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Accessing the synthesis of natural products and their analogues enabled by the Barbier reaction: a review

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The Barbier reaction is significantly referred to as one of the efficient carbon–carbon bond forming reactions which involves the treatment of haloalkanes and carbonyl compounds by utilizing the catalytic role of a diverse range of metals and metalloids. The Barbier reaction is tolerant to a variety of functional groups, allowing a broad substrate scope with the employment of lanthanides, transition metals, amphoteric elements or alkaline earth metals. This reaction is also water-resistant, thereby overcoming the challenges posed by moisture sensitive organometallic species involving C–C bond formation reactions. The Barbier reaction has significantly found its applicability towards the synthesis of intricate and naturally occurring organic compounds. Our review provides an outlook on the synthetic applications of the Barbier reaction and its variants to accomplish the preparation of several natural products, reported since 2020.

1 Introduction

Carbon–carbon bond forming reactions are of substantial interest in organic chemistry to afford the functionalization of chains along with their branching and elongation.[1,2] These reactions have garnered considerable attention in synthetic organic chemistry, thereby leading to the synthesis of intricate molecules.[3,4] Until the end of the 19th century, zinc metal was predominantly employed in several organic reactions.[5,6] P. Barbier and V. Grignard introduced the utilization of magnesium metal in the addition reactions of carbonyl compounds.[7,8] This employment led towards the improvisation of carbon–carbon bond forming reactions, thus exploring the use of other metals in these reactions. Initially, the Barbier reaction reported the utilization of magnesium metal-based turnings in the treatment of methylheptenone **1** with methyl iodide **2** to afford the synthesis of 2,6-dimethylheptenol **3**. The attainment of the target molecule in moderate yield with limited replicability hindered the exploration of the Barbier reaction (Scheme 1).[7]

Later, Barbier's pupil Grignard performed this reaction by modifying the protocol, where he isolated the generated nucleophile *i.e.*, organomagnesium intermediate, rather than exploiting a one-pot reaction. The synthesized nucleophile **5** was then further treated with carbonyl compound **4** resulting in relatively higher yield with consistent replicability (Scheme 1).[8] Ever since 1900, the Grignard reaction has held vital importance in synthetic organic chemistry, owing to its facile pathway towards the procurement of various organic molecules.[9–11] Based on his significant contribution in synthetic chemistry, Grignard was awarded with the Nobel prize in 1912.

Both Grignard and Barbier reactions are regarded as nucleophilic addition reactions of carbonyl compounds by treating them with alkyl halides in the presence of metal or its salts, thus resulting in the synthesis of higher order alcohols. However, they mainly vary on the way, the nucleophilic specie (organometallic specie) is produced followed by its attack on the electrophilic centre of carbonyl functionality.[12,13] Though, Grignard reaction was more frequently employed in past years, most recent modifications that sustain the original one-pot characteristics of Barbier reaction are referred as "Barbier-type reactions".[14] They have been found to be even more favourable than Grignard reactions as they surpass the certain limitations imposed by Grignard reactions which involve the requirement of anhydrous conditions, withdrawal and handling of

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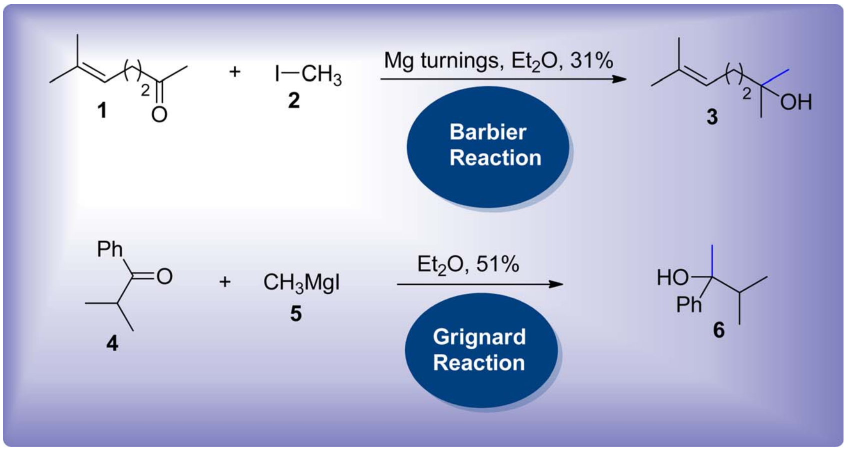


Scheme 1 Synthesis of tertiary alcohol from Barbier and Grignard reaction.

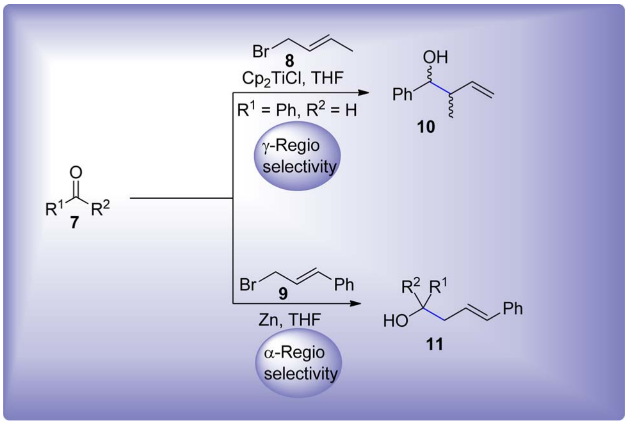
organometallic specie. This issue is resolved by substituting Mg metal with some other metal or amphoteric element that are resistant to moisture.[15,16] Thus, there has been continuous advancement regarding the usage of variety of metals, bimetallic system, zero valent metals and benign metal slats in the Barbier reaction. Moreover, water has been employed as solvent in several methodologies, eliminating the use of toxic and expensive solvents.[17]

Besides the methodological development, substrate scope of Barbier reaction has also been explored and thoroughly investigated in several protocols to include the treatment of various vinyl, alkyl, propargyl and allyl halides in combination with imines, esters, ketones, nitriles, aldehydes and several azo compounds. The broad range of substrate scope has been analyzed in Barbier reaction to produce a diverse range of complicated products.[18–20]

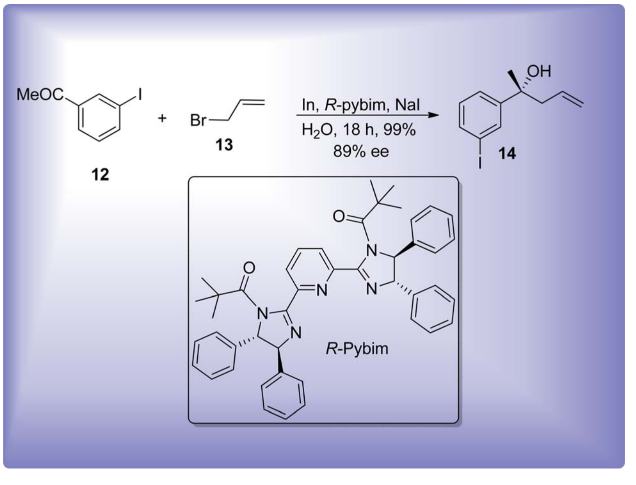
Stereoselectivity and regioselectivity are some other considerable factors in Barbier reaction, which arise under certain conditions. The α or γ-adduct emerges as a result of treating γ-substituted allyl compounds. The nature of regioselective product is dependent upon the solvent, γ-substrate bulkiness, utilized additive and metal promoter species. γ-Adduct is usually obtained predominantly by employing In,[21–23] Sn,[24–26] Zn[27,28] or Ti[29,30] metals in Barbier reaction. However, α-adduct is selectively produced by the introduction of praseodymium[31] and neodymium[32] metals in Barbier reaction utilizing γ-substituted allyl compounds as precursors (Scheme 2).

Furthermore, in order to achieve highly enantioselective Barbier product, chiral additives or ligands *i.e.*, (1*S*,2*R*)-2-amino-1,2-diphenylethanol,[33] *R*-pybim[34] and β-cyclodextrin[35] are significantly employed (Scheme 3). γ-Regioselectivity approach of Barbier reaction has the probability of leading towards two optically active centers in the target molecule, whose relative stereochemistry is defined by the ability of utilized metal towards the formation of cyclic transition state.

Utility of Barbier reaction has also been explored in polymer chemistry where benzoyl group and organic halide constituting monomers were added *via* one-pot A_2, AB and B_2 Barbier polyaddition to attain a catalog of polymethanol substituted polymers.[36] Several one-pot reactions are utilized to accomplish the synthesis of complex organic scaffolds.[37–41] There has been significant advancement towards the synthesis of several



Scheme 2 Layout for γ-regioselective and α-regioselective Ti & Zn-mediated Barbier allylation reaction.



Scheme 3 Layout for an enantioselective In-mediated Barbier allylation reaction.

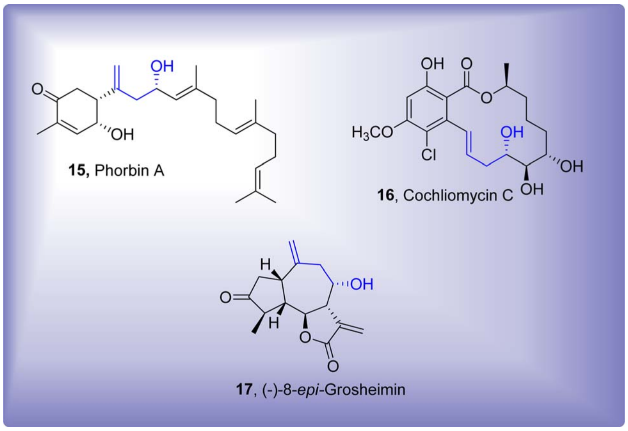


Fig. 1 Synthesis of some naturally occurring organic compounds by employing Barbier allylation reaction as a key step.

biologically active naturally occurring organic compounds.[42–44] Barbier reaction has also found its significance in this specific domain, as it has been found to involve as one of the main reaction steps leading towards the procurement of natural products.[45,46] Phorbin A,[47] Cochliomycin C[48] and (−)-8-*epi*-grosheimin[49] are some of the naturally occurring compounds endowed with homolallylic alcohol functionality, introduced *via* Barbier allylation reaction (Fig. 1).

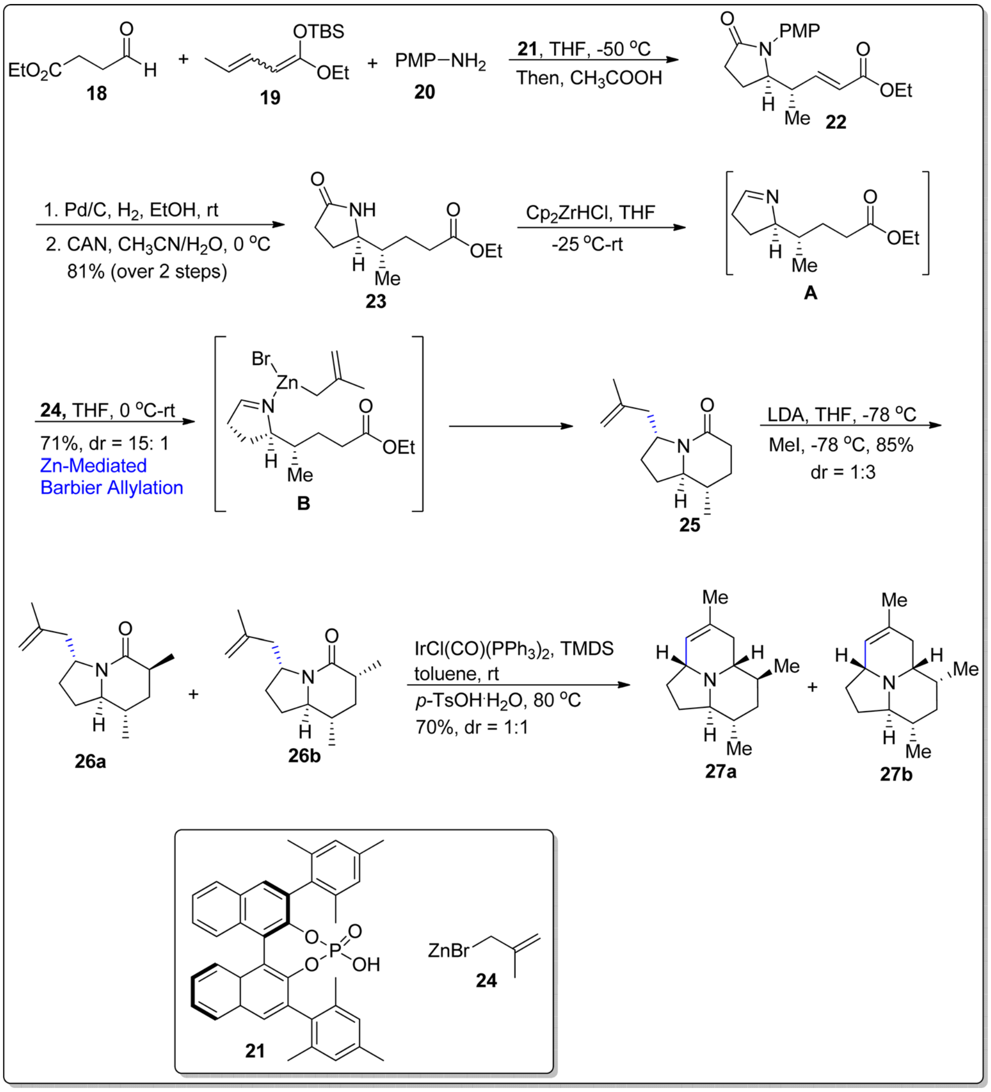
Considering the wide synthetic utility of Barbier reaction and its variants, significant research groups have contributed to summarize its scope, merits and remarkable applications.[50–56] However, very few reports have been published (till now) to emphasize the utilization of Barbier reaction towards the procurement of natural products. Recently, in 2022, Petrides and Georgiades reported a specific overview of stereocontrolled Barbier allylation and its applications towards the synthesis of natural products.[57] The objective of our review is to highlight the latest applications of Barbier and Barbier-type reactions towards the synthesis of a variety of natural products, reported within 2020–2024.

2 Literature review

2.1. Synthesis of alkaloids-based natural products

The alkaloid (−)-205B is a medicinally active and lipid-soluble natural product, which was first came across by Daly and colleagues.[58] The alkaloid (−)-205B is structurally composed of azaacenonaphthylene moiety with five chiral centers.[59] The total synthesis of this naturally occurring alkaloid has been performed by several research groups *via* diverse synthetic and organic transformations. Taking into consideration the medicinal weightage and intricate structure of this alkaloid, Tripathy and Schneider[60] attempted its total synthesis by involving various name reactions *i.e.*, Mukaiyama–Mannich reaction, aza-Prins annulation and zinc promoted Barbier allylation as key steps. Their developed briefest synthetic strategy initiated with vinylogous Mukaiyama–Mannich reaction between aldehyde moiety **18**, tethered ester group **19** and amine **20** in the presence of compound **21** followed by the addition of acetic acid to generate the lactam ring **22** in 73% yield with 98 : 2 enantiomeric ratio and more than 20 : 1 diastereoslectivity ratio. The γ-lactam **23** was easily derived from compound **22** in 81% yield over two steps. In the next step, the lactam **23** was initially reduced to the respective imine **A** on treatment with Cp_2ZrHCl in tetrahydrofuran at −25 °C, which was then further subjected to zinc promoted Barbier allylation using methallylbromide **24** to afford indolizidinone **25** in 71% yield with 15 : 1 diastereomeric ratio, thereby resulting in substrate control optically active center. It was observed that indium promoted Barbier allylation reaction resulted in decreased yield and stereoselectivity of indolizidinone. The next step involved the introduction of methyl group at 6th position of indolizidinone on reaction with lithium diisopropyl amide and tetrahydrofuran to generate the corresponding enolate which was further made to react with methyl iodide in THF at −78 °C. As a result, diastereomeric mixture of methylated compounds **26a** & **26b** was attained in 1 : 3 diastereomeric ratio with 85% yield. The diastereomeric mixture was then subjected to aza-Prins annulation reaction in the presence of Vaska's complex $IrCl(CO)(PPh_3)_2$ and TMDS followed by the treatment with *p*-TsOH·H_2O to afford the target natural product **27a** with its 6-epimer **27b** (*via* elimination reaction) in 1 : 1 diastereomeric ratio. The chromatography technique was carried out to separate the resulting isomers, thereby resulting in the isolation of alkaloid (−)-205B **27a** in 35% yield (overall 12% yield) (Scheme 4).

Indole alkaloids belong to the biologically active class of natural products, which are utilized in several organic transformations.[61] Synthesis of indole alkaloids constituting aza-quaternary optically active center *i.e.*, subincanadine A, arborisidine and taberdivamine B, encounter severe challenges due to their convoluted structural framework. Arborsidine is composed of 5-membered cyclic structure with two chiral centers. It has been found to be potent against gastric cancer cell lines in coordination with pimelautide. Cancer is a deadly disease and researchers are continually making efforts to develop and synthesize anti-cancer agents.[62,63] Till now, two successful total synthesis of arborisidine have been reported.[64,65] In 2021, Wang and Jiao[66] established an efficient asymmetric total synthesis of arborisidine by employing Barbier-type addition reaction as a key step. In order to achieve the asymmetric synthesis of this natural product, Barbier type addition reaction was performed between harmalane **28** and allyl bromide **29** by involving chiral indium reagent in THF/DMF at 35 °C followed by protection of nitrogen with Boc to afford compound (±)-**30** in 51% yield. In the next step, compound (±)-**30** was subjected to palladium mediated intramolecular dearomative asymmetric allylic alkylation (AAA) exploiting diaminocyclohexane (DACH)-phenyl Trost ligand (*R*,*R*)-L1 (*via* parallel kinetic resolution (PKR) regime), which resulted in asymmetric synthesis of compound (±)-**31** & (±)-**32**. The compound (±)-**31** was further treated with benzene sulfenylchloride followed by reaction with 2,4,6-coolidine/tetrabutylammonium chloride involving elimination reaction to forge phenyl sulfide substituted compound (±)-**33**. The compound (±)-**33** then underwent *N*-Boc deprotection with subsequent alkylation to afford corresponding alcohol (−)-**34** in

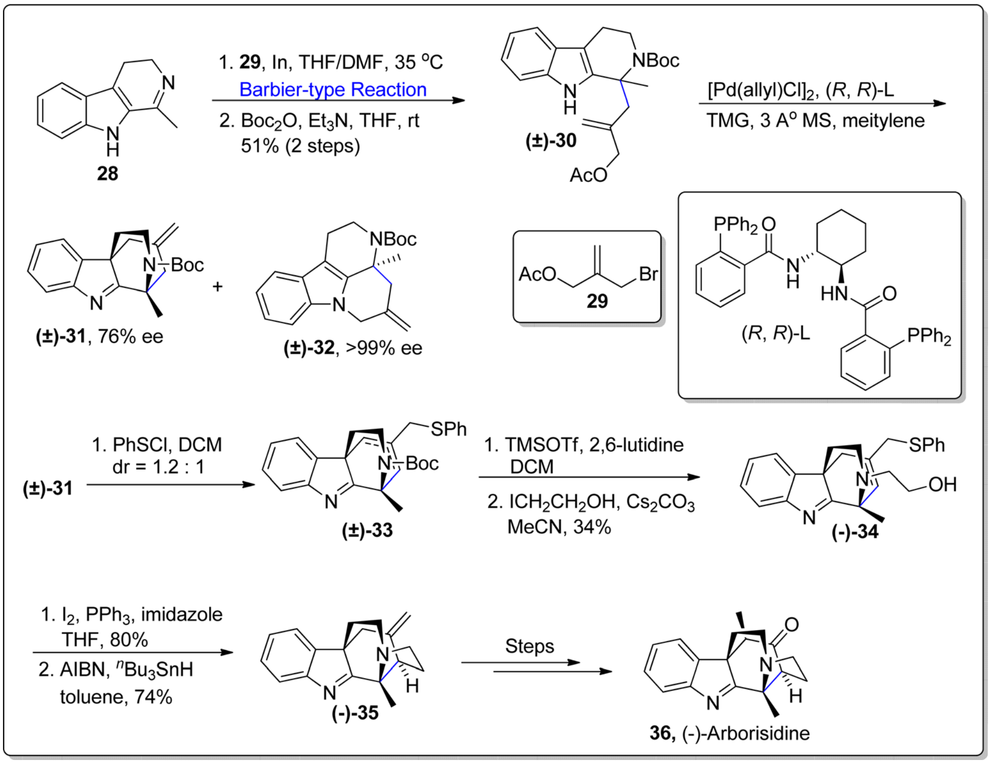


Scheme 4 Synthesis of the alkaloid (−)-205B **27a**.

