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Cite this: *RSC Adv.*, 2023, **13**, 32975

Mukaiyama aldol reaction: an effective asymmetric approach to access chiral natural products and their derivatives/analogues

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Received 26th July 2023
Accepted 21st October 2023

DOI: 10.1039/d3ra05058k

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The Mukaiyama aldol reaction is generally a Lewis-acid catalyzed cross-aldol reaction between an aldehyde or ketone and silyl enol ether. It was first described by Mukaiyama in 1973, almost 5 decades ago, to achieve the enantioselective synthesis of β-hydroxy carbonyl compounds in high percentage yields. Mukaiyama aldol adducts play a pivotal role in the synthesis of various naturally occurring and medicinally important organic compounds such as polyketides, alkaloids, macrolides, *etc.* This review highlights the significance of the Mukaiyama aldol reaction towards the asymmetric synthesis of a wide range of biologically active natural products reported recently (since 2020).

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1. Introduction

The Mukaiyama aldol reaction was first reported by Mukaiyama in 1973, about 50 years ago.[1] He carried out the aldol reaction of an aldehyde or ketone with trimethyl silyl enol ether by utilizing titanium chloride as a catalyst.[2] The electrophilic nature of carbonyl compounds is enhanced using Lewis acid catalyst, thereby leading to a facile attack by the carbon nucleophile. Similarly, Mukaiyama and his coworker Ishida implemented the aldol reaction between silyl enol ether, which was obtained as a derivative of crotonaldehyde, and cinnamaldehyde dimethyl acetal. The aldol reaction, involving these substituents was named vinylogous Mukaiyama aldol reaction (VMAR).[3–5] VMAR results in the synthesis of double bonds containing bulky structural skeletons, which can then be subjected to various reactions including organometallic reactions, dihydroxylation and epoxidation (Scheme 1).[6]

The general mechanism of the Mukaiyama aldol reaction involves the attack of aldehyde oxygen to titanium followed by the release of a chloride ion. The chloride ion then attacks silylenol ether **6** to generate enolate and trimethylsilyl chloride. The enolate then attacks the electron-deficient carbonyl carbon followed by the addition of water to give the Mukaiyama aldol product **7** (Scheme 2).

Silicon[7–9] and boron enolates[10–12] were also employed by Mukaiyama and co-workers to execute the aldol reaction, which is highly stereoselective in nature. A strong base is employed to abstract a proton from the carbonyl compound to generate silicon enolate, which is then reacted with trialkylsilyl chloride.[13] Then, this silicon enolate further undergoes reaction with a carbonyl compound by utilizing a Lewis acid as catalyst. In general, the Mukaiyama aldol adduct is formed by the involvement of an open transition state, however, boron enolates require the use of a weak base with boron Lewis acid and the reaction proceeds through a transition state that is cyclic in nature.[14,15]

Various other Lewis acids *i.e.*, zinc chloride, iron chloride, tin chloride, boron trifluoride and aluminium trichloride have been utilized after the employment of titanium tetrachloride in Mukaiyama aldol reactions.[16] Moreover, there have been further advancements in this reaction by the application of numerous other electrophiles such as acetals, thioacetals, ketimines, imines and ketones.[17–20] Besides electrophiles, many other nucleophiles have now been employed in the Mukaiyama aldol reaction including allylsilanes, silicon dienolates and silyl cyanides.[21,22]

Moreover, a facile reaction between silicon enolates and acetals has been observed in trimethylsilyl trifluoromethanesulfonate, trityl perchlorate and trityl hexachloroantimonate mediated Mukaiyama aldol reactions.[23] In addition, utilization of non-metallic Lewis acids *i.e.*, triphenyl methyl salt has also been reported.[24a] Previously, almost all reported Mukaiyama aldol reactions were carried out in organic solvents. Despite water being an easily accessible and eco-friendly solvent, it was not considered for Mukaiyama aldol reactions due to the possibility of decomposition of silicon enolates. However, later studies revealed that lanthanide triflate catalyzed Mukaiyama aldol reactions were possible using water as solvent, resulting in enantioselective synthesis of aldol adducts in high yields.[24b]

β-Hydroxy carbonyl compounds with two asymmetric centers are produced as a result of the reaction between enolates and carbonyl compounds.[25,26] C–C bonds are formed as a result of this reaction leading to the generation of complicated structures. Sakurai–Hosomo allylation[27] and hetero-Diels–Alder reactions are examples of such C–C bond forming reactions.

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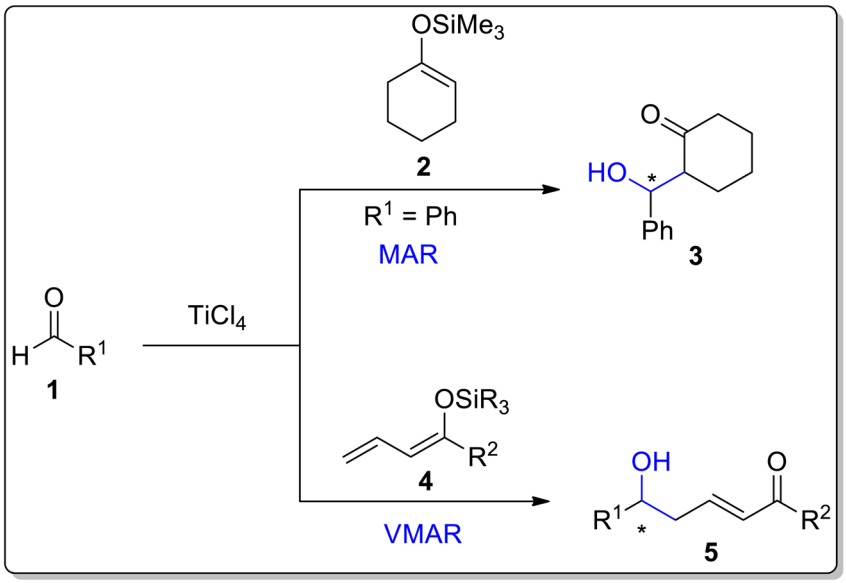
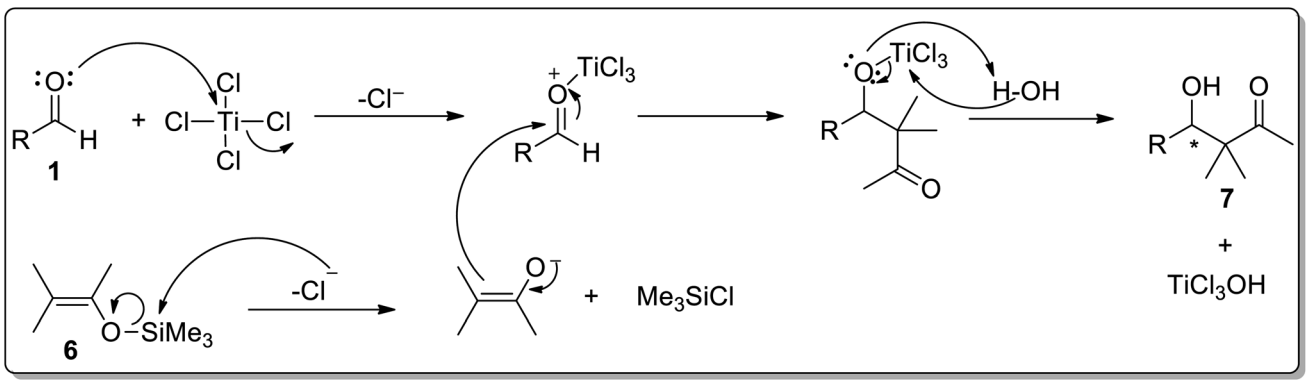


Scheme 1 Titanium chloride catalyzed Mukaiyama and vinylogous Mukaiyama aldol reactions.[6]



Scheme 2 The general mechanism of the $TiCl_4$ catalyzed Mukaiyama aldol reaction.[1,7]

Moreover, chiral Lewis acid catalysts are used to carry out asymmetric transformations. Various natural products constitute β-hydroxy carbonyl groups in their structural framework. Specifically, naturally occurring macrolides and polyketides are known to be derived from β-hydroxy carbonyl compounds. The stereocontrol nature of the Mukaiyama aldol reaction with ambient reaction conditions paved the way towards the synthesis of various natural products.[28–30] There have been

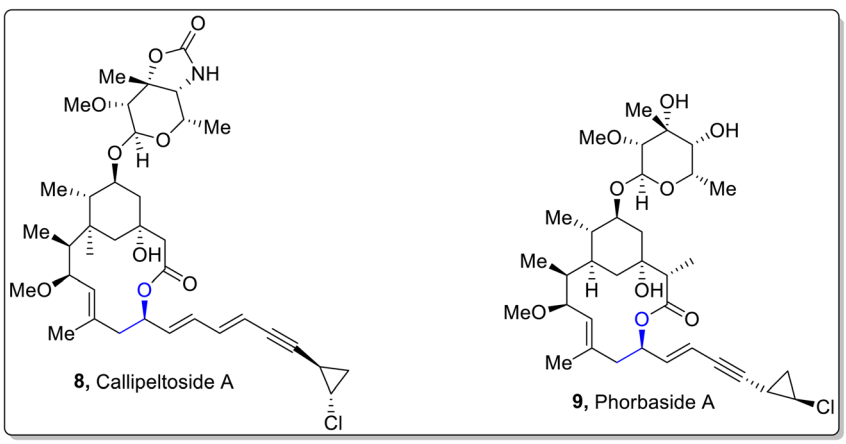


Fig. 1 Structures of some naturally occurring compounds involving Mukaiyama aldol reactions in their total synthesis.

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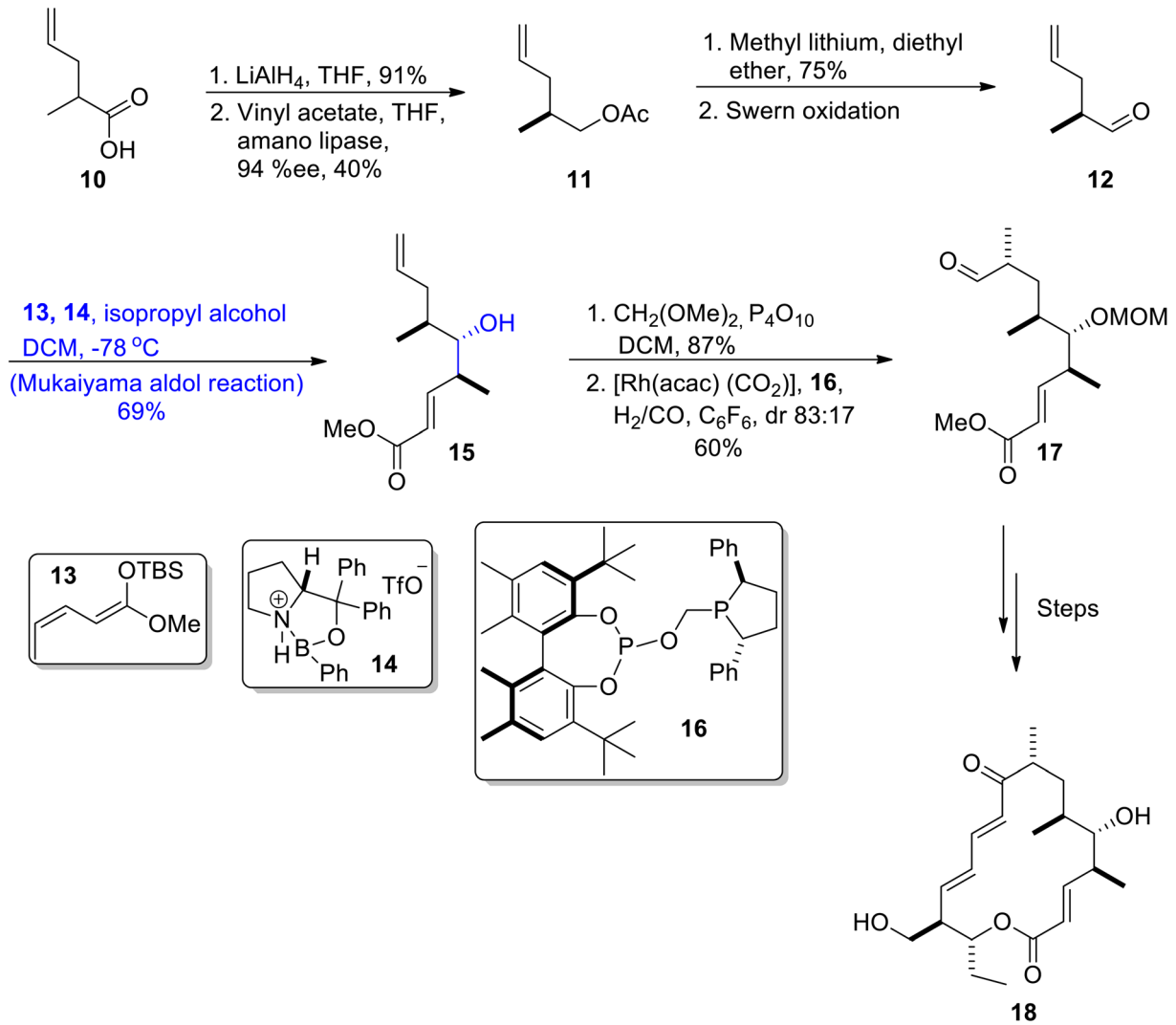
several reports on the incorporation of MAR and VMAR in the synthesis of various natural products. Some of their structures are given in Fig. 1.[31,32]

The synthesis of natural products is a very appealing yet complicated process and there has been a great focus on the procurement of biologically important natural products *via* facile synthetic routes.[33–36] The role of the Mukaiyama aldol reaction towards the total synthesis of organic compounds and natural products has been summarized by various research groups previously.[37,38] The objective of our review is to provide the recent applications of Mukaiyama aldol reaction towards the synthesis of natural products/pharmaceutically important organic compounds, thereby covering the literature reported during the past three years (2020–2023).

2. Review of the literature

2.1. Synthesis of macrolide based natural products

The antibacterial potential of *Streptomyces* species is well known, they are also source of various macrolides. Aldgamycin N has been isolated from *Streptomyces* strain HK-2006-1, and these macrolides have been found to be highly potent against numerous bacterial strains *i.e.*, *Staphylococcus aureus* 209P.[39,40] Aldgamycins are D-mycinose containing mycinolide macrolides having glycosylation at hydroxyl group on carbon 20.[41,42] Herle *et al.*[43] reported the total synthesis of mycinolide IV **18**, which led to the synthetic pathway towards aldgamycin N. The first step of their synthetic route involves the reduction of compound **10** followed by its reaction with vinyl acetate and amino lipase in tetrahydrofuran, which resulted in compound **11** in 40% yield with 94% ee. Acetate **11** was then reacted with methyl lithium in the presence of diethyl ether followed by Swern oxidation to yield aldehyde **12**. In the following step, compound **12** was subjected to the Mukaiyama aldol reaction by treatment with silyl enol ether **13** and compound **14** in isopropyl alcohol and DCM, which resulted in the synthesis of aldol adduct **15** in 69% yield. The compound **15** was further reacted with $CH_2(OMe)_2$, P_4O_{10}, dichloromethane followed by its reaction with $[Rh(acac)(CO)_2]$, and compound **16** to obtain aldehyde **17** in 60% yield. Aldehyde **17** was then



Scheme 3 Synthesis of mycinolide IV **18**.

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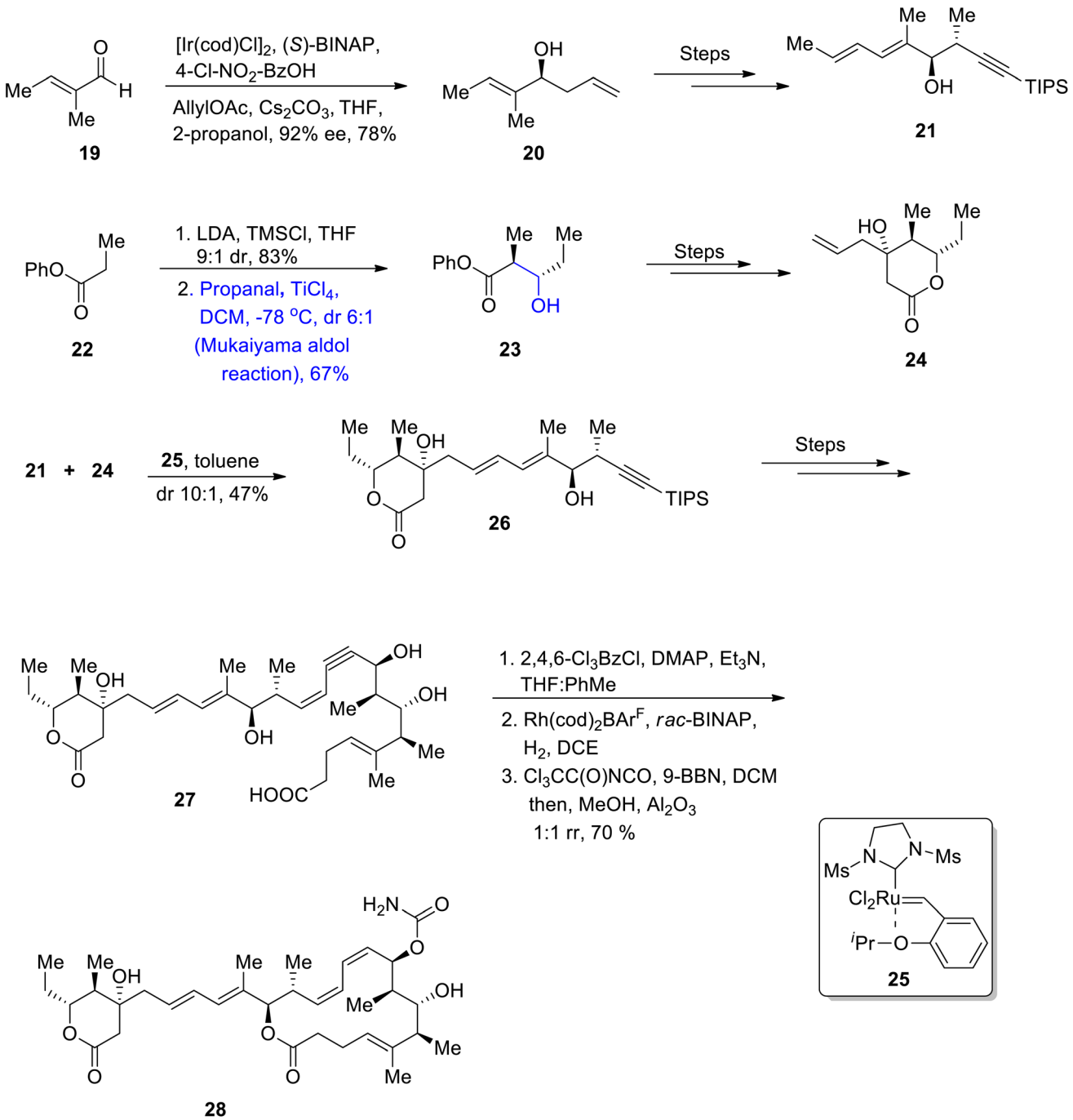

Scheme 4 Synthesis of leiodermatolide A **28**.

reacted over a number of steps to synthesize target molecule **18** (Scheme 3).

The Lithistid sponge of the genus *Leiodermatium* is the main source of anti-mitotic leiodermatolide A, which disrupts the arrangement of microtubules, thereby inhibiting uncontrolled cell division.[44–46] This marine macrolide has found ample significance in medicinal fields; however, its usage is limited as it is not available in sufficient amounts. These factors have led to numerous efforts towards its total synthesis. In 2021, Siu *et al.*[47] reported the efficient and facile synthesis of this structurally complex and medicinally important macrolide by utilizing catalytic enantioselective hydrogenative allylation, the Mukaiyama aldol reaction, crotylation and propargylation as key steps. For this purpose, they obtained homo allylic alcohol **20** in 78% yield with 92% enantiomeric excess as a result of the iridium catalyzed reaction of aldehyde **19** with 4-chloro-nitro benzyl alcohol using (*S*)-BINAP followed by allylation. Homo-allylic alcohol **20** was further reacted *via* several steps to obtain compound **21**. In the next step, ester **22** reacted with lithium diisopropylamide, TMSCl in the presence of THF followed by

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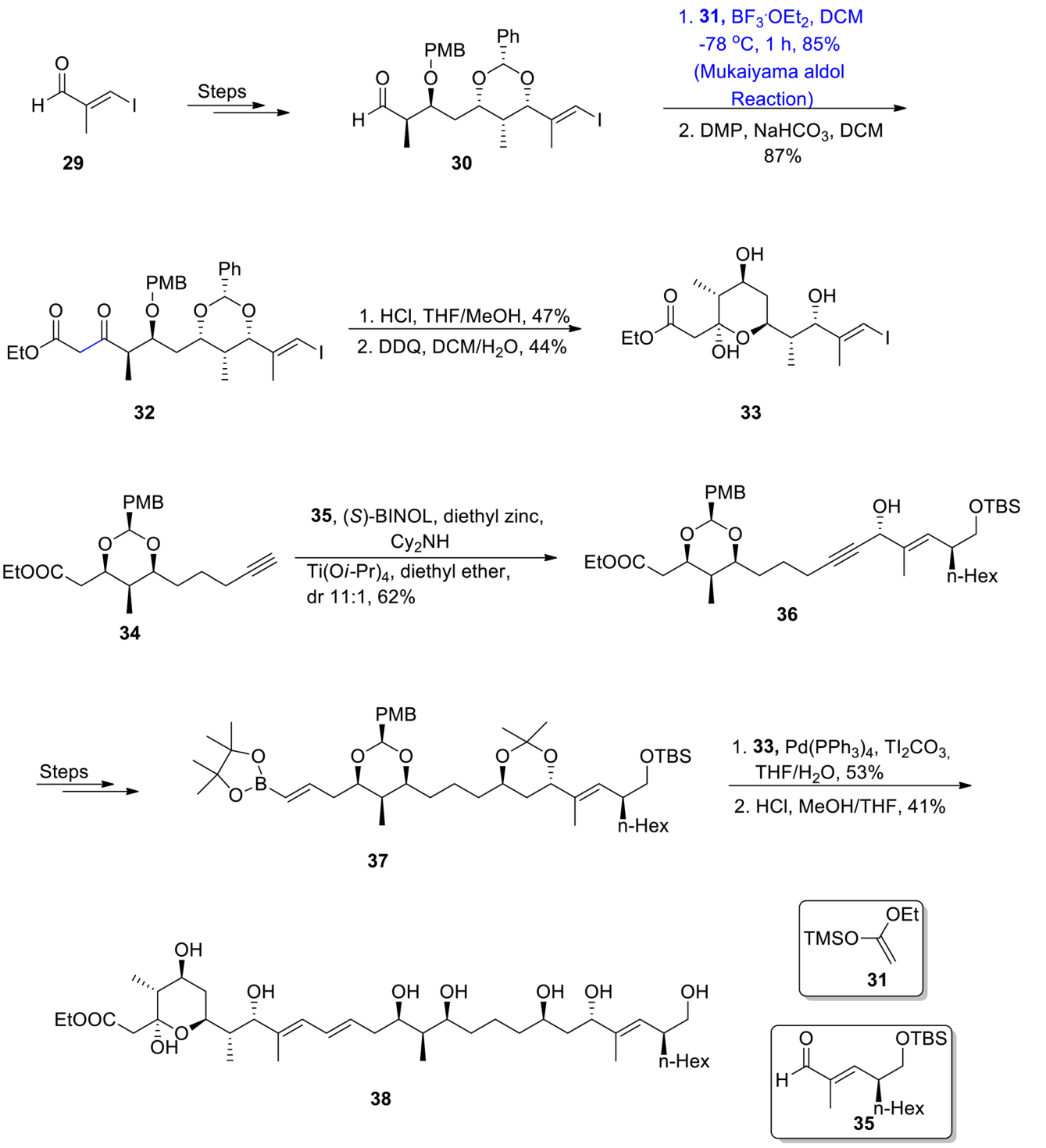

Scheme 5 Synthesis of the C1–C27 Fragment of stambomycin D **38**.

the titanium tetrachloride catalyzed Mukaiyama aldol reaction reacting with propanal in the presence of DCM, which resulted in the synthesis of adduct **23**. Compound **23** was then transformed to compound **24** *via* several steps. Compounds **21** and **24** were then coupled in the presence of **25** and toluene to obtain dienyne **26** in 47% yield, which was then reacted *via* several steps to give conjugated enyne **27**. Later, the conjugated enyne **27** was subjected to react over three distinct steps (including Yamaguchi lactonization) to accomplish the synthesis of leiodermatolide A **28** in 70% yield in a 1 : 1 racemic ratio (Scheme 4).

Stambomycins are naturally occurring and biologically active macrolides containing two chiral centers that are known to be obtained from *Streptomyces ambofaciens*.[48] Confirmation of the

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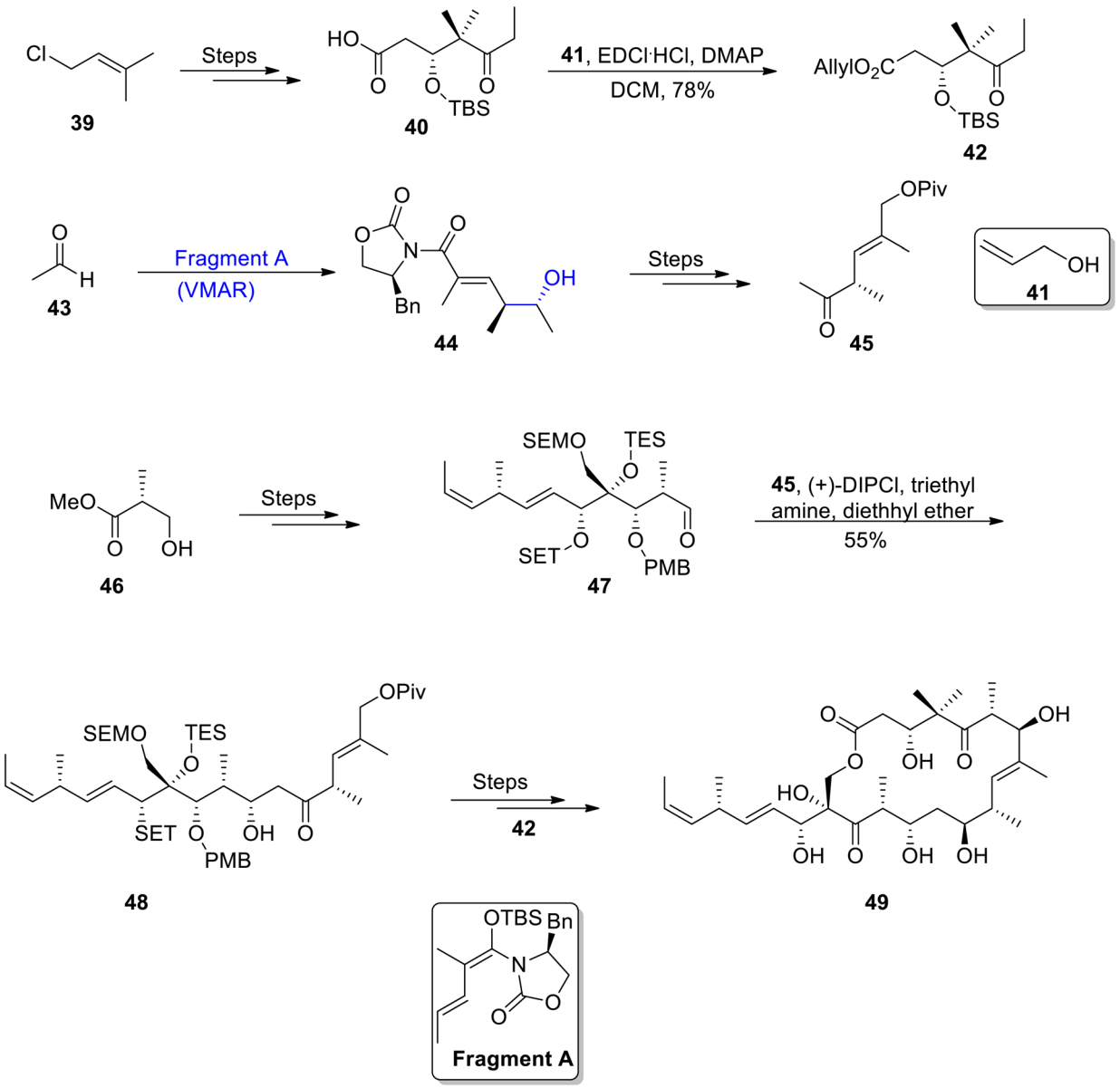
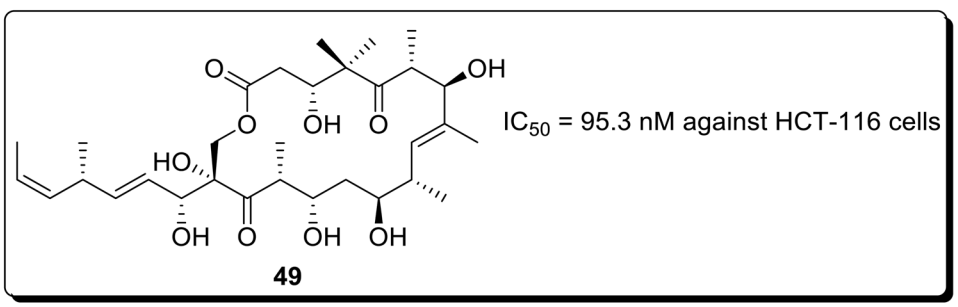
structural framework and stereochemistry of natural products is one of the key factors in devising an efficient synthetic strategy for these molecules. Researchers have confirmed the planar structure of stambomycin D by employing NMR spectroscopy and various efforts have been carried out to get information about their stereochemistry *via* predictive sequence





Scheme 6 Synthesis of desepoxy-tedanolide C **49**.

