RSC Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *RSC Adv.*, 2023, **13**, 35172

Gilman reagent toward the synthesis of natural products

Ramsha Munir,[a] Ameer Fawad Zahoor, *[a] Usman Nazeer,[b] Muhammad Athar Saeed,[a] Asim Mansha,[a] Ahmad Irfan[c] and Muhammad Umair Tariq*[d]

Received 29th October 2023
Accepted 19th November 2023

DOI: 10.1039/d3ra07359a

rsc.li/rsc-advances

With the ever-increasing scope of organocuprates, a well-established Gilman reagent has been considered as an unprecedented synthetic tool in modern organic chemistry. The broad research profile of the Gilman reagent (R_2CuLi in THF or Et_2O) is owing to its propensity to carry out three kinds of reactions, *i.e.*, epoxide ring opening reactions, 1,4-conjugate addition reactions, and S_N2 reactions in a regioselective manner. This review examines the applications of Gilman reagent in the total synthesis of both abundant and scarce natural products of remarkable synthetic pharmaceutical profile reported since 2011. The presented insights will be of a vital roadmap to general organic synthesis and it will contribute to the development of new natural products and their analogues in future drug discovery.

Introduction

Carbon–carbon bond formation is a preliminary step for most of the synthetic transformations in organic chemistry. In this regard, the role of organocopper reagents is at the forefront. These reagents are prepared by reacting organometallics (RMgX, RLi, or RZnX) with copper salts (CuBr, CuI, or CuCN) in the presence of solvents, such as THF, DMS, DCM, or dry ether. The use of various additives, such as HMPA (hexamethyl phosphoramide), TMSCl (trimethylsilyl chloride), and some Lewis acids, along with these reagents has also been reported in the literature.[1–3] Gilman reagent (R_2CuLi) is the first organocuprate compound, discovered by an American chemist, Henry Gilman, in 1952, which was prepared by reacting 2 equivalents of alkyl or aryl lithium with 1 equivalent of Cu salt in the presence of TMS or diethyl ether as solvent (Fig. 1).[4] On dissolving in diethyl ether, this lithium diorganocuprate reagent is expected to exist in a dimeric, eight-membered ring form.[7]

Gilman reagent is usually employed in three kinds of reactions. In the first one (conjugate addition), it acts as an alkylating agent on treatment with α,β-unsaturated carbonyl compound (enone) to give the 1,4-addition product.[5] Secondly, it is used in the regioselective epoxide (or aziridine) ring opening reactions. Thirdly, Gilman reagent is a good nucleophile and undergoes S_N2 reaction (cross-coupling) with primary and secondary alkyl halides or alcohols and exhibits applications in Corey House reactions.[5,10]

With an appreciation for the inscrutable synthetic chemistry of Gilman reagent, Lipshutz *et al.* performed an extensive methodological study by applying a series of Gilman tests (using combinations of various alkyl or aryl halides along with copper salt) and determined the exact composition of the Gilman reagent.[3] According to their spectroscopic observation, properties of the Gilman reagent are directly affected by the kind of CuX (here X = Cl, Br, I, OTf, SCN, or CN).[4–6] Following the inventive study of the conjugate addition of Gilman reagent, Bertz *et al.* studied the reactive profile of iodo-Gilman reagent ($R_2CuLi^{\cdot}LiI$) and cyano-Gilman reagent ($R_2CuLi^{\cdot}LiCN$). The phenyl Gilman reagent (Ph_2CuLi & PhLi) in the presence of ether or THF as a solvent has also been reported as a higher-order catalyst.[7–11] The mechanistic study of Gilman reagent in THF at low temperatures has been conducted, and the formation of π complexes of Me_2CuLi not only with α,β-unsaturated carbonyl compounds but also with aldehydes and ketones has

$$2RLi + CuX \xrightarrow{Et_2O \text{ or } THF} R_2CuLi.LiX$$

Fig. 1 Preparation of Gilman reagent.

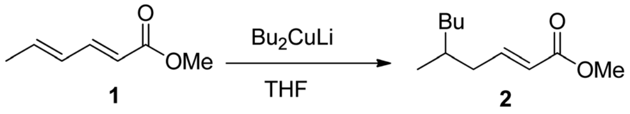


Fig. 2 1,6-Conjugate addition by using Gilman reagent.

---

[a] Department of Chemistry, Government College University Faisalabad, 38000-Faisalabad, Pakistan. E-mail: fawad.zahoor@gcuf.edu.pk

[b] Department of Chemistry, University of Houston, 3585 Cullen Boulevard, Texas 77204-5003, USA

[c] Department of Chemistry, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia

[d] Department of Chemistry, Faculty of Natural Sciences, Forman Christian College University, Lahore 54600, Pakistan. E-mail: UmairTariq@fccollege.edu.pk

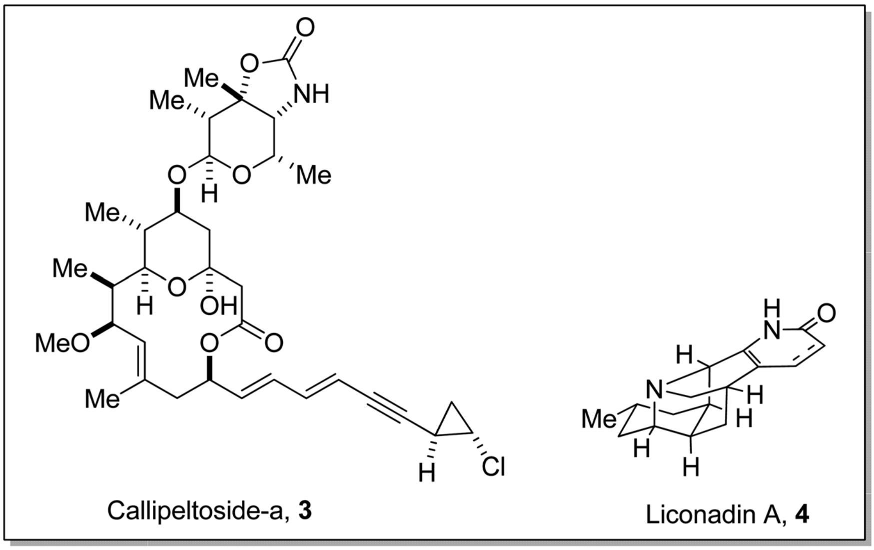


Fig. 3 Structures of callipeltoside-a 3 and liconadin A 4.

been confirmed as a stable synthetic intermediate using spectroscopic analyses.[12,13] The d orbital of copper in Gilman reagent (acting as a base) interacts with the π* of the carbonyl carbons (π acids) to form the d–π complexes. The optimum temperature reported for the formation of these complexes is −78 °C.[14,15] Moreover, Yamamoto *et al.* reported the synthesis of the 1,6-addition product by reacting Bu_2CuLi with methyl sorbate in 82% yield, concluding that the electronic properties of Gilman reagent as a nucleophile greatly affect its regioselectivity (Fig. 2).[16,17]

Gilman reagent has been extensively employed in the synthesis of a number of architecturally unique natural products, such as the C1 to C9 framework of callipeltoside-a **3** (isolated from a marine sponge *Callipelta* sp), which is an anti-HIV agent, liconadin A **4** (a *Lycopodium* alkaloid) (Fig. 3)[18,19] and furosesquiterpenes *i.e.*, isopallescensin-A **5**, isopallescensin-1 **6**, 5-desmethyl-4,5-dehydromicrocionin-1 **7**, which are best known for their diverse biological activities (Fig. 4).[20]

Inspired by the fact that methyl-substituted stereogenic centers are present in various natural products possessing a high pharmaceutical profile, Gilman reagent finds its application as an effective methyl source *via* conjugate addition and plays remarkable roles in the synthesis of these natural products. Further, Gilman reagent is used as a regioselective epoxide ring opening agent to produce 1,2 diols or 1,3 diols. In total synthesis, keeping control of the diastereomeric ratio of these diols, this reagent has been found to be helpful in the development of asymmetric centers with the desired stereochemistry of natural products. Herein, the synthetic compilation based on the employment of Gilman reagent in the synthesis of medicinally important natural products has been reported.

Review of literature

Synthesis of alkaloid-based natural products

Piperidine alkaloid. Piperidine ring-based natural products are well-known for possessing glycosidase inhibitory effects as well as anti-diabetic, anti-cancer, and anti-obesity activities.[21] (+)-α-Conhydrine **15** is an example of a 2-(hydroxyalkyl)-piperidine ring containing alkaloid.[22] Considering the interesting features of this class of natural products, various synthetic methods have been designed regarding the synthesis of (+)-α-conhydrine and its enantiomers. In continuation of this work, Deshmukh *et al.* in 2012 performed the synthesis of (+)-β-conhydrine **16** with a sequence of 8 steps in 26% overall yield (Scheme 1).[23] In their synthetic route, aldehyde **8**, dibenzylamine **9**, and terminal alkyne **10** were allowed to react in the presence of copper bromide as a catalyst and toluene as a solvent, accompanied by deprotection of the TMS group in the presence of THF to give terminal alkyne **11** in 93% yield (in 2

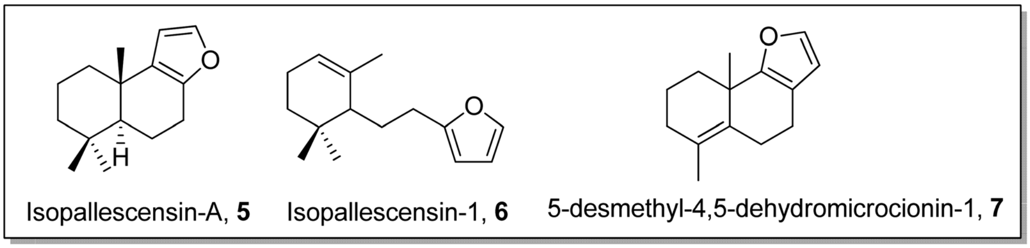
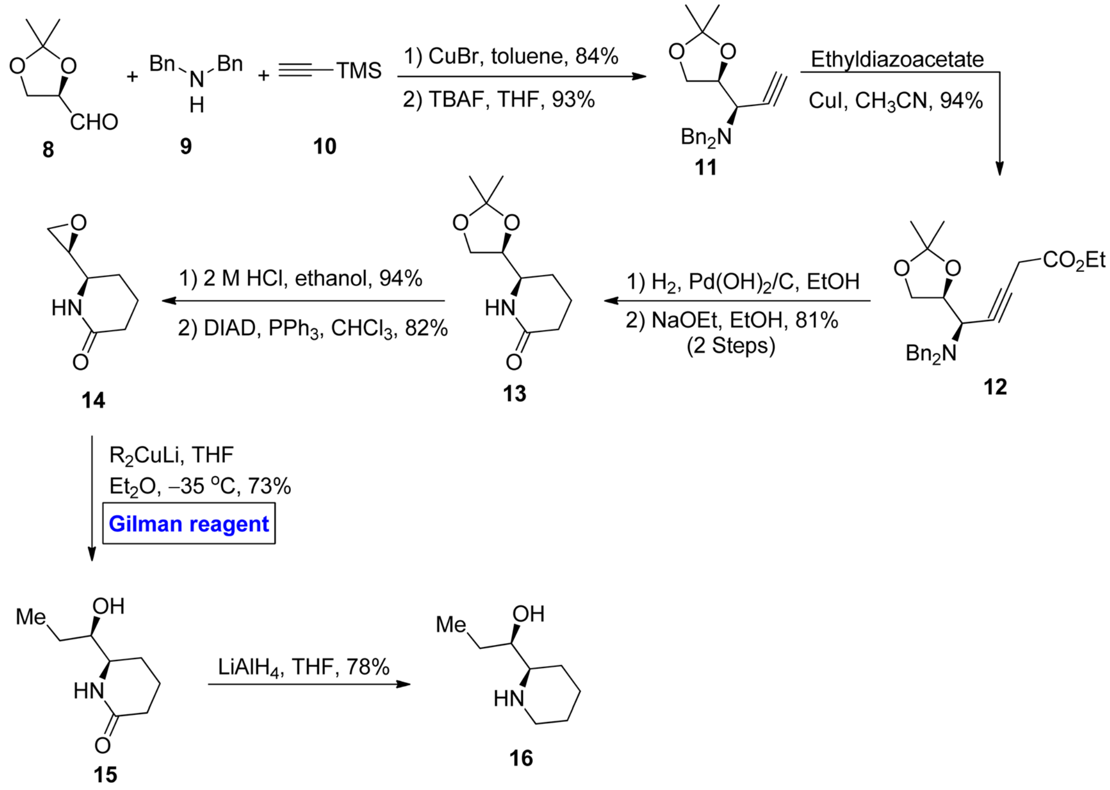
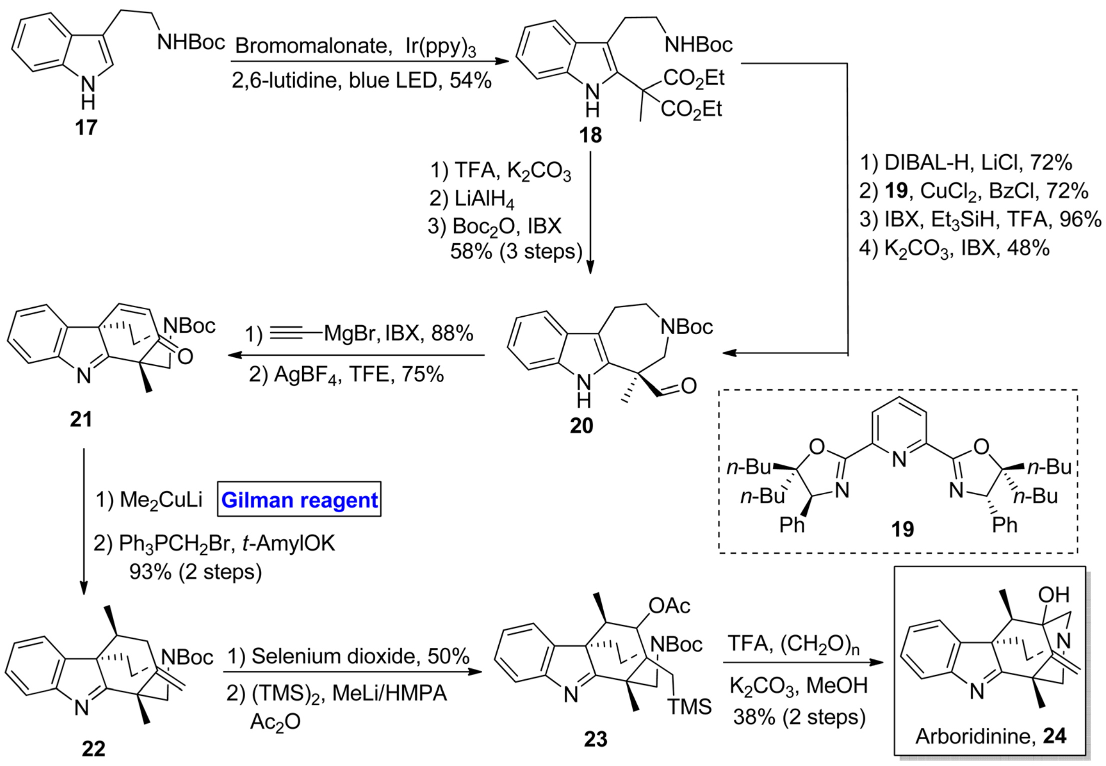


Fig. 4 Structures of isopallescensin-A 5, isopallescensin-1 6, and 5-desmethyl-4,5-dehydromicrocionin-1 7.



Scheme 1 Synthesis of β-(+) conhydrine **16**.

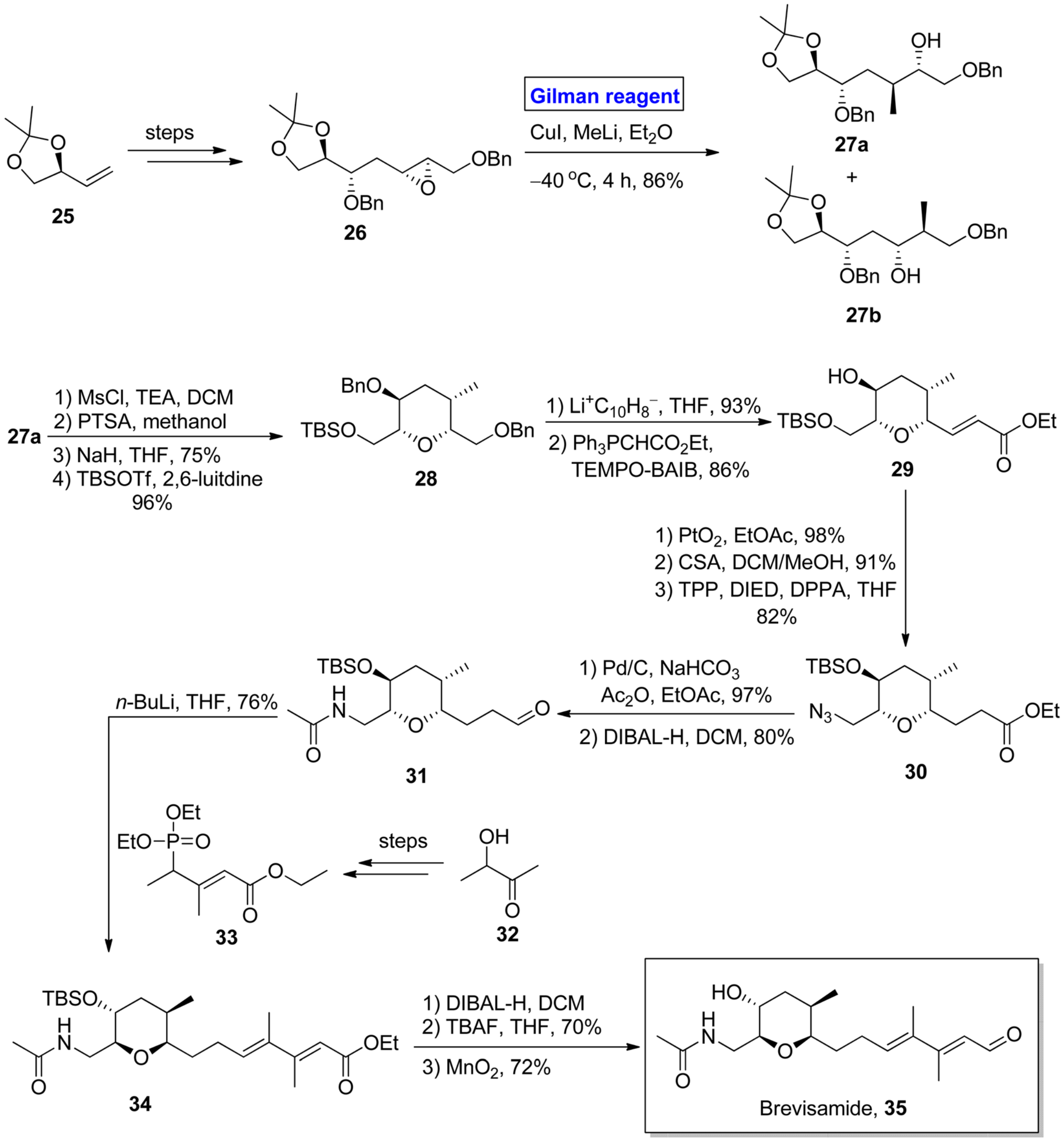
steps). The terminal alkyne **11** was then reacted with ethyl diazoacetate in the presence of copper iodide as a catalyst to acquire compound **12** (in 94% yield), which underwent further hydrogenolysis and subsequent treatment with NaOEt, resulting in compound **13** in 81% yield. In the subsequent step, ketal group deprotection and conversion of diol into epoxide gave



Scheme 2 Total synthesis of arboridinine **24**.

lactam **14** in 82% yield. Further, regioselective ring opening of epoxide was performed *via* the application of a well-suited Gilman reagent in the presence of tetrahydrofuran and diethyl ether at −35 °C that resulted in compound **15** in 73% yield. In the last step, the reduction was performed by using LAH to furnish the desired β-(+) conhydrine **16** in 78% yield.

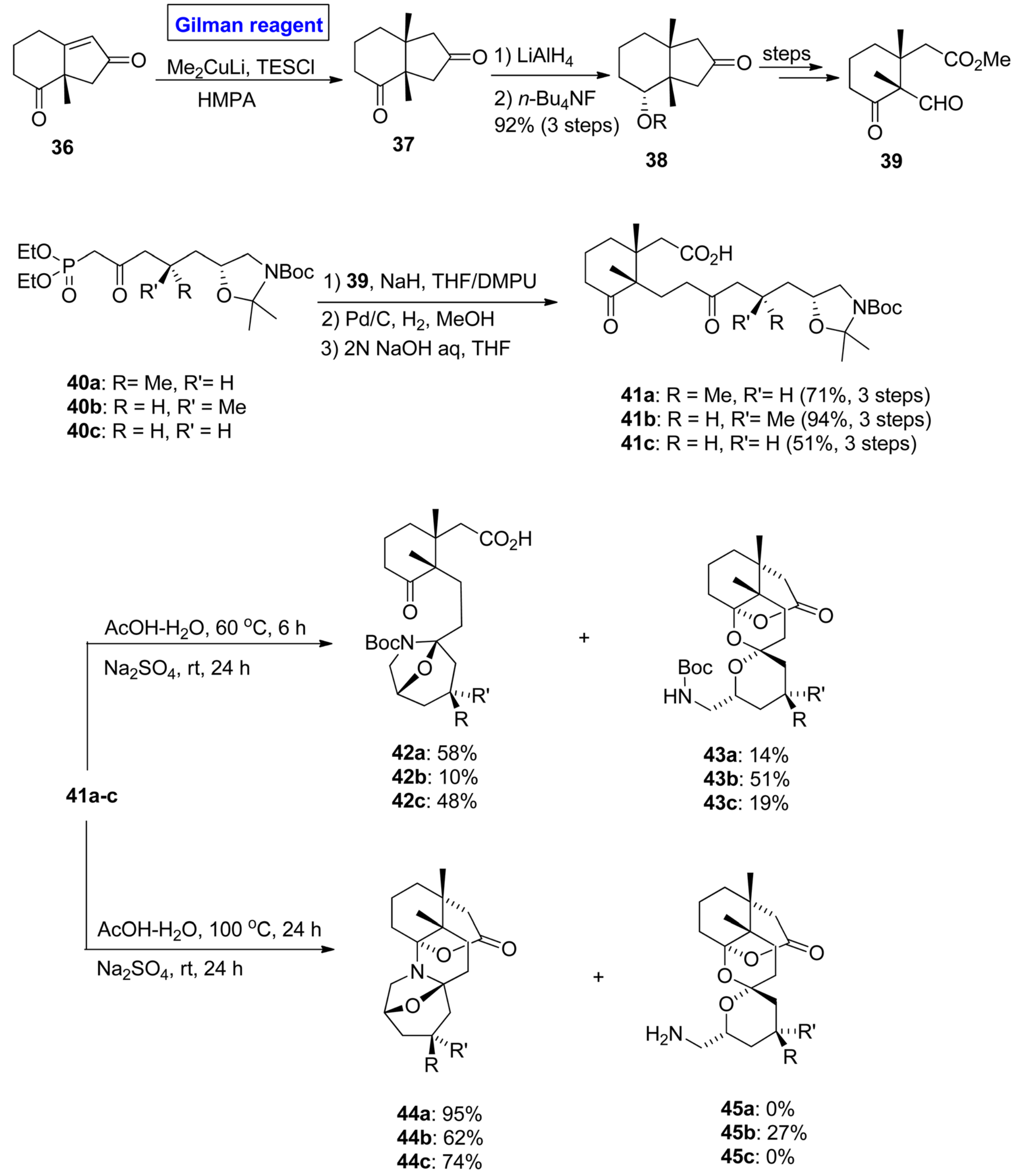
Indole alkaloid. Arboridinine **24** belongs to the class of indole alkaloids isolated from *Kopsia* plants (usually found in Malaysia).[24] Its unprecedented structure consists of a tetracyclic indolenine cage, and it shares its structural features with many other families of alkaloids, making it a unique and interesting scaffold.[25] As a part of the synthetic challenge for many synthetic endeavors, Gan *et al.* in 2018 designed an efficient, scalable, and enantioenriched synthetic scheme towards the synthesis of arboridinine **24** based on a 16 steps sequence using Boc protected tryptamine **17** as a starting material (Scheme 2).[26] Compound **17** was photo-irradiated in the presence of bromomalonate (under suitable conditions) to result in indole **18** in 54% yield. From indole **18**, the aldehyde **20** was prepared by using two routes. In the first one, compound **18** was deprotected by using TFA and potassium carbonate, followed by a sequence of reduction and subsequent oxidation, which furnished aldehyde **20** in 58% yield over 3 steps. The second route, which was more scalable, involved the treatment of compound **18** with DIBAL-H, further reacting with 1,3-diol and ligand **19** in the presence of $CuCl_2$ to give the intermediate, which proceeded further *via* a sequence of oxidation and reduction under suitable conditions. In the following step, the aldehyde **20** was cyclized to afford the α,β-unsaturated ketone **21**. In order to prepare precursor **28** for aza-Prins cyclization, 1,4-conjugate addition of compound **21** was performed by using Me_2CuLi (Gilman reagent) with the successful installation of methyl



Scheme 3 Total synthesis of brevisamide 35.

group and subsequent treatment with Wittig reagent, resulting in alkene **22** in 93% yield (over 2 steps). The alkene **22** was subjected to oxidation *via* selenium dioxide and subsequent 1,4-addition of the TMS group to afford precursor **23**. The last step involved the aza-Prins cyclization and Boc deprotection, concluding the total synthesis of arboridinine **24** (38% yield).