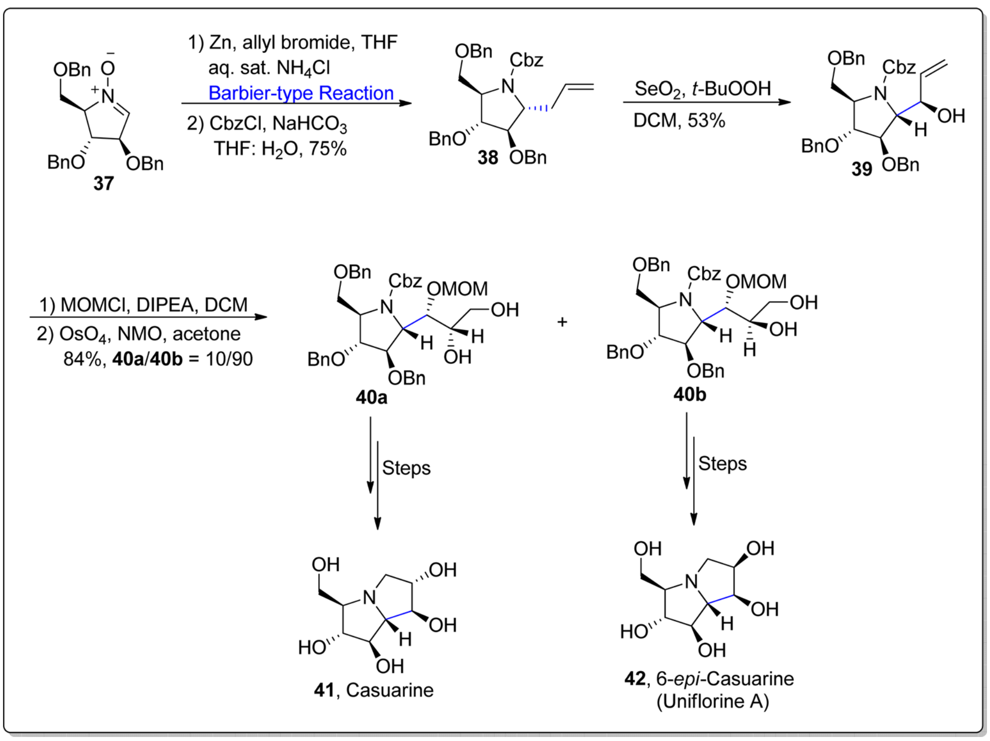
34% overall yield (as a single isomer). The proceeding step involved the iodination of compound (−)-**34** followed by 5-*exo-trig* radical cyclization to result in compound (−)-**35** in 74% yield. Later, the compound (−)-**35** was transformed over few steps to assemble the naturally occurring (−)-arborisidine (−)-**36** in fine yield with efficient diastereoselectivity (Scheme 5).

Casuarine is a natural product that is extracted from *Eugenia jambolana* Lam and *Casuarina equisetifolia* L.[67] Casuarine is composed of pyrrolizidine ring with 6 chiral centers, thus it exists in almost 64 stereoisomers. It also acts as an efficient isomaltase, maltase (rat instetinal) and α-glucosidase inhibitor (rice). Moreover, it has also been found to exhibit the properties of competitive inhibitor of *C. riparius* trehalase, NtMGAM (human N-terminal subunit of maltase-glucoamylase) and *A. niger* amyloglucosidase. In 2021, Li *et al.*[68] reported the synthesis of naturally occurring casuarine **41** and its natural stereoisomer 6-*epi*-casuarine **42** by applying Barbier conditions in one of the key steps. Their synthetic route initiated with the reaction of nitrone **37** (obtained from D-arabinose) with allylbromide in the presence of zinc (Barbier-type reaction) in tetrahydrofuran and ammonium chloride followed by subsequent reaction with carboxybenzyl chloride (CBzCl) in the presence of sodium carbonate to afford compound **38** in 75% yield. In the following step, compound **38** was subjected to SeO_2 promoted allylic oxidation by employing *t*-BuOOH in dichloromethane to give corresponding alcohol **39** in 53% yield (as a single isomer). Here, the Barbier-type reaction involving pathway led to the relatively higher yield of alcoholic isomer **39** in comparison to Grignard reagent involving protocol. In the next step, –OH group of compound **39** was protected with MOM ether followed by diastereoselective dihydroxylation by employing osmium tetroxide and NMO in acetone to furnish the mixture of triols **40a** and **40b** in 84% yield. The isomers **40a** and **40b** were treated individually over few steps to accomplish the synthesis of casuarine **41** and 6-*epi*-casuarine **42** respectively (Scheme 6).

Most of the biologically active natural products consist of spirocyclic frameworks.[69] In 2021, two diastereomeric naturally occurring isoindolinone alkaloids *i.e.*, spirocollequins A and B have been extracted from *Colletotrichum boninense* AM-12-2 (an endophytic fungus).[70] They are composed of a furan ring alongwith isoindolinone skeleton within their spirocyclic skeleton.[71] These isoindolinone alkaloids have the potency to exhibit anti-plasmodial activity. In 2022, Ichikawa and



Scheme 5 Synthesis of (−)-arborsidine (−)-36.

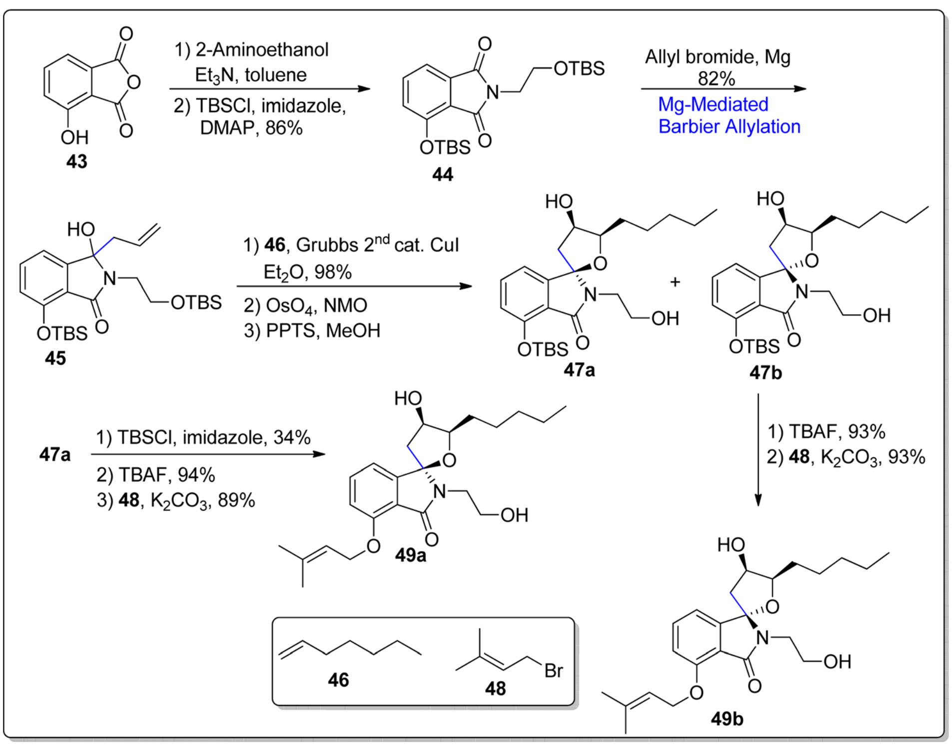


Scheme 6 Synthesis of casuarina 41 and 6-*epi*-casuarine 42.

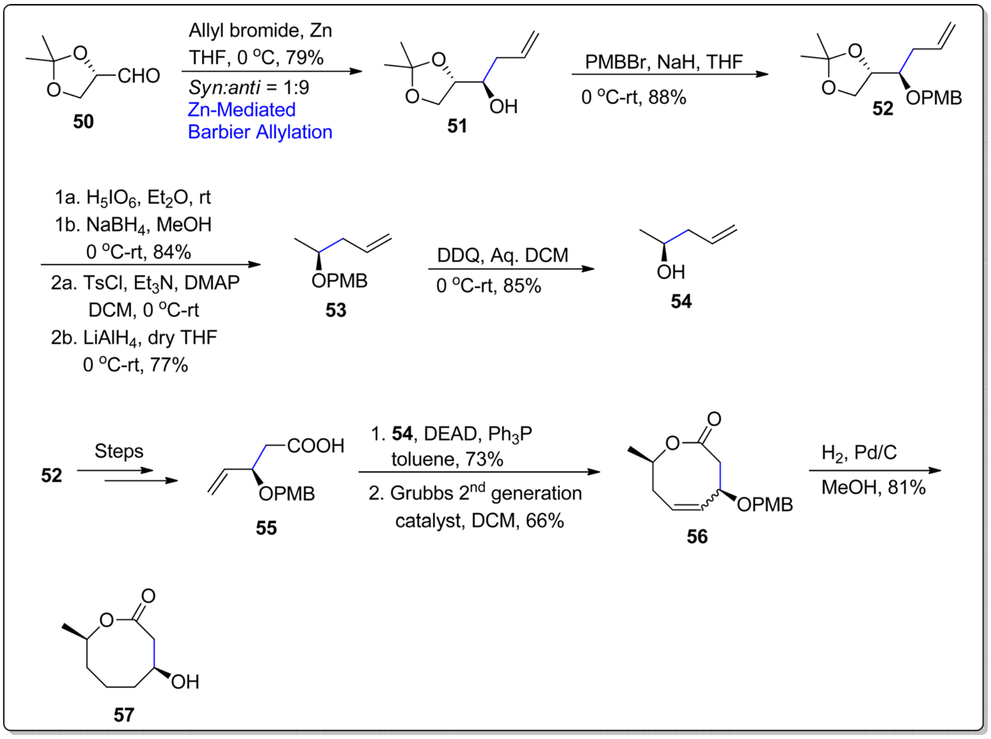
coworkers[72] carried out the first total synthesis of these alkaloids involving Barbier reaction as a key step. Their synthetic endeavor initiated with the reaction of phthalic anhydride **43** with 2-aminoethanol in the presence of triethylamine, which was proceeded by the protection of hydroxyl groups with *tert*-butyl silyl group to furnish compound **44** in 86% yield. In the next step, the compound **44** was subjected to magnesium induced Barbier allylation reaction with allylbromide, resulting in the synthesis of isoindolinone **45** in 82% yield, as a single product. The allylic functionality in compound **45** was further subjected to cross-metathesis reaction on treatment with compound **46**, utilizing Grubb's 2nd generation catalyst with copper iodide in diethyl ether. This reaction was followed by osmium tetroxide NMO induced dihydroxylation followed by treatment with PPTS (pyridinium *p*-toluenesulfonate) to result in diastereomeric mixture of **47a** and **47b** (40% isolated yield). The compound **47a** (34%) was purified *via* selective TBS protection of its hydroxyl functionality. The reaction was proceeded by the deprotection strategy followed by subsequent prenylation reaction to afford spirocollequins A **49a** in 89% yield. On the similar ground, **47b** was converted to spirocollequins B **49b** in 93% yield. As a result, the foremost total synthesis of (±)-spirocollequins B **49b** and A **49a** was achieved in 24% & 19% overall yields, correspondingly (Scheme 7).

2.2. Synthesis of lactones-based natural products

Cephalosporolides are of huge significance owing to their unique structural and medicinal attributes. (−)-Cephalosporolide D is a naturally occurring eight membered lactone which is extracted from *Cephalosporium aphidicola* (fermentation fungus).[73] In 2000, Shiina and coworkers reported the first total synthesis of this naturally occurring lactone along with the ascertainment of its (absolute and relative) stereochemistry.[74] Since then, there have been several reports concerning the synthesis of this bioactive natural product. Being persuaded by the gripping structural and pharmaceutical features of (−)-Cephalosporolide D, Kalavakuntla *et al.*[75] in 2022, carried out an efficient and compact route towards the its total synthesis by employing Barbier allylation reaction, Mitsunobu esterification and RCM (Ring Closing Metathesis) as key steps. Their synthetic approach commenced by treating optically active aldehyde **50** with allylbromide *via* zinc promoted Barbier allylation in tetrahydrofuran at 0 °C to afford carbinols (**51a** & **51b**) in a divisible mixture (*syn* and *anti* = 1 : 9) with 79% yield. The next step involved the protection of alcoholic functionality to ether **52** (in 88% yield) on treatment with *p*-methoxybenzyl bromide by utilizing sodium hydride as base in tetrahydrofuran. PMB ether **52** was then subjected to react with periodic acid followed by sodium borohydride mediated reduction to yield alcohol in 84% yield. The tosyl group was then installed on alcohol proceeded by its subsequent reaction with lithium aluminum hydride in dry tetrahydrofuran to access compound **53** in 77% yield. In the next step, alcoholic compound **54** was obtained (in 85% yield) as a result of deprotection of PMB ether by treating compound **53** with 2,3-dichloro-5,6-cyano-1,4-benzoquinone (DDQ) in aqueous DCM. PMB ether **52** was also transformed to corresponding acid **55** over few steps. The resulting acid **55** then underwent Mitsunobu esterification with already prepared alcohol **54** followed by ring closing metathesis



Scheme 7 Synthesis of (±)-spirocollequins A **49a** & B **49b**.

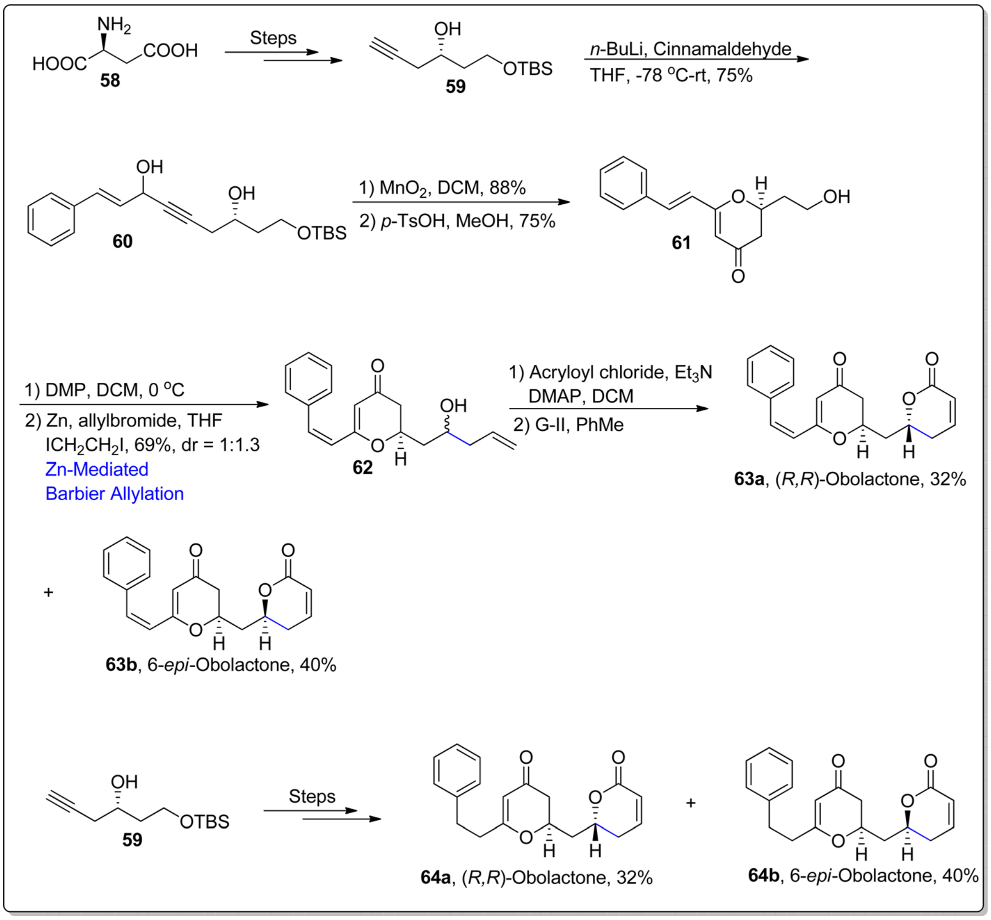


Scheme 8 Synthesis of Cephalosporolide D **57**.

(RCM) reaction (exploiting G-II catalyst) to forge the eight membered heterocycle **56** in 66% yield. Finally, the compound **56** was subjected to Pd/C mediated hydrogenation to accomplish the synthesis of targeted compound **57** in 81% yield (Scheme 8).