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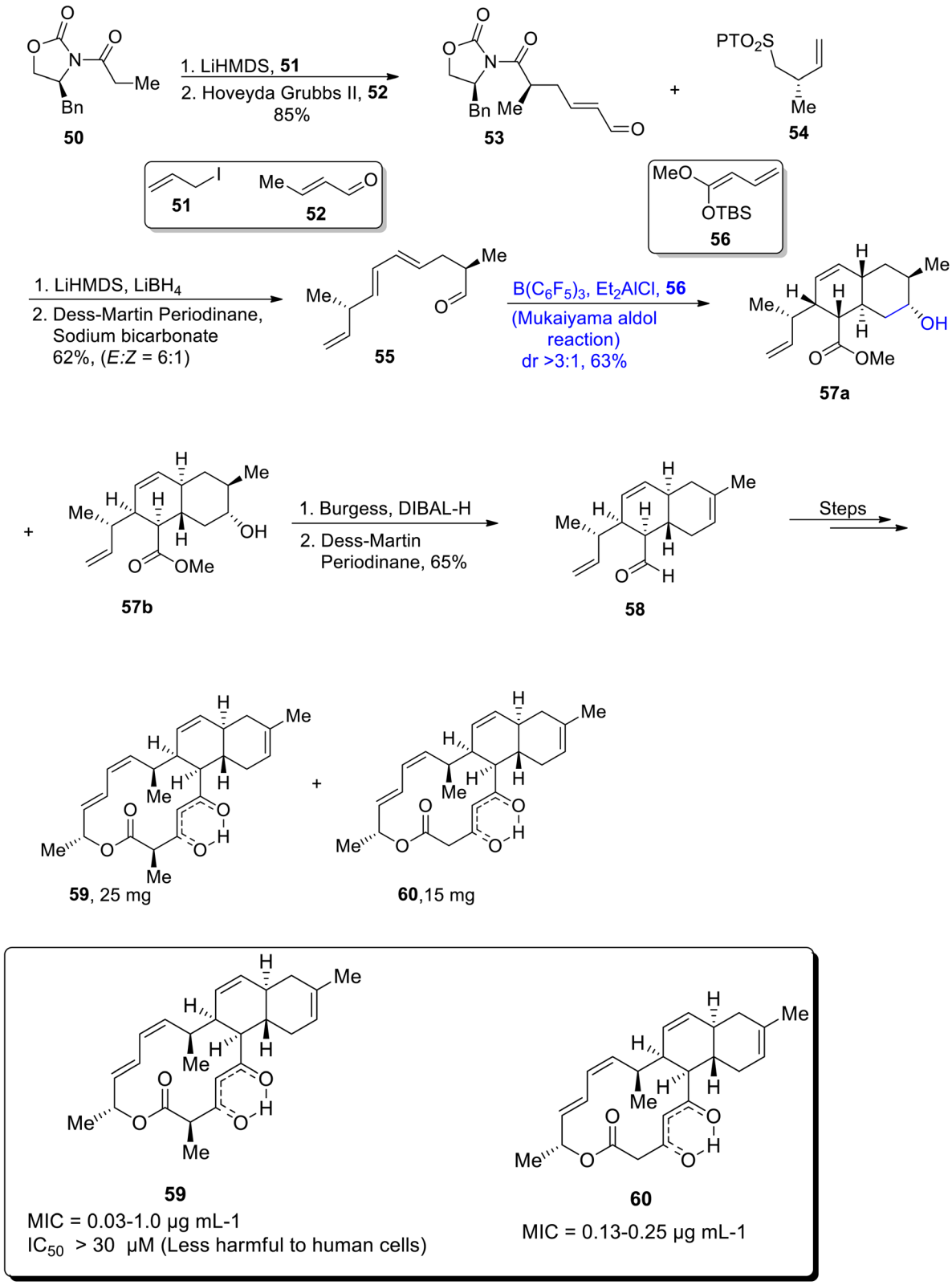

Scheme 7 Synthesis of anthracimycin **59** and anthracimycin B **60**.

analysis.[49,50] In order to ensure the correct stereochemistry of stambomycin D, Lim *et al.*[51] in 2021 reported its total synthesis and then justified its structure through nuclear magnetic resonance spectroscopy. They employed the Mukaiyama aldol reaction in their synthetic approach towards the synthesis of C1–C27 fragment of stambomycin D. The synthesis was

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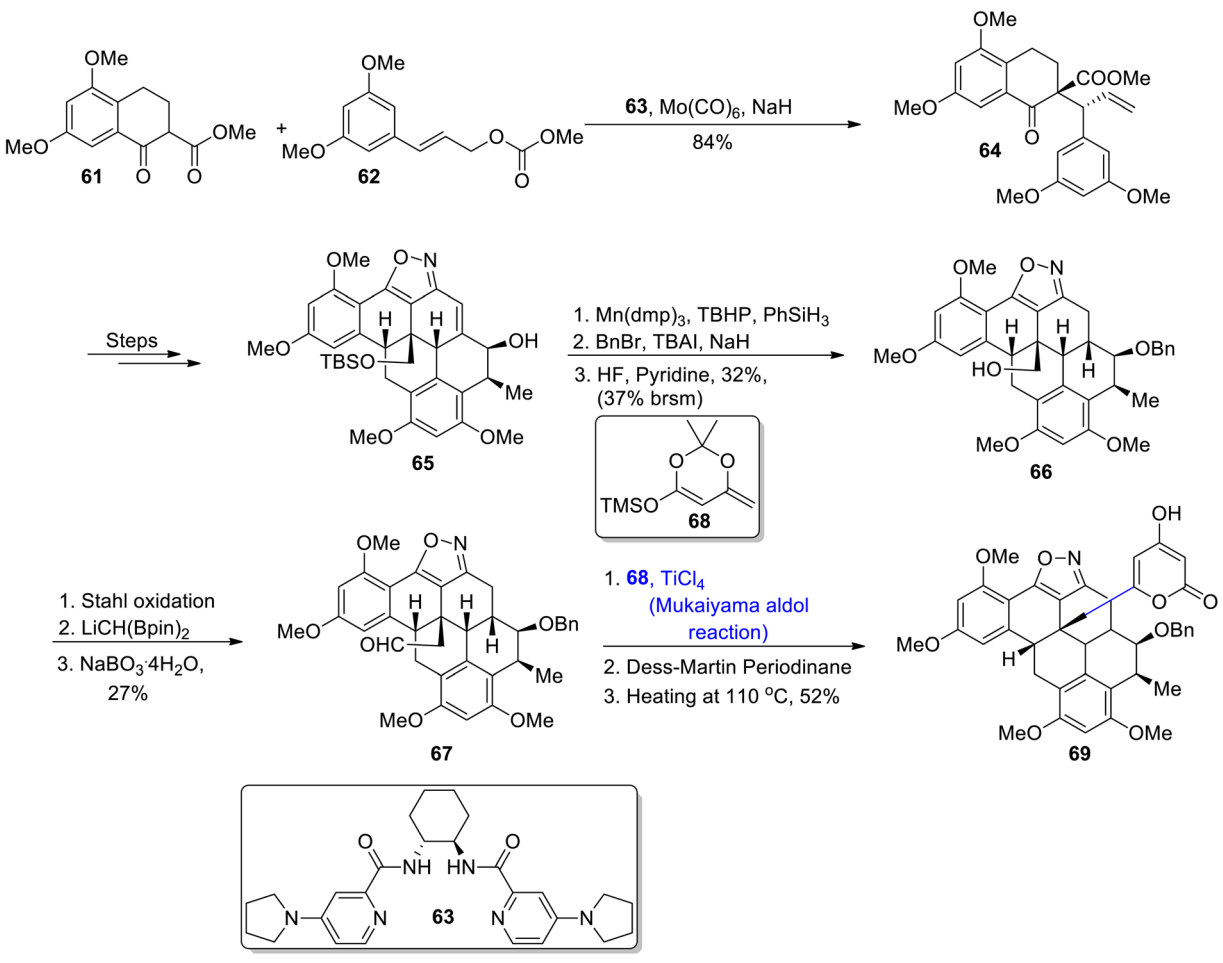
inaugurated with the procurement of compound **30** by reacting aldehyde **29** over a number of steps. Then, compound **30** was subjected to react with silyl enol ether **31** by employing the Mukaiyama aldol reaction, using boron trifluoride diethyl etherate catalyst in DCM, which gave the Mukaiyama aldol product in 85% yield. The next step involved the Dess–Martin periodinane mediated oxidation to obtain β-keto ester **32** in 87% yield. β-Keto ester **32** was reacted with HCl by using a suitable solvent ratio of methanol and THF, followed by deprotection of the alcoholic group to furnish C1–C11 fragment **33** in 44% yield. Furthermore, fragments C13–C22 **34** and C23–C27 **35** were prepared individually, which were coupled in the presence of (*S*)-BINOL, diethyl zinc and Cy_2NH followed by the addition of $Ti(Oi\text{-}Pr)_4$ and diethyl ether, which resulted in the synthesis of propargylic alcohol **36** in 62% yield. Propargylic alcohol **36** was later converted to vinylboronic ester **37**. This synthesized ester **37** was then coupled with C1–C11 fragment **33** by using palladium tetrakistriphenyl phosphine and Tl_2CO_3, thereby leading to the synthesis of target molecule **38** in 41% yield by using the deprotection strategy (Scheme 5).

Tedanolide C is a naturally occurring macrolide extracted from sea sponges *i.e. Ircinia* sp. Excellent cytotoxic activity has been found to be demonstrated by tedanolide C against HCT-116 cell lines *i.e.*, 95.3 nM.[52] Moreover, it plays an important role in interrupting the biosynthesis of proteins.[53] The synthesis of tedanolide C was considered to be a troublesome task due to the primary hydroxyl group containing few macrolactone moieties. Thus, Lucke *et al.*[54] reported the total synthesis of desepoxy-tedanolide C by utilizing the Mukaiyama aldol reaction, Kiyooka aldol reaction and Julia–Kocienski olefination as key steps. The first step of the synthetic scheme involved the synthesis of carboxylic acid **40** which was further reacted with compound **41** in the presence of EDCl, dimethyl aminopyridine and dichloromethane to obtain allyl ester **42** in 78% yield. Fragment A was subjected to the Mukaiyama aldol reaction upon treatment with acetaldehyde **43**, which resulted in the synthesis of aldol adduct **44**. Compound **44** was later reacted over a number of steps to obtain fragment **45**. In the second part of their synthetic scheme, ester **46** was reacted over number of steps, which gave aldehyde **47**. Aldehyde **47** was further subjected to react with previously synthesized fragment **45** in the presence of DIPCl, triethyl amine and diethyl ether, which resulted in the synthesis of compound **48** in 55% yield. Compound **48** was then treated over a number of steps, thus leading to the synthesis of target molecule *i.e.*, tedanolide C **49** (Scheme 6).



Scheme 8 Synthesis of the carbon skeleton of A-74528 **69**.

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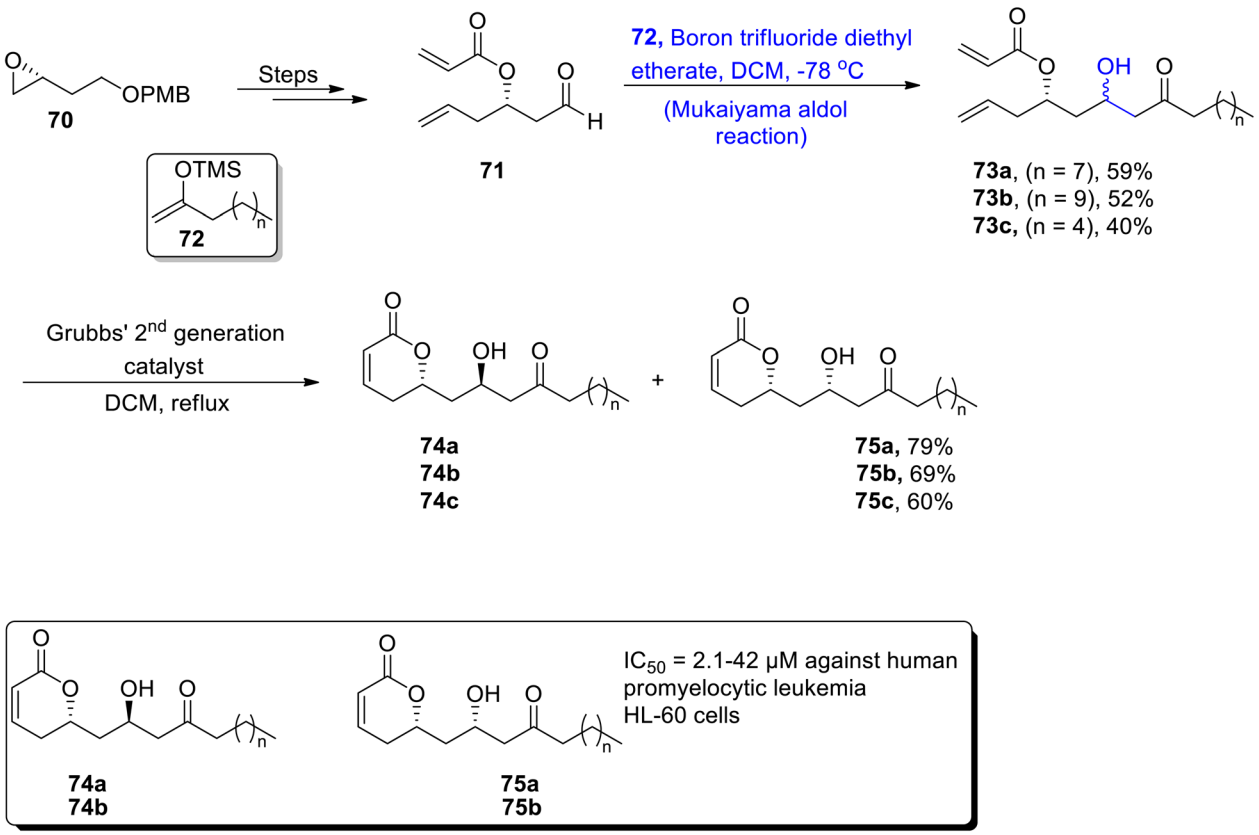
The ability of bacteria to develop resistance against numerous antibiotics has reached dangerous levels, which has led to emphasis on the synthesis and discovery of non-resistant antibiotics to treat bacterial diseases. Anthracimycin is a non-resistible, naturally occurring macrolide that is highly potent against various bacterial strains *i.e. Mycobacterium tuberculosis*, *S. aureus* and *B. anthracis*.[55–57] They are not dangerous to normal human cells and perform their biological activities effectively. Taking into account the high demand of non-resistible antibiotics, Tian *et al.*[58] in 2022 devised a concise and efficient synthetic strategy for the synthesis of pharmaceutically important macrolides *i.e.* anthracimycin and anthracimycin B in 25 mg and 14 mg, respectively. They carried out the Mukaiyama aldol reaction, intramolecular Diels–Alder reaction and olefin-cross metathesis as key steps in their synthetic approach. The synthesis began with the generation of aldehyde **53** in 85% yield from the Evan's symmetric alkylation of xazolidinone **50** followed by treatment with crotonaldehyde *via* olefin cross-metathesis. Sulfone **54** was then made to react with aldehyde **53** in the presence of lithium hexamethyldisilazide and lithium borohydride followed by Dess–martin periodinane oxidation to obtain diene **55** in 62% yield. Diene **55** further underwent triaryl borane catalyzed Mukaiyama aldol reaction with silyl ketene **56** in diethyl aluminium chloride which gave more than 3 : 1 diastereomeric ratio of trienes **57a** and **57b** in 63% yield. In the next step, reduction of ester with Burgess reagent in the presence of DIBAL-H took place, which gave aldehyde **58** in 65% yield on further treatment with Dess–Martin periodinane. This aldehyde **58** later reacted over three different steps to give anthracimycin **59** and anthracimycin B **60** in 25 mg and 14 mg, respectively (Scheme 7).

2.2. Synthesis of polyketide-based natural products

A-74528 is a naturally occurring polyketide, that has been isolated from *Streptomyces* strains. They are highly remarkable in medicinal chemistry as they restrain the release of 2′-phosphodiesterase, hence exhibiting high potency against viral and cancerous cells. Their structure comprises six fused rings along with a pyrone side chain and six asymmetric centers.[59] Despite their significant biological activity, there have been minor contributions towards their total synthesis. Maeir *et al.*,[60] in 2022 attempted to report the total synthesis of A-74528 by employing the Mukaiyama aldol reaction, 1,3-dipolar cycloaddition, spiro epoxide annulation and hydroarylation as major steps. In the first step, tetralone **61** was treated with carbonate **62** by employing a bis-pyridine ligand to obtain ketoester **64** in 84% yield. Later, compound **65** was obtained in 52% yield by reacting keto ester **64** over a number of different steps. Compound **65** was treated with Shenvi's HAT hydrogenation, followed by treatment with benzyl bromide in tetrabutyl aluminium iodide and sodium hydride. Further treatment with HF in the presence of pyridine gave neopentylic alcohol **66** in



Scheme 9 Synthesis of caprolactones A1 and A2, caprolactones **74a** and **75a**, B1 and B2, **74b** and **75b** and their derivatives **74c** and **75c**.

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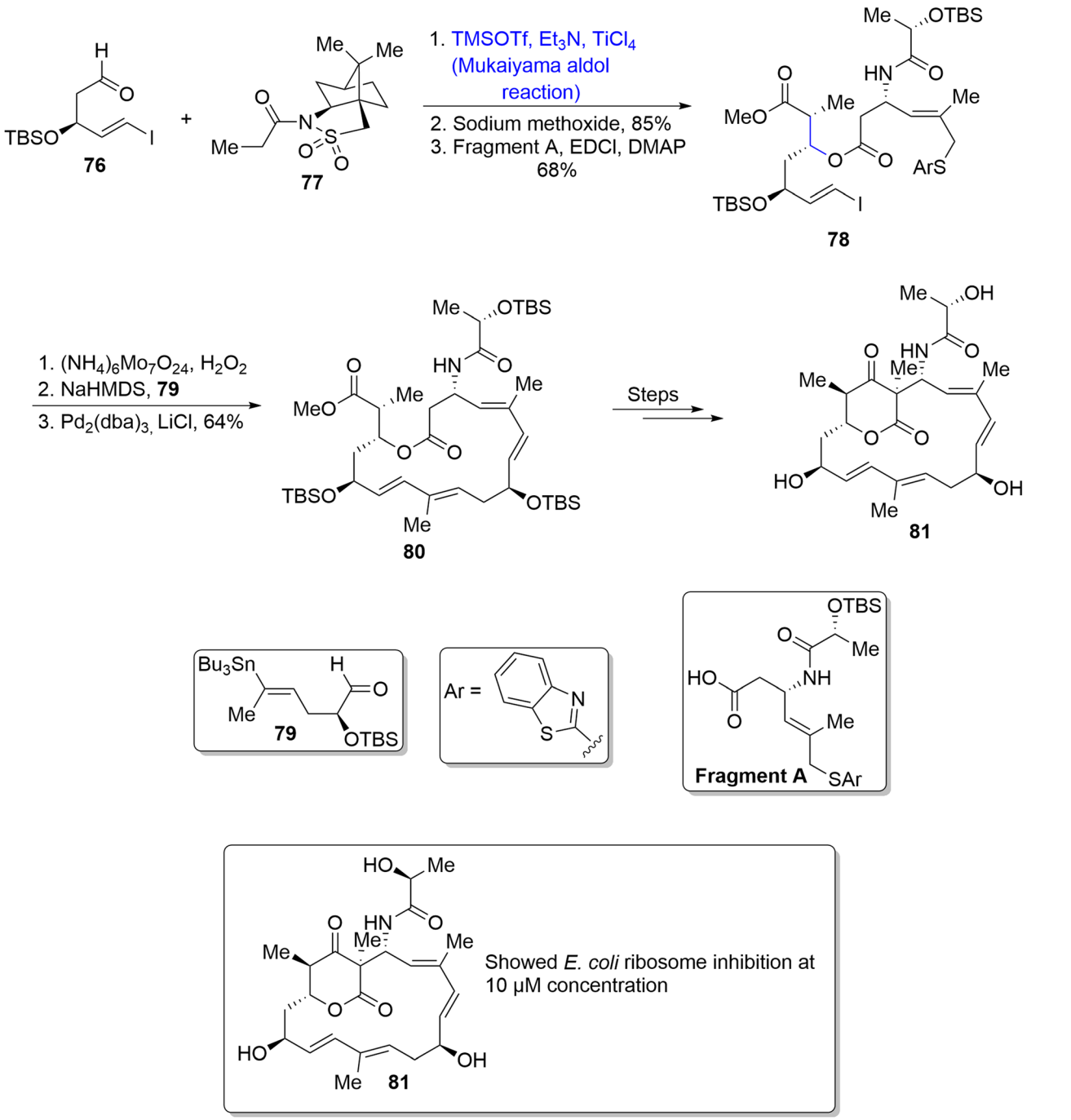
32% yield with 37% brsm. The synthesized alcohol **66** was further subjected to Stahl oxidation, then subsequent treatment with $LiCH(BPin)_2$ and $NaBO_3 \cdot 4H_2O$ resulted in the synthesis of aldehyde **67** in 27% yield. The synthesized aldehyde **67** was subjected to titanium chloride catalyzed Mukaiyama aldol reaction with silyl enol ether **68**. Thus, the carbon skeleton of A-74528 **69** was obtained in 52% yield on subsequent oxidation with Dess–Martin periodinane (Scheme 8).

It has been discovered that many coloured substances isolated from coloured aphids are highly biologically active and are found to be highly potent against a number of bacterial diseases. They are also found to inhibit the proliferation of cancerous cells.[61] In a similar way, Inai *et al.*, isolated pharmacologically important organic compounds from Cryptomyzus species, as a result four different polyketides *i.e.*, caprolactones A_1, A_2, B_1, and B_2 were obtained. These polyketides are α,β-unsaturated compounds that have been derived



Scheme 10 Synthesis of iso-lankacidin **81**.

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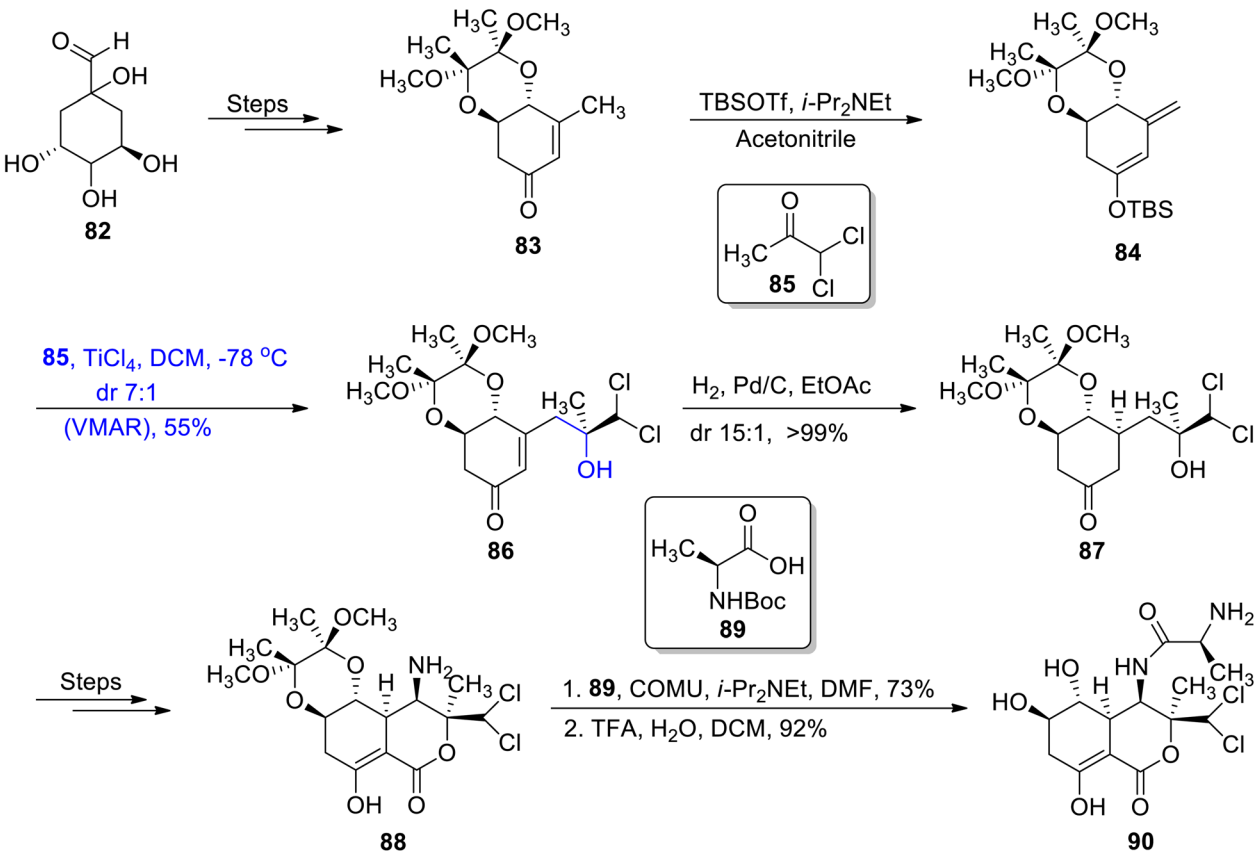
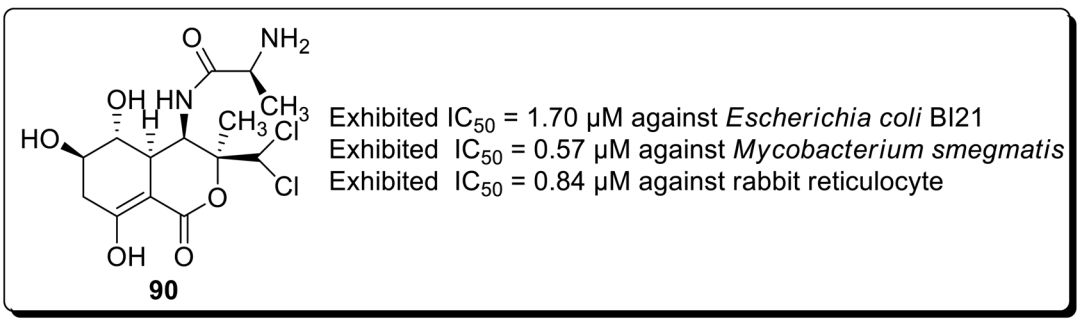
from δ-lactones.[62] These are found to be effective against various diseases as they inhibit the human immunodeficiency virus activity and interrupt the uncontrolled cell division. Inai *et al.*,[63] reacted compound **70** through a number of steps to obtain aldehyde **71**, which was further subjected to react with TMS-substituted moiety **72** *via* a boron trifluoride diethyl etherate catalyzed Mukiyama aldol reaction to give **73a**, **73b** and **73c** in 59%, 52% and 40% yields, respectively. Each of them was reacted with a Grubbs second generation catalyst in DCM to synthesize a mixture of **74a** and **75a** (caprolactones A_1 and A_2), **74b** and **75b** (caprolactones B_1 and B_2) and **74c** and **75c** in 79%, 69% and 60% yields, respectively (Scheme 9).

Soil bacteria *i.e. Streptomyces rochei* are a source of numerous naturally occurring compounds including lankacidins. Lankacidins are pharmacologically important polyketides which are found to be highly potent against bacterial diseases. Their structural formulae contain huge 17-membered cyclic rings.[64,65] Cai *et al.*[66] in 2020 reported the synthesis of naturally occurring members of lankacidin family *i.e.*, iso- and seco-lankacidin and evaluated their efficacy against bacterial strains. Iso-lankacidin was synthesized by involving the Mukaiyama aldol rection as one of the main steps in their synthetic scheme. The synthesis began with treatment of l-camphorsultam derivative **76** with aldehyde 77 *via* titanium chloride catalyzed Mukaiyama aldol reaction (dr = more than 20 : 1). Furthermore, reaction of the Mukaiyama aldol product with sodium methoxide followed by esterification with EDCl in the presence of DMAP resulted in the synthesis of compound **78**





Scheme 11 Synthesis of bactobolin A **90**.

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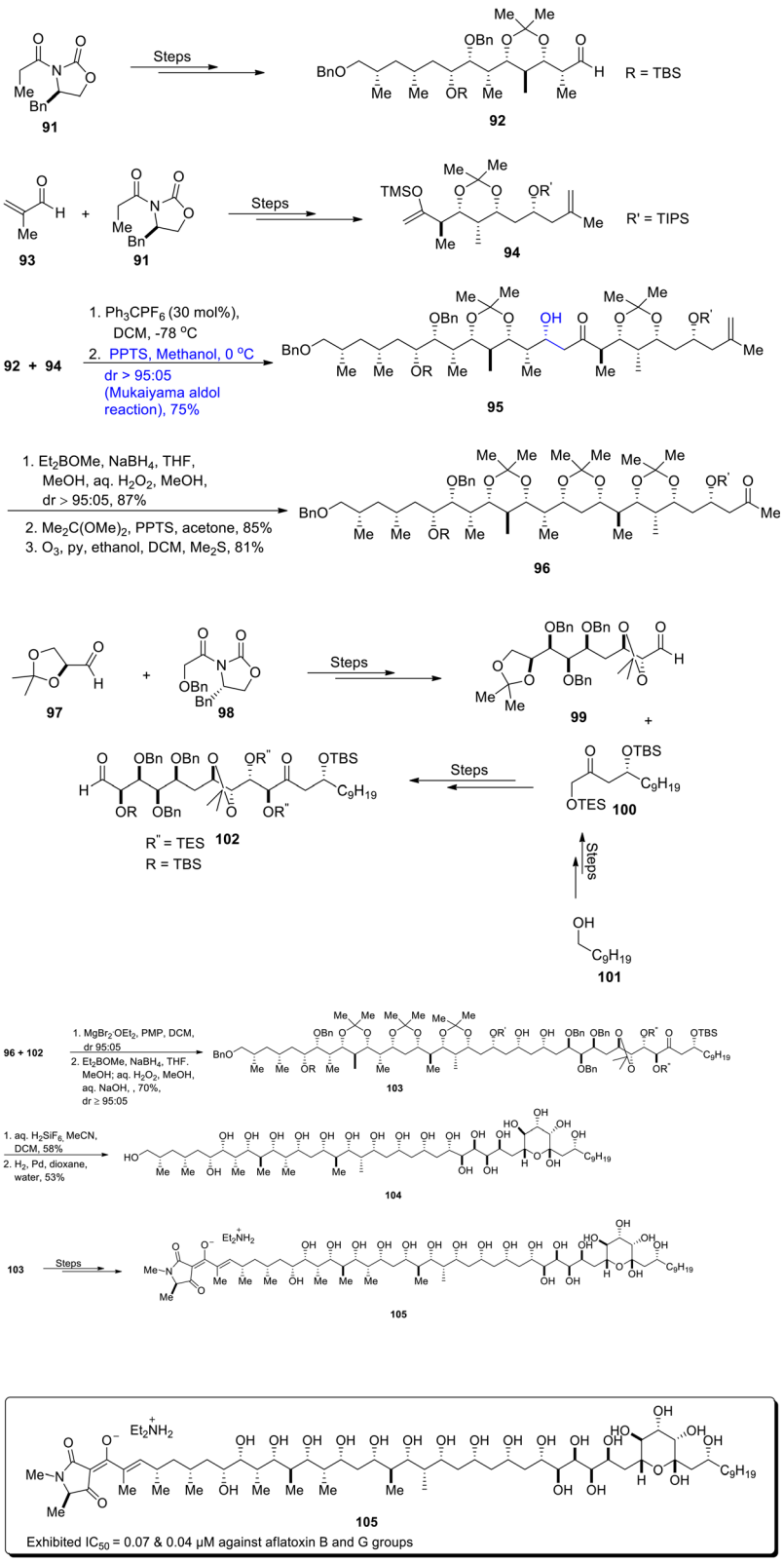
in 68% yield. Compound **78** was further subjected to three different steps; oxidation, Julia–Kocienski olefination and Stille coupling to obtain the macrocyclic ring **80** in 64% yield. Compound **80** was then reacted again over three steps to synthesize iso-lankacidin **81** (Scheme 10).

The naturally occurring polyketide *i.e.*, bactobolin A is extracted from *Pseudomonas* sp. It is employed as a secondary



Scheme 12 Synthesis of Aflastatin A **105**.

