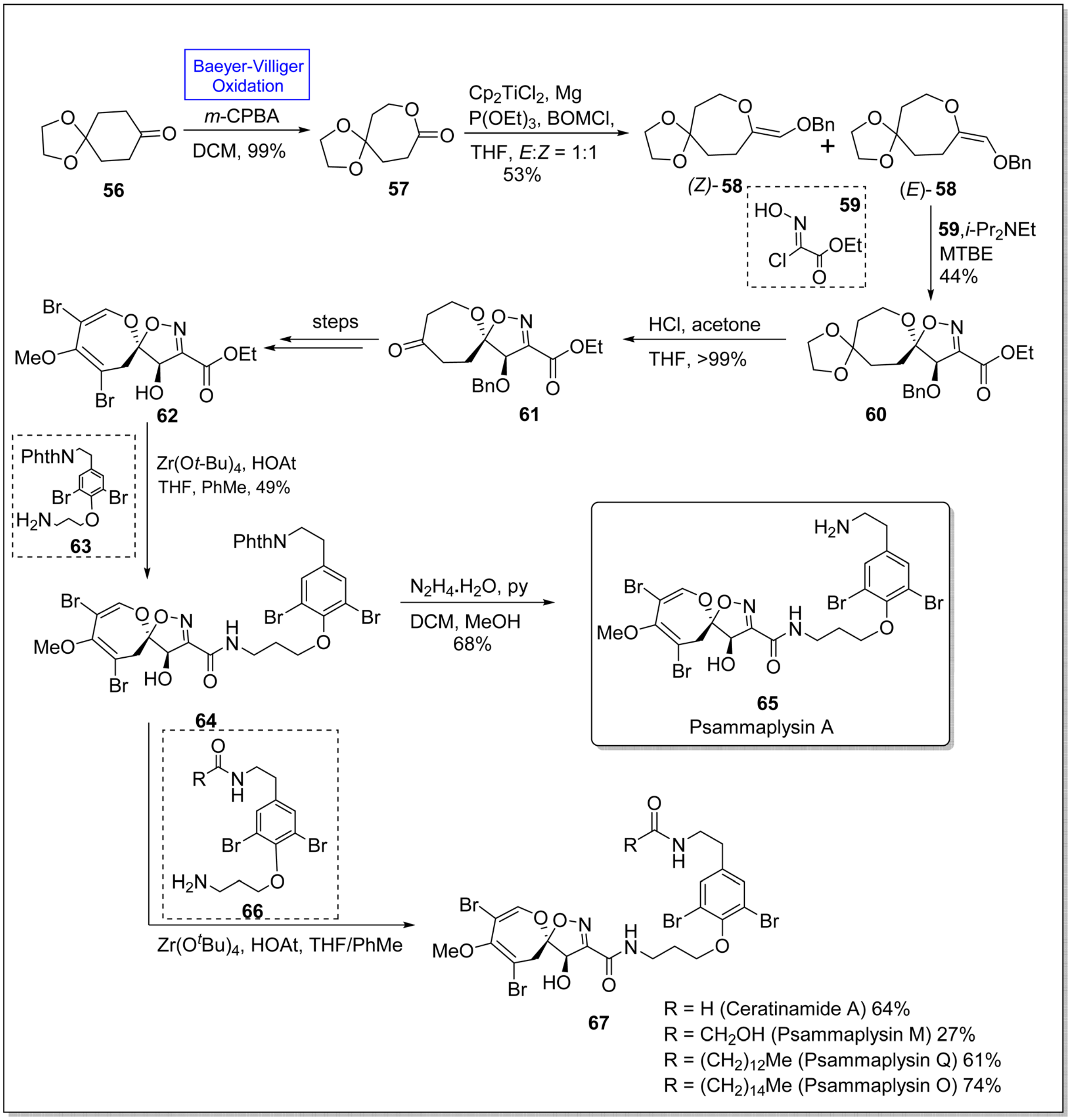

Scheme 8 Synthesis of natural marine alkaloids; psammaplysins **65** and **67** *via* Baeyer–Villiger oxidation.

Cyanogramides (B **38** and C **39**) are marine-derived indole-based alkaloids[70] which possess pyrrolo[1,2-*c*] imidazole system. These were isolated by Lian, Zhang, and associates independently.[71] These show reverse resistance in the cancer cells.[72] In 2018, Sarnes and coworkers attempted to synthesize cyanogramide by employing enantioselective thiourea-mediated spiro-annulation which consisted hydantoin rather than 2-methoxy-2-methylimidazolidinone. This route resulted in failure of ring closure. Later, in 2020, this drawback was addressed by Zhu, Zhang and colleagues by elucidating the biosynthetic process.[73] Marinacarboline E **35** is the precursor for the synthesis of cyanogramide B **38** and C **39**. Sarnes and companions in 2022, presented the synthesis of marinacarboline E **35**, cyanogramides B **38** and C **39** by employing Baeyer–Villiger oxidation as a basic step.[70] In the first step of synthesis, L-tryptophan methyl ester **32** was converted into the natural product stellarine C **33** in 61% yield *via* Pictet–Spengler reaction with an aldehyde in the presence of iodine, *p*-toluene sulfonic acid and methanol. In the next step, methylation of β-carboline **33** in the presence of NaH, MeI in DMF followed by saponification with LiOH in THF to generate the compound **34** in 90% yield. Then, HATU (hexafluorophosphate azabenzotriazole tetramethyl uranium)-mediated coupling of compound **34** with 2-phenyl ethylamine furnished marinacarboline E **35** (for the first time in 4-steps) in 85% yield. Thereafter, the marinacarboline E **35** was subjected to Baeyer–Villiger oxidation with *m*-CPBA in the presence of magnesium monoperoxyphthalate (MMPA) to synthesize tricyclic pyridone **36**. Subsequently, compound **36**

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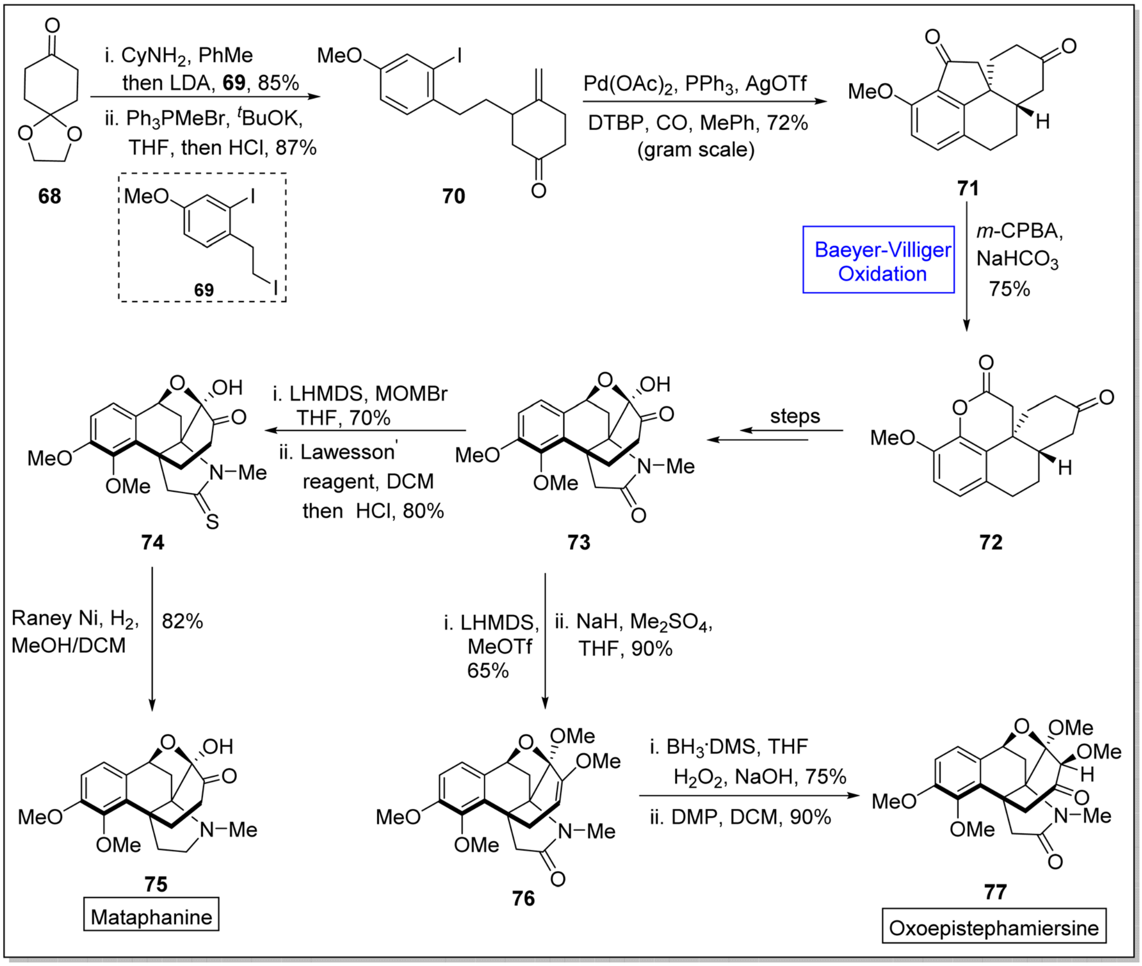

Scheme 9 Synthesis of metaphanine **76** and oxoepistiphemiersine **77** *via* Baeyer–Villiger oxidation.

was converted into ketene aminal **37** over a sequence of a few steps. Furthermore, the ketene aminal **37** was treated with *p*-TsOH and chloroform to afford the cyanogramide B **38** in 80% yield. In the last step, the treatment of natural product **38** with NaH and MeI in DMF furnished the cyanogramide C **39** in 84% yield (Scheme 5).

Psammaplysins are marine alkaloids that belong to natural dihydrooxepine-spiroisoxazoline based-products.[74] Initially, psammaplysin A **44** was extracted by Kashman from *Psammaplysilla purpura*[75,76] in 1982 and it exhibited anti-malarial, antibiotic, anti-cancer, and anti-HIV activities.[77–80] In 2022, Paciorek *et al.* reported the first total synthesis of psammaplysin A **44** in thirteen steps by using Baeyer–Villiger oxidation as an essential step.[74] In the beginning, compound **40** was reacted with NBS, NEt_3, ethyl nitroacetate in MeCN, and then treated with triethyl phosphite ($P(OEt)_3$) and 1,4-dioxane to synthesize a ketone **41** in 99% yield. In the next step, ketone **41** on treatment with TBSCl, imidazole (imH) in DCM followed by *m*-CPBA induced Baeyer–Villiger oxidation in the presence of Na_2HPO_4 and DCM generated a lactone **42** in 87% yield (over 2-steps). Then, lactone **42** was further reacted with potassium hexamethyldisilazide (KHMDS), diphenyl chlorophosphate $(PhO)_2$-POCl, and hexamethylphosphoramide (HMPA) in tetrahydrofuran (THF) to afford the compound **43** in 86% yield. Subsequently, compound **43** delivered the targeted natural product **44** over a few steps (Scheme 6).

Pyrazoles are remarkable five-membered heterocyclic compounds that exhibit broad-range spectrum of pharmaceutical applications and play a vital role in natural product syntheses. For example, these are exploited in the synthesis of psammaplysins by using different synthetic routes. Psammaplysin K, O, and ceratinamides are novel bromotyrosine derivatives obtained from sea sponge[81–84] *Pseudoceratina purpurea*.[85] These exhibit anti-fouling, anti-cancer, and anti-bacterial activities.[86–88] Despite all these excellent activities, no synthetic approach for theses natural spirooxepin isoxazolineswas reported till 2022. However, in 2022, Zhang *et al.* presented the synthesis of 7-deoxypsammaplysins K **155**, O **154b**, and 7-deoxyceratinamide A **154a** by leveraging Baeyer–Villiger oxidation as a key step.[89] The synthesis was initiated with the reduction of 2-bromo-2-cyclohexanone **45** with $NaBH_4$, $CeCl_3\cdot7H_2O$ to produce a compound which was further reacted with *tert*-butyldimethylsilyl triflouromethane sulfonate (TBSOTf) in NEt_3 and then underwent oxidation with chromium trioxide (CrO_3) in 3,5-dimethylpyrazole (3,5-DMP) to synthesize silyl ether **46** in 57% yield. Ether **46** experienced the Baeyer–Villiger

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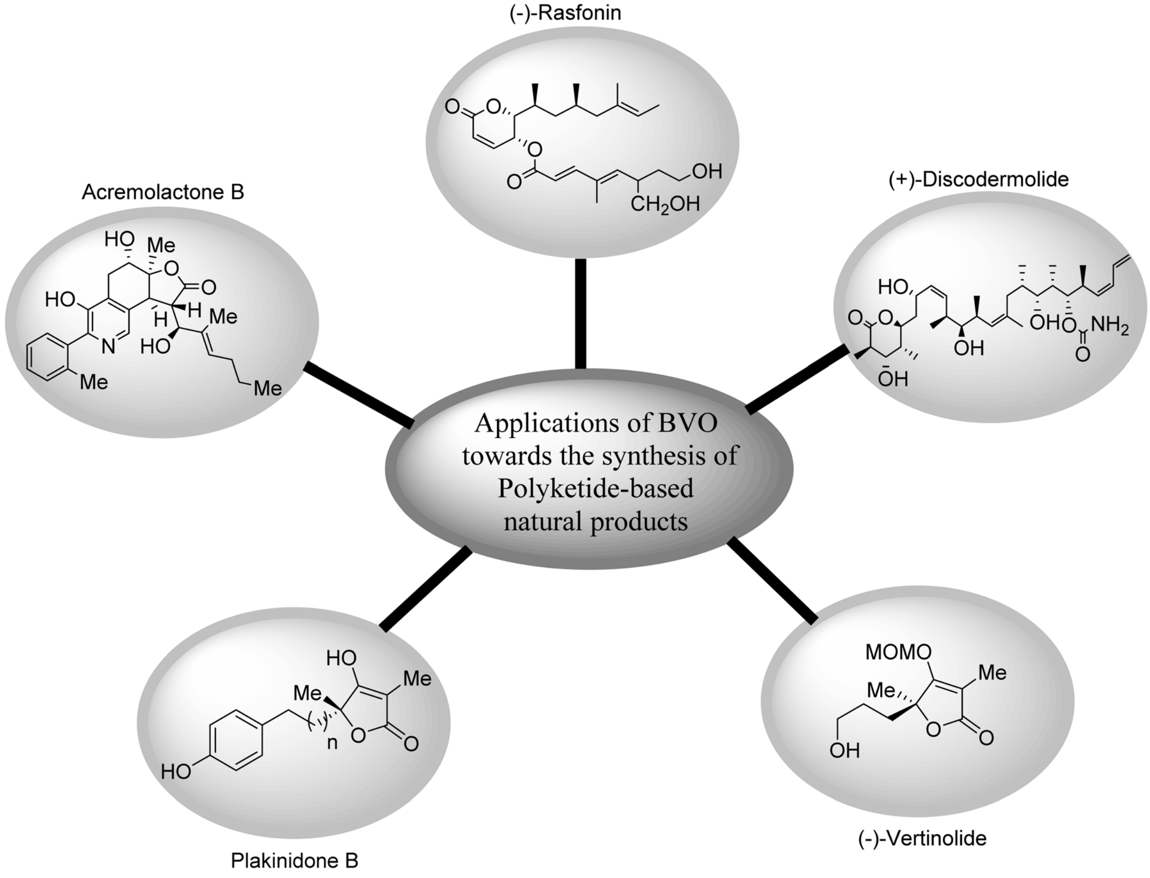

Fig. 3 Structures of some naturally occurring polyketides synthesized *via* Baeyer–Villiger oxidation.

oxidation with urea hydrogen peroxide (UHP) in the presence of Na_2HPO_4 and trifluoroacetic anhydride (TFAA) to furnish a lactone **47** in 52% yield. Furthermore, the reaction of lactone **47** with Petasis reagent (Cp_2TiMe_2) and tetra-*n*-butyl ammonium fluoride (TBAF) in the presence of DMP, NaHMDS, and TfOMe (3-steps) generated oxepine **48** in 50% yield. The compound **48** was further treated with hydroxyamino acetate chloride **49** by using THF, $NaHCO_3$, $NaHPO_4$, *N*,*N*-diisopropylethylamine (DIPEA), DCM, and then with NBS as a bromide agent, tetrabutylammonium tribromide (TBATB), PTB and 2,6-DPBP in DCM to afford an ester **50**. Subsequently, ester **50** was reacted with $LiOH \cdot H_2O$ solution to synthesize an acid **51** which further underwent coupling with **52a** & **52b** and **53** individually in the presence of *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) respectively. These coupling reactions resulted in the construction of corresponding natural products **54a** and **54b** (in 58% and 60% yields respectively) and **55** in 81% yield (Scheme 7).