The 5,6-dihydro-pyrone functionalities are copiously found in several medicinally active natural products as they illustrate efficient potency against various deadly diseases and a wide range of cancer cells. Obolactone and dihydroobolactone are natural products, whose structural formulas are incorporated with 5,6-dihydro-pyrone moieties. *Cryptocaria obovate* is the main source of obolactones, which are known to exhibit potent efficacy against Trypanosoma brucei 5.3 μM nasopharyngeal cancer cells with $IC_{50} = 3$ μM.[76,77] In 2021, Saini *et al.*[78] accomplished the total synthesis of these naturally occurring and pharmaceutically significant organic compounds. Their synthetic pathway initiated with the transformation of L-aspartic acid **58** to alkyne **59** over few steps. In the next step, alkyne **59** was subjected to nucleophilic addition reaction to install the alkynol functionality **60** in 75% yield. Later, compound **60** underwent MnO_2 mediated oxidation followed by *p*-toluene sulfonic acid promoted rearrangement to forge the 2,3-dihydro-pyranone moiety **61** in 75% yield. The alcoholic functionality in compound **61** was subjected to Dess–Martin periodinane oxidation to transform it into aldehyde which further underwent treatment with allylbromide *via* zinc promoted Barbier allylation to result in the synthesis of compound **62** in 69% yield with dr = 1 : 1.3. The substrate directed Barbier approach was chosen to induce chirality within allylation reaction to afford the synthesis of natural products' both diastereomers. The Barbier allylated product **62** was further transformed into naturally occurring (*R*,*R*)-obolactone **63a** (32%) and its separable isomer *i.e.*, 6-*epi*-obolactone **63b** (40%) *via* esterification reaction with ensuing G–II mediated ring closing metathesis (RCM). In the similar manner, alkyne **59** was also subjected to react with 3-phenylpropanal followed by the same series of reactions to afford the synthesis of naturally occurring 7′,8′-dihydroobolactone **64a** and its separable isomer *i.e.*, 6-*epi*-7′,8′-dihydroobolactone **64b** in 33% and 39% yield respectively (Scheme 9).

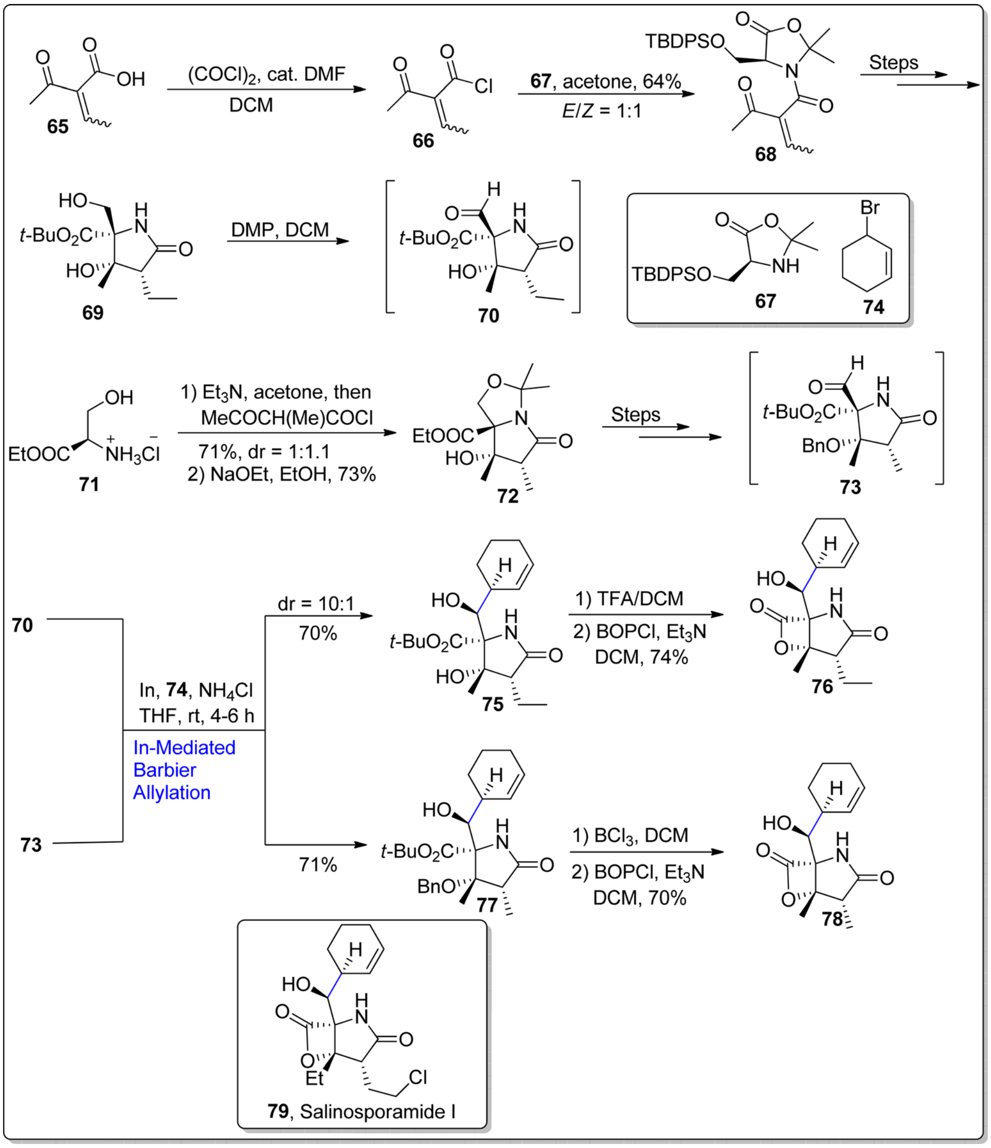
Marine bacteria (of *Salinispora* genus) are involved in the production of salinosporamides based natural products. They are structurally composed of bicyclic framework having γ-lactam-β-lactone functionality. Considering the unique characteristics of salinosporamides, Park *et al.* in 2022,[79] unveiled the synthesis of salinosporamide B, which was initially extracted from the *S. tropica*. Their established protocol involved the use of Barbier allylation as one of the key steps. In the foremost step, β-ketoacid **65** was transformed to compound **66** as a result of reaction with $(COCl)_2$ followed by its condensation reaction with oxazolidinone **67** in acetone to generate required substrate **68** in 64% yield with $E/Z = 1:1$. Later, the compound **68** was treated over several steps to result in compound **69.** In the next step, alcoholic functionality in compound **69** was subjected to Dess–Martin periodinane mediated oxidation to convert it into aldehyde intermediate **70.** The aldehyde **70** was then further subjected to react with bromo cyclohexene **74** *via* indium catalyzed Barbier allylation reaction in the presence of ammonium chloride (additive) and tetrahydrofuran at room temperature to afford the addition product **75** in 70% yield with 10 : 1



Scheme 9 Synthesis of (*R*,*R*)-obolactone **63a**, 6-*epi*-obolactone **63b**, 7′,8′-dihydroobolactone **64a** and 6-*epi*-7′,8′dihydroobolactone **64b**.

diastereoselective ratio. It was observed that the Barbier reaction streamlined the synthetic pathway, thereby affording the product **75** in efficient yield with higher diastereoelectivity. Addition product **75** was then subjected to *tert*-butyl ester hydrolysis *via* TFA proceeded by exposure with BOP-Cl to fulfil the synthesis of salinosporamide B **76** in 74% yield. Recently, in 2023, Park *et al.*[80] also utilized indium promoted Barbier allylation approach to afford the first chiral synthesis of salinosporamide D **78** in eleven steps with 12% overall yield. To start with, D-serine based ester **71** was made to react with triethylamine and acetone followed by coupling with β-ketoacid and reaction with sodium ethoxide in ethanol to procure aldol compound **72** in 73% yield with more than 99% ee (as a single diastereomer). The synthesized aldol compound **72** was converted to corresponding aldehyde over several steps. The aldehyde **73** was then treated further *via* similar In-mediated Barbier allylation to afford compound **77** in 71% yield (as a single isomer). The resulting compound **77** was then made to react with BCl_3 to carry out the removal of benzyl and *tert*-butyl groups proceeded by exposure to BOPCl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) to furnish the total synthesis of salinosporamide D **78** in 70% yield. Similarly, in-promoted Barbier reaction involving allylation approach was employed to synthesize salinosporamide I **79** (Scheme 10).

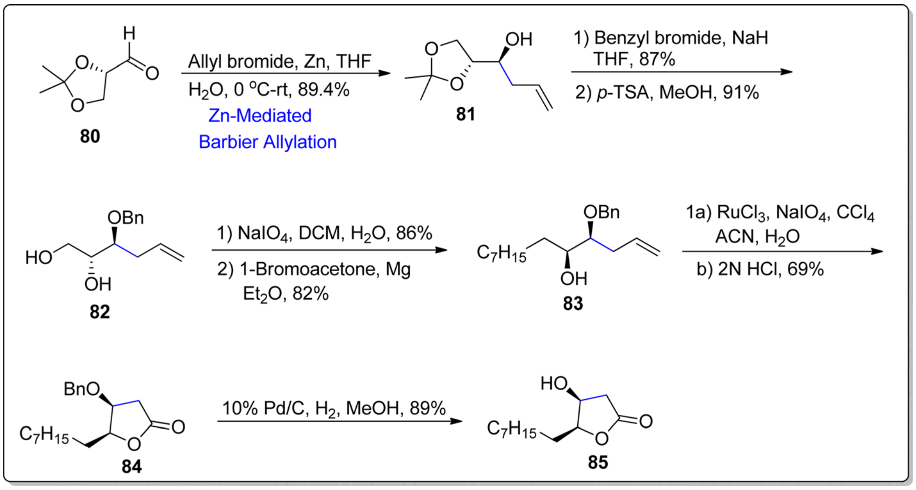
Almost 10% of natural products constitute γ-butyrolactone functionalities, indicating the importance of these organic moieties. The medicinal and pharmaceutical attributes of these butyrolactones have not been studied due to their extraction (from natural sources) in minute quantity. Thus, the need to synthesize these naturally occurring butyrolactones in efficient yields is enhancing continuously. In 2022, Gayke *et al.*[81] adopted a stereoselective route towards the asymmetric synthesis of (4*S*,5*S*)-4-hydroxy-γ-decalactone **85**, which was first isolated alongwith its major isomer ((4*S*,5*R*)-4-hydroxy-γ-decalactone) by Raspotnig group from the secretion of harvestmen Egaenus convexus ejection. In arachnids, these butyrolactones act as defensive agents by releasing exocrine secretions against hazardous chemicals and perpetrators. Gayke and coworkers initiated the synthesis by treating aldehyde **80** with allyl bromide *via* zinc promoted Barbier allylation reaction in tetrahydrofuran and water to generate homoallyl alcohol **81** in 89.4%. The hydroxyl group in compound **81** was protected on reaction with benzyl bromide using sodium hydride as base, followed by removal of acetonide on treatment with *p*-toluene sulfonic acid to forge respective diol **82** in 91% yield. The diol **82** then underwent oxidative cleavage by exploiting sodium periodate and dichloromethane followed by Grignard reaction with 1-bromoacetone using magnesium in



Scheme 10 Synthesis of salinosporamide B **76**, salinosporamide D **78** and salinosporamide I **79**.

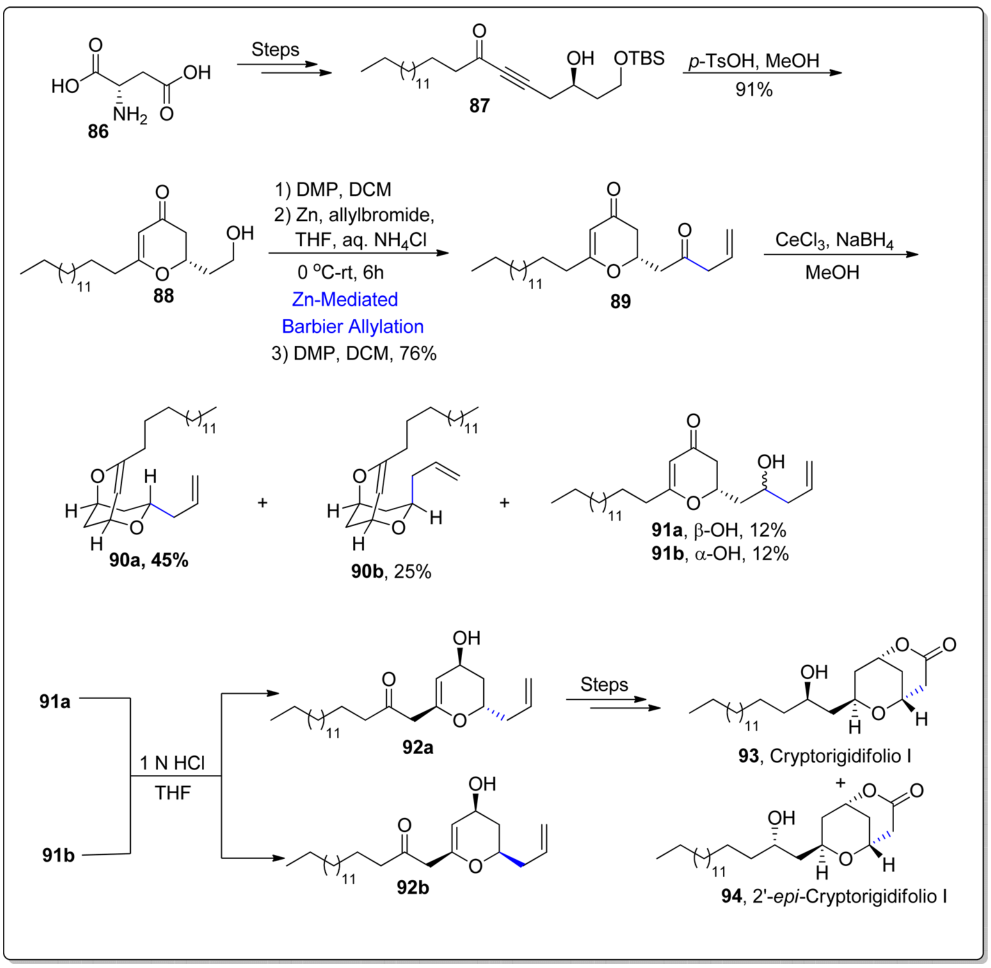
diethyl ether to synthesize compound **83** in 82% yield. The compound **83** was treated further to result in lactone **84** (with 69% yield) on exposure with oxidizing agents ($RuCl_3$ and $NaIO_4$) proceeded by acidic treatment. Finally, deprotection of hydroxyl group furnished the synthesis of naturally occurring minor isomer of (4*S*,5*S*)-4-hydroxy-γ-decalactone **85** in 89% yield (Scheme 11).

Cryptorigidifoliol is a tetrahydrone pyrone constituting oxygenated natural product, which was obtained as a result of extraction from the *Cryptocarya rigidifolia* (in 2015).[82] Cryptorigidifoliol along with its other class members tend to showcase a broad spectrum of medicinal applications, thereby acting as efficient anti-fungal, anti-cancer, anti-inflammatory and anti-bacterial agents.[83,84] Besides its utilization as efficacious analgesics, this natural product has been found to demonstrate cytotoxic activity against specific human cancer cell lines and the antimalarial activity against *Plasmodium falciparum*. Till now, a single report has been documented focusing the synthesis of cryptorigidifoliol I in 10.8% overall yield by Mohapatra and coworkers. Recently, in 2024, Jangid and Fernandes[85] established a successful route to access this naturally occurring compound by employing Barbier allylation as one of the central steps. Their synthetic journey initiated with the procurement of δ-hydroxyalkynone **87** by subjecting L-aspartic acid **86** to a series of consecutive reactions. The δ-hydroxyalkynone intermediate **87** was then transformed into dihydropyranone **88** (in 91% yield) *via* *p*-TsOH mediated rearrangement reaction. The resulting dihydropyranone was then exposed to DMP promoted oxidation in continuation with zinc promoted Barbier allylation reaction with allyl bromide in tetrahydrofuran to afford diastereomeric mixture. The diastereomeric products were feasibly separated *via* column chromatography. The subsequent oxidation step resulted in the synthesis of diketone **89** (within 76% yield). Furthermore, the



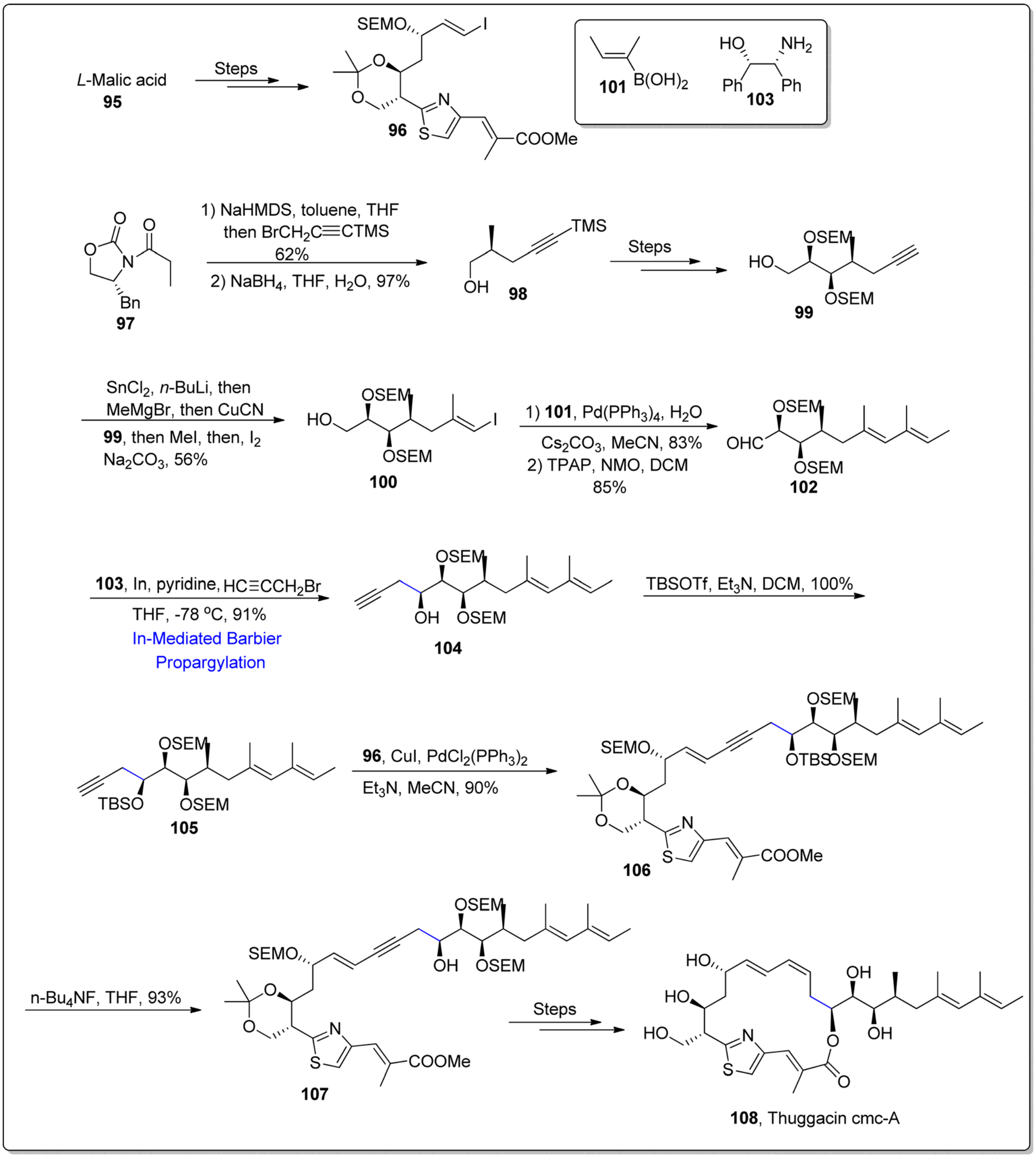
Scheme 11 Synthesis of (4*S*,5*S*)-4-hydroxy-γ-decalactone **85**.