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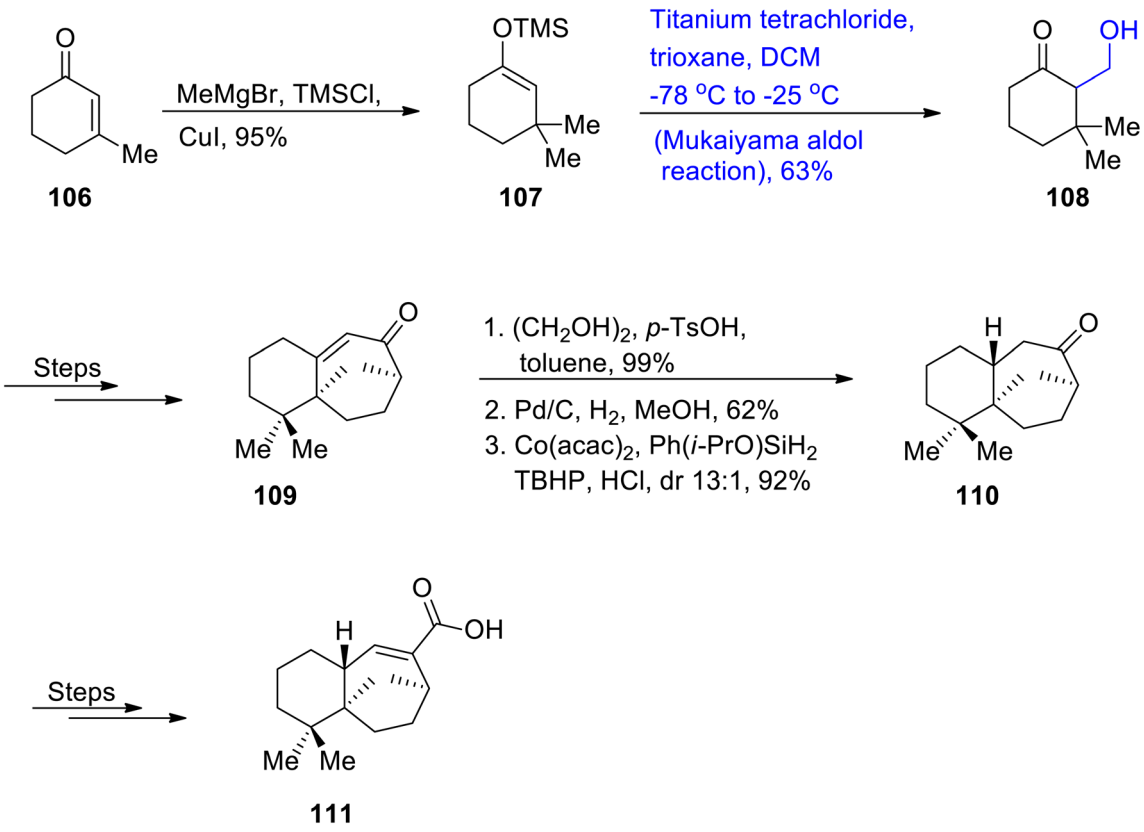
metabolite as it exhibits a wide range of biological activities against both types of bacterial and tumour cell lines. Their structural skeleton comprises a lactone moiety along with five chiral centers.[67,68] Considering the wide ranging significance of bactobolin A, Vojackova *et al.*[69] in 2020 reported their total synthesis by employing the Mukaiyama aldol reaction, rhodium catalyzed amination and alkoxy carbonylation as major steps. The first step of their efficient synthetic strategy involved the preparation of enone **83** by the reaction of quinic acid **82** over a number of steps. In the next step, this enone **83** was made to react with TBSOTf and i-Pr_2NEt by using acetonitrile as a solvent to obtain TMS-silyl enol ether **84**. Silyl enol ether **84** was further subjected to react with compound **85** *via* a titanium chloride catalyzed vinylogous Mukaiyama aldol reaction (VMAR) by using dichloromethane as a solvent to obtain Mukaiyama aldol product **86** in 55% yield with a separable diastereoselectivity ratio of 7 : 1. Later, aldol adduct **86** was hydrogenated in the presence of palladium to obtain ketone **87** in >99% yield. The ketone based compound **87** was further reacted over several steps to furnish amine moiety **88**. Amine **88** was then coupled with acid **89** followed by deprotection of protecting groups in acidic conditions, which led to the synthesis of bactobolin A **90** in 92% yield (Scheme 11).

Aflatoxins are extremely detrimental as they contaminate food which results in the proliferation of cancer cells in animals and humans.[70] In order to prevent the toxic effects of aflatoxins, there is a dire need for aflatoxin growth inhibitors. Aflastatin A, which was obtained from *Streptomyces* sp. MRI142 in 1996, was found to interrupt the growth of aflatoxins.[71,72] Aflastatin A is a naturally occurring and structurally complex polyketide, which contains 29 optically active carbons along with numerous hydroxyl groups. Its structure also contains a derivative of tetramic acid on its lengthy chains. There have been numerous reports on the total synthesis of aflastatin A to date. Recently, Evans *et al.*[73] reported the asymmetric and efficient approach for the total synthesis of aflastatin A in 0.69% overall yield by employing various aldol reactions including the Mukaiyama aldol reaction. The C3–C15 aldehyde **92** was synthesized in 94% yield by treating oxazolidinone **91** over numerous steps. Similarly, oxazolidinone **91** was made to react with aldehyde **93** through different reactions to synthesize C16–C26 enolsilane **94**. Aldehyde **92** and enolsilane **94** were then made to react *via* a trityl-catalyzed Mukaiyama aldol reaction in the presence of Ph_3CPF_6 and DCM, followed by reaction with PPTS and methanol to obtain Mukaiyama aldol product **95** in 75% yield in a diastereoselectivity ratio of more than 95 : 05. It was inferred that the trityl-catalyzed Mukaiyama aldol reaction is highly efficient as compared to the $BF_3 \cdot OEt_2$ mediated Mukaiyama aldol reaction in this case, as the latter resulted in aldol adduct **95** with a lower diastereoselectivity ratio (dr = 57 : 43). Compound **95** was further subjected to Prasad reduction, followed by preparation of acetonide and finally leading to the synthesis of ketone **96** *via* ozonolysis in 81% yield. In order to synthesize C27–C35 aldehyde **99**, aldehyde **97** and oxazolidinone **98** were treated over a number of steps. Aldehyde **99** was then made to react with ketone **100** (which was synthesized by



106 **107** **108** **109** **110** **111**

Scheme 13 Synthesis of (±)-omphalic acid **111**.

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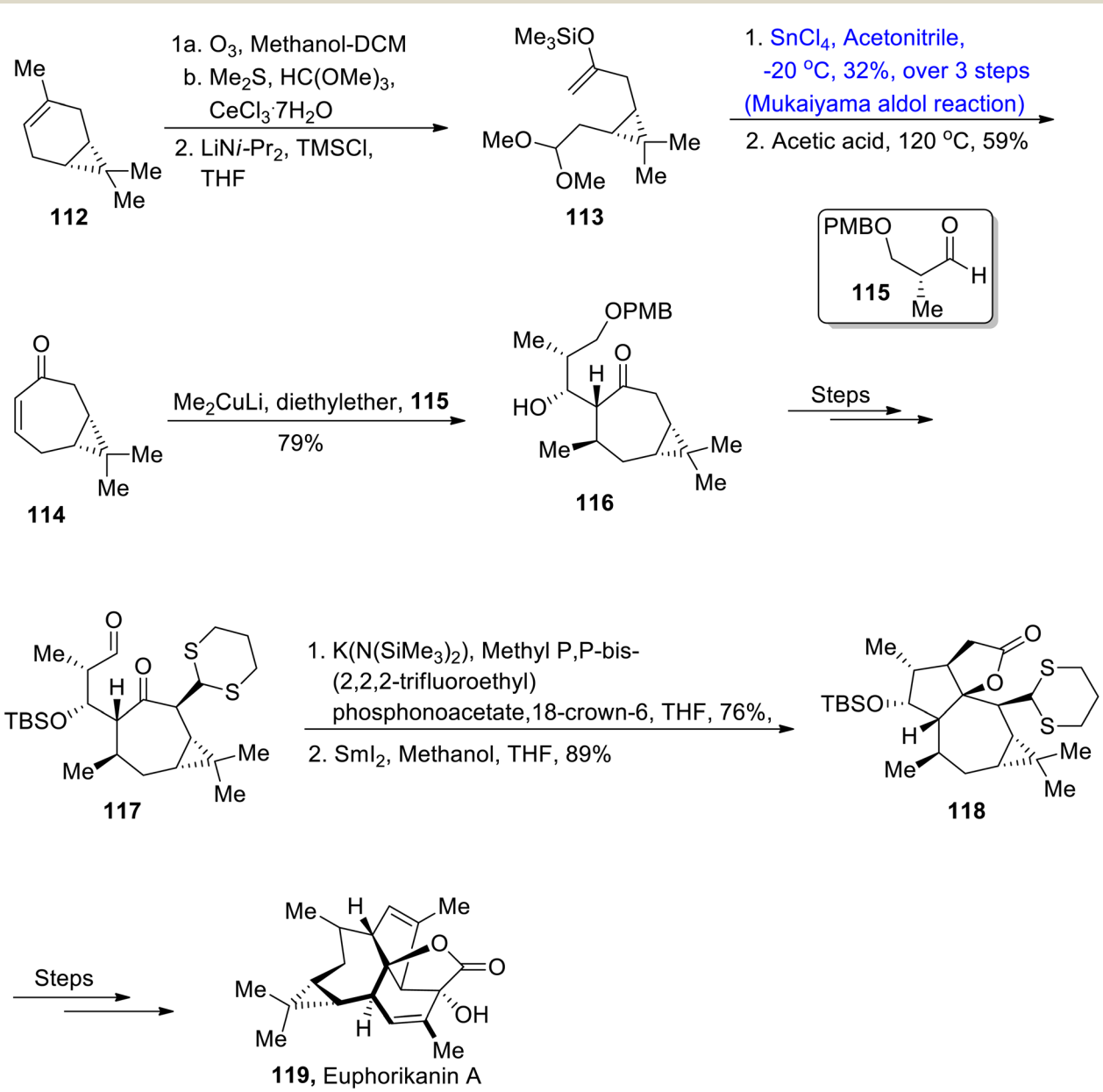
using 1-decanol **101** as the starting reagent) to furnish C27–C48 aldehyde fragment **102** in 80% yield over several steps. C27–C48 aldehyde **102** and C3–C26 ketone **96** were subsequently coupled in the presence of magnesium bromide diethyl etherate, PMP and dichloromethane followed by Prasad's reduction to furnish diol **103** in 70% yield with a diastereoselectivity ratio of more than 95 : 05. In the next step, diol **103** was reacted with aq. H_2SiF_6 and acetonitrile in DCM, followed by reaction with a hydrogen molecule in the presence of palladium to afford naturally occurring C3–C48 fragment **104** of aflastatin A in 53% yield. Furthermore, diol **103** was made to react under a number of steps to synthesize diethylamine salt of aflastain A **105** (Scheme 12).

2.3. Synthesis of terpenoids based natural products

Omphaline sesquiterpenoids are generally obtained from land and sea organisms, and their structure is composed of two consistent quaternary carbon cores. Omphalic acid was the former omphalene sesquiterpenoid, which was extracted from *Omphalanthus filiformis*, that is a Colombian liverwort.[74] Omphalic acid and its corresponding sesquiterpenoids hold prime importance in the natural product family, but owing to their complex carbon framework, it was considered a highly arduous task to successfully carry out their total synthesis. In this regard, Chen *et al.*[75] in 2021 attempted to report the total synthesis of omphalic acid for the first time. For this purpose, they reacted cyclic ketone **106** with methyl magnesium bromide in the presence of trimethylsilyl chloride and cuprous iodide *via* conjugate addition to obtain compound **107** in 95% yield. Conjugate addition product **107** was



Scheme 14 Synthesis of euphorikanin A **119**.

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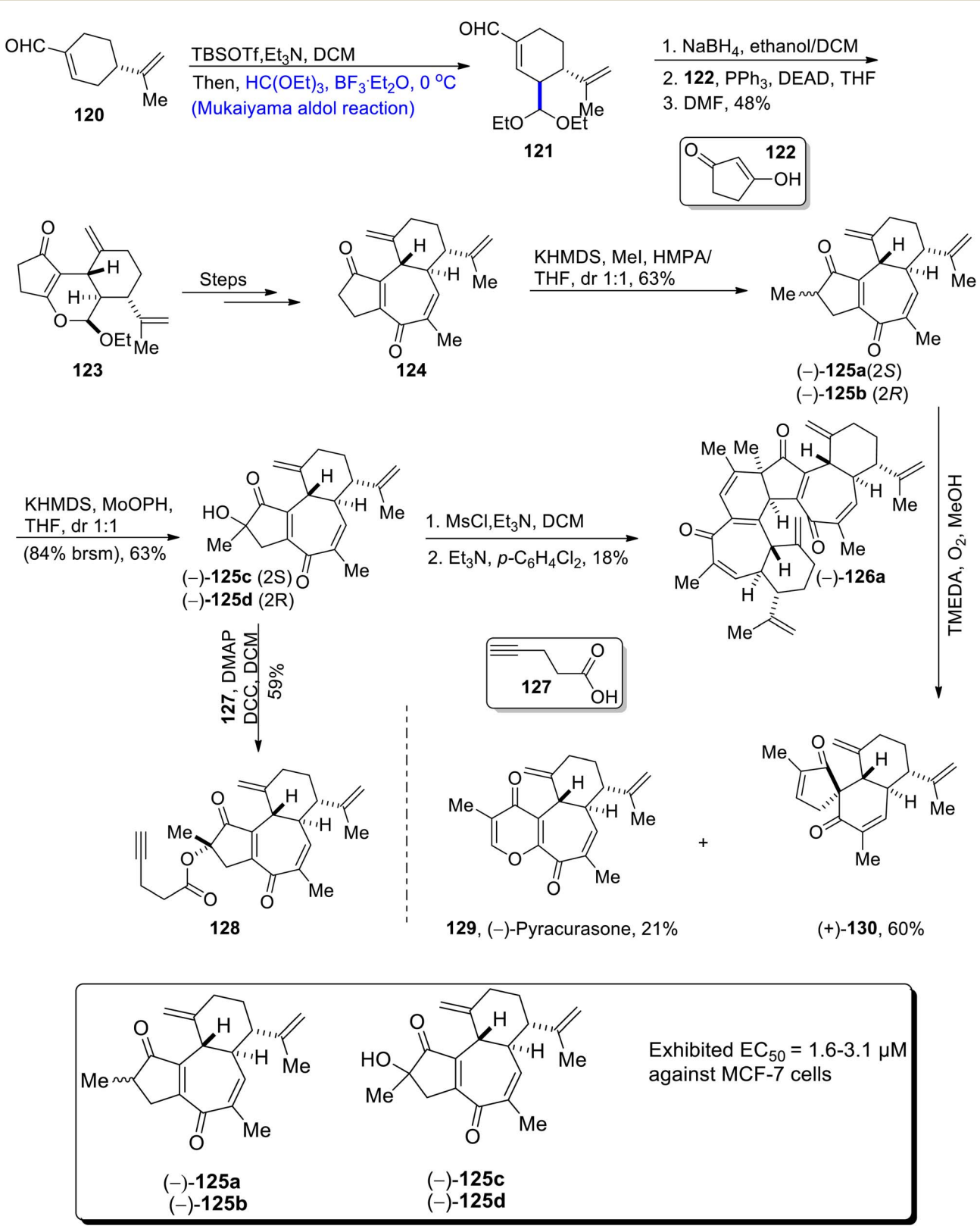
further subjected to the Mukaiyama aldol reaction by reacting with titanium tetrachloride and trioxane in dichloromethane to obtain compound **108** in 63% yield. Mukaiyama aldol product **108** was then transformed to intermediate **109** by undergoing several steps. Intermediate **109** was later subjected to ketone synthesis and isomerization steps followed by palladium catalyzed hydrogenation and HAT hydrogenation to obtain compound **110** in 92% yield with a 13 : 1 diastereoselectivity ratio. In the next step, cyclic ketone



Scheme 15 Synthesis of curcusone diterpenes.

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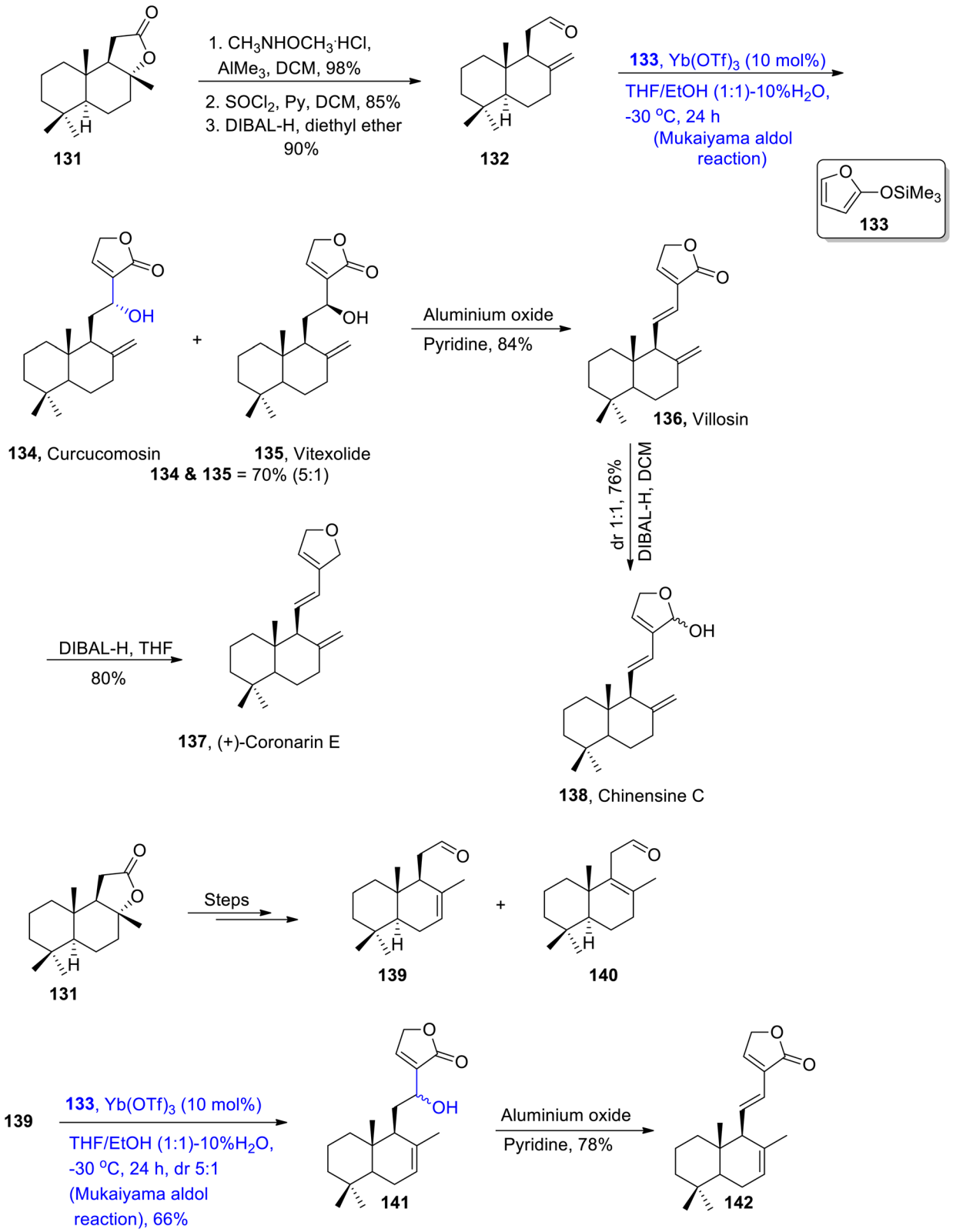

Scheme 16 Synthesis of curcucomosin **134**, vitexolide **135**, villosin **136**, coronarin E **137**, Chinensine C **138** and (*E*)-labda-7,11,13-trien-16,15-olide **142**.

110 was made to react under various conditions, finally leading to the synthesis of target molecule *i.e.* (±)-omphalic acid **111** (Scheme 13).

Most of the natural products are found to be isolated from *Euphorbiaceae*.[76,77] Among them, euphorikanin A is a naturally occurring diterpenoid, which is composed of four fused cyclic

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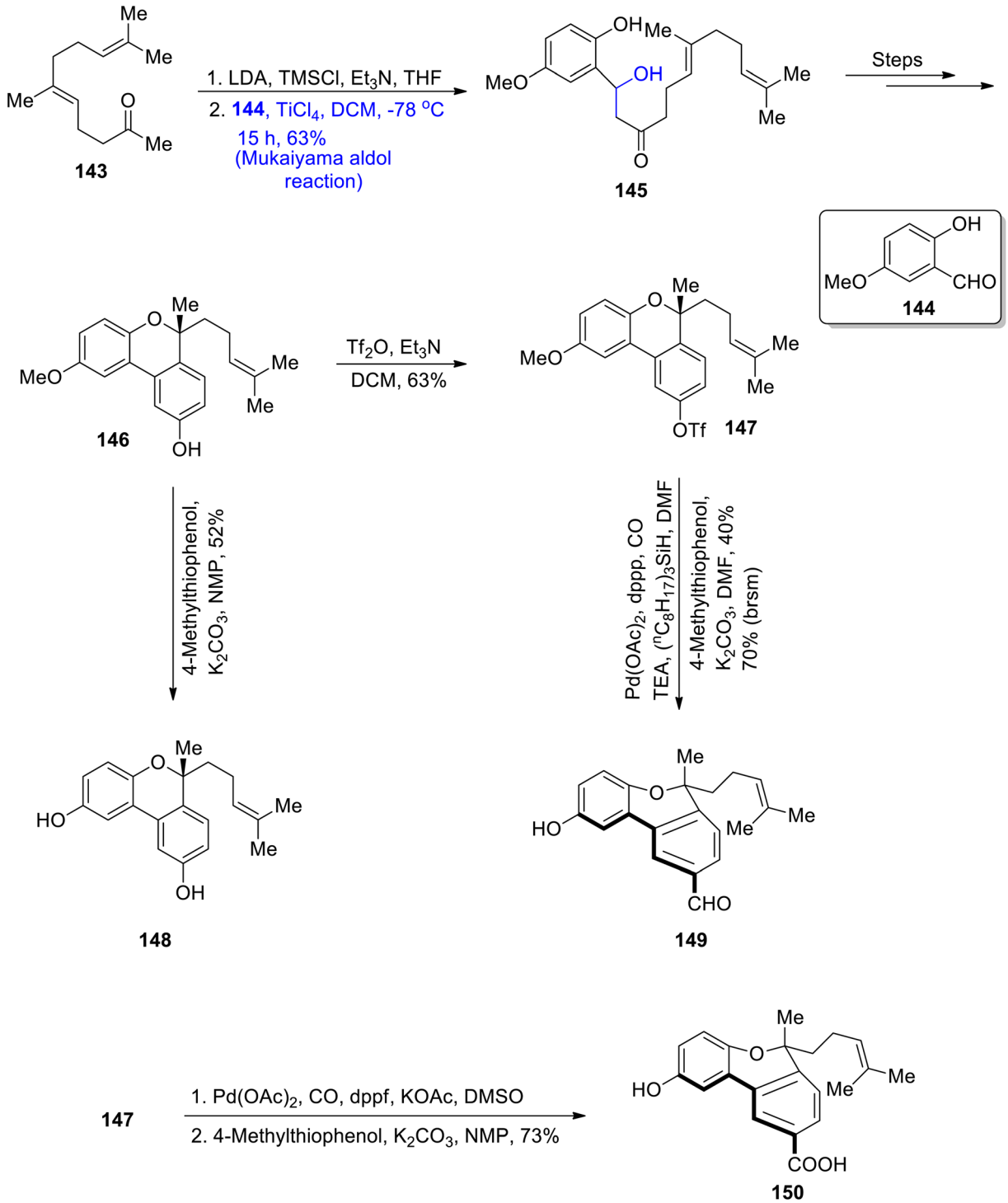
rings with 8 chiral centers, obtained from *Euphorbia kansui*. These are found to be highly active against cancerous cell lines *i.e.*, NCI-446 and HeLa. Classen *et al.*[78] attempted to describe the total synthesis of euphorikanin A by utilizing Mukaiyama aldol reaction in their synthetic strategy. In this regard, they treated (+)-3-carene **112** with ozone, followed by its reaction with dimethyl sulfide and $HC(OMe)_3$ and $CeCl_3 \cdot 7H_2O$. In the next step, enol ether **113** was obtained as a result of reaction with LiN^iPr_2 and TMSCl in tetrahydrofuran. Compound **113** was further made to react with $SnCl_4$ in acetonitrile at −20 °C *via* the Mukaiyama aldol reaction followed by reaction with acetic acid, which gave compound **114** in 59% yield. Aldol adduct **114** was then converted to alcohol containing compound **116** in 79% yield as a result of conjugate addition with aldehyde **115** in the presence of diethyl ether. Alcohol **116** was further treated through several steps to obtain compound **117**. Aldehyde **117**



Scheme 17 Total syntheses of ganocochlearins C–D and cochlearol T.

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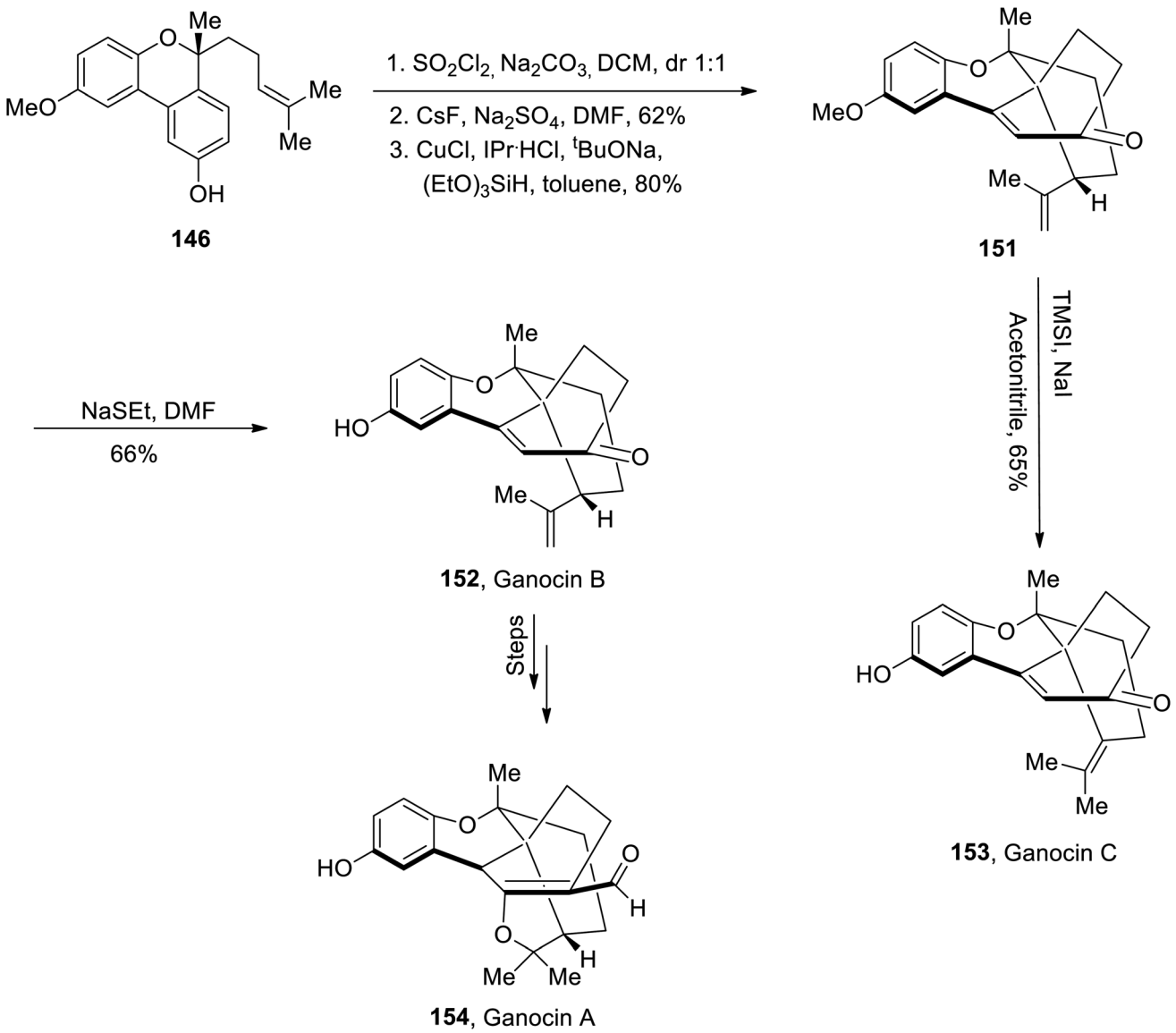
then underwent Still-Gennari olefination followed by reaction with SmI_2 using methanol/THF, which resulted in the synthesis of compound **118** in 89% yield. Compound **118** was then treated over a number of steps, thus leading to the synthesis of euphorikanin A **119** (Scheme 14).

Jatropha curcas is the source of curcusone diterpenes. These diterpenes are used to cure a number of diseases. Their structure is composed of three carbon containing cyclic rings.[79] Owing to the biological significance of curcusone diterpenes, Cui *et al.*[80] in 2021, for the first time reported their total synthesis. The first step of total synthesis involved the treatment of perillaldehyde **120** with TBSOTf, triethyl amine and dichloromethane *via* the Mukaiyama aldol reaction, which further involved the Lewis acid catalyzed reaction with $HC(OET)_3$. Mukaiyama aldol product **121** was subjected to reduction followed by treatment with compound **122** in the presence of triphenyl phosphine, DEAD and tetrahydrofuran, which resulted in the synthesis of compound **123** in 48% yield. Compound **123** was then treated *via* a number of steps to obtain enone **124**. Compound **124** was further treated with KHMDS, methyl iodide in the presence of tetrahydrofuran to obtain curcusone A **125a** and curcusone B **125b** in 63% yield. In the next step, curcusone C **125c** and curcusone D **125d** were synthesized from **125a** and **125b**, as a result of the reaction with KHMDS and MoOPh in tetrahydrofuran. **125c** and **125d** were then subjected to react through two different routes to obtain dimericursone (−)-**126a** and curcusone analog **128** in 18% and 59% yields respectively. Furthermore, curcusone A and B **125a** and **125b** were made to react with TMEDA in the presence of oxygen and methanol, which resulted in 21% yield of pyracurcasone **129** and 60% yield of compound **130** (Scheme 15).

An efficient methodology for treating cyclic dienol silanes with chiral aldehydes has been put forward by using Lewis acid *i.e.*, $Yb(OTf)_3$ or $Zn(OTf)_2$ as catalysts for known Mukaiyama aldol reactions. This efficient methodology was then employed to synthesize various naturally occurring terpenoids. These



Scheme 18 Total syntheses of ganocins A–C **152–154**.