Psammaplysins **65** and **67** are a distinctive class of bromotyrosine-based spiroisoxazolines, which are marine alkaloids. These consist of more than 300 members.[90] Psammaplysins A, M, Q, and O contain more than 35 members linked with amide bond. These compounds exhibit antiviral, antimicrobial, and anticancer activities[74] with sub-micromolar IC_{50} values. Despite the known biological activities, the total synthesis of these compounds had not been achieved for 40 years. For the first time, in 2022, Magauer group synthesized the racemic Psammaplysin A (in 13 steps) by employing Henry reaction but they faced the difficulty installing carbon 7 hydroxyl group. This drawback was eliminated in 2023 by Morrow and Smith by the use of enediol ether dipolarophile. In 2023, Morrow & Smith presented the total synthesis of psammaplysins A **65** and first total synthesis of psammaplysin O, Q, M, (**65** and **67**) and ceratinamide A **67** by utilizing Baeyer Villiger oxidation as a fundamental step to convert 6-membered ketone **56** into 7-membered lactone **57**.[91] The synthesis was started with the preparation of lactone **57** in 99% yield from ketone **56** *via* subsequent Baeyer–Villiger oxidation with *m*-CPBA. Benzyloxymethylenation of lactone **57** afforded enol ether **58** in 53% yield ($E/Z = 1:1$), (*E*)-**58** was further treated with compound **59** under optimized conditions (*i*-Pr_2NEt, MTBE) to furnish a single diastereomer spiroisoxazoline **60** in 44% yield. Ketal deprotection of this compound **60** with acetone and THF in acidic media yielded ketone **61** which underwent many steps to synthesize a spirocycle **62.** Aminolysis of this compound **62** furnished the phthalimide-protected moiety **64** in 49% yield on treatment with compound **63**, zirconium *tert*-butoxide ($Zr(O^tBu)_4$), 1-hydroxy-7-azabenzotriazole (HOAT), THF, and PhMe. Consequently, compound **64** further delivered the

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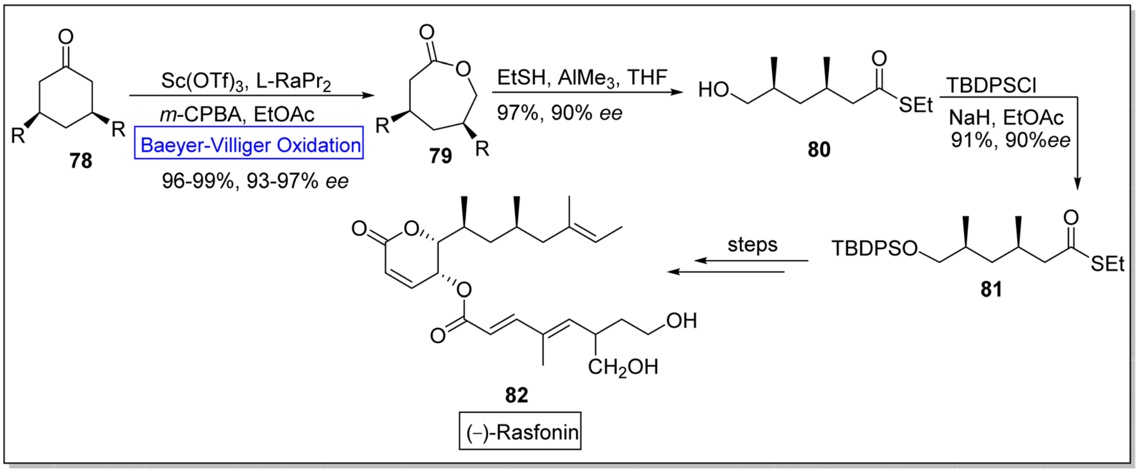
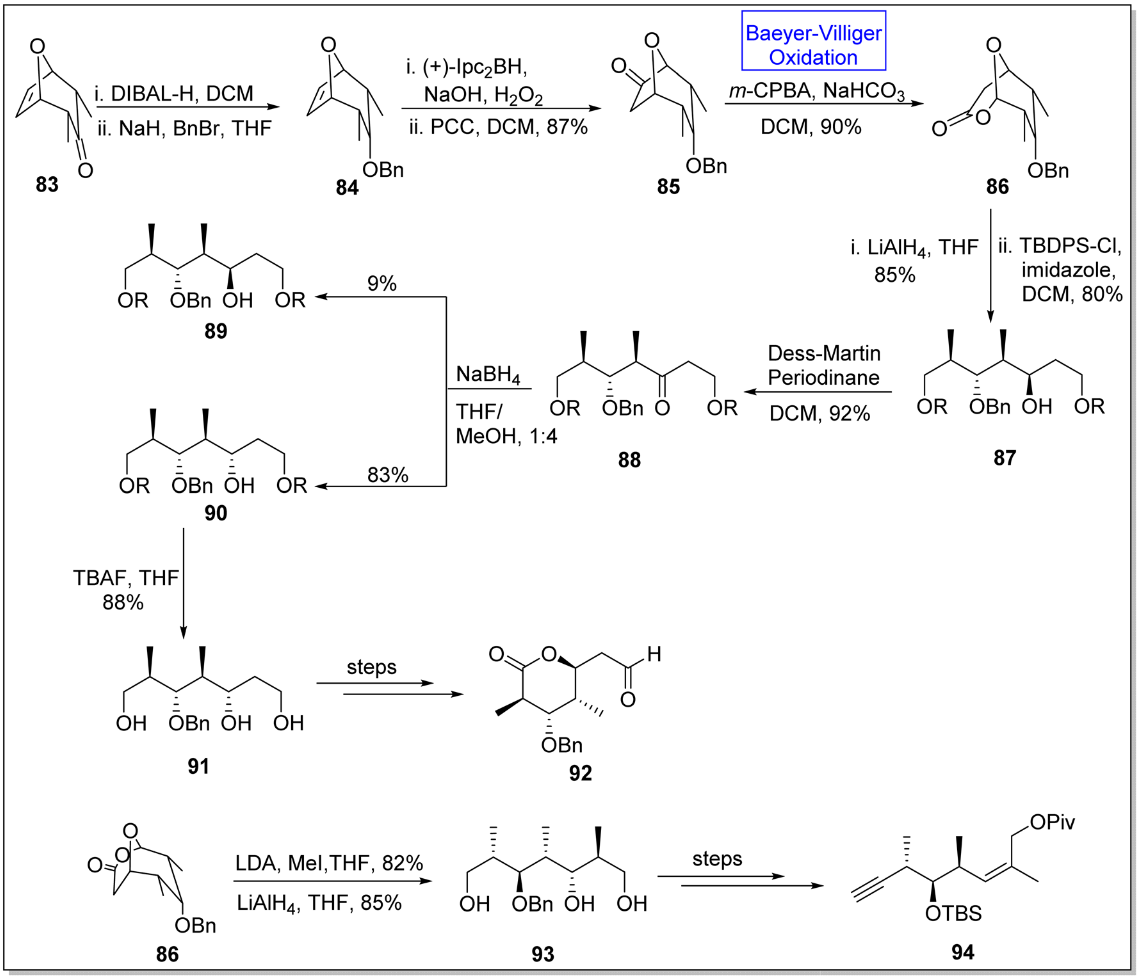


Scheme 10 Synthesis of (−)-rasfonin **82** *via* Baeyer–Villiger oxidation.

desired natural psammaplysin A **65** (in 11 steps) in 68% yield by reacting with hydrazine and pyridine in DCM and methanol. In another approach, compound **64** on treatment with compound **66**, amine, Zr(O^{t}Bu)$_4$, and HOAT in THF generated the respective natural products **67** (Scheme 8).

Metaphanine **75** and oxoepistiphemiersine **77** are hasubanan alkaloids which are isolated from genus *Stephania*.[92] Such alkaloids are widely used in medicines due to their antimicrobial, cytotoxic, and anti-viral activities.[93–96] These share benzannulated aza [4.4.3] propellane skeleton and vary due to



Scheme 11 Synthesis of C_{1-7} **92** and C_{8-15} **94** subunits of (+)-discodermolide *via* Baeyer–Villiger oxidation.

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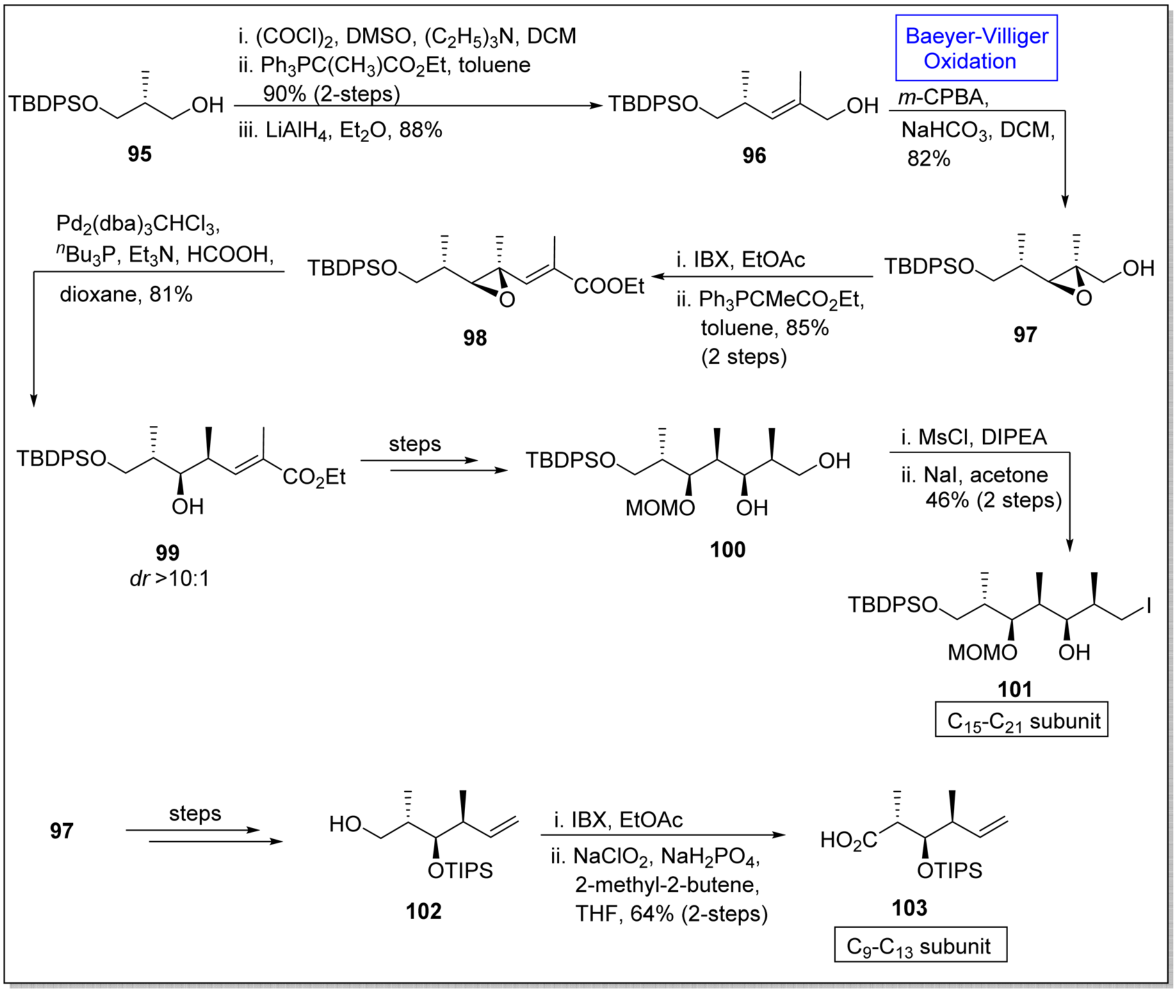

Scheme 12 Synthesis of C$_{15-21}$ **101** and C$_{9-13}$ **103** subunits of (+)-discodermolide *via* Baeyer–Villiger oxidation.

different patterns on arene ring in 2023, Sun *et al.* reported the total synthetic divergent strategy of hasubanan alkaloids (in 12–13 steps) by utilizing Baeyer–Villiger oxidation reaction as a fundamental step.[97] Synthetic scheme was initialized with the condensation of cyclohexanedione monoethylene acetal **68** with cyclohexylamine, deprotection with LDA, and alkylation with iodide followed by treatment with **69**, Ph$_3$PMeBr, ^{t}BuOK, THF, and HCl to generate a compound **70** in 87% yield. Then, the compound **70** gave a tetracyclic diketone **71** in 72% yield under optimized conditions. Compound **71** was further subjected to the Baeyer–Villiger oxidation with *m*-CPBA in the presence of NaHCO$_3$ and it resulted in the synthesis of a lactone **72** in 75% yield with outstanding regioselectivity. Thereafter, lactone **72** yielded a tetracyclic oxo-metaphanine **73** over a few steps, which further delivered a sulphamide **74** in 80% yield by reacting with lithium bis(trimethylsilyl)amide (LHMDS), MOMBr in THF and Lawesson's reagent in DCM. Finally, compound **74** afforded the desired compound, Metaphanine **75** in 82% yield on reduction with Raney Ni in DCM. In another approach, compound **73** generated a methyl enol ether **76** in 90% yield *via* methylation with LHMDS. Finally, Brown's hydroboration-oxidation of enol ether **76** followed by Dess-Martin oxidation furnished the oxoepistiphemiersine **77** in 90% yield (Scheme 9).

2.2. Synthesis of polyketide-based natural products *via* Baeyer–Villiger oxidation

In the field of natural product-based medicines, polyketides are of pivotal significance due to their anti-cancer and anti-bacterial activities.[98] Owing to these activities, many researchers have synthesized different naturally occurring polyketides by employing Baeyer–Villiger oxidation reaction. Fig. 3 shows the pictorial representation of structures of some of naturally occurring polyketides synthesized *via* BVO reaction.

(−)-Rasfonin **82** is a natural polyketide which is obtained from a fungal strain, *Cephalotrichum gorgonifer*.[99] It is a pharmaceutically significant bioactive compound that display anti-tumor activity and induces necroptosis, apoptosis, and autophagy in human cells.[100–103] Wu and co-workers in 2019, reported the total synthesis of (−)-rasfonin by utilizing regio-selective asymmetric Baeyer–Villiger oxidation.[104] The synthesis was commenced with the Baeyer Villiger oxidation of 3-substituted cyclic ketone **78** with *m*-CPBA in the presence of scandium(III) triflouromethanesulfonate Sc(OTf)$_3$ and EtOAc to

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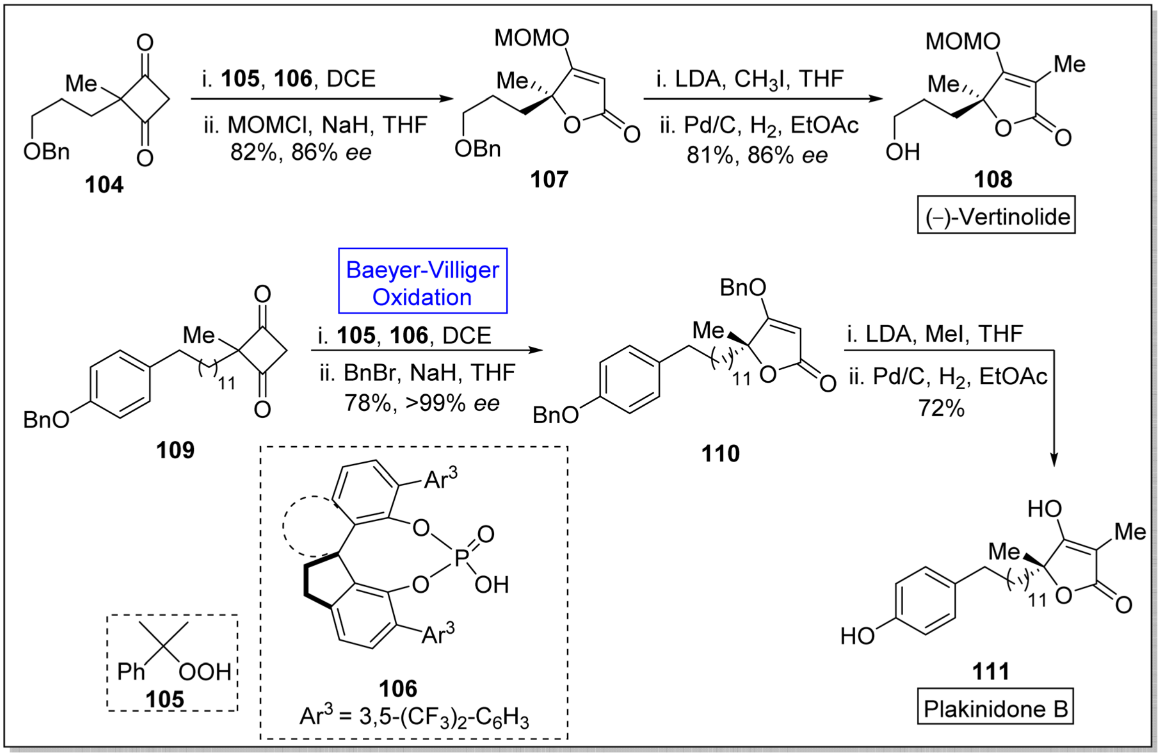

Scheme 13 Synthesis of vertinolide **108** and Plakinidone B **111** *via* Baeyer–Villiger oxidation.

afford a lactone **79** in 96–99% yield with 93–97% ee. Then, the lactone **79** was converted to compound **80** in 97% yield with 90% ee on treatment with EtSH and AlMe$_3$ in THF. Afterwards, compound **80** was made to react with *tert*-butyl(chloro)diphenylsilane (TBDPSCl), NaH, and EtOAc to generate 1,3-dimethyl thioester **81** in 91% yield with 90% ee. Subsequently, thioester **81** further underwent a series of reactions to furnish the (−)-rasfonin **82** (Scheme 10).

(+)-Discodermolide is a recently discovered cytotoxic polyketide. It is a very efficient antimitotic[105,106] natural product which is extracted from a sea sponge *Discodermia dissolute*.[105,107] Gunasekara and coworkers, in 1990, discovered this novel polyketide.[107] This product consists of thirteen chiral centers. Schreiber and associates synthesized the antipods of discodermolide but absolute configuration of this natural compound remained unclear.[108] To achieve the anticipated synthesis of (+)-discodermolide, Dubasi and Verala in 2022, reported the total synthesis of key fragments of the natural product by utilizing Baeyer–Villiger oxidation as one of the key reactions.[109] The synthesis was initiated with the DIBAL-*H* mediated reduction of bicyclic ketone **83** in DCM followed by reaction with NaH, BnBr, and THF to afford compound **84**. Then, the compound **84** experienced asymmetrical hydroboration with Ipc$_2$BH in the presence of PCC and DCM to furnish ketone **85** in 87% yield. Ketone **85** underwent Baeyer–Villiger oxidation with *m*-CPBA and NaOH in DCM to synthesize lactone **86** in 90% yield. Furthermore, compound **87** was obtained in 80% yield by the treatment of lactone **86** with TBDPS followed by reduction with LiAlH$_4$ which further generated a keto compound **88** in 92% yield *via* Dess-Martin periodonane-mediated (DMP) oxidation in DCM. Keto compound **88** was converted into two isomers; β-isomer **89** as minor isomer in 9% yield and α-isomer **90** as major isomer in 83% yield. α-Isomer **90** on reaction with TBAF in THF gave a triol **91** in 88% yield which further afforded the subunit of discodermolide **92** over a few steps. In another approach, methylation of lactone **86** followed by reduction with LiAlH$_4$ generated a triol **93** in 85% yield. In the final step, triol **93** yielded the subunit **94** over a few steps (Scheme 11).