Luche reduction of diketone **89** furnished diastereomeric mixture of bis-ethers **90a** & **90b** (dr about 2 : 1), alongwith reduction products **91a** & **91b**. The acidic hydrolysis of these ethers rendered diospongin analogues **92a** and **92b** respectively. The diospongin analogue **92a** was then made to react over several steps including sequence to accomplish the total synthesis of cryptorigidifoliol I **93** alongwith its epimer **94** (Scheme 12).



Scheme 12 Synthesis of cryptorigidifoliol I **93** and 2′-*epi*-cryptorigidifoliol I **94**.

2.2.1. Synthesis of macrolides-based natural products. Thuggacins A–C are natural products, which were withdrawn from the myxobacterium *i.e.*, *Sorangium cellulosum*.[86] Their structural skeleton is composed of α,β-unsaturated macrolide alongwith thiazole ring and conjugated diene framework. They exhibit potent activity against a diverse variety of microorganisms. They have been found to affect the respiratory chain of *Mycobacterium tuberculosis*, thereby acting as therapeutic agent against tuberculosis. Thuggacin cmc-A (which is composed of 17 members) was isolated by Jansen and colleagues from myxobacterium Chondromyces crocatus Cmc5. In 2021, Tsutsumi *et al.*[87] provided the first total synthesis of thuggacin cmc A **108** by applying indium-mediated Barbier propargylation as one of the central steps. Initially, L-malic acid **95** was treated over a number of steps to afford C1–C12 fragment of thuggacin cmc-A **96.** In order to access C13–C25 fragment, optically active oxazolidinone **97** was treated with sodium hexamethyldisilazide followed by reaction with $BrCH_2C{\equiv}CTMS$ and sodium borohydride mediated reduction to attain corresponding alcohol **98** in 97% yield. The alcohol **98** was then transformed to terminal alkyne **99** over few steps. The reaction of terminal alkyne **99** with (tributylstannyl)methylmagnesium (which was generated within the reaction) utilizing copper cyanide as catalyst proceeded by the addition of methyl group and iodine afforded iodoalkene **100** in 56% yield. Iodoalkene **100** was further made to undergo $Pd(PPh_3)_4$ catalyzed Suzuki–Miyaura coupling with

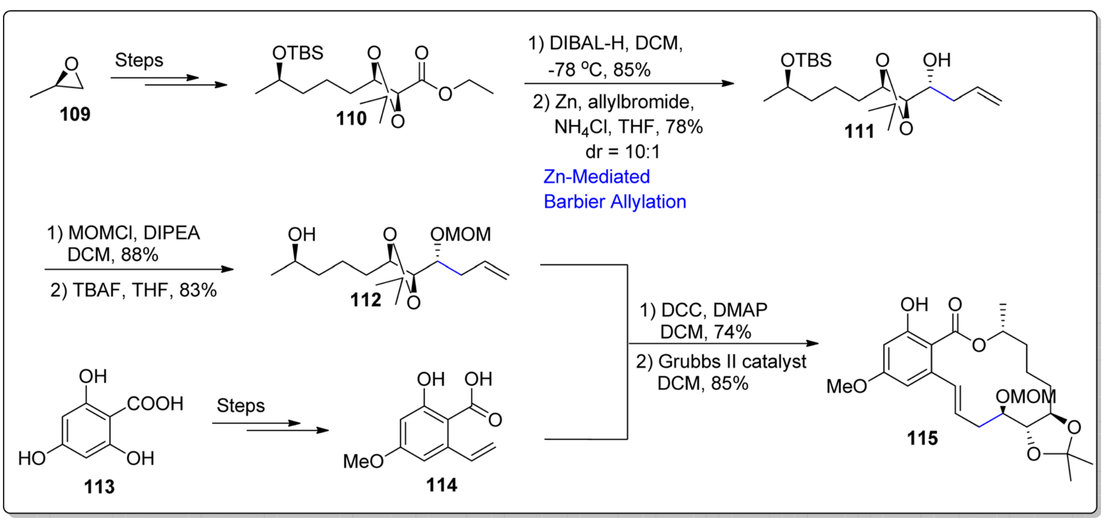


Scheme 13 Synthesis of thuggacin cmc-A **108**.

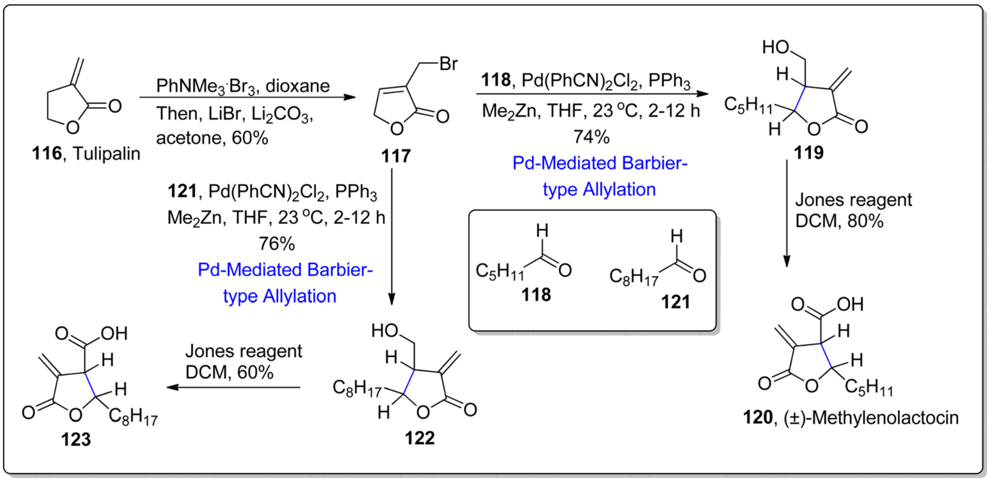
Boronic acid **101** along with subsequent (TPAP-promoted) oxidation to furnish aldehyde **102** in 85% yield. The aldehyde **102** was next subjected to react with aminoalcohol **103** and allylbromide Singaram's developed indium promoted Barbier propargylation to afford the required compound **104** in 91% yield. The Barbier reaction involving propargylation resulted in excellent yield (91%) of a single required isomer in comparison to the addition of Grignard reagent which afforded the product in unsatisfactorily diastereomeric ratio. The hydroxyl group in compound **104** was further protected with *tert*-butyl silyl group to generate fragment C13–C25 **105** in 100% yield. The fragment C1–C12 **96** and C13–C25 **105** were further coupled *via* Sonogashira coupling in the presence of copper iodide, palladium chloride using triethylamine as base to achieve alkyne **106** in 90% yield. The removal of TBS group in alkyne **106** was carried out *via* *tert*-butylammonium fluoride to generate –OH substituted alkyne **107**, which was then reacted over several steps to give rise to thuggacin cmc-A **108** (Scheme 13).

Resorcylic acid lactones are natural occurring compounds, constituting 14-membered macrolides in their structural framework.[88] Ever since the extraction of radiciol, this particular class of natural products has been investigated keenly. It has been found to demonstrate the efficient potency as anti-bacterial, anti-fungal and anti-viral agents. There is continuous progress towards the development of efficient anti-microbial agents.[89,90] In 2012, Chen and colleagues isolated naturally occurring resorcyclic acid lactones *i.e.*, Paecilomycins A–F.[91] In propagation of their strives towards the total synthesis of various Paecilomycins, Gurram and coworkers[92] performed the synthesis of Pecilomycin F by employing Barbier-type allylation as a key step. Initially, they treated epoxide **109** over several steps involving synthetic pathway to forge the iso-propylidine based ester **110**. The synthesized ester **110** was then reduced *via* DIBAL-H in dichloromethane proceeded by zinc mediated Barbier allylation reaction with allylbromide in the presence of ammonium chloride and tetrahydrofuran to afford non-separable diastereomeric mixture of homo-allylated alcohol **111** in 78% yield with 10 : 1 dr. The hydroxyl functionality in compound **111** was protected on treatment with MOMCl and DIPEA in dichloromethane with subsequent removal of silyl group by using tetrabutyl ammonium fluoride to furnish the alcoholic fragment **112** in 83% yield. Furthermore, tri-hydroxy substituted benzoic acid **113** was reacted over a number of steps to result in required acid fragment **114**. In the next step, synthesized alcoholic and acid fragments (**112** & **114**) were joined *via* Steglich esterification to forge ester, which was subjected to Grubbs II catalyst promoted ring closing metathesis to accomplish the synthesis of Paecilomycin F **115** (85% yield) (Scheme 14).

2.2.2. Synthesis of sesquiterpene lactones-based natural products. Sesquiterpene lactones are incorporated with α-*exo*-methylene-γ-butyrolactone which exhibit promising biological activities *i.e.*, deoxyelephantopin, helenalin and arglabin.[93] Structural framework of paraconic acids is also endowed with this bioactive skeleton. The previously employed allylation routes to access bioactive skeleton resulted in *anti*-relationship within substituents, thus another route was required to access the *syn*-relationship. For this purpose, considering the utility of palladium metal in organic synthesis,[94,95] palladium promoted Barbier-type allylation was employed by involving dimethyl zinc as reducing agent. In 2021, Liu *et al.*[96] developed Barbier-type allylation with subsequent translactonization reaction by using $Pd(PhCN)_2Cl_2$ as catalyst with triphenylphosphine ligand in the presence of dimethyl zinc (reducing agent) in THF/toluene to afford the diastereoselective mixture of β,γ-disubstituted α-*exo*-methylene-γ-butyrolactones. Dimethyl zinc was observed to play crucial role in both steps by acting as a nucleophile (for polarity inversion of π-allylpalladium) and Lewis acid respectively. This developed approach was then exploited further to achieve the synthesis of two paraconic acids and two 1,10-seco-guaianolides. In this regard, market ready tulipalin A **116** was transformed to bromolactone **117** in 60%. In the next step, bromolactone **117** was subjected to treat with hexanal **118** *via* developed dimethylzinc involving Barbier-type allylation and



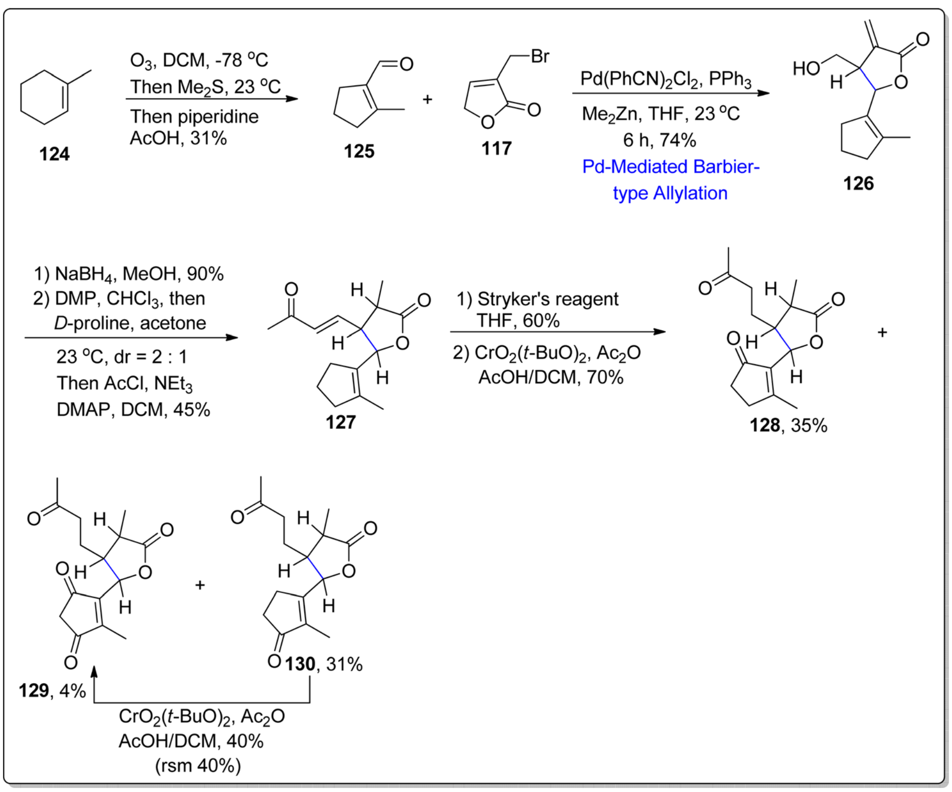
Scheme 14 Synthesis of Paecilomycin F **115**.



Scheme 15 Synthesis of (±)-methylenolactocin **120** and (+)-C75 **123**.

translactonization sequence in tetrahydrofuran to attain the resulting addition product **119** in 74% yield. The addition product was subjected to Jones oxidation to accomplish the synthesis of (±)-methylenolactocin **120** in 80% yield. In another route, bromolactone **117** was made to react with nonanal **121** *via* palladium promoted Barbier allylation and subsequent lactonization to furnish compound **122** in 76% yield. In the final step, Jones oxidation of compound **122** resulted in the synthesis of second paraconic acid *i.e.*, (+)-C75 **123** in 60% yield (Scheme 15).

Further Barbier-type allylation sequence was harnessed for the synthesis of 1,10-seco-guaianolides 3-deshydroxy-iso-secotanapartholide **128** and 1,10-dioxo-1,10-deoxy-1,10-secogorgonolide **129** which are extracted from *Achillea ligustica* and *Artemisia gorgonum* respectively. Initially, alkene **124** was treated over few steps to synthesize corresponding aldehyde **125,** which was further treated with bromolactone **117** *via* developed Barbier-type allylation and translactonization sequence to acquire addition product **126** in 74% yield. The compound **126** was subjected to reduction and oxidation

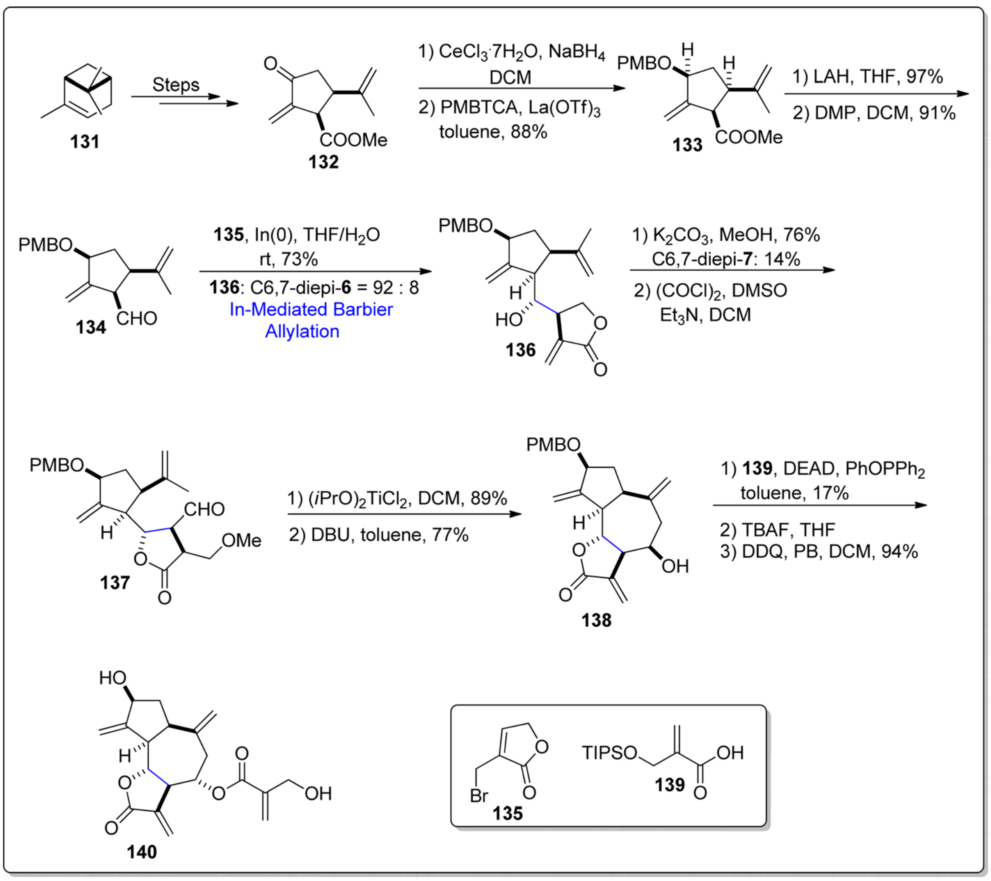


Scheme 16 Synthesis of 1,10-seco-guaianolides **128** and **129**.

followed by proline mediated aldol condensation and acylation to afford conjugated ketone **127** in 45% yield. The conjugated ketone **127** further resulted in the synthesis of mixture of three compounds **128–130** as a result of Stryker's reagent induced reduction (of α,β-unsaturated double bond) followed by allylic oxidation with the addition of $CrO_2(Ot\text{-}Bu)_2$. In this way, two naturally occurring 1,10-seco-guaianolides **128** and **129** were obtained in 35% and 4% yield respectively. Other non-natural compound **130** (from the resulting mixture) was subjected to similar allylic oxidation to transform it into naturally occurring 1,10-seco-guaianolide **129** (Scheme 16).