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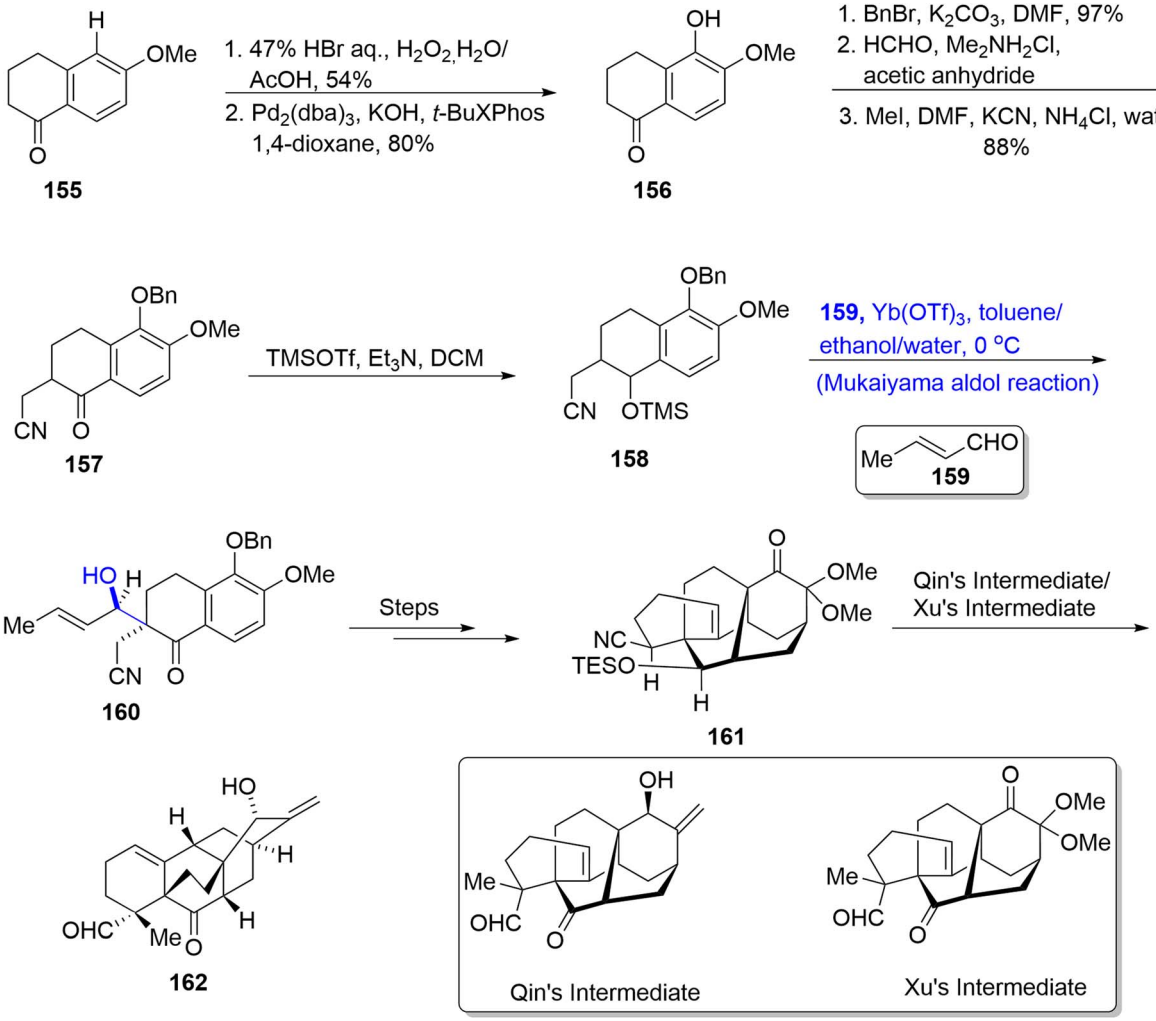
naturally occurring terpenoids have been found to be active against various inflammatory and cancerous diseases.[81,82] These are also used as effective pain killers. In this regard, Adamkiewicz *et al.*[83] reacted sclareolide **131** with CH_3NHOCH_3 in the presence of HCl, $AlMe_3$ and dichloromethane, followed by its reaction with thionyl chloride and then subsequent reduction resulted in the synthesis of compound **132** in 90% yield. Compound **132** was further reacted with silyl enol ether **133** *via* the $Yb(OTf)_3$ catalyzed Mukaiyama aldol reaction, which resulted in the mixture of curcucomosin **134** and vitexolide **135** in 70% yield (5 : 1). This was then reacted with aluminium oxide and pyridine to obtain villosin **136** in 84% yield. Villosin **136** was then subjected to reduction in THF and DCM one by one, thus leading to the synthesis of coronarin E **137** and chinensine C **138** in 80% and 76% yield, respectively. Similarly, sclareolide **131** was transformed into mixture of aldehydes **139** and **140**. Aldehyde **139** was subjected to Mukaiyama aldol reaction to obtain compound **141**, which was further reacted with aluminium oxide and pyridine to synthesize (*E*)-labda-7,11,13-trien-16,15-olide **142** in 78% yield (Scheme 16).

In order to treat various cancerous diseases, Ganoderma fungi has been found to play an effective role. This particular fungus is a source of extraction of a number of triterpenoids and polysaccharides.[84] In a similar way, many biologically active monoterpenoids *i.e.* gonocochlearin A, C, D and ganocins A–C, were isolated from the *Ganoderma cochlear*. Many of these were found to be highly potent against acetylcholinesterase activity.[85] Ganocins A–C are highly structurally complex monoterpenoids with a five-membered cyclic ring. Moreover, their structure constitutes five asymmetric/chiral centers. Beside numerous reported synthetic routes to attain these structurally and biologically diverse molecules, an efficient synthetic methodology for their synthesis was required. For this purpose, Shao *et al.*[86] and Zhang *et al.*[87] in 2020 reported the synthesis of these naturally occurring terpenoids by utilizing the Mukaiyama aldol reaction as a key step. In the first step, geranylacetone **143** was made to react with lithium diisopropyl amide and *tert*-methyl silyl chloride in the presence of triethyl amine and tetrahydrofuran, followed by its reaction with 5-methoxy salicylaldehyde **144** *via* titanium chloride catalyzed Mukaiyama aldol reaction. This resulted in the synthesis of compound **145** in 63% yield. The Mukaiyama product **145** was further converted to phenol **146** by undergoing a number of steps. Compound **146** was subsequently reacted with Tf_2O by using triethyl amine and



Scheme 19 Synthesis of atropurpuran diterpene **162**.

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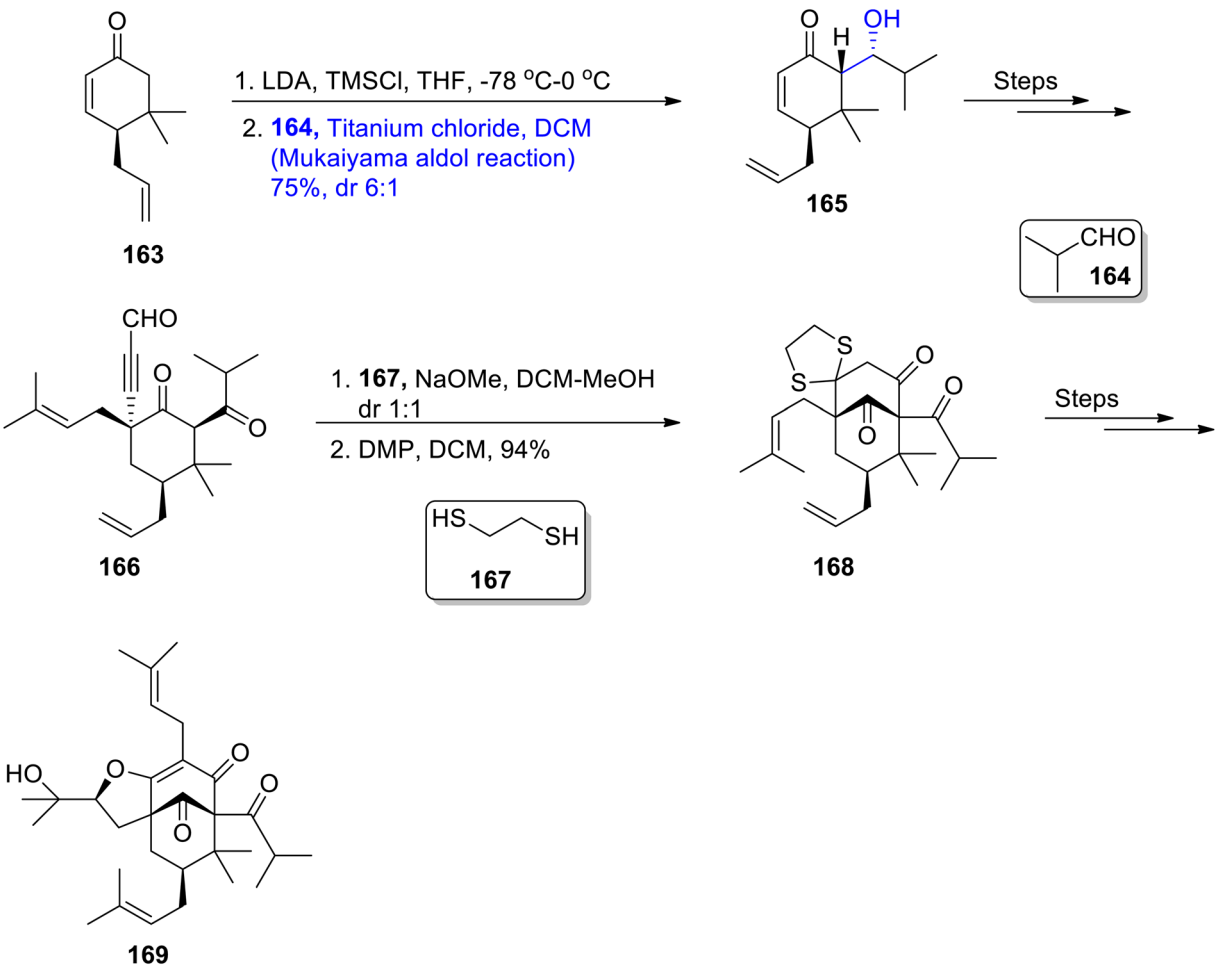
DCM to obtain triflate **147** in 63% yield. Then, the intermediate compounds **146** and **147** were further reacted individually *i.e.*, compound **146** was subjected to demethylation to synthesize cochlearol T **148** in 52% yield. Similarly, compound **147** was subjected to palladium catalyzed carboxylation followed by its reaction with 4-methylthiophenol, which gave ganocochlearin C **149** in 40% yield. The intermediate compound **149** was also subjected to palladium catalyzed carboxylation in the presence of DMSO, followed by subsequent demethylation, which afforded ganocochlearin D **150** in 73% yield (Scheme 17).

Furthermore, intermediate **146** was made to react with SO_2Cl_2 in the presence of sodium carbonate, followed by reaction with cesium fluoride which gave dienone. Dienone was then reduced regioselectively to furnish compound **151** in 80% yield. Compound **151** was further demethylated to give ganocin B **152** and C **153** in 66% and 65% yields, respectively. Ganocin B was subsequently converted to ganocin A **154** by undergoing several steps (Scheme 18).

Aconitum heterophyllum is the source of many diterpenes such as campylopin,[88] atropurpuran[89] and Guan Fu diterpenoid A.[90] Among these, atropurpuran is a non-alkaloidal diterpene whose structural framework constitutes five cyclic rings with tetracyclo and bicyclo units. Suzuki *et al.*[91] in 2022 reported the synthesis of the highly complex structure of atropurpuran by employing the Mukaiyama aldol reaction and intramolecular Diels–Alder reaction in their strategy. The first step involved the reaction of 6-methoxy-1-tetralone **155** with hydrogen bromide utilizing aqueous hydrogen peroxide and acetic acid followed by Hartwig hydroxylation to give phenol **156** in 80% yield. The hydroxyl group was protected by benzyl bromide followed by a subsequent Mannich reaction with formaldehyde and Me_2-NH_2Cl in acetic anhydride. The next step involved the reaction with methyl iodide in the presence of potassium cyanide and ammonium chloride to furnish nitrile **157** in 88% yield. It was then made to react with TMSOTf in triethyl amine and DCM to afford trimethyl silyl enol ether **158**, which then underwent the Mukaiyama aldol reaction with acrolein **159** by utilizing $Yb(OTf)_3$ as a catalyst in toluene or ethanol/water to synthesize adduct **160**. The adduct **160** was further treated over a number of steps to obtain atropurpuran skeleton **161**. This atropurpuran skeleton then resulted in the synthesis of atropurpuran diterpene **162** on treatment with Qin's intermediate or Xu's intermediate (Scheme 19).

Garsubellin A has been found to be isolated from *Garcinia subelliptica*, a tree that is present on Okinawa Japan island.[92] This naturally occurring monoterpene has wide biological significance alongside structural complexities. Their structure is composed of a cyclic framework constituting 13 carbon atoms



Scheme 20 Synthesis of garsubellin A **169**.

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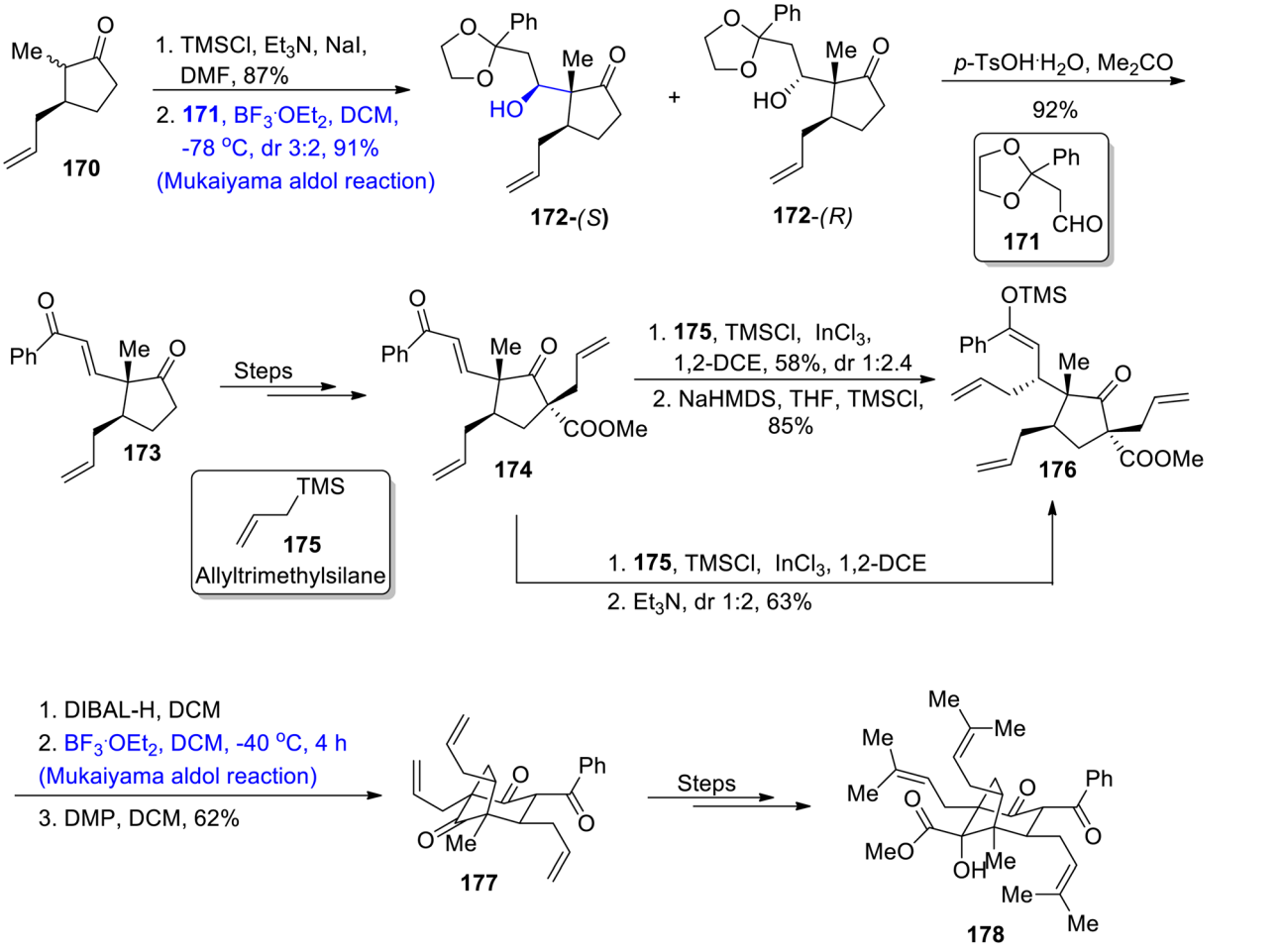
with three quaternary carbons. They are known to boost the activity of acetylcholine transferase thus preventing the onset of Alzheimer's disease.[93] Owing to their remarkable structural framework and biological significance, various synthetic routes have been reported towards their total synthesis. However, these methods resulted in racemic synthesis of target molecules. Jang *et al.*[94] in 2022 attempted to describe the enantioselective synthesis of target molecule. The first step of their synthetic methodology involved the reaction of enone **163** with LDA and TMSCl followed by a titanium chloride catalyzed Mukaiyama aldol reaction in DCM upon treatment with aldehyde **164**. As a result, the Mukaiyama aldol product **165** was obtained in 75% yield, which was then subjected to a number of steps to afford compound **166**. Later, compound **166** underwent conjugate addition in the presence of Ley's conditions followed by subsequent oxidation by using DMP and DCC to furnish triketone **168** in 94% yield. It was then transformed into target molecule **169** by undergoing a number of different reactions (Scheme 20).

Naturally occurring polycyclic polyprenylated acylphloroglucinols belong to the class of monoterpenoids and are known to exhibit potent biological activity against a number of diseases.[95] Newly discovered acylphloroglucinol monoterpenoids containing six-membered rings were derived from *Hypericum patulum* which includes hypatulin A and hypatulin B.[96] Their structure is composed of five-membered carbon rings along with 4 asymmetric centers. Moreover, they are found to be effective against a number of bacterial strains *i.e.*, *E. coli*, *S. aureus* and *B. subtilis*. As hyptaulin A was found to be easily synthesized from hyptaulin B, Leisering *et al.*[97] in 2022 attempted to report the total synthesis of hyptaulin B by carrying out the Mukaiyama aldol reaction and photo-oxidation. The first step of synthesis involved the enolization reaction of cyclopentanone **170** followed by Mukaiyma aldol addition with aldehyde **171** to yield diastereomers **172**-(*S*) and **172**-(*R*) in 91% yield with diastereoselectivity ratio of 3 : 2. Both these diastereomers were further subjected to deacetalization to afford enone **173** in 92% yield. This reaction was followed by the procurement of isomer **174** in 59% yield from enone **173**. Compound **174** was then subjected to Homo-Sakurai allylation followed by the addition of trimethylamine which gave substituted ester **176** in 63% yield with 1 : 2 diastereoselectivity ratio. However, Homo-Sakurai-allylation followed by treatment with sodium hexamethyldisilazide gave ester **176** in 85% yield. Ester **176** was further reduced with DIBAL-H and then subjected to Lewis acid catalyzed Mukaiyama aldol reaction in DCM. Then, oxidation was carried out with DMP, which gave triketone intermediate **177** in 62% yield. This triketone intermediate was



Scheme 21 Synthesis of hyptaulin B **175**.

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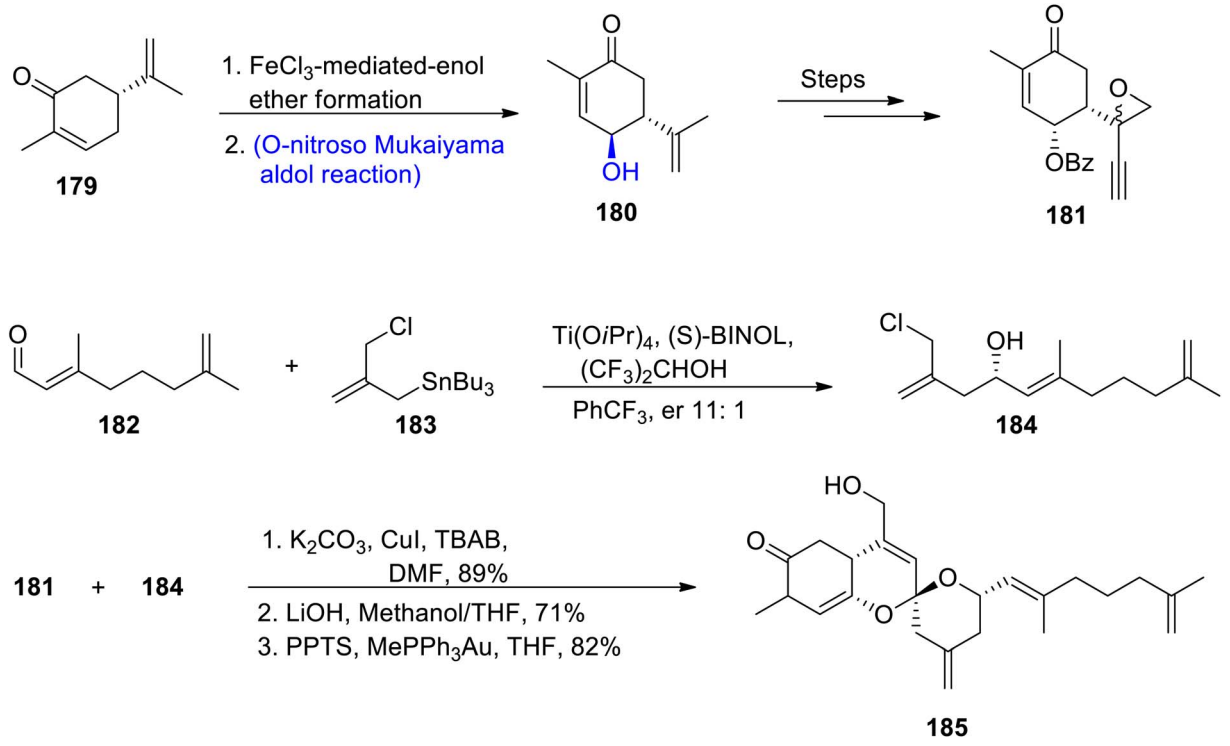
then reacted several times, thereby leading to the synthesis of target molecule **178** (Scheme 21).

Owing to the wide range of biological activities exhibited by naturally occurring spiroketals, continuous efforts towards their total syntheses have been reported by various researchers. Alotaketal A is one of the naturally occurring marine spiroketal that has been found to be obtained from *Hamiegra* species. They are included in the sesterpenoid family as they have a didehydro spiroketal moiety in their structure.[98,99] Lee *et al.*[100] in 2020 attempted to describe the total synthesis of alotketal A by involving the Mukaiyama aldol reaction and epoxide rearrangement along with the gold-mediated spiroketalization approach. The synthesis began with the reaction of *R*-curvane **179** *via* iron chloride catalyzed formation of enol ether, which resulted in the synthesis of hydroxy curvane **180** *via* *O*-nitroso Mukaiyama aldol reaction. Hydroxy curvane **180** further underwent a number of reactions to synthesize coupling fragment **181**. In the next step, aldehyde **182** was made to react with compound **183** in the presence of $Ti(OiPr)_4$, (*S*)-BINOL, $(CF_3)_2$-CHOH and $PhCF_3$ to obtain coupling fragment **184** in 11 : 1 enantioselective ratio. Fragments **181** and **184** were finally coupled by using copper iodide followed by treatment with lithium hydroxide in methanol and gold-mediated-spiroketalization resulted in the synthesis of target molecule alotaketal A **185** in 82% yield (Scheme 22).

Most of the seawater norsesterpene metabolites belong to the family of naturally occurring endoperoxides. Various members of this family have been known to be isolated from different sponges *i.e.*, Diacarnus, Sigmosceptrella, prianos or Mycale. Similarly, Mycale sponges are a source of different mycaperoxides which exhibit significant biological activity against a number of bacterial and viral diseases.[101,102] They constitute 1,2-dioxane ring substituted propionic acid along with a sesquiterpene subunit in their structure. Various researchers have attempted to describe the total synthesis of these naturally occurring endoperoxides, but a concise and efficient stereoselective route has not been developed yet. Thus, Kerim *et al.*[103] in 2022 synthesized various members of the mycaperoxide class for the first time. The synthesis initiated with the generation of cyclopropylidene **187** by treating sclareol **186** over a number of steps. Cyclopropylidene was then subjected to protection with TESCl, followed by reaction with meta-chloroperoxybenzoic acid to give compound **188** in 81% yield. Compound **188** was further converted to peroxyacetal **189** in 84% yield, by undergoing three different steps. In the next step, peroxyacetal **189** underwent the Mukaiyama aldol reaction upon treatment with silyl enol ether **190** by using $Sc(OTf)_3$ as catalyst and dichloromethane as solvent. A subsequent reaction with *p*-toluene sulfonic acid in the presence of methanol gave a mixture of different diastereomers *i.e.*, **191a**, **191b**, **191c** and **191d**. Diastereomer **191a** was further reacted with hydrogen peroxide and lithium hydroxide using THF/H_2O as a solvent. Thus, mycaperoxide D methyl ester **192** was obtained in 76% yield after reaction with $TMSCHN_2$ in methanol (Scheme 23).

A series of similar steps were adopted to synthesize mycaperoxide C methyl ester **196**. For this purpose, compound **193a** was converted to peroxyacetal **194** in 82% yield. Peroxyacetal **194** later underwent reaction with silyl enol ether **190** by using a $Y(OTf)_3$ catalyzed Mukaiyama aldol reaction in DCM solvent, followed by reaction with APTS, which gave a mixture of diastereomers **195a** and **195b** in 96% yield. **195b** was then treated further to obtain mycaperoxide C methyl ester **196** by employing



Scheme 22 Synthesis of (−)-alotaketal A **185**.

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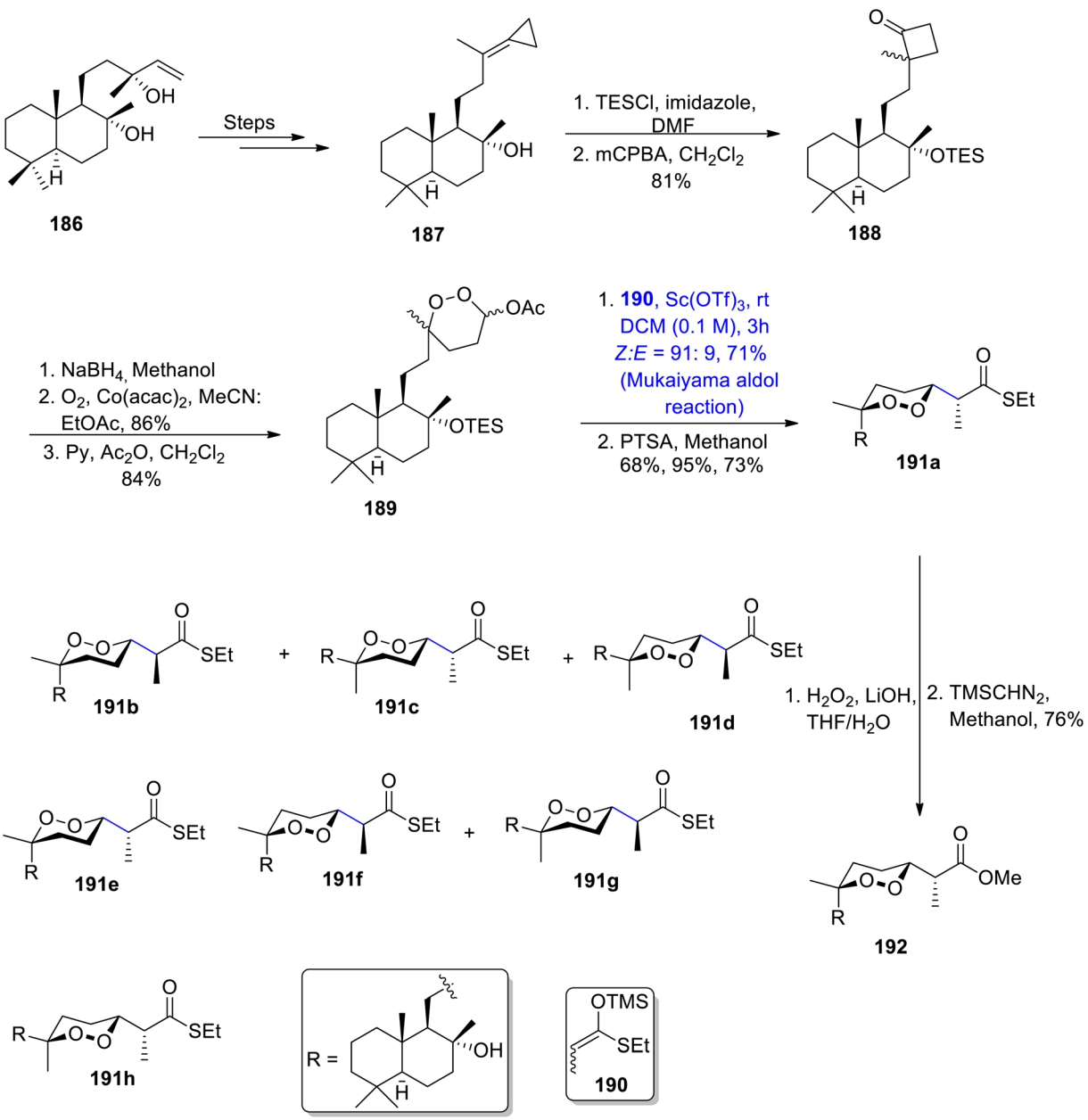
similar steps to those described earlier for the synthesis of mycaperoxide D (Scheme 24).

The Mukaiyama aldol reaction was further employed to synthesize mycaperoxides B and G. For this purpose, compound **193b** was converted to peroxyacetal **197** by undergoing several steps. Peroxyacetal was then subjected to $Y(OTf)_3$ catalyzed Mukaiyama aldol reaction upon treatment with silyl enol ether **190** to furnish aldol adducts **198a** in 32% yield with **198b** and **198c** in a racemic mixture. Adduct **198a** was further made to react with $SOCl_2$ and pyridine to synthesize mycaperoxide G **199c** in 63% yield along with **199a** and **199b**. Similarly, adduct **198c** underwent a reaction with hydrogen peroxide in the presence of lithium hydroxide and THF/H_2O, which gave mycaperoxide B **200a** and compound **200b** in a racemic mixture (Scheme 25).

Leaves of *Cryptocarya laevigata* are a source of a wide range of cryptolaevillactones (CLs). They belong to a class of naturally occurring monoterpenoids whose structural framework comprises a spiro-nonane moiety.[104] Considering the versatility of these cryptolaevillactones, Miura *et al.*[105] in 2022 reported the synthesis of representative members of CLs **206a–206d** by employing the Mukaiyama aldol reaction as the crucial step. The first step of synthesis involved the reaction of cyclohexanone **201** with cyclopropyl phenyl sulfide **202** in the presence of butyl lithium and anhydrous THF followed by treatment with HBF_4 in diethyl ether *via* Trost's and Undheim's method to obtain spiro ketone **203** in 82% yield. Spiro ketone **203** was further treated a number of times to synthesize silyl enol ether **204**. Silyl enol ether **204** was subjected to react with chiral aldehyde **205** *via* Lewis acid catalyzed Mukaiyama aldol reaction



Scheme 23 Synthesis of members of the mycaperoxide family.