Epoxides are three-membered heterocyclic compounds and experience epoxide ring opening reactions due to ring strain. Therefore, these are the substantial intermediates used in natural products synthesis[110] such as synthesis of (+)-discodermolide subunits. (+)-Discodermolide is a natural marine polyketide[107] and a very efficient anticancer agent.[111] In 1990, it was extracted from a sea sponge *Discodermia dissolute* and it possess 13 stereogenic centers. Since several synthetic approaches for this natural compound and its subunits have been reported but in 2020, Si and Kaliappan established the novel non-aldol synthetic strategy for the synthesis of two subunits of (+)-discodermolide by utilizing Baeyer–Villiger oxidation as a key reaction.[112] The synthesis was accomplished with the homologation of alcohol **95** *via* oxidation in the presence of (COCl)$_2$, DMSO, Et$_3$N in DCM followed by Wittig reaction and reduction to afford an allylic alcohol **96** in 88%. In the next step, the alcohol **96** underwent Baeyer–Villiger oxidation with *m*-CPBA to generate an epoxy alcohol **97** in 14 : 1 diastereomeric ratio with 82% yield. Furthermore, this epoxy alcohol

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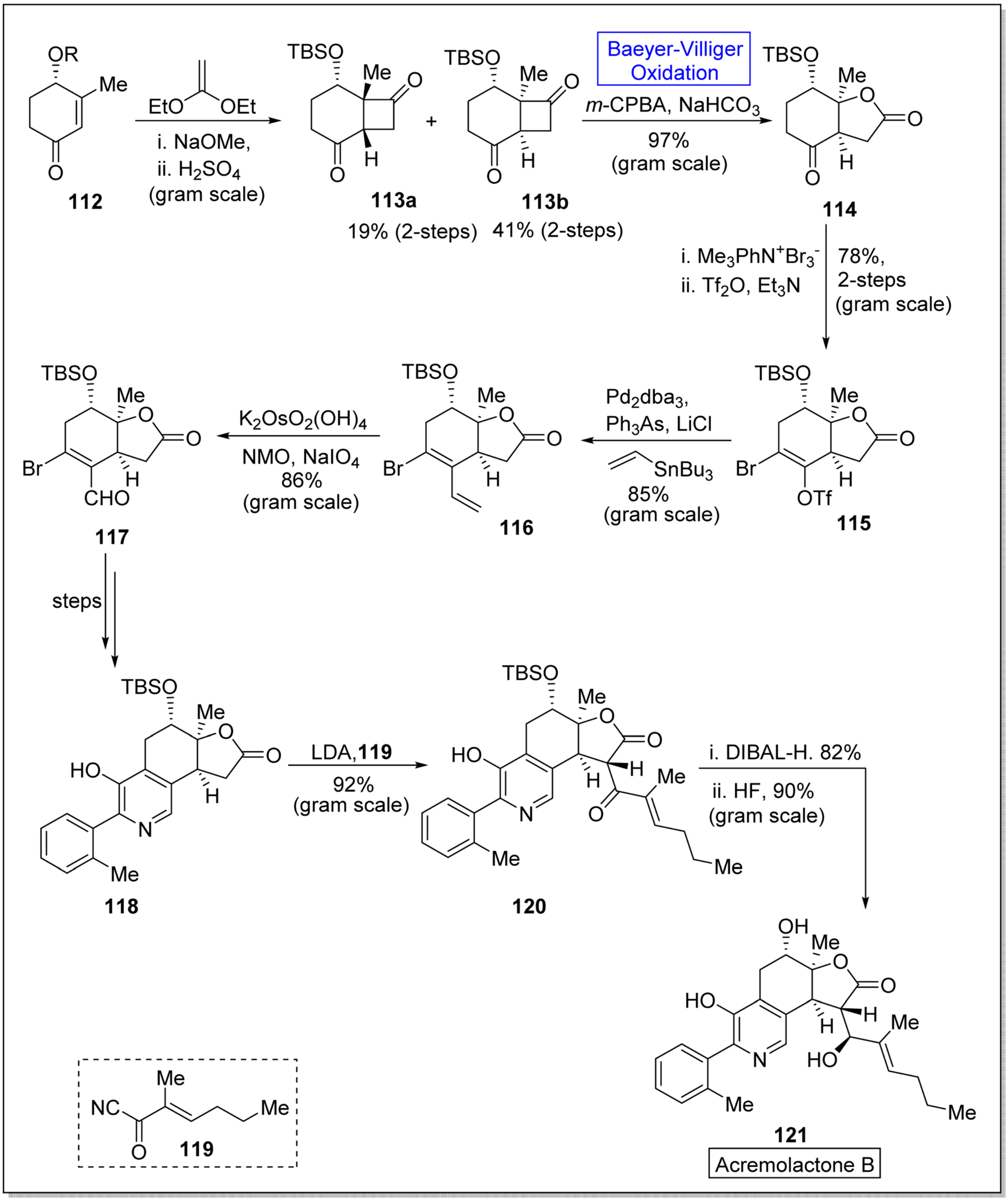

Scheme 14 Synthesis of acremolactone B **121** *via* Baeyer–Villiger oxidation.

97 was subjected to oxidation and homologation under Wittig olefination conditions to synthesize epoxy ester **98** in 85% yield (over 2-steps). Subsequently, Shimizu reaction of compound **98** under optimized conditions provided a hydroxyester **99** in diastereomer ratio >10 : 1 (81% yield). Then, compound **99** synthesized the 1,3-diol **100** in 47% yield over a few steps. Primary alcohol **100** was mesylated with MsCl and underwent Finkelstein reaction to furnish the subunit of discodermolide **101** in 46% yield (over 2-steps). In another route, compound **97** afforded a primary alcohol **102** in 75% yield *via* many steps which further underwent oxidation to yield the C_9–C_{13} subunit **103** of discodermolide in 64% yield over 2 steps (Scheme 12).

Spirocyclic moieties captivate the researchers due to their ring system and effective biological activities. Many natural products contain spirocyclic ring system and are used in pharmaceutical industry.[113] Spirocyclic ligands are also used in the natural product synthesis. Such as vertinolide is a natural product which is synthesized in the presence of spirocyclic

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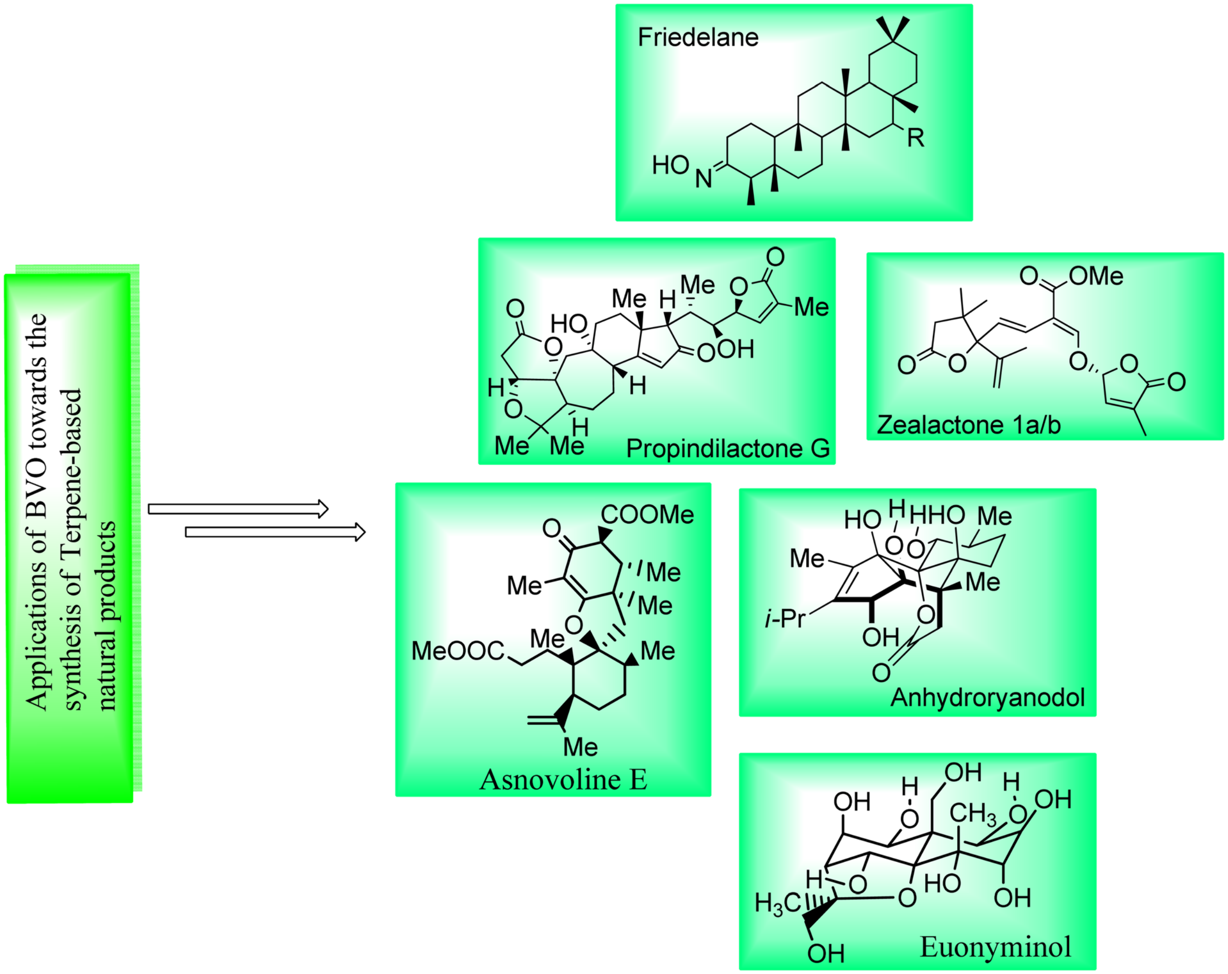

Fig. 4 Pictorial framework elaborating the structures of some terpene-based natural products obtained by involving BVO as a key step.

chiral phosphoric acid ligand **106.** Vertinolide **108** is a derivative of β-tetronic acid and it is extracted from *Verticillium intertextum*. It belongs to fungal-metabolites, myotoxins.[114,115] Vertinolide **108** inhibits the root and shoot growth in Lattuce seedlings. Plakinidone B **111** is a five-membered perlactone which is isolated from *Angulospiculatus* and it exhibits anti-viral and anti-microbial properties. In 2023, Liu *et al.* reported an enentioselective synthesis of vertinolide and 1st total synthesis of the plakinidone by utilizing the highly enantioselective Baeyer–Villiger oxidation as a significant step.[116] The synthesis was begun with the treatment of cyclobutane-1,3-dione **104** with cumene hydroperoxide **105** (Baeyer–Villiger oxidation) and spirocyclic chiral phosphoric acid ligand **106** in the presence of $(C_2H_5)_2Cl_2$ and then protected with methoxy methyl chloride (MOMCl) and NaH in THF to give an enolate ether **107** in 82% yield (86% ee). Then, enolate ether **107** afforded the vertinolide **108** in 81% yield (86% ee) by reacting with LDA, CH_3I, in THF followed by Pd/C-catalyzed reduction in EtOAc. Furthermore, cyclobutene-1,3-dione **109** was reacted with **105** and **106** in DCE and then with BnBr and NaH in THF to synthesize compound **110** in 78% yield (>99% ee). Methylation of compound **110** with MeI and LDA in THF followed by debenzylation furnished the plakinidone B **111** in 72% yield over 2-steps (Scheme 13).

Acremolactone B is an azaphilone-type fungal polyketide. Acrolactones were isolated by Sussa and group from the fungus, *Acremonium roseum*.[117,118] Such natural products have gained significant importance due to vast range of biological activities such as herbicidal, anti-cancer, anti-viral, anti-inflammatory and anti-microbial activities.[119] In 2023, Ba *et al.* reported the first total asymmetric synthesis of acremolactone B on gram scale by utilizing Baeyer–Villiger oxidation as a key step.[120] The synthesis was inaugurated with [2 + 2] photocycloaddition of compound **112** with 1,1-diethoxyethene in the presence of NaOMe and H_2SO_4 to afford the mixture of cis and trans products **113a** and **113b** (19% and 41% respectively) in 2-steps. In the next step, *m*-CPBA-induced Baeyer–Villiger oxidation of compound **113b** generated highly regio and chemo-selective γ-lactone **114** in 97% yield. Then, the reaction of compound **114** with $Me_3Ph_3N^+Br^-$ followed by triflation with Tf_2O in Et_3N generated the compound **115** in 78% yield (over 2 steps). The compound **115** was subjected to Stille-Magita coupling with Pd_2dba_3, Ph_3As, LiCl (Farina Protocol), and tributyl(vinyl)stannane to furnish bromo diene **116** in 85% yield. Subsequently, treatment of compound **116** with $K_2OsO_2(OH)_4$, NMO, and $NaIO_4$ afforded the corresponding bicyclic intermediate **117** with overall 86% yield. Afterwards, a 4-step sequence from

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compound **117** to **118** resulted in the formation of a pyridine ring. Deprotonation of compound **118** with LDA and acylation with acyl cyanide **119** synthesized the compound **120** in 92% yield which upon further reduction with DIBAL-*H* in HF synthesized the natural product **121** in 90% yield (Scheme 14).

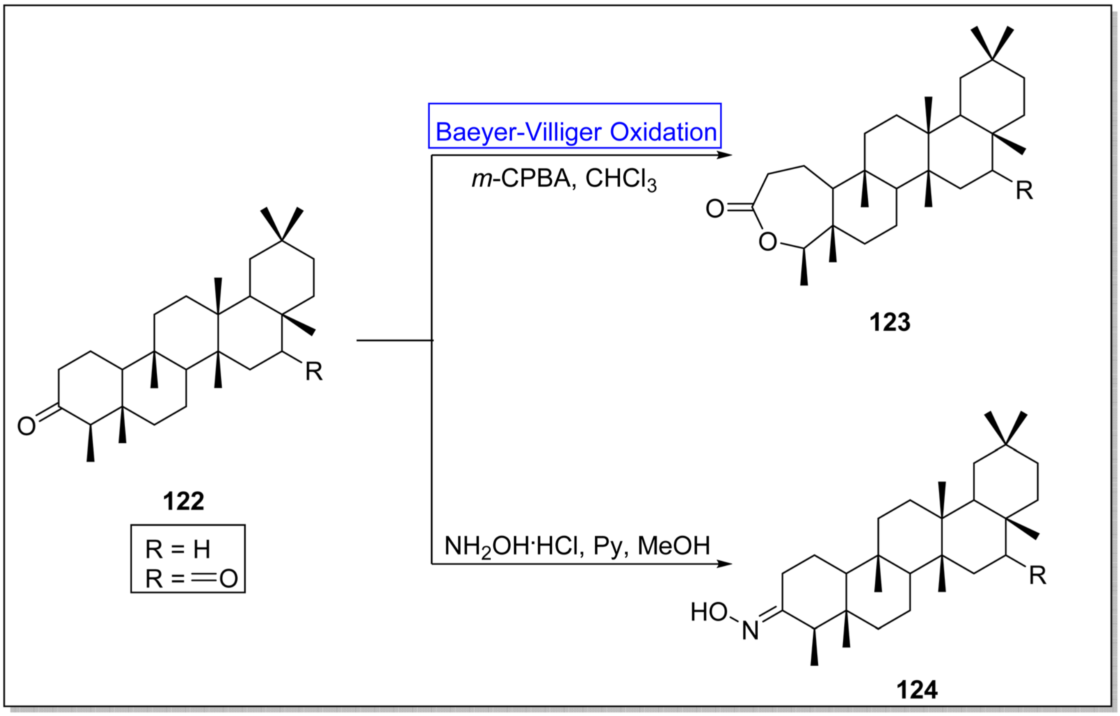
2.3. Synthesis of terpene-based natural products *via* Baeyer–Villiger oxidation

Terpenes are a diverse class of natural compounds. They are isolated from plants, animals fungi, pathogens, insects, and endophytes. They exhibit anti-microbial, anti-inflammatory, anti-cancer, anti-oxidant and anti-diabetic activities.[121,122] Baeyer–Villiger oxidation is one of those appealing reactions used for the synthesis of naturally occurring terpenes and terpenoids (Fig. 4).

Friedelanes are natural triterpenoids obtained from leaves and branches of *Maytenus robusta* Reissek.[123] These exhibit biological potential against breast and ovarian cancer cells[124] with a decrease in IC_{50} value (IC_{50} < 100 μM). In 2020, Aguilar *et al.* presented the synthesis of friedelane derivatives by utilizing Baeyer–Villiger oxidation as a significant step.[123] In the synthetic route, compound **122** was converted into a lactone *i.e.*, friedelane derivative **123** *via m*-CPBA catalyzed Baeyer–Villiger oxidation in chloroform. Similarly, the same compound **122** afforded the other friedelane derivative **124** on treatment with NH_2OH, HCl, and pyridine in methanol (Scheme 15).

Cross-coupling reactions are remarkable synthetic tools that are used for the synthesis of naturally occurring biologically active molecules and their analogues *i.e.*, anhydro ryanodol **131**. Anhydro ryanodol **131** is a diterpenoid[125] and a hydrolysis product of natural compound ryanodine which is isolated from a shrub; *Ryana speciosa*. It exhibits insecticidal properties. Initially, ryanodol was synthesized by Deslongchamps' by harnessing Diels–Alder reaction and oxidative cleavage.[126,127] Prior to 2020, Reisman achieved the synthesis of ryanodol by employing Pauson–Khand reaction and SeO_2-catalyzed polyoxidation.[125] However, in 2020, Du *et al.* reported the unique approach of formal and total synthesis of anhydroryanodol **131** by utilizing the BV oxidation as a key step through the formation of ryanoids (which further led to successful synthesis of anhydroryanodol) and carbocyle formation.[128] For this purpose, an alkyne **125** was treated with Cu-mediated *i*-PrMgCl, iodine, added with MnO_2 in DCM (67%), C_4H_3liO in THF and NBS followed by the reaction with TBSOTf, benzylamine, DCM, and then with $ClRh(PPh_3)_3$, PhH to give a hemiacetal **26** (α and β with 3 : 1 ratio). Acylation of hemiacetal **126** with acyl cyanide **127** followed by methylation with KHMDS and methyl iodide synthesized the 1,3-diketone **128** in 59% yield ($d:r \geq 20$). Then compound **128** underwent Sonogashira coupling and Stille coupling to generate the subsequent enyne **129** in 58% yield. Then, this enyne **142** was converted into compound **130** over a few steps. Finally, compound **130** afforded anhydroryanodol **131** in 38% yield *via* Baeyer–Villiger oxidation with *m*-CPBA, hydration and desilylation followed by the reaction with tris-sulfonium difluorotrimethylsilicate (TASF). Thereafter, compound **131** generated ryanodol **132** in 38% yield *via* epoxidation and reductive cyclization (2-step sequence) in dichloro ethane (DCE) and THF (Scheme 16).

Strigolactones are naturally occurring vital hormones which play a crucial role in agriculture for plant development. Zealactone **137** is an abundant strigolactone, isolated from roots of corn (in eight steps).[129,130] Its naturally occurring diastereomers



Scheme 15 Synthesis of friedelanes 123 and 124 *via* Baeyer–Villiger oxidation.