Cynaropicrin is a naturally occurring sesquiterpene lactone, obtained from *Cynara scolymus* (artichoke). This particular natural product is composed of complex structural framework, consisting of three fused cyclic rings, four exo double bonds with six stereogenic centers. Cynaropicrin has been discovered to play the role of anti-trypanosomal, NF-κB activation inhibitors and anti-hepatitis agents. In 2021, Nakamura *et al.*[97] carried out the first total synthesis of (+)-cynaropicrin **140** by employing Favorskii rearrangement and indium mediated diastereoselective Barbier reaction as major steps. Initially, easily accessible natural precursor *i.e.*, (*S*)-α-pinene **131** was made to undergo several steps to generate corresponding lactone **132**. Lactone **132** then underwent Luche reduction proceeded by hydroxyl group protection with *p*-methoxy benzyl to furnish compound **133** in 88% yield. The ester functionality in compound **133** was reduced by utilizing lithium aluminium hydride followed by Dess–Martin periodinane mediated oxidation to procure aldehyde **134** in 91% yield. The aldehyde **134** was then made to react with compound **135** *via* indium catalyzed diastereoselective Barbier allylation reaction in tetrahydrofuran/water at room temperature, which gave diastereomeric mixture of compound **136** in 92 : 8. It was observed that indium promoted Barbier allylation resulted in better yield with higher diastereomeric ratio as compared to zinc mediated Barbier approach. Compound **136** was then subjected to *trans*-lactonization in step sequence with Swern oxidation to attain aldehyde **137**. The aldehyde **137** was further converted to tricyclic compound **138** (in 77% yield) *via* intramolecular ene reaction succeeded by DBU promoted elimination of methanol. In the next step, Mitsunobu–Mukaiyama inversion reaction between compound **138** and acid **139** installed the side chain to fused tricyclic ring skeleton followed by TBAF and DDQ induced deprotection of hydroxyl group to furnish the desired natural product **140** in 94% yield (Scheme 17).

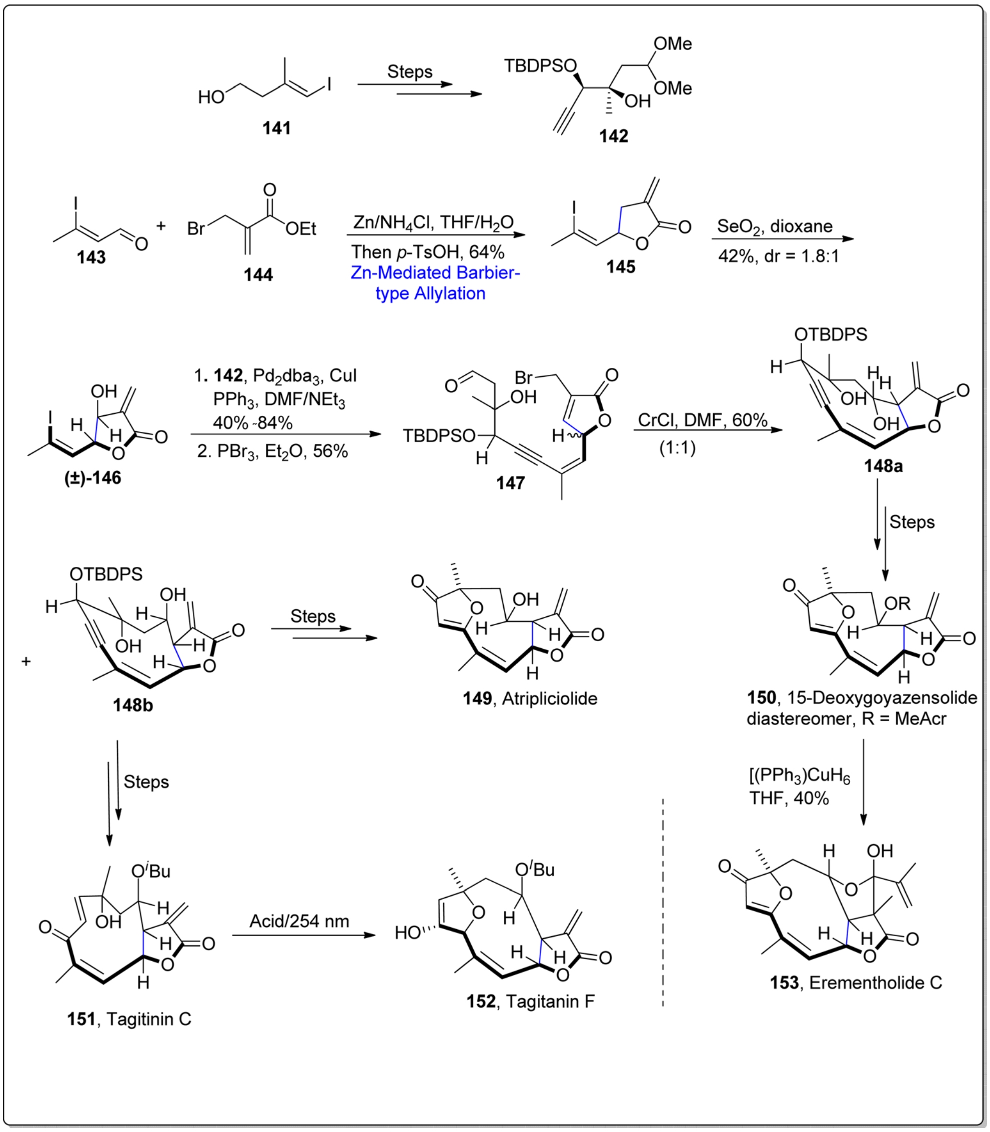
Sesquiterpenes are naturally occurring organic compounds which have been observed to display a significant array of biological activities. As, 15-deoxygoyazensolide has unveiled itself as potent cytotoxic agents in comparison to parent *i.e.*, goyazensolide, which indicates the improvement in pharmaceutical



Scheme 17 Synthesis of 1,10-seco-guaianolides **138** and **140**.

activity on slight structural modifications.[98] In 2021, Liu *et al.*[99] reported the synthesis of naturally occurring sesquiterpenes by carrying out zinc promoted Barbier-type allylation as a key step. To achieve the required task, they initiated the synthetic pathway by treating vinyl alcohol **141** over few steps involving route to procure alkyne **142**. Then, zinc mediated Barbier-type allylation was carried out by reacting aldehyde **143** with allyl bromide **144** in tetrahydrofuran/water using ammonium chloride followed by lactonization to give the substituted iodoalkene **145** in 64% yield. The utilization of Barbier reaction within allylation approach led towards the installation of α-*exo*-methylene-γ-butyrolactone. The synthesized alkene **145** further experienced serium oxide (SeO_2) allylic oxidation to furnish vinyl iodide **146** in diastereomeric ratio of dr = 1 : 8.1 with 42% yield. In the next step, vinyl iodide was made to react with initially generated alkyne **142** *via* Sonogashira coupling reaction proceeded by reaction with PBr_3 in diethyl ether, which resulted in the attainment of compound **147**. The compound **147** was further converted into two diastereomers **148a** and **148b** on reaction with $CrCl_2$ in DMF. The diastereomer **148b** acted as an essential synthetic intermediate to afford the total synthesis of various naturally occurring sesquiterpenes *i.e.*, atripliciolide **149** and tagitinic C **151** (*via* several steps involving synthetic pathway). Exposure of acidic conditions to tagitanin C **151** led to the synthesis of tagitanin F **152**. Similarly, diastereomer **148a** acted as an essential precursor to attain 15-deoxygoyazensolide **150** *via* several steps sequence, which was then subjected to Stryker's reagent to furnish eremantholide C **153** in 40% yield (Scheme 18).

A germacranolide sesquiterpene based lactone *i.e.*, cnicin was initially extracted by Šorm and colleagues in 1959, from the *Cnicus benedictus's* leaves.[100] Cnicin is structurally composed of a diene constrained in a ten-membered ring joined with a lactone ring (5-membered). This naturally occurring



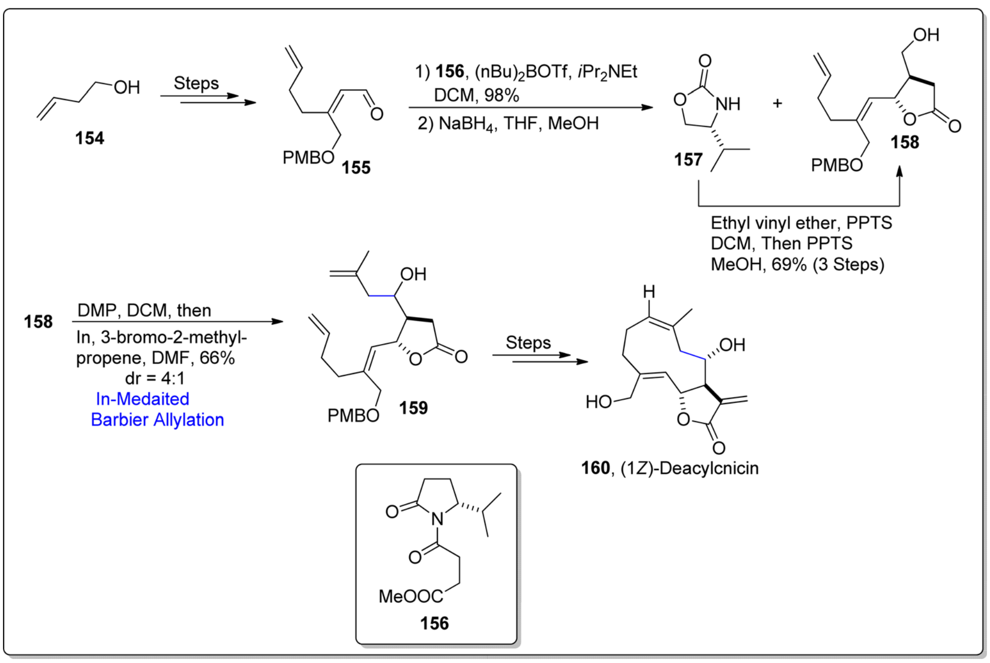
Scheme 18 Synthesis of naturally occurring sesquiterpene lactones **149–153**.

sesquiterpene lactone exhibits allelopathic, anti-myeloma, cytostatic, anti-bacterial and anti-trypanosoma brucei activities.[101] Its striking pharmacological potential urged the Kimura and Usuki[102] (in 2022) to develop an efficient route to access cnicin, exploiting Barbier allylation as a key step. Their synthetic pathway involved the procurement of aldehyde **155** by subjecting alcohol **154** to several steps involving sequence. The synthesized aldehyde **155** was then joined with Evans aldol substrate **156** *via* 1,2-addition reaction in the presence of (n-Bu)$_2$OTf and diisopropyl ethylamine in dichloromethane in sequence with sodium borohydride mediated reduction to afford the inseparable mixture of compounds **157** and **158**. However, treatment of compound **157** with ethyl vinyl ether and PPTS resulted in the synthesis of pure alcoholic fragment **158** in 69% yield (*via* three steps). The alcoholic functionality in compound **158** was oxidized using Dess–Martin Periodinane followed by indium promoted Barbier allylation with 3-bromo-2-methyl propene, thereby yielding diastereomeric mixture of coupled product **159** in 66% yield (dr = 4 : 1). The resulting product **159** was treated over a number of steps (which also involve RCM) to attain the synthesis of cnicin analogue *i.e.*, (1*Z*)-deacylcnicin **160**. The inability of RCM to furnish the 1*E*-form as major product hindered the total synthesis of cnicin, thus paved pathway to result in cnicin analogue (Scheme 19).

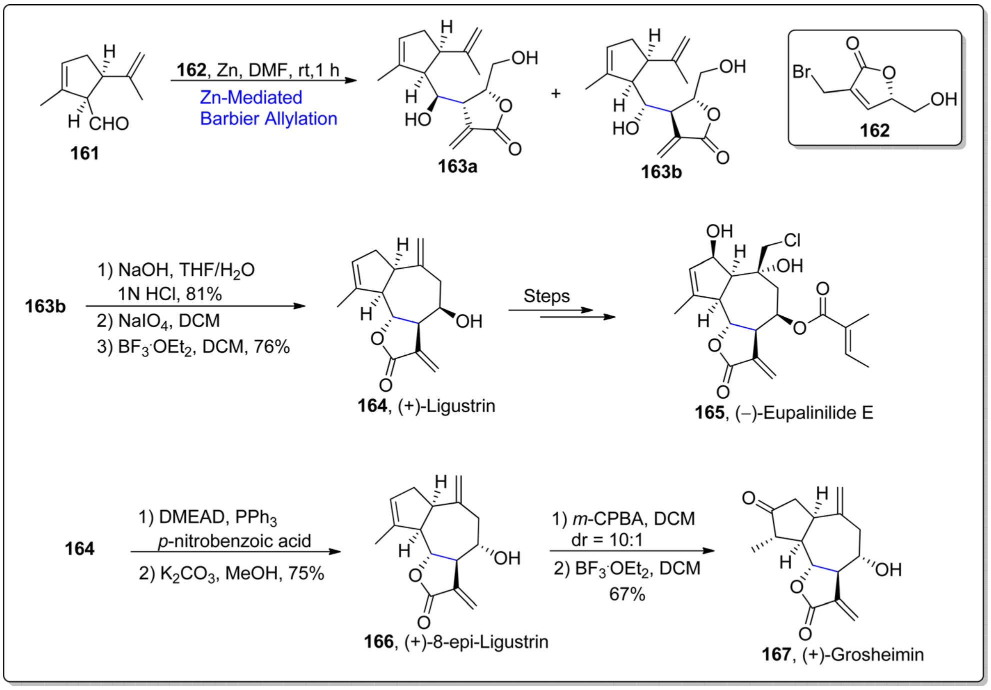
γ-Butyrolactones are abundantly found in the structural skeleton of diverse naturally occurring compounds.[103] These scaffolds have been observed to display a significant array of potent biological activities which include cytotoxic, anti-bacterial, anti-viral, anti-inflammatory and anti-fungal activities.[104] Guaianolides *i.e.*, (+)-ligustrin, (+)-8-*epi*-ligustrin, (+)-grosheimin, (+)-8-*epi*-grosheimin & (−)-eupalinilide are naturally occurring sesquiterpene lactones whose structural constituents involve tricyclic ring system framework with γ-butyrolactone and hydroazulene moieties. These natural products demonstrate remarkable potencies as biological agents. In 2022, Fernandes and Ramakarishna[105] carried out the total synthesis of these sesquiterpene lactones by employing diastereoselective Barbier allylation and translactonization as key steps. The first step of synthetic journey involved the treatment of allyl substituted chiral bromolactone **162** with aldehyde **161** *via* diastereoselective Barbier allylation in the presence of zinc in dimethylformamide to afford the diastereomeric inseparable mixture of three-stereocenters involving compound **163a** and **163b** (dr = 1 : 7.5), which was subjected to column chromatography to obtain dr = 8 : 92 of the resulting mixture. The compound **163b** was further translactonized followed by two steps involving aldehyde-ene reaction, which ultimately furnished the (+)-ligustrin **164** in 76% yield. (+)-ligustrin **164** was treated over few steps involving synthetic route to furnish the synthesis of (−)-eupalinilide E **165**. Furthermore, (+)-ligustrin **164** was transformed to (+)-8-*epi*-ligustrin **166** (in 75% yield) *via* Mitsunobu conditions. Next, epoxidation of (+)-8-*epi*-ligustrin **166** was proceeded by ring opening rearrangement with boron trifluoride diethyl etherate to accomplish the synthesis of (+)-grosheimin **167** in 67% yield (Scheme 20).

2.3. Synthesis of terpenoids-based natural products

2.3.1. Synthesis of sesquiterpenoids-based natural products. Toxicodenane A is a sesquiterpenoid which consists of three fused cyclic rings anlogwith exocyclic double bond and bridged ether functionality. In 2013, it was first withdrawn from *Toxicodendron vernicifluum* by Cheng and coworkers.[106] Racemic isolation of toxicodenane A urged the researchers to carry out its enantioselective synthesis, to evaluate its biological



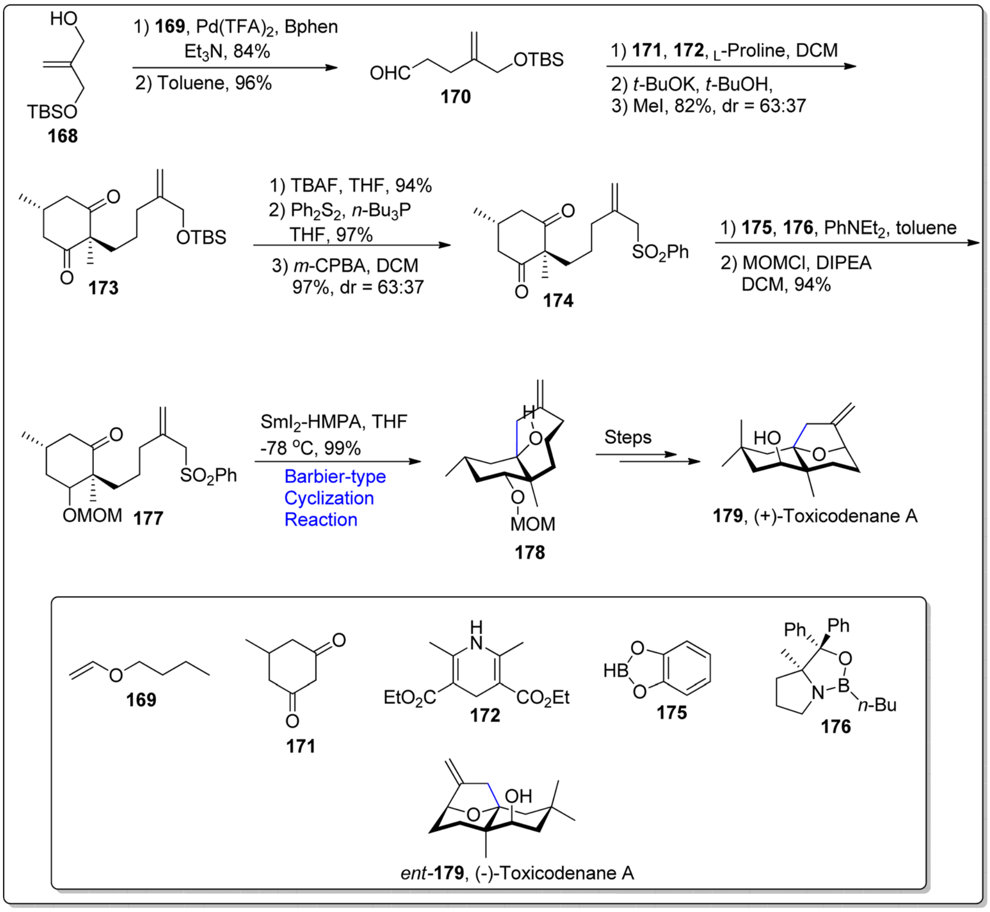
Scheme 19 Synthesis of (1*Z*)-deacylcnicin **160**.