(−)-Brevisamide was isolated from *Karenia brevis*, a dinoflagellate, by Wright and colleagues for the first time.[27] It is a brevenal and exhibits antagonist effects against brevetoxins. Brevetoxins are neurotoxic substances responsible for the death of fish and other marine organisms.[28] Owing to the impressive biological profile of brevisamide, 5 groups of researchers have reported its total synthesis. In the continuation of this study, Yadav *et al.* in 2013, also presented a valuable and stereoselective approach towards its synthesis starting from an easily available starting material, *i.e.*, 2,3-*O*-isopropylidene glyceraldehyde **25** (Scheme 3).[29] The key steps entail the Sharpless epoxidation, ring opening of epoxide by using Gilman reagent, intramolecular S_N2 cyclization, Wittig olefination, and HWE reaction. The compound **25** was modified (in a few steps) into epoxide **26**, which upon treatment with Gilman reagent, *i.e.*, CuI, MeLi, and diethyl ether as a solvent, resulted in a regioselective ring opening to give **27a** and **27b** in 86% combined yield. The compound **27a** was mesylated in the presence of MsCl, and its acetonide group was removed by using PTSA to give the intermediate, which was subjected further to an S_N2 cyclization

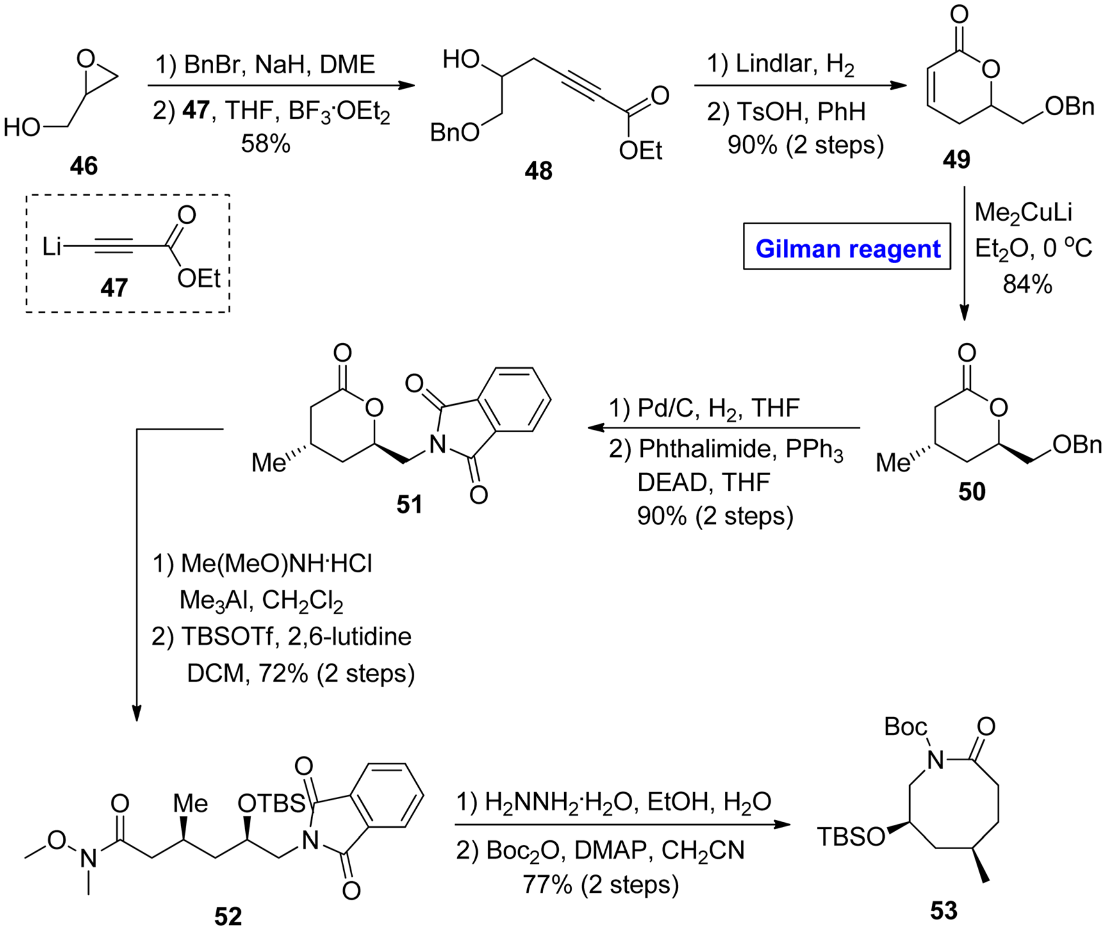


Scheme 4 Synthesis of precursor **41a–c** and its cyclization.

in the presence of NaH and subsequent treatment with TBSOTf in the presence of 2,6-lutidine to give compound **28** in 96% yield. The benzyl group deprotection of compound **28**, its chemoselective oxidation, and Wittig olefination furnished compound **29** with 86% yield. Then, compound **29** underwent a series of protection and deprotection steps under the given conditions to provide compound **31** (*via* intermediate **30**) with 80% yield. In the following step, the HWE reaction of compound **31** with compound **33** (obtained from compound **32**) using *n*-BuLi and THF afforded compound **34** with 76% yield. Deprotection *via* treatment with DIBAL-H, TBAF, and MnO_2 in consecutive steps completed the total synthesis of brevisamide **35** with 72% yield.

Zoanthamine alkaloid. Zoanthamine alkaloids are marine alkaloids, which contain a heptacyclic ring system. It exhibits potent biological activities such as anti-inflammatory, cytotoxic, anti-bacterial, and anti-osteoporotic activities, thus having an effective pharmacological profile.[30,31] Many attempts have been made towards the synthesis of its pentacyclic ring system (based on 8 chiral centers including 3 carbon quaternary and 2 aminal functionalities).[32–34] To accomplish this challenging total synthesis, Nakajam *et al.* in 2011 studied and disclosed the stereochemical effects of a methyl group at the C-4 position towards the bisaminal cyclization in zoanthamine alkaloids (Scheme 4).[35] In their strategy, the enone **36** (for 1,4-conjugate addition) was treated with Gilman reagent, *i.e.*, Me_2CuLi, in the presence of TESCl and hexamethyl phosphoramide to obtain compound **37**. After 1,4-conjugate addition, the compound **37** was immediately reduced in the presence of $LiAlH_4$ and desilylated by using quaternary ammonium salt to synthesize ketone **38** (with 92% yield), which was modified over a few steps to obtain aldehyde **39**. In the next step, the HWE reaction of ketophosphonates **40a–c** and aldehyde **39** by treating it with DMPU in THF afforded precursors **41a–c** in moderate to good yield. In the last step of the synthesis, cyclization was performed with a slight variation in conditions. The treatment of compounds **41a–c** with AcOH in water at $T = 60$ °C for 6 hours, accompanied by the addition of sodium sulphate with 24 hours of stirring at room temperature, provided a diastereomeric mixture of monoaminals **42a–c** (10 to 58% yield) and spiroketals **43a–c** (14 to 51% yield). In another case, the treatment of compounds **41a–c** with AcOH at $T = 100$ °C for 12 hours, followed by the addition of sodium sulfate affected the mode of cyclization and furnished the bisaminal product **44a** and **44c** (in 95% and 74% yield, respectively), along with a diastereomeric mixture (from **41b**) of bisaminal product **44b** and spiroketal **45b** (with % yield = 62 : 27).

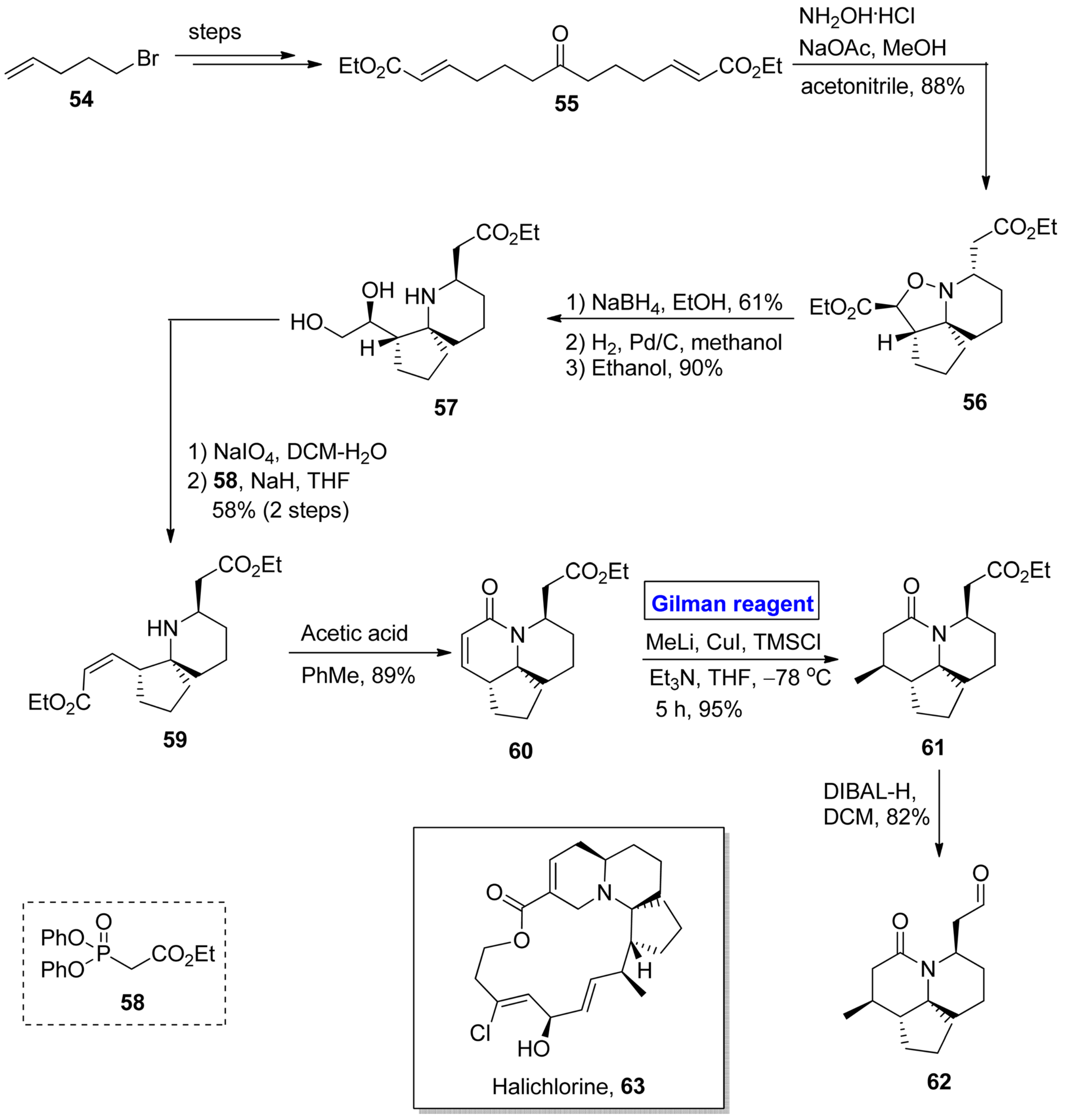
In continuation of synthetic studies on zoanthenol, Bagdanoff *et al.* in 2016, performed an enantioselective and facile



Scheme 5 Synthesis of caprolactam **53** toward the synthesis of zoanthenol.

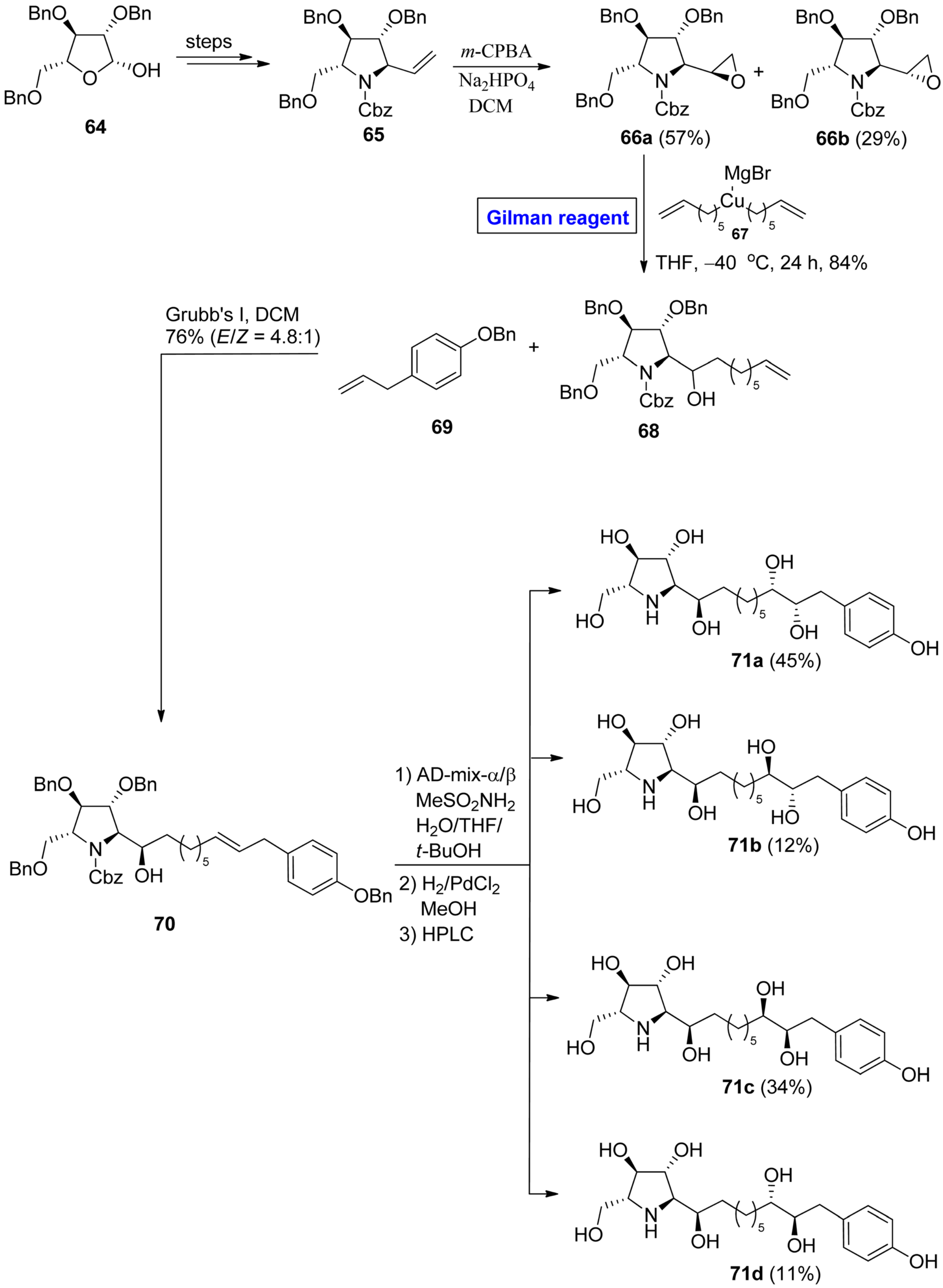
synthesis of caprolactam **53** (as a precursor for zoanthenol) (Scheme 5).[36] The synthesis commenced with the benzyl protection of glycidol **46**, accompanied by a reaction with ethyl propiolate **47** under the given conditions, affording compound **48** with a 58% yield. In the next step, the reduction of compound **48** followed by cyclization provided lactone **49** (in 90% yield), which was subjected to a 1,4-conjugate addition reaction by employing the well-established Gilman reagent (Me_2CuLi) in diethyl ether at 0 °C to furnish compound **50** in 84% yield. The compound **51** (achieved after the palladium-catalyzed reduction of compound **50** and subsequent Mitsunobu reaction)[37] was subjected to Weinreb amide reaction, accompanied by treatment with hydrazine hydrate and subsequently cyclized under given conditions to provide the targeted caprolactam **53** (*via* intermediate **52**) in 77% yield.

Quinolizidine alkaloid. Halichlorine **63** belongs to the class of quinolizidine alkaloids. It was isolated by Uemura and colleagues in 1966 from *Halichondria okadai*, a marine sponge found in Japan.[38] Halichlorine **63** is a suppressor of NF-κB activation and inhibits the expression of vascular cell adhesion molecule 1 (VCAM-1) (which is related to inflammation and tumor cell growth). Halichlorine is also a hypertensive agent as it suppresses *L*-type calcium channels in smooth muscles.[39] Owing to the biochemical potential of this heterocyclic scaffold,



Scheme 6 Synthesis of intermediate 62 towards the synthesis of halichlorine.

various organic chemists have reported its total synthesis, among which the Clive group presented a remarkable route in 2009. Pioneering this work, Gignoux *et al.* devised a concise and two directional strategy for the synthesis of intermediate **62** towards the synthesis of halichlorine **63** in 2012 (Scheme 6).[40] Their synthetic route was based on a 12-step sequence, providing 13.2% overall yield and comprising easily available starting materials (ethyl formate **54**). The ketodiester **55** (after



Scheme 7 Synthesis of **71a–71d** towards the synthesis of glyphaeaside C.

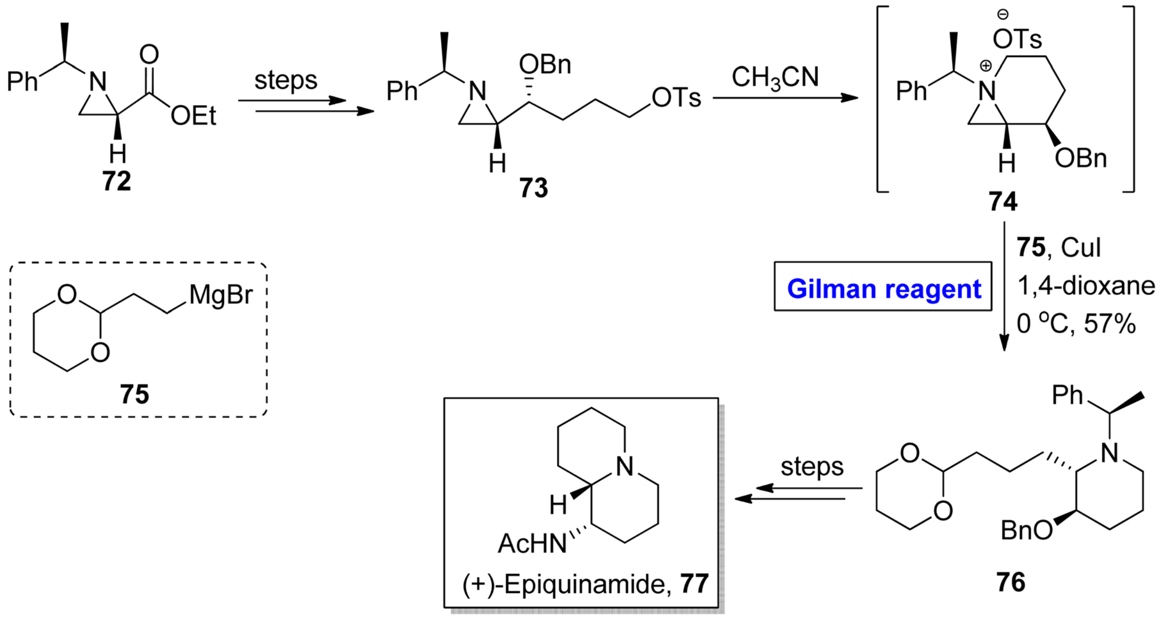
modification from bromide **54** in a few steps) was cyclized under the given conditions to give isoxazolidine **56**, which was then selectively reduced by using $NaBH_4$ in ethanol and subsequently hydrogenated to give diol **57** in 90% yield. The oxidation of diol **57** was followed by a reaction with phosphonate **58** in the presence of sodium hydride, which furnished compound **59** with 58% yield. In the following step, compound **59** reacted with acetic acid in the presence of toluene to give bicyclic lactam **60** in 89% yield. In order to install a methyl group at the C14 position from the upper side, a well-suited Gilman reagent was used. To accomplish this task, compound **60** was treated with methyl lithium, copper iodide, and TMSCl in the presence of triethyl amine and tetrahydrofuran at −78 °C for five hours, resulting in compound **61** with the desired stereochemistry in 95% yield. In the last step, oxidation was performed in the presence of DIBAL-H and CH_2Cl_2 to furnish aldehyde **62** (in 82% yield), a well-designed intermediate toward the synthesis of halichlorine **63**.

Glyphaeaside alkaloids. Glyphaeaside alkaloids were isolated from *Glyphaea brevis*.[41] Structurally, these classes of alkaloids are based on a piperidine iminosugar along with a polyhydroxylated alkyl side chain that ends at the phenyl group and are classified into three types, *i.e.*, A, B, and C. Among these, glyphaeaside C exhibits maximum potential as an inhibitor of snail β-mannosidase and β-glucosidase. It also shows a slight inhibitory effect for α-glucosidase.[42] In 2021, Byatt *et al.* attempted the synthesis and structural elucidation of glyphaeaside C by employing well-suited Gilman reagent[43] starting from compound **64**, which was modified over a few steps to give vinyl pyrrolidine **65** (Scheme 7). The epoxidation of compound **65** in the presence of *m*-CPBA and Na_2HPO_4 provided epoxide (**66a** and **66b**) in 57% and 29% yield, respectively. The epoxide **66a** proceeded for ring opening reaction *via* Gilman reagent (*in situ* generated from compound **67**) in THF at −40 °C for 24 hours to furnish compound **68** in 84% yield. In the next step, compound **68** was made to react with compound **69** in the presence of Grubb's first-generation catalyst, which resulted in a stereoisomeric pair of compounds **70** in 76% yield ($E/Z = 4.8:1$). The compound **70** was first treated with an AD mixture and $MeSO_2NH_2$ and then underwent hydrogenolysis. After chromatographic separation, compounds **71a** to **71d** were achieved in quantitative yield. In a structural analysis of the synthesized derivatives, the compound **71a** was found to be the enantiomer of glyphaeaside C.

Quinolizidine alkaloid. (+)-Epiquinamide **77**, a quinolizidine alkaloid, was isolated for the first time in 2003 from *Epipedobates tricolor* (a poisonous frog).[44] This naturally scarce natural product is renowned as a nicotinic agonist.[45] Owing to this fact, Yadav *et al.* in 2019 disclosed an efficient methodology for the synthesis of (+)-epiquinamide **7** by employing Gilman reagent-induced aziridinium ion ring opening reaction as the key step (Scheme 8).[46,47] In their methodology, compound **73** (modified from aziridine carboxylate **72**) was treated with methyl cyanide to provide aziridinium intermediate **74**, which underwent ring opening reaction *via* treatment with reagent **75** in the presence of copper iodide and 1,4-dioxane as a solvent (for the *in situ* generation of Gilman reagent). The temperature was adjusted to 0 °C and the synthesis of compound **76** was achieved in 57% yield. It took a few steps for the modification of compound **76** into the desired natural product **77**.