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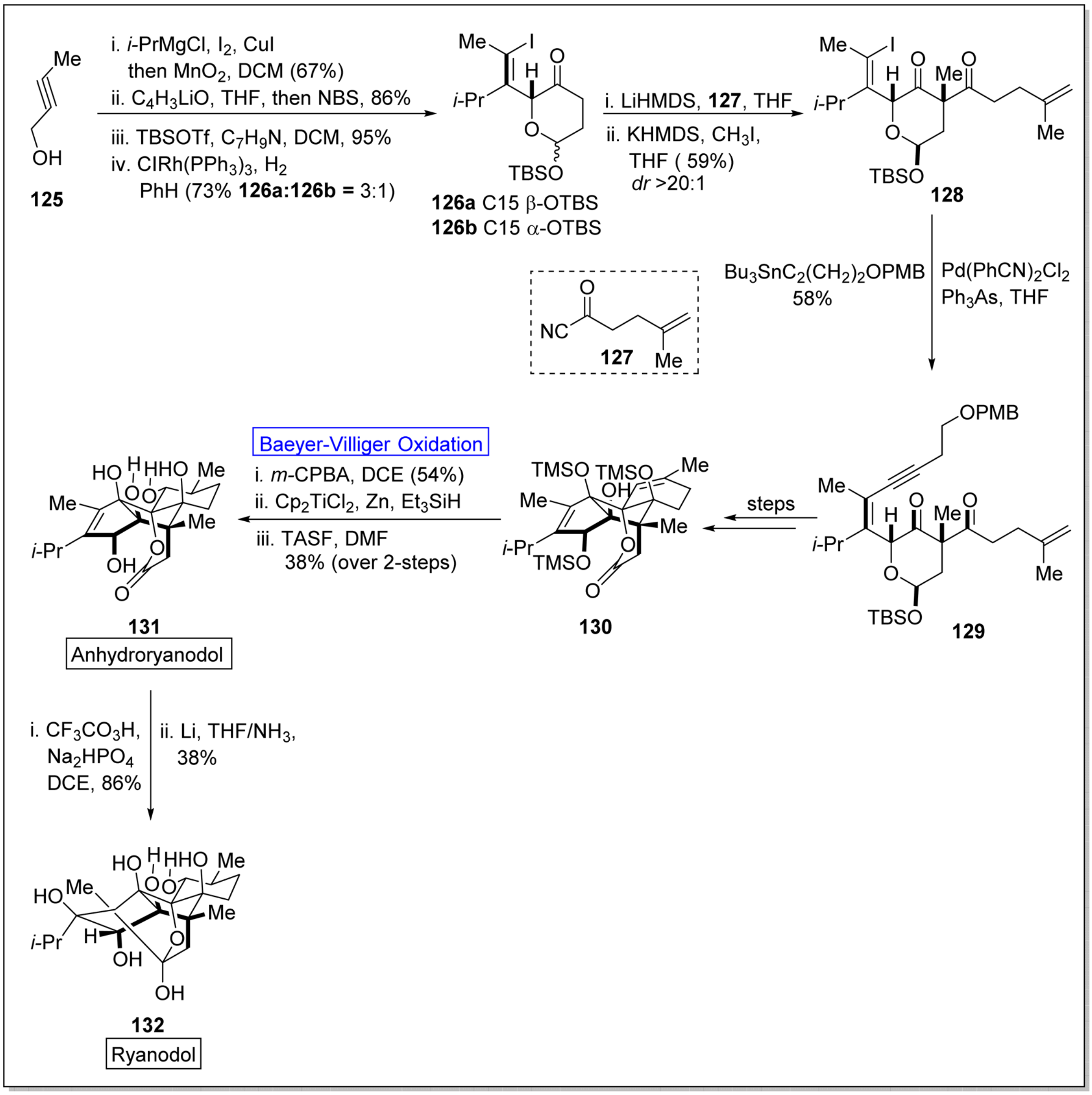

Scheme 16 Synthesis of anhydroryanodol 132 *via* Baeyer–Villiger oxidation.

have IC_{50} value of 0.59 μM against ZmD14-dependent YLG hydrolysis. In 2020, Yoshimura and co-workers established the total synthesis of zealactone 1a/2 in 8 steps with overall 21% yield *via* Baeyer–Villiger oxidation reaction.[131] In the first step of synthesis, cyclobutanone **133** underwent the Baeyer–Villiger oxidation with *m*-CPBA in the presence of Bu_4NOH in DCM to produce a γ-butyrolactone **134** in 61% yield. In the next step, lactone **134** was reacted with TBAF and then it was hydrostannylated with $HSnBu_3$ and azobisisobutyronitrile (AIBN) in toluene to yield the respective stannane **135** in 97% yield. Then, compound **135** was treated with vinyliodide **136**, Pd_2dba_3, $p(furyl)_3$, and 1,4-dioxane to furnish the zealactone **137** in 61% yield (Scheme 17).

Propindilactone G **146** belongs to a large family of polycyclic *Schisandra* nortriterpenoids, which were isolated from Schizandraceae family of plants.[132,133] These reveal herbal medicinal properties and are used to treat insomnia, hepatitis and asthenia.[134] In 2015, Yang and colleagues presented the synthesis of the propindilactone G by employing the Diels–Alder and Pauson–Khand reaction to achieve ring system.[135] However, in 2020, Wang *et al.* reported the biosynthesis of propindilactone G in 58% yield from steroidal lactone by utilizing significant reactions including Baeyer–Villiger oxidation reaction.[134] The synthesis was commenced with the reaction of steroidal lactone **138** with 3-iodobenzoic acid (IBX) followed by selective chlorination and E_2 reaction to afford olefin **139**. Then, compound **139** underwent a series of reactions to generate a ketone **140** in 82% yield. Ketone **140** was further subjected to three steps sequence including demethylation with CH_3I and ^tBuOK, Baeyer–Villiger oxidation with *m*-CPBA and Mukaiyama dehydrogenation with lithium bis(trimethylsilyl) amide (LiHMDS) to synthesize an unsaturated lactone **142** in 62% yield. Compound **142** was converted to a diol **143** in 82% yield by addition of Zn/HOAc and *p*-toluene sulfonic acid in

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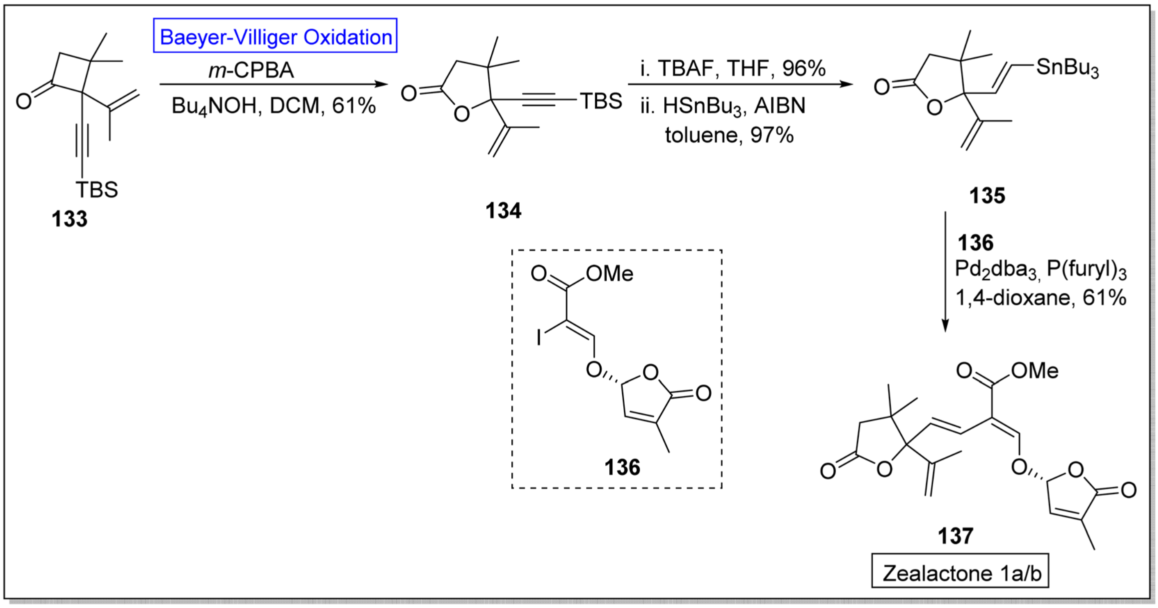
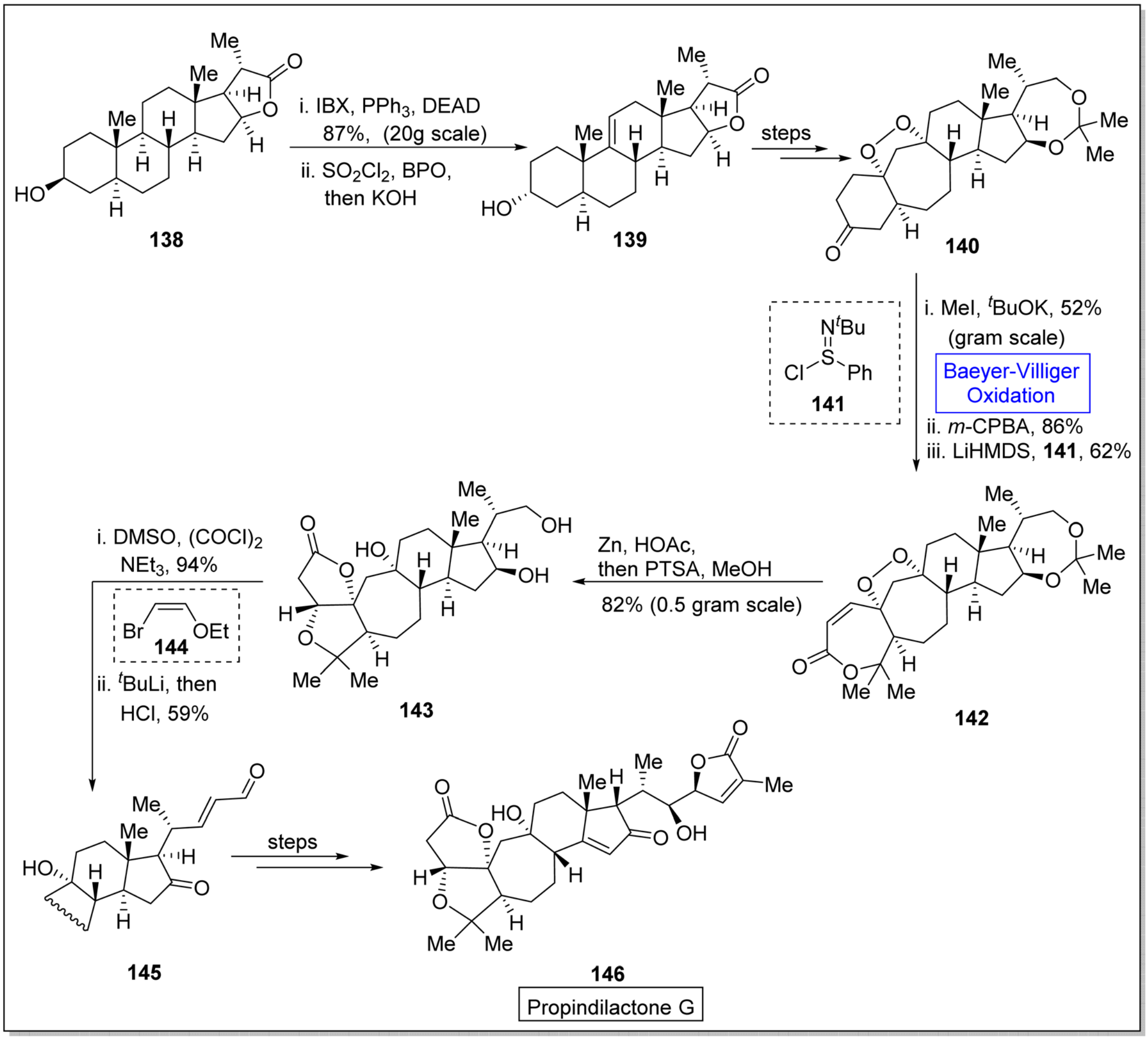


Scheme 17 Synthesis of zealactone **137** *via* Baeyer–Villiger oxidation.



Scheme 18 Synthesis of propindilactone G **146** *via* Baeyer–Villiger oxidation.

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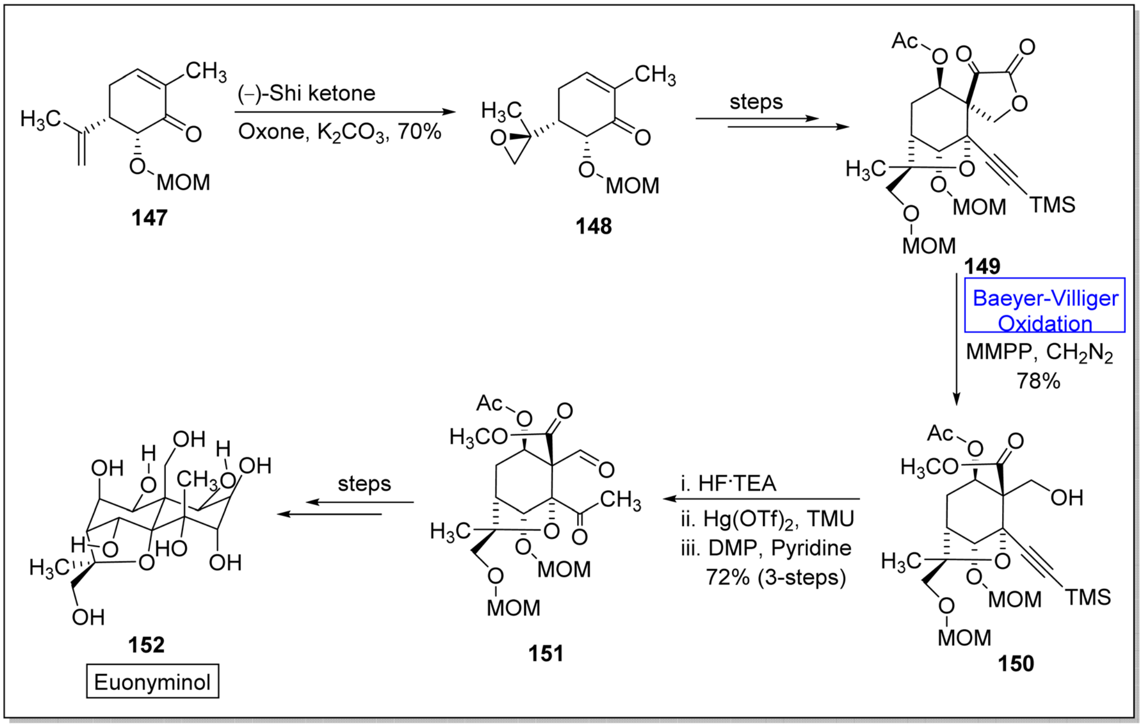

Scheme 19 Synthesis of euonyminol **152** *via* Baeyer–Villiger oxidation.

methanol. Swern oxidation of compound **143** followed by reaction with 2-ethoxyvinylbromide **144** and HCl gave an unsaturated aldehyde **145** in 59% yield which further produced the targeted compound **146** over a few steps. Stereochemistry of target product **146** (at C-17) was opposite to that of steroidal lactone **138** (Scheme 18).

Euonyminol **152** is a sesquiterpene[136,137] with dihydro-β-agrofuran nucleus and is pharmaceutically significant due to anti-proliferative, anti-oxidant, and anti-microbial activities.[137] In 1995, White and coworkers reported the synthesis of less oxygenated euonyminol. In 2021, Tomanik and coworkers presented the first enantioselective total synthesis of highly oxidized euonyminol by utilizing Baeyer–Villiger oxidation reaction as a key step.[138] The synthesis embarked with the conversion of diene **147** into a diastereomer **148** in 70% yield *via* oxidation with Shi ketone and oxone in the presence of K_2CO_3. Then, compound **148** afforded an α-keto lactone **149** over a few steps which further underwent Baeyer–Villiger oxidation using magnesium monoperoxyphthalate (MMPP) and diazomethane to give a methyl ester **150** in 78% yield. Treatment of methyl ester **150** with HF·TEA, $Hg(OTf)_2$, and tetramethyl urea (TMU) followed by Dess–Martin periodinane (DMP) furnishing a neopentyl aldehyde **151** in 72% yield (3-step sequence). Compound **151** generated the natural product, euonyminol **152** in a sequential process (Scheme 19).

Asnovolin A (**158**) and B (**159**) are DMOA (3,5-dimethylorsellinic acid)-derived natural spiromeroterpenoids,[139] which are pharmaceutically pivotal due to anti-bacterial activity.[140,141] Yang *et al.* in 2022, reported the asymmetric total synthesis of asnovolins in 9–11 steps for the first time, by employing many key reactions including regioselective BV oxidation.[142] The synthesis was inaugurated with the conversion of hydroxy enone **153** into neopentyl iodide **154** in the presence of Tf_2O, 2,6-lutidine, DCM, NaI, acetone and $NaBH_4$, in methanol. Neopentyl iodide **154** over a few steps afforded the compound **155** which upon further treatment with IBX, Na_2HPO_4, and DMSO furnishing an enone **156** (72%) with regiocontrol. Compound **156** generated an asnovolin J **157** over a few steps. Subsequently, the product **157** underwent Baeyer–Villiger oxidation with *m*-CPBA in DCM to synthesize an asnovolin A **158** in 76% yield which upon further reaction with *p*-TsOH in methanol afforded the targeted product, asnovolin E **159** in 41% yield (Scheme 20).

2.4. Synthesis of fatty acid-based natural products *via* Baeyer–Villiger oxidation

Baeyer–Villiger oxidation reaction also play a fundamental role in the synthesis of naturally occurring fatty acids which are important in medicinal field due to their biological activities (Fig. 5).