Scheme 20 Synthesis of naturally occurring sesquiterpene lactone **164–167**.

applications. In 2021, Han and colleagues[107] demonstrated the first enantioselective synthesis of toxicodenane A by carrying out Lewis acid catalyzed transacetalation and Prins cascade reaction. In 2022, Nishikawa *et al.*[108] reported an efficient route to achieve the enantioselective synthesis of toxicodenane A followed by the biological assessment of both enantiomers against lipotoxicity. They accomplished the asymmetric synthesis of toxicodenane A by implementing SmI_2 mediated Barbier-type cyclization, allylic oxidation and dehydration induced cyclization as key steps. The synthesis began with the vinylation of silyl ether **168** by involving $Pd(TFA)_2$ and Bphen (bathophenanthroline) followed by Claisen rearrangement to afford required aldehyde **170** in 96% yield. The resulting aldehyde **170** was then subjected to react with cyclohexanedione **171** and compound **172** *via* reductive Knoevenagel condensation which resulted in diastereomeric mixture of **173** in 82% yield (with dr = 63 : 37). The silyloxy group in compound **173** was then transformed to sulfonyl group **174**, which on further asymmetric desymmetrization and protection of hydroxyl group with methoxymethyl gave enantiopure compound **177** in 94% yield. In the next step, compound **177** was subjected to samarium iodide (SmI_2-HMPA) promoted Barbier-type annulation in tetrahydrofuran at −78 °C to afford compound **178** stereo selectively in 99% yield with *cis*-configuration. The cyclized product **178** was then treated over several steps to forge (+)-toxicodenane A **179**. Similarly, the synthesis of (−)-toxicodenane A *ent*-**179** was procured by treating compound **174** with boronic acid **175** and compound *ent*-**176** *via* similar mentioned (Barbier-type annulation involving) protocol. Both the enantiomers were found to protect the cells against lipotoxicity promoted inflammatory effects (Scheme 21).

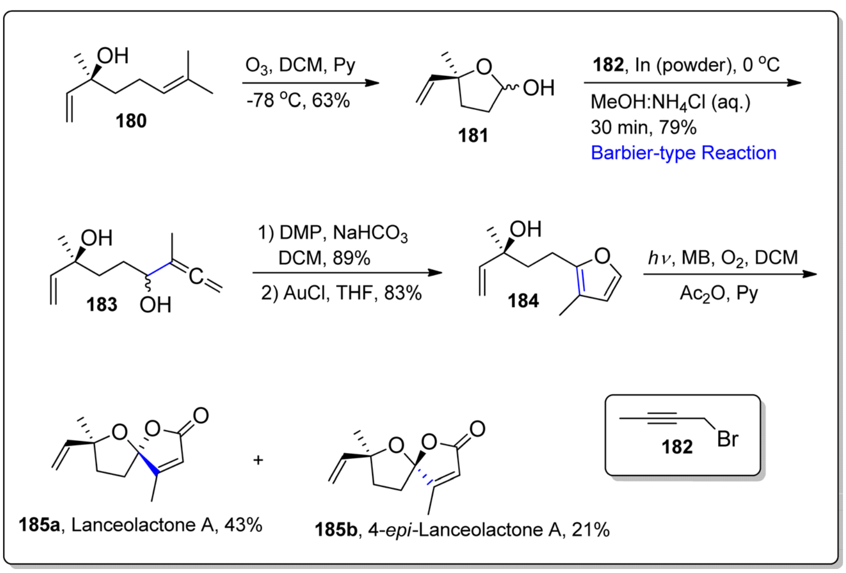
Oxaspirolactone constituting terpenoids are known to exhibit remarkable biological role as they are efficiently employed against several deadly diseases.[108,109] In 2015, Kubo *et al.* first time isolated the oxaspirolactone based tetranorsesquiterpenoids *i.e.*, lanceolactone A and B from the *Illicium lanceolatum*'s leaves.[110] These naturally occurring sequiterpenoids were observed to illustrate the potent antimicrobial activity against teeth pathogen *i.e.*, *Porphyromonas gingivalis*. Nanda's group, in 2018,[111] carried out the initial report on the asymmetric total synthesis of lanceolactone in 16.2% overall yield by employing various name reactions as key steps. Being interested in the chemistry of oxaspirolactones, in 2022, Borade and Kontham[112] established a facile synthetic route to achieve the synthesis of lanceolactone A and its possible stereoisomers by exploiting chiral precursors without installation of any protecting group. They accomplished the synthesis of target natural products by carrying out ozonolysis, Barbier-type addition reaction, gold-promoted cycloisomerization and dye-sensitized photooxidation as significant steps. In the first step, (*S*)-linalool **180** was made to undergo ozonolysis in the presence of pyridine and DCM to afford lactol **181** in 63% yield, without incorporating any protecting group. The synthesized lactol **181** was then subjected to indium powder promoted Barbier-type addition reaction with propargyl bromide **182** in MeOH:NH_4Cl, which gave intermediate *i.e.*, allene-diol **183** in 79% yield. The resulting allene-diol **183** was further subjected to Dess–Martin Periodinane mediated oxidation followed by treatment with AuCl in tetrahydrofuran to synthesize hydroxyalkyl-joined-furan **184** in 83% yield. Compound **184** was further exposed to MB (Mitsunobu–Vassilikogiannakis's) dye-sensitized photo-oxidation reaction, which



Scheme 21 Synthesis of (−)-toxicodenane A **179** and (−)-toxicodenane A *ent*-**179**.

afforded lanceolactone A **185a** and its epimer **185b** in 43% and 21% yield respectively (Scheme 22).

Aculenes A–E are affiliated with bicyclic norsesquiterpene based L-proline associated keto esters or alcohols, which were extracted from *Aspergillus aculeatus* culture media and from *Penicillium* sp. XWS02F62 and SCS-KFD08.[113] These norsesquiterpenes are fungal metabolites endowed with nordaucane framework. Among them, aculenes C, D and E perform the

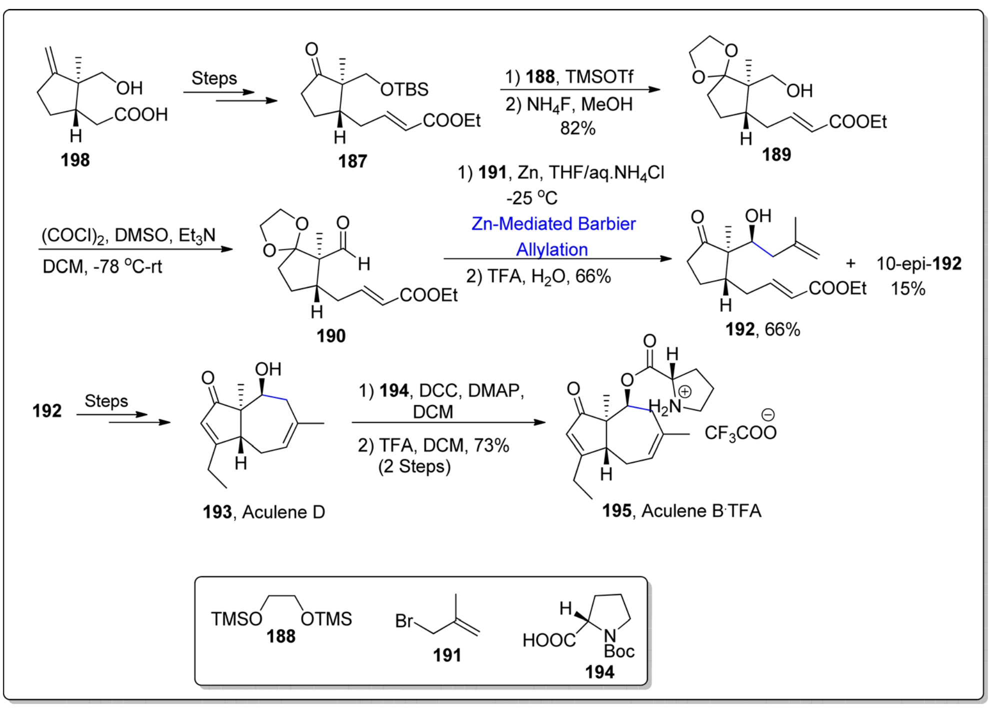


Scheme 22 Synthesis of lanceolactone A **185a** and 4-*epi*-lanceolactone **185b**.

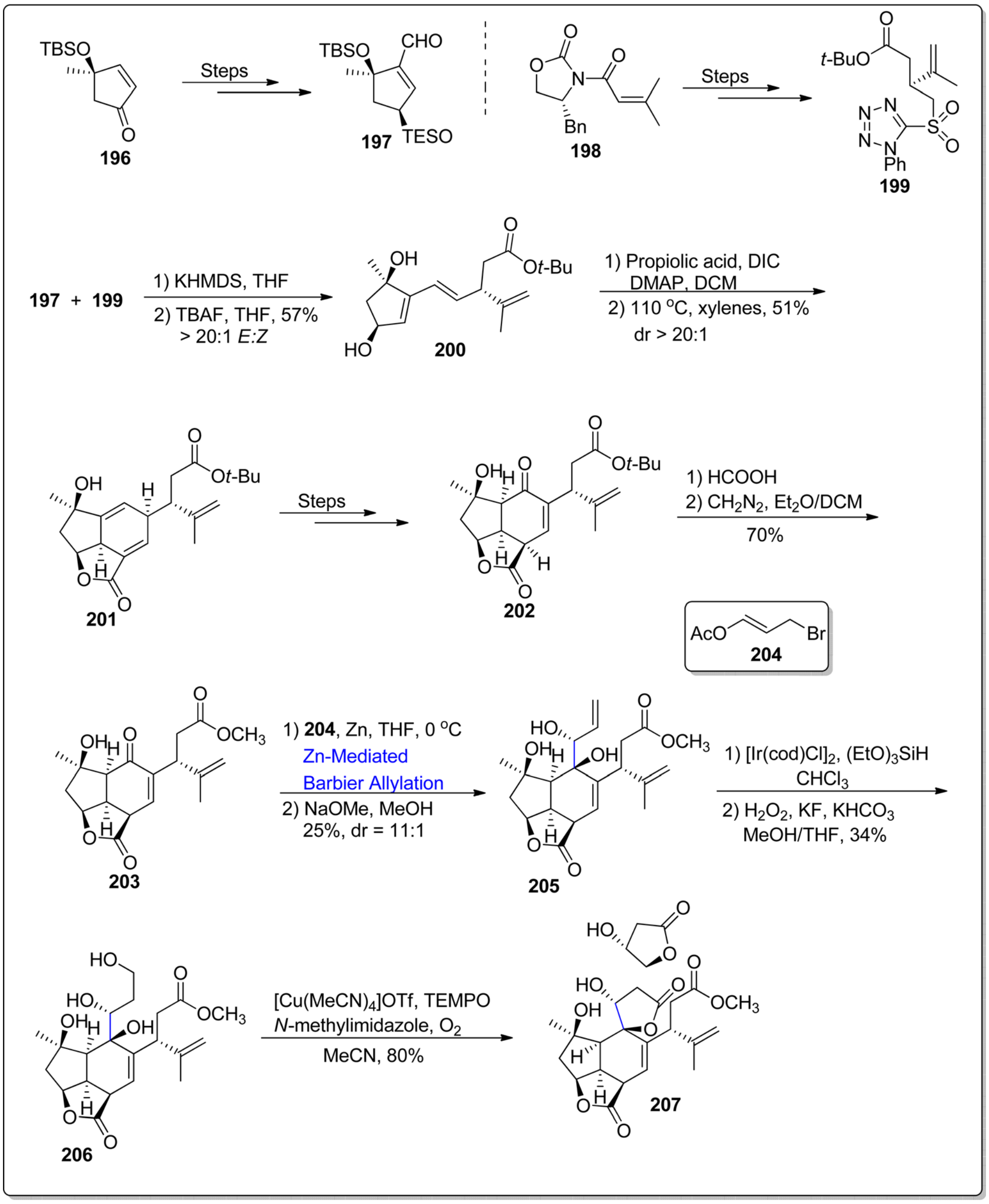
inhibition of bacterial communication (quorum sensing restrictive potency) opposed to *Chromobacterium violaceum* CV026 bacterium.[114] Thus, being persuaded by the efficient pharmacological role of aculenes, Yokokawa *et al.*[115] in 2023, reported a significant pathway leading towards the synthesis of aculene B and D. Their synthetic journey involved the utilization of zinc promoted Barbier allylation as one of the essential steps. The synthesis commenced with the transformation of easily available precursor *i.e.*, carboxylic acid **186** into α,β-unsaturated ester **187** *via* several steps. In the next step, ketone functionality in compound **187** was subjected to acetalization reaction followed by the treatment with tetra ammonium fluoride, thereby giving acetal **189** in 82% yield. The obtained acetal was then subjected to undergo Swern oxidation to afford aldehyde **190**. The aldehyde **190** was then made to undergo zinc-mediated Barbier allylation reaction with allylbromide **191**, thereby giving the required diastereomer **192** in major quantity (66% yield) on subsequent removal of acetal group *via* acidic hydrolysis. The diastereomer **192** was made to react over a number of steps to furnish the naturally occurring aculene D **193**. Aculene D **193** was treated further to acquire aculene B **195** in 73% yield as a result of its Steglich esterification with Boc protected L-proline **194** proceeded by the deprotection of amine (Scheme 23).

2.3.2. Synthesis of diterpenoids-based natural products. Havellockate belongs to the cembranoid family, which was first obtained from *Sinularia granosa*. Its structure is composed of fused tricyclic ring framework with β-hydroxybutanolide ring constituting overall eight chiral centers.[116] Till now, no successful synthesis of havellockate has been presented. Considering the challenges towards its total synthesis, in 2022, Hafeman *et al.*[117] performed the total synthesis of havellockate by utilizing Julia–Kocienski olefination, Diels–Alder cascade reaction, zinc catalyzed Barbier allylation alongwith copper mediated aerobic oxidation as major steps. The synthesis kickstarted with the synthesis of required aldehyde **197** and sulfone **199** individually by treating enone **196** and acyl oxazolidinone **198** respectively over few steps. The aldehyde **197** and sulfone **199** were then coupled *via* KHMDS mediated Julia–Kocienski olefination followed by desilylation to afford diol **200** in 57% yield with >20 : 1 *E* : *Z*. The resulting diol **200** was further made to underwent Steglich esterification with propiolic acid followed by [4 + 2] cycloaddition reaction to furnish Diels–Alder adduct **201** in 51% yield with >20 : 1 dr. The adduct **201** was later treated over several steps to synthesize enone **202**, which was subjected to transesterification reaction to result in ester **203** in 70% yield. The ester **203** further underwent zinc promoted Barbier allylation reaction with substituted allyl bromide **204** in tetrahydrofuran followed by subsequent deacetylation to forge triol **205** in 25% with dr = 1 : 1. The triol compound **205** was later transformed to tetrol **206** in 34% yield as a result of iridium promoted anti-Markonikov hyrdrosilylation alongwith Tamao–Fleming oxidation. In the final step, synthesis of havellockate **207** was achieved in 80% by treating compound **206** *via* copper mediated (aerobic) oxidation/cyclization reaction (Scheme 24).

Synthesis of naturally occurring organic compounds have taken frontseat owing to their applicability as efficient drugs. Makassaric acid and fascioquinol B are meroditerpenoids obtained from sponges *i.e.*, *Acanthodendrilla* and *Fasciospongia* sp. respectively. Makassaric acid acts an efficient inhibitor of MAPKAP kinase 2 (MK2) enzyme,[118] thus acting as potent anti-inflammatory agent. Similarly, fascioquinol B has been known



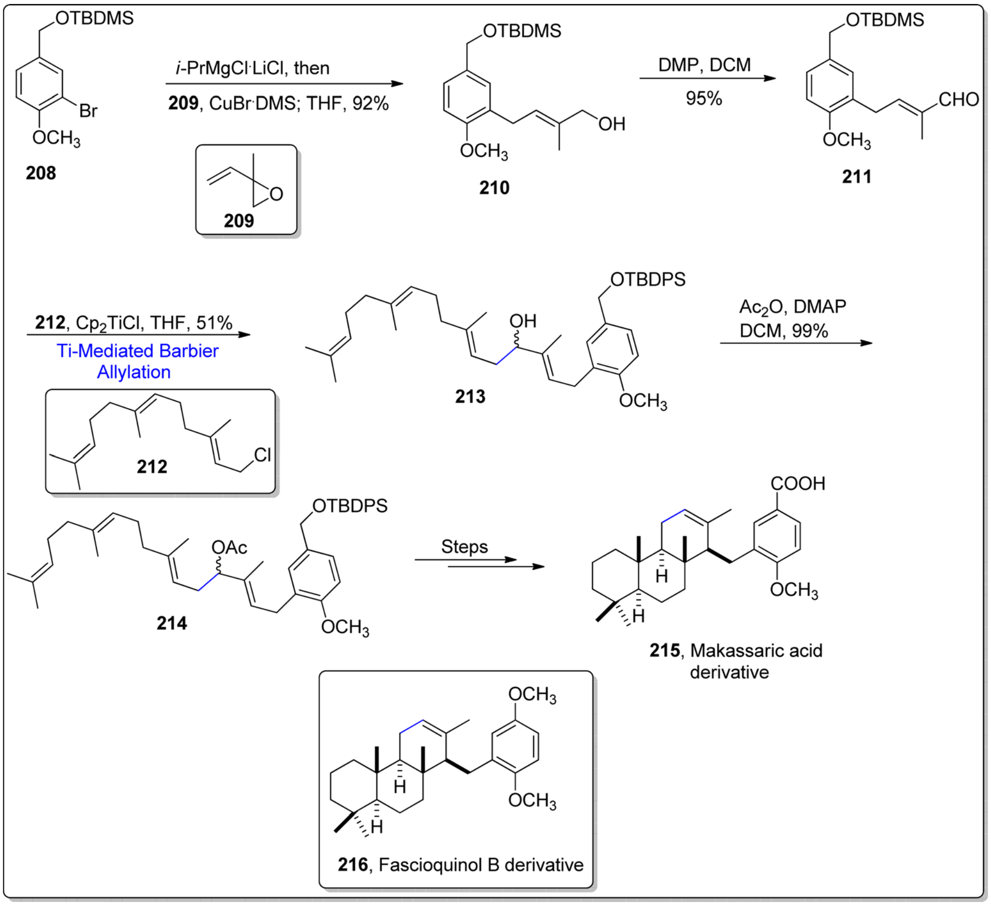
Scheme 23 Synthesis of aculene D **193** aculene B·TFA **195**.