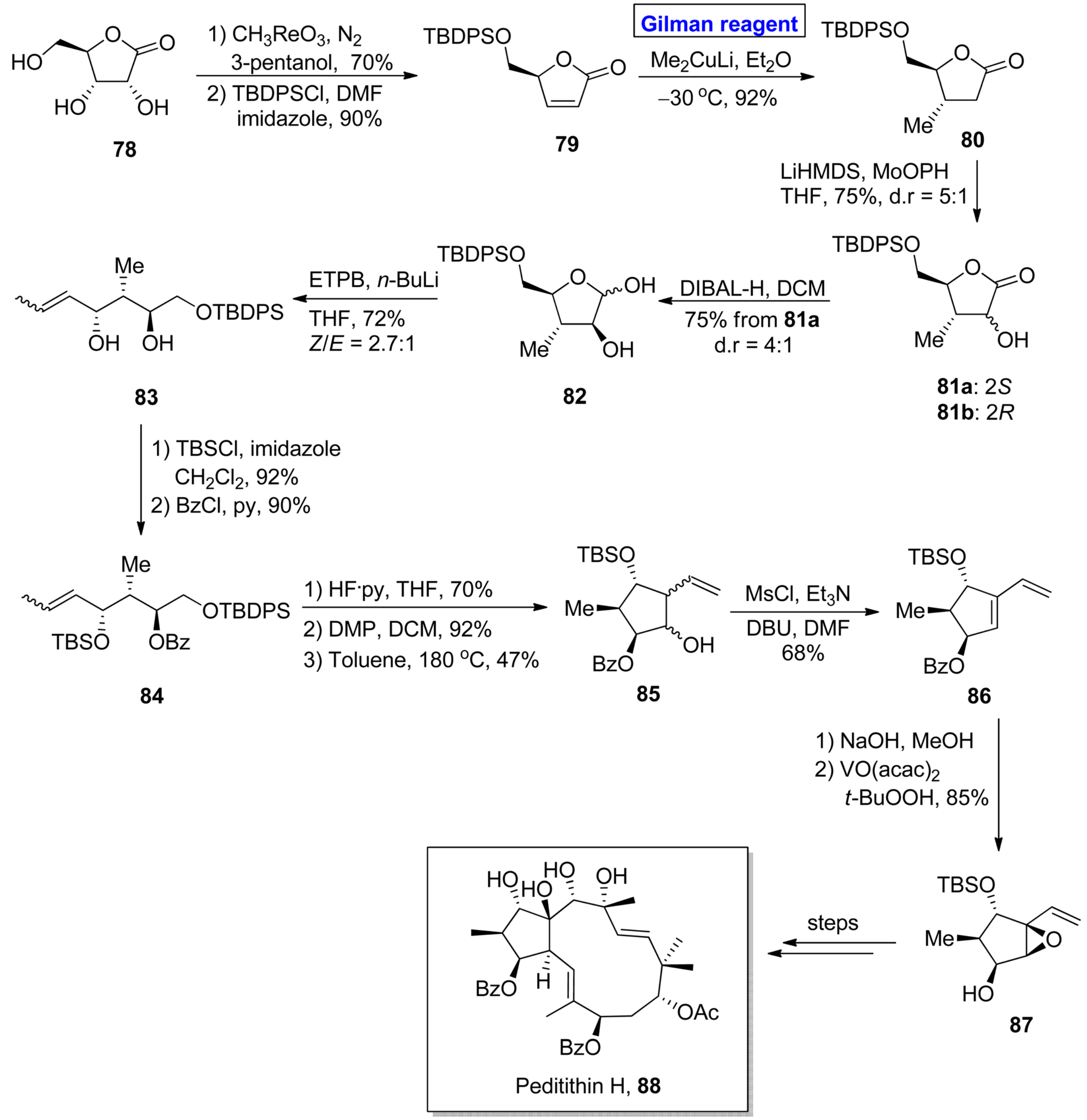
Synthesis of terpenoid-based natural products

Diterpenoids. Pedititthins B–H belongs to the class of Euphorbiaceae diterpenoids, isolated from *Pedilanthus tithymaloides*. These are P-glycoprotein (Pgp) inhibitors and effective anti-cancer agents.[48,49] Methylcyclopentane is a fascinating heterocycle and is incorporated in many diterpenoid-based



Scheme 8 Total synthesis of (+)-epiquinamide 77.

natural products. Structurally, pedititthins H constitute substituted methylcyclopentane as a core, having 5 continuous stereocenters.[50] Various synthetic strategies for the synthesis of methylcyclopentane constituting 3 or 4 stereocenters have been reported. Nonetheless, a synthetic strategy for the synthesis of 5 stereocenters based methylcyclopentane was reported recently. Ni *et al.* in 2020 performed this challenging task and presented an efficient and facile route for the synthesis of methylcyclopentane **87** (containing five stereocenters) as a building block for the synthesis of pedititthins H (Scheme 9).[51] In their synthetic procedure with 14 steps, the easily available lactone **78** was transformed into α,β-unsaturated compound **79** under given conditions. Next, the installation of a methyl group with the desired stereochemistry was accomplished *via* 1,4-conjugate addition using a well-suited Gilman reagent. Thus, the treatment of compound **79** with lithium dimethyl cuprate in the presence of diethyl ether at −30 °C resulted in lactone **80** with a 92% yield. In the next step, hydroxylation of lactone **80** by using Vedejs reagent gave a diastereomeric mixture, *i.e.*, compound **81a** and **81b** in 75% yield with dr = 5 : 1. After chromatographic separation, **81a** was reduced to give hemiacetal **82**, which was subjected to Wittig olefination to furnish compound **83** in 72% yield. Upon TBDPS protection of compound **83**, compound **84** was subjected further to TBS

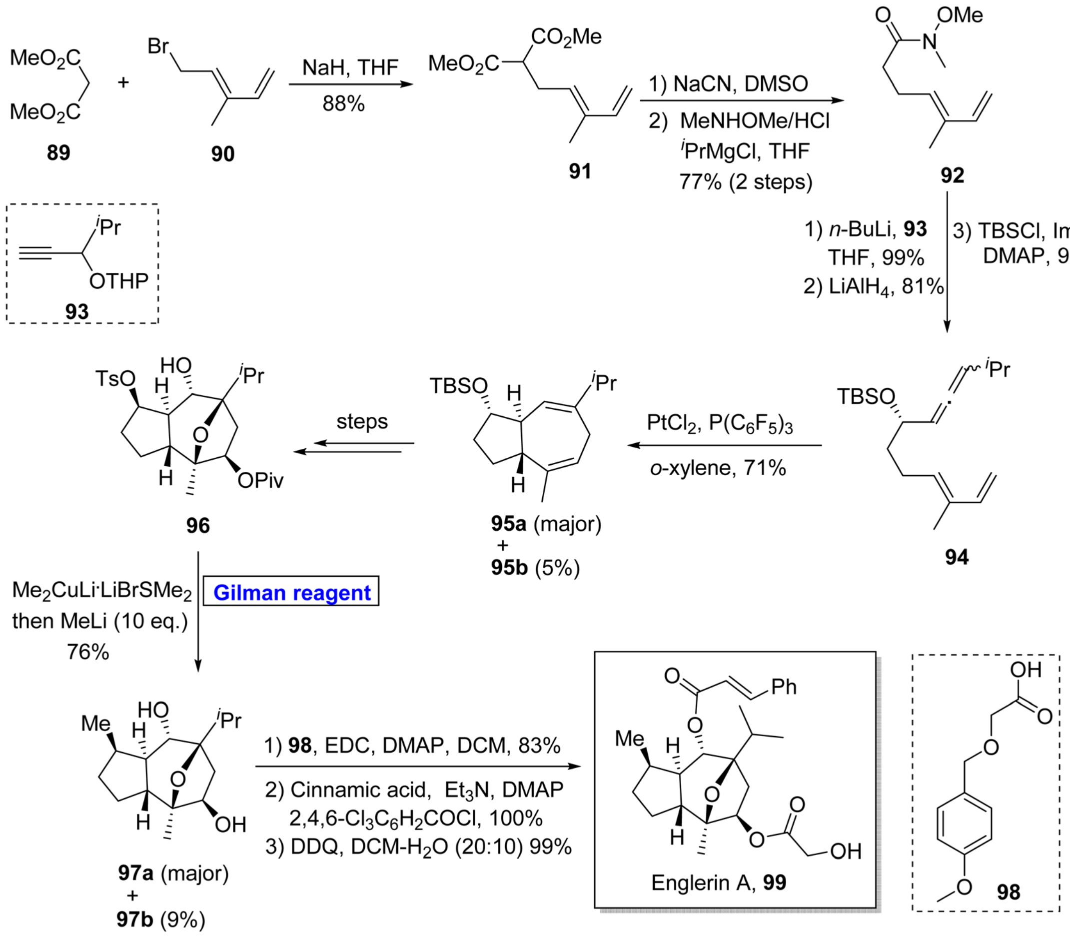


Scheme 9 Synthesis of intermediate **87** towards the synthesis of pedititthin H **88**.

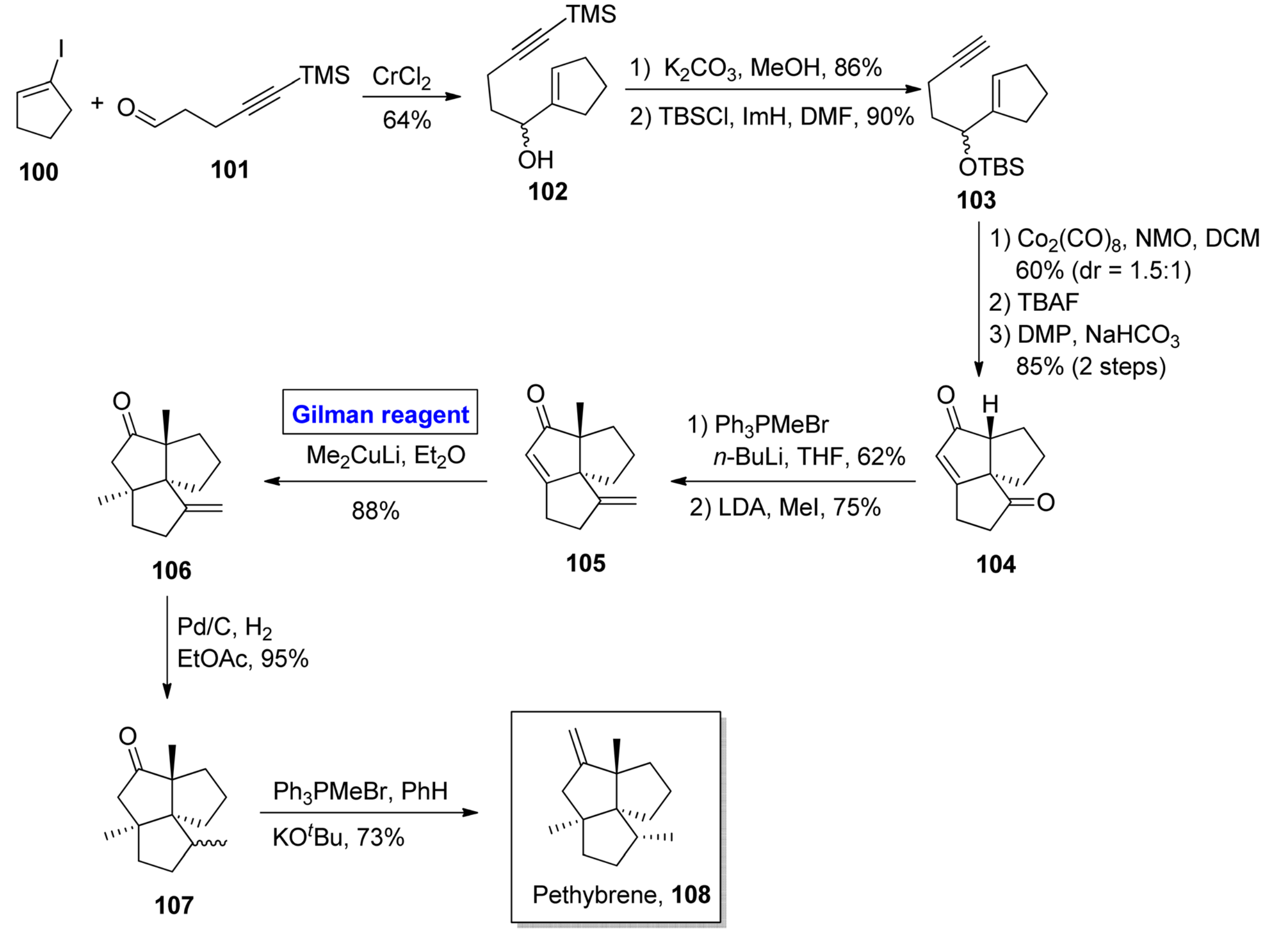
group removal and subsequent oxidation, accompanied by intramolecular carbonyl ene reaction by raising the temperature to 180 °C in toluene, which afforded compound **85** in 47% yield. After mesylation of homoallyl alcohol **85**, the diene **86** was subjected to benzoyl group deprotection and subsequent epoxidation by using a suitable reagent to complete the synthesis of methylcyclopentane **87** with 85% yield.

Sesquiterpenes. (−)-Englerin A **99** belongs to the class of guaiane sesquiterpene, isolated from *Phyllanthus engleri*. It activates the TRPC channel and exhibits potential anti-cancer activities against renal tumor cells.[52] Owing to its impressive biological potential, Ma and colleagues reported the chiral pool approach for the synthesis of (−)-englerin A **99**. Echavarren and colleagues reported the synthesis of an intermediate towards the synthesis of (−)-englerin A based on the Sharpless epoxidation.[53] Pioneering this work, Nelson *et al.* in 2016 reported the most rapid and efficient methodology for the synthesis of this natural product, overcoming all the drawbacks of previous approaches (Scheme 10).[54] Their synthetic scheme was based on a 17-step sequence and 11% overall yield starting from easily available starting materials by employing the Gilman reagent in the key step. In the first step, dimethyl malonate **89** and dienyl bromide **90** were allowed to react in the presence of sodium hydride to give diester **91** (in 88% yield), which underwent decarboxylation to result in amide **92** with 77% yield. The compound **92** was then treated with butyl lithium and after subsequent treatment with $LiAlH_4$ and silyl protection, afforded allenediene **94** (99% yield). In the following step, allenediene **94** was treated with $PtCl_4$ and $P(C_6F_5)_3$ in the presence of *o*-xylene to give a diastereomeric mixture and **95a** as a major product in 71% yield. Over a few steps, compound **96** was obtained, which was treated with Gilman reagent, *i.e.*, $Me_2CuLi\cdot LiBrSMe_2$, and further addition of methyl lithium furnished compound **97a** (as a major product with 76% yield) and **97b** (9% yield). The esterification of compound **97a** using **98** under given conditions and further modification over two steps completed the total synthesis of our desired (−)-englerin A **99** in 99% yield.

Pethybrene **108** is a sesquiterpene isolated from plants of *Petasites hybridus*. Its structural framework is based on fused triquinanes with a unique substitutional pattern.[55] This heterocycle exists in various isomeric forms and rapidly undergoes rearrangement under acidic conditions, which makes it a continuing source of attraction for many synthetic endeavors.[56] Jee & Lee in 2021 presented its total synthesis in 13 steps by employing the Pauson–Khand reaction, 1,4-conjugate addition by Gilman reagent, and Wittig olefination as key steps (Scheme 11).[57] Their synthesis commenced with the NHTK coupling reaction of iodocyclopentene **100** and aldehyde **101** in

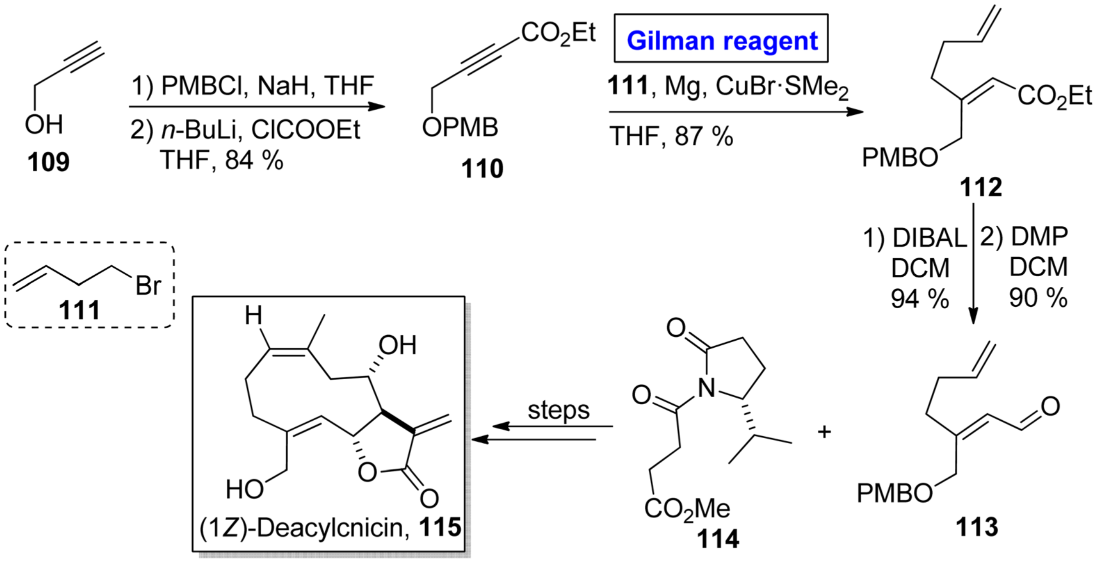


Scheme 10 Total synthesis of englerin A **99**.



Scheme 11 Total synthesis of pethybrene 108.

the presence of $CrCl_2$ to give compound **102** with a 64% yield. The silyl group deprotection of compound **102** and further treatment with TBSCl resulted in silyl ether **103** in 90% yield. The Pauson–Khand reaction of silyl ether **103** and subsequent oxidation provided diketone **104** (with 85% yield), which was subjected to Wittig olefination and methylenation to obtain

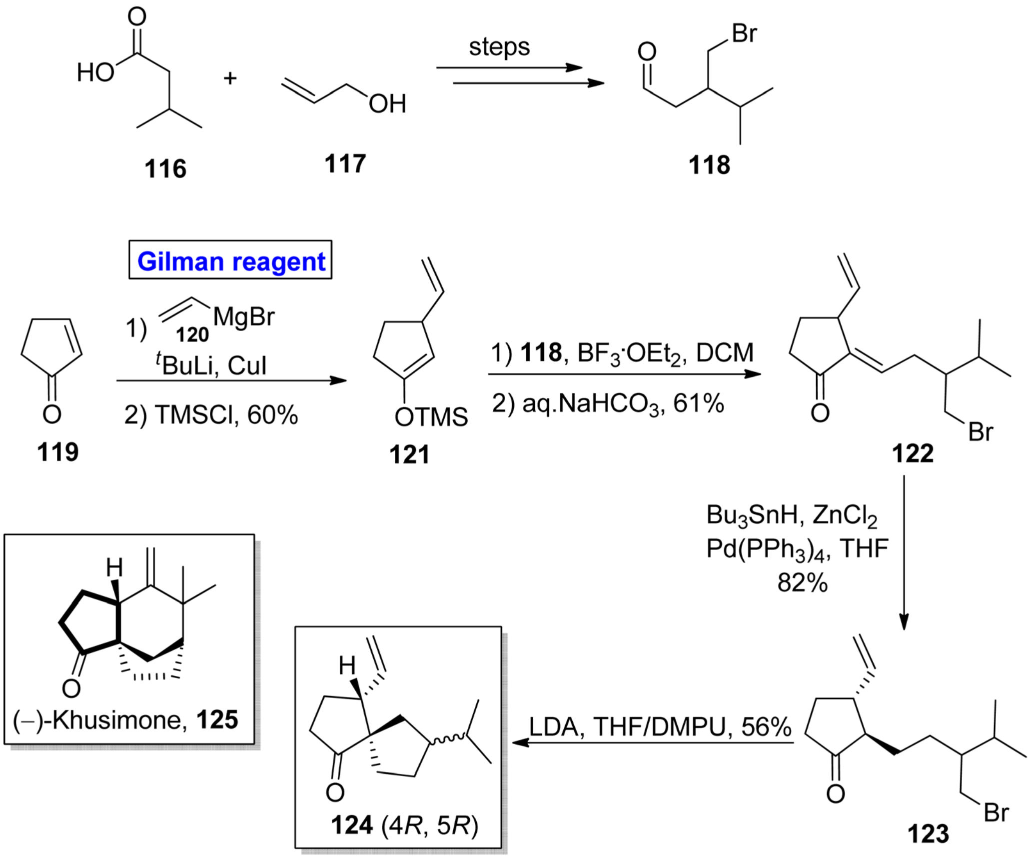


Scheme 12 Total synthesis of (1*Z*)-deacylcnicin 115.

enone **105**. In the next step, 1,4-conjugate addition of compound **105** was performed by employing a well-suited Gilman reagent, *i.e.*, lithium dimethyl cuprate in diethyl ether, to give compound **106** with 88% yield. The hydrogenation of compound **106** resulted in a separable, diastereomeric mixture of compound **107** (93% yield), which was (after separation) subjected to Wittig olefination to furnish our desired pethybrene **108**.

One of the germacranolide sesquiterpene, cnicin, is a 10-membered lactone isolated for the first time from the leaves of *Cnicus benedictus* (in 1959) by Sorm and colleagues.[58] It exhibits a wide range of biological activities such as anti-bacterial, anti-myeloma, and cytostatic activities with allelopathic effects. Cnicin also shows inhibitory effects against *Trypanosoma brucei* with $IC_{50} = 0.4$ μM.[59,60] Since the inception of this natural product, many synthetic pathways have been devised and reported in the literature. In 2022, Kimura and Usuki reported the synthetic procedure towards (1*Z*)-deacylcnicin **115**, which was based on a 15-step sequence with 3.3% overall yield by consuming the easily available starting material, *i.e.*, 2-propyn-1-ol **109** (Scheme 12).[61] In the first step of their synthesis, compound **109** (after PMB group protection) was subjected to esterification under given conditions to afford compound **110** (in 84% yield). In order to perform the conjugate addition reaction of ester **110**, it was reacted with compound **111**, in the presence of Mg and $CuBr \cdot SMe_2$ (for *in situ* generation of Gilman reagent) in THF to furnish compound **112** in 87% yield. The sequence of DIBAL-induced reduction and DMP-induced oxidation of compound **112** provided compound **113** (in 90% yield), which underwent further reaction with compound **114** and took several steps for accomplishing the synthesis of (1*Z*)-deacylcnicin **115**.

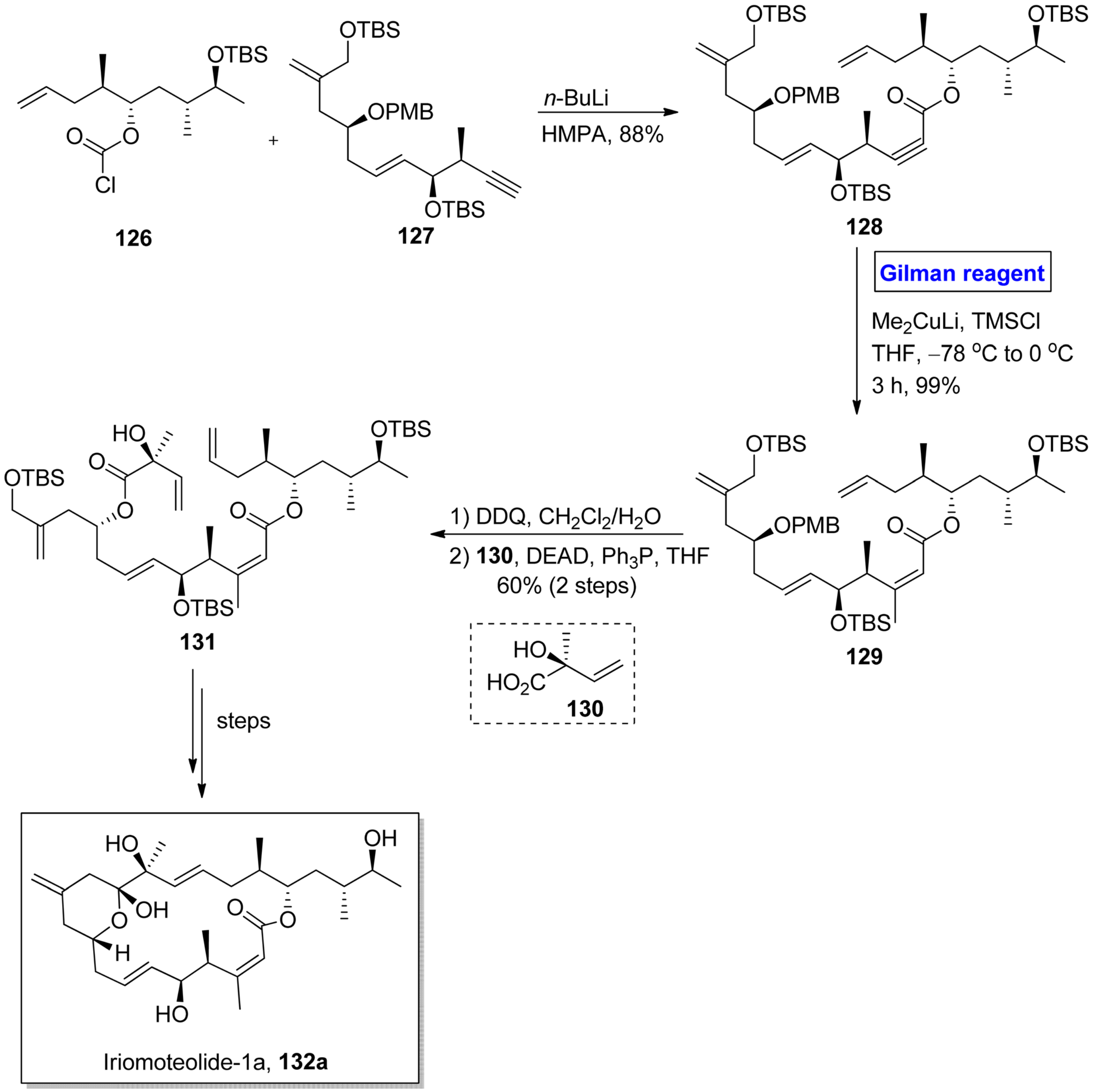
Norsesquiterpene. A tricyclic norsesquiterpene, (−)-khusimone **125** was firstly isolated from *Vetiveria zizanoides* L. (vetiver oil) by Umrani and colleagues.[62] Due to its aromatic nature, it is widely used as a perfume, and its unique structural features have grasped the attention of many researchers.[63] In 2013, Kraft and Denizot performed the facile synthesis of the analogue **124** in 10 steps by utilizing the easily available cyclopent-2-en-1-one **119** (Scheme 13).[64] To accomplish this task, compound **119** was treated with Gilman reagent for nucleophilic substitution reaction in the presence of compound **120**, tertiary butyl lithium, and copper iodide, after which silylation was carried out to provide compound **121** in 60% yield. For aldol condensation, the compound **121** reacted with the compound **118** (from isovaleric acid **116** and allyl alcohol **117**) in the presence of $BF_3 \cdot OEt_2$ and DCM and the subsequent treatment with aqueous sodium bicarbonate provided enone **122** in 61% yield. The palladium catalyzed reduction of enone **122** under given conditions accompanied by LDA induced cyclization (of compound **123**) in THF/DMPU furnished the target compound **124** in 56% yield.



Scheme 13 Synthesis of analogue **124**.