Prostaglandins ($PGF_{2\alpha}$) are significant chemical messengers which exhibit biological activities and have broad range applications in medicinal field.[143,144] These exhibit wide range of pharmaceutical activities in contraction and dilation of smooth muscles, control of hormonal release, cell growth, suppression of acid in stomach and anti-glaucoma drugs.[143] Prior to 2019, Aggarwal and Hayashi achieved the synthesis of different prostaglandins by harnessing bond disconnection

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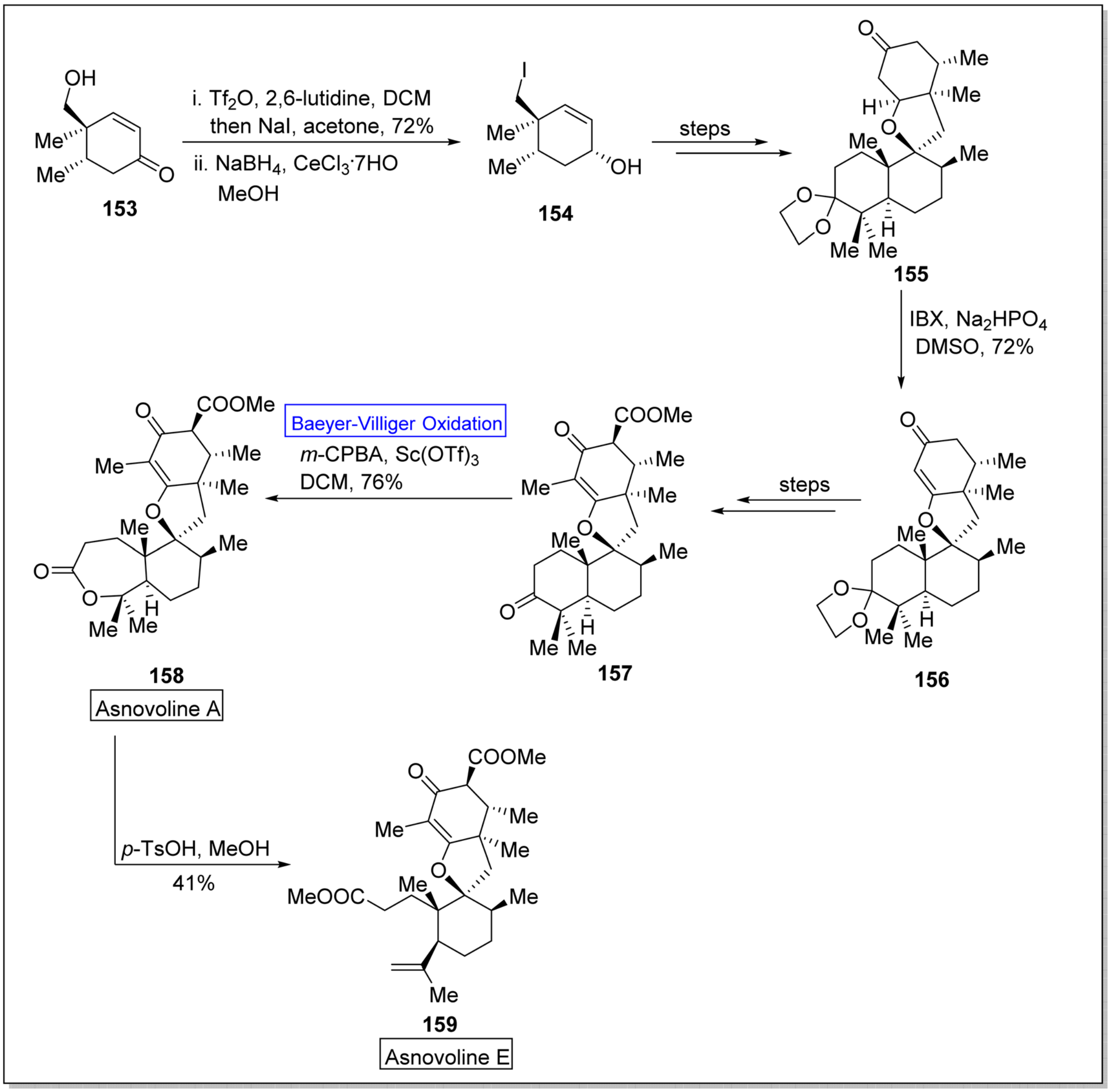

Scheme 20 Synthesis of asnovoline A **158** and E **159** *via* Baeyer–Villiger oxidation.

methodology.[145] However, these syntheses comprised lengthy schemes and complex protection/deprotection protocols. Zhu and colleagues in 2019, presented a novel protocol of enantioselective (90–99% ee) Baeyer–Villiger oxidation for the synthesis of prostaglandins in 8 steps with overall 20% yield from a lactone (−)-**162**.[146] In the first step of synthesis, cyclobutanone **160** was subjected to Baeyer–Villiger oxidation with H_2O_2 in the presence of a catalyst **161** in chloroform to afford the corresponding lactone (−)-**162** in 45% yield with 95% ee. In the next step, reductive dechlorination of lactone **162** with Zn/NH_4Cl followed by Prins reaction with paraformaldehyde and deformylation gave diol **163** in 79% over 2-steps which further furnished an allylic alcohol **164** over a few steps. Reduction of compound **164** with DIBAL-*H* followed by Wittig olefination synthesized the targeted compound **4** with an overall 20% yield (Scheme 21).

Thromboxane B_2 (TxB_2) and thromboxane A_2 (txA_2) belong to lipid family known as prostanoids, which are subclass of eicosanoids containing prostaglandins. TxB2 causes thrombosis[147] and effect immune system[148] and it is considered as a fundamental scaffold to study prostanoid-associated biochemical phenomena. Previously reported synthetic strategies of TxB_2 were lengthy, time consuming, and suffer from poor atom economy. In 2020, Jing *et al.* reported a twelve-step synthesis of natural prostanoid (TxB_2) in overall 5% yield from 2,5-dimethoxytetrahydrofuran.[149] Baeyer–Villiger oxidation is one of the key reactions involved in this asymmetric synthetic strategy. The synthesis was initialized with the formation of enal intermediate **166** in 29% yield (99% ee) from the aldol reaction of succinaldehyde **165** with L-proline. In the next step, treatment of compound **166** with para methoxy benzyl acetal (PMBOH) resulted in the synthesis of two diastereomers α-**167** and β-**167** (β/α 1.7 : 1). Then, α-isomer of PMBOH **167** was

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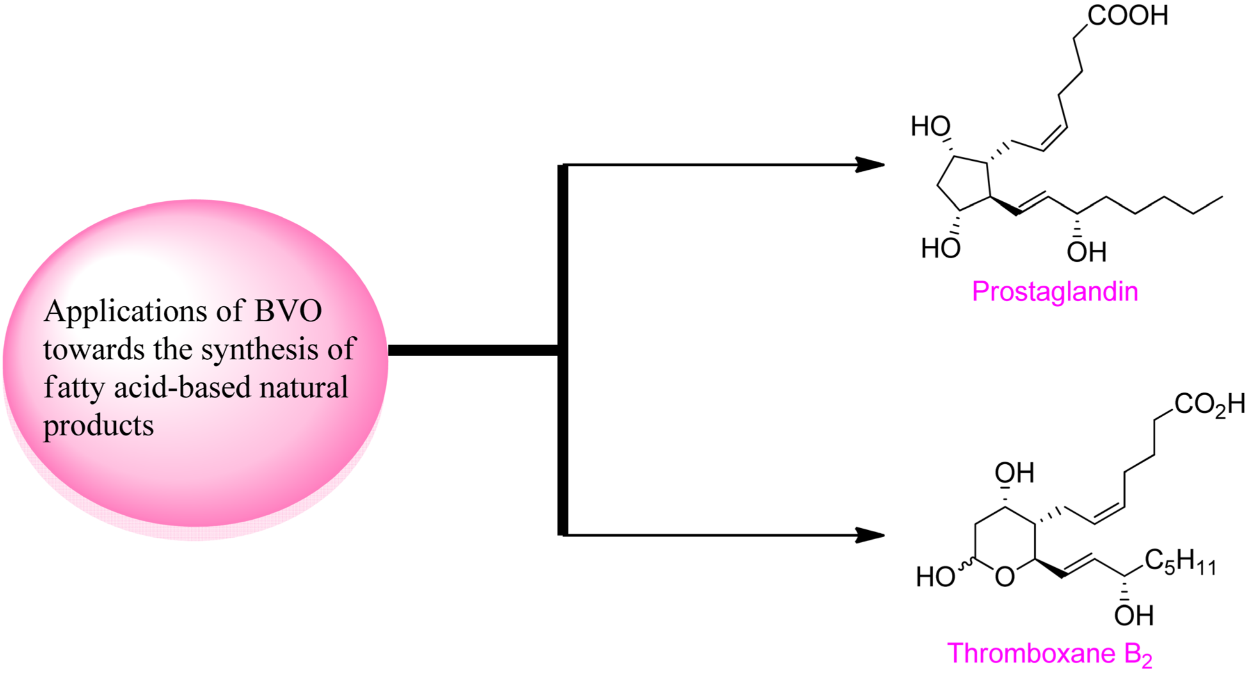
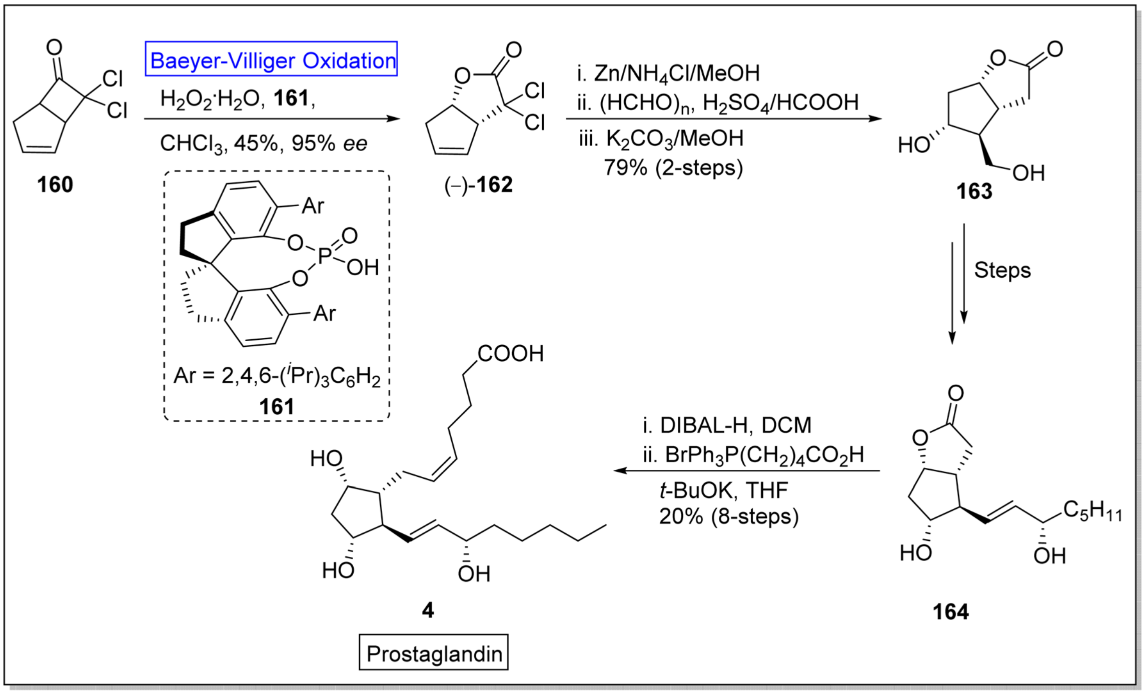


Fig. 5 Fatty acid-based natural products synthesized by involving BVO as a key step.



Scheme 21 Synthesis of prostaglandin **4** *via* Baeyer–Villiger oxidation.

treated with vinyl cuprate using trimethylsilyl chloride (TMSCl), Et_3N, and triphenyl phosphene (PPh_3) to synthesize compound **168**. The compound **168** was subjected to Baeyer–Villiger oxidation with *m*-CPBA to afford a lactone β-**169** in 64% yield and α-**169** in 63% yield (over three steps). Reduction, oxy methylation, and deprotection of PMB of lactone β-**169** furnished a diastereomer β-**170** (in 80% yield) over a few steps. Furthermore, olefination of the diastereomer β-**170** using phosphonium salt with ^{t}BuOK resulted in the corresponding alkene **171** in 97% yield. Consequently, alkene **171** upon further treatment with TBAF in THF followed by hydrolysis generated the final product TxB_2 **172** in 90% yield (Scheme 22).

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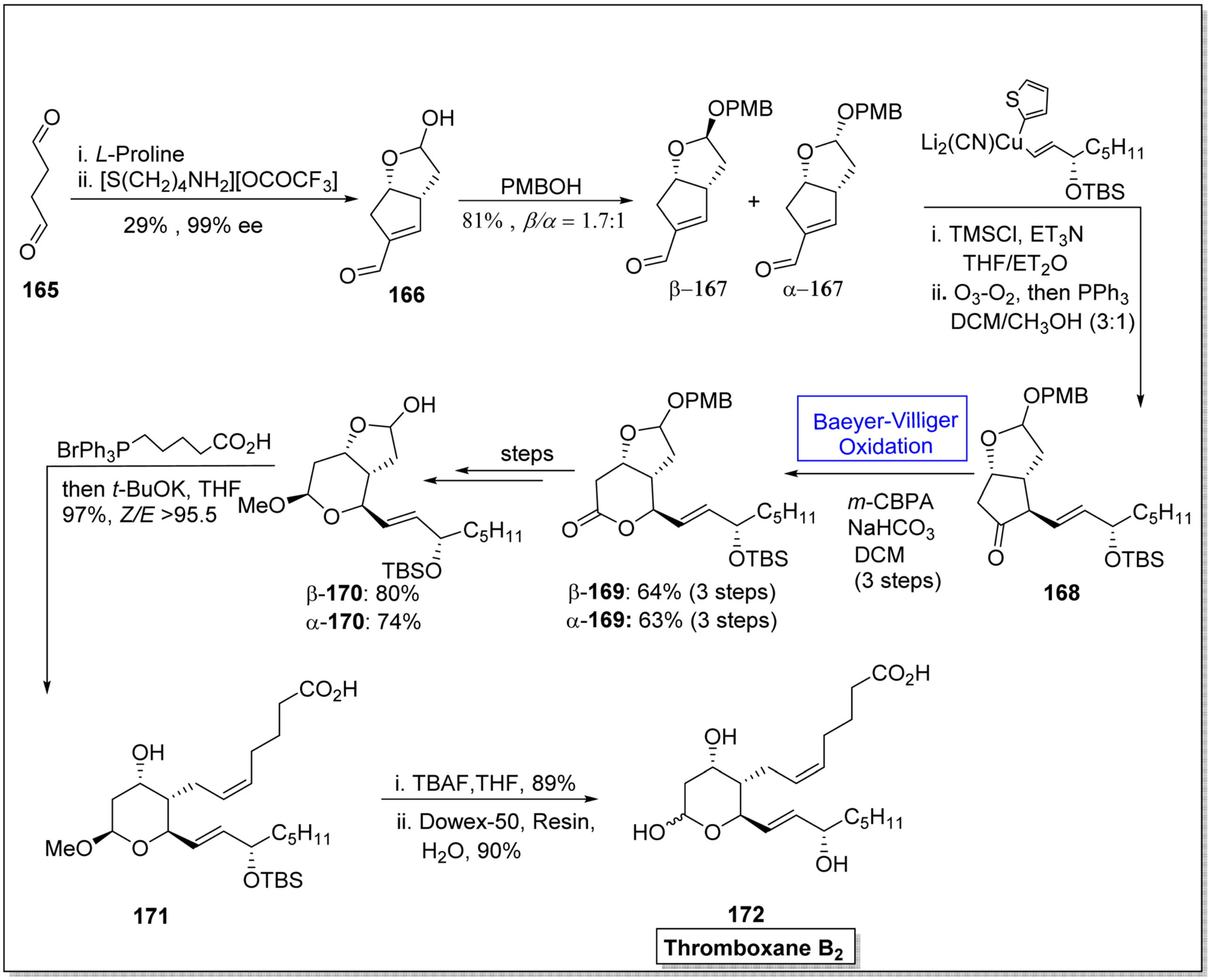

Scheme 22 Synthesis of thromboxane B_2 **172** *via* Baeyer–Villiger oxidation.

2.5. Synthesis of miscellaneous natural compounds *via* Baeyer–Villiger oxidation

Many other natural products can also be synthesized through Baeyer–Villiger oxidation reaction. Such as nepetoidin B, protoanemonin, terfestatins, darunavir; a protease inhibitor, cinnamic acid dimers and some hydroquinones (Fig. 6).

Nepetoidin B **175** belongs to a class of natural products and initially it was extracted from *Plecranthus caninus*, but now it is obtained from various plants and herbs.[150] It reveals many biological activities *i.e.*, anti-bacterial, anti-cancer, and anti-fungal activities.[151,152] Despite of these medicinal features, no synthetic strategies of compound **175** have been reported yet. In 2018, Timokhin *et al.* reported a two-step first synthesis of nepetoidin B (94% ee) in overall 17% yield by employing Baeyer Villiger oxidation as a significant step.[153] In the first step of schematic route, 1,5-bis(3,4-dimethoxyphenyl)-1,4-pentadiene-3-one **173** was converted into tetramethylated nepetoidin B **174** in 40% yield *via* Baeyer–Villiger oxidation with oxone in DMF. In the second step, compound **174** delivered the target product, nepetoidin **175** in overall 17% yield *via* demethylation using BBr_3 (Scheme 23).

Various efforts to synthesize anti-microbial agents have been carried out to overcome several microbes causing diseases.[154] Protoanemonin **179** is an antimicrobial[155] γ-lactone which is obtained from members of Ranunculaceae family.[156] Protoanemonin is famous for its pervasive and irritant properties, hence, may cause dermatitis.[156–159] Alibes and group synthesized protoanemonin in overall 25% yield *via* photo-oxidation process.[160] Similarly, Mliki and Trabelsi attempted to synthesize the targeted compound using CH_3COOH and sodium perborate but did not detect the product.[161] All previously reported methods involved high cost, scarcely available and contaminated reagents. In 2020, Martinez and companions reported the 1st one-pot selective synthesis of γ-alkylidenebutenolide (protoanemonin) in overall 25% yield from D-fructose **176** through 5-(hydroxy methyl) furfural **177** by employing Baeyer–Villiger oxidation.[162] In the beginning, D-fructose **176** was converted into 5-(hydroxy methyl) furfural **177** in 98% yield in the presence of hypophosphorous acid (HPA). Homogenous