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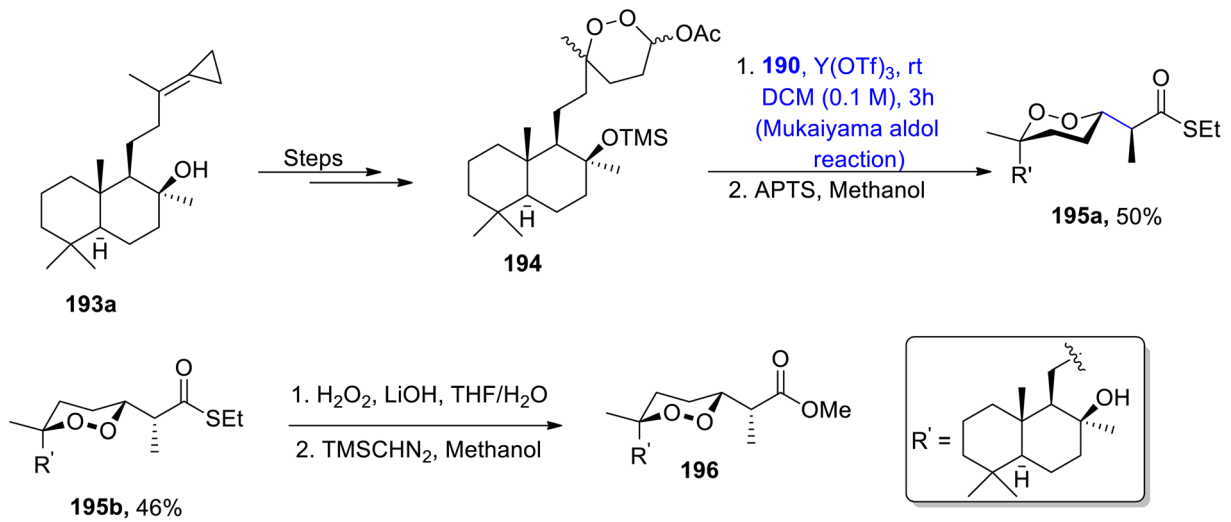
to obtain cryptolaevillactones **206a**, **206b**, **206c** and **206d** in 16%, 16%, 34% and 34% yields, respectively (Scheme 26).

2.4. Synthesis of alkaloid-based natural products

The *Rauvolfia Vomitaria* plant is an isolation source of rauvomines A and B, which are monoterpenoid indole alkaloids. Rauvomine A constitutes a chlorine atom at carbon number 20 and an extra cyclopropane ring is present in the skeleton of rauvomine B.[106] These indole alkaloids have wide medicinal applications and they are found to be highly potent against inflammatory diseases. Owing to their unparalleled biological applications and structural diversity, they have attracted the interest of various researchers. Most recently, Wu *et al.*[107] reported the brief and efficient total synthesis of these compounds by employing the Mukaiyama aldol reaction as one of its key steps. In this regard, compounds **207** and **208** were coupled and reacted in a number of steps, thus leading to the synthesis of ketone **209** in excellent yields. In the next step, ketone **209** was made to react with compound **210** by utilizing potassium carbonate and dimethylformamide followed by its reaction with potassium hexamethyl disilazide and *tert*-butyl dimethyl silyl chloride in tetrahydrofuran to obtain *tert*-butyldimethylsilyl ether **211** in 95% yield. In the next step, ether **211** was subjected to the Mukaiyama aldol reaction upon treatment with titanium chloride in dichloromethane at −78 °C to room temperature. This reaction resulted in the synthesis of aldol adduct **212** in 70% yield, thereby synthesizing the five-membered cyclic ring of the target molecule. The compound **212** was then reacted in the presence of different conditions to obtain the central ring of rauvomines **213a** and **213b**, respectively. Compounds **213a** and **213b** were further individually reacted with $(COCl)_2$, dimethylsulfoxide, trimethylamine followed by treatment with hydrochloric acid to obtain the dextrorotary and levorotatory stereoisomers of compounds **214a** and **214b** in 82% and 85% yields, respectively. In this way, total synthesis of rauvomines can be carried out by employing this synthetic approach, which has been utilized to synthesize a highly complex ring in its structure (Scheme 27).

Various types of indole alkaloids can be extracted from *Tabernaemontana corymbosa* plants.[108] Specifically, vobasinyl iboga-type and chippiine-type indole alkaloids are found to be highly active against cancerous diseases. Kam and colleagues carried out the isolation of tronocarpine in the beginning of 21st century.[109] Tronocarpine holds significant importance in the chippiine-type alkaloids family. Its structure is composed of five-membered cyclic rings, constituting lactams and chiral centers. Owing to the importance of the tronocarpine alkaloid, various synthetic schemes have been proposed by different researchers in recent years. However, previous reported methodologies were too long and time consuming. Hence, Nakayama *et al.*[110] in 2021 demonstrated the efficient methodology for its synthesis. The first step of the synthesis involved the coupling reaction between **215** and α,β-unsaturated ester **216** in the presence of *n*-Bu_3P, acetonitrile and methanol followed by hydrogenation and addition reactions, which led to the synthesis of compound **217** in 56% yield. The compound **217** was further treated with sodium azide in DMF solvent followed by subsequent reduction with DIBAL, which gave aldehyde **218** in 52% yield. Aldehyde **218** was then subjected to Mukaiyama aldol reaction conditions in the presence of TBSOTf, DIPEA and dichloromethane at 0 °C to obtain silyl enol ether. In the following step, acetaldehyde dimethyl acetal and TBSOTf were added to the reaction mixture, which resulted in 35% yield of compound **219** along with 25% yield of by-products *i.e.*, **219a** and **219b**. By-products **219a** and **219b** were then treated with Amberlyst®15 in acetone to obtain **219** in 86% yield. Compound **219** was further reacted *via* several steps to obtain an excellent yield of tronocarpine alkaloid **220** (Scheme 28).

Sirivastava and Ha[111] in 2021 developed a novel approach for the Mukaiyama aldol reaction by employing chiral substituents. A highly stereoselective synthesis of aziridine-2-carboxaldehyde was carried out by employing the Mukaiyama aldol reaction between chiral 1-(α-methylbenzyl)-aziridine-2-carboxylaldehyde



Scheme 24 Synthesis of mycaperoxide C **196**.

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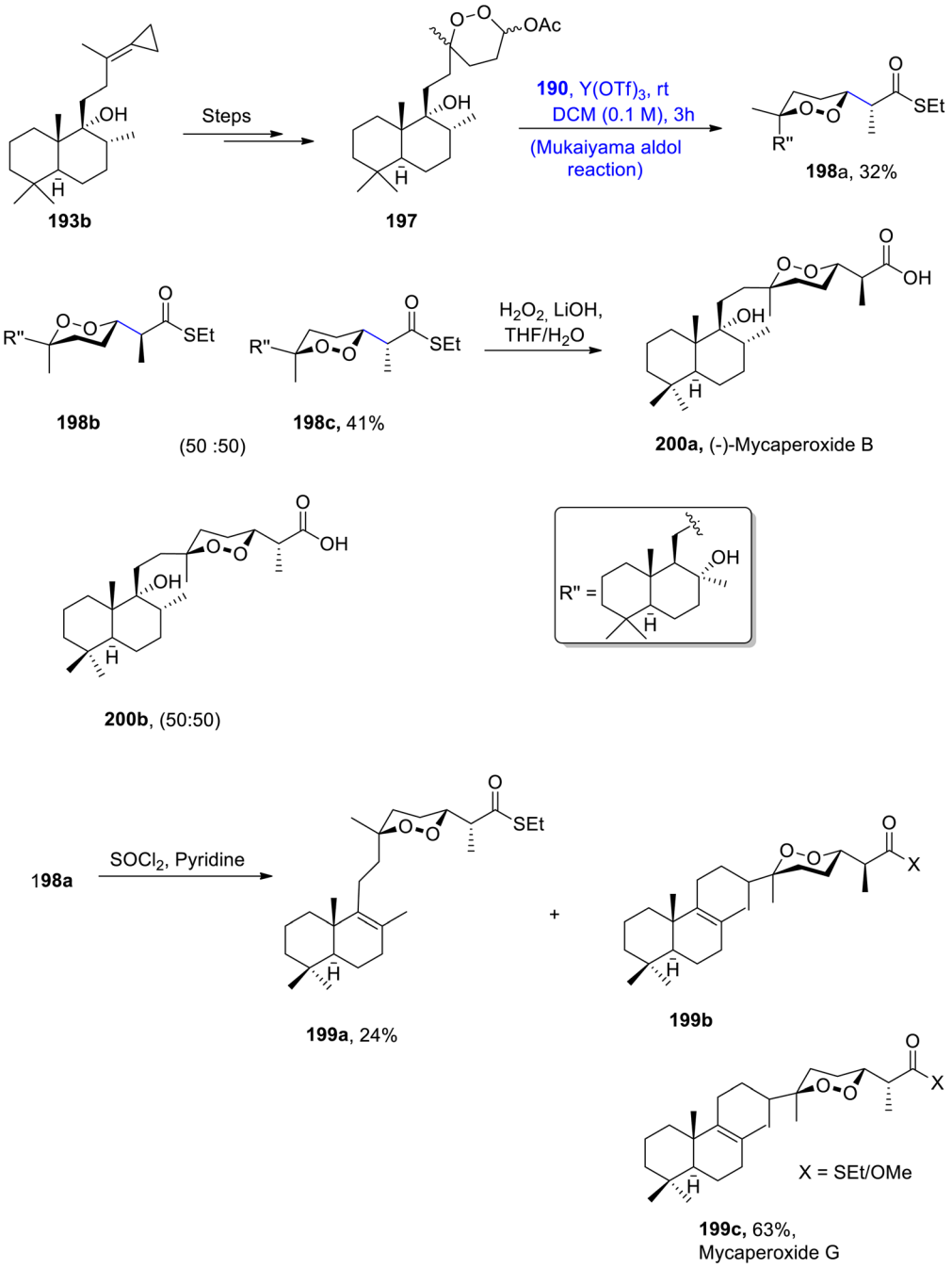
and a diverse range of enol silanes by employing zinc chloride as a catalyst. Most of the alkaloids are known to be synthesized from β-(aziridin-2-yl)-β-hydroxy ketones *i.e.* (−)-*epiallo*-isomuscarine, *epi*-galantinic acid and the (2*S*,3*R*,5*S*)-enigmol analog. Sirivastava also reported the total synthesis of these alkaloids. The first step involved the reaction between carboxyl aldehyde **221** and chiral enol silyl compound **222** *via* a zinc chloride-mediated-Mukaiyama aldol reaction in acetonitrile to



Mycaperoxide exhibits IC_{50} = 0.25-1.0 μg/mL against Herpes simplex virus and vesicular stomatitis virus

Scheme 25 Synthesis of mycaperoxide B **200** and G **199**.

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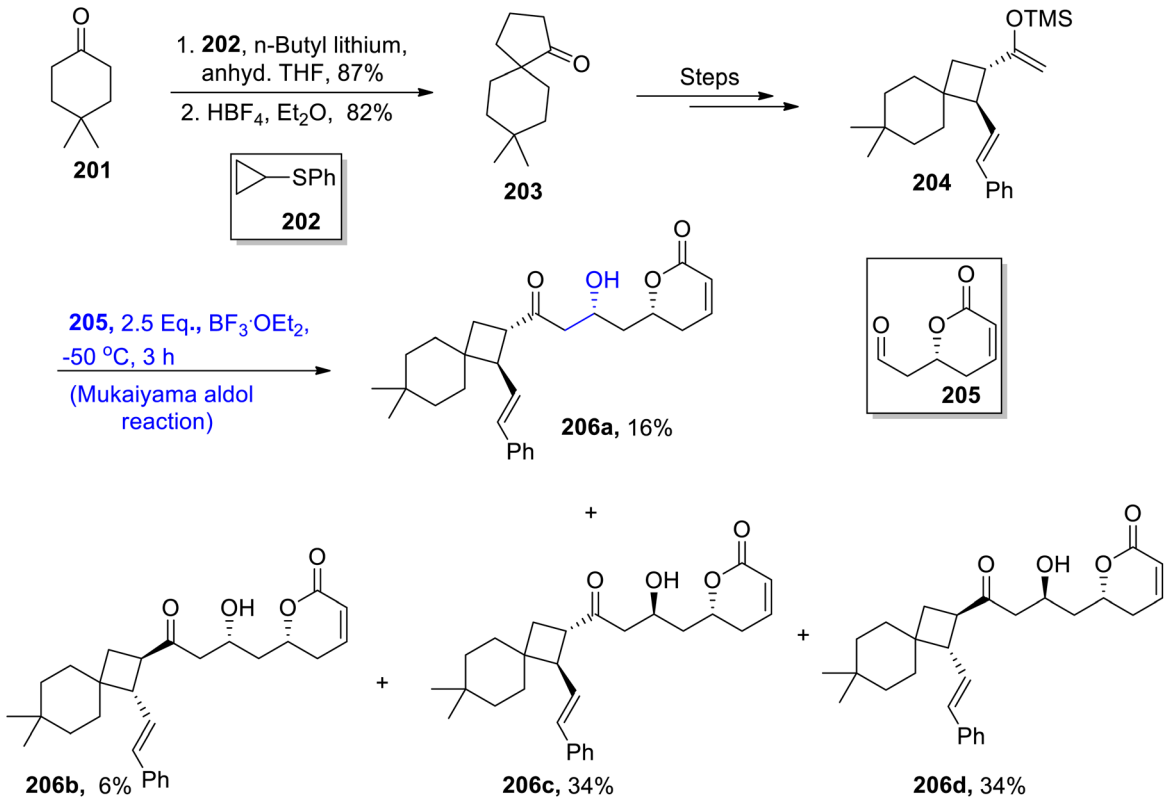

Scheme 26 Synthesis of cryptolaevillactones **206a–206d**.

obtain aldol adduct **223** with a diastereoselectivity ratio of more than 95 : 5. Compound **223** was then made to react with TBSOTf and 2,6-lutidine in the presence of DCM to obtain compound **224** in 88% yield. Compound **224** was then reacted over several steps to synthesize (−)-epiallo-isomuscarine **225** (Scheme 29).

Substituted chiral aldehyde **221** was made to react with trimethylsilyl enol ether **226** by using zinc chloride as the catalyst in acetonitrile to furnish aldol adduct **227**. The aldol adduct **227** was reacted with TBSOTf and 2,6-lutidine utilizing DCM which resulted in the synthesis of compound **228** in 85% yield. Finally, (2*S*,3*R*,5*S*)-enigmol analog **229** was synthesized by treating compound **228** over several steps (Scheme 30).

Substituted chiral aldehyde **221** underwent a zinc chloride catalyzed Mukaiyama aldol reaction with trimethyl silyl enol ether **230** to furnish aldol adduct **231** in a diastereoselectivity ratio of more than 97 : 3. Compound **231** was reacted with TBSOTf and 2,6-lutidine in dichloromethane to afford compound **232** in 83% yield. Compound **232** was further made to react in a number of steps to synthesize *epi*-galantic acid **233** (Scheme 31).

Kobayashi along with colleagues isolated lycopodium alkaloids *i.e.*, lyconesidine A and B from *Lycopodium chinese*. These are naturally occurring alkaloids, which are comprised of Fawcettimine alkaloids type cyclic moiety in their structural framework.[112,113] They are found to be effective in inhibiting the proliferation of cancerous cells, thus behaving as anti-mitotic agents. Compounds with anti-cancerous potential have been widely investigated.[114,115] Specifically, Lyconsesidine B has been found to interrupt the polymerization process of tubulin with $IC_{50} = 250$ μM. Taking into account the structural diversity and anti-cancerous potential of Lyconesidine B, Kurose *et al.*[116] in 2020 furnished the total synthesis of this naturally occurring alkaloid by employing the Mukaiyama aldol reaction as one of its key steps. At the onset of synthesis, enol triflate **234** was reacted over a number of steps to synthesize the tetracyclic ring of lyconesidine B **235**. Tetracyclic ring containing compound **235** was further treated *via* epoxidation in the presence of hydrogen peroxide, Cl_3CCN and potassium carbonate followed by opening of the epoxide ring in the presence of H_2, and Pd/C to obtain compound **236** in 86% yield. Compound **236** was then made to react with TESOTf and 2,6-lutidine followed by reduction utilizing palladium to obtain compound **237** in 96% yield. It was then reacted with TMSOTf and 2,6-lutidine in dichloromethane followed by a scandium triflate catalyzed Mukaiyama aldol reaction with aldehyde in tetrahydrofuran, which resulted in the synthesis of β-hydroxyketone **238** in 76% yield. β-Hydroxyketone **238** later underwent a number of reactions to obtain lyconesidine B **239** (Scheme 32).

Haliclona species, which belong to the sea-water sponge genus, are a source of various naturally occurring organic compounds.[117] These naturally occurring metabolites have been found to be highly potent against cancerous, bacterial and viral diseases.[118] Similarly, seawater cyclic alkaloid, haliclonin A, was obtained from *Haliclona* sp. by Shin and colleagues. In order to attain biologically active nitrogen containing organic compounds *via* synthetic methodology, Luo *et al.*,[119] in 2021

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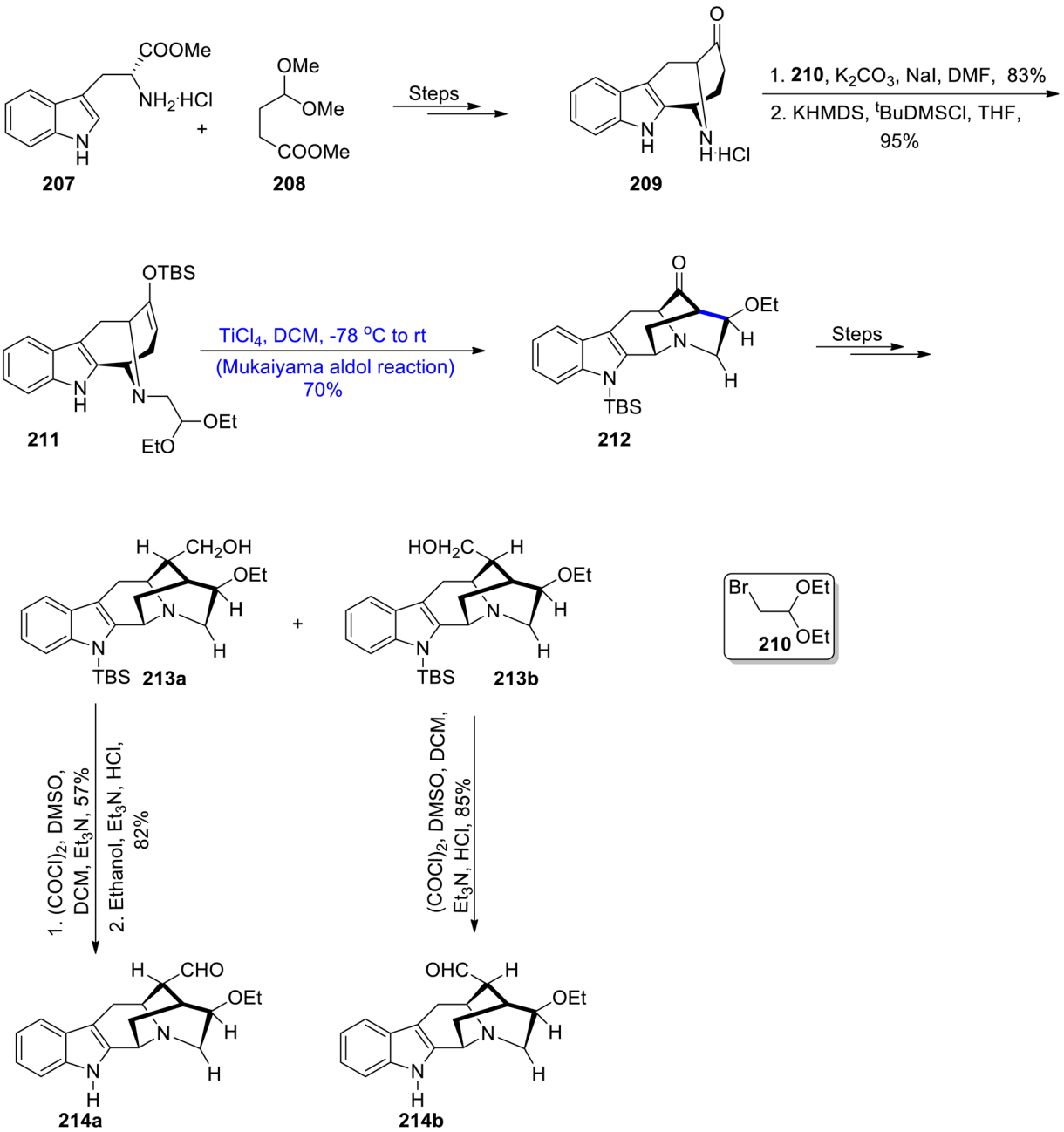

Scheme 27 Synthesis of rauvomines A **213** and B **214**.

reported the efficient synthetic protocol for the synthesis of haliclonin A. The synthesis began with the attainment of nonane core based compound **241** by using enone **240** as precursor. Compound **241** was further subjected to react with compound **242** in the presence of titanium chloride followed by reaction with Grubbs reagent to obtain product in 92% yield. It was then reacted with mesityl chloride and trimethylamine in dichloromethane and DBU to obtain a diastereoselective mixture of **243a** and **243b** in 88% yield with dr = 1 : 1. The racemic mixture was then treated over a number of steps to synthesize ketone based compound **244**. Compound **244** was further subjected to treat with formaldehyde *via* an $Sc(OTf)_3$ catalyzed Mukaiyama aldol reaction in the presence of DBU and TESOTf to obtain Mukaiyama aldol product **245**. The Mukaiyama aldol product **245** was then treated over a number of steps, which led to the synthesis of compound **246**. The next step involved the treatment with magnesium in the presence of methanol followed by treatment with ethyl formate and pyridine to obtain diamide compound in 82% yield. Compound **247** was then obtained by the reaction of TMSI and HDMS. Compound **247** later underwent a number of reactions to synthesize haliclonin A **248** in 82% yield (Scheme 33).

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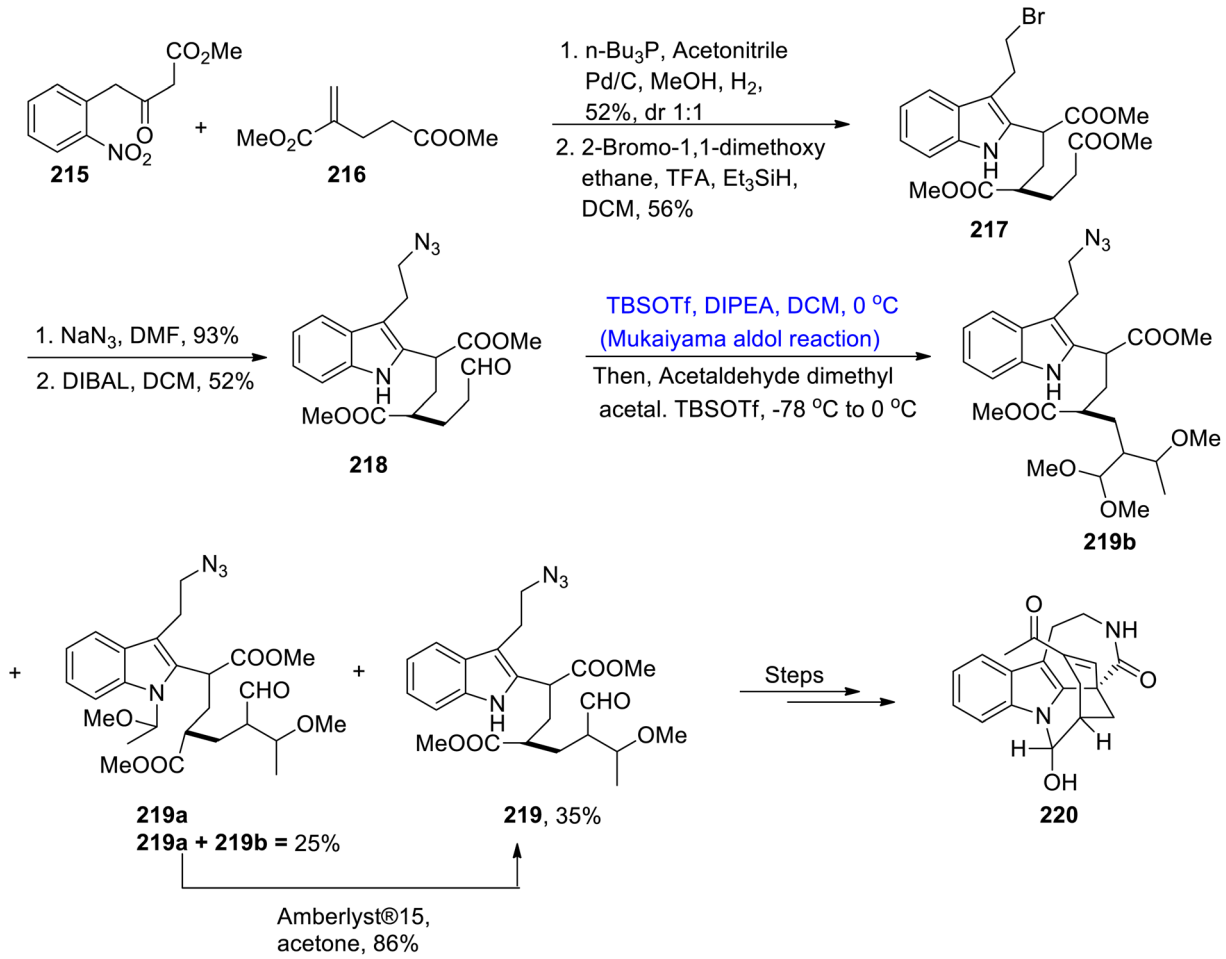
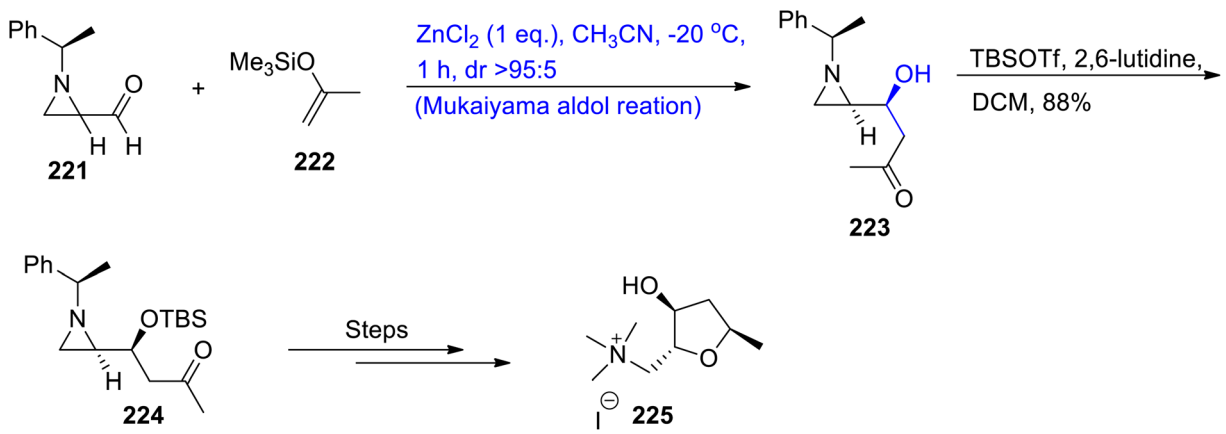


Scheme 28 Synthesis of tronocarpine **220**.



Scheme 29 Synthesis of (−)-*epiallo*-isomuscarine **225**.

2.5. Synthesis of naturally occurring metabolites

Nannocystin along with its natural counterpart is known to be isolated from the *Nannocystis* species. They are biologically active myxobacteria secondary metabolites that are used in the inhibition and proliferation of cancer cell lines.[120,121] Their structure is composed of 21 atoms along with nine stereocenters. Their giant structure with significant medicinal applications inspired numerous efforts to achieve their total synthesis. Zhang *et al.*[122] in 2021 carried out their total synthesis by making use of the Keck asymmetric vinylogous Mukaiyama aldol reaction to obtain component **254** which was then coupled

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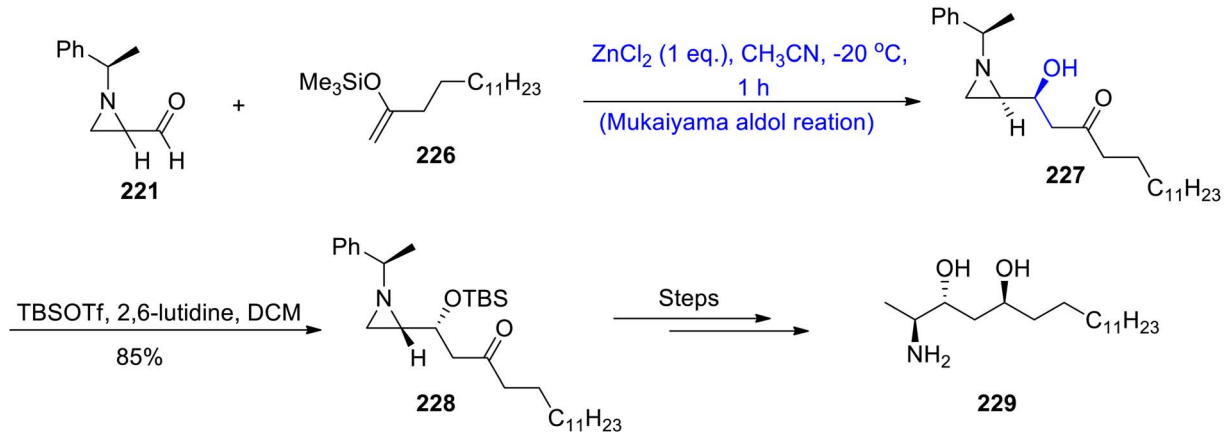
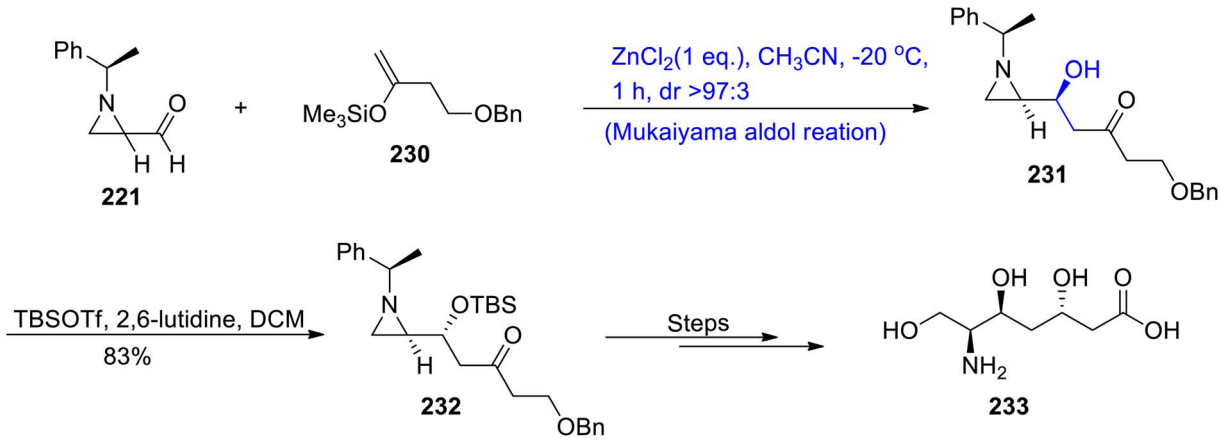


Scheme 30 Synthesis of enigmol analog **229**.



Scheme 31 Synthesis of *epi*-galantic acid **233**.

with other components to synthesize nannocystin A. In their synthetic scheme, unsaturated ester **249** was made to react with LDA and TMSCl in tetrahydrofuran to obtain trimethyl silyl enol ether **250** in 79% yield. Compound **250** was further subjected to the Mukaiyama aldol reaction by treating it with aldehyde **251** in the presence of $Ti(OiPr)_4$ and (*R*)-BINOL, which resulted in aldol adduct **252** with 67% yield. It was observed that utilization of the chiral (*R*)-BINOL reagent resulted in the highly enantioselective synthesis of aldol adducts. Moreover, (*R*)-BINOL can be easily recovered after the reaction as it does not incorporate within the reactants. In the next step, compound **252** was made to react with silver oxide and methyl iodide in acetonitrile followed by subsequent reduction, which gave allylic alcohol **253**. Allylic alcohol **253** was then reacted over a number of steps to synthesize component **254** of the target molecule (Scheme 34).