Synthesis of macrolide-based natural products

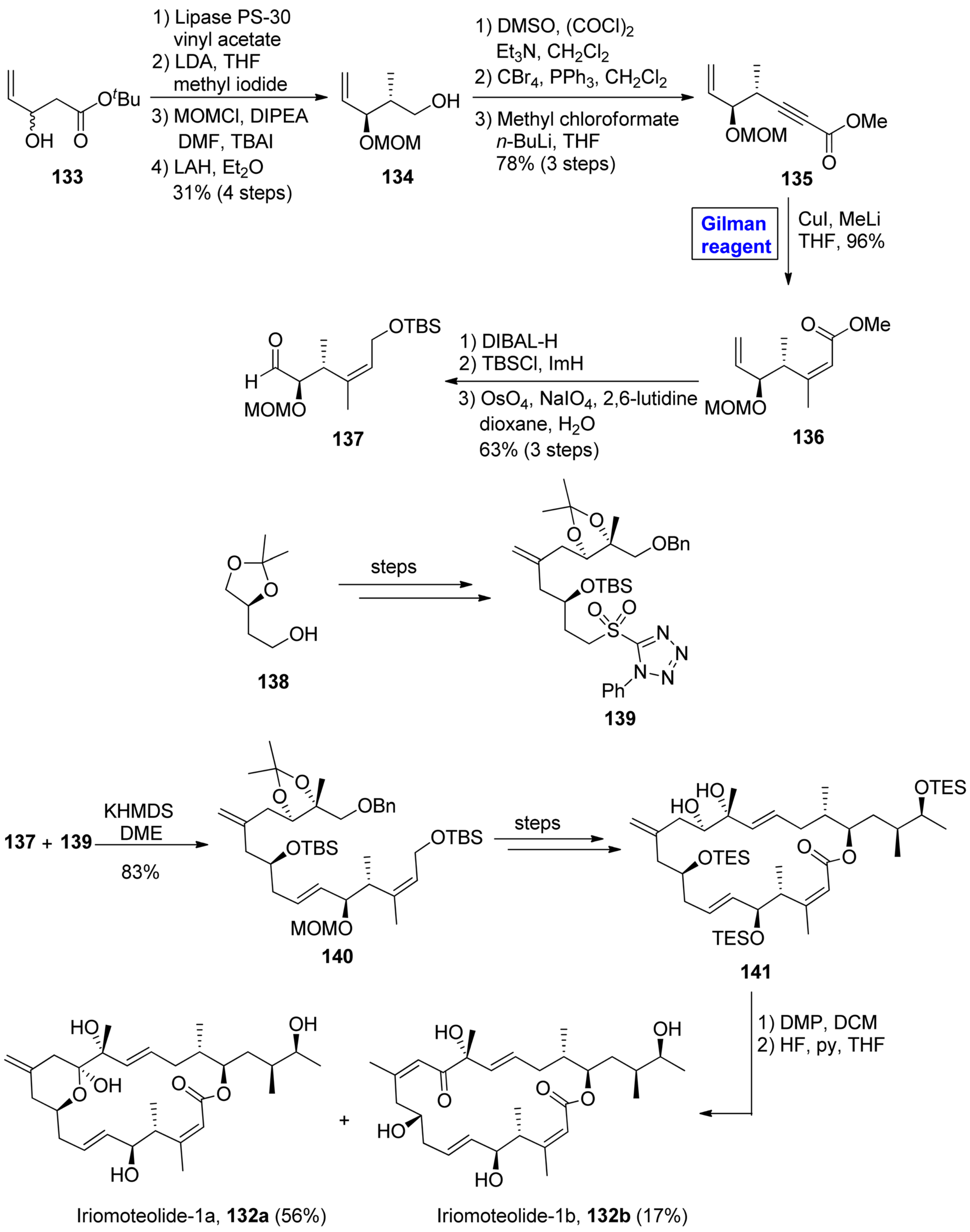
Iriomoteolide-1a **132a** and Iriomoteolide **132b** are twenty-membered cytotoxic macrolides. These were isolated independently by Tsuda and colleagues from the dinoflagellate of *Amphidinium* sp. found in Japan.[65] Both heterocyclic scaffolds are structurally similar with slight differences. In iriomoteolide-1b **132a,** there is a six-membered hemiketal ring with a methylene group at the eleventh carbon. Iriomoteolide-1a is specified for effective cytotoxic effects against human lymphocyte DG-75 cell line (with IC_{50} = 2 ng mL^{-1}) and EBV-infected human lymphocyte (with IC_{50} = 3 ng mL^{-1}).[66] The unique molecular architecture of medicinally important iriomoteolide 1a has always been the target of many synthetic chemists. In this effort, Huang *et al.* in 2012 performed its total synthesis and elucidated its stereochemistry (Scheme 14).[67] Their synthesis commenced with the reaction between chloroformate **126** and compound **127** in the presence of butyl lithium and HMPA to get compound **128** with 88% yield. The compound **128** was subjected to conjugate addition by using Gilman reagent, *i.e.*, Me_2CuLi in the presence of TMSCl and THF. The temperature was adjusted between −78 °C to 0 °C, and it took almost 3 hours to achieve compound **129** in 99% yield. In the next step, the selective deprotection of compound **129** and the subsequent Mitsunobu reaction[37] in the presence of chiral compound **130** furnished compound **131** with a 60% yield. Over a few steps,



Scheme 14 Synthesis elucidated structure of iriomoteolide-1a **132a**.

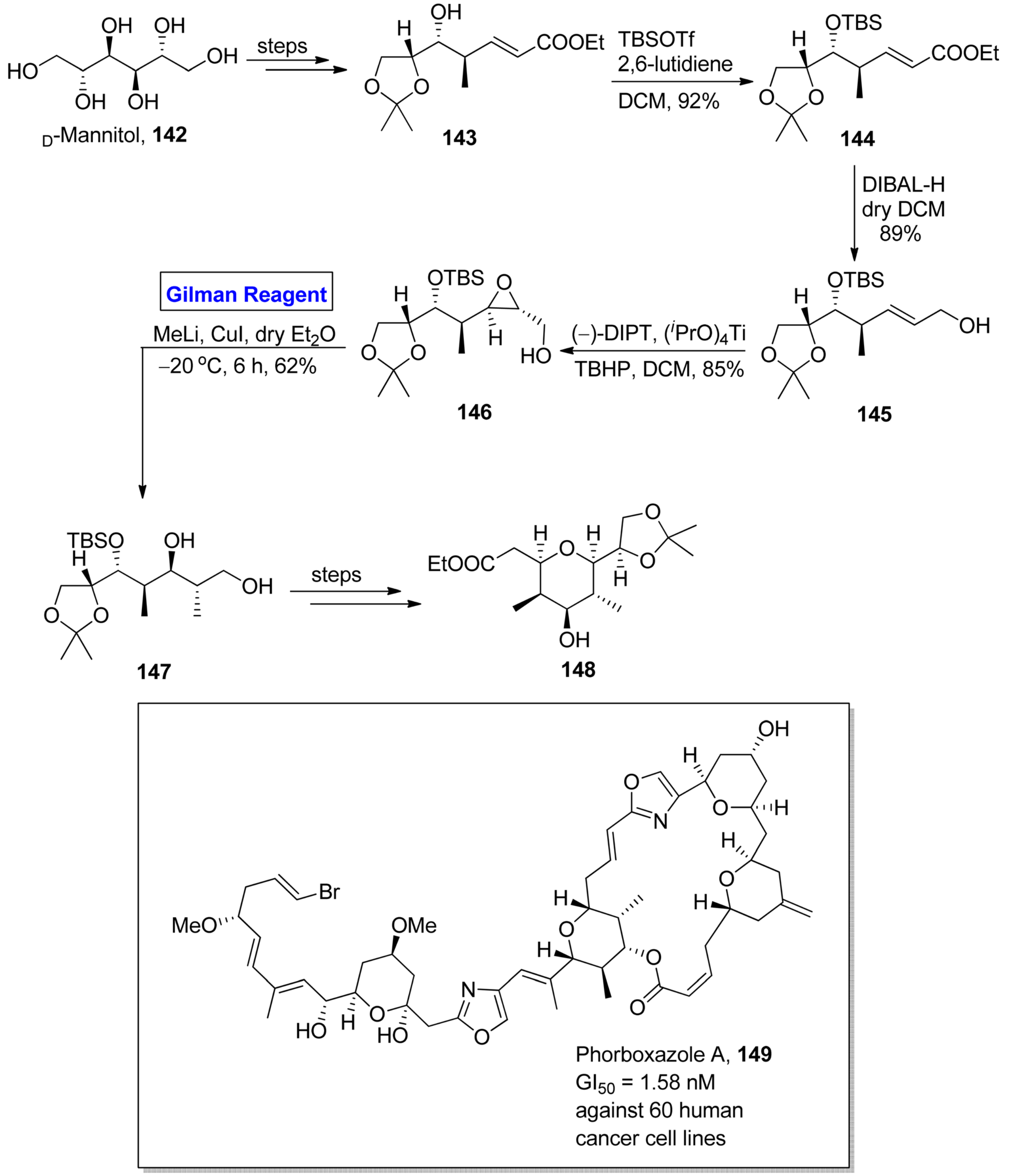
compound **131** was converted into the desired iriomoteolide-1a **132a** with required stereochemistry.

Iriomoteolide-1b **132b** constitutes a cis double bond between the eleventh and twelfth carbons in conjugation with a ketone group at the thirteenth carbon. Iriomoteolide-1b **132b** is also effective against the human lymphocyte DG-75 cell line (with $IC_{50} = 900$ ng mL^{-1}).[68] The interesting biological profile of iriomoteolide-1a **132a** and Iriomoteolide-1b **132b** urged Gosh



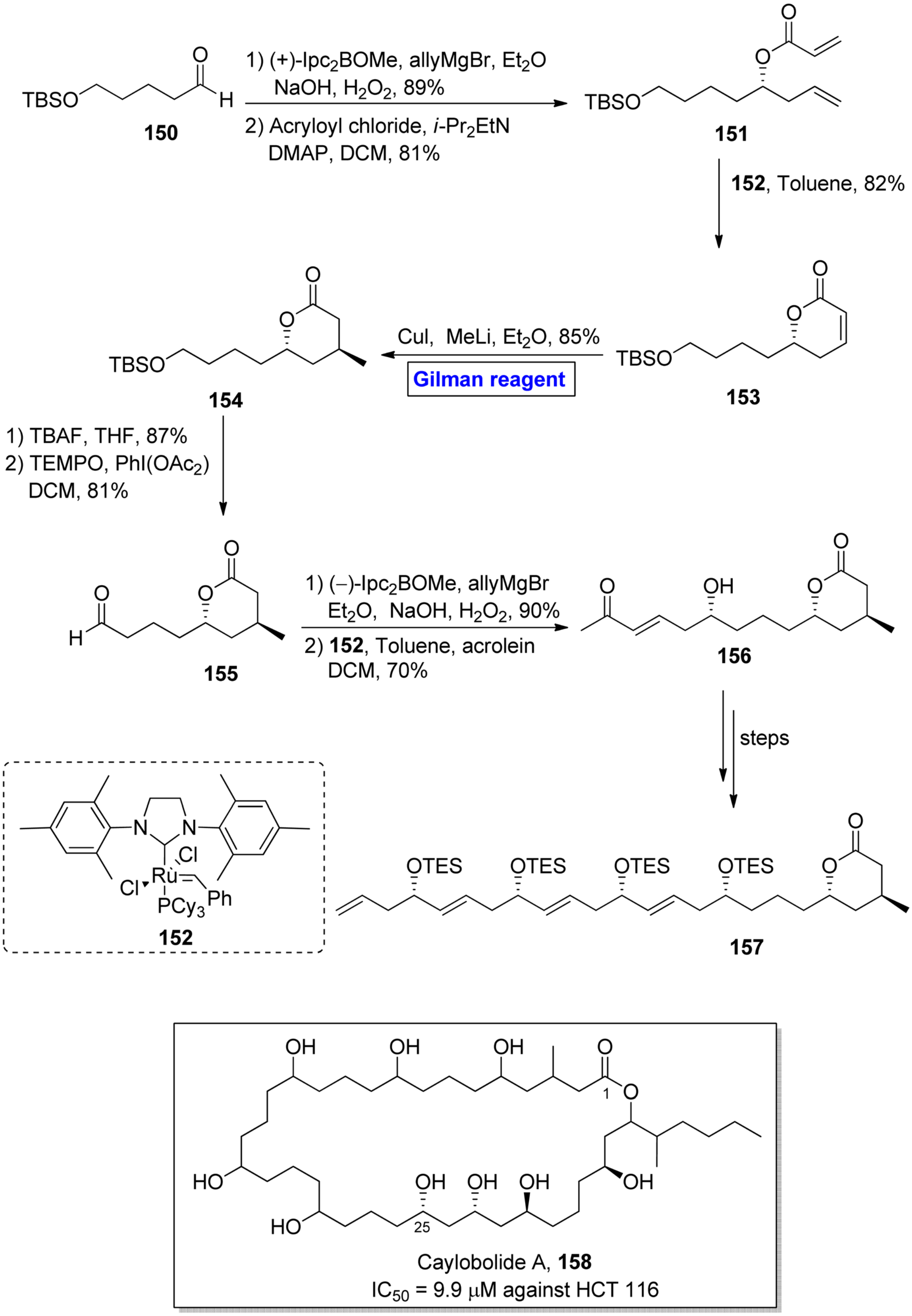
Scheme 15 Synthesis of proposed structures of iriomoteolide-1a **132a** and iriomoteolide-1b **132b**.

and Yuan to perform their total synthesis and structural elucidation by employing the Gilman reagent, Julia Kocienski olefination, and Yamaguchi macrolactonization in key steps (Scheme 15).[69] However, these synthesized structures did not show cytotoxic activity in biological evaluation. Their methodology involved the synthesis of fragment **137** and fragment **139**, which later reacted together and were modified to compound **141**. The synthesis of fragment **137** commenced with the treatment of racemic alcohol **133** with lipase PS-30 catalyst in the presence of vinyl acetate to obtain the enantioenriched product, which underwent reaction with lithium diisopropylamide and methyl iodide, accompanied by MOM protection and the subsequent reduction of the ether group in the presence of lithium aluminium hydride, furnished alcohol **134** with 31% yield. Further, the Swern oxidation of compound **134**, followed by Corey Fuchs homologation and the subsequent reaction with methyl chloroformate and butyl lithium in THF, resulted in alkynyl ester **135** in 78% yield. In order to perform



Scheme 16 Synthesis of the C20–C27 fragment **148** of phorboxazole A.

carbocupration, a well-suited Gilman reagent (CuI and MeLi in THF) was added to achieve the single isomer of olefin **136** in excellent yield (96%). In the next step, compound **136** was reduced by using DIBAL-H, accompanied by silyl protection and oxidative cleavage in the subsequent step to get the desired fragment **137** in 63% yield. The Julia Kocienski reaction of fragment **137** and sulfone **139** (modified from compound **138**) resulted in compound **140** with an 83% yield. After a few steps,



Scheme 17 Synthesis of intermediate **157** towards the total synthesis of caylobolide A **158**.

the compound **141** was oxidized by treating with DMP in DCM, and subsequently, deprotection was performed to get our desired mixture of iriomoteolide-1a **132a** and iriomoteolide-1b **132b**, which were latter on separated by column chromatography in 56% and 17% yields, respectively.

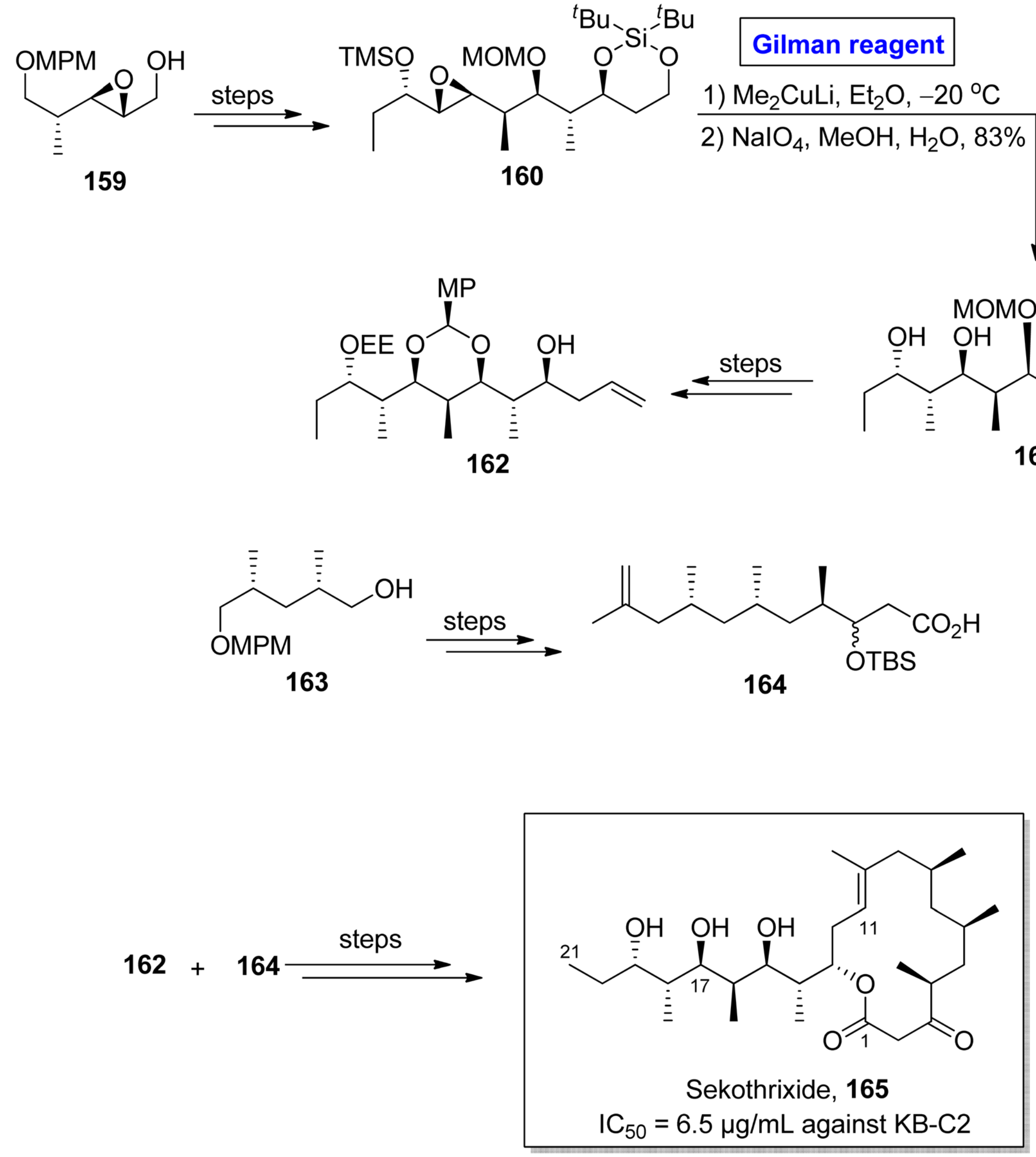
Phorboxazole A **149** is a 21-membered macrolide, which was isolated for the first time by Searl and Molinski from an Indian marine sponge.[70] It exhibits cytotoxic activity against 60 human cancer cell lines, *i.e.*, $GI_{50} = 1.58$ nM. It also shows anti-cancer activity against *Candida albicans* and anti-fungal activity against *Saccharomyces carlsbergensis.*[71] Raju *et al.* in 2015 performed the facile and well-organized synthesis of C20–C27 and C31–C39 fragments of phorboxazole A by using an inexpensive and easily available starting material, *i.e.*, D-mannitol (Scheme 16).[72] The synthesis of the C31–C39 fragment **148** entailed aldol condensation, Sharpless asymmetric epoxidation, and Gilman reagent-promoted epoxide ring opening reaction as key steps. The D-mannitol was transformed into compound **143** (in a few steps), which was subjected to silyllation in the presence of TBSOTf and 2,6-lutidine to furnish compound **144** in 92% yield. The reduction of compound **144** by using DIBAL-H in DCM resulted in alcohol **145** in 89% yield. In the next step, the Sharpless asymmetric epoxidation of alcohol **145** by using diisopropyltartrate, titanium isopropoxide, and 2-phenylpropan-2-yl hydroperoxide in DCM yielded compound **146** in 85% yield. In order to conduct a regioselective epoxide ring opening, Gilman reagent was used, and the reacting compound **146** was made to react with methyl lithium and copper iodide in dry diethyl ether by maintaining the temperature up to −20 °C. After 6 hours, compound **147** was achieved with a 62% yield. The compound **147** was modified over a few steps to furnish fragment **148** successfully in quantitative yield.

Caylobolide A **158** is a 36-membered, lactone-based macrolide. It was isolated for the first time from *Lyngbya majuscule*, a marine cayanobacteria, by MacMillan and Molinski.[73] Caylobolide A **158** has 256 possible diastereomeric structural configurations due to its eight undetermined stereocenters. It exhibited cytotoxic activities against the human colon cancer cell line (HCT 116) with $IC_{50} = 9.9$ μM.[74] These features make the synthesis of this fascinating heterocycle a challenging task to achieve. In 2013, Joarder *et al.* performed the enantioselective synthesis of a 24-carbon-containing intermediate **157** towards the total synthesis of caylobolide A **158** (Scheme 17).[75] The key steps in their synthetic path employed Gilman reagent-induced conjugate addition reaction, ruthenium-catalyzed cross metathesis, and boron-catalyzed allylation reactions. In the first step of their synthesis, the compound **150** was treated with (+)-Ipc_2BOMe, allylMgBr, and Et_2O, followed by the subsequent oxidation under basic conditions, resulting in the intermediate (in 89% yield), which was subjected to esterification with acryloyl chloride, providing compound **151** in 81% yield. Further, the cross metathesis reaction of compound **151** in the presence of catalyst **152** furnished lactenone **153** with 82% yield. In order to perform the regioselective conjugate addition reaction, a well-suited Gilman reagent (CuI and MeLi) was used in the presence of diethyl ether, resulting in lactone **154** in 85% yield. In the following step, desilylation of lactone **154** and subsequent oxidation by using TEMPO and $PhI(OAc_2)$ in DCM provided aldehyde **155** in 81% yield. The reaction of aldehyde **155** with (−)-Ipc_2BOMe, allylMgBr, and Et_2O with a subsequent cross metathesis reaction by using catalyst **152** resulted in aldehyde **156** (70% yield), which after modification over a few steps, furnished the desired intermediate **157**, leading towards the synthesis of caylobolide A **158**.

Sekothrixide **165** belongs to the class of macrolide, and it is renowned for its cytocidal activity against KB-C2 cells (that are usually colchicine resistant) with IC_{50} of 6.5 μg mL^{-1}.[76] It was isolated by Seto and colleagues from *Saccharothrixide* sp. and its structure is based on a fourteen-membered ketolide, having a lengthy side chain, along with seven consecutive chiral centers.[77] The interesting pharmacological profile of sekothrixide **165** prompted Terayama *et al.* to perform its first total synthesis in 2014 by employing Gilman reagent induced-epoxide ring opening reaction (Scheme 18).[78] In their methodology, the compound **160** (obtained from the modification of epoxy alcohol **159** over a few steps) was allowed to react with Me_2CuLi in Et_2O by keeping the temperature at −20 °C, accompanied by treatment with $NaIO_4$ to furnish diol **161** in 83% yield. Next, compound **162** (from compound **161**) and compound **164** (from compound **163**) were reacted and modified over a series of steps to complete the total synthesis of sekothrixide **165**.

Katsumi *et al.* performed the total synthesis of sekothrixide two times, as their first synthetic route contained an extensive number of steps and resulted in a low yield of the target molecule. So, they moved towards a more practical and quick method.[79,80] In 2019, they performed its total synthesis again, in 26 steps, by using 3-silyloxy-2-methylaldehyde **166** (optically active) as the starting material (Scheme 19).[81] The key reaction in their synthetic scheme for the synthesis of the C11 to C21 fragment **174** of sekothrixide, entailed a regioselective ring opening reaction of the TBS-protected epoxy secondary alcohol by employing Gilman reagent. Initially, compound **166** and compound **167** were reacted in the presence of THF to give compound **168** (in 93% yield), which was modified into compound **169** over a few steps. The treatment of epoxide **169** with dimethyl copper lithium in diethyl ether (Gilman reagent) by maintaining the temperature between −30 to 0 °C and the subsequent acid-prompted deprotection resulted in 1,3 diol **170** in 80% yield. After this, benzylidene acetal protection of diol **170** provided compound **171** (in 97% yield and dr = 1 : 2.4), which over a few steps was transformed into intermediate **172**. Further, in order to perform regioselective epoxide ring opening, the Gilman reagent protocol was used, which was assisted by THF deprotection, thus accomplishing the synthesis of diol **173**. The synthesis of the C11 to C21 fragment **174** of sekothrixide **165** was completed by the treatment of compound **173** with DMP and TsOH, affording compound **174** in a 65% yield. Over a few steps, the compound **174** was modified into sekothrixide **165**.