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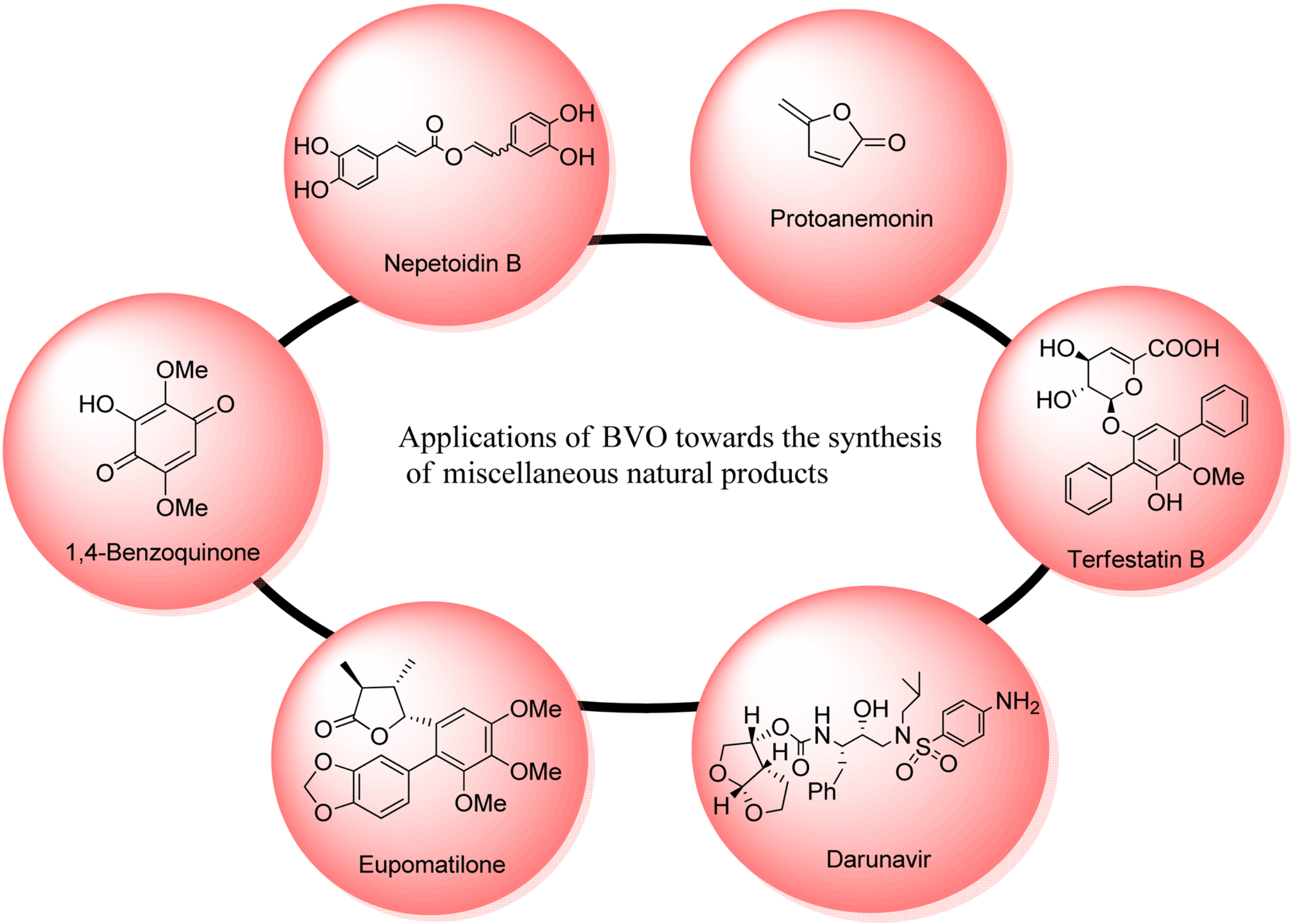
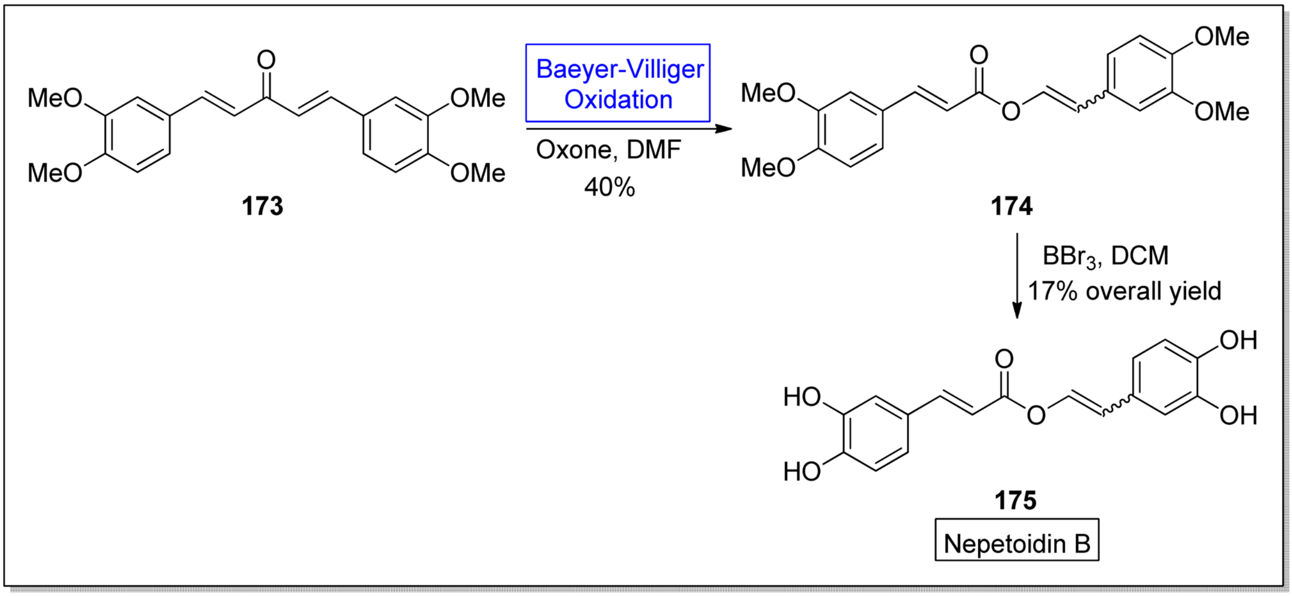


Fig. 6 Miscellaneous natural products synthesized by involving BVO as a key step.



Scheme 23 Synthesis of nepetoidin B **175** *via* Baeyer–Villiger oxidation.

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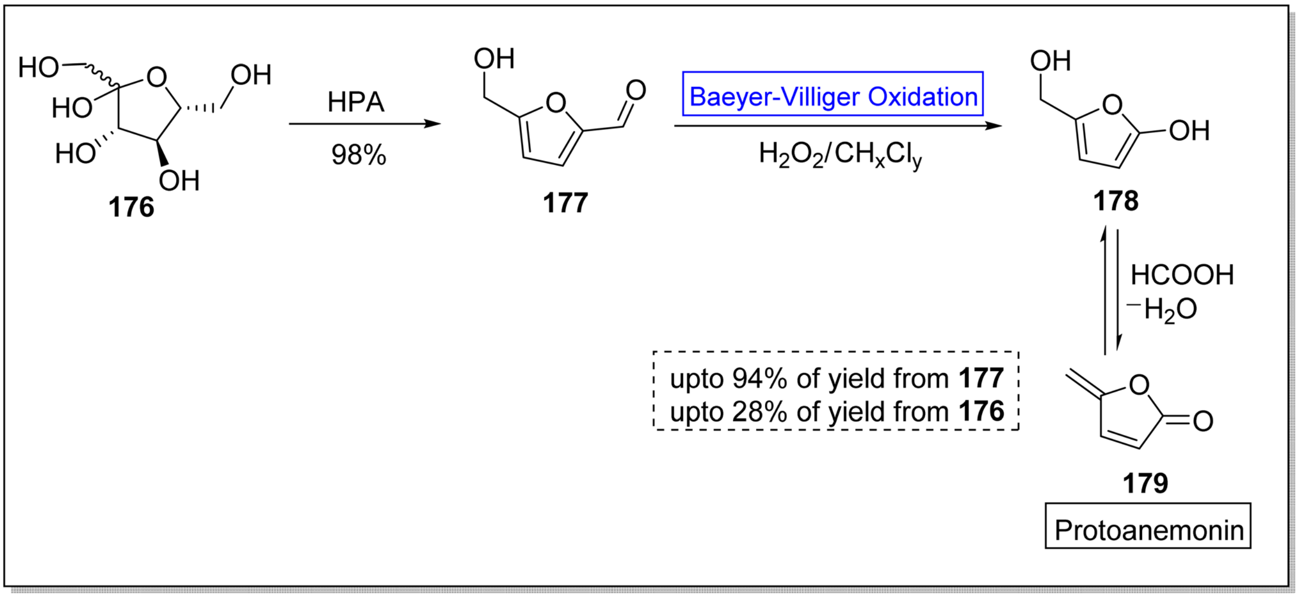

Scheme 24 Synthesis of protoanemonin **179** *via* Baeyer–Villiger oxidation.

autocatalysis and H_2O_2-mediated-Baeyer–Villiger oxidation of compound **177** in chlorinated solvent afforded the protoanemonin **179** in 94% yield from **177** and 28% yield from **176** (Scheme 24).

Terfestatin A **186** and B **187** are natural products which belong to terfestatin family and both are isolated from *Streptomyces* species. Terfestatin A **186** and B **189** reveal potent inhibitory and neuroprotective activities, respectively.[163] In 2020, Sugawara and colleagues presented the synthesis of terfestatin A with 21% overall yield (in 5-steps) and 1st total synthesis of the terfestatin B with 30% overall yield (in 8-steps) from aromatic aldehyde by engaging Baeyer–Villiger oxidation reaction as a key step.[164] For this purpose, 2,5-dibromohydroquinone **180** was converted into an aromatic aldehyde **181** in 78% yield by reacting with hexamethylene tetramine (HMTA) and TFA. Then, aldehyde **181** under optimized conditions afforded a terphenyl derivative **182** in 91% yield. Glucosylation of compound **182** with glycosyl bromide **183** was carried out to give a monomer **184** in 66% yield. Subsequently, the monomer **184** underwent the Baeyer–Villiger oxidation with *m*-CPBA to generate a compound **185.** Furthermore, compound **185** was reacted with TBAF and LiOH, in THF to synthesize terfestatin A **186** in 39% yield. In another approach, *O*-methylation of compound **182** with MeI in the presence of K_2CO_3 in DMF afforded compound **187**. Compound **187** underwent Baeyer–Villiger oxidation with *m*-CPBA to furnish compound **188** in 90% yield which further synthesized terfestatin B **189** over a few steps (Scheme 25).

Darunavir **2** is a potent natural drug which belongs to protease inhibitor therapeutics, an important part of cART (combination antiretroviral therapies) procedure.[165] It is widely used to treat HIV type-1 disease and AIDS.[166,167] The key element of darunavir **2** is bis-THF [bicyclic (3*R*,3a*S*,6a*R*)-bis-tetrahydrofuran] ligand alcohol. Initially, Ghosh and co-workers readily synthesized bis-THF alcohol *via* lipase-promoted enzymatic resolution of employing (3*R*)-diethyl malate as precursor. However, they obtained the target molecule in 92–96% ee. Quaedflieg and colleagues synthesized bis-THF by employing diastereoselective Micheal addition as key step, Black *et al.* reported the synthesis by employing Mukaiyama aldol reaction, and Xie group carried out the Lewis acid-mediated synthesis. In 2020, Ghosh *et al.* extended their work to achieve more enantioselective synthesis of optically pure bis-THF ligand (99% ee) from xylose.[168] The synthesis was carried out by utilizing many named reactions including Baeyer–Villiger oxidation as significant step. The synthesis was commenced with the selective protection of alcohol as benzoate derivative of benzoyl chloride in presence of DMAP and pyridine to generate a compound **191** in 95% yield. Then, Swern oxidation of compound **191** followed by Wittig olefination with (carboethoxy methylene) triphenyl phosphorane in DCM afforded an α,β-unsaturated ester **192** in 85% yield with $E/Z = 1:8$ (over 2-steps). Afterwards, catalytic hydrogenation of *Z*-isomer **192** with 10% Pd/C in ethanol followed by reaction with $BF_3\cdot OEt_2$ and Et_3SiH in the presence of K_2CO_3 and methanol produced a bicyclic alcohol **193** in 87% yield. In the next step, compound **193** was converted into lactone **194** in 41% yield over 3-steps including Dess-Martin oxidation, Baeyer–Villiger oxidation with *m*-CPBA and acidification in MeOH. Reduction of methyl acetal **194** with $LiAlH_4$ in THF gave bis-THF alcohol **195** in 63% yield. When ligand **195** was reacted with active *N*,*N*′-disuccinimidyl carbonate **196** in MeCN, it yielded carbonate **197** in 65% yield. In the last step, compound **197** upon further reaction with Cbz (benzyl chlorocarbonate) derivative **198**, furnished the darunavir **2** in 53% yield (Scheme 26).

Eupomatilones are natural products (cinnamic acid dimers)[169] related to lignan family and these were isolated by Carroll and Taylor (in 1991) from a shrub *Eupomatia bennettii*.[170]

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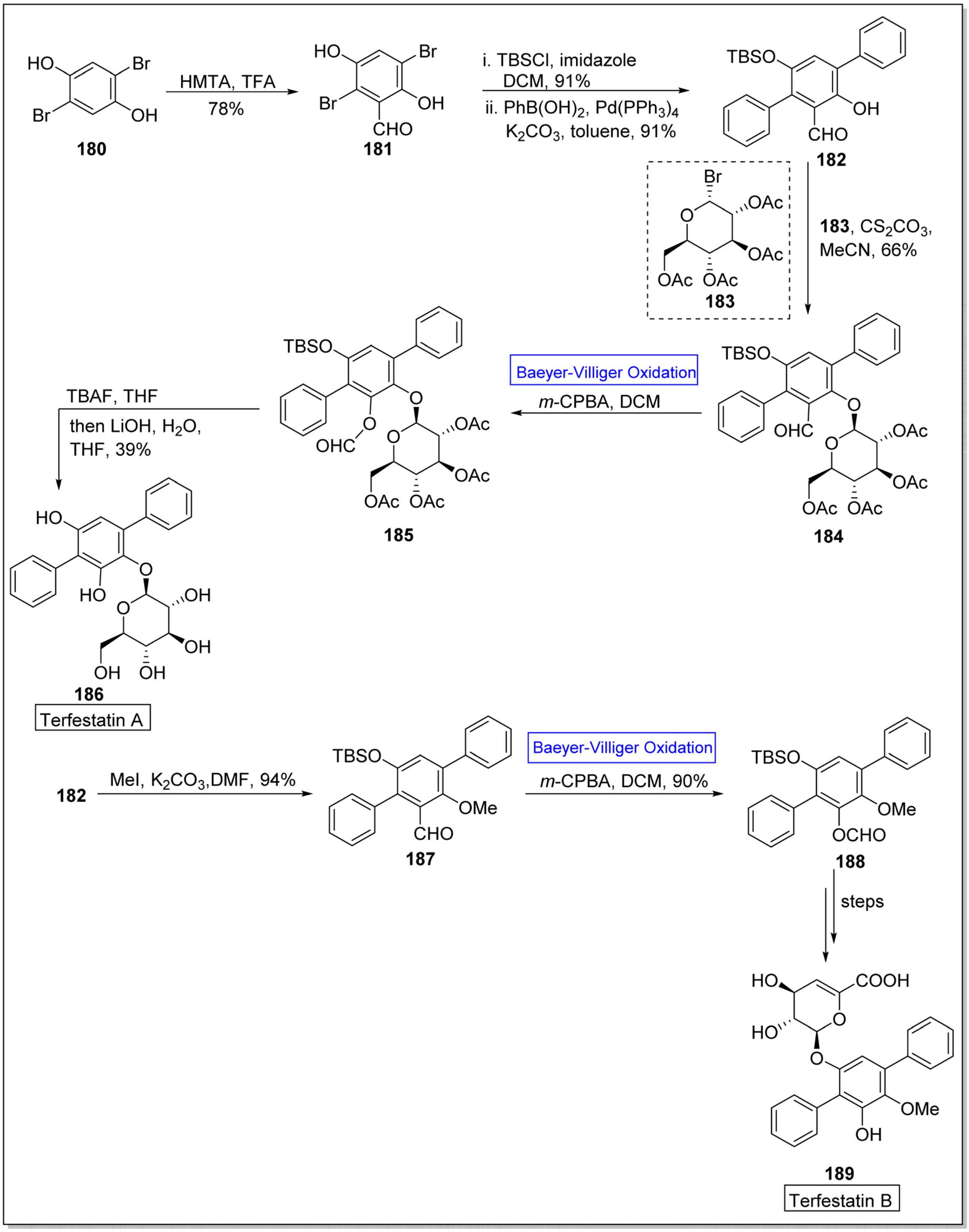

Scheme 25 Synthesis of terfestatin A **186** and terfestatin B **189** *via* Baeyer–Villiger oxidation.

These are dispersed throughout the plant stems, leaves, roots, seeds and fruits, and exhibit anti-fungal, anti-HIV and anti-cancer activities. In 2022, Zhang *et al.* achieved the total synthesis of natural eupomatilones **204** and **205** from a cyclic ketone **199** by employing Cu(II)complex-catalyzed asymmetric BV oxidation.[171] The synthesis was initiated with the Pd-regulated arylation of 3-methylcyclobutanne-1-one **199** with 1-bromo-3,4,5-trimethyloxybenzene **200** to prepare a racemic precursor **201** in 65% yield ($d:r = 5.6:1$). To improve the diastereomeric ratio, the precursor **201** was treated with *p*-toluenesulfonic acid in chloroform. Then, compound **201** underwent Baeyer–Villiger oxidation with *m*-CPBA followed by reaction with $Cu(NTf_2)_2$ to furnish a chiral lactone **202** in 48% yield with 92% ee. Furthermore, lactone **202** afforded a γ-butyrolactone

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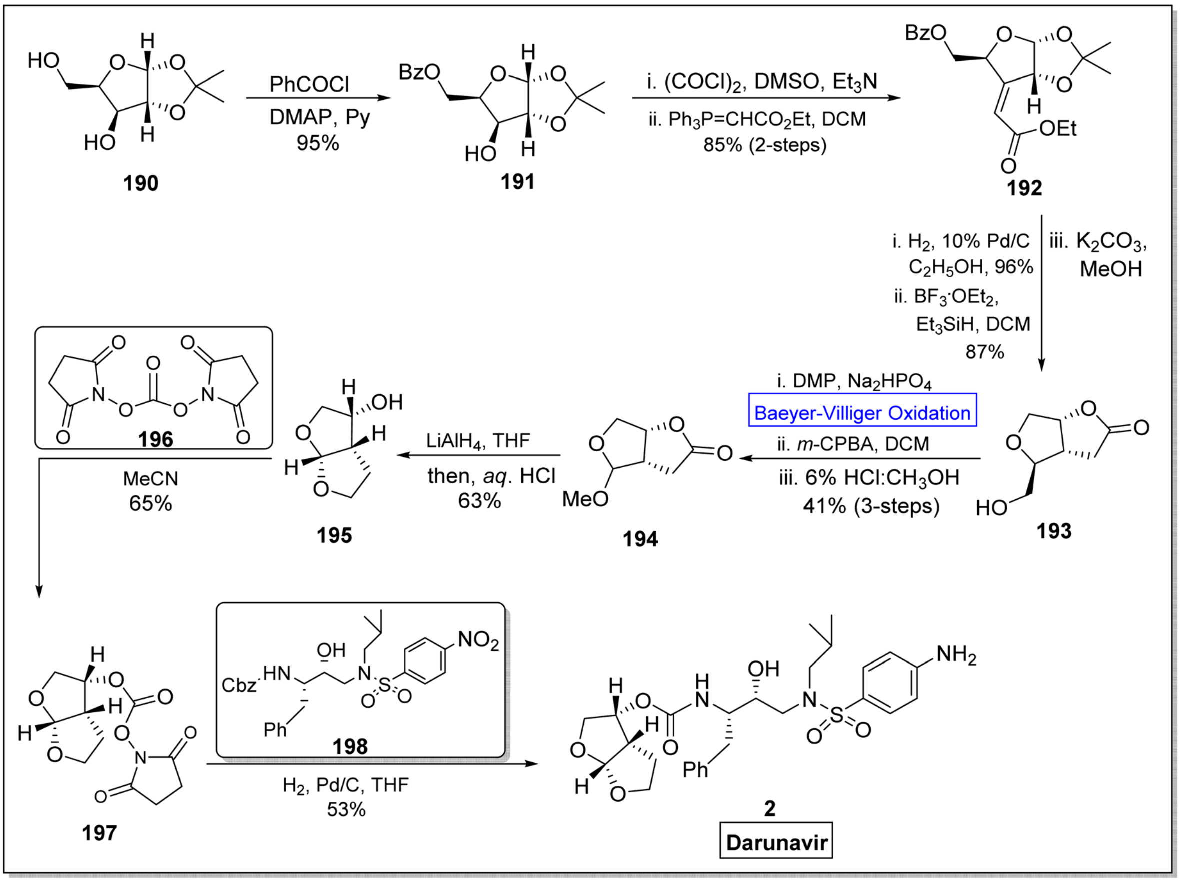

Scheme 26 Synthesis of protease inhibitor; darunavir **2** *via* Baeyer–Villiger oxidation.