Scheme 24 Synthesis of havellockate **207**.

to exhibit remarkable anti-bacterial potency. In 2022, Rosales *et al.*[119] presented a synthetic layout for the accomplishment of these naturally occurring meroterpenoids. For the synthesis of Makassaric acid derivative, initially, Grignard derivative **208** was added to isoprene monoxide by exploiting the catalytic efficiency of CuBr·DMS, to result in 92% of allylic alcohol **210**. The resulting alcohol was then converted to aldehyde **211** *via* oxidation using Dess–Martin periodinane. The synthesized aldehyde **211** was further subjected to exposed to compound **212** *via* Cp_2TiCl mediated Barbier-allylation reaction, which furnished polyene **213** in 51% yield. This catalytic strategy is essential for the formation of diversely substituted integrated polyenes. The hydroxyl group in ploynene **213** was acetylated to afford compound **214** in 99% yield, which was ultimately treated over several steps to procure the naturally occurring makassaric acid's derivative **215**. The similar strategy was adopted by treating 2-bromo-1,4-dimethoxybenzene as a precursor, which followed the above synthetic protocol to furnish the synthesis of a close derivative of fascioquinol B **216** (Scheme 25).

The most enormous class of plants based secondary metabolites generally constitute diterpenoids (subclass of terpenoids).[120] C20 diterpenoids have been structurally classified into same main categories which include *ent*-beyerane, *ent*-kaurane, *ent*-trachylobane, *ent*-gibberellane and *ent*-atisane *etc.* The main reason for the origin of these C8-ethano bridging diterpenoids is the series of cyclization reaction of geranylgeranyl pyrophosphate which gives rise to *ent*-beyeranyl cation I.[121] This cation plays a key role in enzyme-mediated conversions to synthesize a variety of diterpenoids. Taking into consideration



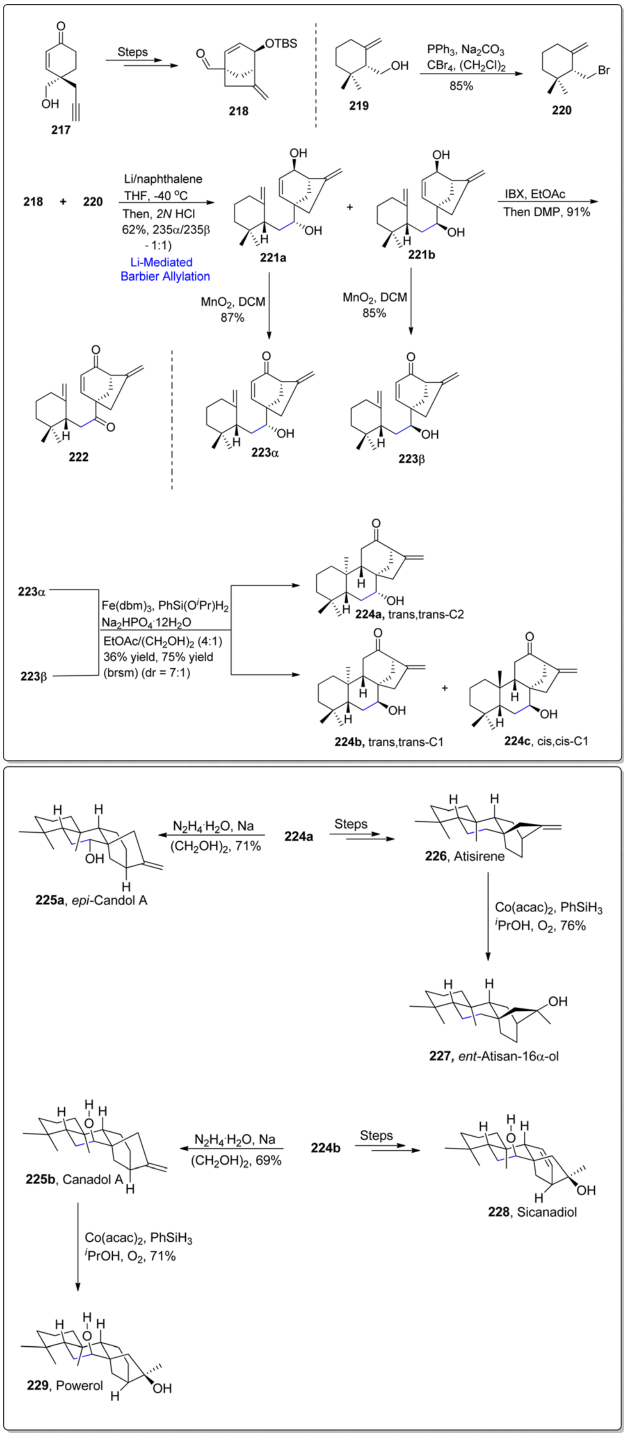
Scheme 25 Synthesis of makassaric acid's derivative **215** & fascioquinol derivative **216**.

the medicinal applications and structural diversity of these diterpenoids, in 2023, Fan group[122] unveiled a unified strategy by exploiting late stage conversions of *ent*-trachylobane and *ent*-kaurane scaffolds to achieve the synthesis of 9 ethano-bridged diterpenoids. The synthetic pathway commenced with the preparation of corresponding aldehyde **218** from optically active cyclohexenone **217**. Meanwhile, Appel substitution reaction of γ-cyclogeraniol **219** afforded optically active allylic bromide **220** in 85% yield. The two resulting monoterpene fragments were then subjected to lithium-mediated Barbier allylation reaction by utilizing lithium/naphthalene in tetrahydrofuran followed by acidic exposure to furnish the diastereomeric mixture of **221a** and **221b** in about 1 : 1 diastereoselectivity ratio. Next, enonols **223α** and **223β** were individually attained as a result of MnO_2 promoted allylic oxidation of **221a** and **221b** respectively. The earlier obtained diastereomeric mixture (**221a** and **221b**) was also exposed to IBX and Dess-Martin periodinane mediated oxidation to procure 91% yield of keto-enone **222**. Enonols **223α** and **223β** were individually subjected to optimized hydrogen atom transfer cyclization (MHAT) to result in the generation of trans,*trans*-C2 **224a** and tran,*trans*-C1 **224b** along with cis,*cis*-C1 **224c**. These precursors were obtained in 36% yield with 75% brsm affording a diastereomeric ratio of 7 : 1. The synthesized *trans*,*trans* C2 **224a** was treated over several steps thereby furnishing the synthesis of atisirene **226**, which was subjected to Muakiyama hydration reaction condition to result in *ent*-atisan-16apha-ol **227** in 76% yield. Similarly, compound **224a** was transformed into *epi*-canadol A **225a** within 71% yield (*ent*-kaurane type diterpenoid) *via* Wolff–Kishner–Huang reaction conditions. Similarly, the *trans*,*trans*-C1 **224b** was transformed into sicanadiol **228** over several steps. This diastereomer **224b** resulted in the synthesis of canadol A **225b** (in 69% yield) *via* Wolff–Kishner–Huang reduction. The resulting canadol A **225b** underwent cobalt mediated Mukaiyama hydration to accomplish the synthesis of powerol **229** in more than 20 : 1 diastereoselective ratio with 71% yield (Scheme 26).

The initially synthezsized keto-enone **222** was also subjected to MHAT cyclization to give rise to *trans*,*trans*-C3-CP **230**, which was treated over numerous steps to achieve naturally occurring trachinol **231a** and *epi*-trachinol **231b**. Similarly, Wolff–Kishner reduction of *trans*,*trans*-C3-CP **230** generated *ent*-beyerane **232** in 62% yield (Scheme 27).

2.4. Synthesis of lignans-based natural products

Phrymarolin II is a 3,7-dioxabicyclooctane framework featuring furofuran lignan, which has been extracted from renowned chinese' traditional medicinal plant *i.e.*, *Phryma leptostachya* L.[123] This plant's roots have been determined to depict the angiogenesis, pesticidal, anti-bacterial and anti-inflammatory

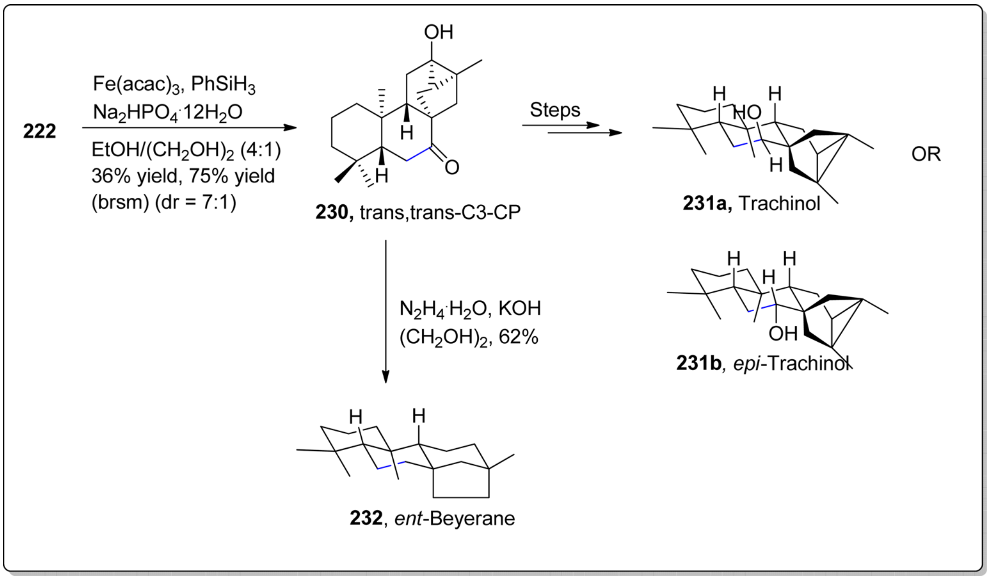


Scheme 26 Synthesis of C20 diterpenoids 224–229.

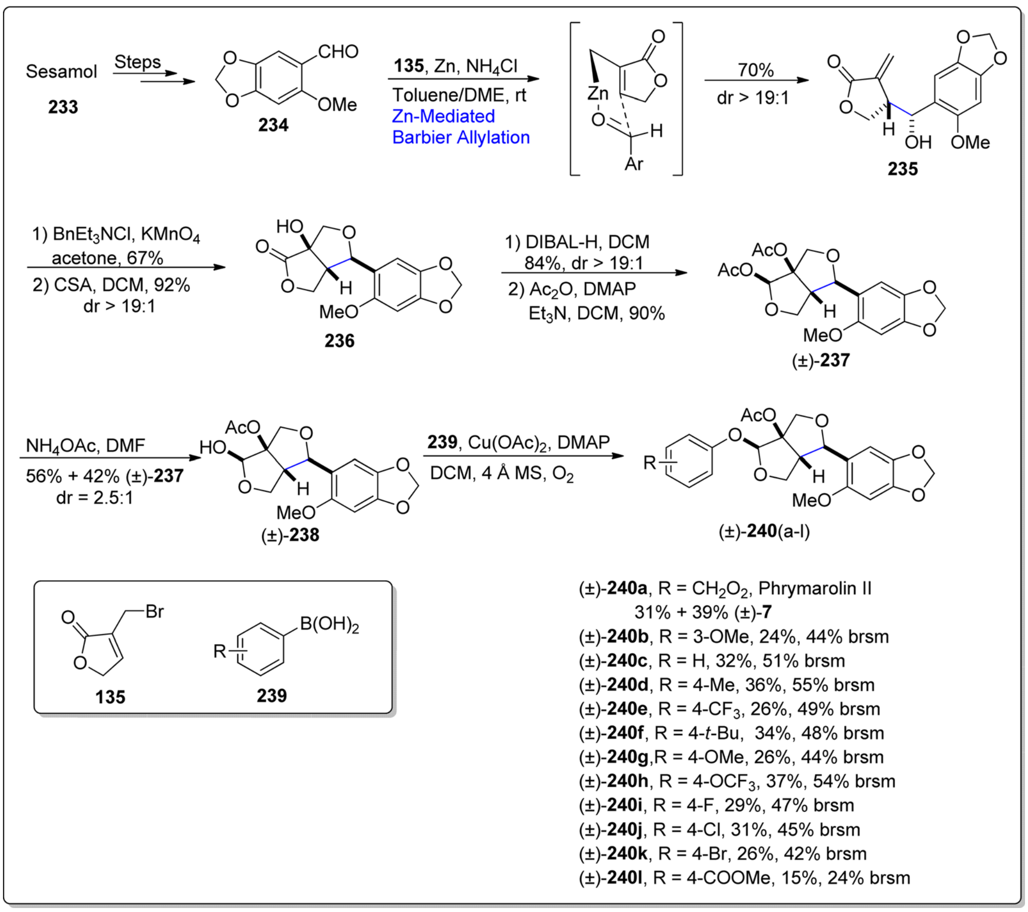
activities. There have been several reports concerning the total synthesis of phrymarolin II and its derivatives in literature, however they were observed to usually suffer from non-economic and low-yielding outcomes. Thus, in order to establish more convenient pathway for the synthesis of naturally occurring lignan, Chi and coworkers in 2021,[124] endeavored an efficient synthetic pathway to access phrymarolin II and its analogues. They utilized the market-ready precursor *i.e.*, sesamol to accomplish the synthesis of this natural product (with overall 5.7% yield) in total nine steps, exploiting Barbier allylation reaction and anomeric *O*-arylation as significant steps. Initially, sesamol **233** was subjected to react over reported two steps to afford carbaldehyde **234**. The resulting carbaldehyde was then made to react with 3-bromomethyl substituted furanone **135** *via* zinc promoted Barbier allylation reaction with the addition of ammonium chloride in toluene/dimethylether, thus procuring compound **235** in 70% yield with more than 19 : 1 diastereomeric ratio. The Barbier allylated product **235** was then exposed to dihydroxylation conditions proceeded by camphor sulfonic acid (CSA) mediated cyclization to forge tetrahydrofuran **236** in 92% yield. In the ongoing step, tetrahydrofuran was subjected to DIBAL-H promoted reduction in sequence with treatment of resulting lactol with acetic anhydride using dimethyl aminopyridine and triethylamine in dichloromethane, thus giving diacetate **237** in 90% yield. Further, deacetylation reaction by employing ammonium acetate resulted in diastereomeric mixture of compound **238** and starting diacetate **237** in 2.5 : 1 dr. Finally, compound **238** was further made to undergo copper acetate promoted Chan–Lam–Evan cross coupling reaction with substituted aryl boronic acids **239** to afford the total synthesis of phrymarolin II **240** and its various analogues. The *in vivo* studies interpret the good to excellent potential of these analogues against the activity of tobbaco mosaic virus, in comparison with ningnanmycin (Scheme 28).

Sacidmulignans A–D are naturally occurring compounds, which have been extracted from the *Sarcostemma acidum* (Roxb.) located in the China's Hainan island.[125] Efforts towards the total synthesis of sacidmulignans A–C (which constitute of 2,7′ cyclolignans structurally) have gained significant momentum in synthetic organic chemistry.[126] Attempts towards the synthesis of sacidmulignan B have been reported by Ramana and Peng group individually, which resulted in 10% and 3% overall yield of this natural product respectively.[127,128] In 2022, Zhuang *et al.*[129] carried out the first racemic total synthesis of sacidmulignan B by exploiting zinc promoted Barbier-type allylation as a key step. Initially, diaryl ketone **241** was subjected to react with crotyl bromide **242** *via* zinc mediated Barbier-type allylation reaction in tetrahydrofuran to furnish the lactone **243** in 84% yield. The resulting lactone **243** experienced two reduction reactions consecutively followed by the selective protection of hydroxyl group to acquire monoalcohol **244** in 90% yield. The resulting tertiary alcohol **244** was subjected to Et_3SiH and boron trifluoride diethyl ether assisted reduction conditions proceeded by the deprotection conditions leading to the removal of *tert*-butyldiphenylsilyl group, which afforded primary alcohol **245** (in 90% yield). The exposure of IBX promoted oxidation conditions to generated alcohol **245** gave the corresponding aldehyde **246** in 88% yield. The compound **246** was further subjected to hydrogenation to deprotect the benzyl protected alcoholic functionality proceeded by the *p*-TsOH mediated (Friedel–Crafts) cyclization, thus procuring sacidmulignan B **247** in 85% yield (Scheme 29).

Tobacco mosaic virus is one the highly afflicting disease of plants, which is responsible for the detrimental and hazardous effects on almost 125 plant species.[130] Considering the

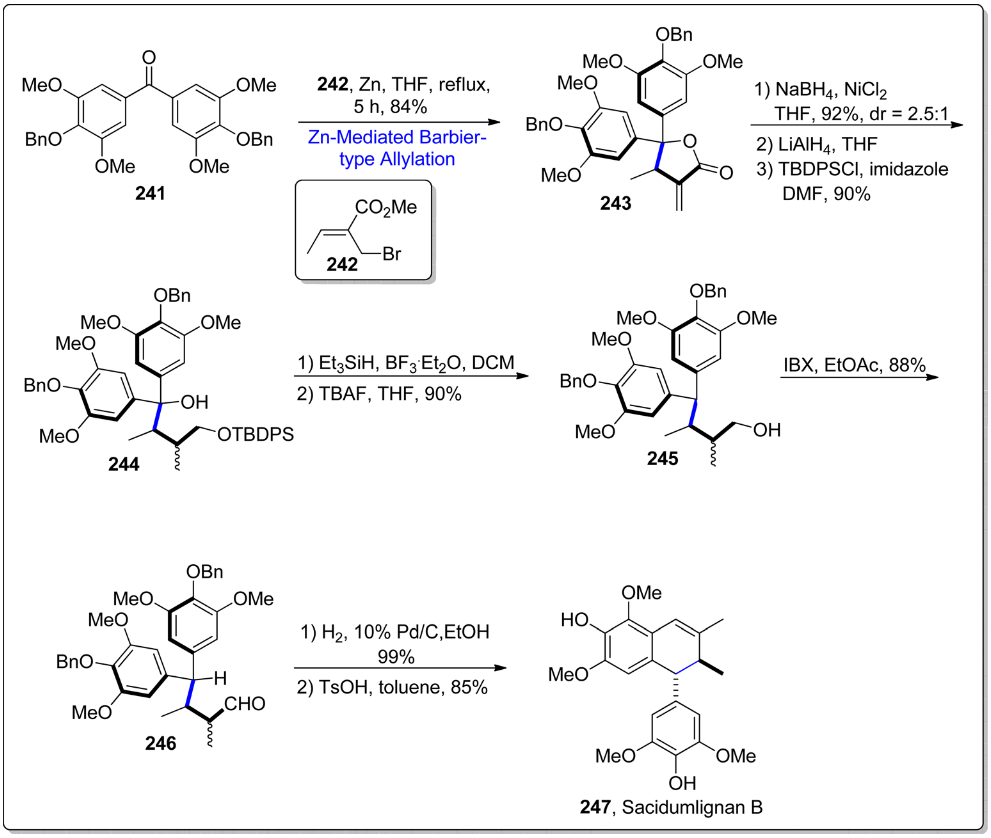


Scheme 27 Synthesis of C20 diterpenoids **231a**, **231b** and **232**.