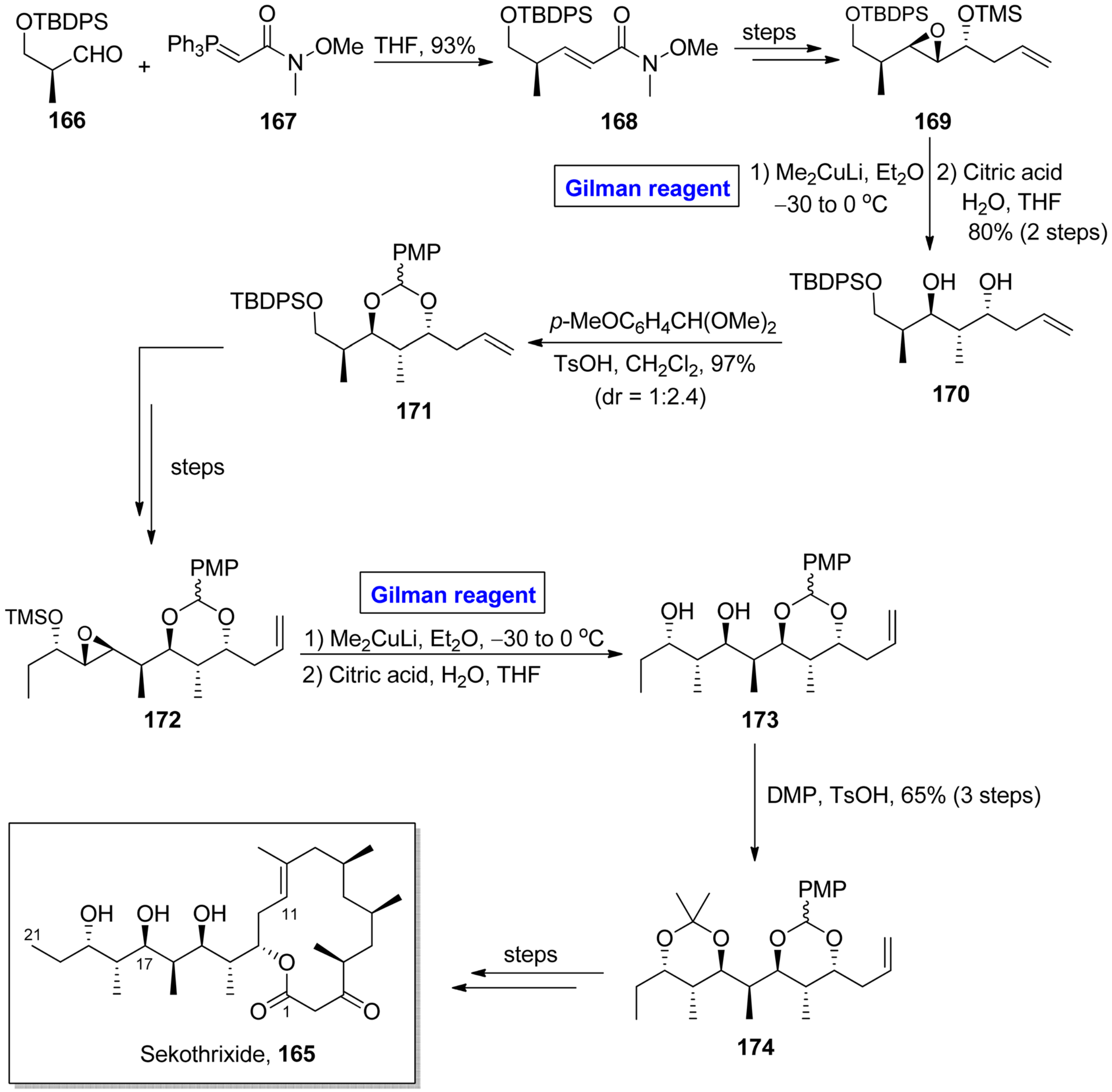
Amphidinolide G **183** and amphidinolide H **184** were isolated from *Amphiscolops* sp. of Okinawan flatworm.[82] The molecular framework of both these compounds constitutes cis diene units, allyl epoxide, 5 hydroxyl groups along with 9



Scheme 18 Total synthesis of sekothrixide **165**.

asymmetric centers.[83] Amphidinolide G **183** is a potential drug candidate against L1210 murine lymphoma (IC_{50} = 5.4 ng mL^{-1}) and KB human epidermoid (IC_{50} = 5.9 ng mL^{-1}). Amphidinolide H **184** also shows cytotoxic activity against both L1210 murine lymphoma (IC_{50} = 0.48 ng mL^{-1}) and KB human epidermoid (IC_{50} = 0.52 ng mL^{-1}).[84] The fascinating molecular architecture and biological potential of both these compounds made them a challenging synthetic target. In this effort, Hara *et al.*, in 2011 developed a new approach towards the synthesis of the C7–C26 fragment of both amphidinolide G **183** and amphidinolide H **184** (Scheme 20).[85] The key steps entailed Sharpless asymmetric dihydroxylation, conjugate addition reaction by Gilman reagent, and aldol coupling reaction. In their methodology, the ketone **177** (obtained from the starting oxazolidinone **175** and allyl iodide **176**) was treated with copper cyanide and methyl lithium (Gilman reagent) in THF at −78 °C for 1 hour to give an isomeric mixture of compounds **178a** and **178b** in 98% yield and dr = 1 : 2.5. After chromatographic separation, the compound **178b** was subjected to Wittig olefination, followed by TES group deprotection and subsequent IBX oxidation affording aldehyde **179** in 98% yield. Lastly, the aldol coupling reaction of aldehyde **179** and ketone **181** (prepared from **180**) in the presence of LHMDS at −20 °C furnished fragment **182** in a 74% yield (*S*/*R* = 1 : 1.5).

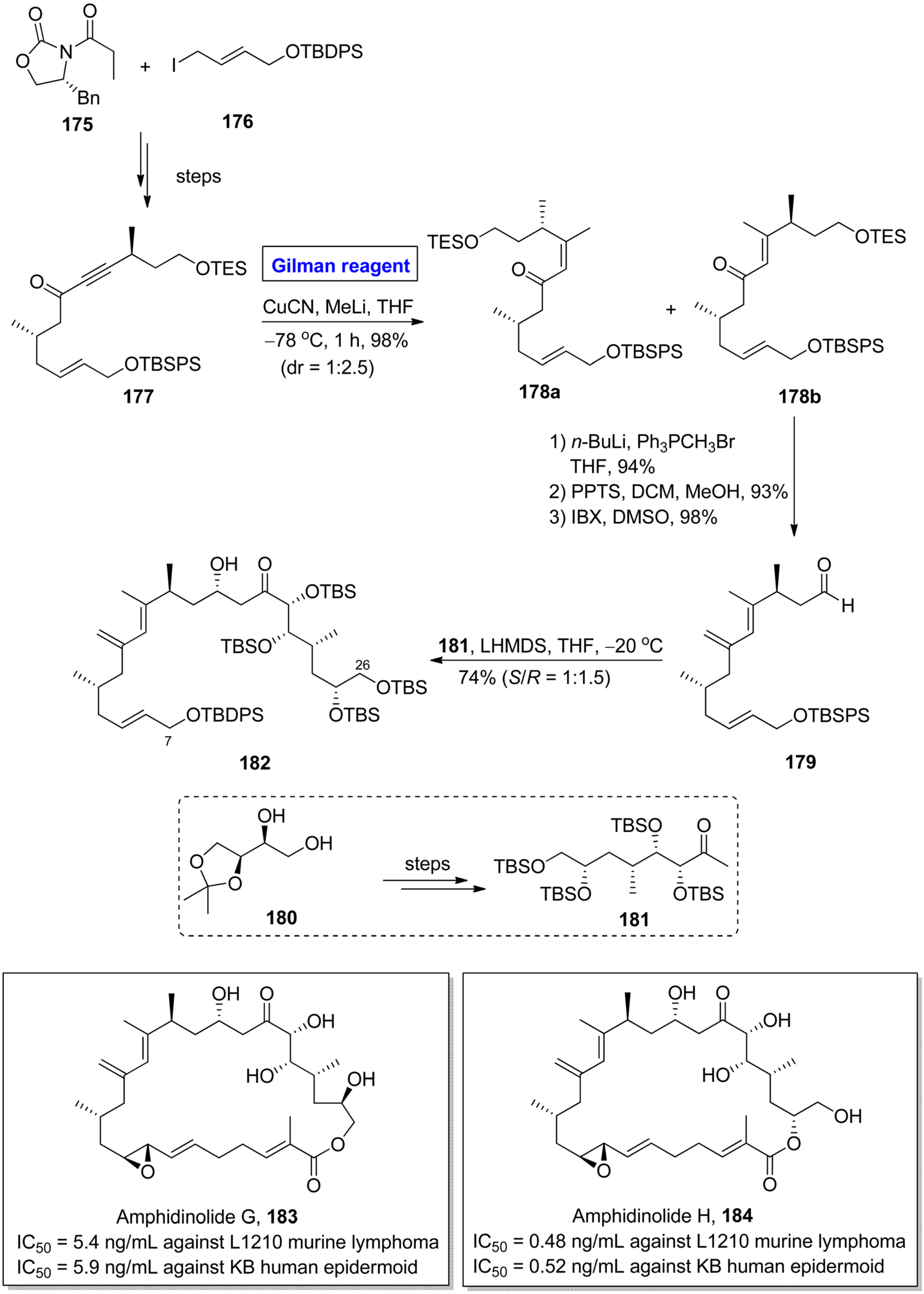
Antascomicins belong to the class of macrolides and show structural resemblance with rapamycin and ascomycin and were isolated firstly from *Micromonospora* by Fehr and colleagues in 1996.[86] This class of natural products can bind with FKBP12 and stimulate neuronal growth. For this reason, antascomicins are expected to be used as potential drug candidates for the treatment of neurodegenerative disorders.[87] Vakiti *et al.* reported the facile synthesis of the C17–C34



Scheme 19 Synthesis of the C11 to C21 fragment of sekothrixide **165**.

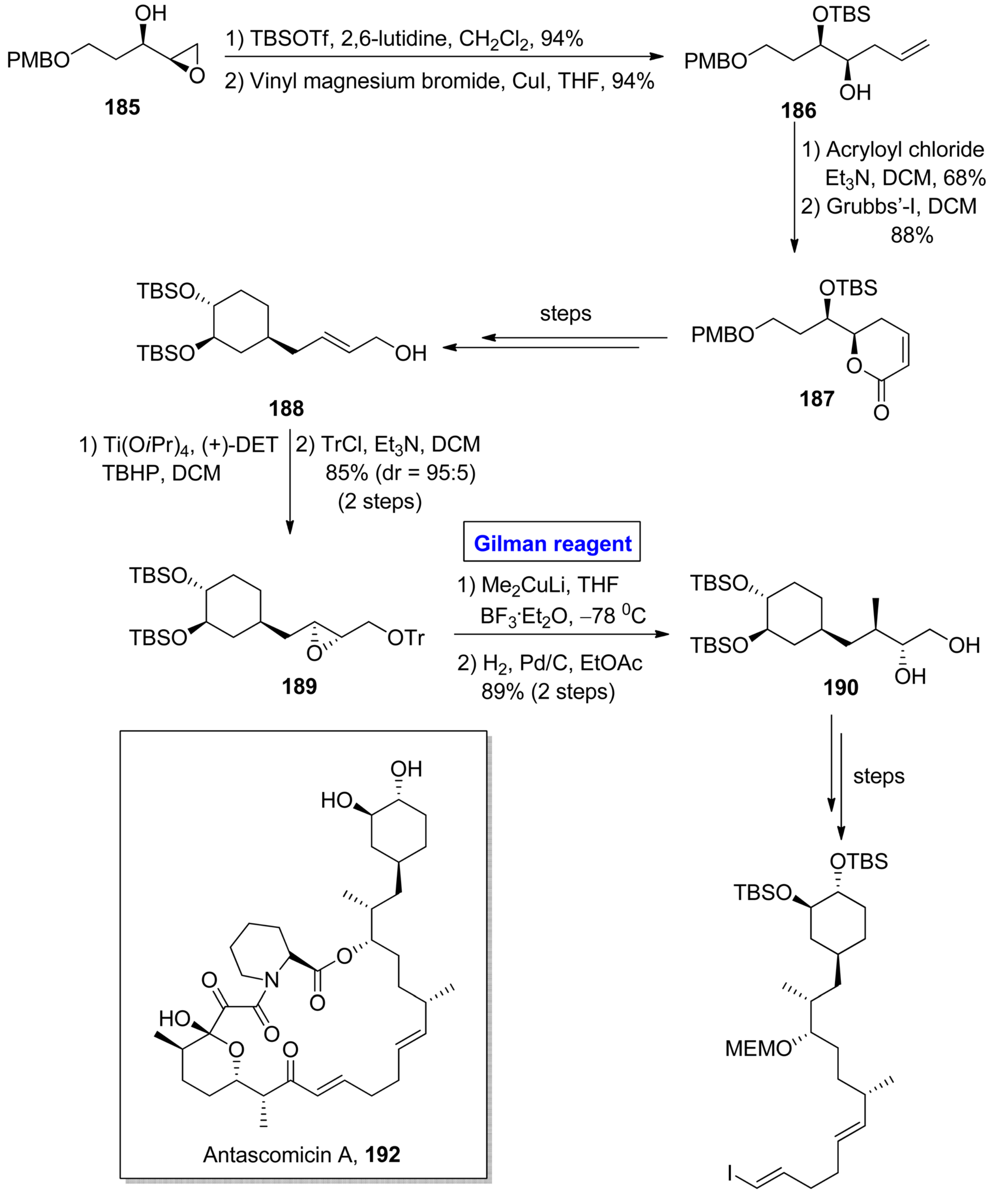
fragment **191** of antascomicins A **192** in 2014 (Scheme 21).[88] The main steps in their synthetic scheme involved Sharpless asymmetric epoxidation, regioselective epoxide opening reaction *via* Gilman reagent, and Julia olefination reaction. In the first step, the epoxy alcohol **185** (after TBSOTf protection) was allowed to react with vinyl magnesium bromide and copper iodide in THF to acquire homoallylic alcohol **186** in 94% yield. The treatment of compound **186** with acryloyl chloride and triethyl amine in DCM and further reaction with Grubb's first-generation catalyst in the subsequent step provided ether **187** in 88% yield. The compound **187** (over a few steps) was converted into compound **188**, which proceeded further for Sharpless asymmetric epoxidation and subsequent protection of the alcoholic group, resulting in compound **189** in 85% yield (dr = 95 : 5). For the ring opening reaction of compound **189**, well-suited Gilman reagent was used by reaction with lithium dimethyl cuprate in the presence of THF and catalytic amount of $BF_3\cdot Et_2O$. The temperature was adjusted at −78 °C, and after completion of the ring-opening reaction, hydrogenation was performed with tosyl group deprotection, which resulted in diol **190** in 89% yield. A few steps later, the diol **190** was converted into the desired fragment **191**, which completed the synthetic process.

(−)-Melearoride A **200a** is a thirteen-membered macrolide, which was first isolated from *Penicillum meleagrinum* (in 2016) and exhibits anti-fungal activities (particularly against *Candida albicans*).[89,90] Reed *et al.* in 2019 accomplished the total synthesis of (−)-melearoride A **200a** and its non-natural isomer (+)-melearoride A **200b** based on a 13-step sequence in 4.3% and 1% overall yield (Scheme 22).[91] The key steps entailed Evans alkylation, Gilman reagent-induced epoxide ring-opening



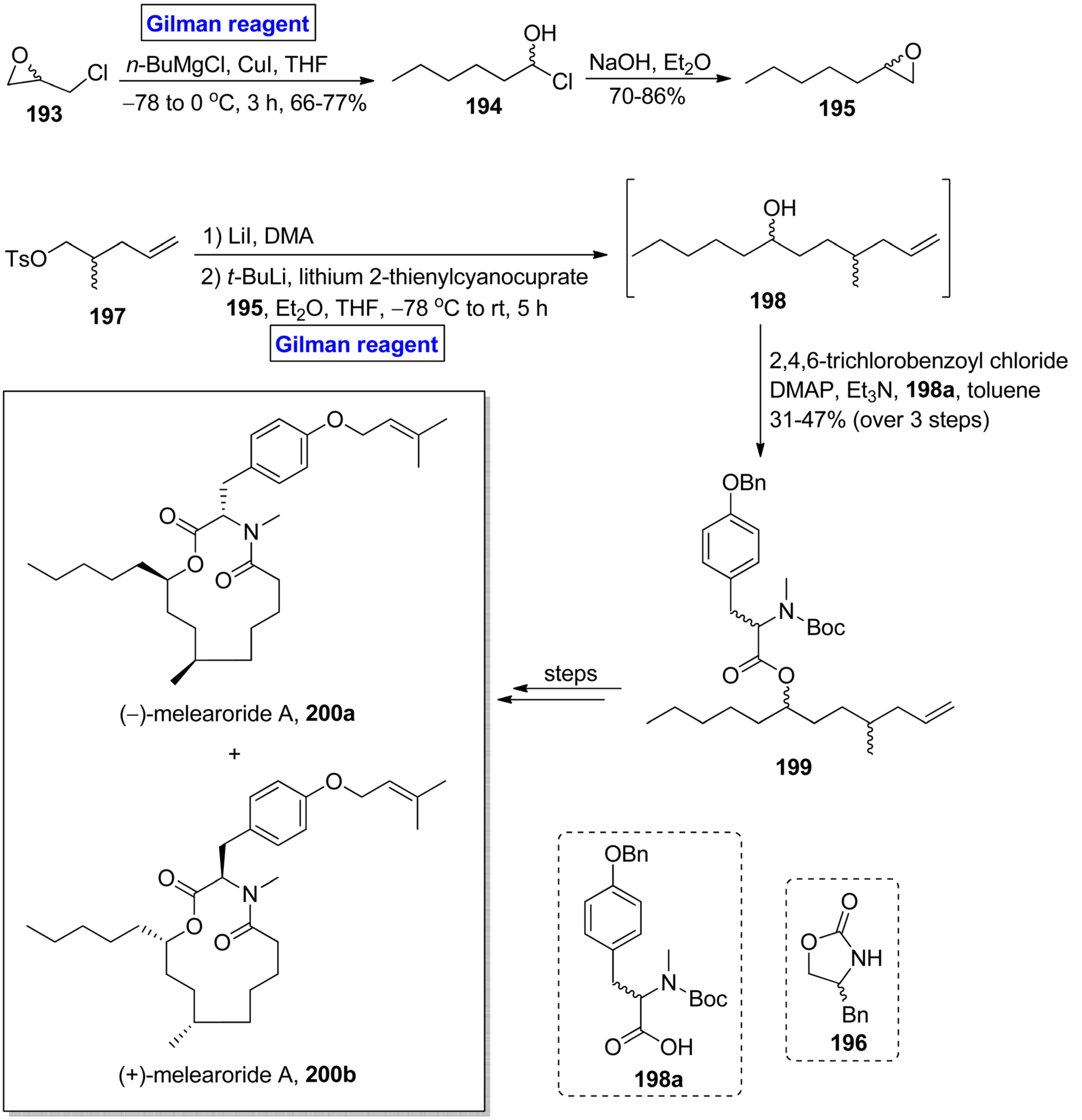
Scheme 20 Synthesis of the C7–C26 fragment **182** of amphidinolide G **183** and H **184**.

reaction, ring-closing metathesis, and Mitsunobu reaction.[37] Their synthetic scheme commenced with the *in situ* generation of Gilman reagent *via* the treatment of epichlorohydrin **193** with butyl magnesium chloride and copper iodide in tetrahydrofuran to achieve compound **194** (in 66 to 77% yield), which underwent treatment with sodium hydroxide and diethyl ether



Scheme 21 Synthesis of the C17–C34 fragment **191** towards the synthesis of antascomicin A **192**.

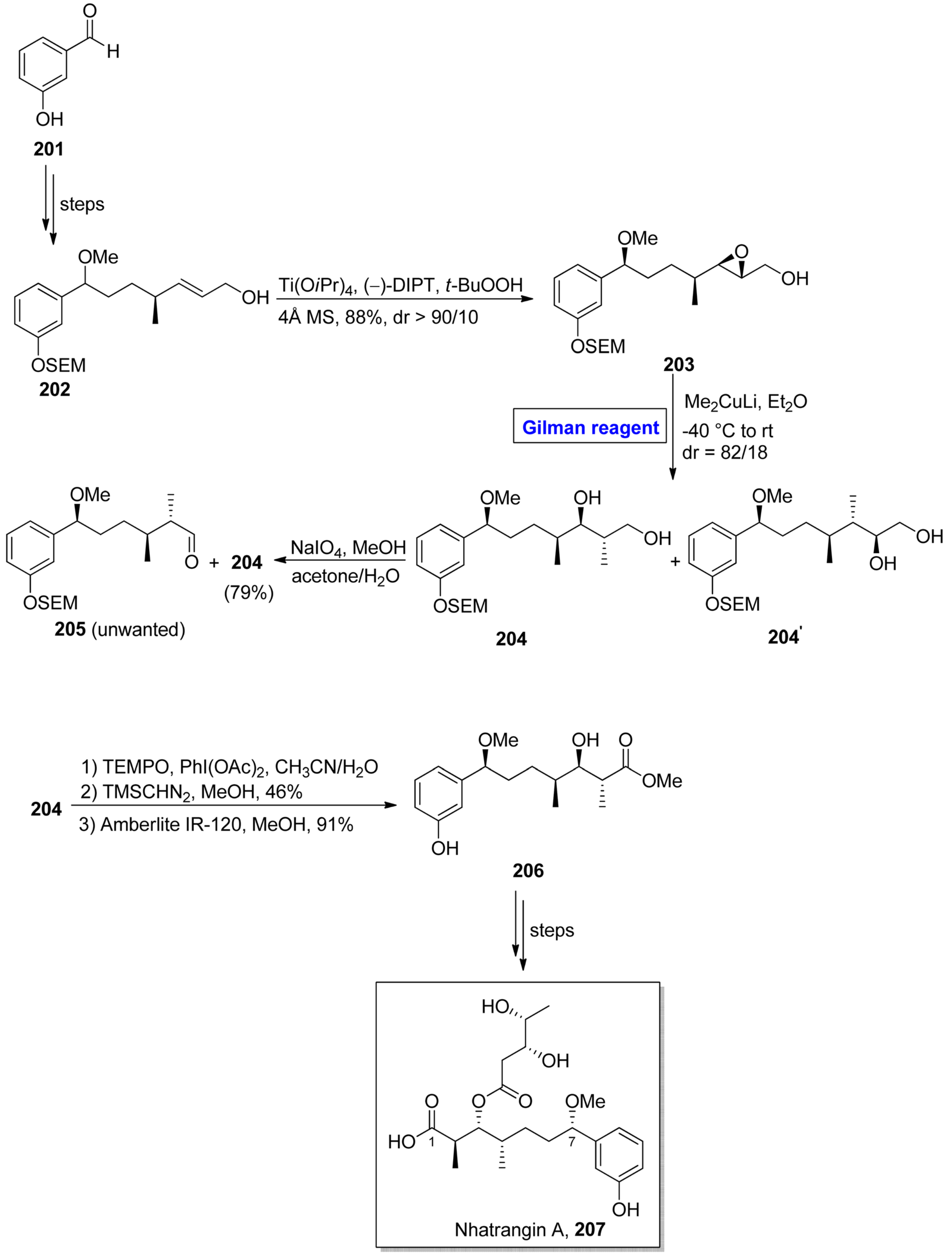
to provide compound **195** in 70–86% yield. Compound **197** (prepared from compound **196**) was subjected to Evans alkylation, accompanied by the reaction with compound **195** in the presence of tertiary butyl lithium, lithium 2-thienylcyanocuprate (Gilman reagent) in a mixture of diethyl ether and tetrahydrofuran at −78 °C to room temperature. It took 5 hours to obtain alcohol **198**, which was then proceeded for esterification with acid **198a** in the presence of 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N in toluene, which resulted in ester **199** in 31 to 47% yield (in 3 steps). A few steps latter, the ester **199** was utilized for the successful synthesis of (−)-melearoride A **200a** and its non-natural isomer **200b**.



Scheme 22 Total synthesis of (−)-melearoride A **200a**.