203 over a few steps. Finally, compound **203** afforded the eupomatilone **204** in 67% yield with 94% ee *via* reacting with Eschenmoser's salt in THF followed by Baeyer–Villiger oxidation with *m*-CPBA. In another route, compound **203** produced eupomatilone **205** in 70% yield with 95% ee *via* methylation with LiHMDS and MeI in THF (Scheme 27).

Hydroquinones and 1,4-benzoquinones are natural metabolites and these are widespread in marine organisms,[172,173] plants, and animals.[174,175] These compounds exhibit antioxidant and anti-cancer activities in animals. In 2023, Tsyganov *et al.* reported the synthesis of 3-hydroxy-2,5-dimethoxybenzo-1,4-quinone1,4-benzoquinone **209** by using Baeyer–Villiger oxidation reaction as a key step.[176] The synthesis was accomplished with the formation of apiol aldehyde **207** from apiol alkene **206** in the presence of KOH, chloroform, methanol, and pyridine. Apiol aldehyde **207** underwent Baeyer–Villiger oxidation with H_2O_2 in the presence of H_2SO_4 and methanol to furnish a phenol **208** in 78% yield. Then, oxidation of phenol **208** followed by ring opening of dioxolane resulted in the synthesis of target compound **209** in overall 73% yield (Scheme 28).

2.6. Baeyer–Villiger oxidation in the biosynthesis of natural products

There is a diversity of enzymes which can be used in selective oxidation reactions in nature. These may include oxidases,[177] peroxidases,[178] monooxygenases,[179] dioxygenases,[180] and dehydrogenases.[177] Baeyer–Villiger monooxygenases play a key role in the biosynthesis of many naturally occurring compounds (Fig. 7).

Bohemamines (BHMs) **214** are pyrrolizidine-based bacterial alkaloids. These are obtained from *Streptomyces* species and homospermidine. These are biologically active natural compounds. These are used for self-defense against amoebae. Baeyer–Villiger monooxygenases BhmK/BhmJ and BhmG has a key role in the economical biosynthesis of BHMs. In 2020, Liu *et al.* presented the biosynthesis of BHMs from genes by utilizing BVMOs (BhmK and BhmJ) as biocatalysts.[181] The synthetic scheme of BHMs was demonstrated into two routes. In the first route, compound BhmJ was treated with a co-enzyme to afford BHM **210** which was further reacted with BhmK to generate **211**. Resulted compound **211** by reacting with Baeyer–Villiger monooxygenase afforded BHM D **212** while in another route, compound **211** synthesized compound **213** which further generated BHMs **214a**, **214b** & **214c** on treatment with BhmA (Scheme 29).

Testosterone **216** is a significant male hormone responsible for the male characteristics. Testololactone is also a steroidal compound used to treat breast cancer, prostate cancer and prostatic hyperplasia.[182] In 2020, Paula *et al.* reported the biosynthesis of testosterone and testololactone by utilizing Baeyer–Villiger oxidation as a key reaction.[182] The conversion

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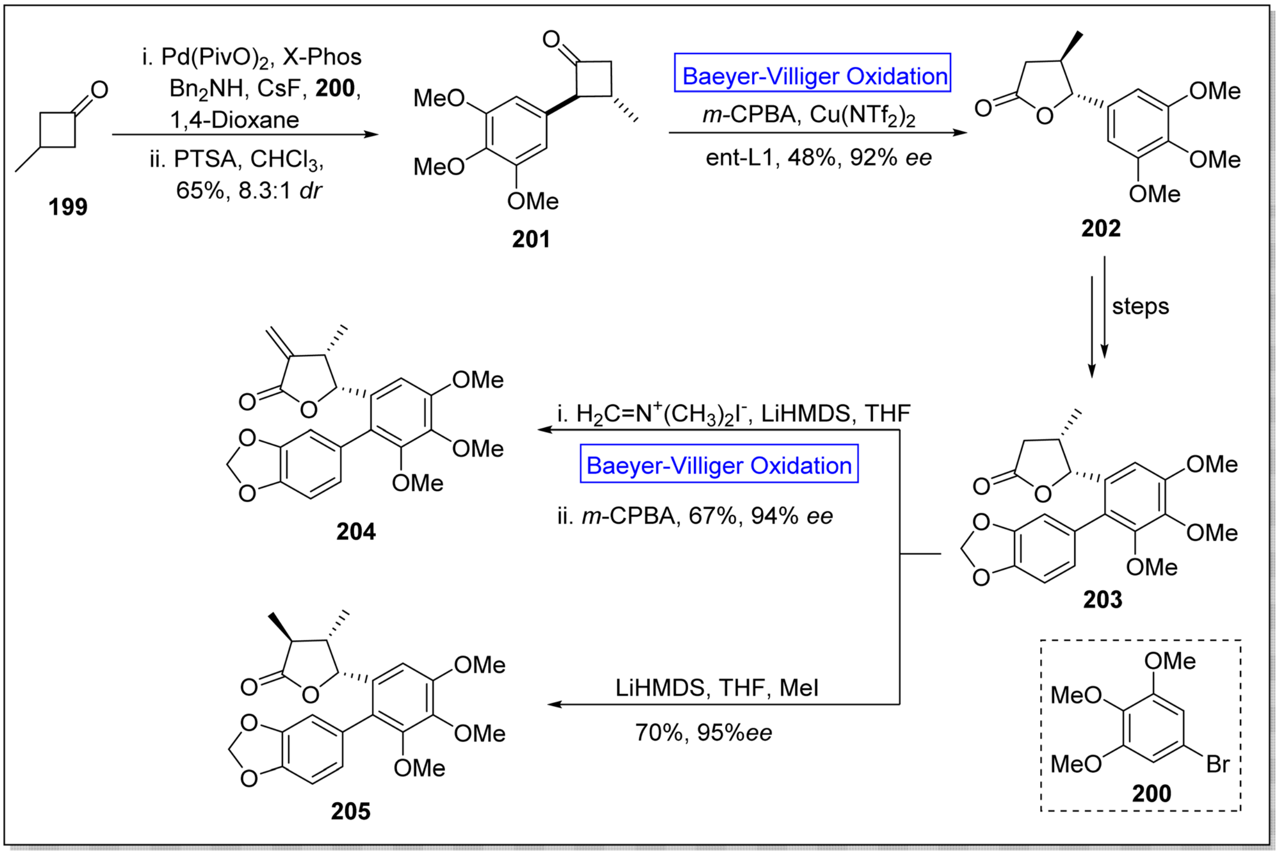
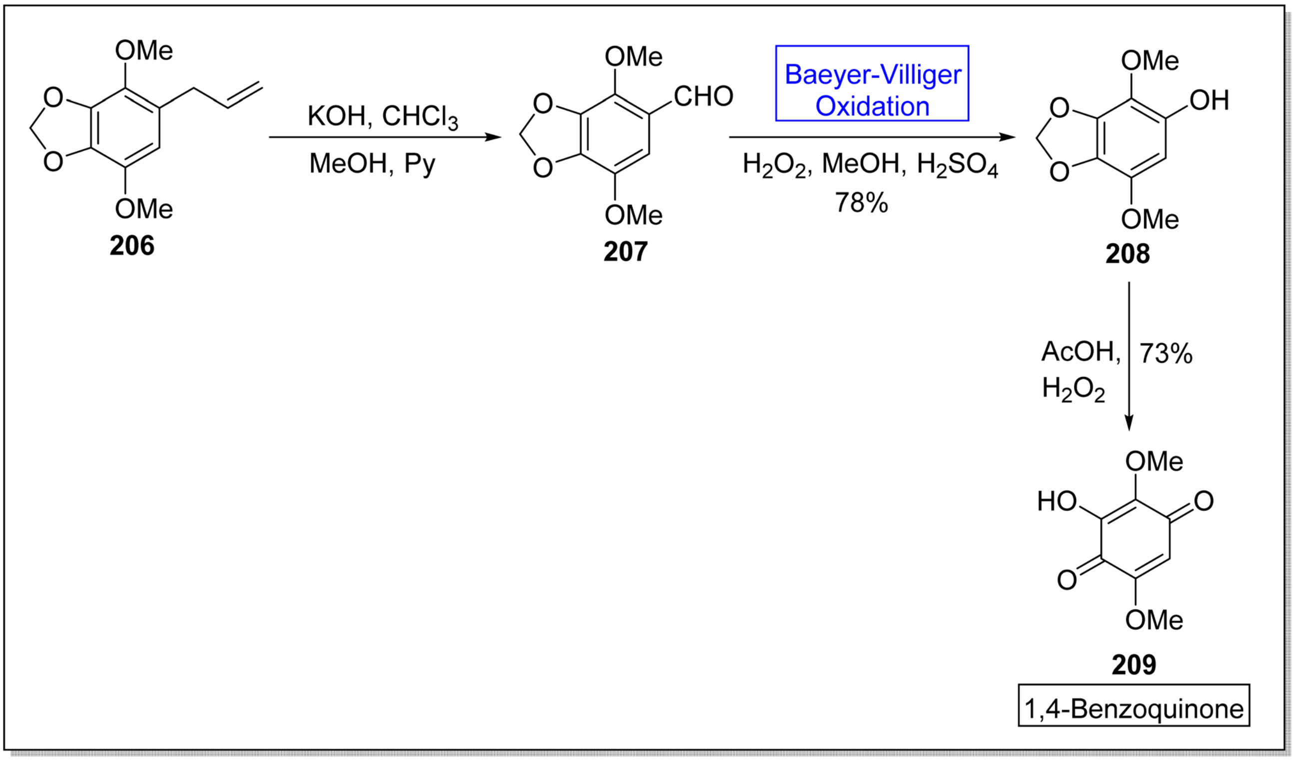


Scheme 27 Synthesis of eupomatilones **204** and **205** *via* Baeyer–Villiger oxidation.



Scheme 28 Biosynthesis of benzoquinone **209** *via* Baeyer–Villiger oxidation.

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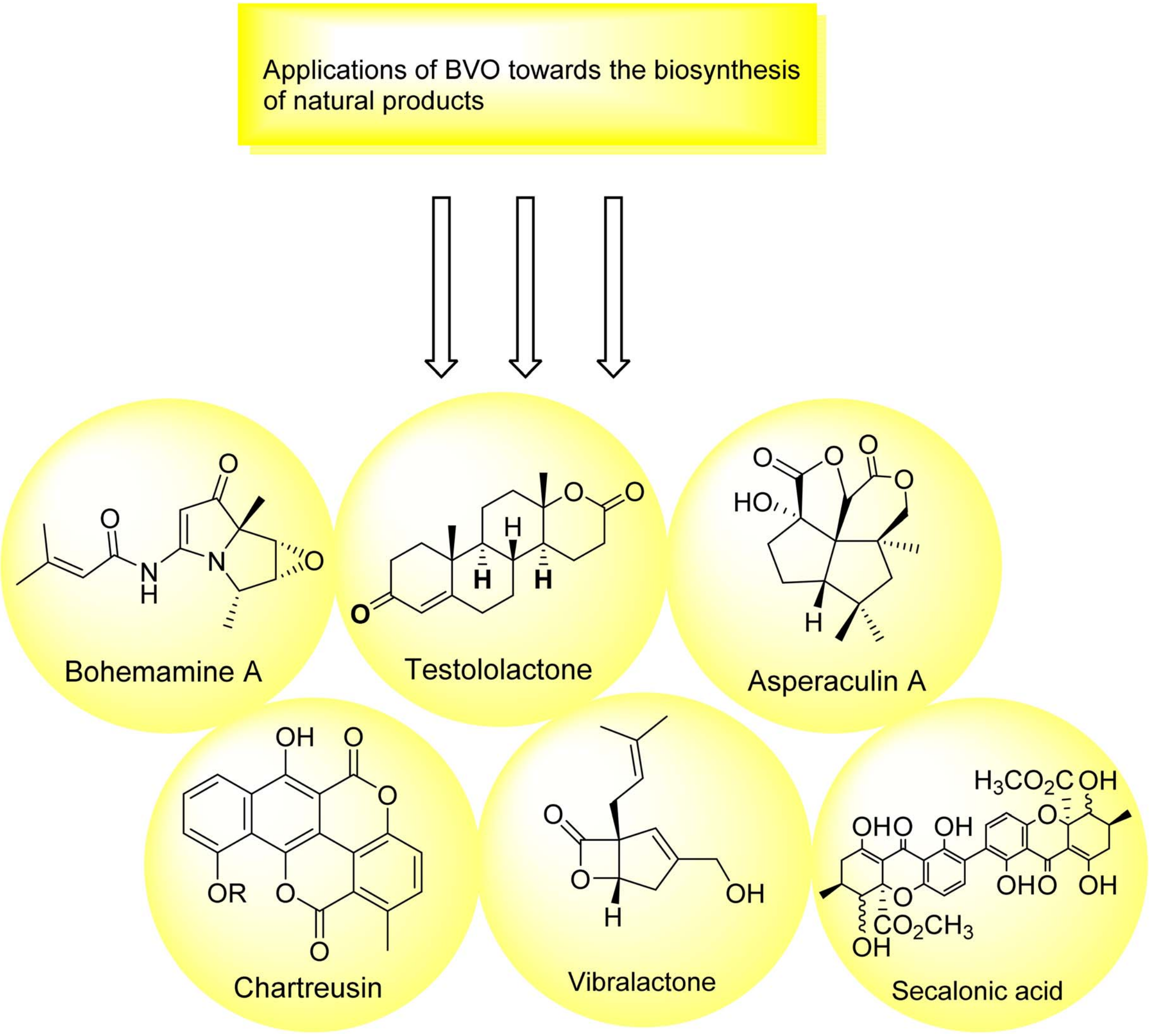

Fig. 7 Pictorial representation of role of BVO in biosynthesis.

was proceeded with the formation of testosterone **216** from progesterone **215** by using Baeyer–Villiger monooxygenase followed by hydrolysis. Then, compound **216** further delivered testololactone **3** *via* dehydrogenation and Baeyer–Villiger oxidation using BVMO (Scheme 30).

Asperculin A **220** and penifulvin D **222** are fungal sesquiterpenes which consist of [5.5.5.6] dioxafenestrane ring.[183–185] These are biologically active natural products. Primarily, asperculin A **220** and penifulvin D **222** were extracted from a terrestrial fungus; *Penicillium griseofulvum* and marine fungus; *Aspergillus aculeatus* respectively. In their previous work, Wei and colleagues reported that a 3-gene cluster (*peni* gene) was responsible for the biosynthesis of penifulvin A. Although the pathway was fully established but stereo and regiochemical hydroxylation on sp^3 carbon remained unclear. In 2021, Wei and co-workers presented the biosynthesis of asperculin A and penifulvin D by using Baeyer–Villiger monooxygenases PeniC and AspeB which provided valuable biocatalysts and wide range of strategies for nonactivated C-oxidation modification.[186] The synthesis was began with the formation of a scaffold silphinene **218** from a precursor FPP (farnesyl pyrophosphate) **217** in presence of sesquiterpene cyclase (PeniA) and AspeG. The scaffold **218** generated penifulvin A **219** over a few steps. Compound **219** in one approach, afforded asperculin A **220** *via* AspeB-catalyzed Beyer–Villiger oxidation in the presence of PeniF and AspeC. In another approach, it furnished penifulvin D **222** on reaction with PeniF (BVMO) after synthesizing penifulvin A **221** in the presence of PeniC (Scheme 31).

Chartreusin **227** is a glycosidic aromatic polyketide which is extracted from *Streptomyces chartreusis*. It is well-known for its potent biological activity against tumor cells.[187] Initially, Xu and colleagues investigated the role of flavin-dependent ChaZ in the gene cluster of cha but chaZ gene suppressed the synthesis of compound **227**. For better understanding, Jiao *et al.* in 2021, presented the biosynthesis of natural compound chartreusin **227** by using flavin-dependent BVMO (ChaZ), redox enzymes, and NADPH-dependent ketoreductase ChaE.[187] Schematic route demonstrated the synthesis of compound **224** from a cofactor-scaffold (acetyl-CoA + MeI-CoA) **223** in the presence of a framework of enzymes which was further converted into decaketide