Salimabromide is a significant naturally occurring myxobacteria metabolite that has been extracted from plesiocystis clade of sea-water myxobacteria. It was found to be active against *Arthobacter crystallopoietes*. This metabolite contains fused cyclic rings with four consistent chiral centers.[123,124] The structural and biological significance of salimabromide with its scarce availability in nature urged researchers to develop an efficient methodology for its synthesis. In order to contribute towards the design of facile methodology for the synthesis of salimabromide, Lu *et al.*[125] in 2022 employed the Mukaiyama aldol reaction as a major step in their synthetic approach. They treated unsaturated lactone **255** with Grignard reagent **256** and compound **257** in the presence of $CuBr \cdot SMe_2$, TMSCl, lithium bromide and THF at −78 °C *via* the Maukaiyama aldol reaction, which gave compound **258** in 15% yield and aldol adduct **259** in 63% yield with a diastereoselectivity ratio of more than 19 : 1. Aldol adduct **259** was further reacted with methyl lithium and $CeCl_3$ in THF followed by oxidation in the presence of PCC, which resulted in the synthesis of cycloheptenone **260** in 83% yield. Compound **260** was then further treated *via* different steps to obtain target molecule **261** (Scheme 35).

2.6. Synthesis of naturally occurring depsipeptides

Most naturally occurring compounds have been found to inhibit the proliferation of cancerous cells. Generally, the structure of members of the rakicidin family comprises 4-amino, 2,4-pentadienolate and this moiety has been found to be effective in combating cancer cell lines effectively. Their wide

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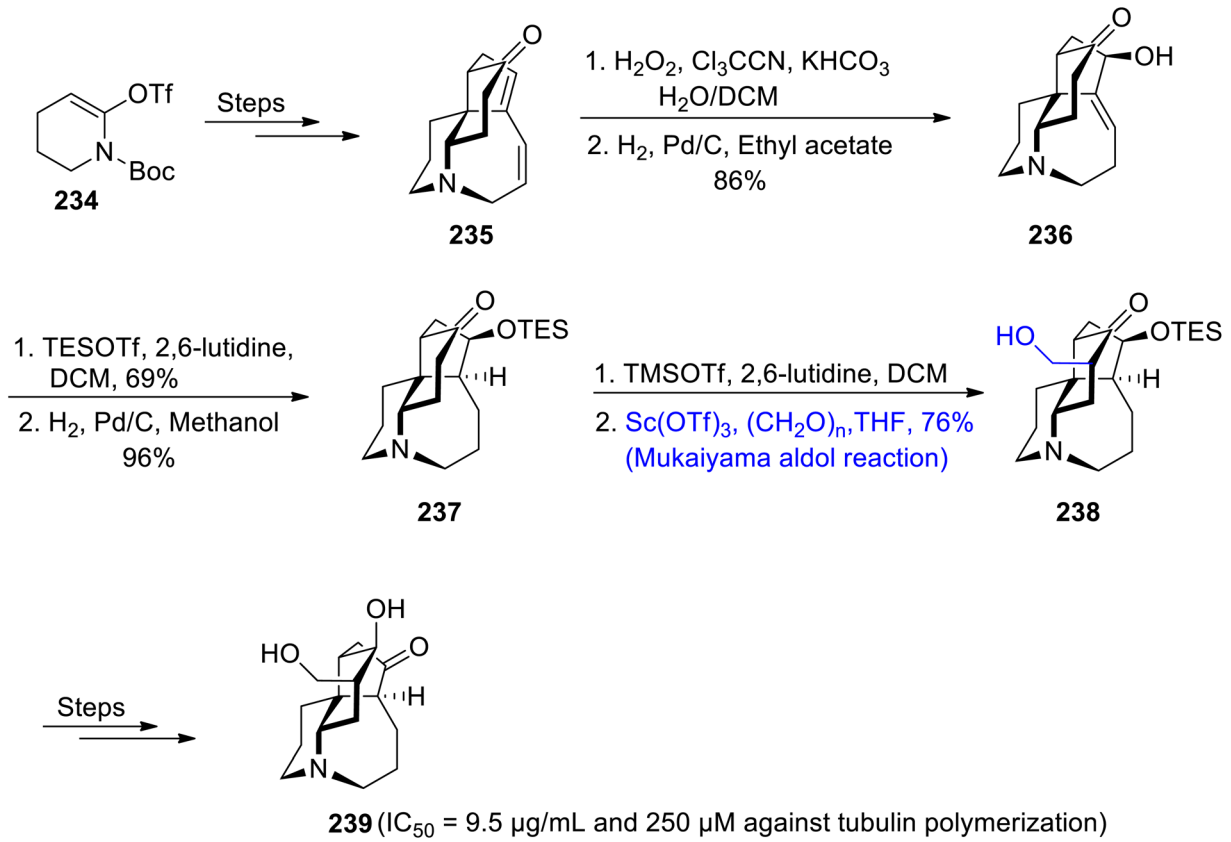

Scheme 32 Synthesis of lyconesidine B **239**.

biological significance and structural properties have attracted various researchers and urged them to attempt the total synthesis of members of the rakicidin family.[126,127] Sea-water sponges *i.e.*, *Streptomyces* species have been found to be an isolation source of rakicidin F. Han *et al.*[128] in 2022, reported the total synthesis of this naturally occurring depsipeptide by employing the Mukaiyama aldol reaction as one of the major steps. The synthetic route commenced with the synthesis of aldehyde **263** from 2-methyl-butanol **262**. Chiral aldehyde **263** was then subjected to react with silyl enol ether **264** *via* the Lewis acid catalyzed Mukaiyama aldol reaction to obtain aldol product **265**. Aldol product **265** was further hydrolyzed in the presence of lithium hydroxide followed by reaction with benzyl bromide in the presence of potassium carbonate. Then, coupling with acid **266** resulted in the synthesis of compound **267** in 95% yield. This coupled compound **267** further underwent several reactions to furnish target molecule **268** (Scheme 36).

Streptomyces species are the source of various naturally occurring secondary metabolites including rakicidin C. The depsipeptides family holds significant importance in medicinal chemistry, owing to their anti-mitotic potential. The structural framework of rakicidin C constitutes a pentadienolate moiety along with five chiral centers.[129,130] Han *et al.*[131] reported the total synthesis of naturally occurring depsipeptide *i.e.*, rakicidin C by employing the Mukaiyama aldol reaction and Oppolzer's alkylation as key steps. The synthetic methodology commenced with the synthesis of chiral aldehyde substituted compound **270** from alcohol **269** through a number of steps. This aldehyde was then subjected to the Mukaiyama aldol reaction in the presence of boron trifluoride diethyl ether by reacting compound **270** with silyl enol ether **264**, thereby giving Mukaiyama aldol product **271**. The aldol product **271** was further treated with lithium hydroxide followed by protection of the benzyl group in three to four steps. The next step involved the coupling of different components upon treatment with acid **266** in the presence of DIC and DMAP to obtain coupled product **272** in 96% yield. It was then finally converted to rakicidin C **273** over a number of steps (Scheme 37).

2.7. Synthesis of miscellaneous natural products

There are number of different sugars secreted by bacteria that are not present in mammals. The lipopolysaccharide layer of Gram negative bacteria has been found to constitute the carbohydrates *i.e.*, D-*glycero*-D-manno-heptose (D,D-Hep) and L-*glycero*-D-manno-heptose (L,D-Hep). These sugars are of significant importance in medicinal chemistry as they are found to be highly active against bacterial diseases.[132,133] In previous years, various synthetic schemes have been designed by different researchers by utilizing different name reactions. However, an efficient strategy for their synthesis was still required. For this purpose, Wang *et al.*[134] in 2020 reported the total synthesis of LPS core trisaccharide 1 of V. parahemolyticus O2 by utilizing

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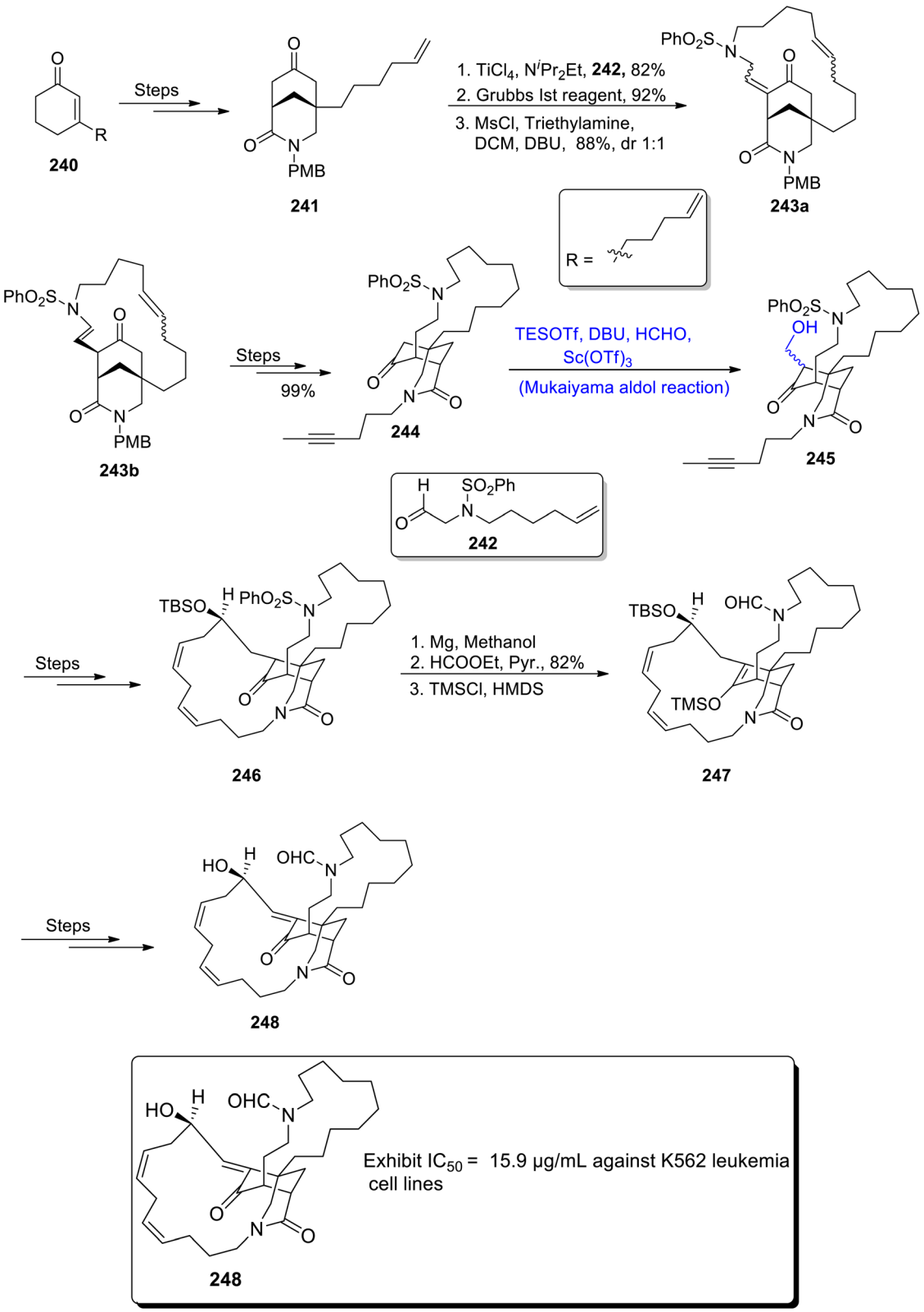

Scheme 33 Synthesis of Haliclonin A **248**.

the Mukaiyama aldol reaction as one of the main steps. In order to achieve the synthesis of the L,D-Hep subunit, they reacted L-lyxose **274** *via* several steps to obtain chiral aldehyde **275**, which was further subjected to react with silyl enol ether **276** by the Mukaiyama aldol reaction in the presence of $MgBr_2 \cdot OEt_2$, DCM and toluene. The Mukaiyama aldol product **277** was obtained in

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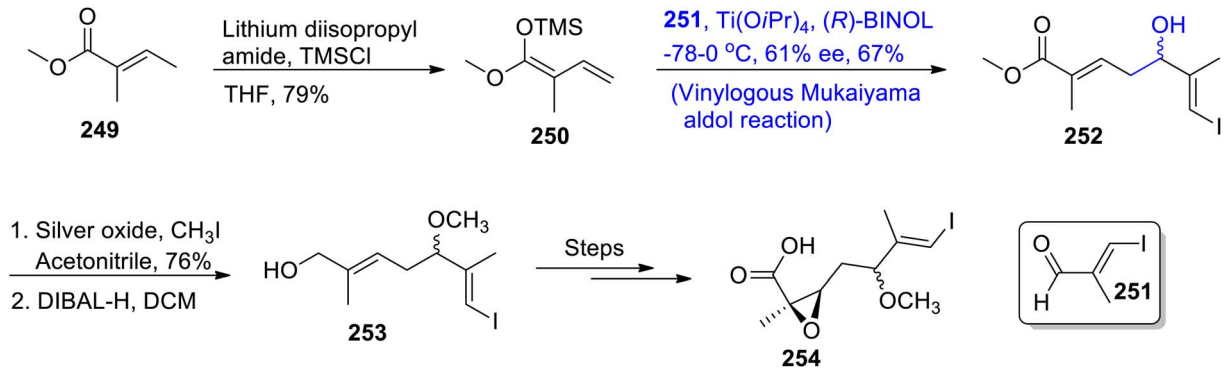
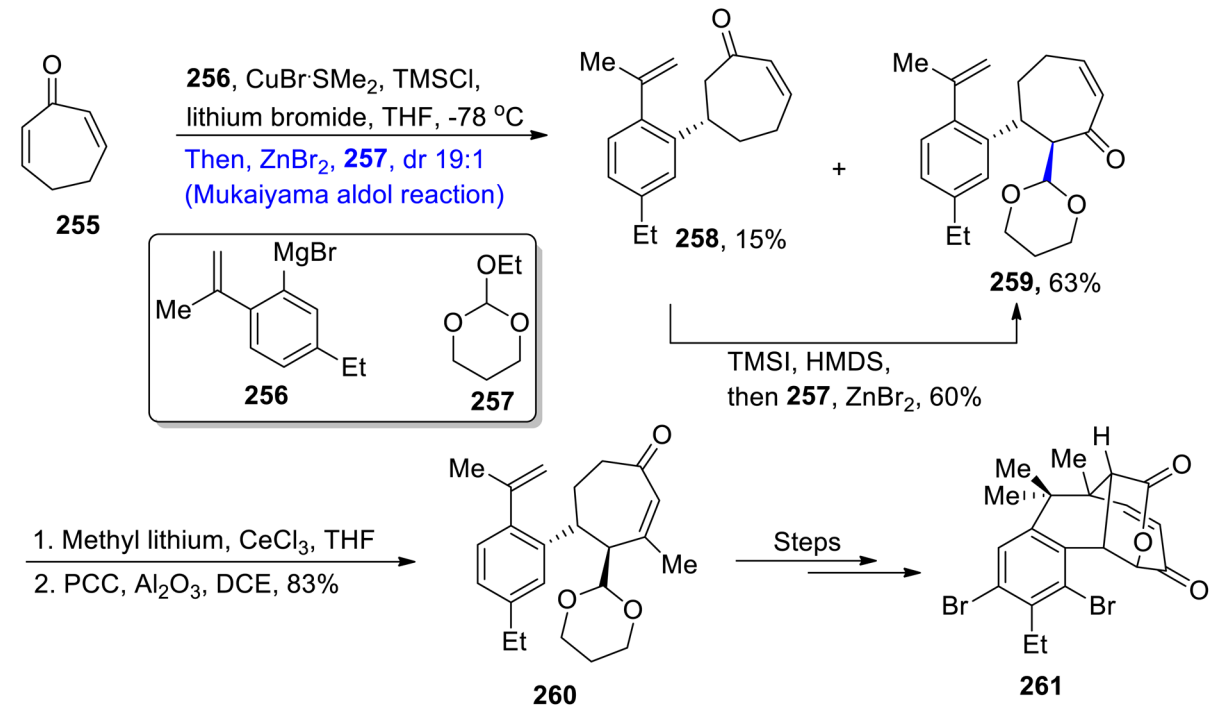


Scheme 34 Synthesis of nannocystin A **254**.



Scheme 35 Synthesis of Salimabromide **261**.

97% yield, which was followed by treatment *via* several steps to give L,D-Hep subunit **278**. Similarly, D,D-Hep subunit **282** was obtained by reacting D-ribose **279** through similar steps. The D,D-Hep subunit **282** was then reacted with compound **283** over a number of steps that involved coupling with subunit **278**, thereby leading to the synthesis of target molecule **284** (Scheme 38).

Amphidinium genus is an isolation source of about 30 members of naturally occurring macrolactones[135] found in sea water. Amphidinolide F, C2 and C3 have a strong resemblance with the amphidinolide C 1 structure with only modifications in the side chain R group. Moreover, these structurally diverse, naturally occurring macrolactones have been found to inhibit the proliferation of various types of cancerous cells effectively. Owing to their significant contribution towards medicinal chemistry, amphidinolides have inspired researchers to devise efficient synthetic pathways to obtain these naturally occurring macrolactones on a large scale. In this regard, two similar yet slightly different synthetic approaches have been reported to attain amphidinolides F, C2, C1 and C3 by Ferrie *et al.*[136] in 2022. At first, retrosynthetic analysis was carried out to obtain different fragments of the target molecule, which were then synthesized individually by using appropriate methodology. The Mukaiyama aldol reaction was carried out to obtain the C1–C9 fragment **289** in 99% yield, which is a common fragment in both synthetic approaches. In order to synthesize the C1–C9 fragment **289**, chiral aldehyde **285** was reacted with silyl enol ether **286** in the presence of TMSOTf and dichloromethane *via* the Mukaiyama aldol reaction, which gave aldol adducts **287a** and **287b** in a 25 : 75 ratio. Aldol adduct **287** was further

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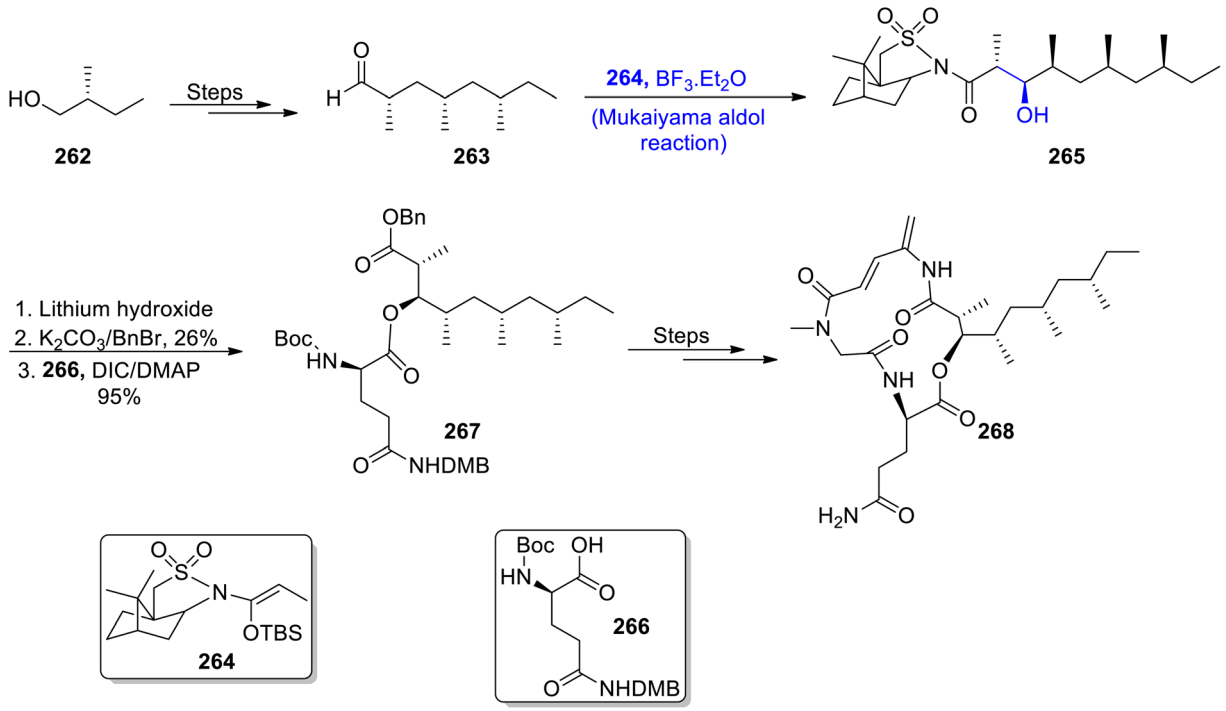
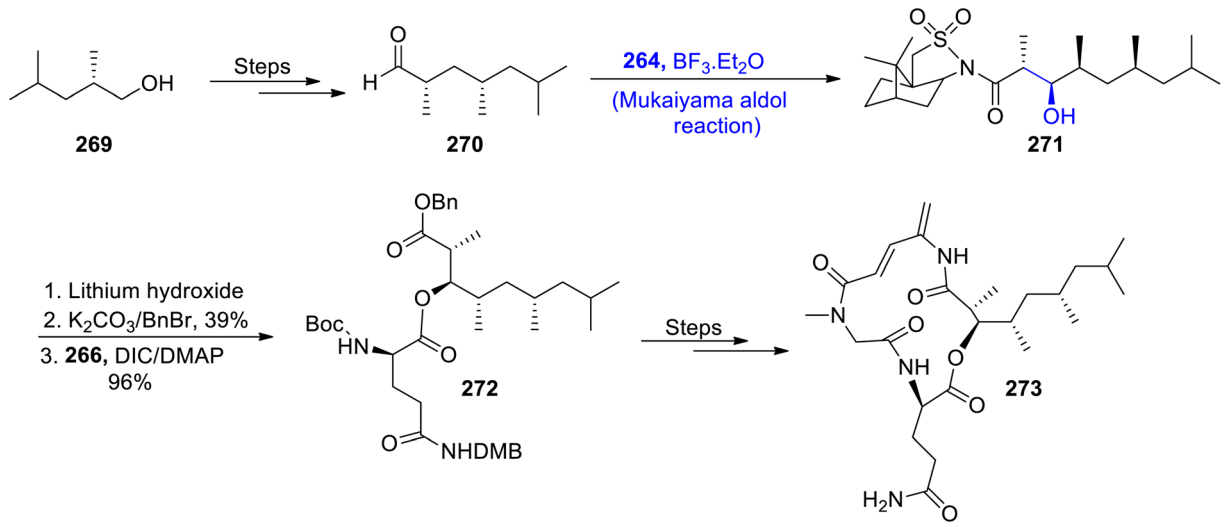


Scheme 36 Synthesis of rakicidin F **268**.



Scheme 37 Synthesis of rakicidin C **273**.

subjected to hydrogenation followed by treatment with TBSCl by using imidazole and DMF to obtain compound **288** in 73% yield with a diastereoselectivity ratio of more than 20 : 1. It was further treated over a number of steps to furnish the C1–C9 fragment **289**. Similarly, other fragments C10–C17 **290**, C18–C34 **291a** were synthesized separately. In order to couple these fragments for the total synthesis of amphidinolide F, fragment **290** was made to react with fragment **291a** by using lithium diisopropyl amide and THF followed by oxidation, which was carried out by employing Dess–Martin periodinane. In the next step, desulfonylation was carried out by using SmI_2 to attain compound **292** in 55% yield. The next step involved the reaction of compound **292** with C1–C9 fragment **289** in the presence of sodium hydride, CuDDP and triphenyl phosphine followed by treatment with the Yamaguchi reagent, which resulted in the synthesis of macrolide **293** in 41% yield. This macrolide **293** later reacted over a number of steps to obtain amphidinolide F **294** (Scheme 39).

In order to synthesize amphidinolide C3, C2 and C1, the individually synthesized C10–C17 fragment **290** and C18–34 fragment **291b** were reacted in the presence of LDA and tetrahydrofuran followed by Dess–Martin periodinane mediated

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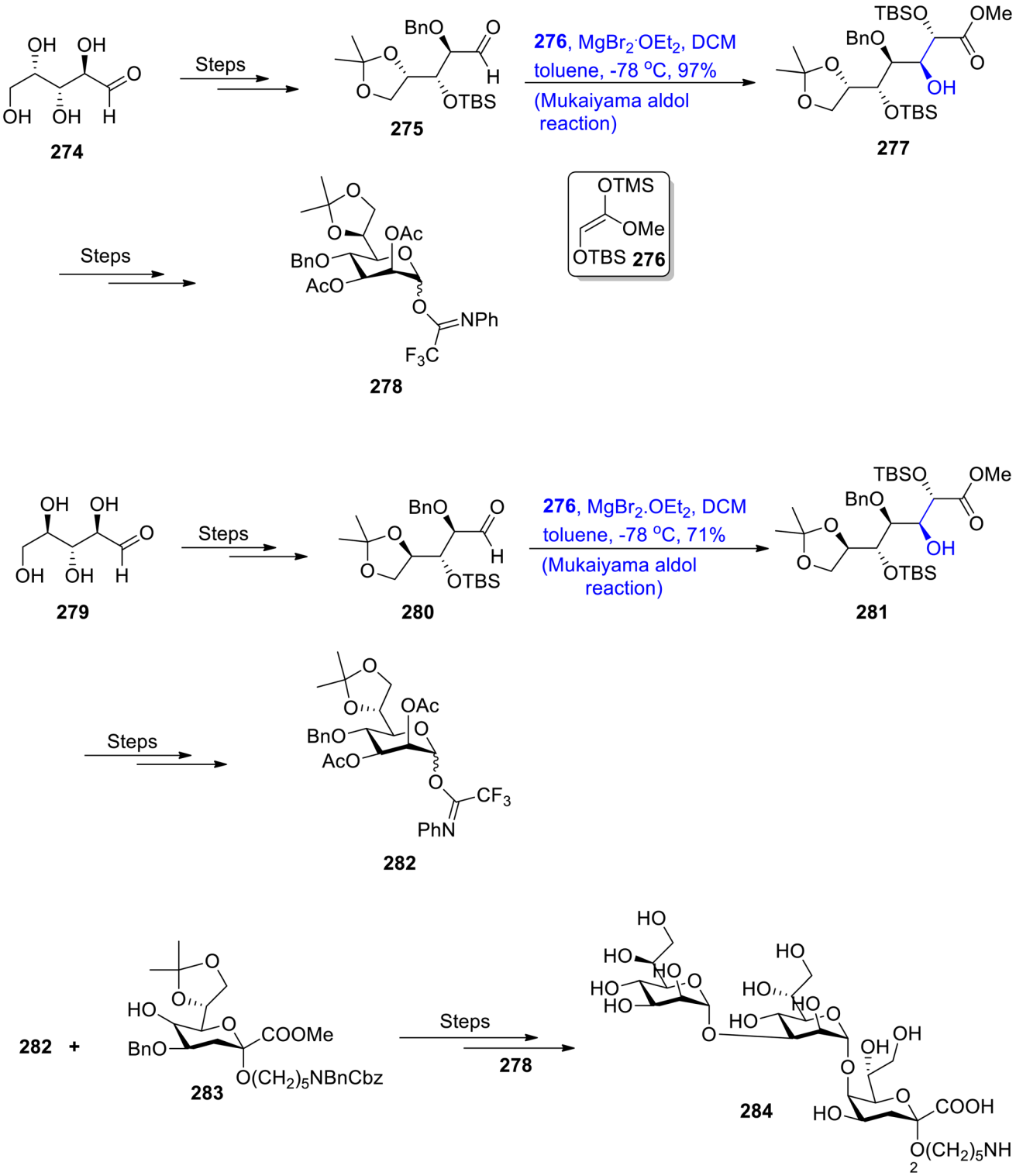

Scheme 38 Synthesis of naturally occurring carbohydrate sugars.

oxidation. Further treatment with SmI_2 in THF afforded compound **295** in 55% yield. Compound **310** was then made to react with C1–C9 fragment **289** under similar conditions to those employed for the synthesis of macrolide **294**. Reaction with hydrogen fluoride pyridine furnished hemiketal **296** in 97% yield. Hemiketal **296** was then reacted over a number of times to convert it into amphidinolide C2 **297**. The newly synthesized amphidinolide C2 **297** was subjected to selective deacetylation to obtain amphidinolide C1 **298**. Moreover, hemiketal **296** was also used to synthesize amphidinolide C3 **298** by undergoing several steps (Scheme 40).

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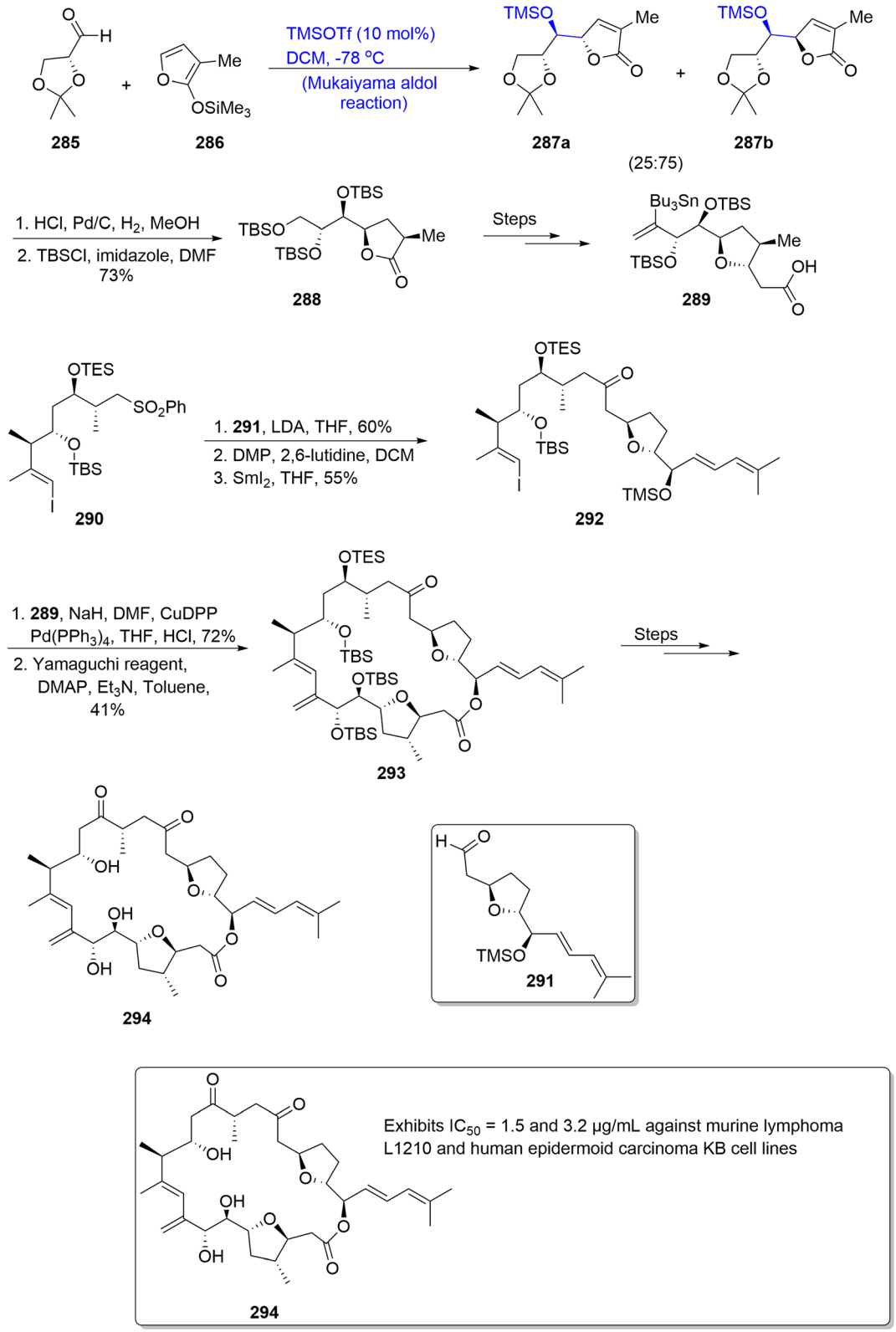

Scheme 39 Synthesis of amphidinolide F **294**.