Synthesis of polyketide-based natural products

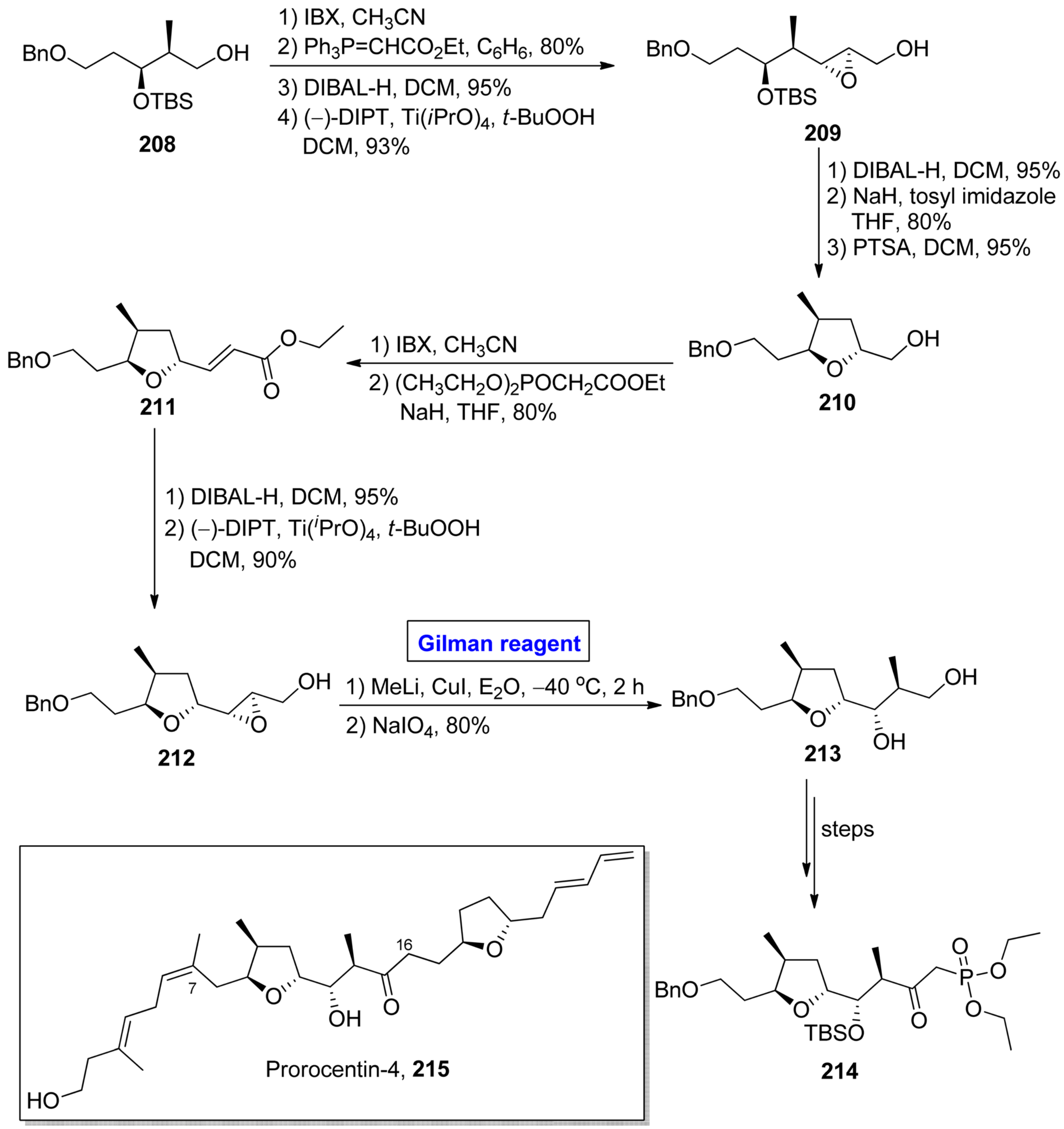
Nhatrangin A **207** belongs to the polyketide class of natural products. In 2010, it was isolated for the first time from a marine cyanobacterium, *i.e.*, *Lyngbya majuscula*, found in Vietnam.[92] The purification of nhatrangin A **207** after its isolation from its natural source did not result in productive yield. Aplysiatoxin is also a natural compound, well-known for its potassium channel inhibition and anti-viral and anti-cancer activities.[93] Nhatrangin A **207** and aplysiatoxin have the same biosynthetic origin and have structural similarities with each other. Owing to these facts, nhatrangin A **1** is supposed to be a potential drug candidate and its total synthesis has been previously reported by Kamal, Yadav, and Dias research groups.[94] In continuation of this work, Feuillastre *et al.* reported the enantioselective synthesis of the C1–C7 fragment **206** of nhatrangin A **207** in 2020 (Scheme 23).[95] It was a 14-step sequenced methodology, starting from the easily available achiral 3-hydroxybenzaldehyde, and the overall yield was 13%. The main steps in their scheme were Sharpless asymmetric epoxidation and Gilman reagent-induced regioselective epoxide ring opening reaction. In their synthetic path, the 3-hydroxybenzaldehyde **201** was converted into allylic alcohol **202** in a number of steps. The allylic alcohol **202** was subjected to Sharpless asymmetric epoxidation under given conditions,



Scheme 23 Synthesis of C1–C7 fragment **9** of nhatrangin A **207**.

which resulted in compound **203** in 88% yield (dr > 90/10). In order to perform the epoxide ring-opening reaction, the compound **203** was allowed to react with lithium dimethyl cuprate in diethyl ether by maintaining the temperature between −40 °C to room temperature, which furnished a diastereomeric mixture of diol **204** (with dr = 82/18). Subsequently, the treatment of this mixture with $NaIO_4$ in a suitable solvent afforded diol **204** (with 79% yield), which was subjected to selective oxidation and suitable deprotection under given conditions to complete the synthesis of fragment **206** in 91% yield.

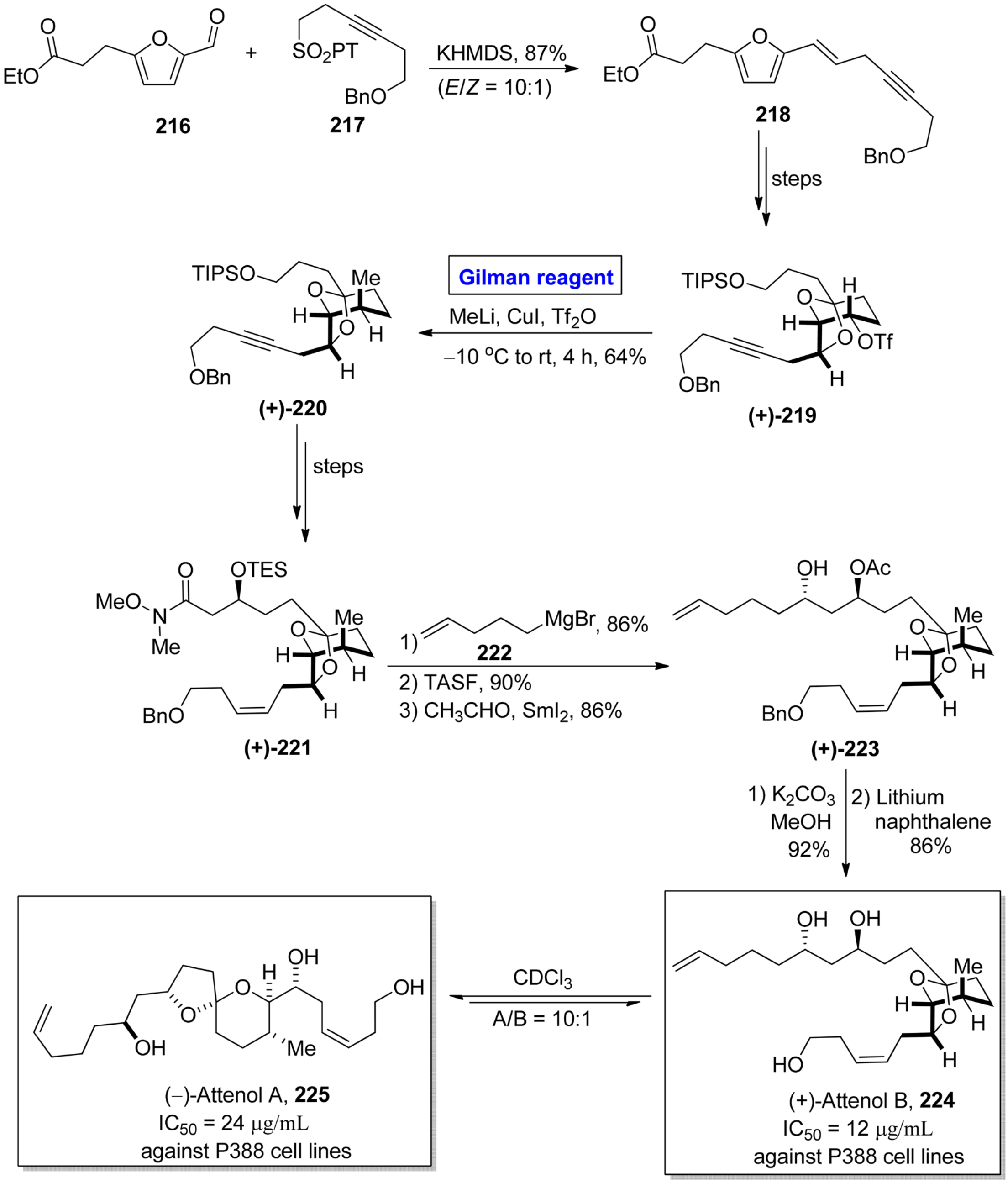
One of the linear polyketides, prorocentin-4 **215**, was isolated from *Prorocentrum* sp. of dinoflagellates, which are found in tropical oceans all over the world.[96] It is a potential cytotoxic agent and is present in okadic acid-synthesizing organisms. Its structure contains two tetrahydrofuran rings and seven asymmetric centers.[97] By focusing on these features, AnkiReddy *et al.* disclosed the synthesis of the C1–C23 fragment of prorocentin-4 **215** in 2018 (Scheme 24).[98] The synthetic path that they adopted is based on the synthesis of three main fragments (C1–C6, C7–C16, and C17–C23). However, the synthesis of the middle fragment C7–C16 **214** entailed the employment of the Wittig reaction, Sharpless asymmetric epoxidation, and epoxide ring opening reaction by Gilman reagent as key steps. Their synthesis of this fragment **214** commenced with the easily available starting alcohol **208** that was oxidized by using IBX and then subjected to Wittig reaction to result in the intermediate in 80% yield. The DIBAL-H induced reduction of the intermediate and Sharpless asymmetric epoxidation in sequence, providing the epoxy alcohol **209** in 93% yield. The synthesis of the tetrahydrofuran ring in compound **210** (in 95% yield) was achieved by DIBAL-H-induced reduction of



Scheme 24 Synthesis of the C7–C16 fragment of prorocentin-4 **215**.

compound **209** followed by the treatment with tosyl imidazole and NaH in THF and subsequent reaction with PTSA in DCM. In the next step, IBX oxidation of compound **210** and subsequent HWE reaction provided ester **211** in 80% yield. Again, DIBAL-H induced reduction and Sharpless asymmetric epoxidation in sequence were employed for ester **211** to furnish diol **212** in 90% yield. Further, in order to carry out the epoxide ring-opening reaction, a well-suited Gilman reagent was employed. Thus, the compound **211** was treated with methyl lithium and copper iodide in diethyl ether, followed by the addition of $NaIO_4$ to get ether **213** (in 80% yield), which was then converted into the desired fragment **214** over a few steps.

The synthesis of scarce natural products has engaged the attention of many organic chemists. One of the Chinese natural products, *i.e.*, attenol A and attenol B were isolated from *Pinna attenuate* by Uemura and colleagues.[99] These are novel ethereal compounds having rare natural existence. Attenol A is made up of a [5,6]-spiroketal ring embellished with three OH groups on two unsaturated flanking chains. (+)-Attenol B is a minor isomer of attenol A and exists under acidic conditions. These two polyketides are cytotoxic. The IC_{50} values of (−)-attenol A **225** and (+)-attenol B **224** against P388 cell lines are 24 μg mL^{-1} and 12 μg mL^{-1} respectively.[100] Owing to the distinctive structural features with a great pharmacological profile, many synthetic

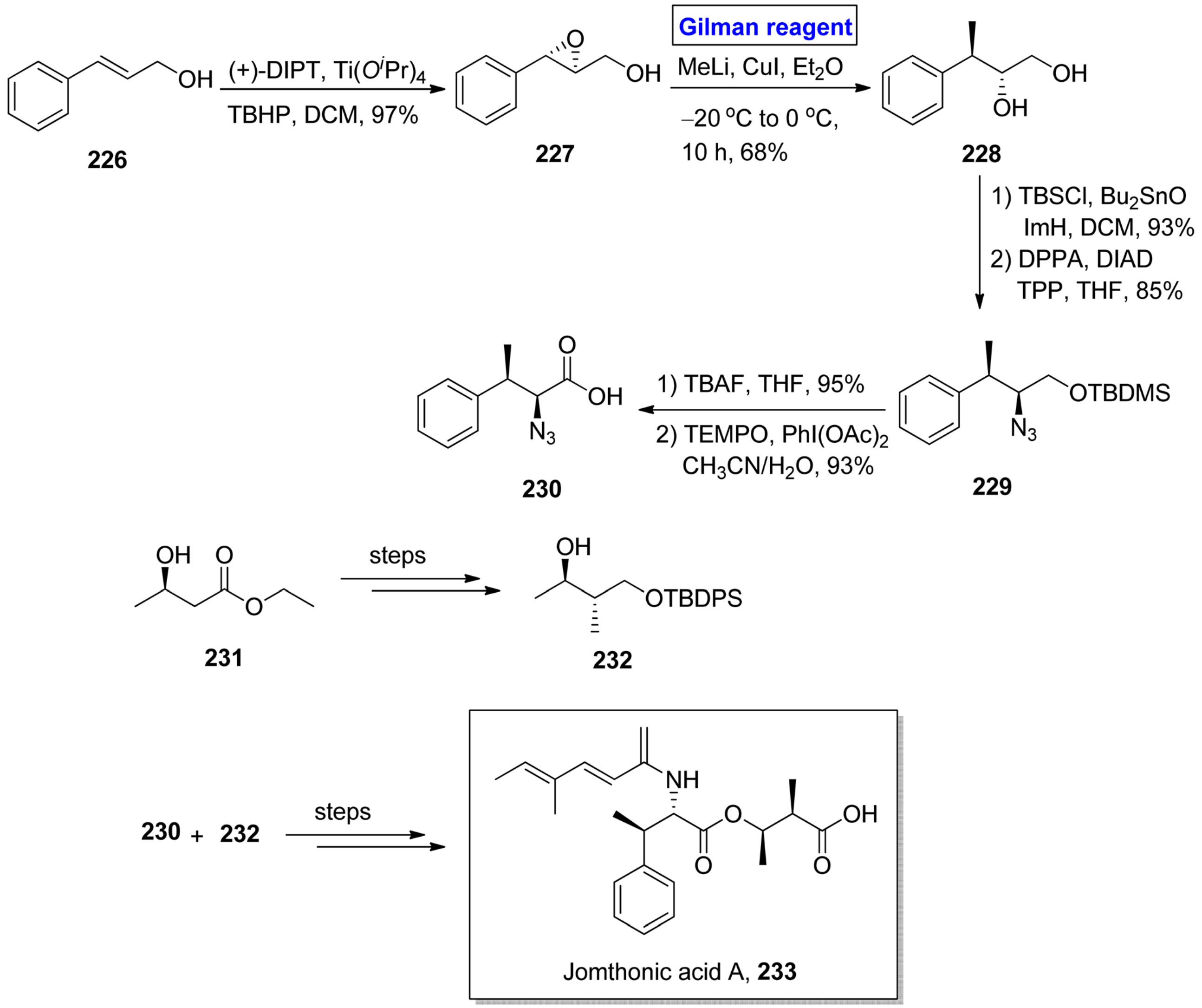


Scheme 25 Total synthesis of (+)-attenol B **224** and (−)-attenol A **225**.

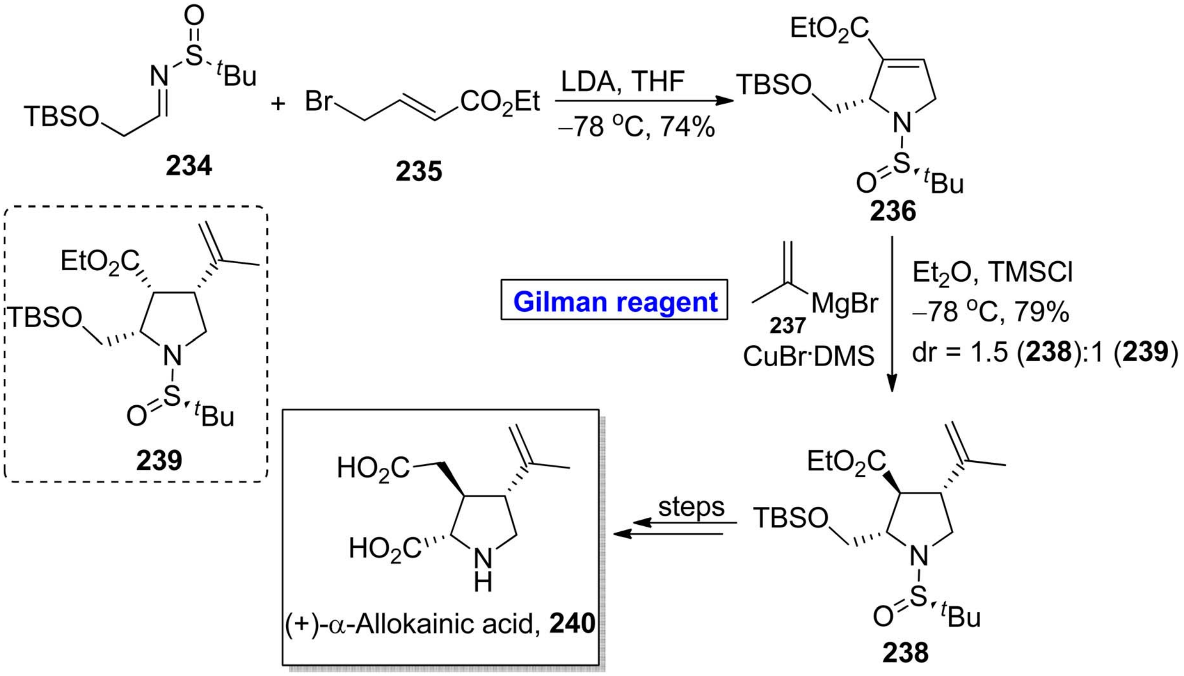
approaches toward the synthesis of these two compounds have been reported in the literature. In continuation of this effort, Ren *et al.* in 2015 disclosed a novel synthetic route towards the synthesis of (+)-attenol B **224** and its isomer **225** as well by employing Gilman reagent (Scheme 25).[101] Their synthesis commenced with the Julia–Kocienski reaction of aldehyde **216** and sulfone **217** in the presence of KHMDS to afford eyne **218** in 87% yield (with $E/Z = 10:1$). After a few steps, triflate **219** (obtained from compound **218**) was subjected to a bimolecular nucleophilic substitution reaction (S_N2) by reacting with methyl lithium and copper iodide (Gilman reagent) in the presence of Tf_2O. The temperature was maintained between −10 °C to room temperature. After 4 hours, the alkyne **220** was obtained with a 64% yield. The compound **220** was converted into compound **221** over a few steps. The treatment of amide **221** with Grignard reagent, accompanied by the desilylation and Evans Tishchenko reaction in sequence, provided the diol derivative **223** in 86% yield. In the following two steps, the deacetylation (in the presence of potassium carbonate and methanol) and debenzylation (in the presence of lithium and naphthalene) furnished the desired (+)-attenol B **224** in 86% yield. The synthesis of (−)-attenol A **225** was achieved in 91% yield ($A/B = 10:1$) by isomerizing (+)-attenol B **224** in the presence of $CDCl_3$.

Synthesis of amino acid-based natural products

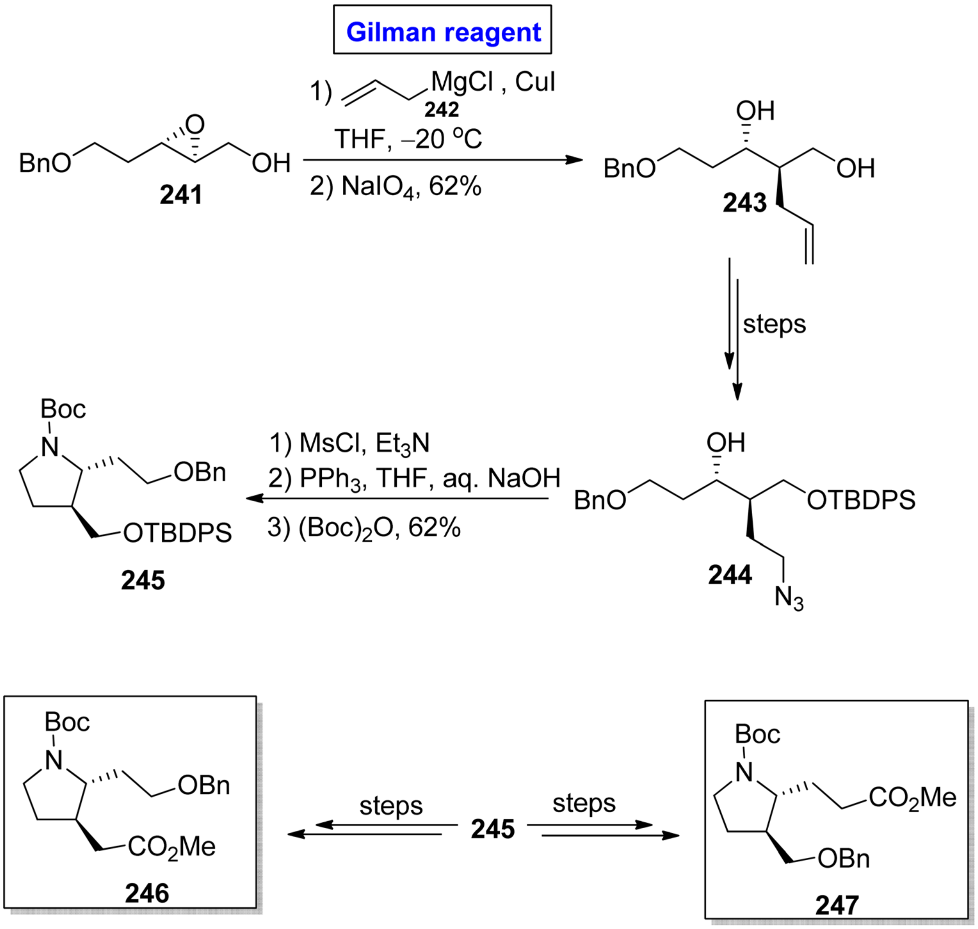
Jomthonic acid A **233** belongs to the class of amino acids isolated from *Streptomyces* sp. of soil antinomycete.[102] Its sophisticated structure is based on fragment **230** and fragment **232**, having 4 stereogenic centers. It shows antiatherogenic and antidiabetic activities against St-13 mice and exhibits preadipocyte differentiation inhibition with $IC_{50} = 2–50$ μM. Their fascinating structure and medicinally important pharmaceutical profile make them a valuable synthetic target.[103,104] Dumpala *et al.* in 2020 presented a concise and efficient synthetic route towards the first total synthesis of this heterocyclic scaffold **233**, with 8.0% overall yield (Scheme 26).[105] The main steps entailed Sharpless epoxidation, regioselective



Scheme 26 Synthesis of jomthonic acid A **233**.



Scheme 27 Synthetic approach towards (+)-α-allokainic acid **240**.



Scheme 28 Synthesis of substituted $\beta^{2,3}$-proline **246** and β^{3}-homoproline **247**.

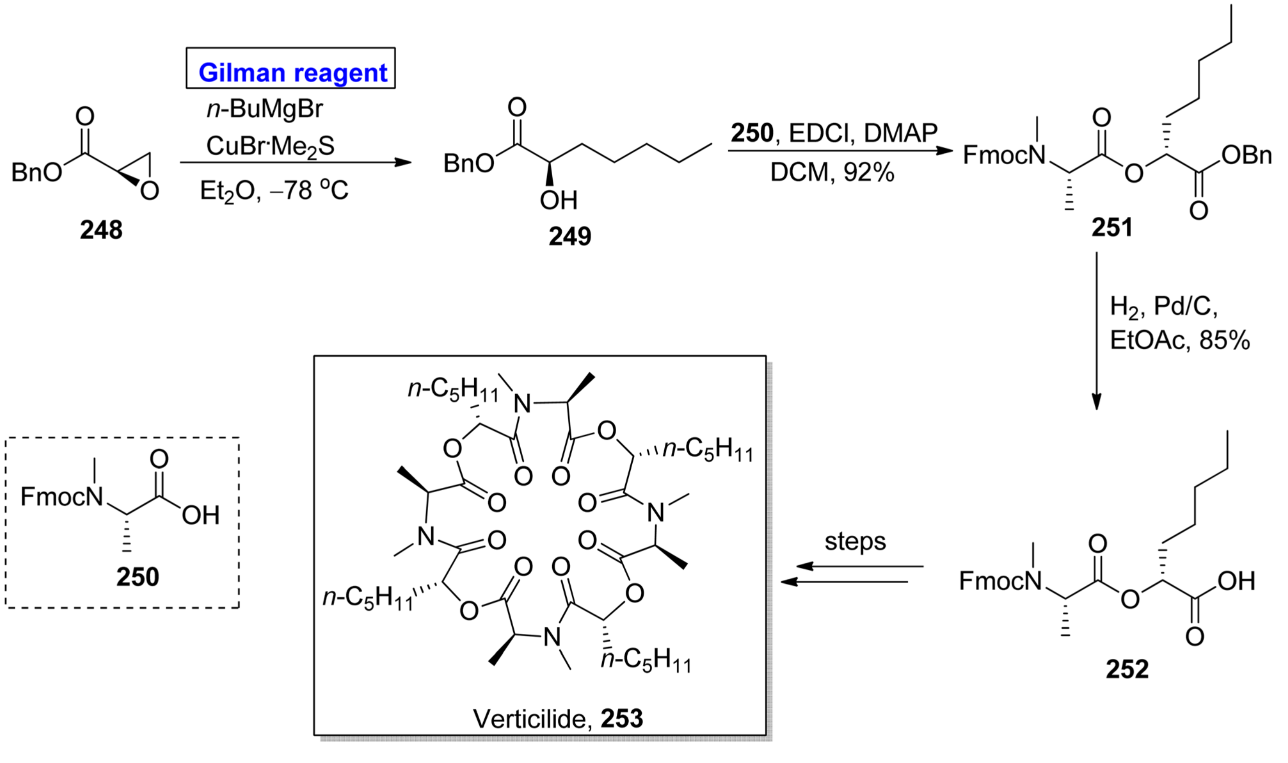
epoxide ring opening by Gilman reagent, Mitsunobu reaction,[37] Yamaguchi esterification, and amide coupling reaction. To accomplish this task, the easily available cinnamyl alcohol **226** was converted into epoxide **227** *via* Sharpless asymmetric epoxidation under given conditions with 97% yield. To perform the epoxide ring opening, the well-suited Gilman reagent was applied by reacting epoxide **227** with methyl lithium and copper iodide in diethyl ether as solvent at −20 °C to 0 °C in 10 hours, which resulted in diol **228**, with 68% yield. The compound **228**, after silyl protection, was subjected to Mitsunobu conditions to afford compound **229** with 85% yield. After this, silyl deprotection of silyl ether **229** and subsequent oxidation in the presence of $PhI(OAc)_2$ and TEMPO provided compound **230** with 93% yield. Later on, fragment **230** and fragment **232** (obtained from compound **231**) were reacted together and (after some modification) in a few steps, which completed the total synthesis by providing jomthonic acid A **233**.