Scheme 28 Synthesis of phrymarolin II **240** and its various analogues.

availaibility of very few anti-viral agents such as ningnanmycin, ribavirin and dufulin, there is a constant urge to discover and develop efficient anti-viral compounds. Naturally occurring norlignan *i.e.*, nicotlactone A, which was extracted from *Nicotiana tabacum*, identified by Hu and colleagues.[131] The anti-viral potency of this naturally occurring product was unveiled to be

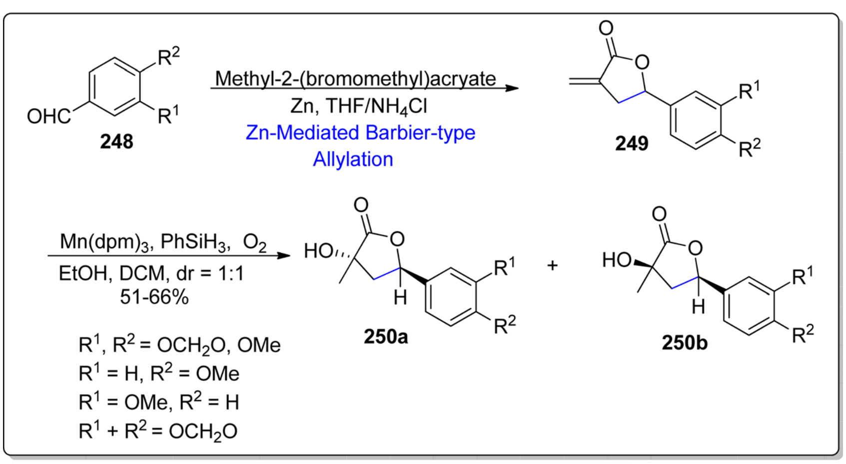


Scheme 29 Synthesis of sacidmulignan **247**.

more efficient as compared to commercially utilized standard *i.e.*, ningnanmycin. These results indicate the capability of nicotlactone A as efficacious lead compound against tobacco mosaic virus. In 2022, He *et al.*[132] procured the synthesis of natural product (±)-8-demethylnicotlactone A and its analogues by utilizing zinc mediated Barbier-type allylation reaction. The substituted benzaldehydes **248** were treated with methyl-2-(bromoethyl)acrylate *via* zinc promoted Barbier-type allylation reaction in tetrahydrofuran and ammonium chloride to afford the corresponding lactones **249.** The synthetic pathway was then proceeded by the Mn(dpm)$_3$ promoted hydration of synthesized lactones to attain the diastereomeric mixture of compound **250a** & **250b** in 1 : 1 diastereomeric ratio (Scheme 30).

2.5. Synthesis of miscellaneous natural products

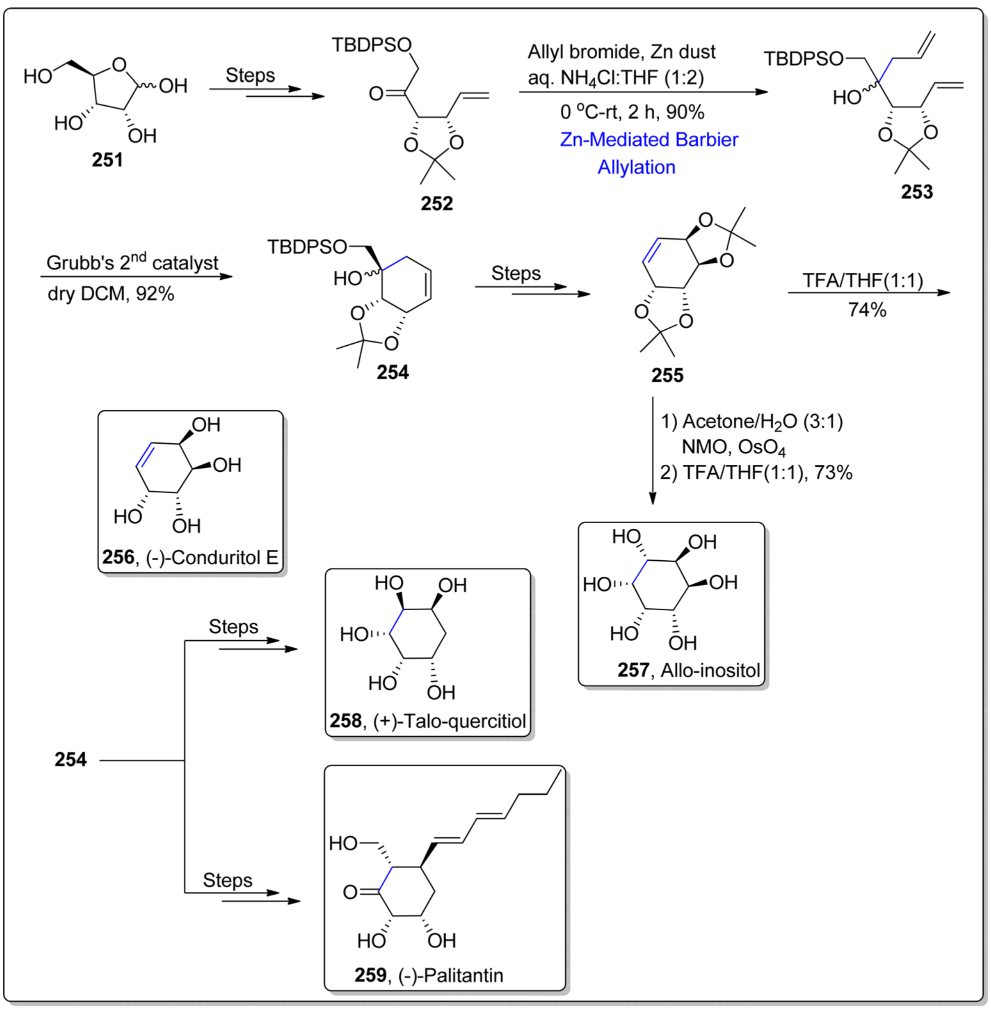
Various natural products can be synthesized in a feasible manner by employing carbohydrates as precursors.



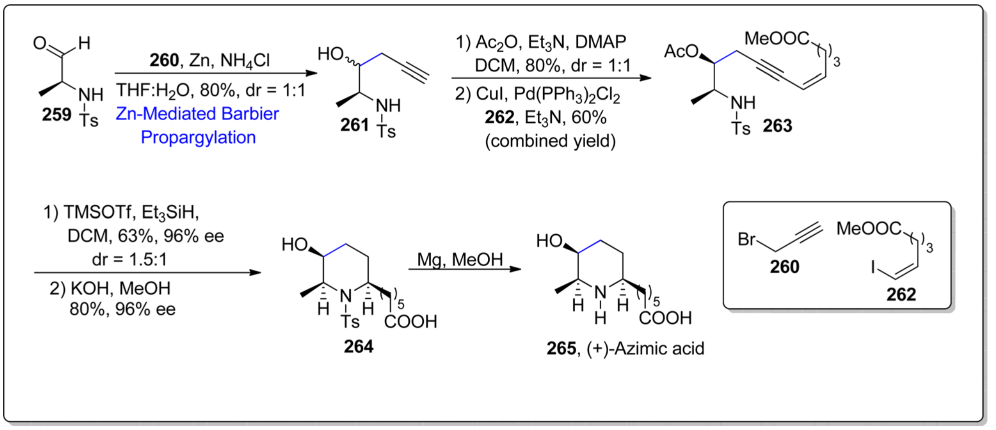
Scheme 30 Synthesis of (±)-8-demethylnicotlactone **250a** and its analogues.

Carbohydrates endowed with several hydroxyl group functionalities bear significant weightage owing to their enhanced water solubility and bio-availability. Synthesis of several natural products by employing a common intermediate is an efficient divergent route, exploited widely in past. On the similar ground, Sivakarishna *et al.*[133] in 2022, carried out the total synthesis of various polyhydroxylated natural products by employing an efficient divergent synthetic route. They demonstrated the synthesis of common intermediate by implementing Barbier allylation and ring closing metathesis as major steps. At first, D-Ribose was transformed to ketone **251** over several steps involving synthetic pathway. In the next step, the resulting ketone **252** was made to react with allylbromide *via* zinc dust promoted Barbier allylation in ammonium chloride:tetrahydrofuran (1 : 2) at 0 °C to room temperature, thereby furnishing the allylation product *i.e.*, diene **253** in 90% yield. The zinc metal was exploited within Babier reaction considering its inexpensive feature. The diene **253** was further subjected to ring closing metathesis (RCM) in the presence of Grubb's 2nd generation catalyst in dichloromethane to afford cyclohexenyl derivative **254** in (inseparable) diastereomeric mixture (92%). The cyclohexenyl derivative **254** was then utilized as a common intermediate to accomplish the synthesis of various natural products. This common intermediate **254** was treated over several steps to generate alkene **255**. The alkene **255** was made to undergo *syn*-dihydroxylation *via* NMO and osmium tetroxide followed by subsequent trifluoroacetic acid mediated acid hydrolysis, which ultimately resulted in the synthesis of allo-inositol **257** in 73% yield. On the other hand, conduritol E **256** was easily accessed in 74% yield (overall 10% yield) *via* acid hydrolysis of alkene **255**. The cyclohexenyl derivative **254** was also utilized to attain the asymmetric synthesis of (−)-palitantin **259** and (+)-talo-quercitol **258** (Scheme 31).

Azimic acid is a trisubstituted piperidine constituting natural product, extracted from the *Azima tetrucuntha* Lam. This hydrolyzed form of azimine alkaloid has been observed to manifest promising medicinal applications. In 2023, Gharpure *et al.*[134] developed a novel approach by subjecting enynyl amines to Lewis acid *i.e.*, TMSOTf (5/6-*endo*-dig) reductive hydroamination in the absence of metal to access piperidne and pyrrolidine based natural products. They conducted the formal synthesis of naturally occurring (+)-azimic acid by employing



Scheme 31 Synthesis of (−)-conduritol E **256**, allo-inositol **257**, (−)-palitantin **259** and (+)-talo-quercitol **258**.

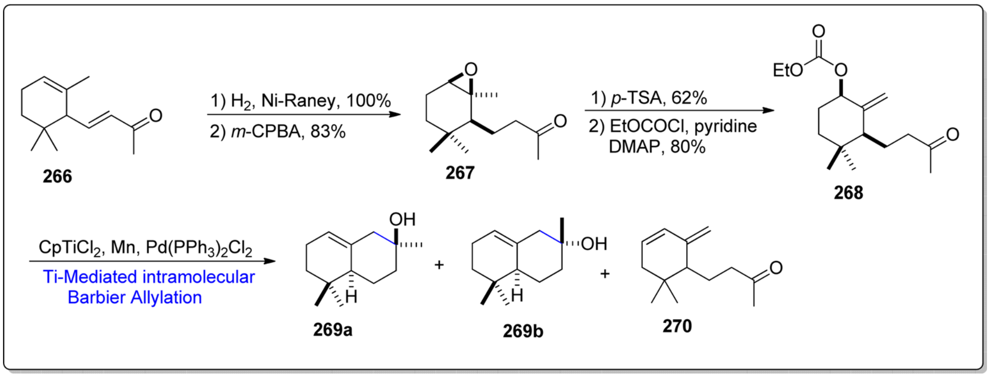


Scheme 32 Synthesis of (+)-azimic acid **265**.

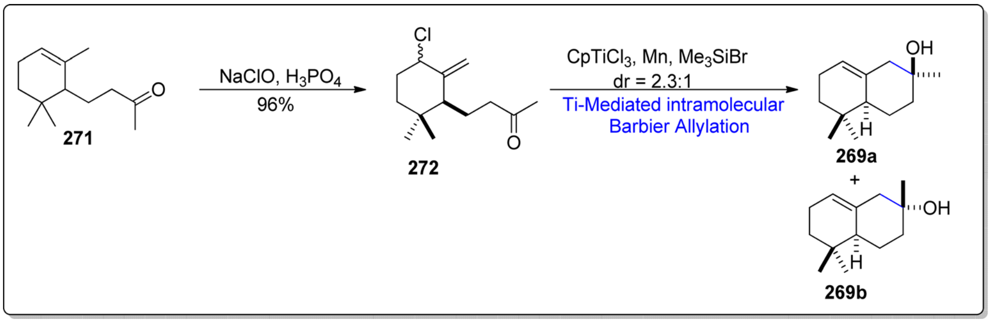
the beneficial aspects of the developed 5/6-*endo*-dig reductive hydroamination and zinc mediated Barbier reaction as key steps. In the first step, aldehyde **259** was made to undergo zinc promoted Barbier propargylation reaction with alkynyl bromide **260** in the presence of ammonium chloride and tetrahydrofuran:water to give alkynylamine **261** in 80% yield (dr = 1 : 1). The alcoholic functionality in compound **261** was then acylated with acetic anhydride followed by the Sonogashira coupling of resulting alkyne with vinyliodide **262** to give enynylamine **263** in 60% yield (syn isomer = 20%). In the next step, generated enynylamine **263** was made to undergo developed reductive hydroamination reaction by using TMSOTf, Et_3SiH in DCM to furnish diastereomeric mixture (dr = 1.5 : 1) of piperidine derivative in 63% yield. Enynylamine **263** was subjected to react with TMSOTf and Et_3SiH in dichloromethane followed by potassium hydroxide involving hydrolysis in methanol to furnish piperidine derivative **264**. The removal of tosyl group from piperidine derivative **264** was carried out in the presence of magnesium in methanol to result in azimic acid **265** (Scheme 32).

Ambergis is a naturally occurring compound, generally produced within the digestive cavity of sperms whales. It is known to constitute (−)-cis-α-ambrinol, which is a naturally occurring product and is highly acclaimed in perfumes industry. In 2023, Martinez *et al.*[135] reported the two pathways for the facile generation of (−)-cis-α-ambrinol **269a** (in 35% over all yield) from α-ionone/α-dihydroionone. In pathway A, market-ready α-ionone **266** was transformed to dihydroionone *via* reduction over raney-nickle, followed by *m*-CPBA mediated oxidation to afford the epoxide containing oxidized compound **267**. Epoxide ring opening reactions result in the synthesis of diverse and useful organic compounds.[136–138] The epoxide ring in compound **267** was treated with acid followed by the formation of carbonate on reaction with ethyl chloroformate. The synthesized carbonate **268** was subjected to Cp_2TiCl_2 mediated intramolecular Barbier allylation reaction to result in *cis*-α-ambrinol **269a** alongwith *trans*-α-ambrinol **269b** and compound **270** (Scheme 33).

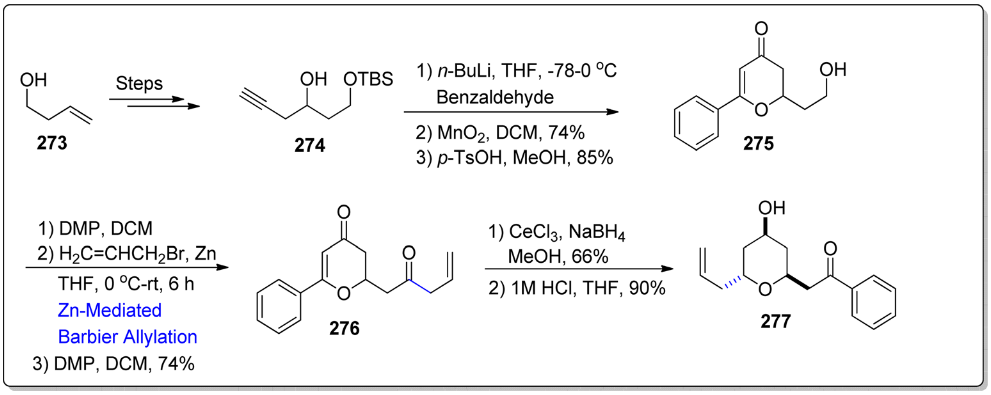
The second synthetic strategy for the synthesis of *cis*-α-ambrinol **269a** involved the chlorination of α-dihydroionone **271** with the addition of sodium perchlorate and phosphoric acid, thereby yielding allylic chloride **272** in 96% yield. The synthesized allylic chloride **272** was then exposed to $CpTiCl_2$ (generated within the reaction as a result of reduction of $CpTiCl_3$ with manganese) promoted intramolecular Barbier allylation in the presence of trimethyl silylbromide to afford the separable diastereomeric mixture of *cis*-α-ambrinol **269a** and *trans*-α-ambrinol **269b** in 2.3 : 1. (46% overall yield) (Scheme 34).



Scheme 33 Synthesis of (−)-cis-α-Ambrinol **269a**.



Scheme 34 Synthesis of (−)-cis-α-ambrinol **269a**.



Scheme 35 Synthesis of diospongin B analogue **277**.

Diospongin B, a disubstituted tetrahydropyran (THP) based natural product, was isolated from *Dioscorea spongiosa*'s rhizomes by Kadota and colleagues.[139] It has been known to demonstrate anti-osteoporotic activity. Recently, in 2024, Fernandes *et al.*[140] attempted the synthesis of Diospongin B analogue by utilizing Barbier reaction and Luche reduction as significant steps. Their synthetic route initiated with the preparation of alkynol **274** by treating alkenol **273** over few steps. The synthesized alkynol **274** was then added to 4-chlorobenzaldeyde with subsequent oxidation reaction and deprotection conditions to yield 2,3-dihydro-4*H*-pyran-4-one **275** in 85% yield. The hydroxyl group in tetrahydropyan compound **275** was subjected to oxidation proceeded by zinc mediated Barbier allylation reaction with allylbromide in tetrahydrofuran to afford diastereomeric mixture of corresponding alcohols. The Barbier product was further oxidized to afford diketone **276** in 74% yield. The diketone **276** was then transformed into diospongin B analogue **277** (in 90% yield) *via* Luche reduction in sequence with acidic hydrolysis (Scheme 35).

3 Conclusion

To conclude, a summary of recent applications of Barbier reaction and its variants to achieve a variety of natural products have been provided in this review. Barbier reaction is one of the renowned C–C bond forming reactions, which possibly results in the formation of optically active center, leading to the stereoselectivity in organic synthesis. This reaction has found several applications in synthetic organic chemistry, most significantly towards the total synthesis of a variety of natural products. In this regard, synthetic layouts of several alkaloids, lactones, terpenoids and lignans *etc.*, harnessing Barbier reaction as one the significant steps, have been overviewed here, documented within 2020–2024. For the synthesis of each natural product, utility of corresponding Barbier methodology has also been highlighted. We envision that this communication will stimulate the synthetic chemists to further delve within the Barbier reaction to unveil its potential beneficiary roles in organic synthesis.

Data availability

No new data has been generated and all data is contained in the manuscript.

Author contributions

A. M. wrote the manuscript. M. N. A., S. G. K., N. A. and U. N. did literature survey and data analysis. A. M., H. A., A. R. C. and A. I. did data analysis and acquired funding. A. F. Z. supervised the project. All authors reviewed and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

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