Uncontrolled proliferation of cancer cells is one of the major reasons for increasing deaths.[137] There have been ongoing continuous efforts to tackle the effects of this deadly disease. In this regard, numerous natural products are found to be active against tumour cells. The hypothetical macroketone, which is an analogue of the migrastatin natural product, plays an effective role as an anti-cancerous agent. Considering the pharmacological importance of this analogue, Choudhury *et al.*[138] in

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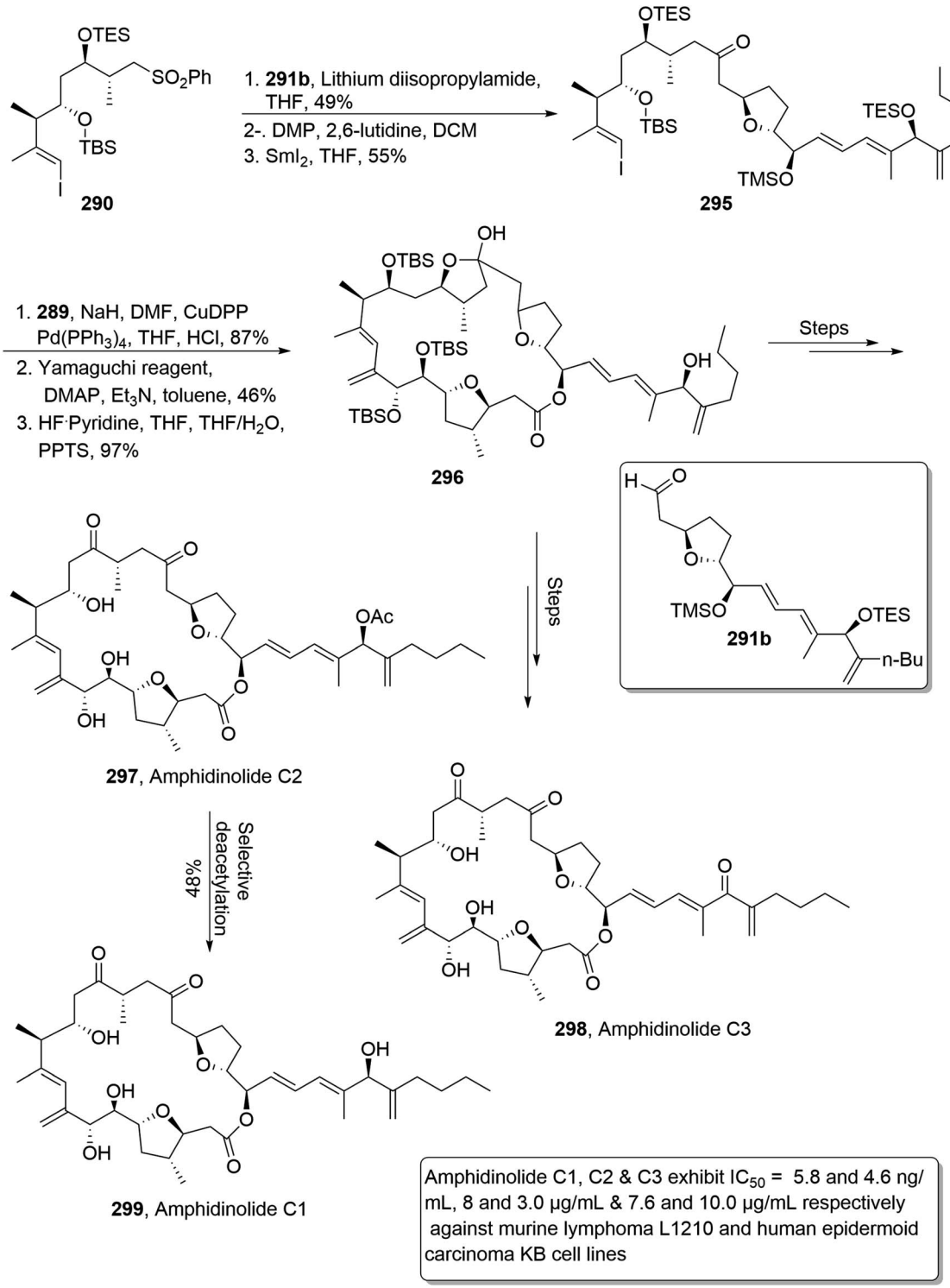

Scheme 40 Synthesis of amphidinolide C1 **299**, C2 **297** and C3 **298**.

2021, reported its total synthesis by utilizing the vinylogous Mukaiyama aldol reaction as one of its key steps. Initial steps involved the synthesis of compound **301** and aldehyde **303** from (*S*)-4-benzyloxazolidin-2-one **300** and 2,3-*O*-isopropylidene-L-tartrate **302** by known methodologies. They were then reacted together *via* the vinylogous Mukaiyama aldol reaction in the presence of titanium tetrachloride and dichloromethane, which gave aldol adduct **304** in 72% yield. Compound **300** was transformed into alcoholic fragment **305** by undergoing a number of steps. In the next step, alcoholic fragment **305** was made to react with carbon tetrabromide by employing triphenyl phosphine and dichloromethane followed by its reaction with β-keto-sulfone **306** in toluene and DBU to obtain compound **307** in

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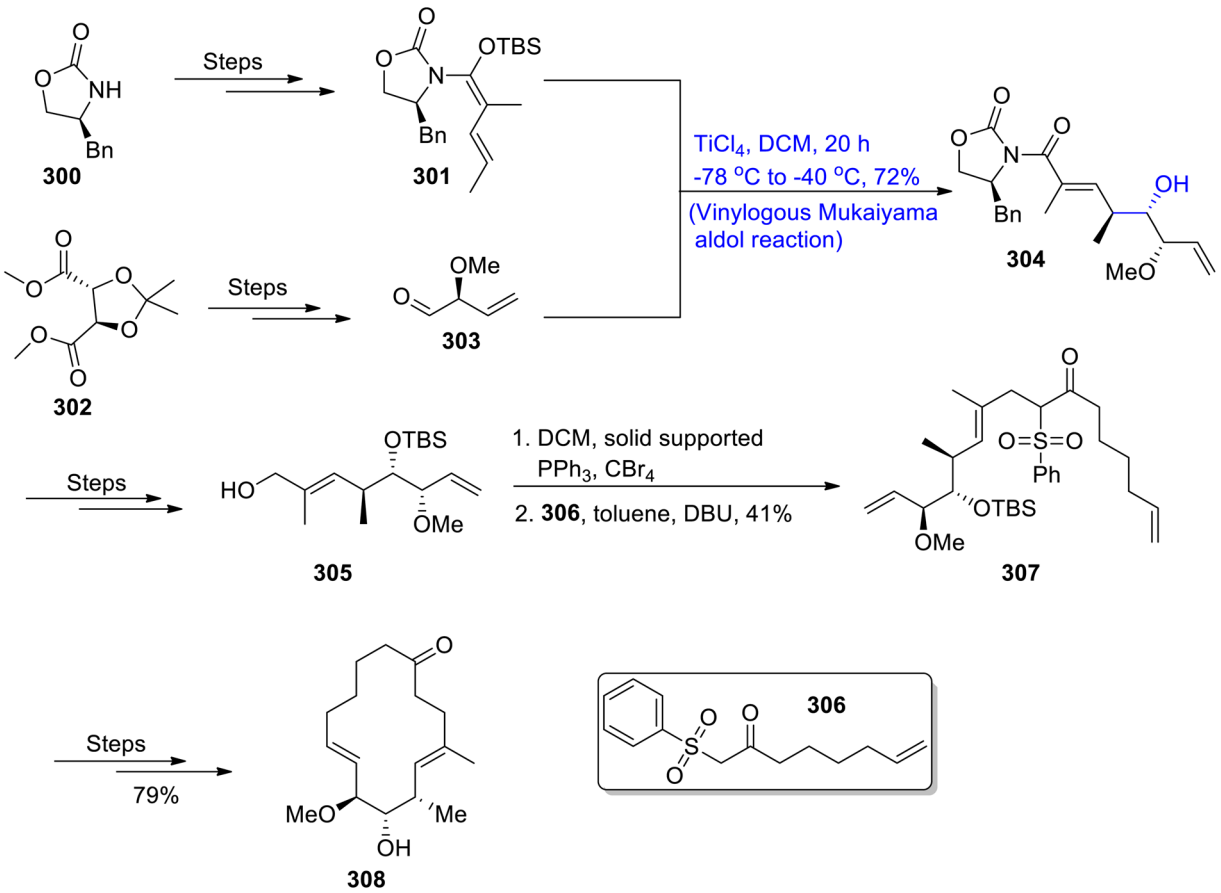

Scheme 41 Synthesis of macroketone **308**.

41% yield. Compound **307** was further treated through different steps to obtain macroketone **308** (Scheme 41).

The structure of boholamide is found to be composed of a long cyclic framework containing a 4-amino-2,4-pentadienolate moiety. It is a natural product, which is isolated from the *Truncatella* species mollusk, and is found to exhibit potent cytotoxic activity.[139] It possesses highly effective anti-tumour potential as compared to other known anti-cancerous agents *i.e.*, rakicidin A, vinylamycin, *etc.* Owing to their wide anti-tumour potential, Han *et al.*[140] in 2021 attempted to report the total synthesis of boholamide. For this purpose, compound **309** was made to react with substituted acyl chloride **310** in the presence of sodium hydride and toluene followed by its reaction with TBSOTf and trimethylamine to obtain intermediate **311**. In the next step, a racemic mixture of compound **312** was subjected to reduction, followed by its treatment with Tf_2O and pyridine. In the next step, reaction with camphorsultam derivative **313** and sodium hexamethyl dilsilazide and subsequent reduction resulted in a racemic mixture of compound **314**. It was then subjected to a reaction with intermediate **311** *via* the Lewis acid catalyzed Mukaiyama aldol reaction which gave aldol adducts **315a** and **315b** in 61% and 63% yields, respectively. These aldol adducts were further reacted with lithium hydroxide followed by protection with benzyl bromide to afford esters **316a** and **316b** in 65% and 62% yields, respectively. These synthesized esters were then reacted with Boc protected L-valine **317** in the presence of DIC and dimethylaminopyridine to obtain a racemic mixture of **318a** and **318b** in 80% and 87% yields, respectively. These were then reacted over different steps to synthesize (*S*) and (*R*) boholamide A **319a** and **319b** (Scheme 42).

Owing to their diverse biological potential, isoquinolines hold a special place in the family of natural products. Fredericamycin A has been found to be active against bacterial and cancer diseases. It is a naturally occurring substance that has been derived from *Streptomyces griseus*.[141] Various synthetic schemes have been reported by various researchers to synthesize the isoquinoline moiety. However, these methodologies suffer from various disadvantages of reaction conditions and stability of functional groups. In order to overcome these issues, Wang *et al.*[142] in 2021, demonstrated the total synthesis of naturally occurring fredericamycin A by utilizing the Mukaiyama aldol reaction and Dieckmann condensation as its key steps. The first step of the synthesis involved the reaction between substituted pyridine moiety **320** and enone **321** in the presence of lithium diisopropyl amide and tetrahydrofuran followed by reaction with sodium hydroxide, Me_2SO_4 and TBAB to synthesize compound **322** in 71% yield. Compound **322** was then subjected to reaction with TMS enol ether **323** *via* a boron triflouride diethyl etherate catalyzed Mukaiyama aldol reaction,

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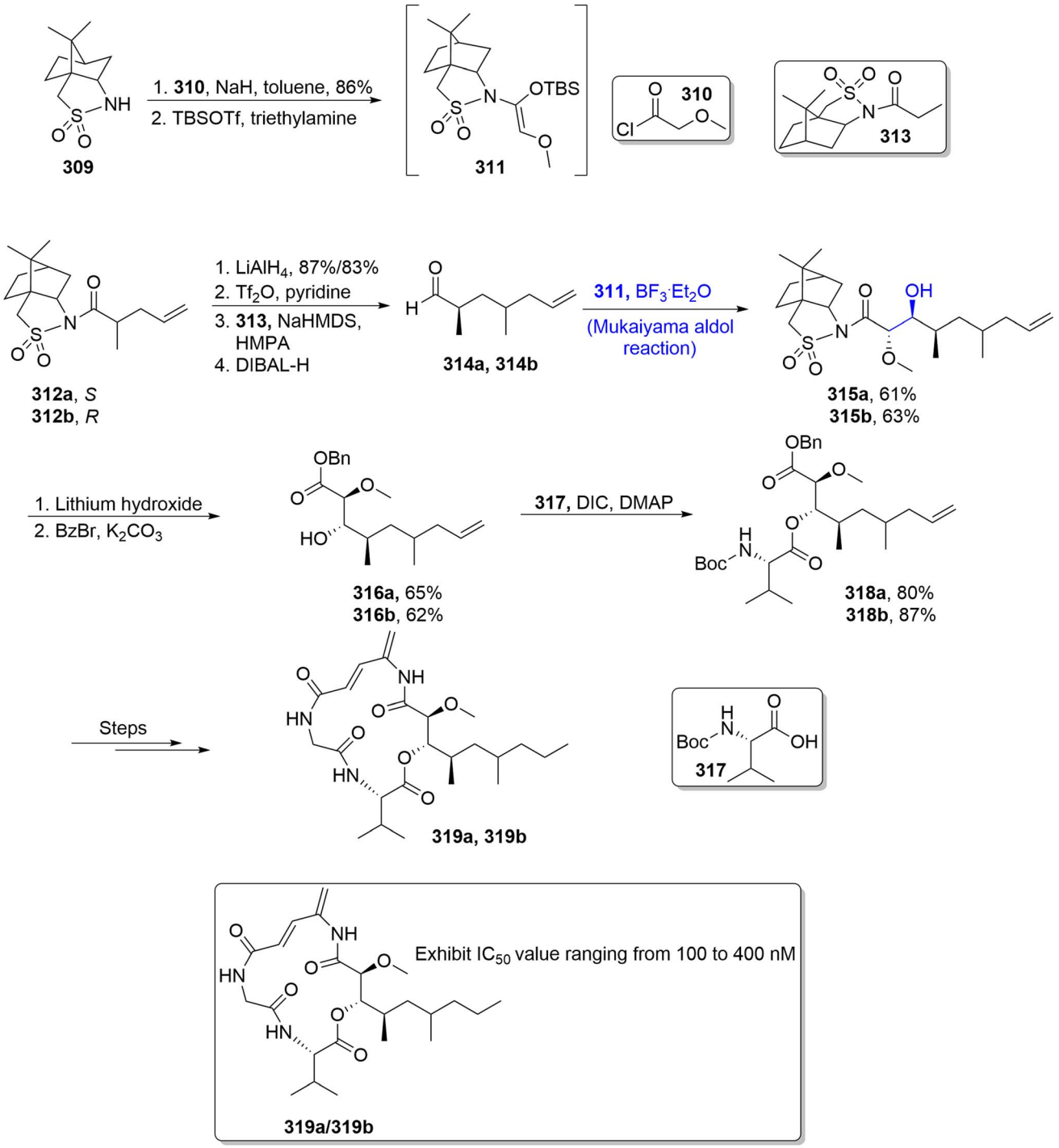

Scheme 42 Synthesis of boholamide A **319**.

which resulted in a 42% yield of spiro diketone **324**. Spiro diketone **324** was further reacted with DDQ and *p*-toluene sulfonic acid in toluene followed by subsequent Dieckmann condensation, which gave coupling product **325** after aromatization. Coupling product **325** was then reacted through several steps, thereby leading to the synthesis of the target molecule *i.e.*, fredericamycin A **326** (Scheme 43).

Hydrindanes are abundant in nature and hold significant importance in medicinal chemistry as they are involved in the synthesis of pharmaceutically valuable organic compounds.[143] Different organic compounds such as maltophilin, clifednamides, amaminol A and ikarugamycin constitute hydrindanes. Various research groups have reported the synthesis of hydrindanes by using the Michael addition reaction. However, Sinast *et al.*[144] reported the total synthesis of hydrindanes based

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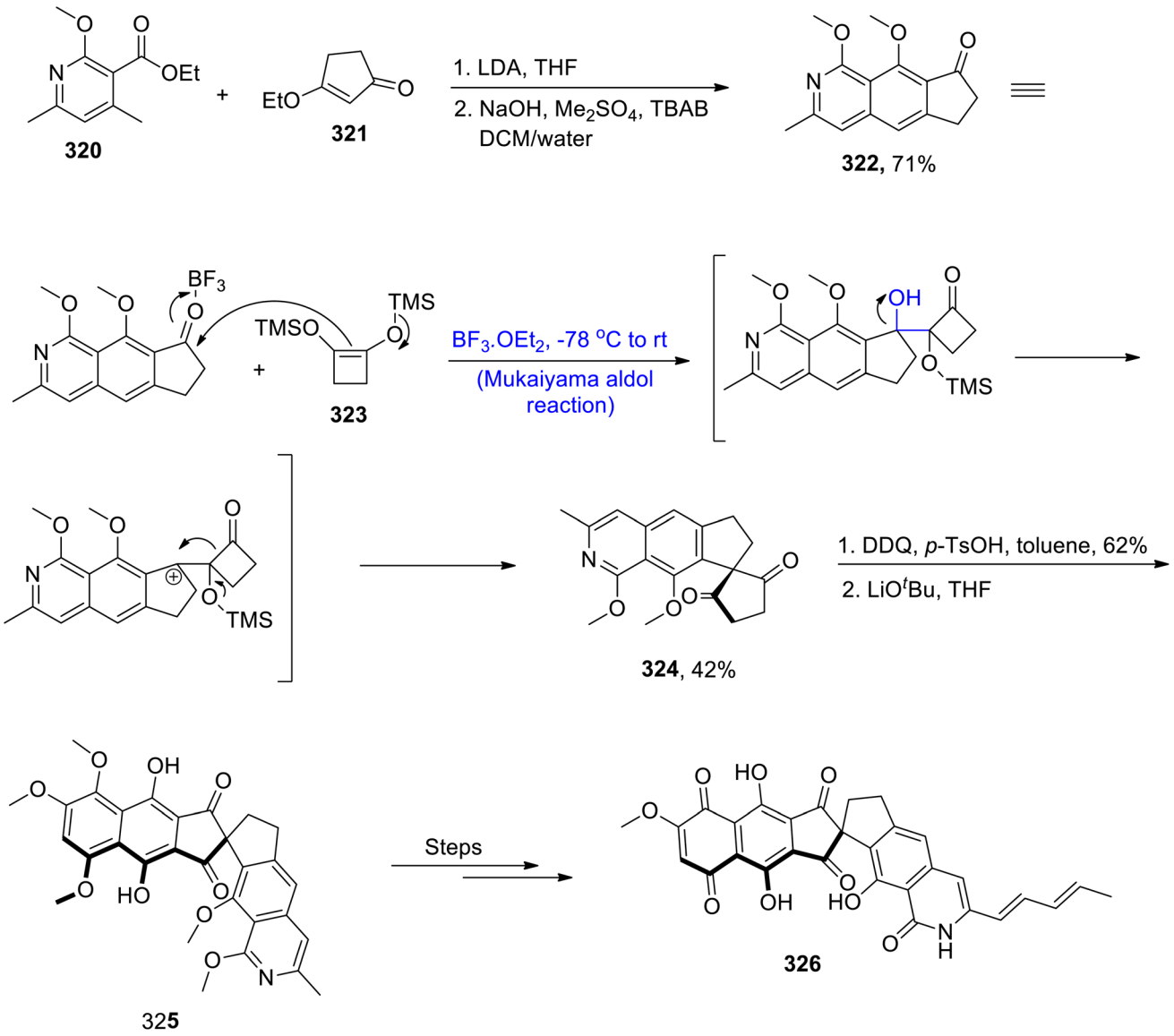

Scheme 43 Synthesis of fredericamycin A **326**.

clifednamides A and B by utilizing the Mukaiyama aldol reaction and Michael addition as the key steps. Streptomyces sp. JV178 are the source of these biologically active organic compounds, which are effective against division of cancer cells. In the first step of synthesis towards hydrindane, dimethyl malonate **327** and crotonaldehyde **328** were reacted in the presence of the Jorgensen–Hayashi catalyst followed by reaction with carbon tetrabromide by using triphenyl phosphine and dichloromethane, which gave compound **329** in 96% yield. Compound **329** was then reacted with lithium diisopropyl amide and trimethyl silyl chloride in tetrahydrofuran, which resulted in the synthesis of TMS alkyne **330** in 80% yield. Compound **330** was further reacted with lithium chloride and water using DMF as the solvent to furnish methyl ester **331** in 81% yield. Methyl ester **331** then underwent the titanium tetrachloride catalyzed Mukaiyama aldol reaction upon treatment with aldehyde **332** in the presence of TMSCl and sodium hexamethyl disilazide to obtain adduct **333** in 66% yield, which was reacted over number of steps, to obtain a racemic mixture of hydrindanes **334a** and **334b**. Hydrindane **334** can then be easily converted into clifednamies (Scheme 44).

Curvulone A and curvulone B are found to be highly biologically active as they play a significant role in combating fungal diseases as well as also inhibiting the proliferation of cancerous cells. They are isolated from the known sea-water algal species *i.e.*, *Gracilaria folifera*.[145] Considering the utility of the curvulone type natural product, Banoth *et al.*[146] in 2020 carried out a brief and efficient total synthesis of curvulone by utilizing the Mukaiyama aldol reaction as one of its key steps. For this purpose, homoallylalcohol **335** was reacted with acrolein and Hoveyda Grubbs II reagent in dichloromethane to obtain unsaturated aldehyde **336** in 87% yield. Aldehyde **336** then underwent the Mukaiyama aldol reaction by reacting with trimethyl(vinyloxy)silane **337** by utilizing iodine and DCM to

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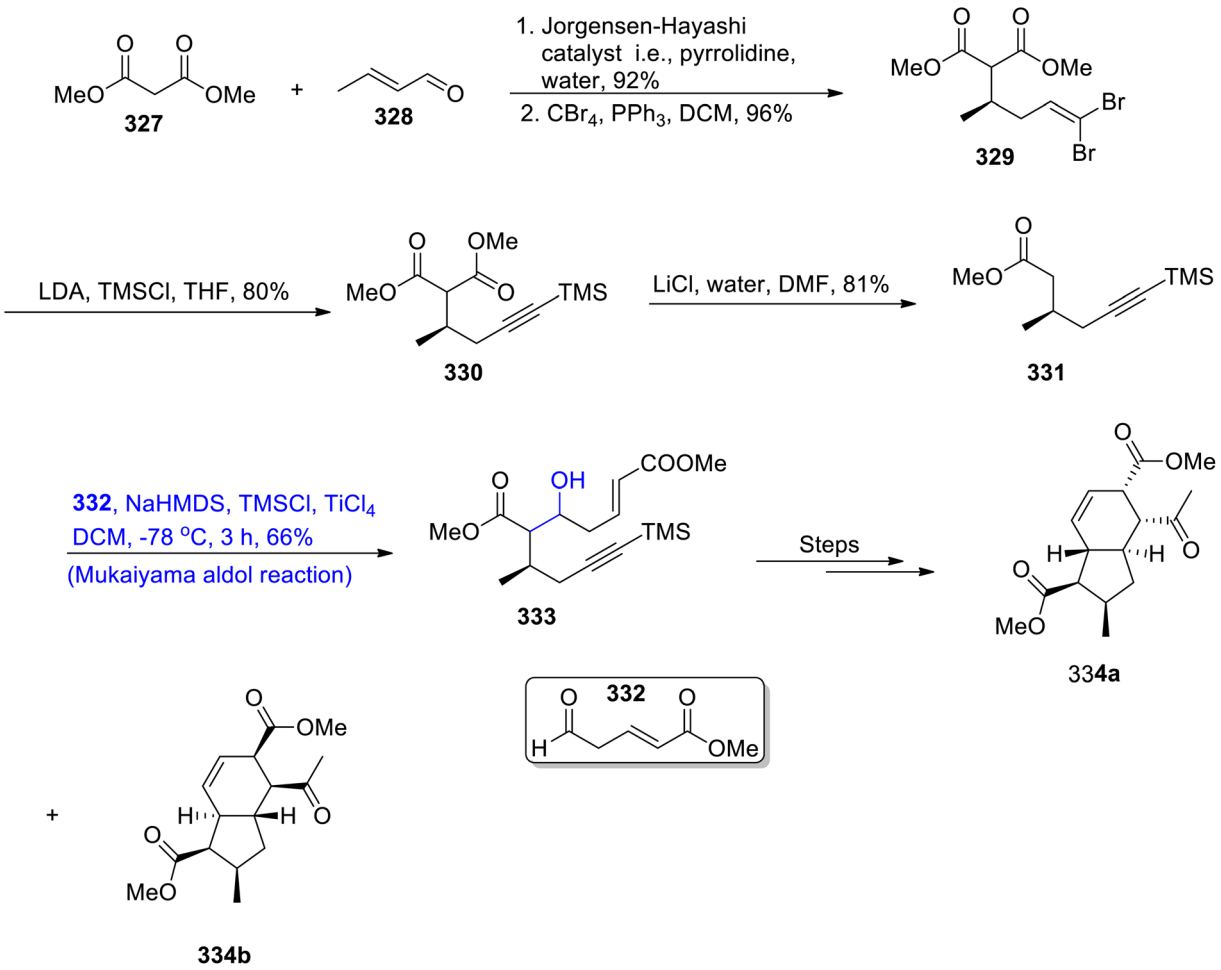
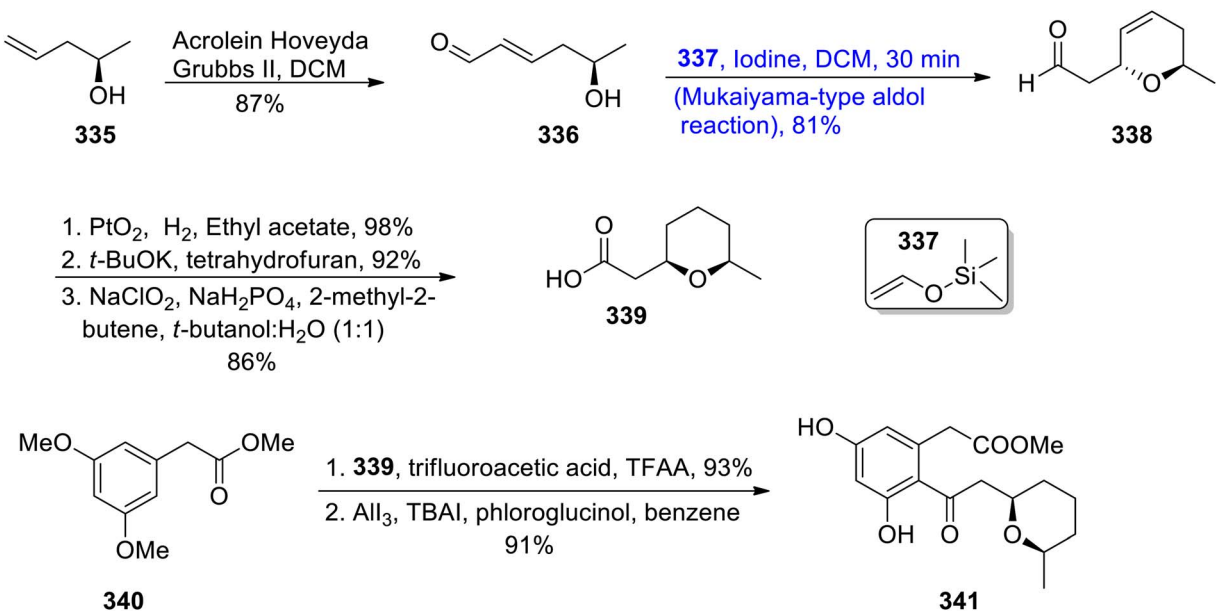


Scheme 44 Synthesis of hydrindanes 334.



Scheme 45 Synthesis of curvulone B 341.

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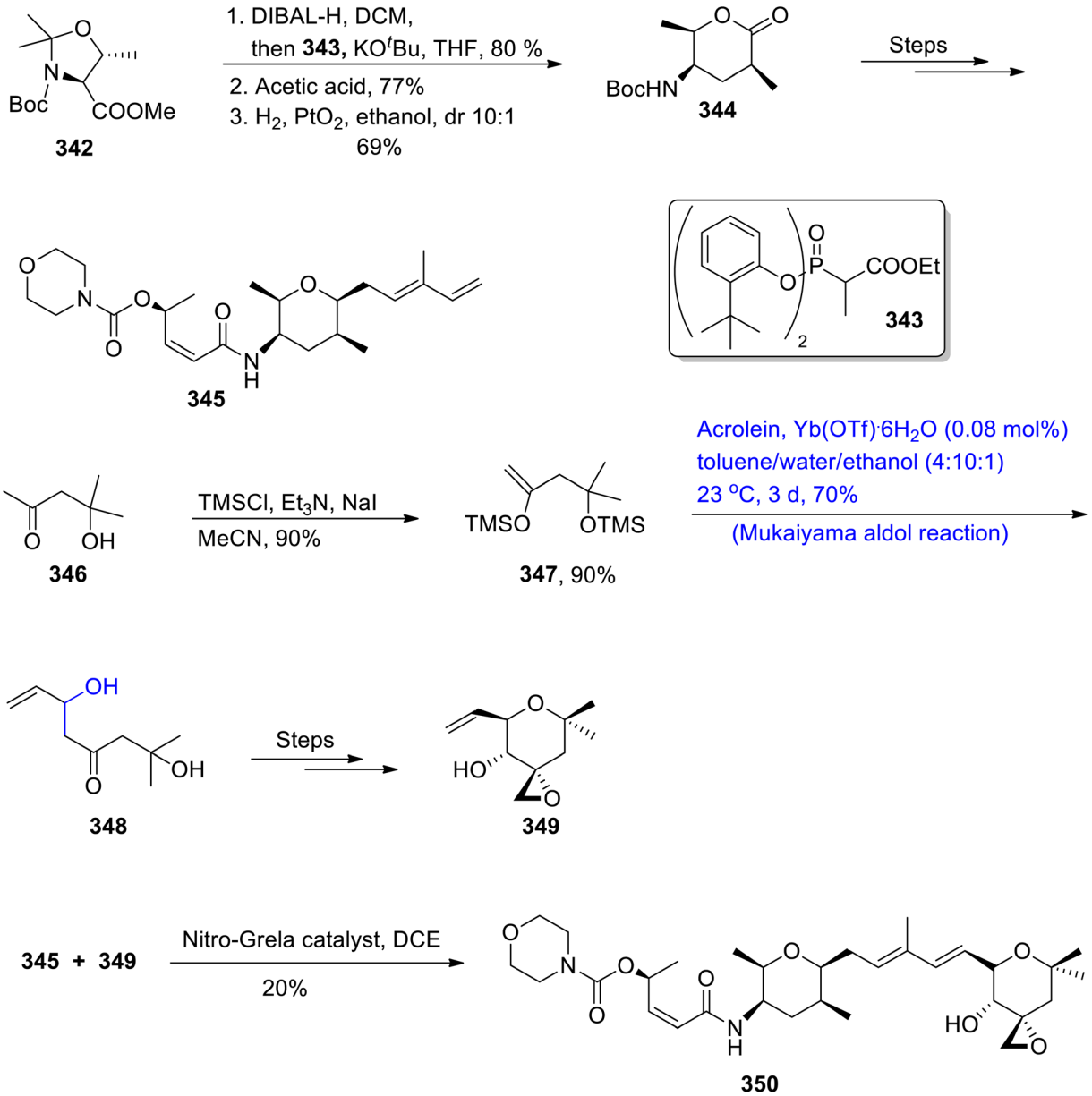

Scheme 46 Synthesis of meayamycin B **350**.

obtain the substituted dihydropyran ring **338** in 81% yield. Compound **338** was further subjected to reduction by employing Adam's catalyst, followed by the oxa-Michael process as a result of the reaction with *tert*-butoxide in tetrahydrofuran. Furthermore, Pinnick oxidation was carried out by using $NaClO_2$, 2-methyl-2-butene, and NaH_2PO_4 in the presence of butanol : water, which led to the synthesis of acid fragment **339** in 86% yield. In the next step, acetate compound **340** was made to react with previously synthesized fragment **339** in trifluoroacetic acid and TFAA. The resulting compound was further demethylated by utilizing Maeir's conditions *i.e.*, AlI_3, TBAI, phloroglucinol and benzene, which resulted in the synthesis of curvulone B **341** in 91% yield (Scheme 45).