Kainic acid is a kainoid based natural product (having 3 stereocenters) with a propenyl group attached at the C4 position. This remarkable naturally occurring amino acid is a glutamate receptor neurotransmitter, therefore, it is an intriguing synthetic target.[106,107] In 2019, Chogii *et al.* proposed an efficient and simple synthetic route towards the synthesis of (+)-α-allokainic acid **240** (Scheme 27).[108] In their synthetic scheme, the imine **234** and compound **235** were made to react in the presence of LDA and THF to provide pyrrolidine **236** (in 74% yield), which underwent further reaction with Gilman reagent *via* treatment with compound **237** in the presence of diethyl ether and TMSCl at −78 °C to furnish a mixture of compound **238** (in 79% yield) and compound **239** (dr = 1.5 : 1). The compound **238** was modified in a few steps to complete the synthesis of (+)-α-allokainic acid **240**.

β-Proline and β-homoproline have the ability to form interactions with collagen and are expected to exhibit antithrombotic activity.[109,110] This concept prompted Basu *et al.* in 2014 to synthesize substituted $\beta^{2,3}$-proline **246** and β^{3}-homoproline **247** monomers as well as their dimers *via* the Gilman reagent synthetic protocol and investigating their conformational studies (Scheme 28).[111] In the first step, the epoxide **241** was subjected to a ring-opening reaction *via* treatment with allyl magnesium chloride **242** and copper iodide in THF (for *in situ* generation of Gilman reagent). In order to avoid the unwanted 1,2-diol, $NaIO_4$ was added, which resulted in diol **243** (in 62% yield) and was then transformed into alcohol **244** over a few steps. The mesylation of alcohol **244**, subsequent reduction (with PPh_3 in THF), and Boc group protection provided the precursor **245** in 62% yield. Later on, compound **245** was utilized for the synthesis of compound **246** and compound **247** over a few steps.

Synthesis of peptide-based natural products

Verticilide **253**, a cyclic depsipeptide, was isolated from *Acremonium variecolor* (a fungus).[112] It is a novel insecticide and a selective inhibitor of ryanodine binding and is structurally based on a 24-membered macromolecular ring consisting of two types of repeating units, *i.e.*, *N*-methyl alanine and 2-hydroxyheptanoic acid.[113] The first total synthesis of verticilide **253** was reported by Watanabe *et al.* in 2020. The same group presented its total synthesis by adopting two different



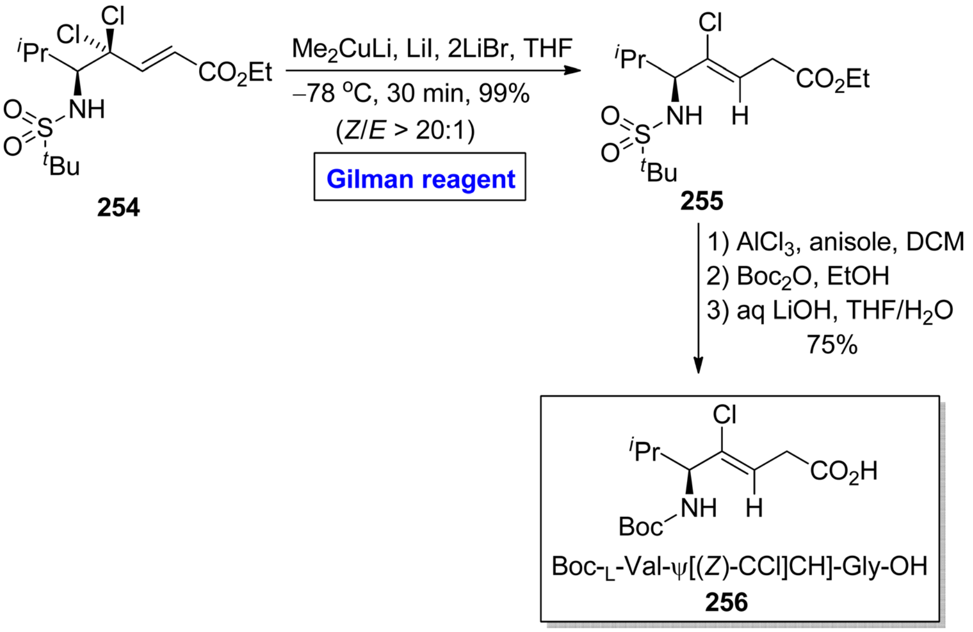
Scheme 29 Synthesis of intermediate **252** towards the synthesis of verticilide **253**.

(economical and safe) approaches for the macrocyclization of fragment **252** (Scheme 29).[114] The names of these two techniques are hydrophobic anchor molecule process and solid phase peptide synthesis. In their synthetic scheme, fragment **252** was synthesized by employing Gilman reagent. Their synthesis was initiated with the ring opening of epoxy benzyl ester **248** (easily available starting material) by treating it with butyl magnesium bromide, copper bromide, and dimethyl sulphide in diethyl ether as a solvent at −78 °C to give *N*-methyl alanine **249** in quantitative yield. Esterification of compound **249** with compound **250** in the presence of EDCl, DMAP, and DCM furnished compound **251** (in 92% yield), which was subjected to hydrogenation to acquire fragment **252** in 85% yield. Further steps involving the macrocyclization of fragment **252** by two different approaches completed the synthesis of verticilide **253**.

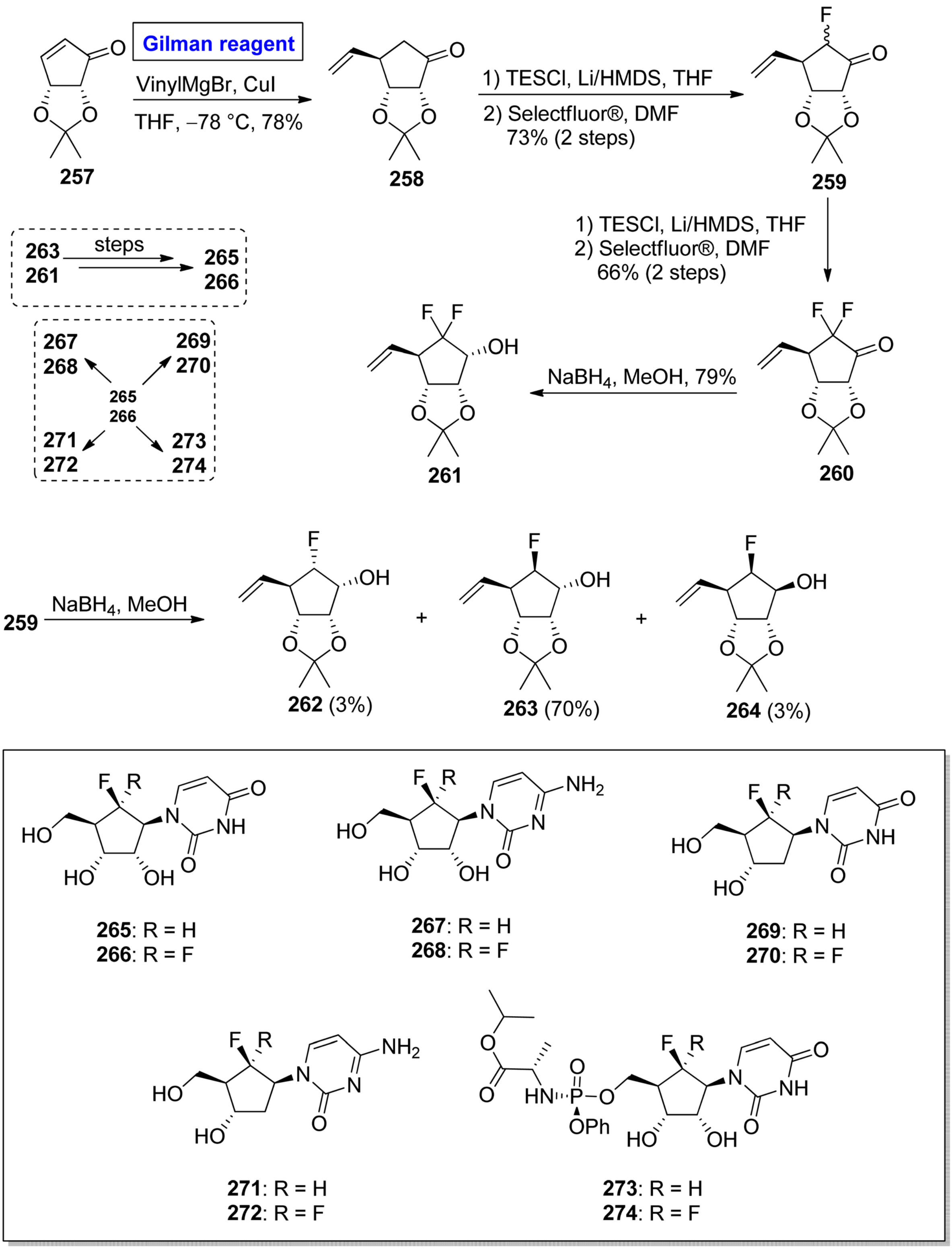
Peptides are medicinally and biologically important heterocyclic compounds. Owing to the rare bioavailability, synthetic chemists are working on replacing the amide group of peptides with alkene-based structures, which resemble peptides with improved biomimetic properties.[115,116] Among these, chloroalkenes are considered the best synthetic intermediate as these are the core motifs of many natural products.[117] In continuation of this work, Kobayakawa and Tamamura performed the synthesis of (*Z*)-chloroalkene-based dipeptide isosteres **256** in 2016 by employing the Gilman reagent (Scheme 30).[118] To perform this task, the compound **254** was allowed to react with lithium dimethyl cuprate, lithium iodide, and lithium bromide in THF at −78 °C, which provided compound **255** in 99% yield ($E/Z > 20:1$). The compound **255** was further converted into compound **256** *via* selective protection and deprotection steps.

Synthesis of nucleoside-based natural products

Nucleoside analogues are considered a cornerstone of the preventive strategies against cancer and various viral diseases (including COVID-19). Among these analogues, the role of carbocyclic nucleosides as naturally existing cytotoxic agents is predominant.[119,120] In 2022, Benckendorff *et al.* presented a scalable and efficient synthesis of monofluorinated and difluorinated carbocyclic nucleoside analogues **265–274** and evaluated their cellular viability against PANC-1 and cancer cell lines U87-MG (Scheme 31).[121] Their synthesis began with the readily available cyclopentenone **257**, which was subjected to a conjugate addition reaction by employing the corresponding Gilman reagent. Thus, the treatment of cyclopentenone **257** with vinyl magnesium chloride and copper iodide in THF, with the adjustment of temperature at −78 °C furnished the compound **258** with a 78% yield. The compound **258** was silylated and subsequently treated with Selectfluor® in DMF to give compound **259** (with successful installation of fluorine) with a 73% yield. In order to install the second fluorine, a sequence of silyation and reaction with Selectfluor® was repeated, this time for compound **259**, which resulted in compound **260** in 66% yield. In the next steps, the reduction of compound **260** by using $NaBH_4$ in MeOH gave compound **261** with a 79% yield. The reduction of compound **259** provided a mixture of compounds **262**, **263**, and **264** in 3%, 70%, and 3% yield, respectively. Later on, compound **263** and compound **261** were used as precursors for the synthesis of compound **265** and compound **266**, respectively, which proceeded further for the synthesis of analogues **267** to **274**. All the synthesized analogues **267** to **274** were evaluated against cancer and PANC-1 cell lines. Among these, the compound **267** exhibited mild cytotoxic activity against U87-MG cells.

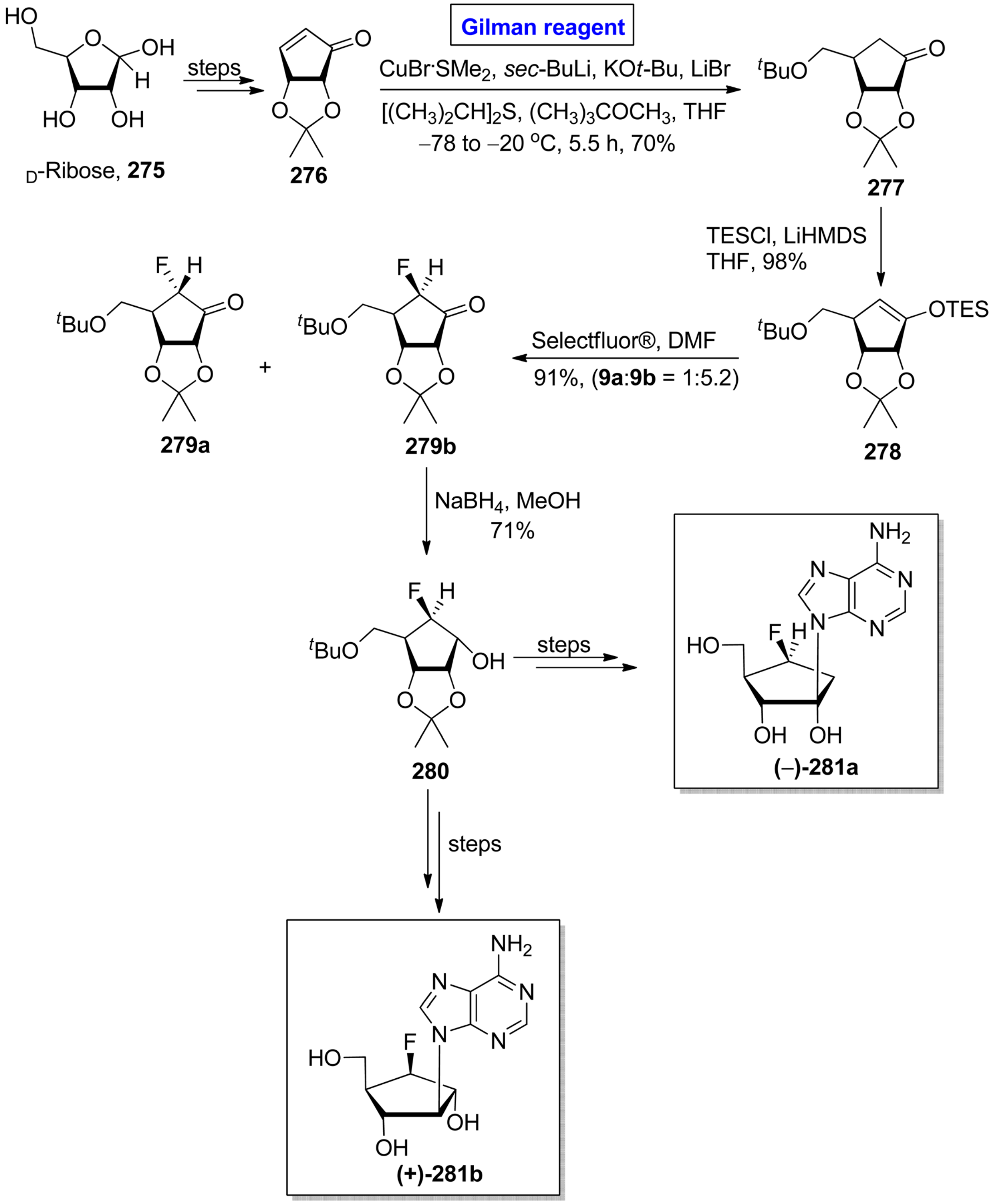


Scheme 30 Synthesis of L-Val-Gly based chloroalkene dipeptide **256**.



Scheme 31 Synthesis of fluorinated carbocyclic nucleosides **265–274**.

One of the carbocyclic nucleosides, (−)-aristeromycin, was isolated from a Gram-positive bacteria, *Streptomyces citricolor*. It is a strong anti-viral agent and adenosylhomocysteine hydrolase (AdoHcy) inhibitor.[122] Its remarkable pharmacological profile prompted endeavors to synthesize this natural product as well as its analogues.[123] In continuation of this effort, Kim *et al.* in 2017 disclosed the synthesis of (−)-6′-β-fluoro-aristeromycin **281a** and (+)-5′-β-fluoro-isoaristeromycin **281b** (Scheme 32).[124]



Scheme 32 Synthesis of (−)-6′-β-fluoro-aristeromycin **281a** and (+)-5′-β-fluoro-isoaristeromycin **281b**.

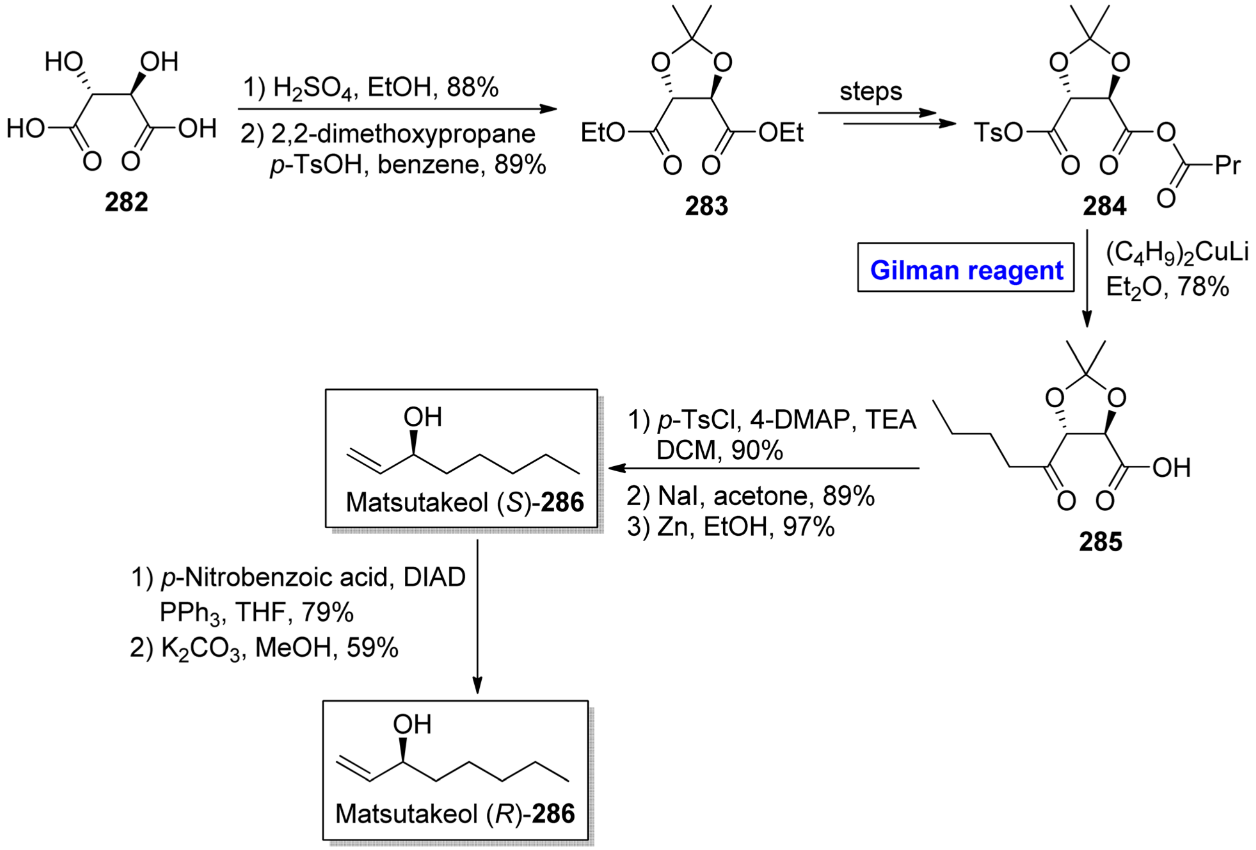
The key steps in their procedure entailed a regioselective conjugate addition reaction by employing Gilman reagent and electrophilic fluorination. In their methodology, compound **276** (modified from D-ribose), was treated with $CuBr\cdot SMe_2$, sec-BuLi, KO^tBu, LiBr, $[(CH_3)_2CH]_2S$, and $(CH_3)_3COCH_3$ (Gilman reagent) in THF to achieve compound **277** in 70% yield. After this, the electrophilic fluorination of compound **278** (from the silylation of compound **277**), by using Selectfluor® in DMF, compounds **279a** and **279b** were achieved in 90% yield (dr = 1 : 5.2). The compound **279b** underwent reduction in the presence of $NaBH_4$ in MeOH to generate the compound **280** in 71% yield. Later on, compound **280** was used as a well-suited intermediate for the synthesis of compounds **281a** and **281b**.

Synthesis of miscellaneous natural products

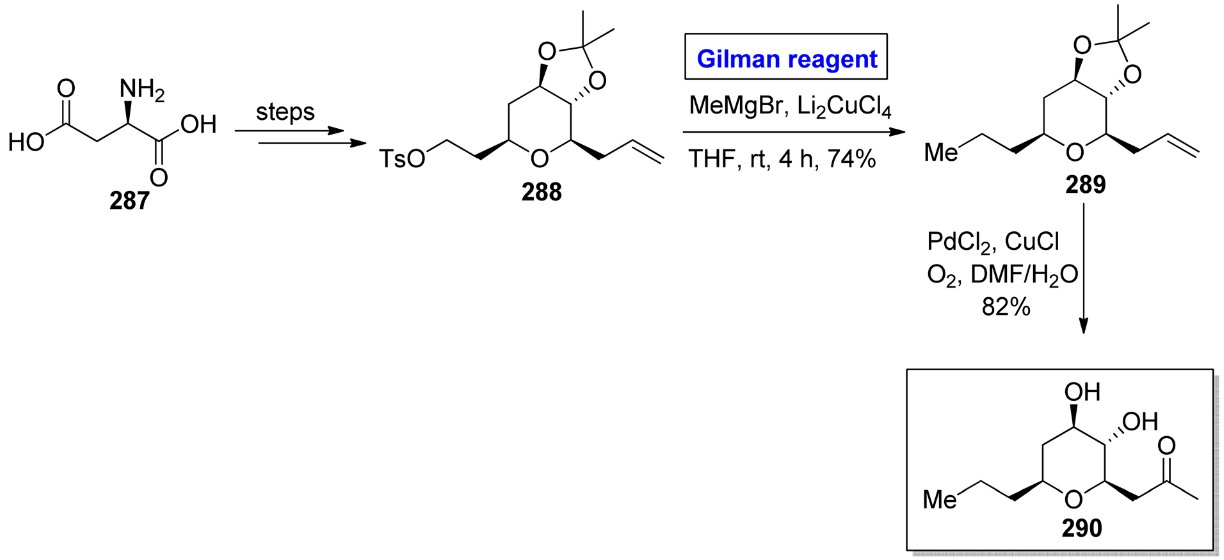
Tricholoma matsutake is an edible and expensive mushroom usually found in China, Korea, and Japan.[125] It exhibits a number of health benefits, such as lowering of blood cholesterol and improvement of blood circulation. It is also an important preventive agent for cancer, diabetes, and certain heart diseases.[126] Matsutakeol is an aromatic alcohol consisting of eight carbons (having a chiral carbon at the C-3 position) and a component (60 to 70%) of matsutake mushroom. In 2016, Lee *et al.* performed the facile and efficient synthesis of (*S*)-(+)-matsutakeol (*S*)-**286** (in 32% overall yield) in just 10 steps involving the employment of Gilman reagent by using inexpensive and easily available starting material, *i.e.*, L-tartaric acid (Scheme 33).[127] Their synthesis started with the esterification of compound **282** accompanied by acetal protection to give compound **283** in 89% yield. A few steps later, the compound **284** was subjected to nucleophilic substitution reaction *via* treatment with $(C_4H_9)_2CuLi$ and Et_2O (Gilman reagent) to furnish alcohol **285** in 78% yield. In the next step, the compound **285** was subjected to tosylation, iodine substitution, and acetal cleavage (in the presence of zinc in ethanol) in sequence to acquire compound (*S*)-**286** in 97% yield. To get matsutakeol (*R*)-**286**, Mitsunobu inversion[37] reaction of compound (*S*)-**286** and further treatment with potassium carbonate in methanol provided the desired compound in 59% yield.

Tetrahydropyran is an intriguing heterocyclic scaffold present in many medicinally important natural products.[128] One of the tetrahydropyran based natural products is phomonol **295**, which was isolated from *Phomopsis* sp. of endophytic fungus. Its structure constitutes 2,3,4,6 tetrasubstituted pyran, having four asymmetric centers.[129,130] Dada and Yaragorla reported an efficient and straightforward approach toward the total synthesis of phomonol **295** in 2022 (Scheme 34).[131] Their synthesis commenced with the easily available chiral starting material, *i.e.*, D-aspartic acid **287**, which was modified in a number of steps to provide acetonide **288**. In order to carry out the nucleophilic substitution reaction, a well-suited Gilman reagent was employed. For this purpose, compound **288** was treated with MeMgBr and Li_2CuCl_4 in THF at room temperature. After four hours, alkene **289** was obtained (in 74% yield), which was subjected to oxidation *via* $PdCl_2$, CuCl in DMF/H_2O to furnish compound **295** in 82% yield.