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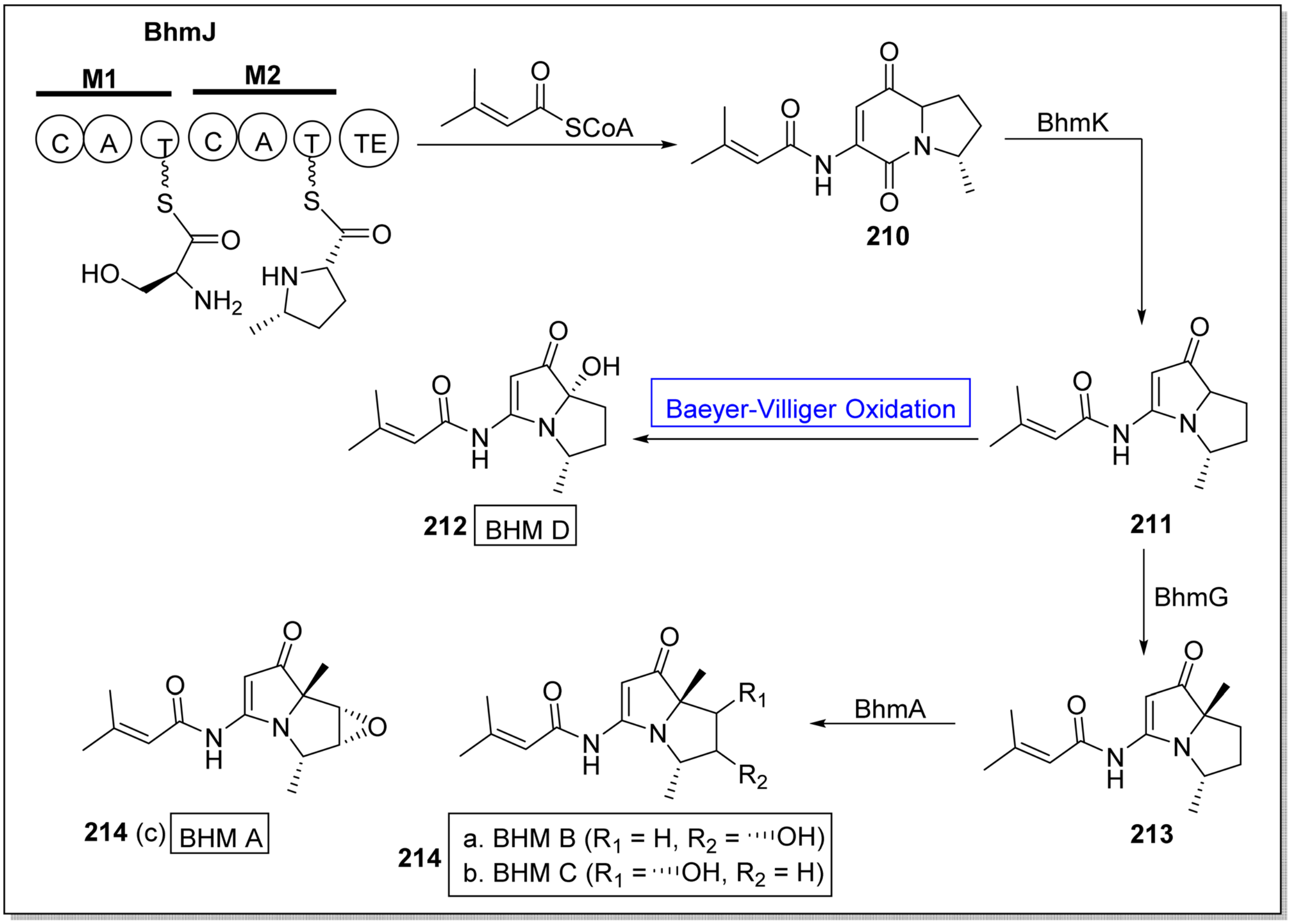
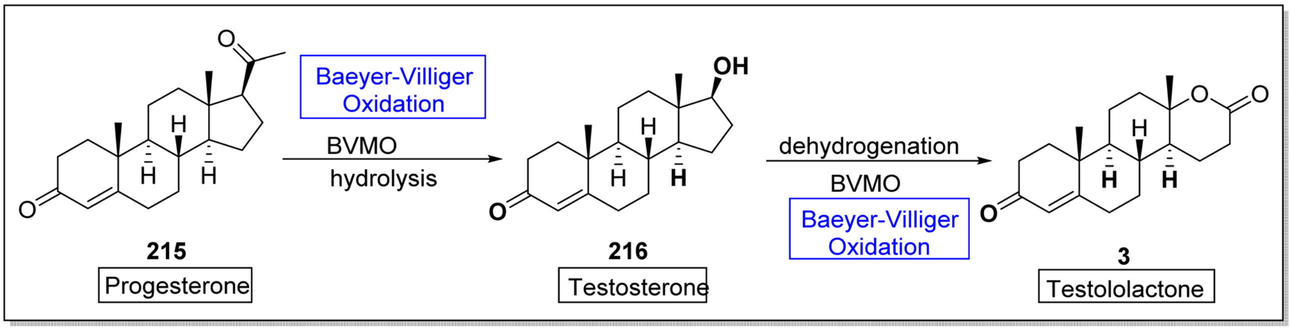


Scheme 29 Synthesis of bohemamines **212** and **214** (a–c) *via* Baeyer–Villiger oxidation.



Scheme 30 Synthesis of testosterone **216** and testololactone **3** *via* Baeyer–Villiger oxidation.

scaffold of tetracyclic intermediate **225** over a few steps. Consequently, scaffold, resomycin C **225** underwent ChaZ-catalyzed Baeyer–Villiger oxidation to furnish a pentacyclic intermediate **226**. Compound **226** generated the desired pentacyclic natural product; chartreusin **227** in the presence of ketoreductase ChaE, dioxygenase ChaP, $ChaGT_1$ and, $ChaGT_2$ (Scheme 32).

Secalonic acid D **231** is a fungal xanthone-based homodimer of blennolide B. It is biologically active natural product which encourages cancerous cells apoptosis,[188] suppresses DNA topoisomerase I,[189] and represses tumor angiogenesis.[190] Broad range specificity of enzyme AacuE (used for the synthesis of dimeric molecules) make it an efficient biocatalyst. Initially, Wei group attempted to achieve the total bioinspired synthesis of compound **231** but they obtained four isomers of targeted compound **231** owing to activity of *A.oryzae* (an endogenous enzyme). In 2021, Wei *et al.* successfully achieved the biosynthesis of secalonic acid D by overexpressing the BVMO (AacuH) that competed with endogenous enzyme.[191] In the beginning, crysophanol **228** underwent AacuH-catalyzed Baeyer–Villiger

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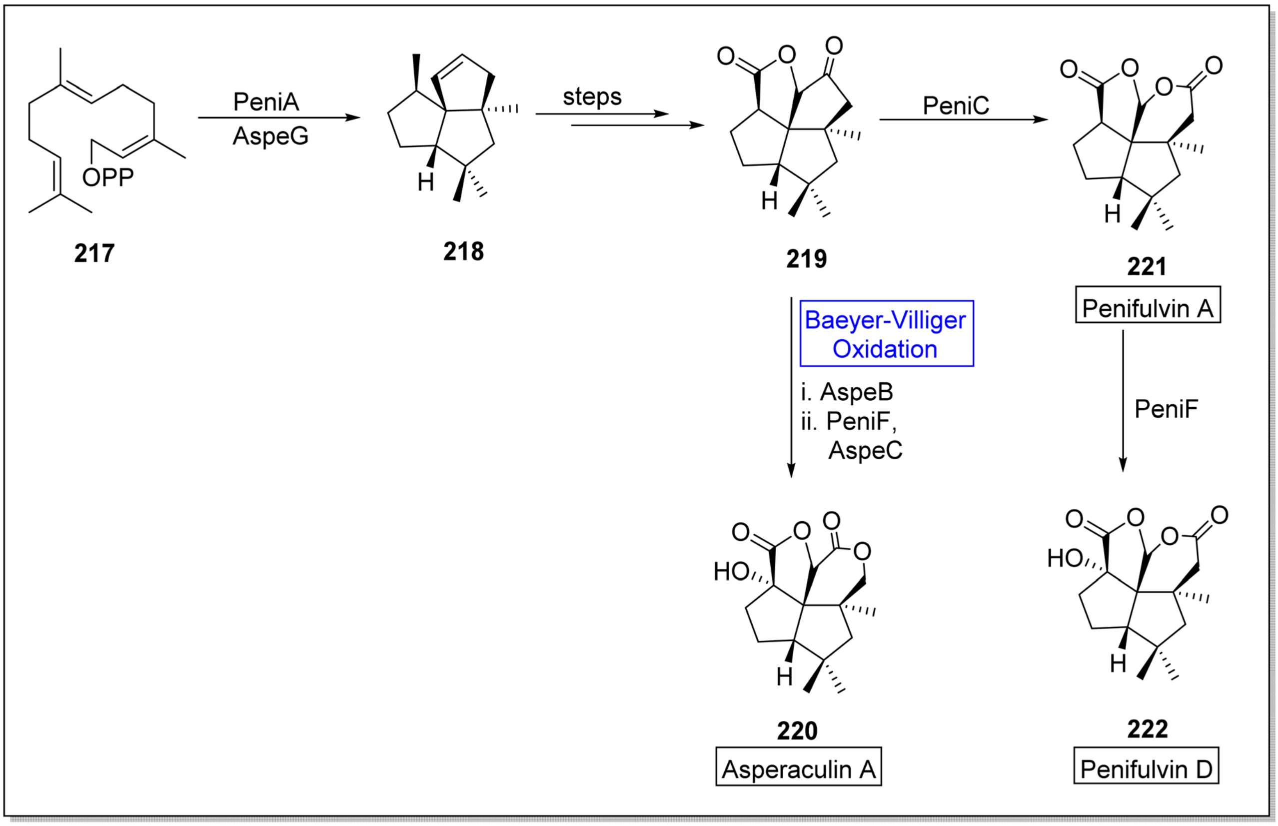
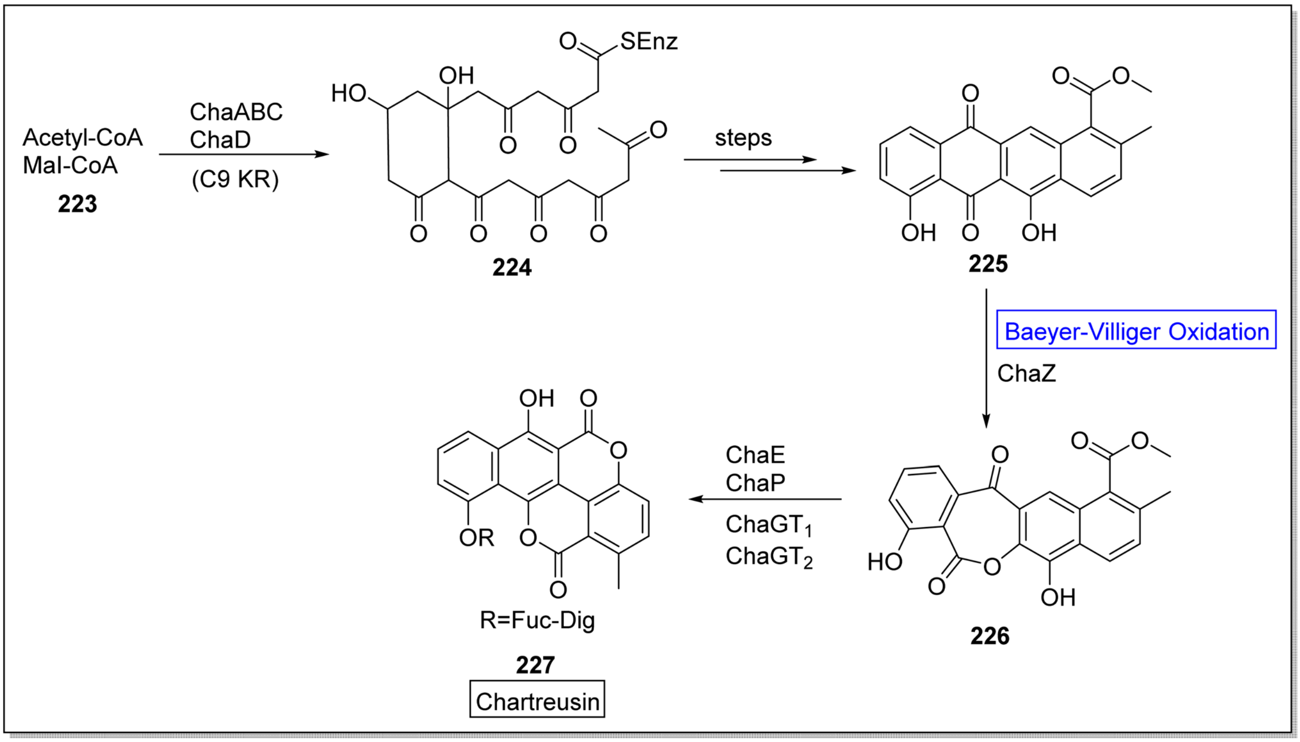


Scheme 31 Synthesis of asperaculin A **220** and penifulvin D **222** *via* Baeyer–Villiger oxidation.



Scheme 32 Synthesis of chartreusin **227** *via* Baeyer–Villiger oxidation.

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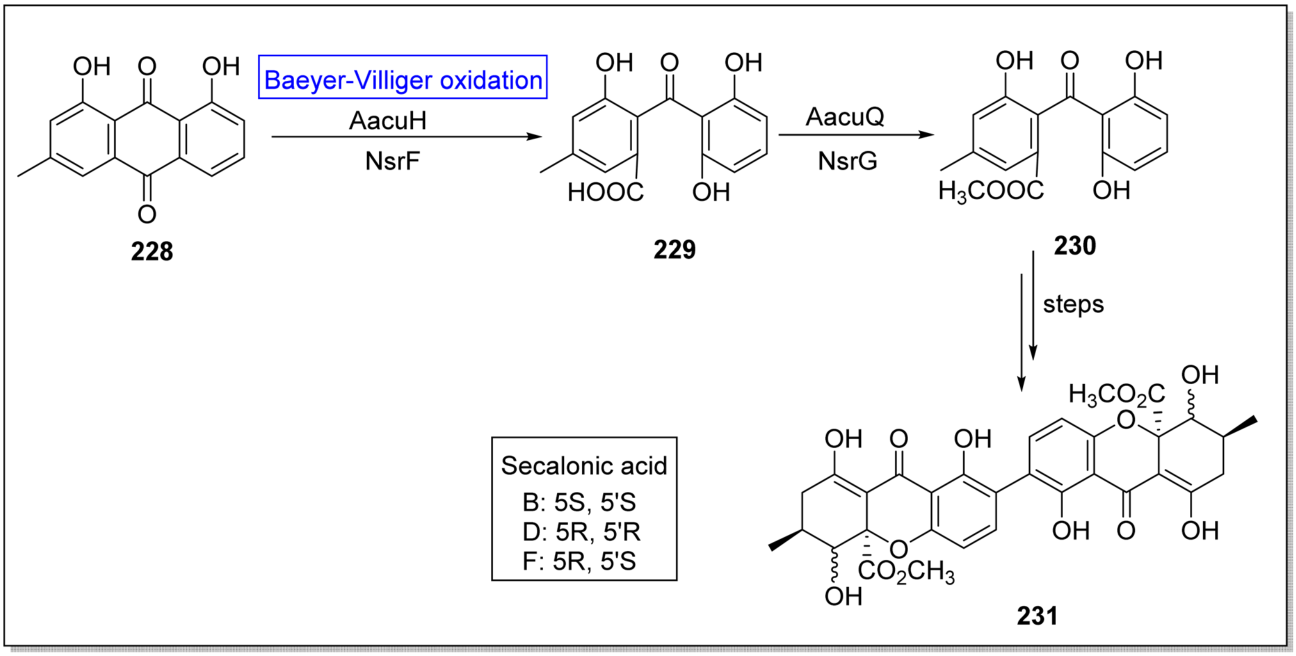
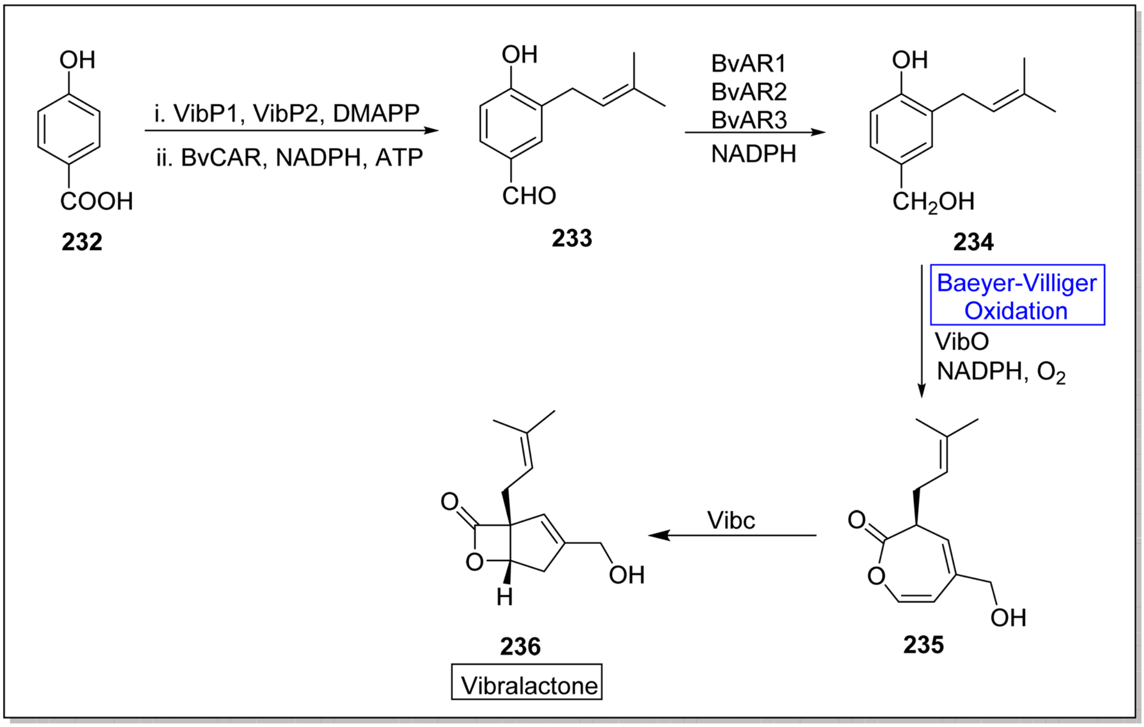


Scheme 33 Synthesis of secalonic acid (B, D and F) **231** *via* Baeyer–Villiger oxidation.



Scheme 34 Synthesis of vibralactone **236** *via* Baeyer–Villiger oxidation.

oxidation followed by hydrolysis to generate monodictyphenone **229**. Then, methyl esterification of compound **229** with methyltransferase AacuQ in the presence of NsrG synthesized the compound **230**. Compound **230** afforded the xanthone diamers (secalonic acid B, D, and F having specific stereochemistry) **231** over a few steps (Scheme 33).

Vibralactone **236** is a rare and potent natural product containing oxepine-2(3*H*)-one ring. It is isolated from a basidiomycete fungus *Boreostereum vibrans*; *Sterum vibrans* and *Stereum* mushrooms, together with 1,5-*seco*-vibralactone. Vibralactone **236** has the potential to inhibit pancreatic lipase with 0.4 μg mL^{-1} value of IC$_{50}$. Feng *et al.* in 2023, reported the total

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biosynthesis of vibralactone **236** by using Baeyer–Villiger monooxygenases.[192] For this purpose, 4-hydroxybenzoate **232** was catalyzed by UbiA prenyltransferases (VibP1/VibP2) in the presence of isoprenoid precursor, dimethylallyl pyrophosphate (DMAPP), a carboxylic acid reductase BvCAR, NADPH and ATP to generate an aldehyde **233**. Then, aldehyde **233** was catalyzed by reductases BvARs and NADPH to furnish a benzylic alcohol **234**. Thereafter, alcohol **234** underwent a VibO-interceded enzymatic Baeyer–Villiger oxidation in the presence of NADPH and O_2 to afford a 1,5-*seco*-vibralactone **235**. Subsequently, compound **235** afforded the targeted product **236** through VibC action (Scheme 34).

3. Conclusion

This review highlights the synthesis of natural products and their derivatives in which Baeyer–Villiger oxidation has been used as a key reaction. Baeyer–Villiger oxidation reaction offers the chiral lactones as valuable intermediates which can be used for consecutive reactions. Such conversions can be carried out in the presence of eco-friendly reagents, novel Baeyer–Villiger monooxygenases and mild reaction conditions to achieve high enantioselectivity, regioselectivity, and desired amount of yield with no or less side products. The utility of BV oxidation in the synthesis of various natural products *i.e.*, polyketides, terpenoids, quinones, fatty acids, and alkaloids which are pharmaceutically important due to their potent biological activities have been demonstrated. The efficiency and superiority of this reaction is expected to motivate organic chemists to focus on Baeyer–Villiger oxidation reaction to develop efficient pathways for further advancements towards the synthesis of natural products in future.

Data availability

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

Conflicts of interest

There are no conflicts to declare.

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