Meayamycin B is widely utilized as a highly active modulator of the splicing factor of 3b subunit 1.[147] The reported synthetic routes for meayamycin B are too long and time consuming. Thus, in order to supplement its availability, Bressin *et al.*[148] in 2020, attempted to describe the total synthesis of meayamycin B by utilizing the Mukaiyama aldol reaction, Corey–Chaykovsky reaction, Nicolaou-type-ring opening reaction of epoxide and altered Horner–Wadsworth–Emmons *Z*-selective olefination as the key steps. The first step of the total synthesis involved the reduction of ester **342**, followed by its reaction with phosphonate **343** and KO^{t}Bu. Furthermore, reaction with acetic acid and then with a hydrogen molecule in the presence of platinum oxide and ethanol gave lactone **344**, which was transformed into fragment **345** *via* several steps. In the next step, ketone **346** was converted to silyl ether **347** in 90% yield, which was then made to react with acrolein by the Yb(OTf)·6H_2O catalyzed Mukaiyama aldol reaction, which gave aldol adduct **348** in 70%

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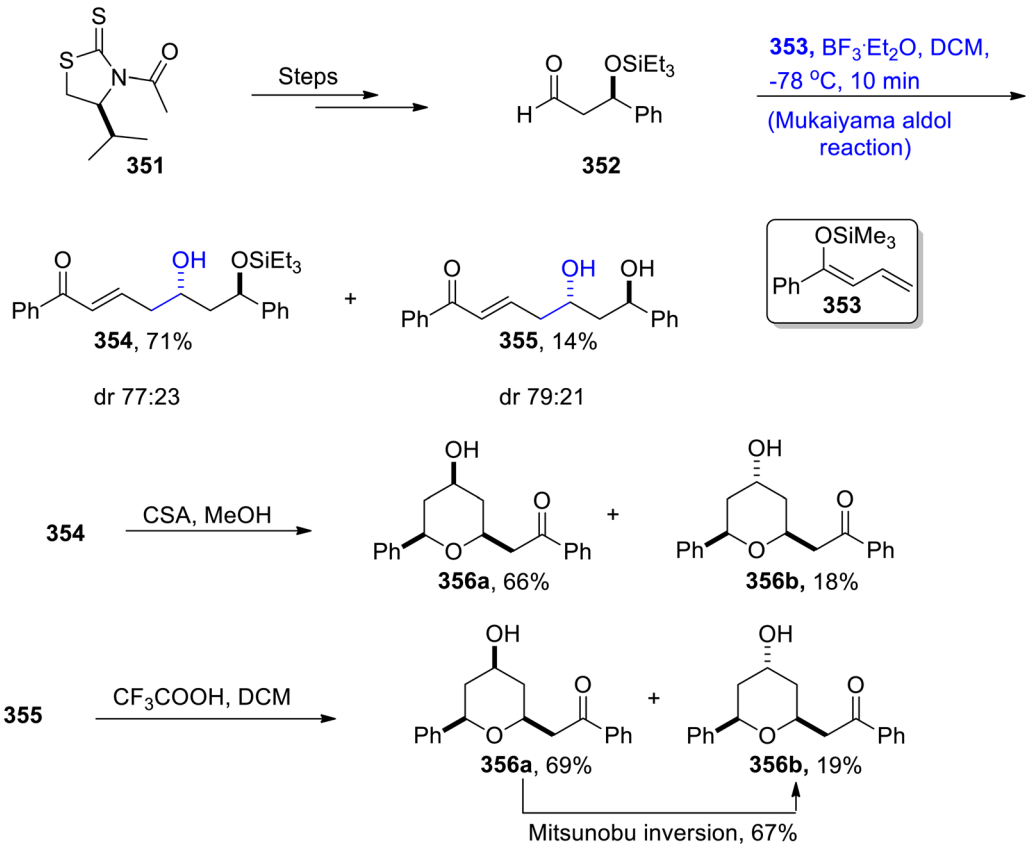

Scheme 47 Synthesis of diospongin A **356b**.

yield. Adduct **348** was further reacted *via* several steps to synthesize fragment **349.** Fragments **345** and **349** were then coupled *via* a Nitro-Grela catalyst in DCE to obtain meayamycin B **350** in 20% yield (Scheme 46).

Pharmacologically important diospongin A and B are obtained from *Dioscorea spongiosa*. These are pyran containing molecules which inhibit the process of the breakage of bones. Various researchers have reported the total synthesis of these natural products by utilizing the oxa-Michael addition and Prins cyclization. However, the concise and efficient total synthesis of diospongin A was reported by Vaithegi *et al.*[149] in 2020 by using the Mukaiyama aldol reaction. For this purpose, they initiated the synthesis of the target molecule by obtaining β-alkoxy aldehyde **352** in 75% yield by reacting compound **351** through several steps. Chiral β-alkoxy aldehyde was further reacted with silyl ether **353** *via* a Lewis-acid catalyzed Mukaiyama aldol reaction in DCM to obtain diastereomers **354** and **355** in 71% and 14% yields, respectively, with 77 : 23 and 79 : 21. Diastereomer **354** was reacted with CSA and methanol, which resulted in the synthesis of 5-*epi*-diospongin A **356a** in 66% yield and diospongin A **356b** in 18% yield. Similarly, diastereomer **355** was further reacted with trifluoroacetic acid in the presence of DCM to obtain **356a** in 69% yield and diospongin A **356b** in 19% yield. Later on, compound **356a** underwent Mitsunobu inversion to synthesize diospongin A **356b** in 67% yield (Scheme 47).

Kong *et al.*[150] reported the efficient and concise total synthesis of grayanotoxin III with a highly enantioselective approach. For this purpose, they treated compound **357** with phosphorus tribromide in DMF and chloroform followed by its reaction with *p*-TsOH and $HC(OMe)_3$ in the presence of methanol, which gave compound **358** in 54% yield. Compound **358** was then made to react with compound **359** and **360** in the presence of TMSOTf and MTBE at −78 °C *via* the Mukaiyama aldol reaction followed by the Hosomo–Sakurai reaction, which resulted in the synthesis of aldol adduct **361** in 58% yield. It was then transformed into compound **362** by undergoing a number of reactions. Compound **362** was further subjected to the *O*-Diels–Alder reaction upon treatment with compound **363**, which led to the synthesis of compound **364** in 65% yield. Compound **364** was then finally treated over several steps, thereby giving target molecule **365** in 51% yield (Scheme 48).

Various natural products containing heterocyclic rings have been synthesized by numerous research groups and their evaluation against bacterial, fungal, viral and cancer cell lines has been carried out. In this regard, Moriyama *et al.*[151] in 2021 reported the chiral total synthesis of both enantiomers of naturally occurring polymuthipyranone B by employing the chiral BINOL reagent mediated Mukaiyama aldol reaction as key step. Moreover, they carried out the synthesis of their three synthetic counterparts. Biological evaluation of these naturally occurring compounds revealed that the enantiomers of

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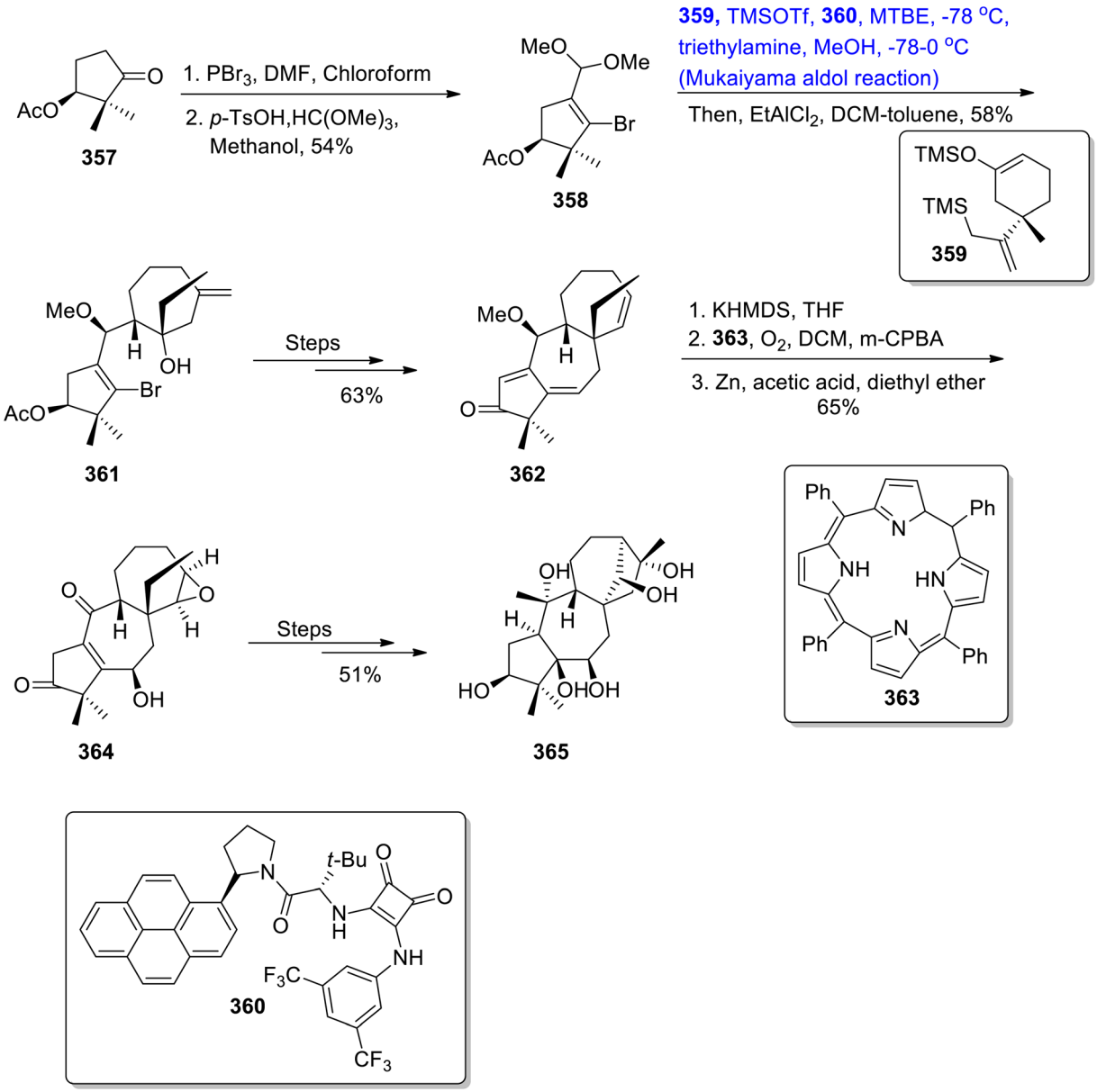

Scheme 48 Synthesis of grayanotoxin III **365**.

polymuthipyranone B were highly active against both cell lines of bacteria *i.e.*, ATCC 43300 and ATCC 33591. The Mukaiyama aldol reaction was utilized for the synthesis of these biologically active scaffolds. Their synthetic scheme involved the reaction of decanal **366** with Chan's diene **367** *via* the Mukaiyama aldol reaction involving $Ti(OiPr)_4$, and (*S*)-BINOL in tetrahydrofuran, followed by treatment with HCl, which gave β-ketoester **368a** in 78% yield with 98% enantiomeric excess. **368a** was further hydrolyzed with potassium hydroxide followed by its reaction with carboxylic acid **370** to carry out the incorporation of the acyl group by using the EDCL reagent in the presence of dimethylaminopyridine and dichloromethane, which furnished the (*R*)-enantiomer of polymuthipyranone B **371a** in 48% yield with 98% enantiomeric excess. Similarly, the (*S*)-enantiomer of polymuthipyranone B **371b** was synthesized in 50% yield with more than 98% enantiomeric excess *via* similar steps and by employing (*R*)-BINOL involving Mukaiyama aldol reaction (Scheme 49).

Pyran substituted compounds are generally found in nature,[152] involving members of kavalactone family and (−)-pestalotin. Kimura and Tamura's group for the first time, isolated (−)-pestalotin from *Pesalotia cryptomeriaecola* and found that (−)-pestalotin work in harmony with gibberellin to promote the growth of plants. Owing to their remarkable usage, there have been numerous reports on the total synthesis of naturally occurring (−)-pestalotin. Moriyama *et al.*[153] in 2020 reported the chiral synthesis of naturally occurring (−)-pestalotin diastereomers by using readily accessible chiral (*R*)-glycidol as the starting reagent. They devised two synthetic routes for the synthesis of this naturally occurring molecule which

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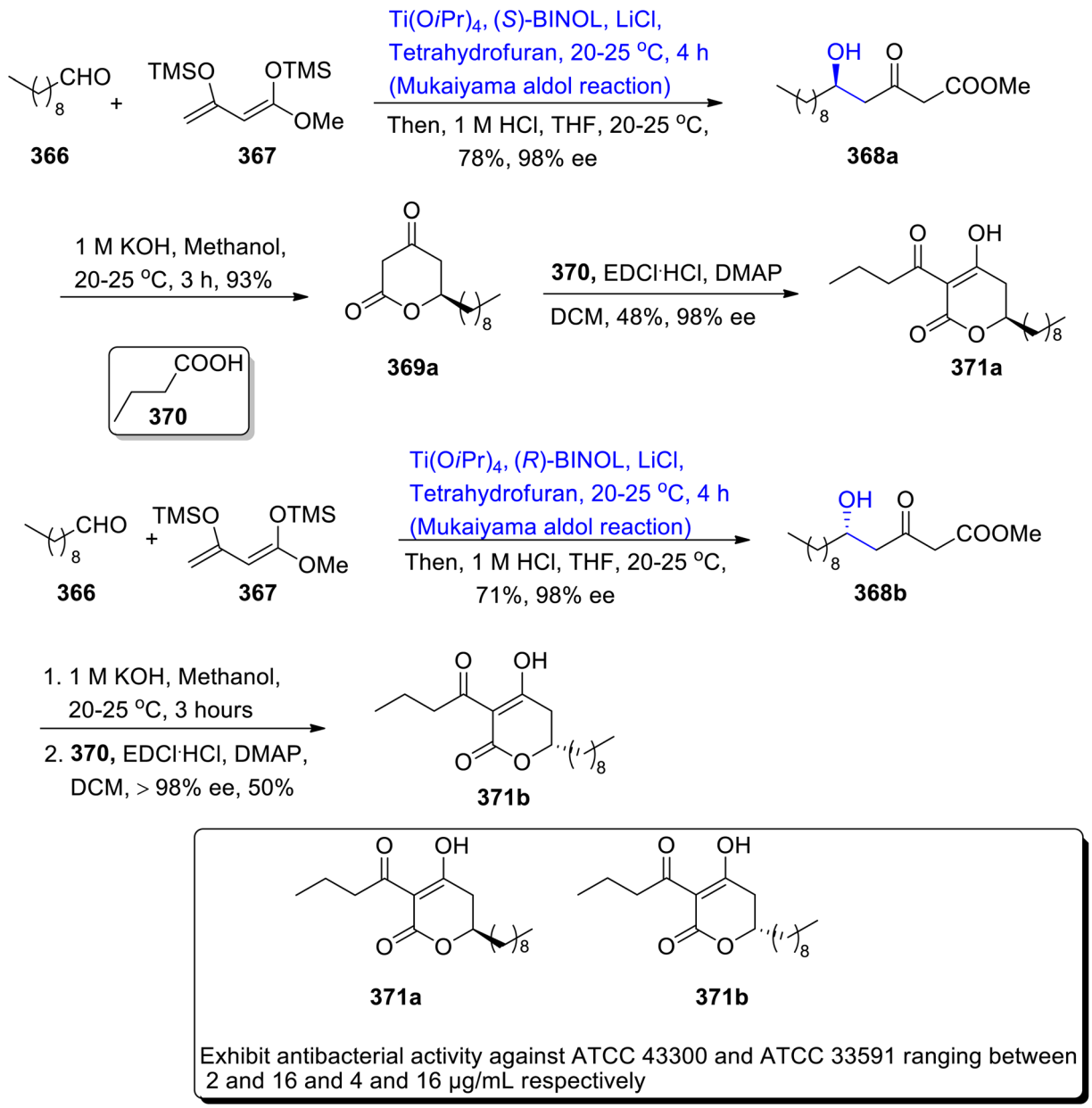

Scheme 49 Synthesis of enantiomers of polymuthipyranone B **371a** and **371b**.

involved the catalytic asymmetric Mukaiyama aldol reaction and the catalytic diastereoselective Mukaiyama aldol reaction. The synthetic scheme began with the synthesis of (*S*)-α-benzyloxy aldehyde **373** from (*R*)-glycidol by undergoing several steps. Benzyloxy aldehyde **373** was then reacted with Chan's diene **374** *via* the catalytic asymmetric Mukaiyama aldol reaction by using $Ti(iOPr)_4$, (*S*)-BINOL and lithium chloride, which resulted in the synthesis of aldol adducts **375a** and **375b** in 31% yield with high dr = 93 : 7. Diastereomer **375a** was further reacted with potassium hydroxide–methanol–water followed by treatment with Me_2SO_4 and acetone to obtain (1*S*,6*S*)-**376** in 88% yield with a 91 : 9 diastereoselectivity ratio. Compound **376** was then reacted with hydrogen and palladium hydroxide/C catalyst to obtain the target molecule *i.e.*, pestalotin **377a** in 60% yield along with unnatural diastereomer **377b** in trace amounts. Similarly, (−)-pestalotin was synthesized by employing the titanium chloride catalyzed Mukaiyama aldol reaction using DCM as solvent. The Mukaiyama aldol adducts **376a** and **376b** were then subjected to deprotection in similar conditions to synthesize pestalotin **377a** (Scheme 50).

Huffman *et al.*[154] in 2021 attempted to report the total synthesis of merilactone A by carefully controlling chirality over the attached ring system. Fused rings having tetrahedral bridgeheads are used in the synthesis of various natural products. The concise and efficient total synthesis of naturally occurring merilactone A was reported by Huffmann *et al.* in 2021 by employing the Mukaiyama aldol reaction as one of its key steps. The synthesis began with the heterodimerization

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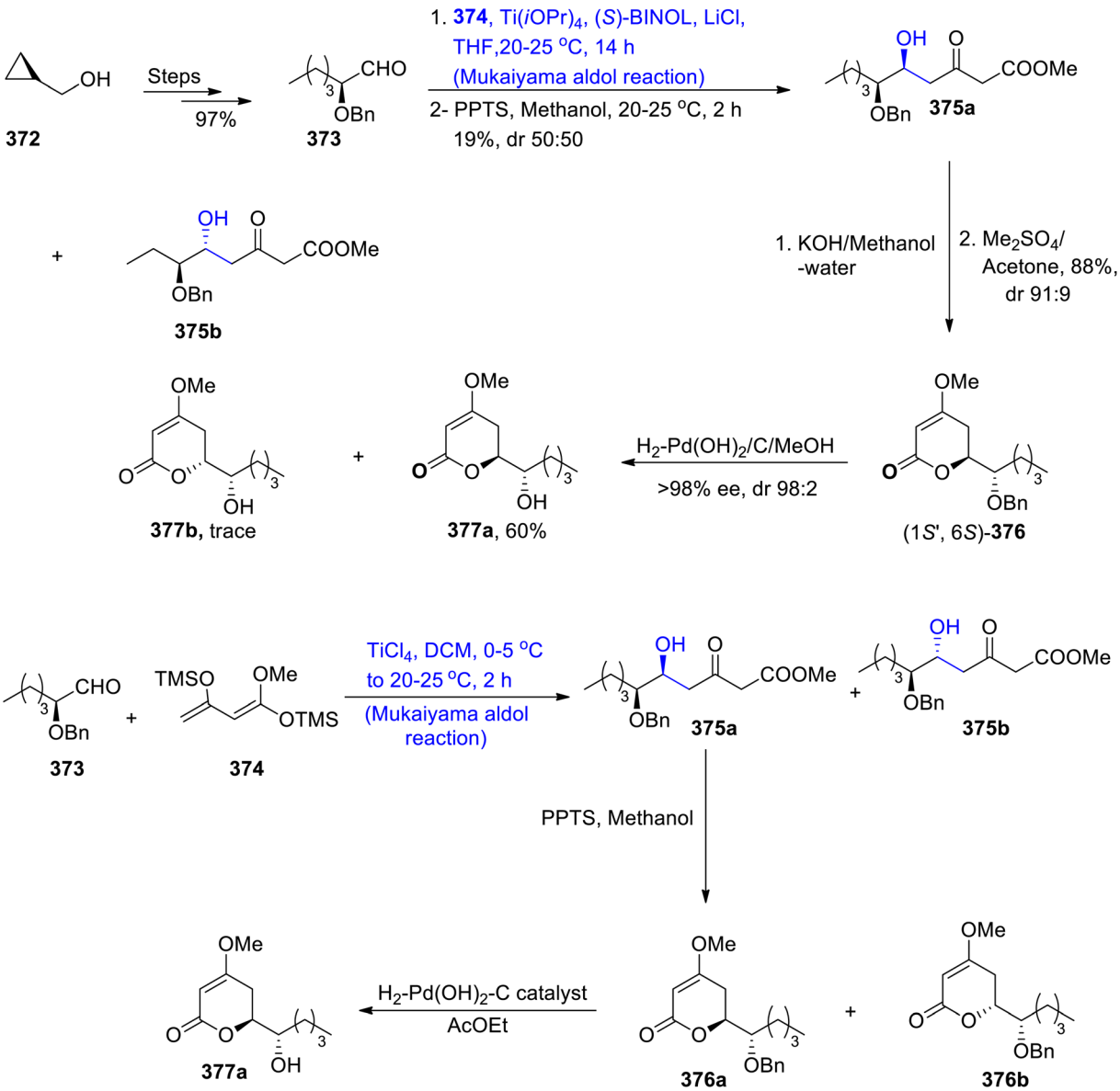

Scheme 50 Synthesis of (−)-pestalotin **377a**.

reaction between thioester butenolide **378** with lithium furan-2-olate **379** in tetrahydrofuran, which gave the product in a 95 : 5 diastereoselectivity ratio. The next step involved the reaction with TIPSOTf in the presence of trimethylamine and DCM followed by methylation, which was carried out by using potassium carbonate and acetone, thus giving compound **380** in 80% yield. Compound **380** was further treated with methyl vinyl ketone (MVK) *via* a titanium chloride catalyzed Mukaiyama–Michael reaction in the presence of dichloromethane, which led to the synthesis of compound **381** in 58% yield with a diastereoselectivity ratio of more than 20 : 1. Compound **381** was then reacted over a number of reactions to synthesize target molecule **382** (Scheme 51).

G-protein incorporated receptor 40 cells are found to be highly demonstrative in pancreatic cells, thus playing an important role in combating diabetes. MK-2305 has been found to play a leading role in the G-protein incorporated receptor 40.[155] Considering the significance of MK-2305, Zhong *et al.*[156] in 2022, reported an efficient and concise route towards its total synthesis. The first step involved the reaction between 3-chloro-4-fluorobenzotriflouride **383** and resorcinol **384** in the presence of potassium hydroxide and dimethylsulfoxide, which gave the phenol substituted compound **385** in 99% yield. Then, compound **385** was made to react with acrylonitrile by using potassium carbonate and *tert*-butanol *via* an oxy-Michael addition reaction. It was followed by treatment with trifluoroacetic acid in the presence of water *via* the Hoeben–Hoesch reaction, which led to the synthesis of chromanone **386** in 80% yield. Chromanone **386** was further subjected to the titanium chloride catalyzed Mukaiyama aldol reaction/elimination array, on reacting with silyl enol ether **387**, which furnished compound

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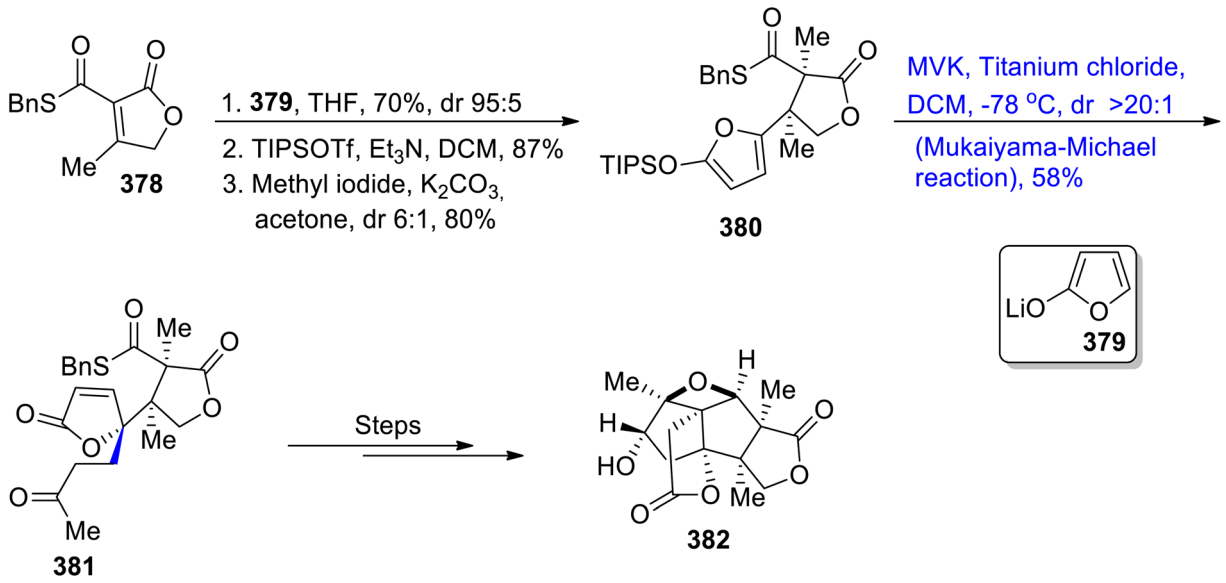
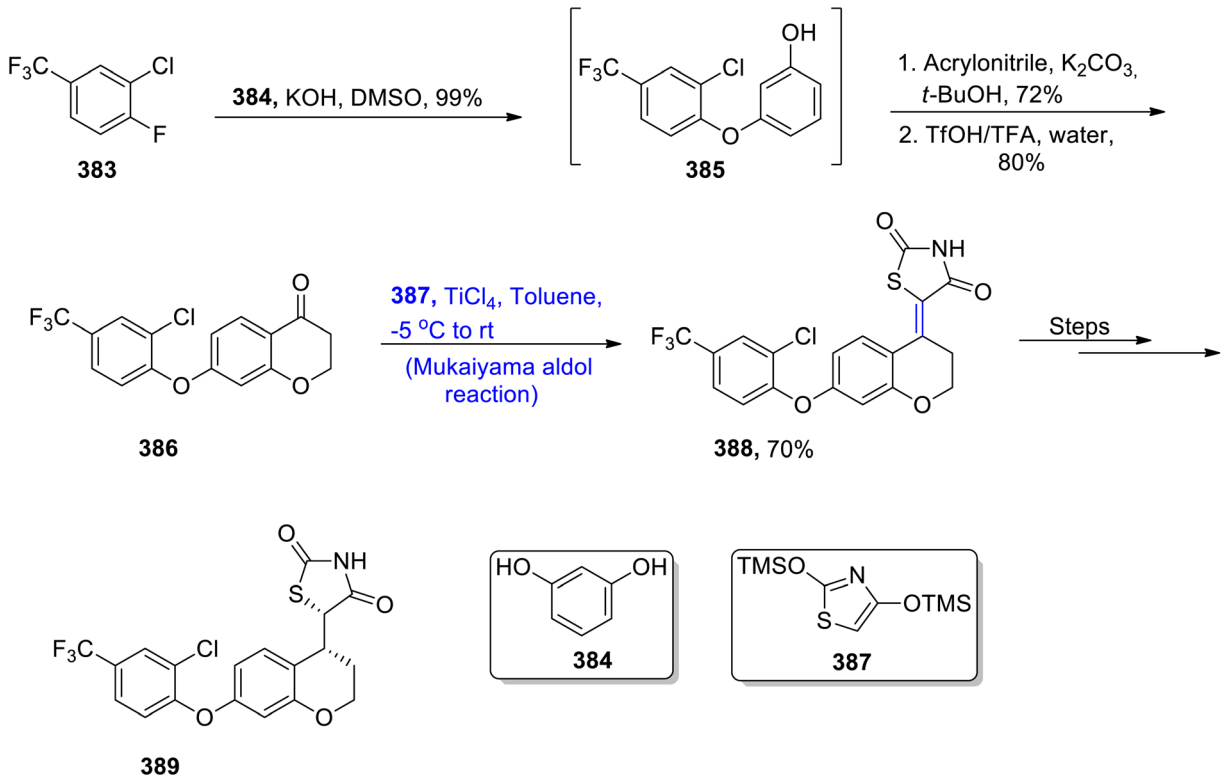


Scheme 51 Synthesis of merilactone A **382**.



Scheme 52 Synthesis of MK-2305 **389**.

388 in 70% yield. It was then reacted over a number of steps, thus leading to the synthesis of MK-2305 **389** (Scheme 52).

3. Conclusions

This review provides a broad overview of the syntheses of a diverse range of natural products, which involve the Mukaiyama aldol reaction as a major step in their synthetic methodologies, reported in the literature during the period 2020–2023. The aldol reaction is a Lewis-acid catalyzed reaction between silyl enol ether and carbonyl compounds which results in the synthesis of aldol adducts that are highly diastereoselective in nature and are generated in enantiomeric excess. The resulting aldol adducts are then utilized to carry out the

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total synthesis of various natural products. Here, a summary of the total synthesis of macrolides, polyketides, alkaloids, metabolites, terpenoids and depsipeptides, *etc.* utilizing the Mukaiyama aldol reaction is reported. We anticipate that our review will inspire researchers to advance further regarding the development of the Mukaiyama aldol reaction to carry out its beneficial aspects in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

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