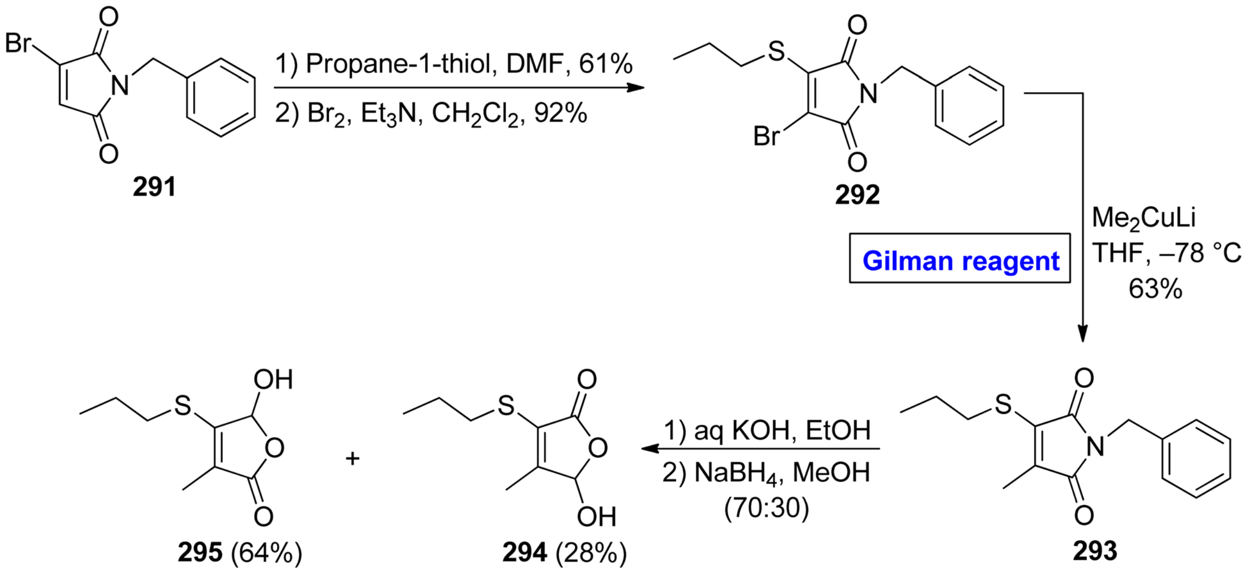
Cancer is a fatal disease and about 400 000 children may develop cancer each year. With the increase in carcinogens in the environment in recent years, the demand for pharmaceutics (as effective anti-cancer agents) has also increased[47,48] 5-hydroxy-3-methyl-4-propylsulfanyl-5*H* furan-2-one **295** is an effective chemopreventive agent, which was isolated first in 2007 from *Allium cepa* (onions), by Parkin and Xiao.[132,133] In 2011, Borikar *et al.* presented an efficient and facile methodology for the synthesis of this unique natural product **295** (Scheme 35).[134] To accomplish this task, bromomaleimide **291** was allowed to react with propane-1-thiol (in DMF) and Br_2 (in the presence of Et_3N in DCM) in sequence to provide bromide **292** in 92% yield. In order to perform the nucleophilic substitution reaction, a well-suited Gilman reagent was employed by treating the bromide **292** with lithium dimethyl cuprate in THF at −78 °C to acquire compound **293** in 63% yield. The hydrolysis



Scheme 33 Total synthesis of matsutakeol (*S*)-**286** and (*R*)-**286**.



Scheme 34 Total synthesis of phomonol **290**.



Scheme 35 Total synthesis of 5-hydroxy-3-methyl-4-propylsulfanyl-5*H* furan-2-one **295**.

of thiomaleimde **293** under basic conditions, followed by treatment with $NaBH_4$ in MeOH, resulted in a mixture of compound **295** (64%) and compound **294** (28%), which was separated by column chromatography to get our desired compound **295**.

Conclusion

Gilman reagent is mainly based on RLi and CuX or R_2CuLi with THF or Et_2O as solvent. In general, the temperature range for the Gilman reaction is between −78 °C to 0 °C. The electronic and steric effects of the *R* group directly affect the regioselectivity of the products formed as a result of the Gilman reaction. With these salient features, the Gilman reagent seems to have opened up new routes in modern total synthesis *via* conjugate addition reaction, bimolecular nucleophilic substitution reaction, and ring-opening reaction of both epoxide and aziridine. This review article is an updated compilation of Gilman reagent-induced synthetic approaches for the synthesis of intriguing natural products with significant biological activities. These natural products entail alkaloids, terpenoids, polyketides, macrolides, amino acids, nucleoside analogues, and some drugs. Further, this review will urge many organic chemists to employ their efforts on the methodological studies of the Gilman reagent so that more efficient synthetic pathways can be developed for future progress in medicinally important natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

A. Irfan extends his appreciation to the Deanship of Scientific Research at King Khalid University for funding through the large group Research Project under grant number RGP2/276/44.

References

1 G. H. Posner, *Org. React.*, 2004, **19**, 1–114.
2 B. H. Lipshutz, R. S. Wilhelm and D. M. Floyd, *J. Am. Chem. Soc.*, 1981, **103**, 7672–7674.
3 B. H. Lipshutz, F. Kayser and K. Siegmann, *Tetrahedron Lett.*, 1993, **34**, 6693–6696.
4 B. H. Lipshutz and B. James, *J. Chem. Soc. C*, 1994, **59**, 7585–7587.
5 E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, 1968, **90**, 5615–5616.
6 G. M. Whitesides, W. F. Fischer Jr, J. S. Filippo Jr, R. W. Bashe and H. O. House, *J. Chem. Soc. C*, 1969, **91**, 4871–4882.
7 C. Eaborn, P. B. Hitchcock, J. D. Smith and A. C. Sullivan, *J. Organomet. Chem.*, 1984, **263**, c23–c25.
8 S. H. Bertz, G. Dabbagh, J. M. Cook and V. J. Honkan, *Org. Chem.*, 1984, **49**, 1739.
9 S. H. Bertz and G. Dabbagh, *J. Am. Chem. Soc.*, 1988, **110**, 3668–3670.
10 S. H. Bertz, A. Chopra, M. Eriksson, C. A. Ogle and P. Seagle, *Eur. J. Chem.*, 1999, **5**, 2680–2691.
11 S. H. Bertz, S. Cope, D. Dorton, M. Murphy and C. A. Ogle, *Angew. Chem., Int. Ed.*, 2007, **46**, 7082–7085.
12 E. R. Bartholomew, S. H. Bertz, S. Cope, M. Murphy and C. A. Ogle, *J. Am. Chem. Soc.*, 2008, **130**, 11244–11245.
13 S. H. Bertz, R. A. Hardin, M. D. Murphy, C. A. Ogle, J. D. Richter and A. A. Thomas, *Angew. Chem., Int. Ed.*, 2012, **51**, 2681–2685.
14 S. H. Bertz, S. K. Cope, R. A. Hardin, M. D. Murphy, C. A. Ogle, D. T. Smith, A. A. Thomas and T. N. Whaley, *Organometallics*, 2012, **31**, 7827–7838.
15 S. H. Bertz, R. A. Hardin and C. A. Ogle, *J. Am. Chem. Soc.*, 2013, **135**, 9656–9658.
16 Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, *J. Org. Chem.*, 1982, **47**, 119–126.
17 A. Vivien, A. Bartoli, J. L. Parrain and L. Commeiras, *Tetrahedron Lett.*, 2020, **61**, 151472.
18 F. Velazquez and H. F. Olivo, *Org. Lett.*, 2000, **2**, 1931–1933.
19 A. Bisai, S. P. West and R. Sarpong, *J. Am. Chem. Soc.*, 2008, **130**, 7222–7223.
20 S. K. Mal, G. K. Kar and J. K. Ray, *Tetrahedron*, 2004, **60**, 2805–2811.
21 J. Vetter, *Food Chem. Toxicol.*, 2004, **42**, 1373.
22 Y. Lu, T. Yao and Z. Chen, *Acta Pharm. Sin. B*, 1986, **21**, 829.
23 S. C. Deshmukh, A. Roy and P. Talukdar, *Org. Biomol. Chem.*, 2012, **10**, 7536–7544.
24 S. P. Wong, C. Y. Gan, K. H. Lim, K. N. Ting, Y. Y. Low and T. S. Kam, *Org. Lett.*, 2015, **17**, 3628.
25 S. P. Wong, K. W. Chong, K. H. Lim, S. H. Lim, Y. Y. Low and T. S. Kam, *Org. Lett.*, 2016, **18**, 1618.
26 P. Gan, J. Pitzen, P. Qu and S. A. Snyder, *J. Am. Chem. Soc.*, 2018, **140**, 919–925.
27 M. Satake, A. J. Bourdelais, R. M. Van Wagoner, D. G. Baden and J. L. C. Wright, *Org. Lett.*, 2008, **10**, 3465.
28 A. T. Hermann, S. R. Matinez and A. Zakarion, *Org. Lett.*, 2011, **13**, 3636.
29 J. S. Yadav, N. M. Reddy, M. A. Rahman, A. R. Prasad and B. S. Reddy, *Tetrahedron*, 2013, **69**, 8618–8625.
30 R. Akhtar, S. A. R. Naqvi, A. F. Zahoor and S. Saleem, *Mol. Diversity*, 2018, **22**, 447–501.
31 M. Kuramoto, K. Hayashi, K. Yamaguchi, M. Yada, T. Tsuji and D. Uemura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 771–779.
32 N. Hikage, H. Furukawa, K. Takao and S. Kobayashi, *Chem. Pharm. Bull.*, 2000, **48**, 1370–1372.
33 C. B. Roa, A. S. R. Anjaneyula, N. S. Sarma, Y. Venkatateswarlu, R. M. Rosser, D. J. Faulkner, M. H. M. Chen and J. Clardy, *J. Am. Chem. Soc.*, 1984, **106**, 7983–7984.
34 D. C. Behenna, J. L. Stockdill and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2008, **47**, 2365–2386.
35 T. Nakajima, D. Yamashita, K. Suzuki, A. Nakazaki, T. Suzuki and S. Kobayashi, *Org. Lett.*, 2011, **13**, 2980–2983.
36 J. T. Bagdanoff, D. C. Behenna, J. L. Stockdill and B. M. Stoltz, *Eur. J. Org Chem.*, 2016, 2101–2104.
37 S. Munawar, A. F. Zahoor, S. Ali, S. Javed, M. Irfan, A. Irfan, K. K. Mojzych and M. Mojzych, *Molecules*, 2022, **27**, 6953.
38 M. Kuramoto, H. Arimoto and D. Uemura, *Mar. Drugs*, 2004, **2**, 39.
39 Y. Tsubosaka, T. Murata, K. Yamada, D. Uemura, M. Hori and H. Ozaki, *J. Pharmacol. Sci.*, 2010, **113**, 208.
40 C. Gignoux, A. F. Newton, A. Barthelme, W. Lewis, M. L. Alcaraz and R. A. Stockman, *Org. Biomol. Chem.*, 2012, **10**, 67–69.
41 D. P. A. Gossan, A. Alabdul Magid, P. A. Kouassi-Yao, J. B. Behr, A. C. Ahibo, L. A. Djakouré, D. Harakat and N. L. Voutquenne, *Phytochemistry*, 2015, **109**, 76.
42 M. Shibano, D. Tsukamoto and G. Kusano, *Heterocycles*, 2002, **57**, 1539.
43 B. J. Byatt, A. Kato and S. G. Pyne, *Org. Lett.*, 2012, **23**, 4029–4033.
44 J. Choi, N. N. Yadav and H. J. Ha, *Asian J. Org. Chem.*, 2017, **6**, 1292–1307.
45 E. Airiau, T. Spangenberg, N. Girard, B. Breit and A. Mann, *Org. Lett.*, 2021, **12**, 528–531.
46 N. N. Yadav, Y. G. Lee, N. Srivastava and H. J. Ha, *Front. Chem.*, 2019, **7**, 460.
47 I. Sarfraz, A. Rasul, G. Hussain, M. A. Shah, A. F. Zahoor, M. Asrar, Z. Selamoglu, X. Y. Ji, S. Adem and S. D. Sarker, *BioFactors*, 2020, **46**, 550–562.
48 I. Shahzadi, A. F. Zahoor, B. Parveen, A. Rasul, Z. Raza, S. Ahmad, A. Irfan and G. A. El-Hiti, *J. Chem.*, 2022, **2022**, 1–8.

49 W. Li, Y. Q. Tang, J. Sang, R. Z. Fan, G. H. Tang and S. Yin, *Org. Lett.*, 2020, **22**, 106.

50 J. Zhu, R. Wang, L. Lou, W. Li, G. Tang, X. Bu and S. Yin, *J. Med. Chem.*, 2016, **59**, 6353.

51 F. Q. Ni, S. Q. Wu, W. Li, Q. Li and S. Yin, *Org. Lett.*, 2020, **22**, 9360–9364.

52 R. Ratnayake, D. Covell, T. T. Ransom, K. R. Gustafson and J. A. Beutler, *Org. Lett.*, 2009, **11**, 57.

53 K. Molawi, N. Delpont and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2010, **49**(20), 3517–3519.

54 R. Nelson, M. Gulías, J. L. Mascareñas, F. López and F. Angew, *Angew. Chem., Int. Ed.*, 2016, **55**, 14359–14363.

55 Y. Saritas, S. H. von Reu and W. A. König, *Phytochemistry*, 2002, **59**, 795.

56 R. Richter, S. Basar, A. Koch and W. A. König, *Phytochemistry*, 2005, **66**, 2708.

57 D. W. Jee and H. Y. Lee, *Asian J. Org. Chem.*, 2021, **10**, 820–826.

58 M. Suchy, V. Benesova, V. Herout and F. Sorm, *Tetrahedron Lett.*, 1959, **10**, 5–9.

59 V. Saroglou, A. Karioti, C. Demetzos, K. Dimas and H. Skaltsa, *J. Nat. Prod.*, 2005, **68**, 1404–1407.

60 K. Johrer, M. Obkircher, D. Neurelter, J. Partell, C. Zelle-Rieser, E. Maizner, J. Kern, M. Hermann, F. Hamacher, O. Markel, N. Wacht, C. Zidorn, M. Scheideler and R. Grell, *J. Mol. Med.*, 2012, **90**, 681–693.

61 K. Kimura and T. Usuki, *Tetrahedron Lett.*, 2022, **107**, 154102.

62 D. C. Umrani, R. Seshadri, K. G. Gore and K. K. Chakravarti, *Flavor Ind.*, 1970, **1**, 623–624.

63 P. Kraft and R. Cadalbert, *Synthesis*, 2002, 2243–2253.

64 P. Kraft and N. Denizot, *Eur. J. Org Chem.*, 2013, 49–58.

65 M. Tsuda, K. Oguchi, R. Iwamoto, Y. Okamoto, E. Fukushi, J. Kawabata, T. Ozawa and A. Masuda, *J. Nat. Prod.*, 2007, **70**, 1661.

66 Y. Liu, J. Wang, H. Li, J. Wu, G. Feng and W. M. Dai, *Synlett*, 2010, 2184.

67 J. Huang and J. Yang, *Synlett*, 2012, **23**, 737–740.

68 M. Tsuda, K. Oguchi, R. Iwamoto, Y. Okamoto, J. Kobayashi, J. Kawabata, E. Fukushi, T. Ozawa and A. Masuda, *Nat. Prod.*, 2007, **70**, 1661–1663.

69 A. K. Ghosh and H. Yuan, *Mar. Drugs*, 2022, **20**, 587.

70 P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126.

71 A. B. Smith III, P. R. Verhoest, K. P. Minbiole and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 4834.

72 K. B. Raju, B. N. Kumar, B. S. Kumar and K. Nagaiah, *Helv. Chim. Acta*, 2015, **98**, 386–399.

73 J. B. MacMillan and T. F. Molinski, *Org. Lett.*, 2002, **4**, 1535.

74 D. De Joarder and M. P. Jennings, *Tetrahedron Lett.*, 2011, **52**, 5124.

75 D. De Joarder and M. P. Jennings, *Tetrahedron Lett.*, 2013, **54**, 5826–5829.

76 M. M. Gottesman, *Annu. Rev. Med.*, 2002, **53**, 615–627.

77 Y. J. Kim, K. Furihata, A. Shimazu, K. Furihata and H. J. Seto, *Antibiot.*, 1991, **44**, 1280–1282.

78 N. Terayama, E. Yasui, M. Mizukami, M. Miyashita and S. Nagumo, *Org. Lett.*, 2014, **16**, 2794–2797.

79 Y. H. Jeon, J. Y. Lee and S. Kim, *Bioorg. Med. Chem.*, 2012, **20**, 1893–1901.

80 H. Nakano, A. Sugawara, T. Hirose, H. Gouda, S. Hirono, S. Omura and T. Sunazuka, *Tetrahedron*, 2015, **71**, 6569–6579.

81 D. Katsumi, K. Nakasone, N. Terayama, E. Yasui, M. Mizukami, M. Miyashita and S. Nagumo, *J. Org. Chem.*, 2019, **84**, 1553–1562.

82 J. Kobayashi, H. Shigemori, M. Ishibashi, T. Yamasu, H. Hirota and T. J. Sasaki, *Org. Chem.*, 1991, **56**, 5221–5224.

83 J. Kobayashi, K. Shimbo, M. Sato and M. Tsuda, *J. Org. Chem.*, 2002, **67**, 6585–6592.

84 T. Usui, S. Kazami, N. Dohmae, Y. Mashimo, H. Kondo, M. Tsuda, A. G. Terasaki, K. Ohashi, J. Kobayashi and H. Osada, *Chem. Biol.*, 2004, **11**, 1269–1277.

85 A. Hara, R. Morimoto, Y. Ishikawa and S. Nishiyama, *Org. Lett.*, 2011, **13**, 4036–4039.

86 T. Fehr, J. J. Sanglier, W. Schuler, L. Gschwind, M. Ponelle, W. Schilling and C. J. Wioland, *Antibiot.*, 1996, **49**, 230–233.

87 M. E. Maier and C. Hermann, *Tetrahedron*, 2000, **56**, 557–561.

88 J. R. Vakiti and S. Ghosh, *Tetrahedron Lett.*, 2014, **55**, 6438–6440.

89 M. Okabe, T. Sugita, K. Kinoshita and K. J. Koyama, *Nat. Prod.*, 2016, **79**, 1208–1212.

90 H. Kumar, A. S. Reddy and R. B. V. Subba, *Tetrahedron Lett.*, 2014, **55**, 1519–1522.

91 C. W. Reed, M. G. Fulton, K. D. Nance and C. W. Lindsley, *Tetrahedron Lett.*, 2019, **60**, 743–745.

92 G. E. Chlipala, P. Huu Tri, N. Van Hung, A. Krunic, S. Hee Shim, D. D. Soejarto and J. Orjala, *J. Nat. Prod.*, 2010, **73**, 784–787.

93 R. C. Yanagita, H. Kamachi, M. Kikumori, H. Tokuda, N. Suzuki, K. Suenaga, H. Nagai and K. Irie, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4319–4323.

94 J. S. Yadav, G. Rajendar, R. S. Rao and S. Pabbaraja, *J. Org. Chem.*, 2013, **78**, 8524–8530.

95 S. Feuillastre, L. Raffier, B. Pelotier and O. Piva, *Org. Biomol. Chem.*, 2020, **18**, 1949–1956.

96 C. K. Lu, H. N. Chou, C. K. Lee and T. H. Lee, *Org. Lett.*, 2005, **7**, 3893–3896.

97 C. K. Lu, Y. M. Chen and S. H. Wang, *Tetrahedron Lett.*, 2010, **51**, 6911–6914.

98 P. AnkiReddy, S. AnkiReddy and S. Gowravaram, *Org. Biomol. Chem.*, 2018, **16**, 4191–4194.

99 K. Suenaga, K. Araki, T. Sengoku and D. Uemura, *Org. Lett.*, 2001, **3**, 527–529.

100 K. Araki, K. Suenaga, T. Sengoku and D. Uemura, *Tetrahedron*, 2002, **58**, 1983–1995.

101 J. Ren, J. Wang and R. Tong, *Org. Lett.*, 2015, **17**, 744–747.

102 Y. Igarashi, L. Yu, M. Ikeda, T. Oikawa, S. Kitani, T. Nihira, B. Bayanmunkh and W. J. Panbangred, *Nat. Prod.*, 2012, **75**, 986.

103 R. García-Salcedo, R. Álvarez-Álvarez, C. Olano, L. Cañedo, A. F. Braña, C. Méndez, C. F. De-la and J. A. Salas, *Mar. Drugs*, 2018, **16**, 259.

104 L. Yu, T. Oikawa, S. Kitani, T. Nihira, B. Bayanmunkh, W. Panbangred and Y. J. Igarashi, *Antibiot.*, 2014, **67**, 345.

105 M. Dumpala, B. Srinivas and P. R. Krishna, *Synlett*, 2020, **31**, 69–72.

106 J. F. Tremblay, *Chem. Eng. News*, 2000, **78**, 14–15.

107 P. A. Evans and P. A. Inglesby, *J. Am. Chem. Soc.*, 2012, **134**, 3635–3638.

108 I. Chogii, P. Das and J. T. Njardarson, *Asian J. Org. Chem.*, 2019, **8**, 1041–1044.

109 F. Kotch and R. T. Raines, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 3028–3033.

110 M. A. Cejas, W. A. Kinney, C. Chen, G. C. Leo, B. A. Tounge, J. G. Vinter, P. P. Joshi and B. E. Maryanoff, *J. Am. Chem. Soc.*, 2007, **129**, 2202.

111 S. Basu, P. S. Kandiyal, V. S. K. Neelamraju, H. Singh, R. S. Ampapathi and T. K. Chakraborty, *Tetrahedron*, 2014, **70**, 1169–1175.

112 M. Fill and J. A. Copello, *Physiol. Rev.*, 2002, **82**, 893–922.

113 K. Shiomi, R. Matsui, A. Kakei, Y. Yamaguchi, R. Masuma, H. Hatano, N. Arai, M. Isozaki, H. Tanaka, S. Kobayashi, A. Turberg and S. Omura, *J. Antibiot.*, 2010, **63**, 77–82.

114 A. Watanabe, Y. Noguchi, T. Hirose, S. Monma, Y. Satake, T. Arai, K. Masuda, N. Murashima, K. Shiomi, S. Omura and T. Sunazuka, *Tetrahedron Lett.*, 2020, **61**, 151699.

115 Y. Sasaki, A. Niida, T. Tsuji, A. Shigenaga, N. Fujii and A. Otaka, *Org. Chem.*, 2006, **71**, 4969–4979.

116 A. Proteau-Gagne, J. F. Nadon, S. Bernard, B. Guerin, L. Gendron and Y. L. Dory, *Tetrahedron Lett.*, 2011, **52**, 6603–6605.

117 D. E. White, I. C. Stewart, R. H. Grubbs and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 810–811.

118 T. Kobayakawa and H. Tamamura, *Tetrahedron*, 2016, **72**, 4968–4971.

119 A. C. Ojeda-Porras, V. Roy and L. A. Agrofoglio, *Chem. Rec.*, 2022, **22**, e202100307.

120 A. Kálmán, T. Yoritsánszky, J. Béres and G. Sági, *Nucleosides, Nucleotides Nucleic Acids*, 1990, **9**, 235–243.

121 C. M. Benckendorff, V. D. Slyusarchuk, N. Huang, M. A. Lima, M. Smith and G. J. Miller, *Org. Biomol. Chem.*, 2022, **20**, 9469–9489.

122 E. De Clercq, D. E. Bergstrom, A. H. John and J. A. Montgomery, *Antiviral Res*, 1984, **4**, 119.

123 E. De Clercq, *Nat. Rev. Drug Discovery*, 2002, **1**, 13.

124 G. Kim, J. S. Yoon, D. B. Jarhad, Y. S. Shin, M. S. Majik, V. A. Mulamoottil, X. Hou, S. Qu, J. Park, H. B. Mu and L. S. Jeong, *Org. Lett.*, 2017, **19**, 5732–5735.

125 X. Yin, Q. You and Z. Jiang, *Carbohydr. Polym.*, 2011, **86**, 1358.

126 R. Zawirska-Wojtasiak, *Food Chem.*, 2004, **86**, 113.

127 W. H. Lee, I. H. Bae, B. M. Kim and Y. B. Seu, *Bull. Korean Chem. Soc.*, 2016, **37**, 1910–1911.

128 Y. Y. Li, M. Z. Wang, Y. J. Huang and Y. M. Shen, *Mycology*, 2010, **1**, 254–261.

129 P. R. Krishna and S. Prabhakar, *Tetrahedron Lett.*, 2013, **54**, 3788–3790.

130 B. V. S. Reddy, L. Srinivas, P. S. Reddy, B. P. Reddy, A. R. Prasad and J. S. Yadav, *Helv. Chim. Acta*, 2014, **97**, 1326–1332.

131 R. Dada and S. Yaragorla, *Synth. Commun.*, 2022, **52**, 445–450.

132 H. Xiao and K. L. Parkin, *Phytochemistry*, 2007, **68**, 1059.

133 L. Gomez-Paloma, M. C. Monti, S. Terracciano, A. Casapullo and R. Riccio, *Curr. Org. Chem.*, 2005, **9**, 1419.

134 S. P. Borikar, V. Paul, V. G. Puranik, V. T. Sathe, S. Lagunas-Rivera and M. Ordónez, *Synthesis*, 2011, 1595–1598.